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Scott-Brown's Otorhinolaryngology Head & Neck Surgery

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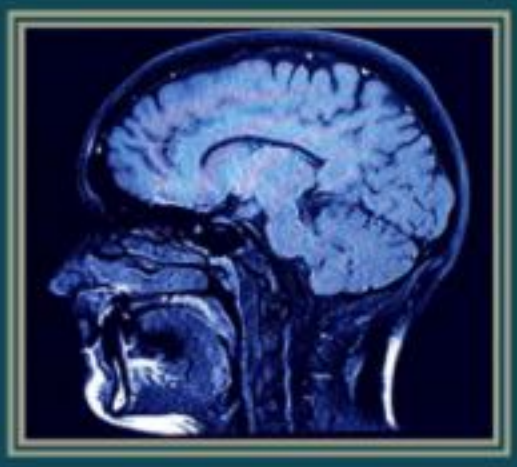
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Scott-Brown's Otorhinolaryngology Head & Neck Surgery



VOLUME 1

Basic Sciences
Endocrine Surgery
Rhinology

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Otorhinolaryngology Head and Neck Surgery

VOLUME 1

Basic Sciences, Head and Neck Endocrine Surgery, Rhinology

VOLUME 2

Paediatrics, The Ear, Skull Base

VOLUME 3

Head and Neck Surgery, Plastic Surgery

Scott-Brown's Otorhinolaryngology Head and Neck Surgery

EIGHTH EDITION

VOLUME 1

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Foreword

The eighth edition of *Scott-Brown* signals the beginning of a new and exciting era for ear, nose and throat surgeons, and also the end of 10 years of very hard work undertaken by John Watkinson and Ray Clarke, the Editors-in-Chief, their team of subeditors and, not least, the publishers. Whatever subspeciality the current generation of trainees decides to follow, they will all have to read and refer to *Scott-Brown* in order to complete their education and gain accreditation. It will be a constant companion and guide throughout their professional lives.

When asked to write the foreword for this edition, I was immediately reminded that I had read John Ballantyne and John Groves's third edition as a trainee, bought the fourth edition as a senior registrar, written chapters for Alan Kerr and Philip Stell in the fifth edition, edited the *Basic science* volume of the fifth edition and was ultimately Editor-in-Chief of the seventh edition. As each edition takes about 10 years to produce, that makes me very old indeed. John and Ray have one final task as Editors-in-Chief: to recommend their successors to the publishers. That was made easy for me as both of them had proved themselves more than capable with the previous edition, and the eighth edition is now their masterpiece. They can enjoy the next 10 years as thousands of surgeons worldwide recognize and thank them for their industry.

This edition reflects the continued expansion of our speciality into fields that Scott-Brown himself could never have imagined. It lays the groundwork for the current generation to make their contribution that will, no doubt, be prompted by technological developments, an evidence base of what is wise and what is not, together with the experience gained by teamwork with other clinicians in today's multidisciplinary approach to patient care.

Simply looking at the table of contents it is clear to see that our role in endocrine surgery has increased dramatically over the last 10 years. The thyroid and parathyroids now account for 30 chapters. How would Scott-Brown have viewed that when the tonsils and adenoids justify just one chapter each, and the sore throat has a mere passing reference? Times have certainly changed and ENT surgery has grown up. We have reflected on our past practices, and the evidence base for our management protocols that was emphasized in the previous edition of *Scott-Brown* has been taken to heart.

I hope that this edition will find its way into every medical library in the world and onto every ENT surgeon's bookshelf. It will serve and guide surgeons throughout the English-speaking world, whether they live in high- or low-income countries. It is said that the tragedy of getting old is that we feel young. Reading these volumes makes me wish that I had my time all over again.

Michael Gleeson

Preface

When we were asked to head up the editorial team for this, the eighth edition of *Scott-Brown*, we were mindful of Michael Gleeson's towering achievement in bringing the seventh edition to fruition. Michael delivered a much-loved text – conceived in the early post-war years when antimicrobials, the operating microscope and the National Health Service were all in their infancy – in an entirely new format that befitted modern surgical scholarship. Authors, editors and readers alike had become acutely conscious of the need to quote high-quality evidence to guide clinical decisions; the concept of grading clinical recommendations – and, by implication, acknowledging gaps in the evidence base of our practice – was born. Recognizing the enormity of Michael's contribution led us into the trap that has befallen every editor who has come before us; we grossly underestimated the task ahead. We had misjudged the pace of change. What began as an 'update' of some outdated chapters became a complete rewrite to reflect the advances that marked the decade between editions, but we were determined to keep the text to a manageable size! In the end, we have 330 chapters, but with a slightly smaller page count than the seventh edition.

The basic science knowledge that underpins our clinical practice is no longer focused just on anatomy and physiology; genetics, molecular biology, new techniques for auditory implantation, information technology, new medical therapies for many old disorders together with seismic changes in endoscopic technology and in medical imaging have transformed our specialty. Today's head and neck surgery would have been unrecognizable to the early authors and editors. Surgical oncologists have recourse to completely different treatment strategies than did their predecessors and now work as part of multidisciplinary teams. They deal with different disease patterns and vastly changed patient expectations. Thyroid and parathyroid surgery has become almost exclusively the domain of the otolaryngologist. Surgery of the pituitary fossa has come within our ambit, as has plastic and reconstructive surgery of the head and neck as well as aesthetic facial surgery. Neurotology, audio-vestibular medicine, rhinology and paediatric otolaryngology are accepted subspecialties, each with its own corpus of knowledge and skills and each warranting a sizeable section of this text. Contemporary otolaryngology is now a collection of subspecialty interests linked by common 'stem' training and a shared passion for looking after patients with disorders of the upper respiratory tract and the head and neck.

There is a view that a single text – even a multivolume tome of this size – cannot cover the entire knowledge base of modern clinical practice. The subspecialist will, of course, need recourse to supplementary reading. The pace of change shows no sign of slowing down, but there is still a need for a comprehensive working text embracing the whole spectrum of our workload. That was the task we set our authors and section editors; we think they have done our specialty proud.

In the new 'digital' editorial world authors create manuscripts on personal computers. They transmit chapters, figures, amendments and revisions across continents and time zones with a few keystrokes. The bulky packages containing grainy photographic prints and the reams of paper with closely-typed and heavily scored text that accumulated on authors' and editors' desks are a distant memory. References, guidelines and systematic reviews are all available online; the editorial 'red pen' has been replaced by a cursor on the screen. This 'new age' has enabled us to look ever further for expertise. We are proud to have enlisted the support of authors from more than 20 countries for this edition. *Scott-Brown* always enjoyed particular affection and respect in Asia, Australia, Africa and the Middle East. It has been a joy to welcome authors in increasing numbers from many of these parts of the world. We are now a truly global specialty and the eighth edition fully reflects this.

What has not changed is the huge time commitment authors and editors need to make. That time now has to be fitted into an increasingly pressurized work environment. Revalidation, mandatory training, more intense regulatory scrutiny, expanding administrative burdens and ever-expanding clinical commitments leave little time for scholarship. Our section editors are all busy clinicians. They have generously given their time, first instructing authors, cajoling them and then editing their chapters, virtually all of which have been completely rewritten since the last edition. Each author was chosen because of his or her specific clinical and scientific expertise and none has disappointed. Authors and section editors receive no reward other than the satisfaction of knowing that they have made a contribution to teaching and learning in a specialty that has given us all so much professional satisfaction. We are profoundly grateful to them and hope that their endeavours spur the next generation of otolaryngologists to carry on this noble tradition. *Scott-Brown* simply wouldn't happen without this generous and dedicated commitment, unstintingly and graciously given.

It is impossible to produce a book like *Scott-Brown* without the contribution of many individuals working behind the scenes. We would like to express our gratitude to our Publishers, Taylor and Francis, and to the staff who have worked on this project from its early days in 2011 to publication in 2018. In particular we would like to mention Cheryl Brandt who with good humour and patience helped to reel in many of the 330 chapters. Miranda Bromage joined the team in 2016 and her publishing experience and enthusiasm for medical education have helped guide this new edition through its final phases to publication. Finally, we are indebted to Nora Naughton who has dedicated so much more than just her extensive publishing skills to this project. Nora's meticulous attention to detail, combined with her warmth and wisdom have encouraged us all at the end of this endeavour.

We are truly 'passing on the torch' of a huge amount of accumulated knowledge and wisdom; it is this that gives us, the Editors-in-Chief, the greatest pleasure.

Read on and enjoy, our thoughts are yours.

RWC
JCW

I wish to acknowledge the love, happiness and inspiration that have been passed on to me by both my parents and grandparents. I recognize and value the friendship of my dear friend Ray Clarke who has been with me all the way on this rewarding and worthwhile endeavour. I would specifically like to thank Esme, Helen and William, without whom none of this would have been achievable. Their love and support has helped guide me through the years leading up to the publication of this tome, and my final thanks go to Angela Roberts and Sally Holden for their typing and editing skills.

JCW 2018

Thanks to my wife Mary for her patience and support. My parents, Emmet and Doreen Clarke, both sadly died during the preparation of this book. They would have been proud to have played a part in such a scholarly enterprise.

RWC 2018



Black Hut on the River Test – Pastel by W G Scott-Brown – circa 1970. Reproduced by kind permission of Mr Neil Weir, who was presented with the original by the artist.

A Tribute to Bill Scott-Brown



Walter Graham ('Bill') Scott Brown. 1897–1987

Walter Graham ('Bill') Scott-Brown was twenty-three when he arrived at Corpus Christi College Cambridge in 1919. One of the generation of young men whose entry to university and the professions was delayed by their participation in the First World War, he had joined the Gunners in 1915 as an 18-year-old. He considered himself blessed to have survived – although wounded – when so many of his contemporaries never returned from the Front. In those early post-WW1 years the medical school at St Bartholomew's ('Barts') in London was keen to attract 'gentlemen'. To this end a series of scholarships – 'Shuter's scholarships' – was established to lure those with humanities degrees from Oxford and Cambridge into medicine. It was via this scheme that the young Scott-Brown qualified MB, BCh in 1925. By now married to Margaret Bannerman, one of the very few women medical graduates of her generation, the two established a general practice in Sevenoaks, Kent. His work here involved looking after children with poliomyelitis, which was then commonplace, and his MD thesis was on polio-related bulbar palsy. It earned him the Copeman Medal for research from the University of Cambridge. While working in general practice, Bill pursued his interest in the then fledgling specialty of otolaryngology, securing fellowships from London and Edinburgh. Postgraduate training was haphazard; there were no structured programmes or even junior posts, so the young Scott-Brown was fortunate to be awarded a Dorothy Temple Cross Travelling Fellowship. Mrs Florence Temple Cross had set up these awards (now administered by the Medical Research Council) in memory of her daughter, who died in 1927 aged thirty-two. They were made available to young physicians to help them travel to overseas centres specifically to study tuberculosis, then rampant and one of the commonest causes of death in young adults. The young Scott-Brown visited the leading pioneers of the day in Berlin, Vienna, Budapest, Stockholm, Copenhagen, Madrid and Venice. Here he developed his considerable endoscopy skills. He reported that his first bronchoscopies were done on a Venetian street entertainer who, for a few coins, would inhale sundry objects that the doctors would then dexterously retrieve from his main stem and segmental bronchi – without of course any anaesthesia!

Times were lean on Scott-Brown's return. Margaret ('Peggy') was now a popular and well-established GP who supported him as his private practice developed. Eventually he secured appointments at East Grinstead, the Royal National and Royal Free Hospitals. He had a thriving Harley Street practice and was the favoured otolaryngologist of the aristocracy. His reputation was such that he become laryngologist to the Royal family, was appointed Commander of the Victorian Order and was a particular favourite of the then Princess Royal, HRH Mary the Countess of Harewood.

By 1938 he was wealthy enough to purchase a farm in Buckinghamshire where he bred prize-winning shorthorn cattle. Ironmongery and blacksmith work were hard to come by during the war years, so Scott-Brown prided himself on his ability to make his own agricultural implements, cartwheels and farm wagons in a makeshift forge he himself established on the farm. He would while away endless hours here at weekends following a busy week in London. An accomplished fly fisherman, he was part of the exclusive Houghton Club whose members fished the River Test in Hampshire, where he numbered aristocrats including the Prince of Wales among his circle.

Scott-Brown's celebrated textbook came about in the early 1950s, when he became ill with jaundice and heart trouble. He was advised to rest, and took 6 months off work. Not satisfied with editing what has become the standard UK textbook, he took up painting as well. He became a celebrated artist whose work is still prized in many private collections. One of his pastels is reproduced on the preceding page.

Bill Scott-Brown lived to be 90. He died in July 1987, six weeks after his beloved Peggy and just as the fifth edition of the celebrated textbook that still bears his name was going to press. His legacy lives on in the pages of this book, and we are proud to continue the tradition of scholarship and learning which he established all those years ago.

We would like to thank Martin Scott-Brown for his help in compiling the biography above.

John C. Watkinson and Raymond W. Clarke
London, 2018

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Abbreviations

1,25-DHCC	1,25 dihydroxycholecalciferol
2D	two-dimensional
3D	three-dimensional
4D CT	four-dimensional computed tomography
5-FdUMP	5-fluoro-2 deoxyuridine monophosphate
5-FU	5-fluorouracil
5-FUMP	5-fluorouridine monophosphate
6MP	6-mercaptopurine
18-FDG	2-18-fluoro-2-deoxy-D-glucose
A	adenine; *or* anterior
AACE	American Association of Clinical Endocrinologists
AAES	American Association of Endocrine Surgeons
AAGBI	Association of Anaesthetists of Great Britain and Ireland
AAOHNS	American Academy of Otolaryngologists/ Head and Neck Surgeons
AAV	adeno-associated virus
ABBA	axillo-bilateral-breast approach
ABG	arterial blood gas
ABPA	allergic bronchopulmonary aspergillosis
ABR	auditory brainstem response
ABRS	acute bacterial rhinosinusitis
AC	air conduction; *or* alternating coupled; *or* adenylate cyclase
ACE	angiotensin-converting enzyme
ACGME	Accreditation Council for General Medical Education
ACh	acetylcholine
AchR	acetyl choline receptor
ACR	Americal College of Rheumatology
ACT	Aid for Children with Tracheostomies
ACTH	adrenocorticotrophic hormone
AD	Alzheimer's disease
ADAM-33	A disintegrin and metalloprotease 33k
ADC	apparent diffusion coefficient
ADCC	antibody-dependent cellular cytotoxicity
ADH	antidiuretic hormone
ADP	adenosine diphosphate
ADR	adverse drug reaction
ADU	avoidable, delayed or undertransfusion
Ad-VEGF	adenovirus-encoding vascular endothelial growth factor
AEA	anterior ethmoidal artery
AED	aerodynamic equivalent diameter
AEF	auditory-evoked cortical magnetic field
AERD	aspirin-exacerbated respiratory disease
AES	assigned educational supervisors
AF	atrial fibrillation; *or* anterior fontanelle
AFAP	attenuated familial adenomatous polyposis
AFIP	Armed Forces Institute of Pathology
AFOI	awake fibre-optic intubation
AFRS	allergic fungal rhinosinusitis
AFU	angiofollicular unit
AGHDA	Assessment of Growth Hormone Deficiency in Adults
AH	adenohypophysis
AICA	anterior inferior cerebellar artery
AIDS	acquired immunodeficiency syndrome
AIFR	acute invasive fungal rhinosinusitis
AIFS	acute invasive fungal sinusitis
AIH	amiodarone-induced hypothyroidism
AIP	aryl hydrocarbon receptor-interacting protein
AIT	amiodarone-induced thyrotoxicosis
AJCC	American Joint Committee on Cancer
AKT	serine/threonine kinase
ALLO	alloimmunization
ALTB	acute laryngotracheobronchitis
ALS	advanced life support; *or* amyotrophic lateral sclerosis; *or* acid labile subunit
ALSPAC	Avon Longitudinal Study of Parents and Children
ALTB	acute laryngotracheobronchitis
AML	acute myeloid leukaemia
AMR	antimicrobial resistance
AN	acoustic neuroma; *or* auditory neuropathy; *or* audiovestibular nerve
ANA	anti-nuclear antibody
AN/AD	auditory neuropathy/auditory dyssynchrony
ANCA	antineutrophil cytoplasmic antibody
ANSD	auditory neuropathy spectrum disorder
ANTS	anaesthetists' non-technical skills
AOM	acute otitis media
AON	anterior olfactory nucleus
AP	anterior–posterior; *or* action potential
APACHE	acute physiology and chronic health evaluation
APC	antigen presenting cell; *or* activated protein C; *or* argon plasma coagulation; *or* adenomatous polyposis coli

APIT activated partial thromboplastic time
APOF aggressive psammomatoid ossifying fibroma
APTT activated partial thromboplastin time
AQP2 aquaporin 2
ARIA allergic rhinitis and its impact on asthma
ARR absolute risk reduction
ARS acute rhinosinusitis
ARSAC Administration of Radioactive Substances Advisory Committee
ART advanced rotating tomograph; *or* antiretroviral therapy
ARIA allergic rhinitis and its impact on asthma
ARS acute rhinosinusitis
ASA aspirin-induced asthma; *or* aspirin-sensitive asthma; *or* American Society of Anesthesiologists
a-SCC anterior semicircular canal
AT ataxia telangiectasia; *or* auditory therapy or training; *or* autotransplantation
ATA American Thyroid Association
ATC anaplastic thyroid carcinoma; *or* air traffic control
ATD ascending tract of Deiters; *or* adult therapeutic dose
ATIII antithrombin III
ATP adenosine triphosphate
ATR acute transfusion reaction
AVP arginine vasopressin
AW anterior wall

BABA bilateral axillo-breast approach
BAC bacterial artificial chromosome
BADS British Association of Day Surgery
BAES British Association of Endocrine Surgeons
BAETS British Association of Endocrine and Thyroid Surgeons
BAT basophil activation test
BCHD bone conduction hearing device
BCP biphasic calcium phosphate
BCSH British Committee for Standards in Haematology
BD Behcet's disease
BDP beclomethasone dipropionate
BFU-E burst-forming unit erythroid
BiPAP bilevel positive airway pressure
BIPP bismuth and iodoform paraffin paste
BIS bispectoral index
BL Burkitt's lymphoma
BMA British Medical Association; *or* bone marrow aspirate
BMD bone mineral density
BMI body mass index
BMP bone morphogenetic protein; *or* bone morphogenic protein
BOR brachio-oto-renal; *or* branchioterenal syndrome
BP blood pressure
BPE bilateral parathyroid exploration
BSAC British Society for Antimicrobial Chemotherapy
BTA British Thyroid Association

C cytosine
CAD caspase-activated DNase
CAF carcinoma-associated fibroblasts
CAG curriculum advisory group
cAMP 3',5'-monophosphate
CAP compound action potential; *or* category of auditory performance; *or* College of American Pathologists
CAPS cryopyrin-associated periodic syndromes
CARD caspase recruitment domain
CaSR calcium-sensing receptor
CASTLE carcinoma with thymus-like elements
CBD case-based discussion
CBF ciliary beat frequency
CCD charge-coupled device
CCH C-cell hyperplasia
CCP cyclic citrullinated peptide
CCR chemokine receptor
CCT Certificate of Completion of Training
CD cluster of differentiation; *or* colloid droplets; *or* compact disk; *or* Cowden's disease
CDA cold dry air
CDAD *C. difficile* associated diarrhoea
CDC Centers for Disease Control and Prevention
CDI *C. difficile* infection
CDK cyclin-dependent kinase
CEA carcinoembryonic antigen
CEFTE carcinoma of the thyroid with Ewing family tumour elements
CEPOD Confidential Enquiry into Perioperative Deaths
CER control event rate
CESR Certificate of Eligibility for Specialist Registration
CEX clinical evaluation exercises
CF cystic fibrosis; *or* characteristic frequency
CFD colour-flow duplex Doppler; *or* computational fluid dynamics
c-FOS fos proto-oncogene

CFTR cystic fibrosis transmembrane conductance regulator
CG clinical governance
CGD chronic granulomatous disease
CGH comparative genomic hybridization
CGIFS chronic granulomatous invasive fungal sinusitis
CGRP calcitonin gene-related peptide
CHI Commission for Healthcare Improvement (UK)
CHOP-R cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab
CI cochlear implant; *or* cardiac index; *or* confidence interval; *or* concha inferior
CICV can't intubate can't ventilate
CIFR chronic invasive fungal rhinosinusitis
CIFS chronic invasive fungal sinusitis
CINCA chronic infantile neurologic cutaneous articular syndrome
CJD Creutzfeldt–Jakob disease
CK cytokeratin
CKD-MBD chronic kidney disease mineral bone disorder
CLL chronic lymphatic leukaemia; *or* chronic lymphocytic leukaemia
CM concha media; *or* cochlear microphonic; *or* cricothyroid muscle
CMAP compound muscle action potential
CML chronic myeloid leukaemia
CMSO complementary metal oxide detectors
CMT Charcot—Marie—Tooth; *or* combined modality therapy
CMV cytomegalovirus
CN cranial nerve; *or* cochlear nuclei; *or* cochlear nerve
CNS central nervous system
CO_2 carbon dioxide
CoAA coactivator AA
COF cemento-ossifying fibroma
COMET Core Outcomes Measures in Effectiveness Trials
CONSORT Consolidated Standards of Reporting Trials
COPD chronic obstructive pulmonary disease
COSI Client Oriented Scale of Improvement
COX-2 cyclo-oxygenase 2
CPA cerebellopontine angle
CPAP continuous positive airway pressure
CPD citrate phosphate dextrose; *or* continuing professional development
CPG central pattern generator
CRC colorectal cancer
CRD component resolved diagnostics
CREB cAMO binding element
CREST calcinosis, Raynaud's, oesophageal involvement, sclerodactyly, telangiectasis
CRF corticotrophin-releasing factor
CRH corticotrophin-releasing hormone
CRH-R corticotrophin releasing hormone receptor
CRP C-reactive protein; *or* canalith repositioning procedure
CRS chronic rhinosinusitis; *or* congenital rubella syndrome
CRSwNP chronic rhinosinusitis with nasal polyps
CRSsNP chronic rhinosinusitis without nasal polyps
CRS chronic rhinosinusitis; *or* congenital rubella syndrome
CS corticosteroid; *or* cell salvage and autologous transfusions
CSC cancer stem cells
CSF cerebrospinal fluid
CSS Churg-Strauss syndrome
CST core surgical training
CT computed tomography; *or* conventional thyroidectomy
CTA composite tissue allograft; *or* computed tomography angiography
CTLA cytotoxic T-lymphocyte-associated antigen
CTM cricothyroid membrane
Cu-ATSM Cu(II)-diacetyl-bis-N4-methylthiosemicarbozone

DA double adenoma
DACH diaminocyclohexane
DAHANCA Danish Head and Neck Cancer Study
DAMPs damage-associated molecular pattern molecules
DAS Difficult Airway Society
DAT direct antiglobulin test
DAVF dural arteriovenous fistulas
dB decibel
DBM demineralized bone matrix
DCE MRI dynamic contrast-enhanced MRI
DCR dacryocystorhinostomy
DD death domain
DDAVP desmopressin
DDE Doctrine of Double Effect
DED death effector domain
DFN3 deafness type 3
DFO-H deferoxamine-hespan
DHI dizziness handicap inventory
DHTR delayed haemolytic transfusion reaction
DI diabetes insipidus
DIC disseminated intravascular coagulation
DIO deiodinases

DISC death inducing signal complex
DIT diiodotyrosine; *or* di-iodothyronine
DLBCL diffuse large B-cell lymphoma
DM diabetes mellitus; *or* decision making
DMARDS disease-modifying anti-rheumatic drugs
DMSA dimercapto succinic acid
DMSO dimethylsulfoxide
DNA deoxyribonucleic acid
DNAR do not attempt resuscitation
dNTP deoxynucleoside triphosphate
DOAC direct oral anticoagulant
DOHNS Diploma in Otolaryngology – Head and Neck Surgery
DOPS direct observation of procedural skills
DPA Data Protection Act (UK)
DPOAE distortion product otoacoustic emission
DR death receptor; *or* drug resistance
DSA digital subtraction angiography
dsRNA double-stranded RNA
DTC differentiated thyroid cancer
DTD DT-diaphorase
dTMP deoxythymidine monophosphate
dUMP deoxyuridine monophophase
DVT deep vein thrombosis
DWI diffusion weighted image

EAACI European Academy of Allergology and Clinical Immunology
EAC external auditory canal; *or* external acoustic canal
EAL ethmoidal artery ligation
EAT endoscopic-assisted thyroidectomy
EBM evidence-based medicine
EBNA Epstein–Barr virus-associated nuclear antigen
EBP evidence-based practice
EBRT external beam radiotherapy
EBSLN external branch of the superior laryngeal nerve
EBUS endobronchial ultrasound
EBV Epstein–Barr virus
ECA external carotid artery
ECAL external carotid artery ligation
ECG electrocardiogram
ECM extracellular matrix
ECMO extracorporeal membrane oxygenation
ECochG electrocochleography
ECog electrocochleogram
ECOG Eastern Cooperative Oncology Group (USA)
ECP eosinophil cationic protein; *or* extra corporeal perfusion
ECS extracapsular spread
EDTA ethylenediaminetetraacetic acid
EEA endoscopic endonasal approach
EEG electroencephalography; *or* electroencephalogram
EER experimental event rate
EFRS eosinophilic fungal rhinosinusitis
EFVPTC encapsulated follicular variant of PTC
EGF epidermal growth factor
eGFR estimated glomerular filtration rate
EGFR epidermal growth factor receptor
ELISA enzyme-linked immunosorbent assay
EMG electromyography
EMT epithelial-mesenchymal transition
EMRS eosinophilic mucin rhinosinusitis
ENA extractable nuclear antigen
ENoG electroneurography
ENS empty nose syndrome
ENT ear, nose and throat
EORTC European Organisation for Research and Treatment of Cancer
EPO erythropoietin
EPOS European position paper on rhinosinusitis and nasal polyps
EQ-5D EuroQol
ER enhancement ratio; *or* endoplasmic reticulum
ERα oestrogen receptor alpha
ERAS enhanced recovery after surgery
ERK extracellular signal-regulated kinase
ERS European Rhinological Society
ES embryonic stem; *or* endolymphatic sac
ESBL extended spectrum β-lactamase
ESPAL endonasal ligation of the sphenopalatine artery
ESR erythrocyte sedimentation rate
ESS endoscopic sinus surgery; *or* Epworth Sleepiness Scale; *or* empty sella syndrome
ET-1 endothelin-1
ETE extrathyroidal extension
ETT endotracheal tube
EUA examination under anaesthesia
EUCAST European Committee on Antimicrobial Susceptibility Testing
EVAL ethylene-vinyl alcohol copolymer
EWTD European Working Time Directive

Fab fragment antigen binding
FACT functional assessment of cancer therapy
FADD Fas-associated death domain

Fas-L Fas ligand
FBC full blood count
Fc fragment crystallizable
FcεRI high affinity IgE receptors
FD fibrous dysplasia
FDA Food and Drug Administration (USA)
FDG fluorodeoxyglucose; *or* 2-[18F] fluoro-2-deoxy-D-glucose; *or* F18-fluoro-2-deoxy-D-glucose
FD-OCT fourier domain optical coherence tomography
FDG-PET 2-[18F] fluoro-2-deoxy-D-glucose positron emission tomography; *or* fluorine-18-labelled deoxyglucose positron emission tomography
FE frontal ethmoidal cell
FEA finite element analysis
FESS functional endoscopic sinus surgery
FEIBA factor VIII inhibitor bypassing agent
F-ETNIM fluorine-18 fluoroerythronitroimidazone
FFP fresh frozen plasma
FGF fibroblast growth factor
FHH familial hypocalciuric hypercalcaemia
FIHP familial isolated hyperparathyroidism
FiO2 fraction of inspired oxygen
FIPA familial isolated pituitary adenomas
FISH fluorescence *in situ* hybridization
FITS functional inferior turbinosurgery
FIV feline immunodeficiency virus
FLAIR fluid attenuated inversion recovery
FMF familial Mediterranean fever
FMISO fluorine-18 fluoromisonidazole
fMRI functional magnetic resonance imaging
FMTC familial medullary thyroid cancer
FN facial nerve
FNA fine-needle aspiration/aspirate
FNAB fine-needle aspiration biopsy
FNAC fine-needle aspiration cytology
FNHTR febrile non-haemolytic transfusion reactions
FOI fibreoptic orotracheal intubation
FRS fungal rhinosinusitis
FS folliculostellate; *or* frontal sinus
FSH follicle-stimulating hormone
fT3 free T3
fT4 free T4
FTC frequency threshold curve; *or* follicular thyroid carcinoma
FT-UMP follicular tumour of uncertain malignant potential
FVPTC follicular variant of papillary thyroid carcinoma

G guanine
GABA gamma-aminobutyric acid
GABHS group A beta-haemolytic streptococcus
GAG glycosaminoglycan
GBI Glasgow Benefit Inventory
GBM anti-glomerular basement membrane
GC glucocorticoid
G-CSF granulocyte-colony stimulating factor
GD Graves' disease
GERD gastrooesophageal reflux disease
GH growth hormone
GHABP Glasgow Hearing Aid Benefit Profile
GHRH growth hormone-releasing hormone
GHRP growth hormone-releasing peptide
GI gastrointestinal
GMC ganglion mother cell; *or* General Medical Council (UK)
GM-CSF granulocyte-macrophage colony stimulating factor
GMS Gomori's methamine silver stain
GnIH gonadotrophin inhibitory hormone
GnRH gonadotrophin-releasing hormone
GORD gastro-oesophageal reflux disease
gp glycoprotein
GP general practitioner
GPA granuloma; *or* granulomatosis with polyangitis
G protein guanine nucleotide-binding regulatory protein
GRADE Grading of Recommendation, Assessment, Development and Evaluation
GRB2 growth factor receptor binding protein 2
Gs G-protein adenylate cyclase stimulator
GSH glutathione
GSP stimulatory G protein
GTN nitroglycerin
GTR guided tissue regeneration
GTV grow tumour volume
GvHD graft-versus-host disease

HA hydroxyapatite
H&E haematoxylin and eosin
H&N head and neck
H2 histamine receptor type 2
HA hydroxyapatite
HAART highly active antiretroviral therapy
HAI hospital-acquired infection
HBME-1 mesothelium-associated antibody
Hb haemoglobin
HbA adult haemoglobin

HBO hyperbaric oxygen
HBOT hyperbaric oxygen therapy
HCG human chorionic gonadotrophin
HD haemodialysis
HDL high-density lipoprotein
HDM house dust mite
HDU high dependency unit
He-Ne helium-neon
HEPA high-efficiency particulate air
HES hospital episode statistics
HFJV high-frequency jet ventilation
HFT hereditary familial telangiectasia
HGF hepatocyte growth factor
HH hypogonadotrophic hypogonadism
HHI Hearing Handicap Inventory; *or* hereditary hearing impairment
HHIE Hearing Handicap Inventory for the Elderly
HHT hereditary haemorrhagic telangiectasia
HHV-6 human herpesvirus 6
HHV-8 human herpesvirus 8
HI hearing impaired
Hib *Haemophilus influenzae* b
HIDS hyper-IgD syndrome
HIT heparin-induced thrombocytopenia
HIV human immunodeficiency virus
HL hearing loss; *or* hearing level; *or* hairy leukoplakia
HLA human leukocyte antigen
HLH haemophagocytic lymphohistiocytosis
HM history of migraine; *or* hemifacial microsomia
HMW high molecular weight
HMWC high molecular weight compound
HMWCK high molecular weight cytokeratin
HNSCC head and neck squamous cell carcinoma
Ho-YAG holmium yttrium aluminium garnet
HPA hypothalamic–pituitary–adrenal axis
HPC haemangiopericytoma
HPT hyperparathyroidism
HPT-JT hyperparathyroidism-jaw tumour
HPV human papillomavirus; *or* human herpes virus 8
HPZ herpes zoster
HR hazard ratio
HRA Human Rights Act
HRQOL health-related quality of life
HR heart rate
HRT hormone replacement therapy
HRV rhinoviruses
HSC haematopoietic stem cell
HSCT haemopoietic stem cell transplant
HSD hydroxysteroid dehydrogenase enzyme
HSE handling and storage errors
HSV herpes simplex virus
HSV-1 herpes simplex virus type 1
HSV-2 herpes simplex virus type 2
HSV-TK herpes simplex thymidine kinase
HTA hyalinizing trabecular adenoma; *or* Health Technology Assessment
hTERT human telomerase reverse transcriptase
HTR haemolytic transfusion reaction
HTT hyalinizing trabecular tumours
HU Hounsfield unit
HUI Health Utilities Index
HVDT health visitor distraction test
Hz hertz
HZV herpes zoster virus

IAC internal auditory canal
IAR intermittent allergic rhinitis
IBCT incorrect blood component transfused
ICA internal carotid artery
ICAD inhibitor caspase-activated DNase
ICAM intercellular adhesion molecule
ICAM-1 intercellular adhesion molecule 1
ICD International Classification of Disease
ICF International Classification of Functioning
ICS intra-operative cell salvage
ICU intensive care unit
IDD intracellular death domain
IDT infant distraction test; *or* intra-dermal test
IFN interferon
IFN-α interferon-alpha
IFN-β inteferon-beta
IFN-γ interferon-gamma
IFVPTC invasive follicular variant of PTC
Ig immunoglobulin
IGD isolated GnRH-deficiency
IgE immunoglobulin E
IGF insulin-like growth factor
IGF-I insulin-like growth factor 1
IGF-II insulin-like growth factor II
IGFBP insulin-like growth factor binding protein
IgG immunoglobulin G
IgGκC immunoglobulin G kappa chain
IGS image-guided surgery
IHC immunohistochemistry; *or* inner hair cell
IIT iodide-induced thyrotoxicosis

IJV internal jugular vein
IL interleukin
IL-1 interleukin-1
IL-2 interleukin-2
IL-3 interleukin-3
IL-5 high interleukin
IL-6 interleukin-6
ILMA intubating laryngeal mask airway
i.m. intramuscular
IMA internal maxillary artery
IMAL internal maxillary artery ligation
IMF intermaxillary fixation
IMP importin
IMRT intensity-modulated radiation therapy
iNOS inducible nitric oxide synthase
INR international normalized ratio; *or* interventional neuroradiology
IOM institute of Medicine
IONM intra-operative neural/nerve monitoring
IOPTH intra-operative PTH
IOQPTH intra-operative quick assay of intact parathyroid hormone
IOUS intra-operative ultrasound scanning
IP Inverted papilloma
IPD invasive pneumococcal disease
iPSCs induced pluripotency stem cells
IPSS inferior petrosal sinus sampling
IRI ischaemia-reperfusion injury
IRS insulin receptor substrate; *or* Intergroup Rhabdomyosarcoma Study
ISAAC International Study of Asthma and Allergies in Childhood
ISCP International Surgical Curriculum Programme
ISL *in situ* ligation
IT inferior turbinate
ITA inferior thyroid artery
ITAM immunoreceptor tyrosine-based activation motif
ITP idiopathic thrombocytopenic purpura
ITU intensive therapy unit
i.v. intravenous
IVIg intravenous immunoglobulin

JAK2 Janus kinase 2
JCST Joint Committee on Surgical Training
JIA juvenile idiopathic arthritis
JLNS1 Jervell and Lange-Nielsen syndrome
JNA juvenile nasopharyngeal angiofibroma
JNK c-Jun N-terminal kinase

K Kirschner
KCCT kaolin cephalin clotting time
KDOQI Kidney Disease Quality Outcomes Initiative
keV kilo electron volt
KOH potassium hydroxide solution prep test
KISS-R kisspeptin receptor (also known as GR54)
KS Kaposi's sarcoma
KTP potassium titanyl phosphate

LA lymphangioma
LAR local allergic rhinitis
LAT lateral aberrant thyroid
LC1 livery cystolic 1
LCM laser capture microdissection
LDH lactate dehydrogenase
LDL low-density lipoprotein; *or* loudness discomfort level
LED light-emitting diode
LFA lymphocyte-function associated antigen
LFJV low-frequency jet ventilation
LH luteinizing hormone
LHB lateral-head-back
LH-R luteinizing hormone receptor
LINAC linear accelerator
LKM liver kidney microsomal
LM laryngeal mask
LMA laryngeal mask airway
LMW low molecular weight
LMWC low molecular weight compound
LMWH low molecular weight heparin
LOCR lateral opticocarotid recess
LOD logarithm to the base 10 of the odds that the markers are linked at a recombination distance of N centimorgans
LOH loss of heterozygosity
LP lamina papyracea; *or* lichen planus; *or* lymphocyte predominant
LPR laryngopharyngeal reflux; *or* late phase reactions
LR likelihood ratio
LR-OCT long-range optical coherence tomography
LTRA leukotriene receptor antagonists
LW lateral wall

M metastases
M2 Matrix 2 ion channels
MAb monoclonal antibodies
MABP mean arterial blood pressure
MAC membrane attack complex; *or* *Mycobacterium avium* complex

MAD mucosal atomization device
MAGE-3 melanoma-associated antigen-3
MALT mucosa-associated lymphoid tissue
MAOI monoamine oxidase inhibitor
MAP minimum audible pressure
MAPK mitogen-activated protein kinase
MAS mandibular advancement splint; *or* macrophage activation syndromes
MBL mannose-binding lectin
MC2R melanocortin 2 receptor
MCP monocyte chemotactic protein
MCS mental component summary
MCT medullary thyroid carcinoma
MCV mean corpuscular volume
MDCT multi-detector row CT
MDS myelodysplastic syndrome
MDT multidisciplinary team
ME middle ear
MEG magnetoencephalography
MEK MAPK/extracellular signal related kinase
MEN multiple endocrine neoplasia
MeSH medical subject heading
MET middle ear transducer
M-FISH multifluor FISH
MGHD multiple gland hyperplasia disease
MGO methylglyoxal
MGUS monoclonal gammopathy of uncertain significance
MHC major histocompatibility complex
MHP massive haemorrhage pack
MI myocardial infarction
mIBG metaiodobenzylguanidine; *or* iodine-123-metaiodobenzylguanidine
MIBI sestamibi; *or* technetium-99m
MIC minimum inhibitory concentration
μOCT micro-optical coherence tomography
MIFC minimally invasive follicular carcinoma
MIP minimally invasive parathyroidectomy; *or* maximum intensity projection; *or* macrophage inflammatory protein;
miRNA micro ribonucleic acid
MIST minimal invasive sinus techniques
MIT monoiodotyrosine; *or* mono-iodothyronine; *or* minimally invasive thyroidectomy
MIVAT minimally invasive video-assisted thyroidectomy
MLKL mixed lineage kinase domain-like protein
MLTB microlaryngotracheobronchoscopy
MMC mitomycin C; *or* Modernising Medical Careers
MMP mucous membrane pemphigoid; *or* matrixmetalloprotease
MMR measles, mumps and rubella
MNG multinodular goitre
MOCR medial opticocarotid recess
MODS multiple organ dysfunction syndrome
MOE malignant otitis externa
MOFT multiple oxyphil follicular tumour
MOS Medical Outcomes Study
MPA microscopic polyangiitis
MPTS Medical Practitioner's Tribunal Service
MPO myeloperoxidase
MPTP 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MR magnetic resonance
MRA magnetic resonance angiography
MRC Medical Research Council (UK)
MRCS Member of the Royal College of Surgeons
MRI magnetic resonance imaging
mRNA messenger ribonucleic acid
MRSA methicillin-resistant *Staphylococcus aureus*
MS multiple sclerosis
MSBOS maximum surgical blood ordering schedule
MSCs mesenchymal stem cells
MSF multi-source feeback
MSSA methicillin-susceptible strains
MT maxilloturbinal; *or* middle turbinate
MTC medullary thyroid carcinoma
mtDNA mitochondrial DNA
mTORC1 mammalian target of rapamycin 1
mTORC2 mammalian target of rapamycin 2
MW medial wall

N nodal
NADP nicotinamide adenine dinucleotide phosphate
NADPH reduced form of nicotinamide adenine dinucleotide phosphate
NANIPER non-allergic non-infectious perennial rhinitis
NAP4 Fourth National Airway Project
NARES non-allergic rhinitis with eosinophilia syndrome
NBCA n-butyl-2-cyanoacrylate; *or* N-butylcyanoacrylate
NBT nitro blue tetrazolium
NCAS National Clinical Assessment Service (UK)
NCEPOD National Confidential Enquiry into Patient Outcome Death (UK)
NCIC National Cancer Institute of Canada
ncRNA non-coding ribonucleic acid
Nd-YAG neodymium-yttrium aluminium garnet
NET nerve excitability test; *or* neuroendocrine tumour

NF1 neurofibromatosis type 1
NF2 neurofibromatosis type 2
NH normal hearing; *or* neurophypophysis
NHANES National Health and Nutrition Examination Survey
NHL non-Hodgkin's lymphoma
NHS National Health Service (UK)
NHSLA National Health Service Litigation Authority
NIBP automatic non-invasive blood pressure
NICE National Institute for Health and Care Excellence (UK)
NIFTP non-invasive follicular tumour with papillary-like nuclei
NIH National Institutes of Health (USA)
NIM nerve integrity monitor
NIPF nasal inspiratory peak flow
NIS Na+/I– symporter
NK natural killer
nLTP non-specific lipid transfer protein
NNT number needed to treat
NO nitric oxide
NO2 nitric dioxide
NOAC novel oral anticoagulant
NOE naso-orbito-ethmoid
NOTSS non-technical skills for surgeons
NOS not otherwise specified
NP nasopharynx; *or* nasopharyngeal
NPC nasopharyngeal cancer; *or* nasopharyngeal carcinoma
NPSA National Patient Safety Agency (UK)
NPT near patient testing
NPV negative predictive value
NRTIs nucleoside/nucleotide reverse transcriptase inhibitors
NSAID non-steroidal anti-inflammatory drug
NSF national service framework; *or* nasoseptal flap
NSHI non-syndromic hearing impairment
NTT near-total thyroidectomy

O3 ozone
OAE otoacoustic emission
OB olfactory bulb
OCT optical coherence tomography
ODP operating department practitioner
OF ossifying fibroma
OFDI optical frequency domain imaging
OIDA observe; interpret; decide; act
OMC ostiomeatal complex
OPC oropharyngeal cancer; *or* oropharyngeal candidiasis
OPCS Office for Population Censuses and Surveys (UK)
OPF osteoplastic flap procedure
OR occupational rhinitis
OREP olfactory event-related potential
ORL otorhinolaryngology
OSA obstructive sleep apnoea
OSATS obstructive structured assessment of technical skill
OTOF otoferlin
OXTR oxytocin receptor

P phosphate; *or* posterior
PA pernicious anaemia
PAC P1 artificial chromosome; *or* pulmonary artery catheter; *or* parathyroid carcinoma
PACS picture archiving and communication systems
PACU post-anaesthesia care unit
PAF platelet-activating factor
PBA procedure-based assessment
PBP progressive bulbar palsy
PCA patient-controlled analgesia
PCC prothrombin complex concentrate; *or* Professional Conduct Committee (UK); *or* pheochromocytoma
PCD primary ciliary dyskinesia
PCOS polycystic ovary syndrome
PCR polymerase chain reaction
PCS physical component summary
PD Parkinson's disease
PDCAT poorly differentiated carcinoma of the thyroid
PDE phosphodiesterase
PD1 programmed cell death protein 1
PDGF platelet-derived growth factor
PDL pulsed dye laser
PDR Physicians' Desk Reference
PDS polydimethylsiloxane
PDT photodynamic therapy
PE polyethylene; *or* pulmonary embolism; *or* pharyngo-oesophageal
PEG percutaneous endoscopic gastrostomy
PER persistent allergic rhinitis
PET polyethylene terephthalate; *or* positron emission tomography
PET-CT positron emission tomography/computed tomography
PET-MRI positron emission tomography-MRI
PF posterior fontanelle; *or* cisplatinum/5-fluorouracil

PF4 platelet factor 4
PFAPA periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis
PFS progression-free survival
PG paraganglioma
PGA polyglycolic acid
PGD2 prostaglandin D2
PGE1 prostaglandin-E1
PGI2 prostacycline; *or* prostaglandin I2
PGL persistent generalized lymphadenopathy
PHPT primary hyperparathyroidism
PI pulsatility index; *or* protease inhibitors
PI3K phosphotidyinositol 3
PICU paediatric intensive care unit
PIII parathyroid III
PIP peak inspiratory pressure
PIV parainfluenza virus; *or* parathyroid IV
PKA protein kinase A
PLAT paraganglioma-like adenoma of the thyroid
PLD potentially lethal damage
PM particulate matter
PNH paroxysmal nocturnal haemoglobinuria
PNIF peak nasal inspiratory flow
p.o. by mouth
POGO prescription of gain and output
POMC propiomelanocorticotrophin
PONV postoperative nausea/vomiting
PP pyrophosphate
PPD purified protein derivative; *or* parathyroid proliferative disease
PPV positive predictive value
PR3 proteinase 3
PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRL polypeptide hormone prolactin
PRP platelet-rich plasma
PRPP 5-phospho-alpha-D-ribose 1-diphosphate
PSA prostate-specific antigen; *or* pleomorphic salivary adenoma; *or* persistent stapedial artery
PS-OCT polarization-sensitive OCT
PT prothrombin time
PTAH phosphotungstic acid haematoxylin
PTC papillary thyroid cancer; *or* psychophysical tuning curve
PTG parathyroid gland
PTH parathyroid hormone
PTHrP parathyroid hormone-related protein; *or* parathyroid hormone-related peptide
PTMC papillary thyroid microcarcinoma
pTNM pathological tumour, nodes, metastases
PTP post-transfusion purpura
PTU propylthiouracil
PUOF1 pituitary-specific positive transcription factor 1
PVA polyvinyl alcohol
PVC polyvinyl chloride
PW posterior wall

QALY quality adjusted life year
QOL quality of life

RA retinoic acid
RAE Ring, Adair, Elwyn
RAF rapidly accelerated fibrosarcoma signal-regulated kinase
RAI radioactive iodine
RANKL regulation of nuclear factor κB ligand
RANTES regulated on activation, normal T-cell expressed and secreted
RAS recurrent aphthous stomatitis; *or* rat sarcoma protein family
RAST radioallergosorbent test
RAT rapid antigen testing; *or* robotic-assisted thyroidectomy
RB retinoblastoma
RBC red blood cell
RCC Rathke cleft cyst; *or* red cell count
RCoA Royal College of Anaesthetists
RCT randomized controlled trial
RET rearranged during transfection
RF rheumatoid factor; *or* radio frequency
RFLP restriction fragment length polymorphism
RFRP RFamide-related peptide
RFTVR radiofrequency tissue volume reduction
rFVIIa recombinant factor VIIa
rhBMP-7 recombinant human bone morphogenetic protein 7
rhPTH recombinant human parathyroid hormone
rhTSH recombinant human TSH
RHD Reported Hearing Disability
RIG radiologically inserted gastrostomy
RLN recurrent laryngeal nerve
RLNP recurrent laryngeal nerve palsy
RNA ribonucleic acid
RNP ribonucleoprotein
ROS reactive oxygen species
ROSE rapid on-site evaluation
ROTEM thromboelastography
RP rapid prototyping; *or* relapsing polychondritis
RR relative risk

RRA radioiodine remnant ablation
RRR relative risk reduction
RSDI Rhinosinusitis Disability Index
RSOM rhinosinusitis outcome measure
RSTL relaxed skin tension line
RSV respiratory syncytial virus
RT radiotherapy
RTOG Radiation Therapy Oncology Group
rT3 reverse triiodothyronine
RTK receptor tyrosine kinase
RUDS reactive upper airways dysfunction syndrome

SA solitary adenoma; *or* situational awareness
SAD supraglottic airway device
SAGM saline-adenine-glucose-mannitol
SAPS simplified acute physiology score
SBS sick building syndrome
s.c. subcutaneous
SCC squamous cell carcinoma or cancer; *or* semicircular canal
SCCA squamous cell carcinoma antigen
SCCHN squamous cell carcinoma of the head and neck
SCID severe combined immunodeficiency
SCIT subcutaneous immunotherapy
SCL-90 Symptom Checklist-90
SCM sternocleidomastoid muscle
SCN severe congenital neutropenia; *or* solid cell nests
SEER Surveillance, Epidemiology, and End Results (program)
SERM selective-oestrogen receptor modifier
SETTLE spindle cell tumour with thymus-like differentiation
SF-36 Medical Outcome Study Short-Form 36-Item Health Survey
SFF speaking fundamental frequency; *or* solid free form fabrication
SHC SH2-containing protein
Shh sonic hedgehog
SHI syndromic hearing impairment
SHOT serious hazards of transfusion
SHPT secondary hyperparathyroidism
SIADH syndrome of inappropriate antidiuretic hormone
sIgE specific immunoglobulin E
SIGN Scottish Intercollegiate Guidelines Network
SIP sickness impact profile
siRNA small interfering ribonucleic acid
SLD sublethal damage
SLE systemic lupus erythematosus
SLICC Systemic Lupus International Collaborating Clinics
SLIT sublingual immunotherapy; *or* sublingually in drops or tablets
SLN superior laryngeal nerve
SMAS superficial or subcutaneous musculoaponeurotic system
SAMD submucosal diathermy
SMR submucosal resection
SMS short message service; *or* indium-111 pentetreotide
SNHL sensorineural hearing loss
SNOT sino-nasal outcome test
SNUC sinonasal undifferentiated carcinoma
SO2 sulphur dioxide
SOCS2 suppressors of cytokine signalling 2
SOE supraorbital ethmoid cells
SOFA sequential organ failure assessment
SOFT solitary oxyphil follicular tumour
SOS guanine nucleotide exchange factor (son of sevenless)
SPA sphenopalatine artery
SPECT single photon emission computed tomography
SPET single photon emission tomography
SPF sphenopalatine foramen
SPLINTS scrub practitioners list of intra-operative non-technical skills
SPT skin prick test; *or* station pull through
SPTX subtotal parathyroidectomy
SRS subacute rhinosinusitis
SS somatostatin
ssDNA single-stranded DNA
SSC superior semicircular canal; *or* Surviving Sepsis Campaign
SSEP steady-state potential
SSLP simple sequence length polymorphism
SSQ speech, spatial and qualities
SSTR1-5 somatostatin receptors 1-5
SSRI selective serotonin reuptake inhibitor
ST superior turbinate; *or* subtotal thyroidectomy
STAT signal transducer and activator of transcription
STD standard deviation
STRP short tandem repeat polymorphism
SUV standardized uptake value
SV stroke volume
SVCO superior vena caval obstruction
SVS selective venous sampling

SVCO superior vena cava obstruction
SVR systemic vascular resistance
Syk signal-propagating kinase

T thymine; *or* tumour
T1WI T1-weighted images
T2WI T2-weighted images
T3 triiodothyronine
T4 thyroxine
TAA tumour associated antigens
TACO transfusion-associated circulatory overload
TAD transfusion-associated dysponea
TAGVHD transfusion-associated graft-versus-host disease
TAM tumour associated macrophages
TB tuberculosis; *or Mycobacterium tuberculosis*
TBG thyroxine-binding globulin
TcT cytotoxic
^{99m}Tc technetium-99m
Tc-99m (v) DMSA pentavalent dimercaptosuccinic acid
TC thyroid cartilage
TCI target-controlled infusion
TCP tricalcium phosphate
TCR T-cell receptor
t.d.s. 3 times a day
TEG thromboelastography
TFT thyroid function test
TG thyroglobulin
TgAb thyroglobulin antibodies
TGF transforming growth factor
TGF-α transforming growth factor alpha
TGF-β transforming growth factor beta
TGF-β1 transforming growth factor beta 1
Th T-helper
Th1 T-helper 1 cell
Th2 T-helper 2 cell
THST thyroid hormone suppression therapy
THW thyroid hormone withdrawal
TI thyroid isthmusectomy
TIL tumour infiltrating lymphocytes
TIVA total intravenous anaesthesia
TKI tyrosine kinase inhibitor
TL total lobectomy
TME tumour microenvironment
TMC1 transmembrane channel-like gene 1
TMJ temporomandibular joint
TNF tumour necrosis factor
TNF-α tumour necrosis factor alpha
TNM tumour, node, metastasis
TNO transnasal oesophagosocpy
TOE transoesophageal echocardiography; *or Trichophyton*, *Oidiomycetes* and *Epidermophyton*
TOF tracheo-oesophageal fistula
TPO thyroid peroxidase; *or* thyroperoxidase
TPP thyrotoxic periodic paralysis
TPTX total parathyroidectomy
TPZ tirapazamine
TRALI transfusion-related acute lung injury
TRAM transverse rectus abdominis myocutaneous
TRH thyrotrophin-releasing hormone
tRNA transfer ribonucleic acid
TSA tumour specific antigens
TSH thyroid-stimulating hormone; *or* thyrotrophin
TSHoma TSH-secreting adenoma
TSH-R TSH receptor
TT thrombin time; *or* total thyroidectomy
TTF-1 thyroid transcription factor-1
TTP thrombotic thrombocytopeniac purpura
TUNEL TdT-mediated nick end labelling

U uracil
UCT unclassifiable complications of transfusion
UICC International Union Against Cancer
UIC urinary iodine concentration
UKRETS UK Registry of Endocrine and Thyroid Surgery
UMP uridine monophosphate
UNICEF United Nations Children's Fund
UP uncinate process
UPSIT University of Pennsylvania Smell Identification Test
URTI upper respiratory tract infection
US ultrasound; *or* ultrasonography
USH Usher syndrome
USH1B Usher syndrome type 1B
USS ultrasound scan
UV ultraviolet

V2R vasopressin type 2 receptor
VA Veterans' Affairs; *or* vestibular aqueduct
VAC vacuum-assisted closure
VAS visual analogue scale; *or* visual analogue score
VATS video-assisted thoracoscopic surgery
VC vocal cord

VCAM-1 vascular cell adhesion molecule-1
vCJD variant Creutzfeldt—Jakob disease
VCP vocal cord paralysis
VDA vascular disrupting agent
VEGF vascular endothelial growth factor
VEGFR vascular endothelial growth factor receptor
VF vocal fold
VHI Voice Handicap Index
VHI-10 Voice Handicap Index-10
VHQ Vertigo Handicap Questionnaire
VILI ventilator induced lung injury
VN vestibular nuclei; *or* vagus nerve
VNO vomero nasal organ
VOC volatile organic compound
VTE venous thromboembolism
VTFF vertex-to-floor
vWD von Willebrand disease
vWF von Willebrand factor
VZV varicella zoster virus

WBS whole-body scan
WDC-NOS well-differentiated carcinoma, not otherwise specified
WDTC well-differentiated thyroid cancer
WDT-UMP well-differentiated tumour of uncertain malignant potential
WHAFFT worrisome histologic alteration following fine-needle aspiration of the thyroid gland
WHO World Health Organization
WIFC widely invasive follicular carcinoma
WMD weighted mean difference
WP Woodruff's plexus
WPBA workplace based assessments
WS Waardenburg syndrome

XLA X-linked agammaglobulinaemia
XM crossmatch

YAC yeast artificial chromosome
YAG yttrium aluminium garnate



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CHAPTER 1

MOLECULAR BIOLOGY

Michael Kuo, Richard M. Irving and Eric K. Parkinson

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: molecular biology, genetics and cell biology.

INTRODUCTION

Molecular biology describes the study of the biochemical processes that govern the behaviour of cells. These processes form the fundamental mechanisms by which cell function, cell–cell interactions and cell turnover are regulated. Disruption of this regulation may lead to disease, whilst an understanding of these mechanisms allows the physician to attempt to predict disease behaviour and to explore methods of restoring this regulation at a molecular level. This chapter reviews the principles of molecular genetics and outlines aspects of the molecular biology of the cell in the context of otolaryngological disease processes and describes some of the techniques that form the backbone of current molecular biology. It should give the reader sufficient background knowledge of molecular biology to understand subsequent chapters discussing the molecular biology of specific otolaryngological conditions.

MOLECULAR GENETICS: DNA STRUCTURE AND FUNCTION

Hereditary information in eukaryotes is stored in the form of double-stranded deoxyribonucleic acid (DNA) and is referred to as the genome. DNA forms a double-helix structure as a result of hydrogen bonds between complementary pairs of nucleotides, adenine (A) with thymine (T) and cytosine (C) with guanine (G). The nucleotides on each strand are organized linearly in triplets, known as codons. Each specific sequence determines a single specific amino acid, for example ACU specifies threonine. However, as there are more triplet combinations (64) than commonly encountered amino acids (20), some proteins may be represented by different codons (e.g. lysine by AAA as well as AAG) and some codons (UAA, UGA and UAG) are 'stop' codons, constituting a signal for arrest of translation. The overwhelming majority of this DNA (99.9%) exists in the cell nucleus as the nuclear genome, which, in the human, is estimated to be 3000 megabase pairs in physical size and encodes 30 000–35 000 genes. The remaining DNA (16.6 kilobase pairs) forms the mitochondrial genome, encoding 37 genes. The mitochondrial genome and its potential role in cancer diagnostics will be discussed later.

Each DNA molecule is packaged into a chromosome by complex folding of the DNA around proteins. Diploid human cells contain 22 pairs of autosomes (1 to 22) and a pair of sex chromosomes (XX or XY) that determines the sex of the organism. One of each pair of chromosomes is maternally inherited and the other is paternally inherited. Each chromosome has a distinctive shape, size and banding pattern, but have the common appearance of two arms apparently separated by a constriction. The centromere is microscopically recognizable as the central constriction separating the chromosome into a long arm (q for queue) and a short arm (p for petit), but its biological role lies in anchoring the chromosome to the mitotic spindle for segregation during cell division. The ends of the chromosomes are capped by telomeres, which are specialized structures containing unique simple repetitive sequences. They maintain the structural integrity of the

chromosome and provide a solution for complete replication of the extreme ends of the chromosome. The conventional nomenclature for chromosomal locus assignment is given by the chromosome number, followed by the arm and finally the position on the arm, for example, 3p21 indicates position 21(two-one) on the short arm of chromosome three.

During normal cell division, DNA replication is achieved by the separation of the two strands by DNA helicase. Each separated single strand then acts as a template for polymerization, catalyzed by DNA polymerase, of nucleotides forming a new complementary strand and thus double-stranded DNA identical to the original dsDNA. As each daughter DNA consists of one original and one newly synthesized DNA strand, the process is known as semi-conservative replication. The specificity of the complementary relationship between the nucleotides on each strand forms the basis for many techniques of modern molecular biology and molecular cytogenetics.[1] The accuracy with which DNA replication takes place is remarkable with an estimated error rate of less than one in 10^9 nucleotide additions. Such accuracy is of vital importance to the individual as a permanent change in DNA, or mutation may cause inactivation of a gene essential to cell survival or cell cycle control. The high fidelity of DNA sequence replication is achieved by unidirectional 5′-to-3′ direction of DNA replication, a rigorous DNA proofreading mechanism that detects mismatched DNA and efficient DNA repair pathways that excise and repair DNA damage. Failure of these mechanisms, such as is encountered in xeroderma pigmentosum, Fanconi's anaemia and ataxia telangiectasia, leads to accumulation of DNA replication errors and a high incidence of malignancies.

Although the human nuclear genome is 3×10^9 base pairs in size, about 90% of it is non-coding, with all the genes being coded by the remaining 10% of the DNA. Within the non-coding DNA are dispersed short arrays of repeat units of pairs or triplets of nucleotides (di-/trinucleotides). The exact function of these microsatellite repeats is not entirely clear, but their existence and frequency of dispersion throughout the genome have greatly facilitated study of the genetics of tumours and many inherited disorders, which will be discussed later.

A gene is a region of the chromosomal DNA that produces a functional ribonucleic acid molecule (RNA). It comprises regulatory DNA sequences that determine when and in which cell types that gene is expressed, exons that are coding sequences and interspersed introns that are non-coding DNA sequences. These regulatory sequences often consist of CpG islands, short stretches of DNA rich in dinucleotides of cytosine and guanine. The methylation status of these CpG islands determines whether that gene is expressed in a particular cell or tissue, being unmethylated in tissues where the genes are expressed. As will be discussed later, aberration of this control is one of the mechanisms of tumour suppressor gene inactivation. However, these same genes can also be regulated by proteins that recognize methylated sequences called histones[2] and these in turn can be regulated by polycomb genes such as *BMI1*.[3] Transcription is the intra-nuclear process driven by RNA polymerase whereby one of the two DNA strands acts as a template for the synthesis of a single RNA strand which is complementary to the DNA, except that uracil replaces thymine in RNA. This primary RNA transcript then undergoes post-transcriptional processing, or splicing.[4] Traditional dogma held that one gene produces one protein and therefore splicing was considered to occur simply in order to remove the non-coding intronic sequences, producing messenger RNA (mRNA). It is now known that by 'alternative splicing', one gene can result in the production of several different but often related proteins in different tissues.[5]

The mature mRNA then migrates into the cytoplasm where it acts as a template for the synthesis of a polypeptide during translation, a process regulated and catalyzed by cytoplasmic ribosomes. Successive amino acids are added to the polypeptide chain according to the triplet code on the mRNA, which is recognized by the transfer RNA (tRNA), to which each corresponding amino acid is covalently bound. Translation is commenced upon recognition of an initiation codon (usually but not exclusively AUG/methionine) and terminated upon recognition of a stop codon. The polypeptide subsequently undergoes a variable degree of post-translational modification and/or cleavage to produce the mature protein product, which may have an intra-cellular role or may be exported to the endoplasmic reticulum and hence to the extracellular space to execute its function.

The mitochondrial genome is considerably smaller than the nuclear genome, but it deserves mention here because of the increasing recognition of the role of mitochondrial DNA (mtDNA) mutations in human disease. The mitochondrial genome is only 16.6 kb in size, comprising 37 genes, which encode polypeptides that are principally involved in the respiratory chain. mtDNA is double-stranded but does not form a double-helix or chromosomes, but instead takes the form of a circular double-stranded DNA structure with a heavy and a light strand. Unlike the nuclear genome, which is inherited from mother and father, the mitochondrial genome of an individual is entirely maternally inherited.

OTHER REGULATORS OF GENE EXPRESSION

In the last few years it has become apparent that gene expression is 'fine-tuned' by several classes of molecule. Small interfering RNAs (siRNAs) were first discovered in plants and are now widely used as research tools to suppress gene expression. However, natural versions of siRNAs exist (microRNAs- miRNAs) and are thought to be biologically significant regulators of gene expression.[6] miRNAs are small non-coding RNA molecules that function through base-pairing with mRNA, thus preventing their translation into proteins. There may be more than 1000 miRNAs in the human genome[7] and some of them are associated with oral cancer; they are also secreted into

body fluids making them candidates for the non-invasive detection of the disease.[8] In addition, long non-coding RNAs (ncRNAs) have been identified that are thought to regulate various aspects of gene expression, including transcription, splicing, translation, siRNA-directed gene regulation and epigenetic regulation.[9] Whilst the study of ncRNAs is still new they have been implicated in a number of diseases, including ageing and cancer.

KEY POINTS

- The double-stranded alpha helical structure of DNA, mainly located in the nucleus, consists of nucleotide triplets called codons which code for specific amino acids and stop signals, and forms the substrate for hereditary information in eukaryotes.
- The 22 pairs of autosomes and one pair of sex chromosomes, each with their distinctive shape, size and banding pattern, represent a complex folding of DNA around proteins to give the characteristic shape of a central constriction (centromere) separating the chromosome into a long arm (q) and a short arm (p) with a telomere cap at each end to maintain structural integrity.
- Chromosome locus nomenclature: chromosome number – 3p21 – position on chromosome arm.
- Semiconservative replication of DNA during normal cell division results in the separation of two strands of DNA by DNA helicase, each strand then acting as a template for polymerization by DNA polymerase. High fidelity is vital to prevent permanent change or mutations.
- A gene is a region of chromosomal DNA which produces functional RNA consisting of:
  - regulatory DNA sequences
  - exons, which are coding sequences
  - introns, which are non-coding sequences.
- Transcription is the intra-nuclear process driven by RNA polymerase whereby one of the two DNA strands acts as a template for single-stranded RNA synthesis complementary to the DNA, except that in RNA T is replaced by U. Splicing refers to post-transcriptional processing of RNA.
- Translation is the cytoplasmic process in which mRNA acts as a template for the synthesis of polypeptide by adding successive amino acids to the polypeptide chain, according to the triplet codon of the mRNA that is recognized by the tRNA to which the corresponding amino acid is covalently bonded. This process is regulated and catalyzed by cytoplasmic ribosomes. Post-translational modification produces mature proteins.
- Gene expression can be modulated by naturally-occurring miRNAs and ncRNAs.

METHODS IN MOLECULAR BIOLOGY

Basic techniques of DNA fragmentation and identification

Unlike RNA, DNA is extremely stable, which is understandable from the function that each has in the cell. For purposes of studying the DNA and in order to clone specific DNA, the DNA molecule needs to be divided into manageable fragments. Although the ability to cut (and also to join up) DNA molecules now appears to be a very straightforward process, it was only 1970 when the first restriction endonuclease was identified in a strain of *Haemophilus influenzae*, hence its name *Hin*dII (pronounced Hin-dee-two). It is believed that this restriction endonuclease acts *in vivo* in bacteria as an immune or host-defence system, recognizing non-self DNA in bacteriophages and cleaving them. By surveying many different bacteria, a wide range of restriction endonucleases is now available, each of which recognizes specific target sites based on sequences of four to eight nucleotides. As a specific, a seven nucleotide sequence (heptanucleotide) will occur less frequently than a four nucleotide sequence (tetranucleotide), statistically, endonucleases recognizing heptanucleotide targets will cut less frequently thereby yielding larger fragments than those recognizing tetranucleotides. As the DNA is double-stranded, the resultant fragments may have blunt ends or cohesive ('sticky') ends (Figure 1.1). The nature of the ends of DNA fragments thus generated impact upon the way in which they can be ligated (joined) into recombinant molecules. Ligation of DNA fragments with cohesive ends is more efficient than joining of blunt-ended fragments.

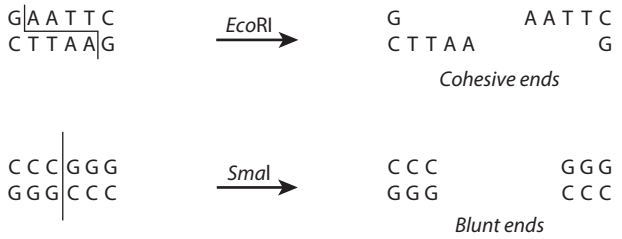


Figure 1.1 DNA cleavage by restriction endonucleases. Derived from Ref. 10, with permission.

Electrophoresis

Negatively charged phosphate groups on the DNA backbone confer a net negative charge on linear DNA. This allows fragments of different sizes to be resolved within a suitable gel matrix by the application of an electric current across the matrix. The DNA will migrate towards the positive electrode with the smaller fragments travelling faster than the larger fragments.[10] The size of the fragment can be estimated by the use of a graduated DNA ladder containing fragments of known molecular weight. The choice of the particular matrix depends on the fragment sizes that one is trying to resolve. Polyacrylamide gels can resolve differences of just one base pair between fragments of several hundred base pairs in size by virtue of a small pore size in the gel matrix. These gels can be used for DNA sequencing and resolution of alleles varying in only one dinucleotide repeat. Agarose gels can resolve fragment sizes from around 100 bp to 20 kb. Beyond that size, electrophoretic mobility is no longer proportional to fragment size. Resolution of fragments sizes in excess of 50 kb, such as larger bacterial artificial chromosomes (BAC) or yeast artificial chromosomes (YAC) require the use of pulsed field electrophoresis.

Hybridization

Hybridization is the specific annealing of single DNA (or RNA) strands, the probe, to a DNA sample, the target. It serves to detect the presence of a specific sequence of DNA either in the cell or on a hybridization membrane and recognition that hybridization has occurred is achieved either by radioactively labelling the probe and localizing the radioactivity by autoradiography or by labelling the probe with fluorochromes that fluoresce when excited by light of specific wavelengths (Figure 1.2). Hybridization on a membrane requires the initial transfer of DNA on to a nitrocellulose membrane from an agarose gel. This elegantly simple process is eponymously known as Southern blotting after the scientist who described the process in 1975. Two other commonly used transfer techniques have their names derived from Southern blotting as jargon terms. Northern blotting is essentially the same process used for transfer of RNA to a membrane. Western blotting is one of the mainstays of protein analysis and involves the transfer of electrophoresed protein bands from a polyacrylamide gel on to a nitrocellulose or nylon membrane to which they bind strongly. Detection of the protein is usually achieved by the use of antibodies to specific antigens presented by the protein with the antibody being labelled radioactively, enzymatically or fluorescently.

Cytogenetics and molecular cytogenetics

Although microscopy had already reached high levels of resolution in the early 1930s, the correct number of human chromosomes was not determined until 1958. The era of classical cytogenetics had thus begun. Cytogenetics is the study of chromosomal abnormalities and rearrangements. It currently has a major role to play in pre-natal diagnosis of Down syndrome and other congenital syndromes characterized by numerical chromosomal abnormalities. In the early part of this century, Theodore Boveri proposed that cancer arose from chromosomal alterations. This hypothesis was not proven until the consistent chromosomal translocation, t(9;22), was demonstrated in chronic myeloid leukaemia. Since that time, cytogenetic analysis has been the mainstay of genetic analysis in reticuloendothelial malignancies, being responsible for the identification of consistent translocations in different leukaemias. Its use in solid tumours has been hampered by the difficulties of establishing short-term primary cultures from head and neck cancers for chromosomal analysis and the erratically acquired chromosomal changes in long-term cell lines, which may have occurred *in vitro*, influenced by culture conditions. Nevertheless, some studies have identified chromosomal areas consistently showing frequent breakpoints suggesting the location of putative tumour suppressor genes (including 3p21, 5p14, 8p11, 17p21, 18q21) and gain or amplification implying the presence of putative protooncogenes at other sites (including 3q, 5p, 8q, 11q13). Although the refinement of karyotyping has been radically enhanced by the introduction of 24-colour combinatorial multifluor FISH (M-FISH), the resolution and therefore utility of solid tumour karyotyping remains limited.[11]

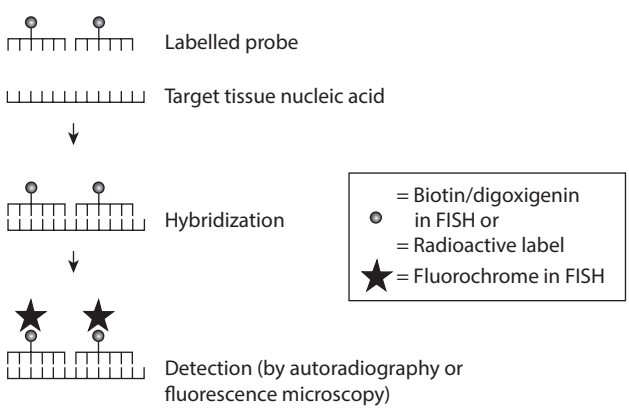


Figure 1.2 *In situ* hybridization.

Hybridization to target DNA in cells, using fluorescence detection, is known as fluorescence *in situ* hybridization (FISH). Fluorescence *in situ* hybridization allows the analysis of copy number of a known specific DNA sequence within intact nuclei. In reticuloendothelial malignancies and solid tumour-derived cell lines, the use of both single-copy probes and centromere alpha-satellite repeat probes on metaphase preparations has enhanced and refined classical karyotyping. Interphase FISH has been applied to solid tumour sections to assess the copy number of a known sequence in breast, prostate, bladder, brain, lung and head and neck tumours.

Fluorescence-labelled hybridization has also been combined with cytogenetics to produce the powerful technique of comparative genomic hybridization (CGH).[12] Comparative genomic hybridization permits the rapid medium resolution screening of the entire genome by comparatively hybridizing matched tumour and normal DNA from a patient, which are labelled with different fluorochromes, on to normal metaphase chromosome preparations. Under red-green dual filter fluorescence microscopy and computer-aided image analysis, areas of genetic 'neutrality' appear yellow, under-representation appears green, and over-representation appears red. Areas of genetic under-representation suggest the possibility of a tumour suppressor gene lying within that region while areas of over-representation may indicate the location of a putative oncogene. This technique has been applied to the rapid genetic analysis of many tumour types including squamous cell carcinomas of the head and neck. The advent of molecular cytogenetics has obviated the need for primary short-term cultures and refined the location of chromosomal aberrations in solid tumours.

Polymerase chain reaction

Perhaps the single molecular technique that has had the most dramatic impact on molecular biology has been the polymerase chain reaction (PCR). The original problem lay in obtaining sufficient quantities of a particular DNA sequence such that DNA profiling (e.g. sequencing) and DNA manipulation (e.g. cloning) could be achieved. The only 'requirement' is that the sequences flanking the stretch of DNA of interest is known. With that proviso,

PCR achieves faithful and exponential amplification of a specific sequence of DNA by repeated cycles each consisting of dsDNA denaturation, hybridization of specific oligonucleotides (primers) and extension of the polynucleotide by rapidly altering the reaction temperature between segments of each cycle. dsDNA denaturation is achieved by raising the temperature of the reaction to 94°C for 30 seconds, thus disrupting the hydrogen bonds between the strands and exposing the hydrogen bond donor and acceptor groups to allow base pairing. The oligonucleotide primers are then allowed to hybridize to the denatured DNA (annealing) at around 55–65°C for 90 seconds before the reaction temperature is raised to 72°C to permit extension of the DNA strand by DNA polymerase in the presence of deoxynucleoside triphosphates (dNTPs). With each cycle resulting in the doubling of the copies of the DNA sequence, a 30-cycle PCR taking approximately two hours would amplify a single copy of a DNA sequence 268 million-fold (**Figure 1.3**). Although the PCR was originally described by Mullis and Faloona in 1987, one practical problem prevented its instant exploitation.[13] The DNA polymerase used in the original reaction was denatured during the DNA denaturation segment and therefore had to be added after each and every cycle. The solution came in 1989 when Lawyer isolated and characterized the DNA polymerase, Taq polymerase, from the thermophilic bacterium *Thermus aquaticus* which normally resided in temperatures above 95°C.[14] This polymerase was therefore 'heat resistant' and did not need to be replenished between cycles.

The PCR holds a central position in many molecular biological techniques as well as clinical diagnostic methods. The fundamental principle of DNA amplification has been adapted to amplify messenger RNA and to amplify areas where the initial flanking oligonucleotide sequences are not known. It is often described as a sensitive and powerful technique, but with great power comes the potential for corruption! In theory, a single copy of DNA can be amplified. Therefore, careless experimental technique may lead to contamination of the DNA sample with other DNA (e.g. from the skin of the investigator) and consequently to an artefactual result. The Taq polymerase originally described in the technique does not have proofreading properties, but newer cloned enzymes such as Pfu polymerase incorporates a proofreading function to increase amplification fidelity for sequencing reactions.

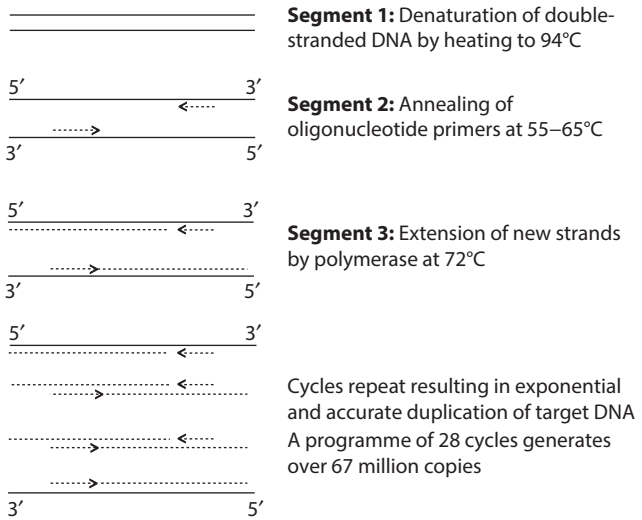


Figure 1.3 The polymerase chain reaction.

The sensitivity of PCR also presented a problem for the analysis of genetic alterations in certain solid tumours. Squamous cell carcinomas of the head and neck are histologically often characterized by a large stromal element within the tumour. The genetic alterations in the tumour may not be present in the stromal tissue and thus total DNA extracted from the tumour will contain DNA from both benign and malignant tissue. This *in situ* contamination can now be eliminated by the use of laser capture microdissection (LCM) of tumours. LCM involves the placement of a laser-activated film over a tissue specimen. When areas of 'pure' tumour cells are identified, a focal laser pulse lifts the tissue on to the film in specimens down to 30 µm in diameter.[15]

KEY POINTS

- Restriction endonucleases are enzymes that were initially identified in bacteria that can cut and join up DNA. They recognize specific target sites based on sequences of four and eight nucleotides.
- Electrophoresis is a technique for resolving the size of DNA fragments, which carry a negative charge from the phosphate groups on their backbone. Using a gel matrix with an electric current applied across it, the DNA will migrate to the positive electrode at a rate inversely proportional to its size.
- Hybridization is the specific annealing of single DNA or RNA strands (probe) to a DNA sample (target) to detect the presence of a specific sequence of DNA in the cell or hybridization membrane. Variants include the eponomously named Southern, Northern and Western blotting techniques.
- Cytogenetics is the study of chromosomal abnormalities and rearrangements important in the diagnosis of congenital syndromes characterized by numerical chromosomal abnormalities (e.g. Down syndrome and leukaemia types).
- FISH refers to fluorescence *in situ* hybridization which involves hybridization to target DNA cells using fluorescence detection and allows the analysis of copy number of a known specific DNA sequence within intact nuclei.
- PCR achieves faithful and exponential amplification of a specific sequence of DNA by repeated cycles each consisting of:
  - DNA denaturation by heating to 94°C to denature hydrogen bonds between strands
  - annealing (hybridization) of oligonucleotide primers to denatured DNA at 55–65°C
  - extension of DNA strand by DNA polymerase.

MOLECULAR ABERRATIONS OF CELLULAR BIOLOGY

Loss of heterozygosity and the expression of recessive mutant alleles

Retinoblastoma is a childhood cancer, which exhibits both hereditary and sporadic occurrence, with the inherited form transmitted as a highly penetrant autosomal

dominant trait. The proposition by Alfred Knudson in 1971, based upon a statistical analysis of the occurrence of retinoblastoma in children, that two genetic events were required to inactivate the gene mitigating against development of the cancer, was a major landmark in the understanding of tumour suppressor genetics.[16] In hereditary retinoblastomas, a single additional somatic event in a cell that carried the inherited mutation was sufficient to give rise to the disease while two somatic events were required to produce a sporadic retinoblastoma. This became known as Knudson's 'two-hit' hypothesis. The subsequent study on matched tumour and blood DNA from patients with sporadic retinoblastoma by Webster Cavenee not only proved Knudson's hypothesis but also established the paradigm for all subsequent investigations of tumour suppressor genes.[17] For the first time, the now widely accepted mechanisms of tumourigenesis were reconciled, viz. that neoplasms can arise in a multistep manner, that chromosomal events can lead to tumour formation and that chromosome loss with or without reduplication can lead to expression of recessive mutations. Perhaps even more strikingly, the authors presciently suggested that development of homozygosity for recessive mutant alleles at the *Rb-1* locus may give rise to the development of other tumours and that other additional dominant mutations may be involved in the development of retinoblastoma. Cavenee proposed the various chromosomal mechanisms that could reveal recessive mutations and these are summarized for a putative tumour suppressor gene in **Figure 1.4,** adapted from the figure in his original paper. To these can now be added hypermethylation of the 5′ CpG island resulting in transcriptional inactivation of the gene, discussed below.[18] The simplest way of revealing a recessive mutant allele is by deletion of the wild-type allele, resulting in hemizygosity at the particular locus on the remaining chromosome. It is inferred from this that areas of frequent allelic loss in tumours may represent the location of putative tumour suppressor genes and this hypothesis underpins the commonly employed method of molecular detection of allelic losses, loss of heterozygosity (LOH).

The practical exploitation of the concepts outlined above hinges on the presence of the previously described microsatellites, highly polymorphic non-coding DNA sequences, also referred to as simple sequence length polymorphisms (SSLP) or short tandem repeat polymorphisms (STRP), which are distributed approximately every 100 000 bp throughout the human genome. These microsatellites contain small dinucleotide or trinucleotide repeat units, the number of which may differ between the two alleles in a particular person. Microsatellite markers are now available which map thousands of these sequences to chromosomal loci. When DNA sequences containing these microsatellite markers are amplified by PCR in a person heterozygous for that

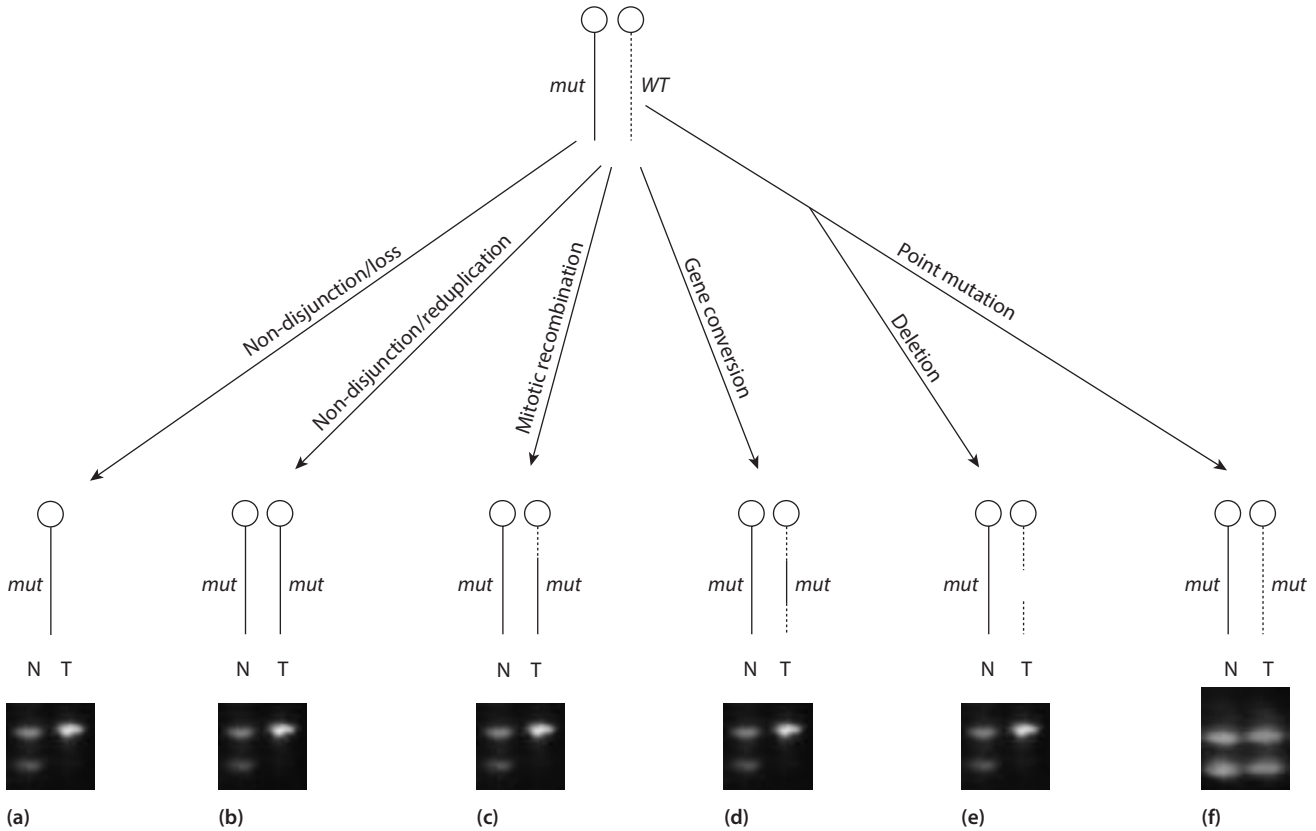


Figure 1.4 Chromosomal mechanisms that could reveal recessive mutations. In this example, before cell division, the tissue concerned carries a mutation in one copy of the hypothetical tumour suppressor gene. In each of the scenarios **(a–f)**, the recessive mutation is revealed. If the individual is heterozygous for a microsatellite marker within or very close to the mutated gene, the hypothetical PCR results are given below each ideotype. The only mechanism that escapes observed loss of heterozygosity is F. *mut*, mutated; N, normal; T, tumour; *WT*, wildtype. After Ref. 17, with permission.

particular microsatellite, the PCR will yield two products of different lengths, which can be resolved on an electrophoretic gel. Where amplification of tumour DNA from such a subject yields only one product, the tumour is said to show LOH, implying allelic loss. Persons who are homozygous for a particular marker are said to be non-informative for that marker. The concept of examining the variation and extent of allelic deletion in tumours was introduced by Vogelstein in an analysis of colorectal carcinomas and termed allelotyping.[19] Allelotypes generated in this fashion have identified several areas of frequent allelic deletion from which some of the responsible tumour suppressor genes have been cloned or identified. The most common areas of loss in HNSCC are at chromosome 9p21, 17p13, 13q14, 4p, 5q21 and several discrete regions on 3p and 8p.[20, 21]

Inactivation of genes and oncogenic transformation

Allelic deletion is only one mechanism by which a copy of a gene can be inactivated. As there are two copies of each gene, inactivation of the gene requires inactivation of both copies of the gene, 'the second hit'. This may occur as a result of a genetic mutation or transcriptional silencing. Conversely, a protooncogene may be converted into an oncogene by a simple increase in the copy number of the gene (gene amplification) resulting in an overproduction of protein or by point mutations that affect the control of protein activity.

Not all mutations result in alteration in function of a gene. DNA mutation may occur as a result of base substitutions, as well as nucleotide insertions and deletions. Insertions and deletions of nucleotides are very rare in coding DNA, but if they occur they may produce a shift in the 'reading frame' that dramatically alters the coding downstream from the mutation. Base substitution is a more common form of mutation in coding DNA, which may have a range of consequences on the function of the gene; a loss of function (e.g. *p53*, *Rb*), a gain in function, often due to stabilization of the active protein (e.g. *c-erbB2*, *K-ras*) or no net functional effect. Since an amino acid may be encoded by different codons with a 'third base wobble' (e.g. GU**A**, GA**C**, GU**G** and GU**U** all encode valine), a substitution of the third base would result in no change to the amino acid. This is known as a silent substitution. At the other extreme is the nonsense mutation, whereby base substitution results in a stop codon which leads to truncation of the polypeptide and a dramatic reduction in function.

Loss of function in the presence of a normal (wildtype) allele may occur as a result of transcription silencing. The methylation status of CpG islands surrounding the promoter regions of genes determines whether a particular gene is expressed within a cell such that methylation of a CpG island 'switches off' the gene that it is regulating. CpG islands regulating housekeeping genes (i.e. genes encoding proteins essential for cell survival) are unmethylated in all cell types whereas those regulating cell-specific genes (e.g. muscle-specific actin gene in muscle cells), are only unmethylated in the relevant cell. Many tumour suppressor genes (e.g. *CDKN2A* (p16^{INK4A}), *APC*, *RASSF1A*) are now recognized to be inactivated by hypermethylation of the promoter region in malignant tumours.

Gene sequencing

Recently a variety of next generation sequencing methods have been applied to the field. One method is to construct a library of DNA fragments and to use biotinylated RNA baits to capture the exomic sequences using streptavidin coated magnetic beads prior to loading them onto the sequencing machine following digestion of the RNA bait and a few cycles of PCR. This strategy was able to obtain 10 or more sequencing reads for over 90% of the targeted bases and this approach and similar strategies have revealed the mutational landscape of head and neck squamous cell carcinoma, including the frequent mutation of the *NOTCH1* gene, which had not been identified previously.[22–24]

Proteomics and metabolomics

As the Human Genome Mapping Project powers its way towards a high-resolution sequence of the entire genome, the natural progression of research has been towards the elucidation of the repertoire of proteins that control cell signalling and cell growth. Proteomics is the profiling of proteins in cells and serum by two-dimensional gel analysis separating proteins by charge and mass, by X-ray crystallography and by mass spectrometry.[25] Proteomics has the ability to identify post-translational modifications, some of which are cancer cell-specific, which would not be detected by genetic or expression profiling. The power of this approach is particularly evident in cancer studies as it has the ability to compare the entire protein pattern of tumour tissue and normal tissue in a manner analogous to comparative genomic hybridization.

However, the functional consequences of changes to the proteome, especially some enzymes, can only be inferred and a more direct approach is to measure the levels of small molecules, or metabolites. Metabolomics is the global analysis of metabolites but is a relatively new discipline and no single technique is suitable for the analysis of all different types of molecule. Therefore, a mixture of techniques such as gas chromatography, high-pressure liquid chromatography and capillary electrophoresis are used to separate metabolites and the molecules are then identified using methods such as mass spectrometry. Metabolomics has already been applied to the detection of oral cancer in saliva[26] and serum.[27]

Telomerase

Aberration of telomere biology has a now well-recognized role to play in cancer development. The length of the telomere is maintained in germline cells by the enzyme telomerase that is absent in normal somatic cells.[28] This observation led to the theory that progressive shortening

of telomeres with each cell division leads to cell senescence and ageing of the organism. Several mechanisms for this have been proposed. A critical shortening of the telomere may leave a non-telomere-free DNA end that signals cell cycle arrest. Telomere loss could also extend to the deletion or inactivation of genes located subtelomerically, again leading to cell cycle arrest. Two important consequences of critical telomere shortening in cells that survive the cell crisis are genomic rearrangements and chromosomal loss, which may in turn lead to malignant transformation. This is particularly relevant to rapidly dividing and regenerating tissues, such as skin and mucosa. Paradoxically, while some of these survivors will subsequently go into cell cycle arrest due to critical telomere length shortening, a proportion will then express telomerase activity. Such activity is capable of cell immortalization by maintaining telomere length indefinitely and its role in cancer is now unquestionable. Telomerase activity has been demonstrated in 80% of oral cancers and around 50% of oral leukoplakia lesions.[29] Even among premalignant lesions, telomerase activity was associated with degree of dysplasia, suggesting that telomerase activation occurs during the late stage of oral premalignancy. The potential for anti-telomerase drugs as a novel treatment remains promising, especially as they are now thought to target cancer stem cells.[30]

KEY POINTS

- Practical techniques based on loss of heterozygosity of tumour DNA are based on Knudson's two-hit hypothesis, which states that two genetic events are required to inactivate the gene that prevents the development of a condition.
- The number of microsatellite repeats (i.e. non-coding base pairs dispersed throughout the genome) may differ between two alleles in the same person making that person heterozygous for that particular allele. If tumour DNA from such a subject when amplified by PCR yields only one product, the tumour is said to show loss of heterozygosity implying allelic loss.
- Inactivation of genes can occur by:
  - allelic deletion
  - genetic mutation
  - transcriptional silencing
  - conversion of protooncogene to oncogene due to gene amplification.
- Some mutations do not result in change of function. They can be silent or nonsense mutations.
- Next generation sequencing has produced a mutational landscape of head and neck cancer.
- Proteomics refers to the profiling of proteins in cells and serum by 2D gel analysis, X-ray crystallography and by examination of protein interactions. This can be used to identify post-translational modifications, some of which are cancer cell specific and are not detected by genetic profiling.
- Metabolomics can be used to detect small molecules accumulating in the tissues and body fluids of oral cancer patients.
- Critical telomere shortening or inefficient telomere DNA repair can lead to both cell cycle arrest and cell immortalization due to expression of telomerase, which, for example, has been demonstrated in 80% of oral cancers.

MAPPING AND IDENTIFICATION OF GENES ASSOCIATED WITH DISEASE

The traditional approach to understanding the molecular biology of disease was to look for and characterize the abnormal protein. Diabetes mellitus and sickle cell anaemia are two conditions that were elucidated at the molecular level in this way. Finding the protein when present in minute quantities, in an inaccessible site such as the inner ear, or when nothing is known of its mode of action, is, however, virtually impossible. This is the case with most of the genes involved in cellular growth control and also in inner ear function. Our approach to understanding such conditions relies on determining the chromosomal location, isolating and sequencing the gene so that the structure of the protein can be determined. This is known as the reverse genetic or positional cloning technique.

Strategies employed in determining the sites of these disease genes include cytogenetic analysis, molecular genetic analysis (typically LOH studies) and linkage analysis. Where a clearcut inheritance of a disease can be demonstrated, then linkage analysis can be useful in determining the location of the responsible gene. The key advance that has made this approach increasingly successful has been the construction of a high-resolution linkage map of the entire human genome. This map consists of genetic markers spaced less than 1 centimorgan apart and the process of linkage involves determining which of these the disease gene is close to. Analysis of the coinheritance of the genetic marker and the disease trait in families allows one to determine the probability of their physical proximity or linkage to each other. The statistical probability of linkage is expressed in terms of LOD scores. LOD is short for logarithm to the base 10 of the odds that the markers are linked at a recombination distance of N centimorgans. An LOD score of 3.0 favours linkage while a score of –2.0 effectively rules out linkage.

Successful linkage analysis typically requires large pedigrees with many individuals known to have the disease trait and likewise many confirmed to be free of the disease. The process involves initial family analysis with clinical evaluation and accurate diagnosis. DNA samples are then obtained from each individual and genotyping and linkage analysis can then be carried out. Linkage and molecular deletion analysis generate genetic markers either side of the disease gene location. These genetic markers can be used to identify 'chunks of genomic DNA' cloned into yeast (yeast artificial chromosomes (YAC)) or bacteria (bacterial artificial chromosomes/P1 artificial chromosomes (BAC/PAC)) and organized into libraries. By a number of methods, these 'chunks' of genomic DNA can be directionally organized to produce a physical map of the region of interest from which candidate disease genes can be identified. The Human Genome Mapping Project has, to a great extent, physically mapped the human genome such that in some cases, when the region of interest is sufficiently small, all genes known to be between the markers can be considered positional candidates. The candidates are then analysed in disease

families until one is found that demonstrates mutations in affected individuals.

To facilitate the identification of the disease gene from a number of candidates within a particular region, several strategies are available. One such approach exploits our knowledge of animal models of the diseases that parallel human inherited disorders. Another potential source of candidate genes is to identify and characterize genes that are expressed within a particular tissue. Genes expressed within the cochlea, for example, represent the genes critical for cochlear function and thus are excellent candidate genes for hereditary hearing loss.

FUTURE RESEARCH

Although giant strides have already been made in the delineation of molecular events underlying disease processes, the knowledge of these events is far from comprehensive. A clearly identifiable adenoma–carcinoma sequence facilitated the correlation between genetic and histopathological progression models in colorectal cancer.[19] Several similar progression models have been proposed in head and neck squamous cell carcinoma evolution from epithelial dysplasia through to frank carcinoma, but the heterogeneity of carcinomas in different subsites precludes a molecular genetic progression model of equal rigour to that in colorectal cancer. Nevertheless, *p16* and *p53* inactivation have been identified as the two most frequent and critical events in head and neck carcinogenesis. An understanding of the sequence of genetic aberrations that occur in pathogenesis of tumours can assist in the prediction of progression from premalignant conditions to frank malignancy. An example of this is seen in the accumulation of genetic abnormalities in oral epithelium leading to the progression of oral dysplasia to oral squamous cell carcinoma. By analysing for loss of heterozygosity at 19 microsatellite loci in a series of oral dysplastic lesions and oral malignancies, Rosin et al.[31] showed that LOH at 3p and/or 9p occurred in virtually all cases of oral dysplasia which progressed to frank malignancy implying a 'gatekeeper' role of genes at those loci in the development of oral cancer, in themselves imparting a 3.8-fold increased relative risk of progression to squamous carcinoma. Furthermore, additional LOH at 4q, 8p, 11q or 17p imparted a 33-fold increased relative risk for developing cancer.[31] In certain cases, molecular genetic profiling has added a new dimension to age-old debates. For example, discordant genetic anomalies in inverted sinonasal papillomas and sinonasal carcinomas lend weight to the opinion that the former does not undergo malignant degeneration into the latter.[32]

Traditional methods of allelotyping and mutational analysis remain extremely time-consuming and labour-intensive. Recent years have seen the development of gene arrays (or 'gene chips') that allow the rapid assessment of the genetic profile of tumours or cell lines.[33] cDNA of up to 30 000 genes can be placed in arrays on glass slides on to which DNA and RNA samples can be allowed to hybridize using an automated two-colour fluorescence method for detection.[34] Hybridization with DNA can yield extensive genomic information, while hybridization with RNA takes genetic profiling a step further by semiquantitatively analysing the expression of genes rather than simply the presence or absence of the DNA. As the genetic aberrations and pathways associated with specific tumour development become better dissected, 'designer' chips can be produced that allow for screening for known mutations of those involved genes.[35] Array technology has also been married with molecular cytogenetics to produce array-based comparative genomic hybridization, which obviates the need for metaphase chromosome spreads for CGH.

The clinician might be forgiven for an expression of cynicism regarding the 'molecular revolution', feeling that little has changed despite ambitious predictions. The translation of molecular biology research into clinical practice – 'from laboratory to bedside' – is without doubt the greatest challenge facing the clinician scientist. Progress so far has been largely at the level of disease classification, premorbid diagnosis and patient counselling. However, several discrete arms to translational research have hinted at the future role of genetic analysis determining the likely effectiveness of existing anti-cancer treatments. There are also isolated examples of effective novel therapeutic interventions.

Molecular analysis played a vital role in differentiating neurofibromatosis type I from neurofibromatosis type II, and it now seems difficult to understand how we ever confused the two in the first place. Such clarity of diagnosis is also anticipated for many syndromic and non-syndromic causes of sensorineural hearing loss as the genes are characterized and the clinical features analysed in more detail. This may enable clinicians to determine in which cases hearing loss will be progressive and target monitoring more appropriately. Diagnostic genetic testing will also become increasingly available to families with hereditary hearing loss and clinicians will need to be conversant with the ethical issues of testing and the implications of the results. By characterizing hearing loss at the molecular level we are also developing a greater understanding of inner ear physiology as the critical proteins involved in hearing become elucidated. This may lead to the development of agents able to repair and regenerate the diseased inner ear. The administration of these agents is already being evaluated using miniature infusion pumps.

It is hoped that in the future molecular characterization of tumour tissue will provide for a more accurate diagnosis and prognosis than conventional histopathological analysis. This may lead to a more rational treatment plan based on molecular features. Some genotype–phenotype correlations have already been made, particularly with respect to radio- and chemoresistance in tumours, but confirmation is needed with larger sample sizes as to their applicability into clinical practice. Refinement of the staging of tumours by probing of resection margins and the detection of histological subclinical metastatic disease in regional lymph nodes have been elegantly demonstrated by Brennan et al.[36] at Johns Hopkins. However, the technical complexity of the methodology has precluded its widespread application in the clinical arena. The development of technically simpler but equally sensitive techniques will inevitably render molecular staging routine in oncological practice. Although surveillance for tumour recurrence is less of a problem in the upper aerodigestive tract when compared with intra-abdominal malignancies, the emergence of molecular markers in saliva and serum will have a role in follow-up protocols for head and neck cancers.[37]

A comprehensive understanding of the molecular mechanisms underlying disease processes gives the potential of therapeutic restoration of DNA or protein function, as well as exploitation of the genetic abnormality for targeting of therapy. An example of the latter is the use of ONYX-015. ONYX-015 is an E1B 55-kDa gene-deleted adenovirus engineered to selectively replicate in and lyse *p53*-deficient cells while sparing normal cells. This tumour-targeting property has led

to a successful phase II trial of concomitant ONYX-015 and cisplatin/5-FU in the treatment of recurrent HNSCC, which indicated substantial objective responses as well as a high proportion of complete responses.[38] Post-treatment biopsies of tumour masses confirmed the replication selectivity of the virus *in vivo*.

A consideration of some of the landmarks in molecular biology (e.g. enzymatic DNA cleavage (1970) and PCR (1987)) readily indicates that molecular biology is a relatively young science. However, the rapid development of molecular techniques of such power and diversity as comparative genomic hybridization and gene array technology has permitted the dissection of molecular pathways and the identification of their disruption in disease processes. Some of these processes in specific diseases will be discussed in subsequent chapters. The future in the laboratory lies in the extension of our understanding of these molecular processes and the future in the clinic lies in the exploitation of these molecular techniques in better informing disease classification, staging and treatment:

- Development of a molecular genetic progression model for head and neck squamous cell carcinoma of similar rigour to that for colorectal carcinoma.
- Development of gene arrays or gene chips that allow the rapid assessment of the genetic profile of tumours and can allow semiquantitative analysis of gene expression.
- Designer chips may be produced that allow for screening for unknown mutations of involved genes.
- Potential role for genetic analysis in determining the likely effectiveness of existing anti-cancer treatments.
- Providing more accurate diagnosis and prognosis than conventional histopathological techniques.
- Potential therapeutic restoration of DNA or protein function, as well as exploitation of a genetic abnormality for targeting therapy (e.g. use of ONYX-015).

KEY POINTS

- Strategies employed in determining the sites of disease genes that code for the abnormal proteins include cytogenetic, molecular genetic and linkage analysis.
- Whilst genomics and other omics has generated a large body of data, cancers are complicated tissues. Future research may shift towards understanding the cancer environment and how perhaps to target this in future therapeutic strategies.

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CHAPTER 2

GENETICS IN OTOLOGY AND NEUROTOLOGY

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using a variety of relevant generic keywords, including: DNA, genetics, hereditary hearing loss, connexin 26, neurofibromatosis 2 and familial paragangliomas.

INTRODUCTION

Advances in molecular genetics have helped to identify causative genes and proteins responsible for pathologies; this knowledge is pertinent to molecular target therapy and promises novel therapeutic interventions.

This chapter aims to review the mechanisms and principles of molecular genetics of hearing impairment, vestibular schwannoma, and glomus tumours, and will keep the reader abreast of new developments that may be relevant to identifying and treating these diseases in clinical practice.

MOLECULAR GENETICS OF HEARING LOSS

Hearing loss is the most frequent sensory impairment in humans, with significant social and psychological implications. Permanent childhood hearing impairment of a moderate or greater degree (i.e. detection thresholds 40 decibels hearing level averaged across 0.5, 1, 2 and 4 kHz) is present at birth in about 1.6 per 1000 live births, of which approximately 1.0 in 1000 are bilateral impairments and 0.6 in 1000 are unilateral impairments.[1, 2] However, studies have shown that the prevalence of permanent childhood hearing impairment continues to increase through infancy, and by the school entry hearing screen (4–5 years of age) possibly affects 3.5 per 1000 children.[2] It is estimated that at least two thirds of cases of childhood-onset hearing loss have a genetic cause, with the remaining third caused by environmental factors (e.g. cytomegalovirus infection, meningitis, acquired conductive loss, and the impact of extracorporeal membrane oxygenation (ECMO)).[3] Improved clinical knowledge, awareness, and advances in antibiotics and vaccines has led to a decline in hearing loss resulting from environmental factors. Likewise, significant progress in the genetics of hereditary hearing impairment (HHI) has improved our understanding of the causes and early detection of HHI.

Classification

The most useful distinction in hereditary hearing impairment (HHI) is syndromic versus non-syndromic. When SNHL occurs in isolation it is termed non-syndromic and when it is accompanied by other systemic disturbances it is termed syndromic. The majority of hearing impairments are non-syndromic (~70%), whereas a minority are syndromic (~30%).

Non-syndromic HHI is further classified by mode of inheritance:

- Autosomal recessive ~80%
- Autosomal dominant ~18%.[4]

Rare modes of transmission include X-linked and mitochondrial transmission, which account for the remaining 2% of hearing impairment.

MOLECULAR GENETICS OF NON-SYNDROMIC HEARING IMPAIRMENT (NSHI)

Thus far, more than 100 forms of non-syndromic hearing impairment (NSHI) have been discovered (see the Hereditary Hearing Loss website at http://hereditaryhearingloss.org). Most of these are still identified as loci: only the chromosomal location of the defective gene is known.

The different gene loci for non-syndromic deafness are designated DFN (for DeaFNess). Loci are named based on mode of inheritance:

- DFNA: Autosomal dominant
- DFNB: Autosomal recessive
- DFNX: X-linked.

The number following the above designations reflects the order of gene mapping and/or discovery and this information is regularly updated on the Hereditary Hearing Loss website.

Genes for NSHI have been categorized by the function of the proteins each gene encodes. Several superfamilies are represented, including gap junctions, myosins, adhesion proteins and ion channels.

Unlike in some conditions where a common mutation in just one gene is responsible for the majority of cases (e.g. the deltaF508 deletion of three nucleotides in the *CFTR* gene in cystic fibrosis), hearing loss is genetically very heterogeneous involving mutations in many genes.[5] It is therefore not possible to predict the risk of developing hearing loss from assessing a single or even a selection of the genes that have currently been identified.[6]

The most frequent causative genes are discussed below.

Gap junction proteins

Thus far, three connexin genes have been implicated in NSHI: *CX26*, *CX30*, and *CX31*, corresponding to the proteins connexin 26, connexin 30, and connexin 31, which are designated by their molecular mass.

GJB2 (connexin 26) is by far the foremost prominent hearing impairment gene. The discovery that *GJB2*, located at the DFNB1 locus, is a causative gene for hearing impairment[7] led to the unexpected revelation that more than half of the recessive NSHL and approximately 30% to 50% of innate hearing loss are due to *GJB2* mutations.[7, 8] Among the 300 mutations documented worldwide up to now (see The Human Gene Mutation Database at www.hgmd.org), one particular mutation, 35delG, is responsible for 70% of all the *GJB2* mutations.[9] This finding made an enormous impact in the hearing loss field, as it facilitated diagnostic and genetic screening of NSHL patients. Another mutation imperative to note is 167delT, which is most frequent among Ashkenazi Jews and is also present in Palestinians.[10]

The connexion-deafness homepage (http://davinci.crg.es/deafness/) provides a database of all published mutations as well as common polymorphisms in *GJB2* and other connexin genes. More than 100 unique non-syndromic *GJB2* gene variants have already been described. The reported mutations mostly include mutation types that can be detected by sequencing analysis, such as nonsense, missense, splicing and frameshift mutations.

Myosins

Numerous types of unconventional myosins have been identified as NSHI causing genes: *MYO1A*, *MYO3A*, *MYO6*, *MYO7A* and *MYO15A* (encoding myosin I, myosin IIIA, myosin VI, myosin VIIA and myosin XVA proteins, respectively). The term 'unconventional' myosins refers to all non-muscle myosin subclasses (in contrast with the 'conventional' myosins that include only the myosin II subclass). Expression of these unconventional myosins is not limited to the cells and tissues of the inner ear, yet the expression of their dysfunction is largely restricted to hearing impairment.

The myosin VI protein was first implicated in the hearing mechanism when it was found to be mutated in the spontaneously deaf mouse Snell's *waltzer* (*sv*).[11] The role of myosin VI in human deafness remains to be determined.

Myosin VII has been linked to both rodent and human deafness. Mutations in the *MYO7A* human homologue were identified as the genetic cause for Usher syndrome type 1B[12] and Usher syndrome type 2A.[13] Contiguous to this discovery, human *MYO7A* was also linked to NSHL in two distinctive loci: DFNB2[14] and DFNA11.[15]

Myosin XV is the largest of all the myosin heavy chains and mutations in myosin XV have been pathogenically linked to DFNB3 in humans and shaker 2 phenotype in mice. Myosin XV is a critical factor in the evolvement of the hair bundle and in the staircase formation of the bundle[16] and it binds another deafness molecule, whirling at the tip link zone, suggesting that the two molecules might control stereocilia elongation patterning during development and may be implicated in stabilizing connections between stereocilia.[17]

Pendrin

Mutations in the pendrin gene *SLC26A4* are the second most frequent cause of autosomal recessive NSHI, accounting for up to 3.5% of cases.[18] *SLC26A4*, which codes for an anion transport protein, also underlies Pendred syndrome, which is one of the most common forms of syndromic hearing impairment.

Adhesion proteins

Adhesion proteins include a diverse group of distinct protein families including integrins, selectins, members of the immunoglobulin superclass family and cadherins.

Cadherin 23 is a vital member of a specific unit designated for maintaining stereocilia inter-cohesion.[18]

More than 20 mutations in the *CDH23* gene have been identified in people with non-syndromic hearing impairment and more than 30 mutations have been shown to cause the Usher syndrome type 1D. The *USH1D* locus was found to coincide with the recessive NSHI locus *DFNB12*, which is associated with prelingual moderate to profound hearing loss. These data suggested that *DFNB12* and *USH1D* in fact are mutually derived from *CDH23* allelic mutations, both resulting in syndromic and non-syndromic forms of hearing loss.[19, 20]

Autosomal dominant non-syndromic hearing impairment

Unlike autosomal recessive non-syndromic hearing loss, in autosomal dominant non-syndromic hearing loss there is not a single identifiable gene responsible for the majority of cases. The clinical manifestations and molecular genetics of known genes causing autosomal dominant non-syndromic hearing impairment are outlined in Table 2.1.

Autosomal recessive non-syndromic hearing impairment

Fifty per cent of people with autosomal recessive non-syndromic hearing impairment have mutations in *GJB2*.[8] The other 50% of cases are attributed to mutations in numerous other genes. The clinical manifestations and molecular genetics of known genes causing autosomal recessive non-syndromic hearing impairment are outlined in Table 2.2.

X-linked non-syndromic hearing impairment

DFNX3 is characterized by a mixed conductive-sensorineural hearing loss, the conductive component of

TABLE 2.1 Clinical manifestations and molecular genetics of known genes causing autosomal dominant non-syndromic hearing impairment

Locus name	Gene symbol	Onset/Decade	Audioprofile	Test availability
DFNA1	*DIAPH1*	Postlingual/1st	Low frequency progressive	Clinical
DFNA2	*KCNQ4*	Postlingual/2nd	High frequency progressive	Clinical
DFNA2B	*GJB3*	Postlingual/4th	High frequency progressive	Clinical
DFNA3	*GJB2*	Prelingual	High frequency progressive	Clinical
	GJB6			Clinical
DFNA4	*MYH14*	Postlingual	Flat/gently downsloping	Clinical
DFNA5	*DFNA5*	Postlingual/1st	High frequency progressive	Clinical
DFNA6/14/38	*WFS1*	Prelingual	Low frequency progressive	Clinical
DFNA8/12	*TECTA*		Mid-frequency loss	Clinical
DFNA9	*COCH*	Postlingual/2nd	High frequency progressive	Clinical
DFNA10	*EYA4*	Postlingual/3rd, 4th	Flat/gently downsloping	Clinical
DFNA11	*MYO7A*	Postlingual/1st		Clinical
DFNA13	*COL11A2*	Postlingual/2nd	Mid-frequency loss	Clinical
DFNA15	*POU4F3*	Postlingual	High frequency progressive	Clinical
DFNA17	*MYH9*	Postlingual	High frequency progressive	Clinical
DFNA20/26	*ACTG1*	Postlingual	High frequency progressive	Clinical
DFNA22	*MYO6*	Postlingual	High frequency progressive	Clinical
DFNA23	*SIX1*	Prelingual	Downsloping	Clinical
DFNA25	*SLC17A8*	Postlingual/2nd–6th decades	High frequency progressive	Clinical
DFNA28	*TFCP2L3*	Postlingual	Flat/gently downsloping	Clinical
DFNA36	*TMC1*	Postlingual	Flat/gently downsloping	Clinical
DFNA39	*DSPP*	Postlingual	High frequency progressive	Research only
DFNA44	*CCDC50*	Postlingual	Low to mild frequencies progressive	Clinical
DFNA48	*MYO1A*	Postlingual	Progressive	Clinical
DFNA50	*MIR96*	Postlingual/2nd	Flat progressive	Clinical
DFNA51	*TJP2 & FAM189A2*	Postlingual/4th	High frequency progressive	Research only

Source: Adapted from Van Camp & Smith [2010] Van Camp G, Smith RJH. The Hereditary Hearing Loss Homepage, 2010, with permission. Available from http://hereditaryhearingloss.org/.

TABLE 2.2 Clinical manifestations and molecular genetics of known genes causing autosomal recessive non-syndromic hearing impairment

Locus name	Gene symbol	Onset	Type	Test availability
DFNB1	*GJB2*	Prelingual	Usually stable	Clinical
	GJB6			Clinical
DFNB2	*MYO7A*	Prelingual, postlingual	Unspecified	Clinical
DFNB3	*MYO15*	Prelingual	Severe to profound; stable	Clinical
DFNB4	*SLC26A4*	Prelingual, postlingual	Stable, progressive	Clinical
DFNB6	*TMIE*	Prelingual	Severe to profound; stable	Clinical
DFNB7/11	*TMC1*			Clinical
DFNB8/10	*TMPRSS3*	Postlingual, prelingual	Progressive, stable	Clinical
DFNB9	*OTOF*	Prelingual	Usually severe to profound; stable	Clinical
DFNB12	*CDH23*	Prelingual	Severe to profound; stable	Clinical
DFNB16	*STRC*	Prelingual	Severe to profound; stable	Clinical
DFNB18	*USH1C*	Prelingual	Severe to profound; stable	Clinical
DFNB21	*TECTA*	Prelingual	Severe to profound; stable	Clinical
DFNB22	*OTOA*	Prelingual	Severe to profound; stable	Clinical
DFNB23	*PCDH15*	Prelingual	Severe to profound; stable	Clinical
DFNB24	*RDX*	Prelingual	Severe to profound; stable	Clinical
DFNB25	*GRXCR1*	Prelingual	Moderate to profound; progressive	Research only
DFNB28	*TRIOBP*	Prelingual	Severe to profound; stable	Clinical
DFNB29	*CLDN14*	Prelingual	Severe to profound; stable	Clinical
DFNB30	*MYO3A*	Prelingual	Severe to profound; stable	Clinical
DFNB31	*DFNB31*	Prelingual	—	Clinical
DFNB32/82	*GPSM2*	Prelingual	Severe to profound; stable	Research only
DFNB35	*ESRRB*	Unknown	Severe to profound	Clinical
DFNB36	*ESPN*	Prelingual	—	Clinical
DFNB37	*MYO6*	Prelingual	—	Clinical
DFNB39	*HGF*	Prelingual	Severe to profound; downsloping	Clinical
DFNB49	*MARVELD2*	Prelingual	Moderate to profound; stable	Clinical
DFNB53	*COL11A2*	Prelingual	Severe to profound; stable	Research only
DFNB59	*PJVK*	Prelingual	Severe to profound; stable	Clinical
DFNB61	*SLC26A5*	Prelingual	Severe to profound; stable	Clinical
DFNB63	*LRTOMT*	Prelingual	Severe to profound; stable	Clinical
DFNB67	*LHFPL5*	Prelingual	Severe to profound; stable	Clinical
DFNB73	*BSND*	Prelingual	Severe to profound; stable	Research only
DFNB77	*LOXHD1*	Postlingual	Moderate to profound; progressive	Clinical
DFNB79	*TPRN*	Prelingual	Severe to profound; stable	Clinical
DFNB84	*PTPRQ*	Prelingual	Moderate to profound; progressive	Research only

Source: Adapted from Van Camp & Smith [2010] Van Camp G, Smith RJH. The Hereditary Hearing Loss Homepage, 2010, with permission. Available from http://hereditaryhearingloss.org/.

which is caused by stapedial fixation. In contrast to other types of conductive hearing loss, surgical correction is precluded because an abnormal communication between the cerebrospinal fluid and perilymph results in leakage ('perilymphatic gusher') and complete loss of hearing when the oval window is fenestrated or removed.

Clinical manifestations and molecular genetics of known genes causing X-linked non-syndromic hearing impairment are summarized in Table 2.3.

Mitochondrial non-syndromic hearing impairment

The genes and mutations associated with mitochondrial non-syndromic hearing impairment are outlined in Table 2.4.

TABLE 2.3 Clinical manifestations and molecular genetics of X-linked non-syndromic hearing impairment

Locus name	Gene	Onset	Type and degree	Frequencies
DFNX1 (DFN2)	*PRPS1*	Postlingual	Progressive sensorineural; severe to profound	All
DFNX2 (DFN3)	*POU3F4*	Prelingual	Progressive, mixed; variable, but progresses to profound	All
DFNX4 (DFN6)	*SMPX*	Postlingual	Progressive sensorineural; mild to profound	All

Source: Adapted from Van Camp & Smith [2010] Van Camp G, Smith RJH. The Hereditary Hearing Loss Homepage, 2010, with permission. Available from http://hereditaryhearingloss.org/.

TABLE 2.4 Mitochondrial Non-syndromic Hearing Impairment

Gene symbol	Mutation	Severity	Penetrance	Test availability
MT-RNR1	961 different mutations	Variable	Highly variable, aminoglycoside induced	Clinical
	1494C>T			
	1555A>G			
MT-TS1	7445A>G		Highly variable	Clinical
	7472insC			
	7510T>C			
	7511T			
MT-CO1	7444G>A	Severe to profound	Complete, aminoglycoside associated; associated with *MT-RNR1* 1555A>G	Clinical

Source: Adapted from Van Camp & Smith [2010] Van Camp G, Smith RJH. The Hereditary Hearing Loss Homepage, 2010, with permission. Available from http://hereditaryhearingloss.org/.

Molecular genetics of syndromic hearing impairment (SHI)

Hearing impairment is denoted as an integral clinical phenotype in more than 400 genetic syndromes.[21] Syndromic forms of hearing impairment are estimated to be responsible for up to 30% of prelingual deafness, but its contribution to deafness is relatively small reflecting the occurrence and diagnosis of postlingual deafness.

Syndromic hearing loss is discussed further by modes of inheritance.

Autosomal dominant syndromic hearing impairment

WAARDENBURG SYNDROME (WS)

WS is mostly a genetic autosomal dominant disorder, considered to be the most frequent autosomal dominant form of syndromic hearing loss, constituting approximately 2% of all congenital hearing impairment.[22]

The primary phenotypes observed in this syndrome may include variable degrees of sensorineural hearing loss, pigmentation abnormalities (skin, hair, eyes), dystopia canthorum (wide distance between the inner corners of the eyes). Gastrointestinal symptoms like constipation and Hirschsprung disease, neural tube and limb defects may also be observed. Four different types of WS (I to IV) have been described, grouped by distinct physical characteristics. WS I characteristically has the presence and WS II the absence of dystopia canthorum. In WS III there are typically limb abnormalities and in WS IV Hirschsprung disease is present.

All of WS1 and some of WS3 cases are associated with mutations in the *PAX3* gene. WS2 is caused by mutations in the transcription factors *MITF* and *SNAI2*. WS4 is due to alterations in *EDNRB*, *EDN3* or *SOX10* genes.[23]

BRANCHIOOTORENAL SYNDROME

Branchiootorenal (BOR) syndrome is the second most prevalent autosomal dominant syndromic type of hearing loss.[24] The major features of this syndrome are hearing loss (conductive, mixed or sensorineural) in association with branchial cleft cysts or fistulae, deformities of the external, middle or internal ear, and renal malformations.

In approximately 40% of families segregating a BOR phenotype, mutations in *EYA1* can be identified; in a few other families mutations have been found in *SIX1*[25] and *SIX5*.[26]

STICKLER SYNDROME

Stickler syndrome comprises of progressive sensorineural hearing loss, cleft palate, abnormal development of the epiphysis, vertebral abnormalities and osteoarthritis. Three types are recognized, based on the molecular genetic defect: STL1 *(COL2A1)*, STL2 *(COL11A1)* and STL3 *(COL11A2)*. STL1 and STL2 are characterized by severe myopia, which predisposes to retinal detachment; this aspect of the phenotype is absent in STL3 because *COL11A2* is not expressed in the eye.

NEUROFIBROMATOSIS 2

The hallmark of neurofibromatosis 2 (NF2) is hearing loss caused by bilateral vestibular schwannomas. Approximately 50% of affected patients have no family history of NF2; therefore these patients represent new germ line mutations in the NF2 gene. This is discussed further in the section on NF2 in this chapter.

Autosomal recessive syndromic hearing impairment

USHER SYNDROME

Usher syndrome (USH) is the most frequent autosomal recessive syndromic form of hearing loss. More than 50% of the deaf-blind community in the USA have USH. According to the genotype and phenotype differences, USH has several subtypes:

- Type I: congenital severe-to-profound sensorineural hearing loss, vestibular dysfunction and onset of retinitis pigmentosa in the first decade of life
- Type II: mild-to-severe sensorineural hearing loss, normal vestibular function and onset of retinitis pigmentosa in the first or second decade of life
- Type III: progressive hearing loss, progressive vestibular dysfunction and onset of retinitis pigmentosa is variable.

To date 15 different loci and 12 genes have been reported (http://hereditaryhearingloss.org). One of these identified genes, *MYO7A*, encoding myosin 7A, is a unique molecular motor for hair cells.[27] Cadherin 23, an adhesion molecule, coded by *CDH23* gene may have an important role in cross linking of stereocilia.[28]

PENDRED SYNDROME

This is the second most common type of autosomal recessive syndromic hearing loss. It is usually characterized by severe congenital sensorineural hearing loss and euthyroid goitre that develops in puberty or adulthood. The deafness is also commonly associated with an abnormality of the labyrinth which may be anatomical (Mondini dysplasia or dilated vestibular aqueduct) and/or functional. Almost 50% of the families have *SLC26A4* (PDS) gene mutation on chromosome 7q21-q34. The gene is responsible for sulfate transport. Its protein product, pendrin, is involved in the transport of iodine and chloride ions. *SLC26A4* gene mutation should be investigated in the patients who have progressive hearing loss, Mondini dysplasia or large vestibular aqueduct syndrome. The same mutation can also cause DFNB4.[29]

JERVELL AND LANGE-NIELSEN SYNDROME

This is characterized by a congenital hearing loss and an elongation of the QT interval on electrocardiography. Affected individuals have episodal syncope and may have sudden death. The JLNS1 locus in the *KVLQT1* gene located on chromosome 11p15.5, or the JLNS2 locus in the *KCNE1* (IsK) gene located on chromosome 21q22.1-q22.2 are responsible for the syndrome. These are potassium channel genes.[30]

BIOTINIDASE DEFICIENCY

This condition results from a deficiency of an enzyme required for the normal cycling of the water-soluble vitamin biotin. Clinically it is characterized by a variable sensorineural hearing loss (in 75% of children), with associated neurological, ophthalmological and dermatological abnormalities. Biotinidase deficiency can be prevented with supplementation of biotin.

REFSUM DISEASE

Refsum disease is characterized by severe progressive sensorineural hearing loss and retinitis pigmentosa caused by faulty phytanic acid metabolism.

X-LINKED SYNDROMIC HEARING IMPAIRMENT: ALPORT SYNDROME

Progressive sensorineural hearing loss, renal disorder (glomerulonephritis, haematuria, renal failure) and eye problems (lenticular and macular abnormalities) are observed. Almost 50% develop progressive bilateral hearing loss, which usually begins in the second decade.[30] This syndrome is X-linked in 85%, autosomal recessive in 15% and autosomal dominant in the remainders. In the X-linked form, males are more severely affected than females. The *COL4A5* gene on Xq22 and the *COL4A3* and *COL4A4* genes on chromosome 2q36–q37 are responsible for the syndrome.[30]

Implication of discovery of genes associated with hearing loss

Why has the genetics of hearing loss become such a focus for researchers?

First, from a biological perspective, the amount of information gained about the auditory and vestibular systems has been dramatic. Second, from a diagnostic aspect, clinicians are now able to discern the aetiology of hearing loss of a large number of patients by relatively simple genetic testing. Third, from a genetic counselling aspect, genetic counsellors are able to predict with much greater certainty what the chances are of another child being born with deafness in the family. Fourth, from a therapeutic aspect, the discovery of genes may provide solutions for treatment and therapy for alleviating hearing loss.[22]

Genetics of aminoglycoside toxicity

Aminoglycoside-induced ototoxicity is a potentially preventable form of acquired hearing loss. The mitochondrial 12S rRNA is a hot spot for mutations associated with both aminoglycoside-induced and non-syndromic hearing loss. Of those, the homoplasmic 1555A>G and 1494C>T

mutations at the highly conserved decoding region of the 12S rRNA have been associated with hearing loss worldwide.[31] In particular, these two mutations account for a significant number of cases of aminoglycoside ototoxicity. The 1555A>G or 1494C>T mutation is expected to form a novel 1494C–G1555 or 1494U–A1555 base-pair at the highly conserved A-site of 12S rRNA. These transitions make the human mitochondrial ribosomes more bacteria-like and alter binding sites for aminoglycosides. As a result, the exposure to aminoglycosides can induce or worsen hearing loss in individuals carrying one of these mutations.[31]

One of these mutations, 1555A>G, has also been reported in hearing-impaired patients with no history of exposure to aminoglycoside antibiotics, suggesting that in some carriers of this mutation aminoglycoside exposure is sufficient, but not necessary, for hearing loss to occur, and additional environmental and/or genetic risk factors likely exist.[32–34] One way to assess individual risk is by careful evaluation of family history. The other is DNA-based mutation detection technologies, which offer a far more precise method for identification of at-risk individuals, but the appropriateness of screening for these two mutations and the circumstances under which screening should be conducted are not yet clear and perhaps screening only high-risk populations would be a better approach. At-risk populations might be defined as those individuals with increased risk of exposure to aminoglycoside antibiotics because of some other, unrelated condition such as cystic fibrosis or an immunological dysfunction, or individuals in whom the use of aminoglycoside antibiotics is under consideration for treatment of infectious disease.

Data on the prevalence of aminoglycoside use in the population are also needed. Data from such studies will provide information about the clinical utility of testing for genetic susceptibility to aminoglycoside ototoxicity and will support discussions of screening for genetic susceptibility to aminoglycoside ototoxicity by identifying high-risk populations. Data from these types of studies will also help establish guidelines for pretest genetic counselling and informed consent of subjects.

GENETICS OF NEUROFIBROMATOSIS TYPE 2

Neurofibromatosis type 2 (NF 2) is much rarer than NF1, with an incidence estimated to be 1:25 000.[35] Disease prevalence has now risen to 1:60 000 on account of better survival and improved treatment.[36]

Neurofibromatosis type 2 is an autosomal dominant condition with the hallmark of bilateral vestibular schwannomas, but is also associated with meningiomas, ependymomas, and pre-senile cataracts. The mean age of onset of symptoms from vestibular schwannoma is estimated to be 20 years.[37] The majority of vestibular schwannomas are sporadic in occurrence and unilateral, presenting in the fifth decade. The bilateral vestibular schwannomas that occur in patients with NF2 represent 2–4% of all vestibular schwannomas[38, 39] and present in the second and third decades of life.

NF1 and NF2 are recognized as separate genetic and clinical diseases with the localization of the respective genes to chromosomes 17 and 22. The NF2 gene was localized to chromosome 22 through a genetic linkage analysis.[40] Subsequently the NF2 locus was further mapped close to the centre of the long arm of chromosome 22 (22q12).[41] In 1993 the NF2 gene was identified by Rouleau et al.[42] and Trofatter et al.[43] and since then mutations in the NF2 gene have been identified not only in NF2 related vestibular schwannomas, but also in sporadic vestibular schwannomas and meningiomas.

The NF2 gene is spread over approximately 100 000 bases (100kb) on chromosome 22q12.2 and contains 17 exons (or encoding segments). The transcribed mRNA is 1785 base pairs long and produces a protein of 595 amino acids designated as merlin or schwannoma.[42, 43]

The gene product is similar in sequence to a family of proteins including moesin, ezrin, radixin, talin and members of the protein 4.1 superfamily. These proteins are involved in linking cytoskeletal components with the plasma membrane and are located in actin rich surface projections such as microvilli, membrane ruffles, and cell contact regions. The N-terminal region of the merlin protein is thought to interact with components of the plasma membrane and the C-terminal with the cytoskeleton. While the exact function of the NF2 protein is as yet unknown, the evidence available suggests that it is involved in cell–cell or cell–matrix interactions, and that it is important for cell movement, cell shape and communication. There is considerable evidence, in both NF2 knockout mice and *in vitro* schwannoma preparations, that loss of function of the merlin protein results in a loss of contact inhibition and consequently leads to tumourigenesis.[44–46]

NF2 gene defects have been detected in other malignancies including meningiomas, malignant mesotheliomas, melanoma and breast carcinoma.

NF2 mutations and their clinical correlation

The NF2 gene has been postulated to represent a tumour suppressor gene. In approximately 50% of cases, there is no family history of NF2. Therefore, these patients represent new germline mutations in the NF2 gene. To date, more than 200 mutations of the NF2 gene have been identified, including single base substitutions, insertions and deletions.

Mutations were identified in 66% of sporadic cases of vestibular schwannomas, but only in 33% of the NF2 cases; therefore the rate of detection of a mutation in unilateral vestibular schwannomas was significantly higher than that of familial schwannomas.[47] Genotype-to-phenotype correlation studies suggest that the mutations in the NF2 gene that result in protein truncation are associated with a more severe clinical presentation of NF2 (Wishart type) – larger, multiple, faster growing tumours – while missense and splice site mutations are associated with a milder

form of the disease (Gardner type) – smaller, few and slow growing tumours. However, this has not been held true in other studies, which showed that some missense mutations associated with a severe phenotype.[47]

Given the heterogeneity of clinical response to various types of mutations, no clear genotype-to-phenotype correlation has been established, and this is further evidenced by the fact that phenotypic variability within the NF2 families with the same mutation has been seen.[48]

Although mutations in the NF2 gene play a dominant role in the biology of vestibular schwannomas, they are not uniformly identified in patients with vestibular schwannomas, which suggests that other genetic loci may contribute to the genesis of vestibular schwannomas and ultimately phenotype of the affected individuals.[49, 50]

Genetic testing and antenatal diagnosis

As detection of tumours at an early stage is effective in improving the clinical management of NF2, presymptomatic genetic testing is now an integral part of the management of NF2 families.

Once a mutation has been identified in an affected individual, a 100% specific test is available for the family; however, mutation screening may not reveal causative mutation. Predictive diagnosis by linkage analysis using intragenic markers or markers flanking the NF2 gene is also possible in the great majority of families with two or more living affected individuals.[51]

Tumour analysis plays a vital role in providing genetic testing for the offspring of sporadic patients. Indeed analysis should if possible first be carried out on the tumour so that a targeted approach can be used on the blood sample.[51] If both mutational events are identified in the NF2 gene in a tumour and neither is present in the blood the patient must be mosaic for one of these mutations.[52, 53] Even if only LOH is identified this still allows exclusion of NF2 in 50% of offspring if they can be shown to have inherited the allele 'lost' in the tumour.[52, 53] At-risk individuals who are shown not to have inherited the mutated NF2 gene do not need further follow-up.

Molecular pathophysiology – a link to drug therapy

Recent work on the mechanisms by which the loss of Merlin in the setting of NF2 influences vestibular schwannoma proliferation, has been translated into clinical trials and we are not far away from approved drug therapy for NF2 associated vestibular schwannomas.

The mammalian target of rapamycin (mTOR) is a tyrosine kinase that serves as a hub in the intracellular communication cascade integrating signals from multiple upstream pathways as well as the local intracellular environment. It belongs to two complexes: mTORC1 and mTORC2. mTORC1 is constitutively activated in Merlin-deficient schwannomas.[54] mTORC1 activation in turn leads to phosphorylation of ribosomal S6 kinase (S6K) and the eukaryotic initiation factor 4E binding protein-1 (4EBP-1), ultimately increasing translation, protein production, and cell growth.[55] Subsequent studies have shown decreased phosphorylation of downstream targets with mTOR inhibitors such as rapamycin. This and recent supporting preclinical animal data suggesting mTOR inhibition influences vestibular schwannomas cell proliferation have led to three ongoing clinical trials testing everolimus in patients with radiographic progression of NF2-associated vestibular schwannomas (NCT01345136, NCT01490476, NCT01419639).[56]

The loss of Merlin protein in NF2 has been shown to result in abnormal activation of the epidermal growth factor receptor (EGFR) receptor tyrosine kinases (RTKs) proteins. The proteins implicated include EGFR, ErbB2 and ErbB3. These proteins all span the cell membrane and contribute to feedback loops that regulate both cell death and cell division. When Merlin is inactive, EGFR, ErbB2 and ErbB3 remain constitutively active allowing increased cell proliferation and resistance to cell death.[57] Lapatinib is an oral dual EGFR/ErbB2 inhibitor approved for use in breast cancer. In preclinical studies lapatinib was shown to have substantial inhibition of both cell proliferation and vestibular schwannomas growth.[58, 59] Lapatinib is now being investigated in two ongoing clinical studies in patients with NF2.

The contribution of abnormal angiogenesis has recently been recognized in benign tumours and provides a novel therapeutic target for NF2-associated vestibular schwannomas. Vestibular schwannomas and peripheral schwannomas have been shown to express vascular endothelial growth factor (VEGF) in both tumour cells and associated endothelial cells.[60, 61] Recent studies indicated that Merlin also regulates angiogenesis via semaphorin 3F (SEMA3F), a protein that inhibits angiogenesis.[62] On these observations, bevacizumab, an angiogenesis inhibitor, is being used in at least two clinical trials.

Ras represents a family of proteins responsible for intracellular communication that are frequently altered in the setting of tumours. Merlin has been shown to regulate the interaction of Ras and various growth factors,[63] and multiple targets in the Ras pathway have been implicated as part of the pathogenesis of NF2-associated tumours. Sorafenib is an oral multitarget inhibitor of several targets downstream from Ras including Raf/Mek/Erk as well as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and c-kit. Similar to sorafenib, nilotinib is a RTK inhibitor of breakpoint cluster region-abelson that also targets PDGF receptor and c-kit. It has also shown promising NF2 *in vitro* and is entering a phase 0 trial with a similar design as described for sorafenib.[64]

GENETICS OF FAMILIAL PARAGANGLIOMAS

Paragangliomas (PGs) are tumours of paraganglionic tissue derived from the migration of neural crest cells during foetal development that occur in both sporadic and

familial forms. In the head and neck these most commonly arise from the carotid body (carotid body tumours), jugulotympanic region (glomus tympanicum), jugular bulb (glomus jugulare) and vagus nerve (glomus vagale). Another well known but rare paraganglioma is the pheochromocytoma (PCC).

The yearly clinical incidences of paragangliomas and pheochromocytomas are estimated as 1:1000000 and 2:1000000 respectively.[65]

Familial PG is inherited in an autosomal dominant manner with maternal imprinting. Therefore, when an individual inherits the PG gene from the mother (regardless of whether she herself is affected), that child is unaffected and becomes a silent carrier of the mutated gene. On the other hand, when a child inherits the PG gene from the father, the offspring will have paragangliomas regardless of the affected status of the father. Subsequently, the affected/unaffected child harbouring the abnormal PG gene will be able to pass the gene to his/her children; he/she will have affected children only if the transmitting parent is a father. This unusual form of incomplete genetic penetrance is caused by sex-specific gene modification during gametogenesis.[66]

Because of this unusual form of inheritance, many sporadic PG could in fact be hereditary PG, and the incidence of familial PG could be much higher than the historically quoted rate of 10%. During the last decade mutations in the genes encoding different subunits of the succinate dehydrogenase (SDH) complex have been linked to familial PCC-PG syndrome, and subsequent genetic screenings have revealed that about 30% of PCC and PG are caused by hereditary mutations.[67, 68] Similar to familial PG, sporadic PG also demonstrates loss of heterozygosity at PGL1 and PGL2, and this was demonstrated in 38% sporadic cases of carotid body tumours and glomus tumours by Bikhazi et al.[69] This indirectly tells us that approximately one-third of all sporadic cases of PG may actually be familial.

Currently, four different types of PG are recognized: PGL1, PGL2, PGL3 and PGL4. These are now briefly discussed.

PGL1

PGL1 is caused by germ line mutations of the SDHD gene, located at 11q21.[70] It is the most common PGL.[71, 72]

Multiple head and neck PGs are a key feature of this syndrome and they develop in the majority of patients (60–79%), either synchronous or metachronous.[72–74] There is also a definite risk of developing pheochromocytomas and extra-adrenal PGs (16–21%).[72–74]

In 2012 Van Hulsteijn et al.[75] presented a systematic literature review and meta-analysis on the risk of malignant PG in SDHB and SDHD mutation carriers and found that the prevalence of malignant paraganglial tumours reported in SDHD patients with manifest disease varied widely, ranging from 0% to 23%. The pooled incidence for malignant PG was 8% in SDHD mutation carriers.[75]

Tumour penetrance in SDHD mutation carriers is high. Neumann et al.[76] first published data on age related penetrance in SDHD mutation carriers in 2004. SDHD mutations conferred 50% penetrance by age 31 rising to 86% by the age of 50. In a study by Hensen et al.[77] published in 2010, age related penetrance in SDHD patients was 54% by age 40 and 87% by age 70. The average range of age at diagnosis of SDHD-linked tumours is 25–38 years.[72, 74, 78] As demonstrated by Heesterman et al.[79] there is also a high prevalence of occult paraganglial tumours in asymptomatic SDHD mutation carriers; in their study, MRI detected HNPGs in 28 out of 47 (59.6%) asymptomatic SDHD patients.

Already in 1989, it was observed that PGL1 families exhibit a peculiar inheritance pattern with a distinct 'parent-of-origin-dependent effect'.[80] Whereas SDHD mutations can be inherited both via the maternal and paternal lines, the PGL almost never develops after maternal transmission of the mutation.[72, 76, 80] As maternally derived SDHD mutation carriers will still pass the mutation to their offspring in 50% of cases, PGL1 can appear to skip generations, which may in part explain the occurrence of SDHD germ line mutations in apparently non-familial cases.[72, 74, 76]

This virtually exclusive paternal inheritance of disease is consistent with maternal imprinting of the disease gene.[80] However, imprinting of SDHD has never been established, and the fact that this inheritance pattern is also found in PGL2 families (linked to the SDHAF2 gene, located on 11q13), but not in PGL3 or PGL4 families, suggests that other factors on chromosome 11 explain this phenomenon. It has been found that in SDHD-linked PGs, the whole maternal copy of chromosome 11 is selectively lost.[81] Interestingly, this implies that a second, paternally imprinted tumour suppressor gene located elsewhere on chromosome 11 plays a decisive role in PG tumourigenesis, at least in PGL1 and PGL2.[81] This hypothesis is supported by genetic analysis of the very few 'exceptions to the rule', the reported instances of maternal transmission of disease in PGL1 families. In these rare cases, it was shown that invariably not only the SDHD or SDHAF2 gene but also the 11p15 region was affected.[82, 83] The identity of this secondary tumour suppressor gene remains to be elucidated.[84]

PGL2

PGL2 has a very interesting history, as it was the first PGL to be described.[84] In 1982 Van Baars et al.[85] reported on a large Dutch family (295 living family members) with familial HNPGs. It was not until the year 2009 though, that Hao et al.[86] identified a mutation of the SDHAF2 gene, situated on 11q13, as the underlying cause of PGL2.[86, 87] SDHAF2, also known as SDH5, plays an important role in flavination of SDHA.[86]

Bayley et al.[87] identified a second family with PGL2 in Spain. The authors also looked for SDHAF2 mutations in 443 additional HNPGs and pheochromocytoma patients without finding another case of PGL2, suggesting that SDHAF2 plays a modest role as a causative gene in PGLs. Like PGL1, the PGL2 is strongly associated with the occurrence of multiple HNPGs (70–91%) but so far,

no extra-adrenal PGs, pheochromocytomas, or malignant PGs have been described in SDHAF2 mutation carriers.[86–88] As in PGL1, in PGL2 families transmission of the PGL occurs exclusively via the paternal line. Tumour penetrance has been described to be very high in both the Dutch and the Spanish family (88–100%), and the average age at diagnosis is 33–34 years.[86–88]

PGL3

Niemann and Müller[89] first identified a mutation in SDHC, located on 1q21, as the underlying cause of PGL3 in 2000. Until October 2005, only four patients with SDHC mutations had been described.[84] Most authors concluded that SDHC mutations must be exceedingly rare and therefore, HNPG patients were not routinely tested for mutations of the SDHC gene. This only changed when Schiavi et al.[90] reported on a total of 22 SDHC mutation carriers in October 2005.

Nevertheless, SDHC mutations have been detected less frequently than SDHD and SDHB mutations.[72]

In sharp contrast to patients with PGL1 and PGL4, SDHC mutation carriers mostly present with benign, single HNPGs.[72] Multiple HNPGs are found in 19–31%, and pheochromocytomas, extra-adrenal PGs, and malignant PGs are seldom reported in SDHC mutation carriers.[72, 73, 90]

In 2009, Neumann et al.[72] and Burnichon et al.[73] found similar prevalence of 4.3% and 3.6% for SDHC mutations in two large HNPG patient series consisting of 445 and 598 PG patients, respectively. The family history is positive in the minority of SDHC patients (12–25%), suggesting a low tumour penetrance.[72, 73] The average age at diagnosis is higher than for the other PGL (38–46 years).[73, 90]

PGL4

The PGL4 locus is situated on the 1p36 chromosomal band. The first description of the SDHB mutation as the cause of PGL4 dates back to 2001.[91]

In contrast to SDHD mutation carriers, patients with SDHB mutation carriers frequently develop extra-adrenal PGs (in 52–84%) and pheochromocytomas (in 18–28%), and less frequently HNPGs (in 27–31%), while multifocal HNPGs are significantly less frequently found when compared to SDHD patients.[72, 78]

The average age at diagnosis is reported to be between 30 and 37 years.[73, 78]

The most striking clinical feature of PGL4 is the high percentage of malignant pheochromocytomas and malignant HNPGs.[72, 78]

Neumann et al.[72] described malignant paraganglial tumours in 13 out of 63 SDHB mutation carriers (20.6%). Ricketts et al.[78] reported on 40 SDHB patients with malignant PGs and pheochromocytomas in a group of 163 SDHB mutation carriers (25.2%). In a literature review by Pasini and Stratakis,[92] 50 malignant paraganglial tumours were diagnosed in 105 out of 256 SDHB mutation carriers (41%).

As reviewed by Van Hulsteijn et al.[75] prevalence of malignant paraganglial tumours in SDHB patients with manifest disease range from 0% to 54% in the literature. In their systematic literature review and meta-analysis on the risk of malignant PG in SDHB and SDHD mutation carriers, the authors found a pooled incidence of 17% in the SDHB group. The pooled risk in prevalence studies, depending on presence of manifest disease, ranged from 13% to 23% in the SDHB group. The authors concluded that incidence and prevalence of malignant HNPGs and pheochromocytomas are higher in SDHB than in SDHD mutation carriers but lower in the SDHB group than hitherto appreciated.[75]

Identification of an *SDHB* gene mutation is also a factor of poor prognosis.[92] Multivariate analysis of a series of 54 subjects followed in France for PG or malignant pheochromocytoma demonstrated that identification of an *SDHB* mutation was the only risk factor for mortality. The 5-year survival probability was 36% for subjects with an *SDHB* mutation versus 67% for subjects without an SDHB mutation with a calculated median survival of 42 months for *SDHB*-mutant patients versus 244 months for wild-type *SDHB* patients.[93]

SDHB mutations follow an autosomal dominant trait of inheritance.[91] Tumour penetrance is somewhat lower than that seen in SDHD mutation carriers. Benn et al.[94] estimated the age related tumour penetrance in SDHB mutation carriers to be at 29% at age 30 rising to 45% at age 40.

KEY POINTS

- Advances in molecular genetics have helped to identify causative genes and proteins responsible for pathologies; this knowledge is pertinent to molecular target therapy and promises novel therapeutic interventions.
- The most useful distinction in hereditary hearing impairment (HHI) is syndromic (majority) and non-syndromic (minority). In autosomal dominant non-syndromic hearing loss there is not a single identifiable gene responsible for the majority of cases whereas in autosomal recessive non-syndromic hearing impairment 50% of people have mutations in the GJB2.
- Waardenburg syndrome, Bronochiootorenal syndrome, Stickler syndrome and NF2 represent the most common causes of syndromic autosomal dominant hearing loss, whereas Pendred syndrome and Jervell and Lange-Neilsen syndrome are the commonest causes of syndromic autosomal recessive hearing loss.
- The mitochondrial 12S rRNA is a hot spot for mutations associated with both aminoglycoside-induced and non-syndromic hearing loss. Of those, 1555A>G and 1494C>T mutations at the 12S rRNA have been associated with hearing loss worldwide and account for a significant number of cases of aminoglycoside ototoxicity.

- The NF2 gene is spread over approximately 100 000 bases on chromosome 22q12.2 and contains 17 exons (or encoding segments). More than 200 mutations of the NF2 gene have been identified, that result in protein truncation are associated with a more severe clinical presentation of NF2 (Wishart type) – larger, multiple, faster growing tumours. While missense and splice site mutations are associated with a milder form of the disease (Gardner type) – smaller, few and slow growing tumours.
- Currently, four different types of PG (tumours of paraganglionic tissue derived from the migration of neural crest cells during fetal development that occur in both sporadic and familial form) are recognized:
  - PGL1- the commonest type caused by germ line mutations of the SDHD gene, located at 11q21
  - PGL2- caused by a mutation of the SDHAF2 gene, situated on 11q13
  - PGL3- caused by a mutation of the SDHC gene located on 1q21
  - PGL4- the locus of which is situated on the 1p36 chromosomal band.

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CHAPTER 3

GENE THERAPY

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline and PubMed Central search using the keywords: gene therapy, cystic fibrosis, head and neck cancer, gene transfer, adenoviral vectors, adeno-associated vectors, ballistic gene delivery, chemosensitization and retroviral vectors.

INTRODUCTION

Gene therapy is the means of delivering exogenous genetic material for therapeutic purposes into the host cell target using vectors. This strategy in principle can be utilized in patients who have genetic defects leading to phenotypic impairment. Gene therapy can be restorative, regenerative or protective in nature by replacing/suppressing/enhancing gene expression. Few new treatment protocols reflect the allure of modern science quite as elegantly as gene therapy. The promise of gene therapy in treating a variety of diseases is, simply put, incredible. This promise has captured the hopes and enthusiasm of the scientific and lay communities alike. Notable initial success in treating severe combined immune deficiency (SCID) seemed to herald imminent success in treating a whole variety of other conditions. In reality, however, progress in bringing the allure of the science to a useful clinical application has been quite limited. Even in the group of SCID subjects[1] – an apparent 'cure' – a patient has died from an unusual lymphoproliferative disease.[2] This has led to a reassessment of the risks of retroviral therapy trials. While great strides have been made in understanding the microbiological complexities of disease states and vectors, the barriers to clinical utility continue to be formidable. However in recent years gene therapy has met major milestones in multiple clinical trials for a number of diseases including Leber's congenital amaurosis,[3, 4] X-linked adrenoleukodystrophy[5] and β-thalassemia.[6] In the 10-year follow-up study of aforementioned SCID subjects, 18 out of 20 patients are still alive, including four who had leukemia and 17 who have their immunodifficiency corrected.[7] Additionally the European commission has recently approved alipogene tiparvovec (Glybera®), an AAV viral vector harbouring human lipoprotein lipase, which will be used for the treatment of familial lipoprotein lipase deficiency disease, making it the first commercial available drug using gene therapy technology in Europe.[8] Thus, after experiencing several major setbacks gene therapy is making small but steady steps towards clinical reality.

As of 2012, some 1800 human clinical gene therapy trials (including phase I to IV) exist worldwide.[9] The disease processes involved can be broadly divided into four groups as listed in descending order of number of clinical trials: cancer, monogenetic diseases such as cystic fibrosis (CF) and haemophilia B, cardiovascular disease, and infectious disease trials, which entirely comprise human immunodeficiency virus (HIV). These studies deliver genetic material to target cells via vectors, which act as delivery vehicles to bypass host defences. In the very select circumstances of the skin or eye, a 'gene gun' can be used. The treatment aims to replace or repair the defective gene causing a given disease or to provide a new or altered function in a cell. The most common vectors are a variety of replication-deficient viruses although non-viral vectors, such as liposomes, are also used. The characteristics of commonly used vectors are summarized in **Table 3.1.** We will first review some commonly used gene therapy vectors.

Delivery

The common goal of all gene therapy is to achieve expression of the gene of interest in the targeted cell. To accomplish

TABLE 3.1 The characteristics of commonly used vectors

	Adenovirus	Adeno-associated virus	Retrovirus/lentivirus	Non-viral vectors
Family	*Adenoviridae*	*Parvoviridae*	*Retroviridae*	n/a
Genome	Double-stranded DNA	Single-stranded DNA	Single-stranded DNA	Unlimited size
Infection/tropism	Dividing and non-dividing cells	Dividing and non-dividing cells	Dividing cells	Dividing and non-dividing cells
Host genome interaction	Non-integrating	Non-integrating	Integrating	Non-integrating
Transgene expression	Transient	Potential long lasting	Long lasting	Transient
Packaging capacity	7.5 kb	4.5 kb	8 kb	Unlimited capacity

Source: Adapted and modified from Gene Therapy Net (http://www.genetherapynet.com).

this goal several barriers must be overcome: (i) targeting – ideally only cells which require the gene would be affected; (ii) binding and internalization (transfection) – once a gene reaches the cells it must bind and become internalized; (iii) cellular trafficking to the nucleus (transduction) – most methods of internalization require the gene to escape from endosomal degradation and traffic through the cell to the nucleus; and (iv) nuclear expression – once in the nucleus the quantity of gene expression and stability of expression for a given strategy also need to be determined. Each method of delivering a gene to a cell varies in its ability to overcome these barriers.

Adenovirus

Adenovirus is a human pathogenic, non-encapsulated, DNA virus. It has been extensively studied as a means to deliver transgenes both *in vitro* and in human trials. Adenovirus has several characteristics that make it suitable as a therapeutic vector in gene therapy. Relatively simple amplification methods have been developed to propagate high-titer replication defective vectors.[10] Adenovirus efficiently infects both dividing and non-dividing cells by binding to the cox-adenovirus receptor.[11] Once a cell binds the viral vector, adenovirus is internalized, escapes from the endosome and is trafficked to the nucleus very efficiently. Even if a specific cell is lacking viral receptors, the virus can be combined with complexes to be internalized via non-receptor-mediated mechanisms. In this alternative pathway of entry, the other components of viral gene delivery remain intact, and therefore efficiency is maintained.[12, 13] This relative versatility, its ease of construction, efficiency of infection and the efficient expression of transgene make adenovirus an attractive vector for gene therapy.

Adenovirus does have some drawbacks compared to other viral vectors and non-viral systems. It is immunogenic that which limits its ability to re-infect.[14] Multiple studies have shown that both cell- and humoral-mediated immune systems are activated after viral delivery, especially if greater than 10^{10} particles are delivered.[15] This toxicity led to the well-publicized death of a subject in a University of Pennsylvania trial.[1] Besides limiting redelivery, this immune response also results in the clearance of cells expressing the transgene.[16] Several strategies have shown promise in overcoming this immune-stimulatory problem. 'Gutted' vectors, missing almost all of the viral genes, have been shown to be less immunogenic and are expressed for longer periods *in vivo*.[17, 18] Immune modulation at the time of delivery may decrease the initial inflammatory reaction to the virus.[17, 18] A further difficulty with adenovirus is that gene expression is transient. The viral genome does not integrate or persist with cell division and gene expression is lost as the cells divide. As demonstrated by more than 50 current open protocols, the adenoviral vector is a very versatile means of gene delivery. As the obstacles of immune stimulation and persistence are addressed, this vector should only become more useful.

Adeno-associated virus

The AAV vector has more recently emerged as a vector with significant therapeutic promise.[3, 8] AAV is a single-stranded encapsulated virus that belongs to the group of human parvoviruses. Several features of this virus make it attractive as a potential therapeutic tool. First, although it infects human cells this virus has not been associated with a pathologic human disease. It may, therefore, be a safer alternative than other viral vectors. Second, because recombinant AAV vectors do not encode viral proteins, delivery of this vector results in very little immunogenicity.[19, 20] AAV also persists and infects dividing and non-dividing cells. Although the mechanisms are not fully clear, it appears that in quiescent cells AAV integrates into the host chromosome and in rapidly dividing cells it persists as an extrachromosal episome.[21] These factors have made this vector a popular delivery vehicle for many preclinical and human trials. AAV viral vector harbouring human lipoprotein lipase AAV, alipogene tiparvovec (Glybera®) became the first commercially available gene therapy drug in Europe to treat familial lipoprotein lipase deficiency disease in 2012.[8] Disadvantages such as limited loading capacity (up to 4.2 kb), inefficient expression and delayed onset of expression have made AAV less attractive in the past; however, newer generations of recombinant AAV are now becoming available and are proven to have shorter turnover of transcription and enhanced gene expression potencies.

Retrovirus/lentivirus

Retroviral vectors have the substantial advantage of persistent gene expression. A discussion of retroviral vectors requires a basic understanding of the viral genome and replication. Retroviruses are small, encapsulating vectors with a genome composed of two identical single strands of RNA. The virus binds and is internalized into the cell via interactions between the cell membrane and viral capsule. Once internalized the RNA genome is reverse-transcribed and transported to the nucleus where it integrates as a provirus into the host chromosome. In a normal infectious process, this provirus would then produce viral proteins and RNA genomes for viral packaging. In all retroviral gene therapy vectors, the genome of the virus has been made replication-incompetent by removing the components of the viral gene required for packaging. Thus, these vectors integrated and express the desired gene but will not produce infectious particles.

Several retroviral systems for gene therapy are currently available. Murine oncogenic retroviruses have been the most extensively analyzed and used in preclinical studies.[22] Because murine retroviruses only infect dividing cells, the clinical utility of these initial retroviral vectors has been significantly limited.[22] To circumvent this obstacle, newer retroviral systems have been developed based on the lentivirus genus of retroviruses. This group of viral vectors that contains the human immunodeficiency virus offers the advantage of infecting dividing and non-dividing cells. They have shown significant promise in preclinical *in vivo* studies.[5, 6, 23] A further biosafety-related issue of retroviruses is that insertion of the provirus is not controlled. It is possible that insertion of the virus next to a proto-oncogene may lead to therapy-induced cancer. Initial evidence from the first successful therapy in patients with severe combined immune deficiency using retroviral gene replacement suggests that a minority of the patients may have developed a non-typable lymphoproliferative disorder as a result of therapy.[1] In addition to controlling insertion, chromosomal silencing of inserted genes has also been reported. In chromosomal silencing, methylation or acetylation of the promoter leads to significant downregulation of transgene expression.[24, 25] For both of these obstacles, current research has suggested potential solutions. These include controllable chromosomal insertion, chromosomal buffers and methods to controllably excise the provirus.

Non-viral vectors

Naked DNA is one of the most extensively studied methods of gene therapy. This non-viral method of gene therapy has several advantages. These include simplicity, ease of large scale production, minimal immune response and safety.[26] The major obstacle for plasmid gene therapy is efficiency. When DNA is placed in an organism, most of the DNA is not internalized. Even if internalization does occur, endosomal degradation destroys nearly all of the remaining plasmid prior to nuclear membrane transit and expression of the desired gene does not occur. In addition, since plasmid uptake is not receptor-mediated, targeting of the plasmid to a specific cell also remains a major obstacle. In the past 25 years, substantial progress has been made in overcoming these obstacles to non-viral gene transfer. Lastly, plasmid-mediated transfer results in transient expression because the plasmid is lost with cell division. Several methods using site-specific integration or expression of viral proteins have shown promise as a means to overcome this difficulty.[27, 28] Many of the past therapeutic attempts to utilize plasmid-mediated gene transfer have shown only modest potential. However, as all aspects of plasmid efficiency increase, this should directly correlate with the ability to utilize this technology in therapeutic interventions.

In reviewing progress to date in gene therapy, two diseases of interest to otolaryngologists encapsulate the potential and difficulties of this technique. We will review an apparently attractive candidate for gene therapy, a disease caused by a single mutation inherited in an autosomal recessive fashion – cystic fibrosis.[29, 30] We will also review progress in a condition with a variety of causalities and a disparate genetic basis, head and neck cancer[31, 32] – a superficially unattractive candidate for gene therapy. These two diverse diseases serve to illustrate many of the principles, advances and frustrations of gene therapy. In both these examples, human trials remain in nascent stages. Trial sample size is small and results so far do not readily lend themselves to the categorization of levels of evidence, as displayed in other chapters in this text.

CYSTIC FIBROSIS

Cystic fibrosis (CF) represents a seemingly ideal disease for gene therapy. It is the most common lethal genetic disease of one of the wealthiest racial subgroups in the world. There are perhaps 30 000 people with CF in the United States and 70 000 worldwide. It is inherited with an autosomal recessive pattern with carrier rates of 5% in some Caucasian populations.[33, 34] Remarkably, the median survival for CF patients is less than 40 years[35] and unfortunately, the disease remains almost uniformly fatal, invariably from its pulmonary sequelae.[33, 34] Despite dramatic improvements in the understanding of the molecular basis of CF, the pathogenesis of CF remains unclear and there has as yet been no clinically useful breakthrough in its treatment. Clearly, new treatments and novel animal models faithfully mimicking CF are needed. Conceptually, gene therapy offers the promise of a dramatic and new treatment for CF, thereby a majority of gene therapy trials targeting inherited monogenic disorders in Europe and the USA are currently performed in CF patients.[9, 30]

Genetic basis

The discovery of the gene for CF in 1989[36] set in motion a remarkable series of events, often covered by the lay press with the hyperbole of popular culture, which have culminated in attempts at gene therapy. CF is caused by mutations in a cystic fibrosis transmembrane conductance

regulator (*CFTR*) gene on the long arm of chromosome 7. This gene encodes a CFTR protein, which has been shown to be a cAMP-dependent chloride channel on the apical surface of the epithelium.[37] Abnormalities of CFTR impairs the chloride channel and dysregulates salt and water transport across a variety of epithelia. This produces the increase of salt in sweat, obstructive pathology of the lung, pancreatic insufficiency, malabsorption of the GI tract and male infertility due to the lack or stenosis of vas deferens.[37] The deletion of three nucleotides results in the deletion of a single phenylalanine residue at position 508 of CFTR, designated ΔF508, is the most common mutation in CF comprising some 70% of cases. Other mutations, now numbering over 1000, are uncommon, occurring in less than 1% of screened populations.

The nasal model for gene transfer in cystic fibrosis

Most interest in CF amongst otolaryngologists has centred on CF sinus disease. Previous reports have claimed benefit from aggressive treatment of CF sinus disease[38] and have also suggested that the rhinologic sequelae of CF are important in production of the eventually life-threatening pulmonary complications. Not as widely reported has been the utility of the nose and sinuses in CF as a model for pulmonary disease.[39] While the eventual goal of CF gene therapy will clearly be intra-pulmonary administration, there are clearly some difficulties using the lungs for routine experimentation.

Chief amongst these concerns is safety. The prospect of an adverse reaction to vector administration in the lungs of a patient with pre-existing pulmonary compromise is real. In a dose-escalating trial reported by Crystal et al.[40] in 1994 of intra-pulmonary adenoviral vector administration, the patient who received the largest dose developed a significant adverse reaction with opacities on chest X-ray. The risk of a significant adverse reaction in a localized area of the nose or sinuses is clearly less.[41] The lungs are also more inaccessible than the nose and the nose and sinuses offer ease of access for vector administration and experimental manipulation. For a variety of reasons, CF clinical trials are performed on adults. These patients invariably have severe pre-existing pulmonary compromise and any incremental benefits in pulmonary function afforded by gene therapy would be difficult to measure.

The nasal potential in CF provides a measurable endpoint for gene transfer experimentation. Nasal mucosa maintains and generates a potential difference across its surface and a characteristic voltage trace can be obtained in normal patients. In CF, the nasal mucosa, like the lung mucosa, exhibits the characteristic chloride transport abnormality. CF patients, because of their abnormal ion transport, produce a nasal potential that is different from normal both in its absolute negativity and in its response to certain pharmacologic influences.[41] This trace is so characteristic for CF that it is referred to as its bio-electric phenotype. This potential can be readily and reproducibly measured, in contrast to a number of bronchopulmonary indices and has been a target of gene therapy strategies in the nose.

In vitro and animal studies

Initially, the feasibility of gene transfer to airway cells was demonstrated *in vitro* and then in a variety of animal experiments. Only one year after the identification of the gene, Rich et al.[42] showed that expression of cDNA for wildtype CFTR corrected the Cl^- channel defect in cultured CF airway epithelia. Zabner et al.[43] demonstrated that recombinant adenoviral vectors could deliver CFTR cDNA safely in both cotton rats and rhesus monkeys. Transgenic CF mice provided a means to perform functional testing of CFTR gene expression and have even allowed reversal of the CF phenotype by gene therapy *in utero*.[44] Unfortunately, however, the CF mice do not produce a disease state comparable to the characteristic manifestations of CF on human lungs or other organ systems.[45] Recently Zabner et al.[30, 43, 46] have cloned transgenic CF porcine models that harbour targeted disruption of both CFTR alleles creating an animal model faithfully recapitulating the human phenotype. These transgenic animals also provide the opportunity to study the ion transport defect in the sinuses to further understand the pathogenesis of CF in the nose and sinuses.[47, 48] Innovative advances in basic science are the basis for the development of novel treatments for CF and for the progression to clinical trials to address questions that could only be answered in humans.

The human CF gene therapy trials: Adenovirus vector

Most of the early human cystic fibrosis gene therapy trials in the United States employed adenoviral vectors. Adenovirus has a degree of tropism for respiratory mucosa and a substantial body of knowledge already existed about adenoviruses as respiratory pathogens. Recombinant viruses are produced by replacing the DNA sequence responsible for replication with CFTR cDNA. The viruses are thus replication-deficient, but still remain sufficiently active to transport genetic material into the target cell. In 1993, Zabner et al.[49] reported correction of the CF bioelectric potential in a single-dose study where an escalating dose of vector encoding CFTR was applied to the nasal epithelium of three CF patients. Two CF patients underwent a sham procedure using saline and served as controls. No change was noted in the bioelectric phenotype in these two patients. One year later Crystal et al.[40] published a study in which an adenovirus containing CFTR cDNA was applied to both the upper and lower respiratory tracts of four patients. No statement was made about the nasal potential, but CFTR expression was detected by immunohistochemistry. This report was notable for the widely publicized event of pulmonary toxicity in one of the participants following vector delivery to the lungs. This toxicity was thought to be due to vector-induced inflammation and a reduction of viral vector dose

has largely overcome the problem of acute inflammation in subsequent studies. Hay et al.[50] produced a further study revealing partial improvement in the nasal potential in a single escalating-dose protocol the following year.

Knowles et al.[51] found molecular evidence of low efficiency gene transfer, but no correction of the nasal potential in a 1995 report. Their experiment involved administration of logarithmically increasing vector doses to four cohorts of three patients. A further study by Zabner et al.[52] in 1996 addressed the likely need for repeat vector administration. Six patients in two centres in the United States received four or five applications of sequentially escalating concentrations of recombinant adenovirus encoding *CFTR*. In this series, the correction of the nasal potential was more subtle and, importantly, evidence of immunologic response to repeat administration was noted.

Studies involving intra-pulmonary vector administration have scarcely fared better. Zuckerman et al.[53] delivered adenovirus encoding *CFTR* to a segmental bronchus in a dose-escalating study. There was evidence of low-level gene expression, as well as evidence of immune and inflammatory responses. In contrast, a single-escalating dose trial from France revealed gene transfer and no detectable immune or inflammatory response after administration of Ad-*CFTR*.[54]

Adenovirus vectors, while efficient delivery vehicles in the laboratory setting, clearly have difficulties in human trials. The human respiratory tract has evolved to efficiently repel a variety of microbial attacks, including of course adenoviruses. Adenovirus does not integrate into the genome and expression is transient thus repeat administration is required. With repeat administration come concerns of inflammation and immunogenicity. All viral vectors aimed at the epithelial surface suffer from the limitation of the viral receptors being located in the basolateral membrane, away from the cell surface. This may be in part overcome by the use of calcium chelators[55] that briefly disrupt tight epithelial functions, allowing the vector access to the basolateral membrane.

Adeno-associated virus vector

Serotypes 5 and 6 of the adeno-associated virus (AAV) enter airway cells from the apical surface.[45] Furthermore, AAV are thought to have the least cell toxicity and minimal immunoreaction compared to other viral vector counterparts and offer the potential for integration into the host genome. In practical terms, however, AAV are also associated with limited loading capacity, inefficient expression and delayed onset of expression, thereby may not be an ideal vector in treating CF. Indeed using the maxillary sinus model, 10 CF patients who had undergone prior maxillary antrostomy had AAV vector encoding CFTR applied to their maxillary sinus.[56, 57] Molecular evidence of gene transfer was detected as late as 41 days. A functional endpoint of maxillary sinus voltage measurement was also employed, although some evidence of functional improvement was detected at day 14. There appeared to be no effect on maxillary sinusitis, as assessed endoscopically. In summary, although the AAV vector is safe and stable the overall level of CFTR reconstitution has been too low to provide any functional improvement.[57, 58]

Lentivirus vector

Lentiviruses are an apparently attractive addition to the list of possible vectors. They have the ability to integrate into and consequently persist in the host genome. They can transduce non-dividing cells – an advantage in airway epithelium where cell turnover is generally low. While a variety of lentiviral options exists, most work has been carried out with the feline immunodeficiency virus (FIV).[45, 59]

Non-viral vectors

The shortcomings of viral vectors have led to the investigation of non-viral delivery systems. These have included purified or naked DNA in plasmid form or ballistic gene delivery, the so-called gene gun. Only exposed surfaces accessible to a microcarrier coated with DNA are candidates for the gene gun. Although successful in mice lungs this approach is difficult to incorporate in animals with larger lungs due to the lack of equipment design that would match the lung size. Most interest in non-viral gene delivery has centred on liposomes. Liposomes bind to DNA, spontaneously forming complexes that have high affinity for plasma cell membranes. DNA containing liposomes are incorporated into the cell by endocytosis. The advantages of non-viral vectors mainly revolve around safety. They are non-immunogenic and there is no potential for insertion mutagenesis. The main difficulties with non-viral vectors relate to transient expression and less efficient gene transfer as compared to viral vectors.

A 20% correction of nasal potential in nine patients, peaking at three days and disappearing by seven days, was reported by Caplen et al.[60] employing a cationic liposome vector. The vector was applied by a nasal pump spray, a practical method for likely repeat administration should clinical gene therapy become a reality. In 1997, Gill et al.[61] showed functional CFTR gene transfer in six of eight subjects in a further nasal mucosal/liposome study. Alton et al.[62] reported a placebo-controlled study of liposome-mediated CFTR transfer to the lungs and nasal mucosa of CF patients. The treatment group displayed some improvement in airway potential not seen in the liposome-only group. Interestingly, some aspects of toxicity were only seen with pulmonary administration leading the authors to question the value of the nasal model, at least from a safety viewpoint.

KEY POINTS

- Remarkable progress has been made in understanding the molecular basis of cystic fibrosis.
- Equally dramatic progress has been made in examining the basic science of vector production and vector interaction with airway cells.
- The challenge remains to apply this new knowledge and *in vitro* gene therapy success to a clinically relevant and measurable endpoint.

HEAD AND NECK CANCER

In 2000, an estimated 130 000 cases of new head and neck cancer were diagnosed in developed countries.[63] Advances in surgical techniques, radiation treatment strategies and chemotherapy medications have improved the survival and quality of life for many of these patients. Unfortunately, despite these innovations, treatment strategies for advanced stage cancer, squamous cancer and certain other head and neck cancer subtypes have not increased survival over the last 40 years.[64] In order to offer therapy in these advanced cases and to potentially augment current successful therapies, alternative treatment strategies have been examined. Many of these therapies have evolved as a result of our appreciation of the biological basis of oncogenesis. Specifically, this increased understanding has given us gene targets to potentially correct by either replacing or blocking the effect of the mutated gene. The various strategies used in gene therapy fall into four major categories: immune modulation, restorative gene replacement, selective oncolysis and chemosensitization. The following discussion will review both the methods to deliver the genes and the various therapeutic strategies used with these vectors.

Therapy strategies

Gene therapy offers a novel paradigm that leads to the destruction of tumour cells in cancer patients. To date, the approaches to target specific cancer cells fall into four basic categories: (i) chemosensitization; (ii) cytokine gene transfer; (iii) inactivation of protooncogene production; and (iv) selective oncolytic viruses. In the discussion to follow, the rationale and specific results from preliminary gene therapy trials will be presented.

CHEMOSENSITIZATION

Selective sensitization of cancer cells using gene therapy would be an ideal way to kill cancer cells. Using this approach, the expected gene is delivered only to cancer cells and then a second therapy (e.g. radiotherapy or chemotherapy) is used to induce killing in the cells that express the transgene. The best example of this model is delivery of herpes simplex thymidine kinase (HSV-TK).[31, 65] In this strategy, HSV-TK is delivered to cancer cells. Once expressed, this enzyme changes the prodrug gancyclovir to its toxic nucleoside analogue, which induces cell death. Using this system one would expect that 100% infection of the cancer cell would be required in order to be effective. In reality, a phenomenon termed the bystander effect increases the efficiency of such therapies. In the bystander effect, the infected cell spreads the expressed genes to the cells surrounding it via cell–cell contacts. Using mixing experiments, it has been shown that because of this effect, only half of the cells need to initially express the toxic gene to have the desired effect.[65, 66] Transfer of *p53* is another example of chemosensitization, as inclusion of this cellular gene sensitizes a cancer cell to apoptosis after treatment with either radiation therapy or chemotherapy.[67] Initial laboratory studies showed great promise for these types of therapies. Preclinical animal studies, however, showed only modest *in vivo* results.[31, 68] Efficiency and targeting have been shown to be difficult *in vivo*. Methods to increase cancer targeting may make these strategies more amenable for human trials in the future. These strategies include redesigning the adenovirus binding site to increase cancer cell selectivity.[69, 70]

IMMUNE MODULATION

The host immune response has been shown to play a role in cancer eradication. Immune suppression increases the risk of cancer development. In addition to generalized suppression, it has been shown that individuals with head and neck cancer lack an effective local immune response even early in the disease.[71] This immune dysfunction begins at the site of the tumour and progresses systemically with disease progression. This dysfunction occurs as a result of the normal immune system not recognizing the tumour cells. Causes of this include immunological ignorance,[72] downregulation of major histocompatibility complexes and loss of costimulatory receptor and pathways.[73] In some tumours, the cytokine stimulatory pathways (interleukin-2 (IL-2), interferon-gamma and IL-12) that normally upregulate the normal tumour immune response are depressed. One method to break this immune dysregulation is to overexpress the downregulated cytokines. The basis of the first cytokine-based trial for locoregional disease was compelling data from preclinical studies in mice.[74] A subsequent phase I trial using soluble proteins showed three complete responses and three partial responses in 10 patients.[75] All these responses were transient. A subsequent phase II trial showed similar transient responses which did not correlate with dose escalation.[76–78] However, when IL-2 is administered systemically, significant toxicity develops, including capillary leak syndrome. Gene therapy offers the ability to increase local expression and possibly improve tumour response while limiting systemic toxicity. Phase I trials using non-viral plasmids expressing IL-2 have been completed; demonstrating dose escalation safety, subsequent phase II trials are underway.[79] Even if such single agent cytokines do not prove useful, it may be possible to deliver combinations, which activate the immune pathway in a synergistic manner. Many such costimulatory questions are currently being examined in preclinical studies.[80–83] As our understanding of tumour immunity increases, better therapies aimed at reactivating the dysfunctional immune response will develop. Gene therapy may likely play a role in the delivery of such therapies.

RESTORATIVE GENE THERAPY

Restoring the function of a key cellular gene whose dysfunction has resulted in cancer progression can be a major goal of gene therapy. Several strategies to replace dysfunctional genes are currently being tested.[84, 85] The majority

of these involve the disrupted apoptotic pathway found in cancer cells. The most common mutations of these genes in squamous cell cancer of the head and neck are *p53* and *p16*. The most extensively studied of these genes in head and neck cancer is suppressor gene *p53*. This gene plays a role in triggering cell death in many different pathways involving apoptosis. Using an adenoviral vector, placed intra-lesionally, this mutated gene was delivered to 33 patients with locally recurrent squamous cell cancer in a phase I trial.[86] The study had two arms, surgical and non-surgical. In the surgical arm, patients received treatment pre-operatively, intra-operatively and post-operatively. Of these patients, four patients were alive and disease-free at one year, nine died of their disease and two died of unrelated causes. In the non-surgical arm, two of 17 had a partial response, six had stable disease and nine had progressive disease. The responses seen were most likely not due to effective replacement of mutated genes because *p53* status did not correlate with response.[86] Gendicine®, a drug with modified adenovirus harbouring *p53* gene was approved by the Chinese State Food and Drug Administration to treat head and neck cancer in China in 2004, becoming the first gene therapy approved for clinical use in humans.[87] However, the western version of Ad-p53 (Advexin®) for the treatment of head and neck cancer was refused for FDA approval in the USA in 2008.[87] The overall efficacy of Ad-p53 therapy in head and neck cancer continues to be closely evaluated.

SELECTIVE ONCOLYTIC VIRUS

Infection with wildtype adenovirus results in viral replication and eventual cell lysis. A therapy that harnesses this virus by only allowing replication in cancer cells would offer a self-propagating treatment that continues to produce virus and lyze cancer cells until a tumour is completely destroyed. Using replication-selective viruses to treat cancer is not entirely new. Initial reports as early as 1912 have used this approach in cancer therapy.[88] With the advent of increased knowledge of the genetic defects in cancer, we have been able to design vectors aimed at only replicating in cancer cells.[89, 90] The ONYX-015 is an adenovirus therapy design to accomplish this goal. ONYX-015 is missing the adenovirus *E1B* gene that normally inhibits the cellular *p53* genes. *p53* cellular expression allows only minimal viral expression. Approximately 60% of squamous cell carcinoma (SCCA) do not express functional *p53*. The ONYX-015 virus will selectively replicate only in SCCA cancers with *p53* mutations. Phase I and II clinical trials have shown significant promise with this strategy.[91–93] The initial phase I trial showed the virus was safe even when given in high doses.[64] Fever and injection site pain were the most common adverse effects. Phase II and III clinical trials are currently underway. In addition to developing this therapy as a single agent treatment, its role in combined therapies is also being examined. Phase II studies have shown this combined approach increases response rates from 33% for chemotherapy (5-fluorouracil (5-FU) and cisplatin) to a 65% response rate when intra-tumoural injections of ONYX-015 are added to the regimen.[93] Another potential advantage of the ONYX-015 vector is that if it is given intravenously it may circulate and offer potential therapy for distant metastasis. The safety of an intravenous delivery approach has been confirmed in phase I trials revealing safe delivery of high titers of viral vectors. The most common side effects were fever, rigours and elevated liver enzymes.[91] To more fully evaluate the potential of this strategy, more work has to be completed in areas of safety and delivery. Overall, however, this self-propagating tumour selective approach offers significant therapeutic promise.

FUTURE RESEARCH

The death of an 18-year-old man in a 1999 adenoviral gene therapy trial in Philadelphia caused scientists around the world to examine more critically the risks of human gene therapy experimentation. Three years later, a three-year-old boy died in France from a leukaemia-like condition, probably as a result of insertional mutagenesis in a retroviral gene therapy trial for SCID. Both of these tragic events have resulted in increased scrutiny for human gene therapy trials. These events have also brought into sharper focus the balance between the risks and the incredible promise of this treatment. However, following these major setbacks, gene therapy seems to have entered a new era with several promising clinical trial results together with recent approval of AAV-based Glybera® as a commercial drug in 2012 in Europe to treat familial lipoprotein lipase deficiency disease. Remarkable progress has been made in the last decade in improving the understanding of the basic science and the complexities of host–vector interaction. The challenge for the next decade continues to be the translation of this new expertise into clinical situations in a safe and effective manner.

KEY POINTS

- Our increased understanding of cellular oncogenesis will lead to the development of novel cancer therapies in the years to come.
- Gene therapy is likely to be a part of these therapies.
- A head and neck oncologist will need to understand both the viral vectors and their strategies of implementation to offer a full range of treatment to the cancer patient.

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CHAPTER 4

MECHANISMS OF ANTICANCER DRUGS

Sarah Payne and David Miles

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: mechanisms of chemotherapy; principles of tumour biology, chemotherapy and head and neck cancer; EGFR inhibitors, EGFR monoclonal antibodies; VEGF inhibitors, immunotherapy and head and neck cancer.

INTRODUCTION

Anticancer drugs have been developed and used medically since the 1940s, following the observation that nitrogen mustard gas, a chemical warfare agent used in the Second World War, interfered with haematopoiesis. Since then there have been significant therapeutic advances in the development of anticancer drugs although a cure for all cancer types remains an elusive goal. Alongside trials using more traditional types of chemotherapy, there is also now significant interest in developing more target-directed drug therapies and novel therapies, including immunotherapy.

PRINCIPLES OF CHEMOTHERAPY

Cancer is defined as the uncontrolled growth of cells coupled with malignant behaviour: invasion and metastasis. It arises through a complex interaction between genetic and environmental factors, causing genetic mutations in oncogenes and tumour suppressor genes. Chemotherapy aims to exploit the resulting differences in biological and proliferative characteristics between normal and cancer cells where most cytotoxic drugs preferentially affect dividing cells in tumours.

PRINCIPLES OF TUMOUR BIOLOGY

Cellular kinetics

CELL CYCLE

The cell cycle (**Figure 4.1**) is divided into a number of phases governed by an elaborate set of molecular switches. Normal non-dividing cells are in **G0**. When actively recruited into the cell cycle they then pass through four phases:

1. **G1:** the growth phase in which the cell increases in size and prepares to copy DNA
2. **S (Synthesis):** which allows doubling of the chromosomal material
3. **G2:** a further growth phase before cell division
4. **M (Mitosis):** where the chromosomes separate and the cell divides.

At the end of a cycle the daughter cells can either continue through the cycle, leave and enter the resting phase (**G0**) or become terminally differentiated. Most anticancer agents do not cause cell death during G0.

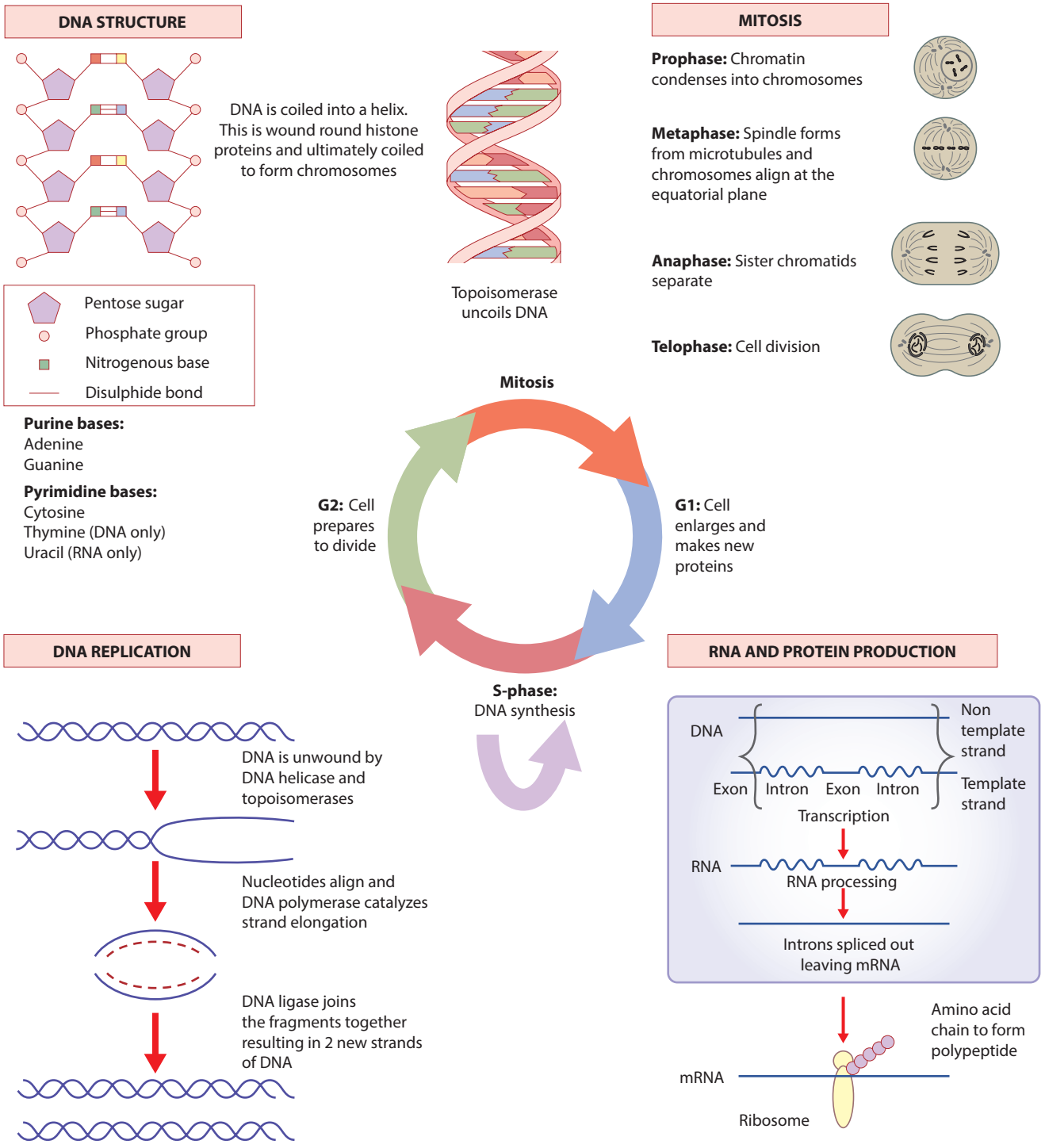


Figure 4.1 Cell cycle: possible targets for chemotherapy.

TUMOUR GROWTH

The kinetics of any population of tumour cells is regulated by the following:

- **Doubling time:** the cell cycle time, which varies considerably between tissue types
- **Growth fraction:** the percentage of cells passing through the cell cycle at a given point in time, which is greatest in the early stages
- **Cell loss:** which can result from unsuccessful division, death, desquamation, metastasis and migration.

Tumours characteristically follow a sigmoid shaped growth curve, in which tumour doubling size varies with tumour size. Tumours grow most rapidly at small volumes (Gompertzian kinetics). Chemotherapy is therefore more likely to be successful in eradicating a small tumour burden. As they become larger, growth is

influenced by the rate of cell death and the availability of blood supply.

Cell signalling

Cells respond to their environment via external signals called growth factors. These interact with cell surface receptors that activate an internal signalling cascade. This ultimately acts at the DNA level through transcription factors that bind to the promoter regions of relevant genes, stimulating the cell cycle and influencing cell division, migration and programmed cell death (apoptosis).

Metastatic spread

A tumour is considered malignant when it has the capacity to spread beyond its original site and invade surrounding tissue. Normally cells are anchored to the extracellular matrix by cell adhesion molecules, including the integrins. Abnormalities of the factors maintaining tissue integrity will allow local invasion and ultimately metastases of the tumour cells.

Mechanism of cell death

There are two main types of cell death: apoptosis and necrosis. Necrotic cell death is caused by gross cell injury, and results in the death of groups of cells within a tissue. Apoptosis is a regulated form of cell death that may be induced or is pre-programmed into the cell (e.g. during development) and is characterized by specific DNA changes and no accompanying inflammatory response. It can be triggered if mistakes in DNA replication are identified. Loss of this protective mechanism would allow mutant cells to continue to divide and grow thereby conserving mutations in subsequent cell divisions. Many cytotoxic anticancer drugs and radiotherapy act by inducing mutations in cancer cells that are not sufficient to cause cell death but that can be recognized by the cell, triggering apoptosis.

FRACTIONAL CELL KILL HYPOTHESIS AND DRUG DOSING

Theoretically the administration of successive doses of chemotherapy will result in a fixed reduction in the number of cancer cells with each cycle.[1] A gap between cycles is necessary to allow normal tissue to recover. Unfortunately these first order dynamics are not observed in clinical practice. Factors such as variation in tumour sensitivity and effective drug delivery with each course result in an unpredictable cell response.

CLASSIFICATION OF CHEMOTHERAPEUTIC AGENTS

Cytotoxic chemotherapy agents have traditionally been classified as phase-specific or non-phase-specific, depending on the effect on the cell cycle. The practical value of this classification is somewhat limited, and as a consequence drugs are more commonly defined by their particular mechanisms of action.

Phase-specific chemotherapy

These drugs (e.g. methotrexate, vinca alkaloids) kill proliferating cells only during a specific part or parts of the cell cycle. Antimetabolites such as methotrexate are more active against cells in the S phase whereas vinca alkaloids are more M-phase-specific. Attempts have been made to time drug administration in such a way that the cells are synchronized into a phase of the cell cycle that renders them especially sensitive to the cytotoxic agent. For example, vinblastine can arrest cells in mitosis. These synchronized cells enter the S phase together and can be killed by a phase-specific agent such as cytosine arabinoside. Most current drug schedules, however, have not been devised on the basis of cell kinetics.

Cell-cycle-specific chemotherapy

Most chemotherapy agents are cell-cycle-specific, meaning that they act predominantly on cells that are actively dividing. They have a dose-related plateau in their cell killing ability because only a subset of proliferating cells remains fully sensitive to drug-induced cytotoxicity at any one time. The way to increase cell kill is therefore to increase the duration of exposure rather than increasing the drug dose.

Some drugs have an equal effect on tumour and normal cells whether they are in the proliferating or resting phase (e.g. alkylating agents, platinum derivatives). They have a linear dose-response curve; that is, the greater the dose of the drug, the greater the fractional cell kill.

According to mechanism

ALKYLATING AGENTS

These include, for example, nitrogen mustards (melphalan and chlorambucil) and oxazaphosphorines (cyclophosphamide and ifosfamide).

These highly reactive compounds produce their effects by covalently linking an alkyl group (R-CH2) to a chemical species in nucleic acids or proteins. The site at which the cross-links are formed and the number of cross-links formed is drug-specific. Most alkylating agents are bipolar (i.e. they contain two groups capable of reacting with DNA). They can thus form bridges between a single strand or two separate strands of DNA, interfering with the action of the enzymes involved in DNA replication. The cell then either dies, or is physically unable to divide or triggers apoptosis. The damage is most serious during the S phase as the cell has less time to remove the damaged fragments.

HEAVY METALS

These include, for example, platinum agents (carboplatin, cisplatin and oxaliplatin).

Cisplatin is an organic heavy metal complex. Chloride ions are lost from the molecule after it diffuses into a cell allowing the compound to cross-link with the DNA strands, mostly to guanine groups. This causes intra- and inter-strand DNA cross-links, resulting in inhibition of DNA, RNA and protein synthesis.

Carboplatin has the same platinum moiety as cisplatin but is bonded to an organic carboxylate group.

Oxaliplatin contains a platinum atom complexed with oxalate and a bulky diaminocyclohexane (DACH) group. It forms reactive platinum complexes that are believed to inhibit DNA synthesis by forming interstrand and intrastrand cross-linking of DNA molecules.

ANTIMETABOLITES

Antimetabolites are compounds that bear a structural similarity to naturally occurring substances such as vitamins, nucleosides or amino acids. They compete with the natural substrate for the active site on an essential enzyme or receptor. Some are incorporated directly into DNA or RNA. Most are phase specific, acting during the S phase of the cell cycle. Their efficacy is usually greater over a prolonged period of time, so they are usually given continuously. There are three main classes: folic acid antagonists, pyrimidine analogues and purine analogues.

Folic acid antagonists

Methotrexate competitively inhibits dihydrofolate reductase, which is responsible for the formation of tetrahydrofolate from dihydrofolate. This is essential for the generation of a variety of coenzymes that are involved in the synthesis of purines, thymidylate, methionine and glycine. A critical influence on cell division also appears to be inhibition of the production of thymidine monophosphate, which is essential for DNA and RNA synthesis. The block in activity of dihydrofolate reductase can be bypassed by supplying an intermediary metabolite, most commonly folinic acid. This is converted to tetrahydrofolate that is required for thymidylate synthetase function (**Figure 4.2**).

Pyrimidine analogues

These drugs resemble pyrimidine molecules and work by either inhibiting the synthesis of nucleic acids (e.g. fluorouracil (**Figure 4.3**)), inhibiting enzymes involved in DNA synthesis (e.g. cytarabine, which inhibits DNA polymerase) or by becoming incorporated into DNA (e.g. gemcitabine), interfering with DNA synthesis and resulting in cell death.

Purine analogues

These are analogues of the natural purine bases and nucleotides. 6 mercaptopurine (6MP) and thioguanine are derivatives of adenine and guanine respectively. A sulphur group replaces the keto group on carbon-6 in these compounds. In many cases, the drugs require initial activation. They are then able to inhibit nucleotide biosynthesis by direct incorporation into DNA.

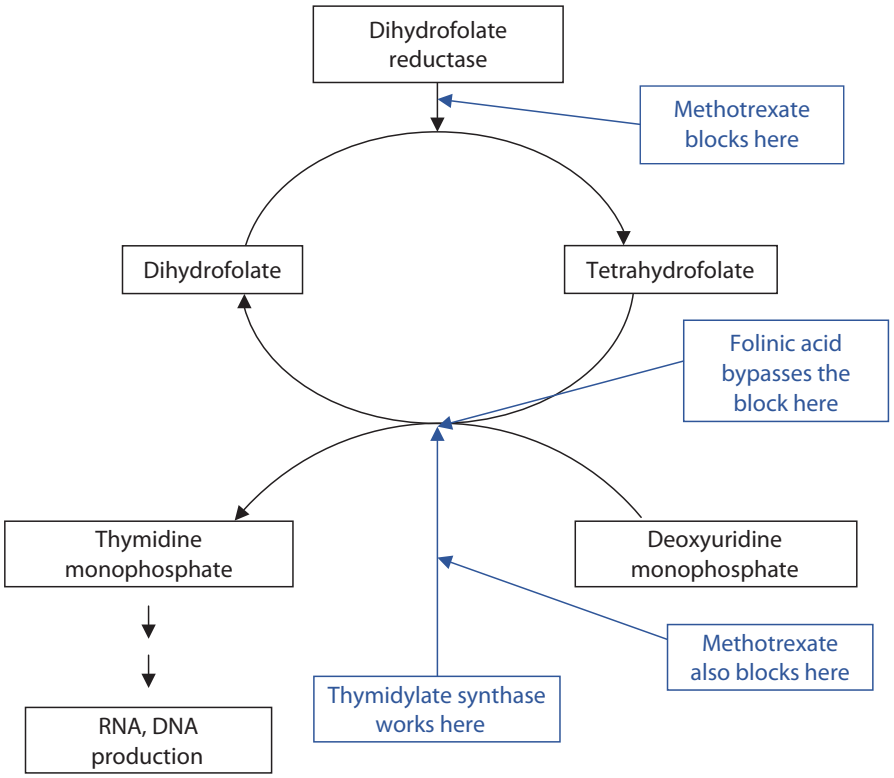


Figure 4.2 Mechanism of action of cytotoxic drugs: methotrexate.

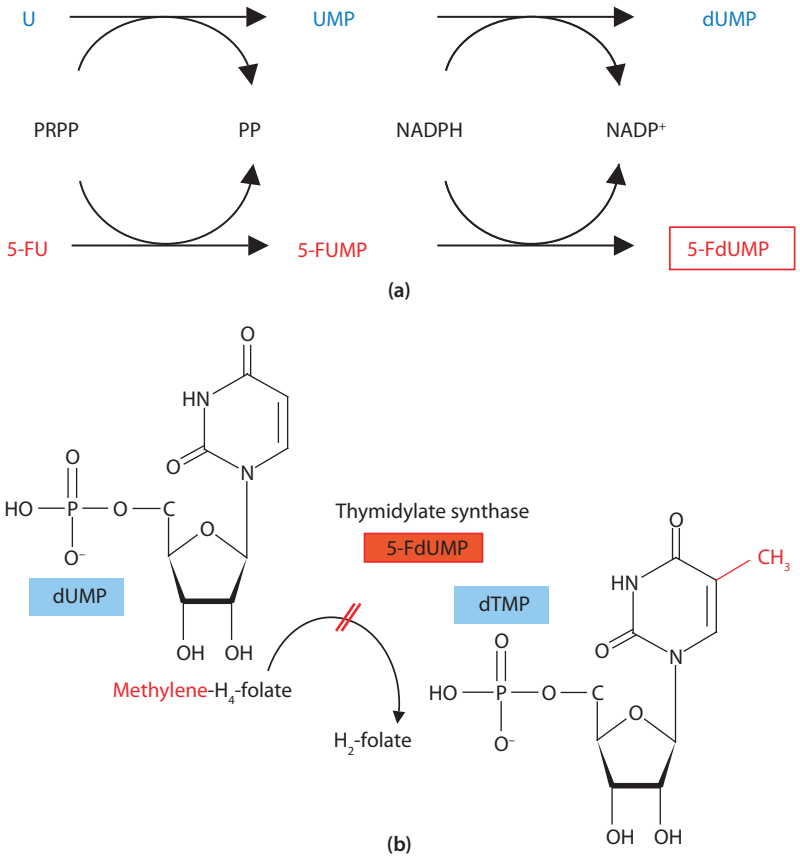


Figure 4.3 Mechanism of action of cytotoxic drugs: fluorouracil. 5-Fluorouracil (5-FU) can participate in many reactions in which uracil would normally be involved. Firstly, it has to be converted to its active form, 5-fluoro-2 deoxyuridine monophosphate (5-FdUMP) **(a)**. This then interferes with DNA synthesis by binding to the enzyme thymidylate synthetase, causing it to be inactivated **(b)**. The binding can be stabilized by the addition of folinic acid. 5-FdUMP, 5-fluorodeoxyuridine monophosphate; 5-FU, 5-fluorouracil; 5-FUMP, binding can be stabilized by the addition of folinic acid. 5-FdUMP, 5-fluorodeoxyuridine monophosphate; 5-FU, 5-fluorouracil; 5-FUMP, 5-fluorouridine monophosphate; dTMP, deoxythymidine monophosphate; dUMP, deoxyuridine monophophase; NADP, nicotinamide adenine dinucleotide phosphate; NADPH, reduced form of nicotinamide adenine dinucleotide phosphate; PP, pyrophosphate; PRPP, 5-phospho-alpha-D-ribose 1-diphosphate; U, uracil; UMP, uridine monophosphate.

CYTOTOXIC ANTIBIOTICS

Most antitumour antibiotics have been produced from bacterial and fungal cultures (often *Streptomyces* species). They affect the function and synthesis of nucleic acids in different ways:

- **Anthracyclines** (e.g. doxorubicin, daunorubicin, epirubicin) intercalate with DNA and affect the topoisomerase II enzyme. This DNA gyrase splits the DNA helix and reconnects it to overcome the torsional forces that would interfere with replication. The anthracyclines stabilize the DNA topoisomerase II complex and thus prevent reconnection of the strands.
- **Actinomycin D** intercalates between guanine and cytosine base pairs. This interferes with the transcription of DNA at high doses. At low doses DNA-directed RNA synthesis is blocked.
- **Bleomycin** consists of a mixture of glycopeptides that cause DNA fragmentation.
- **Mitomycin C** inhibits DNA synthesis by cross-linking DNA, acting like an alkylating agent.

SPINDLE POISONS

Vinca alkaloids

The two prominent agents are vincristine and vinblastine, which act as mitotic spindle poisons. They bind to tubulin, the building block of the microtubules, which inhibits further assembly of the spindle during metaphase, thus inhibiting mitosis. Other examples include vindesine and vinorelbine.

Taxoids

Paclitaxel (Taxol) and docetaxel (Taxotere) promote assembly of microtubules and inhibits their disassembly. Direct activation of apoptotic pathways has also been suggested to be critical to the cytotoxicity of this drug.[2]

TOPOISOMERASE INHIBITORS

Topoisomerases are responsible for altering the 3D structure of DNA by a cleaving/unwinding/rejoining reaction. They are involved in DNA replication, chromatid segregation and transcription. It has previously been considered

that the efficacy of topoisomerase inhibitors in the treatment of cancer was based solely on their ability to inhibit DNA replication. It has now been suggested that drug efficacy may also depend on the simultaneous manipulation of other cellular pathways within tumour cells.[3] The drugs are phase-specific and prevent cells from entering mitosis from G2. There are two broad classes:

1. **Topoisomerase I inhibitors (e.g. irinotecan and topetcan).** These bind to the enzyme-DNA complex, stabilizing it and preventing DNA replication.
2. **Topoisomerase II inhibitors (e.g. etoposide).** These stabilize the complex between topoisomerase II and DNA that causes strand breaks and ultimately inhibits DNA replication.

CHEMOTHERAPY IN HEAD AND NECK CANCER

Chemotherapy is regularly employed in the management of head and neck cancer. It has not changed the cure rates of locally advanced head and neck cancer. It has, however, allowed improved organ preservation when combined with radiotherapy and has led to a reduction in rates of distant metastases.

CHOICE OF CHEMOTHERAPY IN HEAD AND NECK CANCER

The single agents active in head and neck cancer, with response rates between 15% and 40%, include methotrexate, cisplatin, carboplatin, fluorouracil, ifosfamide, bleomycin, paclitaxel, and docetaxel. Cisplatin is one of the most active drugs against squamous head and neck cancer.[4] Taxoids and gemcitabine are gaining favour and are being incorporated into many current drug trials.

CHEMOTHERAPY STRATEGIES

Combination chemotherapy

Combinations of cytotoxic agents are widely used for many cancers and may be more effective than single agents. Possible explanations for this include:

- exposure to agents with different mechanisms of action and non-overlapping toxicities
- reduction in the development of drug resistance
- the ability to use combinations of drugs that may be synergistic.

Combination chemotherapy in head and neck cancers usually includes cisplatin.

Adjuvant chemotherapy

This is the administration of chemotherapy after curative surgery or radiotherapy, in patients considered to be at high risk of relapse. The intention is to eradicate micrometastatic disease. Randomized trials assessing the use of adjuvant chemotherapy for the patients with head and neck squamous carcinoma do not suggest a significant survival benefit.[5] [Level 1 evidence]

Neoadjuvant chemotherapy (induction chemotherapy)

Neoadjuvant, or induction chemotherapy, is the use of chemotherapy prior to definitive surgery or radiotherapy in patients with locally advanced disease. The intention is to reduce the tumour bulk before definitive treatment and hence improve local and distant control of the disease. This will also achieve greater organ preservation and overall survival.

Numerous phase III trials have considered the benefit of neoadjuvant chemotherapy. Unfortunately their approaches have been quite heterogeneous, making meta-analysis difficult.[6] VA Laryngeal Cancer Study Group evaluated induction chemotherapy (cisplatin/5-FU) followed by radiotherapy versus surgery and radiotherapy among patients with stage III/IV disease.[7] Chemotherapy responders subsequently received radiotherapy; non-responders underwent laryngectomy. An 85% chemotherapy response rate was documented in this study. No survival differences were noted, but there was the benefit of laryngeal preservation among responders. Subsequent studies have continued to examine the topic of organ preservation. The Radiation Therapy Oncology Group (RTOG) 91-11 trial randomized 547 patients with stage III/IV disease to three treatment arms; induction cisplatin/5-FU followed by radiotherapy, cisplatin-based concurrent chemoradiotherapy, and radiotherapy alone.[8] Concurrent chemoradiation was superior to induction chemotherapy or radiotherapy alone in terms of organ preservation and locoregional control. No differences were observed in relation to overall or disease-free survival comparing induction therapy or concurrent chemoradiation. Taxane-platinum-based combinations have more recently been evaluated and appear superior to cisplatin-5-FU in terms of overall survival, progression free survival, locoregional failure and distant failure for loco-regionally advanced disease.[9, 10] Toxicity, however, can be quite high.

The role of neoadjuvant/induction chemotherapy continues to remain controversial. It is currently considered on a case-by-case basis and further studies are planned. [Level 1 evidence]

Concurrent chemoradiation (CRT)

This involves the synchronous use of chemotherapy and radiotherapy. In the context of head and neck cancer, this is often used after definitive surgery. The rationale is that chemotherapy can sensitize tumours to radiotherapy by inhibiting tumour repopulation, preferentially killing hypoxic cells, inhibiting the repair of sublethal radiation damage, sterilizing micrometastatic disease outside of the radiation fields and decreasing the tumour mass, which leads to improved blood supply and reoxygenation.

Fractionated radiotherapy, in turn, may sensitize tumours to chemotherapy by inhibiting the repair of drug-induced damage and by decreasing the size of the tumour mass, leading to improved blood supply and enhanced drug delivery. Patients with high-risk features (positive lymph nodes, positive margins, extracapsular spread (ECS), perineural/vascular invasion) have been shown to demonstrate an improved 5-year survival by 13%.[11] Two pivotal phase III studies (RTOG 9501 and EORTC 22931) demonstrated improved locoregional control with the addition of chemotherapy in high-risk patients[12, 13] where a post-hoc analysis of the trials confirmed that ECS of tumour and positive margins were the most important indications for adjuvant chemoradiation.[14] At present there is still debate regarding the optimum chemoradiotherapy programme that should become the standard of care.

Local, regional and metastatic recurrence

Patients with localized squamous cell carcinoma of the head and neck are treated with potentially curative therapy. Unfortunately, many patients develop recurrent disease. The recurrence rate in early-stage squamous cell head and neck cancer is approximately 10–20%,[15] whereas the recurrence rate in locally advanced is approximately 50% with a predominance of locoregional failure.[15–18] Patients with recurrent or metastatic squamous cell head and neck cancer have a poor prognosis with median overall survival of under 1 year[19] and is mostly made up of patients who have recurrence after initial treatment for localized disease. A small percentage of patients with localized recurrence can be treated with curative intent, but the vast majority receive palliative treatment with systemic therapy.

Chemotherapy in the first line setting is associated with disappointing opportunities for disease control. Objective response rates to commonly used therapies (including methotrexate, docetaxel, paclitaxel) drop off to well under 20% and median survival in phase 3 trials has been reproducibly reported at approximately 5–6 months.[19–23]

There is clearly a need to explore novel therapies to try to improve disease outcomes. Options being explored include targeted therapies and immunotherapy.

NOVEL THERAPIES FOR THE FUTURE

Despite the introduction of new cytotoxic drugs, the management of advanced head and neck cancer remains challenging. Over the last years interest has focused on the role of novel agents with more targeted mechanisms of action or agents that are able to manipulate the immune system to provide tumour control (immunotherapy).

Targeted therapy

Targeted therapy aims to specifically act on a well-defined target or biologic pathway that, when inactivated, causes regression or destruction of the malignant process. The main strategies of research have looked at the use of monoclonal antibodies or targeted small molecules.

Monoclonal antibodies

Monoclonal antibodies can be derived from a variety of sources:

- murine – mouse antibodies
- chimeric – part mouse/part human antibodies
- humanized – engineered to be mostly human
- human – fully human antibodies.

Murine monoclonal antibodies may themselves induce an immune response that limits repeated administration. Humanized and, to a lesser extent, chimeric antibodies are less immunogenic and can be given repeatedly.

There are several proposed mechanisms of action of monoclonal antibodies as anticancer agents.[24] These include:

- Direct effects may include:
  - induction of apoptosis
  - blocking of the receptors needed for cell proliferation/function
  - anti-idiotype antibody formation, determinants amplifying an immune response to the tumour cell.
- Indirect effects may include:
  - antibody dependent cellular cytotoxicity (ADCC, conjugating the 'killer cell' to the tumour cell)
  - complement-mediated cellular cytotoxicity (fixation of complement leading to cytotoxicity).

A desirable target for MAbs would have the following properties:

- Wide distribution on tumour cells
- High level of expression
- Bound to tumour, allowing cell lysis
- Absent from normal tissues
- Trigger activation of complement on MAb binding
- Remains unchanged following antibody binding to ensure it remains visible to the immune system (i.e. is not internalized or shredded).

Antibodies have also been used as vectors for the delivery of drugs and radiopharmaceuticals to a target of tumour cells.

Interest in the development of antibodies for solid tumours has become increasingly popular, especially with respect to the epidermal growth factor receptor and the vascular endothelial growth factor receptor.

Epidermal growth factor receptor biology

Epidermal growth factor receptor (EGFR) biology is a 170 kD transmembrane protein composed of an extracellular ligand-binding domain, a transmembrane lipophilic region and an intracellular protein tyrosine kinase domain (**Figure 4.4**). When a substrate binds to the receptor, the

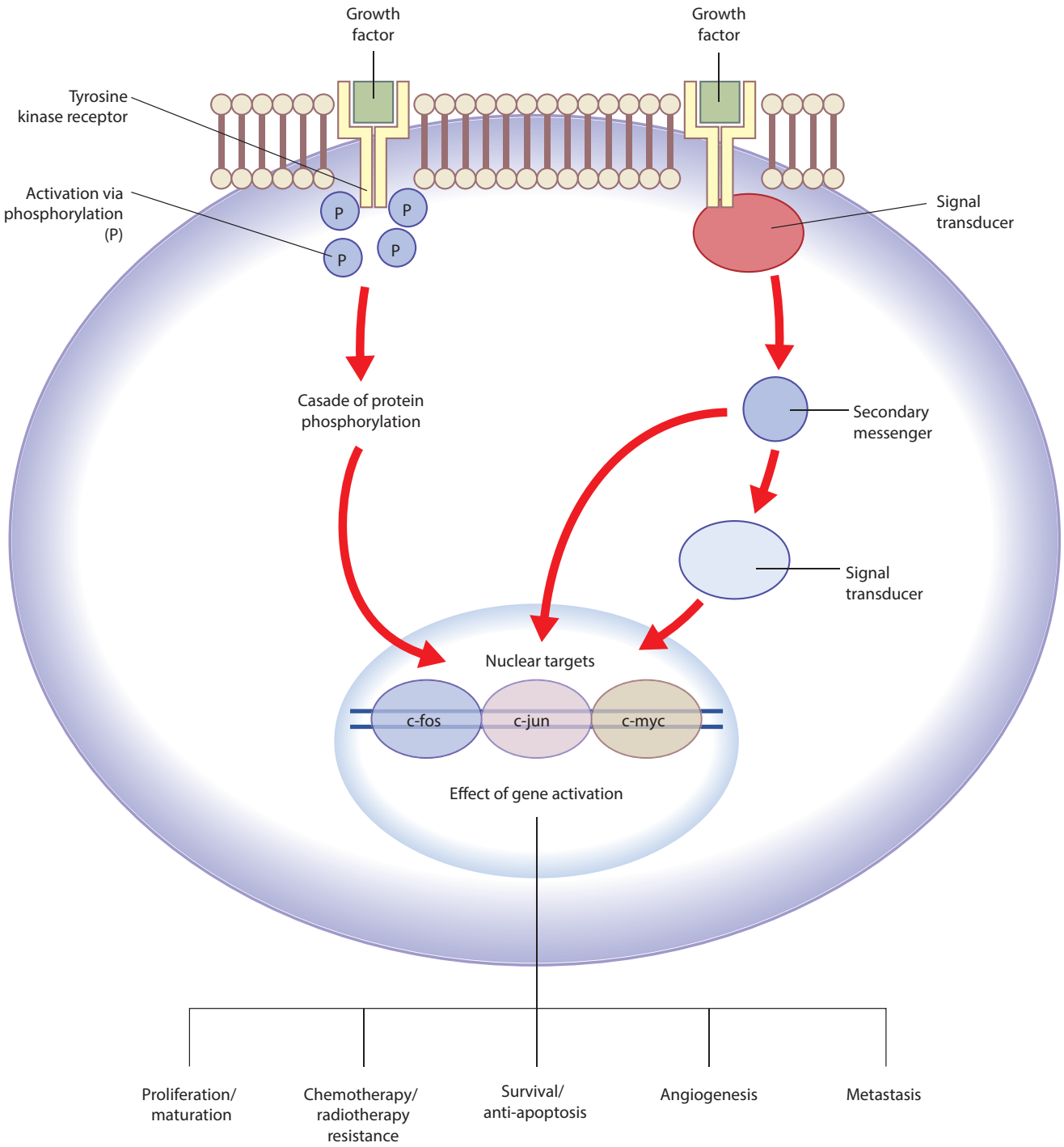


Figure 4.4 Simplified epidermal growth factor receptor signal transduction pathways and opportunities for intervention. GRB2, growth factor receptor binding protein 2; MAPK, mitogen-activated protein kinase; MEK, MAPK/extracellular signal related kinase; SOS, guanine nucleotide exchange factor (son of sevenless); c-fos, c-jun and c-myc, nuclear targets involved in gene transcription/cell cycle progression; P, phosphate; TGFa, transformation growth factor a; PI3-K, phosphotidyinositol 3; AKT, serine/threonine kinase, prosurvival protein; STAT, signal transducing activation of transcription.

ligand-receptor complex dimerizes and is internalized by the host cell. This activates an intracellular protein kinase by autophosphorylation, which in turn activates signal transduction pathways, influencing cell function. This can lead to cell proliferation, as well as invasion and metastasis.

Several investigators have described amplification of the EGFR gene and overexpression of the EGFR surface membrane protein in a large number of human cancers, including squamous cell carcinoma of the head and neck.[25] Overexpression is associated with increased proliferative capacity and metastatic potential and is an independent

indicator of poor prognosis.[26] Blockade of the EGFR pathway has been shown to inhibit the proliferation of malignant cells and also appears to influence angiogenesis, cell motility and invasion.[27] Various strategies have been investigated to manipulate EGFR.

Monoclonal antibodies against EGFR

An example of a monoclonal antibody developed against EGFR is the chimeric IgG antibody cetuximab which has the binding affinity equal to that of the natural ligand and can effectively block the effect of epidermal growth factor and transforming growth factor α.[6, 8] It also causes internalization of EGFR and targets the cytotoxic immune effector cells towards EGFR expressing tumour cells.[27]

LOCOREGIONALLY ADVANCED HEAD AND NECK CANCER

The addition of cetuximab to radiotherapy has been shown to improve locoregional control and survival when compared to primary radiotherapy alone for patients with locoregionally advanced head and neck cancer.[28, 29] Randomized controlled trials however have not demonstrated superiority or non-inferiority of cetuximab-radiotherapy compared to concomitant chemoradiotherapy and so cetuximab-radiotherapy is considered an option for treatment in patients who are not candidates for the chemotherapy used with chemo-radiotherapy. [30] [Level 1 evidence]

RECURRENT/METASTATIC HEAD AND NECK CANCER

The addition of cetuximab to platinum-based chemotherapy prolongs median overall survival, progression-free survival, best overall response rate, disease control rate and time to treatment failure in patients with recurrent or metastatic squamous cell carcinoma of the head and neck compared to platinum-based chemotherapy alone and is an option to consider in the first line setting.[31, 32] [Level 1 evidence]

Targeted small molecules against EGFR

Gefitinib (Iressa) and erlotinib (Tarceva) are orally active epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) that block the EGFR signalling cascade, thereby inhibiting the growth, proliferation and survival of many solid tumours. They have activity as single agents in patients with recurrent or metastatic head and neck cancer, and have an acceptable safety profile compared with conventional chemotherapy.[33, 34] So far, results in locally advanced disease have not demonstrated additional benefit with these drugs.[35, 36]

Inhibitors of angiogenesis

Angiogenesis (**Figure 4.5**) is the process of new blood vessel formation, triggered by hypoxia and regulated by numerous stimulators and inhibitors. It is vital for cancer development.

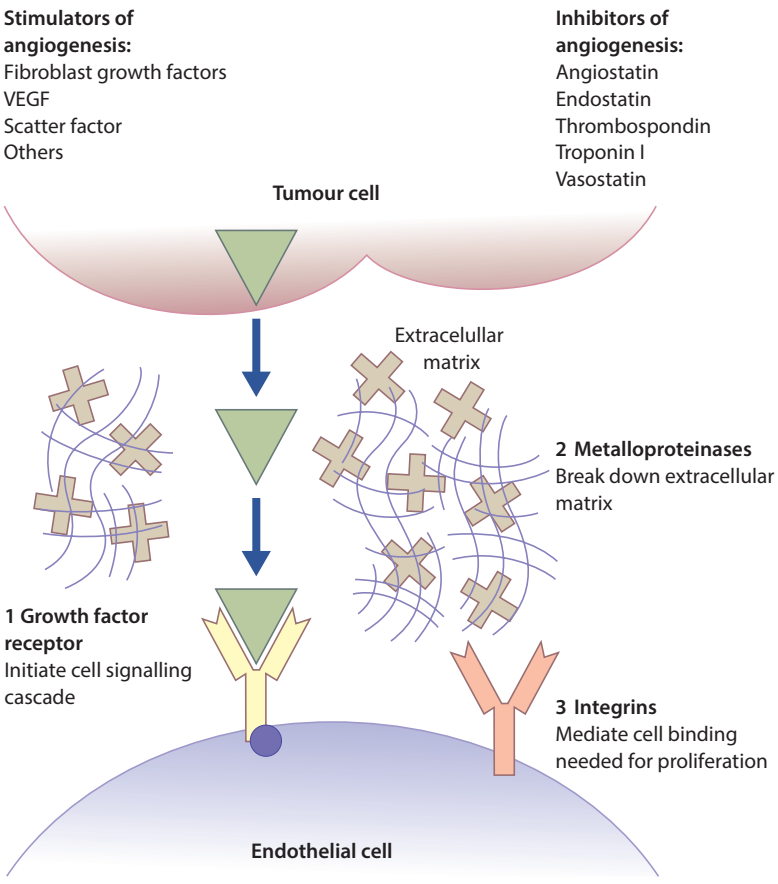


Figure 4.5 Schematic representation of possible anti-angiogenesis targets, including natural stimulators and inhibitors.

A tumour cannot exceed beyond 2–3 mm^3 without inducing a vascular supply. New vessels develop on the edge of the tumour and then migrate into the tumour. This process relies on degradation of the extracellular matrix surrounding the tumour by matrix metalloproteinases such as collagenase that are expressed at high levels in some tumour and stromal cells. Angiogenesis is then dependent on the migration and proliferation of endothelial cells.

It has been found that anti-angiogenic agents tend to be cytostatic rather than a cytotoxic, hence stabilizing the tumour and preventing spread. As a consequence they may be valuable for use in combination with cytotoxic drugs, as maintenance therapy in early stage cancers or as adjuvant treatment after definitive radiotherapy or surgery. There is evidence to support the fact that suppressing angiogenesis can maintain metastases in a state of dormancy.[34]

Vascular endothelial growth factor receptor

Vascular endothelial growth factor (VEGF) receptor VEGF is a multifunctional cytokine released in response to hypoxia and is an important stimulator of angiogenesis. It binds to two structurally related transmembrane receptors present on endothelial cells. High VEGF protein and receptor expression has been demonstrated in certain head and neck cancers and is associated with a higher tumour proliferation rate and worse survival.[37]

Monoclonal antibodies against VEGFR

Bevacizumab (Avastin) is a humanized murine monoclonal antibody targeting VEGF. It is the first anti-angiogenic drug to have induced a survival advantage in cancer therapy.[38] The use of bevacizumab in head and neck cancer is supported by information derived in preclinical trials.[39] Currently clinical trials are exploring the feasibility and the therapeutic potential of a combination of bevacizumab and EGFR-targeted drugs.[40, 41]

IMMUNOTHERAPY

Immune checkpoint inhibitors are a new class of systemic agents being increasingly used in oncology. They function by interrupting the immunosuppressive pathways, called inhibitory checkpoints, which are normally used by tumour cells to prevent detection and elimination by the host immune system.[42, 43] Molecular targets of immune checkpoint inhibitors are found on T cells and include cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein 1 (PD-1) receptor. A third common target is PD-L1, which is found on both tumour and immune cells and is the corresponding ligand to PD-1.[42, 43] There is interest in the role of immune checkpoint inhibitors particularly in tumours with high levels of endogenous PD-L1 expression, which include some head and neck squamous cell carcinomas.[42] Current available clinical trial-generated evidence suggests that immune checkpoint inhibitors present a promising new opportunity for a small number of patients with very advanced disease who progress on standard first-line chemotherapy. Objective response rates to immune checkpoint inhibitors are around 20% in patients who have progressed on first-line chemotherapy combinations for recurrent or metastatic squamous head and neck cancer irrespective of PD-L1 expression status.[42] Data suggest that PD-L1 expression correlates with better efficacy to immune-checkpoint inhibitors; however, this correlation is not definitive and no other reliable biomarker has currently been identified for effectively selecting optimally responsive patient subgroups.[42, 44] Ongoing studies are investigating the role of immune checkpoint inhibitors in patients with both locally advanced disease and metastatic disease.

CONCLUSION

The majority of conventional chemotherapeutic agents cause cell death by directly inhibiting the synthesis of DNA or interfering with its function. This means that they are often not tumour-specific and are associated with considerable morbidity. Trials have demonstrated that combination chemotherapy regimens can cause dramatic regression of head and neck tumours, especially when used concomitantly with radiotherapy. Unfortunately this has not been associated with an increase in survival rates.

There is now considerable excitement over the development of new target-directed cytotoxic agents. These have been developed to modulate or inhibit specific molecular targets critical to the development of or control of cancer cells. Particular interest has focused on the field of monoclonal antibody development, particularly in relation to the epidermal growth factor. Other drugs affecting signal transduction, programmed cell death, transcription regulation, matrix invasion, angiogenesis and immune modulation are currently involved in clinical trials. The results of these are eagerly awaited and will potentially radically change current therapeutic strategies.

FUTURE RESEARCH

The effect of chemotherapy on non-metastatic head and neck cancers is still being evaluated. The optimum combination of chemotherapeutic agents and the timing of their use in relation to surgery have not been defined, especially in combination with radiotherapy. As this continues to be assessed, significant advances are being made in relation to more specific targeted therapies. The results of clinical trials with these new agents and their incorporation into management regimens are eagerly awaited.

KEY POINTS

- Traditional chemotherapy agents interfere with DNA synthesis and function and are classified according to their mechanism of action.
- Unfortunately they are associated with significant side-effect profiles.
- The role of chemotherapy in head and neck cancer is still being defined but there is increasing popularity of concurrent chemotherapy and radiotherapy regimens.
- Current research, however, is now focusing on more novel approaches including molecular targeted therapy and immunotherapy.
- Strategies recently have particularly looked at the use of monoclonal antibodies.
- There are also drugs being designed that specifically influence signal transduction, cell cycle regulation, apoptosis, matrix invasion and angiogenesis.

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CHAPTER 5

RADIOTHERAPY AND RADIOSENSITIZERS

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: neoplasms, radiotherapy, fractionation, radiation-sensitizing agents, chemotherapies, hypoxia and immunotherapies.

INTRODUCTION

Radiotherapy is the therapeutic use of ionizing radiation, typically usually high-energy X-rays (photons). Other modalities (e.g. protons) may be used to optimize the therapeutic effect by seeking to optimize the conformality to the target volume. As the name implies, the radiation interacts with matter by ejecting electrons from their orbits, resulting in ionization. The ejected particles interact with further atoms, ejecting further electrons and causing a cascade of ionizations after each initial interaction. In biological material, the free radicals that result, primarily from interactions with water molecules, are highly reactive and are particularly damaging to the cell when they interact with DNA. In total, about 100 distinct lesions have been identified amongst which strand breaks (i.e. sugar-phosphate backbone damage) predominate in terms of importance at the cellular level. Traditionally, the main cause of cell death following radiation was thought to result from direct damage to the DNA. This has gradually been modified over the last few years as an increasing number of studies have shown that ionizing radiation also targets the plasma membrane where it can initiate multiple signal transduction pathways, many of which lead to radiation-induced apoptosis (e.g. hydrolysis of the membrane phospholipid sphingomyelin by the enzyme sphingomyelinase resulting in the generation of ceramide). DNA damage in mammalian cells triggers three pathways: cell cycle arrest, DNA repair and apoptosis. Historically, three types of damage have been recognized: sublethal damage (SLD), potentially lethal damage (PLD) and irreparable or lethal damage. These categories may not reflect different types of damage, but instead reflect the category of repair processes that act to modify the radiation-induced lesions. If the DNA damage is particularly severe then cell death may result, usually when the cell attempts to divide.

The fact that cell death occurs at a time after the actual exposure to irradiation, depending on the time of cell division (and also upon the tissue structure and life span of the mature functional cells), explains one of the most important clinical observations about radiotherapy, that tissues that are dividing rapidly manifest the effects of radiation sooner than those where cell division is slow. Tissues such as bone marrow, skin and the mucosa of the upper aerodigestive tract manifest the effects of radiation within days (i.e. they are classed as 'acute-reacting' tissues). Connective tissue, bone and neural tissue may only show the effect years later, hence being defined as 'late-reacting' tissues. Squamous head and neck cancers, as might be expected, behave as an acute-reacting tissue, like the squamous mucosa from which they originate. In addition to the kinetics (turnover rate) of the population as a whole, the response of tissues and organs is also dependent upon inherent cellular radiosensitivity. The sensitivity of the cell to radiation is determined to some degree by its state of maturity and its functional role. Generally speaking, immature cells are considerably more sensitive to radiation than mature cells and as mitotic activity increases (metabolic activity, proliferation), sensitivity also increases. There is general agreement as to which of the target cells is responsible for acute effects (stem cells of

rapidly dividing tissues), but the target cells that determine the late effects have not been defined clearly. In general, if any clonogens from acute responding normal (healthy) tissues survive they can rapidly repopulate and replace lost cells. Late-reacting tissues do not have this ability to repopulate rapidly and therefore whilst most acute reactions heal, most late reactions, if anything, may continue to progress with time. It is the severity of predicted late effects that can limit the delivered dose of radiation. Differentiating between acute and late effects is exploited in the concept of fractionation.

FRACTIONATION

The differences between 'acute-reacting' and 'late-reacting' tissues are thus very important to the science of fractionation in radiotherapy. At low single doses, tumour and early-responding tissues are more sensitive than late-responding tissues (more cells are in cycle). At high doses, the non-dividing late-responding cell response that compensates for tissue loss is slow and therefore organs appear more intrinsically radiosensitive than rapidly dividing tumour and early-responding tissues.

A fraction is the individual dose of radiation delivered at a single session of radiotherapy; in the treatment of head and neck cancer a total course of radiotherapy will take several weeks and consist of numerous fractions. The fraction size, measured in physical dose, is traditionally and almost invariably constant throughout a course of radiotherapy. In conventional radiotherapy, fractions are given once a day, five days per week typically for 4–6 weeks. This accords with normal working practices, rather than being founded on a sound scientific basis, and alternative fractionation schedules have been much studied in recent years.

In general, the relationship between the dose of radiation in a single fraction and the number of cells killed approximates closely to a straight line on a semi-logarithmic graph, conventionally drawing dose arithmetically on the x-axis and surviving fraction of cells on a declining logarithmic scale on the negative y-axis. This is shown in Figure 5.1. It should be noted though that while the general relationship is linear, at the lowest doses this is not so, and the line is curved (i.e. it has a 'shoulder'). For most cells, the range in which this shoulder applies is close to most widely used fraction sizes (in other words around 2 Gy) and this has important implications for clinical practice.

The extent of the 'curviness' of the graph varies with many factors. Most importantly for day-to-day routine radiotherapy, late-reacting tissues generally have a more 'curvy' graph than do acute-reacting ones and therefore increasing the fraction size even modestly tends to have a greater effect on late-reacting as opposed to early-reacting tissues: in other words there is more 'late-reacting' tissue damage. The shoulder on the graph is a reflection of the capacity for DNA to repair damaged cells. Thus cells from patients with ataxia-telangiectasia show almost no curve. This is because these patients are deficient in certain mechanisms that act to repair DNA.

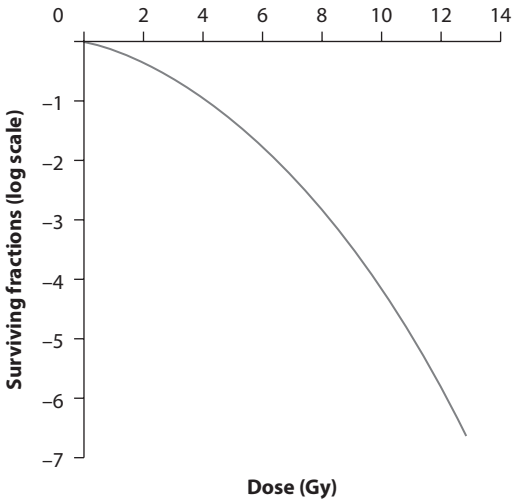


Figure 5.1 Typical radiation dose-response curve following a single radiation exposure. Note that the radiation dose (x-axis) is a linear scale, while surviving fraction (y-axis) is logarithmic. The effect for small doses is relatively 'curvy' compared to that for higher. The consequences of this are explained in the text.

The importance of this shoulder region to radiotherapy relates to the fact that as long as sufficient time elapses between fractions, a subsequent dose of radiation has the same shaped survival curve as an initial dose, including the shoulder (i.e. full repair of the initial damage has occurred). Thus, if the shoulder is considerable, the net effect of two doses is very much less than if the same total physical dose was given as a single fraction. The general shape of the cell survival curves, including the shoulder, is probably best described by the linear quadratic equation:

$$SF = N/No = e^{-}(\alpha D + \beta D^2) \quad \text{or} - \ln SF = \alpha D + \beta D^2$$

In this equation, *No* is the number of cells in the population originally and *N* is the number surviving after irradiation with dose *D*, with *N*/*No* representing the surviving fraction (*SF*). Only two parameters, α (the initial slope) and β (the terminal slope) are required to describe the dose–response curve. Absolute values of α and β are not well known, but the alpha/beta ratio (i.e. the dose at which the contribution to killing from the α component or nonreparable damage, is equal to that of the β component or reparable damage) has been identified with a reasonable degree of approximation for numerous tissues. In general, the α/β ratio tends to be low for late-reacting tissues, and for these the shoulder on the graph is considerable, whereas it is high for acute-reacting tissues, where the shoulder is less marked. When this is translated into practice, the total effect is more fraction size-dependent for late-reacting tissues than for acute-reacting tissues. Thus, for example, the effect achieved with a dose of 70 Gy in 2 Gy fractions given over 7 weeks will differ less from the effect of the same total dose in fractions of 1 Gy for acute-reacting tissues than it will for late-reacting tissues. There will be more 'sparing' of late-reacting tissues by breaking the same total dose up into a greater number of smaller fractions. Having said this, because of the

ability of early-reacting tissue to repopulate rapidly, these comparisons are only valid if the overall treatment time is the same for the different schedules. Otherwise the ability of head and neck squamous cell carcinomas (SCC) like acute-reacting normal tissues will negate the intended benefit. This will necessitate a shorter inter-fraction interval for the schedule of many small fractions. This interval still needs to be long enough though for adequate repair of sublethal damage to occur if the full sparing effect on late reactions by reducing factor size is to be seen.

The corollary of this is that by using many small fractions it will be possible to give a higher total dose, but without increasing the amount of late damage, whereas a greater effect will be seen on acute-reacting tissues and thus squamous head and neck cancer cells themselves. This is the theory of 'hyperfractionation'.

The theoretical benefits of hyperfractionation were confirmed in clinical practice in a randomized trial comparing a 'conventional' schedule of 70 Gy in 7 weeks with a hyperfractionated schedule, in which two fractions of 1.15 Gy were given daily, also over 7 weeks, so that the total dose was 80.5 Gy.[1] Better local control was achieved in the experimental hyperfractionation arm, with no observed increase in late side effects. This approach to improve the therapeutic ratio, however, has not gained wide acceptance in the radiotherapy community largely on logistical grounds.

Other ways of modifying radiotherapy fractionation schedules have also been explored in head and neck cancer. The problem of tumour clonogen proliferation during a prolonged course of radiotherapy has already been alluded to. The consequence of this is that if radiotherapy schedules are prolonged for reasons such as holidays, machine breakdowns and so on, tumour control is adversely affected. A number of retrospective series have confirmed this (it cannot, of course, be ethically tested in a prospective randomized trial). The evidence has been strong enough for the Royal College of Radiologists in the UK to publish guidelines on how to minimize the harm done by such interruptions.[2] Of course, if prolongation of schedules is detrimental in terms of control of tumours, it might well be expected that to shorten the overall time ('acceleration') would result in better control. A number of trials have also been conducted to test this hypothesis. The evidence is convincing that shortening overall time is beneficial in terms of tumour control. One problem that all the trials of accelerated treatments have faced is that increasing the effect on the tumour by shortening the overall time also increases the effect on the adjacent normal mucosa, and severe acute reactions are to some extent unavoidable. The problem is compounded by the fact that very severe acute reactions sometimes lead, rather more than might be expected, to an increase in the extent of late reactions, and this has rather limited the extent to which improvements in outcomes can be achieved by shortening radiotherapy schedules. Even so, the many studies published in this area leave little doubt that it is indeed possible to employ the strategy of acceleration without incurring too high a penalty in terms of normal tissue effects, although the optimum strategy in terms of fraction size, interval, number of fractions per day, number of treatment days per week, total dose and overall time, remains elusive.[3] To some extent this debate has been superseded by efforts focussing on systemic agents and their interactions with conventional fractionation.

RADIOSENSITIZERS

As well as modifying the physical parameters of radiotherapy (time and dose through fractionation as well as the modality), other interesting avenues of exploration have involved using various agents to enhance its effects. It is reasonable to refer to all of these as 'radiosensitizers', although the scientific purists may argue about the appropriate use of this term. Numerous types of agent have been used, with varying degrees of success. The rapid advances that are currently occurring in molecular oncology have made and continue to make this an area of fruitful exploration.

The evidence that emerged from laboratory studies that hypoxic cells were relatively radioresistant to X-rays when compared with fully oxygenated ones prompted the earliest attempts at radiosensitization. As the centre of many tumours are necrotic, it was felt that this was evidence that the proliferation of cells within tumours led to growth outstripping blood supply (i.e. the diffusion distance for oxygen is <150–200 μm from an adjacent blood vessel) and that therefore it was logical to assume that there would be many chronically hypoxic cells within tumours (hypoxia can also be acute (momentary) due to the transient opening and closing of tumour blood vessels). It was hypothesized that chronic and acute hypoxia would make the centre of tumours relatively radioresistant. Modern technology has made it possible to precisely measure oxygen levels in tumour and normal tissues, and this hypothesis has indeed been confirmed. If this hypoxic effect could be overcome, radiotherapy would be more likely to be successful. A significant amount of time and effort has been expended over many years testing whether this could be achieved in clinical practice. Many diverse strategies have been employed and new strategies are continually being investigated.

The earliest avenue explored was probably the most direct. In an attempt to ensure greater oxygenation within tumours, patients were placed in hyperbaric oxygen tanks during radiotherapy. Clinical trial results failed to demonstrate that this approach yielded better results than 'standard' radiotherapy. There have been reports that increasing the haemoglobin level could be beneficial as anaemic patients may respond less well to radiotherapy.[4, 5] Initial studies suggested that those patients given transfusions and hyperbaric oxygenation (HBO) did better than those given HBO alone. However, subsequent results from the DAHANCA study group did not support this.[6] Similarly, studies with recombinant erythropoietin (EPO) have discounted the anticipated benefits of using EPO to correct anaemia with such patients actually faring less well.[7]

An alternative approach used the agent nicotinamide, which is thought to dilate small vessels to improve blood

flow through the vascularized parts of tumours (i.e. to deal with 'acute' hypoxia), in combination with patients breathing carbogen (a mixture of oxygen and carbon dioxide) during radiotherapy in an attempt to ensure good oxygenization (and thus deal with the 'chronic' hypoxia). Combined with accelerated radiotherapy this approach, called ARCON, was tested in a phase II trial with promising local control.[8] A phase III trial showed locoregional benefits with acceptable toxicity but no gain in overall survival.[9]

A number of pharmaceutical approaches have been used in an attempt to make hypoxic tumour cells more radiosensitive through more direct actions on the cellular structure. True sensitizers have little or no cytotoxic action without radiation, but significantly enhance the efficiency of radiation killing when present during radiation. Apparent sensitizers include a variety of compounds, such as antibiotics, alkylating agents and antimetabolites, that act by diverse mechanisms. In general, sensitizers can be regarded as agents that increase the lethal effects of radiation. They should show a gain between tumours and normal tissues (i.e. to enhance the therapeutic ratio). Such a therapeutic gain could result from selective uptake (concentration), a differential absorption rate or biological half-life. Ideally they should be effective at systemically nontoxic dosages, thereby minimizing side effects.

Halogenated pyrimidines (IUdR, BrdUrd) work by being incorporated into actively dividing tumour cells to a greater degree than slowly dividing (cell maintenance) normal tissues. Appreciable quantities need to accumulate for several generations for them to be incorporated to set up stresses in the DNA and make them more susceptible to radiation damage. They therefore seem to be particularly useful with tumours having a high growth fraction and high labelling index. BrdUrd is also a sensitizer to ultraviolet (UV) radiation, therefore skin may be the limiting tissue. This is less of a problem with IUdR.

Hypoxic cell sensitizers are electron affinic and act to increase the sensitivity of radioresistant hypoxic cells by mimicking O_2. They are not rapidly metabolized and therefore have time to diffuse into poorly vascularized areas.

Cells are more responsive to sensitizers if they are depleted of their natural radioprotector, glutathione (GSH), a radical scavenger that eliminates reactive radicals before they have the opportunity of causing DNA damage. This may be accomplished by incubation with thiol binding agents, such as diamide and diethyl maleate, or inhibition of GSH synthesis with buthionine sulfoximine before delivering the radiation. The effectiveness of hypoxic cell sensitizers is measured in terms of the enhancement ratio (ER).

The nitroimidazoles have been extensively evaluated as potential radiosensitizers. One of the first compounds investigated was metronidazole, a trichomonacide. At 10 mM, an ER of 1.6 was obtained with no effect on aerated cells. The large concentrations required led to investigations for more effective derivatives and other nitroimidazole drugs appeared more promising in this respect.

Although many hypoxic cell sensitizers have been investigated (including misonidazole, metronidazole, benznidazole, desmethylmisonidazole, etanidazole, pimonidazole, nimorazole, ornidazole and doranidazole), controversy exists regarding the role of these agents in conventional radiotherapy. So far only one major randomized trial of the many that have been performed has shown a therapeutic benefit and in this Danish trial, a benefit for nimorazole use during radiotherapy of pharyngeal and supraglottic laryngeal cancers when combined with conventional therapy was shown.[10] Although nimorazole has been shown to be of potential benefit, these sensitizers generally show greater benefit in situations where large, single doses of radiation are given (e.g. intra-operative radiotherapy, interstitial radiotherapy, radiosurgery). As only this one trial out of many has shown a statistically significant benefit, the international clinical community remains unconvinced that there is a true benefit for the use of nitroimidazoles, and they are still not widely used outside Denmark to this day.

BIOREDUCTIVE DRUGS

Adjuncts to radiation, which are not true radiosensitizers, include bioreductive drugs and prodrugs. These agents, which are relatively non-toxic to cells under normal oxygenated conditions, when reduced intracellularly form cytotoxic agents. Bioreduction is favoured under hypoxic conditions due to cytochrome P450 and DT diaphorase reductases. The efficiency of bioreductive drugs may be increased further by inducing increased hypoxia in tumours through the use of vasoactive drugs, such as hydralazine. This induces vasodilation in normal tissues thus diverting blood from the tumour. Bioreductive drugs can be divided into three major groups: the quinones, nitroaromatics and organic nitroxides.

Specific examples of bioreductive drugs include mitomycin C (a quinone) and tirapazamine/SR-4233 (an organic nitroxide). The former is an antitumour antibiotic that is bioreduced to form products that cross-link DNA. It is cell cycle non-specific, is more toxic to hypoxic than aerated cells, is usually administered i.v. and is rapidly cleared from plasma (half-life, 10–15 minutes). The drug does not cross the blood–brain barrier and the major toxicity is myelosuppression. Indoloquinone EO9 is a synthetic analogue of mitomycin C (MMC), which was expected to have similar properties to MMC, but fundamental differences have emerged; for example, EO9 is a much better substrate for DT-diaphorase (DTD) and it has the ability to redox cycle more readily than MMC after reduction by purified DTD. In addition, EO9 has the ability to increase the cytotoxicity to hypoxic cells 49-fold over MMC. The overall capacity of the tumour to metabolize EO9 has been suggested to be the most important determinant for EO9 activity. This, along with the rapid clearance of EO9 in humans, has been suggested as one of the reasons for the disappointing results obtained from phase II clinical trials.[11, 12] Another more efficient quinone, porfiromycin, when assessed in a phase III study showed no benefit over MMC.[13]

A more promising group of bioreductive drugs is the organic nitroxide of which tirapazamine (TPZ) is the most widely known. The benefits, however, in the phase II

trials have not been translated into clinical benefits in the phase III setting.[14] It is thought that some of the failure to demonstrate clinical benefit in phase III trials may reflect the need to better identify patient populations with high levels of tumour hypoxia. In addition there is excessive metabolic consumption as it penetrates the extravascular space so that its apparently impressive selectivity for hypoxic cells from 50–300-fold *in vitro* diminishes to a more modest range of 3–5-fold *in vivo*.

To date, as with the hypoxic cell sensitizers mentioned above, there is thus little clinical evidence from large randomized trials of bioreductive agents showing increased efficacy when combined with conventional radiotherapy. There remains a fundamental need to develop drugs that balance small molecule stability against reactivity in a reduction/oxidation equilibrium, so that the intended toxicity is only imparted in tissues that are truly hypoxic. We also need to be mindful that hypoxia is not such a prominent prognostic factor in all forms of head and neck squamous cell carcinomata.[15]

A variety of emerging techniques with more tailored effects on hypoxic tissues are under active investigation:[16]

1. Vascular disrupting agents (VDAs) alter tumour blood flow via activity on the colchicine binding site on tubulin, leading to changes in endothelial cell shape and increased vascular permeability
2. 'New' radiosensitizing agents, e.g. Bevacizumab, a humanized monoclonal antibody specific for vascular endothelial growth factor (VEGF)
3. Drugs that target hypoxia-induced proteins, e.g., Immunomodulating drugs.[17]

CONCURRENT CHEMOTHERAPY

A clinically more successful (therapeutic) strategy than trying to overcome hypoxia thus far has in fact been the rather more empirical approach of simply combining 'conventional' chemotherapy with radiotherapy. Squamous head and neck cancers show a clinical response to a number of chemotherapeutic agents, so the strategy of combining such drugs with radiotherapy seems justifiable.

Many randomized trials have been conducted in which a combination of chemotherapy and radiotherapy have been compared with radiotherapy alone. Although the majority of these trials have been relatively small, when combined there are vast numbers of patients, and the technique of 'meta-analysis' has been applied. This has convincingly shown that the addition of chemotherapy, standardly cisplatin, does give better results than those achieved with radiotherapy alone[18] and confirmed with longer follow-up and later studies.[19, 20] The counterargument has been made that the same could be achieved by simply giving more radiotherapy. However, it is known that beyond a certain level the incidence of complications rises rapidly if additional radiotherapy is given, which is why the doses used in common practice are as they are. It has proved feasible to give chemotherapy in combination with such doses and, to date, there is no strong suggestion that this does lead to an unacceptable increase in damage to normal tissue. The same cannot be said of the proposed strategy of simply giving higher doses of radiotherapy (other than in the context of fractionation trials, particularly hyperfractionation, as discussed previously).[21]

NEO-ADJUVANT CHEMOTHERAPY

Combined chemotherapy and radiotherapy schedules have been tested in randomized controlled trials against a policy of primary surgery for moderately advanced laryngeal and hypopharyngeal cancers. In fact, in these trials the drugs have been given before radiotherapy, so are certainly not acting as 'true' radiosensitizers but are mentioned here for completeness. They have been shown to be no less effective than radical surgery in terms of survival, but confer the advantage of enabling preservation of a functioning larynx in a substantial number of patients.[22, 23] Such 'organ preservation' represents a significant advance in radiotherapy of head and neck cancer, and continues to attract a great deal of attention, with trials of different drug/radiation schedules, and involving other head and neck sites. However there is still no proven benefit in providing chemotherapy prior to definitive chemoradiotherapy for advanced head and neck cancer in terms of improved survival. As such, most consider that further studies are needed to identify potential patient subgroups that may benefit from this treatment intensification.

TARGETED THERAPIES

Our understanding of the molecular mechanisms that drive cancer cells has grown at an accelerating pace within recent years. This has led to the emergence of a range of drugs that act against cancer cells in a more targeted way than the cytotoxic agents that have been the mainstay of chemotherapy in the past. Because of their specificity, such agents hold the promise of being much less toxic than conventional chemotherapy.

Among these new classes of agents there are some interesting suggestions of synergy with radiation. In head and neck cancer, one target has so far attracted significant attention, the epidermal growth factor receptor, EGFR (*erb*B1, HER1). This is one of a family of transmembrane receptor tyrosine kinases, other members being HER2/*neu* (*erb*B2), HER3 (*erb*B3) and HER4 (*erb*B4). Ligand-binding receptor dimerization occurs, which induces a conformational change in the intracellular kinase domain, thereby inducing a cascade of phosphorylation events or activation of signal transduction (e.g. activation of the MAPK or ras signal transduction pathway). As implied by its name and as might be expected in a tumour arising from squamous epithelium, overexpression of this receptor is a very frequent event in head and neck squamous carcinomas and carries with it a worse prognosis.[24] Its overexpression, with or without gene amplification, is often associated with increased production of EGFR ligands, particularly epidermal growth factor (EGF)

and transforming growth factor alpha (TGFα). Selective compounds have been developed that target either the extracellular ligand-binding region of the EGFR or the intracellular tyrosine kinase region.

The first of these target the extracellular ligand-binding domain using a monoclonal antibody approach. Cetuximab is a chimeric 'humanized' monoclonal antibody that competitively binds to EGFR (it has a 2-log higher affinity for EGFR than TGFα and EGF). Once bound to the receptor, the complex is internalized and the receptor thereby rendered inactive. Cetuximab has undergone clinical trials in head and neck cancer used both as monotherapy and as combined therapy (radiation, chemotherapy). Results from a large randomized phase III trial were very impressive in that improved locoregional control (24.4 months versus 14.9 months) and improved survival (49 months versus 29.3 months) have been obtained with little increase in toxicity[25] as compared with radiotherapy alone. Cetuximab may, in addition to exerting antiproliferative effects by inhibiting the MAPK signal transduction pathway, act as an antiangiogenic agent and therefore exert radiosensitizing effects via mechanisms described above.[26] Despite these impressive results concurrent chemotherapy using cisplatin remains the gold standard for locally advanced head and neck cancer unless renal function precludes the administration of platinum.

The second approach available to target receptor tyrosine kinases is via the use of small molecules that compete for the ATP binding site of the kinase domain. The low molecular weight of these molecules may allow them to penetrate tumours better and they can be administered orally making them suitable for chronic therapy. Several agents, including gefitinib and erlotinib, showed promise in clinical trials as monotherapy[27, 28] and in combination with standard chemotherapy. Unfortunately these anticipated benefits do not appear to have been translated into studies with radiotherapy.[29]

Another approach to targeted therapies is through the evasion of programmed cell death and immortalization. It is in this area that there is most excitement for new avenues of therapy for treating and improving the outcomes for head and neck squamous cell carcinomata as alluded to earlier.[17] A recently published study in recurrent squamous cell carcinoma of the head and neck has shown the potential for significant activity with anti-PD1 monoclonal antibodies.[30] The question now being evaluated is whether such activity can be translated into the curative setting alongside radiotherapy.

KEY POINTS

- Conventional radiotherapy uses photons that both directly and indirectly damage the DNA, through the production of ions and free radicals. The majority of damage induced by photons is via this 'indirect action'.
- Although the DNA is generally considered to be the most important target for radiation-induced damage, this dogma is gradually being amended to include effects on other cellular constituents, particularly cellular membranes.
- Tissues that are dividing rapidly manifest the effects of radiation sooner than those where cell division is slow. In addition to the kinetics (turnover rate) of the population as a whole, the response of tissues and organs is also dependent upon inherent cellular radiosensitivity. The sensitivity of the cell to radiation is determined to some degree by its state of maturity and its functional role, immature rapidly proliferating cells generally being more radiosensitive than slowly proliferating fully differentiated cells.
- The response of a tumour to radiotherapy is dependent upon inherent radiosensitivity, tumour cell repopulation, redistribution through the cell cycle (G2/M is the most sensitive phase of the cell cycle, late-S phase is the most radioresistant), repair of radiation induced damage and reoxygenation of tumour tissues between fractions. These parameters represent the '5 Rs of radiotherapy'.
- A fraction is the individual dose of radiation delivered at a single session of radiotherapy. In the treatment of head and neck cancer, a total course of radiotherapy will take several weeks and comprise numerous fractions. In conventional radiotherapy, fractions are given once a day, five days per week. The fraction size is, almost invariably, constant throughout a course of radiotherapy. Increasing the fraction size tends to have a greater effect (altered severity) on late-reacting as opposed to early-reacting tissues.
- Hypoxic cells (those under low O_2 tension) are relatively resistant to X-rays when compared with fully oxygenated ones. Chronic and acute hypoxia make tumours relatively radioresistant. If such hypoxia is overcome, radiotherapy is more likely to be successful.
- Many approaches to overcome tumour hypoxia have been evaluated – these include improving blood flow through the vascularized parts of tumours and pharmaceutical approaches to make hypoxic tumour cells more radiosensitive (radiosensitizer drugs).
- The nitroimidazoles have been extensively evaluated as potential radiosensitizers; however, controversy exists regarding the role of these agents in conventional radiotherapy. So far, only one major randomized trial, of the many that have been performed, has shown a therapeutic benefit (with nimorazole).
- Adjuncts to radiation, which are not true radiosensitizers, include bioreductive drugs. These agents are reduced intracellularly to form cytotoxic agents. A number have been evaluated in head and neck cancers.
- Perhaps a clinically more successful (therapeutic) strategy than trying to overcome hypoxia has been the rather more empirical approach of simply combining 'conventional' chemotherapy with radiotherapy. Meta-analyses have not been able to clearly identify which of the various adjuvant chemotherapy options is the best, although a strategy of giving cisplatin concurrently or in rapidly alternating sequences, with radiotherapy (perhaps with other drugs as well) has consistently emerged as the 'front runner'.
- Novel, molecularly targeted, agents hold the promise of being much less toxic than conventional chemotherapy. Of the agents under evaluation, cetuximab, a humanized monoclonclonal antibody that competitively binds to EGFR, has undergone clinical trials in head and neck cancer used both as monotherapy and as combined therapy (radiation, chemotherapy). Results from a large randomized trial were very impressive in that improved locoregional control and reduced mortality have been obtained with little increase in toxicity. Other areas of optimism are in the field of immunotherapy where studies have demonstrated significant gains in the metastatic setting. Whether this will translate into clinical benefit in the curative setting with radiotherapy remains to be seen.

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CHAPTER 6

APOPTOSIS AND CELL DEATH

Angela Hague

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SEARCH STRATEGY

Data in this chapter may be updated by searching the following keywords used in PubMed: HNSCC, oropharyngeal, apoptosis, necroptosis, autophagy, senescence, radioresistance, p53, HPV (human papilloma virus), cetuximab and epidermal growth factor receptor (EGFR).

INTRODUCTION

The aim of this chapter is to summarize current understanding of apoptosis and cell death from a clinical perspective, focussing on the head and neck. Reviews cited here have been selected for importance or clear explanations. The basis behind some of the methods to measure cell death is explained to assist in evaluating primary research papers. Emphasis is placed on the role of evasion of apoptosis in head and neck squamous cell carcinoma (HNSCC), although the role of cell death in other processes may be of interest to the specialist clinician, for example: cancers of the head and neck; head and neck development; palatal shelf fusion and cleft palate; autoimmune disease; and hearing loss due to ageing, noise, or exposure to ototoxic agents.

INTRODUCTION TO APOPTOSIS

Apoptosis as a mechanism of programmed cell death regulates cell numbers in tissues and is a key response to cellular damage that cannot be repaired. Resistance to apoptosis is one of the hallmarks of cancer,[1, 2] whereas increased apoptosis contributes to autoimmune and neurodegenerative conditions. In the ear, apoptosis of terminally differentiated sensory hair cells contributes to hearing loss caused by ototoxic agents such as aminoglycoside antibiotics and cisplatin chemotherapy, as well as that caused by excess noise over a prolonged time and general age-related hearing loss.[3] Our understanding of apoptosis regulation provides cancer diagnostic and prognostic markers and is leading to development of cancer therapies specifically targeting cell survival pathways or mimicking pro-apoptotic signalling molecules. Approaches involving sensitization to radiotherapy and chemotherapy are being taken as an alternative to the concept of single agent therapies for cancer. These highlight the need for personalized medicine, such that drugs are given to patients whose cancers, and indeed elusive 'cancer stem cells', can be predicted to respond by undergoing programmed cell death.

There are two signalling pathways that result in apoptosis, the mitochondrial (intrinsic) and the death receptor (extrinsic) pathways. Both involve activation of a family of enzymes called the caspases. Caspases are cysteine proteases that cleave after aspartic acid residues. Caspases are named in the order of their discovery, and while caspases 1, 4 and 5 are involved primarily in the processing of inflammatory mediators, caspases 2, 8, 9 and 10 have roles as initiator caspases for cell death signals, activating downstream effector caspases 3, 6 and 7, which target cellular proteins leading to the condensation of the cell and dissolution of the nuclear membrane. Hundreds of proteins are cleaved by caspases, usually at single sites. Some are cleaved as bystanders, but many structural and regulatory proteins are inactivated by caspases. Some substrates can be activated by cleavage – such as other caspases and Bid (see the section 'Death Receptor Pathway to Apoptosis' below). By cleavage of an inhibitor protein (ICAD), they release a caspase-activated deoxyribonuclease (CAD) that cleaves the DNA of the cell into oligomeric fragments that are integer multiples of 180–200 base pairs. This cleavage pattern can be detected on DNA electrophoresis as a

'DNA ladder'. The cleavage of DNA ensures that the cell is no longer capable of replication, and the destruction of the translational machinery restricts protein synthesis.

In haemotoxylin and eosin stained sections of tissue, apoptotic cells are characterized by condensed chromatin that appears intensely purple stained in smooth shapes. Early stages show chromatin condensed around the periphery of the nuclear membrane, prior to its dissolution, frequently in crescent shapes. As the nuclear membrane disappears, apoptotic cells exhibit single smooth chromatin mass, which subsequently fragments to smaller smooth shaped chromatin masses that can be scattered throughout the cell. Loss of cell–cell and cell–matrix contact, along with shrinkage and rounding up of the cell as the cytoskeletal proteins are cleaved, results in the apoptotic cell appearing isolated among the tissue. The plasma membrane is seen to undergo 'blebbing' and the cell may fragment into apoptotic bodies following invagination of the plasma membrane. Cleavage of poly (ADP-ribose) polymerase (PARP-1) by caspases 3 and 7 gives two fragments of apparent molecular weights of 25 and 85 kDa. These have since been designated as 24 and 89 kD from sequence data. The p85/89 large fragment is a popular marker for identifying apoptosis, either by protein electrophoresis or by using antibodies that specifically recognize this fragment of the cleaved protein for immunostaining of cells or tissues. It is an earlier marker than DNA fragmentation (**Figure 6.1**).[4]

All caspases are produced as inactive zymogens, and are activated by either autocleavage (in the case of initiator caspases) or other upstream caspases. The procaspase is cleaved in two places – a prodomain is removed and two subunits are generated, a large subunit and a small subunit. These are assembled into the active enzyme which is a heterotetramer with head-to-tail alignment of the subunits. As a result of this, protein electrophoresis detection of the small and/or large subunits is indicative of caspase cleavage. *In vivo* detection of apoptosis by immunohistochemistry is facilitated by use of antibodies that recognize only the cleaved, active form (**Figure 6.1**).

DNA fragmentation has also been used as a way to detect apoptotic cells. The terminal deoxynucleotide transferase-mediated dUTP-biotin nick end labelling (TUNEL) assay detects both double and single strand breaks by adding labelled dUTP to free 3'-hydroxyl termini of fragmented DNA. The problem with this method is that it picks up DNA fragmentation occurring during necrotic cell death and should therefore be used in conjunction with other methods of apoptosis detection. Alternative *in situ* ligation (ISL) techniques label only 5' double-stranded DNA breaks with either blunt ends or a 3' single base overhang with terminal phosphates, allowing for more specific detection of apoptosis-mediated DNA fragmentation over either necrosis or repairable DNA damage.[5]

The ultimate fate of apoptotic cells *in vivo* is to be phagocytosed by macrophages or neighbouring cells acting as semiprofessional phagocytes. The membrane of apoptotic cells is altered to prevent leakage of intracellular material until phagocytosis, a process involving protein cross-linking by tissue transglutaminase. The lipid components of the membrane are also altered, in that phosphatidyl serine, normally only present on the inner membrane leaflet, is flipped into the outer leaflet and exposed on the cell surface, enabling macrophages to identify and engulf the dying cell. The engulfment of the cell prior to loss of plasma membrane integrity is key to the process of eliminating excess or damaged cells without eliciting an inflammatory response. If this does not occur, the plasma membrane becomes permeable, and the cell is said to undergo 'secondary necrosis', with the leakage of damage-associated molecular pattern molecules (DAMPs) able to elicit a non-infectious immune response. It is exposure of phosphatidyl serine on the outer leaflet that is recognized in the Annexin V assay. Annexin V is an anticoagulant protein from human placenta that binds to phosphatidyl serine lipids.[6] Labelled Annexin V binding in conjunction with propidium iodide staining of unfixed cells distinguishes early apoptosis, as cells that

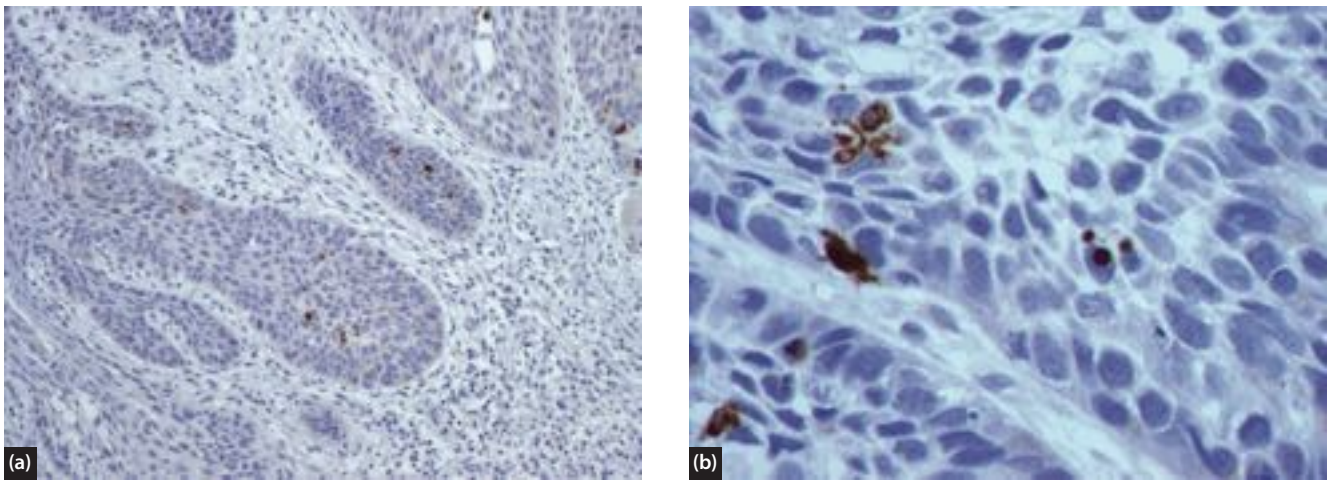


Figure 6.1 Cleaved caspase 3 staining highlights apoptotic cells in human tissue. Staining of apoptotic cells using an antibody that detects active caspase 3 in a human oral squamous cell carcinoma section. **(a)** Low magnification (×10 objective). **(b)** Higher magnification (×40 objective).

are not permeable to propidium iodide but are Annexin V positive. However, once the plasma membrane becomes permeable, it can no longer distinguish apoptosis and secondary necrosis, because Annexin V then has access to the inner plasma membrane leaflet. For use in fixed cells or *in vivo*, the cells are labelled before fixation.

OTHER TYPES OF CELL DEATH

Terminal differentiation

Apoptosis is a physiological event that contributes to maintenance of tissues with constant turnover of cells such as the gut epithelium. Tissue homeostasis is maintained by a balance between cell proliferation, differentiation and cell death. However, terminal differentiation in the skin, and indeed oral epithelium, is regulated by a process involving caspase 14. This is a distinct process from apoptosis.[7]

Necrosis

Apoptosis is distinct from necrosis, a pathological, passive process of cellular destruction (**Table 6.1**). Necrosis involves cell swelling and nuclear chromatin 'flocculation' where the swelling nucleus appears more diffuse than normal. Ultimately the cells lyse without detaching from their neighbours and the release of intracellular contents stimulates inflammation.

Necroptosis

Although necrosis is a passive process, a programmed cell death mechanism resulting in necrotic-like death has been identified that is termed 'necroptosis', specifically signalled by receptor-interacting serine/threonine-protein kinases 1 and 3 (RIPK1 and RIPK3) in response to signalling through the tumour necrosis factor receptor (TNFR) family members, toll-like receptors (TLR3 and TLR4) or T-cell receptors (TCR), or in response to DNA damage and viral infection.[9, 10] RIPK3 phosphorylates mixed lineage kinase domain-like protein (MLKL) which homooligomerizes and relocates to the plasma membrane. This appears to be key to the necroptosis signalling pathway, but RIPK1 may or may not be needed.[11]

Necroptosis primarily appears to occur when caspases are inhibited, and one reason why apoptosis normally takes precedence over necroptosis is because active caspase 8 can cleave RIPK1 and RIPK3.[9] Viral infection is a situation that can result in necroptosis because viruses inhibit caspases. Where tumour cells have become apoptosis resistant (perhaps through similar mechanisms to viral infection) necroptosis might be a useful way to eliminate tumour cells, although the consequences of the induction of inflammation to the tumour microenvironment will have to be considered.[12, 13] While microscopically necroptosis appears as a swollen cell with formation of a balloon-like structure, known as oncosis, methods to identify necroptosis currently involve biochemical and fluorogenic assays on lysates or living cells, use of genetically modified mice or cells with RIPK3 or MLKL knockdown, or use of necrostatin and other more specific RIPK1 inhibitors to block the process.[13]

RIPK3$^{-/-}$ and *MLKL*$^{-/-}$ mice have revealed that necroptosis contributes to ischemia-reperfusion injury and chronic neurodegenerative disorders.[11] Necroptosis is not the only form of 'regulated necrosis' and if multiple pathways lead to cell death with similar morphology, clear understanding of these molecular pathways is needed to devise ways to distinguish these in human tissues as well as to distinguish RIPK3 activation in necroptosis from its role in inflammation.

TABLE 6.1 Summary of differences between apoptosis and necrosis[8]

	Apoptosis	Necrosis
Occurrence	Part of physiological or pathological processes	Always pathological
Initiating factors	Range of extracellular and intracellular factors	Direct result of injury and cellular anoxia
Distribution	Isolated apoptotic cells scattered widely throughout tissues	Occurs in groups/whole areas of tissue
Mechanism	Active process – ATP dependent	Passive
	Regulated mechanism	Regulation lost
Cytoplasmic changes	Cytoplasmic shrinkage	Swelling of cell membrane
	Blebbing of cell membrane into apoptotic bodies	Rupture of cell membrane with loss of contents to extracellular space
	Many organelles preserved and bound into apoptotic bodies	Organelles lost
Nuclear changes	Endonuclease activation, cutting of DNA into oligosomal fragments	Random digestion of DNA
	Chromatin condenses into specific 'crescents' visible on light microscopy	Chromatin flocculates
Effect on surrounding tissue	Little or none	Intense inflammation

Autophagy for survival – or autophagic cell death?

Macroautophagy is a process by which cytoplasm and organelles are engulfed into double membrane bound vesicles called autophagosomes (self-eating), which ultimately fuse with lysosomes for digestion and recycling of contents by lysosomal hydrolases. This process is utilized, for example, in situations of starvation, oxidative stress or hypoxia. Publications frequently specify that it is macroautophagy that is the form of autophagy being referred to (i.e. the use of autophagosomes to transport cargo to the lysosome) and then simply use the term 'autophagy' thereafter. Tumour cells are believed to utilize this process, promoting survival of tumour cells in unfavourable conditions. Autophagy contributes to chemotherapy resistance, for example in esophageal cancer cells treated with cisplatin or 5-fluorouracil.[14] Some agents can induce excessive autophagy leading to cell death, but the consequence of autophagy can be context dependent and the microenvironment can adjust the threshold at which autophagy levels promote cell survival or cell death. There is now believed to be cross-talk between the processes of apoptosis, autophagy and 'regulated/programmed necrosis'.[15]

Measurement of autophagy is difficult, as demonstration of flux of autophagosomes is currently the gold standard method, and this requires living cells in which flux can be blocked at different stages. The autophagy flux reporter mCherry-GFP-LC3 works on the principle that the GFP (green fluorescent protein) signal is sensitive to the acidic and/or proteolytic conditions inside the lysosome, whereas mCherry (red) fluorescence persists. This has been used to show autophagic flux in mouse neurones *in vivo* by adeno-associated virus delivery – autophagosomes appear as yellow dots and autophagolysosomes appear as red dots.[16] A multiprotein class III phosphatidyl inositol-3 kinase (PI3K) complex is needed to produce the isolation membranes that engulf cellular components and pinch off of membranes (usually the endoplasmic reticulum) to form the autophagosomes. Knockdown of active components of this complex can be used to demonstrate if autophagy is important in a particular cellular outcome, for example cell survival or cell death.

KEY POINTS

- Apoptosis eliminates damaged cells or cells in excess to requirement.
- Apoptosis involves destruction of the cell by caspases, but the cells are normally engulfed by phagocytes *in vivo*.
- Excessive apoptosis contributes to autoimmune diseases such as oral lichen planus and degenerative conditions such as apoptosis of the sensory hair cells of the ear, contributing to hearing loss.
- Resistance to apoptosis is a hallmark of cancer and contributes to therapeutic resistance.
- Necroptosis involves signalling by RIPK3 and MLKL and is known as 'regulated necrosis or programmed necrosis'.
- Autophagy involves digestion of cellular material in autophagolysosomes for use as recycled metabolites and is generally a cytoprotective process; it can contribute to resistance to cancer therapy.

MECHANISMS OF APOPTOSIS REGULATION

Mitochondrial pathway to apoptosis

Bcl-2 was originally described as a protooncogene in B-cell lymphomas. In follicular lymphoma the t(8;14) translocation moves Bcl-2 to the immunoglobulin heavy chain locus, leading to its overexpression. Bcl-2 is located in the outer mitochondrial membrane but is also detected in the plasma membrane and endoplasmic reticulum. Its mitochondrial localization allows it to regulate the release of cytochrome c from the intramembrane space into the cytosol and it is this release that is required for the activation of the initiator caspase, caspase 9. Cytochrome c release can be measured as a characteristic marker of a cell's early apoptotic response.[17] A family of Bcl-2 proteins has been identified (**Table 6.2**), some of which are anti-apoptotic like Bcl-2; others are pro-apoptotic.[18] Whereas Bcl-2 is localized constitutively to membranes, the anti-apoptotic Bcl-X_L, Mcl-1 and Bcl-w members of the family are located in the cytoplasm and localize to the mitochondria upon receipt of an apoptotic signal.[19] Bax is a pro-apoptotic protein that was identified as a homologue that bound Bcl-2. When overexpressed, Bax accelerated cell death in response to cytokine deprivation. By contrast, overexpression of Bcl-2 allows cells to tolerate signals to undergo apoptosis. Bcl-2 and other anti-apoptotic family members do this by sequestering pro-apoptotic family members such as Bax and by regulating ion flux to prevent mitochondrial outer membrane depolarization which is required for cytochrome c release.[17] Interestingly, Bax is not always bound to Bcl-2 in viable cells, but cycles on and off mitochondria in a dynamic equilibrium.[20] Bcl-X_L has also been shown to actively transport Bax from the mitochondrial membrane to the cytoplasm.[19] The Bax homologue Bak serves a similar function. Both Bax and Bak function as homooligomeric complexes to release cytochrome c from the mitochondria. Although Bax and Bak mediate responses to different types of cellular stress, the outcome downstream of the mitochondrion is the same, and in fact there is some functional redundancy, as only cells lacking both Bax and Bak molecules fail to undergo apoptosis.[21] By contrast to Bax, which translocates to the

TABLE 6.2 Most commonly studied Bcl-2 family members

Anti-apoptotic	Pro-apoptotic	Pro-apoptotic BH3-only
Bcl-2	Bax	Bad
Bcl-x	Bak	Bim
Bcl-w		Bid
Mcl-1		Puma
Bfl-1/A1		Noxa
		Hrk
		Bik

mitochondrion in response to apoptosis signals, Bak is localized in the outer mitochondrial membrane.

Released cytochrome c binds to the adapter protein Apaf-1, causing a conformational change that allows it to bind dATP. In turn, this triggers oligomerization to a heptomer and exposes the caspase recruitment domain (CARD) of Apaf-1 allowing recruitment of procaspase 9. The heptomeric wheel-like structure carrying procaspase 9 at its hub constitutes an activation platform for caspase 9 and is termed the apoptosome (Figure 6.2). Autocleavage of procaspase 9 generates active caspase 9, the initiator of apoptosis, which subsequently activates further caspases.

While Bcl-2 and most anti-apoptotic proteins of the family have four domains of Bcl-2 homology (BH domains), Bax and Bak have three (BH1-3), which in the folded molecule comprise a hydrophobic groove used for dimerization with the anti-apoptotic proteins. Upstream of the mitochondrion, in addition to Bax translocation, so called 'BH3-only' proteins sense apoptotic signals and transmit these to the mitochondrion. They compete with Bax and Bak for Bcl-2 binding, and displaced Bax is free to

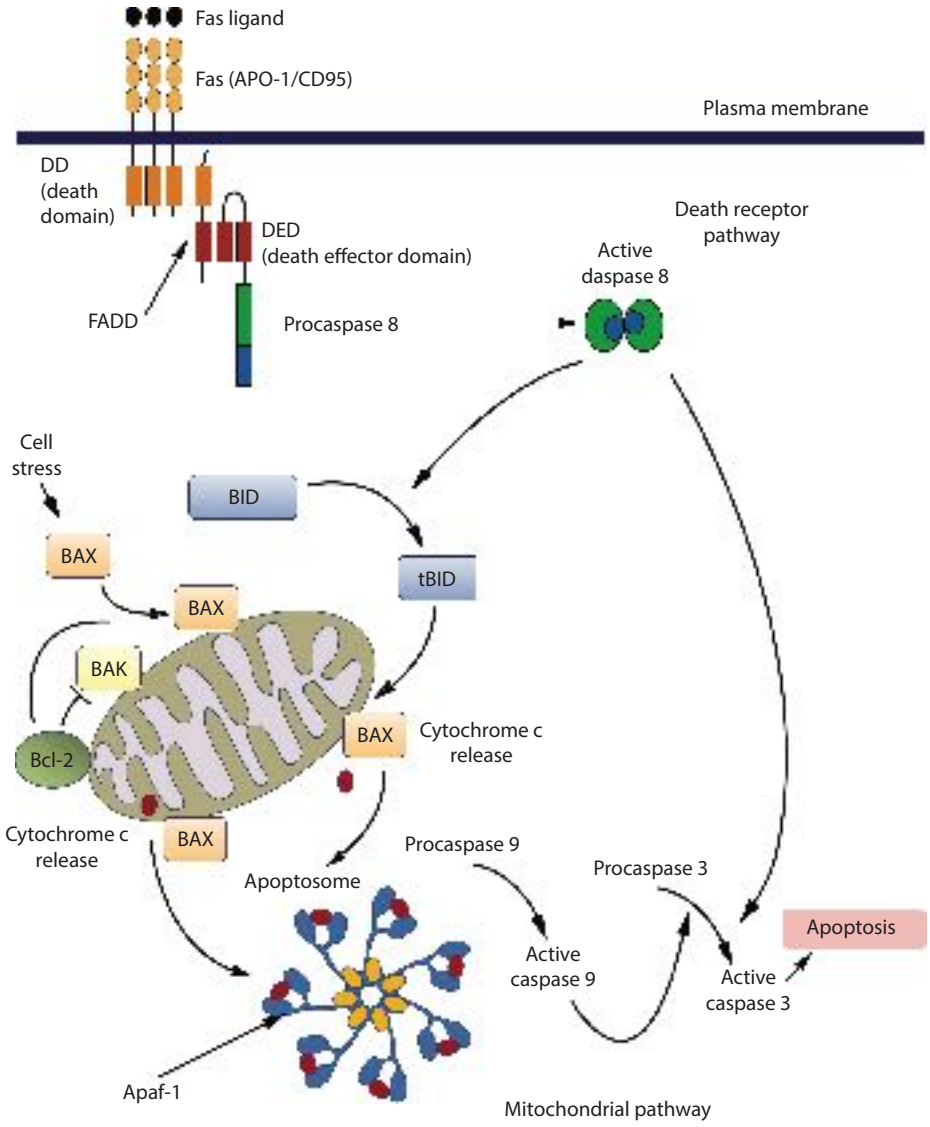


Figure 6.2 Apoptotic signalling. In the mitochondrial cell death signalling pathway, the molecules Bax and Bak can each form homooligomers that release cytochrome c from the inner membrane space of the mitochondrion. These are negatively regulated by anti-apoptotic members of the Bcl-2 family, represented here as Bcl-2. Once released, cytochrome c binds to monomeric Apaf-1, which in the presence of ATP can oligomerize into a heptomer called the apoptosome (blue). Procaspase 9 is recruited to the caspase recruitment domain (CARD) that forms the hub of the apoptosome. Here it autocatalytically cleaves to give rise to a highly active caspase 9 enzyme, which can then activate downstream executioner caspases, represented here by caspase 3. In the death receptor signalling pathway, trimerized receptors recruit the adapter molecule FADD, which recruits procaspase 8, which is autocatalytically processed to form the active enzyme. In type I cells this can result in caspase 3 activation and apoptosis. In type II cells, the BH3-only member of the Bcl-2 family, Bid, is cleaved to a form that can translocate to the mitochondria and interact with Bcl-2 to displace Bax or interact directly with Bax itself and by either of these mechanisms facilitate cytochrome c release, thus engaging the mitochondrial signalling pathway. In type II cells, Bcl-2 overexpression can block death receptor induced apoptosis but in type I cells it does not.

homooligomerize and release cytochrome c. This is the 'sensitizer' function of BH3-only proteins. Some can interact with Bax directly to facilitate conformation change, oligomerization, pore formation and cytochrome c release. This is the 'direct activator' function of BH3-only proteins and a model has been proposed whereby the BH3 protein binds transiently to a rear pocket on Bax distal to the hydrophobic groove.[22] It is likely that Bak does not require this activation because it is already located in the mitochondrial membrane.[19] Whereas Bad is only capable of sensitizer function, Bim, Bid and Puma can serve as direct activators.[23] Different BH3-only proteins mediate different apoptosis signals. In terms of the anti-apoptotic proteins, these may regulate cell life and death during tissue homoeostasis at different stages in cellular differentiation, for example in the colonic crypt, Bcl-2 protects proliferative cells from apoptosis, whereas Bcl-X_L protects the post-mitotic cells in the upper regions of the crypt.[24] The BH3-only proteins also have preferred anti-apoptotic binding partners, for example Bad binds strongly to Bcl-2, Bcl-X_L and Bcl-w, whereas Noxa binds Mcl-1 and Al.[25]

Small molecule drugs have been designed that mimic BH3-only proteins in their action. The most extensively clinically tested of these is ABT-263 (navatoclax; AbbVie), but this does not bind Mcl-1 or Al. Obatoclax (Gemin X) binds both Bad and Noxa targets and is being tested clinically for anti-cancer activity in advanced haematological malignancies. Others are being tested in preclinical models. Interestingly, obatoclax more efficiently induces apoptosis of HNSCC cell lines if autophagy is inhibited by choroquine.[26]

Mitochondrial apoptosis induced by reactive oxygen species is believed to underlie ageing-related deafness and ototoxicity of some pharmaceuticals including aminoglycoside antibiotics such as gentamycin. Resistance to broad spectrum antibiotics and the increase in methicillin-resistant *Staphylococcus aureus* (MRSA) has led to reconsideration of gentamycin. The hair cells are the primary target of ototoxicity but auditory and vestibular ganglion neurons can also undergo cell death.[27] Different *in vitro* and *in vivo* models implicate apoptosis, necrosis or necroptosis as well as cell death subsequent to extrusion from the epithelium. Reactive oxygen species (ROS) generation is believed to induce mitochondrial apoptosis mediated by p53 or c-Jun N-terminal kinase (JNK).[27] Mutations in mitochondrial DNA encoding the 12S ribosomal RNA component of the mitochondrial ribosomes lead to its hypermethylation. Raimundo et al.[28] provided evidence for a model in which A1555G mutation, which confers susceptibility to aminoglycoside-induced deafness, led to enhanced ROS production, and AMP-kinase-dependent induction of the transcription factor, E2F1. E2F1 was expressed at levels high enough to induce pro-apoptotic genes rather than promote cell proliferation. In a mouse model, cleaved caspase 3 positive cells were detected in the stria vascularis and the spiral ganglion neurons, but not in the organ of Corti.[28] A T1095C mutation in the same gene also confers susceptibility to gentamycin mediated apoptosis in an *in vitro* model.[29] Therefore, patients susceptible to gentamycin-induced ototoxicity could be identified by genetic screening. Free radical scavengers have been suggested to protect from aminoglycoside-induced toxicity.[30]

Death receptor pathway to apoptosis

Cells can be induced to undergo apoptosis via engagement of cell surface death receptors (DR) with ligand molecules. These receptors form the tumour necrosis factor receptor family, the other members of which are Fas (APO1/CD95), DR3 (APO3), DR4 (TRAIL-R1) and DR5 (TRAIL-R2). Cell signalling was first elucidated for Fas, which is bound by Fas ligand (Fas-L). The source of Fas ligand may be in membrane-bound form presented on the surface cytotoxic T cells. The Fas ligand-Fas system normally eliminates excess T cells during an immune response, and defects in this signalling can be involved in autoimmune disease. Oral lichen planus involves epithelial apoptosis mediated by Fas ligand due to infiltration of inflammatory cells underneath the oral epithelium. Lichen planus is a condition with a high apoptotic index and is a useful positive control for apoptosis staining.

In apoptosis signalling, receptor trimerization leads to recruitment of FADD (Fas-associated death domain), which binds the intracellular death domain (DD) portion of Fas, and procaspase 8 molecules bind to the death effector domain (DED) of FADD (**Figure 6.2**). Hence, procaspase 8 molecules are clustered and activated by autocleavage on a platform known as the death inducing signal complex (DISC). Trimerized receptors may also cluster into receptor microaggregates. In some cell types (type I cells), caspase 8 activation at the DISC is sufficient for downstream effector procaspase cleavage, but in many cell types (type II cells), the mitochondrial pathway is engaged to amplify the death signal by caspase 8-dependent cleavage of the BH3-only protein Bid, converting it to a form that is able to transmit the apoptotic signal to the mitochondrion. In addition, cytotoxic T cells release perforin, which penetrates the epithelial cell membrane, and granzyme B, a serine protease that can cleave and activate Bid, hence engaging the mitochondrial pathway.

Expression of high levels of Fas ligand by tumour cells can allow them to evade infiltrating T cells that express Fas, so called tumour 'counter-attack'.[31] Tumour-produced Fas may be soluble, as tumour cells may exhibit resistance to Fas-mediated apoptosis. Fas mutations have been found in sporadic myeloma and T-cell leukaemia leading to evasion of apoptosis. FLIP is a molecule that structurally resembles caspase 8 and is able to bind FADD and hence block death receptor signalling. Indeed for death receptors we now know that large complexes can be formed both at the receptors themselves or in complexes that are released into the cytoplasm, and the constitution of these determines downstream signalling consequence. For example, Fas ligand can induce cell survival and contribute to tumour promotion by inducing JNK, ERK (extracellular signal-regulated kinases), NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and PI3K (phosphatidyl inositol 3-kinase)

signalling pathways.[32] Tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) induces apoptosis through two of its receptors DR4 (TRAIL-R1) and DR5 (TRAIL-R2). Decoy receptors that bind ligand but do not signal apoptosis can be overexpressed in some cancers. For example, TRAIL-R3 is overexpressed in acute myeloid leukaemia, especially on cancer stem cells.[33] TRAIL-R4 can signal to activate Akt in HeLa cervical carcinoma cells independently of ligand binding, but the mechanism is not yet understood.[34]

Agonistic antibodies that engage death receptors are in trials for various cancers in which the signalling pathway is intact – for example, the TRAIL-R1 antibody Mapatumumab and the TRAIL-R2 antibody Lexatumumab. As single agents these were initially disappointing, in part because TRAIL receptors must trimerize in order to signal effectively, and an antibody can only cross-link two death receptors.[34] However, their combination with other agents is looking more promising, at least *in vitro*. Agents inducing synergistic apoptosis include chemotherapeutic drugs, histone deacetylation inhibitors, proteosome inhibitors, NF-κB inhibitors and BH3 mimetics. Moreover, new TRAIL receptor antibodies that will form higher order complexes are being developed.[35] Other recent strategies use more stable versions of the TRAIL trimer, targeted delivery of TRAIL in nanoparticles, and tumour-targeting of TRAIL constructs.[36]

p53 'guardian of the genome'

Normally wild type p53 protein is rapidly turned over due to its binding to the ubiquitin ligase HDM2 (the human homologue of MDM2), which ubiquitin-tags it for destruction by the proteosome. In recognition of DNA damage, p53 is stabilized and can be detected as nuclear staining. p53 is extensively post-translationally modified and this regulates its binding partners and which gene promoters it engages with. Hence, p53 can activate transcription of either cell cycle arrest and DNA repair genes or genes encoding proteins that promote mitochondrial apoptosis such as Bax, Puma, Noxa and Apaf-1. p53 can also induce Fas, TRAIL, TRAIL-R2, hence modulating death receptor signalling. More recently, p53 has been shown to activate transcription of autophagy regulators under cell stress conditions.[37] p53 knockout mice are developmentally normal, and therefore p53 is thought to play a minimal role in development. However, defects in developmental genes can lead to p53-dependent apoptosis, for example the apoptosis of neural crest cells resulting in craniofacial hypoplasia syndromes such as Treacher Collins.[38]

THE PI3K/AKT AND MAPK/ERK PATHWAYS TO CELL SURVIVAL

In response to engagement of tyrosine kinase receptors, G-coupled protein receptors, integrins, and toll-like receptors, the lipid kinase PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to generate phosphatidylinositol 3,4,5-triphosphate (PIP3). PTEN antagonizes this pathway by removal of the phosphate at this position of the inositol ring.[39] PIP3 recruits Akt to the plasma membrane ready for activation. Then, upon its activation by phosphorylation, Akt can move to different locations within the cell to phosphorylate many molecular targets, some of which are key regulators of cell survival – for example, Akt-dependent phosphorylation contributes to Bad and caspase 9 inactivation. It also inactivates the Forkhead family of transcription factors that induce expression of pro-apoptotic factors and activates mTOR (mammalian target of rapamycin), a key regulator of autophagy and cell survival in situations of cell stress. The *PIK3CA* gene encodes p110 alpha (p110α) subunit of PI3K and can be mutated in HNSCC.[40]

The mitogen-activated protein kinase MAPK/ERK pathway downstream of Ras activates transcription factors promoting cell survival; however ERK phosphorylation can also lead to phosphorylation, ubiquitination and proteosomal degradation of the 'extra long' isoform of the BH3-only protein, Bim.

Apoptosis and head and neck squamous cell carcinoma

Although resistance to apoptosis is a hallmark of cancer, this does not mean that cancers do not exhibit apoptosis. Apoptosis is uncommon in normal squamous epithelium and eliminates damaged cells rather than contributing to normal tissue homeostasis. The apoptotic index is higher in dysplasia and in HNSCC than corresponding normal tissue.

The genetic changes in head and neck squamous cell carcinoma (HNSCC) have been reviewed by Rothenberg and Ellisen,[41] in particular the exome sequencing results published in *Science* in 2011 by Agrawal et al.[42] and Stransky et al.[43] These include changes that subvert the balance between proliferation, differentiation and apoptosis:

- *CDKN2A* loss (gene encoding tumour suppressor protein and cyclin-dependent kinase inhibitor, $p16^{INK4a}$)
- *CCND1* amplification (gene encoding cyclin D1)
- loss of *TGFBR2* (gene encoding the type II transforming growth factor β receptor) or *SMAD4* (gene encoding the TGFβ signalling molecule), which promote proliferation
- *NOTCH1* loss and/or abnormal expression of *TP63*, both of which deregulate keratinocyte differentiation
- alterations in *CASP8* (gene encoding caspase 8), *EGFR* (gene encoding the epidermal growth factor receptor (EGFR) and *PIK3CA* genes, which promote cell survival.

Loss or mutation of *TP53* is common, leading to defective cell cycle arrest and repair or apoptosis. Mutations in *TP53* can result in stabilized, mutant p53 that lacks function. Alternatively, tumours may lack p53 altogether. Hunter et al.[44] suggested that ~40% of HNSCCs may develop without acquiring immortality and retain wild type p53 and p16. These tumours would likely have

better prognosis. Interestingly, cisplatin induces senescence in HNSCC cells with wild type p53.[45]

In development of HNSCC, *TP53* mutations appear early and contribute to 'field cancerization', whereby epithelium that is histologically normal actually carries mutation, and to around half of HNSCC cases. Hence, ways to kill cells harbouring mutant p53 or reconfigure mutant p53 to a transcriptionally active confirmation are being explored. ONYX-015 (dl1520) is an adenovirus modified to only replicate in and kill cells that harbour p53 mutations. Wild type adenoviruses must disable p53 before viral replication can occur and because ONYX-015 has a mutant E1B 55K gene, it cannot neutralize p53, therefore cannot replicate in cells with wild type p53 and does not kill them. Oncolysis of mutant p53-containing tumour cells leads to spread of viral particles and subsequent rounds of tumour-specific replication and cell killing. This virus is in phase III trials for head and neck cancer in the USA. H101, a similar virus to ONYX-015, is licensed in China for treatment of head and neck cancers.[46] An alternative is to use a replication-deficient adenovirus that expresses wild type p53. Phase II/III trials in HNSCC are showing increased patient survival.[43] Small molecules designed to directly reactivate mutant p53 protein are specific to the type of mutation; PRIMA-1(Met) stabilizes unfolded p53 and a 'first in human' study was published in 2012.[47]

Risk factors for HNSCC are primarily smoking and alcohol consumption, with dietary contribution.[48] However, human papilloma virus (HPV) infection, particularly of subtype 16, can increase the risk of oropharyngeal cancer over 4-fold.[49] Unsurprisingly, human papilloma virus positive (HPV$^+$) is genetically distinct from HPV$^-$ HNSCC,[50] and patients have longer overall survival and respond better to treatment. Viral proteins E6 and E7 accelerate the degradation of p53 and p16 respectively, resulting in cellular immortalization and reduced ability of cells to repair genetic damage or undergo apoptosis. HPV$^+$ tumours rarely carry p53 mutations, as the E6 protein targets p53 for degradation, yet HPV$^+$ cell lines are generally more radiosensitive than HPV$^-$ cell lines, exhibiting a prolonged G2 arrest and increased apoptosis because of residual wild type p53.[50] It should be emphasized that apoptosis can occur by p53-independent mechanisms; for example, HNSCC cells can respond in this way to γ-irradiation.[51]

Since E7 decreases pRb, it frees the transcription factor E2F, normally sequestered by the pRb, permitting cell cycle progresssion. p16 increases in a negative feedback response. Therefore, whereas reduced p16 is common in HPV$^-$ HNSCC, in HPV$^+$ cases it tends to be enhanced. Grønhøj Larsen et al.[52] found by systematic review that studies classifying 'p16 positivity' as tumours with a proportion of cells 70% or greater showed strongest correlation with HPV positivity. Using this scoring system, Rietbergen et al.[53] caution that there is also a possibility that p16 positivity may occur independently of HPV involvement, although they analysed HPV DNA and mRNA from formalin fixed paraffin-embedded tumour material and recommended that assays in fresh frozen tissue be conducted. They noted that p16$^+$/HPV$^-$ tumours had higher frequency of loss of heterozygosity on chromosomes 3p, 19p and 17p, similar to HPV$^-$ tumours.

EGFR activation activates MAPK and PI3K/Akt signalling pathways (**Figure 6.3**). The EGFR and PI3K/Akt/mTOR signalling pathways are of current interest for molecular targeted therapeutics, as they are hyperactivated in HNSCC and contribute to radioresistance.[54] Although the EGFR is rarely mutated in HNSCC, increases in gene copy number do correlate with poor prognosis, and the possibility that EGFR ligands are present in the tumour microenvironment has been suggested.[41] The monoclonal

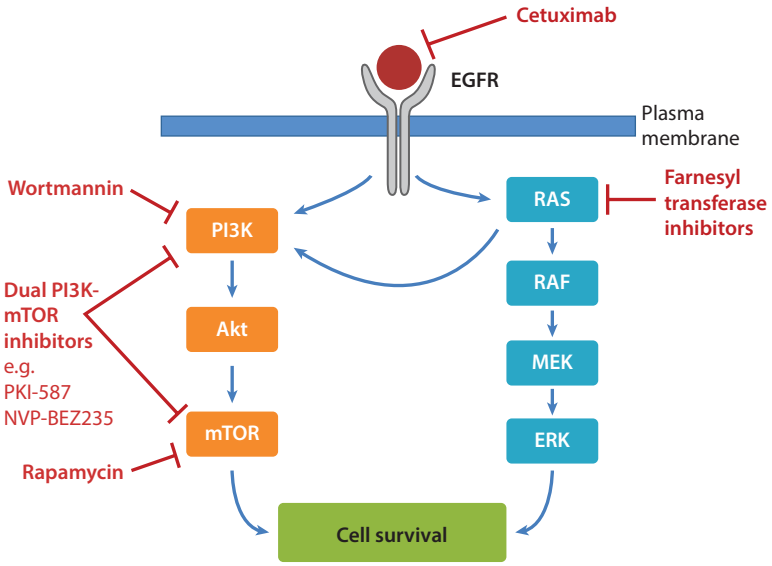


Figure 6.3 Survival signalling and potential targets for cancer therapy. The PI3K and Ras signalling pathways are hyperactivated in HNSCC. There is crosstalk between these two pathways; for example, Ras can potentiate PI3K activity. Targeting a single molecule is ineffective because of development of drug resistance and cells adapt their signalling pathways to overcome the block. Hence strategies are being developed that combine agents with different targets or use drugs with more than one molecular target.

antibody cetuximab targets the EGFR and is now used clinically to significantly enhance patient survival, but resistance remains a problem with downstream activation of PI3K/Akt/mTOR contributing to this. Similarly, resistance to PI3K inhibitors occurs due to the cancer cell's ability to adapt its signalling circuits and to engage feedback mechanisms. Hence, there is a move away from use of single target therapies towards evaluation of combination approaches. Use of PI3K or dual PI3K-mTOR inhibitors in combination with cetuximab is currently being explored. Cancers with *HRAS* mutation are not likely to respond to EGFR-targeted therapies. Active Ras is needed for Akt activation in HNSCC cells.[55] Farnesyl transferase inhibitors that inhibit activity of Ras and Akt could be an area for research. Cetuximab combined with radiotherapy or chemotherapy is more likely to prolong survival for patients with oropharyngeal carcinomas rather than laryngeal or hypolaryngeal cancers. Although it has been speculated that HPV+ cancers may respond better to cetuximab, this has yet to be investigated.[56]

FUTURE RESEARCH

Molecular targeting approaches are being developed to sensitize tumours to mitochondrial mediated apoptosis (BH3 mimetics at the forefront) and to optimize apoptosis utilizing TRAIL receptor signalling pathways, approaches that may potentially be applicable to HNSCC and nasopharyngeal carcinoma. Frequently, work on cancers of the head and neck lags behind that of other more common cancers. Knowledge can be applied across tumour types, if a full understanding of the molecular basis of the cancer is obtained. Even within HNSCC, subtypes exist that need to be considered when testing agents and drug combinations, and in particular when dealing with the potential for resistance. The potential for inhibiting autophagic cell survival mechanisms could be explored further in these cancers. There is current interest in inhibiting PI3K and mTOR survival pathways. Given the increasing HPV+ HNSCC incidence and low take-up of HPV16 vaccination, targeting HPV DNA or E6 protein in HPV+ cancers to sensitize to p53-mediated apoptosis may be appropriate.

KEY POINTS

- Compromised p53 function leads to resistance to p53-mediated cell cycle arrest and DNA repair as well as apoptosis, leading to accumulation of genetic damage.
- HPV+ HNSCC is genetically distinct from carcinogen-induced HNSCC and is more likely to respond to traditional therapies; this may be in part because of residual wild type p53 that is not fully degraded in response to E6 binding.
- Targeting of overexpressed epidermal growth factor receptor (EGFR) using the monoclonal antibody cetuximab is currently used clinically.
- In HNSCC genetic changes resulting in defects in the PI3K/Akt and Ras/MAPK signalling pathways are common and because tumour cells adapt to single target therapies, a combination approach is being tested.
- The diversity of HNSCC tumours calls for screening approaches and personalized treatment to maximize cell death and overcome resistance to therapy.

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CHAPTER 7

STEM CELLS

Navin Vig and Ian C. Mackenzie

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SEARCH STRATEGY

Data in this chapter may be updated by Medline searches based mainly on various combinations of the terms 'stem cells', 'embryonic stem cells', 'tissue regeneration' and 'otolaryngology'. Other sources include published and unpublished information from the author's laboratories.

INTRODUCTION

Tissue abnormalities of the head and neck region, arising from disease, injury or developmental defects, often pose considerable regenerative problems. Historically, the efficacy of surgical reconstruction has been limited by a lack of suitable autologous tissues for reparative or regenerative procedures but the development of methods for *in vitro* and *in vivo* tissue expansion, together with advances in tissue engineering, now provide new therapeutic options.[1] It has become apparent that stem cells, of which there are several varieties, are the cells ultimately responsible for all normal tissue generation and regeneration. Therapeutic regeneration of new tissues therefore also typically depends on direct or indirect manipulation of stem cells and such cells are now a major focus for research. A relatively new aspect of stem cell biology relates to the roles of stem cells in malignancy. This too is of markedly increasing research interest that focuses on their roles in metastasis and the need to target them therapeutically.

Entering the search term 'stem cells' into the PubMed database indicates that more than 20 000 papers relating to stem cells were published in 2015 alone (http://www.ncbi.nlm.nih.gov/pubmed). This brief chapter can only outline some of the aspects of stem cells potentially relevant to otorhinolaryngology and head and neck surgery. The initial aim will be to put stem cells in perspective by outlining the different sorts of stem cells that exist and by describing their common features. The second aim will be to outline current directions of stem cell research related to their potential clinical applications in otolaryngology.

GENERAL BACKGROUND: STEM CELL TYPES AND PROPERTIES

Adult tissue-specific stem cells

It has been known for well over a century that many tissues of the body are continuously renewed by cell division. Detailed studies of cell division in bone marrow, now over 50 years old, indicated that many blood forming cells have some ability to divide but that the ability to divide persistently, the key feature of stem cells, is possessed by only a subset of cells. Subsequent studies indicated that stem cells in the haematopoietic system can be identified by their expression of particular cell surface markers, are clonogenic *in vitro*, and have the ability to completely restore the haematopoietic system in mice whose bone marrow has been destroyed by irradiation.[2] These findings led to the concept of an adult (or 'somatic') stem cell as an immature cell that is capable of dividing indefinitely both to renew itself and produce cells maturing for tissue function. Cells with such properties have now been identified in most normal and malignant tissues.[3]

Although indefinite division is an essential stem cell property, the ability to produce differentiating cells is key to their function of tissue renewal and regeneration.

Some stem cells are able to generate cells entering several different lineages; haematopoietic stem cells, for example, generate cells that differentiate into the diverse range of cell types (e.g. erythrocytes, inflammatory and immune cells) found in blood.[3] Stem cells with the ability to generate many different types of cells are considered 'multipotent'. Other stem cells, for example those of the epidermis, normally produce cells of only a single lineage and are considered 'unipotent'. However, even cells that are normally unipotent may under some conditions, such as wound healing, be capable of generating cells of different lineages.

The advantages of somatic stem cells for clinical use are that they are readily expanded *in vitro*, usually maintain a stable differentiation pattern and, as they can be expanded from autologous tissue, initiate no immune rejection. Examples of established therapeutic uses of somatic stem cells include the transplantation of donor haematopoietic stem cells for the treatment of leukaemia, and the grafting of *in vitro* generated autologous sheets of epithelial cells for the treatment of burns or repair of corneal damage. A large current range of clinical trials of regenerative stem cell procedures include neural stem cell grafting for treatment of spinal cord injuries, embryonic stem (ES) cell-derived retinal cells for treatment of macular degeneration, stem cell-derived β-cells for treatment of Type 1 diabetes, and the use of stem cells to enhance healing after coronary infarction. When somatic stem cells with an appropriate differentiation pattern can be generated from biopsies of autologous tissue this usually forms the simplest approach but, if not, then re-differentiation of a multipotent stem cell of one of the types described below provides an alternative method.

Embryonic stem cells

About 20 years ago, it was discovered that cells of the inner cell mass of mouse blastocysts, the cells that would normally go on to form the embryo, can be isolated, greatly expanded *in vitro* and then differentiated into multiple cell lineages.[4] Such 'embryonic stem cells' (ES cells) were later also derived from human blastocysts. The controlled *in vitro* differentiation of ES cells into a required cell type can be directed using signals that mimic the tissue interactions that guide emergence of regionally appropriate cell lineages during embryonic development. Consequently, ES cells can provide an essentially unlimited source of relevantly differentiated cells.[4] However, ES cells are generated by destruction of living human blastocysts and strong opposition to the use of ES cells has been expressed on ethical grounds. A further major complexity is that tissues produced from ES cells express the histocompatibility antigens genetically determined by the donor embryo and, consequently, their compatibility with recipients is restricted to some immune-privileged sites, requires manipulation of the recipient's immune system, or modification of antigens expressed by the stem cell.

Induced pluripotent stem cells

Studies of ES cells led to the identification of genes associated with the maintenance of 'stemness' and it was found that induced expression of 'stem cell' genes such as *Oct4*, *Sox2*, *cMyc*, and *Klf4* in differentiated cells results in their acquisition of stem cell properties similar to those of ES cells (i.e. the ability to divide indefinitely and the pluripotency that enables differentiation into multiple cell types by *in vitro* manipulation).[5] The generation of such 'induced pluripotency stem cells' (iPSCs) demonstrates a degree of cellular plasticity beyond that previously thought feasible, and iPS cells represent a class of cells able to regenerate a wide range of tissue types. The pluripotency of ES cells, and the possibility of their generation from autologous adult tissues, has greatly stimulated research into their potential clinical use for replacement of tissues that are genetically defective or have been lost to damage or disease.[6] Concerns about potential carcinogenic effects of genetic alterations used to generate iPS cells have been addressed by development of methods for their induction without permanent genetic alteration. In addition to their value for clinical tissue replacement, iPS cells provide *in vitro* models of genetic diseases and for assays of drug effects.

Mesenchymal stem cells

Cells with multipotent stem cell properties can be isolated from various adult and foetal tissues, such as bone marrow, fat, dental pulp and umbilical cord, and it seems likely that similar cells are present in many adult tissues.[7] These mesenchymal stem cells (MSCs) are fibroblast-like, have good expansion and differentiation potentials, and also possess immune-modulatory properties.[8] Typically the cells differentiated from MSCs are osteoblasts or chondrocytes but greater plasticity with an ability to generate cells of non-mesenchymal lineages is suggested by reports of their differentiation into neurons or hepatocytes.[9] The ability to derive MSCs from various tissues and to manipulate their differentiation for use as autologous transplants has generated extensive clinical interest.

TISSUE ENGINEERING: METHODS FOR GENERATION OF TISSUES AND ORGANS FROM CELLS

Methods for the isolation, amplification and differentiation of stem cells can provide the basic cellular materials for tissue reconstruction. However, these biological advances lead to new challenges of how to assemble such cells into functional tissues or organs. Clinical use has so far been largely limited to cells, such as epithelial or chondrocytic stem cells, that are able to self-assemble into an appropriate tissue either *in vitro* or after delivery to an *in vivo* site. The further aim of tissue engineering is to exploit biomaterials and biologically active molecules to facilitate the production of more complex structures. It includes using bioactive substances to control cell behaviour, together with synthetic matrices and engineered scaffolds that both provide physical support for growth and assist with the delivery of constructs. Currently, however,

the construction of tissues that are formed of multiple cell types, and of organs that are too large to rely on simple diffusion for the supply of gases and nutrients needed for cell survival provide many technical problems. Biological approaches to overcome problems of construct vascularization have included supporting the growth of cellularized scaffolds by transplantation to surrogate hosts and by complex genetic manipulations that allow implanted human stem cells to form organs during the embryonic development of other species.[10] Rapid advances are, however, being made in three-dimensional cell culture with bio-printing, allowing patterned deposition of cells, and the development of novel perfusion bioreactors providing better support for cell growth.[11, 12] However, the application of these procedures to the regeneration of large organs remains essentially experimental and the cost of such organ production is a significant factor.

APPLICATION OF STEM CELLS TO CLINICAL PROBLEMS IN OTOLARYNGOLOGY

The anatomical area of interest to otolaryngology contains a wide range of tissues but stem cell research has shown the feasibility of generating a range of appropriately differentiated cells for clinical use in regenerating and reconstructing epithelial, cartilaginous, osseous, neural and mucosal tissues.

The ear and nose

Regenerative stem cell properties have been investigated to rectify common structural or functional problems of the ear, nose, tympanic membrane, cochlea, trachea and other structures. Congenital, traumatic, and neoplastic tissue loss, as well as cosmetic reasons, may generate a need to replace or modify the existing structure of the external ear or nose and existing procedures for reconstruction may involve skin expansion, rib harvesting and multistage surgery. An alternative approach is to use autologous stem cells to produce cartilage after seeding onto appropriately shaped scaffolds.[10] If needed, these can be invested in autologous epithelial sheets derived from epidermal stem cells provided by small epidermal biopsies, a well established technique long-employed for skin replacement of burns patients.[13] Such procedures can be expected to provide consistent results that reduce surgical complexity and post-operative morbidity. Small biopsies of ear or rib tissue can provide cartilage stem cells for expansion and aesthetically successful nasal reconstructions have been reported using engineered cartilage grafts generated from cartilage stem cells in biopsies from the nasal septum.[14] The uses of engineered cartilage for various other types of reconstruction are now being assessed. Augmented repair of chronic tympanic membrane perforation has focused mainly on the use of growth factors and biomolecules that have been demonstrated to enhance healing[15] but this appears to be a feasible area for the generation of matrices populated with autologous chondrocytes and epithelial cells.

Cochlea damage or degeneration

Sensorineural hearing loss resulting from inner-ear cochlear dysfunction involves the loss of sensory hair cells and/or spiral ganglion neurons. Loss of inner hair cells is currently irreversible but a range of stem cell procedures that aim to regenerate cochlea structures, such as hair cells and associated peripheral nerves, has been reported.[9] A primary issue is identifying types of stem cells appropriate for differentiation into sensory and neural progenitor cells, but equally challenging secondary issues are the differentiation of stem cells into the desired structures *in situ,* or the delivery of *in vivo* or *in vitro* differentiated stem cells to the right location. Rodent MSCs and some other stem cell types have been shown to differentiate *in vitro* into cells with hair cell properties indicating the feasibility of stem cell use. Of particular interest, a stepwise *in vitro* process that mimics normal developmental interactions, can differentiate murine ES cells into both functional mechano-sensitive hair cells and into sensory neurones that interact to form specialized synapses.[16]

The trachea

Replacement of lost tracheal tissue has been a focus of successful stem cell research. Autologous cartilage has been harvested to replace small defects but malignancy may be associated with more extensive tissue loss that requires more extensive replacement. Larger constructs require the structural strength to withstand collapse due to the negative pressure of inspiration and the need for transplants to clear secretions points to the need for an appropriately differentiated luminal epithelium within a multi-layered functioning trachea.[17] Successful five-year clinical results have been reported using a tissue-engineering strategy of bioreactor growth of a decellularized donor human trachea repopulated with cultured autologous epithelial stem-cells and MSC-derived autologous chondrocytes prior to transplantation.[1, 18] Further development that avoids the need for donor tissue has been construction of a bioartificial polymeric scaffold that models tracheobronchial size and morphology and which, after *ex vivo* seeding with autologous bone-marrow mononuclear cells and growth factor-induced mobilization of endogenous stem cells, was successfully transplanted as an airway replacement after cancer surgery.[19]

Larynx and vocal cords

Laryngeal injury and vocal cord (VC) disease can significantly impact upon vocal cord function and thus phonation. Current interventions in the management of vocal fold (VF) dysfunction focus on conservative and surgical approaches. However, the complex structure and precise biomechanical properties of the human VF mean that these strategies have their limitations in clinical practice

and may offer inadequate levels of success. Regenerative medicine has the potential to enhance VF recovery beyond that associated with conventional treatments.[20] So far, however, most investigations of the regenerative use of stem cells have been limited to assessment of various types of MSCs in animal models.[21] Cell-free scaffolds of collagen, hyaluronic acid or fibrin enhance laryngeal wound healing and attempts have also been made to activate resident somatic stem cells.[20] MSCs support VC remodelling and reduce scarring when directly injected, either alone or as part of a cell-scaffold composite, and MSCs in hyaluronic acid hydrogels provide both biologically active material and volume allowing for accelerated healing in small animals.[22] However, as VC remodelling can take up to six months in humans, it is uncertain whether MSCs persist long enough to benefit human repair.[22] The non-keratinized epithelium covering the VCs can potentially be replaced by *in vitro* expansion of stem cells from small biopsies of adjacent mucosae but human iPS cells can be differentiated in the presence of matrix molecules and growth factors into an appropriate non-keratinizing epithelium.[23]

Other tissues

Stem cell investigations to assist regeneration of a range of other tissues have been reported. For example, surgery of the head and neck can lead to peripheral nerve damage, with the facial and recurrent laryngeal nerves (RLNs) most commonly affected. Muscle-derived MSCs have been shown to improve outcomes in RLN injuries and work with facial nerve injuries has shown that neural regeneration following axonotomy is enhanced by a combination of neural-induced MSCs and platelet-rich plasma.[24] Interestingly, several regions of the nose act as sources of autologous stem cells, such as olfactory ensheathing cells, which assist neural and other regenerative procedures. Large deficiencies of the maxillofacial skeleton can result from traumatic damage, or resection following malignant invasion, and direct injection of MSCs, together with appropriate materials or scaffolds, can assist regeneration. Stem cells have also been discussed with regard to improvement in scars following surgery or trauma and there is a large body of literature that considers MSCs and scars.

CANCER STEM CELLS: TUMOUR GROWTH, INVASION AND METASTASIS

Many solid tumours respond poorly to current therapies and, on average, only about 50% of HNSCC patients survive longer than five years from diagnosis. Recent work confirms that tumours contain subpopulations of altered stem cells, termed 'cancer stem cells' (CSCs) and that tumour growth is ultimately dependent on these cells.[3, 25] Stem cell patterns have been identified in squamous cell carcinomas and also in the minority glandular tumours.[26, 27] CSCs have unique properties of direct clinical interest including resistance to therapy and the ability to invade locally and metastasize.[25] The mechanisms of the stem cell changes that lead to cancer remain unclear but, despite enhanced stem cell DNA repair,[28] tobacco and alcohol have mutational effects and an increasing number of oropharyngeal tumours result are associated with human papilloma viruses that act to increase the number of SCs and alter their behaviour.[29, 30]

The homeostatic state of renewing tissues such as skin and mucosae is normally maintained by SC divisions that renew the SC population while also producing cells that differentiate. Many signalling pathways that affect division patterns (e.g. Notch, Wnt, Sonic hedgehog) are dysregulated in malignancy leading to a shift of CSC divisions towards greater self-renewal, which leads to an increasing number of CSCs and loss of tumour growth control.[3] Normal stem cells (SCs) have several mechanisms to maintain their integrity and enhancement of these mechanisms in CSCs results in greater resistance when challenged with radiation or chemotherapeutic drugs and provides them with a survival advantage over non-CSCs.[28–31] However, such mechanisms for enhanced tumour growth and resistance do not explain how CSCs escape from a tumour to invade locally or metastasize distantly, the events causing most cancer deaths. Basic research implicates epithelial-mesenchymal transition (EMT) as the process by which tightly cohesive epithelial cells acquire mesenchymal characteristics and lose mutual attachment to gain motility[32] and it is proposed that this mechanism allows CSCs to escape from the tumour and migrate to distant sites where they then revert back to the proliferative epithelial phenotype to produce secondary tumours.[33] The mechanisms of reversion of cells back to the epithelial phenotype are not well understood but the molecular mechanisms of EMT indicate that the level of EMT occurring in a particular tumour depends partly on intrinsic tumour properties and partly on extrinsic stromal factors such as cytokines and hypoxia.[34–36]

CSCs were initially defined by their ability to initiate tumours in immune-deficient mice after their isolation on the basis of their expression of cell surface markers.[3] Such tumour initiating subpopulations of CSC have been identified in both fresh HNSCC and in passaged HNSCC cell lines.[37, 38] Identification was initially achieved using the CD44 marker but a range of other cell surface or enzymatic markers has subsequently been employed. Analyses of CSC behaviour continue to support the conclusion that their elimination is necessary for successful therapy and many different therapeutic mechanisms are being explored to target CSCs.[31] These include using antibodies against particular CSC surface markers to deliver cytolethal agents,[39] development of drugs to inactivate CSC self-renewal pathways,[40] and reducing CSC resistance to radiation or drugs.[41] However, concerning chemotherapeutic drugs, the plasticity of CSCs generates cells that differ in their drug or radiation responses and are also able to switch between phenotypes. Thus elimination of CSCs may require drug combinations and assays to assess drug effects on each of the CSC phenotypic manifestations and these are being developed.[42]

KEY POINTS

- Stem cells are the ultimate origin of the wide variety of cells generated during embryological development and are responsible for all subsequent tissue growth and regeneration.
- Stem cells are also responsible for the growth and treatment resistance of malignant tissues.
- Recent research has disclosed many aspects of the control mechanisms underlying stem cell behaviour and has enabled their manipulation.
- This information is now being used to develop methods for clinical tissue regeneration and for cancer therapy.

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CHAPTER 8

AETIOLOGY AND PATHOGENESIS OF GOITRE

Neil Sharma and Kristien Boelaert

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: thyroid, goitre, pathogenesis, aetiology, nodular and iodine. Reference lists for selected papers were examined for further sources.

INTRODUCTION

Thyroid enlargement is common, and has been recognized for almost two millennia. The exact definition of goitre has evolved over time, depending on the examination methods available. Based on autopsy studies, a thyroid was initially considered to be enlarged if weighing greater than 35 g, and the use of high-resolution ultrasound has led to the currently accepted definition of >18 mL in women and >25 mL in men.[1, 2] Variations in this cut-off globally have meant direct comparison between population studies is often problematic.

Previous autopsy studies reported the prevalence of thyroid nodules to be in excess of 50% in clinically normal thyroids;[3, 4] however, these studies were carried out prior to the iodization programs seen in many parts of the world and this is therefore probably an overestimation, with the current incidence lying between 25% and 50%.[1] Goitre can be classified as physiological or pathological – the former is found often in teenage girls and is without clinical significance. The latter comprises both benign and malignant; the focus of this chapter will be the benign multinodular goitre (**Figure 8.1**), with other causes of thyroid enlargement covered in other chapters.



Figure 8.1 A multinodular thyroid following excision.

FACTORS INFLUENCING GOITRE FORMATION

The aetiology of benign pathological goitre can be broadly split into environmental and genetic factors, although these rarely exist in isolation and a thorough understanding of each is therefore essential.

Environmental factors

IODINE DEFICIENCY

Iodine deficiency is the biggest contributor to goitre. In 2004 the World Health Organization estimated that 2 billion people were iodine deficient, including approximately 285 million school-aged children.[5] It is thought around 45% of Europeans are iodine deficient,[6, 7] and in many parts of the world with universal iodine deficiency, goitre is endemic. The most common dietary sources of iodine are fish and dairy products, with a balanced diet being sufficient to maintain an adequate intake of 150 mcg/day for (non-pregnant) adults.[8, 9] Iodine deficiency is measured using the surrogate marker of urinary iodine concentration (UIC), usually corrected for creatinine excretion. Iodine sufficiency is defined as UIC greater than 100 µg/L, moderate deficiency as UIC below 50 µg/L and severe deficiency as UIC below 25 µg/L.[10, 11] Thyroid volume directly correlates to UIC (Figure 8.2); in addition, increased UIC also negatively correlates with thyroid nodule prevalence.[1]

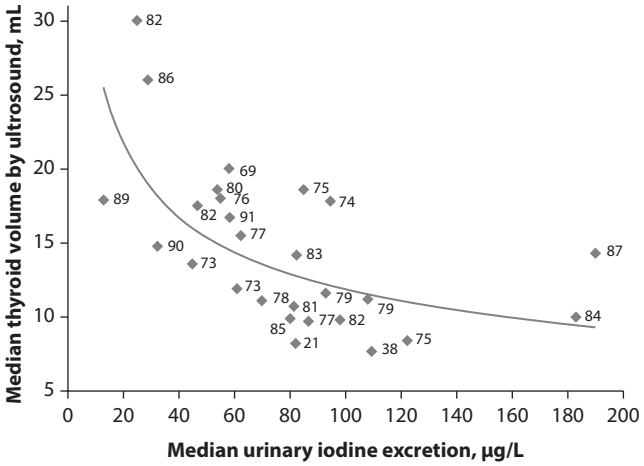


Figure 8.2 Graph demonstrating the fall in thyroid volume as urinary iodine excretion rises. From Carle A, Krejbjerg A, Laurberg P. Epidemiology of nodular goitre. Influence of iodine intake. *Best Pract Res Cl En* 2014; **28**(4): 465–79.[1]

Various programs exist across the developed and developing world to improve iodine status, one of the most effective being mandatory iodization of salt. This is not universal, however, and many countries including the UK do not enforce this. In 2006, the World Health Assembly recommended that countries carry out surveys of iodine status using sampling of UIC as a marker.[10] The first national survey in the UK was carried out in 2011 and found that in female schoolchildren between the age of 14 and 15 years, the median UIC was 80.1 µg/L, with 67% of the cohort being iodine deficient (17% moderately or severely so).[12] The consequences of iodine deficiency in relation to prevalence of goitre among school children are shown in Table 8.1, and these findings therefore potentially pose a significant public health burden.

The consequences in pregnancy are also potentially severe. A recent study examining mother-child pairs in the UK measured maternal UIC in the first trimester of pregnancy and correlated this with the child's cognitive development at age 8 years. The researchers found that even mild iodine deficiency in early gestation was associated with lower scores for verbal IQ, reading accuracy and reading comprehension (Figure 8.3), emphasizing that even in developed countries there is a significant public health risk from iodine deficiency spanning several generations.[13]

Although there are several known environmental goitrogens, all of these must be examined in the context of iodine status of both the individual and the population, as some environmental causes will have significant effects when iodine is deplete, with some or no effect in iodine sufficiency (Table 8.2).

POLLUTANTS

Thiocyanate is found in cigarette smoke and also environmentally in cassava, which is a major source of carbohydrate in Africa and associated with an increased incidence of goitre.[19] Nitrate sources include vegetables and drinking water; contamination of water with nitrate from agriculture leads to an odds ratio for goitre of 3 when assessed in iodine-replete Bulgarian school children,[20] although no link was found between urinary nitrite excretion and thyroid volume in a German study.[21]

TABLE 8.1 Relationship of iodine status to goitre prevalence in schoolchildren

Median UIE (µ g/L)	Iodine status	Goitre among schoolchildren	Consequences
<20	Severe ID	>30%	Endemic cretinism, hypothyroidism, endemic nodular goitre
20–49	Moderate ID	20–29.9%	Endemic nodular goitre, low IQ, hyperthyroidism more often than hypothyroidism
50–99	Mild ID	5.9–19.9%	Hyperthyroidism more often than hypothyroidism, nodular goitre
100–199	Iodine sufficiency	<4.9%	Optimal balance between various thyroid disorders

Source: From WHO, UNICEF, ICCIDD. *Assessment of iodine deficiency disorders and monitoring their elimination*. 3rd ed. Geneva: World Health Organization; 2007.

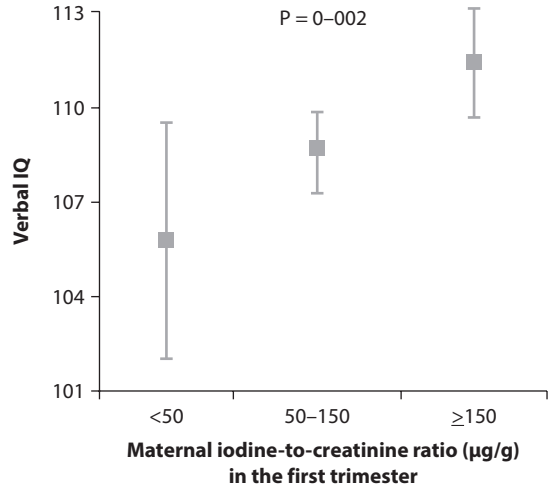


Figure 8.3 A deficient maternal iodine status is associated with poorer performance in a number of cognitive tests in offspring. From Bath SC, Steer CD, Golding J, et al. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Lancet* 2013; **382**(9889): 331–37.[13]

Isoflavones are found in soybeans and inhibit thyroid peroxidase; however, population studies give mixed results in terms of goitre formation.[22, 23] In our laboratory, we have used a soybean rich diet in our mouse models of goitre and see an increased thyroid size, a finding that reported by several other researchers.

Organochlorides present in solvents and pesticides have become less prevalent as most of these are now banned. They have, if any, only a mild goitrogenic effect and this should decline as their use tails off.[24]

Perchlorate, a potent inhibitor of iodine uptake, is found in rocket fuel and accelerants, bleach and some fertilizers. It has not been shown to have any effect clinically on thyroid function at the levels encountered though environmental exposure, and it is therefore unlikely to have any effect on thyroid volume.[25] The US Environmental Protection Agency found perchlorate in 4% of drinking water samples tested nationally, and subsequently has issued notice that the perchlorate content of water will be regulated. The cut-off for detectable levels was, however, many orders of magnitude lower than that thought necessary to cause thyroidal effects.

TOBACCO

Tobacco smoking is another major risk factor for goitre development and is most marked in iodine deficient populations. Different studies report an odds ratio of between 1.5 to 3 for goitre in smokers, although variations in background iodine status make meta-analysis challenging.[18] Thiocyanates are a major constituent of tobacco smoke and it is likely that these contribute to the increased risk.

SELENIUM

Selenium, like iodine, is necessary for thyroid hormone synthesis although to a much smaller degree. In addition, selenoproteins are important in the recycling of hydrogen peroxide generated by thyroid peroxidase. It is likely that selenium deficiency plays a cumulative role in nodule formation alongside iodine deficiency.[26]

ORAL CONTRACEPTIVE PILL

While intuitively it may be thought that the OCP would be a risk factor for goitre development, the converse appears to be true. OCP use is associated with a lower thyroid volume (8.5 mL vs. 9.4 mL^2) and low odds ratio (0.6)[27] for the development of goitre compared with no use; the mechanism for this is unexplained, but one theory is that exogenous oestrogens suppress the endogenous, goitrogenic ones. This is an avenue that warrants further exploration.

METABOLIC SYNDROME AND INSULIN RESISTANCE

Insulin resistance is becoming an increasingly studied risk factor given the rise in prevalence of metabolic syndrome across the Western world. Nodules were found in 53% of patients with insulin resistance compared to 19% without, and these results are mirrored in patients with metabolic syndrome, all in areas with a degree of iodine deficiency.[28, 29] Metformin has shown some positive effects in reducing thyroid volume in these patients, although results are not conclusive.[30, 31]

Genetic Factors

In addition to the well-studied environmental factors affecting thyroid growth, the familial clustering of goitres combined with the higher prevalence in females

TABLE 8.2 Relative contribution of genetic and environmental factors to goitre development with varying iodine status

Study	Country	Iodine status	Genetic factors (%)	Environmental factors (%)
Greig et al. 1967[14]	Scotland	Deficient	39	61
Brix et al. 1999[15]	Denmark	Mildly deficient	82	18
Hansen et al. 2004[16]	Denmark	Mildly deficient	71	29
Hansen et al. 2005[17]	Denmark	Mildly deficient	77	23

Source: Adapted from Knudsen N, Brix TH. Genetic and non-iodine-related factors in the aetiology of nodular goitre. *Best Pract Res Cl En* 2014; **28**(4): 495–506.[18]

suggests a genetic component to the disease, and this is becoming increasingly studied. While genetic factors are more significant in iodine deficient areas, families and small groups around the world show increased thyroid volume despite iodine supplementation, adding further evidence to a genetic cause. On a population level, discrete genetic causes are difficult to ascertain and therefore twin studies provide the best direct evidence of a genetic basis to goitre formation. In both endemic and non-endemic areas, monozygotic twins demonstrate a higher concordance for goitre development than dizygotic twins (Figure 8.4).

THYROID-SPECIFIC GENES

The identification of specific genes that predispose to goitre formation has mainly focused on those that are known to have a role in the normal physiology of the thyroid gland. Generally speaking, genetic mutations leading to suppression of thyroid hormone production/iodination have been associated with increased thyroid volume (i.e. gene alterations in those coding for the TSH receptor (TSHR), sodium iodide symporter (NIS), pendrin (PDS), thyroid peroxidase (TPO) and thyroglobulin (TG)) (Table 8.3).

NON-THYROID-SPECIFIC GENES

A number of putative non-thyroid-specific loci, associated with goitrogenesis, have been identified through genetic linkage analysis. This method uses the rearrangement of known chromosomal markers to identify candidate areas. The specific details are beyond the scope of this chapter but are summarized in Table 8.4; for further information see the review by Krohn et al.[32] It remains to be seen whether the increasing use of next-generation whole exome sequencing will elicit more candidate genes; as yet benign goitre has not been a main focus of this research.

Although multiple genes have been identified that predispose to goitre formation, the majority of cases will be polygenic and heavily influenced by the environmental factors discussed above. These factors, inherent and exogenous, all feed into the pathogenic model for goitre formation discussed below.

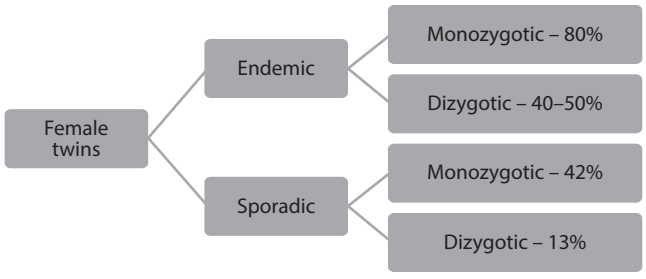


Figure 8.4 Preponderance to goitre in mono- and dizygotic twins. Adapted from Krohn K, Fuhrer D, Bayer Y, et al. Molecular pathogenesis of euthyroid and toxic multinodular goiter. *Endocr Rev* 2005; **26**(4): 504–24.[32]

TABLE 8.3 Thyroid-specific genes with mutations linked to goitre formation

Mutated gene	Thyroid state
TG	Hypothyroid[33, 34]
TPO	Hypothyroid[35] (/euthyroid[36])
TSHR	Euthyroid[37]
PDS	Euthyroid[38]
NIS	Hypo/euthyroid[39, 40]

TABLE 8.4 Non-thyroid-specific genes associated with goitre

Gene candidate	Locus	Reference
MNG-1	14q31	Bignell et al. 1997[41]
MNG-2	Xp22	Capon et al. 2000[42]
MNG-3	3?	Takahashi et al. 2001[43]
N/A	2q, 3p, 7q, 8p	Bayer et al. 2004[44]

PATHOPHYSIOLOGY

Development of a multinodular goitre occurs in two phases: (i) a goitrogenic stimulus leading to global thyrocyte proliferation and increase in overall thyroid size, and (ii) focal increase in proliferation leading to nodules (Figure 8.5). Evidence for this is based largely on older animal studies,[45–47] although the same principles do seem applicable to human disease.

Goitrogenic stimulus

Under the influence of (most commonly) iodine deficiency, or another goitrogen, global hyperplasia occurs with increased thyroid hormone synthesis (there is evidence that some patients will adapt to iodine deficiency with hypertrophy without hyperplasia,[48] although the mechanism for this is unclear). This increased production leads to a rise in hydrogen peroxide (H_2O_2) generation and free

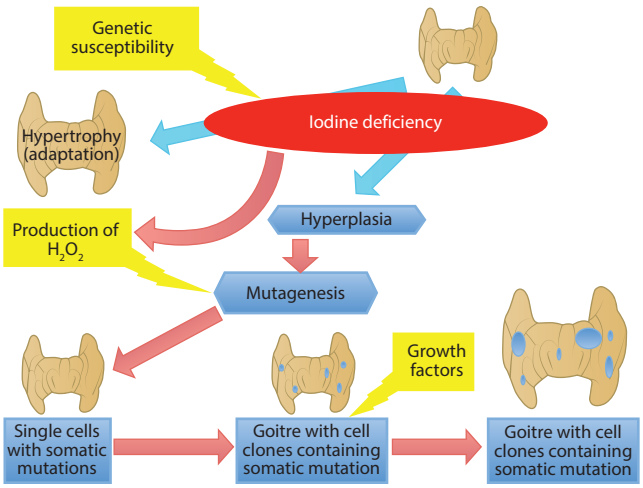


Figure 8.5 The bimodal model for development of goitre. From Krohn K, Fuhrer D, Bayer Y, et al. Molecular pathogenesis of euthyroid and toxic multinodular goiter. *Endocr Rev* 2005; **26**(4): 504–24.[32]

radical formation, resulting in a significant increase in spontaneous mutation rates.

Nodule formation

The combination of high spontaneous mutations coupled with increased cell replication rate results in an increased mutagenic load, and the chances of randomly generated mutations with a growth advantage are therefore significantly increased. The proliferating thyroid will be replete in growth factors (e.g. insulin-like growth factor (IGF), transforming growth factor (TGF), epidermal growth factor (EGF)), which will stimulate the division of all cells, including those with activating mutations. When the goitrogenic stimulus is removed, the proliferation of normal thyrocytes will cease whereas the activated cell clones will continue to proliferate, thus forming nodules. The nature of the mutation will determine whether the nodule is autonomously functioning or 'cold'; for example, an activating mutation of the cyclic AMP cascade will stimulate both growth and function, whereas one in the MAPK pathway will lead to proliferation only and a cold nodule. It follows, therefore, that multinodular goitre is a polyclonal entity, as opposed to a monoclonal one, with different nodules displaying different characteristics, which accounts for their heterogenous appearance on both imaging and pathological studies.

HORMONAL FACTORS REGULATING THYROID GROWTH

Thyroid growth and homeostasis is controlled by a number of factors other than iodine, through endo-, auto- and paracrine pathways. The principal stimulator of growth is TSH, the receptor for which is situated on the basal membrane of thyroid epithelial cells and belongs to the G protein-coupled receptor family. This in turn activates cellular processes including the adenyl cyclase-cAMP system promoting growth. Similar to the Wolff-Chaikoff effect (reduced thyroid function in the presence of very high levels of circulating iodine), high serum TSH concentrations have been shown to have an inhibitory effect on thyroid cell proliferation *in vitro*[49] (Figure 8.6).

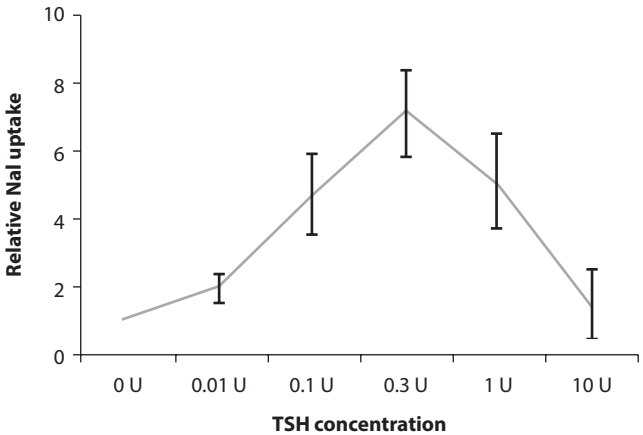


Figure 8.6 Reduction in iodide uptake by primary cultured thyroid cells with high concentrations of TSH.

TABLE 8.5 Growth factors acting on the thyroid gland to promote/inhibit growth

Activation pathway	Factors	Effect
AC-cAMP-PKA	TSH	Stimulatory and inhibitory
	Epinephrine	Stimulatory
Receptor tyrosine kinases	EGF	Stimulatory
	TGF-α	Stimulatory
	FGFs	Stimulatory
	Insulin	Stimulatory
	IGF-I	Stimulatory
	HGF	Stimulatory
	PDGF	Stimulatory
Phosphatidylinositol cascade	TSH	Stimulatory
	Esters	Stimulatory
	TGF-β	Inhibitory
	Iodides	Inhibitory

Source: Adapted from Konturek A. Thyroid growth factors. In: Ward L (ed). *Thyroid and parathyroid diseases*. Intech; 2012.[50]

Other factors that act locally to promote growth and angiogenesis include insulin, EGF, TGF-α/TGF-β, IGFs, fibroblast growth factors (FGFs), hepatocyte growth factor (HGF) and platelet-derived growth factor (PDGF). The particular signalling cascades that involve these mitogenic factors are summarized in Table 8.5.[50]

NOVEL THERAPIES

The surgical management of both benign and malignant thyroid disease is covered in depth in other chapters. It is, however, important to remember that globally, for many patients, surgery is not an option, either through patient non-suitability for general anaesthetic or lack of access to the appropriate facilities. Non-surgical treatment modalities are unfortunately lacking, although laboratory studies are ongoing to identify new therapies, usually by targeting specific growth factors receptors such as VEGF-R and FGF-R.[51]

SUMMARY

Goitrogenesis is a complex process reliant on an interplay of environmental and genetic factors, the extent of which is dependent on the underlying iodine status of the individual. While an understanding of these various processes is important, the most important factor to correct globally in order to reduce the prevalence of goitre is iodine deficiency, which continues to be a focus of the WHO – especially in developing countries. The role of iodine deficiency in the developed Western world, however, should not be ignored and continued efforts to ensure populations achieve their required intake should be supported.

FUTURE RESEARCH

- The role of iodination programs in the developing world to combat endemic goitre.
- Further understanding of the interplay between the metabolic syndrome and goitre formation, especially in view of the worldwide rise in obesity.
- Further characterization of the role of non-thyroid-specific genes in goitre formation and progression.
- Use of gene targeting therapies/recombinant adenovirus treatments in the non-surgical management of goitre.

KEY POINTS

- Benign thyroid enlargement is common.
- The biggest aetiological factor in the development of goitre is iodine deficiency.
- There is a complex interplay between environmental and genetic factors that determines the nature of the goitre.
- An understanding of the growth factors involved in thyroid hypertrophy and hyperplasia will aid the clinician in determining the likely progression of disease and best treatment options.

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CHAPTER 9

GENETICS OF ENDOCRINE TUMOURS

Waseem Ahmed, Prata Upasna and Dae Kim

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: thyroid cancer, molecular biology, parathyroid cancer, parathyroid adenoma and molecular genetics.

GENETICS OF THYROID TUMOURS

Introduction

Thyroid malignancy is the most common cancer of the endocrine organs. Most thyroid cancers originate from thyroid follicular cells and can be subdivided into well differentiated papillary and follicular carcinoma, poorly differentiated carcinoma and anaplastic carcinoma.[1] Medullary thyroid cancer (MTC) accounts for a small proportion of thyroid cancers.[2]

Understanding of the molecular pathogenesis of thyroid cancer has progressed rapidly in the last decade. The genetic aberrations and alterations in signalling pathways have helped reshape our insights into thyroid cancer aetiology and management of patients with thyroid nodules.

Oncogenes and tumour suppressor genes in thyroid cancer

Cancer is a complex, multistep process. However, recent years have seen major advances in understanding the role of two classes of genes that are of particular importance in carcinogenesis that provide a more comprehensive picture: oncogenes and tumour suppressor genes. Several of the known oncogenes have been consistently detected in differentiated thyroid neoplasms. Some are more strongly associated than others and, interestingly, few are limited to specific forms of thyroid tumours.

GENE MUTATIONS

B-RAF (BRAF) mutation

BRAF is a serine/threonine kinase and is a member of the mitogen-activated protein kinase (MAPK) pathway, involved in the transduction of mitogenic signals from the cell membrane to the nucleus within. *BRAF* gene mutations have been shown to be common in many different human cancers.[3] Several studies have recently identified the most common *BRAF (V600E)* mutation, T1796A transverse mutation, in 29–69% of papillary thyroid cancers.[4–8] *BRAFV600E* mutation has been demonstrated to be a novel prognostic biomarker that predicts poor clinic-pathological outcomes such as extra-thyroidal invasion, advanced pathological stage invasion, metastasis and relapse of PTC.[8–9] *BRAF* mutation has also been associated with loss of radioiodine avidity and treatment failures.[10]

In contrast to classical genetic mutations in thyroid cancers such as *RET-PTC* and *RAS* mutations, which are also apparent in some benign thyroid lesions, this mutation has consistently been reported to be 100% specific for PTC. Consequently, *BRAF* mutation has been proposed as a specific molecular marker with high sensitivity for the diagnosis of PTC and represents a useful diagnostic adjunctive technique in the evaluation of thyroid nodules with indeterminate cytological findings.

RAS

The *RAS* proto-oncogene codes for a G-protein, p21, which is found within cell membranes. p21 plays a critical intermediate role in connecting the stimulatory signal

from tyrosine kinases such as EGF receptor and via Raf-1 to a mitogenic cascade involving the MAP kinases.[11] *RAS* mutations are found in 30% of human cancers, making this the most widely mutated human proto-oncogene. Activated *RAS* has been detected previously in 20% of papillary carcinomas and 53% of follicular carcinomas.[12] Three families of *RAS* oncogenes have been identified (*K-RAS*, *H-RAS* and *N-RAS*), each located in separate chromosomal locations. Although downstream targets of *RAS* mutations include MAPK and P13K signalling, there appears to be preferential activation of the P13K-AKT pathway.[13]

The prevailing view is that *RAS*-activation probably represents an early event in thyroid tumourigenesis and is itself not sufficient for malignant transformation. Studies have shown *RAS* to be present in a high proportion of the earliest forms of thyroid tumours. Others have noted normal cells immediately adjacent to *RAS*-containing tumour cells also to harbour *RAS*.[14]

C-Myc, c-Fos, c-Met

Mutations of several other proto-oncogenes such as *c-Myc* (nuclear transcriptional factor family), *c-Fos* and *c-Met* have also been demonstrated in differentiated thyroid cancers (see Reviews).[15–16]

The *c-Myc* proto-oncogene encodes a nuclear protein that binds to DNA and acts as a transcriptional factor for genes involved in growth and differentiation. *c-Fos* is an immediate/early gene that regulates the expression of specific target genes by binding to their regulatory sequence of DNA. Aberrant activation of this transcriptional regulator has been demonstrated in thyroid tumours.[17]

Met protein is a transmembrane receptor with tyrosine kinase activity. Oncogene activation is associated with mitogenesis as well as motogenesis and has been suggested to contribute to tumour aggressive and metastatic behaviour.[18] *Met* oncogene is seen in various cancer human types, including up to 70% of papillary and 25% of follicular carcinomas, although it is not detected either in MTC or in normal thyroid tissues.[19]

GENE TRANSLOCATIONS

RET-PTC gene rearrangements

The thyroid carcinoma gene, *PTC*, is an oncogene found in 25% of papillary thyroid cancers, which was initially described by Fusco et al.[20] Subsequently, it was discovered to be a fusion between a gene of unknown function (*D10S170*) and the TK domain of the *RET* proto-oncogene as a result of a chromosomal rearrangement.[21] The *RET* proto-oncogene codes for a transmembrane protein with tyrosine kinase activity, the activity of which is normally restricted to a subset of cells derived from embryonic neural crest cells.[22]

Although the *RET* proto-oncogene is not expressed in normal thyroid follicular cells, the rearranged *RET/PTC* oncogene is highly expressed in some papillary thyroid cancer cells.[23] *PTC/RET* rearrangements are generally specific for papillary carcinomas and have been found in 5–40% of papillary thyroid cancers (PTC) in adults and are more common in paediatric PTC, as well as in cancers from children exposed to ionizing radiation.[24, 25–28]

There are more than 10 types of translocation, the most common being *RET/PTC1* and *RET/PTC3*.[29–30] The oncogenic capabilities of *RET/PTC* are achieved through activation of both MAPK and P13K-AKT pathways.

PAX8/PPARG rearrangement

The paired box 8 (*PAX8*)–peroxisome proliferator-activated receptor-γ (*PPARG*) fusion gene (*PAX8/PPARG*) rearrangement occurs as a genetic translocation between chromosomes two and three. This inhibits the tumour suppressor activity of *PPARG* and also transactivates certain *PAX8*-responsive genes.[31] The rearrangement occurs in up to 60% of follicular thyroid carcinoma (FTC) and follicular variant of papillary thyroid carcinoma (FVPTC).[32]

TUMOUR SUPPRESSOR GENES

P53

The tumour suppressor p53 regulates cell response to DNA damage and allows for repair or apoptosis when cells are severely damaged. Inactivating mutations of p53 gene are common in human cancers; however, they are only present in 10% of thyroid malignancies.[33] The majority of such mutations are found in poorly differentiated and aggressive histotypes.[34] This suggests p53 plays a minor role in thyroid malignant transformation and in early stages of thyroid cancer, unlike many other human malignancies. However, evidence suggests that although p53 mutations may not occur in thyroid tumours, its activity may be inhibited by other mechanisms,[35] especially in early stage thyroid cancer.[36]

SIGNALLING PATHWAYS

There are several important signalling pathways involved in the development and propagation of thyroid cancer. The common mutations described above are key genes in these signalling pathways.

The MAPK signalling pathway

The mitogen-activated protein kinase (MAPK) pathway plays a major role in the regulation of cell proliferation and survival and in human tumourigenesis. Activation is often due to mutated *RAS*, *BRAF* or by *RET-PTC* reported widely in papillary thyroid cancer.[37] Secondary molecular events amplifying this pathway such as hypomethylation and genome-wide hypermethylation, and upregulation of various oncogenic proteins can also occur. These include chemokines, nuclear factor kB (NF-kB), vascular endothelial growth factor A (VEGFA), matrix metalloproteinases (MMPs), and transforming growth factor-β1 (TGFβ1).[38]

The PI3K-AKT signalling pathway

The role of P13K-AKT pathway in thyroid tumourigenesis became apparent when the association of follicular thyroid adenoma and carcinoma was noted with Cowden's syndrome (caused by germline mutations of *PTEN*),[39]

and high levels of AKT expression established in the latter (when compared to PTC or normal thyroid tissue).[40] Furthermore, evidence of AKT mutations and their occurrence in metastatic thyroid cancer[41] has validated the central role of PI3K-AKT pathway in the invasive and metastatic capabilities of FTC. Aberration of the PI3K/AKT pathway appears to play a pivotal role in tumourogenesis in both FTC and ATC, promoting progression of adenoma to FTC, and subsequently ATC.

The NF-κB signalling pathway

It has been suggested that activation of NF-κB may promote dedifferentiation of PTCs and FTCs.[42] Studies have demonstrated the NF-κB pathway's role in anti-apoptotic and proliferative signalling pathways in thyroid cancer.[43] Emerging evidence of deregulated NF-κB activity in ATC helps provide further insight into the molecular biology of thyroid cancer and identify it as a potential target to inhibit the pro-survival signalling in thyroid malignancy.[43]

The WNT-β-catenin signalling pathway

The pathway plays a role in regulating cell proliferation and differentiation. Abnormal signalling and its role in thyroid tumourogenesis has been established. Activation of WNT-β-catenin pathway is secondary to mutations of *CTNNB1* (which encodes β-catenin),[44] a likely late event not evident in well differentiated carcinomas. Expression of β-catenin, a cytoplasmic protein regulating the coordination of cell–cell adhesion and gene transcription, is more prominent in ATC compared to DTC.[45]

ABERRANT GENE METHYLATION

Epigenetic silencing through aberrant gene methylation are hallmarks of cancers including thyroid malignancy. Methylation of thyrotropin receptor (TSHR), E-cadherin (ECAD), sodium iodide symporter protein (NIS-L) are frequent in PTC.[46] The *BRAFV600E* mutation has been associated with a combination of hypermethylation and hypomethylation of genes involved in important metabolic and cellular functions in PTC.[47] Hypermethylation of several tumour suppressor genes are also associated with increased PTC aggressiveness.[48] Evidence shows down-regulation of PTEN tumour suppressor due to changes in methylation is associated with increased activity of the P13K-AKT pathway, in thyroid cancer.[49]

Genetic alterations in medullary thyroid cancer

Medullary thyroid cancer (MTC) is an aggressive form of thyroid cancer, accounting for less than 5% of thyroid malignancies.[50] It is a neuroendocrine carcinoma arising from the parafollicular C-cells and associated with secretion of calcitonin and various other hormones such as carcinoembryonic antigen (CEA). Sporadic MTC accounts for 75% of cases, with inherited MTC accounting for the remainder. The majority of the latter occurs in association with multiple endocrine neoplasia (MEN) type 2A, MEN2B, and familial medullary thyroid carcinoma syndrome (FMTC) syndromes.

RET GENE

The various forms of hereditary MTC are caused by germline *RET* mutations and are all autosomal dominant with high penetrance. Somatic *RET* mutations are responsible for a subset of sporadic MTC.[51] The *RET* oncogene plays a major role in MTC tumourogenesis, with *RET* mutations being identified in 98% of MEN2A patients, 95% of MEN2B patients, and 88% of those with FMTC.[52] As noted previously, *RET* signalling activates both MAPK and P13K-AKT pathways, playing a key role in cell growth, differentiation and survival.

ABERRANT GENE METHYLATION

Hypermethylation of *RASSF1A* (*RASSF1*), a known tumour suppressor gene within the P13K-AKT pathway, has been noted in the majority of FTCs and less frequently in benign adenomas and PTC.[53] Due to its high prevalence in MTC (85%), it may indicate a role in MTC tumourogenesis.[54]

MICRORNAS

MicroRNAs are small non-coding RNA genes (containing about 22 nucleotides) that function in RNA silencing and post-translational regulation of gene expression. MicroRNAs deregulation in MTC is thought to be an early event in parafollicular C-cell carcinogenesis.[55]

Genetic alterations in anaplastic thyroid cancer

Anaplastic thyroid carcinoma remains a devastating disease. ATC constitutes 5% of all thyroid cancer and yet accounted for 50% of all thyroid cancer deaths in the United States in 2006.[56] Molecular research in anaplastic carcinoma has been limited due to its rarity and aggressiveness, relying mainly on *in vivo* cell line studies. Experimental models involving xenografts in athymic mice has allowed further study of this aggressive endocrine disease. Despite our limited understanding, it is generally accepted that anaplastic cancer does not arise *de novo*, but is likely to evolve from established well-differentiated thyroid cancer (PTC or FTC).[57]

There are two groups of mutations evident in the ATC tumourogenesis. The first set of mutations is abundant within well differentiated thyroid cancer (WDTC) and ATC. Examples include *BRAF* and *RAS* point mutations and are likely to represent early changes.[58] The second group are found largely in ATC and are noted for their absence in WDTC. These are likely to represent late changes and are involved in dedifferentiation; p53 and β-catenin.

Mutations in p53 impairing transcriptional activity are found in 55% of ATCs[58] enabling accelerated genomic

instability, growth, angiogenesis and dedifferentiation. Redifferentiation of ATC tissue has been demonstrated with reintroduction of wild type p53 and the restoration of cellular responsiveness to physiologic stimuli (thyroid stimulating hormone) and re-expression of thyroid peroxidase.[59] E-cadherin and β-catenin are epithelial adhesion molecules in normal epithelium. There is reduced expression of both in ATCs when compared to the originating WDTC from which they evolve, suggesting the E-cadherin/β-catenin complex plays a role in this transformation process.[60]

KEY POINTS

- Several gene mutations and alterations in signalling pathways are now recognized as important events in the development and progression of thyroid cancer.
- *RAS* mutations appear to be an early event, as they are common to benign and malignant tumours. The subsequent pathways leading to follicular or papillary carcinoma are divergent.
- Mutational activation of *BRAF* and *RET/PTC* oncogenes are specific to papillary carcinomas. Conversely, loss of function of a gene on chromosome 11q13, possibly *MEN1* gene, may direct the tumour clone towards a follicular phenotype.
- Mutations of p53 are highly prevalent in anaplastic thyroid carcinomas, and together with mutations in the *RB* gene, may represent the critical transitional step in the progression of well-differentiated tumours into these aggressive thyroid cancers.

GENETICS OF PARATHYROID TUMOURS

Introduction

Primary hyperparathyroidism is a commonly detected endocrine disorder having a prevalence of 1–3:1000 in the general European population.[61] The most common cause of primary hyperparathyroidism is a parathyroid adenoma accounting for ~85% of cases. Parathyroid adenomas are more commonly sporadic, or inherited as part of multiple endocrine neoplasia (MEN) syndromes, familial hyperparathyroidism or hereditary hyperparathyroidism with jaw tumours (HPT-JT). Parathyroid carcinomas are rare and account for less than 1% of cases of hyperparathyroidism.[62]

Parathyroid adenomas

Previous investigations of the molecular pathogenesis of parathyroid tumours have only yielded mutations accounting for the minority of tumours. Investigations of the *PTH* gene, which is located on chromosome 11q15, detected restriction fragment length polymorphism (RFLP) abnormalities in sporadic parathyroid adenomas.[63] Further analysis demonstrated the rearrangement of part of the *PTH* gene onto chromosome location 11q13. The protein that was overexpressed as a result of this rearrangement was designated PRAD 1 (parathyroid adenoma 1), and encodes a novel member of the cyclin-D family of cell-cycle regulatory proteins. Up to 20–40% of sporadic parathyroid adenomas have been shown to overexpress cyclin D1.[64–65]

There has also been interest in the role of cyclin dependent kinase inhibitors (CDK1) genes conferring low-penetrance predisposition to hyperparathyroidism by providing a selective growth advantage to parathyroid cells.[66] Another genetic abnormality that appears to be important in the aetiology of parathyroid adenoma is the tumour suppressor gene associated with MEN type 1; 12–20% of patients with sporadic parathyroid adenomas have been shown to harbour bi-allelic defects in the MEN1 gene.[67] Parathyroid adenomas are also associated with MEN syndrome type 2a. Although *C-RET* mutations are responsible for MEN2a, a search for the most common mutation at codon 634 has proved to be negative, suggesting a different mechanism responsible for the development of sporadic and inherited parathyroid adenomas.

Whole exome and direct sequencing of parathyroid adenomas has lead to mutations being identified in the *ZFX* gene, a gene believed to have a role in the regulation of stem cell renewal. The identified mutations did not overlap with somatic mutations in the *MEN1* gene. Also implicated in other cancers such as that of the larynx, lung and prostate, the *ZFX* gene may as an oncogene provide gain of function in parathyroid tumour cells, possibly linked to cyclin D1.[68]

Parathyroid hyperplasia

Comparison of genes between parathyroid hyperplasia and adenomas does demonstrate greater genetic heterogeneity and more complex expression of genetic mutations in hyperplasia, which is consistent with its polyclonal nature. Examples include the *CDH1* gene, which is not exclusive to but more highly expressed in hyperplasia versus adenoma (but not in carcinoma).[69]

Parathyroid carcinoma

Although rare, parathyroid carcinoma is clinically aggressive. Whether it arises pre-existing adenomas or *de novo* remains controversial. As noted previously, cyclin D1 gene expression is overexpressed in parathyroid adenomas compared to normal parathyroid tissue. Recently, Zhao et al. examined seven parathyroid carcinomas and noted expression of *CCND1* (a gene encoding for cyclin D1) was significantly overexpressed in carcinomas when compared with adenomas.[62]

The *RB* tumour suppressor gene responsible for the pathogenesis of retinoblastomas is involved in the pathogenesis of various other human tumours. Allelic deletion of *RB* gene was demonstrated in all parathyroid carcinomas in one study, with abnormal histological staining patterns for Rb protein in 50% of carcinomas but none in the adenomas.[70] Together, these observations suggests an important role for *RB* gene in the development of parathyroid carcinomas, and may help in the histological diagnosis of parathyroid carcinoma.[61]

Shattuck et al. directly sequenced the *HRPT2* gene (associated with hyperparathyroidism-jaw tumour syndrome) in 21 parathyroid carcinomas from 15 patients who had no known family history of primary hyperparathyroidism or the HPT-JT syndrome at presentation.[71] Parathyroid carcinomas from 10 of the 15 patients had *HRPT2* mutations. In contrast, mutations of *HRPT2* are not evident in benign parathyroid tumours. Some have suggested that all patients with parathyroid carcinoma should be considered for germline testing for *HRPT2* mutations as up to 20% of them may have unrecognized HPT-JT.[66]

INHERITED CANCER SYNDROMES AND GENETIC TESTING

In about 5–10% of individuals predisposition to a specific group of cancers is the result of a heritable mutation in a cancer predisposing gene, so-called germline mutation. The at-risk individuals tend to develop tumours at an earlier age than usual and are at risk of developing more than one primary tumour. In addition, the siblings and offspring of an affected individual each have a 50% chance of inheriting the cancer predisposing mutation, consistent with autosomal dominant inheritance.

Multiple endocrine neoplasia type 1 (MEN1)

MEN1, also known as Wermer's syndrome, represents the combination of more than 20 different endocrine and non-endocrine tumours. A practical definition is a case with two or three main MEN1-related endocrine tumours: parathyroid adenoma, entero-pancreatic endocrine tumour and pituitary tumour. MEN1 syndrome is usually an autosomal, dominantly inherited condition, although in 10% of cases arise *de novo*. The prevalence of MEN in the UK is estimated to be ~10 per 100 000 with equal sex distribution.[72]

Parathyroid tumours occur in 95% of MEN1 patients and is the most common endocrinopathy with a typical age of onset of 20–25 years (reaching nearly 100% penetrance by the age of 50 years).[73] In contrast, MEN1 is rare and represents only 2–4% of all cases of primary HPT. Patients with MEN1 generally have parathyroid tumours in three or all four parathyroid glands. These tumours are asymmetric in size and are regarded as independent clonal adenomas. The issue of which operation is optimal remains controversial.[72–74]

The gene causing MEN1 was localized to chromosome 11q13 by genetic mapping studies. Further studies defined the *MEN1* gene in 1997, consisting of 10 exons that codes a novel 610 amino acid protein named MENIN.[67] MENIN is a ubiquitously expressed nuclear protein that has been demonstrated to have roles in transcriptional regulation, genome stability, cellular proliferation, cell cycle control and apoptosis.[67, 75]

More than 1000 germline mutations of the *MEN1* gene have been described and the majority (>80%) of these are inactivating, and are consistent with its role as a tumour suppressor gene.[72] More than 10% of the *MEN1* gene germline mutations arise *de novo* and may be transmitted to subsequent generations.[76] Importantly, 5–10% of MEN1 patients do not harbour mutations in the coding region of the *MEN1* gene, and these individuals may have mutations in the promoter and untranslated regions, which remains to be clarified. Correlations between *MEN1* mutations and the clinical manifestations are absent, and this contrasts with the situation in MEN2 and the *RET* gene.

MEN1 GENETIC TESTING FOR FAMILIAL MEN1 SYNDROME

The first step in the analysis is to identify the specific *MEN1* mutation in the germline DNA derived from a peripheral blood sample from the affected index case using direct DNA sequencing strategies. In most index cases of familial MEN1, a germline mutation of *MEN1* will be identified. However, many large studies have failed to find a *MEN1* germline mutation in 10–20% of index cases for familial MEN1.[77] Such failures are believed to be due to mutations in untested parts of the *MEN1* gene or large deletions that are transparent to PCR methods. Current recommendations suggest genetic testing should be performed in index cases with two or more MEN1 tumours, and first-degree relatives of a known mutation carrier. All individuals who are offered genetic testing should receive appropriate genetic counselling.[78]

Multiple endocrine neoplasia type 2 (MEN2)

The MEN2 syndrome describes the association of medullary thyroid carcinoma (MTC), pheochromocytoma, and parathyroid tumours. MEN2 is an autosomal dominant syndrome caused by mutations in the *RET* proto-oncogene with variations in the penetrance resulting in three variants: MEN2a; MEN2b; and familial medullary thyroid cancer (FMTC). All variants show a high penetrance for medullary thyroid cancer; 90% of MEN2 carriers will eventually show evidence for MTC. MEN2a is the most common variant (95%), and the development of multicentric MTC (almost 100%) is associated with pheochromocytoma (50%) and parathyroid adenomas (20%). MEN2b, which represents 5% of all MEN2 cases, is characterized by the occurrence of MTC, pheochromocytoma in association with Marfanoid habitus and mucosal neuromas. Parathyroid tumours do not usually occur in MEN2b. FMTC is a variant in which only MTC is the sole manifestation and is the mildest subtype. MTC is the first neoplastic manifestation in most MEN2 patients because of its earlier and overall higher penetrance. Earlier studies reported mortality of 15–20% when treatment was initiated after identification of a thyroid nodule.[79] However, carrier diagnosis before adulthood allowing early thyroidectomy has lowered the mortality from hereditary MTC to less than 5%.[80]

The *c-ret* proto-oncogene encodes a transmembrane tyrosine kinase receptor and is located on chromosome 10q11.2.[81] The RET protein is involved in cellular

signalling pathways that regulate cell proliferation, differentiation, survival and regeneration (ref10). Specific activating mutations of *C-RET* have been described for each of the three MEN2 variants. The aggressiveness of MTC correlates with the MEN2 variant syndrome and with the mutated *RET* codon.[82] Prevention or cure of inevitable MTC is by surgery, and should be performed before the age of possible malignant progress.

The presence of somatic *RET* mutations (which occur in up to 75% of sporadic MTC patients) confers a more aggressive clinical course when compared to *RET*-negative sporadic patients. The absence of *RET* mutations in some patients suggests that other loci may predispose to MEN1 and sporadic MTC.

MEN2 GENETIC TESTING

In 1997, a consensus was reached that the decision to perform prophylactic thyroidectomy in MEN2 should be based predominantly on the result of *ret* mutation testing, rather than CT testing.[83] Genetic testing for MEN2 has enabled detection of nearly 100% of carriers and is one of the few examples of a genetic test that mandates a highly effective clinical intervention. Sequencing DNA for *RET* mutation is effective and widely available. The likelihood of a *ret* germline mutation in a patient with apparently sporadic MTC is 1–7%.[84] Despite the modest mutation yield, all cases of sporadic MTC should be tested for germline *ret* mutation because the critical clinical implications of finding a *ret* mutation. A germline *ret* mutation is more likely if the sporadic MTC is of early age onset or there is multiplicity in the thyroid gland. Further, the specific *ret* codon mutation correlates well with the MEN2 variant and with clinical behaviour. Genetic information allows stratification of MTC risk and provides a basis for a 3-level stratified thyroid management (**Table 9.1**).[85]

Hyperparathyroidism-jaw tumour (HPT-JT) syndrome

The HPT-JT syndrome is an autosomal dominant disorder characterized by the development of parathyroid adenomas and carcinomas and fibro-osseous jaw tumours. In HPT-JT, patients usually have single adenoma or a carcinoma, whilst MEN1 patients will often have multigland disease.

The gene causing HPT-JT, *HRPT2*, is located on chromosome 1q25 and encodes for an ubiquitously expressed 531 amino acid protein PARAFIBROMIN.[87] To date,

TABLE 9.1 Genotype-phenotype correlations, risk levels for MTC and recommended interventions based on ATA risk level of genotype 2015[86]

	RET genotype		MEN2 classification	Recommended start interventions			
ATA group	Exon	Codon mutation		PE/US/Ctn	TTX	Screening PHEO	Screening HPT
HST	16	M918T	MEN2B	1 month	Before the first year of life	11 years	NA
H	11	C634F/G/R/S/W/Y	Classical MEN2A / MEN2A + CL	3 years	At or before 5 years of age	11 years	11 years
	15	A883F	MEN2B				NA
MOD	10	C609F/G/R/S/W/Y C611R/S/W/Y C618F/G/R/S/W/Y C620F/G/R/S/W/Y	Classical MEN2A	5 years	Childhood or young adulthood	16 years	16 years
		C611F	FMTC			NA	NA
		C609G *C611S* *C618/R/S* *C620/R/S/W*	MEN2A + HD				
	11	C630R/Y D631Y S649L K666E	Classical MEN2A			16 years	16 years
	13	E768D	FMTC			NA	NA
		L790F Y791F	Classical MEN2A			16 years	16 years
	14	V804L/M	Classical MEN2A / MEN2A + CL			16 years / NA	16 years / NA
	15	S891A	Classical MEN2A			16 years	16 years
	16	R912P	FMTC			NA	NA

13 different heterozygous mutations translating truncated forms of parafibromin, have been reported in HPT-JT families. Although no consensus clinical guideline exists for *HRPT2* genetic testing, testing for germline HRPT2 mutations are available commercially.[88]

Cowden's disease

Cowden's disease (CD), also known as multiple hamartoma syndrome, is a rare autosomal dominantly inherited disease. Multiple trichilemmomas of the skin are common diagnostic features found in >90% of affected individuals. Patients with CD have an increased risk for carcinomas of the breast and thyroid; up to a 10% lifetime risk of follicular or papillary thyroid cancer. Approximately 70% of people with Cowden syndrome will have benign thyroid abnormalities, including multinodular goitre, adenomatous nodules and follicular adenomas. Marsh et al. identified *PTEN* mutations in 30 of 37 (81%) Cowden disease families.[89] The *PTEN* gene is involved in the previously PI3/AKT or PI3-AKT intracellular signalling pathway. Although no consensus clinical guideline exists testing for germline *PTEN* mutations are available commercially.

Other inherited syndromes

Mutations in the *APC* gene cause FAP and attenuated familial adenomatous polyposis (AFAP). FAP is inherited as autosomal dominant and is characterized by multiple adenomatous polyps in the colon and rectum with a natural history of progression to colorectal carcinoma in nearly 100% of cases, usually by the age of 40. People with FAP have up to a 2% lifetime risk of developing papillary thyroid cancer (PTC). Women with FAP appear to be at greater risk than men (80:1) and develop a particular histological variant of PTC (cribriform morular variant of PTC) that demonstrates more indolent behaviour than the sporadic type.[90]

Gardner syndrome (colonic polyposis, osteomas, and characteristic retinal lesion) is now known to be a phenotypic variant of FAP, caused by mutation in the *APC* gene. Herve et al. estimated that the incidence of thyroid carcinoma in patients with Gardner syndrome approached 100 times that of the general population. Genetic testing for mutations in the *APC* gene is available.[91]

KEY POINTS

- Our understanding of parathyroid tumour biology is less developed than thyroid; however, advancements in genetic testing have demonstrated areas of potential. Several genes have been studied (*MEN1, PTH, HRPT2, ZFX*) and have been postulated to play an important role in the development of parathyroid tumours.
- PCR and immunohistochemistry techniques based on products of specific genetic mutations may aid in differentiation of adenomas, hyperplasia and carcinoma.
- Genetic testing in endocrine disease relates to the MEN syndromes. Genetic testing plays a key role in the management of MEN type 2 and less prominent role in MEN type 1.
- *RET* mutational analysis is a key investigation in the management of patients with MEN type 2. *RET* analysis offers a risk stratification based on the codons mutated and guides clinical management.
- Further identification of genes may allow targeted anti-neoplastic agents in the age of targeted molecular therapeutics.

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CHAPTER 10

SOFT AND HARD TISSUE REPAIR

Sarah Al-Himdani and Ardeshir Bayat

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SEARCH STRATEGY

Data in this chapter may be updated by Medline and Embase searches using the key words: wound healing, tissue repair, tissue regeneration, chronic wounds and wound dressings. Information from these resources was critiqued and the information included is from levels of evidence 1 and 2.

INTRODUCTION

A wound is defined as a break in the integrity of the skin epithelium, often accompanied by concurrent disruption of the underlying dermis.[1] Having a clear understanding of wound healing is fundamental in all aspects of surgery. Whether small or large, acute or chronic, all wounds heal by a complex, dynamic, highly orchestrated biological process and a surgeon's success is largely dependent upon the uncomplicated successful procession through the different phases of normal wound healing.[2] In order to be able to both prevent wound formation and treat pathologic wounds, one must first appreciate the normal process of wound healing.

Wound healing has been divided into four overlapping stages: haemostasis, inflammation, proliferation and remodelling. However, this complex process is by no means constant, with genetics (susceptibility to abnormal scarring), age, site, tension, nutrition and disease all very important influencing factors. A wound is 'healed' when:

- connective tissue repair and complete re-epithelialization have occurred
- skin cover has been resorted with scar tissue without the necessity of drains or dressings.

When the process of wound healing fails to occur in an orderly and timely fashion, wounds become chronic and non-healing, requiring continued management by drainage and dressing.[1]

On the other hand, aberrant healing (excessive scar formation) may also result in the formation of abnormal scarring, such as in hypertrophic scarring or keloid disease.

TYPES OF WOUND HEALING

Primary healing (healing by first intention)

Healing by first intention is characterized by closure of a wound within 12–24 hours of its formation. These wounds are clean and well perfused, for example following surgical excision or a clean laceration. Wound edges are approximated using sutures, skin glue, steri-strips or other mechanical devices/instruments.[1] Apposition of wound edges reduces the distance for epidermal proliferation and wound closure (**Figure 10.1**).

Secondary healing (healing by secondary intention)

Healing by secondary intention usually occurs in large wounds where it is not possible to appose the edges or in wounds that are complicated by infection. Wounds may be

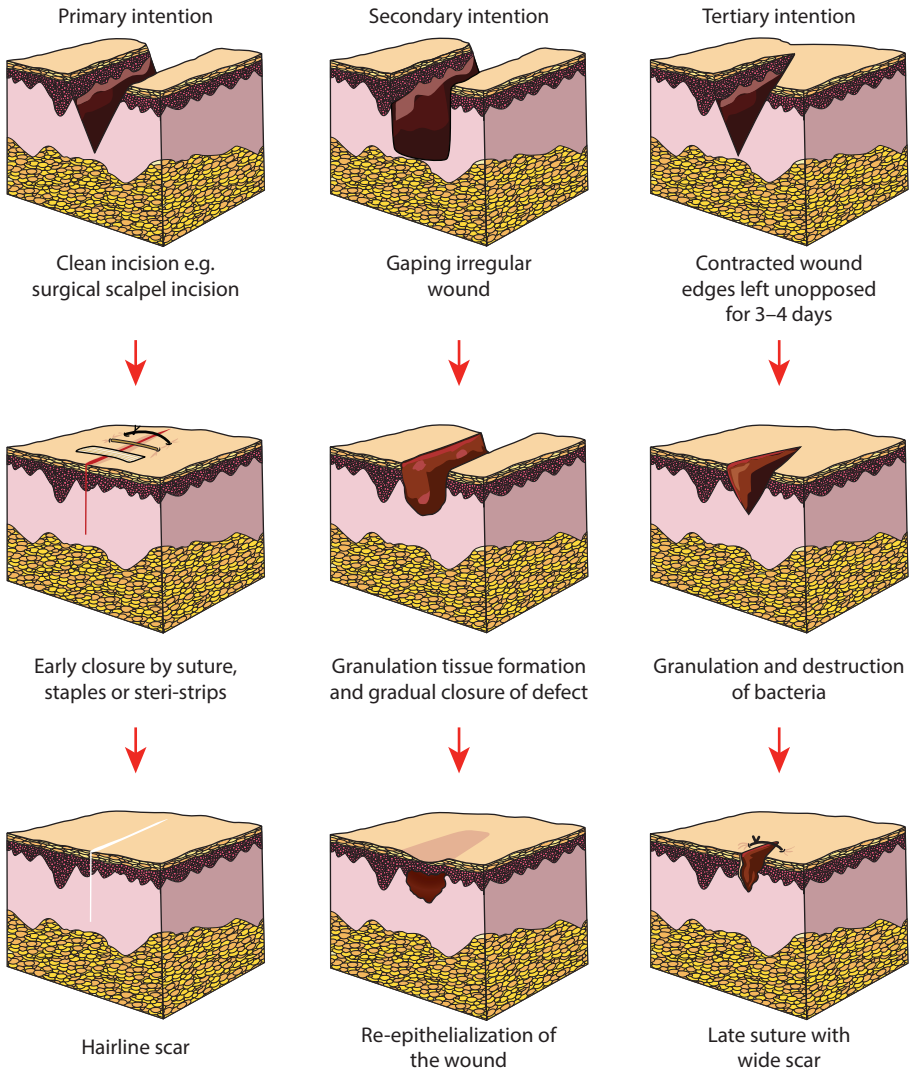


Figure 10.1 Diagrammatic representation of healing by primary, secondary and tertiary intention.

gaping and the edges lacerated. In these situations, sealing of the epithelium across the wound bed does not occur rapidly. Epithelial cells must grow both downwards and across the wound bed, with granulation tissue filling the defect. Healing of these wounds is achieved by wound contraction and subsequent epithelialization. Myofibroblasts play a key role in this process, usually appearing around 3 days following wound formation. Compared to healing by first intention, wound healing by secondary intention is a much slower process and may lead to subsequent contracture formation potentially resulting in functional impairment.[1]

Delayed primary healing (healing by tertiary intention)

This process mainly occurs in contaminated wounds, for example following bites and in abdominal wounds after peritoneal soiling. The wound edges are left unopposed in order for host defences to aid in debridement of the wound. The wound edges are usually approximated after 3–4 days, during which host phagocytes are recruited and inflammatory cells destroy the contaminating bacteria.[1]

Healing of superficial (partial-thickness) wounds

This process occurs following partial-thickness burns, split-thickness skin grafts and following abrasions, can extend through the epidermis and to the papillary dermis. The basal cell layer of the epidermis often remains intact and dermal regeneration can occur from epithelial cells within dermal appendages (hair follicles and sebaceous glands) and from the basal cell layer that replicate and migrate to the wound. The healing process occurs by re-epithelialization and is usually complete.[1]

PHASES OF WOUND HEALING

The complex, co-ordinated cascade of wound healing (as occurs in primary wound healing) is characterized by a number of cellular activities, including phagocytosis, cytokine release, chemotaxis, inflammation and synthesis of the extracellular matrix (ECM).[1] Following tissue

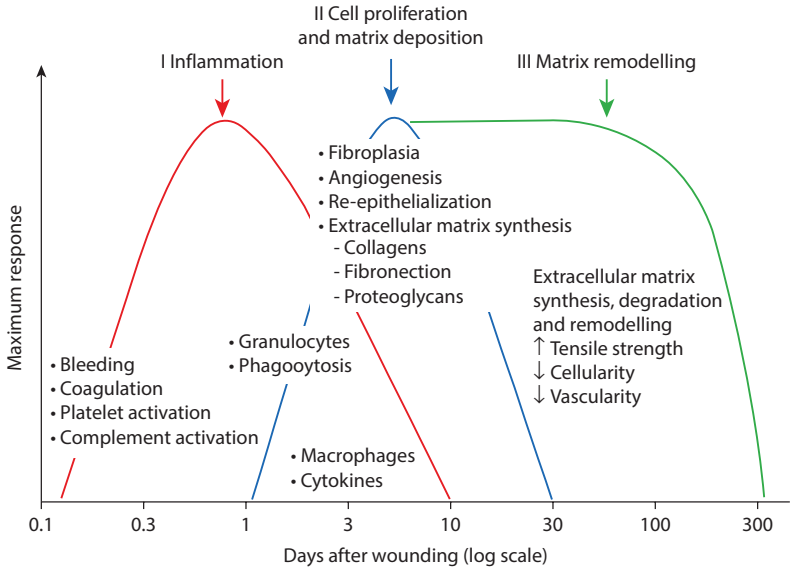


Figure 10.2 Phases of wound healing. Adapted from Greaves et al., 2013.[1]

injury, these processes have been described to occur in four phases: haemostasis, inflammation, proliferation and remodelling (Figure 10.2). Growth factors and cytokines are essential throughout the whole process of wound healing (Tables 10.1 and 10.2).

Haemostasis

Tissue injury results in disruption of the vascular endothelium, extravasation of blood constituents and exposure of the basal lamina. Constriction of endothelial cells and platelet activation then ensues. As well as initiating the coagulation cascade, aggregation, activation and degranulation of platelets leads to the release of several important growth factors that play important roles in chemotaxis (platelet-derived growth factor), deposition of the extracellular matrix (transforming growth factor-β), epithelialization (epidermal growth factor) and angiogenesis (vascular endothelial growth factor).[2–3]

TABLE 10.1 Major cell types and their roles in wound healing

Cell type	Role in wound healing
Platelets	• Clot formation • Release cytokines through degranulation (TGF-β, PDGF, platelet factor-4, β-thromboglobulin)
Neutrophils	• First cells attracted to wound site • Phagocytosis and intracellular destruction of bacteria
Macrophages/ monocytes	• Phagocytosis of bacteria • Remove debris and necrotic tissue • Release important cytokines • Essential for fibroblast division, synthesis of collagen and angiogenesis
Lymphocytes	• Role unclear • May release some cytokines
Fibroblasts	• Produce most of the ECM • Form granulation tissue • Reorganize and structure the ECM • Wound contracture through formation of myofibroblasts
Keratinocytes	• Identification and destruction of foreign microorganisms • Wound re-epithelialization

TABLE 10.2 Major cytokines/growth factors, their sources and roles in wound healing

Cytokine/Growth factor	Sources	Role in wound healing
TGF-α	Macrophages, platelets, epithelial cells	• Stimulates epithelial cells and fibroblasts • Forms granulation tissue
TGF-β	Platelets, macrophages, fibroblasts, neutrophils, keratinocytes	• Stimulates fibroblast and smooth muscle proliferation • Chemotactic for macrophages
VEGF	Platelets, neutrophils	• Stimulates angiogenesis and collateral blood vessel formation in peripheral vascular disease
PDGF	Platelets, macrophages, endothelial cells	• Stimulates proliferation of fibroblasts • Stimulates angiogenesis • Stimulates wound contracture
FGFs	Fibroblasts, endothelial cells, smooth muscle cells, macrophages	• Chemotactic and mitogenic for fibroblasts and keratinocytes • Stimulates angiogenesis
IL-1	Macrophages, lymphocytes	• Activates granulocytes and endothelial cells • Stimulates haematopoiesis

Growth factors attract and activate fibroblasts, macrophages and endothelial cells. Four processes, essential to wound healing, are initiated following these events:

- Clotting cascade
- Complement cascade
- Kinin cascade
- Plasmin generation

The clot that forms acts as a matrix for subsequent cell migration. Vasoactive mediators released from the platelets lead to vasodilatation and increased vascular permeability.

Inflammation

This process usually lasts up to 4 days and can be divided into early and late phases. The cell type and response differ in these phases.

EARLY INFLAMMATION (DAYS 1–2)

Activation of the classical and alternative complement cascades leads to neutrophil infiltration of the wound usually within 24–48 hours of injury. These chemoattractants include:[1]

- transforming growth factor-β
- complement constituents
- bacterial peptide products
- fragments of extracellular matrix proteins.

Neutrophils adhere to endothelial cells of the surrounding blood vessels (margination) and move through the vessel wall (diapedesis). Further neutrophils are attracted to the site and release proteolytic enzymes, which digest the bacteria and debris. Neutrophils also form oxygen-free radicals (through a myeloperoxidase pathway), which sterilize the wound of bacteria.[4]

Throughout this period, basal cells exhibit increased mitotic activity and epithelial cell migration and proliferation occurs across the dermis. Neutrophil activity usually stops within a few days of tissue injury, once the contaminating bacteria and debris have been removed. Macrophages also aid in this process by phagocytosing redundant cells. The main function of the neutrophil is to remove bacterial contamination and debris from the wound and thus prevent infection.

LATE INFLAMMATION (DAYS 2–3)

Monocytes are attracted to the wound by chemoattractants including cytokines, complement components and breakdown products of collagen and elastin. At the wound site, they differentiate into macrophages, which are the most important cell type of the late inflammation stage (48–72 hours). In addition to phagocytosis of bacteria and cell debris, macrophages play a key role in granulation tissue formation and proliferation by releasing important cytokines: PDGF (platelet derived growth factor), TGF-β (transforming growth factor beta), TGF-α (transforming growth factor alpha), FGF (fibroblast growth factor) and IL-1 (interleukin one).[5] Macrophages also play important roles in:

- formation of the ECM by fibroblasts
- proliferation of smooth muscle cells
- endothelial cell proliferation and subsequent angiogenesis
- phagocytosis and enzyme release in the early inflammatory phase.

Macrophage or monocyte depletion leads to poor wound healing with poor debridement, delayed proliferation of fibroblasts, delayed ECM synthesis, inadequate angiogenesis and poor fibrosis.[6] During the late inflammatory stage, collagen fibres become evident at the incision margins of the wound but do not bridge the incision. A thickened epidermal covering layer is produced by continued epithelial proliferation.

Proliferation (day 3 to week 2)

This process, starting around day 3 and which can last up to 4 weeks, encompasses re-epithelialization and granulation tissue formation.

RE-EPITHELIALIZATION

This process involves replication and movement of the epidermal cells from the wound edges in order to reconstitute an organized, keratinized, stratified squamous epithelium. Increased mitotic activity within the basal cells of the wound edges occurs within 12 hours of wounding. Initially, migration of epidermal cells creates a delicate covering over the raw area, a process also known as 'epiboly'. These cells then migrate, usually as a sheet, by extending lamellipodia (from the Latin *lamina* – thin sheet, *pod* – foot) from the free edge of the cut epidermis, across the defect. This process of migration is dependent on the oxygen tension present in the wound and is most rapid in hyperbaric conditions.[7] 'Contact inhibition' prevents movement when epithelial sheets meet. Gradually, a continuous squamous cell epithelium is restored.

In partial-thickness wounds, the skin appendages (hair follicles and sebaceous glands) act as a source of epithelial cells for regeneration of the epidermis. During the process of migration, keratinocytes play an important role in bacteriological control. Foreign particles, once detected are phagocytosed and non-viable tissue is sloughed off.

Migration ceases once the sheets of epidermal cells meet. Re-epithelialization is complete and epidermal cells return to their normal morphology. Through this process, the barrier properties of the skin are restored, preventing the development of complications such as infection.

GRANULATION TISSUE FORMATION

Granulation tissue formation is composed of three important steps: fibroplasia, wound contraction and angiogenesis.

Fibroplasia

This process comprises of recruitment and proliferation of fibroblasts, which are essential in production of the ECM and the organization of components of the granulation tissue.[8] Fibroblasts are attracted to the wound 2–4 days after injury by growth factors including PDGF and TGF-β. Once at the wound site, fibroblasts proliferate and produce a number of important proteins (fibronectin, hyaluronin, collagen and proteoglycans) used to construct the new ECM. After wounding, fibroblasts undergo phenotypic alterations with altered expression of fibronectin.[9] These cells, called myofibroblasts, have capacity for contraction and increased motility and play an essential role in contraction during both normal and pathological wounding.[9] Mechanical tension and PDGF are important factors reported in myofibroblast formation.[9]

Fibroblasts secrete the ECM matrix, composed of fibrous structural proteins (collagen, elastin) and an interstitial matrix (glycoproteins in a proteoglycan and glycosaminoglycan gel). The interstitial matrix becomes organized around the epithelial cells, smooth muscle cells and endothelial cells and forms a new basement membrane. Fibronectin is a glycoprotein secreted in the ECM that aids adhesion of fibroblasts to the ECM, stimulates fibroblast migration, provides support for collagen deposition and mediates wound contraction.

Structural proteins (collagen and elastin) are vital for providing structure and strength. Several growth factors stimulate collagen synthesis during both the proliferative and remodelling phases, including: PDGF, basic fibroblast growth factor, TGF-β, IL-1, and TNF (tissue necrosis factor). Around 18 different types of collagen exist. Collagen type III is secreted maximally within 5–7 days of wounding.

Wound contraction

This begins 7 days after wounding and peaks at 2 weeks. This process reduces the size of the defect and the need for scar tissue, usually occurring at a rate of 0.6–0.7 mm per day.[10] The degree of contraction varies with depth. However, in humans, in whom the skin is relatively immobile, contraction alone rarely completely closes a wound. Contraction must be closely regulated; when there is limited contraction, this can lead to delayed wound closure, bleeding and infection whilst excessive contracture can cause contractures.

Angiogenesis

This is the process of new blood vessel formation, commencing 2–3 days after wounding. This is essential to healing, as metabolic activity in a healing wound cannot occur without a specific blood supply. Granulation is composed of proliferating fibroblasts and loops of capillaries in a loose ECM. Important steps required for angiogenesis include: degradation of the basement membrane of the parent vessel, endothelial cell migration towards the angiogenic stimuli, endothelial cell proliferation with subsequent maturation into capillary tubes.[1]

Important factors inducing angiogenesis include: VEGF, PDGF, TGF-β and basic fibroblast growth factor. Invasion of the wound by capillaries creates a microvascular network within the wound. Chronic wounds, characterized by delayed healing, may occur when vascular supply to the wound is insufficient.[11]

Remodelling and scar maturation (from week 1 to several weeks)

The ECM and collagen fibres are continually synthesized and remodelled throughout the process of wound healing (this occurs simultaneously with granulation tissue formation). As collagen is formed, it is also degraded. Metalloproteinases (collagenases, gelatinases and stromelysins) are proteolytic enzymes synthesized by fibroblasts, neutrophils and macrophages responsible for this process. Regulation of metalloproteinase activity is necessary to ensure that collagen degradation, which in excess may impair wound healing, is closely controlled. Typically, these enzymes are initially inactive and activation is necessary before they can act. Tissue inhibitors of metalloproteinases also prevent their action and allow for control of collagen breakdown. Around 21 days following injury, equilibrium is reached between collagen formation and degradation. Continued remodelling leads to eventual reduced activity of metalloproteinases, reduced macrophages and fibroblasts, reduced capillary outgrowth and reduced size of contractile connective tissue.

Scar maturation results in the breakdown of fibronectin and hyaluronan as well as a larger diameter of collagen bundles. Though increasing in strength through the process of remodelling, the collagen will never reach the same strength as that of unwounded skin and usually a maximum of 80% of the strength in unwounded skin is reached.

REPAIR OF HARD TISSUE/BONE

Repair of bone is similar to that of soft tissue, with an added osteogenic component. Following injury, haemorrhage occurs with clot formation. Neutrophils, macrophages and mast cells move into the injury site and release growth factors and cytokines, stimulating the process of healing. Cytokines of importance in bone formation include:

- TGF-β, which is a potent chemotactic cytokine for osteoprogenitor cells and macrophages. This also stimulates proliferation of mesenchymal and osteoprogenitor cells, osteoblasts and chondrocytes.
- TNF-α, which promotes recruitment of mesenchymal stem cells. Absence of TNF-α prohibits bone formation.
- Bone morphogenic proteins, which regulate the transcription of target genes, in particular playing a critical role in regulation of growth, differentiation and apoptosis of osteoblasts, chondroblasts, neural cells and epithelial cells.

Osteoclasts and macrophages remove wound debris and gradually granulation tissue is formed and replaces the clot. This process usually takes several days, but the duration is also dependent on the site and the severity of the injury.

Vascular endothelial cells and perivascular mesenchymal cells provide osteoprogenitor cells, which become osteoblasts. Several cytokines stimulate osteoblast activation including PDGF, TGF-β, FGFs and bone morphogenetic proteins (BMPs).[12] Chondroblasts may also become activated, particularly when oxygen levels are low. Within the new matrix, mainly at the site of the periosteum, cartilage cells begin to develop. Osteoblasts also release calcium, which is deposited into the new matrix and on to the cartilage. At this stage, the bone is flexible and is called soft callus.

Once the soft callus is formed, subperiosteal and endochondral ossification occurs continually. Hard callus is formed once the ends of the bone become united, after approximately 2 months. Once formed, the remodelling process continues leading to the formation of mature lamellar bone. This process requires osteoblasts and osteoclasts. Through further remodelling, the marrow cavity and the contour of the bone are restored. External forces applied to the bone can alter the remodelling process.

LINKING BASIC KNOWLEDGE TO PRACTICE – KEY QUESTIONS

A number of different pathological processes may lead to abnormal wound healing. Prompt diagnosis and appropriate treatment is key. When incorrectly diagnosed, delayed wound healing followed by other morbid complications may ensue.

1. What are the causes of abnormal wound healing?
2. Which local and systemic factors impede wound healing?
3. How do we assess wounds?
4. How do we manage wounds?

What are the causes of abnormal wound healing?

Several local and systemic factors may impede wound healing (**Figure 10.3**). This section will review some of these important factors in more detail.

PATIENT AGE

Local and systemic factors affecting wound healing are more common in elderly patients. Failure of wound healing can become a chronic disabling condition and may incur significant social and medical costs to the elderly population affected. Ageing has a number of effects on the different stages of wound healing including:[13–15]

- delayed epithelialization
- altered inflammatory and cell adhesion molecule profile

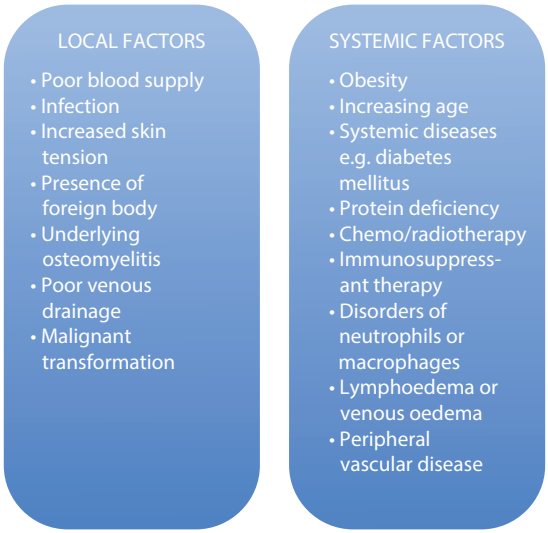


Figure 10.3 Local and systemic factors contributing to impaired wound healing.

- reduced collagen content and 'fragmented' appearing elastic fibres leading to reduced tensile strength
- reduced number of inflammatory cells
- impaired granulation tissue formation
- impaired angiogenesis.

NUTRITIONAL STATUS

Malnutrition adversely affects wound healing. In particular, dramatic degrees of protein calorie malnutrition delays the wound healing response.[16] Additionally, several 'pro-healing' nutrients have been identified including: arginine, vitamins A and C and zinc.

Markers of nutrition identified in previous studies include:[17, 18]

- serum albumin (< 30 g/l), shown to predict delayed wound healing; however, albumin levels can be affected by other conditions such as fluid retention and distribution. It also has a long half-life
- pre-albumin (< 10 mg/dl), an indicator of malnutrition and poor wound healing with a shorter half-life than albumin
- serum transferrin (< 1.5 g/l) also shown to predict delayed wound healing; however, transferrin levels are also dependent upon body iron status.

Assessment of nutritional needs and supplementation is essential in those with or at risk of malnutrition. Dieticians play a vital role in the assessment and management of these patients.

Important screening questions when assessing nutritional intake include[17] height, weight, recent unintentional weight loss, and change in food intake. It is also important to find out how physically active patients are and whether they have had any additional gastrointestinal symptoms such as chronic diarrhoea or vomiting.

Several formal screening tools have also been developed, such as 'MUST'. This categorizes patients into low,

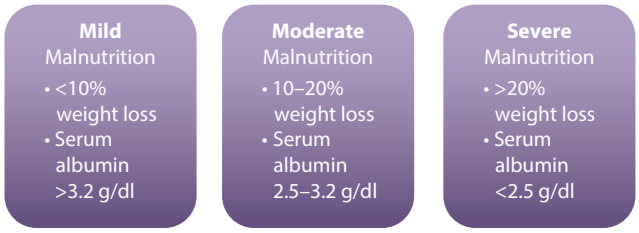


Figure 10.4 Mild, moderate and severe categories of malnutrition.

medium and high-risk groups according to their score. Those at high risk should be assessed by a dietician and receive nutritional support.[19] Pre-operative nutritional support is recommended for patients with moderate to severe malnutrition (**Figure 10.4**).

UNDERLYING CHRONIC CONDITION

Diabetes mellitus, atherosclerosis, hypothyroidism, chronic venous insufficiency and obesity can all delay wound healing. The effect of increased serum glucose, in diabetic patients, on wound healing is multifactorial. Some of these effects include:[20–23]

- increased vascular permeability leading to pericapillary albumin deposition and impaired diffusion of oxygen and nutrients
- inhibition of function of structural and enzymatic proteins due to non-enzymatic glycolization
- glycosylated collagen resistance to enzymatic degradation.

Animal and human models have shown that as a result of these effects, diabetic wounds demonstrate decreased granulation tissue, decreased collagen, slow wound maturation and decreased numbers of fibroblasts.

Animal studies have also demonstrated that reduced thyroid hormone levels can adversely affect fibroblast function and subsequent wound strength. In addition to the specific effects of absent thyroid hormone, systemic complications of the disease such as heart failure can also compound these effects.[20] Treating the underlying condition is an essential step in wound management in patients with both diabetes mellitus and hypothyroidism.

INFECTION

Local wound infection and foreign bodies delay wound healing by prolonging the inflammatory phase. When the bacterial count is greater than 10^5/g of tissue or beta-haemolytic streptococcus is present, the wound will not heal. Bacteria prolong the inflammatory phase of wound healing and also deleteriously affect rate of epithelialization, contraction and collagen deposition.[20]

MEDICATIONS

Patients with chronic wounds often suffer from chronic diseases for which they may take several medications. These medications may contribute to delayed wound healing. It is thus vital to review a patient's list of medications. The following medications may contribute to delayed wound healing:[24]

- steroids,[25] which arrest inflammation by interfering with wound macrophages, angiogenesis and wound contraction
- NSAIDs,[26] which reduce collagen synthesis, thought to be related to impaired prostaglandin metabolism
- chemotherapeutic agents,[24] which reduce wound contraction and fibroblasts proliferation.

CLASSIFICATION OF WOUNDS

Wounds can be categorized in a number of different ways. In this section we will describe some of the important classifications.

Acute vs. Chronic

Acute wounds most often occur secondary to trauma. These wounds generally heal very well.

Chronic wounds usually occur in patients with an underlying condition, for example diabetes mellitus, malignancy and chronic venous insufficiency. These wounds may start from an initial trauma and persist beyond 6 weeks, due to an abnormal underlying physiology affecting the process of wound repair, such as diabetes, or peripheral vascular disease. In addition, these wounds have the potential for malignant transformation, also known as Marjolin's ulcer.

ACUTE WOUNDS

Examples of acute wounds include:

- thermal wounds
- surgical wounds
- traumatic wounds.

Thermal Wounds

Both extremes of temperature and radiation may lead to thermal wounds. Radiotherapy is often used treat head and neck cancers and leads to permanent damage to the skin's microvasculature. These wounds often heal poorly and can become infected.

Burns are the commonest type of thermal injury and exact assessment of the degree/level of depth of burn is critical. Most commonly burns are classified as:

1 Superficial:
   - Wound appears erythematous.
   - This affects the upper layer of the epidermis. Generally no intervention is necessary.
2 Partial-thickness:
   - Appear blistered.
   - Further subdivided into **superficial partial-thickness**, **mid-dermal** and **deep-dermal.**

- This affects the epidermis and part of the dermis. Generally minimal intervention may be required if only the most superficial part of the epidermis is affected, the so-called superficial partial-thickness wounds. Mid-dermal and deep-dermal should be closely observed as skin grafting may be necessary, particularly if these wounds extend.

3 Full-thickness:
- Appear charred/white and insensate
- These wounds affect the epidermis, dermis and can extend into the subcutis. Skin grafts are always required in these wounds.

Surgical Wounds

There are many types of surgical wounds and examples include incisions, excisions, skin grafting (involving split-thickness skin grafts or full-thickness skin grafts), amputations and skin biopsies:

- **Incisions/excisions:** A scalpel is the most common device used to make these wounds. This extends through the whole thickness of the skin to the underlying tissues. If the incision involves removal of tissue, this will be considered an excision. Post-operatively the wound is sutured closed (healing by primary intention) or in the case of excision, this may require skin grafting or use of skin flaps.
- **Skin grafts:** These are commonly used following deep (full-thickness) burn injuries. The grafts can be either split-thickness or full-thickness depending on the depth of the harvest. Split-thickness includes the epidermis and the papillary dermis.
- **Amputations:** This type of wound is created following surgical removal of a limb, either as a result of disease, trauma or infection. Healing of these wounds is usually by either primary or secondary intention depending on the initial indication for the amputation.
- **Skin biopsies:** These wounds usually involved surgical excisional removal of a full-thickness area of skin for histological assessment. These wounds are normally left to heal and close by secondary intention although the larger wounds are closed directly using sutures following the biopsy and healing by primary intention.

Surgical wounds have also been classified according to the level of contamination during the operation from I–IV (Table 10.3).

Traumatic Wounds

These are other acute injuries, which usually result from a physical force. They may result from small, common cutaneous injuries to life-threatening limb/head/trunk injuries. Examples include:

- abrasions
- puncture
- laceration
- bruises
- gunshots
- blisters
- bites
- stab
- crush.

CHRONIC WOUNDS

The vast majority of chronic wounds can be classified into the following categories:

- diabetic ulcers
- pressure ulcers
- venous ulcers
- arterial ulcers.

Diabetic Ulcers

The effect of diabetes on wound healing was described previously. Diabetics have a 15% greater risk of amputations compared to the general population, due to chronic lower limb ulcers.[27] Wounds often form secondary to diabetic neuropathy. Loss of pain perception results and patients often develop wounds from repeated injury that they fail to notice.

Pressure Ulcers

These wounds typically occur over bony prominences where skin is subject to excessive pressure forces. Chronic conditions such as diabetes mellitus may also predispose patients to developing pressure sores. Common sites affected include the heels, shoulder blades and sacrum. Pressure ulcers can be classified according to the depth of the wound:

1. Stage I:
   - Non-blanching erythema
   - Skin temperature, tissue consistency or sensation may be altered

TABLE 10.3 Classification of surgical wounds

Class and type of wound	Description of wound	Wound closure
Class I Clean	• Wound made aseptically • No contact made with respiratory, alimentary or urinary tract	• Closed by primary intention
Class II Clean-contaminated	• Wound made aseptically • Enters respiratory, alimentary or urinary tract	• Closed by primary intention
Class III Contaminated	• Wound is open or involves major breaks in sterile technique or gross spillage from gastrointestinal tract	• Closed by primary or secondary intention. • Requires significant washing before closure
Class IV Dirty	• Dirty infected wounds • This retains devitalized tissue or involves pre-operative existing infection or perforated viscera	• These wounds are often left open for drainage

2. Stage II:
   - Partial-thickness skin loss
   - Involves epidermis and dermis
   - Appears as an abrasion, blister or shallow crater
3. Stage III:
   - Full-thickness skin loss
   - Extends to but not through the underlying fascia
   - Presents as a deep crater
4. Stage IV:
   - Full-thickness tissue loss
   - Extends to muscle, bone, or supporting structures (e.g. tendon or joint capsule)

Venous Ulcers

These are the most commonly occurring ulcers and result from venous insufficiency. Venous drainage and blood supply are reduced in the affected tissue, leading to extensive ulceration following a minor injury.

Characteristics of these ulcers include:

- often located around medial malleolus
- shallow depth
- large in size
- irregular edges
- sloughy base with pink granulation tissue.

Arterial Ulcers

These are caused by a lack of blood flow to the lower limbs. This leads to tissue hypoxia and ischemia. These ulcers occur more commonly in diabetics and smokers.

Characteristics of these ulcers include:

- often sited around the lateral malleolus
- small in size
- regular shape
- deep, often to bone
- no granulation tissue.

Types of wound tissue

GRANULATION TISSUE

This appears red, moist, shiny and granular. On biopsy, an abundance of capillaries, macrophages and fibroblasts may be seen.

EPITHELIAL TISSUE

Once wounds are filled with granulation tissue, a new epithelial layer grows from the edges of the wound moving towards the centre. This tissue appears pink/white in colour. As well as from the edges of the wound, epithelial cells may also be derived from skin appendages, producing islands of skin in the middle of the granulation tissue.

NECROTIC TISSUE

There are two types of necrotic tissue that may appear in a wound: slough and eschar. Slough is dead devitalized tissue that appears moist, loose and stringy. It is typically yellow and found on the wound bed. It is commonly present in chronic or infected wounds. Eschar commonly occurs after burns and appears as dry, thick, leathery tissue. It may be black and should be promptly excised.

INFECTED TISSUE

A number of classical features can be used to identify infected tissue:

- Pyrexia
- Pus
- Erythema (particularly when spreading)
- Malodour
- Wound dehiscence
- Poor healing
- Increased pain
- Sinus formation

When a wound infection is suspected, the following steps should be taken:

1 Wound swab: Traditionally 10^5 bacteria per gram has been used as the cut-off point at which it is thought that bacteria inhibit wound healing. Wounds with this level or greater of bacteria are classed as being infected.
2 Sensitivities: From the wound swab, the sensitivities of the organisms to antibiotic treatment can be determined.

WOUND ASSESSMENT

Size of the wound

The wound size should be assessed on first presentation and regularly thereafter. The outline of the wound can be traced onto transparent acetate sheets. The surface area may be calculated by multiplying the longest diameter in one plane by the longest diameter in the plane at right angles (in a circular shaped wound).[28]

Edges of a wound

Examination of the edges of a wound is useful in identifying the aetiology of the wound. Venous ulcers often have sloping edges whilst arterial appear well demarcated or 'punched out'. When rolled or everted edges are observed, malignancy must be excluded by biopsy.

Location of the wound

The site of a wound also aids in the diagnosis. Venous ulcers most commonly occur in the gaiter region, around the medial malleolus. Diabetic foot ulcers commonly occur over pressure areas such as under the hallux, under the first and fifth metatarsal heads and under the heel.

Wound bed

The appearance of the wound bed gives an indication of the type of wound. Healthy granulation tissue appears pink. Dark red and bleeding granulation tissue

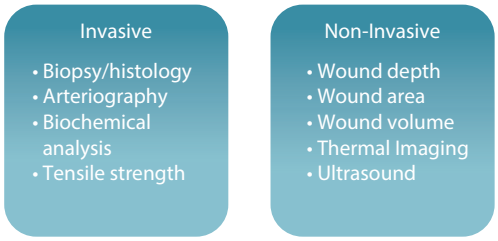


Figure 10.5 Invasive and non-invasive techniques for assessing wounds.

may indicate infection. Excess granulation tissue may be present in chronic poorly healing wounds. This excess tissue must be debrided to aid wound healing. Techniques for assessing wounds may be either invasive or non-invasive (Figure 10.5).

EXCESSIVE WOUND HEALING

Hypertrophic scars and keloids occur as a consequence of excessive wound healing leading to abnormal fibrotic scar formation. These result from overproduction of fibroblasts, collagen, elastin and proteoglycans. These occur in up to 5–15% of all wounds, with rates much higher in the non-Caucasian population with pigmented skin.[1]

Hypertrophic scars

These scars are more common in:[1]

- wounds that are under tension
- deep dermal burns
- wounds healing by secondary intention.

Keloid

This is a benign fibroproliferative scar that continues to grow beyond the confines of the original wound, invading into healthy surrounding tissue.[29] No specific cause has been elucidated, although it is known that keloids have a strong genetic predisposition.[30] In most instances, the magnitude of the injury does not correlate with the size of the keloid scar, although in every case, a form of dermal injury has been associated with development of a keloid scar.

WOUND DRESSINGS

Ideal wound dressings sustain a moist wound environment for optimal wound healing. Dressings can be comprised of synthetic polymers (formed into fibres, wafers or membranes).[31] These membranes are considered to be semi-permeable to gases (oxygen, CO_2 and moisture) and usually impermeable to liquids. These dressings are also named occlusive dressings. There are five types of such dressings:

1 Hydrogels
2 Hydrocolloids
3 Foams
4 Films
5 Alginates.

The principle reasons for applying a dressing include:

- to produce rapid and cosmetically acceptable healing
- to reduce pain
- to remove odour
- to treat or prevent infection
- to cover a cosmetically unpleasant wound.

Several factors should be considered when choosing a dressing including:

- wound-related factors:
  - size
  - depth
  - amount and characteristics of exudate
  - necrotic/viable
  - surrounding tissue appearance (pigmented, scarred or cellulitic)
- product factors
- patient factors.

Dressings for acute wounds

Several dressings may be used for acute wounds. These include:

- low-adherence dressings (e.g. Mepore®, Mölnlycke Healthcare), for example for skin tears
- transparent film (e.g. OpSite™, Smith & Nephew), which is used in clean, dry wounds.

Dressings for chronic wounds

NECROTIC WOUNDS

The aim with these wounds is to rehydrate the skin so that the dead skin/scab will separate from the normal skin. Options include:

- wet dressings using saline or hypochlorite
- hydrocolloid when wounds are dry and necrotic
- hydrogel (e.g. Aquasorb™) when wounds are dry and necrotic
- surgical/mechanical debridement
- biological debridement (e.g. larvae)
- enzymatic debridement (e.g. collagenase).

SLOUGHY WOUNDS

These should be debrided in order to remove the abnormal matrix of slough (inflammatory cells and exudate). This can be done surgically or using an agent which soaks up the debris forming a moist gel. Dressing options include:

- hydrofibres
- hydrogels
- hydrocolloids
- polysaccharide dressings (beads or paste)
- alginate dressings
- mechanical debridement.

GRANULATING WOUNDS

Granulation tissue is highly vascular. It contains collagen and proteoglycans. The dressing choice depends on depth and exudate from the wound.

For light-medium exudative wounds consider:

- hydrocolloids
- thin foam dressings
- hydrogel, sheets or gels.

For shallow exuding ulcers:

- alginate dressings
- hydrophilic foam materials
- hydrocolloids.

For deep cavity wounds:

- alginate fibre ribbons
- foams
- silicone foam dressings
- hydrofibers (e.g. Aquacel®)
- vacuum-assisted closure (VAC) therapy.

EPITHELIALIZING WOUNDS

These are superficial wounds. Dressing choice depends on whether the wounds are dry or exude fluid. For dry superficial wounds, the following dressings are recommended:

- hydrocolloids
- film dressings
- perforated plastic film dressings
- knitted viscose non-adherent dressings.

For exudative wounds (e.g. burns and graft donor sites) dressing options include:

- paraffin gauze covered with gauze and cotton (Gamgee)
- hydrocolloids
- alginates
- hydrofibers (e.g Aquacel®).

For very exudative wounds:

- impregnated gauze dressings may be used. Twice daily dressing changes may be required.

INFECTED WOUNDS

These wounds can have an unpleasant odour. For this reason and in order to prevent spread of infection, they should be covered. Antibacterial agents are included in a number of the dressings:

- framycetin
- fusidic acid
- chlorhexidene
- iodine
- honey dressings
- silver sulfadiazine dressings (e.g. Silvadene) or an ionic silver hydrofiber dressings (e.g. Aquacel-AG).

MANAGEMENT OF SPECIFIC WOUNDS

Over/hypergranulation tissue occurs when the inflammatory phase is prolonged unnecessarily. The most frequent dressing options include:

- change from occlusive to non-occlusive dressings
- light pressure application to wound bed with bandaging
- short-term topical steroid application.

For pressure wounds:

- comfortable dressing, for example an extra-thin hydrocolloid
- off-loading devices such as comfort boots in heel ulcers
- securing dressings in a very moist area such as the sacrum is challenging. A wafer hydrocolloid is a comfortable and highly adherent dressing.

For venous ulcers:

- the dressing type should be according to the tissue type in the ulcer bed
- compression bandages.

For diabetic foot ulcers:

- optimal blood sugar control
- appropriate comfortable footwear
- daily saline dressing to provide a moist wound environment
- debridement if necessary
- antibiotics if soft tissue infection or osteomyelitis present.

For burns or scalds:

- cold running water
- cling film prior to assessment.

For superficial burns:

- semipermeable films
- hydrocolloids
- Aquacel®
- Mepitel®
- foams.

For partial thickness burns:

- Flamazine®
- alginates
- Mepitel®
- Aquacel®.

For full-thickness burns:

- assessment at a specialist burn centre for need for skin grafting
- Flamazine®
- hydrogels
- Mepitel®.

Care of the surrounding skin:

- To secure a dressing when surrounding skin is fragile, hydrogel sheets and non-adhesive foams are useful.
- Topical creams such as Diprobase may be used to rehydrate the skin.

BEST CLINICAL PRACTICE

- ✓ Ensure a relevant history and careful examination is undertaken in order to elicit factors contributing to poor wound healing:
  - ✓ age: delayed wound healing with increasing age
  - ✓ nutritional status: malnutrition impairs wound healing
  - ✓ chronic disease: diabetes, peripheral vascular disease and chronic venous insufficiency all predispose to ulceration and poor wound healing
  - ✓ several medications impair wound healing, in particular: steroids, non-steroidal anti-inflammatory drugs, cytotoxic agents and immunosuppressants
  - ✓ pressure-prone anatomical areas can lead to ulcer formation
  - ✓ infection impairs wound healing.
- ✓ Wounds can be classified in a number of ways:
  - ✓ acute vs. chronic: (i) acute: thermal wounds, surgical wounds and traumatic wounds; (ii) chronic: diabetic ulcers, pressure ulcers, venous ulcers, arterial ulcers and mixed ulcers.
  - ✓ according to the type of wound tissue: granulation tissue, epithelial tissue, necrotic tissue or infected tissue.
- ✓ Wound assessment involves evaluation of: wound size, edges, and location (anatomical site) and status of wound bed and tissue. Invasive as well as a number of non-invasive techniques can be utilized in wound assessment.
- ✓ Five main types of wound dressing are used: hydrogels, hydrocolloids, foams, films and alginates.
- ✓ The following factors should be considered in order to choose the optimal dressing:
  - ✓ type of wound/ulcer
  - ✓ wound size
  - ✓ wound site
  - ✓ depth
  - ✓ amount and characteristics of exudate
  - ✓ necrotic/viable tissue
  - ✓ surrounding tissue appearance (pigmented, scarred or cellulitic).

FUTURE RESEARCH

Pre-clinical studies have demonstrated the potential benefit in the application of topical growth factors onto wounds.[32] Future treatments may include gene therapy with insertion of human growth factors genes direction into wound cells using vectors.[33] Additionally research has demonstrated benefit in utilizing mesenchymal stem cells to promote wound healing.[34]

In addition, the role of electrical stimulation (ES) in acceleration of cutaneous repair has gained recent scientific and clinical interest. A number of recent studies have shown that application of ES can enhance tissue repair not only by increasing angiogenesis but also by reducing inflammation.[35–36]

KEY POINTS

- Wounds may heal by primary, secondary or tertiary intention.
- Healing by primary intention involves:
  - clean wound edges closed within 24 hours
  - surgical incision/laceration
  - approximation using sutures, skin glue or steri-strips
  - hairline scar.
- Healing by secondary intention involves:
  - large gaping or infected wounds
  - epithelial cells grow downwards and across the wound bed
  - contraction and epithelialization occurs
  - slower than healing by primary intention and may lead to contracture formation.
- Healing by tertiary intention involves:
  - contaminated wounds
  - wound edges left unopposed for up to 4 days for phagocytosis to occur
  - wound edges then approximated, often loosely.
- Cutaneous wound healing may be divided into four stages:
  1. Haemostasis
  2. Inflammation
  3. Proliferation
  4. Remodelling.
- The following steps occur in the haemostasis phase:
  - disruption of the vascular endothelium
  - blood extravasation and clot formation
  - endothelial cell constriction and platelet activation
  - release of growth factors and cytokines by platelets.
- The inflammation phase comprises of early and late phases:
  - The early phase (days 1–2) comprises neutrophil infiltration within 24–48 hours of injury. These digest bacteria and debris.
  - The late phase (days 2–3) involves monocyte/macrophage attraction to the wound. Macrophages phagocytose bacteria and release essential cytokines including PDGF, TGF-β, TGF-α, FGF and IL-1.

- The proliferative phase:
  - Occurs from day 3 up to week 2.
  - Encompasses: re-epithelialization and granulation tissue formation (fibroplasia, wound contraction and angiogenesis).
  - Re-epithelialization starts within 12 hours of wounding and is the replication and reconstitution of the organized, keratinized, stratified squamous epithelium.
  - Fibroplasia is recruitment and proliferation of fibroblasts, which produce the extracellular matrix that acts as a scaffold for the healing tissue.
  - Fibroblasts, as well as releasing important cytokines and growth factors also produce important structural proteins (collagen, hyaluronin and proteoglycans). Phenotypic alterations in fibroblasts after wounding (day 7 to week 2) lead to myofibroblast formation. These contract and aid in wound closure.
  - Angiogenesis (day 2–3) is the process of new blood vessel formation and this is essential for the metabolic activity of the wound during healing. Several cytokines induce angiogenesis: VEGF, PDGF, TGF-β and basic fibroblast growth factor. A poor vascular supply leads to poor wound healing.
- Remodelling and scar maturation:
  - Occurs from week 1 to several weeks following tissue injury.
  - Involves collagen formation that is balanced closely with its degradation by metalloproteinases.
  - Continued remodelling eventually leads to scar formation.
  - Scar collagen is usually a maximum of 80% of the strength of unwounded skin.
- Healing of hard tissue/bone involves:
  - A similar process to that of soft tissue, with an added osteogenic component.
  - Important cytokines include: TGF-β, TNF-α and Bone morphogenic proteins.
  - Osteoclasts and macrophages remove wound debris and gradually granulation tissue is formed.
  - Chondroblasts and osteoblasts create a soft callus.

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CHAPTER 11

SKIN FLAP PHYSIOLOGY

Colin MacIver and Stergios Doumas

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: skin flap, tissue transfer, free flap, physiology, biomechanics, vessel and skin.

> Make a plan and a pattern for this plan.
>
> Sir Harold Gillies (1882–1960)

DEFINITION

A skin flap is a block of tissue transferred from the donor site and inserted to the recipient site while maintaining a continuous attachment to the body (the pedicle). The flap may consist of skin and subcutaneous fat but could also include mucosa, fascia, muscle, bone, nerve or combinations thereof.

Traditionally, the term free flap refers to autologous tissue transfer from a distant donor site to reconstruct a defect after the pedicle has been completely detached. Blood supply is reinstated by means of microsurgical anastomoses of donor artery and vein(s) to the recipient artery and vein(s).

Flap viability is initially dependent on its robust blood supply via the pedicle so that metabolic demands of the mobilized tissue are met. Multiple anatomical and physiological factors that hamper adequate perfusion, before the collateral capillary network develops, can be detrimental for the flap survival.

Flaps currently represent the workhorses for head and neck reconstruction. However, allotransplantation holds promise for non-oncological reconstruction. Also, tissue engineering is another fast growing field in head and neck reconstruction.

HISTORY

The term 'flap' is alleged to originate from the Dutch *Flappe*, meaning something broad and loose that hangs attached only at one side.[1]

Reconstructive skin flap surgery owes a great deal to the work of the Indian Ayurvedic medical practice of nasal reconstruction. *Sushruta Samhita*, the classical surgery textbook written around 600 BCE, describes the first cheek flaps utilized for nose repair.[2] The English surgeon Joseph Carpue (1764–1840) is given credit for introducing the Indian forehead rhinoplasty technique into the English language, based on a letter to the editor in 1794 relating the nasal reconstruction of a bullock driver called Cowasjee. An extremely well-referenced discussion of the history of this flap reconstructive technique is given by Nichter et al.[3]

Seminal studies in anatomical description of blood supply, pharmacological manipulation of the circulation and the advent of anaesthesia and aseptic techniques in surgery led to a better understanding of skin flaps. In this context, in 1889 Manchot published on many of the distinct cutaneous vascular territories served by identified named arteries.[4] Spalteholz described the fasciocutaneous vessels, as well as those passing through muscle, and provided the origin of the concept of the musculocutaneous blood supply to flaps.[5] In France, Salmon added to these ideas by performing radiographs on cadaver skin following intraarterial contrast injection.[6]

In 1921, Carl-Olof Siggesson Nylen, a Swedish ear, nose and throat (ENT) surgeon, built the first microscope. However, its use was confined to ENT and neurosurgical procedures. The first modern microscope is credited to Zeiss in the 1950s, and the first diploscope, operated by two surgeons simultaneously, was produced in 1961.[7]

Two years later, McGregor and Morgan described how skin flaps could be considered axial or random and therefore the length-to-width ratio was given an anatomical basis (drawing of random and axial flap). Having studied intra-arterial fluorescine injections in 14 patients, McGregor and Morgan deduced that an axial pattern flap could be safely raised beyond the standard dimensions of a random pattern flap of 1:1 length-to-width ratio and introduced the paramedian forehead flap.[8] They went on to postulate that changes in pressure between one territory and an adjacent territory could create the effect of reverse flow in the adjacent axial vessels. This was further developed by Taylor and Palmer who postulated that each of the composite blocks (angiosomes) were connected by true anastomoses or reduced calibre 'choke vessels'.[9] These choke vessels are analogous with the description by Salmon of 'retiform anastomoses' and as such are the defining limits of the vascular territories. They name the accompanying veins 'oscillating veins' in which flow could occur in any direction. In 1970, Milton reported that 'the surviving length of flaps made under similar conditions of blood supply is constant regardless of width. The only effect of decreasing width is to reduce the chance of the pedicle containing a large vessel'.[10]

The first attempts at free flaps without any magnification assistance were made in the late 1950s. Seidenberg et al. pioneered this by using a free jejunal autograft anastomosed to the superior thyroid artery and anterior facial vein via a stapling method, following a pharyngoesophagectomy for squamous cell carcinoma in 1959. The patient survived for 8 days post-op, apparently dying of an unrelated cerebrovascular accident, with the jejunal graft found to be completely viable on autopsy.[11]

Nevertheless, the first reports of free flaps as we understand them today appeared in the early 1970s. Harry Buncke and Donald McLean used omentum, in 1972, to restore a large scalp defect following squamous cell carcinoma resection with exposed bone.[12]

As microsurgery field research advanced, it became evident that any clinically relevant perforator has the potential to be harvested as either a pedicle perforator flap or a free flap, depending on the diameter and length of the source artery and vein. The perforator flap era began in 1989, when Koshima and Soeda first described an inferior epigastric artery skin flap with the rectusabdominis muscle for reconstruction of floor-of-mouth and groin defects. Recently, Saint-Cyr et al. introduced the term 'perforasome' after conducting a three-dimensional (static) and four-dimensional (dynamic) computed tomographic angiography (CTA) in 40 fresh cadavers.[13] Another breakthrough in the field of free-tissue transfer has been achieved by means of extracorporeal tissue perfusion. This method potentially opens avenues in cases of vessel depleted neck and severed limbs.[14]

FLAP DESIGN

In general, flaps are divided into two main categories, based on whether the pedicle remains attached to the donor site or not; pedicled and free flaps, respectively. The former are further subdivided based on the pattern of blood supply and tissue composition into random, arterial cutaneous (axial), fasciocutaneous, musculocutaneous and venous flaps. Similarly, free flaps are divided into fasciocutaneous, musculocutaneous, osteocutaneous, muscular or combinations thereof (chimeric free flaps). The latter allow for three-dimensional reconstruction of massive defects.

APPLIED ANATOMY AND PHYSIOLOGY

The skin is the outermost human organ in direct contact with the environment. It weighs approximately 3.8 kg and measures about 1.7 m^2 in surface area.[15] The superficial part known as the epidermis is an impermeable, renewing, metabolically active, multi-layered, keratinizing, squamous epithelium. The epidermis consists of keratinocytes, melanocytes, Langerhans cells and Merkel cells. Hence, it serves as a sensory organ as well as a protective organ against insult and infection. Skin appendages, namely hair follicles, sebaceous glands, and eccrine and apocrine sweat glands derive from the epidermis. The epidermis and its appendages are all of ectodermic origin. Epidermis renewal is achieved by the so-called asymmetric division of the interfollicullar stem cells located in the basal layer.[16]

The dermis, derived from mesoderm, is primarily a connective tissue layer between the epidermis and the subcutaneous (subdermal) fat and muscle. Being 15–40 times thicker than the epidermis, it invariably accounts for the skin bulk. It accommodates nerve and vascular networks, epidermal appendages, fibroblasts, macrophages and others. Collagen type I and type III to a lesser extent abound in the extracellular matrix. Elastin fibres and the ground substance (proteoglycans, glycosaminoglycans and filamentous proteins) are also found in dermis. All fibres and the ground substance are synthesized by fibroblasts and confer skin pliability, elasticity and tensile strength.

The superficial layer of dermis has a waveform pattern in proximity to the rete pegs, which is known as the papillary layer. The deeper counterpart is known as the reticular dermis. The papillary dermis has an enriched capillary network that is 10–20 microns in diameter. Deeper to it, there are several arteriovenous shunts (diameter of 10–30 microns), most notable in the reticular dermis. The capillary plexus provides nutritional support to the epidermis, whereas the arteriovenous shunt contributes to the thermoregulation and systemic blood pressure of the body. They are both connected with the deep subdermal plexus. Under normal skin conditions blood flow though the skin amounts to approximately 9 mL/min per 100 g of tissue, 10 times above the rate fulfilling the skin's metabolic needs. In extremely hot climates blood flow can increase up to 20 times with maximal vasodilation.

In contrast, when the body is exposed to cold, blood flow can reduce to levels that are marginal for skin nutrition.[17]

Two sphincter types regulate skin blood flow. The capillary system is controlled by a ring of smooth muscle, the pre-capillary muscle, located at the point where capillaries originate from metarteriole. It is mainly responsible for controlling nutritional support to the skin. Hence, skin hypoxia and metabolic by-products released into the microcirculation result in local vasodilation. However, blood flow can bypass by virtue of the arteriovenous shunts. The so-called pre-shunt sphincters are the main regulators of this system. Low blood pressure and extreme cold lead to pre-shunt sphincter contraction via norepinephrine released by the post-ganglionic sympathetic fibres. A similar effect is achieved by catecholamines released into the blood stream, as skin is perceived as a 'non-vital' organ in generalized hypoperfusion states.[18]

As mentioned above, Taylor and Palmer coined the term 'angiosome' in order to describe the spatial pattern of blood supply in various parts of the integument. Houseman et al. describe 13 angiosomes in the head and neck region mostly supplied from the external carotid, internal carotid and subclavian arteries. All 13 but the lingual, vertebral and ascending pharyngeal angiosomes contribute to the abundant subdermal vascular network (**Figure 11.1**). In the face and scalp, major contributing vessels radiate from fixed points, either from bony foramina or from sites where the deep fascia is attached to the bone. These arteries further arborize into smaller perforators that feed the subdermal plexus by penetrating the underlying muscle or bypassing through its fascia, hence are called musculocutaneous and fasciocutaneous perforators, respectively. Multiple arterial arches are encountered

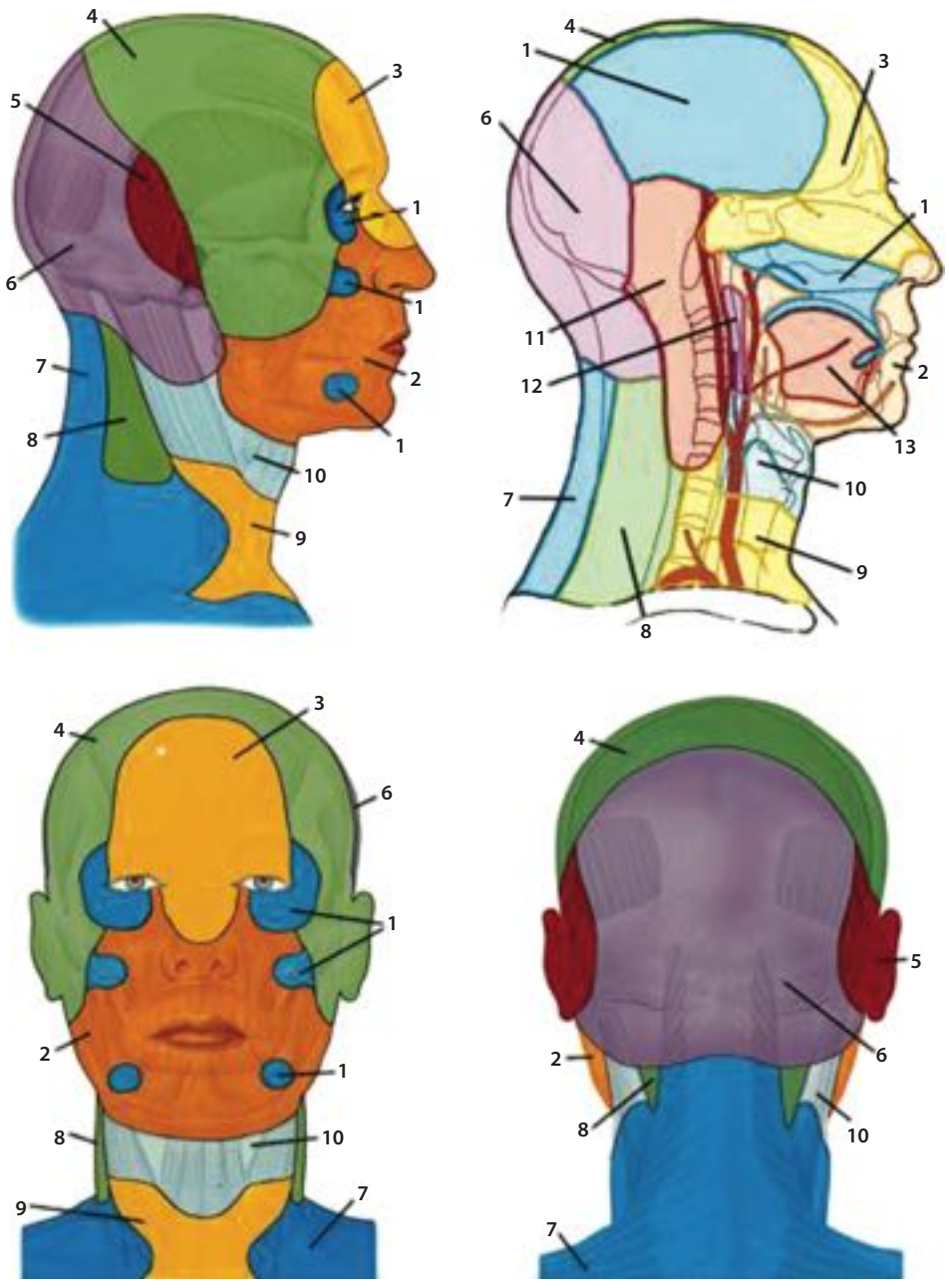


Figure 11.1 The angiosomes of the head and neck coloured and numbered. The additional territories defined in the neck are the transverse cervical (7), deep cervical (8), inferior thyroid (9) and superior thyroid (10) (above, right). Sagittal section showing the three angiosomes, vertebral (11), ascending pharyngeal (12) and lingual (13), which do not reach the skin surface.

in midline by connection of paired arteries. The head and neck region is the smallest one with approximately 25 perforators greater than 0.5 mm in diameter. The average diameter and area of irrigation by a single perforator are 0.9 mm and 32 cm^2, respectively.[19]

In analogy to 'angiosomes', Saint-Cyr et al. recently introduced the term 'perforasomes' as well defined vascular territories nourished by a single perforator. They carried out static and dynamic CTA in order to study detailed vascular anatomy, flow characteristics, and the contribution of both the subdermal plexus and fascia to flap perfusion after raising 247 flaps in 40 fresh cadavers. Perforator flaps on the anterior trunk, posterior trunk, and extremities were studied. They concluded that:

- Each perforasome carries a multidirectional flow pattern that is highly variable and complex. These perforasomes are linked to one another by both direct and indirect linking vessels, which themselves are linked by communicating branches (**Figure 11.2**). These numerous vascular connections confer further protection from ischemia and vascular injury in case of trauma or flap raising. Linking vessels allow communication with adjacent perforasomes and follow a direction that is parallel to the direction of perforator flow. Therefore, perforator flap skin paddles should be parallel to the linking vessel orientation whenever possible. These linking vessels make it possible to harvest large perforator flaps based on a single perforator, such as the extended anterolateral thigh flap.
- When a perforator flap is harvested, all muscle and cutaneous branches from the source artery are ligated, which results in hyperperfusion of the selected perforator. Increased vascular filling pressures clinically dilate the perforator itself and allow extensive inter-perforator flow by means of opening and recruitment of additional linking vessels. These linking vessels, both direct and indirect, are subject to higher than normal filling pressures and are able to capture additional adjacent perforator vascular territories (perforasomes) (**Figure 11.3**).

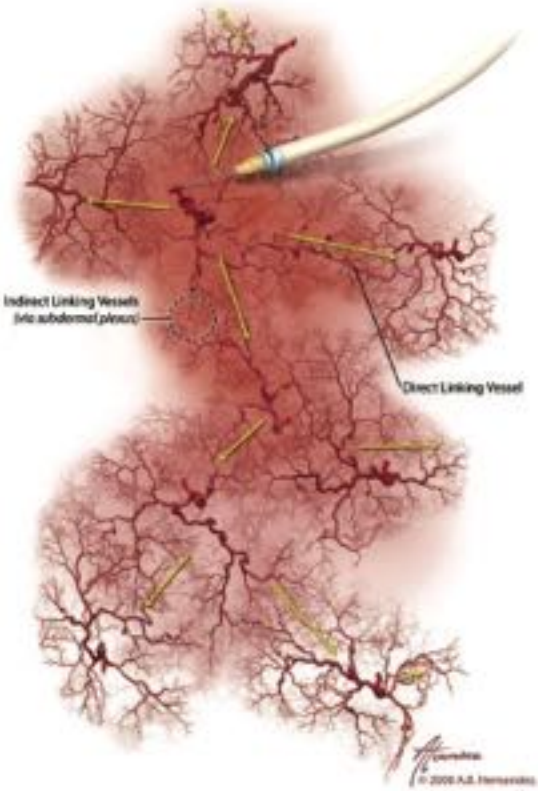


Figure 11.2 Interperforator flow occurs from the selected main perforator to multiple adjacent perforators by means of direct linking vessels and indirect linking vessels (recurrent flow from subdermal plexus). High perfusion pressures through the main perforator opens multiple direct and indirect linking vessels and allows perfusion of multiple other perforasomes. In this way, large flaps such as the anterolateral thigh flap can be harvested based on a single perforator. (Adapted from Saint-Cyr M, Wong C, Schaverien M, et al. The perforasome theory: vascular anatomy and clinical implications. *Plast Reconstr Surg* 2009; **124**: 1529–44. © American Society of Plastic Surgeons.)

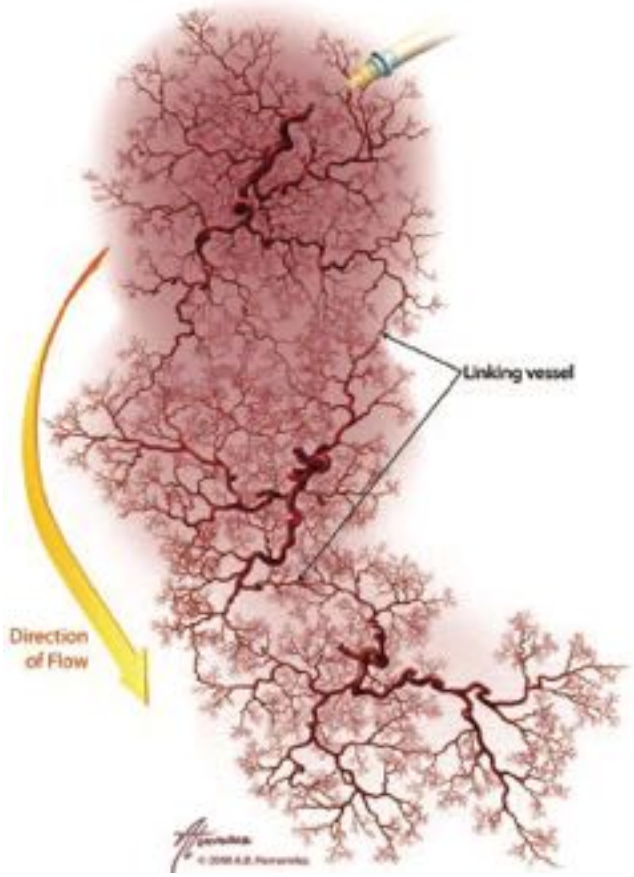


Figure 11.3 Perfusion in multiple perforasomes via linking vessels. Vascular density is maximal within the cannulated perforator and its corresponding perforasome and decreases distally away from the midline of the trunk or an articulation. The orientation of linking vessels determines the orientation of vascular flow within the flap. Direction of flow is predominantly perpendicular to the trunk midline and parallel to the vertical axis of the limbs. (Adapted from Saint-Cyr M, Wong C, Schaverien M, et al. The perforasome theory: vascular anatomy and clinical implications. *Plast Reconstr Surg* 2009; **124**: 1529–44. © American Society of Plastic Surgeons.)

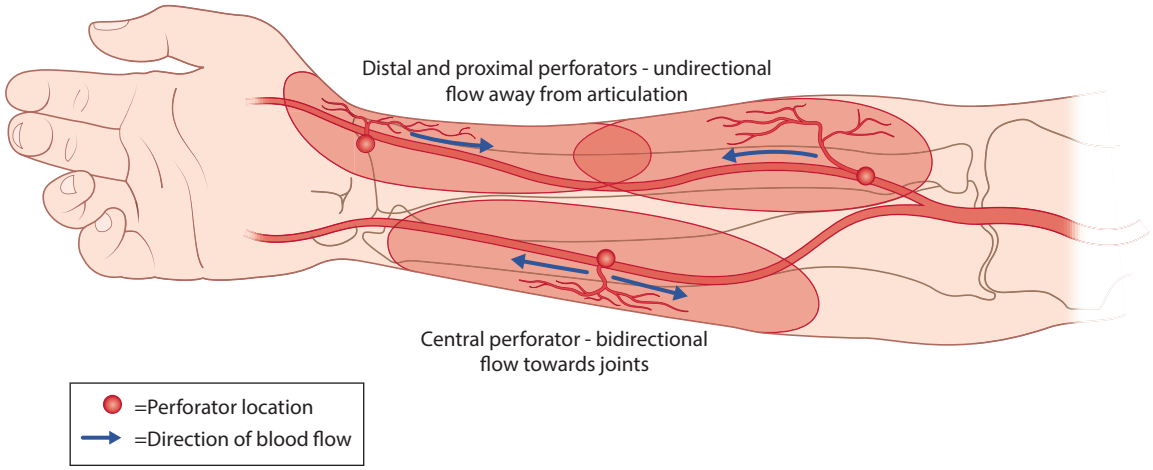


Figure 11.4 Direction of perforator flow between articulations. Perforators in the extremities that are found close to an articulation will have preferential flow away from that articulation, whereas midpoint perforators will have bidirectional flow. (Adapted from Saint-Cyr M, Wong C, Schaverien M, et al. The perforasome theory: vascular anatomy and clinical implications. *Plast Reconstr Surg* 2009; **124**: 1529–44. © American Society of Plastic Surgeons.)

- Perforator flaps designed at a midpoint between two articulations can be designed in multiple fashions because of the multidirectional perforator flow distribution. However, perforators located in proximity to one articulation seem to have unidirectional flow, i.e. distally located forearm perforators (wrist joint) course towards the proximal forearm (elbow joint), and vice versa (**Figure 11.4**).[13]

SKIN VESSEL BIOMECHANICS

Blood flow

Flap survival depends on flow though the pedicle of the flap.[20] Although the fluid mechanics of blood flow are complex, certain factors applicable to the small vessels supplying the flap are well established. Vessel blood flow (Q) is determined by:

- pressure difference (ΔP) between the two ends of the vessel
- the resistance to flow (R) produced in the vessel.

The mathematical expression of this blood flow is:

$$Q = \Delta P/R$$

where the letters are defined above.

The flow of blood through a smooth, straight vessel behaves as if there are concentric laminae, with the fastest flow in the centre creating a paraboloid wave front. The smaller the vessel becomes, the closer the central lamina becomes to the vessel wall. While this formula and lamina flow hold true for a straight, smooth vessel, any deformity such as vessel angulation, branching, obstruction or intraluminal irregularity will interfere with lamina flow. Disturbance in lamina flow is known as turbulence. Because all the flow is no longer in the same concentric laminae, fluid flowing across the direction of flow down the vessel will increase resistance to the flow. Resistance to lamina blood flow in a vessel is created by marginal adherence of molecules to the vessel wall.

The smaller the vessel diameter, the closer the fastest flowing central lamina becomes to the margin. Therefore, these molecules become closer to the slow moving marginal molecules, which increases the resistance to flow. The effect of reducing the vessel diameter can be expressed as mean velocity (í) and described in the formula:

$$í = \Delta P r^2/8çL$$

where í is velocity in cm/s; ΔP is pressure gradient (dynes)/cm²; r is the radius of the vessel in cm; ç is the viscosity in poises; and L is the length of vessel in cm.

The rate of blood flow through a vessel (Q) is related to the velocity of flow (í) multiplied by the cross-sectional area:

$$Q = ð\Delta P r^4/8çL.$$

Thus it can be seen that if $Q = \Delta P/R$ and $Q = ð\Delta P r^4/8çL$ such that:

- the resistance of a blood vessel (R) is directly proportional to the viscosity of the fluid and the length of the vessel
- the resistance is inversely proportional to the fourth power of the radius. Therefore the smaller the vessel (r), the greater the resistance of the flow. Thus, any interference with the resting tone in the blood vessel, which reduces the vessel radius, will have a detrimental effect on blood flow.

$$R = 8çL/ðr^4.$$

In general, radius (r) plays a major role in larger vessels, whereas viscosity (ç) seems to determine blow flow in

smaller vessels. Viscosity varies with the speed of blood flow; the faster the flow, the lower the viscosity because Poiseuille's law does not apply fully *in vivo*. The Fahraeus-Lindqvist effect appears with reducing vessel diameter below 1.5 mm. The viscosity of blood in vessels narrower than 1.5 mm is so much smaller that viscosity in the capillaries is half that of large-calibre vessels. In a 100-micron arteriole, red blood cells randomly orientated whilst in a 15-micron vessel more regular orientation of the red cells occurs. Bloch postulated that the vessel flow has a marginal layer with few cells and red cells congregate in the centre of the stream, which reduces the viscosity of the layer in contact with the vessel wall. In the 10-micron capillary, the red cells travel in single file paraboloids, rather then the usual bioconcave shape.[21]

Vessel wall tension

From Laplace's law, the tangential vessel wall tension (T) is proportional to the vessel diameter (D) and the pressure exerted across the vessel wall (P) such that:

T á DP.

This has critical importance in a small vessel in which vessel diameter reduces, as does the pressure within the vessel. The vessel will collapse at the point elastic tension in the vessel wall exceeds the transmural pressure (P). This is known as critical closure pressure. Any increase in the resting tone in the blood vessel (spasm in clinical setting) that reduces the vessel radius, will thus have a deleterious effect on blood. Equally, any interstitial pressure increase (e.g. severe flap oedema) above the critical closure pressure can compromise the flap. As flap edges distal to the perforator are nourished by smaller calibre vessels they are more vulnerable to ischaemic necrosis. Laplace's law also applies to Milton's theory that 'the surviving length of flaps made under similar conditions of blood supply is constant regardless of width'. This is notably known as fallacy of the length-to-width ratio (**Figure 11.5**).[18]

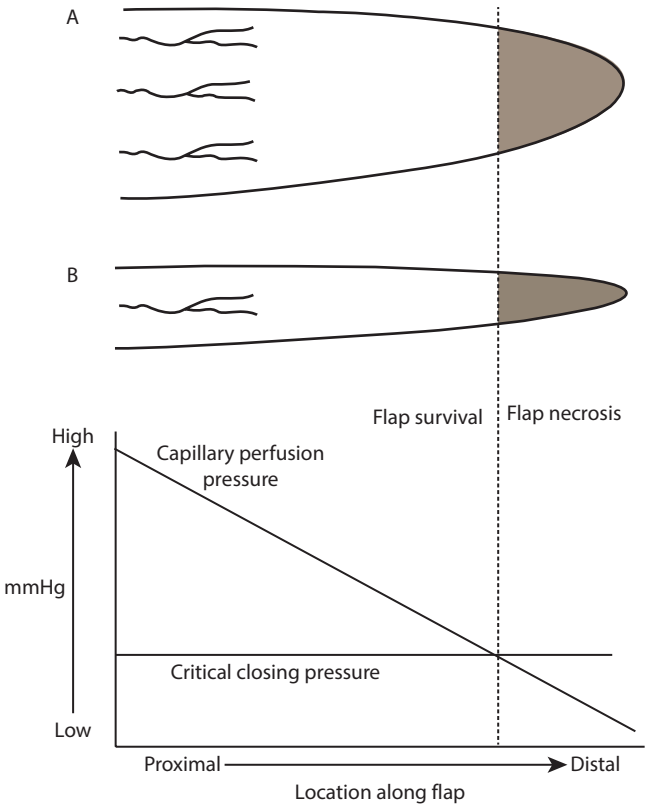


Figure 11.5 Fallacy of the length-to-width ratio. Slope of decreasing perfusion pressure versus flap length does not change with incorporation of additional vessels (flap A versus flap B) with some perfusion pressure. Flap necrosis occurs when perfusion pressure falls below critical closing pressure of the capillary bed. (Adapted from Hom DB, Goding GS. Skin flap physiology. In: Baker SR (ed). *Local flaps in facial reconstruction*. 2nd ed. Philadephia: Mosby Elsevier; 2007, pp. 15–30.)

SKIN BIOMECHANICS

As mentioned earlier, skin is a composite material consisting of a collagen-rich fibrous network embedded in a ground substance matrix. The proteoglycan-rich matrix provides skin its viscous nature at low loads, whereas collagen and elastin provide structural stiffness and elasticity to the skin. Skin exhibits anisotropic, non-linear, viscoelastic properties, in which the direction of minimal extensibility correlates with the fibrous network's principal direction. Skin is also a dynamic tissue, changing with age and influenced by gender.[22]

Recently, finite element analysis (FEA) has been used in order to understand skin flap dynamics. It is a computerized technique that can determine the stresses, strains and displacements in solid body given the geometry, material behaviour and load/displacement boundary conditions acting on that body. In this context, Lovald et al. performed FEA on a monopedicle (advancement) skin flap model concluding that the length of the flap should not exceed 3 times the size of the defect as benefit in reducing deformation is diminished beyond that point. Nevertheless, authors admitted that not all skin mechanical or local anatomical properties were studied. Although simulation models are useful instruments for a better understanding of skin flap biomechanics, success is dependent on the surgeon's ability to choose the best flap pattern on a given patient.[23]

Non-linearity

This property refers to the limited lengthening of the skin when it is acutely stretched. It is ascribed to collagen, elastin, ground substance, capillaries, nerve fibres and lymphatics. Moreover, the relationship between the applied force (stress) exerted on a given skin length and its ensuing length increase (strain) is non-linear. Skin is initially resilient to the forced applied as fibres recruited along the lines of the stress have little resistance. However, in the intermediate stage, further

deformation requires much more stress as more collagen fibres are recruited into a load-carrying role. The final portion demonstrates almost complete rigidity of the skin regardless of the force applied as all of the collagen fibres are deployed in the direction of the stress. The rationale of skin non-linearity is to preserve its structural integrity especially under excessive stress. As eloquently shown in the stress-strain curve diagram, there are age dependent changes in skin deformation. Aged skin is less 'malleable' at initial stages due to the paucity of elastic fibres. However, young and aged skin stress-strain curves coincide in phase 3 alluding to the same degree of refractoriness at higher forces.

Although non-linearity confers protection to skin, lack of further deformation at high forces has a deleterious effect on blood flow. As mentioned above, peripheral (small caliber) vessels are more prone to occlusion due to their decreased diameter. Hence, increasing the amount of flap tension can hamper circulation, leading to necrosis of the distal part of any flap (**Figure 11.6**).[24]

Anisotropy

Anisotropy refers to the directional qualities of the skin. In most regions of skin, there is tension in every direction, being greatest along the relaxed skin tension line (RSTL). Hence, an incision placed perpendicular to the RSTL will result in a wide gaping wound. Increased tension will also affect scarring and flap survival.

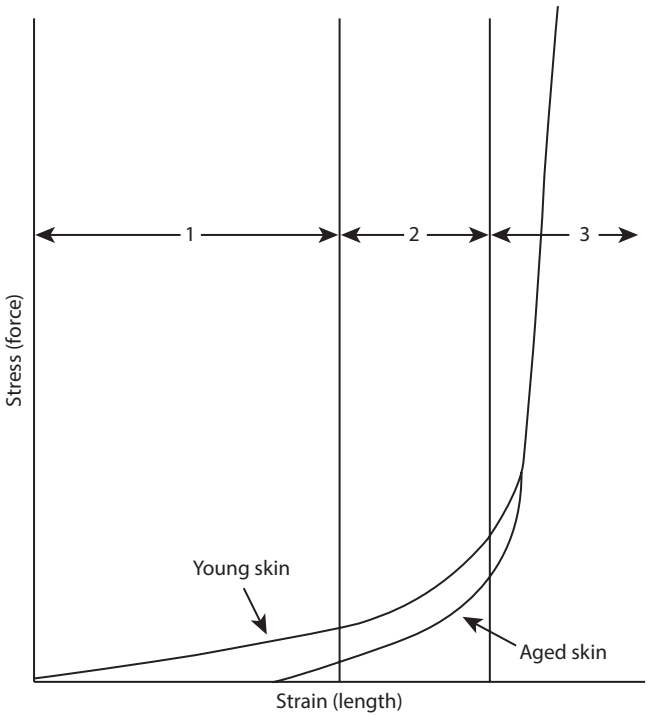


Figure 11.6 Stress-strain curve for isolated skin can be divided into three separate regions. Aged skin deforms under its own weight, shifting apparent origin of the curve along the x axis. (Adapted from Larrabee WF Jr. Immediate repair of facial defects. *Dermatol Clin* 1989; **7**: 661–76.)

Viscoelasticity

Viscoelastic properties of the skin are better understood by the terms *creep* and *stress relaxation*. Creep refers to the increase in strain seen after a sudden constant load applied to the skin. Stress relaxation refers to a decrease in stress by means of stretching when a constant stress is applied to the skin. Viscoelasticity seems to be the background of the tissue expansion and serial sections.[18]

THE COMPROMISED FLAP

'The after care is as important as the planning' is the 15th principle postulated by Sir Harold Gillies.[25] His principle reads, 'How futile it is to lose flap or graft for the lack of a little postoperative care. If in any doubt about the progress slip your hands out of your pockets and get down to the haematoma.' This advice holds as true today as it did when it was published, the most common cause for the flap failure being failure to recognize a compromised circulation.

Indeed, Pohlenz et al. recently conducted a single-centre retrospective study looking at complications and outcomes of 1000 microvascular free flaps transplanted in the head and neck region for the interim between 1987 and 2010. Vascular occlusion (thrombosis) of one of the vessels was the primary (4.5% arterial, 6.8% venous) reason for flap loss, with venous thrombosis being more common than arterial occlusion. The majority of flap failures occurred within the first 36 hours. The main reasons for flap failure were the use of compression bandages, tapes around the neck or tracheal strips with extrinsic compression of the vascular pedicle (n = 7). Tight wound closure or wound haematoma may also compromise the flap by obstructing venous outflow. Major bleeding (4.9%) was a common cause of failure in microvascular free tissue.[26]

Factors affecting flap survival can be considered as either extrinsic or intrinsic.

Extrinsic factors

External compression of the circulation to the flap is either due to a tight dressing, tension in the skin wound closure, which more commonly occurs if the flap is angulated over an underlying rigid bony surface, or soft tissue swelling; this can be due to oedema or a post-operative haematoma. The flap is usually blue and engorged, indicative of venous congestion. Haematomas seem to cause tissue injury even in absence of a pressure effect or pedicle thrombosis by a complex sequence of inter-related biochemical and cellular processes merging on a common pathway of local tissue ischaemia, which the overlying tissue is unable to regulate. In 2012, Glass et al. reviewed the literature relating haematoma to tissue compromise including free transferred tissue, vascularized flap models and brain injury. The authors acknowledged that all experimental data of this study were done in rat or pig modes. They postulated that degraded platelets release cytokines, which attract neutrophils. The latter release reactive oxygen

species (ROS) causing direct tissue damage. Additionally, the complement cascade is triggered by thrombin. Ferrous ions, freed by complement-mediated lysis of erythrocytes and degradation of haemoglobin, also promote generation of ROS. Reactive oxygen species, complement and activated neutrophils cause endothelial cell disruption, leading to activation of pro-thrombotic mechanisms and small vessel occlusion, with consequent tissue ischaemia, which in turn generates further ROS.[27]

The prompt release of thigh bandages, dressings and removal of wound sutures and heamatoma drainage may salvage the situation. If the free flap blood blow is compromised, urgent exploration of pedicle vessels is warranted. In general, earlier intervention confers better outcome in flap survival. In the case of a local flap, repositioning back on to the donor site should be considered if there is concern that the pedicle has been kinked, thus following the old adage, 'It is better to have a live flap out of position than a dead flap in position'.

Intrinsic factors

Reconstructive surgery for the head and neck is mainly aimed at elderly cancer patients with a long history of excessive smoking and drinking. These patients also suffer from other comorbidities (myocardial ischaemia, atherosclerosis/peripheral vascular disease, pulmonary diseases, diabetes mellitus (DM), cachexia, anaemia of chronic disease), hence are more vulnerable to flap-related as well as generalized complications.

Age per se should not be considered as an aggravating factor in terms of free-flap survival. Yang et al. conducted a retrospective cohort study on 53 head and neck cancer patients, aged >80 years, who underwent a free-flap reconstruction from 1996 to 2011 at an academic medical centre. There were zero flap failures or peri-operative deaths. Similar encouraging results were published by others.[28–29]

Rosado et al. performed a systematic review and meta-analysis to determine whether diabetic patients have an increased rate of post-operative complications compared to non-diabetic patients after head and neck free-flap reconstruction. They reported that the prevalence of DM in patients with failed free flaps for head and neck reconstruction is 15%. The incidence of diabetes mellitus in these patients with failed free flaps is 2.3 times higher than in the general population.[30]

Vasospasm in the flap following raising of the flap is a normal physiological response to reduce blood loss. Under normal circumstances, this vasospasm resolves without intra-vascular thrombosis because the spasm empties the lumen of the vessel. In addition, vessel lumen irrigation with heparin can resolve potential clots during anastomosis. In the presence of intact endothelium, the coagulation cascade is not activated. Hence, endothelial cell integrity plays a vital role in the maintenance of blood flow. Where flow to the flap is not established (or is compromised for a prolonged period of time) it has been shown experimentally in rabbits that 'no flow' occurs after a period of several hours of ischaemia. This has become known as 'no reflow phenomenon' coined by Ames et al. in 1968 and studied first in flap reperfusion in 1978.[31–32] In the no reflow phenomenon, reperfusion of the ischaemic tissue results in the formation of oxygen-derived free radicals. Furthermore, it has been shown that the vasodilator effect of acetyl choline is mediated through endothelial production of nitric oxide.[33] The net effect of acetyl choline following reperfusion is the presence of damaged endothelial cells in vasoconstriction.

Nitric oxide is produced by nitric oxide synthase from the amino-acid L-arginine. Elegant experimental research in mice with targeted disruption of the inducible nitric oxide synthase (iNOS) gene (iNOS knockout mice) has shown pharmacological and genetic evidence that iNOS activity promoted survival of ischaemic tissue. The administration of nitro-L-arginine methyl ester (a constitutive NOS, endothelia NOS and neuronal NOS inhibitor) significantly increased flap survival in these mice.

In a pig ischaemia-reperfusion injury flap model, there was a disruption of constitutive nitric oxide synthase expression and activity, which may have led to decreased nitric oxide production.

A great deal of laboratory research has been undertaken to reduce flap failure by pharmacological means. Much attention has been paid to drugs that could act as 'free radical scavengers'. Superoxide dismutase has been shown to improve flap survival in animals[34–35] but not in humans. Angel et al.[36–37] have been at the forefront of superoxide radical scavenger therapy, publishing work on the beneficial effects of the iron chelator deferoxamine. These benefits, however, occur with significant toxicity that can be ameliorated (in pigs) by the conjugated form, deferoxamine-hespan (DFO-H). DFO-H has a longer half-life, but with reduced efficacy in augmenting flap survival. This was postulated to decrease its ability to reach the intracellular oxygen free radicals.[38]

It has also been shown that allopurinol can augment flap survival.[39–40] Allopurinol is a xanthine oxidase inhibitor, although elevated levels of xanthine oxidase and malonylodialdehyde have been noted to be elevated in ischaemic flap tissue in animals.[41] A beneficial effect has yet to be shown in humans. Innumerable other animal experiments have been performed on such things as anti-adrenergic drugs[42] and magnesium-ATP (a supply of high energy phosphometabolites),[43] both approaches being to increase the levels of ATP in the tissues.

Others researchers have looked at prostacycline (PGI2) and prostaglandin-E1 (PGE1). Both cause peripheral vasodilatation and inhibition of platelet aggregation.[44–47]

Endothelin-1 (ET-1) is an endogenous vasoactive (vasoconstrictor) peptide, produced in ischaemic flap tissues. In human microvascular breast reconstruction flaps, a statistically significant increase in (skin biopsy) tissue levels of endothelin-1 after clamping of the flap pedicle has been demonstrated. The authors concluded that endothelin-1 levels were elevated in free flaps following reperfusion.[48]

Recent studies have shown that this detrimental effect can be blocked in experimental porcine transverse rectus abdominis myocutaneous (TRAM) flaps by tezosentan, a endothelin receptor blocker. The authors suggest that

tezosentan improves oxygenation and metabolism in the jeopardized contralateral flap tissue, probably as a result of a decrease in venous vascular resistance and fluid extravasation.[49]

This beneficial effect on the venous outflow would fit with observations on the sensitivity of the human musculocutaneous perforator vessels to vasoconstrictors and vasodilatators *in vitro*. The vasoconstrictor potency of norepinephrine, endothelin-1 and thromboxane-A2 mimetic were shown to be significantly higher in the vein than in the artery, hence the maximal venous effect of ET-1 blockade.[50] The severity of tissue necrosis correlated well with tissue levels of ET-1 in rat skin flaps, whilst topical nifedipine antagonized the vasoconstrictive effects of ET-1.

Topical nitroglycerin (GTN) has also been shown to exert a greater vasodilatator effect on the venous circulation than on arterial vessels. Rohrich et al.[51] reported improved survival of axial flaps in pigs and rats treated with nitroglycerin ointment. Topical GTN paste is used in clinical practice but with variable success. On the contrary, recent meta-analyses have shown that intra-operative use of vasopressors in free flap surgery is safe (hNJ).

Direct smooth muscle relaxants nifedipine and verapamil increased flap survival in rats.[52–54] These are calcium-channel blockers that act on the vascular smooth muscles to cause vasodilatation but are restricted in clinical practice to topical application on to microvascular anastomoses, as there is no trial evidence to support their systemic use.

Surgically induced neutrophil recruitment in skin flaps has been shown to impair flap survival experimentally in the rat.[55] Myeloperoxidase (a marker for neutrophil recruitment) was significantly reduced by low-intraperitoneal calcitonin gene-related peptide (CGRP) without affecting the circulating neutrophil count, with improved random pattern flap survival.

One Japanese group[56] have studied sulphatide which binds to L-selectin and P-selectin, important in the initiation of neutrophil–endothelial interactions. Pre-treated experimental skin flaps showed little histological evidence of leukocyte invasion compared to that in the dermal layer of control flaps 48 hours after elevation. They went on to show augmented protection against ischaemia-reperfusion in rat skin flaps when combining sulphatide with anti-rat ICAM-1 and anti-rat LFA-1 antibodies.

The monoclonal antibody to the primary neutrophil adherence-mediating glycoprotein CD18 improves the survival length of the random pattern flap. Histological examination 24 hours after reperfusion in the treated group demonstrated only slight leukocyte invasion into the flap, and myeloperoxidase activity 24 hours after reperfusion was significantly reduced. This study indicated that sulphatide and monoclonal antibodies combined protect rat skin flaps from ischaemia-reperfusion injury.[57]

The platelet glycoprotein IIb/IIIa receptor antagonist Abciximab promoted experimental skin flap survival secondary to blocked platelet activation/aggregation and decreased activated-platelet deposition on the vascular endothelium in the rat.[58] Thus, administration may save the skin flap from reperfusion injury after a long period of ischaemia.

Dimethylsulfoxide (DMSO) is the only substance that has been shown experimentally to improve flap survival in animals and then been supported in a randomized control trial of mastectomy skin flap survival by Rand-Luby et al.[59] This is one of only two controlled trials referenced by the Cochrane database. The authors concluded that the topical application of DMSO safely reduced human mastectomy skin flap ischaemia.

The other clinical trial on the Cochrane database reported a selective phosphodiesterase III inhibitor (Amrinone), which prevents breakdown of cyclic adenosine monoposphate.[60] Statistically proven to improve positively the microcirculatory blood flow of transferred flaps, the authors proposed that this occurred by relief of intra-operative vasospasm.

Another work in rats by Pang et al. concluded that the administration of exogenous vascular endothelial factor (VEGF) 'could protect flaps from ischaemia-reperfusion injury through the regulation of pro-inflammatory cytokines and the inhibition of cytotoxic nitric oxide production'.[61]

Adenovirus-mediated gene therapy with vascular endothelial growth factor delivered into the subdermal space of compromised epigastric skin flaps in a rat model has improved skin flap survival.[62] Viral transfection with subdermal injections of adenovirus-encoding VEGF (Ad-VEGF) was performed two days before flap elevation. Compared with controls, a significant reduction in the area of necrotic and hypoxic zones of the flap was demonstrated following both local and midline subdermal injections of Ad-VEGF.

Others have reported that the survival of flaps treated with VEGF A165 or B167 cDNA was significantly greater than controls.[63] However, neither study could produce evidence that the mechanism was due to angiogenesis using light microscopy, microvessel count or angiography on the treated flap. This is in contrast with histologically demonstrated angiogenesis at the skin paddle-recipient bed interface following the subcutaneous administration of VEGF into the recipient bed of a skin tube flap.[64]

Further support for VEGF therapy comes from Kryger et al., who showed that all routes of administration (systemic, subdermal into the flap, subfascial into the recipient bed) improved survival of a full thickness random pattern flap in the rat compared with controls.[65]

By contrast, Rinsch et al. demonstrated that FGF-2, was more efficacious than either VEGF(121) or VEGF(165) in treating acute skin ischaemia and improving skin flap survival when delivered from encapsulated cells positioned under distal flap.[66]

Thus, with improved delivery strategies, VEGF and FGF-2 may have a role in the management of surgical ischaemia. However, novel gene therapies to improve flap survival have not yet translated into clinical flap surgery.

Dextran and heparin have been shown to improve flap survival in experimental studies of microvascular anastomoses, but not in improving survival of a failing flap.[67–68]

PHYSICAL INTERVENTIONS

Surgical delay

The only well-established technique to improve skin flap survival is by the 'delay procedure' with which all surgeons should be familiar. 'Delay' is a surgical procedure that renders a flap partially ischaemic several days prior to its transfer in order to increase its viability at transfer. Though much debate exists regarding the actual mechanism of vascular delay, most agree that changes in the microcirculation play a key role.

The latest work by Dhar and Taylor showed that when a flap is delayed, there is a dilation of existing vessels within the flap, not ingrowth of new vessels. The maximal anatomic effect on the arterial tree occurs at the level of the reduced-caliber 'choke' (or linking) anastomotic vessels that link adjacent adjacent vascular territories.

They describe 'an active process associated with both an increase (hyperplasia) and enlargement (hyper trophy) of the cells in all layers of the choke artery wall and a resultant increase in calibre of these vessels'.[69]

Tissue expansion can be considered a form of skin flap delay, where expanded porcine flaps showed 150% greater length survival compared with acute non-delayed flap.[70] The expanded flaps had 50% greater length survival compared with the delayed flaps. Angiography showed increased axial vessel calibre in the tissue expanded flaps, subsequently confirmed by Taylor's work. A controlled clinical trial of TRAM flap breast reconstruction confirmed by colour flow Doppler showed an increase in the diameter of flap vessels in which surgical delay was performed one month prior to transfer.[71] A lower flap necrosis rate was found using a delayed TRAM (7.1%) compare with a standard TRAM (30%).

Conditioning

This term describes an endogenous phenomenon in which the application of one or more brief cycles of sublethal ischaemia and reperfusion to an organ or tissue to protect itself or another one distant to it (remote ischaemic conditioning) from the detrimental effect of ischaemia-reperfusion injury (IRI). Depending on the timing of application in relevance to the actual IRI it is classified as ischaemic pre-, post- or conditioning.

Ischaemic preconditioning was first described in 1986 by Murry et al. in canine myocardiac infract models.[72] In 2003, Zhao et al.[73, 74] introduced ischaemic postconditioning as a procedure to minimize acute myocardial infarction (MI) after applying alternate cycles of ischaemia and reperfusion. Both procedures require direct intervention on the tissue or organ. In contrast, remote ischaemic conditioning achieves a protective effect by applying the sublethal cycles to an easily accessed tissue or organ (i.e. arm).[74]

Kraemer et al. studied the microcirculatory benefits of remote ischaemic preconditioning in 27 healthy individuals. The baseline cutaneous microcirculation of the left thigh (corresponding to ALT flap) was tested using combined Laser-Doppler and photospectrometry. Similar tests in the same skin region were performed after three 5-minute ischaemic cycles on the contralateral arm. Statistically significant increase in tissue oxygen saturation and capillary blow flow (29%, 35%, p = 0.001) was noted.[75]

Extracorporeal perfusion

Recently, there have been attempts to revascularize severed limbs or free flaps in vessel-depleted necks both in animal models and humans via extracorporeal perfusion (ECP). This technique refers to a pump-assisted perfusion of the tissues in order to obviate the deleterious effects of prolonged ischaemia. In 2005, Newsome et al. presented a case report of a boy with chondroblastic osteosarcoma of the right hemipelvis with involvement of the common, internal, and external iliac vessles on the right side. The patient underwent hemipelvectomy and high above-knee amputation of the ipsilateral leg. The amputated extremity was placed on extracorporeal bypass using an extracorporeal machine oxygenation (ECMO) circuit connected to the femoral vessels for 162 min. at 32°C. While maintaining extracorporeal circulation, an anterior thigh free flap was created and later used for soft-tissue reconstruction.

In 2016, Wolff et al. reported successful free flap transfer using ECP in three consecutive cases with vessel-depleted neck.[76, 77]

Lasers

Low energy helium-neon (He-Ne) laser irradiation has been shown to improve the viability of skin flaps in rats and in clinical flap repair after avulsion injury.[78, 79] In rat capillaries and fibroblasts, proliferation was demonstrated histologically while clinical improvement was attributed to improved superoxide dismutate activity.

Leeches

Hirudo medicinalis, the medicinal leech, exerts its effect by injecting hirudin, a naturally occurring anticoagulant, into the affected part. In addition, leeches secrete hyalurodinase into the tissues, as well as a vasodilator, which contributes to prolonged bleeding. The main use for leeches is in the congested microvascular flap when there is no other way of improving venous outflow.[80] Useful in selected cases, there is nonetheless a serious risk of secondary infection with the leech enteric organism *Aeromonas hydrophila*, which can kill the skin flap. Antibiotic cover should be provided when using leeches.

KEY POINTS

- Skin is the largest organ of the human body and confers protection against mechanical and bacterial insults as well as thermoregulation.
- Better understanding of the pertinent anatomy and skin and vessel biomechanics can minimize mistakes and improve outcomes in reconstructive surgery.
- Several intrinsic and extrinsic factors may compromise flap viability.
- Conditioning, surgical delay and/or extracorporeal perfusion may optimize flap survival.

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CHAPTER 12

BIOMATERIALS, TISSUE ENGINEERING AND THEIR APPLICATION IN THE ORAL AND MAXILLOFACIAL REGION

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline and Embase search using the keywords: biomaterials, tissue engineering, head and neck, and focussing on gold standard tissue engineering techniques as well as new developments. Clinical applications are limited due to the novelty of the subject; most of the published research is based on the preclinical applications of biomaterials.

INTRODUCTION

The reconstruction of large defects, particularly bony defects, in the head and neck region continues to be an area of significant debate. These defects are usually created after the surgical removal of cancer lesions or as a result of bone loss following major trauma. The critical size of the created surgical defect, combined with the detrimental effect of post-surgical radiation therapy on the blood supply of the surrounding tissues contribute to the limited healing capabilities of the surgical site and the challenging reconstructions. Most of the available data on the management of such defects are based on expert opinion; the comprehensive studies provide limited objective guidelines for successful treatment.[1]

Bone provides the support and foundation for the overlying soft tissues so its replacement is essential for successful reconstruction. Various bone graft materials have been used for the restoration of head and neck bone defects. An ideal bone graft needs to promote osteogenesis, osteoinduction and osteoconduction.[2] *Graft osteogenesis* is provided by the cellular elements within a donor graft that survive the transplantation and synthesize new bone at the recipient site, an example of which would be mesenchymal stem cell-derived osteoblasts. *Graft osteoinduction* is new bone formation through the active recruitment of host mesenchymal stem cells from the surrounding tissue, which then differentiate into bone-forming osteoblasts. This is a property held by various cytokines including bone morphogenetic proteins (BMP). *Graft osteoconduction* is achieved by new bone formation into a defined supporting scaffold (matrix) that can be the non-vascularized bone itself or with the application of allografts or synthetic substitute. Other important graft properties include biocompatibility, bioactivity, biodegradability and the ability to attain adequate mechanical properties. Because autogenous bone grafts possess all of the aforementioned properties they continue to be the gold standard for the repair of such defects but the morbidity associated with harvesting such grafts inspired the development of substitutes.[3]

This chapter looks at the main types of biomaterials that have been applied for the reconstruction of the oral and maxillofacial region and looks at the various bioengineering methods that have been developed to try and replicate as well as promote the body's natural healing capabilities.

BIOMATERIALS

The biomaterials that will be discussed in this section were developed to support the concepts described previously. The materials described will possess one or more of the three fundamental properties of osteoconduction, osteoinduction and osteogenesis.

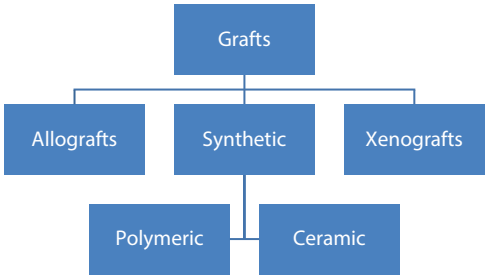


Figure 12.1 The main types of alternative grafts available for use in the head and neck region. Hybrids of these different types are also available.

Scaffold biomaterials used for tissue engineering vary in porosity, composition and biodegradability to best mimic the requirements of the tissue to be replaced. For this reason a vast array of scaffold materials (available as powders, granules, dense blocks, putties, injectable pastes, gels and porous scaffolds) have been developed as they are able to provide osteoconduction and in some cases (e.g. porous block scaffolds) help restore the shape of the critical-sized defect.

Scaffolds can be broadly divided into three main types: allogenic, xenogenic and synthetic graft materials. Allogenic grafts are derived from donors of the same species as the recipient, xenografts are derived from donors that are from a species different to that of the recipient and synthetic grafts, as their name implies, are manufactured in a laboratory. These synthetic grafts are then further subdivided into ceramics and polymeric materials (Figure 12.1). Several hybrids (composites) of all the above scaffolds have also been developed. Most of these grafts only have osteoconductive properties providing a foundation for cells to migrate from the wound edges. Because of this limitation they are usually combined with osteoinductive materials.

Allografts

Allografts are grafts obtained from donors that are of the same species as the recipient. Demineralized bone matrix (DBM) is derived from human cadaveric bone that has been demineralized, processed and sterilized, leaving a denatured form of the protein matrix. This process is required to remove the risk of disease transmission to or an immunological response in the recipient. However, heavy processing can also result in the denaturing of the cytokines in the graft so that it loses its osteoinductive properties and remains only osteoconductive. It has been shown that DBM, when placed in sites where bone is not normally produced, can induce ectopic bone formation.[4]

Xenografts

Xenograft usage in the head and neck region is mostly limited to the use of bone minerals derived from the bones of pigs, cows and horses. The preparation of the materials results in the removal of all organic components leaving a granular, porous material with good osteoinductive properties. Collagen xenografts are also commercially available where the collagen is extracted from porcine small intestine submucosa. Bio-oss is an example of a xenograft derived from bovine bone that is routinely used for augmentation of the jaw bones. The main barriers to the usage of these materials in the past have been the risk of disease transmission; this is now unlikely due to the processing methods. However, the ethical issues related to xenograft usage remain, so detailed informed consent is essential prior to their clinical use.

Synthetic grafts

The most researched synthetic grafts are the ceramics, of which hydroxyapatite (HA), tricalcium phosphate (TCP) or a mixture of the two (biphasic calcium phosphate, BCP) are most widely used (Table 12.1). Ceramics are brittle materials with limited tensile strength but are available in the form of blocks with more extensive interconnected porosity permitting faster bony ingrowth; the ideal pore size is thought to be between 150 and 500 microns.[5] So as to overcome their inherent brittleness, ceramics are also available as composite materials where they have been combined with either polymers or allograft materials such as DBM.[6]

Cytokines

Cytokines are important low molecular weight, soluble cell signalling proteins that are released by cells to stimulate, 'induce', other cells through specific receptors. Usually cytokines act only over a short distance and for short periods of time and must therefore be newly produced. This has to be repeated frequently, usually in response to a stimulus. They are pleiotropic (can influence various cell types) as well as redundant (can share similar functions). Cytokines promote and control immune responses against

TABLE 12.1 Types of scaffolding materials used in tissue engineering

Natural	Synthetic
Collagen: • Gels, nanofibers, porous scaffolds, films Fibrin: • Injectable adhesive gels Alginate: • Hydrogels Silk: • Nanofibers, films Hyaluronan: • Gels, sponges, pads Chitosan: • Sponges, porous scaffolds, nanofibers Agarose: • Hydrogels	Ceramics: • Calcium phosphate cements: • Low-temperature calcium orthophosphate cements • Bioactive glasses • Hydroxyapatite • β-tricalcium phosphate Titanium Polymeric materials: • Poly(α-hydroxy esters): • Poly(L-lactic acid) • poly(glycolic acid) • Poly(lactic-co-glycolic acid) • Poly(propylene fumarate) • polyethylene glycol Ceramic reinforced polymers

inflammation, infections and cancer, with the malignant transformation process being associated with an altered response to cytokine stimulation.[7]

Cytokines such as interleukins (IL-1, IL-3, IL-6, IL-11), tumour necrosis factor (TNF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGF) and vascular endothelial growth factor (VEGF) have been linked with functions that range from further cytokine release, angiogenesis, metastasis and osteoblast/osteoclast development.

There is a complex interaction that takes place between the various bone modelling cells (osteoblasts and osteoclasts) and their haematopoietic precursors as well as the cytokines themselves that results in bone formation or deposition. Cytokines also play an important role in cell activation leading to chemotaxis and release of inflammatory mediators, help in vascular remodelling (neoangiogenesis) and promote the synthesis of matrix enzymes required for the remodelling of cartilage and bone.

BONE MORPHOGENETIC PROTEINS

Bone morphogenetic proteins (BMP) are probably the most effective cytokines in relation to bone formation and healing. There are more than 20 subtypes, all forming part of the transforming growth factor β (TGF-β) superfamily.[8] BMPs induce stem and mesenchymal cell differentiation into osteogenic cells capable of producing bone. BMPs are secreted as signalling molecules that activate intracellular cascades by binding to cell surface receptors. The BMP signalling pathway has been shown to be involved in a number of developmental processes and is critical for the formation of the majority of the craniofacial elements including the cranial neural crest, the facial primordia, teeth, lips and palate.

With the use of recombinant gene technology, large quantities of recombinant human BMPs (rhBMPs) have become readily available. BMP-2 and BMP-7 (also known as Osteogenic Protein-1) are recognized to be the most effective cytokines in the maxillofacial region, inducing osteoprogenitor cells to produce bone, and resulting in chemo-attraction of mesenchymal stem cells to the defect area.[9] They are both approved for clinical use and have been used for spinal fusion, the repair of long bone fractures and non-unions as well as the repair of craniomaxillofacial defects.[9]

Due to their nature cytokines need to be placed in a scaffold, such as the ones mentioned above, to control the shape of the regenerate. Even though they are widely available and appear to be very effective at inducing bone formation, cytokines continue to be very expensive. This is due to the very time-consuming purification and concentration steps before the produced dimer protein can be refolded into its functional form. This currently significantly limits their widespread use.

Mesenchymal stromal cells

The last important bone regeneration property is osteogenesis; this is a property potentially held by pluripotent cells such a mesenchymal stromal cells (MSC). These cells are capable of differentiation into three main cell lineages – osteogenic, chondrogenic and adipogenic – as well as potentially into myogenic, neurogenic and tenogenic lineages. These cells, by their very nature, can therefore be *induced* to transform into bone forming cells if given the right stimulus and microenvironment.[10] This microenvironment is implicated in both the support and maintenance of the MSCs. There are different elements that could affect the cells; these are oxygen tension, glucose concentration, growth factors, the physiochemical nature of the environment including the pH and ionic strength (e.g. Ca^{2+} concentration). Their roles are critical for the maintenance of stem cell properties and the possibility of reprogramming their commitment prior to application in the surgical defect. MSCs can be obtained from the bone marrow, spleen and thymus as well as several other sites including adipose tissue.[11]

Autogenous bone marrow aspirate (BMA) is readily obtainable from the bone marrow of, for example, the anterior iliac crest. The aspirate is highly cellular containing osteoprogenitor cells (osteogenic) and provides a concentration of protein factors (cytokines) that stimulate bone growth (osteoinductive). For this reason it has become a cost effective alternative to the recombinant osteoinductive cytokines mentioned above.[6]

Platelet-rich plasma

Platelet-rich plasma (PRP) is blood that is taken from the patient, centrifuged, ultra-concentrated and then reimplanted after processing. It contains a mixture of platelets and growth factors such as platelet derived growth factors (PDGF), transforming growth factor-β (TGF-β), as well as insulin-like growth factor-I (IGF-I). These growth factors (cytokines) can stimulate mitogenesis of marrow stem cells and angiogenesis.[12] The expensive processing methods for the production of PRP limit its clinical use; for this reason, second generation platelet-rich fibrin (PRF), which requires no biochemical handling, has been developed.[13]

Bioreactors

In tissue engineering a bioreactor is a device that simulates the natural environment of a tissue so as to promote its growth. It is usually a perfusion chamber connected to a pump system that allows peristaltic pumping of fresh medium, and is kept at a controlled oxygen level. This allows the maintenance of ideal physiologic conditions that promote development of the required tissue. This helps to recreate the microenvironment that was described above. Other parameters that can be controlled include the application of forces or stresses to the tissues in both two or three dimensions, thus simulating the environment in which, for example, bone develops.[14] These devices are becoming increasingly popular for the development of grafts for use in

the head and neck region as they are able to overcome one of the main problems in tissue engineering, which is the maintenance of a good oxygen supply and removal of cellular waste products. They also allow the maturation of the graft in the laboratory prior to its placement into the surgical recipient site.

TISSUE ENGINEERING

Bone is a complex tissue with highly porous central spongy bone and solid compact outer cortical bone. Therefore bone tissue engineering requires the design of three-dimensional (3D) scaffolds that closely mimic this anatomical organization of bone. Changes in scaffold geometry can impact on the flow of media across the scaffold and thus affect the supply of gases and nutrients and the removal of metabolites. An increase in pore number and size in various scaffolds is associated with increased vascularization and osseointegration *in vivo*, but the increased pore volume reduces the mechanical stability of the scaffold.[15]

A sufficient blood supply is required to achieve successful tissue regeneration. This remains a significant barrier to the effective reconstruction of large defects in the head and neck region. The stimulation of angiogenesis from endothelial precursors is therefore essential. The best-known angiogenic factor is vascular endothelial growth factor (VEGF), which creates an environment that promotes endothelial cell migration and proliferation.[16]

Clinical trials

The clinical application of the above mentioned novel materials is still in its early stages but some successful outcomes have been reported.

Fibroblast growth factors (FGFs) have been successfully applied for the repair of tympanic membrane perforations[17] as well as the treatment of the ageing vocal folds,[18] due possibly to the effect that this cytokine has on the key extracellular matrix components in the lamina propria.[17]

Recombinant human bone morphogenetic protein 7 (rhBMP-7) in a type I collagen carrier was used for the reconstruction of unilateral and bilateral alveolar cleft defects. The patients were followed up for an average of 6.5 years and objective radiographic evaluation demonstrated very good bone regeneration in the defects.[19]

Cultured bone marrow cells that were exposed to an osteogenic environment and placed in a mineral base of β-tricalcium phosphate and hydroxyapatite were used to treat three clinical cases. These cases had osteoradionecrosis of the maxilla and mandible with pathological fracture; a non-healed fracture with bone loss, and bilateral paraesthesia; and a very large maxillary bone deficiency. All showed signs of osteogenesis, nerve reinnervation and skin regeneration.[20]

Thirteen consecutive cases of cranio-maxillofacial hard-tissue defects in the frontal sinus (three cases), cranial bone (five cases), mandible (three cases) and nasal septum (two cases) were treated with autologous adipose stem cells derived from adipose tissue obtained from the abdominal wall. The cells were seeded onto bioactive glass or β-tricalcium phosphate scaffolds together with recombinant human bone morphogenetic protein 2. Ten out of the thirteen cases had successful outcomes.[21]

A large mandibular discontinuity defect was repaired with a custom bone transplant grown inside the latissimus dorsi muscle of an adult male patient. This was achieved using computed tomography scanning and computer-aided design techniques to produce a virtual replacement (in the form of a titanium mesh) for the mandibular defect. This was filled with bone mineral blocks, recombinant human bone morphogenetic protein 7 and the patient's bone marrow. Seven weeks after placement in the latissimus dorsi muscle the graft was successfully transplanted as a free bone-muscle flap to repair the mandibular defect.[22]

FUTURE RESEARCH

Molecular therapy in bone bioengineering

Modification of the properties of cells at the molecular level can have significant potentially useful effects within tissue engineering. Liposome-mediated and adenovirus cell-mediated BMP-2 gene transfer into MSCs in preclinical studies has resulted in cells that are able to repair critical-size bony defects.[23] Gene-modified cells could potentially be given all the properties required for tissue regeneration and they could be then implanted into the surgical defect. Alternatively these cells could be place in a bioreactor and allowed to create the required tissue 'bone' *ex vivo* after which it would be implanted into the surgical recipient site.

Biomimetic scaffolds

Scaffolds currently used for tissue engineering are either granular or manufactured in predetermined shapes. With the use of computer-based solid free form fabrication (SFF) using 3D printers it is possible to create custom-made scaffolds designed to specifically fit the defect that is being treated. Also the nano-topography and nano-chemistry of the scaffold can be structured in detail to try and reproduce the natural tissue that it is designed to replace, even at the cellular level. This would help promote the growth of all the required cellular elements for tissue regeneration (e.g. blood vessels and bone).

Improved vascularity

New methods that can improve the vascularity of the donor sites/grafts will significantly enhance the regenerative abilities. The bioreactors mentioned earlier can help in this respect but specific methods of inducing controlled vascular proliferation within the surgical site still need to be developed, possibly using synthetic polymers.

KEY POINTS

- The reconstruction of large defects, particularly bony defects, in the oral and maxillofacial region continues to be an area of significant development.
- An ideal bone graft should promote osteogenesis, osteoinduction and osteoconduction, as well as be biocompatible, bioactive, biodegradable and possess adequate mechanical properties.
- The harvesting of the autogenous bone graft 'gold standard' is associated with donor site morbidity; this is the main drive force for the search for synthetic substitutes and further investigation in tissue bioengineering.
- Biomaterial scaffolds can be broadly divided into three main types; allogenic, xenogenic and synthetic graft materials.
- Most synthetic scaffolds have only osteoconductive properties and are combined with osteoinductive materials.
- The ethical issues related to xenograft usage remain, so patient informed consent is essential prior to their clinical use.
- The most researched synthetic grafts are hydroxyapatite (HA), tricalcium phosphate (TCP) or a mixture of the two (biphasic calcium phosphate, BCP).
- Cytokines are important low molecular weight, soluble cell signalling proteins that have an effect on other cells through specific receptors affecting several processes that include tumour growth and bone remodelling.
- Mesenchymal stromal cells, which can be obtained from the bone marrow, spleen, thymus and adipose tissue, are capable of differentiation into the three main cell lineages; osteogenic, chondrogenic and adipogenic.
- The cytokine bone morphogenetic protein induces mesenchymal cell differentiation into osteogenic cells capable of producing bone.
- A bioreactor is a device that simulates the natural environment of a tissue so as to promote its growth.

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CHAPTER 13

DEFENCE MECHANISMS

Ian Todd and Richard J. Powell

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: innate immunity, adaptive immunity, antigen, B lymphocyte, T lymphocyte, antibody, immunoglobulin, antigen presentation, cytokine, complement, inflammation, hypersensitivity, allergy and autoimmunity.

INNATE AND ADAPTIVE IMMUNITY

The immune system has evolved for protection against infectious agents that invade the body. In order to achieve this, the immune system has recognition properties to locate and identify the invader, and to activate defence processes to repel or destroy the invader. There are an enormous number and variety of infectious agents within the main categories of viruses, bacteria, fungi, protozoa and parasitic worms. In order to provide effective immunity against each of these agents, the immune system has to be able to meet the challenges they pose: this is achieved by a diverse range of molecular and cellular components in the body that cooperate with each other in order to maximize their defensive activities. Some of these components generate innate immunity, whereas others provide adaptive (or acquired) immunity. The main cell types of the immune system are the leucocytes that develop from stem cells in the bone marrow.

The innate immune system is evolutionarily older than the adaptive system and provides generic defence against categories of microbes. It is composed of a range of cells and proteins found in the circulation and in tissues: these include macrophages (and their monocyte precursors), granulocytes (i.e. neutrophils, eosinophils, basophils), and mast cells, natural killer cells, complement proteins, regulatory proteins called cytokines. The innate system employs an inherited repertoire of receptor proteins (known as pattern-recognition molecules) that recognize characteristic structures that are commonly expressed by microbes, and changes to cells induced by infection. The advantage of this innate system is that it is rapidly activated by infectious agents that penetrate tissues. However, it is only moderately efficient; hence, an adaptive immune response is also required to enhance the elimination of many pathogens.

Adaptive immunity is mediated by T lymphocytes and B lymphocytes (also known as T cells and B cells). Similar to the leucocytes involved in the innate system, lymphocytes develop from bone marrow stem cells. The precursors of T cells migrate to the thymus to complete their maturation. Each T or B cell expresses receptors that specifically recognize one particular chemical structure of a microbial molecule (known, in this context, as an antigen). Activated B cells also secrete a soluble form of their antigen receptors, known as antibodies or immunoglobulins (Ig). An enormously diverse repertoire of antigen receptors is somatically generated by recombination events involving the receptor genes during the development of lymphocytes, resulting in the potential to recognize millions of different antigens. The recruitment, activation and proliferation of resting lymphocytes specific for the antigens of an invading microbe takes time (possibly several days), but the lymphocytes generate a highly efficient defence. In addition, some of the lymphocytes activated by specific antigens are maintained in the body as resting cells after the elimination of the infection and constitute a memory population of cells that are able to generate a bigger and faster response upon subsequent exposure to the same antigens: this demonstrates the adaptive properties of lymphocytes.

The innate and adaptive systems interact and synergize to generate optimal immunity. Specifically, lymphocyte activation is dependent not only on antigen recognition, but also on co-stimulatory signals provided by cells and molecules of the innate system. Furthermore, the antibodies produced by B cells and the cytokines secreted primarily by T cells enhance the defensive activities of the innate system.

Stages of an immune response

The immediate response to an invading pathogen is mounted by innate components resident within the infected tissues (**Figure 13.1a**). In particular, tissue macrophages (and other cells with innate immune functions) express a range of pattern recognition receptors for microbial structures, including mannose receptor, scavenger receptors and Toll-like receptors, whose ligands include various microbial polysaccharides, lipids and nucleic acids. Complement proteins are also directly activated by microbes via the alternative pathway (see 'The Complement System' below). Inflammatory products of macrophages and complement, together with those released by tissue mast cells activated by the complement peptides C3a and C5a (known as anaphylatoxins), induce the migration of granulocytes, natural killer cells and more complement proteins from the blood stream into the infected tissues (**Figure 13.1b**).

Whilst these innate processes are providing early defence to limit growth and spread of the infection within the body, other processes are set in train to generate the antigen-specific adaptive response (**Figure 13.1c**). The activation of lymphocytes does not initially take place within the infected tissues themselves, but in specialized collections of lymphoid tissues such as lymph nodes, the spleen and mucosa-associated lymphoid tissues (MALT) that includes Waldeyer's ring. Antigens therefore have to be transported from the infected tissues to local lymphoid tissues. Some antigens may be passively carried in the tissue fluid forming the lymph that drains into regional lymph nodes. However, a significant role is played by dendritic cells found in most tissues. These, like the macrophages described above, express pattern-recognition receptors for microbial structures and actively engulf microbial material. This induces maturation of the dendritic cells, which then migrate from the site of infection and carry the microbial antigens to the local lymphoid tissues where T and B lymphocytes have the opportunity to interact with the antigens leading to their activation. Only a very small proportion of the millions of lymphocytes in a particular lymphoid organ will have receptors that specifically recognize the antigens associated with a particular microbe. It is the antigen-activated lymphocytes that proliferate and mature into effector cells contributing to defence against the pathogen. These effector lymphocytes leave the lymphoid tissues and recirculate via the blood stream to the site of infection in order to enhance the destruction and elimination of the pathogen in cooperation with the innate components described above.

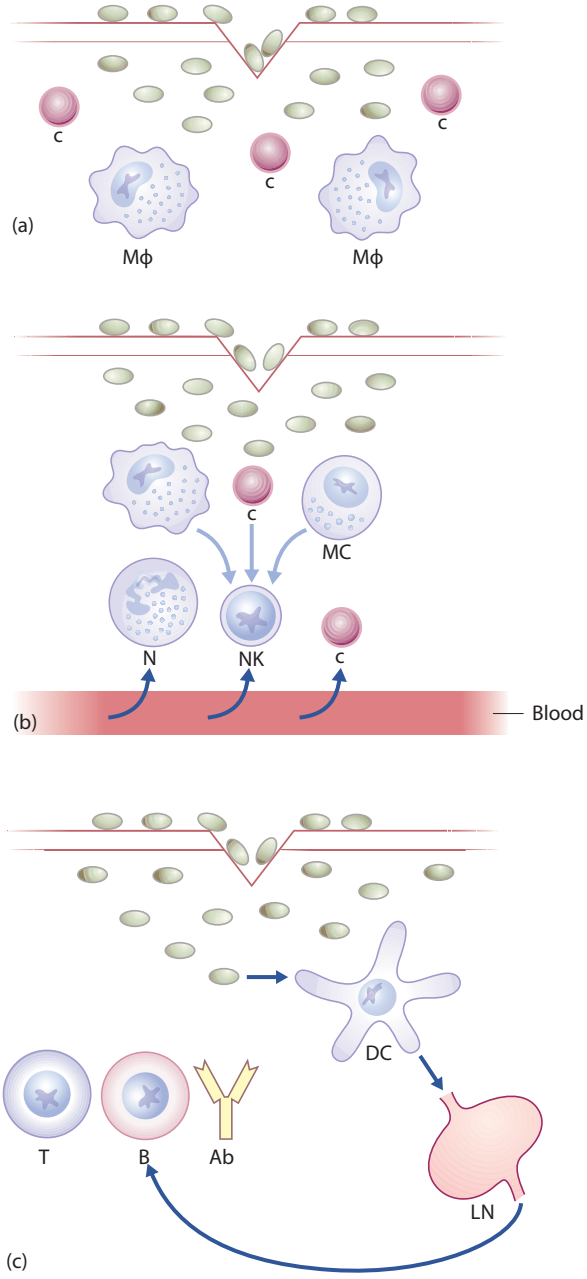


Figure 13.1 Stages of an immune response. (See text for details.) a) Immediate local innate response; b) Early induced response (innate/inflammatory); c) Later adaptive response. Ab, antibody; B, B lymphocyte; C, complement; DC, dendritic cell; LN, lymph node; MC, mast cell; MΦ, macrophage; N, neutrophil; NK, natural killer cell; T, T lymphocyte.

ANTIGEN RECOGNITION

Antigen recognition involves a high affinity interaction between an antigen and the specialized antigen combining site of a lymphocyte's antigen receptor protein (or of an antibody molecule). The binding involves non-covalent intermolecular attractive forces that require the interacting surfaces to have complementary shapes that fit snugly together (rather like a lock and a key), allowing interactions to occur between complementary chemical groups of the antigen and the combining site. Each lymphocyte

clone (i.e. group of cells derived from a single parent lymphocyte) expresses antigen receptors with a single type of combining site that is unique in shape and amino acid composition to that clone contrasting with the millions of other lymphocyte clones in the body: this is why millions of differing antigens can be recognized by the adaptive immune system. Furthermore, the specificity of the adaptive response arises because those lymphocytes whose receptors have the highest affinity for an antigen that enters the body are the ones most likely to bind it and hence be activated by it: this is termed clonal selection.

B cells and antibodies (immunoglobulins)

The B cell's receptor is essentially a membrane bound form of the antibody that a particular B cell secretes, and is called surface immunoglobulin (sIg) (Figure 13.2). It is made up of two identical large polypeptides (heavy chains) and two identical smaller light chains (which can be one of two types called κ and λ light chains). Each chain is composed of a series of homologous globular regions called Ig domains: two in the light chains and four or five in the heavy chains.

The receptor has two identical antigen combining sites, each of which is composed of the amino terminal domains of a heavy and a light chain: these are called variable domains because they vary in structure between different B cell clones, thereby conferring the differences in antigenic specificity between B cells. Different types of chemicals can serve as antigens for direct interaction with different B cell receptors and antibodies, including proteins, carbohydrates, lipids and even nucleic acids.

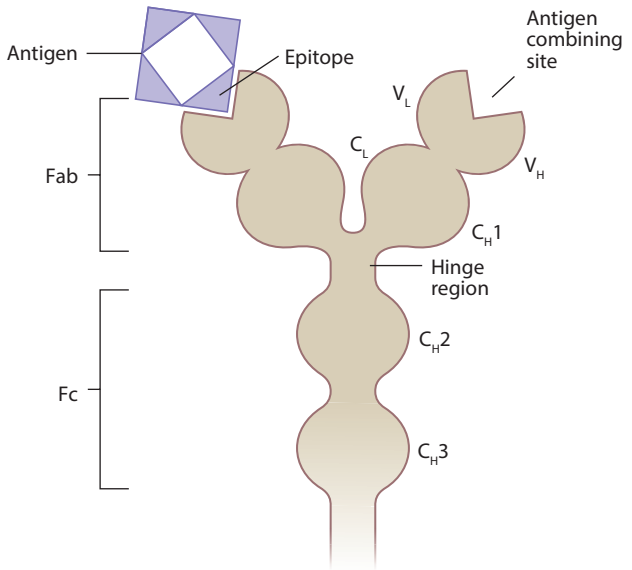


Figure 13.2 A schematic structure of a generic immunoglobulin (surface or secreted). (See text for details.) The variable domains of the heavy and light chains are labelled V_H and V_L, respectively. Similarly, the constant domains are labelled C_H1-3 and C_L. The pale region below C_H3 indicates the transmembrane region and cytoplasmic tail present in sIg, but not in secreted antibodies.

The combining site constitutes only a small part of a whole Ig molecule and can accommodate approximately four to six amino acids of a protein antigen: the precise region of an antigen molecule that interacts with a combining site is termed the antigenic determinant or epitope. Each variable domain contains three hypervariable loops, so called because they differ most in amino acid sequence between different clones of B cells; they are also known as complementarity determining regions, being complementary to the epitope and forming the main interactions with it. Following B cell activation, modifications can occur to the variable domains by somatic mutation. This involves nucleotide changes to the variable domain genes during B cell replication that affect the amino acid sequence (particularly of the complementarity determining regions) and therefore affect the antigenic specificity of the antigen combining sites. This can generate combining sites that fit even more tightly with the epitope, improving further the affinity for the antigen.

The other domains are called constant domains because they have the same structure in the sIg of different B cells. Human B cells can express one of nine different forms or isotypes of Ig (both surface and secreted) that differ in the structure and number of their heavy chain constant region domains, and constitute five immunoglobulin classes. These are called IgM, IgG (with subclasses IgG1, IgG2, IgG3 and IgG4), IgA (with subclasses IgA1 and IgA2), IgE and IgD. All B cells are initially programmed to express IgM (with IgD), but can undergo Ig class switching to produce one of the other isotypes following stimulation by antigen, without changing their antigenic specificity. They do this by changing the heavy chain constant region domains that they express, but maintain expression of the same variable domain on the heavy chain and the same light chain variable and constant domains.

The sIg is anchored in the surface membrane of a B cell by a transmembrane amino acid sequence at the carboxy terminus of the heavy chains. When a resting B cell is activated by an antigen, it can differentiate into a plasma cell that produces large numbers of Ig molecules that lack the transmembrane sequence. These are secreted from the cell as antibodies with the same antigenic specificity and isotype as the B cell's sIg. Because B cells initially express sIgM, the first antibodies produced during an immune response (i.e. on first exposure to a particular antigen) are also IgM (there is little, if any, secretion of IgD systemically), but IgG, IgA and IgE antibodies appear later in the response as activated B cells undergo class switching. Furthermore, the memory population is derived from B cells that have undergone class switching, so that IgG, IgA and IgE are produced at the start of a secondary response on repeated exposure to the same antigen. The advantages of producing a range of antibody isotypes are that they have different physiological and defensive activities.

T cells and antigen presentation

The T-cell receptor (TCR) for an antigen shows both similarities and differences to B cell sIg (Figure 13.3). The TCR is a much smaller molecule, being made up of two

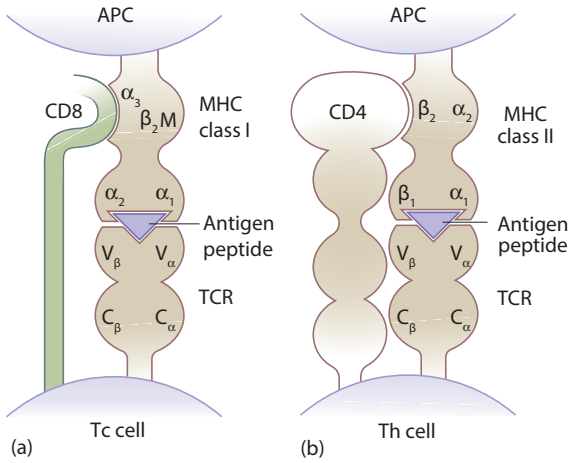


Figure 13.3 Antigen recognition by T cells. (See text for details.) APC, antigen presenting cell; β2M, β2-microglobulin; C, constant domain; MHC, major histocompatibility complex; Tc, cytotoxic T cell; TCR, T cell receptor; Th, helper T cell; V, variable domain.

polypeptide chains each of which is about the same size as an Ig light chain, with both expressing a transmembrane sequence. However, T cells do not produce a secreted form of the TCR (i.e. they do not release proteins equivalent to antibodies). The TCR polypeptides expressed by the majority of T cells are called α and β chains, whereas a minority express γ and δ chains. Each chain is composed of two domains that show strong structural homologies with those of the immunoglobulins. Similar Ig-like domains are found in many other surface molecules of lymphocytes and other cells: this indicates evolutionary genetic relationships between these molecules, constituting the immunoglobulin superfamily. The two amino terminal, membrane-distal domains of the TCR chains are variable between T cells and constitute the single antigen combining site. The membrane-proximal domains are constant in structure.

Unlike B cell immunoglobulins, conventional TCR cannot interact directly with antigenic epitopes of proteins; rather, they only bind to short peptides that are derived from protein antigens, and are expressed on the surface of other cells of the body that are known, in this context, as antigen presenting cells (APC). This is because the main function of T cells is to interact with other cells within the context of an immune response: binding to antigenic peptides held on the surface of a cell thereby directs a T cell to exert effects on that particular APC. There are two main functional types of T cell: helper T cells (Th) regulate the activity of other cells of the immune system, whereas cytotoxic T cells (Tc) kill cells that are infected. In order for this to happen, protein antigens that enter the cytoplasm of an APC are processed (i.e. degraded) into peptides, some of which associate with proteins of the major histocompatibility complex (MHC), known in humans as HLA (human leucocyte antigens). The MHC molecule/peptide complexes are then expressed on the surface of the APC where they can interact with T cells whose TCR have combining sites specific for the particular antigenic peptides presented, much in the same way as an Ig combining site interacts with an antigen epitope. This interaction binds the T cell to the surface of the APC, enabling these cells to exert effects on each other.

There are two types of MHC molecule, called MHC class I and MHC class II (**Figure 13.3**). They have similar three-dimensional structures, but are made up of different types of polypeptide chains. The MHC class I protein is composed of a large α-chain non-covalently associated with the smaller β_2-microglobulin, whereas MHC class II is composed of similarly sized α and β chains. Both class I and class II have two Ig-like domains adjacent to the cell membrane (i.e. they are members of the Ig superfamily), whereas distal to the membrane is the antigen peptide binding cleft. Two α-helices form the walls of the cleft and sit on a platform of β-pleated sheet; antigen peptide is held within the cleft in a linear conformation (rather like a hotdog sausage in a bun!) with its exposed surface available for interaction with a TCR. Peptides eight or nine amino acids in length can be accommodated within the cleft of MHC class I molecules, whereas the peptides that associate with MHC class II molecules can be between 12 and 20 amino acids in length because they can extend beyond the ends of the peptide binding cleft.

MHC class I molecules present antigens primarily to Tc cells because these cells express a protein called CD8 that binds to the side of the class I α-chain when the TCR interacts with the peptide and binding cleft (**Figure 13.3a**). Most tissue cells of the body express MHC class I molecules on their surfaces and thus have the potential to be targets for Tc cells if they become infected by microbes that enter the cytosol, such as viruses. The processing pathway for cytosolic proteins delivers the peptides to MHC class I molecules for binding and presentation. Tc cell clones that specifically bind to these peptides have various ways of killing infected cells by inducing them to undergo apoptosis (programmed cell death):

- The Tc cells secrete two types of proteins stored in cytoplasmic granules: perforins that polymerize to create pores through the plasma membranes of the target cells, and granzymes that enter the target cells through the perforin pores, inducing apoptosis.
- Fas-ligand expressed on the surface of Tc cells, or tumour necrosis factor (TNF alpha) secreted by Tc cells can induce apoptosis when they bind to their receptors on infected target cells (Fas and TNFR1, respectively).

MHC class II molecules present peptides mainly to Th cells because these cells express the CD4 protein that binds to the side of the MHC class II β-chain (**Figure 13.3b**). The expression of MHC class II molecules is mainly restricted to cells of the immune system whose functions are to activate, and be activated by, Th cells: these are dendritic cells, macrophages and B cells. These cells deliberately engulf exogenous antigens that, for example, bind to Toll-like receptors expressed on macrophages and dendritic cells, or specifically bind to the sIg of selected B cell clones. In either case, the surface-bound

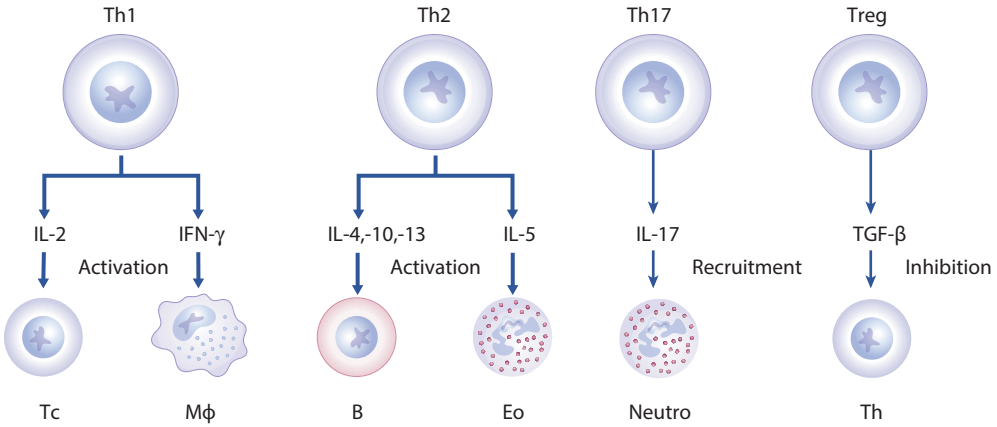


Figure 13.4 Cytokine-mediated regulation by Th1, Th2, Th17 and Treg cells. B, B lymphocyte; Eo, eosinophil; IFN-γ, interferon-γ; IL, interleukin; MΦ, macrophage; Neutro, neutrophil; Tc, cytotoxic T cell; TGF-β, transforming growth factor β; Th1, T helper 1 cell; Th2, T helper 2 cell; Th17, T helper 17 cell; Treg, regulatory T cell.

antigens are endocytosed into membrane-bound vesicles within the cytoplasm. The processing pathway for these vesicular proteins delivers peptides to MHC class II molecules for binding and presentation. Th cell clones that specifically bind to these peptides can then be triggered by the APC to exert their regulatory activities. A range of cell surface and secreted molecules mediate the mutual effects of Th cells and APC. First, there are the interactions of TCR and CD4 with the peptide/MHC class II complex, with the signal resulting from TCR binding being delivered to the interior of T cells by the CD3 protein. Second, a number of other membrane proteins interact between the surfaces of the T cells and APC to deliver co-stimulatory signals: particularly important are interactions of CD28 with B7, and CD40-ligand with CD40, but others include the interactions of CD2 with LFA-3, and LFA-1 with ICAM (in each case on the T cells and APC, respectively). Third, both the APC and the T cells secrete cytokines as soluble regulatory proteins that bind to specific cell surface receptors. For example, interleukin-1 (IL-1) and IL-12 are important T cell activators secreted by dendritic cells.

When activated, different Th cells preferentially secrete differing combinations of cytokines (Figure 13.4). Th1 cells produce interferon-γ (IFN-γ), which is an important macrophage activator, and IL-2, which stimulates T cells (including Tc cells); hence, Th1 cells induce primarily cell-mediated immunity, although they do also stimulate B cells to produce IgG antibodies (subclasses 1-3). In contrast Th2 cells produce IL-4, IL-10 and IL-13, which stimulate B cells to produce antibodies, and particularly induce Ig class switching to production of IgG (subclasses 1-4), IgE and IgA; they also secrete IL-5, which stimulates eosinophils. Th1 and Th2 cells can in fact inhibit each other's activities via the cytokines they release. These patterns of type 1 and type 2 cytokine secretion are observed with other cell types, including Tc cells and B cells. Other subpopulations of T cells have been defined and include Th17 cells, which secrete IL-17, recruit neutrophils to infected tissues and induce the production of inflammatory cytokines and chemokines. Regulatory T cells (Treg cells) inhibit the activity of T helper cells, thereby controlling adaptive immunity; they do this partly by secreting suppressive cytokines, a key example of which is transforming growth factor-beta (TGF-β).

There are several subpopulations of lymphocytes that display properties of both innate and adaptive immunity. These include NKT cells and γδT cells, whose antigen receptors show limited diversity and interact with ligands that differ from the peptide-MHC complexes recognized by 'conventional' T cells. Additional 'innate lymphoid cells' include the well-characterized natural killer (NK) cells and more recently identified lymphoid cells that lack antigen-specific receptors and rapidly produce cytokines when activated.

IMMUNITY TO EXTRA-CELLULAR AND VESICULAR INFECTIOUS AGENTS

Differing defence mechanisms are required to deal with infectious agents that occupy different compartments within the body. A major distinction is whether an infectious agent is in an extra-cellular environment or has entered the cytoplasm of cells, joining the intra-cellular environment (Figure 13.5). This distinction is important because extra-cellular organisms are directly accessible to defensive molecules secreted by cells of the immune system, whereas intra-cellular ones are not. Consequently, antibodies play a major role in the adaptive immune response to extra-cellular pathogens (Figure 13.5a).

Antibody effector functions

Antibodies are bifunctional molecules with one end having the antigen binding properties while the other end triggers the defensive activities. These functional regions are separated by a relatively flexible amino acid sequence between the first and second heavy chain constant

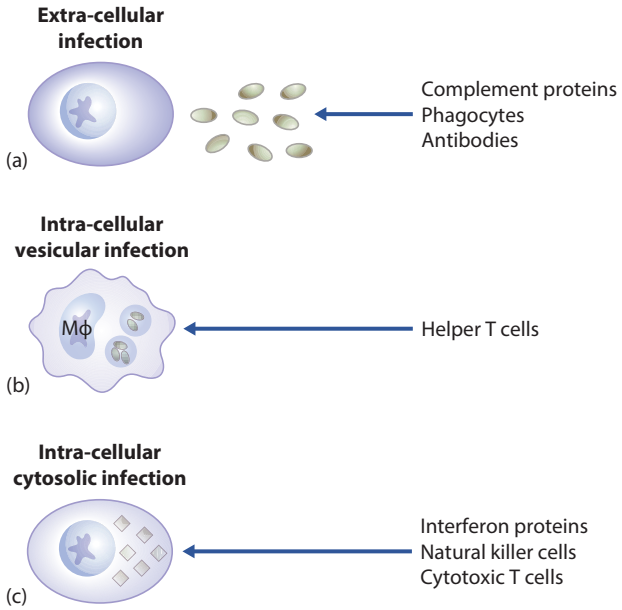


Figure 13.5 Immune responses to different types of infections.

domains called the hinge region (Figure 13.2). The two arms containing the antigen combining sites are called the fragment antigen binding (Fab) regions: each is composed of a light chain and the variable and first constant domain of a heavy chain. The other constant domains of the two heavy chains constitute the Fragment crystallizable (Fc) region (because it can form crystals when isolated experimentally).

As described under Antigen recognition above, there are five classes of Ig molecules expressed as B cell sIg, four of which are also secreted as antibodies (i.e. IgM, IgG, IgA and IgE, but not IgD). The classes have different heavy chain constant domains, and thus differ primarily in their Fc regions (Table 13.1). The heavy chains of IgG, IgA and IgD each have two constant domains in the Fc region, whereas IgM and IgE have three. In addition, IgM forms pentamers (five Ig monomers) held together by a J (joining) chain polypeptide, whereas IgA can similarly form dimers. The large size of IgM results in it being predominantly restricted to the blood stream (except at sites of inflammation), whereas the other classes can more readily diffuse into tissues. IgG is the most abundant antibody class in the blood, and also is transported across the placenta from the maternal to the fetal circulation during the last three months of pregnancy. This maternal IgG in the newborn baby provides the protection against infection until the baby's immune system produces significant levels of antibodies. Very premature babies have limited maternal antibody. IgA in its dimeric form is transported across mucosal epithelia in large quantities and thus constitutes the main antibody class conferring protection in secretions and at mucosal surfaces. Part of the mucosal receptor that binds and transports IgA across the epithelium remains associated with it as the secretory piece. IgA is also secreted into milk and thus confers protection in the gastro-intestinal tract of suckling babies. In humans, IgD is present in secretions of the upper respiratory and digestive tracts where it may play important roles in neutralization of pathogenic microbes and exclusion of commensals.

Antibodies can neutralize microbes and their toxins simply by binding to them, hence inhibiting their functions and infectivity. However, antibodies can also contribute to the destruction of infectious agents by interacting with other defensive components, as described below.

The complement system

(See Figure 13.6.) The complement proteins found in the circulation and tissue fluids constitute an important defensive system that can be activated by the Fc regions of IgM and IgG antibodies in what is termed

TABLE 13.1 Functional properties of antibody classes and subclasses

	IgM	IgG1	IgG2	IgG3	IgG4	IgA1	IgE	IgD
Molecular weight (kDa)	970 (pentamer)	146	146	165	146	160 (monomer)	188	184
Adult serum level (mg/ml)	1.5	9	3	1	0.5	3	5×10^{-5}	0.04
Serum half-life (days)	10	21	20	7	21	6	2	3
Extra-vascular diffusion	±	+++	+++	+++	+++	++ (monomer)	+	+
Transport across epithelium	+	–	–	–	–	+++ (dimer)	–	++
Transport across placenta	–	+++	+	++	±	–	–	–
Neutralization	+	++	++	++	++	++	–	++
Binding to phagocytes	–	+++	±	++	+	+	–	+
Binding to NK cells	–	++	–	++	–	–	–	–
Binding to mast cells and basophils	–	–	–	–	–	–	+++	+
Classical complement pathway activation	+++	++	+	+++	–	–	–	–
Alternative complement pathway activation	–	–	–	–	–	+	–	–

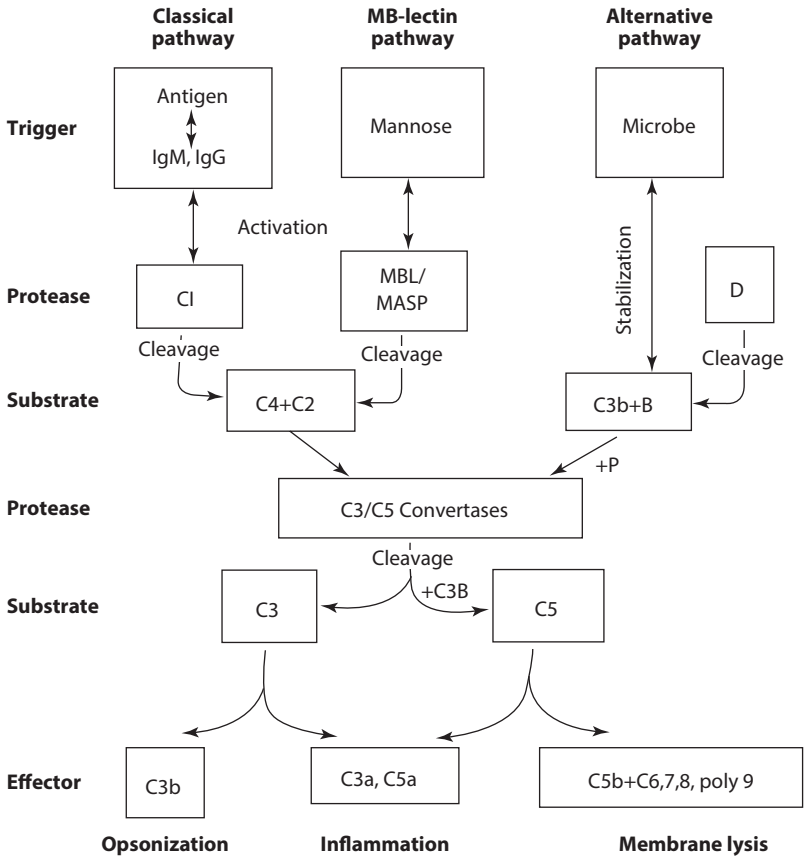


Figure 13.6 Complement activation pathways and effector functions. Ig, immunoglobulin; MASP, MBL-associated serine protease; MBL, mannan-binding lectin.

the classical pathway of complement activation. This is triggered when IgM or several IgG antibodies that are bound to antigen, interact with the complement C1 protein complex, resulting in the formation of a C3 convertase enzyme from C4 and C2 (C4b2a). This same C3 convertase can be generated when the pattern recognition molecule mannan-binding lectin (MBL) interacts with mannose residues of microbial surfaces. (MBL is a member of a family of secreted carbohydrate-binding collagenous defensive proteins called collectins.) A different C3 convertase is produced when certain complement proteins directly form a stable complex (C3bBbP) on microbial surfaces in what is termed the alternative pathway of complement activation. IgA can also activate the alternative pathway.

The conversion, or splitting, of complement protein C3 by the C3 convertase enzymes into fragments C3a and C3b is the central and crucial event during complement activation and generates a range of biological effects. Some of the C3b can be used to generate more of the alternative pathway C3 convertase; it also modifies the activity of the C3 convertase enzymes to split C5 into C5a and C5b. As mentioned in 'Innate and adaptive immunity' above, C3a and C5a activate mast cells and thus promote inflammation: they also attract and activate neutrophils (particularly C5a). The C5b fragment forms the membrane attack complex (MAC) with C6, C7, C8 and several molecules of C9: this last complement protein has structural and functional similarities to perforin and forms pores through lipid bilayers. Thus, the MAC has direct anti-microbial effects by disrupting microbial membranes. Finally, in addition to its other activities, C3b opsonizes (i.e. coats) infectious agents, which facilitates their interaction with leucocytes, as described below.

Digestive and inflammatory leucocytes

Some leucocytes have surface receptor proteins that bind to the Fc regions of antibodies (FcR), and others that bind to complement C3b (CR). As described above, the phagocytes (macrophages and neutrophils) express pattern-recognition molecules that enable them to bind microbes directly. However, they also possess FcR specific for IgG or IgA and CR that have particularly high affinities for their respective ligands. Thus, microbes such as bacteria can be firmly bound to the surface of phagocytes when opsonized by antibodies and C3b. This facilitates and activates phagocytosis (i.e. engulfing) of the microbes into membrane-bound cytoplasmic vesicles. The microbes can then be destroyed by lysosomal enzymes and reactive oxygen molecules.

Some microbes, such as the mycobacteria that cause tuberculosis and leprosy, are relatively resistant to the digestive activities of phagocytes and are able to survive and multiply within the cytoplasmic vesicles

of macrophages. In this environment the microbes are protected from the activities of extra-cellular antibodies and complement proteins. The effective control of such infections is then dependent on the activity of Th1 cells that, as described in 'T cells and antigen presentation' above, produce the potent macrophage activating cytokine IFN-γ: this promotes macrophage digestive activity against microbes in intra-cellular vesicles (**Figure 13.5b**).

Other infective agents, particularly parasitic worms like schistosomes and helminths, are much too large to be engulfed for intra-cellular digestion by phagocytes. In such circumstances, eosinophils are recruited to undertake extra-cellular digestion by releasing their digestive proteins (e.g. major basic protein) onto the surface of the parasites. Eosinophils possess FcR (specific for IgG or IgE) and CR, and so again will bind most avidly to opsonized targets.

The other main cells that express FcR for IgE are the tissue mast cell and blood basophils, whose defensive roles are to promote inflammation, rather than directly destroying pathogens. These cells are activated when an antigen binds and cross-links several FcR-bound surface IgE molecules. This induces the immediate release of pre-formed inflammatory mediators, particularly histamine, that are stored in cytoplasmic granules. It also induces the *de novo* synthesis and later release of leukotrienes. (As mentioned above, mast cells are also activated by the complement peptides C3a and C5a.) Furthermore, IgD produced in the upper aerodigestive tract can bind to receptors expressed by basophils, mast cells, monocytes and neutrophils. Cross-linking of IgD antibodies on the surface of basophils by the antigens to which they bind promotes basophil activity in promoting both innate and adaptive immunity.

IMMUNITY TO CYTOSOLIC INFECTIOUS AGENTS

(See **Figure 13.5c**) Some infectious agents, such as viruses, actively infect cells by entering the fluid cytosol. Viruses are obliged to infect cells in order to use the machinery of the cells they enter in order to replicate themselves. Although antibodies and complement can neutralize viruses whilst they are outside cells, other immune mechanisms are required to interact with intra-cellular viruses.

An innate mechanism of anti-viral defence is the production and secretion of IFN-α and/or IFN-β by the infected cells. These type 1 interferons are structurally unrelated to the IFN-γ (type 2 interferon) that is produced by activated T cells and natural killer (NK) cells. Both types derive their name from their ability to *interfere* with viral replication. Type 1 interferons secreted by virally infected cells induce an anti-viral state in neighbouring non-infected cells by stimulating these cells to produce enzymes that block viral replication. In addition, type 1 interferons enhance MHC class I expression, which is necessary for Tc cell recognition of target cells, and they activate NK cells. Both these types of killer cells are important in the immune response to intra-cellular viruses as killing the infected cells inhibits viral replication and hence spread within the body. NK cells are the first killer cells to be activated, and they employ the same mechanisms of cytotoxicity as those described for Tc cells under the 'T cells and antigen presentation' above. However, unlike Tc, NK cells do not possess antigen-specific receptors; rather, they detect abnormalities in the expression of a cell's own surface molecules that may be indicative of the cell being virally infected. NK cells possess two types of receptors that interact with potential target cells: killer activating receptors; and killer inhibitory receptors, with the latter providing a dominant inhibitory signal that prevents NK cells from killing normal (uninfected) cells. The ligands for killer inhibitory receptors are often MHC class I molecules, whose expression may be reduced by viral infection of a cell: this makes the cell susceptible to the activity of NK cells because they then bind predominantly via their killer activating receptors. The ligands for some of the killer activating receptors are MHC class I-like molecules whose expression on target cells can be induced by infection, malignant transformation or other forms of cellular stress, thereby increasing the susceptibility of these cells to killing by NK cells.

NK cells also express FcR specific for IgG and so can interact with, and kill, target cells via antibodies that have bound to antigens expressed in the surface membranes of the target cells, as may happen during the process of budding by viruses. This is termed antibody-dependent cellular cytotoxicity (ADCC).

Interferons and NK cells are very important in limiting the replication and spread of a virus during the early stages of an infection, but may not be able to eliminate the infection. The adaptive Tc cells will take longer to be activated, as described under 'Stages of an immune response' above, but can then specifically and efficiently target the infected cells, as described under 'T cells and antigen presentation' above.

INFLAMMATION AND HYPERSENSITIVITY

Inflammatory processes are necessary to recruit components of the immune system to sites of infection. The importance of tissue mast cells as a source of inflammatory mediators has been discussed in previous sections, but many cell types can produce a range of inflammatory mediators, including cytokines and other proteins as well as other types of chemicals (e.g. prostaglandins and leukotrienes). A number of these have particular effects on the vessels that supply blood to infected tissues, promoting vasodilatation and increased vascular permeability, and enhancing endothelial expression of adhesion molecules (particularly selectins and integrins). The interaction of

circulating leucocytes with the adhesion molecules facilitates their migration across the blood vessel walls and into the infected tissues in response to chemotactic factors.

In addition to localized inflammatory events within infected tissues, systemic effects are induced by cytokines that enter the blood stream, particularly IL-1, IL-6 and tumour necrosis factor (TNF). These have effects on the hypothalamus to induce fever, on the bone marrow to promote leucocyte release, and on the liver leading to the release of acute phase proteins: in particular the liver-derived pentraxins called C-reactive protein and serum amyloid P possess innate anti-microbial activities.

The enormous destructive potential of the immune system that is unleashed against invading microbes can be equally damaging to the body's own tissues. Thus, during every immune and inflammatory response, a balance must be struck between beneficial and tissue damaging effects. The immune system has evolved regulatory processes to limit the latter but, in some instances, immunological tissue damage becomes the main clinical feature, generating the problems of hypersensitivity.

Allergy and autoimmunity

Tissue damaging adaptive immune mechanisms can be triggered by foreign antigens or the body's own components. The former can be microbes, inducing the immune-mediated tissue damage associated with infective diseases, or can be inert (non-infective) materials that cause allergies. Up to 30% of the population is affected by allergies in developed countries, with a host of different allergens affecting different individuals (e.g. pollen, house dust mite, insect venom, food proteins, latex). Conversely, reactivity to self-components can lead to autoimmune diseases. Collectively, these affect over 3% of the population, with a much higher incidence of sub-clinical autoimmunity. In organ-specific autoimmunity, the stimulating autoantigens are restricted to particular tissues or organs, such as thyroid peroxidase and thyroglobulin in autoimmune thyroiditis, insulin and glutamate decarboxylase in type 1 diabetes mellitus. By contrast, systemic autoimmunity involves reactivity against widely spread tissue components, such as DNA, histones and ribonucleoproteins in systemic lupus erythematosus and IgG and citrullinated proteins in rheumatoid arthritis.

Mechanisms of hypersensitivity

Although allergic and autoimmune disorders differ in the nature of the stimulating antigens, they involve similar mechanisms of tissue damage, referred to as the four mechanisms of hypersensitivity (**Figure 13.7**).

Type I (immediate or reaginic) hypersensitivity occurs in a variety of atopic allergies (**Figure 13.7**). It involves activation of tissue mast cells when an inducing allergen specifically binds to at least two IgE antibodies on the surface of mast cells. The IgE cross-linking induces the release of inflammatory mediators, as described under 'Digestive and inflammatory leucocytes' above, which induce vasodilatation, increased vascular permeability and smooth muscle contraction. For example, inhaled allergens that induce immediate mast cell activation commonly cause allergic rhinitis and extrinsic asthma. These conditions may be seasonal (eg. hay fever), or perennial in allergies to house dust mite and cat, for example. Severe systemic acute forms of type 1 hypersensitivity are seen in anaphylaxis (e.g. to nuts, insect stings, drugs).

Type II (cell or membrane reactive) hypersensitivity involves antibodies of the IgG, IgA or IgM classes that bind to antigens associated with cell surface membranes or basement membranes (**Figure 13.7**). The antigen-bound antibodies then activate complement, which may damage the membranes directly via the membrane attack complex, but also attract and activate neutrophils via the actions of C5a and C3a. The release of digestive enzymes and reactive oxygen species by the neutrophils can then exacerbate the membrane damage. Bullous pemphigoid is an example of a disease involving antibodies to basement membrane antigens. By contrast, in pemphigus, autoantibodies bind to desmoglein in the epidermal intra-cellular cement, and clearly correlate with tissue damage. Goodpasture's syndrome is a further example of a disease where autoantibodies bind to basement membranes; in this case, the autoantigen is type IV collagen in alveolar and glomerular basement membranes, causing the typical haemoptysis and haematuria. The muscle weakness of myasthenia gravis is induced by autoantibodies to the acetylcholine receptors in the post-synaptic membranes of muscles: these antibodies induce complement-mediated damage, receptor internalization and blockade, leading to inhibition of neurotransmission by acetylcholine.

Type III (immune complex mediated) hypersensitivity, like type II hypersensitivity, involves IgG, IgA and IgM antibodies, but in this case reacting with soluble antigens to form cross-linked molecular lattices containing multiple antibody and antigen molecules known as immune complexes (**Figure 13.7**). These complexes can become too large to remain soluble and so precipitate within tissues where they can activate complement and neutrophils, leading to tissue damage. Allergic immune complex disease is exemplified by extrinsic allergic alveolitis that is triggered by inhalation of allergens that form immune complexes in the alveolar walls leading to tissue damage and fibrosis. Common allergens are fungal spores (e.g. in farmer's lung) and avian plasma proteins (e.g. in bird fancier's lung). In systemic lupus erythematosus immune complex deposition can occur in various tissues, including the skin, joints, lungs, brain and kidneys: these complexes are frequently composed of DNA and anti-DNA antibodies, with contributions from other nuclear and cytoplasmic autoantigens.

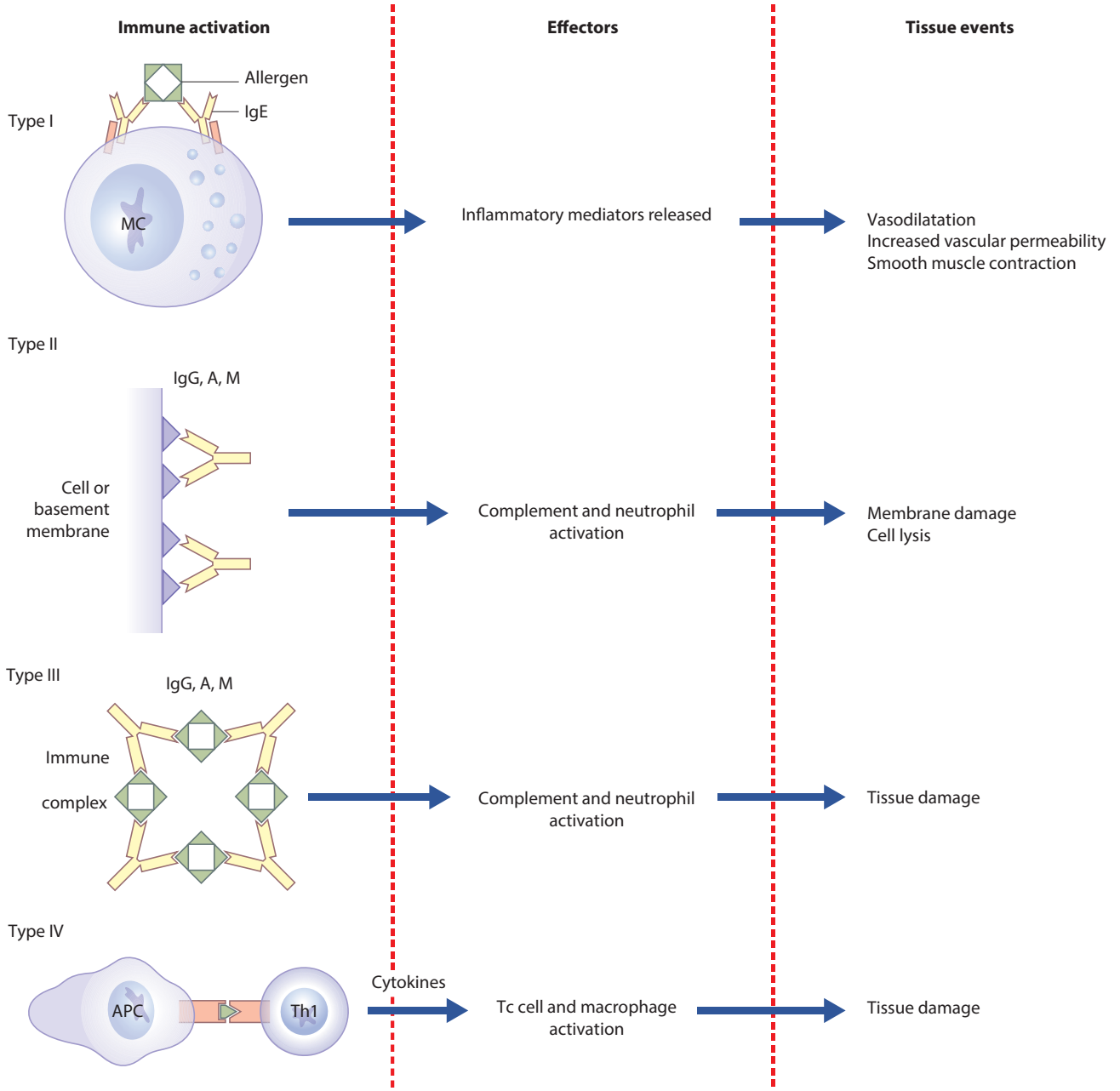


Figure 13.7 Mechanisms of hypersensitivity. (See text for details.) APC, antigen presenting cell; Ig, immunoglobulin; MC, mast cell; Th1, T helper 1 cell.

Type IV (cell-mediated) hypersensitivity is distinguished from the other three types by not involving antibodies. It is principally dependent on the activities of T cell and macrophages with Th1 cells producing cytokines like IL-2 and IFN-γ that activate cytotoxic T cells and macrophages, respectively (Figure 13.7). Much of the tissue damage in autoimmune diseases is brought about by cell-mediated mechanisms, although autoantibodies are also present (e.g. thyroiditis in the autoimmune thyroid diseases, insulitis in type 1 diabetes and synovitis in rheumatoid arthritis). Sjogren's syndrome is characterized by lymphocytic destruction of exocrine tissues, particularly the lacrimal and salivary glands, resulting in dry eyes and mouth. Much of the pathology associated with certain infectious diseases is also due to immune-mediated tissue damage. For example, in tuberculosis, infection of lung macrophages by *Mycobacterium tuberculosis* – which is resistant to intra-cellular digestion – leads to chronic T cell activation and cytokine production.

Despite the clinical problems of hypersensitivity diseases, the severe, persistent, unusual and recurrent infection problems associated with immunodeficiency disorders highlight the vital defensive role of the immune system.

KEY POINTS

- Immunity provides protection against pathogenic organisms, and the functions of the immune system are recognition of these foreign pathogens and defence of the body against them.
- Innate and adaptive immunity constitute the two main arms of the immune system which differ in their recognition and activation properties. Adaptive immunity improves with repeated exposure to the same antigens.
- The early innate response to infection stimulates an inflammatory response and initiates the processes that result in the adaptive lymphocyte response.
- Adaptive immunity involves the specific recognition of antigens by B and T lymphocytes.
- B-cell antigen receptors and antibodies can bind antigen in its native, unmodified form, recognizing accessible surface epitopes. In contrast, T-cell receptors recognize antigenic peptides bound to HLA molecules expressed on the surface of antigen-presenting cells or target cells; this requires processing (fragmentation) of the antigen, and epitopes may be derived from any part of the antigen.
- A typical immunoglobulin/antibody is composed of two identical heavy chains and two identical light chains. The amino-terminal variable domains of a heavy and a light chain form an antigen-combining site within one of the two Fab portions of the molecule. The Fc portion is composed of the heavy chain constant regions on the carboxy-terminal side of the hinge region.
- Cytotoxic function is associated with $CD8^+$ T cells and HLA class I-associated antigen recognition. This facilitates T-cell recognition and killing of abnormal tissue cells.
- Helper function is associated with $CD4^+$ T cells and HLA class II-associated antigen recognition. This facilitates T cell help by interaction with cells such as interdigitating dendritic cells, macrophages and B cells.
- Th1 and Th2 cells secrete cytokines that promote principally cell-mediated immunity and antibody-mediated immunity, respectively. Th17 cells promote inflammatory responses. whereas various types of Treg cells suppress Th cell-driven responses.
- Immunoglobulin isotypes (i.e. classes and subclasses) are defined by differences in their heavy chain constant regions. These determine their biological characteristics, e.g. complement activation, cellular association via Fc receptors and tissue distribution.
- Complement consists of several plasma proteins that operate as an enzyme cascade giving rise to various biological activities, including immune adherence, inflammation and membrane lysis.
- Macrophages and neutrophils are called phagocytes because of their ability to ingest and destroy microbes.
- Mast cells and basophils are activated by multivalent antigens cross-linking surface-bound IgE molecules; this induces the release of inflammatory mediators. Certain mast cell and basophil mediators are preformed and stored in granules (e.g. histamine) and are released immediately upon activation, whereas other mediators are synthesized *de novo* (e.g. leukotrienes and prostaglandins).
- There are two types of killer lymphocytes: cytotoxic T cells (Tc cells) and natural killer cells (NK cells). They are cytotoxic to target cells that have become infected or malignant.
- The immune system can cause inflammatory damage to the body's own tissues that may be triggered by infection, non-infective foreign antigens (in allergies), or the body's own autoantigens (in autoimmune disease).
- The mechanisms of immunologically mediated tissue damage are classified into four main types: Type I, IgE-mediated immediate hypersensitivity; Type II, antibody-mediated; Type III, immune complex-mediated, Type IV: T cell-mediated, DTH. More than one mechanism may operate in an inflammatory process.

FURTHER READING

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CHAPTER 14

ALLERGY: BASIC MECHANISMS AND TESTS

Sai H.K. Murng

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SEARCH STRATEGY

Data in this chapter may be updated by PubMed and Ovidsp Medline searches using the keywords: allergy basic mechanisms, allergic rhinitis, anaphylaxis, skin prick tests, specific IgE, allergen component, basophil activation test, immunotherapy, mast cell signalling. The references of relevant articles were also checked. In addition, major immunology and allergy journals, and immunology textbooks were scanned. The evidence in this chapter is mainly levels 2/3 with some level 1 evidence. The clinical and laboratory recommendations are based on guidance from the UK and international professional associations, grade A and B.

INTRODUCTION

Allergy is defined as a hypersensitivity reaction initiated by specific immunologic mechanisms.[1] By a specific definition, it describes objectively reproducible symptoms or signs initiated by an exposure to a defined stimulus at a dose tolerated by normal persons.[1] *Hypersensitivity* is an altered immune response to an antigen that can cause damage. Immunologically four types of hypersensitivity reactions are generally recognized (**Table 14.1**).

An *allergen* is an antigen (usually protein) that causes allergic diseases. Allergic airway diseases including rhinitis are due to inhaled allergens (**Table 14.2**). *Atopy* is a tendency to become sensitized and produce allergen-specific immunoglobulin E (sIgE) in response to ordinary exposures to allergens. Clinically this is demonstrated by positive skin prick tests and/or increased serum sIgE concentration to one or more allergens. Not all sensitized individuals are symptomatic. Therefore allergy is a disease manifestation of sensitization.

We will consider the basic mechanism of allergy initially in which an individual is predisposed to allergy by sensitization to allergens. Then we will consider the immunological process involved in some allergic diseases and the effect of treatment including current understanding of specific allergen immunotherapy. Finally the principles of diagnostic tests will be considered.

AETIOLOGY OF SENSITIZATION

Type 1 immunoglobulin E (IgE) mediated immediate hypersensitivity occurs only in a sensitized individual. Immune responses to innocuous antigens leading to sensitization are multi-factorial. In general these include host factors such as genetic predisposition and environmental factors such as pollution.

Up to 40% of the population in the industrialized countries have been reported to have a tendency to atopy. An atopic person usually has a high total IgE level, a strong familial tendency and increased susceptibility to allergic diseases such as allergic rhinitis and atopic dermatitis. Many genetic loci have been shown to be associated with allergic diseases. These include chromosome 11q12-13 (encodes β subunit of high-affinity IgE receptor) and chromosome 5 (encodes Th2 promoting cytokines such as IL4, TIM gene family that regulates Th1/Th2 balance, p40 subunit of IL12, β2 adrenergic receptor). Polymorphism in these genes altered disease susceptibility of a person to allergic diseases. Another inherited variation seen in IgE response to specific antigen is human major histocompatibility complex (MHC) class II region (e.g. HLA DRB1*1501 in ragweed pollen sensitization). Therefore an allergic individual can be associated with both general tendency and allergen-specific predisposition to develop a stronger Th2 response than their normal counterpart.

TABLE 14.1 Types of hypersensitivity (adapted from Coombs and Gell Classification)

Features	Type I	Type II	Type III	Type IV
Mechanism	Immediate hypersensitivity	Cytotoxic hypersensitivity	Immune complex reaction	Cell-mediated hypersensitivity
Immune reactant	IgE	IgG	IgG	T cell
Effectors	Mast cells, basophils, eosinophils	Complement, phagocytes	Complement, phagocytes	Macrophages
Disease examples	Allergic rhinitis	Haemolytic anaemia	Serum sickness, SLE	Contact dermatitis

TABLE 14.2 Inhaled allergens

Seasonal	Perennial	Occupational
Grass, trees Weeds Moulds	House dust mites Cats, dogs Horses	Laboratory animals, flour, latex Colophony, isocyanates Acid anhydrides

Environmental factors such as exposure to infectious diseases in early childhood, environmental pollution and dietary changes also contribute to allergic diseases. *Hygiene hypothesis* has been one of the well-known discussions since 1989. Early life exposure to infectious diseases has been shown in mice models as being associated with promoting Th1 rather than Th2 response. Th1 response is proinflammatory and responsible for killing intracellular pathogens and for perpetuating autoimmune responses. Th2 response is not only essential in defence against pathogens such as helminths (e.g. hookworm) but also promotes allergic conditions. Therefore the prevalence of allergic diseases is higher in children who grew up in a hygienic environment (e.g. industrialized Western countries) than in less hygienic regions where infectious diseases are more common.

A *counter-regulation hypothesis* has proposed that regulatory cytokines (e.g. IL10, TGF-β) are upregulated in the presence of infection. As a result atopy is less common despite Th2 response being predominant in infections. In addition proinflammatory cytokines (e.g. interferon-γ) resulting from infection also stimulate dendritic cells (DC) to suppress Th2 inflammation and promote regulatory cytokines.

Regulatory T cells are also considered to have an important role in allergic diseases. This has been supported by a FoxP3 deficient mice model that develops manifestations seen in allergic conditions such as eosinophilia, increased IgE level and allergic airway inflammation suggesting Treg (CD4+CD25+) cell deficiency can predispose to this phenotype.

BASIC MECHANISMS

Mast cells and basophils are the principle effector cells that produce mediators (Table 14.3) responsible for allergic diseases. IgE mediated immediate allergy can be associated with early and late responses. The early phase is due to preformed mediators release (e.g. anaphylaxis). The late phase is due to newly synthesized mediators and infiltration of other leucocytes that can be followed by a chronic allergic inflammation in some conditions (e.g. allergic asthma). Late phase response involves Th2 cytokines resulting in activation of eosinophils and other leucocytes. Chronic allergic inflammation is characterized by tissue destruction and remodelling and is essentially type IV hypersensitivity in nature.

Effectors of allergic diseases

The essential effector cells of immediate hypersensitivity are cells expressing high affinity IgE receptors (FcεRI) such as mast cells, basophils and eosinophils. Other effectors include antigen presenting cells (e.g. dendritic cells) and Th2 cells that promote allergen-specific IgE synthesis by B cells.

MAST CELLS

Mast cells are haemopoietic stem cell derivatives and mature locally. They reside near the surface where our body is exposed to pathogens and allergens. Based on the distribution they are known as either mucosal mast cells or tissue mast cells. They are often found in close proximity to blood vessels. FcεRI is capable of being tightly bound to sIgE even in the presence of a very low serum concentration. On exposure to their specific allergens, cross-linking of the receptor and signalling follow to produce clinical phenomena (Figure 14.1). FcεRII is a low affinity IgE receptor (CD23). It is present in many cells including B cells, activated T cells, monocytes, eosinophils, platelet and follicular dendritic cells. The role of FcεRII in an allergic reaction is not fully understood.

Mast cells granules contain preformed mediators that are responsible for the immediate symptoms of allergic reactions. Mast cells also produce other mediators upon FcεRI signalling. Mediators that are rapidly synthesized are involved in the immediate symptoms of allergic reactions. Other mediators may lead to late phase responses and chronic allergic inflammation (Table 14.4).

BASOPHILS

Basophils develop from bone marrow granulocyte-monocyte progenitor. There is increasing evidence that basophils involve significantly in allergic diseases. They respond to many stimuli including cytokines, antibodies, proteases and antigens. Cross-linking of IgE bound FcεRI receptors on basophils have been shown to produce mediators (Table 14.4). Basophils have been identified in nasal washes of patients with allergic rhinitis.

TABLE 14.3 Physiologic actions of mediators

Types of mediator	Effects
Enzymes: • tryptase, chymase, carboxypeptidase A • eosinophil peroxidase • eosinophil collagenase • matrix proteinase	 – tissue destruction – toxic to target, histamine release from mast cells – connective tissue remodelling – matrix protein degradation
Eosinophil major basic protein	– toxic to parasite, histamine release form mast cells
Proteoglycans - histamine, heparin	– increase vascular permeability, smooth muscle contraction
Cytokines: • TNF-α • IL4, IL13 • IL3, IL5 • TGF-α, TGF-β	 – promote inflammation – amplify Th2 response – activate eosinophil – epithelial proliferation and myofibroblast formation
Chemokines: CCL3, CXCL8	– influx of leucocytes
Platelet-activating factor (PAF)	– attracts leucocytes and increases lipid mediators production
Arachidonic acid metabolites: • prostaglandins D2 (PgD2), leucotrienes C4 (LtC4)	 – smooth muscle contraction and increase vascular permeability

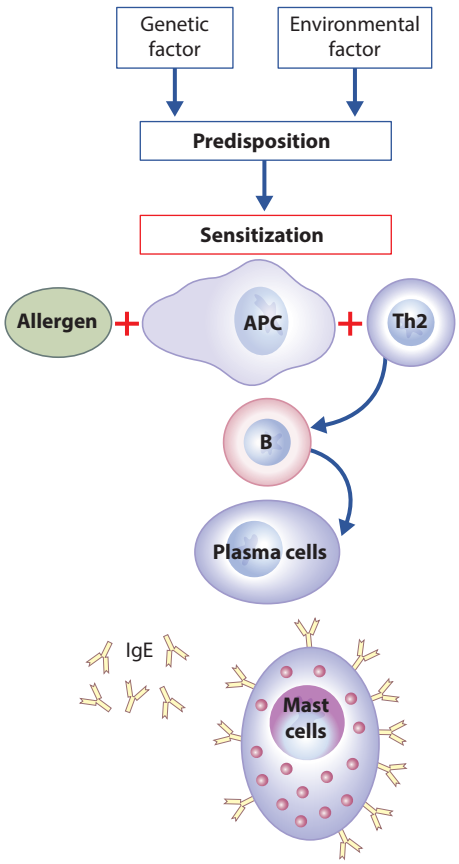


Figure 14.1 Development of sensitization.

EOSINOPHILS

Eosinophils are granular leucocytes that mainly reside in submucosal connective tissue in respiratory, gastrointestinal and urogenital tracts. They play an essential role in defence against helminths. Eosinophils also express FcεRI receptors and are capable of releasing mediators (Table 14.4).

T LYMPHOCYTES

T cells are central to the pathogenesis of allergic diseases since they are the only cells capable of recognizing antigens presented by antigen presenting cells. Maturation of a naive T cell takes place on activation by signals including specific peptide-MHC via T cell receptor and costimulatory signal via CD28. T helper cells (CD3+CD4+) differentiated into many types depending upon the type of immune response taking place and cytokine environment. Th1 cells differentiate in the presence of interferon gamma (IFN-γ) and IL-12, and produce predominantly IFN-γ and interleukin 2 (IL-2). Th2 cells differentiate in the presence of IL-4 and produce IL-4, IL-5 and IL-13 cytokines preferentially. Recruitment of Th2 cells, their activation in tissues and generation of Th2 cytokines are main features of both allergic rhinitis and asthma. Low dose antigen exposure via mucosal surface with inhaled allergen is typical of Th2 response in allergic rhinitis, where as high dose allergen delivered by injection favour Th1 response.

DENDRITIC CELLS

Dendritic cells are professional antigen presenting cells (APC), which are abundant in the epithelium and submucosa of both upper and lower respiratory mucosa in patients with allergic diseases. Traditionally dendritic cells have been classified as myeloid derived DC1 cells (derived from human blood monocytes) or DC2, plasmacytoid cells (derived from lymphoid cells). DC1 cells produce a high level of IL-12 and favour Th1 development. DC2 cells are low IL-12 producers and support preferential Th2 differentiation. However, in dendritic cells subpopulations, differential function may depend on their location, their degree of maturation and local cytokines milieu.

Immature cells express high levels of immunoglobulin receptors and are highly endocytic in keeping with

TABLE 14.4 Mediators of effector cells

Types of mediator	Mast cells	Basophils	Eosinophils
Preformed mediators	tryptase, chymase, carboxypeptidase A, histamine, heparin, TNF-α	histamine, TNF-α	eosinophil peroxidase, eosinophil collagenase, matrix proteinase, eosinophilic cationic protein
Newly synthesized cytokines and lipid mediators	IL4, IL13, TNF-α, IL3, IL5, PAF, PgD2, LtC4	IL4, IL13, PAF, LtC4	IL3, IL5, TGF-α, TGF-β, LtC4, PAF

efficient antigen capture. In contrast, mature cells express high levels of MHC class II and have upregulated CD86 expression and produce abundant cytokines, features consistent with their role in allergen presentation and immune modulation. Rapid maturation (within 2 hours) was observed in dendritic cells within the bronchial wall and not peripheral lung. Rapid dendritic cells recruitment to the bronchial mucosa in atopic asthmatic patients has also been observed within the time frame of late asthmatic responses following local segmental allergen challenge. Plasmacytoid dendritic cells (CD123) IL-3R α-chain+CD45RA+ cells increase dramatically in number following local allergen challenge repeatedly for 7 days. This is of particular interest since plasmacytoid dendritic cells matured *in vitro* can induce preferential Th2 development.

IMMUNOGLOBULIN E (IGE)

IgE concentration is the lowest immunoglobulin isotype (approximately 100–400 ng/mL) in human serum. The majority of IgE is tissue-bound with a half-life of approximately 2 days. FcεRI is a high affinity receptor for IgE, which is mainly present on mast cells, basophils and eosinophils. But low-level expressions are detected in dendritic cells, monocytes, and macrophages that are in different molecular structures. Their significance remains uncertain. IgE also bind to a low affinity receptor FcεRII (CD23) on B cells, monocytes and macrophages.

IgE is developed from isotype switching of IgM. B cells secrete IgM following antigen recognition (Figure 14.2). Isotype switching is influenced by specific Th2 cells and the cytokine environment. IgE production is favoured by IL-4 and Il-13 derived from Th2 cells. It is also perpetuated by IL-4 and IL-13 from mediator release as a result of degranulation in allergic reaction. IgE production generally occurs in the bone marrow and the draining regional lymph nodes. But local IgE production has been reported in local forms of allergic conditions (e.g. allergic rhinitis). Local IgE synthesis has been considered as the cause in some situations – allergic symptoms without sensitization on skin prick test and increased sIgE; some atopic individuals develop rhinitis whereas other develop asthma or eczema, and others may have sensitization without any clinical manifestation.

HISTAMINE

Histamine is generated from histidine decarboxylase and stored in granules of mast cells and basophils. Elevated

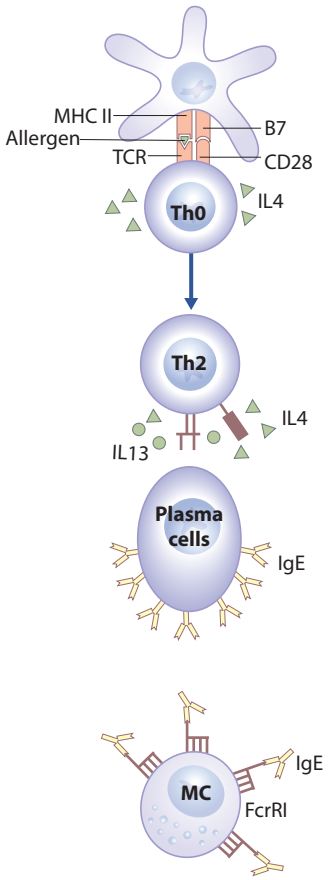


Figure 14.2 Th2 development and IgE production. APC, antigen presenting cell; MC, mast cell.

histamine levels correlate well and indicate higher sensitivity than tryptase in anaphylaxis. Tryptase level is elevated in 60% whereas histamine and PAF are elevated in 70% and 100% respectively in anaphylaxis.[2] However, histamine is highly soluble and rapidly diffuses away after the release. The majority of histamine is metabolized within minutes of release by many enzymes such as histamine N-methyl transferase, monoamine oxidase and diamine oxidase. The short plasma half-life and sample handling issue are major limiting factors for histamine measurement in routine laboratory use. Urinary metabolites (N-methyl histamine) can be detected several hours after anaphylaxis. But there are potential confounding factors for this measurement such as the effect of histamine producing bacteria, histamine containing foods and so on. In scombroidosis, the urinary histamine level can be increased despite a normal serum tryptase level.

SERUM TRYPTASE

Tryptase is produced by mast cells and basophils. In humans, tryptase exists in two isotypes (alpha and beta), which are in two forms – mature and immature. Beta tryptase is the predominant isotype in mast cells. Protryptase is the immature form and is spontaneously secreted by unstimulated mast cells. Mature tryptase is stored in the intracellular granules and released on degranulation. Therefore it is normally undetectable. The normal reference range of total tryptase is 1–13 ng/mL in our laboratory. The total tryptase levels peak 30–60 minutes after the onset of symptoms due to degranulation, and reduce afterwards with a half-life of about 2 hours. Tryptase levels can be measured in both serum and plasma but in a sample left at room temperature for more than 1–2 days may give falsely low values.

Normal tryptase levels do not exclude anaphylaxis. Other causes of increase tryptase levels include mastocytosis, acute myelocytic leukaemia, myelodysplastic syndrome and the myeloid varaints of hypereosinophilic syndrome. Elevated total tryptase has also been reported in some conditions such as onchocerciasis treatment and administration of recombinant stem cell factor.

There are two mechanisms leading to mediators release in mast cells and basophils. The FcεRI signalling as a result of the sIgE-antigen complex is the underlying mechanism in the IgE mediated hypersensitivity. However, mediator release can also occur by other factors that are capable of IgE independent direct stimulation. These include viral proteins (e.g. HIV gp120), bacterail proteins (e.g. LPS), drugs (e.g. opiate), chemical and physical stimuli, complement activation and neuropeptides, cytokines and so on.

High affinity receptor (FcεRI) signalling in allergic reaction

Allergic reactions are overlapping and synergistic physiological effects resulting from mediators release due to the activation of mast cells and basophils through a mechanism generally understood to involve FcεRI signalling. This signalling has been extensively investigated using passive cutaneous and passive systemic anaphylaxis models.[3]

Unlike other immunoglobulin isotypes, the majority of IgE is tightly bound to FcεRI. There is no signalling until these receptors are cross-linked by their specific antigens. The high level of IgE has potential to enhance IgE dependent effector function. FcεRI is a tetrameric receptor consisting of three subunits: a IgE binding unit (α chain); a signal transducing unit (β chain); and two signal regulator units (γ chain).

Allergen–sIgE binding is followed by early signalling events including phophorylation of cytosolic domains of the receptor known as immunoreceptor tyrosine-based activation motif (ITAM). This phophorylation is mediated by Src family proteins. There are two types of Src family protein in these events, namely signal-initiating kinase (Lyn) and signal-propagating kinase (Syk). This is followed by the recruitment of many signalling proteins to form multi-molecular signalling complexes. The downstream effect of this signalling results in an activation of protein kinase C and liberation of intracellular calcium. These lead to degranulation within minutes. In addition eicosanoid generation and activation of transcription factors for the production of cytokines and other mediators of allergic reaction follow within hours (**Figure 14.2**).

ROLES OF SENSORY NERVES

Activation of sensory nerves is an important mechanism in rhinitis in many ways. These include generation of acute rhinitis symptoms, nasal hyper-reactivity to non-specific triggers, release of neuropeptides such as substance 'p' and neurokinin from inflamed sensory nerves. Neurogenic inflammation is self-perpetuating and represents an important component of the allergen-IgE interaction. Nerve growth factor can be detected in nasal fluids in chronic allergic rhinitis. It is increased after allergen challenge. Therefore immediate response is due to a complex interaction between mediators release and target organs such as the sensory nerve, the vasculature and mucus secreting glands. Hyper-responsiveness of target organs associated with late response and day-to-day allergic disease is likely to relate to a combination of both inflammation and increased sensory nerve activation. The contribution of these components varies in different individuals.

Clinical features of IgE mediated hypersensitivity[4–6]

The American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group has estimated that a lifetime prevalence of anaphylaxis is 0.05–2.0%. The clinical features of allergic reactions are the effects of mediator release and may involve many systems. Most commonly, these include cutaneous, respiratory, cardiac and gastrointestinal systems (**Table 14.5**).

The onset of immediate allergy depends on the route of exposure to an allergen but it is usually within minutes. An anaphylaxis due to intravenous allergen (e.g. drug) occurs within seconds. Electrocardiographic abnormalities such as T inversion, supraventricular arrhythmias and bundle branch blocks have been reported in anaphylactic reactions during anaesthesia. In general an immediate allergy develops within 60 minutes of allergen challenge. Myocardial infarctions following anaphylaxis have also been reported. The late-phase reactions (LPR) have been described in respiratory and cutaneous allergy. Biphasic reaction patterns have been reported when both immediate and LPR have occurred.

Post-mortem finding of fatal anaphylaxis often shows few pathologic changes but may reveal oedematous obstruction of the airways, laryngeal oedema, pulmonary hyperinflation, pulmonary oedema, eosinophilic infiltration around the bronchi, and swelling of liver, spleen and intestine.

LOCAL ALLERGIC RHINITIS[8]

Local allergic rhinitis (LAR) has been described as a localized nasal allergic response. In contrast to generally

TABLE 14.5 Clinical features of immediate allergy (adapted from Ring and Messmer[7])

System	Manifestations
Prodromal	– feeling of anxiety, paresthetic sensations on palms and soles
Cutaneous	– pruritus, flush, urticaria, or angioedema
Respiratory	– sneezing, rhinorrhea, dyspnoea due to laryngeal obstruction or bronchospasm, hoarseness, feeling of 'tight throat', cough or wheezing, cyanosis and respiratory arrest
Cardiac	– early tachycardia, changes in blood pressure (sometimes an initial rise, followed by hypotension), arrhythmia, shock, cardiac arrest
Gastrointestinal	– nausea and cramping (uterine cramps may also occur), vomiting, diarrhoea, urination
Non-specific	– sweating, headache and disorientation

Severity grading of an allergic reaction

Severity	Cutaneous	Cardiac	Respiratory	Abdominal
Grade 1	Urticaria, flushing, angioedema			
Grade 2	Urticaria, flushing, angioedema	Tachycardia, blood pressure change (>20 mmHg systolic)	Rhinorrhoea, hoarseness, breathlessness	Nausea
Grade 3	Urticaria, flushing, angioedema	Shock	Laryngeal oedema, wheezing, cyanosis	Nausea, vomiting, diarrhoea
Grade 4	Urticaria, flushing, angioedema	Cardiac arrest	Respiratory arrest	Nausea, vomiting, diarrhoea

known allergic rhinitis (AR), allergic sensitizations are not detectable by serum-specific IgE or skin testing in LAR. LAR is usually diagnosed by a positive nasal allergen provocation test (NAPT). Many patients previously diagnosed with non-allergic rhinitis are now being classified as having LAR. In one of the Spanish cohort, LAR accounts for 15% of all cases of rhinitis.

A local specific IgE production in the nasal mucosa with a TH2 inflammatory pattern response has been considered as a pathophysiologic mechanism in LAR. A proportion of patients with LAR have detectable basal aeroallergen sIgE (e.g. house dust mite, cat, dog, grass etc.) in their nasal secretion. These sIgE levels rapidly increase after NAPT in 22% of LAR with perennial symptoms and 35% of those with seasonal symptoms. Measurement of nasal sIgE in LAR has a high specificity but low sensitivity (up to 40%). Clinically patients with LAR often present with typical symptoms of AR including ocular symptoms and good response to oral antihistamine and nasal corticosteroid.

RHINITIS AND ASTHMA LINK

The link between rhinitis and asthma has been highlighted in a World Health Organization report, *Allergic rhinitis and its impact on asthma* (ARIA).[9] Approximately 30% of patients with rhinitis develop asthma and up to 80% of patients with perennial asthma have rhinitis. However, the causal link between these conditions is not fully understood (Table 14.6).

It is important to recognize and treat asthma in patients presenting with allergic rhinitis. Airflow obstruction should be assessed in an ENT clinic including using peak expiratory flow, spirometry and reversibility testing. If these are unavailable, patients should be referred to a respiratory physician.

Basic mechanisms of treatment of allergic diseases

The majority of current drug treatments for allergic diseases are symptomatic therapies targeting the mediators (e.g. antihistamines and adrenaline) or general immunosuppressive drugs (e.g. corticosteroids). New approaches are now developing to modify the pathogenesis of allergy. The most promising is specific allergen immunotherapy such as pollen desensitization for seasonal allergic rhinitis.

Antihistamines act through histamine H1 receptors. They are effective in the partial suppression of immediate allergic responses in the skin and respiratory tract in AR. However, they have little or no effect in late response in allergic asthma and bronchial asthma.

Corticosteroids bind to intracellular receptors, leading to an anti-inflammatory effect due to alteration in transcription factors. Allergen-induced Th2 proliferation and cytokines secretion are exquisitely sensitive to corticosteroids in low 10^{-10} to 10^{-8} molar concentration. They also act on membrane receptors that lead to non-genetic mechanism, resulting in more rapid action. Corticosteroid has no effect on immediate response but is highly effective in inhibiting allergen-induced late response and bronchial asthma. The topical steroid effects of corticosteroid have been extensively studied in AR. These can be summarized as follows:

- Reduction of inflammatory mediators such as cytokines, prostaglandins, nitric oxide
- Inhibition of inflammatory cells migration by inhibiting the expression of adhesion molecules
- Promotion of apoptosis of leucocytes due to upregulation of endonucleases.

TABLE 14.6 Features of allergic rhinitis and asthma

Features	Similarities	Differences
Anatomical features	Pseudostratified epithelium	• Prominent erectile venous sinusoids and submucosal glands in the nose • Disruption of epithelium with thickening of the sub-basement membrane zone in asthma but intact epithelium with normal basement membrane zone in rhinitis • Airway smooth muscles are present in bronchi and increase in asthma
Pathogenesis	Th2 driven inflammation	Airway remodelling in chronic asthma
Treatment response	Corticosteroid, antileukotriene, anticholinergic	Selective effectiveness of antihistamine in rhinitis and β2 agonists in asthma

Allergen-specific immunotherapy is the only curative approach for allergic rhinitis, allergic asthma and venom allergy. This involves a step-wise administration of increasing doses of an allergen, in order to suppress symptoms on subsequent re-exposure to that allergen. Allergen-specific immunotherapy has been reported to be highly effective in allergic rhinitis in a Cochrane systematic review.[10]

Subcutaneous immunotherapy (SCIT) has an earlier onset of the therapeutic effect than sublingual immunotherapy (SLIT) in seasonal allergic rhinitis. Both have been shown to give long-lasting benefit after stopping treatment. Alternative methods of administration of allergen have been used in smaller cohort to improve the uptake and reduce the side effects. These include nasal immunotherapy, epicutaneous immunotherapy, intra-lymphatic immunotherapy and oral immunotherapy.

The precise mechanism of allergen-specific immunotherapy is being elucidated. Current understanding is based on evaluating benefits and immunological changes following the immunotherapy.[11–13] These can be summarized as follows:

- Inhibition of mediators release due to rapid desensitization of mast cells and basophils by allergens. The exact molecular pathway is not well understood. However, the susceptibility of these cells to degranulation decreases but the subsequent threshold for activation increases. Upregulation of histamine receptor expression on basophils were observed in venom immunotherapy. Rapid upregulation of histamine receptor strongly suppresses FcεRI induced activation of basophils
- Upregulation of blocking specific IgG4 antibodies that reduce the antigen presentation by the relevant cell types as a result of binding to epitopes on the surface of the allergen
- Inhibition of IgE-facilitated antigen presentation due to immunotherapy-induced specific IgG antibodies and subsequent reduction in the activation and proliferation of allergen-specific T-cells that are responsible for the production of cytokines (IL-4, IL-13) and further IgE synthesis
- Skewing effector cells towards regulatory phenotypes due to induction of T-reg and B-reg cells. Numbers of tissue mast cells and eosinophils, and subsequent mediators release decrease.

The clinical effects of immunotherapy have been shown in many studies. It induces an early and further reduction in symptoms/need for medication and reduction in hyperresponsiveness that persist after the end of the treatment period. It has been proposed as a prevention of new sensitivities and progression of disease (e.g. rhinitis into asthma). Therefore immunotherapy has been considered as a potentially curative treatment in allergic rhinitis due to its immunomodulatory effect.

A subcutaneous anti-IgE antibody (omalizumab) has been shown to be effective in a proportion of patients with severe perennial allergic asthma and in seasonal allergic rhinitis. Other therapies such as anti-CD23 monoclonal antibody (IDEC-152) and CCR3 targeted therapy have not been proved with clinical significance so far.

New knowledge arises for more targeted strategies in AR that inhibits Th2 cytokines IL4 and IL5 to prevent the activation of B cells from producing IgE. IL4 induces B cell class switching, upregulates IgE receptors on mast cells, increases VCAM-1 expression on vascular endothelium, induces mucus secretion and promotes Th2 polarization. In a small study, using an inhaled soluble IL-4 receptor during the withdrawal of inhaled corticosteroids has been shown to be effective in preventing relapse in moderately severe atopic asthma.

IL5 is a major factor responsible for terminal differentiation of eosinophils. Inhaled IL5 induces airway hyper-responsiveness and sputum eosinophila. Anti-IL5 blocking monoclonal antibody was effective in reducing allergen-induced eosinophila and deposition of extracellular matrix proteins in the bronchial subepithelial basement membrane zone in patients with mild asthma.

TESTS IN ALLERGY DIAGNOSIS

Allergy diagnosis includes an assessment of clinical presentations followed by *in vivo* and/or *in vitro* tests to identify the culprit allergen responsible for the immunologic mechanism of immediate hypersensitivity. Demonstration of sensitization to a suspected allergen (i.e. the presence of allergen-specific IgE) is required for the diagnosis. But not all sensitized individuals are clinically allergic. Therefore confirmation of allergy diagnosis requires either a convincing relevant history or a reproducible allergic phenomenon by a 'controlled challenge test' (provocation test). Hence, 'challenge test' is accepted as the gold standard test in allergy diagnosis.

Skin testing

Skin testing is a bioassay. When specific allergens are introduced into the skin, cross-linking of the FcεRI occurs if allergen-specific IgEs are present in sufficient quantities on the cutaneous mast cells. Transient wheal and flare responses develop as a result of mast cell activation and mediators release. These represent the immediate phase of the allergic reaction. However, the size of the wheal does not directly correlate with the amount of histamine released. In some individuals deep tissue swellings with warmth, pruritus and erythema at skin test sites may develop 1 to 2 hours after testing and resolve in 24 to 48 hours (late phase responses). But they are not used in allergy diagnosis.

Skin testing is widely used in the diagnosis of a variety of IgE-mediated allergies (Table 14.7). The performance of skin testing in allergy diagnosis is influenced by many factors (Table 14.8). Skin testing and interpretation require specific training and knowledge. The diagnostic utility of skin testing depends on the pre-test probability. It should be performed by an allergy expert, because there is a small but definite risk of a systemic allergic reaction.

The two major methods of skin testing currently in use are the skin prick test (SPT) and the intra-dermal test (IDT). SPT is the most appropriate initial test with overall positive predictive value (PPV) of less than 50% for all allergens but negative predictive value (NPV) is very high (≥95%) (Table 14.9). IDT has much higher sensitivity (100–1000 folds) but lower specificity with a greater risk of a systemic reaction. IDT should only be performed after a negative SPT.

Skin prick test

After cleaning with a 70% alcohol solution, 1:10 or 1:20 weight/volume allergen extract solutions are placed at least 2 cm apart on the volar surface of the forearm or upper back. A separate commercially available test device (lancet) is used to prick through each droplet of allergen.

TABLE 14.7 Indications, cautions and contraindications of skin testing

Indications	Notes
1. Aeroallergy (e.g. rhinitis, allergic asthma)	Well validated
2. Food allergy (e.g. nut, milk, egg)	Well validated
3. Drug allergy (e.g. penicillin)	Often used in the evaluation of many other drugs including antibiotics, chemotherapeutic agents and anaesthetic drugs but the significance of results are less well defined
4. Venom allergy (e.g. wasp, bee)	The diagnostic test of choice; well-validated
5. Latex allergy	The diagnostic test of choice when using standardized test preparations
Cautions and contraindications	**Notes**
1. High risk patients	Poorly controlled asthma, clinical histories of severe reactions to minute amounts of allergen, significant cardiovascular diseases such as coronary heart disease, cardiac arrhythmias
2. Recent anaphylaxis	The skin can render temporarily non-reactive after anaphylaxis for 2 to 4 weeks
3. Interfering medications	Recent antihistamine use
4. Unsuitable skin conditions	Dermatographism, urticaria, dermatitis, cutaneous mastocytosis

TABLE 14.8 Factors affecting results of skin testing

Factors	Notes
Medications	Many drugs can interfere with skin testing and should be stopped prior to skin testing: • Antihistamine – stop 3 days for non-selective short acting, 7 days for long acting (e.g. Cetirizine) • H2 receptor antagonists – stop 48 hours • chronic and relatively high dose systemic corticosteroids (>20 mg/day) may partially suppress skin testing • omalizumab may depress skin reactivity for up to 6 months or longer • tricyclic antidepressants, phenothiazines may decrease skin reactivity for up to 2 weeks • other drugs may affect skin testing – some muscle relaxants and antiemetic drugs with antihistamine action.
Physiologic factors	Extreme age may reduce skin reactivity. Forearms produce smaller wheals than the skin of the back.
Technical factors	The quality of allergenic extracts, testing devices, and techniques: • the major inhalant allergens are well characterized and standardized, except for moulds • although extracts of milk, eggs, peanuts, soy, fish, shellfish, and tree nuts are reliable, most commercially available food extracts are not standardized (e.g. commercial extracts of fruits and vegetables).
Allergen preparation	Allergen extracts used in current clinical practice are obtained mainly from natural sources. There is immense variability in the commercial preparation of these products – season, growth conditions, genetic differences between geographic regions, etc.

TABLE 14.9 Reported diagnostic values of SPT[14]

Preparation	Wheal mm	PPV %
HDM	≥3	95
Peanut	≥8	95
Egg	≥4	95
Grass	≥3	80
Hazel	≥4	80
Dog	≥10	80
Cat	≥7	80
Birch	≥3	80
Cladosporium	≥7	80
Alternaria	≥8	80

PPV = positive predictive value.

Prick by prick testing is a skin prick test (SPT) when a fresh food is used as a source of the allergen. The test device is used to prick the food initially and then the patient's skin. A positive prick prick test (PPT) should be confirmed on a non-allergic individual, to exclude an irritant effect.

Histamine dichloride (10 mg/mL) and a negative control of diluent identical to that of the allergen extracts (usually glycerinated saline) should always be included in the test.idt

A wheal ≥3 mm with flare after 15 to 20 minutes is considered positive – the presence of sensitization. For research purposes, a more precise measurement is usually used – the mean of the longest wheal diameter (D) and the diameter perpendicular to D (d) expressed as (D + d)/2.

Potential systemic reactions are reported to be about 33:100,000 (SPT) and 0.5% of PPT using fresh food in infants. One fatality due to SPT has been reported in a large survey (American Academy of Allergy Asthma & Immunology).[15] Appropriate training and full emergency equipment and medications are essential when skin testing is used.

End-point dilution technique (a variant of IDT) to identify the concentration of an extract that produces a reaction of a defined size is not routinely used in the clinical practice. Potential systematic reactions (0.5%) and fatalities (6) have been reported with IDT without prior SPT.

Serum-specific IgE measurement

Allergen-specific IgE (sIgE) measurement is an *in vitro* test to demonstrate sensitization.[16] Serum sIgE can be measured by sensitive immunoassays such as radioimmunoassay, enzyme immunoassay or fluorescent immunoassay. In these assays a serum is incubated with an allergen of interest bound solid phase. IgEs with the specificity to the allergen of interest will remain on the solid phase, which is then detected by a labelled anti-IgE antibody (Figure 14.3). The level of signal is proportionate to the concentration of sIgE. SIgE can be falsely elevated if total IgE > 1000 kU/L due to non-specific binding. Solid phase varies in different assay systems – the ImmunoCAP by Phadia (cellulose sponge matrix in the form of a small cap), the Immulite System (avidin solid phase) and the HYTEC-288 system (cellulose wafer). Similarly reagents used in the different systems vary. Therefore sIgE results from different systems are not interchangeable. The ImmunoCAP system is currently most widely used for sIgE measurement in the UK.

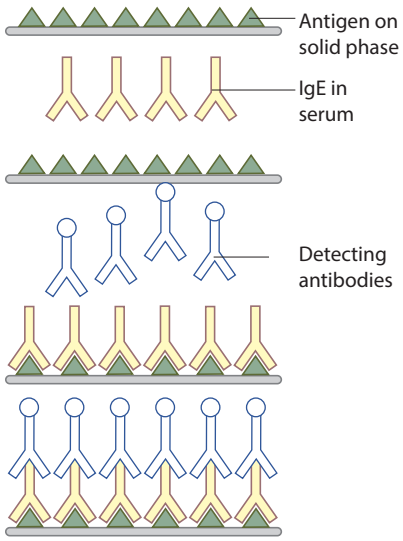


Figure 14.3 Enzyme immunoassay diagram of serum sIgE measurement.

SIgE measurement is indicated in the following situations: high risk for anaphylaxis; use of medications that can cause interference in SPT; skin lesions unsuitable for SPT; small children; and so on. The level of sIgE is not directly correlated with the severity of allergy.

Until recently allergen sources have usually been based on the conventional extract. Allergen extract is a mixture of proteins (components) from the allergen source. More recently component resolved diagnostics (CRD) are used in detecting sIgE to allergen components. CRD has improved our knowledge in risk assessment and treatment such as allergen-specific immunotherapy.

Multiple component-specific IgEs can be detected using microarray techniques (e.g. ImmunoCAP ISAC). This can be useful by providing a sensitization profile for risk assessment. Allergen components can be categorized into species-specific and cross-reactive component. Cross-reactive components labile proteins (e.g. profilin) can be associated with multiple sensitivities and symptoms but are less likely to cause systemic symptoms. In contrast, cross-reactive stable proteins such as non-specific lipid transfer protein (nLTP) are often associated with more systemic symptoms. This knowledge is increasingly being applied in the management of multiple fruit/food allergy (Table 14.10).

Basophil activation test (BAT)

The Basophil Activation Test (BAT) (Figure 14.4) is an in *vitro* study of peripheral basophils responses to stimuli.[18–20] BAT can use whole blood and therefore is more accessible than mast cells to study IgE mediated

TABLE 14.10 Allergen components and clinical relevance[17]

Component	Allergen source	Protein nature	Clinical relevance
Ara h 2	Peanut	Species-specific	Severe peanut allergy
Ves v 1	Wasp	Species-specific	Wasp allergy
Api m 1	Bee	Species-specific	Honey bee allergy
Gal d 1	Egg	Species-specific	Persistent egg allergy
Tri a 19 (O5g)	Wheat	Species-specific	Food dependent exercise induced anaphylaxis
Phl p 1	Timothy grass pollen	Cross-reactive (profilin)	Seasonal allergic rhinitis
Ara h 8	Peanut	Cross-reactive (PR-10)	Oral allergy syndrome
Pru p 3	Peach	nsLTP	Peach allergy/oral allergy syndrome

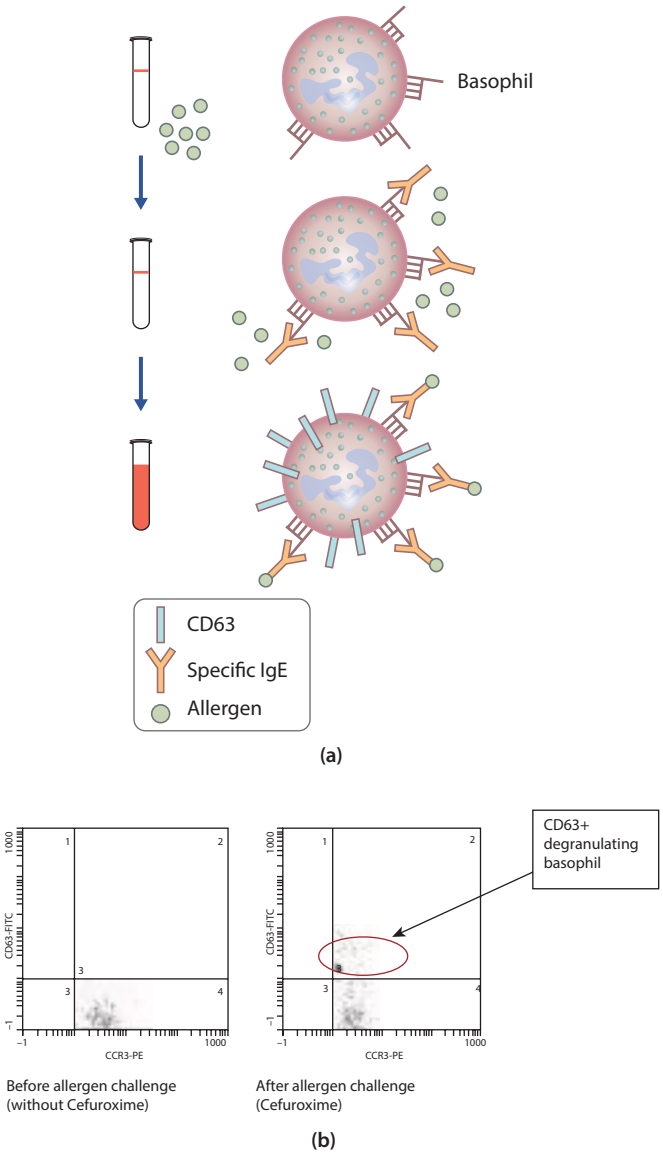


Figure 14.4 (a) Assay principle diagram of basophil activation test. (b) BAT histogram from flow cytometry using activating markers CD63. This patient has a history of anaphylaxis following intravenous cefuroxime. SPT, strongly positive to cefuroxime.

responses in allergic reaction. These can be assessed mainly by two methods: measurement of mediator release (e.g. histamine); or detecting the increase in cell surface molecules or newly expressed cell surface molecules (e.g. CD63, CD69, CD203c).

The whole blood of the patient is incubated with the allergen of interest. Basophils are stimulated due to the cross-linking of the specific IgE-FcεRI on basophil. Degranulation of basophils leads to the expression of molecules (e.g. CD63) on the basophil cell surface. In an unstimulated phase these molecules are anchored on the membrane of intracellular basophil granules, which contain histamine. CD63 expression closely correlates with histamine release in the degranulation. These can be detected by the flow cytometry method.

The assay performance from many studies and reports indicates BAT is comparable to serum sIgE in allergy diagnoses. For house dust mite sensitivity, BAT has claimed to have sensitivity of 85% (allergic rhinitis) and 50% (local allergic rhinitis), specificity of 93%, positive predictive value of 0.92 (allergic rhinitis) and 0.89 (local allergic rhinitis), and negative predictive value of 0.87 (allergic rhinitis) and 0.62 (local allergic rhinitis). BAT has been used to assess allergic response for allergens that are not commercially available for sIgE measurement. These include aeroallergens, drugs, venom and food allergens.

There are limitations in BAT. It is not well standardized (e.g. allergen concentration). It requires a fresh sample and highly skilled technicians. Interpretation of the test demands a highly trained immunologist/allergist given there is a concern about false positive related CD63 expressing platelet. Therefore BAT is currently available in limited numbers of diagnostic laboratories.

Non-validated tests

The following tests have not been validated to be used in allergy diagnosis:

- vega test
- kinesiology
- hair analysis
- provocation-neutralization
- iridology
- leucocytotoxic testing
- auriculo-cardiac reflex.

BEST CLINICAL PRACTICE

- ✓ Diagnosis of allergic disease is principally on a careful clinical history. An approach to allergy diagnosis is outlined in **Figure 14.5**.
- ✓ Allergic rhinitis can cause significant morbidities, and the impact of the disease upon the patient's work and leisure activities should be considered. Respiratory symptoms may indicate the presence of associated asthma.
- ✓ The examination of allergic rhinitis should include nasoendoscopy to exclude other conditions or exacerbating factors (nasal polyps, septal deflection or chronic rhinosinusitis).
- ✓ The presence of sensitization can be demonstrated by *in vivo* or *in vitro* tests, which must be interpreted with the clinical history.
- ✓ The routine panel of skin prick testing to demonstrate atopy includes house dust mite, animal danders (cat fur, dog hair, horse hair), moulds (*Aspergillus, Alternaria, Cladosporium*) and pollens (birch, timothy grass, weeds), positive control (histamine 10 mg/L) and negative control (allergen diluent).
- ✓ Serum sIgE measurement is preferred when SPT is likely to be equivocal in certain conditions such as severe eczema or use of medications that may interfere with the SPT (**Table 14.6**). Serum sIgE has a wider spectrum of allergens than SPT.
- ✓ Pharmacotherapy is the mainstay of treatment for allergic rhinitis. Most medications are designed to target mediators.
- ✓ Antihistamines are H1 receptor antagonists that are effective in early symptoms of allergic rhinitis.
- ✓ Intra-nasal corticosteroids are considered first-line treatment for more severe allergic rhinitis and are highly effective provided they are administered correctly. Training and health education of patients regarding the timing, technique and adequate dosing are essential in order to achieve the maximal benefit.
- ✓ A short course of prednisolone (e.g. 20 mg daily for 5 days) may be prescribed and is highly effective at relieving all nasal symptoms including nasal obstruction in the majority of patients.
- ✓ Sodium cromoglycate is a mast cell membrane stabilizer. It reduces nasal discharge and congestion but is less effective than topical corticosteroids. The eye drop preparations are useful for allergic ocular symptoms.
- ✓ Intra-nasal cholinergic relieves rhinorrhoea but is less effective for other symptoms of allergic rhinitis.
- ✓ Leucotriene receptor antagonists (e.g. montelukast) have beneficial effects in asthma but are less effective in rhinitis.

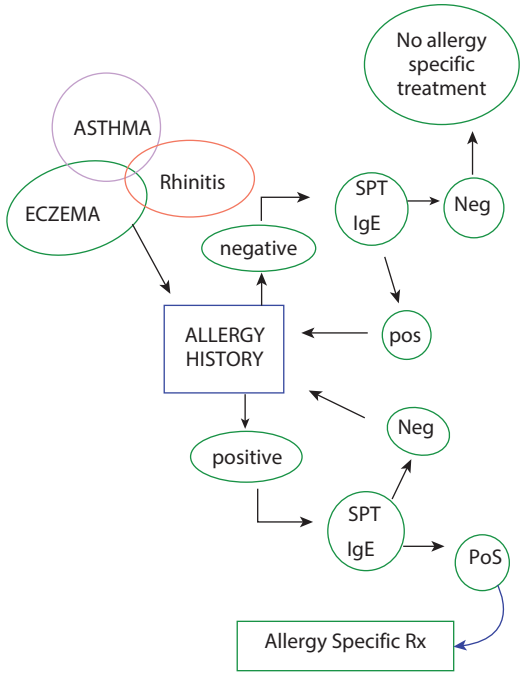


Figure 14.5 An approach to allergy diagnosis.

- ✓ Allergen avoidance is possible and essential for some allergens (e.g. peanut, cat fur, latex) but less effective in allergic rhinitis due to ubiquitous allergen (e.g. grass, house dust mite).
- ✓ House dust mite avoidance is often recommended. However, trials to date have been small and of suboptimal methodology.
- ✓ Allergen-specific immunotherapy is an effective intervention that can modify the disease process and long-lasting benefit has been reported. There are potential side effects including anaphylaxis, especially in patients with concomitant asthma. Efficacy can be limited in patients with multisensitivities. Therefore allergen-specific immunotherapy should be delivered in specialist centres and comply with the clinical guidelines (e.g. British Society for Allergy and Clinical Immunology).

FUTURE RESEARCH

- ➤ Improve understanding of mechanism of different methods of specific immunotherapy
- ➤ Multicentre studies for better application of component resolved diagnostics (CRD) in risk assessment
- ➤ External quality assurance of tests – CRD, BAT
- ➤ Multicentre studies for translation of new biomarkers, use of specific immunotherapy other than SCIT and SLIT
- ➤ Prevention of allergic diseases development

KEY POINTS

- Genetic and environmental factors interact as causes of allergic disease.
- Type 1 IgE mediated immediate hypersensitivity occurs only in a sensitized individual.
- Allergic inflammation is characterized by IgE dependent activation of mast cells and tissue eosinophils infiltration. These events are under the regulation of Th2 cells.
- Biomarkers are useful in allergy diagnosis. Normal levels of tryptase do not exclude anaphylaxis.
- The majority of IgE is tightly bound to FcεRI. There is no signalling until these receptors are cross-linked by their specific antigens.
- Skin testing and sIgE indicate sensitization only and must be interpreted in the context of the clinical history.

- Allergic rhinitis and asthma are commonly associated.
- Corticosteroids are general immunosuppressive agents.
- Allergen-specific immunotherapy is the only curative approach for allergic rhinitis, allergic asthma and venom allergy.
- Of the new novel therapeutic targets in clinical trials only anti-IgE therapy has been successful.

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CHAPTER 15

EVALUATION OF THE IMMUNE SYSTEM

Moira Thomas, Elizabeth Drewe and Richard J. Powell

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SEARCH STRATEGY

Data in this chapter are taken from standard UK immunology laboratory practice. They reflect expert opinion (level 4 evidence) with regards to immunology tests currently performed in the UK.

INTRODUCTION TO EVALUATION OF THE IMMUNE SYSTEM

Evaluation of the immune system broadly encompasses the investigation of immunodeficiency, autoimmune disease including vasculitis, allergy and lymphoproliferative disease. Diagnosis results from studying the combination of clinical presentation and investigations including immunological, haematological, microbiological and histopathological, with increasing recognition of the place of genetic and molecular biological approaches. However, immunology tests in isolation are rarely diagnostic. Some understanding of the sensitivity (proportion of true positives correctly identified), specificity (proportion of true negatives correctly identified), positive predictive value (likelihood an individual has a disease given a positive result) and negative predictive value (likelihood an individual does not have the disease given a negative result) for each test is required.

Interpretation of results is dependent upon the age of the patient. This is particularly important for the investigation of childhood immunodeficiency when, for example, a lymphocyte count that would be normal for an adult could be well below the age-related normal range and may signify an underlying immunodeficiency in an infant. Similarly, a weak positive anti-nuclear antibody (ANA) titre may be a common incidental finding in a middle-aged female whereas may signify an autoimmune process in a child.

The choice of investigations will ultimately depend on the clinical presentation and may be guided through discussion with a clinical immunologist. Whilst rare immunological diseases will only be recognized by the appropriate investigation, consideration must also be given to commoner diseases with a similar presentation, for example, cystic fibrosis.

IMMUNOLOGICAL TESTS

Immunodeficiency

Immunodeficiency should be considered in any patient with persistent or recurrent infections not responding to antibiotics, or patients with unusual or opportunistic infections.[1] Immunodeficiency may be either primary or secondary to therapies such as immunosuppressive drugs or chemotherapy or secondary to diseases such haematological malignancies, diabetes or HIV infection; in many patients the secondary cause will be clearly apparent but in others, infection will be the presenting feature. Primary immune deficiency can arise from defects in any part of the immune system so may manifest in a myriad of ways across a wide age range but with the common hallmark of increased susceptibility to infection. Sinopulmonary infections are a common feature of primary antibody deficiency and ENT clinical staff should look out for these individuals and initiate the appropriate investigations. It is estimated that half of the patients with primary antibody deficiency in the UK remain undiagnosed.[2] Remember that early diagnosis of primary immunodeficiency does lead to an improved outcome, emphasizing the need to consider this diagnosis.

When considering immunodeficiency, the type of pathogen may provide a clue to the underlying disease and appropriate tests required (**Tables 15.1** and **15.2**). Certain tests, especially those involving functional assays, require rapid transport of samples and prior laboratory preparation. Accordingly early discussion with the local laboratory is recommended.

TABLE 15.1 Outline of associations between pathogens and specific immunodeficiencies

Pathology	Immunodeficiency
Bacterial infections	Antibody deficiency
	T cell deficiency
	Complement
	Neutrophil disorders
Viral infections	T cells
	Antibody deficiency
Fungal infections	Neutrophil disorders
	T cells
Neisserial infections	Complement
Abscess formation	Neutrophil disorders
Mycobacterial infection	T cells
	Macrophage/cytokines

TABLE 15.2 Outline of immunological tests for primary immunodeficiency

Deficiency	Tests
T lymphocytes	HIV serology
	Lymphocyte subsets - numbers of CD4 and CD8 T cells, B and NK cells
	Lymphocyte proliferation studies
Antibody deficiency	Immunoglobulins (IgG, IgA and IgM) and serum electrophoresis
	Specific antibodies and responses to immunization
	Lymphocyte subsets
Phagocyte disorders	Differential white cell count (neutrophil numbers)
	Neutrophil respiratory burst analysis
	Neutrophil adhesion markers
Complement disorders	Functional complement assays
	Assay individual complement components

C-REACTIVE PROTEIN

C-reactive protein (CRP) levels reflect the acute phase response and are particularly elevated in bacterial infections and active vasculitis. An elevated CRP may indicate intercurrent infection in immunodeficiency and individuals on high dose steroids. Rarely the lack of an appropriate acute phase response in the face of invasive bacterial infection can be a feature of certain rare immune deficiencies such as Hyper IgE Syndrome.

IMMUNOGLOBULINS

Serum immunoglobulins (IgG, IgA and IgM) are a useful first line test for investigation of immunodeficiency although normal or even high levels do not exclude all forms of immune deficiency. Very low levels of all immunoglobulins are typical in boys with X-linked agammaglobulinaemia (XLA). IgG and IgA levels are typically low in children and adults with common variable immunodeficiency, although, as the name suggests, the pattern can vary and in some patients immunoglobulin levels may only be slightly below the normal range. Other types of immune deficiency such as HIV infection and defects of neutrophil function such as chronic granulomatous disease are characterized by raised immunoglobulin levels. Other indications for immunoglobulin testing include infective and inflammatory diseases in which polyclonal increases in immunoglobulins are often seen and the evaluation of lymphoproliferative disease when serum and urine electrophoresis should also be requested to identify any paraproteinaemia.

SPECIFIC ANTIBODIES (ALSO TERMED FUNCTIONAL ANTIBODIES)

Assessment of dynamic antibody responses to immunization plays an important part in the assessment of antibody deficiency especially in patients with borderline or normal immunoglobulin levels. Specific antibody levels are measured before and 4–6 weeks after immunization with tetanus toxoid, pneumococcal, Haemophilus influenza b or other non-live vaccines depending upon local immunization schedules and availability of specific antibody tests. Failure to mount an adequate response is a pointer to an underlying immunodeficiency. Of course, live vaccines must not be given to any patient with a suspected immunodeficiency.

IMMUNOGLOBULIN G SUBCLASSES

IgG subclasses are sometimes useful in the investigation of possible antibody deficiency where IgG subclass deficiency may be associated with selective IgA deficiency and/or failure to respond to pneumococcal immunization. However, isolated low IgG2 levels may be found in asymptomatic individuals especially in childhood. Increasingly the main indication for the measurement of IgG subclasses is now suspected autoimmune pancreatitis and other IgG4-related diseases. This group of inflammatory disorders, which may affect a wide range of organs including sinuses, salivary glands and thyroid, is characterized by an infiltrate of IgG4 positive plasma cells, fibrosis and raised IgG4 levels.

LYMPHOCYTE PHENOTYPING (ALSO TERMED LYMPHOCYTE SUBSETS)

A reduced lymphocyte count in the full blood count may provide an early clue to the presence of immune deficiency; indeed in infants a persistent unexplained lymphocyte count of $<2.8\times10^9$/l should prompt consideration of severe combined immune deficiency. Lymphocyte phenotyping by flow cytometry allows accurate measurements of the different lymphocyte subsets by detection of cell surface markers. The two main T cell subsets are evaluated by assessing $CD3^+CD4^+$ and $CD3^+CD8^+$ numbers whilst $CD19^+$ cells identify B cells and $CD3^-CD16/56^+$ cells represent NK cells. Very low T cells are characteristic of severe combined immunodeficiency whereas absence of B cells is a feature of X-linked agammaglobulinaemia. However, these findings are not diagnostic and may be affected by drugs or intercurrent infection.

Low $CD3^+CD4^+$ cell numbers are characteristic of human immunodeficiency virus (HIV) infection. However, a normal CD4 count does not exclude HIV nor should it be used as a covert screening test. A wide range of additional cell surface markers and lymphocyte subsets can be measured and so close dialogue with the laboratory is advised in order to select the most appropriate panels for individual patients and also to interpret the results. Lymphocyte phenotyping is also valuable in the diagnosis of lymphoproliferative disease.

LYMPHOCYTE PROLIFERATION AND OTHER FUNCTIONAL ASSAYS

These specialized tests are reserved for the investigation of suspected cellular immunodeficiency usually following discussion with an immunologist. The proliferation of lymphocytes can be measured following *in vitro* stimulation by mitogens such as phytohaemagglutinin, or antigens such as tetanus, to which the patient has previously been exposed. Additional more specialized functional tests are possible, for example to assess production and function of cytokines in the gamma interferon and interleukin 12 pathways in patients with recurrent atypical mycobacterial infections.

COMPLEMENT PATHWAY LEVELS (C3-, C4-, C1-INHIBITOR)

Measurement of C3 and C4 levels is helpful in the assessment of patients with systemic inflammatory disorders. As complement components are acute phase proteins, levels of both C3 and C4 are typically raised in systemic vasculitides, sepsis and other inflammatory disorders. However, complement is consumed in systemic immune complex disorders so levels of both C3 and C4 are typically low in active systemic lupus erythematosus (SLE) and levels may vary with disease activity. Isolated low C3 levels with normal C4 levels are a feature of certain glomerulopathies including post-streptococcal nephritis. Complement levels also play a vital role in the investigation of angioedema. Patients with C1-inhibitor deficiency (hereditary angioedema) have low C4 levels (but normal C3 levels) due to uncontrolled turnover of the classical complement pathway; a normal C4 level during an attack of angioedema essentially excludes this diagnosis. C1-inhibitor levels are low in the majority of hereditary angioedema patients but a small proportion have type 2 C1-inhibitor deficiency whereby they have normal levels of a dysfunctional C1-inhibitor. Functional C1-inhibitor assays can be undertaken in those patients with angioedema without urticaria and a low C4 level. Appropriate care must be taken in handling and transport of the sample to avoid in vitro degradation of C1-inhibitor function.

HAEMOLYTIC COMPLEMENT ACTIVITY

Deficiencies in the classical complement pathway typically present with early onset atypical or severe lupus-like illness or invasive bacterial infection with encapsulated organisms such as pneumococcus. Deficiencies in the alternate and terminal pathways predispose to meningococcal infection especially with unusual serotypes. The CH100 (or CH50) haemolytic complement test assesses activity of the classical and terminal complement pathways and the AP100 (or AP50) haemolytic complement test assesses activity of the alternate and terminal pathways. Thus the combination of these tests can identify the presence and likely location of any deficiency that can be followed up by measurement of the appropriate individual complement components. As haemolytic complement tests rely upon complement function, samples should be taken when patients are clinically stable and blood samples must be separated and frozen within a short time of venepuncture to avoid *in vitro* depletion of complement causing false positive results.

NEUTROPHIL FUNCTION

Patients with chronic granulomatous disease (CGD) have deficient neutrophil respiratory burst and their neutrophils are unable to kill ingested organisms, especially catalase positive organisms such as staphylococcus aureus, serratia and also fungi such as aspergillus. Therefore assessment of neutrophil respiratory burst is indicated in patients presenting with recurrent abscesses and lymphadenitis, deep seated abscesses or recurrent bacterial infections. The traditional nitro blue tetrazolium (NBT) test, which assessed the ability of patient neutrophils to oxidize pale yellow NBT into a dark blue precipitate, has now mainly been superceded by flow cytometric assays. Female carriers of the X-linked form of CGD may also be identified using the flow cytometric test. Neutrophils have a short life span so analysis needs to be carried out within a short period of time after venepuncture whilst cells are still viable, so prior discussion with local laboratory is recommended.

MOLECULAR AND GENETIC STUDIES

Mutations in more than 300 genes are now known to cause primary immune deficiency with the number of causative genes increasing each year. Genetic testing for primary immune deficiency by means of Sanger sequencing of the suspected faulty gene is now routinely available for many disorders and also allows carrier detection and prenatal diagnosis where appropriate. However, with this new genetic knowledge has come the recognition that many primary immune deficiencies have overlapping and wider clinical phenotypes than were initially described. The advent of next generation sequencing technologies is paving the way for new approaches to genetic investigation of suspected immune deficiency by enabling large panels of immunological genes to be examined simultaneously. As well as providing a means to identify lesions in multiple genes known to cause immune deficiency, this approach can also enable the discovery of new genetic conditions.

Allergy

A brief discussion of allergy tests follows, although this subject is discussed further in Chapter 14, Allergy: basic mechanisms and tests. When diagnosing allergy,

a clear and detailed history is paramount. Evidence of sensitization to specific allergens can be detected *in vivo* by skin prick tests or *in vitro* on serum by measuring allergen-specific IgE levels.

SKIN PRICK TESTS

Drops of aqueous solutions of relevant allergens, negative (allergen buffer) and positive controls (histamine) are applied to the skin. A pinprick is made through the drop placed on the epidermis and excess solution removed with tissue. The size of any localized skin reaction is measured at 15 minutes, and results > 2–3 mm diameter larger than the negative control are considered positive. Antihistamines should be stopped before testing, to prevent false negative results. Positive results indicate sensitization but do not necessarily indicate clinical allergy, emphasizing the need to correlate with the patient's history.

IgE

Total IgE levels may be raised in allergic diseases, particularly eczema, and also with certain parasitic infections, immunodeficiencies and lymphomas. Therefore a raised total IgE level does not necessarily imply allergic disease and a normal level does not exclude allergic disease. Very high total IgE levels such as those found in severe eczema can result in many weak false positive allergen-specific IgE levels.

ALLERGEN-SPECIFIC IgE

These are now measured by enzyme-linked immunoassay rather than radioallergosorbent assay test (RAST) although the latter term remains in common usage. A wide range of aeroallergens, food and other allergens is available. Choice of appropriate allergens should be based on the clinical history, for example in patients with seasonal allergic rhinitis the most useful allergens will be the pollens in season at the time of the patient's symptoms; in patients with perennial rhinitis allergens such as house dust mite or household pets are more likely to be informative. The presence of specific IgE indicates sensitization but does not necessarily indicate clinical allergy, emphasizing the importance of correlation with the patient's history. Results also depend upon the sensitivity and specificity of the tests which does vary between individual allergens. *In vitro* tests are especially useful if patients are unable to undergo skin testing (e.g. because they are unable to stop antihistamine therapy, have widespread skin disease or are dermatographic).

ANAESTHETIC REACTION TESTING

Anaphylaxis occurring during surgery may be difficult to differentiate from other simultaneous haemodynamic events. Tryptase is released from mast cells during anaphylaxis and can be measured by laboratories and may be helpful in this setting. Serum tryptase levels typically peak 1–2 hours after onset of an anaphylactic event with levels falling towards normal within 24 hours. Accordingly a series of timed and clearly labelled samples for tryptase is required. However a rise in tryptase is only seen in approximately 60% of anaphylactic events so normal results do not completely exclude anaphylaxis. Allergen-specific IgE can be measured to a limited range of anaesthetic drugs, antibiotics, chlorhexidine and latex but there is an increased risk of false negative results within the first 6 weeks after the acute event. Further specialist assessment and skin testing is often required to identify the most likely culprit allergen.

Autoimmune disease including vasculitis

The detection of serum autoantibodies is a helpful aid in the investigation of autoimmune diseases and vasculitis and should be considered in the light of the clinical history and the outcome of appropriate tissue biopsies.[4] Some autoantibodies such as anti-glomerular basement membrane (GBM) and acetyl choline receptor antibodies play a direct role in disease pathogenesis; these antibodies generally have very high sensitivity and specificity for the disease in question. In contrast, other autoantibodies such as anti-nuclear antibodies (ANA) are thought to be secondary to tissue damage or represent epiphenonoma but are nevertheless useful disease markers; these antibodies are often less specific. Autoantibodies may be useful for diagnosis, assessment of prognosis and disease monitoring, and in some cases may be detected prior to the development of disease.

ANCA AND VASCULITIS

The investigation of suspected vasculitis requires integration of clinical, laboratory and biopsy information. Antineutrophil cytoplasmic antibodies (ANCA) play a critical role in identifying ANCA-associated vasculitis (AAV). ANCA is detected by indirect immunofluorescence on human neutrophils. Two main patterns of fluorescence may be seen; cytoplasmic staining denotes a C-ANCA and is usually due to reactivity against proteinase 3 (PR3) and are associated with polyangiitis with granulomatosis (formally called Wegener's granulomatosis). Perinuclear staining denotes a P-ANCA which is usually due to myeloperoxidase (MPO) antibodies and associated with microscopic polyangiitis, rapidly progressive glomerulonephritis or Churg–Strauss syndrome. Other atypical staining patterns of ANCA may be seen but these are usually due to reactivity against other antigens and are rarely associated with systemic vasculitis. Care is needed in interpreting ANCA results. Negative results can be found in AAV, especially localized polyangiitis with granulomatosis, and false positive results can be found in a range of conditions including HIV infection, infective endocarditis and atrial myxoma, which may mimic vasculitis (**Table 15.3**). Other tests are also useful in the investigation of suspected vasculitis. Complement levels may be useful. For example, if both C3 and C4 are low, SLE, subacute bacterial endocarditis and hypocomplementaemic vasculitis should be considered; if C4 alone is low cryoglobulinaemia should be considered; and if C3 alone is low, then post-streptococcal nephritis should be considered in the differential diagnosis. Other autoantibodies may be useful, for example, anti-nuclear, anti-glomerular basement membrane and anti-phospholipid antibodies, depending upon the clinical picture and organ involvement.

TABLE 15.3 Guide to interpretation of ANCA

Result	Guide to interpretation
Positive C-ANCA with PR3 antibodies	Polyangiitis with granulomatosis
Positive P-ANCA with MPO antibodies	Microscopic polyangiitis
	Churg–Strauss syndrome
Positive C-ANCA without PR3 antibodies	Inflammatory bowel disease
	Infection, malignancy
Positive P-ANCA without MPO antibodies	Vasculitis, connective tissue disease

ANTI-NUCLEAR ANTIBODIES (ANA), DOUBLE-STRANDED DNA ANTIBODIES AND ANTIBODIES TO EXTRACTABLE NUCLEAR ANTIGENS (ENA)

Anti-nuclear antibodies (ANA) are found in systemic lupus erythematosus (SLE). ANA is a useful screening test, as a negative ANA makes SLE very unlikely. However, positive ANAs are also found in other connective tissue disorders and autoimmune hepatitis, as well as a wide range of other autoimmune, inflammatory and infective disorders. ANAs are also found in healthy individuals especially older females. Different patterns of ANA are seen and reflect reactivity against different nuclear antigens including centromere, dsDNA and ENA (Ro, La, Sm, ribonucleoprotein, Scl70 and others) and may help categorize the connective tissue disease present. Whilst antibodies against centromere, dsDNA and ENA are much more specific for individual connective tissue disorders, they are less sensitive. Table 15.4 shows the main disease associations. Advances in technology mean that many multiplex assays are now readily available and often termed 'connective tissue disease screens'. These typically comprise a mixture of the main ENA and dsDNA antigens enabling patient samples to be screened more rapidly with detection of only the more disease-specific autoantibodies. However, there may be a loss of sensitivity and some patients with clinically relevant positive ANA but negative ENA and dsDNA abs may be missed. Clinicians are encouraged to become familiar with the details of the tests offered by their local laboratory as the different methods may differ significantly in sensitivity, specificity and range of autoantibodies included in the screen.

RHEUMATOID FACTOR (RF) AND CYCLIC CITRULLINATED PEPTIDE (CCP) ANTIBODIES

RF and CCP antibodies may both be found in a proportion of patients with rheumatoid arthritis. CCP antibodies are more specific than rheumatoid factor, which is also found in many healthy individuals. Rheumatoid factor is also found in Sjogren's syndrome and cryoglobulinaemia.

CARDIOLIPIN ANTIBODIES AND ANTIPHOSPHOLIPID SYNDROME

Anti-phospholipid syndrome presents with features including recurrent venous and arterial thrombosis, recurrent pregnancy loss, thrombocytopaenia and neurological disease due to both small and large vessel occlusion plus the presence of phospholipid antibodies. These consist of a group of related autoantibodies – anti-cardiolipin antibodies, anti-β-2 glycoprotein 1 antibodies and lupus anticoagulant. Patients may have one or more of these autoantibodies. Repeat testing may be indicated to exclude transient autoantibody production (e.g. secondary to infection).

TABLE 15.4 Interpretation of ANA, centromere, dsDNA and ENA antibodies

Autoantibodies	Interpretation
Anti-nuclear antibody (ANA)	SLE Other connective tissue diseases – Sjogren's syndrome, scleroderma, undifferentiated connective tissue disease Autoimmune hepatitis Other autoimmune, inflammatory and infective disorders, malignancy Healthy individuals – incidence increases with age, females > males
dsDNA antibodies	SLE Autoimmune hepatitis
Ro (SSA)	SLE, Sjogren's syndrome, neonatal heart block in the fetus of a Ro positive mother
La (SSB)	SLE, Sjogren's syndrome
Sm	SLE
Ribonucleoprotein (RNP)	SLE, overlap syndromes eg mixed connective tissue disease
Scl70	Systemic sclerosis
CENP-B	CREST syndrome (calcinosis, Raynaud's, oesophageal dysmotility, scleroderma, telangiectasia)

CRYOGLOBULINAEMIA

Cryoglobulins are immunoglobulins that form gels or precipitates on cooling. Clinical features include purpura, Raynaud's syndrome, thrombosis, neuropathy and vasculitis. They are associated with infections, connective tissue disease and lymphoproliferative disease. Detection relies on the appropriate collection into a prewarmed blood tube in a waterbath/vacuum flask. Cold agglutinins are autoantibodies that reversibly agglutinate erythrocytes in the cold and should not be confused with cryoglobulins.

COELIAC DISEASE

Coeliac disease is characterized by malabsorption and weight loss but can present with oral ulceration, anaemia and malaise. The presence of villous atrophy on duodenal biopsy remains the gold standard for diagnosis but serological tests are an invaluable screen. Over 95% of patients with Coeliac disease have positive IgA tissue transglutaminase or IgA endomysial antibodies; these are essentially the same autoantibodies, the different terminology reflecting the different test methodology. Serology typically becomes negative on a gluten-free diet so it is important to ensure that the patient has been consuming gluten regularly (typically at

least twice a day for at least 6 weeks) prior to testing to avoid obtaining a false negative result. Paradoxically individuals with IgA deficiency (defined as IgA < 0.06 g/l) have an increased incidence of Coeliac disease but of course the usual IgA based serology is of no value. IgG tissue transglutaminase or IgG endomysial antibodies can be measured instead but sensitivity and specificity may be less than that of the IgA based serology.

BULLOUS PEMPHIGOID AND PEMPHIGUS

Bullous pemphigoid and pemphigus are blistering disorders associated with autoantibodies to desmoglein in the basement membrane zone or intercellular type VII collagen respectively. These may be detected in blood or in tissue biopsies using direct immunofluorescence.

LIVER AUTOANTIBODIES

Several autoantibodies are associated with autoimmune liver disease. Typical screens based on indirect immunofluorescence on rodent liver/kidney/stomach multi-block can detect mitochondrial, smooth muscle, liver kidney microsomal (LKM), liver cytosolic 1 (LC1) and anti-nuclear antibodies. M2 mitochondrial antibodies are associated with primary biliary cirrhosis, ANA and smooth muscle antibodies are associated with autoimmune hepatitis, LC1 and LKM antibodies may be associated with more aggressive forms of autoimmune hepatitis. However, overlapping serology and clinical pictures may be seen.

GASTRIC PARIETAL CELL AND INTRINSIC FACTOR ANTIBODIES

Gastric parietal cell antibodies are present in the majority of patients with pernicious anaemia and may pre-date onset of disease. They are also found in up to 15% of the healthy elderly. Intrinsic factor antibodies are much more specific but less sensitive for pernicious anaemia. In the past, recent B12 treatment could interfere with the intrinsic factor antibody assays but this is much less of a problem with modern methodologies.

ACETYL CHOLINE RECEPTOR ANTIBODIES, MYASTHAENIA GRAVIS AND THYMOMA

Myasthaenia gravis is characterized by increased skeletal muscle fatiguability. Facial and bulbar muscle involvement may cause nasal speech, ptosis, diplopia and difficulty in swallowing. Generalized weakness occurs in approximately 85% of patients. Autoantibodies to the acetyl choline receptor (AchR) at the neuromuscular junction are detectable in 90% of patients. Myasthenia gravis is associated with thymoma and other autoimmune diseases.

Lymphoproliferative disease

Many of the immunological tests required to investigate lymphoproliferative disease have already been mentioned and are used in combination with bone marrow and lymph node biopsies.

IMMUNOGLOBULINS, SERUM AND URINE ELECTROPHORESIS AND SERUM-FREE LIGHT CHAINS

Multiple myeloma is a malignancy of plasma cells that produce monoclonal immunoglobulin (paraprotein). Paraproteins may be detectable in both serum and/or urine. Twenty percent of myelomas only produce monoclonal light chains, which may only be detectable in urine as Bence Jones protein or in serum using a serum-free light chain assay. Therefore a full myeloma screen requires both blood for immunoglobulins and electrophoresis plus either serum-free light chains or urine for electrophoresis. This combination of tests will detect all but the very rare non-secretory myelomas. These tests are also required for the investigation of possible AL amyloid. As paraprotein levels may be relatively low and difficult to detect in AL amyloid, close liaison with the laboratory is recommended as more sensitive detection methods such as immunofixation may be required. Although paraproteins are the hallmark of myeloma, Waldenstrom's macroglobulinaemia and AL amyloid, the majority of paraproteins detected in routine clinical practice are not associated with any identifiable lymphoproliferative disorder and are termed monoclonal gammopathy of uncertain significance (MGUS). Some MGUS may progress to lymphoproliferative disease with an overall rate of 1–2% per annum.

BEST CLINICAL PRACTICE

- ✓ Immunological tests always need to be interpreted in the context of the clinical case.

FUTURE RESEARCH

- ➤ The majority of current tests are performed on peripheral blood due to its accessibility. Tests that reflect activity at local surfaces, for example defensins, and tests that are more reflective of *in vivo* pathology, such as intracellular cytokine analysis, may enter clinical practice.
- ➤ Many patients have severe, persistent, unusual and recurrent infections yet no immunological cause is identified. Advancing knowledge, particularly regarding the innate immune system (e.g. toll receptors), may account for such disease and diagnostic tests will subsequently follow.
- ➤ Increasing use of molecular diagnosis and development of tests looking at functional pathways will occur. It is becoming increasingly apparent that individuals with the same genetic mutation may have diverse disease phenotypes, e.g. btk mutation associated with complete absence of B cells or IgG subclass defect. Identification of genetic polymorphisms may predict patients at risk of severe disease requiring a more aggressive management strategy.

KEY POINTS

- Immunodeficiency may present to ENT specialists with severe, persistent, unusual or recurrent infection. Early diagnosis may reduce morbidity and mortality.
- Immunological tests may help in diagnosis and monitoring of disease but must always be considered in association with clinical presentation and biopsy findings.
- Liaise with your clinical immunologist/immunology laboratory to ensure the appropriate tests are being requested. If clinical history is particularly suggestive of a disease, further tests may be required even in the presence of initial negative investigations.

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CHAPTER 16

CANCER IMMUNOLOGY

Osama Al Hamarneh and John Greenman

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SEARCH STRATEGY

This chapter provides an overview of the main concepts involved in the immunology of head and neck tumours, including disease progression, monitoring and immunotherapy. Data in this chapter may be updated by a PubMed search using the keywords: head and neck cancer, tumour microenvironment and Immunotherapy.

INTRODUCTION

Major technical and conceptual advances in immunology and cancer immunology in particular over the last two decades has led to a better, although by no means as yet complete, understanding of the complex relationship between the immune system, tumour initiation and progression, and immunotherapy. Specifically much attention has focused on changes in individual immune profiles of patients treated with conventional, biological or combination therapies; such work is underpinned by high-throughput proteomic and genomic platforms. This has led to a huge amount of interest in using immune biomarkers to both diagnose and monitor tumour response to therapy, as well as acting as a potential therapeutic option alone or in combination with chemo- or radiotherapy.

In this chapter, we endeavour to explore the fundamentals of the complex interactions within the tumour microenvironment and how malignancies effectively 'escape' immune detection. The roles of key immune cells and proteins will be discussed with a focus on tumour biomarkers and the application of anti-tumour immunity knowledge that underpins recent immunotherapeutic trials.

This chapter will discuss concepts of tumour immunebiology that will be of help to clinicians and their patients, focusing on head and neck squamous cell carcinomas (HNSCC), as tumours head and neck originating from squamous epithelia are the most prevalent tumour type within the head and neck region.

TUMOUR MICROENVIRONMENT (TME)

In general, cancers arise from the accumulation of genetic and epigenetic changes, together with abnormalities in the cancer-associated signalling pathways causing the acquisition of cancer-related phenotypes. These changes include limitless replicative potential of tumours, self-sufficiency in growth signals and insensitivity to anti-growth signals, ability to evade apoptosis, increased angiogenesis, invasion and metastasis.[1] However, tumours are complex tissues that not only contain malignant cells but surrounding stroma, which comprises various types of mesenchymal cells, extracellular matrix and immune cells. Collectively, these tissues are referred to as the tumour microenvironment (TME).[2]

As tumours progress, the surrounding microenvironment co-evolves into an activated state through continuous tumour–host interactions.[1] The TME contains many different cell types including normal fibroblasts, carcinoma-associated fibroblasts (CAFs), myofibroblasts, smooth muscle cells, endothelial cells and their precursors, pericytes, neutrophils, eosinophils, basophils, mast cells, T and B lymphocytes, natural killer cells, macrophages and dendritic cells.[2] Many components of the immune system contribute to the rejection of tumours; however, under the influence of the malignancy, they can actually act to promote tumour growth and invasion (**Figure 16.1**). Several studies have shown that tumour stroma contains growth factors and

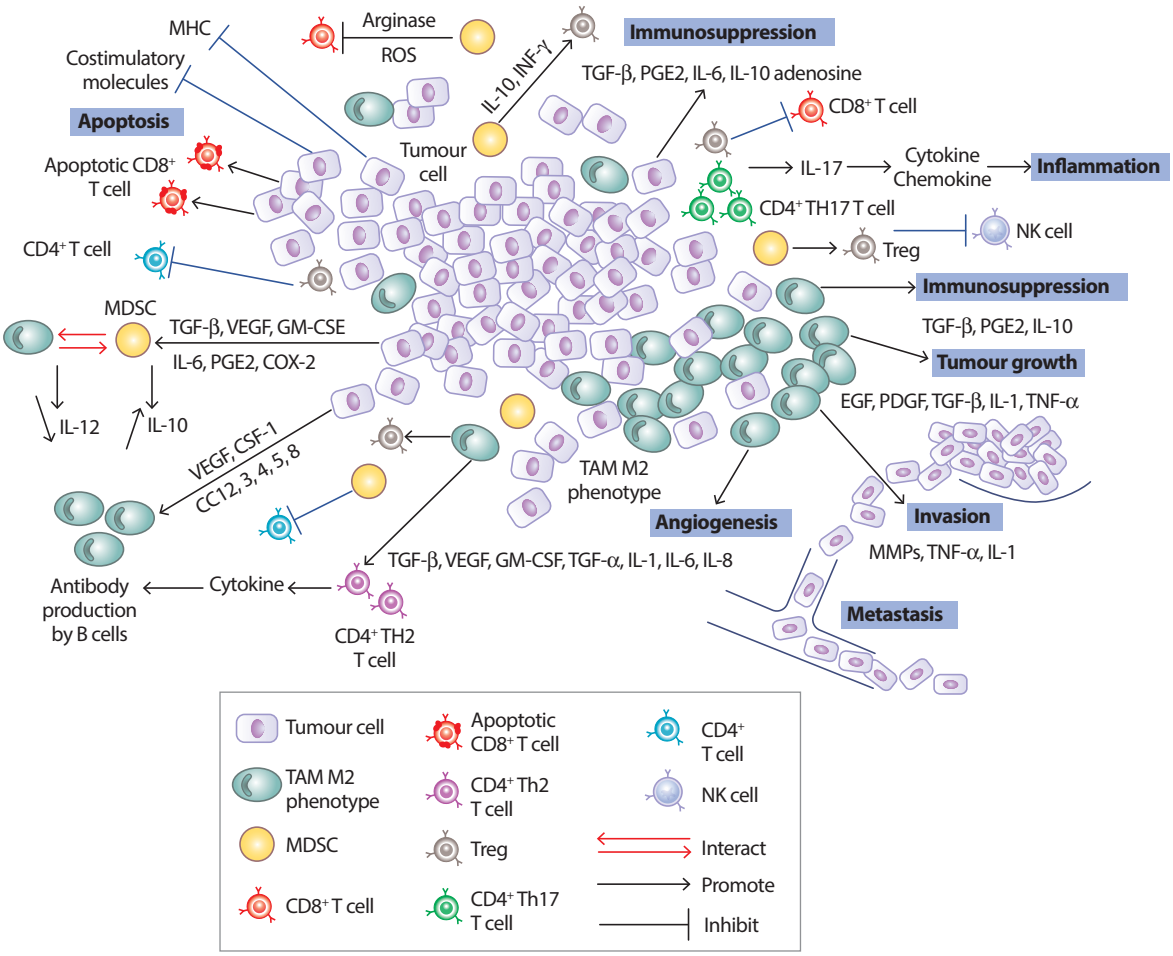


Figure 16.1 Immunosuppressive mechanisms in the tumour microenvironment.

cytokines that can promote angiogenesis, tissue invasion and metastasis. In addition, it has become evident that the stroma provides a chemoresistant capability to the tumour, most likely due to the presence and function of CAF and tumour associated macrophages (TAM) that promote resistance to oncological therapies.[3–5]

The cellular component of TME

T lymphocytes are considered an essential component of anti-tumour immunity. *In vitro*, malignant cells presenting 'altered self' peptides (molecules that have undergone mutations or are aberrantly expressed in the tumour cell) in association with major histocompatibility complex (MHC) class I molecules, can be recognized by CD8+ T cells causing tumour cell-lysis and/or apoptosis through the release of toxic molecules such as perforin and granzymes. Conversely, CD4+ T cells are programmed to release cytokines and may differentiate into one of an ever growing type of T helper cells (i.e. Th1, Th2, Th17) or regulatory T cells (Treg cells), which differ in the cytokine repertoire they produce and therefore their function[6] when interacting with antigen-presenting cells such as dendritic cells or macrophages expressing altered self peptides by host MHC II molecules. In general the CD4+ Th1 cells serve to 'help' and enhance the magnitude and duration of the anti-tumour response.[7] However, CD4+ Th2 cells and CD4+ Treg cells are capable of suppressing effective CD8+ anti-tumour responses.[5] *In vivo* studies by several groups have found dysfunctional circulating and tumour-infiltrating T cells in HNSCC patients, with functional assays identifying multiple defects in T-cell activation and effector functions, suggesting that the tumour has successfully suppressed an otherwise robust lymphocytic response.[8–11]

The TME can become dominated by CD4+ Treg cells that suppress anti-tumour effector T cells by the production of suppressive cytokines such as TGF-β, interleukin-10 (IL-10), prostaglandin E2 (PGE2) and adenosine.[5] Although the full relevance of different subsets of Treg cells is not yet known one subtype, inducible Treg cells (iTreg cells or Tr1 cells), have been shown to very effectively suppress cytotoxic T cell activity both in the TME of several cancers and the peripheral circulation.[12–13] It is becoming increasingly clear that the balance between inflammatory effector cells and Treg cells is critical in producing an effective immune response. A relatively crude measure of the effectiveness is to determine the ratio between cytotoxic CD8+ T cells and Treg cells within the tumour microenvironment. Higher CD8+/Treg cell ratios have been shown to be associated with a favourable prognosis in a range

of human cancers including ovarian,[14] hepatocellular,[15] breast,[16] lung[17] and HNSCC.[13]

Tumour infiltrating lymphocytes (TIL) have been shown to promote angiogenesis and therefore tumour progression and metastasis. Cells with such activity in HNSCC include mast cells,[18] CD34 progenitor cells,[19] Th17 cells[20] and TAM.[21] A high level of infiltration of TAM within HNSCC defined by the overexpression of macrophage content, monocyte chemoattractant protein 1 (MCP1) and macrophage inflammatory protein (MIP)-3alpha levels was also found to be a strong predictor of lymph node metastasis, extracapsular spread and advanced stages of the disease; all considered as poor prognostic markers.[22–23] Stromal cells have been shown to secrete cytokines and growth factors including vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF) and IL-8, which are strong inducers of angiogenesis and tumour progression.[24–26] VEGF expression, which is responsible for facilitating proliferation of endothelial cells and neo-vascularization, correlated significantly with adverse prognosis in HNSCC patients.[27] VEGF-C, a member of the VEGF family, plays an important role in tumour lymphangiogenesis; raised tumour-tissue levels of VEGF-C are associated with a worse prognosis due to increased tumour lymphatic vessel density that correlates with lymph node metastasis in HNSCC.[28]

Carcinoma-associated fibroblasts are the major cell population in the tumour stroma.[2, 29] Within the TME, there is evidence suggesting that CAF use protease and mechanical remodelling of the extracellular membrane to lay tracks along which HNSCC tumour cells invade.[30] When compared with normal oral cavity fibroblasts, CAF were found to exhibit rapid growth, increased proliferation and viability and produce α-smooth muscle actin (α-SMA) and membrane metalloproteinase 2 (MMP-2), which represent markers of chronic inflammation that normal tissue fibroblasts do not produce.[31]

Cytokines and chemokines in TME

Cytokines are small molecular weight molecules that regulate all aspects of the immune response (e.g. inflammation, immunity and haematopoiesis). This group of molecules is divided into subfamilies according to their structure or function and includes: interleukins (IL), interferons (IFN), cytokines, tumour necrosis factors (TNF) and other cell-specific growth factors.[7] Chemokines are a superfamily of small proteins with chemoattractant and activation properties for different cell types involved in inflammatory reactions and are considered the main facilitators of cell trafficking.[32] Cytokines and chemokines are key in controlling communication within and between individual cells in the TME.

Tumours produce cytokines in a dysregulated manner that contributes to an ineffective host immune response.[33–34] One such cytokine is tumour growth factor beta (TGF-β), which acts broadly to suppress cell-mediated immunity and is released by tumour cells and Treg cells conferring inhibitory action.[35] Further observations in HNSCC, as well as in many other cancers, have shown that tumour development can significantly alter serum levels of key Th1 and Th2 type cytokines in the body. Commonly there appears to be an imbalance, towards a Th2 cell cytokine profile that becomes more pronounced at later stages of tumour growth.[36–37] The Th2 cell profile is characterized by the production of IL-4, IL-5, IL-6, IL-10, IL-13 and granulocyte-macrophage colony stimulating factor (GM-CSF) whilst Th1 responses are characterized by the production of interferon gamma (IFN-γ), IL-2, IL-12 and IL-18. Some of the Th2 cell cytokines, particularly IL-10, have been clearly shown to suppress the cellular immune response effectively, thus permitting tumour growth.[38]

Immune suppressive cytokines, whether produced by tumour cells or by stromal cells, seem to control the cross-talk between cells within the TME during tumour progression (**Figure 16.1**). Furthermore the release of such cytokines induces ECM remodelling, basement membrane degradation, tumour cell proliferation and angiogenesis, and hence favours tumour progression and metastasis. In studies on HNSCC cell lines, fibroblasts and stromal endothelial cells have been shown to express a suppressive cytokine/chemokine milieu when co-cultured with HNSCC cells.[39] CAF showed an increase in the expression of a number of pro-inflammatory cytokines and chemokines including CCL7, CXCL1, CXCL2, CXCL3 and CXCL8 when compared with CAF cultured alone.[40] Similarly, type I collagen was found to markedly stimulate immune-suppressive cytokine expression such as IL-1α, IL-1β, IL-6, TNF-α, TGF-β and MMP-2 in metastatic HNSCC cell lines compared with that of the primary cancer cell lines.[41]

Chemokines co-ordinate the trafficking, migration and organization of cells to various tissue compartments.[42–43] Thus understanding alterations in chemokine levels within HNSCC is likely to offer useful prognostic information. Initial work by Muller and colleagues demonstrated that upregulation and activation of CXCR4 and CCR7, facilitate leukocyte migration to regional lymph nodes; in breast cancer this is capable of inducing actin polymerization, migration and invasion both *in vitro* and *in vivo* studies.[44] Upregulation of CXCR4 and CCR7 expression has been observed in tumour tissue and lymph nodes of HNSCC patients.[45–48] Overexpression of CXCR4 was shown to be a significant prognostic indicator for poor survival in patients with oral squamous cell carcinoma[46] while upregulation of CCR7 was also found to correlate with poorer survival in patients with HNSCC.[49] Furthermore, it was reported that hypoxia, a major stimulator of tumour progression, enhances CXCR4 expression by activating hypoxia inducible factor 1 alpha (HIF-1α) in tissue from oral squamous cell carcinoma patients.[50]

A recent systematic review of cytokine/chemokine profiles and their clinical significance in various cancers has shown that, despite tumour heterogeneity, patients with advanced-stage cancer seem to experience a simultaneous immune-stimulation and immune-suppression, with increased concentrations of cytokines Macrophage Inhibitory Factor (MIF), TNF-α, IL-18, IL-8, IL-6, TGF-β, and IL-10. The result of the described cytokine pattern is local immunostimulation and inflammation with

synchronous functional immune-suppression and attraction of immune cells that are then tolerized, thus protecting tumour cells locally from detection and destruction. The review concluded that, independent of tumour histological changes, the immune-suppressive cytokine cascade links the functional status of the immune system with the extent of cancer disease and patients prognosis and ultimately is an expression of the systemic disease in cancer.[51]

Inflammation in TME

A chronic inflammatory environment is associated with neoplastic transformation and progression in many malignancies including HNSCC.[52–54] Oncogenes that are activated early in the development of tumours can incite strong inflammatory responses. For example, lung tumours that are initiated by a mutation in the K-ras oncogene produce chemokines that attract immune cells to the TME;[55] or the *RET*–PTC protein, that causes constitutive activation of the RET tyrosine kinase domains in thyroid tumours, modulates nuclear factor-κB, a transcription factor that controls the production of immune-regulatory cytokines. The *RET*–PTC protein increases the production of GM-CSF and monocyte chemotactic protein 1, that contribute to a pro-inflammatory microenvironment.[56] Products of dying tumour cells (e.g. heat-shock proteins and monosodium urate) are some of the many inflammatory substances that further exacerbate immune responses in a relatively non-specific manner.[57]

The pro-inflammatory conditions within the TME have also been shown to contribute to tumour progression, proliferation and metastasis. Cyclooxygenase (COX)-2 and 5-lipoxygenase (5-LOX) pathways, which both produce derivatives from arachidonic acid, are activated during HNSCC development.[58] The COX-2 enzymes specifically catalyze the production of prostaglandins (PG). PG are increased in HNSCC (e.g. raised PGE2 in HNSCC is known to promote tumour growth and inhibit apoptosis by upregulating Bcl-2 expression). PGE2 is also known to increase the production of angiogenic factors such as VEGF and MMP, resulting in the promotion of invasion and tumour metastasis. Higher expression of COX-2 in tumour cells is seen in parallel with an increased PGE2 expression in HNSCC.[59–60]

TUMOUR ESCAPE MECHANISMS

In order for the immune system to identify and eliminate tumours, it needs to recognize the malignant growth in some way. Some antigens are solely presented by tumour cells and never by normal cells, thus are called tumour-specific antigens (TSA); for example, MAGE-1, a melanoma-specific antigen,[61] or NY-ESO-1 antigen, a molecule that belongs to a family of cancer–testis antigens.[62] Other antigens are presented by tumour cells but at raised levels when compared with normal cells; these are termed tumour-associated antigens (TAA).[63] Examples of TAA in HNSCC include the epidermal growth factor receptor (EGFR)[64] and wild-type p53.[65] Tumours associated with viral infection display viral antigens that can serve as tumour markers. Good examples are the products of the E6 and E7 genes of the human papilloma virus, the causative agent of both cervical[66–67] and oropharyngeal carcinoma,[68] and EBNA-1, the Epstein–Barr virus nuclear antigen expressed by Burkitt's lymphoma and nasopharyngeal carcinoma cells.[69]

The discovery and identification of tumour antigens has helped scientists begin to understand the key steps in an anti-tumour immune response. In animal models, the encounter between the immune system and tumours initiates a process termed 'immunoediting'.[70] This process can bring about three outcomes: elimination of the tumour; tumour equilibrium, in which there is immune selection of less immunogenic tumours during an anti-tumour immune response;[71] and tumour escape, the growth of tumour variants that resist immune destruction.

Tumour escape mechanisms have been broadly divided into two main groups. Either the tumour cells are poor stimulators of immune cells and hence are simply not recognized, and/or they actively interfere with immune function and survival of the immune cells.[72–73] Tumour-escape from immune-surveillance in HNSCC is due to a combination of multiple mechanisms involving tumour cells, cytokines and immune cells (**Table 16.1**). The most common mechanism is the loss of MHC class 1 molecules that reduces/prevents TAA expression, which, coupled with deficient antigen-presenting and processing mechanisms by immature dendritic cells and overexpression of Treg cell, all contribute to avoidance of the immune system. Major regulators behind dysregulated cytokine and chemokine function include imbalanced STAT1/STAT3 signalling within tumour cells,[74] hepatocyte growth factor (HGF) production by tumour-associated fibroblasts,[75, 76] and production of immunosuppressive molecules by TAM such as VEGF, IL-10 and TGF-β.[77, 78] Finally, effector cell dysfunction allows tumour escape through an increased level of spontaneous apoptosis and anergy, as well as signalling defects in the T cell receptor signalling complex (**Table 16.1**).

TABLE 16.1 Immune-suppressive tumour-escape mechanisms in HNSCC

• Spontaneous apoptosis/anergy of tumour infiltrating and circulatory T cells[10, 105, 106]
• Imbalanced and decreased absolute counts of T cell subsets[107, 108]
• Signalling defects in effector cells[109, 110]
• Cytokine imbalance favouring immunosuppression[51, 111, 112]
• Poor expression of co-stimulatory molecules and high expression of co-inhibitory receptors on tumour cells[106, 113, 114]
• Deficient antigen-presenting and processing mechanisms[115–117]
• Loss of HLA class I molecules by HNSCC cells[118, 119]
• Inhibition of NK cell activity[73, 120, 121]
• Overexpression of Treg cells both in the circulation and intra-tumourally[6, 122]

HLA: human leukocyte antigen; NK cells: natural killer cells; Treg cells: regulatory T cells; HNSCC: Head and neck squamous cell carcinoma.

TUMOUR BIOMARKERS

As our knowledge of the anti-tumour response increases the idea of using biomarkers as surrogate endpoints of clinical response is becoming a reality.[2]

Tumour biomarkers can be divided into either disease-related ones (i.e. at the time of diagnosis prior to any therapy) or therapy-related ones (i.e. prior to, during and after therapy).[79]

Seminal work in colorectal cancer (CRC) by Golan and colleagues,[80–83] reporting on TIL using modern techniques of systems biology, and an objective scoring system based on image analysis data, showed that the type, density and location of immune cells within tumours predicted clinical outcome. T cell infiltrates emerged as the strongest independent prognostic factor, more significant than the conventional clinicopathological criteria such as tumour size, depth of infiltration, differentiation, or the nodal status. Based on these results, a proposal has been drafted for a routine evaluation of the tumour microenvironment for the density, location, phenotype and function of T cells in order to define an 'immune score' for each tumour as a part of the standard pathological examination. Although not yet incorporated in routine pathological practice, this approach represents the first serious immunological marker of risk in cancer with a potential to be incorporated into prognostically relevant immune classification of human CRC equal to or better than the conventional TNM classification.[81] In HNSCC, the value of tumour-infiltrating CD4+ T cell subpopulations is under evaluation as a prognostic marker; however, this too has not yet been incorporated into clinical practice.[84–85]

One of the other validated biomarkers is the B cell signature, which has emerged as the most robust prognostic factor in breast cancer.[86–87] A multicentred trial has identified the immunoglobulin G kappa chain (IgGκC) as an immunological biomarker of prognosis and response to chemotherapy breast cancer, ovarian cancer, non-small cell lung cancer, and CRC. The IgGκC was microscopically identified as a product of plasma cells present in the tumour stroma and was validated as a prognostic biomarker by RNA and protein-based expression studies independently performed in thousands of formalin-fixed, paraffin-embedded specimens at 20 different centres.[87] However, the most important finding was that IgGκC predicted responses to neo-adjuvant therapy in breast cancer and thus qualifies it as the first immune marker of response to cancer treatment. Supporting the key role of the B cell signature in HNSCC is a study by Pretscher et al. where intra-tumoural CD20+ B cells were significantly more frequent in metastatic lesions than in primary tumours when 193 tissue cores from 33 patients were examined. Further, large numbers of peri-tumoural B cells together with increased numbers of intra-epithelial CD8+ T cells in metastatic tumours were associated with favourable outcome in patients with oro- and hypopharyngeal carcinoma.[88]

Recent evidence has suggested that the total white blood count and especially the elevated neutrophil count compared with a depressed lymphocyte count (i.e. high neutrophil-to-lymphocyte ratio (NLR)) measured prior to oncological therapies predicts adverse clinical outcome in patients with lung, breast, renal, ovarian and HNSCC. Further, high NLR was found to be a significant but not yet validated marker of poor response to chemotherapy in these cancers.[89] These observations are in agreement with previous studies that reported low lymphocyte counts in patients with HNSCC, for example spontaneous apoptosis of circulating CD8+ antigen-responding effector T cells, leading to rapid lymphocyte turnover and depressed absolute numbers of T cell subsets tested prior to any form of treatment, have been reported.[4]

Multiple other biomarkers have been identified in various cancers including HNSCC, but are not yet validated. Examples include the frequency and function of circulating Treg cells,[13, 90] markers of CD8+ T cell apoptosis such as Fas L+ microvesicles and their immunosuppressive cytokines PDL-1 &TGF-β,[91] the frequency of circulating CD8+ CCR7+ cells,[92] and the functional status of tumour peptide-specific CD8+ T cells.[93] A recent review summarizes the biomarkers measured by immunohistochemistry in the different anatomical subgroups of HNSCC and their clinical relevance;[94] as yet no marker is sufficiently robust to become a routine test in HNSCC.

IMMUNOTHERAPY

Early clinical trials of immunotherapy in the majority of cancers were troubled by systemic toxicity or difficulties in local administration. Now, interest in immunotherapy has been revitalized by mechanistic insights into immune evasion, coupled to ongoing developments of novel immunotherapies.[95]

Any form of immune-based therapy must overcome the main factors hindering an effective immune response; a representative selection of ongoing trials is detailed in **Table 16.2**. Multiple components of the immune system, such as immunization with tumour antigens, cytokines and T cells, have all been studied in multiple immune-based therapies. The aim of these therapies is to cause the tumour to be targeted in a specific fashion by the host immune defences.

Immune-based therapies are classified according to their target cell or molecule. Targeting specific elements of the immune system such as tumour antigens with antibodies and therapeutic cancer vaccines have all shown promising results.[96] Some of the most promising immune-based therapies involve the administration of monoclonal antibodies against tumour antigens (e.g. Trastuzumab, an antibody against the HER2 receptor expressed on 15–25% of breast cancers;[97] rituximab that binds CD20 expressed on 90% of Non-Hodgkin B-cell lymphomas;[97] or cetuximab, that binds to EGFR that is upregulated in HNSCC, lung and colorectal cancer);[98–100] these have all been shown to be clinically effective and are already incorporated into mainstream treatment modalities.

TABLE 16.2 Key areas and promising immunotherapies in HNSCC

Key area	Example of drug mechanisms	Phase of development
TA-specific monoclonal antibodies	**Cetuximab**: Anti-EGFR chimeric IgG1 mAb[98] blocks growth factor signalling	NICE and FDA approved
	Nimotuzumab: Anti-EGFR IgG1 humanized mAb[123] blocks growth factor signalling	II
Targeting cytokines	**IL 12**: Cytokine agonist causes NK cell activation[95]	II
	Bevacizumab: Anti-VEGF IgG1 humanized mAb[123] a drug that inhibits angiogenesis	III
	IRX-2: various cytokines including IL-1b, IL-2, IL-6, IL-8, GM-CSF, IFNγ and TNFα, to enhance anti-tumour immune responses[125]	I/II
Targeting T cell checkpoint inhibitors	**Ipilimumab**: Anti-CTLA4 IgG1 humanized mAb[95] that prevents co-stimulatory signals	I
Therapeutic cancer vaccines	**MAGE-3 and HPV-16 vaccine**: Trojan construct peptide vaccine[126]	I
	HPV pNGVL4a-CRT/E7 (Detox) DNA vaccine: Detoxified E7 DNA in a pNGVL4a plasmid backbone[127]	I
	Multi-epitope p53 vaccine: Wild type peptide/autologous dendritic cell vaccine[95]	I

Examples of key areas during anti-tumour immune responses, where immunotherapeutic agents are being utilized and trialled. TA: tumour associated; EGFR: epidermal growth factor receptor; IgG: immunoglobulin G; mAb: monoclonal antibody; IL: interleukin; NK cells: natural killer cells; VEGF: vascular endothelial growth factor; GM-CSF: granulocyte macrophage-colony stimulating factor; IFNγ: interferon gamma; TNFα: tumour necrosis factor alpha; CTLA4: cytotoxic T-lymphocyte antigen 4; MAGE-3: melanoma-associated antigen-3; HPV: human papilloma virus. (For a current list of immunotherapy-based trials, please refer to clinicaltrials.gov.)

Several mechanisms are developed by cancerous cells to escape the immune system such as a loss or a reduction of the expression of MHC class 1 molecules and co-stimulatory molecules, the expression of FasL to induce apoptosis of tumour-infiltrating lymphocytes and the production of immunosuppressive molecules such as TGF-β, PGE2,IL-6, IL-10 and adenosine. Among the subpopulations of naïve CD4+ T cells, CD4+ Th17 T cells promote inflammation by secreting IL-17 whereas CD4+ Th2 T cells promote antibody production by B cells. Tregs promote tumour progression by inhibiting the functions of CD4+ and CD8+ T cells and NK cells. TAMsM2 phenotype induce the expression of CD4+ Th2 T cell and Tregs. Moreover, M2 phenotype promotes growth tumour (EGF, PDGF, TGF-β, IL-6, IL-1 and TNF-α), angiogenesis (TGF-β, VEGF, GM-CSF, TGF-α, IL-1, IL-6 and IL-8), invasion (MMPs, TNF-α, IL-1), immunosuppression (TGF-β, PGE2 and IL-10) and metastasis. MDSCs induce Treg cells, secrete IL-10, and inhibit CD4+ and CD8+ T cells. (Adapted from Duray et al.[128])

Seminal work by Bonner et al. reported that the administration of cetuximab with radiotherapy, when compared to radiotherapy alone, has significantly prolonged progression free survival without increasing the common toxic effects associated with radiotherapy to the head and neck in a multicentred phase III clinical trial.[98] So far, cetuximab is the only approved antibody by FDA and NICE for use in patients with locally advanced HNSCC. In addition, a variety of other anti-EGFR agents such as the small molecule tyrosine kinase inhibitors (TKI) lapatinib, dacomitinib and afatinib and the anti-EGFR mAbzalutumumab, nimotuzumab and panitumumab, are currently under investigation in phase II and III clinical trials in different HNSCC therapeutic settings. The EGFR-targeting TKI erlotinib is currently in phase III development for oral cancer prevention (NLM Identifer NCT00402779), while bevacizumab, an anti VEGF monoclonal antibody, has been shown to produce favourable efficacy when combined with chemoradiotherapy for locally advanced HNSCC.[101] Numerous other biological agents are in early stages of development for HNSCC treatment, including novel anti-EGFR mAb such as necitumumab, small-molecule TKIs (vandetanib, icotinib and dasatinib), and drugs (temsirolimus and everolimus). Overall, a wealth of clinical trial data are expected in the coming years, with the potential to modify significantly the approach to anti-EGFR therapy for HNSCC.[102]

The key areas for targeting the immune system through immune-based therapies with promising results in HNSCC are summarized in **Table 16.2**. It is worth noting that in HNSCC the degree of immune-suppressive cross-talk suggests that single immunotherapies will be inadequate. Thus, integration of immune therapies with standard treatments for cancer is seen as the best avenue and revealing promising results.[95]

CONCLUSIONS

It is evident now that cancer creates an immunosuppressive environment locally and systemically. This tumour microenvironment interferes with maturation and activation of antigen-presenting cells and naïve cytotoxic T cells,[103] hence creating immune-suppressive conditions that favour tumour proliferation and progression. As our understanding of the TME grows, specific key areas and immune end points can be explored with the ultimate goal that they may act as potential targets for tumour detection, prognosis and ultimately therapy.

In HNSCC, several reports have shown that immune cells within the peripheral circulation, associated lymph nodes and tumour tissue are responsible for supressing effective CD8+ anti-tumour responses and are associated with poorer prognosis in patients. Such cells include CD4+ Th2 cells, TD4+ Treg cells, TAM and CAF. Products of these cells in the form of cytokines and chemokines have also been linked to immune suppression and poor prognosis in HNSCC patients, for example IL-10, TGF-β, CXCR4 and CCR7.

Most tumour biomarkers, whether reflecting cancer presence, progression or response to therapy, have a potential to serve as intermediate biomarkers of outcome.

However only a few, including T-cell and B-cell immune signatures or the NLR, have been validated in independent clinical studies encompassing sufficiently large cohorts of patients with different tumour types to give statistically valid data. In HNSCC, a histopathological 'immune score' of TIL as a robust clinical prognostic marker is under evaluation based on work in colorectal cancer that has been reported recently. HPV p16 status in HPV-associated head and neck tumours is the only validated biomarker in HNSCC to date. Treatment protocols of HNSCC, especially oropharyngeal tumours, have now fully incorporated HPV p16 status in their guidelines.[104]

Precise clinicopathological analysis and clinical follow-up in well-defined, relatively uniform cohorts of patients in each subunit of the head and neck offers the best option for confirming immune endpoints as biomarkers of outcome. This is particularly important in tumours of the head and neck as multiple anatomical subsites with different molecular biology and immune reactions are usually studied and reported together. This point has clearly been shown to be relevant in oropharyngeal tumours, and more precisely tonsillar and tongue base tumours that are HPV related, and nasopharyngeal tumours that are EBV related.[104] Much work remains to confirm the reliable association of immune biomarkers with clinical endpoints and to validate each of these potentially promising biomarkers in a series of prospective clinical trials appropriately powered to determine effects on each head and neck subsite.

Much has been learned about the potential of the immune system to control cancer and the various ways that immunotherapy can boost the potential of the immune system for the benefit of the patient. This knowledge has stimulated the invention of many new therapeutic antibodies, cell-based treatments, and vaccines, which are starting to be used in clinical practice, either alone or in various combinations. Cetuximab, the only immune-based therapy incorporated in the treatment of advanced HNSCC so far, has paved the way for a wealth of ongoing and future trials exploring multiple agents in key areas during tumour progression and spread. Future immune-based therapies in HNSCC specifically, and solid tumours generally, are expected to result in improved cancer treatment.

KEY POINTS

- The tumour microenvironment strongly influences tumour development and outcome through a combination of cell activities; Tumour Associated Macrophages and Treg cell populations appear to play prominent roles.
- Currently, no biomarkers have been identified which possess prognostic or diagnostic value above TMN classification, but it is likely that tumour subtype-specific molecules will be identified in the future.
- The number of trials involving immunotherapies in HNSCC continues to increase; the use of novel checkpoint inhibitors has shown positive preliminary data.

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CHAPTER 17

HUMAN PAPILLOMAVIRUS

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed searches using keywords related to human papillomavirus, molecular biology, cancer pathogenesis and epidemiology.

INTRODUCTION

In recent years there has been increasing evidence related to head and neck cancer pathogenesis and viral infections, particularly human papillomavirus (HPV). In 1907 Giuseppe Ciuffo was able to demonstrate the viral origin of common warts, with the potential for human–human transmission.[1] Subsequently in 1976 Harald zur Hausen was the first to suggest a link between HPV infection and cervical cancers,[2] with HPV now considered a sexually transmitted disease. Our current knowledge of HPV and disease pathogenesis is based mainly on cervical cancer models. This chapter will review the molecular biology of HPV and related cancer pathogenesis.

HPV belongs to the papovaviridae family of viruses, which also includes the polymaviruses. The HPV virion is composed of an 8 kb double-stranded DNA genome contained within a protein capsid, and forms a non-enveloped icosahedral structure measuring 55 nm in diameter. The virus only infects epidermal cells, such as skin or mucosa.

HPV GENOTYPES

To date, more than 120 HPV types have been identified.[3] These can be divided into mucosal or cutaneous genotypes, with approximately one-third causing mucosal infections. Furthermore the HPV types can be classified into low- or high-risk, depending upon their malignant potential. Low-risk HPV includes types 6 and 11, which are traditionally associated with genital warts but are also related to laryngeal papillomatosis. The high-risk HPV types 16 and 18 have been implicated in head and neck squamous cell carcinomas (HNSCC), such as laryngeal and oropharyngeal cancers. Reported HPV prevalence in HNSCC varies between studies, and is dependent on anatomical subsite. For example, the RTOG 0129 randomized controlled study reported 63.8% HPV prevalence among patients diagnosed with oropharyngeal cancer, of whom 96% were HPV 16 positive.[4]

HPV GENOME AND PROTEINS

The HPV genome is composed of approximately 8000 base pairs coding for eight main viral genes, which are subdivided into early and late gene products (**Figure 17.1**). The LCR (long control region) contains *cis*-regulatory elements, which control and regulate viral DNA replication. The functions of the early and late genes are summarized in **Table 17.1**. The key viral proteins involved in cancer pathogenesis are E6 and E7.

HPV LIFE CYCLE

Transmission

HPV is transmitted between individuals by direct contact of skin or mucosa. While HPV can be considered a sexually transmitted disease this is by no means the only mode of transmission. Studies have demonstrated HPV infection in children, which is likely caused by vertical transmission from the mother during birth. Indeed there is evidence that risk of HPV transmission from mother to infant is

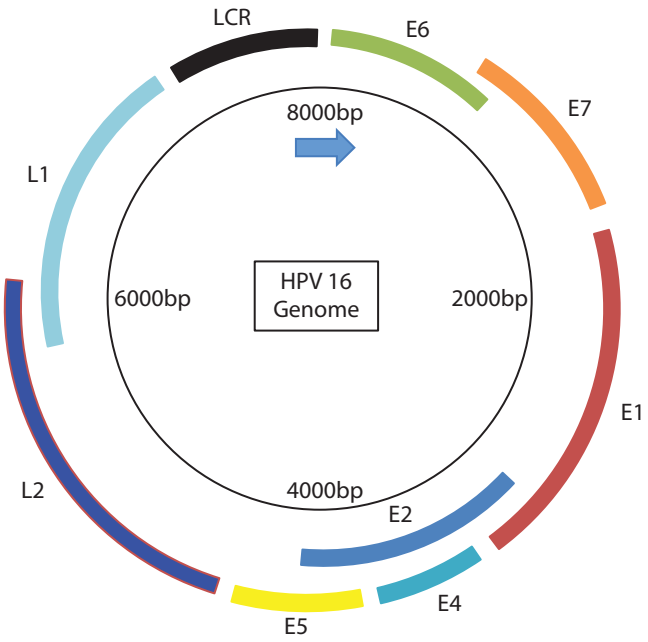


Figure 17.1 Schematic diagram of the HPV 16 genome.

TABLE 17.1 HPV gene products and functions[5,6]

Viral protein	Functions
E1	Initiates viral DNA replication via ATP-dependent helicase activity
E2	Combined activity with E1 to initiate viral replication Regulates viral transcription Suppresses E6 and E7 activity
E4	Disrupts host cell keratin structure Supports viral amplification and maturation
E5	Enhances E6 and E7 activity Role in evading host immune response
E6	Binds to p53 and causes its degradation by proteolysis, leading to inhibition of apoptosis
E7	Binds to and inactivates pRb, causing loss of cell cycle regulation
L1	Major capsid protein
L2	Minor capsid protein

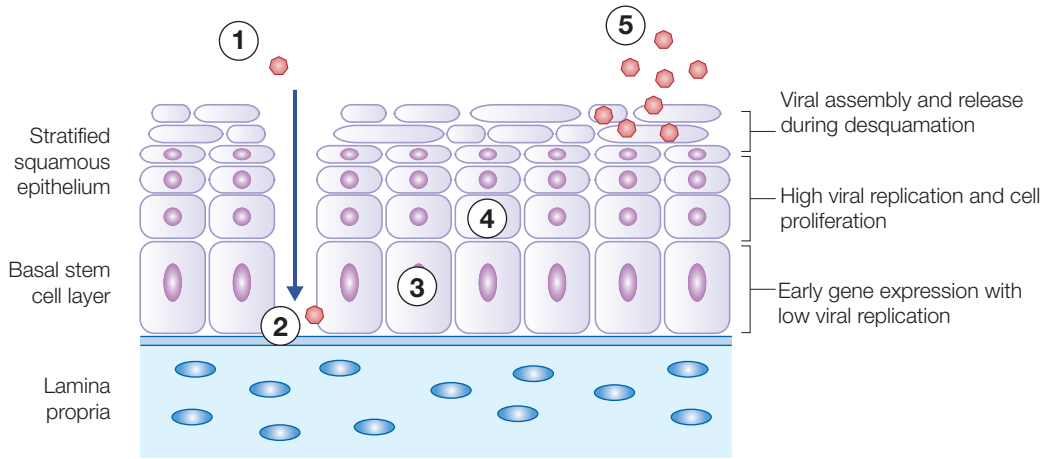


Figure 17.2 Life cycle of HPV. 1) HPV gains access to basal stem cells through areas of micro-trauma in the epithelial cell layer, 2) Entry into basal cells via endocytosis, 3) Maintenance phase with low viral replication, 4) Differentiation-dependent phase with high viral replication, 5) Complete HPV particles are released during normal epithelial desquamation.

reduced in caesarean sections.[7] Transmission may also occur by autoinoculation or indirectly via fomites.[8] The HPV particles are shed by the outermost epithelial layer of skin or mucosa, and are highly infectious. The life cycle of HPV (Figure 17.2) is ideally adapted to the host cell cycle, ensuring evasion from the immune system.

Epithelial exposure

The HPV particle has a tropism to epithelial surfaces but must first acquire access to the dividing basal stem cell layer. This can occur via micro-trauma to the epithelial layer, for example during sexual contact. As the normal host cell response to injury is recruitment of dividing epithelial cells, this enhances the infectious ability of the virus.[9] However, the exact mechanism of establishing HPV infection is not clearly understood, particularly in head and neck sites.

Attachment and entry

In order to gain access into the basal stem cells the virus requires attachment to surface receptors, the L1 and L2 viral capsid proteins are believed to be involved in this process. Initially the L1 capsid protein binds to exposed heparin sulfate proteoglycans and causes a conformational change leading to cleavage of L2 capsid protein by furin.[10] Further interaction with host cell receptors occurs, with α6 integrin proposed as one of the main target receptors.

Entry into the host cells then occurs via endocytosis utilizing various pathways. These include clathrin-mediated and caveloar endocytosis.[10–11] Once internalized the viral particle migrates to the host cell nucleus. The incubation period of the virus can last for weeks, months or even years after initial exposure.

Replication

The replication stage can be subdivided into the maintenance and differentiation-dependent phases.[12] The HPV particle utilizes the host cellular mechanisms to initiate DNA replication within the host cell nucleus and cause persisting infection. During the maintenance phase there are a low number of episomal viral copies produced within the basal stem cells, between 50–100 copies per cell.[13] The E1 and E2 viral proteins function together to maintain viral DNA replication. Dividing stem cells produce daughter cells that either remain within the basal layer or move towards the suprabasal layer. The low number of viral copies within the basal layer ensures evasion from the host immunity. Within the suprabasal layer the cells begin to differentiate, with E6 and E7 viral proteins encouraging further cell proliferation. Cells moving into the suprabasal layer lose their ability to divide and therefore undergo terminal differentiation, with HPV replication entering the differentiation-dependent phase. Activation of late viral promoters during this phase causes a dramatic increase in viral copies to several thousand per cell.[14] The E1, E4 and E5 viral proteins function to support viral amplification and maturation at this stage. While E6 and E7 function to promote cell proliferation the E2 viral protein suppresses their activity to allow cell differentiation and completion of the HPV life cycle. The delayed expression of large viral numbers within terminally differentiated cells prevents an immune reaction and ensures long-term persistence of the virus.

Shedding

Expression of L1 and L2 capsid proteins is the final step prior to release of the viral particles from the host cells. Maturation of HPV occurs in the most superficial layer of the epithelium. Release of complete viral particles occurs during normal epithelial shedding. Unlike other viruses, which lyse the host cells for viral release, the papillomavirus has adapted to utilize the normal epithelial cell cycle. Release of viral particles by this method prevents host cell immune recognition and ensures no abnormal inflammatory response.[12]

Persistence and clearance

Following initial infection the majority of individuals will clear the virus, although the period of active infection is unknown in head and neck sites. Cell-mediated immune response and activation of Langerhans cells play a role in viral clearance from the host cells.[13] However, considering the life cycle of HPV, undetectable infection may persist for an extended period with possible reactivation. Several factors, such as host cell immune status and hormonal levels, are likely to contribute to persistence and future reactivation.

HPV AND CANCER

Pathogenesis

Infection with HPV, particularly high-risk types, increases the risk of developing cancer. Failure to clear the virus is likely to result in unregulated cell proliferation, accumulation of mutations and cancer formation. While the various HPV proteins contribute to viral replication, the E6 and E7 viral oncoproteins are critical in malignant transformation (**Figure 17.3**). Working together they can lead to epithelial cell immortalization. E6 binds to p53 and promotes its degradation via ubiquitin-dependent protease pathways.[15] The wild-type p53 is normally activated by DNA damage or cellular stress, and acts as a tumour suppressor. P53 functions include modulation of cell cycle, regulation of apoptosis and cell senescence.[16] E6 also activates the hTERT promoter to induce telomerase activity, which also leads to cell immortalization.[17]

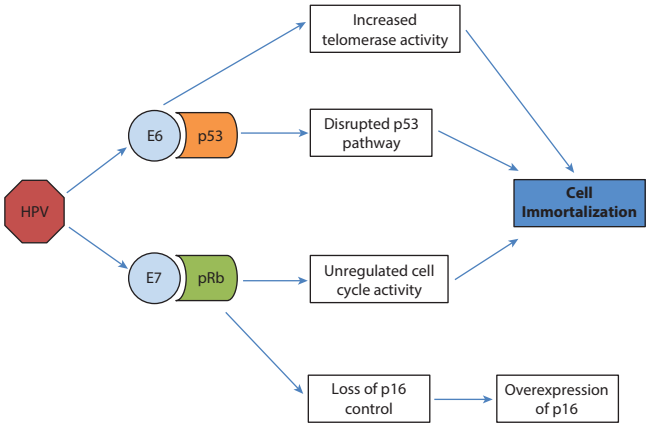


Figure 17.3 Illustration of HPV E6 and E7 interactions with host cell pathways.

The E7 viral protein binds to and inactivates pRb (retinoblastoma protein). The pRb is also an important tumour suppressor. The normal function of pRb is to block cell cycle progression by binding to E2F transcription factor and therefore blocking progression from G1 to S-phase.[18] Disruption of pRb-E2F complex therefore leads to unregulated cell cycle entry into S-phase causing increased cell proliferation. Interestingly unregulated S-phase activity would normally cause apoptosis via the p53 pathway. However, suppression of p53 activity by E6 interrupts this pathway and prevents cell death. Consequently immortalized cells lose the ability to repair DNA damage and therefore accumulate mutations and chromosomal instability. This can eventually lead to cancer formation.

During the complex interactions between E6 and E7 and the host cell pathways numerous cellular proteins can be disrupted, including p16. The p16 gene was first discovered in 1993 and codes for a cyclin-dependent kinase (CDK) inhibitor.[19] The CDK family plays an important role in cell cycle control. The p16 protein acts to prevent G1 to S-phase cell cycle progression, and also interacts with the pRb pathway.[20] The pRb function varies according to its phosphorylated state, which is controlled by the cyclin D-CDK4/6 complex. The p16 protein inhibits CDK4/6 and prevents phosphorylation of pRb. Hypo-phosphorylated pRb binds to and inactivates E2F transcription factors, leading to cell cycle



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arrest as described. Activity of p16 is controlled by functional pRb via a negative feedback mechanism.[21] Considering the effect of E6 on pRb function, an overexpression of p16 is expected in HPV active infections.

Epidemiology and risk factors

Among the head and neck cancers there appears to be a significant increase in the incidence of oropharyngeal cancer (OPC). In a large retrospective study examining incidence rates of OPC within 23 countries between 1983 and 2002, increasing incidence was observed mainly in developed countries such USA, UK and France.[22] In England the incidence rate of OPC more than doubled between 1990 and 2006,[23] with similar trends observed in Sweden and Scotland.[24–25]

Traditional risk factors of HNSCC include smoking and alcohol. However, increasing evidence has implicated HPV in cancer pathogenesis. The majority of HPV-related head and neck cancers occur within the oropharynx. In one systematic review there was a 26% overall prevalence of HPV infection within HNSCC cases, with the greatest proportion in the oropharyngeal cohort with a prevalence of 36%.[26] Other studies have also shown a strong association between HPV positivity and the oropharynx.[27] Recent evidence also appears to show prevalence of HPV infection in oropharyngeal cancer is increasing, whilst prevalence in non-oropharyngeal sites has remained static.[28]

Recently a geographic variation in prevalence has been demonstrated, with high prevalence in oropharyngeal cancers demonstrated in Western Europe (37%) compared with Eastern Europe (6%) and Asia (2%).[29] The increasing prevalence of HPV-related cancers can be attributed to changes in sexual practices. Risk factors for high-risk HPV infection in oropharyngeal cancer include younger age group (< 55 years), higher number of sexual partners, early sexual contact, oral-genital and oral-anal sex.[30–31]

Prognostic markers

There has been increasing interest in the role of HPV in HNSCC and the prognostic significance of HPV-related tumours. Various studies have correlated improved overall survival and disease-specific survival in HPV positive cancers.[27, 32, 33] In a retrospective study of the RTOG 0129 data, 3-year overall survival was 82.4% in HPV positive OPC cases compared to 57.1% in HPV negative cases.[4] Further analysis of the data showed HPV status was the most important determinant of survival, followed by number of smoking pack years. Recently a number of systematic reviews and meta-analyses have confirmed the improved prognostic outcomes in HPV positive HNSCC.[34–36]

Other prognostic markers proposed for HPV infection include p16 overexpression. The use of p16 testing as a surrogate marker for HPV-related OPC is now commonplace.[37] Overexpression of p16 is considered an independent prognostic marker, with improved overall survival and disease-free survival.[38]

Diagnosis

HPV detection can involve several methods including direct and indirect assays. Direct methods include polymerase chain reaction (PCR), in-situ hybridization (ISH), Southern blot analysis and HPV antibody detection. The common detection methods included PCR and ISH. The PCR assay is highly sensitive but not specific, requiring only a low level of viral DNA. However, traditional PCR is time and resource intensive and is unable to distinguish between episomal and integrated HPV infection.

In contrast to PCR, the ISH assay is highly specific but not sensitive. An estimated 10 viral copies per cell are required for a positive reaction.[39] The advantages of ISH are the ability to differentiate between episomal and integrated HPV infection, and it can be a fully automated process.

Indirect HPV testing includes p16 detection, which utilizes monoclonal antibodies against p16. Staining patterns and cut-off values vary between studies and are observer-dependent. HPV testing algorithms incorporating these various methods have been proposed.[40]

FUTURE RESEARCH

- Current knowledge of HPV infection and cancer pathogenesis is based on cervical cancer studies. Further studies are required to determine the exact life cycle and natural history of HPV in head and neck sites.
- Initial infection mechanisms in the upper aerodigestive tract remain unknown.
- Receptors involved in HPV epithelial cell attachment and exact cell entry pathways are yet to be identified.
- Further studies are needed to determine the incubation and latency period of HPV infection in head and neck sites.
- Epidemiological studies into incidence and prevalence rates of HPV infection in the healthy population are required.
- Exact mechanisms of malignant transformation are yet to be elucidated.
- The interaction between host immune system and HPV is not fully understood, particularly the reasons why infection can persist in some individuals.
- Accurate biomarkers are required to determine a causal link between HPV infection and cancer pathogenesis. Ideal assays should be highly sensitive, specific and cost effective.
- The best methods of HPV detection have not been determined, particularly a consensus on accurate p16 testing among researchers.
- Models of risk stratification based on HPV status can have the potential for personalized prognosis and treatments.

KEY POINTS

- The HPV virion is a small, non-enveloped virus composed of an 8 kb double-stranded DNA contained within a protein capsid.
- HPV only infects skin or mucosal epidermal cells.
- Human papillomavirus is considered a sexually-transmitted disease, although transmission can occur by other methods such as vertical transmission between mother and infant.
- More than 120 HPV types have been described and divided into low-risk (e.g. 6 and 11) and high-risk (e.g. 16 and 18).
- The majority of HPV positive oropharyngeal cancers are caused by HPV 16.
- HPV proteins are classified into early and late gene products.
- E6 binds and degrades p53, E7 binds and inactivates pRb. Both E6 and E7 contribute to cell immortalization.
- Persisting HPV infection is likely to cause accumulated mutations and chromosomal instability, leading to cancer pathogenesis.
- p16 overexpression occurs via pRb inactivation, and is considered a surrogate marker of HPV infection.
- Recent evidence suggests improved prognosis for HPV positive HNSCC, particularly oropharyngeal cancer.
- Risk factors for HPV-related OPC include younger age group, increased sexual partners and oral-related sex.

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CHAPTER 18

CONNECTIVE TISSUE DISEASES: ENT COMPLICATIONS

Eileen Baildam

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: ENT complications of autoimmune rheumatic disease, rheumatoid arthritis, spondylarthropathy, sarcoidosis, SLE, Sjögren's syndrome, juvenile idiopathic arthritis, scleroderma, systemic sclerosis, Behçet's disease, dermatomyositis, polymyositis, periodic fever syndromes, PFAPA, mouth ulcers, TMJ arthritis, jaw growth, vasculitis, Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, Kawasaki vasculitis, relapsing polychondritis, lymphadenopathy and polychondritis.

INTRODUCTION

Many rheumatological disorders are multi-system in nature where ENT symptoms and signs may provide a fundamental diagnostic clue to the overall condition, for example, mouth ulcers and lymphadenopathy often seen in systemic lupus erythematosus (SLE). On the other hand, ENT complications may constitute a life-threatening emergency, as in arthritis of the crico-arytenoid with associated vocal cord dysfunction. Long-term secondary damage may occur in under-treated granulomatosis with polyangiitis (GWP), the old Wegener's granulomatosis, where late tracheal stenosis or collapse of the nasal bridge are pathognomic. Sudden onset deafness, trigeminal nerve or facial nerve dysfunction can be seen in many autoimmune and chronic inflammatory rheumatological conditions.

The key to assessment is a whole patient screening review of systems and general examination by the ENT specialist, as well as good ENT assessment by the physician or paediatrician. This ensures that a second or multiple presentation is noticed enabling an early, accurate diagnosis without delay of definitive treatment.[1]

Constitutional symptoms of general malaise, tiredness, weight loss, unexplained fevers, rashes, hair loss, photosensitivity, arthralgia, arthritis, myalgias or muscle weakness, neurological features such as neuropathies, hypertension or unexplained haematuria or proteinuria, mouth ulcers, lymphenopathy, hepatosplenomegaly, shortness of breath, chronic cough, crepitations on chest auscultation, heart murmurs and absent pulses all occur in rheumatic disorders such as in SLE, the vasculitides, complicated rheumatoid arthritis, and in overlap connective tissue disorders.

Localized arthritis of the temporomandibular joints, cervical vertebrae and the cricoarytenoid can present with local and referred pain, or specific signs. Erosion or collapse of vertebrae from arthritis or secondary osteoporosis can present with torticollis (more often in childhood) or loss of movement and/or neurological signs.

ENT PRESENTATIONS IN AUTOIMMUNE RHEUMATIC DISEASE

The clinical symptoms and signs of many conditions may overlap and appear similar so that it is the patterns and combinations of symptoms, signs and subsequent investigations that will lead to the most likely diagnosis. However, as these diagnoses are made by clinical pattern recognition it is important that the expert opinion of a rheumatologist is sought as early as possible to avoid any dangerous delays in making an accurate diagnosis.

ENT management needs to be in conjunction with an expert specialist rheumatology or paediatric rheumatology team depending on the age of the patient.

1. Mouth ulcers and nasal ulcers may be found in Behçet's disease, systemic lupus erythematosus (SLE).
2. Sore throat may be the presenting symptom in:
   a. Acute rheumatic fever
   b. Systemic onset juvenile idiopathic arthritis (JIA)
   c. Macrophage activation syndromes (MAS)/haemophagocytic lymphohistiocytosis (HLH), either primary or secondary to other autoimmune inflammatory states
   d. Periodic fever syndromes including periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome.
3. Lymphadenopathy may be associated with many rheumatological disorders:
   a. SLE
   b. Systemic onset JIA, with or without MAS/HLH
   c. Sarcoidosis or Blaus syndrome
   d. Kawasaki disease
   e. Rosai-Dorfman disease
   f. Kikuchi syndrome.
4. Nasal disorders: GWP, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), relapsing polychondritis and sarcoidosis.
5. Sinusitis: GWP, eosinophilic granulomatosis with polyangiitis, relapsing polychondritis and sarcoidosis.
6. Vasculitic lesions: petechial lesions, ulcerated non-healing lesions (e.g. in pinna, on the palate, nasal mucosa, perforated nasal septum).
7. Hearing disturbances (either through autoimmune neuropathy or with vasculitic damage to small vasa-nervorum). Seen in SLE, GWP, relapsing polychondritis, polyarteritis nodosa, Cogan's syndrome, Sjögren's syndrome, and less frequently in eosinophilic granulomatosis with polyangiitis and Behçet's disease.
8. Stridor:
   a. Arthritis of the synovial joints of the cricoarytenoid joint with an emergency presentation of vocal cord dysfunction. Occurs in rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and gout. Osteoarthritic changes have also been described.
   b. Mucosal inflammation and swelling in GWP, Churg-Strauss vasculitis, rheumatoid arthritis, SLE, extranodal mucosal disease with lymphoid hyperplasia as in lymphomas.
   c. Myaesthenia gravis including neonatal disease with transplacental transfer of anti-Musk antibodies.
9. Dysphonia and vocal cord paralysis is found in association:
   a. Cervical cord changes due to osteophyte
   b. Cervical cord damage associated with cervical vertebral erosion with JIA
   c. Hoarseness from anatomical and functional problems.
10. Sjögren's syndrome. Xerostomia or a dry mouth is a common feature of primary and secondary Sjögren's syndrome (occurring with most autoimmune rheumatological disorders). Salivary gland enlargement may be also seen in these patients, as well as in patients with sarcoidosis. In childhood parotid gland enlargement is the most frequent presentation of Sjögren's syndrome. People with Sjögren's are at increased risk of developing non-Hodgkin lymphoma.
11. Trigeminal nerve dysfunction may occur in patients with Sjögren's syndrome, systemic sclerosis, SLE and mixed connective tissue disease.
12. Peripheral facial nerve palsy may complicate Sjögren's syndrome and sarcoidosis.
13. Motility disorders of upper and/or lower portions of the oesophagus have been reported in patients with dermatomyositis/polymyositis, systemic sclerosis and SLE.
14. Chondritis of the pinna in relapsing polychondritis.
15. Skin thickening, dyspigmentary changes, hemi-facial hypertrophy (Parry Romberg syndrome), gum retraction, tympanic membrane involvement in localized scleroderma.
16. Swallowing difficulties:
   a. Due to weakness in dermatomyositis, myasthenia gravis
   b. Due to oesophageal constriction in scleroderma.

SYSTEMIC SYMPTOMS AND SIGNS THAT ARE RED FLAGS OF AUTOIMMUNE RHEUMATIC DISEASES

- Joint pain, stiffness especially early morning stiffness and joint swelling seen in inflammatory arthritis
- Fevers
- Malaise, tiredness, weakness, weight loss
- Mouth ulcers, nasal ulcers, genital and perianal ulceration
- Rashes:
  - psoriasis
  - photosensitive, malar erythema in SLE
  - salmon pink, urticarial in systemic onset juvenile idiopathic arthritis
  - purple/black ulcerated vasculitic rashes
  - scalp rash or ulceration
  - skin thickening or hardening with dyspigmentary changes in localized scleroderma
  - erythema nodosum in sarcoidosis and streptococcal infection
- Alopecia either with or without scalp rashes in SLE
- Sclerodactyly, sclerodermatous facial pinching with decreased mouth opening in systemic sclerosis
- Puffy eyelids, heliotrope violaceous look around eyelids in diabetes mellitus (DM)
- Skin ulceration in vasculitis
- Nail fold capillary changes in systemic sclerosis, DM, SLE
- Lymphadenopathy (e.g. Kikuchi syndrome, massive lymphadenopathy with histiocytosis)
- Cardio-vascular features in SLE, vasculitis:
  - Raynaud's phenomenon
  - hypertension

  - peripheral vascular pulses loss of diminished, or peripheral aneurysms
  - pericarditis, endocarditis, myocarditis
- Thromboembolic phenomenon from primary or secondary anti-phospholipid syndrome
- Respiratory symptoms (e.g. shortness of breath, chronic cough, interstitial pneumonitis, pulmonary arterial hypertension in SLE, scleroderma, DM)
- Nephritis with haematuria, proteinuria, renal impairment, hypertension in SLE or vasculitis
- Gastrointestinal abdominal pain, dysphagia, altered bowel habit, bloody diarrhoea SLE or vasculitis
- Neurological features of neuropathies, myopathies, CNS direct involvement with various presentations including headaches, reduction in intellectual function, loss of memory in SLE or vasculitis
- Opthalmological disease of uveitis, retinal vasculitis, retinal vein thrombosis
- Laboratory features: raised ESR and or CRP, thrombocytosis, cytopenias, haemolytic anaemia, raised ferritin, abnormal U and Es, LFTs, raised CK, LDH. Abnormal thyroid function tests and thyroid antibodies, raised immunoglobulins, abnormal antibodies antithyroid peroxisomal, antinuclear factor, positive extractable nuclear antibodies, anti-ds DNA, positive p and c ANCA, positive anti-MPO and anti-proteinase 3 (PR3) antibodies, anti-centromere antibodies, anti-scl 70 antibodies.

LABORATORY FEATURES OF SPECIFIC RHEUMATOLOGICAL DISEASE

SLE features include positive antinuclear antibodies (ANA), positive extractable nuclear antibodies (ENA) especially anti-Ro and anti-La, anti-Smith, anti-dsDNA, abnormal thyroid tests, raised immunoglobulins, abnormal antibodies (i.e. antithyroid peroxisomal, raised ESR and/or CRP), thrombocytosis, cytopenias (e.g. lymphopenia, Coombs positive haemolytic anaemia), systemic sclerosis positive ANA, positive anti-centromere antibodies, positive anti-scl 70 (topisomerase antibodies).

Vasculitic suggestive features include raised inflammatory markers, positive ANCA. Raised serum angiotensin converting enzyme may be seen in sarcoidosis. Sjögren's syndrome positive ANA, positive extractable nuclear antibodies, especially anti-Ro and La. Other causes of raised ACE include Hodgkin disease, diabetes, alcoholic hepatitis and hyperthyroidism.

RHEUMATOLOGICAL CONDITIONS WITH ENT FEATURES OR COMPLICATIONS

Vasculitides

There are many ways of classifying vasculitis including the size of the blood vessel involved, whether there is a granulomatous histology, whether there is ANCA positivity, immune complex deposition. Table 18.1 lists most named types of vasculitis. Presentation is often specific with low-grade fever, tiredness, malaise with rashes, arthritis and multi-organ disease.

TABLE 18.1 Classification of vasculitis

I Predominantly large vessel vasculitis	a) Takayasu arteritis b) Giant cell arteritis
II Predominantly medium sized vessel vasculitis	a) Childhood polyarteritis nodosa b) Cutaneous polyarteritis c) Kawasaki disease
III Predominantly small vessel vasculitis	Granulomatous: a) Granulomatosis with polyangiitis (Wegener's granulomatosis); eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) b) Microscopic polyangiitis Non-granulomatous: a) Microscopic polyangiitis b) Henoch-Schonlein purpura/IgA vasculitis c) Isolated cutaneous leucocytoclastic vasculitis d) Hypocomplementic urticarial vasculitis (possibly drug induced) e) Cryoglobulinaemic vasculitis associated with RA, SLE, Sjögren's syndrome f) Anti-GBM disease
IV Variable	Cogan's syndrome Behçet's disease
V Other vasculitides	a) Behçet's disease b) Vasculitis secondary to infection (including polyarteritis nodosa associated with hepatitis B or streptococcal infections), malignancies, drugs (including hypersensitivity vasculitis) c) Vasculitis associated with connective tissue disease (systemic lupus erythematosus, dermatomyositis, rheumatoid arthritis d) Isolated vasculitis of the central nervous system e) Unclassified

NOTES ON SPECIFIC VASCULITIDES WITH ENT IMPLICATIONS

Kawasaki disease

Kawasaki disease is the most common vasculitis seen in childhood. Typical features of Kawasaki disease are fever persisting for at least 5 days (mandatory criterion) plus four of the following five features:

- changes in peripheral extremities or perineal area
- polymorphous exanthema
- bilateral conjunctival injection
- changes of lips and oral cavity: injection of oral and pharyngeal mucosa
- cervical lymphadenopathy.

In the presence of coronary artery involvement (detected on echocardiography) and fever, fewer than five additional features are required to be certain of the diagnosis. Note that atypical cases occur that do not fulfill all criteria.

In terms of ENT features, the mucosal inflammation may present with swollen red tongue and lips, cracked lips, and angular stomatitis enough to make swallowing impossible. Clinically this can look similar to Stevens Johnson syndrome

The eyes may be red with aseptic conjunctivitis. Peripheral oedema of the dorsum of hands and feet may occur with or without rashes. The most frequent feature not in the diagnostic criteria is irritability and may signify cerebral irritation. The illness can be life-threatening acutely from myocarditis or later from coronary artery aneurysms. Treatment is evidence-based with intravenous immunoglobulin and aspirin, although steroids and immunosuppressants may be needed in non-responsive and severe cases. Coronary artery aneurysms can occur in atypical cases with incomplete diagnostic criteria where treatment is still needed.

Granulomatosis with polyangiitis (Wegener's granulomatosis)

Necrotizing granulomatous inflammation usually involves the upper and lower respiratory tracts with rhinosinusitis leading to bloody discharge, chronic nasal ulceration, nasal chondritis (**Figure 18.1**) leading to a saddle nose, laryngeal stenosis, chronic destructive sinusitis, proptosis, orbital wall damage leading to orbitonasal fistulas. Conductive hearing loss caused by middle ear inflammation, or eustachian tube dysfunction, pulmonary granulomata, necrotizing glomerulonephritis, skin rashes, arthritis, neuropathies, CNS, heart and GI involvement can all occur. In the localized phase of the disease 50% are ANCA negative whereas when generalized disease is present 90% are positive for PR3 ANCA.

The disease has a high mortality and requires urgent intensive treatment with high dose steroids, cyclophosphamide, plasma exchange for severe cases with methotrexate and/or rituximab in milder cases.

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)

This is a vasculitis characterized by asthma, hypereosinophilia, pulmonary infiltrates with eosinophilia rich granulomatous inflammation in the respiratory tract. Sinuses are affected with allergic rhinitis, sinusitis and polyps. Myocarditis, neuropathies, arthritis, skin purpura, renal and gut disease can occur. ANCA, usually with anti-MPO specificity, is detected in 40% of patients.

ENT manifestations of Behçet's disease

Behçet's disease (BD) is a multi-system vasculitis characterized by recurrent oral and genital ulceration, skin lesions and ocular inflammation. Diagnostic criteria are based on recurrent oral ulcers occurring three times in 12 months plus two of the following: scarring recurrent genital ulcers, ocular involvement (uveitis or retinal vasculitis), skin lesions (such as erythema nodosum, pseudofolliculitis/pustolosis) and positive pathergy test (skin reaction to needle insertion). Other observed manifestations are arthritis, neurological disease and ENT involvement.

Audiovestibular involvement is frequent with sensorineural hearing loss in 23–32% of patients.[2] This is usually bilateral, affecting high frequencies and may be due

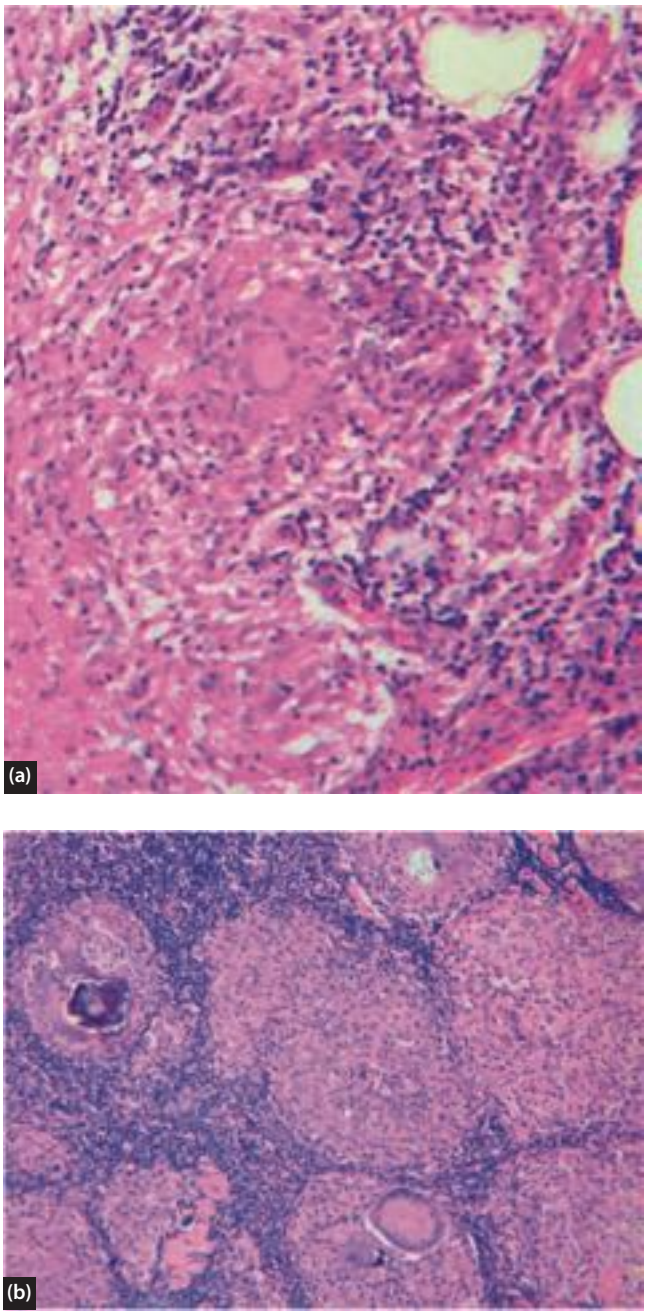


Figure 18.1 The changes in crusting found inside the nose from a patient with active granulomatosis with polyangiitis: (a) shows early changes with an angry mucosa and mucous hypersecretion; **(b)** demonstrates the end result of gross activity.

to vasculitis of vessels supplying the cochlea. Recurrent vertigo, bilateral vestibular hypofunction causing instability and bilateral Meniere's syndrome can occur. Neuro-Behçet's may present with vestibular neuronitis. Although CNS involvement is infrequently seen, peripheral nerve involvement with isolated case reports of facial paralysis and vocal cord paralysis are reported.

Ulceration of the oral cavity is common but oropharyngeal ulceration may be misdiagnosed as tonsillitis or pharyngitis. Rarely, laryngeal or oesophageal ulceration can lead to pharyngolaryngeal stenosis. Infrequently nasal symptoms such as nasal ulceration, dysosmia, obstruction and pain are experienced.

MAGIC syndrome

There is an association of autoimmune disorders such as Behçet's disease with relapsing polychondritis and inflammation of the auricular cartilages seen as part of the MAGIC syndrome (mouth and genital ulcers with inflamed cartilage).

Cogan syndrome

This is an autoimmune disorder of young people characterized by[3]:

- ocular symptoms with non-syphilitic interstitial keratitis
- audio-vestibular symptoms similar to those of Meniere's syndrome (sudden onset of tinnitus and vertigo accompanied by gradual hearing loss)
- an interval between the onset of the ocular and audio-vestibular features of less than 2 years.

Atypical cases occur without any inflammatory ocular manifestations, with interstitial keratitis and with delays of more than 2 years between the eye and ear symptoms. There are often neurological or systemic features of vasculitis with possible infectious or autoimmune triggers. Anti-HSP 70 antibodies may be a marker for the autoimmune nature of the hearing loss. ANCA positivity may occur. Treatment is with corticosteroids followed by immunosuppressive therapy with cyclophosphamide, methotrexate, azathioprine, cyclosporine or anti-TNF blockers such as etanercept and infliximab. Rituximab is also used.

Relapsing polychondritis (RP)

RP is a rare autoimmune disease with episodic flares of progressive inflammatory destruction of cartilage either as a primary condition or overlapping with rheumatoid arthritis, spondlyarthropathies, vasculitis or as a paraneoplastic condition. Acute phase reactants are raised and biopsy of affected tissues is characteristic. Elastic cartilage of the ear, hyaline cartilage of the tracheobronchial tree and joints, and fibrocartilage of the axial skeleton are involved. Because of significant morbidity and mortality systemic immunosuppression is required.

Systemic lupus erythematosus (SLE)

SLE is truly a multi-system inflammatory disorder affecting every organ with multiple presentations, a true masquerading condition where diagnosis can be difficult requiring specialist advice. Recently the Systemic Lupus International Collaborating Clinics (SLICC) classification 2012 has been proposed in addition to the 1997 American College of Rheumatology (ACR) diagnostic criteria (Tables 18.2 and 18.3). Both include a glossary of detailed definitions of component parts but are a start in making sense of a multifaceted disorder.

From an ENT perspective mucosal presentations occur in up to 45% of cases. In the mouth these include irregular raised white plaques with areas of erythema, silvery white scarred lesions, actual ulcers with surrounding redness occurring on soft or hard palates or on the buccal mucosa. These have a wide differential diagnosis including lichen planus, candidiasis, aphthous stomatitis, intra-oral herpes, Behçet's disease, bite induced lesions, leukoplakia and malignancy.

Oral and nasal ulcers occur. These are usually painless and may be the first presentation of the SLE. Discoid lesions may occur on the lips with erythema, swelling or atrophy and depigmented areas. Lymphadenopathy occurs in around 40% of cases with soft, non-tender discrete glands in the cervical, axillary or inguinal regions. These may warrant a biopsy to exclude other causes.

TABLE 18.2 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for systemic lupus erythematosus[4]

Clinical criteria	Immunologic criteria
Requirements; 4 or more criteria (at least 1 clinical and 1 laboratory criteria) OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA.	
1. Acute cutaneous lupus	1. ANA
2. Chronic cutaneous lupus	2. Anti-DNA
3. Oral or nasal ulcers	3. Anti-Sm
4. Non-scarring alopecia	4. Antiphospholipid Ab
5. Arthritis	5. Low complement (C3, C4, CH50)
6. Serositis	6. Direct Coombs test (do not count in the presence of haemolytic anaemia)
7. Renal	
8. Neurologic	
9. Haemolytic anaemia	
10. Leukopenia	
11. Thrombocytopenia (100,000/mm^3)	

From Petri et al., 2012[4]

TABLE 18.3 American College of Rheumatology revised criteria for diagnosis of systemic lupus erythematosus 1997

Criteria	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging: atrophic scarring occurs in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling or effusion
Serositis	a. Pleuritis: convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion, or b. Pericarditis: documented by ECG or rub or evidence of pericardial effusion
Renal disorder	a. Persistent proteinuria > 0.5 g per day or 3+ if quantification is not performed or b. Cellular casts: may be red cell, haemoglobin, granular, tubular or mixed
Neurological disorder	a. Seizures: in the absence of offending drugs or known metabolic derangements (eg. uraemia, acidosis, or electrolyte imbalance) b. Psychosis: in the absence of offending drugs or known metabolic derangements (eg uraemia, acidosis, or electrolyte imbalance)
Haematological disorder	a. Haemolytic anaemia with reticulocytosis, or b. Leucopenia < 4000/mm^3, or c. Lymphopenia < 1500 mm^3, or d. Thrombocytopenia < 100 000 mm^3 in the absence of offending drugs
Immunological disorder	a. Anti-DNA antibody to native DNA in abnormal titre, or b. Anti-Sm, presence of antibody to Sm nuclear antigen, or c. Positive finding of antiphospholipid antibodies based on: (1) an abnormal serum concentration of IgG or IgM anticardiolipin antibodies, (2) a positive test result for lupus anticoagulant using a standard method, or (3) a false positive test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
Antinuclear antibody	An abnormal titre of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with 'drug-induced lupus' syndrome

Autoinflammatory diseases/hereditary periodic fever syndromes (HPFSs)

These rare genetic conditions are characterized by short and recurrent attacks including fever, often with a sore throat, tonsillitis, lymphadenopathy and general debility, with a severe inflammatory reaction (with raised leucocytosis, ESR, CRP, fibrinogen, serum amyloid A protein) with the patient well between attacks. Infection has to be excluded as it is clinically indistinguishable in an individual attack and often it is only after multiple courses of antibiotics that the pattern of the disorders is clear. Genetic testing needs to be through specialist clinics and specialist laboratories. Clinical clues are in recurrent or continuous symptoms, especially fever, rash, joint pain or arthritis, accompanied by very high acute phase reactant with a wide differential diagnosis. If attacks recur for longer than a year and especially if there is a family history, HPFS should be considered. Some may present very late into adult life.

They are disorders of the inflammasome with triggers including emotional and physical stress, the menstrual cycle and pregnancy, vaccination reactions in hyper-IgD syndrome (HIDS), local mucosal trauma (e.g. in PFAFA), cold as in some cryopyrin-associated periodic syndromes (CAPS) syndromes:

- **Familial Mediterranean fever (FMF)** is due to a gene mutation *MEFV,* location 16p13.3 proteins affected pyrin and marenostrin. FMF may cause sensorineural hearing loss.
- **Hyperimmunoglobulinemia D (or hyper IgD syndrome)** with periodic fever syndrome (HIDS) gene mutation *MVK* located at 12q24, proteins affected mevalonate kinase deficiency. Most cases have marked reactions to immunizations. Febrile episodes with lymphadenopathy, rashes sometimes with hepatosplenomegaly, arthralgia, abdominal pain, irritability.
- **Tumour necrosis factor (TNF) receptor–associated periodic syndrome (TRAPS)** gene *TNFRSF1A* located 12p13, proteins affected TNF-receptor Type 1

Cryopyrin-associated periodic syndromes (CAPS):

- **This is a group of hereditary periodic fever syndromes with the same gene mutations but with very different phenotypes.** The gene *NLRP3 (CIAS1) mutation* at 1q44 affects the protein cryopyrin (NALP3/PYPAF1).
- **Muckle-Wells syndrome** (MWS) gene *NLRP3 (CIAS1)* at 1q44 inheritance protein affected cryopyrin (NALP3/PYPAF1). Clinical presentation with conjunctivitis in 44%, hearing loss in 32% with recurrent urticaria and uveitis.
- **Familial cold autoinflammatory syndrome** (FCAS) *NLRP3 (CIAS1),* 1q44 protein affected Cryopyrin (NALP3/ PYPAF1). Symptoms such as lip swelling after cold contact.
- **Chronic infantile neurologic cutaneous articular syndrome (CINCA)**, also known as neonatal-onset multi-system inflammatory disease (NOMID) *NLRP3 (CIAS1),* 1q44 protein affected, Cryopyrin (NALP3/PYPAF1). Although onset is from the

neonatal period, diagnoses may not be made until adult. Features include daily fever, a measles-like macular rash (very like that in systemic onset arthritis), lymphadenopathy, splenomegaly and sensorineural deafness with ocular optic neuritis papillitis, intermittent oligoarticular arthritis with pathognomic patellar overgrowth and learning difficulties preventable with treatment. Treatment is with daily anakinra injections or with canakinumab, both IL1 receptor antagonists.

- **Shnitzlers syndrome** is like CAPS but late onset with no family history. Diagnosed only in adults. Consisting of an IgM gammopathy, chronic urticarial rashes, acute phase reactants, intermittent fever, arthralgia and arthritis, splenomegaly, lymphadenopathy, some deafness. There is a long-term risk of Waldenstrom's macroglobulinemia. It is interleukin-1 (IL-1) driven with 100% of cases responding to anakinra.
- **PFAPA syndrome** (periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome). The most frequent disorder in childhood accounting for around 50% of recurrent fever syndromes. There is no identifiable gene associated with this so the diagnosis is clinical. This disorder often responds to tonsillectomy; however, PFAPA may recover spontaneously. The evidence for adenoidectomy in addition to tonsillectomy is not established.[7] Short courses of oral corticosteroids may help this condition. Although PFAPA is usually self-limiting attacks can occur frequently throughout childhood from a median age of 2.5 years and can last for a decade.
- **Blau syndrome and sarcoidosis:** sarcoidosis is a systemic disorder characterized by non-caseating granulomata affecting the lungs, skin, joints with arthritis, bony changes of osteitis, eyes with uveitis, calcium metabolism causing hypercalcaemia, muscle, and heart with skin lesions of lupus pernio, papules, nodules in infiltrated scars and erythema nodosum. Neurosarcoid can result in cranial nerve palsy and obstructive sleep apnea. Lymphadenopathy occurs in 15%. Salivary gland involvement (e.g. solitary parotid enlargement) occurs. Other ENT presentations include nasal perforation, sinonasal disease (where the nasal mucosa resembles apple jelly; (**Figure 18.2**)), laryngeal disease, and vocal cord deposits, trigeminal nerve or facial nerve mediated pain. Chest X-ray to look for perhilar lymphadenopathy or pulmonary infiltrates, and urinalysis for proteinuria or haematuria suggestive of a nephritis as the rare renal involvement should always be done. Patients should be sent for ophthalmological review for signs of uveitis that may be subclinical. In childhood, chest and kidney involvement is rare. Blau syndrome is associated with CARD15/NOD 2 mutations and is very like young onset sarcoidosis. Most patients develop polyarticular arthritis, with cutaneous and eye manifestations.

Systemic sclerosis

This condition is caused by a combination of low-grade inflammation with increased fibrosis in soft tissues and in blood vessels. As well as Raynaud's phenomenon, the skin becomes stiff and vascular insufficiency can lead to finger-tip ulcers. The antinuclear factor is usually positive. Lung and renal disease and pulmonary hypertension are significant causes of death. From an ENT perspective the soft tissues of the mouth can become stiff with decreased mouth opening.

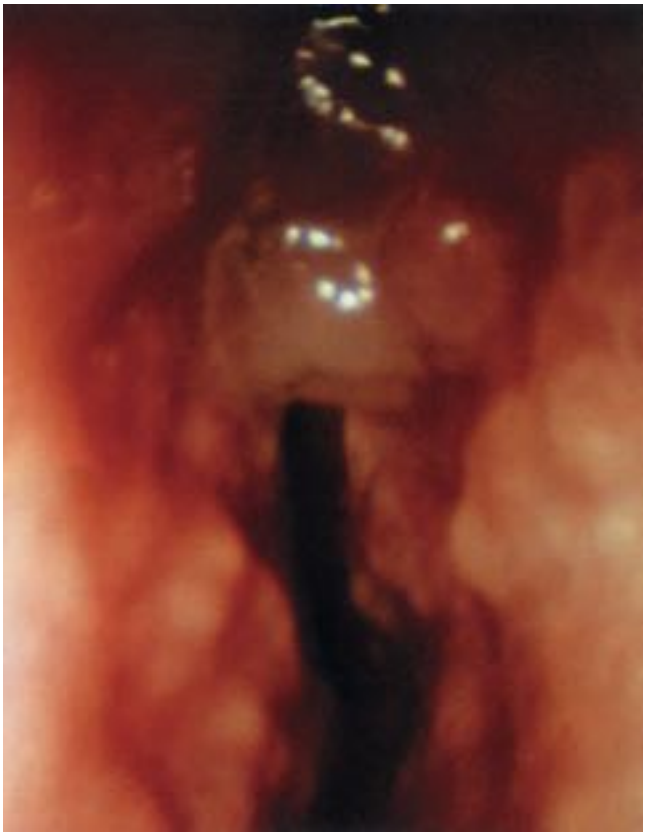


Figure 18.2 Examination of the nasal mucosa from a patient with sarcoidosis reveals apple jelly nodules.

EFFECTS OF IMMUNOSUPPRESSION FROM DISEASE OR TREATMENT

Many of the rheumatological conditions are immunesuppressive in themselves, as are the drugs, including steroids, used to treat the conditions. ENT infections may be increased in these situations. Immunizations against winter flu, pneumococcus and any killed vaccines are safe and are important to reduce infection risk although the efficacy may vary according to the time between vaccination and drug treatments.

TREATMENTS INCLUDING DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS (DMARDS) AND BIOLOGIC THERAPIES

Treatments of the rheumatic disorders include steroids, disease-modifying anti-rheumatic drugs (DMARDS – methotrexate, ciclosporin, azathioprine, leflunamide) cyclophosphamide and biologic drugs against specific

cytokines (e.g. anti-TNF blockers – etanercept, infliximab, adalimumab), anti-IL6 blocker (tocilizumab), anti-IL1 blockers (anakinra or canakinumab and rilonocept), anti-B cell drugs such as rituximab and belimumab and the anti-costimulatory molecule blocker abatacept. Immunomodulatory doses of intravenous immunoglobulin may be used. Colchicine may be used. Several drugs in combination are often required.

FUTURE RESEARCH

- Long-term outcome studies of childhood ENT diseases such as GWP with laryngeal stenosis
- Trials of early aggressive treatment of isolated ENT autoimmune disease

KEY POINTS

- Airway and anaesthetic risks occur:
  - arthritis of the TMJ and decreased jaw growth
  - arthritis of the cricoarytenoid joint
  - arthritis of the cervical spine
  - disorders with tracheal stenosis.
- Patients with systemic sclerosis with tight soft tissues and decreased mouth opening.
- Many rheumatological disorders have a relatively high mortality rate and high morbidity rates if treatment is delayed.
- Multi-system disorders may have ENT features as the clue to diagnosis.
- Lymphomas and leukaemias can be associated with autoimmune presentations with raised auto-antibodies occurring as an epi-phenomenon and unless tissue diagnosis is sought misdiagnoses can occur.

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CHAPTER 19

MICROORGANISMS

Ursula Altmeyer, Penelope Redding and Nitish Khanna

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SEARCH STRATEGY

This chapter collates basic consensus knowledge of bacteriology. Laboratory practices described are based on Public Health England's Standards for Microbiology Investigations (SMI). Data in this chapter may be updated by a PubMed search using the keywords: basic concepts in microbiology; classification of bacteria based on gram staining; gram positive; gram negative; staphylococci, streptococci, enterobacteriaceae, anaerobes; mycobacteriae; spirochetes.

INTRODUCTION

The human body is a habitat that supports single-cell microorganisms in numbers that by far exceed the number of its own cells. Most of these organisms have evolved over millions of years in close association with our own species, forming what is referred to as the human microbiome.

Contained in their ecological niche, these bacteria can be essential for the survival of the host body, although if given the opportunity to leave their niche, for example through injury or surgery, their presence may equally lead to disease. Some of these beneficial, or at least harmless, tenants also have the potential to cause opportunistic infections in host organisms that are particularly susceptible, whether that be due to overall poor health, extremes of age, or constitutional or iatrogenic immunosuppression.

In comparison, the number of pathogens whose presence is always abnormal and will always lead to disease is relatively small.

The advent of antimicrobials in the first half of the 20th century has been one of the most transformative developments in medicine for both good and bad.

The emergence of antimicrobial resistance and the increasing number of resistant strains in circulation together with a lack of new antimicrobial agents means that modern healthcare is under pressure to reassess its attitude towards infection and develop alternative diagnostic and therapeutic approaches.

BASIC CONCEPTS IN MICROBIOLOGY

The human body is colonized with a wide range of microorganisms and different body sites will have a very characteristic normal or resident flora (**Table 19.1**).

A few sites are considered sterile (**Table 19.2**) and recovery of any bacterial growth from such a site should merit consideration of systemic treatment if infection is clinically suspected. In this context it is important to be able to differentiate between possible contamination and infection; this becomes easier if multiple samples can be submitted and examined (**Table 19.3**).

Most organisms commonly recovered from clinical specimens can be identified on the basis of few simple tests:

- Gram staining and light microscopy
- growth requirements (e.g. aerobic or anaerobic growth)
- metabolic properties.

The best known of these techniques is the Gram stain, which was developed by the Danish microbiologist Hans-Christian Gram (1853–1938) as a stain that is able to differentiate between human and bacterial tissue more readily than the histological stains in use at the time. The presence or absence of an outer membrane leads to differences in uptake of methylene blue, and has coined the terms 'Gram positive' and 'Gram negative' (**Figure 19.1**).

This technique is still in daily use and is performed on any positive blood culture and any sterile site sample submitted for bacterial culture.

TABLE 19.1 Resident flora of selected body sites

Site	Examples of resident flora
Skin	Predominantly Gram positive organisms: • staphylococci • streptococci • corynebacteriae Gram negatives may be present on lower body half
Oral cavity	Mixed flora: • staphylococci • streptococci • anaerobic organisms • bacillus species • yeasts Consider cover of oral flora in both human and animal bite wounds.
Upper respiratory tract	Predominantly Gram positives: • staphylococci • streptococci, incl *S. pneumoniae* and *S. pyogenes* Some Gram negative organisms, e.g.: • *Haemophilus influenzae* • *Moraxella catharrhalis* • *Neisseria meningitis*
Digestive tract, especially colon	Mixed flora: • anaerobic organisms • Gram negatives – 'coliforms' • some Gram positive organisms – enterococcus species • yeasts

TABLE 19.2 Sterile sites

Sterile body sites
Blood stream
Central nervous system
Pleural space
Peritoneal cavity
Bones and joints
Deep muscle tissue
Bladder and upper urinary tract
Healthy lower respiratory tract

TABLE 19.3 Contaminant versus infection

More likely contaminant	More likely to represent infection
Few organisms present on microscopic examination	Large number of organisms present on microscopic examination
Lack of white blood cells on microscopic examination	White blood cells present on microscopic examination
Growth absent from routine culture, present in enrichment only	Abundant growth in routine culture
No clinical signs of infection	Patient displays clinical signs of infection

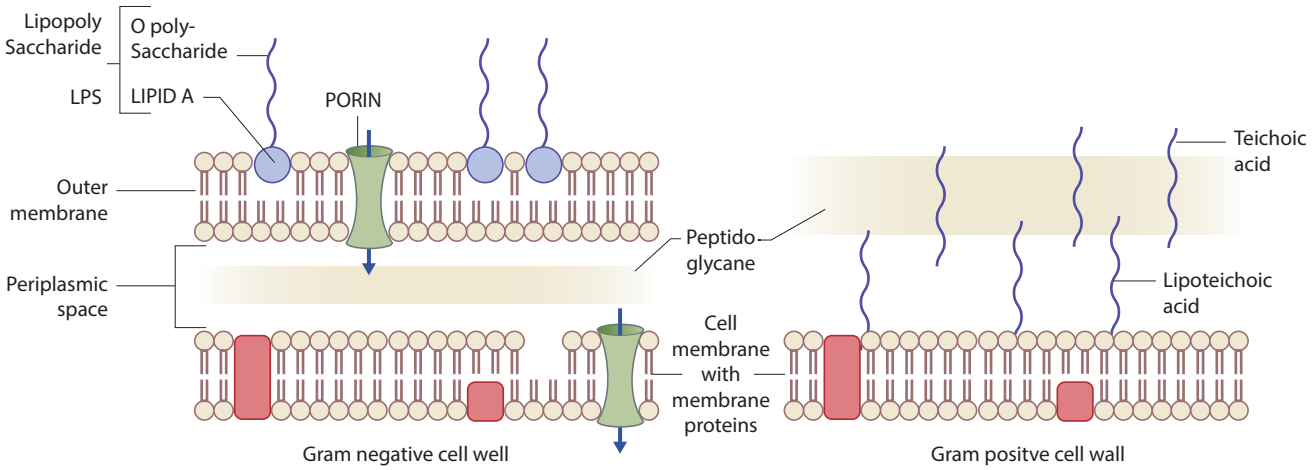


Figure 19.1 Gram positive and Gram negative cell wall structure in comparison.

Depending on the sample site and its resident flora, different sets of bacterial culture media are inoculated and incubated overnight. By careful choice of medium and incubation environment (e.g. CO_2, anaerobic, different incubation temperatures) it is possible to encourage growth of a wide range of potential pathogens.

Clinical information often provides clues about potential pathogens and may therefore play a crucial role in selection of appropriate media, for example selective media for mycobacteria or Actinomyces (Table 19.4).

For some organisms (e.g. *Staphylococcus aureus* or *Streptococcus pyogenes*), a formal identification is possible by performing very simple tests on the first day a growth is observed on the culture medium.

The majority of Gram negative organisms, however, will look very similar in culture and require further differentiation on the basis of their metabolic profiles. This is usually done by automated or semi-automated systems that are able to perform an entire range of different reactions in one step and often also carry out antibiotic susceptibility testing at the same time.

Some tests, especially susceptibility testing, whether performed manually as disc testing or by automation, require the organism to be grown in pure culture and can,

TABLE 19.4 Different types of media used for bacterial culture

Medium type	Use	Example
Enrichment medium	Improves recovery of organisms from sterile sites when only few organisms may be present in the sample and there is no resident flora	Robertson's Cooked Meat Broth Blood culture medium
Nutrient medium	Improves recovery of fastidious organisms	Chocolated blood agar
Selective medium	Selectively allows growth of organisms of interest while suppressing growth of normal flora	Hoyle's tellurite medium for recovery of corynebacterium species

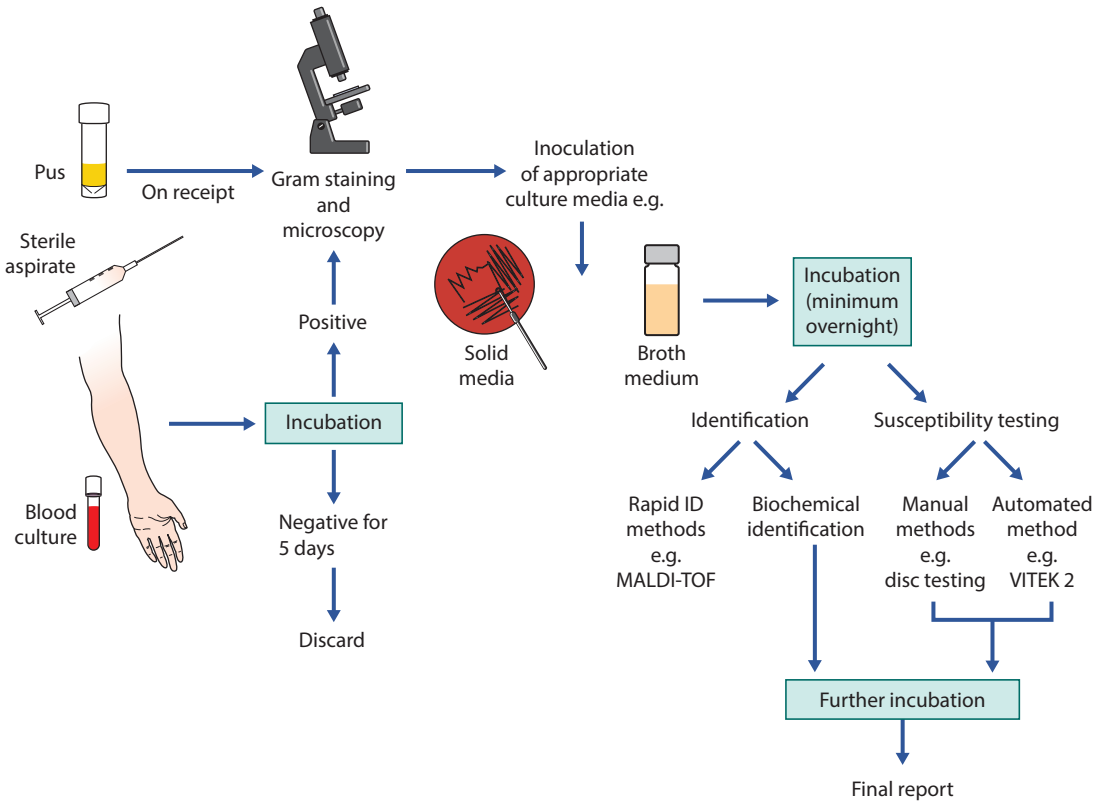


Figure 19.2 Processing of sterile site samples involves several overnight incubation steps. If organisms are not present in pure culture in the original sample a further step of subculture and incubation may be required in order to be able to perform formal identification and susceptibility testing. On average 48 hours are required to produce a final report on a sterile site sample.

at the earliest, be performed after overnight incubation of a sample (Figure 19.2).

Polymerase chain reaction (PCR) has been a mainstay technique in virology for some time and is also available for bacteriological diagnosis. It is widely employed in reference laboratories for typing purposes and CSF is often tested for presence of genomic material from *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria menigitidis*.

Another more rapid diagnostic technique that has recently come into routine use in many laboratories is matrix-assisted laser desorption/ionization and time of flight analysis, or MALDI-TOF, which uses mass spectrometry to measure species-specific profiles of biomolecules, such as peptides and sugars, and larger organic molecules following laser ionization of a sample absorbed onto a specific test matrix. This is currently only possible from a pure culture, but may become available as a technique usable directly on clinical samples.

In the future, whole genome sequencing may come to supersede conventional culture techniques entirely, as it is able to not only identify bacterial species directly from clinical samples, but is also able to deliver a full profile of antimicrobial resistance. This has the benefit of identifying genes responsible for resistance (genotype) as opposed to current conventional susceptibility testing that detects phenotypic resistance.

CLASSIFICATION OF BACTERIAL ORGANISMS

The Gram stain continues to be one of the most frequently used and simple tests performed in clinical microbiology laboratory practice, and gram staining of pus and tissue samples can provide vital early information on possible causative organisms in an infective process. Figure 19.3 provides an overview of gram positive organisms and gram negative organisms (Figure 19.5) commonly encountered in clinical practice.

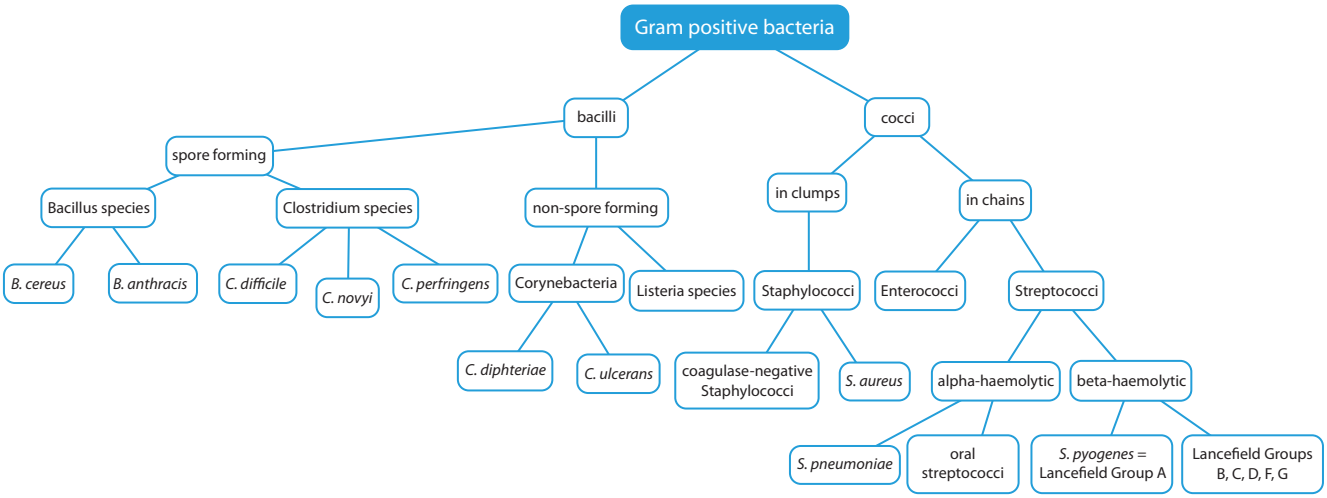


Figure 19.3 Overview of medically important Gram positive organisms.

Gram positive organisms

STAPHYLOCOCCI

Staphylococci are Gram positive, catalase positive organisms that on microscopy after Gram staining lie together in clusters, reflecting the fact that they are able to divide in more than one geometrical plane. Staphylococcal species form part of the normal skin flora.

There are several species of coagulase negative staphylococci. Most are skin commensals with low pathogenic potential, although they are able to cause indolent infections of intravascular devices and implants. An exception to this is *Staphylococcus lugdunensis*, which although coagulase negative, produces infections which present clinically much like infections with *Staphylococcus aureus*.

S. aureus is the major human pathogen in this group and it can be distinguished from other staphylococci by presence of a coagulase, which clots plasma.

This allows the organism to become coated in plasma and evade detection by phagocytes. It also plays a role in the formation of abscesses, which sequester the organism from access by the host immune system. *S. aureus* also produces a hyaluronidase, which facilitates spreading of the organism through host connective tissue.

Some strains are capable of producing exotoxins, among which are several enterotoxins, an exfoliative toxin and a toxin capable of producing staphylococcal toxic shock. Another important exotoxin is the Panton-Valentine leukocidin (PVL) toxin, which is associated with an increased ability to cause disease, usually in the form of skin and soft tissue infection with recurrent abscesses. In the UK, about 2% of all *S. aureus* isolated from clinical samples are PVL positive.[1]

Rarely, strains carrying this exotoxin can cause severe necrotizing pneumonia with a high mortality rate. Specific infection control measures should be adhered to if a patient carries a PVL positive strain and guidance regarding this is available from public health authorities.

S. aureus most commonly colonizes the anterior nares; about 20% of the population are permanent carriers and 60% carry it intermittently; the remaining 20% are non-carriers which are almost never colonized.[2]

The main manifestations of community-acquired disease caused by *S. aureus* are superficial skin and soft tissue infections, purulent infections in the form of folliculitis and deep tissue abscesses. Enterotoxin carrying strains are a cause of food poisoning.

In the hospital environment, the organism plays a major role in hospital-acquired infection, most commonly in surgical site infection, infection of surgical implants and intravascular device infection.

S. aureus bacteraemia (SAB) is a severe complication of *S. aureus* infection, which has a mortality rate of up to 30% and frequently involves secondary deep foci of infection, such as solid organ abscesses, spondylodiscitis and endocarditis. Even if treated adequately with intravenous antibiotics and removal of the focus of infection, a significant number of cases will experience a relapse or develop metastatic infection.

The majority of strains of *S. aureus* currently in circulation produce a penicillinase that renders them resistant to benzyl-penicillin, making penicillinase-stable penicillins, such as flucloxacillin, the first-line treatment. Unless the patient is penicillin allergic, intravenous treatment with one of these agents is the gold standard treatment of invasive *S. aureus* infection.

For penicillin allergic individuals, or if the isolate is methicillin-resistant (MRSA), vancomycin is the agent of choice for invasive infection.

If the infection is clinically severe or likely to involve a biofilm, as in prosthetic joint or intravascular device infections, a second anti-staphylococcal agent is sometimes added. The choice of this second agent will depend on the antibiotic susceptibility profile, but may include agents such as gentamicin, rifampicin, fusidic acid, trimethoprim, and clindamycin. However, there is scant clinical evidence that dual therapy for SAB is any more efficacious than single agent therapy.[3]

Methicillin-resistant *S. aureus* (MRSA) first emerged in the 1960s, but since has become widespread, both within the hospital environment as well as in the community and

causes the same range of infections as the methicillin-susceptible strains (MSSA).

All strains of MRSA are resistant to penicillinase-stable β-lactams such as flucloxacillin; this is mediated by carriage of a resistance gene cassette, *mecA*, which codes for altered cell wall components which the β-lactam agents are unable to bind to.

Susceptibility to other anti-staphylococcal agents varies, but in contrast to initial concerns, vancomycin resistant strains are extremely rare (case reports only from the United States, Japan and most recently Portugal)[4] and the agent remains the intravenous treatment of choice for MRSA infection.

Biofilms

Like many other organisms, *S. aureus* is capable of forming a biofilm, in which the organisms form an aggregate within a slime-like extracellular matrix.

These are well known to form on non-biological surfaces which are immersed in a liquid, such as a intravascular devices immersed in the blood stream, but may also exist on mucosal surfaces within the body, such as the tonsils or the mucosa of the sinuses and the middle ear.[5]

The importance of biofilms is becoming recognized in a range of fields, from treatment of intravascular device infections, in marine engineering and shipbuilding, to use of biofilms for removal of oil spills from marine environments (Table 19.5).

The formation of a biofilm initially involves a stage of reversible attachment of the planctonic (free-living) form of the organism to a surface. As the biofilm develops, this attachment becomes irreversible and the bacterial community becomes covered in an extracellular matrix slime. Within this matrix the individual cells communicate with each other via a process called quorum sensing, which allows regulation of gene expression throughout the colony. A fully mature biofilm is able to release planktonic organisms back into the environment. Biofilms may involve more than one bacterial species.

Treatment of infections involving a biofilm are complicated by both the presence of the extracellular slime, which makes penetration of antimicrobials difficult, and the fact that the bacteria themselves will exhibit reduced metabolic activity and divide less frequently than as their free-living planktonic forms. This renders many antimicrobials ineffective. Agents that act on the ribosome, such as rifampicin or macrolide agents, remain effective in these organisms, unless a resistance mechanism is present. Successful treatment of infections involving a biofilm may require mechanical debridement of the biofilm and if a device is involved, this may ultimately require removal. Development of improved device surfaces that do not allow attachment of the organisms to initiate biofilm formation is a focus of research that may in the future prevent device-related infections.[7]

Research into treatment strategies involving disruption of the biofilm by mechanical measures and eradication of the biofilm with topical agents such a mupirocin or manuka honey may also result in more effective new treatments of biofilm infection.[8]

TABLE 19.5 Examples of biofilms[6]

Biofilms in medicine
• Dental plaque • Otitis media • Chronic rhinosinusitis • Colonization of the lung in chronic respiratory disease, e.g. cystic fibrosis • Colonization of chronic wounds • Osteomyelitis • Intestinal microbiome • Endocarditis • Device-related infections

STREPTOCOCCI

Streptococci form the second group of medically important Gram positive cocci. On microscopy, they appear to lie in chains, the length of which can vary. In the laboratory, they are initially classified by examining growth on a blood agar plate for the presence and type of haemolysis (Figure 19.4 and Table 19.6).



Figure 19.4 Alpha, beta and gamma haemolysis on blood agar. Courtesy of Jasminder Karde and Margaret Woods, Department of Microbiology, Golden Jubilee National Hospital, Clydebank, UK.

TABLE 19.6 Streptococci by type of haemolysis

Type of haemolysis	Examples
α-haemolysis	*S. pneumoniae* Oral streptococci - 'viridans' group Some *enterococci*
β-haemolysis	*S. pyogenes* *S. agalactiae* *S. anginosus/milleri* Some enterococci
γ-haemolysis	Denotes a lack of haemolytic activity

β-haemolytic streptococci

The β-haemolytic streptococci are usually further classified by using a latex agglutination test to determine their Lancefield group.

Medically relevant streptococci usually belong to Lancefield groups A–D, F and G (Table 19.7).

Of the β-haemolytic streptococci, *Streptococcus pyogenes* is particularly worth noting, partly due to the range of clinical presentations caused by this organism, but also due to its particular virulence (Table 19.8). It not only expresses a wide range of proteins which enable it to evade host defence mechanisms, but certain strains also produce an exotoxin capable of acting as a superantigen, leading to streptococcal toxic shock syndrome. This represents a true medical emergency with a high mortality and a substantial number of patients with this presentation require transfer to an intensive care facility as they frequently require circulatory and ventilatory support as well as renal replacement therapy.[9]

S. pyogenes causes a range of suppurative infections from tonsillitis to skin and soft tissue infections, but is also capable of eliciting a number of non-suppurative immunological complications (Table 19.9), with certain M-protein type strains showing association with specific presentations.

S. pyogenes remains sensitive to penicillins and is usually also sensitive to macrolide antibiotics and clindamycin. Clindamycin has a particular role in the treatment of severe infection with *S. pyogenes*, as it reduces toxin production by interrupting protein synthesis at the bacterial ribosome.

Streptococci of the Lancefield groups C and G are also capable of causing severe skin and soft tissue sepsis that is clinically indistinguishable from infections with *S. pyogenes*.

Group F streptococci, also commonly referred to as the *Streptococcus milleri* group, are part of the normal flora of the gut and occasionally the oral cavity. They have a particular propensity to cause deep-seated abscesses and infection should be treated by drainage of the abscess, followed by a prolonged course of antibiotics to minimize the rate of recurrence.

TABLE 19.7 β-haemolytic streptococci by Lancefield group

Lancefield group	Species
A	*S. pyogenes*
B	*S. agalactiae*
C	*S. dysgalactiae, S equisimilis, S equi, S zooepidemicus*
D	*S. bovis, enterococci*
F	*S. anginosus/milleri*
G	*S. canis*

TABLE 19.8 Virulence factors of *S. pyogenes*

Virulence factor	Function
Capsule hyaluronidane	Mimics host connective tissue
Hyaluronidase	Spread through connective tissue
M protein	Adhesion to epithelium and evasion of complement
Protein F	Adhesion
Streptolysin O and S	Evasion, haemolysis
C5a peptidase	Evasion; cleaves complement factor C5a, a potent chemotactic stimulant of neutrophils
Streptococcal pyrogenic antitoxins	Superantigens, responsible for manifestations of scarlet fever and toxic shock syndrome

TABLE 19.9 Clinical syndromes caused by *S. pyogenes*

Suppurative	Non-suppurative complications
Pharyngitis, tonsillitis Impetigo Cellulitis Necrotizing fasciitis Surgical site infection Puerperal sepsis	Rheumatic fever Carditis Glomerulonephritis Sydenham's chorea

α-haemolytic streptococci

Streptococcus pneumoniae is the clinically most important organism amongst the α-haemolytic streptococci. It colonizes the healthy upper respiratory tract, more often in children (carriage rate up to 53%) than in adults (carriage rate 4%).[10]

S. pneumoniae can be more difficult to grow in culture than other streptococci, but when it does it can readily be identified in the laboratory by a characteristic 'draughtsman' shape of the individual colonies, alpha-haemolysis on blood agar and an inhibitory zone to a disc containing optochin, which disrupts the fragile cell wall.

Prior to introduction of the heptavalent pneumococcal vaccine into paediatric vaccination schedules, *S. pneumoniae* was the most common bacterial cause of otitis media in children. It has now been replaced by *Haemophilus influenzae*, but still remains the second most common bacterial cause.[11]

Overall, the introduction of the vaccine has led to a shift of circulating strains from those included in the vaccine to previously less common strains.

In the adult population, *S. pneumoniae* is most commonly found in the classic lobar pneumonia, but also plays a role as a causative agent of bacterial meningitis which may arise from an infected mastoid or sinus cavity and has a high rate of neurological sequelae, especially permanent hearing loss.

Contiguous infection from the mastoid or sinuses may also result in formation of intra-cerebral abscesses. These are a radiological diagnosis, and ideally drainage and sampling should precede initiation of antimicrobial treatment. Drainage itself is mandatory to achieve cure of disease and intravenous treatment with an agent that penetrates well into the brain tissue should be extended to at least 6 weeks.

Invasive strains of *S. pneumoniae* are usually capsulated, rendering asplenic individuals particularly vulnerable to infection and therefore available vaccines against capsulated organisms (i.e. against *S. pneumoniae*, *H. influenzae* and *N. meninigitidis*) should be administered to any patient undergoing splenectomy.

High dose intravenous benzyl-penicillin is the treatment of choice of pneumococcal sepsis, but in some countries, especially in southern Europe, strains with a raised minimum inhibitory concentration for penicillin (MIC) are in circulation, which display intermediate susceptibility or resistance to benzyl-penicillin. Invasive infection with these strains should be discussed with an infection specialist, who may recommend treatment with a third generation cephalosporin, vancomycin and rifampicin or a fluoroquinolone with activity against *S. pneumoniae*, such as levofloxacin or moxifloxacin.

Ciprofloxacin has little useful activity against *S. pneumoniae* and should be avoided.

Other α-haemolytic streptococci, often referred to as viridans streptococci alluding to the green tinge of the blood agar caused by the α-haemolysis, mainly play a role in medicine as causative agents of sub-acute bacterial endocarditis.

ENTEROCOCCI

Enterococci are relatives of the streptococci most commonly found as gut commensals. They are indistinguishable from streptococci on Gram stain and haemolysis on blood agar can be variable. They frequently react with the reagent for the Lancefield group D.

In clinical samples, they often represent colonization rather than infection, especially in samples from chronic wounds or the nasopharynx of patients currently on antimicrobial treatment. They can contribute to intra-abdominal infections and cause urinary tract infections. Enterococcal bacteraemias may lead to infective endocarditis and merit further investigation with an echocardiogram; they should be treated with an appropriate course of intravenous antimicrobials.

Enterococci are commonly sensitive to amoxicillin or vancomycin, but can carry multiple resistance genes, including resistance to glycopeptides (i.e. vancomycin), making treatment difficult.

Gram positive bacilli

The main distinction between the different Gram positive bacilli lies in the presence or absence of spore formation.

Bacillus species, such as *Bacillus anthracis* and *Bacillus cereus* and *Clostridium* species, like *Clostridium tetani*, *Clostridium perfringens* and *Clostridium difficile*, all form spores, which preserve the organism in unfavourable conditions and can remain viable for considerable amounts of time. This has implications for both treatment and infection control aspects – treatment may have to be prolonged, taking into account that spores may reactivate after antimicrobials have been discontinued (e.g. post-exposure prophylaxis of inhalatory anthrax) and any disinfecting agents have to be active against the spore form (e.g. lack of activity of alcohol hand gels against spores of *C. difficile*).

CLOSTRIDIUM DIFFICILE

Toxin-producing strains of this spore forming anaerobic Gram positive rods are the causative agent of a form of toxin-mediated bacterial diarrhoea (now called *C. difficile* infection (CDI), previously referred to as *C. difficile* associated diarrhoea (CDAD)), which may lead to the development of potentially lethal pseudomembranous colitis.

Carriage rates of *C. difficile* vary in different age groups – in infants the carriage rate can be as high as 70%, in healthy adults it is usually < 3%.[12]

The use of certain antimicrobial classes is associated with an increased risk of CDI (**Table 19.10**), although other risk factors, such as use of proton pump inhibitors, presence of naso-gastric tubes, abdominal surgery or length of hospital stay also play a role. One possible control strategy of CDI is therefore restricting the use of these agents.

If CDI is suspected, the patient should be isolated and faecal samples tested for the presence of *C. difficile* toxin. Any contributing factors, such as proton pump inhibitors and antimicrobials should be removed, if possible.

Clinical severity of disease should be assessed and treatment strategies appropriate for the severity of the disease should be chosen. This may include oral metronidazole or vancomycin, but may also include intravenous immunoglobulins or colectomy in life-threatening cases.

Fidaxomycin is a recently licensed macrocyclic antibiotic that targets clostridium species specifically. The agent has recently been approved for restricted use in NHS Scotland, but guidance on its use in English NHS trusts is still outstanding.

As the concept of treating an infection caused by antimicrobials with another antimicrobial is somewhat illogical, non-antimicrobial methods of treating CDI are being investigated. A novel approach to the treatment of recurrent CDI that is becoming increasingly popular is the use of faecal transplantation to replace the abnormal gut flora with organisms that prevent overgrowth of *C. difficile*. This method of enhancing 'colonization resistance' has shown promising results in a number of studies.[13, 14]

Local protocols for treatment and infection control procedures are available in most hospitals.

TABLE 19.10 Antibiotics and CDI

Antibiotic classes most frequently associated with CDI
• Clindamycin • Quinolones • Broad-spectrum penicillin – β-lactamase inhibitor combinations • Cephalosporins

CORYNEBACTERIA

The *corynebacteria* and *listeria* are non-sporeforming Gram positive bacilli.

On Gram staining, both appear as pleomorphic Gram positive rods, often lying together in formations resembling Chinese lettering.

The different species of *corynebacteria* are indistinguishable on Gram stain, and in blood cultures they are frequently found as the result of contamination with skin commensals. These species may be involved in intravascular device associated infection.

Corynebacterium diphtheriae is the most important human pathogen. Diphtheria classically presents as a severe pharyngitis with pathognomonic formation of pseudomembranes. The organism can be grown on selective media containing tellurite and produces characteristic black colonies with a 'daisy head' edge.

There are four subspecies of *C. diphtheriae*, all of which are able to produce diphtheria toxin, the gene for which is integrated into bacterial genome by a lysogenic phage.

This toxin is made up of two protein subunits. Subunit B mediates entry of the toxin into the cell, where subunit A interrupts protein synthesis by inhibiting the elongation factor EF-2.

Mortality may arise from upper airway obstruction as a result of severe soft tissue swelling, but toxin-mediated myocarditis and polyneuritis are important contributing factors and anti-toxin should be administered to prevent death as well as significant neurological sequelae.

As the diphtheria toxoid vaccine is part of the routine childhood vaccination programme and has a good uptake (>94%), diphtheria is rare in the British population. The last case of respiratory diphtheria in Britain occurred in 1997, with only eight cases all in all since 1986. The patients in all cases had travelled to endemic areas (figures from Public Health England).[15]

Arcanobacterium haemolyticum is a Gram positive bacillus that produces haemolysis on blood agar. It is a cause of bacterial pharyngitis associated with a maculopapular rash in young adults, which clinically is similar to pharyngitis caused by Group A streptococci.

Gram negative organisms

As mentioned earlier, Figure 19.5 provides an overview of gram negative organisms commonly encountered in clinical practice.

The Gram negatives are distinguished from Gram positive organisms by a different cell wall structure.

In Gram negatives, the teichoic acid component that stains blue in Gram staining is much thinner and surrounded by an outer bi-layer membrane.

This membrane contains lipopolysaccharides that can act as superantigens and are responsible for triggering cytokine cascades that cause the systemic effects seen in Gram negative sepsis. This is sometimes referred to as the Gram negative endotoxin.

The periplasmic space between the outer membrane and the cell wall is where a number of Gram negative antibiotic resistance mechanisms are located (see also Figure 19.1).

GRAM NEGATIVE COCCI

Neisseria

Neisseria are the medically most important Gram negative cocci.

A number on non-pathogenic *Neisseria* spp. are commensals in the upper respiratory tract, but even the potentially highly pathogenic *N. meningitis* is carried asymptomatically by almost 24% of 19-year-olds; the carriage rates in young children and adults are generally lower than this.[16]

On Gram staining, neisseriae appear as small Gram negative diplococci. They will usually grow readily on a nutrient rich medium, such as chocolate blood agar, but selective media are available.

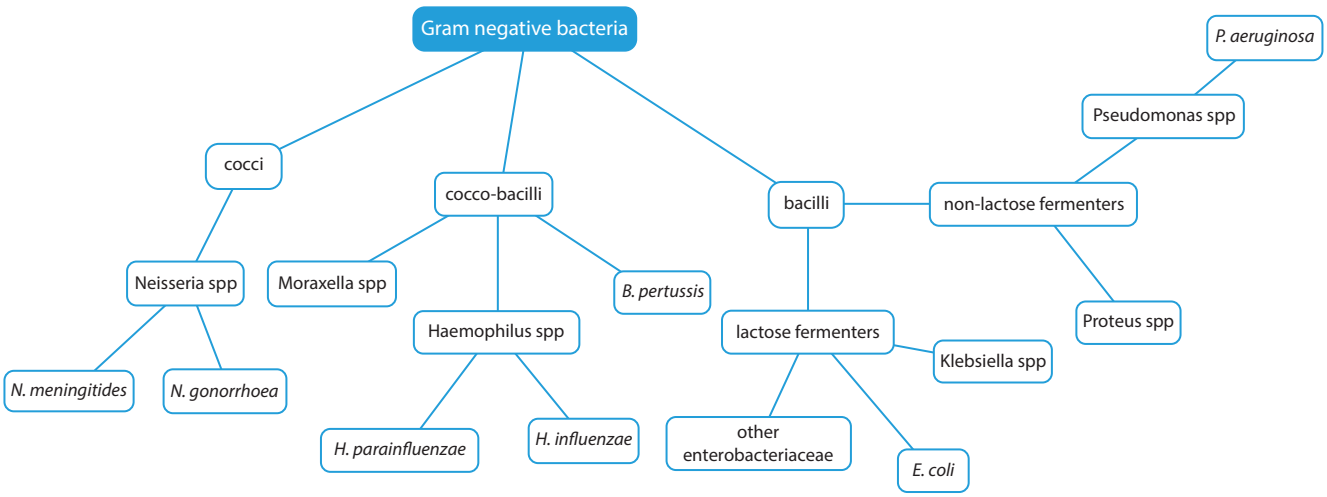


Figure 19.5 Overview of medically important Gram negative organisms.

Clinically *N. meningitis* can present with three distinct clinical syndromes: meningococcal meningitis, meningococcal septicaemia and meningococcal septic arthritis.

The first line treatment for suspected infection with *N. meningitis* is high dose ceftriaxone (i.e. 2 g IV twice daily). In patients with anaphylaxis to penicillins or cephalosporins, therapy should be discussed urgently with an infection specialist.

The infection is a notifiable disease and referral to public health should be made in order to allow early contact tracing and, where indicated, offer post-exposure prophylaxis to household contacts and health-care workers.

Vaccines targeting specific surface lipopolysaccharides are available for all major serogroups of *N. meningitidis*, but at present only the vaccine against serogroup C forms part of the UK vaccination schedule.

Neisseria gonorrhoea is indistinguishable from *N. meningitidis* on both Gram staining and appearance in culture, but they differ in their capability to metabolize glucose and maltose, which is used in the laboratory to identify them biochemically.

N. gonorrhoea can be carried asymptomatically in the upper airway as well as in the genito-urinary tract; infection may present as bacterial pharyngitis and it is not uncommon to isolate them from throat swabs.

Haemophilus influenzae

Haemophilus influenzae appears on microscopy as a Gram negative very short rod or cocco-bacillus. It has specific growth requirements in form of haemin and nicotinamide adenide dinucleotide and therefore grows more readily on a nutrient agar like chocolate blood agar.

Some strains are encapsulated, and six capsular serogroups (a–f) have been described.

Encapsulated strains, particularly strains of serogroup b, are associated with invasive disease. Asymptomatic carriage is common.

Infection can present as otitis, sinusitis or mastoiditis, acute bacterial meningitis and epiglottitis, but the most frequent presentation is as a lower respiratory tract infection.

Similarly to *S. pneumoniae*, *H. influenzae* may also be a causative agent in intra-cerebral abscess formation.

Moraxella catarrhalis is a Gram negative cocco-bacillus which is very similar to *Haemophilus* in that it forms part of the normal flora of the respiratory tract, but can play a role in otitis, sinusitis and infections of the lower respiratory tract, such as bronchitis and exacerbations of chronic obstructive pulmonary disease.

Some strains of *Moraxella* and *Haemophilus* produce a β-lactamase that renders them resistant to amoxicillin, but these strains will usually be sensitive to a penicillin with a β-lactamase inhibitor, such as amoxicillin with clavulanic acid and cephalosporins; other treatment options may include macrolides, quinolones or a tetracycline.

Bordetella pertussis

Bordetella pertussis, the causative agent of whooping cough, is a Gram negative organism of the upper respiratory tract that is exceedingly fastidious and conventional culture of this organism for diagnostic purposes has now been entirely abandoned in favour of PCR and serology.

Whooping cough is characterized by a bi-phasic clinical course. The early stage presents relatively non-specific with malaise and fever and is followed by a lengthy toxin-mediated phase of severe paroxysmal coughing, which may be accompanied by post-tussive emesis and is followed by a rapid intake of breath, the characteristic whooping.

In infants, the paroxysmal coughing can lead to significant hypoxia and be potentially fatal. Other risk groups include the elderly, immunosuppressed individuals and patients with chronic respiratory disease

Whooping cough is notifiable and contacts, especially if small children are among them, should be offered post-exposure prophylaxis.

Cases of pertussis have been increasing in the past few years. The vaccine is included in the vaccination schedule, but it is unclear for how long the vaccination actually protects against the effects of pertussis toxin. Due to this a pertussis booster vaccination is offered to women in the third trimester of pregnancy, as immunity of the mother will minimize the risk of the infant becoming infected.

Gram negative bacilli

As appearances in Gram staining and often also in culture are very similar between different species of this group, identification is usually performed on the basis of biochemical properties.

One of these is dependence on the presence of oxygen; although most organisms are facultative anaerobes that are capable of anaerobic metabolism if required, dependence on oxygen or strictly anaerobic growth can be a useful pointer towards a putative identification of a Gram negative organism.

Another useful reaction is the ability to metabolize lactose, and on the basis of this they can be split into lactose fermenters and non-fermenters. A number of commonly used media for the culture of Gram negative organisms, such as the MacConkey agar, contain a colour indicator and if the organism ferments lactose the resulting change in pH will lead to a colour change (**Figure 19.6**), allowing for a categorization of the organism on the first day that growth is observed.

The third bench procedure that may aid in early identification of certain Gram negative bacilli is the test for the presence of cytochrome oxidase.

Further identification is usually undertaken by means of semi-automated methods.

Overall, there is a large number of Gram negative bacillus species, but of these only a few are commonly found in human disease.



Figure 19.6 Non-lactose-fermenting (NLF) and lactose-fermenting (LFC) enterobacteriaceae on MacConkey agar. Courtesy of Jasminder Karde and Margaret Woods, Department of Microbiology, Golden Jubilee National Hospital, Clydebank, UK.

ENTEROBACTERIACEAE

The enterobacteriaceae are a group of Gram negative bacilli that are part of the resident flora of the human gut. They are facultatively anaerobic and many of these organisms are common in clinical isolates, although only few of them are invariably pathogenic (Table 19.11).

Enterobacteriaceae usually possess one or more flagellae and are therefore mobile – an extreme example of these are *Proteus* spp., which are capable of swarming across an entire agar plate and overgrow other organisms that may be present in the sample.

Clinically, infections with enterobacteriaceae most commonly present as urinary tract or intra-abdominal infections and they play an important in hospital-acquired infection. Most commonly, it will be the patient's own resident Gram negative flora that is involved in these infections.

Gram negative bacilli are frequent colonizers of the skin below waist level, chronic wounds and the mouth and respiratory tract, most frequently in individuals who are undergoing antimicrobial therapy and it can be difficult to judge the relevance of these organisms without careful clinical assessment.

If thought to be clinically relevant, a number of antimicrobial agents are available for treatment, but the choice of agent will usually be based on antimicrobial susceptibilities, as resistance patterns and mechanisms are manifold, widespread and difficult to predict.

Gram negative bacilli that display resistance against broad spectrum penicillins and third-generation cephalosporins via production of extended spectrum β-lactamases as well as the current emergence of carbapenem-resistant Gram negatives are developments that are likely to evolve into a major healthcare challenge.

TABLE 19.11 Examples of species of enterobacteriaceae

Opportunistic enterobacteriaceae	Pathogenic enterobacteriaceae
Escheria coli *Klebsiella* spp. *Serratia* spp. *Citrobacter* spp. *Enterobacter* spp. *Morganella* spp. *Proteus* spp.	*Salmonella* spp. *Shigella* spp.

PSEUDOMONAS

Pseudomonas spp. are aerobic oxidase positive Gram negative bacilli. They are widespread in the environment, but commonly present as opportunistic pathogens in a clinical context.

The best known species is *Pseudomonas aeruginosa*, which is easily recognized in culture due to a characteristic fruity smell and green pigment production by some strains (**Figure 16.7**).

It is a common causative agent of acute otitis externa, but also a frequent isolate from the respiratory tract or chronic wounds.

In the healthcare setting it also plays an important role in infections of venous access lines, as well as catheter-related urinary tract infections and hospital-acquired pneumonia and can cause bacteraemia secondary to these.

Treatment of pseudomonas infection is complicated by the fact that *Pseudomonas* spp. are carriers of a number of antimicrobial resistance genes, which may restrict options for antimicrobial treatment significantly. Severe infection (e.g. bacteraemia) is often treated with dual antimicrobial therapy (e.g. with an anti-pseudomonal penicillin or cephalosporin together with an aminoglycoside), as resistance has been shown

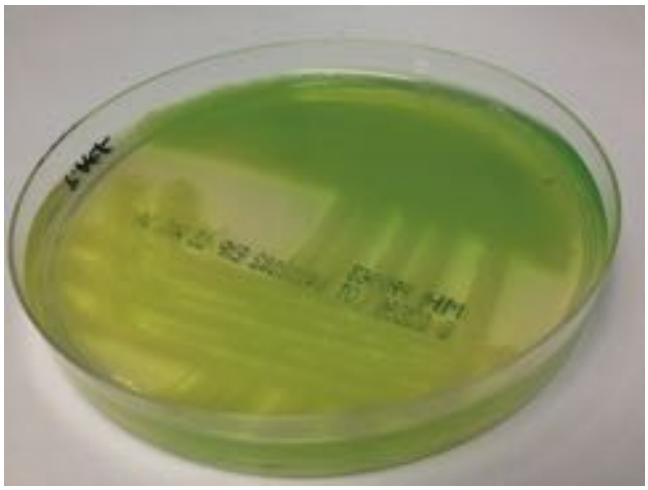


Figure 19.7 A pigment-producing strain of *P. aeruginosa*. Courtesy of Jasminder Karde and Margaret Woods, Department of Microbiology, Golden Jubilee National Hospital, Clydebank, UK.

to develop rapidly using a single agent; however, there is little evidence linking combination therapy with improved outcomes.[17]

Anaerobes

The anaerobes are a phyllogenetically heterogeneous group of organisms that are united by two characteristics – they grow in culture under strict anaerobic conditions and are sensitive to metronidazole (Table 19.12).

Their strictly anaerobic lifestyle makes isolation of these organisms from clinical samples a challenge. It is very difficult to grow them from swabs and recovery from a volume of pus sent in a container or capped syringe with all air expelled is usually more successful. In order to maximize the chances of isolating anaerobes, selective media are incubated in specific anaerobic cabinets for an extended period of time.

Anaerobic organisms form the majority of the resident flora of the gut and are commonly found in the oral cavity and as colonizers in wounds.

Most commonly, anaerobes cause pathology in the context of polymicrobial infections and an anaerobic organism being responsible for significant morbidity and mortality on its own is rare (Table 19.13).

One of these rare exceptions is *Fusobacterium necrophorum*. The name, literally translated, means 'the spindle-shaped bringer of death'. The organism is an anaerobic Gram negative rod, the shape of which is similar to a cigar or spindle.

The organism is classically the causative agent of Lemièrre's syndrome, although other *Fusobacterium* spp. are also able to produce the same presentation.

Lemièrre's syndrome usually affects young healthy individuals who initially develop bacterial pharyngitis with a peritonsillar abscess. In the anaerobic conditions of the abscess fusobacteria are able to multiply rapidly, invade the circulation and go on to cause severe systemic sepsis associated with septic embolic phenomena, classically in the form of lung abscesses arising from a septic thrombus of the internal jugular vein.

As the name suggests the condition is associated with a significant mortality rate.

Common to all anaerobic organisms is the susceptibility to metronidazole, although other antimicrobials such as clindamycin and rifampicin as well as β-lactam-β-lactamase-inhibitor combinations such as amoxicillin with clavulanic acid or piperacillin-tazobactam are also active against anaerobes.

TABLE 19.12 Anaerobic organisms

Examples of anaerobic organisms
Clostridium spp.
Bacteroides spp.
Finegoldia spp.
Peptostreptococcus spp.

TABLE 19.13 Polymicrobial Infections

Type of infection	Common organisms
Bites	Animal: • *Pasteurella multocida* • *Capnocytophaga canimorsus* • Gram negative organisms • Anaerobes Human: • Oral streptococci • Gram negatives • Anaerobes • Nocardia • Actinomyces • Blood-borne viruses
Brain abscesses	• S. pneumoniae • H. influenzae • Oral streptococci • S. aureus • Anaerobes
Necrotizing fasciitis	• S. pyogenes • S. aureus • Gram negatives • Anaerobes

Mycobacteria

The cell wall architecture of mycobacteria is characterized by the presence of mycolic acid, which is found in high concentrations in the waxy hydrophobic outer layer of the cell wall. Arabinogalactan connects this outer layer with an inner peptidoglycan layer. This makes the entire cell wall significantly thicker than that of either Gram negative or Gram positive organisms and conveys its typical staining properties of 'acid and alcohol fastness'.

If subjected to Gram staining, mycobacteria will typically present as slender, Gram positive rods, but the stain is only taken up very poorly, resulting in an irregular or beaded appearance. If a sample is examined for mycobacteria, specific stains such as the Ziehl-Neelsen method or an auramine stain will be performed.

In the laboratory, mycobacteria are subject to specific restrictions in terms of processing and handling in order to minimize the risk of laboratory acquired infection.

If mycobacterial infection is clinically suspected, this should therefore be indicated on the sample request form.

Growth requirements for *Mycobacterium* spp. also differ significantly from most other bacterial organisms. The organisms divide only slowly, which means that incubation times of up to 6 weeks are not unusual. An exception is the atypical or fast-growing mycobacteria, but even those will still grow much less readily that other bacteria. Due to this, PCR methods play currently play an important role in the diagnosis of mycobacterial infection.

Speed of growth is one characteristic by which mycobacteria can be categorized, but nowadays more common is the distinction between tuberculous mycobacteria or *M. tuberculosis* complex, which all cause a clinical presentation of tuberculosis and the non-tuberculous mycobacteria, which are able to cause a pulmonary disease resembling tuberculosis, but also

TABLE 19.14 Examples of mycobacteria

Non-tuberculous mycobacteria	*M. tuberculosis* complex
M. avium intracellulare complex	*M. tuberculosis*
M. kansasii	*M. bovis*
M. chelonae	*M. africanum*
M. fortuitum	*M. microti*
M. marinum	
M. abscessus	
M. gordonae	
M. ulcerans	

cause cervical lymphadenitis in children, skin infections and may cause disseminated disease in immunosuppressed individuals (Table 19.14).

Mycobacterium leprae is characterized by extremely slow growth and is the causative agent of lepra, which is still endemic in areas of the developing world.

Three agents form the mainstay of anti-tuberculous therapy: rifampicin, ethambutol and isoniazid, and most anti-tuberculous regimens will include some or all of these agents. Other agents may include aminoglycosides, such as amikacin or kanamycin.

The aminoglycoside streptomycin was the first available agent for the treatment of tuberculosis, but it has somewhat fallen out of favour due to high resistance rates.

The treatment regimen should be determined on the basis of a susceptibility profile and treatment regimens should be discussed with an infection or respiratory specialist.

It is worthwhile noting that some commonly used antimicrobials like macrolides and quinolones have anti-tuberculous properties and therapy with these in a patient with suspected mycobacterial disease may prevent microbiological diagnosis.

Due to the slow-growing nature of the organism, anti-tuberculous therapy is usually lengthy, often between 6 months and up to a year and in order to minimize resistance development patient concordance with therapy can be monitored.

Spirochaetes

Spirochaetes have a characteristic spiral shape, which is supported by an axial filament that is fixed to either end of the organism, but located outside the cytoplasm. The organisms wrap around this filament, which leads to a tumbling, rotating motion. This can be observed directly in dark field microscopy.

They cannot be grown in routine culture and PCR and serology are the investigations of choice for diagnosis.

There are many non-pathogenic species, but a few cause disease in humans.

Treponema pallidum is the causative agent of syphilis, which is a sexually transmitted disease which, if untreated, follows a multi-phasic course of initial painless ulcers at the site of entry which may be genital, anal or oral (primary syphilis) followed by early systemic symptoms such as a rash involving palms and soles (secondary syphilis), a period of latency and later systemic manifestations, including tabes dorsalis, dementia, polyneuropathy and mesaortitis (tertiary syphilis).

Borellia burgdorferi is transmitted via tick bites and causes Lyme disease, which initially causes a characteristic skin rash, the erythema migrans, and may be followed by a number of systemic effects, such as arthritis, cardiac conduction abnormalities and neuropathy, which may present as facial nerve palsy.

Actinomycetes

Actinomyces spp. are a group of Gram positive bacilli that are strictly speaking facultative anaerobes, but generally grow best under anaerobic conditions.

They are part of the normal oral and gut flora.

On Gram film, individual rod-shaped organisms form a structure that looks like fungal hyphen, giving the organism its Greek name that translates as 'ray fungus'.

The organism is slow growing and usually requires specific culture media for optimum recovery.

Infection with actinomycetes usually presents as a deep soft tissue or intra-abdominal abscess and is usually the result of penetrating trauma into the oral cavity or viscus.

Pus drained from actinomycotic collections characteristically contains the organism in distinct granula, often called sulphur granules due to their colour.

Treatment of tissue actinomycosis is usually with penicillins; alternatives are clindamycin, tetracyclines or cephalosporins. Depending on the site of infection and its accessibility for drainage, treatment is continued for anything between 6 months and life-long.

KEY POINTS

- A large variety of bacterial organisms can be involved in clinical infection. Some of these form part of the human normal bacterial flora and it may be difficult to distinguish between colonizing and infecting agents.
- Most organisms display characteristic virulence factors, such as formation of biofilms or toxin production, which will influence a therapeutic approach to infection with a specific organism.
- Processing of clinical specimens in the laboratory involves several steps that require overnight incubation. The average time from receipt of a sample to formal identification and sensitivities in a sterile site sample is 48 hours.
- Bacterial culture results need to be interpreted in the context of the clinical assessment in order to identify significant results.

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CHAPTER 20

VIRUSES AND ANTIVIRAL AGENTS

Richard B. Townsley, Camille A. Huser and Chris Hansell

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed/Google Scholar search using the keywords: virus, head and neck, and specific virus names.

INTRODUCTION

Viruses are small acellular infectious agents that can only replicate within cells. They characteristically comprise of genetic material made of nucleic acids (DNA or RNA) encased in a protective capsule of proteins, the nucleoprotein or nucleocapsid (Figure 20.1). Some also contain lipid envelopes. Envelopes originate from the cells in which the virus particle was made (through a process called budding), and are essentially lipid bi-layer vesicles enclosing the virus particle. During budding, the cell's membrane proteins are replaced with viral proteins, which are important for the virus's entry into a new host cell. Although they vary in size and shape enormously (range 20 nm to 500 nm), at a mode of around 100 nm in diameter, they are approximately 10 times smaller than bacteria. Viruses are therefore not normally visible by light microscopy. Classifying viruses is done according to three parameters: type of nucleic acid; shape and size of capsid; and presence of a lipid envelope.

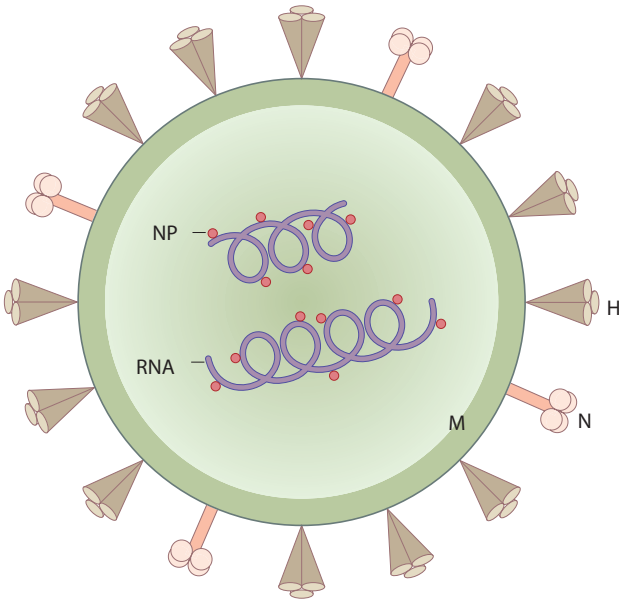


Figure 20.1 Diagram of influenza virus. H, haemaglutinin; M, matrix protein; N, neuraminidase; NP, nucleoprotein; RNA, ribonucleic acid.

VIRAL PROTEINS

The virus genome codes for viral proteins, which usually fall into two categories: structural proteins, such as those

comprising the capsid (including haemagglutinin, neuraminidase and matrix protein); and non-structural proteins such as viral enzymes (including integrase and reverse transcriptase), usually essential for viral replication.

VIRAL GENOMES

There are four main categories of viral genome: double-stranded DNA (dsDNA), single-stranded DNA (ssDNA), double-stranded RNA (dsRNA) and single-stranded RNA (ssRNA) viruses. The genomes of dsDNA viruses exist as a single DNA molecule, and usually contain a small amount of genetic information. On the other hand, the genome of dsRNA viruses is usually split into several fragments. ssRNA viruses are the most common type of virus. The RNA is termed either positive strand (if it can be used directly as a template for mRNA) or negative strand (if it must first be made into complementary RNA).

THE VIRUS LIFE CYCLE

There are as many life cycles as there are viruses, but there are some shared or common aspects (Figure 20.2). Firstly, viruses attach to the cells they will infect. The attachment is usually dependent on binding between proteins on the virus's surface and receptors on the cell membrane. This allows specificity of viruses for particular species and cell types: the virus can only infect cells that express the appropriate receptor on their surface. Following attachment, the virus enters the cell, usually through endocytosis. Once inside the cell, the viral capsid is removed in a process called uncoating, which involves proteases from either viral or cellular origin. Once the virus has uncoated and the genetic material is exposed, viral proteins are expressed and replication of the genetic material occurs, using both viral and cellular proteins and enzymes. Finally, new virus particles are assembled and released through host cell lysis or budding for viruses with envelopes.

DETECTION OF VIRUSES IN CLINICAL SAMPLES

Diagnostic virology has now become part of mainstream medicine for several reasons. Firstly, novel antiviral therapies, which are expensive and have side effects, have generated a need to precisely identify virus infections in order to treat patients appropriately. Secondly, novel technologies allow precise and rapid identification of a wide range of viruses. Thirdly, viral identification plays a greater role in the clinical management of chronic diseases such as HIV and hepatitis C. Finally, specific viral diagnosis is important for public health to track and control potential epidemics. There are several methods used to identify viruses: viral culture, antigen detection, nucleic acid detection and serology.[1] Viral culture is the more traditional method, and is slow and expensive. It involves growing the virus in cultured cells, and looking for characteristic phenotypic changes. Although it is slowly being phased out by molecular methods, it is the only method capable of maintaining a viable isolate for further tests. Antigen detection involves the use of specific tagged antibodies (usually to a fluorescent molecule) to detect specific viral proteins in clinical samples. Antigen detection using techniques such as enzyme-linked immunosorbent assay (ELISA) is of particular use for viruses that grow very slowly in culture, but is not suitable for certain viruses with wide antigenic heterogeneity, such as rhinoviruses. Serology, the detection of virus specific antibodies, is limited to cases in which

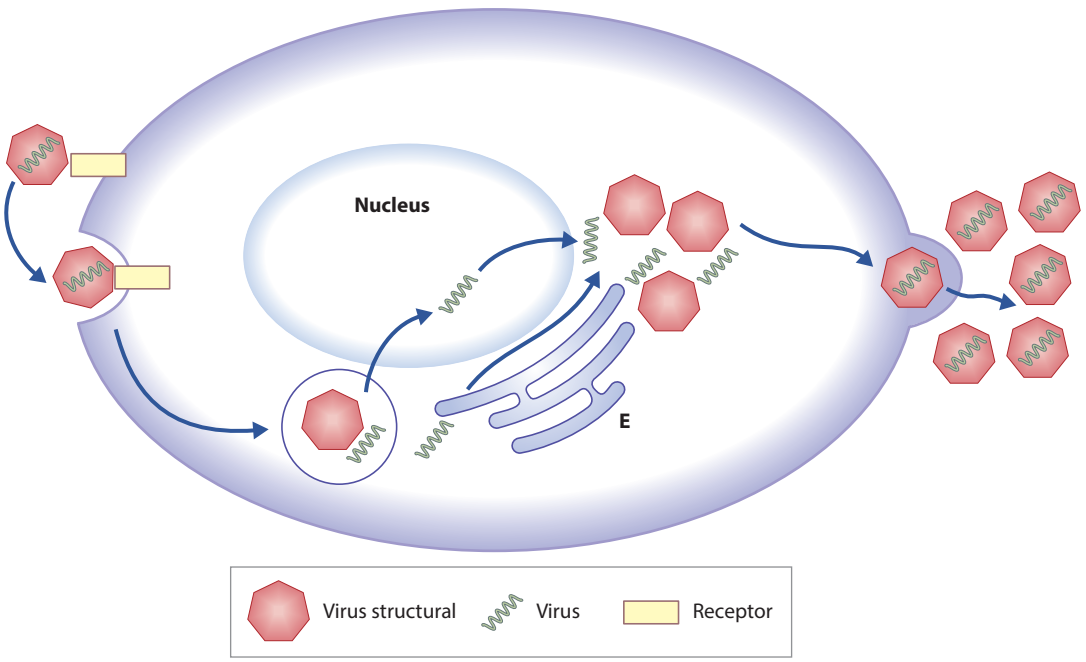


Figure 20.2 Schematic of a virus life cycle.

differentiation between acute and convalescent infection is essential. Differentiation is established by analysing levels of IgM (acute disease) and IgG (convalescent infection). Many diagnostic laboratories are adopting polymerase chain reaction (PCR) to identify viruses and virus strains. PCR is a technique used to specifically detect nucleic acid sequences, and can potentially detect the presence of any virus for which at least part of the genomic sequence is known. PCRs are sensitive and specific. Furthermore, viral RNA can be measured, giving an indication of viral load as well as strain using quantitative real-time reverse transcription PCR. Multiplex PCRs allow for the detection of a number of different viruses within one test, and can even detect viruses and other pathogens within a single test. Viral diagnostic tests can be performed on respiratory, cutaneous or blood specimens, depending on virus location.

RESPIRATORY VIRUSES

Respiratory viruses are the most common cause of illness in humans, and cause around 30% of child deaths in the developing world.[2]

Rhinoviruses (HRV)

Rhinoviruses (**Figure 20.3**) are a group of ssRNA viruses, which cause approximately half of all upper respiratory tract infections, otherwise known as the common cold.[3] The ssRNA genome of Rhinoviruses consists of a single gene, which is then cleaved to produce message for 11 proteins. Most rhinoviruses use the receptor ICAM-1 to enter cells and others use the low density lipoprotein receptor (LDLR). A new species of rhinoviruses was recently identified (HRV-C), whose mechanism of entry remains to be identified. Rhinoviruses are transmitted through contact or aerosol, via the intra-nasal or conjunctival routes. Rhinoviruses generally do not cause much pathology in the upper respiratory tract, but do disrupt the epithelial cell barrier, allowing transmigration of bacteria and exposure of toll-like receptors. In addition, it is now understood that rhinoviruses can exacerbate asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis.

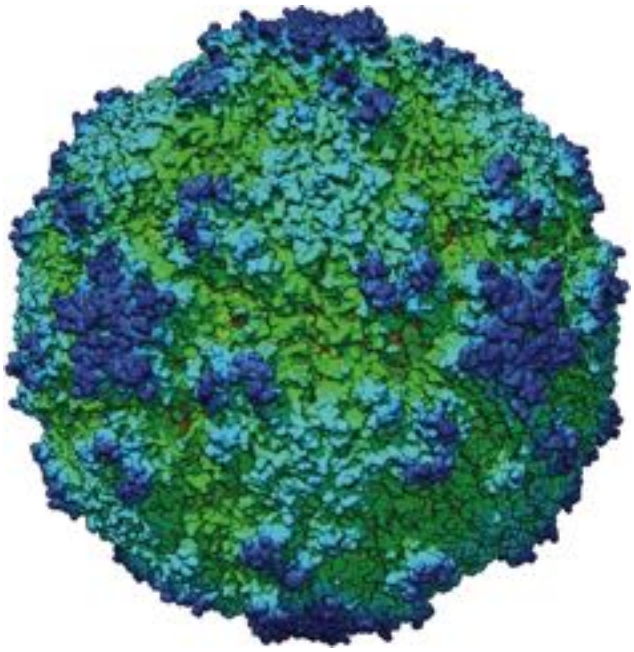


Figure 20.3 Rhinovirus. Courtesy of Dr. D. Bhella, MRC-University of Glasgow Virus Research Centre.

Corona viruses (HCoV)

Corona viruses are enveloped positive strand ssRNA viruses. They cause around 15% of upper respiratory infections otherwise known as common colds. There are two serotypes of corona viruses that were identified in the 1960s: group I or 229E, and group II or OC43. A third strain, SARS-CoV was discovered in 2003, followed by a fourth strain, HCoV-NL63. There are no vaccines available and immunity following infection wanes after a year or two.

Adenoviruses (HAdV)

These dsDNA viruses (**Figure 20.4**) cause acute respiratory disease, epidemic keratoconjunctivitis, as well as pharyngitis and pharyngeal-conjunctival fever in infants.[4] At the latest count, there were 67 different serotypes that are known to infect humans, and new serotypes are still being discovered. The large number of serotypes is due to frequent homologous recombination of viral genomes, and the detection and classification is greatly aided by improved methodologies such as rapid whole genome sequencing and bioinformatic analysis. In epithelial cells, HAdV infection causes the lysis of the cell when new viral particles are released. In lymphoid cells, fewer virus particles are released and the cell remains intact. HAdV have been linked to oncogenic transformation by two mechanisms: viral proteins such as E1A and E1B can transform human cells and the adenoviral DNA can integrate within the host cell DNA to cause oncogenic transformation.

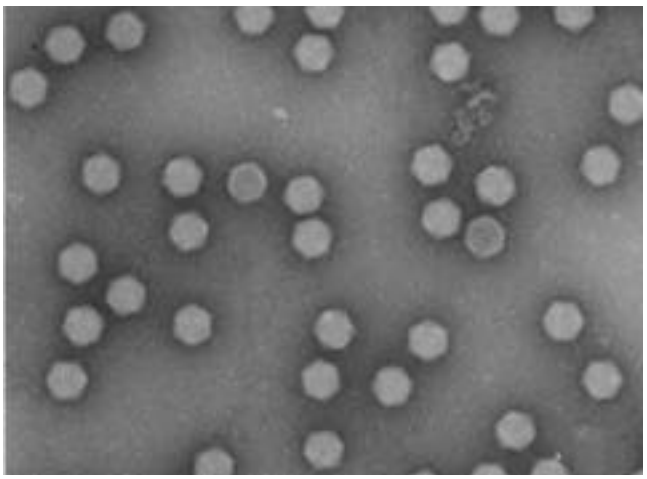


Figure 20.4 Electron micrograph of adenovirus. Courtesy of Dr D. Bhella, MRC-University of Glasgow Virus Research Centre.

Influenza

Enveloped and containing negative sense ssRNA, influenza viruses (Figures 20.5 and 20.6) are responsible for both seasonal endemic infections and occasional pandemics.[5] They cause respiratory disease with significant morbidity and mortality. Complications such as pneumonia, haemorrhagic bronchitis or laryngotracheitis (croup) can arise in patients with co-morbidities such as chronic pulmonary or cardiac disease, or diabetes mellitus. There are three subtypes of influenza virus: A, B and C. Types B and C are almost exclusive to humans while type A infects a very wide range of species. Influenza A viruses are further divided according to the antigenic subtype of their surface proteins haemagluttinin (H) and neuroaminidase (N). There are 16 H variants and 9 N. Currently, H3N2 and H1N1 ('swine flu') are the dominant circulating types, and H5N1 is the 'avian flu' type. Vaccination and antiviral drugs are used for prophylaxis. However, influenza viruses display continuous antigenic drift (i.e. they continuously acquire mutations which allow them to escape established immunity) so the vaccines are not effective for long. For this reason, the World Health Organization continuously monitors influenza infections in order to predict which specific vaccine will be required. Furthermore, the RNA genome of influenza viruses is segmented, and can recombine between two viruses of different subtypes if co-infection occurs in the same patient or animal. This allows antigenic shift and is how new subtypes such as H5N1 arise.

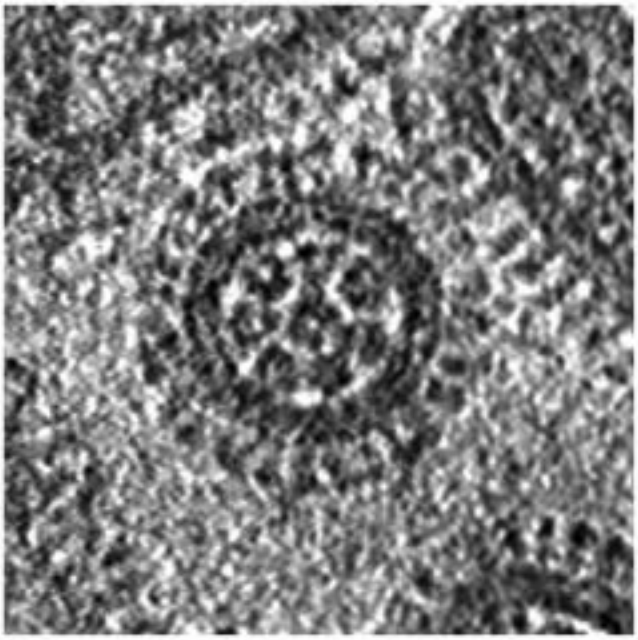


Figure 20.5 Electron micrograph of influenza virus. Courtesy of Dr D. Bhella, MRC-University of Glasgow Virus Research Centre.

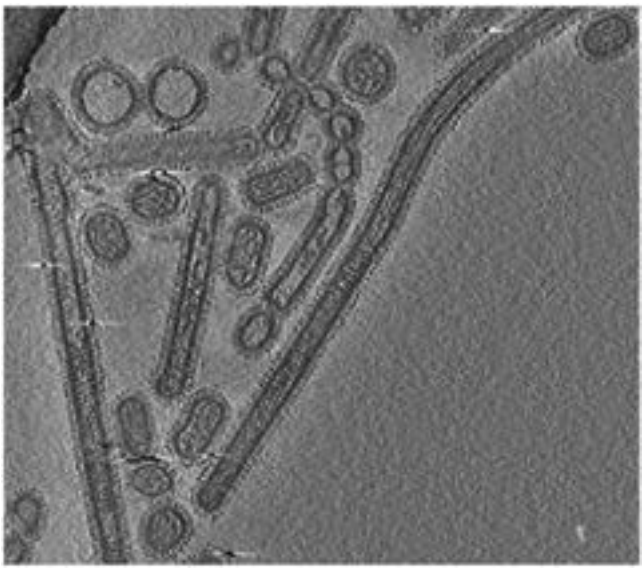


Figure 20.6 Tomogram slice of influenza-A virus. Courtesy of Dr D. Bhella, MRC-University of Glasgow Virus Research Centre.

Paramixoviridae

The paramixoviruses are a family of enveloped negative strand ssRNA viruses (Figure 20.7), responsible for a number of significant human diseases including those listed below.

RESPIRATORY SYNCYTIAL VIRUS (RSV)

RSV is the most common cause of respiratory tract infection in humans. In 1–2% of cases, complications such as broncholitis can occur, and are especially dangerous in infants and the elderly. Furthermore, it can exacerbate asthma and COPD. Despite ongoing research, no vaccine has yet been licensed for RSV, and the use of the neutralizing monoclonal antibodies palivizumab and motavizumab has at best, mild effects.[6]

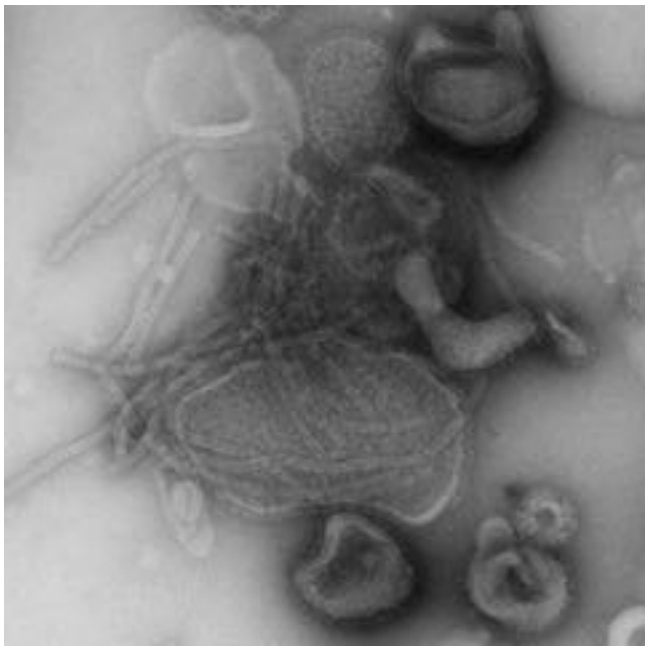


Figure 20.7 Electron micrograph of a paramixoviridae. Courtesy of Dr D. Bhella, MRC-University of Glasgow Virus Research Centre.

PARAINFLUENXA (hPIV)

This group of viruses is the second most common cause of child hospitalization for respiratory illness after RSV. There are four subtypes, which cause diseases such as croup (laryngotracheobronchitis, hPIV-1 and -2), bronchiolitis and pneumonia (hPIV-3). hPIV-4 causes asymptomatic or mild disease. There are also rare associations with viral meningitis and Guillain-Barré syndrome.

MUMPS

Mumps (Parotitis) is highly infectious and spreads through saliva. The virus probably penetrates the body via the mouth and can be detected in the oral cavity 1–6 days prior to the appearance of swollen salivary glands (especially parotid glands), a symptom that typifies the disease.[7] Other symptoms include fever and complications include oophoritis, orchitis, pancreatitis and viral meningitis. Transient hearing loss is a common symptom (approximately 1 in 20), but in extremely rare cases (1 in 20 000) can become permanent. Although the illness can occur at any age, most cases present in children between the ages of 5 and 10. The disease is self-limiting and in most children the symptoms are generally not severe. There is no cure for mumps and therefore treatment is restricted to symptom relief. Clearance of the virus leads to lifelong immunity and immunization with the live virus MMR vaccine between the ages of 12 to 15 months provides a similar level of immunity and protection from subsequent infection.

MEASLES

Measles is extremely contagious, and causes coryza, conjunctivitis, fever, and a typical maculopapular rash that appears 1–3 days after the onset of other symptoms. The infective stage extends from around 2–4 days prior to the appearance of a rash to 2–5 days after. In the early phase of the disease the infection is primarily spread via contact with nasal or oral excretions, and in the later stages via contact with the rash itself. Measles infection is associated with a number of serious complications including encephalitis and pneumonia, leading to death in approximately 1 in 5000 cases.[8] The group most at risk of developing such complications are infants less than 12 months old. In around 1 in 1000 cases, measles causes permanent bilateral deafness. Like mumps there is no cure for measles, and treatment is focused on ameliorating symptoms. However, the MMR vaccine given to children between the ages of 12 and 15 months elicits a highly effective and lifelong protection.

HERPES VIRUSES

Herpes viruses (HHVs) are a class of enveloped double-stranded DNA viruses that most commonly cause oral mucosal infections. They affect patients of all ages, and can cause significant pain and dysfunction.

Herpes simplex virus

Herpes simplex virus Type-1 (HSV-1) is the most common HSV affecting the mouth and is usually the cause of blisters in the skin and mucosal membrane called ‘cold sores’, although in rare cases, HSV-2 (which normally causes genital herpes) may be involved.[9] Lesions heal with a characteristic scab. HSV chronically but latently infects cells of the nervous system, hiding in the cell bodies. HSVs are spread through contact with saliva. The initial infection is resolved by the innate immune system, while the adaptive immune system clears the remaining active infection. The latent infection cannot be treated at present, but general antivirals are used to treat active infections.

Epstein-Barr virus

Epstein-Barr virus (EBV) is also called human herpes virus 4 (HHV4), and is the cause of infectious mononucleosis or ‘glandular fever’. It is transmitted through contact with saliva. Viral entry into cells occurs through binding to CD21 (entry into B cells) and β1 integrin (entry into epithelial cells). Similarly to HSV, after the primary infection, the infection enters a chronic latent phase that at the moment cannot be cured. As further detailed below, EBV is associated with several malignancies.

RETROVIRUSES

One large class of single-stranded RNA viruses are the Retroviridae, or retroviruses, which contain the enzyme reverse transcriptase, allowing them to synthesize double-stranded DNA from their RNA genome. One such virus is the human immunodeficiency virus (HIV), which is discussed in Chapter 23.

RUBIVIRUS

Rubella, also known as German measles, is a positive sense ssRNA virus with a lipoprotein envelope. Viral replication occurs in cells of the respiratory system. It is a purely human virus, with no animal reservoir, so could theoretically be eliminated with global vaccination strategies. In developed countries, vaccination has reduced the incidence of rubella to non-endemic levels. If contracted during pregnancy, rubella can cause congenital rubella syndrome in the foetus, with profound and serious consequences including ocular and neurological abnormalities and deafness.[8]

HUMAN PAPILLOMA VIRUS

Human papilloma virus (HPV) is a family of DNA viruses. There are at least 70 subtypes of HPV so far identified. Many of these are thought to be asymptomatic; however, a subset of HPV subtypes is associated with human disease (**Table 20.1**).

TABLE 20.1 Conditions associated with particular HPV types

Condition	Usual HPV type	Less common HPV type
Oral papilloma	6, 7, 11, 16, 32	
Common warts	2, 7, 22	
Plantar wart	1, 2, 4, 63	
Anogenital warts	6, 11, 42, 44	
Heck's disease	13, 32	
Multiple papillomatosis	6, 11	67
Laryngeal papillomatosis	6, 11	16
Oropharyngeal carcinoma	16, 18	6, 11, 30
Inverted papilloma	6, 11	18
Genital cancers	16, 18, 31, 45	various

CONDITIONS WITH A VIRAL AETIOLOGY

Viruses are responsible for a wide range of pathologies involving the head and neck (see Table 20.2 for a non-exhaustive list), and some of the most common ones are briefly described below.

Laryngeal papillomatosis

HPV6, 11 and more rarely HPV 16 are specifically associated with laryngeal papillomas. Treatment requires repeated laryngoscopy and bronchoscopy to facilitate surgical ablation of forming papillomas and avoid airway obstruction. Although malignant transformation can occur it is rare and typically associated with patients with additional risk factors such as smoking or long-term illness.

TABLE 20.2 Pathologies and associated viruses

Pathology	Virus(es)
Acute otitis media (AOM), and miringitis bullosa	Parainfluenza viruses, influenza viruses, rhinovirus, RSV, adenovirus
Asthma exacerbation	HRV, RSV, influenza, hPIV, adenovirus
Cold sores	HSV-1
Bronchiolitis	RSV, hPIV-3, influenza, adenovirus
COPD exacerbation	HRV, RSV, influenza, hPIV, adenovirus
Conjunctivitis	Adenovirus, HSV, VZV, HIV, poxvirus, picornavirus, measles
Typical maculopapular rash	Measles, rubella, parvovirus B19, HHV 6,7, EBV
Encephalitis	HSV-1,2, VZV, CMV, EBV, HHV6, adenovirus, influenza, measles, mumps, rubella, arboviruses
Cystic fibrosis exacerbation	HRV
Keratoconjunctivitis (epidemic)	Adenoviruses
Facial paralysis	Herpes zoster
Guillain-Barré syndrome	hPIV, EBV, HIV
Hearing Loss	Mumps, measles virus, VSV, cytomegalovirus, rubella virus, herpes zoster, parainfluenza viruses, influenza viruses
Infectious mononucleosis (glandular fever)	EBV
Labyrinth disease	HSV, varicella zoster, rubella, cytomegalovirus
Laryngeal papillomas	HPV-6, -11, -16
Laryngotracheitis (croup)	hPIV-1, hPIV-2, influenza viruses
Oophoritis	Mumps
Orchitis	Mumps
Parotitis	Mumps, HIV
Pharyngitis	Adenovirus, Coxsackie A, parainfluenza viruses, enterovirus-echo, HSV, EBV, VRS, influenza viruses, cytomegalovirus
Pneumonia	Influenza, hPIV-3, measles
Rhinitis	Adenovirus, coronavirus, parainfluenza viruses, rhinoviruses
Rhinosinusitis (predisposing to bacterial infection)	hPIV, influenza viruses, adenovirus, rhinoviruses
Stomatitis	EBV, HSV
Tonsillitis	Adenovirus, parainfluenza viruses, EBV, other viruses (42%)
Viral meningitis	Enteroviruses, hPIV, mumps, EBV, HSV, VZV, measles

Bell's palsy

Bell's palsy is an acute, idiopathic mononeuropathy affecting the facial nerve. The annual incidence is approximately 11–40/100000 with a lifetime risk of 1 in 60. The course is usually benign with complete resolution in 71% of untreated cases.[10] Although the aetiology remains unknown, one theory that has gained popularity is that the reactivation of latent varicella-zoster virus or herpes simplex causes inflammation and entrapment of the facial nerve in the narrow labyrinthine segment. This theory gained popularity after detection of the HSV-1 genome in endoneurial fluid in patients with Bell's palsy. However, a recent Cochrane review has shown antivirals against HSV are no more effective than placebo treatment in producing complete recovery.[11] This casts doubt on HSV being the causative agent for Bell's palsy. More recently, HPV-6 has been suggested as a possible causative agent after detection of significantly higher DNA copies in the saliva of Bell's palsy patients in comparison to healthy donors.[12]

Sensorineural hearing loss

Many viruses, including those that cause the common cold, have been implicated in sensorineural hearing loss (SNHL).[13]

In congenital hearing loss, cytomegalovirus (CMV) and rubella are the implicated viruses. CMV is the most common cause of non-hereditary congenital SNHL. In infants with congenital CMV infection, 33% of symptomatic and 21% of asymptomatic infants were found to have SNHL. The hearing loss progresses in 11% and fluctuates in 16%of cases.[14] A histological study of inner ear lesions in congenitally CMV infected foetuses identified the structures within the inner ear infected with the virus. These structures were all involved in endolymph secretion and potassium homeostasis and the authors therefore postulated that the mechanism of damage to the inner ear may be related to potassium dysregulation, which causes secondary degeneration of the sensory structures.[15]

Idiopathic sudden SNHL is often attributed to viral aetiology. Potential viruses involved include measles, mumps, rubella, CMV, HSV, varicella zoster virus (VZV), EBV, HHV, adenoviruses and arenaviruses. The viral hypothesis postulates two potential direct mechanisms, the first being cochleitis or neuritis, in which the virus invades the fluid and soft tissues of the cochlea or the cochlear nerve, respectively. The second mechanism involves reactivation of a latent virus in inner ear tissues. A third, indirect, viral mechanism has been hypothesized, which implicates a systemic or distant viral infection that either elucidates an antibody response which cross-reacts with an antigen in the inner ear, or that triggers a circulating ligand that in turn produces a pathologic activation of the cellular stress pathways in the cochlea.[16]

Acute otitis media

Acute otitis media (AOM) is a polymicrobial disease that in many cases occurs following a viral upper respiratory tract infection (URTI). One third of children with viral URTI develop AOM within four weeks of its onset.[17] Viral URTI plays a pivotal role in the pathogenesis of AOM by causing nasopharyngeal inflammation, alteration of mucous properties, reduction of the normal mucociliary clearance of the epithelial cells in the nasopharynx, middle ear and Eustachian tube. This causes changes in bacterial adherence properties and Eustachian tube dysfunction.

In viral AOM, rhinovirus and RSV are most commonly detected and adenovirus, coronavirus and PIV are found less frequently.[18] Furthermore, viral-bacterial interactions are thought to play a significant role in the pathogenesis of AOM.

VIRUSES AND MALIGNANCY

A virus that can cause cancer is called an oncovirus. In 2008, of the estimated 12.7 million new cases of cancer worldwide, 1.9 million were attributable to hepatitis B and C virus, human papilloma virus and helicobacter pylori infections.[19] With regard to primary head and neck malignancies, the International Agency for Research on Cancer has identified Epstein-Barr virus and human papilloma virus as causative oncoviruses for nasopharyngeal cancer and oropharyngeal cancer respectively.[20]

Epstein-Barr virus

Epstein-Barr virus (EBV), the first identified human oncovirus, was isolated from Burkitt Lymphoma (BL) cells in 1964[21] and its association with nasopharyngeal cancer was first recognized in 1966.[22] It has been implicated in a number of malignant diseases including nasopharyngeal carcinoma, Burkitt's lymphoma (BL) and B-cell lymphoma.

BL is a B-cell tumour typically involving the mandibular area and occurs in children aged 4–12 years. Malaria is considered a cofactor as BL is endemic in certain areas of Africa where malaria is hyperendemic. EBV can be detected in 95% of BL tumours.[23] Cyclophosphamide is the treatment of choice.

Nasopharyngeal carcinoma has a high incidence in south China, Indonesia and Vietnam. As well as racial predisposition and genetic factors, environmental factors have also been identified, in particular the consumption of salted fish and other processed foods containing volatile nitrosamines. In addition, EBV is widely accepted as a cofactor in the development of nasopharyngeal carcinoma. Higher EBV antibody titres are observed in most nasopharyngeal patients. Latent EBV infection is identified in cancer cells of virtually all cases of nasopharyngeal cancer in endemic regions. The clonal EBV genome is consistently detected in invasive carcinomas and high-grade dysplastic lesions.[24]

Hairy oral leukoplakia is considered a pre-malignant condition consisting of painless, white, raised lesions on the lateral aspect of the tongue. The condition occurs in

HIV infection and other causes of immunosuppression. Squamous epithelial cells have been demonstrated to contain large amounts of actively replicating EBV. Acyclovir inhibits EBV replication but only allows transient lesion regression.

Lymphomas occur more commonly in immunocompromised and HIV-infected individuals. In Hodgkin's and oral T-cell lymphoma, EBV proteins are expressed by tumour cells. Persistent EBV infection becomes uncontrolled in the immunosuppressed and there is an increase in viral replication and the numbers of virus-carrying B lymphocytes. Although this condition can remain 'silent', loss of immune control can lead to EBV-associated lymphomas.[25]

Human papilloma virus

Human papilloma virus (HPV) is a double-stranded DNA papovavirus with a predilection for human epithelial cells. It is causally associated with benign and malignant diseases of the upper airway. Multiple studies and reviews have collected sufficient evidence to link infection with HPV-16 to the development of oropharyngeal cancer.[26, 27] The association is strongest between HPV16 and tonsil cancer.[28] However, recent research has indicated that HPV positive head and neck squamous cell cancer is associated with improved prognosis over those which are HPV negative.[29]

VACCINES

Vaccination has been highly effective in controlling measles, mumps, rubella and influenza viruses. They are however ineffective against viruses which have multiple serotypes, such as rhinovirus.

Vaccines can be produced in a number of ways.

Live attenuated vaccines, such as the measles, mumps and rubella vaccines, use a weakened version of the live virus. This can be created by passaging the virus through a series of cell cultures or animal embryos. In this way, the virus loses its ability to replicate in human cells, creating a virus that can be recognized by the immune system and elicits an immune response, but cannot replicate well enough to cause disease.

Inactivated viruses, such as the polio and hepatitis A vaccines, are created by inactivating the virus using heat or chemicals. This renders the virus unable to replicate yet allows recognition of the virus by the immune system.

Subunit vaccines, such as the HPV vaccine, contain only elements of the virus. The HPV vaccines are created by the isolation of a single viral protein from each strain. These particles contain no genetic material from the virus but prompt an immune response that confers future protection against HPV infection.

ANTIVIRALS

Antivirals are a large class of drugs used to treat or prevent viral infections. Antivirals do not 'kill' the virus, but impede its replication or function. For this reason, specific antivirals are required for each virus type.

Matrix 2 ion channel blockers

The Matrix 2 ion channels (M2) are part of the influenza virus envelope, and play a crucial role in viral infection and replication. M2 blockers such as amantadine and rimantadine are effective for treatment of influenza A infections, but resistance is an increasing problem. For this reason, and as they are not well tolerated, these compounds are not recommended to treat influenza.[30]

Interferon

Interferons (IFN) were the first cytokines that demonstrated efficacy in the treatment of viral infections. They are a group of naturally occurring cytokines with important immunomodulatory and antiviral activities. Clinically, they have uses in the treatment of certain malignancies and also as antiviral agents. IFNs exert their therapeutic action both by direct cellular effects, via action on cell surface receptors leading to activation of signalling pathways, and by indirect mechanisms involving induction of host anti-tumour responses.[31] Interferon as a therapeutic agent is less effective *in vivo* than hoped. Unpleasant adverse effects such as 'flu-like' symptoms and haematological complications limit its use. However, alpha-interferon is used with success in chronic hepatitis B and C infection, often in conjunction with lamivudine and ribavirin, respectively.

Acyclovir

Acyclovir, a pro-drug, is phosphorylated by the thymidine kinase of the herpes virus. The active monophosphate inhibits herpes DNA replication. Acyclovir is used in the treatment of HSV and herpes zoster (HZV) infections and given as prolonged courses in those with recurrent HSV-1 and -2 infections. It is used as prophylaxis in bone marrow and organ transplant patients. High doses are given for varicella zoster virus (VZV) or HSV in the immunocompromised and HSV encephalitis.

Ganciclovir is a related compound with more activity against cytomegalovirus (CMV) than acyclovir. It is also more toxic and usually reserved to treat conditions such as CMV oesophagitis and retinitis in the immunocompromised.

Influenza neuraminidase inhibitors

Neuraminidase is a protein found on the surface of the influenza virion. Its function is to enable the release of progeny virions from the cell surface and prevent their self-aggregation. These antiviral agents prevent release and spread of progeny virions by blocking neuraminidase function.[32] Zanamivir is an influenza A and B neuraminidase inhibitor administered by powder inhalation. A Cochrane review of the use of zanamivir

and oseltamivir in healthy adults found that both drugs shortened the duration of symptoms of influenza-like illness by less than a day and that oseltamivir did not affect the number of hospitalizations. Prophylaxis trials showed that oseltamivir and zanamivir reduced the risk of symptomatic influenza in individuals and households. Oseltamivir was associated with side-effects, but zanamivir showed no increased risk of reported adverse events in adults.[33] Current guidance is that oseltamivir and zanamivir should only be used prophylactically for 'at risk adults' who have not been effectively protected by vaccination[34] and that use of these drugs in the treatment of influenza should also only be used for 'at risk' patients when national surveillance schemes indicate that influenza A or B is circulating.[30]

Ribavirin

Ribavirin is a synthetic analogue of guanosine. *In vitro* it has good activity against a range of viruses including RSV, measles, influenza A and B, hepatitis A, B and C as well as HIV. However, *in vivo* it has dose-limiting toxic effects and few clinical indications. It is used in hepatitis C infection and is administered by aerosol inhalation in paediatric cases of severe RSV infection. Its efficacy is controversial with many studies failing to show significant benefit.[35]

BEST CLINICAL PRACTICE

- ✓ Influenza immunization is recommended for at risk groups including those over 65, patients with chronic liver, cardiac, respiratory and renal disease, diabetes, immunosuppression and those in institutions.
- ✓ Influenza neuraminidase inhibitors are recommended only for 'at risk' patients.
- ✓ Although acyclovir is not always necessary in the immunocompetent patient, it is recommended in the immunocompromised, and at high dose in serious infection.
- ✓ In recurrent HSV infection, famciclovir or valacyclovir should be taken immediately upon the appearance of symptoms.
- ✓ There is no significant benefit in the use of anti-HSV antivirals in the treatment of Bell's palsy.

FUTURE RESEARCH

- ➤ **Virotherapy:** In recent years, research into the use of viruses for disease treatment has been re-energized by the ability to genetically engineer viruses. One category showing promise are oncolytic viruses, which kill cancer cells. For example, reovirus, a natural cancer cell-targeting virus that does not otherwise cause disease in humans is currently in Phase III trials for head and neck squamous carcinoma, in conjunction with chemotherapy. Viruses are also being engineered for their use in gene therapy, as a method of delivering therapeutic genes specifically to cancer cells. However, caution remains with integrating viruses, as inadvertent insertional mutagenesis and hence cancer development can result, as was seen in the trials for *Il2rg* gene therapy. To date, only one gene therapy treatment, Gendicide, is licensed for head and neck squamous cell cancers in China, but many clinical trials are ongoing internationally.
- ➤ Bacteriophages, a sub-group of viruses that infect bacteria are used to treat some bacterial infections. Future research may allow them to play a greater role in antibacterial treatment.
- ➤ **Novel antivirals:** Some specific novel small molecule compounds are showing promise as antivirals for influenza A and B by either interfering with the polymerase complex or with the RNA promoter. Other small molecules have been shown to interrupt protein interactions in a range of virus processes. It is possible that in the future, the emergence of specific small molecule antiviral therapeutics will improve treatment of viral diseases, but will require improved diagnostics due to their specificities for virus species and strains.
- ➤ **Vaccines:** Vaccine research is ongoing. Clinical trials and studies are underway to ascertain the impact of polyvalent HPV vaccines in the treatment of recurrent respiratory papilomatosis and in the prevention of head and neck cancers.

KEY POINTS

- Respiratory viruses are very common and cause significant morbidity and mortality.
- EBV and HPV are associated with a variety of malignant and pre-malignant conditions in the head and neck.
- Vaccination is highly effective in certain viral diseases. In others the characteristics of the virus have prevented effective vaccine development.
- Some antivirals, such as acyclovir, are highly effective while others have a limited role in controlling illness.

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CHAPTER 21

FUNGAL INFECTIONS

Emily Young, Yujay Ramakrishnan, Laura Jackson and Shahzada K. Ahmed

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: fungal infections in ENT, fungal infections in otolaryngology, fungal sinusitis, fungal rhinosinusitis, invasive fungal sinusitis, acute invasive fungal sinusitis, chronic invasive fungal sinusitis, chronic invasive granulomatous fungal sinusitis, fungal ball, allergic fungal sinusitis, oropharyngeal candida, otomycosis and speech valves fungal infection.

INTRODUCTION

Many thousands of species of fungi have been identified and these organisms are extremely diverse in terms of morphology and habitat. Only a small proportion of these organisms, however, are medically important pathogens, and even fewer of these are commonly encountered in otolaryngology practice.

In this chapter, we aim to expand upon previous editions by providing an introduction into the basic science of fungal infections, and their laboratory identification, as well as providing a concise update on the subject of fungal infections in ENT. This is presented in a subsite specific manner, and is based upon a comprehensive review of the literature on the subject. The basic science material has been obtained from salient texts[1–3] along with online resources aimed at scientists and medical professionals, and governed by the national mycological associations of Britain, America and Australia.

FUNGAL TAXONOMY

Fungi are one of four major groups of microorganisms (bacteria, viruses, parasites and fungi). They are eukaryotic organisms that reproduce through spore formation, and are distinct from both plants and animals. Based on the case or sac in which the spores are produced, fungi are classified into four divisions: Ascomycota (sac fungi), Basidiomycota (club fungi), Zygomycota (zygote forming fungi) and Deuteromycota (imperfect fungi).

Fungi exist in nature in one of two forms: as unicellular yeasts or as branching filamentous moulds. Some fungi are dimorphic – they change from one form to another depending on their environment. While yeasts cannot be seen with the naked eye, moulds can be seen as growths on ageing foods, or as mildew in damp bathrooms. Of the vast array of fungi in the environment, less than 200 species are associated with human disease and of these, only 20 to 25 species are common causes of infection.[1, 2]

Fungi with importance in otolaryngology typically belong to the divisions Ascomycota and Deuteromycota, divisions to which *Aspergillus* species and *Candida* species belong respectively. Whilst Candidiasis and Aspergillosis account for the majority of fungal infections, Zygomycetes also contribute to a significant proportion.[4] Pathogens in the Zygomycota phylum, including Mucor, Apophysomyces, Rhizomucor, Rhizopus and Absidia, more frequently cause infections in immunosuppressed patients with underlying conditions, such as diabetes and malignancy.[5]

FUNGAL TISSUE DIAGNOSIS

Specific tests are used to determine the causative agent of a fungal infection, and to guide the clinician towards appropriate treatment. For many superficial skin and yeast infections, a clinical examination of the patient and microscopic examination of the sample may be sufficient to determine that a fungal infection is present. Identification of the specific organism is not always necessary as several topical and oral antifungal treatment options are available for clinicians to prescribe empirically based on best practice guidelines and personal experience.

Fungi do not stain well with routine stains and special silver-impregnated fungal stains are required. The latter is not species specific. Other fungal tests including potassium hydroxide solution (KOH) prep test also detect fungi but are not species specific. This is a rapid test, which dissolves non-fungal elements in a sample. It is widely used on skin scrapings, tissue, body fluids and sputum. After the non-fungal elements of the sample are dissolved, yeast cells and fungal hyphae can be visualized directly on a microscope slide.

Similarly, the Calcofluor white stain (**Figure 21.1**) detects fungi rapidly in a non-specific manner from a similar range of samples to the KOH prep test. The stain binds to fungal elements in a sample and fluoresces under ultraviolet light allowing direct visualization on a microscope slide.

Fungal cultures are used to identify the specific fungi present in persistent fungal infections and in those that penetrate into deeper tissues or cause systemic infections. Fungi are typically slow-growing and must be isolated in specific fungal enrichment media that inhibit bacterial growth. Fungal culture can take several weeks depending upon the species isolated. Susceptibility testing performed on fungi isolated from a culture is used to determine which antifungal is best to use for treatment

When a fungal infection is persistent, involves deep tissues or there is systemic upset, more extensive testing may be required. As a minimum, susceptibility testing following fungal culture determines the most effective antifungal agents to use. This can take days to weeks after primary culture.

Serology for fungal antigens and antibodies may be used to determine if a patient has a specific fungal infection. They are more rapid than fungal cultures but only test for a specific fungal species, so are limited by the index of suspicion for a specific organism that the requesting clinician has. Fungal antibodies can also be present from a prior exposure to the organism so a single antibody test cannot always confirm the presence of a current infection in isolation. If antibody tests are requested to see if antibody titres are changing, results may take several weeks.

Molecular tests for nucleic acids are also available that detect genetic material of certain specific fungi. These are performed on samples of fungus isolated in culture and are not yet widely available (https://labtestsonline.org). The results of these tests may take days to weeks from the sample reaching the lab.

ASPERGILLUS SPECIES

The genus *Aspergillus* includes over 185 species. Around 20 species have so far been reported as causative agents of infections in humans. They are ubiquitous fungi found in the environment and are commonly isolated from soil and plant debris. The most commonly isolated species are *Aspergillus fumigatus* (**Figure 21.2**), *Aspergillus flavus* and *Aspergillus niger* (**Figure 21.3**). All three of these species are implicated in otomycosis, a superficial fungal infection of the ear canal, although in general *Aspergillus niger* is the most commonly isolated; this can be population dependent.[6]

Aspergillus species (*Aspergillus* spp.) are implicated in opportunistic infections, allergic states and toxicoses. Immunosuppression is the major factor predisposing to development of opportunistic infections. These can present as minor local infections or disseminated aspergillosis.

Almost any organ or system in the human body may be involved. In ENT practice, *Aspergillus* spp. most

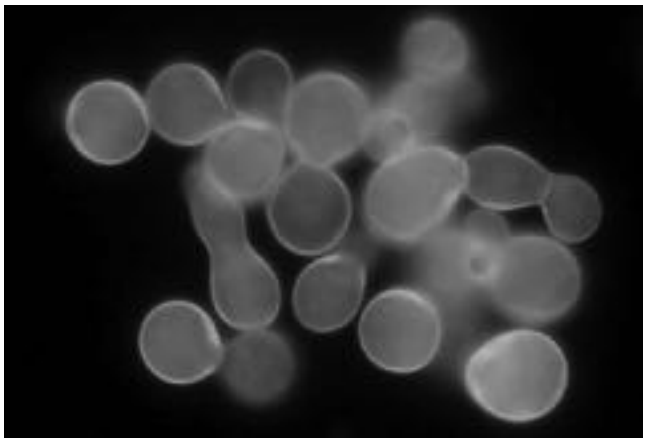


Figure 21.1 Blastomycosis-Calcofluor white stain of yeast phase growth at 30°C (1000x magnification). Courtesy of http://www.mycology.adelaide.edu.au/gallery/dimorphic_fungi/

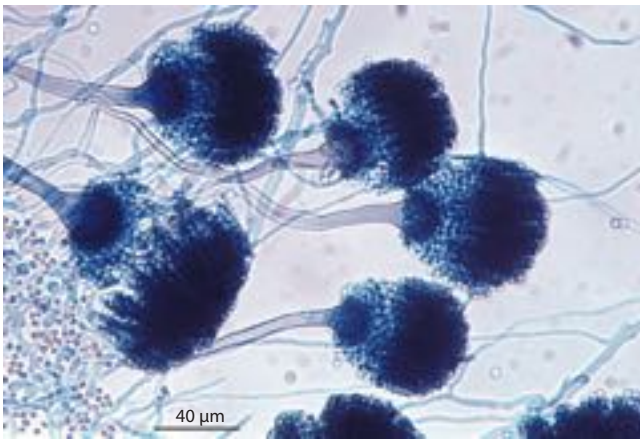


Figure 21.2 *Aspergillus fumigatus* colony growth on Czapek dox agar showing atypical blue-green surface pigmentation. Courtesy of http://www.mycology.adelaide.edu.au/gallery/hyaline_moulds/

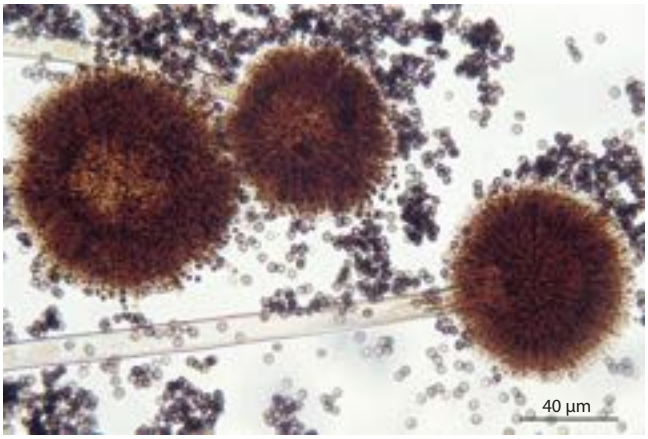


Figure 21.3 *Aspergillus niger* – microscopic morphology.
Courtesy of http://www.mycology.adelaide.edu.au/gallery/hyaline_moulds/

commonly infect the sinuses, which can rarely result in meningitis or cerebral aspergillosis, and the external ear canals, resulting in otomycosis. Construction in hospital environments poses a major risk for development of aspergillosis by unearthing spores from the environment. This is particularly risky in immunosuppressed, or neutropenic patients.

It is important to note, however, that since *Aspergillus* spp. are found in the natural environment, they are also common laboratory contaminants and therefore an awareness of the clinical features of their infections is paramount to allow for accurate clinical correlation of laboratory reports.

Within the Aspergilli, the major macroscopic features remarkable in species identification are the growth rate, colour of the colony, and thermotolerance. For the otolaryngologist, these finer details are something to be aware of, but will not be considered further in the context of this chapter.

CANDIDA SPECIES

Candida species (*Candida* spp.) are yeasts and the most common cause of opportunistic mycoses worldwide. *Candida* spp. are frequent colonizers of human skin and mucous membranes lining the mouth, vagina and gastrointestinal tract. As well as being a colonizer and opportunistic pathogen, it is found in the environment, on leaves, flowers, water and soil.

The genus *Candida* includes around 154 species, the majority of which are not frequently isolated in human infections. While *Candida albicans* is the most abundant and significant species, there has been a recent increase in infections due to non-albicans *Candida* spp. Patients who receive fluconazole prophylaxis, for example head and neck oncology patients, are at risk of infections with fluconazole-resistant *Candida krusei* and *Candida glabrata* strains. The diversity of pathogenic *Candida* spp. is expanding and the emergence of other species is a real possibility.



Figure 21.4 *Candida albicans* – microscopic morphology.
Courtesy of http://www.mycology.adelaide.edu.au/gallery/yeast-like_fungi/

Infections caused by *Candida* spp. are in general referred to as candidiasis. The clinical spectrum of candidiasis is extremely diverse. In otolaryngology, the most frequently encountered candida infections are of the oropharynx, larynx and external ear canal, although almost any organ or system in the body can be affected. Infection can be superficial and local or deep-seated and disseminated. Disseminated infections tend to arise via haematogenous spread from the primary infection site. *Candida albicans* (**Figure 21.4**) is the most pathogenic and most commonly encountered species. Its ability to adhere to host tissues, produce secretory aspartyl proteases and phospholipase enzymes, and transform from yeast to hyphal phase are the major determinants of its pathogenicity. Several host factors predispose to candidiasis including pregnancy, extremes of age, trauma, immunosuppression (including steroid use), endocrine disease and antibiotic use.

Candidiasis is mostly an endogenous infection, arising from overgrowth of the fungus inhabiting in the normal flora. However, it may occasionally be isolated from exogenous sources (such as catheters or prosthetic devices such as speech valves in laryngectomy patients) or by person-to-person transmission, such as oral candidiasis in neonates of mothers with vaginal candidiasis.

TRICHOPHYTON

Trichophyton is a dermatophyte that ordinarily inhabits soil. It is a leading cause of hair, skin and nail infections in humans and is most commonly encountered by the otolaryngologist as a causative agent of pinna dermatosis. There are several species of Tricophyton, most commonly being *Trichphyton mentagrophytes*, *Tricophyton rubrum* and *Trichophyton schoenleinii*. Trichophyton is a keratinophilic filamentous fungus with the ability to invade keratinized tissues. It produces enzymes such as proteinases, elastase,

and keratinases, which are the major virulence factors of these fungi.

CONIDIOBOLUS

The genus Conidiobolus contains several species. The most common ones are *Conidiobolus coronatus*, *Conidiobolus incongruus* and *Conidiobolus lamprauges*. Conidiobolus is a mould most commonly found in soil and decaying plant debris. It is mostly distributed in tropical areas and particularly in Central America, equatorial Africa and India (www.mycology.adelaide.edu.au). The most common clinical picture caused by *Conidiobolus* spp. is a subcutaneous infection involving nasal mucosa and maxillofacial tissues. This chronic inflammatory granulomatous disease is also referred to as entomophthoromycosis conidiobolae.[7] It involves facial subcutaneous tissues and paranasal sinuses, leading to formation of firm, subcutaneous nodules or polyps. The infection may be acquired via inhalation of spores or a minor trauma such as an insect bite. The infected host is frequently an otherwise healthy individual working outdoors in tropical areas. However, the infection may also develop in patients with underlying pathologies, such as neutropenia or Burkitt's lymphoma.

On potato dextrose agar and following incubation at 25° *Conidiobolus* spp. produce rapidly growing colonies which are glabrous and waxy initially and become powdery after development of aerial hyphae. The colonies mature in about 5 days. (mycosesstudygroup.org)

In vitro data on the activity of antifungal agents against Conidiobolus isolates are very limited.

There is as yet no standard regimen for treatment of Conidiobolus infections. Potassium iodide, trimethoprim sulfamethoxazole, and azole derivatives have been used.

CRYPTOCOCCUS

Cryptococcus is an encapsulated yeast. Following its first identification in nature from peach juice samples, the major environmental sources of *Cryptococcus neoformans* have been shown to be either soil contaminated with pigeon droppings (*Cryptococcus neoformans* var. *neoformans*) or eucalyptus trees and decaying wood forming hollows in living trees. The genus Cryptococcus includes around 37 species. Among these, *Cryptococcus neoformans* is the only species that is pathogenic. It has four serotypes, A to D. *Cryptococcus neoformans* was generally accepted to include two varieties; var. *gattii* and var. *neoformans*.

The definitive identification of *neoformans* and *gattii* varieties is possible by biochemical tests, such as resistance to canavanine and EDTA.

Cryptococcus neoformans is the causative agent of cryptococcosis. Given the neurotropic nature of the fungus, the most common clinical form of cryptococcosis is meningoencephalitis. The course of the infection is usually subacute or chronic.

The polysaccharide capsule and phenol oxidase enzyme of *Cryptococcus neoformans*, as well as its ability to grow at 37°C, are its major virulence factors. The infection commonly starts following inhalation of the yeasts.

Colonies of *Cryptococcus neoformans* are fast growing, although the growth rate is slower than *Candida* and usually takes 48 to 72 h. It grows well at 25°C as well as 37°C. Ability to grow at 37°C is one of the features that differentiates *Cryptococcus neoformans* from other *Cryptococcus* spp.

RHINOSPORIDIOSIS

Rhinosporidiosis is an infectious disease caused by an aquatic protozoan previously considered to be a fungus. The aetiologic agent of rhinosporidiosis, *Rhinosporidium seeberi*, is closely related to several protoctistiae fish pathogens. The infection affects nasal mucous membranes and ocular conjunctivae of humans and animals, producing slowly growing masses that degenerate into polyps. As this is no longer considered to be a fungal pathogen it will be considered no further in this chapter.

FUNGI IN ENT CLINICAL PRACTICE

Otomycosis

Otomycosis is a fungal infection of the external ear canal that can also affect mastoid cavities and in complicated cases, the middle ear. It is more common in hot, humid climates compared to temperate ones. Approximately 9% of cases of otitis externa are due to otomycosis.[8] Other studies have reported a prevalence of up to 30% in patients presenting with inflammatory conditions of the ear.[9] There is no preponderance of either gender, and it can affect any age, although it is rare in young children.

PREDISPOSING FACTORS

The most common causal fungal organisms are *Aspergillus niger*, *Candida albicans*, *Actinomyces*, *Trichophyton*, *Aspergillus fumigatus* and *Candida tropicalis*. Common predisposing factors include prolonged treatment with topical antibiotics, hearing aid use, regular swimming in contaminated water, trauma to the ear canal and immunosuppression.[10]

CLINICAL FEATURES

The symptoms of otomycosis are non-specific and include itching, otalgia, otorrhoea, aural fullness, hearing loss and tinnitus. Furthermore, although the classic sign of otomycosis is the presence of waving conidiophores, this is not universally present. Yeasts, such as *Candida* species, do not form the closely woven mass of hyphae that are formed by moulds, such as *Aspergillus* (**Figure 21.5**).[8]

More common is the finding of generalized inflammatory changes of the external canal (oedema, hyperaemia, granulomatous myringitis and aural discharge of variable colour.[11]

COMPLICATIONS

Fungal malignant otitis externa is a skull base osteomyelitis and occurs when inadequately treated fungal infection spreads through small gaps in the cartilaginous floor of the external ear canal, and spreads medially to the skull base. From here, bony destruction continues, with cranial nerve palsies occurring, particularly affecting the facial nerve. Other lower cranial nerves including IX, X, XI and XII can also be affected. Malignant otitis externa should be suspected in a patient with severe otalgia, which interrupts sleep, and often occurs in immunocompromised patients. In a review of all reported cases of fungal malignant otitis externa, 84% of patients had conditions causing immunocompromise, including diabetes, AIDS and acute myeloid leukaemia.[12] Forty-four per cent had an associated cranial nerve palsy. Amphotericin B is traditionally used as a treatment for fungal malignant otitis externa, although more recently voriconazole has become more popular, due to its more favourable side effect profile.[13]

MANAGEMENT

The treatment for otomycosis includes elimination of predisposing factors, thorough aural cleaning and antifungal agents. Topical antifungals can be specific (clotrimazole, miconazole, econazole, nystatin, tolnaftate, potassium sorbate) or non-specific (acetic acid, alcohol, boric acid, m-cresyl acetate, and gentian).[14]

Overall, there are four main classes of antifungal treatments: azoles, polyenes, nucleoside analogues and echinocandins. Azoles are synthetic agents that block the synthesis of ergosterol, an essential component of fungal plasma membranes. Clotrimazole is one of the most widely used azoles in otomycosis and is highly effective, with efficacy rates of between 95% and 100%.[15] Other azoles that are widely used include fluconazole, ketoconazole and miconazole. Polyenes, such as nystatin, are thought to interact with sterols in the fungal plasma membrane, causing pores to form within the membrane, thus causing altered permeability and fungal death.[16] Although nystatin is not available as an otic preparation it can be prepared as a solution or suspension, or applied as a cream, ointment or powder. Amphotericin B, another polyene antifungal agent, is used in severe, life-threatening infections, such as fungal malignant otitis externa. Nucleoside analogues, such as flucytosine, interfere with fungal DNA, RNA and protein synthesis. Flucytosine has a reported efficacy of 90% and is available as an ointment.

Other agents less commonly used include Gentian Violet, boric acid and cyclopiroxolamine. Boric acid is a keratolytic non-specific agent, more commonly used in countries with less availability of specific antifungal agents.

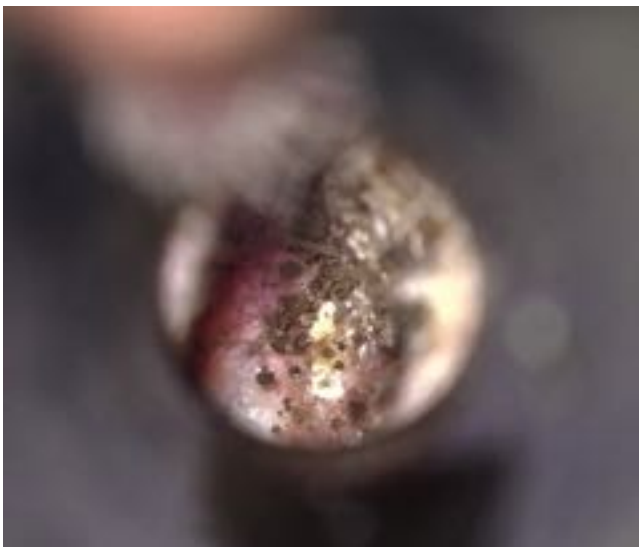


Figure 21.5 *Aspergillus niger* causing otitis externa.

Fungal disease of the paranasal sinuses

Fungi can affect the paranasal sinuses through inhalation of spores. Fungi are ubiquitous within the environment, but can rarely cause disease within the paranasal sinuses, often but not always in the presence of predisposing factors. The spectrum of disease is largely dependent on the immunological competence of the host.

Fungal disease affecting the sinuses can be defined as acute or chronic (lasting over 4 weeks) or as invasive or non-invasive. Invasive fungal disease is defined as the presence of fungal hyphae within mucosa, submucosa, bone, blood vessels and nerves of the paranasal sinuses. Non-invasive fungal disease implies colonization of the surface of epithelial tissues, rather than invasion. Currently, fungal rhinosinusitis is classified into three invasive (acute necrotizing, chronic invasive, and granulomatous invasive) and two non-invasive (fungal ball and allergic fungal) subgroups (**Table 21.1**).

Acute invasive fungal rhinosinusitis (AIFR)

AIFR is a rare but rapidly progressive disease process that can result in fatality within days. It is the most lethal form of fungal sinusitis with mortality rates of at least 50%.[17] *Aspergillus* and *Zygomycetes (*particularly *Mucor* and *Rhizopus)* are the causative fungi in most cases. A high degree of clinical suspicion is required in order to correctly and promptly diagnose and manage this condition.

Following inhalation of spores, the fungi grow and invade neural and vascular structures, leading to vessel thrombosis and resultant mucosal necrosis. The fungi then extend beyond the affected sinus through a combination of bony destruction, perineural and perivascular spread.

PREDISPOSING FACTORS

Two main groups of patients are thought to be at risk of AIFR: diabetics, particularly with ketoacidosis, and patients who are immunocompromised (severe neutropenia, haematologic malignancy, systemic chemotherapy, steroid therapy, bone marrow transplantation, AIDS). Diabetic patients are particularly at risk from

TABLE 21.1 Definitions of fungal disease affecting the paranasal sinuses

	Non-invasive		Invasive		
	Fungal ball (mycetoma)	**Allergic fungal sinusitis**	**Acute invasive fungal; sinusitis**	**Chronic invasive fungal sinusitis**	**Chronic granulomatous invasive fungal sinusitis**
Pathogen	*Aspergillus* species; *Pseudallescheriaboydii*	Primarily dematiaceous species: *Bipolaris, Alternaria, Curvularia*; also *Aspergillus* species and multiple other moulds	Mucormycosis (Diabetics); *Aspergillus Fumigatus* (immunocompromised), *Candida* species, *Fusarium*	*Aspergillus flavum, A. fumigatus*	*Aspergillus flavum*
Immune status of host	Immunocompetent	Atopic	Immunocompromised	Immunocompetent or mildly immunocompromised	Immunocompetent
Geographical distribution	Humid area	Humid area	Non-specific	Non-specific	North Africa
Radiological findings	Hyperdense on CT, especially maxillary and sphenoid sinus	CT-heterogenous sinus opacification, bony remodelling +/– erosion MRI – signal void on T2 depending on metal concentration within mucin	CT-sinus opacification, bony erosion and tissue infiltration	CT-sinus opacification, bony erosion and tissue infiltration	CT-sinus opacification, bony erosion and tissue infiltration
Treatment	Surgical	Surgical + medical	Reversal of underlying Immunocompromise, surgical + antifungal therapy	Surgical + medical	Surgical + medical

Zygomycetes (*Rhizopus, Mucor*) as these organisms have an active ketone reductase system and thrive in high glucose acidotic conditions. *Aspergillus* species commonly affect immunosuppressed patients.[18] Iron-overload is also thought to be a predisposing factor, particularly after treatment with deferoxamine, an iron chelator, for iron overload due to multiple blood transfusions. *Rhizopus* binds to deferoxamine and uses it to bind iron, which it requires for growth.[19]

CLINICAL FEATURES

The clinical hallmark of AIFR is febrile neutropenia and facial pain with or without nasal congestion and orbital signs.

Symptoms and signs occur rapidly, often within hours, depending on the pattern of invasion into nearby structures. Nasal features include discolouration of nasal mucosa, granulation, ulceration and crusting. Later, spread to the orbit and intra-cranially can result in proptosis, diplopia, visual loss and neurological deficit. Infection can extend to the cavernous sinus via the orbital apex, causing palsies of cranial nerves III, IV and VI resulting in opthalmoplegia and orbital pain (ophthalmic division of trigeminal nerve). Orbital signs and symptoms are common presentations, occurring in around half of patients in a recent systematic review by Turner et al. examining survival outcomes in AIFR.[20] Thrombosis of the cavernous section of the carotid artery can extend to other branches at the circle of Willis. As a result once disease has spread to the cavernous sinus, cerebral or brainstem infarction is almost inevitable. Intra-cranial extension presents as headaches, neurological deficit, seizures and coma. Around a fifth of patients in Turner's systematic review presented with altered mental status.

Interestingly, patients can present with advanced AIFR with orbital and cerebral complications with few signs or symptoms of rhinosinusitis and nasoendoscopy may be essentially normal.[21] This reinforces the need to have a high degree of suspicion in patients with immunocompromise presenting with orbital or cerebral signs, with or without symptoms of sinus disease.

DIAGNOSIS

Changes in mucosal appearance and/or sensation (anaesthesia) are typical on endoscopic examination. In the early stages, the mucosa may appear pale. Necrosis resulting from angioinvasion results in black crusts and sloughing of the mucosal surface of the nose and septum; septal perforation may be present. Biopsies should be taken from multiple sites, particularly the middle turbinate and septum in order to confirm the diagnosis and the causal fungal organism. The gold standard of diagnosis is pathological examination of permanent sections, prepared in potassium hydroxide. This allows the identification of invasive features, and can often distinguish *Mucorales* from *Aspergillus* fungi. However, this process is time

consuming and may delay the diagnosis and institution of treatment. Frozen section is a technique that is useful in order to provide rapid evidence of invasion, and has been found to have a sensitivity of 84% and a specificity of 100% for the diagnosis of AIFR compared to gold standard permanent sections.[22] Culture should also be undertaken in order to confirm the species of fungus responsible and sensitivity to antifungal agents, although culture has been found only to have a sensitivity of 54%.

Both CT and MRI are invaluable in the diagnosis of AIFR. CT allows detection of bony destruction while MRI is better at detecting mucosal, skin invasion, orbital or intra-cranial involvement. Non-contrast CT may show hypoattenuating mucosal thickening in the affected sinuses, bony erosion and/or thickening of periantral fat planes. MRI is superior at evaluating extra-sinus disease, such as intra-cerebral and intra-orbital spread. Early orbital changes include inflammatory changes in orbital fat and extra-ocular muscles and resulting proptosis. There may be subtle obliteration of periantral fat. Early changes in the cerebrum include leptomeningeal enhancement, which may preclude the development of frank abscesses or granulomas. There may be evidence of cerebral infarction or subarachnoid haemorrhage due to either thrombosis of the carotid artery and branches or mycotic aneurysm.[23]

MANAGEMENT

The mainstay of treatment is reversing the underlying immunosuppression (e.g. ketoacidosis or neutropenia) aggressive surgical debridement and broad spectrum antifungal therapy. Hyperglycaemia should be reversed and blood glucose levels should be tightly controlled. Reversal of neutropenia, if possible, improves survival, and there may be a role for granulocyte-colony stimulating factor in these patients.[18, 24]

Surgical treatment (endoscopic or open) aims to confirm the diagnosis and remove non-viable tissue. Debridement is carried out until clear, bleeding margins are observed. There is little evidence that radical resection, including orbital exenteration and radical maxillectomy, improves survival. In fact, in the systematic review carried out by Turner et al.,[20] patients who underwent endoscopic resection had significantly improved survival compared to those who underwent open surgery, although this may partly be due to the fact that patients undergoing open surgery had far more advanced disease. There is little consensus as to the role of orbital exenteration, although most agree that it should be reserved for those with a completely non-functioning eye.[25] A multidisciplinary approach utilizing ophthalmology, maxillofacial and neurosurgical expertise is paramount.

Broad-spectrum antifungal therapy should be started as soon as a diagnosis of AIFR is suspected. Fungal cultures are essential in determining sensitivity to anti-fungal agents. Amphotericin B is a polyene antifungal with activity against both *Mucorales* and *Aspergillus*. Amphotericin B deoxycholate is used as the mainstay of treatment prior to identification of the causal fungus, usually at doses of 1–1.5 mg/kg per day. However, the toxicity of amphotericin B has led to the development of safer lipid-formulations of the drugs such as amphotericin B lipid complex and liposomal amphotericin B. These formulations are less nephrotoxic and can be used at higher concentrations for longer. Liposomal amphotericin B is used at doses of 5–10 mg/kg per day, and although expensive is safer and may be more effective than amphotericin B deoxycholate, particularly in cancer patients with mucormycosis.[26]

Once mucormycosis is ruled out, treatment may be changed to a less toxic azole that is more effective against *Aspergillus* but has less reliable activity against mucormycosis. A randomized unblinded trial showed that voriconazole led to improved survival and fewer side effects in patients with invasive aspergillosis compared to amphotericin B.[27] Voriconazole is used at an initial dose of 6 mg/kg iv for two doses, followed by 4 mg/kg iv every 12 hours. It is now recommended as first line treatment for invasive aspergillosis of the sinuses by the Infectious Disease Society of America. An alternative azole, posaconazole may be used as a step-down to oral treatment when clinical improvement is seen, to enable long-term treatment.

Hyperbaric oxygen therapy (HBOT) has been proposed an adjunct to treatment of AIFR.[28] HBOT acts directly via increased production of oxygen-based free radicals and indirectly by reversing growth-promoting lactic acidosis and restoration of phagocytosis.[29] To date there is no clear evidence of the efficacy of HBOT in the treatment of AIFR.

PROGNOSIS

In the recent systematic review by Turner et al.,[20] diabetic patients were found to have better prognosis, despite often more aggressive disease, possibly due to the fact that their underlying condition was more easily reversed than other conditions. Patients who have intra-cranial involvement, or who do not receive surgery as part of their therapy, have a poor prognosis.

Chronic invasive fungal rhinosinusitis

Chronic invasive fungal rhinosinusitis (CIFR) has a similar clinical appearance to AIFS but a slower progressive course, occurring over months to years. It also tends to occur in immunocompetent individuals.

Aspergillus spp. (*flavus* or *fumigatus*) or *Mucor* spp. are the most common causative organisms.[30] In the initial stages of disease symptoms may be subtle and non-specific and include unilateral bloody nasal discharge, nasal obstruction, headache, cacosmia and purulent nasal discharge. Patients may present with advanced disease with proptosis, orbital apex syndrome and cranial nerve deficits reflecting invasion into the orbit. Destruction of the bony walls of the maxillary sinus causes palatal erosion and soft tissue swelling of the cheek. Disease invading into the cribriform plate and anterior cranial fossa may cause chronic headache, seizures and focal neurological deficit.

DIAGNOSIS

CT imaging may mimic the features of malignancy, which is the primary differential in most cases. CT shows a hyperattenuating mass in one or more of the sinuses with destruction of the sinus bony walls. MRI typically shows decreased signal intensity on both T1- and T2-weighted images.[23] Invasion into anterior cranial fossa may result in meningitis seen as meningeal enhancement on contrast enhanced MRI. Cavernous sinus thrombosis typically results in a swollen non-enhancing sinus with compression of the carotid artery on coronal post-contrast T1-weighted MRI.

Biopsies should be obtained to assess for mucosal invasion. Microsopically, there are few inflammatory cells (unlike AIFS) and CIFS lacks granulomas often witnessed in granulomatous invasive fungal sinusitis.

MANAGEMENT

The treatment of CIFS is similar to AIFS, that is, a combination of surgical and antifungal treatments. Surgical resection should be carried out until clear, bleeding margins are observed. Systemic and topical amphotericin B should be started until cultures exclude *Mucor* species. Amphotericin B has proven efficacy against invasive Aspergillosis, although its side effect profile may limit the length of treatment and the optimal dose.[27] Whilst newer lipid-formulations are safer they are also more expensive and can only be given in the intravenous route. Azole drugs such as voriconazole and itraconazole are promising alternatives as they are effective via the oral route and are therefore easier and cheaper to administer for longer term treatment but are less effective against *Mucor* spp. A prospective randomized unblinded study compared amphotericin B (conventional or liposomal) and itraconazole in the management of CIFR and found that both were equally efficacious.[31]

Chronic granulomatous invasive fungal sinusitis

Chronic granulomatous invasive fungal sinusitis is distinguished from CIFS by the geographical distribution of the disease, type of pathogen and microscopic findings. It is rarely seen in the West and is more common in North Africa, the Middle East and Asia. *Aspergillus flavus* is the most common causative fungi. It is defined by the presence of non-caseating granulomas with Langhan's type giant cells and fungal hyphae, although it may coexist with other types of fungal sinusitis.[32] Similar to CIFR, it follows an indolent cause and may be found in both immunocompetent and immunodeficient patients.

It is treated by surgery (resection of involved tissues to bleeding margins) followed by antifungals. Antifungals like voriconazole instead of amphoteracin may be used as the disease is caused by *Aspergillus flavus*. Rupa et al.[32] recommend post-operative treatment with either oral itraconazole or voriconazole for disease with limited extension and oral voriconazole for advanced disease extending to the brain. Amphotericin B was not recommended as first-line therapy for CGFS.

Allergic fungal rhinosinusitis

Allergic fungal rhinosinusitis (AFRS) is a non-invasive fungal disease, first reported by Safirstein[33] in 1976 in a patient with allergic bronchopulmonary aspergillosis (ABPA). This condition shares similar histopathologic features with ABPA. Unlike other forms of sinusitis, it has distinct clinical, histopathological and prognostic findings. Debate concerning the underlying pathogenesis and optimal treatment strategy is ongoing.

AFRS is more common in younger individuals (mean age 21–33 years) compared to CRS. It is also more frequent in warm, humid environments and lower socioeconomic status.[34] Atopic individuals tend to suffer from AFRS.

DIAGNOSTIC CRITERIA

Allergic fungal rhinosinusitis is often misdiagnosed, and there are many controversies surrounding its diagnosis and even its very existence. However, most experts use Bent and Kuhn criteria[35] for diagnosis (**Table 21.2**). These consist of both major and minor criteria, and all five major criteria must be met in order for a diagnosis to be made. The presence of minor criteria supports the diagnosis of AFR.

De Shazo et al.[36] proposed a slightly revised set of criteria, reflecting the controversy surrounding the role of atopy in AFRS, and suggested the following: (1) sinusitis confirmed on CT scanning; (2) the presence of allergic mucin; (3) demonstration of fungal hyphae within the allergic mucin; (4) the absence of fungal invasion; and (5) the absence of diabetes or immunodeficiency states. In 2004 a panel of experts redefined AFRS as 'histological confirmation of eosinophilic mucin and the presence of type 1 hypersensitivity to fungi in CRS patients'.[37]

PATHOGENESIS

The pathogenesis of AFRS is not completely understood and subject to controversy. The most common pathogens in AFRS are the dematiaceous species (*Curvularia, Bipolaris, Alternaria*). Due to the histopathological similarity of AFRS to ABPA, a common pathophysiological mechanism was attributed. In ABPA, both elevated IgE and IgG to either *Aspergillus fumigatus* or *A. flavus* are present. Both Type I (specific IgE antibody-antigen interaction) and Type III (IgG antibody-antigen complex) reactions have been postulated in the pathogenesis of ABPA. The immune pathogenesis of AFRS is supported

TABLE 21.2 Bent and Kuhn diagnostic criteria

Major	Minor criteria
Type I hypersensitivity (history, skin test or *in vitro* testing)	Asthma
Nasal polyposis	Unilateral disease
Characteristic CT findings	Radiological bone erosion
Eosinophilic mucin without invasion	Fungal cultures
Positive fungal stain	Serum eosinophilia
	Charcot-Leyden crystals

by Manning and Holman;[38] eight AFRS patients with culture-positive Bipolaris showed skin test positivity to Bipolaris as well as RAST IgE to Bipolaris and ELISA IgG antibodies for Bipolaris. In contrast, only 1 in 10 controls had a positive skin test for Bipolaris, as well as IgE and IgG antibodies to Bipolaris. On examination of mucosal specimens from AFRS patients, eosinophilic mediators predominated over neutrophil-derived mediators compared to control patients with unrecognized AFS.

In AFRS, a Type I (and possibly Type III hypersensitivity reaction) to inhaled airborne fungi is believed to result in tissue inflammation, oedema and production of an 'eosinophilic mucin'. This consists of eosinophilic inflammator cells and Charcot-Leyden crystals (breakdown of cells by eosinophilic enzymes).

Interestingly, some patients with a clinical picture of AFRS did not display signs of systemic allergy. Collins et al[39] proposed a theory that AFRS is the result of a local Type I hypersensitivity rather than a systemic response. His study demonstrated fungal-specific IgE in sinus mucin in AFRS patients and may explain why the response was confined to the nose and paranasal sinuses without systemic involvement.

However, controversy exists about whether a Type 1 sensitivity reaction is central to the pathogenesis of AFRS. Ponikau et al.[40] prospectively studied 210 patients with CRS, with or without nasal polyps, and used rigorous methods to collect and culture fungus from nasal mucin. Cultures were positive for fungus in a surprising 96% of patients with CRS. Furthermore, all healthy control patients, with no history of sinonasal disease, had fungal-positive cultures, suggesting that fungi are ubiquitous within the sinuses and nasal passages. When using deShazo's criteria for a diagnosis of AFRS, 93% of CRS patients undergoing surgery (thereby providing samples for histological examination), had AFRS. Of patients diagnosed with AFRS, less than a third had elevated fungus specific IgE level by RAST. Ponikau's study has been criticized for a number of reasons. Furthermore, Ponikau states that 'allergic mucin' (required for a diagnosis of AFRS) was found in the vast majority of patients with CRS, whilst multiple studies have estimated the prevalence of allergic mucin to be much lower in patients requiring surgery for CRS.[41] AFRS is usually associated with the production of copious amounts of allergic mucin, whereas the patients in Ponikau's study often only produced small pockets of mucin.

There is strong evidence that patients with 'simple' CRS show abnormal immunological responses to fungal elements within the nose and sinuses. Shin et al.[42] demonstrated that patients with simple CRS showed exaggerated humoral and cellular responses to commonly found airborne fungi compared to healthy controls. However, it is important to recognize that whilst fungal allergy may play a role in the pathogenesis of simple CRS, AFRS is a distinct entity with very strict criteria for diagnosis, and more is needed for diagnosis over and above merely the existence of allergy to fungal elements in a patient with sinusitis.

CLINICAL FEATURES

Typically patients presenting with AFRS are young, immunocompetent individuals, with a history of atopy or asthma. They present often with unilateral, but sometimes bilateral, symptoms of nasal congestion, post-nasal drip, and a thick dark nasal discharge. There is often a history of recurrent symptoms following previous treatment or surgery and typically patients show an excellent response to oral corticosteroids, but not antibiotics. Patients may also present with signs and symptoms of bony erosion and involvement of the orbit, including proptosis and telecanthus.

On examination, there is usually gross nasal polyposis with thick, highly viscous mucin, classically described as the consistency of peanut butter. Green or black casts consisting of allergic mucin may be present. Microscopic examination of the fungal mucin with haematoxylin and eosin (H&E) staining typically shows the presence of Charcot-Leyden crystals and eosinophilic breakdown products, and often the eosinophils themselves form sheets. Fungi do not stain with H&E staining, but can be seen on special stains. Culture of the mucin may or may not be positive for fungus; however, this does not rule out AFRS as the yield of culture is typically fairly low. The fungi most commonly identified in the eosinophilic mucin include *Alternaria, Bipolaris, Cladosporium, Curvularia, Drechslera* and *Helminthosporium* from the dematiaceous family and *Aspergillus* species.[43]

IMAGING

CT imaging typically shows characteristic pansinusitis, hyperattenuation of the intrasinus contents (representing thick allergic mucin) surrounded by lower attenuation hyperplastic mucosa. The 'double density' sign may be seen in affected sinuses (i.e. heterogeneous signal intensity due to the deposition of heavy metals within the mucin) (**Figure 21.6**). The affected sinus is often expanded and there may be erosion of the sinus walls (**Figure 21.7**). This erosion is not due to invasion by fungal elements, but due to local inflammation and the expansive nature of mucin, which differentiates it from invasive fungal sinusitis.[44] MRI, if interpreted in the absence of CT, can be misleading; on T2-weighted images, the high metal concentration within proteinaceous allergic fungal mucin may show up as a signal void, mimicking the appearance of a normally aerated sinus. On T1-weighted images the material is hypointense to isointense.[23] Both T1- and T2-weighted images shows peripheral enhancement (**Figure 21.8**).

MANAGEMENT

The mainstay of AFRS treatment remains surgery although adjunctive medical management is critical for optimal outcomes. The aim of functional endoscopic sinus surgery (FESS) is to remove all antigenic fungal elements, and to re-establish drainage of the affected sinuses. During the endoscopic procedure, all specimens including polyps and allergic mucin should be sent for microscopic examination



Figure 21.6 Coronal CT sinus showing classic 'double density' sign seen in AFRS.

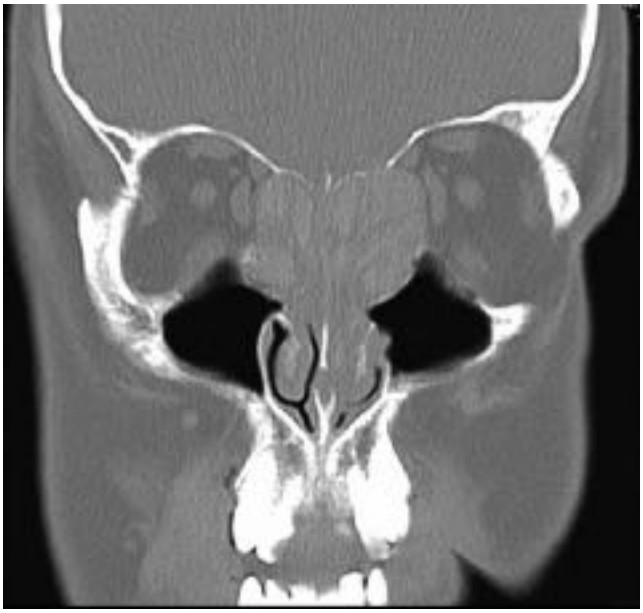


Figure 21.7 Coronal CT sinus demonstrating erosion of lamina papyracea and skull base.

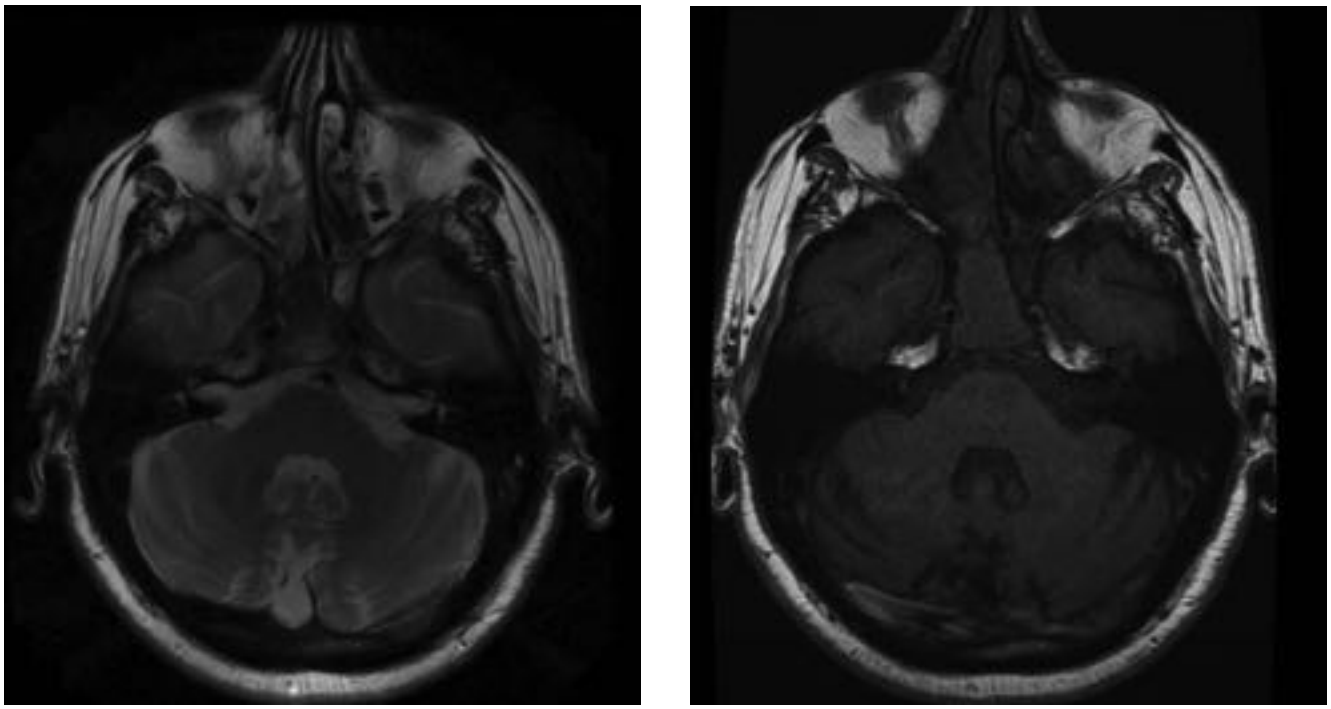


Figure 21.8 Axial MRI sinus showing near signal void in sphenoid sinus on T2-weighted (left) compared to T1-weighted images (right).

and staining for fungi, and all should be sent for culture. In particular, invasion of vasculature or mucosa should be excluded.

In 2014 Gan et al.[45] published an evidence-based approach for the post-operative medical management of AFRS. The review concluded that post-operative systemic and standard topical nasal steroids are recommended; oral antifungals, and immunotherapy are options in cases of refractory AFRS; and did not provide recommendations for topical antifungals and leukotriene modulators due to lack of evidence. Recently, AFRS which is refractory to surgery and conventional medical treatment has been shown to be responsive to anti-IgE antibody, omalizumab.[46]

Oral steroids

Gan et al.[45] recommend the use of oral steroids in the post-operative period, using grade B evidence from four studies (level 2b: 2 studies, level 4: 2 studies), and report a reduction in post-operative mucosal disease and inflammatory markers. The four studies included a total of 76 patients

fulfilling the Bent and Kuhn criteria for AFRS, although two were case series lacking comparison with control. In 2010, Rupa et al.[47] published a prospective, randomized, placebo-controlled trial of post-operative oral steroids in AFRS comparing the use of oral prednisolone (n = 12) and placebo (n = 12). They concluded that post-operative oral steroid in a tapering dose produces significant subjective and objective improvement of patients with AFRS.

Topical nasal steroids

Topical nasal steroids achieve effective drug concentration at the sinonasal mucosa with few systemic side effects. There is little evidence for the use of topical steroids post-operatively in AFRS. A randomized controlled trial examined the use of post-operative topical nasal steroids and nasal douching in patients with AFRS compared with nasal douching alone, and nasal douching plus itraconazole. This study showed no significant benefit at 6 months for topical nasal steroids, although there were limitations to the study.[48]

Oral antifungals

The use of oral antifungals in AFRS should theoretically reduce fungal sinus load and therefore reduce the type 1 hypersensitivity reaction. However, there are numerous side effects associated with oral antifungals, and therefore they should be used with caution. Three level 4 studies (all case series) were included in Gan's review[45] and their use was restricted to patients with a poor post-operative response to oral or topical steroids. These studies show a reduction in symptoms, prevention of disease recurrence and reduced dependence on oral steroids (level C evidence). Itraconazole was used at a dose of 200 mg to 400 mg daily in divided doses for up to 6 months.

Topical antifungals

Topical antifungals may be used to reduce the risk of side effects associated with oral antifungals. However, to date there is no high quality evidence regarding the use of topical antifungals in AFRS.

Immunotherapy

There is level C evidence (two case-control studies and three prospective case series) that allergen immunotherapy shows improvement with reduced reliance of post-operative steroids, post-operative exacerbations and revision surgery.[45] Double-blind placebo controlled trials are lacking, and therefore conclusive evidence of efficacy is not yet available.

Bassichis et al.[49] studied a database of 82 patients and compared patients with AFRS who had been treated with post-operative immunotherapy against those who had not (36 versus 24 patients). They found a re-operation rate of 33% in those who did not receive immunotherapy compared to 11.1% in those who did. Folker et al.[50] published a case-control study comparing 11 patients who received IT for at least 12 months with those who did not and found improvements in mucosal endoscopic staging, quality of life and reliance on oral and systemic steroids. It is less clear if immunotherapy leads to significant reduction in recurrence of disease in the long term.[51]

To date, there remains no evidence of unusual side effects or immune complex formation in AFRS patients receiving immunotherapy.

Leukotriene modulators

To date there is no evidence that leukotriene modulators, such as montelukast, have a role in the treatment of AFRS. Only one case study has reported a benefit from using 10 mg oral montelukast in a patient with recalcitrant AFRS, with recurrent symptoms following three previous attempts at sinus surgery.[52]

Fungal ball

A fungal ball consists of sequestered fungal hyphal elements within a sinus without invasive or granulomatous changes. It is distinct from saprophytic fungal infestation, which corresponds to fungal spores found on crusts and mucus in the nose. Fungal balls are typically found in immunocompetent individuals and may coexist with other forms of fungal sinusitis.

DEFINITION

DeShazo[53] developed a clear definition for the diagnosis of fungal ball of the paranasal sinuses. A dense mass of hyphae is found in the affected sinus, which separates easily from the sinus mucosa, and macroscopically resembles a clay-like or cheesy material. Microscopically there is no evidence of invasion of the mucosa, vessels or bone. There are typical radiological changes (see below) and non-specific inflammatory changes of the mucosa, with no predominance of eosinophils, no granuloma and no allergic mucin.

PREDISPOSING FACTORS

There is little evidence that the presence of pre-existing medical conditions predispose to fungal balls, and furthermore, no evidence that pre-existing sinus disease or anatomical abnormalities does so either. An association between previous dental treatment, particularly fillings, and fungal balls has been suggested with reports showing that between 56% and 84% of patients found to have fungal balls have had previous dental treatment.[54]

PATHOGENESIS

Two theories as to the pathogenesis of fungal balls have been proposed. The first proposes that a large amount of inhaled fungal spores enter the sinuses through the natural ostium (the aerogenic pathway). The second suggests that fungal colonization of the sinuses occurs via an iatrogenic pathway when an oro-antral fistula is created during endodontic treatment with overfilling of the dental canal. Commonly used endodontic sealers may promote the growth of fungus, as demonstrated by experimental work, which showed that zinc oxide found in sealers promotes the growth of *Aspergillus*, whereas the second component, a liquid called eugenol, may inhibit its growth. Over time, however, the inhibitory effect of eugenol fades,

allowing the promotion of fungal growth many years after the initial dental treatment. This would explain why the maxillary sinus is the most commonly affected sinus, and why many patients with fungal balls have a history of previous endodontic treatment.

CLINICAL FEATURES

Fungal balls most often affect one sinus, most commonly the maxillary sinus (94%), followed by the sphenoid sinus. Symptoms are non-specific, and the patient may be completely asymptomatic, hence the reason why patients are often diagnosed late. Other symptoms include headache or facial pain, post-nasal drip and cacosmia. Fungal balls affecting the sphenoid sinus may present with retro-orbital pain at the vertex. Symptoms may be recurrent, coinciding with superimposed bacterial sinus infection, with relatively symptom-free periods between episodes.

Examination findings may be unremarkable, but careful examination with a flexible or rigid endoscope may reveal localized inflammatory changes at the natural ostium of the affected sinus, including the presence of small polyps or purulent mucopus (**Figure 21.9**).

Macroscopically the fungal ball consists of cheesy like material, which is green, yellow, brown or black. The underlying mucosa may be normal or hypertrophic. Microscopically at low power the ball is seen to consist of densely packed hyphae, and may have an onion-skin-like appearance, due to the alternating zones of dense and less-dense growth. The mucosa may show non-specific inflammation, but in particular there is an absence of invasion by fungal elements, or granulomatous reaction.

Aspergillus is the most commonly identified fungus in fungal balls, and can often be seen on haematoxylin-eosin slides. However, all samples, including mucosa and fungal samples should be stained with silver impregnation stains in order to identify the presence of fungi. Whilst stains may be able to identify their presence, only culture will confirm the species of fungus. However, culture typically has a low yield of up to 50%.[54]



Figure 21.9 Endoscopic findings of AFRS showing nasal polyposis and thick mucinous secretions.

IMAGING

CT scanning is the imaging of choice for suspected fungal balls. Five CT features are commonly found on CT imaging of fungal balls, including a heterogenous soft tissue density in a single unilateral sinus, absence of an air-fluid level, erosion of the inner wall of the sinus, sclerosis of the lateral sinus wall and the presence of calcification. In particular, the presence of erosion of the inner wall of the sinus and the presence of calcification have a positive predictive value in the diagnosis of fungal balls of 94.6% and 93.2% respectively.[55] The presence of calcification is thought to be due to the deposition of calcium salts within the fungal ball.

MRI scanning is not usually necessary, but may be used as an adjunct to CT imaging to differentiate mucosal swelling or mucous retention from a fungal ball. On T2-weighted MR imaging fungal balls are often hypointense compared to mucous or mucosal swelling, which is hyperintense.

MANAGEMENT

The treatment of fungal balls is surgical with no adjunctive medical treatment usually necessary. Functional endoscopic sinus surgery (FESS) is employed to create a wide opening of the affecting sinus ostium. All fungal material should be removed, and biopsies taken from the underlying mucosa to rule out invasion. Any dental filling material present in the sinus should also be removed. In immunocompetent patients there is no role for the use of systemic antifungal agents.

Oropharyngeal candidiasis

Fungal infection of the oral cavity and pharynx is most often caused by fungi belonging to the genus *Candida* (*Candidiasis*). There are three subtypes of oropharyngeal candidiasis (OPC) that are recognized: pseudomembranous, atrophic and hyperplastic candidiasis. Whilst candidiasis of the oral cavity is not uncommon, and is in most cases easily treated, in this section we consider oropharyngeal candidiasis in two populations: patients with HIV and head and neck cancer patients.

OROPHARYNGEAL CANDIDIASIS IN HIV PATIENTS

Candida albicans is found as part of the normal skin, genitourinary and gastrointestinal microflora, and may be isolated in up to 65% of healthy individuals. Prior to the development of antiretroviral therapy (ART) for treatment of HIV, OPC was seen in up to 90% of patients with

HIV, reflecting their underlying immunosuppression.[56] Since the introduction of ART, the incidence of OPC has declined, although it remains a problem for patients with limited access to ART, those with a poor response to ART and those with infections resistant to conventional antifungal treatment. In one study of 122 patients with advanced HIV, 81% were colonized by oral candida, and of these 33% had symptomatic infection.[56] *Candida albicans* was the most common candida species isolated in 54% of samples, with *C. dublinensis* and *C. glabrata* next most common. Rarer species of *Candida* may often be resistant to fluconazole and are important causes of recalcitrant oropharyngeal candidiasis.

HIV patients are at greater risk of OPC once their immunity drops to a certain level, normally taken to be an absolute CD4+ T-lymphocyte count of less than 200 cells/μL. Viral load is also found to be a contributing factor for the development of OPC, and the risk of OPC increases as HIV viral load surpasses 10,000 copies/mL.

Pseudomembranous candidiasis is the most common subtype of OPC in HIV patients. Painless, often asymptomatic plaques appear on the tongue, buccal mucosa and oropharynx, and can typically be wiped away leaving an erythematous base, which may bleed (**Figure 21.10**). Patients may complain of altered taste or pain if ulceration occurs. Distal spread to the larynx or oesophagus causes dysphonia, odynophagia and dysphagia. Erythematous OPC may also be seen in the HIV patient and clinically appears as flat, red lesions anywhere in the oral cavity, but often the dorsal tongue or palate. Hyperplastic candidiasis presents as firm, white plaques of varying sizes, which, in contrast to pseudomembranous OPC cannot be removed. These are important lesions to recognize as whilst they are rare in all populations, they have malignant potential.

Mild disease can be treated with topical nystatin suspensions, whilst more severe disease will require a 14-day course of fluconazole 200mg daily.[57] However, there is increasing recognition of *Candida* species that are resistant to fluconazole, estimated to cause up to 5% of OPC. A multicentre randomized trial evaluating posaconazole as an alternative to fluconazole has shown posaconazole to be as effective and even better at sustaining clinical remission and is an alternative for fluconazole-resistant disease. Posaconazole suspension is given at a dosage of 400mg twice daily for 3 days, followed by 400mg daily for up to 28 days. Other alternatives include voriconazole, itraconazole or amphotericin B oral suspension. Refractory candidiasis may require parenteral treatment with amphotericin B or caspofungin.[57]



Figure 21.10 Chronic oral candidiasis of the tongue and mouth corners (angular chelitis) in an adult with an underlying immune deficiency. Courtesy of http://www.mycology.adelaide.edu.au/gallery/yeast-like_fungi/

OROPHARYNGEAL CANDIDIASIS IN HEAD AND NECK CANCER PATIENTS

Pseudomembranous and erythematous OPC are the most common variants of candidiasis in head and neck cancer patients.[58] The prevalence of OPC in patients receiving either radiotherapy or chemotherapy for head and neck cancer is approximately 38%.[58] *Candida albicans* is the most frequent species isolated, but other species are recognized including *C. tropicalis* and *C. glabrata*. The increased risk of OPC in these populations is likely related to salivary hypofunction. Amisfostine, an agent that acts to preserve salivary gland function, has been shown to reduce the risk of clinical OPC in patients receiving radiotherapy.[59] OPC in cancer patients is important to treat and recognize early as maintenance of oral intake and nutritional status is vital in patients receiving chemotherapy and radiotherapy. In addition, patients receiving such treatment are vulnerable to systemic dissemination of fungal infection via lesions associated with oral mucositis; this can be fatal. Non-albicans species are more likely to spread into the systemic circulation.

Treatment of OPC in head and neck patients is similar to the treatment of OPC in other populations; however, topical treatment may be uncomfortable in patients with significant mucositis. Oral fluconazole is the recommended first-line treatment for moderate or severe OPC. The use of fluconazole as a prophylactic measure should be used with caution, in view of the emergence of fluconazole resistant strains of OPC and should be restricted to frequent and disabling infection.

Laryngectomy patients with silicone trachea-oesophageal voice prostheses may develop the formation of *Candida* biofilms, which can invade the silicone, causing deterioration of the valve. Valves deteriorate fairly rapidly after placement and normally need replacing after between 3 and 5 months. The main reason for replacement is leakage of fluid into the trachea via an incompetent valve, which is thought to be related to biofilm formation. In 100 Provox2 voice prostheses that were analysed following removal due to leakage of fluid, the most common isolate from the biofilm was *Candida albicans* (53% of isolated fungi), followed by *C. krusei* and *C. tropicalis*.[60] Eighty three per cent of the valves were found to have biofilms of fungi and bacteria. A promising area has been the development of a nontoxic deoxyribonuclease that has been shown to be effective *in vitro* at dispersing biofilms from discarded voice prostheses contaminated with mixed biofilms.

KEY POINTS

- Fungi exist in nature as yeasts or branching moulds; of the thousands of fungi present naturally in the environment, only around 30 species are commonly associated with human disease.
- Fungal infection within the ear canal results in otomycosis, most commonly caused by *Aspergillus niger* and *Candida albicans*. Rarely, in immunocompromised hosts, fungal otomycosis can result in malignant otitis externa.
- Fungal infection affecting the sinuses can be divided into five main groups: acute invasive fungal sinusitis, chronic invasive fungal sinusitis, chronic granulomatous invasive fungal sinusitis, allergic fungal sinusitis and fungal ball.
- Oropharyngeal candidiasis can be a significant issue in patients with immunocompromise, particularly patients receiving treatment for HIV or head and neck cancer.

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CHAPTER
22

ANTIMICROBIAL THERAPY

Ursula Altmeyer, Penelope Redding and Nitish Khanna

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SEARCH STRATEGY

The information in this chapter is based on standard clinical microbiology practice in the UK; evidence level 4 (Expert opinion). Laboratory practices described are based on Public Health England's Standards for Microbiology Investigations (SMI). Data in this chapter may be updated by a PubMed search using the keywords: classification of antimicrobials; antimicrobial spectrum; susceptibility testing; antimicrobial resistance and principles of antimicrobial treatment.

INTRODUCTION

Historically, the prevention and treatment of infection had been one of the most pressing problems medicine was trying to solve. Following the introduction of anti-infective agents in the first half of the 20th century, it seemed as if infection had in all but the most severe cases become a manageable event, rather than a potentially life-threatening catastrophe.

The advances afforded by effective antimicrobial treatments in terms of both surgical and medical interventions have saved millions of lives.

However, shortly after introduction of antimicrobials into clinical practice, resistant organisms developed and began to spread.

When penicillin was first introduced in 1942, all strains of *S. aureus* were susceptible to it and its use during the Second World War contributed to a significant drop in infection associated mortality among wounded soldiers. Already by the mid-1940s, though, the first penicillin resistant strains had developed; they now dominate the circulating strains of *S. aureus* entirely.

Bacterial generation times are short (only 10 minutes for a division of *Escherischia coli*) and their inaccurate genetic replication mechanisms favour random point mutation. Any of these mutations has the potential to result in a new antimicrobial resistance mechanism.

Initially, the development of new antimicrobial compounds was rapid (Table 22.1) and able to keep at least apace with emerging resistances, but since the early 1990s there has been a decline in production of novel agents.

In short: this is a competition in which we're unlikely ever to retain the upper hand.

The threat posed by antimicrobial resistance is now widely recognized (Table 22.2). In March 2013 the Chief Medical Officer, Dame Sally Davies, highlighted the emergence of antimicrobial resistance as a major challenge in her annual report, stating:

> *The supply of new replacement antimicrobial agents has slowed dramatically and we face the prospect of a future where we have far fewer options in the treatment of infectious disease and infections that, previously easy to control, will become much more significant threats to health. Standard surgical procedures, such as hip replacements, could become riskier with widespread antimicrobial resistance, as would treatments that result in immunosuppression, such as chemotherapy or organ transplant, which rely on the ability to treat infections that occur in this very vulnerable group of patients.*

TABLE 22.1 Historical overview of antimicrobial development

Year	Antimicrobial
1935	Protonsil - sulphonamide pro-drug
1942	Benzyl-penicillin
1944	Streptomycin – first aminoglycoside
1948	Chlortetracycline
1949	Chloramphenicol
1952	Erythromycin – first macrolide
1955	Vancomycin – first glycopeptides
1960	Metronidazole
1964	Cephalotin – first cephalosporin
1967	Rifampicin
1968	Clindamycin
1971	Gentamicin
1972	Amoxicillin
1980	Amoxicillin-clavulanic acid
1982	Ceftriaxone – 3rd generation cephalosporin
1987	Ciprofloxacin
1990	Clarithromycin
1992	Piperacillin-tazobactam
1996	Meropenem
2000	Linezolid
2011	Fidaxomycin

TABLE 22.2 Current and emerging problem resistances

- Methicillin resistant *S. aureus* (MRSA)
- Vancomycin resistant enterococci (VRE), also known as glycopeptide resistant enterococci (GRE)
- Penicillin-intermediate or resistant *S. pneumoniae*
- Extended spectrum β-lactamase (ESBL) producing enterobacteriaceae
- Carbapenemase-producing enterobacteriaceae

CLASSIFICATION OF ANTIMICROBIAL AGENTS

Antimicrobial agents can be classified according to several characteristics:

- chemical structure (e.g. β-lactams, quinolones)
- site of action (e.g. cell wall or ribosome)
- mode of action (i.e. bactericidal or bacteriostatic).

A summary of the properties of the most frequently used classes of antibacterial agents can be found in Table 22.3. Tables 22.4–22.7 list important antibacterial agents with their expected spectrum of activity. Please note that the information in these tables should be correlated with local resistance data, and cannot replace local empirical antimicrobial guidance.

SUSCEPTIBILITY TESTING

Once the identity of an organism is known, typical susceptibility patterns can be predicted for some organisms, for example penicillin susceptibility in strains of *S. pyogenes*.

These expected susceptibility patterns form the basis of empirical antibiotic choices.

The majority of resistance patterns are however highly variable and any isolate thought to be clinically significant will be tested formally against panels of antibiotics for their susceptibilities and resistances.

The panels in use may vary from laboratory to laboratory, depending on prevailing patterns of susceptibilities and local antimicrobial policies.

Several different methods for antimicrobial susceptibility testing exist.

Which method will be used may differ between certain organisms, but ultimately all methods demonstrate in vitro presence or inhibition of growth of the organism when exposed to a defined concentration of the tested antimicrobial.

The most accurate method for determining this is the broth dilution method (Figure 22.1), in which test tubes containing a broth medium are spiked with serial dilutions of the tested antimicrobial. A standardized inoculum of the organism of interest is then added and the tubes are observed for the presence of bacterial growth after a period of incubation. The first dilution with which no growth is observed represents the minimum inhibitory concentration (MIC) of the tested antibiotic.

While this process will yield very accurate information, it is time and labour intensive and routine use in a diagnostic lab is impractical; however, it forms the basis of most automated methods of susceptibility testing.

An alternative method that is in widespread use is antimicrobial disc diffusion testing (Figure 22.2).

In this, a specific testing medium is inoculated evenly with a standardized suspension of the test organism and a selection of paper discs containing defined amounts of antimicrobials is placed on the medium.

The antibiotic will diffuse from the disc into the medium, leading to a gradient of concentration with the highest concentration just around the disc.

A check for growth patterns takes place after a defined period of incubation and the zone of inhibited growth is measured. In order to be classified as susceptible, this zone must be equal or greater than a certain diameter, which varies between different organisms and different antimicrobials.

The interpretation of these results relies on extensive databases of susceptibility break points (i.e. zone diameters that are deemed to represent clinical susceptibility or resistance). Such databases are compiled by external agencies, such as the British Society for Antimicrobial Chemotherapy (BSAC) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

A third method, known as the E-test, uses plastic strips that are coated with the tested antimicrobial forming a concentration gradient along the strip. This is placed on a testing medium inoculated with the test organism and

TABLE 22.3 Commonly used classes of antimicrobials

Chemical class	Site of action	Mode of action	Comments
β-lactams: • Penicillins • Cephalosporins	Cell wall	Bactericidal	• Short plasma half lives requiring frequent dosage intervals • Optimum action on actively dividing organisms • Cephalosporins have good penetration through the blood–brain barrier
Carbapenems	Cell wall	Bactericidal	• Very broad spectrum • Cautious use, ideally only if confirmed resistances • Once daily dosing possible with some agents • Good penetration through blood–brain barrier
Glycopeptides: • Vancomycin	Cell wall	Bactericidal	• Large molecules • Not absorbed from GI tract • Penetration into tissues variable • Potential nephrotoxicity • Require therapeutic drug monitoring
Aminoglycosides: • Gentamicin • Amikacin	Ribosome	Bactericidal	• Rapidly bactericidal • Nephrotoxic • Ototoxic • Require therapeutic drug monitoring
Macrolides	Ribosome	Bacteriostatic	• Good oral absorption • Gastro-intestinal side effects, but less pronounced with newer agents
Trimethoprim	Di-hydrofolate reductase	Bacteriostatic	• Contra-indicated in pregnancy, especially 1st trimester
Sulfamethoxazole	Di-hydropteroate synthetase	Bacteriostatic	• Given with trimethoprim as Cotrimoxazole • Inhibits earlier step in tetrahydrofolate synthesis • Contra-indicated in pregnancy, especially 1st trimester
Quinolones	DNA topoisomerase II, gyrase	Bacteriostatic	• Good oral bioavailability • Good tissue penetration
Lincosamides: • Clindamycin	Ribosome	Bacteriostatic	• Good tissue penetration
Oxazolinidones: • Linezolid	Ribosome	Bacteriostatic	• Excellent tissue penetration • Bone marrow toxicity
Nitroimidazoles: • Metronidazole	Directly damages DNA and proteins through formation of radicals	Bactriocidal	• Exclusively anaerobic cover • Excellent tissue penetration

TABLE 22.4 Commonly used penicillins

Agent	Expected spectrum of activity
Penicillin V Benzyl-penicillin	Alpha-haemolytic streptococci *S. pneumoniae* *S. pyogenes*
Amoxicillin	Streptococci, enterococci Some Gram-negative cover
Flucloxacillin	Methicillin-sensitive *S. aureus*
Amoxicillin with clavulanic acid Piperacillin with tazobactam	Broad spectrum Gram-positive, Gram-negative and anaerobic cover, but not MRSA

TABLE 22.5 Commonly used cephalosporins and carbapenems

Commonly used cephalosporins	Expected spectrum of activity
Cefuroxime (2nd generation) Cefotaxime (3rd generation) Ceftriaxone (3rd generation)	Broad spectrum Gram-positive and Gram-negative cover, but not MRSA
Commonly used carbapenems	
Meropenem Ertapenem	

TABLE 22.6 Commonly used macrolides

Commonly used macrolides	Expected spectrum of activity
Erythromycin Clarithromycin	*S. pyogenes* *S. pneumoniae* *S. aureus,* including some strains of MRSA

TABLE 22.7 Commonly used quinolones

Commonly used quinolones	Expected spectrum of activity
Ciprofloxacin Levofloxacin Moxifloxacin	Broad spectrum Gram-negative cover *S. aureus* Levofloxacin and moxifloxacin have enhanced Gram-positive cover especially against *S. pneumoniae*

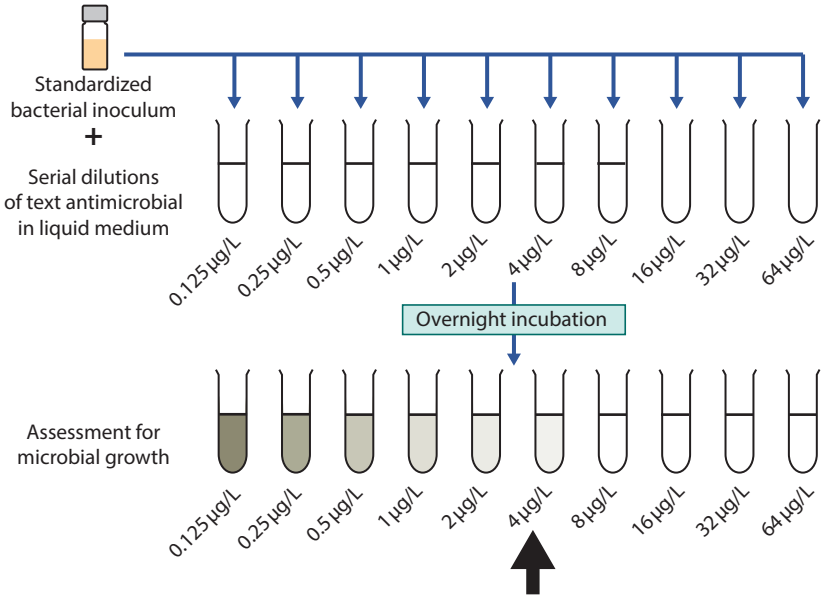


Figure 22.1 Determination of minimum inhibitory concentration by broth dilution method.

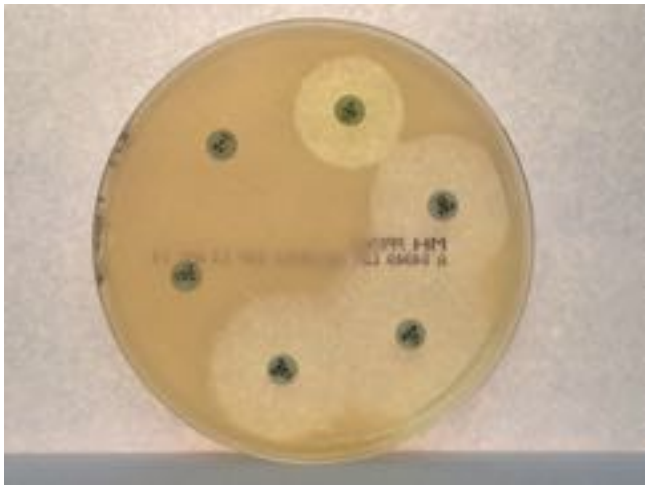


Figure 22.2 Disc diffusion method of susceptibility testing. Courtesy of Jasminder Karde and Margaret Woods, Department of Microbiology, Golden Jubilee National Hospital, Clydebank, UK.

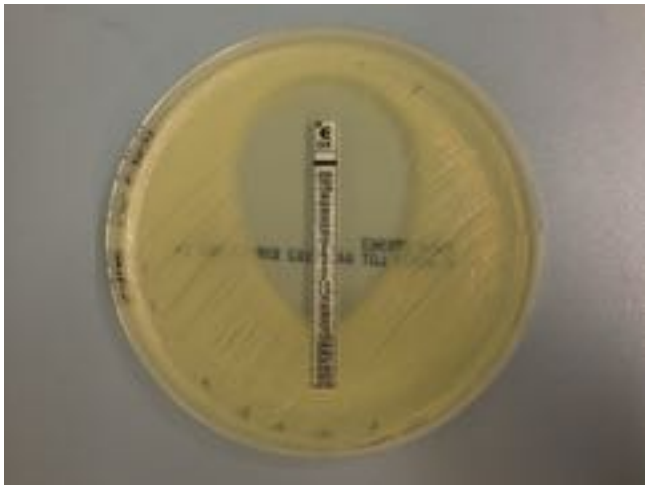


Figure 22.3 Determination of MIC by E-test. The MIC is read where the inhibition zone intersects the test strip. Courtesy of Jasminder Karde and Margaret Woods, Department of Microbiology, Golden Jubilee National Hospital, Clydebank, UK.

again read after a period of incubation. An elliptical zone of inhibition is visible around the test strip, which intersects it at the measured MIC (Figure 22.3).

This test combines aspects of both the above methods – it yields information regarding the minimal inhibitory concentration, while retaining the ease of use of the disc diffusion method.

ANTIMICROBIAL RESISTANCE (AMR)

Broadly speaking, there are two principal types of antimicrobial resistance: intrinsic resistance and acquired resistance.

Intrinsic resistance

In 1984 the bodies of two members of an Arctic expedition led by the British explorer Captain Sir John Franklin in 1845 were exhumed on Beechey Island and autopsied. *Clostridium* spp. were isolated from their guts which were resistant to clindamycin and the second-generation cephalosporin cefoxitin, although they could not have been exposed to any modern antimicrobial.[1]

This is an example of intrinsic resistance, which has its basis on traits common to all strains of an organism, such as characteristics of the cell wall or the metabolism, which render them impervious to the effects of an antimicrobial (Table 22.8).

TABLE 22.8 Examples of intrinsic resistance

Organism	Intrinsic antimicrobial resistances	Mechanism
Gram-negative organisms	Vancomycin	Agent unable to penetrate outer membrane of cell wall
Aerobic bacteria	Metronidazole	Aerobic metabolism unable to reduce the agent to its active form
Anaerobic bacteria	Aminoglycosides	Active uptake of agent dependent on oxidative metabolism

TABLE 22.9 Mechanisms of horizontal gene transfer

Mechanism	Genetic element transfer	Method of transfer
Transformation	Free genetic material from lysed organisms	Uptake of exogenous DNA from the environment
Conjugation	Mobile genetic elements, e.g. plasmids or transposons	Via direct cell-to-cell contact or through specific cell bridges (pili)
Transduction	Mobile genetic elements, e.g. plasmids or transposons	Introduction of foreign genetic material via viral (phage) vector

Acquired resistance

If a bacterial organism becomes resistant to an antimicrobial agent or class to which it was previously susceptible, it is said to have developed an acquired resistance.

This may be the result of a new mutation or the transfer of resistances from other organisms.

Chromosomal resistance is the result of a randomly occurring spontaneous mutation, resulting in resistance to an antimicrobial agent. If the host is exposed to the antimicrobial in question, organisms carrying the mutation will have a survival advantage and replace the susceptible isolates. The mutation will be passed on to the progeny of this organism with every cell division; this is referred to as vertical transfer and may lead to treatment failures, but the resistance is unlikely to spread to other strains or types of organisms.

The second, and more worrying, way of acquiring resistance is via mobile genetic elements, which can spread easily between different strains of the same organism, but also between different types of organisms.

This is called horizontal transfer and there are several ways this transfer can occur (Table 22.9).

MECHANISMS OF RESISTANCE

While there are many resistance genes, the effects of them fall broadly into three categories.

Alteration or removal of the antimicrobial's target

Resistance to flucloxacillin in *S. aureus* is the result of the alteration of the binding site of penicillin in the organism's cell wall components.

Usually, penicillin disrupts cell wall synthesis by attaching to a part of the peptidoglycan component known as the penicillin binding protein (PBP) and prevents cross linking of the components into a normal cell wall structure.

The *mecA* gene of methicillin-resistant strains of *S. aureus* (MRSA) encodes for an altered penicillin binding protein called PBP2a, which does not allow attachment of any β-lactam agent and therefore renders the organism resistant to this class of antibiotic.

Alteration of the drug leading to loss of activity

Many Gram-negative organisms produce enzymes called β-lactamases that are able to cleave the β-lactam ring of penicillins, rendering them resistant to their effects. They are usually located in the peri-plasmic space between the outer membrane and the peptidoglycan cell wall.

This enzyme can be inhibited, and several penicillin-β-lactamase inhibitor combination agents are available, such as amoxicillin with clavulanic acid or piperacillin with tazobactam.

If the enzyme is able to cleave not only the β-lactam ring of penicillins, but also that of third-generation cephalosporins, this enzyme would be classed as an extended spectrum β-lactamase (ESBL).

If the enzyme in question cleaves not only the β-lactam ring of penicillins and third-generation cephalosporins but also the carbapenem ring, it is classed as a carbapenemase.

Gram-negative organisms carrying various β-lactam resistance mechanisms are endemic in many parts of the world and frequently carry resistance mechanisms conferring resistance to additional classes of antimicrobials, rendering the organisms difficult to treat.

Alteration of the drug's access to its target

The easiest way of preventing a drug from acting on its target is by removing the drug before it even reaches the target.

Many bacteria have incorporated efflux pumps that share some molecular components with the flagellar apparatus into their cell walls. This comes at a price – while many of these efflux pumps are able to remove more than one type of antibiotic, the transport of the drug across the membrane is an active process that uses significant amounts of energy.

Resistance to tetracyclines in Gram-positives is the result of such an efflux pump.

Resistance to an agent may be mediated via different mechanisms in different organisms and different mechanisms conferring resistance to multiple antimicrobial classes may coexist in the same organism; listing all possible combinations of organisms and resistance mechanisms would be beyond the scope of this chapter.

CONTROLLING ANTIMICROBIAL RESISTANCE

The rise of resistant organisms has been recognized as a major healthcare challenge on a national and international level and the World Health Organization and the British Department of Health have both recently published guidance documents on AMR control.

The issue is a complex one, as antimicrobials in the form of antibacterial, antifungal, antiviral and antiparasitic chemotherapy are used not only in a human healthcare setting, but also in veterinary medicine and agriculture.

In addition to this, resources, prescribing practice and surveillance programmes differ markedly between countries, making it difficult to develop an approach that is suitable for global application.

In the UK, the following key factors have been identified by the Department of Health:[2]

- Enhanced surveillance in order to identify existing and novel resistance patterns quickly
- Optimizing prescribing practice and antimicrobial stewardship, ensuring that antibiotics are only prescribed when needed and the correct agent is given for the correct amount of time
- Improving infection prevention and control
- Encouraging the development of new antibiotics, diagnostic strategies and novel therapies

PRINCIPLES OF ANTIMICROBIAL TREATMENT

Antimicrobials are amongst the most commonly prescribed medication in both primary and secondary care. Approximately one-third of all inpatients at any given time are receiving some form of antimicrobial treatment.[3]

In order to ensure that unnecessary prescribing is minimized, it is good practice to adhere to some basic principles when considering antimicrobial treatment.

Identification of the source of infection

Ideally, antibiotics should only be prescribed when a clear clinical source has been identified. This relies heavily on careful clinical examination and consideration whether or not a bacterial infection is likely.

In suspected deep-seated infections, such as intracranial abscesses, imaging forms an integral part of the diagnostic process.

Appropriate sampling

Clinical samples from the suspected focus of infection should be collected before any antimicrobial therapy is commenced.

If the patient is septic (i.e. fulfils the criteria of systemic inflammatory response with a suspected infective focus), at least one set of blood cultures should be taken peripherally, and from any vascular access devices if present.

If a deep infection is present and the patient is stable, it may in some cases be possible to delay antimicrobial therapy until a diagnostic tap or drainage can be performed in order to maximize the chances of recovering the causative organism.

Source control

If the source of infection is identified as an abscess or collection, this should be drained wherever possible, as abscesses are not vascularized and penetration of antimicrobials into the cavity is very poor, even if given intravenously.

Recovery of organisms is more likely to be successful if a volume of pus in a sterile container is sent to the laboratory as opposed to a swab.

If the infection involves prosthetic material or a device, treatment success may depend on removal of the foreign material as this is obviously not perfused and may harbour bacteria in a sticky polysaccharide matrix known as a biofilm.

Choice of initial antimicrobial agent

Empirical antimicrobial therapy targets the most likely causative agents of a clinical syndrome, and local policies should be adhered to as they will take into account local resistance patterns.

Ideally, empirical broad-spectrum cover should be avoided as it will disrupt the normal protective gut flora and may also prevent a microbiological diagnosis. In a patient assumed to be bacteraemic, inclusion of a rapidly bactericidal agent in the regimen should be considered.

Appropriate dosing

Giving an appropriate dose of the correct antimicrobial maximizes the chance for cure of disease and may prevent development of resistance due to exposure to subtherapeutic levels of antimicrobials.

A variety of reasons may prompt dose adjustments in antimicrobial treatment.

Patients with renal disease and low creatinine clearance require dose adjustments for many classes of antimicrobials.

The dosing of aminoglycosides and glycopeptides is usually adjusted to the patient's body weight and creatinine clearance. Local guidelines for dose calculation should be adhered to.

A special case is the dosing of antimicrobials in the morbidly obese, where standard dosing may not result in achievement of therapeutic serum or tissue levels.

These cases should be discussed with a pharmacist to ensure that appropriate doses are prescribed and serious side effects are avoided.

Route of administration

Many uncomplicated infections, especially in the primary care setting, will only require oral antimicrobial treatment. Indeed, depending on the source of infection, topical antimicrobials alone may be indicated, for example in the treatment of mild otitis externa.

However, if the infection is accompanied by signs of systemic upset and sepsis is suspected, the patient may well be bacteraemic and antimicrobial treatment should be given intravenously initially.

Bacteraemia should always be treated with an appropriate intravenous antimicrobial; the duration of intravenous treatment may depend on the organism involved and the underlying source of infection.

In deep-seated infections or infections in poorly vascularized tissue, intravenous treatment is likely to continue for a prolonged course.

De-escalation and switch to oral administration of treatment

Once culture results are available, antimicrobial therapy should be adjusted according to the susceptibility of the organism in order to allow targeted treatment with a narrow spectrum agent.

If treatment has commenced via the intravenous route and clinical improvement is observed, the administration route should be reviewed after 48 hours by the latest and a switch to oral antimicrobials considered, provided blood cultures remained negative and oral treatment is appropriate for the source of infection.

Completing a course of treatment

Giving an antimicrobial for an appropriate amount of time maximizes the rate of cure of disease and reduces the risk of relapse and need for further courses of likely broader spectrum antimicrobials.

The duration of the course will differ between different foci and also partly depend on the organism involved. Generally speaking, deep-seated infections and infections in poorly vascularized tissue such as cartilage and bone will require extended courses of treatment with agents that are able to penetrate into these tissues to reach therapeutic levels.

KEY POINTS

- Antimicrobials may be classified by chemical class and mechanism of action.
- Organisms can display intrinsic resistance to certain agents.
- Acquired resistance may arise as a direct consequence of exposure to antimicrobial agents. There are a number of resistance mechanisms, some of which can spread within bacterial populations and between different bacterial species via mobile genetic elements.
- The control of antimicrobial resistance is a major public health challenge.
- Any decision to commence antimicrobial therapy should comply with best practice principles.

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CHAPTER 23

HUMAN IMMUNODEFICIENCY VIRUS

Neil Ritchie and Alasdair Robertson

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: acquired immunodeficiency syndrome, antiretroviral therapy, highly active, HIV, HIV infections, lymphadenopathy, otolaryngology, otorhinolaryngologic diseases, sarcoma and kaposi.

INTRODUCTION

Human immunodeficiency virus (HIV) has had a profound impact on global healthcare in the 30 years since its discovery. In 1981 healthy young men in America started to become gravely ill with atypical infections and tumours, previously only seen in the severely immunocompromised; the term acquired immuno-deficiency syndrome (AIDS) was coined. In 1983, HIV was isolated and identified as the causal agent. HIV is now a worldwide epidemic that affects individuals of every age, sex and socioeconomic group, with 34 million people infected.[1]

Sub-Saharan Africa continues to bear the brunt of the epidemic, and accounted for 69% of all people living with HIV and 72% of new cases in 2011. Since 1998 more than 1 million people a year have died from HIV infection in Sub-Saharan Africa. South Africa alone has 5.6 million infected people, compared to 1 million in Western and Central Europe and 1.3 million in North America. The number of people infected with HIV continues to increase; however, the number of new cases per year and the number of deaths per year have been falling since the peak of the disease in 1997. Eastern Europe and Central Asia (particularly the Russian Federation and Ukraine) are bucking the trend for HIV control, with a 250% increase in HIV infection from 2001 to 2010. Changing health policies and new treatments are responsible for the relative decline of the HIV epidemic. Public health campaigns have helped to change behaviour with an increase in condom use and a decrease in the number of sexual partners. Antiretroviral therapy for pregnant HIV-infected women has reduced mother-to-child spread. Targeting of high-risk groups such as sex workers (free condoms) and intravenous drug users (needle exchange programmes) has been effective. The effectiveness of these interventions is impeded by the number of people living with HIV who are unaware of their infected status; 84% of HIV-infected adults in Kenya were unaware of their infection[2] and in the UK the figure is 24%.[3]

Head and neck manifestations of the disease are prevalent and up to 100% of HIV patients will have some head and neck presentation of the disease during the course of their illness.

HUMAN IMMUNODEFICIENCY VIRUS

HIV is a retrovirus, of the lentivirus genus. There are two strains of the virus: HIV-1 and HIV-2. HIV-1 is the global epidemic strain, while HIV-2 is largely limited to West Africa and is less virulent. The HIV genetic material is a diploid, single-stranded ribonucleic acid (RNA) that uses the enzyme reverse transcriptase to

convert its single-stranded RNA into double-stranded deoxyribonucleic acid (DNA). The viral RNA encodes three virus specific genes: *pol, gag* and *env*. *Pol* encodes the enzymes for viral replication (polymerase, integrase and protease) while *gag* encodes the inner structural proteins. *Env* encodes the glycoproteins responsible for the viral envelope; this envelope contains two glycoproteins, gp41 and gp120, which form a complex essential for viral proliferation. gp120 binds to the glycoprotein receptor CD4 on the host-cell membrane. CD4 is found in highest concentrations on T helper lymphocytes and it is through these cells that HIV primarily proliferates. Once gp120 and CD4 are bound, the viral and host cell membranes fuse. This allows the viral contents to be injected into the host cell. Reverse transcriptase then catalyses the synthesis of viral DNA from RNA. The viral DNA then migrates into the host nucleus and is incorporated into the host cell genome through the action of integrase. This means that the viral genome is replicated along with the host cell DNA and passed onto progeny cells. Once activated, the provirus begins to synthesize new virus particles using host cell transcription machinery. Cells of the monocyte/macrophage lineage also express CD4 and thus can be infected by HIV and act as reservoirs.[4, 5]

HIV infection is characterized by three distinct phases: seroconversion, asymptomatic infection and AIDS. Seroconversion starts within 2 weeks of inoculation; viraemia occurs with widespread dissemination of the virus throughout the body. Reservoirs of infection are created in macrophages. The viral load is high and a sharp decline in the number of CD4+ cells occurs. The individual is very infectious at this stage. Eventually the immune system attains a degree of control and this leads to a reduction in the viral load and a recovery of the peripheral CD4 cell count but infection is not eradicated. Half of seroconverting patients experience symptoms, typically a 'flu-like' illness with fever malaise and generalized rash. The next phase of HIV infection lasts for several years, during which the patient is asymptomatic. During this latency period viral replication and CD4 lymphocyte destruction continues; however, the body's immune response keeps the viral load in check. Circulating CD4 counts are generally high during this period. Once the CD4 count starts to decrease, symptomatology may resume, beginning with fatigue and generalized lymphadenopathy. Further decreases in CD4 count produce more constitutional symptoms including fever, sweats, chills, weight loss, night sweats and diarrhoea. Eventually the CD4 cells reach a level where an effective immune response can no longer be mounted (less than 200 cells per microlitre). At this stage, the incidence of opportunistic infections and AIDS associated neoplasms greatly increases. T helper cells are important in the immune response against viruses and fungi, hence these infections are the most commonly encountered. Conditions such as *Pneumocystis carinii* pneumonia and Kaposi's sarcoma are diagnostic for AIDS. Untreated AIDS is universally fatal.

HIV TESTING

With prompt treatment, HIV morbidity and mortality can be minimalized. One of the most important factors in poor prognosis is late presentation.[6] Furthermore, undiagnosed individuals pose a significant risk of further transmission. Detection of HIV infection is therefore an essential pillar of HIV interventions. There are two main misconceptions regarding HIV testing: it requires extensive pre-test counselling and it will have an impact on future insurance polices for the patient. Where an HIV test is clinically indicated, extensive pre-test counselling is not required. Informed consent should be taken including discussion of the benefit of testing and how the results will be given. It is recommended that if a test is positive the clinician should have identified the appropriate local treatment providers and established a clear plan for onward referral prior to the consultation.[7]

Testing for HIV, by an otolaryngologist, should be carried out whenever HIV infection enters the differential diagnosis. In particular otolaryngologists should test patients with the following conditions: unexplained oral candidiasis, hairy leukoplakia of the tongue, atypical head and neck cancers, parotid cysts, cervical lymphadenopathy, chronic parotitis and pyrexia of unknown origin. High-risk groups should also be offered testing. In the UK all patients who attend antenatal, genito-urinary medicine clinics and drug dependency services are offered HIV testing. In the United States, the Preventative Services Task Force has recommended screening for all individuals aged between 15 and 65.[8]

THERAPY

Over the past 15 years significant progress has been made in the treatment of HIV-infected individuals. Highly active antiretroviral therapy (HAART) has transformed the prognosis for people living with HIV, turning the disease from a fatal affliction into a manageable chronic condition. HAART is a treatment consisting of various regimens of multiple pharmaceutical agents. Each drug in a HAART regimen inhibits a different part of the viral lifecycle. By inhibiting the virus at multiple stages effective viral suppression can be obtained. The commonly used drugs inhibit one of the three main viral enzymes for replication: reverse transcriptase, protease and integrase.

Two classes of drugs inhibit reverse transcriptase; nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). NRTIs are the oldest antiretroviral drugs and still have a central role in antiretroviral therapy. NRTIs are structurally similar to DNA nucleosides. Since reverse transcriptase lacks error correction, when it incorporates NRTIs into the proviral DNA, the replication process is terminated. NNRTIs inhibit reverse transcriptase by binding directly to its active site.

HIV protease catalyses the maturation of viral particles by cleaving polypeptides responsible for capsule

formation. Protease inhibitors (PIs) are highly robust antiretrovirals but their complex absorption kinetics require complex regimes and lack patient acceptability. However, the use of the PI ritonavir as a pharmacological booster has revolutionized their use by allowing once or twice daily regimes without difficult dietary restrictions.

Other classes of antiretrovirals include integrase inhibitors, entry inhibitors and fusion inhibitors but these are usually reserved for patients intolerant of first-line therapy or with resistant infection.

When used as monotherapy, antiretroviral resistance rapidly develops through the accumulation of mutations in viral genome caused by the relatively imprecise action of reverse transcriptase. This means that antiretroviral therapy must be delivered as combinations, usually of three drugs. The most common first-line regimes consist of two NRTIs (the backbone) with either a NNRTI or PI. With current HAART regimes, up to 95% of patients can achieve viral suppression with an undetectable viral load.

Not all people living with HIV need HAART. Current UK guidelines suggest healthy patients in the asymptomatic phase with a high CD4 count only require monitoring. Current British HIV Association guidelines suggest a CD4 threshold of 350 cells/ul. Development of serious HIV related infections or malignancies are other indications for initiation of HAART.

OTORHINOLARYNGOLOGICAL MANIFESTATIONS

The relative sparing of the humoral immune response in HIV-infected patients means that the incidence of most bacterial infections is similar to non-HIV-infected patients. Conditions such as bacterial otitis externa, bacterial sinusitis and tonsillitis have generally the same infective agents and treatments in HIV and non-HIV patients. This chapter will concentrate on the more challenging and unusual conditions that HIV patients encounter.

ACUTE HIV INFECTION

Patients recently infected with HIV can present to the otolaryngologist with the symptoms of their initial infection. Detection of infection at this stage is important both for the patients and from the perspective of public health. Patients with acute infection usually have a very high viral load and are therefore highly infectious. Early diagnosis gives an opportunity to intervene before further infections occur. Acute infection usually presents non-specifically; however, common symptoms include fever, pharyngitis, lymphadenopathy, oropharyngeal ulceration and rash. Heterophile antibody testing is usually negative but there are reports of positive tests in acute HIV.

UK testing guidelines recommend all patients with a mononucleosis-like illness should be offered an HIV test.

CERVICAL LYMPHADENOPATHY

The presence of peripheral lymphadenopathy is common in patients infected with HIV. In the era of HAART, AIDS-associated malignancies have become less common and it has become clear that patients with HIV are also at increased risk of non-AIDS malignancies including head and neck, lung and upper-gastrointestinal cancers with an overall odds-ratio of around 2–4.

Persistent generalized lymphadenopathy is a common feature of early symptomatic HIV infection, with cervical nodes the most commonly involved. Lymph nodes are usually small, symmetrical and non-tender. Biopsy is not required unless an alternative diagnosis is suspected and is usually prompted by continued enlargement or asymmetry. When biopsy is conducted, it reveals follicular hyperplasia and no treatment is required.

Other causes of lymphadenopathy common in patients with HIV include non-Hodgkin's lymphoma, Hodgkin's lymphoma, tuberculosis, syphilis, Kaposi's sarcoma (KS) and metastatic solid organ malignancies. Less common causes include infections such as mycobacterium avium complex, syphilis, dimorphic fungi and toxoplasmosis.

Castleman disease is a rare lymphoproliferative disorder. In most immunocompetent patients it is a localized disorder that rarely causes systemic symptoms. However, in HIV associated disease most patients present with constitutional symptoms associated with organ involvement (multicentric disease). The disorder is associated with human herpes virus-8 (HHV-8) infection, which is also the viral cause of KS.[9] Patients with multicentric Castleman disease present with fever, weight loss and lymphadenopathy. Diagnosis is made with excision biopsy.

KAPOSI'S SARCOMA

Kaposi's sarcoma (KS) is a malignant spindle cell tumour. Initially it was a rare condition seen in elderly Mediterranean men (classical KS); however, it is now mostly associated with HIV infection. KS is an AIDS-defining condition and is the most common HIV-related tumour. KS is caused by the co-infection of HIV and HHV-8. Untreated HIV KS is an aggressive tumour; however, the advent of HAART has lead to a decrease in the incidence and severity of KS.

KS presents with cutaneous or mucosal lesions, most commonly in the head and neck. Visceral organs and lymph nodes can also be involved. Cutaneous lesions are variable in nature; the colour varies from purple to dark brown, the size is from a few millimetres to several centimetres, there may be multiple lesions or a single lesion, and the lesions may be flat, raised or nodular. Oral mucosa lesions are classically raised and red and may ulcerate. Patients with suspected KS should have an HIV test and CD4 count; a biopsy will confirm the diagnosis.

HAART is the mainstay of KS treatment; as the immune system recovers the condition regresses. In advanced cases HAART may not be sufficient and local treatment is required. Localized radiotherapy to cutaneous or oral

lesions provides good control of the disease although HIV patients are more prone to radiation side effects.[10] Surgical excision also provides local control; however, recurrence is common even with clear margins of excision. Other treatment modalites include topical retinoids, intra-lesional chemotherapy, laser coagulation and cryotherapy.

Bacillary angiomatosis is a condition that mimics KS and should be considered in the differential diagnosis. Bacillary angiomatosis is a bartonella infection in HIV patients that causes a vascular proliferation. The resulting lesions have an angiomatous appearance very similar to KS. Biopsy and microbiological studies will differentiate from KS. Bacillary angiomatosis resolves with antibiotics; erythromycin is the drug of choice.

OTOLOGIC

External ear

Malignant otitis externa (MOE) has a higher incidence in HIV patients. Osteomyelitis of the skull base causes facial nerve or cranial nerve dysfunction. Diagnosis can be confirmed using a computerized tomography (CT) scan of the temporal bone or a technetium 99m bone scan. The causative agent for malignant otitis externa is usually *Pseudomonas aeriuginosa*, although in patients with very low CD4 count *Aspergillus* is common and can be very invasive.[11, 12] In *Pseudomonas aeriuginosa*, the treatment is 6–8 weeks of antibiotics. A combination of an antipseudomonal third-generation cephalosporin with either ciprofloxacin or aminoglycoside is appropriate.[13] Invasive *Aspergillus* should be treated with intravenous antifungals such as amphoteracin B. Surgical debridement may be necessary in more severe cases.

Pneumocystis jiroveci (previously known as *Pneumocystis carinii)* can infect the extenal auditory canal but may also involve the middle ear and mastoid bone. It may present as either a cyst or polyp, and the cyst if allowed to grow can occlude the external auditory canal or spread to the middle ear cleft and middle cranial fossa. The diagnosis is made by biopsy. Treatment with trimethoprim/sulphamethoxazole and/or dapsone[14] usually results in resolution of infection.

Middle ear

The most common otologic entities seen in HIV-positive individuals are serous and recurrent otitis media. There are a variety of aetiologies that includes Eustachian tube dysfunction, nasopharyngeal neoplasms, adenoid hypertrophy and sinusitis/allergies. Nasopharyngeal neoplasms should be ruled out in HIV-infected individuals, particularly with unilateral otitis media. Myringotomy and tympanostomy tube placement can offer symptomatic relief easily and quickly. Treatment of associated sinusitis or allergies should be instituted. Adenoidectomy may be indicated when more conservative measures fail.

Mycobacterium tuberculosis (TB) is a common infective agent in HIV. *Mycobacterium tuberculosis* should be considered in patients with an otitis media unresponsive to conventional therapy. The classical TB otitis media signs of multiple tympanic membrane perforations, granulations, painless otorrhoea and bone necrosis may not be evident in HIV patients. Tissue biopsies and microbiology cultures may be diagnostic; however, false negatives are common. Antituberculous chemotherapy should be continued for a minimum of 6 months. Surgery to remove sequestrum may speed up recovery; however, a conservative approach has also been shown to be effective.[15, 16] Atypical mycobacteria such as *Mycobacterium avium* complex are also reported to cause otitis media in patients with HIV.[17]

Inner ear

Vestibular and cochlear symptoms are common in HIV-infected individuals. Sensorineural hearing loss is reported to be more common than in uninfected patients and to correlate with stage of disease.[18] Sudden sensorineural hearing loss is also reported to be more than twice as common in this patient population.[19] Identified causes of hearing loss include direct HIV central nervous system involvement, opportunistic infection, immune-reconstitution and drug induced ototoxicity.

Opportunistic infections associated with hearing loss include cytomegalovirus, herpes simplex virus, varicella zoster virus, Cryptococcus neoformans and syphilis. The role of antiretrovirals in sensorineural hearing loss is unclear; a cohort study suggested an association with NRTIs but this was not confirmed prospectively. Other drugs commonly used in patients with HIV associated with hearing loss include macrolides, aminoglycosides and isoniazid. There is some evidence that patients with HIV are more susceptible to aminoglycoside ototoxicity.

Otosyphilis is a rare but important cause of hearing loss in HIV. Patients with HIV can have an abbreviated course of syphilis with features of neurological involvement occurring early. Otosyphilis classically presents with hearing loss sparing the mid-range frequencies, tinnitus and vertigo mimicking Meniere's disease. Diagnosis is with serological testing. Treatment is with high dose procaine penicillin in combination with probenecid. The role of corticosteroids is controversial and evidence is limited but some experts recommend their addition.

Facial nerve palsy can occur in up to 7.2% of HIV patients and is referable to direct infection by the HIV, neoplasms, opportunistic infections, AIDS encephalopathy and toxoplasmosis. Bell's palsy is the most frequent diagnosis given for CN VII paralysis. It is postulated to be caused by HSV and is a diagnosis of exclusion. Complete recovery usually occurs within 3 weeks to 3 months.

Ramsay Hunt syndrome (herpes zoster oticus) usually occurs later in HIV infection and is more prevalent in AIDS patients. Symptoms include peripheral facial nerve palsy, herpetic vesicles along the seventh nerve dermatome and in the conchal bowl, and severe herpetic pain. Treatment is with high-dose acyclovir and high-dose steroids when not contraindicated.

Bilateral facial nerve palsies have been reported[20] and usually represent a systemic disease. Serology tests for

syphilis, cytomegalovirus, herpes simplex, herpes zoster and Epstein Barr virus should be carried out. MRI of the brain and CSF analysis will aid the diagnosis.

Patients with a low CD4 count may present with central nervous system disease with few or ambiguous clinical signs. There should be a low threshold for neuroimaging and lumbar puncture. Investigation and management should be undertaken in consultation with a physician with expertise in the management of HIV.

NOSE AND PARANASAL SINUSES

Thirty to sixty-eight per cent of HIV-positive patients will manifest some form of nasal and/or sinus symptom.[21] Nasal obstruction secondary to a variety of aetiologies is a complaint that commonly causes these patients to see an otolaryngologist. Adenoidal hypertrophy can present as nasal obstruction, as can hypertrophy of any of the tissues in Waldeyer's ring. Any non-paediatric patient with adenoid hypertrophy should be tested for HIV.

Neoplasms such as KS or non-Hodgkin's lymphoma can also cause nasal obstruction. Both lesions can arise from the nasal cavity or nasopharynx. Kaposi's sarcoma can also arise from the nasal septum. Non-Hodgkin's lymphoma can also arise from the sinuses.

Sinusitis in HIV-positive individuals is similar to that in non-infected persons with *S. pneumonia, M. catarrhalis* and *H. influenzae* the main infective agents. In HIV-positive persons with fever of unknown origin, the sinuses should always be investigated for possible infection. The bacteriology of chronic sinusitis differs from that of acute sinusitis. In patients with CD4 counts less than 200/mL, *S. aureus, P. aeruginosa* and anaerobes become more prominent, and antibiotic therapy should be broadened to include these organisms. As the CD4 count decreases below 50/mL, fungal infection of the sinuses can occur (**Figure 23.1**), with the majority of fungal infections caused by *Aspergillus*. Other pathogens reported in the literature include CMV, *Microsporidia*, *Acanthamoeba castellani* and *Legionella pneumophila*.

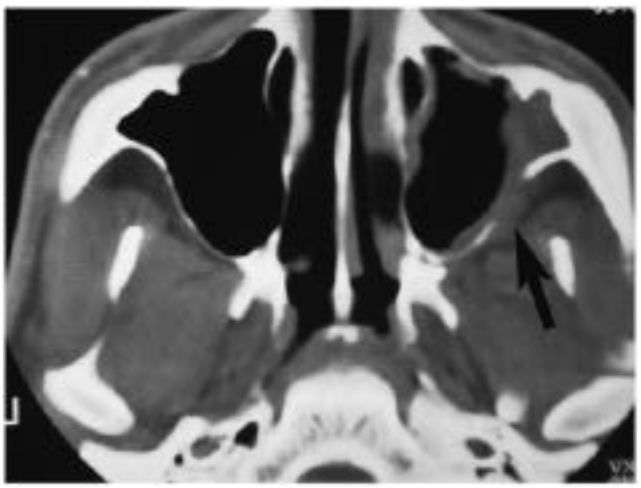


Figure 23.1 In advanced HIV disease, invasive fungal infection of the paranasal sinuses must be considered. As seen in this axial CT scan, subtle bony erosion with extension into the infratemporal fossa (arrow) indicates an invasive fungal process.

Evaluation of sinusitis in HIV involves bacteriology culture, nasal endoscopy and CT scanning. The mainstays of medical management of sinusitis are antibiotics and decongestants. First-line antibiotics include amoxicillin, co-amoxiclav, cephalosporins and co-trimoxazole. Topical nasal steroids may also be considered as an adjunctive therapy. There is also evidence suggesting a role for guaifensin therapy for these patients.[22]

Surgery is advocated in patients with persistent symptoms despite medical therapy, or in any patient at any time with extra-sinus symptoms (mental status changes, cranial nerve dysfunction, intra-cranial extension, abscess, etc.). Endoscopic sinus surgery is safe and effective. The goal of surgery should be symptomatic relief, as well as optimizing nasal anatomy to facilitate drainage of the sinuses. However, as HIV disease progression continues and CD4 counts decrease, the physician can expect recurrent sinus infections that become more difficult to treat.

ORAL CAVITY

Oral cavity manifestations of HIV are extremely common and have been reported in up to 100% of AIDS patients. Oral manifestations are also common in patients with relatively high CD4 counts and are often the first manifestation of HIV in otherwise asymptomatic patients. Oral manifestations are also common in patients on HAART, despite the generally low incidence of manifestations of immunosuppression in this group.

Recurrent apthous ulcers are common in immunocompromised patients and are generally larger than those in non-immunocompromised patients. On examination, the lesions are solitary or multiple, have anerythematous halo that is well circumscribed, and may have an exudate or pseudomembrane. The lesions are tender to palpation, and in giant apthous ulcers can cause severe odynophagia and pain. In severe cases, the pain may accentuate the anorexia and dehydration common in advanced HIV. Treatment is primarily to provide symptomatic relief. Topical anaesthetics or steroids are often effective in less severe cases. Topical tetracycline or systemic clindamycin are effective agents when superimposed infection is present. An intralesional steroid injection with triamcinolone acetonide has been shown to have analgesic effects within 24–48 hours after injection, and has very few side effects.[23] Oral thalidomide has been shown in some studies to heal ulcers completely in 55% of patients and partially in 90% of patients, but is only recommended to be used for 2–4 weeks at a time secondary to increased HIV viral load. Thalidomide also has teratogenic effects limiting its use in women. Ulcers that do not respond to local treatment should be biopsied for pathological examination.

Oral candidiasis is a common infection in HIV patients. The most prevalent form is pseudomembraneous candidiasis (thrush) and is characterized by a tender white plaque atop an erythematous and erosive mucosal surface. In the

chronic hypertrophic form, the plaques are heaped up and not easily removed with scraping. As with recurrent apthous ulcers, the lesions can be extremely painful, leading to malnutrition, dehydration and wasting if not effectively treated. Oesophageal candidiasis can coexist with oropharyngeal lesions and patients should be questioned about oesophageal symptoms since oesophageal involvement will require systemic therapy. Treatment of mild disease consists of Nystatin mouthwash. Clotrimazole or amphotericin lozenges are also effective. Systemic therapy is indicated in patients with worsening immunocompromise or thrush unresponsive to topical agents. Fluconazole is the most commonly used agent – failure to respond can indicate resistance and samples for culture should be sent for sensitivity testing. A minority of cases require intravenous therapy with amphotericin or echinocandins.

Hairy leukoplakia is unique to HIV-positive individuals and typically arises on the lateral border of the tongue as a white, raised, corrugated or filiform lesion. It can also arise on the dorsal tongue, buccal and labial mucosa, floor of mouth or soft palate. It requires no treatment and is usually asymptomatic (**Figure 23.2**).



Figure 23.2 Hairy leukoplakia of the tongue.



Figure 23.3 While often presenting as solitary lesions, oral papillomas can be widespread covering much of the oral and oropharyngeal mucosa. This patient has multiple papillomas of the dorsal tongue, which predictably recurred following surgical management.

Oral herpes simplex commonly presents as herpes labialis (fever blisters, cold sores). The lesions frequently present as small bullae that form ulcerations after they rupture. These lesions are painful and are generally larger in HIV patients than in immunocompetent individuals. Treatment consists of oral acyclovir; long-term secondary prophylaxis may be required for frequent recurrence.

Gingivitis in HIV patients tends to be more severe than in non-infected patients. Bleeding from the gums can occur with minimal or no trauma. Periodontitis presents as loosening of periodontal attachments. It can progress to acute necrotizing ulcerative gingivitis, which is an ulcerative process along the gingival margin leading to destruction of the periodontal soft tissues. Treatment consists of antibiotics aimed at anaerobic organisms and topical irrigations with chlorhexidine gluconate. If available, a referral to a dentist or oral surgeon should be made early in the process.[24]

Human papilloma virus can present as a verrucous, flat or spiky lesion in the oral cavity. It appears similar to venereal warts and usually appears in synchrony with anal or genital lesions. While often solitary lesions, these can occur as widespread involvement of the entire oral cavity and oropharyngeal mucosa (**Figure 23.3**). Treatment consists of surgical excision, but recurrence is likely.

Xerostomia secondary to chronic inflammation of the major and minor salivary glands is frequently seen in HIV patients. The treatment is for symptomatic relief and consists of oral irrigations, saline rinses, salivary substitutes and sialogogues.

KS is the most common HIV-related oral malignancy, with the majority arising on the palate. This tumour can also appear on the gingiva (**Figure 23.4**) or oropharynx.

Non-Hodgkin's lymphoma (NHL) may also arise in the oral cavity. In AIDS patients, NHL is usually a poor prognostic indicator of disease progression. Recurrences are common despite chemotherapy and radiation. The lesions may present as ulcerative lesions, but typically appear red and exophytic. They usually involve the gingiva and alveolar ridges and may arise from Waldeyer's ring.[25]



Figure 23.4 The gingival is a common site for presentation of Kaposi's sarcoma.

TABLE 23.1 Characteristics and treatment of the most common oral manifestations of HIV

Disease		Management	Comment
Gingival disease	Can develop gingival tissue loss, tooth loosening/loss, bone exposure	Best treatment is frequent dental cleanings, flossing, etc. Aggressive antibiotics and/or surgical management when advanced	Common in HIV. Requires close dental evaluations and frequent management
Oral thrush	Pseudomembranous candidiasis: • Typical plaque-like lesions • Atrophic form with erythematous lesions on palate, buccal mucosa, tongue • Angular cheilitis	Topical agents such as clotrimazole. Systemic agents (e.g. fluconazole) for refractory cases in patients with advanced disease	Prolonged or frequent use of fluconazole increases risk of azole-resistance candidiasis
Oral aphthous ulcers	Lesions may be large. Biopsy confirms non-neoplastic, non-viral aetiology	Topical steroid therapy. Intra-lesional or systemic steroids. Thalidomide. Antiretroviral therapy	Are usually difficult to treat. Produce severe pain, odynophagia. Often cause substantial morbidity
Kaposi's sarcoma	Typically on hard, soft palate. Occasionally on gingival, buccal mucosa	Symptomatic relief. When functionally problematic, low-dose radiotherapy or intra-lesional vinblastine or systemic chemotherapy	
Radiation mucositis	Side effect of treatment for other oral lesions	Topical therapy (steroids, antifungals, etc.) Supportive care – nutrition, pain management, hydration	Can result even from low doses of radiation
Hairy leukoplakia	Usually occurs on side of tongue. Probably Epstein-Barr virus related	No treatment necessary if asymptomatic	Must be differentiated from other more serious oral disorders

Table 23.1 reviews the characteristics and treatment of many of the most common oral manifestations of HIV disease.

PHARYNX, LARYNX AND OESOPHAGUS

Many of the same processes that affect the oral cavity can also affect the larynx and pharynx. Many of these processes present with similar symptoms: odynophagia, dysphagia and in some cases, chest pain. Correctly identifying and treating these processes can not only provide symptomatic relief but also in many cases help in dealing with the wasting and malnutrition that can occur.

Candidiasis of the oesophagus and pharynx can cause severe dysphagia, odynophagia and weight loss. Laryngeal infection presents as hoarseness and in severe cases stridor and shortness of breath. Barium swallow will show an irregular cobblestone surface to the mucosa. Direct visualization can be obtained with panendoscopy and biopsy will exclude KS. Treatment is with systemic fluconazole.

Cytomegalovirus is the second most common infectious ulcerative condition of the upper aerodigestive tract. Of patients who fail empirical antifungal therapy, approximately one-third will have CMV ulcerations.[26, 27] These ulcers tend to occur more commonly in the distal oesophagus with a raised indurated border and necrotic base. While occasionally occurring as solitary ulcers, CMV can also form multiple or diffuse ulcerations and lacking any defined pathognomonic appearance. Unfortunately, other than biopsy and culture, there are also no disease specific clinical characteristics that differentiate this from other forms of ulcerative oesophagitis. Once the diagnosis has been established, treatment can be instituted using intravenous ganciclovir or foscarnet.

Herpes simplex viral infection in the pharynx, larynx or oesophagus can present with similar symptoms as oesophageal and laryngeal candidiasis. Examination reveals discrete vesicles with mucosal ulceration. Biopsy and viral culture of lesions confirm diagnosis. The occurrence of HSV is usually associated with significant immune dysfunction, usually occurring only when the CD4 level is well below 100/mm[28] Treatment usually starts with intravenous acyclovir followed by oral agents.

Idiopathic oesophageal ulcer arises with the same frequency as CMV oesophagitis. Its aetiology is unclear and there is usually no associated specific infectious aetiology. These lesions also usually occur with severe immunocompromise. The endoscopic appearance is similar to CMV lesions, often with solitary, large ulcerations with raised indurated margins. Treatment has been effective using systemic steroids.[29] Successful treatment has also been described with thalidomide.[30]

Kaposi's sarcoma can present primarily in the pharynx and/or larynx or extend to adjacent areas including the oral cavity. Oesophageal KS may present with dysphagia or odynophagia. Laryngeal lesions may present as shortness of breath, hoarseness or severe airway compromise.

SALIVARY GLANDS

Both major and minor salivary glands can be involved in disease processes in the HIV-infected individual. The most common complaint is xerostomia.

Lymphoepithelial cysts is a disease process that is almost diagnostic of HIV infection. Lymphoepithelial cysts present as progressive parotid swellings, which are usually multiple, bilateral and non-tender (Figures 23.5 and 23.6).

Facial nerve dysfunction should lead the physician to suspect a malignant neoplasm. Fine-needle aspiration



Figure 23.5 The most common etiology of an asymptomatic parotid mass in the HIV-infected patient is the lymphoepithelial cyst (arrow).

reveals fluid with lymphocytes and squamous epithelial cells. Computed tomography or ultrasound imaging will show multiple thin walled cysts in the parotid gland. With fine-needle aspiration biopsy (FNAB) and imaging, open biopsies or surgical excision for diagnosis is rarely indicated. The cysts usually resolve with HAART and surgery is only necessary for enlarged lesions that are a cosmetic challenge or where the diagnosis is equivocal. Needle aspiration of cyst contents is ineffective for long-term cure

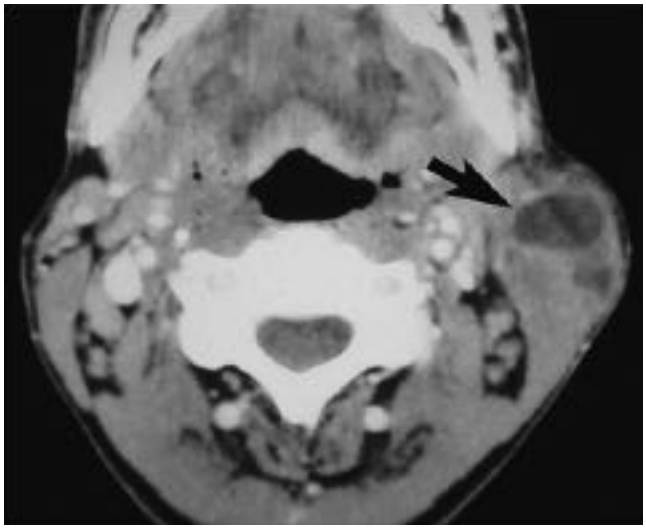


Figure 23.6 This axial CT scan demonstrates the typical findings (arrow) of a benign parotid lymphoepithelial cyst.

as recurrence almost always happens.[31] In patients not receiving HAART, slerotherapy with alcohol or sodium morrhuate can be effective.[32, 33]

KEY POINTS

- HIV infection continues to be a global health problem.
- Infection with the Human Immunodeficiency Virus leads to immunosuppression, opportunistic infections and Acquired Immunodeficiency Syndrome.
- Highly active anti-retroviral therapy (a combination of various anti-retroviral agents) is an effective treatment for HIV infection.
- Otolaryngologists should test for HIV infection whenever it enters the differential diagnosis.
- ENT manifestations of HIV infection are very common.
- Kaposi's sarcoma is a malignant tumour caused by the co-infection of HIV and Human Herpes Virus 8.

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CHAPTER 24

BLOOD GROUPS, BLOOD COMPONENTS AND ALTERNATIVES TO TRANSFUSION

Samah Alimam, Kate Pendry and Michael F. Murphy

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: transfusion, components, alternatives, blood sparing and adverse events.

INTRODUCTION

Surgical specialties are responsible for the transfusion of up to 40% of blood and blood components in the UK. It is therefore imperative for those in surgical practice to have a sound understanding of the principles of safe transfusion, the appropriate use of blood and measures for blood avoidance (**Box 24.1**).

The UK has been successful at improving the safety of blood and blood component transfusion over the last 25 years. The risk of death has dropped to under 3 in 1 000 000 per blood components issued, since the serious hazards of transfusion (SHOT) scheme started in 1996. This reduction has been largely due to increased awareness of the hazards of transfusion, better screening of donors and improvements in the processing of blood and its components. A frequently encountered error in blood transfusion remains that of ABO incompatibility as a consequence of clerical error. Examples of this and other transfusion complications will be covered later in the chapter.

BOX 24.1 Principles of safe and appropriate transfusion

1. Do not just act on numbers. Not all anaemic patients need transfusing – consider the patient's symptoms, comorbidities and possible treatable underlying cause.
2. Transfuse based on clinical assessment and evidence-guided practice.
3. Involve the patient in the decision to transfuse (or not) and obtain consent.
4. Ensure the right blood is transfused to the right patient at the right time in the right place and for the right indication.

Blood is used in the management of anaemia, in surgical blood loss and in patients with acute massive haemorrhage. However, blood and its components are a scarce resource both within the UK and worldwide. Only 5% of eligible adults in the UK are blood donors, and this valuable resource needs to be used in a responsible and safe manner.

In relation to ENT surgery, a retrospective review of transfusion in patients undergoing sinus surgery in Germany found that only 0.46% of these patients actually needed a transfusion; this likely represents excellence in surgical techniques and patient management to avoid blood transfusion.[1] A study in the United States concluded that transfusion is no longer necessary during routine bimaxillary orthognathic surgery. Patients requiring double-jaw procedures are often the ENT patients most likely to require a blood transfusion.[2]

BLOOD DONATION

Extensive screening of altruistic, unpaid volunteers has been a major factor in the provision of safe blood in the UK. First-time donors in the UK have to be between the ages of 17 and 65 years, minimum weight of 50 kg, in good health and undergo a thorough health questionnaire and screening programme to exclude high-risk donors. There is no upper age limit for donors but after the age of 66 years, donors are required to undergo an annual review. Male donors can donate blood every 12 weeks up to a maximum of four donations in 12 months. Female donors can donate every 16 weeks up to three times a year. The minimum haemoglobin concentration (Hb) required for donation is 125 g/L for female and 135 g/l for male donors (for full eligibility criteria consult https://www.blood.co.uk).

Following thorough cleaning of the skin at the needle entry point, blood is collected into a sterile bag containing anticoagulant and preservative. It is labelled with the donor details and transported to a blood centre where it is processed. Whole blood is filtered and then separated into its blood components. Filtration eliminates leucocytes, which are associated with several complications of transfusion including febrile (non-haemolytic) transfusion reactions, human leukocyte antigen (HLA) alloimmunization and transmission of cytomegalovirus (CMV). Leucocyte depletion was introduced as a variant Creutzfeldt–Jakob disease (vCJD) risk reduction measure and the other effects were a useful by-product of this decision. From each unit of blood donated, red cells, platelets, fresh frozen plasma and cryoprecipitate can be obtained.

A sample from the donor on each occasion is tested for blood-borne viruses and syphilis (Table 24.1). Platelets undergo bacteriological testing requiring incubation for 36 hours to exclude any significant bacteria before release.

Due to concerns regarding the transmission of vCJD by blood transfusion, universal leucocyte-reduction of blood components was implemented in the UK in 1999. In addition, a number of restrictions on blood donors were put in place to reduce the risk of transmission. Individuals are restricted from donating if they have:

- previously received a blood transfusion after 1980
- received human pituitary-derived hormones, graft of human dura mater, cornea, sclera or other ocular tissue
- come from a family at risk of inherited prion disease
- been notified that they are at risk of vCJD due to exposure to infected individual via blood transfusion, transplanted tissue or surgical instruments
- been notified they are at risk because a recipient of their blood or tissue has developed a prion-related disease

Additionally, individuals born after 1996 who require plasma products are only transfused with non-UK plasma.

BLOOD GROUPS

There are more than 300 blood groups with around 23 being clinically significant. The most important are the ABO and RhD groups because of their association with haemolytic transfusion reactions and haemolytic disease of the newborn. However, some patients especially those who are multi-transfused may develop antibodies against other blood group antigens and thus it is important to look beyond the ABO and RhD in patients requiring transfusion.

ABO group

The ABO grouping of blood was first recognized in 1901 by Landsteiner. The ABO system is the most important because of the presence of naturally occurring anti-A and anti-B antibodies, which develop in the first months of life. The ABO system consists of three allelic genes – A, B and O – and each of these is responsible for production of antigens on the surface of red blood cells (Table 24.2). ABO incompatible transfusions are very serious because anti-A and anti-B are IgM antibodes causing intravascular haemolysis activation of coagulation and cytokines resulting in major morbidity and mortality. In the UK, blood group O is commonest, found in 47% of the population. Historically, blood group O individuals were considered to be universal donors and AB universal recipients. As a result, Group O, RhD negative blood is often used in emergency situations. Group O RhD negative blood is in short supply, consequently except in true emergencies it is desirable to establish the ABO and RhD group of emergency patients to ensure group specific blood is issued. Group AB is the rarest group in the UK and due to lack of donors they are often given group A or B blood.

TABLE 24.1 Screening for infectious agents

Routine screening of donor blood	Further screening may include (depending on travel history):
• Hepatitis B • Hepatitis C • Human immunodeficiency virus • Human T cell lymphotropic virus • Syphilis	• Malaria • West Nile virus • Trypanosoma cruzi

TABLE 24.2 ABO groups

Blood group	Antigen	Antibody	UK frequency %
0	None	Anti A, Anti B	47
A	A	Anti B	42
B	B	Anti A	8
AB	AB	None	3

Rh antigens

The Rh system was discovered later by Landsteiner and Weiner in 1940. The RhD antigen is the most important, although others do also exist (Cc and Ee). The RhD gene maybe either absent or present (i.e. RhD+ or RhD–); 85% of the UK population is RhD+. Rh antibodies are IgG antibodies causing extra-vascular haemolysis. They do not occur naturally but as a result of sensitization secondary to transfusion or pregnancy. The commonest significant event is that of a RhD– mother, developing an antibody as a result of carrying a RhD+ foetus. If not addressed, this can result in the fatal haemolytic disease of the newborn or hydrops fetalis. The UK programme of antenatal administration of anti-D for the prevention of RhD immunization in pregnancy and postpartum has reduced its incidence. However, it is imperative that all RhD– women of childbearing age only receive RhD– blood components.

BLOOD GROUPING AND CROSSMATCH PROCESS

Compatibility testing is carried out in accredited hospital blood transfusion laboratories by trained biomedical scientists. There is now increasing use of automated processes but there is still an important role for the clinical scientist.

As previously mentioned, the first step is determination of the ABO and RhD groups of the recipient: 'blood grouping'. This is rapid and can be done in less than 15 minutes. Once a patient is grouped an antibody screen is performed to identify any clinically significant red cell antibodies; this process takes up to 45 minutes in total. If the antibody screen is positive, the blood group specificity of the antibodies should be identified by testing the patient's plasma against panels of red cells with a wide range of known blood group antigens.

The full crossmatch takes up to 60 minutes and involves testing the patient's plasma against a sample of the donor red cells to be transfused. In many hospitals this serological crossmatch has been omitted as a negative antibody screen makes it highly unlikely that there will be any incompatibility with the donor units. A greater risk is that of a transfusion error involving the collection of the patient sample or a mix-up of samples in the laboratory. Laboratories can use their information system to check the records of the patient and authorize the release of the donor units (computer or electronic crossmatching/issue).

Electronic blood issue, as described above, can be extended to issue previously unallocated blood at blood fridges remote from the main laboratory ('remote blood issue'). This is possible using blood fridges electronically linked to the blood transfusion laboratory information system. The printing of compatibility labels for the blood and its collection are under electronic control using the same rules as electronic issue from the main laboratory. Issue of blood using this process reduces the time it takes to provide blood for patients needing it urgently, particularly at hospitals without a blood transfusion laboratory because transport of blood from the central laboratory is not required.

In an emergency it is possible to provide group specific blood (same ABO and RhD groups as the patient) within a few minutes and follow this up with a full crossmatch. If time is short it is possible to administer group O blood, and for women of childbearing age this must also be RhD negative.

In elective surgical patients, blood grouping and antibody screening can be done weeks in advance of surgery. The British Committee for Standards in Haematology (BCSH) guidelines[3] recommend a second sample be tested for confirmation of ABO group for all patients undergoing transfusion for the first time. With regards to the timing of pre-transfusion compatibility testing the following is recommended:

1. Samples should not be more than 3 days old in those who have been transfused or pregnant within last 3 months.
2. An extension to 7 days can be considered for those regularly transfused or pregnant women with no significant alloantibodies.

PLANNING FOR SURGERY

Many operations can take place without the need for transfusions. Blood transfusion laboratories can issue blood and blood components rapidly if there is unexpectedly large bleeding, and there is rarely a need to provide large numbers of units in advance.

It is important in elective surgical procedures to optimize the patient's Hb prior to surgery to minimize the need for transfusion. If there is evidence of anaemia this should be investigated and treated pre-operatively. Thirty per cent of patients found to be anaemic pre-operatively are iron deficient; this can be corrected with oral iron or, in patients who are intolerant to oral iron or those that have a short pre-operative period, intravenous iron can be used.

Maximum surgical blood ordering system (MSBOS)

In surgical procedures that have a high probability of requiring transfusion, an MSBOS should be agreed between the surgical team and transfusion laboratory. This must specify the number of units of each blood component that should be reserved routinely guided by evidenced based practice (Table 24.3). The recommended aim is to have a crossmatched to transfused ratio of <2:1 with regular review and audit of actual blood use.

TABLE 24.3 Examples of MSBOS

Surgical procedure	MSBOS
Tumour of palate	Group and Save only
Laryngectomy	2 units
Radical neck dissection	2 units
Commando	4 units

EMERGENCIES

Emergency requests for blood require clear communication between the clinical team and laboratory staff. If there is a massive haemorrhage (i.e. blood loss greater than 50% of patients' blood volume in 3 hours or more than one total blood volume within 24 hours or greater than 150ml per minute associated with shock), the 'massive haemorrhage protocol' must be activated. Figure 24.1 gives an example of such a protocol. Early recognition and intervention to stop bleeding is vital for patient survival. It is important for the clinical team to liaise closely with the

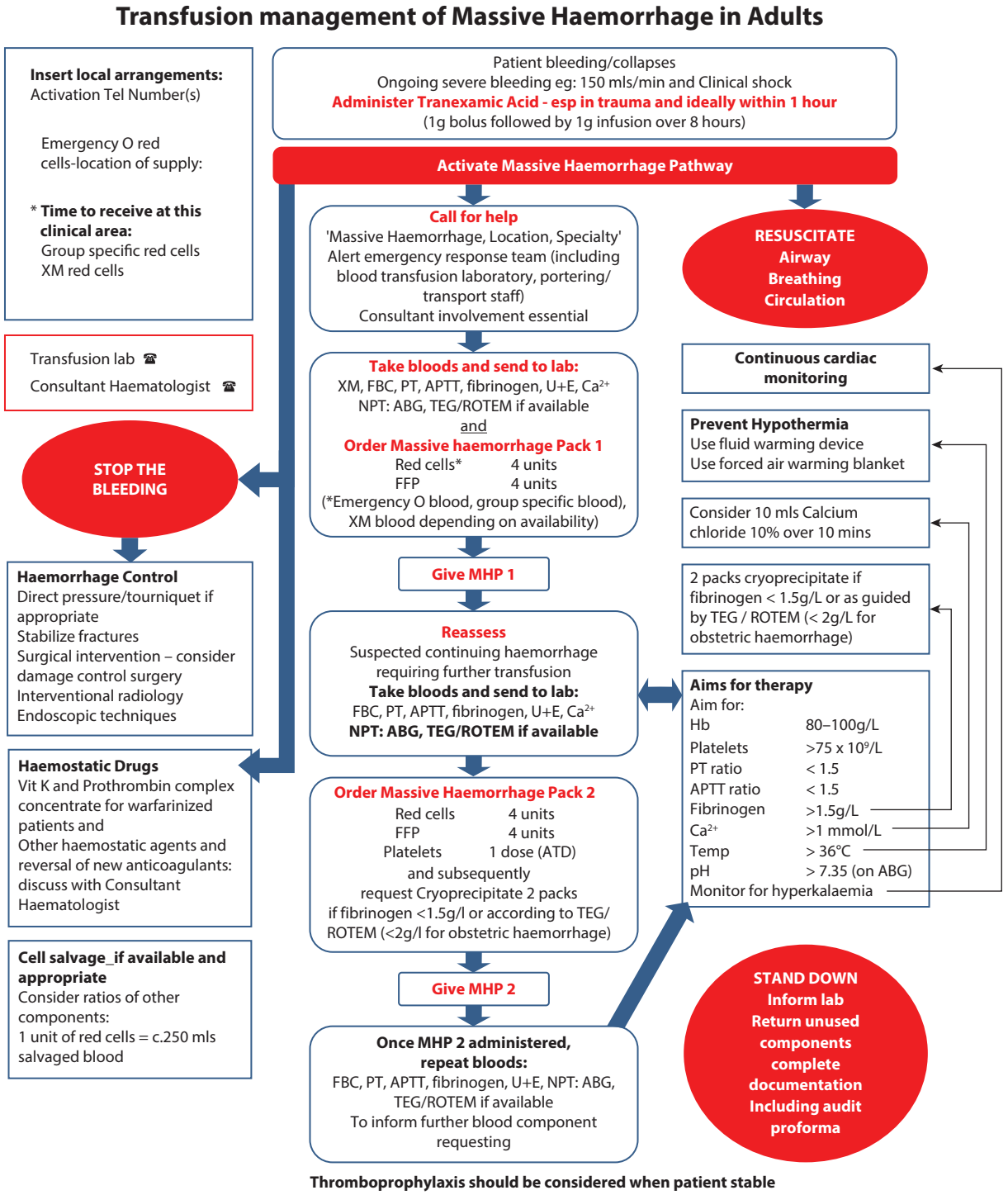


Figure 24.1 Suggested algorithm for management of massive haemorrhage. (Adapted from the North West Massive Hemorrhage tool kit with permission from Dr Kate Pendry.)

blood transfusion laboratory and ensure the appropriate products are requested, issued and administered rapidly. Close monitoring of haemostasis is essential as a massive transfusion can result in platelet and coagulation factor depletion especially of fibrinogen, which will require replacement.

BLOOD COMPONENTS

Whole blood is composed of a number of components that are separated during blood processing in transfusion centres. Whole blood is not used in modern clinical practice and use of individual components makes for more efficient and safer therapy. Figure 24.2 outlines the different components of blood and their preparation.

Red blood cells (RBC)

Red blood cells are responsible for the transport of oxygen. Transfusion of RBC is indicated in massive haemorrhage, symptomatic anaemia, after chemotherapy and in chronic haematological conditions. ABO and RhD compatibility are essential for safe transfusion as described above. RBC are stored at 2–6 °C for up to 35 days. Irradiated blood, which is required for immunocompromised individuals at risk of transfusion-associated graft versus host disease (TA-GVHD), has a shorter shelf life of 14 days. It is important for the clinical team to inform the transfusion laboratory of this requirement. TA-GVHD is explained in more detail later in this chapter.

There is no universal agreed trigger for the transfusion of RBC, and it is important to be aware of local guidelines. Patients must be assessed clinically for symptoms of anaemia or bleeding. Emphasis must be on clinical evaluation over correction based purely on numbers. A Cochrane review has recommended evaluated transfusion triggers and recommended target haemoglobin of 70 to 80 g/L and the transfusion of 1 unit followed by assessment of the patient's response. This current trend in practice favours restrictive rather than liberal transfusion; the groundbreaking TRICC study[4] reported no significant difference in 30-day mortality in critically ill patients who were randomized to either a restrictive or liberal transfusion strategy. Additionally the group was able to demonstrate a benefit in outcomes in younger patients who received the restrictive transfusions.[4] The recommendation that followed from this trial changed critical care practice, as now unless contraindicated the recommended policy is not to transfuse until haemoglobin has fallen below 70 g/L aiming for a target haemoglobin of 70 to 90 g/L. This restrictive transfusion practice has received support from other randomized controlled trials in cardiac surgery and acute upper gastrointestinal haemorrhage and is now widely adopted throughout clinical practice. The only exceptions to this are patients with acute cardiac ischaemia and those on long-term transfusion programmes, for example thalassaemia and myelodysplastic syndrome, who may have a trigger haemoglobin of 80 g/L or greater to maintain a good quality of life (this should be discussed with the haematologist).

Platelets

Platelets are central to haemostasis. Platelet transfusions may be needed in patients with thrombocytopenia or platelet function disorders. Platelet concentrates are prepared either by centrifuging whole blood or from a single donor via plateletpheresis using a cell separator. Platelets are stored at 22 °C in an incubator that is constantly agitated for optimal platelet storage. Platelets have a shelf life of 7 days following the recent introduction of bacterial screening in the UK.

Platelets have ABO antigens on their surface and ideally should be ABO compatible. Although adverse reactions are rare, the survival time may be reduced if there is an ABO mismatch. As with RBC, only RhD negative platelets should be given to women of childbearing age. Irradiated platelets should be administered to those at risk of transfusion-associated graft-versus-host disease TA-GVHD. Platelets express HLA antigens and some patients with HLA antibodies fail to increase their platelet counts with platelets from random donors and require HLA-matched platelets. If HLA-matched platelets are required, early recognition is necessary as advance notice is required to identify compatible donors.

It is important to investigate the cause of thrombocytopenia to determine if it is autoimmune, secondary to bone marrow failure, drug-induced or secondary to platelet sequestration in the spleen or consumption, for example, in disseminated intra-vascular coagulation (DIC). In a haemodynamically stable patient with ear, nose or throat bleed with bleeding associated with thrombocytopenia or a platelet function disorder, it is important to consider

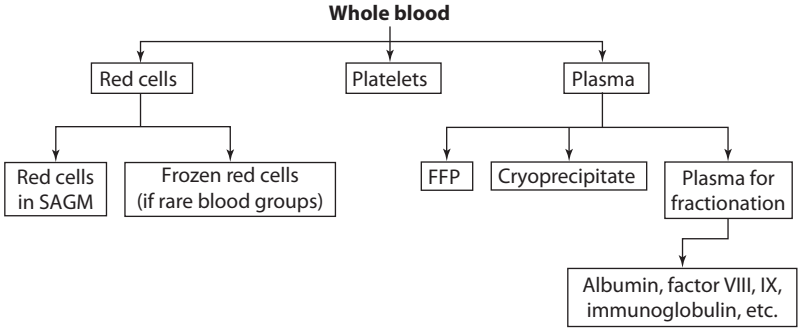


Figure 24.2 Blood components and products derived from whole blood.

TABLE 24.4 Examples of platelet thresholds

Procedure where platelet threshold is greater than 50	Procedures where platelet threshold is greater than 100
• Lumbar puncture • Gastroscopy and biopsy • Insertion of indwelling lines • Transbronchial biopsy • Liver biopsy • Laparotomy or similar procedures	• Ocular region • Neurosurgery *Spinal anaesthesia requires platelet count >80*

measures such as tranexamic acid or surgical repair of bleed as well as a platelet transfusion.

The BCSH guidelines (2003)[5] suggest the thresholds for platelets in surgical and medical procedures as outlined in Table 24.4. However, transfusion of platelets must be assessed on an individual basis taking into consideration clinical factors and the presence or absence of other disorders of haemostasis. After a platelet transfusion it is important to assess whether it has been effective in stopping bleeding (if it was administered to a patient with thrombocytopenic bleeding) and perform a repeat sample 15–30 minutes later to determine its effect on the platelet count.

Platelets are relatively contraindicated in patients with thrombotic thrombocytopenic purpura and heparin-induced thrombocytopenia due to increased thrombotic risk. However, in bleeding patients with these conditions, it is advised to discuss the patients with a haematologist.

Fresh frozen plasma (FFP)

Fresh frozen plasma is derived from whole blood through centrifugation; it is rich in coagulation factors. FFP must be ABO compatible because of the presence of anti-A and anti-B in the plasma. FFP is indicated for the treatment of coagulation factor deficiency where a suitable factor concentrate is not available, coagulopathy associated with liver disease, massive haemorrhage and DIC. The usual dose is 12–15 ml/kg. FFP is no longer recommended for the reversal of warfarin. Reversal of warfarin and the newer anticoagulants will be covered later in the chapter. The response to FFP can be monitored by measuring the patient's prothrombin time and activated partial thromboplastin time.

FFP is frozen at –25 °C to maintain the activity of the coagulation factors and can be stored for up to 36 months. When requested it must be thawed, which can take up to 30 minutes. Once thawed it can be stored at 4 °C for 24 hours. In the UK, children born after 1 January 1996 should receive FFP from countries with a low risk of vCJD; the preparation provided in the UK is also treated with methylene blue, which inactivates bacteria and viruses.

Solvent detergent plasma, which is prepared from more than 1000 donation pools of plasma, undergoes pathogen inactivation including bacteria and viruses such as hepatitis B and C and HIV. Donations are sourced from countries at low risk of vCJD. As it is pooled, the concentration of coagulation factors is more standardized. It is recommended for patients who have thrombotic thrombocytopenic purpura.

Cryoprecipitate

Cryoprecipitate is made from thawing FFP at 4 °C. It is rich in fibrinogen, factor VIII and von Willebrand factor. It is used as source of fibrinogen, especially in massive haemorrhage where fibrinogen concentration is less than 1.5 g/l. The recommended dose is two pools of 5 units (1 unit per 5–10 kg body weight). Cryoprecipitate is stored at –25 °C and has a shelf life of 36 months. Once thawed, it must be used within 4 hours.

TRANSFUSION REACTIONS

All transfusion-associated reactions and errors should be reported to the transfusion laboratory and/or hospital transfusion committee, who report them to the national haemovigilance scheme, serious hazards of transfusion (SHOT). SHOT produces an annual report with recommendations about transfusion safety, which is accessible online. In 2012, 62% of the errors reported to SHOT were secondary to preventable mistakes in the transfusion process, highlighting the scale of the problem (Figure 24.3).[6] Blood sampling errors resulting in 'wrong blood in tube' continue to be a major preventable problem that can result in ABO-incompatible red cell transfusions with severe consequences.

Although not a drug, blood and its components should be treated as such. Blood products should be prescribed and administered by trained individuals. Patients should be transfused in areas where they can be directly monitored; observations should be performed and documented before transfusion, after 15 minutes to detect any immediate transfusion reaction, and at the end of transfusion. Transfusions should generally be avoided overnight unless they are urgently needed.

Acute transfusion reactions

These present within 24 hours of the transfusion and vary in severity. The diagnosis of an acute transfusion reaction can be challenging especially in the acutely unwell patient. As acute transfusion reactions can have profound morbidity, it is essential for the clinical staff to recognize them and respond promptly. Box 24.2 summarizes a suggested approach to acute transfusion reactions:

SEVERE ACUTE TRANSFUSION REACTIONS

Immediate haemolytic transfusion reaction

Immediate haemolytic transfusion reactions are the most severe transfusion reactions caused by acute haemolysis secondary to destruction of donor red blood cells by IgM complement-fixing antibodies present in the recipient's serum, usually anti-A and/or anti-B. These antibodies can result in rapid intravascular destruction of donor red blood cells. It can also result in activation of coagulation and

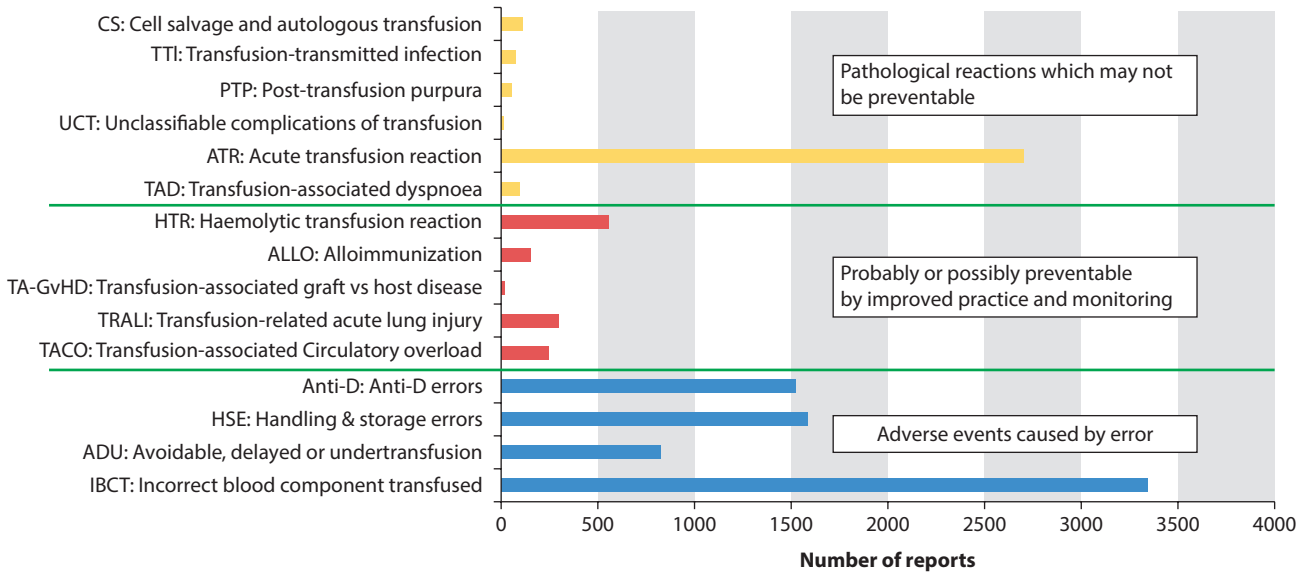


Figure 24.3 Cumulative data from SHOT reports 1996–2012.

BOX 24.2 Approach to management of an acute transfusion reaction

1. Stop the transfusion.
2. Assess patient: Airway, Breathing and Circulation.
3. Maintain venous access with physiological saline.
4. Check the identification of the patient and compatibility of the blood component.
5. Inspect the component for clumps or discolorations (important in platelets).
6. Assess for evidence of blood loss.
7. Unless mild allergic or febrile reaction, perform full blood count, renal and liver screen, blood culture if temperature rise, direct Coombs test, repeat group and screen urine for haemoglobinuria.
8. Inform the transfusion laboratory.
9. Unless mild allergic or febrile reaction, return the blood components to the transfusion laboratory.
10. Report to SHOT.

release of cytokines and cause renal failure and disseminated intravascular coagulation. It is commonly caused by human clerical error and occurs in around 1 in 180 000 red cells transfused. Features include pain at infusion site, chest and back pain, hypotension and haemoglobinuria. Mortality can be as high as 10%.

Bacterial contamination

Although a rare complication of transfusion, it may be fatal. The patient becomes acutely unwell, pyrexial, hypotensive and may develop septic shock. The actions that should be taken when a bacterial contamination of blood is suspected include checking the appearance of the contents of the transfused component; there may be clots or purple discoloration of red cells, platelets may have clumps or green discoloration. Blood cultures should be taken immediately and the patient commenced on broad spectrum antibiotics. The component should be returned to the transfusion laboratory for microbiological testing and the transfusion service should be informed so that other components from the same donor can be recalled.

Anaphylaxis

Severe anaphylaxis following transfusion is very rare but can be fatal. Symptoms may include wheeze, stridor and angioedema. Flushing and urticaria may occur in less severe reactions. Immediate resuscitation is imperative with administration of intramuscular adrenaline, intravenous chlorpheniramine and intravenous hydrocortisone. If further transfusions are needed, management should be discussed with the immunologist and haematologist.

Transfusion-related acute lung injury (TRALI)

TRALI typically occurs after transfusion of platelets or FFP. It has been the commonest cause of severe morbidity and mortality after transfusion. It is due to antileucocyte antibodies in the donor plasma reacting with the recipient's neutrophils, monocytes and pulmonary endothelium. Severe hypoxia may develop immediately or at the latest within 6 hours of the transfusion and be associated with hypotension and bilateral lung infiltrates. It is important to differentiate TRALI from acute respiratory distress syndrome and pulmonary oedema. Treatment is supportive with high flow oxygen and ventilator support if required.

Transfusion-associated circulatory overload (TACO)

This is a common adverse effect of transfusion in older patients and those with history of cardiac disease. It is often not diagnosed in a timely manner. It is defined as acute or worsening pulmonary oedema within 6 hours of transfusion.

Features include dyspnoea, tachycardia, hypertension and a positive fluid balance. Treatment involves stopping transfusion, administering oxygen and diuretics. TACO can be avoided by careful assessment of its risk factors and appropriate measures for its avoidance such as co-administration of diuretics and the use of single unit transfusions in small frail adults.

LESS SEVERE ACUTE TRANSFUSION REACTIONS

Febrile non-haemolytic transfusion reactions (FNHTR)

This is a very common transfusion-associated reaction. However, as it is associated with the recipient's anti-leucocytes antibodies, its incidence has reduced since the implementation of universal leucocyte-reduction of blood components in the UK. Features include pyrexia accompanied by rigours, nausea and muscle pain. Mild reactions, where temperature is greater than 38 °C but less than 2 °C above starting temperature can be managed by slowing the transfusion and/or giving anti-pyretic agents such as paracetamol. If the temperature rise is greater than 39 °C or greater than a 2 °C rise, the transfusion should be discontinued. When fever is associated with transfusion, immediate haemolytic transfusion reactions and bacterial contamination should be excluded.

Mild allergic reactions

Urticarial reactions to donor plasma proteins can be treated by slowing the transfusion rate and using antihistamines whilst the patient is monitored carefully. If repeated reactions occur and do not respond to antihistamines, washed red blood cell or platelet transfusions (washed in saline to remove plasma proteins) may be appropriate management for future transfusions.

DELAYED TRANSFUSION REACTIONS

Delayed haemolytic transfusion reaction (DHTR)

Delayed haemolytic transfusion reactions can occur in those who have had previous transfusions or have had a previous pregnancy and result from alloantibodies (e.g. Rh, Kell, and Duffy) that have fallen to low levels so they are undetectable in compatibility testing. Re-exposure to the antigen results in a secondary immune response with production of IgG antibodies and consequent extravascular haemolysis of the transfused red cells, usually a few days after the transfusion has taken place. Typical features include jaundice, haemoglobinuria, fever and fatigue. Investigations reveal a drop in haemoglobin, a positive direct Coombs test and rise in bilirubin. Renal failure may also be a feature. It is important to perform a repeat group and screen on the pre-transfusion and post-transfusion blood samples of the patient.

Post-transfusion purpura

In this condition, there is severe thrombocytopenia usually with a platelet count $< 10 \times 10^9$/l 7–12 days post-transfusion. There may be severe bleeding. It usually occurs in previously pregnant and/or transfused females who are HPA-1a antigen negative and who develop high levels of anti-HPA-1a after the transfusion. It has become rare since leucocyte-reduction of blood components. The condition responds well to administration of high-dose intravenous immunoglobulin.

Transfusion-associated graft versus host disease (TA-GVHD)

This is a rare and usually fatal complication of blood transfusion caused by donor lymphocytes engrafting in the recipient and mounting an immune response against the transfusion recipient. Initial symptoms of TA-GVHD include fever, rash, diarrhoea, jaundice and bone marrow failure. It can occur up to 30 days post-transfusion.

Immunocompromised patients at risk of TA-GVHD include those with inherited immunodeficiency, HIV, recipients of certain chemotherapy agents such as fludarabine and post bone marrow transplant. It is important to identify at-risk patients and provide gamma irradiated blood components that prevent TA-GVHD.

REVERSAL OF ANTICOAGULATION

FFP is no longer first-line recommended management for the reversal of warfarin therapy. The BCSH guidelines (2012)[7] recommend the use of Vitamin K (oral or IV in emergencies) and prothrombin complex concentrate (PCC). FFP should only be used if PCC is not available. PCC contains factors II, VII, IX and X. It is used for the reversal of warfarin in patients with a raised INR and significant bleeding. It has also been used in treating coagulopathy associated with liver disease. There is a small thrombotic risk associated with its use but this has to be weighed up in light of bleeding risk. It is given intravenously and the recommended dose is 25 to 50 units/kg based on the INR.

There is increasing use of the new oral anticoagulants such as the direct thrombin inhibitor Dabigatran and the anti Xa inhibitor Rivaroxaban, which are increasingly prescribed for the treatment of atrial fibrillation and deep vein thrombosis. There is no licensed antidote to these agents. However, if severe bleeding occurs, it is recommended to consider the use of PCC or recombinant factor VIIa and contacting the haematology team for further guidance.

ALTERNATIVES TO BLOOD TRANSFUSIONS

There have been many recent developments in the use of alternatives to blood and the avoidance of transfusion. The use of these alternative measures requires organization and a multidisciplinary approach to the patient, which is now often described as 'patient blood management'.

Pre-operative anaemia management

Surgical patients who are anaemic are more likely to require blood transfusion, have post-operative infection and a prolonged hospital stay, and so patients who have a low Hb should be identified prior to surgery. In collaboration with the pre-operative team these patients should be investigated and managed to optimize the Hb before surgery. It is important to identify if there is any iron or haematinic deficiency and also exclude any underlying causes such as an undiagnosed malignancy.

Where iron deficiency is identified, it should be treated with oral iron, but if it is not tolerated or there is no response after 4–6 weeks, or if surgery is urgent, then intravenous iron can be used. In patients who have anaemia on a background of chronic renal failure, malignant diseases or haematological conditions such as myelodysplasia, recombinant erythropoietin can be used with good effect to improve the Hb before surgery. Erythropoietin is not widely employed due to the considerable health economic costs associated with its use.

Any drugs known to increase risk of bleeding, such as aspirin and clopidogrel, should be withdrawn in advance of surgery; advice should be sought from the prescribing physician if necessary. Post-operatively, non-steroidal anti-inflammatory drugs should be avoided as they may contribute to bleeding.

Acute normovolaemic haemodilution

Blood is removed immediately prior to surgery, often post-anaesthesia, and returned post-operatively or if significant bleeding occurs. The patient's blood volume is maintained by the infusion by crystalloid or colloid fluids. There is little evidence for its effectiveness and thus this technique is rarely employed outside of cardiac surgery.

Cell salvage

Cell salvage can be used intra-operative or post-operatively.

INTRA-OPERATIVE CELL SALVAGE (ICS)

A number of devices are available and are widely in use. Blood lost during surgery is aspirated into a collection reservoir and filtered to remove any debris. Blood is treated with heparin and citrate to prevent clot formation. If adequate blood is collected and the patient meets requirements for transfusion, the collected blood is centrifuged, washed and re-infused via a leucocyte-reduction filter in a closed and automated system within 4 hours. ICS is indicated in surgery where anticipated blood loss is greater than 20% of the patient's blood volume, greater than 1l in an adult (e.g. major orthopaedic, cardiac, vascular and cancer surgery).

POST-OPERATIVE CELL SALVAGE

This has very little role in ENT surgery. Blood is collected from wound drains and filtered or washed before it is re-infused via a closed automated system.

Tissue sealants

These are biological agents derived from human or animal clotting products such as thrombin, fibrinogen and calcium. They are applied directly to the bleeding point and fibrin clot formation occurs, impeding blood loss. Tissue sealants are commonly used in accident and emergency departments and minor injury clinics for minor cutaneous bleeds.

Tranexamic acid

Tranexamic acid is an antifibrinolytic drug that inhibits the conversion of plasminogen to plasmin and hence hinders fibrinolysis. It is inexpensive and can be given orally, topically or intravenously. It has a recognized role in the management of massive haemorrhage and reducing bleeding post-operatively. There is also a mouthwash preparation that can be helpful in managing minor oral cavity bleeds.

JEHOVAH'S WITNESSES

Jehovah's Witnesses have contributed considerably to the understanding of minimum blood requirements. JWs do not accept red cell transfusions, whether donor blood or their own pre-donated blood, although most patients will accept the use of cell-salvaged blood provided the blood is returned to them without a break in the circuit. When treating patients, it is important to take an individualized approach and discuss all options for blood avoidance. Most hospitals will have a Jehovah's Witness liaison committee that can be consulted.

KEY EVIDENCE

- The use of blood in surgery is in decline.
- There is increasing recognition that surgical patients can avoid transfusion through the application of patient blood management practices and more restrictive thresholds for transfusion.
- An organized approach to massive haemorrhage is key for improved survival.
- There is no role for FFP in the reversal of warfarin. Prothrombin complex concentrates should be used.

FUTURE RESEARCH

Patient blood management is integral to modern transfusion practice, with increasing evidence favouring restrictive blood transfusion. Ongoing trials are evaluating the expansion of restrictive transfusion to patient groups other than those undergoing critical care. Further research is needed to determine the optimal use of alternatives to transfusion.

KEY POINTS

- Before requesting a blood transfusion, assess the patient clinically, evaluate laboratory investigations and consider whether it is necessary.
- Patient identification is essential: ensure the right blood is transfused to the right patient at the right time in the right place.
- Early recognition of transfusion reactions is essential. Stop the transfusion, maintain intravenous access and assess the patient. Follow local protocols and inform the transfusion laboratory.
- Correction of pre-operative anaemia is fundamental in minimizing transfusion requirements.
- Surgical planning is key. A group and screen should be done a minimum of 24 hours pre-operatively. Where a large volume of blood is anticipated, agree with the transfusion laboratory how much blood should be provided.
- Early recognition of massive haemorrhage is imperative; activate local protocols and ensure a coordinated process takes place.
- There are many alternatives to blood transfusion that should be considered and discussed with patients.

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CHAPTER 25

HAEMATO-ONCOLOGY

Robert F. Wynn and Mark Williams

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: haemostasis, erythropoiesis, leukaemia, lymphoma, myeloma, sickle cell disease, otolaryngology, fungal rhinosinusitis and ototoxicity.

INTRODUCTION

Many patients with haematological malignancies will present initially to an ENT surgeon, for example with nodal disease of the head and neck. Patients with known haematological disease can also develop numerous problems of the ear, nose and throat as a result of either their disease or its treatment. Similarly many of the therapies used for primary ENT disorders can have important haematological effects.

The aim of this chapter is to provide clinically relevant information that enables practicing ENT surgeons and trainees to interpret basic haematological laboratory parameters, recognize the haematological disorders that present to their services and facilitate appropriate timely referral, manage the haematological complications of ENT disorders and interventions, understand potential ENT complications of haematological therapies and appreciate special considerations in the management of ENT conditions in patients with chronic haematological disorders.

OVERVIEW OF BASIC HAEMATOLOGY

Components of blood: their function and production

Blood is a liquid tissue whose cellular compartment consists of red cells (erythrocytes), white cells (leukocytes) and platelets. Erythrocytes, the most numerous blood cells, are bi-concave discs that contain an abundance of haemoglobin, the protein responsible for oxygen transportation in vertebrates.[1] They have a lifespan of approximately 120 days after which they are removed by the spleen.[2] Leukocytes are a diverse group of cell types that are capable of migration into tissues where they have vital roles in the processes of immunity, inflammation and wound healing. Neutrophils are the most common white cell in adult peripheral blood and are a key component of innate immunity, providing defence against bacteria, which they are able to ingest and kill. Lymphocytes are the cellular effectors of the adaptive immune system and are capable of producing antibodies or recognizing and killing virally infected cells; some are long-lived, permitting anamnestic immune responses.[3] Platelets are the cellular element of the haemostatic system but they also have functions in tissue repair and cytokine signalling. Their life span is 8–9 days.[4] The liquid phase of blood is plasma, which contains a wide range of hormones, electrolytes and proteins; including albumin, immunoglobulins, fibrinogen, clotting factors and complement.

All of the cellular components of blood are derived from a common progenitor, the haematopoietic stem cell (HSC), which is capable of self-renewal as well as giving rise to a variety of progenitors and from there all cells of the blood (**Figure 25.1**).[5] The presence of various combinations of haematopoietic growth factors, such as erythropoietin (EPO) and granulocyte-colony stimulating factor (G-CSF), will determine which progenitors successfully proliferate and differentiate, thus ensuring homeostatic

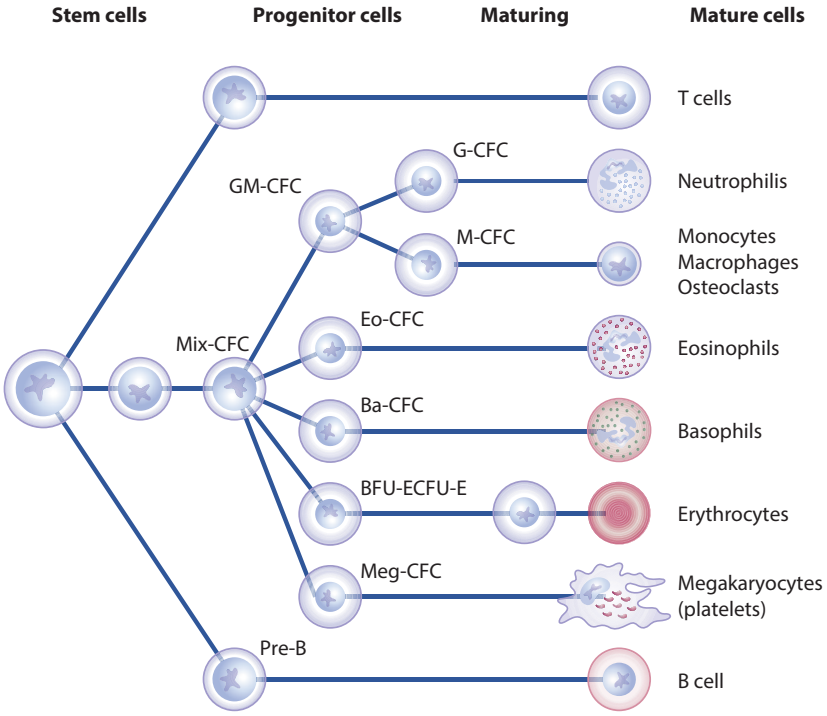


Figure 25.1 Schematic representation of haemopoiesis.

control over mature cell numbers.[6] For example, in response to tissue hypoxia the kidney secretes EPO, which increases red cell production and restores oxygen delivery.[7] Understanding the haematopoietic hierarchy helps to predict the behaviour of haematological malignancies (see below) and the effects of commercially available recombinant growth factors (G-CSF and EPO).

Haematopoiesis initially occurs in the yolk sac of the embryo, followed by the foetal liver and spleen. During the third trimester HSCs migrate to the bone marrow, which becomes the dominant site of haematopoiesis by term. Whilst the majority of the infant bone marrow is active, by adulthood only the axial skeleton and the proximal ends of the long bones are haematopoietic.[8] However, if increased cell production is required then haematopoiesis can expand back down the long bones, resume activity in the liver and spleen and can even occur in soft tissue deposits outside these organs. This is seen in several haematological disorders such as thalassaemia major and myelofibrosis and it also explains the propensity for many haematological malignancies to involve the liver and spleen.[9]

Lymphatics and the mononuclear phagocyte system

The lymphatic system consists of a network of vessels that drain extracellular tissue fluid through a series of nodes and back to the venous circulation.[3] This organization ensures that foreign material passes through lymph nodes where lymphocytes can compete for survival on the basis of their affinity for the antigen, allowing the selective expansion and activation of cells that are capable of producing an effective antibody. The architecture of lymph nodes reflects these complex processes and the pattern of its disruption gives vital clues as to the nature of lymphoid malignancies (see below).[10]

Monocytes are produced by the bone marrow but migrate into tissues where they develop specialized functions, often involving the phagocytosis of debris. Examples include the Kupffer cells of the liver, lymph node dendritic cells, alveolar macrophages and the microglia of the central nervous system.[11] Collectively these cells are known as the mononuclear phagocyte system; the spleen is the largest component and has multiple functions, including the removal of senescent blood cells, recycling of iron and the phagocytosis of antibody coated bacteria.

Haematological malignancy: Principles of diagnosis and management

The cells of the bone marrow are actively dividing throughout life, predisposing them to the acquisition of genetic mutations. Lymphocytes also perform somatic recombination to produce their immunoglobulin, which involves breaking DNA and risks chromosomal translocation; with the result that translocations are commonly found in lymphoid tumours and frequently involve the immunoglobulin loci.[12] Haematological malignancies are the result of cells that have acquired defects in their apoptotic and/or proliferative pathways giving them a survival advantage that allows their uncontrolled expansion; leading to tissue disruption, organ damage and, ultimately, death. Whilst exposure to radiation and certain chemotherapeutic agents certainly increases the risk of myeloid malignancy, in practice this accounts for a small number of patients and the majority of cases of haematological malignancy are sporadic relating to the accumulation of somatic mutation. Notable exceptions include endemic Burkitt's lymphoma, believed to be caused by EBV infection in the

context of chronic malaria, and adult T-cell leukaemia/lymphoma, which is caused by the virus HTLV-1.[13]

Oncogenesis can occur at any stage in the haematopoietic hierarchy (**Figure 25.1**), resulting in a diverse spectrum of malignancies. Diagnosis is frequently dependant on the demonstration that a population of cells are 'clonal', meaning that they are all related to a common ancestor. Clonality can be confirmed by unique patterns of expression of cell surface antigens (immunophenotype), the presence of a shared genetic aberration (cytogenetics, molecular genetics) or by expression of the same immunoreceptor (immunoglobulin/TCR rearrangement studies).[14] Whilst the concept that a malignant population consists of many identical cells remains clinically useful there has been increasing evidence in recent years that these cancers are genetically diverse disorders with multiple clones often populating the same patient.[15] For example, acute myeloid leukaemia (AML) was shown to consist of 2–5 distinct clones in just over half of patients studied. It is likely that such studies significantly underestimate the number of clones present as current methods can only detect clones of a certain size (> 5–10% of cells).[16] The prognostic significance of the clonal structure remains unclear at this time.

Haematological malignancies will generally involve predominantly the blood and bone marrow (leukaemias) or the lymph nodes (lymphomas), but there is often considerable overlap. Many of these cancers are 'liquid', insofar as they are widely circulating at presentation and conventional notions of anatomical staging do not apply (e.g. acute leukaemia); others behave as solid tumours with orderly spread to contiguous lymphatic regions (e.g. Hodgkin's lymphoma). Bone marrow involvement frequently presents with pancytopenia causing fatigue, breathlessness, infection and bleeding. Whereas nodal disease presents with visible enlargement, the effects of local compression, or constitutional symptoms such as weight loss and night sweats.

The nature of the presenting symptoms will guide the diagnostic process; pancytopenia requires prompt assessment of the bone marrow by aspiration, trephine biopsy, flow cytometric evaluation and cytogenetic analysis. Nodal disease will require imaging to assess the extent of the disease followed by biopsy.

Treatment usually involves combination chemotherapy, the principles of which are similar to that of solid tumour regimes.[17] Most haematological malignancies are radiosensitive but the widespread nature of these conditions restricts the use of radiotherapy to the control of troublesome deposits or the treatment of localized lymphomas. Increasingly monoclonal antibodies and small molecule inhibitors are used to target and disrupt disease-specific processes. The most striking example is the tyrosine kinase inhibitor (TKI), imatinib, which has transformed the management of chronic myeloid leukaemia (CML) from an often-fatal disease to one that is held in remission by oral medication.[18] In the era before TKIs CML would invariably transform into an acute leukaemia that was usually fatal. The only patients who survived were a proportion of those who were fit enough to undergo a stem cell transplant. With current therapies >90% of patients remit and contemporary trials are exploring the possibility of stopping treatment in those who appear to be cured.

Whilst some haematological cancers can be cured with conventional therapy many have high rates of relapse and patients with responsive diseases who can tolerate the procedure are offered haematopoietic stem cell transplantation (HSCT). Allogeneic HSCT is an extreme form of immunotherapy that involves conditioning the recipient with immunosuppressive chemotherapy to allow engraftment of infused haematopoietic stem cells from a matched donor.[19] The donor stem cells form a new immune system that is capable of engaging the recipient's neoplasm, but the price of this graft-versus-disease effect is graft-versus-host disease (GvHD). Acutely GvHD typically presents with diarrhoea, rash and liver dysfunction, whereas chronic GvHD is a truly protean disorder, with inflammation and scarring affecting any tissue.[20] GvHD is one of the major complications of HSCT, causing considerable morbidity and mortality and the management can be very challenging. To reduce the incidence of GvHD patients are given immunosuppressive therapy (typically Ciclosporin) for a period after transplantation, but in contrast to solid organ transplantation where lifelong immunosuppression is mandated, stem cell transplant recipients will typically stop these medications 3–9 months post-HSCT.

HAEMATOLOGICAL DISORDERS PRESENTING TO ENT

Head and neck lymphadenopathy

The most common presentation of a haematological malignancy to an ENT surgeon is that of a 'neck lump'; most lumps are cervical lymphadenopathy and a significant proportion of these will be lymphoma.[21] It is important that lymphoma is considered early in the diagnostic process as an appropriately focused history and examination can save the patient time, stress and unnecessary investigations.

Symptoms of unexplained fever, drenching night sweats and weight loss (>10% in 6 months) are highly suspicious of lymphoma; in this context they are termed 'B-symptoms' and are also of prognostic significance, typically predicting an inferior outcome.[22] However, these symptoms also occur in a range of infections and chronic inflammatory disorders, especially tuberculosis (TB); careful attention to any history of TB exposure should help to make this distinction. Generalized pruritus or alcohol-induced lymph node pain suggest Hodgkin's lymphoma (HL), which is the lymphoma most commonly associated with localized cervical disease, especially in younger patients, and usually has an excellent prognosis. Attention should also be paid to the time course of the symptoms as these give an indication of the pace of the disease and important clues as to the likely diagnosis. Indolent lymphomas can cause stable lymphadenopathy over many years, the nodes of HL often fluctuate in size with observation, whilst the most aggressive lymphomas can enlarge over the course of days and may require admission for urgent therapy.

Examination should be used to describe the neck lump and its relationship to surrounding structures, as well as establishing the extent of nodal involvement elsewhere; this must include examination of the liver and spleen, enlargement of the latter being highly suggestive of lymphoid malignancy. The oropharnyx should be inspected for involvement of Waldeyer's ring, which is infiltrated in 5–10% of non-Hodgkin's lymphoma (NHL) but rarely in HL. The nodes of lymphoma are usually painless, often rubbery to palpate and can be mobile or fixed depending on whether the capsule has been infiltrated. In the absence of symptoms asymmetric palatine tonsils carry a low risk of malignancy. A review of 792 patients undergoing tonsillectomy identified 53 patients with asymptomatic asymmetric tonsils, all of whom had normal histology.[23] However, the presence of pain, dysphagia, ulceration, progressive enlargement or B-symptoms should prompt biopsy/removal. A more recent meta-analysis has suggested that whilst there is an association between tonsil asymmetry and lymphoma the risk is dramatically increased by the presence of other signs of malignancy.[24]

Distended neck veins and facial oedema suggest superior vena cava obstruction (SVCO) by mediastinal disease, most commonly bronchogenic carcinoma but also HL or lymphoblastic lymphoma.[25] SVCO is a medical emergency that mandates urgent imaging and immediate referral to oncology/haematology, thoracic surgery and radiology.[26] In the case of lymphoid malignancy high dose dexamethasone can provide rapid relief. However, the tumour response to steroids can be so impressive that the diagnostic yield of subsequent biopsy is significantly reduced (see 'Airway obstruction' below). Careful consideration must therefore be given to the timing of biopsy and early involvement of oncology/haematology and thoracic surgery is vital in this regard.

A full blood count should be performed as pancytopenia suggests bone marrow infiltration and lymphocytosis raises the possibility of circulating disease. Chronic lymphocytic leukaemia (CLL – synonymous with small lymphocytic lymphoma) is the most common leukaemia in adults, has typical blood film appearances and can usually be diagnosed by performing flow cytometry on peripheral blood, without recourse to lymph node biopsy.[27] Renal and liver biochemistry should also be taken as derangement can suggest infiltration or compression and organ function is an important consideration when planning chemotherapy.

If malignancy is suspected then computed tomography (CT) of the chest, abdomen and pelvis should be performed to stage the disease. Early involvement of haematology or oncology at this point is helpful so that the most appropriate type and site of biopsy can be planned. The diagnosis of a specific lymphoma usually requires an extended immunohistochemical panel to be performed and an appreciation of the growth pattern within the node is often useful; as such whole node biopsies are preferred.[10] Core biopsy can be useful when the tumour is inaccessible (e.g. retroperitoneal), but contains little information regarding architecture making the diagnosis of certain low-grade NHLs challenging.

Fine-needle aspiration (FNA) is commonly used in the initial investigation of neck lumps because it is quick, safe and diagnostic of many malignancies; but its role in lymphoma diagnosis has been controversial. Some lymphomas (especially HL) consist of small numbers of malignant cells within a reactive cellular background; in this situation FNA may yield only reactive cells and wrongly suggest an infective or inflammatory aetiology. This has led many organizations to advise against the use of FNA for suspected lymphoma, to avoid diagnostic delay or false negative results. However, increasing use of flow cytometry and immunocytochemistry has enabled many lymphomas to be accurately defined cytologically and the ability of this technique to provide fresh samples for DNA microarray analysis suggests that there may be an increasing role for FNA in the future.[28] Centres with sufficient expertise in these techniques are able to use FNA for preliminary diagnosis, although excision biopsy is often performed for confirmation and uncertainty can still arise with certain low grade B-cell malignancies, such as marginal zone lymphoma, where the markers themselves are not specific and an appreciation of tissue architecture is needed.[29] Overall we would still advocate proceeding directly to whole node biopsy when symptoms are highly suggestive of lymphoma, and using FNA only when there are several possible diagnoses and there is sufficient local expertise for cytology to be discriminatory.

Airway obstruction

On occasion lymphomas of the oropharynx, larynx or neck can cause intrinsic occlusion or extrinsic compression of the airway. In this context ENT surgeons can be asked to provide direct visualization with fibre-optic laryngoscopy and to advise regarding the security of the airway. Where a malignant condition is suspected then consideration must be given to both the immediate stabilization of the patient and the need for urgent diagnosis. Dexamethasone can be used to shrink tumours and rapidly relieve compressive symptoms, but the effect on certain lymphomas can be so dramatic that the diagnosis cannot be ascertained unless tissue is sampled prior to the administration of steroids. Clearly the priority in a situation of life-threatening airway compromise is to secure the airway, but where the presentation is less acute then priority must be given to urgently obtaining tissue for diagnosis, as this will allow definitive treatment to be started. Regular (daily) assessment will allow surgery that is both safe and likely to yield diagnostic tissue.[30]

Extranodal and extramedullary disease

A quarter of NHL patients will present with extranodal disease, which commonly involves the CNS or GI tract, but can occur anywhere. Extranodal sites of head and neck lymphomas include salivary glands (marginal zone lymphoma – especially in patients with Sjögren's syndrome,[31] sinuses (usually diffuse large B-cell lymphoma) and the nasal cavity (NK/T nasal type lymphoma). Bone marrow malignancies such as acute myeloid leukaemia

and myeloma are also capable of forming extramedullary deposits, referred to as chloromas and plasmacytomas respectively. The latter commonly involve the head and neck and frequently present diagnostic difficulties. Whilst most occur in the context of systemic myeloma a minority are solitary and potentially cured with radiotherapy.[32–33] Deposits of extramedullary haematopoiesis can also occur at any site and often mimic the appearance of tumours; these should be considered when a paranasal lesion is found in a patient with chronic anaemia, especially a child with thalassaemia major or sickle cell disease.[9]

Hyperviscosity and leucostasis

Both myeloma and lymphoplasmacytoid lymphoma are capable of secreting large amounts of immunoglobulin; if the concentration of this paraprotein is sufficiently high it will thicken the blood and cause impairment of the microcirculation, a condition known as hyperviscosity syndrome. Leucostasis refers to a similar situation that results from very high white cell counts (typically $>100 \times 10^9$/L), usually at initial presentation of acute myeloid leukaemia or CML. Impairment of blood flow causes a constellation of symptoms and signs that may include blurring or loss of vision, headache, hearing loss, vertigo, nystagmus, tinnitus, diplopia and ataxia. Untreated these conditions can progress to seizures, stroke, coma and death.[26] Plasmapheresis or leucopheresis can be used to rapidly remove the excess immunoglobulin or malignant cells (respectively), but the essence of successful management is the prompt instigation of disease directed therapy (e.g. chemotherapy). Although rare there have also been several case reports of sudden-onset bilateral deafness as the initial presenting feature of CML.[34]

Bony disease

Multiple myeloma can affect any bone and cases of temporal bone involvement causing otitis media, hearing loss and mastoid effusions have been reported. Whilst this would be a rare presentation, myeloma is a common malignancy and should be considered whenever lytic bone lesions are identified.[35–36]

ENT COMPLICATIONS OF HAEMATOLOGICAL THERAPIES

Infections

Patients with haematological malignancies are often severely immunocompromised as a result of both their disease and the effects of treatment, making them susceptible to infection from a wide range of common organisms and opportunistic pathogens, including bacteria, viruses, fungi and protozoa. Whilst patients are often taking a variety of prophylactic antimicrobials these offer incomplete protection.

Certain congenital (constitutional) haematological disorders are associated with either neutropenia or disordered neutrophil function and similarly increase the risk of bacterial or fungal infection. These disorders not infrequently present with discharging ears or lymphadenitis.[37]

These infections can be of unexpected severity or duration and can occur at unusual sites; clinical signs can be subtle or misleading as the inflammatory response that usually produces symptoms is often attenuated or absent. Fungal rhinosinusitis can be fatal.[38]

Bacterial infections are most frequent in patients with neutropenia (post-chemotherapy, acute leukaemia, aplastic anaemia etc.) or impaired neutrophil function (myelodysplasia). Otitis media and sinusitis are common acute infections that can become chronic and problematic for patients with persistent neutrophil defects.[39]

Viral infections are common in patients rendered hypogammaglobulinaemic by CLL, HSCT or myeloma; they are usually upper respiratory tract infections or rhinosinusitis and tend to last longer than in an immunocompetent host, sometimes persisting for several weeks. More profoundly suppressed patients can experience reactivation of latent CMV, VZV or HSV 1+2; the latter is often associated with severe ulceration of the oropharynx and even abscess formation.[40]

Fungal spores are ubiquitous in the environment and are continuously inhaled, often leading to colonization of the respiratory tract. Invasive infection is less common but occurs in the context of prolonged neutropenia or patients with GvHD, who have impaired immune reconstitution and are often taking multiple immunosuppressive agents.[41–42] Acute fungal rhinosinusitis is an invasive infection with a high mortality usually caused by *aspergillus* species or pin moulds (mucorales).[38] The initial symptoms include fever, nasal congestion, facial pain and epistaxis; examination of the oral cavity and nasal passages may reveal mucosal thickening or areas of necrotic tissue. Invasion of the palate, orbit, cavernous sinus, cranial nerves and brain can occur within hours, days or weeks depending on the specific organism and the depth of immunosuppression.[43] Some patients have extension beyond the sinuses at presentation leading to visual disturbance, diplopia, facial numbness, altered cognition or seizures.

Rapid diagnosis is essential for survival so a high index of suspicion is required when immunocompromised patients develop sinus symptoms; early input from radiology, ENT and pathology is vital in this regard. Multiple sinuses are usually involved and can be recognized using CT by the presence of opacification, mucosal thickening and bony erosions; the maxillary and ethmoid sinuses are the most commonly affected.[44] If invasion of surrounding structures is suspected then magnetic resonance imaging (MRI) is needed to characterize intra-cranial involvement.[45] Whilst imaging is not diagnostic of fungal infection, it is important to define the extent of the disease and identify extension into the brain or orbit, so that surgical intervention can be planned. Early nasal endoscopy is crucial to look for necrosis, which can appear as sloughing or perforation of the nasal septum, or palatal eschars;[46] biopsy of the affected area should be performed and sent for both culture and histopathology. Diagnosis depends on

histological demonstration of fungal hyphae penetrating surrounding tissue and blood vessels, to distinguish invasive infection from colonization. Culture of the specimen permits identification of the fungus, which has important consequences for the choice of antifungal therapy.

When fungal infection is first suspected empirical therapy with intravenous amphotericin B should be commenced. The mucorales are resistant to voriconazole and this agent should only be considered if mucormycosis has been excluded.[47] Other species of fungus have varying sensitivities, highlighting the importance of early identification of the organism and discussion with microbiology. Where immunosuppression can be withdrawn then this should be considered, although in the context of haematological malignancy and HSCT it is often a case of buying time with antifungal therapy whilst immune reconstitution occurs. The surgical management of fungal rhinosinusitis can be challenging and is discussed in detail in Chapter 96 (Fungal Rhinosinusitis).

Mucormycosis of the palate and middle ear have also been described in the context of haematological disease and HSCT, emphasizing the need to keep an open mind when assessing ENT problems in this population.[47–49]

Ototoxicity

Cisplatin and carboplatin are platinum-containing chemotherapy agents that are used for the treatment of relapsed lymphomas and numerous non-haematological malignancies. They are potent neurotoxins that are capable of damaging the outer hair cells and the epithelium of the lateral wall of the cochlea. Cisplatin is the most ototoxic of this class, typically causing high-frequency sensorineural hearing loss with tinnitus in 15–20% of patients; audiometric changes can be demonstrated in many more, up to 75% in some studies.[50] Onset is variable with some patients suffering severe hearing loss after a single dose, whilst others develop symptoms several months after the last dose. The toxicity is dose dependant but there is considerable variation between individuals, suggesting significant polymorphism in the pathways responsible for the drugs metabolism. Risk is increased by the presence of renal failure and the concomitant use of other ototoxic therapies, especially radiotherapy (RT), which has a synergistic effect and also causes serous otitis media, potentially complicating assessment. Children are particularly susceptible, partly because of age but also the regimes that they receive are commonly high dose, combined with RT or contain two platinum based compounds. Avoiding ototoxicity is particularly important in children as it has profound consequences for speech and language development.[51] Extended high-frequency audiometry is recommended to allow early detection of hearing loss before the frequencies required for hearing speech are affected.[52] Distortion product otoacoustic emissions (DPOAEs) are also more sensitive than conventional audiometry and can be used in children under 5 years of age. Damage is typically irreversible and management should focus on prevention through early recognition and dose reduction or cessation where possible.[53] Sodium thiosulphate has been trialed as a protective agent but the development of this and similar agents has been hampered by a lack of consensus regarding ototoxicity assessment criteria.

The ototoxicity of the aminoglycosides is well documented and gentamicin is commonly used in combination with extended spectrum penicillin for the treatment of neutropenic sepsis. Other ototoxic agents used in the management of haematological disorders include desferrioxamine (used to prevent iron overload in the chronically transfused), loop diuretics, vancomycin, amphotericin B, cytarabine, methotrexate and the vinca alkaloids.[54]

Stridor during treatment of haematological malignancy

The ENT surgeon may be called to the haematology ward to see patients with respiratory compromise due to airway obstruction. Several causes should be considered:

- There may be mucosal inflammation of the mouth and pharynx secondary to intensive chemotherapy. This is known as mucositis and is related to the intensity of chemotherapy. It occurs in the weeks after such therapy and is self-limiting. There is evident inflammation of the mucosa with thick secretions that might contribute to airway compromise.[55]
- Stridor secondary to vocal cord paralysis is rarely recorded secondary to vincristine chemotherapy, which is usually part of the treatment of childhood leukaemia.[56] The paralysis may be of long-standing duration.

LABORATORY HAEMATOLOGY AND THE ENT SURGEON

The full (complete) blood count

All basic laboratory haematology is fully automated. The full (or complete) blood count (FBC) will give the requesting clinician the following:[57]

- The number of red cells (red cell count, RCC), their size (mean corpuscular volume, MCV) and the haemoglobin concentration within them (mean corpuscular haemoglobin, MCH or mean corpuscular haemoglobin concentration, MCHC).[58] It will also measure the haemoglobin concentration (Hb) within whole blood. The haemoglobin can be low and the red cell count high if those red cells don't contain much haemoglobin within them (as in certain haemoglobinopathies). Most analysers will also offer a reticulocyte count. Reticulocytes are simply young red cells recently made in the marrow and if the reticulocyte count is high then the marrow is making lots of red cells.
- The total white cell count; and usually a 5-part differential giving the number of neutrophils, monocytes, lymphocytes, eosinophils and basophils. The counters discriminate these cells on the basis of size and staining.
- The platelet count.

The analysers are good but abnormalities may be confirmed after examination of the blood smear. Samples that are clotted or diluted give erroneous results and should be repeated. Similarly samples that are not freshly analysed may give inaccurate results.

Cytopenia indicates reduction of a blood cell number and pancytopenia is a reduction in the blood of all cell types – red cells, white cells and platelets. Any cytopenia is either caused by diminished production of the cell in the marrow or by increased peripheral consumption. The causes of pancytopenia are given in Box 25.1.

BOX 25.1 Causes of pancytopenia

- Decreased bone marrow function
- Aplasia
- Acute leukaemia, myelodysplasia, myeloma
- Infiltration with lymphoma, solid tumours, tuberculosis
- Megaloblastic anaemia
- Paroxysmal nocturnal haemoglobinuria
- Myelofibrosis
- Haemophagocytic syndrome
- Increased peripheral destruction
- Splenomegaly

Anaemia

The haemoglobin (Hb) is low on the analyser FBC. The practising ENT surgeon should be readily able to discriminate the likely causes for any anaemia from the clinical situation of the patient and the details of both the red cell parameters and the reticulocyte count:

- **Bleeding**. This might be obvious from the history of the patient. The red cells are usually normal in size and shape (unless the bleeding has been chronic and associated with iron deficiency) and there should be a raised reticulocyte count as the marrow compensates for the blood that has been lost with increased production. Note that reticulocytes are larger than normal cells and a reticulocytosis might be associated with a raised MCV and note also that the platelet count maybe increased by bleeding.
- **Iron deficiency**. Iron is needed to make haemoglobin and when there is iron deficiency then the Hb will be low. The red cells will be small (low MCV) without much haemoglobin within them (low MCH and MCHC). The diagnosis can be confirmed by measuring the serum iron or the ferritin. Iron deficiency may be associated with a poor diet or with chronic blood loss. If the patient is female then take a history of menstrual bleeding and consider the gut as a source of bleeding – this might be asymptomatic and referral to the gastroenterology team might be indicated.
- **Haemolytic anaemia**. Haemolysis is shortened red cell survival so that they are surviving for fewer than their usual 120 days. The marrow should compensate for the shortened survival with a reticulocytosis (perhaps with a raised MCV). Red cell breakdown will result in unconjugated hyperbilirubinaemia. The cause might be immune mediated with antibody on the red cell surface, which will manifest as a positive Coombs test (direct antiglobulin test, DAT).
- **Anaemia of chronic disease**. Sick patients will often be anaemic. This will include those with cancer and those with chronic infection or autoimmune disease. The anaemia is usually normochromic and normocytic (normal red cell parameters) or slightly microcytic.
- **Anaemia associated with haematological diseases**. Patients known to haematology services may have anaemia associated with their primary disease or its treatment.

Polycythaemia

This is a raised Hb with a raised red cell count. It may be secondary to hypoxia, which itself is most commonly associated with chronic cardiopulmonary disease and the arterial oxygen saturation is low. Such patients simply need more red cells to deliver oxygen to the tissues since each red cell delivers less since it picks up less in the lung. Sometimes polycythaemia might be part of a myeloproliferative condition where there is an endogenous and primary overproduction of red cells by the bone marrow.

Disorders of platelet number

An increase in the platelet count is known as thrombocytosis. Just as with polycythaemia it might be secondary or part of a myeloproliferative condition. Primary causes include bleeding and surgery. The count may also be raised in chronic inflammatory disease including infection.

Thrombocytopenia is a reduced platelet count. It may present with bleeding including bleeding from the nose and into the mouth. Causes that the surgeon should consider must include:

- Immune thrombocytopenic purpura (ITP). In this condition then there are autoantibodies directed at the platelet. The platelet count may be dramatically low (into single figures). In children it may resolve spontaneously. Steroids and other immunosuppressant drugs are used to improve the count, especially in adult patients.[59] Referral to haematology services is indicated.
- As part of a coagulopathy including disseminated intravascular coagulation (DIC). In DIC there is activation and consumption of clotting factors and platelets in association with severe illness such as severe bacterial infection or widespread metastatic malignancy. Where there is thrombocytopenia the coagulation profile should be checked and the hallmarks of DIC are prolongation of the prothrombin time (PT) and activated partial thromboplastin time (APTT) with reduction in fibrinogen and elevation of fibrin degradation products (expressed as FDP or D-Dimers).[4]
- Heparin can cause thrombocytopenia and there may be paradoxical thrombosis, which can be severe in heparin-induced thrombocytopenia (HIT). If HIT is suspected then an urgent referral to haematology is

indicated as there are specific investigations to detect the culpable antibodies and specific intervention will be initiated.
- Thrombocytopenia might be associated with primary haematological illness.

Disorders of neutrophil number

Neutrophil leucocytosis – an increase in the neutrophil count – is usually secondary to bacterial infection. It may be secondary to other inflammatory illness, to malignancy and it will frequently be raised post-operatively. Sometimes it may be part of a primary haematological process including myeloproliferative disease and leukaemia.

Neutropenia may also be associated with infection including viral infections and significant bacterial infection. As with ITP there may be immune mediated neutropenia. It may be associated with primary haematological disease and its treatment.

Abnormalities of lymphocyte appearance and number

The practising surgeon should recognize that lymphocytes deal with viruses and may be altered in number or appearance in viral infection or primary haematological disease. Certain conditions are worthy of specific mention:

- The lymphocyte may appear differently – often referred to as 'atypical mononuclear cells' or 'atypical lymphocytes' – in certain viral infections and particularly in the EBV infection know as infectious mononucleosis. In this illness there maybe be fever, lassitude, sore throat, with atypical lymphocytes seen on the blood smear.[60] Diagnosis is with EBV serology. Note that this illness may be indistinguishable from other virus infection such as CMV.
- There may be a lymphocytosis in other viral infections. It may be elevated in bacterial infection especially in children and classically with pertussis infection (whooping cough).
- The lymphocyte count may be chronically elevated in chronic lymphocytic leukaemia (CLL). There will often be associated lymph node enlargement as the malignant cells infiltrate nodes. The diagnosis can easily be made from peripheral blood investigations (starting with blood smear and then flow cytometry) and biopsy of an enlarged node might therefore be avoidable.

Monocytes, eosinophils and basophils

Monocytosis is seen in chronic infection and in primary haematological disease. Where it is part of a reactive picture there is usually an associated neutrophil leucocytosis.[60]

Eosinophila is seen in allergic conditions (asthma, eczema), in parasitic infections and in association with certain drugs. It is classically also seen in Hodgkin's lymphoma and the association of lymphadenopathy with eosinophilia should alert the clinician to this potential diagnosis.[61]

Basophils are infrequently found in the peripheral blood. They may be increased in chronic myeloid leukaemia where the total white cell count is usually typically greatly elevated.

SPECIAL CONSIDERATIONS IN CHRONIC HAEMATOLOGICAL DISEASES

Sickle cell disease

Sickle cell disease is a common haemoglobinopathy, which is encountered worldwide, although usually in patients of Afro-Caribbean, Middle Eastern or Asian ancestry. There is a single base pair substitution leading to a single amino acid change in the β-globin chain of the haemoglobin molecule.[62] It can be considered as two diseases:

- There is a haemolytic anaemia with shortened red cell survival and anaemia with the generic features of haemolysis including reticulocytosis and jaundice.
- There is also a vaso-occlusive illness. The red cells occlude blood vessels during crises and either affect the oxygen delivery to that organ (stroke, painful crisis) or affect blood flow from that organ (sequestration crisis).

There are several points that the ENT surgeon should note.[63] All children with a possible diagnosis of sickle cell anaemia should be screened prior to surgery since there is an increased risk associated with anaesthesia. Safe surgery requires the meticulous avoidance of dehydration, hypoxia or hypothermia as these may trigger sickling.[64]

In some countries including the UK there will have been implemented a national neonatal screening strategy. Otherwise it is easy to screen rapidly by testing for sickling in the lab (the sickledex test) and by looking at the blood film. Haemoglobin electrophoresis will detect haemoglobin S and distinguish it from normal adult haemoglobin A.

There is an increased risk of sensorineural deafness in children with sickle cell disease presumably as a consequence of the vasculopathy of sickle cell. Affected children have an increased incidence of obstructive sleep apnoea caused by adeno-tonsillar hypertrophy and surgical correction might reduce the risk of painful crises. Priapism of the nasal turbinates is a cause of nasal obstruction and partial turbinectomy might be indicated.[63]

Bone marrow (stem cell) transplant

During stem cell transplant the recipient receives a stem cell donation from either a relative or an unrelated individual as part of their treatment of a primary haematological malignant or non-malignant disease. The stem cell donation follows a period of 'conditioning' high dose chemotherapy or radiotherapy that gets rid of both the patient's

immune system so that the donation is not rejected and the patient's own bone marrow so that there is 'space' for the donated stem cells to engraft into.

The conditioning therapy will regularly and reliably generate mucositis (see 'Stridor during treatment of haematological malignancy' above). There will be the risk of infection including fungal infection that is discussed in 'Infections' above and in the management of which the ENT team will be not infrequently involved.

The transplant may involve immunological rejection of host tissue by the engrafted, regenerating donor immune system. This is the process of graft versus host disease (GvHD) and is the opposite of graft rejection. GvHD in the early months after transplant will involve attack on the skin (presenting as rash), the gut (presenting as diarrhoea) and the liver (presenting as jaundice). However there may be involvement of any organ in the months that follow. During this chronic GvHD phase there may be immunological destruction of the salivary gland and xerostomia.[65] Management is supportive and symptom-directed but also immunosuppressive.

Splenectomy

The spleen protects against infection with encapsulated organisms including *pneumococcus* and *haemophilus* species.[3] Hyposplenism is rarely constitutional but usually follows surgical splenectomy, which may be done following trauma or as part of treatment of a haematological condition. The patient will usually receive protection against such infection with prophylactic antibiotics and with regular vaccination against *pneumococcus*, *meningococcus* and *haemophilus*. Malaria prophylaxis in endemic areas is also important. The FBC may be abnormal in the splenectomized individual with leucocytosis and thrombocytosis. The smear will show Howell-Jolly bodies in the red cells – these are nuclear fragments that the spleen will usually remove from the mature, circulating red cell.[60]

KEY POINTS

- Haematological malignancies often present to the otolaryngologist as nodal disease in the neck.
- Patients with haematological malignancies may have severely compromised immune systems due both to the disease process and the treatment. This leads to increased risk of severe upper respiratory infections including rhinosinusitis, mastoiditis, supraglottitis and neck space infections.
- Invasive fungal rhinosinusitis can complicate haematological disorders.
- Lymphomas of the head and neck can progress rapidly in size, leading to airway obstruction.
- Severe mucositis of the aerodigestive tract can complicate the treatment of haematological malignancies.
- Vincristine is an uncommon but important cause of vocal cord palsy.

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CHAPTER 26

HAEMOSTASIS: NORMAL PHYSIOLOGY, DISORDERS OF HAEMOSTASIS AND THROMBOSIS

Elizabeth Jones and Russell David Keenan

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: haemostasis and thrombosis.

INTRODUCTION

It is common for surgeons to come across disorders of haemostasis. The three main scenarios are: i) peri-operative severe and potentially life-threatening bleeding; ii) pre-operative assessment that identifies or suggests a patient may be at increased risk of bleeding; and iii) post-operative thrombosis. The aim of this chapter is to provide the physiological and practical knowledge to manage these scenarios together with your haematology team.

In order to interpret laboratory tests and manage patients' safely it is important to have a working understanding of blood clotting. Blood clotting is somewhat confusing as clotting factors are numbered according to when they were discovered and this is not related to where they are in the clotting cascade. They are labelled in Roman numerals. Factors III, IV and VI are not referred to because, following their discovery, it became clear that they were already known substances (i.e. thromboplastin, calcium and factor Va).

While the traditional cascade model of clotting is not exactly what happens in the body it is still useful and important to understand in order to interpret laboratory tests and safely manage patients. In the body, blood clotting is a much more dynamic process also involving other blood cells and the blood vessel walls. It involves a fine balance between excessive bleeding and clotting, either of which is pathological.

CLOTTING CASCADE

Blood clotting is the conversion of soluble fibrinogen (coagulation factor I), which is present as small monomers, to insoluble long chains of fibrin. Long strands of fibrin are insoluble; however, they are not strongly bound together until the long fibrin strands are cross-linked. This cross-linked fibrin is very strong and stable and the principal structure of the blood clot.

Thrombin is the only factor able to cause fibrino**gen** to **gen**erate fibrin, so thrombin generation is therefore essential for clot formation. Thrombin also controls many other parts of the blood clotting system including forming the cross-linked bonds through activation of factor XIII (**Figure 26.1**).

Common pathway

Prothrombin (factor II) is cleaved to form thrombin and itself can only be activated by activated factor X (Xa). This involves a complex reaction with factor V as a cofactor. Calcium and phospholipid are also required for this to occur.

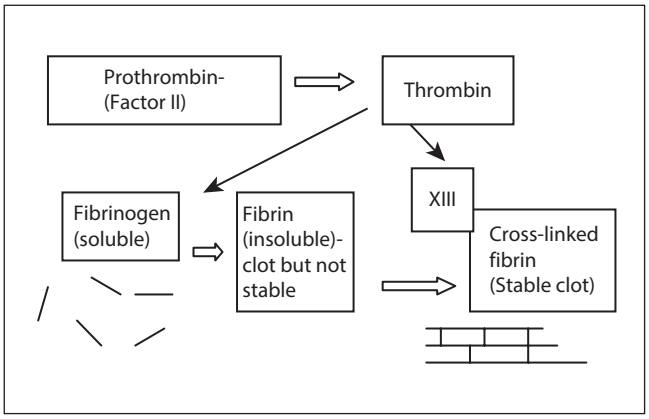


Figure 26.1 The action of thrombin to form cross-linked fibrin.

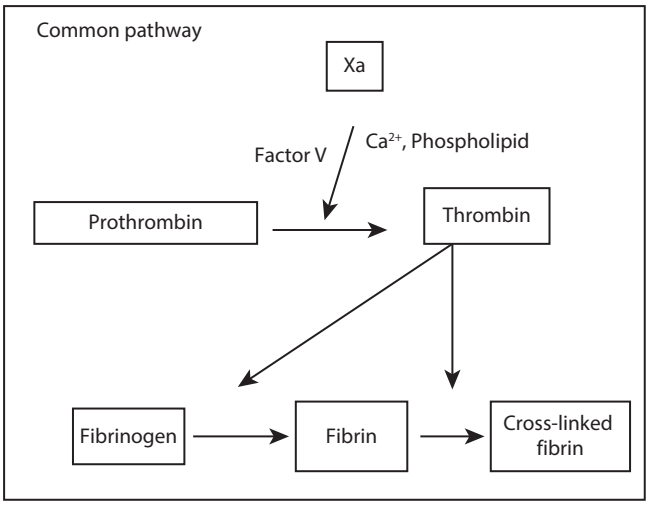


Figure 26.2 The common pathway of blood coagulation.

This section of the process is referred to as the common pathway (Figure 26.2). Descriptions of the clotting cascade are traditionally referred to as the common pathway, the intrinsic pathway and the extrinsic pathway. These will be discussed shortly.

Factor Xa can be formed in the laboratory in two different ways. In the prothrombin time (PT) test an **external** factor called 'tissue factor' is required; hence this is called the **ext**rinsic pathway. In the partial thromboplastin time (PTT) – also known as activated partial thromboplastin time (APTT) or Kaolin cephalin clotting time (KCCT) – there is no additional biological factor so all the factors are already present **in** the plasma so it is called the **in**trinsic pathway.

Extrinsic pathway (Figure 26.2)

The PT is the time, in seconds, for a clot to form once tissue factor (made from rabbit's brain) and calcium are added to the patient's plasma. During this time factor VII is activated by tissue factor and calcium to become factor VIIa, which in turn directly activates factor X to become Xa, and so on through to the formation of fibrin (Figure 26.3).

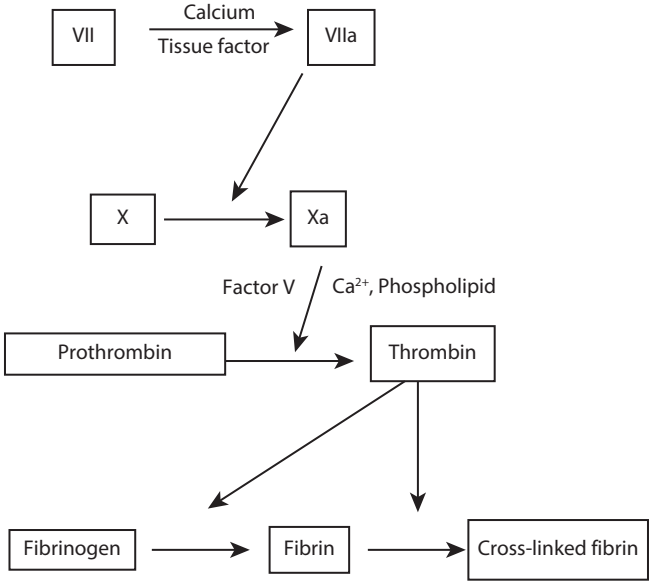


Figure 26.3 The extrinsic and common pathway of blood coagulation.

Note that the PT includes all of the cascade from factor VII through to fibrin formation, but does *not* include cross-linked fibrin (so the PT is normal in factor XIII deficiency).

Intrinsic pathway

The PTT measures the time in seconds for a clot to form once calcium is added to the patient's plasma after a preincubation with kaolin which acts as a catalyst (required within laboratory testing to allow the reaction to occur). This covers the time from the conversion of factor XII to XIIa, which then drives activation of factor XI to XIa. Factor XIa in turn activates IX to IXa, which leads to the activation of X to Xa. Factor VIII is a cofactor required for the action of IXa (Figure 26.4).

The physical structures of cofactors VIII and V (in the common pathway) are very similar to each other and they participate in similar ways in the reactions. The PTT measures the time for the process from Factor XII through to formation of fibrin, but again *not* to cross-linked fibrin so again this is also normal in factor XIII deficiency.

While the above pathways do not precisely represent what occurs in the body it is a useful working understanding of clotting in laboratory testing that can be used to identify deficiencies in specific factors. The above screening tests allow a measure of the presence and function of the patient's factor levels. However, the differences that occur within the human body include thrombin, also providing positive feedback towards the formation of factors IX, X, XI and VII. Within the body factor VII also activates primarily factor IX, factor IX then activates factor VII in a positive feedback. These extra levels of positive feedback accelerate the process, and create a powerful amplification of the cascade. At each stage of the reaction the amplification is such that one molecule of a particular

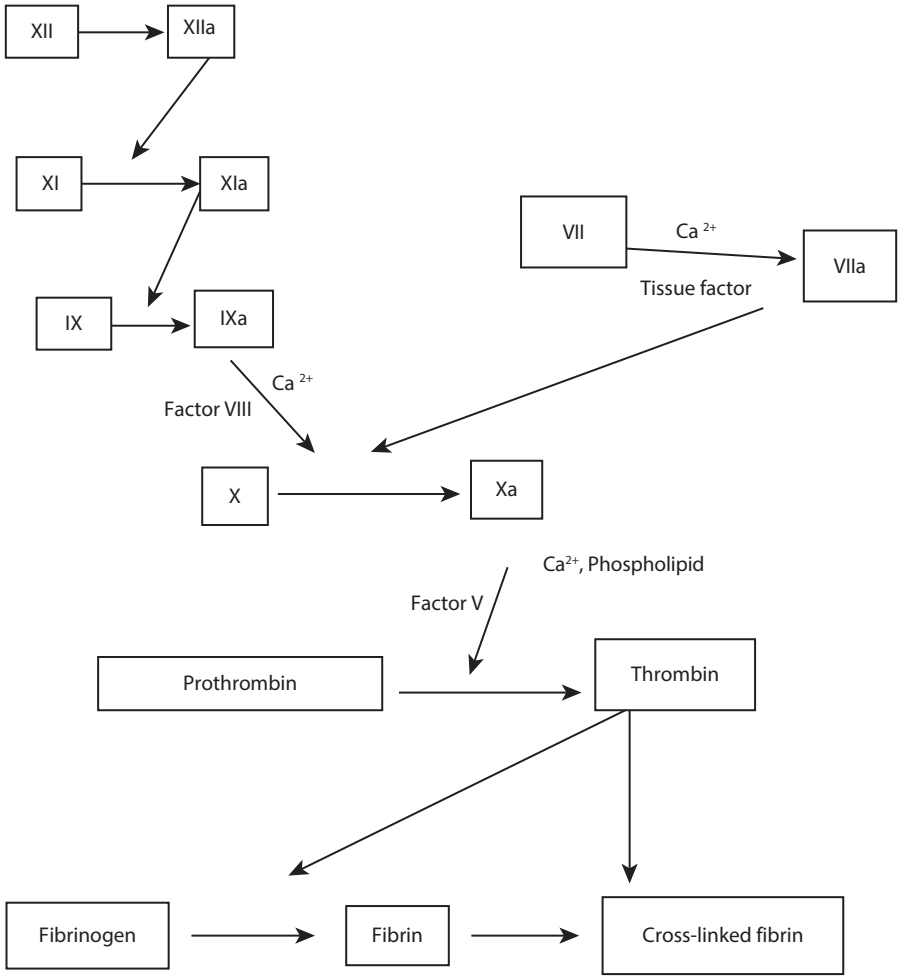


Figure 26.4 The intrinsic, extrinsic and common pathways of blood coagulation.

factor activates 100 molecules of the next factor in line. This allows rapid clot formation from a small initial stimulus. This speed is obviously essential when somebody is bleeding and differs from other much slower enzymatic reactions in the body.

Inhibitory systems

Inhibitory systems are in place to prevent clotting continuing extensively where it is not required. There are two main inhibitory systems; 1) antithrombin (previously referred to as antithrombin III) and 2) protein C with protein S.

Antithrombin's main action is, as the name suggests, inhibition of thrombin. Antithrombin also inhibits at multiple other levels within the cascade, the serine proteases, factors X, IX, XI and XIIa, which share some molecular features.

Factors V and VIII are structurally similar to each other but very different from the other factors. Not surprisingly, therefore, they have a different inhibition system, protein C and its cofactor protein S.

Deficiencies in any of these inhibitory proteins are a risk factor for the generation of clots in patients. An abnormality of the blood clotting system that predisposes to clots is called thrombophilia ('clot loving').

The role of platelets

Platelets are the smallest cell in the body and are fragments of cytoplasm formed from megakaryocytes in the bone marrow. Platelets contain 'packages' (granules) of various elements needed for coagulation, including clotting factors, ADP, serotonin, von Willebrand factor (vWF) and fibrinogen. They have two main receptors on their surface allowing them to stick to exposed collagen on a damaged blood vessel wall and allowing them to stick to each other directly and via vWF.

The steps in platelet function include:

- adherence – sticking to collagen exposed by damaged endothelium
- activation – secreting a range of chemicals to induce clot formation, vasoconstriction and start the healing process
- aggregation – sticking together (stimulated by ADP and thromboxane) (Figure 26.5).

ADHERENCE

This is the platelets sticking to exposed collagen underlying the damaged endothelium. There are two main

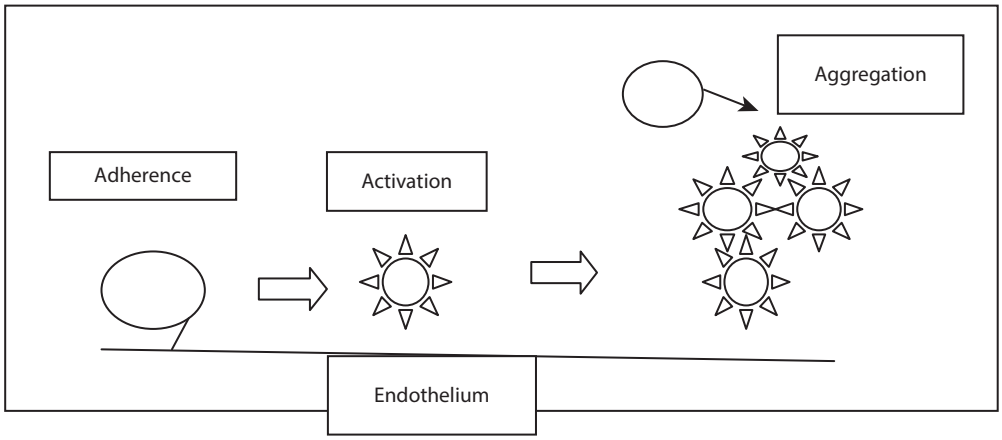


Figure 26.5 Platelet adherence, activation and aggregation.

membrane bound sticky molecular complexes that have this function:

1. Glycoprotein IIb/IIIa complex, which sticks to collagen directly. If this glycoprotein is missing it causes a severe bleeding disorder called Glanzmann's thrombasthenia.
2. Glycoprotein Ib/V/IX complex, which sticks to collagen indirectly via von Willebrand factor. If this glycoprotein is missing it causes a severe bleeding disorder called Bernard Soulier disease.

ACTIVATION

This is the process of locally secreting factors that promote blood clot formation, platelet aggregation, vasoconstriction and the start of tissue healing. One critical process is the 'arachidonic acid pathway'. Arachidonic acid is freed from cell membrane phospholipid molecules and converted to prostaglandin by cyclo-oxygenase (COX) enzymes. In turn the prostaglandin then forms thromboxane (via thromboxane synthetase present in platelets) and prostacyclin (via prostacyclin synthetase in endothelial cells). The thromboxane is a vasoconstrictor that stimulates further platelet aggregation and activation (aspirin irreversibly blocks this process, rendering the platelet function reduced for the rest of its 12-day life span), whereas prostacyclin has opposite effects, causing vasodilation and platelet inhibition.

Aggregation

This is when the activated platelets recruit other platelets to an enlarging 'platelet aggregate'. Much of this is by the release of ADP from dense granules and also through generation of thromboxane.

The role of von Willebrand factor

Von Willebrand factor (vWF) is in plasma and platelets. It is also released from the special storage granules in the endothelium called Weibel Palade bodies.

vWF has two main functions:

1. It makes platelets stick to each other and to damaged blood vessel walls. This can only occur when the vWF sticks to itself in ultra large high molecular weight multimers. These multimer molecules can be huge (from 500 to 20 000 kDa)
2. It chaperones circulating factor VIII – this stabilizes factor VIII to prolong the half-life.

Interpreting laboratory results and diagnosing von Willebrand disease is not straightforward and is beyond the scope of this chapter. Difficulties arise firstly in that vWF is a highly labile protein that goes up with stress (which could include surgery) and also in pregnancy. In addition, the laboratory tests are difficult and results are not always robust, commonly giving falsely low levels.

The role of the vessel wall

The formation of a clot usually starts when there is damage to the endothelial wall. The endothelial wall in its healthy state is active in inhibiting platelet adhesion by the production of substances such as nitric oxide and prostacyclin. It therefore functions as a 'non-stick' surface. When collagen is exposed, allowing platelets to come into contact, they then become active. The two main anticoagulant systems discussed earlier (i.e. antithrombin and proteins C and S) are potentiated by normal endothelium. Antithrombin is bound on the endothelial cell surface by 'heparin like' glycosaminoglycans and is made much more powerful. Another molecule on the endothelial surface called thrombomodulin binds thrombin. Thrombin, instead of being the critical promoter of coagulation, then stops all procoagulant function and potentiates protein C. In effect thrombin becomes an anticoagulant in the presence of normal endothelium and limits the clot to the damaged surface (Figure 26.6).

When a platelet plug has formed, the larger blood vessels in particular need cross-linked fibrin to stabilize it. In smaller vessels this is not always a vital step and this partly explains the difference in bleeding manifestations in different disease states.

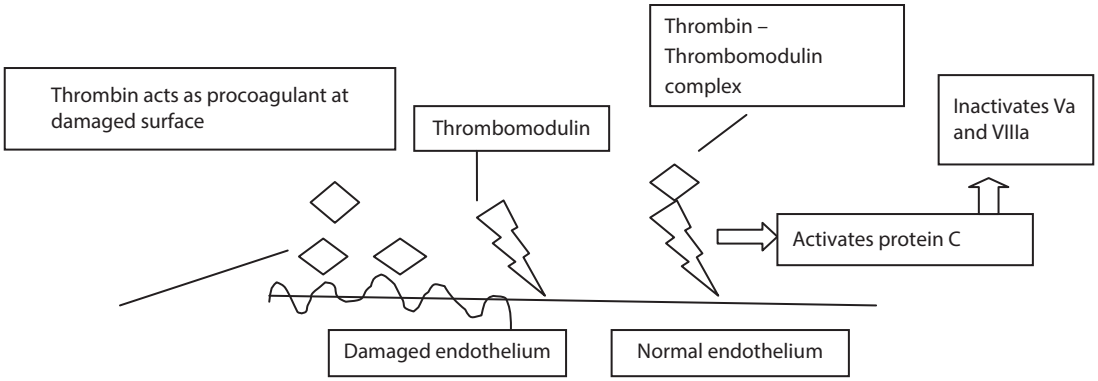


Figure 26.6 Natural anticoagulation via thrombomodulin, protein C and protein S pathway.

The flow of blood within the blood vessel can also affect the type of clot formed. Red clot, mostly erythrocyte (red cell) and fibrin, is formed where flow is reduced with no blood vessel damage (i.e. cases of DVT); they are generally treated best with anticoagulants. White clot is platelet and fibrin, forming where blood vessel damage has occurred and characteristically occurs in faster flow vessels/arteries (i.e. myocardial infarction), which is best treated with antiplatelets. Of course clots may be both white and red, especially where white clots are initially formed leading to alteration of flow and additional formation of red clot.

Blood clot breakdown (fibrinolysis)

As soon as a clot is formed the process of clot breakdown called fibrinolysis starts and is mediated via plasmin. Plasmin is **gen**erated from plasmino**gen**, which is bound by fibrin. It is then converted to its active form by plasminogen activators. There are inhibitors to this process, which prevent the degradation occurring too quickly (e.g. plasminogen activator inhibitor PAI-1 and activated protein C) (Figure 26.7). All of the products of this breakdown are call fibrin degradation products. D-dimer is the specific product formed only by breakdown of cross-linked fibrin and can be used as an indicator of thrombus formation; however it will also be raised in other states of inflammation/infection.

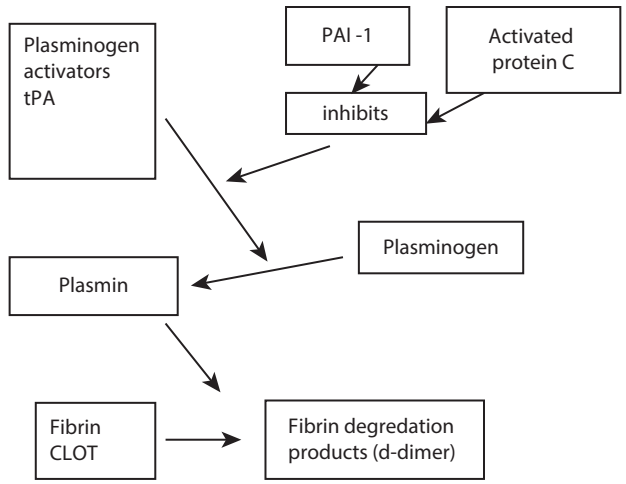


Figure 26.7 Fibrinolysis.

INTERPRETATION OF COAGULATION SCREENING TESTS

(See Table 26.1)

International normalized ratio

Technically, an international normalized ratio (INR) should only be used for monitoring of warfarin as this is the setting validated for its use. In all other instances the PT should be requested. The INR is purely the PT ratio multiplied by a 'fiddle factor' specific to the laboratory to allow comparison between laboratories. Therefore there is no additional information in an INR compared with a PT.

With suspected Vitamin K deficiency (if time allows) the usual practice would be to treat with Vitamin K, either oral or IV, depending on concerns regarding gastrointestinal absorption (i.e. 10 mg for 3 to 5 days with a repeat test following this as a 'proof of suspicion') rather than checking Vitamin K levels.

Thromboelastography/rotational thromboelastography

In many settings there is now increasing use of thromboelastography (TEG) and rotational thromboelastography (ROTEM). This technology gives a quick guide as to the global coagulation functioning indicating the patient's current status. It produces a trace providing information of time to formation of clot, and its stability, enabling a more 'real time' guide to product use (Figure 26.8). It has particularly been employed in setting with major blood loss (i.e. trauma, vascular surgery).

The trace has a variety of measurements that help in interpreting (Figure 26.8):

- **R time** – time until clot first detected (prolonged if on anticoagulants or factor deficiency)
- **K time** – time to clot formation (time from initiation of clot to maximum amplitude/strength)
- **alpha angle** – helps guide if the patient is in a hypercoagulable state.

TABLE 26.1 Interpretation of abnormal laboratory tests

Test	Causes	Further laboratory investigations to consider
Prolonged PT only (with other tests normal). Can only be caused by factor VII deficiency, which in turn may be related to a variety of causes	• Vitamin K deficiency • Antagonists, e.g. warfarin • Dietary. Vitamin K in green vegetables • Early liver disease • Congenital deficiency (very rare)	• LFTs • FVII assay • If dietary deficiency is considered, giving oral Vitamin K and repeating the PT is a simple way of excluding other serious causes.
Prolonged APTT only (deficiency of one or more of: factor VIII, IX, XI, XII)	• Heparin • Lupus anticoagulant or other inhibitor • Congenital deficiency (haemophilias)	• Thrombin time • Reptilase time, which neutralizes heparin
Prolonged PT and APTT	• DIC (also may have low platelets and low fibrinogen) • Liver failure • Vitamin K deficiency • Warfarin • Factor X or V or II deficiency	• LFT • Fibrinogen, factors V, X, II
Low fibrinogen	• DIC • Afibrinogenaemia/dysfibrinogenaemia	• Fibrinogen assay (In routine coagulation testing the result is often a derived value rather than direct testing).
Low platelets	• Clumping/artefact • ITP • Bone marrow failure (many causes) • Drug cause • Infection/DIC	• If a single low count that is unexpected, repeat sample • Blood film • Further investigation depends on the history
Normal tests but abnormal bleeding	• **Consider surgical causes**; it may be obvious but surgery is the commonest cause of bleeding post-operatively • LMWH • Abnormal platelet function • Von Willebrand disease • Factor XIII deficiency • Mild factor deficiency	• Von Willebrand screen • Factor XIII assay • Platelet aggregation studies

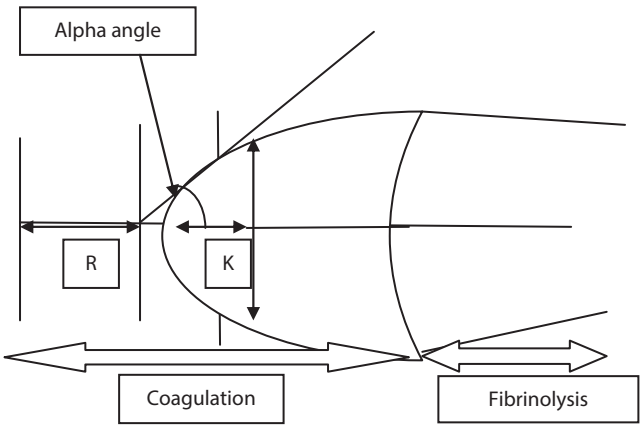


Figure 26.8 Thromboelastography.

The shape of the trace produced gives a lot of information on the coagulation and fibrinolysis and very typical traces can be seen in pathological states such as disseminated intravascular coagulation (DIC) when a patient is hypercoagulable with reduced R and K times and secondary fibrinolysis.

Specific factor assays

These are performed to quantify the levels of specific coagulation factors in a patient. They are needed for initial diagnosis and then for guiding response treatment and further management. Using a plasma known to be deficient in a specific factor (which are now manufactured, although can be plasma from patients known to have haemophilia) and normal plasma, either the PT or PTT test can be performed, depending on which factor is to be assayed. By mixing the 100% normal plasma and 0% deficient plasma in different proportions to create a standard curve, the patient's plasma can then be tested and a specific factor level deduced from this curve. This is the basis of testing for all factor levels in the extrinsic and intrinsic pathways.

BLEEDING DISORDERS

It is vital to identify any underlying bleeding disorder prior to surgery. Patients with severe bleeding disorders can have life-threatening bleeding even with minor procedures. Patients with bleeding disorders should always be managed jointly with the haematology team.

Different bleeding disorders present with different bleeding symptoms, for example joint bleeds in haemophilia and mucocutaneous bleeding (i.e. bruising, bleeding from the nose, mouth and menorrhagia) with von Willebrand disease and platelet disorders. This is because the defect in the clotting system affects different aspects

of function. Bleeding disorders may be genetic/congenital or acquired. The history is crucial to guide further investigation and it is not always possible to fully interpret the laboratory investigations without the history.

It is useful to know that bleeding symptoms are common in the normal population. In a survey of normal controls, up to 25% of males and 46% of females with normal haemostasis are likely to have at least one bleeding manifestation (including menorrhagia, post-operative bleeding, bleeding post dental extraction).[1] Almost all of us will get a nose bleed at some point and 25% of younger children have recurrent nose bleeds. Most children experience fewer nose bleeds by the time they are teenagers. In some studies 65% of normal women in the control population would describe themselves as having menorrhagia. Bruising is normal with an active childhood lifestyle and if easy bruising is a symptom then objective questioning on the location, frequency, size and trauma associated with the bruising is essential. Bleeding scores have been developed to aid decisions on how significant the history is, but they are not necessarily in widespread use.

COAGULATION FACTOR DISORDERS

Haemophilia

One of the better known bleeding disorders is haemophilia. The genetic forms of this are grouped as haemophilia A (deficiency of factor VIII) or haemophilia B – Christmas disease (deficiency of factor IX). These are then classified as mild, moderate or severe depending on the patient's baseline factor level (mild is factor level < 30%, moderate < 5% and severe < 1%). In most haemophilias the genetic defect 'runs true' within the family, therefore the severity of haemophilia also runs true within families.

Haemophilia A and B are X-linked genetic disorders and as such classically affect males. However, there are rare instances of female carriers presenting with increased bleeding tendency related to a low factor level (i.e. carriers of severe haemophilia). There are also instances of affected females with very low factor levels due to other complicated inheritance genetics (extreme X chromosome lyonization and mosaicism). Lastly it should be remembered that there are rare families who have two completely separate bleeding disorders, which can lead to some individuals having a much more severe bleeding phenotype than would be normally expected because they have inherited both. This means the patient's personal history and bleeding manifestations are of vital importance in treatment decision-making.

Severe and moderate haemophilias are usually diagnosed in childhood with many cases having been suspected antenatally when family history is known. Milder cases may present in adulthood. Spontaneous new mutations occur in approximately 20% of cases (therefore there is no family history). People with severe haemophilias have increased bruising but this does not usually cause a problem. The main issues for these patients are spontaneous joint and muscle bleeds and excessive bleeding following even minor procedures. All patients with a diagnosis of or suspected haemophilia should have surgery managed in a centre with specialist haematology experience.

Patients with haemophilia A or B would be expected to have a significantly prolonged APTT on screening tests. Further assays can then be performed to ascertain specific factor levels.

Management of haemophilia

The management of patients ideally revolves around appropriate intravenous recombinant or plasma derived factor replacement. This can be 'on-demand' treatment for bleeds or 'prophylaxis' given regularly (usually 2–3 times weekly and often taken when sports or activities dictate). No oral factor replacement therapy is available as yet. Many patients who are newly diagnosed are now given primary prophylaxis and may not have experienced significant bleeds. Patients (particularly older ones) are generally very knowledgeable about symptoms of joint bleeds and most will self-treat at home, only attending hospital for review by the medical team if significant bleeding is experienced or if it is not settling. Acute bleeds require increased factor administration (i.e. often at least twice a day) with rest initially being advised followed by appropriate physiotherapy.

In developing countries expensive recombinant factor is often not available. Plasma derived factor is often cheaper but can carry the risk of blood-borne infection transmission. Simple measures of bleed management should always be considered in addition to factor replacement including RICE (rest, ice, compression and elevation) along with use of the relatively inexpensive tranexamic acid (an antifibrinolytic agent).

Management of any bleeding condition is a partnership between patient and multidisciplinary team. Perioperative management and dosing of factor replacement will usually be guided by exact levels and review of bleeding symptoms. The administered factor will be consumed more quickly in the face of bleeding and close monitoring of bloods may be required for a week or more post-operatively in the event of major surgery. Treatment options include bolus and continuous infusion of factor.

The management of haemophilia (and other bleeding disorders) may be complicated further by the development of inhibitors. This is an immune response with neutralizing antibodies against the factor treatment, which is viewed by the body as a foreign protein. The development of an inhibitor would be suspected in cases where there is an inadequate clinical response to treatment. Inhibitors are also usually monitored via laboratory testing as part of routine follow-up care. As the factor therapy is rendered ineffective, patients with inhibitors are very difficult to treat and can suffer life-threatening bleeding. Surgery should be avoided where possible until the inhibitor is controlled. Acute bleeds in these situations require administration of factor VIII inhibitor bypassing agent (FEIBA), which is a plasma derived concentration of a number of other factors or high dose recombinant factor VIIa (rFVIIa) to gain control. Patients with significant problems with inhibitors generally require treatment aimed at eradicating the inhibitor; however, this usually takes many months to be an effective strategy.

Acquired haemophilia

Acquired haemophilia is very rare but is important to mention as it can present to surgeons and has disastrous consequences if not identified. This usually occurs in older adults but can also occur in pregnancy. It is a type of autoimmune disease where patients develop (auto)antibodies to a coagulation factor (their own endogenous factor). This is most commonly FVIII or von Willebrand factor. It can present with no past history of bleeding manifestation. On presentation their bleeding, manifestations tend to be very different to those with congenital haemophilia and may consist of very extensive bruising and prolonged surgical bleeding. It does not usually lead to joint bleeds. From a laboratory point of view they will have a similar finding of markedly prolonged APTT, which would of course require further investigation. There will be a very low factor level. A 50:50 mix of patient plasma and normal plasma is a quick and easy test that all laboratories can perform even out of hours. The prolonged APTT does not correct as the inhibitor also destroys the factor in the normal plasma that is added (whereas it would normally correct in a congenital deficiency as enough factor is added with the 'normal plasma' and it is not destroyed by antibody). There may be an underlying condition driving the formation of the antibodies (i.e. malignancy, pregnancy). Patients with acquired haemophilia are complex and unbelievably expensive to manage and require two aspects of treatment: i) management of acute bleeding, which is similar to the management of a patient with congenital haemophilia who has an inhibitor; and ii) immunosuppression in an attempt to control the antibody, often with agents such as steroid, ciclosporin or Rituximab (a monoclonal antibody directed against CD20 cell marker that destroys mature B lymphocytes). Patients may spontaneously remit depending on whether an underlying driver can be treated but may have further episodes of relapse.

Von Willebrand disease

Von Willebrand disease is an inherited bleeding disorder. It can be seen with autosomal dominant or recessive inheritance. It is categorized into three types. The most common is type 1. This is usually a relatively mild partial quantitative deficiency, that is, a reduced amount of a normal von Willebrand factor (vWF). Type 2 is split into further groups but all involve abnormal vWF, usually with reduced function. Type 3 is near absence of vWF that leads to a severe bleeding phenotype very similar to severe haemophilia A.

It is often quoted that von Willebrand disease is very common at around 1% of the population.[2] This is false. The 'rumour' followed an Italian study that identified nine normal school children with low vWF levels out of 1000 tested. This in reality was just validating the reference range, which if set at 2 standard deviations from the mean will exclude 5% of the normal population (2.5% below and above). This paper is still repeatedly quoted today in literature but what is rarely quoted is the follow-up paper on the nine children, most of whom had surgery and none of whom had any clinically relevant bleeding problems. In 2004–2005, UK international diagnostic guidelines were published that were much more restrictive.[3] This is important as it will not be uncommon for someone to present with a historical diagnosis of von Willebrand disease and when you contact your haematologist to review they may retract the diagnosis.[4] It is also recognized that as people get older their levels often improve, which may be another reason for altered management.[5]

Surgeons will frequently encounter patients with a personal or family member with a historical diagnosis. The international diagnostic guidelines have minor differences but essentially the diagnosis relies upon clinical significant bleeding symptoms and a vWF antigen (or activity level of vWF) of 40 iu/dL or less on repeat occasions. A patient's blood group is also related to vWF levels, with group O patients having 30% lower levels then group A and B. This may well be the reason why blood group O patients are less likely to have thrombotic problems such as ischaemic stroke.

MANAGEMENT OF VON WILLEBRAND DISEASE

Management of vWD in most cases is by use of DDAVP (which leads to release of endogenous stores of vWF and factor VIII) or plasma derived product containing vWF and FVIII. There is as yet no recombinant product available. DDAVP is not effective in all cases so for routine surgery patients would normally have a trial of DDAVP prior to the procedure to assess response. Of course levels would still need to be checked prior to surgery even if a previous good response has been demonstrated. DDAVP leads to a rise in plasma level of FVIII and vWF, caused by increase release from Weibel Palade granules in endothelial cells. Once these storage granules release their contents there is a latency period before the treatment will be effective again. DDAVP should be avoided in patients with evidence of atherosclerosis. Fluid retention can be a problem post-administration, often leading to headaches, so patients should be fluid restricted following it. DDAVP also cannot be used in very young children who are prone to life-threatening sodium toxicity. It should be noted that different strengths of DDAVP are available depending on the indication so it is vital to ensure the correct formulation is used.

Other rare congenital factor deficiencies

Patients can present with deficiency of any coagulation factor. The next most common factor deficiency is factor XI. This is a very variable cohort of patients and the factor level does not necessarily correlate with bleeding manifestations. It can be treated with factor concentrate but levels should not be increased to above 70% as the risk of thrombosis becomes high. Tranexamic acid (an antifibrinolytic agent) should not be used at the same time as factor replacement in this group but could be an alternative strategy. As only small amounts of factor XI are required in mild factor XI deficiency adequate haemostasis can often be achieved with FFP.

Dys- or afibrinogenaemia may be a qualitative or quantitative defect of fibrinogen. It may manifest as abnormal bleeding following trauma or surgery. The severity depends on the exact defect. It is managed by replacement with fibrinogen concentrate; often twice weekly is sufficient.

Factor VII plays a vital role in initiating coagulation but only a small amount is required. However, a severe deficiency causes a similar bleeding phenotype to haemophilia with spontaneous bleeds occurring. Factor VII has the shortest half-life and therefore replacement during a bleed is required 3–4 times per 24 hours. There is a recombinant product available.

Factor II, V and X deficiency are all exceedingly rare. There are also cases of deficiencies seen in combination that can lead to diagnostic confusion.

Factor XIII is important in fibrin stabilization, so has a typical delayed bleeding after surgery. The classical presentation is in neonates with prolonged umbilical stump bleeding. It has a long half-life and in deficient patients treatment once a month with concentrate is adequate prophylaxis. Plasma derived concentrate has been used for many years but a recombinant factor XIII is available in some countries.

Factor XII deficiency leads to a prolonged PTT but it does not lead to clinical bleeding or symptoms, so is only relevant in relation to its effect on the laboratory parameter.

Disseminated intravascular coagulation (DIC)

Disseminated intravascular coagulation (DIC) can be a confusing condition with both bleeding and clotting problems being present. There is widespread over-activation of the coagulation system leading to significant, usually arterial, thrombosis. The extensive formation of tiny blood clots throughout the body can lead to consumption of coagulation factors. These deficiencies can then lead to bleeding. It is usually bleeding that causes the life-threatening problems (Table 26.2).

TABLE 26.2 The causes of disseminated intravascular coagulation (DIC)

Infection
Trauma: • bleeding post-surgery • shock/hypotension
Tissue necrosis (e.g. organ destruction, e.g pancreatitis)
Malignancy-solid tumours, leukaemia
Obstetric-amniotic fluid embolism, placental abruption, pre-eclampsia
Vascular abnormalities – haemangioma and vascular aneurysm
Severe liver failure
Toxic and immunological insults-snake bites, drugs, ABO incompatible transfusion

The management revolves around 'treating the underlying cause' (Table 26.2) and supportive care (either by transfusion and other organ support, with or without anticoagulation dependent on the most problematic symptom). From a laboratory perspective it is usually diagnosed when an abnormal clotting screen is present with low platelets. The trend of blood counts should be monitored[6] and would include a rising PT and APTT, reducing fibrinogen and platelets with a raised D-dimer. The decision to use FFP and/or cryoprecipitate depends on the relative PT, PTT and fibrinogen, and the clinical problem. Again it is wise to involve a haematologist if this condition is suspected to guide on what is likely to be the most effective product and to ensure that the laboratory is expecting and turning around samples and provision of blood products quickly.

PLATELET DISORDERS

Immune thrombocytopenic purpura

Immune thrombocytopenic purpura (ITP) is a relatively common cause of an isolated low platelet count. Platelets are usually produced normally but are destroyed by the immune system so it is an auto-immune phenomenon. In the paediatric setting it is usually a condition that spontaneously resolves often not requiring specific treatment. However in the adult setting, and occasionally in children, it can be a chronic condition. In either case patients generally do not respond well to platelet transfusion, only getting poor transient increments due to rapid destruction. Patients who have a low platelet count should be discussed with the haematology team whether they have a specific diagnosis already or not. When a patient newly presents, other causes of thrombocytopenia would need to be ruled out. A repeat full blood count (FBC) is always essential as clumping of platelets can give a falsely low result on automated counters. A blood film can confirm if it is a consistent result and look for other abnormalities. Advice on management would depend on the clinical presentation, mainly if the patient has haemorrhagic manifestations. The platelet count does not always correlate with the level of bleeding or bruising and in ITP patients often tolerate very low counts without symptoms.

If an immediate rise in platelet count is needed, advice is likely to include administration of intravenous immunoglobulin (IVIg) to gain a quick response, high dose steroid (IV or oral), which takes longer to act, and platelet transfusions.[7] Despite a likely poor response, platelets are usually advisable in an emergency setting. IVIg is also often employed in an elective perioperative management plan. If a patient has previously been diagnosed they may well be on treatment which could include oral steroid or immunosuppression (i.e. azathioprine, ciclosporin, etc). Another treatment becoming more commonly used is Rituximab. Splenectomy can be very effective in some patients, but this leads to increased risk of sepsis, particularly from encapsulated organisms. Lastly the thrombopoetin (TPO) agonists are a newer treatment option with

oral and subcutaneous administration routes that stimulate increased platelet production.

Thrombocytosis

Very high platelet counts (>1000) can also lead to thrombosis or bleeding as the platelets are dysfunctional and also absorb increased amounts of von Willebrand factor, which then becomes depleted, contributing to the problems. The most common scenarios that cause this are myeloproliferative disorders, usually essential thrombocythaemia in older adults. The platelet count in this situation needs to be controlled because of both the bleeding risk and the risk of stroke or other thromboembolic events. Thrombocytosis in children is very rarely due to a primary blood disorder and is usually in response to infection or inflammation. This reactive picture is also seen in adults and in this situation no specific action is required other than monitoring.

Heparin-induced thrombocytopenia (HIT)

Many patients on prolonged heparin can develop a mild thrombocytopenias. This is not usually a clinical problem and heparin can often be continued. However, a rare drug reaction can be a severe thrombocytopenia that paradoxically also causes thrombosis as well as bleeding. This is a complication whereby a patient forms antibodies to heparin and the antibodies form immune complexes with heparin and PF4, which bind to platelet Fc receptors and lead to aggregation and thrombocytopenia. It may be suspected when a platelet count falls when on heparin (usually to between 20 and 50 or a drop of 50% compared with the baseline, with no other explanation) and when new thrombosis occurs. There are scoring systems to assess the likelihood, and testing for causative PF4 antibodies can be undertaken.[8] Heparin should be stopped and treatment should be given with an alternative anticoagulant (i.e. danaparoid, argatroban, bivilarudin, Fondaparinux). The platelet count should increase over the next 2–5 days. Patients should not be re-exposed to heparin (or low molecular weight heparin) as recurrence is common.

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) is a rare life-threatening condition that requires urgent treatment when recognized. It is a haematological emergency. Patients present haematologically with low platelets and anaemia (due to haemolysis) with fragments of red cells (schistocytes) seen on blood film, a microangiopathic haemolysis. Patients can have clinical symptoms of fever and neurological features (confusion, seizures) along with renal failure. In TTP the low platelets are caused by thrombosis in small blood vessels. The fibrin strands act as a 'cheese wire' leading to the red cell fragments. The underlying pathology is a reduction in a protein called ADAMTS13, which is normally involved in controlling vWF. With reduced ADAMTS13 vWF builds up into even bigger multimers than normal. The molecules can even get to the size of cells. Treatment is aimed at the underlying cause, reducing the abnormal vWF molecules and also replacing ADAMTS13. At the moment this is most effectively done by plasma exchange. Steroids and further immunosuppressive agents are also needed to gain control of the underlying drivers in the acquired form (there is a congenital variant of the condition with deficiency of ADAMTS13 and replacement by plasma infusion is sufficient treatment). When the platelet count rises thromboprophylaxis should be instigated as thrombosis is common in recovery.

Bone marrow failure syndromes

Myelodysplastic syndrome (MDS) is a collection of conditions where blood cell production in the bone marrow is abnormal and can affect one or all blood cell lines. Patients may therefore have features of anaemia, low platelets or low white cells. In most surgical situations patients will be managed with platelet transfusions if there is a bleeding risk. They may also need antibiotics to cover infection.

Other causes of bone marrow failure include conditions such as leukaemia and aplastic anaemia. Again the mainstay of bleeding management involves platelet transfusion. It may be appropriate to check a 'platelet increment', that is, repeat an FBC either 1 hour after the transfusion or 24 hours after. This may be particularly relevant if the patient has had previous transfusions and therefore a greater possibility of antibodies adversely affecting response to transfusion, or if a major procedure is planned to determine if further treatment is required.

Abnormalities of platelet function

Platelet function abnormalities generally present with post-surgical bleeding, mucocutaneous bleeding and/or menorrhagia. Platelet function abnormalities are most usually seen secondary to medication but there are very severe inherited disorders worth discussing here. Investigation of platelet function disorders will depend on a significant bleeding history usually with normal coagulation tests. A prolonged bleeding time is characteristic of platelet function disorders. A bleeding time is a very simple test where a cut of defined length, thickness and depth is made on the medial anterior aspect of the forearm and the time is measured in seconds until the bleeding stops. The bleeding time is rarely used as it is difficult to control and there is significant observer variability as well as the risk of scarring. Other platelet tests available include a screening test called the PFA-100 and more formal platelet aggregation studies. Platelet aggregation studies take a senior coagulation scientist a few hours and must be performed on fresh platelets. Therefore, this is an assay that must be booked with your laboratory in advance. In addition, intracellular platelet nucleotides can also be measured to aid diagnosis. Lastly, confirmation of some disorders may be sought by use of flow cytometry with monoclonal antibodies directed against absent receptors.

Platelet storage pool disorder is a term that covers abnormalities of the granules in the platelet cytoplasm. It includes deficiency of either alpha granules (grey platelet syndrome) or dense granules (MYH9 anomalies, Hermansky-Pudlak etc.) or both.

Platelet receptor anomalies include Glanzmann's thrombasthenia, where there is absent or abnormal glycoprotein IIb/IIIa (a receptor for fibrinogen and vWF), and Bernard Soulier disease with absent or abnormal glycoprotein Ib/V/IX complex (a receptor for vWF).

Management of bleeding problems in these structural platelet disorders will usually include platelet transfusions. However, these patients often need repeated platelet transfusions throughout their lives and frequently develop antibodies to the platelet antigen in the transfused platelets that they are missing. For this reason when planning minor procedures, where possible, the use of platelets is avoided. Other treatment options may include use of an antifibrinolytic such as tranexamic acid (mouthwash/PO or IV), avoiding antiplatelet agents and on occasion recombinant factor VIIa. Surgical technique should also be considered to minimize bleeding problems. To reduce the chance of developing antibodies any transfused platelets should be HLA matched irradiated and leucodepleted.

Medical problems

RENAL DISEASE

Renal disease and uraemia mostly affects platelet function, although anaemia also contributes to bleeding manifestations. The platelets, as the smallest constituent in blood, normally flow and travel along next to the endothelium so they are closest to the site where they will function. In anaemia they are not pushed out to the side as much, therefore increasing bleeding when injury occurs. Correcting the anaemia and the use of agents such as tranexamic acid or DDAVP are useful strategies to improve haemostasis in these patients when bleeding.

LIVER DISEASE

Liver disease has a potentially large impact on coagulation due to its role in the production of coagulation factors, particularly the Vitamin K-dependent ones (II, VII, IX, X and protein C and S) along with fibrinogen and the other coagulation factors. Portal hypertension can also lead to splenomegaly, which in turn can lead to a thrombocytopenia due to increased destruction of platelets.

THROMBOTIC DISORDERS

When a patient presents with thrombosis (the pathological formation of blood clot) an assessment should be undertaken as to the potential drivers behind clot formation. According to Virchow's Triad, three broad categories of factor contribute to thrombus formation: i) hypercoaguability (i.e. problems within the blood); ii) haemodynamic/blood flow changes; and lastly, iii) endothelial injury or dysfunction. Within this framework it is easier to see how certain states contribute towards a hypercoagulability by one or more mechanism (i.e. surgery, inflammatory conditions, infection, pregnancy, dehydration, immobility). Most hospital inpatients are assessed on admission and a decision made regarding prophylaxis for venous thromboembolism (VTE), most commonly with low molecular weight heparin (LMWH).

Investigation of thrombosis may include a thrombophilia screen, although this is done much less frequently now, as usually the results do not change the management of the patient. However, where it would alter management it should be taken into account.[9] Thrombophilia tests are best delayed until after the acute thrombus setting, ideally being done around 6 weeks after discontinuing anticoagulation treatment. Some patients will be tested because of their own history (e.g. VTE at a young age); however, some may be tested because of their relatives and family history. For the purposes of this chapter we will concentrate on the haematological abnormalities that lead to clots rather than the acquired non-haematological ones, of which there is a long list (i.e. dehydration, malignancy, advanced age, obesity, vascular malformation).

Table 26.3 gives an idea of comparable relative risks for various states in a large retrospective study.[10] It is worth noting that a prospective study found much lower risks for both heterozygosity (3.7) and homozygosity (24) for factor V Leiden.[11]

Thrombophilia screen

This includes:

- deficiency of natural anticoagulants (antithrombin; protein C; protein S)
- other genetic thrombophilias (factor V Leiden, an abnormal form of factor V protein which is resistant to protein C inactivation; prothrombin gene mutation (causing increased production of thrombin).

Deficiencies in protein C, protein S and ATIII mostly occur as a genetically inherited phenomenon. Heterozygous inheritance (one abnormal gene copy) of factor V Leiden or prothrombin gene mutation leads to only a small increase

TABLE 26.3 Relative risk factors for thrombosis

Risk factor	Relative risk
Antithrombin deficiency (Heterozygous)	5
Factor V Leiden	8.1
Factor V Leiden homozygous	80
Hospitalization	11.1
Immobilization	8.9
Oral contraceptive	3.8
Pregnancy	4.2
Protein C deficiency	3.1
PT gene mutation	2.8
Puerperium	14.1
Surgery	5.9

in risk of thrombosis compared to the normal population and, depending on the clinical scenario, would not require any specific treatment. However, where there is homozygous expression, or co-inheritance with other defects the risk increases significantly and patients would often be on long-term anticoagulation, particularly if there is a personal history of blood clot (Table 26.3).

Patients with a deficiency of antithrombin, protein C or S generally have a more severe clotting phenotype and each case should be assessed on an individual basis with regards to anticoagulation.

Hyperhomocysteinaemia, which can be inherited or acquired, can also lead to increased propensity to clot, this raised level of homocysteine affects collagen and causes damage to the endothelial wall. It is managed by vitamin B6, B12 and folic acid (B9) supplementation as this reduces the concentration of homocysteine in the blood. This is not necessarily included as part of the basic screen.

Acquired causes of thrombosis

Antiphospholipid syndrome is an acquired condition and has strict criteria for diagnosis requiring both clinical (thrombotic events, unexplained miscarriage or premature labour) and laboratory findings (two out of; anticardiolipin antibodies, anti beta-2 glycoprotein or a lupus anticoagulant found persistently over a period of 3 months). Again with these patients anticoagulant decisions should be made upon consideration of their clinical history. It is important to mention that a lupus anticoagulant is a relatively common cause of a prolonged APTT and when found without other features mainly causes 'diagnostic issues' rather than clinical problems.

Rarities

There are also other haematological conditions such as paroxysmal nocturnal haemoglobinuria (PNH) and myeloproliferative disorders that can lead to an increased propensity to form clots. These should also be considered if investigating for thrombophilia, particularly where rare or unusual thrombus occurs (i.e. intra-abdominal) but they would commonly have an associated abnormality on the full blood count.

Treatment of venous thrombosis

When a patient presents with venous thrombosis, initial treatment is usually with low molecular weight heparin (LMWH) followed by warfarin or a direct oral anticoagulant (DOAC). Apixiban, Dabigatran, Edoxaban and Rivaroxaban are all licensed DOACs and are in increasing use. Decisions need to be taken regarding the length of treatment based on an assessment of risk factors, depending on whether it was provoked, the family history, whether hereditary thrombophilia is present, whether symptoms have resolved and if the risk factors present are modifiable or are going to resolve.

Post-operative deep vein thrombosis (DVT) without other suspected predisposition can usually be treated for 3 months, previously treatment for pulmonary embolus (PE) was given for 6 months, although there are more recent suggestions that 3 months may be adequate for PE if long-term anticoagulation is not indicated. When considering the risks of repeat events it is worth bearing in mind that it is most common to have the same type of event again, so if a patient has a PE they are more likely to have a further PE rather than DVT. There is evidence now to suggest that a raised d-dimer following the completion of treatment can be predictive of a repeat clot and this may be taken into account and a discussion between patient and medical team about the risks of recurrent clot versus the risks of side effects/bleeding on the anticoagulant is needed to decide if long-term anticoagulation should be continued. Decisions on anticoagulation need to be reviewed and the risk benefit balance needs to be reassessed if there is a change in the patients' situation.

Managing a patient on anticoagulation who needs surgery

Managing a patient on anticoagulation in an emergency requires consideration of how best to reverse it (if possible). For an elective procedure 'bridging' anticoagulation should be considered, depending on whether the patient is low or high risk for clotting (i.e. atrial fibrillation (AF) is low risk, compared with metallic heart valve or recent clot-high risk) and whether surgery is low or high risk for serious bleeding (tonsillectomy would be considered a high risk procedure in terms of bleeding, dental extraction of tooth low risk). If the patient is low risk and the surgery high risk, discontinuation of anticoagulation may be required. However if the patient is high risk and the surgery low risk it may be reasonable to continue as normal. In the middle of these extremes it may be necessary to switch onto an alternative, such as from warfarin to LMWH, which can be discontinued 24 hours before the procedure and restarted when haemostasis is secured post-operatively (24–48 hours). With NOACs generally, their half-life allows discontinuation 24–48 hours prior to an operation depending on renal function (although up to 5 days may be advisable in some cases). Where a clot has occurred recently (within 6 weeks to 3 months) an IVC (inferior vena cava) filter may be considered to add a level of protection from PE on the discontinuation of anticoagulation for theatre. Filters should be removed as soon as possible post-procedure otherwise they become permanent and have potential long-term complications. Again, discussion with the anticoagulation team or haematologist should be helpful in managing these situations

Medication affecting haemostasis

WARFARIN/COUMARINS

Warfarin is often described as a Vitamin K antagonist. It does not actually antagonize Vitamin K but it inhibits the enzyme that recycles Vitamin K (Vitamin K epoxide reductase) and therefore active Vitamin K will run out, which usually takes 2–3 days. The Vitamin K dependent

clotting factors are depleted (II, VII, IX and X), leading to increased bleeding tendency and the intended benefit of reducing clot formation. However, when it is first initiated patients are rendered prothrombotic because protein C and S are also dependent on Vitamin K and their levels can reduce before the other factors. When patients present with an acute clot it is advisable to overlap initial treatment with LMWH and warfarin until therapeutic. All coumarins have a narrow therapeutic window and, due to various polymorphisms, are metabolized with a lot of inter-individual variation. Warfarin needs to be monitored by the international normalized ratio (INR). The INR is a PT ratio of the patients compared to normal, to the power of an adjustment factor called the ISI that is specific for the laboratory. This gives a result that is comparable amongst laboratories internationally. The indications for coumarins include: treatment of VTE; prevention of VTE; anticoagulation for prosthetic heart valves; and reduction of stroke risk in AF. Patients may be on them for a period of a few months, or may be on lifelong treatment. The most common side effect is bleeding.

REVERSING A RAISED INR DUE TO WARFARIN

The availability of product needs to be taken into consideration if the patient is bleeding and also how quickly reversal is required. In reversing a patient's anticoagulation there should always be discussion with your haematologist. The need for reinstating anticoagulation also needs to be considered.

HEPARIN AND LOW MOLECULAR WEIGHT HEPARIN

Unfractionated heparin (UFH, administered by intravenous infusion) acts by binding to antithrombin and causing a conformational change. The antithrombin then inactivates thrombin, along with the other proteases, mostly factor Xa. Low molecular weight heparins (LMWH, administered by subcutaneous injection) are much smaller molecules so their mechanism of action is mediated more predominantly through anti-factor Xa action. The main indications for these drugs are acute VTE or coronary thrombotic event. Some patients remain on LMWH long term, particularly those with malignancy. Unfractionated heparin (UFH) is monitored by APTT ratio and LMWH by anti-factor Xa levels. Most patients do not require monitoring of LMWH (the exceptions where it is useful include children, pregnancy, renal impairment, obesity and when in long-term use).

There is no specific reversal treatment, although protamine sulphate can have some neutralizing effect if given soon after administration, particularly when IV unfractionated heparin has been used. It is much less predictable in subcutaneous LMWH reversal and can act as a weak anticoagulant in its own right in high dose. Prior to surgery, UFH will be fully reversed if stopped 6 hours before with normal renal function; LMWH prophylaxis dose should be last given 12 hours before procedures and treatment doses 24 hours before.

OTHER PARENTERAL ANTICOAGULANTS

These are rarely used. Danaparoid is a heparinoid with mostly anti-Xa action and a little anti-IIa activity. It is renally excreted with no specific antidote. Fondaparinux is a pentasaccharide (synthetic) that acts indirectly through its anti-Xa activity. Again, it is renally excreted with no specific antidote. Bivalirudin is a direct thrombin inhibitor and has a short half-life but IV infusion is required for ongoing anticoagulation, so stopping it and general haemostatic measures are usually adequate.

DIRECT ORAL ANTICOAGULANT AGENTS (DOACS)

Dabigatran is an oral direct thrombin inhibitor. It has a half-life of 13 hours and is mostly excreted by the kidney. There is a specific antidote available called Idarucizumab for use in an emergency setting.

Rivaroxaban, Apixaban and Edoxaban are direct anti-Xa inhibitors. Both are 75% metabolized by the liver with 25% excreted unchanged by the kidney. They are both used as prophylaxis or treatment in VTE or used in stroke prevention in atrial fibrillation. Emergency management of bleeding consists of general haemostatic measures and use of prothrombin complex concentrate (PCC), activated PCC, also known as factor eight bypassing agent (FEIBA) or rFVIIa as there are no specific antidotes currently available,[12] although reversal agents have been developed and are likely to be available shortly

ANTIPLATELET AGENTS

Antiplatelet agents (i.e. aspirin, clopidogrel, dypirimdamole, ticagrelor, abciximab, other NSAIDs, prasugel)

TABLE 26.4 Reversing a raised INR

Product/drug	Dose	Advantages	Disadvantages
Vitamin K	0.5–10 mg	Cheap	Slow, takes over 7 hours for detectable effect and takes up to 24 hours for complete reversal
FFP	15 mls/kg	Cheap	Plasma product, not very effective as doesn't replace some of the factors enough
Prothrombin complex concentrate (ideally 4 factor)	25–50 units/kg	Quick to act	Plasma product with more of factors II, IX and X
rVIIa	90 mcg/kg	Quick to act	Expensive, prothrombotic; not viewed as first line treatment

generally have a short half-life although the length of effect depends on whether the effects are irreversible or not. There are no specific reversal agents. If they have irreversible binding (like aspirin) the action lasts as long as the life of the platelets, and in many cases they need to be discontinued 7–14 days before procedures where possible. The mechanism of action of most of the agents is as P2Y12 antagonists or as GP IIb/IIIa inhibitors.

Aspirin acts by irreversibly inhibiting cyclo-oxygenase (COX) 1 and 2 (in contrast to some NSAIDs that reversibly act). Aspirin in low dose blocks the formation of thromboxane A2 in platelets for the life of the platelet; however, there is little effect on prostacyclin (because endothelial cells have a nucleus to produce further enzyme to produce more prostacyclin). The balance of increasing prostacyclin and reducing thromboxane A2 inhibits platelet aggregation. Platelet transfusion is the only way to reverse the effects of antiplatelet agents and only really helps if the drug has not been taken recently (otherwise the transfused platelets will also be affected).

FIBRINOLYTIC AGENTS

Fibrinolytic agents (i.e. streptokinase, tenecteplase, urokinas) all act by promoting plasmin indirectly and thus mediating clot breakdown. They are short acting and all potentially give a high bleeding risk. They are most commonly used in the acute management of stroke and myocardial infarction. In the event of serious bleeding, use of tranexamic acid and FFP or fibrinogen concentrates is indicated with other treatment guided by coagulation tests.

BLOOD PRODUCTS AND FACTOR REPLACEMENT IN BLEEDING DISORDERS

Included in this section is a brief summary of products.[13,14] Most of the coagulation factor therapies are either very expensive or extremely expensive. When available, recombinant factor concentrates are preferred as there is almost zero risk of infection transmission. In the 1980s, plasma derived coagulation factors caused tremendous (unintentional) suffering in a generation of patients with transmission of HIV/AIDS, and hepatitis B and C. Concerns over transmission of prion (specifically vCJD) have led to the UK government abandoning all UK sourced blood donors as sources for plasma factor concentrates. In an era of significantly improved safety of product and increased knowledge regarding use of prophylactic treatment the younger generations of patients have a good chance of not developing such disabling chronic joint problems that previous generations have suffered.

Platelets

Platelets are suspended in patient plasma, either apheresis units from one donor or pooled units from a few donors. Each unit is approximately 250 ml and they are stored at 22 °C. They are therefore a higher risk for bacterial transfusion transmitted infection. Usually used as one adult dose, more may be required in order to gain an appropriate increment for surgery. They are useful in major haemorrhage, platelet dysfunction and bone marrow failure; but are generally not indicated in ITP or TTP, except with life-threatening bleeding. They are generally administered over 15–30 minutes.

Fresh frozen plasma

Plasma is the 'liquid' part of the blood, therefore it contains coagulation factors. It is indicated for bleeding where there are abnormal coagulation results. Fresh frozen plasma (FFP) is used to correct multiple coagulation factor defects and in major haemorrhage. It is also beneficial as replacement of congenital factor deficiency where a specific concentrate is not available.

Dosing is usually 15 mls/kg (approximately 4 units in a 70 kg adult). Each unit is given over around 15–30 minutes. They must be defrosted prior to being issued and made from human plasma.

Cryoprecipitate

Cryoprecipitate is made by the controlled thawing of FFP to produce a cryolobulin concentrate, which is rich in fibrinogen, FVIII and von Willebrand factor. It is administered over 15–30 minutes and a dose of 2 pooled units would be expected to give a rise of 1 g/L in fibrinogen. It is mainly used as a more concentrated form of fibrinogen compared to FFP (see also fibrinogen concentrate).

Prothrombin complex concentrate

Prothrombin complex concentrate (PCC) can be 3 or, ideally, 4 factors (II, VII, IX and X but also contains protein C and S). It is made from human plasma. Dosing is usually 25–50 units per kg. It is indicated for reversal of warfarin and can be used in liver disease, especially where volume overload is a problem or in bleeding with DOACs.

Recombinant factor

This is available following discovery of the genes used in production of factor (first used in FVIII). It is produced by recombinant DNA technology, whereby a cell line (usually animal-based) is modified to express the gene that produces the factor protein. Therefore no exposure to human plasma occurs and a high purity, safe product is formed. They have no risk of transmission of blood-borne virus or prion. Currently there are recombinant products for FVIII, FIX and rVIIa. Other factors are becoming available including Factor XIII.

Plasma derived factor concentrate

There are specific factor concentrates available for FVIII, IX, X, XIII and von Willebrand disease (containing

VIII and vWF). They are treated to reduce risks associated with administration of human plasma but still carry a possibility of infection transmission. They are rarely used where a recombinant factor is available and affordable.

Fibrinogen concentrate

Fibrinogen concentrate is currently licensed for congenital fibrinogen disorders, although some centres are using it in acquired states of low fibrinogen. It is made from donor plasma, but again has had viral inactivation treatment.

Intravenous immunoglobulin

This product is made from large pools of donor plasma. It is used in the treatment of autoimmune phenomena (i.e. ITP). In other settings it is also used as replacement therapy in hypogammaglobulinaemia and targeted against specific infection in the immunocompromised.

HOW TO GET THE BEST FROM YOUR LOCAL HAEMATOLOGIST

Most patients with a significant bleeding or thrombotic disorder should be managed in conjunction with the clinical and laboratory haematology team so that a perioperative treatment plan can be agreed upon. Discussion is needed to weigh up the risk factors for bleeding and thrombosis. It is important the patient is aware of the management plan, particularly as many are experts in their own condition.

This section gives some guidance on how to get the best advice.

Information to communicate to a haematologist about a bleeding patient

- The patient's personal history regarding bleeding (previous procedures and obstetric history; severity of bleeds, i.e. requiring transfusion; type of bleeds i.e. mucocutaneous).
- Whether the patient has ever had treatment for bleeding or thrombosis.
- Their family history, especially regarding siblings, parents, children, grandparents, aunts/uncles' bleeding and how their condition was managed.
- Medication the patient is currently on or has previously used, especially anything that could lead to bleeding and, if they have a diagnosis, what product they usually have (i.e. factor brand, as it is usual to try and continue with the same one).
- Do they have an alert/ information card with diagnosis details and baseline factor levels?
- Ensure FBC, PT, APTT and fibrinogen results are available. Where possible if an elective procedure is planned results should be reviewed with time to carry out further investigations or the procedure should be delayed.
- What surgery is planned, with an idea of what bleeding would be expected in a haemostatically normal patient. Do not assume a haematologist will know a lot about procedures, particularly if new or complex.

For significant bleeding disorders it is usually advisable to carry out surgery at a centre of haemostasis expertise so the medical and laboratory advice is easily accessible. Usually, NSAIDs would be avoided, along with intramuscular injections. It is important to remember that patients on treatment may have a similar (or even higher) risk of thrombosis so VTE prophylaxis may still be indicated. In planning surgery patients may require admission even if the procedure is usually done as a day case for closer observation. Post-operatively they will require both clinical and laboratory assessment to guide further use of factor replacement.

Information to communicate to a haematologist about a clotting patient

- The patient's personal history regarding thrombosis including the type of clot, when it occurred and precipitants (i.e. hormones, perioperative, related to malignancy and treatment).
- Whether they have ever had treatment for bleeding or thrombosis.
- Their family history, especially regarding siblings, parents, children, grandparents, aunts/uncles' thrombosis and how it was managed.
- Medication they are currently on or have previously used, particularly anticoagulants and antiplatelets, and the indication.
- What surgery is planned. Do not assume a haematologist will know a lot about procedures, particularly if new or complex.

For advice on management of anticoagulation in an emergency (e.g. warfarin reversal in a patient who has attended A&E with significant bleeding) it is important to have information about why they are on the drug and how quickly reversal is required.

For warfarin, a weight is helpful so that dosing of PCC can be discussed. For LMWH, antiplatelets and DOACs it is important to know renal function and when the last dose was taken. Other comorbidities should be also taken into account to aid management.

The commonest cause of post-surgical bleeding is surgery

Post-surgical bleeding does not always equal a problem with the clotting system. Surgical causes and the need for a return to theatre should always be considered.

FUTURE RESEARCH

- More experience in direct oral anticoagulation agents (DOACs) and specifically in their reversal
- Further work on global coagulation testing and its applications
- Gene therapy as treatment and other novel therapies for haemophilia and other bleeding disorders

KEY POINTS

- Patients with bleeding disorders should be managed with close liaison between the haematology, laboratory and surgical teams.
- Pre-operative assessment should include bleeding history and medication. Where possible when screening coagulation tests are performed they should be reviewed with time for further investigation prior to procedures when needed.
- Bridging of anticoagulation therapy needs consideration for elective procedures.

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CHAPTER 27

DRUG THERAPY IN OTOLOGY

Wendy Smith

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: otitis externa, ear drops, antibiotics, betahistine, gentamicin, Menières, acyclovir and sodium fluoride.

INTRODUCTION

Medicines are commonly prescribed in the management of otological diseases. Whilst the efficacy of some treatments may be uncertain, it is important to understand how these drugs act, their indications, contraindications and side effects. This chapter discusses these factors in relation to a number of specific types of otological medications.

TOPICAL EAR PREPARATIONS

Ear drops are solutions or suspensions of medicaments in water, glycerol, diluted alcohol, propylene glycol or other suitable solvent for instillation into the ear. A solution comprises a solute (drug) dissolved in the solvent, whereas a suspension consists of an insoluble drug distributed in a liquid. Some preparations used in otology are also used as eye or nose drops. Since these drops are in multiple-application containers, the vehicle contains a bactericidal and fungicidal agent such as benzalkonium chloride (0.01%). Other adjuvants in ear and eye drops include buffers such as sodium metabisulphite and disodium edetate. The buffers are used to maintain the pH to minimize breakdown of the active constituents or to increase comfort for the patient. Both sodium metabisulphite and disodium edetate are effective at retarding oxidation reactions and the latter can enhance the bactericidal activity of benzalkonium chloride and chlorhexidine acetate. Information on excipients contained in drops is found in the British National Formulary or its equivalent. This information is useful since some patients may be allergic to topical ear medication and this allergy may not be to the primary constituent but to the excipients.

Ear drops are dispensed in coloured fluted glass bottles with a plastic screw cap incorporating a glass dropper tube and rubber teat, or, more commonly, in plastic squeeze bottles fitted with a plastic cap incorporating a dropper device. Such containers are designed to prevent light degradation of the contents.

Some ear preparations are available as creams or ointments where the antimicrobial and/or anti-inflammatory substance is prepared in a suitable base such as liquid paraffin, wool fat and yellow soft paraffin. Both are semi-solid preparations but in a cream the base is absorbed into the skin, whereas in an ointment only the medication is absorbed from the greasy base. In general, ointments are useful in dry scaly conditions whereas creams can also be used in weeping skin conditions.

Again, warnings that the preparation contains lanolin (wool fat) are useful since some patients are allergic to lanolin.

Topical ear preparations for inflammatory and infective conditions

INDICATIONS

A number of topical ear preparations in the form of drops or ointments are available for the treatment of otitis

externa and discharging mastoid cavities. Many are also used in discharging ears with a perforated tympanic membrane or ears with a grommet *in situ*. In this latter situation this is an unlicensed indication for the use of many of these preparations. Manufacturers' data sheets continue to state that even plain steroid drops are contra-indicated in the presence of a perforation. In chronic suppurative otitis media, it has been shown that aural toilet and topical antibiotics, especially a quinolone, is effective in resolving otorrhoea and eradicating bacteria from the middle ear. This treatment used by specialists is now recognised in the BNF.[1] Topical antibiotic preparations are more effective than oral preparations and the addition of oral therapy to topical antibiotics confers no greater benefit than the latter used alone.[2]

SPECIFIC PREPARATIONS

Acetic acid 2% has antifungal and antibacterial properties and can be used to treat mild otitis externa. Aluminium acetate is an astringent that can be applied as drops or onto a gauze wick. An astringent is an agent that causes shrinkage or constriction and is usually applied topically. The hydroscopic effect reduces oedema in the inflamed ear canal, opening the meatus. Aluminium acetate has a tendency to form crystals in the ear. Regular aural toilet is required to remove both the crystals that form as well as the debris produced by the inflammatory process. This treatment can be safely used in pregnancy. Boric acid has been used in the past for its weak fungistatic and bacteriostatic activity and is used as a mild disinfectant in lotions, ointments and powders in concentrations of up to 5%. It is absorbed through damaged skin and may cause systemic toxicity. Acute and chronic toxicity can occur, presenting with gastrointestinal disturbance, rash, central nervous system and renal involvement that may result in death. Slow excretion of boric acid can lead to cumulative toxicity during repeated use.

Some preparations contain only a steroid and are used in eczematous otitis externa. The steroid reduces inflammatory swelling and helps control irritation. The steroid stimulates the synthesis of lipocortin in leukocytes. This protein inhibits phospholipase A_2 that reduces the formation of arachidonic acid, the precursor of many inflammatory mediators. Betamethasone sodium phosphate (Betnesol®) and prednisolone sodium phosphate (Predsol®) are steroids available as ear drops. These steroids are combined with anti-infective agents for use in the management of infected otitis externa. Other steroids found in combination with anti-infective drugs include dexamethasone (Otomize® – with neomycin and glacial acetic acid; Sofradex® – with framycetin sulphate and gramicidin), flumetasone pivalate (Locorten-Vioform® – with flumetasone pivolate and clioquinol), hydrocortisone acetate (Gentisone HC® – with gentamicin; Neo-Cortef® – with neomycin sulphate) and triamcinolone acetonide (Audicort® – with neomycin undecanoate and Tri-Adcortyl Otic® – with gramicidin, neomycin and nystatin). Clioquinol (found in Locorten-Vioform) is an 8-hydroxyquinolone with both antibacterial and antifungal properties and is useful when a mixed infection is suspected. Its use is contra-indicated in patients with iodine sensitivity. The other antibiotics included in ear preparations are framycetin sulphate, gentamicin and neomycin sulphate which are all aminoglycosides. They are bactericidal, inhibiting microbial protein synthesis and are effective against aerobic Gram-negative bacteria. Bacteria may acquire resistance via plasmids against one aminoglycoside but these bacteria rarely exhibit resistance to other aminoglycosides. This accounts for the benefit in changing the ear drops if the otitis externa fails to respond to one preparation.

Some of these preparations are available as ear sprays (Otomize), and there is some evidence that these cover the external meatus more effectively than traditional ear drops[3] and are easier for the elderly to apply. However, in some clinical situations, drops are more likely to reach the infected and inflamed parts of the external ear, middle ear or mastoid cavity at which treatment is aimed. Prolonged use of antibiotic/steroid preparations may sensitize the skin and may lead to fungal infections.

Clotrimazole is an azole derivative with a broad-spectrum antifungal activity that acts by inhibiting ergosterol synthesis in the fungal cell membrane. At lower concentrations, clotrimazole merely inhibits fungal growth but at higher concentrations, fungi are killed by clotrimazole action causing direct membrane damage. Clotrimazole should be continued for at least 2 weeks after apparent resolution of the infection. Increasingly, ciprofloxacin eye drops are used as ear drops in the management of *Pseudomonas* spp. ear infections. This is an unlicensed use in the UK where licensed ciprofloxacin ear drops are unavailable. Ciprofloxacin drops have been used widely in the rest of Europe, North America and beyond.

CONTRAINDICATIONS

The use of preparations containing only a steroid is contraindicated in untreated infections since the immunosuppressive effect of corticosteroids may exacerbate the infection. More controversial is the use of preparations with anti-infective agents in the presence of a perforated tympanic membrane because of the potential for ototoxicity.

SIDE EFFECTS

The most common side effects with these preparations are hypersensitivity reactions and local irritation, burning and itching.

The use of anti-infective ear drops in the presence of a tympanic membrane perforation

The product licences do not permit the use of anti-infective ear drops in ears with perforated tympanic membranes as a result of cochlear damage that occurred when such drops were instilled into guinea pig ears.[4, 5] These authors

recognize that the round window niche in humans is relatively deep and often protected by a pseudomembrane whilst in the guinea pig the round window is completely exposed. In patients with active chronic suppurative otitis media there is no evidence that the use of these ear drops causes sensorineural deafness.[6–8]

Topical ear preparations for removal of ear wax

Many cerumenolytics, including oils and aqueous preparations, are available to soften wax prior to syringing or to disintegrate or disperse the wax, to avoid the need for syringing altogether. Burton and Dorée[9] undertook a systematic review and found nine clinical trials. All had a small number of participants, and most were of poor methodological quality. The review concluded that there is insufficient evidence to favour any one particular cerumenolytic. Water and sodium chloride 0.9% seem to be as effective as any proprietary agent. Sodium bicarbonate 5% ear drops, olive or almond oil ear drops are also safe and inexpensive although their effectiveness has not been evaluated in randomized controlled trials. These findings were supported by Clegg et al. in a more recent systematic review.[10] If the wax is impacted, these drops can be used twice a day for a few days prior to syringing. Some proprietary preparations contain organic solvents (chlorbutanol, paradichlorobenzene) that may cause irritation to the meatal skin. The rational for inclusion of these ingredients in the preparations is not clear and the vehicle alone is often effective.

SYSTEMIC ANTIBIOTICS

Indications

Systemic antibiotics are prescribed in the otological conditions of acute otitis media (AOM), cellulitis associated with furunculosis, otitis externa and perichondritis.

In AOM, the use of antibiotics is controversial. Venekamp et al.[11] found that antibiotic usage in AOM in children varied from 31% in the Netherlands to 98% in the USA and Australia. Their Cochrane review concluded that antibiotics provide a small benefit; however, since most cases resolve spontaneously, this benefit must be weighed against possible adverse reactions. Twenty children must be treated to prevent one child from having pain after 2 days. Antibiotic treatment did however produce a statistically significant reduction in tympanic membrane perforations and contralateral AOM episodes. Antibiotic treatment may play an important role in reducing the risk of mastoiditis in populations where it is more common. It is recommended that in children without systemic features, antibacterial treatment may be started after 72 hours if no improvement or earlier if systemically unwell or if at a high risk of serious complications (patients who are immunocompromised, the presence of mastoiditis or in children under 2 years with bilateral otitis media). If antibiotics are used, amoxicillin appears to be the first-line treatment, with clarithromycin in those who are penicillin sensitive. Should treatment fail, second-line agents include co-amoxiclav and cephalosporins. Usually 5 days treatment is required but may be longer if severely ill.

Conservative management of acute mastoiditis (without subperiosteal abscess) has been adopted since a third of patients will settle in 24–48 hours with intravenous antibiotics.[12–14]

Flucloxacillin is the antibiotic of choice in treating cellulitis due to staphylococcus. Penicillin V is used in erysipelas due to streptococcus.

Ciprofloxacin is the drug of choice in malignant otitis externa and is also used in treating perichondritis due to *Pseudomonas aeruginosa*.

Mechanisms of actions

The penicillins have a bactericidal action, inhibiting cell wall synthesis by preventing the formation of peptidoglycan cross-bridges. The penicillinase-resistant penicillins, flucloxacillin, cloxacillin and methicillin, are semisynthetic penicillins, resistant to penicillinase by virtue of an isoxazolyl group on R_1. Many bacterial β-lactamases are inhibited by clavulanic acid, and a mixture of this inhibitor with amoxicillin (co-amoxiclav) is available. The cephalosporins are also bactericidal. They contain a β-lactam ring and their mechanism of action is similar to the penicillins.

The macrolides, for example erythromycin, act by inhibiting bacterial protein synthesis. It binds to the 50s bacterial ribosome subunit inhibiting translocation.

Metronidazole was initially used in protozoal infections but was found to be very effective against anaerobic bacteria. The drug is reduced to active metabolites that interfere with nucleic acid function. Ciprofloxacin is a fluoroquinolone and acts on both stationary and dividing bacteria by inhibiting DNA gyrase, an enzyme that compresses the bacterial DNA into supercoils. Cell death is thought to occur as a result of the unwinding of the supercoils.

Antibacterial spectrum

Table 27.1 demonstrates the antibacterial spectrum of the various antibiotics. The penicillinase-sensitive penicillins have a greater spectrum of activity than the β-lactamase resistant drugs, but the combination of clavulanic acid with amoxicillin enables protection of the β-lactam ring, allowing this essential part of the penicillin molecule to remain active.

Dosage

Specific dosage recommendations can be found in the British National Formulary.[1] Phenoxypenicillin, amoxicillin and flucloxacillin have better oral absorption than ampicillin but all should be taken at least 30 minutes before food since they are destroyed, to some extent, by gastric acid. The penicillins have good penetration to most tissues but poor entry to CSF (overcome by giving higher doses intravenously). Dosage modification is required in patients with severe renal failure.

TABLE 27.1 The antibacterial spectrum of antibiotics

Penicillins	**Antibacterial spectrum**
Benzylpenicillin and phenoxymethylpenicillin	Streptococcal, non β-lactamase producing staphylococcal, pneumococcal, clostridial infection, meningococcal, gonococcal, spirochaetes (syphilis), anthrax, actinomycosis
Ampicillin and amoxicillin	As above and *Strep. faecalis*, most *Haemophillus influenzae* and many coliforms
Methicillin, cloxacillin, flucloxacillin	Similar to penicillin but less active. Stable to staphylococcal β-lactamase
Carbenicillin and ticarcillin	Similar to amoxicillin and in addition activity to *Ps. aeruginosa*, most *Proteus* spp. and against bacteroides
Mezlocillin, azlocillin, piperacillin	Similar to ticarcillin and in addition to *Klebsiella* spp. and greater activity against pseudomonads
Mecillinam	Coliforms, little activity against Gram-positive bacteria
Cephalosporins	**Antibacterial spectrum**
First generation: cephaloridine, cephalothin, cephalexin, cefradine and cephazolin	Broad spectrum except against *Strep. faecalis, Ps. aeruginosa, H. influenzae* and *Bacteroides* spp. Staphylococcus is sensitive, except for MRSA
Second generation: cefaclor, cefuroxime, cefamandole, cefoxitin	Broad spectrum with stability against β-lactamases. Active against *H. influenzae* and *Bacteroides* spp. but less activity against staphylococcus
Third generation: cefotaxime, latamoxef, ceftazidime, cefsulodin, ceftriaxone, cefixime, cefpodoxime proxetil Fifth generation: ceftaroline fosamil	As for second generation but also active against *Ps. Aeruginosa* Similar to cefotaxime but also against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* and multidrug-resistant *Streptococcus pneumonia.*
Macrolides: erythromycin, azithromycin, clarithromycin	See penicillins but also active against *H. influenzae*, *Bord. Pertussis*, *Bacteroides* spp., *Campylobacter* spp. *Legionella pneumophilia*, *Mycoplasma pneumoniae* and *Chlamydiae*
Sulphonamides and trimethoprim: co-trimoxazole	Broad, active against Gram-positive and Gram-negative bacteria except *Ps. aeruginosa*
Aminoglycosides: gentamicin, tobramycin, netilmicin, amikacin, kanamycin and neomycin Carbapenems: imipenem, meropenem, doripenem and ertapenem	Coliforms, *Ps. aeruginosa* and staphylococci; streptomycin; mycobacteria Broad spectrum of activity including many Gram-positive and Gram-negative bacteria and anaesrobes.Good activity against *Pseudomonas aeruginosa* except ertapenem
Vancomycin	Staphylococci including MRSA, streptococci and clostridia
Tetracyclines: tetracycline, chlortetracycline, oxytetracycline, doxycycline, minocycline	Broad; Gram-positive and -negative bacteria, brucellae, *M. pneumoniae,* rickettsia, *Coxiella burneti* and *Chlamydiae*. Some resistance to *Strep. pyogenes*, pneumococci and *H. influenzae*. *Ps. aeruginosa* and *Proteus* spp. resistant
Metronidazole	Anaerobic bacteria and protozoa
Ciprofloxacin	Broad; Gram-negative bacteria including *Ps. aeruginosa*, staphylococci including MRSA, streptococci less sensitive
Monobactams: aztreonam	Narrow, active against aerobic Gram-negative bacteria (less sensitive to *Ps. aeruginosa*)

Ciprofloxacin can achieve high concentrations in bone and soft tissue, even after oral administration. A dosage of 1.5 g daily over a period of 6–12 weeks has been recommended in the treatment of malignant otitis externa.[15, 16]

Contraindications

In all cases the prescribing of these drugs is contraindicated when the patient is known to be allergic to the ingredients or related compounds. Immediate hypersensitivity to penicillins occurs in 0.05% of patients, the severity of which ranges from urticaria or wheezing to a life-threatening anaphylactic response. Less than 5% of patients may develop a delayed hypersensitivity response to penicillins, usually a rash. Occasionally, haemolytic anaemia, leukopenia and interstitial nephritis may occur. There is a 10% hypersensitivity crossover with cephalosporins.

Precautions

The prolonged use of antibiotics may result in superinfection with unsusceptible organisms. There is no evidence that the penicillins, cephalosporins or erythromycin are hazardous in pregnancy but metronidazole should be avoided in high dosages and ciprofloxacin must be avoided in all trimesters of pregnancy. Antibiotics are secreted into breast milk and ciprofloxacin should be avoided in lactation. Other antibiotics, such as the penicillins and cephalosporins, are secreted into breast milk but may not be harmful to the infant. Antibiotics, such as the cephalosporins and ciprofloxacin, cleared by the kidneys may require dosage adjustments in patients with renal impairment. Similarly, antibiotics metabolized by the liver, for example erythromycin, may require dosage adjustments or to be avoided in patients with liver failure.

Interactions

Before prescribing a specific medication, the reader is advised to check for interactions in, for example, The British National Formulary.[1] Antibiotics may lead to oral contraceptive failure, probably because of diminished enterohepatic circulation. The anticoagulant effect of warfarin is affected by the penicillins, macrolides, metronidazole and quinolones.

Erythromycin interacts with some antihistamines and cisapride, resulting in cardiac arrhythmias. It also increases the plasma level of a number of drugs.

Metronidazole produces a disulfiram-like reaction with alcohol. Acetaldehyde accumulates in the body producing facial flushing, headaches, palpitations, nausea and vomiting.

Indigestion, iron or zinc therapies must not be taken within 2 hours of ciprofloxacin since absorption of this antibiotic is significantly affected.

Side effects

Most antibiotics may produce diarrhoea, rashes, blood disorders, nausea and vomiting. Ampicillin and amoxicillin have a unique adverse effect, comprising a rash, in up to 90% of patients with mononucleosis or chronic lymphocytic leukaemia. Reversible hearing loss has been reported with erythromycin. Angioneurotic oedema and anaphylaxis are, fortunately, relatively rare.

PREPARATIONS USED IN THE MANAGEMENT OF VERTIGO

Betahistine

Betahistine hydrochloride is commonly prescribed in the management of vertigo, usually when associated with Menière's disease or syndrome.

Betahistine is thought to reduce the endolymphatic pressure through improved microvascular circulation in the stria vascularis of the cochlear[17] or by inhibiting activity of the vestibular nuclei.[18]

There is insufficient evidence from high quality randomized trials to say whether or not betahistine has any effect on Menières.[19] It may reduce vertigo, and possibly tinnitus, but does not seem to influence the hearing loss.

Betahistine should be used with caution in patients with asthma, a history of peptic ulcer disease, in pregnancy and breastfeeding. It is contraindicated in patients with phaeochromocytoma. The side effects include gastrointestinal disturbance, headaches, rashes and pruritis; however, these are uncommon. Betahistine is prescribed initially at 16 mg three times a day; a maintenance daily dose of 24–48 mg has been recommended.

Dopamine antagonists

Prochlorperazine (Stemetil®) is a dopamine antagonist and acts centrally by blocking the chemoreceptor trigger zone and thereby blocking the vomiting centre. The vomiting centre also has afferent input from the vestibular apparatus. This region has a high concentration of muscarinic receptors and histamine H_1-receptors.

Prochloperazine belongs to group three of the phenothiazines. This means it has less sedative effects, fewer antimuscarinic effects but more pronounced extra-pyramidal side effects when compared to the other phenothiazine groups.

Prochloperazine is available as tablets, syrup, effervescent sachets, injection, suppositories and as a buccal preparation (Buccastem®). These last two preparations are useful because patients using prochlorperazine often vomit and fail to absorb the orally ingested form. The oral dosage varies from 5 mg three times a day increasing to 30 mg daily.

Antihistamines

The antihistamines are competitive antagonists of histamine at H_1-receptors, and their main action is on the vomiting centre rather than on the chemoreceptor trigger zone. They have weak anticholinergic effects and may occasionally produce a dry mouth and blurred vision. Drowsiness, occasional insomnia and euphoria are side effects that have been reported. These central effects are accentuated with alcohol. Cinnarazine (Stugeron®) and cyclizine (Valoid®) are less sedating than promethazine teoclate (Avomine®). Cinnarizine has been used in the prophylaxis and treatment of Menière's at a dosage of 30 mg three times a day. Cyclizine may be given in the acute attack orally or parentally at a dosage of 50 mg three times a day.

Gentamicin therapy in Menière's disease

Intra-tympanic gentamicin therapy was described by Beck and Schmidt[20] in 1978 and has been used both in Canada and the UK. Since its introduction, a variety of gentamicin dosage regimens and methods of administration have been developed and remain in clinical practice. These range from injection through the tympanic membrane, through a grommet or via intra-tympanic or round window catheters.

Other medical treatment for Menières disease

The use of salt restriction and diuretic therapy (hydrochlorothiazide, acetazolamide and co-triamterzide 50/25 (Dyazide®) are aimed at reducing the accumulation of endolymph. Although a study with Dyazide showed a reduction in vestibular symptoms, there was no effect on hearing loss or tinnitus. Acetazolamide may initially increase the hydrops and Brookes and Booth[21] concluded that this drug has no place in treating Menière's disease. Steroids and immunological therapy have also been proposed by those who believe that a disorder of the immune system underlies Menière's disease or syndrome.

DRUGS USED IN SUDDEN SENSORINEURAL HEARING LOSS

Corticosteroids

Steroids are commonly used in patients with sudden sensorineural hearing loss (SSNHL), but evidence for their effectiveness is lacking. There are several alternative dosage regimes when a 'short reducing course' of steroids is required. One such consists of enteric-coated prednisolone, 60 mg on the first day, 50 mg on the second day, 40 mg daily for 3 days, 30 mg daily for 3 days and a further reduction so that therapy is discontinued after 3 weeks.

Antiviral agents

Aciclovir (acycloguanosine) is an antiviral agent active against herpesviruses and is prescribed in patients with Ramsay Hunt syndrome (herpes zoster oticus). It acts by inhibiting nucleic acid synthesis. Herpes simplex and varicella zoster contain a thymidine kinase that converts the aciclovir to a monophosphate that is then phosphorylated by the host cell enzymes of acycloguanosine triphosphate that inhibits viral DNA polymerase and viral DNA syntheses. Selectivity for infected cells is achieved since the DNA polymerase of herpesvirus has a much greater affinity for the activated drug than the cellular DNA polymerase.

Aciclovir may be administered orally at a dosage of 800 mg five times a day for 5 days. If treatment is commenced prior to 72 hours after the onset of the rash, acyclovir may shorten the rash duration and acute symptoms and reduce the incidence of post-herpetic neuralgia.[22] Aciclovir should be used with caution in patients with renal impairment or who are pregnant or breastfeeding. Side effects include nausea, vomiting, gastrointestinal disturbances, rash, photosensitivity and, rarely, hepatitis, acute renal failure and neurological reactions. Two newer antiviral agents are famiclovir (a prodrug of penciclovir) and valaciclovir (an ester of aciclovir), which, depending on indication and co-morbidities, are administered up to three times a day (see British National Formulary[1] for further details).

SODIUM FLUORIDE TREATMENT IN OTOSCLEROSIS

Sodium fluoride has been used for 35 years in an attempt to slow down or arrest sensorineural hearing loss in patients with stapedial otosclerosis or after stapedectomy. It has also been used in patients with 'pure' cochlear otosclerosis.

Sodium fluoride is an enzyme inhibitor and reduces osteoclastic bone resorption. The clinical benefit of sodium fluoride is controversial. Causse et al.[23] found that in 'otospongiosis-otosclerosis', sodium fluoride influenced the underlying bony changes in the labyrinth so as to arrest or prevent the onset of hearing loss. In their prospective clinical double-blind, placebo-controlled study of 95 patients, Bretlau et al.[24] found that there was a statistically worse deterioration of hearing loss in the placebo group than in the active treated (40 mg sodium fluoride daily) group. Further work by Colletti[25] showed benefit in 50% of patients 5 years after a 2-year treatment with sodium fluoride (dosages up to 16 mg/day). Cruise et al. in a review of the literature 1966 to 2009 concluded that there is low evidence suggesting sodium fluoride may be of benefit to preserve hearing and reduce vestibular symptoms in patients with otosclerosis.[26] Treatment doses used vary greatly and the optimum treatment time has yet to be determined. Deka et al.[27] suggested the use of Florical at a dosage of two capsules three times a day in active cochlear otospongiosis. Their study showed that variation in absorption occurs with the use of different preparations and also amongst individuals.

The side effects of sodium fluoride need to be considered. In a prospective case-controlled study of ten patients with otosclerosis receiving sodium fluoride 30 mg/day and matched healthy volunteers, Das et al.[28] found a high incidence (70%) of dyspeptic symptoms in those taking sodium fluoride, as well as histological and electron microscopic abnormalities.

BEST CLINICAL PRACTICE

- ✓ Before prescribing, ensure that the patient is not known to be allergic to the medicine or adjuvants (such as the preservatives).
- ✓ Ensure medication does not interact with patient's established medication or medical conditions.
- ✓ Prescribe medicines at the lowest dose for the shortest time that is effective.
- ✓ Review whether medication is still required.

FUTURE RESEARCH

- ➤ There is insufficient evidence to favour any one particular cerumenolytic and a randomized controlled trial may be useful to determine the most clinically and cost-effective preparations for this purpose.
- ➤ There is insufficient evidence from high-quality randomized trials to determine whether betahistine, diuretics, steroids and immune therapy have any effect in Menière's disease.

KEY POINTS

- Topical ear preparations can be used for a limited period in discharging ears with a perforated tympanic membrane or a grommet *in situ*.
- The use of topical ear preparations containing a steroid only is contraindicated in untreated infections since the immunosuppressive action of the corticosteroid may exacerbate the infection.
- Flucloxacillin is the antibiotic of choice in cellulitis due to staphyloccus. Penicillin V is used in erysipelas due to streptococcus. Ciprofloxacin is the antibiotic of choice in malignant otitis externa.

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CHAPTER
28

DRUG THERAPY IN RHINOLOGY

Wendy Smith

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: acute rhinosinusitis, chronic rhinosinusitis, nasal polyposis, fungal rhinosinusitis and medical treatment. The chapter has also relied on a review produced by the European Rhinological Society and the European Academy of Allergology and Clinical Immunology (EAACI) that was published as a supplement by *Rhinology* in March 2012, and their abbreviations are used in this chapter.

INTRODUCTION

This chapter covers the medical treatment, in particular the use of corticosteroids and antibiotics, in managing the various types of rhinosinusitis. A separate section is devoted to other medicines that are used in the management of rhinosinusitis. Finally, other medical treatments used in rhinology are discussed under related topics.

Rhinosinusitis is a significant health problem that reduces the quality of life for individuals and places a large financial burden on society. The evidence for the effectiveness of medical treatment of rhinosinusitis has been reviewed by the European Rhinological Society (ERS) and the European Academy of Allergology and Clinical Immunology (EAACI), and the authors of this chapter have relied on the ERS/EAACI review.[1]

Rhinosinusitis is an inflammatory process involving the mucosa of the nose and one or more of the sinuses. Factors contributing to the inflammation include mucociliary impairment, bacterial infection, allergy, swelling of the mucosa for other reasons and mechanical obstruction. Inflammation around the osteomeatal complex is of particular importance and treatment is aimed at reducing the factors causing inflammation and ensuring adequate ventilation in this area. The classification of rhinosinusitis includes: acute rhinosinusitis (ARS) (viral or post-viral; a few of these having acute bacterial rhinosinusitis (ABRS)), and then chronic rhinosinusitis with (CRSwNP) or without (CRSsNP) nasal polyps.[1]

TREATMENT OF RHINOSINUSITIS WITH CORTICOSTEROIDS

Topical corticosteroids have improved the treatment of rhinosinusitis and asthma. Their efficacy may partly depend on their ability to reduce the viability and activation of eosinophils and to reduce the secretion of chemotactic cytokines by the nasal mucosa. This is mediated through activation of intracellular glucocorticoid receptors that are expressed in many tissues and cells. Other beneficial effects of steroids include: change of vascular permeability, reduction of mast cell degranulation and reduction of squamous metaplasia of allergic nasal polyps.

Acute rhinosinusitis (ARS)

In published studies, where either a placebo or a topical steroid has been added to antibiotic treatment for ARS, the results generally show that the patients who were treated with a topical corticosteroid improved more rapidly than

when the antibiotic was combined with a placebo. A representative study by Meltzer et al.[2] found Mometasone furoate 400 µg a day improved the symptom score more than placebo in patients with ARS also treated with amoxicillin clavulanate potassium for 21 days. Recently a double-blind, double-dummy, placebo-controlled trial found topical corticosteroid given twice daily as monotherapy to be more effective than amoxicillin twice daily in ARS[3] and has been supported by others[4, 5] as well as a Cochrane review.[6]

Gehanno et al.[7] looked at the effectiveness of systemic steroids in the treatment of ARS. Eight milligrams of methylprednisolone was given three times a day for 5 days as an adjunct to 10 days' treatment with amoxicillin clavulanate potassium in patients with ARS. The diagnostic criteria consisted of facial pain, purulent nasal discharge and purulent secretions from the middle meatus, together with opacities on CT scan. The conclusion was that there was no difference in the therapeutic outcome at day 14 between the steroid group and the placebo group, although 4 days after initiating treatment, the headache and facial pain was significantly less in the steroid group. A Cochrane review suggests systemic steroids may be a useful adjunctive therapy to oral antibiotics in the short-term relief of symptoms of ARS.[8]

There is very low evidence for a prophylactic effect of nasal corticosteroids in preventing recurrence of acute rhinosinusitis.[1]

Chronic rhinosinusitis without nasal polyps (CRSsNP)

Most studies compare topical steroid versus placebo as an adjunctive treatment to antibiotics. Two large trials of 407 and 967 patients, respectively, found that mometasone furoate produced a significant improvement in symptom score over the placebo. In one study topical steroid did not help the symptom of post-nasal drip[9] but it did in the second study.[10] There was no statistical difference in the CT findings of the treatment group compared with placebo.

A systematic review of level 1 or randomized controlled trials (RCTs) failed to demonstrate a universal benefit of local intra-nasal corticosteroids in CRSsNP. The method of delivery and post-surgical improved access were significant but the type of corticosteroid was not.[1] Epistaxis, dry nose, nasal burning and nasal irritation may occur as side effects to topical corticosteroid use but these are usually mild, the benefit outweighing the risk. There is a lack of clinical data to support the use of systemic corticosteroids in patients with CRSsNP.

Chronic rhinosinusitis with nasal polyps (CRSwNP): Topical steroids

In patients with CRSwNP the studies have tended to consider the effectiveness of the treatment on the rhinitic symptoms and then, as a separate outcome measure, the effect of the treatment on the size of the polyps. In a landmark paper published in 1979, Mygind et al.[11] showed that beclomethasone dipropionate (BDP) was more effective than placebo at reducing nasal symptoms in CRSwNP but no reduction in the size of the polyps occurred in 3 weeks.

A systematic review found 34 studies in which a topical steroid has been compared to placebo. Three compared two agents and three compared topical steroid against no intervention in patients with CRSwNP. Topical steroid is more effective than placebo in reducing symptoms, particularly nasal blockage. About half report improvement in sense of smell and reduction in polyp size. The response was greater in post-surgical patients; however, their improvement in symptoms and nasal flow was not statistically significant.[1]

A comprehensive study compared fluticasone propionate 400 µg daily, with BDP 400 µg daily and with topical placebo over a 12-week period in a double-blind randomized parallel group that was conducted in a single centre study.[12] The symptom score was significantly improved in the fluticasone group and the nasal cavity volume improved in both active treatment groups when measured with acoustic rhinometry. The peak nasal and inspiratory flow also improved in both active groups but the improvement was quicker in the fluticasone propionate group. After 12 weeks there was no difference statistically in the symptoms between the two active groups.

In conclusion, therefore, there is good evidence that topical corticosteroids improve the symptoms associated with nasal polyps, in particular nasal blockage, nasal secretions and sneezing, and in some patients they are effective at improving the sense of smell. In the majority of patients, topical corticosteroids also appeared to reduce the size of the nasal polyps, provided they were used for several weeks.

Chronic rhinosinusitis with nasal polyps (CRSwNP): Systemic steroids

A Cochrane review updated in 2010 identified three level 1 studies supporting the use of systemic steroids in CRSwNP. In one study, oral prednisolone was given in doses of 60 mg daily to 25 patients with severe nasal polyposis for 4 days and, for each of the following 12 days, the dose was reduced by 5 mg daily. Antibiotics and antacids were also given. Seventy-two per cent of patients experienced a symptom improvement due to the involution of polyps and in 52% of patients an improvement was seen on the CT. Nasal obstruction reduced and sense of smell improved. This study supports the general clinical impression that systemic steroids are highly effective in treating patients' symptoms whilst taking the systemic steroid but the beneficial effects seem to be lost once the steroid is stopped.[13] The chronic nature of CRSwNP has to be considered along with the short-lived benefits of systemic corticosteroids. Local corticosteroid treatment appears to be useful so long as it can be administered effectively.

The post-operative treatment of patients with chronic rhinosinusitis and nasal polyps (CRSwNP) with steroids

Six studies have found topical steroids do reduce the recurrence rate of nasal polyps after nasal polyp surgery. To quote from two of the representative studies, Karlsson and Rundcrantz[14] treated 20 patients with BDP and 20 were followed with no treatment after polyp surgery. The follow-up period was for 30 months. After 6 months, there was a statistically significant difference between the groups in favour of BDP and its effect increased during the study period over the next 30 months.

Hartwig et al.[15] used budesonide 6 months after polypectomy in a double-blind parallel group on 73 patients. In the budesonide group, 'polyp' scores were significantly lower than in the controls after 3 and 6 months. Interestingly, this difference was only significant for patients with recurrent nasal polyposis and not those who had had a polypectomy operation for the first time.

TREATMENT OF RHINOSINUSITIS WITH ANTIBIOTICS

The exact incidence of rhinosinusitis within populations is not known but it is a common condition for which antibiotics are frequently prescribed. According to the National Ambulatory Medical Care Survey in the USA, rhinosinusitis is the fifth most common diagnosis for which antibiotics are prescribed, accounting for 9% of all paediatric antibiotic prescriptions and 21% of all adult antibiotic prescriptions written in 2002.[16]

Recurrent acute rhinosinusitis

A recent Cochrane review compared antibiotics against placebo or between antibiotics of different classes in the management of acute maxillary sinusitis in adults.[17] Fifty-nine studies met the appropriate criteria for inclusion in this review and included six placebo-controlled studies and 53 comparing different classes or dose regimens of antibiotics. Compared to placebo only a slight statistical difference in favour of antibiotics was found although the clinical significance was equivocal with cure or improvement being high in both the placebo (80%) and antibiotic group (90%).

A previous Cochrane review in which comparisons were made between the newer non-penicillins (cephalosporins, macrolides, minocycline) versus penicillins (amoxicillin and penicillin V), no significant differences were shown. The rates of cure or improvement appeared to be 84% for both antibiotic classes. Adverse effects were infrequent with no significant difference between the two groups of antibiotics. Sixteen trials (4818 patients) compared newer non-penicillin antibiotics (macrolide or cephalosporin) to amoxicillin/clavulanate with similar cure or improvement rates (72%) but less adverse effects occurred with cephalosporin antibiotics. Relapse rates within one month of successful therapy did not differ between the groups.[18] Six trials, of which three were double-blinded (1067 patients), compared a tetracycline (doxycycline, tetracycline, minocycline) to a heterogeneous group of antibiotics (folate, cephalosporin, macrolide, amoxicillin) and no relevant differences were found.

The Cochrane reviewers[18] concluded that for recurrent ARS, confirmed radiologically, current evidence is limited but supports the use of penicillin or amoxicillin for 14–17 days. In the Cochrane review, local differences in susceptibility of microorganisms to antibiotics used were not acknowledged, although it is known that resistance patterns of predominant pathogens, such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, vary considerably.[19] The prevalence and degree of antibacterial resistance in common respiratory pathogens is also increasing worldwide, presumably because of the increase in antibiotic consumption. The choice of which antibiotic is used may depend on local resistance patterns and disease aetiology.

Antibiotic treatment for chronic rhinosinusitis

It is significantly more difficult to evaluate the efficacy of antibiotic treatment in chronic compared to intermittent ARS because of the difficulties of defining the clinical diagnosis of CRS in the literature. In many studies there is no radiological diagnosis and, therefore, data supporting the use of antibiotics in CRS are limited; however, a number of open studies using macrolides have shown a response rate of 60–80%.

In a double-blind prospective study by Legent et al.,[20] 251 adult patients with CRSsNP were treated with ciprofloxacin or amoxicillin/clavulanic acid for 9 days. Only 141 of the 251 patients had positive bacterial cultures from the middle meatus at the beginning of the study. At the end of the treatment period, the nasal discharge disappeared in 60% of the patients in the ciprofloxacin group and 56% of those in the amoxicillin/clavulanic acid group. The clinical cure and bacteriological eradication rates were 59% and 89% for ciprofloxacin versus 51% and 91% for amoxicillin/clavulanic acid, respectively. The differences were not significant. In 2002 Namyslowski reported the results of an open parallel randomized clinical trial of 206 adults with exacerbation of CRS had either amoxicillin/clavulanic acid or cefuroxime axetil. The clinical response was similar (95% and 88% respectively) as was the bacterial cure rate (65% and 68% respectively).[21] Short-term treatment of CRSsNP may be considered in exacerbations with a positive culture. In patients with CRSwNP one RCT has shown that doxycycline for 3 weeks had a small effect on polyp size and post-nasal discharge but no effect on other symptoms compared to placebo.[22]

There is some evidence that long-term treatment with low-dose macrolide antibiotics may be effective in treating patients with CRSsNP that has not been cured by surgery or corticosteroid treatment. In animal studies, macrolides have been shown to increase mucociliary transport and

reduce goblet cell secretion. There is evidence *in vitro*, as well as clinical experience, that macrolides reduce the virulence and tissue damage caused by chronic bacterial colonization without actually eradicating the bacteria, that is their action is immune-modulatory rather than anti-bacterial.

Clinical studies have shown that long-term treatment with macrolide antibiotics increases ciliary function.[23] In a prospective RCT, 90 patients with CRSwNP and CRSsNP were randomized to erythromycin for 3 months, or endoscopic sinus surgery, and followed up over a year. The outcome measures included a symptom score, the SNOT 22, the SF 36, nitrous oxide levels, acoustic rhinometry, saccharine clearance times and nasal endoscopy. Both the medical and surgical treatment of CRS significantly improved almost all the subjective and objective parameters with no significant difference between the two groups, or between CRSwNP and CRSsNP, except for the increase in total nasal volume, which was greater following surgery.[23] Further studies are necessary to determine the effect of long-term treatment with antibiotics in CRSwNP.

There are two placebo-controlled studies on the effectiveness of long-term antibiotic treatment. One using roxithromycin showed efficacy in patients with CRSsNP. The other study included CRSwNP as well and although more responded in the treatment group this was not significant. Data suggest patients with high IgE levels are less likely to respond to macrolide treatment than patients with normal IgE levels.[24] Studies comparing different antibiotics did not show any significant difference between ciprofloxacin versus amoxicillin/clavulanic acid. The few available prospective studies showed a positive effect on the patient's symptoms in 56–95% of patients.

Long-term low-dose macrolide treatment may be of use if surgery and/or steroids and saline irrigation have failed. Further placebo-controlled studies should be performed to establish the efficacy of macrolides if this treatment is to be accepted in the future. There is also an urgent need for randomized placebo-controlled studies to investigate the effectiveness of antibiotics in general for CRS.

There are three placebo-controlled trials with topical antibiotics in CRSsNP. None showed any additive effect compared to saline.[25–27] There are no data on the effect of topical antibiotics in CRSwNP.

TREATMENT OF RHINOSINUSITIS WITH OTHER MEDICINES

Decongestants

After corticosteroids and antibiotics, the medications that are perceived to be most useful for treating rhinosinusitis are decongestants. The rationale behind the use of decongestants is to improve sinus ventilation and drainage. Radiological studies using CT and MRI scanning show that topical decongestants markedly reduce the size of the inferior and middle turbinates and improve osteomeatal complex patency but have no effect on ethmoidal and maxillary sinus mucosa.[28, 29]

Experimental studies suggest that topical decongestants (xylometazoline and oxymetazoline) have a beneficial anti-inflammatory action that is caused by decreasing nitric oxide synthetase.[30] A controlled clinical trial showed improved mucociliary clearance *in vivo* after 2 weeks of oxymetazoline for ABRS when compared to fluticasone and hypertonic saline and saline. The clinical course of the disease between the three groups, however, was not significantly different.[31] This, together with another study using decongestants in addition to a penicillin treatment in acute maxillary sinusitis, suggests that decongestion of the sinus ostia is not of primary importance during the healing of ARS.[32]

Topical decongestants are also recommended for individuals who have problems clearing their ears while flying or diving. The decongestants are all alpha adrenergic agonists and act on the two types of alpha receptor, one of which controls the venous capacitance vessels of the nasal tissues, which are responsible for erectile function, and the other alpha receptors, which mediate contraction of arterioles that supply the mucosa.

Ephedrine nasal drops (0.5% and 1%) are weak sympathomimetics whilst oxymetazoline and xylometazoline are more potent causing intense vasoconstriction. The rebound effect that occurs after the vasoconstriction wears off is more with the potent decongestants and patients should be advised not to use topical decongestant for more than 10 days. In patients who become addicted to decongestant drops or sprays, there is a risk of developing rhinitis medicamentosa where the nasal mucosa becomes permanently damaged.

One preparation combines the steroid dexamethasone isonicotinate with the sympathomimetic tramazoline hydrochloride (Dexa-Rhinaspray Duo). The spray is promoted for the treatment of allergic rhinitis. The suggestion is that the decongestant allows better mucosal access for the steroid. Clinical experience suggests that this is a useful spray. The use of all sympathomimetic preparations is contraindicated in patients on monoamine oxidase inhibitors (MAOIs) and they should be used with caution in patients with hypertension, hyperthyroidism, cardiovascular disease, diabetes mellitus and closed angle glaucoma, and in infants of less than 3 months of age.

The use of decongestants for CRS has not been evaluated in any RCTs. There are no controlled trials to test the efficacy of decongestants for the treatment of nasal polyps.

Systemic decongestants appear to be less effective than local preparations but rebound nasal congestion on withdrawal of the drug does not arise. Pseudo-ephedrine is available over the counter in the UK, both in tablet form and as a linctus. Little evidence supports the use of systemic decongestants in the treatment of rhinosinusitis.

Mucolytics

The rationale for using mucolytics in the treatment of rhinosinusitis is to reduce the viscosity of the nasal secretions. There is minimal evidence to support the use of mucolytics in the treatment of rhinosinusitis. One RCT study

(report in Italian) suggests bromhexine is superior to placebo in acute rhinosinusitis.[33] In one paediatric study, an RCT did not prove bromhexine to be superior to saline inhalation for children with CRS.[34]

Antihistamines

These can be used orally and as a nasal spray. Clinical experience suggests that they reduce rhinorrhoea, sneezing and itching, but have little effect on nasal obstruction. There is no evidence that antihistamines reduce or abolish the symptoms of the common cold. The non-sedating antihistamines acrivastine (Semprex), cetirizine hydrochloride (Zirtek), desloratadine (Neoclarityn) and fexofenadine hydrochloride (Telfast) cause less sedation and psychomotor impairment because they penetrate the blood–brain barrier to a lesser degree than the older type of antihistamines. Side effects of antihistamines include hypotension, hypersensitivity reactions, extrapyramidal effect, dizziness, blood disorders and liver dysfunction.

In the treatment of ARS, the beneficial effect of loratadine (the predecessor of desloratadine) for patients with allergic rhinitis was confirmed in a multicentre randomized double-blind placebo-controlled trial. Patients receiving loratadine as an adjunct to antibiotic treatment suffered significantly less sneezing and obstruction on daily visual analogue scale (VAS) scores.[35]

In CRS there is little evidence that antihistamines are effective. However, they are often prescribed for patients with CRS, particularly in the USA. One randomized placebo-controlled trial on patients with residual or recurrent nasal polyps was identified using cetirizine 20 mg twice a day or placebo for 3 months. Inhaled steroids for asthma was allowed. The end point was poorly defined and no significant improvement in symptoms found using cetirizine over placebo.[36] The use of antihistamines may be useful in patients with CRSwNP with concomitant nasal allergies. No RCTs are identified for treatment of CRSsNP or CRSwNP with antihistamines without previous sinus surgery.

Sprays such as azelastine hydrochloride (Rhinolast) and levocabastine (Livostin) are topical antihistamines that are promoted for use in allergic rhinitis. Topical antihistamines are considered less effective than topical steroids and good evidence to support their use is lacking.

Sodium cromoglicate

Sodium cromoglicate is available as a 4% aqueous nasal spray (Rynacrom) and a 2% nasal spray (Vividrin), and it is also combined with xylometazoline (Rynacrom) and is promoted for prophylactic use in allergic rhinitis. Depending on the preparation, it needs to be taken either four or six times a day. Its mechanism of action is debatable; it was originally thought to act by preventing mediator release from mast cells. However, agents subsequently developed with this property do not demonstrate the same anti-asthmatic affects as cromoglicate. There is some evidence that cromoglicate depresses the exaggerated neuronal reflexes generated by irritant receptor stimulation. Side effects are few and include local irritation and transient bronchospasm. It may have a role in the treatment of allergic rhinitis in children but the fact that it needs to be taken several times a day means that compliance is low.

Antifungal agents used in rhinology

Fungal infections may be superficial or systemic. Antifungal agents can be classified into polyenes, fluocytosine, imidazoles and triazoles. The polyenes, amphotericin and nystatin interact with ergosterol in the fungal cell membrane. Pores are formed through which the fungal cell contents are lost. Selectivity is obtained since the human cell membrane contains mostly cholesterol rather than ergosterol.

Amphotericin has a wide spectrum of activity and is used parentally in severe systemic infections since oral absorption is poor. Side effects are common and include nausea and fevers. Renal impairment can occur but is reversible if detected early. Liposomal amphotericin is significantly less toxic but is more expensive. It is likely that it will become the agent of choice. Nystatin is used principally for *Candida albicans* infections of the skin and mucosal membranes.

Flucytosine is given orally or intravenously to treat systemic candidiasis or cryptococcal infections, often in combination with amphotericin to prevent resistance. Flucytosine is converted in fungal cells to flurouracil which inhibits DNA synthesis.

The imidazoles, miconazole, ketoconazole and clotrimazole, are mostly used to treat topical infections. They are broad-spectrum antifungals that prevent ergosterol synthesis. Ketoconazole is better absorbed by mouth than the other imidazoles but it has been associated with fatal hepatotoxicity.

The triazoles include fluconazole and itraconazole and both can be given orally and parentally. Itraconazole is active against Aspergillus but has been associated with heptatoxicity.

There has been interest in the role of fungi as a possible cause for the various types of rhinosinusitis. Antimycotics have been used topically and systemically and as an adjunct to sinus surgery in the treatment of allergic fungal rhinosinusitis, invasive fungal rhinosinusitis and conventional recurrent ARS.

Surgery is considered the first-line treatment for allergic fungal rhinosinusitis,[37] and surgery and systemic antimycotics are used in the treatment of invasive fungal rhinosinusitis.[38] Although the use of antimycotics in the treatment of allergic fungal rhinosinusitis has not been tested in controlled trials, a high dose of post-operative itraconazole, combined with oral and topical steroids in a cohort of 139 patients with allergic fungal rhinosinusitis, reduced the need for revision surgery.[39] The antifungal prophylaxis in immunocompromised patients did not prevent the development of invasive zygomycosis but treatment with liposomal amphotericin B resulted in improved response and survival rates with early detection being as important as the surgical and antifungal treatments.[40]

Researchers from the Mayo Clinic proposed that CRS may arise because of a local immune response to fungi that are present in nasal and sinus secretions.[41] Given the correct equipment, fungi can be detected in nasal secretions in virtually all patients with CRSwNP, but also in a controlled disease-free population. There is no definitive proof that fungi are involved in the aetiology of the inflammatory response in some patients. One double-blind randomized placebo-controlled trial in 60 patients with CRSwNP, comparing topical treatment with amphotericin B with saline douching,[42] found radiological and subjective scores were actually worse in the treatment group. One trial with nasal amphoteracin B treatment significantly reduced symptoms at 2 but not 4 weeks and endoscopy scores and fungal culture rates did not significantly differ. This treatment is not recommended in CRSsNP.[43]

MEDICATION THAT MAY IMPROVE THE IMMUNE RESPONSE

Since an altered immune response to bacterial infection or fungal infection may be responsible for some of the episodes of recurrent rhinosinusitis, there is interest in medications that may alter the immune response.

Bacterial lysate preparations

Bacterial lysate preparations (e.g. ribosomal fractions of *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae*) have been tested against placebo in three multicentre placebo-controlled trials and the evidence from these studies suggested that this type of therapy may reduce the need for antibiotics in the treatment of chronic rhinosinusitis.[44–46] Based on the results of one RCT oral OM-85 BV treatment may be considered as an adjunct to standard medical treatment in adults with CRSsNP.[1]

Treatment with more expensive agents that either stimulate or modulate the immune system (e.g. recombinant human granulocyte colony stimulating factor) have been tested in a randomized controlled trial in a group of patients with CRS that were refractory to other types of treatment. The studies showed there was no significant improvement with this expensive treatment.

A pilot study has looked at treatment with gamma interferon and it suggested that this treatment may be beneficial in treating resistant CRS; but the number of patients was small.[47]

NASAL AND ANTRAL IRRIGATION WITH SALINE

Saline irrigation

A number of RCTs have tested nasal irrigation with isotonic or hypertonic saline in the treatment of ARS and CRS comparing modalities of application. There was limited evidence of benefit with nasal saline irrigation in adults with ARS.[48] The evidence is that nasal washout with isotonic or hypertonic saline is beneficial in alleviating symptoms and improves endoscopic findings in patients with CRS. Irrigation with saline has also shown to significantly improve nasal mucociliary clearance, as measured by saccharine tests in healthy volunteers.[49]

ANTILEUKOTRIENES

The role of leukotrienes in the pathogenesis of bronchial asthma has been well documented and increased levels of these mediators have been detected in patients with rhinosinusitis and nasal polyps. Antileukotrienes have been evaluated in the treatment of asthmatics, especially in those with the aspirin-induced asthma (ASA) triad.

When seasonal allergic rhinitis was considered, antileukotrienes were not found to be superior to placebo in reducing symptom scores in a randomized controlled trial.[50]

For patients with CRSwNP, one study looked at antileukotriene treatment in 36 patients and found that when antileukotrienes were added to standard treatment regimes, there was a significant reduction in symptom score.[51]

Two other studies support the use of antileukotriene treatment as an adjunct to standard treatment in patients with nasal polyps, asthma and aspirin intolerance.[52, 53]

Leukotriene antagonists can cause skin rash, mood changes, tremors or shaking and occasionally can worsen the symptoms of sinus symptoms and asthma. Currently data do not support the use of antileukotriene antagonist in CRSwNP.

Aspirin desensitization

This treatment has been used in patients with aspirin-exacerbated respiratory disease (AERD) having CRSwNP, bronchial asthma and hypersensitivity to Cox-1 inhibitors (including aspirin). It was observed that following exposure to aspirin, these patients became refractory to the effects of aspirin for 24 to 72 hours. Several case series suggest a weak clinical benefit from oral aspirin desensitization.[54, 55] There is no randomized placebo-controlled trial on oral aspirin in AERD patients. In one trial, 14 patients who reacted to an aspirin provocation test were allocated to 100 mg or 300 mg aspirin daily for 1 year. It was found that all patients on 100 mg aspirin had recurrence of nasal polyps but no polyps were found in patients on 300 mg aspirin daily.[56]

Nasal administration of lysine-aspirin may reduce the risk of severe hypersensitivity reactions as well as gastrointestinal side effects. In a randomized, double-blind placebo-controlled trial patients with AERD were given either 16 mg lysine-aspirin or placebo every 48 hours for 6 months but no significant clinical benefit was found in the treatment group compared to the placebo group.[57]

Based on current data, the benefit of oral or nasal aspirin desensitization in patients with AERD has yet to be determined.

AGENTS USED TO BLOCK THE PARASYMPATHETIC NERVOUS SYSTEM

Ipratropium bromide (Rinatec) is a muscarinic receptor antagonist blocking the parasympathetic nervous system. It should be effective in anyone with a wet dripping nose due to parasympathetic overactivity. In practice, it is effective for some elderly men with a dripping nose! Side effects include a dry mouth, epistaxis and dryness of the nose. A Cochrane review identified seven studies and concluded that ipratropium bromide is effective in reducing the rhinorrhoea with no effect on congestion experienced by those with the common cold.[58]

VACCINATION

Although vaccination does not have a direct effect in the treatment of ARS, a study showed that in the 5-year period following the introduction of 7-valent pneumococcal vaccination when compared to the previous 5-year period, the cause of acute maxillary sinusitis by *Streptococci pneumonae* decreased by 18% but *Haemophilus influenza* increased by 8%.[59]

RELATED TOPICS

Preparation of the nasal mucosa prior to surgery

Cocaine solution (5% or 10%) or cocaine paste (25%) has been used to prepare the nose prior to surgery for more than 100 years. The majority of rhinologists believe it to be the most effective way of ensuring good operating conditions providing sufficient time for the drug to work is allowed. The application of Moffat's solution by a spray (Figure 28.1) is one method of preparing the nose and it is sensible to do this immediately after the induction of anaesthesia.



Figure 28.1 The application of Moffat's solution by a spray.

Moffat's solution consists of 2 mL of 5% cocaine, 1 mL of 1 : 1000 adrenaline and a small amount of bicarbonate solution. In order to avoid systemic effects, the maximum dose recommended for application to the nasal mucosa in fit adults is 1.5 mg/kg. The solution is dyed pink reducing the risk of it being mistaken for other drugs in the anaesthetic room.

Vestibulitis

Non-infective vestibulitis may be treated by applying vaseline or a mild topical corticosteroid to the vestibule. In the presence of infection an antibiotic ointment active against *Staphylococcus aureus* is required. A combination of chlorhexidine and neomycin (Naseptin) or mupirocin (Bactroban nasal) are available. The latter is used as a second-line agent for the eradication of methicillin-resistant *Staphylococcus aureus* (MRSA). The ointment is applied three times a day for 5 days and a swab is taken 2 days later to determine whether MRSA has been successfully eradicated. Naseptin includes arachis (peanut) oil and should not be used in patients with peanut allergy. Naseptin is contraindicated in pregnancy.

Hereditary familial telangiectasia

The epistaxis associated with hereditary familial telangiectasia (HFT) is difficult to treat and a variety of medical and surgical treatments have been tried. Systemic and topical oestrogen provoke squamous metaplasia of the epithelium and in this way provide a protective coat over the blood vessels. Ethinyloestradiol may be used under supervision for the treatment of HFT in women. The side effects include nausea, fluid retention and thrombosis. It is not popular in men because of the gynaecomastia it induces.

Atrophic rhinitis

Steam inhalation, humidification and saline nasal douching are useful in atrophic rhinitis. A 25% glucose in glycerine solution restores moisture to the nasal mucosa: 25 g of glucose is dissolved in 75 g glycerine (gently warmed). Once bottled the drops have a 3-month life span. The drops can be used several times a day and provide some relief to this distressing condition.

METHODS OF ADMINISTERING TOPICAL NASAL PREPARATIONS

If two nasal sprays are to be administered to each nostril, one spray should be directed upwards and the other backwards whilst the patient does not breathe or breathes in gently.

The best position for administering nasal drops is head-down, as in Figure 28.2.

Fluticasone propionate nasules (400 µg) can be used to increase the topical dose of steroid. One nasule is shared between each nostril once daily; thus the dose given is precisely known.



Figure 28.2 The best position for administering steroid drops.

BEST CLINICAL PRACTICE

- ✓ Topical steroids improve the symptoms associated with nasal polyps and reduce the recurrence rate of nasal polyps after surgery.
- ✓ The best position for administering steroid drops is head-down (**Figure 28.2**).
- ✓ One way of introducing cocaine into the nose is by spraying Moffat's solution into the nose immediately after induction of anaesthesia, increasing the chances of obtaining a 'bloodless surgical field'.
- ✓ Before prescribing naseptin, ensure the patient is not allergic to peanuts and is not pregnant.

FUTURE RESEARCH

- ➤ Topical steroids reduce the recurrence rate of nasal polyps following surgery but there is yet to be an effective long-lasting medical polypectomy.
- ➤ The optimum length of treatment with topical steroids is yet to be established with the different clinical scenarios.
- ➤ A large prospective study is required to determine the role of antibiotics in preventing acute complications.
- ➤ The aetiology of polyps is yet to be identified.

KEY POINTS

- Rhinosinusitis is one of the most common healthcare problems. It diminishes patients' quality of life and consumes resources.
- Corticosteroids are useful topically in post-viral ARS, CRSsNP and CRSwNP (in both adults and children). Oral steroids are useful in adults with CRSwNP.
- Antibiotics with oral corticosteroids in adults and topical corticosteroids in children are effective treatments for acute bacterial rhinosinusitis.
- Oral antibiotic therapy (<4 weeks) may be useful in CRS during exacerbations.
- Topical decongestants are a useful adjunct to analgesia and antihistamines in viral ARS in adults.
- Antihistamines reduce rhinorrhoea, sneezing and itching but not nasal obstruction and may be useful in patients with CRSwNP in allergic patients.
- Saline irrigation of the nose is an effective treatment for rhinosinusitis.

ACKNOWLEDGEMENTS

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CHAPTER 29

DRUG THERAPY IN LARYNGOLOGY AND HEAD AND NECK SURGERY

Wendy Smith and Rogan Corbridge

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: antiplatelet, anticoagulant, antibiotic prophylaxis, and head and neck surgery. This chapter relied on the medicines listed in the *British National Formulary*.[1]

INTRODUCTION

The laryngologist and head and neck surgeon prescribes medicines for prophylactic purposes, for example antibiotics and anticoagulants, as well as for therapeutic use in the management of infections, immune conditions and voice/throat problems. An appreciation of the pharmacology, preparations available, side effects and contraindications is required for appropriate and safe prescribing. This chapter addresses these matters.

ANTIPLATELET DRUGS

These reduce platelet aggregation and thereby thrombus formation in the arterial circulation where thrombi are primarily composed of platelets with little fibrin. Aspirin, clopidogrel and dipyridamole are often encountered in ENT patients with comorbidities to prevent atherosclerotic and thromboembolic events (see NICE guidelines[2]). The decision to stop these preparations prior to surgery is based on the balance of risk of bleeding versus the risk of thrombus formation. Sylvester and Coatesworth[3] found that there is a significant morbidity and mortality associated with early cessation of antiplatelet agents but evidence from cardiac surgery suggests that the operative blood loss is only marginally greater in patients on aspirin and clopidogrel. They, like others,[4] suggest the management of these patients in the perioperative period should be made after multidisciplinary consultation.

ANTICOAGULANTS

The perioperative management of patients taking anticoagulants may be complex and should be considered on an individual patient basis, taking into account the increased risk of haemorrhagic complications in that procedure with the risk of thromboembolism if the anticoagulation therapy is stopped. Where necessary, involvement of the haematology/medical teams is advised.

The anticoagulant drugs heparin and warfarin are widely used in the prevention and treatment of venous thrombosis and embolism perioperatively. Anticoagulants should not be used where there is a history of haemorrhagic disorders, peptic ulcer disease, severe hypertension and severe liver disease. **Figure 29.1** illustrates the clotting pathway and the action of heparin and oral anticoagulants.

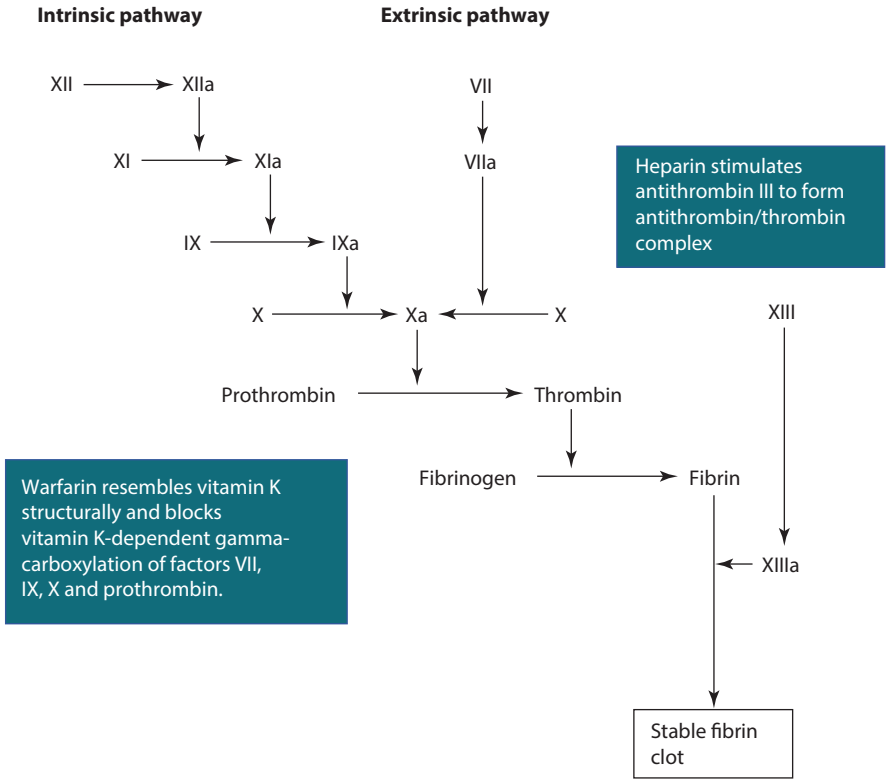


Figure 29.1 The clotting pathway and the mechanism of action of heparin and oral anticoagulants.

Heparin is a family of mucopolysaccharides with a molecular weight of 4000–30 000. The molecules are attached to a protein backbone consisting entirely of serine and glycine residues. Heparin is found in mast cells, in plasma and in the endothelial cell layer of blood vessels. This highly acidic substance is extracted from beef lung or hog intestinal mucosa for therapeutic use. Heparin's main action is preventing fibrin formation by interacting with the protease inhibitor antithrombin III enhancing (by 1000-fold) the binding of antithrombin III with thrombin. In addition, the heparin–antithrombin III complex has inhibitory effects on factors IXa, Xa, XIa and XIIa.

Heparin is not absorbed from the gastrointestinal mucosa because of its charge and large molecular weight; therefore it must be given intravenously or by subcutaneous injection. Intramuscular injection is avoided to prevent haematoma formation. The onset of action of heparin is immediate and it has a half-life of 40–90 minutes. It is inactivated by heparinase in the liver and platelet factor IV released from activated platelets may also have a role.

When used for prophylaxis of deep vein thrombosis in surgery, 5000 units of heparin should be given 2 hours before surgery, then 8–12-hourly for 7 days or until the patient is ambulant. Monitoring is not required in this situation but when used to treat a thrombosis, a regime of 5000 units intravenously followed by 15–25 units/kg/hour intravenous infusion or 15 000 units 12-hourly necessitates monitoring of the thrombin time, which should be increased by a factor of 2 to 3.

Low molecular weight heparins (certoparin, dalteparin, enoxaparin, reviparin and tinzaparin) are also effective in the prophylaxis of venous thromboembolism and their once daily subcutaneous administration is more convenient. These can also be used to treat deep vein thrombosis and monitoring is not required.

Platelet counts should be measured in patients receiving heparin since thrombocytopenia (an immune reaction) may occur but this does not usually happen until 6 to 10 days after the start of treatment. Should thrombocytopenia, or a 50% reduction of the platelet count occur, and further anticoagulation is required, patients should be given the heparinoid, danaparoid, or the hirudin, lepirudin.

Heparin inhibits aldosterone and may result in hyperkalaemia, especially in patients with diabetes mellitus, chronic renal failure, acidosis, raised plasma potassium or those taking potassium-sparing drugs.

The oral anticoagulants prevent the reduction of vitamin K that is required as an active cofactor of carboxylase in factors II, VII, IX and X. The effect on fibrin formation depends upon the balance between the decreased rate of carboxylation and the unaltered rate of degradation of factors already carboxylated. Warfarin has a half-life of 40 hours and a duration of action between 2 and 6 days. It takes at least 48–72 hours for the anticoagulant effect to develop fully and so heparin is also used initially when an immediate anticoagulant effect is required. Warfarin is the most commonly prescribed oral anticoagulant; nicoumalone and phenindione are rarely used. The drugs are metabolized by the mixed function oxidases in the liver.

Monitoring of the prothrombin time (usually reported as the international normalized ratio, INR) is required and dose adjustments made accordingly. Target INR values (usually between 2 and 4) are detailed in the

British National Formulary. The INR can be dramatically altered by coprescribing other medication and the reader is again directed to the British National Formulary[1] prior to coprescribing.

ANTIBIOTICS

Antibiotics are commonly prescribed prophylactically, even in so-called clean operations.[5, 6] The use of antibiotics post-tonsillectomy has failed to show a reduction in the secondary haemorrhage rate but may reduce pain at day 5 post-operatively.[7, 8] Where there is no violation of mucosa, no pre-operative inflammation and no drain, the incidence of wound infection in the head and neck is 2%. In surgery such as laryngectomy, prophylactic antibiotics with a broad spectrum are used to prevent wound infections. A pre-operative dose (given to allow a high tissue level at the time of surgery) and three post-operative doses of a cephalosporin and metronidazole are suitable. Violaris and Bridger, using a cephalosporin at 8 hours pre-operatively with the premedication and three doses 8-hourly post-operatively, reduced the development of pharyngocutaneous fistulae.[9] Johansen et al.[10] found prophylactic metronidazole resulted in a highly significant decrease in the frequency of post-operative fistulae.

Antibiotic prophylaxis is also necessary in patients with artificial heart valves or cardiac valve disease. Local policies may vary but amoxicillin 3 g orally or 1 g intramuscularly can be given 1 hour before surgery and 6 hours post-operatively.

The choice of antibiotic to treat an established infection is initially on a 'best guess' policy based on the probable pathogen until swab results and sensitivities become available.

PREPARATIONS USED TO IRRIGATE WOUNDS

Before closing a wound following tumour excision it has been recommended that it should first be washed out well. Stell and Maran[11] describe the use of Savlon, hydrogen peroxide and sterile water as suitable solutions since it appears that the mechanical process of washing rather than the lytic action on the cells is important. They recommend the use of at least 1 L of solution. In a xenograft model of tumour-cell wound contamination, Allegretto et al.[12] found that irrigation with water, saline or gemcitabine delayed tumour development: the latter two improved rates of long-term disease control.

LOCAL ANAESTHETIC SPRAYS AND LOZENGES

These preparations are used to desensitize the mouth and pharynx prior to examination, investigation or treatment. Lidocaine (lignocaine) is effectively absorbed from mucous membranes and is available as a pump spray as a 10% solution (maximum dose is 20 sprays in pharynx, larynx or trachea) and more commonly as a topical 4% solution (maximum dose is 7.5 mL). Benzocaine is a neutral, water-insoluble local anaesthetic of low potency and is only used for surface anaesthesia in non-inflamed tissue in the mouth and pharynx. It is available in lozenges and sprays, sometimes combined with antiseptics. Sensitization may occur and there is little evidence for the benefit in using these combined preparations. Patients should be advised not to eat or drink until the numbness has worn off. Lidocaine belongs to the amide class, benzocaine to the ester class of local anaesthetics. Both bind to a receptor on the sodium channel in the axon preventing the opening of the channels, thereby preventing depolarization of the nerve. In over dosage, cardiac toxicity can occur.

MOUTHWASHES

Mouthwashes are usually aqueous solutions in a concentrated form of substances with deodorant, antiseptic, local anaesthetic or astringent properties. Sometimes they should be diluted before use. They have a mechanical cleansing action. Hydrogen peroxide mouthwash is a 6% solution and 15 mL should be diluted in half a cup of warm water two to three times daily. It contains an oxidizing agent and is useful in the treatment of acute ulcerative gingivitis. It froths in contact with oral debris, thereby having a mechanical cleansing effect, hence its use in the management of secondary tonsillectomy haemorrhages. Chlorhexidine gluconate, used when tooth-brushing is not possible or in combating oral infection, inhibits plaque formation on teeth but has the side effect of causing reversible brown staining of the teeth. Since chlorhexidine gluconate can interact with some of the ingredients in toothpaste, a 30-minute interval is advised between using this mouthwash and toothpaste.[1]

THROAT LOZENGES AND PASTILLES

Lozenges and pastilles are both used to deliver medicaments for local effect, either to soothe or treat infections. Lozenges consist of medicaments incorporated into a flavoured base that dissolves or disintegrates slowly in the mouth. They are prepared either by moulding and cutting or by compression. Colours, flavours and sweetening agents may be incorporated. Heavy compression is used to ensure slow disintegration in the mouth.

Pastilles consist of medicaments in a base containing gelatin and glycerol or a mixture of acacia and sucrose. Sodium benzoate and citric acid monohydrate may be used as a preservative and antioxidant, respectively. Flavourings such as lemon oil may be incorporated.

SOLUTIONS, SUSPENSIONS AND SYRUPS

Solutions are liquid preparations containing one or more soluble ingredients, usually dissolved in water. They may be used internally, externally or for instilling into body

cavities and may be sterile or unsterilized depending on the application. Solutions given orally usually result in rapid absorption. Problems with solubility, taste and stability may prevent this formulation being available for a particular drug.

Suspensions are formulations in which the drug does not dissolve in the solvent but is distributed within it. It usually provides a more rapid dispersion and dissolution of the drug when compared to tablets and capsules so long as the drug has a suitable particle size and does not settle or cake on storage. The primary particle size may grow due to the action of surfactants, emulsifiers and other adjuvants.

Syrups are concentrated aqueous solutions of sucrose or other sugars to which medicaments or flavourings are added. Glycerol, sorbitol and polyhydric alcohols may be added to reduce the rate of crystallization of sucrose and to increase the solubility of other ingredients. Growth of microorganisms is usually retarded by sucrose concentrations greater than 65% w/w.

TREATMENT OF DRY MOUTH

Artificial saliva can be useful to relieve dry mouth resulting from radiotherapy or diseases affecting the salivary glands. These preparations should be of neutral pH and contain electrolytes approximating to the composition of saliva. These preparations are available as oral sprays, lozenges and pastilles. Pilocarpine (Salagen) is a muscarinic and can stimulate any residual salivary gland function. Side effects relate to the muscarinic action and its use is contraindicated in those with significant respiratory and cardiovascular disease, angle-closure glaucoma, pregnancy and breastfeeding.

COUGH MEDICINES

These are divided into cough suppressants and the expectorant and demulcent cough preparations. After excluding an underlying cause of a cough, such as asthma and gastro-oesophageal reflux, cough suppressants may be used. It is thought that these drugs act by an ill-defined central action in the nervous system and may depress the 'cough centre' in the brain stem. The narcotic analgesics are effective as antitussives in subanalgesic doses. Codeine phosphate is useful for dry or painful coughs but it also inhibits the secretion and mucociliary clearance of sputum, is constipating and dependence can develop. Pholcodine (related to codeine) and dextromethorphan (a non-narcotic, nonanalgesic) have lesser side effects. Over the counter preparations include sedating antihistamines, such as diphenhydramine, and may work by causing drowsiness.

There is no evidence that expectorants (ammonium chloride, ipecacuanha and squill) are effective at promoting expulsion of bronchial secretions. Their action is more placebo. Demulcent cough preparations may relieve a dry irritating cough by virtue of the fact that they contain a syrup or glycerol that has a soothing effect. Simple linctus (a sugar-free preparation is also available) is harmless and inexpensive.

MANAGEMENT OF STRIDOR

The treatment required depends upon the cause and severity of the stridor. Heliox is useful in an acute situation but antibiotics, adrenaline, steroids and antihistamines may be required, as may surgery.

Helium is a colourless, odourless, tasteless gas that when mixed, one volume of helium to two volumes of air, diffuses more rapidly than air itself. Breathing such a mixture requires less effort due to the lower density. An air–helium mixture or a mixture of 21 volumes of oxygen and 79 volumes of helium (Heliox) has been used in the management of stridor.

DRUG THERAPY IN ANGIONEUROTIC OEDEMA

Swelling of the face and lips, and occasionally of the larynx, occurs in angioneurotic oedema of allergic origin. Antihistamines and corticosteroids are prescribed and, if life-threatening, 1 mL/1 : 1000 adrenaline can be administered subcutaneously. The non-allergic type results from a serum deficiency of the C1 esterase inhibitor protein. An acute attack is treated with an intravenous injection of 1000 units of C1 esterase inhibitor protein (derived from human plasma). This can also be given prior to surgery for prophylaxis. Conestat alfa (contraindicated if allergic to rabbits) and icatibant are also licenced in treating acute attacks of hereditary angioedema in adults with C1 esterase inhibition.[1] Long-term prophylaxis is achieved with epsilon aminocaproic acid or its derivative tranexamic acid or with androgen methyltestosterone or its derivative danazol. These stimulate the production of C1 esterase inhibitor protein.

USE OF BOTULINUM TOXINS IN SPASMODIC DYSTOMIA

Botulinum is available as botulinum A toxin–haemagglutinin complex (Botox, Dysport) and botulinum B toxin (NeuroBloc). The dosage is specific to each individual preparation and therefore the product literature must be consulted prior to use. In laryngeal dystonia, localization of the involved muscles and confirmation of correct needle position can be achieved by electromyographic guidance. The effect of botulinum toxin is observed within a few days. Patients may initially have worsening of their voice, dysphagia with the potential for aspiration and occasionally airway compromise. Improvement is seen 2 weeks post-injections and the effects of treatment may last for 3 to 6 months.

Botulinum toxin is contraindicated in patients known to be hypersensitive to ingredients, bleeding disorders,

pregnancy and lactation, concurrent or potential aminoglycoside or spectinomycin administration (neuromuscular blockade is enhanced). It should not be used in patients with generalized muscle disorders such as myasthenia gravis. No information is available on its use in patients with renal or hepatic impairment. Adrenaline should be available in case anaphylaxis occurs.

COLLAGEN INJECTION OF PARALYZED VOCAL CORDS

As a result of Teflon injection being unavailable in the UK, collagen (Contigen) is now used to medialize paralyzed vocal cords. It is a purified bovine dermal gluteraldehyde cross-linked collagen and has been used in genuine stress incontinence. A skin test (0.1 mL collagen and lignocaine, injected intra-dermally into the volar surface of the forearm) should be carried out 4 weeks prior to the treatment. Many patients requiring this treatment have a short life expectancy and so a compromise with the skin test performed only a week prior to vocal cord injection is practised. A positive response is defined as erythema, induration, tenderness or swelling with or without purities, persisting for more than 6 hours or first appearing more than 24 hours after the injection.

The use of collagen injection is contraindicated in patients hypersensitive to the ingredients, with a positive skin test, in pregnancy and lactation and in patients with autoimmune disease or a history of multiple severe allergies.

DRUGS USED IN THYROID DISEASE INCLUDING THE MANAGEMENT OF HYPOCALCAEMIA

Thyroid hormones

The two preparations levothyroxine sodium/thyroxine sodium (Eltroxin) and liothyronine sodium (Tertroxin) are available for use in the management of hypothyroidism, diffuse non-toxic goitre, Hashimoto's thyroiditis and thyroid carcinoma. Levothyroxine sodium (thyroxine sodium) is used for maintenance therapy, usually as a single dose before breakfast. The initial dose is 50–100 µg daily increasing at 2- to 3-week intervals by 25–50 µg increments until normal metabolism is obtained. In the elderly, patients with cardiac insufficiency or severe hypothyroidism, the initial dose is 25 µg, increased by 25 µg every 4 weeks until normal metabolism is achieved. The usual maintenance dose is 100–200 µg, the higher dose is used to suppress T4 in thyroid carcinoma.

Liothyronine has a shorter half-life with a more rapid onset of action and shorter duration of action. Twenty micrograms of liothyronine is equivalent to 100 µg of thyroxine sodium. It can also be given intravenously. A pre-therapy ECG should be performed since hypothyroidism can produce changes resembling ischaemia. The starting dose is 10–20 µg every 8 hours. The usual maintenance dose is 60 µg daily in three divided doses. Sometimes it is coadministered with carbimazole to treat thyrotoxicosis. It may be used in severe hypothyroid states when a rapid response is required and is used in patients awaiting radioactive iodine scan following thyroid surgery. The latter enables patients to remain euthyroid in this interval period and patients need to stop liothyronine only 2 days prior to the scan.

These thyroid hormones must be used with caution in patients with hypertension, diabetes mellitus and insipidus, cardiovascular disorders, angina, the elderly, lactation, pregnancy (especially the first trimester) and in adrenal insufficiency. Interactions include sucralfate, phenylbutazone, warfarin, carbamazepine, phenytoin, rifampicin, barbiturates and propranolol. The side effects of arrythmias, insomnia, tremor, palpitations, sweating, weight loss, thyroid crisis, vomiting, diarrhoea and headache have been reported.

Drugs used in hyperthyroidism

Antithyroid drugs are used for hyperthyroidism either pre-operatively or for long-term management. Carbimazole (Neo-Mercazole) is the most commonly used in the UK; propyluracil is used in patients sensitive to carbimazole. Both are thionamides containing a thiocarbamide group (S=C–N) that is essential for their activity. Carbimazole is rapidly converted to methimazole *in vivo*. Methimazole is available in the USA. Thioamides prevent the synthesis of thyroid hormones by competitive inhibition of I^- to I^2 by peroxidase and also block the coupling of the iodotyrosine, especially in forming diiodothyronine. More controversial is the possibility that the thionamides have immunosuppressive properties. These drugs are administered orally and accumulate within the thyroid gland. Their delayed onset of action of 3 to 4 weeks results from the need of preformed hormones to be depleted first.

The main concern with thionamides is the development of neutropenia and agranulocytosis. Carbimazole has an incidence of causing agranulocytosis in 0.1% of patients; propylthiouracil has an incidence of four times this (explaining the preference for carbimazole in the UK).

The Committee on Safety of Medicines recommends that:

- patients should be asked to report symptoms and signs suggestive of infection, especially sore throat
- a white blood count should be performed if there is any clinical evidence of infection
- the drug should be stopped promptly if there is clinical or laboratory evidence of neutropenia.

Iodine is used as an adjunct to antithyroid drugs in the pre-operative management of thyrotoxicosis. An aqueous iodine oral solution (Lugol's solution) is given at a dose of 0.1–0.3 mL three times a day, taken well diluted with water or milk. Patients may develop flu-like symptoms, headache, rashes, insomnia, lacrimation, conjunctivitis, laryngitis and bronchitis. It must be used with caution in pregnancy and be avoided in lactation.

Drugs used in hypocalcaemia

Following thyroid or parathyroid surgery, patients may develop hypoparathyroidism either temporarily or permanently. Parathormone (PTH) is the most important regulator of the extracellular calcium concentration. Hypocalcaemic tetany is first managed by an initial intravenous injection of 10 mL 10% calcium gluconate followed by a continuous infusion of 40 mL daily or oral calcium with careful monitoring of the plasma calcium concentration. Bradycardia, arrhythmias and irritation after intravenous injection may occur as can gastrointestinal disturbances after oral administration. Failure to obtain and maintain a corrected calcium concentration within the normal range with calcium supplements alone necessitates the additional administration of a vitamin D preparation. **Figure 29.2** demonstrates the control of calcium plasma concentration by vitamin D. Vitamin D is a prohormone, metabolized to hormones that increase intestinal absorption of calcium, mobilize calcium from bone and inhibit renal excretion. The hypocalcaemia of hypoparathyroidism often requires doses of up to 2.5 mg (1 000 000 units) calciferol daily. Calcifediol is the main derivative of liver hydroxylation and this is further hydroxylated in the kidney to the potent calcitriol. The latter step is regulated by PTH. A synthetic derivative of vitamin D commonly prescribed in hypoparathyroidism is alfacalcidiol.

TREATMENT OF REFLUX OESOPHAGITIS AND LARYNGOPHARYNGEAL REFLUX

Initial treatment depends on the severity of the symptoms and treatment response. Changes to lifestyle (avoid excess alcohol and fatty foods), weight reduction, stopping smoking and raising the head of the bed may be advised. Antacids and alginates alone may be used for mild symptoms. The alginates are said to form a raft on the surface of the stomach's contents to reduce reflux and protect the oesophageal mucosa. McGlashan et al. in a prospective randomized controlled trial demonstrated a significant improvement in symptom scores and clinical findings with liquid alginate suspension compared to the control group in patients with laryngopharyngeal reflux.[13]

Histamine H_2 receptor antagonists (cimetidine, famotidine, nizatidine and ranitidine) block the action of histamine on the parietal cells and reduce acid secretion. They should be used with caution in patients with liver or renal disease, in pregnancy and breastfeeding. Side effects include diarrhoea, altered liver function tests, rashes and, more rarely, hypersensitivity reactions, AV block and blood dyscrasias. Cimetidine has been reported to cause gynaecomastia and it binds to cytochrome P-450 reducing the hepatic metabolism of drugs such as warfarin.

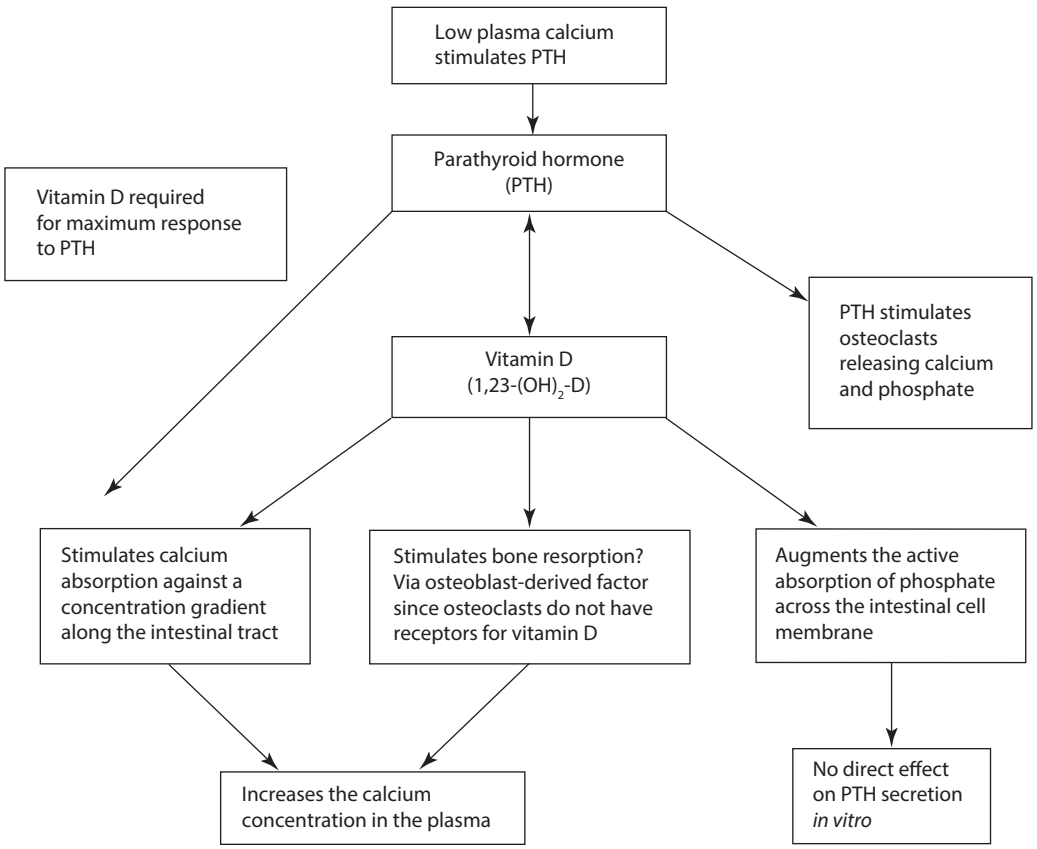


Figure 29.2 Calcium homeostasis and the role of Vitamin D.

The proton pump inhibitors (omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole sodium) react with sulphydryl groups in the H^+/K^+ ATPase (proton pump) responsible for the transportation of H^+ ions out of the parietal cells. Although their use is well established in the treatment of reflux oesophagitis, their use in larygopharyngeal reflux is based on poor levels of evidence from uncontrolled studies. The few randomized controlled trials failed to show any benefit over placebo in this condition.[14]

CHEMOTHERAPEUTIC AGENTS

These drugs are used either alone or in combination with surgery and/or radiotherapy with the aim to cure or palliate a cancer. They inhibit the mechanisms of cell proliferation and rely upon malignant tumours having a greater proportion of cells undergoing division than in normal proliferating cells, especially in the bone marrow, gastrointestinal mucosa and in hair follicles. Chemotherapeutic agents are classified with respect to their site of action, as demonstrated in Figure 29.3.

Alkylating agents (mustine, cyclophosphamide, chlorambucil, cisplatin and busulphan) cross-link the two strands of the double helix of DNA. The antibiotics actinomycin D, doxorubicin, mitomycin, mithramycin and bleomycin interact with the DNA preventing RNA production. DNA synthesis is prevented by a group of antimetabolites (methotrexate, flurouracil, mercaptopurine and thioguanine) that prevent purine or pyrimidine synthesis. The vinca alkaloids (vincristine and vinblastine) bind to the microtubular proteins inhibiting mitosis. Glucocorticoids are included in regimes since they inhibit cell division by interfering with DNA synthesis.

Side effects such as nausea and vomiting, intestinal ulceration, diarrhoea, alopecia and bone marrow suppression are common but may become life-threatening.

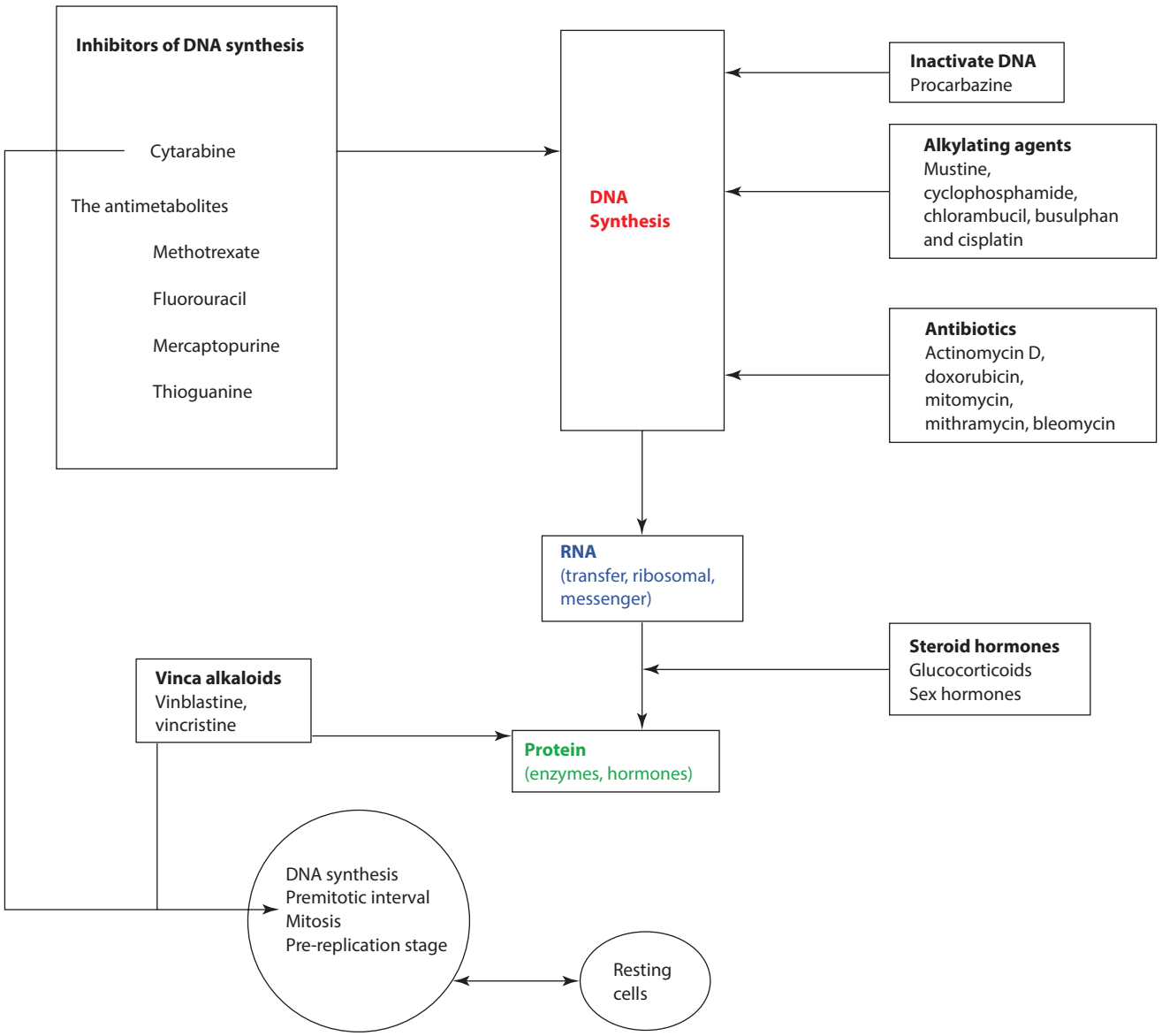


Figure 29.3 Site of action of chemotherapy.

MANAGEMENT OF FUNGATING WOUNDS

Charcoal dressings have been used to help combat malodorous fungating tumours. When this fails, topical metronidazole gel (Anabact or Metrotop) can be applied to the cleaned wound once or twice a day and covered with a non-adherent dressing. The metronidazole has antimicrobial activity against the anaerobes likely to be responsible for the odour.

Alginate dressings may stop bleeding from fungating wounds and, if moistened prior to a dressing change, the risk of bleeding at this time can be reduced.

BEST CLINICAL PRACTICE

- ✓ The starting or stopping of antiplatelet drugs and anticoagulants should be in accordance with guidance from the haematologist and medical colleagues, taking into account other prescribed medications that may interact.
- ✓ Platelet counts should be monitored in patients on heparin to detect any thrombocytopenia.
- ✓ Cefuroxime and metronidazole should be given at induction and for at least three post-operative doses in head and neck procedures where the mucosa is breached.
- ✓ Heliox is easier to breathe than air and buys useful time in patients with stridor; however, it is important to take additional steps to treat the underlying cause and to secure the airway.
- ✓ First-line treatment of angioneurotic oedema consists of intravenous antihistamines and steroids with nebulized or subcutaneous adrenaline but C1 esterase inhibitor protein is the first-line treatment of hereditary angioedema.
- ✓ In order to avoid severe hypersensitivity reactions, pre-operative test injections of collagen are necessary where this is used to perform vocal cord medialization.

KEY POINTS

- Perioperative antibiotics have not been shown to reduce bleeding rates after tonsillectomy but may reduce pain.
- The use of perioperative cephalosporins and metronidazole reduce the rates of fistula formation in head and neck operations.
- Pilocarpine (used in the treatment of dry mouth) is contraindicated in patients with significant respiratory/cardiovascular disease, glaucoma, pregnancy or breastfeeding.
- Rarely, carbimazole can cause agranulocytosis.
- Botulinum is available as botulinum A toxin–haemogglutinin complex and botulinum B toxin. It is important to realize that the dosage is specific to each preparation.

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CHAPTER 30

PREPARATION OF THE PATIENT FOR SURGERY

Michael Murray and Urmila Ratnasabapathy

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SEARCH STRATEGY

This included recent publications in scientific journals, from professional bodies and the UK Department of Health. Data may be updated using keywords such as consent, enhanced recovery, suitability for day surgery, pre-operative assessment, pain, anti-coagulation, pre-operative preparation and venous thromboembolism prevention.

PATIENT PATHWAY

The patient pathway describes the 'route' taken by a patient from initial referral to regaining health. A pathway includes processes and documentation, and should be amenable to audit and external review. Generally, the surgeon makes a broad judgement at the time of seeing the patient as to whether or not the patient is fit for surgery. The in-hospital segment of the pathway begins here and, within the confines of a busy clinic, the patient requiring surgery should be placed into one of five routes:

- day surgery
- inpatient, scheduled admission within a few weeks
- inpatient, elective surgery, fit patient
- planned inpatient but requiring prior medical/anaesthetic review
- immediate admission.

Suitability for day surgery

There are guidelines[1] about which patients are suitable for day surgery in a particular hospital. There are three main criteria for the selection of patients as being suitable for same day surgery: social, medical and surgical.

Social factors

- The patient must understand the planned procedure, post-operative care and have consented to day surgery.
- Following most procedures under general anaesthesia, a responsible adult should escort the patient home and provide support for the first 24 hours.
- The patient's domestic circumstances should be appropriate for post-operative care.

Medical factors

- Fitness for a procedure should relate to the patient's health as determined at pre-operative assessment and not be limited by arbitrary limits such as ASA status (Table 30.1), age or body mass index (BMI).
- Patients with stable chronic disease such as diabetes, asthma or epilepsy are often better managed as day cases because of minimal disruption to their daily routine.
- Obesity per se is not a contraindication to day surgery as even morbidly obese patients can be safely managed in expert hands, with appropriate resources. The incidence of complications during the operation or in the early recovery phase increases with increasing BMI. However, these problems would still occur with

TABLE 30.1 Physical status grading of American Society of Anesthesiologists

Grade	Physical status
Grade 1	Normal healthy patient without any clinically important comorbidity
Grade 2	Patient with a mild systemic disease
Grade 3	Patient with one (or more) severe systemic disease which does not present a constant threat to life
Grade 4	Patient with systemic disease processes which present a constant threat to life
Grade 5	Patient not expected to survive more than 24 hours

inpatient care and have usually resolved or been successfully treated by the time a day case patient would be discharged. In addition, obese patients benefit from the short-duration anaesthetic techniques and early mobilization associated with day surgery.

Surgical factors

- The procedure should not carry a significant risk of serious complications requiring immediate medical attention (e.g. haemorrhage, cardiovascular instability).

Pre-operative assessment is an essential part of perioperative management in order to determine primarily if the patient is a suitable patient for day surgery. It is part of the UK governmental strategy to have 75% of all elective surgical cases carried out as day case surgery as it confers significant cost savings. The NHS Institute for Innovation and Improvement, Delivering for Health[1] suggests a fundamental shift in patient and NHS culture so that day surgery is regarded as the norm for elective surgery. Expansion of day surgery as an anaesthetic speciality in its own right and interest therein has grown vastly in recent times.

The following statements are from the consensus document[1] produced by expert members of a working party established by the Association of Anaesthetists of Great Britain and Ireland (AAGBI) and British Association of Day Surgery (BADS):

- Day surgery is a continually evolving speciality performed in a range of ways across different units.
- In recent years, the complexity of procedures has increased with a wider range of patients now considered suitable for day surgery.
- Effective pre-operative preparation and protocol-driven, nurse-led discharge are fundamental to safe and effective day and short stay surgery.
- Patients presenting with acute conditions requiring urgent surgery can be efficiently and effectively treated as day cases via a semi-elective pathway.
- Central neuraxial blockade and a range of regional anaesthetic techniques, including brachial plexus and paravertebral blocks, can be used effectively for day surgery.
- Each anaesthetist should develop techniques that permit the patient to undergo the surgical procedure with minimum stress and maximum comfort, and optimize his/her chance of early discharge.
- Every day surgery unit must have a clinical lead with specific interest in day surgery and whose remit includes the development of local policies, guidelines and clinical governance.
- Good quality advice leaflets, assessment forms and protocols are in use in many centres and are available to other units.
- Effective audit is an essential component of good care in all aspects of day and short stay surgery.
- Enhanced recovery is based on established day surgery principles and is aimed at improving the quality of recovery after inpatient surgery such that the patient is well enough to go home earlier and healthier.

PRE-OPERATIVE ASSESSMENT

Pre-operative assessment is often carried out by specialist nursing staff in the outpatient setting using pre-agreed screening forms. Significant issues detected are referred to an anaesthetist who can make recommendations for optimization or review the patient in a pre-admission clinic. The anaesthetic assessment includes review of:

- patient and family history of anaesthetic and/or surgical problems
- cardiorespiratory system including blood pressure measurement
- significant other medical conditions
- coagulation disorders (i.e. bleeding tendency or thromboembolic risk)
- assessment of difficulty with airway management or presence of airway aspiration risk
- likelihood of post-operative nausea and/or vomiting (PONV)
- difficulties with pain control
- medications, allergies, weight
- smoking, alcohol and illicit drug use
- home/family circumstances for post-operative discharge.

Cardiovascular disease

The pattern of presentation of cardiovascular disease and recommendations for assessment has changed markedly over the last 20 years with the advent of earlier detection and better management of these conditions.

In pre-operative assessment, the main considerations are as follows.

DETECTING PREVIOUSLY UNDIAGNOSED DISEASE BY MEANS OF CAREFUL HISTORY-TAKING AND RELEVANT INVESTIGATIONS

If a patient can manage two flights of stairs then this is a good indicator of cardiac ability and is generally used as an assessment of functional capacity. Investigations for a

patient with moderate or severe dyspnoea on mild exertion or at rest may include chest X-ray and echocardiography. As a screening test for left ventricular dysfunction a normal ECG corresponds with around a 95% chance of having a normal echocardiogram.[2] All patients should get blood pressure recorded. Uncontrolled hypertension should be controlled before elective surgery. ECG (electrocardiogram) is undertaken for selected patients (see preoperative investigations below). Note that dysrhythmias are uncommon but can be detected by examination or ECG.

ASSESSMENT OF EXISTING CARDIOVASCULAR DISEASE

Deteriorating pathology, exhibited by increasing symptoms (e.g worsening angina) or decreasing exercise capacity, are indications for further investigation and management. Heart failure may present with limited exercise tolerance, dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea and ankle oedema. Echocardiography will demonstrate size of chambers, wall thickness, wall motion, valve function and allow an estimate of ejection fraction.

MANAGEMENT OF SPECIFIC CONCERNS

Antiplatelet therapy for coronary stenting

There is considerable variation regarding the use of aspirin in the perioperative period. In a recent study, it had no impact on myocardial infarction or pulmonary embolus but was associated with an increase in bleeding.[3] There is still uncertainty regarding definitive treatment and large trials are necessary to determine optimal management.[4] In patients with coronary arterial stents the situation is complex and advice should be sought from a cardiologist.

There is considerable variation in risk for transient ischaemic attack and stroke in atrial fibrillation ranging between 1% and 18% depending on risk factors.[5]

Discontinuation of aspirin or other thrombo-prophylactic therapy is calculated on the individual risk benefit ratio for the patient (i.e. the risk of bleeding vs the time of discontinuation of therapy). Aspirin is usually discontinued 5 to 7 days before an operation as it affects platelet function irreversibly. Patients who are on warfarin usually need inpatient management with discontinuation approximately 3 days prior to surgery and use of either low molecular weight heparin or an intravenous heparin infusion. Direct thrombin inhibitors such as dabigatran should be managed in a similar way as warfarin. These drugs are however of greater concern in emergency surgery as no reversal agent is currently available.

Cardiac medications

Cardiac medications may need to be considered perioperatively and the anaesthetist will usually advise on this.

Pacemakers

Pacemakers should be checked for correct functioning, preferably by a pacemaker clinic, and implantable defibrillators should be turned off immediately before surgery and on again post-operatively. Patients with valvular disease, prosthetic valves or cardiomyopathy are at risk of bacterial endocarditis and should receive antibiotic prophylaxis at surgery.

Review by a cardiologist may sometimes be required pre-operatively to review patients with new onset, severe or increasing frequency angina. The cardiologist may arrange additional testing (e.g. exercise stress testing or coronary angiography) and optimize cardiac medication.

Risk indices[6] have been developed over the years and, generally, coronary artery disease, heart failure, cerebrovascular disease, elevated creatinine, insulin-dependent diabetes and high-risk surgery have all been associated with increased perioperative cardiac morbidity. Age is another risk factor[7] with the overall 30-day mortality associated with surgery and anaesthesia rising from 2.2% (age 60–69 years) to 8.4% (age > 90 years).

Respiratory disease

Common conditions are chronic bronchitis, emphysema, chronic obstructive airways disease and asthma. Generally, a patient with known, mild, stable disease under review by the GP or respiratory department will not need special pre-operative assessment. Accurate assessment of disease severity is important. In the absence of clinical signs, chest X-ray is generally unhelpful. Asthmatic patients often know their normal peak flow measurement and this is a simple test to carry out. An assessment of functional exercise capacity, clinical examination and pulse oximetry are generally more helpful than pulmonary function tests. A respiratory physician and/or anaesthetic review should be sought for patients with severe respiratory disease. All patients should be advised to stop smoking.

Acute respiratory tract infection is an indication for postponement of elective surgery until resolution because of an increased risk of intra-operative bronchospasm and post-operative chest infection.

PRE-OPERATIVE INVESTIGATIONS

The National Institute for Clinical Excellence (NICE)[8] produced recommendations for the use of routine preoperative tests for elective surgery which were updated in April 2016. Specific recommendations are made according to grade of surgery (minor, intermediate, major, complex), ASA status, presence of diabetes, obesity, cardiovascular, respiratory or renal comorbidities and consideration of existing medication (NG45). Pre-operative tests may be ordered on a selective basis for purposes of guiding or optimizing perioperative management, but should not be ordered routinely. The Association of Anaesthetists of Great Britain and Ireland[9] states that 'blanket routine preoperative investigations are inefficient, expensive and unnecessary'.

Written guidelines are, therefore, hospital or department-based and should be discussed during induction of new department members. Reasonable guidelines

for pre-operative tests in adult patients undergoing head and neck surgery are:

- dipstick urinalysis
- haemoglobin in all females, males aged over 40 years and any patient in whom blood grouping will be undertaken
- urea and electrolytes in all patients over 40 years or when indicated by disease process or medication
- clotting studies when indicated by history
- sickle cell testing in all patients of African or Afro-Caribbean origin
- pregnancy testing when pregnancy is possible
- blood grouping (group and save) in patients with a normal pre-operative haemoglobin and an anticipated blood loss of 10–15% blood volume (blood volume 70 mL/kg in adult), and all patients who have had a previous blood transfusion in case of the presence of antibodies
- blood grouping and cross-matching in all patients with an expected blood loss in excess of 15% blood volume (> 750 mL in the average adult) or at significant risk of sudden severe haemorrhage. The number of blood units requested for a particular surgical procedure should follow written guidelines drawn up in consultation with the hospital transfusion committee
- electrocardiography (ECG) in any patient with cardiovascular disease or in asymptomatic patients aged over 60 years.

Audiometry should be undertaken on all patients undergoing surgery on the middle ear, and vocal cord function visualized when surgery might damage the recurrent laryngeal nerve.

Failure of the initial broad screening will direct the patient into the wrong pathway and may lead to substantial delays or frustration and patient harm. It is the pathway of medical/anaesthetic review prior to surgery that is particularly testing since it involves initial detection of problem patients, sending them for review, initiating treatment as required and waiting for optimal response before admission for surgery. It is clear that perioperative mortality is reduced by pre-operative optimization, particularly of cardiac and respiratory disease.[10]

OBTAINING PATIENT CONSENT FOR PLANNED SURGERY

Currently, in the UK, the process of obtaining informed consent for planned surgery is carried out by a member of the surgical team and, ideally, by the surgeon who will be performing the operation. In taking consent, it is important that full information is provided to the patient including indications for the proposed treatment including its implications and significant as well as common risks. Some ENT departments (e.g. Cambridge University Hospital) have consent forms for specific surgeries (e.g. tonsillectomy, tympanoplasty), which detail surgical risks relevant to the specific operations.[11] The process of consent should be seen as a stimulus for active discussion with patients about treatment options and decision-making following that discussion. ENT UK have produced 22 patient information leaflets which cover some common operations but also conditions.

Patients who have consented to surgery are considered to have implied consent to anaesthesia as specific written consent for anaesthesia is not required in the UK. However, as anaesthesia is associated with its own specific risks that are quite distinct and separate from those associated with the surgery, anaesthetists are advised to obtain specific consent for anaesthesia.[12] Ideally, each patient should receive a general leaflet about anaesthesia in the outpatient clinic.[13] This allows the patient time to consider relevant anaesthetic issues. Discussion between the anaesthetist and patient should include:

- previous medical/surgical/anaesthetic history including problems (e.g. latex allergy, anaphylaxis, difficult or failed intubation, pulmonary aspiration, post-operative nausea or vomiting, awareness, suxamethonium apnoea, malignant hyperpyrexia or unexpected admission to a high dependency or intensive care unit)
- likely difficulties in provision of anaesthesia for the planned surgery (e.g. possibility of fibreoptic tracheal intubation/tracheostomy under local anaesthesia/alternative method of securing the airway)
- local anaesthesia options (either as an adjunct to analgesia or as an alternative to general anaesthesia)
- general conduct of general anaesthesia to include fasting advice, pre-medication, administration of intravenous fluids, blood transfusion, pain relief, control of nausea/vomiting, urinary catheterization, nasogastric tube insertion, placement of arterial and central venous lines
- immediate recovery period and post-operative destination (e.g. HDU/ITU/ward/day case discharge)
- complications related to anaesthesia (e.g. dental damage, cardiovascular complications).

Patient anxieties in relation to anaesthesia are predominantly around the issues of death, brain damage, intra-operative awareness, loss of control, memory loss, pain control, nausea or vomiting and needle insertion.[14] Deaths caused by anaesthesia are very rare. A collection of 14 articles about specific risks associated with having an anaesthetic has been developed to be used with the patient information leaflets. The risk articles are available on the website www.rcoa.ac.uk/patientinfo

In the UK, the pre-operative anaesthetic visit often occurs only minutes before planned surgery. Ideally, all patients should be seen in an outpatient anaesthetic clinic before surgery. This gives time for proper pre-operative assessment, pre-operative preparation and discussion of anaesthetic options and this is what UK services should strive for as it allows for better patient satisfaction, same day admissions (therefore better use of resources) and a smaller likelihood of short notice cancellation due to poor patient preparation.

Patients should have adequate time to consider the indications and implications of any potential operation.[15] The process of informed consent for surgery is a continuous process and rushing a patient to give consent has ethical as well as medico-legal consequences. The UK General Medical Council (GMC) code of Good Medical Practice was updated in 2008 and comprehensively covers consent issues.[16] Ideally, consent for elective procedures should be taken well in advance of the proposed surgery (e.g. at a pre-assessment clinic). This gives the patient time to assimilate the information, discuss with family members if they wish and make appropriate choices. There have been successful cases of litigation when consent has been taken on the day of surgery.[17]

There is a specific consent form in the UK both for parents consenting for children and for those adults that are unable to consent (incapacity form). For those adults that lack capacity, the clinician has to record on this form how they have come to the conclusion that the patient lacks capacity to make this particular healthcare decision and why the proposed treatment would be in the patient's best interests.

Acute pain management plans

Acute pain management plans are made after discussion with the patient in the pre-operative period. Modifications to the WHO analgesic ladder[18] may be useful when considering prescribing post-operative analgesia for patients. Some patients may already be on analgesics pre-operatively. Those patients who are on larger doses of opioids pre-operatively will require larger amounts of analgesia intra- and post-operatively to treat pain. Early liaison with the acute pain team should be made for patients in whom acute pain is anticipated to be difficult to manage.

Simple analgesics include paracetamol and ibuprofen/diclofenac. The vast majority of patients undergoing surgery will receive some intravenous opioid intra-operatively (e.g. fentanyl, alfentanil or morphine). Some patients may require continuing opioids (e.g. codeine or morphine) for a period post-operatively. Tramadol is another analgesic that may be considered.

Drugs should be given orally as far as possible. If they cannot be taken orally then other routes to be considered include sublingual, parenteral (including patient controlled analgesia (PCA)), rectal suppository, nasogastric/percutaneous endoscopic gastrostomy (PEG)/radiologically inserted gastrostomy (RIG) tube and transdermal patch. It is important to know doses, duration of action, contraindications and side effects of analgesics prescribed. The British National Formulary can be a useful guide if there are no local prescription procedures in place.

The correct dose of analgesic for the individual patient should be given at regular intervals to achieve adequate pain relief with minimal side effects and titrated according to pain intensity using regularly measured pain severity scores. It is important to ensure that the patient understands and is involved in their pain management.

As part of multi-modal analgesic delivery, surgeons can infiltrate wound sites with chirocaine (Levo-Bupivacaine) 0.5% (maximum dose 2 mg/kg) at the end of surgery. Elastomeric pumps that can deliver local anaesthetic infusions into wounds are also used particularly in free tissue transfer surgery. By providing a continuous infusion, the pumps have the potential to provide continuous analgesia, eliminating the peaks and troughs in analgesic effect that occur with intermittent local or systemic analgesics. Unlike simple incisional infiltration with local anaesthetics, evidence for the efficacy of local anaesthetic wound catheters is abundant.[19] In a recent systematic review[20] it was concluded that continuous local anaesthetic wound infiltration resulted in a consistently reduced requirement for post-operative opioids, a subsequent reduction in post-operative nausea and vomiting, quicker return to normal bodily function and ambulation and a reduced length of hospital stay, especially in cardiothoracic and orthopaedic populations. Despite the cost of the equipment, the reduction in complications may lead to overall cost savings.

Local anaesthetic infiltration and infusions have recently been incorporated into enhanced recovery programmes.

CONSIDERATION OF VENOUS THROMBOEMBOLISM (VTE) PROPHYLAXIS

VTE is a recognized complication in hospital inpatients. It is associated with significant morbidity and mortality hence the importance in assessment and regular reassessment in patients with a view to the need for anticoagulation. Approximately 25 000 patients in England die each year from preventable hospital acquired VTE.[21] The cost of treating non-fatal symptomatic VTE and associated long-term disability is around £640 million per year. It is not surprising therefore that efforts should be focused on prevention.

In the UK the DoH,[22] the National Institute of Clinical Excellence (NICE)[23] and the Scottish Intercollegiate Guidelines Network (SIGN)[24] have stated that risk assessment and preventative measures for VTE are major patient safety interventions that must be made to save lives. Government policy states that every adult patient should undergo an individual risk assessment for VTE on admission to hospital and this should be a systematic and auditable process.[25]

Therefore, medical and surgical patients who are expected to be in hospital for more than 24 hours are assessed for risk (of both VTE and bleeding) and risk stratified based on various factors including age, period of immobility, obesity and malignancy so that appropriate VTE preventative measures may be instituted (unless contraindicated or refused by the patient). Assessment outcomes must be documented. All patients (or carers) should receive written guidance and verbal information on VTE.

Methods of prophylaxis to be considered include general measures (mobilization, hydration), mechanical techniques (anti-embolic stockings, pneumatic compression boots) and pharmacological agents. Haematology opinion should be sought if hypercoagulable states are present

(e.g. protein C or S deficiency) or if patients are on long term anti-coagulation for other medical conditions.

Reassessment must be carried out every 24–48 hours and after any major clinical change. Appropriate discharge VTE prophylaxis should be prescribed.

CONSIDERATION OF SPECIAL REQUIREMENTS

Patients undergoing surgery in the head and neck region may lose, temporarily or permanently, sensation or motor activity in the distribution of the cranial nerves. Particularly important from a patient's perspective are the loss of communication arising from impairment of hearing, speech or vision, disabling sensation such as vertigo through vestibular dysfunction or alteration to normal activity such as eating, drinking or breathing. Patients who will be unable to speak post-operatively require a plan for communication, such as a bell to attract attention, prepared cards indicating common needs, pen and paper or the use of hand-signals. For those patients undergoing laryngectomy, the pre-operative period is the appropriate time to discuss voice reconstruction options and for the patient to meet the speech therapist and another patient who has undergone, and recovered from, similar surgery.

The disease process or nature of surgery may interfere with nutrition. Failure of adequate nutrition may lead to morbidity and mortality through infection, failure of wound healing and gross catabolism. Nutrition may be provided orally, through a nasogastric tube, via a percutaneous or open gastrostomy, via an open feeding jejunostomy or intravenously. The enteral route is superior in all regards to the intravenous route and should be used whenever possible. Poorly nourished patients require pre-operative supplementation and there is some evidence that a week of enteral (but not parenteral) nutrition improves outcome. A feeding gastrostomy or jejunostomy can be placed in a planned manner at the time of extensive surgery to cover post-operative feeding.

Patients in whom the small or large bowel is required for surgical reconstruction of the upper gastrointestinal (GI) tract may require bowel preparation with a low residue diet or intravenous fluids and laxatives.

PLANNING AND SCHEDULING OF THEATRE TIME AND POST-OPERATIVE CARE

The Confidential Enquiry into Postoperative Deaths (CEPOD) process identifies patients as being **elective** when the surgery can be planned for the convenience of the patient and surgeon, **scheduled** when admission will be prioritized within a few weeks of initial referral, **urgent** indicating an unplanned admission where resuscitation can be achieved before theatre and **emergency** in which surgery is required coexistent with resuscitation. A better scheme starts by indicating whether the patient is listed or unlisted, since the classification of CEPOD urgent or emergency is not always understood or useful.

The operating theatre list should be presented to the theatre reception in the manner required within that hospital. Generally, a theatre list should contain the patient's name, hospital number, date of birth or age and planned surgery. The side of surgery should be recorded as left or right. Some hospitals use the Office for Population Censuses and Surveys (OPCS) or Read codes. The first patients on a list are generally children in ascending age, or shorter operations before longer ones or patients with diseases such as diabetes. Patients with latex allergy must be scheduled first to allow correct preparation of the operating theatre. Similarly, the anaesthetist and senior charge nurse in theatre should be informed regarding patients who are either MRSA positive or have other infections as far in advance as possible. These patients should be placed last on the list wherever possible to allow the theatre to be cleaned adequately after the procedure. Scheduling problems should be resolved by discussion between the surgeon, anaesthetist and theatre sister. Some patients will require a planned extended stay in recovery, or admission to a high dependency unit (HDU) or intensive therapy unit (ITU). Generally, this will be for longer, major procedures, when ventilation is required post-operatively, when the airway is at risk or if extended patient monitoring is required for cardiorespiratory disease. Patients should know about the plans for the immediate recovery period (which may change) and may benefit from seeing the HDU/ITU pre-operatively or talking to a nurse from the unit.

PREPARATION ON THE DAY OF SURGERY

It should be possible to estimate a provisional time of surgery and preparation aims to make certain that the patient is ready when the theatre calls for the patient. Most units use a form with tick boxes to cover the areas of baseline blood pressure, heart rate, weight, allergies, false or capped teeth, patient's wrist band present, consent form signed, notes and X-rays present, investigations present, blood cross-matched, time of last oral intake and details of pre-medication. The side and site of surgery should be indicated with an indelible marker by the surgeon who reviews the patient on the day.

Oral intake on the day of surgery

Fasting guidelines are in existence for planned surgery to minimize the risk of regurgitation and aspiration pneumonitis at induction of anaesthesia.

Historically, surgical patients were fasted routinely from food and drink for unnecessarily prolonged periods sometimes exceeding 12 hours before anaesthesia. Recent studies have shown that reduced pre-operative fasting time without increasing risk of harm from adverse events[26] is beneficial in terms of patients' well-being to include increased patient comfort and hydration. Shortening the

fluid fast may also lead to less anxiety pre-operatively[27] and less nausea and vomiting post-operatively.[28] The volume of administered fluids does not appear to have an impact on patients' residual gastric volume and gastric pH when compared to a standard fasting regimen.[29]

The Royal College of Nursing has produced fasting guidelines[30] for elective surgery. There is a '2–6' rule for adults, which advises that patients may have unlimited amounts of water and other clear fluid up to 2 hours before induction of anaesthesia and solids including milk containing drinks up to 6 hours before surgery. For children, there is a '2–4–6 rule' which recommends that water/clear fluids are advised up to 2 hours, breast milk at 4 hours and formula milk, cows' milk or solids 6 hours before induction of anaesthesia. As an advance to these guidelines the AAGBI guidance[31] allows chewing gum as long as it is not swallowed, for up to 2 hours before induction of anaesthesia.

Regular medication taken orally should be continued pre-operatively unless there is anaesthetist/surgeon advice to the contrary. Diabetic medication needs to be specifically addressed by the anaesthetist. Up to 30 ml water may be given orally to help patients take their medication. If an elective operation is delayed, consideration should be given to giving the patient a drink of water to prevent excessive thirst and dehydration.

ENHANCED RECOVERY AFTER SURGERY

Enhanced Recovery After Surgery (ERAS) is a multimodal perioperative care pathway designed to achieve early recovery for patients undergoing major surgery. ERAS reviews traditional practices and replaces them with evidence-based best practices if applicable. It encompasses all areas of the patient's journey throughout the surgical process.[32] Use of the ERAS pathway has been shown to result in a significant reduction in both length of hospital stay and post-operative complications.[33]

ERAS has mainly been studied in colorectal surgery,[34] vascular surgery,[35] thoracic surgery[36] and radical cystectomy.[37] The rationale behind these programs is to try to modify the physiological and psychological responses to major surgery.

The key principles of the ERAS protocol[38–40] include:

- pre-operative patient counselling
- pre-operative nutrition, avoiding use of bowel preparation, carbohydrate loading* up to 2 hours pre-operatively, early commencement of feeding post-operatively
- goal directed fluid therapy and a standardized anaesthetic
- avoiding opioid analgesia
- early mobilization
- maintaining intra-operative normothermia.

There has been a recent publication wth consensus recommendation[40] from the ERAS Society for Peri-operative Care in major Head and Neck surgery free flap reconstruction. In the OMFS Regional Centre in Glasgow, an Enhanced Recovery after Head and Neck Cancer Surgery (ERAHNCS) protocol for major free flap reconstructive surgery for OMFS/ENT oncology patients was introduced in 2013. The multimodule integrated care pathway focuses on multidisciplinary team involvement to achieve early recovery for patients undergoing head and neck oncology surgery.

There is a drive to introduce early enteral feeding to patients particularly as a component of part of the ERAS programme. Nutritional status is assessed (e.g. Malnutrition Universal Screening Tool (MUST) score in Greater Glasgow and Clyde) pre-operatively and regularly reassessed. There should be a critical care/ward policy in place for introduction of enteral feed for those who require it.

At the Glasgow Centre referred to above, carbohydrate-containing oral drinks are consumed the night before surgery and 2 hours before induction of anaesthesia. This has been shown to reduce hospital stay.[40] If the patient is unable to take oral intake or swallow then the drinks are administered via an enteral feeding tube. Currently, patients with delayed gastric emptying, galactosaemia and diabetes are excluded from the carbohydrate loading aspect of the ERAHNCS programme.

* The stress response to surgery results in a catabolic state and insulin resistance, which is a known risk factor for post-operative complications. Aggressive insulin therapy post-operatively has been shown to reduce morbidity and mortality. Similar results can be achieved when insulin resistance is attenuated and protein losses minimized by the use of pre-operative carbohydrate loading.

BEST CLINICAL PRACTICE

- ✓ The patient should be directed into the correct pathway as soon as surgery is contemplated, and sufficient oral and written information given to inform the patient and initiate the consent process.
- ✓ Attendance at a pre-admission clinic a few weeks before surgery allows a full history and examination to be taken, leading to the identification of any medical, anaesthetic or personal problems. This is particularly important when the interval between scheduling and admission for surgery is more than a few months.
- ✓ The requirement for specific pre-operative blood tests, investigations and blood cross-matching should be agreed by the whole team and produced in a written form which is available to doctors and nurses involved in pre-operative preparation.
- ✓ Pre-operative assessment of the problem patient by an anaesthetist, preferably the one who will be involved, is valuable and ideally should be arranged.
- ✓ Pre-operative tests taken at pre-admission should be reviewed before the admission for surgery so that abnormalities can either be treated in time or the patient rescheduled.

KEY POINTS

- Consider day surgery where possible.
- Assess the risk balance of operation/anaesthesia.
- Moderate or severe cardiorespiratory disease requires medical/anaesthetic review.
- Routine pre-operative tests are expensive and unnecessary.
- Valid, written consent is required for most surgery.
- Consider venous thromboembolism prevention.
- Consider the need for an HDU/ITU bed post-operatively.

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CHAPTER 31

RECOGNITION AND MANAGEMENT OF THE DIFFICULT AIRWAY

Valerie Cunningham and Alistair McNarry

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: difficult intubation, difficult airway, obstructed airway.

DEFINITIONS

The difficult airway is the clinical situation in which a practitioner experiences difficulty with adequate maintenance and/or protection of the airway. The most commonly used adjunct airway devices that help maintain a patent airway are the face mask, with or without a guedel airway, the laryngeal mask, and the tracheal tube. These devices are designed to maintain the patency of an airway and hence reduce impedance to ventilation. A cuffed tracheal tube offers the airway the highest level of security from obstructions or contaminations as the other devices are 'supraglottic'. Tracheal tubes are often the adjunct of choice in head and neck surgeries.

Two broad categories of airway problems can be defined: difficult ventilation and difficult intubation. Difficult mask ventilation is defined by the American Society of Anesthesiologists (ASA)[1] as the 'inability to maintain the oxygen saturations above 90% by face-mask inflation with 100% inspired oxygen or to reverse signs of inadequate ventilation'. Oxygen stores in the body are exhausted within a few minutes and difficulty or failure to ventilate will rapidly result in morbidity or mortality from hypoxaemia. Maintenance of oxygenation but inability to ventilate effectively (we will discuss this later) may still be associated with significant morbidity and mortality related to hypercarbia.

Difficulty or failure to intubate is defined by the ASA as 'the inability to establish tracheal intubation within three attempts at direct laryngoscopy or within ten minutes'. In the UK, the Difficult Airway Society (DAS) guidelines for failed intubation also recommend no more than three attempts at direct laryngoscopy before accepting that intubation by this method has failed.[2] Provided that face-mask ventilation is possible, failed tracheal intubation by itself should not result in hypoxaemia unless the failure of airway protection leads to gross airway soiling from gastric contents, blood, pus or debris. Failure to recognize that tracheal intubation has been unsuccessful is associated with morbidity and mortality. This may occur in cases of unrecognized oesophageal intubation or dislodgement of endotracheal tubes. Continuous capnography from induction to extubation of the patient in the perioperative period is now a basic recommended standard of practice.

Cormack and Lehane[3] described the commonly used classification of the best view of laryngeal structures seen at direct laryngoscopy. Grade I is visualization of the entire laryngeal aperture, grade II is visualization of the posterior portion of the laryngeal aperture, grade III is visualization of the epiglottis only and grade IV is no view of any laryngeal structures. Difficulty with intubation of the trachea is more likely in laryngoscopy grades III/IV and in cases where multiple attempts at conventional direct laryngoscopy in these grades have failed to improve the direct view of the larynx.[4] Classification of laryngeal view has also been described as a percentage of glottic opening or POGO scoring. This method is reported to have good inter- and intra-physician reliability when grading the

laryngeal view; however, there is limited evidence for this and in general it is the Cormack and Lehane system that is most commonly used.[5,6] If there has been a requirement to use a specialized aid or device to aid direction of the endotracheal tube when intubating, this also would indicate that there has been a level of difficulty to intubate. Specialized devices such as tube stylets or gum elastic bougies are used to direct endotracheal tubes towards the glottis opening in cases of difficult laryngeal view. In addition different blades used with the direct laryngoscope, for example the Millar or Henderson straight blades, can be used to improve laryngeal view in 'poor grades' III and IV. The recognition of the need for additional adjuncts or devices has led to theatre suites ensuring specifically stocked carts or trolleys are available for use in cases of difficult or failed intubation. Difficult direct laryngoscopy is only one cause of difficulty with intubation. It may be easy to visualize the larynx but intubation is unsuccessful because the larynx, subglottis or trachea are abnormally narrowed or distorted.

PREVALENCE

Both difficult intubation and difficult ventilation are uncommon. The prevalence of Cormack and Lehane laryngoscopic grade III is 1.5% in the general population. Requiring more than three attempts at direct laryngoscopy occurs in approximately 0.4% of patients and the average anaesthetist will abandon intubation in approximately 1:2500 of general surgical patients. In 1200 consecutive ENT and general surgical patients the overall prevalence of difficult intubation (defined as requiring specialist equipment) was 4.2%.[7] The highest prevalence was 12.3% in ENT cancer surgery, 3.5% in ENT non-cancer surgery and 2.0% in general surgical patients. This confirms the clinical impression that difficult intubation is more common in patients undergoing head and neck surgery, particularly in those patients following extensive surgery, flap reconstruction and post-operative radiotherapy or with an obstructed airway.

It is difficult to know the precise prevalence of difficult face-mask ventilation.[8] Catastrophic failure leading to serious morbidity or mortality is generally quoted as 1:10000–1:100000. However, in any large series, a number of problem patients are identified pre-operatively and these patients may not receive a general anaesthetic. A North American study that involved 18500 patients of whom 18200 were intubated under general anaesthesia quoted that only 1.8% of patients required more than two attempts at direct laryngoscopy and no patient was impossible to mask ventilate.[9] Approximately 300 patients underwent awake intubation and it is this group of patients that is likely to contain those who would have proved difficult to ventilate if anaesthetized. Another study of 1502 patients determined a prevalence of difficult mask ventilation of 5% but the definition used was that the anaesthetist considered the difficulty was clinically relevant and could have led to potential problems if mask ventilation had to be maintained for a longer period.[8] More recent data from the Fourth National Airway Project (NAP4) run by the Royal College of Anaesthetists (RCoA) of Great Britain and Ireland in 2012 reported an incidence of adverse airway events as 1 : 22000 and an incidence of death related to an airway event as 1 : 180000. More than 3 million anaesthetics were audited in this data collection.[10]

EVALUATION

The aim of perioperative airway management is to adequately maintain and protect the airway throughout this period. Adequate assessment and evaluation of each individual patient is paramount to make the most appropriate management strategy. Face-mask anaesthesia is impractical and provides no airway protection for head and neck surgery patients and so has limited application. The appropriate use of either a supraglottic airway or a tracheal tube is dependent on multiple factors such as patient comorbidity and pathology, the length of surgery and the level surgical access to the head and neck structures needed. The need for positive pressure ventilation during the procedure and minimizing the risk of airway soiling from blood, pus, cerebrospinal fluid or gastric contents are also of major importance.

The airway may be evaluated according to the scheme outlined in Table 31.1.

History

The anaesthetic or hospital notes may indicate previously encountered difficulty with airway management. The patient may pass on verbal or written information from a previous anaesthetist that they are difficult, or difficulty may be inferred from a history of displaced front teeth, bruised lips, excessive sore throat or an unexpected stay in ITU. Past surgery or radiotherapy, or the current surgical condition, may be relevant if it affects the head, neck or mediastinum. A number of medical conditions, such as rheumatoid arthritis, obstructive sleep apnoea and acromegaly, have some association with difficult airway management. For example, the incidence of Cormack and Lehan grade III larynx, which is associated with difficult intubation, is reported as 10% in acromegalics. This is six to eight times higher than in the general population.[11] In this group there is also an association with difficulty with

TABLE 31.1 Scheme for evaluation of the airway

Evaluation	
History	Previous airway difficulty Previous surgery Current surgical condition Current medical condition
Examination	General Specific predictive tests
Investigations	MR imaging CT imaging Flow-volume loop Flexible nasendoscopy

bag valve mask ventilation due to the soft tissue hypertrophy of the tongue. Rheumatoid arthritis patients may have reduced neck mobility or have had surgery for fusion of cervical vertebrae and therefore the optimum position for intubation or the 'sniffing the morning air' cannot be achieved. There are a number of congenital conditions, such as Treacher-Collins and Pierre-Robin, in which airway management, particularly intubation, is often difficult. Anatomical hypoplasia of the mandible in these conditions is often associated with poor laryngeal view.

Figure 31.1 illustrates a patient with Hunter's syndrome, in which abnormal mucopolysaccharide is deposited in the tissues. Characteristically, he was difficult to intubate for a tonsillectomy to alleviate obstructive sleep apnoea and required an emergency tracheostomy in the recovery period. He is pictured in his late teens when his original standard tracheostomy tube had been replaced by one designed to circumvent lower tracheal and carinal deposits. This T-Y silastic stent passes from just below the vocal cords into each main bronchus (an inverted Y shape) with a limb passing out through the tracheostomy (the T component).

Examination

General examination is aimed at identifying individual physical findings that may be associated with difficult intubation:

- trauma, burn, swelling, infection, scarring, haematoma of the mouth, tongue, larynx, trachea or neck
- large tongue, receding jaw, high-arched palate, prominent upper incisors, short thick neck, large breasts, microstomia, fixed larynx, impalpable cricothyroid membrane, limited mouth opening, limited head/neck movements
- voice change, shortness of breath, stridor, inability to lie down.

A number of these factors, such as the appreciation of a short neck or receding jaw (Figure 31.2), are subjective. This does not diminish their importance since professional judgements may often be subjective.

A number of subjective tests are used as predictors of difficult intubation. The five tests most commonly used are gape, jaw slide, thyromental distance, Mallampati and atlanto-occipital movement.

GAPE

Patients with small mouths, large teeth, previous surgeries or obvious physical deformity, among other things, may have reduced mouth opening.

Gape is the measurement of maximal mouth opening and is usually expressed as inter-incisor distance in fingerbreadths (fb) or centimetres. Normal values are 3 fb or 5 cm. A mouth opening of 2 fb is limited and 1 fb is severely limited, making direct laryngoscopy very difficult. It is difficult to insert a laryngeal mask when the gape is less than 2 cm (Figure 31.3). Relatively long upper incisors may also contribute to difficulty.



Figure 31.1 Mucopolysaccharidosis (Hunter's syndrome).



Figure 31.2 Receding jaw.



Figure 31.3 Limited mouth opening due to dental abscess.

JAW SLIDE OR MANDIBULAR PROTUSION

Patients with a prominent overbite may be considered more likely to be an intubation challenge, as are patients who are unable to bring their mandibular incisors anterior to their maxillary incisors. The relationship between the maxillary and mandibular incisors during normal jaw closure and voluntary protrusion of the mandible have been graded in an attempt to predict significance to difficulty with intubation.

Functions are graded as follows:

- class A if the lower jaw can be protruded beyond the top teeth
- class B if the lower teeth can only reach the top teeth
- class C if the lower teeth will not reach the top teeth

The value of testing this function is that, in intubation by direct laryngoscopy, the lower jaw must slide forward. In some scoring systems, mouth opening and jaw slide are combined, the greatest difficulty indicated by a gape of < 3.5 cm and class C jaw slide. Another method of testing mandibular protrusion is the upper lip bite test[12] in which the patient demonstrates how much of the upper lip may be covered by the lower incisors. Class 1 indicates 'biting' above the vermilion line, class 2 below the vermilion line and class 3 an inability to bite the upper lip.

THYROMENTAL DISTANCE

Patients who physically have short, fat, thick necks or reduced compliance of the submandibular space (e.g. radiotherapy, induration) may also be difficult to intubate. Many of these patients could have reduced thyromental distances.



Figure 31.4 A normal thyromental distance.

This measurement, described by Patil,[13] is from the mentum to thyroid notch in full neck extension. The normal measurement is 6–7 cm or 3 fb (**Figure 31.4**). A short distance (2 fb) indicates a 'high' larynx and difficult direct laryngoscopy.

MALLAMPATI

Mallampati scoring is a commonly used scoring system for anaesthetists. While the scoring system may not be highly sensitive it is an easy bedside test that is generally regarded as useful in prediction of difficulty with intubation. Mallampati grading is commonly recorded on anaesthetic records.

Mallampati's contribution was a test to assess oropharyngeal space. The test asks a seated patient to open their mouth fully and extend the tongue maximally. The practitioner notes which posterior pharyngeal structures are visible. Mallampati described only three grades:

- class 1 indicates that the posterior pharyngeal wall, fauces and uvula are visible
- class 2 indicates that only a part of the fauces, posterior wall and uvula are visible
- class 3 indicates that the tongue meets the palate; the uvula is not visible.

Samsoon and Young[14] arbitrarily introduced a subdivision of class 3 (tongue against soft palate) and class 4 (tongue meets hard palate).

ATLANTO-OCCIPITAL MOVEMENT

Optimal head and neck positioning for direct laryngoscopy requires cervical spine flexion and almost maximal extension of the head on the spine. A simple clinical test to look at atlanto-occipital movement is for the clinician to ask the patient to flex their neck maximally and then nod; the observer's hand placed posteriorly on the neck makes certain that the nodding motion is at the level of the cranium on the upper cervical vertebrae. Atlanto-occipital extension may be clinically graded as normal or reduced or measured and the normal value is 35°. Connective tissue conditions such as ankylosing spondylitis and

rheumatoid arthritis are associated with pronounced reduction in atlanto occipital movement. Instability of the cervical spine may render movement of the spine impossible due to the presence of a collar, traction or halo frame.

Investigations

Plain X-rays may demonstrate abnormalities, such as enlargement of the retropharyngeal space (Figure 31.5), a swollen epiglottis, tracheal deviation or narrowing, a radio-opaque foreign body or obstructive emphysema suggesting a ball-valve obstruction in the relevant bronchus. However, imaging of the whole airway by CT or MR scan is better and will show narrowing or distortion and allow planning of airway instrumentation. Flexible nasendoscopy under topical anaesthesia is extremely useful in delineating supra- or glottic pathology, and a longer flexible fibrescope can inspect the whole respiratory tract although generally this requires sedation.

Another useful test is the flow-volume loop. This expresses flow during expiration and inspiration as a function of lung volume. Airflow is measured during inhalation from residual volume to total lung capacity and exhalation back to residual volume. Extrathoracic obstruction causes limitation of inspiratory flow whilst intrathoracic obstruction causes limitation in expiratory flow. Limitation in expiratory flow is particularly noticeable because the highest flow-rates are usually present in peak expiration.



Figure 31.5 Retropharyngeal abscess.

PREDICTION OF DIFFICULTY

The practitioner forms a professional judgement as to whether airway management plans need to be altered from that carried out normally based on information gathered from the history and examination of the patient, the nature of the pathological process and surgeries planned and investigations and imagine undertaken. Key predictors of difficulty as previously discussed would be a known history of failed intubation, presentation with breathing difficulty or stridor, absent mouth opening or previous head and neck reconstructive surgery. In pathological processes of the laryngopharynx supraglottic tumour is highly predictive of difficulty with intubation,[15] as is the presence of tracheal compression, the presence of dyspnoea and cancerous pathology in patients with a goitre undergoing thyroid surgery.[16]

However, when there are no abnormalities in the anaesthetic, medical or surgical history, the presenting disease process does not affect the head, neck or mediastinum and the patient does not 'look' difficult, then it is not possible to predict difficulty accurately.

Most attention has been on predicting difficult direct laryngoscopy using various specific or predictive tests (described above), combination of tests and scoring systems. All are imperfect and the reason is partly the low prevalence of difficult intubation. Test sensitivity indicates the ability of the test to label a difficult patient as difficult, test specificity the ability to label a normal patient as normal and the positive predictive value (PPV) is the proportion of patients found to be difficult out of all patients predicted by that test to be difficult. Table 31.2 shows values of test sensitivity, specificity and PPV for the various tests. It can be seen that an individual test, such as Mallampati, has a low PPV indicating that most patients predicted to be difficult will, in fact, be normal.

It is likely that the upper lip bite test and the Mallampati are both poor predictors as single screening tests;[17] however, the more tests that are abnormal in one patient, the increased likelihood that the patient will be difficult to intubate.

Another approach may be to produce a score from consideration of various predictive tests, with appropriate weighting. This may provide a system with higher

TABLE 31.2 Test sensitivity, specificity and positive predictive value from the literature and reference[19]

Test	Sensitivity %	Specificity %	PPV %
Thyromental	65–91	81–82	8–15
Mallampati	42–56	81–84	4–21
Wilson risk sum	42–55	86–92	6–9
Mouth opening	26–47	94–95	7–25
Neck movement	10–17	98	8–30

sensitivities and specificities; however, the subject of prediction of difficulty is fraught with difficulties arising from studies with small numbers of patients, definitions, curious mathematics and inappropriate conclusions.[7, 18, 19] Some meta-analysis data of bedside screening tests for predicting difficult intubation in apparently normal patients propose that they have limited value.[20]

Objective tests aim only to predict difficult direct laryngoscopy when the tongue has a normal compliance and the respiratory tract is normal. Viewing the larynx using direct laryngoscopy with a standard Macintosh blade is reliant on anterior elevation of the mandible and sweeping the tongue to the left while at the same time lifting the epiglottis to open the laryngopharyngeal space and view the glottis. Restriction of tongue movement due to poor tissue compliance may result because of multiple pathologies including tumour, infection, post-radiotherapy or scarring and oedema. Fixation or restricted movement of the tongue is known to cause difficulty.[21] Unexpected difficulty with intubation occurs in cases such as a vallecular cyst and lingual tonsillar hypertrophy, which may be symptomless but will not be predicted, but also in cases with no physical pathology who have anatomically high and anterior larynx which are poor Cormack and Lehane views.[3, 22, 23]

Airway evaluation is an essential part of pre-operative assessment. It may be rewarded by the detection of severe or obvious problems that necessitate a strategy different to 'normal' management. When there are no obvious problems, evaluation is imperfect and safe airway management in all circumstances depends on the adoption of an airway strategy that is able to respond to unexpected difficulty with intubation or oxygenation.

STRATEGY

The recommendations of the ASA on management of the airway[1, 4] promoted the five-step linear model of evaluation of the airway, preparation for difficulty, strategy at intubation, strategy at extubation and follow-up. The ASA difficult airway algorithm presents an overall scheme of planning airway management (**Figure 31.6**).[24]

In September 2004 the Difficult Airway Society Guidelines were published in the United Kingdom. Similarly to the ASA guidelines, they were aimed at providing a standardized logical series of steps following a failed intubation in particular circumstances. The guidance was issued for unanticipated difficult intubation during routine induction of anaesthesia and following rapid sequence induction in the non-obstetric adult patient. They are widely accepted in the UK as a gold standard of care in airway management and they are based on a series of consecutive plans from A to D (**Table 31.3**).

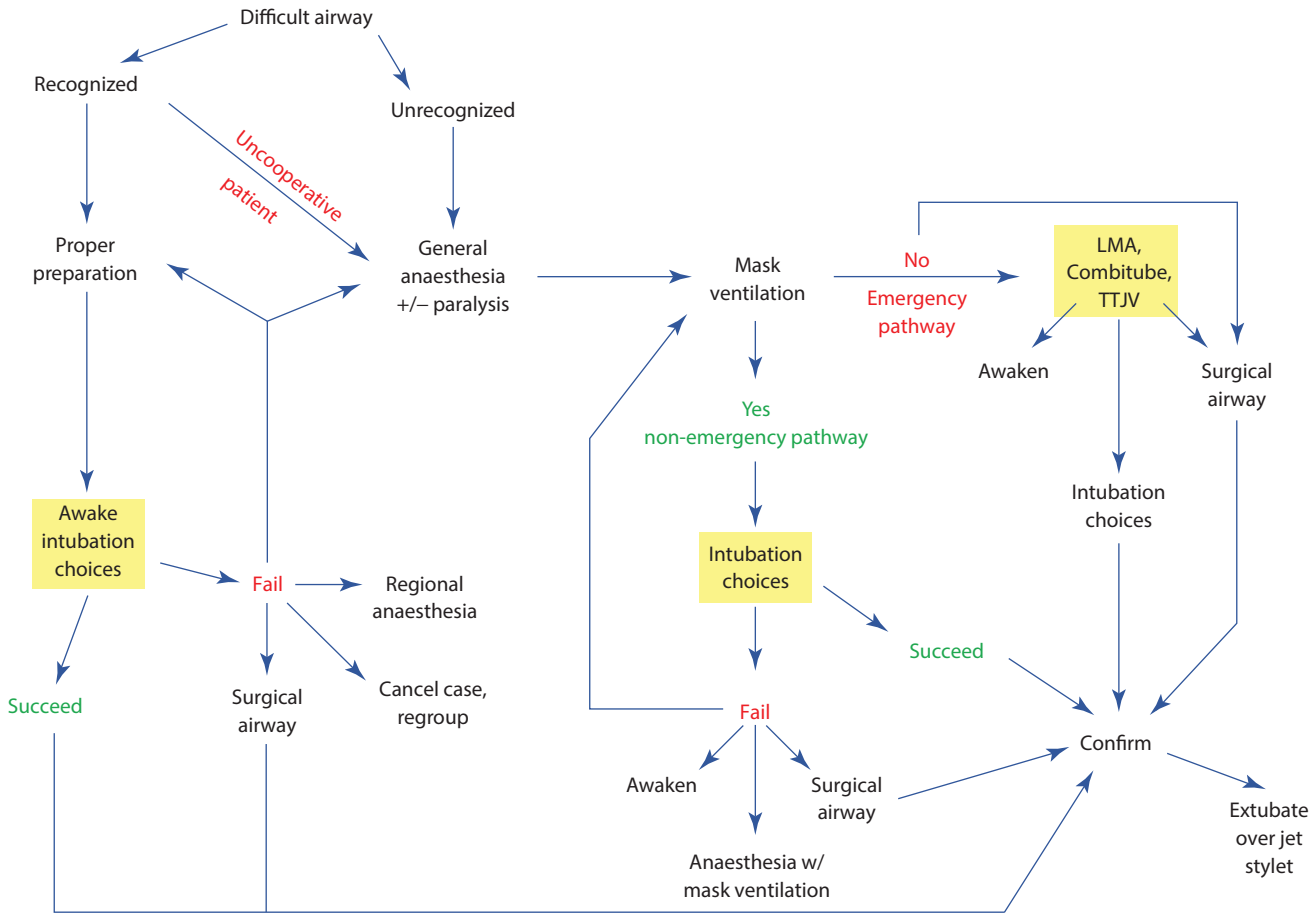


Figure 31.6 ASA difficult airway algorithm. Redrawn from ref. 20, with permission.

TABLE 31.3 Plans A–D in the failed intubation flowchart

Plan	Step following direct laryngoscopy, any issues arising and immediate call for help
A	Initial tracheal intubation plan; no more than four attempts at intubation while maintaining oxygenation with face mask
B	Secondary tracheal intubation plan following failure to intubate; supraglottic airway (LMA) not more than two insertions plus or minus fibre-optic/Aintree catheter guided assistance
C	Maintenance of oxygenation ventilation, postponement of surgery and awakening
D	Rescue techniques in the can't intubate can't ventilate scenario/proceed to needle or surgical cricothroidotomy

Forming a 'management strategy' rather than one isolated plan is the underlying principle of both societies' guidelines. The practitioner is encouraged to plan in advance the steps they will take based upon the success or failure of the first-line plan or 'plan A' that they make following assessment of the patient. Following the publication by the RCoA of the NAP4 study data, it was concluded that this 'strategy' is fundamental to improving outcome from problems resulting from airway difficulties. This conclusion was consolidated by analysis of the reasons that problems arose during airway management. Such problems were shown to be potentiated by poor forward planning, preparation, training and communication. In 2011, the DAS published guidelines on extubation. This followed the recognition that although complications at intubation have been decreasing since the turn of the century, the incidence of complications at extubation has not improved.[25] Extubation scenarios will be discussed later.

Management strategies may not necessarily mean the initial plan A will employ the technique of direct laryngoscopy or the standard curved Macintosh blade to intubate the trachea; however, this is by far the commonest first-line approach. Recommendations when this approach fails are first to attempt to perform basic manoeuvres. Reposition the patient, maximize jaw thrust and neck extension, possibly in combination with backward upward pressure on the larynx by external manipulation to improve the view. During rapid sequence induction relaxation of cricoid force may be needed. Introduction of the tube may be aided by low-tech devices such as a tube stylet, bougie or Magills forceps.

The bougie is a useful 'low-tech' device (**Figure 31.7**) with proven success rates.[26] Its correct use during attempted direct laryngoscopy is by placement through the glottis, either blindly or by educated guess. Correct placement is confirmed by feeling the tracheal rings and hold-up at 25 cm when the bougie contacts the carina. This is followed by railroading the tracheal tube with the laryngoscope still *in situ*. There are traumatic complications to bougie use, epithelial damage or placement into the bronchus resulting in trauma. Caution should be exerted when railroading the tube not to further advance the bougie towards the smaller airways as the tracheal tube is passed over it.



Figure 31.7 The gum-elastic bougie is an effective aid to intubation.

It is widely accepted that generally no more than three or four attempts should be made at direct laryngoscopy, including a change from a Macintosh blade to a straight or alternative blade, and there is some evidence to suggest morbidity with more than two attempts.[27] The correct decision is to acknowledge early a 'failed intubation' and abandon plan A. Defaulting to plan B, both failed ventilation and failed intubation are addressed by using alternative techniques to direct laryngoscopy with a standard Macintosh blade.[2]

ALTERNATIVE TECHNIQUES TO MACINTOSH LARYNGOSCOPY BLADES

Although the Macintosh curved design is the blade most commonly used by anaesthetists, there are a variety of blades that have proven their worth. Straight blades (for example, the Millar and Henderson blades) are used by a slightly different technique to the paraglossal approach with the Macintosh and they have been reported to provide superior views in some cases of lingual tonsillar hypertrophy.[28] It is a similar technique to the rigid laryngoscopy that is employed by head and neck surgeons. Another blade, originally invented by McCoy, employs a lever to increase markedly the angulation of the tip (**Figure 31.8**). A number of direct laryngoscopy blades have been introduced over the years incorporating prisms or mirrors to try and provide an indirect view of the larynx but these have not become mainstream devices.

Videolaryngoscopes

Rigid fibrescopes like the Upsherscope and Bullard, which incorporated fibre-optic viewing bundles into rigid curved blades, have been superceded by new generation videolaryngoscopes (**Figure 31.9**).[29] These devices, designed as aids to intubation, provide an indirect view of the larynx on a small LCD screen on a handheld device or a satellite screen and they have been shown to improve the view at laryngoscopy.[30, 31] There is evidence suggesting that they have a shorter learning curve than direct laryngoscopy, may improve the learning of direct laryngoscopy and require less mouth opening.[32] The LCD camera on these

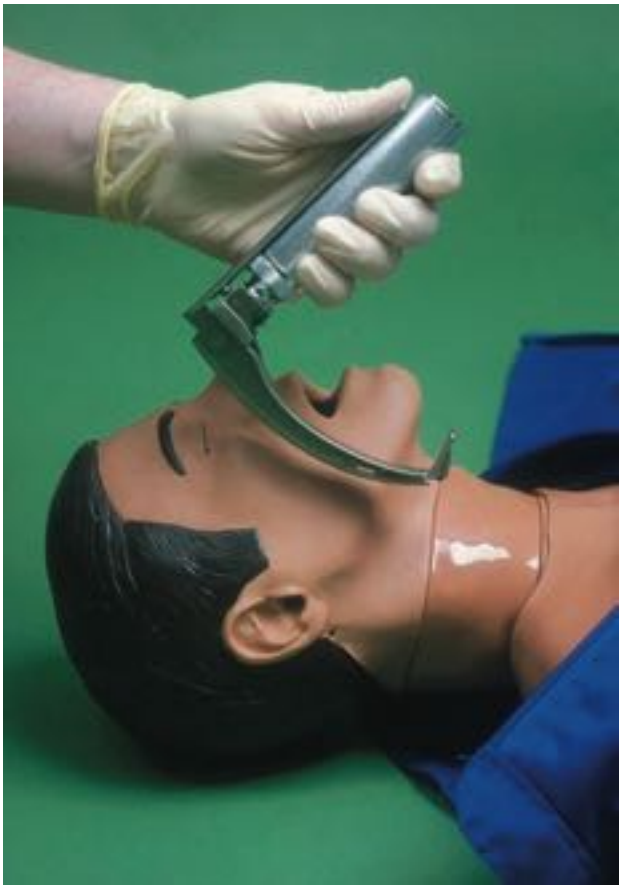
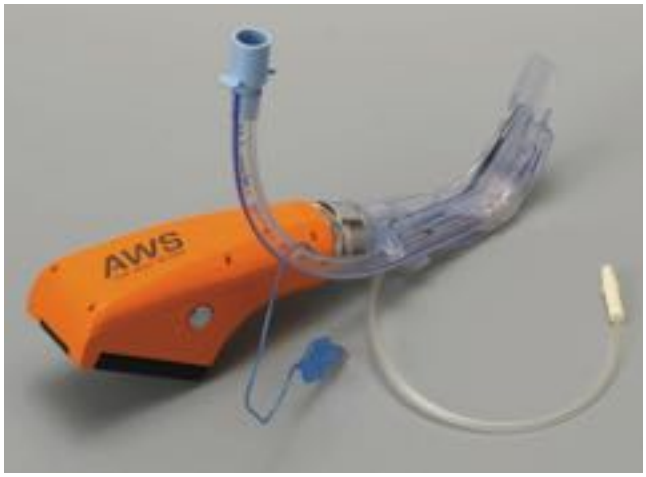


Figure 31.8 McCoy blade with a hinged tip.

handheld devices was developed from CMSO (complementary metal oxide detectors) technology and provides high fidelity small screens similar to those on current phones such as the iPhone 4 and HTC. Videolaryngoscopes can be divided into two large categories: those with Macintosh style blades (direct and indirect view of the larynx is possible); and those with difficult airway blades (indirect view possible only).

Some videolaryngoscopic devices, such as the McGrath MAC and Stortz CMAC, have both types of blade attachment. Some devices have a guide channel for side mounting endotracheal tubes to help direct the tip through the laryngeal inlet, while others require the use of a stylet or bougie to mould the tube to the correct hockey stick shape or guide the tube through the inlet. Although scientific evidence suggests that videolaryngoscopes will consistently improve the view of the larynx there is little evidence to support one particular device over the other.[33] Currently videolaryngoscopes are in widespread use and are gaining in popularity. It can be assumed that successful use of the technique is dependent not only on adequate training but also on operator dexterity and skill, judgement and patient selection. The technique of videolaryngoscopy involves four stages: introduction of the device under direct vision into the mouth, followed by obtaining the best view indirectly by using the LCD screen, followed by introduction of the tracheal tube into the mouth or nose under direct vision. Ultimately the tube is advanced



(a)



(b)

Figure 31.9 (a) Pentax AWS videolaryngoscope side mounted channel; difficult airway blade. **(b)** McGrath MAC videolaryngoscope with a Macintosh style blade.

while observing indirectly on the screen. Within a management strategy these devices would be used within one of the four attempts at intubation in plan A.

Flexible fibre-optic scopes

Tracheal intubation using the flexible fibrescope was first described in 1967 by Peter Murphy,[34] an anaesthetic senior registrar working at the National Hospital, Queen Square, London, and flexible intubating fibrescopes have

been commercially available for over 20 years. Several textbooks[35, 36] are concerned solely with the technique. A standard adult intubating fibrescope has a length of 60 cm and a nominal external diameter of 4 mm. Its narrow diameter allows it to pass through the nose or mouth, its flexibility allows it to conform to the anatomy of the patient, the working channel can be used to instil local anaesthesia, oxygen or to pass wires in the antero- or retrograde direction to aid intubation, the technique is visual and can be used to confirm correct positioning of the tube in the trachea. It is fairly easy to use anaesthetic breathing system connectors or attachments that allow concurrent ventilation of the patient during intubation, or specially adapted airways to make oral intubation easier. It is not surprising that such an instrument has become the safest and most successful technique of intubation. A failed intubation rate of 0.045% is reported in one study and a success rate of 98.4% in another.[37, 38] The complication rate is extremely low.

Fibre-endoscopic skills appear in the core competencies for trainee anaesthetists and include visual inspection of the respiratory tract for diagnostic purposes and placement of double lumen tracheal tubes. The problems associated with the intubating fibrescope are that it is a skilled technique requiring training and practice, the devices are expensive and require careful handling, and disinfection requires chemical agents. There has been particular concern over the inability of cold sterilizing agents to destroy prions. The recommendation from the Department of Health is that a register should be maintained such that all patients treated with an individual fibrescope can be traced easily. Fibre-optic intubation may be part of a practitioners initial plan A strategy or part of a plan B, possibly an asleep fibre-optic intubation or in conjunction with an intubating laryngeal mask airway or supraglottic airway device–Aintree catheter technique.

Intubating laryngeal mask airway

The intubating laryngeal mask was devised by Brain and introduced in 1999. The intubating laryngeal mask airway (ILMA) kit (**Figure 31.10**) differs from the classic laryngeal mask (LM) in several ways. The stem is a rigid highly curved metal tube with a handle, there is an epiglottic elevator bar, a ramp at the junction of the stem and bowl directs the tube appropriately and it is supplied with a special wire-spiral tracheal tube with novel bevel. Single use systems are now widely available. The described technique of intubation in the anaesthetized, paralyzed patient is for the mask to be placed and the patient ventilated through it. Mask placement appears to be easy provided the mouth opening is more than 2 cm. The tracheal tube is inserted through the stem and advanced slowly without force. As the tip of the tube emerges from the stem, it lifts the epiglottic elevator bar and the route is now clear for the tube to be advanced into the trachea. This blind intubation has a success rate of 95% or so if two to three manipulations of mask position and tube advancement are allowed. A fibre-optic modification is recommended that allows a visually guided technique and would seem to be preferable. Published figures suggest a successful intubation rate of 96.5% with a blind technique and 100% when used with the fibrescope[37, 38] although a small North American study[39] compared intubation by the ILMA in anaesthetized patients with awake fibre-optic intubation with suspected difficult intubation and found them both to be 100% successful.



Figure 31.10 Components of the intubating laryngeal mask airway.

Lighted stylets

The technique of transillumination of the neck to guide oro- or nasotracheal intubation was described first in 1959. A lighted stylet[40] uses the principle of trans illumination and takes advantage of the anterior or superficial location of the trachea. A number of commercially available devices have been produced over the years and the most recent, the Trachlight, appears to be the most successful. The tracheal tube is loaded onto the stylet, which has a distal bulb, and the stylet is shaped into a hockey-stick. The lighted stylet is introduced into the oropharynx from the side and brought into the midline. The tip of the light wand is passed around the tongue and a bright, well-circumscribed circle of light seen externally at the level of the hyoid indicates that the tip lies in the vallecula. The tube is advanced into the trachea without resistance. In skilled hands it has been shown to be an effective and rapid technique although it has not gained widespread popularity in the UK. Concerns over heat damage to the mucosa from the lighted stylet Trachlight™ during prolonged attempts have led the manufacturers to design the bulb to flash on and off every 20 seconds.

LARYNGEAL MASK AIRWAYS

The Classic laryngeal mask (LM) has proven itself highly successful among supraglottic airway devices for maintenance of the airway. The classic laryngeal mask airway (LMA™) is the original design of the mask, which consisted of an elliptical high volume low pressure silicone cuff, a breathing tube and connector piece for connection to a breathing circuit or bag. Large study data put the incidence of failed placement as 1:600 patients. They were designed and marketed from the late 1980s for maintenance of the airway in planned, elective surgery

and within three years of launch had been used in over 2 million anaesthetics. There are now many different companies marketing their own disposable version of the device. LMA use has the advantages, when compared with tracheal intubation, of easier placement, no requirement for muscle relaxation and is tolerated *in situ* by the awakening patient. The major disadvantages are that it does not offer the same level of airway protection as a cuffed tracheal tube against gross gastric regurgitation and it does not traverse the larynx, so is no protection against airway occlusion by glottic or infraglottic pathology. LMA design has evolved in recent years with second-generation laryngeal masks (proseal LMA, LMA supreme) having the proposed benefit of a better pharyngeal seals allowing for more efficient controlled ventilation.

They also aim to provide an oesophageal seal or protection reducing the likelihood of aspiration of gastric contents and some (for example the LMA Supreme™ Teleflex®) have integral bite blocks. They have the advantage of having a drainage channel that, when positioned correctly, lies over the oesophageal opening and can be used to assist placement of the mask or pass a gastric tube. The NAP4 study executive summary now recommends the use of a second generation LMA in cases where there is a small but increased concern about regurgitation in preference to first-generation LMAs. There is also a recommendation that all hospitals should have second-generation LMA with an integral bite block available for use. LMAs in general have proved themselves to be a very useful device in difficult airway management and appear in several places in airway algorithms (**Box 31.1**).

BOX 31.1 Role of the classic LM in difficult airway management

- As the desired airway device
- Instead of a tracheal tube
- Rescue device in failed ventilation
- Conduit during emergence
- Conduit for fibre-endoscopy of the airway
- Conduit for intubation:
  - blind
  - bougie
  - fibre-optic-guided bougie
  - fibre-optic
  - Aintree catheter

Intubation via the LM

In normal use, the LM should be seated in close proximity to the vocal cords and it is not surprising that it can provide a route for passage of a tracheal tube. There are five methods for this (**Box 31.1**). A size 6.0 mm will pass through the stem/connector of a size three or four Classic LMA™ and a size 7.0 mm tube will pass through the size five Classic LMA™. This may not be the case for different brand disposable LMAs and should be checked in advance by any practitioner who would use the technique of intubating through these devices as part of a management strategy. Blind placement, in which the tube is lubricated and advanced blindly, has a success rate of only 50–90% and passing a bougie through the LM first has an even lower success rate. Techniques under vision have appreciably higher success rates and flexible fibre-optic techniques are particular useful. It is now not recommended that blind placement of the tube is attempted where fibre-optic equipment is available.

Fibre-optic-assisted techniques are useful because they are visually guided (**Figure 31.11**). The core technique is to insert the LM, load a 6.0 mm tube onto the fibrescope, pass the fibrescope into the trachea through the stem of the LM and slide the well-lubricated tube into the trachea. It is also possible to ventilate an anaesthetized patient through the LM whilst intubation is in progress. This introduces the concept of the laryngeal mask as a dedicated airway,[41] a device used for maintenance of the airway whilst other airway interventions (e.g. intubation) are in progress. Development of this concept led to the design of the Aintree catheter,[42] a hollow bougie that may be placed over the fibrescope and inserted through the LM into the trachea (**Figure 31.12**). Effectively, the technique places a hollow bougie under vision into the airway, over which a tracheal tube is railroaded.



Figure 31.11 The laryngeal mask is a good conduit for fibre-optic intubation.



Figure 31.12 Aintree catheter – a hollow bougie inserted over a fibrescope.

FAILED VENTILATION AND EMERGENCY CRICOTHYROTOMY

Failed ventilation refers to the situation where a patient has been anaesthetized and muscle relaxants administered but it is not possible to provide positive pressure ventilation by use of the face mask and oral airway. A prepared sequence of steps (for example, DAS guidelines steps plan A–C) should commence to provide rescue oxygenation as quickly as possible. Bag/mask ventilation in which two hands are used to try to maintain airway patency and another hand squeezes the anaesthetic reservoir bag should be followed by insertion of an LMA. This may prove life-saving and must always be considered. If oxygenation cannot be achieved by face mask or LM, it may be worthwhile attempting intubation by direct laryngoscopy. This must be a brief attempt only and must not delay oxygenation by the next step.

In a can't intubate and can't ventilate scenario (CICV), and if it is known that the patient has normal airway anatomy or no airway pathology, it may be a consideration to follow the 'awaken patient' limb of the algorithm. If a non-depolarizing muscle relaxant has been given Sugammadex, a modern reversal agent should be administered and anaesthesia discontinued. Sugammadex is a synthetic modified gamma-cyclodextrin. It is the only selective binding agent that provides rapid reversal of the neuromuscular blockers rocuronium and vecuronium. It should be given in a dose of 16 mg/kg for reversal of neuromuscular blockade within approximately 7 minutes of administration of vecuronium or rocuronium. Careful consideration may be given to reversal of benzodiazepines or opiates to increase the speed of emergence.

Airway deaths, unfortunately, often involve prolonged fruitless attempts to intubate when oxygenation is the immediate necessity. Prolonged attempts to intubate patients who initially may have been low risk and appropriate to attempt wakening up may lead to a situation where this cannot be performed due to airway trauma or unconsciousness as a result of hypoxia and hypercarbia. The CICV accounts for 25% of all anaesthetic deaths.

When the anaesthetized patient cannot be oxygenated by face mask or LM, and tracheal intubation is not possible, the practitioner should proceed with emergency oxygenation attempts directly into the respiratory tract below the level of the vocal cords. When attempting emergency front-of-neck access, routing via the cricothyroid membrane (CTM) has a number of desirable properties:

- superficial
- easy landmarks to locate
- present in most patients
- rarely calcifies
- relatively avascular
- wide enough to accept 6.0 mm tube
- inferior to vocal cords
- cricoid ring holds airway open
- posterior lamina protects back wall.

There are three types of cricothyrotomy as detailed in the following sections.[43]

Needle or small bore cannula cricothyrotomy

A narrow-calibre rigid needle or flexible cannula is inserted through the CTM in a caudad direction. In adults, an appropriate size is 14 G with an internal diameter of 2 mm (Figure 31.13). Anatomically bevelled kink resistant cannulas specifically designed for cricothyroid puncture are commercially available. The old-fashioned technique of using a venous cannula has become obsolete. The resistance to flow through such a small calibre needle is high and this has implications for inspiration and expiration. In inspiration, adequate gas flows cannot be obtained by the pressures generated within a standard anaesthetic breathing system and exhalation of 500 mL takes >30 seconds. Inspiratory gas flows of 500 mL/s require oxygen at a pressure of 2–4 bar supplied by a jet injector (Figure 31.14). Traditionally the Sanders injector has been described for jet injection via a cricothyroidotomy cannula. It attaches to the 4 bar (400 kPa, 4 atmospheres) oxygen pipeline and has a hand-operated lever to control gas flow during inspiration and historically has been the common injector available in head and neck surgery for jet injection during rigid bronchoscopy. More recently the



Figure 31.13 Ravussin style cricothyrotomy cannula.



Figure 31.14 Sanders injector.



Figure 31.15 Ventrain device.



Figure 31.16 Planned use of transtracheal jet ventilation.

Manujet (VBM Medizintechnik GmbH, Sulz, Germany) has been widely used. It has the advantage of an adjustable pressure gauge to tailor inspiratory pressures between 0.5 and 4 bars. Other disposable devices for jet injection are available, such as the ENK flow modulator (Cook) and the Ventrain device (Dolphys medical; Figure 31.15), which can actively assist expiration. It is recommended that the pressure that should be used need be only the minimum required to raise the chest wall for inspiration (individual considerations would have to be accounted for if the patient had poor chest wall or lung compliance).

Exhalation occurs through the upper airway and particular attention must be taken to ensure that this happens, otherwise airway pressures rise and pulmonary barotrauma develops, as do haemodynamic consequences. A needle cricothyrotomy is a temporary measure; it will provide for oxygenation and so will give some time. However, it does not allow for adequate gas exchange and fatal hypercarbia can ensue. Consideration must be given to creation of a tracheostomy or competent airway allowing for adequate ventilation in relevant circumstances. It is possible for ventilation via needle cricothyrotomy to be used in the planned elective or urgent case. Figure 31.16 shows a patient whose partial denture had fallen into the pharynx in such a position that the larynx was obscured. The cricothyrotomy needle was placed in the awake patient and its correct position in the trachea confirmed by aspiration of free air and attachment of the capnograph to show an appropriate trace. Following intravenous anaesthesia and muscle relaxation, the Sanders technique of intermittent application of high-pressure oxygen provided adequate oxygenation and ventilation. Exhalation through the upper airway was unobstructed.

Large cannula cricothyrotomy

A purpose-built cannula with an internal diameter of >4 mm allows adequate inspiratory gas flows with the pressures generated by the standard breathing system and exhalation of 500 mL takes approximately 5–6 seconds. This is an advantage because there is no requirement for high-pressure oxygen. It is easy to attach the capnograph



Figure 31.17 Combined Melker cricothyroidotomy set.

to the circuit for confirmation of correct positioning within the trachea, and to suction the respiratory tract. Exhalation occurs through the cannula, even in the presence of complete upper airway obstruction. The cannula may be a cannula-over-needle or a Seldinger-type dilatational device. Cannula-over-needle devices place an uncuffed tube whereas the Melker Seldinger device allows positioning of a 6.0 mm cuffed tube (Figure 31.17). There are advantages in placing a cuffed tube in allowing controlled positive pressure ventilation and protecting the airway.

Surgical cricothyrotomy

The technique is to make a 3 cm midline incision in the skin followed by a horizontal stab incision in the inferior part of the cricothyroid membrane. The incision is spread horizontally and vertically and a 6 mm tube is inserted. The complication rate was 40% in one series of 38 emergency surgical cricothyrotomies. Misplacement and bleeding requiring ligation of vessels were the most common problem. A more rapid four-step technique has been described[44] in which a single horizontal incision is made

through the skin and cricothyroid membrane together. In a cadaver study, emergency physicians compared the standard and rapid technique. The rapid technique was faster than the standard 43 versus 134 seconds, but the complication rate was higher. The horizontal incison through the skin may cause more haemorrhage. A cricothyrotomy tube should not be left in place for more than a few days and conversion to tracheostomy prevents the complications of dysphonia and subglottic stenosis.

OBSTRUCTED AIRWAY

The obstructed airway[45] is one in which the primary symptoms or signs are due to narrowing or distortion of the airway. There are two broad clinical presentations. In acute obstruction (**Figure 31.18**), a previously normal person develops problems over a matter of minutes or hours. The aetiology is usually one of inhaled foreign body or abnormal fluid accumulation, such as blood, pus or oedema. Typical clinical scenarios are infections in the head and neck, post-operative haematoma, and airway swelling secondary to anaphylaxis or angiotensin-converting enzyme inhibitors. The rapidity of onset produces prominent signs of difficulty with breathing and the patients may present in extremis. Imaging of the airway by X-ray, CT or MR scan is desirable but often inappropriate because the patient may be unable to adopt the necessary position to complete the procedure and the radiology suite is not an appropriate location for a patient with a deteriorating airway. The management of acute obstruction includes 100% oxygen by face mask and continuous positive airway pressure (CPAP), adrenaline (epinephrine) if oedema is prominent, steroids intravenously and a trial of administration of heliox. This is known as CASH management, with the rapid institution of these measures in a stridulous patient aimed at buying time until pus is drained and tracheal intubation, emergency cricothyrotomy or tracheostomy is performed and the airway secure. Heliox is a combination of oxygen 21% and helium 79% and is three times less dense than air because of the low atomic weight of helium (4) compared with nitrogen (14). In airway obstruction, turbulent gas flow is inversely proportional to the square root of density and the use of heliox improves gas flow in turbulent conditions and also promotes laminar flow (**Figure 31.19**). It is suggested also that carbon dioxide molecules diffuse four to five times faster through heliox than an equivalent oxygen–nitrogen mixture and this may enhance carbon dioxide excretion in the airway.

In chronic obstruction, the airway pathology has developed over a period of weeks or months and is usually due to growth of tissue or to scarring. The slow onset allows development of enlarged intercostal muscle mass and patients can tolerate a very significantly narrowed airway without symptoms. Generally, a patient will not be dyspnoeic at rest until the airway is narrowed to < 5 mm diameter, although they are likely to be short of breath on exercise. The slower time course of obstruction allows complete imaging of the airway and controlled intervention. Appropriate imaging in the stable, chronic condition is through flexible nasendoscopy and CT or MR imaging of the entire airway. Flow-volume loops may be helpful in detecting that a patient's problem is large airway narrowing and not truly pulmonary, or assessing the degree of tracheal narrowing before planning surgery.

Evaluation of the obstructed airway seeks to define the degree of obstruction, likely site, rapidity of onset and likely time course of deterioration by history, examination and special investigations. The history from the relative or patient usually indicates whether this is acute, chronic



Figure 31.18 Patient with Ludwig's angina.

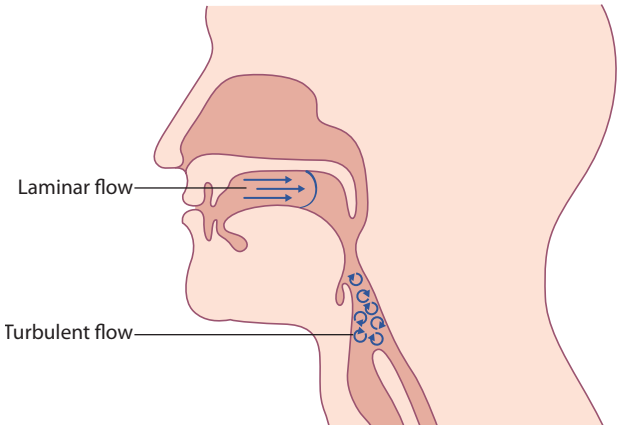


Figure 31.19 Laminar to turbulent flow.

or acute-on-chronic. Specific symptoms/signs in airway obstruction are degree of difficulty with breathing, stridor (noisy breathing) and phase of respiration of any stridor. Stridor indicates that the airway is narrowed to < 50% of normal diameter, but this degree of airway narrowing is not always accompanied by stridor. Expiratory stridor indicates an infraglottic problem and inspiratory stridor a supra or glottic aetiology. There may be a positional aspect to the difficulty with breathing and patients may be more comfortable in the sitting or lateral position. Voice change and difficulty with swallowing may indicate the site or extent of disease, and pyrexia or sepsis indicates an infective component. Unilateral reduction in breath sounds indicate specific bronchial obstruction. With progressive obstruction, signs of ineffective ventilation and poor gas exchange are present. These include agitation, anxiety, confusion, restlessness and depressed level of consciousness. Increased work of breathing is indicated by a high respiratory rate, use of accessory muscles of respiration, flaring nostrils, sweating and tachycardia. Oximetry is not a good monitor of work of breathing and normal oxygen saturation does not indicate that all is well. In severe acute obstruction with untrained respiratory muscles, exhaustion occurs relatively quickly with a resulting decrease in effective minute ventilation, hypoxaemia, bradycardia and death.

Management strategy in the obstructed airway

Deaths resulting from an airway that is obstructed due to a pathological process are usually due to the underlying disease process. However, cases with these pathologies where the airway has been difficult to maintain in the theatre or recover unit have led to deaths.[46] In the NAP4 study 70% of adverse events reported in patients having head and neck surgeries were in patients with an obstructed airway. This includes patients with stridor but also those without. Patients with friable necrotic tumours may be made much worse by attempts at intubation causing swelling, oedema and bleeding and progressive difficulty in face-mask ventilation and this was reflected in the case studies that were reported. In addition, gas induction with the maintenance of spontaneous respiration in patients with obstruction is difficult, the airway liable to deterioration as anaesthesia deepens and airway tone is lost. Those patients with painful faces or necks associated with obstruction are liable to laryngospasm when the chin is lifted and pressure is placed on painful tissues by a face mask. This is explored in more depth later.

Patients should be seen by a senior surgeon and anaesthetist who consider carefully the plan for securing the airway and a backup strategy. Imaging of the airway should be obtained, if possible, to allow delineation of whether the airway is narrowed at supraglottic, glottic or infraglottic level. There should be coherence between the individual plans A–D. For example if a long-acting muscle relaxant is used in plan A, plan B cannot rely on a patient 'waking-up'. If a surgical tracheostomy is the back-up plan, anaesthesia should start in the operating theatre with the equipment, surgeon and theatre team immediately ready – it is foolish to start anaesthesia in the anaesthetic room and scramble into theatre when plan A fails. There has been much discussion in the anaesthetic literature about provision of anaesthesia in the presence of the abnormal airway but general agreement that classification according to the site of obstruction is helpful. Currently, the terms used by anaesthetists are not as precise as the ones used by surgeons to localize tumours.

'SUPRAGLOTTIC' OBSTRUCTION

In 'supraglottic' obstruction the obstruction is above or superior to the glottis and the glottic aperture is of normal dimensions. An example would be a base of tongue tumour (**Figure 31.20**), although clearly this is not truly a supraglottic structure in disease terminology. Direct laryngoscopy is likely to prove difficult and may cause bleeding if the blade contacts the tumour. It may also prove difficult to ventilate by face mask following induction of general anaesthesia. In this circumstance it is helpful to retain spontaneous respiration and to use an alternative means of intubation. Awake fibre-optic intubation (**Figure 31.21**) by the nasal or oral route has much to recommend it.[47] It is used successfully in adult patients with deep neck infections including classical Ludwig's angina.[48]

Awake intubation is a misnomer because it is very difficult to intubate a truly awake patient. The more correct term is tracheal intubation under topical anaesthesia with conscious sedation. It has a very good record of safety in airway management because the patient maintains his or her own airway and continues with spontaneous respiration until the airway is secure. It is possible for the patient to adopt a change in position, such as sitting up, and to aid intubation by protruding their tongue, vocalizing or taking deep breaths. There are a number of intubation techniques in an awake patient, such as oral direct laryngoscopy, blind intubation through the nose, through the classic or intubating laryngeal masks or a retrograde wire technique, although none of these are commonly practised.

Awake fibre-optic intubation (AFOI) appears to be the best technique, combining awake intubation with a

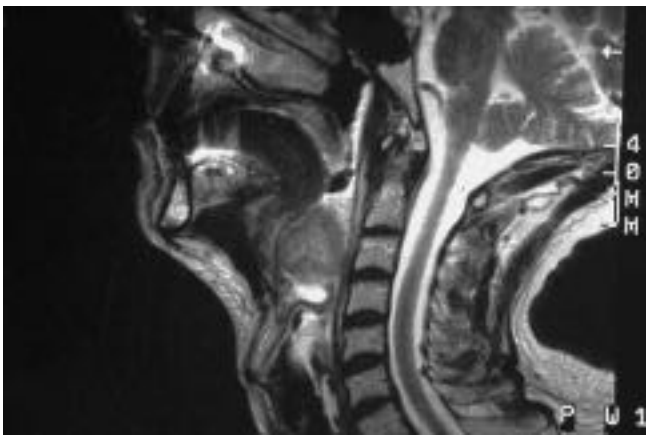


Figure 31.20 Magnetic resonance image of tongue base tumour.



Figure 31.21 Awake fibre-optic intubation.

visually guided method of both inspecting and intubating the airway, applying local anaesthesia to the airway and confirming correct positioning of the tube within the trachea. Fibre-optic intubation is generally easier in the awake rather than anaesthetized, paralysed patient because airway patency is maintained, the airway opens and closes with respiration and the flow of gas indicates the route to the larynx.

There are a number of specific practical steps and attention to detail is required. Premedication may be employed if there is no airway embarrassment, but should be avoided if there are symptoms or signs of airway obstruction. An antisialogogue is important and absence of secretions allows earlier and more profound topical anaesthesia, and easier fibre-endoscopy. Pre-operative intramuscular atropine 0.6 mg, hyoscine 0.4 mg or glycopyrrolate 0.4 mg are suitable. Although it is common to administer glycopyrrolate 0.2–0.4 mg intravenously as soon as the patient arrives in the operating room, the antisialogogue effect when used this way is limited and patients may develop tachycardia.

Sedation aims to provide a comfortable patient who maintains spontaneous respiration, airway patency and verbal contact.

Remifentanil is an ultra-short-acting opioid that is commonly used nowadays by target-controlled infusion (TCI) or in micrograms per kilogram per minute for conscious sedation. It has a profound effect on airway reflexes and the cough response that is desirable during AFOI. It is often used as the sole sedative technique for AFOI.[49]

Small incremental doses of a benzodiazepine and opioid may administered, taking care not to produce over sedation. Typical total doses are midazolam 1–5 mg and fentanyl 25–100 µg. Both drugs have a peak onset of 5 minutes and a specific antagonist (flumazenil and naloxone, respectively). Benzodiazepines cause relaxation of genioglossus and destabilization of the airway and opioids are associated with central respiratory depression so neither drug is benign. However, appropriate doses produce a compliant patient who is not unduly upset by airway topicalization or instrumentation, and is usually amnesic.

Propofol, an anaesthetic agent, provides sedation at subhypnotic concentrations and is used by some anaesthetists for conscious sedation by target-controlled infusion. TCI devices are sophisticated syringe pumps that incorporate a pharmacokinetic model of the relevant drug. The operator enters the age and weight of the patient and the desired blood level. The TCI pump calculates and delivers the appropriate bolus dose to reach the required blood level and the subsequent infusion required to maintain it. Appropriate starting blood levels for propofol are 0.5–1.0 µg/mL.

There are a variety of ways of topicalizing the airway with lignocaine, most practitioners having their 'own way' of administering the local to the mucosa. There is no evidence reporting one technique being better than the other; however, it is important to keep in mind the that local anaesthetic effect will be reduced if tissues are acidotic and that local anaesthetic toxicity is a small risk when using larger doses that are then followed by infiltration of tissues as part of a surgical procedure. The majority of lignocaine administered by topicalization will be swallowed and metabolized by first pass metabolism and so will contribute little to plasma concentrations. However, that fraction that reaches the larynx trachea and bronchial tree will raise blood levels.

If the nasal route is chosen for intubation, a topical vasoconstrictor should be applied. This may be xylometazoline or phenylephrine spray, ephedrine 0.5% drops or cocaine (3 mL 5%), which produces both vasoconstriction and topical anaesthesia. The use of cocaine as a vasoconstrictor for AFOI has reduced in popularity in the last 10 years.

Topical anaesthesia with lignocaine may be provided by:

- nebulization
- translaryngeal administration
- specific nerve blocks
- transendoscopic administration.

Nebulization sounds attractive but use of the technology that provides particles for alveolar deposition of drug (e.g. salbutamol nebulizer) may lead to disappointing results, partly because the particles are too small but also because a large amount of the drug escapes to the atmosphere. High drug concentrations may be effective and nebulized lignocaine 10% in a dose of 6 mg/kg has been described as effective.

A useful variant is the production of a larger droplet size produced during inspiration. This manual spray-and-inhale technique historically employed a 22 g Venflon attached to a constant oxygen flow rate of 1–2 L/min. Specific mucosal atomizer devices are now widely available for this purpose. Small increments of lignocaine 4%

are injected and coordinated with inspiration. One spray-and-inhale regime is to use 3 mL lignocaine 4% with ephedrine 15 mg to the nose, wait 3 minutes and apply the second 3 mL lignocaine 4%, asking the patient to inspire deeply and slowly through the nose. The droplets are inhaled and deposited onto the larynx and trachea. After a 3-minute wait, a further 3 mL lignocaine 4% is nebulized during slow forced inspiration. Maximum lignocaine dosage should be 9 mg/kg.

Translaryngeal administration has a long history of safe use.[50] A 22 G cannula or needle is passed through the cricothyroid membrane or trachea and 3–4 mL lignocaine 4% is injected preferably at end-expiration. The injection provokes a short period of intense coughing, which distributes the drug to the glottis and above. The experimental addition of methylene blue to the local anaesthetic shows staining of the superior aspect of the vocal cords in 95% of patients.

Appropriate specific nerve blocks are of the superior laryngeal and glossopharyngeal nerves and are uncommonly used for AFOI. The internal branch of the superior laryngeal nerve supplies sensation to the under surface of the epiglottis and the superior surface of the vocal cords. It may be blocked on each side as it traverses the thyrohyoid membrane. Extension of the head and neck aids identification of the hyoid and thyroid cartilages. A 22 G needle is placed inferiorly to the greater horn of the hyoid, passed into the membrane and 2 mL lignocaine 2% is injected. The glossopharyngeal nerve supplies sensation to the posterior third of the tongue, superior part of the epiglottis, lateral pharyngeal wall and inferior surface of the soft palate. The nerve may be blocked behind the anterior pillar of the tonsillar fossa. With full mouth opening the tongue is grasped and pulled to the contralateral side. A 20 G spinal needle is inserted to a depth of 5 mm into the base of the anterior tonsillar pillar at the level of the reflection onto the tongue, and 2 mL lignocaine 2% injected. Bilateral glossopharyngeal nerve blocks will abolish the gag reflex and allow greater manipulation in the oropharynx or direct laryngoscopy, perhaps when placing a large double lumen tube. These specific nerve blocks are not performed routinely.

Transendoscopic administration of lignocaine 4% through the working channel of the intubating fibrescope is an extremely effective means of applying local anaesthetic to the airway under vision. This spray-as-you-go technique is highly favoured and non-invasive. The intubating fibrescopes have connectors for injection but an easier alternative is to place an epidural catheter, cut to produce one terminal hole, substantially into the working channel (**Figure 31.22**). Aliquots of lignocaine 4% to a maximum dose of 9 mg/kg are administered.

It is helpful for the fibrescope to be attached to a CCTV system, particularly for training. An appropriate size tracheal tube is loaded onto the fibrescope and the scope is introduced under vision into the mouth or more patent nostril. The fibrescope is advanced without touching the mucosa until the vocal cords are seen. Additional local anaesthetic may be applied before the fibrescope is advanced to the carina. The tube is advanced or railroaded over the fibrescope. This may be difficult because the bevel impinges on the larynx. Use of a small diameter tube and rotation of the tube minimize this problem.

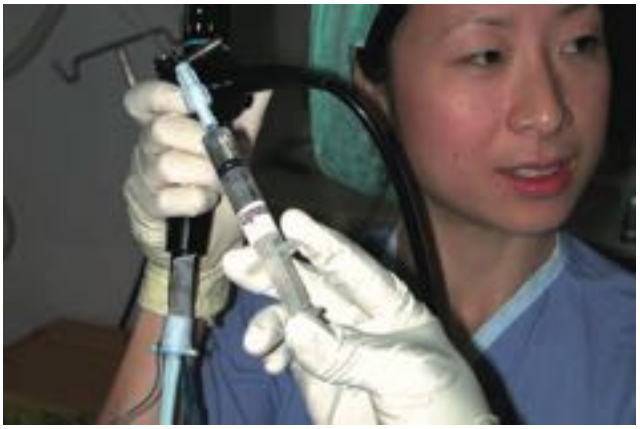


Figure 31.22 Injection of lignocaine through an epidural catheter inserted into working channel of fibrescope.

Awake fibre-optic intubation may be difficult when the airway anatomy is abnormal and when there is blood or secretions in the airway. An illustrative case scenario indicates some of the pitfalls in management. An adult patient underwent removal of a fishbone impacted in the lower pharynx/upper oesophagus. Three days later the patient was pyrexial, with a sore throat, unable to swallow and with limited mouth opening. A lateral X-ray of the neck showed a retropharyngeal abscess. The patient was seen by two anaesthetic trainees, who did not inform the consultant on call. They decided on an awake fibre-optic intubation but administered too much sedation. In a deteriorating situation with a semi-rousable patient they attempted nasal fibre-optic orotracheal intubation (FOI) with the patient supine. They were unsuccessful and were moved aside by the consultant surgeon who managed to intubate the patient fibre-optically with the patient sitting, leaning forward on the edge of the operating table. Mistakes made here include failure to appreciate the seriousness of the condition and to inform a consultant, failure to realize that awake nasal FOI in the supine position would be difficult in the presence of retropharyngeal swelling and failure to realize that airway patency would be compromised by any sedation.

PERIGLOTTIC/GLOTTIC OBSTRUCTION

In these situations it may be difficult to visualize the vocal cords by direct laryngoscopy and the glottic aperture may be significantly narrowed or distorted. Much lively discussion is evident over the correct anaesthetic technique. When awake fibre-optic intubation is used, it allows visualization of the airway but becomes less useful in the patient with stridor due to glottic narrowing. The fibrescope has little rigidity to 'push' through a narrow hole and attempts to do this may precipitate bleeding and oedema. If the scope is passed through a small hole, the airway is completely obstructed for a short time and patients feel uncomfortable at this stage. Panic and ongoing obstruction with this 'corking the bottle' effect

can lead to airway catastrophe. There have been a few reports[51, 52] of destabilization of the airway by applying anaesthetic agent to the airway and this is a reminder of the need to work at all times in the correct environment for immediate activation of the pre-formulated back-up plan. Awake fibre-optic intubation is, therefore, a technique that should always be considered but may not be suitable. It is not appropriate when adequate operator skill is not present, in children and uncooperative adults and in the opinion of some anaesthetists when stridor is present.

Mason and Fielder[53] argue that the correct anaesthetic technique in the presence of stridor due to periglottic/glottic pathology is inhalational induction of general anaesthesia. This permits a gradual onset of anaesthesia and maintains spontaneous respiration, even at a depth of anaesthesia appropriate for direct laryngoscopy and intubation. The maintenance of spontaneous respiration is viewed as highly desirable with supraglottic airway obstruction. A typical case scenario would be a child with epiglottitis and, in a survey of college tutors in the UK, 98% of anaesthetists would choose this form of anaesthesia. The face mask is applied to the patient who is in the most comfortable position (sitting if necessary) and 100% oxygen administered for a few minutes. The volatile agent is administered in increasing concentrations until a surgical level of anaesthesia is obtained. The agent commonly used initially is either halothane or sevoflurane and both drugs are non-irritant so do not provoke coughing. The speed of onset of anaesthesia is inversely proportional to the blood–gas solubility and is therefore faster with sevoflurane (0.6) than halothane (2.4). However, it is more difficult to establish sufficient depth of anaesthesia to instrument the airway with sevoflurane and it has a more rapid offset than halothane. Halothane may be associated with increased cardiac rhythm irritability and is now difficult to obtain in the UK. It is usual, therefore, to start with sevoflurane and consider a change over to isoflurane which does permit adequate levels of anaesthesia.

It is not an easy anaesthetic to administer in the presence of stridor and requires a sanguine anaesthetist. There may be periods of increasing obstruction due to glottic irritability or change in position. Generally, there should be no change in the position of the anaesthetist's hands or the face mask and no attempt in light planes of anaesthesia to provide positive pressure ventilation. Insertion of an oral airway is risky but there may be benefit in a nasopharyngeal airway, although it is perhaps useful to have applied a vasoconstrictor to the nasal mucosa first. Glottic irritability is confined to light planes of anaesthesia and should resolve, although induction may take much longer than normal because of the reduced alveolar ventilation. When an adequate depth of anaesthesia is reached, which may take 20 minutes, direct laryngoscopy is undertaken. The view may be quite abnormal and it may be necessary to press on the chest and observe the egress of bubbles to detect the glottis. A small tube will be needed and the use of a bougie should be considered. If intubation is not possible, the face mask is reapplied and a tracheostomy undertaken. Plan B must be formulated and ready so that anaesthesia is induced in the operating theatre with the surgeon scrubbed and ready to undertake tracheostomy.

It is apparent that the safety of any approach is the combination of plans and the close cooperative working of the surgeon, anaesthetist and theatre team. In the common scenario of a known obstructing glottic tumour that requires initial histology and debulking, it is possible to construct a primary plan of (in the operating theatre) preoxygenation, followed by intravenous induction and rapid muscle relaxation. Direct laryngoscopy using a bougie and size 5.0 mm microlaryngeal tube is attempted. If it is unsuccessful, the surgeon is in the best situation to undertake tracheostomy – the patient is as well oxygenated as possible, unconscious and remains still. This technique is logical and popular but appears 'heretical' since it abolishes spontaneous respiration. However, it illustrates that safety lies in the combination of plans rather than any particular plan A. It also demonstrates that the site of obstruction requires plans that are specific for that level of obstruction and the safety that arises from the close working of experienced surgeon and anaesthetist.

There is an increasing evidence-base to the practice of planned prior placement of a transtracheal ventilation catheter under local anaesthesia and using this as a route for oxygenation and ventilation during intubation attempts under general anaesthesia.[54]

TRACHEOSTOMY UNDER LOCAL ANAESTHESIA

This should be considered in any patient with an obstructed airway. It is particularly appropriate as the primary plan when the disease process is a large friable mass or abscess in the supraglottis or glottis and intubation attempts may destabilize or compromise the airway. There are differences between countries and between surgeon–anaesthetist pairs as to when the patient undergoes traditional intubation in the awake or anaesthetized state or awake tracheostomy. Elements within the decision-making are the availability of a skilled fibre-endoscopist, the ability of the patient to cooperate with the procedure and adopt a suitable position, the pretracheal anatomy and the likely time for resolution of the disease process. It may be a very difficult procedure in patients with short stocky necks, a previous tracheostomy or post-radiotherapy with respiratory distress. Considerations may be complicated by front-of-neck pathology or the patient's inability to lie flat.

Tracheostomy under local anaesthesia is undertaken in the operating theatre with the patient breathing oxygen or heliox, monitored by non-invasive blood pressure, ECG and pulse oximetry with intravenous access. CASH management can be continued throughout the procedure in the semi-sitting position with a roll under the shoulders and neck extension is ideal. Generally, reassurance is given to the patient but intravenous sedation is not required and should be used cautiously. Restlessness during the procedure may be due to hypoxia, hypercarbia or an inability to breathe in that position. Sedation may destabilize the airway leading to sudden hypoxia and

loss of consciousness. Consideration may be given to conscious sedation with remifentanil with the primary aim of obtunding the airway reflexes and improving the distress of the patient; however, caution is highly advisable. The anaesthetist must be prepared for the back-up plan if the patient deteriorates. Placement of a cricothyrotomy needle at the outset may be useful when it is known that the pathology is supraglottic. The cricothyrotomy needle does not interfere with a surgical tracheostomy and can be used to provide oxygenation. If the patient becomes so restless that the surgeon is unable to operate, consideration should be given to providing general anaesthesia and oxygenation through the needle.

Another option in the distressed patient is to provide sedation/anaesthesia by addition of a volatile anaesthetic agent, such as sevoflurane, to the breathing system with 100% oxygen. At best, the airway proves to be adequate enough to allow a surgical plane of anaesthesia to be reached and the tracheostomy is undertaken in a relatively unhurried fashion on 100% oxygen/sevoflurane by face mask. At worst, the airway deteriorates with the onset of sedation/anaesthesia but the patient stops moving and a rapid emergency tracheostomy can be undertaken. In a rapid tracheostomy, the surgeon enters the airway with one or two incisions and a small cuffed microlaryngeal or armoured tube size 5.0–6.0 mm is inserted. Once the patient has been stabilized, a more measured exploration of the neck and fashioning of a formal tracheostomy may be undertaken.

It is important to verify that the tube is within the trachea before ventilation starts, otherwise gas may be forced into the mediastinal tissues. Signs of correct placement when undertaking a tracheostomy under local anaesthesia (with the patient breathing spontaneously) are firstly regular respiratory movement of the reservoir bag of the anaesthetic breathing system connected to the tracheostomy tube, and the presence of six successive breath-related carbon dioxide traces on the capnograph. If no carbon dioxide is detected in the breathing system, inflation of the cuff of the tracheal tube or tracheostomy and connection of the capnograph to the breathing system should be checked first. If both are correct, failure to detect carbon dioxide indicates that the tube is not in the airway. When an emergency tracheostomy is undertaken in an apnoeic patient, the confirmatory signs of anaesthetic bag movement and capnography can be obtained only by applying a number of positive pressure breaths. If the tube is not within the trachea, these positive pressure breaths into the mediastinum may prove deleterious. An alternative confirmatory device in these circumstances, although not widely used, is the oesophageal detector device. The principle is simple and takes advantage of the structural differences between the oesophagus and trachea. In the original version described by Wee in 1988,[55] an empty 60 mL syringe is attached to the 15 mm connector of the inserted tracheal tube and aspiration attempted. Aspiration of air is not possible if the tube is in the oesophagus because the mucosa is 'sucked' over the end of the tube, whereas the more rigid cartilaginous structure of the trachea allows free aspiration of air. The syringe can be replaced by a self-inflating bulb with a volume of approximately 75 mL and in this version the bulb is squeezed flat before being attached to the inserted tube. If the bulb re-inflates immediately, the tube is in the trachea and if the bulb does not re-inflate the tube is in a false passage or the oesophagus.

SUBGLOTTIC AND MIDTRACHEAL OBSTRUCTION

Imaging is particularly useful in delineating the length of narrowing, the diameter of the airway at its narrowest and that sufficient distance is present inferiorly to the obstruction to permit the cuff of a tracheal tube to be positioned above the carina. The obstruction may arise from external pressure, such as a retrosternal goitre or other mediastinal mass, from a mass arising from the trachea, from an inflammatory condition such as Wegener's granulomatosis, from previous surgery or from damage due to prolonged intubation. The type of narrowing may range from a short subglottic stenosis due to previous prolonged intubation to a narrowing of several centimetres in the midtrachea due to tumour. In the presence of stridor, the principles of management vary according to whether it can be bypassed by tracheostomy. This will be true for subglottic disease but the Confidential Enquiry into Patient Outcome and Death (CEPOD) assessors noted that in two patients it had been difficult to bypass a mid/low tracheal lesion with a standard length tracheostomy tube. Awake fibre-optic intubation has a role in management of trachea narrowing, allowing inspection of the airway and confirmation that the tip of the tracheal tube has passed beyond the obstruction. Rigid bronchoscopy is an extremely effective means of managing these patients.

LOW TRACHEAL OBSTRUCTION

Narrowing of the lower trachea or carina presents great difficulty. The anaesthetic literature contains case reports of failed airway maintenance leading to death.[56] This characteristically occurs after induction of general anaesthesia or muscle relaxation when, presumably due to loss of muscle tone, airway patency is lost. Tracheal intubation may not provide an adequate airway because the obstruction is beyond the tip of the tube. Occasionally, the presence of carinal obstruction is not known and anaesthetic induction, intubation or indeed extubation may result in unexpected disaster. When imaging has provided good pre-operative localization of obstruction, a number of options may be used. Rigid bronchoscopy is invaluable and will often provide a route for ventilation (**Figure 31.23**). The rigid bronchoscope may also act as a guide to therapy, such as lasering of a tumour or introduction of a tracheobronchial stent. Surgical resection of carinal lesions requires specialist anaesthetic techniques including jet ventilation and undertaking surgery during cardiopulmonary bypass.



Figure 31.23 Rigid bronchoscopy used for ventilation and conduit for tracheal stent.

JET VENTILATION

Jet ventilation as an in-theatre technique is associated with allowing access in Head and Neck/ ENT surgery and also as an airway rescue technique. It has also been described as a technique for facilitating thoracic radiology procedures and rigid bronchoscopy, and was first described as such over 40 years ago.[57–59] This chapter does not consider its use as a mode of ventilation on critical care.

It is best considered by its nature (high- or low-frequency) and by its position (supraglottic, subglottic or transtracheal). Delivery of each of these has advantages and disadvantages. High-frequency jet ventilation is defined as a respiratory rate of between 1 and 10 Hz and requires the use of a specific device. Low-frequency jet ventilation can be delivered by a Manujet (VBM) at a lower rate (**Figure 31.24**). More complex modes of jet ventilation are described. Superimposed High-Frequency Jet Ventilation combines HFJV with LFJV and has been shown to be effective in patients and offers potential benefits in terms of end-expiratory volumes.[60, 61]

Mechanism: The most common mistake made about jet ventilation is in its mechanism of action. It does not work by the Venturi effect; it works by friction. There are actually six postulated mechanisms as to how it might function:

1. Convective or Bulk flow.
2. Laminar flow in the small airways.
3. Pendelluft.
4. Cardiogenic mixing.
5. Molecular Diffusion.
6. Taylor type dispersion.

Describing jet ventilation

Jet ventilation can be defined in terms of the Driving Pressure (up to 4 bar), the pressure generated by the ventilator, the frequency (or cycles per second) of jet ventilation (between 60 and 600 Hz) and the pause pressure. Pause pressure is sensed in the last 10 milliseconds of the expiratory pause. If the pause pressure alarm calue is exceeded then cycling is stopped preventing breath stacking. This is well described by Wiedemann and Mannle.[62]



Figure 31.24 A low-frequency jet ventilation system. Simple to use, however lacking the safeguards of a more complex high-frequency jet ventilator.

Various articles have looked at the complications of jet ventilation. Hu et al reported a series of 839 cases using the Hunsaker tube.[63] They reported a complication rate of 5.8%, although 47 of the 58 complications were cited as hypoxia (Spo2 < 90%) or hypercarbia (CO2 > 60 mmHg). There were 2 cases of barotrauma and 4 cases of airway obstruction. They cited risk factors for complication as being a higher BMI, ASA class 3 or 4, history of heart disease, history of previous laryngeal surgery, longer case duration, and use of a laser. Patel and Rubin have reported 2 series; 142 cases who were grade I laryngoscopy with a complication rate of 0.7% (Rubin JS 2005) and a difficult airway series looking at 89 cases where they reported no anaesthetic or surgical complications, but noted that higher BMI patients required an increased driving pressure.[64, 65] Jaquet et al. reported a series of 734 jetted patients with 24 minor complications and 4 major ones.[66] Transtracheal jet ventilation was associated with a significantly higher complication rate than transglottal jet ventilation. Serious complications occurred when jetting took place in the presence of airway outflow obstruction. They concluded that the use of a transtracheal jet ventilation catheter was the major independent risk factor. Bougain et al. provide different evidence of transtracheal

jet ventilation.[67] In their series of 643 episodes of transtracheal high-frequency jet ventilation they reported a 1% pneumothorax rate (57% required drainage) and an 8.4% rate of surgical emphysema. They concluded that transtracheal ventilation from an automatic ventilator with a cut-off alarm was safe for experienced users.[67] In their survey in 2008 Cook and Alexander noted that complications over a5 year period were evenly spread between subglottic, supraglottic and transtracheal techniques although deaths all occurred in departments using low-frequency jet ventilation (no pressure alarms).[68] The three centres performing more than 100 cases of transtracheal jet ventilation did not report any serious complications.

The future

In 1990, Smith suggested that high frequency ventilation was here to stay.[69] However, in recent years, there have been innovations that may offer an alternative technique. The ventrain was designed by Enk, as an alarm-free manually operated device that permits transtracheal ventilation.[70] Driven by a conventional wall oxygen flowmeter it can generate a driving pressure for inspiration of 2.3 bar (pressure). However, crucially it can also generate a suction pressure to facilitate expiration (EVA-expiratory ventilation assistance) and avoid air trapping. Unfortunately, clinical trials of the device are limited at present. Unlike other forms of jet ventilation the Ventrain works by the Bernoulli principle.

High-flow oxygen therapy may also an alternative to jet ventilation; however this technique is yet to be evaluated in patients under general anaesthesia.[71]

EXTUBATION AND RECOVERY

At the end of surgery a decision is made as to where and when the airway device should be removed. There is little problem with removal of a laryngeal mask. This is usually tolerated well by a patient until they are awake. Tracheal intubation is common in head and neck surgery due to the constraints of providing clear operative fields for the surgeon and maintaining a secure airway to the distal trachea. Extubation requires as much thought, and gives rise to as much difficulty, as intubation. Transient difficulties with oxygen saturations are common due to coughing, breath-holding and laryngospasm, particularly in children. Extubation problems may arise in those patients who were difficult to intubate and those who were not difficult to intubate but in whom surgery has affected the airway. Of the NAP4 reports, 28% of airway complications were reported at emergence or during recovery from anaesthesia and in all cases airway obstruction was the problem.

Default strategy at extubation when no difficulty is expected is for the anaesthetist to remove any pharyngeal packs, suction the pharynx under direct vision, administer 100% oxygen, antagonize residual neuromuscular blockade and consider whether to remove the tube in the anaesthetized or awake state. After extubation, 100% oxygen is administered by face mask and the patient observed by the anaesthetist until it is clear that the patient is safe to go to the post-anaesthetic care unit (Recovery).

In the patient with a normal airway who was difficult to intubate, it is prudent to make certain that oxygen stores are maximal and to extubate in the awake state. Lung oxygen stores can be considered maximal when the end-tidal (i.e. alveolar) oxygen is 91%. This may take at least 5 minutes of breathing 100% oxygen or longer if nitrous oxide has been used. Awake extubation refers to removal of the tracheal tube when the person has opened their eyes and is able to obey commands. An additional option is to assess the leak around the tube before removal. This may be carried out by applying positive pressure to the tube, deflating the cuff and listening for egress of gas around the tube, or alternatively occluding the tube in spontaneous respiration and making certain that inspiration can occur around the tube. Failure of a leak test indicates that the tube is a very tight fit within the airway and an inadequate air passage may be left after extubation.

In the patient with an abnormal airway, either present pre-operatively or due to surgery, consideration should be given to keeping the tracheal tube in situ for 24–48 hours until any airway oedema subsides. The patient should be nursed in a high-dependency unit with an appropriate level of sedation to avoid inadvertent removal of the tube. In some circumstances it is appropriate to perform a tracheostomy to provide a secure airway in the first few post-operative days.

Extubation of the high-risk airway requires a strategy. Anticipation of complications may be possible, for example long complicated head down surgeries may be accompanied by laryngeal oedema. Awake extubation after maximal oxygenation in the presence of an anaesthetist in a well-equipped environment may be a good plan A, but what happens if it fails? The situation rapidly becomes critical with a struggling, hypoxic patient possibly with blood in the oropharynx. One possibility is to extubate over a thin bougie and to leave the bougie in the airway for a period until it is certain that the patient is coping satisfactorily. The bougie acts as a guide if reintubation is required and, if it is hollow, may be used for emergency oxygenation.

Problems may arise in the Recovery unit or post-operatively on the ward. Of most concern is post-operative bleeding following carotid endarterectomy or removal of a parapharyngeal mass. The physical presence of a mass of blood may compress the airway itself but also induces mucosal oedema, perhaps by impairment of lymphatic drainage. The deterioration of the airway may be very dramatic and necessitate emergency cricothyrotomy or tracheostomy as part of resuscitation. In a dire situation it is always worth fitting an LM. It is helpful to open the wound and evacuate the blood clot and this may provide temporary improvement. The patient is returned to theatre for surgical exploration. Intubation should take place with the patient breathing spontaneously, if possible. This may be by awake intubation or with inhalational anaesthesia. Blood in the pharynx may impair the view and the first response



Figure 31.25 Post-extubation emergency tracheostomy.

is to try suctioning. An LM may cover the larynx and provide some respite before being used as a conduit for intubation. Emergency tracheostomy may be required. In the patient in **Figure 31.25**, drainage of a peritonsillar abscess had been undertaken with intubation by awake fibre-optic intubation. The patient had been extubated and returned to Recovery. Approximately 45 minutes later, the patient developed severe breathing difficulties and was returned immediately to the operating theatre. Awake intubation was not possible due to soiling of the airway, the patient was too restless to adopt a position suitable for formal tracheostomy and, in a deteriorating situation, the surgeon managed to carry out a rapid emergency tracheostomy.

The Difficult Airway Society have recently seen published extubation guidelines in an effort to reduce complications at extubation.[23]

FOLLOW-UP

Following difficulties with airway management, a certain scheme should be followed. An account of the problem and management should be written in the anaesthetic record and in the hospital notes. The patient needs to be reviewed clinically to detect and treat any morbidity, an explanation is required for the patient with details of the problem encountered and management, and a written account should be sent to the patient with a copy to their general practitioner.[72] If the problem with airway management is likely to be recurrent with subsequent anaesthetics, consideration should be given to the patient registering with Medic Alert and wearing a bracelet or to registering the patient with the difficult airway database supported by the Difficult Airway Society.

Immediate morbidity or mortality from difficult airway management arise from the effects of severe hypoxia, hypercarbia or cardiovascular responses, from failure to adequately protect the airway leading to aspiration and from physical trauma to the airway during attempts at intubation or resuscitation. Airway damage may occur even when airway management has not been notably difficult. Valuable information can be obtained from detailed analysis of the medical information contained in insurance reports, once claims for negligence have been settled or closed. In an analysis of such closed claims in North America,[73] 6% of 4460 claims were for airway injury. The most frequent sites of injury were the larynx (33%), pharynx (19%) and oesophagus (18%). Approximately 20% of laryngeal injuries were associated with difficult intubation and included granuloma formation, arytenoid dislocation and hoarseness. Injuries to the pharynx and oesophagus had a much stronger association with difficult airway management. Half of all pharyngeal injuries and 68% of pharyngeal perforations were associated with difficult intubation.

There were five deaths in the pharyngeal injury claims and all involved perforation and the development of mediastinitis. The oesophageal injuries involved a significantly greater proportion of females and patients older than 60 years than the other sites and oesophageal perforation involved difficult intubation in 67% of claims. Oesophageal injuries were the most severe and were associated with a poor outcome with 19% mortality. Pharyngo-oesophageal perforation is a serious condition (overall mortality 25%) and risk factors include difficult intubation, emergency intubation and intubation by inexperienced personnel. Perforation may also be caused by passage of a nasogastric tube. The triad of surgical emphysema, chest pain and pyrexia should be sought and treatment with antibiotics, limitation of oral intake and surgical review initiated as soon as possible. In the closed claims study, surgical emphysema was only evident in 56% of patients and the diagnosis was sometimes delayed. It is suggested that treatment within 24 hours improves outcome.

BEST CLINICAL PRACTICE

- ✓ All patients should undergo airway evaluation as part of preoperative assessment.
- ✓ Strategy must cover unexpected failed intubation and failed ventilation.
- ✓ The LM is a versatile airway device and should always be available.
- ✓ Decisions about management of the obstructed airway are made by senior anaesthetists and surgeons.
- ✓ Awake fibre-optic intubation and tracheostomy under local anaesthesia should be considered in the obstructed airway.
- ✓ Maintenance of spontaneous respiration is recommended when general anaesthesia is employed in the presence of upper airway obstruction.
- ✓ Consider placement of a transtracheal ventilation catheter prior to inducing general anaesthesia in the difficult upper airway.
- ✓ Always confirm correct placement of the tube in the trachea.
- ✓ A strategy is required for extubation.
- ✓ Follow-up is important to detect and treat morbidity caused by airway management.

FUTURE RESEARCH

- Unified surgical and anaesthetic terms describing the location of disease pathology in the airway.
- Randomized comparative studies of anaesthetic techniques in management of the obstructed airway.
- National collection of serious adverse incidents resulting from airway management in head and neck disease.
- National audit of attempts at emergency cricothyrotomy.
- Annual publication of circumstances of death within 28 days of surgery for the obstructed airway.

KEY POINTS

- The difficult airway is an important feature in head and neck surgery.
- Difficult intubation and difficult mask ventilation are different entities.
- Evaluation of the airway is imperfect and may fail to predict difficulty.
- Airway obstruction may be acute or chronic.
- Imaging of the airway is essential, when possible, to delineate the level of obstruction.
- Airway strategy means a primary plan A and back-up plan B.
- The anaesthetic room is an inappropriate location for plan A if plan B is a surgical tracheostomy.
- Pharyngo-oesophageal perforation due to intubation attempts has a high mortality and needs early detection and treatment.

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CHAPTER
32

ADULT ANAESTHESIA

Daphne A. Varveris and Neil G. Smart

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: anaesthesia, ear, nose, throat and maxillofacial, and combinations of the words. Reference lists of retrieved papers were searched manually as were reference lists of standard text (listed in the reference list at the end of the chapter).

As is the case with anaesthesia in general the evidence levels are largely from observational, non-experimental, non-controlled studies or expert opinion (i.e. levels 3 and 4), or in the case of clinical evidence from low-quality case-controlled/cohort studies or clinical series and expert opinion (i.e. grades C and D). This arises purely due to the paucity of randomized controlled trials or meta-analyses of the common questions covered in this chapter.

PRINCIPLES OF GENERAL ANAESTHESIA

Derived from the Greek 'an aesthesis' meaning 'without sensation', anaesthesia is a relatively modern speciality. In 1846, Dr William Morton publicly demonstrated the use of ether to facilitate successful ENT surgery (the removal of a neck tumour). By the early twentieth century, the importance of pain relief and reduction of the stress response in reducing mortality had been recognized. Anaesthesia has continued to evolve not only to enable surgery but also to provide organ support, patient stabilization and long-term pain relief. Based on perioperative mortality statistics, anaesthetic care is often cited as a model for its improvements with regard to patient safety.[1] High quality, low morbidity anaesthesia is tailored to individual patients and their concurrent illnesses and begins with meticulous pre-operative assessment. The role of the anaesthetist as perioperative physician continues to develop.

To facilitate surgery, modern practice seeks to deliver the 'triad' of anaesthesia:

1. Hypnosis – loss of consciousness, implicit and explicit memory
2. Akinesia – prevention of movement
3. Analgesia – obtundation of subconscious response to pain, stress and trauma.

At first a single agent such as ether or chloroform was used to achieve these aims but at perilously high doses. In contrast, modern anaesthesia tackles the triad of anaesthesia using a combination of drugs or agents to satisfy each of the aims separately. This has become known as 'balanced anaesthesia'.

In balanced anaesthesia, the 'anaesthetic vapour' (isoflurane, sevoflurane or desflurane) is used to depress cognitive function and provide the element of 'hypnosis'. This is achieved at relatively low concentrations far below

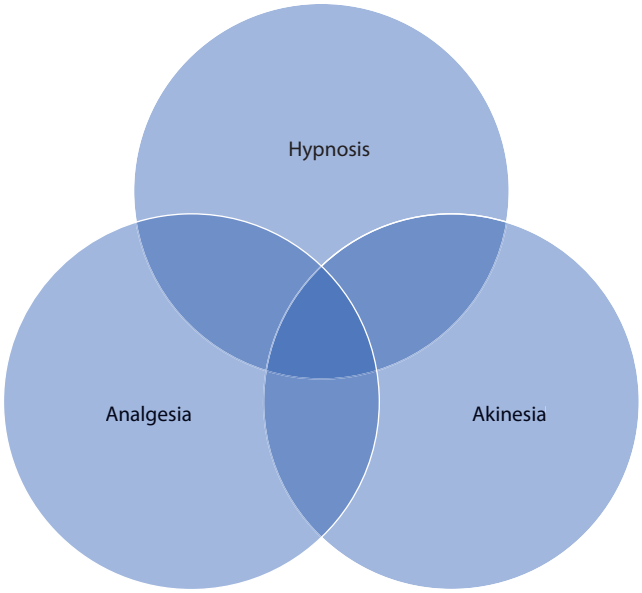


Figure 32.1 Triad of anaesthesia.

those required to achieve akinesia and analgesia and far below concentrations associated with respiratory depression and cardiovascular collapse.

Analgesia is provided by specific drugs such as the opioid fentanyl or the opiate morphine, or by supplemental use of regional or local anaesthetic blocks.

The combination of hypnotic and analgesic drugs may also be sufficient to provide akinesia and abolish movement in response to stimulus yet the patient may still breathe spontaneously. However, it may be desirable to abolish all movement and to relax the tone in all skeletal muscle, for example to facilitate endotracheal intubation or to provide good conditions for laser surgery. This can be achieved by specific drugs such as rocuronium or atracurium, which block the neuromuscular junction and paralyse skeletal muscle. When the element of akinesia is provided in this way, it is possible to reduce the doses of hypnotic and analgesic drugs yet further. So by judicious use of hypnotics, analgesics and muscle relaxants, a state of balanced anaesthesia can be achieved in which the dose of anaesthetic agent is a fraction of that which would be required if it were used as a sole agent (Figure 32.1).

PREMEDICATION

Premedication was originally introduced in the nineteenth century to reduce the amount of chloroform required and thereby speed the onset of surgical anaesthesia. Morphine and its derivatives were often combined with an anticholinergic antisialagogue such as atropine and this reduced patient anxiety and facilitated anaesthesia. Although now uncommon, the combination of an antisialagogue with or without an opiate can still find use prior to an anticipated fibre-optic or difficult intubation.

With the advent of quicker acting anaesthetics and the move to day surgery and same-day admission, sedative premedicant drugs have fallen out of favour. In very anxious patients, an anxiolytic may still be indicated and oral short-acting benzodiazepines such as temazepam are most commonly used in such circumstances. These need to be given approximately one hour prior to surgery.

Other premedication drugs are still commonly administered to improve patient safety and facilitate anaesthesia. For example, pulmonary aspiration of gastric contents can cause a severe pneumonitis. In at-risk patients such as those with diabetes, renal impairment, obesity or gastro-oesophageal reflux disease (GORD), H2 blockers (ranitidine), proton pump inhibitors (omeprazole), gastric alkalinizers (sodium citrate) or prokinetic agents (metoclopramide) may be used.

Paracetamol and non-steroidal anti-inflammatory agents can also be administered orally prior to surgery. These are well absorbed from the stomach and oral administration is cost-effective. Evidence that this is better in preventing pain in the early post-operative period than a similar analgesic treatment initiated after surgery, so called pre-emptive analgesia, is weak. Although widely used, care must be taken with non-steroidal anti-inflammatory drugs (NSAIDS), particularly in the elderly and in patients with dyspeptic symptoms or renal impairment. Altered platelet function and coagulation is an additional consideration in some types of surgery.

KEY POINTS

- Sedative premedication is seldom used in modern anaesthetic practice, especially as day-case surgery is increasing.
- Antiemetic and antacid prophylaxis should be given pre-operatively to high-risk patients.
- Pre-operative oral administration of simple analgesics is cost-effective but NSAIDS must be prescribed with caution in some patient groups.

ANAESTHETIC AGENTS

Intravenous agents

Intravenous (i.v.) anaesthetic agents are most commonly used to induce anaesthesia although they can also be used for maintenance. Their rapid onset of action relates to their high lipid solubility, which allows them to diffuse rapidly into the lipid-rich brain. The brain has a high blood flow and so the drug is delivered quickly to its site of action. After a single induction dose, plasma levels rise and then fall rapidly. This is not due to metabolism, but rather redistribution to other lipid-rich tissues with lower blood flows. Metabolic clearance mostly occurs after hepatic metabolism but this accounts for a much slower 'background' elimination of drug and in most clinical situations plays no part in emergence from anaesthesia.

For many years, the thiobarbiturate thiopentone dominated this class of drugs. However, by far the most commonly used i.v. induction agent in the Western world is propofol, which is a derivative of phenol. This white emulsion mixture has a rapid onset and offset as a consequence of its short context-sensitive half time so patients wake up quickly. The quality of recovery is good with a

low incidence of post-operative nausea and vomiting and a quick return to street fitness. Further benefits include bronchodilation, safety in porphyria and in malignant hyperpyrexia patients, and a lack of active metabolites.

Like most anaesthetic agents, thiopentone and propofol are associated with a fall in blood pressure mediated by a number of mechanisms, including a reduction in central sympathetic vasomotor tone and cardiac contractility. These features are particularly marked in the elderly and patients who are dehydrated or hypovolaemic.

Propofol, unlike thiopentone, can also be used to maintain anaesthesia. This relates to its favourable pharmacokinetics. With a large volume of distribution (Vd), recovery occurs quickly even after prolonged infusions due to drug redistribution. Again the quality of recovery is good with a low incidence of post-operative nausea and vomiting.

Algorithms using population-based pharmacokinetic models (Marsh or Schneider) allow the delivery of propofol by target-controlled infusion and this makes administration safe and predictable.

Propofol is often used in combination with remifentanil, an ultra short-acting synthetic opioid, as part of a total intravenous anaesthesia (TIVA) technique. Remifentanil is metabolized by non-specific plasma esterases and with a context sensitive half-time of 3 minutes and elimination half-time of 6 minutes, it has minimal active metabolites. Used by infusion including target control with the Minto pharmacokinetic model, remifentanil has a short, predictable duration of action with no accumulating effect. Deep intra-operative analgesia can be achieved quickly and yet reversed rapidly. This can contribute to improved intra-operative cardiovascular stability and may also be used to negate the need for neuromuscular blocking drugs, useful when nerve monitoring is required. At the end of surgery, faster recovery and less respiratory depression are achieved in comparison with other opioids but the short duration of action means that alternative post-operative analgesia is required.[2] Remifentanil can also be used to provide sedation during awake fibre-optic intubation. By suppressing airway reflexes, it facilitates excellent intubating conditions (**Figure 32.2**).[3]



Figure 32.2 Target controlled infusion pumps for propofol and remifentanil. Pharmacokinetic algorithms calculate drug delivery taking into account patient age, weight and, for remifentanil, height.

KEY POINTS

- Intravenous induction agents owe their rapid onset and offset of action to rapid diffusion across the blood–brain barrier due to their high lipid solubility.
- Hepatic clearance is moderately slow, and does not play a significant part in the return of consciousness after a bolus dose of intravenous agent.
- Propofol by target-controlled infusion can be used to maintain anaesthesia.
- Remifentanil is a short-acting synthetic opioid often administered intravenously along with propofol as part of a total intravenous anaesthesia technique.

Inhalational agents

Inhalational or 'volatile' agents may be used for induction and/or maintenance of anaesthesia, although they are more commonly used for maintenance alone. The historical archetype is 'ether' (actually diethyl ether), now replaced with less flammable and toxic modern agents such as isoflurane, desflurane (halogenated methyl-ethyl ethers) and sevoflurane (isopropyl ether). Like the intravenous agents, the volatile agents are lipid soluble; the higher the lipid solubility, the higher the potency. Modern agents are extremely lipid soluble and so their potency is sufficiently high to require only an inspired concentration of a few percent to induce anaesthesia. The depth of anaesthesia is determined by the partial pressure (i.e. the effective concentration) of the volatile agent in the brain. Since the brain is in equilibrium with the arterial blood, and the latter is in equilibrium with the alveolar gas, then the depth of anaesthesia should be determined by the partial pressure (or concentration) of volatile agent in the alveoli. Given that the concentration of the anaesthetic vapour in the alveoli (i.e. in the expired breath) can be measured easily, the anaesthetic depth can therefore be estimated reliably. In contrast, there is no means of doing this for intravenous agents.

Volatile agents can also be used to induce anaesthesia, and some do so more quickly than others. The rate of onset (and offset) of a volatile agent is determined by its blood solubility. It has already been stated that the depth of anaesthesia is determined by the partial pressure of the agent in the alveoli/blood/brain. In the blood, only molecules that are not in solution contribute to the partial pressure. For more soluble agents such as halothane, the rate of rise of alveolar partial pressure is comparatively slow because some of the agent is able to enter the blood in solution rather than remaining in the alveolus to contribute to the rise in partial pressure. In contrast, modern agents such as sevoflurane and desflurane have a high lipid solubility and so low blood solubility. This results in a rapid rate of rise in partial pressure in the alveolus and in the blood and brain in turn and so induction is quick. Likewise, when volatile administration is discontinued, elimination is rapid and recovery quick with an early return of airway reflexes.

Sevoflurane is preferred to desflurane for inhalational induction because of its lack of airway irritation. Desflurane has a rapid rate of recovery in prolonged cases and has an important place in some ENT procedures of long duration.

KEY POINTS

- Older agents (ether, halothane) have high solubility in blood and therefore a slow onset and offset of action.
- Modern agents (sevoflurane, desflurane) have low solubility in blood and therefore rapid onset and offset of action.
- Because vapour concentrations can be measured in the expired breath, adequate depth of anaesthesia can be determined with confidence.

DEVICES USED IN AIRWAY MANAGEMENT

The sections above outline the drugs that can be used to induce and maintain anaesthesia. This section examines the devices used in airway management during anaesthesia. One of the hallmarks of anaesthesia for ENT surgery is the concept of the 'shared airway'. The surgeon operates in the same anatomical region as the anaesthetic devices used to maintain the airway. Therefore, the detailed properties of the airway device selected and precise conduct of anaesthesia are particularly important to ENT surgery as compared with many other types of surgery.

The simple face mask

The upper airway is composed of a wide array of soft tissues, muscles and bony structures that modulate its patency. Induction of anaesthesia invariably causes a degree of collapse and the oropharynx behaves as a Starling resistor with airflow critically dependent on pharyngeal tone and transmural pressure.

Pharyngeal collapse is governed by a complex interplay of mechanical and neuromuscular factors but reduction in the tone of the pharyngeal dilator muscles and genioglossus is key. These muscles are innervated by the efferent outflow of the 'respiratory centre', and tone varies cyclically in much the same way as does the diaphragm under the command of the phrenic nerve. Drugs that depress the respiratory centre and have a tendency to produce a 'central' apnoea, also by this mechanism have a tendency to produce an 'obstructive' apnoea. Central and obstructive apnoeas are therefore inextricably linked and cannot adequately be categorized as separate entities.[4]

If neuromuscular blocking drugs are used, then spontaneous ventilation is abolished completely. All these factors require the use of devices that both give anatomical support to the upper airway and facilitate ventilation. Perhaps the simplest means of achieving these aims is a face mask that, when connected to a suitable supply of oxygen and anaesthetic gas, may be used to support the airway manually or (if spontaneous ventilation is absent) allow hand-ventilation of the patient's lungs. Problems with the face-mask technique include poor surgical access to the face, head or airway; it requires that one or both of the anaesthetist's hands are occupied in airway maintenance; and active ventilation of the patient's lungs can often be inefficient as not all the tidal volume administered enters the patients lungs, some being lost as a 'leak'.

Supraglottic airway devices

A range of supraglottic airway devices (SADs) have been developed which reduce some of these problems. First introduced into clinical practice as the classic LMA (cLMA), these are tubes with a distal component, often inflatable, to 'hold' the airway in place. They lie in the oropharynx, above the level of the glottis. SADs allow spontaneous breathing and, similar to the face-mask techniques, facilitate active ventilation. However, since SADs lie above the glottic opening and so do not seal it, there is a risk that positive pressure ventilation of the lungs may not always be possible with leakage of ventilating gas into the oesophagus and stomach. If gastric fluid should then regurgitate, SADs will not completely protect the airway from lung soiling. Second generation SADs such as the ProSeal, LMA Supreme and i-gel, seek to improve on the classic laryngeal mask airway to improve efficacy (airway seal) and safety (gastric access and protection from aspiratiob). These are modified with an oesophageal drain tube and structures to improve the seal with positive pressure ventilation. They have significant use in modern airway management and resuscitation; however, their value in ENT is more restricted when a 'shared' airway is required (**Figure 32.3**).[5]

Tracheal tubes

Tracheal tubes maintain airway patency and protect against aspiration of gastric contents. In adult anaesthesia

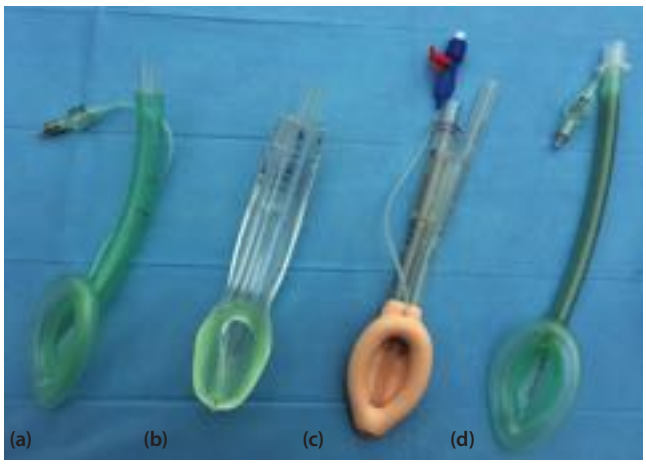


Figure 32.3 SADs **(a)** standard disposable; **(b)** i-gel (intersurgical) – a second generation mask with non-inflatable cuff, improved seal pressure over cLMA, and gastric vent; **(c)** Proseal – has additional posterior cuff and deeper mask. Drain tube acts as vent if regurgitation occurs; **(d)** flexible wire reinforced SAD allows tube to be moved out of surgical field without cuff displacement and is resistant to compression.

cuffed tracheal tubes are most commonly used and these are sited so that the tip lies in the trachea above the carina. To minimize the risk of late onset tracheal stenosis, high volume low-pressure cuffs are preferred and these are inflated with air (saline or methylene blue in laser surgery). The cuff improves the efficiency of ventilation by minimizing leaks and helps maintain the tube in the centre of the trachea. In addition, the airway is protected from soiling by blood coming from above in mouth, nose or laryngopharyngeal surgery and from regurgitated gastric contents.

Since tracheal tubes form a sealed conduit into the trachea, they are primarily used when the patient is paralysed and requires positive pressure ventilation (there is no risk of blowing air into the stomach). It is indeed possible to allow the patient to breathe spontaneously through a tracheal tube, but since the glottis and trachea are richly innervated, deep anaesthesia is required to prevent the patient from reflex coughing. The dose required to achieve this may lead to dose-related side effects (as described below). Whereas most SAD devices can be used effectively after relatively short periods of training, the techniques used by the anaesthetist to insert a tracheal tube are more specialized and are described in more detail in Chapter 31, 'Recognition and management of the difficult airway'.

Tracheal tubes may be passed either orally or nasally and choice of route can depend upon the type of surgery performed. For example, a nasotracheal tube better facilitates surgical access for oral surgery, but is clearly a hindrance during operations of the nose.

The shape, size and material used in manufacture are important in relation to the intended use. Preformed endotracheal tubes (ETTs), such as the Ring, Adair, Elwyn (RAE) tube, direct anaesthetic circuits away from the surgical field to improve access whilst wire-reinforced ETTs also prevent obstruction from kinking. Microlaryngoscopy ETTs are small diameter, large cuff tubes of long length (e.g. 31 cm long, 4–6 mm internal diameter) designed to optimize the surgical view on direct laryngoscopy (**Figure 32.4**).

In thyroid and parathyroid surgery the Nerve Integrity Monitor (NIM) electromyography (EMG) ETT can be used to identify and monitor the recurrent laryngeal and vagus nerves. With two integrated bipolar stainless steel electrodes on each side of the low-pressure cuffed silicone tube, it is placed in close contact with the vocal cords to allow monitoring of the EMG activity of the intrinsic laryngeal musculature. Electrode contact with the true vocal cords is important to ensure adequate response. Nerve stimulation is carried out using a sterile monopolar or bipolar probe. Both electrodes and nerve stimulators require grounding electrodes, usually placed on the sternum or shoulder. These are then attached to the NIM monitor, which produces an audible and visual electromyographic signal whenever the recurrent laryngeal nerve or vagus nerve is stimulated (**Figure 32.5**).[6]

Endotracheal tubes designed for airway laser surgery are constructed to minimize the potential damage to surrounding tissues from heat and toxins. These are further discussed below.

Regardless of which airway device is selected, it is vital that there is constant communication between surgeon and anaesthetist regarding the other's needs during surgery. The airway device must not hinder the surgical process because of its size or shape; it must be properly secured in place to prevent dislodgement during head movement by the surgeon and the direction of the airway device shaft must be appropriate to the operation. Use of surgical gags and props may compress the airway device, so the anaesthetist must be vigilant about the patency of the airway. Even with the presence of a cuffed tube, throat packs are commonly used to protect the airway from blood soiling in nasal surgery and careful removal of these prior to extubation must be ensured. Airway obstruction may occur not only during induction of anaesthesia, but also after extubation and in some circumstances it is important that the surgeon is present at extubation.



Figure 32.4 Different types of endotracheal tube. **(a)** RAE oral south; **(b)** RAE nasal north; **(c)** reinforced; **(d)** microlaryngoscopy (MLT).



Figure 32.5 Medtronic Xomed NIM tube. Two of the four exposed wire electrodes can be seen in the blue area. These come into contact with the mucosa of the vocal cords.

Jet ventilation techniques and tubeless surgery

Jet ventilation was first described in 1967 by Douglas Sanders as a technique to allow patient ventilation during rigid bronchoscopy. It improves access to the airway, particularly in laryngeal surgery, and avoids the need for an endotracheal tube. Low (LFJV) and high frequency jet ventilation (HFJV) systems are available. Both systems work on the premise that high pressure jets of gas are delivered intermittently either manually or automatically. This generates a tidal volume supplemented by the entrainment of gases at the jet nozzle. Expiration is a passive process. No volatile agents can be administered by jet and total intravenous anaesthesia is required.

In LFJV, gas exchange is achieved by direct alveolar ventilation or bulk flow. Most commonly, a hand-triggered manual jet ventilator (e.g. Sanders injector /Manujet III) is used and the lungs insufflated at a frequency of 8–10 breaths per minute to allow adequate expiration. The gas source (usually oxygen piped at 4 bar) is passed through pressure reducing valves, which can be further adjusted via a regulator to a pressure that produces the desired chest-wall movement and maintains oxygenation. It is important for the injector cannula to be aligned with the airway to improve ventilation and prevent gastric distension, particularly when placed in the supraglottic position. Ventilation may be difficult in patients with poor lung or chest wall compliance (**Figure 32.6**). End-tidal CO_2 ($ETCO_2$) is not usually monitored except when a Hunsaker tube is used.

In high frequency jet ventilation, tidal volumes smaller than anatomical dead space are delivered at supraphysiological frequencies of 1–10 Hz. Gas exchange takes place by Pendelluft, Taylor dispersion and cardiogenic mixing.

HFJ ventilators such as the Mistral or Monsoon jet ventilator (Acutronic Medical Systems) humidify and warm gas jets to minimize heat loss and reduce the likelihood of complications arising from the airway drying out. Peak airway pressures are limited by an automatic cut-out device and are lower than with LFJV but barotrauma remains a risk. Surgical conditions are very good with minimal movement of the surgical field (**Figure 32.7**).

Jet ventilation can be applied above or below the vocal cords or in emergencies via the cricothyroid membrane. The supraglottic approach allows a completely tubeless surgical field although there is greater vocal cord movement than with other techniques and a risk of blowing debris including tumour into the distal airway. It is not possible to monitor end-tidal CO_2 ($ETCO_2$) or airway pressures and there is a risk of gas trapping and barotrauma. The inspired oxygen concentration is unknown as significant entrainment occurs. The airway is maintained during the procedure by the surgeon and the quality of ventilation can be impaired by misalignment of the jet with the airway during attempts to access the operative site. Good communication between surgeon and anaesthetist is thus required to ensure adequate ventilation.

In comparison, the subglottic approach requires a narrow catheter or tube such as a Hunsaker and this may limit surgical access posteriorly. However, vocal cord movement is minimal. Furthermore, $ETCO_2$ can be monitored and with minimal entrainment of air, inspired oxygen delivery is more consistent (**Figure 32.8**).[7] Transtracheal jet ventilation can be used as a rescue technique.

KEY POINTS

- Anaesthesia and loss of consciousness result in reduced tone in the pharyngeal dilators and posterior displacement of the tongue.
- The oropharynx behaves as a Starling resistor: airflow is critically dependent on pharyngeal tone and transmural pressure.
- A variety of devices and techniques can be used to maintain the airway during anaesthesia and include the simple face mask, supraglottic airway device and tracheal tube, as well as jet ventilation.
- Jet ventilation is useful in airway surgery to improve the surgical field but TIVA is required and high driving pressures increase the risk of barotrauma.



Figure 32.6 Manujet LFJV directly attached to surgical laryngoscope for supraglottic ventilation.



Figure 32.7 Monsoon jet ventilator Acutronic Medical Switzerland.



Figure 32.8 Laser safe Hunsaker tube provides self-centring, subglottic ventilation with both manual and automated jet ventilation. The jet ventilator is attached via the luer lock and there is a gas sampling lumen.

FACTORS INFLUENCING CHOICE OF DEVICE IN AIRWAY MANAGEMENT

The selection of airway device in individual patients is influenced by several considerations. In general terms, these can be divided into patient factors and surgical requirements.

Patient factors influencing choice of airway device

Of the many patient factors determining choice between an SAD or endotracheal tube, preventing aspiration, maintaining airway patency and facilitating ventilation are the most important.

GASTRO-OESOPHAGEAL REFLUX

Hiatus hernia, symptomatic reflux, pregnancy, abdominal sepsis or injury and recent ingestion of solids or particulate liquids all predispose to regurgitation of gastric contents. Endotracheal intubation minimizes the risk of subsequent aspiration and lung soiling. In high-risk cases, rapid sequence induction with cricothyroid pressure is employed to reduce the time between loss of protective airway reflexes and lung protection by inflation of the tracheal cuff.

OBESITY

Obese patients do not always find it easy to breathe when lying supine, even when awake. This results from both a reduction in lung volume and a restrictive defect. When anaesthetized, this difficulty is exacerbated and tracheal intubation is often necessary to facilitate positive pressure ventilation.

OBSTRUCTIVE SLEEP APNOEA

Closely correlated with morbid obesity, although other ENT related abnormalities of the nose, pharynx and larynx can also be the cause, obstructive sleep apnoea (OSA) is characterized by repetitive intermittent pharyngeal airway collapse during sleep. This results in obstruction of the airway, apnoea and desaturation. Anaesthesia exacerbates OSA and an airway secured with an endotracheal tube is preferred. Potential difficulties with intubation require identification pre-operatively and formulation of an appropriate management plan. Risk extends into the post-operative period following extubation.

PATIENTS WITH KNOWN OR ANTICIPATED DIFFICULT AIRWAY

In cases of known or anticipated difficult intubation where general anaesthesia is the sole option, it can be argued that it is prudent to intubate the trachea electively and so achieve a definitive 'secured airway' before surgery begins. While it is also acceptable to use a SAD device (and sometimes necessary should tracheal intubation fail), the risk remains that, should urgent tracheal intubation be necessary during the course of surgery, this might be difficult or impossible to achieve in a short space of time.

Surgical factors influencing choice of airway device

A number of surgical requirements reasonably influence the choice of airway device.

FACTORS RELATED TO THE 'SHARED AIRWAY'

As a result of the large distal cuff, most SAD devices do not permit a good view of structures distal to the oropharynx. Thus, for almost all periglottic, laryngeal and subglottic operations in which an unobstructed view of the relevant anatomy is required, a tracheal tube is preferred. A tracheal tube is also less likely to be dislodged by excessive movements of the head and neck.

SAD devices may, however, be used for operations related to the tonsils, anterior tongue, nose, teeth and ears without obstructing the surgical field. There may be reduced incidence of coughing and gagging at emergence but care must be taken to ensure the orophaynx is clear of blood to prevent soiling of the airway.

LASER SURGERY

Standard (polyvinyl chloride) tracheal tubes can ignite if struck by a laser beam and manufacturers discourage the use of unprotected PVC tracheal tubes in such airway operations. Wrapping conventional tubes with metallic tape or other materials to shield the flammable material from laser contact has also been described and this reduces the risk of combustion.

More effective protection is provided by specialized laser resistant endotracheal tubes. A number have been developed and these are manufactured from a variety of materials including metals, ceramics and Teflon. Double cuffs



Figure 32.9 Metal spiral armoured laser tube. Note the twin cuffs, which are inflated with saline or methylene blue.

reduce the leak risk resulting from cuff damage and so minimize the fire risk resulting from an oxygen leak. None are completely laser-proof and may combust in certain circumstances (Figure 32.9).

The flexible wire reinforced laryngeal mask airway has also been shown to have some laser-resistance but is not used routinely. Anaesthesia for laser surgery is further discussed below.

REQUIREMENT FOR NEUROMUSCULAR BLOCKADE

Neuromuscular blockade is a reliable way of preventing patient movement, coughing and swallowing and this is particularly important for certain operations such as skull base, laryngopharyngeal, and laser surgery. With paralysis, positive pressure mechanical ventilation is required and an endotracheal tube is most commonly used to facilitate this. Rocuronium, a short acting non-depolarizing aminosteroid neuromuscular blocker, has the advantage that it can be reversed quickly and reliably with sugammadex, a cyclodextrin that encapsulates and binds the active drug. Profound muscle relaxation can thus be used for short procedures including panendoscopy.

POST-OPERATIVE PLAN

After some major operations of the head and neck the risk of post-operative swelling and subsequent obstruction is best mitigated by admission to an intensive care unit with an endotracheal tube *in situ*. Post-operative ventilation might also be necessary in the presence of certain medical conditions such as poor lung function.

KEY POINTS

- In ENT, shared airway surgery is common; a variety of airway devices exist and appropriate selection is particularly important.
- Choice of airway device is influenced by a variety of medical and surgical factors.
- Communication between surgeon and anaesthetist is vital.

Conduct of anaesthesia: Principles guiding induction of anaesthesia

Anaesthesia is planned taking into consideration the requirements of the surgical procedure and the comorbidities of the patient that may impact on safety. Both intravenous and inhalational induction can result in haemodynamic instability, loss of airway tone, apnoea and desaturation. Risk can be reduced with preoxygenation and appropriate monitoring.

Preoxygenation

Before induction of anaesthesia, it is common to preoxygenate by administering 100% oxygen via a tight fitting face mask for two to three minutes. Perhaps counterintuitively, breathing 100% oxygen in this way may not increase the oxygen content of the blood. This is because for most patients, the arterial blood is almost fully saturated with oxygen even when breathing room air, so breathing oxygen cannot really improve on this. Rather, the purpose of this manoeuvre is to wash out the nitrogen-rich air within the lungs and thereby increase the mass of oxygen within the alveolar compartment. A reservoir of oxygen is created that serves to delay the rate of desaturation during a subsequent apnoea. As an alternative, four successive vital capacity breaths of 100% oxygen over 30 seconds can provide effective preoxygenation.

Intravenous induction

The commonest method of induction of anaesthesia is by intravenous administration of one of the drugs listed above but most commonly propofol. Surgical anaesthesia is rapidly induced in one 'arm–brain circulation time' and Guedel's stage 2 anaesthesia, first described using ether and associated with coughing, vomiting, struggling and laryngospasm, is avoided.

The dose of intravenous agent is guided by patient weight but should be titrated slowly according to the observed effect. Injudicious dosing can result in cardiovascular compromise and loss of spontaneous ventilation.

If there is any doubt that ventilation can be maintained post-induction, then the safety of the technique should be questioned and alternative management plans considered. The details and nature of these doubts (i.e. the ability to predict a patient who is difficult to intubate or ventilate) are discussed in Chapter 31, 'Recognition and management of the difficult airway'.

Prior to neuromuscular blockade it is not uncommon to 'check' the ability to ventilate by face mask. This precaution is predicated in the belief that if for some reason the trachea cannot be intubated, then ventilation can at least be achieved and oxygenation preserved. This practice is not universal and in the 'can't intubate, can't ventilate' group of patients neuromuscular blockade with short acting muscle relaxants such as suxamethonium or rocuronium has been advocated as a rescue route to improve mask ventilation.[8]

The Fourth National Airway Project (NAP4) recognizes the importance of a rescue plan in all patients but highlights the importance in head and neck patients, in whom 40% of the serious airway complications occurred.[9]

Rapid sequence induction

Rapid sequence induction seeks to protect the airway from soiling by minimizing the time between loss of protective reflexes and inflation of the ETT cuff. It is particularly indicated in emergency surgery where a patient may have a full stomach or in hiatus hernia with active reflux. It may also be considered where there is airway or gastrointestinal haemorrhage.

Following preoxygenation, a bolus of intravenous induction agent is administered and quickly followed with a neuromuscular blocker. Either suxamethonium or rocuronium (1 mg/kg) are used. No attempt is made to confirm that the lungs can be ventilated by face mask prior to administration of neuromuscular blocker.

As soon as consciousness is lost, the anaesthetic assistant applies 'cricoid pressure' to the larynx. A force of 40 N (4 kg weight) applied to the cricoid cartilage using the finger and thumb compresses the oesophagus posteriorly against the C6 cervical vertebral body and so prevents passive spillage of gastric contents. Laryngoscopy and intubation are now undertaken in the usual manner.

Inhalation induction

Inhalational induction is now relatively uncommon but still remains relevant in ENT practice, particularly in the management of the difficult airway. One advantage of the technique is that spontaneous ventilation is maintained. If the upper airway collapses as anaesthesia deepens and breathing becomes obstructed, then no further anaesthetic vapour can enter the lungs. The anaesthetic is redistributed during apnoea and the patient begins to wake up, thereby restoring upper airway tone and breathing. For this reason, inhalational induction has been advocated as a safe option for patients with perilaryngeal tumours and stridor. In contrast to intravenous induction, therefore, inhalational induction may be used even when there are doubts about the ability to intubate the trachea or maintain ventilation.

Inhalational induction may also be the technique of choice in patients with little cardiovascular reserve and relatively stable conditions can be provided in patients at risk from hypotension, hypertension and tachycardia.

However, there are some practical disadvantages. First, because induction is slow, there is a danger that the stage of excitability is prolonged. Second, should collapse of the upper airway occur during inhalational induction then not only anaesthetic vapour but also oxygen is prevented from reaching the lungs. Thus, inhalational induction may not be as safe or controlled as may be claimed.

In clinical practice, sevoflurane has now largely supplanted halothane for inhalational induction, its rapid onset and offset being accompanied by a pleasant smell and minimal airway irritation.

Induction after securing the airway

Certain conditions require techniques that achieve tracheal intubation with the patient awake or sedated, anaesthetic induction occurring only after the airway is secured. These methods are discussed further in Chapter 31, 'Recognition and management of the difficult airway'. Planned awake tracheostomy under local anaesthesia is an additional option.

MONITORING IN ANAESTHESIA

Derived from the Latin *monere*, to warn, monitoring is used to describe measurements whose prime purpose is to 'warn' of imminent (possibly injurious) events, and allow action to be taken to avoid them, or moderate their effect. The Association of Anaesthetists of Great Britain and Ireland publishes guidelines for minimum monitoring standards, and these are reviewed from time to time (**Figure 32.10**). Both at induction and throughout the operation, the most important 'monitor' is undoubtedly the anaesthetist who can synthesize information derived from clinical observation and specialized devices and take appropriate action.

BASIC INTRA-OPERATIVE MONITORING

ECG

Continuous ECG recording is universally used, its purpose being to detect the development of dysrhythmias and myocardial ischaemia.

The lead II configuration best displays rhythm disturbances (atrial fibrillation, heart block, asystole, ventricular tachycardia, ventricular fibrillation) while the CM5 placement best detects myocardial ischaemia (ST depression, T wave inversion).

The ECG gives no information about pump function and circulation.



Figure 32.10 Minimal standards of monitoring; ECG, pulse oximetry, $ETCO_2$, NIBP.

Pulse oximetry

Pulse oximetry provides safe, non-invasive monitoring of arterial oxygen saturation. Based on spectrophotometry and the different light absorption characteristics of oxygenated and deoxygenated blood, these devices shine two different wavelengths of red light through an extremity (usually a finger) and measure the absorbance of transmitted light. A number of substances absorb or scatter this light, including arterial haemoglobin, venous haemoglobin, skin, bone and nail-bed. However, in addition to the background absorbance, there is a component that varies throughout the cardiac cycle, and this pulsatile absorbance is due to the added volume of arterial blood that enters during or shortly after systole. If this pulsatile signal is subtracted from the background, the resulting absorbance signal is wholly accounted for by the composition of arterial blood. The proportions of oxygenated and deoxygenated haemoglobin can then be identified and Sp02 calculated.

The pulsatile waveform displayed on the oximeter screen also gives a beat-to-beat indication of circulation, the electronic equivalent of keeping one's finger on the pulse.

Most accurate above 90% saturation, reliability decreases at lower saturations below 70%. Accuracy is also affected by poor peripheral perfusion, electrical interference, and the use of dyes such as methylene blue.

Oxygenation rather than ventilation is measured. Hence patients breathing supplemental oxygen may still be well saturated, despite being virtually apnoeic and at risk of imminent respiratory arrest. In high-risk patients at risk of respiratory depression or obstruction post-operatively, pulse oximetry must not be relied upon to monitor the adequacy of ventilation.

Automatic non-invasive blood pressure

Automatic non-invasive blood pressure (NIBP) monitoring uses the principle of oscillotonometry applied to an inflatable cuff around the arm. These devices record blood pressure intermittently and have gained widespread acceptance because they are safe and easy to use but they do have limitations.

While the mean blood pressure measurement is reasonably accurate, the systolic and particularly the diastolic values are less so and low pressures tend to be overestimated and high pressures underestimated. Readings may be inaccurate or difficult to record in the presence of an irregular cardiac cycle resulting from a rhythm disturbance such as atrial fibrillation, or in patients who are shocked or peripherally shut down.

As blood pressure measurement is not continuous, detection of sudden changes including cardiovascular collapse may be delayed.

Invasive monitoring of blood pressure

Blood pressure can be measured invasively through a cannula sited in a suitable artery, usually the radial. This allows beat-to-beat measurement and the detection of rapid changes in real time. The morphology of the arterial 'waveform' including the rate of upstroke, pulse pressure and the presence of 'pulsus paradoxus' provides useful information on circulatory and vasotonic status. Blood gas sampling via the arterial cannula is also facilitated. Unlike non-invasive blood pressure measurement, invasive monitoring is reliable and accurate in both high and low pressure states. Disadvantages are few, but include the fact that siting such cannulae can be difficult, and the disposables are relatively expensive. There is a very small risk of unrecognized disconnection and bleeding, drug injection error, thrombosis, distal ischaemia and infection.

Oxygen analysis

It is axiomatic that oxygen is vital for safe anaesthesia. Since it is odourless and colourless, the use of an oxygen analyzer with audible alarm is vital to monitor the composition of gases leaving the anaesthetic machine and entering the patient airway. Gas is continuously sampled from the airway and a rapid gas analyzer displays the concentration of inspired and expired oxygen breath-by-breath. Most analyzers are also capable of monitoring other gases including CO_2 and anaesthetic vapours.

Inspired and expired CO_2

Inspiration of CO_2 raises $PaCO_2$ and severe hypercapnia may be life threatening, hence inspired CO_2 should be zero or near zero. Rising inspired CO_2 concentrations indicate that the patient is rebreathing exhaled breath and this usually results from a faulty breathing circuit, inadequate gas supply from the anaesthetic machine, or exhaustion of the CO_2 absorber.

The capnograph measures end-tidal CO_2 ($ETCO_2$) and is one of the most important monitors in anaesthesia. It provides robust evidence of tracheal intubation; expired CO_2 confirms endotracheal placement while the absence of an alveolar waveform is strongly suggestive of oesophageal intubation.

'End-tidal' refers to the concentration at the very end of expiration and is taken to be representative of alveolar gas. The $ETCO_2$ is therefore useful to confirm the adequacy of alveolar ventilation and identify hypoventilation and hyperventilation.

In metabolic states such as malignant hyperpyrexia and thyroid storm, a rising $ETCO_2$ on capnography can assist in diagnosis.

Capnography can also play a part in the identification of a number of cardiorespiratory abnormalities including a falling cardiac output, pulmonary embolus, and V/Q mismatch.

Inspired/end-tidal anaesthetic agent concentration

By sampling the concentration (or partial pressure) of anaesthetic vapours in the expired breath, the anaesthetic partial pressure in the alveolar gas and hence the arterial blood and brain can be estimated. This is a reliable way of

monitoring anaesthetic depth because the dose-response curves (or more accurately the partial pressure-response curves) for these agents show very little inter-individual variation.

Airway pressure and tidal volume

Measurement of airway pressure and expired volume is important, particularly during mechanical ventilation. Airway pressure is influenced by the compliance (or elastance) of the lung and chest wall and by the resistance to airflow. Compliance is influenced by muscle paralysis, surgical manipulation and pneumothorax. Sudden changes in airway pressure resulting from increased resistance to airflow may result from bronchospasm, endotracheal tube displacement or compression by a Boyle Davis gag.

Temperature

Patients tend to cool during anaesthesia and inadvertent hypothermia is associated with adverse effects which include delayed wound healing, depressed immunity, increased risk of pressure sores and impaired coagulation.

Defined as a core temperature below 36 °C, hypothermia develops as a consequence of:

- heat loss to the environment (cold theatre, exposed body surface/cavities, vasodilation caused by anaesthetic drugs)
- altered thermoregulation under anaesthesia
- loss of the behavioural response to cold.

Effective temperature management begins with accurate measurement. The thermistor probe is the most commonly used type of measurement device. Common sites for placement include oro/nasopharynx, tympanic membrane, rectum and bladder. Several different types of patient warming device are available for prevention and treatment and the National Institute for Health and Clinical Excellence (NICE) recommends forced air convection warming (e.g. Bair-Hugger) and the Inditherm warming mattress. Fluid warmers are of value should the administration of cold products such as blood or blood products be required.

Monitoring of neuromuscular function

Neuromuscular blockade is measured by means of a peripheral nerve stimulator, now considered essential when using muscle relaxants. Four successive supramaximal stimuli are delivered at 2 Hz, 50 mA by two adhesive electrodes placed on the skin over a convenient peripheral nerve (usually the ulnar, facial or common peroneal). With increasing degrees of block, the twitches in the train of four progressively fade. The only reliable guarantee of return of safe motor function is a train of four ratio > 0.9.

This differs from the facial nerve monitor used by the ENT surgeon, which detects microvolts of EMG activity, rather than gross movement. It is possible for patients to be moderately but adequately blocked from the anaesthetic perspective but sufficiently unblocked for safe facial nerve monitoring. The important point here is that if this approach is used, the surgeon needs to be aware of it.

The problems of neuromuscular blockade in the context of facial nerve monitoring in middle ear and parotid surgery are discussed below.

Central venous pressure/pulmonary artery wedge pressure/cardiac output/transoesophageal echocardiography

This is **not** routine monitoring, but is used where indicated by:

- the patient's pre-operative medical condition (e.g. left ventricular failure, sepsis)
- surgery that is likely to produce significant deviations in these parameters (e.g. large blood loss or compression of the mediastinum and great vessels).

The aim is to detect and correct changes in left and/or right ventricular preload, afterload or contractility indicated by changes in venous and pulmonary pressures, arterial pressure and cardiac output.

Transoesophageal echocardiography (TOE) has grown in popularity as it provides information on ventricular volume rather than pressure. Initially used mainly as a monitor of left ventricular ischaemia, it now provides real-time dynamic information about heart physiology and can be used to guide therapy in haemodynamically unstable patients

Depth of anaesthesia monitors: EEG/AEP/BIS

A number of devices that measure and process EEG signals are available for estimating anaesthetic depth during surgery. Such monitors are recommended in patients at greater risk of awareness and in patients receiving TIVA. However, data on effectiveness remains mixed and such devices should be used along with clinical observation. For patients breathing spontaneously and unparalyzed, 'awareness' under anaesthesia has an incidence of 1 : 136 000. In contrast, the incidence rises to 1 : 8000 when muscle relaxants are used. This likely reflects difficulty in detecting the early warning signs of awareness such as movement and coughing in this group.

ANAESTHETIC TECHNIQUE: PRINCIPLES FOR SPECIFIC ENT OPERATIONS

The above sections indicate broad principles used to determine choice of anaesthetic drugs, airway device, mode of induction and monitoring. We now turn to some specific operations in ENT surgery and the particular

TABLE 32.1 Considerations for anaesthesia in ENT

Shared airway	• Communication • Surgical access • Inaccessible airway intra-operatively (head position distant to anaesthetist) • Disconnection/displacement/ compression potential • Airway soiling • Hidden blood loss
Positioning	• Reverse Trendelenburg to reduce bleeding, neck extension and complications
Dental trauma	• From anaesthetic or surgical access
Laser	• Airway fire prevention
Nerve monitoring	• E.g. facial/recurrent laryngeal nerve
Post-operative	• PONV • Airway soiling • Tracheostomy care • Airway irritation (coughing) • Post-operative airway oedema

challenges posed. In general terms, anaesthesia for ENT has many unique considerations and these are summarized in Table 32.1.

Tonsillectomy and adenoidectomy

In adults, the most common indication for adenotonsillectomy is chronic or recurrent infection. Although tonsillitis is less common in adults than in children, it tends to be more severe and in some cases is complicated by peritonsillar abscess (quinsy). Obstructive sleep apnoea syndrome (OSA), snoring resulting from upper airway obstruction secondary to tonsillar hypertrophy and excision biopsy for suspected malignancy are also strong indications.

PERIOPERATIVE MANAGEMENT

Tonsillectomy in adults is associated with an increased risk of post-operative bleeding and pain when compared with the paediatric population.

Pre-operative consideration should include identification and assessment of OSA.

Either intravenous or inhalational induction with sevofluane can be employed but the intravenous route is preferred in adults because hypertrophied adenotonsils can be associated with early airway obstruction and a more challenging induction.

In management of the shared airway, an endotracheal tube or reinforced laryngeal mask can be placed. A preformed south-facing RAE endotracheal tube is commonly used to protect the airway from soiling by blood and to facilitate ventilation. Secured in the midline, it is designed to point 'south' (or caudad) thereby facilitating surgical access by allowing placement in the split blade tongue depressor of the Boyle-Davis gag. A careful check of ventilation and airway pressures should be made when the gag is deployed to exclude obstruction or displacement of the tube. Alternatively, a reinforced tube with an integral metallic spiral in the shaft provides protection from external compression and kinking.

The flexible, reinforced version of the LMA is also kink resistant and with a narrower shaft than the standard LMA, provides good surgical access. In adenotonsillar hypertrophy, initial placement may be problematic but dislodgement on neck extension is rare. The inflated cuff sits around the outside of the laryngeal inlet and acts as an effective barrier to lung soiling with blood. There is no requirement for neuromuscular blockade and the device is well tolerated at emergence with a low incidence of coughing. Complications include laryngospasm and, as with an endotracheal tube, airway obstruction from the throat gag.

Neck extension is necessary to facilitate surgical access and is most commonly achieved with a pad under the shoulders. Care should be taken to ensure that the ETT or LMA has not been displaced by movement.

Opioid analgesia is the mainstay of perioperative analgesia but non-steroidal anti-inflammatory drugs and paracetamol also have an important part to play. A Cochrane database review suggests that the use of NSAIDs in tonsillectomy does not increase the incidence of bleeding but that nausea and vomiting may be reduced. Paracetamol administered orally (pre-operatively), rectally (in children) or intravenously (intra-operatively) reduces the opioid requirement. Local anaesthetic administration into the tonsillar bed has not been shown to reduce post-operative pain.

The incidence of post-operative nausea and vomiting is high without antiemetic prophylaxis and may be a cause of prolonged stay. High dose dexamethasone decreases the incidence of nausea and vomiting and may also reduce pain, although higher doses may be associated with an increase in haemorrhage.

Ketamine and dexmedetomidine have been used as analgesics but as yet their benefit is unclear and they are not in routine use.

EXTUBATION/RECOVERY

At the end of the case, the laryngeal inlet is examined under direct vision to confirm haemostasis and the oro/nasopharynx judiciously suctioned. In intubated adult patients, extubation is most commonly performed awake after the return of protective reflexes. Deep extubation reduces the risk of immediate haemorrhage by reducing coughing but is associated with a higher risk of laryngospasm. During this time, the risk of blood or secretions soiling the airway can be reduced if the patient is placed in the left lateral/head down 'tonsil position' and this should be maintained until laryngeal reflexes return.

In the post-anaesthesia care unit (PACU), oxygen should be administered until the patient is fully recovered. Opiates may be required and regular paracetamol and ibuprofen should be prescribed if appropriate. Routine observations should include pulse and blood pressure for evidence of post-operative bleeding, and respiratory rate and pain scores should also be recorded.

Variant Creutzfeldt-Jakob disease may be transmitted between patients undergoing tonsillectomy due to

the presence of prions in lymphoid tissue. Single use ETTs, LMAs and either sheathed or single use laryngoscope blades are recommended to reduce the risk of cross-contamination.

The post-operative bleeding tonsil

This is a serious complication. Bleeding can occur in the first 24 hours following the operation (primary), or later (secondary). Patients with secondary bleeds frequently present between 5 and 9 days after their procedure. Management is based on **fluid resuscitation, airway protection and haemostasis at the bleeding site.** Most of the blood may have been swallowed so blood loss cannot be measured and fluid resuscitation may be required prior to theatre. Induction poses special problems for the anaesthetist due to the probability of a full stomach and a high risk of regurgitation and aspiration. A rapid sequence induction minimizes the risk. At the same time the trachea may be difficult to intubate due to the presence of blood in the oropharynx and oedema from the recent surgery. There must be good communication between the teams and the surgeon must be prepared to establish an emergency surgical airway or tracheostomy should tracheal intubation fail. At the end of the procedure, extubation should be performed awake. A prolonged stay in PACU is advisable to ensure that the bleeding has stopped.

Thyroid and parathyroid surgery

THYROIDECTOMY

Thyroid surgery is the most common endocrine surgery and is almost always elective. Indications include thyroid cancer, symptomatic goitre or failure of medical treatment in hyperthyroidism. Patients with uncontrolled myxoedema or hyperthyroidism are at considerable risk and pre-operative management seeks to achieve a euthyroid state.

In hyperthyroidism, a thyroid storm is life-threatening and function can be normalized pre-operatively with radioactive iodine ablation, antithyroid drugs such as propythiouracil, and Lugol's solution, which may help reduce iodine uptake and the vascularity of the gland. In the presence of uncontrolled hyperthyroidism, additional treatment with beta blockers in addition to steroid may be required. Increased risk extends into the post-operative period and care should continue in a high dependency unit (HDU) setting.

From an anaesthetic perspective, it is important to define the size and location of the thyroid in relation to the trachea and vascular structures. Laryngeal deviation, tracheal compression, vocal cord changes or previous thyroid or neck surgery raise the possibility of difficulties with airway management. Assessment should include diagnostic indirect laryngoscopy and CT scanning.

The vast majority of thyroidectomies are carried out under general anaesthesia using a reinforced ETT to maintain airway patency. The more recent use of intra-operative nerve monitoring requires optimal placement of a specialist silicone wired reinforced endotracheal tube with embedded or surface electrodes in contact with the vocal cords (Nerve Integrity Monitor EMG ETT – see above). This allows monitoring of the recurrent laryngeal nerve directly or indirectly via vagal stimulation. Muscle relaxation is contraindicated.

Alternatively, a laryngeal mask and spontaneous breathing allows endoscopic evaluation of vocal cord movement. Total intravenous anaesthesia may be of benefit by reducing the incidence of coughing and improving the quality of recovery.[10] However, the risk of mask displacement is high and careful team work is required.

Local anaesthesia with deep and superficial cervical plexus blocks used in combination with sedation or general anaesthesia has also been described but remains uncommon.

Post-operatively, surgical infiltration with local anaesthetic, simple analgesics such as non-steroidal anti-inflammatories and paracetamol, or weak opioids are usually sufficient to provide good post-operative analgesia.

PARATHYROID SURGERY

Primary hyperparathyroidism (PHPT) is most commonly caused by a benign parathyroid adenoma and surgery is the only curative treatment. Secondary hyperparathyroidism is a compensatory response to hypocalcaemia from another disease process and the majority of patients are managed with medical therapy, although in around 25% this is unsuccessful. Pre-operatively, symptomatic patients or those with significantly raised calcium levels require medical control with adequate hydration, diuretics and biphosphonates. Cardiac arrhythmias resulting from hypercalcaemia should be excluded.

With improved identification of the parathyroid gland, minimally invasive surgery can be performed under local anaesthesia in some patients. In more challenging cases or those with concomitant thyroid disease a general anaesthetic is required, the considerations being similar to those described above for thyroid surgery.

Hypocalcaemia is a common problem after parathyroidectomy but is usually mild and transient. In 'hungry bone syndrome' hypocalcaemia is rapid in onset and severe with associated hypophosphataemia and hypomagnesaemia. It results from sudden removal of the effect of high circulating levels of parathyroid hormone (PTH) in patients with severe PHPT and pre-operative high bone turnover. Plasma calcium levels should be monitored post-operatively to allow early detection and prompt management.

Salivary gland surgery

Salivary gland excision may be performed for tumour, stone or chronic infection. The most common procedure is complete or superficial parotidectomy and carries with it the risk of facial nerve injury. EMG monitoring may minimize this by identifying the facial nerve and its branches. Needle electrodes are placed in the orbicularis oculi and oris muscles and these detect EMG potentials generated as a result of surgical or electrical stimulation of the facial nerve. The electrical activity is converted into an audible

signal, which warns of the proximity of the nerve. A functioning neuromuscular junction is a prerequisite and muscle relaxants should be avoided or used with caution. Long-acting neuromuscular blockers should be avoided altogether but it is possible to use a short-acting alternative to facilitate intubation on the premise that the effect will have worn off by the time monitoring is required. Offset of muscle relaxation should be confirmed with a peripheral nerve stimulator. Partial neuromuscular blockade does not significantly interfere with the facial EMG but the information derived may be unreliable.

Alternatively, intubation may be accomplished without muscle relaxants by administration of high doses of opioids or volatile anaesthetic agents. An infusion of remifentanil often produces good conditions for intubation and allows stable levels of anaesthesia during surgery.

The facial nerve monitor can be tested before surgery by using the peripheral nerve stimulator. A short burst of tetanic stimulation applied in front of the ear over the facial nerve produces visible muscle contractions and both visual and audible alerts from the monitor.

Laryngeal microsurgery

Direct laryngoscopy is performed for diagnostic or therapeutic purposes and may be combined with an examination of the pharynx, oesophagus or bronchial tree. Rigid instruments are used requiring the atlantoaxial joint to be fully extended and so underlying pathology should be excluded. Often, lasers are used to treat isolated lesions of the larynx.

Competition for space within the airway necessitates the use of a small size (6 mm or less) microlaryngeal tube that is sufficiently flexible and long that it does not interfere with the surgical field. If lasers are to be used an appropriate laser-resistant type is required. Alternatively, a tubeless technique using jet ventilation can be used (see above).

The operation is usually relatively short, but a severe sympathetic-mediated stress response may be provoked with up to 4% of patients showing signs of cardiovascular ischaemia post-operatively.

Laryngospasm, bleeding or post-operative airway obstruction due to oedema of the vocal cords may occur. The risk of oedema may be minimized if steroid (for example dexamethasone 8 mg intravenously) is used perioperatively.

Laser surgery

The use of laser has become widespread, especially for laryngeal microsurgery. Also used for stapedectomy, tympanoplasty, turbinate surgery and oropharyngeal surgery, there are various types of laser (CO_2, Nd:Yag, KTP) all named after the source of substrate for the laser beam and producing light at different wavelengths. Most commonly used in ENT surgery is the CO_2 laser, which can be used as a precision cutting tool or to vaporize tissue.

The neodymium-doped yttrium-aluminium-garnet (Nd:Yag) laser was introduced in the 1980s and penetrates tissue more deeply than the CO_2 laser. It can also be delivered by means of a flexible fibre-optic light cable that can be used in conjunction with a fibre-optic bronchoscope to treat lesions in the trachea and bronchi. The potassium titanyl phosphate (KTP) laser is a variant of the Nd:Yag, in which the laser beam is passed through a potassium titanyl phosphate crystal.

Airway management in laser surgery can be challenging. Aside from the underlying pathology and its impact on safe airway management, the greatest concern is the possibility of uncontrolled combustion of either tissues or extraneous materials including airway devices and surgical drapes. A fire in the airway is always serious and often fatal. Oxygen and nitrous oxide both support combustion; nitrous oxide should be replaced by air as the carrier gas and the lowest inspired oxygen concentration which maintains oxygen saturation should be used. In practice, inspired oxygen concentration is usually between 21% and 30%. A number of special laser-resistant endotracheal tubes are available.[11] These diminish but do not abolish the risk of tube fire and reflection damage to adjacent tissue. The cuffs of tracheal and SAD devices are more vulnerable to laser strike than are the shafts. Therefore, the cuffs should be filled with saline (or water coloured with methylene blue) rather than air. This protects them, to some extent, from combustion with laser strike; it slows any deflation of the cuff after strike; it aids, to some extent, in preventing spread of any fire; and the leak of fluid allows the surgeon to see that the cuff has been ruptured.

Surgical access can be improved by use of a 'tubeless' technique employing jet ventilation. This may reduce the fire risk because there is no endotracheal tube as a source of ignition. However, not every patient can be successfully ventilated by jet, and there is a risk of barotrauma including pneumothorax and pneumomediastinum. A TIVA technique is required.

Post-operatively, airway obstruction can arise from tissue oedema. This may be delayed following Nd:YAG use. Again intra-operative dexamethasone can reduce oedema as well as acting as an antiemetic.

BEST PRACTICE IN LASER SURGERY

- ✓ Direct laser strikes to the airway device should be avoided. This risk might be minimized during oral surgery if a Boyle Davis gag without the Doughty modification is used, thus protecting the shaft of most airway devices. If the Doughty modification is used, then the shaft of the airway device might be protected using damp gauze or swabs.
- ✓ The minimum power output of the laser should be used and the duration of laser strike limited. The risk of combustion increases with duration of strike at the same power.
- ✓ Eye protection for both patient and staff is important as CO_2 lasers are associated with corneal injuries and Nd:YAG with retinal damage. For patients, taping the eyes shut and then covering them with saline soaked gauze provides protection. For staff, protective goggles matched to the wavelength of light emitted by the laser are used.
- ✓ A smoke evacuator and appropriate face masks should be used especially if virus particles are present to reduce the potential risk of cross-infection.

Laryngectomy

Usually performed for tumour of the larynx, a total laryngectomy involves removal of all the tissues from the vallecula (and sometimes base of tongue) to the second or third tracheal rings. Occasionally, the thyroid gland also needs to be removed. The pharynx is closed in a T-shape, and the trachea is brought out to the skin as a stoma (so no special tube is required long term to maintain airway patency). There are variations of this operation. A supraglottic laryngectomy involves resection of all tissue from the base of tongue to the vocal cords (which are left intact). The strap muscles are also preserved. A temporary tracheostomy is required post-operatively. A hemilaryngectomy involves removal of the epiglottis and just one half of the larynx (including one true and false vocal cord).

Areas of consideration for anaesthesia include:

- pre-operative comorbidities
- tracheal intubation at induction
- change of airway device during surgery.

PRE-OPERATIVE PATIENT STATE

Laryngeal tumours most commonly occur in elderly smokers, often with coexistent cardiovascular and respiratory disease. Where possible, coexistent medical conditions should be optimized pre-operatively with particular attention to nutritional status. Intra-operatively, invasive arterial pressure, and less commonly central venous monitoring placed distant to the site of surgery, may be necessary. If lung function is poor, a period of elective post-operative ventilation in intensive care may be required.

TRACHEAL INTUBATION

The presence of a laryngeal tumour may make tracheal intubation difficult. Previous radiotherapy is also a risk factor and may make bag and mask ventilation difficult. Imaging, which may include nasendoscopy, in combination with good communication between surgeon and anaesthetist, is essential in formulating a management plan.

Specialized techniques such as awake fibre-optic intubation may be necessary and these are further discussed in Chapter 31, 'Recognition and management of the difficult airway'.

THE AIRWAY DURING SURGERY

To facilitate access as surgery proceeds, the oro/nasotracheal tube is exchanged for a tracheal tube inserted percutaneously into the trachea and shaped to lie against the neck, pointing caudally. Examples include the Montandon tube, RAE tube or reinforced flexible tube. Then when the permanent end-tracheostomy is fashioned the tracheal tube is removed. Thus, the anaesthetist needs to have ready a number of sterile airway devices, sterile connectors and tubing, which often need to be sited directly by the surgeon. Close communication is clearly necessary.

Tracheo-oesophageal puncture allows the placement of a voice prosthesis between the trachea and the oesophagus. The voice prosthesis is a one-way valve that allows air to pass from the trachea to the pharynx when the tracheal stoma is occluded, thus preserving voice, but preventing contamination of the trachea from above.

KEY POINTS

- Anaesthesia for head and neck surgery epitomizes the quintessential anaesthetic 'art' of airway mastery.
- It requires a unique dialogue between surgeon and anaesthetist who share the same territory. As such it requires, perhaps more than any other branch of surgery, an understanding of, and respect for each other's contribution towards a common end.

Nasal and sinus surgery

Nasal surgery is performed for cosmetic or functional restoration of the nasal airway, and includes operations such as septoplasty (operation to the nasal septum), rhinoplasty (operation to move the nasal contour), turbinectomy or these combined. Sinus surgery is performed to eliminate infection, polyps or neoplastic conditions of the sinuses, and the goal is to provide aeration of the sinuses so that secretions can drain adequately into the nasopharynx.

Anaesthetic considerations for all these operations are similar. An oral rather than nasal airway device is necessary, usually an ETT in combination with a throat pack to collect any debris from the nose. Topical cocaine mixtures have long been used to shrink the nasal mucosa, reduce bleeding and so improve the surgical field. The intense vasoconstriction is accompanied by a local anaesthetic action that contributes to post-operative analgesia. However, mucosal surface uptake is rapid and large doses are associated with severe hypertension and dysrhythmias. Cophenylcaine (Phenylephrine 0.5% and Lidocaine 5%) may be a safer alternative,[12] but again the maximum safe dose should not be exceeded.

At the end of surgery, coughing and straining can exacerbate bleeding and smooth extubation may be challenging. The nose is usually packed so a good oral airway is essential. Swallowed blood can be an irritant and antiemetic prophylaxis should be given intra-operatively.

Ear surgery

Surgery on the external ear is performed for a variety of reconstructive or cosmetic indications.

Middle ear surgery is performed to restore hearing, eliminate infection, treat cholesteatoma and rarely for neoplasm. Outcomes have been improved by advances in technology including high magnification microscopes, enhanced imaging and improved nerve monitoring. Surgery tends to be complex, long and delicate. The principle aim of anaesthesia is to obtain a clear dry operative field by minimizing even small amounts of bleeding that could obscure the view. This can be achieved by maintaining a stable depth of anaesthesia, having a moderate

degree of hypotension (without compromising vital organ perfusion particularly in the elderly) and restricting or preventing extrinsic movement caused by monitoring or patient movement.

Blood in the surgical field may arise from arterial, capillary or venous bleeding. Arterial bleeding is directly proportional to mean arterial blood pressure (MABP). Moderate controlled hypotension to achieve a MABP of 60–70 mmHg provides optimal operating conditions. Techniques to reduce the blood pressure using hypotensive agents such as beta blockers (esmolol or labetalol), sodium nitroprusside or calcium channel blockers have in general been superseded by the use of short acting opioid agents. Remifentanil is an effective and titratable hypotensive agent during ear surgery.[13]

Capillary bleeding depends on local flow in the capillary bed, which in turn is dependent on upstream arterial pressure and downstream venous tone, in addition to local metabolic factors. Capillary bleeding can be moderated by the use of locally infiltrated adrenaline (although the systemic effects of this will transiently confound the anaesthetist's attempts to control blood pressure) and by reduction in arterial and venous partial pressure of carbon dioxide (PCO_2) by hyperventilation.

A reduction in venous tone and backpressure will reduce both capillary and venous bleeding. Venous tone can be moderated by the use of intravenous nitrates, and a 25° head uptilt can reduce the hydrostatic venous pressure.

The surgical approach is often a post-auricular route through the mastoid. The head must be turned so that the ear on which the operation occurs is uppermost. Unlike most other ENT procedures, the airway is not 'shared' and so anaesthetic rather than surgical considerations predominate in choice of airway. Access may be difficult intra-operatively and so tracheal intubation using a south facing ETT and IPPV ventilation is commonly employed. A flexible SAD is an alternative and may reduce coughing at emergence. However, there is a greater risk of displacement, particularly if controlled ventilation is required to prevent hypoventilation.

Facial or cranial nerve monitoring may be required and the use of muscle relaxants is best avoided post-induction. Smooth emergence and prevention of post-operative nausea and vomiting are important to prevent graft failure.[13]

Where tympanoplasty, tympanomeatal flaps, stapedotomy or stapedectomy is performed it is advisable to avoid nitrous oxide. Due to its relative solubility, nitrous oxide enters the middle ear cavity at a rate faster than nitrogen (the ambient gas in the air) leaves the space. Consequently, there is a rise in middle ear pressure that can displace the structures being operated on. Care must be taken to prevent extensive head turning and to protect the eyes from corneal abrasions.

Myringoplasty, mastoidectomy and stapedectomy are increasingly carried out as day surgery procedures and TIVA is commonly used. Advantages include improved cardiovascular stability, decreased post-operative nausea and vomiting and a short recovery time. Post-operative pain is relatively low and is well managed with paracetamol and NSAIDs except in the mastoidectomy group when opioid analgesia is required. Routine use of antiemetic prophylaxis with dexamethasone and a 5HT3 antagonist is advisable.

KEY POINTS

- Care should be taken when positioning patients for ear surgery.
- Moderate hypotension may help to reduce bleeding in the surgical field.
- Short acting opioids such as remifentanil allow greater control of cardiovascular stability and facilitate moderate hypotension.
- Hypotension should be limited in patients with uncontrolled hypertension, cerebrovascular or ischaemic disease.

FUTURE RESEARCH

Looking into the future, several new issues are emerging.

The imperatives of improving quality of care, reducing length of stay and limiting the physiological impact of surgery so that return to 'normal' is rapidly achieved provide significant drivers for change.

Current IV anaesthetic agents have limitations. To address the broadening agenda, new drugs based on etomidate, benzodiazepines and propofol are under development

In the search for a hypnotic agent with pharmacokinetic properties similar to remifentanil, methoxycarbonyl etomidate showed initial promise. This has an ester moiety which is very rapidly hydrolyzed by plasma esterases but potency is low and therefore large amounts are required. To overcome these limitations, other spacer linked etomidate esters are under development and these are more potent and metabolized more slowly.

Remimazolam is a benzodiazepine that acts on gamma-aminobutyric acid (GABA) receptors but has organ dependent metabolism similar to remifentanil. Following prolonged infusions, residual effects are minimal. Preliminary data suggest that it has potential for sedation in theatre and ITU.

Fospropofol is a prodrug of propofol. Unlike propofol, it is water-soluble and benefits include less pain at the site of intravenous administration, less potential for hyperlipidemia with prolonged administration, and a reduction in the incidence of bacteraemia. Slower in onset than propofol, further research is needed to establish an appropriate role for fospropofol in sedation, anaesthesia and the management of the critically ill.

The search for new drugs that minimize or treat post-operative nausea and vomiting (PONV) is also important. PONV is a significant cause of patient distress and effective management not only improves quality of life but also reduces costs by reducing delayed discharge from hospital. Neurokinin-1 receptor antagonists such as aprepitant were originally developed for chemotherapy-induced nausea and vomiting. When used in surgery, aprepitant may decrease the incidence of vomiting by 70–80% and has similar efficacy against nausea and greater efficacy

against vomiting compared with other commonly used antiemetics. Administered orally, its expense currently limits its use to high-risk patients. An intravenous preparation is also available.

Outwith the development of novel drugs in anaesthesia, recent advances in airway management have seen the introduction of videoscopes such as Airtrach and McGrath. These have reduced the requirement for expensive fibre-optic techniques, which also require considerable training and expertise. Further development of equipment for the management of the difficult airway in head and neck surgery that is low-cost and requires minimal expertise remains desirable. However, developing such devices or techniques will require far more understanding of the reasons underlying the concept of the 'difficult airway' than we have at present.

Beyond the more technical aspects of anaesthesia described above, attention is turning towards the dramatic variation in patient outcomes for major surgery between different centres. Although harm directly attributable to the conduct of anaesthesia is rare (less than 1 : 50 000 mortality), these differences have spurred interest in the role of the anaesthetist as perioperative physician. Stretching across the care pathway, from pre-operative optimization to intra-operative management, which includes measures to reduce post-operative side effects and into the post-operative management of pain and identification and treatment of early complications, the changing contribution of the anaesthetist may well be an important driver of future improvement.

KEY POINTS

- Anaesthesia for ENT surgery requires constant communication and cooperation between anaesthetist and surgeon. The pre-operative surgical brief is particularly important in planning management to achieve a satisfactory outcome.
- Anaesthetic technique must balance safe airway management with surgical requirements such as nerve integrity monitoring, difficult access requiring a tubeless field or laser surgery.
- In patients undergoing head and neck surgery, the complications associated with a 'shared airway', positioning of the patient to facilitate surgery and the high risk of dental trauma should be considered.

Tonsillectomy and adenoidectomy

- Evidence supports the use of either endotracheal tube or laryngeal mask airway and the choice is one of operator preference.
- The post-operative bleeding tonsil is a serious complication which poses special problems for the anaesthetist due to the probability of a full stomach and obscured laryngoscopy.

Ear surgery

- A stable depth of anaesthesia, moderate hypotension without compromising vital organs perfusion particularly in the elderly may help to reduce bleeding in the surgical field.
- Best practice during laser surgery should be maintained at all times to ensure patient and staff safety.

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CHAPTER 33

ADULT CRITICAL CARE

Robert I. Docking and Andrew Mackay

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: critical care, sepsis, ventilation and organ support.

INTRODUCTION

The development of modern critical care started during the polio epidemic of the 1950s, when the need to deliver positive pressure ventilation on a widespread scale encouraged the design and production of ventilators that allowed the continuation of ventilation into the post-operative period. This facility allowed surgeons to undertake more invasive and complicated procedures that would be impossible without an option for extending recovery (ruptured aneurysms, cardiothoracic surgery), and the experience gained was then used to improve the support of critically ill medical patients.

Modern critical care units are now essential to the function of any acute hospital, with resources including equipment, medical and nursing staff as well as ancillary support including physiotherapy and outreach teams. Traditionally in the UK, medical staffing has originated from anaesthesia, but the recent establishment of the Faculty of Intensive Care Medicine has led to creation of an independent specialty that allows doctors from a wide range of disciplines to complete training as critical care specialists.

Normally a high dependency unit (HDU) would care for Level 1 and Level 2 patients (Box 33.1), whereas an intensive care unit (ICU) would take in Level 2 and Level 3 patients. A national trend towards specialization and centralization of specialist and tertiary services has led to consolidated critical care areas, based on the premise that caring for higher volumes of patients leads to improved outcomes through refinement of processes and more rapid cycling of quality improvement measures. This has led to larger units with a broader spread of intensity from patients with simple post-operative analgesia requirements such as an epidural catheter to patients receiving multiple modes of organ support. Having units with such diverse intensity, or a geographically close HDU/ICU setup means that 'stepping up' and 'stepping down' as the clinical case evolves is easier and more efficiently done.

Critical care is truly a multidisciplinary specialty. The medical and nursing teams should be trained specifically in critical care, and be supported by the referring teams for specific issues. Critical care units will also have

BOX 33.1 Definitions

In 2000 the United Kingdom Department of Health authored a document, *Comprehensive Critical Care*, which sought to classify critical care as to the intensity of care delivered:

- **Level 0:** Patients whose needs can be met through normal ward
- **Level 1:** Patients at risk of their condition deteriorating or with higher levels of care whose needs can be met on advice and support from the critical care team
- **Level 2:** Patients requiring more detailed observation or intervention, single failing organ system or post-operative care, and higher levels of care
- **Level 3:** Patients requiring advanced respiratory support alone or basic respiratory support together with support of at least two organ systems. This level includes all complex patients requiring support for multi-organ failure

significant requirements for physiotherapy, nutrition, microbiological and laboratory input. The medical staff should have no competing commitments during their time working in the unit, and should be easily accessible both to referring teams and the nursing staff. The lead clinician should spend the majority of their time in the critical care environment, and be able to take an overview of the issues confronting the unit. In terms of physical environment, the unit should have the space to safely look after patients, with suitable distance between beds to minimize cross-infection rates and facilitate patient care and procedures.

The management of critical care has been subject to several models. To illustrate differing approaches one may look at 'open' versus 'closed' models of care. The open model allows all admission and treatment decisions to be made by the referring specialties, with the critical care team providing only the procedural and nursing input as outlined by the referrer. This is difficult to support as continuity of care is hard to maintain, and treatment decisions can be delayed and potential harm incurred. The closed model sees all decisions made by the critical care team, often without reference to the originating parent team. While this aids continuity and speeds decision-making time, it can lead to professional friction and barriers and removes the valuable knowledge resource of the referring team when it comes to specialist input. A more cohesive approach aims to involve referring teams in the ongoing care of their patients, but with clear boundaries regarding the decision-making process.

The decision to admit a patient to critical care is often a challenging one, made after consultation with the patient, their family and their parent team. However, the nature of critical illness is such that often many of the discussions that would be useful are impossible to pursue in the available time period. Admission to critical care should only be made when there is a potential for reversal of pathology/organ failure, and with an assessment as to whether the burden of treatment is acceptable for the patient. A stay in critical care carries with it substantial physical and psychological ramifications, with recovery to a similar pre-morbid level often taking a year or more following hospital discharge. This must therefore inform part of the decision-making process prior to and during an admission to critical care.

Scoring systems

Illness severity scores are widely used in the critical care environment to predict outcome, assess organ dysfunction and analyse use of resources. The multitude of scoring systems that have been developed support the fact that there is no single gold standard; each system will have individual merits and a composite of these scores is likely to be most useful. Scoring systems in ICU can be broadly divided into:

- scores that assess disease severity at point of admission in an attempt to predict outcome (Acute Physiology and Chronic Health Evaluation (APACHE), Simplified Acute Physiology Score (SAPS), Mortality Probability Model (MPM))
- scores that assess the presence and severity of organ dysfunction (Multiple Organ Dysfunction Score (MODS), Sequential Organ Failure Assessment (SOFA))
- scores that assess nursing workload use (Therapeutic Intervention Scoring System (TISS)).

The most commonly used system is APACHE-II. The original APACHE score was described in 1981 and scored both physiological derangement of the acute illness and an assessment of chronic health. APACHE-II was a refinement of the original with fewer physiological variables, each scored on the most deranged value in the first 24 hours, combined with age and chronic health evaluation to give a score of up to 71, which is then combined with admission diagnosis to give a predicted mortality.[1] Although on an individual basis scoring systems have little value, as ICU survival is a binary outcome, the score permits population studies and objective comparison of outcomes between patient groups or even different units.

ORGAN SUPPORT

The fundamental approach of critical care is diagnosing the cause of illness, and direct efforts to treat the underlying cause while providing appropriate organ support until such point that the patient's intrinsic organ function returns. Multiple negative trials of 'magic bullet' interventions (Activated Protein C, TNF-alpha antagonists, steroid use for septic shock) have reinforced the need for reliable and safe implementation of relatively uncomplicated modes of support, and the introduction of 'bundle' approaches to help clinicians achieve the reliability that is required in the high-risk critical care environment.

At all times the progress of the patient should be considered, and if improvement is either slow or absent then alternative diagnoses should be investigated. A failure to improve at an expected time course is often a sign that either the wrong diagnosis has been made, or that the severity of the illness has been underestimated. Complications often have differing implications depending upon the diagnosis. For example, atrial fibrillation in the setting of pneumonia is a sign of disease severity whereas following an oesophagectomy it may suggest an anastomotic leak with mediastinitis and therefore the investigation and treatment of the same arrhythmia will differ significantly.

Respiratory support

For many, the provision of respiratory support is the defining element of critical care. There has been a rapid increase in the range, variety and nomenclature of modes of both non-invasive and invasive ventilation in the last decade, but the fundamental aim remains the same: to augment oxygenation and to clear carbon dioxide while limiting iatrogenic harm.

The provision of intensive ratios of nursing care means that critical care units are the only places outwith theatre where prescribed oxygen therapy can be reliably and accurately provided. Humidification of delivered gases reduce the toxic drying effects of high flow gas, and allied to regular physiotherapy help mobilization of secretions and reversal of atelectasis.

The classification of respiratory support suffers from a variety of differing nomenclature, driven by both clinicians and manufacturers. Table 33.1 separates those that require tracheal intubation, and those that do not:

Institution of invasive respiratory support carries with it both benefits and risks. It reduces or eliminates the work of breathing, which reduces patient discomfort and oxygen consumption, and allows access to the lower respiratory tree for clearance, suction and reinflation. However, it usually requires sedation, bypasses the usual defence mechanisms of the upper airways and equally opens the lower respiratory tree up to damage by excesses of pressure, volume and infection – so-termed ventilator induced lung injury (VILI).

Weaning off respiratory support is the process whereby support is gradually reduced to the point where the patient can breathe unaided. There is little to support one way of doing this over another, but it generally takes the form of establishing a spontaneous mode of ventilation then reducing the support until extubation can occur. For any weaning process to be successful, several things need to have occurred:

- The underlying diagnosis needs to have been appropriately treated.
- The patient needs an adequate respiratory drive.
- Any source of pain needs to be identified and controlled.
- The patient needs a reasonable cough and swallow mechanism.

Predicting successful extubation is not an exact science, but reintubation is associated with poorer outcomes in critical care. Whether this is associative or causative is more difficult to ascertain. The use of non-invasive ventilation as a treatment for failed extubation is difficult to support, unless there is strong evidence of chronic obstructive pulmonary disease in which case extubating straight to non-invasive ventilation is an option. In all but this subset there seems to be an excess mortality associated with non-invasive 'rescue', most probably due to delaying reintubation and loss of reserve.

Acute respiratory distress syndrome (ARDS) is a clinical and pathological diagnosis that is the common final pathway of many disparate pulmonary and extra-pulmonary conditions, typified by bilateral diffuse airspace oedema, without overt ventricular failure, and resultant hypoxaemia. The current consensus criteria[2] are:

- acute onset, < 1 week after insult
- bilateral widespread radiological infiltrates unexplained by other pathology
- no clinical signs of LV failure or fluid overload
- hypoxaemia, with a PaO_2/FiO_2 ratio of < 40 for mild ARDS, < 27 for moderate ARDS and < 13 for severe ARDS.

The treatment of ARDS can exacerbate the underlying disease process by using harmful techniques to try and 'normalize' physiological parameters. Many therapies have been tried, but the best evidence supports relatively simple interventions including 'lung protective ventilation', a strict attention to management of fluid balance and early treatment of infection. The best evidence for ventilation comes from the ARDSnet RCT from 2000,[3] which compared a ventilatory strategy that aimed to normalize blood gas values with high tidal volumes and pressures (12 ml/kg tidal volume and plateau airway pressures of < 50 cmH_2O) and a low volume strategy (6 ml/kg tidal volume and pressures of < 30 cmH_2O). This large RCT was stopped early due to a mortality reduction of 8.8% in the low volume group, and this has formed the central tenet of modern ventilatory strategy for ARDS.

The realization that ventilation can exacerbate, prolong and worsen the pathophysiological effects of critical illness has led to a renewed interest in alternative treatment strategies, particularly extracorporeal membrane oxygenation (ECMO). This approach of using an extracorporeal circuit to oxygenate and remove carbon dioxide from blood has evolved from cardiopulmonary bypass techniques, and has been well established in the neonatal and paediatric critical care environment. A protagonist-driven RCT from the UK,[4] randomizing patients with severe ARDS to management in their hospital of origin, or transfer to a centre for consideration of ECMO showed a small but significant reduction in mortality or disability.

TABLE 33.1 Classification of respiratory support

Non-invasive		Invasive
Variable performance devices (concentration depends on effort/rate)	• Nasal cannulae • Hudson masks • Non-rebreathing 'trauma' masks	• Spontaneous modes (CPAP, ASB, APRV) • Mandatory modes (VCV, PCV) • Mixed modes (SIMV, BIPAP, ASV)
Fixed performance devices (concentration is independent of effort/rate)	• Venturi masks • High-flow nasal oxygen	
Pressure delivery devices	• Continuous pressure airway pressure masks (CPAP) • Bilevel airway pressure masks (NIV, NIPPV, BiPAP)	

This was published during an H1N1 influenza pandemic that resulted in a large number of young critically hypoxic patients presenting to critical care, and encouraged the formation of regional specialist centres where ECMO can be used to reduce iatrogenic lung damage. The circuits require the use of significant anticoagulation and there are appreciable complications involving spontaneous bleeding, albeit in a patient group with a high predicted mortality.

Cardiovascular support

The primary function of the heart is to deliver oxygen to tissues, which requires a flow from the lungs, through the left heart and on to the peripheral tissues. At that point uptake can be blocked on a cellular or mitochondrial level, but generally the aim of critical care cardiorespiratory support is to increase tissue oxygen delivery.

As can be seen from the equations in Box 33.2, increasing oxygen delivery can be achieved in a number of ways, including using fluid challenges, vasoactive drugs, transfusion of blood and optimizing oxygenation. Choosing which of these methods to use, and how to assess the efficacy of the chosen intervention is an ongoing source of debate in the critical care community.

BOX 33.2 Increasing oxygen delivery

$DO_2 = CO \times CaO_2$

$CO = HR \times SV$

$CaO_2 = (Hb \times 1.34 \times SaO_2) + (0.003 \times PaO_2)$

Abbreviations: *DO_2 = oxygen delivery; CO = cardiac output; CaO_2 = arterial oxygen content; HR = heart rate; SV = stroke volume; Hb = haemoglobin; SaO_2 = arterial oxygen saturation; PaO_2 = dissolved arterial oxygen tension*

Commonly used ways of assessing both inadequate oxygen delivery and the response to treatment include: trends in serum lactate as a marker of anaerobic metabolism; central venous oxygen saturation as an index of oxygen extraction; and more basic methods like peripheral warmth and capillary refill time.

In the past extrapolation of the use of pulmonary artery catheters (PACs) in high-risk surgical patients led to the widespread use of PAC as cardiac output monitoring in the majority of critical care patients.[4] Following a prospective trial,[5] and large retrospective database analyses, no evidence for benefit was found and significant numbers of procedure-related complications have resulted in far lower rates of use. Less invasive cardiac output monitors have been introduced to the market with reasonable concordance with PAC-derived values, but there remains a lack of evidence that their use improves outcome. The modes vary in their alleged benefits as detailed below, but can give trending values of most haemodynamic variables. Some of these are directly measured but many are calculated using a variety of assumptions based on normative data that may or may not be true in the critically ill patient. A summary of the available cardiac monitors can be seen in Table 33.2.

In terms of the drugs used to aid the cardiovascular system during critical illness, the majority are related to the catecholamine family and increase sympathetic tone. Unlike in theatre where intermittent boluses are given, most patients receiving vasoactive drugs will receive them as continuous infusions with nursing staff adjusting dosage in response to monitored variables. Alpha agonists like noradrenaline predominantly produce increased vascular tone and therefore raise blood pressure, while beta agonists like dobutamine or adrenaline increase myocardial contractility and heart rate and thus increase cardiac output directly. Catecholamines all increase myocardial oxygen consumption, and have diverse effects including modulation of the immune response, glycaemic metabolism and gut blood flow.

TABLE 33.2 Cardiac output monitors

	Mode of action	Strengths	Weaknesses
Pulmonary artery catheter	Inserted as a central line, measures thermodilution in pulmonary circulation, Fick principle	• 'Gold standard' • Direct measurements of flow and pressure	• Invasive • Potential complications include PA rupture • Infections
Oesophageal Doppler	Nasal Doppler probe that measures blood flow in thoracic aorta	• Easy to insert • Few complications	• Prone to movement and measurement artefact • Poorly tolerated unless deeply sedated
LiDCO	Pulse contour analysis of arterial line, calibrated with transpulmonary lithium dilution	• Easy to use • Does not require central access	• May not respond accurately to interventions • Inaccurate with dysrhythmias
PiCCO	Pulse contour analysis of arterial line, calibrated with transpulmonary thermodilution	• Relatively easy to use • Large number of displayed variables	• Requires central access and modified arterial line • Inaccurate with dysrhythmias
Echocardiography	Ultrasound examination of heart and great vessels, either trans-thoracic or trans-oesophageal	• Direct visualization • Able to diagnose cause of low/high cardiac output	• User dependent • Interpretation variable • Intermittent observation

Fluids

In the early stages of a critical care admission there is often the need for large volume fluid resuscitation, either to correct overt hypovolaemia or relative underfilling in vasodilated states like sepsis. The debate as to what is the ideal replacement fluid is ongoing, as is the debate as to how to assess response to therapy.

In terms of fluid type, both crystalloid and colloids are available for use. Crystalloids have a better safety profile in terms of anaphylaxis and cost less, but larger volumes may be required to produce an equivalent response. The disparity between the two is probably far less than the previously quoted 3:1 ratio, and crystalloids seem to have less of a deleterious effect upon the glycocalyx of the basement membrane than colloids. Use of balanced 'physiological' solutions is on the rise, as non-physiological solutions like 0.9% NaCl being linked to hyperchloraemic acidosis and impaired renal function.

Colloids are solutions with polymers suspended within them. Examples include gelatins like Gelofusin, starches like Voluven and non-synthetic colloids like human albumin solution. Many fluid optimization papers have used colloids for their bolus regimes, but concerns over safety have led to the decline of colloid use and withdrawal of starches from the European market.

After the initial resuscitation period fluid requirements revert to basal needs. These needs can be met by intravenous fluid, gastric feed and drugs. Patients on multiple antibiotics and drug infusions can receive over 2 L of fluid a day from drugs alone, and without a watchful eye on fluid balance can become cumulatively overloaded. Positive fluid balance during a critical care stay has a strong association with poorer outcomes and although causation is harder to prove, avoiding fluid overload in the post-resuscitation phase is a worthwhile aim. In the case of ARDS, a restrictive fluid therapy regime improved gas exchange, shortened duration of ventilation and had no harmful effects on renal function.[6] Conversely, positive fluid balance has been shown to worsen outcomes in acute kidney injury although this again may well be indicative of disease severity.

Renal support

The development of renal failure in critical care is usually multifactorial, with sepsis as the most common aetiology. The degree of failure can be quantified by looking at changes in serum creatinine or urine output with the RIFLE or AKIN criteria.[7] Support focuses on treating the underlying condition, ensuring adequate hydration and lack of urinary tract obstruction and if complications supervene then providing renal replacement therapy (RRT).

Generally accepted indications for RRT include:

- hyperkalaemia
- acidosis
- uraemia – urea >30
- fluid overload/pulmonary oedema
- toxic drug accumulation

RRT can be achieved using either dialysis or haemofiltration,[8] with the latter being the most common modality used in critical care. A dedicated large bore central line is used to pump blood through a membrane lined filter, which utilizes a concept called 'solute drag', whereby water that passes out of the filter pores draws solutes like urea and creatinine alongside it. This results in a large amount of ultrafiltrate that needs to be replaced and therefore commercially manufactured replacement fluids containing physiological concentrations of solutes are added to the 'return' limb of the renal line. This extracorporeal circuit normally requires a degree of anticoagulation to reduce the likelihood of clot formation, and most units use an unfractionated heparin infusion for this purpose.

The optimum dose of renal replacement therapy is another area of contention. More intense sessions, either judged by frequency of dialysis or volume of replacement in haemofiltration, have a physiological rationale for providing better clearance of waste products. This was examined in a single centre trial[9] where three separate effluent doses were targeted for patients receiving haemofiltration. This trial showed a significantly increased mortality in the low dose group, and no significant complications in the higher dose groups. This work was replicated in the field of intermittent haemodialysis,[10] comparing three times a week dialysis with six times a week, showing a significant mortality benefit in the more frequent group. This concept of intensity has been re-examined by two much larger studies,[11, 12] which were unable to replicate the mortality benefit. There is likely to be a complex dose-response curve with renal replacement, and while under-dosing should be avoided there is insufficient evidence to support higher dose intervention.

Nutritional support

In order to survive critical illness, nutrition must be maintained and supported. For short stays of <48 hours there is no rush to institute feeding, but for stays longer than this an assessment of how to feed must be made. There is little firm evidence that enteral nutrition is necessarily better than parenteral nutrition other than the risk of central line associated infection, but most units will pursue the enteral route as first line. If the enteral route fails, or is contraindicated, then parenteral nutrition should be used through a dedicated feeding line if possible.

Feeding can be difficult to establish due to slow gastric emptying, impaired hormonal flux and altered enteral circulation. Methods of encouraging successful enteral nutrition include gradually increasing feeding rate, prokinetic drugs and insertion of postpyloric feeding tubes rather than the standard nasogastric placement. The standard approach is to target an energy intake of 25 kcal/kg/24 hrs, with a mix of protein, fat, carbohydrate and essential vitamins. Enthusiasm has waxed and waned for 'immunonutrition' with supplementation of substances purported

to boost immune function, but there is not enough evidence to support this when subjected to meta-analysis.

Poor glycaemic control is linked to increasing infection rates, poorer wound healing and worse outcomes in a variety of disease states. Critically ill patients tend to develop hyperglycaemia in response to a number of factors including the stress response, relative insulin resistance, increased circulating levels of cortisol, catecholamines as well as exogenous administration of drugs including steroids and additional catecholamines as part of their support. Interest was raised when a 2001 RCT[13] comparing a 'tight' glycaemic control protocol targeting blood glucose values of 4.4 to 6.1 mmol/L against a 'conventional' protocol target of 10 to 12 mmol/L was published and showed a raft of positive effects including reduction in all-cause mortality, incidence of AKI needing RRT, bloodstream infections and critical care acquired weakness. Many centres adopted this so-called 'intensive insulin therapy' approach, but a subsequent trial by the same group[14] looking at a wider range of patients (as opposed to the original cardiac surgery cohort) failed to support the same findings. A more recent 2009 RCT,[15] far larger than the previous cohorts, compared the intensive target to a conventional target of < 10mmol/L and showed an increased all-cause mortality in the intensive group, seemingly independent of the effects of hypoglycaemia. Certainly hyperglycaemia should be avoided and treated if it occurs, but intensive control cannot be supported.

Sedation

The majority of patients in critical care will require some form of sedation or analgesia to help provide their care. The presence of an endotracheal tube is intensely stimulating, so the use of opioids for their anti-tussive effects is key. Acute pain related to operations, critical care related procedures and positioning is extremely common and critical illness interrupts the sleep-wake cycle meaning that sedation is also often required.

The most commonly used regime involves the short-acting anaesthetic agent propofol, alongside an opioid (morphine, alfentanil, remifentanil). Benzodiazepines, such as midazolam, have lost favour due to the implication of increasing the incidence of delirium. Stopping sedation on a regular basis may help to shorten stay, and allows for more accurate assessment of neurological function.[16]

Delirium, an acute alteration in consciousness and alertness associated with many disease states, has recently become far more readily recognized in critical care. Up to 70% of critical care patients will experience an episode of delirium, and it is associated with longer stays, longer duration of ventilation, increased mortality and long-term cognitive decline. There are no proven interventions to treat delirium, but generally non-pharmacological measures (sedation breaks, orientation aids like clocks and natural light) have fewer side effects than the pharmacological measures like haloperidol and atypical antipsychotics.

THE INTERFACE BETWEEN CRITICAL CARE AND ENT

Post-operative care

Like all other surgical specialties, patients undergoing ENT operations may be admitted to critical care either in a planned or unplanned fashion. The type of admission can be generalized into one of three categories as follows:

1. Caused by the acute illness (e.g. the ongoing management of shock following post-tonsillectomy haemorrhage)
2. Caused by the nature of the surgery (e.g. major head and neck operations where it is anticipated that airway swelling or compromise may persist for several days after the operation)
3. Caused by pre-existing disease processes (e.g. severe left ventricular dysfunction in someone undergoing an unrelated ENT procedure)

Early discussion with critical care allows for potential pre-operative optimization, or modification of intra-operative management to aid post-operative recovery. Depending on developments in the post-operative period these admissions may be brief, or unexpectedly protracted. Regular communication between the ENT and critical care team allows for both sides to improve decision-making processes and support the patient and family during what is an emotionally fraught time.

Sepsis

ENT can be involved in the management of sepsis in critical care either in ENT patients who have developed perioperative sepsis either as a primary or secondary infection, or in the investigation of occult sepsis in non-ENT patients. Most critical care patients have indwelling tubes through the nasal passages, and as such are at increased risk of sinusitis that may be difficult to diagnose. In such cases ENT may be asked to help investigate, or provide washouts to remove a potential source of sepsis.

Although the terminology has been well defined, various phrases are used interchangeably, which can lead to diagnostic confusion. Initial consensus definitions derived three states of sepsis, increasing in severity: sepsis; severe sepsis; and septic shock. The most recent iteration of the Surviving Sepsis Campaign (SSC) guidelines[17] classes these as shown in **Table 33.3**.

The underlying pathophysiology of sepsis is that of an uncontrolled physiological response to infection leading to systemic vasodilation produced by a host of cytokines including, but not limited to, Il-6, Il-18, TNF-α, inducible nitric oxide synthase and arginine. The 'classic' septic patient will display a hyperdynamic circulatory pattern with low filling pressures, maintained or increased cardiac output and microcirculatory dysfunction. This textbook presentation is often not seen, with a wide range of patients from those with a maintained blood pressure but

TABLE 33.3 Three states of sepsis

Sepsis	Severe sepsis	Septic shock
Documented or suspected infection with the presence of systemic manifestations of infection	Sepsis with signs of organ hypoperfusion (hypotension, raised creatinine, raised bilirubin, prolonged INR, hypoxia, thrombocytopaenia, lactataemia)	Severe sepsis with hypotension refractory to initial resuscitation – classed as a MAP <70 mmHg or systolic <90 mmHg after 30 ml/kg fluid resuscitation and initial vasopressor use

organ dysfunction, to those with marked sepsis-induced myocardial dysfunction who are far from hyperdynamic.

The early and aggressive management of sepsis has been a focus of recent media attention with campaigns including Surviving Sepsis and the UK-based Sepsis Six, based on work that suggests that both early administration of antibiotics[18] and resuscitation targeted to endpoints[19] reduced mortality and morbidity in sepsis. Management hinges on having a high suspicion of the diagnosis, investigating the potential sources using microbiology, radiology and surgery early, restoring tissue oxygen delivery by resuscitation and administering appropriate broad-spectrum antibiotics tailored to the most likely source of sepsis. The following list summarizes the Sepsis Six approaches that are recommended to be implemented within this first hour of a patient being diagnosed with sepsis:

1. Administer high flow oxygen.
2. Take blood cultures.
3. Give broad spectrum antibiotics.
4. Give intravenous fluid challenges.
5. Measure serum lactate.
6. Measure hourly urine output.

This bundle approach aims to make the early diagnosis and management of sepsis more reliably achieved within a short timeframe by junior staff, but does require ongoing senior input including making the escalation to critical care if appropriate.

Improving tissue oxygen delivery relies upon the restoration of both an appropriate circulating volume, and perfusing pressure. As previously mentioned, the SSC guidelines advocate the use of a 30 ml/kg crystalloid resuscitation approach, with early use of noradrenaline as the first-line vasopressor alongside fluid resuscitation to restore organ autoregulatory flow. Suggested endpoints for resuscitation include trends in lactate, venous oxygen saturations, or urine output. In cases of reduced cardiac output suggested by findings such as low venous oxygen saturations, echocardiography or lack of response to vasoconstrictor therapy, predominantly inotropic agents like dobutamine or adrenaline are indicated.

Airway management

The involvement of ENT with airway management in critical care falls into two main groups. The first is the management of difficult or potentially difficult airways in critical care, while the second is the provision of tracheostomies for patients with an ongoing need for ventilatory support.

DIFFICULT AIRWAYS

Difficult airways can be known, suspected or not recognized. The experience of the clinician assessing the airway is key, as is access to previous documentation if available. A national UK survey of airway complications[20] showed that 20% of all reported complications occurred in the critical care unit, and that the degree of harm that occurred to these patients was far higher than those that happened in theatre or the emergency department. The majority of complications were related to tracheostomies, both new and existing, but securing *de novo* airways also featured heavily. Common reasons identified for complications included lack of training, lack of equipment and lack of preparation. Reasons for increased complication rates include the above, but also the rapid need for intubation in the critically ill, the lack of cardiorespiratory physiological reserve, and the regular lack of an escape option where abandoning the need for ventilation is not possible.

The difficult airway can be due to obstruction or distortion at any level, and the potential management options will vary due to aetiology:

- supralaryngeal – tumour, infection, anaphylaxis
- laryngeal – infections, tumours, surgery, anaphylaxis
- infralaryngeal – tumour, infection, tracheomalacia, subglottic stenosis.

Where possible, the most senior staff available should be present, with full monitoring as would occur in theatre, and with trained skilled assistance. If predicted to be difficult there is a strong case for attempting the intubation in a theatre setting.

TRACHEOSTOMY

For patients who have an ongoing need for ventilation, there are several potential benefits for exchanging a translaryngeal tube for a tracheostomy tube. These include:

- reduced sedation needs due to lack of glottic stimulation
- reduced deadspace (probably less important than previously thought)
- reduced tube resistance and work of breathing
- improved mouth care
- ongoing bronchial toilet when weaned.

These benefits need to be balanced against the complications of tracheostomy insertion, the patient specific factors like coagulopathy or body habitus and the predicted duration of ventilation need. There is little evidence to support the optimal timing of tracheostomy insertion, with a

recent UK trial[21] comparing early (before day 4) and late (after day 10) tracheostomy insertion. This trial stopped early due to difficulties in recruitment, but with 900 of 1200 planned recruited patients failed to show a benefit in mortality with early tracheostomy insertion with similar lengths of stay, ventilation and antibiotic use.

The method of tracheostomy insertion is essentially between a percutaneous dilational technique, most often performed by critical care staff under bronchoscopic control, and traditional open surgical tracheostomies. Meta-analysis[22] has shown equivalence of the techniques, with a percutaneous approach leading to less wound infections and a similar complication rate. The percutaneous techniques involve partial withdrawal of the endotracheal tube under general anaesthesia and neuromuscular blockade, then a Seldinger based technique of needle insertion, guidewire pass and dilation using a serial dilator, graduated dilator or blunt forcep dilation before placing the tracheostomy tube over the wire.

There are situations where surgical techniques are more appropriate and these include:

- obesity, more for the availability of suitable percutaneous kit
- anatomical variance including previous surgery and goitres
- coagulopathy or bleeding diatheses.

ASSESSING VOCAL CORDS

This may be asked for in patients who have failed extubation, who have impaired cough mechanisms or suspected recurrent aspiration. Cord dysfunction may be due to mechanical issues after long-term intubation, surgical complications especially after thyroid or parathyroid surgery, or some apical lung tumours. Other nerve dysfunction should be sought, including bulbar or pseudobulbar dysfunction that may suggest alternative diagnoses. Assessment can be performed at the bedside using either rigid or flexible bronchoscopy methods, ideally without neuromuscular blockade.

DEATH AND DYING IN ICU

Mortality in critical care is steadily decreasing, despite dealing with ageing populations with increasing comorbidity. Figures vary between countries and case mix, but in a mixed medical and surgical ICU in a first world country, one would expect a unit mortality of around 20% and a hospital mortality of 35%. While improvements in mortality are encouraging, this still means that around one in five patients admitted will die and therefore medical and nursing staff need to be familiar with the caring of the dying patient and the support of their family.

Communication

Communication with both the patient and their family is a key part of the critical care workload. Often critically ill patients are unable to communicate or retain information, and the bulk of the communication given is to the family. This carries with it issues surrounding confidentiality and it is always best to have the patient give their permission prior to such conversations. This is not always possible, and the situation must be approached with tact and careful judgement. It should be remembered that having a relative who is critically ill is a heavy emotional burden for any family, and that even simple messages may have to be repeated at each conversation to ensure understanding.

Identification of the next-of-kin is a useful approach, allowing for clarity of communication and the reduction of misinterpretation. It is a laudable aim for a senior clinician to meet with a family within the first day following admission, and to have continuity of communication throughout the stay especially if prolonged.

Regardless of communication content, a few key points are universal:

- Time for communication must be made, ideally free from interference, in a dedicated relatives' area.
- Introductions should be clear, outlining roles and responsibilities and ensuring that you know who you are addressing.
- It is valuable to spend time at the beginning of each conversation investigating what has previously been said, and what has been understood – this can help to reduce 'mixed messages'.
- Be familiar with the case, including dates of admission and significant events.
- Always aim to summarize your conversation aims at the end, and allow time for questions.

Care of the dying in critical care

Every day in a large critical care unit there will be a patient who has their focus of care changed from a curative intent to the provision of palliation. This change in focus can happen quickly, or follow a more indolent course. It is usually due to a patient worsening, or a recognition that the patient would not wish to survive with such a marked reduction in functional outcome or quality of life. The latter is a particularly difficult decision to make, and needs to be carefully approached given the inherently subjective nature of such judgements.

Such decisions should be made in conjunction with the patient if their condition allows it, the family, and the referring team.[23] Concordance in the decision is the most desirable outcome, and if there is dissent then the best approach is to address this openly and to continue ongoing support until an agreement is reached.[24] As the emotional element of such decisions is so high, the process can often be reached over a longer period of time allowing time for grieving and acceptance of the situation at hand. Pursuing a decision in the face of unease or unhappiness is a common finding in complaints.

In critical care, the change of focus to palliation often encompasses either limitation of therapy or withdrawal of organ support. From an ethical standpoint the two are identical, but some will struggle with withdrawal

of support more than non-institution. Regardless of the mode of palliation, the comfort and the dignity of the patient are paramount, and only interventions that will increase patient comfort should be pursued. This may include starting or increasing analgesic infusions, extubation if appropriate, and cessation of blood sampling whilst continuing to ensure good oral cleaning, regular position changes and good nursing care. Communication should continue with the family, and addressing any concerns they may have during the process.

'Do not attempt resuscitation' (DNAR) orders are ways of communicating advance decisions regarding the appropriateness of undertaking cardiopulmonary resuscitation. The forms themselves are not legally mandated in the UK, but are seen as good clinical practice as they prompt medical teams to discuss decisions about resuscitation with patients and their families. Controversies surrounding DNAR decisions mainly stem from lack of communication, and misunderstanding of the role and realistic outcomes of cardiopulmonary resuscitation.

FUTURE RESEARCH

One of the major problems facing research in critical care is the application of single interventions to heterogeneous disease states. A desire to classify and compartmentalize broadly similar presentations has lead to umbrella terms, such as ARDS or sepsis. While these approaches make sense in terms of broadly similar pathophysiology or clinical presentation, the application of targeted treatments to clustered disease states does lead to potentially missing true treatment effects.

A common theme in modern critical care developments has been the early identification of organ dysfunction. A promising area of research is the development of reliable biomarkers of organ dysfunction that could allow early intervention and prevention of further deterioration. For example, serum lactate has been identified as a marker of tissue hypoxaemia that can be used to guide resuscitation and monitor progress in sepsis; and development of point-of-care tests could allow for quicker detection of the critically ill patient. This and other potential biomarkers would all have to be validated and suitable levels of sensitivity and specificity agreed upon.

As mentioned earlier in the chapter, an admission to critical care carries with it a substantial morbidity and the effect this has on future quality of life in survivors forms a key research priority. There is emerging evidence that an episode of acute inflammation such as a critical illness can lead to a chronic low-grade pattern of inflammation. This can have effects upon an individual's ability to recover from their acute event, and upon the potential for future accelerated organ deterioration. Both qualitative and quantitative research in this area is needed to help inform clinicians about the burden of admission on patients.

KEY POINTS

- Critical care has evolved to occupy a central role in the modern acute hospital.
- The most important interventions in critical care are the assiduous application of good basic medical and nursing care.
- Critical care admission is a multifactorial decision incorporating acute and chronic medical, social and ethical considerations.
- Advanced organ support is crucial to optimize the physiological state and permit time for definitive interventions to take effect.
- The majority of interactions between ENT and critical care will be for the provision of elective and emergency post-operative care and for advanced airway intervention, including difficult airway management and tracheostomy.
- Due to the high mortality rate among ICU patients, management of death and the dying patient is of paramount importance, as is recognizing that effective and empathetic communication assists this process.

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CHAPTER 34

PAEDIATRIC INTENSIVE CARE

Louise Selby and Robert Ross Russell

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SEARCH STRATEGY

Data for this chapter are mostly generic management strategies for children in intensive care. The target audience is ENT surgeons involved in caring for children, rather than paediatric intensivists who are looking after ENT patients. The material is relevant to both groups within the chapter.

The data were gathered through reference to standard texts on paediatric intensive care, notably Rogers and Nichols' *Textbook of Paediatric Intensive Care*.[1] Specific information on ENT trauma in children was obtained through PubMed using the keywords: 'laryngeal trauma and laryngeal injury', limiting the search to children aged 0–18 years. This revealed 90 review articles of which 7 were found relevant and scrutinized. Information on bronchoscopy was located on PubMed using the keywords: 'fibreoptic bronchoscopy and intensive care', limiting the search to children aged 0–18 years. This yielded five papers, but by looking at related citations we were able to find two relevant articles.[2, 3]

INTRODUCTION

Children are liable to present acutely with ENT pathologies, many of which are specific to the paediatric population and may require intensive care management. Those children undergoing major ENT surgery also frequently require admission to a paediatric intensive care unit in the post-operative period. This chapter aims to outline the general management principles of ENT patients within the paediatric intensive care setting. Important differences in the anatomy and physiology of children compared to adults are reviewed. A systematic approach to evaluation of children admitted to the paediatric intensive care unit (PICU) is outlined, together with general principles of fluid and analgesia management in children. Specific issues relating to the care of the major paediatric emergencies, as well as the post-operative management of patients undergoing major ENT surgical procedures are discussed. Finally, indications for performing flexible and rigid bronchoscopy are outlined.

GENERAL PRINCIPLES

Anatomical and physiological considerations

The paediatric airway differs from the adult airway in many aspects. Understanding these differences in structure is essential in order to manage the paediatric airway successfully. The head of the infant and small child is proportionately larger, accounting for nearly 10% of body surface area compared to 3.5% in adults. Infants and young children have a more prominent occiput with a shorter neck and these factors in combination increase neck flexion. Children also have a relatively large tongue and a small mandible, potentially making airway access difficult.[4]

In all young children the epiglottis is a 'horseshoe shape' and the larynx sits high (opposite the third cervical vertebrae, compared to the fifth or sixth in an adult) and anterior. The larynx itself is conical, unlike the cylindrical

TABLE 34.1 Physiological parameters at different ages

Age	Heart rate (bpm)	Respiratory rate (bpm)	Mean BP (mmHg)
Newborn	110–140	50–60	50–60
1 year	90–110	30–40	70–90
2–5 years	75–90	25–30	80–100
5–12 years	60–90	20–25	90–110
>12 years	50–80	15–20	100–120

adult larynx and the narrowest part lies at the cricoid cartilage. Finally the tracheal cartilage is often less rigid than in adults, and may compress if the neck is overextended.[5]

Infants up to the age of 6 months are obligate nasal breathers.[5] When this is combined with the relatively small airways and risk of mucus obstruction, airway compromise is common. Between 3 and 6 years of age, tonsillar and adenoidal hypertrophy further contribute to airway obstruction.

Physiologically, there are also substantial and important differences. Respiratory muscle function is affected by the position of the ribs in infants, which lie perpendicular to the spine rather than running caudally as in adults. This makes the diaphragm the only effective inspiratory muscle. Infants and children have a faster respiratory rate than adults (Table 34.1), which is partly related to an increased metabolic rate. In infants, increased chest wall compliance can increase the work of breathing substantially.

In the cardiovascular system, a limited stroke volume necessitates a faster heart rate in children and they also display a lower mean blood pressure. Their response to cardiovascular stress is limited and cardiac output can only be increased significantly by increasing the heart rate, therefore tachycardia is common.

Evaluation

Admission of a child into the PICU is a difficult and important moment in the child's care. The care of the child is transferred to a new team of doctors and nurses and the family are moved to a new and stressful environment. It is essential that handover of the child is structured and complete. Ideally there should be a face-to-face handover between medical and nursing teams involved in the care of the child. The background history, current problems and care plan should be clearly documented.

The family of the child need to be included in this handover. When the admission is planned, for example post-operatively, families should be offered the chance to visit the intensive care unit prior to the surgery so they have met some of the staff and seen the environment. There should be an area for them to stay whilst procedures are being carried out and regular progress updates from medical and nursing staff.

The doctors admitting the child also need to evaluate the child carefully on admission. This should follow a standard 'ABC' assessment, assessing the airway, breathing and circulation. Issues regarding fluid balance, medications and results of investigations should also be clarified (Table 34.2).

TABLE 34.2 Issues to be considered on admission of a child to PICU

	Issues to consider
Airway	Clear? ETT position? ETT secured properly?
Breathing	Air entry? Adequate ventilation?
Circulation	Peripheral perfusion? Adequate access?
Fluids	Drug infusions? Blood sugar? Urine output?
Analgesia/sedation	Pain control and sedation adequate? Muscle relaxant needed?
Tests	Blood gas? Electrolytes? Full blood count?

Fluid management

The principles of fluid balance in children are the same as in adults but there are complicating factors. Any fluids that need to be given are based on a child's weight or occasionally body surface area (tables for which are found in the British National Formulary for Children). The distribution of fluids between compartments is different for adults and children. Total body water is distributed between the intracellular, interstitial and intra-vascular spaces, moving from one compartment to another. At birth approximately 80% of a baby's body weight is water, with this percentage falling gradually to 60% in adulthood. The infant has approximately one third of their body weight as interstitial fluid – twice as much as in an adult.[1]

Normally fluid balance is tightly controlled by thirst, hormonal responses and renal function. In illness and injury there may be rapid fluid shifts with clinical consequences.

THE NEWBORN INFANT

The full term infant requires approximately 150 ml/kg per day of fluid from day 5 of life (less in the first few days). Of this, approximately 30 ml/kg will be accounted for by insensible losses. Normal fluid intake is entirely as milk, which provides fluid and nutrition for approximately the first 6 months of life. Fluid requirements (per kg) gradually reduce thereafter as shown in Table 34.3; however, these requirements may require adjustment in disease.[5]

Electrolyte requirements also vary with age, though not as dramatically as fluid volume. In the infant, immature renal function increases the salt requirements and 3 mmol/kg of sodium and 2 mmol/kg of potassium are required daily. In older children this falls to approximately 2 mmol/kg per day of each ion. Calcium, magnesium and other ions are broadly in the same dose (per kg) as adults.

Glucose requirements are critical, especially in young children. The daily calorie requirement of infants is approximately 100 kcal/kg, more than double that in adults.

TABLE 34.3 Fluid and electrolyte requirements at different ages

Age	Daily fluid requirements	Sodium/potassium requirements
1 day	60 ml/kg	2–3 mmol/kg/day
5 days	150 ml/kg	2 mmol/kg/day
1 month	120 ml/kg	1–2 mmol/kg/day
6 months	110 ml/kg	
1 year	100 ml/kg	
>1 year	1000 ml for the first 10 kg, 500 ml for the next 10 kg, then 20 ml/kg for the rest of body weight	

Maintenance of adequate glucose levels in infants is critically important and hypoglycaemia can cause brain damage. In infants and small children, enough glucose must be given to maintain blood glucose levels.

THE UNWELL CHILD

Fluid requirements following surgery can be quite variable. In most units, children are started on a regime restricting their input to approximately two-thirds of normal requirements. This is especially true if oral feeds are not to be used and fluids are being given intravenously. Intravenous fluids should be chosen with care. A National Patient Safety Agency (NPSA) alert in 2007 prompted the removal of hypotonic fluids (0.18% saline) from paediatric wards following incidences of mortality secondary to hyponatraemia.[6] Solutions containing adequate sodium (such as 0.9% saline, or 0.45% saline and 5% dextrose) are therefore recommended. Whatever regime is used, it needs to be remembered that children are prone to becoming dehydrated or fluid-overloaded quite rapidly (particularly during illness) and need to be monitored carefully. In infants especially, blood glucose levels need to be measured up to every 4 hours.

Analgesia

Appropriate analgesia needs to balance the sedative and respiratory suppressive effects of opiates against the need for good pain control. Oral paracetamol and other non-steroidal anti-inflammatory drugs (NSAIDs) may be adequate, but opiates (e.g. morphine) may be needed. A morphine infusion of 10–30 mcg/kg/hour can be given or as a patient-controlled analgesia pump for older children. Infusions can be set up to give background rates of 10 mcg/kg/hour with additional boluses for breakthrough pain but should be discussed with an anaesthetist. Midazolam is a sedative and amnesic drug and may be needed for patients in the PICU, especially if they are ventilated or undergoing painful procedures. Midazolam can be given as bolus doses of 0.1 mg/kg up to every 4 hours or as an infusion (50 – 250 mcg/kg/hour). Patients need close observation of physiological parameters with either bolus dosing or intravenous infusions.[5]

ENT EMERGENCIES IN PICU

Trauma

All trauma cases, including those who have sustained craniofacial trauma should be managed acutely according to paediatric life support guidelines, with immediate evaluation of airway, breathing and circulation.[5] Laryngeal trauma consists of a rare but precarious set of injuries, often requiring a high index of suspicion to promptly diagnose and appropriately treat. Cases of blunt laryngeal trauma are rare. Laryngeal trauma is seen less frequently in infants and children because of their involvement in fewer car crashes and cases of 'interpersonal conflict'.[7] They may occur if a child is unrestrained in a car involved in a road traffic accident if they hit the dashboard when the head and neck are in a hyperextended position. In the child presenting with laryngotracheal injuries in the absence of such a history, the possibility of non-accidental injury with a direct blow to the anterior neck should be considered as a possible aetiology.

Children surviving a near strangulation event are at risk for significant airway compromise. Studies looking at near hanging events between 2001 and 2010 found four cases with documented laryngeal injury and one child requiring a tracheostomy.[8] 'Near hanging' or 'choking games' are reported in the teenage population.[9]

Management of laryngeal trauma must begin by evaluating the adequacy and patency of the airway. If airway obstruction is a concern, a surgical airway in the form of emergency tracheostomy should be established urgently. The preferred management in children consists of gas anaesthesia with rigid bronchoscopy to evaluate the injuries as well as securing the airway so tracheostomy can be performed over the rigid bronchoscope.[8] Orotracheal intubation must be undertaken with caution to avoid extending damage or losing the airway.

In patients with moderate injuries, the degree of damage can be further assessed using CT scanning once the airway has been protected. Open exploration is recommended where the injuries are severe, and laryngeal trauma is commonly associated with other injuries to the neck or chest.[8]

Upper airway obstruction

The small cross sectional area and conical shape of the paediatric airway renders children particularly susceptible to upper airway obstruction. Airway resistance is inversely proportional to the fourth power of the radius of the airway. Therefore a relatively small reduction in the radius of the airway through mucosal oedema, secretions or a foreign body results in a significant increase in airway resistance.[5]

Stridor on inspiration is indicative of upper airway obstruction. In children where severe upper airway obstruction is suspected as a diagnosis it is imperative to avoid all invasive procedures and aspects of the examination that may distress the child as this may cause complete upper airway occlusion. Children should be kept warm and calm while experienced anaesthetic and surgical staff are assembled. Examination can then be undertaken in a

controlled manner. A full examination of the child is also needed at a convenient point. Birthmarks and haemangiomas should be recorded as this may indicate there is a vascular laryngeal lesion. If a child is dysmorphic, a genetic opinion may help identify a syndrome that may have airway implications. Patients with micrognathia as seen in Pierre Robin syndrome, Robin sequence and Treacher Collins syndrome, and those with the mucopolysaccharidoses where progressive dermatan sulphate accumulation in body tissues including the oropharynx and airway, can make airway management challenging.[4]

The patient recovering from burns presents additional challenges. Contractures of the face, neck and chest may result in microstomia, granuloma formation, subglottic stenosis, tracheomalacia and fixed flexion of the neck.[10]

EPIGLOTTITIS

The vaccine included in childhood immunization schedules should protect against *Haemophilus Influenzae B* (Hib) infections and has led to a marked decline in the incidence of epiglottitis such that it is a rare condition. Occasional cases do occur in unimmunized children or in those in whom the vaccine has failed.

The clinical presentation is a child usually aged between 2 and 7 years who is toxic, stridulous and drooling. Immediate management is to secure the airway either by endotracheal intubation by experienced personnel or by emergency tracheostomy. The child will remain ventilated in intensive care whilst receiving intravenous antibiotics (third generation cephalosporins) until the swelling of the epiglottis has reduced, usually within 24–36 hours.[11]

CROUP

Acute viral laryngotracheobronchitis (viral croup) is a common cause of upper airway obstruction in children characterized by hoarseness, barking cough and inspiratory stridor. *Parainfluenzae* virus type 1 is the agent most commonly identified in cases of croup. Only severe cases require admission to the PICU.

Localized inflammation and oedema of the upper airway caused by a virus can increase airway resistance and significantly increase the work of breathing in young children. Glucocorticoids in the form of nebulized budesonide or systemic dexamethasone are believed to reduce the degree of upper airway inflammation and swelling leading to decreased effort in breathing. A recent Cochrane review found when corticosteroids were compared to placebo in treatment for croup, dexamethasone and budesonide were effective in relieving symptoms as early as 6 hours after treatment, resulting in reduced hospital stay and fewer hospital re-admissions.[12] Some clinical improvement can occur within 30 minutes of glucocorticoid dose.[5]

If airway obstruction is severe, short-term relief can be achieved by nebulizing adrenaline (1 ml/kg of 1 : 1000 up to a maximum dose of 5 ml) with oxygen. A small number of children with croup (< 5%) will require intubation. However glucocorticoids and nebulized adrenaline have both been shown to reduce length of hospital stay in management of croup.[12, 13] A comparison of the clinical features of croup and epiglottitis are included in Table 34.4.

TABLE 34.4 Features of croup vs epiglottitis

	Croup	Epiglottitis
Age	1–3 years	2–7 years
Cause	Parainfluenza viruses	Hib
Prodrome	1–2 days coryza	Hours, sore throat, dysphagia, drooling.
Fever	<38°C	>38°C
Appearance	Lethargic	Pale and toxic, drooling and dysphagia, sitting with neck extended
Stridor	Barking cough, loud stridor	Muffled stridor
Hypoxia	Unusual	Frequent
Severity	<5% hospitalized cases require intubation	All require intubation

Bacterial tracheitis

Bacterial tracheitis, or pseudomembranous croup, is much less common than viral croup but it is potentially life threatening. The majority of patients (over 80%) will require intubation to secure their airway whilst receiving treatment with intravenous antibiotics. The responsible pathogens are usually *staphylococcus aureus, streptococci* or *Haemophilus influenzae B*, which infect the tracheal mucosa causing necrosis and the production of purulent secretions that may occlude the upper and lower airway. Clinically, a child with bacterial tracheitis is septic with a high fever, barking cough and signs of progressive upper airway obstruction. Coughing without drooling can help to distinguish it from epiglottitis.[5]

Foreign body inhalation and ingestion

Foreign body inhalation most commonly occurs in children aged 1 to 3 years and should be suspected if there is sudden onset of stridor and upper airway obstruction with no preceding fever or illness (please see Chapter 31 for more details). Without early treatment it is a cause of morbidity in children, sometimes resulting in a fatal outcome.[14] Foreign body injuries can be described by anatomical site. Upper airway involvement varies from complete obstruction with hypoxia and cardiorespiratory compromise to partial obstruction with cough, stridor, and respiratory distress. Lower airway involvement can lead to pulmonary changes depending on the site of the impaction including collapse and consolidation of the bronchopulmonary segment seen on chest X-ray.[15] Foods, particularly nuts and seeds, are the usual cause. However, small magnets or other metallic parts found within some toys can become lodged in the hypopharynx

or oesophagus and rapidly cause pressure necrosis of mucosal tissues.[16]

If a child presents with increasing dyspnoea, apnoea or loss of consciousness that has not responded to simple airway manoeuvres then advanced paediatric life support guidelines for managing a choking child should be followed. Blind finger sweeps of the mouth are not recommended as these can push the object tighter into the larynx. In the older child the Heimlich manoeuvre can be safely attempted, or if the child is unconscious and supine then abdominal thrusts may be as effective.[5]

On clinical examination there may be unilateral wheeze and reduced breath sounds. A chest X-ray may show air trapping possibly with (mediastinal shift), atelectasis, pneumothorax or have a normal appearance.[15] Patients require general anaesthetic for rigid bronchoscopic removal and may require admission to the PICU post procedure. Complications of delayed diagnosis of inhaled foreign body can include tracheal lacerations, inflammation, oedema, atelectasis and bronchopneumonia[12, 13] contributing to prolonged hospital stay. There can also be bleeding with manipulation of the object and it can be difficult to dislodge and retrieve.[16]

Laryngopharyngeal injury can also occur following accidental ingestion, particularly of liquid detergent capsules. These contain irritant cleansing ingredients that can cause rapid onset of mucosal oedema. Consequences can be severe, with possible oesophageal perforation and necrotic extension to the tracheobronchial tree requiring endotracheal intubation or tracheostomy.[17]

MAJOR SURGERY

Craniofacial surgery and cleft lip and palate

Children who undergo craniofacial surgery or a cleft lip or palate repair may require admission to the PICU or high dependency unit (HDU), particularly if there is a risk of the airway becoming compromised by post-operative swelling. If the child returns from theatre ventilated, sedation and analgesia need to be maintained for the duration of ventilation. A partially sedated child may struggle against an endotracheal tube (ETT) and this may damage a palatal or laryngeal repair. It may be necessary to muscle relax a child once they are adequately sedated, usually by using short acting anaesthetic agents, so if extubation is planned the child can be woken quickly. Using longer-acting drugs can lead to accumulation of the drug within the tissues and a period of suboptimal wakefulness as it is metabolized.

Other important considerations include the use of an orogastric rather than nasogastric tube best sited intra-operatively (nasogastric tubes can traumatize a palate repair). Nursing staff should be aware to use a soft wide-bore flexible suction catheter to remove visible oral secretions. Patients should not be nursed close to other children who may be infectious if at all possible.

Surgery of the nose and upper airway

Patients who have nasal surgery rarely require admission to the PICU in the post-operative period; however, infants requiring surgery for choanal atresia or stenosis may require a nasal stent and close observation for the first few days post-operatively.

Those undergoing surgery to the upper airway are frequently admitted to the PICU for a period post-operatively due to the high risk of developing upper airway obstruction as oedema evolves around the surgical site. This includes operations for laryngeal reconstruction but also for more minor procedures such as aryepiglottoplasty and those children who have undergone adenotonsillectomy for severe sleep apnoea. It is therefore important to ensure a PICU/HDU bed is available before proceeding with surgery. Children who have major upper airway surgery, such as laryngotracheal reconstruction, are electively ventilated for a period of 5 to 7 days post-operatively to allow the oedema to resolve before the ETT is removed. In these patients, sedation and analgesia are critical (see 'Craniofacial surgery and cleft lip and palate', above). Muscle relaxants are used in this patient group to prevent trauma to the surgical site and exacerbation of upper airway oedema due to movement of the ETT whilst *in situ*. Close observation of cardiovascular parameters in muscle-relaxed patients will detect tachycardia and hypertension suggestive of inadequate sedation or pain. It is important that if a significant leak is allowed to develop around the ETT before extubation is attempted this may signify that the post-operative oedema is resolving and that extubation is more likely to be successful.

Laryngeal surgery and tracheostomy

Managing a tracheostomy in the PICU involves the management of the newly formed stoma, care of an established tracheostomy and training requirements for families looking after long-term tracheostomies. In children, tracheostomy is most frequently performed in the first year of life as a result of premature infants requiring prolonged ventilation.[18]

In the first week after a tracheostomy is formed the airway is dependent on the tracheostomy stent (i.e. the tube) to maintain airway patency. Loss of the stent over this period can allow the airway to close, and reinsertion of a tube through an immature tracheostomy can be difficult, as the tracheal opening can be obscured and the tube can easily be passed into the wrong place causing airway obstruction and ventilation of the neck tissues. This complication, known as accidental tube dislodgement, is minimized in a fresh tracheostomy when stay sutures are used. These are attached to the edges of the trachea at surgery and allow the trachea to be brought to the surface of the neck in an emergency, facilitating tube reinsertion. Additionally, maturation sutures attach skin directly to the edge of the trachea to reduce creation of a false passage during the first tracheostomy tube change. Velcro tracheostomy tube ties can also be used if available.[18]

However, many departments prefer to use ties rather than Velcro in the early post-operative phase.

If a tracheostomy tube does become dislodged in this period and cannot easily be reinserted, then (in a child with an adequate upper airway), a conventional ETT should be inserted to secure the airway. This allows planned replacement of the tracheostomy tube at a later stage.

Following the first tracheostomy tube change (usually at 7 days post-operatively), the tracheostomy is more secure. Care of an established stoma involves the establishment of routine tube changes, tape care and training for care givers. The development of difficulties with tube insertion or bleeding should raise the possibility of obstructive granuloma formation.[18]

Bronchoscopy in PICU

FIBREOPTIC BRONCHOSCOPY

Fibreoptic bronchoscopy is a safe and effective method of investigating airway problems when used in a planned and controlled manner.[2] It is a useful technique to directly visualize the lung by passing a fibreoptic scope through an ETT. The scope can visualize all lobes of the lung and identify static (e.g. mucus plugging) and dynamic (e.g. bronchomalacia) problems. The general difficulties with bronchoscopy include hypoxia and hypercapnia as a result of an inability to effectively ventilate through the scope and a narrow suction channel that blocks easily. The scope can be passed through a rubber valve in the ETT allowing continued ventilation around the scope, but this is difficult if the scope diameter is close to that of the ETT. Ventilation may also be worsened for hours after the procedure due to removal of endogenous lung surfactant and atelectasis.The main contraindication to bronchoscopy is that it may provide no useful information.[2, 3]

Bronchoscopy can be classed as 'diagnostic' to assess airway patency and anatomy or obtain lavage specimens to aid diagnosis or 'therapeutic' to aid secretion clearance for example.[19]

RIGID BRONCHOSCOPY

This technique is much more effective at removing debris from the airway, and may be easier to use in the very unstable patient as ventilation can be continued through the scope during the procedure.

There are several indications for either fibreoptic or rigid bronchoscopy in PICU:

- **Persistent collapse of lobe/lung:** Ventilated children may develop complete collapse of a lung, usually secondary to blockage of the major airways with secretions and mucus plugs (secondary to severe pneumonia). This can lead to major ventilatory problems with shunting. Fibreoptic bronchoscopy down the ETT can often identify the degree of blockage but a rigid bronchoscope may be needed to clear thick secretions. Intra-tracheal recombinant human DNAase (rhDNase) has been reported to be of benefit in segmental collapse.[18]
- **Assessment of malacia:** Clinical tracheo or bronchomalacia may be difficult to confirm. Flexible bronchoscopy may help locate the site and degree of weakness, but needs to be carried out with the patient self-ventilating as positive pressure ventilation can stent the airway open artificially.
- **Assisted intubation:** This is a rare indication as conventional intubation is usually relatively easily accomplished. However if a child has a craniofacial syndrome that may make this particularly difficult and bronchoscopic intubation may be indicated. The bronchoscope is threaded through an appropriately sized ETT and the endotracheal tube is advanced over the fibreoptic bronchoscope into position.
- **Collection of broncho-alveolar lavage:** The diagnosis of lung pathogens can be difficult, particularly in patients who are immunosuppressed. Many probable pathogens for pneumonia in these patients are not tracheal commensals. Broncho-alveolar lavage may be very useful in this situation. It can be carried out 'blind' by passing a nasogastric tube into the lungs, washing in 0.9% saline then aspirating or using a fibreoptic scope to direct the lavage to a particular part of the lung. If a good quality lavage is negative then an open lung biopsy maybe necessary.

SUMMARY

Principles of care for children are similar to those of adults, but physiological responses seen in children vary with age. Some ENT procedures are also specific to the younger age group, and in units that are not undertaking paediatric surgery frequently, well maintained guidelines for the care of these children is essential.

BEST CLINICAL PRACTICE

- ✓ General principles:
  - ✓ Anatomical and physiological differences between adults and children need to be recognized.
  - ✓ Fluid and electrolyte administration must be age and weight appropriate.
  - ✓ Appreciation of family carers and their involvement is essential.
- ✓ ENT emergencies in PICU:
  - ✓ Laryngeal trauma in children may require a tracheostomy.
  - ✓ Epiglottitis is now rare in the UK because of the Hib vaccination.
  - ✓ Foreign body inhalation is an important, if uncommon, cause of acute respiratory distress in young children.

- ✓ Major surgery:
  - ✓ Muscle relaxation may be needed following palatal and tracheal surgery to avoid damage from a struggling child.
  - ✓ Infection is a major cause of palatal breakdown in children following surgery.
- ✓ Flexible bronchoscopy in children can clear secretions, but the size of the bronchoscope limits its suctioning ability.
- ✓ Suspected foreign bodies should be removed through a rigid bronchoscope.

FUTURE RESEARCH

Many of the clinical practices on PICU have evolved through sharing of experience rather than being substantiated by medical evidence or clinical trials and the potential for research projects aimed at providing evidence to support or refute current practices is huge. However there are significant practical limitations to undertaking such research, for example the ethics of research in children, difficulties obtaining parental consent for entry into trials and recruiting sufficient numbers of patients to achieve adequate power.

KEY POINTS

- Paediatric anatomy and physiology differs significantly to that of an adult.
- Foreign body inhalation (or ingestion) should be suspected in any child with unexplained stridor or respiratory problems.
- Fluid and electrolyte prescriptions for children individually according to body weight.
- All patients with suspected epiglottitis require intubation.
- Trauma and infection are threats to palatal repairs.
- Good evidence to support clinical practice in PICU is limited.

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CHAPTER 35

TRAINING, ACCREDITATION AND THE MAINTENANCE OF SKILLS

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: otolaryngology, training, surgical education, educational models, clinical competence, academic legislation & jurisprudence, European Union and United Kingdom.

PRINCIPLES OF TRAINING

A training programme in any postgraduate medical specialty, which includes otorhinolaryngology (ORL), is designed to ensure that a doctor progressing through that programme is competent to perform as an independent specialist within the healthcare system in which they work. It follows that the first goal to agree upon, when designing a programme, is the level at which competence should be set and what the scope of the competencies should be. A curriculum will then be written, agreed upon by stakeholders and published. A curriculum has the following areas of content:

- aims and objectives
- content or syllabus
- resources
- assessment strategy
- evaluation.

Aims and objectives

A clearly stated aim of a curriculum is required to ensure that it has the right content and assessment strategy. In the UK in 2016 the aim of the curriculum in ORL for postgraduate training is to train a surgeon who is emergency safe and has the ability to develop an area of special interest. Being emergency safe requires a high degree of knowledge as well as technical and clinical skills, not least because of the need to manage a wide range of unselected patients with a variety of conditions. To demonstrate safe management of emergencies the curriculum can identify elective procedures that may be used as proxy for the less common emergency procedures. For example, competence in a (relatively common) selective neck dissection can, in conjunction with clinical, non-operative experience, be used as a proxy for competence in managing neck trauma and deep neck abscesses. This requirement for a high level of technical expertise in managing emergencies has the consequence of lengthening training time compared to a programme where competence in emergency care is not a prerequisite for completion of training. Shorter specific fellowship programmes should also have a curriculum with specific aims so that one can assess competence against curriculum objectives. So, for example, an advanced otology fellowship programme may state that an aim of the programme is 'competence in cochlear implant surgery'.

The aim of a curriculum should take into account a variety of stakeholders. Indeed, one motivation could be political, whereby a particular programme is designed with a public health policy in mind that needs to be implemented. A specialist needs to be 'fit for purpose' and capable of working effectively within a healthcare system. Therefore, when designing a curriculum, it is imperative to consult patient groups, employers,

commissioners, trainee representatives and, importantly, those responsible for delivering training (e.g. in England these are the Local Education and Training Boards (LETBs)) to ensure that a specialist is in the best position to deliver care to those who receive it (the patients) and those who commission it (ultimately the government). With increasing input from lay people and non-specialists in the design of surgical curricula, there has been a greater emphasis on professional and leadership skills where the importance of effective communication, leadership, teaching and keeping up to date is made, as well as assessed.

In the UK, the General Medical Council (GMC), along with specialty input, is responsible for the design and delivery of curricula. The process of curriculum approval by the GMC is governed through the Curriculum Advisory Group (CAG), where medical royal colleges, faculties and specialty associations are held accountable to the standards and requirements for curricula and assessment systems in accordance with the Medical Act 1983.[1, 2]

Syllabus

Once the primary aim of a curriculum is established, a syllabus then needs to be formulated that allows the delivery of curriculum objectives in a clear, unambiguous way. A syllabus will define in a variable amount of detail the areas that need to be learnt and the requirements needed to demonstrate competence to ensure the aim is realized. A syllabus will usually be written in sections or topics where the knowledge, clinical and technical skills required are defined against the level of competence necessary. A syllabus is defined by a specialty curriculum group which takes into account the breadth of skills required, the caseload available for training, as well as the level of expertise at which those who are awarded a Certificate of Completion of Training (CCT) should expect to be competent. The concept of 'desirability' of inclusion of topics, with the understandable aspiration for expertise in all areas, must be balanced with 'deliverability' whereby a pragmatic approach to setting competence levels should be adopted so that competence can be achieved by all. For example, it is unnecessary in the UK programme for all trainees to be expected to be competent in stapedectomy and neither is it realistic to be able to deliver this training opportunity to all. A syllabus indicates the supreme aims of a programme through ensuring that trainees understand what is required to achieve competence, and in what areas they will be assessed to demonstrate competence, prior to certification.

Resources

Once an aim of a programme is agreed and a syllabus written, the resources required to deliver it need to be established. If appropriate resources are not available, then the curriculum may need to be reviewed and modified, as it is a *sine qua non* that a curriculum can only be achieved if the resources required to fulfil it are available to all. The following resources are required for curriculum delivery:

- **Caseload:** Enough cases are needed to enable *all* trainees to have equitable access sufficient to meet training needs. With healthcare delivery evolving this requires regular evaluation. For example, over the next few years exposure to transnasal oesophagoscopy (TNO) is likely to increase in the UK, whilst with the changing management of head and neck oncology, exposure to total laryngectomy is likely to reduce.
- **Faculty:** There should be adequate access to expert faculty to train those going through the programme. In surgical programmes faculty is represented by consultant surgeons who have competing interests for their professional responsibilities. Faculty need to be trained and accredited for their role within a teaching programme.
- **'Off the job' training:** Increasingly there is an emphasis on simulated or technology enhanced learning, which has the principle of providing a safe environment to hone essential technical and non-technical skills before exposure to real patients (e.g. in human factors training).[3] There is some evidence that simulation training improves the rate of acquisition of skills, but this has to be balanced with the increased cost of equipment, time away from patient care and requirements for trained faculty to supervise learning in this environment. There is a move in the UK towards mandatory simulated surgical training in order to satisfy some aspects of the curriculum.
- **Time for training:** A purely supernumerary trainee is aspirational, with the tradition for service delivery as a means of acquiring competence embedded in UK training. Training lists and clinics take longer than pure service lists, and the balance needs to be struck between the two. Skilful supervision will mitigate the time lost to training whilst developing a trainee's skills and this is one of the aims of courses in educational supervision.
- **Pastoral support:** Support for those experiencing difficulties in achieving outcomes is necessary to ensure all trainees have the opportunity to achieve the aims of the curriculum of the programme they are training in.

Assessment

Trainees within programmes need to be assessed to ensure they are on track in their development and to prove that they have achieved the aims of the programme. Assessments may be formative (assessment for learning), which tend to use workplace-based assessments (WPBA) on a regular basis, or summative (assessment of learning), which are high stakes assessments (i.e. a pass/fail exam). Each is complementary, but a continuous cycle of low stakes 'on the job' assessments will, when used correctly, encourage reflective learning and steady development in clinical, technical and professional skills. Summative assessments need to be developed and assured that they are assessing the whole curriculum and assessing trainees at the correct level in their training.

In the UK this is overseen by the GMC as part of its role in quality assuring all aspects of postgraduate training.

Evaluation

Programmes also need to be evaluated to ensure that they are fit for purpose, that is, delivering a surgeon capable of achieving the aim of the programme. This can be achieved by 'triangulation' of feedback from trainees, faculty and users of the service. Analysis of assessments can also demonstrate that a programme is delivering a properly trained surgeon. Evaluation should feed into the review of a curriculum so that it can be modified appropriately to best reflect the requirements of service users, whilst also ensuring trainees are being treated fairly and receiving support and opportunities to accomplish their aims. In the UK the annual GMC and Joint Committee on Surgical Training (JCST) trainee survey is producing increasingly meaningful data capable of evaluating programmes and helping to identify areas for development. Analysis of data from workplace-based assessments within trainee portfolios are being used to demonstrate the validity and utility of such tools.[4]

GMC STANDARDS OF ASSESSMENT

The GMC supervises the standards that medical royal colleges, faculties and specialty associations must apply in developing, monitoring and assessing curricula. The GMC defines an assessment system as an integrated set of assessments that is in place for the entire postgraduate training programme and that is blueprinted against and supports the approved curriculum. The importance of a robust assessment system is to:[5]

- determine whether trainees are meeting the standards of competence and performance specified at various stages in the curriculum for surgical training
- provide systematic and comprehensive feedback as part of the learning cycle
- determine whether trainees have acquired the common and specialty-based knowledge, clinical judgement, operative and technical skills, and generic professional behaviour and leadership skills required to practise at the level of CCT in the designated surgical specialty
- address all the domains of *Good Medical Practice* and conform to the principles laid down by the GMC.[6]

In order to be included in an assessment system, the assessment methods selected must meet the following criteria:[5]

- **Validity:** To ensure face validity, WPBAs comprise of direct observations of workplace tasks. The complexity of the tasks increases in line with progression through the training programme. To ensure content validity all the assessment instruments have been blueprinted against all standards of *Good Medical Practice*.
- **Reliability:** In order to increase reliability, there will be multiple measures of outcomes. Intercollegiate Surgical Curriculum Programme (ISCP) assessments make use of several observers' judgements, multiple assessment methods (triangulation) and take place frequently. The planned, systematic and permanent programme of assessor training for trainers and assigned educational supervisors (AES) through the Deaneries/LETBs is intended to gain maximum reliability of placement reports.
- **Feasibility:** The practicality of the assessments in the training and working environment has been taken into account. The assessment should not add a significant amount of time to the workplace task being assessed and assessors should be able to complete the scoring and feedback part of the assessment in 5–10 minutes.
- **Cost-effectiveness:** Once staff have been trained in the assessment process and are familiar with the online ISCP portfolio, the only significant additional costs should be the extra time taken for assessments and feedback and the induction of a new AES. The most substantial extra time investment will be in the regular appraisal process for units that did not previously have such a system.
- **Opportunities for feedback:** All the assessments, both those for learning and of learning, include a feedback element. Structured feedback is a fundamental component of high-quality assessment and should be incorporated throughout workplace-based assessments.
- **Impact on learning:** The workplace-based assessments are all designed to include immediate feedback as part of the process. A minimum number of three appraisals with the AES per clinical placement is built into the training system. The formal examinations all provide limited feedback as part of the summative process. The assessment process thus has a continuous developmental impact on learning, a process enriched further with emphasis on reflective practice within the portfolio.

EVOLUTION OF SURGICAL TRAINING

Postgraduate surgical training has undergone significant change over recent decades. Historically surgical training in the UK was considered to be an apprenticeship, taking several years to learn the theoretical background and cultivate operative competence to achieve expertise.[7] Although there were advantages to the conventional time-based apprenticeship model of training and it did successfully produce competent consultant surgeons over many years, several limitations did exist and it gradually became outdated. Training was considered unstructured, occurring over an undefined period of time, and often consisted of unsupervised service rather than training. This was associated with an inherent difficulty in measuring trainee competence and was criticized for lacking transparency, reliability and validity. This not only failed to meet training needs, but also did not satisfy the changing expectations and demands of both patients and an evolving

National Health Service requiring a greater number of consultants to deliver care and train the next generation of surgeons, due to both the mounting demands of patient safety and the ever increasing medico-legal unacceptability of complications due to inexperience.

The Calman Report in 1993 outlined the future direction of training and this was reinforced further in the chief medical officer's report, *Unfinished Business*, in 2002, in which recommendations were made for the establishment of a national benchmark for training, comprehensive specialty curriculums and regular assessment of trainee competence, as well as consultant-delivered, rather than consultant-led, patient care.[8, 9] As a result, Modernising Medical Careers (MMC) was initiated in 2003 and this was followed by the implementation of a shortened, restructured continuous pathway of specialty training based on a model of proficiency in developing trainee competence according to predetermined approved standards.[10] A shift to a more competency-based form of training has assured the provision of a high standard of training with less importance placed on service delivery and a greater emphasis on formal supervision from consultant trainers appropriately qualified to train, assess and give feedback. Following satisfactory completion of training, having developed the required competencies to practice independently and having reached a definite educational end point after a predetermined period of time, a trainee is awarded a certificate of completion of training (CCT) and is able to practice as a consultant.

A further challenge has been the delivery of a shortened and reorganized training paradigm within the restrictions imposed by the compulsory implementation of the European Working Time Directive (EWTD).[11, 12] The significant reduction in the time available to train has had a dramatic impact, especially on surgical specialties, where developing and achieving expertise relies heavily on operative experience and exposure. The concept of experiential learning suggests that to truly understand something a learner must experience it first-hand.[13] With a traditional time-based model of training, trainees would have had an estimated 25–30,000 hours of training before reaching consultant level, allowing deliberate practice so that replication of events leads to a full understanding and the development of subconscious pattern recognition. The current competency-based training is thought to only offer around 6000 hours.[14] To attain a level of expertise in a certain field subconscious pattern recognition is vital, and it has been suggested that at least 10,000 hours of training is necessary for this to occur.[15]

As such, a greater need has been identified in order to maximize learning, develop acquired competences, accelerate skills acquisition and reduce learning curves in order to meet the educational needs of surgical trainees within the confines of a 48-hour working week. Accordingly, higher surgical training curricula have also evolved to incorporate alternate educational modalities, such as simulation, in order to bridge this gap and compensate for the significant reduction in the time available for training (**Figure 35.1**). Simulation provides a realistic exposure equivalent environment that allows deliberate practice in order to achieve expertise in a non-threatening environment without risk to patients.[15] Behavioural models have shown high fidelity controlled environments akin to real life can show correct practice and through accumulative experience cement learning.[16] Objective assessment is also possible, enhancing the learning process by facilitating reflection and reinforcing positive behaviours and identifying negative actions.

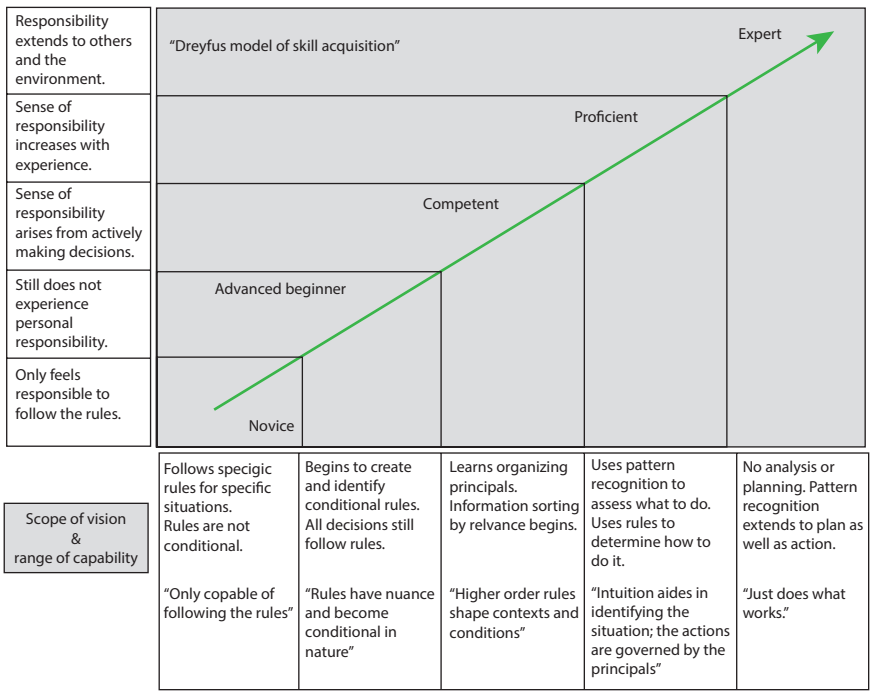


Figure 35.1 Dreyfus model of skills acquisitions. Learning through simulation hopes to alter the trajectory to quicken the learning curve passing from novice to attaining expertise.[17]

STRUCTURE OF UK POSTGRADUATE AND ENT SPECIALTY TRAINING

Trainees begin their postgraduate medical education by entering the foundation training programme, which was implemented in 2005 as part of MMC. This has replaced the traditional house officer and senior house officer grades, and allows junior doctors to rotate through core disciplines in order to develop the generic skill set required to practice safely in their onward specialties. Those wishing to pursue a career in surgery then apply to a generic 2-year Core Surgical Training (CST) programme, themed to their chosen surgical discipline (**Figure 35.2**). The CST programme is a broad-based initial training in surgery that enables trainees to establish the necessary competences, fundamental skills and breadth of experience required for progress on to higher specialty training (HST). Membership of the Royal College of Surgeons (MRCS) and Diploma in Otolaryngology – Head and Neck Surgery (DOHNS), or alternatively the MRCS (ENT) examinations are sat at this stage, and are, along with other defined mandatory criteria, an essential component of satisfactory completion of CST, before being eligible to apply to an HST programme. Recruitment to both CST and HST is through competitive national selection.

ORL HST is a 6-year programme that allows trainees to develop the necessary competencies in order to achieve a CCT. During this period a trainee can embark on additional out of programme activities (OOPA) in addition to conventional training, such as alternative training or experiences (OOPT/OOPE), research (OOPR) or fellowships. Towards the end of HST, the Fellowship of the Royal College of Surgeons (FRCS(ORL-HNS)) exit exam is sat.

Subspecialization in ENT surgery has been well established for many years and trainees are encouraged to show a special interest in a particular subspecialty during their training period. Fellowship programmes offer this additional training opportunity to pre- and post-CCT trainees and are available both in the UK and abroad. The JCST interface group, in conjunction with allied surgical specialties, offer interface fellowship programmes for UK trainees in ORL, plastics and maxillofacial surgery.[18] These fellowship programmes are accredited and have a structured, defined syllabus, and are monitored regularly for quality assurance. Alternative UK, European and international fellowships in other subspecialties also exist.

The Certificate of Eligibility for Specialist Registration (CESR) is a route to entry onto the specialist register for those doctors who have not entered through HST but are able to demonstrate experience, skills and knowledge equivalent to CCT. The application process is arbitrated by the GMC, and the JCST has issued specialty-specific guidelines for applicants applying through this process that outline the relevant supporting evidence, mapped to the four domains of *Good Medical Practice*, which are required.[18] Applications should also be supported by six consultant referees who are able to give a structured report regarding a candidate's clinical and non-clinical performance. The submitted documents are assessed against these requirements, as well as against the current ORL HST curriculum, by a GMC-approved assessor before CESR is awarded.

DELIVERY OF TRAINING

The aim of a competency-based surgical curriculum is to provide an assured, high quality of surgical training to ensure it produces proficient trainees able to deliver a high standard of surgical care, safely to patients. A competency model of training satisfies the need for an objective measurement of surgeon competence and performance. This delivers reassurances to the public that surgeons are being trained to an appropriate standard, whilst providing evidence to educational peers that trainees are demonstrating

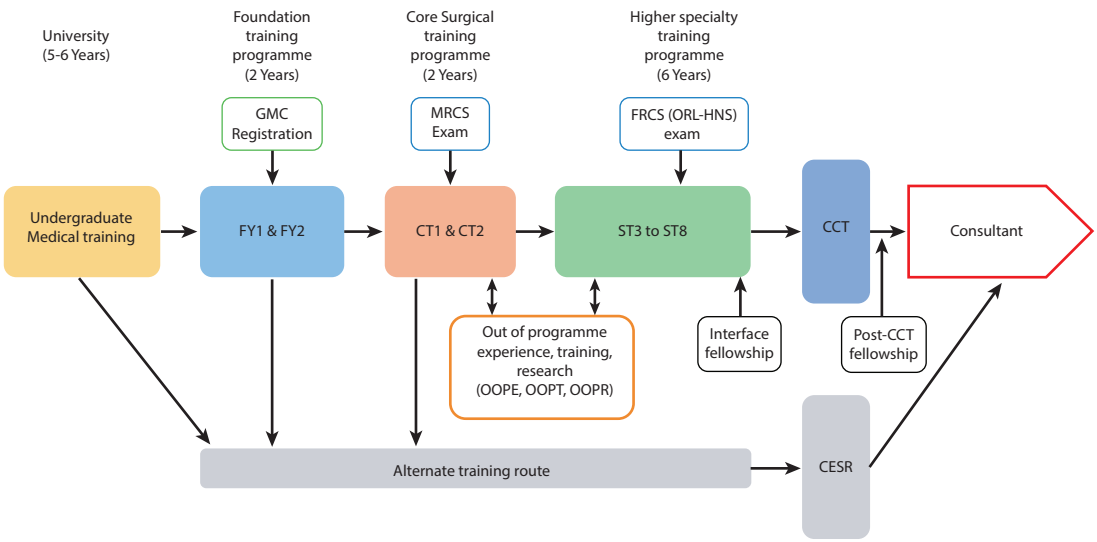


Figure 35.2 Current typical UK postgraduate training pathway for a career in ORL.

continuous development commensurate with their stage of training. The ISCP, a real time, online web portfolio (https://www.iscp.ac.uk), allowing an interface between trainer and trainee, has become a central component in supporting this process.[5] It has a clearly defined competency-based syllabus to which trainees are able to integrate their completed WPBA and additional educational achievements and map them to the curriculum as evidence of progress through training. Summative records of formal educational meetings and annual appraisal are also recorded to form a comprehensive record of training.

During their 6 years, ENT specialty trainees will expect to rotate to at least three different training units within their Deanery/LETB in order gain exposure to all the ENT subspecialties and to develop the required skill set and competences to satisfy curriculum standards. Rotation to a particular unit may be decided by trainee preference, individual educational requirements and stage of training. Each training placement is expected to be able to provide:

- at least three or more consultant supervised outpatient clinics per week, including a combination of routine, emergency and special interest clinics, limited to 10–14 new and follow-up patients
- four (or more) supervised operating sessions per week with a suitable elective and emergency case mix in a unit with a minimum output of 500 cases per year per trainee
- opportunities to manage patients presenting acutely at least once a week
- weekly formal local teaching, as well as regular regional teaching
- exposure to audit, research and other educational activities to develop teaching, management and leadership skills.

For each placement a trainee will have an AES with an overall educational and supervisory responsibility for the trainee, along with other departmental consultant trainers, or clinical supervisors (CS), who will also deliver teaching, train and have involvement in the assessment process. Traditionally, it may have been assumed that all consultants were good trainers. However, it is increasingly apparent that this is not true, and the skills required to teach, train and give feedback may not necessarily be inherent, but instead need to be learned and developed. The key to an effectively deployed competency-based curriculum are suitably qualified trainers able to reliably assess and give constructive feedback. As such, there is an increasing expectation that consultant trainers, and even trainees during their higher specialty training, undergo formal training or gain a higher qualification in teaching principles and methodology before they assume a formal role as a trainer.

Although consultant trainers do have a facilitatory role, the responsibility of training remains primarily with the trainee. At the start of each placement a 'learning agreement' (LA) is set by the trainee with their AES, agreeing on the educational objectives for the forthcoming placement. This is recorded on the ISCP and is revisited with the trainee during interval formative and summative appraisals typically in the middle and at the end of the placement. Throughout the placement trainees are expected to complete a set number and a variety of WBAs assessing knowledge, clinical judgement, procedural and technical competences, as well as professional behaviour and attitudes such as communication, team working and management skills. These include:

- case-based discussion (CBD)
- clinical evaluation exercises (CEX)
- direct observation of procedural skills (DOPS)
- procedure-based assessment (PBA)
- multi-source feedback (MSF).

Assessment is made to determine whether a trainee is meeting curriculum standards of competence and performance expected for their stage of training. Each completed WPBA can be linked to the ISCP syllabus as evidence and can be used to demonstrate evolving progression up to demonstrating fully competent, independent practice as a trainee progresses through specialty training. As training is no longer time-defined, assimilating acquired competences may vary according to trainee exposure and ability. In addition, WPBAs can also effectively be used as a formative tool at the time of completion. The process of reflection and feedback helps consolidate the learning process by reinforcing positive practice, but also enables the trainee to identify specific learning points for onward development. Learning through objective feedback is an essential component of enhancing the educational process by directing learning towards desired outcomes. WPBAs can, however, be incorrectly used and seen as a time-consuming 'tick-box' exercise, which can have a negative impact on the reliability and validity of the assessment. In order for these assessments to retain their educational value, they must be used correctly, as a continuous, formative tool to provide constructive feedback to trainees.

Collectively, WPBAs, in addition to the end of placement AES and CS reports, and additional recorded evidence of educational activity (including involvement in audit, research, publications, attendance at courses and conferences), are evaluated in an annual review of competence progression (ARCP). This summative face-to-face appraisal is to assess whether a trainee is developing satisfactorily and has achieved the necessary competencies in order to progress to the next stage of training. Equally, if a trainee is underperforming, this can be identified and additional support given to meet their specific educational needs.

Towards the end of specialty training, and provided a trainee is meeting their educational requirements of training, they are able to sit the FRCS(ORL-HNS) exit exam. This traditional summative assessment complements competency-based training positively by formally assessing what has been learnt throughout specialty training. In order for recommendation to be made to the GMC for an award of the CCT, a trainee should have gained all required curricula competencies, passed the FRCS(ORL-HNS), and

completed a pre-defined number of 'index' operative procedures (elective and emergency) to a specified level of competence, in addition to the total number of defined major operations required to be completed in the generality of ORL so as to cover the fundamental subspecialties (head and neck, rhinology, otology and paediatric ORL).

MAINTENANCE OF SKILLS

Continuing professional development (CPD) is the engagement in lifelong self-directed learning outside formal postgraduate training. It is the duty of all doctors to keep up to date, and maintain and improve their knowledge and skills in order to provide a high standard of care to patients and the public throughout their career. The obligations of doctors are specified in *Good Medical Practice* and *Good Surgical Practice*.[6, 19] The key points addressed are:

1. The essence of CPD is to be competent and up to date across all clinical and non-clinical aspects of the practice.
2. CPD should be a combination of formal and informal teaching and should include the activities within the local institution as well as at regional, national and international levels. Surgeons should aim for a mix of at least three activities including clinical, academic and professional (including managerial).
3. The minimum requirement for CPD in the UK is 50 credits per annum. One credit represents one hour of activity. To encourage a range of activities, normally no more than 20 of the minimum 50 hours per year should come from a single activity.[20]
4. Surgeons are encouraged to record the activities electronically, such as in the 'surgeons portfolio' developed by the Royal College of Surgeons (RCS), which helps to record the activities securely and assists surgeons with the appraisal and revalidation process (**Table 35.1**).[20]
5. There is a range of organizations that accredit the CPD activities including the medical royal colleges, specialty associations and LETBs. The RCS has established criteria and standards for accreditation of CPD activities.[21] ENT-UK accredits educational activities relevant to the specialty. The organization seeking accreditation must demonstrate compliance to the academic and competence standards:
   - CPD is awarded on the basis of course content and delegates' feedback.
   - The activity should have clear scientific and educational purpose and should address the learning needs of the participants.
   - The course organizers and faculties should have a proven relevant expertise, and appropriate skills and knowledge.
   - Robust quality assurance is required with course inspection and evaluation.
   - Attendance records should be maintained.
   - Feedback forms should be submitted for further accreditations of the event.

APPRAISAL AND REVALIDATION FOR SURGEONS: SPECIALTY-SPECIFIC GUIDELINES

Appraisal and revalidation is based on the principles of *Good Medical Practice*. Doctors practising in the UK must participate in an annual appraisal process to reflect on their practice and performance based on which the responsible officer (RO) makes recommendation to the GMC to renew their licence to practice every 5 years. The GMC and RCS have provided a number of documents to describe the supporting information required for appraisal and revalidation.[23] The surgeons are expected to collect and maintain a portfolio of supporting information to demonstrate that they are continuing to meet the principles and values set out in *Good Medical Practice*, which consists of four domains as follows:[6]

1. Knowledge, skills and performance
2. Safety and quality
3. Communication, partnership and teamwork
4. Maintaining trust.

Checklists are available to guide the surgeon through the suggested components of the revalidation process (**Table 35.2**).

Individual surgeon and departmental outcome measures are playing an increasing role in the surgical appraisal

TABLE 35.1 Examples of activities that will qualify for CPD[18]

	Internal	External	Personal
Clinical	Courses, workshops and meetings	Courses, workshops and meetings	Self directed learning, e.g. reading journals
Academic	Audit, research	Participating in national audits, research trials and presentations	Publications and peer-reviewing articles
Professional	Teaching, training and mentoring activities	Examiner, e.g. undergraduates, MRCS, FRCS Standard setting for exams	Courses on management, leadership and teaching/training

Note: The list in this table is not exhaustive and individuals should discuss with their appraiser to plan the activities that will address individual educational needs.

TABLE 35.2 Supporting information for revalidation checklist based on the Academy of Medical Royal Colleges and Faculties' Core Guidance[22]

General information	Personal information Scope of work Record of annual appraisal Personal development plan (PDP) Probity Health	Current job plan Description of clinical and non-clinical activities Appraisal portfolio Agreed objectives from previous PDP Self declaration of Probity and health
Keeping up to date	CPD	Evidence of CPD activities
Review of current practice	Clinical audit Review of clinical outcome Case review or discussion Clinical incidents	Details of participation in local/national audits Details of outcome data Participation mortality and morbidity meeting Records of clinical incidents and reflection
Feedback on your practice	Patients' feedback Colleagues' feedback Complaints and compliments	Multisource feedback from colleagues and patients Details of complaints and compliments

and revalidation process. This supports best practice and ultimately improves patient care. ENT-UK supports the participation in national clinical audit and, for example, has previously jointly collaborated with RCS of England to conduct and publish outcomes of the national prospective tonsillectomy audit. Currently ENT-UK is managing surgeon activity data for laryngeal surgery and airway intervention registry for paediatric balloon dilatation procedures for airway stenosis. It is important to also mention that some recorded individual surgeon's outcome data can be published and subsequently accessed by the public, a development aiming for greater transparency and accountability. For example, members of the British Association of Endocrine and Thyroid Surgeons (BAETS) are required to participate in the UK Registry of Endocrine and Thyroid Surgery (UKRETS), which is an electronic audit of endocrine operations. All thyroid surgeries must be recorded in UKRETS, which is the published openly via the surgeon specific outcomes report for endocrine surgery.

FUTURE OF TRAINING IN ENT

The specialty of ORL has evolved significantly over the last four decades with expanding subspecialization, introduction of new technologies and as a result of the development of new surgical techniques. Furthermore, the move in the UK to the provision of full '7-day working' and an anticipated shift of the provision of ORL services to both community outpatient-based and super-specialized tertiary centres will have a dramatic impact on the provision of training and the expectations of the ENT surgeon. This will inevitably need to be matched by constant review and subsequent modifications of learning curricula in future ORL surgical training. The challenge is to address new advancements and potential changes in training within a safe timeframe in order to continue to create a surgical workforce that is able to deliver competent, safe and high quality patient care.

KEY POINTS

- The objective of the curriculum for higher surgical training in ENT is to train a surgeon who is emergency safe and competent to practice independently in the healthcare system.
- In the UK, the General Medical Council (GMC) supervises the standards of the curriculum developed by the Royal colleges, faculties, and specialty associations.
- The syllabus is written in sections where the knowledge, clinical and technical skills required are defined against the level of competence necessary. The trainees are expected to achieve those set competencies in order to progress in their training to obtain completion of certification of training.
- In the UK, post-graduation training begins with two years of foundation training and a further two years core surgical training in a chosen specialty to gain broad-based initial training prior to progressing on to higher surgical training which is six years for ENT.
- Throughout the placement, trainees are expected to complete a set number of work-based assessments to assess the knowledge, clinical and procedural skills, professional behavior and attitudes. To gain CCT, trainees are expected to achieve all competencies outlined in the curriculum, completion of FRCS (ORL-HNS) and performance of a defined number of 'Index' procedures.
- Doctors practising in the UK must participate in an annual appraisal process and revalidation once in every five years to renew their license to practice by the GMC. The above process is to ensure doctors are up to date, maintain their skills and knowledge to provide a high standard of care to the patients.
- ENT specialty is evolving rapidly with expanding subspecialization and introduction of new diagnostic and surgical techniques. There is a need for constant review and modification in the surgical curriculum and training in future to match the changes.

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CHAPTER
36

COMMUNICATION AND THE MEDICAL CONSULTATION

Uttam Shiralkar

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SEARCH STRATEGY

Data in this chapter may be updated by Medline, Embase and PsychINFO searches using the keywords: communication skills, doctor-patient communication, communication skills and surgeons, training communication for health professionals, communication and clinical outcome.

INTRODUCTION

How important is it for a surgeon to have good communication skills? Not many people would think this to be of 'life-and-death' importance. Unfortunately, this was exactly the case for one plastic surgeon in Madrid, who was killed by one of his dissatisfied patients. That was not a unique incident. Between 1995 and 2005, five surgeons were killed by disgruntled patients in the USA.[1] Although these extreme acts of violence are rare, many surgeons face abuse, complaints or legal actions due to communication problems between them and patients. Every day of our working lives we rely upon communication skills to build up relationships with our patients. These skills are vital in establishing trust with those who come to us with problems. This chapter explores the communication issues related to outpatient visits. Since practical communication training is available in various formats such as written material, workshops, videos and online training, this chapter will focus on the fundamentals to deliver a broader perspective.

As a doctor, consultation is the most common clinical procedure we employ. Our communication with a patient has a therapeutic effect. Compared to other therapeutic modalities, communication has an immediate palliative effect as it can reduce a patient's distress instantly. Comparatively, it has a wider therapeutic index since this treatment-related morbidity and mortality has never occurred! The most common problem observed regarding its use is suboptimal dosing.[2] Good communication is not just 'being nice' or having a 'touchy-feely' talk. It is a specific task and observable behaviour that includes interviewing a patient to obtain clinical information, explaining diagnosis or prognosis, and giving treatment advice and information needed for an informed consent to undergo procedures. It also involves providing counselling to patients to motivate participation in the management.[3] Conventionally our management tends to focus only on bio-medical aspects of the treatment since we adopt a 'disease perspective'.[4] Lately there has been a realization of the limitation of a narrow 'disease perspective' and the need to treat the patient from an 'illness perspective'. When doctors interact with the patient through the 'illness perspective' the impact of a disease on the patient from a personal aspect is taken into account so that the care becomes 'patient-centred'. Patient-centred care entails involving the patient in decision-making and activating their sense of responsibility.[5] Without appropriate communication skills the surgeon will not be able to deliver patient-centred care.

WHY COMMUNICATION SKILLS ARE IMPORTANT FOR DOCTORS

There are various advantages of taking the skill of communication seriously:

- A skilful interview improves diagnostic accuracy by gathering a superior quantity and quality of information.[6]
- Doctors with excellent communication skills establish good understanding with their patients and consequentially improve the patients' compliance and outcomes.[7]
- In contrast, poor communication seems to be correlated with patient dissatisfaction.[8] Studies have shown that communication skills are the single most important factor in patients' satisfaction. Practising surgeons will be interested to know that a satisfied patient will tell, on average, three other patients about their positive experience. On the other hand, patients who are dissatisfied with their encounter will tell, on average, 19 other individuals about their unpleasant experience.[9]

WHY COMMUNICATION SKILLS ARE IMPORTANT FOR SURGEONS

Communication between surgeons and their patients is particularly important. A randomized trial specific to surgical communication showed that patients undergoing surgery had better pain scores and lower analgesic use postoperatively when the pre-operative communication with the patient was appropriately conducted.[7] Patients visiting surgeons, in comparison to visiting other specialists, may be more anxious due to the concerns of undergoing invasive procedures. Surgeons need to conduct conversations about complicated medical issues, treatment choices and complexities of surgical options, and they have to address patients' anxieties.[10]

A study that analysed surgeons' communication behaviours identified that failure to adequately explain the medical condition, failure to show interest in the patient, failure to ask whether they had any questions and failure to answer their questions were the main factors for patients not recommending the surgeon.[11] There is evidence showing that very few patients or their families are able to absorb what the surgeon has explained to them before surgery. Six months after surgery, patients may be unable to recall what kind of information the surgeon gave to them during the informed consent process. Additionally, some patients may even deny that this process occurred despite the existence of objective evidence.[12]

A stereotypical image of a surgeon is someone who is not a very good communicator.[13] Studies have found disparities between surgeons' self-assessments and patient's perceptions about the surgeons' communication skills.[14] There is a need to acknowledge these gaps and to make efforts to reduce them. It has been observed that when surgeons improve their communication skills, it is not just patients but the surgeons themselves who are beneficiaries. Good communication makes working in a specialty more enjoyable and acts as a preventative factor to burnout.[15, 16] After an untoward incidence in surgical practice, the possibility of the matter ending up in court is greater if the communication with the patient is not handled satisfactorily. Sometimes malpractice suits are the results of differences in expectations between a patient and the surgeon. Good communication helps the surgeon to understand patient expectations, thereby reducing liability exposure.[17]

WHY COMMUNICATION SKILLS ARE IMPORTANT FOR ENT SURGEONS

For ENT surgeons there is a need to take a particular interest in communication for various reasons. Otorhinolaryngology is a unique surgical specialty dealing with clinical problems that have a wide range of psychological implications for the patient. Otolaryngologists perform procedures like rhinoplasty purely for cosmetic improvement but also head and neck cancer surgery to improving a patient's survival. We perform emergency procedures, such as the removal of a foreign body, that give immediate relief, and we perform surgical interventions in rhinosinusitis where the patient may continue to experience some symptoms despite surgery. Some patients with sensorineural deafness may not be offered a cure but with a successful stapedectomy, hearing improvement is instant. Thus we need to prepare the patient, as well as ourselves, for the anticipated outcome, whatever that may be.

Patients visiting otolaryngologists experience symptoms that have an emotional contribution. Significant percentages of patients who experience symptoms such as dysphonia, vertigo or facial pain have underlying psychological problems.[18] Unless these psychological factors are addressed, symptom resolution will not be achieved. Chronic pain anywhere in the body invokes emotional reactions and pain in the facial region carries far more emotional reaction. An otolaryngologist with good communication skills will be able to pick up psychological cues, thereby avoiding delay in symptomatic relief.

Otolaryngologists come across patients (e.g. those with allergic rhinosinusitis) for whom curative surgery is not possible or for whom surgery will offer only partial relief. Appropriate consultation will help the patient to accept the best possible treatment. In some cases, like inoperable malignancy, the surgeon will be not be able to offer the patient anything apart from empathetic conversation, the efficacy of which is directly proportional to the surgeon's communication skills.

Otolaryngologists deal with patients who have difficulties with important sensory organs (i.e. hearing). There is a special responsibility to be sensitive to the sensory loss and at the same time not to underestimate the patient's ability to adapt.[19] This can be understood only with the help of efficient communication.

In the era of technological development and implementation of new techniques, adequate communication between otolaryngologist and patient is very important. This is especially relevant if the procedure is not very well established. In the event of a complication after the use of an uncommon or novel technique, the surgeon may be accused of not adequately explaining the consequences.[20]

LITERATURE

Despite the importance of effective communication to surgeons, the vast majority of literature in the field of medical communication has focused on primary care interactions. There have been relatively few studies describing communication between surgeons and patients.[21] The first ever study on communication between surgeon and patient was published in 1999.[4] This study underscored the differences in both the content and process of routine surgical visits compared with primary care visits. The study concluded that unlike other medical specialties, surgical consultations had a narrow biomedical focus with little consideration of the psychosocial problems the patient might experience due to the disease.

A systematic review on directly observed surgeon–patient communication was recently published.[22] The reviewers evaluated 2794 citations, 74 full-text articles, 21 studies and 13 companion reports. This systematic review highlighted the gaps that need to be addressed by training both trainee and practicing surgeons. The studies confirmed that surgeons spend the majority of consultation time in educating patients and discussing treatment options.[4, 23] Thus, surgeons use the communication mostly for the purpose of informed decision-making. Studies found that surgeons are good in providing information about the surgical conditions.[10, 24] However, they are lacking in areas such as assessing patients' understanding of therapeutic options and discussing risks. Since these elements are important for patients to make good informed choices, there is a need to improve the quality of informed decision-making conversations in surgery. It is also felt that surgeons need to focus greater attention on the emotional aspects of consultation.

LEARNING COMMUNICATION SKILLS

Although the clinical value of these skills has been known for the last few years, it has traditionally been difficult for many to accept the idea that something as supposedly intuitive as communication could or should be influenced by teaching. It was a commonly held belief that communication skills could not be taught; they were natural talents – inborn attributes of the 'good doctor' – and a young doctor was either endowed with them or not. It was debated whether these techniques could be learned, and whether anything could be done to bring the awkward communicator to a reasonable level. Mounting evidence has clearly shown that these goals are achievable and that these skills can be taught, do change patient satisfaction and can be retained over time.[25]

Surgeons receive limited formal education in the communication skills necessary for patient-centred care, although they perform more than 100 000 consultations during their careers.[26] In one study researchers developed an innovative empathy-relational skills training protocol focusing on the underlying neurobiological mechanisms of empathy and the interpersonal processes that positively affect the patient–doctor relationship. The authors tested the effectiveness of this protocol with ENT trainees. The results showed that a brief series of three empathy-training sessions significantly improved the surgeon's knowledge of the neurobiology and physiology of empathy, as well as their self-reported capacity to empathize with patients. As a result of improved empathetic consultation, improvement in patient satisfaction was observed.

From a practical perspective, improving communication skills is similar to improving operating skills. It involves seeking information, implementing the techniques and evaluating the outcome. The efforts that are put into improving clinical communication do make an indelible impression on patients. If done poorly, the patient may never forgive the surgeon; if done well, they may never forget the surgeon![27]

COMMUNICATION MODELS

There have been various attempts to describe the overall structure of a doctor–patient relationship and to create a standard model of conversation between the two that aims to facilitate training and the learning of communication skills.[27] The Calgary-Cambridge model is one model that describes a sequence of tasks to aid an effective consultation.[28]

There is no single way that a consultation plays out. Every interaction is unique, as it depends on how the surgeon and the patient contribute and react to the interactions. However, if a surgeon is aware of the basic tenets of an ideal consultation, it will provide a useful framework to build upon (**Figure 36.1**).

Engagement

Engaging the patient requires making a personal connection with him/her. This can be achieved by appropriate body language and introductory conversation. Initial questions like 'How can I help you?' will initiate the engagement. It is strongly recommended that you listen to the response to this question patiently. Patients usually disclose most of the useful information within the first two minutes; however, it is observed that a surgeon often interrupts a patient in less than half a minute and starts asking specific or closed questions.[6] Closed questions at this stage of the conversation are unlikely to reveal what is of greatest concern to the patient. Instead of closed questions, comments like 'tell me more about that' or 'what concerns do you have about that' will allow the patient to give their own view and initiate the engagement.

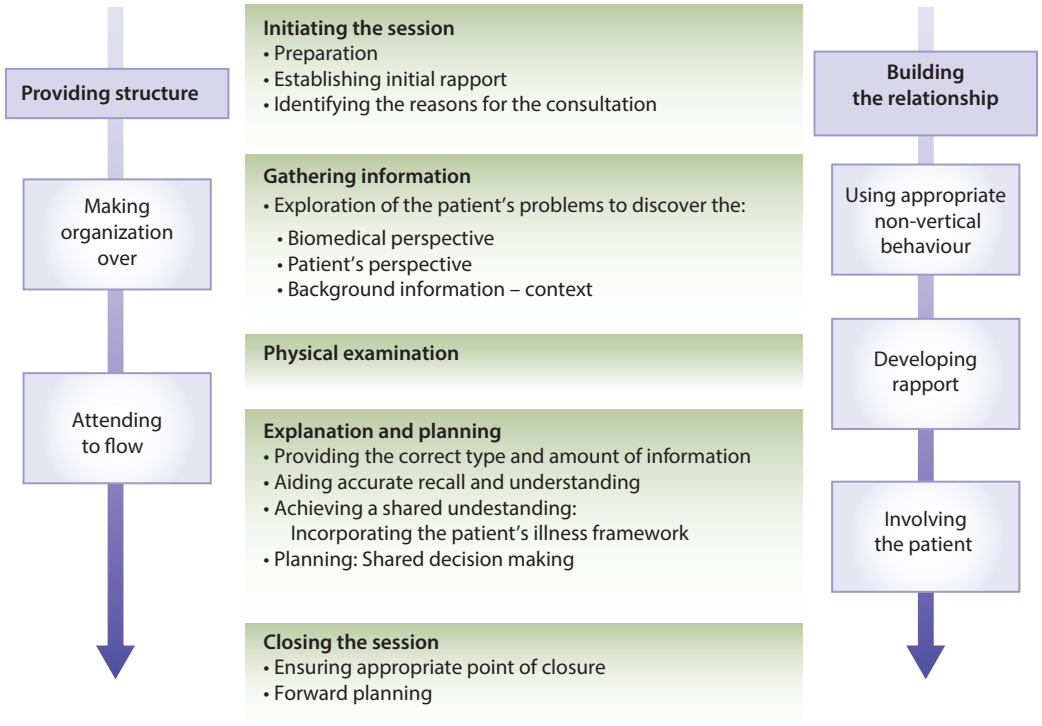


Figure 36.1 Expanded framework.

BOX 36.1 The 5 Es of communication

A review by Tongue et al. offered a framework and practical tips on conducting an interview.[29] It describes the 4 Es of communication:

1. **E**ngagement
2. **E**mpathy
3. **E**ducation
4. **E**nlistment
5. **E**nding

These 4 Es supplement the 3 Fs of clinical surgical practice:

1. **F**ind the problem (diagnosis)
2. **F**ix the problem (treatment)
3. **F**urnish the service (delivery)

Adapted from Refs 29 and 30. (Figure 36.2).

Empathy

'The patient will never care how much you know until they know how much you care.'[31]

Unfortunately, the most common weakness in communication with patients is a failure to demonstrate an empathic response. Studies show that surgeons often miss opportunities to express empathy.[32] The potential effect of this is that patients may feel that their surgeons have not addressed their concerns. The gaps between the patient's expectations and the surgeon's approach leads to patient dissatisfaction.[33, 34]

Empathetic conversation reveals the surgeon's understanding of and concern about the patient's thoughts. It involves acknowledging the emotional content of the communication, without necessarily sharing the emotion itself. It is necessary to clarify the difference between

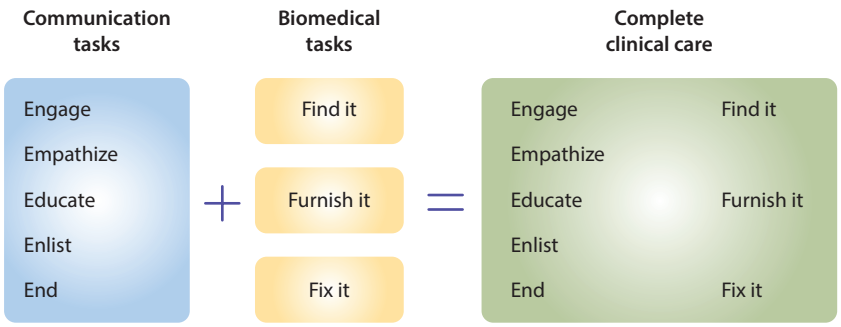


Figure 36.2 The five Es and three Fs of communication. From Tongue JR, Epps HR, Forese L. Communication skills for patient-centered care: Research-based, easily learned techniques for medical interviews that benefit orthopaedic surgeons and their patients. *J Bone Joint Surg* 2005; **87**(3): 652–58.

empathy and sympathy. Sharing the emotion fully would be sympathy and, although we may be sympathetic with some emotions, we generally do not share the emotions of most of our patients. It is not expected – in fact, it may be unhelpful for a surgeon to experience what the patient is feeling. As the saying goes, you don't need to have pain in your own right iliac fossa in order to diagnose a patient's appendicitis.

However, good communicators are expected to reflect a patient's emotion in the conversation, for example: 'It must be frightening to lose your hearing suddenly. Many people would feel that way.'

The process of acknowledging emotions is not too complex. The empathic response consists of three steps:

1. Identifying the emotion
2. Identifying the source of the emotion
3. Responding in a way that shows you have made the connection between the first two steps.

Surgeons may run short of time during consultations; hence they may be reluctant to address emotional issues, thinking that it may lengthen the consultation. However, several studies have uncovered a positive relationship between addressing the emotions and the length of the visit. Levinson et al. found that visits in which the surgeon directly addressed a patient's clue about a concern or worries were shorter than visits in which the clue was ignored.[35] This observation could be explained as the patients whose worry was addressed were able to put the concern to rest more quickly than those whose concern was unaddressed. Similarly, Braddock et al. found that visits with more complete, informed, decision-making conversations were only modestly longer than those that were less complete.[36]

Education

Educating the patient involves providing the diagnosis, the prognosis and the options for treatment in a language that the patient understands. It is necessary to be aware that the amount of information the patient requires will vary. It may be helpful to ask, 'Does that match what you have been thinking about this problem?' That will allow the patient to bring up other outstanding issues. In the later part of the consultation it is a good idea to check that important details have been understood. Providing supplementary written material – especially about important pre-operative or post-operative instructions – should be considered.

Enlistment

Enlisting or enrolling extends an offer to the patient to actively participate in decision-making. Enlistment acknowledges that the patient controls much of what can happen in his or her healthcare treatment plan.[37] Different surgeons and patients will vary in their preferences about the degree of patient involvement. Orienting patients to the process of care and discussing risks frankly but positively will help to empower patients facing surgery.

Ending

The last E that needs to be considered is Ending the consultation on a positive note, with an expectation of a satisfactory outcome, phrased accordingly. Closing in a manner that gives patients hope is an effective strategy. It is worth reiterating that after leaving the consulting room, patients normally forget a significant part of what has been said during the consultation. Written material can supplement, but not replace, effective communication.

NON-VERBAL COMMUNICATION

Patients are particularly sensitive to non-verbal cues from their doctors, although many doctors are unaware of their influence in this respect. It is said that in a consultation less than 35% of contact is established through verbal means, while 65% is conveyed through non-verbal cues including facial expression and eye contact.[38] It is important to recognize the importance of subtle behavioural cues that are highly influential in determining the direction of consultation and the subsequent outcome.

Some consideration of how some non-verbal factors are effective through the clinic set-up arrangements is necessary. These factors include the layout of furniture, the relative positions of doctor and patient and the distance between them. A relaxed interaction is likely when both chairs are positioned at the same height to ensure good eye contact. The ideal positioning between a surgeon and the patient is approximately 2–4 ft (0.6–1.2 m). It is advisable for the surgeon not to stand while the patient is seated during the medical interview.

A desk represents a potential barrier between the doctor and patient and may be an important factor limiting the free flow of conversation. In one interesting experiment, the influence of the desk was analysed during consultations between a cardiologist and his patient. On alternate days the cardiologist removed the desk from his consulting room to assess the impact upon non-verbal cues and body language. When the desk was absent, more than half of all patients sat back and relaxed, but when the doctor was positioned behind the desk fewer than 1 in 10 assumed a relaxed body posture and this corresponded with a drop in the level of meaningful interaction between the two.[38]

Knapp looked into the importance of seating arrangement. He identified four sitting positions for any interaction: the corner position, the cooperative position and the competitive-defensive position (**Figure 36.3**). In the corner position, the individuals are positioned in such a way that the corner of the desk intervenes. It usually results in casual friendly conversation. It allows unlimited eye contact and a full appreciation of gesture. The corner of the desk behaves as a partial barrier but does not intrude as a territorial division.[39]

The cooperative position differs from the corner position in the absence of any barrier and a straight face-to-face sitting posture. While this favours a mutualistic

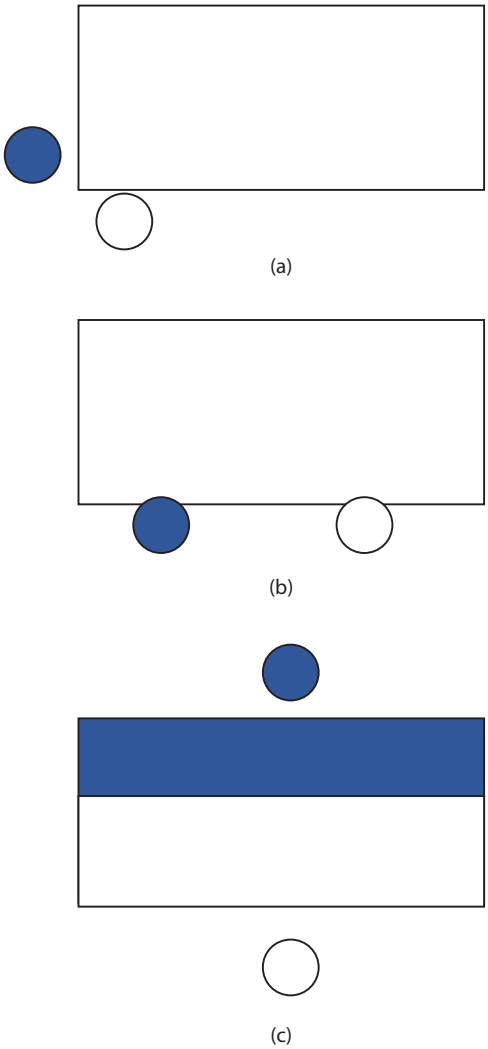


Figure 36.3 Examples of seat and desk arrangements. (a) The corner position; **(b)** The cooperative position; **(c)** The competitive-defensive position (the territorial line); Redrawn from Ref. 39, with permission.

relationship, a number of individuals feel threatened by the lack of a firm boundary. In the competitive-defensive position, the desk constitutes a firm physical barrier. Not only does this prevent intimacy, but it may also create competition for control of the consultation.

BOX 36.2 Optimizing communication

Behaviours in Western culture that can communicate to the patient that the surgeon is making an effort to optimize the personal aspect of the communication experience include:[40]

- shaking hands
- maintaining eye contact
- welcoming the patient
- thanking the patient for coming
- apologizing for being late
- appearing relaxed
- appearing genuinely interested
- acknowledging emotions
- not writing and listening at the same time.

COMMUNICATING ADVERSE INCIDENTS

Bad news is a routine part of many surgical practices. A good surgeon will offer the appropriate words and actions in the setting of a dangerous operation or devastating diagnosis. Patients need to be able to absorb bad news, and they need to be able to prepare for the worst while hoping for a cure. This requires careful, balanced communication. Learning the skills to break bad news can prevent interactions in which it is delivered insensitively or too bluntly. Such 'hit and run' delivery of bad news may result from a surgeon's own emotional discomfort.

Sharing bad news with patients is difficult to do well. A number of simple techniques may help you to undertake this more sensitively. Some techniques may appear obvious, like planning the consultation in advance, checking the facts and avoiding interruptions to ensure privacy. Breaking bad news can take a significant amount of time and it is important to avoid being rushed. The use of simple straightforward language and avoiding jargon is helpful. Many patients value an invitation to bring a relative or close friend for support, and it is necessary to establish the nature of their relationship in order to understand how the news will impact upon them also.

As mentioned earlier, non-verbal messages are as important as verbal ones. Patients need to be given sufficient time for silence, tears or anger. Even when the future looks bleak, we need to be careful in using the phrase 'nothing can be done'. There are always ways of encouraging hope in any dire situation. However, it is equally important to admit when we do not know the answers to difficult questions, such as life expectancy after a diagnosis of terminal disease. Most patients value the offer of ongoing support, and follow-up is especially valuable.

BOX 36.3 SPIKES

Oncologist Robert Buckman has suggested a framework called SPIKES when breaking bad news, standing for setup, perception, invitation, knowledge, emotions, summarize and strategy.[41]

- **S**etup refers to finding an appropriate time and place for a discussion, somewhere quiet, private, seated, at eye level and free of distractions.
- **P**erception indicates the technique of asking the patient what he/she knows about the situation. This is a good starting point for the discussion as they may already know the bad news or have guessed it. However, they still want further clarification.
- **I**nvitation means asking the patient what else they would like to know or whether they would like to know more.
- **K**nowledge implies offering information. Many patients want to know all that the doctor knows or understands.
- **E**motions are commonly expressed when facing loss of health or loss of life. These emotions should be acknowledged and empathized with. Sometimes silence on behalf of the surgeon may constitute effective communication. 'I wish' statements can be used to convey empathy.
- **S**ummarize and strategy.

ADDRESSING ISSUES AROUND LOSS

Patients may experience concern about potential disfigurement and loss of function as a result of surgery. The surgeon has a duty to address these issues in appropriate depth. Within otolaryngology, patients undergo loss of speech, swallowing, balance or hearing. Perhaps not surprisingly, those who cope less well with the loss of body function are those with a history of pre-morbid anxiety or depression, and these are factors that are easy to overlook in a busy consultation. Consequently, a professional assessment of mental health may be useful part of preoperative planning for some patients prior to surgery.[42]

The effect of hearing loss depends greatly on the age of onset and the extent of any residual function. The distinction between truly deaf individuals and those who become deafened later in life is important. Properly nurtured, the congenitally deaf individual is able to develop normal communication skills within the deaf community without any requirement for the spoken word. However, the individual who encounters hearing loss after normal development suffers an immeasurable handicap without augmentation or alternative aids.

For patients with acquired hearing loss there are a number of simple methods for improving communication within the consultation. Slow, deliberate speech of adequate volume in a room with low ambient noise will assist those with a modest hearing loss. A face-to-face position and clear enunciation of words enables lip-reading in those with long-standing loss. Other simple measures include diagrams and picture boards.

DISCUSSING MEDICAL ERRORS

Surgical error seems pervasive today, mostly because it is increasingly sought and increasingly recognized. Surgeons face a difficult dilemma when deciding whether and how to disclose a harmful error to a patient. When a patient has had an adverse outcome and if the surgeon's reaction is defensive, it results in the patient not being fully informed. However, it is recommended to follow appropriate disclosure. A study found that patients who had received full disclosure after an error were less likely to change doctor and had greater satisfaction[43] than patients who did not receive full disclosure. In some cases, disclosure decreased the risk of legal action, although a positive response was not guaranteed since it was dependent on the clinical outcome and the details and severity of the error.[44] In another study, investigators assessed the attitudes of 149 randomly chosen adults about medical errors. Patients were more likely to commence litigation following moderate and severe errors if there had been no disclosure.[45]

A study, the first to assess how surgeons currently disclose errors, revealed that surgeons vary widely in their approach and in many cases, surgeons fail to use recommended error disclosure skills.[46] After a harmful error patients expect reliable information: an explicit statement that an error occurred, what the error was, why the error happened, how the error will impact their health and an apology. They want someone to take responsibility. Many surgeons struggle with these aspects. A surgeon's reluctance to state explicitly that an error has occurred might in part reflect the advice they receive that the disclosure of an error should not include any statements that could constitute an admission of liability. However, a surgeon's failure to communicate clearly about errors can make patients feel angry and misled, feelings that frequently contribute to the decision to file a malpractice claim.[47, 48]

While communicating errors, direct, clear statements are important, as are their delivery, particularly the tone of voice. One interesting study analysed the quality of surgeons' speech and malpractice history.[49] They observed that surgeons who were judged to be more dominant in their tone were more likely to have been sued than those who sounded less dominant. These findings indicate that even brief exposure to a surgeon's speech may be perceived by patients as expressing dominance and lacking concern. Dominance in the voice may imply a surgeon's indifference and lead a patient to launch a malpractice suit when poor outcomes occur.

Empathetic communication is especially important when discussing difficult issues like error. However, some aspects of errors, such as a surgeon's discomfiture about an error or concerns about liability, may make it difficult for them to discuss empathetically. Validating patients' views may also conflict with the surgeon's desire to persuade the patient that the error was not as serious as it may appear to them. However, failing to communicate empathetically with patients may give an impression that the surgeon is not concerned about what happened.[50, 51]

There are some techniques that are useful in communicating adverse error events. The conversation may start with, 'I am afraid I have some bad news'. It is advised to communicate in a manner that is open as well as acknowledging emotional responses. Complex reactions of fear, anger and mistrust can be expected. An apology without assigning blame is acceptable and does not denote an admission of liability. Statements like 'I am sorry this has happened to you' will go some way in that regard. Many patients also want to know that steps are being taken to continue their care or rectify the error, and that steps are being taken to minimize a similar error happening in future. Thus, at the end of the discussion it will be effective if the patient is given an explicit plan of the support to be provided.

Communication is of significant importance with a somatizing patient. These are patients for whom no organic cause for their symptoms can be found and they fail to respond to the standard treatment. In interacting with these patients, surgeons experience a sense of frustration or irritation; some identify them as 'heart-sink' patients. These patients need to be managed by improved communication strategies including the identification of underlying situations that cause the stress that is responsible for the lack of therapeutic response. A number of special skills exist to combat the heart-sink encounter including a 'holding strategy' for listening and understanding the patient's problem without feeling the need to tackle all issues in that consultation.

BOX 36.4 Compliance

Research has shown that compliance depends on three factors:

1. Good understanding of advice
2. High level of satisfaction
3. An ability to recall information given by the doctor.

Evidence suggests that following the end of the consultation the patient retains surprisingly little factual information. For example, in one study over a third of patients failed to recall the name of their prescription medicine and a quarter failed to appreciate the duration of the course of their medication. Simple and effective techniques for increasing compliance include provision of written information, keeping explanations simple and repeating important points.[52]

CONCLUSION

As clinicians, consultation is the most common clinical procedure we employ. Our communication with patients has a therapeutic effect, and can be positive as well as negative. A stereotypical image of a surgeon is someone who is not a very good communicator. It has been observed that when surgeons improve their communication skills, it is not just patients but surgeons themselves who are beneficiaries. Mounting evidence has shown that improvement in communication skills is achievable and that these skills can be taught, do change patient satisfaction, and can be retained over time. Improving communication skills is similar to improving operating skills. It involves seeking information, implementing the techniques and evaluating the outcome.

KEY POINTS

- Communication is the most commonly used therapeutic tool in ENT practice.
- The surgeon needs to be mindful of verbal as well as nonverbal communication.
- Like operative skill, good communication is a skill that needs to be developed. It involves seeking information, applying appropriate techniques and monitoring outcome.
- There are various models of doctor-patient communication. One needs to choose appropriate model according to the situation and personalities.
- Special consideration is advisable in communicating undesired.

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CHAPTER 37

CLINICAL GOVERNANCE AND ITS ROLE IN PATIENT SAFETY AND QUALITY IMPROVEMENT

Samit Majumdar and S. Musheer Hussain

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search as well as reports for the Department of Health and website Institute of Health Improvement (IHI) using the keywords: clinical governance, patient safety, quality improvement and adverse events.

HISTORICAL BACKGROUND

> *'The only way to be sure that they do the right thing is to keep an eye on them, to challenge them, to hold them to account and, above all, to take part in them.*
>
> The Nolan Committee[1]

The last decade of the twentieth century saw some colossal tragedies in our practice of medicine in the UK, including the cases of Beverly Allit,[2] Harold Shipman[3] and Bristol Paediatric Cardiology practice.[4] While we were coming to terms with these tragedies, trying to make sense of and learn from them, on the other side of the Atlantic the Institute of Medicine (IOM) published a report that sent shock waves around the world. *To Err Is Human: Building a safer health system*[5] made a conservative estimate that 98 000 people die in hospitals in the United States every year due to medical errors while they are receiving some form of healthcare intervention. The US Department of Health and IOM set out robust steps to reduce the mortality by 50% in the 5 subsequent years. The patient safety revolution crossed many geographical and political boundaries and the World Health Organization set up the World Alliance for Patient Safety in response.

To Err Is Human helped us to understand that medical errors are often the result of multifactorial problems within a healthcare delivery system – it is rarely the fault of a single individual. The importance of teamwork in patient safety and quality improvement emerged as a more fundamental need. The focus shifted from the healthcare professional to the structural clarity and robustness of the operating system, that is, the organization (microsystem, mesosystem, macrosystem).

Dealing with the serious public repercussions of a number of significant tragedies in the National Health Service, the then Labour government came up with a new plan to reform the health service with a new philosophical concept of practice: clinical governance. In December 1997, the new Labour government published a White Paper,[6] *The New NHS*. In July 1998, the Chief Medical Officer, Liam Donaldson, co-authored a paper in the *British Medical Journal* titled 'Clinical governance and the drive for quality improvement in the new NHS in England'.[7] We saw the birth of clinical governance – an eclectic concept that was strangely alien to most of the frontline workers in the NHS. As a new cognitive structure, it incorporated **clinical audit**, **risk management**, **incident reporting** and **continuous professional development** (**CPD**). It was described

as a package that housed all the disparate and fragmented practice of quality improvement.

DEFINITION

> '*Clinical governance is a system through which NHS organizations are accountable for continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish.*'[8]

A robust framework of a high-performance system was proposed where healthcare professionals and managers would be working together towards a common goal of delivering safe and high quality care to our patients. This vision of a healthcare system was described based on an integrated intelligent matrix of communication pathways connecting all its parts and people. The capability of preserving and learning from our experience (memory) of individuals and groups on the front line was described. This new phrase clinical governance was partly harvested from the Cadbury report (1992)[9] on the financial aspects of corporate governance with some intrinsic support from the NHS constitution. For the first time, quality improvement was put at the heart of medical practice in the NHS. The chief executive officers of the NHS hospital and primary care trusts were made accountable for the quality of care provided by their organization. The attention was expected to shift from the traditional target- and performance-driven, management-led organizational culture, to a refreshingly appropriate practice of medicine within an established framework of patient safety and quality improvement, led by senior clinicians. Safe, effective, patient-centred care with efficient utilization of resources and focused practice of risk management became the essence of good quality service. In 1997, the Department of Health introduced a 10-year programme to improve the quality of clinical care provided by NHS organizations and positively change the public perception. The National Institute for Clinical Excellence (NICE) was created to establish clear national standards through National Services Frameworks. The Clinical Governance Support Team, National Patient Safety Agency and National Clinical Assessment Authority were also established to support the development and good practice of clinical governance. The Commission for Health Improvement (CHI) was founded in 2000 by the Health Act 1999, as an external body to review the performance of each healthcare provider.[10]

Scally and Donaldson[7] described the integrated approach to the practice of clinical governance under six interconnected domains:

1. Culture:
   - good leadership
   - ethos of teamwork
   - patient partnership
   - education and research valued
   - open and participative
2. Coherence:
   - goals of individuals, teams, organizations aligned
   - excellent communication
   - external partnership forged
3. Infrastructure:
   - access to evidence
   - time allowed to plan
   - training and development strategies
   - information technology supports practice
4. Risk avoidance:
   - well trained staff
   - safe environment
   - clear procedures
5. Quality methods:
   - good practice spread
   - clinical policies evidence based
   - lessons learned from failures
   - improvement process integrated
6. Poor performance:
   - early recognition
   - decisive intervention
   - effective self-regulation
   - feedback on performance.

It is important to note the World Health Organization has used the term clinical governance in relation to building high quality healthcare service. WHO had described it as four dimensions of quality:

1. Patient satisfaction
2. Professional performance
3. Risk management
4. Resource allocation.

In essence, clinical governance is a framework of safety with a whole system integrated approach to care and continuous quality improvement.

The main principles of clinical governance are:

- clear lines of responsibility and accountability for the overall care
- a comprehensive programme of quality improvement
- education and training
- clear policies for risk management
- managing poor performance.

In 1999, the Secretary of State for Health stipulated proposals for professional regulations of staff in the consultation document, *Supporting doctors, protecting patients*. Professional regulation of individuals working at the frontline of the NHS was considered necessary and plans were unveiled. *An organisation with a memory*[11] was published in the year 2000. This report of an expert group on learning from adverse events in the NHS highlighted the extent of the harm patients could face when under the care

BOX 37.1 The 7 pillars of clinical governance

1. Patient and public involvement
2. Risk management
3. Clinical audit
4. Staffing and staff management
5. Education and training
6. Clinical effectiveness
7. Use of information

of our NHS hospitals. It stated that adverse events resulting in patient harm occur in around 10% of all admissions to NHS hospitals. This is equivalent to an incidence in excess of 850 000 patients per year. The estimated cost of managing this is £2 billion a year in additional hospital stays alone. The establishment of NICE in 1999 and CHI in 2000 aimed to safeguard patient care through evidence-based support and regulation. CHI described clinical governance as a platform held up by the 7 pillars of clinical governance (Box 37.1). It was widely perceived that changing organizational culture and creating a robust, well-connected system with clarity of structure and function was the essential key to successful clinical governance and the survival of the NHS beyond its 50th birthday.

THE 7 PILLARS OF CLINICAL GOVERNANCE

Patient and public involvement

The National Health Service belongs to the citizens of the UK and is run on public funding. The voices of patients and the public are essential to maintain its integrity, growth and evolution. Feedback from patients and the public should be dealt with carefully so as not to miss any learning opportunity that may come with it. The creation of clear structures for handling such feedback ensures the generation of functional memory and creates a learning environment that allows us to improve our provision of care every day.

Risk management

DEFINITION OF RISK

Risk can be defined as any potential for the occurrence of an unwanted effect because of an intended action.

RISK TO PATIENTS

The practice of medicine is a high-risk business. Every healthcare intervention must be risk assessed and continuously monitored to reduce any risk to patients. All incidents and near misses must be reported, recorded in the organizational memory and carefully analyzed. Knowledge gained from these and through significant clinical event analysis should change behaviours of clinical practice with resultant reduction of both non-human factors and human factor-related risk and incidents. All critical events must be audited. The introduction of surgical checklists has led to a reduction of risk and adverse incidents in surgical patients. Statutory regulatory bodies (i.e. Medicine Control Agency, Data Protection Act, etc.) can help in the reduction of risks and incidents. The use of software (e.g. DATIX) can facilitate all aspects of risk management and the successful use of these has been reported by some health organizations. Regular training of staff and routine and random checks of systems and practices are essential for maintenance of the highest standards of safety.

RISK TO THE PRACTITIONER

Protecting healthcare professionals from occupational hazards by immunization, improving and creating a safe work environment, assessing and reducing human factor-related incidents are recommended good practice.

RISK TO THE NHS ORGANIZATION

Any incidence of poor practice has the potential to damage the professional reputation of an organization. Significant events of poor practice are usually the reflection of poor organizational culture and serious lack of leadership across all parts of the system. Examples of such tragedies are plentiful in our recent history (i.e. Bristol, Mid-Staffordshire, Lanarkshire, Blackpool, etc.). The Francis, Keogh and Berwick reports will speak of the risk associated with poor organizational culture for decades to come. We must not miss the opportunity to learn from these situations.

Aligning the individual, team and organizational values creates resonance and avoids conflicts of interest. This is essential for the success of clinical governance.

Clinical audit

Clinical audit is a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and implementation of change.[12, 13]

In 1989, medical audit was introduced in the NHS by the Department of Health,[14] with clear instructions for all hospital doctors to take part in audit by 1991. This had been duly endorsed by the General Medical Council in its advice to all doctors. In 1997, clinical audit was integrated into clinical governance. Clinical audit comprises the essential core of clinical governance. It is the most appropriate way to check for the safety, effectiveness and quality of all healthcare interventions, both processes and outcomes. When applied carefully and methodically, clinical audit is excellent in its ability to monitor healthcare delivery services in its entirety. The recommendations from the Report of the Public Inquiry into Children's Heart Surgery at Bristol Royal Infirmary (1984–95) strongly supported audit to be the tool for monitoring clinical performance. It also stressed that clinical audit should be thoroughly supported by all healthcare organizations and all healthcare professionals should be contractually bound to take part in local audits. The recent introduction of the revalidation

process for renewal of doctors' licence to practise by the General Medical Council requires all doctors to perform clinical audits.

Factors contributing to the success of any audit are:[15]

- organizational support
- evidence-based guidelines
- participation of patients
- good relationship with patient support groups
- improved record-keeping
- good use of information technology
- professional help and support in designing and application.

Lack of ring-fenced time within doctors' job plans, lack of resources, poor microsystems and organizational culture and deficient managerial support in efforts towards clinical quality improvement can all be significant deterrents to effective clinical audit. Johnston et al. reviewed 93 publications to explore the barriers and facilitating factors for effective clinical audit. They have highlighted professional attitudes and presence of coherent strategies as significant variables influencing outcomes of clinical audits.[16]

The tragedies of Bristol Royal Infirmary should deter anyone from dismissing the significant role of clinical audit in achieving patient safety and quality improvement.[12]

Staffing and staff management

Recruiting highly trained staff with a passion for working in the NHS is fundamental to providing excellent patient care. Of equal importance in the provision of safe, effective and patient-centred care is ensuring the optimum skill mix of well supported staff in every clinical area. Tired, harassed, psychologically disengaged staff cannot provide good quality care.[17]

Education and training

Continuous professional development through well supported in-house and national courses is essential to keep all NHS staff up to date with the rapid pace of progress of modern medicine. The reduction of junior doctors' training hours to comply with European working time directives has certainly caused difficulties in terms of the training of doctors because of the significant lack of the most important resource – time. The introduction of consultant contracts with 90% of time spent in direct patient care, with a paucity of time and funding for study leave time, has a serious detrimental effect on the education and training of senior doctors.

The education and training of all healthcare professionals, throughout their career, must be supported and guarded as sacrosanct in order to allow safe and best quality practice to thrive. It is a duty of all employers to safeguard this. A very good example of this is the work of NHS Education for Scotland.[18]

Clinical effectiveness

Ensuring that each and every patient gets safe and effective healthcare is the core function of clinical effectiveness. Standards of safety and quality of care must not fluctuate across timelines or postcodes. All aspects of healthcare should be based on the current body of evidence and be patient centred. Clinical effectiveness is all about doing the right intervention, for the right patient, at the right time, in the right way. Eradicating wastage, minimizing harm and variations of practice should be at the heart of the practice of clinical effectiveness. In essence, clinical effectiveness measures how good an intervention is at achieving what it is intended for and is weighed up by the hierarchy of evidence. This has been derived from the evidence-based medicine movement of the 1990s.

The development of CHI, NICE and the Scottish Intercollegiate Guidelines Network (SIGN) have been at the heart of the promotion of good practice based on the best evidence. It has also been established that safe and effective practice is also more cost-effective.

Use of information

Effective and efficient management of information is the key to the ultimate success of an operational system, that is, the NHS organization (macrosystem). This involves understanding data protection, methods of collection, evaluation, interpretation and application of all relevant data to improve processes and, therefore, the outcomes of a system. A good example of this is the improvement of clinical performance based on monthly or annual outcome data of one or many interventions. Data are extremely powerful tools to show the quality of any practice (i.e. patient feedback information allows us to improve our care pathways). Data handling is hugely labour intensive. Every NHS organization needs to ensure modern technology and appropriately trained staff are in place to harvest and make good use of data. This is a key infrastructure requirement for the success of clinical governance.

RELATIONSHIP BETWEEN CLINICAL GOVERNANCE, PATIENT SAFETY AND QUALITY IMPROVEMENT

The concept of clinical governance was introduced by the Department of Health in 1997 as an integrated framework within the NHS to safeguard patient safety and continuous quality improvement. For clinical governance to be successful it is imperative that an organization will have safe, effective and patient centred care in day-to-day practice. Patient safety and continuous quality improvement are at the heart of clinical governance and should not be separated. However, NHS organizations often show separation and conflicts between clinical and managerial approaches to patient safety and quality improvement.

Realignment of organizational goals with the goals of the frontline healthcare professionals will ensure that patient safety remains at the heart of the practice of clinical governance.

FRANCIS, KEOGH AND BERWICK REPORTS

Hope is not a plan and a plan is not always a good strategy that can survive the test of time. 2013 saw the publication of several landmark government-funded reports into failures of healthcare delivery systems. Many devastating high-profile failures of provision of care, mishaps and deplorable quality of practice plagued us throughout the early twenty-first century. The second cycle of the Francis report made 290 recommendations over 1782 pages.[19] The essential recommendations were: openness, transparency and candour throughout the healthcare system (including a statutory duty of candour); fundamental standards for healthcare providers; improved support for compassionate caring; committed nursing; and stronger healthcare leadership.

Bereaved and angered patients' families and friends had questions. Many of these questions sadly still remain unanswered. A review of mortality figures in 14 hospitals in England was the next revelation to hit the medical profession. Keogh summarized his recommendations as eight ambitions.[20] Listening to the frontline staff (i.e. the nurses and junior doctors) is one of the most highlighted areas, along with the need for the creation of a climate of safety and positive organizational culture.

Don Berwick, founder and past president of the IHI, a physician, philosopher and a passionate believer of robust systems, individual accountability and the human touch in patient care, was the third leader invited by the government to analyze and report on the problems affecting patient safety in NHS hospitals. Berwick expressed his thoughts succinctly in the form of four eloquent letters in a document, *A promise to learn – a commitment to act: improving the safety of patients in England*.[21] The summary of his recommendations is simple, clear, extremely powerful and poignant (**Box 37.2**).

BOX 37.2 Four recommendations by Don Berwick

1. Engage, empower, and hear patients and carers throughout the entire system, and at all times.
2. Foster wholeheartedly the growth and development of all staff, especially with regard to their ability and opportunity to improve the processes within which they work.
3. Insist upon, and model in your own work, thorough and unequivocal transparency, in the service of accountability, trust and the growth of knowledge.
4. Embrace transparency unequivocally and everywhere, in the service of accountability, trust and the growth of knowledge.

CURRENT ISSUES

There are a number of issues that can be highlighted to show why clinical governance has not thrived:

- lack of defined input, structure and process for clinical governance
- poor organizational culture
- poor and deficient leadership
- disengaged, disillusioned staff
- historical glass walls of poor culture or practice separating clinicians and managers
- financial targets and misaligned performance indicators
- disconnected microsystems
- confines and silos of good practice
- poor, cumbersome feedback system
- lack of patient involvement and regular public scrutiny.

ROLE OF CEO, NHS BOARD AND SENIOR MANAGEMENT

In 1998, chief executives of all NHS primary and secondary care organizations were made directly accountable for the quality of the service provided by their organizations. In the absence of a clear, defined framework of safety, clinical governance will fail to meet any of its lofty goals. The chief executive officer with the senior management team and board members need to ensure there is an environment where good practice thrives. The lines of accountability and responsibility for overall patient safety and quality improvement must be clearly identified. Organizational goals aligned with those of individual healthcare professionals dedicated to value-based practice will create an environment in which clinical governance will thrive.

CONCLUSIONS

Primum non nocere, the Hippocratic Oath of first doing no harm in our every endeavour, has been at the core of our medical practice for centuries. Patient safety and quality improvement is everyone's business. Without willing contribution from the majority of NHS staff, the goals of patient safety and quality improvement will never be realized. However, we urgently need some effective measures to engage our disillusioned staff in value-based patient care. This will not be possible until the clinical priorities are met.

It should be our goal to see that all staff are well connected, well informed, well supported and working in resonance towards their common goal of delivering safe, effective and patient-centred care to every patient every time, 365 days a year. Financial, political and performance related goals should not override the goals for patient safety and quality improvement.

The National Health Service[22] was born on 5 July 1948. It did not have any intrinsic or extrinsic system for safety or quality improvement for the first four decades

of its existence. The 10 years leading to its 50th birthday saw some major failures, with consequent public scrutiny. This triggered a deluge of white papers, reforms and introduction of laws. Despite the implementation of all these measures, British citizens have seen repetitions of many mistakes in the NHS. Sadly its recent history has demonstrated that the NHS as an organization does not have a functional memory and has failed to learn from its major mistakes. We cannot solve a problem with the same level of intelligence that created it – a paradigm shift in organizational culture is required to ensure that patient safety and continuous quality improvement are at the heart of the practice of medicine throughout the NHS.[23] This will only be possible with strong leadership from front-line clinicians in partnership with excellent senior managers.

KEY POINTS

- Clinical governance is a system through which NHS organizations are accountable for continuously improving the quality of their services and safeguarding higher standards of care by creating an environment in which excellence in clinical care will flourish.
- Clinical audit comprises the essential core of clinical governance.
- Data are a key infrastructure requirement for the success of clinical governance.
- Medical errors are often the result of multifactorial problems within a healthcare delivery system – it is rarely the fault of a single individual.
- Feedback from patients is the most valuable resource. It should be actively encouraged at all parts of a patients' journey.
- Risk can be defined as any potential for the occurrence of an unwanted effect because of an intended action.
- Tired, harassed, psychologically disengaged staff cannot provide a decent quality of care.

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CHAPTER
38

MEDICAL ETHICS

Paul Baines

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: ethics, methods, autonomy, interests, welfare, principles, consequentialism, deontology, reasons, informed consent, children, relativism, research ethics, resource allocation, truth-telling and confidentiality.

WHAT IS ETHICS?

> '*The purpose of ethical reflection is to help us to decide how to act in the real world, all things considered. This means ethical reflection must take into account all aspects of a proposed course of action, it must rely on good factual evidence and on an understanding of the social and legal contexts in which action has to take place.*'[1]

Sometimes decisions in medical ethics are presented as though they are separate from mainstream medical decisions, but this is not so. Succinctly, good medicine demands good ethics and this requires correct facts: ethics necessarily cannot be divorced from the real world.

Two broad academic approaches can be distinguished in ethics. The first, empirical ethics, describes ethical interactions through the methods of social sciences, using questionnaires, interviews and focus groups (amongst others) in studying what happens, or how people approach situations that involve ethics. The methods are both quantitative and qualitative and often come from psychology or sociology.[2] The other broad approach (adopted in this chapter) is philosophical, or analytic, ethics. This is the study of what *ought* to be done and includes questions such as what ethics is and how doctors should behave towards patients and each other. Ethical questions in this tradition are about what *should* happen, not about what does happen. Within this approach to ethics, some consider more abstract questions, such as whether there are moral facts or whether moral truths are relative to society. This discipline is called meta-ethics. These questions are not immediately relevant to clinical practice. Others ask more down to earth questions, such as: What is needed for research to be ethical? Is abortion acceptable? This discipline is called normative ethics. Meta-ethics and normative ethics are not independent, as answers to meta-ethical questions may inform normative conceptions and vice versa. The important difference between these disciplines and empirical ethics is that these studies describe the world, recounting how things are, whereas philosophical ethics concentrates on what would be *right* or how things *should* be. As an example of the distinction, empirical ethics can report on whether or not abortion is carried out and the reasons that people offer for their involvement (or non-participation) in abortion, but philosophical ethics attempts to answer the question of whether or not abortion should be performed. That abortion is (or is not) performed does not indicate whether it ought to be performed.

The distinction between how things are and how they should be, or between what people do and what they should do is one manifestation of the 'is-ought gap'. Hume argued, 'In every system of morality which I have hitherto met with, I have always remarked, that the author proceeds for some time in the ordinary way of reasoning, and establishes the being of a God, or makes some observations concerning human affairs; when of a sudden I am surprised to find that instead of the usual copulations of propositions, *is*, and *is not*, I meet with no proposition that is not connected with an *ought*, or an *ought not* ... a reason should be given, for what seems altogether inconceivable,

how this new relation can be a deduction from others, which are entirely different from it'.[3] This distinction is important: clinicians are educated in biomedical scientific methodology, but the methods, and knowledge, of ethics are different from those that they are used to.

Most pressingly, ethics asks the question: What should *I* do? As Singer argues in criticising relativism, 'Anyone who has thought about a difficult ethical decision knows that being told what our society thinks we ought to do does not settle the quandary. We have to reach our own decision.'[4] When a clinician is confronted by an ethical decision, particularly one that is disputed or troubling, the choice that must be made seems deeply personal, and in that way is different from technical questions in medicine (such as the choice of antibiotic to treat sinusitis in a previously well 20-year-old). Although colleagues or confidantes can offer advice and guidance, there is much less sense that an expert can know the right decision when it comes to matters of ethics than in matters of technical medicine (indeed, the notion of whether or not there are ethics experts is contested).[5, 6] However, what I want to emphasize is the strong sense that what I do in ethics matters personally.

At different times different questions have concerned those interested in medical ethics. Partly this has been driven by advances in biomedical knowledge and expertise (an example is the advances in reproductive techniques) and partly this has been driven by a change in the focus of ethical interest to different aspects of medical practice. In the recent past medical ethics was more concerned with the professional behaviour of doctors (for example, the acceptability of advertising, and in relationships between doctors); then focus turned to the relationship between the individual clinician and the patient. More recently attention has turned more towards public health ethics and the ethics of the distribution of the social determinants of health.

Some people believe that it is unlikely that there will be progress in ethics because ethics have been studied for several thousand years, so there is nothing new to say, but others are more optimistic: 'Some people believe that there cannot be progress in Ethics, since everything has already been said … I believe the opposite. How many people have made Non-Religious Ethics their life's work? ... Non-Religious Ethics has been systematically studied, by many people, only since the 1960s. Compared with the other sciences, Non-Religious Ethics is the youngest and least advanced.'[7]

In this chapter I will briefly consider the methods that are used in ethics, then continue to consider some important concepts that are used in ethics and conclude by considering some topics of relevance to practising otolaryngologists. Although I will review the ethics of clinical research there are topics that I will not consider (including, for example, the concerns around stem cell therapies).

METHODS IN ETHICS

The emphasis, in clinical medicine, is on the evidence-base that justifies the performance of diagnostic tests and the effectiveness of medical interventions. Medical decisions that are not supported by a high standard of empirical evidence are taken to be suspect. But this approach will not work in ethics as the questions are different. Ethics involves claims about what *should* be done and what *ought* to happen. These normative questions are different from the questions of evidence-based medicine. To answer these different questions, different methods are needed.

The methods of ethics are essentially those of philosophy or critical thinking and include the critical evaluation of concepts and the use and evaluation of rational arguments in a logical and consistent fashion. The techniques are many and varied but a sense of them can be found in books such as *The Philosopher's Toolkit*[8] and *Thinking from A to Z*[9] and can often be found in introductory textbooks such as *Medical Ethics and Law: The Core Curriculum*.[10] However, as well as philosophy, a broad range of disciplines contribute to medical ethics including, amongst others, legal scholars and lawyers, theologians and historians alongside practising clinicians and other healthcare professionals.

Reasoning and rational justification is at the heart of ethics. In ethics it is important that the conclusions are justified by reasons (though it is important to acknowledge the position that emotion may have in ethics). An important commitment in ethics is that judgements are universalizable. This means that is that there is a requirement to treat all similar cases in the same way. There can be no special pleading along the lines of 'she's my daughter': a reason for your daughter is a reason for all daughters, for all girls, for all children. This means that significant weight is placed on deciding whether two cases are morally similar, or alternatively morally different. One approach in ethics that has achieved prominence in recent times is reflective equilibrium.[11] In this approach all of a person's beliefs and theories are involved when making a decision. Neither the facts of the situation, nor any high level abstract principles take priority over other beliefs, there is a to-and-fro examination of the complete set of a person's beliefs in an attempt to develop a coherent approach. Should there be disagreement or inconsistency, then all of the person's beliefs may be revisited in order to achieve a coherent and consistent set of thoughts. Importantly, all beliefs are subject to revision. Abstract principles do not necessarily trump more down-to-earth concerns.

Within the discipline of normative ethics several different approaches are used to analyze the ethics of medical interventions. These methods include principlism, the claim that principles guide moral action. The most popular principlist approach is the four principles advocated by Beauchamp and Childress,[12] but this is only one form of principlism. Another approach is casuistry, which objects to the 'top-down' approach that starts with abstract principles, insisting that we should attend to the particular circumstances of individual cases. Virtue ethics, another approach, characterizes ethical actions as those in which the virtuous person will 'assess each situation individually, searching for action guidance in considering what a characteristically virtuous person would do'.[13] And yet another is the ethics of care, originating in the work of

Carol Gilligan, emphasizing empathy and compassion, describing ethics in terms of relationships. Gilligan found (in empirical work) that women took the care ethics approach, whereas men appealed more to abstract principles (such as 'justice') in ethical analysis. This is not an exhaustive list of the approaches to ethical analysis.

Importantly, although ethics and law are related, the two are separate disciplines. Some laws neither have nor need an ethical underpinning (the legal requirement to drive on one side of the road for example). Other laws may have some ethical justification, but even in these cases the relationship between ethics and law is not straightforward: some actions are legal but unethical (some would want to describe abortion – legal in many countries – in this way). Some actions are ethical but illegal (some would want to describe assisted suicide, which is illegal in the UK, as an example). And even if there were clear agreement over which actions were ethical and which were not, it is a separate question whether an action that is unethical should be illegal: 'it is one thing to show what a woman ought to do in relation to her unborn child and quite another thing to say that this obligation ought to be enforced'.[14] One way in which it is clear that there is not a direct relation between the law and ethics is the differences in laws between adjacent, but similar, countries. For example, abortion is illegal in Ireland, but legal, in certain circumstances, a 30-minute flight away in the UK. Furthermore, although there is some moral obligation to obey the law, there are also circumstances in which there may be a moral obligation to disobey a bad law. The civil disobedience campaigns in the United States are examples of this.

Similarly the relation between religion and ethics is troubled. Important contributions have been made to ethical thought by religious scholars (amongst other examples in the analysis of the doctrine of double effect), but the foundations of religious ethics – that they are the revealed word of God, or some equivalent, and so their authority is unquestioned – are not accepted by all. And this is compounded by the several different competing religions in pluralistic societies (alongside the arguments of militant atheism). No one dominant religious approach is able to claim a secure knowledge of the good.

Many different institutions and agencies develop and have developed prescriptive guidance on matters of ethics. For example, in the UK, the body responsible for licensing doctors, the General Medical Council (GMC), produces guidance[15] in the form of pamphlets guiding medical practice in general, and pamphlets that also address specific areas of practice such as dealing with children, or research. In law, the GMC's guidance is often taken to indicate the correct approach. As well as GMC guidance, professional bodies such as the British Medical Association and the Royal Colleges (responsible for postgraduate medical education in the UK) produce ethical guidance. Although the guidance may be useful in practice, it requires interpretation by the practitioner to be applied. As well as this, even with clear guidance, there may be conflict between different components of the guidance. Again, interpretation and ethical wisdom is needed in the clinical application of advice.

IMPORTANT CONCEPTS IN ETHICS

Relativism

Relativism is the claim that ethical judgments are made relative to a particular society and time. If this is true, there is no single correct ethical judgement for all and 'when in Rome, do as the Romans do' is true. One support for relativism is the presence of differences between societies in their approaches to ethics. This evidence then leads to the claim that there are no right answers in ethics, just different right answers in different contexts. But this need not be the response; in some circumstances disagreement just indicates that one side is wrong. If we disagree about the distance from Paris to London it doesn't mean that there isn't a right answer, just that one (or both) of us is wrong.

With the prominence of respect for autonomy, relativism can seem the correct response to the challenge 'who are you to judge?' Amongst the advantages of relativism is that it is sensitive to the criticism of ethical imperialism and, in avoiding the claim that a person is wrong, may encourage negotiation instead of confrontation. Confrontation is likely to entrench disagreement whereas negotiation may lead to reasoned agreement.

However, there are significant problems with relativism. Firstly, relativism implies that there is no progress in ethics. If ethical relativism is true, then in slave-owning societies slavery is not wrong. The recognition of the wrongs of slavery and the moral progress in banning slavery is not acknowledged. A second problem for relativism is that ethical disagreement becomes a matter of fact. So again, the claim that slavery is wrong is just a factual claim about a society. But the wrong of slavery is not something that anthropology can judge. Ethical wrongs are not anthropological disagreement.

Importantly, there are different ways that a person can be a 'relativist', and so two relativists can disagree with one another. This brief review only skims the complexity of relativism.[16]

Principles

Principles are laws or truths that offer guidance in ethics. The dominant approach in medical ethics is the four principles approach of Beauchamp and Childress.[12] There are several different principled approaches (see Veatch[17] for a summary of some of these), all with competing justifications. The justification that is often offered is that the chosen principles best condense moral intuitions, or best reflect common-sense morality. Perhaps the most famous principle-based approach is that of Kant[18] with his single categorical imperative (see below).

Not all ethical approaches depend on principles. Some reject a principled approach. Moral particularism claims that 'moral judgment can get along perfectly well without any appeal to principles … abandoning the mistaken link between morality and principles is if anything a defence of morality rather than an attack on it'.[19] As well as this, other approaches, such as virtue ethics, do not depend on principles.

Autonomy

Respect for autonomy has become the pre-eminent value of our times, and not just in medical ethics: 'to be autonomous is to be one's own person, to be directed by considerations, desires, conditions, and characteristics that are not simply imposed externally upon one, but are part of … one's authentic self'.[20] Although autonomy may seem straightforward, it is highly contested. It includes, at least, freedom from external manipulation (neither physical nor emotional control by others) as well as an internal ability to control oneself (a person does not choose unwisely, driven by impassioned urges or addiction).[20, 21] As rational, morally responsible people, we should adopt our own long-term commitments, goals and values and make our own important decisions about how to live our own lives. Only in this way are we truly human, living a genuine life as a rational person.

Respect for autonomy replaced a more paternalistic model of medicine, where because the technical expertise of the doctor in medicine was respected and accepted, the clinician chose what was best for the patient. However, requirements of autonomy are such that although the clinician has technical expertise, the person with the medical problem knows better the effects of the disease and the therapies on their own life and life goals. In this way it is only the person, guided by the clinician, who is able to make the right decisions about medical interventions.

Kant's morality grounds autonomy in the demands of pure reason. Kant distinguished a hypothetical imperative from the moral categorical imperative. A hypothetical imperative recognizes that one should act in a certain way to achieve a specific goal: consult the map *if* you want the quickest route to the next town. The categorical imperative (the rational demand of morality) is universal, and (in one construction) states, 'Act as if the maxim of your action were to become through your will a universal law of nature' [Kant, 1948; 84].[18] An autonomous decision then is not just simply an individual's choice, it is a supremely rational decision, devoid of misinformation and faulty reasoning, standing for all people for all time: it is the right action. Amongst the criticisms is that such a choice is an impossibly demanding standard. Importantly, many choices do not approach this stringency and so are not (in this sense) autonomous. A different justification that personal choice should be respected comes from libertarianism – such as Mill's. Mill set out the harm principle, 'the only purpose for which power can be rightfully exercised over any member of a civilized community, against his will, is to prevent harm to others. His own good, either physical or moral, is not a sufficient warrant.'[22] This is because when another person chooses they are 'quite as likely to be wrong as right'.[22] Even so, Mill recognizes some limits. He gives the example of a person crossing an unsafe bridge who may be 'seized and turned back' if unaware of the danger. A Millian justification of respect for choice is less demanding than a Kantian justification.

An autonomous decision is one that affects only the individual involved. So preventing smoking in public based on the risks of passive smoking does not conflict with the respect that is due to autonomous choices (it is not paternalistic). One criticism is that very few, if any, decisions have repercussions only for the individual concerned. Almost all of us have family and friends: we are not atomic individuals bound by rights. The Nelsons argued that the locus for medical decisions should be the family and not the individual.[23] Feminist criticism of autonomy draws attention to the fiction of the lone 'autonomous' individual free of ties, drawing attention to the relational nature of autonomy. A further criticism of autonomy is that pervasive discrimination can impoverish a person's self-esteem and so desires. If so, the choices a person makes are not truly autonomous: 'our desires are shaped by our expectations which are shaped by our circumstances'.[24]

Sometimes autonomous individuals can choose a course that seems (at least to others) not to be good for the individual (even the individual themself may come to recognize their choice was mistaken). Some deny this, arguing that an autonomous individual is always the best judge of their welfare (for example, 'Competent adults are allowed to define their own concept of "best interests"...'[25]). That an individual makes the correct choice about their welfare depends on the individual being informed and reasoning correctly. We can all recognize episodes when we have been mistaken about what would be good for us as individuals, in which our choices have not been to our benefit. In this way there is a tension between autonomous choices and an individual's welfare. Bosk observed that 'the dark side of patient autonomy is abandonment'.[26]

An ethics based on respect for autonomy does not account for public health commitments (to water fluoridation or to clean water and air as examples). These cannot be a matter of autonomous choice for individuals, as it is unlikely that all individuals will choose (or refuse) them.

Some people are not autonomous, lacking some – or all – of the abilities needed to be autonomous. Young children are one group. They will be considered later on. Another is incompetent adults. When dealing with incompetent adults, all attempts should be made to maximize the person's capacity. Incompetence may be temporary (perhaps while ill or intoxicated) or permanent (in severe dementia). Sometimes a person's capacity, and so their competence, fluctuates. The broad approach to those who lack autonomy (if they were previously competent) is to choose as the individual would have chosen. Medical decisions can be guided by written instructions that the individual has left (an advance directive). Alternatively, the now incompetent person may have chosen someone to make decisions on their behalf (in the UK this is named a Lasting Power of Attorney). In the absence of these, evidence of the incompetent person's preferences (from family and friends) guides medical decisions, in order to choose as the person would have chosen (a substituted judgement). As well as this, the views of the not competent individual should be sought so that their views may be included. In the absence of all of these, the decision for an incompetent person will be based on some objective or impersonal sense of the individual's best interests.[27]

Welfare, well-being, 'good for', in a person's (best) interests, beneficence

Often the role of medicine is taken to be to make people better, specifically to improve their health, but there can be disagreement about what this means. One problem is that there is not a clear boundary between health and disease, nor is there a clear boundary between treating disease, preventing disease and improving health. Some believe that although doctors treat disease caused by smoking, clinicians overreach their role in campaigning against smoking or advocating restrictions on smoking. Importantly non-healthcare interventions can improve health. Literacy campaigns reduce overall mortality and neonatal mortality,[28] but would not usually be taken to be a healthcare intervention. Some seek to define the role of medicine as the treatment of physiological disorders, appealing to the role of disturbances to what is 'scientifically' normal function. There are many difficulties with these approaches. One example is in reproduction. Medical roles encompass both abortion, in terminating pregnancy, and assisted reproductive techniques in initiating and maintaining pregnancy. A physiological definition of medical goals is unhelpful here. Importantly, as well as benefits for physical health, mental well-being is also important.

Medicine is not limited to the treatment of disease (an example is the importance of health promotion exemplified by vaccination programmes) but how far into the promotion of health medicine should go is controversial. The WHO defines health as 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity'.[29] Daniels responds, 'Health is not all there is to well-being or happiness, contrary to the famous World Health Definition (WHO) definition … The WHO definition risks turning all of social philosophy and social policy into health care.'[30] In general in medicine, clinicians act in a way that is 'good for' their patients, though their actions are limited both by the law and by the consent of the patient.

This aim can be expressed in several different ways: that clinicians should do good for their patients; that they should act in their patients' interests; or best interests; or with attention to their patients' welfare or well-being or for their good. In this sense, a person's interests are at the core of ethics. Or, describing it another way, when acting or choosing between actions, a significant (although perhaps not the only) factor in ethics is the effect the action will have on people's interests.

However, in modern pluralist societies there are often different senses of what would be good for someone. In a well-rehearsed example, Jehovah's Witnesses believe that the voluntary acceptance of blood transfusion leads to damnation, so a blood transfusion, even when life-saving, is not in their interests. Others would see that a blood transfusion is clearly beneficial. Can we resolve these dilemmas? Philosophers disagree about how best to conceptualize a person's interests, some (utilitarians) arguing that what is best is what makes most people most 'happy' (though they may disagree about what is meant by happiness). Others argue that what is best is where more of a person's desires are fulfilled and fewer desires are left unfulfilled (desire-satisfaction theories). A further approach is that some things are just good for people (sufficient food) and some things are just bad for people (pain). To be healthy is just good. This is called an objective list account. There is insufficient space in this chapter to take this further (but see Degrazia's[31] paper or Griffin's book *Wellbeing*[24]), but we should recognize that not only do we not have a clear grasp of a person's interests but we also do not have a clear way to go about working out what a person's interests are. These concerns led the House of Lords to claim '"best interests" is probably the most abused and misunderstood phrase in health and social care. It has too often been the vehicle for poor decision-making'.[32]

It is rare that any medical intervention is a source of unmitigated benefit; all interventions have some adverse effects in terms of pain or unpleasantness, or even (for the most trivial of interventions) the time that the intervention requires could have been spent more profitably. So in considering the benefit to an individual, the severity and the likelihood of harm (maleficence) must be considered alongside the extent and likelihood of benefit in coming to a conclusion about the benefits of medical intervention. For example, in the Belmont Report (considering the ethics of research), harm is included in the calculation of beneficence which is described as '(1) do not harm and (2) maximize possible benefits and minimize possible harms.'[33] Beauchamp and Childress,[12] in their influential four principles, separate beneficence from non-maleficence.

Non-maleficence

Avoidance of harm is sometimes prioritized as a first principle, often phrased in the Latin *primum non nocere* – above all do no harm. I have argued already that it is usually necessary to balance benefits and harms each against the other in judging the overall advantage (or disadvantage) of medical interventions. If the first, overriding, responsibility is taken to be to do no harm, then it is likely to rule out all medical interventions as none can be guaranteed to be without adverse effects.

A reason to separate non-maleficence from beneficence is that a person may have a broader responsibility to avoid harm to others, than to do good to them. A clinician has a responsibility to benefit her patients, but she need not help others. The clinician, though, does have a more general responsibility to avoid harm even to those who are not her patients.

Paternalism

Paternalism describes an intervention that is done solely to benefit a person, but which that person has not chosen, or perhaps would not choose (there are different forms of paternalism). This sort of intervention is excluded by Mill's harm principle. Failing to intervene (refusing to refer for abortion for example) can also be paternalistic. Because of the importance of the principle of respect for

autonomy the objection 'you're being paternalistic' is generally taken to knock down a proposed action. The only justification for intervention should be that an autonomous individual has consented to it. However, paternalism is manifest in different forms and there is some sense of appropriate paternalism: '"paternalistic" in an innocent, non-pejorative sense, namely that of "protective in a manner characteristic of parents"'.[34] Others resist this claim, arguing that paternalism is always wrong.

Paternalism has been characterized further, to distinguish when paternalism may be appropriate, though the terms used are used inconsistently (see for example Dworkin[35] and Childress[36]). Amongst other distinctions, some interventions involve autonomous persons, others non-autonomous persons, and sometimes the person's autonomy is uncertain. Another distinction lies in separating pure paternalism (the intervention solely benefits the person involved) from impure paternalism (justified by benefits both to the person involved and to others – such as laws restricting smoking that benefit both the smoker and those around her). A further distinction is found when the intervention helps a person to achieve values they hold (soft paternalism) contrasted with hard paternalism where the person does not accept the goals of the intervention. Accepting these distinctions, it is clear that paternalistic interventions need not be wrong and the important point lies in deciding when paternalism is unjustified. The waters have been muddied still further by the inclusion of 'maternalism'[1] and nudging, efforts to guide people in the right direction.

Rights

Rights are commonly, and increasing commonly, used in moral discourse. Codes or declarations of rights, having started with the UN Declaration of Human Rights in 1948 (provoked by the outrages of the Second World War) are increasing in number. Legal rights must be distinguished from moral or natural rights. Legal rights are ensconced in law, and are a matter for legal debate, for lawyers to resolve, and so are not the concern here. I will consider natural or moral rights that are independent of and go beyond the law, so that a person in a country where there is no right to free speech (for example) can say, 'I have a right to speak'. This is an appeal to a human right, not a legal right. Some dispute the existence of human rights at all, most famously Bentham: 'right with me is the child of the law … a natural right is a son that never had a father'.[37]

How could we know whether a claim is a human right or just a matter of convention, politeness or good manners? One response is to look to the codes or declarations of rights, but problematically the codes differ in their content. Furthermore, this response just pushes the question back one step: why are *those* rights in the declaration?

Regardless of these concerns, rights-based claims are common. The power of rights-based claims is in demanding access to healthcare for individuals and groups who are ignored or discriminated against. They are less useful in clinical problems where conflicting rights may not clearly be resolvable. Diane Pretty (afflicted by multiple sclerosis) used the European Convention of Human Rights (her right to life, a prohibition from torture, and a right to private and family life alongside a prohibition of discrimination) to ask that her husband would not be prosecuted should he assist her in ending her life. The UK government argued successfully against her claimed rights.[38] Often, when rights come into conflict there is no clear way to decide which right should triumph and which will be vanquished.

Justice

The concept of justice used in medical ethics is that of distributive justice. A formal statement of justice is that equals should be treated equally, but the presence of significant morally relevant differences indicates individuals should be treated differently.

The weight then is placed on deciding which differences are morally relevant. Most would want to agree that age or gender are not relevant differences in determining medical interventions. Some diseases are a consequence of personal choice (for example, smoking-inflicted diseases, such as coronary artery disease). If we agree that people are responsible for the consequences of the choices that they make, and if we agree that personal choices are an important cause of some diseases, then (the argument runs) treatment for smokers should be assigned a lower priority, than treatment for (the same conditions) for non-smokers. And the reason for the lower priority is that smokers deserve a lower priority because they are at least partly responsible for their disease. There are several concerns with this argument. One response is that smokers are addicted to smoking: smoking is not the free, uncoerced 'autonomous' choice that people should be held responsible for. Furthermore, many smokers started smoking when they were young (often when they were less than 16 years old), at the age when children should be protected from unwise choices. Similar arguments run for other diseases that may be self-inflicted (such as those provoked by alcohol or obesity). These arguments for responsibility are less often used for other self-inflicted diseases (the orthopaedic injury of the sportsman) and the concern here is that we are then imposing our choice of values on individuals who should be free to make their own choices. Be this as it may, the concept of justice is that if people are to be treated differently then there should be clear reasons why this is justified.

Consequentialism

Consequentialist approaches to ethics distinguish the ethically correct course as that which produces the best outcomes. Consequentialists differ in the outcomes that they value. Utilitarianism is one form of consequentialism in which the outcome that matters is 'utility' taken as the balance between pleasure and pain. Utilitarians seek to maximize overall utility.

Consequentialism is implicitly appealing to many healthcare practitioners, in seeking the best outcome: when choosing between two treatments, it seems obvious to choose the intervention, which has the least mortality or highest function or whatever, both for an individual patient and for populations. In fact it is a puzzle to many why anything other than the best outcome should be sought (I will consider a contrasting approach – deontology – in the next section). A consequentialist approach underlies the use of quality adjusted life years (QALYs) in the allocation of limited healthcare resources. There are often ethical decisions to be made about what is the 'best' outcome.

Consequentialist approaches can differ in what is taken to be the best outcome. One difference lies in the outcome that is taken to be best. As an example, a longer life is usually taken to be a better outcome, but some would choose a life of 60 years of full health with a sudden end in contrast to a life of 65 years, the last 10 years of which are blighted by unremitting pain. Another difference lies in the way that outcomes are amalgamated. In maximizing consequentialism, the best outcome is sought with no attention to the distribution of the outcomes. Often in health promotion programmes those who are most likely to suffer from the disease are least likely to take advantage of the programme. If so the intervention with the greatest efficiency in reducing disease increases inequality.[39] Most would agree that inequality matters and that it should not be exacerbated by healthcare interventions. I do not intend to resolve the debate here, just to note that even if consequentialism is taken to be a preferred approach, there are important questions about which form of consequentialism should be adopted.

Deontological

Consequentialism is often contrasted with deontological approaches. Deontology has its origin in the Greek work *deon*, meaning duty. Deontological theories are those that characterize ethics in terms of duty: actions are obligatory, permissible or forbidden. The paradigmatic deontological approach (though not by any means the only one) is the well-worked out ethics of the Roman Catholic Church.

Deontological approaches can be seen in contrast to consequentialist theories. One criticism of consequentialist theories is that they are too demanding. In consequentialist approaches, an individual is obliged always to choose the action that will maximize the good. Consequentialists may recognize no distinction between acts and omissions. A person then should act in the best way for the overall outcome. If so a person may have no time for their own projects, indeed they almost cease to be a person (with characteristics and individual values) becoming a machine to produce the best outcome. In contrast a deontological approach is characterized by permissible and forbidden actions. Some actions are required (for example those of a parent in relation to their child), but the required actions are much less frequent than the forbidden actions. Because of this, the deontologist does not face the overwhelming demands of a consequentialist (see, for example, Singer[4]).

Another distinction between deontology and consequentialist theories is that consequentialism permits too much. If only consequences matter, then any action may be acceptable in pursuing the outcomes. An example of these fears is the well-worked transplant example. Imagine that a surgeon has two dying patients, whose lives could be saved by organ transplantation. Some consequentialists would allow (or even demand) the sacrifice of a randomly chosen individual whose organs could save the two (or more) lives.[40] Deontological approaches, in which some actions are impermissible, forbid the taking of an innocent life, whatever the potential gains.

Medical practice, in which doctors are guided or constrained by the guidance provided by the various official bodies, often seems to have a deontological underpinning.

The four principles approach (Beauchamp and Childress)

Beauchamp and Childress[12] developed and popularized the four principles approach, which has become the dominant paradigm in Western medical ethics. The four principles are: respect for autonomy; beneficence; non-maleficence; and justice. These have been considered individually. Although used to the greatest extent in medical ethics these four principles are claimed to underlie a common approach to ethics. As Gillon has it, 'the four principles approach to ethics will be recognized to have far wider moral relevance than its application to health care ethics. Indeed I predict its increasing acceptance as the basis for a global ethics, compatible with and acceptable across the range of the world's moral cultures, sensitively negotiating the delicate path between moral relativism and moral imperialism.'[41]

There are many other approaches that are advocated by their supporters; several have been mentioned already. There is insufficient space to discuss the other approaches in any detail. The important point is that although the four principles may seem to be the only approach, there are other approaches used to analyze the ethics of medicine. Introductions to the other approaches can be found in *Principles of Health Care Ethics*[42] or in the Festschrift edition of the *Journal of Medical Ethics*[43] devoted to methods in ethics.

SOME PRACTICAL MATTERS IN MEDICAL ETHICS

Informed consent

Given the importance of autonomous choice, consent becomes crucial for medical interventions. In an early medico-legal case Cardozo stated, 'Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent, commits an assault'.[44] For significant interventions, consent is usually written, giving proof that a consent discussion

took place (and perhaps in giving a signature the person recognizes a greater significance to the consent discussion) but what is important is the consent of the person – not the signature. Should someone withdraw consent, the document is no longer evidence of consent.

Consent requires a persistent sense of self with personal values, an understanding and knowledge of the available choices, and an ability to reflect on (and judge between) the options, and having done this, to communicate the decision. The person must have sufficient information about the available options. What counts as 'sufficient' information is disputed, but broadly it is the information that would affect the person's choice, recognizing that different factors may be important to different individuals. There is a tension between an attempt to limit the information needed to make decisions easier for those on the boundaries of competence (to prevent people being overwhelmed by information), but also to provide more information (so that people are more fully informed). Consent suggests that the patient agrees to one of the options put forward by the clinician; true respect for autonomy requires negotiation and agreement and is perhaps better described as concordance.

Consent may be modified in various ways. Implied consent is not explicit. An example is when a patient pulls their sleeve up when informed a blood test is needed, though no formal consent discussion has taken place. Another form of consent is assumed consent, where interventions are assumed to have consent. Patients may have been informed by posters or by mailed information. Examples of assumed consent are to the use of data collected for other purposes, and to patients being examined by students. Here assumed consent is often not consent at all, but a lack of resistance or lack of dissent. A further modification of consent is deferred consent. In emergencies, the research subject may be unconscious and so unable to consent, or the intervention may need to be administered quickly allowing no opportunity for an informed consent discussion. Here deferred consent may be used. The question here is: what is the person consenting too when asked later on? Not to the intervention (which has already taken place) but to the use of their information, or to continuing participation in the research, if the intervention is continuing. And if so, then the justification for the research intervention at the time it starts is different from the justification offered by 'true' consent.

Consent is important in medical ethics, but some adults are unable to consent. They will be considered in the next section.

The incompetent adult

Some adults are not competent to make decisions about their own healthcare. The presumption is that adults are competent to make their own choices, but some adults are temporarily (perhaps through drugs or disease), and others permanently incompetent to make their own decisions. All attempts should be made to ensure that a person is most able to make decisions for themselves, perhaps by delaying decisions if there is a prospect that competence may return. If not, decisions are made in a variety of ways, which have been discussed above.

The fact that a patient disagrees with a clinician's proposed treatment does not in itself indicate that the patient is incompetent; a competent patient may disagree with a clinician. However, if disagreement over treatment is likely to harm a patient, then the patient's competence may come into question (though it may not were he to agree with proposed treatment).

Children

Children range from a newly born baby, totally dependent on others, to adolescents on the cusp of competence who may fare perfectly well on their own and so have varied abilities. All are described as children. Not all children are incompetent to make their own medical decisions (in England and Wales this is established as the concept of Gillick Competence[45] and in the United States there is the concept of mature minors).

Children differ from others who are incompetent for a variety of reasons. Children grow towards personhood and the most important achievements of their lives, whereas most adult incompetents fall away from moral personhood: their achievements lie behind them. As well as this, parents play a particularly important role in their child's life that is not matched by the role of relatives of grown adults. Importantly, the way that children are treated will affect, sometimes determining, the adult that the child becomes. Parents are offered broad latitude, though not complete freedom, in the way that they bring up their children.

Young children cannot be taken to be competent. The mainstream approach is that parents consent for treatment that is in their child's interests, and the only treatment that should be offered is treatment that is in the child's interests. But it is not so simple. Firstly there may be dispute about what treatment is in a child's interests (an example is male circumcision, which some will claim is in a child's interests though others deny this). Secondly, sometimes parental authority extends to the refusal of treatment that is unequivocally in a child's interests (the requirement for parental consent for vaccination is an example of this). As children grow older, the approach to medical decisions changes so that the child's views should be taken into account when decisions are taken, but medical decisions are still made by the child's parents. And as children approach maturity, they may be recognized to be competent to make their own medical decisions.

I have already described problems with knowing a person's interests, and because children have the potential to develop in many different ways, one response to this is to claim a 'right to an open future' for children:[34] children should mature with as many life choices as possible. One practical application is that interventions with momentous consequences should (when possible) be delayed until the child is able to make their own decision. But this is not always possible. Cochlear implantation provides an example. Two broad approaches can be adopted for deaf children. Conventionally, deafness is taken to be

a disability. Oralism encourages the use of spoken language. Hearing aids (and now cochlear implants) maximize the child's ability to hear, and are combined with intensive speech therapy. Sign language is banned in some cases, to encourage children to interact with spoken language. Some deaf children, particularly those with some hearing, achieve success with this route, but others, especially those with profound deafness, don't. The second strategy embraces Deaf culture and the Deaf World (with a capital 'D'), encouraging signing and rejecting spoken language. Deaf culture is celebrated. Communication is fundamentally different: imagine poetry in sign language. As a result there are two separate paths for deaf children: oralism or Deaf culture. The earlier a person starts to sign, the better their signing becomes and vice versa. Compounding this, those who have some hearing or use verbal communication may not be taken to be 'properly' deaf and so are excluded from the Deaf community. The reverse may also be true. In deciding how to rear their deaf child, Deaf parents are at some advantage. They have their own experiences, and they may have considered the possibility of a deaf child (and indeed some have chosen a deaf child*). A compounding problem is that the Deaf community may have expectations of the choices that Deaf parents should make (to preserve the Deaf community). Parents of deaf children have important choices to make at an early stage in their child's lives: 'Deaf people in the hearing world are always going to be at a disadvantage. So the question is whether people prefer to be marginal in a mainstream world, or mainstream in a marginal world and many people quite understandably prefer the latter.'[47] And the question must be answered when the child is young. An attempt to keep both options open – a right to an open future – is unlikely to lead to success in either option.

Research

Research is vital to maintain and advance scientific medical practice. Whereas interventions by clinicians are intended to benefit the patient in front of them, the aim of research is to further knowledge. Although research may benefit patients in the future, the advantage may not accrue to individual research participants. There are many examples in medical research, where the new 'better' intervention has worse outcomes than the traditional 'control' therapy (and indeed the point of therapeutic research is to determine which of the tested treatments is better).

Appropriate ethical standards in research are protected by the requirement that research should only take place with the consent of the research participant, and through an extensive system of research governance, policed by the healthcare practitioners' professional bodies (the GMC and the World Medical Association as examples), and the academic journals and universities and hospitals, and (in many countries) by the law. An important principle is that research depends on the consent of the research participant. An influential statement dates from the Nuernberg War Crimes Trial: 'the voluntary consent of the human subject is absolutely essential'.[48] Since then it has generally been accepted that all research should be preceded by consent. Any variation to this requirement requires good reasons (for example, deferred consent may be acceptable in emergency situations where prior consent is impossible). This statement could be taken to exclude research participation by children, but an equivalent for children's participation is generally taken to be the consent of the child's parents and (if appropriate) the assent of the child.

As well as this, there are extensive systems of research governance, professional standards are often reinforced by the law. The Nuernberg standards for research were updated in the World Medical Association's Declaration of Helsinki (and are kept up to date by further revisions). The requirements are broad and include that research is reviewed before it starts, that the research is performed to standards to ensure the scientific validity of the findings, and that research participants are protected (as best they can be) from harm. As part of the review, the risks and benefits of the project to participants are assessed and minimized, and must be proportionate to the benefits of the research. An important part of the review is that patients should be involved in determining research priorities and designing trials.

There are different sorts of research, some involving medical interventions, perhaps with random allocation, some involving patients, but with more trivial interventions and some involving only identifiable information about patients. Different standards may be required for these different forms of research.

Sometimes the boundary between research and audit is unclear. Some projects are clearly research – for example, the random allocation of children to different fluid resuscitation regimes – but some projects are clearly audit – for example, monitoring post-operative mortality or infection rates. The distinction between research and audit is taken to be important because of the rigour of research governance. However, this may not be the important distinction. Merely because an activity is taken to be audit does not mean that it is ethically unproblematic, as audit may produce the same sort of ethical concerns (confidentiality, for example) as research. And the correct response is to recognize that research and audit should be carried out to the same standards.

The distinction between acts and omissions

A common view is that we are more responsible for the consequences of our acts than we are for our omissions. This may be why some believe that it is acceptable not to intervene towards the end of life ('passive' euthanasia) whereas an act to shorten life ('active' euthanasia) is often taken to be wrong. Others do not recognize the distinction between acts and omissions. Consequentialists judge actions by their outcomes, and so hold a person as

* 'A deaf lesbian couple in the United States deliberately created a deaf child. Sharon Duchesneau and Candy McCullough used their own sperm donor, a deaf friend with five generations of deafness in his family, to ensure that their child would be deaf.'[46]

responsible for the consequences that follow from a failure to act as they do for those that result from actions. Rachels seeks to undermine what some see as the clear difference between acts and omissions. He asks us to imagine two uncles. Smith deliberately drowns his cousin in the bath in order to benefit from a large inheritance. In another family, Jones enters the bathroom to drown his cousin (to benefit from an inheritance) to see that his cousin has slipped, is submerged unconscious, and will drown if unaided. Jones merely stands by while his cousin drowns. Rachels asks, 'Smith killed the child, whereas Jones "merely" let the child die … Did either man behave better from a moral point of view?'[49]

Despite Rachels' arguments, there is a strong intuition that we are more responsible for our acts than our omissions. Why is this? It may be that there are other aspects that often go along with the distinction between acts and omissions, but that are separable from it. These include the fact that causation is often stronger for actions. Another difference between acts and omissions is the intention of the person involved. But the moral importance of intention can be questioned and our ability to know another's intention must be questioned.

Perhaps the solution is that the distinction between acts and omissions is blurred. Ethics depends on many overlapping considerations and the distinction between acts and omissions is one, but only one, amongst many factors that need to be evaluated in assessing the morality of an action.

The doctrine of double effect

The doctrine of double effect (DDE) is sometimes invoked towards the end of life, allowing that interventions that may have adverse effects (and so that by deontology's values are *always* forbidden) may be used if the bad results are *foreseen* but not *intended*. The paradigm case is the use of opiates towards the end of life to alleviate pain, whilst accepting that opiates may shorten life (a bad effect is foreseen but not intended). The origins of the DDE lie in Aquinas' justification of murder in self-defence. For the DDE to be applicable, several conditions must be fulfilled: the act itself must be morally good or indifferent; the agent must not intend (but merely foresee) the bad effect; the benefit must not be obtained *by* the bad effect (DDE could not be invoked for euthanasia for a patient in severe pain, as the benefit occurs through the bad effect); and the final condition is that there is proportionality between the bad effect and good effect.

Although these may seem clear conditions, there are several problems with the DDE. How can the outcomes that are 'intended' be distinguished from those that are merely 'foreseen'? The criticism is that the DDE is just sophistry: wordplay allows an unacceptable action to become acceptable.

Rationing and resource allocation

Rationing, or resource allocation decisions, recognizes that there are situations where treatment is not determined solely by the autonomous choice of the patient (or the welfare of an incompetent patient) but that – at times – limited resources must be distributed in some way that is fair.

Resource allocation decisions need to be made at different levels. The highest (macro) level decisions involve decisions at governmental level regarding the total spending on health, and how much allocation within the whole of the health budget should be on geriatrics and how much on paediatrics, amongst many other decisions. The micro-allocation level involves direct clinical decisions at the level of individual patients. So an example would be the decision in a flu epidemic of which of two patients who need intensive care should be admitted to the single remaining critical care bed. There are other resource allocation decisions that must be made between these two levels.

Sometimes these decisions are made by default, or on the basis of historical priorities. In the UK, the National Institute for Health and Care Excellence (NICE) was established so that decisions about NHS resource allocation are made in a consistent and structured way. These decisions may be less pressing when healthcare is purchased and so distributed to those who are able to pay, but even in these systems during periods of limited resources, or excessive demand (such as a flu epidemic), decisions about resource allocation may be needed. There are a variety of ways in which these decisions can be made, none of which are agreed.

Truth-telling, deception, and disclosure of errors

Until recent times, medicine was practised paternalistically: clinicians often deliberately concealed diagnoses and treatments and were certainly less likely to inform patients. There was greater respect for expertise and alongside the power imbalance between doctor and patients, the expectations that patients would be fully informed and (on occasion) even told the truth were lower. But with acknowledgement of the importance of autonomous choice, truth-telling is fundamental to respect for people and consent. Consent is essentially meaningless if it is uninformed.

What then are the circumstances under which a commitment to truth-telling may be undermined? A relatively straightforward justification is when the context is entirely inappropriate. For example, if a clinician is in the supermarket and encounters a patient who asks, 'My tests were okay, weren't they Doc?', the clinician may justifiably dissemble if they weren't, and arrange an early appointment.

Another threat to honest communications comes from patient's relationships. A patient may require that relatives are not informed of a diagnosis, sometimes to 'protect' them. Parents may sometimes not fully inform their children (of the risks of death or the unpleasantness of therapies) and may ask that the clinical team join in their deception. As parents play a fundamental role in the care of a child their requirements may seem reasonable in some circumstances (perhaps with younger children) but may seem wrong in other circumstances (with older children).

With deception, there is always the possibility of inadvertent disclosure by staff who are used to dealing with fully informed patients. The child themself may see they are admitted to the oncology ward and ask what oncology is. Some clinicians may accept a passive role in failing to inform the child but cannot condone a direct lie. The relationship with the child will be destroyed if the clinician isn't honest and the lie is discovered, but the therapeutic relationship with the parents may be destroyed if clinicians refuse to join in the deception. In these situations it is sensible to explore the parent's reasons for withholding information from their child in order that any misunderstandings can be corrected. Many children understand more than their parents believe. Often both parents and child will benefit from the opportunity for a frank discussion with acknowledgement of the reality of the situation.

In a discussion of truthfulness, it is important to acknowledge that there are many steps between complete truth and a deliberate lie. It may be acceptable to fail to mention a complication (if it is rare or of minor importance) but a direct question about the same complication deserves an honest response. Although there is a fundamental commitment to full and honest disclosure, at times, as Higgs (a strong proponent of truth-telling) argues, 'unwavering honesty can seem as pathological as paternalistic concealment'.[50] In these situations a deviation from truthfulness demands explicit reasons.

An important part of truth-telling is that errors should be disclosed to patients when they have happened. This is for several reasons. Firstly, we should treat patients with respect, and this means that they deserve full information. This is how we would choose to be dealt with ourselves. A further reason is that, following medical accidents or an adverse outcome, many patients give their reasons for suing as the fact that no one would tell them what had happened. It is likely that giving patients full information at the time would prevent at least some of the malpractice lawsuits.

Confidentiality/privacy

Confidentiality is the requirement that the information that is disclosed in the course of healthcare consultations should remain confidential to the treating clinical team. This is justified by respect for the patient's autonomy and by the doctor's professional responsibilities and duties. There are also pragmatic justifications that if it were known that clinical teams did not keep information confidential then people would be cautious in disclosing information to clinicians that could be embarrassing or harmful. Without complete clinical information, diagnosis and treatment become more difficult.

Healthcare has become more dependent on technology, which has provided many challenges to confidentiality, with the development of computerized records adding the problems of loss or deliberate hacking of electronically stored information to concerns in confidentiality. As well as this, as healthcare is more often delivered by large teams and as healthcare governance teams extend the number of those who need (or believe that they need) information, the demands in maintaining confidentiality are not as simple as they were in the past.

The right to confidentiality is not absolute and, if there are good reasons, confidentiality may be broken. Situations where it may be appropriate to breach confidentiality include those where there is a threat of harm to the patient or to others. If confidentiality is to be broken, it may be appropriate to negotiate the disclosure with the patient. Where the individual lacks capacity and is incompetent to make choices about their own healthcare, it is likely to be appropriate to disclose information in the patient's interests, but again the disclosure should be negotiated with the patient. The disclosed information should be limited to that which is necessary and no more, and should be to the appropriate authorities.

The threat of harm to a competent individual (and harm only to that person) is unlikely to justify disclosure of confidential information. However, disclosure of confidential information can be justified if there is the prospect of harm to another individual. Again there should be an attempt to negotiate disclosure with the person: they may agree. However, there may be situations where disclosure is justified, even when the person does not agree. Indeed, disclosure of confidential information is sometimes required by law; for example, the Abortion Act (1991) in the UK requires that the name and address of the woman is notified to the appropriate authorities. There are several other statutory obligations in the UK (listed by the GMC).[51]

Clinical ethics committees and consultation

In some situations, clinicians may be concerned about the ethics of a particularly complex clinical situation, or a novel clinical scenario. When ethical concerns appear, what can clinicians do? A first response is to discuss the circumstances and the focus of the concern with colleagues. Even just laying out the problem to another may lead to a solution, but if not, talking through the problem with clinical colleagues may provide a solution to the ethical concerns. Another approach is to consult official guidance and policy. In the UK these include sources such as the Royal Colleges, who oversee education, or the institutions responsible for licensing doctors (in the UK the GMC offers useful advice in pamphlets that are available on its website) and the medical societies (the British Medical Association in the UK, for example, has an ethics department, and the specialist societies often have written guidance and policies). However, the guidance is rarely directly applicable to individual situations and needs to be interpreted in application to clinical problems.

More recently the importance of clinical ethics advice has been acknowledged and clinical ethics has developed as a specialism. Many hospitals have appointed clinical ethics specialists and have established clinical ethics committees.[52] These are often distinct from the longer-established research ethics committees. The committees may have several roles, but one important role is to advise on clinical case consultations. Other roles may involve

policy development, education and the organizational ethics of the hospital. Usually there is a broad representation of healthcare staff on the committee, alongside members from those outside the organization. Specific disciplines that are often included are lawyers and religious representatives such as chaplains or leaders of other faiths. Some committees encourage the participation of patients and their families when considering ethical problems, and indeed it would seem wrong to fail to canvass the opinion of the patients and those close to them.

CONCLUSIONS

In this chapter I have given a brief introduction to medical ethics. Medical ethics is a large and developing field, in which some of the more outlandish claims made by some who are remote from clinical practice may cause clinicians to dismiss medical ethics as irrelevant to clinical practice. This is the wrong response. The correct response when challenged by conclusions that seem to be incorrect is to engage with the arguments that are given, to work out the flaws in the arguments, and so demonstrate the weaknesses of the mistaken claim. It is also useful to rehearse the arguments of one's own position, making sure that these are sufficiently strong. Good arguments for one's own position are insufficient in their own right: if each side has good arguments to support their position, but neither can demonstrate a flaw in the opposing arguments, there is insufficient reason to come to a conclusion. Often it is through the conflict of two claims that a third, more defensible solution is found.

Should the reader wish to study ethics further, several useful texts are given in the reference list. *Medical Ethics and Law: The Core Curriculum*[10] is a sound introductory text. Beauchamp and Childress'[12] book is almost the bible of medical ethics, but advocates strongly for only one approach – the four principles. The second edition of the *Principles of Health Care Ethics*[42] is intimidatingly large, but magisterial and comprehensive. There are several short courses in ethics and many universities have developed Master's level degrees in medical ethics, often combined with law, for further study.

KEY POINTS

- The methods used in ethics generally – and so in medical ethics – are different from the methods of evidence-based medicine.
- Respect for the informed autonomous choice of a patient is a dominant approach in western medical ethics.
- The patient's (and patients') welfare, well-being or interests are an important factor in medical decisions for incompetent patients, children and populations.

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CHAPTER 39a

MEDICAL JURISPRUDENCE IN OTORHINOLARYNGOLOGY

Maurice Hawthorne

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SEARCH STRATEGY

Data in this chapter are based largely on the author's long experience as an expert witness and on landmark legal judgements, some of which are alluded to in the text.

INTRODUCTION

The last two decades have seen some changes in how claims of clinical negligence are decided but the developments in other fields such as consent, confidentiality and clinical performance have been much more significant. The medical profession in general has been put in the spotlight by very major events that were subject to intense media interest. The Bristol Royal Infirmary Inquiry into unacceptable complication rates in the paediatric cardiac surgery unit and the events following the trial of Harold Shipman, who was convicted of murdering an unknown number of his patients, have changed the way that the public views the medical profession. The response from politicians has been to try to tighten the legal framework in which doctors practise so that the public can be reassured that such events can never happen again.

The law differs in different jurisdictions, even within the UK, but most of the principles are the same. The first major subdivision is into criminal law and civil law. In criminal law, the state prosecutes an individual or an organization (the defendant) alleging breach of a law or statute. If the case is proven, the individual or organization is subject to a sentence, often a fine or a custodial term of some kind. In civil law, one individual or organization (now known as the claimant) brings a suit for damages against a defendant and seeks redress from that defendant. Ideally, the damages would exactly redress the loss suffered by the claimant. For instance, a claimant proved to have been swindled out of his car by a defendant might be happy merely to have his car back. In medical negligence cases, it is manifestly impossible to restore negligently caused losses so the damages are monetary. There are three important forms of monetary damages in clinical negligence: general; special; and punitive or exemplary.

General damages are those awarded to compensate the successful claimant for pain and suffering. Special damages are those awarded to take account of loss of income, special nursing needs and so on, arising from the negligence. Punitive damages are exactly what they say they are: damages awarded to the claimant to punish the negligent defendant. These are similar in a way to a fine in criminal cases but are not awarded in clinical negligence cases in the UK where most defendants have insurance to cover any damages awarded against them.

Civil and criminal processes differ in two other important ways: in the standard of proof required and in the influence of statutes. In criminal cases, the standard of proof is 'beyond reasonable doubt', which is often taken to imply a probability of guilt of at least 95%. In civil cases the standard of proof is 'on the balance of probabilities' which means greater than 50% probability. The source of the criminal law is founded in the common law and on statutes passed by Parliament and European law.

Statutes, precedent and European legislation state what actions constitute criminal behaviour. In the course of a criminal trial, counsel may well cite a precedent of what has been said and what decisions were made by courts in the past in similar cases. In a civil trial, there may be no statute that has any relevance to the questions to be decided so the decisions are based almost entirely on what happened in previous cases. This is referred to as the common law. The common law is in a state of continuous development as civil cases are tried by high courts, such as the Court of Appeal and the House of Lords, which can introduce subtle changes in decisions that then become the common law. Much argument may then occur as to what exactly their Lordships meant. Was what they said in a previous case relevant to the one currently being tried? Even more debatable is whether or not the important remark was part of a judgement or some sort of subjunctive aside to the judgement in the form of 'if this case had been similar to case A then I would have decided as follows'. The next section of the chapter (see 'Causation', below) illustrates exactly how one word in a judgement can be important when the case referred to as Bolitho[1] is considered.

Besides major sections devoted to clinical negligence and the duties of an expert medical witness, this chapter examines the two most common issues raised via a medical indemnity organization's helpline: consent and the doctor's duty of confidentiality. The criminal law and the role of the coroner as they are likely to apply to surgeons in their professional activities are discussed. The duties of a consultant surgeon as a doctor and the mechanisms that are or shortly will be in place to ensure that these are complied with are described and the additional duties of that consultant as a trainer are also mentioned.

TORT

Before discussing clinical negligence and consent issues, it is relevant to review the legal principle on which these are largely based. This is the law of tort or wrong done by one party to another. The two forms of tort that are relevant to surgeons are negligence, and assault and battery.

There are four essential elements of the legal tort of negligence:

- there must be a duty of care
- there must be a breach of that duty
- harm must have occurred
- the breach must have caused the harm.

Negligence occurs when party A is considered to owe a duty of care to party B, to have breached that duty and, as a result, harm has come to B. It must be shown that A could reasonably have foreseen that the breach might cause the harm. For instance, a driver travelling quickly on a country road should have it in mind that there might be a cyclist just around the corner. A second important aspect of negligence on which many clinical negligence cases fail is causation. This works on the so-called 'but for' test. It must be proved that, 'but for' the breach of duty by the defendant, the damage suffered by the claimant would not have occurred.

Assault is the threat of physical violence, and battery is any unlawful touching or physical contact of one person by another. Only with consent does a medical examination become lawful. Without consent, approaching a patient with a shining Lack's tongue depressor at the ready is an assault and using it to depress the tongue is a battery. Although the act of opening the mouth probably implies consent, the patient has the option of lodging a civil claim alleging battery or even of reporting a possible criminal battery to the police. It is important to note that civil actions for battery, unlike those for negligence, do not require that there has been any harm. Patients seeking damages for lack of adequate consent can sue either in negligence (where the 'but for' test applies but consent must be truly informed) or in battery (where causation is not an issue but a much less rigorous consent is enough to refute the allegations).

NEGLIGENCE

Standard of skill and care

In deciding negligence the claimant must establish first the four essential elements of tort.

To establish a duty it is necessary for a doctor/patient relationship to be in existence. There is no Good Samaritan law in the UK, and doctors only have a legal responsibility to people they have agreed to treat. In general practice the agreement arises by virtue of accepting a patient onto one's list. In a hospital setting, the agreement arises either out of the doctor's terms and conditions of employment or, with private patients, as a result of contract.

Patients tend to be seen by several different doctors and, therefore, the question 'who owes the duty of care?' may be a pertinent one. In the National Health Service (NHS), the employing authority will usually be named as first defendant as it would be liable to pay damages arising from any successful action by virtue of the principle of vicarious liability. Individual doctors may then be named as subsequent defendants.

An unresolved issue is who should be sued if a patient is placed on a waiting list but suffers additional damage in the time it takes to receive a first appointment. Is the defendant the referring GP, or the authority, or the NHS Trust at whose clinic the patient is awaiting an appointment?

The standard of care is that of the reasonably skilled and experienced doctor. The appropriate test, known as the Bolam (*Bolam v. Friern Hospital Management Committee*) test,[2] states that it is:

> *the standard of the ordinary skilled man exercising and professing to have that special skill. A man need not possess the highest expert skill; it is well-established law that it is sufficient if he exercises the ordinary skill of an ordinary competent man exercising that particular art.*

The standard of care relates to the specialty in which the doctor practises. A GP will not be required to possess the skills of a specialist. An inexperienced doctor cannot rely on his lack of experience as a defence to alleged negligence (*Wilsher v. Essex Area Health Authority*).[3] However, a junior doctor may discharge his duty by seeking the help of a superior.

While a doctor is under a duty to keep him- or herself appraised of developments in his area, this is subject to the bounds of reasonableness. Failure to read one article, which might have prevented the negligent act, could be excusable, while failure to be aware of new techniques that have become widespread may be inexcusable (*Crawford v. Board of Governors of the Charing Cross Hospital*).[4]

A doctor will not be negligent simply because he acted in a way that another doctor would not have done. The Bolam test establishes that a man is not negligent if he is acting in accordance with a practice merely because there is a body of medical opinion that would take a contrary view, provided there is a responsible body of opinion that supports the practice. A body of opinion must consist of at least two people. This statement has recently been qualified by the case referred to as Bolitho (*Bolitho v. City and Hackney Health Authority*).[1]

Causation

In Bolitho, a registrar in paediatrics was accepted to be in breach of her duty of care by failing to visit an infant with breathing difficulties. Her defence was that, given the clinical circumstances at the time she should have visited, she would not have intubated the infant. The Court of Appeal had found that the failure to attend the infant constituted negligence. The House of Lords heard opposite expert opinions, one asserting that there was a body of opinion that would undoubtedly have intubated in those circumstances and the other that there was also a responsible body of opinion that would not have intubated. Their Lordships then reversed the judgement saying that the defendant's assertion that she would not have intubated, a practice supported by a reasonable body of opinion, meant that on the balance of probabilities the brain damage would have occurred even if the registrar had visited. The causal link from the failure to discharge her duty of care by visiting the patient to the harm suffered was therefore broken so no negligence could be proved.

Bolitho is important because it clearly brings Bolam into the field of causation and also because of the dissenting judgement of Lord Browne-Wilkinson. Referring to the reasonable body of medical opinion that would allow a Bolam-based defence, Lord Browne-Wilkinson said, 'The use of these adjectives – responsible, reasonable and respectable – all show that the court has to be satisfied that the exponents of the body of opinion relied on can demonstrate that such opinion has a **logical** basis' (our emphasis). Later in judgement he qualified this by saying, 'it will very seldom be right for a judge to reach the conclusion that views genuinely held by a competent medical expert are unreasonable'. It is not yet clear how these comments will be used as precedents for future cases but they certainly will be. An example might be the practice of stripping all the mucosa from a vocal cord in Reinke's oedema. There may still be a body of expert opinion that would condone the practice but, in view of our knowledge of the physiology of the superficial lamina propria, is it logical to operate in this way and can that body of expert opinion be considered responsible?

Proof of medical negligence

The onus lies upon the claimant to prove that the surgeon's negligent treatment caused the injury. It is not sufficient simply to prove that the surgeon's actions were reprehensible or even reckless if the claimant cannot go on to show that their injury is directly attributable to the surgeon's poor performance. Hence, while it was clear that a casualty officer was in breach of his duty of care when he failed to examine a patient attending his department with the obvious signs of poisoning, there was a complete defence (*Barnett v. Chelsea & Kensington Hospital*)[5] when it was shown that there was no antidote to the poison taken by the patient. This is similar to the reasoning in Bolitho above, although that case was much more complicated than Barnett. In Barnett, it was a straightforward and uncontested statement that the workmen who had accidentally ingested arsenic in their tea were doomed whether or not they received medical attention. In Bolitho the courts had to decide whether or not, on balance of probabilities, the hypoxic brain damage would have occurred even if the registrar had visited the child.

The standard to which the claimant must prove his case is on the balance of probabilities. This means that the claimant must show that his version of events and expert analysis are more likely to be true than those put forward by the defence. If the case for each side is evenly balanced then the claimant will fail. Hence, where a patient suffers a nerve palsy that could equally have been due to negligence, or could have occurred as an inherent risk of the operation even when performed with proper skill and care, the claimant's case will fail in the absence of some item of evidence to tip the scales in favour of negligence (*Ashcroft v. Mersey Regional Health Authority*).[6]

An apparent reversal of the burden of proof can occur where the likelihood of negligence is so obvious that it 'speaks for itself' (*res ipsa loquitur*). In other words, a defendant may find that he is obliged at least to provide an explanation of the patient's injury that is consistent with reasonable care having been taken, even where the claimant has no positive evidence of negligence, where:

- there is no evidence as to how or why the accident occurred
- the accident is such that it would not occur without negligence
- the defendant is proved to have been in control of the situation in which the accident occurred.[7]

The doctrine first evolved in simple personal injury cases concerning falling objects (*Scott v. London & St Katherine's Docks*,[8] *Byrne v. Boadle*[9] and *Pope v. St Helen's Theatre*[10]),

but has obvious attractions to a claimant in a medical case, where there may well be very real uncertainty as to how an injury came about, and where the often unconscious patient is entirely under the control of the medical team. Despite the fact that it is often pleaded, in England the doctrine has more often been conceded than litigated in medical cases, and so its ambit is unclear.[11] In practice the courts are reluctant to apply a doctrine derived from the relatively simple 'bumps and thumps' of stevedoring to the complex issues of causation found in medical litigation. It has been said (*Girard v. Royal Columbian Hospital*[12]):

> *The human body is not a container filled with a material whose performance can be predictably charted. ... because of this medical science has not yet reached the stage where the law ought to presume that a patient must come out of an operation as well or better than when he went into it.*[12]

Thus, as a matter of law, the onus of proving negligence will almost always fall on the claimant, although in cases where there is a strong and obvious inference of negligence from the very facts themselves (e.g. a retained swab (*Mahon v. Osborne*)[13] or where the claimant woke from his anaesthetic with the septic finger still attached and an adjacent one in the bucket[14]) the defence may well find that onus discharged unless they are able to provide some alternative theory, not involving negligence, to answer the claimant's case.

Damages

A claimant having established negligence, and having proved injury as a consequence, the question turns to the assessment of the compensation to be paid. The court must award a sum of money that will, as nearly as possible, put the injured person in the same position as he would have been had he not been injured (*Livingstone v. Rawyards Coal Company*).[15] In some jurisdictions (notably the United States) an element of punitive damages may be awarded. Such an approach has been rejected in England and Wales (*Kralj v. McGrath*)[16] and the rest of the UK for mere inadvertent negligence.

Damages are broadly classified into two categories: general damages and special damages.

GENERAL DAMAGES

These include damages for pain, suffering and loss of amenity. This is the aspect of the claimant's loss that is not ascertainable by a mathematical calculation of economic loss and, in the past, was determined by a jury (*Ward v. James*).[17] Juries were effectively abolished in personal injury trials in the mid-1960s. While the level of general damages will depend on the claimant's circumstances, and the suffering which the particular injury has caused the individual, a general bracket for a particular injury will be determined with reference to awards (adjusted for inflation) from previously decided cases. Obviously, it is impossible to 'compensate' someone for loss of a limb or for a life of continual pain so the awards are essentially conventional figures. As a guide, the current conventional figure for injuries of the utmost severity is between £150 000 and £170 000, and so injuries of lesser significance will be a proportion of that 'maximum'.

SPECIAL DAMAGES

These are the specific 'out-of-pocket' monetary expenses and losses the claimant has incurred up until the date of the trial. These will include loss of earnings, medical expenses, travel costs and the cost of any special equipment consequent upon the injury. Often there will be a claim for losses expected in the future. (Future loss is technically an item of general damages as its assessment is uncertain and it was formerly a matter for the jury to determine. As a matter of practice, the calculation of future loss is inseparable from that of past loss, many of the same arguments rehearsed in both, and one flows naturally to the other.) The amount of money at issue will depend almost exclusively on the particular circumstances of the claimant (*Lim v. Camden Health Authority*),[18] guided by the principle that a claimant should only recover what he has lost as a result of the injury. He must prove that his expenditure was (or will be) reasonably necessary, and that his needs cannot be met more cheaply by other reasonable means.

As a rule, English law seeks to compensate a claimant by way of a single lump sum award. This creates obvious problems where a claimant is likely to remain unemployed or requires continuing care for many years in the future. The only certain result is that the claimant will be either under- or overcompensated, depending on how circumstances unfold. This problem has not been solved, but ameliorated in certain cases. Where a claimant suffers a condition that may deteriorate significantly in the future, rather than receive a small sum to represent the risk, they can apply for an order for 'provisional damages', which leaves it open to the claimant to come back to court at a later date.[19]

In very large claims where the claimant's life expectancy will determine the level of the award, the risk can be borne by an insurance company by the purchase of an annuity. This is known as a 'structured settlement'.

Dealing with medical negligence claims

What happens when a surgeon is sued?[20] The 86th update of The Civil Procedure Rules 1998[21] came into effect on 3 October 2016. They require that, in cases of clinical disputes, a pre-action protocol be followed. This sets procedures and time limits for various stages of the process of being sued. There are also recommendations for Trusts about how they should respond to a claim and what processes should be in place to ensure that they are able to respond in an appropriate and timely way. In effect, the pre-action protocol will penalize a Trust that has such a poor clinical governance structure that it is unable to respond to a claim in a relatively short time.

What the individual consultant surgeon will experience if his patient sues him alleging negligence will differ in

some ways, depending whether the patient was a private patient or an NHS patient. The first stage of the proceedings is the same: the patient, having found some means of financial support for his or her claim against the healthcare provider (a matter outside the remit of this chapter but considerably more difficult than formerly) will request, via a solicitor, release of notes. In private practice, the consultant will need to release these notes himself and is wise to check with his anaesthetist, the private hospital and other doctors involved in the secondary care that they will do the same. The consultant would be most unwise at this stage if he did not inform his medical indemnity organization and seek their help and advice. If the case is an NHS one, the matter must be referred to the Trust's legal department immediately. If the clinical governance system in the Trust is working well, there is a good chance that the events have already been reported to the legal section via an incident form and that contemporaneous statements have already been taken and filed in preparation for a potential claim. Alternatively, the claimant may already have used the NHS complaints procedure so all the statements from that will be available. A Trust is vicariously liable for the actions of its employees and so the legal department should take over all further responses to solicitors and communication with the defendant legal team. Both Trusts and independent practitioners have 40 days to provide the copy medical records and failure to meet this deadline will prejudice any defence.

The potential claimant's solicitors will now obtain an expert report on the medical records with examination of their client, if appropriate, and can decide whether or not the claim has merit. If it has, they will serve a letter of claim on the healthcare provider setting out a summary of facts, the main allegations of negligence, description of injuries and an outline of losses. This may include an offer to settle. The defendant organization or individual must provide a reasoned answer within three months of receipt.

In addition, the defendant's solicitors will be concerned to obtain guidance from experts swiftly and, once received, be able to form an initial view about whether or not the claim is defensible. The assessment of a claim at this stage will be facilitated by recent rule changes that have been made concerning the conduct of personal injury actions, including medical negligence litigation. These changes require that at the time of service of a writ, a claimant must also submit a medical report setting out the claimant's condition and prognosis, together with a Schedule of Special Damages said to result from any alleged negligence. Traditionally, such information was not available until much later in the litigation process. The change has resulted in a defendant's solicitors being able to assess the potential value of a claimant's claim at an early stage. Accordingly, following that initial expert opinion, a settlement can be proposed early in the proceedings on behalf of the otolaryngologist, if appropriate.

If settlement is desired but cannot be negotiated between the solicitors, then the solicitors acting for the otolaryngologist may try to settle the claim by what is known as a 'payment into court'. In making a payment into court, the defendant can make an assessment of the damages that might be awarded in due course at trial, if negligence is established. If the trial judge awards a sum higher than the level of the payment in, the claimant will receive his or her costs in the usual way. If, however, the sum awarded is the same or a lesser sum then, as a general rule, all costs of the action, including the defendant's costs after the payment into court, must be borne by the claimant. The claimant has 21 days to decide whether or not to accept the payment in. Thereafter the costs conservancies will operate. In cases where the claimant is legally aided, this device is of more limited assistance to a defendant. In other circumstances, there may well be a strong incentive to a claimant to accept a payment into court through fear of being prejudiced on costs in this way.

Following the service of a defence, in response to allegations contained in the statement of claim, both parties may raise requests for further information about their respective pleadings, and the claimant may choose to file a reply to the defence.

Directions concerning the conduct of a claim will be given by the court, usually after the pleadings are completed. In the High Court, a formal hearing will take place to consider these directions, but in personal injury actions brought in the County Court, a series of so-called automatic directions is given by the court. These are rarely, if ever, appropriate in medical negligence cases and it is therefore usual for the parties to apply to the court for specific directions to be given. These directions will provide for, among other things, the disclosure of witness statements as to fact and expert reports. It is usual for witness statements to be disclosed, followed shortly thereafter by expert reports, in order that experts can consider this information available from the other side in preparing the report. The exchange of both statements and reports gives a further opportunity for review of the case, both by claimant and medical defendant. At this stage the claimant may realize that the claim is weak and the case may be discontinued. Equally, the defence may feel that the case is not defensible and settlement negotiations or a payment into court may follow.

TRIAL AND PREPARATION FOR TRIAL

If the exchange of witness statements and expert reports does not promote the settlement of a claim, then the case proceeds towards trial. In medical negligence actions, a fixed date for trial will usually be given by the court because of the significant number of clinicians who may have to make themselves available, either as experts or as witnesses of fact.

By way of preparation for trial, both parties should arrange conferences with counsel in order to review the case in detail, and ensure all preparations are complete. If the defence considers that the case should be settled, or there are certain aspects of the case where a defendant may be vulnerable, a payment into court may be made. The payment in may be limited to those aspects of the claim where the defendant could be found liable. The claimant has 21 days within which to accept the payment in before the penalty of costs starts to run. As a significant

proportion of the costs of an action result from the trial itself, the defendants are usually anxious to make any payment into court before 21 days in advance of the trial. Thereafter bundles of documents must be prepared for use in the court by all parties, which will include the pleadings, medical records, witness statements and expert reports.

A proportion of cases are settled literally at the doors of the court, the last opportunity for compromise before further significant costs of trial are incurred.

If no compromise can be reached, the trial will commence with an explanation of the case to the judge by counsel for the claimant, setting out the relevant events and the nature of the allegations. The claimant's counsel will then call witnesses of fact, usually followed then by expert witnesses. Each witness will be cross-examined in turn by the defence, and then re-examined by claimant's counsel if necessary. When the claimant's evidence has been called, the defence case is then put in the same way, and usually in the same order.

The trial judge may allow variation in this order of evidence, particularly in complex cases, so that witnesses for both sides are called first, to be followed then by experts. This will allow experts to hear all the evidence of fact before giving a final opinion. However, the present arrangements for disclosure of witness statements make such variation rare.

At the conclusion of the case, the judge will usually hear submissions from counsel on the law to be applied and the appropriate level of damages to be awarded if the claimant is successful. It is usual then for the judge to reserve judgement, to be delivered at a later date, as most negligence cases are complex and will require some consideration. Once judgement is given, and if the claimant is successful, the judge will indicate the level of damages to be awarded. Only at that stage is the judge informed about any payment into court that may have been made, and the costs to be awarded can then be considered.

FUNDING OF NEGLIGENCE CLAIMS

Otolaryngologists may well have been concerned at the possibility that medical negligence actions in England and Wales will follow the pattern of the United States, and that the perceived increase in the number of actions here may continue. However, with the reduction in the eligibility for legal aid, many actions that would have been funded by legal aid in the past will now have to be funded privately. The introduction of contingency or conditional fees is unlikely to assist all those who are no longer eligible for legal aid. As an incentive for the claimant's solicitor, the conditional fee system[22] will allow the solicitor to claim twice the rate of fees they might have otherwise obtained in a successful action. There is a risk that the solicitor might receive no payment at all if the case is unsuccessful. As suggested above, solicitors acting for patients are therefore likely to take on fewer claims,[23] concentrating on those where liability is obvious and can be quickly established. The result is likely to be that there will be no significant increase in the number of medical negligence actions in the short term. Indeed, it is possible that there will be a reduction at the expense of patients who might otherwise have had successful claims for compensation.

The *NHS Litigation Authority 2015/2016 Annual Report*[24] stated that the number of new clinical negligence claims received that year had fallen by 4.6% from 11 497 to 10 965. Damages paid out that year to patients rose from £774.4 million to £950.4 million. That is an average pay out to patients of £86 675 per claim. The provision set aside to pay agreed and estimated future damages is £56.4 billion with 75% of it due to be paid in 2021 and beyond.

DUTY OF CANDOUR

The Health and Social Care Act 2008 (Regulated Activities) (Amendment) Regulations 2015[25] extend the fit and proper person requirement for directors and the duty of candour to all providers from 1 April 2015. Regulation 20 defines what constitutes a notifiable safety incident for health service bodies and all other providers (such as primary medical and dental practices, adult social care and independent healthcare providers). Specifically, paragraph 8 defines the harm thresholds that trigger the duty of candour for health service bodies. Paragraph 9 defines the thresholds for all other providers.

The introduction of Regulation 20 is a direct response to recommendation 181 of the Francis Inquiry report into Mid Staffordshire NHS Foundation Trust,[26] which recommended that a statutory duty of candour be introduced for health and care providers. This is further to the contractual requirement for candour for NHS bodies in the standard contract, and professional requirements for candour in the practice of a regulated activity. In interpreting the regulation on the duty of candour we use the definitions of openness, transparency and candour used by Robert Francis in his report:

- Openness – enabling concerns and complaints to be raised freely without fear and questions asked to be answered
- Transparency – allowing information about the truth about performance and outcomes to be shared with staff, patients, the public and regulators
- Candour – any patient harmed by the provision of a healthcare service is informed of the fact and an appropriate remedy offered, regardless of whether a complaint has been made or a question asked about it.

This does not mean that a consultant should immediately give his version of an adverse event to a patient or relative. It does mean that the consultant should report the adverse event using standard reporting facilities within his Trust. This then allows the adverse event to be thoroughly investigated, after which the truth can be shared with the patient and their relatives. There is an inherent risk in relatives getting only a partial truth or inaccurate information should there be an immediate 'knee-jerk reaction' to tell the patient what has gone wrong. This does not mean, though, that the patient should not be told that an adverse event has occurred and is being investigated.

CONSENT

Much medical litigation is caused by the practitioner's failure to disclose adequate information about the risks inherent in a given procedure. Common law recognizes the principle that every person has the right to have his or her bodily integrity respected. There is a presumption that a person should not be exposed to risk unless he has voluntarily accepted that risk, based on adequate information and adequate comprehension.

Obtaining consent to carry out an operation is necessary to avoid three sorts of legal jeopardy. The first and second arise because any touching of another person is a potential battery. (Assault is the threat of causing physical injury. An unconscious person can be battered but cannot be assaulted.) This means that, in very exceptional circumstances, a surgeon performing an operation without consent may be prosecuted in the criminal courts for alleged criminal battery. A more likely outcome of such surgery is a civil case seeking damages for the tort (or wrong) of battery. There is no need to show that anything went wrong with the surgery, merely that it was carried out without valid consent. The third, and much the most likely legal outcome regarding consent, is that the claimant tries to show that he was not warned of the risks of a proposed therapy that resulted in harm and that, had he been warned of those risks, he would have refused the treatment. An example might be a patient with a dead ear after a competently performed stapedotomy who was not warned of that risk before surgery. He may well be able to claim damages from the surgeon because he can say that 'but for' the surgeon's failure to warn of the risk, he would not have undergone the surgery. It is immediately obvious that any careful surgeon must record what potential adverse outcomes of a proposed operation have been discussed with a patient. If it is not recorded in the notes, courts have become sceptical of a statement such as 'it is my usual practice to warn of these risks'.

The question of how much information must be given to the patient would vary from situation to situation, but was generally set by the professional standard according to the Bolam test, with doctors being arbiters of how much information should be given. This meant that, in the example above, if the defendant surgeon could assemble a responsible body of opinion whose practice would not be to warn of the risk of dead ear, his conduct did not breach a duty of care.

This was modified to a degree by the case of Sidaway (*Sidaway v. Board of Governors of the Bethlem Royal Hospital*)[27] in which the House of Lords held that where the proposed treatment involved a substantial risk of grave or adverse consequences such that, notwithstanding any practice to the contrary, a patient's right to decide whether to consent to the treatment was so obvious that no prudent medical man could fail to warn of the risk (save in emergency or some other sound clinical reason for nondisclosure), then it would be negligent not to warn. To continue the example above, the claimant could argue that total deafness in one ear is such a disability that any reasonable patient would wish to be told about it pre-operatively.

Accordingly, the right of the doctor (acting in accordance with a reasonable body of medical opinion) to decide what the individual patient should be told remained enshrined in English case law. Such medical paternalism, which may be in the best interest of some of our patients, is currently and repeatedly being questioned. The doctor should realize that in Sidaway when the question 'Is informed consent a part of English law?' was put to the five law lords, the answer was not unanimous. Scarman said 'yes'; Diplock said 'no'; and Bridge, Keith and Templeman said 'yes with reservations'.

In assessing which material risks should be mentioned, doctors should consider the degree of probability of the risk materializing and seriousness of possible injury if it does. A risk, even if it is a mere possibility, should be disclosed if its occurrence would cause serious circumstances (*Hopp v. Lepp*).[28] Medical evidence will be necessary for the court to assess the degree of probability and the seriousness. A further medical factor upon which expert evidence will also be required is to assess the character of the risk; that is, is this risk common to all surgery or is it specific to the particular operation? Special risks inherent in a recommended operation are more likely to be material.

The legal standard of disclosure required in response to direct questions is also set by the professional standard (*Blyth v. Bloomsbury Health Authority*).[29] Although the amount of information given must depend upon the circumstances, as a general proposition it was governed by the Bolam test (supra).

In Australia, the doctrine of informed consent went one stage further from Sidaway where the reasonable patient was considered the arbiter of what risks should or should not be disclosed pre-operatively. In *Rogers v. Whittaker*,[30] it is clear that the risks that must be disclosed are those that affect that one patient and not the generality of reasonable patients. To take the stapedotomy analogy one last stage further, few surgeons would warn of a dead ear risk of 1 in 2000 operations and probably the reasonable patient would be unlikely to want to know that this was a complication as it is so unlikely. The question arises of whether the patient having that operation on an only hearing ear might view the risk differently and want to be aware of it in making a decision.

In 2004, the issue of consent moved further in the patient's favour in the case of *Chester v. Afshar*.[31] In this case whilst the injury occurred despite a competent surgical technique, the claimant argued that had she known about the risk she would have taken time to consider the risk that would have resulted in the surgery occurring at a different time and therefore the adverse outcome would not have occurred in this spinal surgery case.

Montgomery v. Lanarkshire Health Board[32] heard in the Supreme Court in Scotland in 2016 has now shifted the requirements of what a patient should be told to 'what a reasonable person would expect to be told'. The claimant alleged that had she been told that there was a significant risk of shoulder dystocia resulting from a vaginal birth that occurred in 1999 she would have elected for a caesarean section. The law lords found unanimously in favour of the claimant, effectively ending the era of

Bolam applying to consent. This has now enshrined in law the principles laid down in the 2008 GMC guidance, *Consent: Patients and Doctors Making Decisions Together*.[33]

Who can give consent?

There are three categories of patient described in the Department of Health's reference guide to consent for examination or treatment: the adult with capacity to consent; the adult without capacity to consent; and children and young people.

CHILDREN

Section 8(1) of the Family Law Reform Act 1969 provides that a person over 16 may give a valid consent to medical treatment as though he was an adult. As regards children under 16, the general principle is that laid down in the Gillick (*Gillick v. West Norfolk and Wisbech Area Health Authority*) case,[34] that the parental right to determine whether or not a child under 16 should have medical treatment terminates when the child achieves a significant understanding and intelligence to enable him or her to understand fully what is proposed. Until such time, the parents, or others acting *in loco parentis*, may give their consent or refusal to medical treatment. Recent case law suggests that it may still be possible to treat a seemingly competent child who is refusing to give consent, providing someone else with the capacity to consent provides consent on the child's behalf (in Re R, and in Re W).[35, 36]

MENTALLY INCOMPETENT PATIENTS

Where a patient is unable to provide consent on his or her own behalf by reason of mental incapacity, no one else, including a court, may give consent on that person's behalf. The doctrine of necessity, however, permits a doctor to lawfully operate on or give other treatment to adult incompetent patients, provided that the treatment is in their best interest, either to save their lives or to ensure improvement in their physical or mental health (Re F).[37] However, mental illness does not mean mental incompetence as was tested in the case of Re C (1994),[38] a paranoid schizophrenic held at Broadmoor, when he refused consent to have a gangrenous leg amputated despite the wishes of his managing medical team.

The Mental Capacity Act 2005 sets out five principles on which the legal requirements are based. The principles are:

1. A person must be assumed to have capacity unless it is established that they lack capacity.
2. A person is not to be treated as unable to make a decision unless all practicable steps to help him or her do so have been taken without success.
3. A person is not to be treated as unable to make a decision merely because he or she makes an unwise decision.
4. An act done or decision made, under this Act for or on behalf of a person who lacks capacity must be done, or made in his or her best interests.
5. Before the act is done, or the decision is made, regard must be had to whether the purpose for which it is needed can be as effectively achieved in a way that is less restrictive of the person's rights and freedom of action.

That a person has been judged to lack capacity in relation to a previous decision regarding their care does not mean that they lack capacity to make decisions in all situations. Capacity of an individual to make decisions should be made on a situation-by-situation basis. Capacity can vary with the nature of the decision and may change over time.

Understanding what constitutes acting in the best interests of a patient who lacks capacity can present challenges as to what the person's best interests are. Section 5 of the Mental Capacity Act 2005 states that 'An act done or decision made, under this Act for or on behalf of a person who lacks capacity must be done, or made in his best interests'; and that 'As long as these acts or decisions are in the best interests of the person who lacks capacity to make the decision for themselves, or to consent to acts concerned with their care or treatment, then the decision-maker or carer will be protected from liability'.

In deciding the best interests of a person lacking in capacity the ENT surgeon should:

- encourage the patient to take part in the decision-making process and take all reasonable steps to improve their ability to be involved in making the decision
- identify, as far as possible, all factors that patients lacking capacity would consider, were they to decide for themselves
- make all reasonable efforts to establish the patient's views including past wishes, beliefs, behaviour, decisions and values (e.g. religious, moral, political cultural or personal) and any other relevant factors that may have a bearing on their best interests; reasonable efforts include talking to family members and, where appropriate, seeking the support of an individual mental capacity advocate
- avoid making assumptions on a person's interests based solely on factors such as age, race, gender or condition
- decide whether the person may regain capacity at a later time and, if so, whether the decision can be safely delayed till this is possible
- never be motivated in any way by a desire to bring about the death of the person without capacity in decisions concerning life-sustaining treatment
- remember that the person who lacks capacity has a right to privacy and dignity and so it may not be appropriate to share all information with everyone involved in their care or those related to them through family ties.

JEHOVAH'S WITNESSES

Certain groups of patients, including Jehovah's Witnesses, may refuse to receive blood transfusions or other life-saving therapies. The Court of Appeal has affirmed patients' rights to refuse medical treatment, even if this will result in

their death; nevertheless, for such a refusal to be effective, the court must be satisfied that at the time of refusal the patient's capacity is not diminished by illness or medication or given on the basis of false assumptions or misinformation. In the case of Re T,[39] Lord Donaldson said:

> *An adult patient who suffers from no mental incapacity has an absolute right to choose whether to consent to medical treatment, to refuse it or to choose one rather than another of the treatments being offered.*

A decision to refuse medical treatment does not have to be sensible, obviously rational or well considered, and in the case of a competent patient, the doctor cannot override the patient's wishes because he believes it to be in the patient's best interests.

OTHER SPECIAL GROUPS

Pregnant women, patients who are human immunodeficiency virus positive or suffering from acquired immunodeficiency syndrome and the elderly do not represent special categories for the purposes of consent. Although the amount of information that has to be given to a patient varies from case to case, a decision to withhold information solely on paternalistic grounds that it may deter the patient from accepting the therapy is not justified in law.

CONFIDENTIALITY

Doctors are well aware of their duty of confidentiality, originally stated in the Hippocratic oath. What is often not appreciated is the common law and statutory basis of this duty and the circumstances in which confidential information may legally be revealed. There is a common law duty placed upon professionals to guard confidential information. A patient may sue a doctor through the civil courts if there is alleged to have been damage as a result of breach of confidentiality. The Data Protection Act (1997) places a statutory duty on anyone who holds patient identifiable data (in any form) to guard and release that information under strict controls. Any surgeon who keeps any sort of patient identifiable information at his residence (where his employer's blanket registration under the act will probably not apply) and who is not registered with the data commissioner breaches the provisions of the Act. It is particularly important to note in this context that, if disclosure is properly requested, it is an offence to fail to disclose **all** of the records, both computerized and manual.

The second statute that obliges surgeons to care for information appropriately is the Human Rights Act (1998). This enshrines in UK law the sixth clause of the European Convention on Human Rights granting citizens an absolute right to privacy and to family life.

There are a number of instances in which confidential information can be released. The first is with the consent of the patient. This is sometimes implied consent such as applies when a GP releases confidential information in a referral to a consultant (and so to both secretaries). On other occasions, there needs to be expressed consent, for instance in release of information to insurers when a holiday must be cancelled. Sometimes a doctor is obliged to release information. The statutory examples concern the Terrorism Act 2000 and its successors such as the Terrorism Act 2006, the Counter-Terrorism Act 2008, the Abortion Act 1967 and the infectious diseases regulations. A court has power to require disclosure of records and there are several cases where disclosure is appropriate in the public interest. These are to protect the rights of others, such as reporting to prevent or detect serious crime or to prevent suspected child abuse and in reports to the Driver and Vehicle Licensing Authority. In all cases of this nature where the disclosure is not governed by the Data Protection Act, the information released must be no more than that necessary to comply with the public duty. A surgeon with any doubt as to how to resolve the conflict between duties of confidentiality and the public interest is well advised to consult his or her medical indemnity organization and to ensure that the final decision is one with which a responsible body of medical opinion would concur (Bolam).

The situation after the death of the patient is different. Doctors have a duty to disclose on death certificates and to national confidential enquiries as well as to the police and courts, especially the coroner. Data protection no longer applies and the relevant statute is the Access to Health Records Act 1990. This clarifies that executors or, failing them, next of kin can consent to release of medical records. It appears that anyone with a legitimate claim to view the record can see that part of the record that is relevant.

THE CORONER

The Coroners and Justice Act 2009 was implemented in 2013 and saw a change in the coroner service in the UK. Going forward, newly appointed coroners now have to be legally qualified. The Act also created the post of the Chief Coroner. The coroners' service remains a local service funded by the local authority and provides a service to the local community. There has been a dramatic reduction in the number of inquests still open after a year and it has been proposed that a system of medical examiners be introduced, which is likely to reduce the number of deaths reported to the coroner's office.

When the coroner is mentioned, most doctors ask three questions: What deaths must be reported to the coroner? What verdicts can be brought and will these criticize the doctor? And what must I do if required to write a report for or appear before the coroner?

The following must be reported to the coroner:

- violent or unnatural death
- death in custody (even if the prisoner was licensed on leave to attend the hospital)
- death where no doctor is able to issue a death certificate.

Most jurisdictions also have local agreements about the reporting of deaths within a certain period after hospital

admission and after surgical procedures. Coroners usually wish to know about deaths from notifiable diseases and industrial diseases, and deaths of those in receipt of war pensions.

The range of verdicts that the coroner can return is limited. The coroner's court (in theory at least) is not adversarial and no finger of blame should be pointed by the court. The coroner's remit is to establish the identity of the deceased, the time and place of death and the mode of death. Although death due to gross neglect is an acceptable verdict, death due to negligence is not. In practice, of course, the family of the deceased and their lawyers may use the proceedings of the coroner's court to assess whether or not an action in negligence is likely to succeed.

What about the surgeon called upon to provide a report to the coroner? The first piece of advice would be for the surgeon to contact his or her defence organization for support. The report itself should be factual, full and directed to a non-medical audience. The report should not contain opinion but just facts. In particular, a report to a coroner should never contain the words 'negligent' or 'negligence'. Not only are these a matter of opinion and not fact, but they also have special well-defined meanings for lawyers that may not be apparent to doctors.

In most cases, the report will be all that the coroner needs and the doctor will not be required to appear. If the coroner feels that the evidence that the doctor can give may be crucial to his investigations, then he will summon the doctor to the inquest. Sometimes the family of the deceased will see this as their opportunity to confront the doctor, who they see as the source of their grief. To be fair, sometimes the process works well, the family see that the doctor is not some kind of ogre and the resentment fades. Even if this does not occur, the coroner should ensure that the family do not persecute the doctor and that the proceedings remain directed towards establishing the who, when, where and how but not why the deceased perished.

If the doctor anticipates a difficult inquest, he may be accompanied by legal assistance but the solicitor may not answer for him and there is no cross-examination of the other side. Defence organizations can advise the doctor but there is always a risk that the presence of a legal advisor will make the family (and the coroner) suspect that some sort of cover-up is being attempted.

Doctors summoned to the coroner's court need to follow the usual rules of court appearances – dress smartly but conservatively and do show appropriate respect to the coroner. Bring the notes or fair copies and copies of the reports already supplied and read them through before the case opens. Remember that the doctor is a witness and not an advocate or defendant and so there is no problem in asking for a question to be repeated or for a pause while the notes are consulted before answering.

THE ROLE OF THE EXPERT

An expert medical witness is instructed by either the defence or the claimant to give his or her opinion on the medical matters pertinent to the case to the court. This evidence is different from that of a material witness who is asked for the facts. The expert's job is to interpret the facts for the court. In simple terms, it is 'to give impartial advice and opinion'. Many otolaryngologists will be called upon to give expert opinion on personal injury cases where neither the claimant nor the defendant is a clinician. The many reports on noise-induced hearing loss that have been written by otolaryngologists are a form of written expert testimony in just such personal injury cases. A few otolaryngologists will be asked to prepare reports that assist courts in deciding clinical negligence claims and the special circumstances that pertain to these are discussed below.

Until the Civil Procedure Rules 1998 came into force, experts were retained by either the claimant or defendant's side and to some extent this remains the case. In theory, an expert's report would be the same whether he was instructed by the solicitors of the claimant or those of the defendant. The 1998 Rules have made it clear that the duty of an expert, whether he is expecting to be paid by the defendant or by the claimant, is to produce for the court an unbiased opinion. The 1998 Rules encourage a court, where practical, to appoint a single joint expert to produce such an opinion. They also give direction about exchange of reports, communication between and with experts and the expert's right to ask the court for directions.

In practice, the expert's evidence is usually contained in a report and it is rare for an expert to have to appear in court. The form and content of an expert report were previously based upon a well-known civil case.

In the Ikarian Reefer (*National Justice Compania Naviesa SA v. Prudential Assurance Company Ltd, The Ikarian Reefer*),[40] Mr Justice Cresswell stated that he considered that a misunderstanding on the part of some of the expert witnesses had taken place concerning their duties and responsibilities which had contributed to the length of the trial. Although this was a shipping case, the seven duties and responsibilities laid down have equal validity for medical experts:

1. Expert evidence presented to the court should be, and should be seen to be, the independent product of the expert uninfluenced as to form or content by the exigencies of litigation.
2. Independent assistance should be provided to the court by way of objective unbiased opinion regarding matters within the expertise of the expert witness. (An expert witness should never assume the role of advocate.)
3. Facts or assumptions upon which the opinion was based should be stated together with material facts that could detract from the concluded opinion.
4. An expert witness should make it clear when a question or issue fell outside his expertise.
5. If the opinion was not properly researched because it was considered that insufficient data were available then that had to be stated with an indication that the opinion was provisional. If the witness could not assert that the report contained the truth, the whole truth and nothing but the truth, then that qualification should be stated on the report.

6. If after exchange of reports an expert witness changed his mind on a material matter then the change of view should be communicated to the other side through legal representatives without delay and when appropriate to the court.
7. Photographs, plans, survey reports and other documents referred to in the expert evidence had to be provided to the other side at the same time as exchange of reports.

More recently, the Civil Procedure Rules have modified these directions. The expert should obtain the Civil Procedure Rules Chapter 35 and read sections 1.1 to 1.6, which is too extensive to reproduce here.

Before writing a report the expert should be aware of what the solicitor requires. Reports usually refer to one or more of the following six areas:

1. An initial statement on the possible merits of an allegation for a claimant before notes and other evidence are obtained
2. Liability
3. Causation
4. Current condition
5. Prognosis
6. Expert opinion on an area of medicine.

A quote should be given on the cost of the report in advance. Lawyers may have no concept of the cost in time and research to answer what to them may be the simplest of questions. The solicitor will not be pleased to receive a report of 100 pages with detailed bibliography costing £2000 when the damages sought are only £500 for a relatively minor event.

The report should be double spaced and typed on A4 paper. Each sheet should have the name of the claimant or defendant typed in the top right-hand corner and be separately numbered. It is also helpful to number the paragraphs. The names of the parties should be stated, as should the requesting solicitor or insurance company. It is inadvisable to use the word 'negligent' in the report. Negligence may be implied by using phrases such as 'falling below an acceptable standard' or 'followed a course of action that could not be supported by any body of medical opinion'. Phrases such as 'reckless action' or 'flagrant disregard' may have a special meaning and lead to criminal charges rather than a civil case.

There is always the possibility that the credentials of the expert will be tested in court. It is extremely unwise for the expert to step outside his field. Should he be forced to comment outside his field of expertise he should add the rider that he is speaking only as an average medical practitioner. The expert will need to be *au fait* with up-to-date research in his own field.

The medical expert in clinical negligence

The medical expert retained in a case of medical negligence is usually asked to elucidate the areas of medical contention within a case. He needs to be aware of the various views on current practice, even if these views are held by a minority of doctors, provided always that the minority is a reasonable one and that the practices supported are logical (Bolitho). Although the temptation is to be an arbitrator of medical colleagues, in court, this is the province of the judge. Nevertheless, the expert will be asked to comment as to whether the claimant's complaint has merit. When acting for the defence the expert will inevitably come across cases where defence is impossible. Here it is the expert's duty to advise that a speedy settlement be made to the aggrieved patient. This will have the secondary benefit of avoiding a colleague's professional shortcomings being exposed to public criticism in court. Rarely, some doctors expect their colleagues to defend them whatever the circumstances. Hence, being an expert can lead to criticism or alienation by colleagues.

Medical negligence cases can take an inordinate amount of time. Not only may the expert have to inspect all the records, examine the claimant and prepare reports, he will have to do research, attend meetings with solicitors and counsel and attend court. A single case may, in unusual circumstances, take up to 100 hours of time or more. The expert should never take on a case if he cannot afford the time.

Subsection 1.6 of the practice direction requires that experts comply with the relevant approved expert's protocol. As might be expected, there is a detailed pre-action protocol for the resolution of clinical disputes. Although this is aimed primarily at the legal profession, it is required reading for any doctors involved in providing expert testimony in clinical negligence cases. In particular, the times allowed by the court for the completion of various stages of the claim and the defence are clearly stated.

The doctor as an expert witness in court

The purpose of expert opinion given in court is to persuade the judge that one side of a case has greater merit than the other. This does not mean that he should ignore inconvenient facts which mitigate against his argument. In persuading the judge, the expert should be seen to weigh up all the facts both in favour of his view and those in favour of an alternative view. Then he should give the reasons why the judge should favour one interpretation of the facts over another. It is the judge who will decide between the two sides of the argument. The expert should not be tempted to usurp the role of the judge for this may do untold damage to his own side or at the very least earn a rebuke which may undermine his confidence.

In court, the expert should wear conservative clothes. Evidence should be given in a straightforward, unequivocal manner. A personal view may be represented especially in response to a direct question but should always be tempered with information about acceptable alternative practice and opinion. He should always be prepared to concede points if it is appropriate to do so, and not to adhere rigidly to one view when that cannot be sustained. The expert often has difficult concepts to convey to the judge. The expert should not hesitate to use pictures, models or even video to illustrate a point but should avoid being seen as a flamboyant 'show off' lest he discredits himself by not giving due respect to the court.

The usual course of examining a witness in court is that the barrister for the side calling the witness will examine that witness and try to anticipate and pre-empt difficult questions from the other side. Counsel for the opposing side will then cross-examine the witness and may attempt to undermine the evidence given by the expert or the standing of the expert in his profession. Above all, the expert must not see this as a personal insult lest he should lose his temper and hence his dignity. After this potentially hostile cross-examination, the first barrister is permitted to re-examine the witness and try, if necessary, to restore the faith of the judge in that witness.

PERFORMANCE AND COMPLAINTS

Besides using the legal system to sue a surgeon in tort, patients have recourse to a number of mechanisms to resolve concerns about how they have been treated or managed. Some of these mechanisms have the potential to involve doctors in disciplinary or performance investigations so the two elements are considered together. A patient or a family unhappy with the outcome of a surgical process can of course sue in the tort of negligence but this is expensive and will succeed in only a few cases. Another option is a complaint to the Trust employing the surgeon. Trusts are obliged to have a complaints procedure and the patient is entitled to a prompt reply from the chief executive. In practice, the time limits are so tight that, especially when the complaint is a complex clinical one (rather than the more usual gripes about hospital food or parking for visitors), the first reply is a letter of acknowledgement. Following this the complaint should be answered point by point with an apology if appropriate. The chief executive must report to the complainant what action has been taken. Among the possible actions are Trust disciplinary procedures or referral of staff to their regulatory body. If this is rejected by the patient then the patient may request that the Health Service Commissioner investigate the complaint. This officer, also referred to as the ombudsman, can review the decisions made by the Trust. There may also be grounds for appeal to the ombudsman if there are problems with the terms of reference or the conduct of an independent review.

If the investigation of a complaint leads to further investigation of the conduct or performance of a doctor, there are a number of forms that this can take. One is an internal investigation by the doctor's Trust. Although there are regulations that govern the conduct of such investigations, there is such a variety of approaches that this chapter cannot be dogmatic. It is clear that a Trust must not unjustifiably suspend a doctor pending investigation and then drag its heels in the investigation. There may well be a case against the trust under the Human Rights Act (1998) and the doctor is probably best advised to consult his or her defence organization.

Two NHS organizations may put a doctor's reputation or right to practise in jeopardy. These are the National Clinical Assessment Service (NCAS) and the Care Quality Commission (CQC). The NCAS, which has been part of the NHS Litigation Authority since 2013, will deal with concerns about the performance of individual doctors by investigating problems and arranging performance assessments where necessary. Memoranda of understanding have been agreed between the NCAS and both CQC and the GMC as well as some of the medical Royal Colleges so it is clear that a suggestion of deficient performance or conduct uncovered by one of the three organizations may well be reported to the other two.

The organization that these newer groups feed to and that has disciplinary control over doctors in the UK is the General Medical Council (GMC). This organization has a statutory duty to maintain standards and ensure that doctors registered with the GMC do not endanger the public. The GMC is bedevilled by lots of committees with similar acronyms but there are basically three routes through the system. The first stage is usually the reporting to the GMC by a Trust, by a member of the public, by another doctor or the NCAS.

Increasingly, the GMC is looking at reports in the media that suggest poor performance or conduct, and is initiating proceedings on the basis of these. The complaint is screened and the decision made to reject it at this stage or to refer it on for investigation. The screener decides which of the three routes – health, conduct or performance – is the most appropriate. More than one route may be pursued.

In 2012 the adjudication process was split off from the GMC and delegated to the Medical Practitioner's Tribunal Service (MPTS). If the screener at the GMC feels that the allegations against a doctor are serious or pose a threat to patient safety the doctor's case can be brought before the Interim Orders Tribunal, which can temporarily suspend or restrict a doctor's registration whilst the allegations are investigated or a performance assessment undertaken.

Health procedures are aimed at rehabilitating a doctor whose illness is affecting his or her work. The four stages of the process are: initial assessment; medical examination; then decision by two case examiners, one medical and one lay.

The performance procedures apply where there is 'a departure from good professional practice … sufficiently serious to call into question a doctor's registration'. Referrals are examined and the doctor is likely to be asked to have a performance assessment. If he or she refuses, the Interim Orders Committee of the MPTS may order an assessment. Two case examiners consider the outcome of the assessment process.

After an investigation of a doctor's conduct, health or performance assessment the case examiners will: decide that no further action is required; agree undertakings with the doctor such as counselling, training, or that restriction of practice are required; issue a warning; or decide that the case is so serious that referral to the MPTS is required (this is also the case if the doctor has refused assessment). A Medical Practitioner's Tribunal can leave a doctor's registration intact, impose conditions, suspend or erase. A Medical Practitioner's Tribunal hearing is, to all intents and purposes, a court of law with a panel, advised by a legal assessor, sitting in judgement. The GMC and the doctor can be represented by barristers if necessary and, unlike the health process, the tone is adversarial. Formerly,

outcomes of all three processes could be appealed to the judicial committee of the Privy Council but now appeals are heard by the High Court.

Recently, the government has established the Professional Standards Authority. If it is felt that a decision of the GMC or the MPTS has been too lenient then the decision can be appealed through the courts by this commission in the interests of protecting the public.

THE HUMAN RIGHTS ACT

Perhaps the two most potentially influential recent statutes affecting surgeons are the Data Protection Act (DPA) (1998) and the Human Rights Act (HRA) (1998). The first of these is discussed under the heading of confidentiality, where its effects, although far-reaching, are relatively easy to predict. The HRA formally enshrines in UK legislation, the European Convention on Human Rights.

The European Convention on Human Rights

Many people understand this convention to be a product of the European Community and compliance with it to be a condition of membership. In reality it is a convention to which the UK government signed up in the 1950s. The requirement until the HRA became law was that national legislation should be interpreted in accordance with the convention. The HRA enshrines the rights defined in the convention in UK law, allowing UK citizens to claim in UK courts that their rights have been breached and seek damages or perhaps a stay of criminal proceedings.

A number of rights are described in the HRA and these are divided into qualified and absolute rights. The ones of most relevance to otolaryngologists are Articles 2, 3, 6 and 8.

Article 2 states the right to life. There are a number of ways in which this is relevant. Perhaps this is another route by which the family of a dead patient may seek redress if there is the suggestion that the death occurred due to corporate or individual error. The verdicts that are open to a coroner are discussed under the criminal law below, but, as described, this important field is changing. The coroner is a public body under the terms of the HRA and so must ensure that verdicts are in line with that act. Will we soon see a verdict of death in contravention of Article 2 of the European Convention on Human Rights returned as a halfway house between death by misadventure and unlawful killing? What would be the consequences for a subsequent negligence claim? If the strong lobby seeking to legalize assisted suicide in certain circumstances is successful, how will this sit with the right to life? It is not clear in the legislation how a patient can personally renounce his or her rights under Article 2.

Article 3 is the right not to be subject to torture or to inhumane or degrading treatment or punishment. This appears to influence the facilities that must be made available by hospitals for the care of patients as well as powerful implications for the whole consent process. Surely it will not be long before a Trust is sued by a patient alleging that the wait on a trolley for 24 hours in casualty constituted inhumane or degrading treatment. There is also a suggestion that the coroner will have to pay regard to Article 3 as well if, in his view, there was inhumane and degrading treatment leading to a death.

There are two other Articles with relevance to otolaryngologists: Articles 6 and 8. These two interact with each other when the question of GMC and other legal and paralegal proceedings are considered. Article 6 affirms the right of all citizens to a fair and timely trial. A magistrate in the UK has already stayed a prosecution because he judged that the prosecution had taken an unreasonably long time to bring the case to trial. As the defendant was a doctor and now leaves the criminal court without even having been tried, let alone convicted, it is possible that this judgement will profoundly affect his treatment by the GMC.

Since GMC committees are trials within the meaning of the HRA, they are subject to exactly the same legal liabilities as courts and coroners. It is here that Article 6 may begin to conflict with Article 8, which grants the right to respect for private and family life. Consider the position of a surgeon seeking to refute at the GMC committee on professional performance an allegation that there is a consistent pattern of poor professional competence. In order to defend himself and to liaise with his professional advisers (solicitors and counsel), he would surely need access to the notes of the patients that he cared for and to whom he may have given substandard care. Also, the GMC might wish to call the patients as material witnesses to the substandard care. At present, there is no obligation on a patient, unwittingly a witness at a GMC committee, to grant consent to release of his or her confidential information to either the doctor or the GMC. The patient has rights under the DPA to know what is being done with his or her data and, except in certain circumstances, to withhold consent for release of that information. The exceptions do not seem to apply to GMC proceedings. Surely a patient who found out that a Trust had divulged notes to a surgeon and his legal advisors or to the GMC, in pursuit of a fair trial, could bring action under both the HRA and the DPA. Perhaps also, a patient or even a doctor other than the one being investigated, obliged by subpoena to attend a GMC hearing as a witness and subsequently hounded by the press, can argue that no respect has been shown to his or her privacy.

The whole question of how the HRA (1998) will affect surgeons is under active consideration at present. The only guarantee in this field is that lawyers will continue to use the act to push the common law in new and unusual directions.

THE CRIMINAL LAW

Otolaryngologists rarely face criminal proceedings in connection with medical practice, but mention should be made concerning two types of criminal offence that may flow from medical treatment.

INVOLUNTARY MANSLAUGHTER

In recent years, an increasing number of doctors have faced the prospect of prosecution following the deaths of their patients, allegedly as the result of medical malpractice. The English law relating to involuntary manslaughter has been in a confused state, and clarification has only very recently been provided by the Court of Appeal. Traditionally, the test for involuntary manslaughter has been one of gross negligence. In the words of the then Lord Chief Justice, Lord Hewart, in the case of *R v. Bateman*,[41] in order to establish criminal liability the facts must be such that 'the negligence of the accused went beyond a mere matter of compensation between subjects and showed such a disregard for life and safety of others as to amount to a crime against the state and conduct deserving of punishment'. Adjectives such as 'gross', 'wicked' and 'criminal' were used to describe the degree of negligence required. This is effectively something of a 'gut reaction' test for the jury. In a crime of this nature, it is arguably best left open to the jury to make the determination of criminality.

An attempt was made to further define gross negligence by the House of Lords in the case of *Andrews v. DPP*.[42] In that instance, 'reckless' was considered to be the *adjective* that most closely described the concept. In this way, the House of Lords was endeavouring to ascribe as guilty states of mind the appreciation of risk, coupled with a determination to run it, or the wilful indifference to the question of whether such a risk existed. However, 'mere inadvertence' was not considered to merit criminal responsibility.

The test was thrown into confusion in 1981 as a result of decisions in two cases (*R v. Caldwell*[43] and *R v. Lawrence*[44]) by the House of Lords, which redefined the concept of 'recklessness'. The cases concerned the offences of criminal damage and causing death by reckless driving. It was determined that the defendant would be reckless if his action created an obvious and serious risk (to a victim in the case of manslaughter) and the defendant either appreciated the risk but went on to run it or failed to appreciate the risk. This test has been criticized as being unduly harsh. It allows no realistic explanation of the defendant's state of mind to be put forward. Thus, a doctor under pressure, perhaps through overwork and being asked to perform tasks which he or she should not otherwise have been required to do, would have no opportunity to explain those circumstances as part of defence. The mere fact that an obvious and serious risk had been created to the patient, as a result of which the patient had died, would be sufficient to secure a conviction.

The test was applied in a case of motor manslaughter (*R v. Seymour*)[45] by the House of Lords in 1983. Thereafter, however, there was significant confusion as to whether the case should extend to all cases as an involuntary manslaughter. As a result, in some cases involving doctors charged with involuntary manslaughter the traditional test of gross negligence was applied; in others the new harsh formulation for recklessness was considered appropriate. In yet other cases, attempts were made to combine the two tests.

This unsatisfactory situation has been resolved to a degree by the case of *R v. Prentice and Sulliman*.[46] The case involved two junior doctors, Dr Prentice being a pre-registration house officer who, as part of the chemotherapy treatment, injected vincristine intra-thecally in error. As the Court of Appeal observed, the mitigating circumstances in relation to both doctors were many, but a version of the recklessness test was put to the jury, resulting in their convictions. These were quashed by the Court of Appeal (*R v. Prentice and Sulliman*)[47] on the basis that the test of recklessness was not appropriate for cases of involuntary manslaughter where a breach of duty is concerned, particularly for cases involving doctors, where the court observed: 'Often there is a high degree of danger to the deceased's health, not created by the defendant, and pre-existing risks to the patient's health is what causes the defendant to assume the duty of care with consent. His intervention will often be in situations of emergency.' The traditional test for gross negligence was preferred.

The court set out the matters that need to be established for a prosecution of manslaughter, namely the existence of a duty of care, the breach of the duty causing death, and gross negligence which the jury considers justifies criminal conviction. The Court of Appeal went on to set out various states of mind that it considered could probably lead the jury to making a finding of gross negligence:

- indifference to an obvious risk of injury to health
- actual foresight of a risk coupled with the determination nevertheless to run it
- an appreciation of the risk, coupled with an intention to avoid it but also coupled with such a high degree of negligence in the attempted avoidance as the jury considers justifies conviction
- inattention to or failure to avert a serious risk that goes beyond mere inadvertence in respect of an obvious and important matter that the defendant's duty demanded he should address.

The first three are not unduly onerous. The fourth, however, may present particular problems to medical practitioners. Medical treatment generally may be considered to amount to an obvious and important matter. Further, many serious risks are inherent in treating patients and, accordingly, medical practitioners remain in danger of falling foul of the criminal law relating to manslaughter. At the conclusion of the judgement of the Court of Appeal in the case of Drs Prentice and Sulliman, the court expressed the view that the Law Commissioners should look at the law in relation to involuntary manslaughter as a matter of urgency.

In Canada,[48] manslaughter may be committed where a doctor causes the death of a patient by, among other things, criminal negligence that may be committed where someone under a duty shows a wanton or reckless disregard for the lives or safety of others. The precise meaning of 'wanton or reckless disregard' is in doubt. In a recent case (*R v. Tutton and Tutton*)[49] the Supreme Court of Canada was divided between those who considered that

a defendant should have an intention to run a prohibited risk, or a wilful blindness to the risk, and those who considered that a marked and substantial departure from a standard of behaviour expected of a reasonably prudent individual would suffice. This dilemma is similar to that recently addressed by the Court of Appeal in this jurisdiction in the case of Drs Prentice and Sulliman.

In the Court of Appeal in the matter of *R v. Sellu*,[50] the conviction of Mr Sellu was quashed as being unsafe following the finding that the instructions to the jury of the trial judge on the meaning of gross negligence manslaughter were inadequate. In the judgement their Lordships made the point that 'mistakes even very serious mistakes, errors of judgment even very serious errors of judgement, and the like, are not enough for a crime as serious as manslaughter to be committed. You must go on to consider the nature of the carelessness.' They go on to say that 'the key is that the breach of duty must be gross. It must have been so bad, so obviously wrong, that, having regard of the risk of death involved in it, it can be properly condemned as criminal.'

In New Zealand (*R v. Yogasakaran*),[51] the test for manslaughter is that of mere negligence, and a breach of the civil standard of care resulting in the death of a patient is all that is required. Similarly in Greece, the offence under the Greek Criminal Code[52] is of causing death by negligence, mere civil negligence being sufficient. The charge is often seen as a precursor to civil proceedings, where a victim's family may make complaint to prosecuting authorities, effectively as part of the bargaining process for compensation.

ASSAULT, BATTERY AND BODILY HARM

Charges of assault and battery are considered very infrequently by the prosecuting authorities in this jurisdiction in relation to medical practitioners. Courts are reluctant to consider actions in tort for battery arising out of a failure to obtain consent, let alone criminal charges. Very few doctors will intend to inflict harm on a patient, the overall aim being to provide some form of therapeutic benefit. However, where the clinician performs a procedure that goes substantially beyond that to which the patient has consented and that is known to the clinician, or the clinician is reckless as to whether or not the patient's consent will authorize the procedure actually performed, then such an offence may be made out, even if it is of therapeutic benefit. In circumstances where surgical intervention takes place, an offence of greater seriousness than mere assault may result, for example, assault occasioning grievous bodily harm.

Punitive damages

Punitive (exemplary) damages are not normally awarded in jurisdictions of the UK and Australasia but in 2002 the Privy Council heard the case of *A v. Botrill*[53] from New Zealand. This case involved the wholesale misreading of cervical smears by a private pathologist in Gisborne, New Zealand. Between 1990 and 1994 he examined four smears from Mrs A. After Mrs A had a radical hysterectomy for invasive cancer the smears were reviewed and all four slides had been misread or misreported. Mrs A made a successful claim for accident compensation. Disciplinary proceedings against Dr Botrill found him guilty of conduct unbecoming of a medical practitioner. Mrs A then brought court proceedings claiming exemplary damages. Justice Young dismissed the action, applying the principle 'exemplary damages may be awarded, but only if the level of negligence is so high that it amounts to outrageous and flagrant disregard for the plaintiff's safety, meriting condemnation and punishment'.

Two events then occurred: Mrs A found another 10 women whose slides had been misread, and there was public concern about smear reporting in the Gisborne area. This led to a review of Dr Botrill's slides, which showed that Dr Botrill's false reporting rate was 50% or higher. In the light of the new evidence Mrs A applied for a retrial, which was granted. Dr Botrill then appealed this decision and his appeal was successful. Mrs A sought leave to appeal to the Privy Council, which was granted. The argument for Mrs A was that cases of reprehensible wrongdoing that are totally unacceptable to the community but arise from inadvertent negligence should not be put beyond the reach of exemplary damages. Dr Botrill's argument was that there was no conscious, outrageous and flagrant disregard for the plaintiff's safety. The Privy Council agreed with Mrs A and allowed her appeal on a majority decision.

Although this is a New Zealand case it now brings the possibility of punitive damages for reprehensible wrongdoing even if there was no flagrant disregard of risk. It seems that now inadvertent negligence may lead to exemplary damages in selected cases of the worst kind of professional practice.

GUIDELINES

Nowadays, many treatments are the subject of guidelines or protocols, drawn up locally or nationally from organizations such as the National Institute for Health and Clinical Excellence (NICE). These documents purport to set proper standards. Although from a litigation viewpoint they are best considered to be indicative of an accepted course of practice rather than the final arbiter of professional standards, contravention of them without good reason may make defence of a claim very difficult. Where guidelines are departed from the wise practitioner will take particular care to record the reasons in the patient records.

HOSPITAL ADMINISTRATION

A claim may arise where a patient has been lost to follow-up and only represents with an extensive recurrence of a cancer or a complication of a chronic disease such as chronic suppurative otitis media or a systemic condition such as sarcoid. Such cases may have a prospect of being

successful where the patient can establish that had there been a regular examination advancing disease would have been easily identified at an early stage.

It is therefore important that health trusts have a robust system of tracking down those patients who fail to attend for their expected appointment. Trusts should be seen to communicate with the GP in order to establish whether the address that they have is correct, and furthermore to inform the GP that the patient has not attended and request the GP to investigate the reasons why. Failure to do so may be difficult to defend, unless the trust can establish that they have emphasized to the patient the importance of regular follow-up and examination following treatment for the tumour. There is considerable merit in a letter being sent to the patient, giving details of the diagnosis, treatment and the planned follow-up care, for the purposes of identifying early recurrence of disease. It is not uncommon for an expert to examine a claimant's notes and identify frequent non-attendance in outpatient departments of various specialties. However, the claimant usually alleges that they failed to receive the appointment in the mail. Although the treating physician may have a healthy scepticism of such allegations, it must be borne in mind that many people live in multiple occupancy dwellings in which security of mail may indeed be in doubt. As such, where follow-up is important, it is advisable that the GP is asked to investigate for repeated failures to attend.

BEST CLINICAL PRACTICE

- ✓ Where there is evidence of a flagrant disregard for safety or recklessness in performing a surgical technique, then the public may need to be protected by requesting the General Medical Council for a competency assessment.
- ✓ Where an adverse outcome of treatment has occurred, prompt offer of transfer to another department and another surgeon may assuage the patient's anger.
- ✓ Trusts should have a robust system of tracking down those patients who fail to attend for their expected appointment.
- ✓ It will be increasingly difficult to justify a single surgeon operating in excess of four hours without having a short rest.

KEY POINTS

- Clinical negligence is a matter for civil law.
- Damages awarded are general and special.
- The standard or proof is 'on the balance of probabilities'.
- There are four essential elements of the legal tort of negligence:
  - there must be a duty of care
  - there must be a breach of that duty
  - harm must have occurred
  - the breach must have caused the harm.
- The standard of care is that of the reasonably skilled and experienced doctor.
- 'It will very seldom be right for a judge to reach the conclusion that views genuinely held by a competent medical expert are unreasonable.'
- If the case for each side is evenly balanced then the claimant will fail.
- The court must award a sum of money that will, as nearly as possible, put the injured person in the same position as she would have been had she not been injured.
- The result of the introduction of contingency fees is likely to be that there will be no significant increase in the number of medical negligence actions in the short term.
- Where a proposed treatment involves a substantial risk of grave or adverse consequences such that, notwithstanding any practice to the contrary, a patient's right to decide whether to consent to the treatment was so obvious that no prudent medical man or woman could fail to warn of the risk, then it would be negligent not to warn.
- The parental right to determine whether or not a child under the age of 16 should have medical treatment terminates when the child achieves a significant understanding and intelligence to enable him or her to understand fully what is proposed.
- 'An adult patient who suffers from no mental incapacity has an absolute right to choose whether to consent to medical treatment, to refuse it or to choose one rather than another of the treatments being offered.'
- Any surgeon who keeps any sort of patient identifiable information at his or her residence and who is not registered with the data commissioner breaches the provisions of the DPA.
- The coroner's remit is to establish the identity of the deceased, the time and place of death and the mode of death.
- Articles 2, 3, 6 and 8 of the HRA are those most relevant to surgeons.
- Modifications to the law on involuntary manslaughter are awaited; currently the traditional description of gross negligence resulting in death usually applies.
- Just because a recognized complication occurs, it does not automatically mean that surgical technique has been below a satisfactory standard.

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CHAPTER 39b

MEDICAL NEGLIGENCE IN OTORHINOLARYNGOLOGY

Maurice Hawthorne

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SEARCH STRATEGY

Data in this chapter are based largely on the author's long experience as an expert witness and on landmark legal judgements, some of which are alluded to in the text.

INTRODUCTION

Chapter 39a dealt with the general principles that govern legal aspects of medical practice in otorhinolaryngology. This chapter explores recurrent themes to guide safe practice and then focuses on specific scenarios that give rise to claims of negligence in general otolaryngological practice and within the subspecialties.

INTERPRETATION OF IMAGES

In many hospitals, there is no radiologist with a special interest in ENT. Consequently, the experienced consultant ENT surgeon may be just as competent at reading radiological films as the specialist radiologist. In all departments it is wise that both the clinician and the radiologist assess the radiological films within the clinical context of the patient's disease. From time to time, a difference of opinion may arise, and a failure to address this difference of opinion can lead to a delay in diagnosis, with a significant impact on prognosis for the patient. Where films have been discussed, and a difference of opinion continues, then it is advisable that a further opinion is sought from a radiologist with a special interest in the field. Nowadays, films can be easily transferred electronically and the vagaries of the postal system do not have to be endured. Where there is a difference of opinion between the clinician and the radiologist, most patients would expect the radiological investigation to be repeated after some weeks. Although the radiologist, and indeed the clinician, may have some concerns about the increased dosage of X-rays necessitated by repeat films, where there is a possibility of malignancy, the patient will see this risk as being trivial, and would be much more concerned about obtaining peace of mind about what they see as a real and existing problem, compared to some theoretical risk of developing a malignancy in the future. Therefore, the wise clinician should argue for a repeat investigation or discuss with his radiological colleague using another imaging modality.

In the field of endoscopic sinus surgery, whether it is functional, diagnostic or treating an iatrogenic complication, it is essential to have a complete demonstration of the radiological anatomy by computed tomography (CT) scan. The nose should be scanned from its rostral extremity as far back as the basilar artery. In addition, it is essential that the window setting is such as to maximize the bony detail and also a second series should be saved with window settings to give some soft tissue information. Litigation may arise when the clinician either has not viewed the imaging or ignores a report demanding that action should be taken. For example, it is normal practice that immediate post-operative plain films of

cochlear implants are taken. In two cases, settlement had to be explored where an electrode had partially slipped out immediately following surgery, and was shown on the post-operative films but only detected by the team when the films were reviewed some months later as the patient was not doing as well as expected.

INTERPRETATION OF HISTOLOGICAL INVESTIGATIONS

Much of what has been said above on radiological investigations also applies to histopathological investigations. The wise otolaryngologist will be well aware of the pitfalls that can arise. These are especially true in salivary gland and nasal neoplasia. Also, fine-needle aspiration cytology needs to be carefully considered in the light of the clinical picture and if a lesion deemed benign on cytological examination does not appear to be behaving clinically as such, rebiopsy should be undertaken speedily.

FAILURE TO CONSIDER CONSERVATIVE TREATMENT

This issue appears to arise more commonly in private practice. It is not uncommon for the patient who has had a mishap following sinus surgery to state that conservative options for treatment, such as oral steroids and antibiotics in the case of nasal polyposis, had never been discussed, but that an immediate recommendation for surgery had been made by the practitioner. In the case of simple, benign, nasal polyposis in a fit individual, there is rarely any defence for not discussing the possibility of a course of oral steroids, with or without antibiotics. If there is doubt as to the nature of the polyps, a simple biopsy can be undertaken, followed by conservative treatment, rather than an attempt to radically clear the disease, as first-line treatment.

In those patients with nasal obstruction due to enlarged inferior turbinates, first-line treatment should normally be conservative. Adequate investigation to identify the presence of any allergy and then treatment either by allergen avoidance or topical steroid treatment would usually be first-line treatment. If the general practitioner has already undertaken this in an adequate and thorough manner, it may be reasonable to proceed with an offer of surgery. However, a significant complication occurring following turbinate surgery in the patient who has not been offered an initial trial of conservative treatment can be very difficult to defend.

PATIENT SELECTION

When a patient attends with trauma or cancer, the surgeon has little choice but to either provide the treatment that is necessary or refer on to a specialist who is more fitted to handle the case. Ultimately, the patient is going to require treatment and a failure to provide prompt treatment after diagnosis may in itself lead to litigation.

However, in the non-urgent situation, there is time for the patient to choose his surgeon and also for the surgeon to choose his patient. The wise surgeon will pay heed to features that suggest an increased risk of dissatisfaction, and will attempt to manage these before undertaking any surgical treatment. Only once the surgeon is convinced that a patient understands what the experience and the result of surgery is likely to be should the planned surgery proceed. This is especially so where there is a cosmetic element to the proposed treatment.

Beware the patient with no physical abnormality. A patient who has a physical abnormality visible to the surgeon and a clear understanding of what he or she wishes to be achieved is more likely to be satisfied with the result of cosmetic surgery than a patient with no visible abnormality. If a patient's nose is too long or too wide, the tip too bulbous or deviated, and is obviously outwith the norm, then successful surgery is possible. A patient who refuses to accept that the nose is within the range of normality and clearly believes it to be too large may be suffering from dysmorphophobia. These patients will be dissatisfied with surgery and should be referred to a psychiatrist with experience in the field for assessment and possible treatment.

Beware the patient whose appearance is at either end of the normal spectrum, obsessively neat and tidy or dishevelled and unkempt. Both types may prove difficult for the surgeon to achieve a result that satisfies the patient. The immaculate patient may be seeking a result beyond the capability of surgery, and may also find the normal scar maturation process too slow. The patient who does not care about his or her appearance may not comply post-operatively, compromising the result. If such a patient is looking for an improvement in social life, attention to personal hygiene may be more appropriate than changing facial appearance. In particular, it requires considerable tact to explain this, but undertaking a cosmetic surgical procedure on his or her face is unwise.

Beware the patient who is dissatisfied with other surgeons or the results of previous surgery. The surgeon who has refused a patient elsewhere is likely to have had good reasons for not proceeding. Furthermore, the patient's perception of these reasons will almost certainly be given with a bias that the wise would recognize. If the patient has had an unacceptable result from surgery and yet in your evaluation the result is well within the range of results produced by most competent practitioners, then dissatisfaction from further surgery is likely. However, there are those who see plastic surgery as an adjunct to all the other means of enhancing appearance, and a patient seeking another plastic surgical operation on a part of the body that has not been enhanced before should not necessarily be seen as a potentially problematical patient, particularly if the patient expresses satisfaction at previous operative procedures.

Beware the patient with the bizarre request. Occasionally, patients may present with a request that is so bizarre, the surgeon is unlikely to have come across it before. For example, a patient may believe that he or she is part-snake, part-human, and consequently requests

splitting of the tongue to give it a forked appearance. Underlying such requests may be a psychotic delusion and, whenever the surgeon is in doubt, an opinion from a psychiatrist should be sought before offering surgery.

Beware the aggressive and violent patient. Individuals who express their dissatisfaction or who fail to solve their daily problems by the spoken word and consequently resort to violence may hide an underlying personality disorder. Such people may have problems with interpersonal relationships that they have focused onto one aspect of their appearance. If this aspect is changed and their interpersonal relationship problems do not improve, they may seek retribution from the surgeon. Surgeons have been murdered by dissatisfied patients.

CONSENT TO SURGERY

Issues of consent on their own are rare in relation to sinus surgery and they are much more common when coupled with allegations of incompetent surgical technique. However, it is in the field of turbinectomy, particularly in the adolescent and young adult, that issues of consent arise. Torrential haemorrhage following inferior turbinectomy is not uncommon, probably happening in most surgeons' practice, with an incidence of between 1 in 60 and 1 in 200 cases. It does appear to be more common where a posterior turbinectomy has been undertaken, rather than removal of the anterior end of the interior turbinates. Nevertheless, torrential haemorrhage can happen in any form of turbinate surgery. When this occurs, and the patient has undergone the usual treatment to arrest the haemorrhage and correct the blood loss, an allegation of permanent psychological damage may arise, accompanied by the allegation that the patient was not warned of the risk and had they been, then they would have refused consent for the surgery. In taking consent, the wise surgeon must assess the personality of the patient and ask himself whether they would have the mental fortitude to withstand the psychological trauma that can accompany a severe nasal haemorrhage, particularly as it may appear life-threatening to the patient and their family. If the patient, despite warning of such haemorrhage, still wishes to proceed with the surgery, then it should be carefully annotated in the notes that the warning has been given and understood.

Since the introduction of functional endoscopic sinus surgery on a wide basis, between 1988 and 1992, consent for these procedures seems, on the whole, to be well annotated in the case-notes, particularly from the point of view of the risks of injury to orbital contents and breach of the dura. However, where contention may arise, it is not that the patient was warned of these anatomical risks, but that they did not understand the consequences of these risks on their day-to-day life or that, should such risks occur, secondary complications may supervene. One patient, an intelligent banker, freely admitted that he had been warned of the risk of cerebrospinal fluid leaking from his nose, but was adamant that he had been given no warning that this could lead to meningitis and subsequent intellectual impairment, which had occurred in his particular circumstances.

However, the claimant may find it difficult to establish in court that, had they been fully warned, they would not have gone on to subject themselves to the surgical procedure.

The landmark Australian case, *Rogers v. Whitaker*,[1] in which it was felt the risk of sympathetic ophthalmitis, with a risk of approximately 1 in 30 000, should have been explained to a patient, has not found favour in the English courts. The risk of blindness as the result of submucosal diathermy, or the use of adrenalin-containing local anaesthetic in rhinological surgery, is somewhat similar. In one case, a young woman woke up following a general anaesthetic for a submucosal diathermy to the inferior turbinates and had totally lost sight in one eye. Thorough investigation did not reveal any evidence of direct trauma to orbital or retro-orbital structures, and a literature search revealed that this can happen despite competent surgical technique. On the Bolam principle, as virtually no ear, nose and throat surgeon practising in the UK would warn of this risk, her case would fail and therefore her solicitor advised that she should not pursue the issue. A Legal Aid Certificate was not granted to test the principle that such a loss was so catastrophic that, despite its rarity, it should have been warned of and that any reasonable patient would expect that this issue be mentioned. Now in the post-Montgomery era it is likely that such a complication would meet the reasonable patient test and so the issue may be tested in the courts in the future. A major point of debate will be around just what really rare complications the consenting surgeon should actually be aware of.

Time should be spent carefully outlining: the common complications; the likelihood of them occurring; what the effects of them would be; what treatment may be necessary to correct matters should such complications arise; and, most importantly, whether such extra treatment will be charged for. Providing this free of charge goes a long way to having a satisfied patient and reduces the chance of litigation. Carefully worded patient information leaflets are helpful, either sent to the patient to read before the consultation or given for reading afterwards, but they are not a substitute for proper discussion and informed consent. The surgeon should take care to ensure that such leaflets are directly applicable to the patient's problem and to the way in which the surgeon plans to treat the patient, both at the operation and post-operatively. Some commercial leaflets are too vague or, worse, impart information that does not apply to your practice or the patient concerned. This may cause litigation problems later.

Patients should not make a final, irrevocable decision about surgery at the initial consultation. A period of time, perhaps two weeks, for the patient to reflect upon what has been said is invaluable. Many patients will undertake their own research, often using the internet or discussing matters with friends or relatives during this period. Although the surgeon may be inconvenienced or disappointed if a patient changes his or her mind and decides not to undergo a procedure, the wise surgeon will realize

that she or he has probably been saved a considerable amount of time and inconvenience by not performing the operation discussed.

TUMOUR RECURRENCE

An allegation of inadequate primary resection of a tumour, either malignant or benign, usually follows the unexpected diagnosis of a recurrence. This may seem surprising to the profession, but sadly a combination of belief in modern surgical techniques, plus the confident statement from the operating surgeon that 'all the tumour has been removed', can lead to an accusation of incompetent technique. Clearly, a confident statement on tumour resection is meant to reassure the patient and improve their psychological well-being. However, there is no excuse to take on a patronizing role, supported by frank lies. It is important that the patient is told the exact situation, as best as can be determined, and if the outcome for the future appears to be bleak, then such bad news needs to be adequately supported with appropriate psychological therapy. It is possible that any psychological damage may be looked upon seriously by the courts, and appropriately rewarded, especially when the major defence to the bulk of the claim is that 'the patient would have died anyway'.

In circumstances where resection margins are being monitored by frozen section examination during the surgery, it is vital that all specimens are sent. Thus, when a report says that the tumour is at the margin of resection, on one specimen it is useful to have a subsequent specimen indicating that there is a clearance. Obviously, where the tumour is up to, but not invading, a nerve sheath, the surgeon may have to exercise clinical judgement and decide whether to resect such a nerve sheath or not. These points should be carefully noted in the records. Thus, a histological report that indicates that the margin of resection is up to the edge of the tumour can be seen to have been acted upon appropriately.

SPECIFIC CONDITIONS AND PROCEDURES

Just because a recognized complication happens, it does not automatically mean that surgical technique has been below a satisfactory standard. A complication such as damage to the medial rectus muscle in endoscopic sinus surgery may occur, despite all care being taken by the surgeon. On the other hand, it may occur as a result of a 'gung ho' or slapdash technique, in which due respect and identification of the relevant surgical landmarks has not been attempted. For the claimant, it can be difficult, if not impossible, to prove that the damage has occurred because of the latter surgical technique, rather than the former. It would indeed be rare for a claimant to successfully identify a witness, present at the time of the surgery, who was willing to testify in court as to incompetent technique practised by the surgeon.

Increasingly, video is used in theatre and, in the case of endoscopic sinus surgery, operating via camera is a common technique. If the surgery is recorded and the tapes kept until it is established there is no significant post-operative complication, the recording may be available to both parties in which an adverse outcome to the surgery has developed.

In a recent MPTS case, examination of recordings kept on DVD by an expert was key evidence that led to the erasure from the medical register of the surgeon.

For example, in one case, a trainee undertook a difficult nasal polypectomy endoscopically. The procedure was recorded and a breach of the anterior cranial fossa, and how it was acquired, could clearly be seen on the video. In this particular instance there was a dehiscence of the cribriform plate, with absence of bone in the anterior cranial fossa. The repair was also filmed. An explanation was given to the patient, who was quite satisfied. However, his children, who lived some distance away, attended the hospital some days later. One daughter, a nurse in a maxillofacial surgical department, clearly felt that causing a cerebrospinal fluid (CSF) leak had to be negligent. Fortunately the video material was available, which was immediately shown to the family and carefully explained. This diffused the aggression and was successful in preventing litigation.

Occasionally, massive injury can be sustained in which the degree of damage is so gross that basic surgical technique has to have been ignored, or not understood. For example, in one case a patient failed to regain consciousness from the anaesthetic following intra-nasal surgery. On arrival at the intensive care unit, a $2 \times 1 \times 1$ cm piece of cerebral cortex was retrieved from the oropharynx; subsequently an extensive resection of the anterior cranial fossa was identified, and the nose contained a huge herniation of the brain. The neuroradiological expert in the case felt that there was clear evidence of instrument tracks within the substance of the frontal lobes of the brain, suggesting that instruments had been passed repeatedly into this brain substance. In this particular case, pre-operative CT scans did not reveal any evidence of a congenital abnormality of the anterior skull base. Not surprisingly the surgeon's insurers sought a settlement early on in the process of the case.

Where the evidence is strong that the lack of standard of care would suggest a flagrant disregard for safety, or recklessness in performing the surgical technique, then the public may need to be protected by requesting a competency assessment by the General Medical Council.

RHINOLOGY AND FACIAL PLASTIC SURGERY

Negligence in general practice in relation to rhinological disease is unusual. It appears to occur mainly due to a failure in recognizing the significance of certain symptoms or signs.

One of the most common areas is in failure to arrange timely treatment for a nasal fracture. In most practices,

the best opportunity in effectively manipulating a nasal fracture is within the first 21 days of the injury. Failure to undertake timely treatment may lead to the necessity of performing a formal septorhinoplasty. The consequence of this is a longer period off work than would otherwise be necessary, as well as additional pain and suffering such as periorbital bruising. A delayed referral can rarely be defended and usually the best outcome is to seek a speedy settlement. There are exceptions and one of the most important is the cartilaginous injury of the nasal tip or septum when simple manipulation does not give the best results and a septorhinoplasty is indicated as first-line treatment.

A delay in referral of sinusitis is also a common area that leads to litigation. The general practitioner (GP) usually fails to realize when a sinus infection has spread beyond the sinus and is involving the orbit, bone, meninges or soft tissues. The most common examples of this are orbital and forehead swelling. It is only the onset of symptoms in relation to brain abscess, meningitis, blindness or severe orbital swelling that leads to a speedy referral.

The significance of unilateral nasal symptoms, such as discharge, may be ignored by the GP and so a delay in diagnosis of a tumour or foreign body occurs.

Sadly, it is not just the GP who may fall into the situation of delaying a diagnosis. Inexperienced trainees within the specialty, accident and emergency doctors, and occasionally other specialists within hospital practice, may all find themselves at the centre of litigation arising from these relatively common areas of negligence.

Inadequate pre-surgical management

Failure to investigate significant symptoms arises from time to time. Wegener's granulomatosis is a condition that regularly goes unrecognized. Often it may be mistaken for atrophic rhinitis or even industrial rhinitis, and the patient treated symptomatically, without adequate investigation. It is only when other systems are involved, such as the renal or respiratory system, that adequate investigations are triggered and the condition identified. Clearly if the condition has progressed to frank renal failure requiring dialysis before diagnosis has been made, then the patient may have a strong claim. It is common to find that other conditions, such as scleritis, flitting arthropathy or skin lesions, have not been not linked to the nasal symptoms.

Circumstances arise in which the investigations for this condition, such as a raised plasma viscosity or erythrocyte sedimentation rate (ESR), which are usually raised, are within the normal range. Occasionally even the antineutrophil cytoplasmic antibody (ANCA) test is negative, and where adequate investigations have been undertaken but the diagnosis has been delayed, a reasonable defence can be mounted.

From time to time, a post-nasal space carcinoma may present as a neck lump to another specialist. Although the malignant nature of the neck lump is identified, occasionally the primary site is missed. The ear, nose and throat (ENT) expert may be asked to comment on such a delay. It is of course inappropriate for him to deal with issues of liability concerning delay in diagnosis by another specialist, but it would be expected for him to comment on how the delay may affect the prognosis of the patient.

Similarly, a restriction in eye movement may indicate early involvement of orbital contents or a cranial nerve by a sinus malignancy. Clinical examination may not reveal an obvious restriction in movement, due to the partial nature of the malignant process. Sudden onset of double vision, without an obvious cause such as head injury, or orbital displacement should never be ignored, and requires thorough investigation to exclude a pathological cause requiring treatment.

External drainage of the frontal sinus

Frontal sinus trephine may lead to supratrochlear nerve damage and indeed supraorbital nerve damage. Where there is significant oedema in the surgical area, most surgeons could understand how the supraorbital nerve might be stretched by retractors, or indeed cut. However, in a simple drainage procedure, there can be no excuse for extending the incision so far laterally as to divide the supraorbital nerve. The Lynch–Howarth procedure gives wider access to the frontal and ethmoid sinuses. In extensive disease it may be necessary to sacrifice the supraorbital and the supratrochlear nerve. This should be anticipated before the surgery and the patient warned. In addition, the patient should be warned of the possibility of double vision post-operatively due to the detachment of the trochlea.

Caldwell-Luc procedure

Caldwell-Luc surgery is now rarely undertaken. Resting cheek retractors against the supraorbital rim in a Caldwell-Luc procedure, or similar surgery, can lead to a neuropraxia of the supraorbital nerve. This usually recovers; however, it is a well-recognized risk and adequate precautions can usually be taken to prevent it happening. On the other hand, infraorbital nerve neuropraxia in Caldwell-Luc surgery can be inflicted despite all care being taken, and does not indicate *de facto* substandard technique.

Septal surgery

A major saddle deformity of the supra tip area, following septal surgery, causes such a deformity that it can be difficult to prevent the angry and embittered patient from seeking redress. If the complication has occurred as the result of a post-operative septal abscess, and the patient has been warned of the possibility when consent was taken, then sympathetic handling can usually prevent the patient seeking redress through the court. A careful explanation that infection had destroyed the septal cartilage may suffice. Rarely the saddle could be due to a failure to recognize and diagnose disorders such as Wegener's granulomatosis, sarcoidosis or relapsing polychondritis. The wise surgeon, when presented with such an unexpected outcome, should take the appropriate tests to exclude such

disorders. Clearly the presence of an alternative explanation for a septal collapse or perforation may present an opportunity for a defence.

Septal perforation is another common complication, especially in submucous resection of the nasal septum that causes such symptoms that a patient may seek compensation. It should always be mentioned when septal surgery is being offered. The presence of a perforation does not automatically imply a substandard technique; it is more likely to be an indicator of a severely fractured nasal septum or the presence of another disease, such as atrophic rhinitis or a granulomatous disease.

The circumstances of a submucosal resection, in which the surgeon has made an error of judgement and resected too much cartilage, are likely to be much more difficult for the patient to accept. Once more, recognition of the patient's concern is the key to good management. In addition to offering surgery to correct the deformity, it is important to recognize that the patient may no longer have confidence in the surgeon, or indeed even in the hospital in which they have been treated, and so a prompt offer of transfer to another department and another surgeon may assuage the patient's anger.

In the last few years the author has seen a rise in claims in which there has been a subtle change in the appearance of the nose following septoplasty. In these cases the surgery has clearly been performed competently but the patient claims that they were reassured that the operation would not alter their appearance.

Examination under anaesthesia and diagnostic sinus lavage

Prior to the 1980s, it was very common practice to undertake a 'proof puncture' of the maxillary antra. This would often be done at the time of a tonsillectomy or adenotonsillectomy, in older children and young adults. It was considered a legitimate investigation to detect the possibility of chronic sinus infection. Many surgeons advocated its routine use, even in the absence of any sinus or nasal symptoms. Such an invasive procedure, which carries the risk of damage to unerupted secondary dentition, the inferior orbital nerve and the orbital contents, in the absence of sinus symptoms, can no longer be justified without taking a formal consent for the procedure and offering alternative methods of investigation. In addition, several cases have arisen due to misunderstanding of the term 'examination under anaesthesia'. Some claimants who have sustained complications as a result of such procedures have asserted that they only gave consent for the surgeon to look, but not to biopsy. A typical examination would be obtaining consent for examination of the post-nasal space in a child or adult with glue ear, and then proceeding to perform an adenoidectomy having identified a significant pad of lymphoid tissue in the post-nasal space, the damage occurring usually being a secondary haemorrhage. It is important therefore, in taking consent, to include the potential risks that may arise for any additional procedure, usually a biopsy of an excisional or incisional nature.

Intra-operative monitoring

This term usually invokes thoughts of nerve monitoring in the context of ENT surgery, but it is still particularly important in rhinological surgery, although the monitoring may be purely visual in nature. In endoscopic sinus surgery, it is the orbital contents that are at risk. Clues to a significant intra-orbital incursion can be obtained by careful observation of both eyes during the procedure. This may not be possible by the operating surgeon, as it is likely that he or she will be observing the operating field either indirectly through a camera or directly through an eye-piece. However, an operating assistant, such as a scrub nurse or other colleague, should be in a position to observe both orbits and watch for the tell-tale signs of a complication arising. These may include a sudden movement of the globe of the eye, the development of proptosis or subconjunctival haemorrhage. Although in the early parts of the procedure it is important to protect the cornea from damage, at points in the surgery in which the eye may be in a critical, or vulnerable state, it is permissible for the eyelid to be opened and the globe observed for brief periods. Early identification of an incursion into the orbit is essential to reduce the risk of damage. Equally, in the recovery area, post-operative observation of the orbits and eyes is essential, particularly if a significant retrobulbar haemorrhage is to be identified, monitored and, if necessary, treated before permanent damage to the eyesight occurs.

Post-operative monitoring

Even though frontal sinus infection has been adequately drained at surgery, the patient still has the potential of developing an intra-cranial complication, though this is now much less. It is likely that the infection has spread through the venous system prior to the actual drainage of the sinuses and so the intra-cranial symptoms usually commence 24–48 hours after surgery. Complaint of severe headache that is progressive, along with drowsiness, confusion or disinhibition, should alert the wary to the onset of a frontal lobe infection. Usually the patient should be on an antibiotic with a high ability to cross the blood–brain barrier, but if this is not the case, then with the onset of these symptoms the antibiotic will need to be changed. Inadequate monitoring in the post-operative period may also lead to delay in detection of a cerebrospinal fluid leak. Although these may be blatantly obvious when there is a striking flow of clear fluid from the nose and the patient has an accompanying headache, the occasional case may be intermittent. In one case, the patient re-attended the hospital on three occasions complaining of watery nasal discharge, which was ignored. No investigations were undertaken, other than admission and observation on the ward, on one occasion only for 48 hours. On the final attendance at hospital the patient presented with a small bottle containing a sample of the CSF and symptoms of frank meningitis. The confusing issue is that nasal discharge that may be watery in nature is not uncommon following sinus surgery, or indeed may be related to the

underlying sinus disorder. It is quite likely that minor CSF leaks are probably more common than is actually realized, but fortunately they close spontaneously without any secondary damage.

Benign skin lesions

Patients often believe that small skin lesions can be removed without leaving a scar. It is very important that the inevitability of a scar, its length and width, the duration of the scar maturation process and the risk of scar hypertrophy and/or keloid formation is explained to the patient as part of the informed consent procedure.

When excising a skin lesion as an ellipse, the length of the scar will be two or three times the diameter of the lesion. Once the sutures have been removed, the scar will initially be a relatively fine line. As the proliferative phase of wound healing progresses, the vascularity increases, making the scar red and noticeable. This appearance may last for between two weeks and two months after injury.

With entry into the collagen maturation phase the appearance of the scar improves, but full maturation may take up to two years in some patients. Those with a heavy, sebaceous skin, or ginger colouring, may have a noticeable scar for longer than average. Overexposure of an immature scar to ultraviolet light from bright sunshine or from a sun bed will cause burning more easily than in normal skin or a mature scar. Patients should be advised to avoid or protect the skin from such overexposure by applying high protection factor sun cream and by keeping out of the direct rays of the sun.

The patient dissatisfied with the early appearance of a scar should be advised that early revision is rarely indicated as many scars settle without surgery being necessary. Regular communication with the patient whilst the scar matures is the keystone of treatment, as brushing off the patient or disregarding the patient's perception that there is a problem may lead to litigation. Although the scar may well settle whilst the complaint proceeds, the problems of having an ongoing case are not to be dismissed lightly. Regular outpatient consultations, encouragement that the scar is likely to settle in time and sympathy with the patient will minimize the risk of litigation.

Patients with factors known to adversely affect the final appearance of scars must be counselled about this. Adolescents with spotty, pubertal skin are best not operated on until their skin has calmed down unless there is a suspicion of malignancy. Patients with previous hypertrophic scarring, patients with coloured skin and those with lesions on areas of the face more likely to make a hypertrophic scar, such as along the line of the mandible, must be warned appropriately. In some parts of the face, particularly the tip of the nose, it is difficult to achieve a fine scar even with no adverse factors.

In trauma, the method of injury influences the final appearance of a scar. Dirty or infected wounds, traumatic tattooing, closure under tension, non-perpendicular wound edges and wounds crossing skin tension lines will lead to poor quality scars. Trapdoor scarring is a particular problem in traumatic wounds: a flap of skin is raised, often tangentially and thus with bevelled edges, and the scar heals with contraction and localized lymphoedema within the confines of the scar. Simple excision and resuture is unlikely to resolve the problem and a patient must be advised clearly of the limited improvement that may be achieved by scar revision.

Suture marks are not acceptable and, if they occur, litigation will be difficult to defend. Careful choice of suture material and its thickness, accurate placement of the sutures and their tightness, and timing of removal are critical. It has been suggested that scar stretching can be minimized using subcuticular sutures left in place for weeks or months, but clinical experience does not generally support this.

All lesions excised should be submitted for histological examination, however benign the lesion looks, unless the patient specifically instructs that this is not to be done. In such a situation, this instruction must be recorded in the notes.

Keloid and hypertrophic scars

Both hypertrophic and keloid scars contain excess collagen. In a hypertrophic scar, the collagen remains within the borders of the scar, but in a keloid scar it extends into the surrounding undamaged skin. Hypertrophic scars usually settle spontaneously, although they may take a few years and leave unsightly scars, but keloid scars persist. Hypertrophic scarring is more common in young people, can occur on any part of the body and is more common if there has been wound infection and breakdown or healing by secondary intention. Keloid scarring may be familial, is much more common in Afro-Caribbeans than in Caucasians and has a predilection for certain parts of the body, such as in the head and neck, the ear lobes and more rarely the postauricular skin.

Treatment of keloid scarring is difficult and often unsuccessful. Patients find it difficult to believe that simple excision will not solve the problem and that keloid recurrence is not only inevitable but may be worse. Triamcinolone injections are the mainstay of treatment, although great care must be taken that the steroid is of the correct strength (10 mg/mL and not 40 mg/mL) as the concentration of steroid used for intra-articular injections rapidly causes localized fat atrophy which takes two or more years to recover. Steroid impregnated tape and topical application of hydrocortisone can also help, as can pressure garment therapy.

Patients should be warned pre-operatively of the risk of keloid scarring occurring with an indication of the degree of risk for the site or procedure. For example, keloid scars developing after a pinnaplasty are rare but when they occur it is a cosmetic disaster and frequently the cause of a claim. It can be difficult when the effect of the complication is so great to defend such a claim on the grounds simply that the complication is rare and that the patient therefore did not need a warning.

Nasal trauma

DELAYED TREATMENT

Nasal fractures with bony deformity should ideally be reduced within at most 10 days following the injury to avoid callus formation and rigid bony union. Delayed treatment may lead to permanent osseocartilaginous deformity, which can only be corrected by septorhinoplasty. This may lead to a successful claim for negligence. It is essential to have a referral mechanism between accident and emergency departments and otolaryngology departments so that early assessment can take place and arrangements can be made for manipulation of a nasal fracture under anaesthesia. The decision to manipulate a nasal fracture is clinical. Plain X-rays have little to offer.

SEPTAL HAEMATOMA

Failure to recognize acute septal haematoma can lead to a permanent deformity if a septal abscess subsequently develops. In most instances of septal abscess, a doctor has not previously examined the child but occasionally a haematoma is missed or is diagnosed but not drained. The saddle nose deformity that results can be difficult to correct and as such the compensation can be relatively expensive to cover the pain and suffering of additional surgery and the cosmetic deformity.

Rhinoplasty and septorhinoplasty

The importance of proper selection of the patient and the procedure appropriate to that patient in connection with a rhinoplasty cannot be overemphasized as it is an area in which expectations are very high. It is particularly important to identify those patients who are being unrealistic. Those bringing cuttings from magazines showing the nose that they want and those with concerns about a deformity that the surgeon cannot see should make the surgeon wary of proceeding.

Pre-operative photographs must be taken and studied carefully as they may show abnormalities that the surgeon has missed on examination, or which the patient may be unaware of, such as an asymmetry that might otherwise be blamed later on the operation.

In most rhinoplasties, osteotomies are performed which narrow the nasal airway. This may cause obstructive symptoms, and assessment of the airway pre-operatively is important if nasal obstruction is to be avoided.

Patients who have a congenitally wide nose may require alar base reduction at the same time as a rhinoplasty. This will leave a permanent scar at each nostril base and patients must be warned of this.

There is a recognized revision rate following rhinoplasty, which ranges from 5% to 15% in published series. Patients must be advised that this may be required and should be regarded as normal. It is wise to include the cost of this surgery in the price quoted for the initial rhinoplasty, or to agree the cost before the first operation, as additional unexpected charges can turn a patient from accepting a less-than-perfect outcome to starting litigation.

Elderly patients with thin, fine skin are particularly difficult to manage. Any material left under the skin, such as bone dust or fragments, can easily show through once the healing process is complete. Furthermore, if the osteotomies are not carefully positioned and the bone fragments align in an unsatisfactory position, the edges of the bone or the osteotomies themselves may show through the skin. Occasionally, it may even be wise to advise a patient with such skin not to undergo a rhinoplasty procedure. Elderly skin will have lost its elasticity and will not retract satisfactorily when it is re-draped over the bony and cartilaginous framework at the end of the procedure, so resection, particularly of a bony hump, must be very conservative to avoid unsightly, redundant skin.

Tight application of a plaster-of-Paris splint against the unyielding bed when osteotomies have not been performed can lead to skin necrosis. Paper splints, such as self-adhesive dressing strips, are best used instead to prevent subdermal haematomas. Many surgeons overlap these strips and care needs to be taken that they overlap adequately otherwise a bleb of skin can herniate between them, become strangulated and lead to an ulcer and subsequently a permanent external scar.

The occurrence of unacceptable deformities, such as the pollybeak and the columella retraction deformity, do not always indicate a substandard technique and may arise from tissue loss as the result, for example, of infection. Infections must be treated promptly and with the appropriate antibiotics, either by the operating surgeon or by the patient's GP. It is important to record the treatment in the patient's records, if only to rebut a later legal claim.

The surgical technique is vitally important, not only to achieve a patient's aspirations but also to avoid complaints and litigation. A successful rhinoplasty is a balance between resection and preservation of cartilage. As the nasal skin is simply redraped over the modified cartilage framework, the cartilage left behind is at least as important as what is resected. Excision should generally err on the conservative side as a small excision can result in a significant and adequate change but a large excision can cause an unacceptable deformity, such as excessive bony hump removal.

Many changes that patients may express concern about are normal post-operative appearances and are not the result of negligent surgery. Patients will need reassurance about these changes and regular follow-up. Discharging a dissatisfied patient even though the surgeon knows that the complication is likely to resolve spontaneously may well lead to a complaint, and once this has happened the patient will be much more difficult to satisfy. These complications include particularly those occurring within the first six months after surgery, such as discolouration, loss of tip sensation and oedema. As post-operative oedema settles, irregularities of shape may appear. These may settle spontaneously but may be those that occur in the 10–15% of patients who require revision surgery. This sort of irregularity tends to be minor in size, such as a small ridge or lump on the bridge line, but a patient can become so focused on it that they feel that the deformity is noticeable to every casual observer. In most cases, any

revision rhinoplasty should be delayed until at least one year to allow the tissues to mature and soften, giving time for any resolution to occur, making the surgery easier, and giving the surgeon the best chance of rectifying the problem.

More major abnormalities, such as a saddle nose or ski-slope deformity, alar retraction, pollybeak deformity, tip and alar-columella deformities, and pinching of the lateral alar walls, are likely to be due to surgical failure. With any revisional surgery, the patient must be warned that post-operative settling takes much longer after a second operation. The final result may not be seen until a year afterwards.

A saddle nose or ski-slope deformity usually results from over-resection of dorsal bone and cartilage, but can arise after post-operative trauma leading to a septal haematoma or following an abscess, causing loss of septal support. Rarely, a granulomatous or autoimmune disease can be the cause. The treatment requires augmentation, ideally with a cartilaginous autograft. Alloplastic materials may be used as an alternative, but patients must be warned preoperatively of the risks of infection and rejection.

Alar retraction is usually caused by excessive excision of cartilage and vestibular skin. The combination of lack of support and contraction causes retraction of the ala. These patients sometimes also get nasal obstruction due to loss of the external valve. Treatment should follow the basic plastic surgical principle of replacement of all parts of the missing tissue, and thus both cartilage and skin will be required. A composite graft, such as from the concha, will be needed and support from the graft will help to keep the external valve patent.

Causes of the pollybeak deformity, or supratip fullness, include both inadequate and excessive resection of dorsal septal cartilage, and excessive lower lateral cartilage excision, leading to loss of tip support. Despite careful surgery, however, some patients still develop a pollybeak deformity. This is commonest in patients with thick skin. Treatment is by correction of the cause with further resection or augmentation with cartilage grafts.

Tip and alar-columella deformities include bossa formation (knob-like protuberances in the region of the domes), pinching of the nasal tip, columella retraction and alar retraction. A bossa occurs after extensive lower lateral cartilage surgery or by leaving sharp or rough edges after cartilage resection. Typically, it is not evident in the early post-operative period but shows up as the swelling settles. It usually requires revision as it is unsightly. Pinching of the lateral alar walls results from over-excision of the lower lateral cartilage. It may be accompanied by collapse of the external nasal valve, causing obstructive symptoms. Cartilage grafting is needed.

Columella retraction is usually due to over-excision and is treated by a composite graft or a cartilage graft.

In a septoplasty, one particular complication is supratip depression. A careful septoplasty technique should avoid this complication but this cosmetic disaster can still occur if a septal abscess develops or the nose sustains significant trauma in the immediate post-operative period. Commonly, however, supratip depression presents because a submucous resection technique has been used and excessive cartilage removed.

A subdermal haematoma can also occur after a septorhinoplasty, collecting underneath the dressings. Such a haematoma may go unnoticed until the external plaster or dressings are removed a week later. If this has occurred then evacuation of the haematoma is required promptly in order to try and ameliorate any adverse cosmetic result.

Pinnaplasty

There are two commonly used techniques in this surgery. One is the anterior cartilage scoring technique as described by Stenstrom. The other is the placing of permanent nonabsorbable sutures to hold the pinna back as described by Mustardé. Whichever technique is used, the patient, and the patient's parents if the patient is a child as is often the case, must be warned of the risk of recurrence of the deformity, what surgery if any will be required to correct such a recurrence, the presence of a post-auricular scar, and the rare but cosmetically disastrous risk of keloid scarring behind the ear.

In both techniques the skin and cartilage are marked with ink. It is important not to use Indian ink as this can leave permanent tattoo marks. Methylene blue is the ink of choice, but Bonney's blue and gentian violet are alternatives.

In the cartilage scoring technique the skin is elevated off the cartilage of the pinna. This can lead to haematoma collection and, subsequently, cauliflower ear deformity. Great care needs to be taken in haemostasis and the application of the dressings to prevent haematoma formation and also to ensure that the dressings do not come off prematurely in the active child. Haemostasis must, however, be achieved carefully as it is very easy to cause a full-thickness burn of the anterior pinna skin with diathermy, causing a permanent and visible scar.

Patients and parents must be warned that constant pain post-operatively, particularly if unilateral, must be reported to the surgeon who will need to remove the dressings to see if a haematoma has developed. If so, the haematoma must be drained to minimize the risk of cartilage necrosis. Once a haematoma has formed and revision surgery has been required, antibiotics should be prescribed as there is the additional risk of infection and this also may lead to permanent deformity of the pinna. Excessively tight bandages or knots from ribbon gauze placed to pull the bandages away from the eyes may cause skin ulceration and are indicative of substandard care.

In the Mustardé technique, there is a significant risk of the sutures either cutting out or becoming undone, leading to a recurrence of the bat ear deformity. In young children the cartilage may be particularly soft and so the Mustardé technique may be unsuitable. The surgeon needs to evaluate each case and decide a technique appropriate to the child.

The advantage of the Stenstrom technique is that it generally gives a good result and the ear is less likely to unfold with a return of the original deformity than in the

Mustardé technique where the recurrence rate is of the order of 15%.

Skin cancer, flaps and grafts

DELAY IN DIAGNOSIS

Despite head and neck skin cancer being one of the most common cancers in this country, cases of delay in diagnosis are unusual. The condition is more common in the elderly and occasionally diagnosis may be delayed in those that suffer from dementia, who live alone and fail to attend their GP. If there has been an administrative error within the NHS and an appointment has not been received, such patients may not seek clarification of the situation about their outpatient appointment until many months have passed.

Occasionally, an amelanotic melanoma is not recognized. It can be thought to be a benign skin lesion and may be excised in a minor surgery procedure by the family doctor or otolaryngologist. This is not a problem if the specimen is sent for histology but occasionally the excised lesion may be discarded and the true nature of the disease not picked up until a recurrence or distant metastasis develops at a later date.

In dealing with skin lesions it has been suggested that a failure to use Mohs technique for surgical excision amounts to substandard care *de facto*. However this is not the case. It is but one technique for treatment of skin cancers. Many hard-pressed histopathology departments are unable to offer the service due to shortages of staff or lack of training. In addition, in many parts of the country the histopathology department is on a different site to where the surgery is undertaken. In these circumstances it is not practicable to rush specimens by taxi from one hospital to another. Finally, there are certain parts of the face in which the technique would be inappropriate, such as the inner surface of the nasal vestibule.

Excision of the lesion with frozen section monitoring of the margins of excision is a widely used technique that is an acceptable alternative to Mohs surgery. If this is not available then excision with clinically adequate margins and repair with a skin graft rather than a flap can be carried out, the graft being removed and replaced by a flap at a later stage once histological clearance has been given and if the graft is unlikely to give an acceptable cosmetic appearance.

SKIN GRAFTS

If a patient requires a skin graft to repair a defect after trauma or excision of a lesion, appropriate pre-operative warnings must be given. Patients generally think that a skin graft looks the same as normal skin (i.e. there is an invisible mend) but it should be emphasized that this is not the case, that there may be a significant colour, texture or contour mismatch, and that other complications such as hyper- or hypopigmentation and hypertrophy may occur.

Ideally there should be 100% take of a graft. The commonest causes of graft failure are haematoma or seroma formation, infection and shearing of the graft on its bed. Small areas of graft loss should be managed conservatively but large areas may need regrafting. In both situations the scarring is likely to be worse than if there had been normal healing.

Patients should be warned of the slight risk of graft loss and that grafts look very unsightly for several weeks after surgery. Crusting of grafts is extremely common and requires application of moisturising cream. Grafts may change colour as they heal: split grafts from the abdomen, buttocks and thighs may become yellowish, and full thickness grafts may look redder than the surrounding skin.

Split skin graft donor sites should heal within two to three weeks. If when harvesting the graft, too deep a graft is taken, healing will be longer and the eventual scarring more noticeable, particularly as it may become hypertrophic. If a full thickness cut is made whilst taking the graft this should be sutured immediately and the patient told. A linear scar which heals well will leave a scar but when the scar is fully mature 6–12 months after surgery its appearance is not likely to be as bad as might seem initially.

Full thickness grafts should be taken from an area where a good colour match is more likely, such as the postauricular or supraclavicular regions. Unfortunately, even grafts from these areas may not match well or develop hyperpigmentation, a troublesome problem that is very hard to treat. Full thickness donor sites appear as linear scars and can undergo hypertrophy, remain narrow or stretch, all of which a patient should be warned about.

Split thickness skin grafts donor sites also become crusty for the first few months and require moisturizing cream. Milia may appear initially but these stop within a few months. Most donor sites become pale within 6–12 months but occasionally pigmentation or hypopigmentation occurs, particularly in coloured skin. Immature donor sites should be protected from excessive ultraviolet light or else they may pigment or burn.

SKIN FLAPS

A flap is needed rather than a skin graft when repairing an avascular wound, such as in an irradiated area, or to restore more tissue than can be achieved by a graft. The disadvantages of a flap are that an additional wound is made, the secondary defect, with additional scarring, that designing and raising a flap safely is technically demanding and may be got wrong, that flaps can necrose and that a flap can be too bulky, needing revision. Like grafts, the colour of a flap may not match the surrounding skin, but pigmentary changes do not usually occur.

Facelift

There are many potential problems with facelift surgery, ranging from physical complications, such as facial nerve injury and unsatisfactory scarring, to more generalized problems, such as disappointment with the rejuvenating effect of the procedure. The latter may be caused by unrealistic expectations.

The surgeon should ask why a patient wants a facelift, and look for initiating factors that might indicate the potential for dissatisfaction, such as recent occupational or marital stresses. Surgery will not alter a patient's lifestyle and will not cure failing relationships or difficulties at work. The surgical goal should be reasonable. The ideal patient will have been thinking about a facelift for some time and not just for a very short period, will have specific signs of ageing that can be seen, such as jowls or excess baggy skin under the chin, and will understand that surgery will refresh the face rather than make them look younger, particularly not taking 10 years off the appearance. Patients falling outside these groups run a high risk of being disappointed with the result of a facelift and may need to be advised against proceeding.

Patients who are dissatisfied with previous facial rejuvenation surgery, who have fallen out with other surgeons, who have a history of litigation, and who have seen several other surgeons, are very high risk medicolegally. Careful consideration should be given before accepting them for surgery.

As with other forms of facial plastic surgery, the preoperative assessment of the patient is very important. Clinical photographs should be reviewed with the patient so that he or she has a clear indication of what might and, perhaps more importantly, might not be achieved by the proposed surgery. The patient's hairstyle and use of makeup should be noted as these may alter the placement of the incisions.

With increasing age, damage from excessive sun exposure and previous irradiation therapy, the elasticity of the skin, the flap vascularity and the skin's healing ability lessen. This will affect the result of a facelift and may increase the complication rate.

Dark-skinned patients may develop hyperpigmentation post-operatively. Specific questions should be asked about: any previous facial surgery as this will affect the site of incisions; any history of alopecia as this may herald post-operative hair loss; and whether there has been a previous Bell's palsy as this might recur. Generalized medical problems should also be enquired about, such as hypertension or other cardiovascular problems, chronic obstructive airways disease, diabetes and coagulation disorders, including anticoagulant therapy and the taking of aspirin or similar drugs that can lead to post-operative bleeding. Cigarette smoking is a relative contraindication for surgery because of the high risk of flap necrosis, particularly in the post-auricular region, and smokers should stop for at least two weeks pre-operatively.

Each part of a facelift operation has its own risks and these must be explained to the patient. Care must be taken over the amount of local anaesthetic that is infiltrated to reduce bleeding, particularly if extensive neck procedures are being performed. The maximum dose of lignocaine and/or adrenaline must not be exceeded, and care must be taken for the injections to be in the right plane to avoid injury to the frontal and marginal mandibular nerves.

Correct placement of the incision is important as incorrect siting may lead to a complaint about unsightly or particularly visible scarring, pulling forward of the tragus to expose the external auditory meatus, or an abnormal shape of the earlobes. The incisions should be hidden within the hair as far as possible and must be made parallel to the direction of the hair follicles to prevent post-operative hair loss.

Flap elevation is in the superficial subcutaneous plane to achieve a thin flap but to retain the viability of the subdermal-dermal plexus. Haemostasis must be meticulous to prevent haematoma formation. The flap must be a consistent thickness or else post-operative irregularities in the contour will be visible. Special care when elevating the flap is needed to protect the frontal and mandibular branches of the facial nerve and the greater auricular nerve, the latter causing permanent numbness of the pinna. Dissection of the superficial musculo-aponeurotic system (SMAS) puts the facial nerve at risk, and SMAS plication may injure the buccal nerve or the parotid gland with the risk of a parotid fistula.

Draping of the skin flap after SMAS plication must be carried out with care as excessive posterior tension or failure to rotate the flap will give an unsatisfactory appearance. Excess tension near the tragus may pull it forward.

If liposuction is performed at the same time as a facelift, it is important to achieve a smooth result. The port of the liposuction tube should be held with the port away from the dermis to avoid 'buttonholing' the skin and excessive fat removal.

As with any operation, post-operative complications can occur after a facelift. Prompt and adequate treatment is required to avoid permanent unwanted effects. Haematoma is the commonest early complication. Some are minor and can be aspirated or milked after removal of some sutures but many require drainage. If untreated, at best an inflammatory response occurs leading to soft tissue irregularities, and at worst skin necrosis and infection.

Skin flap necrosis is not common, except in smokers or if the dressings are applied too tightly. It is best managed expectantly initially, but a large area will require skin grafting when the wound is clean. Careful wound care and, when appropriate, antibiotic therapy is vital. The patient will need much reassurance about the prolonged healing time and the resultant scars.

Facial nerve paralysis occurs in 0.5–3% of patients, most commonly involving the frontal and marginal mandibular branches. Most paralyses resolve spontaneously. Unless an injury is noted at the time of surgery, in which case it should be repaired, nerve injuries should be managed conservatively. Permanent paralysis may require additional surgery, such as an eyebrow lift. Sensory changes, such as hypoaesthesia of the facial skin, are common for several weeks. The greater auricular nerve may be injured. If it is noticed at surgery that the nerve has been divided it should be sutured, but otherwise treatment should be conservative. Permanent numbness will occur and a troublesome neuroma may develop.

Later complications include: hypertrophic scarring, often post-auricular and made worse by haematoma; infection and skin flap necrosis; earlobe distortion from excessive tension, a permanent deformity possibly needing further surgery such as a V-Y plasty; unfavourable

hairline changes, alopecia, permanent hair loss occurring in approximately 2–3% of patients, temporary loss with thinning more frequently but with hair regrowth within several weeks; bald scars due to incorrect bevelling of incisions; and hyperpigmentation from bruising or just spontaneous.

Mentoplasty

This is indicated as part of a rhinoplasty or as a separate procedure. A slight increase in projection of the chin is usually carried out with an alloplastic implant, usually Silastic. Projection of more than 1 cm may require a sliding genioplasty. Choosing the correct size and shape to match the shape of the patient's chin is important, particularly the curve of the implant and the length of it as it wraps round the mandible. Excessively long implants may result in the prosthesis being visible or palpable.

The surgical approach can be intra-oral or submental. The intra-oral incision is made in the labial sulcus. In a submental approach the incision must be posterior to the submental crease or else it will become visible as it is pulled forward by the implant. In both approaches a subperiosteal pocket for the implant is then created. Failure to match the size and shape of the implant exactly may lead to movement of the implant later, and great care must be taken not to damage the mental nerves. Other complications include haematoma, seroma and infection. In the long term, implants tend to give rise to some bone resorption.

Malar augmentation

Malar implants can be inserted through an intra-oral, a subciliary or a conjunctival approach. In the intra-oral route, care must be taken to avoid Stensen's duct. In the subciliary incision, a submuscular approach reduces the risk of eyelid retraction. The infraorbital nerve must be preserved. The implant is placed subperiosteally through a periosteal incision placed anterior to the orbital rim to minimize adhesions that might cause ectropion and lower lid contracture. The implant can be sutured in place to minimize the risk of movement out of place.

Eyelid surgery

A full pre-operative assessment for eyelid reduction surgery is very important. This should include assessment of the lid margin for ptosis, differences in the level of and ptosis of the eyebrows, the level of the lid creases, the degree of excess skin and the location and extent of fat pads. Lid laxity should be assessed with the snap test and the pinch test.

Pre-operative photographs are necessary in case there are minor degrees of asymmetry more visible photographically rather than clinically. These may be the cause of a complaint post-operatively if not detected.

Eliciting any pre-operative history of dry eye is very important and lacrimal secretion should be assessed by the Schirmer test if there is doubt. Patients with dry eyes can have a blepharoplasty but artificial tears and ophthalmic lubricants will be needed. Care must be taken to limit the degree of skin excision in both upper and lower eyelids to minimize the risk of intractable dryness.

Patients should be warned pre-operatively about the recognized complications of blepharoplasty, dry eyes, haematoma, globe injury, infection, lagophthalmos and ectropion, the possibility of visual loss, irregularities in healing and the need for secondary surgery in a small percentage of cases.

A post-operative haematoma may be a cause of visual loss. It also delays resolution of periorbital oedema and can lead to subcutaneous haemosiderin deposits that cause pigmentation.

Injuries to the cornea and globe should not occur in blepharoplasty and cannot be defended. Swabs are very abrasive and easily cause corneal abrasions. Instruments should not be passed over the eyes during surgery. Corneal protectors may be used for added security but may distort the shape of the lid. The inadvertent injection of local anaesthetic into the globe can occur. This can cause a selective parasympathetic palsy with a fixed dilated pupil.

Under- or over-resection of the fat pads, particularly on the lower lids, may give a poor cosmetic appearance. Rarely, the lacrimal gland may be injured or even resected, causing dry eye symptoms.

Poor placement of lid scars is difficult to correct. If the upper lid incision goes too far medially, an epicanthal web may develop needing a Z-plasty to correct it. If the upper lid incision is too close to the lid margin or too high, the scar will be visible. Correction is difficult. In the lower lid, the incision should be made close to but not involving the eyelashes or else permanent loss of the lashes will result.

Great care must be taken over the amount of skin that is excised. Lagophthalmos, incomplete upper eyelid closure, is a normal occurrence in the first 48 hours after surgery. It usually resolves spontaneously but a large lagophthalmos (greater than approximately 3 mm), or if it persists, indicates overexcision of upper eyelid skin. If left untreated, dry eye symptoms and corneal exposure occur. The best treatment is replacement of the excised skin, providing that this has been stored in a refrigerator at the time of the operation, as this provides the best match. Ectropion is often due to excessive removal of skin but may be due to other causes such as scar contracture or a lax lid margin. Taping of the lower lid, and if necessary a support stitch, for a few weeks may resolve the problem but permanent ectropion will require skin grafting that will leave additional scars.

Loss of vision is the most feared complication following blepharoplasty. It is very rare but, because it is such a serious complication, all patients considering a blepharoplasty should be warned of the risk of it happening. The mechanism of action is not clear but it may be due to acute elevation of intra-ocular and intra-orbital pressures due to retrobulbar haemorrhage from a bleeding artery retracting into the retrobulbar space. The elevated intra-orbital pressure leads to optic nerve head ischaemia and central retinal artery occlusion. Meticulous haemostasis is the best prevention.

Laser skin resurfacing

Lasers are commonly used for reducing wrinkles around the mouth and eyes, ablating areas of actinic damage and generally 'tightening up' the skin due to elastosis. The two lasers used are the pulsed carbon dioxide (CO_2) and the erbium:yttrium-aluminium-garnet (Er:YAG). The CO_2 laser removes 50–100 µm of tissue with each pass of the laser, whereas the Er:YAG laser removes only 25–30 µm of tissue. There is less collateral dermal energy with the latter and adverse effects, such as the risk of scarring, may therefore be less. Pre-operative assessment must include careful assessment of the skin, including photographs. Contraindications to surgery include active acne, recent retinoid treatment and an active herpes lesion.

Post-operative infection, including fungal and viral infections, will cause scarring and must be treated early. Post-operative pigmentation problems are most likely to be troublesome in patients with type IV and type V skin. Patients with black skin should not be treated because of the likelihood of hypopigmentation. All patients will experience some erythema after treatment but more unwelcome complications are persistent hypopigmentation and hyperpigmentation. Hypopigmentation may respond to topical treatment. For several weeks after treatment, exposure to bright sunshine may cause hyperpigmentation.

Rhinophyma

Rhinophyma is a bulbous enlargement of the nose and is caused by hypertrophy of the sebaceous glands, soft tissues and blood vessels of the nasal tip. If large, it can lead to obstruction of the nares. Misdiagnosis by assuming that the bulbousness is due to the underlying nasal cartilage may make the surgeon excise nasal cartilage instead of the soft tissues, leading to an abnormal shape of the nasal tip. Rhinophyma is usually treated by direct excision with a scalpel or by dermabrasion, but laser excision or cryotherapy can be used. Great care must be taken not to excise or dermabrade too deeply or else the area will heal slowly and by secondary intention, leading to unsightly scarring. If the patient develops an infection in the excised area, deepening of the skin loss may occur, leading to additional scarring which the patient may find unacceptable. Full thickness excision of all the rhinophymatous tissue followed by skin grafting has been advocated in the past but this is not considered now to be an acceptable procedure because of the extensive resultant scarring.

OTOLOGY AND NEURO-OTOLOGY

Hearing disorders

DELAYED DIAGNOSIS

Although parents may be convinced that there has been a significant delay in the diagnosis of a child with profound hearing loss, it is often difficult for them to prove this. Often the child will have passed the health visitor screening tests early in life; the claimant may find it difficult to establish that these were improperly undertaken and led to the wrong conclusion. A child may be born with a mild to moderate hearing impairment, which gradually deteriorates.

A delay in diagnosis of meningitis may also account for a claim for profound hearing impairment. In the case of pneumococcal or meningococcal meningitis this may amount to only a matter of hours, and there is often dispute as to whether the signs and symptoms of meningitis were evident at the time when the first doctor missed the diagnosis at the onset of the illness. This is especially so in babies. If not, a case can be defended successfully as there is evidence that the onset of profound deafness is early in the course of the disease, especially in pneumococcal cases. In one case, tuberculous meningitis was misdiagnosed as a viral infection, despite the fact that at the same time the child's mother had just been diagnosed with open tuberculosis. Nobody had linked the presence of the tubercular cough as being a likely source of infection and cause of the baby's ill health.

ESTABLISHING DAMAGES

Even if there is clear evidence from GP records that a child's mother attended on frequent occasions complaining about the child's ability to hear, the mother may have grave difficulties in establishing that the child has been damaged by any delay that may have occurred. The problem becomes more difficult if the child has other developmental abnormalities, particularly if they affect language development. A child in whom the diagnosis is delayed until the age of, say, two-and-a-half years may then be fitted with hearing aids and it is uncertain what deleterious effect the delay brought about. If the child is older and the optimum time for fitting a cochlear implant has been missed, then the prospect of the child developing the ability to understand spoken language and to communicate orally may have been lost. With a trend towards earlier implantation it has become more difficult to argue that diagnostic delay did not bring about adverse consequences.

NEGLIGENT CAUSATION

Profound deafness at birth may arise from a negligent act in the antenatal period. For example, in one case a mother was established as lacking immunity to rubella following the birth of her first child. The hospital failed to arrange a rubella vaccination, as did the GP. A year later the mother attended at nine weeks gestation with her second pregnancy, having just contracted rubella. The GP reassured her that, as it was coming to the end of her first trimester, there was no risk to the foetus of damage from the maternal rubella infection. As a result of this advice, the mother decided not to pursue a termination of the pregnancy, which had been her original intention. The child was born profoundly deaf. Judgement was in the claimant's favour.

DEAFNESS WRONGLY DIAGNOSED

Litigation may also arise due to decisions made on the false assumption that the child has a profound hearing impairment. In the young infant and toddler, a detected

hearing loss assessed by brain stem evoked response audiometry may give thresholds in the region of 80 dB. The child may be fitted with hearing aids, and educational decisions based on a hearing difficulty may lead the child to be placed in a school for children with special needs. Such a child may also have a fluctuating conductive hearing loss, due to otitis media with effusion, and the true sensorineural thresholds may only become established when the child reaches the age of 5 or 6. At this point, it may become clear that the hearing impairment is only in the order of 30–40 dB, and that placement in a mainstream school can be considered. The parents of such a child often feel aggrieved.

They may feel that their child is being disadvantaged educationally and attempt to seek compensation. Although the diagnosis in such circumstances of the degree of hearing loss may have been incorrect, it is a challenge for the claimant to establish that alternative management would firstly have been instituted, and secondly would have led to a materially different and improved outcome.

Congenital fixation of the stapes

Rarely, a child may present with a conductive hearing loss and no middle ear effusion or significant past history of middle ear suppuration. This may be misdiagnosed in the older child as otosclerosis and surgery recommended. In these circumstances a range of congenital abnormalities can be present and not be recognized by the inexperienced. When a stapedotomy is attempted, the result is frequently a dead ear secondary to a perilymph 'gusher'. Problems may also arise from attempting to perforate a mobile thin footplate. This happens when the anterior crus is attached to the promontory rather than to the footplate. This abnormality, rather than a fixed footplate, accounts for the conductive loss. Correct management is to either divide the anterior crus alone or else close the ear. It is rare that poor outcomes from stapes surgery in children can be defended. Not only do surgical errors occur, but also often the consent has been inadequate, not taking into account the special problems of such surgery in children. Where a stapedectomy is planned in a child under 10, most experts in the field would expect that high definition CT scans of the cochlear and vestibular aqueducts had been obtained beforehand. Congenital abnormalities of the inner ear are a specific contraindication to such surgery.

Matters become more complex in the case of the adult with congenital fixation of the stapes, as not surprisingly there are often no records from childhood. The past history of childhood hearing loss can be then erroneously ascribed to otitis media with effusion.

Ear syringing

Nearly all of the cases of negligent ear syringing take place in general practice.[2] The first common failure is failure to take an adequate history, asking in particular for previous ear surgery or ear infections with perforation of the eardrum as contraindications to undertaking the procedure.

The advent of the pulsed jet of water produced by a device connected to a simple pump has, in recent times, reduced the number of injuries sustained as a result of faulty bulb or barrel ear syringes disassembling during syringing.

Occasionally, irrigation fluid at the wrong temperature can cause the patient to move suddenly. This can happen either because excessively hot or cold liquid surprises the patient or, more commonly, a marked caloric effect with dizziness causes the patient to become stressed. Rarely, a sudden movement may lead to trauma of the external auditory canal.

Failure to ensure that all the wax has been removed can lead to a soggy mass of wax and dead skin left in the external auditory canal. This almost inevitably leads to an external ear infection and a dissatisfied customer. If the eardrum is perforated through trauma then it is probably wise to give a short course of prophylactic antibiotics to reduce the risks of otitis media. The presence of a perforation of a traumatic type following ear syringing does not automatically imply negligence: a perforation of the eardrum can still happen even if an adequate history has been taken and the procedure was performed competently. This usually happens in those patients who have had a previous perforation in the past, which has healed by a thin two-layer repair. The patient may not be aware that this has happened in the past and consequently have failed to declare the problem. However, a defence is unlikely to be successful if there is clear evidence in the GP's records of a previous acute otitis media that settled following an episode of aural discharge.

Otosclerosis

It should always be remembered that a bilateral conductive audiogram is a common finding in assessing a patient for surgery in otosclerosis. This presents the dilemma of wondering whether it is a true bilateral conductive hearing impairment or whether the phenomenon of central masking has led to the failure to detect a dead ear on one side.[3] In the patient who has had no previous surgery and appears to derive benefit from a single hearing aid worn in either ear, it is reasonable to assume that the patient does have a bilateral conductive hearing impairment. The problem arises in those patients who have had a stapedectomy on one side that has been unsuccessful, in that the hearing has not improved and the audiogram is showing a bilateral conductive hearing impairment. These patients would usually confirm that wearing a hearing aid in the operated ear provides no benefit. However, the only reliable way of determining whether there is inner ear function in both ears is to undertake pre-operative electrocochleography. In one case in which the patient had had several procedures on one ear it was decided that a stapedectomy should be undertaken on the ear that had never had any previous operations because his audiogram showed a bilateral conductive hearing loss. When the patient awoke following this surgery he had no hearing left whatsoever and subsequently had to be managed with a cochlear implant (unpublished data*). Electrocochleography should

be seriously considered in those patients who detect no improvement in hearing from a hearing aid worn in one ear, or where a previous stapes operation has been performed without apparent benefit.

Having established that the patient has a true bilateral conductive hearing impairment then the process of consent for surgery commences. It is important that the patient clearly understands that a hearing aid is a valid and relevant treatment. Once the patient has been counselled of the risks of stapedectomy including loss of hearing, balance dysfunction and tinnitus, the patient should be asked once again whether they are absolutely sure that they do not wish to consider at least a trial of wearing a hearing aid. It should be clearly documented in the notes that the patient has refused to either continue using a hearing aid or is absolutely refusing a hearing aid trial despite counselling.

Stapedotomy is the preferred operation in managing otosclerosis for more than 35 years. Stapedectomy is rarely indicated and is probably only appropriate as a management in certain complications of the stapedotomy operation. There are two basic techniques in stapedotomy: the first is where the fenestra is closed with a vein graft prior to positioning the prosthesis; and the second is where the fenestra is closed directly by the prosthesis itself. Both techniques are still widely practised and, despite the arguments put forward by the proponents of each, both techniques are still acceptable practice.

Complications may arise directly relating to the prosthesis itself. In the type of prosthesis in which the barrel is made of Teflon attached to a piece of wire, there have been incidences of the Teflon barrel becoming detached from the wire during the operation. In one case the Teflon barrel fell through the fenestra into the inner ear. In these circumstances probably the wisest thing to do is to close the fenestra with a vein graft but sadly, in this case, the surgeon attempted to remove the Teflon barrel and the patient subsequently developed a total loss of hearing (unpublished data*).

Litigation may arise post-operatively where a dead ear is the result of either a perilymph fistula or granuloma formation. Prompt diagnosis of a suspected stapedectomy granuloma with urgent exploration of the ear does have a reasonable chance of saving some inner ear function. This can also occur in sudden significant perilymph fistula. However, the patient with the suspected minor perilymph leak that is being treated conservatively is a much more difficult management problem from the point of view of choosing the optimum time for surgery. In many instances it can be reasonably demonstrated that even if surgery had taken place promptly there was still a likelihood that a total loss of hearing would occur. If conservative management is advocated with bed rest then it is essential to monitor the hearing daily and if the sensory thresholds are falling exploration and sealing any perilymph leak is required.

Iatrogenic facial nerve damage

This is a rare complication and is probably sustained as a result of negligence in about 1 in 600–1500 major ear operations. In the author's hospital there have been only two cases of permanent inadvertent iatrogenic facial nerve damage in middle ear surgery over a 20-year period, which gives an approximate incidence of 1 in 2000 cases of middle ear surgery excluding minor procedures, such as ventilation tube insertion and procedures on the external auditory canal (in which there were no palsies). In 1982, Wiet[4] estimated the risk of iatrogenic damage as being 0.6–3.6% in the USA, which is considerably higher than in the UK, but not all cases of iatrogenic damage are due to negligence. It has been reported in operations such as stapedotomy, but is so rare that it was doubtful that even despite the devastating effect that a palsy has, it was not a requirement to warn patients as part of the consenting process. This may no longer be the case in this post-Montgomery era. In the UK in 2016 the patient should be advised about the risks to the facial nerve from cholesteatoma surgery even if the surgeon has evidence from personal audit that it is not a common risk in their hands.

The occurrence of a facial palsy following an ear operation does not *de facto* indicate that a negligent surgical technique has been employed. In cases where the disease has exposed the nerve or where the nerve is covered in granulation tissue as a response to infection, facial palsy can occur despite the fact that all care has been taken. Also in cases where the nerve is found in a congenitally abnormal position[5] and is injured as a result then often a defence can be mounted. However, in these rare situations it is advisable to make detailed records supplemented by verification by another surgeon or photography if at all possible.

There are several common errors made in ear surgery that account for a facial palsy that are usually impossible to defend:[6]

- thermal injury as a result of drilling with inadequate irrigation
- failing to find the nerve in an area of normal anatomy and following it into the area where the pathology lies
- inexperience in recognizing the cardinal anatomical landmarks in a normal temporal bone.

This final situation is most common in trainees and usually occurs when undertaking a cortical mastoidectomy and the descending portion of the nerve is injured.

Injury to the facial nerve is much more common in parotid surgery and also joint replacement surgery on the temporomandibular joint.

Sadly, although the cause of the injury may be defensible, it is all too often that the management of the injury is substandard. The unexpected facial palsy that does not recover in a few hours goes unexplored, even though it is clear from the notes that the surgeon has no idea how the nerve has been injured. When an unexpected facial nerve injury occurs, the wise surgeon seeks guidance from a colleague and the patient is reassured that the injury is being taken seriously. Where neuronography indicates that a serious injury has been sustained, then urgent exploration of the facial nerve with repair is required.[7]

Settlements in the United States for facial nerve damage are much higher than in the UK. Wiet[8] quotes settlements of between US$200 000 and US$1.6m, whereas the largest settlement excluding loss of earnings in the UK is £40 000 (US$62 000). Dr Yeager of the Medical Inter-Insurance Exchange of New Jersey reported that in the 10 years from 1977 to 1987 they settled a total of 79 cases (four were iatrogenic facial palsies) arising from ear surgery.[9]

Nerve monitoring has now become widely available. Facial nerve monitoring has the ability to give the surgeon warning of proximity to the nerve in those cases where the nerve is dehiscent or in an abnormal position. However, such cases are usually defensible anyway. As yet, it is not standard practice to use a nerve monitor in major ear surgery, such as for cholesteatoma. In all the cases of iatrogenic facial nerve palsy that I have opined upon, only one case was the result of surgery by a consultant, with the rest due to operations performed by various grades of trainee or non-consultant career grade doctors. Usually the injury was gross with complete transection of the nerve and one of the circumstances indicated in the records is a failure to identify the major landmarks that indicate the position of the nerve. In the case of a trainee, there was usually no direct supervision. In all cases that are indefensible, adherence to the cardinal rules of mastoid surgery and adequate supervision by a trainer would have prevented the accident. It is debatable that these cases can be prevented by the use of facial nerve monitoring. A large prospective series of monitored mastoid procedures undertaken by trainees would probably be enough to convince the profession or, even better, a randomized controlled trial, but this is unlikely to happen for some time given the UK's track record on multicentre studies of otological surgery. Interestingly the last six cases of iatrogenic facial nerve injury that I have opined upon were all fitted with a facial nerve monitor.

Cholesteatoma

DIAGNOSTIC OR TREATMENT DELAY

Delay in diagnosis usually occurs due to a failure of the GP to refer a patient with a chronic aural discharge. Occasionally, particularly in those cases of congenital cholesteatoma with an intact eardrum, a mother may have attended either the GP, and/or the hospital, complaining that their child has a unilateral hearing impairment. It is quite permissible in those children under the age of 8, particularly if the tympanogram is abnormal, to wait the usual three months for a middle ear effusion to resolve. If the condition has not resolved, then serious consideration should be given to an examination of the ear under anaesthesia, and if there is any doubt, a CT scan. Plain radiography often gives a clue in these cases, due to the loss of the septae in the air cell system, as well as the cloudiness due to the presence of the cholesteatoma.

Although parents may be aggrieved by the delay in diagnosis, they are usually unable to establish that any additional damage has occurred as a result of the delay, unless there has been an intra-cranial complication.

If patients have been referred and diagnosed and placed on the waiting list for excision of a cholesteatoma, complications such as facial nerve paralysis, meningitis or other intra-cranial sepsis may occur whilst the patient is on the waiting list. In these cases it is rarely possible to prove negligence, as it is difficult for the claimant to establish that the waiting list has been managed such as to amount to providing substandard care. However, whether increased delays to some patient's treatment caused by prioritizing 'long waiting' patients amounts to negligence has not been tried in the courts. Cholesteatomas are often large in children despite a relatively short history and consequently it is probably only a matter of time until there is a challenge to waiting list management arguing that a child with a cholesteatoma should be given priority over an adult who may have waited longer. This may be especially so today as waiting list management is increasingly being taken out of the hands of consultants who know the patients and is being controlled more by hospital managers. As such managers are not medically qualified, there is an argument that the Bolam principle should not apply.

The cornerstone of the argument that is usually advanced in cases that develop intra-cranial complications while on the waiting list is that the patient should have been given priority over routine mastoid surgery. For example, in one case a patient lost all hearing in their only hearing ear while waiting for excision of cholesteatoma in that ear and the consultant and defence argued that all cholesteatomas were potentially life-threatening and as such should be treated in the order that they presented. The claimant argued that the fact he had such poor hearing in the other ear meant that should he lose all hearing in the diseased ear then he was going to have a greater loss than the other patients on the waiting list. The defence also was on Bolam. The case settled out of court in favour of the claimant (unpublished data*).

NEGLIGENT MANAGEMENT

As yet no litigation has arisen as a result of creation of an open cavity. However, patients are becoming increasingly sophisticated in their expectations and demanding of being involved in choices concerning their health, which has been upheld by the Montgomery case.[10] Having an open cavity effectively bars the patient from many jobs and, in particular, from joining the armed forces. In areas where the armed forces are major employers of young men who have little prospect of any other employment, choice of ear operation to eradicate cholesteatoma is important. Patients have been angry to discover that there was a choice of either canal wall up surgery or canal wall down surgery, and had a canal wall up procedure been undertaken there would have been a prospect of passing an army medical. They were angry that an open cavity had been created and as such there was now a considerable restriction on job opportunities. It is only a matter of time until this point is litigated.

Technical errors in performing mastoid surgery are still all too common. In one case, an aural polypectomy was

performed that revealed cholesteatoma. Several months later, an atticotomy for cholesteatoma was undertaken on the same ear. Five days following surgery the child was admitted to another hospital with meningism and cerebritis. An exploration of the ear was undertaken by an experienced ear surgeon who found that extensive cholesteatoma still remained. This was despite the operation note for the atticotomy indicating that all cholesteatoma was removed. The case was settled for an interim payment of £15 000 as fortunately, the child had made a full recovery from the brain infection, but should epilepsy subsequently develop then further compensation would be paid.

Ossiculoplasty

Ossicular reconstruction appears to attract remarkably little litigation. This suggests that in everyday practice not that many cases of ossicular reconstruction are being undertaken, or else those that are doing them are not making errors. The key to a satisfied patient is to manage their expectations. The patient with normal hearing in the other ear needs particularly careful handling. In these circumstances, for the patient to appreciate a significant improvement, the operated ear will need to reach within about 20 dB in the important speech frequencies of the other ear for the patient to notice a benefit. Consequently, if there is a significant sensorineural component on the side with the conductive loss, it may be impossible to give the patient a noticeable hearing benefit. To offer ossicular surgery in these circumstances would generally be considered substandard care. Fortunately, litigation in these circumstances is rare as even if the operation is successful all the patient feels is that the operation did not work. It usually requires a loss of amenity for the patient to seek redress, such as the development of chronic discharge, pain, tinnitus or altered taste sensation.

Rarely, serious damage can occur during ossicular surgery. This has included gluing an instrument to the stapes with histoacryl glue with accidental removal of the stapes on removal of the instrument.

Recently two cases have occurred where a prosthesis with a shoe that rests on the footplate has given trouble. In this design there is a central wire core to the prosthesis. This wire has gone through the shoe and penetrated the footplate causing a perilymph leak.

Sudden sensorineural deafness

From time to time, a patient will attempt to litigate following a sudden loss of hearing. This usually arises when the patient presents to a specialty other than ENT, such as general practice or orthopaedics. Examples include patients told by their GPs that they had colds with middle ear effusion, although they had no cold symptoms, and patients awaking from non-otological surgery with total hearing loss in one ear. Cases that subsequently litigate have usually been told to consult their GP. There can be trouble if they are subsequently told that prompt treatment with a vasodilator or steroids would have restored their hearing. These cases can usually be defended as there is no evidence that any therapy is effective in acute sudden sensorineural deafness apart from acyclovir in herpetic infection and perhaps steroids in acute autoimmune cochleitis and tertiary syphilis.

Dizziness

Failure to diagnose a cause of dizziness can lead to litigation, but the likelihood of success usually depends on the final diagnosis. Vestibular schwannoma appears to be the number one disorder for which the public will attempt litigation if diagnosis has been delayed. However, cases are rarely successful due to the slow growth rates of the tumour and difficulties in establishing that any damage has been caused by the delay. It is in those disorders where there is an effective, reliable treatment that litigation is likely to be successful.

A good example is provided by the failure in one case to diagnose bilateral labyrinthine failure in a young professional. The patient attended her GP with acute rotatory vertigo and was seen by her local ENT surgeon. Following a history, and a brief clinical examination with audiometry and a magnetic resonance scan, the surgeon diagnosed acute vestibular neuronitis and reassured the patient that she would get better. Six months later the patient was still off work despite having seen her local physiotherapist. The patient then went privately to see another ENT surgeon with a special interest in balance dysfunction. By the end of a half-hour consultation that impressed the patient, the surgeon diagnosed bilateral vestibular failure, which was confirmed by caloric tests, and instituted Herdman exercises. The patient was back to work within six weeks and felt considerably better. She litigated for the six months' loss of salary and brought a complaint against the original specialist through the NHS complaints procedure (unpublished data*).

Benign paroxysmal positional vertigo is another disorder that if missed may lead to a prolonged period off work but there has not yet been litigation for failure to diagnose and treat this condition as far as I am aware.

Dizziness can be the presenting symptom for a number of serious conditions. Failing to be suspicious of cardiac causes and undertaking a basic examination in a patient presenting with dizziness can lead to allegations of negligence. Checking someone's pulse will detect arrhythmia and heart block. Failing to identify such serious disorders will depend on the circumstances and the symptoms complained of but could lead to litigation. Similarly, failing to diagnose and act on severe untreated hypertension or marked hypotension can lead to a successful claim.

Menière's disease

Failure to diagnose Menière's disease is unlikely to succeed as the patient would have to establish that they would have been successfully treated within the time frame of the delay. Litigation therefore tends to arise because of side effects of the treatment that the patient was not expecting.

SACCUS DECOMPRESSION SURGERY

The structures that are at risk of damage in this procedure are the facial nerve, posterior semicircular canal, the dura and the lateral venous sinus. Damage to the facial nerve or the posterior semicircular canal is usually indefensible unless the nerve is in a congenitally abnormal position. Opening the dura with cerebrospinal fluid leak is an inherent risk of many of the advocated procedures on the sac, such as excision, insertion of a valve, and so on, and so a defence can often be mounted. In one case the lateral sinus was injured and led to major complications. During the procedure a cutting burr opened the sinus. The surgeon chose not to repair the sinus but to pack it. Before doing this he chose not to refer to the scans that had been done to exclude a vestibular schwannoma. Following the procedure, the patient developed bilateral VI nerve palsies and chronic headache due to packing of the only lateral sinus, as there was a congenital absence on the other side. This may be seen as incredibly bad luck, but it is a complication that could have been foreseen and prevented by the simple measure of having the scans in the theatre and checking them before deciding on how to manage the complication (unpublished data*).

The unusual

Occasionally the bizarre turns up. The following are some of those cases that have occurred that could not be foreseen by most experts in the field of otology.

HYPERSALIVATION

The patient complained of having excessive mucus and saliva at the back of the throat. She was a senior executive in a stressful occupation with an introspective personality. Despite normal sinus radiology the surgeon undertook a range of sinus procedures including washouts and intranasal antrostomies, none of which produced any long-term resolution of her symptoms, which she was beginning to dwell on. He then diagnosed 'hypersalivation', even though the patient was not on any medication known to cause this, and advocated a tympanic neurectomy, which was duly carried out and produced no benefit. He then persuaded her to have a tympanic neurectomy on the other side, which did not help either. At this point, the patient sought a second opinion.

SHAM SURGERY

A patient with Menière's disease attended an otologist privately and after a consultation and discussion it was agreed that a saccus decompression should take place. After the operation the patient was no better and thus sought a second opinion. On this occasion, a computed tomography scan was undertaken as part of the investigations, which revealed that no saccus decompression operation could have taken place as the mastoid air cell system was present and normal. The patient had not received the operation for which she had paid and, as such, had been defrauded. The patient chose to treat this as a criminal matter and reported it to the police who subsequently took action against the doctor concerned. It is essential when billing a patient that they are billed for exactly what they received.

Causation of loss of hearing

From time to time, expert opinion is sought on the matter of causation of deafness, where the alleged injury has been perpetrated by a doctor from another specialty. There are some areas of practice in which this happens again and again.

FAILURE TO DIAGNOSE MENINGITIS

Usually the doctor involved is a paediatrician, accident and emergency specialist or GP. In most circumstances, the date and time when the disease should have been diagnosed can be established with some certainty. It is usually easier to express an opinion if the infecting organism is known. Placing the hearing loss in the context of other neurological damage is much more difficult. In other words, it may be possible to state with some conviction that hearing would have been saved, but it is much more difficult in some cases to assert that the interpretation of sound would have been normal, especially if it is likely that other central neurological damage would have occurred. In expressing an opinion on such matters, it is useful to discuss the hearing loss and neurological damage with a neurologist. This is particularly important if requested to give an opinion on the management of the claimant's current condition with a cochlear implant and the claimant also has a severe neurological deficit.

OTOTOXICITY

It is unusual for the claimant to allege that the negligence occurred at the hands of an otolaryngologist, but from time to time indiscriminate use of ototoxic ear drops are accused of causing deafness. Establishing causation can be difficult. First, it may be claimed that the deafness has occurred because of chronic suppuration. Second, there is nothing in the medical literature that establishes beyond doubt that topical ear drops are ototoxic when used in short courses. Third, it may be argued that when used to treat Menière's disease, buffered gentamicin does cause deafness and the literature gives many accounts of this; however, the counter-argument is that topical gentamicin ear drops are not buffered and therefore do not act in the same way as buffered gentamicin. Nevertheless, where a patient has been using ototoxic ear drops in the presence of a perforation or mastoid cavity on a daily basis for many months or years contrary to the advice in standard texts, it is a real possibility that having heard the scientific argument a judge will give the benefit of the doubt to the claimant.

Ototoxicity is much more common where the drug has been administered parenterally. Consequently, where the drug is an aminoglycoside, knowledge of renal function

and inspection of the drug charts and any blood levels usually makes it clear at what point the ototoxic deafness occurred. Rarely, the doses and drug levels appear to be within the therapeutic range, yet there appears to be no other explanation for the deafness occurring other than ototoxicity. In these circumstances the possibility of synergy between drugs causing an ototoxic effect has to be considered. Common synergistic combinations are furosemide and/or vancomycin with an aminoglycoside. Also a rare genetic predisposition to ototoxic effects of aminoglycosides could explain deafness where drugs have been used within recognized therapeutic parameters. Opinion from a clinical pharmacologist may be valuable in trying to determine the possible cause of the claimant's deafness.

Dermatological products containing steroid and aminoglycoside may cause sensorineural deafness after prolonged usage on inflamed skin. Any patient presenting with symmetrical deafness should be asked about usage of skin preparations. A typical situation may be prolonged usage of Betnovate® with neomycin to manage generalized eczema. The patient should be advised of the possible cause and, after excluding other causes, it is reasonable to attribute the hearing loss to the obvious. As usage has been prolonged, often over many years, it is much more difficult to advise the court at what point the hearing loss started as opposed to when the claimant noticed a problem. The easiest way may be to quantify the hearing loss and then divide it by the number of years over which the product was used. However, this may not be fair as the history of usage of the product is not likely to indicate even consumption but variation as the underlying skin disorder waxes and wanes.

The court, however, needs a practical solution, which may often be reached following discussion with the expert for the other side. Both experts need to demonstrate that they have considered all reasonable ways of calculating the onset of the hearing loss and why they have discarded some methods in favour of another.

POST-SURGICAL LOSS OF HEARING

Very rarely, sudden sensorineural deafness can occur as a result of surgery in the posterior cranial fossa. The otologist may be asked to give an opinion as to the likely cause. This may be a 'fishing expedition' on behalf of the claimant by their lawyers. Any operation in the posterior cranial fossa can cause deafness. The cause may be obvious, such as vestibular schwannoma surgery or a meningioma involving the VIIth and VIIIth nerve. On the other hand, it may be something unrelated to the VIIIth nerve such as a microvascular decompression of the Vth nerve for trigeminal neuralgia or VIIth nerve for hemifacial spasm. The cause of the deafness is frequently not clear. Each case has to be considered individually but in most cases the answer comes down to vasospasm, embolism, thrombosis, dividing the blood supply or venous drainage surgically, or cutting the VIIIth nerve.

Embolism causing deafness is rare but it occurs most commonly on heart bypass surgery and following major limb injury when it is believed to be fat embolism in the presence of a right to left cardiac shunt, say through an atrial septal defect.

PAEDIATRIC OTOLARYNGOLOGY

Tonsillectomy and adenoidectomy

DENTAL DAMAGE

Most anaesthetists will advise that loose milk teeth are removed prior to surgery and consequently inhalation of a milk tooth is unusual. Occasionally, secondary dentition can get chipped in the older child or adult. Many hospitals now have speedy internal access to dental services to effect a repair, which often forestalls litigation.

CONSENT AND BLEEDING

One of the commonest sources of complaint revolves around post-operative haemorrhage. Many parents when they are giving consent do not grasp that a haemorrhage can be large, require a blood transfusion and even become life-threatening. Most parents will acknowledge that they were warned that bleeding could occur, but most do not have in their mind a collapsed, shocked child with a young doctor desperately trying to get venous access – or even worse, medical and nursing staff showing signs of panic as they realize they are losing control of the situation. Parents who have come through this scenario with their child almost all say that they would not have consented had they known of this risk. Actual haemorrhage rates are between 5% and 10% with severe bleeds happening in approximately 1–2%. A landmark case in October 2004 in the House of Lords[11] now means that it is no longer necessary for the claimant to establish that had they known of the risk they would not have had the surgery; it is just necessary to establish that they would have delayed surgery whilst they sought further advice. This effectively means that it is now essential that every parent be warned of the risk of major haemorrhage and blood transfusion.

Occasionally, the haemorrhage can go unrecognized by nursing staff. This can happen when nursing staff do not follow post-operative instructions on monitoring or, worse, carefully chart a rising pulse in a restless child up to the point that the child has a massive haematemesis or even loses consciousness.

Errors in the resuscitation of the shocked child may be less common now with the introduction of paediatric life support and advanced paediatric life support training courses.

POOR SURGICAL TECHNIQUE

Diathermy burns in the mouth and on the lips are still produced. Considerable care needs to be taken especially if using diathermy dissecting instruments or scissors as these can cause large burns, particularly on the tongue. It is generally impossible to mount a defence.

Perforation of the palate – deemed to be due to negligent surgery – has been reported with diathermy dissection.

Excessive resection of the soft palate leading to velopharyngeal incompetence can occur. Where these changes in speech and swallowing reverse within a few weeks a defence can usually be mounted. However if the changes due to nasal escape persist beyond two years the loss of soft palate tissue is usually so excessive that a defence is impossible.

Acute epiglottitis

Since the introduction of haemophilus influenzae B (HiB) vaccination, epiglottitis is on the decrease. No child died from epiglottitis in England and Wales in 2013 while there were nine adult deaths, all aged over 45. In the recent past it was failure to diagnose or suspect the condition that would lead to a patient being sent home only to return hours later with grave breathing problems or even to die at home. Not only may it be a failure to recognize clinical symptoms and signs, but also the classical radiographic appearance can go unrecognized, thus leading to an indefensible claim.

Acute airway obstruction is more commonly due to acute laryngotracheobronchitis (ALTB or croup), especially in infants. If an artificial airway is needed this is now best managed by intubation. The anaesthetist may wish to have an ENT surgeon standing by to undertake a tracheotomy should intubation be impossible and the airway become compromised. Emergency tracheotomy in this situation is nowadays extremely rare. If the airway is not quickly secured, brain damage ensues. Whether substandard care is deemed to have occurred will depend on each individual case.

Tracheotomy

Problems with the operation being undertaken as a planned procedure are unusual. Rarely, in very young children a pneumothorax can develop as can injury to the brachiocephalic vein. In the immediate post-operative period, should the tracheostomy tube become dislodged then there can be problems with maintaining the airway. This is why the tube may be sutured to the skin or stay sutures placed on either side of the tracheal incision to help find the opening should the tube be dislodged.

Most litigation relating to tracheotomy surgery can be attributed to complications arising from poor nursing care. Many patients who have tracheotomies have been long-stay patients on intensive care. These patients frequently have chest infections with production of thick secretions. The secretions leading to acute airway obstruction can block the tracheostomy tube. Speedy identification of the problem by close monitoring of the patient usually results in aggressive suction of the airway with saline lavage or bronchoscopy with lavage if necessary. If this does not cause a rapid relief of the problem, the tracheostomy tube can be removed altogether. Unfortunately problems arise on general wards where the nursing staff may have many patients to look after and are unfamiliar with tracheostomy care. Ward nurses on ENT and neurosurgery wards are often experienced in nursing tracheotomies patients but this cannot be said for the other wards. The timid nurse is often frightened to introduce a suction catheter deep into the lungs. In fact it is failing to pass the catheter right through the tube into the trachea that leads to the deep part of the tube obstructing with dried secretions. Also, these nurses may not have been trained to undertake bronchial lavage to loosen secretions and so bronchial plugging happens, which reduces the patient's oxygenation.

When the patient's airway obstructs, speedy removal of the 'inner' tube and aggressive suction is required. If there is no inner tube then rapid removal of the whole tracheostomy tube and insertion of a clean tube is required. The tracheotomy tube is then connected to an Ambu-bag for inflation of the lungs. Despite the obvious fact that the tracheotomy was undertaken for obstruction to the airway above the stoma, there have been cases where the nursing staff attempted ventilation via the mouth with a facemask and ignored the tracheostomy. It was only when the cardiac arrest team arrived that the blocked tracheostomy was dealt with, but by then severe brain damage had been sustained.

Foreign bodies

THE EAR

The safest way to deal with a foreign body in the ear of a small child is under a general anaesthetic. Attempts to remove a foreign body from the ear without a general anaesthetic by syringing or the use of a strong electromagnet are often successful and carry a low risk of injury. However, instrumentation of the ear in a fractious child can lead to serious injury; such an action can only rarely be defended. Fortunately the injury is usually just limited to laceration of meatal skin, but perforation of the eardrum, ossicular injury and even complete avulsion of the stapes has occurred.

THE NOSE

Failure to diagnose a foreign body is a common cause of complaint and even litigation. The presence of a unilateral or even bilateral foul nasal discharge, which does not settle, should alert the otolaryngologist to the possibility of a foreign body in the nose in a child. In most cases the mother has attended on several occasions at the GP, the accident and emergency department and the ear, nose and throat department where a junior doctor has failed to realize the significance of the problem.

It is a common practice to wrap the small child in a blanket, then to remove the foreign body. However, if this method is employed, it is vital that all care is taken to avoid injury and the practice should not be used on those at risk of atlanto-axial subluxation. Injury occurring in these circumstances is difficult to defend when it could be argued that a general anaesthetic carries less risk.

THE OESOPHAGUS

Problems usually only arise with sharp foreign bodies. The main risk is of perforation but often this can be defended with a sharp foreign body. However, litigation is more likely to arise when there is a delay in recognizing the perforation or inappropriate management once recognized.

THE AIRWAY

Occasionally an inert foreign body can be present for some time before it is recognized. Complaint usually only arises when a significant symptom such as stridor is ignored and then subsequently it is found to have been due to a foreign body.

An unjustifiable delay in undertaking an examination where a foreign body has been inhaled may lead to problems. Any history of a suspected inhaled foreign body accompanied by a severe bout of coughing or noisy breathing mandates an examination of the airway and bronchoscopy. This is especially so when the foreign body is of a vegetable material such as a peanut. The delay can lead to swelling of the peanut with subsequent obstruction to that lung segment and bronchiectasis or lung abscess.

It should always be remembered that a normal chest radiograph does not exclude a foreign body and is not a defence against neglecting to undertake a bronchoscopy.

BUTTON BATTERIES

These modern foreign bodies can cause considerable damage if left in place for any length of time. If they are left in place in the nose or oesophagus they cause caustic burns with marked swelling and a risk of subsequent stenosis. Litigation may arise if a child is not treated as an emergency but is left until the next available routine list.

IATROGENIC FOREIGN BODIES

My experience of this includes a nasal splint retained for 17 years, a guidewire left in the airway for several weeks after a percutaneous tracheotomy and swabs left in the airway after adenoidectomy.

Cervical lymphadenopathy

Once a patient presents with a neck lump, delay in referral is rare. When it occurs it is nearly always in young adults or children.

Once a patient is referred there can be a preoccupation with investigating for cancer rather than on some of the more esoteric conditions such as infections, for example tuberculosis and cat scratch fever. History taking may be inadequate so that exposure to an infection is missed and investigations are not considered. Fortunately, investigating for cancer does usually bring to light the alternative diagnosis.

Surgery may be considered to establish a histological diagnosis in persistent cervical adenopathy. Trauma to the accessory nerve with resultant shoulder drop can arise as a result of dissection in the posterior triangle. Patients need to be explicitly warned of this risk and its consequences prior to surgery. Ultrasound imaging may avoid the need for surgery in some neck masses. Proper surgical technique will avoid injury to the accessory nerve. Firstly it is usually best to undertake the open biopsy under a general anaesthetic without muscle relaxant or infiltration of local anaesthetic. The accessory nerve should be found in an area of normal anatomy and traced towards the node that is being biopsied. Traction should be used judiciously and use of the diathermy kept to a minimum and always where the tissue being cauterized is seen. On completion of the surgery it is well worthwhile assessing accessory nerve function and recording it.

If an injury to the nerve is identified then it should be thoroughly assessed. If neuronography suggests a major lesion then exploration of the nerve should be undertaken and a repair effected if necessary. If a lesion is detected after some months then EMG evaluation can be useful to predict likely recovery or to indicate a major lesion. Discussion can then take place on the pros can cons of late exploration of the injured nerve.

Salivary gland tumours and congenital anomalies in children

This is a complex group of disorders. Claims usually arise because of delay in diagnosis or facial paralysis. Adverse outcomes occur especially where a surgeon is persuaded to manage a condition that he has little or no experience of rather than insisting the child is seen in a tertiary referral centre.

Epistaxis

In children, the commonest site for repeated epistaxis is the nasal septum. Cautery with silver nitrate is still commonly practised. This rarely causes a problem, but excessive use on both sides of the nasal septum at the same time can lead to a septal perforation. This can also occur when hot wire cautery is used. In occasional circumstances, a severe vestibulitis following the cautery may be a significant contributory factor. Usually, such a complication cannot be defended.

Trichloroacetic acid is rarely used nowadays in the UK to cauterize the nasal septum. However it is now more commonly seen being used as a chemical peel agent in facial plastic surgery. This needs to be handled very carefully as if too much or the wrong concentration is applied it can run on to the upper lip and cause a permanent scar.

Complicated sinusitis

The usual practice is to treat the frontal and ethmoidal sinusitis with decongestants and antibiotics, which is often successful. However, if there is a failure to respond or there is evidence of infection spread beyond the sinus, then drainage of the sinus is required. Failure to recognize that the infection beyond the sinus can lead to orbital abscess and intra-cranial infection. Within the hospital setting,

spread of the infection should be recognized within 24 hours of the first signs or symptoms of this complication developing.

If the infection spreads beyond the frontal sinus, then infection of the bony walls of the sinus can be inferred, as well as thrombosis of the venous channels through the bone. This infection is difficult to eradicate and requires prolonged use of antibiotics in the order of 8–12 weeks. When a patient presents with marked swelling of the soft tissues of the forehead, perhaps with a subperiosteal abscess, there may be an initial settling of the symptoms with a two-week course of antibiotics. The dramatic improvement in the patient's condition may lull either doctor and/or patient into a false sense of security and the antibiotic course is terminated as a result. Then, weeks later, the features of chronic osteomyelitis develop or even secondary intra-cranial sepsis. It is indefensible not to give a prolonged course of antibiotics where there is a significant risk of osteomyelitis.[12]

Atlanto-axial instability

Children with trisomy 21 (Down syndrome) have a high risk of atlanto-axial instability. This can result in excessive movement of the odontoid process during anaesthesia, such as to cause pressure on the spinal cord and neurological dysfunction, including permanent tetraplegia. It is often the anaesthetist who is blamed, especially if the induction has been fraught and the parent was present. However, it is more likely that it is the surgeon and the theatre team who cause this event by over-vigorous movement of the head while the child is hypotonic under the anaesthetic, often with muscle relaxants. High-risk children should be assumed to have the disorder. The practice of ordering routine plain radiographs of the cervical spine prior to surgery on Down syndrome children is outdated and no longer appropriate. It is more important to ensure that all theatre personnel move the child's head with extreme care. There is a salutary lesson to be learned with reference to this: a case was brought after a myringoplasty from which the child awoke with a partial tetraparesis. Post-operative radiology indicated that it was a rotational injury probably caused by the surgeon pushing the head away from himself to get a view of the anterior margin of the perforation whilst trying to position the graft. The mother dropped the case when she learned that it was more likely that the surgeon rather than the anaesthetist had caused the injury, as she liked the surgeon and thought he was a kind and caring doctor.

HEAD AND NECK SURGERY

Thyroid surgery

In times gone by it was standard practice to leave a clip remover attached to the end of the bed of any patient that had thyroid surgery so that, should a haemorrhage arise, rather than the patient having an airway obstruction with death or brain damage, they just got a bad scare. I was surprised only this year to have two cases where no clip remover was present. In one the patient died; in the other, by the time the sutures were released the patient had sustained a major brain injury. This should not happen and I would suggest that this misadventure would be a good candidate to join the list of never events.

Recurrent laryngeal nerve injury remains the mainstay of clinical negligence in thyroid surgery. The key to preventing litigation is to ensure that training covers the techniques of finding the recurrent and superior laryngeal nerves; the key to defending litigation is a good operation note that details how the recurrent laryngeal nerves were identified and protected during the surgery. Monitoring can also be used and can be especially helpful where the gland is grossly enlarged and in supervising trainees. It is extremely unusual to find a claimant who alleges they had no warning of recurrent laryngeal nerve injury and the risk of change of voice; however there appear to be occasions when the risk of bilateral recurrent nerve palsy and its consequences has not been mentioned. It is such a devastating injury that a claimant having surgery for a benign condition has a good chance of persuading the court that they would have postponed surgery or considered an alternative treatment such as radio iodine. In operative cases where the vagus nerves and/or the recurrent laryngeal nerves are at risk it is wise to record vocal cord function found at a pre-operative laryngeal examination as occasionally a patient will be found to have an unrecognized cord palsy.

It is essential that all thyroid specimens are subject to histology. This also goes for thyroglossal cysts as rarely a malignancy may be found.

Acute loss of parathyroid function can occur. In some cases it can even be predicted, such as the risk occurring after removing a functioning parathyroid tumour or after a total thyroidectomy for cancer. It is the unsuspected case that catches out the unwary. As a general rule if both lobes of the thyroid have been disturbed and not necessarily at the same operation then it is wise to monitor calcium function and blood levels at least once in the post-operative period. The same holds true in laryngectomy surgery even if a thyroid lobe with its parathyroids has been preserved.

Submandibular gland surgery

STONES

The main issue with stones is failing to warn of the risk of leaving a stone behind when opening the duct in the floor of the mouth to extract stones. Usually there is a floor of mouth radiograph to compare the extracted stones with. It is also wise to lavage the duct after removing the stones just to wash out any grit that might be present. However, despite these steps, occasionally a stone will be encountered that will not come out easily. If the patient has been duly warned there is rarely a problem. However, if there

is a post-operative infection secondary to a retained stone litigation can follow.

SUBMANDIBULECTOMY

If a discrete lump can be felt within the gland then it is malignant until proven otherwise. Fine-needle aspiration cytology can be of particular help when it confirms a malignancy but if it is equivocal or even if a report of a benign condition comes back, the wise surgeon should still treat the gland as potentially containing a cancer. Stones and sialectasis can usually be confirmed radiologically.

It is essential to warn of the risks of marginal mandibular branch of the facial nerve palsy, lingual, and hypoglossal nerve injuries. Anaesthesia of the skin over the gland post-operatively is common.

Some series quote as many as 30% of excisions as being accompanied by a nerve injury with mandibular branch of the facial leading the way with an external excision technique and the lingual with an intra-oral approach.

There are two techniques for managing the marginal mandibular branch of the facial and the technique used should be recorded. In the first technique the lower border of the gland is identified and the capsule incised. The capsule of the gland is left attached to the skin and subcutaneous tissues, in which will be the nerve. The dissection is performed in the subcapsular plane. This is also the quickest technique. The other way is to actually find the retromandibular vein and follow it superiorly to locate the nerve and then dissect the nerve. In this way the nerve is always kept in view and the risks of injury reduced. Care has to be taken to dissect close to the gland in benign cases to reduce the risk of injury to the hypoglossal and lingual nerves on the deep aspect of the gland. Injury to the nerve is not *de facto* evidence of poor surgical technique but to convince a court that the operation was done competently, a good note dealing with how these nerves were protected is important.

Parotid disease

Management of chronic sialadenitis leads to litigation as it is often underestimated by both surgeon and patient. Problems arise when the patient has unrealistic expectations of the surgery. The risk to the facial nerve is extremely high when attempting a total resection of the gland. Opinion is divided as to whether total excision is required of the whole gland. As a general rule if any glandular tissue is left behind there is a risk of further active infection but radical excision of the gland carries high risk of facial nerve injury. The golden rule is always to try and treat conservatively. If a point comes where there is no choice but to operate then it is essential that the patient accepts that they will probably have some degree of loss of facial movement.

Salivary gland fistulae if persistent can lead to allegations of substandard care. It is generally accepted that botulinum toxin injected into the remaining gland is first line treatment. Should this fail, ligation of the fistulous tract is worth a try. In recent times histoacryl glue has been used to block the fistula and the National Institute for Health and Clinical Excellence (NICE) has produced guidance on this technique. Once again litigation can be avoided by managing patient expectations from the outset. It is a risk that should be mentioned at consent and when it occurs the patient needs to understand that they can be troublesome to stop. However, leaving the patient to leak saliva from the incision with only reassurance is unacceptable care.

PAROTID TUMOURS

If the histology of a tumour has not been revealed by a fine-needle aspiration cytology then the lump needs to be excised with a substantial cuff of tissue around it. This is because, should the tumour be malignant or a pleomorphic adenoma, then local recurrence is a real risk and will be difficult to defend. Occasionally a GP will remove a parotid lump, often expecting it to be a benign skin lesion such as a sebaceous cyst, and get a surprise when the histology of a pleomorphic adenoma comes back. If such a patient is referred, the hospital consultant has a choice as to what to recommend to the patient. The choices are radiotherapy, revision superficial parotidectomy or watch and wait. There is no right thing to do and each case has to be weighed up, taking into consideration the size of the specimen removed and the age of the patient. Should the tumour be a low-grade malignancy then total parotidectomy with facial nerve preservation is usually the treatment of choice but all such cases now should be managed through a multidisciplinary team (MDT).

Where a tumour is located hard up against the skull base at the stylomastoid foramen it is substandard to try and locate the main trunk of the facial, as the tumour will for sure have moved the nerve to an abnormal anatomical position. The nerve should always be located in an area of normal anatomy. If the tumour is known to be benign then it best to identify a peripheral branch such as the marginal mandibular branch of the facial nerve and trace it back towards the main trunk and the tumour. This will usually effect a successful excision without a nerve palsy. Where the tumour is malignant then it is best to open the mastoid and identify the descending facial nerve and follow it towards the tumour. This has the advantage that in a low-grade malignancy the nerve can usually be kept intact but if that is not possible grafting is permitted.

With an increasing interest in patient outcomes it is wise for the ENT surgeon to keep a record of all his salivary gland surgery and the outcomes and complications so that he can defend his position if there is any argument about his competency.

Chronic laryngitis

Poor outcomes of surgery lead to litigation especially in the professional voice user. One of the commonest

allegations is lack of conservative management in the early course of the condition and going for a surgical option without trying alternatives. In some instances this can be defended, especially where the patient abuses tobacco and alcohol and cancer is suspected. Nevertheless the wise surgeon should explain his reasons for recommending biopsies in the larynx and counsel on any long-term risk to the voice.

The main reason for a poor result is post-operative tethering of the mucosa, often as a consequence of stripping away too much tissue and damaging the underlying vocal ligament.

Another reason for litigation is misdiagnosis or failure to make a diagnosis at all of rare neurological conditions that can affect the voice and larynx. Such conditions include Shy Drager syndrome, laryngeal dystonia, motor neurone disease, neuroferritinopathy and neuroacanthocytosis. These conditions usually present with such a range of symptoms that affect other parts of the body as well as the larynx that they rarely present in an ENT department and when they do the systemic nature of the disorder is usually spotted. In the early stages they can just present with voice and laryngeal symptoms or the ENT surgeon fails to ask about any general symptoms. I have seen a case of delayed diagnosis of Shy Drager syndrome in which the ENT surgeon completely failed to appreciate the significance of the patient's fainting episodes and chronic diarrhoea. She went into a crisis requiring an emergency tracheotomy after six months of progressing problems and subsequently successfully litigated.

DELAY IN DIAGNOSIS

Delays in diagnosing cancer rarely occur in general practice these days. Prompt referral of patients with a greater than six-week history of voice change to the two-week wait clinic is the norm, meaning that more than 90% of patients in the two-week wait clinic do not have cancer. Problems arise when biopsies come back showing dysplasia or just chronic inflammation. Discharge of patients back to the GP or on to speech and language therapy for a course of treatment can only be justified if there are no 'red flag' symptoms suggesting cancer, such as persistent unilateral earache in a normal ear or intractable pain in the throat. A good rule for patients who smoke and/or drink who have symptoms of cancer but a negative biopsy is that they have cancer but just require more in-depth urgent investigation. A three-month wait in a smoker with intractable earache and evidence of laryngitis cannot be justified. Rebiopsy, PET scanning or CT scanning should be seriously considered on receipt of a negative biopsy and tests ordered even before discussion at an MDT.

Rare tumours or common cancers with unusual presentation can be diagnosed late. Examples of these include sarcomas, malignant tumours of blood vessels and locally destructive tumours such as ameloblastoma. There is no doubt that if the patient sees someone inexperienced, such as a young consultant or trainee, then there is an increased risk of delay. In the cases where litigation is successful there has usually been a reluctance on behalf of the managing practitioner to bring the case to a more experienced colleague or to discuss the case at an MDT. In addition there is often a series of errors. Another common error is in the management of the case with an unusual presentation. In such cases, it is important to go back to first principles taught at medical school and take a thorough history followed by detailed examination. If the surgeon does not go back to first principles, important steps that may give key clues to the diagnosis may get missed. Examples include failure to palpate the tongue, transilluminate or auscultate a lump.

Delays in diagnosis have differing consequences. The commonest allegation is that a resection would have been smaller, which may lead to allegations that a different less disfiguring reconstruction would have been used, a prosthesis would have been avoided or neurological deficits would not have occurred.

The next allegation is that surgery would have been avoided and another treatment modality would have been used such as radiotherapy in cancer of the larynx.

Conversely, allegations may include that chemotherapy and side effects such as ototoxicity would have been avoided or that radiotherapy with consequent scarring, stricture formation or xerostomia would have been avoided.

SURGICAL INFECTION

Allegations of substandard surgical technique in the management of head and neck cancer are unusual and mainly revolve around salivary gland and thyroid surgery. Where allegations occur is in the ward management of the post-operative patient. These usually revolve around the management of infection. MRSA (methicillin resistant *Staphylococcal aureus*) infection can lead to the claimant alleging failure to adhere to Trust policies on infection control. Nowadays with the emergence of resistant strains of bacteria there is wisely an increasing reluctance to use antibiotics, especially where wounds are dirty or contaminated, but there is little indication of systemic or spreading infection. Not surprisingly, getting such wounds to heal especially if there are salivary fistulae can take many weeks. Claimants can make allegations that but for the failure of prescribing antibiotics they would have been discharged earlier and with less scarring.

Conversely, allegations arise in the case of hospital-acquired infections (HAI) such as *C. difficile* and their consequences, which would not have occurred but for the injudicious use of antibiotics in the post-operative period. This can be difficult to repudiate if the claimant has been on an antibiotic for weeks with no evidence of review.

BEST CLINICAL PRACTICE

- ✓ Sudden onset of double vision should never be ignored.
- ✓ It is wise that both the clinician and the radiologist assess the radiological films, within the clinical context of the patient's disease.
- ✓ In the field of endoscopic sinus surgery, it is essential to have a complete demonstration of the radiological anatomy by CT scan.
- ✓ If a lesion deemed benign on cytology does not appear to be behaving clinically as such, rebiopsy should be undertaken speedily.
- ✓ In the case of simple, benign, nasal polyposis, there is rarely any defence for not discussing the possibility of a course of oral steroids, with or without antibiotics.
- ✓ A post-operative saddle nose deformity could, rarely, be due to a failure to recognize and diagnose disorders such as Wegener's granulomatosis or sarcoidosis. In such an event, the appropriate tests to exclude such disorders should be taken.

KEY POINTS

- Ear syringing and stapes surgery are the commonest procedures leading to litigation in otology.
- The only reliable way of determining whether there is inner ear function in both ears is to undertake pre-operative electrocochleography.
- The argument that is usually advanced in cases that develop intra-cranial complications while on the waiting list is that the patient should have been given priority over routine mastoid surgery. Disease in the other ear with hearing loss is usually given as the reason for priority.
- Cases of failure to treat sudden deafness can usually be defended as there is no evidence that any therapy is effective except acyclovir in herpetic infection.
- Establishing that sensorineural deafness is caused by ototoxic ear drops can be difficult.
- Wegener's granulomatosis is a condition that regularly goes unrecognized.
- Issues of consent on their own are rare in relation to sinus surgery.
- Where contention may arise is not that the patient was warned of anatomical risks, but that they did not understand the consequences of these risks on their day-to-day life, or that, should such risks occur, secondary complications may supervene.
- Infraorbital nerve neuropraxia in Caldwell-Luc surgery can occur despite all care being taken and does not indicate de facto substandard technique
- A decision not to investigate is probably only best confined to those patients who have such gross comorbidity that no surgeon or anaesthetist would consider them for surgical management.
- Unless progressive sensorineural deafness in a young adult is investigated, cases of treatable disease such as neurofibromatosis will be missed.
- Failure to act on a unilateral sensory neural deafness is rarely defensible.
- Misinterpretation of brainstem-evoked responses can lead to a failure of instigating radiological tests and subsequently a delay in diagnosis of a vestibular schwannoma.
- Failure to diagnose an olfactory groove meningioma usually occurs when there is another plausible explanation for the loss of smell.
- Meningitis is such a devastating disease when it occurs that clearly a degree of risk has to be considered acceptable when undertaking the investigations for a suspected CSF leak.
- In lateral skull base surgery, every surgeon should now give careful consideration as to which lower motor cranial nerves should be monitored.

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CHAPTER 40

NON-TECHNICAL SKILLS FOR ENT SURGEONS

Simon Paterson-Brown and Stephen R. Ell

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SEARCH STRATEGY

The information described in this chapter comes directly from the NOTSS project, with details in the reference section. Further details can be found at www.rcsed.ac.uk/professional-support-development-resources/learning-resources.

All tables provided in this chapter are based on those developed in the NOTSS project but adapted for use by ENT surgeons.

INTRODUCTION

Technical skills in ENT surgery relate to the hand-eye coordination that enables the surgeon to move the scalpel or drill exactly, to cut with the correct pressure to a precise depth without injuring adjacent structures; to hold the tissues gently; to create the space to work and to diathermy only the bleeding vessel, keeping collateral damage to a minimum. Technical skills are the craftsmanship of surgery.

Non-technical skills relate to those additional abilities of situational awareness, decision-making, communication and teamwork, and leadership that allow the technical work to proceed efficiently, safely and calmly, and are equivalent, in aviation, to crew resource management skills, which are part of the human factors well known in aviation circles. The influence of these skills in healthcare on both good and poor performance is now well recognized. Surgery is particularly susceptible to complications and these adverse events are much more likely to follow failures in non-technical rather than technical skills.[1] It has been estimated that adverse events, not directly related to the underlying condition, occur in 10–15% of hospital admissions. Half of these occur in surgical patients and around half are avoidable.[2]

Despite the introduction of the World Health Organization (WHO) peri-operative surgical checklist, which reported significant reduction in morbidity and mortality,[3, 4] there remains an alarming rate of 'never events'.[5] The problem, until recently, was that the surgical fraternity did not know much about these so-called 'non-technical' skills,[6] what they were and how they could be observed, taught or even assessed. These skills are not new or mysterious behaviours; they represent what the safest and most efficient surgeons do on a consistent basis. In ENT, training in 'theatre behaviour' was given only by example, both good and bad, was incomplete, was random and depended on the awareness and perspective of the training consultant. It is now clear that these skills underpin everything surgeons do, supporting technical and clinical excellence, reducing errors and improving outcomes. In a reply to an anonymous postal survey in South East Scotland, 68 consultant surgeons from all specialties identified 70 skills that they considered important to be a successful surgeon.[7] Only 19 (27%) of these were technical and 22 (31%) clinical; 29 (41%) related to communication, teamwork and the application of knowledge. Problems with decision-making, communication and teamwork have been shown to be related to surgical failure.[8–10]

Following the example of civil aviation and other high risk industries (e.g. offshore oil exploration and nuclear power generation) that have developed training and assessment of non-technical skills,[11] surgery has developed its own 'non-technical skills for surgeons' (NOTSS) that are required in the intra-operative environment to support the surgeon's technical expertise. These were identified in a joint project between

Aberdeen University and the Royal College of Surgeons of Edinburgh,[12] and an associated classification was developed along with good and poor behavioural markers, which can be used to assess surgeons. Several studies have now demonstrated that these are usable, reliable and reproducible, and can be informative for trainee feedback.[12–14]

BEHAVIOURAL MARKERS

Observational methods for identifying and rating non-technical skills in medicine were first developed for anaesthetists,[15] now called anaesthetists' non-technical skills (ANTS). Other studies have explored team factors, which support good surgical performance.[16–18] NOTSS is a system designed 'by surgeons for surgeons' to observe and rate individual surgeons. Subsequent phases of the NOTSS project have used the classification for debriefing trainees after surgery,[12] in surgical simulation, and as a central part of a master-class to train surgeons to observe and rate non-technical skills.[19] NOTSS has also been subject to an independent trial of workplace assessment systems along with procedure-based assessment (PBA) and objective structured assessment of technical skill (OSATS),[20] with encouraging results in the operating room.[21] NOTSS has been adopted by the Royal Australasian College of Surgeons as part of their competence assessment and recommended by the Accreditation Council for General Medical Education (ACGME).[22] A large-scale trial in Japanese hospitals is also underway.[23] A similar system has subsequently been developed for theatre scrub practitioners: scrub practitioners list of intra-operative non-technical skills (SPLINTS).[24]

THE NON-TECHNICAL SKILLS FOR SURGEONS (NOTSS) SYSTEM

The aim of the NOTSS project was to develop a non-technical skills classification, with associated behavioural markers, which could be used in the training and assessment of surgeons during the intra-operative phase of surgery. The resulting NOTSS classification is made up of four main skills categories, each with three levels of associated elements as shown in Table 40.1.

TABLE 40.1 Non-technical surgical skills classification

Skill category	Level	Element
Situational awareness	I II III	Gathering information Understanding information Projecting and anticipating future state
Decision-making	I II III	Considering options Selecting and communicating options Implementing and reviewing decisions
Communication and teamwork	I II III	Exchanging information Establishing a shared understanding Coordinating team activities
Leadership	I II III	Setting and maintaining standards Supporting others Coping with pressure

It is important to understand that this is not about personality, but about observable characteristics within the operative environment. For training purposes, to provide feedback, and to assess surgeons, behaviours associated with each element may be scored as follows:

- **Good** (score 4): Performance of a consistently high standard, enhancing patient safety, which could be used as a positive example for others
- **Acceptable** (score 3): Performance of a satisfactory standard, but could be improved
- **Marginal** (score 2): Performance indicated a cause for concern, considerable improvement is needed
- **Poor** (score 1): Performance endangered, or potentially endangered, patient safety; serious remediation is required.

Sometimes a particular behaviour is not required, or not relevant, in a particular situation. In this case 'Not Applicable' or 'N/A' is recorded. This is not to be used if the behavioural skill is lacking. If the skill is lacking then a score of Poor (score 1) or Marginal (score 2) is recorded.

Although these elements appear distinct, several of the elements may occur at the same time during a particular event. For example, gathering information about a developing, urgent, life-threatening situation, such as worsening stridor, will require good communication, exchanging information about all possible options and potential outcomes, establishing a shared understanding, and leading to a balanced decision on the next best step to take to maintain standards and safety, all the time coping with the stress. Although NOTSS relates to the intra-operative environment, these skills are also important in all aspects of surgical care, on the wards, in the clinics, and when dealing with managerial and secretarial staff. For each category, shown in Tables 40.2–40.13, a selection of 'good' and 'poor' behaviours associated with each of the three elements within that category, relevant to ENT surgeons, will be discussed, though the broader picture may be applied to all surgeons. Examples from aviation and industry may be used for comparison or illustration.

SITUATIONAL AWARENESS (SA)

Situational awareness is the ability to develop and maintain a dynamic awareness of the present situation based on fitting together environmental information, understanding its meaning and thinking ahead to what might happen next. Good SA in the operating theatre is essential for all the other non-technical skills and comprises three distinct levels, which may be inferred from the above definition: Level I – gathering information; Level II – interpreting the information, which requires understanding; and Level III – projecting and anticipating future states based on this information.[25]

Level I – gathering information

The information gathered relates to ensuring the safety of both patients (clinical information) and staff (non-clinical information), and forms the foundation of forward

TABLE 40.2 Situational awareness Level I. Gathering information – examples of good and poor behaviours

Good behaviours	Poor behaviours
• Has reviewed patient in the clinic and explained relevance of investigations to surgery: begins consent process • Carries out pre-operative checks of patient notes, especially previous surgery • Ensures that all relevant imaging/investigations are available and have been reviewed in detail, e.g. CT sinuses before FESS • Identifies hazardous anatomy on CT, e.g. sloping skull base (Keros I), Onodi cells; exposed ant. ethmoid artery and optic nerve • Liaises with anaesthetist about comorbidities affecting anaesthetic plan, e.g. hypotension and tolerable blood loss • Monitors staff well-being • Asks anaesthetist for regular updates on e.g. blood loss	• Has not seen the patient before the day of surgery • Doesn't see the patient pre-operatively, but expects the trainee to have done so • Reviews results superficially at the last minute, or does not review them at all • Is unaware of the pressures on the operating theatre staff, e.g. numbers, skill mix, impending urgent cases • Does not listen to the concerns of the anaesthetic team, e.g. about using hypotension during FESS or ear surgery to reduce bleeding in a patient with cardio-vascular disease • Asks theatre staff to read from patient notes during procedure because surgeon has not read notes pre-op. • Fails to review pertinent information collected by the operating theatre team • Ignores the assistant/nurse who may be struggling to assist, or standing for long periods of time, for reasons unknown to the surgeon • Ignores anaesthetic or theatre alarms • Is unaware of patient's allergies

planning to make the surgical procedure as efficient and free of complications as possible. If information is poor or absent, all future planning will suffer. This information may be obvious, or subtle. Obvious information should be noted by all but the most obtuse; subtle information may be observed only by the experienced (e.g. a past history of significant peri-operative bleeding, despite all blood and clotting parameters being normal, may indicate a rare platelet malfunction under certain surgical conditions).

In order to gather information the surgeon needs to be able to manage mental focus. Focus, or level of concentration, may be classified as broad or narrow, external or internal, and the agility to move observational abilities from broad to narrow focus, and vary the intensity of the focus, as the situation demands, is an important skill for situational awareness and other non-technical skills. Managing focus is important in managing fatigue.

A broad external focus, which may be thought of as a relaxed focus with reduced concentration, would best be used when all appears to be going well. This may be thought of as 'scanning the horizon' for signs of trouble, for gathering less critical information, such as the number of medical and nursing staff available and their skill mix with respect to the complexity of an oncoming difficult procedure, and observing any staff health issues, both emotional and physical, that may reduce their resilience under pressure. A narrow external focus, which may be thought of as intense focus, would best be used when absolute concentration is needed for the moment, such as decompressing a facial or an optic nerve, or placing a stapes prosthesis, or carving an incus for a transposition ossiculoplasty. The operating theatre is often a busy and noisy place, but during these moments of intense focus, distractions must be reduced to a minimum, since all the surgeon's senses will be heightened, especially hearing. Background conversation, or music, or both, must be stopped, no doors allowed to slam and telephones switched to silent. All this must be communicated to the surgical team at the WHO pre-op team briefing as a 'critical step', so that all who are present in the operating theatre are prepared for 'silent running' (a maritime term used to describe submarines in stealth mode), and the surgeon is freed from distraction and able to concentrate wholly on the critical task. In aviation this 'silent running' is called 'sterile cockpit', used during take-off and landing, or in an emergency, when non-essential communication or distractions cease, and messages are confirmed by repeating the message back.[26]

Equally, due to the intense concentration of narrow external focus, which is tiring, the surgeon may either miss other information, or miss its importance. This is termed 'inattentional or perceptual blindness'.[27] It is important to recognize the psychological draining effect of prolonged intense concentration and a mid-procedure break is wise, especially during long cases using the microscope. A 5-minute break in a 2–3-hour operation speeds up the procedure significantly. It gives time to review progress, to plan the rest of the operation, to relieve the nurses and to have a hot drink. This broadens the focus, de-stresses the mind and facilitates 'coping with pressure' (*vide infra*), and is why all craftsmen have a tea break. Clearly, the surgeon must focus on the task in hand, but must also realize constantly, perhaps at a subconscious level, that important information might be missed. The most perfectly placed stapes prosthesis would be to no avail if the patient was arresting under the hypotensive anaesthetic. During such an event, even when locked within the high concentration of narrow focus, the surgeon must listen to the theatre environment and secure the operating field as quickly as possible, get away from the patient and hand over control to the anaesthetic team. Even in less dramatic circumstances, such as a disconnected monitor lead, stopping the procedure to reassess the situation and discuss progress with colleagues will help regain Level I situational awareness. In these examples, decision-making and communication and teamwork also play a large part in the NOTSS.

Level II – understanding information

After all the relevant information has been received, the surgeon must understand its significance, which requires training and experience. Inexperienced surgeons may

TABLE 40.3 Situational awareness Level II. Understanding information – examples of good and poor behaviours

Good behaviours	Poor behaviours
• Changes surgical plan in proportion to the patient's condition, when appropriate • Acts according to information gathered from previous investigations • Studies the CT scan and points out important features • Reflects and discusses significance of information with team, e.g. links stridor and tracheomalacia in a child with a trachea-oesophageal fistula (TOF) • Discusses surgical priorities	• Overlooks or ignores important results until hazard encountered peri-op, e.g. history of bleeding • Asks questions that demonstrate a lack of understanding or preparation • Poorly coordinates investigation: essential blood tests done in theatre • Flicks through the CT scan and misses hazardous anatomy • Fails to prepare, e.g. a ventilating bronchoscope for MLTB in a patient with a TOF and tracheomalacia • Reads the summary of the radiologist's report, not the report detail • Discards rather than discusses results that don't 'fit the picture'

be unaware of the significance of certain facts and may not respond, or respond differently, from more experienced surgeons. This process is dynamic, since new information will require processing within the context of established information, and different interpretations may lead to different actions. When interpreting information, it is important that the surgeon avoids 'confirmation bias', whereby ill-fitting information is filtered out, since it does not fit with the surgeon's established view. Yet ill-fitting information may suggest an alternative path and require an unpleasant course of action, which must be faced. This error may be avoided by analyzing all the available information (co-morbidities, blood results and imaging) with the anaesthetic, radiological and surgical teams in their turn, and discussing what actions or precautions are required (e.g. an unusually low or perhaps dehiscent skull base, unreported on the scan, may indicate a surgical hazard).

Level III – projecting and anticipating future state

After receiving and understanding the information available, the surgeon must then anticipate what might happen next and this will help to decide on the best plan of action. Incorrect anticipation can be avoided by discussing possible future situations with colleagues and reviewing alternative strategies. A good example of this would be management of a difficult airway problem in theatre, depending on the urgency. The team briefing would extend the 'critical steps' discussion and include various 'what if' events, such as a failure to intubate, tracheal bleeding after removal of a foreign body or tracheal biopsy, or a peanut splitting in two and blocking each main bronchus. For each potential situation, the surgeon rehearses what they would do and tells the team. Each member of the team can then rehearse what they would do for each situation and three levels of situational awareness repeated until all are content. Although this process improves situational awareness, it relies on good communication and teamwork (see below). In this example, the anaesthetist would plan, with the operating department practitioner (ODP), which methods she might use to intubate and the equipment needed, and define what parameters determine failed intubation, so the surgeon knows when to act. The surgeon would go through, step by step, what facilities need to be ready and in place for a swift tracheostomy: position of the patient, surgical instruments and suction ready and working before intubation is attempted. This rehearsal is especially important when transferring responsibility of the airway between the anaesthetist and the surgeon in paediatric cases using the ventilating bronchoscope, or for peanut recovery, or to prevent both lungs filling with blood after a tracheal biopsy. In aviation, and in the film industry, this process is called 'pre-visualization' and improves situational awareness by predicting difficult or unexpected circumstances. Pre-visualization enables all in the team to plan and to know their role, so the team can act swiftly in a coordinated fashion, should such disasters occur. Making 'pre-visualization' a habit helps prepare for complications with routine surgery too (e.g. excessive bleeding from adeno-tonsillectomy).

TABLE 40.4 Situational awareness Level III. Projecting and anticipating future state – examples of good and poor behaviours

Good behaviours	Poor behaviours
• Has contingency plans for peri-operative complications: requesting required equipment to be available: cerebrospinal fluid (CSF) repair kit, fibrin glue, Floseal® • Keeps anaesthetist informed about procedure progress, e.g. exposed dura or venous sinus, and estimated finish • Verbalizes what may be required later in operation • Anticipates post-op problems: a tracheostomy tube placed in the TOF	• Overconfident attitude and continues with no regard for what may go wrong • Does not discuss potential problems with team • Tells the anaesthetist about excessive bleeding late, or not at all • Fails to anticipate a predictable problem and responds late • Does not plan ahead, assuming 'all will go well', rather than 'all will go ill' • Fails to tell the anaesthetist about potential problems in recovery; tracheomalacia in the presence of a TOF which may require an ITU bed post-operatively • Failing to plan (= planning to fail)

Projecting and anticipating the future state is fluid and dynamic and will change many times during the course of an operation. Surgeons with good situational awareness will regularly stop what they are doing (even if only mentally) to avoid 'inattentional blindness' and reassess how the operation is progressing, asking themselves the question: are we where we expect to be at this time? If not, what needs to be done to get the operation back on track? This will undoubtedly require the ability to collect all the relevant information including non-verbal clues (anaesthetic activity, scrub nurse concerns and monitor warnings), understanding what they all mean and what is likely to occur later. Non-operating observers with a broad focus can often see a problem developing, which operating surgeons would recognize if they were not locked within intense concentration. In this situation, the scrub nurse should be informed and she would look for a safe opportunity to alert the surgeon, allowing action to be taken well before the inevitable 'event' occurs.

DECISION-MAKING (DM)

Decision-making may be defined as the thought process of selecting the best logical choice of an appropriate course of action from the available options. This means considering all the alternatives and weighing the positives and negatives of each option. To be effective, the surgeon must also be able to forecast the outcome of each option and determine which would be best for a particular situation. This skill requires thinking time, which is dependent on the understanding gained through surgical experience and the urgency of the situation. Although experience helps, it does not create expertise, and expertise is not infallible: sometimes the decision made, on the information available at the time, is not the best when viewed leisurely with hindsight.

Although the various types of decision-making have been much studied and written about, the simplest model is that described by Daniel Kahneman[28] in his book *Thinking Fast and Slow*. Fast thinking, also known as *System 1* thinking, is quick, automatic, requires little or no effort, and has no sense of voluntary control. *System 1* decisions, often made in stressful situations, reduce threats and can be both instinctive, such as fear of blood loss, and learned through prolonged practice and experience, such as recognizing the subtle change in pitch of the drill when it touches the *tegmen tympani*: the sound moving away from the rumble and towards the scream as the thin plate of bone vibrates under the touch of the burr; or the glimpse of the whiter bone of the skull base; or the yellow tinge of the *lamina papyracea* during endoscopic sinus surgery. *System 1* thinking may be thought of as intuitive, and instantly tells the experienced surgeon to hold back and proceed cautiously, and is used when the risk is high and time is short; however, it is not always correct. The pallor of the skull base, seen in the distance, may be a simple mucous retention cyst, yet it could be a meningocele, or an encephalocele. In these situations the main consideration is safety; danger is recognized and disaster averted. Fast, *System 1* thinking can also be called *recognition-primed* DM (RPD) and is a type of pattern recognition that experts use to make satisfactory decisions under times of high stress or time-pressure.[29]

Slow thinking, or *System* 2 thinking, also termed *analytical* DM, is more familiar and is the type of thinking used to check the validity of a complex logical argument. *System 2* thinking allocates mental processing capacity or focused attention to the effortful analysis of a situation; assessing options, weighing up the pros and cons and deciding on a course of action. Often this produces a better course of action than *System 1* thinking and is used when risk is low and time is available. Clinically, *System 2* thinking would be used to diagnose and treat, for example, a patient with complex balance problems. In theatre, *System 2* thinking would be used to plan the next few steps of an operation, with diversion options in mind if the plan fails, and alternative reconstruction methods if the pathology is not as expected, as used in head and neck surgery, or in otology, for example following a cholesteatoma avoiding dehiscent structures while considering primary or staged hearing reconstruction possibilities.

Analytical DM requires more focused concentration than recognition-primed DM. In times of stress, when an individual's working or short-term memory is overloaded, 'freezing' can occur, which is the inability to make any decision at all. In this situation, someone else can help by taking on some of the mental workload, freeing up working memory and allowing the individual to think about what to do next (see below). One recent study demonstrated that during the intra-operative phase of surgery, surgeons use analytical DM in around 50% of cases.[30]

There is another main form of decision-making, which is *rule-based*, and is somewhere between fast and slow thinking in terms of the working memory required. It is particularly useful in times of stress when 'thinking' is more difficult. It is used by both trainee and expert surgeons and follows the algorithmic process of 'if X occurs then I'll do Y'. This is usually based on well-known guidelines and protocols; for example, when a cerebrospinal fluid leak occurs during sinus surgery, while the fibrin glue is defrosted, the bleeding is stopped, the area is cleaned, fat is harvested and mucosal flaps lifted in preparation for repair. An injured dural sinus during mastoid surgery is covered immediately with a damp swab, the head lowered to prevent air embolus, followed by a muscle graft, or haemostatic gelatin (Floseal®), or occlusive BIPP packing: all these critical events having been discussed at the WHO pre-op team briefing.

For completion, DM that relies on creating brand new solutions in theatre should only be a last resort when the above three methods fail, and, in general, it requires an inordinate amount of time and does not work well. Pre-visualization works better.

There are three elements of decision-making: Level I – considering options; Level II – selecting and communicating options; and Level III – implementing and reviewing decisions.

Level I – Considering options

When the situation is urgent and high risk, and a decision is needed swiftly, there may be only one option. When there is more time and less risk, alternative options may be weighed in the balance.

Level II – Selecting and communicating options

This should progress naturally from considering alternative options, but one option can only be selected if the surgeon appreciates the alternatives. Ignoring valid alternatives ensures an easy decision, but which sometimes is wrong. Telling the team which option has been selected is a 'sense check' and strengthens the team's cohesion.

Level III – Implementing and reviewing decisions

Once a decision has been made and acted upon, reviewing progress should run in parallel to monitor if all is going well, or badly, so that alternative choices can be made in a timely manner; for example, the decision to carve an incus remnant, for a transposition ossiculoplasty, may be abandoned in favour of a prosthesis or a bone chip, if the incus remnant proves to be too small or too crumbly. In this situation the three levels of decision-making are repeated, but this can be done only if the original decision is reviewed.

Situational awareness and decision-making represent the two cognitive non-technical skills in the NOTSS classification: the skills that require 'brain power'. In aviation, these are reduced to the more rapid process of observe; interpret; decide; act (OIDA) and this pattern is followed repeatedly, so the pilot's mind flies 'in front of the aircraft'. Surgeons work in the same way when concerned with patient care, thinking ahead to the next step. The next two non-technical skills are the social skills of communication and teamwork, and leadership.

TABLE 40.5 Decision-making Level I. Considering options – examples of good and poor behaviours

Good behaviours	Poor behaviours
• Weighs the chances of success of primary or staged reconstruction • Considers changing list order for clinical need • Considers autograft versus prosthetic ossicular reconstruction with respect to comorbidities • Considers asking for help if in difficulty • Considers early start to list to prevent late finish • Considers an alternative instrument to do the same manoeuvre • Is open to new options suggested by others	• Reconstructs the same way regardless of the clinical situation • Reconstructs in suboptimal conditions, e.g. myringoplasty in presence of *pseudomonas* infection • Fails to consider changes to list order, e.g. for diabetics, young children, anaesthetist's request • Considers it a failure to request help with a procedure/list • Fails to consider alternatives when new information becomes known • Does not consider any alternative • Insists on a particular instrument when another would work almost as well, e.g. periosteal elevators • Ignores alternative suggestions made by others

TABLE 40.6 Decision-making Level II. Selecting and communicating options – examples of good and poor behaviours

Good behaviours	Poor behaviours
• Tells the team the decision in an urgent situation (*System 1* thinking) • Requests a moment to think when decision is complex (*System 2* thinking) • Verbalizes options, with associated pros and cons • Absorbs information provided by others to refine selected option	• Selects an option but does not tell the team, e.g. decides on an ossicular prosthesis but gives no prior warning • Is unable to make a selection of a technique, an instrument set, or tool, so requests everything • Does not select an option when there are clear alternatives and ignores resources: skill of a colleague, nurse/anaesthetist. • Uses information unrelated to patient care to select an option

TABLE 40.7 Decision-making Level III. Implementing and reviewing decisions – examples of good and poor behaviours

Good behaviours	Poor behaviours
• Makes a decision and sets a timescale for review of progress, e.g. estimates duration of operation and updates anaesthetist peri-operatively • Checks a decision is acceptable, e.g. changes in list order • Reviews the quality of the decisions/work in progress; is flexible	• Does not make a clear decision and continues with no clear direction • Makes a decision and carries on regardless of new information • Ignores poor progress, or the poor outcome of a decision made, when re-evaluation may improve matters • Assumes repair is satisfactory when it could be tested peri-operatively, e.g. ossicular reconstruction or a repaired CSF leak (with an anaesthetic Valsalva)

COMMUNICATION AND TEAMWORK (C&T)

Communication skills, and working as part of a team, are important skills for the surgeon that underpin and link the other non-technical skills of situational awareness, decision-making and leadership. Being able to communicate clearly and succinctly, and hear others' perspectives, ensures the team has a shared understanding of the situation, of the challenge to be faced and the overall objective, so that individuals can complete their tasks by working together effectively. These skills are important throughout the peri-operative period, but particularly so during the WHO pre-op team briefing. Knowing each team member by name improves prompt information exchange and efficient working when under pressure. Communication and teamwork may be divided into three levels: Level I – exchanging information; Level II – establishing a shared understanding; and Level III – coordinating team activities.

Level I – Exchanging information

This is the free exchange of information pertinent to the situation, from all members of the team, and a complete picture is best gained if the atmosphere is easy and unstrained. This is not the didactic surgeon telling the team how it is and who should do what in a bombastic way, brooking no argument. Each member of the team brings a personal understanding of what might be required of them, but not how that might fit in with other members of the team; therefore, individuals tell the rest of the team their thoughts, concerns and impressions, that they feel are important to their role in the team. Clarity is achieved by questions and answers; however, reticent members of the team may need to be 'drawn out' and asked directly if there is anything they would like to say, or ask. Information given by one member of the team may trigger further information or questions from another and sufficient time needs to be allocated for this. All relevant concerns should be shared. Holding back information, or minor concerns, because these are thought to be unimportant, may not be helpful, since a situation may arise when these concerns become highly important. Experienced professionals develop a 'sixth sense' when something is about to go wrong and sensing this may initiate checking emergency equipment, such as additional means of intubation, or that the crash trolley is well stocked and has serviceable defibrillators. This process of exchanging information is necessary to develop a 'shared mental model' of the situation.

The exchange of information is not confined to the WHO pre-op team briefing. It is also a crucial part of the communication between the scrub nurse and the surgeon to avoid misunderstanding and increase efficiency, especially during critical phases of the operation. In aviation, during critical phases of the flight, instructions from Air Traffic Control (ATC) are repeated back to ATC by the pilot, for example take-off and landing. This confirms to ATC that the pilot has received the message correctly. If the pilot makes an error, the word 'correction' is used and the process is repeated. Although this sounds like practising to be a parrot, and seems to be a waste of time, it is the most efficient way to communicate when misunderstanding could be fatal. In surgery, this method is used, especially for critical moments of the procedure, for example, the surgeon requests an instrument by name: 'micro-scissors'. The scrub nurse hands over the instrument and repeats back the name: 'micro-scissors'. If the surgeon initially asks for the wrong instrument, for example, the surgeon says: 'Knife, correction, Beaver Blade', the nurse diverts to the correct instrument and passes this to the surgeon and repeats back: 'Beaver Blade'. This discipline reduces the chances of a wrong instrument being used at a critical moment and is good practice at all times when using sharp instruments.

Level II – Establishing a shared understanding

Once there has been a full exchange of information, each individual has a greater appreciation of the whole situation, its challenges and objectives, and how they, as individuals, might contribute to achieving the objectives by working with other members of the team; how they might help others, and in turn, be helped by others to ensure the work progresses in a coordinated fashion. This is especially important for the surgeon, anaesthetist, scrub nurse and ODP, for example, in the case of an airway emergency when time is of the essence. Prior practice and pre-visualization promotes performance. Once a shared

TABLE 40.8 Communication and teamwork Level I. Exchanging information – examples of good and poor behaviours

Good behaviours	Poor behaviours
• Has a relaxed attitude allowing individuals to speak • Asks if anyone has any questions/concerns at the end of the WHO team briefing • Explains need for 'silent running' during times of intense concentration at briefing • Encourages scrub nurse to repeat back instrument names, especially sharp instruments • Is clear about when the operation is paused and control is handed over to the anaesthetic team, e.g. during a cardiac arrest	• Overconfident attitude and disregards others' concerns • Does not communicate with, or consider the pressures on, the operating theatre staff, e.g. numbers, skill mix. • Intimidates colleagues/juniors, allowing no-one else to raise concerns about clinical safety • Shouts/speaks harshly to theatre staff to be quiet during the procedure • Shouts/speaks harshly to scrub nurse because she misheard the name of the instrument requested

TABLE 40.9 Communication and teamwork Level II. Establishing a shared understanding – examples of good and poor behaviours

Good behaviours	Poor behaviours
• Checks everyone understands what needs to be done • Checks that objectives are clear • Pre-visualizes alternative situations and rehearses what each person would do, e.g. in an airway emergency • Communicates clearly to all when the situation has changed, so all understand an alternative route is underway • Re-explains patiently if someone in the team is unsure	• Does not communicate with anaesthetist, especially, e.g. over a shared airway during a laryngeal procedure, or blood pressure control during FESS or ear surgery • Does not ensure all team members are clear what needs to be done if things do not go as planned • Assumes all can tell when things are not going well and ignores the resources and help of the anaesthetic and nursing team • Is intolerant of inexperience

TABLE 40.10 Communication and teamwork Level III. Coordinating the team – examples of good and poor behaviours

Good behaviours	Poor behaviours
• Fits in when other team members lead when appropriate • Coordinates with scrub nurse when setting up, each doing separate things for efficiency, e.g. surgeon sets the endoscope demister, nurse sets the diathermy • Tells the nurse when 'silent running' is needed peri-operatively • An unscrubbed surgeon follows theatre communication etiquette when another surgeon is operating	• Insists on being in command at all times • Positions the patient after towelling up, when it would have been easier to coordinate before • Fails to warn staff of the procedure duration, so staff are unprepared for the next case • A visiting surgeon speaks directly to an operating surgeon without waiting for the scrub nurse to indicate a good time to speak

understanding has been established, potential changes to that situation, causing diversions from the plan, are readily apparent to all and the team can change direction as one with little disturbance to the smooth running of the case.

Level III – Coordinating the team

This is more likely to be successful once Levels I and II have been followed, but coordinating the team does not fall to one person at all times. There will be times when the anaesthetist and ODP coordinate activity, such as transfer of the patient to and from the operating table when the surgeon may act as a helper. During patient positioning, the anaesthetist and ODP help the surgeon. During towelling up, the surgeon and the scrub nurse work together with the anaesthetist to ready the patient for surgery. During times of 'silent running', when the surgeon is in intense concentration and fully occupied, the scrub nurse coordinates the (silent) theatre, but in a medical emergency, such as a cardiac arrest, the anaesthetist takes command. This flexibility of hierarchy, like the Knights of the Round Table, uses the skill mix of the team to maximum effect and is most efficient when teams work together regularly.

Not surprisingly, problems with communication are usually associated with the most adverse events.[8, 10, 31] When communication improves between members of the team, the shared mental model will undoubtedly be better and overall teamwork and performance will benefit.

LEADERSHIP

There are many industrial definitions of leadership, but in the operating theatre the skill of leadership may be considered as: 'a social process of influence that ensures the best work of the theatre team to achieve the objective of safe, high quality patient care', in other words, a successful operation. Leadership skills are essential for the efficient and safe performance of the surgical team and require emotional intelligence.

Leadership is not an inherent part of seniority, associated with fancy titles or domineering or charismatic personal attributes, and it is much more than the ability to command or to realize a vision: it incorporates the ability to earn respect and trust. Respect and trust may be earned by maintaining high standards of clinical care, being considerate to others and being calm under pressure.

During the NOTSS development process, the leadership behaviours were grouped into three elements: Level I – setting and maintaining standards; Level II – supporting others; and Level III – coping with pressure. These social leadership skills were more reliably rated than the cognitive skills in NOTSS.[32] Leadership skills may be divided into those related directly to the *team* and those related to the *task*.[33] There is a degree of overlap between these three levels. For example, by reviewing blood results and scans, and setting up the microscope before an otological procedure in good time, the surgeon sets an example for trainee surgeons, supports the nursing staff by being ready and eases the stress of last minute or peri-operative microscope adjustments.

Level I – Setting and maintaining standards

In theatre, this includes adhering to theatre protocols of sterility, communication and etiquette, and respecting the high standard of care given by the anaesthetist, the nurses

TABLE 40.11 Leadership Level I. Setting and maintaining standards – examples of good and poor behaviours

Good behaviours	Poor behaviours
• Endorses the WHO checklist • Changes gloves/gown when advised sterility has been compromised • Follows theatre etiquette • Allows for inexperienced team members • Respects seniority	• Arrives late, or has to be searched out by theatre staff • Does no pre-op planning, delegates the briefing to a junior • Disregards theatre protocols • Is impatient with inexperienced staff • Does not use facial nerve monitor appropriately when it is available

TABLE 40.12 Leadership Level II. Supporting others – examples of good and poor behaviours

Good behaviours	Poor behaviours
• Supports trainees appropriately for their surgical skill level • Liaises with the anaesthetist and accepts constraints associated with comorbidities • Is approachable, takes heed of staff well-being • Is tactful and discreet when supporting those having a tough time.	• Leaves trainee to 'go solo' with an operation beyond their skill level • Intolerant of anaesthetic constraints, fails to suggest requesting more senior help, if appropriate • Is bullish, unapproachable and intolerant of staff 'excuses' • Is tactless and indiscreet, so is denied knowledge useful for the smooth running of the operating list.

and the ODP. Although the most important person in the theatre is the patient, the surgeon and anaesthetist are close behind: the operating surgeon holding the knife or drill, and the anaesthetist for keeping the patient alive despite, on occasion, the activities of the surgeon. Theatre personnel rely on the surgeon to set an example and also for guidance, for doing the right thing and upholding the culture of safety, for example endorsing the WHO checklist as an important method of preventing errors and maintaining standard of care.

Checklists have been used in aviation for decades and have been honed and refined to prevent basic errors of omission, manage complex technology and free up mental processing capacity (working memory) to focus on the current task. Once the checklist is complete, the surgeon (and pilot) can relax, knowing nothing has been missed, and can concentrate on operative planning.

In the UK, personal attributes of politeness and good manners are respected and rudeness and bad manners are not; however, what is polite in one culture may be considered rude in another and, in certain company, it would be respectful to be culturally aware.

Level II – Supporting others

A team works well because the strength of one team member makes up for the weakness of another. In the operating theatre, all are trained, or are being trained, to the high standards essential for safe patient care. In those being trained, technical and knowledge deficiencies are expected, and they are supported by further training and study to improve deficiencies until the trainee can 'go solo'. Supporting anaesthetic and surgical colleagues in theatre, by being receptive to the anaesthetic constraints of comorbidities, and to the skill needs of trainees, has been written into the traditions of operating theatre culture since surgery began; however, not all traditional surgeons have been receptive, approachable and willing to help secure patient safety by supporting others.

Supporting others in non-technical terms is a social skill, which, for some, can be difficult to master in the cut and thrust of the operating theatre. Not all members of the team are strong at all times, and most will not complain if they are feeling unwell, or are dealing with stressful issues away from the operating theatre. Most people do not allow personal difficulties to interfere with their professional work; they 'keep calm and carry on'. To support those going through a tough time, it is a social skill to be aware that all is not well, yet not to enquire too deeply into personal matters.

An approachable surgeon is more likely to be advised of such a situation, since it is likely that he will adjust his mental model of the team's strengths and weaknesses and ensure the team is able to make allowances and cope with the pressures of the operating list. This becomes important when the team is under pressure and good judgement is required to know how far someone can be pushed without buckling, or if that person needs some time out, or even time off work.

An unapproachable surgeon, insensitive to the needs of others, bullish in manner or both, is unlikely to listen to any excuse for poor work and is likely to be intolerant in the operating theatre, which puts the rest of the team under greater pressure. The work must go on, the operation takes priority and supporting others can be a delicate business and difficult to get right every time. It is also linked with how well the surgeon can cope with the pressure of operating (see below) when she depends on the strength of the team supporting her.

Level III – Coping with stress

Potential stressful situations can be countered before they escalate by making a practice of assessing situational awareness, decision-making, communication and teamwork; however, coping with stress can be difficult and depends on the degree of stress. Forward planning and training can mitigate most stressful situations by having the resources and the ability to deal with the situation.

TABLE 40.13 Leadership Level III. Coping with pressure – examples of good and poor behaviours

Good behaviours	Poor behaviours
• Has pre-assessed the situation and is aware of potential difficulties • Carries out a 'stress assessment' and raises concerns pre-operatively (WHO checklist) • Rehearses dealing with potential complications (pre-visualization) • Forward-plans equipment needs • Calls for help appropriately • Mentally checks I'M SAFE and makes adjustments	• Is unaware of potential difficulties • Is unprepared for the operation and unaware of potential complications • Tackles an operation outside comfort zone without asking for help from a colleague • Is unprepared for an operative complication • Is unable to remain calm under pressure • Blames others for personal failings

Confidence in your technical ability to complete the surgery to a high standard reduces the stress of complex procedures and is learned through focused training. In most theatre lists this is the normal situation. There are, however, technical and non-technical factors that increase the stress, which vary in number and severity. Many small stressors may be equivalent to one big stressor. As a general rule, more than two big stressors are too many and steps need to be taken to reduce the number and severity of the stressors. In the same way that risk is assessed by a risk assessment, it is wise for the operating surgeon to do a 'stress assessment' pre-operatively, even if this is just mentally rehearsing the procedure and dealing with potential peroperative complications. This surgical pre-visualization may be done whist scrubbing up and uses a narrow internal focus (see above). Often this will bring to mind the need for additional equipment, for example, fibrin glue and the Rhoton® neurosurgical micro-dissectors to facilitate the repair of a cerebrospinal fluid (CSF) leak occurring during FESS, which may have been forgotten during the WHO pre-op team briefing.

If a procedure is outside your comfort zone because you supra-specialized (e.g. an otologist tackling a neck stabbing), then swallowing your pride and calling for help from a friendly colleague reduces stress. Your colleague provides more than technical know-how; they also provide support that is emotional, practical, informative (advice) and provides companionship (EPIC), and all these ease the stress significantly.

Sometimes a case is especially tricky and having the support of a well trained, familiar theatre team is essential. Confidence in the nurse's ability to provide the exact instruments in a timely manner ensures a flowing, relaxed procedure, and knowing the anaesthetist and ODP will keep the patient safe, and asleep, during surgery is quite calming. Unfortunately, this is not always so. If the case is complex and high risk, such as a third revision mastoid exploration in an only hearing ear, in which the lateral semi-circular canal, facial nerve and dura are exposed, and the nurse is new to the procedure and has not memorized the instruments, some of which may be missing or damaged, and you are expected to train an inexperienced registrar, and explain the procedure to medical students, and your new anti-hypertensive medication is associated with postural hypotension, there are too many stressors, especially when a peri-operative complication occurs and you are being handed the wrong instruments.

It would be wise to explain, at the team briefing, that this case is complex, delicate and requires your full concentration. Politely request the help of an experienced scrub nurse; ask the registrar or the anaesthetist, or both, to teach the students quietly, outside theatre if possible; request more instruments and a comfortable chair to sit on during the procedure. Warn the theatre staff that there will be episodes of 'silent running' (i.e. when dissecting matrix off the lateral semi-circular canal, facial nerve and dura).

It would be unwise to get deep into the procedure before requesting these things; it would be even wiser to arrange all this before surgery after your assessment of the situation is complete (situational awareness), and perhaps quietly tell a friendly colleague of the situation so your mind benefits from EPIC support, even if this is remote.

A surgeon's ability to cope with stress is also proportional to his well-being and this was alluded to above when mentioning the surgeon's hypertension. A surgeon who is hydrated, fed and rested is more likely to operate more skilfully (and be less stressed and less grumpy) than a dehydrated, hypoglycaemic and tired surgeon. In aviation safety, to check if a pilot is fit to fly, the well-known personal mnemonic: I'M SAFE is used and we can use this in surgery to check if we are fit to operate. This is a quick check-list to cover:

- **I**llness (Am I well? Is my angina under control?)
- **M**edication (Are there side effects?)
- **S**tress (Feuds and performance targets?)
- **A**lcohol (No alcohol in the bloodstream is the only safe option)
- **F**atigue (Enough sleep, well rested?)
- **E**ating (Had something suitable and nutritious to eat before operating?)

This self-assessment would be an example of broad internal focus (see above).

A responsible surgeon with such insight will know when he is unsafe and, if unsure, will discuss with a trusted colleague. Better this than the patient coming round to discover he is being intubated by the anaesthetist while the ODP bounces on his chest underneath an arc of spurting blood coming from his carotid.

THE SURGICAL CHECKLIST AND NOTSS

As discussed throughout this chapter, the WHO introduced the concept of the 'surgical checklist' in order to provide a final error trap before surgery.[3] In addition to providing a final 'check' before surgery, it has undoubtedly contributed to the improvement of the various non-technical skills required for better team-working in the operating room. *Situational awareness* around the diagnosis and procedure, along with the instruments/equipment required and possible difficulties that may be encountered (projection/anticipation), are all discussed. *Decision-making* is improved by early identification of possible difficulties and *communication* throughout the team is expressed out loud and acknowledged. *Teamwork* has to be improved by the knowledge of all the names of people in the operating room. Good *leadership* can be observed by completing the checklist in the appropriate manner, demonstrating a commitment to patient safety and both recognizing the roles, and supporting other members, of the operating team.

Practising these skills in the day to day running of the operating theatre will ensure they become habitual and instinctive, so that during an urgent surgical emergency the pre-visualized processes can be followed swiftly and smoothly, reducing the likelihood of error.

SUMMARY

This chapter has described those non-technical skills that have been identified by experienced surgeons as being important for safe and successful surgery, recognizing that technical proficiency alone is not enough. These skills are both cognitive and social and can be observed by the demonstration of good and bad behaviours, as outlined in each section of the chapter. As surgeons strive to improve their operative performance, they will need the support of the whole operating team. Only with good non-technical skills will errors and adverse events be reduced and outcomes improved. Now that these skills have been recognized the challenge in the future is to incorporate them into undergraduate teaching as well as post-graduate training and assessment.

KEY POINTS

- Good surgeons have good 'non-technical skills' which support good operative performance and better outcomes for patients.
- These non-technical skills for surgeons (NOTSS) have now been identified as Situational awareness, Decision-making, Communication & Teamwork and Leadership
- Using the NOTSS taxonomy these skills can be observed, assessed, rated and taught.
- Better understanding of these skills will improve overall clinical performance and outcomes for patients with reduced adverse events.

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Further information can be found at: www.rcsed.ac.uk/professional-support-development-resources/learning-resources

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CHAPTER 41

EPIDEMIOLOGY

Jan H.P. van der Meulen, David A. Lowe and Jonathan M. Fishman

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: epidemiology; public health; clinical trials; research; research design; patient outcome assessment; statistics; epidemiological studies; methods; data interpretation; sample size; evidence-based medicine; bias (epidemiology) and confounding factors (epidemiology).

INTRODUCTION

This chapter presents epidemiology as a methodological discipline that provides important principles for clinical and health services research. It introduces the 'determinant-occurrence relationship' as a key epidemiological concept. On the basis of this concept, we will demonstrate how epidemiological methods and techniques can be used to address a wide range of questions. This chapter is intended to inform those who want to read the medical literature and evaluate research evidence. In other words, it has been written especially with the needs of the 'consumers' of research in mind.

We will concentrate on the choice of a study design for different types of research questions with the ultimate aim of developing a study that produces results that are relatively precise (free of random error) and accurate (free of systematic error or bias). An additional consideration is that the study needs to be efficient (affordable in terms of time and money). Strengths and weaknesses of study designs will be discussed as much as possible on the basis of examples related to diseases of the ear, nose and throat.

This chapter is not based on a specific literature search strategy. It amalgamates information and points of view as can be found in major textbooks and reviews of epidemiology, methods of health services research and evidence-based clinical practice.

Example: The indication for tonsillectomy

Simple, but well-designed, epidemiological research can be of great importance for clinical practice. A recent systematic review indicated that the effectiveness of tonsillectomy in adults is uncertain (although modest in children)[1] and in turn, that the indications for tonsillectomy are controversial. Nevertheless, tonsillectomy is one of the commonest surgical procedures carried out in children as well as in adults.

In the 1930s, an estimated 200 000 tonsillectomies were performed annually in England and Wales, a huge number compared to an annual number of approximately 40 000 in the year 2000. In the pre-war period, tonsillectomy had become popular to the point of being fashionable, and there was marked variation in its frequency according to geographical location, social class and sex.[2] It was estimated that at least 85 children lost their lives each year as a direct result of tonsillectomy.

Another study, carried out in the 1940s, demonstrated that there was great uncertainty about effectiveness and indications,[3] as cited in a book by Sackett and co-workers.[4] Among 389 11-year-old schoolchildren with intact tonsils examined by a group of clinicians, tonsillectomy was recommended in 174 (45%). A second opinion was requested in the 215 schoolchildren for whom tonsillectomy was

not recommended, and tonsillectomy was recommended for 99 (46%). The remaining 116 children, in whom on the two previous occasions tonsillectomy was not recommended, were then examined for the third time, and tonsillectomy was recommended in 51 (44%) of them. The most remarkable finding is that tonsillectomy was recommended in each of the three cycles for approximately 45% of the children.

These historical examples illustrate that uncertainty about diagnostic and management decisions can lead to overtreatment, which may have serious consequences for patients. Given the fact that there is still no high-quality evidence on the effectiveness of tonsillectomy more than 50 years later, the same problem may still exist, albeit to a lesser extent. The only published study on the effectiveness of tonsillectomy that could be included in one systematic review studied 91 children and was affected by important baseline differences in the characteristics of the surgical and the control group.[1] It is obvious that this kind of clinical uncertainty can only be solved by epidemiological evidence of high quality.

WHAT IS EPIDEMIOLOGY?

Epidemiology is a relative young discipline, but during its short life many definitions of epidemiology have emerged.[5] Many of these describe epidemiology in terms of its subject matter. The perhaps most frequently cited definition in this context states that epidemiology is the study of the distribution and determinants of disease frequency in human populations.[6] These three closely related components – distribution, determinants and frequency – encompass many epidemiological principles and methods.[7] For example, an epidemiological study that would fit perfectly within this definition is that of the frequency of head and neck cancer in a certain geographical area. This study could also consider the distribution of the disease among different subgroups. The determinants of disease occurrence would then derive from these two.

Although this definition has its merits in that it covers many epidemiological studies, some of which attracted large media attention (for example, smoking and lung cancer, cholesterol and heart disease, effect of diethylstilbestrol on offspring, unprotected sex and the acquired immune deficiency syndrome), a growing number of epidemiologists feel that the above-cited definition does not cover their work. The reason is that the subject matter of what can be considered epidemiological studies has become rather heterogeneous. Attempts to produce a definition of epidemiology based upon its subject matter therefore produce confusion rather than clarity.

The concept of the determinant-occurrence relationship

In the last two decades, an alternative definition has arisen that defines epidemiology as a discipline that studies the functional relationship between the occurrence of disease (or related health outcomes) and its determinants.[8] This may seem a trivial step, but this focus on the concept of the 'determinant-occurrence relationship' rather than the subject matter has considerably broadened the scope of epidemiology in medicine.

One of the major reasons why epidemiology has gained such far-reaching importance lies in the nature of medical knowledge. Medical knowledge is, to a large extent, derived from the experience obtained in groups of similar patients. Medicine is therefore an empirical science, and many of the empirical relationships in medicine can be considered as determinant-occurrence relationships. It is especially this realization on the basis of which epidemiology has become a basic science in medicine.

Epidemiology as a methodological discipline

An alternative approach to clarify the definition of epidemiology is to consider it as a methodological discipline. From this perspective, the subject of epidemiological inquiry is not so much the determinants of the occurrence of disease and other health outcomes, but the principles and methods for the study of determinant-occurrence relationships.

As a methodological discipline, epidemiology allows a large number of different questions to be answered. As explained earlier, it may play a role in describing the distribution of health and disease in a population. Who is affected? Where and when does this health problem occur? Why does it occur in a particular population?

However, other questions can be considered as well. Once a health problem occurs, epidemiology also provides methods for monitoring the course and outcome of a health problem. What is the outcome of the health problem? It may answer questions regarding the outcomes of interventions. Is intervention A more effective than intervention B? How well does a diagnostic test distinguish between people with and without the target disorder?

Epidemiological research is also essential for the assessment of the burden of disease and the need for health services and evaluation of the access to services. How much suffering does this health problem cause in a population? How many people need a certain intervention? Who uses the intervention? What factors explain differences in healthcare use?

'STREAMS' OF EPIDEMIOLOGY

Given the extension of the boundaries of epidemiology – based on the introduction of the determinant-occurrence relationship as the key epidemiological concept and the realization that epidemiological principles provide the methodological underpinning for the study of a wide range of questions – one can recognize several 'streams'

of epidemiological research. These streams differ largely according to the types of questions they address, but they share most of the methodological concepts and principles.

Classical epidemiology

The first stream of research is 'classical epidemiology', sometimes referred to as 'aetiological epidemiology' or 'risk factor epidemiology', of which the ultimate goal is 'the elaboration of causes that can explain patterns of disease occurrence'.[5] The geographical distribution of a disease, the variations in its frequency over time, and the special characteristics of people affected by it, are typical objects of study.

There is often a natural progression in this type of epidemiological research.[7] First, there is a concern about the possible influence of a particular factor on the occurrence of disease. This suspicion can have many origins – clinical practice, laboratory research, theoretical speculation – but it often arises from examination of disease distributions, and leads to the formulation of a specific hypothesis about its causes. It can then be further explored in studies of individuals that include an appropriate comparison group. A systematic collection and analysis of data may reveal that a statistical association exists. It is then essential to assess whether random errors or systematic errors might be responsible for the findings. Finally, a judgement needs to be made about whether an observed association represents a cause-effect relationship.

An otolaryngological example of this type of epidemiological research is the study of the distribution of head and neck cancers and the association of the occurrence of this disease with traditional risk factors such as diet, smoking and drinking habits or socioeconomic status. Another more specific example is the testing of the hypothesis that there is a link between human papillomavirus and the occurrence of a subset of these cancers. The result of aetiological research may guide the first steps towards the development of primary prevention that keeps disease from occurring at all.

However, the reductionist nature of classical epidemiology has been criticized. It has been argued that epidemiological studies often ignore 'the interdependence of multiple agents and how human populations become exposed and susceptible to them'.[9] Epidemiological research that focuses on the effect of risk factors measurable at the level of the individual neglects the population context and the social and cultural determinants that act at population level.

Clinical epidemiology

The second stream of research is 'clinical epidemiology'. The adjective 'clinical' is added because clinical epidemiology 'seeks to answer clinical questions and to guide clinical decision making with the best available evidence'.[10] Clinicians are mainly concerned with problems of individual patients. It may seem paradoxical that results of epidemiological studies that are derived from groups of patients should be applicable to the problems of individual patients. It is obvious, however, that this is because the best evidence to solve a clinical problem is derived from the experience of a large number of similar patients.

Advocates of evidence-based medicine have addressed this paradox directly. They state that clinicians need to carry out 'the particularization, to the individual patient, of our prior experiences (both as individual clinicians and collectively) with groups of similar patients'.[4] A good clinician should therefore use the best available external evidence together with his own unsystematic clinical experience and intuition – based on a blend of knowledge derived from anatomy, physiology and other basic sciences.[11] Evidence alone is never sufficient to make a clinical decision. Decision-makers always trade the benefits and risks, inconvenience and costs associated with alternative management strategies, and in doing so should especially consider the patients' values and preferences.

The significance of the definition of epidemiology as a methodological discipline that addresses determinant-occurrence relationships is based on the reach of the concept of determinant-occurrence relationships in itself. If one considers the presence of disease as the outcome and the diagnostic information as the determinant, then this represents a diagnostic problem. The object of study is, in this case, the functional relationship between diagnostic information and the presence of disease. If one considers the occurrence of a disease or a health-related event in the future as the outcome and the presence of certain patient characteristics as the determinants, then this represents a prognostic problem. One of these patient characteristics can be the use of a specific therapy, and in that case, this represents a therapeutic problem. In the latter case however, to achieve accurate results the '*ceteris paribus* principle' – the condition that all other determinants are equal – is a fundamental notion that we will explicitly address in the section 'Randomized controlled trials' below.

A study of the diagnostic accuracy of fine-needle aspiration as a test for malignant disease in patients with nodular thyroid disease is an otolaryngological example of diagnostic research. The influence of the age of patients with an oropharyngeal carcinoma on long-term survival constitutes a prognostic research question. The effect that early surgery compared with watchful waiting for glue-ear has on language development in pre-school children represents a therapeutic research question.

It is useful at this point to distinguish between the epidemiological terms, 'incidence' and 'prevalence'. Incidence is defined as the number of new cases that occur in a specific time period. Prevalence is defined as the proportion of the population that actually has a disease, or condition, at a specific point in time. Unlike prevalence, incidence is a true rate because it includes a measure of time. Prevalence on the other hand is a 'snapshot' of a situation at a single point in time and for this reason is sometimes also called the 'point' prevalence.

Epidemiology and health services and public health research

Epidemiology is also one of the core disciplines of health services research and public health. Whereas classical epidemiology and clinical epidemiology focus largely on determinants of health and disease and related conditions in individuals, health services research is more directed towards questions addressing the quality and organization of healthcare systems and public health research towards the health and healthcare problems in communities. One could consider this as a third stream of epidemiological research.

Important questions for health services research are those that address the variations in processes and outcomes of healthcare services, as well as the determinants of these variations. Research in public health may be concerned with the influence of environmental factors, socioeconomic conditions and health services on health in the community. It will be clear by now that many of these questions take the form of determinant-occurrence relationships, which again confirms the crucial role of an epidemiological approach.

A study comparing the outcome of thyroid surgery performed by experienced surgeons and surgeons in training is an example of an epidemiological study directly addressing a determinant of the quality of otolaryngological care.[12] Another example is a study of the impact that the publication of a guideline on the treatment of persistent glue-ear in children had on the rate of surgery.[13] A systematic review of studies addressing the effectiveness of screening young children to undergo early treatment for glue-ear is a third example of public health research.[14]

THE 'ANATOMY' AND 'PHYSIOLOGY' OF EPIDEMIOLOGICAL RESEARCH

We cannot discuss the different study designs before we have examined what epidemiological research is made up of and how it works. The easiest way to do this is to describe the components of a study protocol and the way results are used to draw inferences from the study results about the truth in the universe. The following sections are based largely on the introductory chapters of a recent book by Hulley and colleagues about designing clinical research.[15]

Essential components of a protocol for an epidemiological study

A research protocol is a document that provides all essential details of a study. A protocol is necessary for guiding all the decisions that need to be made in the course of the study. The process of writing a protocol itself helps the investigator to enhance the scientific rigour and efficiency of the project. Most research involves teamwork and a written document ensures that all members know how the study should be implemented and what they are expected to contribute. A good protocol provides answers to a number of essential questions.

WHAT QUESTION WILL THE STUDY ADDRESS?

The research question defines what you want to achieve. Many experienced researchers will agree that formulating a question that can be translated into a feasible and valid study can be surprisingly hard. What often happens is that instead of a 'research question', a 'topic' is formulated. 'Framing' the research question is the first step for every new project, of which the importance cannot be overestimated. Conversely, many studies fail not so much because the study design is flawed or the execution of study is poor, but because the question was not formulated adequately in the first place.

An otolaryngological example of such a 'topic' that needs further research is the concern about the rising complication rate after tonsillectomy in the UK. It is clear that we need to provide more detail and structure before we are able to formulate a relevant and answerable 'research question'. The concept of the determinant-occurrence relationship may provide some guidance in this context. In other words, we need to be specific about what outcomes we want to study as well as what determinants we want to consider. Finally, we need to specify the target population, the kind of people for whom the study should provide answers.

In epidemiological research, a good research question therefore has four components, which can be summarized by the acronym PICO:

1. the target population or participants (P);
2. the intervention (I);
3. the comparison or control group (C), at least if there is any;
4. the outcome(s) of interest (O).

An example of a 'good' research question for a study addressing the complication rates after tonsillectomy could be: 'In patients undergoing tonsillectomy for recurrent tonsillitis, does the use of the bipolar diathermy forceps increase the occurrence of tonsil bleeds severe enough to require return to theatre in the first 28 days after surgery, compared to other tonsillectomy dissection types?' Admittedly, this is a rather convoluted sentence, and is only given here to illustrate how the four components of a research question can be covered in one question. In practice, the question will be shortened to 'Does bipolar diathermy increase the haemorrhage rate after tonsillectomy', but in that case the details that define the target population, intervention, comparison and outcome of interest need to be provided separately.

WHY IS THE STUDY QUESTION IMPORTANT?

Good epidemiological research should also pass the 'so what' test. In the Introduction or Background section of a protocol, it should be argued that answering the research question will provide a significant contribution to our

state of knowledge or, in other words, add to what is already known about the problem. It is therefore important to be on top of the published literature before developing a study. It should also be clear that the results of the proposed study will help to resolve current uncertainties, which may lead to new scientific understanding and influence clinical and public health policies.

It is often 'scholarship' that will identify the gaps in the current knowledge and how these can be addressed in an optimal way by learning from the work of others. For example, a recent systematic review of the literature on the effect of tonsillectomy in patients with chronic or recurrent tonsillitis concluded a lack of evidence to guide decision-making for this surgical intervention in adults or children.[1] More importantly in this context, the authors of the systematic review also concluded on the basis of the results of their review that future trials should address the effectiveness of tonsillectomy in subgroups according to age, severity and disease frequency, and that patients should be followed up for at least one year to assess outcomes such as general well-being, behaviour, growth, sleep and eating patterns in addition to severity and frequency of infections. These conclusions based upon a systematic review provide powerful arguments for the direction of future research.

HOW IS THE STUDY STRUCTURED?

Choosing the study design is a complex issue. The actual choice depends strongly on the research question. The study should be designed in such a way that it produces results that are relatively precise (free of random error) and accurate (free of systematic error or bias). An additional consideration is that the study needs to be efficient (affordable in terms of time and money).

A simplistic 'taxonomy' of study designs, presented in **Figure 41.1**, shows that two fundamental decisions have to be made. First, the investigators have to decide whether they want to assign the determinants themselves in an 'experimental study', or whether they want to examine events as nature takes its course in an 'observational study'. Second, if an observational study design is chosen, the next step is to decide whether the study needs a comparison or control group. If so, the study is often called 'analytical'. If not, it is a 'descriptive' study. Descriptive studies are often used as a first step into a new area of study – the scientific 'toe in the water',[15] and followed by analytical studies to answer questions that can address determinant-occurrence relationships.

A more detailed presentation of study designs follows under the section 'Choosing the study design' below.

WHO ARE THE STUDY SUBJECTS AND HOW WILL THEY BE SELECTED AND RECRUITED?

A good choice of the study subjects ensures that the results of the study will accurately represent what is going on in the population of interest, the target population, the set of people best suited to the research question (for example, patients with early laryngeal squamous cell carcinoma for a study comparing radiotherapy and surgery for laryngeal cancer). The protocol must also specify the study sample, which is the subset of the target population available for study (for example, all consecutive patients with this disease condition referred to a regional head and neck cancer centre in a defined period of time). The study sample should be a subset of the target population that can be studied at an acceptable cost and is large enough to control random error and representative enough to control systematic error.

In many cases, controlling both random error and systematic error sets conflicting demands, which is sometimes referred to as the 'precision–bias' dilemma. For example, a study that aims to evaluate the usefulness of the endoscope compared to the headlamp for sinonasal surgery should carefully consider which patients to include.

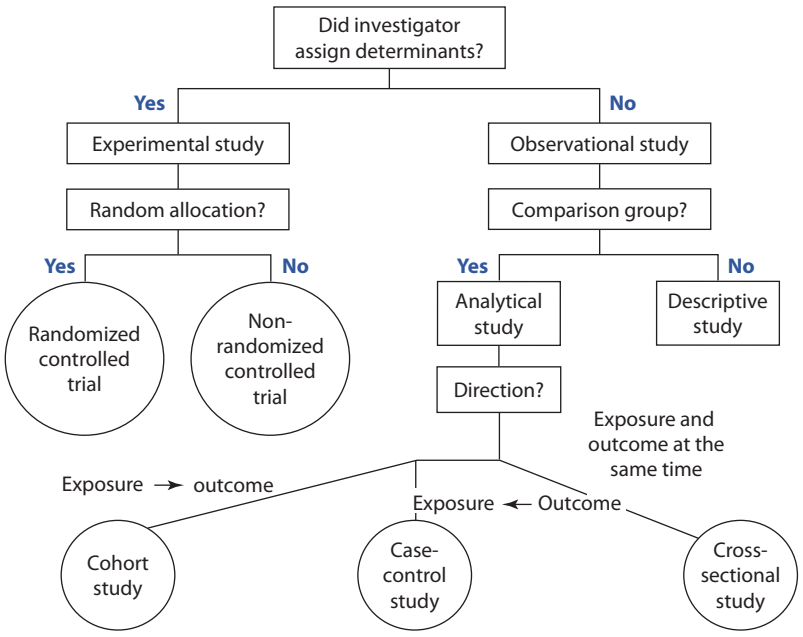


Figure 41.1 Algorithm for classification of types of clinical research. Reproduced from Grimes and Schulz, 2002,[16] with permission from Elsevier.

It is highly likely that the results of the study will differ according to the extent of the surgery. The comparison might be most relevant for patients who undergo surgery for procedures around the middle meatus and the anterior ethmoid. Including patients who undergo only simple polypectomy, who comprise approximately 50% of the total number of patients who undergo a form of sinonasal surgery, may seem an attractive option because it will double the size of the study. However, including these patients will diminish the extent to which the study sample represents the population for which the research question is of interest.

In an ideal world without practical and financial limitations, we would study the entire target population. Often, if not always, the target population is too large and the study will be carried out in a sample. Earlier, we gave as an example the study comparing radiotherapy and surgery for early laryngeal carcinoma that was carried out in consecutive patients visiting a regional centre in a defined period of time. This type of sampling, including patients that are easily accessible to the investigator, is called 'convenience sampling'. It is very frequently used in clinical research. It has obvious advantages in terms of costs and logistics, but its drawback is that it might not sufficiently represent the target population. Consecutive sampling, including without interruption all accessible people, is especially useful in this context given that it reduces the possibility that selection either by the investigators or self-selection by the subjects influences the results. Probability sampling is the gold standard for ensuring that the study sample is representative of the target population, except for the effect of chance variation. There are several probability-sampling methods. With simple random sampling, every individual in a population has the same chance of being included. However, in some cases, a form of stratified sampling (random sampling with a known sample size within subgroups) is desirable. For a study of patient satisfaction of patients visiting an otolaryngology outpatient clinic, for example, the investigators may wish to divide patients in 'strata' according to their diagnosis or the procedure that was being carried out, and then sample specified numbers from each stratum.

The choices made about the selection of the study subjects (the intended sample) are important as they have an impact on the extent to which the study findings can be generalized. The sampling procedures can affect the generalizability of the results in a number of ways. First, the actual sample might be different from the intended sample. For example, people who were eligible for the study might have refused, and people who participated might be different (more or less healthy, dependent on the study context) from those who did not. Second, the study sample should be sufficiently similar to the target population. For example, the 'spectrum' of disease in patients with laryngeal squamous cell cancer might differ from one centre to the next, and in turn the effects of radiotherapy and cancer might differ as well. Third, the investigator must form an opinion about whether the results can be generalized to people outside the target population. In terms of our example, do radiotherapy and surgery have similar effects in other countries, in patients with more advanced disease, or in patients who are on average older or younger? This will always be a subjective judgement that depends on findings in other studies, more general scientific knowledge, and what is sometimes called 'a feeling for the organism'. It is not a yes-or-no decision, and may trigger debate among experts. This debate may be informed by the study itself if the study population is diverse enough to explore the constancy of effects in different subgroups within the study.

WHAT MEASUREMENTS WILL BE MADE?

The quality of a study depends on how well the variables measured in the study represent the phenomena of interest. Another concern is how the variables of interest can be measured as precisely (free of random error) and accurately (free of systematic error) as possible without making the study unreasonably expensive.

It is important to have some understanding about the types of variables that are encountered in epidemiological research, and how they can be measured. Any variable can be considered to be of one of two basic types: continuous variables and categorical variables. This distinction determines the way in which these variables should be measured as well as analyzed. As a general rule, with categorical variables, the analysis will involve a description or comparison of the proportion of subjects falling into the various categories. With continuous variables, the descriptions or comparisons are most often presented in terms of average values or medians if the sample is small and the average value is considered to be inappropriate to describe the 'midpoint' of the variable's distribution.

Theoretically, continuous variables can take all possible values on a continuum along a specific range. Many clinical parameters are continuous. Variables, such as blood pressure, body weight, body temperature, are not restricted to particular values and are only limited by the accuracy and precision of the measuring procedures. The units in which a continuous variable is expressed specify a uniform difference along the entire length of the scale. A difference in blood pressure of 10 mmHg has the same interpretation irrespective of whether it occurs at the lower or the upper end of the blood pressure scale.

Discrete variables can only take certain numerical values – in most cases only integers (whole numbers). If discrete variables have a considerable number of possible values, they can often be treated as if they were continuous. Examples of these 'quasi-continuous' variables are counts (such as the number of cigarettes smoked, number of episodes of acute tonsillitis in last year, or number of days spent in hospital) or scores on 'clinimetric scales' (such as the 20-item Sino-Nasal Outcome Test) that measures symptom severity of sinonasal conditions on a scale with discrete values ranging from 0 (no symptoms) to 100 (very severe symptoms)[17] or the Epworth Sleepiness Scales, used in patients with obstructive sleep apnoea, that can take discrete values from 0 (no daytime sleepiness) to 24 (very severe daytime sleepiness).[18] Strictly speaking, considering

scores on a clinimetric scale as continuous is somewhat problematic, as the interpretation of a difference of one unit may vary along the length of the scale. For example, does an increase from 5 to 10 on the Epworth Sleepiness Score correspond to an increase from 15 to 20?

Phenomena that cannot be measured quantitatively can often be measured by classifying them into categories, and then counting the number of subjects that fall within the defined categories. In its simplest form, there are only two categories (such as man/woman, or dead/alive), and these variables are called dichotomous or binary variables. When there are more than two possible categories, the variables are termed poly- or multichotomous variables. Polychotomous variables can be further classified into those that are ordered, called ordinal variables, and those that are not, called nominal variables. Socioeconomic status, ASA grades describing fitness to undergo surgery,[19] and degree of pain are examples of the former, and race, marital status and blood type are examples of the latter.

As a general rule, continuous variables are more 'informative' than categorical variables. It is therefore advisable to use continuous variables as much as possible. For example, 'body temperature' as a continuous variable should be preferred to a categorical variable dividing patients into those with a temperature below and above a certain threshold.

Good measurements are precise and accurate. There are largely three sources of random and systematic error: (i) variability due to the observer; (ii) variability due to the subject; and (iii) variability due to the instrument used.

A number of strategies can be followed to increase simultaneously both precision and accuracy of the measurements. First, the measurement procedures should be standardized and clearly described in the study protocol. Second, those who are involved in taking the measurements should be trained and their performance monitored in the course of the study. Third, the measurements should be carefully chosen in terms of what is known about their performance. Fourth, calibration procedures should be carried out against a 'gold standard'. This is especially essential for mechanical devices such as weighing scales, thermometers and blood pressure measuring devices. Furthermore, a simple and rather effective approach to increase measurement precision is to repeat the measurements and to use the mean of two or more observations. The latter approach is commonly used in studies measuring blood pressure. An important approach to reduce systematic error is blinding, which conceals information about determinants, or in some cases outcomes, to the observers and/or subjects. This reduces the possibility that the observers or the study subjects distort the overall accuracy of the measurements, consciously or unconsciously. Blinding, however, does not ensure overall accuracy of the measurements, but it may eliminate 'differential bias' that affects one study group more than another. Blinding is especially relevant for measurements that incorporate some subjective judgement. For example, a study comparing early surgery with watchful waiting for glue-ear in pre-school children used a tester of language development who was unaware of what treatment the children had received.[20]

HOW WILL THE RESULTS BE ANALYZED?

The main statistical methods that are going to be used to analyze the results should be defined in the study protocol. Choosing the statistical methods after the results have become available will increase the likelihood of finding associations between determinants and outcome on the basis of chance alone.

An important element of the analysis plan is the description of how the outcome variable is going to be analyzed. For example, a trial on early surgery for glue-ear that measured language development with the Reynell development language scales (a test of expressive language and verbal comprehension abilities in children aged 6 months to 6 years) could analyze the Reynell data as a continuous variable.[20] Conversely, it could define groups with normal language development and with delayed language development by dichotomizing the Reynell data, and use this categorical variable as the main outcome measure.

If a categorical variable is used as the outcome measure, the 'denominator problem' should be considered. Figure 41.2 summarizes the questions that have to be answered in this respect. The first question asks whether the numerator is going to be included in the denominator. If the answer is yes, the next question is whether time is included in the denominator or not.

Let us first consider the case when the numerator is included in the denominator, but time is not. A first example of this would be a measure of the occurrence of sensorineural hearing loss in neonates. One could simply report the proportion of neonates with hearing loss: the numerator would be the number of neonates with hearing loss and the denominator would be the total number of

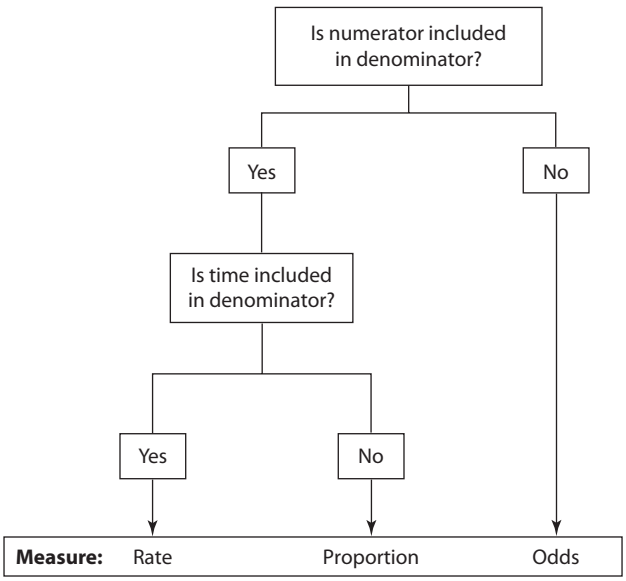


Figure 41.2 Algorithm for distinguishing rates, proportions and odds. Adapted from Grimes and Schulz, 2002,[16] with permission from Elsevier.

neonates included in the study. This proportion is often referred to as *prevalence*. A second example would be a measure of the occurrence of head and neck cancer in people, initially free of the disease, who developed the disease within a specified time period. The numerator would be the number of subjects who developed the disease during follow-up and the denominator would be the total number of subjects at the beginning of the study. This proportion is often referred to as *cumulative incidence*. Suppose that 1000 smokers are followed up during 5 years and that 15 develop head and neck cancer, the cumulative incidence would be 1.5%.

The calculation of a proportion as an estimate of disease occurrence, as described above, assumes that the entire study sample has been followed up for the specified time period. This is often not the case. Some subjects might enter the study later, and others might be lost to follow-up. An alternative way of measuring outcomes that takes these varying follow-up time periods into account is to include time in the denominator. The numerator would be exactly the same as for proportions, but the sum of the time that each individual was followed up and at risk of becoming a case would be used as the denominator. In this case, an incidence rate (also called incidence density, force of morbidity/mortality, hazard) could be calculated that is equal to the number of people who develop cancer divided by the total person-time at risk during follow-up. For example, on the basis of the previous example of the occurrence of head and neck cancer in smokers, one could have expressed the incidence rate of cancer as approximately 3 cases per 1000 people per year (or 15 divided by approximately 5 × 1000 years of person-time at risk). Because the incidence is very low, a simple relationship holds: cumulative incidence ≈ incidence × average follow-up time.

Many epidemiological studies report, in some form or other, outcomes expressed as 'odds'. It is important to distinguish odds from probability. A probability can be estimated as the proportion of people in whom a particular characteristic, such as the presence of disease, is present. The larger the group of people under study, the better the observed proportion of people with the disease reflects the 'true' probability. Odds, on the other hand, represents the ratio of two complementary probabilities. For example, if the probability of disease is 0.20, then the odds are 0.20%/0.80 = 1:4 = 0.25. Another way of calculating the odds is by dividing the number of subjects with the characteristic by the number without it. In other words, the numerator is not included in the denominator (**Figure 41.2**).

Most frequently, it is not the odds itself that is reported in epidemiological studies, but the odds ratio – the ratio of odds in different groups. This can be the 'outcome odds ratio', or the ratio of the odds of the outcome of interest in the group with the determinant to the odds of the outcome in the group without the determinant. Conversely, this can also be the 'determinant odds ratio', or the odds of the determinant in the group with the outcome compared to the odds of the determinant in the group without the outcome of interest. One reason why epidemiologists find odds ratios so attractive is that 'outcome odds ratios' are equivalent to 'determinant odds ratios', which is a fact used in the analysis of case-control studies (see 'Case-control studies' below). For example, **Table 41.1** presents fictitious findings of a study on risk factors for post-operative complications after tonsillectomy. The outcome odds ratio is the same as the determinant odds ratio, which can be easily understood as both odds ratios simplify to the 'cross product' of the cell frequencies of a 2 × 2 table. The 'outcome odds ratio' can be calculated as

TABLE 41.1 'Outcome odds ratios' and 'determinant odds ratios' – fictitious example of complication rates after tonsillectomy

Dissection instruments used	Post-operative complication					
	Yes		No		Total	
Bipolar diathermy	36	a	264	b	300	a+b
Other	24	c	676	d	700	c+d
Total	60	a+c	940	b+d	1000	

$$\frac{\frac{a}{a+b}}{\frac{c}{c+d}} \Big/ \frac{\frac{b}{a+b}}{\frac{d}{c+d}} = \frac{a/b}{c/d} = \frac{a \times d}{b \times c} = \frac{36 \times 676}{24 \times 264} = 3.8.$$

Similarly, the 'determinant odds ratio' can be calculated as

$$\frac{\frac{a}{a+c}}{\frac{b}{b+d}} \Big/ \frac{\frac{c}{a+c}}{\frac{d}{b+d}} = \frac{a/c}{b/d} = \frac{a \times d}{b \times c} = 3.8.$$

When a dichotomous outcome variable is used (for example, alive/dead, or disease present/absent) 'risk differences' and 'risk ratios' are commonly used as 'measures of effect'.[10] The 'risk' in this circumstance can represent 'prevalence', 'cumulative incidence', 'incidence' or even 'odds', as described above. One might ask, 'What is the additional risk of head and neck cancer in people who smoke, over and above that in people who do not?' The answer to this question is obviously a risk difference. In a previous fictitious example, we supposed that we followed up 1000 smokers for a period of 5 years and that we found that 15 of them developed head and neck cancer. The cumulative incidence of cancer in this group is therefore 1.5%. We can also suppose that we did the same in 1000 non-smokers and that we found cancer in 7 of them. The cumulative incidence in non-smokers is 0.7%. The risk difference attributable to smoking is therefore 0.8% (= 1.5–0.7%). On the other hand, one might ask, 'How many times are smokers more likely to get head and neck cancer compared to non-smokers?' Following our example, we could calculate the risk ratio as 2.1 (= 1.5%/0.7%). In other words, smokers are approximately twice as likely to develop head and neck cancer over a 5-year period as non-smokers. This risk ratio does not tell us anything about the magnitude of the risk difference. Even for large risk ratios, the risk difference might be quite small if the

outcome is uncommon. As a rule of thumb, risk differences are more meaningful as a measure of effect in clinical situations, because it represents the actual additional probability in those exposed. On the other hand, relative risks are more meaningful as effect measures of a causal relationship in aetiological studies.

HOW LARGE IS THE STUDY GOING TO BE?

A major problem of many studies is that the study size is too small. Small studies lead to imprecise results. Small studies often increase, rather than reduce, the scientific and clinical uncertainty in a specific area. Although one might argue that small studies have a value of their own because they might be included in a systematic review and meta-analysis, which would mimic the results of a larger study, it should be the goal of every study to include a number of subjects that would in itself produce 'meaningful' results. A considerably less frequent problem is that of a study that is larger than necessary to be meaningful. Larger studies are more difficult to carry out and may be more costly than necessary. The most important issue in this context is of course to determine what can be considered meaningful.

How can the appropriate size of a study be determined? This question is most commonly answered on the basis of a statistical 'sample size calculation'. Although the answer of a sample size calculation is exact (for example, the number of subjects to be included in a study), in many cases it depends on a number of rather subjective choices. The way that the sample size of study is to be calculated depends on whether it is an analytical study (study with a comparison or control group) or a descriptive study.

For analytical studies, a research hypothesis should be formulated that further refines the study question. This hypothesis sets out the basis for statistical significance testing. Because this hypothesis guides the statistical analysis, it should be simple (addressing one determinant or comparison and the occurrence of one outcome) and specific (defining unambiguously the target population, the control and comparison group, and the outcome of interest). For the purpose of statistical significance testing, this hypothesis should be given in the form of a 'null hypothesis' that states that there is no association between the determinant and the outcome. A statistical test helps to estimate the probability that an association observed in a study is due to chance (the '*p*-value'). The 'alternative hypothesis' states that there is such an association. Sometimes, a distinction is made between one-sided and two-sided hypotheses. Two-sided hypotheses state only that an association exists between determinant and outcome, whereas one-sided hypotheses specify the direction of the association. For example, the null hypothesis of a study comparing early surgery with watchful waiting for glue-ear in pre-school children could be that there is no difference in the language development in the two treatment groups. The one-sided null hypothesis would state that language development with early surgery is poorer than with watchful waiting. One-sided *p*-values are appropriate in selected circumstances, when only one direction of the association is important. One-sided *p*-values may seem attractive as, generally speaking, with a one-sided significance test the *p*-value would be half the size of that with a two-sided test, but, on the other hand, if the results of the study would suggest that the language development is indeed poorer with surgery, then this would produce a large *p*-value as it is likely to observe a result like that given that the null hypothesis (language development with surgery is poorer) is true. For this reason, it is convention to use two-sided hypotheses when planning the size of a study as well as two-sided *p*-values when analyzing the results, unless there are well-argued reasons for the contrary.

When developing a study protocol for an analytical study, the investigator does not know the size of the effect that the determinant of interest has on the outcome, as one of the objectives of the study is to estimate it. For example, the investigators of the study of the effect that early surgery has on language development in children with glue-ear had to decide the smallest effect of surgery that in their view would be of clinical importance. This quantity is often called effect size or target difference. Determining this effect size is the most arbitrary step in a sample size calculation. The smaller the effect size, the larger the study needs to be, other things being equal. Previous studies could help to make a guess about what can be expected, but they do not provide any guidance about what is an important difference and what is not.

Before a sample size can be calculated, two further arbitrary choices need to be made. First, the 'alpha level' or 'significance level' has to be chosen that defines the cut-off point for the *p*-value – conventionally 0.05 – to classify a result either as 'significant' (if *p*-value ≤ cut-off), in which case the null hypothesis is rejected, or as 'not significant' (if *p*-value > cut-off), in which case the null hypothesis is not rejected. Second, the 'power' of the significance test has to be chosen – commonly used values are 0.80 or 0.90 – that defines the probability to obtain a significant result if we assume that the defined effect size or target difference would be the 'true effect' or 'true difference'.

Finally, and only if a continuous outcome variable is going to be analyzed, a measure of the variability (spread) of that outcome – standard deviation or variance – is needed. The greater the variability in the outcome variable among the subjects, the more difficult it will be to demonstrate a difference between two groups, and the larger the study needs to be.

The required sample size can be obtained on the basis of the above-described ingredients either by using the formulae presented in statistical textbooks, from published tables or by using commonly available statistical software packages. The ingredients and the formulae for study size are purely technical. They do not take into account the value of the information obtained in the study. The most important decision is to determine the 'right balance' between the value of greater precision in study results against the greater costs. Essentially, this decision boils down to a cost-benefit analysis in which the benefits are more difficult to quantify than the costs.

For descriptive studies, concepts such as null hypothesis, effect size, alpha level and power do not apply. Instead, descriptive statistics, such as means and proportions, are presented. The sample size of descriptive studies depends on how precise the investigator wants these descriptive statistics to be. Confidence intervals, such as 95% or 99% confidence intervals, are commonly used to represent the precision of the estimates. For example, a study of the 5-year survival after surgical treatment in 228 patients with hypopharynx carcinoma found that the survival was 27.2% with a 95% confidence interval ranging from 21.5% to 33.5%.[21] This interval indicates that we can be 95% confident (which can be considered more or less the same as saying that there is 95% chance) that the 'true' 5-year survival probability lies within this interval. When estimating the sample size for descriptive studies, the investigator specifies the desired width of the confidence interval, and the sample size derives from that and can be read from tables or obtained from statistical software packages. This approach can be followed for any type of descriptive variable for which confidence intervals can be calculated.

CHOOSING THE DESIGN STUDY

The taxonomy of study designs presented in **Figure 41.1** provides a simple decision aid for choosing the most appropriate design. A number of questions have to be answered with the ultimate goal being to create an affordable study that provides results that are relatively precise (free of random error) and accurate (free of systematic error or bias). A first distinction that has to be made is that between studies in which the investigator actively assigns the determinants (experimental studies) or those in which this is not the case (observational studies). A second distinction that has to be made is that between observational studies that do or do not have a comparison or control group. If so, the study is called analytical, if not, descriptive.

The following sections are largely based on a series of short essays on clinical research published in the *Lancet*,[16] and chapters of recent books about designing clinical research by Hulley and colleagues[15] and clinical epidemiology.[10] We start this section by describing observational studies and will end with the description of experimental studies (randomized controlled trials).

Levels of evidence

Individual studies are frequently graded according to a hierarchy whereby those at the top are considered to provide stronger evidence than those lower down the scale. The Oxford Centre for Evidence-Based Medicine has provided one such framework as shown in **Table 41.2**.

Caution, however, is recommended in exercising such a rigid hierarchical approach to all studies. Thus, randomized controlled trials (RCTs) for a particular intervention are not always available and not all interventions can be evaluated in RCTs; a lack of RCT evidence does not equate to a lack of evidence. In addition, although guidelines are based on the best available published evidence, not all evidence makes it into the literature. Finally, this approach fails to take into consideration the quality of individual studies. A well-designed and properly conducted cohort or case-control study may provide better evidence than a small or poorly conducted RCT.

TABLE 41.2 Oxford Centre for Evidence-Based Medicine – classification of levels of evidence

Level	Evidence
1a	Systematic review of RCTs; meta-analyses
1b	Individual RCT
2a	Systematic review of cohort studies
2b	Individual cohort study
2c	'Outcomes' research
3a	Systematic review of case-control studies
3b	Individual case-control study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion, anecdotal evidence, case reports or based on physiology, bench research or 'first principles'

Modified from http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009

An alternative approach is to classify studies not only by their *design* but also according to the *quality of evidence* they provide. For example, The Grading of Recommendation, Assessment, Development and Evaluation Working Group (GRADE Working Group) has developed a system for grading the quality of evidence.[22]

Minimizing bias and confounding

We indicated earlier that the precision of study results depends mainly on two factors: the size of the study design and the methods used to obtain the measurements. Furthermore, a study should be designed in such a way that it avoids systematic error or bias. A great number of different types of bias have been documented but it is not a major simplification to consider all these types of biases in three categories: selection bias, information bias and confounding.

To examine whether selection bias would introduce systematic error in the study results, two questions need to be answered: 'Do the sample of study subjects sufficiently represent the population of interest?' and 'Are the groups that are going to be compared similar in all important respects apart from the determinant(s) of interest?' The first question is especially relevant when designing a randomized controlled trial, because trials usually enrol patients who tend to be different (often healthier) from the target population and the results tend to overestimate the effects compared to what they would be in routine practice. This contributes to the differences between the efficacy of a therapy observed in the highly controlled circumstances in selected clinical settings and the effectiveness

of a treatment in actual practice. The second question refers directly to the comparability of the groups. In other words, do the groups differ importantly aside from the comparison that is being studied?

Information bias results from incorrect information about the determinant or the outcome or both. The important question that has to be answered is: 'Has information been gathered in the same way?' In cohort studies (see 'Cohort studies' below), information about the outcome should be obtained in the same way for those with and without the determinants under consideration. Also, those who collect the information about the outcome should be unaware of ('blind to') the determinant status of the subjects as much as possible. In case-control studies (see below), information about the determinant status should be collected in the same way for cases and controls.

Confounding occurs when two determinants or risk factors are associated with each other. In that case, the effect of one is confounded with, or distorted by, the effect of the other. Confounding can occur because of selection bias, by chance, or because the two determinants are really associated in nature. Selection bias and confounding are not mutually exclusive, but they are often presented differently as they represent problems at different stages in a study. Selection bias is an issue when the sampling procedures for patients are determined during the design phase of a study, whereas confounding is an issue to consider during the analysis phase.

Often in the same study more than one bias operates, as in the following example. Imagine a study that compared the effect that surgical and non-surgical management had on speech and language development in children with persistent otitis media with effusion. In this example, selection bias could have been present if the children who received surgical treatment came from a different background and had parents who were on average of higher socioeconomic status, or if they had a family history of chronic ear infection. Information bias could have occurred because the assessment of language development might have been influenced by the fact that those who were applying and interpreting the speech and language tests knew the treatment the children had received. Finally, the conclusion that surgical treatment improved speech and language development might have been the result of confounding if the children who received surgical treatment had had more serious or more frequent ear infections. The latter bias is often referred to as 'confounding by clinical indication'.

When designing studies, investigators should try as much as possible to rule out bias. The concerns about bias need to be thought through very carefully. This relates directly to the three components of a good research question, and these components should be represented adequately in the study design. First, the study sample should adequately represent the target population. Second, the measurement of the determinants should adequately represent the comparison of interest. Third, the measurements of the outcomes should adequately represent the outcome(s) of interest.

When confounding is anticipated, the investigator should consider design and analysis strategies to control its influence on the outcomes. The simplest approach in the design phase is restriction or specification. For example, investigators could decide to include only non-smokers in a study on the effect of human papillomavirus and oropharyngeal cancer. The disadvantage of this strategy is that it reduces recruitment and prohibits generalization of the results to smokers. Another potential approach in the design phase is matching, which means that subjects with matching values for the confounding variables are included. This can be done individually (pair wise matching) or in groups (frequency matching). However, the use of matching has many disadvantages. The recruitment process can become rather cumbersome. Special analytical techniques are required that represent the fact that the subjects are not sampled independently. There is also the danger of overmatching – matching on the basis of a variable that is not a confounder, which would reduce the study's power. Given these disadvantages, matching should be avoided if other strategies could provide sufficient control for confounding.

In the analysis phase, the investigator can use either stratification or adjustment. Stratification ensures that the analysis compares like with like, first by comparing subjects within a group (or stratum) of subjects with similar values of one or more confounding variables and then, in a second step, by calculating an overall estimate by pooling the stratum-specific results. The most important disadvantage of this approach is the limited number of variables that can be controlled for. Adjustment on the basis of a statistical multivariate model does not suffer from this limitation, but its effects depend on the adequacy of the model fit. Both approaches depend on the completeness, precision and accuracy of the measurements of the confounders.

Observational studies

DESCRIPTIVE STUDIES

Descriptive studies can describe the experience in only one individual, a case report, or a report on a series of individual cases, the case-series report. Case series are the most frequently published studies in surgery. An important function of descriptive studies is that they can describe the distribution of diseases or disease-related conditions and events in a specified population.

Good descriptive research should address the five 'W' questions – who, what, why, when and where – although as soon as these questions are addressed on the basis of the data, the distinction between descriptive studies (no comparison) and analytical studies (comparison between groups essential) starts to disappear; but a distinctive characteristic of descriptive studies is that they cannot directly quantify the risk that can be attributed to a specific determinant. For example, a series of three cases was published recently of perichondritis of the pinna as a result of 'high' ear piercing, and was used to focus attention on the risks of body piercing.[23] The study also presented the increasing trend in the number of hospital admissions for perichondritis of the pinna in the UK and Wales from

approximately 600 in 1990–91 to approximately 1200 in 1997–98. The latter is an example of a surveillance study, which is another important type of descriptive study. A surveillance study is an ongoing and systematic collection, analysis and interpretation of health data essential to the planning, implementation and evaluation of health services and public health practice. The fact that this particular descriptive study cannot quantify the attributable risk might not be a weakness as most cases of perichondritis of the pinna may be due to piercing practices in the first place.

The strength of descriptive studies is that they often use existing data and thus are inexpensive and efficient to carry out. Furthermore, few ethical limitations exist. The disadvantages are that there is a danger of over-interpretation. For example, in early 2001 the UK government recommended that single-use instruments should be used for adenotonsillectomy to minimize the risk of transmission of variant Creutzfeldt-Jacob disease (vCJD). In the course of the same year, suspicion was raised about the post-operative haemorrhage rate. It was thought that the increase in the haemorrhage rate was due to the poor quality of the single-use instruments and, in late 2001, the UK government recommended the reintroduction of reusable instruments. The need to consider alternative explanations arose later as more detailed analyses of hospital admission data revealed that there also had been a gradual increase in the post-tonsillectomy complication rate from 3.9% in 1995–96 to 7.3% in 2000–01.[24]

Analytical studies

An important distinction that is often made with respect to observational studies that are analytical is whether the determinants and outcomes relate to phenomena that occur at the same time. If so, it is called a cross-sectional study. If not, it is either a cohort study (looking forward in time from determinant to outcome) or a case-control study (looking backward from outcome to determinant).

CROSS-SECTIONAL STUDIES

The single most important characteristic of cross-sectional studies is that the determinant(s) as well as the outcome(s) measured occur at the same time, and that there is no follow-up period. Cross-sectional designs are very well suited to describe the prevalence of health and disease-related conditions and their distribution patterns. For example, a study was carried out in 864 school children in the UK to investigate the effect of parental smoking on middle ear disease.[25] Data on parental smoking were collected with a questionnaire and glue-ear was considered to be present in children with a flat tympanogram. The study identified 82 cases in total, 45 in the 407 households with at least one smoker and 37 in the 457 households with no smokers, and a risk ratio of 1.4 (=11.0%/8.1%, with a 95% confidence interval ranging from 0.9 to 2.1) could be calculated.

The major strength of cross-sectional studies is that they examine the presence or absence of an outcome and determinant at the same time. Cross-sectional studies are therefore fast, relatively cheap, and there is no 'loss to follow-up'. A major disadvantage of cross-sectional studies is that they provide only a snapshot of complicated temporal relationships between determinant and outcome. Parental smoking, for example, is likely to be persistent, but chronic middle ear infection in children is an intermittent disease. As a consequence, causal relationships are difficult to establish with cross-sectional studies. For the same reasons, they are not suitable for producing information on prognosis or the natural history of a condition.

Studies of the accuracy of diagnostic tests are a special case of cross-sectional studies. A key feature of such studies is that the diagnostic test results and 'gold standard information' or reference test results about the presence or absence of the conditions of interest are collected at the same time. The subjects should have both undergone the diagnostic test in question (for example, ultrasound-guided fine-needle aspiration to diagnose malignant disease in patients with nodular thyroid disease), as well as the reference test (histology after surgical resection). The results of one test should not be available to those who are carrying out the other. In terms of the example, the pathologist examining the surgical specimen should be 'blind' to the results of the fine needle aspiration. Another important criterion for a valid evaluation of the diagnostic accuracy is that the diagnostic test is evaluated in 'an appropriate spectrum of patients' (such as those in whom we would use it in practice).

The accuracy of a diagnostic test, a measure of how well the test results help to distinguish between individuals with and individuals without the disease or target disorder, is often expressed in terms of sensitivity and specificity. However, it is important to realize that this is, in most cases, a simplified representation of the diagnostic accuracy. Sensitivity and specificity can only be calculated for a test with dichotomous results, often called 'positive' if the result suggests that the disease is present and 'negative' if it suggests that disease is absent. The sensitivity is estimated as the proportion of individuals with the disease who have a positive test result. The specificity corresponds to the proportion of individuals without the disease who have a negative test result. The sensitivity and specificity of a 'perfect' test are 100%. The sum of the sensitivity and specificity is sometimes used as a single measure of the diagnostic accuracy. The sum of the sensitivity and specificity for a 'worthless' test, a test that would perform no better than tossing a coin, is expected to be 100% and for a perfect test 200%.

In many cases, however, relying on sensitivity and specificity as measures of diagnostic accuracy is too simplistic. For example, many tests, if not all, have more than two possible outcomes, and dichotomizing the results in a positive and a negative test result reduces the amount of diagnostic information that a test can provide. Furthermore, if one would like to dichotomize the test results, it is not immediately obvious what the cut-off value between positive and negative results should be. Lastly, the actual aim of performing a diagnostic test is

not to distinguish between individuals with and without the disease, but to identify those individuals for whom the expected benefit of treatment outweighs the expected harm. This indicates that the classic diagnostic 'stepping-stone approach', jumping from signs and symptoms to diagnosis and then from diagnosis to treatment, is rather artificial in many cases. This should be reflected in studies assessing diagnostic tests. They should focus on clinical effectiveness (effect on patient outcomes) rather than on diagnostic accuracy alone (for a comprehensive review of methods for the evaluation of diagnostic technologies, see Knottnerus).[26]

COHORT STUDIES

Cohort studies follow groups of individuals over time. The word 'cohort' originates from the Latin word for a group of 300 to 600 soldiers in a Roman legion. This is appropriate as the same rule applies for epidemiological cohorts as once for Roman cohorts: if a person joins a cohort, he will be a member of that cohort forever, which emphasizes the need for the completeness of follow-up. Most follow-up studies are analytical (comparing the occurrence of outcomes according to presence or absence of certain determinants), but they can be descriptive as well.

The design of many cohort studies is relatively straightforward. A group of people is assembled, none of whom have experienced the outcome of interest, but all of whom could experience it. On study entry, people may be classified according to the determinants of interest. These people are then observed over time to see in which of them the outcome of interest occurs. Despite this simple design, the terminology used to describe these studies can be confusing. For example, terms such as 'longitudinal study', 'prospective study' or 'incidence study' are often used interchangeably. The only real problematic issues in this respect is the use of the term 'prospective study', as cohort studies can consider data that are collected prospectively as well as retrospectively.

The terms 'retrospective' and 'prospective' refer to the way that the data have been collected rather than to the study design. The essential characteristic of prospective data collection is that data are being collected on determinants and outcomes that manifest themselves after the establishment of a study protocol. In all other situations, the data collection should be considered to be retrospective. Retrospective data collection can be based on data recorded in the past for other purposes or on the memory of the study subjects, investigators or other parties. It is obvious that the precision and accuracy of prospectively collected data can be expected to be better than retrospectively collected data. Cohort studies can be based entirely on retrospective data (using retrospective data on both the determinants and the outcome), based entirely on prospective data (using prospective data on both the determinants and the outcome), or based on a mix of retrospective data on determinants and prospective data on the outcome.

Cohort studies have many attractive features. They are the best way of ascertaining the incidence of a disease or health-related event or condition, as well as the natural history of a disorder. They also provide insight into the temporal order of determinants and outcome, which strengthens the inferences that can be made about whether an observed risk factor is a cause of the outcome. Furthermore, multiple outcomes can be considered, which is especially relevant if cohort studies are compared with case-control studies (see 'Case-control studies' below). However, the dangers of considering multiple outcomes are also obvious since testing many hypotheses may lead to misleading results. Lastly, prospective cohort studies are especially valuable for the study of fatal diseases, or more general studies of the occurrence of disease-related conditions with a short duration. When these kinds of conditions are studied retrospectively, the observed occurrences may be an under-representation of all occurrences.

The major drawback of cohort studies is that they are relatively expensive and therefore an inefficient way to study rare outcomes. Cohort studies become more efficient as the outcomes become more common. Another disadvantage for cohort studies that collect outcome prospectively is that the results may not be available for a long time. A prospective study of the effect of passive smoking on the head and neck cancer incidence may take more than 10 years to come up with relevant results.

However, not all prospective cohort studies need to take a very long time to complete. A cohort study could be used, for example, to study the risk factors for complications after tonsillectomy. Such a study could prospectively collect patient characteristics as well as data on surgical technique, instruments used and experience of the surgeons. Every patient could be followed up for a certain period, say one month, and the occurrence of complications could be registered. Such a study would provide insight into the incidence of complications – it might even distinguish between primary haemorrhage, secondary haemorrhage as well as infection, and also in the way this incidence depends on relevant risk factors.

CASE-CONTROL STUDIES

Case-control studies can be considered as 'research in reverse'.[16] Many epidemiologists consider them as one of the most important tools in their armamentarium. The design of case-control studies can be appreciated by again considering the example of the study on risk factors for complications after tonsillectomy. For this study, we could also use a case-control design. All the patients who experience a complication in the first month after surgery could be considered as 'cases', and patients without postoperative complications as 'controls'. The investigators then have to look back in time to find data on the patient's risk factors that were present at the time of surgery.

The essential feature of a case-control study is that not all controls need to be included but that a selection would suffice. Many case-control studies include only one control for each case, whereas others included more but hardly ever more than four or five. The reason that the number of included controls per case is seldom higher is that including more controls will have only a small effect on the power of the study and on the precision of

the estimates ('law of diminishing returns'). The fact that only information has to be collected for a selection of the controls makes that, in many circumstances, case-control studies are the most efficient design in terms of time, effort and therefore money. Hence, case-control studies are especially relevant if the occurrence of the outcome of interest is low. However, if the frequency of the determinant of interest is low, case-control studies might become inefficient. For example, if the frequency of a certain risk factor of post-tonsillectomy complications is low, investigators have to examine many cases and controls to find some who have been exposed. Some have advocated a 'rule of thumb' stating that cohorts are more efficient than case-control studies if the occurrence of the outcome is more frequent than that of the determinant and vice versa.

Unlike cohort studies, case-control studies cannot produce an estimate of the occurrence of the outcome of interest since we lack information about the denominator. A case-control study of post-tonsillectomy complications will neither provide information on how many patients underwent the operation nor on what their risk factors were. The relevant effect measure that a case-control study can provide is the odds ratio for a determinant, derived from the proportions in cases and in controls (more precisely, the odds) in whom the determinant is present. Earlier, we referred to this odds ratio as the 'determinant odds ratio'. This determinant odds ratio is equivalent to the 'outcome odds ratio' and the odds ratio obtained from a case-control study can therefore be used as a measure of relative risk.

The advantage of case-control studies (efficiency in time, effort and money) comes at a price, however, because two methodological issues may introduce major systematic errors: selecting the control group and obtaining information about the determinants. The selection of cases is relatively straightforward provided that the definition of the outcome being studied (the 'case definition') is clear. The selection of the control group is more problematic. Two criteria need to be met. First, controls should be representative of the population at risk of becoming cases. In other words, the controls should have been selected as cases had they developed the disease or outcome of interest themselves. Second, selection of the cases should be independent of the determinant(s) being investigated. Therefore, a case-control study of risk factors for post-tonsillectomy haemorrhage should include as controls only patients who underwent a tonsillectomy themselves. Furthermore, it seems inappropriate to select as controls all patients who underwent a tonsillectomy immediately after patients who developed complications. If that were the case, it would be very likely that the same surgeon using the same technique and the same type of instruments treated these patients. It is left as an exercise for the reader to decide what an appropriate strategy to select controls would be.

RANDOMIZED CONTROLLED TRIALS

Randomized controlled trials are cohort studies with prospective data collection. Their distinctive feature is that they use a random allocation scheme to assign the determinant. With randomization, you can expect that the prognostic characteristics of the randomized groups or 'arms' of the trial are similar except for differences due to chance variation. Randomization eliminates the influence of both known and unknown confounders that are present at the time of randomization. Without randomized treatment allocation, it cannot be excluded and is in practice very likely that imbalances in prognostic factors between the groups occur that are the result of selection bias – a type of bias often called 'confounding by clinical indication'.

The ethical argument in favour of a random process deciding what intervention patients receive is that there is equipoise, or a state of genuine uncertainty on the part of the clinical investigator regarding the comparative merits of each intervention. If there is genuine uncertainty about which treatment is best, it is not possible to recommend one over the other, which justifies that a random process decides. The problem, however, is that equipoise depends on subjective judgements and that therefore experts may disagree. Furthermore, preferences of patients or those who are candidates to receive the intervention have to be taken into account. The process of informed consent should address all these issues to ensure that patients can evaluate the potential risks and benefits of the study from their own perspective before they agree to participate.

It is important that the randomization process is 'concealed' from the investigators who include the participants into the trial. Proper allocation concealment requires that the investigators do not know the arm to which a participant will be allocated until the participant has definitively been recruited and included in the study. Concealment of the randomization is the only way to prevent the investigators influencing the balance of the prognostic characteristics between the groups that are being compared. For example, prior knowledge of the next allocation may allow investigators to exclude certain candidate participants from the trial because they are perceived to be allocated to an inappropriate group. More directly, the investigators may try to influence the order of inclusion. Concealment of treatment allocation is so important that with inadequate concealment a randomized controlled trial should be considered non-randomized. Empirical studies have shown that trials with inadequate concealment overestimate the treatment effect by as much as 40% on average.

Another important feature of many randomized controlled trials is the use of a form of blinding, which prevents the participants and the investigators who are in contact with the participants from being aware of which treatment has been offered. Blinding can help to prevent bias in a number of ways. First, if participants do not know what treatment they are receiving, it is less likely that their perceptions and expectations of the treatment that they receive can influence their compliance and the physical and psychological response to the intervention. For example, most patients expect that a new treatment is better than an existing one. Second, blinding investigators is important, as this would prevent them consciously or unconsciously managing the participants in

the trials differently. Also, their attitude towards the treatment can influence how patients respond to the treatment. Third, blinding participants and investigators will prevent outcomes from being assessed differently. The terms 'single-blind' and 'double-blind' are often used to indicate trials in which only the participants or both the participants and the investigators are blinded.

Double blinding is impossible in almost all surgical trials. To avoid biased management, the investigators should then try to standardize other potential treatments as much as possible. Approaches to minimize biased assessment of outcomes could include the use of a third party who is unaware of the treatment originally given. When blinded assessment is not possible, one should try as much as possible to use 'hard outcomes' (based on measurements resistant to bias). Another alternative includes the use of standardized outcome measurement scales that can be completed by the participant. This approach is likely to produce less biased outcomes than the judgement of an investigator.

Many people also consider the use of a placebo treatment as an essential feature of a randomized controlled trial. Placebo treatment is a form of treatment indistinguishable from the 'active treatment' under study, but it does not have a specific known mechanism to influence a patient's health. Blinding often requires the use of placebo treatment. Apart from that, the choice whether to use placebo treatment depends on the question that the trial tries to answer. First, if the question is whether intervention A is better than intervention B, then it is obvious that one should compare the effects of A and B with each other and not against placebo treatment. Second, if the question is whether intervention A is better than no treatment at all, the answers may be different for researchers and clinicians. Researchers are likely to be more interested in the specific effects – effects that can be attributed to the 'active component' of an intervention. Clinicians are likely to be more interested in the combined effects of the active and placebo components. On the other hand, it is always useful to know what part of the total effect is due to the active component and what part to the placebo when balancing the potential benefits against potential harms and costs, which are likely to differ between the active and placebo components. It is obvious that placebo treatment is rarely an option for randomized controlled trials in surgery. For example, in a trial comparing tonsillectomy with non-surgical management, it would require a form of 'sham surgery' to provide a placebo treatment. It is left to the reader to decide what the advantages and disadvantages of using such a form of placebo treatment in this context would be.

If a substantial number of participants do not receive the study interventions, do not comply with the study protocol or are lost to follow-up, the trial is likely to be underpowered and its results biased. Strategies to maximize compliance and follow-up should therefore be an integral part of every trial protocol. An obvious strategy is to make participation in a trial as convenient, painless and enjoyable as possible. Some trials have a 'run-in period' that can be used to 'screen out' patients who may not adhere to the study protocol and the follow-up procedures. It is essential to ascertain that compliance and completeness of follow-up do not differ between the trial arms as this could lead to biased estimates of the effects of the interventions.

The results of trials can be analyzed in two ways. First, the comparison of the intervention can be carried out according to the intervention to which the patients were randomized ('intention-to-treat' analysis) or according to the treatment they actually received ('per protocol' analysis). The advantage of an intention-to-treat analysis is that the question that is being addressed corresponds exactly with the one clinicians and patients try to answer in clinical practice. The disadvantage is that if many patients do not receive the treatment they were randomized to, this would obscure the difference between the trial arms. Per protocol analysis, on the other hand, addresses which intervention is better more directly. With this form of analysis, the treatments are being compared according to the treatments that the patients actually received. The problem with this approach is that if many patients do not receive the treatment to which they were randomized, the study no longer represents an experimental study.

The analysis should focus on a single outcome – often referred to as the 'primary endpoint' – to avoid the problems of interpreting the outcome of multiple hypothesis tests. This primary endpoint should also be used for the power calculation in the design phase of the trial. It is often desirable to consider a number of secondary endpoints – outcomes that represent different aspects of the outcome of interest – to provide a more detailed picture of the effects of the interventions under study. For example, a randomized controlled trial of tonsillectomy and non-surgical management could consider the reduction in the number of episodes of tonsillitis or sore throat as primary endpoint, but could also collect information on post-operative complications, reduction in time off work and reduction in the use of certain drugs, such as analgesics and antibiotics.

Subgroup analyses are comparisons between randomized groups in a subset of the patients with specific characteristics. The most important question that subgroup analyses try to answer is whether the effect measure is different in different subgroups by carrying out a statistical test for interaction (or 'effect modification'). For example, one could investigate – when analyzing the results of the trial on tonsillectomy – whether the effects of tonsillectomy on recurrence of tonsillitis are different in children younger than 5 years compared to children of 5 years and older.

Subgroup analyses can be dangerous and misleading, but they can also provide an important extra insight into the generalizability of the results. One danger arises from the fact that multiple comparisons are carried out, which increases the risk of producing false-positive results. To avoid this risk, only a limited number of subgroup analyses should be carried out and they should be specified in the study protocol, in other words, before the results of the trial are known and on the basis of patients characteristics that are measured before randomization.

Furthermore, the actual number of subgroup analyses carried out should be reported. Another approach to minimize the risk of false-positive results is to reduce the significance level of the statistical tests for interaction (for example, from the conventional 0.05 to 0.05 divided by the number of tests carried out as specified by the Bonferroni method). A further danger is the limited power of the subgroup analyses, because the group size is, by definition, smaller than that of the original trial population.

An important problem of randomized controlled trials is that of generalizability. Most trials are carried out in highly controlled conditions in a selected group of patients. Their results therefore provide evidence about the efficacy of an intervention (does the treatment work under ideal circumstances?) and not about the effectiveness (does the treatment work in actual practice?). It depends on the question that needs to be answered as to what extent the design of a trial should focus on efficacy or on effectiveness. An explanatory trial (addressing the efficacy question) is needed in the early stage of a new intervention. However, a pragmatic trial (addressing the effectiveness question that aims to create study conditions that reflect as much as possible actual practice when effectiveness is more important) is more appropriate to answer whether an intervention should be included in the 'repertoire' of available services.

The Consolidated Standards of Reporting Trials (CONSORT) statement has been developed to alleviate the problems arising from inadequate reporting of randomized controlled trials.[27] The CONSORT statement is an evidence-based, minimum set of recommendations for reporting randomized trials and offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation.

It is obvious that not all questions about the effectiveness of surgical procedures can be addressed with a randomized controlled trial.[28] A number of obstacles have been identified that make randomized controlled trials inappropriate (outcome of interest relatively rare, relevant outcomes far in the future, or randomization affecting the effectiveness of a procedure), impossible (refusal of clinicians or patients to participate, ethical obstacles) or inadequate (low generalizability of experimental studies).[29] As an example, the EaStER trial (Early Stage glottic cancer: Endoscopic excision or Radiotherapy) was closed early with recruitment of only 17 patients. Four principle reasons were found to contribute to poor recruitment into the trial: (i) surgeons and nurses involved in the trial were not in equipoise between the two trial arms and did not fully agree with the trial protocol; (ii) surgeons differed about primary outcome measures; (iii) recruiters focused on the treatment process rather than treatment per se; (iv) logistical issues in some centres made trial participation difficult.[30] If the obstacles are insurmountable, carefully designed observational studies should be considered.

Studying surgical innovation

Innovations are essential to the advancement of otolaryngology. However, the overall number of RCTs in surgical innovation remains small compared with the number of RCTs evaluating medical interventions. On this backdrop, The IDEAL Collaboration was set up in Oxford, UK. They concluded that innovation in surgery follows a different pathway to that of pharmacological developments and that a different approach was needed. The collaboration proposed a framework for the stages in surgical innovation (idea, development, exploration, assessment, and long-term study) and developed a set of recommendations on how evaluation should be conducted at each stage.[31]

Schwartz described three categories of surgical innovation: practice variation (minor changes to routine surgical practice); experimental research (formal trials); and a 'transition zone' between the two.[32] She outlined the ETHICAL model for studies in this 'transition zone' (expertise, technical skill, hazard awareness, informed consent, conflict of interest avoidance, analysis of results, and literature publication). This seeks to protect patients and surgeons, guides decision-making and assists in the generation of scientific hypotheses, without unduly hampering surgical progress.

CONCLUDING REMARKS

This chapter introduces the 'determinant-occurrence relationship' as a key concept for medical research, and epidemiology as a methodological discipline with immediate relevance for otolaryngological research. A basic understanding of epidemiological principles is therefore essential for all people who are involved in clinical research and desirable for all clinicians who want to read the medical literature critically.

We have only presented a broad picture of epidemiological concepts and principles, but it will be clear to the reader that studies vary according to the likelihood that their results are accurate (free of systematic error) and precise (random error). For this reason, a 'hierarchy of evidence' has been suggested.[11] For therapeutic issues, this hierarchy ranges from well-conducted randomized controlled trials at the top – preferably summarized in a systematic review and meta-analysis – to case-reports and expert opinion at the bottom (used throughout this book). For diagnostic and prognostic issues, very different hierarchies are necessary. These hierarchies of evidence are not absolute. If the therapeutic effects are very large in comparison to the potential effects of bias – for example, effects of insulin in ketoacidosis – a description of a series of cases may already provide compelling evidence. Nevertheless, it should be a leading principle that users of research try to look for the best available evidence from this hierarchy.

KEY POINTS

- Epidemiology is a methodological discipline. Epidemiological concepts and principles will help to design empirical studies that are relatively precise (free of random error), accurate (free of systematic error or bias) and efficient (affordable in terms of time and money).
- The 'determinant-occurrence relationship' is a key epidemiological concept, and many clinical research questions can be 'framed' as determinant-occurrence relationships.
- Epidemiological studies can be distinguished into experimental studies (investigators assign the determinants themselves, e.g. randomized controlled trial) and observational studies (investigators examine events as nature takes its course). Observational studies without a comparison or control group are called descriptive studies.
- A research protocol is a document that provides all essential details of a study. It should contain information on:
  - research question
  - study design
  - selection and recruitment of the subjects
  - measurements
  - statistical analysis
  - sample size calculation.
- A 'hierarchy of evidence' has been suggested on the basis of the likelihood that results are accurate and precise. For therapeutic issues, this hierarchy ranges from well-conducted randomized controlled trials at the top – preferably summarized in a systematic review and meta-analysis – to case-reports at the bottom.

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CHAPTER 42

OUTCOMES RESEARCH

Iain R.C. Swan and William Whitmer

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SEARCH STRATEGY

There is a vast literature on this subject, so there was no formal literature search.

AIM OF CHAPTER

The aim of this chapter is to explain the background to patient-based outcomes research. The emphasis is on instruments relevant to otolaryngology. The instruments described are simply examples for the reader. The authors do not suggest that these are the best instruments in their subject area. A list of recommended reading is included for readers who wish further information.

INTRODUCTION

Clinical outcomes research examines the outcomes of treatment or of disease. Traditionally outcomes of medical care are based on clinical observations or laboratory measurements. While these measures provide useful information for the clinician, they are often of limited interest to patients. There is often poor correlation between clinical outcomes and functional capacity and well-being, which are the areas of most interest to the patient. There has been increasing recognition that traditional measures need to be complemented by some measure reflecting the impact of the intervention on the patient in terms of health status and health-related quality of life. These terms refer to experiences of illness such as pain, fatigue, disability and broader aspects of the individual's physical, emotional and social well-being. Medicine, in particular surgery, formerly had the principal objective of reducing mortality and morbidity. These objectives are usually straightforward to assess. Nowadays, a large proportion of clinical practice is either cancer or chronic disease. There has been little improvement for some time in survival in cancer while treatments often have associated side effects and functional impairment that significantly affect the patient's quality of life. There is an increasing prevalence of chronic diseases with an ageing society and here the aims of treatment are to arrest or reverse decline in function.[1] These factors have led to an increased interest in patient-based outcome measures.

At the same time, increased attention is being given to patients' opinions and wishes in relation to their health. Patients should be involved in decisions about their treatment. To contribute usefully, they need information about the outcomes of treatment, not just in terms of surgical results but in terms of the possible effects on their quality of life. Financial resources limit healthcare around the world, and increasingly the distribution of these resources is influenced by the benefits perceived by patients, their carers and society as a whole.

WHAT ARE PATIENT-BASED OUTCOME MEASURES?

Patient-based outcome measures are, in general, questionnaires that ask patients about their perception of their health. Usually these instruments are made up of

a number of items or questions. These items are linked in a number of domains or dimensions. A domain refers to an area of behaviour or experience, such as mobility, self-care, depression, pain, social functioning and general well-being. Many questionnaires focus on physical function, such as the patient's ability to walk, climb stairs, wash and dress themselves. Others ask about the impact of health on various areas of an individual's life, such as ability to socialize with members of their family and friends. These are aspects of health-related quality of life (HRQoL). Overall quality of life is influenced by many factors other than health, such as social, financial and physical factors. Patient-based outcome measures assess only one aspect of quality of life and are not measures of overall quality of life.

Patient-based outcome measures assess some aspect of the patient's subjective experience of health and the consequences of illness – and of treatment. As these experiences are those of an individual patient with an individual personality and lifestyle, they cannot be objectively verified. This point is sometimes raised as a criticism of patient-based outcome measures, but it should be borne in mind that many clinician-based outcomes are the subjective opinion of the clinician.

WHY USE PATIENT-BASED OUTCOME MEASURES IN RESEARCH?

In the early days of research, few if any studies included assessment of health-related quality of life. It is increasingly argued now that clinical trials should include patient-based outcome measures except where it is clear that these are not relevant outcomes. The UK Medical Research Council (MRC), the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) all have policies stating that the likely impact on quality of life should be assessed, or justification provided for not doing so.[2] Patient-based outcome measures have been used as the primary outcome measure in randomized controlled trials in many areas including cancer and heart disease. They are also useful in providing evidence of the overall value of a treatment in a way that allows comparison with other treatments in the same area or in other areas.

Patient-based outcome measures are particularly relevant in otolaryngology. Head and neck cancer forms a small proportion of our patients, though a much larger proportion of our clinical workload. The majority of our patients do not have a life-threatening condition and the morbidity is small. Most of our patients simply want us to make them feel better. In many cases we do not have reliable, objective clinical measures to assess the outcome of treatment. To justify our treatment we need patient-based outcome measures to demonstrate the efficacy of treatment – improvement in HRQoL. We also need patient-based outcome measures to demonstrate the effects of these non-life-threatening conditions on HRQoL.

Even when we have objective measures (e.g. closure of a tympanic membrane in myringoplasty), we often know little about the effects on HRQoL. There are also occasions where there is disagreement between clinical measures of success and HRQoL outcomes (e.g. septal surgery for deviated nasal septums). It is likely that the results from one of the measures are unreliable or that they are measuring different things – the validity of both measures should be questioned.

ASSESSMENT OF PATIENT-BASED OUTCOME MEASURES

There are eight criteria that should be applied to patient-based outcome measures: appropriateness, validity, reliability, responsiveness, precision, interpretability, acceptability and feasibility (Table 42.1).[3] There are few patient-based outcome measures for which there is sufficient evidence to allow judgement on all of these criteria.

Appropriateness

The first and most fundamental question when selecting a patient-based outcome measure is how to identify one that is appropriate to the aims of the particular trial. The aims of the trial, the patient group being studied, the type of treatment and the relevant quality of life questions should be carefully considered. The instrument should measure aspects of patients' lives that patients consider important, and should not omit aspects of HRQoL that are important to the patients in the trial.[4] Clinicians often think that they know what aspects of HRQoL are important to patients. Many studies have demonstrated, however, that patients' views often differ from those of clinicians. The most effective way of establishing the importance to patients is asking patients their views. A list of aspects of HRQoL can be drawn up by clinicians and patients. A group of

TABLE 42.1 Assessment of patient-based outcome measures

Criterion	Meaning
Appropriateness	Does the content of the instrument match the intended purpose of the trial?
Validity	Does the instrument measure what it claims to measure?
Reliability	Does the instrument produce the same results when repeated in the same population?
Responsiveness	Does the measure detect clinically meaningful changes in the patient condition?
Precision	Can the instrument detect small differences between patient groups?
Interpretability	Can results from the measure be interpreted clinically and are they relevant?
Acceptability	Are the format of the instrument and the questions acceptable to the planned subjects?
Feasibility	Is it feasible to use this instrument in this setting with these subjects?

patients can then be asked which of these items are problems for them and how important these items are. This is the method commonly used in creating the patient-based outcome measures that are widely used, such as the SF-36 (see 'Generic instruments' below).

The purpose of the trial must be specified precisely in order to select an instrument that fits that purpose. In many studies, the rationale for selection of outcome measures is not clear. Careful consideration of content and relevance of a questionnaire to the purpose of the trial should be given. The instrument selected must be as relevant to the health problem and the proposed intervention as possible.

It is often recommended that one generic and one disease-specific instrument be used in a trial to increase the likelihood of appropriate assessment of outcomes.

Validity

The validity of a measure is an assessment of the extent to which it measures what it claims to measure. Validity is not a fixed property of a measure but is assessed in relation to a specific purpose and setting.[5] It is, therefore, meaningless to refer to a validated outcome measure, as many reports do. Evidence of validity of an outcome measure in one situation does not mean that there will be adequate validity in another research setting.

This apparently simple property depends on a range of different types of evidence including how the content was chosen and its relationship to other variables. There are several different ways of assessing validity of a patient-based outcome measure. No single set of observations is likely to determine validity, so assessment of validity in relation to a specific trial is not straightforward.

CRITERION VALIDITY

Criterion validity is the correlation of a measure with an objective or 'gold standard' measure. As gold-standard measures rarely exist in assessment of quality of life, criterion validity is rarely relevant in patient-based outcome measures, and validity is judged by more indirect assessment of content and construct validity. It can be assessed when a shorter version of an instrument is used to predict the results of a full-length version.

FACE AND CONTENT VALIDITY

Face and content validity are among the most relevant issues for the use of patient-based outcome measures in clinical trials. They address whether items clearly address the intended subject matter and whether the range of aspects is adequately covered. They are explained by Guyatt et al.:[6] 'Face validity examines whether an instrument appears to be measuring what it is intended to measure, and content validity examines the extent to which the domain of interest is comprehensively sampled by the items or questions in the instrument.' In other words, does the questionnaire look right and does it cover the right things? Face and content validity are mainly based on careful examination of the content of the instrument and qualitative judgement rather than statistical criteria. Evidence of how the questionnaire was initially developed is useful. Questionnaires with good validity are constructed in phases with involvement of patients with experience of the particular health problem. The content of poor-validity questionnaires is chosen without consultation.

CONSTRUCT VALIDITY

Construct validity is also very relevant but is a quantitative assessment of the relationship of a construct to other variables. A construct is a theoretical idea about the domain to be measured. For example, patients with hearing disability should have poorer audiometric thresholds. Many patient-based outcome measures are multidimensional: they assess, for example, physical, psychological and social aspects of an illness. Those questions related to psychological aspects should correlate with each other much more than with questions assessing physical function. The internal structure of such instruments is established by construct validation, most commonly factor analysis. For a detailed discussion of assessment of construct validity, the reader is referred to Fitzpatrick et al.[3]

Reliability

Reliability is the reproducibility and internal consistency of an instrument. It assesses the extent to which the instrument is free from random error. It is essential to establish that any changes observed in a trial are due to the treatment and not to problems in the measuring instrument. As the random error increases, the size of the sample required to produce an accurate result increases.

REPRODUCIBILITY

Reproducibility is the degree to which an instrument gives the same results on repeated applications with the same subjects, and is also known as the test-retest reliability. An instrument should produce the same or very similar results on two or more administrations. This should be relatively straightforward to assess but care must be taken with the time interval between tests. Repeat measurements should be far enough apart in time for the subject to forget their earlier answers but not so far apart that their health status might have changed. This is commonly reported as a correlation coefficient. However, a correlation coefficient measures the strength of association between two measures and not the extent of agreement. Bland and Altman recommend plotting the scores from the two tests graphically, which is certainly a simpler method than a statistical comparison of repeated scores.[7]

INTERNAL CONSISTENCY

More than one question is usually used to measure one domain in a questionnaire because several related observations will produce a more reliable estimate than one. Individual questions in a domain should correlate highly

with each other and with the total score for questions in that domain. This is the internal consistency of a patient-based outcome measure. The correlation is often measured using Cronbach's alpha.[8, 9] If all the questions in a domain are the same, Cronbach's alpha will be 1, while if there is no relationship Cronbach's alpha will be 0. If the correlation is too high, it is likely that the questions are addressing a very narrow aspect of an attribute and some items may be redundant, which then reduces the content validity. It is therefore suggested that Cronbach's alpha should be between 0.7 and 0.9.[10]

Responsiveness to change

Responsiveness is the ability of an instrument to detect clinically important change, even if that change is small.[11] This is sometimes called sensitivity to change but the term sensitivity has other, more general uses. It is particularly important in clinical trials when changes might correspond to therapeutic effects of treatment. An instrument can be both reliable and valid but not responsive to change.

There are several statistical methods of assessing responsiveness. The simplest method is to compare change scores for an instrument over time with changes in another variable or variables. The other variable preferably should be an objective indicator, such as a physiological measurement, or a clinician-based outcome measure.

An alternative method of assessing responsiveness is calculation of the effect size in a given clinical situation. This is the size of change in a measure between assessments, for example before and after treatment, compared with the variability of scores for that measure on one assessment. The effect size is defined as the mean change in a variable divided by the standard deviation of that variable.[12] The effect size can then be expressed in standardized units that allow comparisons with other outcome measures. It has been suggested that effect sizes can be used to assess the size of change in a study arm: an effect size of 0.2 is small, 0.5 is medium and 0.8 or greater is a large change.[12]

Other more complex statistical measures of responsiveness are described by Fitzpatrick et al.[3]

One of the main limitations on the responsiveness of an instrument is when the wording of questions does not allow reporting of very good or very poor health states: ceiling and floor effects. Subjects with initial high scores may not show any improvement following effective treatment and those with initial poor scores may not show any deterioration when their clinical situation deteriorates.

As with validity, evidence of responsiveness in one situation does not mean that there will be adequate responsiveness in another research setting.

Precision or sensitivity

The preferred term is precision as sensitivity has a number of other uses in research. Precision is the ability of the instrument to reflect true differences in health states. As clinical trials often aim to detect small differences between patient groups, precision is a desirable capability.

One of the main influences on the precision of an instrument is the format of the answers. The simplest answers are 'yes' or 'no' but they do not allow any assessment of difficulty or severity. The most commonly used graded response is a Likert scale, such as:

- very satisfied
- satisfied
- neither satisfied or dissatisfied
- dissatisfied
- very dissatisfied.

There is some evidence that using seven response categories rather than five increases precision, though this is rarely used.

The main alternative to a Likert scale is a visual analogue scale, where patients can mark any point on a line to represent their answer. Though this would appear to offer more precision, comparison studies of Likert scales and visual analogue scales have found no advantage of visual analogue scales. In addition, it appears that visual analogue scales are less acceptable to many patients, who find it difficult to translate their feelings into numbers. It is important to note that the questions should be worded as to potentially elicit all points along whichever scale is used (i.e. avoid wording that elicits only yes or no responses).

Patients' responses in patient-based outcome measures are generally converted into numerical values for statistical analysis. Most instruments use simple ordinal values, for example 1 to 5 (or 7) for a Likert scale, which are capable of less precision. However, the majority of published reports of health status measures use parametric statistical analysis that is appropriate for interval scales,[13] though the interval between 1 and 2 (very satisfied and satisfied) may not be the same as between 4 and 5 (dissatisfied and very dissatisfied).

Some patient-based outcome measures use an explicitly derived weighting system for responses. The weights can be assigned by a panel of patients and health professionals, for example the Nottingham Health Profile,[14] or be based on preference measurements obtained from a random sample of the general population, such as the Health Utilities Index.[15, 16] The fact that weighted scoring systems appear to be much more exact with their scoring suggests that they might be more precise but this may well be deceptive. Several studies have compared weighted and ordinal scoring systems and have not shown any significant difference in precision between these two methods of scoring.

Ceiling and floor effects may influence scores of instruments. Some patient-based outcome measures do not include questions that would identify very poor levels of health, so all patients with poor health have similar scores and further deterioration will not be identified. Sometimes patients with minor health problems will be scored as having excellent health so treatment of their problem will not result in any improvement in score.

One other important factor in precision is bias. This can be reduced by general aspects of study design, such as making assessments blind to intervention. In many cases it is not possible to keep the patient blind to which treatment

arm of a trial he is in, so his judgement of outcomes may be influenced.

Patient-based outcome measures may therefore vary in how precisely their scores relate to underlying distributions of patients' health status. Researchers need to carefully consider factors that might influence precision. The degree of precision required of a patient-based outcome measure will depend on other aspects of trial design such as sample size and the expected differences between arms of the trial.

Interpretability

Can results from the measure be interpreted clinically and are they relevant? The interpretability of an instrument is concerned with how meaningful are the baseline scores or a change in scores. Clinically important changes in scores can be estimated by comparison with clinical or laboratory tests in the same patient group. Representative data are available from the general population for some widely used instruments such as the Health Utilities Index (see 'Utility measures' below) and the SF-36. The scores from the trial patients can be compared with the means and standard deviations for the general population. A significant change in the score in the trial could be set at one-and-a-half standard deviations from the population mean.[10] Normative data can be key to interpreting both state and change questionnaires, as assumptions of no treatment resulting in no change in outcome can be erroneous. For example, in a study of hearing-aid interventions, those who were not given hearing aids exhibited participant acquiescence: a statistically significant increase in benefit without intervention.[17]

Acceptability

Clearly it is essential that the format of the instrument and the questions are acceptable to patients. An instrument should not cause distress to patients or be difficult to understand. In general, shorter instruments are more acceptable to patients. The instructions to patients should make it very clear that their answers will not influence their treatment. Acceptability is also important in order to obtain high response rates to questionnaires to make results of trials easier to interpret, more generalizable and less prone to bias due to non-response. When choosing an instrument, it is useful to know if the instrument has been used in similar settings before.

Ideally acceptability of an instrument should be directly tested at the design stage by seeking the views of patients. Subsequently, evidence of acceptability can be found in patient response rates.

Feasibility

The feasibility of an instrument is dependent on the time available for its completion and the staff available to help with its completion, either by interviewing patients or explaining the instrument to patients. The data collected have to be entered onto a computer and the time required and ease of entering has to be considered. The measure must be short enough to be completed or administered in the intended setting and with the types of patients and families involved in the trial. This is one of the criteria of patient-based outcome measures that can usually be easily judged by investigators in the research setting. If in doubt, feasibility can be assessed by piloting the study methods.

TYPES OF PATIENT-BASED OUTCOME MEASURE

There are two basic types of patient-based outcome measure: generic and specific. Generic instruments access multidimensional health profiles, overall medical condition and personal function. Specific instruments focus on the problems found in individual diseases, disabilities and patient groups.[11] Within each of these categories there are different types of instruments (Table 42.2).

TABLE 42.2 Types of patient-based outcome measure

Category	Type	Example
Generic	Health profile	SF-36, Sickness Impact Profile, Nottingham Health Profile, Glasgow Benefit Inventory.
	Utility	Health Utilities Index (HUI), EQ-5D
Specific	Disease-specific	Dizziness Handicap Inventory (DHI)
	Site-specific	Sino-Nasal Outcome Test (SNOT-20)
	Dimension-specific	McGill Pain Questionnaire

GENERIC INSTRUMENTS

Generic instruments are designed to access a broad range of aspects of health status and the consequences of illness and therefore to be relevant to a wide range of patient groups and conditions. The advantage of generic instruments is that they can be used for a broad range of health problems and this enables comparisons across different groups of patients with diverse conditions. Because of their broad range of content and general applicability, such instruments have been used to assess the health of samples from the general population. Such data have been used to generate normative values across populations with which other groups of patients with specific health problems can be compared. Since generic instruments are used more often than specific instruments, there are usually more data available about their reliability and validity.

As generic questionnaires cover a broad range of aspects of health status, many items may be irrelevant to a particular condition. These items result in a wide range of scores that are not relevant to the condition being studied. As there are few questions relevant to a specific condition, the instrument may be insensitive to changes that might occur as a result of treatment for that condition.

Health profile

SF-36

The most commonly used health profile instrument is the Medical Outcome Study Short-Form 36-Item Health Survey (SF-36).[18, 19] The SF-36 is a 36 item, self-completed questionnaire that measures health status in eight dimensions: physical functioning; role limitations due to physical problems; role limitations due to emotional problems; social functioning; mental health; energy and vitality; pain; and general perceptions of health. It can be completed by the patient in less than 10 minutes. Responses are summed to give a score for each dimension: physical component summary (PCS) and mental component summary (MCS).[20] It has been used in a wide variety of patient groups and conditions, including many otorhinolaryngological conditions (**Table 42.3**). Data from trial subjects can be compared with normative data for the population.[21] Garratt et al.[22] identified 408 papers that included aspects of development and evaluation of the SF-36 over a 10-year period (1990–99). It can also be used in a reduced 12-item version that is a subset of the original SF-36.[23] However, the larger instrument gives more reliable estimates of individual levels of health and is therefore the better choice of instrument in small studies.

Recently, Brazier et al.[24] derived from the SF-36 a preference-based single index measure, the SF-6D, to make the instrument more useful in evaluations of cost-effectiveness (see 'Utility measures' below). This weighted scoring model could potentially be applied to any SF-36 data set. However, initial validation studies demonstrated some inconsistencies and further assessment of the scoring model is required.[25]

WORLD HEALTH ORGANIZATION DISABILITY ASSESSMENT SCHEDULE 2.0

The World Health Organization's Disability Assessment Schedule 2.0 (WHO-DAS 2) was designed to measure domains coincident with the definitions of the WHO's International Classification of Functioning (ICF), a replacement for the stigmatized labels of impairment, disability and handicap. It is very similar to the SF-36 except that its six domains – cognition, mobility, self-care, interaction, life activities (e.g. leisure and work limitations) and 'social participation' (e.g. emotional and social burden) – fit the ICF framework. To date, it has only been applied in otorhinolaryngology with regard to hearing aids, where it was found to be sensitive to intervention, but the effect size was modest compared to hearing-specific questionnaires.[17]

TABLE 42.3 Examples of the use of the SF-36 in otolaryngology

ORL condition	Reference
Chronic rhinosinusitis	van Agthoven et al.,[26] Gliklich and Metson,[27] Piccirillo et al.[28]
Chronic otitis media	Nadol et al.[29]
Dysphonia	MacKenzie et al.[30]
Laryngeal cancer	Stewart et al.[31]
Meniere's disease	Lopez-Escamez et al.[32]
Rhinoplasty and otoplasty	Klassen et al.[33]

SICKNESS IMPACT PROFILE

The Sickness Impact Profile (SIP) is a general health-status questionnaire comprising 136 questions answered as either 'yes' or 'no'.[34] They are grouped into 12 categories: walking; body care and movement; mobility; social interaction; alertness behaviour; emotional behaviour; communication; sleep and rest; eating; home management; recreational activities; and work. Each item is weighted, and the scores of all answered questions are combined. There are 12 category scores, 2 summary scores (physical and psychosocial) and a total score. The scores are standardized and range from 0 to 100 points, with 100 indicating the poorest function. The test-retest reliability and internal consistency are high and it has good content and construct validity.[34] It is, however, a long questionnaire and is usually administered by interview. Its acceptability and feasibility in a trial must be carefully considered.

NOTTINGHAM HEALTH PROFILE

The Nottingham Health Profile is a generic, self-administered questionnaire designed to measure perceived physical, social and emotional health problems.[14, 35] An initial pool of statements was collected from patients at interview, and from this pool 38 items were chosen relating to six dimensions: physical mobility, pain, social isolation, emotional reaction, energy and sleep. The scores can be compared with the average scores in a population matched for gender and age.

GLASGOW BENEFIT INVENTORY

As other generic instruments are often insensitive to the non-acute disorders generally seen in an ORL clinic, the Glasgow Benefit Inventory (GBI) was developed for use in patients with otolaryngological conditions.[36] The GBI is a post-intervention questionnaire that assesses the effects of interventions on the health status of patients, rather than the actual health status. The GBI has 18 items in three domains: psychological, social and physical well-being. Rather than attempt to assess the difference between before and after treatment measures, it asks directly about the change in health status resulting from treatment. It is likely, therefore, to be more sensitive to such change than two separate instruments before and after intervention. In addition, compliance will be significantly higher because patients are only required to complete one questionnaire. The response to each question is based on a five-point Likert scale, for example: 'Since your *operation/intervention*, have you found it easier or harder to deal with company?' The words in italics (*operation/intervention*) in each question are replaced by words appropriate to the intervention of interest. Responses are scored using

TABLE 42.4 Examples of the use of the GBI

ORL intervention	Reference
Bone-anchored hearing aids	Dutt et al.[38]
Hearing aids	Swan et al.[39]
Cochlear implants	UK Cochlear Implant Study Group[40]
Treatment of acoustic neuroma	Brooker et al.[41]
Speech therapy for dysphonia	Wilson et al.[42]
Rhinoplasty	McKiernan et al.[43]
Tonsillectomy	Bhattacharyya et al.[44]
Surgery for snoring	Uppal et al.[45]

a weighted scale from a population sample to give a score between –100 and +100.

The GBI has been used to assess the benefit experienced by patients following various treatments (Table 42.4). Details of the questionnaire and its use can be found at www.ihr.gla.ac.uk. Hendry et al.[37] wrote a comprehensive review of the use of the GBI.

Utility measures

Multi-attribute utility measures access a broad range of aspects of health status, like other generic instruments, but have a particular form of numerical weighting or valuation of health states. Utility measures have been developed from economics and decision theory in order to provide an estimate of individual patients' overall preferences for different health states. They are scored as a single number between 1 (full health) and 0 (death). The weighted scoring method is based on preference measurements obtained from samples of a general population. They are asked to value different aspects of health as defined by the instrument using one of a number of valuation techniques, most commonly standard gamble, time trade-off and visual analogue scales (see Brazier et al.[46] for explanation).

Utility scores reflect the health status and value of that health status to the patient. As utility measures are scored as a single value, they do not define individual dimensions of health that contribute to the individual's overall sense of well-being. They are relatively insensitive to small but relevant changes in health and are therefore more suited to studies of large populations.

There are several health utility measures that have been widely used. Brazier et al.[46] carried out an extensive review of these and recommended the Health Utilities Index (HUI) and the EuroQol (EQ-5D) as the instruments of choice.

HEALTH UTILITIES INDEX

The Health Utilities Index (HUI-I) evolved from studies in neonatal intensive care.[47] A second version (HUI-II) was developed to assess outcomes in long-term survivors of childhood cancer but is suitable for use in a wider range of children.[16] Though it is claimed to be a generic instrument, its content is explicitly aimed at children with questions specifically aimed at developmental age.

The HUI-II was revised to make it more relevant to an adult population. The HUI-III assesses eight aspects of health status: vision, hearing, speech, ambulation, dexterity, emotion, cognition, self-care and pain.[48] It has 15 questions with 4 to 6 available responses for each and is easy for patients to complete. The HUI-III has been used in a wide variety of clinical studies and has been shown to be reliable and responsive.[49] It is one of the few generic patient-based outcome measures that specifically assesses hearing and speech and is therefore potentially useful in many areas of otolaryngology. Normative data have been collected from large populations and from these data weighted scoring scales have been devised.[16] It has been used in a cost-utility study of cochlear implants[50] and in the UK cochlear implant study.[51]

EQ-5D

The EQ-5D is a self-completed questionnaire with five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[52] It is easy to complete and is very acceptable to patients. Responses can be scored using a weighted scale from a large general population sample.[53] It is very brief with only five questions and three levels of response for each.[54] It was compared with the Euroquol and the SF-36 in a survey of 1980 adults and the Euroquol was found to be less sensitive.[54] However, it was originally intended to complement other forms of health-related quality of life measures. It has been widely used and its test-retest reliability is good.[55]

SPECIFIC INSTRUMENTS

Disease- or condition-specific instruments

The aim of these instruments is to provide the patient's perception of the problems related to a specific disease or condition. It should be remembered that disease may have a broad impact on the patient's life. To make these instruments comprehensive, a detailed survey of patients suffering from the condition should be conducted when developing the instrument. They may also not detect problems associated with a disease and its treatment that have not been anticipated by the developers if patients have not been involved in the planning. As all of the questions are developed specifically to assess a particular health problem, the content should be very relevant for use in studies of that condition: high validity. They are more likely to detect changes that occur in that particular condition as there should be few if any irrelevant questions: high responsiveness. They are also more acceptable to patients as the relevance of the questions to their condition is obvious so completion rates should be high.

The major disadvantage of disease-specific instruments is that they do not allow comparison to be made with other patient groups with other diseases or conditions.

Such comparisons require generic instruments designed for use with any health problem, and for this reason it is often useful to combine a specific instrument with a generic one.

VERTIGO

The Dizziness Handicap Inventory (DHI) is a 25-item questionnaire designed to measure the self-perceived disability and handicap caused by dizziness or imbalance.[56] They reported good internal consistency and test-retest repeatability. The questions were grouped in three domains of functional, emotional and physical aspects of dizziness with three possible answers to each question: yes, sometimes and no. The questions were selected from an initial bank of 37 questions chosen from the case histories of patients. They take a clinical perspective of disability and handicap in daily activities and therefore content validity should be carefully inspected before choosing this instrument for use in a trial. It is preferable to have more input from patients in the selection of items to include in a questionnaire (see 'Face and content validity' above. This instrument has been widely used in studies of imbalance in general. It has been shown to have a moderate correlation with balance performance measures.[57]

The Vertigo Handicap Questionnaire (VHQ) was developed from patients' accounts of the problems that they experienced with vertigo.[58] It has 25 questions about restriction of physical and social activities and emotional distress, each scored on a 5-point Likert scale. It has good reliability and validity but has not been widely used.

HEARING

There are many instruments that have been developed for use in audiology. Assessing hearing disability has one major difference from assessing most other disabilities in otolaryngology – there is a gold standard, at least for audibility – pure-tone audiometry. One of the most widely used measures is the Hearing Handicap Inventory for the Elderly (HHIE).[59] This instrument has been shown to have good face and content validity.[60] Further, it has good sensitivity and specificity when used properly in tandem with an audioscope.[61] A more in-depth instrument is the Speech, Spatial and Qualities of Hearing questionnaire (SSQ),[62] which asks situation-specific questions on understanding speech, locating sound sources, and various qualities of sounds (e.g. detection, naturalness), resulting in an overall score and the three subscales of its title. It has shown good validity and reliability, and has been translated into many languages. Details of the SSQ and its use can be found at www.ihr.gla.ac.uk.

While there are reliable tools for measuring hearing, assessment of the efficacy of hearing aid provision and comparison of benefits from different prescription strategies are heavily reliant on patient-based outcome measures. The HHIE has been used for this purpose[63] but it has been shown to have poor precision when changes in the HHIE were compared with changes in the Speech Intelligibility Index when using a hearing aid.[64] This is probably because the HHIE assesses predominantly the emotional and psychological response to hearing impairment. There are many self-report hearing-aid tools available, to such an extent that a good guide for how to choose one already exists.[65] Two of the more popular hearing-aid questionnaires that deserve additional mention are the Glasgow Hearing Aid Benefit Profile (GHABP)[66] and the Client-Oriented Scale of Improvement (COSI).[67] The GHABP was developed as a measure of hearing disability and the benefit obtained from use of a hearing aid.[66] It assesses unaided disability, handicap, benefit from a hearing aid, residual disability and patient satisfaction in eight listening situations – four specified and up to four chosen by the patient. It has been used as one of the primary outcome measures in the NHS programme of modernizing hearing-aid services in England. Details of the questionnaire and its use can be found at www.ihr.gla.ac.uk. The COSI asks the patient to provide (up to) five specific situations that are important to them. Communication ease is then rated before and after fitting (or change in fitting) for those specific situations, and benefit derived from the pre/post-fitting difference in ease. The 'open-set' approach of the COSI is notable in avoiding the assumption of experience with the hypothetical situations proposed by many questionnaires.

OTITIS MEDIA

The Otitis Media-6 (OM6) was developed for use in children with recurrent acute otitis media and otitis media with effusion.[68] Six domains (physical suffering, hearing loss, speech impairment, emotional distress, activity limitation, caregiver concerns) are each addressed by a single question. Test-retest repeatability was high, and responsiveness was demonstrated by significant change in scores after surgery for ventilation tube insertion.[69] The criterion validity has been questioned, however, in that it does not correlate well with other markers of disease severity, such as audiometry and severity of symptoms of recurrent acute otitis media.[70] Kubba also suggested that the instrument lacks precision as it does not differentiate between children with otitis media and others with sore throats.[70]

CANCER

The European Organization for Research and Treatment of Cancer Quality of Life Study Group developed the EORTC QLQ-C30 as an instrument of 30 items for use in international trials in cancer.[71] Further modules have been developed which can be added to the core instrument to provide assessment of specific cancers, for example head and neck cancer.[72] This allows collection of data for comparison across cancer groups and additional data that are particularly relevant to specific cancers. The questionnaire has been translated into more than 60 languages and is widely used around Europe and the rest of the world.[73]

Site-specific instruments

These instruments contain items that are particularly relevant to patients having treatment for a specific region of the body and should be sensitive to changes experienced

by patients following treatment in that region. They are particularly useful in otolaryngology and have the advantage that patient groups are not limited to a specific disease classification. They thus allow comparison of patients with similar symptoms but different pathology. Because they have a narrow focus, they are unlikely to detect any change in broader aspects of health or quality of life following intervention.

SINONASAL DISEASE

Many patient-based outcome measures have been designed for use in sinonasal disease. The 20-item Sino-Nasal Outcome Test (SNOT-20)[74] is a modification of the previously used 31-item Rhinosinusitis Outcome Measure (RSOM-31).[28] The 20 questions refer to specific sinonasal symptoms and some general health questions. It has good internal consistency (Cronbach's alpha 0.9), and showed good responsiveness to change. Face and content validity seemed good and the construct validity was high when compared with clinical assessment of disease. Test-retest scores were highly correlated (r = 0.9) though this measures the association between tests rather than repeatability (see 'Reproducibility' above). Piccirillo et al.[74] report the SNOT-20 to be a valid outcome measure in their particular research setting. The questionnaire is easily completed by the patient and acceptability is high. It has since been modified with the addition of two further questions (the SNOT-22);[75] its validity and ease of use were confirmed in a study of more than 2000 patients.

VOICE

There is no generally accepted objective test to serve as a 'gold standard' for the assessment of voice disorders. Various questionnaires have been developed for evaluation of the consequences of dysphonia. The Voice Handicap Index (VHI) was designed to assess the self-perceived effect on quality of life of voice disorders.[76] It is a 30-item questionnaire divided into 3 subscales: functional handicap, emotional handicap and physical handicap. The questions use a 5-point Likert scale. It has been used to assess the impact of a number of voice disorders, including vocal cord polyps, cord palsy, spasmodic dysphonia and functional disorders. Its construct validity has been confirmed by comparing its subscales with appropriate subscales of the SF-36 in assessment of the health-related quality of life in patients after treatment for laryngeal cancer.[31] A shortened version, the Voice Handicap Index-10, has been proposed as an equally effective alternative.[77] Carding et al.[78] wrote a review of measures of voice outcomes.

Dimension-specific instruments

These instruments assess one specific aspect of health status. The most commonly assessed dimension is psychological well-being. Another common dimension, more relevant to otolaryngology, is pain. The McGill Pain Questionnaire is one of the most widely used measures of pain severity for both clinical and research purposes.[79] It comprises 20 subclasses of pain descriptors that provide pain severity scores across sensory–discriminative, motivational–affective and cognitive–evaluative dimensions. It has been found to have good short-term repeatability in chronic pain conditions, and it discriminates well between different types of pain syndromes. A short form of the McGill Pain Questionnaire has been developed.[80] It is highly correlated with the original longer version and has comparable sensitivity. It may be a useful instrument in situations in which the standard questionnaire takes too long to administer.

The advantage of dimension-specific instruments is that they provide a more detailed assessment in the area of concern than is possible in more general instruments. They are perhaps most useful in a study where they are used in combination with another instrument (e.g. van Agthoven).[26]

HOW TO CHOOSE A PATIENT-BASED OUTCOME MEASURE

The choice of patient-based outcome measure depends on the purpose of the study. To assess the effects on health-related quality of life of a disease or condition, a generic instrument is required. Specific instruments are of little value as they do not allow comparison with other conditions. A specific instrument may provide additional information by assessing the severity of the disease if no objective measure is available, for example in tinnitus. Comparison of the scores from the specific instrument with the generic instrument may be valuable.

If the aim of the study is to assess the efficacy of treatment, it is usually recommended that two instruments be combined, a generic and a specific instrument. The two different measures are likely to produce complementary evidence. A disease-specific measure will be more responsive to the main effects of intervention, and therefore produce the evidence most relevant to the clinician. A generic measure may allow comparisons across interventions and disease groups, but is likely to be relatively insensitive to the effects of the intervention. It is possible, however, that the additional burden on the patient may reduce overall compliance, especially if there is overlap between questions in the two instruments.

WHICH GENERIC INSTRUMENT?

Acceptability to the patient and feasibility of completing the questionnaires are obviously important. The time required to complete the commonly used instruments varies. The Health Utilities Index (HUI) Mark II takes 3 minutes, the SF-36 10 minutes and the Sickness Impact Profile 20 minutes.[81]

Appropriateness depends on the study. Utility measures are, in general, only appropriate for studies with large numbers of subjects. Small studies would probably be better to choose a generic health status questionnaire. Some generic instruments have been shown to be better than others in assessing patients with particular problems. Edelman et al.[81] reported that the HUI was better used for

evaluating relatively healthy populations because of some floor effects, while the SIP was better for more severely ill populations as their study patients were grouped at the healthy end of the scale. Other authors have similarly reported that the SIP has ceiling effects.[82–84]

A careful evaluation of reports of the use of these instruments in similar patient groups and study settings should be carried out before making a final choice. In the absence of this, the SF-36 appears to be the safest choice. The HUI Mark III is suitable for large studies and has the advantage for otolaryngology research of including items about hearing and speech.

THE FUTURE

Development of a valid and acceptable patient-based outcome measure takes a lot of time and effort. Large numbers of subjects are needed as development requires several stages. Patient involvement in the selection of items is essential. There have been many patient-based outcome measures that have been reported once and never used again. On the other hand, the currently available and widely used patient-based outcome measures are not ideal. We need better ones.

KEY POINTS

- Patient-reported outcome measures assess the patient's subjective experience of illness and of treatment.
- Generic instruments access a broad range of aspects of health status, enabling comparisons across different patient groups with diverse conditions, but may not be sensitive to particular illnesses or treatments.
- Specific instruments are more sensitive to the effects of specific diseases or conditions, but do not allow comparison to be made with other patient groups with other diseases or conditions.
- The best assessment is usually achieved by using both a generic and a specific outcome measure.

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FURTHER READING

Streiner DL, Norman GR. *Health Measurement Scales: a practical guide to their development and use*, 5th edn. Oxford: OUP, 1995.

An invaluable practical guide for those who wish to develop a new patient-based outcome measure. Very good and readable explanation of theory behind these instruments.

Fitzpatrick R, Davey C, Buxton MJ, Jones DR. Evaluating patient-based outcome measures for use in clinical trials. *HTA* 1998; **2**(14): i–iv, 1–74.

Extensive review of the literature to describe the range of patient-based outcome measures available and the criteria for selecting an instrument for use in a trial.

Fayers PM, Hopwood P, Harvey A, et al. Quality of life assessment in clinical trials – guidelines and a checklist for protocol writers: the UK Medical Research Council experience. *Euro J Cancer* 1997; **33**: 20–28.

Good advice from authors with experience of reviewing grant applications submitted to the MRC.

Coons SJ, Rao S, Keininger DL, Hays RD. A comparative review of generic quality-of-life instruments. *Pharmacoeconomics* 2000; **17**: 13–35.

De Korte J, Mombers FM, Sprangers MA, Bos JD. The suitability of quality-of-life questionnaires for psoriasis research: a systematic literature review. *Arch Dermatol* 2002; **138**: 1221–7.

These two papers provide good reviews of the three most widely used generic instruments: the SF-36, the Nottingham Health Profile and the Sickness Impact Profile.

Whitmer WM, Wright-Whyte KF, Holman JA, Akeroyd MA. Hearing Aid Validation. In: Popelka G., Moore B., Fay R., Popper A. (eds). *Hearing Aids*, 2016. Springer Handbook of Auditory Research, vol 56. New York: Springer.

Extensive look at hearing-aid specific outcome measures, including an examination of the repetition of domains, followed by a discussion of the different perspectives on the measuring of benefit.

CHAPTER 43

EVIDENCE-BASED MEDICINE IN MEDICAL EDUCATION AND CLINICAL PRACTICE

Phillip Evans

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: evidence-based medicine and EBM.

INTRODUCTION

Professor David Sackett's definition of evidence-based medical (EBM) practice still holds true: 'the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients'.[1] The principles are now considered to be 'core' in professional practice and praxis, across the four main phases of training, in the UK (Figure 43.1). Furthermore, endorsement by the World Federation of Medical Education and the World Health Organization secures it as an international characteristic of the medical profession, and therefore one that should be promoted globally.

EBM may be described as a patient-centred cycle with three linked phases: the clinical phase, the search phase and the evidence review phase (Figure 43.2). Taken together, this becomes a framework for teaching, learning and curriculum delivery in the continuum of professional training.

BEGIN WITH THE PATIENT

In addition to being at the heart of the ethos of care, the patient has a central role in medical education.

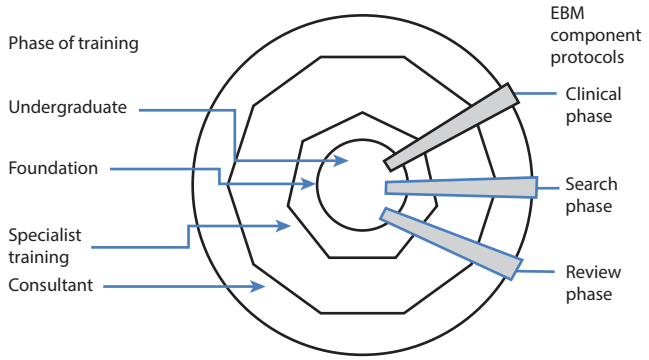


Figure 43.1 Evidence-based medicine is core to all four professional phases.

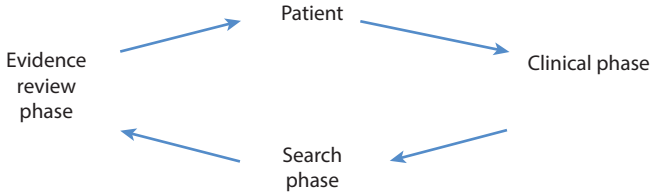


Figure 43.2 Patient-centred evidence-based cycle.

The patient may be actual, or described as a theoretical case, or the two may be used in combination. As actual cases for teaching and learning, real patients are frequently 'opportunistic', and therefore theoretical cases are normally constructed by clinicians as a vehicle for teaching and learning. The topics for the cases are chosen because they are common or frequent or, if rare, because they are important in understanding the fundamental principles or concepts of a particular condition. One such example is the autoimmune condition known as Wegener's disease. A portfolio of cases in otolaryngology will include examples from the following areas:

- plastic surgery
- oral and maxillofacial surgery
- general upper GI surgery
- neurosurgery
- paediatric surgery
- cardiothoracic surgery
- ophthalmology
- accident and emergency medicine.

Well-structured cases may be prepared using a systematic framework (Figure 43.3), which is intended to encourage students and trainees to explore the bio-medical spectrum of relevance to that particular condition.

The cases themselves normally relate to the learning outcomes that are relevant and appropriate to the particular professional stage (Table 43.1). In the UK, these may be sourced from Tomorrow's Doctors, The Foundation Programme,[3] and the college documentation.[4]

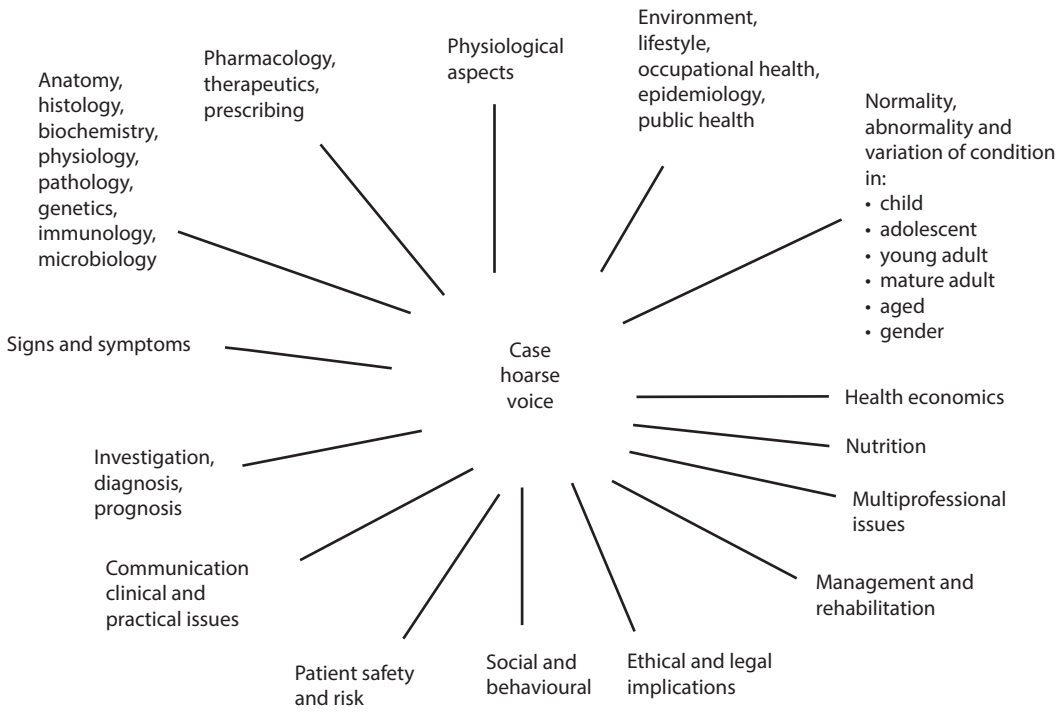


Figure 43.3 Factors to consider in writing and analyzing a case.

TABLE 43.1 A matrix for developing cases appropriate to the stage of expertise

	Outcomes relevant to the stage of the student		
Core case from	**Undergraduate**	**Foundation**	**Specialist training**
Plastic surgery			
Oral and maxillofacial surgery			
General upper GI surgery			
Neurosurgery			
Paediatric surgery			
Cardiothoracic surgery			
Ophthalmology			
Accident and emergency medicine			

Outcomes are entered by the teacher in the relevant column.

Whilst it is suggested that EBM is used routinely for keeping up to date, clinical supervisors and other teachers should offer their students or trainees selected cases as part of the training process. The supervisor should give one case at the beginning of the week, with the expectation of it being presented as the basis for discussion with the supervisor towards the end of the week, together with a report summarizing the key points and a reasoned evidence-based appraisal of the critical points of the case. This might be included in the student's reflective portfolio. There may be an advantage for the student or trainee to work with a partner (peer-assisted learning) or in a small group (case-based learning). The case itself is part of the normal spectrum of activities in the student's or trainee's normal experience of workplace learning and assessment, and may be linked to a DOPS, MiniCex or video-based discussion. The cases should be central to the curriculum, should form a structured framework for the student's or trainee's self-directed learning, and should be part of the normal provision of teaching and learning activities (blended learning). The case presentation at the end of the week confirms and tests the professional judgement of the student or trainee, and provides an opportunity for extending their understanding.

The student or trainee will undertake the following steps to prepare and present the case thoroughly:

1. Appraise the patient and the condition
2. Identify and ask the questions, in an appropriate way
3. Establish the evidence
4. Critique the evidence
5. Present the conclusions and discuss the case.

ASK THE RIGHT QUESTIONS

At all stages, the trainee should think ahead, and form a judgement as to how best to proceed, and this normally requires asking two categories of questions:

1. What do I need to know to understand the case?
2. What do I need to know to form a clinical judgement?

The nature and quality of the questions posed will vary according to the age and stage of the student or trainee. Clearly an undergraduate student will be expected to read more widely about the basic and clinical science related to the case. In addition, they will also require more guidance about appropriate communication skills, performing the clinical and practical skills, and interpretation of tests. Trainees with more experience will consolidate their knowledge and extend their understanding of diagnosis and management of the condition.

Questions related to the 'best' clinical judgement require greater thought and refinement, and a higher level of skill with respect to searching the literature and interpreting the available evidence. A suitable search strategy should take into consideration the following aspects:

- an overall structure for the search
- anticipation of the nature of papers found in the search
- forethought about conducting the search itself
- a strategy for reading the literature.

STRUCTURING THE SEARCH

PICO is the acronym commonly used as a strategy when searching the bibliographic databases:

P = **Patient/Population:** Who was the subject of the investigation?
I = **Intervention:** What was done?
C = **Comparison:** What are the alternatives and appropriate options?
O = **Outcome:** What are you trying to accomplish or achieve with this case?

The search structure should seek the best evidence for diagnosis, therapy, prognosis, and harm or aetiology, and at this stage it is also useful to anticipate the nature of the papers present in the literature. The most common categories are:

- **Cases.** Reports of individual patients, groups of patients or cohort studies, which may be retrospective or prospective, are highly valid and authentic, but have low reliability.
- **Randomized controlled clinical trial.** An RCT is a carefully structured prospective study, in which bias and influence have been carefully controlled. These are highly specific.
- **Systematic reviews and synopses.** The author has undertaken an extensive literature search and review of a particular clinical topic, and has prepared our systematic analysis of the quality of the evidence. Such papers are beneficial as they save the individual a great deal of time, but the assumption is that the review is up to date. Therefore it is wise to search for the most recent evidence.
- **Meta-analysis.** This combines the results of valid studies in that field, and uses statistical analysis to combine the results in a way that expresses the conclusions as if the collected reports were a single study.
- **Qualitative or humanistic enquiries.** These explore questions and issues related to psycho-social and attitudinal aspects that cannot be measured in a prospective randomized controlled trial.

CONDUCTING THE SEARCH

The search should be organized and planned[5] by focusing on the purpose of the search, and identifying the characteristics that are sought (Table 43.2).

TABLE 43.2 The purpose of the search

Focus	Outcomes sought
Goal	Establish the recommendations
Perspective	Establish the clinical evidence
Coverage	Selective and relevant
Organization	That the scientific style is robust
Audience	What type of clinician?

TABLE 43.3 Establishing alternative terms

Question component	Subject or MeSH term	Synonyms
Patient	Patient Inpatient Outpatient	Person Case
Cause		Reasons
Sudden hearing loss (SHL)	Hearing loss, sudden	Deafness

A search of the literature is essentially a text-matching exercise between the search question and the text in the databases. The first step is to clarify one key question,[6] for example, 'What is the cause of sudden hearing loss?'.

Due to the complexity and ambiguity of the English language, it is necessary to establish alternative words (refer to a thesaurus), keywords or medical subject headings (MeSH terms) used by other authors. These are identified and written down at the start of the search, and may be augmented with experience from the search (Table 43.3).

The search terms will be used, with truncations (if appropriate) and use 'variant spelling' if possible, singly and then in combination, using the Boolean operational commands, AND, OR, NOT and AND & OR.

SETTING THE SCOPE

It is desirable to establish the scope of the search by establishing the inclusion and exclusion criteria of the paper. Examples of inclusion criteria are:

- meta-analyses
- systematic reviews of randomized trials
- physiological studies
- English language only
- time-frame (last 5 years).

Examples of exclusion criteria are:

- studies that do not cover clinical evidence
- studies published prior to the 5-year cut-off, except key papers or definitive studies.

GATHERING THE EVIDENCE

Searching the literature in otolaryngology may be relatively straightforward. The options are to conduct an electronic search of NICE, the Cochrane Collaboration (Embase) and databases such as Medline (PubMed), and to complete a 'hand-search' of specific journals. Google Scholar may be an unattractive alternative because it can throw up an enormous number of results, though there may be benefits if it highlights 'grey literature', such as book reviews and web pages. Reference manager software, such as Mendeley or Zotero, is an aid in managing the papers found in the literature.

A pathway for completing the exercise is given in Figure 43.4.[7]

CRITICAL EVALUATION

A critical evaluation of the significant papers is necessary at this stage. The first step is to review the type of paper. Categories are as follows:

- randomized controlled trial (RCT)
- systematic review of RCTs
- methods that are not RCTs
- systematic review of papers that are not RCTs
- basic science paper (physiology, microbiology, genetics)
- other (clinical observation or case study, synopsis, guideline).

A critique of each paper entails a systematic evaluation of the following points:

- The title: is it relevant?
- The method: is it valid?
- The results: what are they?
- The conclusions: in what way are they useful?

The summary in Table 43.4 is an example of a useful, but not definitive, framework for the process.

Evidence for each phase of the case report should be set out and considered using questions that are appropriate for the information available. The framework in Table 43.5 might be used as an example.

The papers may also be categorized using the PICO approach. Dividing the papers into these categories allows a systematic analysis of the evidence about diagnosis, therapy, prognosis and risk of harm. It is necessary to establish that the validity and significance of the evidence has been demonstrated in the paper. If it has not, then the necessary data may be extracted and analyzed by an appropriate statistical instrument to establish the level of confidence.

PREPARING THE EVIDENCE

The final case discussion should provide an overview of each stage in the process, setting out the evidence used in determining the conclusions. The correct answer is not arriving at the diagnosis, but understanding the basis on which the clinical judgement is made, and declaring the evidence (Table 43.6).

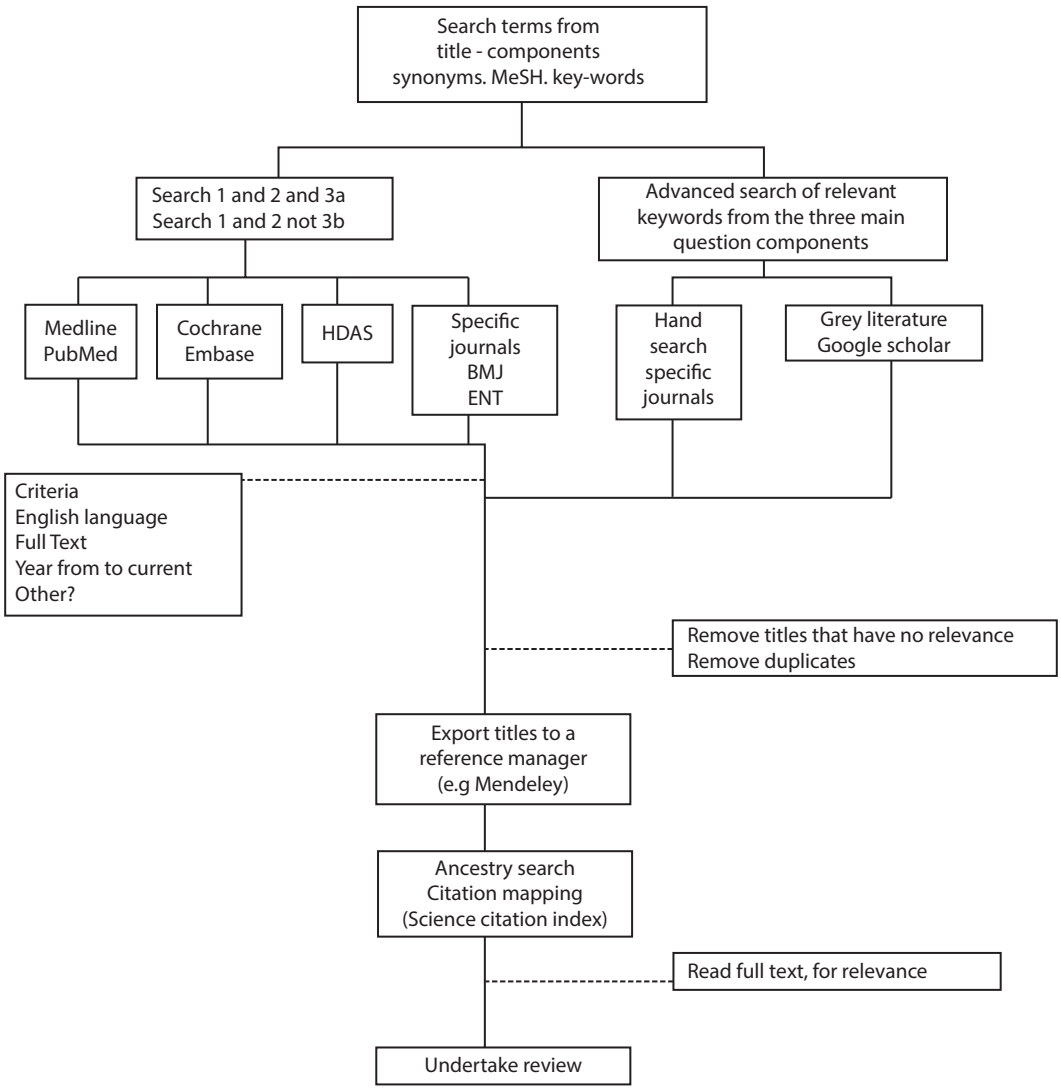


Figure 43.4 Flow chart of search strategy.

TABLE 43.4 Example framework

	Paper		
	1. Author/ Year	**2. Author/ Year**	**3. Author/ Year**
Type of study			
Participants: • cohort • cross-sectional • purposive selection			
Method: • how was the evidence gathered? • instruments for analysis			
Results • do they answer the question? • significance			
Conclusions • relevance			
Limitations, bias			
Other points and your conclusions			

Adapted from Sackett et al.[8]
Information to be entered in Table 43.4 from the papers found in the literature search.

TABLE 43.5 Framework for considering evidence

	Evidence from the literature	Relevance to patient (information to be completed by the user, with reference to the patient.)
History and examination	Were these controlled and confirmed?	
Aetiology	Were these reported and recorded?	
Test results	Confirmed by replication? Levels of probability? Results presented in sufficient detail? Was the index test compared to a gold standard?	
Diagnosis	Based on a blind trial? Representative sample? Reference standard? Specificity? Sensitivity? Predictive validity?	
Therapy	Was it a 'blind' trial? Did the sample change? Assigned or randomized? Were other variables controlled? Size and nature of impact?	
Prognosis	Was it a 'blind' trial? Was the sample declared and described? Was the follow-up sufficient?	
Risks	Placebo rate (control)? Absolute risk? Relative risk? Numbers needed to treat?	
Care and compliance	Were all variables considered and controlled? What was the sample size?	

Adapted from Sackett et al.[8]

TABLE 43.6 Providing an overview and setting out the evidence

	PICO component (information to be added by the student with relevance to the patient)			
	Problem	**Intervention**	**Comparison**	**Outcomes**
History				
Examination				
Aetiology				
Possible diagnosis				
Differential diagnosis				
Tests				
Management options				
Care and compliance				

CONCLUSION

The exponential increase in scientific papers, and expansion of 'what is known' makes it almost impossible not to make clinical judgements without some reference to the evidence in the literature. It may be argued that the expansion of the literature has surpassed our capacity to maintain a comprehensive review of all the information available. However, as the flexibility of modern information technology allows convenient access to a wide range of resource materials, this is less problematic now than in times past. Indeed, web-based information is a commonly used platform for learning and keeping up to date. Therefore, acquiring a rational and systematic competence in finding and using valid, reliable and appropriate information is a fundamental part of clinical praxis. However, this is not to dismiss the values of professional judgement based on experience and often 'gut reaction'. Indeed, it has been acknowledged that the capability of forming a professional judgement is a greater order of magnitude than mere technical competence.[9] Yet it is certainly the case that, in this digital age, evidence in the literature does provide a significant input into informing the *best* clinical judgement.

KEY POINTS

- EBM is fundamental to clinical practice, globally.
- It has a series of skills that require mastery
- It contributes to an informed clinical judgement.

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CHAPTER 44

CRITICAL APPRAISAL SKILLS

Paul Nankivell and Christopher Coulson

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: critical appraisal, evidence-based care, evidence-based healthcare, systematic reviews. As this chapter is essentially a 'How I do it,' there was no formal strategy used.

WHY DO WE NEED CRITICAL APPRAISAL?

Evidence-based practice (EBP) begins and ends with patients. We can harm patients by giving inaccurate information about prognosis, make assumptions about diagnostic test results that are false, give therapy that is ineffective or harmful, or fail to give effective therapy. The only way to prevent this happening is to ensure that we have the most up-to-date knowledge available so that we can share that information with patients.

There were 26 randomized control trials regarding otitis media alone published in the last two years. Therefore, even with maintaining a diligent approach to reading journals during continuing professional development (CPD) time and attending postgraduate seminars, it is becoming increasingly difficult for clinicians to keep up to date with everything that is important affecting their patients. EBP starts with the clinician accepting that there is uncertainty about what we do and that sometimes (when that uncertainty occurs frequently or when it is important) we should search for the latest knowledge. Pragmatically, what we do at present is ask colleagues. The inherent flaw here is the inability to assess the quality of the evidence presented to you by your colleague. Does this matter? If the question is important or frequent then yes, it does matter.

Research evidence can be approached from two angles. The first is the clinician who wants to undertake research and the second is the clinician who wants an answer to a clinical question. The latter wants to know what to believe. Is it the randomized trial, or the case series or case-control trial? What papers should they look for to answer their question?

Levels of evidence have been proposed to help clinicians identify trials most likely to yield the 'truth' and associated with these are grades of recommendation. For questions about the efficacy of a therapy, these state that a systematic review of homogenous trials is likely to be the most believable evidence.

The process of EBP therefore requires that one searches for the best evidence. For therapeutic decisions, this is usually going to be a systematic review, where data from relevant randomized control trials on the topic of interest have been identified and screened according to pre-defined inclusion criteria. Data may potentially be combined together in the form of a meta-analysis. Systematic reviews should include the data from all up-to-date trials with this completeness being one of the significant advantages of this method of review. Yet, it is not an approach to be underestimated. A search for papers to be included in the review might often generate a list of more than a thousand papers, with all the titles and abstracts being read to select relevant articles. The full text of these relevant articles must then be obtained (in itself a time-consuming and expensive task) and read to ensure they meet the selection criteria. The data then have to be independently abstracted from the selected articles. Undertaking a valid,

well carried out systematic review is no easy task, but is essential for clinicians to determine the latest evidence.

Once a trial or trials have been found that seems to answer your question, you have to check three things. Is the study valid? What are the results? Can these be applied to my patients?

The need to check for validity seems, on the surface, to be bizarre. Surely this is what journals should be doing. That assumption is correct but in reality the job of a journal is primarily to make a profit. Therefore you will find articles with flawed trials in even the most highly cited journals.[1]

Journals started as the diaries of researchers. These were then passed around colleagues so that the information could be shared. The development of trials and the assessment of bias are subsequent to that descriptive era. What we are now faced with are seemingly complex long papers with obscure statistical analyses. The scenario is no different to a medical student facing their first anatomy class. By reading around the subject and by practice, will be able to quickly identify key anatomical structures. The same is true of reading scientific articles. You can learn certain aspects of trial design very quickly to be able to assess whether an appropriate design was used for a certain research question. The journal *Evidence-Based Medicine* critically appraises the literature from over 100 journals. However, it only includes a few that are likely to change the way you think about a problem or change the way you practise. Sadly for the other articles, we must appraise them ourselves.

The need to assess the methodology of individual trials is extremely important. In large systematic reviews of the same clinical outcome with the same therapy, researchers have compared the results of those trials that were randomized and those that were not randomized. There are some large differences in certain studies that are more than one would expect by chance. One cannot always say that randomized trials show less effect than non-randomized trials.[2]

However, it is not enough to accept that a trial is believable at face value. There is now overwhelming evidence that trial methodology has a major influence on the results of therapeutic trials.[2, 3] Concealment of randomization, masking and randomization itself are three main components of randomized trial design. The numbers of patients involved in the study and their follow-up are the other key features.

Inadequate concealment of randomization may exaggerate the efficacy of a treatment compared to trials where adequate concealment has occurred. The size of this effect may be considerable, over 40% in some studies although it should be noted that it is not possible to quantify the size or direction of such bias on effect size from study to study.[4, 5] Surprisingly, perhaps of lesser importance is blinding (masking) – the doctor looking after the patient, or the patient themselves, knowing whether they are giving (being given) the experimental or placebo treatment. If there is no blinding, the results may exaggerate the effectiveness of the treatment by 15%. If less than 80% of patients are followed up, one cannot tell what is happening and the results become meaningless.

To assess a study there are checklists some of which have now been incorporated into computer programmes such as that found at the Centre for Evidence-Based Medicine website (www.cebm.net) that enable health professionals to appraise the quality of the evidence for themselves.

Systematic reviews therefore need to assess the individual validity of the trials that are included. If they do not assess whether there was concealed randomization, for example, then you, the reader, may be given incorrect information. The assessment of methodological quality – now better termed risk of bias – of a randomized controlled trial may be carried out using a variety of available systems. The Cochrane Collaboration has recently updated their tool for assessing risk of bias in randomized trials.[6] Furthermore, systematic reviews should be conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses.[7] The PRISMA guidelines have replaced the previously used Quorum statement.[8]

For systematic reviews, effective transparent searches and defined inclusion and exclusion criteria are important. The homogeneity (similarity) of the studies is also critical in determining whether a meta-analysis of the data is appropriate. The meta-analysis (combination of the results of the individual trials) is usually only appropriate when there is clinical and methodological homogeneity (that is, the methods and clinical outcomes and starting points are similar). In addition, the results must be put into context of present formats of care.

The need to understand how trials may come to the 'wrong' conclusion is as important as understating the treatment itself. Clearly, all this may be daunting to a busy clinician so there are sensible short cuts. Always start by looking at evidence that has already been appraised such as that in *Evidence-Based Medicine* and *Clinical Evidence*. The essential part of effective clinical practice is to continue to ask questions.

We need to make sure that what we do is based on the soundest evidence possible. If the only evidence is experiential and anecdotal then that is perfectly satisfactory. However, if there is a systematic review of randomized control trials that all point to an alternative treatment being more effective then that should only be ignored at your patients' peril.

TIPS FOR PRACTISING EVIDENCE-BASED HEALTHCARE

Tip 1: Ask questions

Try making one question per clinic. Select one question because:

- There is likely to be an answer.
- The question has arisen more than once or is important:
  - record briefly the problem, for example, 'Sudden onset hearing loss'

- write down the question, for example, 'are steroids an effective treatment (efficacy and morbidity)?'
- put time aside each week to research the answer to the question.

Tip 2: Searching

- Search one question regularly: every two weeks, every month or every quarter!
- Conduct your search in a logical order:
  - clinical evidence
  - journal EBM
  - Cochrane
  - PubMed.

Keeping up to date with literature searches can be facilitated by developing highly specific search strategies (for example using PubMed). These searches are set up to deliver regular alerts directly via email. Any new articles relevant to the topic of interest will then be sent through on a regular basis without the need to specifically perform a search each time.

Often you will find too few articles, or that the articles you do find are not in your library or will take a long time to obtain. Sometimes you will find too many articles and a systematic review is needed. Unless you have time and the question is desperately important, pass and move on to the next question – let someone else answer this one!

Appraise only the article(s) that answer your question, have the highest level of evidence and are readily available.

Tip 3: Appraisal

- Look for letters about the article in subsequent issues of the journal.
- Appraise with others until confident.
- Appraise using worksheets or using software, for example CATmaker.
- Mark (highlight) on the printed article where you found the important data.
- Get someone else to check it for you.
- Appraise the article as part of a departmental journal club.

Tip 4: Share your knowledge

- Try sharing uncertainty with your colleagues.
- Discuss your questions with colleagues (maybe they have already answered them).
- Find fault with the article(s) rather than your colleagues.

BASICS OF CRITICAL APPRAISAL

Read the abstract

Assuming you have three or four articles to appraise, how should you start? First read the abstract. Read it briefly trying to gain an overview firstly of the methods used and secondly the results. For example, a parent brings in a child referred by their GP for recurrent epistaxis but is worried about surgery (describing cautery in dramatic terms) and wonders whether a cream used by a friend's child might help (Naseptin). You make a note of this and later formulate the question 'In children with recurrent epistaxis, is Naseptin effective, compared with placebo, at reducing attacks of epistaxis?' and find this paper.[9] The abstract is available online. It takes a minute or two to read through the abstract:

> *Epistaxis is common in children. Trials show antiseptic cream is as effective as cautery, but it is not known whether either is better than no treatment. We wished to know the efficacy of cream in children with recurrent epistaxis. The design was a single-blind, prospective, randomized controlled trial set in the otolaryngology clinic in a children's hospital.*
>
> *The participants were 103 children referred by their general practitioner for recurrent epistaxis. Excluded were those with suspected tumours, bleeding disorders or allergies to constituents of the cream. Referral letters were randomized to treatment and no treatment groups.*
>
> *Treatment was antiseptic cream to the nose twice daily for four weeks, which was prescribed by the general practitioner before clinic attendance. All children were given an appointment for eight weeks after randomization.*
>
> *The main outcome measures were the proportion of children in each group with no epistaxis in the four weeks preceding clinic review. Complete data were available for 88 (85%) of the children. Of the treatment group, 26/47 (55%) had no epistaxis in the four weeks before the clinic appointment. Of the controls, 12/41 (29%) had no epistaxis over the four weeks. This is a relative risk reduction of 47% for persistent bleeding (95% CI 9–69%) and an absolute risk reduction of 26% (95% CI 12–40%), giving a number needed to treat of 3.8 (95% CI 2.5–8.5).*
>
> *We conclude that antiseptic cream is an effective treatment for recurrent epistaxis in children.*

The format of any abstract should be similar to this. If there is a complex description of the trial that is confusing, ask yourself why. Is it because the authors are hiding an overall negative result or is it really a necessary peculiar design?

So, in this study there were 103 patients with epistaxis in a single blind randomized controlled trial with various outcomes described and a promising result overall.

Does the paper answer the question you are asking?

This is a qualitative judgement that you must make on reading the abstract. Unless the paper is the highest level of evidence (systematic review) and deals specifically with the question you have posed it will be necessary to next look for individual randomized controlled trials that address the specific outcomes relevant to your patient.

Find answers to the validity questions using a checklist for the relevant study

It is very much easier to read an article when you know what you are looking for. The same occurs when an experienced doctor finds it easier to filter the enormous number of questions and signs they can ask or examine for, and homes in on specific areas they think are relevant. This ability to put the patient's symptoms quickly into context is the key to skilful practice. In exactly the same way, learning what to look for in a research article is key. When teaching medical students, we give them exactly the same list of questions that are shown below. This gives them focus and they will work through an article in 10 minutes answering all the validity questions.

The first place to check for validity questions about the methods employed is, not surprisingly, in the methods section of the paper. However, you will frequently find that certain elements of the methodology may be mentioned in the introduction, results or even the discussion. So if you cannot find out, for example, the rate of follow-up in the methods, then scan the rest of the text for the answer.

What sort of research design is the trial?

You may have to resort to checking the methods section of the paper to obtain this. The trial under discussion was a randomized control trial with single blinding.[9]

Assess the level of bias

At this stage, you have all the methodology neatly summarized. For example, in the paper under discussion there were some problems with follow-up. They had data available on 88 of the 103 patients randomized, but 15 of these were assessed by telephone. This introduces an element of bias that may reduce the validity. If this was less than 80% then really the trial is so severely compromised that you cannot make any interpretation of the result. If there is not concealed randomization (see 'Concealed randomization' below) then the results *may* overestimate the effectiveness of the treatment. So, assessing bias is the art of appraisal. In the end you have to decide whether the effect of the treatment demonstrated is likely, taking into consideration the level of bias, to translate into benefit in your patient.

Translate the results into something clinically meaningful

If the article describes analysis data with quoted figures for risk reduction, how does that apply to an individual patient? A frequent term used now is numbers needed to treat. This puts the effect into the context of the patient and lets them decide whether the benefit is worth the trouble or potential side effect(s).

How can I implement this?

Does this help my practice, either by reinforcing what I know and making me more confident, or does it change my practice? If it is the latter, how am I going to go about implementing that change?

The numbers

The most frequent fear expressed is that of the statistics. How can I tell whether these were the correct statistics to be used? This can initially be tackled obliquely. First, ask what is likely to represent a clinically beneficial outcome for your patients. Is a reduction in mortality of 1% enough for an invasive procedure, or should it be 5%? This is by far the most important feature of the results. If the trial was designed to establish a benefit that you regard as clinically insignificant then no further examination of the study is necessary.

Following this example a little further, assume a 5% reduction in mortality is considered a clinically meaningful difference, and the results of the trial demonstrate that this was achieved. The statistical test is there to show you that this difference was very unlikely to have occurred by chance in two ways. First, that the difference observed in this trial was unlikely to have happened by chance (p value) and, second, if this trial were repeated 100 times, 95% of the trials would have shown a similar result (confidence interval). How they determine the p value (i.e. with a student t test or a chi-square) is beyond the scope of this article but a quick tip is to check the letters written in response to the article because, if the article is in a major journal, statisticians will be quick to point out the incorrect use of statistics. In our experience, there is much less use of incorrect statistical tests than there is of poor trial methodology.

To summarize, check that the difference is clinically significant and did not occur by chance.

Summary

Critical appraisal is a logical way of assessing the likely truth of a piece of research, evaluating the results in terms of individual patient care, and then assessing the whole and determining whether it is useful for your practice. It combines some knowledge of trial design, a small amount of basic arithmetic and some qualitative judgements.

FORMING ANSWERABLE QUESTIONS

The reason we do not usually ask questions is they are so difficult to answer. This was clearly illustrated in the *Hitchhiker's Guide to the Galaxy* when the super computer gave the answer '42' to the Ultimate Question of Life, the Universe, and Everything.[10] The people asking the question were horrified and angry. The computer calmly suggested that, instead of panicking, they should go back and consider the question and that he would of course help them do this. Clearly, this is an extreme example of where

the question has been so badly formed that the answer is meaningless.

Imagine a patient with diabetes. Their control has been haphazard and they have had repeated haemoglobin A1C (HbA1C) tests performed over the last year. Their control seems better now but the HbA1c test is expensive to perform. How effective is blood glucose at monitoring diabetes? A search for 'blood glucose' and 'diabetes mellitus' identifies 25 000 articles.

Two mistakes were made here. The search was unstructured, the terms so vague that a manageable list of relevant items unable to be generated. This arose partly because of the unfocused nature of the question. The goal was to discover how 'effective' the test is. What is meant by that? If it is negative does that rule out poor control – or if it is positive (high) does that mean they have poor control? In this case it is the former that really is of interest.

You could start with a textbook and read thoroughly about diabetes. For a broad overview of the topic area textbooks may be ideal; however, they are often many years out of date. For understanding more about therapy in general, a resource such as *Clinical Evidence*[11] is extremely valuable (*Clinical Evidence* cites all the evidence from which therapeutic recommendations are made). This form of enquiry is termed a 'background question' or one that helps the person understand the problem in general. This in contrast to what is being discussed here, which are termed 'foreground questions' or decision-making questions. As a student, you ask mainly background questions but as your experience with a condition increases and the clinical need for decision-making increases, the proportion of background questions fall as the foreground questions rise (**Figure 44.1**).

Incorporating this, the question now becomes: In diabetics, is fasting blood glucose (compared with HbA1c) effective at excluding poor diabetic control?[12] (A fasting blood glucose < 7.8 rules out poor glycaemic control.)

The query is becoming better but the first part is still vague. Including something about non-insulin-dependent diabetics would further refine the question. By structuring a question, the answer may be found more efficiently.[13] It is therefore important to try to break the question down into several parts, the most common approach being to use the PICO format:

- patient and problem
- intervention (or diagnostic test)
- comparison intervention (optional)
- outcomes.

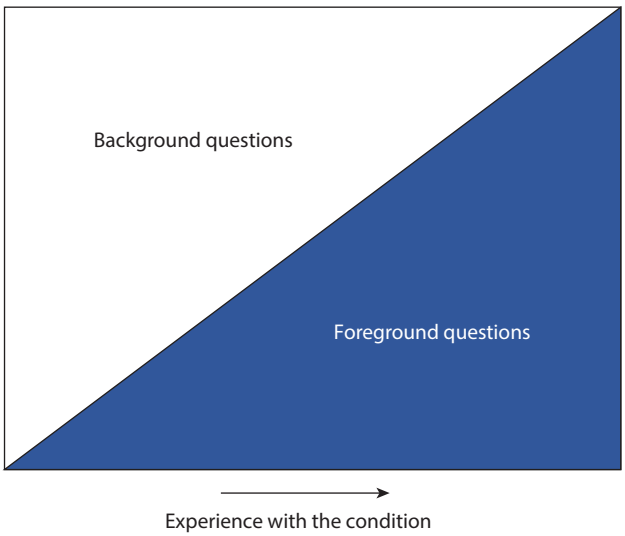


Figure 44.1 Foreground and background questions.

Patient and problem

The first part is to identify the problem or the patient. Some healthcare problems are not always about patients! For example, an administrator may want to know whether having acute medical beds in a temporary holding ward next to the accident and emergency department is any better than having conventional acute medical wards in the hospital. Make sure at this stage in the question you are describing the problem or patients that you see. However, if you are too specific at this stage you may miss some important evidence and there is a balance to be struck between obtaining evidence about exactly your group of patients and obtaining all the evidence about all groups of patients.

Intervention

The intervention is equally important. It may in fact be a postponement of an action, such as an operation. In patients with abdominal pain lasting less than 12 hours, does an additional 24-hour delay before referral to hospital alter outcome? Most interventions are more straightforward, such as types of dressings, drug therapies or counselling. Alternatively, they can be about the provision of differing environmental factors, such as the décor of waiting rooms or dealing with the way in which information is given to patients, i.e. positively or negatively.[14]

The intervention can be a diagnostic test. However, specify whether you are trying to detect or exclude a disease.

Comparison intervention

Sometimes, there is a comparison of the intervention. For example, you might seek papers comparing the use of an active compound compared with either a placebo or another active drug. Considering whether you are looking for comparative studies will help when searching for that evidence. You may be comparing one diagnostic test against another.

Outcomes

Outcome measures are particularly important when considering the question. It is worth spending some time working out exactly what it is you want. In serious diseases it is often easy to concentrate on the mortality and miss the important aspects of morbidity. For example, the use of toxic chemotherapies for cancer may affect both aspects.

This is also the time when it is important to know what outcome is relevant to the patient. In Menière's, deafness and tinnitus may occur but the patient may only really be interested in controlling one problem as a priority. The search should primarily focus on that outcome. The Core Outcome Measures in Effectiveness Trials (COMET) initiative aims to develop and encourage application of agreed standardized sets of outcomes, known as 'core outcome sets'. These can be applied to both controlled and non-controlled trials. The intention is not to limit the range of outcomes measured but to ensure a minimum core set is included in all studies of a particular condition such that pooling or comparison of trial data can be more meaningful.[15]

Type of question

Once we have created a question, it is helpful to think about what type of question you are asking, as this will affect where you look for the answer and what type of research you can expect to provide the answer. For example, although randomized controlled trials (RCTs) are a very valid type of study, it would be unethical to perform an RCT on harm. (Would you volunteer for the exposure arm of such a study?) Questions about harm should look for different types of research, such as case-control studies or cohort studies.

APPRAISING DIAGNOSTIC ARTICLES

Diagnoses are usually made through interpreting and combining information from a combination of the clinical history, examination findings and the results of investigations, such as blood tests and X-rays. An important component of evidence-based healthcare is working out how useful these different pieces of information are in making a diagnosis. For example, if you test a patient's urine and find protein in it, how likely is it that this represents kidney disease? A test result needs to be interpreted in the light of how accurate you think the test is, and what you already know about the patient.

In making a diagnosis you are consciously (or subconsciously) weighing up probabilities. Each question you ask or each observation changes those probabilities. For example, if a patient limps in then there is a probability of arthritis being the cause of the limp. If the patient is 70 years of age, the probability is higher than if the patient is 30. The age of the patient is a diagnostic test, either increasing or decreasing the probability. It is essential, when contemplating a test, that the person requesting the test has some idea of the probability of the diagnosis. They will also need to decide whether the test is helping them exclude or include the diagnosis. Finally, they need to know what is the likely probability of the diagnosis after a positive or a negative result.

What is meant by test accuracy? Accuracy is a description of how well the test diagnoses and excludes the disease when the result is positive or negative (see 'What are the results?' below).

Sensitivity reflects the ability of a test to identify people who have disease and specificity reflects the ability of the test to identify 'normality', or people who do not have disease. So this means that tests with very high sensitivities and specificities can be extremely useful at either excluding or including a diagnosis. It is not uncommon to spend time seeing the worried well. These are patients who present with symptoms caused by a mild or self-limiting disease but are naturally worried that it may be something more serious. In these cases what is required are tests that mainly exclude disease. In hospital, where patients are potentially significantly unwell, what is required is to be able to make a diagnosis (including disease).

To see an example of how high sensitivity and specificity values of a test can be used in clinical practice, let us consider how general practitioners deal with patients with a sore throat. This is a common presenting complaint in general practice and it would be useful to know whether a new 'rapid test' could be useful in helping diagnose bacterial sore throats.[16] This particular paper is selected for illustrative purposes rather than it being the 'best' level of evidence.

In the paper four patient features were determined:

- fever ≥38°C
- lack of cough
- tonsillar exudates
- anterior cervical lymphadenopathy.

Five hundred and fifty-eight patients older than 11 years presenting with sore throat were swabbed and examined for these features. They all also had a rapid streptococcal antigen detection test for detecting group-A B-haemolytic streptococcus (GABHS).

The next step was to go through the paper checking for validity.

Is the study valid?

- **Did the authors answer the question?** The question is often found at the end of the introduction section of the paper. Some authors leave you guessing as to what the original question might have been. If the paper does not have a clear question, it cannot give any clear answer, so you can save yourself time by moving on to the next paper. You should also consider whether the research question is relevant to your clinical question.
- **What were the characteristics of the groups?** This would contain some description about the numbers of patients, their race and gender, age and any other features that are pertinent to the study. This would also include any characteristics that are known or likely confounders (i.e. factors that might introduce bias if highly represented in one group compared to the other).
- **Is it clear how the test was carried out?** To be able to apply the results of the study to your own clinical practice, you need to be confident that the test is performed in the same way in your setting, as it was in the study.

What was the test undertaken? How was it done and by whom? Was it a multi-level test (i.e. a serum level) with different thresholds?

- **Is the test result reproducible?** This is essentially asking whether you obtain the same result if different people carry out the test, or if the test is carried out at different times on the same person. One thing to consider here of course is the distinction between reproducibility and validity. It is perfectly possible for a study to generate a series of results that are reproducibly wrong.
- **Was the reference standard (gold standard) appropriate?** To start with, we need to find out how the study found out what the 'truth' really was about patients. That is to say, how did the investigators know whether or not someone really had a disease? To do this, they will have needed some reference standard test (or series of tests) which they know 'always' tells the truth.
- **Were the reference standard and the diagnostic test interpreted blind and independently of each other?** If the study investigators know the result of the reference standard test, this might influence their interpretation of the diagnostic test and vice versa. The potential effect of non-blinding of investigators has already discussed.
- **Was the reference standard applied to all patients?** Ideally, both the test being evaluated and the reference standard should be carried out on all patients in the study. There may be a temptation, for example, if the test under investigation proves positive, not to bother administering the reference standard test. In many cases, the reference standard test may be invasive and may expose the patient to some risk and/or discomfort. While it would usually be ethical to use such a test on a patient in whom you had grounds to suspect that it might be positive, it would not be ethical if you thought that the test would be negative (i.e. if the diagnostic test being evaluated had been negative). Therefore, when reading the paper, you need to find out whether the reference standard was applied to all patients, and if it was not look at what steps the investigators took to find out what the 'truth' was in patients who did not have the reference test.
- **Was the test evaluated on an appropriate spectrum of patients?** Another complication is that a test may perform differently depending upon the sort of patients on whom it is carried out. For example, the more severe a disease is, the easier it tends to be to detect. Thus, you might find that testing for bacterial sore throats might be 'better' at detecting infection when evaluated in patients who attend an ENT clinic, than in those attending family practice. This may be because people with chronic disease who attend an ENT clinic will be more symptomatic and have more bacteria in general, making it easier to detect. This problem is referred to as spectrum bias. A test is going to perform better in terms of detecting people with disease if it is used to identify it in people in whom the disease is more severe, or advanced. Similarly, the test will produce more false-positive results if it is carried out on patients with other diseases that might mimic the disease that is being tested for.

The issue to consider when appraising a paper is whether the test was evaluated on the typical sort of patients in whom the test would be carried out in real life.

The optimal study method for the assessment of a diagnostic test is a cohort study evaluating the test in a group of patients thought to be at risk of having the disease. A less valid alternative method that has been used is a case-control study. The latter method studies patients known to have the disease and control patients without the disease. The performance of the test in the two groups is compared. This sort of study has been shown to overestimate the effectiveness of the diagnostic tests.[17]

What are the results?

In an ideal world, a positive test would mean that someone has disease, and a negative test would mean they do not have disease. Unfortunately, this is rarely the case. When a test is carried out, there are four possible outcomes:

1. The test can correctly detect disease that is present (a true positive result).
2. The test can detect disease when it is really absent (a false-positive result).
3. The test can correctly identify that a disease is not present (a true negative result).
4. The test identifies someone as free of a disease when it is really present (a false-negative result).

These possible outcomes are illustrated in Table 44.1.

Given that a test may potentially mislead us if we obtain a false-positive or a false-negative result, we need to have some way of characterizing how accurate the test really is (Table 44.2). What does this mean? The high specificity means that there is a high true negative rate (359 out of 375). Or put another way, only a few (16) falsely positive test results were found out of the 375 people who did not have GABHS. So that means (using some reverse logic) that if the rapid test was positive (going across the row), by inference they almost certainly have the disease.

We can simplify this to say that in tests with high **specificities**, where the result is **positive**, it rules the diagnosis **in**. The mnemonic for this is **SpPIn**.

TABLE 44.1 Possible outcomes of a diagnostic test

Test result	'True condition status'		
	Condition present	**Condition absent**	**Totals**
	a	b	a+b
Positive	True positive	False positive	
	c	d	c+d
Negative	False negative	True negative	
Totals	a+c	b+d	a+b+c+d

Sensitivity = a/(a+c) Positive predictive value = a/(a+b).
Specificity = d/(b+d) Negative predictive value = d/(c+d).
Prevalence = (a+c)/(a+b+c+d).
Accuracy = a+d/a+b+c+d.

TABLE 44.2 Results of rapid test screening for group-A ß-haemolytic streptococcus (GABHS) in patients with a sore throat

	'True condition status'		
Test result	**GABHS+ve**	**GABHS–ve**	**Totals**
Positive	119	16	135
Negative	64	359	423
Totals	211	375	558

Sensitivity = 119/211 = 65%.
Specificity = 359/375 = 96%.
Positive predictive value = 119/135 = 88%.
Negative predictive value = 359/423 = 85%.
Prevalence = 211/558 = 33%.
Accuracy = 478/558 = 85%.

In tests with high **sensitivities** and the test is **negative** then it rules **out** the disease. So the mnemonic for this is **SnNOut**. Clearly it is not 100% accurate at excluding (that would only happen if the sensitivity was 100%). How you take that finding and put it into practice depends on the severity of the disease as well as the other symptoms and signs that indicate the pretest probability of the disease.

In reality, patients who are well where you are trying to exclude disease need tests with high sensitivities (primary care). Patients who are ill need tests with high specificities to determine the cause of the illness. This is an oversimplification of the process of diagnosis but is helpful in terms of remembering what tests do.

Often, of course, we are faced with tests whose sensitivity and specificity are not so high that we can use the test to rule in or rule out a disorder. For such cases, we need a measure of a particular test result's ability to predict the presence or absence of disease.

We might think that this is provided by the positive and negative predictive values (for positive and negative results, respectively). However, in practice we find that these values can change depending on the prevalence of the target disorder amongst the test population: if the disorder is more common, the positive predictive value will be higher and the negative predictive value lower.

For example, if the results show a much lower prevalence (Table 44.3), the sensitivity remains similar and the specificity is the same but the positive predictive value drops considerably. Now the test only has a 50:50 chance of detecting someone with disease. You can see how the prevalence will sometimes significantly alter the effectiveness of a test. It is important always to consider the setting before recommending tests that perform well in an alternative healthcare setting.

TABLE 44.3 Potential results of a rapid test screening for GABHS in patients with sore throat in an imaginary low prevalence setting

	'Truth'		
Test result	**GABHS+ve**	**GABHS–ve**	**Totals**
Positive	12	16	28
Negative	6	359	365
Totals	18	375	393

Sensitivity = 67%.
Specificity = 96%.
Positive predictive value = 43%.
Negative predictive value = 98%.
Prevalence = 4.5%.

However, since sensitivity and specificity are not affected by disease prevalence, we can combine them to create a combined measure of the efficacy of a particular test result. This can be thought of as, for a given test result, the likelihood that a patient with the disorder would yield that test result compared to the likelihood that a patient without the disorder would yield that same test result. This is the likelihood ratio (LR). As a rule of thumb, for positive test results, an LR of 10 or above shows that the test result is good at ruling in disease; for negative test results, an LR of 0.1 or less shows that the test result is good at ruling out disease.

Two additional benefits of the LR are that they can be used to generate specific post-test probabilities for your patient and that, where we have multiple independent tests, the LRs can be multiplied together to yield a much more powerful test.

The prevalence of GABHS was 33%. If the test is positive it is very likely they have GABHS, but what about if it is negative?

What you can do is work out the likelihood ratios: Figure 44.2 shows the nomogram for likelihood ratios. To use the nomogram a line is drawn from the pre-test probability of 33% through 16 (on the likelihood ratio line) to obtain a post-test probability of approximately 90% if the result is positive and through 0.36 (roughly) to obtain a post-test probability of approximately 12% if the result is negative.

But what if our patient has a lower pre-test probability? For example, this might be a patient with only a 20% pre-test probability. Using a ruler, see what their post-test probability would be. The nomogram lets you quickly see the implications of a positive or negative result in terms of post-test probability.

Will the results help my patient?

ARE THE RESULTS RELEVANT TO YOUR PATIENT?

So far, we have considered how to interpret results of tests for your patients. However, it may be that you feel that the results of studies carried out to assess the accuracy of the test are not generalizable (or relevant) to your setting, or you may consider that it would not be helpful to your patient to perform the test.

GENERALIZABILITY TO YOUR SETTING

One aspect to consider is whether the assessment(s) of test validity that have been carried out are applicable to your setting. We have already seen how predictive value is dependent upon prevalence, so the predictive value of a test in one setting is usually not the same in another setting.

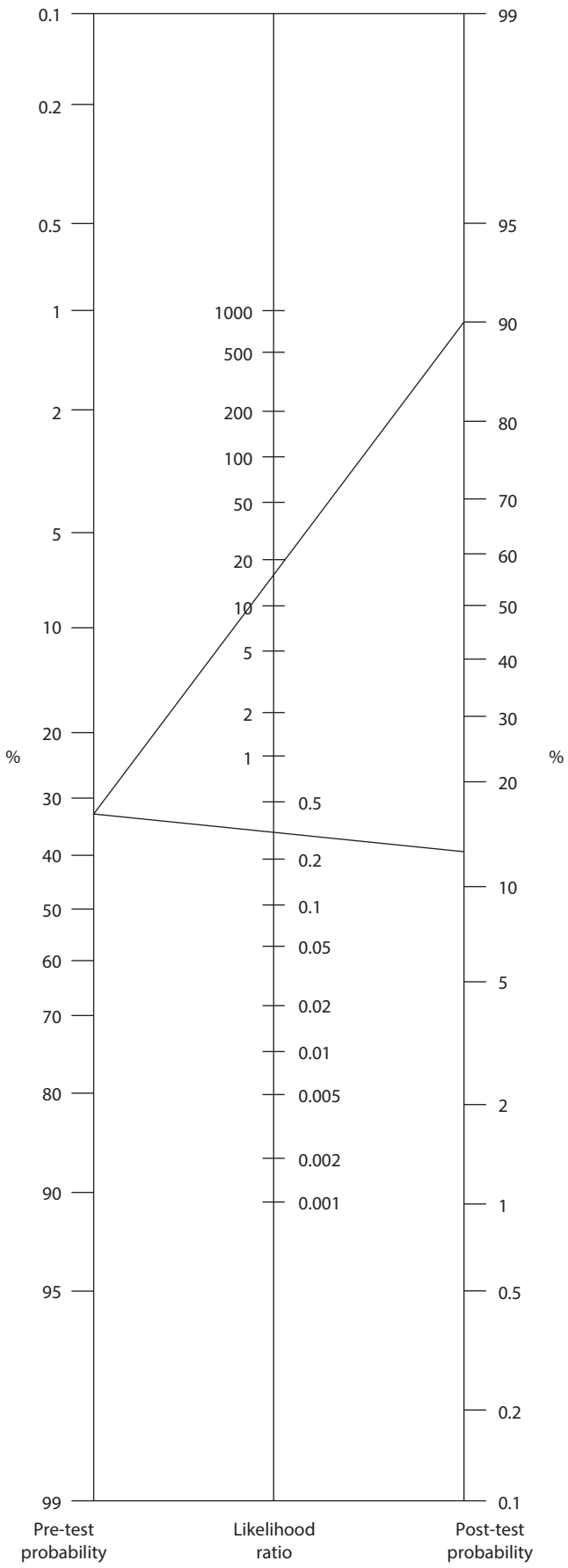


Figure 44.2 Nomogram for likelihood ratios.

Sensitivity and specificity (and likelihood ratios) are not dependent on prevalence, but they can vary according to the type of patients on which the test is carried out. The sensitivity of a test will depend upon the severity of disease in the population being tested. The more advanced or severe the disease, the more likely the test is to identify it.

The specificity of a test will depend upon the prevalence of other diseases in the population that might lead to false-positive results. The more that other diseases are present, the more likely a false-positive result.

A second aspect to consider is whether the test is carried out the same way in your setting as it was in the study. Some diagnostic tests depend upon the skill of the person carrying out the test, and the skill of the people interpreting the test result. Tests may be carried out in different ways, and it is important to know that it is carried out the same way in your local hospital or laboratory as it was in the study which evaluated the test.

WILL IT HELP YOUR PATIENT?

One way to think about whether or not to perform the test is whether it will influence the management of the patient or groups of patients you are likely to see. If you think that a disease is unlikely in a particular patient, it may be that if you carried out the test and it was positive, you would still think that the disease was unlikely, so it would not influence your management. Conversely, if you think that a disease is likely in a given patient, it may be that a negative test result would not stop you treating the patient, since you would still think that the disease is likely whatever the test result. Putting this in terms of pre- and post-test probabilities, in the first instance the pre-test probability of disease is so low, that even with a positive test result, the post-test probability will be less than 50%. In the second instance, the pre-test probability of disease is so high that even with a negative test result, the post-test probability will be more than 50%.

In practice, knowledge about the accuracy of diagnostic tests will perhaps be most useful when planning protocols or guidelines to manage particular groups of patients.

Summary

An evidence-based approach to deciding whether a test is effective for your patient involves the following steps:

- Frame the clinical question.
- Search for evidence concerning the accuracy of the test.
- Assess the methods used to determine the accuracy of the test.
- Find out the likelihood ratios for the test.
- Estimate the pre-test probability of disease in your patient.
- Apply the likelihood ratios to this pre-test probability using the nomogram to determine what the post-test probability would be for different possible test results.
- Decide whether or not to perform the test on the basis of your assessment of whether it will influence the care of the patient, and the patient's attitude to different possible outcomes.

APPRAISING THERAPY ARTICLES

When we are required to answer a question about therapy, the identification of information from an article is not straightforward. The layout is frequently different depending on the journal you are reading. One is often relying on the editorial board of the journal, as well as the people who reviewed the article, to have ensured the quality of the article. There may be confusing statistics that make interpretation of the data seem difficult. These problems seem to be very daunting when one is trying to identify information that may affect the care of a patient. These following questions will help you identify the real validity of the therapy article.

- **Is the study valid?** Did the authors answer the question? For this example I shall be using the Kubba paper[9] on Naseptin and epistaxis. The abstract of this article is shown under 'Read the abstract' above. Kubba et al.[9] have answered their question about the effectiveness of Naseptin in epistaxis. They state clearly how they did this and what they used to determine 'effective'.
- **What were the characteristics of the groups?** This would contain some description about the numbers of patients, their race and gender, age and any other features that are pertinent to the study. This is usually found in Table 1 in most papers but in this case is described in the protocol part of the subjects and methods section.
- **Are the comparison groups similar?** To determine whether bias has occurred in the selection procedure, certain potentially relevant characteristics of the two populations should be displayed in tabular form. Usually these include age, sex, duration of illness and other demographic and functional characteristics. This is covered in the first paragraph of the results section of the paper being considered here. There were more boys than girls, but the age and duration of history were the same in both groups. Is it likely that girls and boys would differ in response? The aim is not to find whether there are statistical differences between the two groups but to find whether there are clinically significant differences. You as a clinician reader should judge whether you think the differences are clinically significant.
- **What was the treatment?** In this case it was either Naseptin or nothing. The authors describe clearly the reasons for not using a placebo.

Equal treatment

The groups in the trial were treated equally throughout apart from the experimental intervention. It should be clear from the article that, for example, there were no co-interventions that were applied to one group but not the other, or more frequent or detailed assessments on one group compared to the other.

Placebo control

Patients do better if they think they are receiving a treatment than if they do not, even if the treatment is an inactive substance: the placebo effect is a widely accepted potential bias in trials. A placebo is an inactive treatment that is given so that the patient does not know whether he or she has been given the active treatment; the control group in a trial will often receive a placebo treatment so that this effect is equal in both groups. Patients in both groups of the trial should not know whether or not they are receiving the active therapy. However there is a twist in the tail – one can have a placebo-controlled trial where the patients are having active treatments in both arms of the study in addition to the new treatment or the placebo. So the term 'placebo-controlled trial' does not exclude the use of active treatments (as long as both groups get the same).

Follow-up

There are three major aspects to assessing the follow-up of trials:

- Did so many patients drop out of the trial that its results are in doubt?
- Was the study long enough to allow outcomes to become manifest?
- Were patients analyzed in the groups to which they were originally assigned (intention-to-treat)?

Drop-out rates

A good clinical trial requires the complete follow-up of patients in both the control and experimental groups. If less than 80% of patients are adequately followed up then the results may be invalid. In this study they had problems and had to phone subjects as they did not attend the outpatient clinic. This weakness of the study was evaluated in the discussion.

Length of study

The length of the study is critical in determining the clinical significance of the results. For a disease of short duration, such as an acute infectious disease, the period of the study need only be long enough to cover the course of that infection. Where the disease is more progressive and lengthy then the duration of the study needs to reflect that. The question that the research is trying to answer will also be helpful in deciding the appropriate length of the study.

Intention-to-treat

Because anything that happens after randomization can affect the chances that a patient in a trial has an event, it is important that all patients are analyzed in the groups to which they were randomized. This is an essential prerequisite for valid evidence about therapy. For example, it has been repeatedly shown that patients who do and do not take their study medicine have very different outcomes, even when the study medicine they have been prescribed is a placebo. The correct form of analysis, in which patients

are analyzed in the groups to which they were assigned, is called 'intention-to-treat' analysis.

Were the groups randomized?

The major reason for randomization is to prevent bias. The largest potential cause of bias in research about effectiveness of an intervention is if the patients allocated to the treatment group are different from those allocated to the control group in a way that might influence outcome. To reduce this bias as much as possible, the decision as to which treatment a patient receives should be determined by random allocation. Why is this important?

There could be any number of confounding variables that affect a given situation, some of which we know about, but also others that our knowledge of human physiology has not yet uncovered. Randomization is important because it spreads all confounding variables evenly amongst the study groups, even the ones we do not know about. Occasionally, simple randomization may not ensure that there is an equal balance between treatment groups of known confounding variables. Where there are important confounders known and a need to be sure these are balanced between two groups, a process of stratified randomization can be employed.

CONCEALED RANDOMIZATION

As a supplementary point, clinicians who are recruiting patients into a trial may consciously or unconsciously distort the balance between groups if they know the treatments that will be given to patients. For this reason, it is preferable that the randomization list be concealed from the clinicians. The amount of impact the lack of concealment may have is larger than if the trial was not blinded. If there is inadequate concealment, the size of the effect may be overemphasized by as much as 30%.

BLINDING

It is also important that, if possible, both clinician and patient be 'blind' to whether or not they are receiving treatment. Lack of blinding may lead to exaggeration of the effectiveness of the therapy by as much as 20%.[3]

Outcome measures

To determine the impact of an intervention on patient health, one needs to define clearly the outcome that needs to be measured. This sounds straightforward enough but it can take up a larger amount of the preparation time of the research. An outcome measure is any feature that is recorded to determine the progression of the disease or problem being studied. In this paper a comprehensive questionnaire was used to determine outcomes.

What are the results?

- How large is the treatment effect?
- How precise is the estimate of the treatment effect?

In any clinical therapeutic study there are three explanations for the observed effect:

- the effect of the treatment
- chance variation between the two groups
- bias.

Good research will explicitly endeavour to reduce the effects of chance and bias by using special designs, as we have seen.

NUMBERS NEEDED TO TREAT

The most common approach is to describe the effect of a drug in terms of the risk reduction. The risk is usually of continuing to have, for example, pain or an event. When evaluating a paper on a therapeutic manoeuvre, it is possible to establish its clinical effectiveness by determining the proportion of patients receiving treatment who gain benefit.

Table 44.4 shows the results drawn from the paper.

From the paper the following results are drawn:

The simple statement above obscures the fact that identifying the correct table in the paper and then obtaining the correct figures from it is often not as easy as it sounds. This is one of the parts of appraisal that it is often useful to share with others to ensure you have the correct data.

From Table 44.4 it can be seen that 47 patients were assigned to the active treatment (or experimental) group and 41 to the watchful waiting (or control) group. There were a total of 50 children with epistaxis; 21 occurred in the experimental group and 29 in the control group.

EVENT RATES

It is important to set some standard methods of describing these data. In therapy, we start by converting the numbers of patients into event rates. In the control group, 29 out of 41 patients had epistaxis. This may be presented as an event rate of (29/41) = 0.71. So the control event rate (CER) is 0.71 (this number is also the risk of epistaxis in the control group, and corresponds to a percentage risk of 71%).

In the experimental treatment group there were 21 children with epistaxis out of 47 children. The experimental

TABLE 44.4 Results of a trial of Naseptin against watchful waiting in stopping epistaxis in children

	Epistaxis	No epistaxis for four weeks	Total
Active treatment (Naseptin)	21	26	47
Watchful waiting	29	12	41
Total	50	38	88

event rate (EER) was therefore 0.44 (44%). Now that we have these numbers we can start working with them.

RELATIVE RISK

One way of combining the event rates is to use relative risk (RR). Here, we make a ratio of the two risks to show which group has a higher or lower risk. The relative risk is calculated by dividing the risk of having epistaxis in the treatment group by the risk of the control group = 0.44/0.71 = 0.62. This means that the risk of epistaxis continuing with Naseptin was 0.62 (or 62%) of the risk without Naspetin.

Relative risk reduction

It is also possible to show the extent of the benefit compared to the original risk by calculating the relative risk reduction (RRR). This is similar to relative risk, except that we take the difference in risk between the two groups and divide that by the control group's risk: RRRs are often presented as percentages.

The RRR means that the treatment reduced the risk of continued nosebleeds by 38% relative to that occurring in this control population (the RRR given by the authors is for persistent bleeding whereas I have calculated for cessation of bleeding). This is a large risk reduction in a population that are all bleeding. But what if it was an RRR for primary stroke reduction where the events are far fewer? So the RRR has to be judged against the prevalence of the outcome we want to prevent.

Absolute risk reduction

The absolute risk is that 71% of individuals in the placebo group had nosebleeds and that 44% of the treatment group had nosebleeds. The difference (absolute risk reduction (ARR)) between these gives us another view of the effectiveness of the treatment. The ARR of this therapy is 0.27 (CER – EER = 0.71–0.44).

ARR = CER – EER

Consider 100 people given this treatment. We would expect 27 fewer children to have epistaxis if this group were given Naseptin than if they were not. We can convert this into how many people we would need to treat to prevent one child continuing to have epistaxis. This number is the reciprocal of the ARR. In this example 1/0.27 = 3.7. Therefore, to prevent a child continuing to have epistaxis we need to treat four people. This is the number needed to treat (NNT). It is more useful than relative measures because, as well as measuring the benefit of a therapy, it also represents the baseline risk and the absolute benefit you can expect from the therapy.

NNT = 1/ARR

Sometimes, papers will present their results in the form of NNTs, as in this one, which is very helpful, but often they do not, and prefer to present risk ratios (perhaps not surprisingly, since these tend to make beneficial results look more spectacular) or similar measures. You will often be required to calculate NNTs from the data in the study. Fortunately, the arithmetic is fairly straightforward. Some other examples of NNTs are included in Bandolier (http://www.bandolier.org.uk/band59/NNTcalc.html).

This is a small study and like the relative risk there is a confidence interval around the NNT. To calculate this[18] it is easier to use software (www.ebm.net). Also, there is the 'believability' issue of a relatively small trial. This is where the clinical judgement comes in – would you use this treatment based on 100 patients?

Will the results help my patient?

- Can the results be applied to my patient?
- Were all clinically relevant outcomes considered?
- Are the benefits worth the harms and costs?

Given that your patient was not in the trial and may not even have been eligible for it (due to age, sex, comorbidity, disease severity or for a host of other sociodemographic, biologic or clinical reasons), how can you extrapolate from the external evidence to your individual patient? (We use the term 'extrapolate' here, although this might more accurately be described as 'particularizing' the results of a trial (which looks at a generic population) to your particular patient.) This requires that you apply some of your knowledge of human biology and clinical experience to answer the question: 'Is my patient so different from those in the trial that its results cannot help me make my treatment decision?'

When analyzing the results of a trial it is important therefore to identify whether the trial has been designed to be explanatory or pragmatic in its approach. The former is often used to test whether the intervention works under ideal conditions – often in a highly selected cohort. This design may also be able to quantify the magnitude of any effect. A pragmatic design on the other hand often has much less strict inclusion criteria and consequently much more closely represents a 'real world' scenario. The results of a pragmatic trial may be more easily translated into a likely benefit for your particular patient.

HOW MUCH BENEFIT CAN YOU EXPECT FOR YOUR PATIENT?

Given that you have decided that your patient is sufficiently similar to those in the study for the effect to be applicable, the next questions is how much? Here is one way of going about this.

f method

First estimate, as a decimal fraction, your patient's risk compared to the control group from the study. Thus, if your patient is twice as susceptible as those in the trial, $f = 2$; if half as susceptible, $f = 0.5$. As long as the treatment produces a constant RRR across a range of susceptibilities, the NNT for your patient is simply the trial's reported NNT divided by f. (This is a big assumption and we are

only beginning to learn when assuming a constant RRR is appropriate (for numerous medical treatments such as antihypertensive drugs) and inappropriate (for some operations such as carotid endarterectomy, where the RRR rises with increasing susceptibility). So, in the above example, we might assign an f of 0.7 (70% chance of having epistaxis to the control group of subjects), which would yield an NNT of $(3.7/0.7) = 5$.

INCORPORATING YOUR PATIENT'S VALUES AND PREFERENCES

What does your patient think? Have you talked to them about their personal preferences, concerns and expectations? Here, we must try to determine whether the outcome of the therapy actually serves the values and preferences of the patient. Many factors can come into play, not least the difficulty of representing them. Sometimes, the situation may be very clear-cut or demand immediate action. For example, in a patient having a heart attack, the value of survival and the preference for a simple, low-risk intervention such as aspirin, given the efficacy of this regimen, usually makes this decision quickly agreed and acted upon. In other cases, the answer may take weeks and several visits to sort out, such as in choosing between radiation and adjuvant chemotherapy for stage II carcinoma of the breast.

These questions are perhaps the most important, yet have the least written about them in this chapter. That is because they are also the most complex and depend to a great extent on the clinical situation.

Summary

An evidence-based approach to deciding whether a therapy is effective for your patient involves the following steps:

- Frame the clinical question.
- Search for evidence concerning the accuracy of the test.
- Assess the methods used to carry out the trial of the therapy.
- Determine the NNT of the therapy.
- Decide whether the NNT can apply to your patient, and estimate a particularized NNT.
- Incorporate your patient's values and preferences in to deciding on a course of action.

APPRAISING SYSTEMATIC REVIEWS

What happens when there is more than one randomized control trial on the same treatment or diagnostic test? In this case you want to look for a paper that has combined these trials together.

What you need here is a systematic review, a publication that collects all of the evidence in a particular area and summarizes it. More formally, a systematic review is 'a review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research, and to collect and analyze data from studies that are included in the review. Statistical methods may or may not be used to analyze and summarize the results of the included studies.'

This section will look at how you appraise studies that search for all research on a specific question and in some way combine it.

You may be familiar with the narrative reviews traditionally found in many journals. Normally someone, usually an expert, looks at the evidence in a certain area. Mulrow[19] argues that traditional reviews do not routinely use systematic methods to identify, assess and synthesize information. Thus, normally there is no methods section for the actual conduct of the review. The reader then has no way of knowing whether the review is based on a systematic review of the evidence, or on a collection of papers that the author has found in a less systematic way and thus the evidence presented may not be complete. There is a need for systematic reviews of the evidence. This needs to be undertaken in just as rigorous a way as any primary piece of research, with a clear question and explicit methods for all stages of the process, such that another person could replicate the review. Three key features of such a review are:

- a strenuous effort to locate all original reports on the topic of interest
- critical evaluation of the reports
- conclusions drawn based on a synthesis of studies that meet preset quality criteria.

When synthesizing results, a meta-analysis may be undertaken. This is 'the use of statistical techniques in a systematic review to integrate the results of the included studies', which means that the authors have attempted to synthesize the different results into one overall statistic.

Where can you find systematic reviews?

Systematic reviews have been published in a variety of journals, and in addition the Cochrane Collaboration provides an important resource in this area. The Cochrane Collaboration is an international collaboration that is committed to 'preparing, maintaining and disseminating systematic reviews of the effects of health care'. It promotes and publishes the Cochrane Library (www.cochrane.org). This contains the Cochrane Database of Systematic Reviews. These reviews have a prespecified protocol, where every stage of the process of undertaking the review is made explicit.

Sections covered in a protocol include background, objectives, criteria for considering studies for the review (including types of participants, types of interventions, types of outcome measure, types of study), search strategy for identification of studies, study selection, methodological quality assessment, data extraction, meta-analysis, the comparisons to be made, subgroup analysis and sensitivity analysis to be undertaken. The point to note here is that all these aspects of the protocol are set out before the review is undertaken. The PRISMA guidelines are freely available online (www.prisma-statement.org) and contain a checklist to assist when performing a systematic review.

Many journals now require adherence to these guidelines and will ask for the article to be peer reviewed against them.

Many of the systematic reviews so far completed are based on evidence of effectiveness of an intervention from RCTs.

Is the review valid?

In this section we will focus on systematic reviews of therapy. Of course, systematic reviews exist for other types of research.[20]

- **What databases and other sources did the authors of this review search?** The paper should give a comprehensive account of the sources consulted in the search for relevant papers, and the search strategy used to find them. Since standard databases fail to correctly index up to half of published trials, and negative trials are less likely to be published in the first place, the search strategy should include hand searching of journals and searching for unpublished literature. Other questions to ask yourself about the search strategy are: Have any obvious databases been missed? Did the authors check the reference lists of articles and of textbooks? Did they contact experts (to obtain their list of references checked for completeness and to attempt to find out about ongoing or unpublished research)? Search terms used are also important – has an obvious medical subject heading (MeSH) (a standard thesaurus for medical indexing) term been missed or is there another term they have not used? For example, when searching for papers looking at care of the elderly, use of the term 'senior' in the North American literature may be overlooked. Searching should include languages other than English. Unpublished data are useful to include because studies with significant results are more likely to be published than studies without significant results, known as publication bias. For example, research that is carried out by non-English language teams is more likely to be published in English if it shows a strong result in favour of an intervention than if it shows a negative or indifferent result.
- **How were the studies selected – eligibility criteria?** You should look for a statement of how the trial's validity was assessed, using criteria such as those in the therapy guides. It is particularly reassuring when two or more investigators applied these criteria independently and achieved good agreement in their results. You need to know what criteria were used to select the research. This should include who the study participants were, what was done and what outcomes were assessed. A point to consider is that the narrower the inclusion criteria, the less generalizable are the results. However, this needs to be balanced with using very broad inclusion criteria, when heterogeneity becomes an issue. Such studies may cover a wide range of patients and/or interventions and/or outcomes and the justification for then combining these differing groups comes into question. The importance of a clear statement of inclusion criteria is that studies should be selected on the basis of these criteria (that is, any study that matches these criteria is included) rather than selecting the study on the basis of the results.
- **How were the data abstracted?** Data are usually obtained by two individuals working separately (independently) and then compared later. Where consensus between reviewers cannot be reached it is customary for a third reviewer to act as arbiter. Often the data are not available within the paper and there may be a statement about obtaining the raw data from the authors.
- **Is there a description of the quality of each trial?** A table of the studies meeting the inclusion criteria should include some data on the validity checks itemized in the section on randomized control trials.[4]
- **Were the results consistent from study to study?** Although we might expect some variation from study to study, we would be concerned if some trials confidently concluded a beneficial effect of the therapy, while others confidently concluded harmful or no effects. Unless this heterogeneity can be explained to your satisfaction (such as by differences in patients, dosage or duration of treatment), this should lead you to be very cautious about believing any overall conclusion about efficacy from the review.

Statistical heterogeneity exists when there is greater variation between the results than is likely due to chance. The chi-square statistic on which they are based has on average a value equal to its degrees of freedom. Values much larger than the degrees of freedom suggest a smaller p value and thus significant statistical heterogeneity. This means greater variation exists between the studies than is likely by chance alone. One might then conclude that the studies are so different that it makes no sense to combine them. Since this test of heterogeneity is described as having a low power, a non-significant test cannot be interpreted as evidence of homogeneity. The aim of the authors should be to clearly describe the influences of specific clinical differences between the studies, rather than purely relying on an overall statistical test of heterogeneity.

Clinical and statistical heterogeneity need to be distinguished. Clinical heterogeneity refers to differences between settings, patients, techniques and outcomes, which might lead you to suggest it does not make sense to combine the data.

What are the results?

Terms that you will probably come across when looking at systematic reviews include odds ratios, relative risks, weighted mean differences and fixed and random effects, amongst others.

BINARY OR CONTINUOUS DATA

The type of data will dictate what you see when you look at a meta-analysis:

- binary data (for example, an event rate: something that happens or it does not, such as myocardial infarction, stroke, improved/not improved) is usually combined using odds ratios

- continuous data (for example, numbers of days, peak expiratory flow rate) are combined using differences in mean values for treatment and control groups (weighted mean differences (WMDs)) when units of measurement are the same (for example, all using the same anxiety scale), or standardized mean differences when units of measurement differ (for example, using a variety of anxiety scales, where one numerical value could mean very different things, depending on the scale used). Here, the difference in means is divided by the pooled standard deviation.

Thus when you look at a meta-analysis, you will see odds ratios or relative risks and/or weighted mean differences or standardized mean differences, depending on the outcomes measures that have been used in the included studies.

ODDS RATIO

Odds are another way of describing risk. The odds of an event are the probability of it occurring compared to the probability of it not occurring. We cannot do a randomized control trial to assess whether gastrooesophageal reflux disease (GERD) may be associated with laryngeal neoplasm. However, we can do a case-control study looking at people with and without cancer.[21]

We do not know the incidence of laryngeal cancer in the population from this study as they took cases with cancer and compared them to controls, but we can work out the odds (Table 44.5). For GERD, the odds of having cancer is 731/1315 = 0.555. This clearly is not the risk in the general population! The odds of having laryngeal cancer in non-GERD patients was 0.237. The odds ratio was 0.555/0.237 = 2.3. So patients with GERD in this study had 2.3 times the odds of having laryngeal carcinoma. This was unadjusted for the other major risk factor of smoking. In large studies, odds ratios approximate risk ratio.

Clearly, as in randomized controlled trials with risk reduction, unless we know the baseline risk it is impossible to put odds ratios into context. A number needed to treat can be derived from an odds ratio but remember that many assumptions have been made in that process and treat them with some caution.

Many systematic reviews use odds ratios to represent differences between treatment and control groups. Relative risk and absolute risk reduction may also be used to express these sorts of differences, as we have already seen.

TABLE 44.5 Prevalence of gastrooesophageal reflux disease (GERD) in a case control study of patients with and without laryngeal cancer

	GERD	No GERD
Laryngeal cancer	731	7497
No laryngeal cancer	1315	31,597
Total	2046	39,094

WHAT DO ODDS RATIOS USED IN A META-ANALYSIS LOOK LIKE?

The square box on the Forrest Plot (Figure 44.3) is the individual study effect (technically referred to as the point estimate), with its associated confidence interval as lines either side of that box (technically known as the interval estimate). Sometimes the size of the box may vary to reflect the weight that particular study is given, with larger boxes representing higher weighting. Lower weighted studies are usually those with smaller samples and large confidence intervals. The overall or summary effect (from combining or pooling the studies) is usually depicted as a diamond. Since patients may respond differently to treatment, this pooling may need to be supplanted by summarizing evidence along multiple covariates of interest. Thus, although one overall number is appealing in its simplicity, it may oversimplify a more complex situation.

An odds ratio of 1 on a linear scale means there is no difference between the experimental and control group. This value of 1 is the line down the middle of the figure (sometimes with the wording 'favours treatment' on one side and 'favours control' on the other). If the confidence interval does *not* cross the line, it means that there is a 95% chance that there is a true difference between the groups. That is, that there is a significant difference on that particular outcome between the intervention and control groups. If the confidence interval does cross this vertical line labelled '1' it means that any difference in that outcome between the treatments could have occurred by chance (that is, there are no statistically significant differences). It may be that a very wide confidence interval is due to a very small sample size, and it would reduce with more people in the study. A 95% confidence interval covers likely results from a set of similar studies. It therefore provides a more realistic view of what will happen in practice than a point estimate, because it takes potential variability into account.

It is worth noting that a lack of evidence for an intervention is not the same as evidence of a lack of effect.

HOW PRECISE ARE THE RESULTS?

This is asking whether there are any confidence intervals used, so the reader can see the range of values around the effect size, where one has 95% confidence that the 'true' effect would lie. The *Cochrane Handbook* (2011)[22] defines precision as 'a measure of the likelihood of random errors. It is reflected in the confidence interval around the estimate of effect from each study … more precise results are given more weight'. Thus the more precise the results, the narrower (smaller) the confidence interval. NNTs can be calculated from the odds ratios. However, these should be treated with caution as they can oversimplify.

WILL THE RESULTS HELP ME IN CARING FOR MY PATIENTS?

- **Can the results be applied to my patient care?** How similar are the patients you care for to those included in the review? The wider the type of patients included

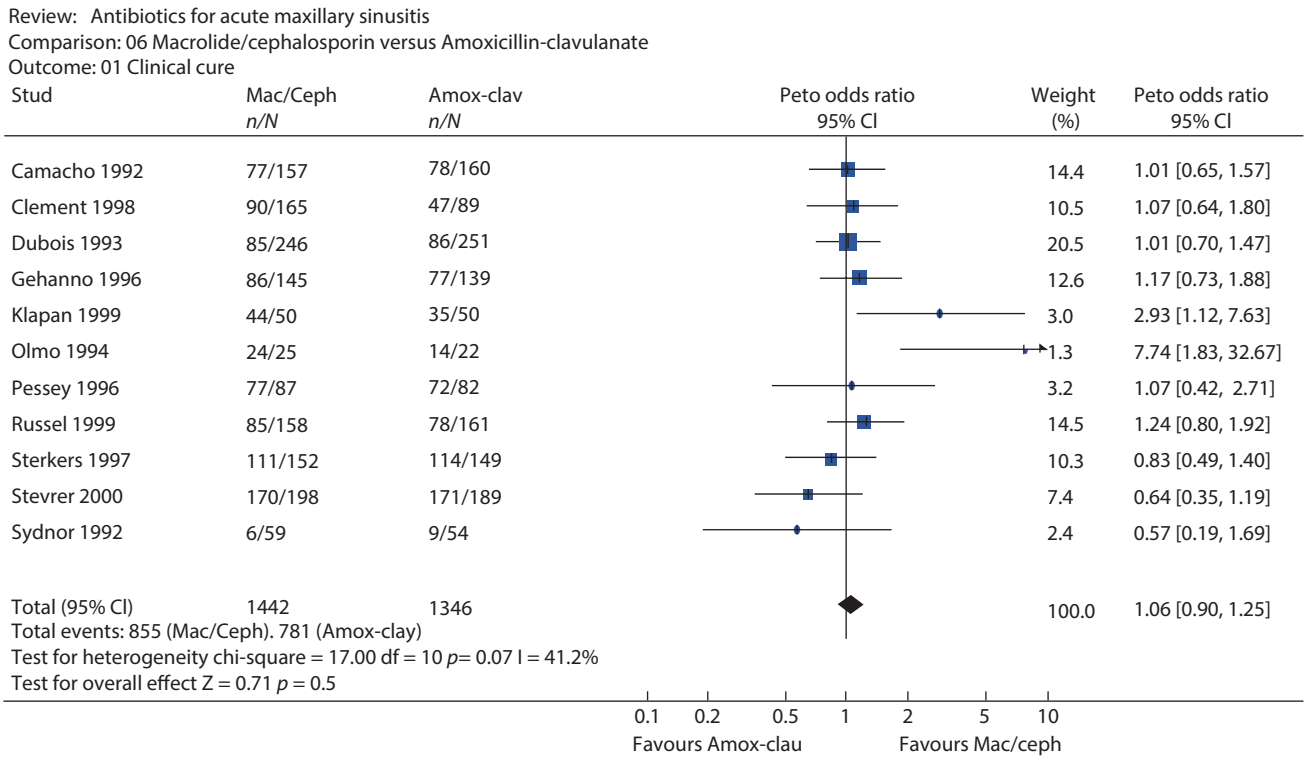


Figure 44.3 A Forrest plot. Redrawn from Ref. 23, with permission.

in the review, the more likely you are to feel the results may apply across a range of different patients. However, it is sometimes a difficult decision to know whether, for example, something that works on men will be equally effective on women, or something that works in younger people will work in the same way in older people. Subgroup analysis may be one way of addressing this, although there are concerns with this approach.

- **Were all clinically important outcomes considered?** What is clinically important can depend on your perspective. Sometimes, whilst factors such as bone density may be included in a review to assess the effectiveness of certain orthopaedic procedures, it may be some other outcome, such as ability to get to the shops, that needs to be considered as this sort of outcome may be crucial from the patient's perspective.
- **Are the benefits worth the harms and costs?** This may cover a range of factors, such as benefit of early treatment following a positive cervical smear versus the harms of high anxiety. Or it may be the benefits of a chemotherapeutic agent versus its unpleasant side effects. An economic evaluation may be included.

What is sometimes difficult using a set of criteria like this, is that you end up with a variety of 'no's' or 'can't tell's' in answer to the questions you pose. It is sometimes difficult to decide when a review is 'too bad' to give you any confidence in the findings. Perhaps one pragmatic approach would be that when you have several 'no's' or 'can't tell's' you are more wary about the validity and robustness of the review's findings. What this does illustrate is that, like undertaking a systematic review, critically appraising these reviews is not an exact science, but there are many subjective decisions along the way. Just like undertaking a systematic review, making explicit your decisions in the critical appraisal is therefore very important.

Although a systematic review can provide you with high quality evidence, clinical experience and patient preferences are an important part of evidence-based medicine. It may be that even high quality evidence does not apply to a particular patient. Similarly, Cochrane reviews do not include recommendations, as reviewers cannot know the local situation or the patient, and this is the province of the health professional caring for the patient.

Levels of evidence

Table 44.6 provides a breakdown of the types of research that answers questions on therapy, prognosis, diagnosis, differential diagnosis or prevalence and economic studies. For each type of research a level of evidence is shown. This helps the reader identify the likely validity of the research. It does not mean that all systematic reviews are 'better' than randomized controlled trials. It should be used more as a pointer for searching and then a guide to the likely level of evidence. If one has a therapeutic question then looking for a systematic review first is logical. If there is no review then one next looks for a randomized controlled trial, etc.

If there is no trial evidence then consensus statements becomes the highest level of evidence answering that question. This just makes the grade of recommendation D rather than A if there was a systematic review. The grades

TABLE 44.6 Levels of evidence

Level	Therapy/prevention, aetiology/harm	Prognosis	Diagnosis	Differential diagnosis/ symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity)[a] of RCTs	SR (with homogeneity)[a] of inception cohort studies; CDR[b] validated in different populations	SR (with homogeneity)[a] of Level 1 diagnostic studies; CDR[b] with 1b studies from different clinical centres	SR (with homogeneity)[a] of prospective cohort studies	SR (with homogeneity)[a] of level 1 economic studies
1b	Individual RCT (with narrow Confidence interval)[c]	Individual inception cohort study with >80% follow-up; CDR[b] validated in a single population	Validating[k] cohort study with good[h] reference standards; or CDR[b] tested within one clinical centre	Prospective cohort study with good follow-up[c]	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none[d]	All or none case-series	Absolute SpPins and SnNouts[g]	All or none case-series	Absolute better-value or worse-value analyses[j]
2a	SR (with homogeneity)[a] of cohort studies	SR (with homogeneity)[a] of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity)[a] of Level >2 diagnostic studies	SR (with homogeneity)[a] of 2b and better studies	SR (with homogeneity)[a] of level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR[b] or validated on split-sample[f] only	Exploratory[k] cohort study with good[i] reference standards; CDR[b] after derivation, or validated only on split-sample[f] or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	'Outcomes' research; Ecological studies	'Outcomes' research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity)[a] of case–control studies		SR (with homogeneity)[a] of 3b and better studies	SR (with homogeneity)[a] of 3b and better studies	SR (with homogeneity)[a] of 3b and better studies
3b	Individual case–control study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations
4	Case-series (and poor quality cohort and case–control studies)[e]	Case-series (and poor quality prognostic cohort studies)[l]	Case–control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'	Expert opinion without explicit critical appraisal, or based on economic theory or 'first principles'

The levels of evidence used throughout this book are as stated in the prelims on the How to use this book page. These are very similar to the five levels given in this table, except that Levels 3 and 4 of the system described in this table are equivalent to Level 3, and Level 5 (expert opinion) is equivalent to Level 4 in the system used in this book.

Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes and Martin Dawes since November 1998.

Users can add a minus sign '–' to denote the level of that fails to provide a conclusive answer because of:

- EITHER a single result with a wide confidence interval (such that, for example, an ARR in an RCT is not statistically significant but whose confidence intervals fail to exclude clinically important benefit or harm).
- OR a systematic review with troublesome (and statistically significant) heterogeneity.
- Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

[a] By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a '–' at the end of their designated level.

[b] Clinical decision rule. (These are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category.)

[c] Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (e.g. 1 to 6 months acute, 1 to 5 years chronic).

[d] Met when *all* patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but *none* now die on it.

[e] By poor quality *cohort* study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality *case–control* study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.

[f] Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into 'derivation' and 'validation' samples.

[g] An 'Absolute SpPin' is a diagnostic finding whose Specificity is so high that a Positive result rules-*in* the diagnosis. An 'Absolute SnNout' is a diagnostic finding whose Sensitivity is so high that a *Negative* result rules out the diagnosis.

[h] Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.

[i] Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. *Poor* reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.

[j] Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.

[k] Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.

[l] By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in < 80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.

TABLE 44.7 Grades of recommendation

A	Consistent level 1 studies
B	Consistent level 2 or 3 studies **or** extrapolations from level 1 studies
C	Level 4 studies **or** extrapolations from level 2 or 3 studies
D	Level 5 evidence **or** troublingly inconsistent or inconclusive studies of any level

'Extrapolations' are where data are used in a situation that has potentially clinically important differences than the original study situation.

of recommendations vary from country to country and organization to organization and should only be considered as a guide (Table 44.7).

WORKSHEETS

The worksheets shown in Figures 44.4, 44.5 and 44.6 can be used to appraise a randomized controlled trial, a diagnostic study or a systematic review. They are aide memoirs about the items to look for in a paper when appraising the validity, identifying the results and assessing the applicability.

They can be used in journal clubs or in other settings when an important new paper is being discussed. The data from these checklists can be entered into software to make your own electronic database of critical appraisals and saved as web pages or text documents.

KEY POINTS

Appraising diagnostic articles

- Criteria for validity of diagnosis trials: was there a reference standard, was it appropriate and was it applied blind, independently and to all patients?
- Appropriate spectrum of patients; clear and reproducible description of test, follow-up, intention-to-treat.
- Outcome measures.
- Measures of the accuracy of diagnostic tests: sensitivity, specificity, positive predictive value negative predictive value, likelihood ratios.
- Applying the results to your patient: pre- and post-test probability, SpPin and SnNOut.

Appraising therapy articles

- Criteria for validity of therapy trials: randomization, blinding, placebo control, equal treatment, follow up, intention-to-treat, outcome measures.
- Measures of the importance of the results of therapy trials: risk, event rates, NNTs.

Appraising systematic reviews

- Criteria for validity of systematic reviews: search for relevant trials, assessment of included trials' quality, heterogeneity.
- Measures of the importance of the results: risk, event rates, NNTs, odd ratios.

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The answer:

Are the results of this single preventive or therapeutic trial valid?

PICO QUESTION	
Search terms used	
Databases searched to find this article	
Citation of article	
Why did you select this article(s)?	
Did the authors answer the question?	
1. What were the characteristics of the patients?	
2. Were the groups similar at the start of the trial?	
3. Aside from the experimental treatment, were the groups treated equally?	
4. What was the treatment and what was it compared against (placebo)?	
5a. Was the assignment of patients to treatments randomized? 5b. and was the randomization list concealed?	
6a. Were all patients who entered the trial followed up at its conclusion? 6b. and were they analyzed in the groups to which they were randomized (Intention to treat)?	
7. Were patients and clinicians kept 'blind' to which treatment was being received?	
8. Was the length of study appropriate?	

Are the valid results of this randomized trial important?

YOUR CALCULATIONS:

		Absolute risk reduction (ARR)	Number needed to treat (NNT)	Relative risk reduction (RRR)
Control group rate (CER)	Experimental Group Rate (EER)	CER-EER	1/ARR	ARR/CER

95% Confidence Interval (CI) on an NNT = 1/(limits on the CI of its ARR) =

$$+/-1.96 \sqrt{\frac{\text{CER} \times (1-\text{CER})}{\text{No. of control pts.}} + \frac{\text{EER} \times (1-\text{EER})}{\text{No. of exp. pts.}}} =$$

Can you apply this valid, important evidence about a treatment in caring for your patient?

Do these results apply to your patient?	
Is your patient so different from those in the trial that its results cannot help you?	
How great would the potential benefit of therapy actually be for your individual patient?	
Method I: f	Risk of the outcome in your patient, relative to patients in the trial. expressed as a decimal: _____ NNT/F = _____/_____ = _____ (NNT for patients like yours)

Are your patient's values and preferences satisfied by the regimen and its consequences?

Do your patient and you have a clear assessment of their values and preferences?	
Are they met by this regimen and its consequences?	

Figure 44.4 Randomized control trial worksheet.

The Answer:

Are the results of this diagnostic study valid?

PICO QUESTION	
Search terms used	
Databases searched to find this article	
Citation of article	
Why did you select this article(s)	
Did the authors answer the question?	
1. What were the characteristics of the patients?	
2a. New diagnostic test description. Is it clear how the test was carried out? 2b. Is the test reproducible in your setting?	
3a. Gold standard description. 3b. Was there an independent, blind comparison with a reference ('gold') standard of diagnosis?	
4. Was the reference standard applied regardless of the diagnostic test result?	
6. Was the diagnostic test evaluated in an appropriate spectrum of patients (like those in whom it would be used in practice)?	

YOUR CALCULATIONS:

		Target disorder		Totals
		Present	Absent	
Diagnostic test result	Positive	a	b	a + b
	Negative	c	d	c + d
	Totals	a + c	b + d1770	a + b + c + d

Sensitivity = a /(a + c) =
Specificity = d/(b + d) =
Likelihood ratio for a positive test result = LR+ = sens/(1−spec) =
Likelihood ratio for a negative test result = LR−= (1−sens)/spec =
Positive predictive value = a /(a + b) =
Negative predictive value = d/(c + d) =
Pre-test probability (prevalence) = (a + c)/(a + b + c + d) =
Pre-test-odds = prevalence/(1−prevalence) =
Post-test odds = Pre-test odds x likelihood ratio =
Post-test probability = post-test odds/(post-test odds + 1) =

Can you apply this valid, important evidence about a diagnostic test in caring for your patient?

Is the diagnostic test available, affordable, accurate and precise in your setting?	
Can you generate a clinically sensible estimate of your patient's pre-test probability (from practice data, from personal experience, from the report itself or from clinical speculation)	
Will the resulting post-test probabilities affect your management and help your patient? (Could it move you across a test-treatment threshold?; Would your patient be a willing partner in carrying it out?)	
Would the consequences of the test help your patient?	

Additional notes:

Figure 44.5 Diagnosis worksheet.

The Answer:

Are the results of this systematic review of therapy valid?

PICO QUESTION	
Search terms used	
Databases searched to find this article	
Citation of article	
Why did you select this article(s)?	
Did the authors answer the question?	
1. What databases and other sources did the authors of this review search?	
2. What were their eligibility criteria (inclusion and exclusion) for papers in this study? Do these seem appropriate?	
3. Was their independent data extraction of the results by the reviewers (then compared later)?	
4. Is there a description of the quality of each trial included?	
5. Were the results consistent from study to study (Homogeneous)?	

Are the valid results of this systematic review important?

What was the odds ratio?	
What was the control group rate (PEER)	

Can you apply this valid, important evidence from a systematic review in caring for your patient?

Do these results apply to your patient?	
Is your patient so different from those in the overview that its results cannot help you? How great would the potential benefit of therapy actually be for your individual patient?	
To calculate the NNT for any OR and PEER $\text{NNT} = \dfrac{1 - (PEER^{*}(1 - OR))}{(1 - PEER) * PEER^{*}(1 - OR)}$ Or use calculator from www.cebm.net	

Are your patient's values and preferences satisfied by the regimen and its consequences?

Do your patient and you have a clear assessment of their values and preferences?
Are they met by this regimen and its consequences?
Should you believe apparent qualitative differences in the efficacy of therapy in some subgroups of patients? Only if you can say 'yes' to all of the following:
Do they really make biologic and clinical sense?
Is the qualitative difference both clinically (beneficial for some but useless or harmful for others) and statistically significant?
Was this difference hypothesized before the study began (rather than the product of dredging the data), and has it been confirmed in other, independent studies?
Was this one of just a few subgroup analyses carried out in this study?

Additional notes:

Figure 44.6 Systematic review (of therapy) worksheet.

CHAPTER 45

ELECTROPHYSIOLOGY AND MONITORING

Patrick R. Axon and Bruno M.R. Kenway

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: intra-operative monitoring, facial nerve, cranial nerve and auditory evoked potentials.

DEVELOPMENT OF FACIAL NERVE MONITORING

The first description of intra-operative cranial nerve stimulation was by Fedor Krause in 1898.[1] During cochlear nerve section for tinnitus, he noted 'unipolar faradic stimulation of the (facial) nerve-trunk with the weakest possible current of the induction apparatus resulted in contractions of the right facial region, especially of the orbicularis oculi, as well as the branches supplying the nose and mouth'. Over the next three-quarters of a century, a series of articles refined the technique, all relying on observing movement of the face in order to confirm the functional integrity of the facial nerve.[2–7] The evoked facial twitch was observed by either the anaesthetist or ancillary staff under the drapes using a flashlight or mirror. These techniques lacked both quantitative control of the stimulus and objective recording of the evoked responses.

In 1979, Delgado and colleagues first described the use of evoked compound muscle action potentials (CMAP) to monitor facial nerve function in response to stimulating the intra-cranial portion of the facial nerve.[8] The introduction of facial electromyography (EMG) enabled not only facial nerve identification either by electrical stimulation or inadvertent manipulation, but also the possibility of mapping its course through the temporal bone and assessing changes in function during surgical resection of tumour from the nerve's surface.[9] Facial nerve monitoring has proved an invaluable aid during vestibular schwannoma surgery.[10–12] The introduction of an auditory signal enabled instantaneous real-time auditory feedback to the surgeon during tumour dissection without information passing through an intermediary.[13, 14]

Three trials tested the hypothesis that facial nerve outcome improved when using intra-operative facial nerve monitoring. Harner and colleagues[12] demonstrated the usefulness of facial nerve monitoring in 91 consecutive cases of vestibular schwannoma resection via the suboccipital route. At 1 year, 78% of those patients who were monitored demonstrated facial function, compared with 65% in an unmonitored group, these data were not studied statistically. Niparko and colleagues[15] described the results of 29 patients who underwent translabyrinthine removal of vestibular schwannoma and compared them with a similar group of 75 unmonitored patients. They demonstrated that monitoring was associated with a significant improvement of facial function at 1 year for tumours over 2 cm intra-cranial diameter. Kwartler and colleagues[16] demonstrated that monitored patients with tumours over 2.5 cm had a significant improvement of facial function when compared with a matched unmonitored group.

The benefit of facial nerve monitoring during surgery for chronic middle ear disease is less certain. Facial nerve injury after otological surgery is rare in experienced hands and there are no randomized controlled trials examining its efficacy. Silverstein and others recommend that

the facial nerve should be monitored during all general anaesthetic cases where the facial nerve is at risk.[17, 18] This view is in contrast to most American otolaryngologists, although those who trained in the 1990s, those in an academic setting and those who perform more otology than other types of surgery are more likely to use monitoring techniques.[19, 20] Hu et al. reported a survey that showed an increase in the number of surgeons who felt that facial nerve monitoring should be used as a standard of care from 32% in a similar study performed 10 years previously, to 49% in their more recent survey group.[21] This proportion is thought to be higher in the UK and Australia, however.[22]

Increasing usage of nerve monitors has implications for litigation cases. In general such cases question whether a reasonable body of practitioners would employ a nerve monitor during surgery (Bolam test). If any such body is likely to recommend use of monitoring, then failure to use a monitor would likely become indefensible, as breach of duty could be established. The principle remains, however, that if any adverse outcome would have occurred regardless of the lack of nerve monitoring, then the claim would fail. The claimant must therefore establish causation. At the time of writing, a freedom of information request from the NHS litigation authority had identified 15 claims for facial nerve injury during otological surgery from 2003 to 2013, 9 of which had been successful with total damages claimed of £488,571.

Facial nerve injury often occurs when there is an unexpected change to normal middle ear anatomy, precisely the time when monitoring is so valuable. The senior surgeon must take responsibility to ensure that the equipment is functioning normally. A simple technique for confirming equipment function is described under 'Technique for continuous facial nerve monitoring' below. Intra-operative facial nerve monitoring is no substitute for experience in the otological setting and should not replace good surgical practice, but if the operating team adopt the approach that all patients are monitored, the set-up technique becomes routine and more reliable. With developments in robotic surgery, investigators have evaluated facial nerve monitoring systems that have been integrated into the drill system, to determine whether such systems could reliably warn of impending facial nerve contact during robot-assisted direct cochlear access procedures. At present, however, such systems lack sensitivity and repeatability.[23]

TECHNIQUE FOR CONTINUOUS FACIAL NERVE MONITORING

The operating theatre is filled with electrical interference generated by the equipment surrounding the anaesthetized patient. Monitoring techniques have developed to minimize this interference and amplify only relevant information. Two sets of subdermal platinum or stainless steel needle recording electrodes are inserted into the upper and lower face. The electromyographic electrical response is biphasic (as electrical potential moves past one electrode it becomes negatively charged compared to its paired neighbour, until it reaches that electrode and the situation reverses). The amplifiers amplify the difference between the potentials recorded at each electrode. This arrangement has the advantage of common mode rejection; electrical interference from other sources is recorded by both electrodes equally and therefore does not create a potential difference between the two closely aligned electrodes. A number of commercial EMG cranial nerve monitoring systems are now available including the NIM-2 (Xomed Treace, Jacksonville, FL, USA) and the Neurosign (Magstim, Whitland, UK). They rely on recording facial muscle activity and delivering the information as a visual and audible representation of the CMAP response. The audible response is presented as either raw EMG activity or a characteristic sound when EMG activity reaches a set threshold.

All systems are isolated and self-contained electrical nerve stimulator and monitoring units. The electrodes are connected to a preamplifier pod, which is attached to the operating table. The recorded electrical signal is filtered through high- and low-pass filters and either rectified and displayed on a logarithmic bar chart or presented as a CMAP waveform. Different systems use different methods of presenting the same information to the surgeon. The logarithmic bar chart has a delayed response decay to enable calculation of rectified CMAP amplitude. Systems that present a CMAP waveform present it as visual and audible real-time information or utilize image capture strategies that also give waveform amplitude information. This allows the surgeon time to examine the waveform and size of the CMAP. So-called 'repetitive responses' occur as a result of repetitive depolarizations after surgical manipulation has ended. They can be used as a measure of nerve irritability as a result of early damage (e.g. from thermal injury). Compare this with non-repetitive responses that are indicative of direct mechanical stimulation of the nerve.

Familiarity with the set up and function of a chosen monitoring system is essential. The senior surgeon must take responsibility and should check that the equipment is functioning normally. Tapping the skin overlying the two sets of subdermal electrodes will generate a recorded response on the monitor. This confirms that electrodes are connected to the preamplifier pod and in turn the preamplifier pod is connected to the monitor, which is switched on. The volume should be checked so that a response is audible over background theatre noise.

Facial nerve stimulation is delivered as a short (0.1 ms) electrical pulse. This is the default setting for most monitors. The stimulating electrode is either monopolar or bipolar. The monopolar electrode is favoured because it is simple to use, but has the disadvantage of stimulating a larger area. The bipolar electrode requires careful positioning of both electrode tips on to the tissue surface; this can prove difficult in the tight confines of the temporal bone. The use of constant voltage stimuli has an advantage over constant current stimuli because it delivers a relatively reliable current to the nerve whatever the medium that surrounds the nerve. In 2013 the American Society of Neurophysiological Monitoring established a position statement on intra-operative motor evoked potential

monitoring, based upon best available evidence,[24] which included guidelines on proper usage, interpretation and general anaesthesia use in a variety of clinical settings including facial nerve monitoring. Regarding general anaesthesia, Choe et al. also concluded that induction of total intravenous anaesthesia with propofol and remifentanil provided reliable conditions for facial nerve monitoring during complex ear surgery.[25]

PREDICTING POST-OPERATIVE FACIAL FUNCTION

A number of studies have described an objective technique that correlates parameters of the evoked CMAP to eventual facial outcome.[15, 26–29] The test gives non-dichotomous results and therefore a retrospective cut-off point is used to predict those patients who have a good prognosis. Results indicate that a low stimulation threshold, across the site of tumour dissection, is a valuable prognostic indicator of good long-term facial function. The technique, which is simple to perform, assesses the minimum current required to evoke a muscle response after tumour resection. The drawback to the described technique is that the majority of patients have some degree of facial function immediately after surgery. This group will almost certainly have good long-term outcome.[30] It is the small group of patients with poor facial function immediately after surgery that will benefit most from a sensitive and specific predictive test. Axon and Ramsden compared post-dissection minimal stimulation thresholds with immediate post-operative facial function for predicting long-term facial function in 184 patients undergoing vestibular schwannoma surgery.[30] Post-dissection stimulation thresholds demonstrated only a moderate relation to eventual outcome, which was of limited clinical value. The test criteria were then applied to patients with poor immediate post-operative facial function for predicting long-term outcome; the predictive accuracy fell, further reducing test validity.

Some studies compared the supramaximal CMAP to either facial nerve stimulation proximal and distal to tumour dissection or before and after tumour dissection. These techniques have been advocated as more accurate methods of analysing data, because they remove absolute amplitude comparisons and rely on comparison of ratios.[31, 32]

DIFFICULTIES OF MONITORING FACIAL FUNCTION

All otological procedures rely on a facial muscle response, warning the surgeon that the facial nerve is near. A simple audible noise is all that is required. Recent monitoring systems have increased the amount of information available to the surgeon, stimulating the desire to expand monitoring techniques and so improve patient outcome. This information is superfluous to most procedures and of benefit to only a few. Facial CMAPs represent a complicated interplay between groups of muscle fibres depolarizing in response to facial nerve stimulation. The muscles of the face are very different to those found in the limbs. The facial motor units are small, often having only 25 muscle fibres supplied by each motor neuron compared with many thousands in more peripheral muscles. As a consequence, each muscle has a wide, ill defined motor endplate zone. The muscles are also arranged in an almost haphazard arrangement, overlying each other and aligned in different directions. This makes meaningful electrophysiological recording difficult. Intra-subject variability (test-retest variability) is high and intersubject comparison almost impossible. The CMAP waveform is usually multiphasic instead of the well-recognized biphasic responses recorded from peripheral muscles, a consequence of phase cancellation. Calculation of maximum amplitude or area under the waveform bears little relation to the number of motor neurons innervating the muscle fibres that create the response.

MONITORING FACIAL FUNCTION FOR NON-OTOLOGICAL PROCEDURES

The facial nerve is at risk of iatrogenic injury in the cerebellopontine angle and parotid. Intra-operative facial nerve monitoring has been advocated during microvascular decompression and superficial parotidectomy.[33, 34] Arguments for adopting its use for all surgical procedures are the same as those for otological surgery.

MONITORING AUDITORY FUNCTION

The aim of monitoring the status of the auditory pathway during cerebellopontine angle (CPA) surgery is the prevention of avoidable post-operative hearing deficit. The achievement of this laudable aim is fraught with difficulty and hearing preservation rates in comparison with facial nerve outcomes remain poor.[35] The cochlear nerve is sensitive to mechanical manipulation and easily damaged, as the intra-cranial section of the nerve is sheathed in central myelin and has no perineurium.[36] Additionally, the cochlear nerve is intimately involved with pathologies, such as vestibular schwannoma, and hence at very considerable risk during the surgical removal of such lesions, even when every care is taken to preserve the nerve anatomically. The basic principle of intra-operative monitoring is that changes in recordable neuroelectric potentials occur whilst the injury is still reversible and before permanent deficits result.[37] Recent research[38] has demonstrated that this principle holds for changes in auditory brainstem responses (ABR) wave V amplitude (and to a lesser extent latency) in rat auditory nerves manipulated in a fashion analogous to that undergone in humans during vestibular schwannoma removal. It is therefore theoretically feasible that monitoring auditory function may inform the surgeon of reversible injury to the cochlear nerve.

One prerequisite of monitoring auditory function during surgery is that sufficient pre-operative hearing must remain such that meaningful recordings may be made in the operating theatre and change observed if and when it occurs. If ABR or electrocochleography (ECochG) are the monitoring techniques of choice, a further prerequisite is for pre-operative recordings with that technique. Monitoring with ABR is not possible if waveforms are absent or of grossly abnormal morphology.

Whilst the techniques and equipment utilized for auditory monitoring may seem familiar from the outpatient clinic, their use in monitoring is significantly different. Rather than comparing an individual's data with group data, in monitoring, one is comparing a sequence of waveforms over time and evaluating for change. The time allowed for eliciting each recording is limited and this will influence the choice of recording parameters. The decision whether to inform the surgeon of a change in recorded activity is both urgent and crucial. As such, the person undertaking monitoring should be familiar with the operating theatre environment and team, and be able to interpret and communicate observed and measured change to the surgeon confidently and concisely.[39] Such skills are rare and this may prove to be a hindrance to the widespread adoption of these techniques.

Lloyd et al.[40] have shown that patients benefit from cochlear implantation after a translabyrinthine approach for acoustic neuroma excision with cochlear nerve preservation. Such findings highlight the clinical relevance of being able to monitor the eighth nerve intra-operatively in order to reliably predict who might benefit from such strategies.

TECHNIQUES

Otoacoustic emissions

Cane et al.[41] undertook a feasibility study of the use of otoacoustic emissions (OAE) as a technique for monitoring the auditory pathway during surgical removal of a vestibular schwannoma. The experience was that OAE recordings were feasible despite the noise within the surgical environment, but the study did not indicate that OAE would be a useful indicator of early, reversible injury. Theoretically, OAE recording may furnish evidence of cochlear function, but as the site of surgery is the internal auditory canal (IAC), one would not be measuring activity deriving from the point of possible injury. OAE monitoring might therefore give information about ischaemic or noise injury to the cochlea, but it has not yet been demonstrated that this would be at a point where the injury was reversible. At the present time, however, the use of OAE in monitoring auditory function during surgery is rare.

Electrocochleography

Similarly, electrocochleography records activity associated with cochlear function and the distal portion of the cochlear nerve, rather than the intra-cranial portion of the cochlear nerve, which is acutely at risk during surgery. As such, even strong advocates of ECochG in monitoring have seen it as adjunct to ABR, and not providing the surgeon with the required information when used alone. There is research evidence that responses to auditory stimulation recorded by ECochG persist after complete transection of the eighth nerve in the rat,[42] and so this technique has the potential to mislead if used in isolation.

One potential advantage of the use of ECochG is the large amplitude of the activity recorded.[43] This allows interpretation of the elicited waveform after fewer averages, so that decision-making may be more rapid.[44] As with ECochG in the outpatient context, there is debate about the optimal site of the recording electrode, with advocates for extratympanic intra-meatal placement[36] and transtympanic placement.[45] A further advantage is that ECochG recordings are less compromised by acoustic noise or by electrical artefact as may occur during cautery, and may serve some purpose whilst these are present.[46]

Auditory brainstem responses

Auditory brainstem responses have a theoretical advantage over other techniques in that certain peaks within the waveform derive from anatomical structures at risk of injury during surgery. The generator of wave I is considered to be the distal portion of the cochlear nerve, the site also held to be the generator of the N1 component of the compound action potential recorded by ECochG.[36] Wave II is associated with the proximal section of the cochlear nerve,[37] wave III with the lower pons (specifically the superior olivary complex)[47] and wave V with the inferior colliculus.[47] The generators of waves III and V are, therefore, unlikely to be directly challenged by surgical manipulation during hearing preservation surgery for space occupying lesions of the CPA, but the latencies of these easily identifiable waves are used during monitoring as change reflects latency change of waves I and II.

Specific methodologies and parameters utilized in intra-operative ABR have been described in detail. The reader who intends to perform this procedure is directed to the comprehensive reviews by Moller[37] and Martin and Mishler.[36] Several points should be noted. There is considerable variability in the methods advocated and clinical trial evidence is not apparent. Second, this variability may account in part for the lack of a strong evidence base for the benefits of auditory monitoring. Further, the reviews cited underline the difference between utilizing ABR in the outpatient clinic and the operating theatre, the need for the technique not to inconvenience surgical techniques and the utility of clear and timely interpretation and communication of change in recordings to the surgeon. In more recent work the importance of obtaining pre-operative ABR has been highlighted.[48] The authors concluded that knowledge of the ABR before surgery helps to solve problems such as choosing to monitor the interaural latency difference of wave V, cochlear nerve action potential or alternative sound-evoked ABR.

Direct recordings from the cochlear nerve

The need for rapid acquisition of responses may be met by recording directly from the cochlear nerve, the large amplitude of the elicited activity obviating the need for lengthy averaging.[49] This technique was first developed to monitor cochlear nerve function during microvascular decompression surgery, but has been adapted for use during surgical removal of space occupying lesions of the CPA.[44] The site of recording is usually the root entry zone, and both monopolar and bipolar electrodes have their advocates.[50] Click stimuli similar to those used in ABR are used to elicit the response, which comprises a compound action potential. Changes in latency, amplitude and morphology should all be reported to the surgical team.[37] Ehrmann-Müller et al.[51] compared direct cochlear recordings using a ball electrode, to ABR results, to evaluate its effectiveness in predicting hearing outcomes after acoustic neuroma excision. They found that such direct recordings gave a sensitivity of 100% and specificity of 70%, and it was possible even in cases where they were unable to obtain reliable ABR results.

Combining techniques

Given that each of the techniques described above has technical challenges and shortcomings, many teams choose to utilize more than one, the most common combination being direct cochlear nerve recording and ABR.[52]

EVIDENCE OF THE EFFICACY OF MONITORING AUDITORY FUNCTION

Authors have reported hearing preservation rates following vestibular schwannoma excision, but the heterogeneity of pathological status, surgical technique, surgical experience and criteria for reporting of hearing preservation combine to frustrate analysis of the clinical utility of auditory monitoring. Observational evidence in this area abounds.[53–55] The need for well-designed, hypothesis-driven clinical trials in this field is paramount.

A similar dearth of evidence is found when determining the relative efficacy of techniques or combinations of techniques. Several studies have reported that direct cochlear nerve recordings are more effective in the maintenance of hearing function than ABR, to an extent that is statistically significant.[56, 57] This effect is said to be due to the immediacy of direct recordings.[58]

Despite the lack of evidence, a consensus is building that monitoring auditory function during CPA surgery is best practice,[50] and that a combination of ABR and direct cochlear nerve recording is optimal,[43] with the adjunctive use of ECochG if desired.[45]

BEST CLINICAL PRACTICE

- ✓ Regarding monitoring of facial nerve function, there is evidence that these techniques offer benefit in improving facial nerve outcomes in surgery that may challenge the facial nerve. As such it is strongly indicated.
- ✓ The evidence base for monitoring auditory nerve function is less robust, but it should be regarded as best clinical practice.

FUTURE RESEARCH

- ➤ Further work is required to develop an intra-operative technique that enables accurate assessment of clinical facial nerve function at any point during skull base procedures. Only accurate estimation of motor neuron function will give the surgeon a true representation of immediate facial function and hopefully then enable development of a valid predictive technique.
- ➤ The specialty as a whole requires a good evidence base to support the use of intra-operative facial nerve monitoring as the standard for all otological procedures that place the facial nerve at risk.

KEY POINTS

- Monitoring facial nerve function is straightforward and neither hampers nor impedes surgery.
- There is good evidence that monitoring facial nerve function improves outcomes of facial function.
- A consensus has not yet been reached on techniques for monitoring auditory function, but it looks likely that a combination of techniques will be optimal.

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CHAPTER 46

OPTICAL COHERENCE TOMOGRAPHY

Jameel Muzaffar and Jonathan M. Fishman

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SEARCH STRATEGY

Data in this chapter may be updated by PubMed, Embase and the Cochrane Library performed by an information specialist librarian. Searches used the following keywords: optical coherence tomography, needle biopsy, surgical guidance, nasal, vocal cord and/or otology. Levels of evidence are not really applicable to the scientific principles of this area, but the human studies that underlie the discussion of optical coherence tomography as applied to otorhinolaryngology are observational, or at best non-randomized.

INTRODUCTION

Medical imaging technology has advanced rapidly over the past 25 years, providing physicians with essential information on the macroscopic anatomy of patients. Techniques capable of imaging subepithelial structure *in situ*, such as conventional X-ray radiography, magnetic resonance imaging (MRI), computed tomography (CT) and ultrasonography have allowed the non-invasive investigation of relatively large-scale structures in the human body, with resolutions ranging from 100 µm to 1 mm. Resolution on this scale, however, is insufficient to detect the subtle changes in tissue microstructure characteristic of many ear, nose and throat (ENT) pathologies.

In the field of laryngology, light endoscopy currently forms the cornerstone of clinical imaging and biopsy guidance, yet conventional light endoscopic techniques are unable to reveal information concerning subepithelial tissue. Since many laryngeal pathologies originate near the boundary between the epithelium and the underlying mucosa, or within the mucosa itself, the inability to image subepithelial tissue represents a serious limitation of conventional light endoscopy. Even as a method for guiding biopsy, conventional light endoscopy gives only a relatively coarse indication of prospective biopsy locations. Frequently, a large number of biopsies are required to achieve high diagnostic accuracy, a situation that is often undesirable or unfeasible given the fragility of adjacent structures. This is particularly true for the vocal folds, which have a specialized and delicate microstructure that is highly intolerant of trauma. These limitations restrict the effectiveness of light endoscopy for the diagnosis, monitoring and treatment of many laryngeal pathologies. Clinical laryngology would thus greatly benefit from a non-invasive imaging technology capable of resolving subepithelial tissue microstructure in the range of conventional biopsy.

Optical coherence tomography (OCT) is a relatively new optical imaging modality that allows high-resolution, cross-sectional imaging of tissue microstructure. OCT can image with an axial resolution of 1–15 µm and has an imaging depth of 2–3 mm in non-transparent tissue. OCT was first applied in 1991 to imaging optically transparent structures, such as the anterior eye and retina.[1, 2] Subsequent technological advances have enabled high-resolution imaging of non-transparent tissue in the cardiovascular system[3] and the gastrointestinal,[4] urinary[5] and female reproductive tracts.[6] In addition, the application of OCT to surgical guidance[7] and carcinoma detection[6, 8] has been explored.

The aforementioned imaging studies have demonstrated that OCT is particularly informative in tissues in which non-keratinized epithelium is separated from the underlying stroma by a smooth basement membrane zone, suggesting that OCT may have a strong clinical relevance

in laryngology. This indication is further strengthened by several features of the OCT system itself:

- OCT imaging can be performed *in situ* and non-destructively, enabling the imaging of tissue for which biopsy should be avoided or is impossible.
- OCT gives images of high resolution, 10–100 times that of conventional MRI or ultrasound.
- Imaging can be performed in real time, without the need to process a specimen, as in conventional biopsy, and without the need for a transducing medium, as in ultrasound imaging.
- OCT is fibre-optically based and can thus be interfaced to a wide range of instruments including catheters, endoscopes, laparoscopes and surgical probes.
- OCT systems can be engineered to be compact, portable and low cost, depending on the desired system specifications.

Although now entering human trials in a variety of areas within otolaryngology, early research focused on the potential applications of OCT to laryngeal tissue, imaging of the middle ear[9] and of rat cochlea[10] *ex vivo* and nasal tissues[11] with promising results. Before presenting and discussing OCT images of larynges *ex vivo*, it is useful to briefly describe the basis by which OCT systems form subepithelial images.

OCT: SYSTEM OPERATION

Optical coherence tomography performs high-resolution tomographic imaging by measuring light backscattered, or backreflected, from internal tissue structures. OCT imaging is analogous to ultrasound B-mode imaging, but is based on the detection of infrared light waves, instead of sound. Like acoustic waves, light is characterized by its propagation direction. Light is distinct, however, in that it has an additional vector characteristic known as polarization. The polarization direction is orthogonal to the propagation direction and can be influenced by the medium in which the light propagates. This is known as 'birefringence'. Polarization measurements can be used to provide additional insights into the microscopic structure and integrity of tissues. An adjunct to conventional OCT, polarization-sensitive OCT (PS-OCT), exploits birefringence as an additional contrast mechanism for imaging tissue. PS-OCT will be discussed in further detail under 'Polarization-sensitive OCT' below.

The analogy with ultrasound is a useful starting point for understanding the basics of OCT. In ultrasound, a high frequency acoustic pulse travels into the tissue and is reflected, or backscattered, from internal structures having different acoustic properties. The magnitude and the delay time of the echoes are electronically detected, and the structural properties of the internal tissues are determined from the measured signals. In OCT, imaging is performed by measuring the echo delay time and magnitude of light backreflected, or backscattered, from internal structures with distinct optical properties. Unlike in ultrasound, though, the speed of light is very high, rendering electronic measurement of the echo delay time of the reflected light impossible. OCT systems circumvent this limitation by using low coherence interferometry, also known as white light interferometry, to characterize optical echoes.

The most common OCT echo detection scheme is based on a Michelson interferometer set up with a scanning reference delay arm, shown in **Figure 46.1**. Within the interferometer, the beam leaving the optical light source is split into two parts, termed the reference and sample beams, at the beam splitter. The reference beam then travels to a mirror, located at a known distance from the detector and subsequently returns to the beam splitter. The sample beam travels to the tissue sample and is reflected back towards the detector by scattering sites within the tissue. Light reflecting from deeper tissue layers has traversed a greater optical pathlength (optical distance) and therefore arrives at the detector at a later time. In addition, the various backreflected parts of the sample beam will have different amplitudes based on the differing strengths of the scattering sites. The reflected portions of the sample beam then return to the beam splitter where they interact with the reflected reference beam and are directed towards the detector.

When two waves from the same source recombine in this manner, an interference pattern will result if the optical path length travelled by the two waves is identical. The output detector measures the intensity of this interference pattern and thus only measures information contained in the portion of the sample beam that has travelled the same optical distance as the light in the reference arm. Information about the remaining tissue layers can be extracted by moving the mirror in the reference arm, which changes the optical path length travelled by the reference beam. Two- or three-dimensional images are produced by scanning the beam across the sample and

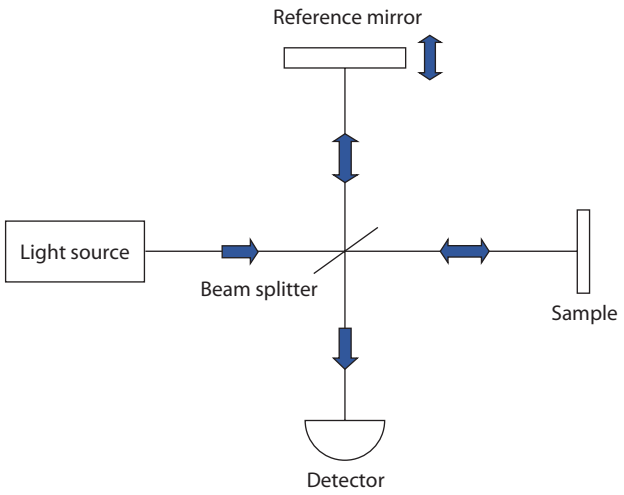


Figure 46.1 Schematic of an optical coherence tomography system using a Michelson interferometer with scanning reference delay arm.

recording the optical backscattering versus depth at different transverse positions. The resulting data is a two- or three-dimensional representation of the optical backscattering of the sample on a micron scale.

OCT IMAGING OF THE LARYNX

To assess the potential value of OCT imaging technology in improving visualization and pathology, as well as the diagnosis and treatment of a given organ system, it is essential to first image normal tissue from that particular organ and then reference the resulting OCT images to parallel histology.

Initial studies of the laryngeal imaging using OCT[12, 13] have focused on the following structures due to clinical relevance:

- the laryngeal surface of the epiglottis
- the false folds
- the inferior surface of the true folds.

The images presented are based on a similar focus. It should be noted, however, that since OCT can be readily adapted to fibre optic-based probes, other areas of traditionally poor visibility in light endoscopy, such as the anterior commissure, the subglottis and the laryngeal ventricle, could also be readily imaged using this technology.

In Figure 46.2, an OCT image of the laryngeal surface of an ovine (sheep) epiglottis and the associated histological section are shown. Several different layers of the epiglottic tissue are visible, with epithelium, lamina propria and cartilage being clearly demarcated. Glandular structures and vessels are also frequently visible.

Figure 46.3 presents an OCT image taken along the inferior portion of a porcine true fold, as evidenced by the transition from free-edge non-glandular mucosa to subglottal glandular mucosa observed in the OCT image and corresponding histological section. This image illustrates the ability of OCT to allow visualization of the epithelium, basement membrane and lamina propria of the true fold, as well as of certain structural features, such as glands and vessels. Note in particular that local epithelial thickness and transparency of the true fold can be readily deduced from these images, implying that OCT may prove useful for the diagnosis of hyperplasia, early-stage keratosis and papillomas, and other pathologies resulting in epithelial abnormalities not normally visible by conventional light endoscopy until an advanced stage. Since many laryngeal pathologies originate at the border between the mucosa and the epithelium, the ability to observe the integrity

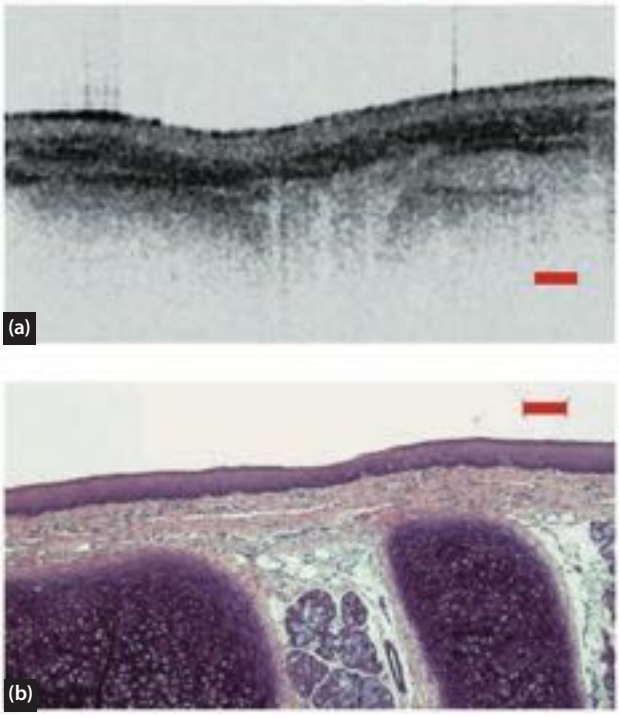


Figure 46.2 (a) OCT image of an ovine epiglottis; **(b)** corresponding haematoxylin and eosin histology section. Scale bars represent 150 μm.

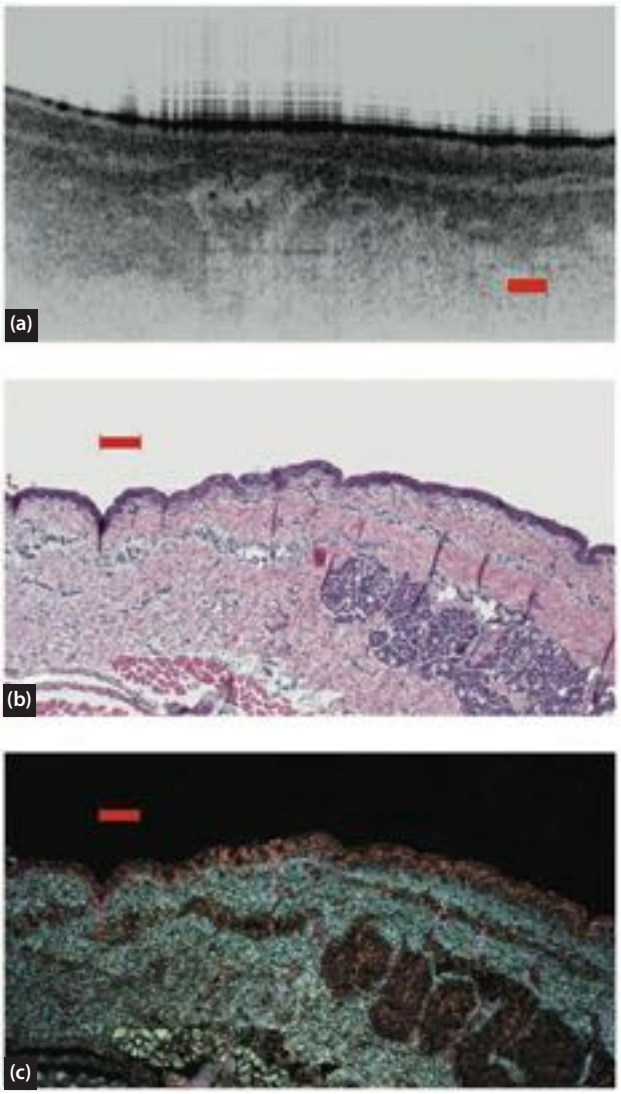


Figure 46.3 (a) OCT image of the inferior surface of a porcine true fold; **(b)** corresponding haematoxylin and eosin histology section; **(c)** phase-contrast viewing of the stained histology section. Scale bars represent 150 μm.

of the basement membrane via OCT imaging may have important implications for the use of this technology in aiding the diagnosis and monitoring of such laryngeal disorders, possibly including early stage carcinoma.

POLARIZATION-SENSITIVE OCT

A monochromatic light wave carries three potential sources of information contained in the amplitude, phase and polarization state of its electrical field vector. Conventional OCT, by detecting only the intensity of the interference pattern resulting from interaction of the sample and reference optical beams, fails to quantify the effects of tissue on the polarization state of the sample light beam. An adjunct to conventional OCT, known as polarization-sensitive OCT, therefore has focused on exploiting the information contained in the polarization state of the light backreflected, or backscattered, from the sample relative to that of the reference beam to obtain information about the tissue microstructure.

In order to appreciate the power of PS-OCT and its potential applications, it is helpful to describe briefly the main mechanisms by which tissue alters the polarization state of light. Two mechanisms dominate the changes in the polarization state of light propagating through biological tissue: scattering and birefringence. Scattering changes the polarization of light mainly in a random manner, so it is generally not useful in mapping tissue structure. Organized linear structures, on the other hand, such as collagen fibre bundles with a clear orientation, can exhibit birefringence, resulting in a predictable change in polarization state. Many biological tissues exhibit birefringence, such as tendons, muscle, nerve, bone, cartilage and teeth.[14] Since changes in birefringence may, for instance, indicate changes in functionality, structure or viability of tissues, PS-OCT images may contain information that can be used to evaluate tissue microstructure and health beyond the level possible with the use of OCT alone.[15]

The potential implications for clinical laryngology of the sensitivity of PS-OCT to organized linear structures, such as oriented collagen fibre bundles, are numerous. To illustrate, the human vocal fold lamina propria is generally subdivided into the superficial, intermediate and deep layers, with each layer having a characteristic composition and functionality. The relative thickness and integrity of these various layers appear to have a profound impact on voice. This idea is supported by the fact that the average adult will experience marked thinning of the superficial lamina propria relative to the intermediate and deep layers with increasing age,[16] with a concomitant reduction in voice quality.

Histological studies of normal adult human vocal fold tissue have repeatedly noted increased density and longitudinal orientation of collagen fibres as one progresses from more superficial to deeper lamina propria layers.[16] PS-OCT, due to its sensitivity to oriented collagen fibre bundles, may thus allow indirect detection of these lamina propria layers *in situ* and hence monitoring and possibly improving treatment of voice ageing. In the case of vocal fold scarring, the biomechanical integrity of the lamina propria is disrupted, resulting in reduced vocal fold pliability and thus decreased vocal range and quality. Scar tissue has collagen fibre orientation and density that is generally distinct from that of normal tissue and therefore PS-OCT may also prove useful in visualizing, localizing and treating vocal fold scars within the lamina propria. These capabilities could have a profound impact in the area of voice management.

Figure 46.4 compares a PS-OCT image of the inferior surface of a human true fold with the corresponding OCT image and histological section. Note the banding pattern apparent in the PS-OCT image of the vocal fold. A transition from white to black banding indicates a change in the polarization state of light. In particular, observe the marked increase in the thickness of the initial subepithelial white band in the leftmost portion of the PS-OCT image (corresponding to the true fold free edge) relative to that in the more subglottic tissue. The spatial location of this thickened initial band corresponds closely with the increased prominence of the superficial lamina propria in this region. Since collagen in normal superficial lamina propria is sparse and relatively randomly oriented, a net change in the polarization state of light will be slow to occur in this region. Hence, the thickness of the superficial lamina propria can potentially be inferred from the thickness of the initial subepithelial PS-OCT band. The true fold superficial lamina propria features critically in vocal health and disease. Although the presented results are not definitive, the potential of PS-OCT to detect changes in the superficial lamina propria thickness and collagen alignment is an exciting area for future study.

Again, it must be stressed that further studies must be carried out to determine what the observed vocal fold polarization patterns truly indicate. In the case that these studies show that the relative thickness and/or health of the lamina propria layers can indeed be indirectly assessed by this imaging adjunct, PS-OCT could prove very useful to the study of lamina propria health and in the development of targeted scar treatment strategies.

CLINICAL STUDIES UTILIZING OCT

A number of studies have explored OCT use *in vivo*. Whilst these studies are predominantly non-randomized pilot or proof of concept studies they illustrate potential clinical applications for widespread clinical practice.

The most studied area of interest in otolaryngology has been for imaging of the larynx. A number of studies have utilized OCT in conjunction with microlaryngoscopy, with or without histology for a range of benign and malignancy pathologies.[17, 18] Initial experience is promising, with good correlation between OCT and histological diagnosis. However, the exact role of OCT remains unclear and we currently lack large-scale studies to justify replacement of histological confirmation.

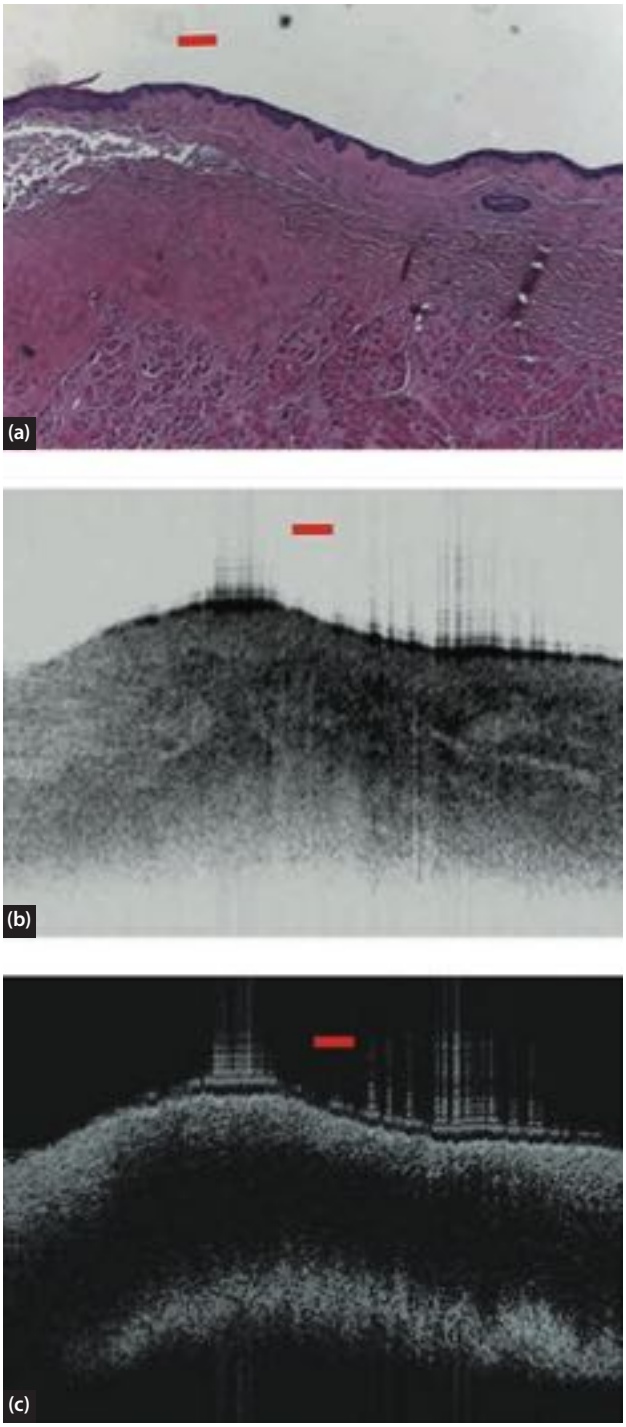


Figure 46.4 (a) Haematoxylin and eosin histology section of the inferior surface of a human true fold; **(b)** corresponding OCT image; **(c)** corresponding PS-OCT image. Scale bars represent 150 µm.

In paediatric otolaryngology studies have explored the use of fourier domain optical coherence tomography (FD-OCT) and long-range optical coherence tomography (LR-OCT) for the development of computerized airway models for predicting neonatal subglottic stenosis following intubation[19] and localizing the site of upper airway obstruction in children with sleep disordered breathing.[20] Furthermore, OCT may be helpful to evaluate cartilage in the lower trachea or bronchi. Congenital absence of cartilaginous tracheal rings associated with esophageal atresia and trifurcated carina: a novel anomaly?[21] Again whilst these avenues show promise there remains some distance from definitive trials likely to change routine practice.

In head and neck surgery, one study has demonstrated the feasibility of using two newer generation OCT systems – optical frequency domain imaging (OFDI) and micro-optical coherence tomography (µOCT) imaging – to identify parathyroid tissue with histology-like levels of certainty, without the need for frozen section.[22] It is not too much of a leap to imagine a handheld probe used in a similar manner to a nerve stimulator for intraoperative localization, though this is not currently available. Another study reported two cases where OCT was combined with endobronchial ultrasound (EBUS) for the potential identification of residual hypertrophic and persistent inflammatory tissue (known contributors to stricture recurrence) following laryngotracheal dilation of post-intubation laryngotracheal stenosis, with some promising results, although the sample size was small.[23]

Within Otology OCT imaging has been demonstrated in combination with robotic surgery for localization and electrode placement for cochlear implantation has been demonstrated on dry-fixed human temporal bones.[24] Further small case series advocate the use of OCT to identify the stapes footplate in revision stapes surgery[25] and as an adjunct to otomicroscopy for the identification of myringitis and potential biofilm formation.[26]

SUMMARY

OCT and OCT adjuncts have enormous potential for improving the diagnosis, monitoring and both surgical and non-surgical management of diseased ENT tissues. Conventional OCT provides objective information concerning the structure of tissue elements with distinct optical backscattering and backreflection properties. With regard to the larynx, conventional OCT studies of healthy laryngeal tissues *ex vivo* have demonstrated that OCT can detect spatial changes in the thickness and transparency of the epithelium, the content of the connective tissues in terms of glands and vessels, as well as pronounced transitions in connective tissue type and the architecture of the basement membrane.[27] PS-OCT holds promise for permitting indirect visualization of the layers of the true fold lamina propria, as well as of vocal fold scar beds. In addition, a number of other OCT adjuncts, such as spectroscopic OCT[28] and phase dispersion tomography[29] exist, or are currently in development, each with distinct imaging advantages and capabilities over conventional OCT imaging. Whilst not yet in widespread use in clinical practice, OCT has the potential to significantly alter the diagnostic and treatment pathway across the range of otolarygology. The next few years provide the opportunity for future research and discovery in this fascinating field.

FUTURE RESEARCH

Although OCT and OCT adjuncts hold substantial promise for improved visualization of ENT-related tissues, OCT/OCT-adjunct feasibility studies for most of these tissues are either extremely limited or entirely lacking. For those ENT tissues that have been imaged with OCT, the primary focus of the imaging studies has been the necessary, but insufficient, first step of assessing the degree to which normal tissue microstructure can be accurately identified from OCT images. Before the OCT imaging modality can be regarded as a diagnostic tool in ENT, rigorous correlation of OCT/OCT-adjunct images of diseased tissue with parallel histology must be carried out to demonstrate that a given disease state can be accurately and reliably identified from OCT image structures. In the case of the larynx, although conventional OCT images of pathological laryngeal structures *in vivo* have been recorded,[12] the corresponding histology necessary to guide OCT image interpretation has most often been lacking. Thus, whether OCT/OCT-adjuncts can reproducibly and accurately identify laryngeal pathology or other ENT pathologies remains to be determined and constitutes an exciting and vital area of future work.

In addition to pathology identification, OCT or certain OCT adjuncts may prove useful in guiding laser and non-laser-based microsurgery of ENT tissues. In laser microsurgery, PS-OCT may be particularly applicable, since laser damage of collagenous tissue has been shown to alter the tissue's effect on the polarization state of incoming light.[30] This is yet another exciting avenue for future research.

In brief, the following are a few of the many vital areas for current and future investigation:

- correlation of histology with OCT images of pathologic laryngeal specimens
- further investigation of the potential use of OCT in laryngology and correlation of PS-OCT images to laryngeal microstructure
- investigation of other OCT adjuncts, such as spectroscopic OCT, to laryngeal imaging
- further exploration of the possible applications of OCT/OCT adjuncts to ear-related imaging and a feasibility study of OCT applied to nasal tissue
- exploration of the use of OCT in conjunction with image guidance and/or robotic systems.

KEY POINTS

- The diagnosis and treatment of many ENT pathologies would benefit from the ability to image subepithelially and with high resolution *in situ*.
- Optical coherence tomography enables subepithelial imaging of tissue with a resolution ranging from 1 to 15 µm and is fibre-optically based, allowing OCT systems to be interfaced with a wide range of instruments, including catheters and endoscopes.
- Conventional OCT appears to be able to detect spatial changes in the thickness and transparency of laryngeal epithelium; the content of the connective tissue, including the presence of glands and vessels; and the integrity of the basement membrane.
- Polarization-sensitive OCT, with its sensitivity to organized linear structures, such as oriented collagen fibre bundles, may prove useful for vocal fold visualization and health assessment.
- OCT and OCT adjuncts hold substantial promise for improved diagnosis and treatment of many ENT disorders, a potential that remains largely untapped and constitutes an exciting avenue for future research, development and discovery.

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CHAPTER 47

RECENT ADVANCES IN TECHNOLOGY

Wai Lup Wong and Bal Sanghera

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SEARCH STRATEGY

This chapter is based on literature obtained by electronic searches of four biomedical databases (Medline, Embase, Cochrane Library, PubMed) using combinations of keywords including PET, PET-CT, FDG, positron emission tomography, tomography emission computed, FDG, head and neck, cancer, neoplasm, squamous cell cancer, thyroid cancer, neck, staging, nodal metastases, occult primary, recurrence, surveillance, MR . Studies were also sought from hand searches of H&N surgery and other relevant journals, and scanning the reference lists of relevant articles. No beginning date limit was used and the search was updated on November 2, 2016.

PET-CT has replaced PET. Notwithstanding, there is good justification for continuing to take into account the FDG PET evidence when considering FDG PET-CT as both assess the same aspects of tissue metabolism . Also, the whole body is routinely scanned in both techniques. Furthermore, there is evidence that PET-CT is more accurate as a diagnostic test compared with PET because PET-CT can more sensitively detect radiotracer emitted from the body and more accurate anatomical localization of the radiotracer emitted.[1] In other words, PET studies set a baseline for performance which is likely to be improved by PET-CT.[2]

POSITRON EMISSION TOMOGRAPHY (PET) – COMPUTED TOMOGRAPHY (CT)

The main role of PET-CT in head and neck surgery is in the assessment of people with head and neck (H&N) cancer using the radiotracer 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG). So the focus of the chapter, after consideration of the principles of PET-CT, is on FDG PET-CT in people with H&N squamous cell cancer (SqCC). Separate short commentaries are provided on the role of FDG PET-CT for other tumours and on the evolving role of radio-tracers beyond FDG. In addition, brief observations are made on the current status of PET-MR.

Computed tomography (CT), magnetic resonance (MR) and ultrasound predominantly produce anatomical images, whereas positron emission tomography (PET) identifies pathology based on altered tissue metabolism. Modern whole-body PET scanners are physically integrated with standard CT scanners enabling the creation of accurately computed combined [registered] fused PET-CT scans.

CT component of PET-CT

The CT component of PET-CT has two important functions. Firstly, it contributes directly to more accurate diagnosis. It does this by facilitating precise anatomical location of radiotracer activity which leads to more exact anatomical localization of pathology and more accurate distinction between pathology and normal appearances. Secondly, the CT component corrects for the reduction in PET signal [attenuation] as it travels through the patient's body; the deeper the site the signal arises in the body the greater the attenuation. The correction results in more accurate measurement of radiotracer uptake.

CT is usually performed with a lower radiation dose than conventional diagnostic CT. Also, unlike conventional diagnostic CT, PET-CT is commonly performed without intravenous contrast. This is because there is

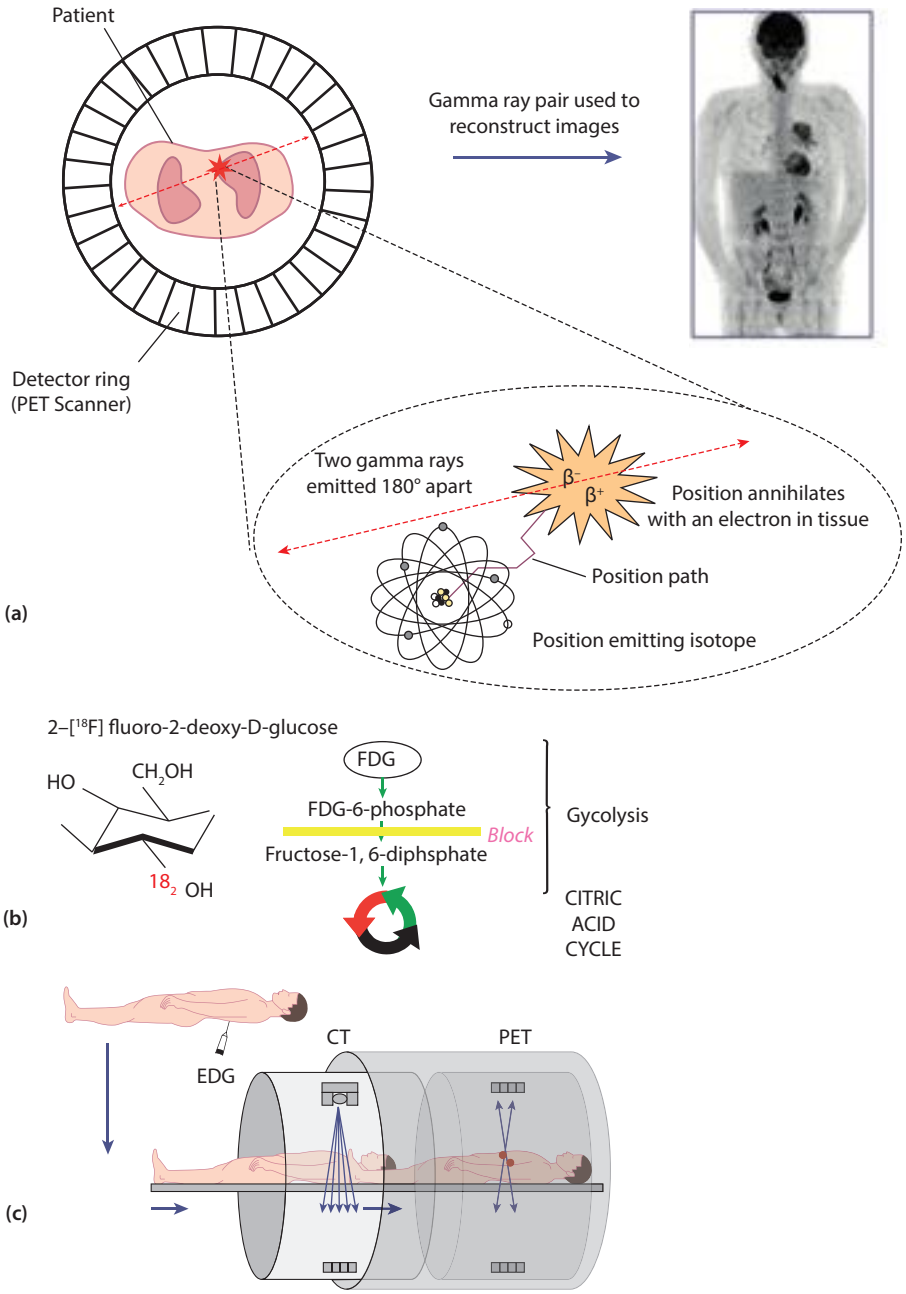


FIGURE 47.1 **(a)** Projection FDG-PET shows a patient with a primary bronchogenic carcinoma with extensive bony and cutaneous deposits. **(b)** Schematic representation of FDG metabolism. **(c)** Schematic representation of scanning with integrated PET/CT. The radiation burden is equivalent to two whole body diagnostic CTs. The CT is usually obtained using a low-voltage technique with no intravenous contrast given, but it provides diagnostic information.

some evidence to suggest that intravenous contrast results in PET artefacts. That said, the actual impact intravenous contrast makes to interpretation of clinical PET-CT scans is debatable. This has prompted some centres to carry out PET-CT scanning with intravenous contrast in an effort to reduce the number of investigations for patients. More typically, however, if a contrast-enhanced CT is required it is performed following low dose attenuation CT.

Recently, similar to CT, manufacturers have introduced continuous bed motion PET acquisition systems with potential for less artefacts and increased sensitivity. This is in contrast to conventional whole-body PET-CT scans which comprises a series of overlapping static 'step and shoot' bed acquisitions taking approximately 30 mins in total to perform.[3]

PET component of PET-CT

PET is a functional imaging technique which relies on a radioactive molecule (radiotracer) that decays with positron emission. The radiotracer is given intravenously to the patient and is taken into cells. The cell recognizes it as

being 'foreign' and as a consequence it is trapped early in its metabolic pathway. Malignant cells trap more radiotracer compared with non-malignant cells. The local radiotracer concentration can be measured *in vivo* since these unstable radiotracers decay by positron emission. Positrons travel a short distance in tissue before colliding with electrons. When they collide, the annihilation reaction results in two photons also known as gamma rays of 511 kilo electron volts (keV) each emitted at approximately 180° to each other. The photons are detected by opposing detectors. A computer reassembles these signals into images that represent radiotracer uptake in the part of the body scanned.

One of the main strengths of PET is the ability to perform quantitative studies. Absolute quantification is not often carried out in clinical practice as it is complicated to obtain and can demand direct arterial blood sampling. The standardized uptake value (SUV), which provides a semi-quantitative index of radiotracer uptake is widely used in clinical PET:

$$\frac{\text{Tracer uptake (MBq/mL)}}{\text{Administered activity (MBq)/(patient weight (kg)} \times 1000)}$$

Depending on the radiotracer used, different aspects of tissue metabolism can be studied, such as distribution of blood flow, oxygen utilization and protein synthesis. The overwhelming majority of clinical studies are in conjunction with an analogue of glucose, 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG), which reflects glucose metabolism. Cancer cells have a greater avidity for glucose than normal cells. Otto Warburg and colleagues made this observation in the 1920s.[4] FDG can be used to exploit the differences in glucose metabolism between cancer cells and normal cells.

FDG-PET has been used effectively for imaging of a variety of malignancies including breast, lung, colorectal, oesophageal cancer, brain tumours, malignant melanoma and lymphoma.[45] Seifert and others demonstrated that H&N cancers take up FDG, an observation which was subsequently confirmed by other studies.[6]

Occult primary tumours

The cornerstone for investigating people with malignant nodes and no primary site on usual assessment is biopsy of suspicious sites and sites likely to harbour the primary site at examination under anaesthesia (EUA). There is universal agreement that FDG PET-CT should be included prior to EUA.[7] Applied in this context, FDG PET-CT influences the management plan in three main ways. Firstly, and primarily, FDG PET-CT detects an unexpected primary site, and with FDG PET-CT superior to FDG PET. A National Institute of Care and Health Excellence (NICE) review, based on the combined results of 5 FDG PET-CT studies and 198 patients, provided an estimated sensitivity of 0.89 and specificity 0.73.[8] In addition, one meta-analysis of eight studies which included 430 people, FDG PET-CT detected 31.4% more primary sites not diagnosed at usual assessment.[9] This compares favourably with FDG PET where in a meta-analysis of 16 studies with 302 patients FDG PET detected 24.5% more primary sites not apparent after conventional work-up.[10] However, the exact likelihood of detecting an unexpected primary site will depend on the investigations prior to FDG PET-CT, and the more investigations the less likely the value of FDG PET-CT.

Secondly, FDG PET-CT improves diagnosis by contributing directly to detecting unexpected nodal and unexpected distant metastases, albeit infrequently.

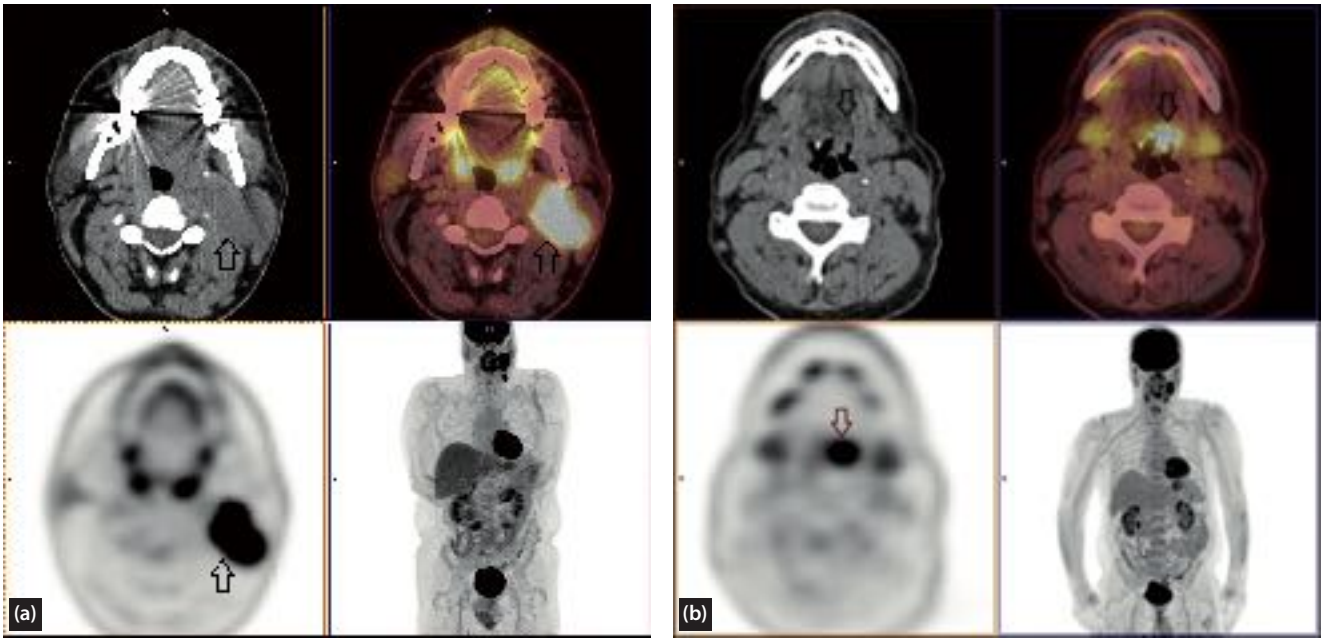


Figure 47.2 A 55-year-old man presented with a left neck lump due to an enlarged neck node infiltrated with SqCC. No primary site on clinical assessment and usual assessment including indirect laryngoscopy and MRI. FDG PET-CT **(a)** shows the left neck node (hollow arrows), and **(b)** the subtle base of tongue primary site (hollow arrow), confirmed at subsequent EUA and biopsy.

In a retrospective cohort study of 78 people, one of the largest studies in this area, FDG PET-CT detected primary tumours in 30 people not identified on usual assessment which included flexible fibre-optic nasoendoscopy and CT/MR or both; unexpected contralateral neck nodal disease in two, mediastinal nodal disease in one, and liver metastases in one.[11] Finally, occasionally, but importantly, FDG PET-CT detects occult synchronous cancers, most often silent lung and colorectal cancers.[9, 10] The former because of the linked causes between H&N and lung cancer and the later because colorectal cancer is a common cancer and is often initially asymptomatic.

Currently, many centres offer FDG PET-CT only after clinical assessment and CT/MR shows no primary site, and prior to EUA and biopsy. Increasing confidence in the use of FDG PET-CT and the wider availability of PET-CT scanners is leading to a growing view that FDG PET-CT should be considered as the initial investigation, reserving CT/MR only if necessary for treatment planning.[12] This approach is justified on the grounds that it will improve patient experience by reducing the number of investigations prior to EUA and without overall compromise to detection of occult primary sites.

That said, the diagnostic pathway requires critical consideration. Firstly, it does not take into account the complementary potential of emerging MR techniques, and specifically diffusion MR.[13, 14] In addition, one study showed FDG PET-CT was cost effective in N1 and N2 occult H&N primaries but questioned the cost effectiveness of FDG PET-CT for N3 occult H&N primaries.[15] Finally, given that in HPV-positive people the occult primary site is almost invariably in the tongue base and palatine tonsil the question arises whether a different approach should be taken in HPV-positive people from those who are HPV negative; specifically, as to whether FDG PET-CT should be only for the HPV-negative group. While for those who are HPV-positive, advancing those patients directly to surgical diagnostic assessment, including consideration of emerging techniques such as narrow-band imaging and tongue-base mucosectomy, if no primary site is identified on CT/MR.[16]

SQUAMOUS CELL CARCINOMA

Primary disease

STAGING

FDG PET-CT has a limited use in the staging of the primary site and for assessment of nodal disease in the neck. FDG PET-CT can detect the majority of clinically visible primary tumours. This capability is of limited clinical value in the main, but can occasionally be utilized to more precisely delineate the primary tumour where submucosal extension of disease is a feature, such as in post-cricoid carcinoma and tracheal carcinoma.

With regard to the neck, FDG PET-CT is also of limited clinical value. It is clear from the literature that FDG-PET cannot consistently detect subclinical disease and that reactive nodes can be FDG avid.[14–20] So FDG PET-CT cannot obviate elective neck treatment. However, it can have a role in those with equivocal nodal disease following conventional assessment. In those with a moderate to high risk of neck metastases, a positive FDG PET-CT scan will be highly indicative of neck nodal disease and this can be particularly useful for highlighting possible contralateral or bilateral nodal disease. Conversely, in those with a low risk of nodal metastases, a negative FDG PET-CT is highly indicative of no nodal disease. In other words, FDG PET-CT can highlight possible additional



Figure 47.3 A 49-year-old man with nasopharyngeal cancer (NPC). Staging FDG PET-CT **(a)** shows the primary NPC (red hollow arrow), bilateral neck nodes (red arrowhead), and **(b)** two bone metastases, one in a vertebral body (arrow), corresponding to a lucent lesion on CT component (arrow) and one in the RT femur (hollow arrowhead).

unexpected nodal disease which may have a direct and immediate impact. In some it will justify further neck assessment; this is most often initially ultrasound with fine-needle aspiration cytology. In others, treatment may be modified to include the suspicious node or nodes. Determining which nodes are potentially significant is largely influenced by the probability of nodal disease at the location and this will influence the interpretation of nodes that are potentially significant. If the node lies in the nodal drainage area for the primary site and there is a moderate to high probability for nodal disease at this site then the node, notwithstanding its relatively small size and mild FDG uptake, requires consideration. On the other hand, if a node lies outside the drainage area and there is low probability for disease at this site then it is unlikely that the node contains tumour. For example, a right level II node, 8 mm, mildly FDG avid, SUVmax 3.0, in a person with nasopharyngeal cancer must be viewed with much more suspicion than that of a node in a person with a left maxillary antral cancer.

The main role of FDG PET-CT in the assessment of people with primary disease is in the detection of distant metastases. In a significant number, FDG PET-CT detects metastases not diagnosed on usual assessment.[21–23] In a meta-analysis, including 1147 patients from eight studies, FDG PET-CT had a pooled sensitivity and specificity for detecting distant metastases of 0.83 and 0.96 respectively, compared with usual assessment, 0.44 and 0.96, respectively. In addition, the superiority of FDG PET-CT applied to both nasopharyngeal cancer and non-nasopharyngeal head and neck cancers.[24] Specifically with regard to bone metastases, in a meta-analysis which included 1184 patients from five comparative studies, which compared FDG PET CT to bone scanning, FDG PET-CT was more sensitive, with a pooled sensitivity of 0.85 compared with 0.55.[25]

There is divergence in guidance as to whom should be offered FDG PET-CT. Taking cost-effectiveness considerations into account, recent NICE guidelines recommend offering FDG PET-CT only to people with T4 nasopharyngeal and hypopharyngeal cancer and to people with advanced neck disease (N3).[8] Other guidelines recommend FDG PET-CT more extensively.[7] This divergence highlights the many factors that come into play with complex decision-making processes, beyond guideline development process and methodology, and they include the value beliefs and value systems of the individual on the panel making the decisions.[7]

Post-treatment assessment

FDG PET-CT has a high negative predictive value, greater than 90%, 8 weeks or more after chemo-radiotherapy (CRT).[26, 27] Stratification for neck dissection with FDG PET-CT after chemo-radiotherapy results in fewer neck dissections and a reduced incidence of complications.[28] In a prospective study of 564 people with H&N SqCC and advanced neck nodal disease following CRT, 282 were recruited into the neck dissection arm, 282 had FDG PET-CT 8–12 weeks following CRT and neck dissection only if FDG PET-CT showed residual disease. Fifty-four neck dissections were performed in the surveillance arm with 22 surgical complications; 221 neck dissections in the neck arm with 85 complications. FDG PET-CT surveillance was cost-effective compared to planned neck dissection with a £1,415 per person saving and an additional gain of 0.07 quality added life years (QALY).[28]

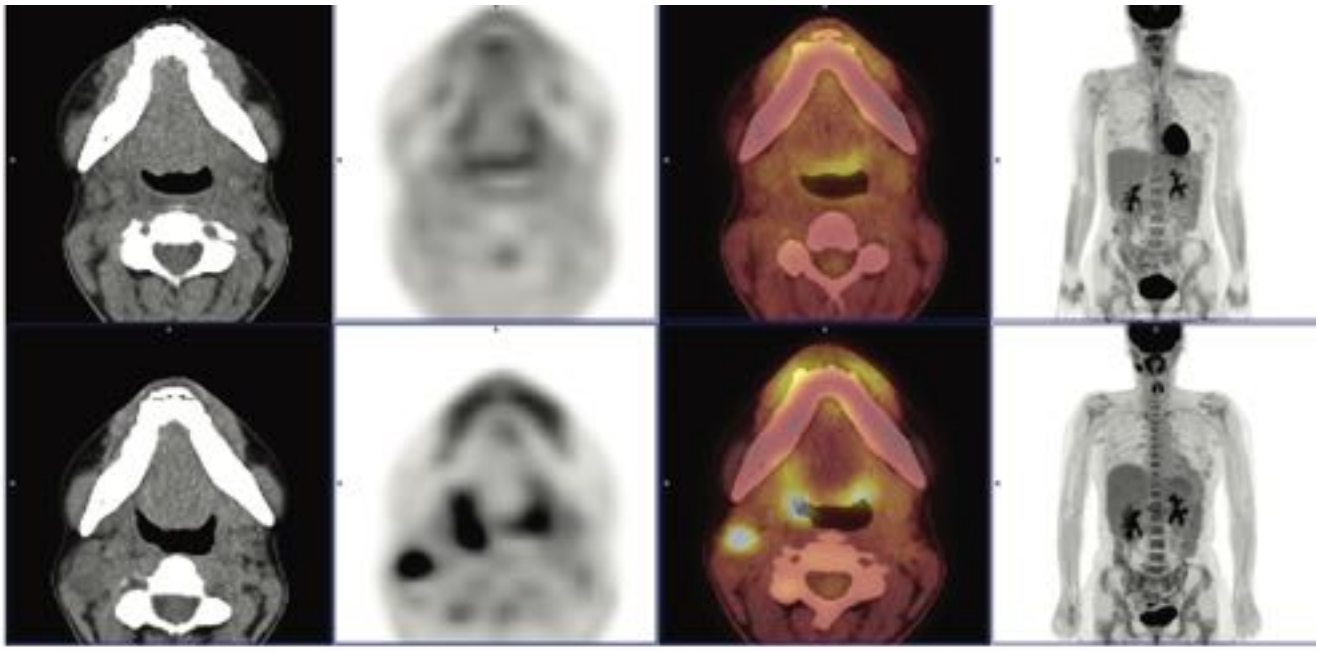


Figure 47.4 FDG PET-CT (bottom row) shows intense FDG avidity of the right glosso-tonsillar fossa SqCC and right neck nodal disease. FDG PET-CT 12 weeks post chemo-radiotherapy (top row) there is resolution of FDG uptake at the primary site and no FDG uptake in the residual right neck node on CT.

Of current interest is the influence of HPV status on FDG PET-CT in the assessment of residual nodal disease following CRT.[29] HPV-positive nodal disease can take longer to involute.[30] So enlarged nodes with no residual disease occur at the 12-week assessment following CRT. Several studies have shown that FDG PET-CT is more accurate than CT for distinguishing nodes with residual disease from those with no disease.[31, 32] In one study, FDG PET and PET-CT at a mean of 12 weeks following treatment, with a range of between 8 and 16 weeks, was significantly more accurate at predicting complete response compared to contrasted CT assessment, 90% compared with 46%, and especially for the HPV-positive group, 93% compared with 50%.[31] In one of the largest studies to date which specifically considered FDG PET-CT response in HPV-positive oropharyngeal cancer, FDG PET-CT at 12 weeks post-CRT demonstrated high-negative predictive value for loco-regional failure though the positive predictive value and sensitivity was disappointing.[32] However, Pryor et al. demonstrated that surveillance strategies including FDG PET-CT was more cost effective than CT-guided surveillance alone, regardless of HPV status. Furthermore, that study showed that combined strategies using CT followed by FDG PET-CT in non-responders were only marginally more cost effective than FDG PET-CT alone, and were highly sensitive to changes in circumstances.[33] Therefore, some advocate that HPV-positive people with enlarged nodes but with no FDG avidity after 12 weeks post-CRT may be considered for close surveillance with serial scanning, with limiting neck dissection for those with FDG avid enlarged nodes, especially if HPV-negative or at high risk and HPV-positive.

This approach however is challenged. In one prospective study, FDG PET-CT had no advantage over CT in low-risk non-smokers with HPV-positive oropharyngeal primaries. In addition, in that study, FDG PET-CT was only better than CT in high-risk patients who have HPV-negative disease, non-oropharyngeal primaries or who have a smoking or alcohol history.[34] The authors acknowledge that the study is limited for several reasons. Firstly, it was performed in a high-throughput cancer institution where the proportion of high-risk patients and radiotherapy non-responders may be greater than in other treatment settings. Secondly, FDG PET-CT nodal response was assessed at a mean of 8 weeks, with a range of between 5 to 12 weeks following treatment, which may not be the optimal timing for FDG PET-CT after radiotherapy.[30, 31] Finally, histopathology of post-CRT neck dissection was used as evidence of persistent disease, which is known to overestimate persistence.[27, 33]

As yet, independent validation of CT scan-driven response systems or comparison with PET-CT-driven systems in multicentre, randomized settings have not been published. As a final comment, even if further studies establish that FDG PET-CT is of limited value in HPV-positive patients, in many countries, HPV-positive patients constitute only a minority, and FDG PET-CT would still have an important role in the majority of patients.

RECURRENT DISEASE

FDG PET-CT is accurate at detecting recurrent disease. A survey of the literature identified 23 studies which

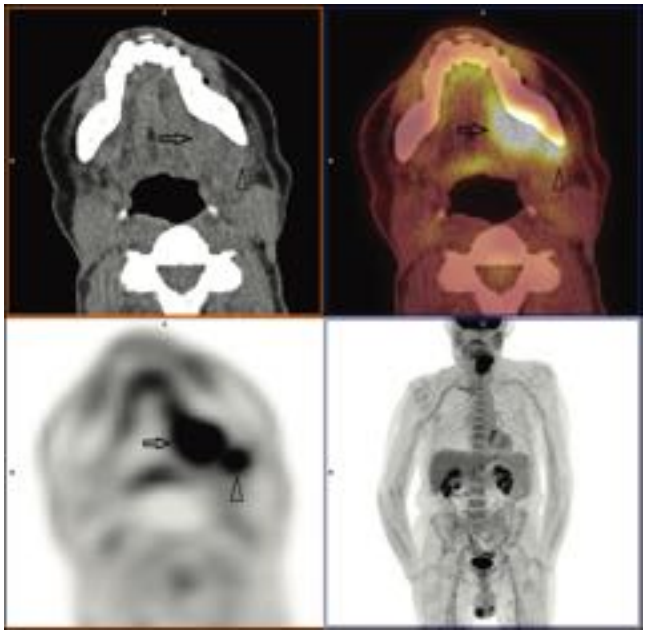


Figure 47.5 A 73-year-old man with clinical suspicion of floor of mouth SqCC recurrence. FDG PET-CT shows the left floor of mouth recurrence (arrow) and a metastatic ipsilateral level IB node (arrowhead).

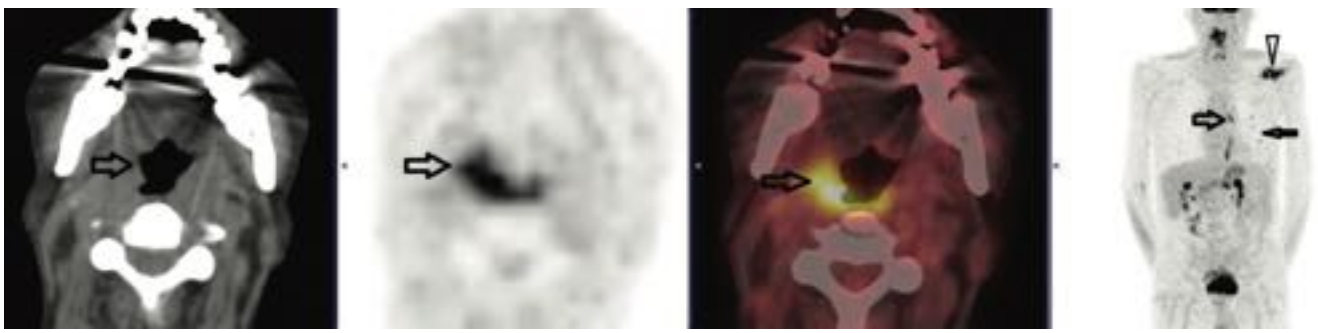


Figure 47.6 FDG PET-CT shows the right poster-lateral oropharyngeal wall recurrence (arrow). It also shows metastases in the lungs (narrow arrow) and within subcutaneous tissue around the left shoulder (arrowhead). It also shows incidental linear FDG in the chest due to oesophagitis (broad arrow).

considered the accuracy of FDG PET-CT done at least 4 months after therapy for detecting active disease at the primary site, within neck nodes and distant metastases.[35] Drawing on the pooled data of 2247 patients from 12 FDG PET and 11 FDG PET-CT studies, the pooled sensitivity and specificity for detection of disease were 0.92 and 0.87, respectively. The pooled sensitivity and specificity performed 4 to 12 months after treatment were 0.95 and 0.78, respectively, and for scans performed at or more than 12 months after treatment, 0.92 and 0.91 respectively. These results concur with a meta-analysis which reported a sensitivity and specificity for the primary site of 0.92 and 0.87, respectively, and for neck nodes 0.90 and 0.94, respectively.[36] Another meta-analysis which included 10 studies reported a sensitivity of 0.92 and specificity of 0.95 for detecting distant metastases in people with suspected head and neck cancer.[36] Individual studies show varying results and this is a reflection not only on the small number of patients in each study, but also on the various clinical situations where FDG PET was used.[35–37]

Compared with other imaging, prospective studies provide evidence that FDG PET is effective and superior to CT and MR for distinguishing active disease from treatment sequelae in people who develop symptoms during follow-up.[38-45] In a study of 38 people, FDG PET differentiated between post-irradiation laryngeal recurrent cancer from laryngeal oedema with an accuracy of 79% and was superior to CT (61%) and clinical assessment (43%).[44]

In addition, a recent study evaluated the accuracy of FDG PET-CT with intravenous contrast for suspected recurrent H&N SqCC in 170 people who underwent FDG PET-CT, which consisted of non-contrast-enhanced and contrast-enhanced CT, to investigate suspected recurrence. Diagnostic performance of FDG PET-CT / contrast enhanced CT (FDG PET-CT/ceCT), FDG PET-CT / non-contrast-enhanced CT (FDG PET-CT/ncCT) and contrast-enhanced CT (ceCT) for local or regional recurrence, distant metastasis, overall recurrence and second primary cancer was evaluated. FDG PET-CT was a more accurate restaging tool than ceCT. The added value of ceCT to FDG PET-CT is minimal.[46] The study supports the conclusion from a previous retrospective study which compared FDG PET-CT to that of contrast-enhanced CT and to standard-of-care follow-up, physical examination and endoscopy, in detecting locally recurrent H&N cancer. FDG PET-CT had higher accuracy than contrast-enhanced CT alone and increases the sensitivity and negative predictive value of physical examination and endoscopy.[47]

The value of FDG-PET as a surveillance tool for patients with high risk of relapse remains unclear. A survey of the literature extending to March 2012 found a lack of evidence to support FDG PET-CT surveillance of people with H&N cancer.[2] There have subsequently been several further published studies. These studies show FDG PET-CT can detect disease before it is clinically evident. One retrospective review included 512 patients who underwent surveillance FDG PET-CT. FDG PET-CT was performed at 3-month intervals, starting 2 months after the conclusion of therapy with scans routinely obtained at 2, 5, 8 and 14 months after therapy. Patients were assessed clinically and radiographically for at least 12 months from their last FDG PET-CT (mean, 26 months; median, 28 months; range, 12–89 months) to determine recurrence rates. All suspected recurrences underwent biopsy for confirmation. A single FDG PET-CT with negative findings carried a NPV of 91%, which is not adequate to defer further radiological surveillance. Two consecutive FDG PET-CT examinations with negative findings within a 6-month period, however, resulted in a NPV of 98%, which could obviate further radiological imaging in the absence of clinical signs of recurrence.[48]

One single institution prospective study performed FDG PET-CT at 6 months after the end of treatment in all 116 patients treated for histologically proven H&N cancer from April 2009 to May 2012 who did not show any findings suggestive of recurrence at 6 months of their usual follow-up. FDG PET-CT findings were correlated with histopathology or imaging follow-up. Results from the study included 116 patients. Of the 82 FDG PET-CT considered as negative, only one had a recurrence. Among the 34 positive FDG PET-CT, 22 relapsed whereas 12 did not show evidence of recurrence. The sensitivity and specificity of FDG PET-CT were 96% (22/23) and 87 % (81/93), respectively. The positive predictive value was 65% (22/34). The negative predictive value was 99% (81/82). The overall accuracy was 89% (103/116). Of the 116 patients, FDG PET-CT highlighted 22 (19%) subclinical recurrences. These results confirmed that FDG PET-CT is more accurate than conventional follow-up physical examination alone in the assessment of recurrence after previous curative treatment for H&N SqCC.[49] One retrospective review was performed on a series of H&N patients at a single institution who had undergone FDG PET-CT as an integral part of follow-up after definitive treatment. Of the 123 patients, 24 (20%) had asymptomatic lesions (either recurrent or new primaries) on FDG PET-CT (8% of surveillance scans) at an average interval of 35.7 weeks post treatment. Asymptomatic lesions were detected most frequently at distant sites, with 50% being thoracic, but also included were primary (9%), regional (9%), and other distant (32%) sites. At last follow-up of the 24 patients in whom an asymptomatic lesion was detected, 14 have died of disease; 10 remain alive, 4 with disease; and 1 patient had a subsequent recurrence treated and is currently disease-free. The authors concluded that FDG PET-CT is an effective tool for detecting asymptomatic disease in people previously treated for H&N cancer. Disappointingly, they found that even with early detection of recurrent disease, the mortality rate remains high.[50] In a 10-year retrospective analysis of H&N cancer patients with long-term serial imaging, those with negative 3-month imaging appear to derive limited benefit from subsequent FDG PET-CT surveillance. Furthermore, no survival differences were observed between PET/CT-detected and clinically detected recurrence.[51] So even if results substantiate the ability to predict recurrence

earlier than conventional assessment, there remains the question of whether earlier detection afforded by FDG PET-CT results in an improved clinical outcome.

Other comments

CHARACTERIZATION OF INDETERMINATE LESIONS

In common with other cancers, FDG PET-CT is a key investigation for the assessment of lesions indeterminate on usual assessment when improved characterization can change the treatment plan. These indeterminate lesions are usually in the lung, liver and adrenal glands, with the lung being the most common site. FDG PET has been shown to be an accurate non-invasive test for the diagnosis of pulmonary lesions. In a meta-analysis limited to pulmonary nodules including 13 studies with a total of 450 nodules, FDG PET had a sensitivity of 93.9% and specificity of 85.8% respectively.[52] Another meta-analytic comparison of the cross-sectional imaging modalities for the diagnosis of malignancy in SPNs (up to 3 cm diameter) from a pooled analysis of 1008 nodules from 22 eligible studies reported a similar sensitivity and specificity of FDG PET, 95% and 82%, respectively.[53] Abscesses and granulomas including those due to sarcoid, tuberculosis (TB), anthracite and fungus (asperilloma, blastomycosis, coccidiomycosis, cryptococcosis, histoplasmosis) can mimic malignant lesions.[54, 55] False-negative FDG PET-CT results are unusual, although mucinous carcinomas such as those arising from the stomach, highly-differentiated neuroendocrine carcinoma and adenocarcinoma, especially within a scar, can cause confusion.[54, 55] Lesions smaller than 1 cm across can be detected by FDG PET-CT, as detection is influenced not only on size but also FDG avidity of the lesion. That said, with lesions less than 1 cm false-negative results occur and so a negative FDG PET-CT must be interpreted with caution and cannot reliably exclude malignancy.[55] Recent British Thoracic Society Guidelines recommend FDG PET-CT as the preferred investigation in the further evaluation of pulmonary nodules, partly because it is widely available and partly because no alternative investigation shows superiority.[56]

In detection of synchronous and metachronous malignancies (**Figures 47.7** and **47.8**) FDG PET-CT will detect synchronous other H&N cancers and lung cancers, linked by their common aetiologies. In addition, FDG PET-CT will also diagnose unexpected other cancers. The cumulative incidence of a second malignancy following H&N cancer is up to 18%.[57] Fewer than half will have a detectable synchronous primary malignancy and almost half will be detected by a thorough clinical assessment and a further number by chest CT. So the expected pick-up rate of FDG PET-CT at the time of primary diagnosis is likely to be in the order of 2–3%. This is substantiated by one South Korean study of 349 patients. FDG PET-CT detected second primary H&N cancer over 2 years in 14 people, 10 (2.8%) at initial staging and 4 (1.2%) during the follow-up, with a mean duration of 15 months; H&N cancer arising from the nasal cavity: one, lung cancers: seven, colorectal cancer: two, thyroid: two, upper GI tract: two.[57] The low rate of synchronous malignancy perhaps does not justify routine screening. However, when FDG PET-CT is indicated for other reasons, detection of an unexpected second cancer

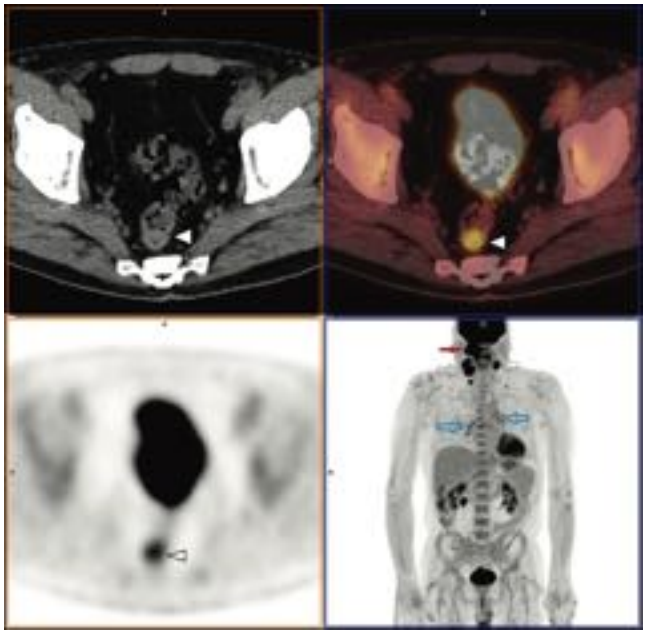


Figure 47.7 A 45-year-old man with nasopharygeal cancer. FDG PET-CT shows incidental focal intense FDG uptake in the pelvis (arrowhead). Excision biopsy confirms a small rectal cancer. The maximum intense projection (MIP) image shows the nasopharyngeal cancer (red arrow) and bilateral neck nodal disease (hollow arrow). It also shows FDG avid nodes in the chest due to a sarcoid like reaction (blue arrow).

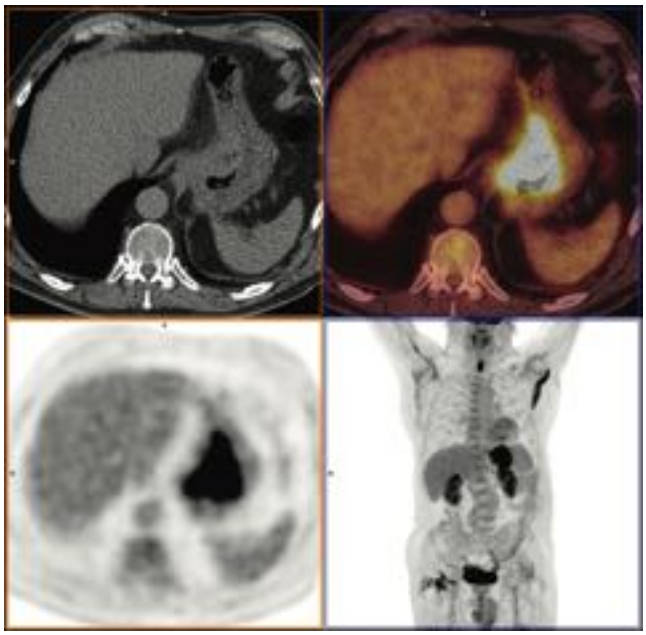


Figure 47.8 FDG PET-CT shows the primary laryngeal cancer. It also shows a silent synchronous stomach cancer. FDG uptake in the stomach is usually due to Helicobacter Difficile infection, which can be focal or diffuse and FDG PET-CT cannot reliably distinguish between the two conditions.

may influence the plan of treatment. The main dilemma is that both malignant and benign incidental lesions are FDG avid and often only biopsy or excision of the lesion can distinguish between the two. This may lead, in some people, to unnecessary investigations and in some the additional unnecessary tests may contribute to delayed initiation of treatment.

FDG uptake and outcomes

There is increasingly strong evidence that pre-treatment FDG PET-CT uptake at the primary site and within involved nodes is an independent predictor of subsequent prognosis. Two meta-analyses concluded that there was a correlation between SUVmax and outcome in people with H&N cancer.[58, 59] Most studies included in the meta-analyses, however, report either univariate or relatedly small multivariate analyses. More recently, one single-centre study which included 287 people confirmed FDG uptake retains statistical significance in multivariate analysis and has a clinically relevant prognostic impact.[60] The contribution of FDG uptake to personalized treatment of H&N cancer has yet to be formally assessed.

EMERGING APPLICATIONS

Response assessment

The role of FDG PET/CT in this area is evolving. With revived enthusiasm in chemotherapy for H&N SqCC, there is interest in non-invasive imaging which can distinguish responders from non-responders early during treatment. FDG PET-CT has been shown to predict early-on response to neo-adjuvant chemotherapy in a variety of solid tumours including oesophageal carcinoma. There is currently one published study for H&N SqCC. In 15 patients, an FDG response after two cycles of chemotherapy predicted event-free survival.[61]

Radiotherapy (RT) planning

FDG PET-CT is increasingly used for radiotherapy target volume delineation.[62] Benefits include inter-observer variability in gross tumour volume (GTV) delineation reduction, GTV size reduction and identification of tumour that would not otherwise have been treated but for PET-CT, reducing geographical misses. However, two major challenges prevail. Firstly, inflammation leads to tumour margin over-estimation. Secondly, there is presently no reliable, universally accepted, standardized method of identifying tumour margins. Notwithstanding, two small retrospective studies show significantly better overall survival and event-free survival applying FDG PET-CT-based intensity modulated radiotherapy (IMRT), compared with the control group.[63, 64] More studies are needed to clarify the benefits of FDG PET-CT in this area.

NON-SQUAMOUS CELL CARCINOMA

Thyroid cancer

FDG PET-CT is of limited value for the pre-operative assessment of thyroid nodules as both malignant and benign thyroid lesions can be equally avid for FDG.[65] However, it has an important role in the assessment of differentiated thyroid cancer, which includes papillary and follicular histological types, following treatment.[66] In this group, metastases have an alternating pattern of uptake with 131-iodine and FDG where either some 131-iodine uptake combined with low FDG trapping or no 131-iodine uptake combined with high FDG trapping.[67] The hypothesis was that persistent iodine metabolism is consistent with better cell differentiation, while the loss of this ability together with increased glucose metabolism is consistent with dedifferentiation.[67] A meta-analysis of 958 patients from 20 studies which

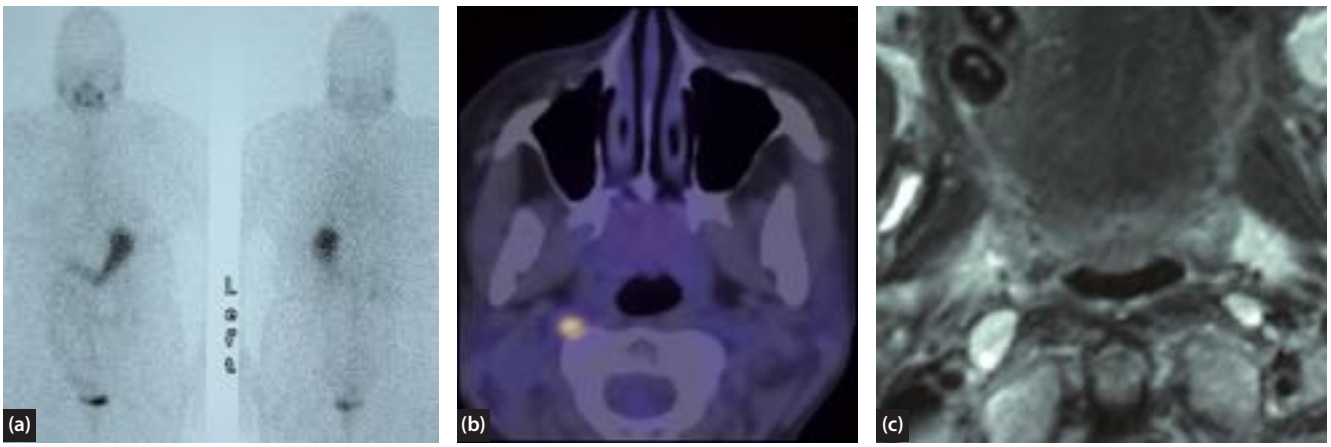


Figure 47.9 A 48-year-old woman following treated for follicular thyroid cancer with elevated and raising serum thyroglobulin levels. **(a)** No unaccountable uptake on 131 I-iodine scan **(b)** FDG PET-CT shows a left prevertebral node in keeping with active disease at this site. It also shows no other suspicious areas. **(c)** The node corresponded to an indeterminate node on MRI. Subsequent surgery confirmed the FDG PET-CT; subsequent fall in serum thyroglobulin level following surgery.

included 11 studies that used FDG PET only, 7 FDG PET-CT only and 2 studies which used both FDG PET and FDG PET-CT, confirmed the value of FDG PET-CT in treated papillary and follicular thyroid cancer patients who have suspected recurrent disease and negative 131-iodine scan, with a pooled sensitivity of 95%, and specificity 81%, respectively, and compared favourably with FDG PET, sensitivity and specificity 84%.[66]

With regard to other histological types of thyroid cancer, FDG PET-CT can detect Hurthle cell carcinoma and anaplastic carcinoma.[68, 69] However, the clinical role of FDG PET-CT in these tumours is currently unclear. Concerning medullary thyroid cancer, preliminary results suggest FDG PET to be an accurate technique for detecting metastases and recurrent disease. The largest study in the literature, a German multicentre retrospective survey, reviewed 100 FDG PET studies performed on 85 patients.[70] The results of the FDG PET were compared with 46 indium-111 pentetreotide (SMS) studies, 33 Pentavalent technetium dimercaptosuccinate acid (DMSA) scans, 8 hexakis (2 Methoxyisobutyl isonitirile) technetium-99m (MIBI) scans, 64 CT and 37 MR. One hundred and eighty-one lesions were identified by at least one technique; FDG PET detected the majority of lesions with a lesion detection probability of 68% compared with 25% for SMS, 29% for DMSA, 6% for MIBI, 53% for CT and 58% for MR. In the 55 lesions confirmed histologically, FDG PET had the highest overall accuracy with a sensitivity of 78% and specificity of 79%; MR had a slightly higher sensitivity of 82%, but a specificity of 67% and MIBI had a specificity of 100%, but a sensitivity of only 25%.

OTHER MALIGNANT TUMOURS

There is limited evidenced guidance for the use of FDG PET-CT here, beyond anecdotal reports, as these tumours are extremely rare. Notwithstanding, FDG PET/CT is often done prior to treatment and for several reasons. Firstly, to demonstrate that the tumour is FDG avid. And if so, FDG PET-CT is considered for pre-treatment staging, and subsequently to detect residual/ recurrent disease.

In one published report of post-operative parathyroid carcinoma, FDG PET provided more accurate information compared with other imaging.[71] FDG PET-CT cannot reliably distinguish between malignant and benign major salivary gland tumours as both can be equally FDG avid.[72] It can, however, be useful for distinguishing active disease from sequelae of treatment.[73] Caveat, muco-epidermoid and adenoid cystic cancers may not be FDG and particularly following treatment.[74] FDG PET-CT is effective for detecting lymphoma except low-grade non-Hodgkin's lymphoma and extra-nodal marginal zone B-cell lymphoma, which are not consistently FDG avid.[75, 76] H&N malignant melanomas, sarcomas and paraganglionomas have been shown to be FDG avid.[77, 78]

Normal variants and artefacts

Brown adipose-tissue FDG uptake can be difficult to distinguish from adjacent small FDG avid nodes, especially when there is slight mis-registration of PET to CT.

Skeletal muscle FDG uptake is usually linear and symmetrical and does not pose a diagnostic quandary. Occasionally, pre-vertebral muscle FDG uptake and

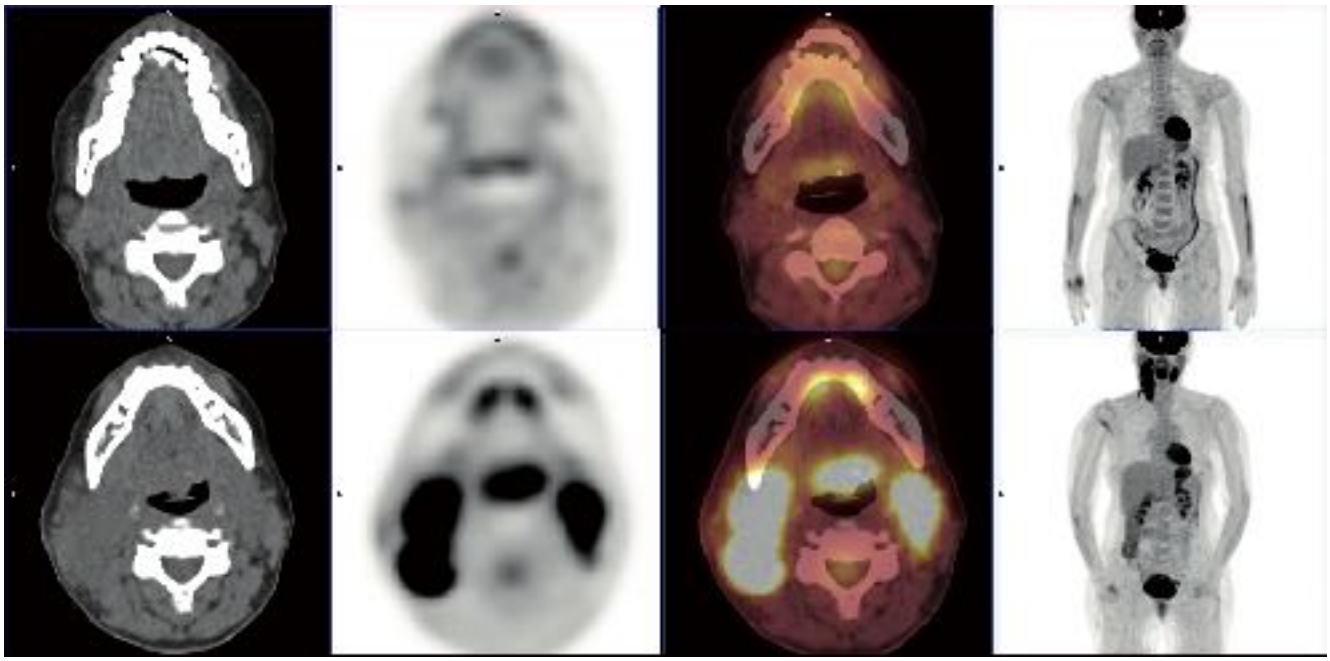


Figure 47.10 A 36-year-old woman with non-Hodgkin's lymphoma. **FDG PET-CT** shows (bottom row) intense FDG uptake in enlarged nodes in the neck on both sides and within Waldeyer's ring lymphoid tissue in the tongue base, (top row) following completion of chemotherapy, there is resolution of FDG activity in the tongue base and neck nodes; all that remains are indeterminate non FDG avid nodes in the neck.

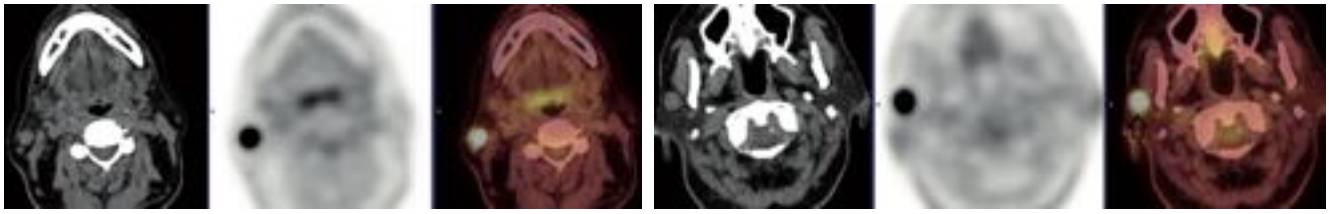


Figure 47.11 A 25-year-old woman who presented with a neck node due to malignant melanoma. FDG PET-CT shows (top row) intense FDG uptake in the involved right neck node. It also shows (bottom row) an intensely FDG avid nodule within the right parotid gland. Malignant and benign parotid lesions are FDG avid and so fine-needle aspiration cytology was required to confirm the diagnosis. Both lesions were resected and provided histological confirmation of the FDG PET-CT diagnosis. Importantly, FDG PET-CT demonstrated that there was no disease beyond the head and neck.

especially when asymmetrical, needs separating from pre-vertebral nodal FDG uptake, and this may not be possible without resorting to correlation with MR or post-intravenous contrast CT.

Waldeyer's ring normal lymphoid tissue FDG uptake in the nasopharynx, tongue base (lingual tonsil) and palatine tonsils needs careful distinction from FDG uptake from an occult primary tumour arising at these sites, these being common sites for an occult primary tumour. That said, the role of FDG PET-CT is not to make the diagnosis but to increase the number of malignancies diagnosed at EUA and biopsy. In this setting, a low threshold for diagnosing abnormality should be adopted and any asymmetrical FDG uptake at these sites reported. SUV measurement is of limited use because of the overlap of values between tumour and normal lymphoid tissue.[79]

Dental amalgam causes FDG uptake in the anterior two thirds of the mouth. In practice, this rarely poses a clinical dilemma. If there is doubt as to the cause, direct inspection and palpation will almost invariably provide reassurance.

LIMITATIONS/PITFALLS

As on CT/MR, branchial cysts can be challenging to distinguish from necrotic nodes. No FDG uptake in the wall of the lesion favours the diagnosis of a branchial cyst. On the other hand, presence of FDG uptake in the lesion wall does not assist, as both pathologies can show this appearance, the necrotic node due to tumour and inflammation and the branchial cyst due to inflammation.

Granulomatous disease mimicking metastases deserve comment. Firstly, sarcoid and sarcoid-like reaction. With FDG uptake in chest nodes careful distinction needs to be made between those due to sarcoid-like reaction and cancerous nodes. Sarcoid-like reaction is not rare in H&N cancer. There is also an increased likelihood in recurrent disease. The pattern of FDG uptake assists. FDG uptake in normal-sized nodes which include those in paratrachea, both hila and subcarina would favour sarcoidosis, especially if there are no FDG avid neck nodes, but even when there is neck nodal disease.[80] In addition, sarcoid can mimic disease beyond chest nodes including in the lung, liver and bone.[81] Secondly, TB needs distinction from malignancy, and especially from lung metastases and synchronous lung malignancy.

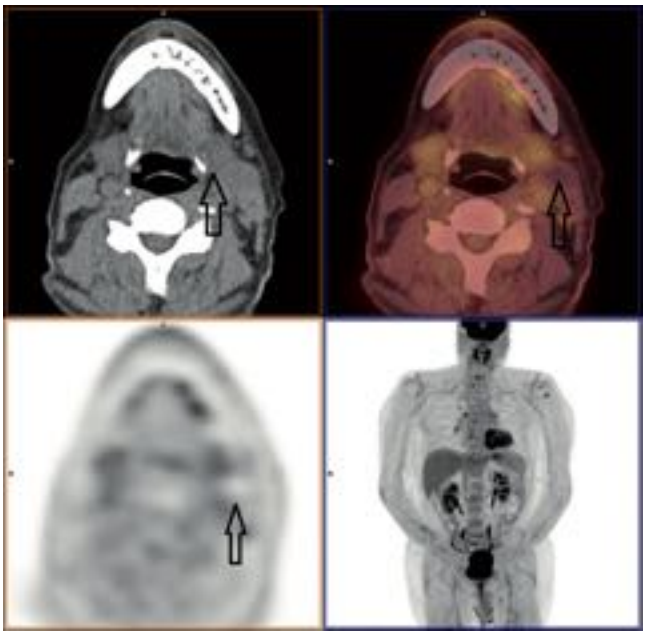


Figure 47.12 Branchial cyst. FDG PET-CT shows a left level IIA cystic lesion with no FDG uptake (hollow arrow).

Lung metastases and synchronous lung cancers can pose a challenge to diagnosis. Adeno-carcinoma may not be FDG avid. Also small sub-centimetre lung metastases may not be FDG avid.

Post-treatment, before making the diagnosis of residual or recurrent disease FDG uptake due to treatment sequelae needs careful consideration (**Table 47.1**). In clinical practice, taking a pragmatic approach, and drawing from experience, a definitively positive FDG PET-CT should be taken as highly suspicious of disease as long as there is no infection. A negative scan is highly likely to represent absence of active disease, but still demands careful surveillance as microscopic foci of active disease cannot be excluded. An equivocal scan requires biopsy of areas of FDG activity or an early repeat FDG PET-CT. False-positive and false-negative results occur and so FDG PET-CT findings must be interpreted, not in isolation but in the context of the overall assessment.[35–37, 38–45] This is especially pertinent as determination of definitely positive, definitely negative and equivocal FDG uptake is still relatively subjective as, notwithstanding efforts, there is

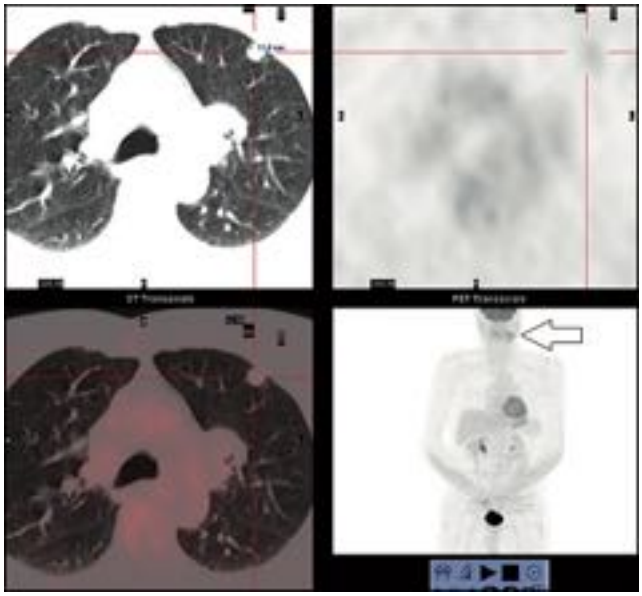


Figure 47.13 A 61-year old-man with SqCC recurrence in the left post-treatment neck FDG PET-CT shows the neck recurrence (arrow) and a left upper lobe lung adenocarcinoma, which shows no FDG uptake (centre of red cross-hairs).

currently no universal consensus agreement on the meaning of these terms.[82]

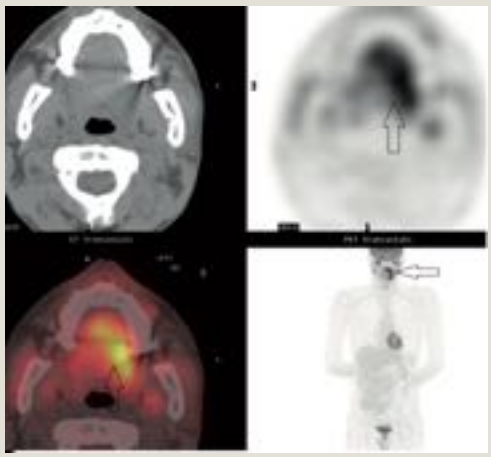
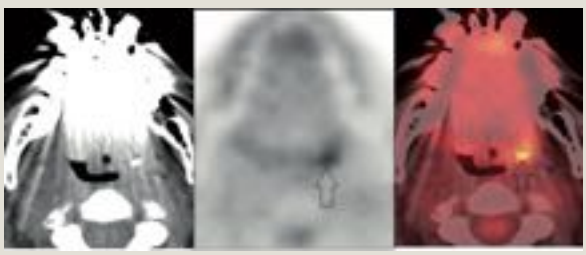
There is a commonly held view that recent biopsies cause focal FDG uptake in the H&N. This concern is probably overestimated as biopsies are usually tiny and limited to the mucosa.

RADIOTRACERS OTHER THAN FDG

Thymidine 3-Deoxy-3-^{18}F-fluorothymidine [FLT]

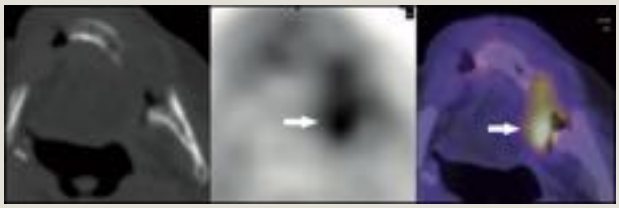
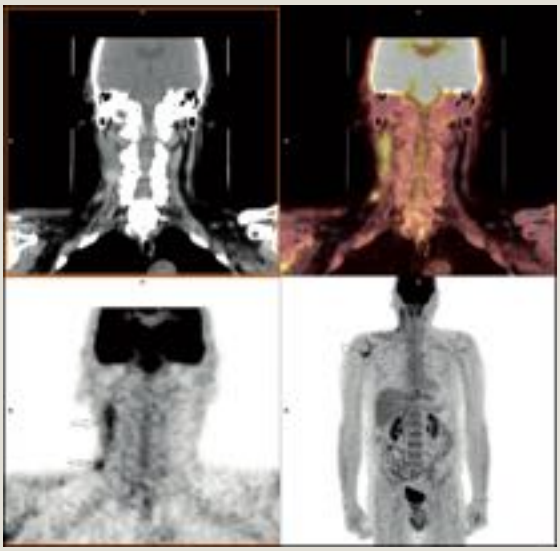
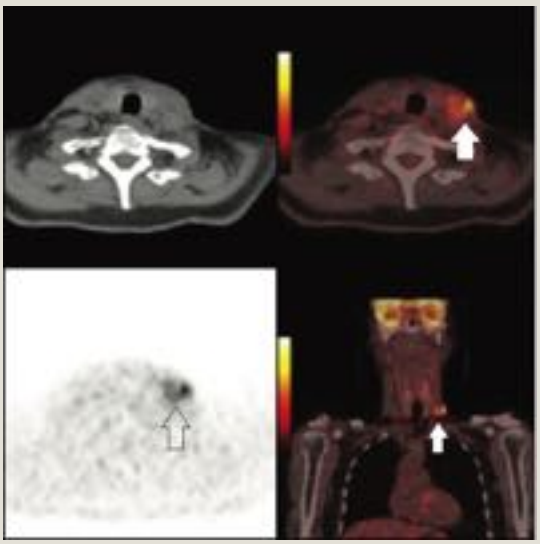
Currently, its only potential role is for more accurately distinguishing lung metastases and from benign lesions, compared with FDG.[83–85] However, if confirmed that FLT is only taken up by malignant cells, then this may be of value on the rare occasion when more information on the extent of disease at the primary site is required following usual assessment for treatment planning. Also, FLT may be effective for detecting residual disease following RT and chemotherapy and to predict the outcome to RT and chemo-RT.[86–88]

TABLE 47.1 Sequelae of interventions that mimic active disease following surgery

Residual tongue mimicking recurrent disease Asymmetrical FDG uptake in the oral cavity and oro-pharynx following partial resection of the tongue and hypertrophy of the normal residual tongue. Such an appearance also occurs following radiotherapy to the tongue.	 FDG PET-CT shows intense FDG uptake in the left oral cavity and oro-pharynx following radiotherapy which included the right side of the oral cavity and oropharynx [hollow arrow].
Post-tonsillectomy The normal palatine tonsil mimics a palatine tonsil lesion, particularly relevant when looking for an occult primary site or assessing for recurrent disease.	 The normal left palatine tonsil mimics a palatine tonsil lesion. [hollow arrow], following a previous right tonsillectomy,

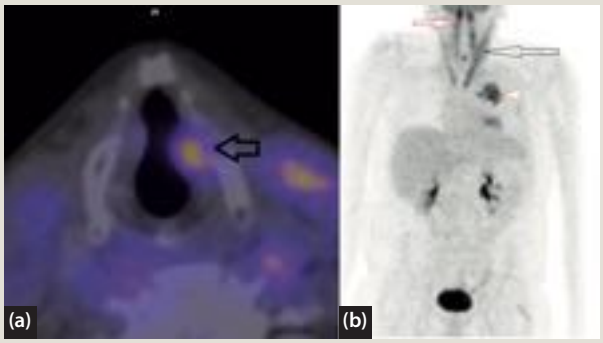
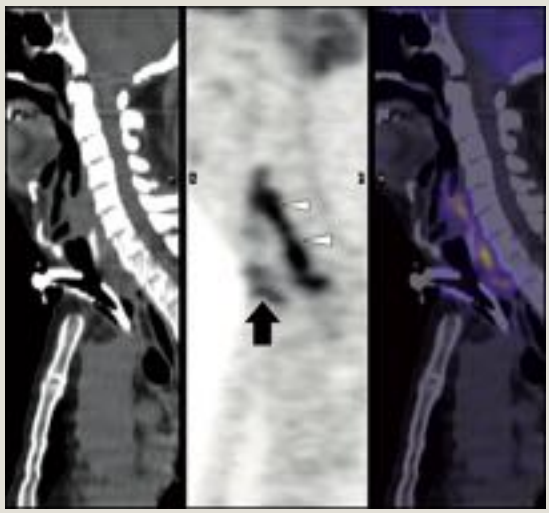
(Continued)

TABLE 47.1 *(Continued)* Sequelae of interventions that mimic active disease following surgery

Osteonecrosis following surgery This can also occur following radiotherapy. FDG PET-CT cannot reliably distinguish osteonecrosis from infection and recurrence.	 FDG PET-CT shows intense FDG uptake due to osteonecrosis following surgery to the left mandible (arrow).
Following recent neck dissection FDG uptake occurs directly related to inflammation post-surgery. Cylous collections also cause FDG uptake.	 FDG PET-CT shows intense FDG uptake in the right neck 6 weeks following neck dissection (arrow). Right gleno-humeral joint synovitis due to osteoarthritis causing incidental FDG uptake (arrowhead).  FDG PET-CT shows intense FDG uptake related to a cylous collection complicating neck dissection.

(Continued)

TABLE 47.1 ***(Continued)*** Sequelae of interventions that mimic active disease following surgery

Granulomas Specifically, vocal cord injection with Teflon and collagen needs distinction from a primary vocal cord cancer. Stitch granuloma following neck dissection also very rarely causes increased FDG uptake and needs distinction from a neck node containing disease.	 **(a)** FDG PET CT shows intense FDG uptake related to a granuloma post vocal cord injection (hollow black arrow). **(b)** FDG PET-CT also shows the cause of the left vocal cord palsy, namely a left upper lobe non-small cell cancer invading the mediastinum and causing left recurrent laryngeal nerve paralysis (arrowhead). There is also FDG uptake in normal prevertebral (hollow red arrow) and steno-mastoid muscles (hollow black arrow).
Following other interventions	
Radiation myelitis A very rare complication with modern radiotherapy techniques.	
Around stoma sites FDG uptake due to inflammation needs consideration as an alternative to recurrence around the tracheostomy stoma site and tract. FDG uptake is also present around gastrostomy stoma sites.	 Increased FDG uptake around the tracheostomy stoma site and tract (arrow). There is also FDG uptake related post cricoid SqCC (arrowhead).
Gastrostomy stoma site	
Post-chemo-radiotherapy neck Especially in HPV-positive people mild FDG uptake can persist in post-treatment neck nodes beyond 8 weeks.	

Radiotracers for detecting hypoxia

There has been considerable interest in PET tracers which can detect hypoxia in H&N SqCC, because inadequate treatment of hypoxic cells is one of the main causes of failure to effectively treat the primary site. Hypoxic cells require three times more radiation to kill compared with non-hypoxic cells; often it is not possible to deliver the required dose because of the damage it will cause to surrounding normal tissue. Imaging of hypoxia would provide the opportunity to apply RT to the subvolume of hypoxic cells only.[89, 90]

Fluorinated nitromidazole compounds, including 1-[2-nitro-1-imidazolyl-3[^{18}-F]fluoro-2-propanol [[^{18}F]FMISO], have been used for imaging hypoxia in H&N SqCC*. Copper isotopes of varying half-life, including ^{60}Cu, ^{61}Cu, ^{62}Cu and ^{62}Cu labelled to copper-diacetyl-bis(N^4-methyl-thiosemicabazone) [Cu-ATSM] and copper-pyruvaldehyde-bis(N^4-methylthiosemicarbazone [Cu-PTSM] have also

* Other florinated nitromidazole compounds that have been studied include 1-(5-[^{18}F]fluoro-5-deoxy-α-D-arabinofuranosyl)-2-nitro-imidazole [[^{18}F] FAZA], ^{18}F-2-(2-Nitro-imidazol-1-yl)-N-(3,3,3-trifluropropyl)-Acetamide [^{18}F-EF3] and ^{18}F-Fluoroerythronitromidazole [^{18}F-FETNIM]

been studied. There is as yet no one clear front runner. [^{18}F]FMISO is the most commonly used and best validated tracer and most studies have shown correlation between hypoxia and [^{18}F]FMISO uptake.[91] But it is only slowly cleared from the blood compartment and the radiotracer passively diffuses into the cell which takes a relatively long time. This means that for imaging to be effective it has to be done between 2 to 3 hours post-injection.[92] There are as yet inadequate data to recommend the other tracers as superior.

11C-choline PET/CT

In a pilot study^{11}C-choline improved the delineation of orbital and skull involvement compared with FDG PET/CT in people with nasopharyngeal cancer.[93] This is because physiological ^{11}C-choline uptake in the brain and extra-ocular eye muscles is minimal compared with FDG. The advantage of ^{11}C-coline beyond this specific scenario has been questioned.[94]

PET-MRI [magnetic resonance imaging]

Integrated PET-MRI is an emerging technology, a development of registering PET with MRI obtained from different scanners.[95] Combining PET with MRI for assessment of H&N cancer is an area of considerable interest because MRI is often performed as a complement to PET-CT in the assessment of H&N cancer. The added value of PET-MRI compared with separate PET-CT and MRI scanning has yet to be fully evaluated. Beyond a significantly lower dose of ionizing radiation, the advantage of PET-MRI as an alternative to PET-CT is unclear. A pilot study of 25 patients designed to evaluate the accuracy of FDG PET-MR for loco-regional tumour evaluation compared to FDG PET-CT and MRI in initial tumour and recurrence diagnosis in histo-pathologically confirmed H&N SqCC found no significant differences were observed in T and N staging among the three modalities. In 13 patients undergoing hybrid imaging for cancer recurrence diagnosis, diagnostic accuracy was 57% with MRI and 72% with FDG PET-CT and FDG PET-MRI, respectively.[96] In a study designed to evaluate and compare the diagnostic potential of FDG PET-MRI to FDG PET-CT for people with cancer of unknown primary a total of 20 patients underwent a dedicated head and neck and whole-body FDG PET-CT and subsequent simultaneous FDG PET-MRI. Both hybrid imaging techniques provide a comparable diagnostic ability for detection of primary cancer and metastases, with comparably high-lesion conspicuity and diagnostic confidence, offering superior assessment of cervical lesions in PET-MRI and potentially of pulmonary lesions in PET-CT.[97]

BEST CLINICAL PRACTICE

FDG PET-CT is not necessary for all people with Head and Neck cancer. For many, clinical assessment complemented by conventional imaging will give all the necessary information for providing the person with H&N cancer with enough information to make an informed choice of treatment and for the planning treatment. However, with the current evidence:

In SqCC:

- ✓ Offer FDG PET-CT in T3, T4 nasopharyngeal and hypopharyngeal cancer and N3 nodal disease; consider FDG PET-CT in others with a moderate and high risk of disseminated disease.
- ✓ Consider FDG PET CT where staging is difficult clinically; for example, where there is uncertainty on other imaging or equivocal findings that would preclude radical treatment.
- ✓ Offer FDG PET-CT following completion of chemo-radiotherapy in advanced neck nodal disease to inform the need for neck dissection.
- ✓ Consider FDG PET CT when there is suspicion of recurrent disease and equivocal on radiological assessment.

Consider FDG PET-CT in occult primary tumours prior to EUA.

Offer FDG PET-CT in papillary and follicular thyroid cancer post-treatment with suspected recurrence.

Consider FDG PET-CT in treated medullary thyroid carcinoma associated with elevated calcitonin levels with equivocal or normal cross-sectional imaging, bone and octreotide scintigraphy.

Consider FDG PET-CT pre-treatment in rare cancers to confirm that the tumour is FDG avid, and especially if there is a reasonable chance that subsequently FDG PET-CT may be considered for detection of residual / recurrent disease.

Consider FDG PET-CT in indeterminate lesions which are not accessible to biopsy or where a biopsy would be particularly hazardous.

FUTURE RESEARCH

- ➤ Large prospective studies evaluating FDG PET-CT as an early predictor of response to neo-adjuvant treatment in Head and Neck SqCC.
- ➤ Large prospective studies evaluating the value of FDG PET-CT as a surveillance tool in Head and Neck SqCC with high risk of recurrence.
- ➤ PET-CT studies with hypoxic and cell proliferation markers for evaluating the biology of malignant Head and Neck tumours.

KEY POINTS

- The use of FDG PET-CT in Head and Neck cancer is supported mainly by data from observational and non-randomized studies. There are limited randomized controlled trials available.
- The body of evidence shows that FDG PET-CT appropriately used can contribute to more accurate assessment of Head and Neck cancer, including more accurate staging, earlier and more accurate detection of residual and recurrent disease, improved detection of the occult primary and earlier detection of occult disease in treated differentiated thyroid cancer.

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CHAPTER
48

IMAGE-GUIDED SURGERY, 3D PLANNING AND RECONSTRUCTION

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: image-guided surgery, endoscopic sinus surgery and skull base surgery.

INTRODUCTION

The use of X-ray images to guide a surgeon dates back to the middle of the 20th century. Pioneering attempts to use Cartesian coordinates to determine locations of target points in the brain in three-dimensional space predated the development of computers. The limitations of radiographic images did not stop scientists from developing over 40 stereotactic apparatus by the 1950s.[1]

The development of both computers and digital imaging opened up the field of computer-aided surgery to include their use in diagnosis, pre-operative planning, surgical simulation, intra-operative image guidance, robotics, telemedicine and, no doubt, numerous other applications yet to come.

The term computer-aided surgery is used to describe computer-aided surgical planning, surgical simulation, intra-operative image guidance, robotics and prosthetics design and manufacture. Computer-aided surgery has become an integral part of modern surgical practice and training in all surgical specialties including neurosurgery, otorhinolaryngology, maxillo-facial, general and orthopaedic surgery.

BACKGROUND AND OVERVIEW

A CT or MRI scan produces a stack of digital images to create a 3D volume.[2] The data within this volume can be extracted and used as an accurate representation of the patient anatomy. Anatomical structures can be displayed in a variety of ways to show skin, bone, muscles, tumour and other structures, including vessels, nerves and so on.[3] The data can then be made to be transparent/semi-transparent, opaque and even colour coded. Multiple data sets can be superimposed to show different tissues and structures. An MRI could be fused to a CT 3D volume and displayed simultaneously to show accurately bone and soft tissues.

A CT scan contains an extremely accurate coordinate system of the patient data. This can be used to generate 3D models of every structure including a whole head (using skin coordinates), bones, blood vessels, lesions and bone defects. These 3D models can then be used (on screen) to make measurements, and drive numerically controlled milling machines and 3D printers to create physical models representing the patients anatomy. In maxillo-facial surgery, this is extensively used to produce prostheses for reconstruction of defects in the skull.[4]

Digital image processing algorithms have been developed to segment (extract), enhance and suppress the display of any structure contained within the 3D volume.

The 3D volume of data as well as virtual surgical tools can be aligned (registered) with the patient's real world coordinates such that the surgeon would be able to navigate surgical tools and these be displayed on a computer screen to indicate their position in relationship to patient anatomy.

The display of the data to the surgeon may be presented as three orthogonal 2D images or as a 3D volume. Augmented reality displays present the real-world patient with 3D structures or even vectors superimposed to guide the surgeon. These images may be displayed through the operating microscope as overlays on the surgical field.[5]

Alternatively, part of the 3D data set can be superimposed on the patient's anatomy, thus providing the surgeon with an extraordinary 'X-ray' type vision[6] (**Figure 48.1**).

As the normal anatomy is often distorted by disease, trauma or previous surgery, and as minimally invasive surgical techniques have been developed, intra-operative image guidance has become became an invaluable tool.[7]

These 3D virtual models can be used to simulate surgery. Using appropriate devices, the surgeon is able to practice surgical techniques using a virtual model and virtual tools. These virtual tools may be used to simulate different actions including cutting, suturing, manipulation and drilling. Exercises can be designed to improve hand–eye coordination and to monitor and measure a trainee's progress and development. Some of these surgical simulators include a haptic feedback mechanism that produces a realistic 'feel' to the tool that is being used. Haptic feedback allows mistakes to be made that are essential to understanding limitations as the exercises can be repeated over and over until the trainee develops the confidence needed to perform surgery on real patients.

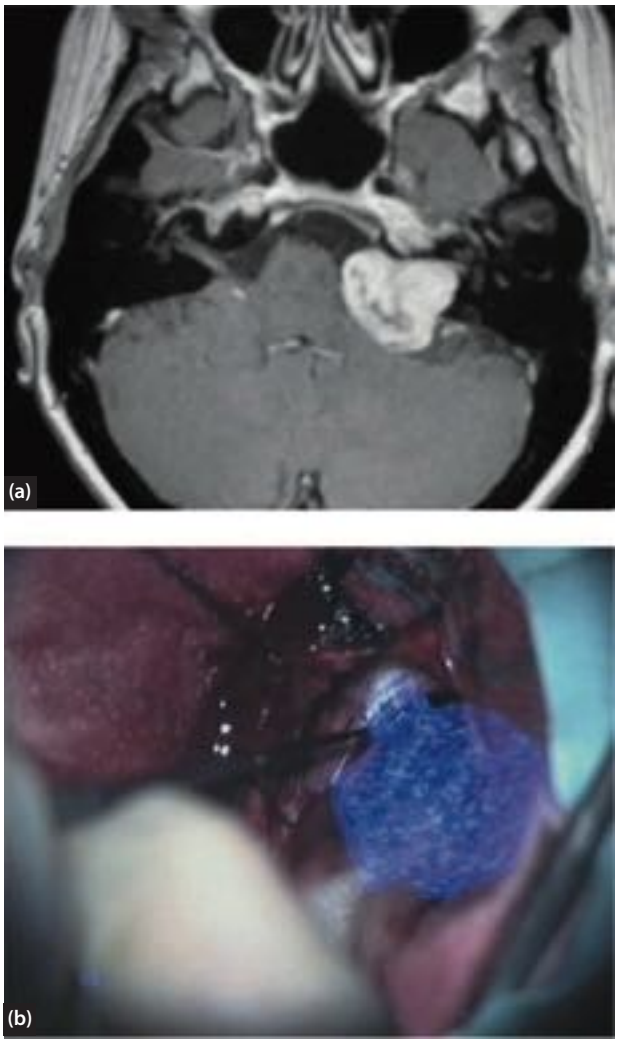


Figure 48.1 Vestibular schwannoma. (a) MR scan; **(b)** intra-operative view through the microscope with the segmented image data overlain on the operative scene.

Trainers are able to monitor progress by reviewing technical data produced by the simulator to enable them to decide whether to progress the trainee on to the next step in their surgical training.

Today's doctors are relaxed and comfortable with using computers in all aspects of their lives and this extends to their surgical practice. The use of 3D models and reconstructions as well as image processing algorithms to enhance images extends to diagnosis and pre-operative surgical planning. It is difficult to imagine a surgeon performing endoscopic sinus surgery without first reviewing a CT scan (with a bone window) of the patient's individual anatomy. The surgeon still has to reconstruct a 3D model, in his or her mind, using these 2D images and their learned and prior knowledge of anatomy. 3D reconstruction removes the guesswork and utilizes all the information to make surgery safer and to provide better training of future surgeons.

Robots have, for some time now, been used by orthopaedic surgeons to perform accurate drilling of the femur and tibia during hip and knee replacement surgery. Urologists now routinely use robots to perform prostatectomy surgery and indeed general surgeons have started to use these robots when performing minimally invasive laparoscopic surgery. ENT as a specialty has now started to use robots in transoral resection of tumours as well as thyroid surgery. The size of the robotic arms prohibits them from being used as an aid in endoscopic sinus surgery, yet it is only a matter of time before these arms are made smaller to facilitate their use as an aid to endoscopic sinus and skull base surgery.

Robots offer several advantages that enable accurate, safer and ultimately better surgery for the patient. They are extremely accurate and, when operated by a surgeon, eliminate tremor. They provide a higher degree of freedom, which enables the surgeons to perform manoeuvres that are not normally possible. The surgeon's hand movement can be magnified or miniaturized to enable extremely small and delicate movements in a small or confined space.[8,9]

The geometric accuracy of these robots and of the image guidance devices depends, not only on the precision of these instruments, but also the accuracy of the 3D data that are input to represent the patient coordinates. It is also dependent on the accuracy of registration of the data to real-world coordinates, image reconstruction and segmentation, tracking devices and the displays. In the next section we will discuss these components to enable a better understanding of the principles of computer-aided surgery, image navigation and guidance.

IMAGE RECONSTRUCTION

CT and MRI data are acquired on a 2D plane. Sequential 2D images are then stacked to create a 3D volume. The geometric accuracy of the 2D slices is extremely high and in the case of CT is even higher to a resolution as high as 0.2 mm per pixel on a 512 × 512 matrix. The 2D slices can be as thin as 0.5 mm and this, along with slice separation,

will affect the resolution in the Z (longitudinal) direction and therefore affect the resolution of the coronal and axial reconstructions. This is also applicable to multislice spiral CT scanners that acquire images in a contiguous manner. These scanners are faster, have a better resolution and expose the patient to less radiation.

Pixels and voxels

Two-dimensional slice sections are composed of pixels, which are the smallest picture elements. The more pixels, the better the resolution. Currently, the highest resolution available for both CT and MRI is 512×512 pixels per image. In a field that is 30×30 cm, this gives a high definition picture, whereas in a larger field this gives a low resolution. By convention, the image resolution is stated by the number of pixels in the x and y axis.

Each pixel has a value ranging, in the case of the CT scan, from –1000 to 3096. This is referred to as Hounsfield units (HU). CT scans are calibrated such that the value of 0 equates to the density of water. By convention, high pixel values are displayed as white. The lower the value, the lower the density of the tissue (X-ray absorption) and the darker the pixel would appear. Pixels are two-dimensional, but it is possible to convert these picture elements into a 3D block. This 3D block is referred to as a voxel or a volumetric picture element. Voxels can be a cube or cuboid depending on the inter-slice distance.

Volume averaging

If a structure falls partially within a pixel, the true value of that structure will then be assigned a value less than the normal value of the structure. In the case of bone, which has a value of say 1000 HU, the value of a pixel that includes a part of that part of the bone will be much less, perhaps 500 HU. This is referred to as partial volume averaging and is a major problem in delineating where the edge of a structure should lie within a given image. Higher resolution images would overcome that problem to some extent. This is not always possible as higher X-ray dosages would be required and an order of magnitude increase in the complexity of the hardware. Algorithms have been developed to overcome this problem and define the edge of a structure with a greater degree of confidence. Each one has its own unique problems and for clinical use in the area of neurosurgery and otorhinolaryngology the accuracy difference is submillimetric and can be ignored.

VISUALIZATION OF IMAGE DATA

Many factors have to be considered when deciding which visualization technique to use. The clinical purpose for which the data are to be used is the most significant and the image data are rendered for that purpose. *Rendering* is the process of generating computer images that represent the three-dimensional anatomy with varying degrees of tissue transparency.[10]

Surface rendering

Optical surface scanners produce structured 3D coordinate point sets that relate to an anatomical surface.[9] Triplets of data points are generally grouped as the vertices of adjacent triangles that interconnect to make up the entire surface. These triangular surface patches are known as facets or polygons.

The rendering of surfaces from volume data requires pre-processing. The properties of voxels containing anatomical surfaces must first be decided and voxels with these properties can then be processed. Usually voxels are considered to lie on a surface if they are connected and all have the same associated property within a given range of values. The derived surfaces are called isosurfaces and are selected to correspond to the surfaces of anatomical structures or to surfaces of equal functional activity.

Geometric primitives are also derived from volumetric data by processes such as contour tracing, surface extraction or boundary following. Alternatively, voxels belonging to anatomical parts may be isolated from the full data set by applying thresholds to the data values associated with them. This extraction of tissue topology has become known as ‘segmentation’. The derived geometric primitives (such as polygon meshes or contours) are rendered for display using conventional computer graphics techniques.

Figure 48.2b shows the rendering of a facial surface that is made up of a large set of triangular facets that are also shown in **Figure 48.2a**. This type of image can be produced using data from an optical scan of the face.

Volume rendering can be undertaken for notional surfaces between distinct tissue types. The surface normals are derived directly from the voxel values neighbouring the boundary. These derived surface normals are used for calculating the final image using algorithms. A technique of this sort was used to produce the image depicted in **Figure 48.2c**.

Volume rendering

Volume rendering has become the most commonly used method with which to visualize 3D medical image data. The basic idea is that 3D volumes are composed of voxels and that these are analogues of their 2D counterparts, the pixels. Fine details throughout a volume of interest are displayed, enabling a more direct understanding of visualized data with fewer artefacts.

This visualization technique works by projecting each voxel on to a viewing plane with a value related to the physical property represented in the voxel array. For example, a voxel containing bone with a high X-ray absorption coefficient might be projected with a high value. The most advanced systems allow the operator to construct a look-up table that relates the physical value associated with the voxel to the value it contributes to the image at the chosen viewing plane. A pixel in the viewing plane usually receives contributions from many voxels and the operator may control the manner in which these contributions are composed. For example, the operator may choose to

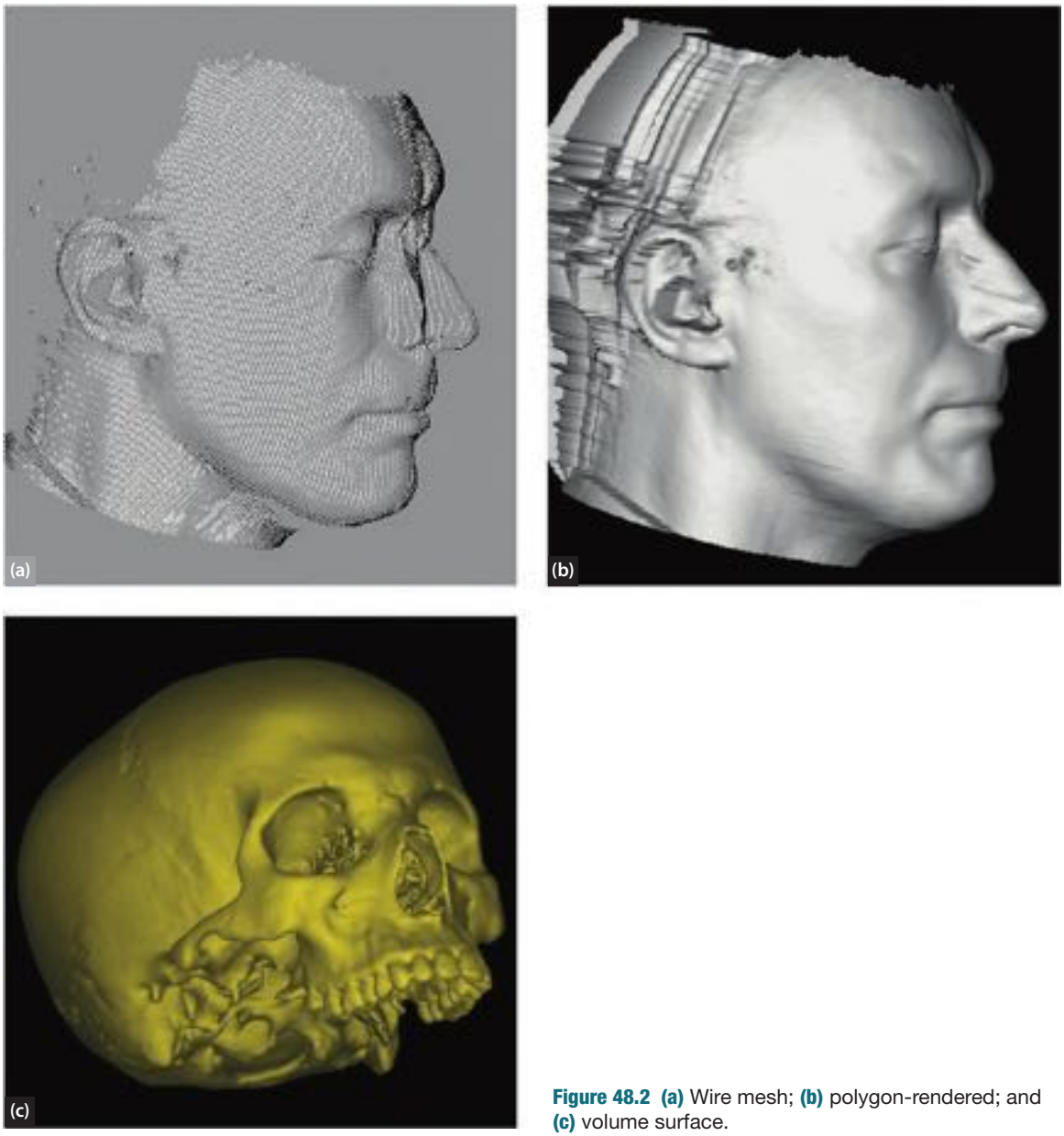


Figure 48.2 **(a)** Wire mesh; **(b)** polygon-rendered; and **(c)** volume surface.

display only the maximum contribution from any voxel along a ray. This produces an image known as the maximum intensity projection (MIP). On the other hand, any individual voxel-associated value may be assigned a maximum opacity value to produce the same images as would be produced by surface rendering.

Figure 48.3 shows two volume-rendered images with different look-up tables. These demonstrate how different anatomical structures may be made visible through others that are being rendered transparent. Major blood vessels, for example, may be effectively rendered visible within the anatomical data set.

Generally, a volume-rendered image appears different from that of a surface-rendered image in that anatomical structures are presented as having some degree of transparency. For some clinical procedures, such as image-guided biopsy or transcutaneous thermal ablation, transparency may greatly enhance depth perception and thus increase the accuracy of the procedure. It is apparent that surfaces are not explicitly rendered, but human perception reconstructs images that are perceived to be in the correct spatial relationship. The transparency that volume rendering offers also enables the placement of surgical instruments within 3D structures with great accuracy.[10]

Registration

Once the patient is secured on the operating table, registration of the Cartesian coordinates of the CT scan to that patient in the theatre is achieved by one of two methods. The first is by locating anatomical landmarks visible both on the patient and image data using a probe that is visible to the tracking device. For example, using navigation

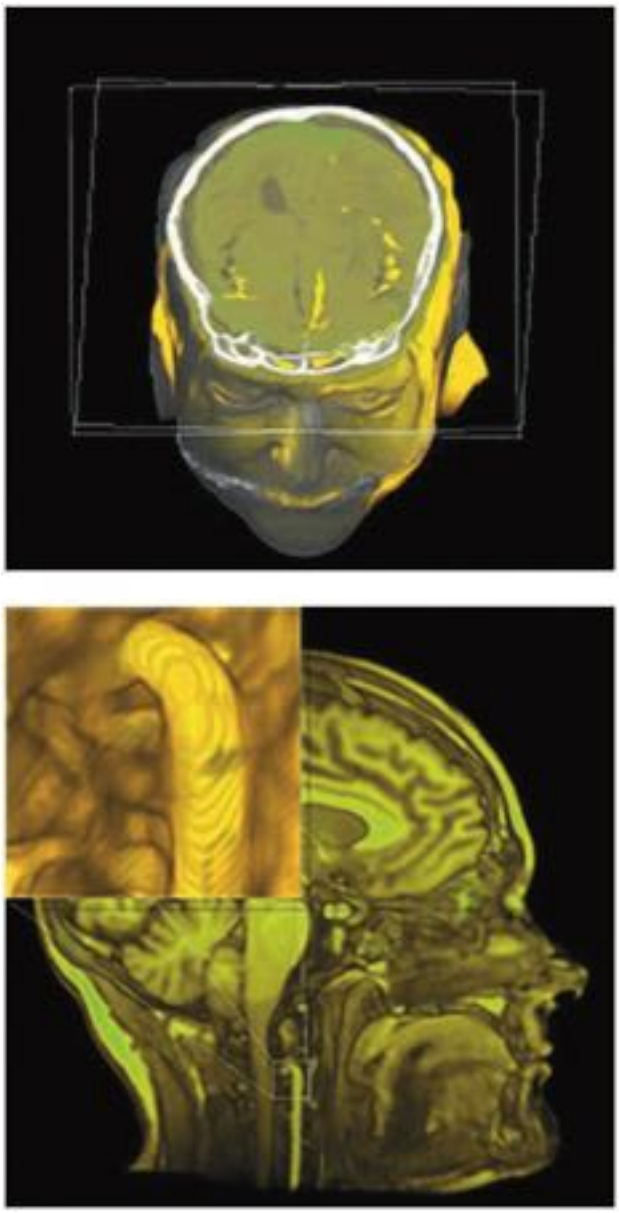


Figure 48.3 Volume-rendered data with different look-up tables.



Figure 48.4 **(a)** A laser registration being undertaken before endoscopic sinus surgery; **(b)** the laser beam is shone on to the skin around the operative site; **(c)** a band onto which fiducial balls have been mounted is attached to the patient's head.

software, the surgeon would point to pre-specified landmarks, such as the tragus, outer canthus and nasion. This is usually sufficient to achieve a registration accuracy or error of 3–4 mm. This can then be improved by entering a random sample of points from around the operative region (typically 40–100 points) using the probe. The position of the tip of the probe is identified by the tracking device and the coordinates are fed back to the navigation software. In this way, accuracy/errors of 2–3 mm can be achieved.

Other methods of registration use masks[11] and laser scanning tools (Figure 48.4)[12] that speed up the acquisition of surface points. With all these methods, calculations made in real time indicate the point accuracy. It is then up to the surgeon to reject or accept that point in order to improve the overall registration accuracy. Some types of image guided systems make use of fiducial markers that are applied to the patient before scanning on the day of surgery. These markers are clearly visible in both MR and CT data sets and, of course, on the patient when in theatre. They help to improve the accuracy of registration.

No matter whether skin fiducials or anatomical landmarks are used for registration, these reference points

should describe or be immediately adjacent to the surgical field. Failure to pay attention to this results in navigational inaccuracies. It is important to realize that the registration error is only a measure of the accuracy of correlation between selected points in the virtual data set and the fiducial markers or anatomical landmarks identified on the patient. It is not synonymous with target error, which is the error that could be expected if a probe was placed on a random point of interest within the surgical field. The target error is influenced by the registration error and is unlikely to be much worse if the target is within the volume described by the fiducial markers. However, if the point is outside that volume, the target error will be proportionately greater.

Tracking

Sensors that provide dynamic positional information are known as 'tracking devices'. They are employed in a multitude of everyday situations that range from virtual reality games, GPS systems, to missile guidance and electronic tagging of prisoners.[13] Although these measurement acquisition systems may be similar, each has different tracking properties that are optimal for a particular application. Without some form of tracking device, it would not be possible to move the patient once they had been registered. In surgical practice, tracking systems must be very precise, consistently accurate, fast enough to provide more than 25 readings per second, and be insensitive to changes in air temperature, unaffected by metal objects and able to track at least two objects simultaneously.

Several tracking systems have been employed over the years. Some of the earliest devices were mechanical arms fitted with potentiometers at every joint. These were fast and accurate but were cumbersome, had a restricted range of movement and hindered the movement of the tracked object to which they had to be attached. Systems based on magnetic field distribution are effective and relatively cheap. However, their disadvantage is that tracking accuracy can be both easily and significantly affected by the presence of metal objects. The quality and accuracy of these types of tracking devices is constantly improving and because there are no line-of-site issues, these are ideal for ENT applications. The latest types of electro-magnetic tracking devices are flexible, again making them ideal for areas that are difficult to reach such as the frontal sinus.

Infrared light sensors are the most commonly used image-guided surgical systems. They are referred to as either active or passive devices. Active devices sense infrared light from light-emitting diodes (LED) attached to the patient or location probe. Passive tracking devices detect infrared light reflected from metallic balls attached to the patient or probe. In the latter case, the infrared light source is situated on the sensing device itself (Figures 48.5 and 48.6). In order to detect changes in the patient's head position, haloes or arches with light-emitting diodes or reflective spheres can be fitted to a Mayfield clamp or the patient's head. Systems based on light-emitting diodes are reliable if the light path is not impeded.[14] Within the operating theatre an accuracy of 2–5 mm can usually be achieved.[4] In general, optical tracking systems are expensive. Cheaper variations do exist, but they lack high degrees of accuracy.

Inertial trackers have also been developed that are small and accurate enough for virtual reality applications. These devices generally provide one rate of change of rotational measurement only; hence, a number would be required. They are also not accurate for slow position changes. Systems based on standard ultrasound signals have the potential to achieve much greater accuracy, but are susceptible to changes in temperature and air currents. Other drawbacks include long lag times and interference from echoes and other noises in the environment.



Figure 48.5 A patient with their head held in a Mayfield clamp being prepared for image-guided surgery. An arc with metallic ball fiducials has been attached to the clamp. The arc describes the operative volume. A laser light is being centred on the field to find the optimal position for the tracking device.



Figure 48.6 An infrared optical tracking system. In the centre of the gantry is a laser light that is used to position the arm during the set-up procedure.

Clinical applications

Image-guided surgery (IGS) offers most promise in the areas of skull base and endoscopic sinus surgery. Skull base surgeons have found this technology particularly useful for pre-operative surgical planning, design of bone flaps, identification of important structures and for finding small tumours in obscure parts. This takes on additional importance when normal anatomy is distorted by disease or anatomical variations.

In rhinology, IGS systems are already in use in difficult revision endoscopic sinus surgery where there are no recognizable anatomical landmarks (**Figure 48.7**).[15] In particular, surgeons have found the guidance systems useful to localize the frontal recess during Draf type 2 and 3 procedures, where the floor of the frontal sinus is to be opened.[16] With the help of these systems, the need to perform open, external procedures will become less. Extended applications of endoscopic sinus surgery include trans-sphenoidal, trans-nasal endoscopic hypophysectomy where conventionally X-ray image intensifiers have been used to localize the sella.[17–19]

In the field of otology, IGS has been used to aid the surgeon in locating the facial nerve, identifying and localizing lesions of the petrous apex[20] and tumours, particularly in the internal auditory meatus. These include meningiomas and vestibular schwannomas.[21, 22] It is possible that when these systems gain in acceptance, are more accurate and involve shorter set-up times, they may become mainstream intra-operative equipment in all types of mastoid surgery. Their role then would be to aid the surgeon in localizing important anatomical structures such as the facial nerve, dura, brain and jugular bulb, as well as diseases such as cholesteatoma and acoustic schwannoma.

Surgical planning

Surgical planning is usually carried out in the surgeon's mind, drawing on past experience, knowledge of anatomy and anatomical variation. Some individuals are able to do this very well, others are not. In endoscopic sinus surgery, the surgeon must have the ability to think in 3D, having studied the information available from 2D CT slices. Surgeons may or may not be able to communicate their impressions to other surgeons. Furthermore, their mental image cannot be reviewed, audited or measured by other surgeons or indeed by the surgeon themselves when assessing patients at a later date. Planning using reconstructed 3D data enables the surgeon to assess the patient's anatomy objectively, to communicate this with other surgeons and to review these films at a later date. The data can be segmented and manipulated to familiarize the surgeon with specific features pertinent to that patient and the procedure to be performed.



Figure 48.7 Functional endoscopic surgery being undertaken using image guidance.

Surgical simulation

The major driving force behind the development of surgical simulators was the morbidity that accompanied the introduction of new techniques such as endoscopic 'keyhole' surgery. These techniques were conceptually different from traditional surgery. Surgeons had to operate using a 2D image on a television monitor and had to develop new hand–eye coordination skills not previously required for open surgery. Training surgeons in these new skills and the assessment of their competence was entirely different from the 'apprentice–master' approach that had been the mainstay of traditional surgical teaching. Three-dimensional reconstructions of image data can be used for surgical simulation. Simulators that create a virtual surgical environment or a set of tasks that enhance hand–eye coordination skills seem to be the answer.[23, 24]

Surgical simulators are now being developed and employed in other surgical specialties, for example skull base surgery. They are being used by trainees and experienced surgeons who might find it useful to practise a specific difficult surgical technique before performing the actual operation. Surgeons are able to 'virtually' manipulate, move and drill the mastoid process, to perform laparoscopic or endoscopic sinus procedures. The sensations and resistance encountered during real surgery may be simulated using positive feedback mechanisms in the form of a passive robotic arm.

IMAGE-GUIDED SURGERY

A thorough knowledge of anatomy is essential for all types of surgery, particularly those using microscopes and endoscopes. Pre-operative imaging alerts the surgeon to variations of anatomy that are either inherent in the patient or caused by a disease process or previous surgery. As stated before, image guidance offers the surgeon the ability to use the patient's image data intra-operatively to determine position, distance to vital organs and other anatomical features that might be hidden from direct vision. Structures in the vicinity of the skull base are either embedded or closely adherent to bone, making this region ideal for image guidance as CT has great spatial accuracy.

Two fundamental processes are required for intra-operative image guidance, registration and tracking. Registration is the process that relates the patient in the operating theatre to pre-operatively acquired

image data sets. Tracking is the mechanism of following the position of the patient or an instrument within the operative field. Both processes are potentially subject to significant mathematical error and it is vital that how this might happen is fully appreciated.

FUTURE RESEARCH

- Image-guided and augmented reality surgery relies heavily on technology research in the areas of computer hardware (processors, graphics and tracking) and software for segmentation and registration. Developments in these fields are driven by a variety of customer-driven demands. It is vital that clinicians make these demands and provide ideas for the computer scientists.
- The most important requirements are for accurate, robust, fail-safe systems that will give clinicians greater confidence. These systems must be user-friendly and ergonomically efficient. Computer user interface remains the biggest deterrent to regular use of these systems. These need to be simplified and easy to operate. Surgeons will eventually develop trust in the accuracy of these systems.
- In the future, we are likely to see more developments in the areas of surgical simulation and planning. Surgical training should benefit from simulators that will enable the trainee to develop their hand–eye coordination skills prior to applying them in clinical practice.
- At present, augmented reality still has to prove its position in surgical practice. Several research groups are producing encouraging results and future reliance on these types of systems is likely to replace traditional IGS systems.
- Robots are already being used for drilling in the field of orthopaedics and to manoeuvre and control cameras in laparoscopic surgery. These are far more accurate than humans and are likely to enter other fields of surgery where there is a reliance on power instrumentation, including drills and debriders.
- In the future, we are likely to use IGS systems to audit surgical procedures as they already have the inherent capacity to store all information relating to intra-operative navigation. This will be an invaluable and auditable operative record.

KEY POINTS

- IGS aids the surgeon in diagnosing the extent of disease, planning surgery and providing intra-operative positional information.
- Image-guided surgical techniques may reduce complications in endoscopic sinus surgery.
- IGS techniques offer greater accuracy and confidence in structure and disease localization.
- Major applications are skull base and revision nasal surgery where there is complex or distorted anatomy.

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CHAPTER 49

INTERVENTIONAL TECHNIQUES

James V. Byrne

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: interventional neuroradiology, endovascular therapy, embolization, meningioma, paraganglioma, epistaxis, tumour embolization.

INTRODUCTION

This chapter reviews the role of interventional neuroradiology (INR) in the management of patients with pathologies of the head and neck and describes common techniques. Endovascular embolization originated in surgery when Brooks[1] closed a cavernous-carotid fistula with a muscle embolus introduced by arteriotomy in 1930. The need for vascular imaging to monitor embolization was obvious, but the capacity developed slowly after the first description of cerebral angiography by Egas Moniz in 1927.[2] As a result, embolization for head and neck pathologies is generally performed in Neuroradiology departments.

Endovascular embolization is the most common technique. It is used to treat arterio-venous shunts, devascularize tumours and close large arteries prior to surgical resections. But also included in the INR repertoire are percutaneous techniques for embolization of vascular malformations and tumours, image guided biopsy and focused endovascular delivery of chemotherapy agents. The technologically driven evolution of the discipline will almost certainly produce new methods and applications to replace more invasive surgery in the future.

INDICATIONS

MR or CT scanning is usually adequate for diagnosis and pre-operative assessment of head and neck lesions so digital subtraction angiography (DSA) is rarely needed unless there is a possible role for INR. Combining embolization using DSA means that the indications for INR techniques should be considered early in treatment planning. This process involves considering a lesion's blood supply as well as its extent and relationship to normal structures. Pre-operative embolization may be indicated and information about adjacent major vessels may be vital, either because of tumour proximity or because their sacrifice may be a necessary component of the surgical approach or resection.

Embolization of vascular tumours is indicated prior to surgical resection to reduce intra-operative blood loss, operation times and facilitate complete resection. It can be considered as the definitive intervention in patients with minimal symptoms in whom surgery is contraindicated. It may also be indicated as palliative treatment to relieve pain for patients when surgery, radiotherapy or chemotherapy are unsuitable or to manage haemorrhage or increasing neurological symptoms. It is most effective in tumours with high blood flows. In most instances this can be inferred from the degree of contrast enhancement evident on CT or MR scanning but it should be remembered that the uptake of radiographic contrast within a tissue reflects the degree of extravascular leakage of these agents and not necessarily the blood supply. So occasionally tumours showing pronounced enhancement are not suitable for embolization.

Embolization is targeted to occlude the smaller arteries of the tumour vascular bed since the proximal occlusion of arteries is a relatively ineffective method of causing tumour necrosis and/or regression.

Large artery occlusions are sometimes indicated as pre-operative manoeuvres and rarely for tumour palliation. Emergency embolization may be required to manage tumour haemorrhage.

Functional testing by temporary vessel occlusion is indicated prior to endovascular ligations and may be useful when surgical resections are likely to require the ligation of a large artery or vein. Blood flow in the target vessel is occluded by inflating a balloon with the patient awake so that neurological examination can be performed and collateral blood flows can be assessed by DSA. Permanant occlusion by endovascular ligation is performed after a satisfactory test. The potential of INR to access lesions under imaging control, either using highly flexible endovascular microcatheters or by direct puncture, can also be exploited for the selective delivery of drugs for sclerotherapy, chemotherapy or functional tests of nerve function using sedative agents, such as barbituates (in brain) or lignocaine (in spine).

The decision to perform an INR procedure depends on clinical and anatomical factors. These should be reviewed in multidisciplinary consultations between the treating otolaryngologist (or other specialist) and interventional neuroradiologist. For pre-operative embolization, the guiding principle is that an additional INR procedure should not add to the management's overall risk. This risk/benefit analysis may require information that can only be obtained at the time of DSA. Therefore close cooperation and a team approach is needed, to ensure that the risks of complications caused by embolization or pre-operative invasive functional tests are acceptable and are justified because they are likely to improve the outcome of subsequent surgery. These issues, as they apply to specific tumour types, and the use of embolization in the management of epistaxis, will be discussed below. The purpose and potential benefits of INR techniques are summarized in Table 49.1.

TOOLS AND TECHNIQUES

Endovascular catheters

The catheters used for transarterial or transvenous catheterization are available in a range of sizes and shapes. They are used to select and inject radiographic contrast media in cranial vessels for angiography or as guiding catheters for smaller catheters used for the selection of small vessels (i.e. microcatheters). Microcatheters are generally 0.02 inches (0.5 mm) or smaller in diameter and are used to inject embolization materials. They are constructed with flexible distal ends for navigation through tortuous vessels and stiffer proximal sections to allow the operator to advance them by pushing.

Two basic types of microcatheter are used: flow directed and over-the-wire catheters. The former have extremely light and supple distal ends so that they are carried by antegrade blood flow to the target position. The latter are pushed over a guide wire to the objective. Flow directed catheters work best when blood flow is increased and are therefore used to treat arteriovenous shunts. Their size limits their use to the injection of liquids or very small particles. Over-the-wire catheters are used when blood flow is slower. The combination of guide wire and a stiffer catheter makes navigation easier and their larger lumen allows the delivery of liquids and both particles or coils. They are usually used in the treatment of head and neck tumours.

Materials used for embolization

PARTICLES

Embolic agents can be categorized on various criteria. Traditionally, they are divided according to whether the resulting devascularization is permanent or temporary. Examples of temporary agents are autologous blood clot, gelfoam powder and microfibrillar collagen, which are biodegradable, whilst particles manufactured from non-degradable materials are considered permanent agents (Table 49.2). However, the effectiveness of embolization using non-degradable particles is liable to be temporary because small vessel occlusions may be circumvented by the development of new collateral vessels.[3, 4] In practice, the development of a new blood supply is likely given time but is less likely if particles can be deposited in small vessels within the tumour bed rather than in proximal arteries. To ensure the deep penetration of injected particles, they are engineered to mix well with radiographic contrast so that they can be injected as an even suspension. Non-degradable particles in current use are made of polyvinyl alcohol (PVA),[5] trisacryl gelatin[6] or cellulose porous beads,[7] which are coated or mixed with radiographic contrast material to make them radioopaque and visible on X-ray fluoroscopy. They are available in sizes varying between 40–800 microns in diameter. The choice

TABLE 49.1 Interventional neuroradiology techniques and their uses

Procedure	Technique	Purpose/benefit
Biopsy	Percutaneous needle	Histology and treatment selection
Functional testing	Temporary balloon occlusion	Assessment of collateral blood supply prior to surgical or endovascular ligations
Embolization of small vessels	Particle, liquid embolics, sclerosants	Devascularization of tumour to reduce operative blood loss, palliation or cure
Embolization of large vessels	Balloon, coils, plug devices, liquid embolics,sclerosants	To aid surgical exposure/dissection, palliation or cure
Chemotherapy	Endovascular or intra-lesion injection	To maximize drug delivery to the lesion

TABLE 49.2 Embolic agents

Agent	Embolization	Target vessels
Autologous blood clot	Temporary	Afferent arteries
Gelfoam	Temporary	Afferent arteries
Polyvinyl alcohol particles	Permanent	Tumour vessels
Trisacryl gelatin particles	Permanent	Tumour vessels
Coils	Permanent	Large arteries/veins
Balloons	Permanent	Large arteries
Alcohol (ethanol)	Permanent	Malformations or tumour vessels
Sodium tetradecyl sulphate	Permanent	Malformations or tumour vessels
Cyanoacrylate adhesives (NBCA)	Permanent	Malformations or tumour vessels
Ethylene vinyl alcohol copolymer (Onyx)	Permanent	Malformations or tumour vessels

of particle size is important because, though smaller particles will penetrate to smaller vessels, they are more likely to pass through arteriovenous shunts and reach the lungs. They are also more likely to cause ischaemic damage to normal tissues. On the other hand larger particles occlude proximal arteries and achieve less reliable tumour devascularization.[8]

The effect of PVA or gelatin particles on tissues is to cause an initial acute inflammatory response, which is followed by a chronic foreign body reaction within weeks.[4, 9] Devascularization causes ischaemia and necrosis within hours, which in turn causes tumours to swell (exacerbating symptoms and causing pain) or haemorrhage. For this reason pre-operative embolization is often performed immediately prior to operation.

COILS AND BALLOONS

Embolization coils are made from steel, tungsten or platinum. Because of problems of corrosion, tungsten is generally no longer used and platinum, though expensive, is preferred because it is inert and not liable to magnetization effects during MRI. A new development is to enhance their effect by adding a thrombogenic coating. The materials used include collagen, bioabsorbable polymers and dacron fibres.[10] Originally coils were simply pushed through a delivery catheter and could not be retrieved or repositioned. Retrievable coils with controlled delivery are now standard. There are various methods for controlling their detachment from a delivery wire. These include couplings released by mechanical or hydrostatic pressure, electrolysis or thermal heating.[11]

Balloons are made of latex or silicone.[12] They are either fixed to a catheter tip for temporary test occlusions or can be detached for vessel occlusion. They are inflated by injecting fluid; usually radiographic contrast media. Detachable balloons are released mechanically from a delivery microcatheter but their detachment is less reliable than the newer methods developed for coils. In many centres they have been superseded by coils.

Coils or balloons are used for large artery occlusion (i.e. endovascular ligations), usually after a satisfactory temporary balloon occlusion test. High blood flow fistulas are occluded with coils or balloons positioned at the point of transition between artery and vein. The delivery of coils is easier to control than balloons and they can be positioned more accurately. They are used to embolize large veins or dural sinuses in order to close dural arteriovenous fistulas (DAVF) and less often for tumour embolizations.

LIQUID EMBOLIC AGENTS

Various liquids are used for embolization including sclerosants, adhesives and soluble plastics. They have the advantage over coils and particles of being injectable via smaller lumen catheters or needles. Most commonly used are quick-setting adhesives and polymers. Examples of liquid agents are the tissue adhesive N-butyl-2-cyanoacrylate (NBCA) and ethylene-vinyl alcohol copolymer (EVAL). There are various commercial formulations available (e.g. NBCA marketed as Histoacryl and Glubran, and EVAL marketed as Onyx).[13, 14] NBCA thickens and sets on exposure to blood and copolymers set after injection as the solvent (e.g. dimethyl sulfoxide) in which they are dissolved disperses. Both agents are liable to embed the delivery catheter within vessels and require considerable expertise to deliver safely, but they are generally regarded as producing the most permanent form of embolization. They are therefore preferentially used for definitive or palliative treatments as well as for pre-operative embolization. Sclerosants such as ethanol or sodium tetradecyl sulphate are used to treat facial vascular malformations, bleomycin is effective in certain types of low flow vascular malformations[15] and mannitol has been used to embolize meningiomas.[16]

APPLICATION OF EMBOLIZATION TECHNIQUES

Tumour embolization

TRANSARTERIAL

Embolization of tumours of the head and neck is most often performed to reduce blood loss and facilitate surgical resection or for palliation. It is rarely curative. Pre-operative embolization is performed for vascular tumours such as meningioma,[9, 11, 17] haemangioblastoma, juvenile nasopharyngeal angiofibroma,[18] schwannoma and paraganglioma[19] (**Table 49.3**). Pre-operative functional evaluations by temporary balloon occlusion of at-risk major arteries can also be performed. Pre-operative embolization is largely reserved for extra-axial intra-cranial tumours and only rarely are highly vascular intra-axial CNS tumours, such as haemangioblastoma, treated.

Pre-operative transarterial embolization is usually performed with PVA particles (sized to occlude the pathological circulation) or liquid agents (e.g. NBCA or Onyx).[20]

TABLE 49.3 Head, neck and skull base tumours treated by embolization

Commonly treated tumours	Less frequently treated tumours
Meningioma	Schwannoma
Paraganglioma	Carcinoid
Juvenile angiofibroma	Alveolar sarcoma
Haemangiopericytoma	Thyroid carcinoma
	Granular cell myoblastoma
	Capillary haemangioma
	Esthesioneuroblastoma
	Neurinoma

Liquid agents can also be injected directly into tumours (see below). Serious procedural complications occur in about 4% of patients and these include cranial nerve palsies (including blindness), stroke due to unrecognized spread of emboli and induced bleeding due to vessel perforation or secondary to tissue necrosis.[21] Complicating cranial nerve palsies are more common when very small particles or NBCA are used.[22] Though technically relatively straightforward, safe embolization of skull base lesions should only be undertaken after adequate training. Safe embolization demands a sound knowledge of vascular anatomy and the potential sites of spontaneous external to internal carotid artery or vertebral artery anastomoses, if cerebral or spinal migration of emboli is to be avoided.[23]

PERCUTANEOUS EMBOLIZATION

This technique involves the injection of a liquid embolic or sclerosant directly into tumour vessels. The objective is to devascularize tumours before surgical resection or for palliation of symptoms by causing tumour involution. Pre-operative embolization is usually performed following percutaneous puncture but perioperative needling can be performed. The technique was first used to devascularize hypervascular juvenile angiofibromas[24] but has also been used to treat haemangiopericytoma and paraganglioma.[25,26] The technique is particularly attractive for the management of recurrent lesions and has been reported to achieve total or near-total tumour devascularization.[27]

Delivery of chemotherapy agents

Selective catheterization allows endovascular delivery of chemotherapy drugs directly into tumours to maximize the local dose. Direct puncture of tumour vessels under X-ray or ultrasound imaging is an alternative. The objective is to deliver higher doses in the target tumour whilst avoiding systemic toxic symptoms. The amount of drug delivered to a tumour is proportional to its rate of plasma clearance within the tissue and inversely related to tumour plasma flow.[28] Selective catheterization allows the delivery rate to be fine-tuned to the prevailing rate of blood flow. This benefit has been used in studies of local chemotherapy for cancers of the head and neck, specifically advanced squamous cell carcinomas.[29] Combination therapies with radiotherapy, for example RADPLAT, have been effective at inducing remission and Kumar and Robbins[30] recently reviewed their use. The systemic toxic effects of Cisplatin can be mitigated by the simultaneous intravenous administration of its competitive antagonist thiosulphate. Despite logistical problems associated with catheterization and long infusion times, preliminary trials have shown the technique to be effective at causing tumour shrinkage.[31]

Temporary and permanent large artery occlusions

Temporary endovascular occlusion of large arteries prior to head and neck surgery allows neurological testing of the awake patient and angiographic assessment of the consequences of vessel sacrifice.

There are many described protocols for temporary artery occlusion and dynamic testing. Only two elements are common to all: that the procedure is performed under local anaesthesia so that the patient is accessible for neurological examination; and that anticoagulants are given. Test occlusion involves inflating a balloon in the target artery for 20–30 minutes and assessing the effect on cerebral blood flow. The adequacy of collateral blood flow to the territory of the occluded vessel can be demonstrated by angiography, Doppler ultrasound, xenon CT, single photon emission computed tomography (SPECT) and positron emission tomography (PET) scanning. Additional provocative testing can be performed by simultaneously lowering the systemic blood pressure or administering a vasodilator drug such as acetazolamide.[32] All these techniques are designed to improve the reliability of the test but the lack of a consensus protocol testifies to the fact that there remains a risk of the collateral blood flow being inadequate, despite normal test data.

It is generally accepted that preliminary testing reduces the risk of delayed stroke, but its value depends on risk posed by the test. Reported rates of morbidity come largely from audits of its use in aneurysm patients.[33,34] Amongst patients undergoing ligation for skull base tumours, rates for complications range between 5% and 20%.[35] The additional risks faced by cancer patients was documented in a single institution report, which found the complication rate to be 10% whilst that of aneurysm patients was only 3%.[36] Following a satisfactory period of temporary occlusion, the artery is permanently occluded by detaching the balloon or replacing it with embolization coils. Some practitioners prefer the latter because the detachment systems for coils are more reliable. It is obviously important that permanent occlusion is performed at the same arterial level (i.e. at the same place) as the test occlusion.

EMBOLIZATION FOR SPECIFIC TUMOURS

The commonly treated tumour types will be described in detail to illustrate the goals of INR in the management of patients with tumours of the skull base and neck.

Meningioma

These typically benign tumours originate from arachnoid cap cells found in arachnoid granulations. They therefore arise in continuity with dura. Though generally intracranial they are found at extra-cranial sites by extension from a dural origin or rarely occur entirely extra-cranially (presumably from ectopic dural rests). Thus tumours may involve the skull base, orbit and cervical spine or the upper neck. They occur in middle age, affect women twice as commonly as men and are linked to a genetic deficit on chromosome 22. Multiple lesions occur in patients with neurofibromatosis II and meningiomatosis.[37,38] Associations have been reported with exposure to ionizing radiation[39] and hormonal influences due to the presence of androgen and other hormone receptors.[38] They may be locally invasive and the WHO classification of histological findings recognizes three grades (grade 1 – benign, grade 2 – atypical and grade 3 – anaplastic), which are independent of the traditional histopathological descriptions of meningothelial, fibrous, transitional, syncytial and psammomatous subtypes. They are usually highly vascular tumours with the transitional subtype being most vascular and the psammomatous subtype least vascular.

Clinical presentation varies according to location and imaging by CT scan or MRI is usually adequate for diagnosis and pre-operative assessment. Tumour calcification and skull hyperostosis is easier to recognize on CT than MRI and suggests a less vascular subtype. Enlarged vessels within or adjacent to more vascular tumour are easier to see on MRI. Tumour enhancement after intravenous contrast media administration is typical and is more avid in vascular tumours, but such enhancement does not imply that a particular lesion is suitable for embolization.

Treatment is by resection, and radiotherapy is reserved for more aggressive histological types. Pre-operative embolization in indicated for vascular tumours and for the palliation of inoperable newly diagnosed or recurrent tumours. Intra-arterial angiography is required to assess the extent of tumour vascularity and therefore the potential of embolization. In a minority of tumours, dense calcification on CT or lack of enhancement after contrast media administration, imply a less vascular tumour and that embolization will not contribute to management but the majority warrant angiography to select tumours likely to benefit from embolization.

The vascular supply to meningioma seen on DSA is typically arranged in a radial pattern of dilated feeding arteries of decreasing size with a delayed venous phase of contrast passage (often termed a 'blush') through the tumour bed. Arterial supply may be from external carotid artery branches or from dural or trans-pial branches of the internal carotid artery or a mixture of the two (**Figure 49.1**). The endovascular therapist therefore needs a detailed pre-embolization DSA to evaluate the feasibility (and risks) associated with superselective catheterization and embolization. In practice treatment and diagnostic DSA are usually combined in the same session and scheduled as part of the patient's overall treatment plan.

A universal need for pre-resection embolization is controversial and patients are usually selected on a case-by-case basis after multidisciplinary review. The goal is to reduce operative blood loss and facilitate complete resection. It may be performed using particles (e.g. PVA), or liquid embolic agents (e.g. NBCA or Onyx). Since the typical blood supply is by arteries and arterioles of gradually reducing size, small particles (for example, 150 microns) are used first to obstruct intra-tumour vessels and larger particles injected subsequently to obstruct larger afferent arteries (**Figure 49.1**). Effective embolization will cause acute tumour infarction and swelling. The optimum timing of subsequent operation is debatable; the argument for early operation is that symptoms due to swelling or haemorrhage are avoided whilst for delayed surgery that operative blood loss is lessened and surgery facilitated.[40] If operation is delayed then steps must be taken to ensure that worsening neurological symptoms or signs are quickly detected and treated. Rarely, tumour necrosis causes bleeding and life threatening expansion of tumours. Prolonged delay risks revascularization, due to growth of vessels and new blood supply to the meningioma, which can occur within as short a period as 3–4 weeks after particulate embolization.

Another indication for meningioma embolization is to arrest or impede tumour growth when lesions are inoperable and radiotherapy inappropriate.[41] In theory, particles delivered into the tumour bed only, will cause tissue ischaemia/necrosis without stimulating growth of collateral blood vessels. In this situation, very small particles (50 microns) are injected slowly and no attempt is made to obstruct larger feeding arteries. Tumour devascularization and shrinkage is monitored by MRI enhanced by intravenous gadolinium administration. Areas of non-enhancement imply devascularization (**Figure 49.3f**).

The efficacy of pre-operative embolization is difficult to objectively evaluate. Criteria used in reported studies include comparisons of blood transfusion volumes between tumour resection operations performed with or without pre-operative embolization, surgery times, lengths of hospital stay, extent of tumour necrosis and clinical outcomes. A reduced need for blood transfusion was reported by Teasdale et al.[42] and Oka et al.,[43] shorter lengths of hospital admission by Dean et al.[44] and Oka et al.,[43] and improved clinical results by Oka et al.[43] when adjuvant embolization was performed. A reduction in neurological complications after surgery was reported by Oka et al.[43] but this benefit was only evident for patients with large tumours (greater than 6 cm in diameter). Delaying surgery until 7 days or more after embolization is associated with lower blood transfusion volumes[45] and greater induced tumour necrosis.[46] The conduct and evaluation of such studies is difficult because of the variations in size and site of the tumours studied.

Several specific complications have been reported after meningioma embolization due to inadvertant occlusion of vessels supplying normal tissues, the effects of tumour swelling and haemorrhage. Intra-tumoural haemorrhage resulting from devascularization may occur 24–36 hours after embolization. In the author's practice, this complication has occurred once in 40 treatments over the

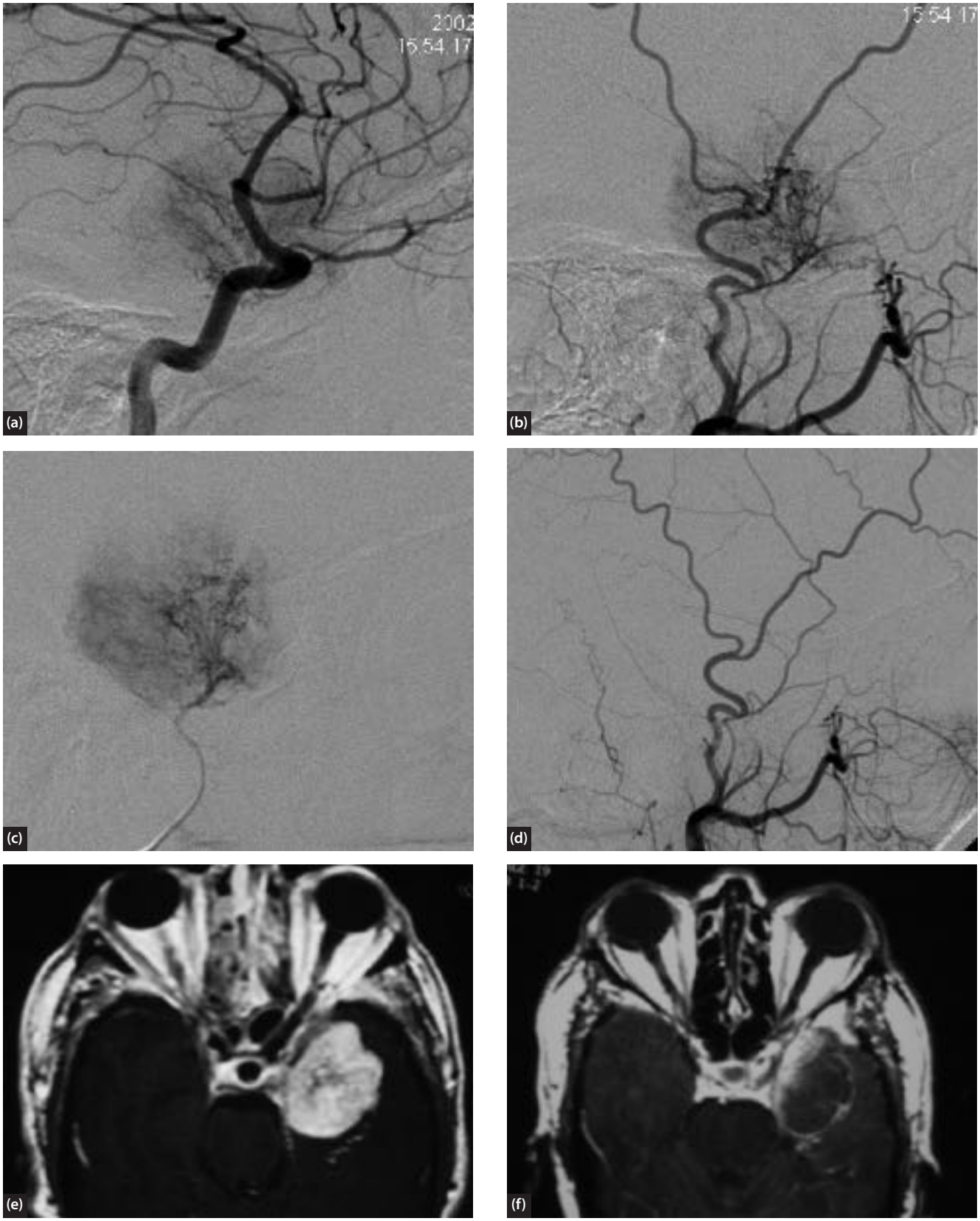


Figure 49.1 Parasellar meningioma. This tumour is supplied by meningeal branches arising from both internal and external carotid arteries. Figures **(a)** and **(b)** are lateral views from internal and external carotid injections respectively. Pre-operative embolization of the external carotid supply only was performed after selective catheterization of the accessory meningeal artery **(c)**. The effect of embolization is seen in **(d)**; compare this DSA with **(b)**. Figures **(e)** **(f)** are axial T1W gadolinium enhanced MRI of the tumour before and after embolization of the external carotid blood supply. Note that enhancement occurs in only the medial portion of the tumour on **(f)**.

last 5 years. Selective catheterization risks causing vessel damage, perforation and rupture. The last is more likely to occur at sharp bends in vessels. Such bends occur in the course of the middle meningeal artery (a common route for meningioma embolization) and rupture of this artery has been reported to cause bleeding or delayed arteriovenous shunting.[32,33] The incidence of complications related to pre-operative embolization ranges from 3% to 6% with about half due to haemorrhage.[20, 21] Gruber et al.[47] reported morbility of 6.4% and mortality of 6.2% in a small series of patients treated with combined surgery and embolization.

Paraganglioma

These benign but locally invasive tumours arise from paraganglionic chemoreceptor cells of neural crest origin. About 50% occur in the temporal bone, arising from either the cochlear promontory (i.e. typanicum) or the jugular blub (i.e. jugulare), 35% in the carotid body, 12% in the region of the high cervical vagus and the rest at various other sites in the head and neck.[48]

Though relatively rare tumours they are usually targets for embolization because of their highly vascular nature. Most occur sporadically though familial cases occur with autosomal dominant inheritance. In approximately 10% of patients tumours are multifocal and up to 5% of tumours secrete catecholamines. Symptoms are related to tumour location and typically are due to compression of adjacent structures, tinnitus (tympanicum) cranial nerve palsy (jugulare, vagale) and pain. The role of imaging by plannar scanning is to support the clinical diagnosis and usually includes both CT and MRI. The former (performed with high resolution parameters) will best demonstrate bony involvement and MRI will best demonstrate the soft tissue character of tumours. Tumour vascularity and extent can be assessed from scans performed after intravenous contrast administration and evidence of involvement of the carotid artery or intracranial invasion should be sought. Intra-arterial angiography is usually undertaken as part of a pre-embolization evaluation rather than diagnosis.[49] Though the typical angioarchitecture of this tumour type makes angiography a very specific diagnostic test and it should be considered prior to biopsy.

On intra-arterial angiography feeding arteries are found to be enlarged and there is an early and intense blush in the tumour bed. The intra-tumoural angioarchitecture comprises centripetally orientated arterioles estimated to be 90 microns in diameter at the periphery and 300–600 microns in the centre of the tumour with arteriovenous shunts (**Figure 49.2**).[50] To further complicate embolization, the majority of tumours show a multicompartment pattern of blood supply with arterial and venous supply confined to haemodynamic unit so that separate injections of embolic agent have to be made into each feeding artery. The technique for embolization has evolved with the development of embolization particles small enough to penetrate the smaller peripheral arteries (**Figure 49.3**). The presence of intra-tumour shunts may justify the use of the percutaneous (or intra-operative) direct puncture technique with injections of a liquid embolic agent[26] since spread of emboli to the lungs is less likely; however, AV shunting is rarer in paraganglioma than within the vascular bed of some other tumour types (e.g. nasopharyngeal angiofibroma, see below).[51]

Embolization is usually performed as an adjuvant to surgical resection. When surgery and/or radiotherapy are considered inappropriate, embolization may alone provide symptomatic relief by stabilizing tumour growth.[52] The benefits of pre-operative embolization have been demonstrated in several single institution reports.[53, 54]

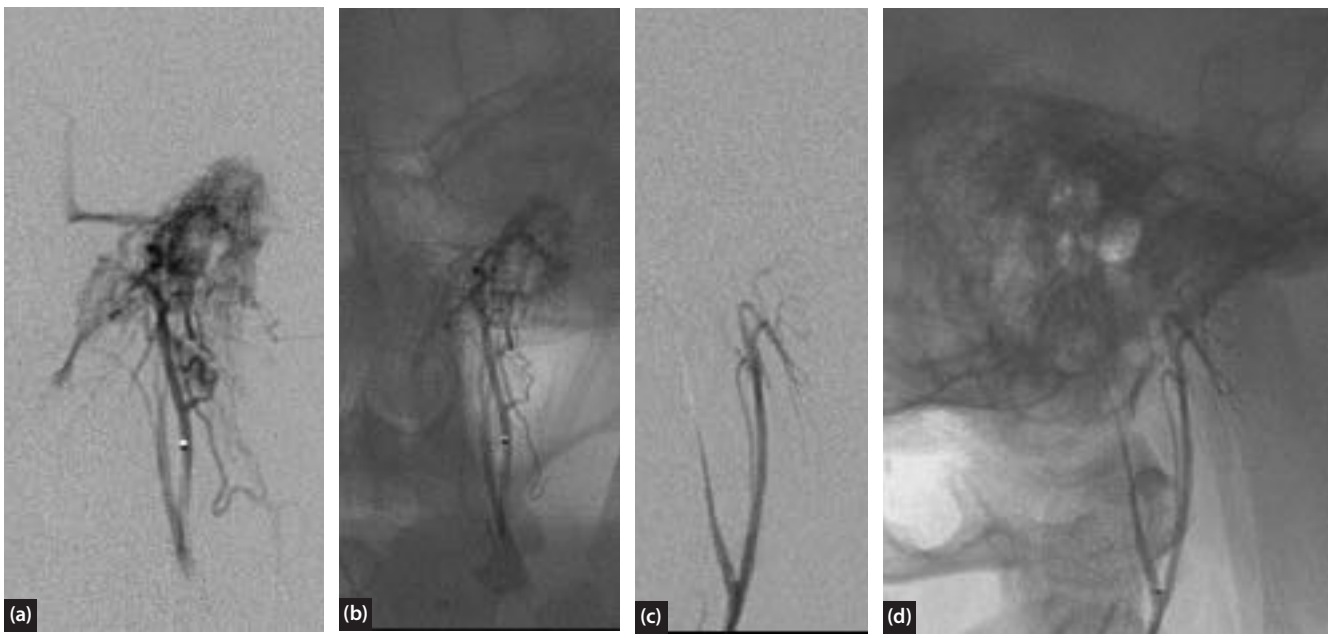


Figure 49.2 Temporal paraganglioma. Lateral subtracted **(a) (c)** and unsubtracted **(b) (d)** angiograms following selective injections into the ascending pharyngeal artery before **(a) (b)** and after **(c) (d)** embolization with particles.

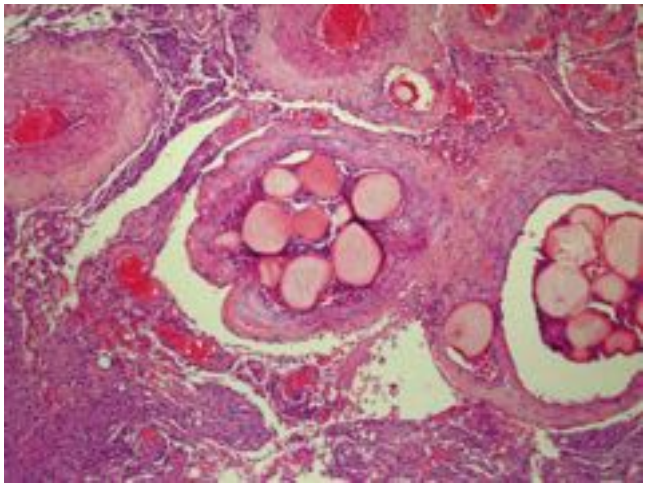


Figure 49.3 Histological section showing embolization particles (trisacryl gelatin microspheres) within tumour vessels.

Murphy and Brackmann assessed the effects of pre-operative embolization in a cohort of 35 glomus jugulare tumour patients, and found pre-operative embolization reduced the volume of operative blood loss and the duration of procedures but not the length of bed stay.[55] Tikkakoski et al. reported that pre-operative embolization improved operating conditions with subjective benefits to surgical results if performed by superselective catheterization with effective devascularization of the tumour vascular bed.[56]

Juvenile nasopharyngeal angiofibroma

These benign locally invasive tumours of the nasopharynx are also commonly embolized prior to surgical resection. The histological features include the presence of vascular cavities with an endothelial layer but no muscle layer which are mixed with a more conventional arteriocapillary tree with muscle layers. There are similarities between the appearance of cells of the nasal mucosa, genital erectile tissue and vascular spaces of this tumour type. The target cells of the nasal mucosa are assumed to develop into muscularized vascular channels secondary to testosterone stimulation and oestrogen hypersensitivity at pubery.

Patients present with epistaxis and symptoms due to nasal obstruction. Epistaxis may lead to anaemia and require embolization for control though embolization is usually performed as part of planned resection procedures.

CT and MRI performed with contrast enhancement should define the extent of the tumour and be able to differentiate tumour extension into adjacent paranasal sinuses from sinusitis due to retained secretions. Diffuse or patchy enhancement with bone expansion suggests tumour invasion, and dural enhancement may suggest intra-cranial extension. The blood supply arises from branches of the external carotid artery and the internal carotid artery if local spread has occurred. DSA typically shows enlarged intra-tumoural vessels mixed with more regular arterioles (**Figure 49.4**). In the venous phase there is an intense inhomogenious blush which shows the full extent of tumour.

Complete surgical removal is the optimum treatment. Pre-operative embolization is a well established surgical adjuct to induce tumour shrinkage, improve surgical access and reduce blood loss.[51] Originally embolization was performed transarterially with particles (i.e. PVA) or liquids (i.e. NBCA) and since most tumours are supplied by branches of the external carotid artery it is relatively straightforward with a low risk of complications.[57] Intra-cranial tumour spread and supply by branches of the internal carotid arteries increase the risk of embolization causing neurological deficit and limits the potential for complete devascularization.[58] For this reason a direct tumour puncture technique with injections of liquid emobolic agents (i.e. NBCA or Onyx) was introduced.[59] The goal is to facilitate surgery and reduce operative blood loss since pre-resection embolization does not appear to improve long-term outcomes.[60]

The introduction of the direct puncture technique with Onyx injection has been shown to improve the extent of devascularization after embolization[61] but the transarterial method still has its advocates.[62] Similarly the introduction and success of endoscopic surgical resection has changed some surgeons' opinion on the need for pre-operative embolization for smaller tumours (i.e. without spread) with some now considering pre-operative embolization unnecessary.[63]

Pre-operative embolization commonly causes a facial dull ache. Other reported effects are generally mild. These include transient facial numbness and hemiparesis.[59, 64] But there have been case reports describing blindness and permanant disability.[65]

EMBOLIZATION FOR EPISTAXIS

Transarterial embolization using particles, coils or balloons has been used to control intractable idiopathic epistaxis. For effective embolization, superselective catheterization of the sphenopalatine artery is performed after locating the bleeding site. This goal is hampered if prior surgical ligation of the internal maxillary artery has been performed or if the site of bleeding cannot be established. In these situations, particles may need to be injected via both internal maxillary and facial arteries.

There is no consensus on the most effective timing of embolization after the onset of spontaneous epistaxis and different definitions of intractable epistaxis make it difficult to compare published reports. The vast majority of patients admitted to hospital with epistaxis respond to packing, balloon tamponade or local cautery and only a small minority will need embolization.[66] Whether embolization is substantially safer or more effective than internal maxillary artery (IMA) ligation is also debated. In a recent review of the literature comparing embolization with IMA ligation, Cullen and Tami[67] found that embolization was generally reported to be more reliable, but this was not the case in their institution, where outcomes were similar but the procedural complication rate was

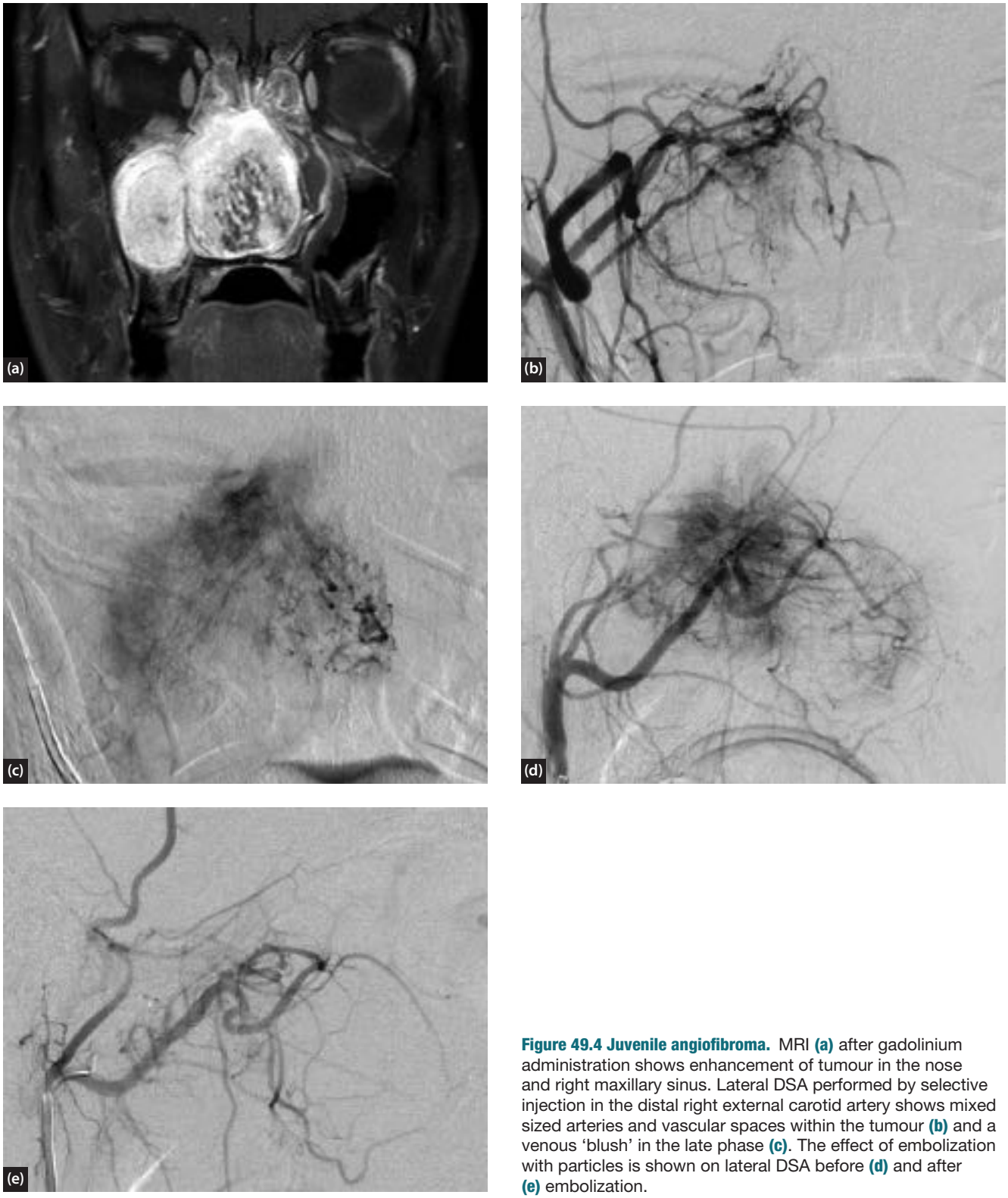


Figure 49.4 Juvenile angiofibroma. MRI **(a)** after gadolinium administration shows enhancement of tumour in the nose and right maxillary sinus. Lateral DSA performed by selective injection in the distal right external carotid artery shows mixed sized arteries and vascular spaces within the tumour **(b)** and a venous 'blush' in the late phase **(c)**. The effect of embolization with particles is shown on lateral DSA before **(d)** and after **(e)** embolization.

higher after IMA ligation. Even if the risks are no greater, it is logical to perform embolization before IMA ligation because ligation limits the effectiveness of subsequent embolization.

For patients with epistaxis secondary to a vascular malformation or nasal tumour, particulate embolization is indicated to stop acute haemorrhage. In patients with Osler-Weber-Rendu disease, multiple sessions may be required to induce remission and embolization is rarely curative.[10] In patients with epistaxis due to the rare internal carotid aneurysm or pseudoaneurysm that erodes the sphenoid bone and bleeds intra-nasally, emergency

embolization can be life saving. Embolization also has a small but important role in the management of patients' bleeding as a result of head and neck cancers. Haemorrhage may occur from large or small vessels and may be associated with radiation induced tissue necrosis. A variety of embolization techniques using particles, coils, stents and balloons may be needed to control such bleeding.[68]

FUTURE RESEARCH

The evidence-base for most INR treatments is lacking. Research has largely involved reports of single institute case audits. Large-scale trials are difficult because relatively small patient numbers are treated at each hospital and multicentre cooperation is needed. This problem is being addressed by various specialist interest groups who organize case registries and multicentre trials to study the efficacy of embolization in different situations.

Areas for future research include:

- **Technical:**
  - Development of non-X-ray imaging. Fluoroscopy using magnetic resonance imaging is now feasible. This avoids the potential hazards of ionizing radiation but requires the development of new catheters and embolic agents. Attempts to develop liquid agents that remain stable in high strength magnetic fields are proving difficult. A great deal of investment is being made to develop ways of monitoring minimally invasive surgical techniques without X-ray fluoroscopy.
  - Current liquid embolic agents are to a greater or lesser extent adhesive and non-adhesive materials that remain coherent during delivery and permanent need to be developed.
  - Improvements in reliability of data from functional tests are needed. A great deal of research has been directed at the problem of falsely reassuring temporary vessel occlusion tests. A completely reliable protocol is still needed.
- **Biological:**
  - The evolution of embolized tissue has been studied but we do not know much about the mechanisms that cause secondary haemorrhage in some tumours.
  - The potential benefits of local delivery for gene therapy and future chemotherapy agents will probably open new areas of research. The *in vivo* response of lesions will need further study.

KEY POINTS

- Pre-operative embolization should be considered for all vascular tumours.
- Tumour vascularity can only be inferred from CT and MR scans. Intra-arterial angiography is still required to identify tumours suitable for embolization.
- Functional testing of vessels 'at risk' during surgery is performed under local anaesthesia by temporary inflation of an endovascular balloon.
- Most embolizations are performed transarterially but direct percutaneous injections of tumour or vascular malformation vessels, or transvenous injections are also possible.
- Occasionally embolization alone is used for palliation and management of inoperable tumours.
- Embolization should be considered early rather than late in the management of intractable epistaxis

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CHAPTER 50

LASER PRINCIPLES IN OTOLARYNGOLOGY, HEAD AND NECK SURGERY

Brian J.G. Bingham

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: head and neck cancer and photodynamic therapy.

INTRODUCTION

Laser is the acronym for light amplification by stimulated emission of radiation. Surgical lasers are devices that amplify light and create coherent light beams ranging from the infrared to the ultraviolet parts of the spectrum.

HISTORY

In 1917, Albert Einstein described the theory of stimulated emission that is the underlying process for laser action. The American physicists, Arthur Schawlow and Charles Townes, described the working principles of lasers in 1958.[1] In 1960 Theodore Maiman demonstrated the first laser action in solid ruby[2] and a year later Ali Javan built the first helium-neon gas laser.[3] C Kumar N Patel introduced the carbon dioxide (CO_2) gas laser in 1962. In 1972, in Boston, USA, Jako and Strong were the first to pioneer the use of the CO_2 laser in otolaryngology, head and neck surgery.[4–6]

PRINCIPLES OF LASER ACTION

A laser empowers atoms to store and emit light in a coherent form. The electrons in the atoms of a laser medium are first pumped or energized to an excited state by an external energy source. These electrons are then stimulated by external photons to emit their stored energy in the form of photons. This process is 'stimulated emission'. The photons emitted have a frequency characteristic to their atoms and travel in step with the stimulating photons. These photons now strike other excited atoms to release even more photons. These photons move back and forth between two parallel mirrors triggering further stimulated emission. This part of the process is known as 'light amplification'. One mirror in the laser tube is partially silvered and it allows the exit or leak of the intense, collimated, monochromatic and coherent laser light.

Nature of laser light

A beam of laser light is:

- **coherent:** the photons or waves travel in step, or in phase with one another
- **collimated:** the laser light travels in one direction
- **monochromatic:** one wavelength or colour (if the energy is in the visible spectrum).

Types of lasers

Depending on the type of laser medium used, lasers can be classified as solid state, gas, semiconductor, liquid or free electron.

A pioneering example of a solid-state laser is the ruby laser. The neodymium yttrium aluminium garnate (YAG) laser and the related (frequency doubled) potassium titanyl phosphate (KTP) are examples of solid-state lasers in surgical practice.

The carbon dioxide laser (CO_2) is a very efficient gas laser that delivers laser light as an invisible continuous wave beam. The carbon dioxide surgical laser has been the most widely applied laser in oral and laryngological practice. The helium-neon laser is a gas laser with high frequency stability, good colour stability (red) and minimal beam spread. The helium-neon gas laser is often superimposed on an invisible laser beam, such as the CO_2, to facilitate surgical targeting. Activation of chemicals in photodynamic therapy can be achieved with the helium-neon laser.

The gallium arsenide laser is the most commonly used semiconductor laser. This laser is used in CD players and laser printers and has some surgical applications.

The most common medium for a liquid laser is an inorganic dye contained in a glass vessel. This laser is pumped or energized by intense flash lamps or by a gas laser in a continuous wave mode. The frequency of a tuneable dye laser can be altered with the aid of a prism inside the laser cavity. Tuneable dye lasers can be well suited for treating pigmented cutaneous lesions.

Lasers that utilize beams of electrons unattached to atoms and spiralling around magnetic field lines were initially developed in 1977 and are important research instruments. Free-electron lasers are tuneable and, in theory, could cover the electromagnetic spectrum from infrared to X-rays. Free-electron lasers could be capable of producing very high power radiation and may have medical applications in the future.

Patterns of laser output

The configuration of the resonator cavity and the method in which an energy source is applied to the 'active laser medium' will determine the pattern of a laser output. The output may be continuous wave or pulsed. A continuous wave laser operates with a constant intensity. A laser that operates with a continuous output for longer than 0.1 seconds is considered a continuous wave laser. A pulsed laser produces a single or train of pulses with each individual pulse less than 0.1 seconds. A Q-switch is an electro-optical component that facilitates the production of a very short (less than 1 microsecond) but high intensity pulse of laser energy.

Basic laser tissue interaction

The reaction of laser energy with living tissue can be photoablative, photochemical, photomechanical or photothermal. Most lasers react with a combination of all these mechanisms although for a specific wavelength and delivery system one form of tissue reaction may predominate:

- **Photoablative** reactions occur when molecular bonds are divided. The ruby laser, for example, can split the molecular bonds of tattoo ink with minimal local thermal damage. Macrophages remove the tattoo ink after the molecular bonds are broken.
- **Photochemical** reactions occur when infrared, visible or ultraviolet laser light interacts with photosensitizers to produce chemical and physical reactions. This forms the basis for photodynamic therapy that is discussed later in this chapter.
- A **photomechanical** effect occurs when the laser energy is pulsed to disrupt tissue or stones by the mechanism of shock waves. An example of this mechanism would be the use of the Holmium YAG laser to shatter ureteric and renal calculi.
- The conversion of absorbed laser light into heat is a **photothermal** reaction. The tissue effect can be cutting, coagulation or vaporization depending on the laser wavelength and the laser delivery device. The photothermal mechanism is predominant in laser use in otolaryngology and examples include CO_2 microlaryngoscopy and the argon laser for stapedotomy.

LASER LIGHT DELIVERY DEVICES

Many delivery devices are available to deliver laser energy to tissue in a safe and efficient manner. Most delivery devices are suited specifically for the wavelength that they transmit. Examples of delivery systems would be an articulated arm, a mirror lens system, micromanipulator, fibre optic fibre, shaped tip fibre optic fibres and robotized scanners.

An articulated arm uses a system of hollow tubes and mirrors to direct the laser beam to the target area. Most articulated arms have a lens system to focus the emerging beam on the target tissue. The carbon dioxide laser wavelength is absorbed in fibre optic material and hence this laser energy is delivered with an articulated arm system.

Micromanipulators and other focusing devices can be connected to microscopes. Micromanipulators and focusing devices will create an accurate and reproducible spot on target tissue. This facilitates very accurate and multiple laser strikes, which suits surgical techniques in otology and laryngology.

Laser energy exits from a micromanipulator or focusing device in a similar style to the 'laser beam weapon' of science fiction. This means that inadvertent strikes beyond the target tissue or misdirection from a reflective surface are a significant operative risk. This also means that a mirror can deliberately redirect a 'laser beam'. An example of this would be to use a mirror to redirect CO_2 laser energy on to adenoid tissue or on to lymphoid tissue on the base of the tongue.

The bare fibre optic fibre is the most common technique for delivering laser energy to tissue. The flexibility and diameter of fibre optic fibre facilitates their use with both rigid and flexible endoscopes. This means that laser energy can be delivered to almost any tissue that can be seen with an endoscope.

Laser light exits the tip of the fibre optic fibre in what is called the 'angle of divergence'. The light exiting from the tip of the fibre projects in a similar manner to water projecting from the nozzle of a hosepipe. The smallest light spot and, consequently, the highest concentration

of energy is found very close to the fibre tip and as the distance from the fibre to tissue increases, the projected area of light decreases and the energy intensity reduces. Consequently, the tissue response to laser energy exiting from the tip of a fibre can be controlled by altering the distance of the fibre from the tissue. Changing the distance between the fibre and the tissue can produce all the tissue photothermal effects of coagulation, incision and vaporization. A fibre 'in contact' with tissue will create an incision. The cut is similar to a saw rather than a knife. This means that some tissue is removed like the kerf of a saw as compared to being split with a scalpel. There is a degree of tactile control with a laser fibre 'in contact' mode. As the fibre is retracted and hovers above the tissue (2–4 mm), it is in the 'near contact' position and vaporizes tissue. As the laser fibre is retracted even further from tissue into the 'non-contact' mode, then the tissue effect is coagulation.

A fibre optic laser cable can be inserted through the biopsy channel of a fibre optic endoscope. The end of the laser fibre must protrude beyond the end of the endoscope or heat damage to the endoscope can occur when the laser is fired. To simplify this problem one can perform a preliminary check of the length of fibre required to achieve a satisfactory distal position and then mark the laser fibre with a 'steristrip' at the entry port.

A fibre optic laser fibre can be inserted through a narrow metal tube to help direct the laser energy. In otology, for example, the laser fibre can be presented through a hollowed out needle. An aspiration channel can be added to the hollow metal fibre carrier to remove smoke from the surgical site. **Figure 50.1** shows a modified ear suction tube and fibre holder that is used for endoscopic intra-nasal surgery. In the design of these instruments, the curves of the fibre carrier should create sufficient resistance that when combined with the torque of the laser fibre it results in a fibre that is 'held' in position without any additional mechanism. In **Figure 50.2**, the 0.6-micron laser fibre can be set at the position of choice for the surgeon and will not move unless the surgeon applies additional pressure. The indent of the finger shows the pressure to overcome the self-retaining torque.

A shaped tip laser is a laser fibre with a tip constructed of another material, such as metal or synthetic sapphire. The laser energy heats the tip and it is the conduction of heat from the tip that produces the tissue interaction. Different materials and shapes of tip will create different tissue reactions. Some tips become so hot that a secondary cooling mechanism is required. An example of this type of device in head and neck practice would be a sapphire tipped neodynium YAG fibre used to ablate tracheobronchial tumours.

Robotized scanners can facilitate laser treatment by reproduction of previous instrument settings or by being able to control precisely the distance a laser is placed or 'hovered above' the target tissue. A robotized scanner can 'trace' an area of treatment before delivery of laser energy to ensure accuracy or can apply a pattern to the area of laser treatment. At present, the greatest use for robotized scanners is in the cutaneous treatment of pigmented lesions and for skin resurfacing or recontouring.



Figure 50.1 A 0.6-micron laser fibre inserted through a modified aural suction tube to create a laser delivery device. The natural torque of the fibre holds the laser fibre in place.

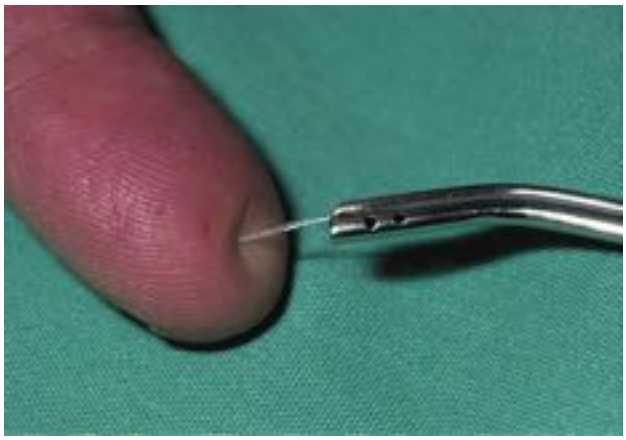


Figure 50.2 The pressure required to move or regress the laser fibre tip into the delivery device.

LASER–TISSUE INTERACTION

When laser light strikes tissue, it scatters until all the laser energy is either absorbed or reflected. The absorption of laser energy heats tissue. The volume of tissue affected is larger than the area shown by the laser spot size. The depth of penetration by a given wavelength of laser light is determined by the absorption and scattering of the type of tissue and the wavelength of the laser.

The strength of the tissue effect is altered by changing the fluence. Fluence is defined as the laser power in watts, multiplied by the length of exposure in seconds, divided by the area (mm^2) of the target tissue. This implies that when the distance between a fibre optic tip and the tissue varies, the spot sizes become bigger or smaller and the fluence will accordingly increase or decrease.

The heat in the tissue produces a series of changes in the tissue as the temperature rises. The changes are denaturation, coagulation, vaporization, carbonization and incandescence. Cutting with a laser is narrow controlled

vaporization! The heat produced by the absorption of laser light is partly dissipated into air but also produces a secondary thermal effect in surrounding tissue. This lateral thermal effect produces haemostasis by coagulation. The lateral haemostasis effect varies with wavelength of laser, the rate at which the energy is applied, fluence and the nature of the tissue.

LASER APPLICATIONS IN OTOLARYNGOLOGY

The specific clinical applications of lasers are not described in this chapter, but the following list identifies particular lasers for disease-specific regions:

- stapedectomy and tympanomastoid surgery: CO_2 laser, KTP laser, argon laser
- endonasal dacrocystorhinostomy: Holmium YAG laser, KTP laser, 810 nm laser
- nasal and sinus surgery, including tumour surgery, telangectasia destruction, antrostomy creation and turbinate reduction: Holmium YAG laser, KTP laser, Nd YAG laser, argon laser, 810 nm
- nasal polyp reduction: CO_2 laser 'swiftlase' (oscillating device)
- microlaryngeal surgery: CO_2 laser
- laryngopharyngeal tumour resection/ablation: CO_2 laser.

LASER SAFETY

Throughout the world each country applies different safety regulations. Usually the Medical Devices Agency of a country or state will produce guidance for clinicians and hospitals. In the UK, the local Medical Physics Department will produce local laser rules (based on national guidance) and ensure training of all staff involved in the use of the laser. Training for medical and nursing staff should be mandatory. A laser company will typically provide a safety manual on their particular wavelength of laser. Staff should read the laser safety manual and in many countries produce signed documentation that the manual has been read.

The principles of safety are as follows:

- A laser beam may hit or damage objects outside the target area and cause a fire, tissue damage or eye/visual damage.
- The patient should be shielded by wet gauze or fireproof material from accidental strikes.
- The anaesthetic tube and airway should be protected from accidental strikes that could produce a fire.
- All personnel in the operating room should wear correct eye protection appropriate to the wavelength of the laser.
- A warning sign plus locked doors should prevent unprotected and unprepared individuals from walking into the operating room when the laser is in use.
- The key to switch on the laser should be held by a senior member of the operating team to ensure only properly qualified individuals use the laser.
- The operating room and windows should be laser protected.
- Endoscopic equipment should be blackened to reduce accidental reflective strikes of the laser.

PHOTODYNAMIC THERAPY IN OTORHINOLARYNGOLOGY

Principles of photodynamic therapy

Phototherapy is the use of light in the treatment of disease. An example would be the treatment of neonatal hyperbilirubinaemia with visible light.

Photochemotherapy is a subset of phototherapy where a treatment requires the administration of a drug in addition to the application of light. An example would be treatment of a skin condition such as psoriasis with the combination of a furocoumarin sensitizer drug and UV-A (320–400 nm) light.

Photodynamic therapy (PDT) is a subset of photochemotherapy where, in addition to an administered drug and the application of light, oxygen is required to complete the process. The administered drug is known as a 'photosensitizer'. This type of drug accumulates within a cell and reacts with light and oxygen to form 'singlet' oxygen. The 'singlet' oxygen damages the cell membranes and produces cell death.

One of the attractions of PDT for oncology is that the photosensitizer drug is, typically, retained in tumour tissue for a longer period than in normal tissue. This improves the therapeutic effect while reducing toxicity to normal tissue. The use of PDT is not affected by prior radiotherapy, chemotherapy or surgery. To date, the principle shortcomings of PDT have been the limited depth of tissue penetration and extensive skin phototoxicity. This skin phototoxicity requires that the patient is not exposed to daylight during treatment or they develop extensive and painful skin reactions.

In photodynamic therapy for head and neck cancer the photosensitizer is usually administered by intravenous infusion. The perfect photosensitizer drug would be absorbed selectively only by tumour tissue in the drug uptake period (also called the drug–light interval). The drug uptake period may last between 3 and 96 hours. The tumour is then irradiated with a measured light dose. Singlet oxygen is released to kill only tumour cells and thus destroy the target tumour.

The tumour targeting arises firstly from the structure of the photosensitizer that leads to the selective uptake by a tumour and secondarily by the accurate application of an appropriate light wave.

There are many potential applications for PDT but few, currently, in routine practice. The diseases in which trials of photodynamic therapy have taken place include malignant tumours, such as squamous carcinoma of the oral cavity, squamous carcinoma of the nasopharynx,

oesophageal carcinoma and metastatic squamous carcinoma of the neck. Non-malignant disease such as inverted papilloma of the sinonasal cavity has also been targeted.

Photodynamic clinical reports in otorhinolaryngology

Both palliative and curative therapy has been reported for oesophageal cancer. The patients receive a photosensitizer followed by light delivered via optical fibres through a flexible endoscope. A phase II trial[7] randomized 218 patients to receive palliative oesophageal PDT (porfimer sodium sensitizer) versus Nd:YAG laser ablative therapy. Each arm gave an equivalent improvement in dysphagia but with fewer perforations in the PDT group (1 versus 7%, $p < 0.05$).

Overholt and Panjehpour[8] reported the results of 55 patients with dysplasia or early carcinoma in Barrett's mucosa of the lower end of the oesophagus treated with PDT. The patients received porfimer sensitizer followed at 48 hours with red light therapy. There was a good response at the 6-month follow-up. Forty-three patients with high-grade dysplasia/adenocarcinoma had endoscopic-proved ablation of their problem. Eleven of the 12 patients with low-grade dysplasia had no dysplasia on endoscopic review. Oesophageal stricture, however, developed in 53% of the patients.

There has been hope for PDT in the treatment of head and neck tumours. The endoscopic access to squamous tumours of the upper aerodigestive tract combined with the tendency to develop 'field cancerization' make these tumours good candidates for PDT. Gluckman[9] treated a mixture of carcinoma *in situ*, early and advanced squamous cell carcinoma of the head and neck. Dihaematoporphyrin ether and light at 630 nm were used to treat these patients. The best results were obtained in the oral cavity and oropharynx where 11 out of 13 patients had a complete response and 2 out of 13 a partial response. Four of these tumours had recurrence within 1 year of treatment. Eight patients with advanced tumours were treated palliatively, but the results were no better that with standard regimes of the time.

Karakullukcu et al.[10] analyzed the outcomes of photodynamic therapy in 170 patients with early stage oral cavity and oropharynx neoplasms giving results of a 90% response rate and a 70% complete response (cure) rate.

Biel[11] treated 25 patients with early squamous cell tumours of the larynx, obtaining a complete response in patients despite the fact that radiation therapy had previously been unsuccessful in 17 of them.

Biel[12] also reported a summary of the results of a collection of studies on the treatment of early squamous cell carcinoma of the head and neck with PDT. There were a total of 217 patients. One hundred and ninety-four (89%) showed a complete response to treatment, 23 (10.6%) showed a partial response and no patient failed to show any response to the therapy.

Dilkes et al.[13] had considerable experience with the use of PDT using the sensitizers m-TPHC, photofrin II and ALA for squamous carcinoma at multiple sites in the head and neck during the mid-1990s. The patients they treated included palliative, primary and adjunctive forms of treatment and, in nearly all cases, the authors identified a visible response to the effects of PDT. Their complications included local pain at the photosensitizer injection site and, in some patients where appropriate precautions had not occurred, post-treatment skin photosensitivity.

Lofgren et al.[14] used PDT in 5 patients with circumscribed nasopharyngeal carcinoma. The drug was activated with laser light under topical anaesthesia and after 4 years, 3 of the patients has no evidence of disease.

FUTURE RESEARCH

All of the papers on photodynamic therapy for head and neck cancer suggest that photodynamic therapy has a significant place in the future management of this disease. The problem is in determining the exact type of photodynamic therapy associated with which photosensitizer and whether primary therapy, adjunctive therapy or palliation is the optimum course.

KEY POINTS

- Laser light amplification by stimulated emission of radiation.
- Laser light – collimated, coherent and monochromatic.
- Laser tissue action – photoablative, photochemical and photomechanical.
- Laser 'star wars' beam of micromanipulator – hosepipe type jet of fibre optic laser delivery.
- Read and follow the safety regulations for your laser and operating room.
- PDT requires administered drug, light and oxygen.
- Skin phototoxicity and limited tissue penetration are the current PDT shortcomings.
- PDT has a future place in head and neck cancer management.

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CHAPTER 51

CONTACT ENDOSCOPY OF THE UPPER AERODIGESTIVE TRACT

Mario Andrea and Oscar Dias

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: contact endoscopy, mucosal vascular network, narrow band imaging and Methylene blue.

INTRODUCTION

The investigation of blood vessels and their microcirculation has been an area of interest to surgeons for many years. In 1970, surgeons[1] started research on the arterial vascularization of the larynx. Over the years, anatomical and clinical research on the pathways of extension of laryngeal tumours has been published.[2–5] The systematic evaluation of operated specimens allowed for a better understanding of the progression and invasion of the laryngeal tumours.

In order to enhance the evaluation of the operative specimens, nasal endoscopes and endoscopes of other territories and specialities were used. It soon became obvious that the endoscopes offered a superior view compared the operative microscope alone.[6] With the microscope the assessment is limited by a straight line of vision.

A group of endoscopes were produced by Karl Storz (1995)[7] that were specifically designed for the intraoperative evaluation of the larynx. This technique is called contact endoscopy and typically involves examination of the superficial epithelium of the larynx. Rigid endoscopy associated with microlaryngoscopy[8–9] allowed the direct observation of the vascular networks and alterations. This led to the the next phase in which contact endoscopy was used to visualize the microvascular networks.[10]

The first description of contact endoscopy is atributed to Desormaux in 1865,[11] who observed the vascular network of the bladder mucosa. The development of this technique was only possible due to technological progress. In 1955, Jaupitre[12] promoted contact cystoscopy associated to photography and cinematography and in 1983, Hamou[13] developed the microcolpohysteroscopy used in gynaecology. This technique allowed for the better comprehension of the pathology of the uterine cervix, but due to its complexity and difficulty, its use remained only within a limited number of centres.

The contact microlaryngoscope was developed in 1995[14] and the study of the larynx using contact endoscopy was initiated.

Contact endoscopy, using amplifications of 60x and 150x, allows for the *in vivo* and *in situ* observation of the mucosal vessels. By staining the mucosa with methylene blue, it is possible to visualize the cells of the superficial layer of the mucosa of the larynx, which allows diagnosis, the evaluation of the extension of the lesions and,

when tumour is present, defining the safety margins. The advantages of this technique led to it being used daily in clinical practice.[15–22]

Contact endoscopy was further developed and systematized for the other areas of the aerodigestive tract. Confronted with the richness of the microcirculatory and cellular images obtained with contact endoscopy, new endoscopes were designed and produced by Karl Storz, for use in the nasal fossa, in the nasopharynx, mouth, oropharynx, hypopharynx and trachea.[23–26]

In 2007, observation of the mucosal vascular network was enhanced by combining contact endoscopy with an Olympus system of illumination called 'narrow band imaging'.[27] This produces a specific wavelength, which is selectively captured by haemoglobin and allows a better contrast of the vessels relative to the neighbouring tissues. This enhances the visualization of the deeper vessels.

With contact endoscopy, anatomical-pathological concepts of mucosal illnesses are evaluated clinically in multiple sites and stages, at times associated with aetiopathological factors. With this technique vascular and cellular alterations of the mucosa can be observed both in the outpatient clinic and in the operating theatre.

With contact endoscopy, the notion of illness has surpassed the classic concept of the macroscopic lesion that was biopsied.

With these techniques, the non-invasive pathological evaluation can be made during an endoscopic examination. This allows, in many cases, for the diagnosis to be made at the time of observation, having a direct implication on the planning and method of treatment that is chosen. Contact endoscopy may deliver further information on the subclinical staging and improve understanding of the physiopathology of the diagnosed condition.

The objective of contact endoscopy is not to visualize at the surface what is expected to be observed from histological sections and it should not be considered a substitute for biopsy. Instead it is a clinical method that adds to the information available during an endoscopic examination. It is an anatomical-pathological examination that supports the cytology.

The development of contact endoscopy of the upper aerodigestive tract has led to establishing parallels with other areas such as gynaecology, gastroenterology, pulmonology and opthalmology, as we further converge at the pathological and cytological level.

Contact endoscopy is now used in centres with benefits for patients around the world. The same principles are being used in other specialties, as can be seen through work published in the medical literature.[28–49] Technological evolution and collaboration between centres will contribute to the further development of this technique.

TECHNIQUE

The contact microlaryngoscope (Karl Storz 8715 AA) is an endoscope with a diameter of 5.8 mm, and 24 cm in length. Another contact endoscope with an angulation of 30° (Karl Storz 8715 BA) was manufactured in order to improve the access to certain locations of the larynx. Later, shorter contact endoscopes (18 cm) with a smaller diameter (4 mm) for the observation of the nasal cavity, the oral cavity, the oro- and the nasopharynx (Karl Storz 7215 AA e 7215 BA) have also been designed.

At the level of the larynx and hypopharynx contact endoscopy is performed under general anaesthesia with endotracheal intubation. The nasal mucosa, nasopharynx, mouth and oropharynx can be observed, in many cases, without the need for any anaesthetic.

For the observation of the vessels the contact endoscope is applied directly on the mucosa without any staining. The microcirculation is visible with illumination from a regular endoscopy light source. However when the illumination is changed for the Olympus 'narrow band imaging', the emitted light is absorbed by the haemoglobin of the erythrocytes, improving substantially the visibility of the vascular network allowing the identification of deeper vessels.

To observe the cells of the epithelum the mucosa is stained with methylene blue. The contact endoscope is gently applied to the mucosal surface. The colouration lasts for 4 to 5 minutes.

The contact endoscope has a round control near the proximal ocular end that allows a change of magnification (60× to 150×) and controls focus. Sliding the contact endoscope over the mucosa, it is possible to visualize the cells and their alterations at the level of the lesion and of the neighbouring areas. Furthermore, it allows mapping of the disease or the various diseases that can occur in distinct sites and stages.

Contact endoscopy must always be performed with video recording and if possible in high definition. The image is immediately shared and the recording can be reviewed and analyzed later by the otolaryngologist and pathologist or cytologist.

CELLULAR AND MICROVASCULAR STRUCTURE OF THE MUCOSA OF THE UPPER AERODIGESTIVE TRACT

The mucosa that covers the upper aerodigestive tract is constituted by ciliated epithelium and by squamous stratified epithelium in accordance with the function of the different regions. Acting as an interface with the external environment, this mucosa is subjected to frequent stimuli and insults that may cause clinical and subclinical alterations at different tissue levels. Alterations of one part of the aerodigestive tract may cause consequences of other anatomical territories within the aerodigestive tract.

Contact endoscopy in otolaryngology reinforces clinical evaluation through the concept of the anatomical and functional units, as it allows a non-invasive method to identify alterations at various anatomical territories that would not be perceived in other ways.

NORMAL AND PATHOLOGICAL PATTERNS

The systematic observation of the various organs and territories of the upper aerodigestive tract with contact endoscopy allows a better understanding of how the mucosa reacts to the conditions and insults to which it is subjected. In each of the territories the pathology acquires specific characteristics; however, the overall behaviour of the mucosa, in general, is very similar.

Normal pattern

When observed by contact endoscopy the cells of normal squamous epithelium have a polyhedric shape, being in continuity with each other. The nuclei are round and dark. The cytoplasm has a light blue colouration. The nucleus:cytoplasm ratio is regular and the general morphological pattern is homogeneous (Figure 51.1).

The ciliated epithelium observed with contact endoscopy has a distinct appearance. The nuclei are round and dark but the cytoplasm limits are difficult to define. The nuclei are very close to each other creating a higher density of nuclei per optic field (Figure 51.2). The filamentous structures displaced by the endoscope are due to bundles of cillia. These bundles of cillia may have variable size, being very exhuberant at the level of the nasal and nasopharyngeal mucosa.

The transition of squamous to ciliated epithelium is easily observed with contact endoscopy. In some cases there is a very sharp line of separation (Figure 51.3). In other cases the transition is less well defined. Occasionally islands of squamous epithelium are found in the middle of the ciliated epithelium.

Glandular orifices are observed scattered through the mucosa of the upper aerodigestive tract.

The mucosa undergoes a process of metaplasia with age and particularly when submitted to damaging factors. For example, the ciliated epithelium of the larynx changes into squamous epithelium in chronic smokers. The same happens with the trauma of reflux at the posterior commissure of the larynx. The same phenomena occur at the nasal and nasopharyngeal sites when exposed to traumatic factors.

Contact endoscopy allows a detailed observation of the mucosal vessels. The most superficial microvascular network is situated immediately below the basal membrane. The morphology of the vascular network is conditioned by the topography and function of the mucosa. In most of the mucosa of the upper aerodigestive tract the vessels have a course parallel to the surface and are connected by many anastomoses constituting a plexus. In specific sites, vessels with a perendicular course to the surface are identified in gums, hard palate, cheek mucosa, superior surface of the tongue and in the papillae of the nasal mucosa. At the level of the vocal cords the blood vessels are parallel to each other (Figure 51.4) and are connected by transverse anastomostic vessels. This arrangement favours the vibratory movements of the vocal mucosa.

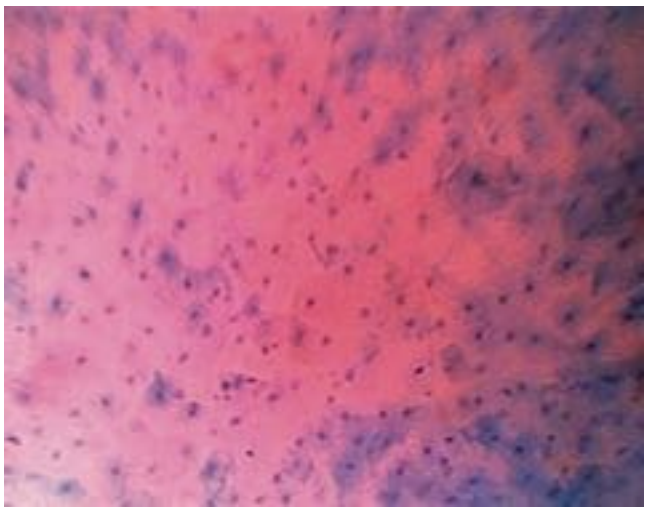


Figure 51.1 Normal squamous epithelium of the vocal cord. The nuclei are regular and homogeneous, 60X.

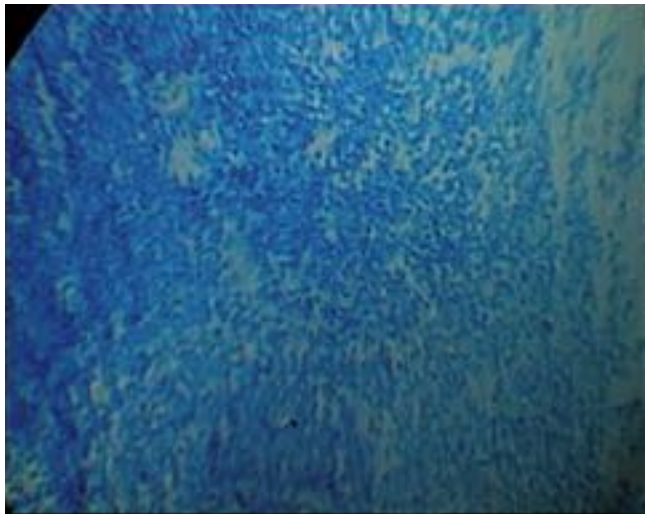


Figure 51.2 Normal ciliated epithelium of the vocal cord, 60X.

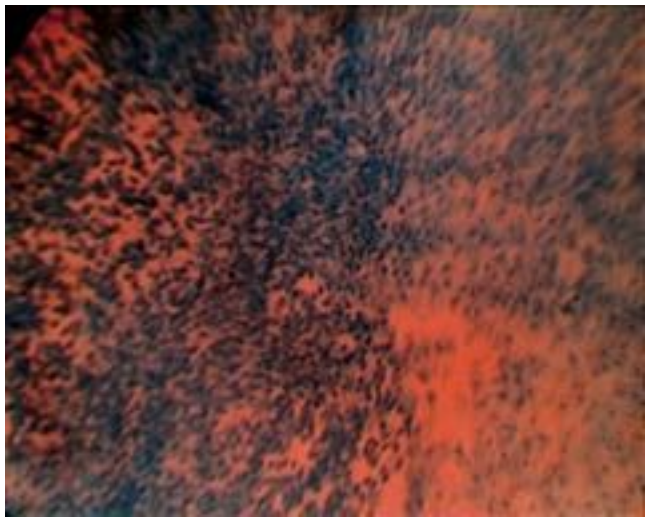


Figure 51.3 Transition of the ciliated epithelium to squamous epithelium of the vocal cord, 60X.

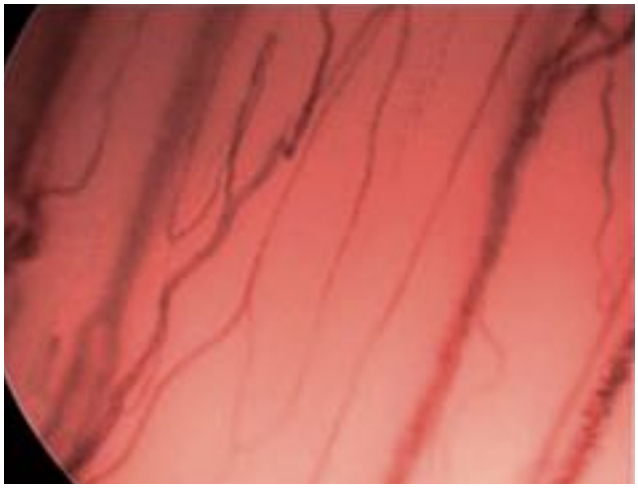


Figure 51.4 Normal vessels of the vocal cord. The vessels are thin and parallel, 60X.

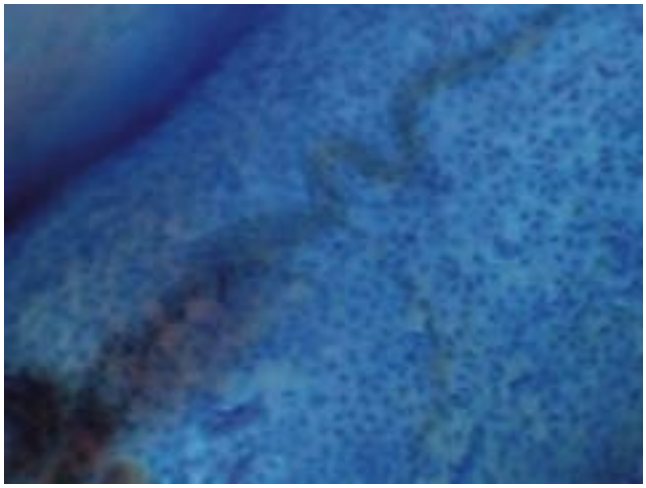


Figure 51.5 Chronic laryngitis. The nuclei are of increased size with a homogeneous pattern, 60X.

The more superficial microvascular network drains to venules that go to collecting vessels of larger calibre at the deeper planes. The angioarchitecture of this deeper plane depends on the thickness of the mucosa and the neighbouring structures. Contact endoscopy offers a fascinating image of the blood flow. The red cells circulate to the rhythm of the heartbeat and travel in several directions, and sometimes change direction with the pressure of the contact endoscope on the mucosa.

Chronic inflammation

When chronic inflamed mucosa is observed through contact endoscopy, the general aspect of the squamous epithelium is homogeneous, but the size of the nuclei is larger with an increased nucleus/cytoplasm ratio (Figure 51.5). As the cellular turnover is accelerated due to the inflamation, more immature cells become visible at the surface, similar to those that are observed at the intermediate layers of the normal epithelium.

The mucosa of chronic inflammation has a higher vascular density due to the increased number of vessels and vessel enlargement. However, the pattern of distribution remains organized.

FUNGAL INFECTION

In some cases of chronic inflammation, in addition to the typical pattern of increased diameter of the nuclei, it is possible to identify with contact endoscopy small dark dots that seem to spoil the image. These correspond to fungal spores (Figure 51.6). Hyphae and miceliums can also be observed as well as filamentous structures.

Contact endoscopy has identified that fungal infections are in many cases associated with chronic inflammatory changes, and dysplastic or neoplastic lesions in different anatomical sites. In general the fungal infection does not disturb the microcirculation more than inflammation due to other aetiologies. However, in more aggressive forms of disease there are profound vascular changes, including aberrant shaped vessels causing thrombosis and tissue necrosis.

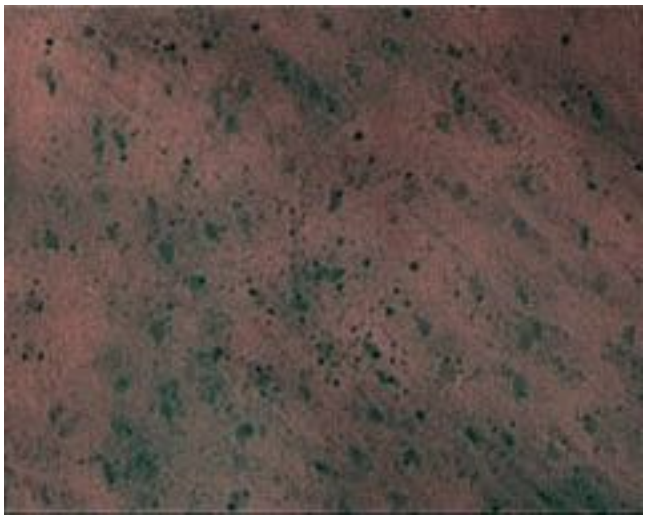


Figure 51.6 Laryngeal fungal infection and dysplasia, 60X.

KERATOSIS

In the same patient, and even within the same lesion, different degrees of keratinization can be observed by contact endoscopy. Initially isolated cells without nuclei are identified. Unfortunately, it is not possible to identify individual cells in areas of amorphous or laminar structure (Figure 51.7). Keratosis is present in different clinical entities. In some cases keratinization is very discrete while in others it is pronounced. Occasionally keratosis is not suspected and its finding with contact endoscopy is a surprise.

With leukoplakias, in addition to keratosis, other types and degrees of cellular alterations can be observed by contact endoscopy, including heterogeneity of the cellular population. The variety of the cellular images can be accounted for as different pathological alterations such as

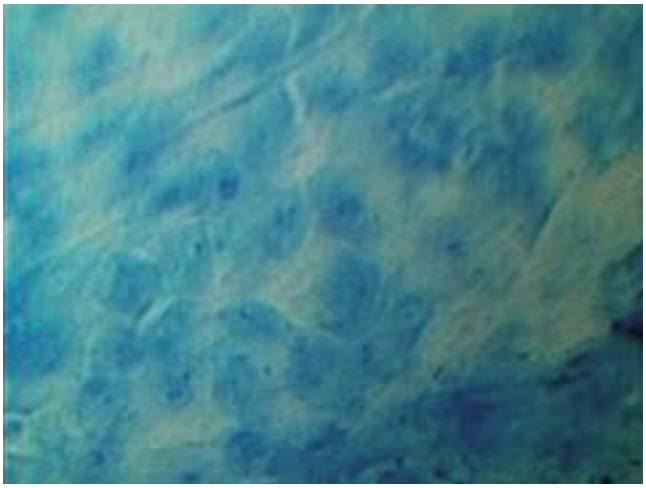


Figure 51.7 Keratosis of the vocal cord, 60X.

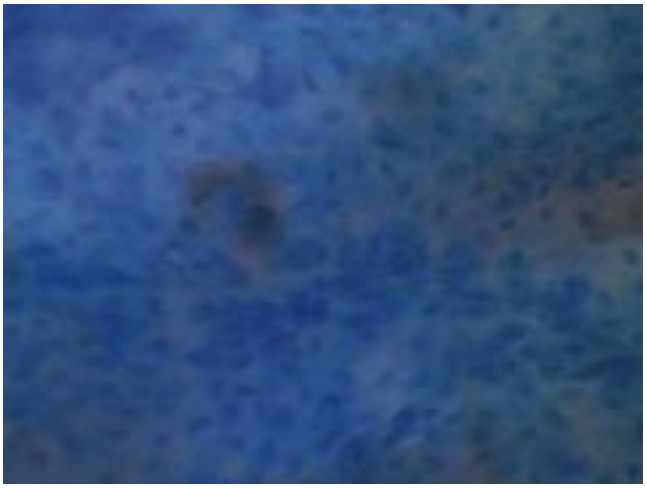


Figure 51.8 Dysplasia, 60X.

hyperkeratosis and dysplasia can occur simultaneously. In other clinical entities such as chronic inflammation, papillomas and tumours, keratosis can also exist in different degrees.

While in some cases the vessels pass below the area containing keratosis they may sometimes surround the leukoplastic lesion.

DYSPLASIA

In the majority of the cases of dysplasia, there are alterations at the superficial layers, making it accessible to contact endoscopy. Most tissue alterations that are necessary for the diagnosis of dysplasia by a pathologist are also identifiable by contact endoscopy, specifically alterations in size, shape and colouration of nuclei, altered nucleus:cytoplasm ratio (dyskaryosis and anisokaryosis) and keratosis (Figure 51.8). The more pronounced the changes observed by contact endoscopy the more severe is the dysplasia.

The microvascular alterations that accompany the dysplastic lesion are fundamental to the understanding of the pathology hence its treatment. The normal microvasculature is substituted by vessels with different degrees of alteration.

When the vascular network becomes disorganized and the vessels are irregular it can be interpretated that the pathology of the epithelium has passed the boundary of the basal membrane, which may be damaged, thus allowing the vessels to penetrate the epithelium. The mobility of the contact endoscope allows assessment of the regions neighbouring the lesion. This information benefits an understanding of the main lesion.

TUMOUR

In carcinoma, contact endoscopy identifies the marked cellular irregularity and heterogeneity. The nuclei have different sizes, shapes and colouration. The nucleus:cytoplasm ratio is very irregular (Figure 51.9). Sometimes nuclear inclusions, prominent nucleoli and mitosis are identified.

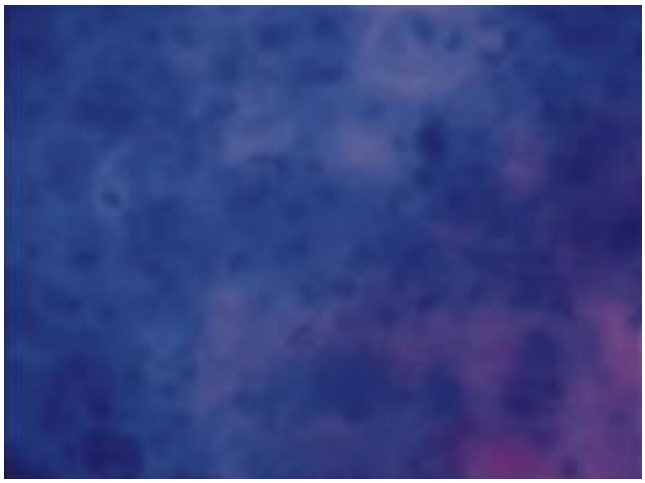


Figure 51.9 Tumour of the larynx observed by contact endoscopy. Nuclei are irregular in size, shape and colouration.

The angioarchitecture is also very disturbed. The blood vessels are atypical with differences in size and shape, but also ectasias, haemorrhages and reduced blood flow, which results in thrombosis (Figure 51.10).

Depending on the anatomical region of the tumour, distinct images can be observed. In places where the tumour growth infiltrates the deep planes but does not reach the surface, vascular alterations can be identified with normal superficial epithelial cells.

The direct demonstration *in vivo* and *in situ* of a tumoural pattern in the operating room and in the outpatient clinic is a reality. Contact endoscopy also allows the assessment of transition areas, the identification of early stages of disease, guidance of biopsies, guidance of sample collections for cytology, establishment of safe margins and demonstration of different diseases.

PAPILLOMA

Contact endoscopy contributes to the assessment of the papilloma, allowing the identification of its extent, offering

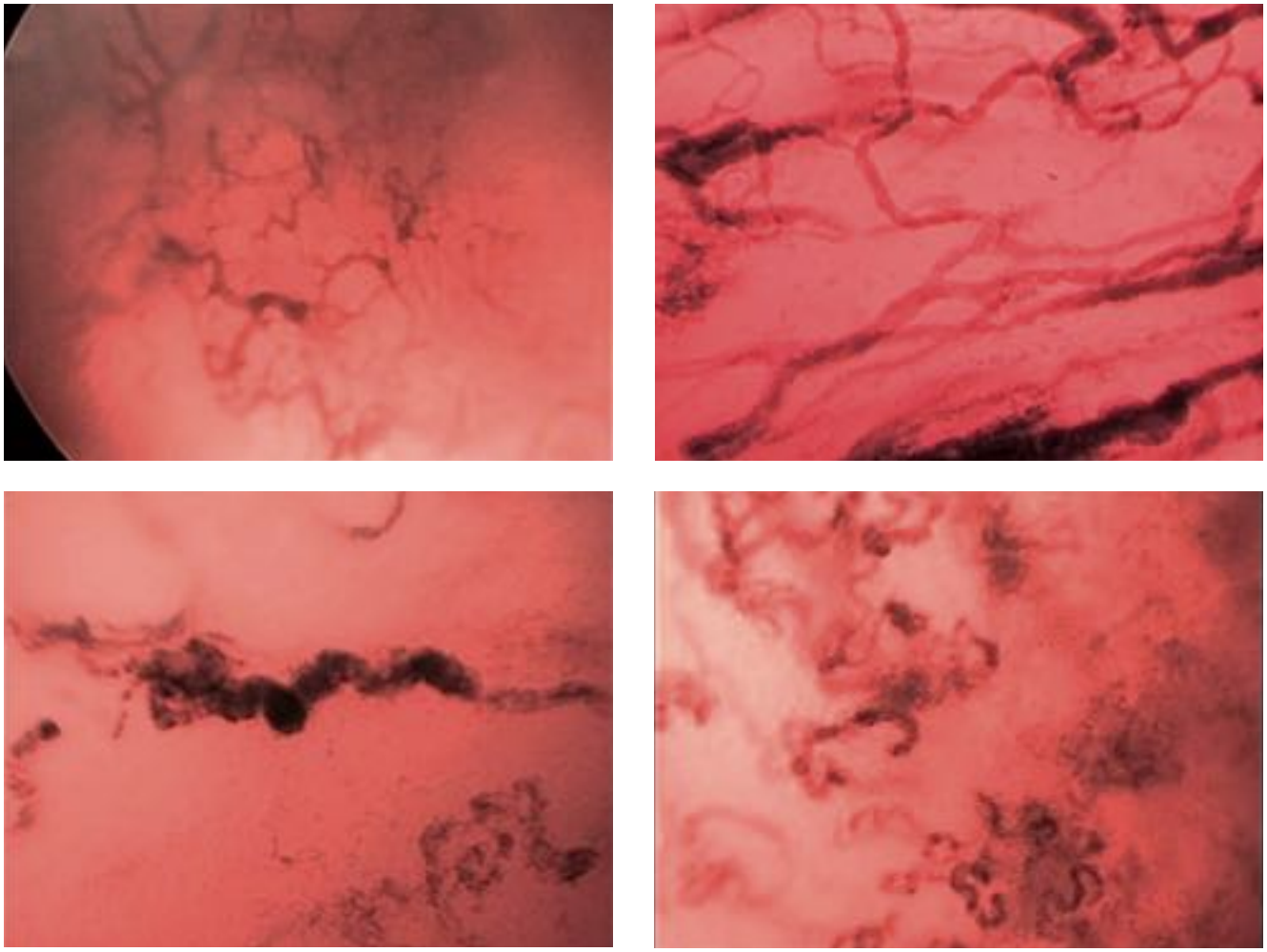


Figure 51.10 Tumoural vessels.

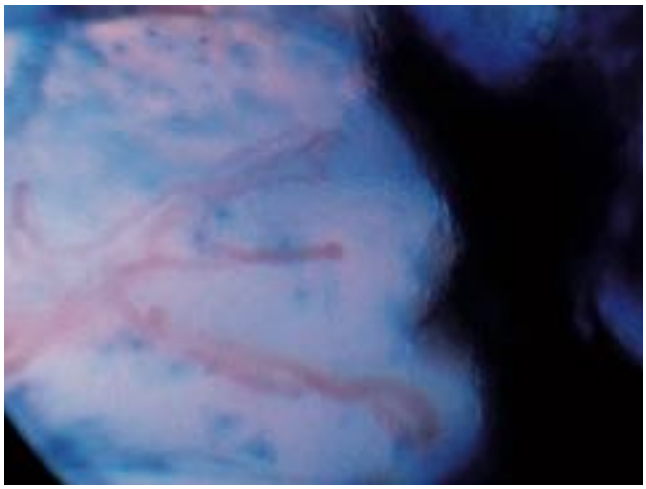


Figure 51.11 Papilloma of the larynx. Vascular axis of the papillas, 60X.

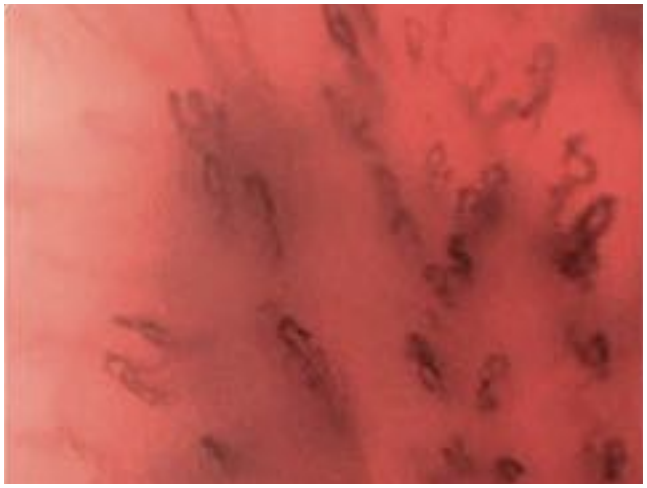


Figure 51.12 Papilloma of the larynx. Vascular axis of the papillas observed with NBI, 60X.

better conditions for removal and potentially reducing the risks of residual disease.

The direct application of the contact endoscope allows the identification of the typical vascular loops (Figures 51.11, 51.12). The degree of visualization of the vascular structure depends on the density of the keratosis that is associated with the disease in some cases.

With the vital stain, in some cases it is possible to identify the typical koilocytes (ballooned cells) (Figure 51.13) and inflammatory infiltrates. Koilocytes are typical of human papillomavirus infected cells.

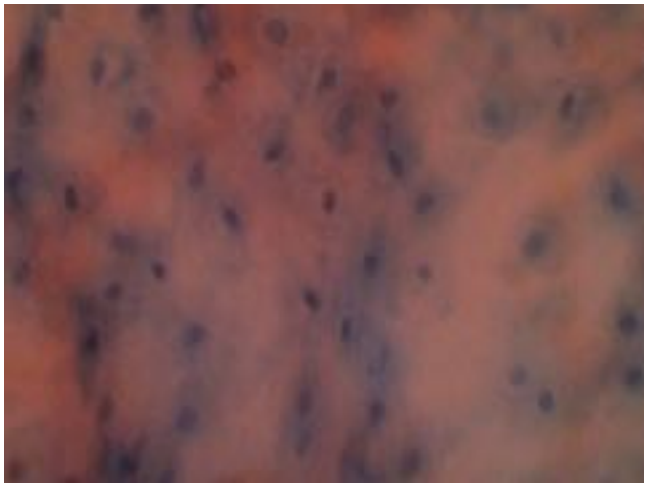


Figure 51.13 Papilloma of the larynx. Koilocytes are identified, 150X.

Beyond the characterization of the lesions, contact endoscopy allows the assessment of neighbouring areas, and sometimes it is possible to identify subclinical stages of the disease.

CONCLUSION

Contact endoscopy is a non-invasive clinical technique and is currently the only technique that allows an *in vivo* and *in situ* assessment based on the observation of the microvascular networks and of the cells of the superficial layers of the epithelium.

In some cases, the cellular alterations precede or are more evident than the vascular alterations. In other cases the modifications of the vascular networks and the course of the vessels that are present occur before the identification of cellular changes.

Contact endoscopy allows not only the observation of vessels and cells of the lesion or of a suspected area identified macroscopically, but also of all the anatomical territory. The application of the contact endoscope to several anatomical sites allows an assessment of the extent of pathology and importantly the transition of a normal to pathological tissue.

The information that is obtained (vascular and cellular alterations of a pathological entity) is obtained in real time. These alterations are not limited to the macroscopic lesion and become integrated in a much wider concept – the concept of disease. This occurs in the subclinical stages that become associated with the main lesion.

The visualization of vascular network alterations simultaneously with the observation of the cells of the superficial layers of the mucosa opens an enormous window for the understanding of the physiopathology allowing a more correct and precise diagnosis, with repercussions in the therapeutic planning, in the follow-up and prognosis.

Contact endoscopy of the upper aerodigestive tract, with the exception of the larynx and trachea, can be performed in the outpatient setting. Beyond being minimally invasive, it does not cause pain to the patient, typically does not even require local anaesthesia and the image recording of the image allows a single endoscopy. The high definition video technology allows a more detailed analysis.

The association of contact endoscopy with the 'narrow band imaging' is currently the most detailed way (in clinical practice) of studying the microvasculature of the mucosa of a patient with upper aerodigestive pathology.

Combining the conventional endoscopic techniques with contact endoscopy and analyzing the patterns with the cellular and vascular changes, it is possible to aid diagnose in a more precise way for chronic inflammation, fungal infections, some viral infections, mechanical trauma, metaplasia, keratosis, dysplasia and tumours, hence improving the mapping of alterations of the disease.

Having access to all this information can modify the therapeutic approach, medical as well as surgical, and in some cases changing both simultaneously.

Whatever the developments of new therapies, there is little doubt that a more detailed and profound knowledge of a disease with the *in vivo* and *in situ* observation of the vascular networks combined with the alterations at the cellular level will create a new way of thinking.

Contact endoscopy represents a new phase of the development of endoscopy. With experience from different centers and technological progress, new ideas, concepts and instruments will occur. If all this progress facilitates a more thorough examination it will also require a more detailed knowledge and understanding of each organ and anatomical territory of the upper aerodigestive tract.

Images obtained by contact endoscopy promote intense and fruitful interdisciplinary work. This will continue to be fundamental to the development of the technique.

KEY POINTS

- Contact endoscopy allows non-invasive evaluation of micovasculature and cells.
- Contact endoscopy allows appreciation of cellular differences at transition zones.
- Most upper aerodigestive mucosa has vessels which run parallel to the surface mucosa.
- Contact endoscopy may assist the identification of safe margins during surgery.

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Section 2
Head and Neck Endocrine Surgery

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CHAPTER 52

HISTORY OF THYROID AND PARATHYROID SURGERY

Waraporn Imruetaicharoenchoke, Ashok R. Shaha and Neil Sharma

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: thyroid, goitre, history, endocrine, surgery. Key historical texts were consulted in print where possible, or via online access if not. Reference lists were examined for further sources of evidence.

THYROID SURGERY

The dark ages: Shoe laces, seaweed and the King's touch

Thyroid surgery has its roots over one millennium ago, with goitre being recognized well before that. Pliny the Elder (AD 23–73) in his work *Naturalis Historia* mentions hernia gutteres, as does Aëtius of Amida (*c*.5th–6th century) in his compilation the *Tetrabiblion*. In this time, the thyroid gland was not recognized as a normal structure and these enlargements were considered new formations. In time, the thyroid was seen as a normal organ, although its function was still unknown. In 1511, during the Italian Renaissance, Leonardo Da Vinci was the first person to draw the anatomical shape of the thyroid gland correctly, but he misinterpreted its function as only filling up empty space in neck. In the 16th century, Andreas Vesalius described the thyroid structure, considering it a laryngeal gland, while Bartholomeus Eustachius correctly noticed that this gland had two lobes conjoined by isthmus; Aelius Galemus reported its role was lubrication of the larynx. In 1656 Thomas Wharton named it the 'glandulae thyroidea' or 'thyroid' because of the juxtaposition to the thyroid cartilage, which is shield-shaped.[1, 2]

Treatment of thyroid goitre was first described in 2700 BC in Chinese literary works; this involved administering seaweed and burnt sea sponge (we now know this is due to their high iodine content). The earliest recorded operation on the thyroid was performed by Albucasis (Abu al-Qasim al-Zahrawi, AD 936–1013), a Moorish physician, using simple ligatures and hot cautery irons; however, his works seemed to be forgotten. Indeed, Ruggiero Frugadi (pre AD 1140–1195) of the Salerno School of Surgery is often credited as performing the first goitre surgery in 1170, using bootlaces as setons to ligate and transfix a pedunculated goitre, allowing it then to slough off.[3] King Henry IV of France (1553–1610) practised the 'King's touch', akin to the laying on of hands, in the 16th century. This technique was famous in Europe between 1100 and 1600 with many thousands of people reportedly 'cured' of different ailments.

The true beginnings: Foolhardy performances and horrid butchery

Despite these early attempts, thyroid surgery did not progress for several centuries. Early attempts by Benjamin Gooch (1708–1776) resulted in fatal haemorrhage and the thyroid's adherence to the trachea meant that for many years it was considered impossible to safely separate the two structures. During the French Revolution, Pierre-Joseph Desault (1744–1795) performed a successful thyroidectomy on a 20-year-old woman.[4] He demonstrated that careful dissection coupled with ligation of the key vessels would allow the surgeon to remove the thyroid gland and for the patient to survive through the postoperative period. For many years, Desault's technique was the accepted standard, but mortality in 1850 was still in the region of 41%.[5] Most patients suffered with both primary or secondary haemorrhage and an almost inevitable sepsis.

The unacceptably high mortality and morbidity rates, both short- and long-term, led to the French Academy of Medicine banning thyroid surgery. It was described as 'breathtaking heroics fraught with danger to the patient and almost certain bereavement for the family'.[6] Johann Dieffenbach (1792–1847), a German surgeon who reportedly tried every method known to treat vesicovaginal fistula, thought of thyroid operations as 'foolhardy performances' and 'one of the most thankless, most perilous undertakings which, if not altogether prohibited, should at least be restricted'.[7] Even the great American surgeon Samuel Gross (1805–1884) wrote that 'every step he takes will be environed with difficulty, every stroke of his knife will be followed by a torrent of blood, and lucky will it be for him if his victim lives long enough to enable him to finish his horrid butchery' and 'also no honest and sensible surgeon will ever engage in it'.[8] However, as the 19th century progressed, the practice of thyroid surgery was revolutionized by three advances that took it from the realms of a last-ditch approach for the rapidly succumbing patient to a recognized, valid treatment for goitre.

The new dawn: Three great advances and the fathers of thyroid surgery

During the mid 1800s, three important discoveries changed the evolution of thyroid surgery.[5] In 1842 Crawford Williamson Long (1815–1878), an American surgeon, was the first doctor to administer inhaled ether as an anaesthetic agent, although at the time the credit was given to the dentist Horace Wells (1815–1848) and the surgeon John C. Warren (1778–1856) for an operation in 1846. The first thyroidectomy under ether anaesthesia took place in St Petersburg under Nikolay Pirogoft (1810–1881) in 1849.[9] Secondly, and a few years later in 1867, Joseph Lister's (1827–1912) theories of antisepsis using carbolic acid, followed shortly after by asepsis, dramatically reduced the infection and sepsis rates after surgery and did a great deal to reduce mortality.[4] The last development was of haemostatic forceps, used in central Europe in 1870 by Thomas Spencer Wells (1818–1897)[10] and redesigned as the operative haemostat in 1874 by Jules-Emile Péan (1830–1898).[6] These led to improved haemorrhage control over the traditional methods such as the artery hook, mass ligature, crushing forceps and crude cautery.

These three developments prepared the way for Christian Albert Theodor Billroth (1829–1894) (**Figure 52.1a**), arguably the most famous surgeon of his day. Billroth trained at the University of Berlin before becoming the chair of surgery at the University of Zurich at the age of 31. In his first year at Zurich, he performed 20 thyroidectomies, but his mortality rate was around 40%, mostly from sepsis. Despite becoming disheartened and abandoning thyroid surgery for almost 10 years, he returned to it when he moved to the chair of surgery at the University of Vienna. He embraced anaesthesia and initiated the use of antisepsis and haemostats. He was also the first surgeon to wear gloves, albeit cotton, when operating, and his mortality rate fell from nearly 40% to 8%, making him the most well-known thyroid surgeon at that time. Despite this, he was still troubled by post-operative tetany and damage to the recurrent laryngeal nerve.

Billroth's most valuable contribution to thyroid surgery is arguably the students he taught, many of whom went on to become outstanding surgeons in their own right. Anton Wölfler (1850–1917), Anton von Eiselsberg (1860–1939), Jan von Mikulicz-Radecki (1850–1905) and Hans von Haberer (1875–1958) all contributed not only to thyroid surgery but to surgery in general. However, Billroth's greatest student, and the surgeon who can be truly considered the 'Father of thyroid surgery', was Emil Theodor Kocher (1841–1917) (**Figure 52.1b**).

Having trained with Lucke, Billroth and Langenbeck, Kocher studied and acted on the successes and failures of those around him, constantly updating his technique to give better results. His knowledge of anatomy and circulation aided his meticulous dissection technique, and he adopted the now standard collar incision that bears his name in 1890.

Kocher was also one of the first surgeons to audit his own results. In a review of his 101 cases in the mid 1880s, he found that most of his unilateral excision patients were well, but all of the total resections were suffering with symptoms we would now recognize as hypothyroidism. This had also been described by Jacques-Louis Reverdin, with patients who underwent total thyroidectomy experiencing



Figure 52.1 The fathers of thyroid surgery. **(a)** Theodor Billroth, **(b)** Theodor Kocher, **(c)** William Halsted, **(d)** Thomas Dunhill.

personality change and distressed physical features named 'myxoed me operatoire'.[11] Kocher realized that this adverse condition was caused by deprivation of thyroid hormone, and then called it 'cachexia thyreopriva', acknowledging that the thyroid gland had a function. Subsequently, Kocher prohibited total thyroidectomy except in the treatment of thyroid cancer, to avoid this condition. His method of preventing damage to the recurrent laryngeal nerve was to switch from extracapsular to intracapsular dissection, leaving thyroid tissue behind posteriorly. He was also an early proponent of iodinizing drinking water to prevent goitrogenesis. Kocher kept detailed outcome records and it is a testament to his ability as a surgeon and innovator that, when he presented his surgical experience to the Swiss Surgical Congress in 1917, his mortality was 0.2% for ordinary goitre and 2% for what we now consider hyperthyroid goitre, all in an era before antithyroid drugs and radioactive iodine.[12] His work in physiology, pathology and surgery on thyroid gland led to the award of the Nobel Prize in Medicine in 1909.[13]

Kocher went on to train William Halsted (1794–1878, **Figure 52.1c**), an American surgeon who studied in Vienna. On his return to America, Halsted popularized the use of haemostatic forceps and his work on parathyroid preservation and post-operative calcium/parathyroid extract supplementation to prevent hypocalcaemia did much to improve thyroid surgery. Halsted also swapped Billroth's cotton gloves for ones made from rubber. He later concluded that: 'The extirpation of the thyroid gland for goiter typifies perhaps better than any other operations the supreme triumph of the surgeon's art'.[9]

Another difficulty that thyroid surgeons were encountering was that of the patient with exophthalmic goitre. First described by Caleb Hillier Parry (1755–1822) in a posthumous publication in 1825,[1] the condition we now know as Graves' disease linked thyrocardiac symptoms, such as palpitations and tachycardia, with exophthalmos, extreme nervousness, and goitre. Surgery in these patients was reserved for those in extremis as the operation was fraught with difficulty, and mortality was very high. Nevertheless, in 1884 Ludwig Rehn (1849–1930) reported the full recovery of patients from thyrotoxic symptoms following thyroid surgery due to compressive goitres. In 1887, Theodor Kocher demonstrated increased vascularization of the thyroid gland in a patient diagnosed with Graves' disease and recommended that the thyrotoxic symptoms originated by an increase in thyroid hormone level. Thereafter, he practised staged thyroidectomy, first ligating the main feeding vessels to the gland and then removing one lobe at a second operation.

Over the following decade, the mortality rate for surgery for Graves' disease improved to around 6%; however, 25% patients developed recurrent disease requiring a second operation.[14] In 1905 Frank Hartley advocated that the cure rate of thyroidectomy for Graves' disease relied on removing a sufficient amount of the thyroid gland, and he recommended resecting one thyroid lobe and some portions of the opposite lobe for treatment of hyperthyroid patients.[15] Thomas Dunhill (1876–1957) (**Figure 52.1d**) followed Hartley's theory and in 1912 published the outcomes of 380 thyrotoxic patients who underwent surgery, with a mortality of around 1% and a minimal recurrence rate.[16] Over the next two decades, Dunhill gradually moved to carrying out bilateral subtotal thyroidectomy, as Jan Mikulicz-Radecki (1850–1905) did for the treatment of simple goitre.[17]

The pre-operative preparation of hyperthyroid patients became more widely recognized as key to reducing complications. Charles Mayo (1865–1939) and George Crile (1864–1943) worked closely with the endocrinologist Henry Plummer (1874–1936), pioneering this cross-specialty collaboration in the United States.

Plummer began treating hyperthyroid patients with iodine before passing them on to Mayo for surgery; this approach decreased the incidence of thyroid storm and also mortality rate.[18] Consequently, the staged thyroid operation could be abandoned and the whole gland removed in one sitting. The improved survival and cure rate moved thyroidectomy for Graves' disease from an operation reserved for moribund patients to a curative procedure for those with much milder disease. The introduction of radioiodine in Boston and Berkley for the treatment of thyroid cancer and Graves' disease in 1942[19, 20] did much to improve outcomes further, as did the use of the antithyroid drugs thiourea and thiouracil created and advocated by Edwin Bennett Astwood (1909–1976) in Boston.[21]

The modern age

The history of thyroid surgery belongs to general surgery, but over the past three decades we have seen a shift towards otolaryngologists and head and neck surgeons working together with endocrine surgeons. Endocrine surgery has now come of age and, from a thyroid and parathyroid point of view, multidisciplinary and collaborative specialist work began when Dick Welbourn founded the British Association of Endocrine Surgeons (BAES) in 1983 (later to become the British Association of Endocrine and Thyroid Surgeons (BAETS)). This organization focused on specialist endocrine multidisciplinary working to include education and research and welcomed the ear, nose and throat (ENT) surgeon into its fold. It was much more recently that the American Association of Endocrine Surgeons (AAES) included otolaryngology in their membership.

Modern-day greats of endocrine/head and neck surgery reflect the shared responsibility between general surgery and otolaryngology. In the United States, general surgeons Jatin Shah, Ashok Shaha, Keith Heller and Joseph Attie (New York) and Orlo Clark from San Francisco as well as Samuel Wells from Duke have led the way in both surgical techniques and education. Significant contributions from otolaryngology in the USA have come from David Terris (Augusta), Greg Randolph (Massachusetts), and David Eisele and Ralph Tufano (both Baltimore). In Australia, Leigh Delbridge and Tom Reeve (Sydney) did much to advance endocrine surgery, in particular the creation and maintenance of prospective surgical databases.

In Europe, Charles Proye from Lille and Jean Françoise Henri from Marseilles (both general surgeons) led the way; in the United Kingdom, much is owed to Professor Malcolm Wheeler (general and endocrine surgery) from Cardiff and Omar Shaheen (otolaryngology) from Guy's Hospital; the link between general surgery and otolaryngology in the UK and the USA was cemented when John Watkinson (Birmingham) was the first ENT surgeon to be elected President of the BAETS (2011–13) and recently Greg Randolph has become the first otolaryngologist member of the AAES.

With the advent of thyroid specialists, the operative technique has undergone significant refinement and subsequent changes in the extent of surgery performed. While initially total thyroidectomy/lobectomy were the procedures of choice, concerns over preservation of the parathyroid glands and recurrent laryngeal nerves, as well as maintaining some functioning thyroid tissue, led to a move towards sub-total thyroidectomy. This has been largely abandoned now, however, and the current recommendations are for either total lobectomy or total thyroidectomy as the only valid operations, with near-total acceptable to preserve a nerve at risk. These changes have resulted from the era of evidence-based medicine and subsequent focus on outcomes. The prognostic factors and risk group analyses in thyroid cancer were very well defined by Hay from the Mayo Clinic[22] and Cady from the Lahey Clinic,[23] as well as Shaha from Memorial Sloane Kettering.[24] The American Thyroid Association (ATA) has now incorporated these risk groups into the third edition of their thyroid cancer guidelines, published in 2015, which is a landmark document for the management of thyroid cancer.[25] For medullary thyroid cancer, Sam Wells defined the implications of RET mutation and the role of prophylactic thyroidectomy in these patients,[26] and recent guidelines have further detailed the timing of surgery.[27]

While other chapters will cover the latest technological advances that relate to thyroid surgery, a review of their development is appropriate here. The first major change has been the approach to the gland itself. While Kocher's classic 8–10 cm transverse incision was the standard for almost a century, the move towards minimally invasive approaches has resulted in scars commonly of 3–6 cm in length being usual for both thyroid and parathyroid surgery.[28] As well as smaller scars for access, the use of the endoscope has found its way into the thyroid surgeon's armamentarium. First described in 1997 by Paulo Mucozi,[29] this has evolved into minimally invasive video-assisted thyroidectomy (MIVAT) with access from the neck,[30] the axilla[31] or lateral approaches.[32, 33] Thus far, complication rates are comparable to open surgery[34] and although operation time is longer, cosmesis and recovery appear improved over open. An almost inevitable extension from endoscopic thyroid surgery has been robot-assisted operations as pioneered by Chung at Yonsei University, South Korea. Designed to address the limitations of two-dimensional visualization and basic endoscopic instruments, a number of centres are now performing robotic thyroidectomy more often. The advantage of absent neck scar is currently countered by the extra dissection needed to reach the thyroid bed, longer operation time, learning curve and significant cost associated with the procedure. Whether this technique represents the future of thyroid surgery remains unclear.

The tools available to the surgeon have also advanced greatly, although their uptake has been variable. The intraoperative nerve monitor epitomizes this, with surgeons divided across the world as to its benefits versus disadvantages. As litigious medicine becomes more universal, the requirement for both real-time monitoring and assessment following surgery will surely increase. Dissection tools such as the harmonic scalpel and Ligasure™ are most widespread, and proponents herald the associated reduced operating time and improved haemostasis. Again, cost is a factor that rules these out for many units.

Surgical outcomes are now routinely measured in some manner by all hospitals, whether this be a personal or national audit. With the increased demand for transparency from the public, the requirement to participate in a national audit will become mandatory, as will the need for multidisciplinary meetings for suspected cancer cases.

The medical treatment of thyroid disease has also seen great leaps over the past half-century. In the post-war period, radioiodine treatment, antithyroid drugs and the technology surrounding thyroid surgery have advanced significantly. For thyrotoxic patients, medical treatment now carries high remission rates and reduces the number of patients requiring surgical treatment. Those who do progress or choose to have an operation are usually rendered euthyroid pre-operatively to decrease peri- and post-operative morbidity and mortality.

What is without doubt is that, in the modern era, the thyroid surgeon must act as a 'thyroidologist', capable of understanding the complexities of medical care as well as the nuances of surgery, and be willing to adapt their techniques and methods as modern technologies continue to gain ground.

PARATHYROID SURGERY

What we now know as the parathyroid glands were first identified by Sir Richard Owen, Hunterian Professor and Conservator of the Museum at the Royal College of Surgeons of England, in 1862 when he was asked to perform an autopsy on a Great Indian Rhinoceros. Owen described 'a small compact yellow glandular body attached to the thyroid at the point where the vein emerged',[35] resulting in the occasional use of the name 'Owen's glands'. However, the naming and description of the parathyroid glands is credited in 1880 to the Swedish medical student Ivan Viktor Sandstrom (1852–1889). Sandstrom's finding was unrecognized for more than 10 years until in 1891 Eugene Gley (1857–1930) repeated his discovery and also found that removal of these glands in animals resulted in tetany.[36] William George MacCallum (1874–1944) and Carl Voegtlin (1879–1960) subsequently discovered that the tetany produced by parathyroidectomy could be treated with a calcium infusion.[37] In parallel to these findings, Friedrich von Recklinghausen (1833–1910),

a pathologist in Strasbourg, described the characteristics of a specific bone disease which correlated with parathyroid lesion in 1891,[38] followed by the report in 1904 by Max Askanazy (1865–1940) of a female patient with a severe bone condition and a tumour lateral to her thyroid gland. Askanazy incorrectly interpreted that the parathyroid lesion was secondary to the bone disease rather than being the primary lesion itself.[39] In 1915, Friedrich Schlagenhaufer (1866–1930) suggested that parathyroid tumours themselves are the primary lesions affecting severe skeletal changes.[40] Nearly a decade later, Felix Mandl (1892–1957) treated a patient suffering from osteitis fibrosa cystica of the femur who had failed treatment with thyroid and parathyroid extract. Mandl planned to perform a parathyroid transplantation, but on exploring the neck he discovered a parathyroid tumour, which he proceeded to excise. The patient's post-operative serum calcium levels returned to normal and their bone disease recovered, supporting Schagenhaufer's hypothesis.

In 1926, Edward Delos Churchill (1895–1972) set out to explore the neck in a patient with primary hyperparathyroidism but failed to find a parathyroid tumour.[1] Just 3 years later, however, David Barr and Harold Bulger carried out the first successful parathyroidectomy for a patient with parathyroid disease, and they originated the term 'hyperparathyroidism'.[41] More surgeons began to perform the procedure, although there were still patients in whom no tumour was found.

One such patient was Captain Martell, treated by Oliver Cope (1902–1994). Cope, a student of Churchill who went on to become a leader in parathyroid surgery in his own right, performed numerous unsuccessful neck explorations before asking Churchill's opinion. Churchill proceeded to find the adenoma in the anterior mediastinum via a partial sternotomy, becoming the first surgeon to describe this.[42] As well as the anatomical variants of the parathyroid glands, advances in the understanding of the physiology of parathyroid hormone (PTH) continued throughout the early to middle 20th century. PTH was first isolated in 1923 by Adolph Hanson (1888–1959) and successfully extracted by James Collip (1892–1965).[43] It was Gerald Aurbach (1927–1991), however, who first purified the hormone in 1959.[44] In 1963, Solomon Aaron Berson (1918–1972) and Rosalyn Yalow (1921–2011) developed a radioimmunoassay to quantify PTH levels in the bloodstream, which greatly aided the diagnostic process.[45] After that period, determination of parathyroid disease and parathyroid surgery were greatly advancing.

From then to the present day, as for thyroid surgery, the management of parathyroid disease has been improved through previously described multidisciplinary working and advances in imaging, medical therapies and surgical techniques. Key among these advances is the use of localization studies (ultrasound, sestamibi and computed tomography (CT), specifically SPECT-CT scans and 4D CT with venous sampling) to identify the site of a diseased gland, thus greatly reducing the need for multigland exploration, and the risks inherent to operating in the central compartment on both sides of the neck – all of this facilitates minimally invasive techniques and targeted approaches. Intra-operative PTH measurement has allowed the surgeon to check for a fall in the PTH minutes after removing a suspect adenoma, again to determine whether further exploration in needed.

However, despite all the advances, the key to parathyroid surgery remains as it was when Edward Churchill described it: 'the success of parathyroid surgery must lie in the ability of the surgeon to know a parathyroid gland when he saw it, to know the distribution of glands, where they hide, and also be delicate enough in technique to be able to use this knowledge'.[42]

SUMMARY

The history of thyroid and parathyroid surgery is rich in the names of famous surgeons who advanced the practice from butchery to art form. With technological advances being made regularly, we can expect to see further changes over the coming years, although it will be some time before the original operation, described by Kocher over a century ago, ceases to be the gold standard.

KEY POINTS

- Thyroid surgery has a rich history stretching back a thousand years, and it is replete with the names of the most famous surgeons of the day.
- While technology has leapt forward over the past 50 years, thyroidectomy is still based on Kocher's original description.
- More recent advances have led to both thyroid and parathyroid surgery becoming increasingly specialized.

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CHAPTER 53

DEVELOPMENTAL ANATOMY OF THE THYROID AND PARATHYROID GLANDS

Julian A. McGlashan

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SEARCH STRATEGY AND EVIDENCE BASE

Much of the evidence for this topic is well documented in standard tomes on this subject such as *Werner and Ingbar's The thyroid*[1] and Bilezikian's *The parathyroids – Basic and clinical concepts*.[2] Medline, Embase and Google Scholar searches were performed for the years 1993–2013 to review new evidence pertinent to the topic using the keywords: thyroid gland, parathyroid gland, developmental anatomy, embryology, histopathology, and microstructure.

INTRODUCTION

Study of the developmental anatomy of the thyroid and parathyroid glands helps in the understanding of the normal and abnormal variations in anatomy seen at surgery and the related pathology of these organs. Although the main steps in the developmental anatomy have been known for over half a century, it is only in the last decade that the morphogenesis, control of cell growth and cellular differentiation of these organs have begun to be unravelled.[3] This has followed significant advances in our understanding of the molecular biology[4, 5] and genetic[3, 6–8] basis of thyroid and parathyroid function in health and disease in the last 20 years. There is now increasing knowledge of the role of the cellular aspects of thyroid stem cell biology[9] and pathogenesis of many thyroid and parathyroid diseases.[6, 10] Much of the information has been obtained from limited human studies and more extensive investigations in rodents and sheep. The events of thyroid development are roughly comparable to humans except for the timing.[11] Detailed discussion is beyond the scope of this chapter, which will focus on summarizing the key anatomical features and stages in the development of the thyroid and parathyroid glands relevant to surgical practice. There is also an emphasis on the link between developmental abnormalities and some of the more common clinical presentations. Further information on the physiology of the thyroid and parathyroid glands can be found in Chapter 55. For details of cellular development and their abnormalities, see Chapter 9, Genetics of endocrine tumours.

THE THYROID GLAND

Macroscopic anatomy

The thyroid gland is situated in the lower anterior neck straddling the upper trachea. It is the largest endocrine organ in the body. It weighs 15–20 g in adulthood.[12, 13] It is a highly vascular, reddish-brown, bi-lobed structure with each lobe joined together by a narrow isthmus (**Figure 53.1**). Each lobe is pear-shaped, measuring approximately 5 cm in length, 3 cm in width and 1.5 cm in depth. The apex of each lobe is narrow and extends beneath the sternothyroid muscle up to its insertion on the oblique line of the thyroid cartilage. The more rounded lower pole extends down to the level of the fourth or fifth tracheal ring. It lies lateral to the trachea and oesophagus and medial to the carotid sheath. The isthmus overlies the second to fourth tracheal rings.

The thyroid gland, together with the oesophagus and trachea, is invested in a visceral layer of deep fascia known as the pretracheal fascia.[1] It is attached superiorly to the hyoid bone and extends inferiorly into the mediastinum, fusing with the fascia surrounding the aorta, pericardium and parietal pleura at the level of the carina. Laterally the fascia blends with the carotid sheath. Anteriorly the fascia forms a distinct layer separating the thyroid from the strap muscles and posteriorly it merges with the prevertebral fascia. On the posterior aspect of the isthmus the fascia is sometimes known as the anterior tracheal ligament and is perforated by small

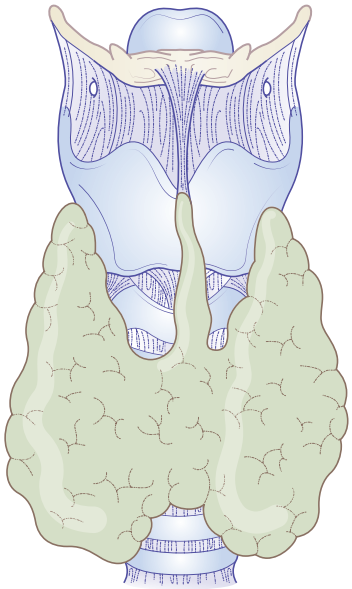


Figure 53.1 Relationship between thyroid gland, larynx and trachea. A pyramidal lobe +/– a fibrous or fibromuscular band is a common finding, particularly on the left side. It may arise from the isthmus or upper poles of the thyroid and extend a variable distance up to the body of the hyoid.

tracheal vessels, but at the upper part on each side it is much thicker and binds the gland firmly to the sides of the cricoid cartilage and first tracheal ring. This condensation is known as the lateral ligament of the thyroid or the 'suspensory ligament of Berry'. Its fixation to the trachea causes the thyroid gland to move up and down on swallowing. During thyroid surgery it must be divided with care and by sharp dissection as the recurrent laryngeal nerve may lie lateral, medial or within the ligament just before it enters the larynx.

Microscopic anatomy

The thyroid gland is made up of multiple lobules supplied by a lobular artery.[14] A thyroid lobule consists of 20 to 40 follicles which are spherical in shape and 0.02–0.9 mm in diameter.[15] Each follicle is an aggregate of follicular cells which are one cell thick surrounding a central pool of viscous colloid (**Figure 53.2**). When the gland is relatively inactive, the cells are flattened and the colloid is abundant, dense and homogenous in appearance. On prolonged and excessive thyroid-stimulating hormone (TSH) stimulation the follicular cells become hypertrophied and hyperplastic and they adopt a more columnar shape.

The follicular cells have the characteristic cytoplasmic features of an endocrine gland in that they have long segments of rough endoplasmic reticulum and a large Golgi apparatus for synthesizing and packaging protein and prominent electron-dense lysosomal bodies. The plasma membranes of the apical and basal layers have separate functions and are kept separate by tight junctions which bind adjacent cells together. This allows the cell to control the storage of the thyroid hormones in the colloid and their release into the circulation. When stimulated

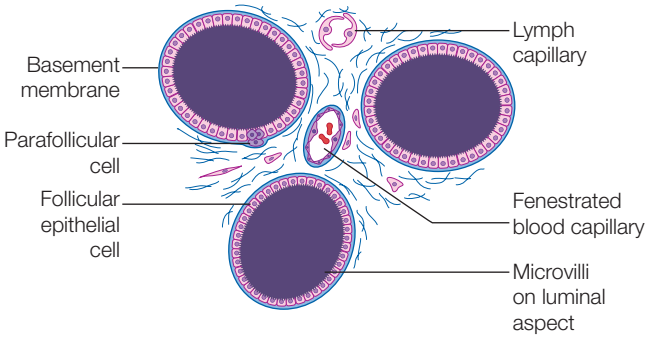


Figure 53.2 Angiofollicular unit and relationship between thyroid follicles and parafollicular cells.

by TSH, the intracellular organelles become more prominent and microvilli develop on their apical surfaces.[16] The microvilli enable the colloid to be absorbed by endocytosis. This is associated with the development of 'reabsorption lacunae' and a reduction in the size of the follicular lumen. The process is also associated with an overall increase in vascularity of the gland. The thyroid hormones released into the circulation ensure that the metabolic demands of the tissues of the body are met by stimulating oxygen consumption and regulating carbohydrate and lipid metabolism. They are also essential for embryonic development, normal growth and especially for brain maturation.

Each follicle is invested and interlaced with loose connective tissue (stroma) containing a close-meshed plexus of fenestrated capillaries forming morphological and functional angiofollicular units (AFUs).[17, 18] The inter-follicle connective tissue spaces are relatively large and contain a collagenous matrix, fibroblasts, unmyelinated nerve fibres with Schwann cells, and fat cells, plasma cells, macrophages, expanded lymphatics and lymphocytes.[14, 16, 19] The fibroblasts form a highly organized 'neuro-reticular network' by linking their long, thin, branching cytoplasmic processes. These processes are surrounded by autonomic nerve endings in a similar manner to that found in bone marrow and in the submandibular gland. The presence of CD34-positive antigen on the fibroblasts may mean they play an important role in immune surveillance.[19]

Scattered in the stroma are some embryologically distinct cells known as parafollicular cells or C cells (**Figure 53.2**). They are found either singly or in small clumps and are characterized by their polygonal or spindle shape, their relatively large size and their 'light' cytoplasm.[14, 20] They secrete calcitonin in response to elevated serum levels of calcium or gastrin. A total thyroidectomy does not always abolish calcitonin secretion as it can be produced by other organs such as the brain, gastrointestinal tract, urinary bladder, thymus and lungs.[21] Calcitonin lowers serum calcium and phosphate levels by inhibiting the osteoclastic resorption of bone and enhancing the excretion of calcium by the kidneys. Its physiological importance is debatable as parathyroid hormone and vitamin D are thought to be more important in calcium haemostasis.[22]

Developmental anatomy

The thyroid gland is the earliest endocrine organ to appear in mammalian development. It is formed from both the endodermal cells of the primitive pharynx, known as the median anlage, and from neural crest cells from the lateral anlagen or ultimobranchial bodies.[3, 23–25]

MEDIAN ANLAGE

The median anlage (**Figure 53.3**) develops from a midline thickening of the ventral surface of the endodermal epithelium of the primitive pharynx between the first and second branchial arches adjacent to the developing myocardium. A diverticulum forms from this thickening at about the sixteenth or seventeenth gestational day. This out-pouching expands laterally at its distal tip to form a rudimentary bilobed structure. It is pulled into position by the descent of the heart and reaches its final location, immediately anterior to the trachea, in the seventh gestational week. Initially the descending thyroid remains attached to the pharyngeal floor by a tubular stalk. During the seventh to tenth week the lumen of the stalk becomes filled with cords of thyroid progenitor cells but eventually fragments and disappears before birth. The residuum of the attachment of the stalk forms the foramen caecum in the midline at the junction of the posterior third and anterior two-thirds of the tongue.[25]

LATERAL ANLAGEN (ULTIMOBRANCHIAL BODIES)

The two lateral anlagen (**Figure 53.3**), also known as the ultimobranchial bodies, are thought to develop as evaginations of the fourth pharyngeal pouches.[25, 26] They become separated from them by attenuation and rupture from the common pharyngobranchial duct. The ultimobranchial bodies fuse with the median thyroid anlage by the sixth week of development, contributing approximately 10% of the mass of the thyroid gland.[25, 27] It is thought that rarely the ultimobranchial bodies can fail to fuse resulting in a true 'lateral thyroid lobe', although this has been disputed.[28] The ultimobranchial bodies also contribute the calcitonin-producing parafollicular cells (C cells). The exact origin of these cells in humans remains controversial although they are thought to migrate from the neural crest.[23–25]

HISTOGENESIS OF THE THYROID FOLLICLE

Histological differentiation of follicular cells can be seen to pass through three stages, defined by their production of colloid.[23]

1. The 'precolloid stage' (7–13 weeks) is from the first appearance of immature follicular cells to the beginning of differentiation into cells that are capable of producing colloid.
2. In the second stage (13–14 weeks) an intracellular structure known as the canaliculus begins to dilate. This structure is thought to be an extension of the smooth endoplasmic reticulum and is associated with the accumulation of increasingly electron-dense material. This material is then discharged into the extracellular space where it is retained by the intracellular connections to form a central colloid space.
3. In the third stage there is an increase in colloid production and storage with a consequent increase in size of the follicles. The follicular cells also show an increase in the number of lysosomes representing endocytosis of the colloid in preparation for storage and release of the thyroid hormones into the circulation.

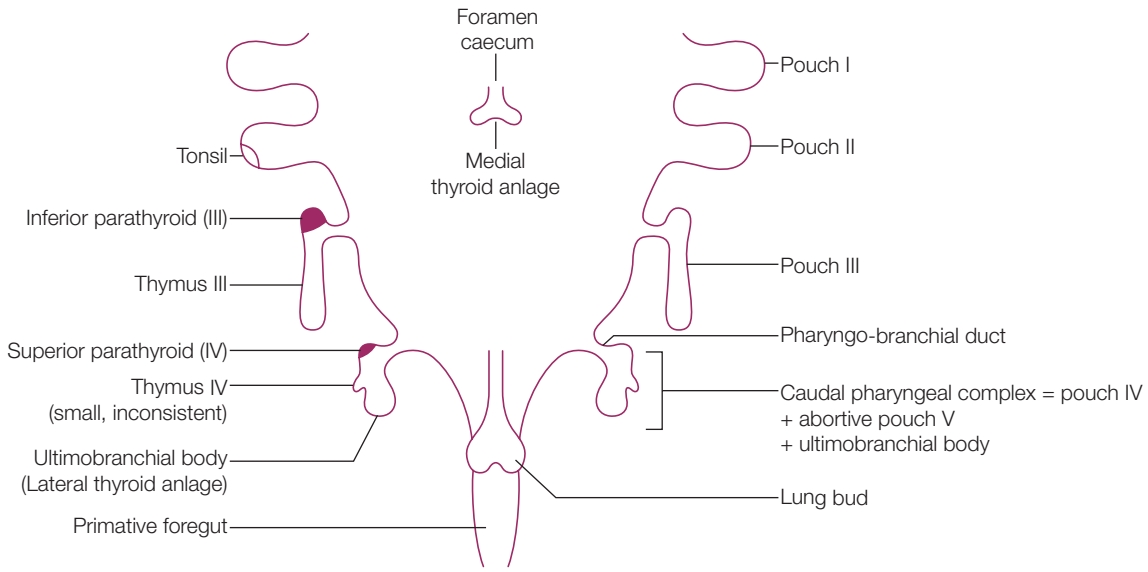


Figure 53.3 Schematic representation of the early development of the median and lateral analagen of the thyroid gland and the parathyroid glands.

TABLE 53.1 Timeline of development of thyroid gland in humans

Gestational age	Development
Embryonic day 10	Endodermal thickening seen
Embryonic day 16–17	Median and lateral anlagen discernible
Embryonic day 24	Median anlage has developed a thin, flask-like diverticulum, extending from the floor of the buccal cavity down to the fourth branchial arch
Embryonic day 30	Formation of bi-lobulated structure
Embryonic day 40	Median and lateral anlagen have fused Degeneration of thyroglossal duct into fibrous stalk
Embryonic day 50	Lateral expansion Descent of the heart and thyroid reaches its final location, immediately anterior to the trachea Precolloid phase starts
Embryonic day 60	Definite shape Follicle formation Onset of thyroglobulin expression
Gestational week 10	Colloid phase Thyroid hormone receptors detectable in brain Fibrous thyroglossal stalk disappears
Gestational week 11	Histogenesis of the thyroid is virtually complete Foetal thyroid is capable of trapping and oxidizing iodide Thyroglobulin present in foetal thyroid Thyroxine can be detected in foetal serum
Gestational week 16	Increasing TSH secretion the principal regulator of thyroid hormone biosynthesis and secretion Significant increase of thyroid hormone receptors in foetal brain
Gestational week 17.5	Structural maturity of thyroid gland
Gestational week 20	Increasing organification of iodide and foetal T4 secretion
Gestational week 24	T3 detectable
Birth	Gland weight 1.5 g

Thyroxine can be detected in foetal serum at 11 weeks.[29] Structural maturity of the foetal thyroid gland is achieved at 17.5 weeks (Table 53.1).[30]

Anatomical variations and pathological conditions resulting from developmental abnormalities of the thyroid gland

ASYMMETRIES AND COMMON NORMAL VARIANTS

Asymmetries of the gland are frequently found with the right side being larger than the left.[12] A third conical protrusion known as the **pyramidal lobe** is present in 12–81% of cases. The prevalence depends on the method of identification, i.e. autopsy, ultrasonography, CT, scintigraphy, intra-operative finding, the presence of pathology and possibly the population studied.[31–33] Most authors report the pyramidal lobe to originate more commonly on the left side, from either the medial aspect of the upper poles or the isthmus (40–60%),[34] but it can also arise from the midline of the isthmus or the right lateral lobe. Reported as being between 3 mm and 63 mm in length,[34] it can extend superiorly as a short stump or a long process that can reach the upper border of the thyroid cartilage or even the hyoid bone[32, 34, 35] (Figure 53.1). Its high prevalence indicates that this is a normal variant and represents the persistence of the distal part of the embryonic thyroid and thyroglossal duct.[34, 36] Its apex may be replaced by fibrous or fibromuscular tissue when it is then known as the 'levator of the thyroid gland'.[36]

KEY POINT

The prevalence of the pyramidal lobe is high enough to warrant exploration in every case of thyroid surgery. If a pyramidal lobe is present on the side of surgery, it should be removed with the main lobe to avoid leaving behind functioning thyroid tissue.[34]

The **tubercle of Zuckerkandl** is a lateral or posterior projection of the thyroid lobe which can be identified in up to 60% of surgical dissections.[14, 37, 38] It is thought to represent the point of embryological fusion of the ultimobranchial body and median anlage.

KEY POINT

The surgical importance of the tubercle of Zuckerkandl is threefold:

- the recurrent laryngeal nerve most often runs medial to it
- the superior parathyroid gland is usually attached to its cranial aspect
- when enlarged as part of the goitre, a significant portion of thyroid tissue may be inadvertently left behind if subtotal thyroidectomy is performed.

ABNORMAL DESCENT AND DEVELOPMENT OF THE THYROID GLAND

Rarely the migration of the thyroid may become arrested anywhere along the descent pathway from the foramen caecum to low in the neck.[39] The most common abnormality is a lingual thyroid. Ectopic thyroid tissue may also be found in the sublingual, high cervical and mediastinal regions or within the cardiac endothelium.[39] Hemiagenesis with absence of a lobe or lobe and isthmus can be rarely encountered.[40, 41] The left lobe is more commonly absent (5 : 1) than the right.[41]

More commonly the descending thyroid stalk can persist anywhere between the foramen caecum and thyroid isthmus. Subsequent infection of adjacent lymphoid tissue to the tract is thought to stimulate the epithelial remnants so that they undergo cystic change.[42] Typically thyroglossal duct cysts are midline with 25% being paramedian; 60–80% are found below the hyoid bone.[28, 43–45] The tract is in close proximity to the hyoid bone, lying within the periosteum or even passing through the bony substance. During development, the point of origin of the embryonic thyroid is situated anteriorly to the second branchial arch so the thyroglossal tract ends up running ventrally to the developing hyoid bone. As the hyoid matures it rotates to assume its adult position. During this rotation the thyroglossal tract is drawn posteriorly and cranially around the inferior edge of the bone. It then continues descending downward and anteriorly to thyroid membrane.[42] A persisting thyroglossal tract may become entrapped in the midline mesenchymal condensation that is now thought to form the body of the hyoid bone in the midline.[46, 47]

Lateral aberrant thyroid rests

Normally the ultimobranchial bodies fuse with the expanding lateral lobes of the median thyroid and differentiate into thyroid tissue, which is usually indistinguishable from the rest of the thyroid gland. Aberrant follicular thyroid tissue or gland has been identified lateral to the main body of the thyroid gland and situated lateral to the internal jugular vein and not associated with any lymphoid tissue. The majority of these deposits or nodules are likely to represent metastatic follicular or follicular variant papillary thyroid carcinoma and perhaps should be managed as such.[48] On rare occasions a few follicles of normal thyroid tissue can also be found within the capsule of cervical lymph nodes situated in the central compartment of the neck. Again, the majority are likely to represent metastatic deposits but on rare occasions with no evidence of a carcinoma in the thyroid gland on painstaking histological examination they have to be attributed to ectopic tissue.[48]

Solid cell nests

These are irregularly shaped clusters of inter-follicular cells delineated by basal lamina within the thyroid gland. The dominant cell component comprises polygonal to fusiform cells with an epidermoid appearance.[49] Less commonly they show glandular morphology and may be microcystic, micropapillary and/or mucinous.[49] They may be found in approximately 25% of resected thyroid glands and are thought to represent remnants of the ultimobranchial apparatus.[9, 31, 50] They are more prevalent in the thyroid of infants and children and gradually decline with advancing age. Their biological significance remains controversial but there is some evidence that they harbour stem cells with capacity for self-renewal and end differentiation. They can be a source of confusion in thyroid pathology as they can mimic a number of pathological conditions.[51]

Medullary carcinoma

Normally the calcitonin-producing parafollicular cells (C cells) migrate to become distributed throughout the thyroid gland. However, they often remain more numerous near the point of fusion between the two anlagen.[52, 53] There is therefore a tendency for medullary carcinomas to develop in the central portions of the middle and upper thirds of the thyroid lobes.[53]

Struma ovarii (thyroid tissue within the ovary)

This is not a developmental anomaly of the thyroid but a germ-cell tumour, i.e. a monodermal teratoma. It accounts for approximately 5% of ovarian teratomas and the teratoma must comprise more than 50% of thyroid tissue to be classed as Struma ovarii. The thyroid tissue in this condition rarely functions but there have been rare instances of thyrotoxicosis (5–8%)[54] and malignancy with peritoneal and distant metastases.[55–57]

PARATHYROID GLANDS

Macroscopic and microscopic anatomy

The parathyroid glands are generally found in close proximity to the posterior surface of the thyroid gland. They are small, yellowish-brown, oval or bean-shaped and their colour often darkens with age. In most cases (84%) there are four parathyroid glands.[58] The size of each gland can vary but on average they are 6 mm in craniocaudal dimension and 3–4 mm in transverse diameter. They are usually paired and named superior and inferior glands. Around 85% of superior glands are within a 2 cm diameter of a point 1 cm above the crossing of the inferior thyroid artery and recurrent laryngeal nerve.[58–60] The inferior glands are frequently situated below the artery level or within 1 cm of the lower pole of the thyroid gland.

The parathyroid glands are enveloped by a thin fibrous capsule which extends into the parenchyma partitioning the gland into lobules. The parenchymal cells are arranged in clusters or cords nourished by a rich capillary network. Within the fibrovascular stroma there are other cells including adipocytes, macrophages and mast cells. They are likely to be involved in parathyroid hormone (PTH) secretion, signalling functions and as a detoxification storage site for lipophilic agents such as Vitamin A. The amount of stromal fibroadipose tissue increases with age, eventually comprising 50% of the gland substance in the elderly.[61]

The dominant cell type within the parathyroid glands are known as chief cells or principal cells. They produce PTH and together with calcitonin and an active metabolite of vitamin D, 1.25-dihydroxyvitamin D3, play an essential role in calcium homeostasis. Tight regulation of serum calcium levels is essential for neural transmission, muscle contraction and relaxation, exocrine secretion, blood clotting and cellular adhesion. Chief cells undergo morphological changes corresponding to different stages of the secretory cycle. They range from being cuboidal in shape in the inactive phase to oval or polygonal in the active phase.[4] They are characterized by their rather scant, slightly eosinophilic cytoplasm. This is in contrast to the other main cell type, the oxyphil cells. Oxyphil cells are much less prevalent and are found singly or in small clusters. They can be identified by their larger size, eosinophilic cytoplasm due to their high mitochondrial content, prominent nucleoli and randomly enlarged nuclei.[2] Oxyphil cells are thought to be derived from chief cells and their numbers increase with age or after excessive functional stress (e.g. long-term stimulation of the parathyroid glands or chronic kidney disease).[4] Their function is not fully understood but they have the potential to produce PTH, PTH-related protein (PTHrP) and calcitriol. They may also have autocrine and paracrine functions.[62] A further cell type known as parathyroid water-clear cells can occasionally be found in normal parathyroid glands. They are much more prevalent in hyperfunctional parathyroid states associated with hyperplasia and parathyroid adenomas.[63]

Developmental anatomy

In humans the parathyroid primordia first appear at about 32 days of embryonic development.[59] Each superior parathyroid gland is derived from the endoderm of the dorsal part of the fourth pharyngeal pouch together with the ultimobranchial body.[4] It is commonly referred to as Parathyroid IV (PIV) in the embryological literature to indicate its site of origin. Each inferior parathyroid gland (Parathyroid III (PIII)) develops from endodermal cells from a common parathyroid/thymus primordium found in the third pharyngeal pouch (**Figure 53.3**). The dorsal/anterior part of the common primordium contributes the parathyroid component while the ventral/distal part contributes to the thymus component. PIII migrates with the thymus and PIV migrates together with the ultimobranchial bodies respectively at about 44 days (**Figure 53.4**).

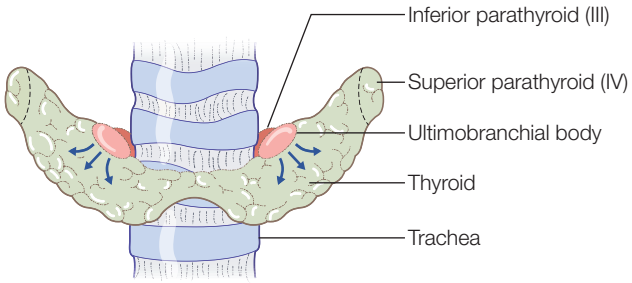


Figure 53.4 Schematic representation during development of relative positioning of the parathyroids and ultimobranchial body during fusion.

Later in development the inferior glands separate from the thymus and come to lie caudal to the superior parathyroids.

Anatomical variations and pathological conditions resulting from developmental abnormalities of the parathyroid glands

GLAND NUMBERS, SIZE AND POSITION

Although four parathyroid glands is the commonest number present, the number can range from two to six with some authors reporting as many as twelve glands.[64] Each gland weighs 30–40 mg, giving a combined weight of the glands in adults of 120 ± 3.5 mg in men and 142 ± 5.2 mg in women.[65] If a single gland's weight is greater than 60 mg, it is considered pathological.

As the thymus has a longer course of descent into the superior mediastinum, the accompanying inferior parathyroids have a more variable location, and a higher chance of ectopic location. They are responsible for supernumerary glands most commonly found in the cervical thymus (39%) or within the mediastinal thymus itself (6%).[60] Normal superior parathyroids can occasionally be found in the posterior neck, retropharyngeal–oesophageal space, carotid sheath and posterior mediastinum (1–4%). Parathyroid adenomas are found in posterior locations in 40% of cases. Most 'intrathyroidal' parathyroids reported on histological resections are located within indentations of the thyroid gland surrounded by perithyroidal fat.[2] Intravagal parathyroid tissue has been documented in 6% of cases in autopsy reports.[66]

KEY POINTS

- In most cases (84%) there are four parathyroid glands but the number can vary between two and six.
- 85% of superior parathyroid glands are within a 2 cm diameter of a point 1 cm above the crossing of the inferior thyroid artery and recurrent laryngeal nerve.
- The inferior glands have a more variable position but are frequently situated below the artery, level or within 1 cm of the lower pole of the thyroid gland.
- Ectopic or supernumerary glands can be found in the thymus gland, posterior neck, retropharyngeal – oesophageal space, carotid sheath and posterior mediastinum.

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CHAPTER 54

DEVELOPMENTAL ANATOMY OF THE PITUITARY FOSSA

John Hill and Sean Carrie

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SEARCH STRATEGY AND EVIDENCE BASE

This chapter was prepared from anatomy and physiology texts and supported by a Medline search using the keywords anatomy, endoscopic, pituitary and cavernous sinus. The anatomical studies quoted constitute level 3 evidence.

EMBRYOLOGY

The adenohypophysis is derived from the placodal ectoderm of the stomodeum roof. The neurohypophysis is derived from an evagination of the floor of the forebrain and the third ventricle.

There is a saccular depression in the roof of the stomodeum immediately in front of the oropharyngeal membrane. This saccular depression evaginates to form the pouch of Rathke. This area remains in close contact with the ventral surface of the forebrain. The pouch of Rathke develops into the adenohypophysis. The anterior part becomes the pars anterior and the posterior part, in contact with the forebrain, becomes the pars intermedia. The section of the forebrain in close contact with the pars intermedia becomes the neurohypophysis (Figure 54.1). In foetal life and childhood the vestige of Rathke's pouch remains as the hypophyseal cleft separating the pars anterior and pars intermedia. The pars intermedia is rudimentary in humans and is of little functional significance. Remnants of Rathke's pouch may persist below the sphenoid in the roof of the nasopharynx forming a pharyngeal pituitary. The clivus and the dorsum sellae of the future sphenoid bone are formed from mesenchymal condensations surrounding the hypophysis.[1] The cavernous sinus is derived from the primary head vein (Figure 54.1).

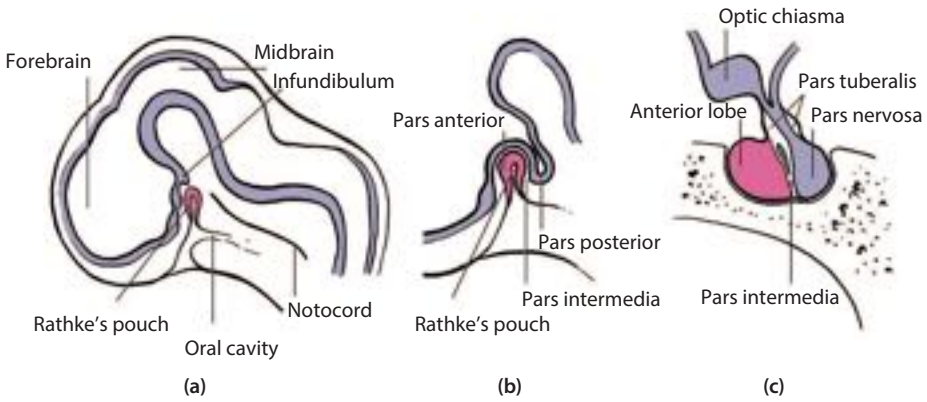


Figure 54.1 Embryological development of the hypophysis.

ENDOSCOPIC ANATOMY OF THE SPHENOID AND ANTERIOR SELLA WALL

The anatomical considerations for the endoscopic pituitary surgeon are:

- the degree of pneumatization of the sphenoid and the localization of the anterior sella wall
- the position of the intra-sphenoid sinus septae
- the positioning of the carotid arteries and optic nerves in the posterior sphenoid wall.

The degree of pneumatization of the sphenoid was originally described by Hammer and Radberg in 1961.[2] They divided the sphenoid sinus into three types: sellar, presellar and conchal. In the sellar type the sphenoid is well pneumatized and the floor of the pituitary fossa (sella) performs an easily identifiable bulge in the posterosuperior aspect of the sphenoid sinus. In most series this arrangement is found in approximately 80% of sinuses. The posterior wall of the sphenoid sinus is in the same plane as the midpoint of the pituitary fossa or more posteriorly placed. In a small subgroup the pneumatization can be described as 'post-sella' whereby the entire sella floor protrudes down from the roof of the sphenoid sinus. In 'pre-sella' pneumatization (approximately 20%), the posterior wall of the sphenoid sinus is in the same plane as the anterior wall of the sella. In these cases it may be difficult to delineate the anterior bulge of the anterior sphenoid wall and intra-operative radiology or navigation systems may be needed to help the endoscopic surgeons. In 2% of cases there is no pneumatization of the sphenoid. This arrangement is much more common in Asian populations where it may occur in up to 28% of cases.[3]

Intra-sphenoid sinus septae

The arrangement of the septae is highly variable. The standard textbook depiction of a single septum running in the midline from the rostrum of the sphenoid back to the anterior pituitary fossa wall is found in only 14% of individuals. Almost any arrangement of septae can be encountered by the surgeon. The commoner arrangements are of a single septum (48%) or two septae (48%) rather than multiple septations. The septae may be incomplete or complete whereby they extend from the anterior to the posterior wall of the septum. Anteriorly, a complete septum is usually inserted in the midline, but its posterior attachment is variable. Midline posterior attachment occurs in only 14% of individuals and more commonly the arrangement is that the posterior attachment is laterally placed close to the paraclival carotid eminence. In 87% of cases at least one septum will be inserted posteriorly close to the carotid.[4] Care is therefore needed when drilling down these septae to gain surgical access (Figure 54.2).

Transverse septations as well as vertical septations are also encountered. Where there are horizontal sphenoid septae, this is due to posterior ethmoids pneumatizing over the top of sphenoid sinuses. This can be surgically relevant: if they are not opened, the surgeon may not be able to visualize and reach all of the anterior wall of the pituitary fossa.

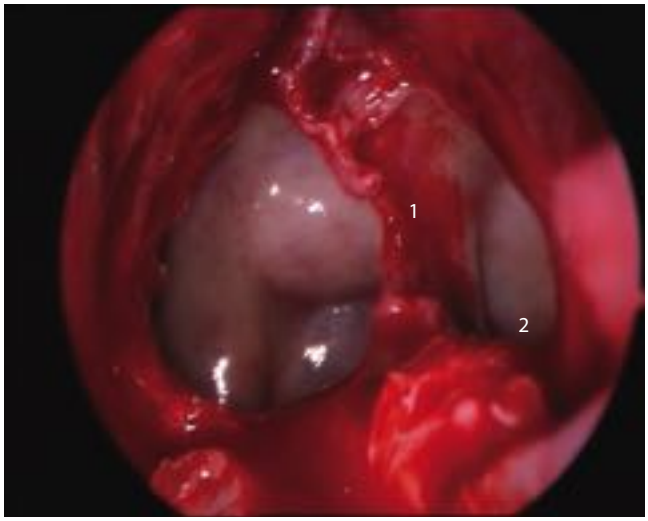


Figure 54.2 Endoscopic view of sphenoid. Single intra-sphenoid septum (1) inserting into the left carotid artery eminence (2).

Carotid arteries and optic nerves

In a well-pneumatized sphenoid the pituitary fossa will form a bulge in the midline in the posterosuperior aspect of the sinus. Figure 54.3 shows that inferolateral to the fossa is the paraclival carotid (a). Lateral to the fossa is the bulge formed by the carotid as it curves anteriorly then posteriorly as it ascends in the cavernous sinus (b). Superolateral to the fossa is the position of the optic nerve (c), although this is visible in only a small proportion of the sphenoid sinuses. The small fossa bounded by the

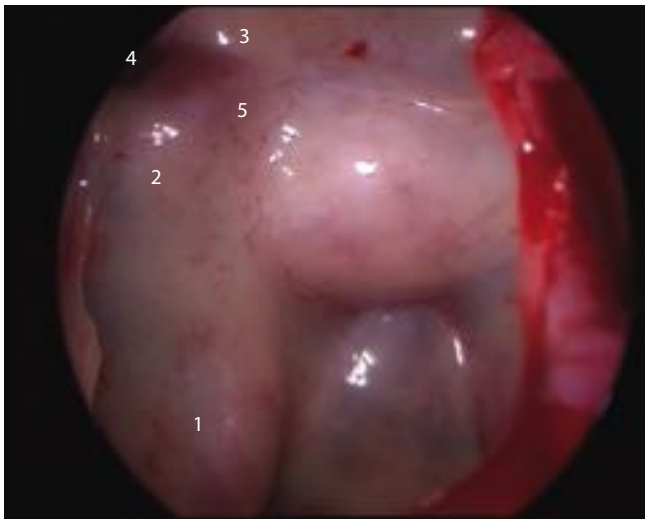


Figure 54.3 Endoscopic view of posterior wall of sphenoid. Indentations caused by the internal carotid artery (1,2) and optic nerve (3), lateral opticocarotid recess (4) and medial opticocarotid recess (5).

optic nerve superomedially and the carotid artery inferomedially is termed the lateral opticocarotid recess (LOCR) and it corresponds to the anterior clinoid process intracranially. The triangular depression bounded by the optic nerve superolaterally, the carotid inferomedially and the the pituitary fossa medially is termed the medial opticocarotid recess (MOCR) and that corresponds to the medial cliniod intra-cranially.

The bony covering over the sella is thin, usually less than 0.5 mm. In cases where an adenoma is present, the bony covering may be absent. The carotico-optic recess is triangular in shape and is limited by the optic nerve superiorly, the carotid artery inferomedially and the oculomotor nerve laterally. The carotid protuberance or C shape of the carotid artery is immediately lateral to the pituitary fossa and is formed by the serpentine carotid artery as it bends forwards in the cavernous sinus before curving backwards as it ascends before entering the anterior cranial fossa medial to the anterior clinoid process.

The optic nerves and the carvernous sinuses are usually covered by bone, although a dehiscence over the carotid artery is present in up to 5% of cases.[5]

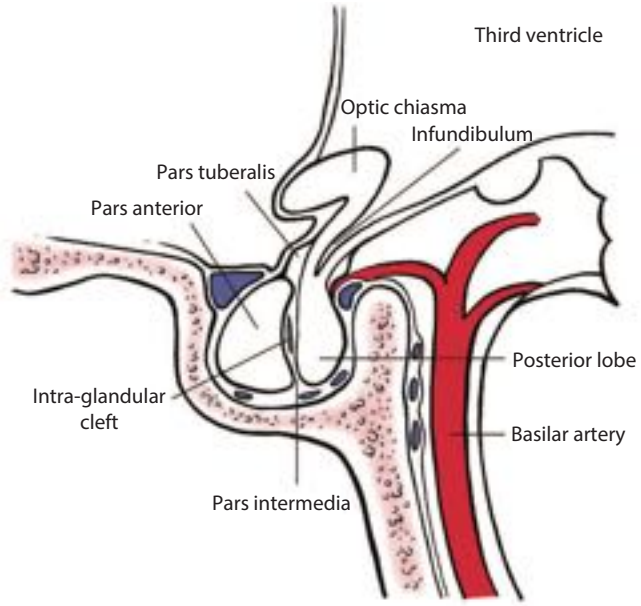


Figure 54.4 Lateral view of the hypophysis in the sella turcica. The intercavernous venous sinuses are indicated in blue.

PITUITARY GLAND ANATOMY

The pituitary gland or hypophysis cerebri is an ovoid body measuring approximately 8 mm in the anteroposterior diameter by 12 mm transversely by 4 mm high. By the age of puberty it weighs approximately 100–500 mg. It doubles in size during pregnancy and usually remains larger in females. The adenohypophysis constitutes two-thirds of the volume.

There are two major parts to the hypophysis:[6]

- **adenohypophysis:** includes the pars anterior, pars intermedia and pars tuberalis
- **neurohypophysis:** includes the pars posterior, infundibular stem and median eminence.

Both these parts include parts of the infundibulum and are preferred to the old terms anterior and posterior lobes (**Figure 54.4**).

Adenohypophysis

This structure is highly vascular and consists of epithelial cells arranged in follicles and cords between which lie thin-walled, vascular sinuses. This arrangement is supported by a delicate skeleton of reticular tissue.

Traditionally, cell types of the adenohypophysis have been divided up by their staining characteristics into chromophil (acidophilic, basophilic) and chromophobe cells. Modern immunohistochemical techniques allow us to identify cells by the hormones that they produce, as follows.

- **Somatotrophs:** (acidophilic), the largest and most abundant chromaphil cells, these secrete the protein somatotrophin or growth hormone (GH).
- **Mammotrophs:** (acidophilic), secrete the polypeptide hormone prolactin (PRL). They become the dominant cell during pregnancy and lactation.
- **Mammosomatotrophs:** (acidophilic) secrete growth hormone and prolactin simultaneously.
- **Corticotrophs:** (basophilic), produce the precursor molecule pro-opiomelanocorticotropin (POMC), which is broken down into adrenocorticotropin (ACTH), beta-lipotropin and beta-endorphin.
- **Thyrotrophs:** (basophilic), secrete thyroid-stimulating hormone (TSH).
- **Gonadotrophs:** (basophilic) secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH).
- **Chromophobe cells:** these small cells constitute the majority of the cells in the adenohypophysis. They include stem cells and degranulated secretory cells.
- **Folliculostellate (FS) cells:** these are the supporting cells of the adenohypophysis, with growth factor and cytokine activity. Their expression of cytokeratins supports the theory that the adenohypophysis is derived from Rathke's pouch.[7]
- **Pars tuberalis:** this contains large number of blood vessels as well as the secreting cells listed above. In some species this area is rich in receptors for the pineal hormone melatonin.

Neurohypophysis

Axons with their cell bodies in the supraoptic and paraventricular nuclei of the hypothalamus run to the neurohypophysis. Some terminate in the median eminence from where they can influence the action of the adenohypophysis (see below); others run down through the stalk of the hypophysis to the main mass of the neurohypophysis where they terminate close to the sinusoids. The latter transport polypeptide hormones in conjunction

with a glycoprotein (neurophysin) to the neurohypophysis where they are stored prior to release. The two hormones secreted in this way are:

- anti-diuretic hormone (ADH) or vasopressin
- oxytocin.

Blood supply of the hypophysis

The arterial supply of the hypophysis is from single inferior hypophyseal arteries and several superior hypophyseal arteries on each side, all of which are branches of the internal carotid. The superior hypophyseal arteries supply the median eminence and the infundibulum. The inferior hypophyseal arteries anastamose to form an arterial ring around the infundibulum, which gives fine branches supplying the capillary bed of the neurohypophysis. The adenohypophysis does not have a direct arterial supply but is supplied by long and short portal vessels, which run from the median eminence and the lower infundibulum respectively to the capillary bed of the adenohypophysis (Figure 54.5).

The hormones of the adenohypophysis are secreted by exocytosis into the nearby sinusoids. The major signal for this secretion involves the release of specific releasing factors from neurones in the median eminence, which are then transported to the adenohypophysis by the portal system.[8]

The venous drainage of the hypophysis is less clear but has important implications in understanding the control of pituitary hormone secretion. Possible drainage is via:

- long and short portal vessels to the infundibulum
- large inferior hypophyseal veins into the dural venous sinuses
- the median eminence to the hypothalamus
- reversible flow between the adenohypophysis and neurohypophysis.

Pituitary gland capsule

The gland has a capsule made up of soft fibrous tissue that is in continuity with the fibrous connective tissue of the gland. The gland appears to be loosely attached to the surrounding connective tissue, which forms a smooth nest for the hypophysis. Bridging veins, capsular arteries and fibrous bundles cross this space.[9]

SELLA TURCICA

The sella turcica or Turkish saddle is the deep depression in the body of the sphenoid bone. It contains the hypophysis cerebri, dural layers and the intercavernous sinuses. The hypophysis fills 50–85% of the fossa.

The bony landmarks around the fossa are as follows (Figure 54.6):

- The **optic canal** lies between the roots of the lesser wing and the body of the sphenoid medially. It descends slightly anterolaterally, and it contains the optic nerve, ophthalmic artery and meninges.
- The **anterior clinoid process** is the posterior projection from the lesser wing of the sphenoid.
- The **tuberculum sellae** is a midline ridge in the anterior slope of the sella turcica.
- The **dorsum sellae** is the posterior wall of the sella turcica. The superolateral projections of the dorsum form the posterior clinoid processes.
- The **groove** for the internal carotid artery is formed as the artery turns anteriorly from the foramen lacerum. The groove can be seen on the sphenoid lateral to the sella turcica.
- The **middle clinoid process** is a small elevation in the median edge of the groove. In approximately 10% of skulls the middle and anterior clinoid processes are joined to form a continuous ring called the carotico-clinoid foramen.[10]

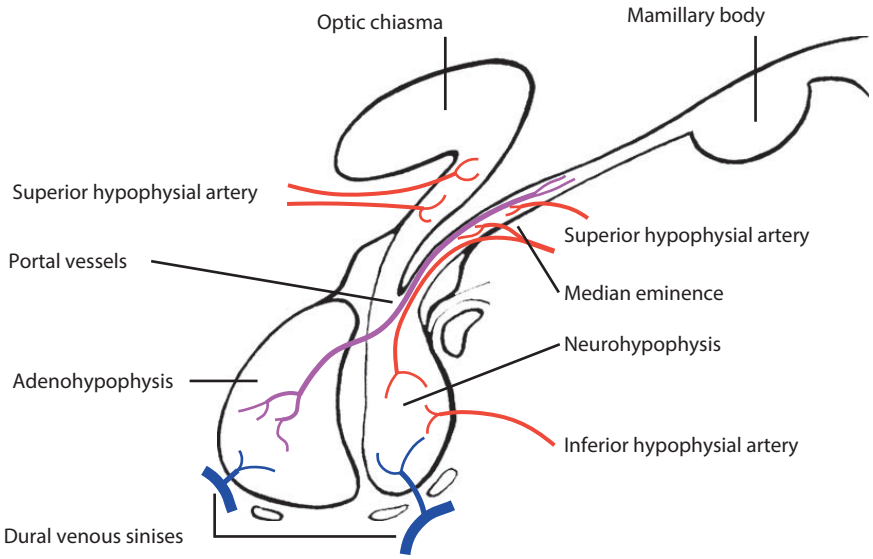


Figure 54.5 Vasculature of the hypophysis.

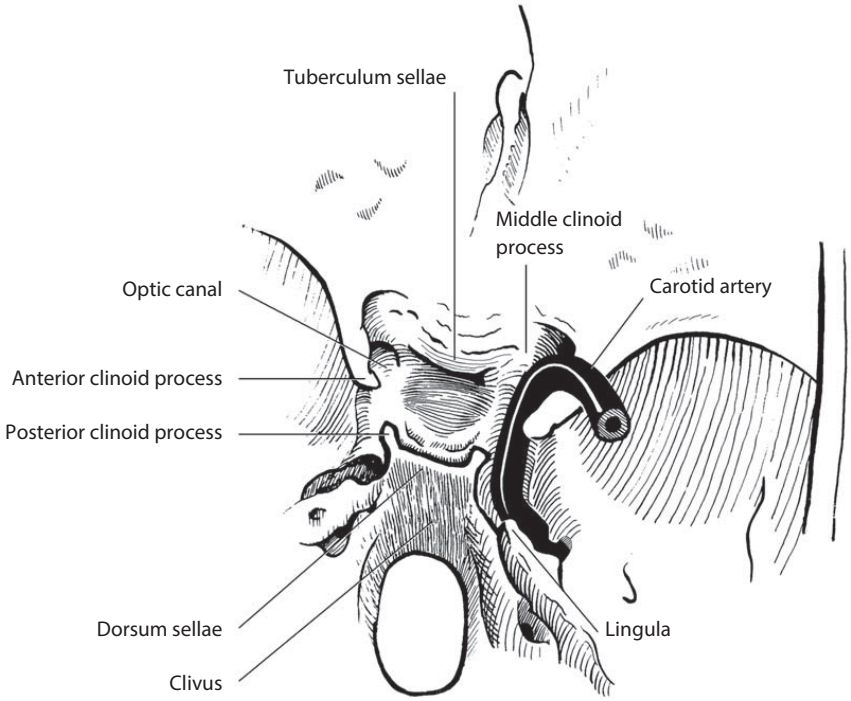


Figure 54.6 Posterosuperior view of the sella turcica of a skull. The position of the right internal carotid is demonstrated.

- The **lingula** is a small projection arising on the posterolateral aspect of the carotid groove.
- The **clivus** is made up of the body of the sphenoid bone behind the dorsum sellae and the basioccipital bone. The upper part of the pons lies adjacent to the clivus.

In approximately 2% of skulls there is a bony bridge joining the anterior clinoid and posterior clinoid processes called the tinea interclinoidea. In approximately 1% of skulls there is a bony projection in the floor of the sella called the sella spine. It is a bony spicule that projects from the junction of the anterior and inferior walls of the sella towards the middle of the hypophyseal fossa and it is usually 1 mm in diameter and 2–5 mm in length. It probably represents an ossified remnant of the notochord.[11]

Dural reflections

The diaphragmatica sella is a sheet of dura mater that forms the roof of the sella turcica. This small, flat, horizontal circular sheet covers over the fossa between the clinoid processes and is continuous with the roof of the cavernous sinus. There is a central defect in the diaphragm called the foramen diaphragmatis to allow through the pituitary stalk or infundibulum. It is of variable diameter up to 5 mm.[12] In the region of the foramen of the dura, arachnoid and pia mater fuse with each other and with the capsule of the pituitary gland to form one fibrous layer that lines the hypophyseal fossa. In the fossa it is not possible to differentiate the fibrous layers and there are no subdural or subarachnoid spaces. Therefore there is no cerebrospinal fluid (CSF) in the normal pituitary fossa. The diaphragmatica sella separates the contents of the pituitary fossa from the CSF in the region of the foramen. The barrier may be very thin and consist of only arachnoid mater.[13]

The tentorium cerebelli is the main dural sheet that loops around the brain stem and separates the cerebral hemispheres from the cerebellum, forming the floor of the middle cranial fossa. It arises from the anterior clinoid processes and has a U-shaped free border looping posteriorly. The peripheral attachments of the tentorium run from the anterior clinoid process backwards as a ridge of dura mater to the apex of the petrous temple bone. This ridge is at the junction of the roof and the lateral part of the cavernous sinus. From here the attachment runs backwards to the posterior clinoid process, forming the roof of the cavernous sinus, and is continuous with the diaphragmatica sella. The remainder of the peripheral attachment of the tentorium is to the superior surface of the petrous temporal bone in the region of the superior petrosal sinus and to the occipital bone in the region of the transverse sinuses.

Intercavernous venous sinuses

The two cavernous sinuses are connected across the floor of the pituitary fossa by the intercavernous venous sinuses. Some texts indicate that there is a single anterior and single posterior vein in the floor of the fossa, hence the old term ‘inferior circular sinus of Winslow’. Cast studies have shown, however, that the arrangement is much more variable, with multiple interconnections across the floor possible. The superior and inferior connections may be found behind the anterior wall of the fossa and the connections may widen out laterally as they enter the cavernous sinuses (**Figure 54.4**).[14]

Relations of the pituitary fossa

Superior:

- The diaphragmatica sella
- The pituitary stalk and infundibulum
- The optic chiasm anterior to the infundibulum; 5–10 mm above the diaphragm
- Anterior cerebral artery and anterior communicating artery anterior to the optic chiasm
- Internal carotid artery/middle cerebral artery lateral to the infundibulum
- CSF surrounds the above structures above the diaphragmatica sella
- The third ventricle lies above the infundibulum

Posterior:

- Lamellar bone of the dorsum sella
- Dura mater of the poster fossa, behind the lamellar bone
- Basilar artery, behind the dura mater
- CSF

Lateral:

- Upper part of the cavernous sinus containing:
  - horizontal portion of the internal carotid artery
  - oculomotor, trochlear and abducens nerves

Anterior and inferior:

- Sphenoid sinus
- Intra-sphenoid sinus septum

ENDOSCOPIC ANATOMY OF THE PITUITARY FOSSA

There is a thin layer of bone (<0.5 mm) over the anterior surface of the pituitary fossa. In pathological cases where a macro-adenoma is present the bone may be dehiscent or thinned.

In a cadaver study, the average dimensions of the anterior sella wall were measured.[15] The distance between the medial margins of the optic nerves at the level of the carotico-optic recess was found to be 12 mm; the width of the pituitary fossa between the carotid prominences was 21 mm; and the height of the anterior sella wall was 8 mm. Inside the pituitary fossa the height of the pituitary gland was 7 mm and the average separation of the superior aspect of the gland from the optic chiasm was 5 mm. There is, however, great variation in the normal anatomy of this region and the inter-carotid distance can be much narrower (**Figure 54.7**). The pathological processes will also distort the anatomy and macroadenomas can result in the intra-carotid distance being increased to up to 3 cm.[16]

During the endoscopic surgical approach to the fossa the first layer encountered will be the bony covering of the anterior sella wall, followed by a layer of dura lining the fossa. This is a single layer of dura except where it splits to accommodate the intercavernous sphenoid sinuses (see above). Inside the dural layer is the substance of the gland itself. *In vivo* normal healthy pituitary gland tissue is slightly yellowish in appearance. There is a clear plane of dissection between the substance of the gland and its soft fibrous capsules. If the pituitary gland is removed *in vivo*, it is possible to see the diaphragm bulging down from above. The diaphragm is an easily identifiable sheet of fibrous tissue. Laterally the soft fibrous tissue of the medial wall of the cavernous sinuses is visible.

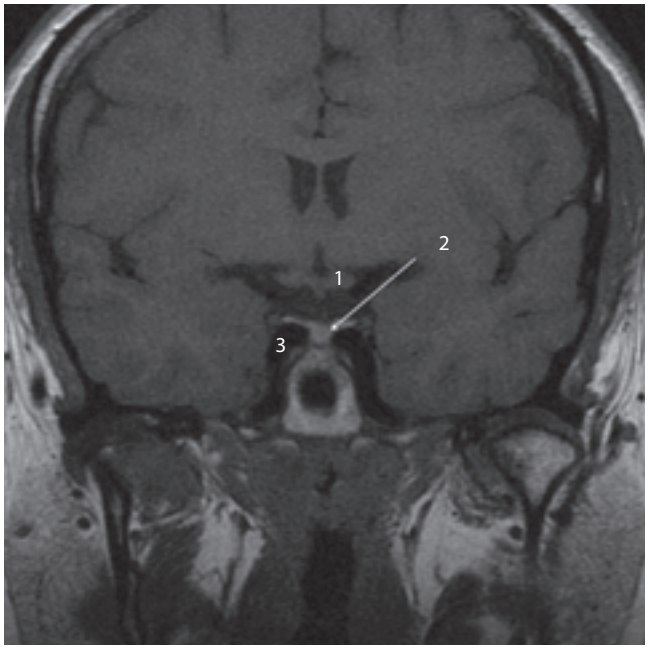


Figure 54.7 Coronal MR scan. The optic chiasm (1) and the pituitary gland (2) between medially placed carotid arteries (3).

CAVERNOUS SINUSES

These sinuses lie on the lateral aspect of the sphenoid body and are the lateral relations of the sella turcica. The term 'cavernous' was adopted when it was thought that these sinuses were a single cavern with a few trabeculae. Work using corrosion casts has established that these sinuses are plexiform in nature, i.e. they are made up of an intertwined network of thin-walled venous channels of varying sizes that divide and coalesce and incompletely surround the carotid arteries.[17]

The sinuses are approximately 1 cm wide and 2 cm long and are wider at the roof than at the base. They extend forwards from the apex of the petrous temporal bone to the superior orbital fissure. The carotid arteries have a variable course inside the sinuses. They enter posteroinferiorly, having passed through the carotid canal, and then turn anteriorly, passing horizontally through the sinus before turning superiorly to enter the anterior cranial fossa medial to the anterior clinoid processes. The horizontal portion of the artery is usually the lateral relation of the hypophysis. There is significant individual variation and the artery may be up to 7 mm away from the gland with the intervening space filled with venous plexus or it may be

as close as 1 mm with little intervening venous tissue. The lateral wall of the cavernous sinus is a thick sheet of dura mater; the medial wall is much thinner. There is no thick dural sheet and the capsule of the pituitary is the only barrier to spread of adenoma from the pituitary fossa.

The oculomotor nerve, trochlear nerve and ophthalmic division of the trigeminal nerve are closely related to, but not in, the lateral wall of the sinus as they pass anteriorly towards the superior orbital fissure.[18] The abducens nerve runs inferolaterally to the carotid artery in its horizontal portion. The sympathetic plexus runs with the carotid artery.

The sinus receives tributaries from the superficial middle cerebral vein, inferior cerebral vein, sphenoparietal sinus, inferior ophthalmic vein and sometimes the central retinal vein and frontal tributaries of the middle meningeal vein. The sinus then drains into the internal jugular vein via the inferior petrosal sinus, to the transverse sinus via the superior petrosal sinus, and small emissary veins drain through the foreman lacerum and foramen ovale to the pterygoid plexus.

ENDOSCOPIC ANATOMY OF CAVERNOUS SINUSES

If the bone of the posterior sphenoid sinus is taken down laterally to the anterior sella wall, the anterior aspect of the cavernous sinus is exposed. The prominent anatomical feature is the bulge of the C-shaped curve of the intra-cavernous portion of the internal carotid artery (**Figure 54.8a**). The nerves in the cavernous sinus are all placed laterally to the carotid artery and the carotid artery needs to be displaced medially in order to identify these (**Figure 54.8b**). Along the lateral wall of the cavernous sinus the oculomotor, trochlear and abducens nerves may be seen. In addition, the ophthalmic and occasionally the maxillary divisions of the trigeminal nerves may be visible. The oculomotor nerve is large and easily recognizable. It is located superiorly closest to the optic nerve, the trochlear nerve is smaller and is found just below the oculomotor nerve, and the abducens nerve is located more medially and inferior to the carotid artery.[19]

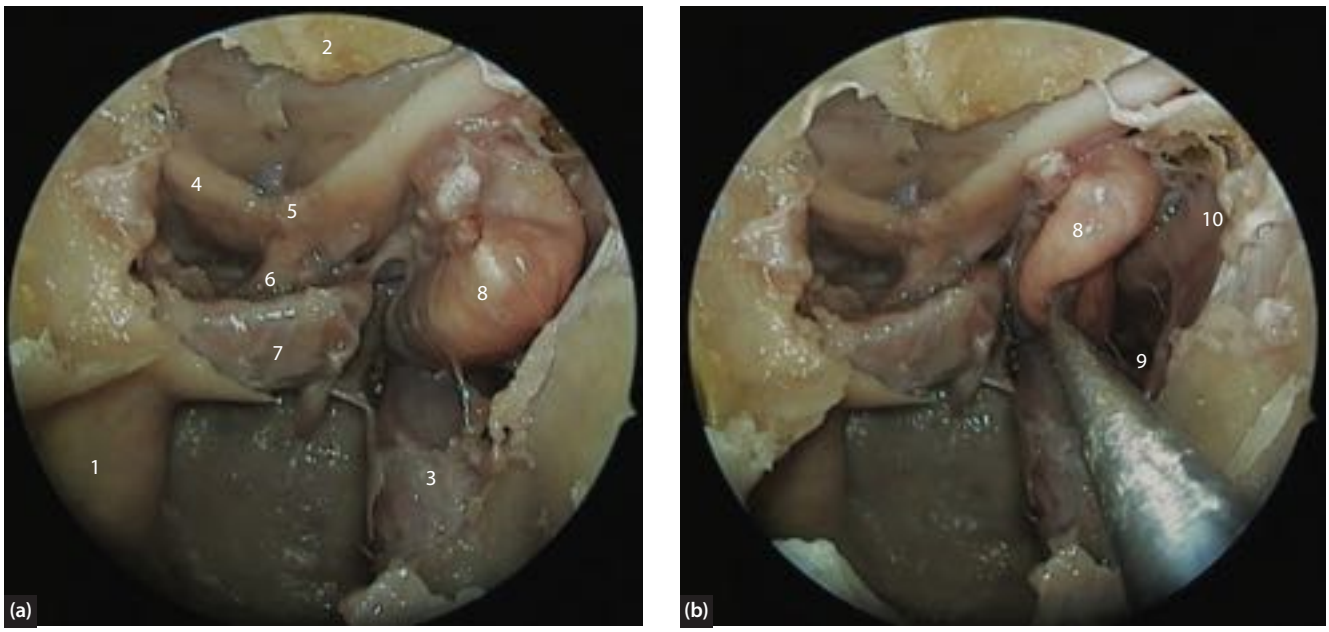


Figure 54.8 Endoscopic view of the sella and cavernous sinus in a frozen cadaver. (a) The right ascending carotid (1) is behind its bony covering. Bone, dura and the diaphragm have been removed over the pituitary fossa and left cavernous sinus up to the roof of the sphenoid (2). The left ascending carotid (3), optic nerves (4), chiasm (5), pituitary stalk (6) and the pituitary gland (7) are exposed. The anterior bulge of the left carotid artery (8) is seen in the cavernous sinus. **(b)** The left carotid artery (8) is displaced medially to show the cavernous sinus (9) and the oculomotor nerve (10) in its lateral wall.

KEY POINTS

- Intra-sphenoid septae are highly variable and often inserted close to the carotid artery on the posterior sphenoid wall.
- Endoscopic view allows good visualization of the posterior sphenoid wall and the landmarks of the carotid arteries and optic nerves are often visible.
- The lateral optico-carotid recess corresponds to the anterior clinoid process intracranially.
- Understanding the variable, tortuous course of the carotid artery in the sphenoid and cavernous sinus is the key to performing safe pituitary surgery.
- The pituitary fossa does not normally contain CSF but does contain small inter-cavernous venous sinuses.

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CHAPTER 55

PHYSIOLOGY OF THE THYROID AND PARATHYROID GLANDS

Martin O. Weickert

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: thyroid, parathyroid glands, hypothyroidism, thyrotoxicosis, thyroid-stimulating hormone (TSH), thyroglobulin, thionamides, neutropenia, osteoporosis, vitamin D.

The information in this chapter summarizes the physiology of the thyroid and the parathyroid glands, with a focus on aspects that are important for the endocrine surgeon.

INTRODUCTION

The thyroid is the largest endocrine organ, weighing 10–25 g. The highly vascular gland is located in front of the trachea in the anterior neck and consists of a left and a right lobe, connected by the isthmus. The parathyroid glands can vary in number and location, but in over 80% of humans there are four glands which are most commonly located posterior to the thyroid, although the location especially of the inferior glands can be more variable. Importantly, apart from sharing anatomical neighbourhood and part of the name, thyroid and parathyroid glands are independent endocrine organs that share no obvious functional similarities. However, due to the close anatomical location, surgery of the thyroid can impair parathyroid function transiently or permanently.

At the beginning of modern thyroid surgery in the 1860s, the mortality associated with thyroidectomy was high,[1, 2] mainly related to thyroid storm in thyrotoxic patients, as well as post-surgical hypothyroidism and hypocalcaemia. 'Cachexia strumipriva' in patients after total thyroidectomy, as described by Kocher in 1883,[3] was later causally linked to surgical hypothyroidism. Tetany was thought to be caused by 'hysteria'. The parathyroid glands in humans were discovered in 1880 by Sandstrom,[4] but the fact that hypocalcemia was the definitive cause of tetany was not accepted until decades later.[2]

Improved insights in the physiology of thyroid and parathyroid glands have made a major contribution to transforming surgery of these organs to relatively low-risk routine procedures. The aim of this chapter is to provide a brief overview of the physiology of the thyroid and parathyroid glands, with a focus on aspects that are relevant to the ENT surgeon.

PHYSIOLOGY OF THE THYROID GLAND

Hormones secreted by the thyroid are critical for the development of the foetus and newborn, with key influences on the development of the brain and normal growth. In adults, major roles of the thyroid include involvement in the regulation of energy homoeostasis.[5] Thyroid hormones influence the function of various target organs, primarily by stimulating cell metabolism and activity. Both over- and under-function of the thyroid influence the well-being of the patient, with major dysfunction in both directions being potentially life-threatening.

Key controlling factors of thyroid hormone synthesis include the availability of external iodine; and regulation by the hypothalamic–pituitary axis (HPA).

The thyroid produces and releases tetraiodothyronine (T4) and triiodothyronine (T3), which are essential hormones for the regulation of metabolic processes. Iodine from dietary sources is absorbed and carried to the thyroid as iodide, where it is actively concentrated via the natrium (sodium) iodide symporter (NIS) and transported

TABLE 55.1 Effects and key functions of thyrotoxic or hypothyroid states in adults

	Thyrotoxicosis	Hypothyroidism
Energy metabolism	Increased basal metabolic rate Heat intolerance Weight loss*	Decreased basal metabolic rate Cold intolerance Weight gain
Carbohydrate metabolism	Stimulation of carbohydrate metabolism	
Lipid metabolism	Stimulation of lipolysis, T3 mediated down regulation of SREBP1c mRNA;47 reduction in body fat mass[1]	Reduced lipolysis, increase in body fat mass
Protein metabolism	Protein degradation, reduction of body lean mass	Decreased protein synthesis, increased body mass
Cardiovascular	Increased efficacy of catecholamines, tachycardia, tremor, peripheral vasoconstriction (skin) with increased central blood flow	Decreased efficacy of catecholamines, bradycardia, reduced exercise tolerance and myocardial contractility, exacerbated heart failure
Central nervous system	Enhanced catecholamine activity	Impairment of intellectual activity, movement and speech, impaired memory, delayed tendon reflexes, muscle weakness
Bone	Increased bone turnover, osteopaenia, osteoporosis¶	Decreased bone turnover
Various	Turnover of vitamins, increased gut motility, erythropoiesis, involvement in the regulation of the menstrual cycle	Dry/coarse skin, hair loss, breathlessness, oligomenorrhea/amenorrhea, menorrhagia, normocytic anaemia

* In some 10% of patients, weight loss can be observed in the thyrotoxic state, related to increased appetite which may override the catabolic metabolic state.
¶ Related to activation of osteoclasts.

into thyroid follicles. The endoplasmic reticulum of the thyrocyte produces thyroglobulin (Tg) and thyroid peroxidase (TPO). Iodide is then attached to Tg via TPO, resulting in the production of mono-iodothyronine (MIT) and di-iodothyronine (DIT), with subsequent production of T3 and T4 via enzymatic coupling.

Thyroid hormone release is a complex process, involving endocytosis of Tg-containing vesicles and fusion with follicular epithelial phagolysosomes, proteolytic digestion and cleavage of Tg, intra-cellular deiodination of MIT and DIT and reuse of iodide, and finally release of T3 and T4 from the basolateral membrane into the circulation.[5,6] Almost all of these steps are influenced by thyroid-stimulating hormone (TSH).[7] **Table 55.1** summarizes some of the key functions of thyroid hormones in adults.

Hormones secreted by the thyroid

The thyroid produces thyroid hormones T4 and T3 and releases them into the circulating blood. Approximately 80% of thyroid hormone is secreted as T4 and peripherally converted via deiodination into T3, which shows around fivefold more potency. The half-life of circulating T3 is ≅1.5 days, as compared with ≅7 days of T4. Combined, this results in ≅40-fold higher plasma concentrations of T4 versus T3.[5] T3 production is reduced in acute illness and starvation. Locally produced T3 plays important roles in several fundamental mechanisms, including thyroid homeostasis, energy balance and glucose metabolism.[8]

Thyroid hormones are bound to binding proteins in the peripheral blood. In circulating blood, only the free hormones (fT3 and fT4) exert relevant physiological actions. To assess the function of the thyroid, it is usually sufficient to measure plasma fT4, along with TSH. However, the measurement of plasma fT3 can be valuable in situations where there is suspected excess production and release of T3, i.e. in patients with a toxic thyroid adenoma.

Synthesis of thyroid hormones

Iodine is a crucial component of thyroid hormones, which are iodothyronines. By weight, iodine comprises 65% of T4 and 58% of T3. Ingested iodine is absorbed in the small intestine and transported via the plasma to the thyroid follicular cells, where it is concentrated. Thereafter, iodine is rapidly oxidized and bound to tyrosyl residues in Tg. This is followed by intra-colloidal modification of Tg, which comprises iodination of tyrosine residues; formation of iodothyronines by oxidative coupling of two iodotyrosines; and storage of iodinated Tg as colloid. The next steps include endocytosis of iodinated Tg, merging with lysosomes and finally, mediated via TPO, conversion of the respective iodinated tyrosine residues MIT and DIT to the thyroid hormones T3 (from MIT + DIT) and T4 (from DIT + DIT) (**Figure 55.1**).[6,9]

Selenium is another essential element for thyroid hormone synthesis. It is involved in synthesis of various enzymes, especially glutathione peroxidase.[10]

Antithyroid drugs interfere with the synthesis of thyroid hormones. The most important inhibitory drugs of thyroid hormone synthesis are the thionamides: methimazole and, more widely used in the UK, its prodrug carbimazole; and propylthiouracil. Propylthiouracil shows a less favourable side-effect profile compared with the thiamazoles in terms of possible agranulocytosis (not dose-dependent) and hepatic reactions, but it is preferred during the first trimester of pregnancy, due to the extremely rare possible side effect of aplasia cutis of the scalp in the foetus that has been observed with treatment with carbimazole.

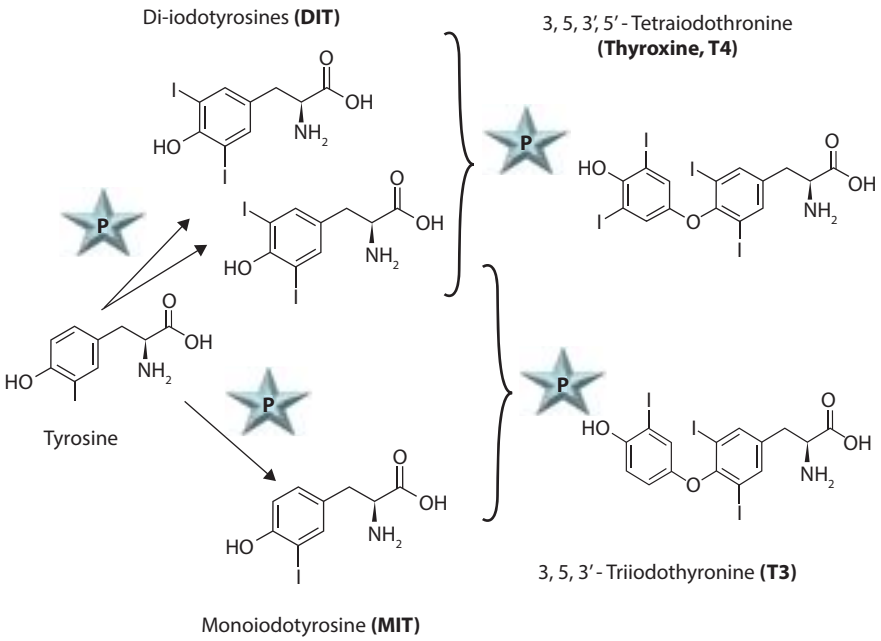


Figure 55.1 Thyroid hormone synthesis. Following the uptake of iodide into the follicular thyroid cell, thyroid peroxidase drives the iodination of tyrosine residues within the thyroglobulin matrix. Iodothyronines are formed by peroxidase coupling of iodothyrosyl residues, with 2 di-iodothyrosines (DIT) forming T4 and 1 MIT + 1 DIT forming T3. P, thyroid peroxidise.

Control of thyroid hormone synthesis

Release of thyroid hormones into the circulating blood involves the negative feedback system of the HPA.[11] A decrease in circulating T3 concentrations or a low metabolic rate signal the hypothalamus to secrete thyrotropin-releasing hormone (TRH), which in turn stimulates the secretion of TSH from the anterior pituitary gland. On the contrary, elevated circulating T3 concentrations inhibit the release of TRH and TSH directly.[7] T4 plays an indirect role, exerting inhibitory roles mainly after conversion to T3 within the pituitary or hypothalamus. Figure 55.2 depicts the feedback inhibition of thyroid hormones on the release of TRH and TSH.[6]

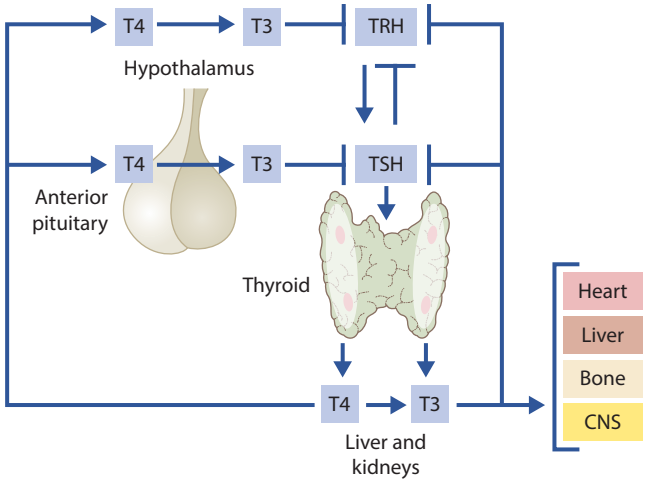


Figure 55.2 Feedback inhibition of thyroid hormones. The anterior pituitary gland increases the secretion of thyroid-stimulating hormone (TSH) when stimulated by hypothalamic thyrotropin-releasing hormone (TRH). The action of TRH is inhibited either directly by circulating T3, or indirectly, after conversion of T4 to T3, by the hypothalamus and pituitary.

TSH is a glycoprotein hormone from the anterior pituitary that influences almost all steps in both the synthesis and the release of thyroid hormones. The α-subunit is similar to that of luteinizing hormone, follicle-stimulating hormone and human chorionic gonadotropin, whereas the β-subunit is unique to TSH. It stimulates the TSH receptor (TSH-R) on thyroid follicular cells. The effects on thyroid hormone secretion appear to be mediated through the cAMP cascade, whereas the effects on synthesis are mediated by the Gq/phospholipase C cascade.[7] TSH stimulates the expression of NIS, TPO and Tg, the generation of hydrogen peroxide (H_2O_2), and the formation of T3.[7] Further functions of TSH involve altering the priority of iodination and hormonogenesis among tyrosyls and promoting the rapid internalization of Tg by thyrocytes. These steps are interrelated and have the net effect of increasing available iodine to the cells and finally of producing and releasing an increased amount of biologically active T3.[7]

Stimulation of TSH-R also increases the vascularity of the thyroid, an effect that is mediated via vascular endothelial growth factor (VEGF) secretion by the follicular cells. Presence of stimulating TSH-R antibodies explains that patients with Graves' disease can show excessive vascular flow in the thyroid. Although TSH is the primary regulator of thyroid function, there is evidence for additional autoregulation of the thyroid, mainly related to iodine transport and organification.

Normal range for TSH

Expert opinion on the normal range for TSH varies widely. Some assays give excessively wide 'normal ranges' from 0.35–6 mU/L, which is in part related to the use of not well-characterized cohorts from cross-sectional studies, including assumed healthy individuals with occult thyroid disease.[12, 13] The American Association of Clinical Endocrinologists (AACE) defines a normal range for TSH

of 0.3–3.0 mU/L and the National Academy of Clinical Biochemistry of 0.4–2.5 mU/L.[14] Notably, the population mean for TSH in various ethnicities appears to be lower, at 1–2 mU/L.[15–18] Even higher normal TSH levels (>2.5 mU/L) may be related to adverse outcomes, which include associations with parameters of metabolic risk.[19] After thyroidectomy, it appears reasonable titrating TSH within the ideal range in most patients. In subjects with moderate or high risk differentiated thyroid carcinomas, where TSH suppression is indicated, fT4 should be titrated towards the upper normal range. Importantly, TSH suppression is sufficient, whereas over-treatment resulting in excess fT4 levels is unnecessary and should be avoided due to risks of palpitations, atrial fibrillation and depletion of bone mass.

Iodine

Iodine is an essential mineral and the main substrate involved in thyrocyte metabolism. Potassium iodide is a man-made salt compound of iodine with increased absorption in the intestine. The normal human thyroid maintains a concentration of iodide that is 20–50 times higher than plasma concentrations, depending on the amount of available iodine and the activity of the gland.[20]

The thyroid concentrates iodide from the extracellular fluid by an active, energy-dependent and saturable process via NIS, which is located at the basolateral membrane of the acinar cell.[6] Iodide then diffuses via pendrin channels from the cell to the lumen at the apical membrane. Several types of control have been identified, which involve rapid and transient TSH-mediated stimulation of iodide efflux, TSH-induced blunted capacity of the active iodide transport, and transient inhibition of thyroid blood flow by iodide.[9] The rate of uptake of iodide by the thyroid normally exceeds the rate of its incorporation into amino acids (organification) and diffusion back to the extracellular fluids, which ensures high intra-thyroidal iodide concentrations.

Adequate dietary intake of iodine is essential for thyroid hormone synthesis. The daily iodine intake of adult humans varies from less than 10 µg in areas of extreme deficiency to several hundred milligrams. In the United States, urine iodine concentrations indicate generally sufficient intake of iodine[21], but intake in most of Europe appears to be lower. The Institute of Medicine has set the Recommended Dietary Allowance (RDA) for iodine in adults at 150 mcg/day. The minimum daily requirement to prevent goitre from iodine deficiency is thought to be 50–75 mcg/day. Both under- and over-supply of iodine influence thyroid function. Low supply with iodine is common and leads to impaired production of thyroid hormones, causing increased TSH secretion and possibly goitre in an compensatory attempt.[7] Various other iodine deficiency disorders of the thyroid have been reported.[22]

Excess iodide acutely inhibits the synthesis of thyroid hormones, the Wolff–Chaikoff effect.[23] Possible mechanisms include inhibiting the production of H_2O_2 and thus blocking the iodination of TG.[24] Importantly, this effect is typically short-lived, often lasting for several days only (escape from the Wolff–Chaikoff effect). Thereafter, in patients with pre-existing goitre, excess iodine can cause severe thionamide-resistant thyrotoxicosis. Blocking an overactive thyroid with high-dose iodine before surgery is therefore not encouraged by all centres; if this procedure is chosen, thyroid surgery should be performed within the next few days. Thyrotoxic effects of excess iodine can also be observed in thyrotoxicosis type-1 induced by amiodarone (an antiarrhythmic drug that contains 75 000 µg of iodine per tablet) and in patients with goitre following the use of iodine-containing contrast medium when performing computer tomographic (CT) scans.

Thyroglobulin

Tg is the most abundant protein in the thyroid gland, with up to 200-300 g/L being stored in the follicular lumen. The main function of Tg is to provide the polypeptide backbone for the synthesis and storage of thyroid hormones.[7] Further functions include depot capacity for the storage of iodine, thereby compensating for fluctuations in the supply of external food derived iodine. Thyroid hormones that are bound to Tg are biologically inactive.

Given that Tg is exclusively produced in thyroid, it can serve as a tumour marker after complete removal of the thyroid (total thyroidectomy followed by radioiodine treatment in patients with differentiated thyroid cancer). However, the presence of anti-Tg antibodies needs to be excluded. Interference of these antibodies with various assays can lead to either false positive and false negative results, possibly delaying the detection of a relapse, or resulting in unnecessarily repeated investigations involving radiation.

Thyroid peroxidase

TPO is produced in the endoplasmic reticulum of the thyrocytes. TPO oxidizes iodine, thereby facilitating the formation of T3 and T4 (**Figure 55.1**). The presence of TPO antibodies increases the risk of developing autoimmune thyroiditis.

Release of thyroid hormones

Unlike most other endocrine organs, which do not store relevant amounts of hormone, the thyroid contains the supply of Tg-bound thyroid hormones for several weeks.[6] Upon stimulation by TSH, iodothyronines are released from Tg due to effects of lysosomal proteases, with fT4 and fT3 diffusing from the thyroid cell into the bloodstream. Both iodide and TG normally remain in the thyroid cells and are reused for hormone resynthesis.[6] After variable periods of storage in thyroid follicles, Tg is proteolysed and the released hormones are secreted into the circulation, where specific binding proteins, most notably thyroxine-binding globulin (TBG), transport them to their respective target tissues.

Thyroxine-binding globulin in plasma (TBG)

In circulating blood ≅80% of T4 and T3 are bound to TBG and other binding proteins, which help maintain

TABLE 55.2 Effects of various factors on circulating thyroxine-binding globulin (TBG)

Circulating TBG	Causal factors
Increased TBG	Pregnancy Hepatitis Acute intermittent porphyria Drugs (i.e. oestrogen, tamoxifen, opiates, etc.) Hereditary TBG excess
Decreased TBG	Genetic reasons Chronic liver disease Nephrotic syndrome Malnutrition Cushing's disease Drugs (i.e. androgens, steroids, etc.) Acromegaly

serum free T3 and T4 concentrations within a tight range. Only unbound thyroid hormone is available to the tissues and therefore biologically active. T3 is less strongly bound than T4 and has a more rapid onset of action.

Oestrogens stimulate the expression of TBG in the liver. Therefore, from about 20 weeks of gestation, pregnant women with hypothyroidism need their L-thyroxine replacement doses to be increased to avoid hypothyroidism (Table 55.2).

Action of thyroid hormones at the tissue level

At the tissue level, the biological activity of thyroid hormone is regulated by deiodinases (DIO). DIO-1 and DIO-2 are responsible for the generation of T3 from T4, whereas DIO 3-is the major inactivating enzyme, leading to an increase of reverse T3 (rT3).[25] The ratio between T3 and rT3 (T3/rT3-ratio) is a sensitive indicator of peripheral thyroid hormone metabolism. The ratio is positively influenced by DIO-1 and DIO-2 and negatively by DIO-3. The T3/rT3-ratio is relatively independent of both thyroidal T4 production and thyroid hormone-binding protein variation in serum.[25]

Calcitonin

Calcitonin is produced by the neural crest cell-derived parafollicular C-cells. The role of calcitonin in humans is not completely understood.

Calcitonin (and, less specific, carcinoembryonic antigen – CEA) can be used as tumour markers in medullary thyroid carcinoma (MCT), a rare (≅4% of all thyroid cancers) and frequently aggressive cancer that is often located in the upper central lobe of the thyroid gland. C-cell hyperplasia defines a MTC *in situ*, with better prognostic features. Around 80% of MCT occur sporadically. The remaining 20% are inherited syndromes such as multiple endocrine neoplasia (MEN) types 2A, 2B, or MTC only. Catecholamine-producing pheochromocytomas are a concern in MEN-2, with important implications when preparing for safe thyroid surgery.

FUTURE RESEARCH

- To develop uniform evidence-based recommendations for the follow-up of patients with differentiated thyroid cancers, with respect to risk assessment (low, medium or high risk)
- Advanced strategies to avoid inadvertent damage to the parathyroids in patients requiring total thyroidectomy
- Potential differences between thyroid hormone action in circulating blood, as compared to cellular and tissue levels
- Influence of age and developmental status on thyroid function
- Further defining risk assessment in patients with thyroid nodules
- Molecular treatment approaches for different histotypes of thyroid cancer

KEY POINTS

- TSH is the best overall parameter for assessing thyroid function and for monitoring replacement therapy.
- In medium- to high-risk thyroid cancer, TSH suppression with high normal fT4 is the aim.
- Replacement with L-thyroxine (T4) is standard. Replacement with Liothyronine (T3) is more likely to result in fluctuations of thyroid function tests and side effects, but it may be needed in rare conditions with impaired conversion of T4 to T3 or for preparation of radioiodine treatment if recombinant TSH is not available.
- Thyroid hormones should be taken at least 30 min before breakfast and isolated from caffeine-containing beverages and other tablets to facilitate more reliable absorption.
- TSH can react slowly to changes in hormone supply, especially after longer term dysfunction. Here, monitoring of fT4 (or fT3, if appropriate) gives more timely information.
- Thionamides are the treatment of choice to control thyrotoxicosis prior to surgery.
- Replacement of vitamin D before total thyroidectomy reduces the risk of severe hypocalcaemia related to inadvertent damage to the parathyroid glands.
- Screening for catecholamine-producing tumours is mandatory before performing surgery for MCT.

PHYSIOLOGY OF THE PARATHYROID GLANDS

The main function of the parathyroids is the regulation of calcium homoeostasis via the secretion of PTH. There are usually four (40 mg each) parathyroid glands. Five per cent of the population have only three glands and an additional fifth gland can be found in 12–15%, with six or more glands being occasional findings.[26] The secretion of PTH is under negative feedback regulation by ionized calcium in the extracellular fluid. However, PTH remains detectable even when serum calcium is excessively raised, indicating that further factors contribute to the regulation of PTH secretion.

Calcium homoeostasis

Calcium homeostasis is a complex process, involving serum calcium, phosphate, 1,25-dihydroxyvitamin D3 (synonyms: 1,25$(OH)_2$ vitamin D3, 'active' vitamin D, or calcitriol) and PTH. The main involved organs are the parathyroid glands, bones, kidneys and the intestine; the skin, kidneys and liver regulate vitamin D metabolism.

More than 99% of the human calcium reserve (≅1.1 kg) is stored in the bones and teeth. 'Free' ionized calcium, comprising ≅50% of body calcium, has crucial physiological roles including cell signalling, the functioning of the heart and the nervous system, the contraction of muscles and the clotting of blood.[6] The remainder of the calcium pool is protein-bound (40%) or forms soluble complexes with phosphate and citrate (10%). Most protein-bound calcium is attached to albumin and influenced by the pH, with acidosis increasing and alkalosis decreasing ionized calcium levels.[5]

Serum calcium concentrations are tightly regulated (normal range 2.14–2.6 mmol/L, assay-dependent). Even relatively mild acute changes can be symptomatic. Major changes in both directions can be life-threatening.

Parathyroid hormone (PTH)

The parathyroid glands secrete parathyroid hormone (PTH) after cleavage from pre-pro-PTH (115 amino acids) to pro-PTH (90 amino acids) and finally the active peptide hormone (84 amino acids). PTH is released when calcium sensors on the surface of the parathyroid glands detect low circulating serum calcium concentrations, and rapidly increases serum calcium levels. The release of PTH is inversely proportional to serum calcium, with small calcium fluctuations producing large changes in PTH secretion.[26] PTH blocks the renal reabsorption of phosphate in the proximal tubule and facilitates the reabsorption in the ascending loops of Henle, distal tubules and collecting tubules. In addition, PTH activates the enzyme 1-hydroxylase in the proximal renal tubules, thereby converting 25-OH vitamin D to its active metabolite, calcitriol.

In the bone, PTH promotes the absorption of calcium via a rapid and a slow phase.[27] The rapid phase appears to be mediated at the level of the bone cells. In response to hypocalcaemia, PTH concentrations change within 1 min, peak in 4–10 min and decline again within 60 min. The half-life of PTH is approximately 3 min. The slow phase of bone resorption is regulated via activation and proliferation of osteoclasts, with effects taking several days. These actions appear to be mediated by the differentiation of osteoclast precursors which, unlike mature osteoclasts, possess vitamin D and PTH receptors; or via cytokines that are released by activated osteocytes and osteoblasts.[27] Feedback inhibition of PTH release occurs primarily by direct effects of circulating calcium at the level of the parathyroid gland.

In humans, PTH fluctuates episodically at a frequency of 6–7 bursts per hour. Non-pulsatile secretion accounts for ≅70% of total PTH secretion. Patients with excess PTH secretion (i.e. primary hyperparathyroidism, PHPT) show both pulsatile and tonic excess secretion but unchanged pulse frequency. Constantly elevated PTH has detrimental effects on bone mass density and bone structure,[28] primarily due to up-regulation of nuclear factor κB ligand (RANKL) and inhibition of osteoprotegerin expression, leading to an increase in osteoclast formation and activity.[29] In contrast, intermittent administration of recombinant PTH stimulates bone formation, explaining its pharmacological use for the treatment of osteoporosis.[30] In hypercalcaemic states, measurement of PTH is the most important measure to distinguish between PHPT and other causes of hypercalcaemia where circulating PTH is typically low, i.e. in patients with Vitamin D intoxication or malignancy (where hypercalcaemia can result from PTH related peptide (PTHrp) excess; osteolytic bones metastases; immobilization or dehydration. Importantly, patients with raised PTH together with low or lower end of normal adjusted calcium concentrations have secondary hyperparathyroidism (frequently caused by vitamin D deficiency or insufficiency), which is a physiological reaction of the parathyroids to increased serum calcium levels. Here, imaging of the parathyroids or surgical intervention would be inappropriate.

Vitamin D

Vitamin D3 (colecalciferol, previously cholecalciferol) is formed in the skin when a cholesterol precursor, 7-dehydroxycholesterol, is exposed to ultraviolet light (UV-B). 'Active' vitamin D (1, 25-$(OH)_2$ vitamin D3) occurs after (i) 25-hydroxylation in the liver and (ii) 1-hydroxylation in the kidney (**Figure 55.3**), with major effects on calcium homoeostasis. Compared with PTH, vitamin D exerts much slower but long-acting regulatory effects on calcium balance.

Active vitamin D is calciotropic, raising serum calcium by several mechanisms. These include promoting the absorption of calcium in the intestine and stimulating the formation of calcium-binding protein in the intestinal epithelial cells. Further functions include increasing bone resorption and renal calcium reabsorption, actions that are in part shared with those of PTH. Vitamin D also promotes intestinal absorption of phosphate. In bone, vitamin D may play a synergistic role with PTH in stimulating osteoclast proliferation and bone resorption, with high PTH and low phosphate levels as stimulating and with low PTH and high phosphate as inhibiting factors.[6]

Recent research also links calcitriol precursors to various physiological functions. The exact mechanisms of how increased vitamin D3 intake intake inhibits PTH secretion need further investigation but are unlikely to be exclusively dependent on circulating calcitriol.[31–34] Local mRNA and protein expression of 1-alpha hydroxylase has been described in human parathyroid glands, and this expression appears to be altered in various disorders of the parathyroids.[33, 35, 36] Further proposed mechanisms include non-1,25$(OH)_2$ vitamin D-mediated effects of colecalciferol or other vitamin D metabolites on PTH production, or stimulation of parathyroid tissue vitamin D receptors.[32–34] Further actions may include vitamin D-mediated regulation of the expression of the calcium-sensing receptor (CaSR).[31, 37, 38] Treatment of

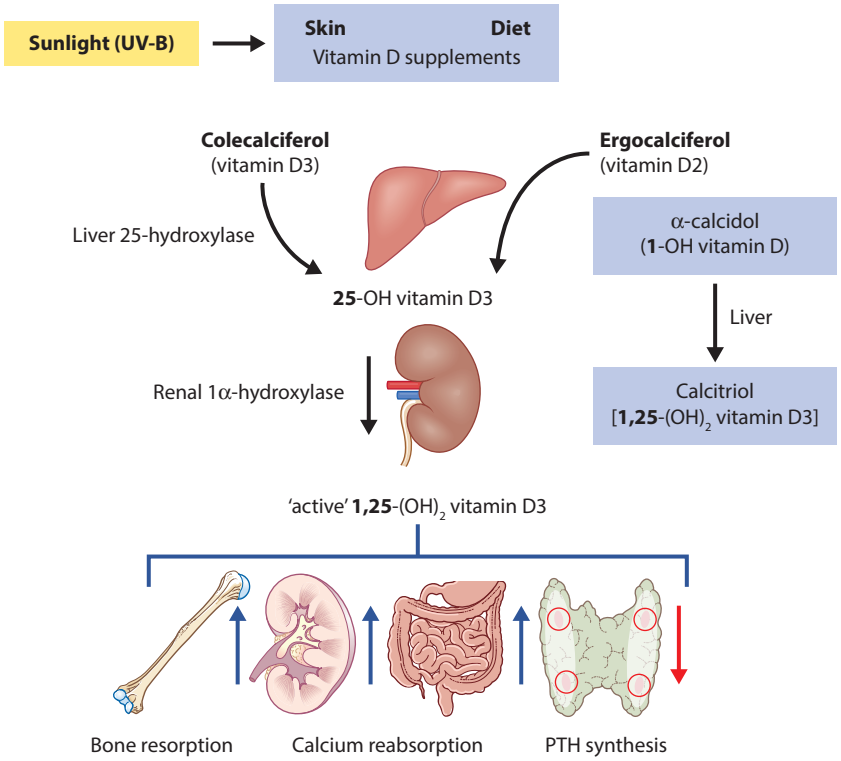


Figure 55.3 Vitamin D metabolism and replacement drugs. Unlike calcitriol, alfacalcidol is a prodrug that is inactive prior to hydroxylation in the liver. This process can be impaired in patients with liver disorders.

vitamin D deficiency appears to reduce circulating PTH in patients with PHPT, without adverse effects on serum calcium concentrations.[31] Various factors support the replacement of vitamin D deficiency in patients with PHPT: suboptimal dietary intake of vitamin D stimulates parathyroid adenoma growth and reduces the calcaemic response to PTH.[31] Apart from elevated markers of increased bone turnover,[39, 40] patients with coexisting PHPT and vitamin D deficiency are more likely to have a larger parathyroid adenoma and higher PTH levels.[34, 41] Recent guidelines encourage vitamin D replacement to serum 25-OH vitamin D concentrations above 50 nmol/L in all monitored patients with pHPT.[42]

Post-operative hypoparathyroidism

Post-operative hypoparathyroidism can result in severe hypocalcaemia. Early symptoms may include anxiety, tingling of the fingers and toes, or peri-oral numbness. Acute and severe hypocalcaemia may result in papilledema, tetany, seizures and even death. In patients with MEN type 1, all parathyroids should be removed, although autotransplantation of half a gland into the sternocleidomastoid muscle or forearm is advised to avoid severe hypocalcaemia and often major fluctuations in serum calcium levels despite replacement with active vitamin D. Post-operative hypoparathyroidism happens accidentally, for example during total thyroidectomy for thyroid cancer, Graves' disease, or surgery for multinodular goitre. It is more often temporary but can be permanent. Frequency of this complication is usually reported as 5%, but could be as high as 20% after combined thyroidectomy and radical neck dissection.[2, 43] Treatment with radioiodine may play a role as well, but is considered to be a rare cause of symptomatic hypocalcaemia.

Post-operative hypoparathyroidism is most frequently caused by disruption of the fine vessels that supply the parathyroids, rather than by accidental removal of all parathyroid glands.[2] The risk of accidental devascularization can be reduced by dissecting close to the thyroid capsule and by ligating the branches of the inferior thyroid artery on the thyroid capsule distal to their supply of the parathyroid glands, rather than by ligating the inferior thyroid artery as a single trunk.[2]

There is an increased risk of severe and potentially life-threatening hypocalcaemia in patients with combined PHPT and vitamin D deficiency following parathyroidectomy.[41] Correcting vitamin D deficiency has been shown to reduce both the incidence of post-operative hypocalcaemia and the length of stay in hospital.[44]

Calcium-sensing receptor

The calcium-sensing receptor (CaSR) is a class C G-protein coupled receptor which senses extracellular levels of calcium ions. In the parathyroid gland CaSR controls calcium homeostasis by regulating the release of PTH. Mutations that inactivate the CaSR gene cause familial hypocalciuric hypercalcemia (FHH), which generally is asymptomatic and does not require treatment. Therefore, it is important to distinguish this benign disorder from PHPT. Not all patients with PHPT require surgical treatment, and there is consensus that asymptomatic patients with adjusted calcium concentrations below 3 mmol/L and absence of end-organ damage related to longer-term PTH excess such

as osteoporosis can be safely observed. Calcimimetics are a class of drugs with calcium-sensing receptor agonist properties that act directly on the parathyroid gland and decrease PTH release and serum calcium levels, and may also beneficially influence parathyroid tumour growth. Calcimimetics can be useful in patients with PHPT who are not eligible for surgical intervention.

Calcitonin

Calcitonin counteracts many of the functions of PTH in various species. However, in humans the biological role of calcitonin is not well defined, with both lack of calcitonin after thyroidectomy and excess of calcitonin in medullary thyroid carcinoma exerting no obvious effects on serum calcium or bone mass. Calcitonin of some other species (e.g. that of salmon, which is >15-fold more potent) is used pharmacologically for the treatment of osteoporosis and malignant hypercalcaemia.[6] Calcitonin acts in response to acute changes in serum calcium concentrations by inhibiting calcium resorption from the bones and tubular reabsorption in the kidneys.[5] Physiological stimuli of calcitonin secretion include hypercalcaemia and high circulating levels of gastrin.

SUMMARY OF CONSIDERATIONS OF PATIENTS WITH DISORDERS OF THE THYROID OR PARATHYROIDS

Patients undergoing surgery of the thyroid should be euthyroid. Correction of thyrotoxicosis is assessed by measurement of serum fT3 (and more slowly reacting fT4, due to longer plasma half-life; note that fT4 will show delayed decrease when the conversion of fT4 to fT3 is pharmacologically blocked), whereas a suppressed TSH alone does not define risk and may need weeks to normalize. Hypothyroidism should be treated before surgery, if possible. In emergency situations, intravenous treatment with thyroid hormones for patients with severe hypothyroidism can be provided during surgery. In patients with thyrotoxicosis and contraindications against thionamides drugs (i.e. due to carbimazole-induced agranulocytosis, with known cross-reactivity of at least 50% with all other drugs in this class), urgent surgery is mandatory to save the patient's life. Measures to reduce risk in this situation may include high-dose treatment with propranolol (>140 mg/day are needed to block conversion T4 to T3), high-dose hydrocortisone, low-dose lithium (400–500 mg daily) (unlicensed use; with various inhibiting effects on thyroid hormone synthesis and release;[45] higher doses are discouraged and increase the rate of side effects only); or iodine, although with the latter the situation may worsen in patients with multinodular goitre related to pre-existing iodine deficiency; and surgery must be performed within the next few days.

Following total thyroidectomy, the replacement dose of L-thyroxine is usually ≅1.6 µg/kg body weight, to be taken first thing in the morning and at least 30 minutes before food, caffeine-containing beverages and any other tablets or supplements to facilitate more reliable absorption. Initially smaller doses with stepwise increases are advised, especially in geriatric patients and patients with risk factors such as atrial fibrillation. When TSH needs to be raised transiently (typically to >30 mU/L) prior to radioiodine treatment, the preferred choice is administration of recombinant TSH over 2 days. Alternatively, L-thyroxine can be paused and replaced by Liothyronine (T3; 20% of the dose of L-thyroxine), which is eliminated more rapidly after withdrawal. Although more cost-efficient, this method results in significant morbidity related to overt hypothyroidism, which can include severe weight gain and clinically relevant depression.

Measurement of serum-adjusted calcium, 25-OH vitamin D and PTH concentrations, and pre-operative replacement of vitamin D are recommended in patients undergoing total thyroidectomy or surgery of the parathyroid glands. Endoscopic or indirect laryngoscopy should be performed to exclude potentially asymptomatic pre-existent lesions of the vocal cords. In patients following removal of parathyroid gland(s) or in patients who underwent total thyroidectomy, close monitoring of serum calcium levels and appropriate replacement with active vitamin D preparations is crucial to avoid significant morbidity.

In patients with PHPT due to MEN 1, all parathyroid glands need to be explored and thymectomy considered, particularly when fewer than four parathyroid glands are identified.[46] Leaving a viable remnant or performing autotransplantation is recommended to avoid major swings in serum calcium levels following surgery. Patients with MTC require pre-surgical assessment (and treatment, if appropriate) for possible coexisting catecholamine excess.

FUTURE RESEARCH

- Additional strategies for preserving parathyroid function in patients undergoing total thyroidectomy; and improved strategies for the long-term treatment of patients with permanent hypoparathyroidism and hypocalcaemia
- Improved methods for the pre-operative identification of small parathyroid adenomata
- Further improvement of decision pathways for performing surgery vs. an observational approach in patients with PHPT
- Improved diagnostic and therapeutic strategies for patients with parathyroid carcinoma

KEY POINTS

- PTH concentrations are altered within 1 min, peak in 4-10 min and decline in 60 min. Absence of PTH (e.g. after inadvertent damage to the parathyroids) can result in major problems including life-threatening hypocalcaemia.
- Additional vitamin D deficiency in patients with PHPT may introduce additional (secondary) stimulation to the parathyroid glands, with further negative effects on bone mass.
- Correcting vitamin D deficiency before parathyroid surgery and total thyroidectomy can reduce both the incidence of postoperative hypocalcaemia and the length of stay in hospital.
- Alfacalcidol is a prodrug and may not work effectively in hypoparathyroid patients with impaired liver function.
- Patients with MEN 1 generally have tumours in several or all four parathyroid glands and may have additional ectopic glands (e.g. in the thymus). Minimally invasive parathyroidectomy is not recommended. Leaving a viable remnant or performing autotransplantation is recommended to avoid major swings in serum calcium levels following surgery.

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CHAPTER 56

PHYSIOLOGY OF THE PITUITARY GLAND

Mária Hérincs, Karen Young and Márta Korbonits

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: pituitary hormones, growth hormone (GH), prolactin (PRL), adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), luteinising hormone (LH), follicle stimulating hormone (FSH), argenine vasopressin (AVP) and oxytocin.

INTRODUCTION

The existence of the pituitary gland (also referred to as hypophysis cerebri, derived from the Greek words *hypo*, meaning under, and *physis*, meaning growth) was known before the time of Aristotle, but its role in physiology puzzled scientists for many centuries. In AD 150, the Greek physician and philosopher Galen described the pituitary gland in detail, proposing that its role was to drain the phlegm from the brain to the nasopharynx. The gland was named with this in mind – from the Greek *ptuo* (to spit) and the Latin *pituita* (mucous) and *pituitarius* (mucous-secreting). The pituitary gland's true functions emerged over the 19th and 20th centuries, when its function as an endocrine organ was finally recognized.[1]

The pituitary gland is usually less than 8 mm in length when measured in the craniocaudal plane. However in certain physiological conditions, such as puberty and pregnancy, it can be enlarged (reaching 10–12 mm). It is quite remarkable that such a small organ controls diverse and complex functions of the whole body. Although the pituitary gland is often referred to as the 'master gland' of the body (since many other endocrine glands depend on hypophyseal stimulation), the hypothalamus is the true superior regulator of the hormonal system.[1] The hypothalamus (forming the most ventral part of the diencephalon or 'midbrain') is a key regulator of homeostasis, controlling not only the release of pituitary hormones but also a range of autonomic and behavioural functions including temperature regulation, food and water intake, sleep, circadian rhythms and mediation of emotion. The various nuclei located within the hypothalamus allow signals to pass between the nervous and endocrine system, via the pituitary gland. The hypothalamus receives both hormonal and neural input from the periphery and the brain, and it exerts its action via neural as well as humoral pathways. There are extensive vascular (long portal vessels) and neural (axons in the pituitary stalk) connections between the hypothalamus and the anterior and posterior lobe of the pituitary, as well as a vascular connection between the anterior and posterior lobe via the short portal vessels.[2]

Control of the endocrine system is primarily achieved by negative feedback loops, which not only act as the main form of regulation but are also important in fine-tuning the functions of the hypothalamic–pituitary–peripheral organ axis. The interplay of stimulatory and inhibitory hormones from the hypothalamus and the pituitary hormones is influenced by negative feedback loops between the periphery and central organs, as well as between the pituitary and the hypothalamus (**Figure 56.1**). Positive feedback also exists, primarily in the gonadal axis at the time of puberty and ovulation.[3]

Diagnosing pituitary tumours is often challenging, as symptoms can initially be rather non-specific. In later stages the pituitary mass may lead to local tumour effects,

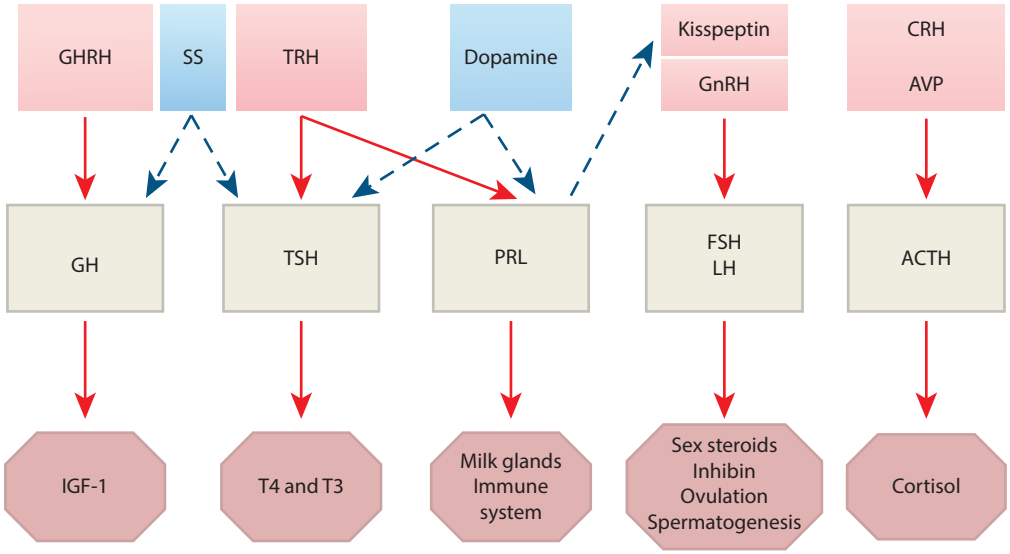


Figure 56.1 Interplay of stimulatory and inhibitory hormones from the hypothalamus and the pituitary hormones. Primary hormone deficiency results from the damage of the peripheral gland or its function, which usually leads to elevated pituitary stimulatory hormone levels. For example, primary hypothyroidism results in high TSH, adrenal failure leads to high ACTH levels, etc. Secondary hormone deficiency is due to damage to the pituitary, such as a pituitary lesion destroying the gland. Tertiary deficiency is due to damage to the hypothalamus. Blue arrows show inhibition; red arrows show stimulatory effects.

Abbreviations: GHRH: growth hormone-releasing hormone; SS: somatostatin; TRH: thyrotrophin-releasing hormone; GnRH: gonadotrophin-releasing hormone; CRH: corticotropin-releasing hormone; AVP: arginine vasopressin; GH: growth hormone; TSH: thyroid-stimulating hormone; PRL: prolactin; FSH: follicle-stimulating hormone; LH: luteinizing hormone; ACTH: adrenocorticotropic hormone; IGF-1: insulin-like growth factor 1; T3: triiodothyronine; T4: thyroxine.

such as headaches and characteristic visual field defects if the tumour is large enough to compress nearby tissues, particularly the optic chiasm.

ANTERIOR LOBE OF THE PITUITARY GLAND

The anterior lobe of the pituitary, the adenohypophysis, comprises approximately 75% of the total pituitary volume. It is functionally linked to the hypothalamus by blood vessels in the pituitary stalk which transmit regulatory hypothalamic hormones to the pituitary. These stimulate or inhibit the synthesis and release of pituitary hormones. The anterior pituitary consists of five major cell types (each secreting specific hormones), organized into cords of cells located around venous sinusoids. The six major hormone products of the anterior pituitary (Table 56.1) are secreted into the sinusoids from which they enter the circulation.

Other less common cells in this area include somatomammotrophs, a rare cell type that secretes both growth hormone (GH) and prolactin (PRL) and a unique star-shaped, non-endocrine cell type, the so-called folliculostellate cell. These cells have been shown to be important for cell-to-cell interaction and regulation within the pituitary.[4] More recently, a few stem cell-like cells have also been discovered in the adult pituitary located mostly at the border of the anterior and posterior lobe ('marginal zone') and their role in pituitary tumorigenesis is currently under investigation.[5, 6]

The growth hormone axis

The existence of a hormone responsible for growth was first proposed by Cushing in the early 1910s but the hormone itself was not isolated until 1956.[7] Growth hormone (GH) is a 191-amino acid polypeptide synthesized by the somatotroph cells, which make up 40–50% of anterior pituitary cells. The main functions of GH are to stimulate growth and regulate cell turnover and repair. At a cellular level, this results in enhanced protein synthesis, facilitating amino-acid transport, mobilizing free fatty acids from adipose tissues, decreasing glucose uptake and increasing gluconeogenesis. The most notable targets of GH are the growth plates of long bones leading to the characteristic increases in bone length seen during childhood, but GH also regulates soft-tissue growth. GH excess in childhood results in overly increased linear bone length and gigantism, while in adults (in whom the epiphyseal plates are now fused, preventing further elongation of the long bones) increases in bone width occur instead, resulting in the characteristic facial and hand/foot changes associated with the diagnosis of acromegaly. Other clinical features of acromegaly include prominent soft-tissue swelling of internal organs, such as the heart, bowels and liver. Cartilaginous enlargement also occurs, leading to rheumatological problems and altered laryngeal anatomy, with resultant deepening of the voice. Finally, as the skull enlarges, the paranasal sinuses also increase in size, particularly the frontal sinuses, and the jaw enlarges with resultant malocclusion and prognathism.

GH acts via the GH receptor (GHR), which belongs to the type I cytokine receptor family. GH binding to the dimerized GHR activates Janus kinase 2 (JAK2) and signal transducer and activator of transcription (STAT) (Figure 56.2). While

TABLE 56.1 Main cell types of the anterior pituitary gland

Cell type	Percentage of total pituitary cells (%)	Hypothalamic regulatory hormone	Hormone secreted	Main target organs
Somatotrophs	45–50	Stimulation: growth hormone releasing hormone (GNRH) and ghrelin Inhibition: somatostain (SST)	Growth hormone (GH)	Liver, muscle, bone, cartilage, adipose tissue
Thyrotrophs	5	Stimulation: thyrotrophin releasing hormone (TRH)	Thyroid-stimulating hormone (TSH)	Thyroid gland
Lactotrophs	10–30	Stimulation: TRH Inhibition: dopamine	Prolactin (PRL)	Mammary gland
Gonadotrophs	10–15	Stimulation: gonadotrohin releasing hormone (GnRH)	Follicle-stimulating hormone (FSH) Luteinizing hormone (LH)	Ovary and testis
Corticotrophs	10–20	Stimulation: corticotrophin releasing hormone (CRH), argenine vasopressin (AVP)	Adrenocorticotrophic hormone (ACTH)	Adrenal gland (cortex)

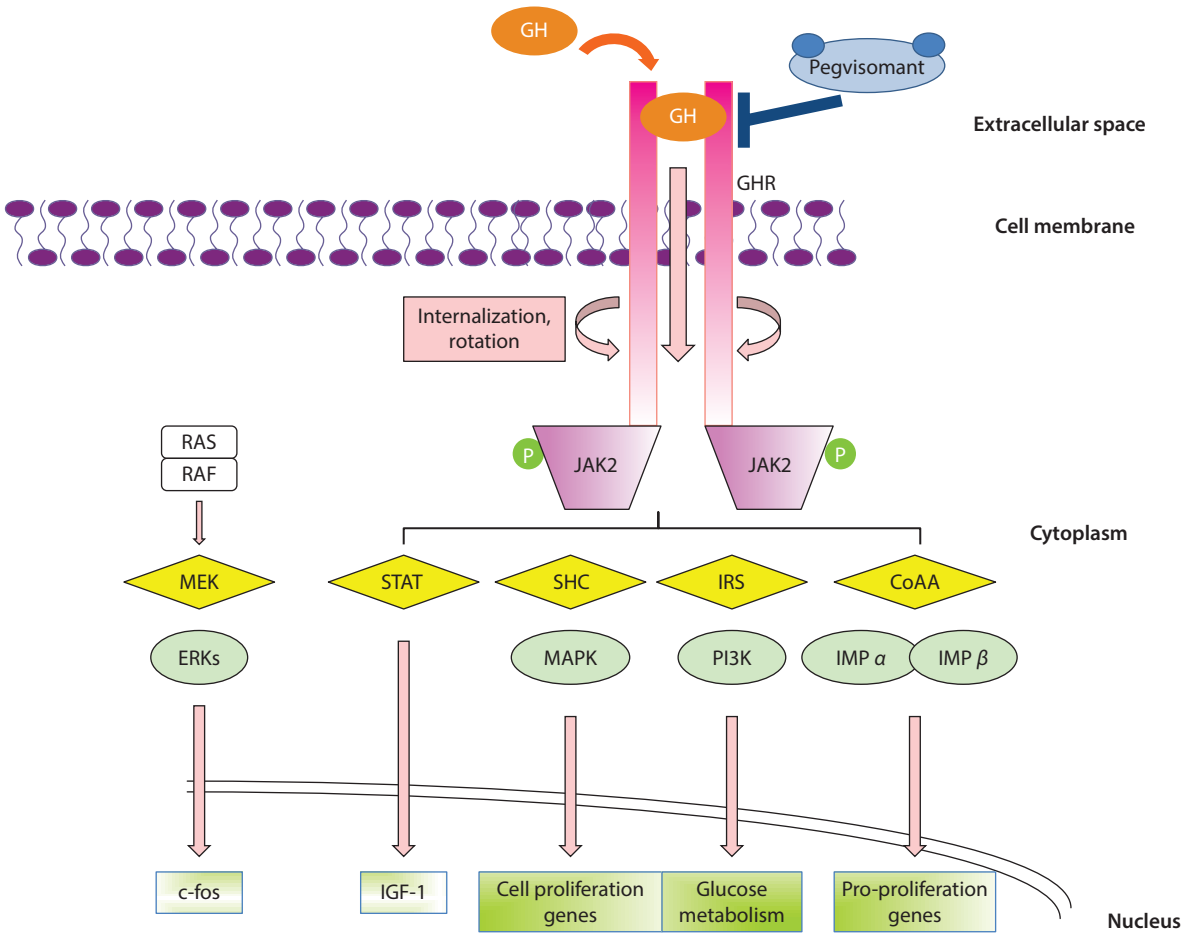


Figure 56.2 GH action. Ligand binding to the pre-formed GHR dimer results in internalization and relative rotation of the subunits in the homodimer, subsequently causing JAK2 phosphorylation (P) and signal transduction. GH signalling may be mediated by JAK2-independent signalling (Src/ERK) pathways. GH targets include IGF-I, c-fos, genes involved in cell proliferation, glucose metabolism and cytoskeletal proteins. IGF-I may also block GHR internalization, acting in a feedback loop. The GHR antagonist pegvisomant used in the treatment of acromegaly, blocks GHR signalling via inhibitory rotation.

Abbreviations: GH: growth hormone; GHR: growth hormone receptor JAK2: Janus kinase 2; P: phosphor group; STAT: signal transducer and activator of transcription; SHC: SH2-containing protein; IRS: insulin receptor substrate; CoAA: nuclear receptor coactivator AA; IMP α/β: importin α/β; MAPK: mitogen-activated protein kinases; PI3K: phosphatidylinositide 3-kinase; ERK: extracellular signal-regulated kinase; MEK: MAP kinase kinase; RAS: rat sarcoma protein family; RAF: rapidly accelerated fibrosarcoma protein kinase family; c-fos: Fos Proto-Oncogene; AP-1: Transcription Factor Subunit; IGF-1: insulin-like growth factor 1.

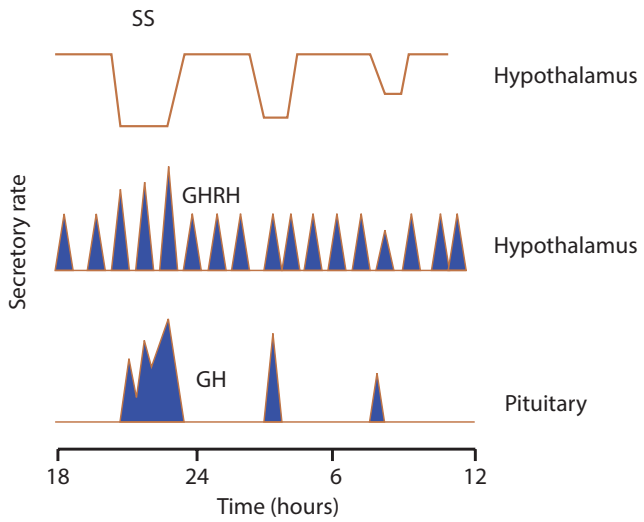


Figure 56.3 Secretion of growth hormone. A simplified schematic representation of pulsatile secretion of growth hormone (GH) in response to growth hormone-releasing hormone (GHRH) and growth hormone inhibitory hormone (SS, somatostatin) impulses. (Adapted from Hartman et al. Temporal structure of *in vivo* growth hormone secretory events in humans. Redrawn from ref.)[9]

GH exerts its direct metabolic effects via this pathway, other effects are exerted through insulin-like growth factor type 1 (IGF-1), synthesized not only in the liver but in all local tissues, and responsible for the growth effects of the hormone. IGF-1 binds to the type 1 IGF receptor, which belongs to the membrane-bound tyrosine kinase receptor family.[8]

GH is secreted in a pulsatile manner (**Figure 56.3**)[9] in response to an interplay of hypothalamic hormones. GH release is stimulated by both growth hormone-releasing hormone (GHRH) and ghrelin (the brain-gut peptide, mainly synthesized by neuroendocrine cells in the gastric mucosa) while somatostatin (SS) is inhibitory in action. Animal data suggest that ghrelin-induced GH release has a role in maintaining glucose levels during fasting.[10] GHRH, SS and ghrelin act by binding G-protein coupled receptors: the GHRH receptor, five major subtypes of SS receptors and the type 1a growth hormone secretagogue receptor (also called ghrelin receptor). Animal data suggest that a tightly regulated network of somatotroph cells, known as 'clusters', allows rapid, large increases in circulating GH levels.

GHRH has a complex regulatory function on GH:

- It causes immediate release via activation of cAMP and Ca2+ in somatotrophs.
- GHRH triggers GH synthesis by stimulating the transcription factor POU class 1 homeobox 1 (PUOF1, previously called Pit1).
- It increases GH cell number.
- It stimulates the formation of GH cell clusters.

An understanding of the second messenger pathway of the GHRH receptor is important, since several genetic defects involving this pathway can result in excess GH secretion and its associated complications (**Figure 56.4**). The stimulatory subtype of the alpha subunit of the G protein (Gsalpha) activates adenylyl cyclase, following which

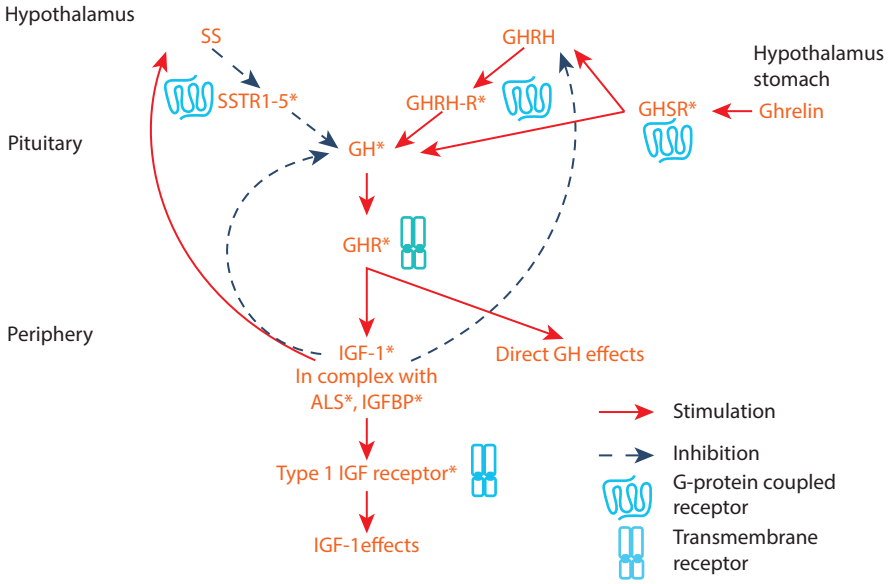


Figure 56.4 Growth hormone axis. A simplified scheme of the growth hormone (GH) axis. Inhibitory somatostatin (SS) and stimulatory growth hormone-releasing hormone (GHRH) impulses coming from the hypothalamus regulate GH release from the pituitary. GH exerts its effects either directly or via IGF-1. GH stimulates IGF-1 synthesis in all peripheral tissues. Circulating IGF-1 primarily represents liver IGF-1 synthesis. Ghrelin is also a potent GH-releasing hormone. IGF-1 regulates GH release via negative feedback to the hypothalamus and the pituitary.

Abbreviations: GH: growth hormone; GHRH: growth hormone releasing hormone; GHRH-R: growth hormone releasing hormone receptor; SS: somatostatin; SSTR1-5: somatostatin receptors 1-5; IGF-1: insulin-like growth factor 1; IGFBP: insulin-like growth factor binding protein; ALS: acid labile subunit.

*Mutations in these components of the pathway have been described in patients presenting with short stature.

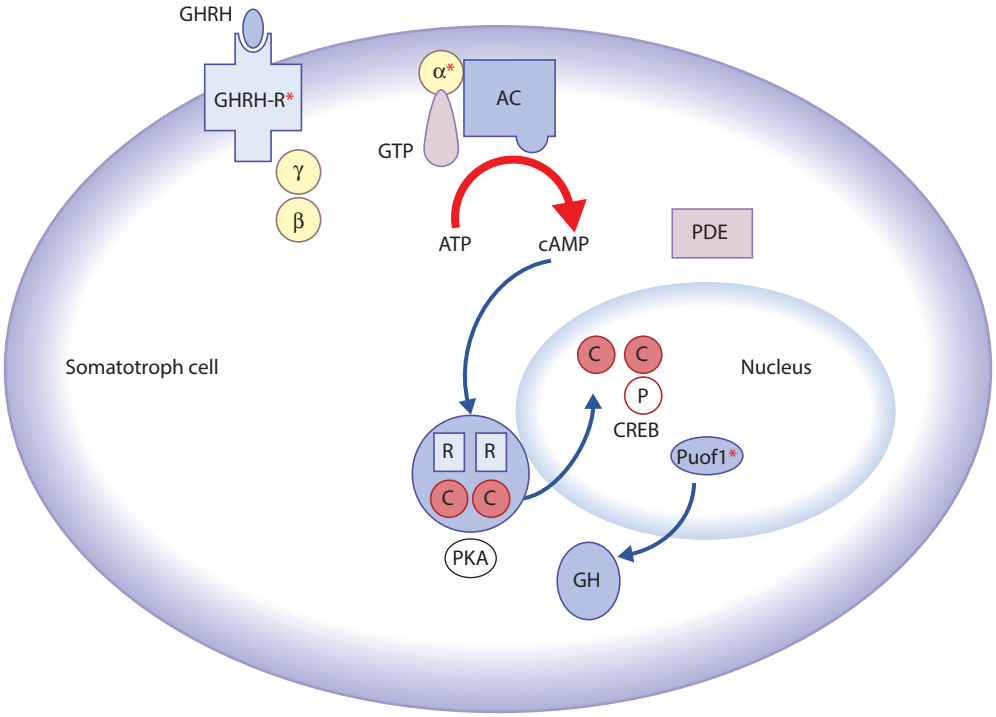


Figure 56.5 Signal transduction in the growth hormone cell. Following ligand binding, the alpha subunit of the Gs protein dissociates from the beta and gamma subunits and activates AC. cAMP is synthesized, and this binds to and inhibits the regulatory subunit (R) of protein kinase A (PKA). The catalytic subunit (C) is now free to enter the nucleus and phosphorylate the CREB, which upregulates GH synthesis. A gain of function mosaic (McCune-Albright syndrome) or somatic mutation (seen in 40% of sporadic acromegaly adenomas) in the Gs alpha subunit (GSP) leads to GHRH-independent upregulation of the pathway. In Carney complex there is a loss of function in the regulatory subunit of PKA, or gain of function of the catalytic subunit leading to cAMP-independent activation of PKA. Alterations are marked with yellow leading to different disease conditions.

Abbreviations: Gs: G-protein adenylate cyclase stimulator; AC: adenylate cyclase; cAMP: cyclic adenosine monophosphate; PDE: phosphodiesterase; PKA: protein kinase A; CREB: cAMO binding element; GH: growth hormone; GHRH: growth hormone releasing hormone; GHRH-R: growth hormone releasing hormone receptor; ATP: adenosine triphosphate; Puof1: pituitary-specific positive transcription factor 1; GSP: stimulatory G protein.

*Mutations in these components of the pathway have been described in patients presenting with short stature.

synthesized cAMP binds and inhibits the regulatory subunit of protein kinase A. The catalytic subunit of protein kinase A phosphorylates the cAMP response element binding protein which in turn upregulates PUOF1 and GH synthesis (Figure 56.5).[11]

GH levels change throughout life. The highest levels occur during puberty, after which there is a gradual decline (Figure 56.6).[12] GH levels also show circadian variation with the highest levels occurring during the night, and low, often undetectable levels during the day. We clinically utilize this circadian rhythm when serial GH samples are taken in the diagnostic workup of GH-excess or GH-deficient patients.[13] IGF-1 circulates in a complex with IGF-binding proteins (mostly IGFBP3). The acid labile subunit and IGF-1 levels are steady during the day and a gradual decline is seen with age, therefore age-specific normal ranges should be used to assess circulating hormone levels.

The regulation of growth and the GH axis is a complex process. It is influenced by various activities such as sleep (GH levels are high during the night), calorie intake (GH levels increase at fasting), exercise (increases GH release) and inflammation (chronic inflammation reduces the activity of the growth axis). Oestrogen stimulates GH release both via the hypothalamus and by direct action on the pituitary gland but it inhibits GH effects via upregulating an inhibitor of GH receptor signalling pathway SOCS2 (suppressors of cytokine signalling 2).[14] Overall, females need higher GH levels to achieve the same IGF-1 level.

The thyroid axis

Thyroid-stimulating hormone (TSH) is synthesized in the thyrotroph cells and its release is triggered by binding of thyrotrophin-releasing hormone (TRH) to the TRH receptor (Figure 56.7). TRH is synthesized in the paraventricular nucleus of the hypothalamus. TSH secretion is inhibited by somatostatin.[3] Interestingly, TRH also stimulates prolactin release from the pituitary. This is clinically relevant since in untreated primary hypothyroidism the high TRH level stimulates prolactin release, leading to hyperprolactinaemia and hypogonadism, which could pose a diagnostic problem if the link were not appreciated.[3] The glycoprotein hormone TSH is a heterodimer comprising two subunits. The alpha subunit, a protein made up from 89 amino acids, is common to TSH, LH, FSH and human choriogonadotrophin (HCG), while the beta subunit (112 amino acids) is specific to TSH. TSH is produced by the thyrotroph cells of

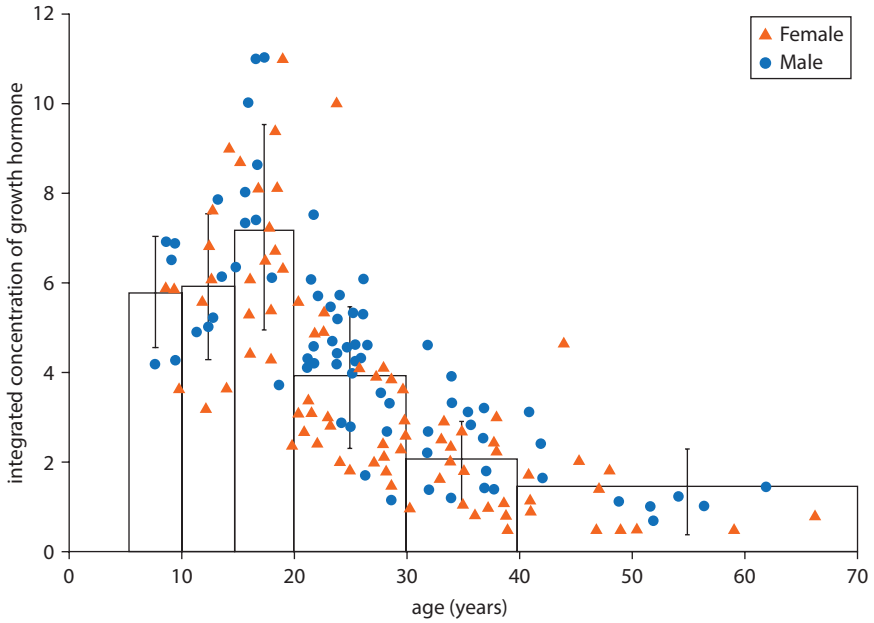


Figure 56.6 The 24-hour integrated concentration of GH. The mean 24-h concentration of growth hormone, designated the integrated concentration levels change throughout life, reaching a peak level during puberty then decreasing by age. Figure adapted from Zadik et al.[12]

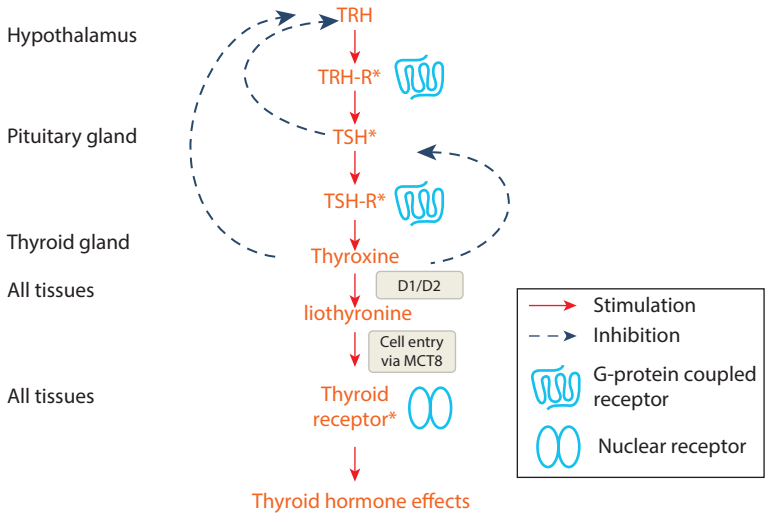


Figure 56.7 Thyroid axis. A simplified scheme of the hypothalamo–pituitary–thyroid gland axis. Hypothalamic hormone TRH stimulates TSH release from the pituitary. TSH binds to the TSH-receptor on the thyroid gland and activates thyroid cells, which results in increased iodine uptake, thyroglobulin synthesis, thyroid peroxidase activity and thyroxine release.

Abbreviations: TRH: thyroid releasing hormone; TRH-R: thyroid releasing hormone receptor; TSH: thyroid stimulating hormone; TSH-R: thyroid stimulating hormone receptor.

* Mutations in these components of the pathway have been described in patients presenting with abnormal thyroid function.

the anterior pituitary and is essential for regulating the thyroid gland and consequently the metabolic activity of the body.[2,3] TSH activates thyroid cells by binding to the TSH receptor, thus stimulating the cAMP pathway, leading to increased iodine uptake, thyroglobulin synthesis, thyroid peroxidase activity and thyroxine release.[15] Iodine is a crucial component of both thyroxine and triidothyronine, and lack of iodine in the diet can lead to reduced thyroid hormone synthesis, therefore elevated TSH due to negative feedback and significant thyroid enlargement (endemic goitre). Recently, 'thyrostimulin', an alternative TSH receptor ligand, has been identified, but its precise physiological role is yet to be elucidated.[16]

Circulating TSH is known to exhibit a circadian rhythm with higher levels during the night and its pulsatile secretion is synchronized with hypothalamic PRL pulses, as TRH has a stimulatory effect on the release of both PRL and TSH.[3] The availability of sensitive TSH assays allows us to diagnose subclinical hypo- or hyperthyroidism. Screening for congenital hypothyroidism using the Guthrie-devised heel-prick blood test relies on sensitive TSH measurements to identify hypothyroidism in neonates 2–3 days old. Recent data suggest that women planning pregnancies should have strictly normal TSH levels for the optimal central nervous system development of the foetus. Patients with pre-existing thyroid hormone replacement need usually increase the dose of hormone replacement during early stages of pregnancy.

Thyroid cells synthesize thyroxine (T4) and in smaller amounts its active derivative triidothyronine (T3), which has a much shorter half-life. Thyroid hormones circulate in the bloodstream in a ratio of approximately 20:1 T4:T3,

bound to thyroglobulin (Tg), which is synthesized by the follicular cells of the thyroid gland. Thyroglobulin levels can be used as tumour markers in patients with papillary or follicular thyroid cancers, hence regular Tg level monitoring may facilitate detection of early recurrence. Sex steroids can alter thyroglobulin synthesis, so measurement of free thyroid hormones (fT4 and fT3) is a better reflection of thyroid status.[17] T4 is converted to the active T3 form in peripheral tissues; T3 is inactivated by conversion to reverse T3 (under the influence of D3 deionidase enzyme). Deiodinase enzymes contain selenium, therefore dietary selenium insufficiency can result in low T3 levels and there is now evidence that selenium supplements are beneficial for patients with Graves' ophthalmopathy.

Thyroid disease is one of the most common endocrine diseases. A wide range of congenital and acquired aetiologies underlie thyroid disease including: euthyroid goitre (due to mild iodine deficiency), thyroid nodules, thyroid cancer, autoimmune hypothyroiditis (Hashimoto's thyroiditis) or hyperthyroidism (Graves disease), contrast agent- or amiodarone-induced abnormalities, TSH-secreting pituitary tumours and a range of genetic syndromes affecting pituitary transcription factors. Less common causes include sick euthyroid syndrome, where the patient's blood tests demonstrate a pattern of thyroid hormone alterations during non-thyroidal illness with normal TSH, low total T4, fT3 and elevated reverse T3 levels,[18] and Pendred syndrome, a congenital autosomal recessive disease which results from a mutation in the iodine/chloride transmembrane transporter pendrin. In thyroid cells, pendrin transports iodine from the cytoplasm to the colloid, where it is organized into thyroglobulin during thyroid hormone synthesis. Mutations in this transporter cause progressive bilateral high-frequency sensorineural hearing loss (often secondary to minor head trauma) possible vestibular dysfunction and abnormal thyroid hormone synthesis with goitre developing in early puberty/young adulthood.[18] This condition is often associated with Mondini malformation of the cochlea and enlarged vestibular aqueducts.

Prolactin

The lactotroph hormone prolactin (PRL) was discovered in the early 1930s and was named for its effect on lactation and mammary gland development.[19] Both PRL (198 amino acid protein) and its receptor share similarities with GH. Primarily synthesized and secreted by the lactotroph pituitary cells,[20] PRL is also secreted by extrapituitary sites such as the mammary gland, placenta, uterus and T lymphocytes.[21] The most prominent effects of prolactin are the effect on milk production, inhibition of the gonadal axis and regulation of immune function. Its hypothalamic control is different from other pituitary hormones. The hypothalamus has a primary inhibitory input on prolactin synthesis and release, therefore any damage to the hypothalamus or pituitary stalk can result in hyperprolactinaemia.[19]

Prolactin levels in maternal blood rise from the fifth week of pregnancy and peak at parturition. Loss of placental oestrogen and progesterone disinhibits the milk ejection response to suckling.[2, 20] Basal prolactin level typically returns to normal within a couple of weeks after the delivery, but each nursing episode results in temporarily increased PRL secretion.[2] Prolactin exerts its inhibitory action on the gonadal axis via inhibiting kisspeptin release from the kisspeptin neurons.[23] Furthermore, it has been shown to counteract the effects of dopamine on sexual arousal (dopamine rises during intercourse and decreases rapidly afterwards), which may explain the decreased libido frequently reported by patients suffering from hyperprolactinaemia. TRH stimulates prolactin release and this is of clinical importance in primary hypothyroidism, since mild hyperprolactinaemia frequently accompanies primary hypothyroidism.[19–21]

Although high prolactin is a typical sign of a prolactin-secreting pituitary adenoma (prolactinoma), the differential diagnosis of hyperprolactinaemia is broad. High prolactin levels occur physiologically during pregnancy, stress and exercise. PRL can be elevated by administering dopamine antagonist drugs including psychotropic drugs (used to treat depression and schizophrenia), as well as verapamil, metoclopramide, opiates, cocaine and protein inhibitors, even after short-term use. It is also affected by some medicinal herbs, such as star anise, fenugreek, fennel seeds and red clover.[2] Other causes of raised prolactin levels include polycystic ovary syndrome (PCOS), herpes zoster infection of the chest, thoracic surgery, renal failure and liver cirrhosis.[24, 25] PRL levels can double due to stress, increase to 5 times the upper limit of normal due to stalk effect (pituitary stalk compression), increase 5–10 times due to small microadenomas or drugs, and 10–100+ times due to larger adenomas. Pituitary-dependent hyperprolactinaemia can result from a prolactinoma or an adenoma (endocrinologically active or inactive) compressing the pituitary stalk, preventing dopamine (prolactin release inhibiting hormone) reaching lactotrophs.[26, 27] Prolactin-secreting tumours lead to inhibition of the gonadal axis and can induce galactorrhoea and cause local tumour effects. Small adenomas (microprolactinomas, <1 cm) are more commonly identified in females, while males usually harbour macroprolactinomas (>1 cm) at presentation. In the majority of the cases dopamine agonist drugs (cabergoline or bromocriptine) have an excellent effect both on hormone reduction and on tumour shrinkage.[24, 25] Prolactinomas can be part of multiple endocrine neoplasia type 1 syndrome (MEN1) which is associated with hyperparathyroidism and pancreatic adenomas.

The gonadal axis

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are glycoprotein hormones. Although they are both synthesized in the gonadotroph cells and regulated by the same stimulatory hypothalamic hormone gonadotroph-releasing hormone (GnRH), their levels vary considerably during the female cycle. The frequency of GnRH pulses is the main determinant of this differential regulation with slow pulses leading to FSH release and rapid pulses to LH release.[3] Numerous further factors regulate the system (**Figure 56.8**). Pulsatile GnRH secretion is an important hallmark of gonadal regulation. If continuous GnRH secretion is present, the GnRH receptors in the

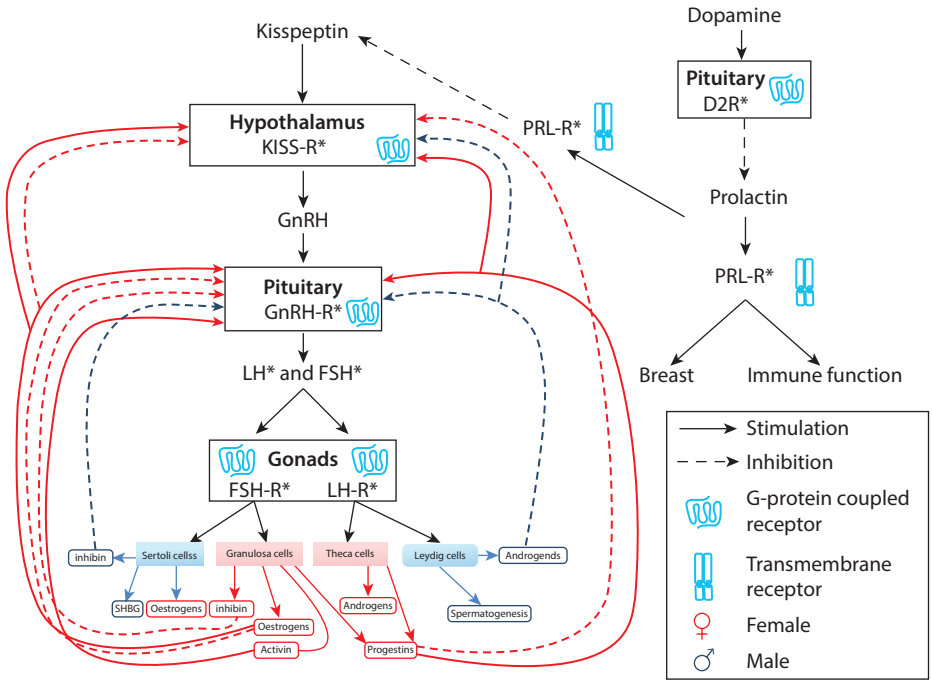


Figure 56.8 Gonadal axis. A simplified scheme of the gonadal axis. Hypothalamic hormone GnRH stimulates LH and FSH release from the pituitary gland. Prolactin inhibits the gonadal axis by inhibiting kisspeptin release from the kisspeptin neurons in the hypothalamus. As shown in the diagram, there are differences between male (blue lines) and female (red lines) with respect to signalling and feedback loops. SHBG (in the testis, also called androgen binding protein).

Abbreviations: KISS-R: kisspeptin receptor (also known as GPR54); GnRH: gonadotrophin releasing hormone; LH: luteinising hormone; LH-R: luteinising hormone receptor; FSH: follicle stimulating hormone receptor; SHBG: sex hormone binding globulin; D2R: dopamine receptor 2; PRL-R: prolactin receptor.

*Mutations in these components of the pathway have been identified in patients with abnormal gonadal hormone synthesis.

pituitary desensitize and the gonadal axis is turned off. This phenomenon is utilized in treatment of some diseases where gonadal steroids need to be inactivated, such as prostate cancer, breast cancer and endometriosis, or when premature puberty needs to be delayed.[28] Patients with tertiary hypogonadism (hypogonadotrophic hypogonadism) can be treated with pulsatile GnRH treatment using a pump device.[28]

Secretion of GnRH is primarily regulated by 17β-oestradiol (E_2) acting via oestrogen receptor alpha (ERα). However, as GnRH neurons do not express ERα, regulation of hypothalamic function by oestradiol is mediated by kisspeptin neurons, which do express this receptor and are thought to relay information regarding oestrogen levels directly to the GnRH neurons.[29] In addition, the inhibitory feedback of prolactin on the gonadal axis occurs via kisspeptin, as GnRH neurons do not express prolactin receptors either, therefore rendering them insensitive to circulating prolactin levels.[30] Kisspeptin and its receptor KISS-R (G-protein-coupled receptor 54, GPR54) are recently identified members of the gonadotroph axis. Kisspeptin is synthesized in several hypothalamic nuclei including the arcuate nucleus and the preoptic area. More recently, a gonadotrophin inhibitory hormone (GnIH) has been described in birds.[31] The role of its mammalian counterpart RFamide-related peptide (RFRP) and its putative G-protein coupled receptor OT7T022 (also known as neuropeptide FF receptor type 1) is currently under investigation.

There is an interesting interface between the gonadal axis and the olfactory system. During embryogenesis, GnRH cells are located at the top of the nasal cavity together with cells of the olfactory system. GnRH cells then migrate to the hypothalamus. Patients with loss-of-function mutations in peptides involved in this migration develop hypothalamic hypogonadism. When this condition occurs in combination with decreased sense of smell, either partial (hyposmia) or total (anosmia), the underlying condition is referred to as Kallmann syndrome.[32] From an ENT perspective, the condition is associated with craniofacial defects such as cleft palate and sensorineural hearing loss.

LH

In females, LH is responsible for follicular development, ovulation and development of the corpus luteum, while in the male it acts on Leydig cells within the testis, stimulating testosterone production.[2] Binding to the G-protein-coupled transmembrane receptor, the luteinizing hormone receptor (LH-R) exerts its effects on the ovarian theca cells to enhance oestrogen production of the granulosa cells. At the beginning of the cycle, FSH stimulates these granulosa cells, leading to elevated oestrogen levels and follicular maturation. Elevated oestrogen levels may lead to ovulation by a positive feedback effect on arcuate kisspeptin neurons that stimulate GnRH, thus leading to sudden LH release. This 'LH surge' acts as the trigger for

ovulation, resulting in the egg leaving the follicle and the follicle beginning to become the corpus luteum, secreting progesterone to make the endometrium ready for implantation.[2]

Slightly elevated LH levels are observed in polycystic ovary syndrome and precocious puberty. Marked elevation is typically due to the lack of gonadal negative feedback, which results in excessive production of LH and FSH in the anterior pituitary, such as in primary ovarian failure and the menopause. Low LH levels are associated with hyperprolactinaemia, eating disorders and certain congenital conditions where patients present with infertility. Synthetic LH-analogues (such as human chorionic gonadotropin – better known as HCG) are commonly used for ovulation induction and managing male infertility.

FSH

FSH stimulates follicular growth. Its level drops after the follicle has reached full maturation but rises slightly again at the end of the menstrual cycle, contributing towards the initiation of the next cycle. In males, FSH stimulates the gonadal Sertoli cells to produce spermatozoa as well as inhibin, which in both females and males inhibits FSH production. Low FSH secretion can be observed in conditions resulting in infertility and loss of gonadal functions.[2] High FSH is an early sign of the menopause or primary gonadal damage (e.g. autoimmune or cytostatic-induced). Synthetic FSH is available for ovulation induction or induction of spermatogenesis.

The hypothalamic–pituitary–adrenal axis

Adrenocorticotropic hormone (ACTH), secreted by corticotroph cells, is derived from the pro-hormone pro-opiomelanocortin (POMC). Typically produced in response to stress, ACTH functions to increase production and release of corticosteroids. It stimulates cortisol synthesis and release from the adrenal cortex (but it also has some effect on aldosterone and androgen secretion) (Figure 56.9).[2] ACTH release from the pituitary is regulated by corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP), both synthesized in the paraventricular nucleus. The latter hormone reaches the anterior pituitary gland via the short portal vessels.[2]

Nearly all types of stress, physical or emotional, and food intake lead to immediate and significant increase in ACTH and cortisol secretion.[2] There is a prominent circadian rhythm operating in the HPA axis, with high hormone levels in the early morning hours. This is followed by a gradual reduction in hormone levels through the day such that cortisol levels during the night are undetectable.[2]

In addition, ACTH secretion has a superimposed pulsatile release pattern. The increase in cortisol is crucial for the appropriate stress response of the body and, if the hypothalamic–pituitary–adrenal (HPA) axis is compromised, cortisol treatment is life-saving in stress situations such as infection or surgery. Since ACTH is derived from POMC, conditions that lead to synthesis of large amounts of ACTH will also result in accumulation of other POMC-derived peptides. Raised levels of the alpha melanocyte-stimulating hormone lead to characteristic

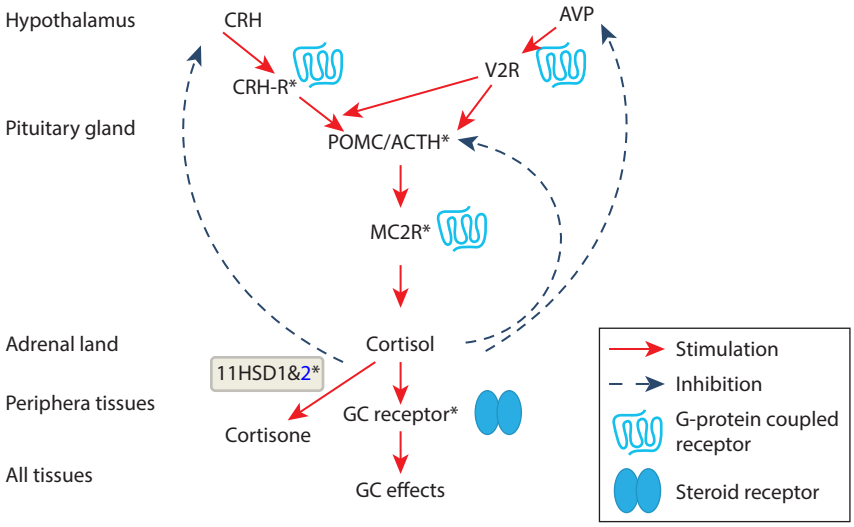


Figure 56.9 Hypothalamic–pituitary–adrenal (HPA) axis. A simplified scheme of the hypothalamic–pituitary–adrenal (HPA) axis. The hypothalamic hormone CRH stimulates ACTH release. Arginine vasopressin (AVP), which is also a hormone of the posterior pituitary and has a role in regulating water balance, is another significant stimulator of ACTH. Its main effect is acting synergistically with CRH, but it also has a direct effect on the pituitary. It has been suggested recently that CRH is the basis of constant basal release of ACTH, while AVP adds peaks in stress situations. ACTH binds to its receptor MC2R and stimulates cortisol release. Cortisol may undergo alteration via the 11 beta hydroxysteroid dehydrogenase type 1 and 2 (11HSD1&2) before binding the glucocorticoid receptor.

Abbreviations: CRH: corticotrophin releasing hormone; CRH-R: corticotrophin releasing hormone receptor; POMC: pro-opiomelanocortin; ACTH: adrenocorticotropic hormone; MC2R: melanocortin 2 receptor; GC: glucocorticoid; HSD: hydroxysteroid dehydrogenase enzymes.

* Mutations in these components of the pathway have been identified in patients with abnormal HPA axis hormone synthesis.

darkening of the skin. This phenomenon is seen in adrenal insufficiency, ectopic ACTH-secreting tumours and Nelson syndrome.

Abnormalities can occur in the HPA axis at several levels. Depression can cause chronic central stimulation of the HPA axis. ACTH-secreting adenomas, ectopic ACTH-secreting tumours and adrenal cortisol-secreting tumours lead to Cushing's syndrome. Cushing's syndrome is a hormone disorder that results from high levels of cortisol in the blood, while Cushing's disease refers to one specific cause of Cushing's syndrome, a corticotroph adenoma in the pituitary gland that produces large amounts of ACTH. POMC mutations lead to glucocorticoid deficiency together with altered skin colouring and obesity due to the lack of ACTH and alpha melanocyte-stimulating hormone. Damage to the adrenal gland (causes include autoimmune and infective, e.g. tuberculosis) results in Addison's disease (primary adrenal insufficiency). Familial glucocorticoid deficiency arises secondary to mutations in the *MC2R* or its accessory protein MRAP (*MC2R* accessory protein), and further genes have been recently identified in the steroidogenic pathway. Abnormalities in the steroid synthesis pathway (as seen in congenital adrenal hyperplasia) may lead to glucocorticoid deficiency in some cases. Finally, abnormalities in the pre-receptor metabolism of cortisol or mutations in the glucocorticoid receptor itself will also lead to abnormalities in the HPA axis.

The most common and clinically relevant situation regarding the HPA axis occurs in patients receiving exogenous glucocorticoid treatment, usually in the form of prednisolone or dexamethasone. In these patients the endogenous HPA axis is suppressed and they do not exhibit a normal stress hormone response. For infections, doubling the standard glucocorticoid replacement dose is advisable; for surgery, intra-muscular 100 mg hydrocortisone every 8 hours for 24 hours and then oral treatment in gradually decreasing doses is recommended.

POSTERIOR LOBE OF THE PITUITARY GLAND

The posterior lobe of the pituitary gland, the neurohypophysis, consists of nerve fibres originating from the supraoptic and paraventricular nuclei of the hypothalamus. The supraoptic and paraventricular nuclei synthesize two cyclic nonapeptides. The resulting hormones are known as arginine vasopressin (AVP, previously known as antidiuretic hormone, ADH) and oxytocin, respectively (**Figure 56.10**). The hormones are transported to the posterior lobe of the pituitary gland via the pituitary stalk, loosely bound to their carrier protein neurophysin. Within the posterior lobe of the pituitary, nerve axon terminals are located close to blood vessels. Upon activation, the secretory granules rapidly release the hormones by a calcium-dependent exocytic process,[2] allowing them to diffuse into the local capillary network. The role of AVP in rapid ACTH release has been well described.[2]

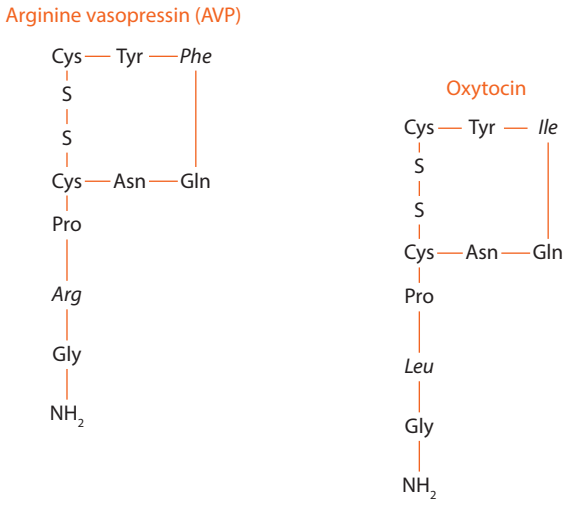


Figure 56.10 The chemical structure of arginine vasopressin (AVP) and oxytocin. Both AVP and oxytocin are nine amino acid peptide hormones (nonapeptides) released from the posterior lobe of the pituitary gland. Their structural similarity (they have all but one amino acid in common) may be the reason behind their functional similarities.

Arginine vasopressin

Arginine vasopressin (AVP) is primarily produced in response to reductions in plasma volume and/or increased plasma osmolality.[2] The plasma half-life of AVP is relatively short (15–30 minutes) therefore plasma levels can vary greatly over short periods of time.[33] AVP regulates renal excretion of water and is the primary determinant of urine concentration. Very small amounts of AVP can have a significant inhibitory action on water excretion in the kidneys, an effect known as antidiuresis. AVP is released from the posterior hypothalamus in response to increases in plasma osmolality (**Figure 56.11**). As more water is reabsorbed, the urine becomes more concentrated. Certain drugs can modify AVP plasma levels: for example, ethanol, mineralocorticoids and glucocorticoids decrease AVP level, while selective serotonin reuptake inhibitors (SSRIs), nicotine and carbamazepine can increase its level in peripheral blood.

The precise mechanism by which increased plasma osmolality triggers AVP release is yet to be elucidated; however, it is suggested that osmoreceptor cells release water upon higher fluid concentration via osmosis, ultimately leading to increased AVP production and secretion in the hypothalamus and neurohypophysis.[2] In addition to increasing osmolality, carotid, aortic and pulmonary baroreceptors detect the resulting hypotension, which stimulates vasopressin release (**Figure 56.12**).[2]

In patients with complete absence of AVP, the collecting tubules and ducts are almost impermeable to water resulting in daily fluid loss of up to 20 litres via the urinary tract.[2, 34]

Insufficient AVP or reduced AVP action results in production of excessive amounts of inappropriately dilute urine, a hallmark of diabetes insipidus (DI). This disease can be either central (hypothalamic) or nephrogenic. In central DI there is a defect in AVP synthesis or secretion, typically due to pituitary stalk damage, head trauma,

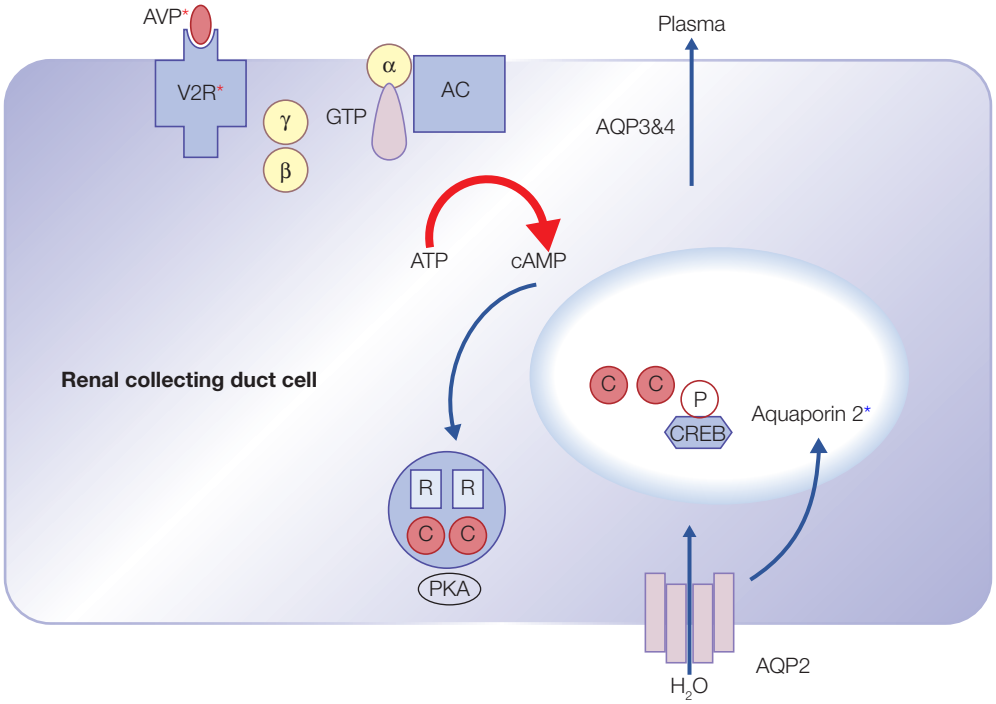


Figure 56.11 Signal transduction in the renal collecting duct cell. Following the binding of AVP by the V2R, the alpha subunit of the Gs protein dissociates from the beta and gamma subunits and activates adenylyl cyclase. cAMP is synthesized, which binds to and inhibits the regulatory subunit (R) of protein kinase A (PKA). The catalytic subunit (C) can enter the nucleus and phosphorylate the cAMP binding element (CREB), which upregulates aquaporin 2 synthesis. Four AQP2 molecules assemble to create a water channel at the luminal border, allowing water to be reabsorbed from the collecting duct back to the cell, and then via AQP3 and AQP4, from the cell back to the plasma.

Abbreviations: AVP: argenine vasopression; V2R: vasopressing type 2 receptor; AC: adenylate cyclase; GTP: guanosine triphosphate; ATP: adenosine triphosphate; cAMP: cyclic adenosine monophsphate; PKA: protein kinase A; CREB: cAMP binding element; AQP2: aquaporin 2.

*Mutations in these components of the pathway have been identified with abnormal function.

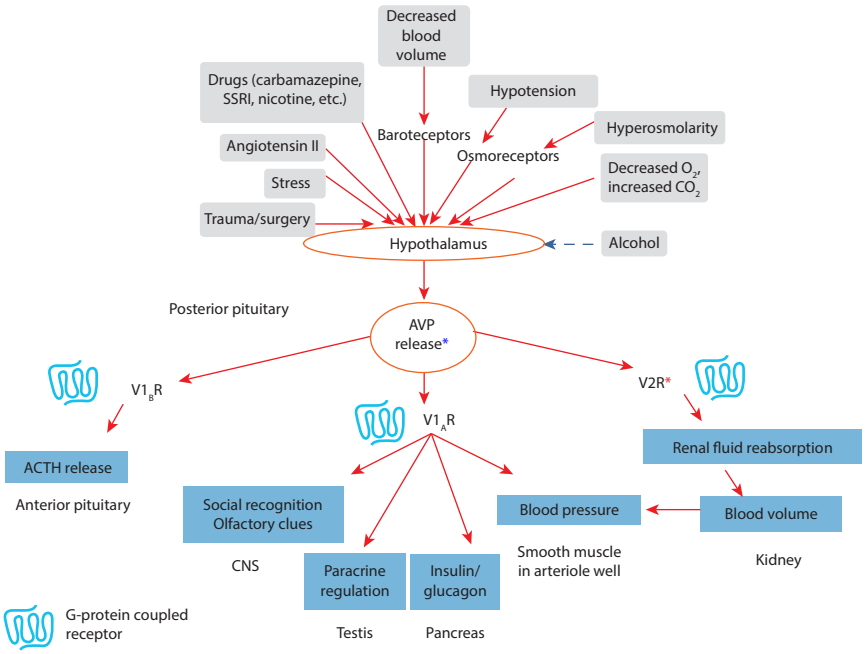


Figure 56.12 Regulation of AVP release. AVP release stimulators increase AVP release from the posterior pituitary. AVP then acts via three receptor subtypes: V1AR, V1BR and V2R. V1AR and V1BR are responsible for the vasoconstrictive effect, and V2R for the antidiuretic effect.

Abbreviations: AVP: argenine vasopressin; VR: vasopressin receptors 1A, 1B and 2; CNS: central nervous sytem; ACTH: adrenocorticotrophic hormone.

*Mutations in these components of the pathway have been identified with abnormal function.

infection or tumour or mutation in the AVP gene; in nephrogenic DI the kidneys are unable to respond to AVP because of renal disease or a mutation in the vasopressin type 2 receptor (V2R) or in aquaporin 2 (AQP2).

Central DI is managed by administering an exogenous AVP analogue. The analogue used in clinical practice is desmopressin, which, with its strong antidiuretic but relatively low vasopressive effect, is a good therapeutic option not only in central DI but also as treatment for enuresis in children. In nephrogenic DI, thiazide diuretics can be beneficial (inhibiting reabsorption of sodium (Na^+) and chloride (Cl^-) ions from the distal convoluted tubules in the kidneys by blocking the thiazide-sensitive Na^+-Cl^- symporter as well as increasing calcium reabsorption at the distal tubule). In contrast, the syndrome of inappropriate antidiuretic hormone (SIADH or Schwartz-Bartter syndrome) is characterized by excessive release of AVP from the posterior pituitary gland or from neuroendocrine tumours, typically small-cell carcinoma of the lung. This is treated using V2R antagonists, which block the V2R receptors in the collecting duct and therefore result in aquaresis (excretion of water that is free of electrolytes). V2R blockers must be used cautiously since rapid reversal of hyponatraemia carries a risk of severe central nervous system complications.

Oxytocin

Oxytocin was first discovered by British pharmacologist Sir Henry Dale in 1906.[35] The name (derived from the Greek words meaning 'quick birth') refers to its well-known role in stimulation of uterine-contraction during delivery.[35] Oxytocin acts via receptors which activate the phospholipase signalling pathway.[36–38] Plasma oxytocin levels are markedly elevated in late pregnancy and during labour, but sexual activity and stress also stimulate its release. In addition to its role in inducing uterine contractions during labour, oxytocin also plays a major role in the process of milk-ejection of the breasts. The trigger for oxytocin secretion is the suckling itself. Activation results in release of oxytocin that acts on myoepithelial cells that lie around the alveoli of mammary glands, triggering contraction (**Figure 56.13**). Approximately 30–60 seconds after suckling starts, milk begins to flow. This whole process is referred to as the 'let-down reflex'.[2] Despite the fact that suckling is a unilateral stimulus, both breasts will start to produce milk. The importance of emotional cues are clear from observations that hearing the baby crying (or even cuddling the baby) provides sufficient emotional signal to the hypothalamus to trigger milk ejection.[2] Oxytocin released during breastfeeding also plays a role in reduction of uterine size after birth by stimulation of contractions.

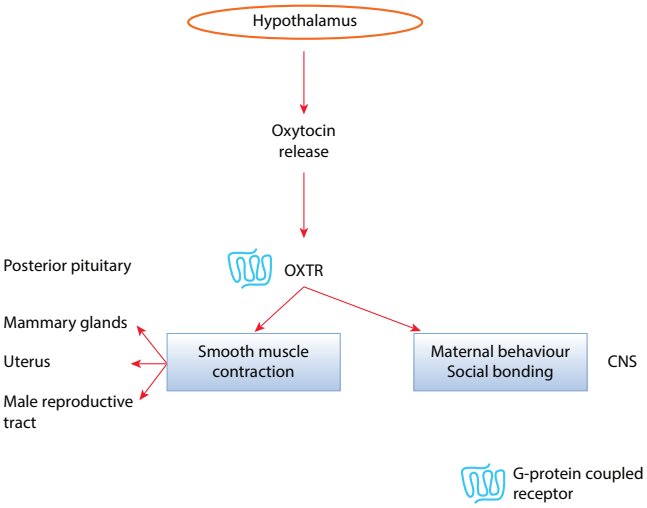


Figure 56.13 Oxytocin effects. Upon hypothalamic stimulation, the posterior pituitary releases oxytocin that binds to its receptor on target smooth muscle cells of the mammary glands and uterus, leading to their contraction. This results in lactation and uterine contractions. It has also been observed that oxytocin in the central nervous system (CNS) plays a role in social bonding and maternal behaviour, and more recently it has been referred to as the 'love hormone'.

Abbreviations: OXTR: oxytocin receptor; CNS: central nervous system.

Extensive research over the past few years has revealed the role of oxytocin in social recognition, pair bonding, maternal behaviour and sexual interaction as well as social anxiety.[39] Oxytocin has gained fame as the 'love hormone', with recent studies implying that it has a determining role in bonding between mothers and their babies,[40, 41] as well as in establishing long-term relationships and falling in love.[42] Recent human studies showed that intra-nasal oxytocin induces increased eye contact and trustful behaviour.[43, 44] CNS effects modulating both the neuronal and behavioural processes associated with alcohol, cocaine and opiate administration in rodents were described,[45, 46] extending possible therapeutic indications to various psychiatric disorders, including drug addiction.[36] A large number of studies have outlined the possible use of intra-nasal oxytocin in behavioural and neural disorders with minimal side effects.[47]

CONCLUSION

The pituitary gland is the central regulator of peripheral hormones. Due to the vicinity of the cells regulating different pathways, abnormalities in the gland can result in a complex pattern of signs and symptoms providing diagnostic and therapeutic challenges.

KEY POINTS

- Pituitary function affects multiple aspects of growth and metabolism.
- Pituitary hormones usually work in tightly controlled feedback loops.
- Both hormone excess and deficiency can lead to complex endocrine disease with multi-system effects.

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CHAPTER 57

IMAGING IN HEAD AND NECK ENDOCRINE DISEASE

Steve Colley and Sabena Fareedi

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: thyroid, parathyroid, pituitary gland and pituitary tumour.

THYROID GLAND

INTRODUCTION

Ultrasound (US) is the primary imaging modality used to assess size, morphology and pathology of the thyroid gland, and it is the best method for assessing thyroid nodules and possible thyroid cancer. In addition it has the benefit of being able to assess neck lymphadenopathy, and guide appropriate fine-needle aspiration (FNA) for cytological diagnosis.

Since US cannot penetrate bone or air-containing structures, computed tomography (CT) is used to assess the degree of retrosternal extension of thyroid masses. It is also used to image the chest in cases of thyroid malignancy. Magnetic resonance imaging (MRI) is rarely used to assess the thyroid but can occasionally help assess potential tracheal cartilage invasion by cancer.

Positron emission tomography (PET-CT) is sometimes used in the follow-up imaging of thyroid cancer. Thyroid scintigraphy is used less commonly to assess thyroid nodules, with the majority of nuclear isotope scans being therapeutic ^{131}I to treat potential thyroid cancer metastases.

Thyroid nodules and thyroid cancer

Nodules within the thyroid are ubiquitous. Palpable nodules occur in up to 4% but are seen on imaging studies in up to 60–70% of patients, the incidence increasing with age.

US is the best imaging method to assess thyroid nodules. No single US sign has high enough sensitivity or specificity to confirm or exclude malignancy, but a combination of signs or US features can be used in summation to provide an excellent guide to the risk of underlying malignancy. Multiple papers confirm the ability of US to 'risk stratify' nodules and provide an accurate assessment, firstly of whether an FNA is required and secondly which nodule should be sampled.[1, 2] Further technology such as US elastography, assessing how firm or compressible a nodule is, have been shown in some studies to assist in this regard.

Features associated with benign nodules[3] are cysts, predominantly cystic nodules with thin septations, cysts with thin peripheral isoechoic tissue, spongiform nodules (microcystic spaces comprising over 50% volume of a nodule), isoechoic well-defined nodules and multiple nodules similar in appearance to isoechoic largely replacing the normal thyroid parenchyma.

Indeterminate or follicular lesions tend to be well defined and iso- to hyperechoic, usually with a thin, low echogenicity halo and often increased internal blood flow. These lesions are usually benign (follicular adenoma), but cytology/biopsy cannot exclude a follicular carcinoma and diagnostic hemithyroidectomy should be considered.

There are a number of US features strongly associated with malignancy: a solid hypoechoic appearance, ill-defined nodule margins, a taller-than-wide shape, and microcalcifications all suggest papillary thyroid cancer and are considered suspicious US features. By using these four characteristics as a guide to FNA of nodules, we can reach a NPV for presence of thyroid cancer of 97%,[4] without undertaking biopsy of the majority of thyroid nodules. If we then consider FNA of well-defined hyperechoic nodules with a peripheral halo (i.e. follicular lesions),

our performance is even better. Abnormal neck nodes, either cystic or containing microcalcification, also raise the likelihood of thyroid cancer and usually warrant FNA.

Nodule size and nodule growth have been shown to have poor correlation with underlying thyroid cancer and should not be used as a guide for FNA, but rather the nodule appearances should guide management.

Medullary cancers look very similar to papillary cancers (i.e. solid, hypoechoic, ill-defined), but calcifications are described as more globular in nature. Follicular carcinomas are diagnosed on pathology post excision, not imaging or cytology. Anaplastic cancers, thyroid lymphoma and thyroid metastases from alternate primaries all appear as large, low-echogenicity masses, often with a rapidly progressive history.

Scoring systems, such as the Mayo Clinic Thyroid Ultrasound Chart and the new British Thyroid Association guidelines for the management of thyroid cancer[5] can assist in risk stratifying nodules and improve patient care by reducing unnecessary FNA, speeding up patient pathways and reducing costs.[6]

Benign thyroid disorders

GRAVES' DISEASE

The thyroid gland appears diffusely hyper-reflective on US without nodules. An increase in intrinsic blood flow is seen on Doppler imaging.

HASHIMOTO'S THYROIDITIS

The thyroid is diffusely hypoechoic, often with hyperechoic fibrous bands seen between the areas of affected thyroid. The gland may be of normal size or enlarged. Increased internal blood flow may be seen.

MULTINODULAR GOITRE

The role of imaging in multinodular goitre is to identify the extent of thyroid enlargement (retrosternal extension, superior and inferior extent), tracheal deviation or narrowing, and the presence of any suspicious nodules or masses to suggest whether there may be a thyroid malignancy present.

Ultrasound outperforms CT and MRI in the assessment of the nodules within a goitre. The presence of multiple isoechoic nodules throughout both lobes, with varying degrees of cystic change, is almost certainly due to benign disease and does not represent the pattern of thyroid cancer.

Malignant thyroid disease

Papillary carcinoma is the most common thyroid malignancy. On US, papillary cancer demonstrates four cardinal signs: solid and hypoechoic, ill-defined margins, microcalcifications and a 'taller-than-wide' shape. If none of these four features is present, then the negative predictive value (NPV) for absence of thyroid cancer is in excess of 97%.[4] Papillary cancers may be multifocal and occasionally may be partially cystic; in this setting, it is the appearance of the solid portion of the mass that should be assessed with US.

CT and MRI less reliably show the features of thyroid cancer and rely on extrathyroidal extension or a large ill-defined thyroid mass.

Nodal metastases may be detected by US, CT or MRI. Typically, abnormal nodes from metastatic thyroid cancer show microcalcification or have a propensity for cystic change.

FOLLICULAR CANCER

Unlike papillary cancer, follicular cancer tumours are solitary. Lesions tend to be well defined and iso- to hyperechoic to normal thyroid, with a well-defined peripheral low-echogenicity halo and often prominent internal blood flow.

Metastatic lymph nodes are uncommon. Tumours tend to metastasize to bone and lungs. Tumours tend to take up ^{131}I, and this can be used to treat and follow up metastatic deposits.

ANAPLASTIC THYROID CANCER

Almost exclusively seen in older patients, anaplastic carcinoma has a poor prognosis due to its rapid progression. On US, a large, ill-defined solid low-echogenicity mass with extra thyroidal spread and nodal metastases is typical.

THYROID LYMPHOMA

Extranodal lymphoma of the thyroid may occur following long-standing thyroiditis. Appearances are of a large, hypoechoic mass, which can be indistinguishable from anaplastic carcinoma, requiring core biopsy to differentiate between the two pathologies.

PARATHYROID GLANDS

The parathyroid glands are derived from the third (lower) and fourth (upper) pharyngeal pouches. There are normally four glands, but up to 25% of individuals have more than this. The superior glands are more constant in position, lying posterior to the upper pole, near the recurrent laryngeal nerve (RLN). The lower glands have a more varied position: more commonly glands lie posterior to the lower pole, near the vascular pedicle, but they can vary in location from the level of the hard palate superiorly down to the superior mediastinum.

The role of imaging in hyperparathyroidism is to localize abnormal or hyperfunctioning glands, in order to guide surgical exploration and removal. The major imaging modalities can all be used with varying degrees of success.

Ultrasound

- **Benefits** of US are that it can visualize abnormal parathyroid glands in the region of 10 mm diameter. Abnormal glands appear of low echogenicity compared to adjacent thyroid. Reported sensitivities and specifities vary,

but range between 40% and 80%, with specificity up to 98%.7 US is operator-dependent, but in experienced hands it can outperform nuclear medicine.[8]

- **Limitations** of ultrasound imaging include ectopic glands (ultrasound cannot visualize mediastinal lesions and struggles with tracheaoesophageal lesions) and glands lying posterior to a multinodular goitre.

Nuclear medicine

Nuclear medicine scintigraphy utilizes radioactive substrates that are taken up by both thyroid and parathyroid glands. Technetium (^{99m}Tc) sestamibi is taken up by both thyroid and abnormal parathyroid glands but these have different speeds of washout. Subtraction of the images from one another allows visualization of abnormal parathyroid glands.

- **Benefits** of nuclear medicine are that multiple glands may be visualized in multigland disease, and ectopic glands in the mediastinum may be seen. Reported sensitivity of sestamibi scanning is 70–100%.
- **Disadvantages** include uptake by thyroid nodules/adenoma and poor spatial resolution. The latter has been improved by combining (fusing) the nuclear medicine scan with a low-dose CT study for anatomical and functional detail.

In many centres, the initial investigation may be ultrasound or nuclear medicine, and a combination of the two is a very common method of investigation.

Computed tomography

Contrast enhanced CT is a newer imaging technique for visualization of abnormal parathyroid glands. Adenomas show arterial phase enhancement, with rapid washout of contrast, whereas adjacent lymph nodes show gradual increasing enhancement. Polar feeding vessels may also suggest adenomas.

- **Benefits** include accurate anatomical detail, aiding surgical exploration, and accurate visualization of multigland disease and ectopic glands. Reported sensitivity and specificity appears high, and anatomical information is greater than with US or nuclear medicine techniques.
- **Disadvantages** of CT are radiation doses, as the scan utilizes multiple phases of scanning (typically three or four scans). For this reason, multiphase CT is usually limited to patients with failed surgical exploration or recurrent disease, or where clinical and biochemical suspicion is high and US and nuclear medicine have not provided a potential abnormal gland.

PITUITARY GLAND

The pituitary gland is contained within the sella turcica, a concave depression within the sphenoid bone (basisphenoid). The gland is composed of two lobes, the anterior pituitary or adenohypophysis (AH) and posterior pituitary or neurophypophysis (NH).

The **anterior pituitary** comprises 75–80% of the gland, and it produces somatotropin (growth hormone), prolactin, TSH, FSH, LH and ACTH. The **posterior pituitary** comprises 20–25% of the gland and is an inferior extension of the hypothalamus. The pars nervosa secretes ADH and oxytocin that are both produced by the hypothalamus.[9] The posterior pituitary is subdivided into the large **pars nervosa** and smaller **infundibulum** (pituitary stalk).

Imaging techniques

The best technique for multiplanar imaging of the pituitary gland is high-resolution MRI. A standard pituitary MR imaging study is 3 mm thick coronal and sagittal images pre- and post-contrast. The coronal images are best for simultaneously visualizing the sellar and parasellar structures and the position of the infundibulum in relation to the pituitary gland. The sagittal images demonstrate the midline structures and anterior and posterior extent of any related lesion. Axial T2W images of the brain 5 mm thick aid in excluding any other brain pathology and 3 mm thick coronal T2W images are also acquired to aid in differentiating types of pathology and consistency of any lesion.

ENHANCEMENT PATTERNS

The pituitary gland and infundibulum lack a blood–brain barrier therefore enhance rapidly and intensely after contrast is given.

In patients unable to undergo an MRI study, multislice CT (1 mm) pre- and post-contrast enhancement is an alternative. This can then be reconstructed in coronal and sagittal planes as required.

PRE-OPERATIVE EVALUATION

In those patients suitable for surgery to this region, a pre-operative CT scan is performed to delineate the bony anatomy of the adjacent paranasal sinuses to facilitate a transnasal, endoscopic operative approach.

PITUITARY TUMOURS

Pituitary adenomas constitute 10–15% of all intra-cranial tumours. Small adenomas occur in up to 15% of glands at autopsy and more than 20% of imaging studies. They usually occur in adults and are mostly benign. Tumours less than 1 cm are microadenomas and those greater than 1 cm are macroadenomas (Figures 57.1 and 57.2).

Around 25% of pituitary tumours lack hormone activity and are often diagnosed later than hormone-secreting tumours only when they compress adjacent structures (e.g. visual field defects from optic nerve compression or cranial nerve deficits from cavernous sinus invasion) (Figures 57.3 and 57.4). Up to 10% of pituitary adenomas invade the cavernous sinus. Clinical signs occur late, as cavernous sinus cranial nerves are lateral to the ICA. An adenoma that extends inferiorly may present as a sphenoid sinus mass.

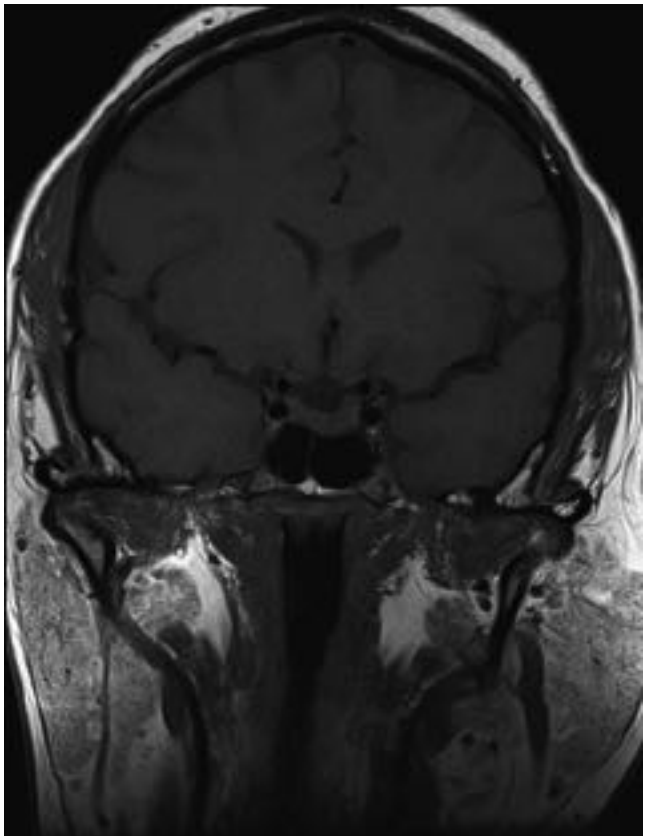


Figure 57.1 Coronal T1W image illustrates a bulky left side of the pituitary gland. There is a slight inferior slope of the sella floor also on the left. The round, dark areas either side of the pituitary gland are due to 'flow voids' which are normally seen due to the cavernous part of the internal carotid artery within the cavernous sinuses.

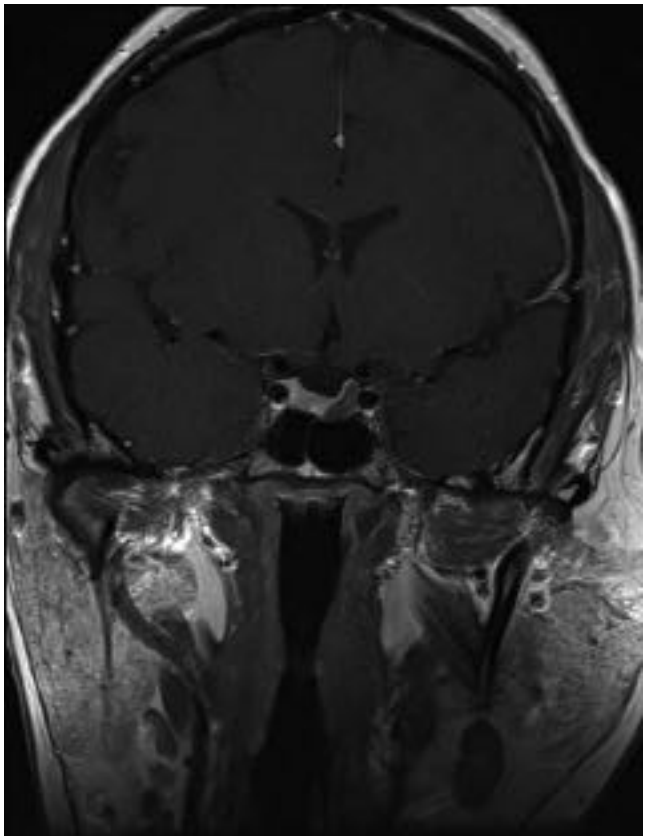


Figure 57.2 Post-contrast coronal T1W image demonstrates the non-enhancing microadenoma within the left side of the pituitary gland. The rest of the pituitary gland enhances normally.

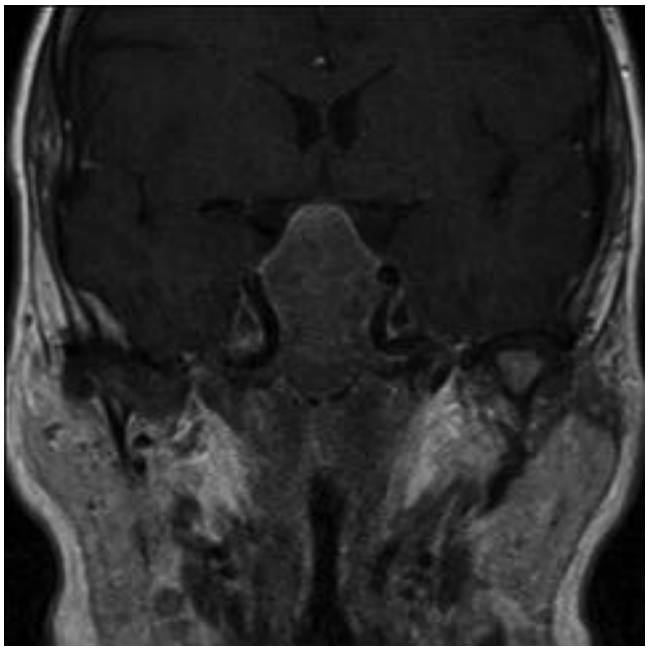


Figure 57.3 Coronal post-contrast image shows a large pituitary macroadenoma. The suprasellar extension causes compression of the optic chiasm in this case. There is also invasion of the adjacent cavernous sinuses.

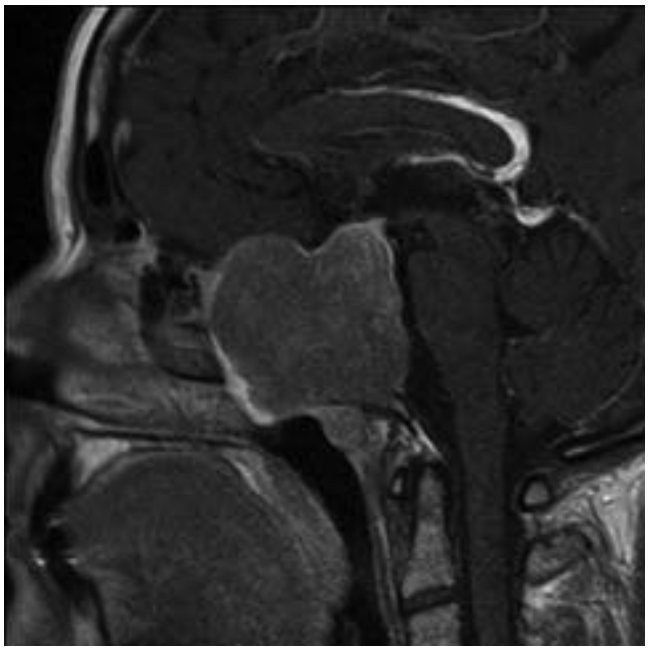


Figure 57.4 Sagittal post-contrast image of the same pituitary macroadenoma shows superior extension up to the optic chiasm and slight posterior extension into the pre-pontine cistern. There is also anterior and inferior extension and inferiorly causing a slight depression of the sella floor.

Most pituitary tumours are sporadic, only 5% being familial. The four inherited familial tumour syndromes are MEN1 (multiple endocrine neoplasia type 1, where pituitary tumours are present in 15–40%), Carney complex, McCune–Albright syndrome and FIPA (familial isolated pituitary adenoma syndrome).[9]

Adenomas originate from the anterior pituitary. The two most common types are prolactinomas and growth hormone (GH)-secreting tumours, which are usually present laterally. TSH, ACTH, LH/FSH-secreting tumours tend to occur in the midline. The most common functioning adenomas are prolactinomas. Clinical symptoms include amenorrhoea, galactorrhoea, infertility and loss of libido or impotence and hence they are more likely to present earlier in premenopausal women than in men and postmenopausal women.

The next most common pituitary tumours produce ACTH and GH. GH-secreting tumours cause gigantism in children and acromegaly in adults. ACTH secretion causes Cushing's disease. **'Dynamic post-contrast' scans** are useful in the investigation of microadenomas caused by suspected Cushing's disease. This utilizes the property of microadenomas having a slower uptake of contrast than the normal pituitary gland. A microadenoma is then visualized as a filling defect (dark) within the rest of the normally enhancing gland. Serial images are acquired of the pituitary gland during intravenous contrast injection to demonstrate the microadenoma. The range of times for optimum detection varies from 30–50 seconds to 1–2 minutes post contrast. Soon after this the contrast within the pituitary gland reduces and the adenoma becomes no longer visible.[10] Cases with known high prolactin levels and a normal-sized gland with or without a filling defect on a normal post-contrast study are treated medically and hence would not require dynamic post-contrast imaging.

Macroadenomas often extend superiorly through the opening of the diaphragm sellae. Cysts and/or foci of haemorrhage are seen in approximately 50% of cases. Most macroadenomas enlarge slowly over years. Imaging features are those of an intrasellar or intra- and suprasellar mass where the pituitary gland cannot be separated from it. Bony CT can show an enlarged sella turcica due to remodelling of the bone. A 'giant' or very large macroadenoma can erode and appear to invade the skull base.

On MRI macroadenomas are usually isointense with cortex and enhance well but heterogeneously with contrast. Tumours that have hyperintense foci on T2W images may be soft or partially necrotic. This knowledge pre-operatively is useful in pre-surgical counselling as a soft tumour can be easily removed compared to a lesion with a more fibrous nature (Figure 57.5).

Differential diagnosis

A number of features help to distinguish sellar masses:

- location: is the mass intrasellar, suprasellar, infundibular or a combination of these locations?
- connection: is the mass separate from the pituitary gland or not?
- age of the patient.

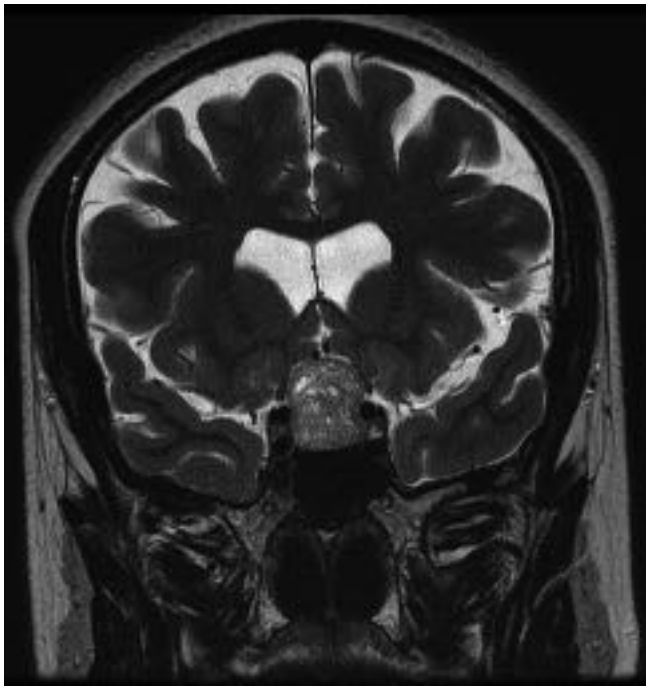


Figure 57.5 Coronal T2W image demonstrates a pituitary macroadenoma with hyperintense foci within it indicating the tumour is 'soft' or partially necrotic. It is extending up to and compressing the optic chiasm which is draped over its superior aspect.

MENINGIOMA

This tumour is rare in children and usually seen as separate from the pituitary gland. Most arise from the undersurface of the diaphragma sella but they can also arise from the walls or floor of the sella. Meningiomas more commonly arise from the parasellar regions and project into the sella turcica.[11] Intrasellar meningiomas are rare.[12]

MRI demonstrates these lesions to be hypointense to isointense to grey matter on T1W and T2W images. They enhance rapidly and avidly and have a 'dural tail'. The most useful feature in allowing differentiation of a sella meningioma from an adenoma is identifying the pituitary gland as separate from the sella mass (Figure 57.6). Also hyperostosis of adjacent bone is seen in 34% of cases. These lesions are benign but can be locally aggressive and recur after incomplete resection. They can encase and eventually occlude the internal carotid artery (ICA). Because most are very vascular tumours, pre-operative embolization is used in some cases to reduce intra-operative blood loss.

METASTASIS

Metastases to the infundibulum and/or pituitary gland are infrequent. They most commonly arise from lung and breast.[13] The posterior pituitary is generally most affected but breast metastases tend to affect the anterior pituitary. It can be difficult to differentiate these lesions from pituitary adenomas. Imaging features that may help to distinguish a pituitary metastasis are: thickening of the infundibulum, loss of high T1W signal from the posterior pituitary,



Figure 57.6 Sagittal T1W post-contrast image demonstrates a sella and suprasellar meningioma. The lesion enhances avidly and can be seen separate from the non-enhancing, normal-appearing pituitary gland seen within the posterior aspect of the sella. A 'dural tail' is seen as linear enhancement along the floor of the anterior cranial fossa.

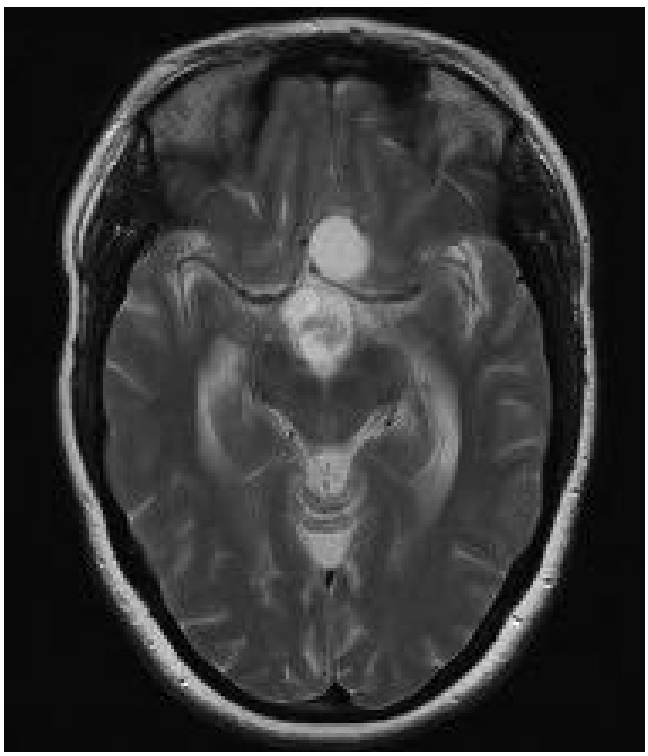


Figure 57.7 Axial T2W image illustrates the high signal intensity cystic components in a suprasellar craniopharyngioma. The posterior aspect of the lesion has some solid material within it which is seen as intermediate signal intensity.

isointense signal on T1W or T2W images, invasion of the cavernous sinus and sclerosis around the sella turcica. These appearances, however, are not specific for pituitary metastasis.

CRANIOPHARYNGIOMA

These tumours arise from epithelial remnants of Rathke's pouch. In children these are the most common suprasellar mass. They have a bimodal age distribution with one peak at 5–10 years of age and another at 50–60 years. Most are suprasellar lesions but a quarter have an intrasellar component. Intrasellar craniopharyngiomas are rare. They can measure from a few millimetres to several centimetres. The large lesions can extend to the anterior and middle cranial fossa (**Figures 57.7** and **57.8**). Two types exist: 90% are adamantinomatous and 10% papillary.

The common type of craniopharyngioma is a multilobulated, mainly cystic suprasellar mass with a solid component. It may contain cysts that are full of viscous 'machinery oil' fluid due to the cholesterol content. Calcification is common and most enhance. The papillary type has a smoother surface and is often solid. Any cysts contain a clear fluid. These tumours rarely calcify. They occur in adults with a peak at 40–44 years. Imaging features are those of a partially calcified, mixed solid and cystic mass. The pituitary can sometimes be seen as separate from the mass.

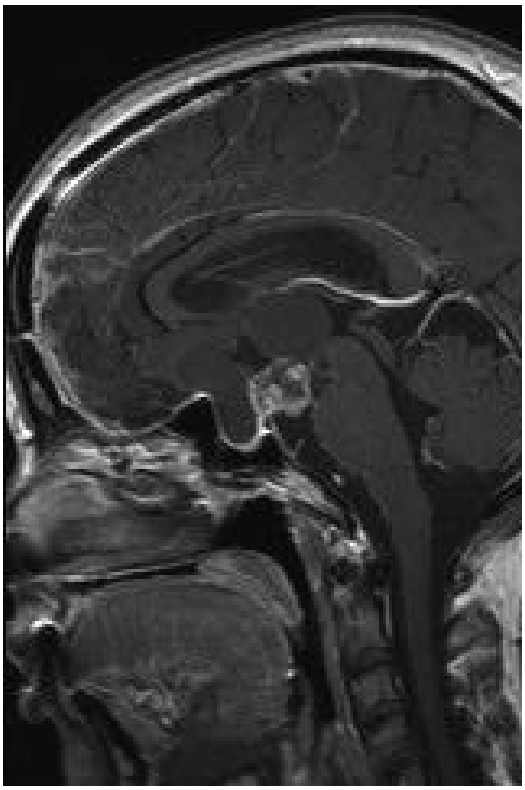


Figure 57.8 Sagittal post-contrast image demonstrates the same lesion as in Figure 57.7. The partially solid, posterior, retrosellar component exhibits patchy enhancement. The anterior and superior cystic components are non-enhancing. A thin rim of pituitary tissue is seen compressed within the sella floor, which is also depressed.

RATHKE CLEFT CYST

Craniopharyngiomas need to be differentiated from Rathke cleft cysts (RCCs). The latter do not calcify, which helps distinguish them. RCCs are a remnant of the embryonic Rathke cleft. Approximately 40% are intrasellar and 60% suprasellar.[9]

If they cause symptoms, patients with an RCC can present with pituitary dysfunction, visual disturbance and headache. MRI signal varies according to the cyst contents, which are mainly mucoid but can be serous.[10] Those which contain mucoid fluid may be indistinguishable from cystic craniopharyngiomas on MRI, with both being hyperintense on T1W and T2W images. They are usually hyperintense on FLAIR imaging. The serous cysts have imaging features of typical benign cysts, that is, low signal (dark) on T1W and high signal (bright) on T2W images. After contrast they have an enhancing rim or 'claw sign' of compressed pituitary gland around the non-enhancing cyst. Around 40–75% of RCCs have an intracystic nodule (**Figures 57.9** and **57. 10**).

NON-ADENOMATOUS PITUITARY TUMOURS

These are rare, WHO grade 1 tumours and are classified as pituicytoma, spindle cell oncocytoma and granular cell tumour.[9] They can also present with visual loss and endocrine disturbance.

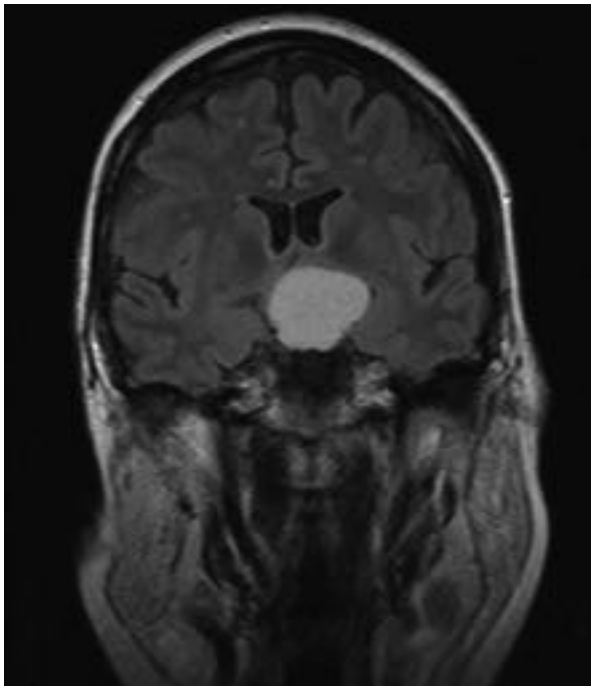


Figure 57.9 Coronal FLAIR image of a Rathke cleft cyst with mucoid fluid within it. This fluid does not 'suppress' like water or CSF on FLAIR imaging and therefore appears hyperintense.

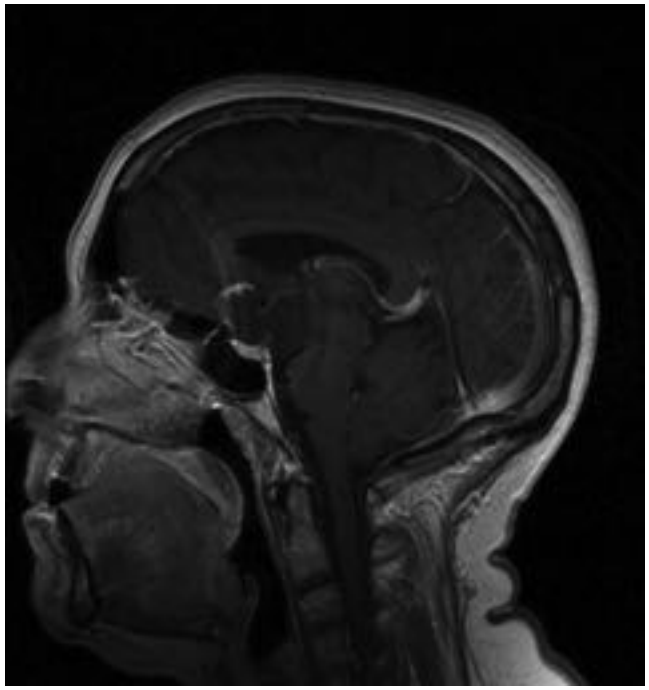


Figure 57.10 Sagittal post-contrast image of a Rathke cleft cyst illustrates the rim-enhancing cystic lesion which has suprasellar and retrosellar extension. There is a normally enhancing pituitary gland within the sella seen separate from the lesion.

KEY POINTS

- Best imaging technique is thin-section multiplanar MRI with a small field of view obtained before and after contrast.
- To distinguish the different types of sellar masses, first consider the location – is the mass intrasellar, suprasellar, infundibular or a combination of these locations?
- Is the mass separate from the pituitary gland or not?
- The age of the patient; as certain lesion are common in adults but not in children.
- Further imaging features of whether the mass is cystic, calcified and its signal intensity on MRI are also helpful.

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CHAPTER 58

THYROID AND PARATHYROID GLAND PATHOLOGY

Ram Moorthy, Sonia Kumar and Adrian T. Warfield

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: benign thyroid disease, thyroid cancer, thyroiditis, benign parathyroid disease, parathyroid cancer, fine needle aspiration cytology and frozen section examination.

INTRODUCTION

The endocrine pathology discussed in this chapter is that affecting the extracranial endocrine system, viz. the thyroid and parathyroid glands found in the anterior triangle of the neck bilaterally. The chapter is not intended to be an encyclopaedic treatise, more a summary overview with selective consideration of clinically important differential diagnoses. Surgical pathology is a visual subject, therefore no apology is offered for the liberal use of illustrations to supplement the text.[1]

THYROID GLAND

The normal thyroid gland

The term 'thyroid gland' was first coined by Thomas Wharton in the 17th century to describe the gland in close proximity to the shield-shaped (scutiform or scutate) thyroid cartilage.[2]

The thyroid gland is the largest of the discrete endocrine organs typically weighing between 15 g and 25 g (roughly 0.4% of body mass), being slightly larger in women,[2] dependent upon age, nutritional and hormonal status. Macroscopically the normal thyroid gland presents a bilobate structure with a reddish-brown colour. The two lobes are connected by a central isthmus. A vestigial, accessory pyramidal lobe is present in 40% of the population.

EMBRYOLOGY

Embryologically, the thyroid gland develops from the median anlage and the two lateral anlagen. The median anlage starts as a thickening of the endodermal epithelium in the foregut between the 1st and 2nd branchial arches at the base of the tongue close to the developing myocardium,[2, 3] which in later life constitutes the foramen caecum. The cells proliferate to form the thyroid bud and then a diverticulum, which expands and migrates from the base of tongue to lie anterior to the trachea. The track between the thyroid gland and base of tongue typically disappears by birth. The two lateral anlagen (known as the ultimobranchial bodies) develop from the caudal aspect of the 4th pharyngeal pouch supplemented by migratory neural crest elements and fuse with the median anlage as the thyroid gland descends in the neck. The median anlage forms the thyroid follicular cells and the lateral anlagen form the clear parafollicular cells (C-cells).[4]

CAPSULE

There is no clearly defined anatomical thyroid capsule proper, rather a thin investing fibrous pseudocapsule, which is continuous with the pre-tracheal fascia. This capsule is discontiguous or focally interrupted in approximately 60% of individuals and extracapsular thyroid tissue is present in almost 90% of glands. A variety of pericapsular inclusions, sometimes intra-thyroidal, such as parathyroid tissue, heterotopic thymus, lymph nodes and autonomic paraganglia,

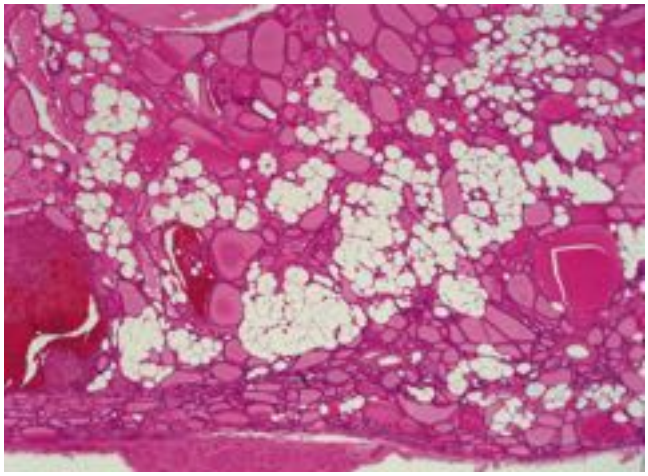


Figure 58.1 Intrathyroidal mature adipocytes intermingled with normofollicular thyroid gland parenchyma. The slender anatomical thyroid gland pseudocapsule is barely discernible at this magnification (*H&E stain, low magnification*).

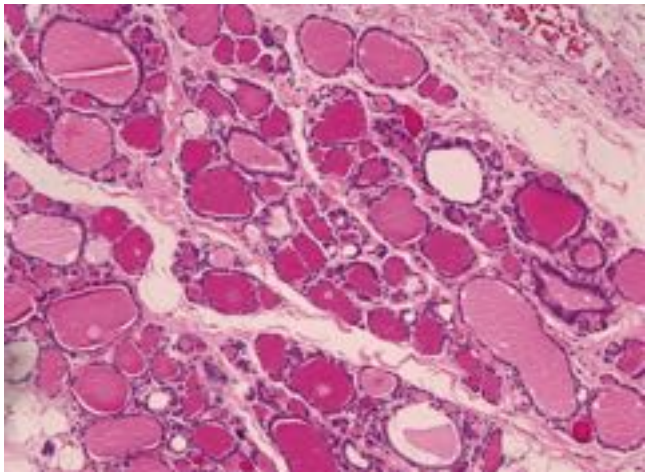


Figure 58.2 Normal thyroid gland demonstrating a lobular architecture with uniform, round/ovoid follicles. The latter contain plentiful stored colloid with fine marginal vacuolation. The parallel linear marks in the colloid ('ripple' or 'wave' effect) are an artefact of microtomy. The C-cell population is typically inconspicuous (*H&E stain, low magnification*).

are considered normal. Mesenchymal-derived inclusions within the thyroid gland include stromal adipocytic, skeletal muscular and cartilaginous elements[5] (Figure 58.1). Awareness of potential comorbid pathological changes in perithyroidal structures is helpful, for example medial calcification of arteries (Monckeberg's sclerosis), which may also occasionally synchronously affect vasculature within the thyroid gland and rarely be encountered in lesional tissue itself.

Breach of this pseudocapsule by tumour constitutes extrathyroidal extension (ETE), defined by infiltration into perithyroidal tissues, typically eliciting inflammatory and/or desmoplastic response. Where discernible grossly to the unaided eye, this is described as macroscopic (or extensive/major/massive/marked). If only appreciable during microscopy, this is designated microscopic (or minimal/minor/limited). This distinction is important prognostically – macroscopic ETE portends a higher recurrence rate and lower disease-free survival than microscopic ETE. Direct infiltration into parathyroid gland is rare but may be arbitrarily regarded as minimal ETE owing to close proximity.

MICROSCOPICAL APPEARANCE

Microscopically, the functional unit of the thyroid gland is the follicle, which in the euthyroid state consists of a monolayer of cuboidal or flattened epithelial cells (thyrocytes) surrounding a central lumen containing stored colloid. The follicles are loosely aggregated into lobules (thyromeres), each containing around 20–50 follicles separated by slender connective tissue septula (Figure 58.2). Intracolloidal birefringent oxalate crystals (Figure 58.3), brown cytoplasmic lipofuscin ('wear and tear') pigment and haemosiderin pigment are usually of incidental portent, though these may be increased with age and in certain disease states.

The C-cells form a minor cell subpopulation, accounting for less than 10% by number, and are typically concentrated at the junction between the middle and upper thirds of the lateral lobes in a hypothetical central longitudinal

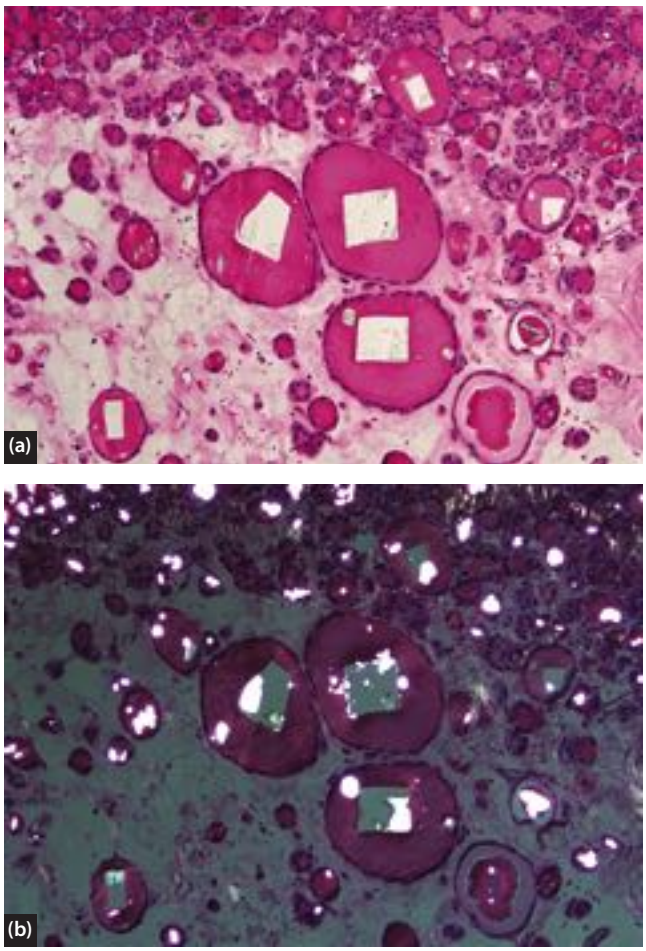


Figure 58.3 Thyroid gland parenchyma with intrafollicular rhomboidal and petaloid oxalate crystals. (a) Viewed under non-polarized brightfield light showing apparent empty geometrical spaces within the stored colloid (*H&E stain, medium magnification*). **(b)** Identical field illuminated by cross-polarized light disclosing many more strongly birefringent crystals against a dark background (*H&E stain, medium magnification*).

axis, corresponding to the planes of medial and lateral anlagen fusion – solid cell nests, C-cell hyperplasia and medullary thyroid carcinoma, therefore, do not ordinarily occur in the isthmus. C-cells are usually larger, more rounded, polyhedral or fusiform in shape, with paler cytoplasm than follicular epithelium.

Solid cell nests

So-called solid cell nests (SCNs) are collections of non-follicular cells, found in approximately 25% of resected thyroid glands, which probably represent remnants of the ultimobranchial apparatus. They are present in greater numbers in infants and children and gradually decline with advancing age. The role of SCNs in the normal structure and function of the thyroid gland is incompletely understood and their biological significance remains a source of controversy and debate. SCNs may harbour minimal properties of a stem cell phenotype with capacity for self-renewal and end differentiation.

SCNs comprise irregularly shaped clusters of interfollicular cells delineated by basal lamina. The dominant cell component (main cell) comprises polygonal to fusiform cells disposed in solid array sometimes with an epidermoid appearance, though generally non-keratinizing and devoid of intercellular bridges (prickles). They less commonly show a glandular morphology and may paradoxically be microcystic, micropapillary and/or mucinous. SCNs co-express cytokeratins, carcinoembryonic antigen (CEA, CD66e), galectin-3 and many pan-neuropeptides such as chromogranin A, synaptophysin and somatostatin, but they are negative for markers of terminal differentiation, viz. thyroglobulin (Tg), thyroid transcription factor-1 (TTF-1) and calcitonin (**Figure 58.4**). They also contain a minor subpopulation of C-cells, which show a partially differentiated immunophenotype. SCNs consistently stain for p63, a homologue of p53, a nuclear transcription factor that induces expression of cytokeratin 5 (CK5) and cytokeratin 14 (CK14). The gene for p63 is universally expressed in basal cells of stratified epithelia and plays a major role in triggering the maturation of these into squamous epithelium.

Solid cell nests are postulated to be precursors of certain thyroid gland neoplasms, notably papillary thyroid carcinoma. They may also play a role in the histogenesis of Hashimoto's thyroiditis, which is also associated with papillary thyroid carcinoma. Papillary thyroid carcinoma and Hashimoto's thyroiditis may therefore be linked in pathogenesis via a common population of pluripotent p63 positive embryonal stem cell remnant progenitors.[6]

Fine-needle aspiration cytology

Fine-needle aspiration cytology (FNAC) is generally recognized as a valuable and cost-effective first-line investigation in the evaluation of a thyroid swelling.[7–10] In experienced hands, FNAC of the thyroid gland is accurate with a sensitivity of 65–98%, a specificity of 72–100%, a false-positive rate of 1–8% and false-negative rate of 1–11%.[7, 11] The non-diagnostic or inadequate rate can be as high as 28%[11] but targeting by ultrasound (US) guidance can reduce the incidence of a non-diagnostic FNAC.[12] US guidance is recommended in nodules with a higher chance of non-diagnostic FNAC by simple palpation. These include cystic nodules and smaller or non-palpable lesions.[10] Thus, as a screening test FNAC is highly sensitive, but it lacks specificity: approximately 15–40% of aspirates designated suspect of a follicular neoplasm ultimately prove to be malignant, ergo the remaining 60–85% or so of nodules are benign in the final analysis. Immediate assessment of samples for adequacy at the time of aspiration (rapid on-site evaluation, ROSE) can reduce the rate of unsatisfactory specimens and aid collection of material for ancillary tests.

FNAC is substantially a screening/triage procedure for follicular carcinoma, identifying those patients who require further investigations, and a primary diagnostic test for other thyroid malignancies, principally papillary

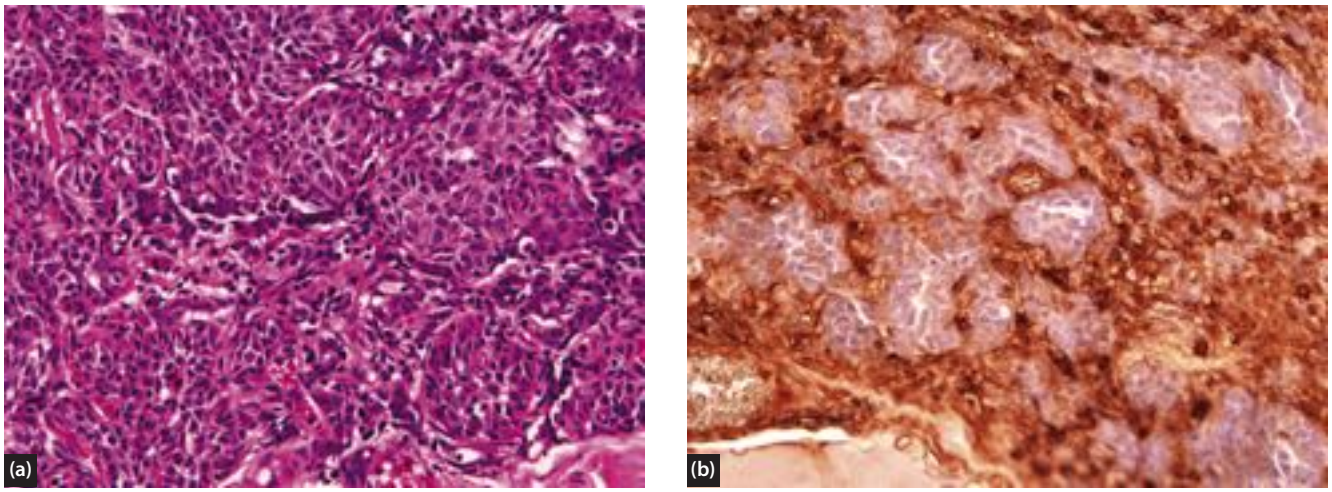


Figure 58.4 Solid cell nests. (a) Ultimobranchial apparatus rests (solid cell nests) disposed as discrete congeries of squamoid (epidermoid) cells without keratinization, discovered incidentally in a thyroidectomy specimen indicated for partially treated Graves' disease (*H&E stain, medium magnification*). **(b)** Such cell rests typically express pan-neuroendocrine immunomarkers but not thyroglobulin and they are thus shown here in negative relief (*thyroglobulin IHC, medium magnification*).

thyroid carcinoma, medullary carcinoma, undifferentiated (anaplastic) carcinoma and lymphoma.

The results of FNAC may reassure that a lesion is benign, triage patients for diagnostic surgery, or provide a definitive diagnosis of selected thyroid malignancies, thereby expediting single-stage therapeutic intervention.[9, 10] There is plentiful experience based upon the traditional wet-fixed and air-dried direct smear methodology, aspirate washings and cyst fluid samples, supplemented by cell concentration techniques, such as centrifugation, filtration and cell blocks. Newer liquid-based technology is favoured by some centres, dependent upon local resources and experience, furthermore handling of FNAC specimens may be influenced by the prospect of ancillary investigations. The success of thyroid FNAC is demonstrably operator-dependent – the cytopathologist can only ever be as good as the quality of the aspiration sample that he or she receives.

Despite acknowledged cytodiagnostic pitfalls, some outlined below, the use of FNAC in the preliminary evaluation of solitary or dominant nodules reduces the use of surgery by approximately one-third, doubles the proportion of malignancies among surgical resections and increases cost-effectiveness. FNAC may be employed in the investigation of suspect lymph nodes and measurement of thyroglobulin in needle wash samples may augment diagnostic accuracy. Molecular studies may also refine the diagnostic process in thyroid FNAC samples. Serious diagnostic delay due to false-negative FNAC is uncommon where there is appropriate clinical follow-up.[13]

Historically, the diagnostic criteria and reporting nomenclature employed internationally have varied somewhat though these have ultimately evolved to broad consensus, aimed at national standardization, stratified for risk of malignancy with corresponding evidence-based recommendations for further patient management.[14] These are epitomized by the North American National Cancer Institute (Bethesda) terminology (2007),[15] Italian (2007, 2014), Australian (2014), Japanese (2013) and British Thyroid Association/Royal College of Pathologists (2002, 2007, 2016) guidelines.[16] The terminology for non-diagnostic, benign, malignant and suspect for malignancy is similar across each of these classifications with minor differences in emphasis for the equivocal/indeterminate category. These schemata and the anticipated rates of malignancy attributed to each diagnostic category are outlined in **Table 58.1**. It is sometimes salutary when deliberating management options during multidisciplinary team conferences to remind participants of the reciprocal likelihood of benignity for each category to maintain a sense of perspective.

The shorthand alpha-numeric diagnostic category codification intrinsic to some of these systems is not intended to supplant a focused narrative cytology report or stymie more comprehensive communication, where appropriate. Additionally, the vernacular habit of grouping together non-diagnostic/unsatisfactory and non-neoplastic/benign aspirates under the rubric of negative reports should be dispelled. As a fundamental principle, it is emphasized that, while the presence of malignant cells is diagnostic, a lack of malignant cells can never be wholly exclusionary – absence of evidence is not *prima facie* evidence of absence.

LIMITATIONS OF FNAC OF THE THYROID GLAND

The follicular-patterned lesion is the most commonly encountered type of thyroid FNAC specimen in clinical practice. Distinction between a hyperplastic (adenomatoid) nodule in a multinodular goitre and a follicular-patterned neoplasm may not always be achievable. The presence of dispersed colloid, monolayered sheets of bland thyrocytes and macrofollicular structures are more typical of hyperplasia. Dense colloid globules, paucity of colloid and microfollicular configuration (**Figure 58.5**) tend to support neoplasia. It is necessary to focus on the predominant cytoarchitectural pattern, rather than a minor subpopulation of microfollicles, with the proviso that this approach is predicated upon adequate cell sampling. The agreed criterion for this is that samples from solid lesions should contain at least six groups of thyroid follicular epithelial cells across all the submitted slides, each composed of at least ten well-visualized epithelial cells. Note that this constitutes a minimum standard, that the degree of diagnostic confidence should increase with higher yield samples and that this threshold does not necessarily preclude a positive diagnosis of malignancy if a lesser quantum of characteristic cells is present.

Reliable discrimination between a benign adenoma and differentiated follicular carcinoma on subjective morphological grounds is now realized to be always difficult, often impossible. While the presence of high cellularity, cell crowding, tri-dimensional (acervate) groups, nucleomegaly, cytonuclear atypia, three or more nucleoli per cell, irregular karyoplasm and necrosis are individually not absolute, in aggregate they tend to favour a diagnosis of malignancy. Follicular variant of papillary thyroid carcinoma (FVPTC) enters the differential diagnosis, where a scrupulous search for its characteristic nuclear morphology is indicated. The diagnosis of non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is not sustainable from SNAC appearances alone. The separation of minimally invasive from widely invasive follicular carcinoma on FNAC, contingent upon extent of extracapsular invasion is obviously untenable *ab initio*.

Oncocytic (oxyphil) cell lesions are problematic on FNAC. Hashimoto's thyroiditis and oncocytic (oxyphil) metaplasia in multinodular hyperplasia are generally separated by conspicuous lymphocytosis in the former (**Figure 58.6**) though the degree of inflammatory cell infiltrate varies with the natural history of the disease and paucilymphocytic variants are described. The cytological distinction between Hürthle cell adenoma and carcinoma is unreliable – benign oncocytic (oxyphil) cells may display extreme pleomorphism and, paradoxically, there is often less cytonuclear variation in Hürthle cell neoplasms. Confident recognition of the rare oncocytic (oxyphil) variant of papillary thyroid carcinoma on FNAC is extremely difficult. The conclusion oncocytic (oxyphil) cell lesion or neoplasm, not otherwise specified, is occasionally the best that can be achieved with a recommendation for excision, as clinically indicated. A solitary thyroid nodule composed of predominantly oncocytes on FNAC merits excision because oncocytic (oxyphil) thyroid neoplasms show on average a 30% malignancy rate based on histology. Moreover, the larger an oncocytic tumour,

TABLE 58.1 Comparison of the BTA/RCPath, Bethesda[16] and other contemporaneous international classification systems for reporting thyroid gland FNAC specimens together with their clinical implications[10, 14]

RCPath	Bethesda	Italian	Australian	Japanese
Thy1 Non-diagnostic for cytological diagnosis Thy 1c Non-diagnostic for cytological diagnosis – cystic lesion	I. Non-diagnostic or unsatisfactory Virtually acellular specimen Other (obscuring blood, clotting artefact, etc.) Cyst fluid only	TIR 1 Non-diagnostic TIR 1c Non-diagnostic cystic	1 Non-diagnostic	1 Inadequate
0–10%	0–10%	Not defined	0–10%	10%
Thy 2 Non-neoplastic Thy 2c Non-neoplastic cystic lesion	II. Benign Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.) Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context Consistent with granulomatous (subacute) thyroiditis Other	TIR 2 Non-malignant	2 Benign	2 Normal or benign
0–3%	0–3%	<3%	0–3%	<1%
Thy 3a Neoplasm possible, suggesting follicular neoplasm	III. Atypia of undetermined significance or follicular lesion of undetermined significance	TIR 3A Low risk Indeterminate Lesion (LRIL)	3 Indeterminate or follicular lesion of undetermined significance	3 Indeterminate B Others
5–15%	5–15%	<10%	5–15%	40–60%
Thy 3f Neoplasm possible, suggesting follicular neoplasm	IV. Follicular neoplasm or suspicious for a follicular neoplasm Specify if Hürthle cell (oncocytic) type	TIR 3B High risk Indeterminate Lesion (HRIL)	4 Suggestive of a follicular neoplasm	3 Indeterminate A Follicular neoplasm A-1 Favour benign (<15%) A-2 Borderline (15-30%) A-3 Favour malignant (40–60%)
15–30%	15–30%	15–30%	15–30%	
Thy 4 Suspicious of malignancy	V. Suspicious for malignancy Suspicious for papillary carcinoma Suspicious for medullary carcinoma Suspicious for metastatic carcinoma Suspicious for lymphoma Other	TIR 4 Suspicious of malignancy	5 Suspicious of malignancy	4 Malignancy suspected
60–75%	60–75%	60–80%	60–75%	>80%
Thy 5 Malignant	VI. Malignant Papillary thyroid carcinoma Poorly differentiated carcinoma Medullary thyroid carcinoma Undifferentiated (anaplastic) carcinoma Squamous cell carcinoma Carcinoma with mixed features (specify) Metastatic carcinoma Non-Hodgkin lymphoma Other	TIR 5 Malignant	6 Malignant	5 Malignant
97–99%	97–99%	>95%	97–99%	>99%

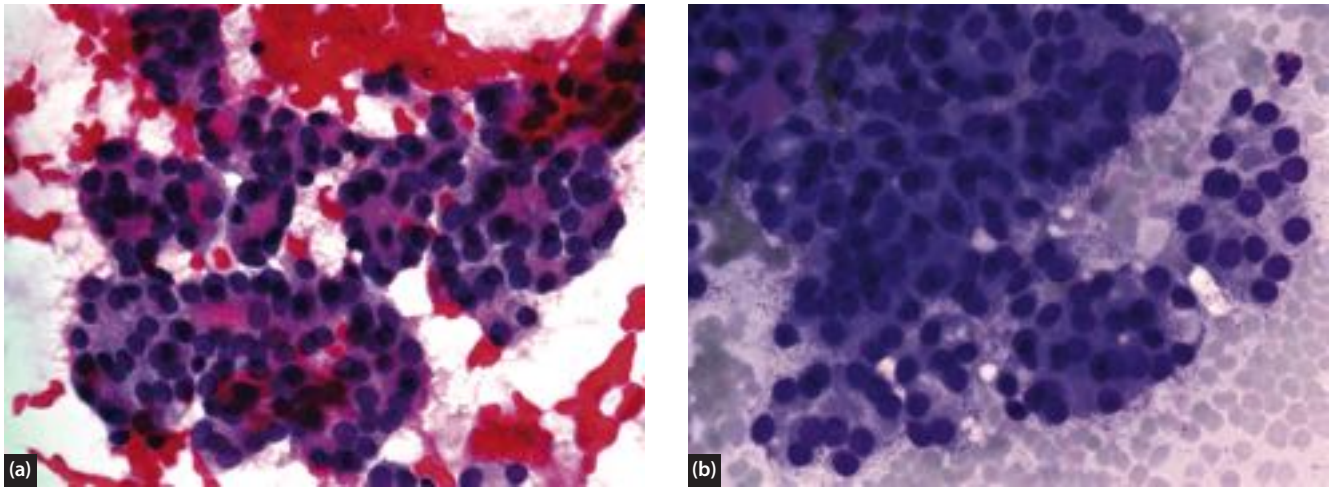


Figure 58.5 FNAC. (a) Cellular FNAC specimen suggestive of a follicular neoplasm. Note several microfollicular structures (defined as 12 or fewer circumferential thyroid epithelial cells, in contrast to macrofollicles composed of 20 or more peripheral cells).[15] Structures of normofollicular configuration are defined within these two extremes (*Pap stain, high magnification*). **(b)** Similar microfollicles seen on its companion air-dried smear. There is sparse colloid in some of the follicles (*MGG stain, high magnification*).

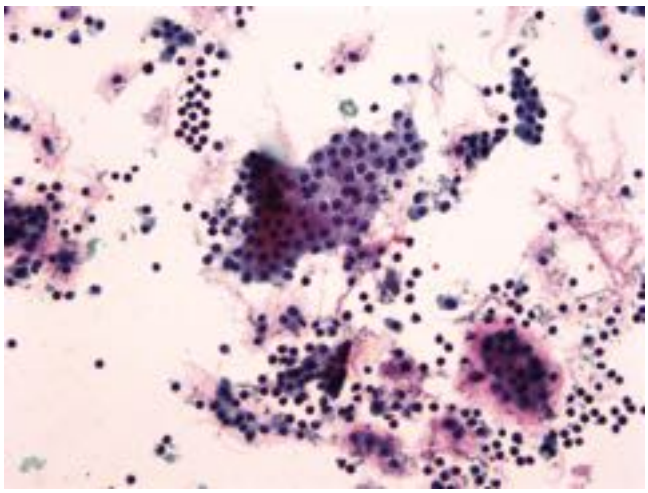


Figure 58.6 FNAC from Hashimoto's thyroiditis. Loosely cohesive, monolayered clusters of mildly pleomorphic oncocytic (oxyphil or Hürthle cell) thyrocytes can be seen admixed with polymorphous small lymphocytes (*Pap stain, medium magnification*).

the greater the likelihood of invasive malignancy: there is a 65–80% chance of malignancy in oncocytic neoplasms exceeding 4 cm maximum dimension.

Aspirates from cystic lesions may not be fully diagnostic, particularly if there is limited or degenerate epithelial sampling. Cysts of any type tend to contain variform inflammatory cells, foam cells, pigmented macrophages and cytolytic debris (Figure 58.7). Copious dispersed colloid favours benignity, though in the absence of adequate epithelial cell content the possibility of a cystic neoplasm or cystic degeneration in a neoplasm, of which papillary thyroid carcinoma is paradigmatic, cannot be completely ruled out on FNAC microscopical appearances in isolation since up to 10% of thyroid carcinomas missed on FNAC harbour a cystic component.

The diagnosis of high-grade non-Hodgkin lymphoma is generally straightforward with adequate FNAC material.

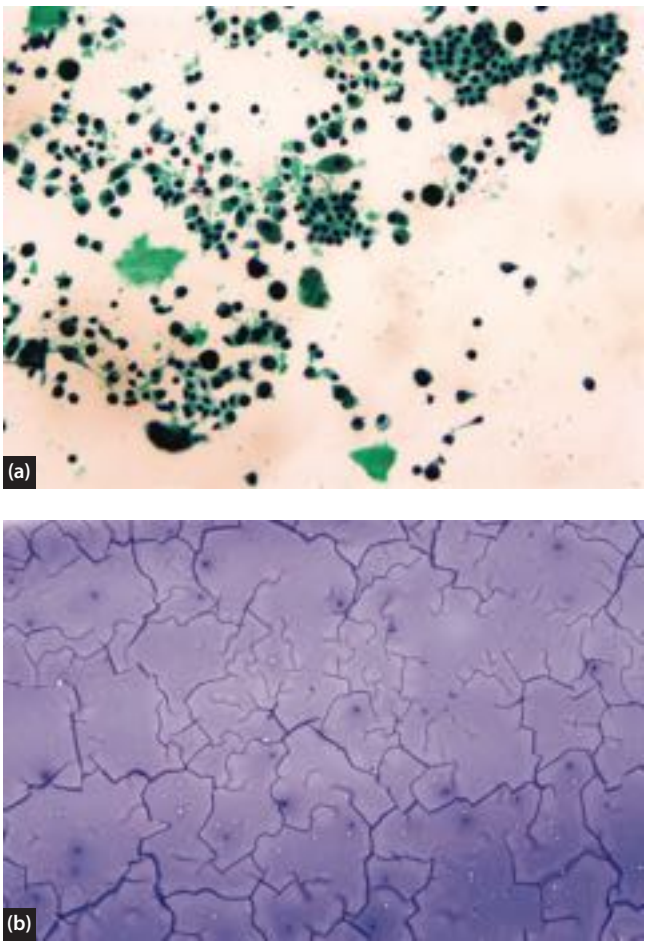


Figure 58.7 Fine-needle aspiration cytology. (a) FNAC from a benign thyroid cyst showing monolayered sheets (honeycomb or frog spawn) of cohesive, isomorphic epithelial cells amidst foam cells and pigmented macrophages with minimal necrolytic debris (*Pap stain, medium magnification*). **(b)** FNAC of the contents of a benign colloid cyst/nodule illustrating abundant, evenly dispersed, tessellated (cracked or 'parched earth') colloid. There is no cell sampling in this field.

Recognition of low-grade non-Hodgkin lymphoma, typically extranodal marginal zone lymphoma ('MALToma'), however, is sometimes fraught, especially if arising in the context of autoimmune thyroiditis where monomorphism of the neoplastic lymphocytes, which triggers the suspicion of neoplasia, is diluted or obscured by reactive lympho-proliferative elements. Histological examination is typically advised, particularly if more definitive subclassification is desired.

FNAC-INDUCED IATROGENIC CHANGE

Although FNAC is popularly considered to be a comparatively atraumatic procedure, the technique is known to induce histological changes, which may modulate or even obscure the underlying pathology and potentially mislead the unwary.

Several studies propose an incidence for FNAC-induced iatrogenic changes of close to 100%.[17] Relevant factors include the nature and size of the target lesion, the calibre of the needle used, the number of passes attempted, the precise FNAC technique employed, how meticulously such effects are sought and the interval between FNAC and excision surgery. The retrospective nature of such audit is prone to underestimate the true frequency.

The resultant secondary damage may broadly be classified into tissue damage and repair effects, tumour and tissue infarction, and epithelial dislodgement/displacement phenomena. The acronym WHAFFT ('worrisome histologic alteration following fine-needle aspiration of the thyroid gland') was originally proposed and has further been divided into acute WHAFFT and chronic WHAFFT.[18]

The tissue damage and repair aspect includes haemorrhage, fibrovascular granulation tissue organization and regenerative/degenerative atypia. Haemorrhagic needle tracks and associated proliferation of fibroblasts/myofibroblasts are typically pericapsular and radiate to the centre of the lesion, perpendicular to the capsule. The influx of inflammatory cells, siderophages, linear fibrosis/hyalinization, cholesterol granulomata, dystrophic mineralization, epithelial metaplasia and epithelial and endothelial atypia may on occasion be so exuberant and kaposiform as to closely mimic a sarcoma (so-called post-FNAC spindle cell nodule) (**Figure 58.8**).

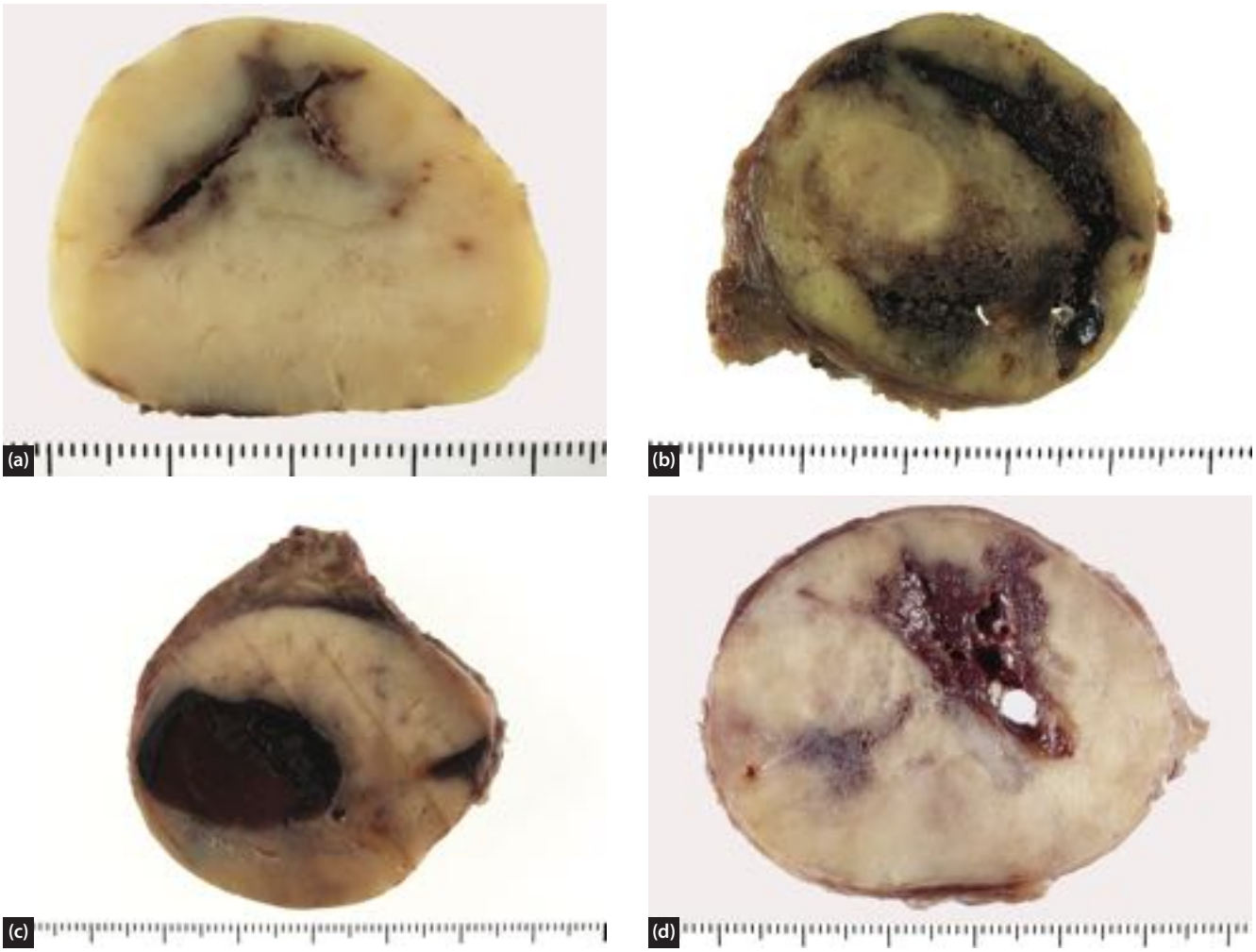


Figure 58.8 FNAC-induced iatrogenic changes. (a) Recent FNAC needle tracks in a follicular neoplasm. The crossed swords ('double skewer') sign indicates that at least two passes of the needle in different directions were conscientiously made by the aspirator. The rectilinear, subcapsular configuration is typical. **(b)** This haemorrhagic recent FNAC needle track, however, appears more curvilinear. **(c)** Circumscribed encysted haematoma post-FNAC. **(d)** Another follicular neoplasm showing post-FNAC linear haemorrhagic infarction with early macrocystic change.

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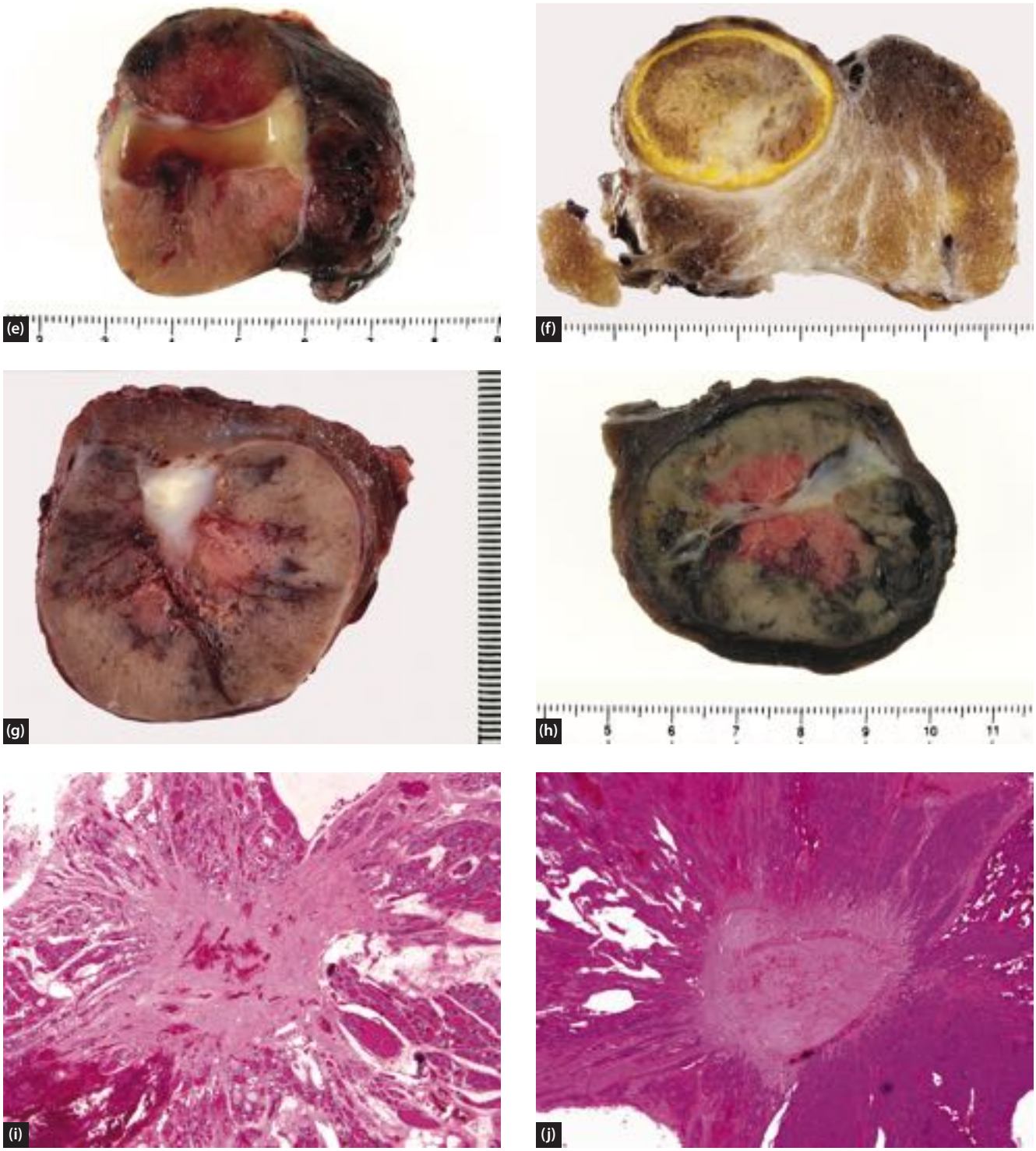


Figure 58.8 (Continued) FNAC-induced iatrogenic changes. (e) Established macrocystic degeneration with localized mural vascular granulation tissue response and limpid, mucoid contents. **(f)** Globally infarcted oncocytic (oxyphil) cell neoplasm, not further subclassifiable, following FNAC displaying complete yellow ischaemic type necrosis. **(g)** Obvious healing rectilinear FNAC artefact perpendicular to the capsule with a retracted, cuneiform, fibrous pericapsular scar in an otherwise minimally invasive follicular carcinoma. **(h)** Post-FNAC linear fibrous scar traversing an oncocytic (Hürthle cell) neoplasm, contiguous with wedge-shaped, retracted capsular defect. **(i)** Post-FNAC artefact manifest as radial scar-like, central fibroblastic granulation tissue and haemorrhage distorting surrounding lesional parenchyma (*H&E stain, low magnification*). **(j)** Another example of an older post-FNAC radial scar presenting a haemosiderotic, hyalosclerotic nidus with centripetal contracture deformity of lesional architecture (*H&E stain, ultra-low magnification*).

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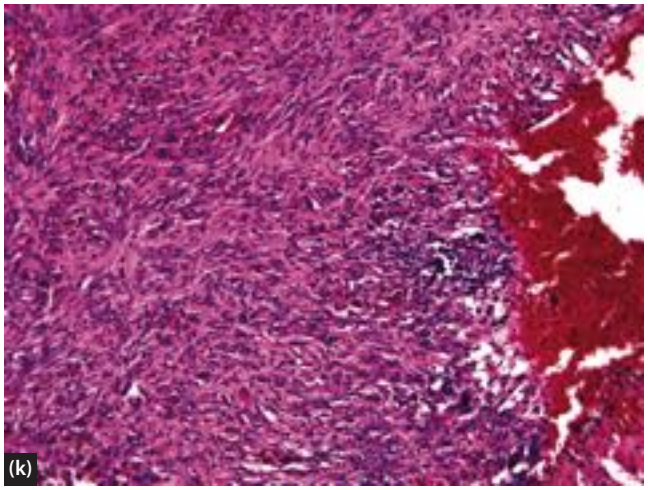


Figure 58.8 (Continued) FNAC-induced iatrogenic changes.
(k) Post-FNAC spindle cell nodule composed of richly vascularized myofibroblastic (kaposiform) stroma bordering encysted haematoma (*H&E stain, medium magnification*).

The thyroid gland is a richly vascularized organ (receiving approximately 2% of total cardiac output) and post-FNAC vascular effects include venous thrombosis, recanalization and papillary endothelial hyperplasia, sometimes to an extent to resemble angiosarcoma (pseudoangiosarcomatoid). Mitochondrion-rich oncocytic (oxyphil) cell lesions are exquisitely sensitive to ischaemia, and therefore characteristically susceptible to partial or global infarction, either spontaneously or post-FNAC. Where extensive, such infarction may render definitive histological evaluation difficult or impossible and a diagnosis of oncocytic neoplasm, not further specified, may be the best that can be proffered under these circumstances. However, a minor population of better-preserved tissue, the ghost-like outlines of devitalized papillae, necrotic cells or psammoma bodies, together with review of the original FNAC material, may yield some insight into the underlying pathology. Immunocytochemical positivity for certain epitopes persists for a surprising time after infarction – leukocyte common antigen (CD45) and CD20 staining, for example, may reproducibly define lympho-proliferation long after tumour cells have cytolyzed, though antibodies such as carcinoembryonic antigen (CD66e) is more capricious and stains fields of necrotic tissue and abscess cavitation indiscriminately.

Angulated follicles and reparative stromal response, accompanied by nuclear hyperchromasia, fusiform epithelial morphology and squamous metaplasia, may appear infiltrative (pseudo-infiltration), and therefore merit serious consideration of follicular carcinoma, squamous cell carcinoma or muco-epidermoid carcinoma.

Epithelial displacement and/or tumour implantation along FNAC needle tracks into soft tissues or skin does occur, though apart from the uncommon sarcomas such deposits usually disintegrate and viable tumour seeding is rarely of serious clinical importance. Fields of reactive papillary endothelial hyperplasia (Masson's pseudotumour) in pericapsular vasculature may closely mimic lymphovascular involvement by papillary thyroid carcinoma. Mechanical tumour cell dislodgement into blood vessels may resemble vascular invasion. Rigorous criteria are recommended, notably the presence of a protruberant connection with the vessel wall, partial or complete endothelialization of the tumour tissue and/or admixture of tumour cells with blood/thrombus, all indicative of a vital response. Opinion is divided as to whether immunostaining (e.g. CD31, CD34 for vascular and D2-40 for lymphatic endothelium) ought to be routinely or selectively utilized. Pericapsular defects in various stages of healing must not be misconstrued as capsular infiltration (pseudoinvasion) or evidence of extrathyroidal extension.

Developmental conditions

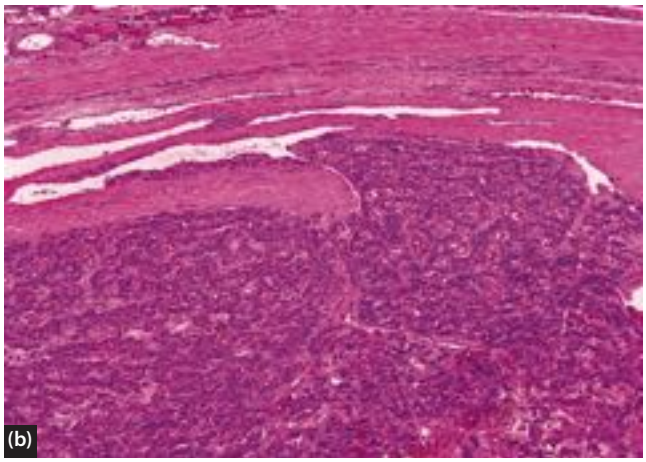
Developmental conditions involve the presence of normal thyroid tissue in sites outside the normal thyroid gland (heterotopia or ectopia, hamartoma and choristoma). This includes lingual thyroid, mediastinal thyroid, benign lymph node inclusions, so-called 'lateral aberrant thyroid gland' and sequestrated (parasitic) thyroid nodules. Mature adult cystic teratoma (dermoid cyst) of the ovary may show a preponderance of thyroid tissue (struma ovarii) sometimes with carcinoid elements (strumal carcinoid). The same repertoire of pathological conditions that affect eutopic thyroid gland may also be rarely encountered at these other sites (**Figure 58.9**).

THYROGLOSSAL TRACT ANOMALIES

Thyroglossal duct remnants persist due to failure of involution of the thyroglossal duct following embryological descent of the thyroid gland. They are the commonest cause of a congenital neck mass and the second most common cause of a cervical mass in childhood.[19]

Thyroglossal duct remnants can occur at almost any site from the base of the tongue to the suprasternal region, predominantly at four locations, namely intralingual, suprahyoid, thyrohyoid and suprasternal[20] (**Figure 58.10**). Cysts predominate with fewer sinuses and fistulae. Counterintuitively, follicular thyroid tissue is not a prerequisite for diagnosis. Thyroglossal duct carcinoma is rare, estimated as occurring in no more than 1% of thyroglossal duct cysts and, when it supervenes, it is usually a subtype of papillary thyroid carcinoma.





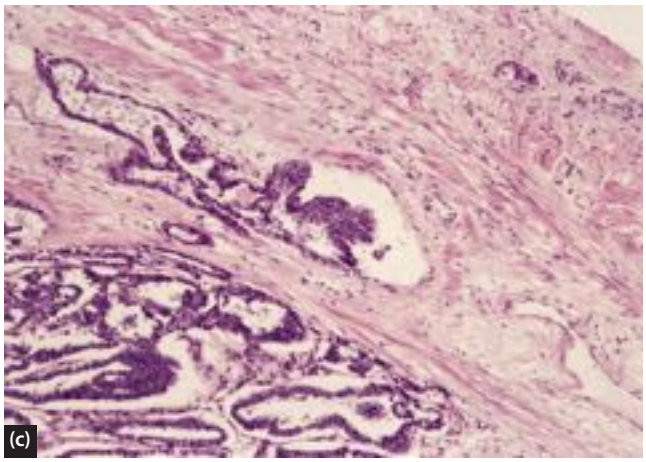


Figure 58.9 Developmental conditions. (a) Adult cystic ovarian teratoma (dermoid cyst). The solid component is substantially follicular thyroid tissue with clinically unsuspected fields of minimally invasive (angioinvasive) follicular carcinoma microscopically. **(b)** Minimally invasive follicular carcinoma ex-ovarian teratoma (struma ovarii). The endothelialized tongue-like angioinvasion is identical to that seen in such tumours occurring in eutopic thyroid gland (*H&E stain, medium magnification*). **(c)** Lymphovascular invasion in well-differentiated papillary thyroid carcinoma, classical pattern ex-struma ovarii. Again, this is identical to that occurring in eutopic thyroid gland proper (*H&E stain, medium magnification*).

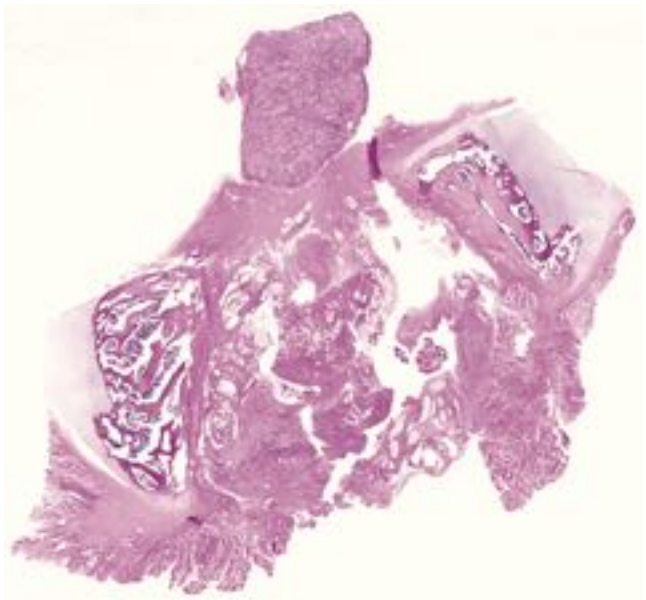


Figure 58.10 Whole mount preparation of a Sistrunk's procedure specimen. It shows hyoid bone, closely associated connective tissue plus a nubbin of normofollicular thyroid tissue representing thyroglossal duct remnants (*H&E stain, ultra-low magnification*).

SQUAMOUS DIFFERENTIATION

The presence of squamous epithelium is not uncommon. It is usually either an acquired, adaptive response (metaplasia) due to inflammation, or related to developmental rests of cells (heteroplasia)[21, 22] though it may also occur in some neoplasms (differentiation) (Figure 58.11 and Table 58.2).

Non-neoplastic squamous epithelium is usually microscopically bland though may sometimes show an alarming degree of reactive/reparative cytonuclear atypia. Benign squamous epithelium generally presents the same immunophenotype as elsewhere, viz. cytokeratins (notably CK5 and CK14), epithelial membrane antigen (EMA) and p63 positivity, usually with thyroglobulin, thyroid transcription factor-1 (TTF-1) and carcinoembryonic antigen (CEA, CD66e) negativity. Malignant squamous differentiation, however, may not conform to this profile and anomalous epitope expression (e.g. CD 56) may be confounding.

ONCOCYTIC CHANGE

Oncocytic (oxyphilic) cells are characterized by swollen, granular, mitochondrion-rich cytoplasm and may occur in both endocrine tissues and non-endocrine organs, including pituitary, parathyroid, thyroid, adrenal, lacrimal and salivary glands, kidney, pancreas, intestine, lung

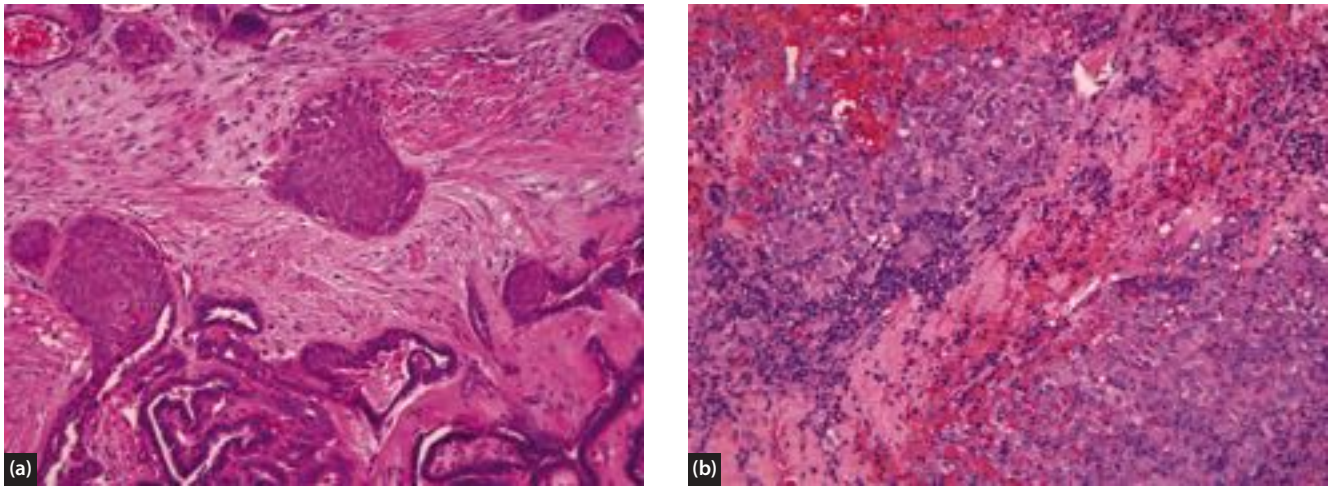


Figure 58.11 Squamous differentiation. (a) Papillary thyroid carcinoma exhibiting isolated areas of squamous differentiation (squamous morulae), which are seen focally in up to 50% of cases. The squamoid cells do not show the typical nuclear features that define PTC (*H&E stain, medium magnification*). **(b)** Carcinoma with thymus-like elements (CASTLE) showing smooth-contoured lobules of non-keratinizing squamoid epithelial cells demarcated by a central broad fibrous septum, percolated by lymphocytes and plasma cells (*H&E stain, medium magnification*).

TABLE 58.2 Conditions associated with squamous epithelium in the thyroid gland

Non-neoplastic	Neoplastic
Nodular hyperplasia (goitre)	Papillary carcinoma
Chronic lymphocytic thyroiditis and variants	Squamous cell carcinoma, primary or secondary
Hashimoto's thyroiditis	Mucoepidermoid carcinoma, primary or secondary
Following FNAC, core biopsy or contralateral lobectomy	Carcinoma with thymus-like elements (CASTLE)
Developmental solid cell nests and thymic rests	Teratoma

TABLE 58.3 Conditions associated with oncocytic (oxyphilic) epithelium in the thyroid gland[22, 24]

Non-neoplastic	Neoplastic
Hashimoto's thyroiditis	Follicular adenoma
Nodular hyperplasia	Follicular carcinoma
Graves' disease	Papillary thyroid carcinoma
Post-irradiation	Medullary carcinoma
Ageing	Anaplastic carcinoma

and sinonasal tract. The incidence of oncocytic change increases with advancing age and may be extensive at any one site (oncocytosis). When such cells occur in the thyroid, they are termed Hürthle cells (Askanazy cells). It is a purely descriptive term and does not in itself indicate biological potential – oncocytic cells occur in both non-neoplastic and neoplastic (benign and malignant) conditions (mitochondriomas) (Table 58.3).

Oncocytic metaplasia is believed to occur in response to pathological or physiological stress and the oxygen-sensitive nature of the mitochondria renders the cells unusually susceptible to traumatic/ischaemic injury. There is ongoing debate as to whether such oncocytic transformation is a form of metaplasia or more correctly represents a process of transdifferentiation.[23] The pathogenetic mechanisms underpinning oncocytic change are complex. The genetic events driving oncocytic change involve mutations in mitochondrial DNA and somatic mutations that affect mitochondrial function. Importantly, these changes are largely unrelated to the genetic events that result in proliferation and neoplastic transformation of thyroid follicular epithelial cells.

There is hallmark concomitant nuclear enlargement often with striking nuclear pleomorphism, coarse karyoplasm and conspicuous nucleolation, even in benign oncocytes. The distinction between oncocytic hyperplasia and neoplasia can be difficult, particularly in the context of thyroiditis. Note that, in autoimmune thyroid disease, oncocytic change is not restricted to Hashimoto's thyroiditis but may also be encountered in long-standing Graves' disease. Oncocytic change occurring in follicular nodules and/or multinodular goitre is conventionally regarded as hyperplastic, whereas clonality studies have demonstrated that many of the larger nodules are in fact monoclonal, thus the biologically correct approach would be to regard these as follicular adenomas.

The mitochondria themselves stain with the phosphotungstic acid haematoxylin (PTAH) method. Positive immunostaining for cytokeratins (notably CK14), vimentin, anti-mitochondrial antibody and weakly for thyroglobulin (TG) is typical. Carcinoembryonic antigen (CEA/CD66e) reactivity is variable. Electron microscopy demonstrates abnormally configured mitochondria (Figure 58.12).

Thyroiditis

The various manifestations of thyroiditis are summarized in Table 58.4. These may be either non-autoimmune or autoimmune, the latter typified by Hashimoto's thyroiditis and Graves' disease and their variants. Drug-induced thyroiditis is associated with the use of a number of drugs including amiodarone, lithium, interferon-alpha and interleukin-2 (Figure 58.13).

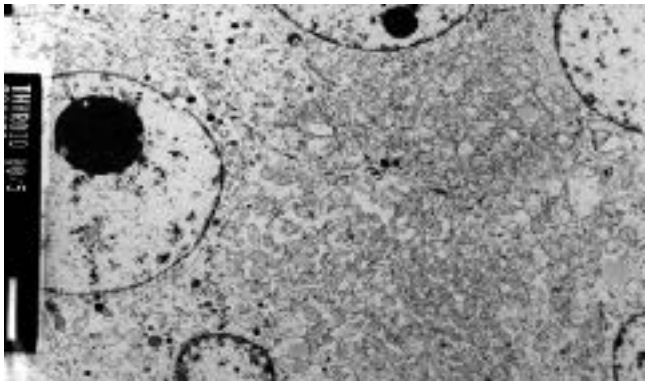


Figure 58.12 Transmission electron micrograph of several tumour cells from a poorly differentiated oncocytic (oxyphil) carcinoma of the thyroid gland. Note the cytoplasmic expansion by scores of swollen mitochondria and paucity of other cell organelles. Two prominent osmiophilic macronucleoli are also plainly seen (*TEM, ultra-high magnification*).

TABLE 58.4 Classification and features of thyroiditis[20,22]

Characteristics	Hashimoto's thyroiditis (chronic lymphocytic or chronic autoimmune thyroiditis)	*Painless* Postpartum thyroiditis (subacute lymphocytic thyroiditis)	*Painless* Sporadic thyroiditis (subacute lymphocytic thyroiditis)	*Painful* Subacute thyroiditis (de Quervain's, giant-cell, pseudo-granulomatous thyroiditis)	*Suppurative* Thyroiditis (infectious, bacterial, pyogenic thyroiditis)	Riedel's thyroiditis
Age	All ages, peak 30–50	Childbearing age	All ages, peak 30–40	20–60	20–40	30–60
Sex ratio	8–9 : 1		2 : 1	5 : 1	1:1	3–4 : 1
Cause	Autoimmune	Autoimmune	Autoimmune	Unknown	Infectious	Unknown
Thyroid function	Hypothyroidism	Can be thyrotoxic, hypothyroid or both	Can be thyrotoxic, hypothyroid or both	Can be thyrotoxic, hypothyroid or both	Euthyroid	Euthyroid
TPO status	High	High	High	Low	Absent	Present
ESR	Normal	Normal	Normal	High	High	Normal
Gross pathological features	Symmetrical diffuse enlargement of the thyroid gland Firm consistency, pale colour and multilobulated	Firm to hard, tan white appearance and nodules of varying size	Firm to hard, tan white appearance and nodules of varying size	Firm to hard, tan white appearance and nodules of varying size	Variable appearance including focal or diffuse enlargement and abscess formation Can appear normal	Thyroid replaced by dense, tan-white, firm to hard tissue

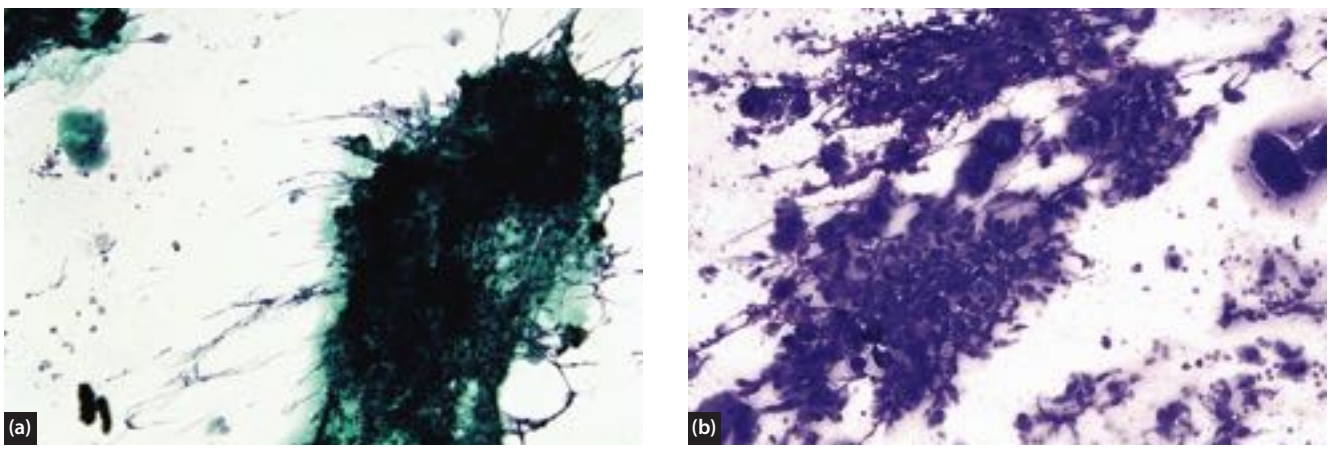
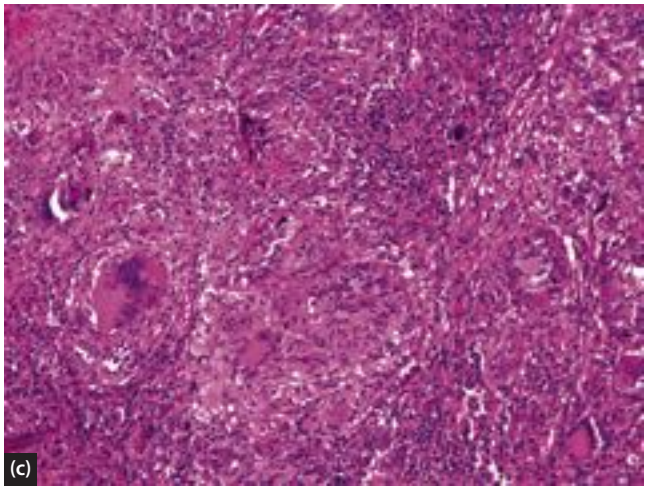
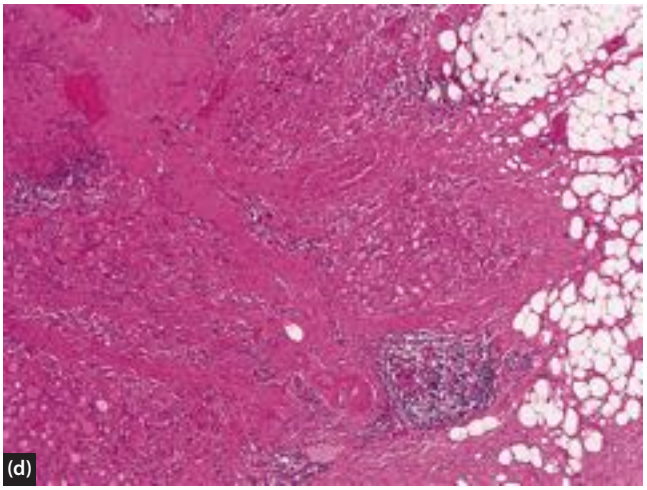


Figure 58.13 Thyroiditis. (a) FNAC sample in granulomatous thyroiditis, suspect of tuberculosis. Part of an epithelioid histiocytic granuloma is shown with characteristic overlapping, tangled, angulated ('hockey sticks') and elongated (smeared or streamed) nucleoplasm plus an adjacent dissociated polykaryocytic giant cell. There is no colloid content and no obvious necrosis (*Pap stain, medium magnification*). **(b)** Complimentary FNAC smear from the same case. Several epithelioid histiocytic granulomata are noted with more numerous plurinucleate giant cells. Again, there is minimal colloid. Care must be taken to discriminate between multi-nucleate giant cells, often of Langhans' type, of mononuclear/macrophage/histiocyte lineage and aspirated intact tri-dimensional thyroid follicles (pseudo-giant cells) (*MGG stain, medium magnification*). *(Continued)*





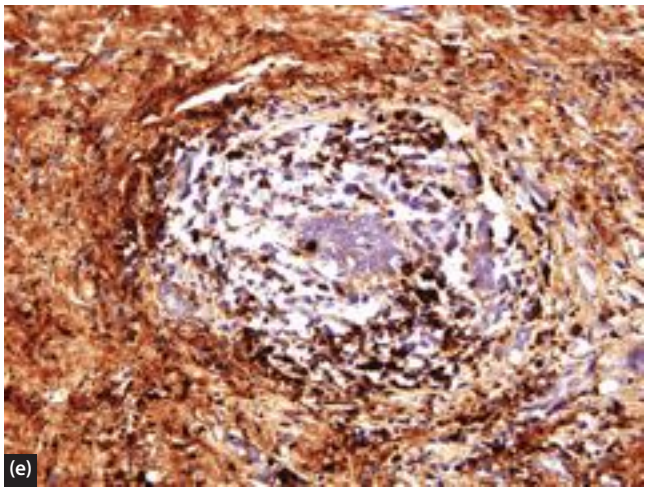


Figure 58.13 (Continued) Thyroiditis. (c) Non-necrotizing granulomatous thyroiditis typical of subacute (De Quervain's) thyroiditis. There is folliculocentric lymphohistiocytic inflammation, loose epithelioid granuloma formation with multinucleate giant cell transformation, follicle destruction and localized colloidophagy. There is little fibrosis in this early phase of the disease (*H&E stain, medium magnification*). **(d)** Riedel's thyroiditis (Riedel's struma, ligneous thyroiditis), acute phase illustrating destructive, non-granulomatous fibroinflammatory tissue percolating beyond thyroid gland pseudocapsule into perithyroidal fat with occasional lymphoid aggregates. Phlebitis and nodular fibro-occlusive vasculopathy were seen throughout this thyroid gland (*H&E stain, low magnification*). **(e)** Replicate section of Riedel's thyroiditis stained for IgG4, highlighting excess numbers of positive plasma cells plus more diffuse background reactivity, presumably of serum origin, supportive of IgG4-related sclerosing disease. Both the IgG4 positive plasma cell count per high-power field and the IgG4:IgG plasma cell ratio were elevated, though not uniformly throughout the specimen (*IgG4 IHC, high magnification*).

Lateral aberrant thyroid tissue

Lateral aberrant thyroid (LAT) tissue or gland describes anomalous deposits of follicular thyroid tissue in the lateral neck. Originally believed to indicate persistent lateral thyroid anlage, the modern view is that the overwhelming majority, but not all, actually represent metastatic follicular thyroid carcinoma or follicular variant of papillary thyroid carcinoma (PTC), the cytonuclear morphology of which may be so deceptively bland as to be virtually indistinguishable from normal or hyperplastic thyroid parenchyma proper.[23]

Pragmatically, any such deposits lateral to the carotid sheath ought to be regarded as metastatic disease until otherwise proven. Those extracapsular deposits medial to the carotid sheath may represent either benign sequestrated (parasitic) thyroid nodules (**Figure 58.14**), which generally recapitulate the appearances in the body of the main gland proper, or metastatic tumour. Benign thyroid tissue inclusions in cervical lymph nodes are rarely encountered and are difficult to confirm with certainty.

Hyperplastic nodules

Historically, multiple nodules as part of multinodular goitre, either incompletely capsulated or unencapsulated, are designated hyperplastic (adenomatoid or cellular colloid) nodules. One or more may predominate, thereby simulating a solitary nodule clinically and/or radiologically (**Figure 58.15**). They do not normally compress the adjacent gland, which oftentimes displays a similar growth pattern. Secondary retrogressive changes frequently present, sometimes extensive, include coarse fibrosclerosis (sometimes resembling a radial scar), cystic degeneration, calcification, infarction, fresh haemorrhage, haemosiderosis, siderophages, foam cells, cholesterol granulomata, endarteritis obliterans and localized inflammation. Squamous, lipocytic, chondroid, osseous and oncocytic (oxyphil) metaplasia are occasionally seen. Simple papillae (papillary hyperplastic nodule) do rarely occur and the papillae tend to radiate towards the centre of the lesion (**Figure 58.16**).[25] Exhaustive efforts to exclude papillary thyroid carcinoma must be pursued under these circumstances.

The concept of thyroid follicular epithelial dysplasia remains theoretical. Up to 70% of hyperplastic nodules are in fact clonal proliferations and can express various markers of malignant follicular-patterned thyroid tumours. However, no morphological, immunohistochemical or molecular study to date has been able to discriminate between adenomatoid nodules, follicular adenoma and follicular carcinoma with absolute sensitivity and specificity.[26]

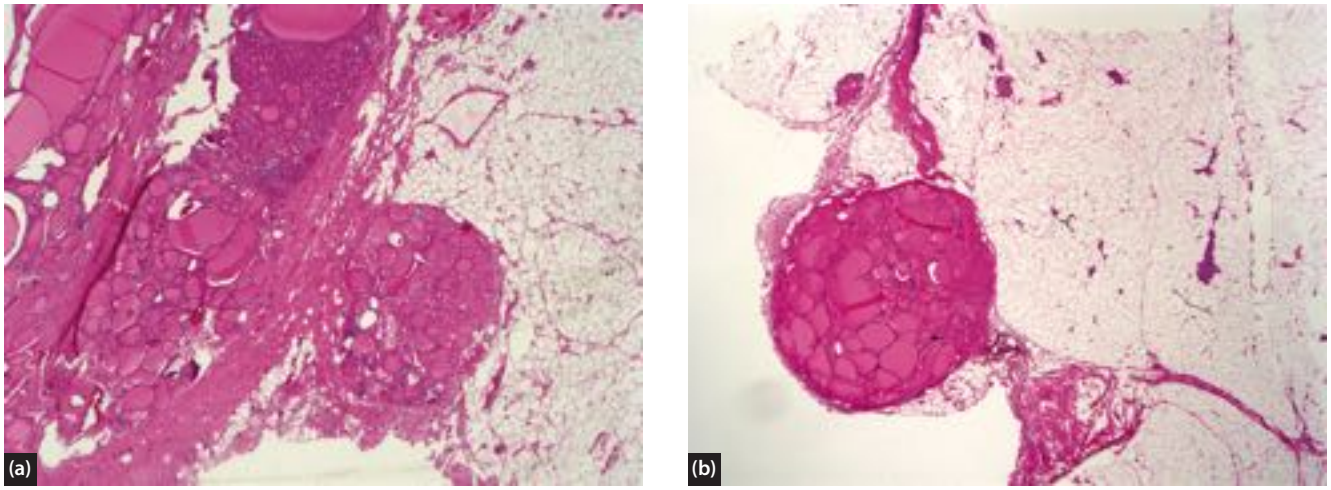


Figure 58.14 Lateral aberrant thyroid tissue. (a) Pericapsular thyroid nodule protruding outside the confines of the anatomical thyroid pseudocapsule, impinging upon perithyroidal fat with an expansile contour. This is the formative stage of sequestration (*H&E stain, low magnification*). **(b)** Extraglandular sequestrated (parasitic) thyroid nodule, completely detached from eutopic thyroid gland proper, but still within the confines of the central neck compartment (*H&E stain, low magnification*).



Figure 58.15 Total thyroidectomy specimen showing a protruberant, well-circumscribed, ovoid mass arising from the left lower pole, clinically excised as a solitary thyroid nodule. This proved to be a dominant hyperplastic (adenomatoid) nodule arising in chronic lymphocytic (Hashimoto's) thyroiditis with several smaller intraparenchymal nodules throughout the main body of the gland bilaterally.

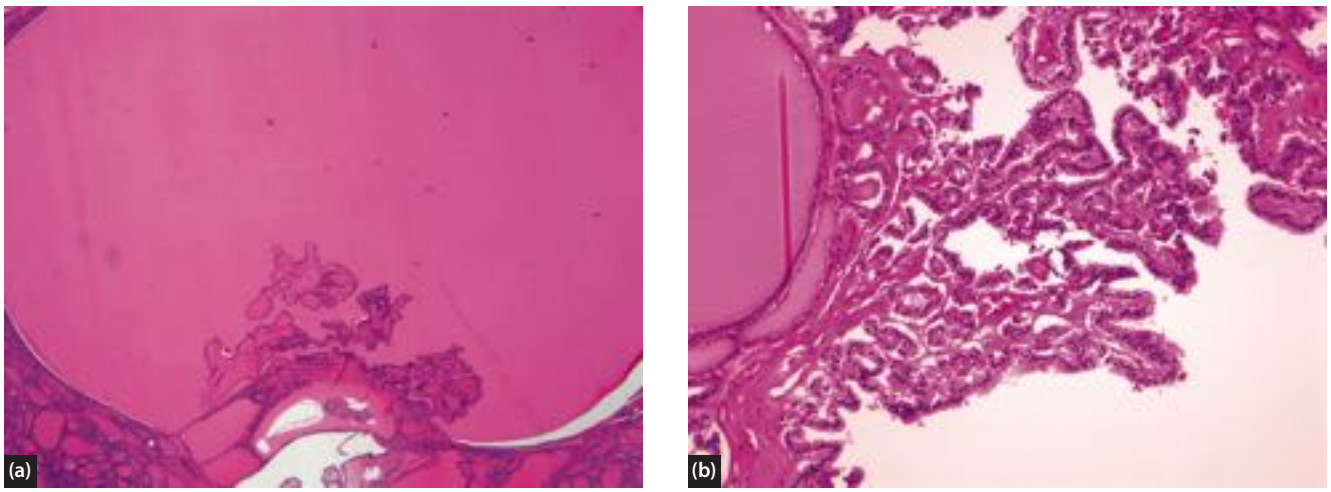


Figure 58.16 Hyperplastic nodules. (a) The edge of a papillary hyperplastic nodule showing localized intracystic mural papillary proliferation immersed in colloid. The papillary projections are simple in contour and tend to project towards the epicentre of the lesion (*H&E stain, low magnification*). **(b)** Part of a different intracystic papillary hyperplastic nodule, also illustrating arborescent centrifugally projecting papillae. The epithelial cells are monolayered, well-polarized and bland. There were no cytonuclear or architectural features to indicate papillary thyroid carcinoma despite a rigorous search (*H&E stain, medium magnification*).

TABLE 58.5 WHO classification of tumours of the thyroid gland[35]

Follicular adenoma
Hyalinizing trabecular tumour
Other encapsulated follicular-patterned thyroid tumours Follicular tumour of uncertain malignant potential Well-differentiated tumour of uncertain malignant potential Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
Papillary thyroid carcinoma (PTC) Papillary carcinoma Follicular variant of PTC Encapsulated variant of PTC Papillary microcarcinoma Columnar cell variant of PTC Oncocytic variant of PTC
Follicular thyroid carcinoma (FTC), NOS FTC, minimally invasive FTC, encapsulated angioinvasive FTC, widely invasive
Hürthle (oncocytic) cell tumours Hürthle cell adenoma Hürthle cell carcinoma
Poorly differentiated thyroid carcinoma
Anaplastic thyroid carcinoma
Squamous cell carcinoma
Medullary thyroid carcinoma
Mixed medullary and follicular thyroid carcinoma
Mucoepidermoid carcinoma
Sclerosing mucoepidermoid carcinoma with eosinophilla
Mucinous carcinoma
Ectopic thymoma
Spindle epithelial tumour with thymus-like differentiation
Intrathyroid thymic carcinoma
Paraganglioma and mesenchymal/stromal tumours Paraganglioma Peripheral nerve sheath tumours (PNSTs) Schwannoma Malignant PNST Benign vascular tumours Haemangioma Cavernous haemangioma Lymphangioma Angiosarcoma Smooth muscle tumours Leiomyoma Leiomyosarcoma Solitary fibrous tumour
Haematolymphoid tumours Langerhans cell histiocytosis Rosai-Dorfman disease Follicular dendritic cell sarcoma Primary thyroid lymphoma
Germ cell tumours Benign teratoma (grade 0 or 1) Immature teratoma (grade 2) Malignant teratoma (grade 3)
Secondary tumours

Follicular adenoma

The WHO (4th edition, 2017) classification of tumours of the thyroid gland is reproduced in Table 58.5.[27] Follicular adenoma classically occurs as a solitary benign, encapsulated tumour, which shows follicular epithelial differentiation with no evidence of either capsular or vascular invasion and neither architectural nor cytonuclear features of papillary thyroid carcinoma (Figure 58.17). It possesses a circumferential, smooth-contoured or gently undulating, slender, fibrous delimiting capsule, usually displaying little variation in thickness – fields of capsular augmentation warrant a conscientious search to exclude a carcinoma, especially if FNAC has not previously been attempted. Surrounding native gland may be compressed and/or atrophic.[8, 22] Internally, there may be a variety of growth patterns, such as normofollicular, microfollicular (foetal), macrofollicular (colloid), solid, trabecular and organoid, though the architecture tends to be fairly uniform within any individual example. Mitoses are few. Degenerative stromal changes, particularly post-FNAC, are identical to multinodular hyperplasia but squamous metaplasia is uncommon and, where present, merits consideration of papillary thyroid carcinoma, follicular variant (FVPTC).

Histological subtypes of adenoma include solid, foetal, oxyphilic (oncocytic), clear cell, signet ring cell (Figure 58.18) and lipoadenoma, defined according to the predominant growth pattern (accounting for over 75% of the overall tumour). These, however, do not differ clinically or in biological behaviour from conventional follicular adenoma. There is some commonality in architecture and cytological pattern across the follicular tumours, both adenomas and carcinomata (Box 58.1).

Atypical adenoma (follicular tumour of uncertain malignant potential, FT-UMP) is used to describe follicular neoplasms that display some worrisome microscopical features though falling short of unequivocal capsular or vascular infiltration.[28] These include irregularly thickened capsule, partial thickness incursions into, but not completely through, the capsule, hypercellularity, increased mitoses and/or abnormal forms and nuclear atypia (Figure 58.19).



Figure 58.17 The cut surface of a benign follicular adenoma showing a largely solid, fleshy texture with localized cystic change. The perimeter is evenly contoured and the investing capsule is uniformly slender.

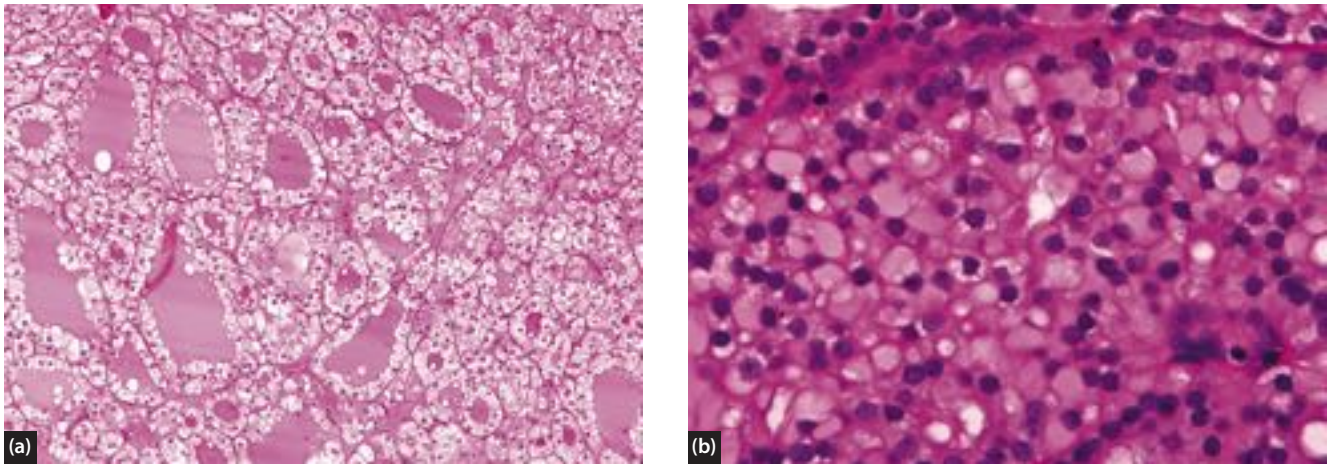


Figure 58.18 Follicular adenoma. (a) Clear cell variant of follicular adenoma. Virtually the entire tumour was composed of colloid filled follicles bounded by thyrocytes possessing abundant faintly reticulated, optically clear cytoplasm (*H&E stain, medium magnification*). **(b)** Signet ring variant of follicular neoplasm. The individual cells are bloated by dense eosinophilic cytoplasm sometimes displacing and/or compressing the nucleus to the cytoplasmic periphery (signet ring appearance) (*H&E stain, high magnification*).

BOX 58.1 Histological variants of follicular neoplasms

- Hyalinizing trabecular adenoma and carcinoma
- Signet ring adenoma and carcinoma
- Mucinous variant
- Clear cell follicular neoplasm (lipid-rich adenoma)
- Follicular adenoma with papillary hyperplasia
- Encapsulated papillary oncocytic neoplasm (follicular adenoma and carcinoma, oncocytic variant with papillary growth)
- Glomeruloid variant
- Meningioma-like tumour of the thyroid
- Follicular neoplasm with lipomatous stroma (adenolipoma/lipoadenoma/thyrolipoma)
- Follicular neoplasm with cartilaginous metaplasia
- Atypical adenoma
- Follicular adenoma with bizarre nuclei
- Hyperfunctioning follicular tumours ('hot nodules')

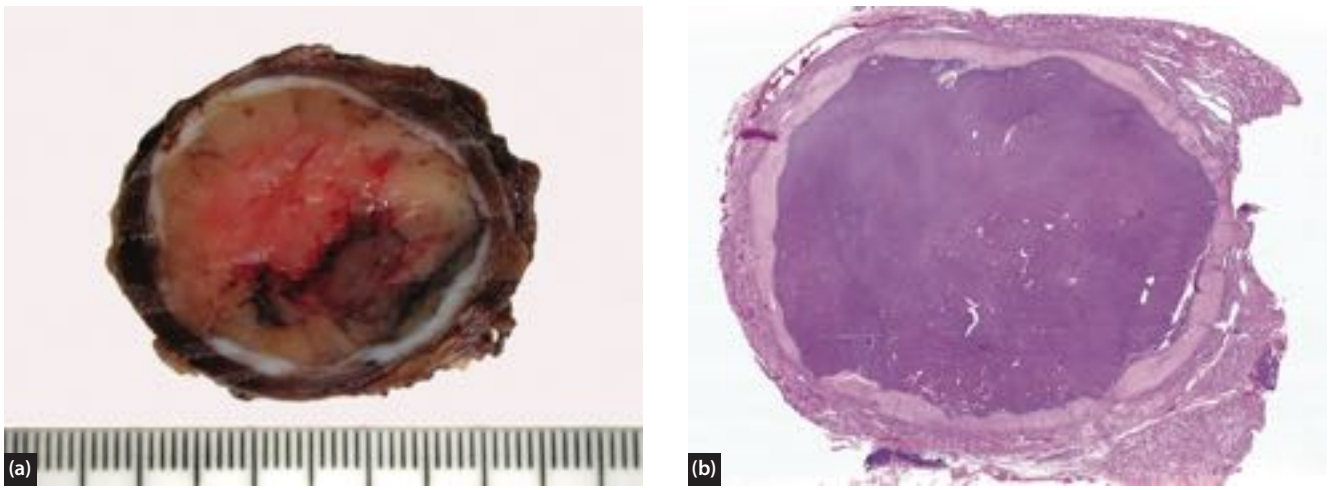


Figure 58.19 Atypical follicular adenoma. (a) A cross-sectional slice through an atypical adenoma (follicular tumour of uncertain malignant potential, FT-UMP). Despite the widespread capsular fibrosis and multiple, irregular, virtually full-thickness internal incursions, at no point can convincing complete transcapsular infiltration be demonstrated. **(b)** Whole mount preparation of the same lesion. Circumferentially, tumour does not invade beyond the original capsular contour (*H&E stain, ultra-low magnification*).

Hyalinizing trabecular tumours

Hyalinizing trabecular tumours (HTTs) are a group of neoplasms originally regarded as adenomas (hyalinizing trabecular adenoma/HTA, paraganglioma-like adenoma of the thyroid/PLAT). It has subsequently transpired that the supposed characteristic organoid growth pattern with interstitial perivascular hyalinization may also be seen focally in nodular hyperplasia plus a number of other benign and malignant thyroid neoplasms, many, though not all, showing histological features of papillary thyroid carcinoma, including *RET/PTC* gene rearrangements. In those examples of pure HTT architecture without papillary carcinomatous morphology

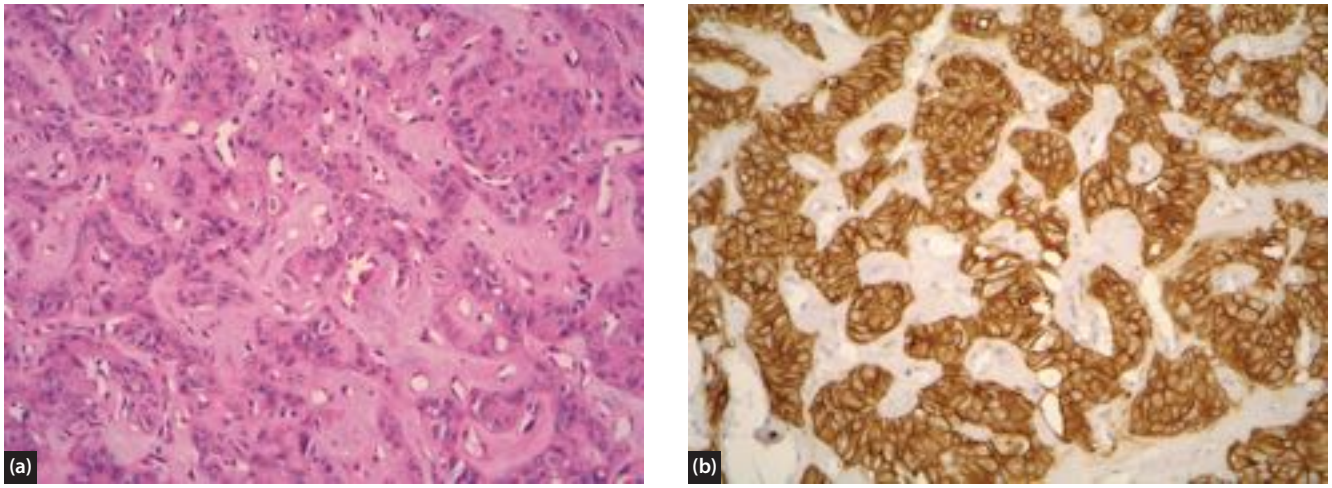


Figure 58.20 Hyalinizing trabecular tumour. (a) Minimally invasive hyalinizing trabecular carcinoma demonstrating the typical organoid nested and trabecular architecture separated by hyalinized interstitium, richly endowed with blood vessels. Elsewhere, this example showed mushrooming transcapsular growth. There are no features to suggest papillary thyroid carcinoma in this neoplasm but there was synchronous classical papillary thyroid carcinoma separately in the specimen (*H&E stain, medium magnification*). **(b)** The same tumour illustrating universal Ki67 (MIB-1) immunoreactivity. Note that this is peculiarly membranous and cytoplasmic in distribution and is antibody clone/manufacturing source dependent. Ki67 is conventionally used as a proliferation marker where, in other circumstances, it stains the nuclei only of those cells in certain phases of the cell cycle (*Ki67 IHC, medium magnification*).

there appears to be a spectrum of biological potential ranging from adenoma to carcinoma, both minimally invasive and widely invasive by conventional criteria.[29] A proportion of such neoplasms exhibit characteristic, peculiar, avid cytoplasmic Ki67 (MIB-1) immunostaining (Figure 58.20). Immunopositivity for cytokeratins, thyroglobulin and vimentin generally with negative panneuroendocrine marker and calcitonin staining discriminates HTT from paraganglioma proper and medullary thyroid carcinoma.

Follicular carcinoma of the thyroid

Follicular thyroid carcinoma (FTC) is a malignant epithelial tumour arising in both eutopic thyroid gland and/or heterotopic thyroid tissue, showing follicular cell differentiation and bereft of the characteristic features of papillary thyroid carcinoma (PTC). It accounts for 5–15% of all thyroid cancers in iodine-sufficient regions. It spreads via haematogenous routes, preferentially to bone and lung with metastatic disease as a presenting feature in 11% of patients. It is divided into two basic categories defined by the extent of capsular infiltration and/or presence of vascular invasion (Table 58.6) and meticulous examination of the tumour capsule and interface with native gland is consequently of paramount importance.

Minimally invasive follicular carcinoma (MIFC) is the common variant and is characterized by microscopical transcapsular invasion and/or pericapsular vascular infiltration.[30] With experience, obvious capsular violation and/or accompanying fibrous capsular thickening may be appreciated in the gross specimen by the unaided eye (Figure 58.21), but not more subtle capsular transgression or vascular permeation.

Widely invasive follicular carcinoma (WIFC) is readily identified grossly by infiltrative, destructive or sometimes multinodular growth, the latter separated by fibrous bands, expanding into surrounding native gland. This may be so strikingly obviously nodular as to be mistaken for multinodular hyperplasia by the unwary, particularly if there is no clearly identifiable vestige of pre-existing capsule for reference.

The interpretation of capsular invasion remains somewhat controversial. Most authorities require full-thickness capsular transgression beyond the original lesional contour (capsular invasive MIFC), whereas a dwindling minority of authors accept a given neoplasm as MIFC if it shows only partial-thickness capsular penetration. Full-thickness violation manifests as multiple foci, less commonly a single nidus, of mushrooming herniation bulging into and displacing surrounding native follicles, without infiltrative/permeative growth. Lateral fibrous capsular thickening (buttressing) and neocapsule formation along the advancing tumour to gland interface are paradigmatic,

TABLE 58.6 Classification of follicular thyroid carcinoma[27]

Traditional	AFIP 2015		WHO 2017
Minimally invasive	Minimally invasive	With capsular invasion	Minimally invasive
		With limited vascular invasion (<4 vessels)	Encapsulated angioinvasive
		With extensive vascular invasion (≥4 vessels)	Widely invasive
Widely invasive	Widely invasive		Widely invasive

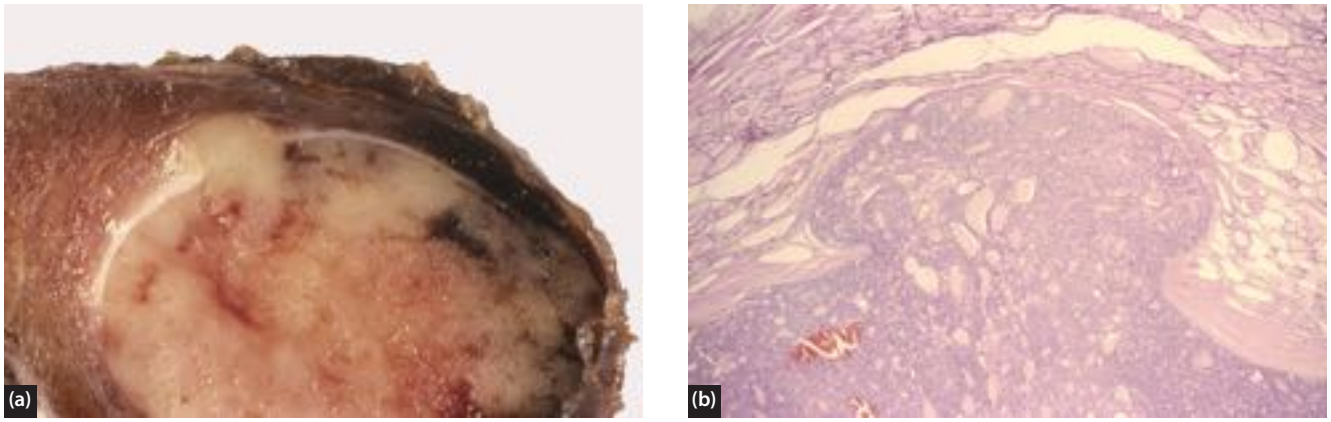


Figure 58.21 Minimally invasive follicular carcinoma. (a) Obvious mushrooming, full-thickness, transcapsular herniation qualifying as minimally invasive follicular carcinoma, easily discernible to the unaided eye during dissection. There is slight lateral capsular buttressing but negligible neocapsule formation along the advancing margin in this example. Note that there is no universally endorsed maximum size limit for this phenomenon. **(b)** The same area viewed histologically corroborates streaming impingement into perilesional native gland with no tentacular/permeative infiltration and neither significant host inflammatory nor stromal response (*H&E stain, low magnification*).

but not invariable. Incomplete capsular encroachment includes areas of irregular, serratiform and/or undulating inner capsular contour, perpendicular dentate capsular incursions and horizontally disposed (entrapped) intracapsular follicles, which do not qualify, though they should prompt further detailed scrutiny, as should any unexplained area of capsular expansion. Circumscribed extracapsular (satellite) nodules may represent MIFC visualized outside the plane of connection with the body of the tumour (though such a pedicle may sometimes be impossible to demonstrate) or a sequestrated (parasitic) congerie of benign follicles. Comparison of the cytonuclear features with the main tumour bulk may aid discrimination here. Current recommendation is that, unless there is identifiable connection with the main tumour mass, such satellitosis should not be regarded as definite evidence of capsular violation.

Artefactual capsular puncture, healing and distortion following FNAC should be interpreted with caution and the entry/exit site of normal capsular blood vessels, where there is typically smooth curvilinear capsular interruption, not misconstrued. Well-sampled tumours that fall short of these criteria are termed follicular tumour of uncertain malignant potential (FT-UMP).

There are studies indicating that both the existence and the extent of vascular invasion are of portentous significance. Whilst there is a general consensus as to what defines angioinvasion (grossly encapsulated angioinvasive MIFC), there remains some dissent. The majority opinion is that tumour penetration should be into medium-calibre or large-calibre intracapsular or extracapsular blood vessels and polypoidal intraluminal growth should be endothelialized with/or without thrombus, though not necessarily adherent (**Figure 58.22**). Tumour invasion and obturation of large calibre veins is sometimes a feature, extending beyond the confines of the thyroid gland, in a pattern akin to infiltration of the renal vein/vena cava by clear cell carcinoma of the kidney. A point of attachment of tumour to vessel wall is a prerequisite for some observers. Free-lying nests of tumour cells may represent artefactual dislodgement. Tumour cells occupying capillary-sized intracapsular vessels are of no proven clinical importance and should be discounted. Tumour within intralesional or subcapsular vessels does not qualify. Reactive vascular endothelial hyperplasia may simulate angioinvasion and, when recognized, ought to prompt a rigorous search for vascular invasion proper. Immunostaining for vascular endothelial markers (e.g. CD31, CD34) and lymphatic endothelium (e.g. D2-40) may be helpful in selected instances. Cognizant that absolute discrimination between blood vessel invasion and lymphatic space infiltration may ultimately be impossible, the RCPath defines vascular invasion as involvement of any definite endothelial-lined space and the current College of American Pathologists (CAP) protocol recommends merging the two and reporting under the unifying designation of lymphovascular invasion.[32]

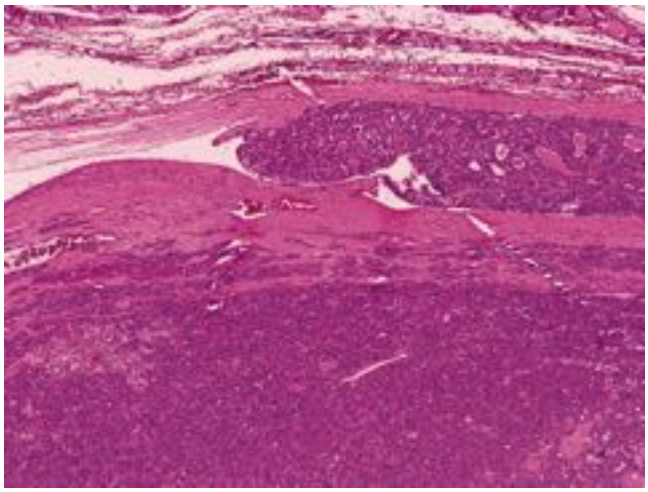


Figure 58.22 Pericapsular angioinvasion qualifying as encapsulated (angioinvasive) minimally invasive follicular carcinoma. There is a broad tongue of endothelialized tumour unequivocally protruding into a large-calibre intracapsular vessel (*H&E stain, low magnification*).

Capsular invasive MIFC without lymphovascular invasion portends an extremely low risk of metastasis (less than 1%), justifying the option of a conservative management approach with treatment by lobectomy, acknowledging that there is a small risk of undertreatment in a minority of cases. The term grossly encapsulated angioinvasive follicular carcinoma has been proposed for encapsulated tumours with any foci of lymphovascular invasion, based on the premise that access to even one or a few endothelial-lined vessels confers the capacity for more aggressive behaviour with heightened risk of recurrence, thereby offsetting a designation of minimal invasion. Encapsulated angioinvasive MIFC with limited (minimal) vascular invasion, defined as a few microscopic foci (up to 4 foci) is said to show a low risk of metastasis (approximately 5%). MIFC with more extensive lymphovascular infiltration (defined as 5 or more foci) is said to portend a higher likelihood of metastasis (up to 42%)[33, 34] and the term grossly encapsulated follicular carcinoma with extensive angioinvasion acknowledges this. Specifying a precise threshold for the number of foci of lymphovascular invasion is, however, controversial, not least because a histological section is a two-dimensional representation of a tri-dimensional system and inadvertent replication by counting infiltration potentially into the same vessel visualized in close proximity and/or in a different plane of section is of dubious biological validity and reproducibility.

WIFC is an aggressive neoplasm with a high risk of distant secondaries (29–66%). It displays infiltrative growth within and beyond the anatomical thyroid pseudocapsule proper, sometimes in the form of successive generations of herniating capsular transgression (**Figure 58.23**). Vascular penetration is common and the more widespread it is, the worse the prognosis.

Extrathyroidal extension (ETE) describes involvement of perithyroidal soft tissues by primary thyroid carcinoma. This may be further subdivided into microscopic (minimal/minor/limited) ETE and macroscopic (extensive/major/massive/marked/gross) ETE. As previously noted, the thyroid pseudocapsule is not a discrete anatomical structure, is incomplete or focally absent in a majority of individuals, is additionally fenestrated by lymphovascular channels and contains small nerve radicles. The histological evaluation of minimal ETE into immediate peri-thyroidal soft tissue is consequently subjective, prone to poor reproducibility and, owing to its limited prognostic value, has been expunged from the UICC/TNM (8th edition, 2017) staging schema.[35] Importantly, both adipocytes and skeletal muscle bundles may be normally encountered within the thyroid gland and may also be a component of a variety of pathological thyroid conditions. The identification of a desmoplastic response, adipocytic and/or muscular impingement in close proximity to large-calibre, thick-walled vessels and/or large nerve trunks, on the other hand, may be more helpful, as such would not be expected within the confines of the thyroid gland proper. Extensive ETE is characterized by direct infiltration well beyond the limits of the thyroid gland into anterior strap musculature (sternohyoid M, sternothyroid M, thyrohyoid M and/or omohyoid M), subcutis, neighbouring viscera including larynx, trachea, oesophagus, recurrent laryngeal nerve, carotid artery or mediastinal vasculature. Extensive ETE is invariably obvious, typically identified by the surgeon perioperatively.

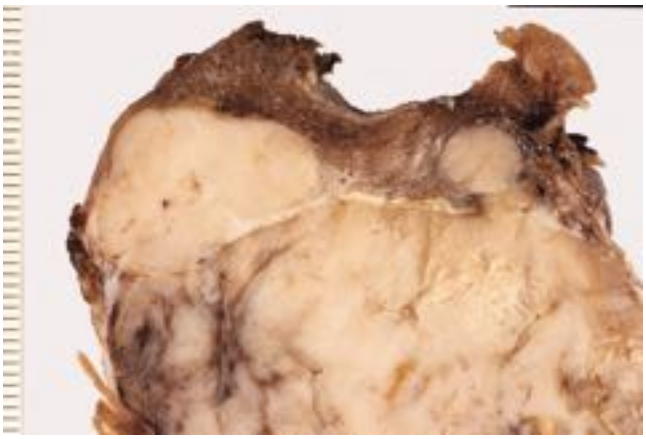


Figure 58.23 The cut surface of a widely invasive follicular carcinoma demonstrating successive generations of capsular transgression to the point where the original lesional capsule becomes almost obscured.

The prognosis for those carcinomas with minimal ETE worsens referenced against those without ETE. Similarly, the survival prospects for those suffering carcinomas with extensive ETE are significantly diminished in comparison with minimal ETE.

Gross or microscopic involvement of surgical margins informs the TNM R stage of a tumour and is of prognostic significance. There is no evidence-based definition for the distance required for complete excision, simply that non-neoplastic tissue is interposed between tumour and excision plane. The exercise of measuring the distance of tumour to closest resection margin is therefore somewhat arbitrary.[33, 36] Initial studies suggesting that a microscopically positive posterior margin poses a significantly higher risk of recurrence than a positive anterior margin merits further scrutiny.[33]

Oncocytic (oxyphil) cell tumours

Follicular neoplasms comprising 75% or more oncocytic (oxyphil) cells are designated as such and are subclassified according to the same criteria as their non-oncocytic counterparts based upon morphology, immunohistochemical profiling and molecular markers as oncocytic (oxyphil) adenoma, oncocytic (oxyphil) tumour of uncertain malignant potential, minimally or widely invasive oncocytic (oxyphil) carcinoma (Hürthle cell carcinoma). Oncocytic variants of papillary thyroid carcinoma, poorly differentiated thyroid carcinoma, undifferentiated (anaplastic) carcinoma and medullary thyroid carcinoma are recognized. Focal clear cell change is common in oncocytic tumours and, where this constitutes over 75% of the lesion, it is traditionally designated as clear cell carcinoma. Under such circumstances, it is imperative to exclude metastatic carcinoma (e.g. renal or adrenal),[37] malignant melanoma, intrathyroidal parathyroid gland neoplasms and clear cell variant of medullary thyroid carcinoma.

Grossly, they are usually single nodules (solitary oxyphil follicular tumour, SOFT) (**Figure 58.24**), although they may be multiple (multiple oxyphil follicular tumour, MOFT) and

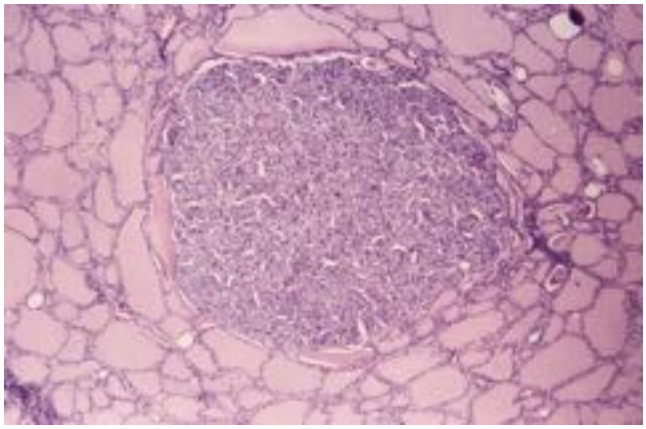


Figure 58.24 A small, benign solitary oncocytic (oxyphil) cell follicular tumour (SOFT), occurring sporadically in a background of chronic lymphocytic (Hashimoto's) thyroiditis. Despite its lack of capsule and occasional rudimentary papillae, there were no diagnostic features to suggest papillary thyroid carcinoma (*H&E stain, low magnification*).



Figure 58.25 The cut surface of a classical papillary thyroid carcinoma illustrating a solid, granular appearance with adjoining encysted elements distended by inspissated colloid. The yellow punctate structures represent psammoma calcification and imparted a gritty texture.

are sometimes associated with Hashimoto's thyroiditis and/or conventional papillary thyroid carcinoma (PTC). A higher proportion of oncocytic (oxyphil) tumours are malignant than other follicular lesions, and when staged comparably there is some experience that they fare worse than their non-oncocytic counterparts, possibly a sequela of their low avidity for radioiodine. The incidence of malignancy in oncocytic (oxyphil) cell neoplasms increases with size, with 17%, 23% and 65% or more associated with maximum dimensions of less than 1 cm, between 1 cm and 4 cm and larger than 4 cm respectively.[38] Most examples are sporadic. Familial examples are rare and may indicate a germline mutation.[39]

Macroscopically they are classically mahogany brown tumours with a propensity for ischaemic infarction, either spontaneously or post-FNAC. They may show numerous histological patterns, including papillary areas, which may morphologically overlap with oncocytic (oxyphil) papillary thyroid carcinoma (PTC). They are typified by cytonuclear atypia and mitoses, though in isolation these do not reproducibly predict biological behaviour.

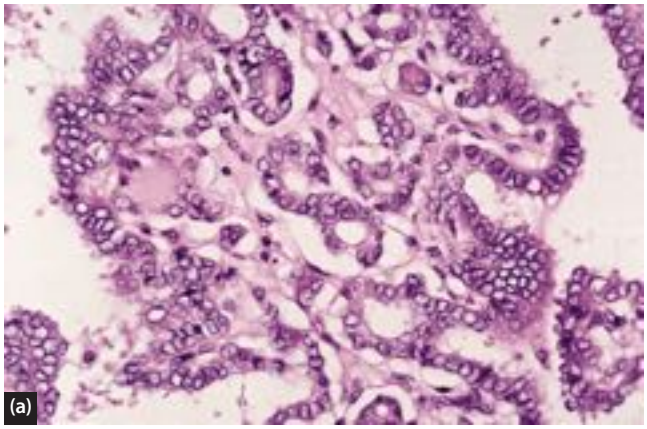
Oncocytic (oxyphil) parathyroid gland neoplasms should always be considered when evaluating a potential oncocytic (oxyphil) thyroid neoplasm, as they may be indistinguishable by routine orthodox microscopy without recourse to immunostaining.

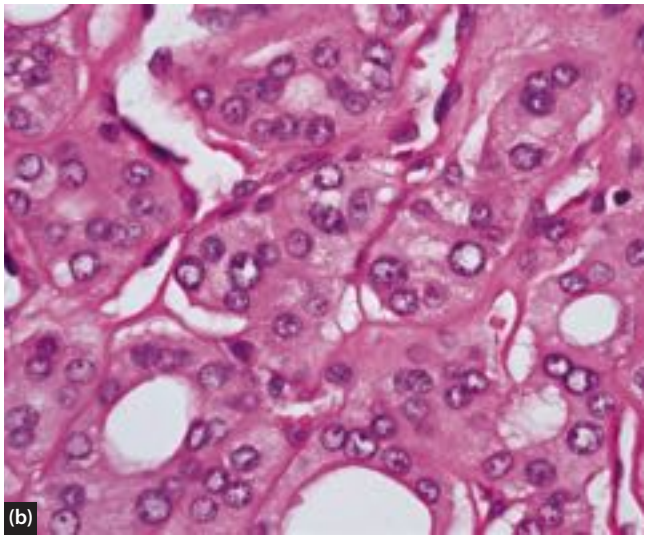
Papillary thyroid carcinoma

Papillary thyroid carcinoma (PTC) is a malignant epithelial tumour showing follicular cell differentiation with characteristic nuclear features. It accounts for approximately 80% of all thyroid cancer and is also the commonest paediatric thyroid malignancy. In adults it typically occurs between the ages of 20 and 50 years with a female preponderance with less pronounced gender bias in patients over 50 years old. It normally carries an excellent prognosis, especially in younger patients. In areas of adequate dietary iodine, papillary thyroid carcinoma usually presents as a solitary thyroid nodule. In regions of iodine insufficiency multinodular goitre is common and papillary thyroid carcinoma can present as a more prominent or distinctive nodule. It has a propensity for lymphatogenous spread, initially to locoregional lymph nodes.

The potential macroscopical and microscopical manifestations of PTC are protean. Prototypically, it is invasive with irregular outline and either a scirrhous or granular, gritty texture often with multiloculated cystic change and colloid contents (**Figure 58.25**). The encapsulated follicular variant of PTC (EFVPTC, Lindsay tumour) is usually well circumscribed possessing a solid, fleshy cut-surface, closely resembling an adenoma.

The principal defining feature of PTC is its nuclear morphology by light microscopy (**Figure 58.26**), thus the diagnosis of PTC is sustainable even in the absence of invasive growth. Crucially, however, the distinctive appearances may be very localized and, in an appropriate context, the diagnosis may still be entertained in their absence. Ordinarily, there is at least focal nucleomegaly, nuclear crowding and nuclear overlap ('basket of eggs'). Homogenization of karyoplasm ('ground glass' nuclei) with margination of chromatin (likened to the empty-looking, pupil-less eyes of Harold Gray's cartoon strip characters, most famously the waif Little Orphan Annie and her canine companion Sandy) is characteristic, but not pathognomonic. It is not invariable, it is rarely present in FNAC and frozen sections, it may be encountered in other non-neoplastic conditions (notably Hashimoto's thyroiditis, Graves' disease and dyshormonogenetic goitre), it may be simulated by suboptimal tissue fixation (bubbly or pseudo-clear artefact) and is subject to vagaries of inter-observer and intra-observer reproducibility. Longitudinal nuclear grooves ('coffee beans'), nucleolemmal scalloping ('rat bites'), rents and irregularity formed by redundant, folded nuclear membrane and intranuclear cytoplasmic inclusions (pseudo-inclusions) formed by cytoplasmic herniation are typical and may be visualized on both FNAC and frozen section (**Figure 58.27**), but these again are not exclusive and may be mimicked by emptier looking intranuclear bubble artefact (pseudo-pseudo-inclusions,





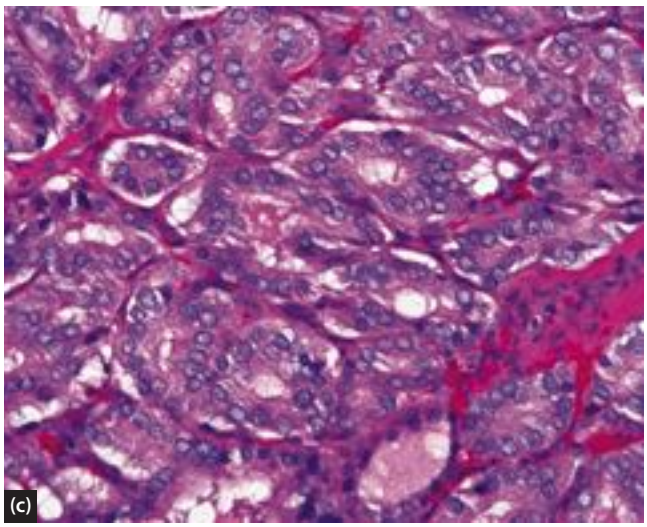


Figure 58.26 Papillary thyroid carcinoma. (a) The characteristic nuclear enlargement, nuclear crowding, nuclear overlap (basket of eggs) and optically clear karyoplasm (Little Orphan Annie eye) of papillary thyroid carcinoma. A few nuclear grooves (coffee beans) and isolated intranuclear cytoplasmic inclusions are also present. **(b)** For comparison, this depicts pseudo-clear (bubbly) nuclear artefact, consequent upon suboptimal tissue fixation and processing. Although there is some anisonucleosis and margination of chromatin, there is no real nuclear crowding or overlap. The nucleoplasm is polyvacuolated with conspicuous nucleolation. Pseudo-inclusions (vacuoles or holes) are numerous, much less densely staining than the thyrocyte cytoplasm and they lack any sharply delimiting nucleolemmal rim. Furthermore, these changes are strikingly zonated, seen towards the centre of a dominant hyperplastic nodule and gradually merged with propitiously preserved follicles more peripherally (*H&E stain, high magnification*). **(c)** Dyshormonogenetic goitre from an adolescent with Pendred's syndrome. Again, there is apparent homogenization of chromatin with plentiful nuclear grooves ('coffee beans'), albeit with evenly disposed nuclei and preponderant follicular-patterned growth. The very comprehensive, bilateral and diffuse distribution of these changes throughout the entire gland with preserved lobular architecture militates against malignancy here, with the proviso that this may be a vexatious differential diagnosis (*H&E stain, high magnification*).

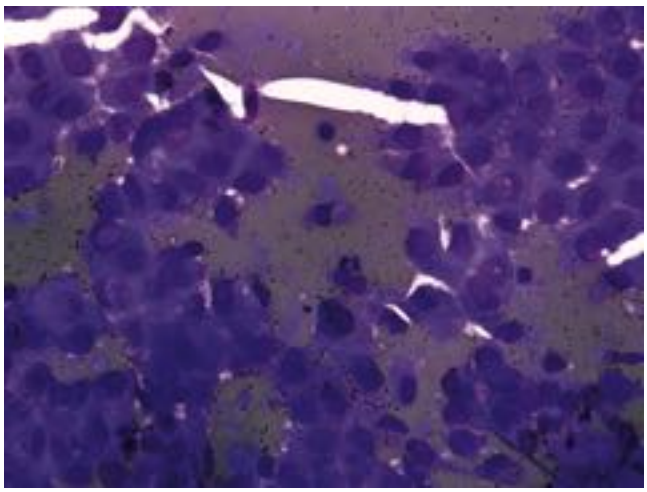


Figure 58.27 FNAC preparation illustrating numerous rounded intranuclear cytoplasmic inclusions and several longitudinal nuclear grooves (coffee beans) in papillary thyroid carcinoma (*MGG stain, high magnification*).

vacuoles, holes). The latter is often unduly widespread and lacks the discrete nuclear membrane rimming of true intranuclear cytoplasmic inclusions in *forme pleine*.

A papillary architecture is typical though by no means universal. The papillae are often well vascularized and complexly arborescent, sometimes oedematous (hydropic), hyalinized, fibrocellular, calcified or micropapillary in configuration (Figure 58.28). Follicles are usually present, albeit with an elongated, tortuous or crenated outline ('twisted' follicles) sometimes with rudimentary or abortive papillae and colloid is often more densely hypereosinophilic compared to autochthonous follicles. Intrafollicular multinucleated giant cells of macrophage/histiocyte lineage phagocytosing colloid (colloidophagy) are more often seen in PTC than in other lesions (Figure 58.29).

Psammoma bodies (laminated calcospherites) are present in roughly 50% of PTCs histologically, less frequently on FNAC and are virtually pathognomonic. They probably represent mineralized stromal cores and, therefore, must be stromal in location, in contradistinction to calcified, inspissated intrafollicular colloid (psammomatoid calcification or pseudo-psammoma bodies) seen in normality and other

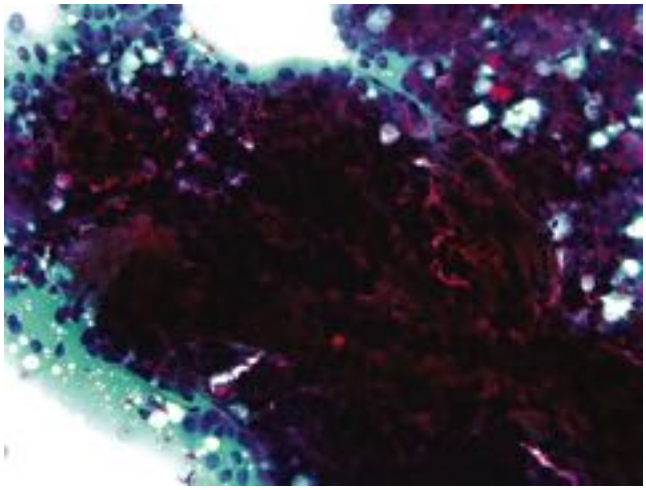


Figure 58.28 FNAC tissue microbiopsy from a papillary thyroid carcinoma. Despite its thickness, obscuring much cytonuclear detail (a few nuclear inclusions and nuclear grooves are nonetheless visible), the branching vascularized fronds are a useful diagnostic feature. Colloid, where present, tends to be globular or in strands ('chewing gum' or stringy colloid) (*Pap stain, medium magnification*).

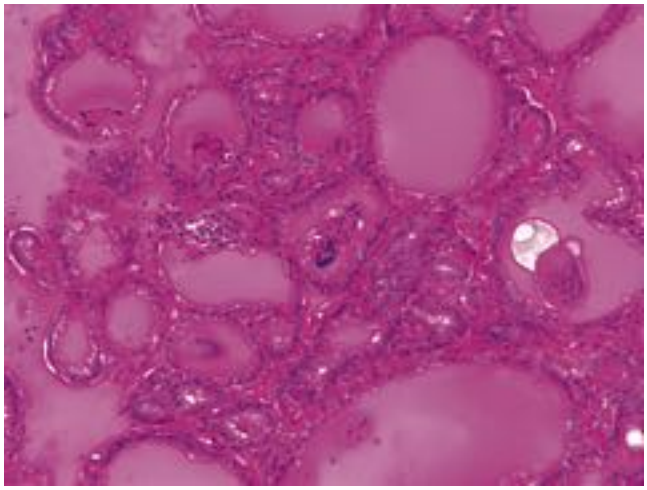
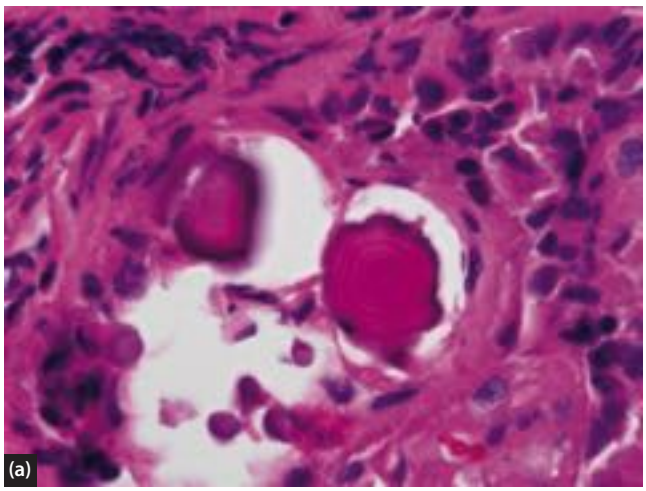


Figure 58.29 Several intrafollicular multinucleate giant cells, of macrophage/monocyte lineage, phagocytosing vacuolated colloid (colloidophagy) in a PTC. This phenomenon is often seen in PTC, but not exclusively so (*H&E stain, high magnification*).

disease states (such as oncocytic tumours) (Figure 58.30). Importantly, psammoma bodies may also be seen in other neoplastic and non-neoplastic conditions, both within and outside the thyroid gland. Rarely, psammoma bodies or linear scoring artefact following microtomy provide the only presumptive evidence of regressed or infarcted PTC. Multicentric PTC is common and represents either intrathyroidal lymphatic spread or synchronous primary tumourogenesis with different *RET/PTC* translocations.

Numerous variants of PTC have been described, none mutually exclusive within an individual tumour (Box 58.2). A single tumour is classified according to its predominant histological pattern. Most subtypes are of no prognostic significance, although tall cell, diffuse sclerosing, diffuse follicular, solid, trabecular, hobnail/micropapillary and dedifferentiated variants (Figure 58.31) are biologically more aggressive in contrast to the encapsulated variant (where conventional infiltrative growth may not be apparent), which portends a highly favourable outcome. Increased mitoses (over two mitoses per ten high-power fields) and tumour necrosis signify worse survival in PTC. PTCs measuring less than 1 cm are associated with an excellent prognosis and the outlook worsens for those tumours exceeding 4 cm. Positive lymph nodal metastasis in PTC is usually an indication for radioactive iodine therapy and the presence of extranodal extension heightens risk of distant metastasis and death. Areas of squamous differentiation (morulae) occur in approximately 50% of cases



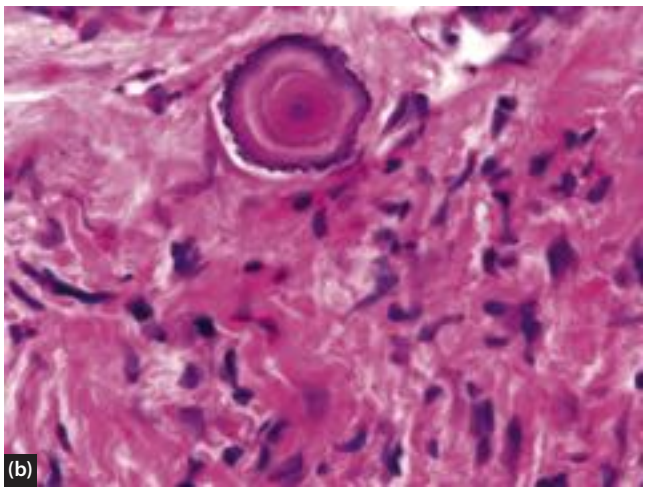
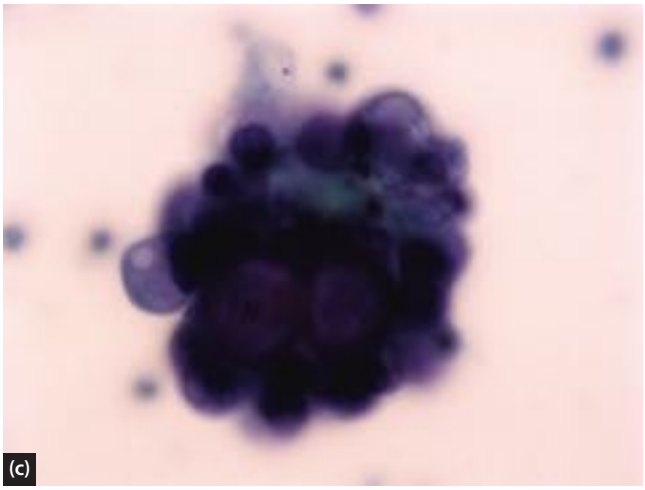


Figure 58.30 Psammoma bodies. (a) Psammoma bodies in papillary thyroid carcinoma. These concentrically laminated concretions are stromal in location. They are often said to represent mineralized tombstones to a mummified cell or papilla, the latter forming the initial nidus for mineral encrustation. They may occasionally be large and complex in configuration. Some of these have splintered during microtomy. Any calcified deposits or other hard objects are prone to dislodgement by the microtome blade and being swept across the tissue section to give parallel linear score artefact (*H&E stain, medium magnification*). **(b)** Psammoma body within fibroblastic interstitium encountered as part of retrogressive change in multinodular hyperplasia. There was no evidence of neoplasia (*H&E stain, high magnification*). *(Continued)*



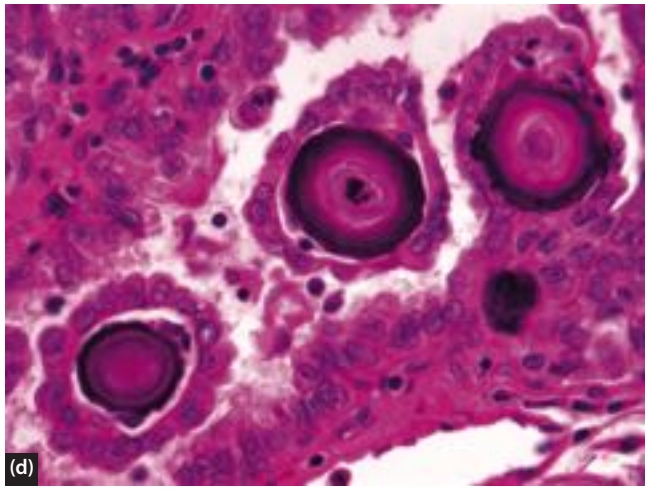
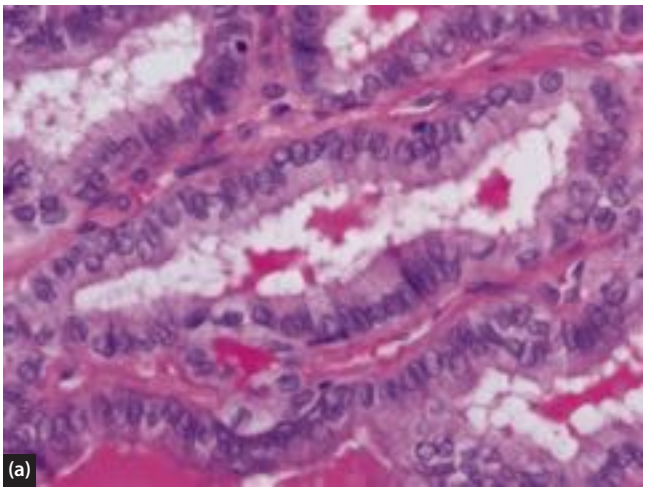


Figure 58.30 (Continued) Psammoma bodies. (c) FNAC from a papillary thyroid carcinoma showing two concentrically lamellated psammoma bodies mantled by vacuolated epithelial cells. Psamoma bodies are seen in 40–60% of papillary thyroid carcinomas in histological sections but in only 20% of cases in FNAC specimens[36] (*H&E stain, high magnification*). **(d)** Three psammomatoid spheroliths (concretions or pseudo-psammoma bodies) occupying follicular lumina, again composed of inspissated, partially mineralized intrafollicular colloid in a case of PTC, but also commonly a feature of oncocytic (oxyphil or Hürthle cell) neoplasms (*H&E stain, high magnification*).

BOX 58.2 Histological variants of papillary thyroid carcinoma[22]

Non-invasive follicular tumour with papillary-like nuclei (NIFTP)
Encapsulated follicular variant (EFVPTC)
Invasive follicular variant
Diffuse follicular variant
Macrofollicular variant
Classical papillary carcinoma
Papillary microcarcinoma (papillary microtumour)
Micropapillary variant.
Tall cell variant
Columnar cell variant
Clear cell variant
Oncocytic (oxyphil/Hürthle cell)
Warthin tumour-like variant
Hobnail variant
Solid pattern
Diffuse sclerosing pattern
Trabecular pattern
Cribriform-morular (including familial adenomatous polyposis-associated carcinomas)
Papillary carcinoma with lipomatous stroma
Variant with exuberant nodular fasciitis-like stroma
Variant with spindle cell metaplasia
Adenoid cystic-like variant
Angiomatoid variant
Dedifferentiated variant

Note that fields of squamous differentiation (common), ossification (uncommon) and mucinous differentiation (rare) may be independently encountered.



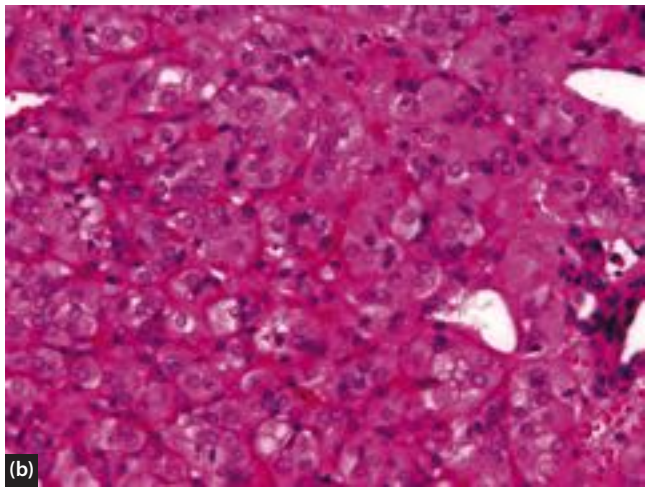


Figure 58.31 PTC variants. (a) Tall cell variant of papillary thyroid carcinoma. The cells are columnar, their height being at least three times greater than their width, and they are not hyperstratified, in contradistinction to columnar cell carcinoma (*H&E stain, high magnification*). **(b)** Solid variant of papillary thyroid carcinoma. The small cell nests demonstrate the distinctive nuclear features. This example behaved extremely aggressively (*H&E stain, high magnification*). *(Continued)*

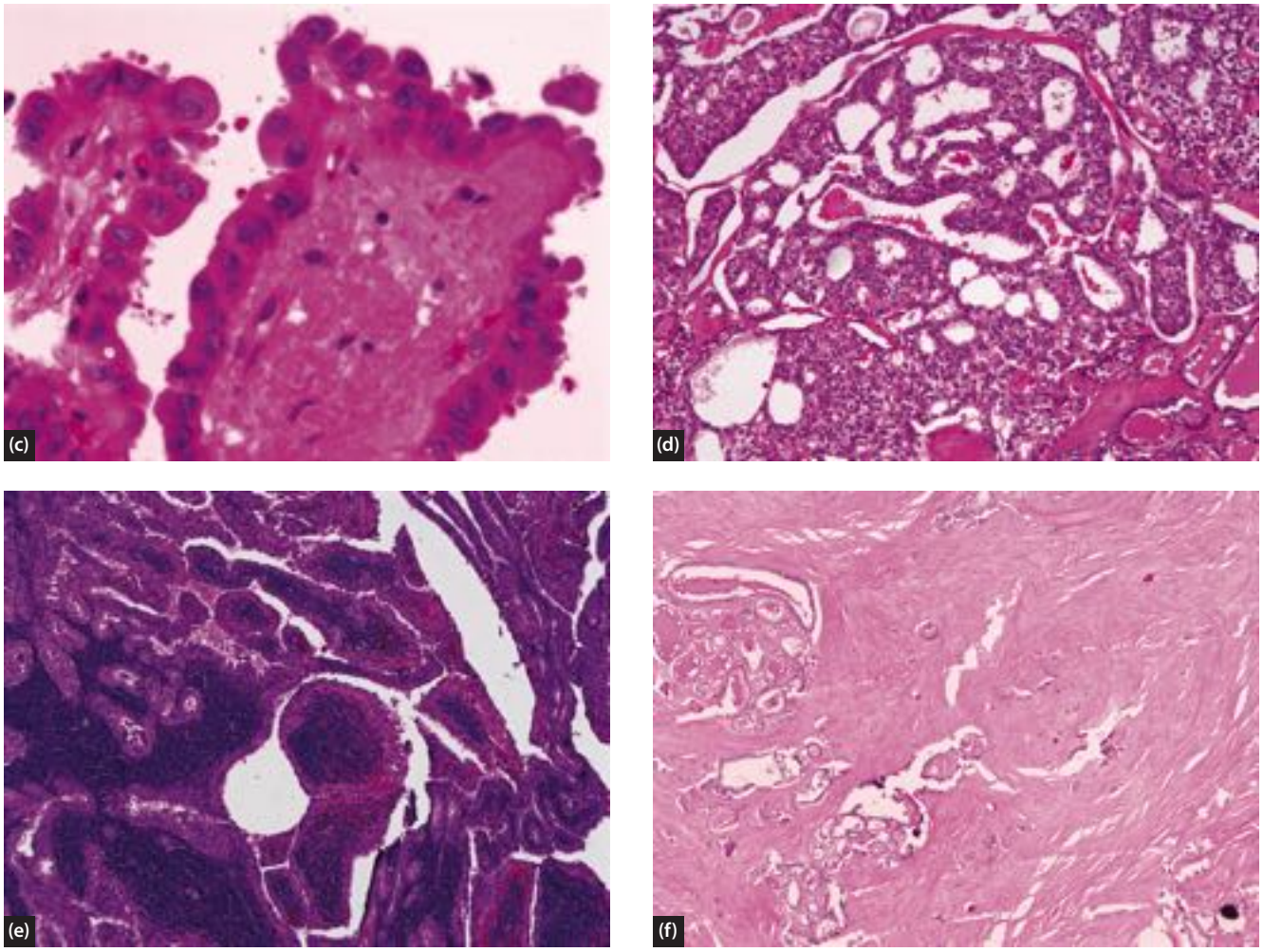


Figure 58.31 (Continued) PTC variants. (c) Hobnail variant of PTC characterized by a significant proportion of the cells showing reverse nuclear polarity with protruberant apical nuclei and/or luminal blebs (snouting) of cytoplasm (*H&E stain, high magnification*). **(d)** Contiguous tubulocribriform arcades of thyrocytes of the pattern seen in cribriform-morular variant PTC (*H&E stain, medium magnification*). **(e)** Papillary thyroid carcinoma, Warthin tumour-like variant, microscopically resembling Warthin's tumour (adenolymphoma) of salivary gland (usually parotid gland) derivation. The epithelium is oncocytic (Hürthle cell) and there is marked reactive lymphocytosis expanding papillary stromal cores (*H&E stain, low magnification*). **(f)** Diffuse sclerosing variant of PTC dominated by dense, acellular, paucivascular sclerohyaline stroma. Psammoma body formation and associated parallel linear microtomy score marks traversing the section are exemplary (*H&E stain, medium magnification*).

and the distinctive PTC nuclear morphology is absent from such areas (Figure 58.11a). The WHO definition of tall cells in PTC is merely a preponderance of tumour cells whose height is at least threefold (previously twofold) greater than their width, and this pattern should not be confused with columnar cell carcinoma. Note that there is presently no unanimous agreement on the percentage of tall cell morphology required to define an entire PTC as tall cell variant. The appellation solid variant is reserved for tumours displaying 50% or more solid growth pattern.

PTC stains immunohistochemically for cytokeratins (CKs), thyroglobulin (Tg) and thyroid transcription factor-1 (TTF-1) but not pan-neuroendocrine markers. Areas of squamous differentiation lose their Tg and TTF-1 reactivity. A plethora of markers have been proposed to aid discrimination between follicular variant of PTC and other follicular lesions, notably high molecular weight cytokeratins (HMWCKs), low-molecular weight cytokeratin (cytokeratin 19/CK19), Hector Battifora mesothelial-1 antibody (HBME-1), galectin-3 (GAL-3), neural cell adhesion molecule (NCAM), (CD56), Leu7 (CD57), LeuM1 (CD15), fibronectin-1 (FN-1), platelet-derived growth factor (CD44), p63 protein, trophoblastic cell surface antigen (TROP2), paired box gene 8 (PAX8), Thyroid transcription factor-2 (TTF-2), thyroperoxidase (TPO), BRAF mutation specific antibody and *RET* among others. None, individually or in combination, is entirely sensitive or specific for PTC: they may be capricious even in classical PTC, and a number of inflammatory and other neoplastic conditions may yield ambiguous and/or spurious results. CK19 staining in isolation has a low specificity and low sensitivity. The panel of cytokeratin 19 and HBME-1 has a higher exclusionary power than positive predictive power: if both markers are negative, this militates against a diagnosis of PTC, whereas positivity of either, or both, is supportive but not conclusive (Figure 58.32). CD56 is expressed by normal thyrocytes,

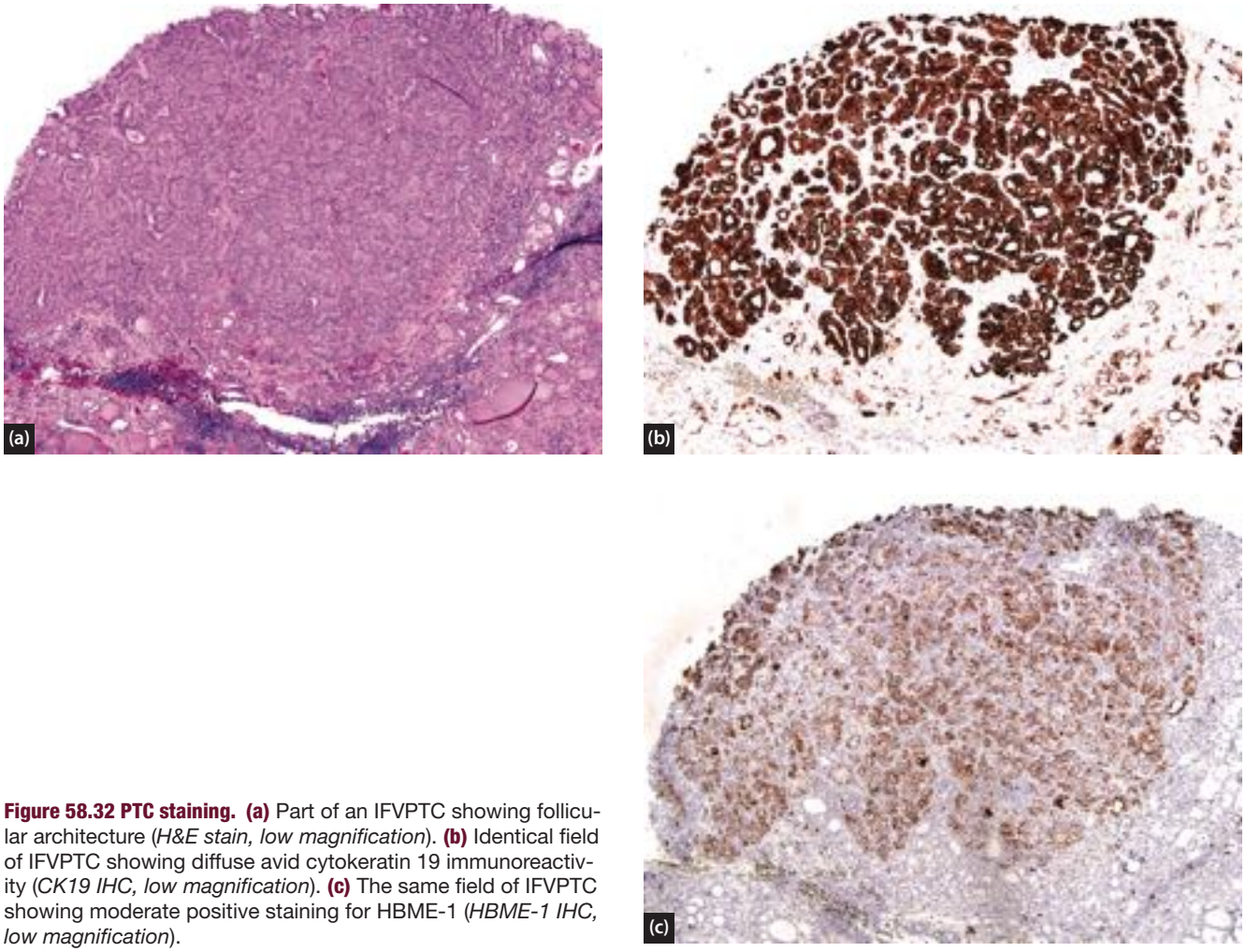


Figure 58.32 PTC staining. (a) Part of an IFVPTC showing follicular architecture (*H&E stain, low magnification*). **(b)** Identical field of IFVPTC showing diffuse avid cytokeratin 19 immunoreactivity (*CK19 IHC, low magnification*). **(c)** The same field of IFVPTC showing moderate positive staining for HBME-1 (*HBME-1 IHC, low magnification*).

benign and malignant follicular lesions but generally not by PTC. Absent, or low, CD56 expression (typically less than 5% or so, confined to the tumour-native tissue interface) in a follicular-patterned neoplasm is claimed to be consistently specific and extremely sensitive for PTC, more so than CK19. In the appropriate context, CD 56 immunonegativity, or loss of CD56 expression in various degrees, is supportive of malignancy and may compliment diagnostic accuracy of PTC when used as a panel in conjunction with CK19, p63 protein and/or HBME-1 antibodies. However, undue reliance should not be placed upon immunostaining in isolation.

Three independent molecular pathways are recognized in the tumourogenesis of PTC with distinct gene expression profiles, namely activation of the proto-oncogene receptor tyrosine (*RET*) kinase, mutation of the gene for B-raf (*BRAF*) and *ras* mutation. *RET* kinase activation consequent upon chromosomal translocation is collectively referred to as *RET/PTC* translocation and occurs in up to 60% of PTCs. *RET/PTC 1* fusion correlates to classical PTC and papillary microcarcinoma. *RET/PTC 3* fusion is seen in tall cell and solid PTC variants plus irradiation-induced tumours. *RET/PTC* expression is not a feature of follicular carcinoma, poorly differentiated carcinoma or undifferentiated (anaplastic) carcinoma. Mutation of the gene for B-raf (*BRAF*) accompanies 29–69 % of PTCs, more prevalent in classical PTC, tall cell, Warthin tumour-like and oncocytic (oxyphil) variants. FVPTC harbours *ras* gene mutations and may show *PAX8/PPARy* translocation, but rarely *RET/PTC* translocation or *BRAF* mutations, a profile akin to that of follicular adenoma and follicular carcinoma.[4]

Follicular-patterned tumours of uncertain malignant potential

Perhaps the most controversial development relating to thyroid pathology over the past two decades has been the recognition and incorporation into mainstream classification of a group of well-differentiated follicular-patterned neoplasms (intermediate or borderline) that lie morphologically and behaviourally between follicular adenoma and follicular carcinoma/FVPTC – tumours of uncertain malignant potential (atypical adenoma, adenoma with atypia, well-differentiated tumour of uncertain behaviour). Whether these lesions constitute distinct entities, and if so, whether they qualify as carcinoma/neoplasms of low malignant potential has yet to be categorically determined.

Historically, limited follow-up data, compounded by subjective judgement and well recognized poor inter-observer concordance and intra-observer variation has

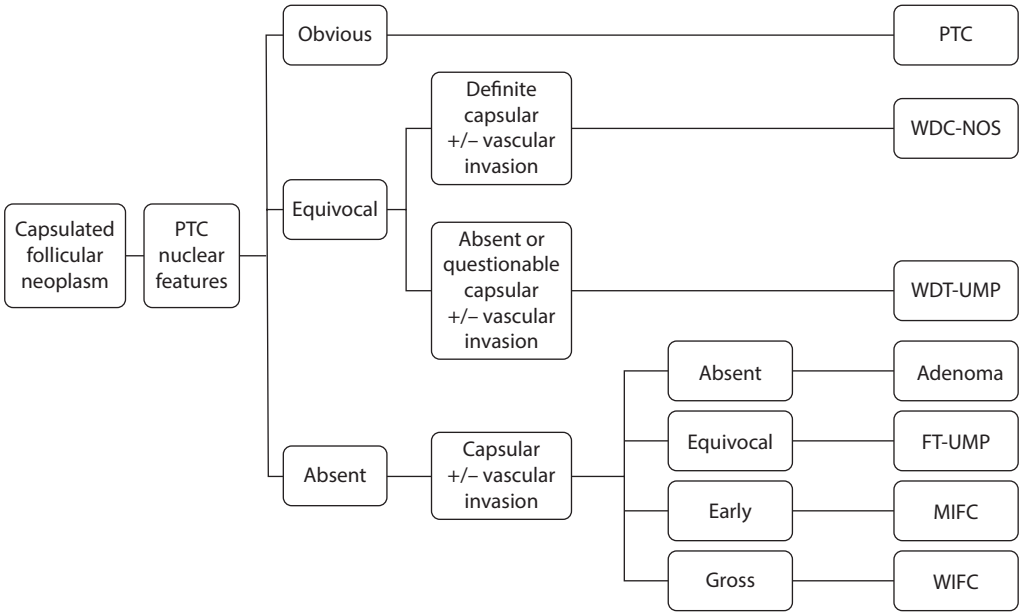


Figure 58.33 Chernobyl Pathologists' Group nosology and diagnostic algorithm for resolution of the differential diagnosis of encapsulated follicular-patterned lesions of the thyroid gland. PTC: papillary thyroid carcinoma; WDC-NOS: well-differentiated carcinoma, not otherwise specified; WDT-UMP: well-differentiated tumour of uncertain malignant potential; FT-UMP: follicular tumour of uncertain malignant potential; MIFC: minimally invasive follicular carcinoma; WIFC: widely invasive follicular carcinoma.

been problematical, prompting recourse to a pragmatic *ipse dixit* diagnosis.[25] Furthermore, RET/PTC expression in some cases of FVPTC shows multicentric rather than diffuse alterations, suggestive of carcinomatous transformation ex-adenoma, though by convention it is recommended that the entire encapsulated lesion is arbitrarily regarded as PTC for staging purposes.[26]

In recognition of these difficulties, the Chernobyl Pathologists' Group proposed alternative nomenclature to accommodate this diagnostic uncertainty and this is summarised in Figure 58.33. For more than a decade this provided a more descriptive schema, which could be invoked in the minority of cases where diagnostic equivocation was irresolvable by conventional morphology and the stigma of malignancy was potentially unjustifiable and equally undesired. Until recently, however, this approach was not wholly accepted into mainstream diagnostic practice. The Armed Forces Institute of Pathology (AFIP) fascicle 2015 did embrace this philosophy and adopted the terminology into its classification (Table 58.7). Subsequently, the WHO (4th edition, 2017) classification has refined this further (Table 58.8).[27]

For encapsulated follicular-patterned tumours indeterminate between follicular adenoma and follicular carcinoma, lacking nuclear features of PTC, where capsular invasion is equivocal, the WHO (4th edition, 2017) classification retains the descriptor *follicular tumour of uncertain malignant potential (FT-UMP)*, but has expanded its scope to include equivocal vascular invasion.[27]

For encapsulated, or well circumscribed, follicular-patterned tumours with well-developed or equivocal nuclear features of PTC, the term *well-differentiated tumour of uncertain malignant potential (WDT-UMP)* was also adopted by the AFIP fascicle 2015. The WHO (4th edition, 2017) classification further recognizes that non-invasive encapsulated FVPTC is associated with an excellent prognosis and possesses molecular features more akin to follicular adenoma/carcinoma than those of conventional PTC – the term *non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)* has been introduced to encompass non-invasive encapsulated follicular-patterned tumours previously called encapsulated FVPTC as well as *WDT-UMP*.[27] The designation *WDT-UMP* is reserved in this classification for well-developed or incompletely developed PTC-type nuclei and questionable capsular or vascular invasion.

Where diagnostic distinction between invasive follicular carcinoma and invasive PTC is difficult, the generic

TABLE 58.7 AFIP recommended nomenclature for encapsulated well-differentiated follicular-patterned tumours based on the presence or absence of PTC nuclear features and capsular invasion, AFIP fascicle 2015.[27]

		Capsular invasion		
		Present	**Questionable**	**Absent**
Nuclear features of PTC	**Present**	Follicular variant of PTC		
	Questionable	Well-differentiated carcinoma, NOS	Well-differentiated tumour of uncertain malignant potential	
	Absent	Follicular carcinoma	Follicular tumour of uncertain malignant potential	Follicular adenoma

TABLE 58.8 WHO classification recommended nomenclature for encapsulated follicular-patterned tumours on the basis of presence or absence of PTC nuclear features and capsular or vascular invasion, WHO, 4th edition, 2017.[27]

		Capsular or vascular invasion		
		Present	**Questionable**	**Absent**
Nuclear features of PTC	**Present**	Invasive encapsulated follicular variant of PTC	Well-differentiated tumour of uncertain malignant potential	Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
	Questionable	Well-differentiated carcinoma, NOS		
	Absent	Follicular carcinoma	Follicular tumour of uncertain malignant potential	Follicular adenoma

rubric *well-differentiated thyroid carcinoma, not otherwise specified (WDT-NOS)* may still rarely be employed, though every effort to sub-classify more precisely should be expended.[40]

NON-INVASIVE FOLLICULAR THYROID NEOPLASM WITH PAPILLARY-LIKE NUCLEAR FEATURES

The follicular variant of papillary thyroid carcinoma (FVPTC) is the most prolific variant of PTC, accounting for around 30% of all PTCs. Small variations in outcome (dependent upon the presence/absence of invasion) notwithstanding, the long-term prognosis is near universally excellent, supporting the notion that these tumours are biologically indolent. Discounting the rare diffuse follicular and macrofollicular variants of PTC and encapsulated papillary carcinoma (the latter denoting classical PTC bounded by a thick capsule but with dominant papillary rather than follicular architecture), further subclassification into invasive follicular variant (IFVPTC), encapsulated follicular variant with invasion (EFVPTC) and encapsulated follicular variant without invasion (non-invasive follicular thyroid neoplasm with papillary-like nuclear features, NIFTP), is clinically useful.

In terms of follicular growth and nuclear morphology, IFVPTC is identical to EFVPTC, except that capsulation is typically incomplete and it shows wide infiltration into adjacent parenchyma with commensurate risk of locoregional recurrence and likelihood of metastasis, behaviour more analogous to classical PTC.

Both EFVPTC (which encompasses non-capsulated and incompletely capsulated but circumscribed tumours) and NIFTP are associated with an excellent outcome when managed conservatively, with disease persistence/recurrence rates of 3% and less than 1% in the first 15 years, respectively, such that NIFTP is not now considered a malignant neoplasm. This terminology is intended to encourage more conservative management and to spare the psychological burden of cancer diagnosis for indolent tumours that may be adequately managed by lobectomy or hemi-thyroidectomy alone. This proposed nomenclature and shift in emphasis has been provisionally accepted internationally, justifying inclusion in the revised WHO (4th edition, 2017) classification of thyroid tumours ('blue book').[27]

An algorithm has been proposed along with standards to stringently define this NIFTP subset, stipulating inclusion and exclusion criteria (**Figure 58.34**) supplemented by an objective nuclear scoring schema (**Table 58.9**). There is

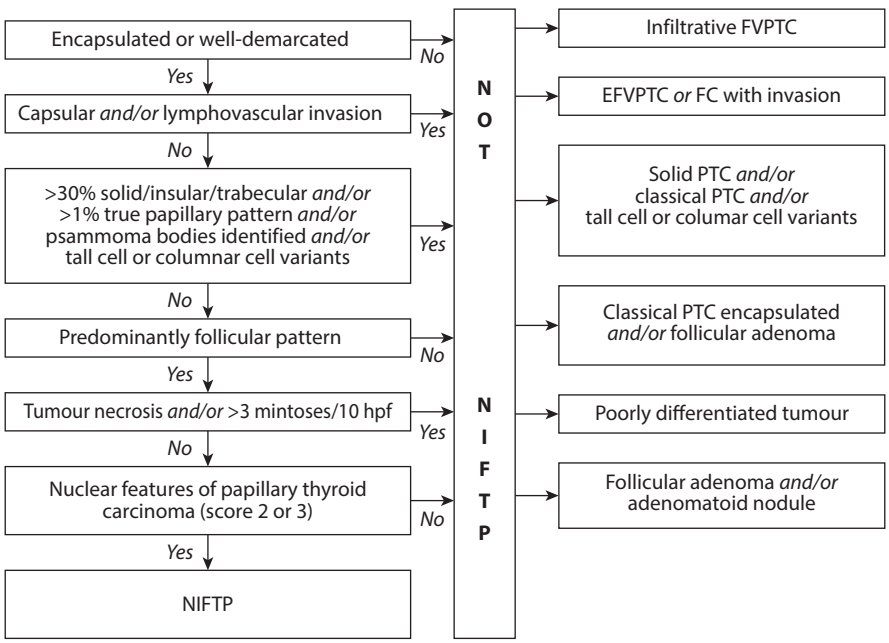


Figure 58.34 Algorithm aiding the subclassification of a follicular-patterned thyroid lesion where NIFTP is a consideration.[38]

TABLE 58.9 Nuclear morphology scoring system intended to enhance reproducibility in the diagnosis of NIFTP[41, 42]

Three-point scoring criteria for the nuclear features of papillary thyroid carcinoma		
Nuclear features	**Score = 0**	**Score = 1**
1. Size and shape Enlargement, elongation, crowding, overlapping	Absent or only slightly expressed	Present or well-developed (1 point for each feature)
2. Membrane irregularities Irregular contours, grooves, folds, intranuclear cytoplasmic inclusions		
3. Chromatin characteristics Chromatin clearing, margination to the nuclear membranes, glassy nuclei, fine–even delicate chromatin		
Total score: 0 or 1: Not diagnostic		
Total score: 2 or 3: Diagnostic of PTC nuclei		

no prescribed minimum size criterion and the terminology is not fully validated for sub-centimetre or incidentally discovered tumours, indeed it may be challenging to apply the diagnostic criteria to neoplasms measuring less than 0.5 cm. Equally there is no prescribed upper size limit, with the proviso that the collective experience of NIFTP exceeding 4 cm maximum dimension is restricted. Importantly, where possible the entire lesional capsule should be submitted for microscopical scrutiny. Careful fixation and tissue processing are obligatory. A conclusive diagnosis of NIFTP is not feasible on frozen section or FNAC examination.[41]

Major inclusion criteria include sharp demarcation, majority capsulation, dominant follicular growth (less than 1% papillae), less than 30% other architecture (solid, trabecular or insular) and papillary nuclear characteristics (scored for size and shape, membrane irregularity and chromatin characteristics). Minor inclusion features are listed as dark colloid, follicular irregularity and haphazardly scattered microfollicles (sprinkling sign) often displaying artefactual retraction clefts (**Figure 58.35**). Exclusion criteria dictate any capsular or vascular invasion, true papillae (exceeding one percent of the tumour), psammoma bodies, infiltrative interface, coagulative necrosis (excepting ischaemic FNAC injury), increased mitoses (at least 3 per 10 hpf), features of some other aggressive PTC variant (tall cell, columnar cell, cribriform-morular, hobnail/micropapillary, diffuse sclerosing or dedifferentiated) and oncocytic (Hürthle cell) lesions.[42] Lymph node metastasis at presentation is incompatible with a diagnosis of NIFTP, cognizant that central cervical compartment lymph nodal micrometastasis might represent spread from a different occult primary thyroid carcinoma and that heterotopic (ectopic) lymphadenoidal inclusions enter the differential diagnosis.

Papillary thyroid microcarcinoma

Papillary thyroid microcarcinomas (papillary microtumours) are by definition less than 10 mm in diameter, constituting pT1a disease. They may be an incidental finding in thyroid glands removed for other pathology or serendipitously detected on imaging of the thyroid gland (latent carcinoma).[43] Alternatively, they may be found retrospectively in patients presenting with metastatic disease from an initially unsuspected small primary lesion (occult/cryptic/covert carcinoma). Historical subdivision into tumours less

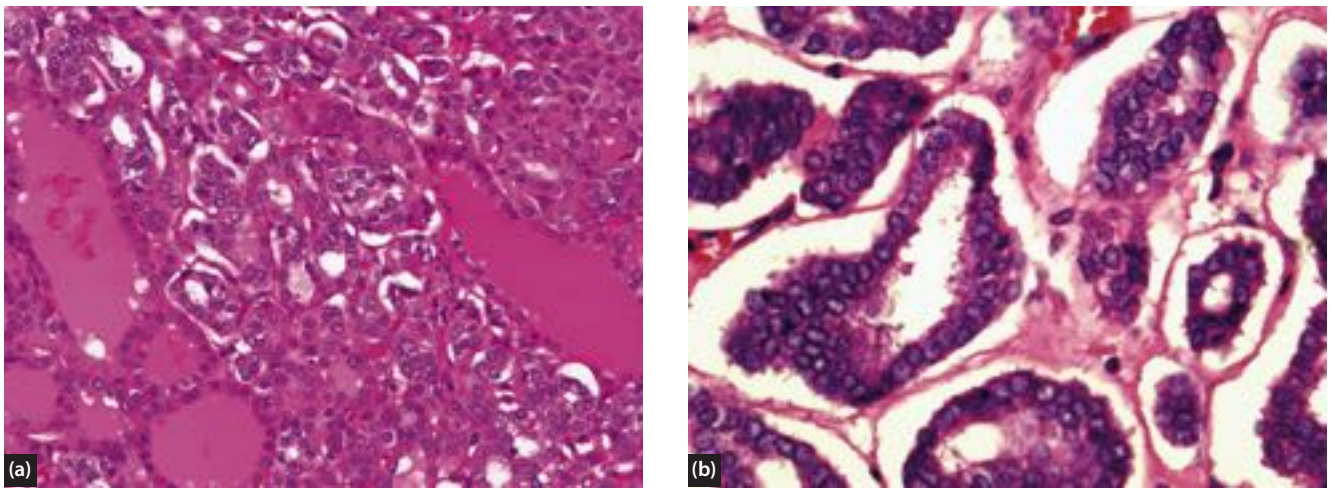


Figure 58.35 Non-invasive follicular thyroid neoplasm with papillary-like nuclear features. (a) A congerie of small follicles displaying PTC nuclear features nested between larger non-descript follicles in NIFTP (sprinkling sign). There is limited artefactual perifollicular clefting (shrinkage artefact) (*H&E stain, medium magnification*). **(b)** A similar nidus of small follicles displaying PTC nuclear characteristics in NIFTP, albeit with very florid, diffuse follicle-stromal interface retraction artefact (*H&E stain, high magnification*).

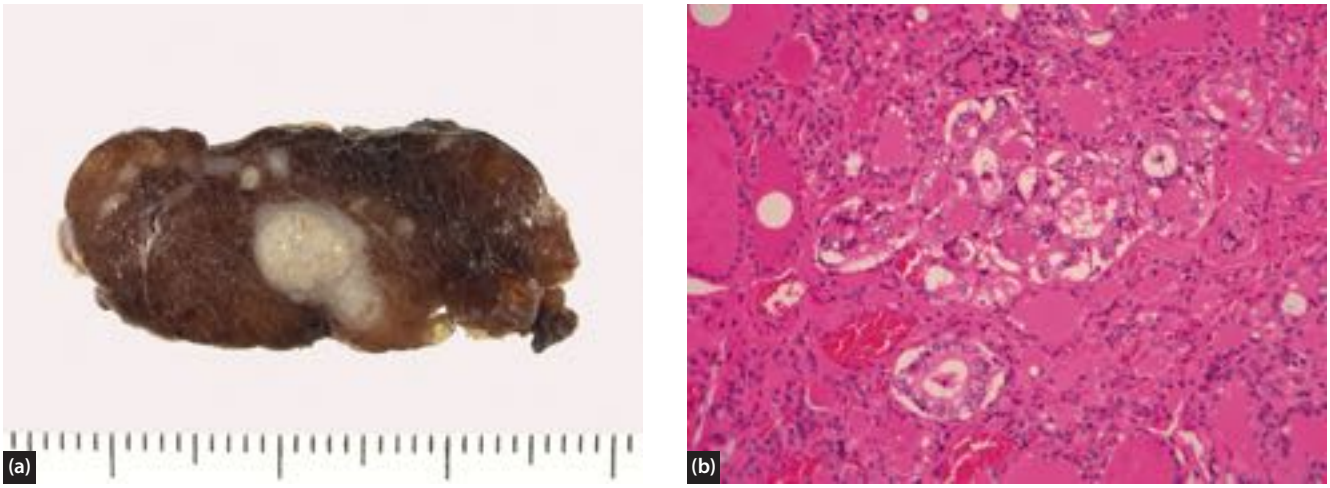


Figure 58.36 Papillary thyroid microcarcinoma. (a) Multicentric papillary thyroid microcarcinoma each deposit measuring less than 10 mm in diameter. These show a sclerotic morphology. **(b)** Microscopical deposit of papillary microcarcinoma. This is poorly demarcated and is eliciting no stromal or inflammatory response whatsoever. Such foci are readily overlooked on cursory or low-power examination (*H&E stain, medium magnification*).

than 5 mm ('minute') and 5 mm to 10 mm ('tiny') maximum dimension is of no clinical relevance. Occult and latent papillary carcinomas may or may not be microcarcinomas. Follicular and medullary microcarcinomas are independently recognized though less frequently encountered.

Most studies report a prevalence for latent papillary microcarcinomas of around 5% to 10%, but figures as high as 30% or so are acknowledged. Despite their propensity for multifocality in one lobe (23%), bilaterality (17%) and locoregional lymph node metastasis (16%), they almost always pursue an indolent clinical course with excellent prognosis, usually not requiring aggressive intervention.[43] Exceptionally, however, papillary microcarcinomas behave more aggressively and the presence of two or more foci, lymphovascular invasion, extrathyroidal extension and higher risk morphology (e.g. tall cell features) may prompt more comprehensive treatment, despite limited long-term vindication for this. A significant number of sub-centimetre PTCs occurring in children and adolescents harbour extrathyroidal extension and/or distant metastasis, prompting the CAP recommendations to restrict use of the term papillary thyroid microcarcinoma to those over 19 years of age.[33]

Morphologically, papillary microcarcinomas are usually either infiltrative and sclerotic or circumscribed but unencapsulated, located between native follicles without discernible host response (**Figure 58.36**). Such microscopical foci therefore are therefore easily missed on cursory histological screening and are apt to mimic solid cell nests or even heterotopic thymic rests on scanning magnification.

Poorly differentiated thyroid carcinoma

Poorly differentiated carcinoma of the thyroid (PDCAT) encompasses a spectrum of heterogeneous tumours showing limited evidence of follicular cell differentiation associated with biological behaviour intermediate between differentiated (follicular and papillary) thyroid carcinoma and undifferentiated (anaplastic) carcinoma.[44]

Poorly differentiated carcinomas typically arise *de novo*, but they may occur through transformation of differentiated carcinoma (**Figure 58.37**). They may progress to undifferentiated (anaplastic) carcinoma either *ab initio* or after recurrence (**Figure 58.38**).

PDCAT may be defined mainly on the basis of growth pattern. Insular (primordial) carcinoma represents the archetype and is composed of large solid nests (insulae) punctuated by occasional primitive follicles (**Figure 58.39**). Minor elements of classical papillary thyroid carcinoma and/or follicular carcinoma may be recognized. Obversely, an insular growth pattern is by no means exclusive to poorly differentiated carcinoma and important differential diagnoses include medullary thyroid carcinoma, solid variant papillary thyroid carcinoma and undifferentiated (anaplastic) carcinoma.



Figure 58.37 Transverse slice through a total laryngopharyngectomy and bilateral radical neck dissection specimen for advanced stage, poorly differentiated thyroid carcinoma. The bulk of the specimen comprises heterogeneous tumour largely enclaving upper trachea and cervical tubular oesophagus. Microscopically this showed intermingled areas of papillary thyroid carcinoma, follicular carcinoma and insular carcinoma with localized squamous differentiation.

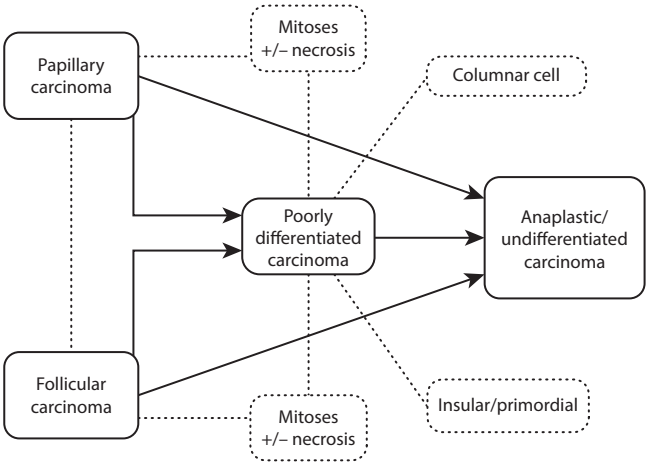


Figure 58.38 Schematic outlining the theoretical developmental relationships between differentiated, poorly differentiated and undifferentiated (anaplastic) thyroid carcinomas.

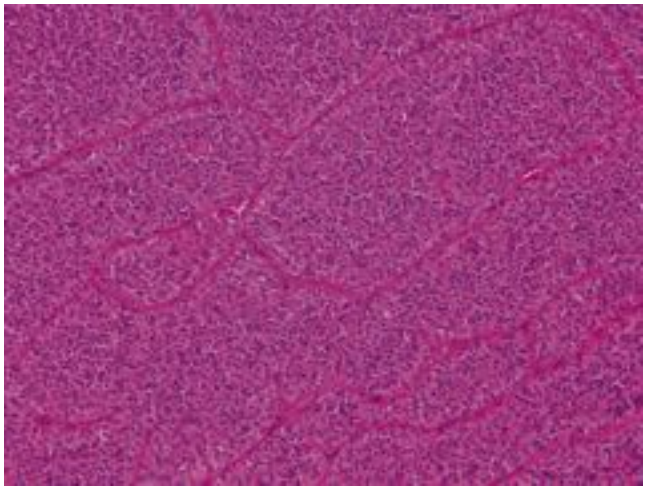


Figure 58.39 Classical poorly differentiated (insular) thyroid carcinoma displaying the characteristic solid tumour cell islands (insulae) separated by narrow fibrovascular septa. There is no hint of follicular or other differentiation here (*H&E stain, medium magnification*).

Alternatively, PDCAT may be specified according to mitotic state (exceeding 5 mitoses per 10 high-power fields ×400) and/or comedo-like tumour necrosis. These portend a survival rate of 60% at 5 years, irrespective of tumour architecture. Furthermore, the combination of solid growth and the presence of at least one of convoluted nuclei, tumour necrosis and/or over 3 mitoses per 10 high-power fields is a powerful predictor of poor outcome. This group constitutes the major cause of radioiodine refractory positron emission tomography (PET)-positive incurable thyroid carcinomas. Some authors propose a so-called 'high-grade carcinoma' of the thyroid as a malignancy in which there are recognizable elements of differentiated thyroid carcinoma but which also show histological and cytological features placing the lesion into a 'high-grade' category. However, this concept has yet to be endorsed in the WHO (4th edition, 2017) classification and most would classify such neoplasms under the rubric of PDCAT.[27]

Confusingly, the term poorly differentiated carcinoma is also applied by some observers to differentiated carcinomas showing a solid, trabecular or scirrhous pattern, to tall cell papillary carcinomas and to columnar cell carcinomas. There are insufficient data to determine whether the spectrum of PDCAT should be widened to incorporate a small subset of tumours that exhibit high-risk pathological and clinical features despite low-grade histomorphology.[49] This lack of consensus may explain conflicting data as to whether a minority component of insular carcinoma in an otherwise differentiated carcinoma is an independent prognostic factor or not and, if so, at what threshold this begins to be a clinically valid observandum. When such poorly differentiated carcinoma comprises the majority of tumour mass (greater than 50%), pragmatically the lesion is best classified as poorly differentiated overall.[36] The response of PDCAT to radio-iodine is generally poor.

Unsurprisingly, the tumour cells demonstrate cytokeratins (CK), thyroglobulin (Tg) and thyroid transcription factor-1 (TTF-1) immunopositivity but negative pan-neuroendocrine markers and calcitonin.

Columnar cell carcinoma

Columnar cell carcinoma is a rare thyroid neoplasm, which once invasive pursues a more aggressive course than other differentiated thyroid carcinomas. Where it remains encapsulated, however, there appears to be little risk of metastasis.[44] There is disagreement as to whether it is best classified as a distinct entity rather than a variant of papillary thyroid carcinoma. There is indeed morphological overlap between columnar cell carcinoma, the cribriform-morular variant of papillary thyroid carcinoma and also so-called FAP-associated thyroid carcinoma, remembering that thyroid carcinomas of conventional pattern also occur in familial adenomatous polyposis (FAP) patients.

This notwithstanding, the typical architecture resembles that of intestinal and endometrioid carcinomas with complex glandular, cribriform and solid growth. The individual cells are tall and columnar but striking nuclear pseudostratification and hyperchromasia enable separation from tall cell variant of papillary thyroid carcinoma (**Figure 58.40**). Immunohistochemically, it is usually CK, Tg and TTF-1 positive.

Undifferentiated (anaplastic) carcinoma

Undifferentiated (anaplastic) carcinoma is a highly malignant tumour typically seen in elderly patients with preponderance in females. It accounts for approximately 2–10% of all malignant thyroid neoplasms,[45] with a predilection for iodine-deficient regions though its overall incidence is declining.[46] Undifferentiated (anaplastic) thyroid carcinoma is usually widely invasive at presentation and inoperable in roughly half of cases. It carries a high mortality and accounts for nearly half of all deaths associated with thyroid malignancy.[8] The overall median survival is 4 months and the 5-year survival rate is less than 10%.

All undifferentiated (anaplastic) thyroid carcinomas are arbitrarily UICC/TNM staged as pT4 due to their anticipated

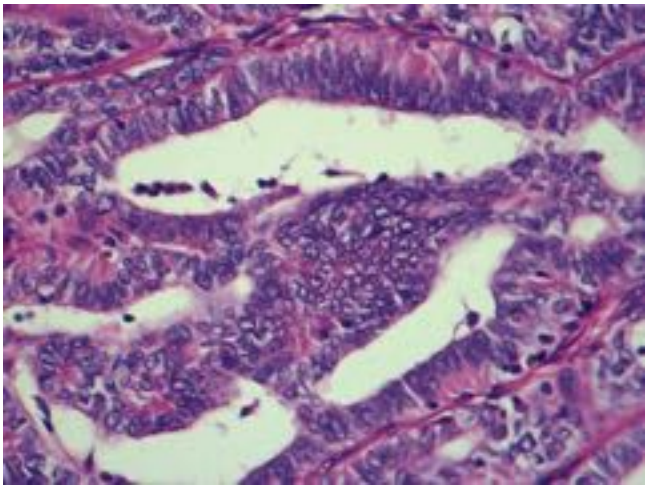


Figure 58.40 Columnar cell carcinoma illustrating the classical, complex glandular growth pattern resembling gastric, colorectal or endometrial adenocarcinoma. The tumour cells are columnar with characteristic nuclear pseudo-stratification (*H&E stain, high magnification*).

aggressive behaviour, classically showing widespread infiltration of surrounding structures, regional lymph node metastases and distant metastasis to any site.[8] Presentation with early, intracapsular anaplastic carcinoma, which is more amenable to surgical extirpation, portends a slightly more favourable outlook but is uncommon. Where there is any focus of anaplasia within a differentiated tumour, the lesion is conventionally classified overall as undifferentiated (anaplastic) carcinoma thereby by default becomes stage T4 disease. Obversely, the presence of better-differentiated elements may mitigate the poor prognosis of undifferentiated (anaplastic) carcinoma to some extent.

Undifferentiated (anaplastic) carcinoma can arise *de novo* but the presence of synchronous better-differentiated carcinomatous elements in over 50% of cases is taken as evidence of de-differentiation of a pre-existing neoplasm.[45] Ergo, there may be a history of long-standing thyroid disease complicated by a recent phase of accelerated growth. The histological features are tremendously variable with two main patterns being pleomorphic epithelioid (giant cell) and spindle cell (sarcomatoid) (Figure 58.41). A variety of other microscopical

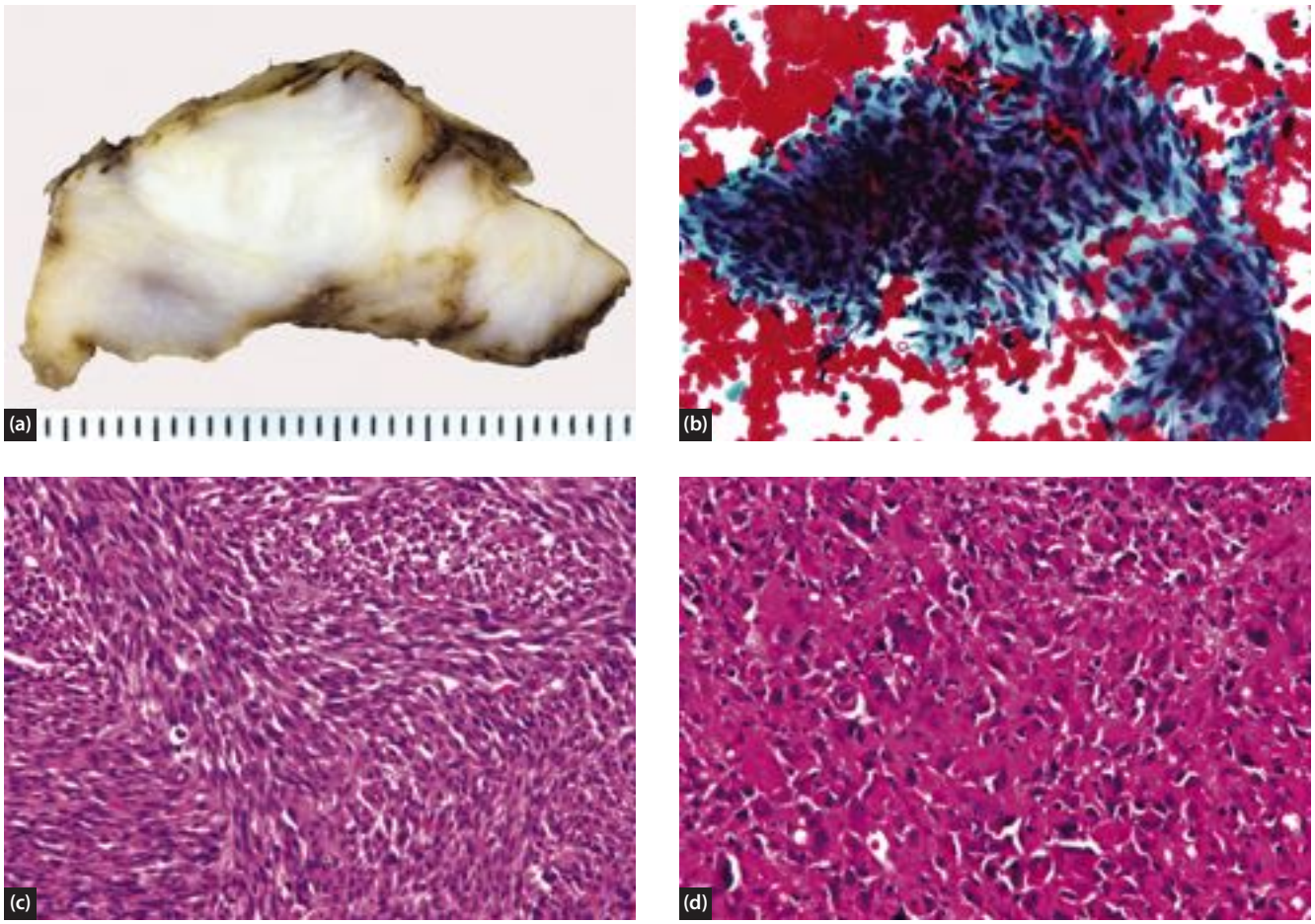


Figure 58.41 Undifferentiated (anaplastic) carcinoma. (a) A cross-sectional slice through a thyroid lobectomy specimen substantially replaced by undifferentiated (anaplastic) thyroid carcinoma. The solid, dense, featureless and infiltrative nature is paradigmatic. **(b)** FNAC specimen from undifferentiated (anaplastic) thyroid carcinoma showing a tri-dimensional, acervate clump of pleomorphic, high-grade malignant spindle cells (*Pap stain, medium magnification*). **(c)** A field of fibrosarcoma-like undifferentiated (anaplastic) thyroid carcinoma composed of fasciculated, malignant fusiform cells (*H&E stain, medium magnification*). **(d)** Undifferentiated (anaplastic) thyroid carcinoma showing highly pleomorphic epithelioid tumour cells with numerous bizarre giant cells and monster cells ('monstrocytes'), some polykaryocytic (*H&E stain, medium magnification*).

TABLE 58.10 Recognized histological variants of undifferentiated (anaplastic) thyroid carcinoma and their mimics. Note that any individual tumour may present a mixture of appearances in any combination or permutation

Pattern	Major differential diagnosis
Epithelioid	Poorly differentiated (insular) carcinoma Papillary carcinoma, solid variant Metastatic carcinoma
Sarcomatoid	Sarcoma proper
Angiomatoid	Angiosarcoma
Osteoclastic	Pleomorphic sarcoma
Rhabdoid	Rhabdomyosarcoma
Lymphoepithelioma-like	CASTLE
Paucicellular/fibrosing	Riedel's thyroiditis
Carcinosarcomatoid	Osteosarcoma Rhabdomyosarcoma
Adenosquamous	Metastatic carcinoma Sclerosing mucoepidermoid with eosinophilocytosis
Squamous cell carcinoma	Metastatic disease Direct extension Papillary thyroid carcinoma CASTLE

patterns are recognized and are renowned for troublesome differential diagnosis (Table 58.10). Angiolymphatic penetration is characteristic and a brisk inflammatory response is often encountered.

While the term carcinoma is conventionally applied, compelling proof of epithelial differentiation is not always forthcoming by light microscopy, morphologically or immunophenotypically, and the diagnosis ultimately rests upon an acceptable histological pattern allied to an appropriate clinicoradiological context. Immunohistochemical staining for cytokeratin and vimentin are at least focally positive in around 90% of cases with epithelial membrane antigen reactivity in 50% of examples. Tg, TTF-1, calcitonin and pan-neuroendocrine epitopes are typically negative; diffusion of thyroglobulin from destroyed follicles, however, may give rise to spurious immunopositivity. The thyroid lineage marker PAX 8 is retained in roughly half of all cases and immunopositivity may assist in the exclusion of metastatic giant cell lung cancer, which is generally negative. Endothelial markers (CD31, CD34 and factor VIII) may be focally demonstrated in some tumours presenting an angiosarcomatoid morphology, which may rarely prevail. EDFR, VEGFR and ALK may be expressed with the prospect of targetted protein kinase inhibitor therapy. Occasional cases are completely immunoinert and ultrastructural studies are seldom rewarding. Where appropriate, a haematolymphoid immunopanel should always be considered, particularly on FNAC and needle core biopsies, so as not to overlook high-grade or anaplastic non-Hodgkin lymphoma.

Medullary thyroid carcinoma

Medullary thyroid carcinoma (MTC) is a malignant tumour displaying parafollicular C-cell differentiation,[47] which secretes calcitonin and often a variety of other neuropeptides.[48] It is an uncommon tumour accounting for 5–8% of all thyroid cancers.[50] It may occur sporadically or against a background of an inherited autosomal dominant trait related to a mutation of the *RET* proto-oncogene, which causes multiple endocrine neoplasia (MEN) types 2A or 2B or familial MTC (FMTC).

Sporadic MTC is more common in females and presents at a mean age of 50 years. MEN 2A presents in adolescence or young adults, while MEN 2B presents in infancy or childhood.[8] Sporadic tumours are usually single whereas hereditary tumours are often multicentric and/or bilateral. FMTC arises from C-cell hyperplasia, which is considered a precursor lesion and can be identified histologically with due diligence.

Regional lymph node metastasis and distant lymphatogenous spread are found in 20% and 8% of cases at presentation, respectively. Secondary sites of predilection include lung, liver, adrenal and bone. MEN 2B MTC generally pursues a more aggressive course than MEN 2A MTC, which in turn portends a less favourable prognosis than sporadic MTC, though for those with neoplasms confined to within the thyroid gland, overall long-term survival approaches 95%, and many patients survive for years despite secondary systemic involvement.[4] Micro-MTCs (defined as smaller than 1 cm maximum dimension) detected through screening are associated with a better outcome than those examples over 1 cm.

MTCs may be well demarcated or infiltrative, sometimes encapsulated (Figure 58.42). They are commonly located in the middle third of the lateral lobes, where C-cell concentration is greatest. Microscopically, they comprise solid sheets, nests and trabecula of cells separated by slender fibrovascular septa (Figure 58.43). A panoply of histological variants is seen, most of no clinical importance other than they may masquerade as other tumours (Box 58.3). There is often a mixed pattern in any individual example. There is usually only modest nuclear pleomorphism but necrosis may be a feature. Amyloid protein deposition is present in around 80% of cases (Figure 58.44) and may mineralize or elicit a foreign body granulomatous response.



Figure 58.42 The cut surface of multicentric medullary thyroid carcinoma occurring in MEN2B demonstrating widespread effacement of thyroid tissue by infiltrative, solid, white tumour, which abuts and focally violates anatomical thyroid capsule.

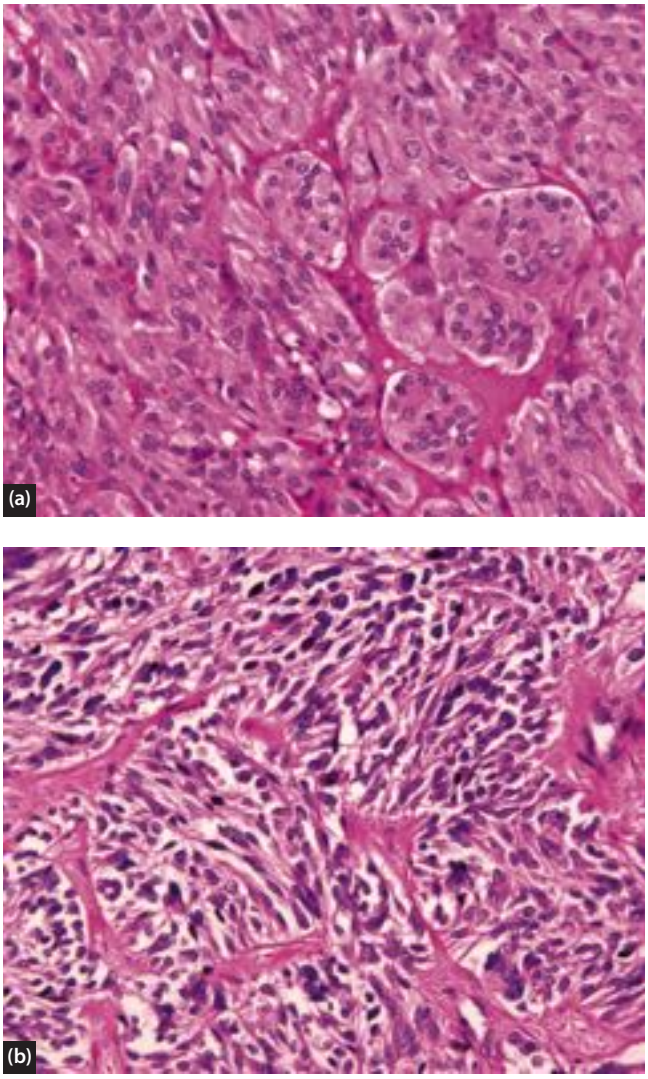


Figure 58.43 Medullary thyroid carcinoma. (a) The typical nested or pseudo-alveolar (Zellballen) architecture of medullary thyroid carcinoma, *type ordinaire*. These tumour cells are largely epithelioid and monotonous (*H&E stain, high magnification*). **(b)** This field shows mild pleomorphism and a more fusiform cell morphology (*H&E stain, high magnification*).

BOX 58.3 Histological variants of MTC

Follicular (glandular/tubular)
Oncocytic (oxyphilic)
Giant cell (anaplastic)
Pigmented
Papillary (pseudo-papillary)
Neuroblastoma-like
Paraganglioma-like
Small cell
Clear cell
Spindle cell
Squamous melanotic
Amphicrine
Angiosarcoma-like (Pseudo-angiosarcomatoid)
Carcinoid-like
Medullary microcarcinoma (latent carcinoma)
Encapsulated ('C-cell adenoma')

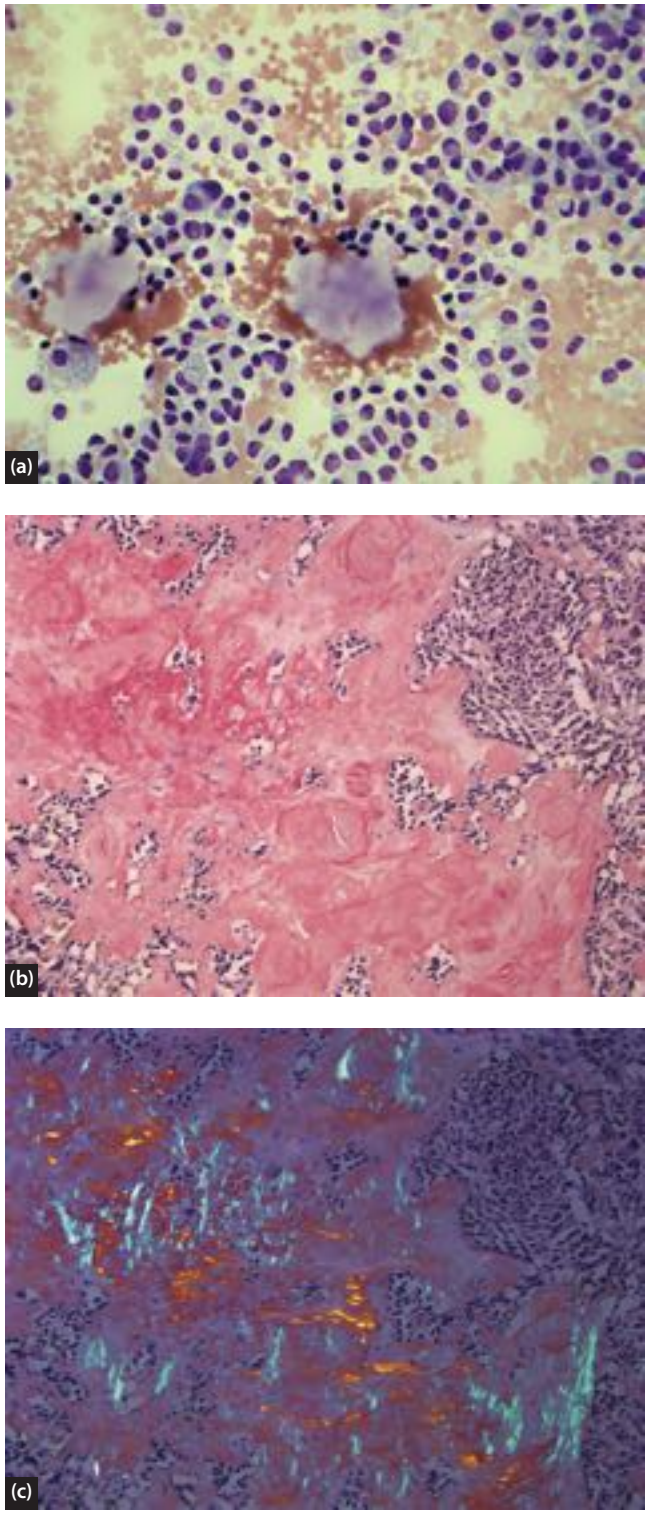


Figure 58.44 MTC. (a) FNAC preparation from medullary thyroid carcinoma, depicting loosely cohesive, moderately pleomorphic, plasmacytoid tumour cells together with several globules of amorphous amyloid protein (*MGG stain, high magnification*). **(b)** Medullary thyroid carcinoma with conspicuous amorphous, dense, pink/red amyloid protein stroma separating groups of tumour cells (*Congo red stain, low magnification*). **(c)** The identical field viewed under high intensity, cross-polarized light corroborates anomalous red/green colouration (sometimes incorrectly termed 'apple green birefringence') highly characteristic of amyloid protein (*Congo red stain, high magnification*).

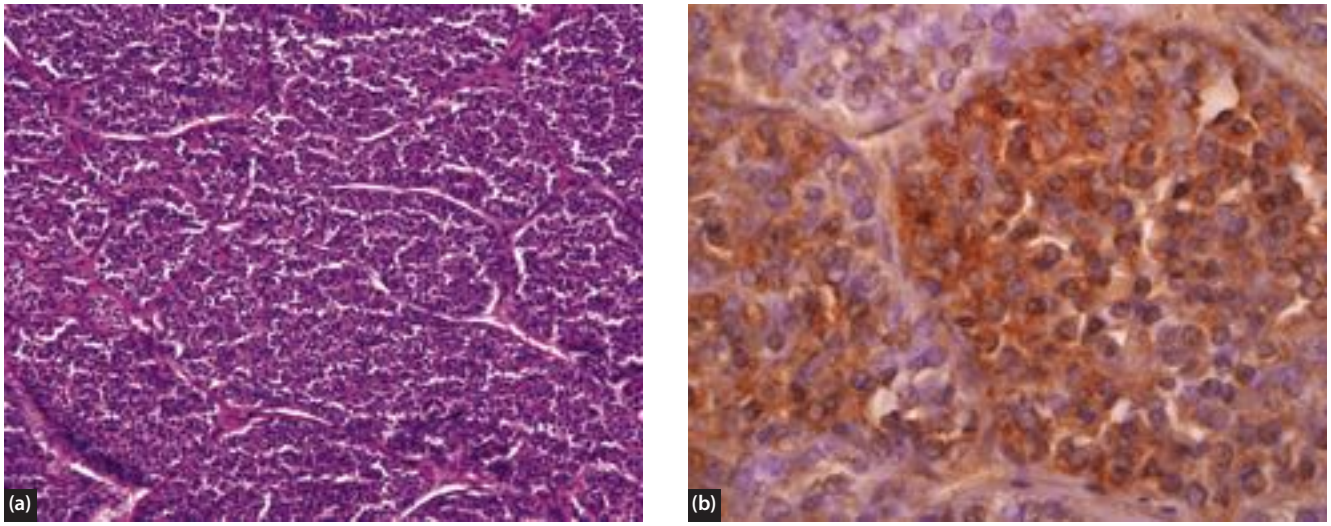


Figure 58.45 Small cell variant MTC. (a) Calcitonin-poor, small cell variant of medullary thyroid carcinoma. Note the insular growth pattern (*H&E stain, intermediate magnification*). **(b)** The same tumour exhibiting carcinoembryonic antigen (CEA, CD66e) positivity. This example was negative for calcitonin and only weakly positive for chromogranin A, reflecting a paucity of intracytoplasmic storage granules, despite raised circulating serum calcitonin levels (*CEA IHC, high magnification*).

The usual immunophenotype is positive for CK, calcitonin, TTF-1, CEA, (CD66e) and pan-neuroendocrine markers. Calcitonin-depleted tumours may behave more aggressively, but almost invariably stain for CEA (Figure 58.45). Other neuropeptides may be demonstrated including calcitonin gene-related peptide, somatostatin, ACTH, serotonin, gastrin, bombesin and histaminase amongst others. An S100 protein-positive subpopulation of sustentacular cells is more commonly seen in hereditary cases (Figure 58.46), potentially overlapping morphologically with paraganglioma, though paragangliomas (with the rare, anomalous exception of those involving the cauda equina) are cytokeratin negative. It is wise to be aware that neuroendocrine neoplasms other than MTC may sometimes express aberrant calcitonin immunoreactivity, for example laryngeal and bronchopulmonary atypical carcinoid tumours, although the latter are typically immunonegative for CEA (CD66e) and there is more often than not normocalcaemia.

Electron microscopy identifies membrane-bound electron-dense storage granules ranging from 100–300 nm in diameter with augmented rough endoplasmic reticulum and Golgi apparatus (Figure 58.47).

C-cell hyperplasia and neoplasia

FMTC develops in a milieu of C-cell hyperplasia and there is no recognized benign C-cell adenoma counterpart. Reactive (physiological) C-cell hyperplasia occurs with advancing age, in thyroiditis, in hyperparathyroidism, in close proximity to other thyroid neoplasms or solid cell nests and in hypergastrinaemia. There is no unanimously accepted definition of nodular (neoplastic, MTC *in situ*)

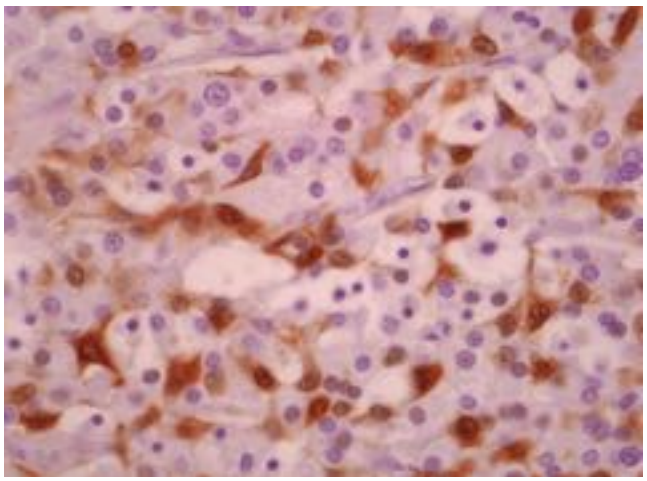


Figure 58.46 Medullary thyroid carcinoma in MEN2 showing typical S100 protein reactive, spindly sustentacular cells mantling small nests of secretory tumour cells (*S100 IHC, high magnification*).

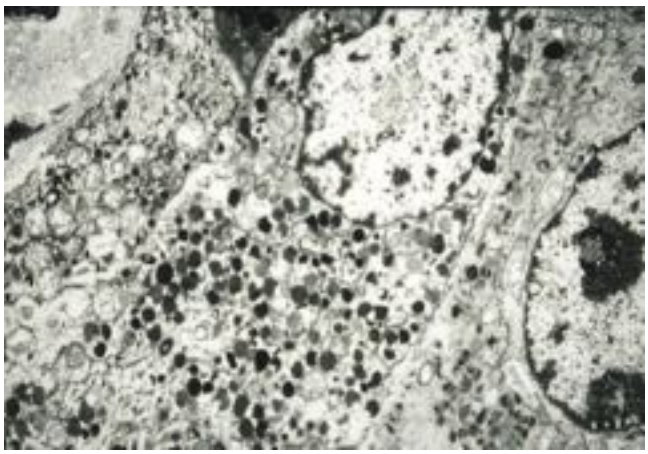


Figure 58.47 Transmission electron micrograph depicting several tumour cells from a medullary thyroid carcinoma, occurring in a child with known MEN2B. Numerous dense, membrane-bound neurosecretory vesicles are present in the cytoplasm (*TEM, ultra-high magnification).*

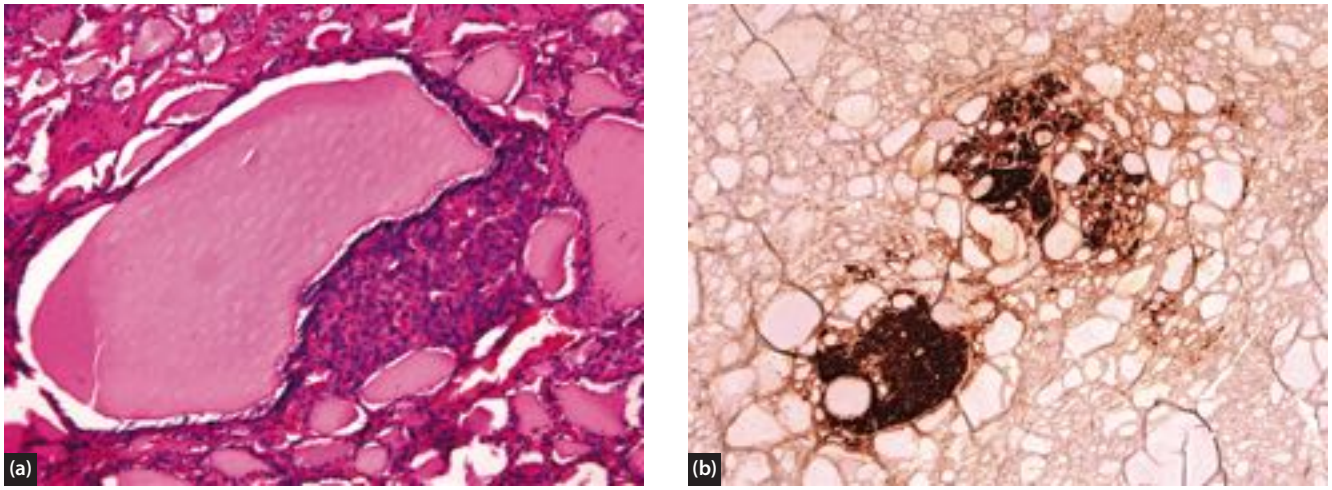


Figure 58.48 C-cell hyperplasia. (a) Early nodular (neoplastic) C-cell hyperplasia in MEN2, readily identified on routine staining. There is expansion of C-cells within the follicular basement membrane but no destructive or infiltrative growth (*H&E stain, medium magnification*). **(b)** More marked and multicentric nodular (neoplastic) C-cell proliferation with follicular obliteration and interstitial expansion. This probably amounts to at least medullary carcinoma *in situ*, if not medullary thyroid microcarcinoma (microtumour) proper (*calcitonin IHC, high magnification*).

C-cell proliferation but over 50 C-cells per ×100 field has been proposed,[51] where there is obliteration of follicular spaces by solid, intrafollicular C-cell growth delimited by basement membrane, as demonstrated by immunostaining for collagen IV (Figure 58.48). Once there is violation of basement membrane and/or tumour-derived basal lamina reduplication, that intuitively constitutes MTC proper, although the distinction between medullary microcarcinoma (minute MTC) and intrathyroidal spread of MTC may be impossible.

C-cells cannot be reliably identified by morphology on routine histological slides without recourse to calcitonin or pan-neuroendocrine immunophenotyping. This has, however, assumed less importance with the advent of more sensitive and specific molecular analysis looking for *RET* proto-oncogene germline mutations in the diagnosis of hereditary MTC syndromes.

Tumours displaying joint follicular and C-cell differentiation

The concept of mixed follicular–parafollicular carcinoma (mixed medullary and follicular thyroid carcinoma, MMNFTC) is enigmatic. Collision (combined) tumours include follicular carcinoma plus MTC and papillary carcinoma plus MTC. True follicular–parafollicular carcinoma (differentiated carcinoma of intermediate type) occurring as a genuine hybrid (composite/compound/biphasic) neoplasm is exceptionally rare. Theoretically, the two cell populations may either share origin from a common stem cell or be of dual clonality. The follicular component is sometimes non-neoplastic, thereby raising the possibility of implicated follicles within a slowly growing MTC. False-positive Tg staining may result from passive diffusion out of nearby native follicles or following active pinophagocytosis by tumour cells, rather than endogenous synthesis proper. The conventional ontogenetic explanation proposing different origins for follicular cells and C-cells, however, fails to reconcile the observation of apparent genuine coexpression of both Tg and calcitonin by the same tumour cell.[4]

An appreciation of primary small cell thyroid tumours and allied variants, with or without neuroendocrine features, is however emerging. What was initially described as small cell primary non-neuroendocrine thyroid carcinoma has more recently been redesignated carcinoma of the thyroid with Ewing family tumour elements (CEFTE) on the basis of *EWSR1/FLI1* gene rearrangement studies, and as such may overlap with so-called adamantinoma-like Ewing tumours. Rare examples of non-medullary primary neuroendocrine carcinoma closely resemble small cell neuroendocrine carcinoma of lung, also with absent C-cell differentiation. There is some immunophenotypic overlap between this and non-small cell calcitonin-free medullary carcinomas (calcitonin-negative neuroendocrine tumours of the thyroid). Some authors have postulated that this phenotype is a manifestation of least differentiated tumours of C-cell histogenesis that have lost the capacity to secrete calcitonin but maintain calcitonin gene-related peptide expression, thereby potentially providing a developmental pathway to explain the controversial concept of so-called mixed medullary–follicular/papillary carcinoma.[52]

Other neoplasms and tumour-like lesions

Rare, but distinct forms of primary thyroid carcinoma may morphologically simulate tumours of salivary gland derivation, notably muco-epidermoid carcinoma, muco-epidermoid carcinoma with eosinophilia and secretory carcinoma/mammary secretory analogue carcinoma. There are very many other less common or incredibly rare neoplasms affecting the thyroid gland of epithelial, mesenchymal, haematolymphoid, thymic, parathyroid gland and developmental origin, together with a few tumour-like lesions (Box 58.4). The list

BOX 58.4 Uncommon or rare tumours and tumour-like lesions described in the thyroid gland

Squamous cell carcinoma
Mucoepidermoid carcinoma
Mucoepidermoid carcinoma with eosinophilocytosis
Mucinous carcinoma
Spindle cell tumour with thymus-like differentiation (SETTLE)
Carcinoma showing thymus-like differentiation (CASTLE)
Malignant lymphomas and leukaemias
Extramedullary plasmacytoma
Langerhan's cell histiocytosis
Angiosarcoma
Solitary fibrous tumour
Smooth muscle neoplasms
Peripheral nerve sheath tumours
Paraganglioma
Teratoma
Fibromatosis
Granular cell tumour
Synovial sarcoma
Haemangiopericytoma
Lipoma
Liposarcoma
Chondrosarcoma
Osteosarcoma
Haemangioma
Lymphangioma
Rhabdomyoma
Epithelioid haemangioendothelioma
Small cell neuroendocrine carcinoma
IgG4-related sclerosing disease/inflammatory pseudotumour

is not exhaustive and a few may arguably be reclassified differently in the light of modern thinking.

Metastatic tumours

The thyroid gland is commonly affected by metastases either by direct extension from neighbouring structures, haematogenous or lymphatic spread. Local structures include the larynx or lymph nodes and common non-head and neck primary sites include bronchopulmonary, breast, malignant melanoma and renal cell carcinoma (Figure 58.49). The latter may occur metachronously following an interval of up to 19 years or be a synchronous presenting feature of the disease.[37]

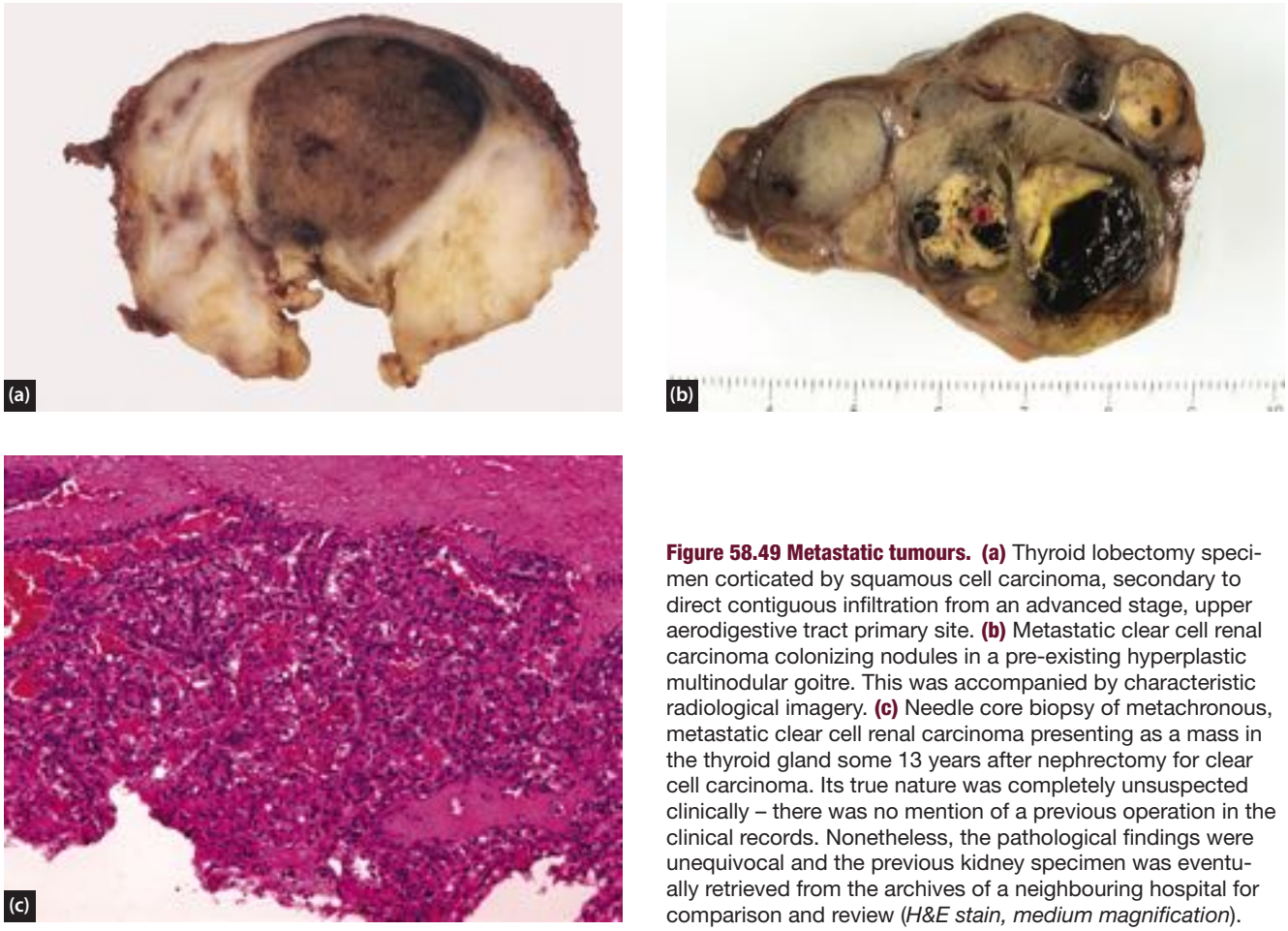


Figure 58.49 Metastatic tumours. (a) Thyroid lobectomy specimen corticated by squamous cell carcinoma, secondary to direct contiguous infiltration from an advanced stage, upper aerodigestive tract primary site. **(b)** Metastatic clear cell renal carcinoma colonizing nodules in a pre-existing hyperplastic multinodular goitre. This was accompanied by characteristic radiological imagery. **(c)** Needle core biopsy of metachronous, metastatic clear cell renal carcinoma presenting as a mass in the thyroid gland some 13 years after nephrectomy for clear cell carcinoma. Its true nature was completely unsuspected clinically – there was no mention of a previous operation in the clinical records. Nonetheless, the pathological findings were unequivocal and the previous kidney specimen was eventually retrieved from the archives of a neighbouring hospital for comparison and review (*H&E stain, medium magnification*).

Intra-operative frozen examination

The use of peri-operative frozen section examination to assist in the diagnosis of thyroid lesions has dwindled in recent years. The widespread adoption of FNAC has enabled broad pre-operative categorization of many lesions, which by their very nature cannot be further refined by frozen section assessment, for example follicular lesion, follicular neoplasm and oncocytic (oxyphil) neoplasm. Frozen section examination on a lesion, definite for malignancy on FNAC, is also unlikely to confer any significant benefit – if the distinction between high-grade lymphoma and undifferentiated (anaplastic) carcinoma has not already been made on FNAC or needle core biopsy, then frozen section is equally unlikely to resolve this. Fleshy, solitary encapsulated lesions are likely to represent follicular adenoma, MIFC, EFVPTC or even MTC, but attempts to comprehensively sample the capsule in the fresh state should be resisted pending tissue fixation with a view to proper paraffin sections in order to obviate artefactual disruption and distortion of the all important peri-capsular tissue planes. The indications for peri-operative frozen section examination of thyroid gland lesions are best agreed by the relevant multidisciplinary team at a local level, taking into consideration local circumstances, individual experience and preferences, together with clinical expectations.[53]

Thyroid cancer staging

The UICC/AJCC TNM classification of malignant tumours is internationally ratified, currently in its 8th edition (2017) (**Table 58.11**).[54] Most importantly, the definition of T3 has been revised for papillary, follicular and medullary thyroid carcinomas, compared to the 7th edition (2009) and the age threshold for a poor prognosis has been amended from over 45 years to over 55 years.

TABLE 58.11 UICC/TNM 8th edition staging schema for thyroid carcinoma[54,55]

THYROID GLAND (ICD-o-3 C73.9)[54]	
Rules for Classification	
The classification applies only to carcinomas. There should be microscopic confirmation of the disease and division of cases by histological type.	
The following are the procedures for assessing T, N, and M categories: *T categories* Physical examination, endoscopy, and imaging *N categories* Physical examination and imaging *M categories* Physical examination and imaging	
Regional Lymph Nodes The regional lymph nodes are the cervical and upper/superior mediastinal nodes.	
TNM Clinical Classification	
T – Primary Tumour*	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour 2 cm or less in greatest dimension, limited to the thyroid
	T1a Tumour 1 cm or less in greatest dimension, limited to the thyroid
	T1b Tumour more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid
T2	Tumour more than 2 cm but not more than 4 cm in greatest dimension, limited to the thyroid
T3	Tumour more than 4 cm in greatest dimension, limited to the thyroid with gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, or omohyoid muscles) T3a Tumour more than 4 cm in greatest dimension, limited to the thyroid T3b Tumour of any size with gross extrathyroidal extension invading strap muscles (sternohyoid, sternothyroid, or omohyoid muscles)
T4a	Tumour extends beyond the thyroid capsule and invades any of the following: subcutaneous soft tissues, larynx, trachea, oesophagus, recurrent laryngeal nerve
T4b	Tumour invades prevertebral fascia, mediastinal vessels, or encases carotid artery
Note: *Including papillary, follicular, poorly differentiated, Hürthle cell and anaplastic carcinomas.	
N – Regional Lymph Nodes*	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis N1a Metastatis in Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes) or upper/superior mediastinum N1b Metastasis in other unilateral, bilateral or contralateral cervical (Levels I, II, III, IV or V) or retropharyngeal

(Continued)

TABLE 58.11 *(Continued)* UICC/TNM 8th edition staging schema for thyroid carcinoma[54,55]

THYROID GLAND (ICD-o-3 C73.9)[54]

M – Distant Metastasis

M0	No distant metastasis
M1	Distant metastasis

pTNM Pathological Classification

The pT and pN categories correspond to the T and N categories. pM1 denotes distant metastasis microscopically confirmed. Note that pM0 and pMX are not valid categories – the MX category is considered to be inappropriate as clinical assessment can be based on physical examination alone (the use of MX may result in exclusion from staging). The categories M1/pM1 may be further specified employing dedicated codes denoting anatomical site(s) of metastasis, i.e. pulmonary, osseous, hepatic, brain, lymph nodes, bone marrow, pleura, peritoneum, adrenals, skin and others.

pN0	Histological examination of a selective neck dissection specimen will ordinarily include 6 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

Histopathological Types

The four major histopathological types are:

- Papillary carcinoma (including those with follicular foci)
- Follicular carcinoma (including so-called Hürthle cell carcinoma)
- Medullary carcinoma
- Anaplastic

Stage

Separate stage groupings are recommended for papillary and follicular (differentiated), medullary, and anaplastic (undifferentiated) carcinomas:

Papillary and Follicular* under 55 years			
Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1
Papillary or Follicular 55 years and older			
Stage I	T1a, T1b, T2	N0	M0
Stage II	T3 T1, T2, T3	N0 N1	M0 M0
Stage III	T4a	Any N	M0
Stage IVA	T4b	Any N	M0
Stage IVB	Any T	Any N	M1
Medullary			
Stage I	T1a, T1b	N0	M0
Stage II	T2, T3	N0	M0
Stage III	T1, T2, T3	N1a	M0
Stage IVA	T1, T2, T3 T4a	N1b Any N	M0 M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1
Anaplastic			
Stage IVA	T1, T2, T3a	N0	M0
Stage IVB	T1, T2, T3a	N1	M0
Stage IVB	T3b, T4a, T4b	N0, N1	M0
Stage IVC	Any T	Any N	M1

Note: *Including papillary, follicular, poorly differentiated, and Hürthle cell carcinomas.

(Continued)

TABLE 58.11 *(Continued)* UICC/TNM 8th edition staging schema for thyroid carcinoma[54, 55]

PROGNOSTIC FACTOR GRID – Papillary and Follicular Thyroid Carcinoma[55] Prognostic factors for survival in differentiated thyroid carcinoma of follicular cell derivation			
Prognostic factors	**Tumour-related**	**Host-related**	**Environment-related**
Essential	Extrathyroid extension T category M category Post-treatment Thyroglobulin	Age	Residual disease: R0, 1 or 2
Additional	N category Site of metastases BRAFV600E mutation	Gender	Extent of resection Iodine ablation Endemic goitre
New and promising	Molecular profile		
PROGNOSTIC FACTOR GRID – Medullary Cancer[55]			
Prognostic factors	**Tumour-related**	**Host-related**	**Environment-related**
Essential	Pre- and post-operative calcitonin and CEA	Age	Extent of resection
Additional	MEN Germline mutation Calcitonin doubling time		
New and promising	Molecular profile		

PARATHYROID GLANDS

Normal parathyroid glands

Most individuals possess at least two pairs of parathyroid glands (PTG). The cephalad pair are embryologically derived from the 4th branchial cleft and are usually located over the posterior surface of the thyroid gland close to the point of entry of the inferior thyroid artery. The caudad glands are of 3rd branchial pouch origin and typically lie over the lower thyroid gland pole, though they are more variably placed and may be found within the mediastinum or even the pericardium, consequent upon co-migration with the thymus, which is similarly of 3rd branchial pouch ontogeny. Supernumerary or heterotopic (ectopic) glandular tissue may consist of less well-formed, more diffuse cell aggregates within cervical soft tissues (parathyromatosis) often in close proximity to eutopic glands and this pattern also characterizes surgically implanted gland tissue.[5]

The parathyroid glands secrete parathyroid hormone (parathormone, PTH), which elevates serum calcium via direct effects on kidney and bone and indirectly through the intestine. To the unaided eye, the glands are a yellow-brown colour. At operation, brown fat, yellow fat, sequestrated thyroid tissue, thymus, lymph node and autonomic ganglia may all mimic these appearances and these are not infrequently submitted for frozen section examination in lieu of parathyroid gland proper. Microscopically, in the normal state, the glands are lobulated, richly vascularized and composed of nests and/or trabecula of polygonal parenchymal cells, viz. a mixture of chief (principal) cells, water-clear cells and oncocytic (oxyphil) cells, interspersed with adipocytes (**Figures 58.50** and **58.51**). The number, size and composition of the glands, however, are subject to wide normal and abnormal variation (**Table 58.12**) influenced by age, gender, nutritional and hormonal status. With advancing age, congeries of oncocytic (oxyphil) cells are increasingly encountered.

Hyperparathyroidism

Hyperparathyroidism is defined by elevated serum PTH and is the commonest pathological condition affecting the parathyroid glands. It is classified into primary, secondary and tertiary forms dependent upon the identification of a driving stimulus (**Table 58.13**) though the end result is an absolute increase in parenchymal cell mass affecting one or more glands (**Figure 58.52**). Parathyroid proliferative disease (PPD) is a collective term encompassing all histological causes of hyperparathyroidism.

In primary parathyroid gland hyperplasia, all of the parathyroid glands are enlarged, albeit unevenly in some cases. In parathyroid gland adenoma, paradigmatically only a single gland is enlarged, the remaining glands being of normal size or small. This is typically accompanied by marked diminution in intraglandular adipocytes and reduced or absent intracytoplasmic lipid droplets (**Figure 58.53**), though rarely the latter may paradoxically be more abundant in chief cells located between hyperplastic nodules. Additionally, foci of irregularly distributed stromal fat cells may persist, recapitulating a rim of normal glandular tissue which, when juxtaposed to a fat depleted hyperplastic nodule, may lead to erroneous interpretation as an adenoma. The most reliable discrimination between hyperplasia and adenoma is achieved through histological examination of multiple glands augmented by multiple sections through larger glands. If only one parathyroid gland is available for

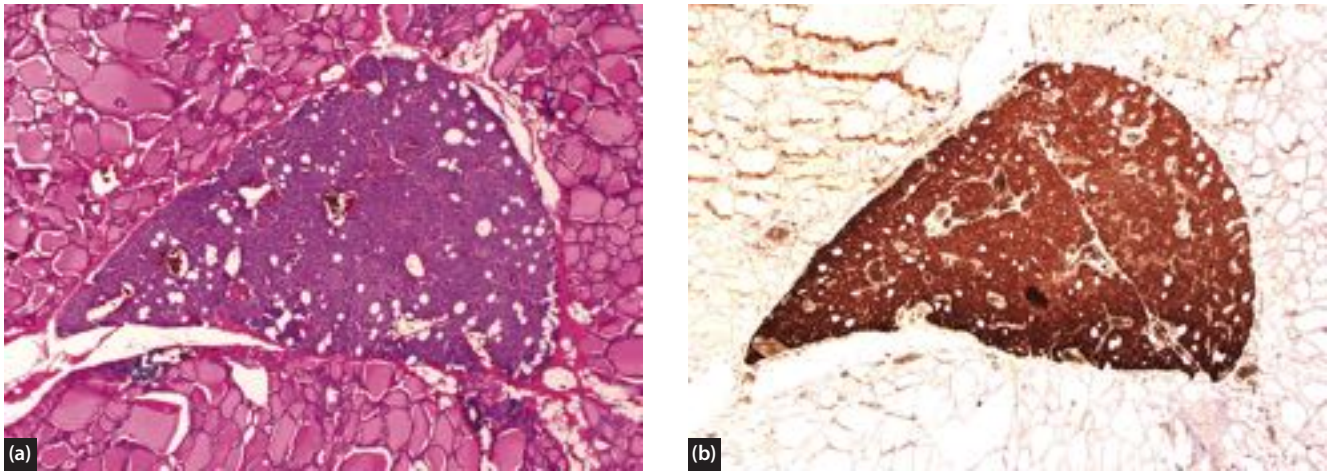


Figure 58.50 Normal parathyroid glands 1. (a) An intrathyroidal parathyroid gland presenting a normal vascularized, lobular microarchitecture comprising parenchymal cells interspersed with a normal complement of mature fat cells that are of haphazard distribution and density. Note its clear circumscription and delicate fibrous capsule (*H&E stain, low magnification*). **(b)** A replicate section immunostained with anti-PTH antibody showing intense parenchymal positivity, in sharp contrast to the surrounding negative thyroid gland follicles acting as an internal control (*PTH IHC, low magnification*).

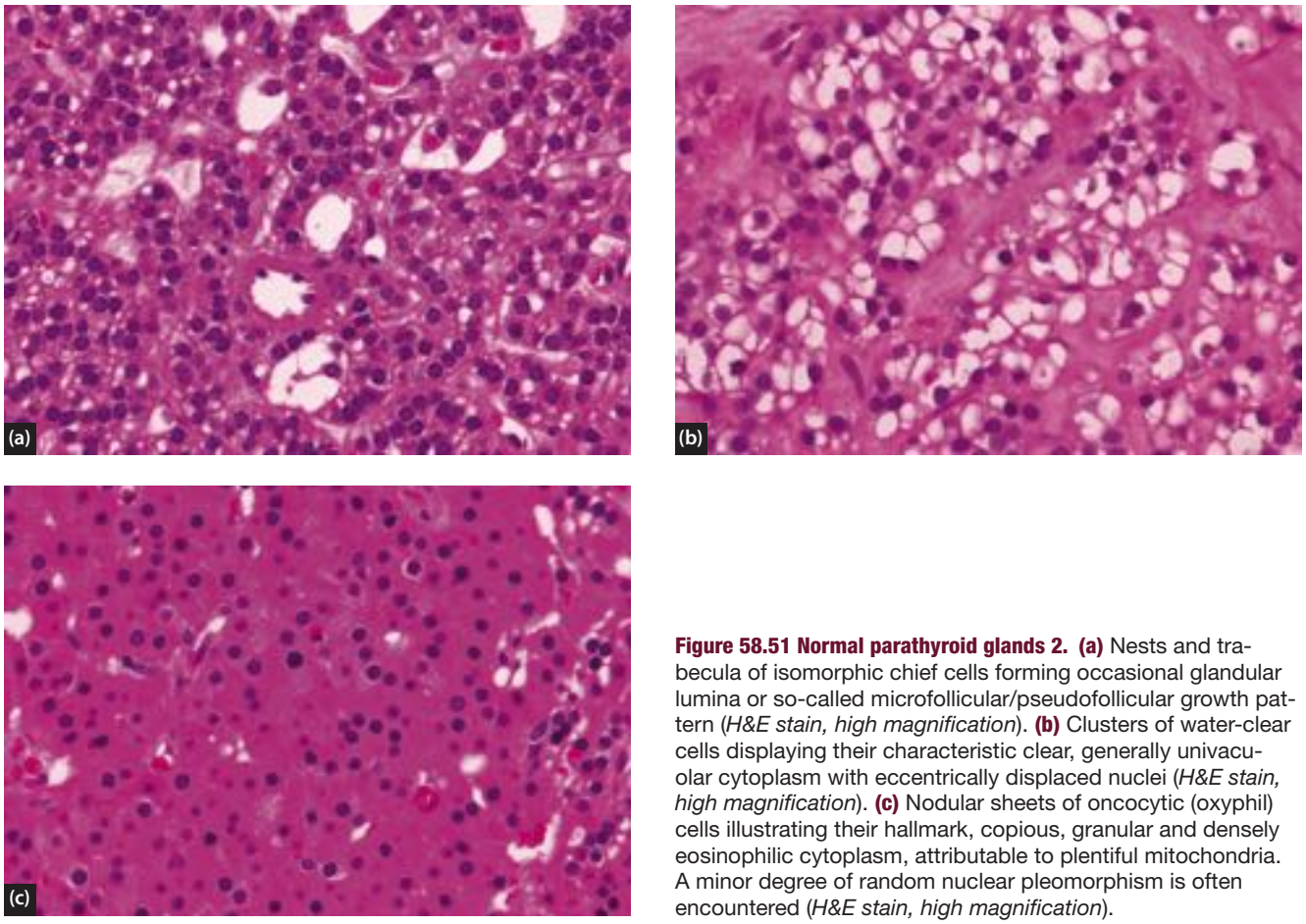


Figure 58.51 Normal parathyroid glands 2. (a) Nests and trabecula of isomorphic chief cells forming occasional glandular lumina or so-called microfollicular/pseudofollicular growth pattern (*H&E stain, high magnification*). **(b)** Clusters of water-clear cells displaying their characteristic clear, generally univacuolar cytoplasm with eccentrically displaced nuclei (*H&E stain, high magnification*). **(c)** Nodular sheets of oncocytic (oxyphil) cells illustrating their hallmark, copious, granular and densely eosinophilic cytoplasm, attributable to plentiful mitochondria. A minor degree of random nuclear pleomorphism is often encountered (*H&E stain, high magnification*).

examination and proves to be enlarged and/or hypercellular, definitive pathological distinction between hyperplasia and adenoma cannot always be reliably achieved.

The term lipohyperplasia may be used to designate the extremely rare occurrence of hyperplastic glands with plentiful fat, in which the glands are enlarged albeit with predominant lipocytes and limited parathyrocyte cell content.

Parathyromatosis is a rare cause of persistent or recurrent hyperparathyroidism characterized by multiple nests of hyperfunctioning parathyroid tissue throughout the neck and mediastinum. These may range in size from

TABLE 58.12 Attributes of normal and abnormal parathyroid glands in man[4]

Characteristic	Normal range	Abnormal
Number	Usually 4, but ranges from 1–12	
Size	Length 3–6 mm Width 2–4 mm Depth 0.5–2 mm	>6 mm in any plane
Weight	Each gland approx. 30 mg – the inferior glands are often heavier than the superior ones Total parathyroid gland mass 120 ± 3.5 mg in males 142 ± 5.2 mg in females	Any individual gland >60 mg
% fat	17–50% Male average 20.5% Female average 15.6%	Complete absence or very marked reduction
Intracytoplasmic lipid	Abundant	Absent or sparse

TABLE 58.13 Classification of hyperparathyroidism

Type	Definition	Causes	Pathological changes
Primary	Overproduction of PTH due to intrinsic abnormality of one or more glands causing elevated serum calcium with depressed serum phosphate	PTG adenoma 85% PTG carcinoma 1% PTG hyperplasia 14% • Sporadic • MEN 1 • MEN 2 • Familial isolated hyperparathyroidism • Familial hypocalcuric hypercalcaemia	Adenoma or carcinoma changes Chief cell hyperplasia Reduced or absent intra-parenchymal fat Diffuse or nodular changes
Secondary	Compensatory hyperplasia of parathyroid glands due to decreased serum calcium, usually resulting in normocalcaemia	Chronic renal failure Malabsorption Vitamin D deficiency Renal tubular acidosis	Hyperplasia of all glands May be indistinguishable from primary hyperparathyroidism Multinodular or diffuse
Tertiary	Autonomous parathyroid gland hyper-function following secondary hyperparathyroidism	Any cause of secondary hyperparathyroidism	Very similar to secondary hyperparathyroidism though glands are typically larger and multinodular May rarely be associated with adenoma or carcinoma



Figure 58.52 Left and right upper and lower parathyroid glands in quadriglandular hyperplasia of secondary hyperparathyroidism following renal transplantation. These each weighed between 0.5 g and 1.2 g and were incised bivalvate peri-operatively to disclose the variegated, multinodular cut surfaces seen here to be irregular, both within and between glands. The lower glands are often asymmetrically larger than the upper glands.

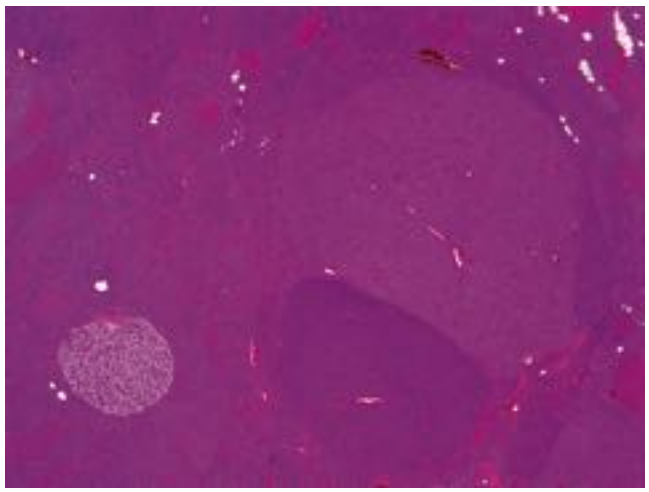


Figure 58.53 A hyperplastic gland in hyperparathyroidism, secondary to chronic renal disease, displaying hypercellularity with hugely reduced stromal fat cell content. The multinodular appearance is due to proliferation of groups of cells with different cytological features, mostly chief cells here with, unevenly distributed, water-clear cell and oxyphil cell nodules (*H&E stain, ultra-low magnification*).

microscopical congeries of cells within skeletal muscle and fat to larger soft yellow/white nodules visible to the unaided eye. Primary parathyromatosisis is associated with the MEN syndromes, most commonly MEN 1. Secondary parathyromatosis occurs as a sequela of surgical exploration of the neck, supposedly due to inadvertent contamination of the operative field following spillage (seeding) of cells. It may mimic invasive carcinoma to the unwary.

Only primary and tertiary hyperparathyroidism are associated with hypercalcaemia and its attendant systemic sequelae, but all three forms may manifest with bone disease. Aberrant PTH-related peptide secretion may occur as a paraneoplastic phenomenon (humoral hypercalcaemia of malignancy) in some malignant neoplasms, notably squamous cell carcinoma of primary bronchopulmonary, upper aerodigestive tract and female genital tract origin, sometimes with renal cell carcinoma. Approximately 50% of metastatic prostatic adenocarcinoma deposits evince anomalous PTH immunopositivity, cross-reacting with PTH-related protein, which may prove to be a source of differential diagnostic confusion. Hypercalcaemia directly related to the osteolytic effects of bone metastasis, independent of PTH-related protein, may occur in mammary carcinoma and haematological malignancies. Lithium therapy prescribed for psychiatric disorders may induce a form of primary hyperparathyroidism, which abates on cessation of the drug, though parathyroidectomy may still be indicated.

Parathyroid gland adenoma

The WHO (4th edition, 2017) classification of parathyroid gland tumours is reproduced in Table 58.14.[27] Parathyroid gland adenoma is the predominant cause of primary hyperparathyroidism. It may occur spontaneously or within the context of various syndromes. Irradiation of the neck is a potential risk factor with a latency/interval period in the order of 30–40 years. Excision of the abnormal gland is curative and results in normalization of biochemical indices and increased bone mineral density. Up to 10% of patients relapse, sometimes after an interval of many years. Adenomas are not usually palpable clinically, unless cystic, and rarely cause compressive symptoms. Haemorrhagic infarction, either post-FNAC or spontaneously, complicated by haematoma, may result in an acutely painful neck lump.

TABLE 58.14 WHO classification of tumours of the parathyroid glands[35]

Parathyroid carcinoma
Parathyroid adenoma
Secondary, mesenchymal and other tumour

The morphological spectrum of parathyroid adenomas occurring in supernumerary glands and in heterotopic sites such as mediastinum, thyroid gland or oesophagus is identical to that in eutopic locations. However, not only may they lead to unsuccessful cervical exploration, they may mimic thyroid gland adenomas or medullary thyroid carcinoma histologically.

Double adenomas may rarely occur (responsible for between 1.7% and 12% of cases of primary hyperparathyroidism) and are usually bilateral. All of the patients are symptomatic and show a higher PTH level and tumour weight compared to solitary adenoma and parathyroid gland hyperplasia. Distinction from asymmetrical parathyroid gland hyperplasia, particularly in the context of MEN, is extremely difficult. The diagnosis is therefore only considered conclusive when follow-up after removal of two abnormal glands shows no recurrence. Gene profiling studies indicate that multiple gland neoplasia represents a distinct molecular entity.

Parathyroid gland adenomas occur more frequently in the lower parathyroid glands. The mean weight is 0.55 g but tumours weighing as much as 53 g are recorded and, generally, the more severe the hypercalcaemia, the bulkier the adenoma. Macroscopically, parathyroid gland adenomas are well marginated, soft and vary from yellow-red to orange-brown in colour (Figure 58.54), more blue tinged if toluidine blue has been used as an aid to peri-operative



Figure 58.54 **(a)** The external surface of a parathyroid gland adenoma, weighing 1.2 g in primary hyperparathyroidism, demonstrating a delicate capsule with ramifying surface blood vessels. **(b)** When transected, its variegated, multinodular texture is very similar to a hyperplastic gland, though in this instance it was the only abnormal gland of those recovered at operation.

localization. The oncocytic (oxyphil) cell variant presents a so-called mahogany brown cut surface, characteristic of such mitochondria-rich tumours at many sites. Secondary haemorrhage and/or cystic change (**Figure 58.55**) may be encountered, either spontaneously occurring or post-FNAC. The remaining, uninvolved parathyroid glands should be normal or reduced in size.

Microscopically, parathyroid gland adenomas are circumscribed and may be lobulated or nodular. They are hypercellular and substantially or completely bereft of intraglandular adipocytes, with the exception of lipoadenoma. An attenuated, part-circumferential mantle of normal or compressed parathyroid gland tissue is identified in 50% or so of cases, dependent upon the planes of section examined (**Figure 58.56**), often near the vascular hilum of the gland, with the caveat that a compressed tissue rim is occasionally encountered around hyperplastic nodules. The tumour cells may be disposed in solid sheets, cords, acini, follicle-like and/or microcystic configuration. Glandular structures may contain eosinophilic colloid-like secretions (pseudo-follicular growth). These are dPAS-positive but immunonegative for thyroglobulin. Intrafollicular or interstitial amyloid protein may rarely be deposited.

Most adenomas are composed of chief (principal) cells, though oncocytic (oxyphil) cells and/or water-clear cells are often present, either dispersed or in nodular aggregates. The chief cells of an adenoma are usually larger than their non-neoplastic counterparts present in the uninvolved rim of parathyroid tissue, where present, and in the remaining, non-neoplastic glands. They also typically possess less intracellular fat than the uninvolved tissue and the other suppressed glands. Mitoses usually number less than 1 per 10 high-power fields without abnormal forms. There may be random nuclear pleomorphism and/or multinucleation

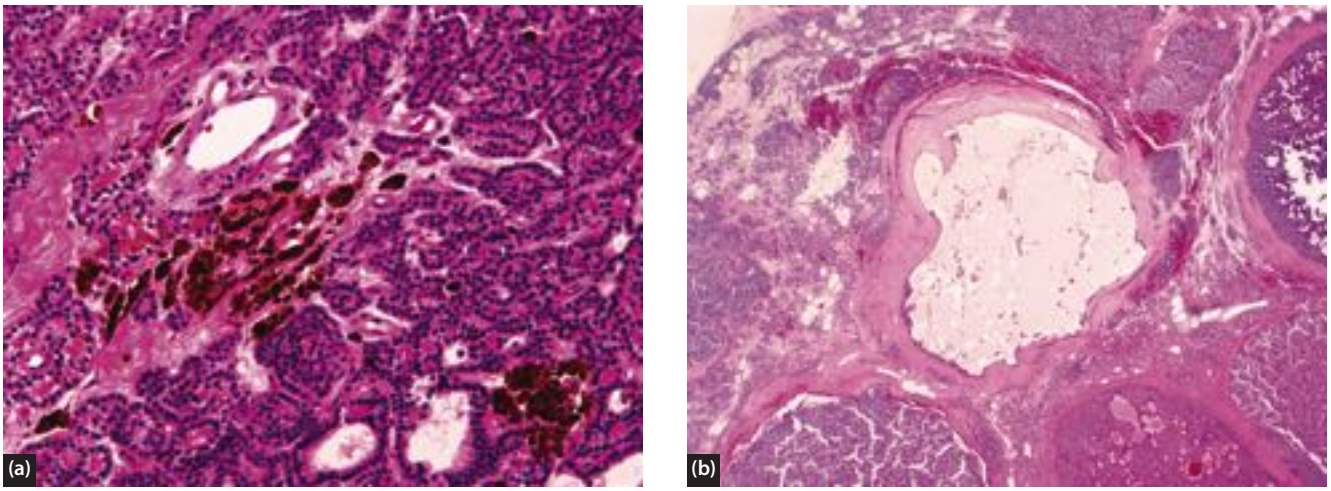


Figure 58.55 (a) This adenoma shows scattered collections of interstitial siderophages containing phagocytosed, coarsely granular, golden brown haemosiderin pigment, indicative of antecedent haemorrhage (*H&E stain, intermediate magnification*). **(b)** Another example displays focal cystic change with accompanying fibrocollagenous scar tissue plus part-circumferential, dystrophic, mural calcification (*H&E stain, low magnification*).

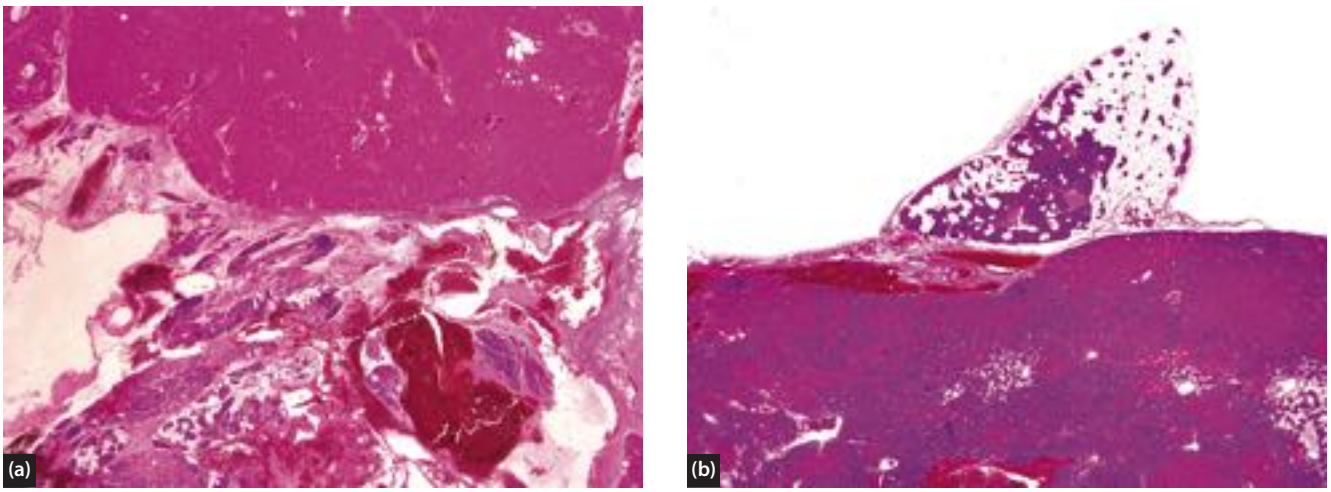


Figure 58.56 (a) View of the edge of a parathyroid gland adenoma. Note its sharp demarcation, hypercellularity and absence of intratumoural lipocytes. There is a peripheral nubbin of attenuated-looking parathyroid glandular tissue with preserved intraglandular fat cells for comparison (*H&E stain, ultra-low magnification*). **(b)** Perimeter of another parathyroid gland adenoma depicting extrinsic atrophic looking parathyroid gland remnant with juxtaposed vascular hilus (*H&E stain, ultra-low magnification*).

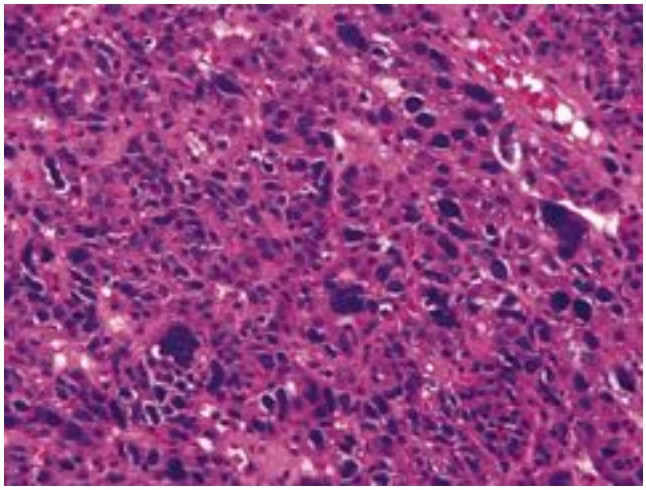


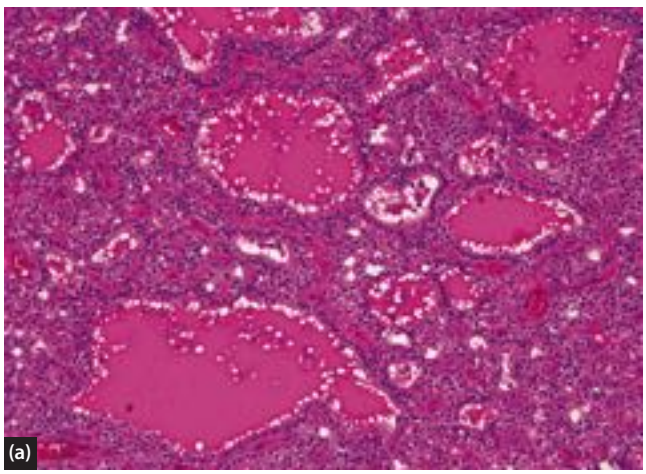
Figure 58.57 The presence of bizarre giant cell transformation (monster cells), some polykaryocytic, possessing enlarged hyperchromatic nuclei, albeit without mitoses or other worrisome features, against a background of bland-looking cells should not be taken as evidence of malignancy (*H&E stain, medium magnification*).

sometimes with bizarre, hyperchromatic giant cells (Figure 58.57), though in the absence of other indicators of potential malignancy these should not be misconstrued as evidence portending aggressive behaviour. Flow cytometry is of limited assistance in discriminating between parathyroid gland adenoma and carcinoma because aneuploidy is found in up to 25% of histologically and clinically benign tumours.

VARIANTS OF PARATHYROID GLAND ADENOMA

In addition to their fundamental cytological and architectural patterns, parathyrocyte proliferations, including adenomata, are susceptible to a host of engrafted secondary phenomena, mostly retrogressive, none entirely specific diagnostically. These include inflammation, infarction, haemorrhage, haemosiderosis, Gamna–Gandy nodulosis, hydrops, necrosis, hypervascularity and peliosis-like (pseudo-angiomatoid/telangiectatic) change, microcystic and macrocystic degeneration, fibrosis/hyalinosis, lipometaplasia, metaplastic ossification, mineralization and pseudo-invasion (Figure 58.58). These may occur *de novo* or in response to trauma, such as FNAC. The following histological subtypes, however, are recognized.

- **Cystic adenoma** may be cystic *ab initio* or secondarily as a consequence of subsiding haematoma post-infarction. Morphologically, it may mimic a benign simple parathyroid cyst but should not be confused with adenoma *type ordinaire* displaying a minority cystic growth pattern.
- **Lipoadenoma (parathyroid hamartoma)** is a very rare occurrence showing admixture of parenchymal cells with copious mature adipocytes and/or brown fat cells, the fat content variably accounting for 20–90% of the tumour (Figure 58.59). There may be accompanying inflammation, mineralization and mucomyxoid change (myxoid lipoadenoma) and, where dominant, the term myxoadenoma is sometimes invoked.[56] Distinction should be drawn diagnostically between lipoadenoma, benign lipoma thymolipoma and lipohyperplasia. Approximately 50% of lipoadenomas are associated with hypercalcaemia. The uninvolved parathyroid glands are normal.
- **Papillary variant** is rare and apt to be mistaken for papillary thyroid carcinoma.
- **Water-clear adenoma** is substantially or wholly composed of water-clear cells. The histological differential diagnosis includes adenoma composed of hydropic and/or vacuolated chief cells (rather than ultrastructurally distinct water-clear cells proper) and water-clear cell



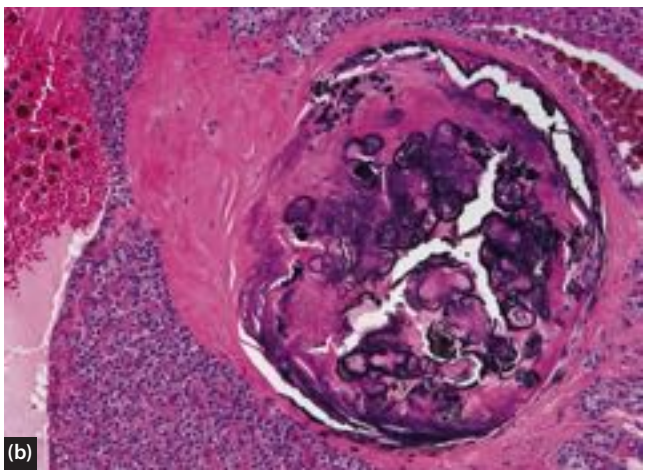
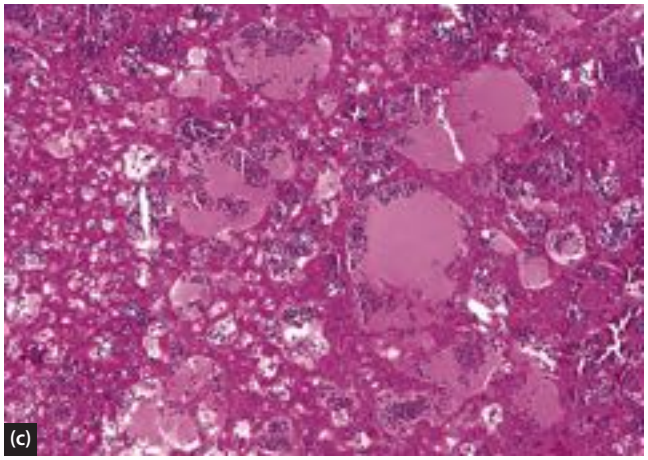


Figure 58.58 (a) Pseudo-follicular growth in a parathyroid adenoma closely resembling normofollicular and macrofollicular thyroid gland follicles with stored colloid-like secretions, even mimicry of marginal vacuoles (*H&E stain, medium magnification*). **(b)** Parathyroid gland adenoma showing sequelae of prior haemorrhage, i.e. localized haemosiderosis with adjacent Gamna-Gandy body. These fibrosiderotic nodules consist of degenerate elastin fibres encrusted with iron and calcium salts upon a hyalinized background. They are by no means exclusive to either haemoglobinopathies or the spleen and may occasionally be encountered in tumours at other sites, for example cardiac myxoma (*H&E stain, medium magnification*). *(Continued)*



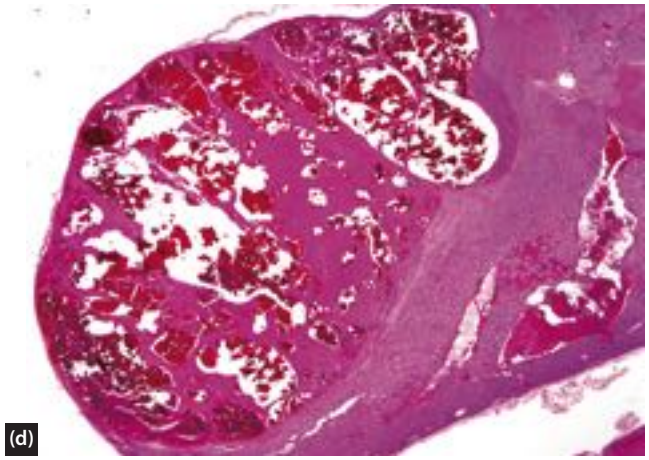
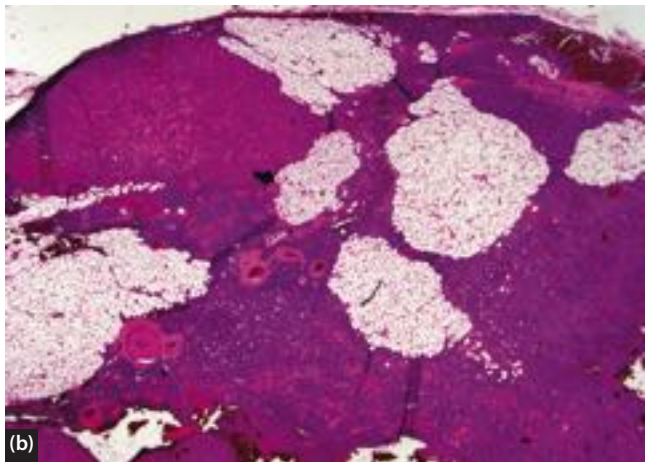
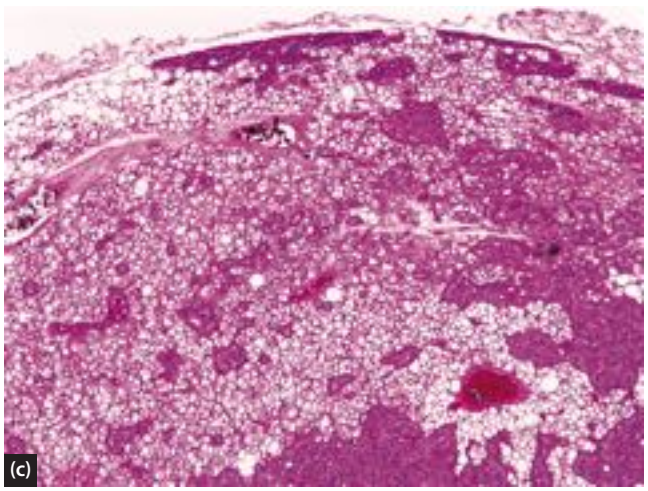


Figure 58.58 (Continued) (c) Parathyroid adenoma showing a conspicuous field of spongiform microectatic cisternae filled with erythrocytes, resembling so-called peliosis (pseudoangiomatoid change) more commonly encountered in the liver, spleen and lymph nodes. Its significance at this site is unknown but it should not be mistaken for a vascular malformation, haemangioma or vascular tumour (*H&E stain, low magnification*). **(d)** Another parathyroid adenoma exhibiting circumscribed pseudoangiomatoid growth (*H&E stain, ultra-low magnification*).







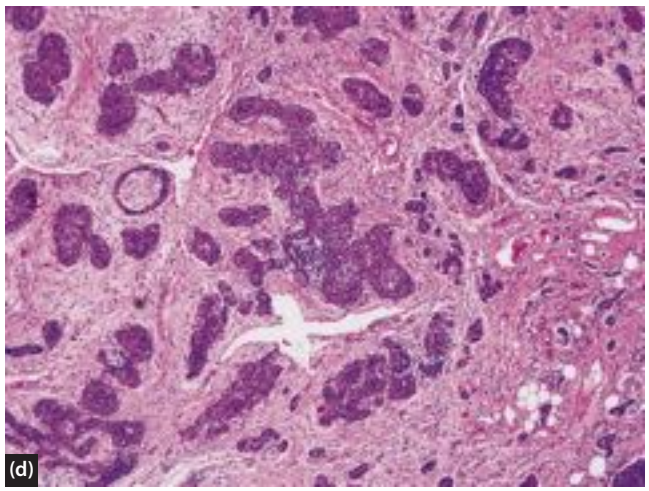


Figure 58.59 (a) The cut-surface of a parathyroid gland lipoadenoma illustrating its multinodular architecture comprising solid parenchymal elements interspersed with yellow fat. **(b)** The same lesion histologically confirms solid paratyhyrocyte nodules intimately admixed with mature lipocytes (white fat cells), all within the confines of the delimiting capsule (*H&E stain, low magnification*).**(c)** The pericapsular region of a different lipoadenoma showing similar features, albeit with brown fat cells predominant (*H&E stain, low magnification*). **(d)** Myxoid lipoadenoma comprising prominent loose mucomyxomatous interstitium enclaving discrete islands and sheets of parathyroid cells. A minority cluster of mature adipocytes is evident within the right lower quadrant of this particular field and these provide a clue to the diagnosis (*H&E stain, medium magnification*).

hyperplasia. It may be mistaken for a clear cell neoplasm of the thyroid gland, including metastasis, and paraganglioma.

- **Follicular variant** shows a predominant pseudofollicular (acinar) architecture often with intraglandular secretions and may be misinterpreted as a follicular-patterned thyroid neoplasm.
- **Oxyphil adenoma (oncocytic adenoma)** is comprehensively composed (at least 90% of the cell population) of mitochondria-rich oncocytic (oxyphil) cells and may or may not be functional. It must be distinguished from nodular oxyphilic cell change with advancing age and, when intrathyroidal, from oxyphil (Hürthle) cell neoplasms of the thyroid gland. Commensurate nuclear pleomorphism with polykaryocytosis and bizarre giant cell transformation (monster cells) often feature and, in isolation, should not be overinterpreted as evidence suggestive of malignancy.
- **Microadenoma** is defined as a single lesion of less than 6 mm maximum dimension, weighing no more than 0.1 g, occurring in an otherwise grossly normal parathyroid gland. It may present as an unencapsulated micronodule wholly or partially within the substance of the gland, as a hypercellular proliferation affecting an entire gland or as an area of hypercellular growth showing poor demarcation from juxtaposed normal glandular parenchyma. Demonstration of these may be surgically and pathologically challenging.
- **Parathyroid adenoma with prominent lymphocytic infiltrate** is an unusual histological phenomenon, not necessarily associated with autoimmune response. There may, or may not, be background chronic lymphocytic parathyroiditis of adjacent remnant parathyroid tissue, where glandular destruction may be seen, at least focally. Caution must be exercised to exclude lymphoma.[56] Very rarely parathyroid gland adenoma may present with granulomatous infiltration, not associated with sarcoidosis, underlying infection or other primary granulomatous conditions, themselves associated with hypercalcaemia independent of parathyroid gland disease (**Figure 58.60**).
- **Atypical parathyroid gland adenoma** (*parathyroid neoplasm of uncertain malignant potential*) is a descriptive term attributed to a parathyroid gland tumour that displays equivocal, worrisome, borderline or suspicious features of parathyroid carcinoma, though falls short of fulfilling the first-order criteria for a confident designation of malignancy. This rubric acknowledges the limitations of predicting the behaviour of an individual tumour based upon conventional histomorphological assessment (it is the pathologist who is uncertain, not the tumour) and it is not proffered as a distinct clinicopathological entity. Only a small minority of such atypical adenomas are expected to recur and/or metastasize and the rank importance of second-order criteria in quantifying this small risk of more aggressive behaviour has yet to be established.

Atypical parathyroid gland adenomas are generally indistinguishable from adenoma of usual type by the unaided eye (**Figure 58.61**). The commonest microscopical features, ranked according to frequency, however, include intracapsular entrapment (87%), intratumoural fibrosis (75%), haemosiderosis (58%), cyst formation (50%), mitoses (25%) and peritumoural fibrosis (25%). The Ki67 proliferative index typically lies intermediate between adenoma and frank carcinoma. The value of ploidy studies in predicting local recurrence is based upon small studies. Nonetheless, the use of this terminology serves to highlight those patients who merit closer surveillance, such as regular serum calcium measurements, while avoiding the stigma of a firm label of malignancy, wholly unjustified in most cases.[4]

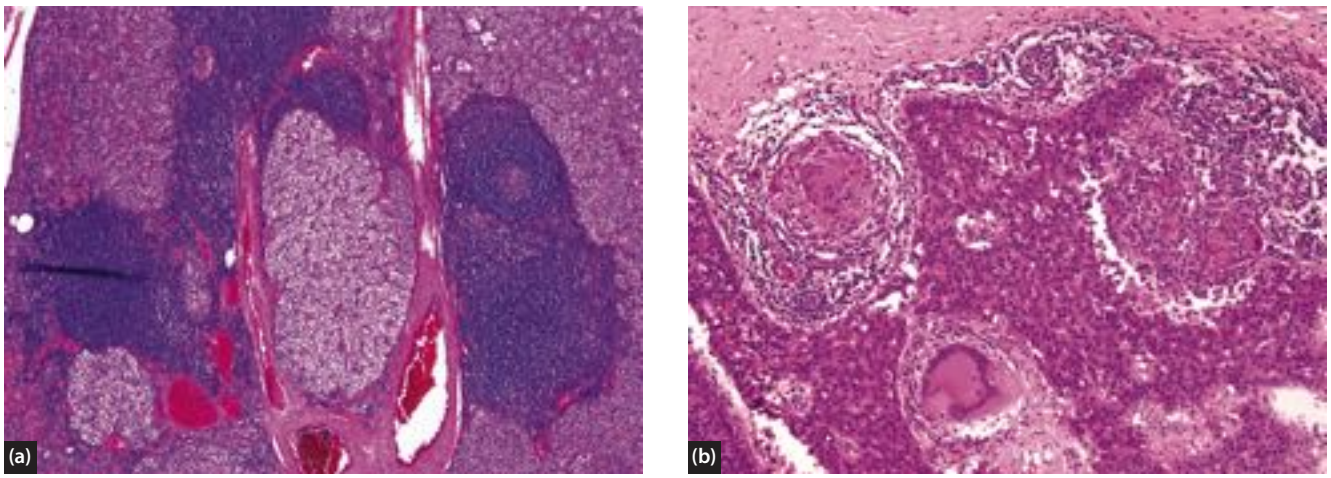


Figure 58.60 **(a)** Parathyroid adenoma variant with prominent lymphocytic infiltrate, demonstrating sheets of chief cells and nodules of water-clear cells intimately associated with a population of lymphocytes and mature plasma cells. Two lymphoid follicles, one with reactive germinal centre formation, are present (*H&E stain, low magnification*). **(b)** Parathyroid adenoma associated with non-necrotizing granulomatous inflammation. Three sharply circumscribed epithelioid histiocytic granulomata, each containing multinucleate giant cells, one of Langhans' type, are visible. This is a rare occurrence and should prompt efforts to exclude comorbid systemic granulomatous disease (*H&E stain, medium magnification*).



Figure 58.61 This atypical parathyroid gland adenoma is macroscopically indistinguishable from adenoma *type ordinaire.* The cut surface displays subtle capsular irregularity and localised fibrous thickening. First-order criteria of malignancy were absent.

Immunohistochemistry is occasionally valuable in the differential diagnosis between parathyroid gland adenoma and other neoplasms, notably of the thyroid gland, and it also has a role in differentiating between atypical adenoma and parathyroid carcinoma. Parathyrocytes are cytokeratin-positive and stain for many pan-neuroendocrine markers, both membrane-bound peptide products, such as PTH, chromogranin A and synaptophysin, and cytosol epitopes including neuron-specific enolase. Chief cells show nuclear immunoreactivity for thyroid transcription factor-1. Reciprocal negative staining for thyroglobulin may also be helpful. Typically, nuclear parafibromin immunoreactivity is globally or focally lost in parathyroid carcinoma. Atypical adenomata expressing parafibromin are said to behave as adenomata, in contradistinction to those with loss of immunopositivity, which portend a heightened risk of recurrence. Immunostaining for anti-mitochondrial antibody highlights oncocytic (oxyphil) differentiation, but in itself it does not discriminate between oncocytic parathyroid gland tissue and oncocytic change in other tissues. Staining for fat on frozen section is seldom of diagnostic help.

Molecular genetic studies by X-linked restriction fragment length polymorphism provide evidence for monoclonality in many parathyroid gland adenomas. Tumour-specific DNA alterations are present in the PTH gene in some cases. A minority of cases demonstrate pericentric inversion of chromosome 11, which causes translocation of the cyclin D1 gene with the PTH gene resulting in overexpression of cyclin D1 and cell proliferation. Cyclin D1 expression is identified by immunohistochemistry more frequently than this cyclin D1 gene rearrangement, suggesting that other molecular factors are operant in cyclin D1 deregulation. Cyclin D1 is also common in parathyroid hyperplasia and parathyroid carcinoma.

The germline mutation underlying MEN 1 is associated with some sporadic parathyroid gland adenomas. The *RET* proto-oncogene germline mutation underlying MEN 2 does not appear to be involved in the genesis of sporadic parathyroid gland adenomas. Other chromosomal abnormalities are detected by comparative genomic hybridization and fluorescence *in situ* hybridization (FISH) techniques.

Parathyroid carcinoma

This is defined as a malignant neoplasm of parathyroid parenchymal cells and is responsible for approximately 0.5–2% of all cases of primary hyperparathyroidism, though some series report as high as 5%. It occurs most frequently in the fifth and sixth decades (i.e. roughly a decade younger than adenomas) with no gender predilection. Most patients are severely hypercalcaemic with active bone and renal disease at presentation, they tend to suffer worse symptoms attributable to this compared to those with adenoma and there is more often a palpable neck mass, though this presentation is by no means invariable. Initial designation as adenoma may be revised at a later time following recurrence and/or metastasis.[57]

Parathyroid carcinoma tends to invade local structures, is slow-growing and metastasizes late. Complete surgical excision at first operation affords the best opportunity for cure, though this relies upon early recognition of its malignant nature, which cannot always be achieved. Following surgery, approximately 30% of patients suffer local recurrence, usually within 3–5 years. Roughly 30% develop metastasis, typically late in its course, generally to regional lymph nodes (30%), lungs (40%), liver (10%) and bone. Survival is 60–85% and 40–70% at 5 years and 10 years respectively with an average survival following recurrence of 7–8 years. Non-functioning examples may behave more aggressively than functioning ones. Death is usually attributable to the metabolic complications of hypercalcaemia rather than overwhelming tumour burden. Repeated surgery may palliate and adjuvant radiotherapy has a limited role. The response to chemotherapy is poor. The hypercalcaemia may become refractory to medical management and specialist anti-PTH immunotherapy has proven beneficial in very severe cases (**Figure 58.62**), occasionally eliciting a direct anti-tumour effect.[58]

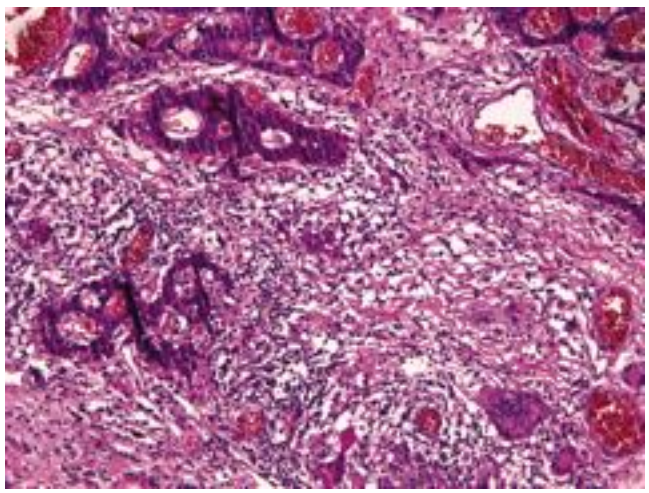


Figure 58.62 Metastatic parathyroid carcinoma in the lung, following anti-PTH immunotherapy for refractory, severe hypercalcaemia. Note the vigorous granulomatous inflammatory response, secondary to Freund's complete adjuvant, which was used to intensify the immune response, closely associated with the nests of residual tumour cells (*H&E stain, medium magnification*).

The tumour size is generally larger than that of parathyroid gland adenoma with an average weight between 6.7 g and 12 g, although smaller tumours are being identified earlier in recent times. It may be encapsulated or obviously infiltrative. There may be a soft, brown appearance indistinguishable from adenoma, or a firm, grey-white texture. Troublesome intra-operative dissection, owing to adherence to contiguous structures, should alert the perceptive surgeon to a possibility of malignancy.

Microscopically, parathyroid carcinomas may be deceptively bland or overtly malignant and anything in between. It is the biological behaviour, however, which ultimately defines parathyroid carcinoma. In rare cases, there may be no histomorphological clues to indicate potential aggressiveness. Nonetheless, first-order morphological criteria of malignancy (absolute criteria) include invasion into adjacent tissues and/or histologically documented metastasis. When these are absent or inconclusive, a combination of second-order facultative features (features associated with malignancy), each in themselves not fully diagnostic, are invoked (Table 58.15).

The capsule is often thickened and is classically contiguous with broad internal fibrous septula, dividing the tumour into irregular nodular compartments. (This must be differentiated from scarring in an adenoma, secondary to spontaneous infarction, FNAC or previous surgery.) Invasion beyond the delimiting capsule (Figure 58.63) may or may not be obvious (and can be mimicked by pseudo-infiltration, sequestration/benign entrapment and/or implantation of benign tissue following rupture of a parathyroid adenoma capsule). Fibrosis and haemosiderin deposition may be encountered in hyperplasia, degenerate adenomas and carcinomas. Pericapsular vascular invasion (Figure 58.64) is virtually diagnostic of malignancy (though artefactual dislodgement of cells simulating tumour embolus must be considered) but is present in only 10–15% of cases. Perineural infiltration is also diagnostic of malignancy but is also an uncommon finding. There may be a variety of growth patterns and a trabecular or rosettoid architecture favours malignancy (but it is not common and not entirely specific). Diffuse growth of isomorphic cells with elevated nucleus–cytoplasmic ratio is

TABLE 58.15 Microscopical criteria for the diagnosis parathyroid carcinoma[53]

First-order criteria	Second-order criteria
Presence of either or both of the following: 1 Invasion into surrounding tissues • Thyroid • Oesophagus • Nerves • Connective tissue 2 Histologically documented locoregional or distant metastasis	In the absence of first-order criteria, at least two or more of the following: • Capsular invasion • Vascular invasion • Mitoses >5 per 10 hpf • Broad intralesional fibrous septa with division into nodules • Coagulative-type necrosis • Diffuse growth with elevated nucleus to cytoplasmic ratio • Diffuse cellular atypia • Abundant macronucleoli

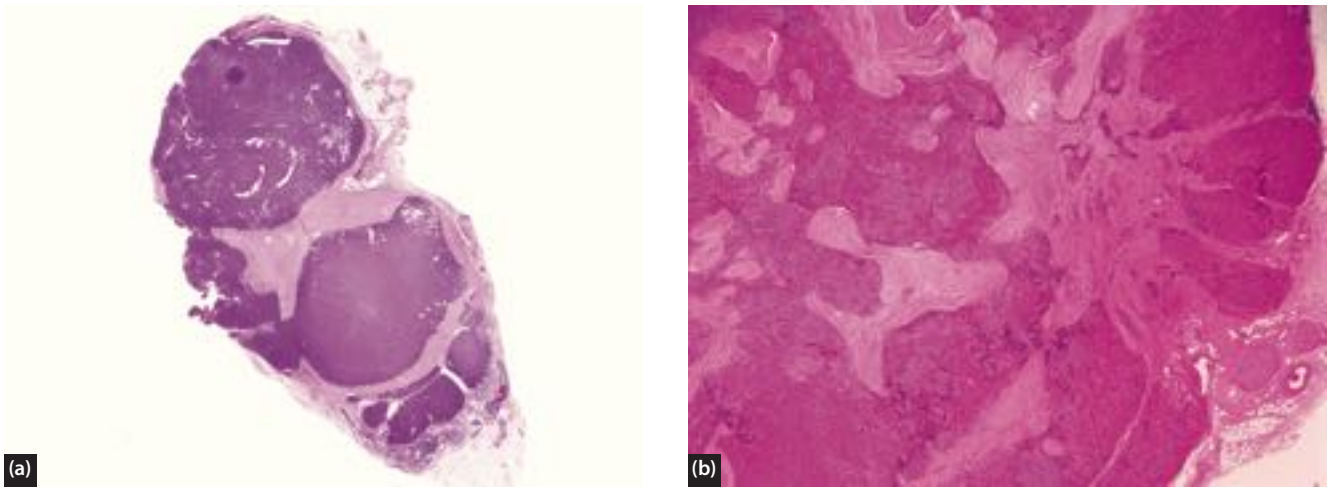


Figure 58.63 **(a)** Whole mount preparation of an oncocytic parathyroid carcinoma in a patient with MEN2 demonstrating irregular, thick fibrous capsulation contiguous with conspicuous internal fibrous septa. This gland was adherent to surrounding structures at operation and dissected out with some difficulty (*H&E stain, ultra-low magnification*). **(b)** The edge of another parathyroid carcinoma depicting an irregular, thick peripheral capsule, together with coarse intratumoural fibrous bands separating the expansile tumour nodules. This presents a broad advancing margin with surrounding soft tissues, rather than direct tentacular, permeative infiltration (*H&E stain, low magnification*).

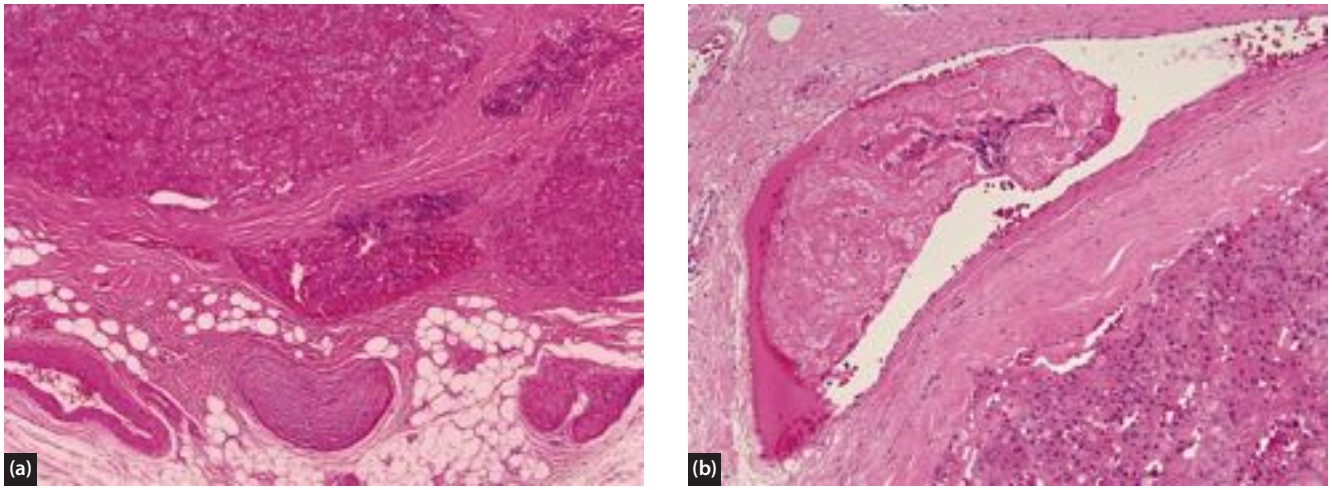


Figure 58.64 (a) A pericapsular neurovascular bundle showing endothelialized intravascular tumour invasion characteristic of parathyroid carcinoma (*H&E stain, medium magnification*). **(b)** Angioinvasion of a medium-calibre blood vessel at the perimeter of a parathyroid carcinoma, exemplified by parathyrocytes enveloped in endoluminal fibrin clot (*H&E stain, high magnification*).

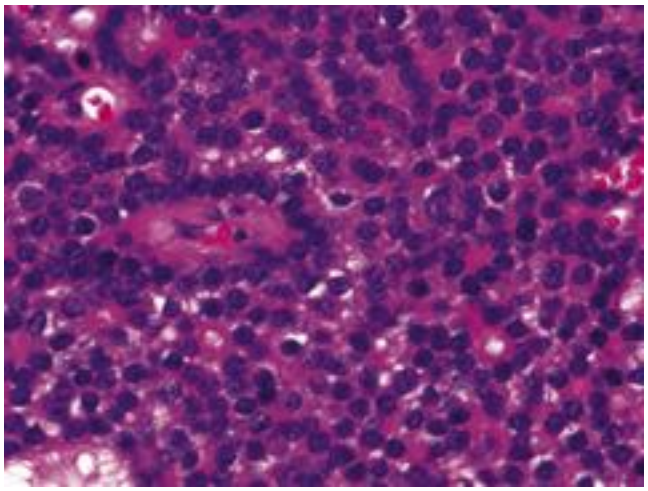


Figure 58.65 Parathyroid carcinoma composed of monotonous tumour cells showing raised nucleus-cytoplasmic ratio, nuclear hyperchromasia, coarse chromatin, macronucleolation and focal multinucleolation. A solitary mitosoid body is present towards the upper left-hand corner (*H&E stain, high magnification*).

a tocsin (Figure 58.65), as is generalized nuclear pleomorphism (in contrast to focal, random cytonuclear atypia). Macronucleolation may be conspicuous. Areas of coagulative necrosis may be seen (and should not be mistaken for ischaemic damage or haemorrhage). The interpretation of mitoses has proven controversial: mitoses are present in both hyperplasia and adenoma, though generally below 1 mitosis per 10 high-power fields (obversely, mitotic figures may be completely absent in some metastasizing carcinomas and care must be taken to distinguish mitoses in endothelial and other stromal elements from those in tumour cells). The presence of very many mitoses and/or abnormal forms, however, is usually taken as presumptive evidence of malignant potential. The proposed UICC/AJCC TNM staging classification[35] for parathyroid carcinomas is given in Table 58.16. T staging predicated upon size criteria has also been proposed.[59]

The immunohistochemical proliferation marker Ki67 (MIB-1) is slightly higher in parathyroid carcinoma than adenoma, though there is overlap, with a proliferative index greater than 5% suggestive of malignancy. Ki67 may also help in discriminating genuine mitotic figures from pyknotic nuclei (mitosoid bodies) in equivocal cases. An immunopanel comprising Ki67 in combination with galectin-3, parafibromin and PGP9.5 augments both specificity and sensitivity, compared to a single marker. Alternative studies, including retinoblastoma protein, cyclin D1, bcl-2, adenomatous polyposis coli antibody and p27 immunostaining, are presently of limited diagnostic and/or prognostic utility. Cytokeratin 14 (CK14) immunoreactivity has been reported as positive in oncocytic (oxyphil) adenomas but never in oncocytic carcinomas.

An increased incidence of parathyroid carcinoma is reported in some hereditary hyperparathyroidism syndromes. Familial hyperparathyroidism represents a clinically and genetically heterogeneous group of disorders that includes multiple endocrine neoplasia type 1 (MEN 1), multiple endocrine neoplasia type 2 (MEN 2), familial hypocalciuric hypercalcaemia (FHH), hyperparathyroidism-jaw tumour (HPT-JT) syndrome and familial isolated hyperparathyroidism (FIHP). Parathyroid carcinoma is seen in 10–15% of the autosomal dominant HPT-JT syndrome but it is exceptionally rare in MEN 1 and MEN 2. Early studies of FIHP suggested an increased risk of parathyroid carcinoma, but the inclusion of some patients with HPT-JT syndrome casts doubt upon this conclusion. There are no reported cases of parathyroid carcinoma with FHH.

TABLE 58.16 Proposed TNM staging schema for parathyroid carcinoma

T – Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Atypical parathyroid neoplasm (neoplasm of uncertain malignant potential)
T1	Localized to the parathyroid gland with extension limited to soft tissue
T2	Direct invasion into the thyroid gland
T3	Direct invasion into laryngeal nerve, oesophagus, trachea, skeletal muscle, adjacent lymph nodes, or thymus
T4	Direct invasion into major blood vessels or spine
N – Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes) or upper/superior mediastinal lymph nodes
N1b	Metastasis to unilateral, bilateral or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal nodes
M – Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis
Stage	
There are not enough data to propose a formal staging system at this time.	

Source: Adapted from AJCC Cancer Staging Manual, 8th edition, 2017. Note that there are insufficient data to enable stage group stratification.[35]

Other parathyroid gland tumours

Paraganglioma may rarely occur at this site. Tumour-like lesions, which may on occasion enter the differential diagnosis, include parathyroid cysts, branchiogenic cysts and amyloidosis. Secondary neoplasms may be the result of direct extension from adjacent structures, such as larynx or thyroid, or from distant metastatic disease, most commonly of primary mammary, haematolymphoid, renal, malignant melanoma or bronchopulmonary derivation. Despite their close proximity, metastasis to parathyroid gland from a primary thyroid carcinoma is uncommon (Figure 58.66).

Frozen section examination

Intra-operative frozen section examination of parathyroid gland tissue in cases of hyperparathyroidism is intended to establish the nature of the excised tissue and ascertain whether it is normal or abnormal. Without knowledge of the status of the remaining glands, a more definitive diagnosis of hyperplasia or adenoma (very rarely carcinoma) cannot always be proffered. Incisional biopsies render the task more difficult, as do freezing (ice crystal) artefact, other technical constraints and sampling error. The process is inevitably subject to inter-observer variation. Some workers advocate routine lipid stains as an adjunct to assessing intracytoplasmic fat; others do not. Oncocytic (oxyphil) cells, however, contain minimal lipid and occasional non-oncocytic hyperplastic and adenomatous parathyrocytes may retain significant lipid content. This notwithstanding, the overall accuracy of frozen section evaluation is surprisingly high and demonstrates good concordance with subsequent paraffin sections in experienced hands (Figure 58.67). The frozen section diagnosis of parathyroid carcinoma is understandably seldom sustainable, although alerting the surgeon to the possibility may alter pre-operative management should there be other suspect features.

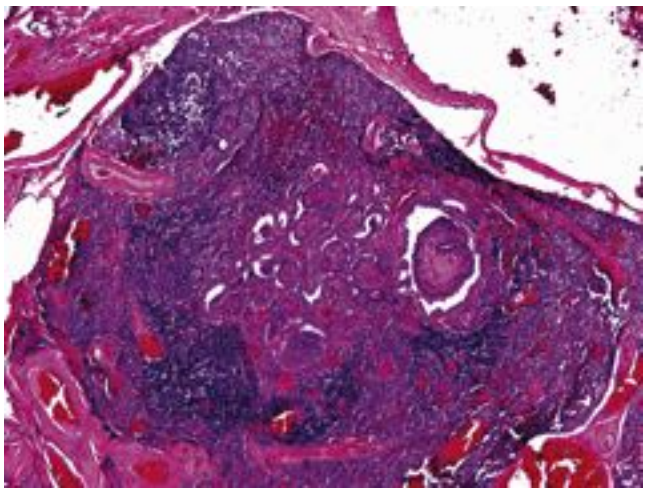


Figure 58.66 Parathyroid gland of normal size, albeit with diminished fat content, containing an intracapsular deposit of metastatic papillary thyroid carcinoma. There was no contiguity with similar tumour elsewhere in the neck (*H&E stain, low magnification*).

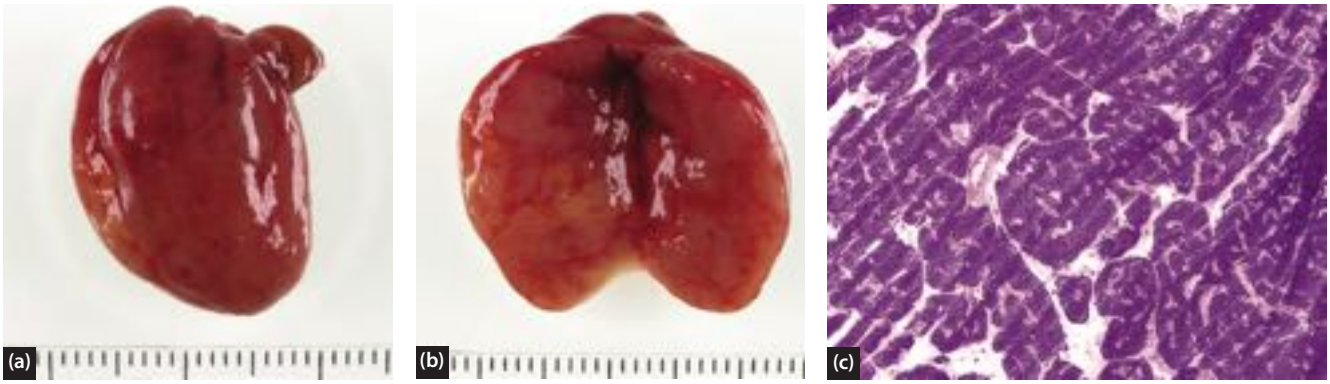


Figure 58.67 **(a)** The external surface of a fresh parathyroid gland nodule, weighing 1.8 g, sent for intra-operative frozen section examination – see Figure 58.54 for comparison with the appearances of a similar fixed specimen. **(b)** The same nodule bivalved in the unfixed state to demonstrate ill-defined parenchymal multinodularity. **(c)** Frozen section histology confirms hypercellular parathyroid gland tissue devoid of intraglandular fat. The entire consultation was completed in less than 5 minutes following receipt of the specimen in the laboratory. The linear striations and folds/rents in the section are artefactual. Without knowledge of the status of the remaining parathyroid glands, this could represent either an adenoma or hyperplasia. This notwithstanding, the findings supported the clinical impression of an adenoma. Subsequent paraffin sections on routinely processed tissue served as a quality audit (*H&E stain, medium magnification*).

Based on the premise that most primary hyperparathyroidism is due to single gland disease, there is sound rationale for unilateral neck exploration to remove the adenoma and visualize and/or biopsy any ipsilateral gland(s). Furthermore, advances in pre-operative localization techniques now facilitate targeted minimally invasive parathyroidectomy (MIP), variously through a mini incision, video-assisted surgery or endoscopic operation alone. Intra-operative frozen section or cytology examination merely confirms tissue nature rather than functional status. Intra-operative quick assay of intact parathyroid hormone (IOQPTH) can be undertaken prior to and post removal of a gland – a significant reduction in parathormone concentration predicts extirpation of abnormally functioning tissue, indicative of cure. Radioguided parathyroidectomy is guided by pre-operative radionucleide injection and radioguidance is helpful in second-look parathyroidectomy. MIP is, however, unsuitable in individuals with discordant imaging and/or comorbid thyroid disease.

KEY POINTS

- Accurate and timely pathological tumour subtyping, tumour grading and tumour staging underpin subsequent effective clinical management of thyroid gland and parathyroid gland neoplasia.
- Morphology remains the gold standard of histocytological diagnosis, increasingly facilitated, but not yet supplanted, by advances in ultrastructural, immunohistochemical, molecular and genetic understanding of normality and disease states.
- Advancement in diagnostic pathology has traditionally evolved along heuristic lines, assimilating observational studies with careful clinico-pathologico-radiological and treatment outcome correlation at population and individual case study levels. This has enabled recognition of new entities and clinically relevant reclassification and/or subclassification of existing conditions with time.
- There is a new era of pathological, clinical and molecular integration informing our understanding of thyroid disease and enabling patient management and clinical treatment decisions to be guided by evidentially based risk stratification with de-escalation of therapy in differentiated thyroid carcinoma.
- The apparently limited repertoire of thyroid gland disease belies its subtlety, masking some of the most highly contentious fields in any area of current surgical pathology.
- Fine needle aspiration cytology (FNAC) of the thyroid gland is a generally accepted first-line investigation for triage of solitary thyroid nodules, is helpful in evaluating diffuse, non-toxic goitre, aids the diagnosis of clinically suspected malignancy and potentially discriminates between treatable lymphomas and poor prognosis undifferentiated (anaplastic) carcinoma.
- Papillary thyroid carcinoma in its numerous guises accounts for approximately 80% of all thyroid malignancies. It generally portends an excellent prognosis, particularly in younger patients, modulated by both patient-specific and tumour-specific variables.
- The capsule of any follicular-patterned neoplasm should be comprehensively sampled specifically searching for both capsular and lymphovascular microinvasion.
- Oncocytic (oxyphil, Hürthle cell) change is a cellular adaptive process occurring in a wide variety of non-neoplastic and neoplastic conditions. It is subject to its own molecular basis, independent to that of any underlying tumour.
- There remain a number of unresolved issues in the histopathological diagnosis of thyroid carcinomas. Large clinicopathological studies subject to long-term follow up are still required with anticipation that many of these controversial areas will be ultimately resolved with evidential basis.
- The role of ancillary immunohistochemical, molecular and genetic studies in the determination of malignancy of the thyroid gland is evolving and has yet to be fully realized in routine diagnostic practice.
- All patients newly diagnosed with medullary thyroid carcinoma should be offered genetic testing given its association with multiple endocrine neoplasia syndromes.
- The value of peri-operative frozen section examination of thyroid gland lesions is disputed amongst pathologists and surgeons. The indications for such are best agreed by the local multi-disciplinary team according to local circumstances, preferences and experience.
- Parathyroid carcinoma is rare, slow growing and metastasizes late in its natural history. The diagnosis is predicated upon clinical, biochemical, imaging and pathological criteria.

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CHAPTER 59

CLINICAL EVALUATION OF THE THYROID PATIENT

Andrew Coatesworth and Sebastian Wallis

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SEARCH STRATEGY

Data in this chapter may be updated by on a PubMed search using the keywords: hypothyroidism, hyperthyroidism, Grave's disease, thyrotoxicosis and thyroid nodule.

This chapter succinctly covers the various clinical presentations of differing thyroid pathologies. More detail of specific presentations is available in chapters specific to those presentations.

INTRODUCTION

Thyroid disorders are common; serious or sinister problems are rare. They can broadly be divided into disorders of function, and disorders of structure, with a few miscellaneous others.

Thyroid disorders are managed by primary care and endocrine physicians, and endocrine and ENT surgeons.

FUNCTIONAL DISORDERS

Endocrine thyroid disorders affect approximately 2% of the adult population, with a 10:1 female to male ratio. Hypothyroidism is predominantly diagnosed and treated in primary care. Hyperthyroidism is primarily managed by physicians, with a surgical opinion generally being sought in cases where medical treatment has failed. It is therefore rare for a patient with an endocrine disorder to present *de novo* to an ENT clinic in the UK.

Symptoms and signs of hypothyroidism

The majority of patients with an underactive thyroid will have little or no symptoms or signs. The commonest symptoms are fatigue, weight gain with a poor appetite, and feeling cold.[1] Other recognized symptoms are poor concentration and memory, hoarse voice, shortness of breath, abnormal sensation, and a change in menstruation.[1] Constipation and dyspepsia are also recognized.[2] Coma is a rare life-threatening state of extreme hypothyroidism. Untreated congenital hypothyroidism can result in cretinism.

Signs of hypothyroidism are: dry coarse skin, cool extremities, hair loss and bradycardia. Reinke's oedema, myxoedema, delayed tendon reflexes, carpal tunnel syndrome, pleural effusion, ascites and pericardial effusions have all been described, but these are generally rare and late features.[1] Reinke's oedema is far more commonly associated with smoking.

Symptoms and signs of hyperthyroidism

Graves' disease, toxic multinodular goitre and toxic adenoma are the commonest causes of thyrotoxicosis. Overactivity of the thyroid gland can cause a wide range of symptoms. These include: weight loss, often in the presence of an increased appetite; nervousness, anxiety and irritability; sweating, palpitations and tremor; thin skin, thin hair and muscle weakness; gastrointestinal and menstrual disturbance. Eye symptoms are a feature of Graves' disease, with bulging eyes, a staring appearance and diplopia. In severe cases, a thyroid storm may occur with tachydysrhythmia, pyrexia, vomiting, diarrhoea and mental agitation. This is a medical emergency which has a 20–50% mortality even when treated.[3]

Signs of thyrotoxicosis are: agitation, evidence of weight loss, perspiration, tremor, palmer erythema and proximal muscle wasting. Thin skin and thin hair, tachycardia and/or atrial fibrillation can also be found.

Thyroid ophthalmopathy is a feature of Graves' disease, and is strongly associated with smoking. Axial proptosis with lid lag (von Graffe sign), lid retraction (Dalrymple sign), and conjunctival injection (Goldzeiher's sign) can be elicited. Diplopia, particularly on upward gaze in abduction, occurs with increased pressure at the orbital apex. In severe cases optic neuropathy can occur.[3]

Graves' disease can also cause dermopathy, with pre-tibial myxoedema and thyroid acropachy. Pre-tibial myxoedema presents with waxy indurated skin that itches. It can extend onto the dorsum of the foot, and rarely affects other parts of the body.[4] Thyroid acropachy is characterized by soft-tissue swelling of the hands which can be in association with clubbing.[5]

STRUCTURAL DISORDERS

Thyroid nodules are common in adults and may be palpated in 3–7% of cases.[6] If ultrasound is used, the prevalence is nearer 70%.[7] The majority of thyroid nodules are solitary, but they may be part of a multinodular goitre. A focal or diffuse goitre can occur physiologically, and in association with thyroiditis. A first-degree relative with thyroid cancer, and prior exposure to radiation, increase the likelihood of malignancy.[7]

Symptoms and signs of thyroid swellings

The commonest presentation of a thyroid nodule is with an asymptomatic lump. Increasingly referrals are arising as incidental findings from radiological investigations. Pain, rapid increase in size, hoarse voice and the presence of a lateral neck mass are all features that raise concern about a malignant underlying pathology, but the commonest cause for a sudden painful thyroid nodule is bleeding into a pre-existing cyst, and the commonest presentation of a differentiated thyroid cancer is an asymptomatic nodule.[8] Prior exposure to ionizing radiation is a risk factor for developing thyroid cancer. Patients may also have a relevant family history.

With increasing size, goitres can cause compressive symptoms; these are usually at or above the level of the thoracic inlet, causing cervical dysphagia, exertional dyspnoea, inspiratory or biphasic stridor, and venous congestion of the superior vena caval territory.[9]

A thyroid nodule can often be diagnosed when the patient swallows on their way into the clinic room. Berry first described the fascial attachments of the thyroid to the trachea.[10] This means that thyroid swellings elevate with swallowing.

A hard mass that is tender to touch is more likely to indicate malignancy or Riedel's thyroiditis. Associated cervical lymphadenopathy and fixation to surrounding structures are also highly worrisome findings. Tracheal deviation can be elicited by examining the neck from the anterior aspect. The lower extent of a retrosternal goitre cannot be felt when the neck is examined from behind and the patient swallows. Percussion of the anterior chest wall to elicit the lower extent of a retrosternal goitre is largely of historical interest with the emergence of readily available cross-sectional imaging techniques. A large retrosternal goitre can cause venous congestion of the head, neck and upper torso. When venous congestion is impending, it can be elicited by asking the patient to raise both arms until they touch the side of their face, and holding that position for a minute (Pemberton's sign). There may also be cyanosis and respiratory distress induced by this manoeuvre.[9]

Flexible nasendoscopy can reveal a vocal cord palsy, Reinke's oedema, tracheal deviation and, in severe cases, tracheal compression. Direct invasion of the upper aerodigestive tract may also be seen.

MISCELLANEOUS OTHERS

Structural thyroid disorders can arise as part of an underlying systemic disorder.

Medullary thyroid cancer is part of multiple endocrine neoplasia syndrome type 2 (MEN2) in 20% of cases, along with phaeochromocytoma. In those cases not diagnosed through genetic screening, medullary thyroid cancer is the commonest initial manifestation.[11] With MEN2a, parathyroid hyperplasia occurs causing primary hyperparathyroidism. With MEN2b mucosal neurofibromas and Marfanoid features may be evident.

Lymphoma of the thyroid gland can occur in isolation, or as part of wider haematological malignancy. As such, it can be associated with lymphadenopathy in the axilla and groins, and hepatosplenomegally. The patient may also have the 'B' symptoms of lymphoma, with fever, unintentional weight loss, and drenching night sweats.[12]

BEST CLINICAL PRACTICE

- ✓ Clinical evaluation of the thyroid patient starts when the patient enters the clinic room. Features of hormone dysfunction and the presence of a goitre may be apparent before the patient sits down.
- ✓ The history should cover systemic as well as locoregional symptoms, and also elicit any family and past history of relevance, including prior exposure to ionizing radiation.
- ✓ ENT examination covers the upper aerodigestive tract and neck, including flexible nasendoscopy. There are systemic signs of thyroid disease in a minority of cases that are evaluated by the ENT surgeon.

KEY POINTS

- Thyroid disorders are common.
- They are often asymptomatic but can be associated with a diverse range of locoregional and systemic signs and symptoms.
- They are managed by a wide range of clinicians.
- They can broadly be broken down into functional and structural disorders.
- Thyroid nodules are common.
- Rapid growth, pain and hoarseness are worrying symptoms for thyroid cancer. The commonest cause for a rapidly enlarging painful swelling, however, is bleeding into a pre-existing cyst, and the commonest presentation of thyroid cancer is with an asymptomatic nodule.

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CHAPTER 60

INVESTIGATION OF THYROID DISEASE

Anthony P. Weetman

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords hyperthyroidism, hypothyroidism, thyroid function, thyroid nodule and thyroid cancer, and published guidelines which are cited in the chapter.

INTRODUCTION

Clinical signs and symptoms are inadequate to diagnose the presence of any thyroid disorder. Even sophisticated scoring systems are unable to categorize around 40% of euthyroid individuals,[1] and there is considerable inter-user variation in the findings made from thyroid palpation.[2] The investigation of thyroid disease can be broken down into three sets of tests aimed at: (i) determining whether there is biochemical thyroid dysfunction (i.e. hypothyroidism or thyrotoxicosis); (ii) determining the cause of any thyroid dysfunction and (iii) determining the nature of any structural lesion in the thyroid, most typically nodular thyroid disease. This chapter will not cover the use of fine-needle aspiration biopsy (FNAB) to evaluate thyroid nodules but it is worth recording here that FNAB can also be a useful investigative tool in rare non-neoplastic circumstances, for instance where there is an unexplained diffuse enlargement of the thyroid gland or to obtain material to diagnose acute (suppurative) thyroiditis.

INVESTIGATION OF THYROID DYSFUNCTION

Measurement of thyroid-stimulating hormone

Current sandwich immunoassays, employing two monoclonal thyroid-stimulating hormone (TSH) antibodies to immobilize and identify TSH, are highly reliable and capable of measuring TSH levels as low as 0.01 mU/L, although not all available assays perform equally well.[3] Serum TSH levels show a log-linear relationship to serum free thyroxine (FT4) levels and this makes the TSH the most sensitive test to detect primary dysfunction of the thyroid.[4] A number of factors can affect TSH levels and need to be taken into consideration in interpreting TSH measurements (Box 60.1).

Elevation or suppression of the TSH level, outside the reference range, may be associated with normal levels of

BOX 60.1 Factors affecting the measurement of serum TSH levels

Serum FT3 and FT4; TSH is inversely proportional to free thyroid hormone levels

Physiological factors: intra-individual variation is ±0.5 mU/L (and there is an insignificant diurnal variation) but inter-individual variation is greater due to the effects of age, genetic factors and obesity

Pituitary or hypothalamic disease; TSH ↓

First trimester of pregnancy; TSH ↓ due to thyroid-stimulating effects of human chorionic gonadotrophin

Non-thyroid illness, including psychiatric disorders; typically TSH ↓, but depends on phase of illness

Drugs; TSH ↓ by dopamine, somatostatin and high dose glucocorticoids

Assay-specific artefacts, especially interference by heterophilic antibodies

free tri-iodothyronine (FT3) or FT4. These are the biochemically defined states of subclinical hypothyroidism and subclinical thyrotoxicosis[5] and their recognition depends therefore on the cut-off levels used to define the TSH reference range. This is an area that has provoked recent debate, with some data suggesting that the reference range for TSH should be narrowed from around 0.4–4.5 mU/L to 0.4–2.5 mU/L.[6] On balance, however, the arguments for lowering the upper limit of the reference range in iodine-replete populations are insufficient to warrant a change.[7, 8]

Measurement of FT3 and FT4

Over 99% of circulating T3 and T4 is bound to thyroxine-binding globulin, albumin or pre-albumin, and variation in the levels of these binding proteins can thus have a profound impact on measurements of total thyroid hormone levels. To eliminate such artefacts, a number of immunoassays have been devised to measure the concentration of free (active) thyroid hormone, and although these may still give anomalous results in certain circumstances (**Box 60.2**), by and large these assays are robust and reliable.[9] If a serum FT3 or FT4 measurement is unexpectedly abnormal, especially if it is inconsistent with the serum TSH level, more detailed analysis is necessary, including measurement of total thyroid hormone levels.

Measurement of FT3 is particularly indicated in the following circumstances: (i) diagnosis of T3-toxicosis, the earliest stage of overt thyrotoxicosis in which the TSH is suppressed and FT4 is still normal, and (ii) if the patient is taking propylthiouracil or amiodarone, both of which impair the deiodination of T4 to T3 and so give rise to euthyroid elevations of FT4. On the other hand, FT3 measurement is not indicated in the diagnosis of hypothyroidism as FT3 levels are frequently normal until very late in the disease process, despite low FT4 and elevated TSH levels.

Evaluation of the symptomatic patient

Several guidelines have been produced which address the optimal strategy to diagnose thyroid dysfunction.[4, 10–12] Local policy will generally dictate whether TSH alone is used as a first-line test, progressing to measurement of FT4 only if the TSH is abnormal; the drawback of this approach is that rare cases of hypothyroidism and thyrotoxicosis which are secondary to pituitary or hypothalamic disease may be missed.[13] If such an approach of using the TSH level as a screening test is adopted, the limitations of TSH measurement have to be continually borne in mind (**Box 60.1**).[14] In general, however, a normal serum TSH level rules out primary thyroid disease. If the TSH is elevated, the most likely diagnosis is hypothyroidism; other causes are detailed in **Box 60.3**. If the TSH is suppressed, the most likely cause is thyrotoxicosis; other causes are detailed in **Box 60.4**.

BOX 60.2 Factors affecting the measurement of serum FT3 and FT4 levels

Thyroid dysfunction; overt primary or secondary hypothyroidism or thyrotoxicosis

Non-thyroidal illness, including psychiatric disorders; typically ↓ FT3, but ↑ FT3 and ↓ or ↑ FT4 possible

Drugs; non-steroidal anti-inflammatory drugs, furosemide, phenytoin, carbamazepine, heparin may rarely affect some assays; propylthiouracil and amiodarone inhibit deiodinase activity, altering the ratio of FT3 to FT4

Pregnancy; FT3 and FT4↓ by 30% in the last trimester

BOX 60.3 Causes of an elevated TSH

Primary hypothyroidism
- Subclinical (FT3 and FT4 normal)
- Overt (FT4 ↓; FT3 ↓ in 25%)

Non-thyroidal illness (FT3 and FT4 variable), especially during recovery phase

TSH-secreting pituitary tumour (FT3, FT4 ↑)

Rare cases of thyroid hormone resistance (FT3, FT4 ↑)

TSH assay interference (FT3 and FT4 normal)

BOX 60.4 Causes of a suppressed TSH

Primary thyrotoxicosis
- Subclinical (FT3 and FT4 normal)
- Overt (FT3 ↑, FT4 usually ↑)

Secondary hypothyroidism due to pituitary or hypothalamic disease (FT4 ↓, FT3 normal or ↓)

Non-thyroidal illness (FT3 and FT4 normal)

Treatment with dopamine or glucocorticoids (FT3 and FT4 normal)

First trimester of pregnancy (FT3 and FT4 normal)

Hydatidiform mole, choriocarcinoma (FT3 and FT4 ↑)

Activating TSH-receptor mutations (FT3 and FT4 ↑)

Screening for thyroid disease

Given the frequency of thyroid disease in the population, the question arises as to whether population-based screening is worthwhile. At present there seems to be no overall benefit, given that most of the cases identified will have subclinical thyroid dysfunction and the benefits of treating this are not yet clear due to the lack of robust trials.[11, 15]

The occurrence of postpartum thyroid dysfunction in up to 5% of women after pregnancy, and the association between impaired fetal neurological development and untreated maternal hypothyroidism, have suggested there may be a benefit from screening women prior to conception. However, a recent review has indicated that there is insufficient evidence to recommend for or against universal TSH screening at the first trimester visit[16] and in any case there is no evidence that treatment of unrecognized maternal hypothyroidism improves fetal outcome.[17]

There is a stronger case for screening certain high-risk populations for thyroid dysfunction, although formal cost–benefit analysis has not been performed: these include individuals with another associated autoimmune disorder (e.g. Addison's disease, vitiligo, coeliac disease, pernicious anaemia, type 1 diabetes mellitus) or who are taking drugs which may precipitate thyroid dysfunction (e.g. lithium, amiodarone, alpha-interferon, alemtuzumab, sorafenib, sunitinib). The risk of congenital hypothyroidism is around 1 in 3500 births and routine neonatal TSH screening on heel-prick specimens is now well established in all developed countries.[18] Following irradiation of the neck for cancer, including lymphoma, the frequency of hypothyroidism is very high and annual TSH screening is recommended.[19]

Monitoring treatment for thyroid dysfunction

In patients receiving antithyroid drug treatment for hyperthyroidism, persistent suppression of TSH levels may occur during and even after cessation of treatment, which is then associated with a higher risk of relapse.[20] As a result, such treatment is best monitored by measuring serum FT4 levels; in patients taking propylthiouracil which blocks T4 deiodination, FT3 levels may be a more accurate indicator of thyroid status. Thyroid hormone levels can fluctuate rapidly in some patients following radioiodine, with transient episodes of thyrotoxicosis or hypothyroidism during the first 6 months.[21] Routine measurement of serum TSH and FT4 levels should be made around 6 and 12 weeks after first treatment, and then every 3 months until a year after radioiodine. Thereafter annual monitoring is indicated. After subtotal thyroidectomy, serum TSH levels often rise and may indicate either a temporary state in which the thyroid remnant is developing capacity to resume function under TSH stimulation, or permanent hypothyroidism. Recent guidelines recommend near-total or total thyroidectomy for Graves' disease and toxic multinodular goitre, if surgery is chosen as treatment, and in these circumstances levothyroxine is commenced immediately after the operation without the need for further testing.[11]

Monitoring the adequacy of levothyroxine replacement in primary hypothyroidism depends on measurement of serum TSH levels, which provide an integrated estimate of the effect of treatment during the preceding weeks.[12, 22] Measurement of TSH should only be made 2 months after any change in levothyroxine dosage, as the TSH level does not stabilize before then. There is no place for measuring serum FT4 levels in the management of primary hypothyroidism, as TSH provides far more reliable information, but FT4 is the only available method to monitor treatment in secondary hypothyroidism: levothyroxine dosage should be adjusted to give a FT4 level in the upper third of the reference range.[23] Once the dose of levothyroxine is stable, TSH should be measured annually, or prior to conception if a pregnancy is planned between annual tests.

Thyroid function testing in pregnancy

Pregnancy has many effects on thyroid function (**Box 60.5**). As a result of these changes, it is recommended that trimester-specific reference ranges for TSH and FT4 should be applied during pregnancy; in their absence, the following are recommended for TSH: first trimester 0.1–2.5 mU/L; second trimester 0.2–3.0 mU/L; third trimester 0.3–3.0 mU/L.[16]

BOX 60.5 Effects of pregnancy on thyroid function

Increase in human chorionic gonadotrophin during first trimester, reciprocal ↓TSH and ↑ FT4 (in some cases, this effect may be so large that it may cause transient gestational hyperthyroidism, often associated with hyperemesis gravidarum)

Increase in thyroxine-binding globulin; ↑ in total T3 and T4

Increase in plasma volume; ↑ T3 and T4 pool size

Placental type III deiodinase; ↑ T3 and T4 degradation

Increase in iodine clearance; ↓ in T3 and T4 depending on iodine intake

Serum FT3 and FT4 ↓ by 20–40% during the last trimester but also prone to assay artefacts depending on methodology

TSH-receptor autoantibodies ↓ leading to remission of Graves' disease in second half of pregnancy

DETERMINING THE CAUSE OF THYROID DYSFUNCTION

Thyroid antibodies

The diagnosis in the vast majority of cases of spontaneous hypothyroidism is autoimmune hypothyroidism, and in hyperthyroidism, around 60–80% of cases are due to Graves' disease, caused by TSH-receptor stimulating antibodies. Measurement of serum thyroid antibodies can confirm the aetiology of thyroid dysfunction, but there are two important caveats: (i) thyroid antibodies are found in around 10% of the healthy, euthyroid population, and (ii) measurement of thyroid antibodies is only indicated clinically if it alters management. For instance, if radioiodine is going to be used in a particular hyperthyroid patient, it matters little whether TSH receptor antibodies are positive, whereas it would be futile to consider using a course of antithyroid drug treatment to achieve cure in a hyperthyroid patient unless the diagnosis of Graves' disease is firmly established.

Thyroglobulin (Tg) and thyroid peroxidase (TPO) antibodies were originally measured by immunofluorescence or haemagglutination methods, but more sensitive and reliable immunoassays calibrated against standard sera are now widely used.[24, 25] Almost all patients with autoimmune thyroid disease who have Tg antibodies also have TPO antibodies, but the reverse is much less common,[26] and therefore some laboratories only offer TPO antibody measurement to diagnose autoimmune thyroid disease.

The main indication for the estimation of Tg antibodies is in patients being followed up after treatment for differentiated thyroid cancer. In these individuals, measurement of Tg (see below) is only reliable in the absence of Tg antibodies, especially when immunometric Tg assays are used.[27] There is some evidence that the presence of Tg antibodies, found in 15–20% of such patients, is itself a marker for persistent thyroid tissue and a decline in Tg antibody level over time is a good prognostic sign.[28] On the other hand, the presence of Tg antibodies has been associated with a higher risk of malignancy in patients presenting with a thyroid nodule.[29]

Measurement of the TPO antibodies is helpful in defining the risk of overt hypothyroidism developing in individuals with subclinical hypothyroidism (**Figure 60.1**).[30, 31] If a patient presents with subclinical hypothyroidism, the TSH and FT4 should be repeated after 3 months, since an elevated TSH may simply be the result of a non-thyroidal illness and in these cases the elevation is only transient. In those who have an isolated elevated TSH, or isolated TPO antibodies, the annual risk of progression to overt hypothyroidism is 2% per year, but it is 5% per year if both are present. Those with positive TPO antibodies are also more likely to develop hypothyroidism after amiodarone or alpha-interferon treatment, or with other drugs which affect the immune system.[32, 33]

The availability of new, robust immunoassays for TSH receptor antibodies has improved the diagnosis of Graves' disease, as these have sensitivities of around 95% with nearly 100% specificity.[34] Although this test does not distinguish between those antibodies which stimulate the receptor and those which block it, in practice this distinction is readily made by taking into account the biochemical picture: a patient with thyrotoxicosis and positive TSH-receptor antibodies must have Graves' disease, while those with blocking TSH-receptor antibodies will be hypothyroid. Occasionally patients switch production from one functional type of antibody to the other, with sometimes confusing consequences unless this possibility is recognized.[35]

The two other clinical situations in which measurement of TSH receptor antibodies can be helpful are (i) in predicting the possibility of neonatal Graves' disease by measuring these antibodies in the serum of pregnant women previously treated for Graves' disease[16, 36] and (ii) in the diagnosis of euthyroid Graves' opthalmopathy.[37] Persistently raised TSH receptor antibody levels are an adverse feature for a successful outcome after antithyroid drug treatment for Graves' disease, but the results are not sufficiently sensitive or specific for routine use in individual patients.[38] High levels of TSH-receptor antibodies are an independent risk factor for the development of ophthalmopathy in patients with Graves' disease.[39]

Inflammatory markers

The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) measurements are useful in the diagnosis of subacute thyroiditis, although these inflammatory markers may also be raised in acute suppurative thyroiditis and even in occasional patients with Hashimoto's thyroiditis.[40]

Thyroglobulin

The measurement of serum thyroglobulin (Tg), alone or following recombinant TSH stimulation, is most useful in the follow-up of patients with differentiated thyroid cancer.[28, 41] A low serum Tg level before giving radioiodine to ablate any thyroid remnant has 94% negative predictive value for the absence of disease at future follow-up.[42]

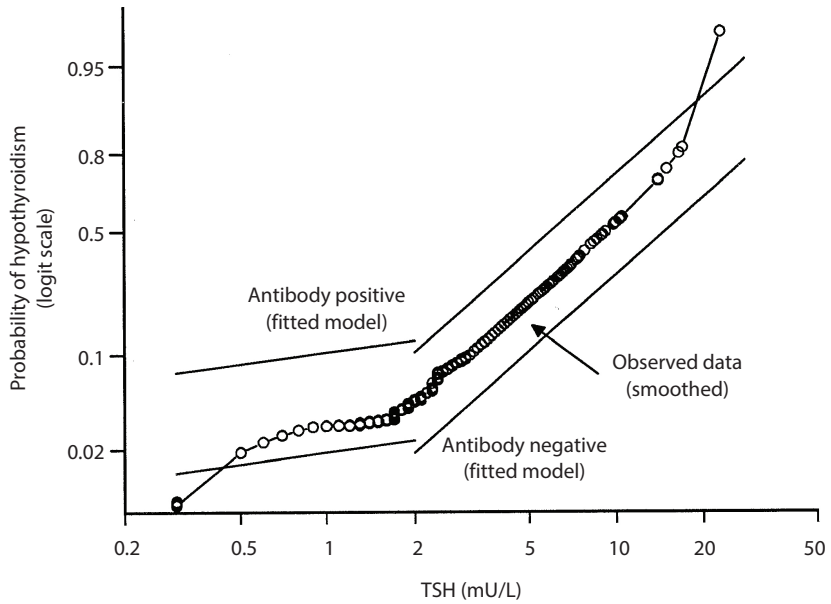


Figure 60.1 Probability of developing overt hypothyroidism in patients with subclinical hypothyroidism. The risks increase in proportion to the initial TSH at the time of diagnosis of subclinical hypothyroidism and the upper line shows the additional risk conferred by having positive thyroid autoantibodies. From Vanderpump et al. The incidence of thyroid disorders in the community – a twenty-year follow-up of the Whickham survey. *Clin Endocrinol* 1995; **43**: 55-69, with permission.

There is no utility in measuring Tg in the initial evaluation of a thyroid nodule. However, there is a role for its measurement in diagnosing factitious thyrotoxicosis, in which the Tg level is low, rather than elevated as in other types of thyrotoxicosis.[43]

DETERMINING THE NATURE OF STRUCTURAL LESIONS

Scintiscanning

The use of radioisotope uptake tests and thyroid scintiscanning has declined markedly in the last two decades with the introduction of better blood tests and thyroid ultrasound. In benign thyroid diseases, ^{99m}Tc is the most frequently used isotope for scanning and is particularly useful (i) to localize congenital anatomical defects of the thyroid,[44] and (ii) to distinguish between thyrotoxicosis caused by destructive thyroiditis (e.g. subacute thyroiditis, postpartum thyroiditis), in which the uptake of isotope is reduced, and hyperthyroidism (e.g. Graves' disease, nodular thyroid disease), in which the uptake is increased (**Figure 60.2**). Radioisotope uptake is also reduced in factitious thyrotoxicosis and in the presence of excessive stable iodine (e.g. after administration of amiodarone or iodine-containing contrast media).

American guidelines for the management of newly presenting thyroid nodules recommend the use of scintiscanning with ^{99m}Tc or I123, for any nodule associated with a subnormal TSH,[41] as a hyperfunctioning nodule is only rarely associated with malignancy. Others take the view that the role of scintiscanning is limited and do not recommend routine use of scintiscanning in the initial evaluation of thyroid nodules.[45] The use of isotope scanning in the management of treated thyroid cancer is considered elsewhere (see Chapters 62 and 66).

Ultrasound

Thyroid ultrasound is now the most cost-effective approach to gaining structural information about the gland and is increasingly being performed by endocrinologists and surgeons, rather than being confined to use by radiologists.[46, 47] Most benign thyroid diseases can be diagnosed by clinical presentation and appropriate blood tests, but colour-flow Doppler ultrasonography has utility in distinguishing between the hyperthyroid (type 1) and destructive (type 2) forms of amiodarone-induced thyrotoxicosis; blood flow is increased in the former and reduced in the latter.[32]

Ultrasound is recommended in the evaluation of all thyroid nodules, including multinodular goitre, as simple palpation is imprecise and insensitive.[41, 48] Features suggestive of malignancy are shown in **Box 60.6** and **Figure 60.3**. It is important to emphasize that ultrasonography is complementary to FNAB in making a diagnosis; for instance, ultrasound is useful in planning the extent of surgery when FNAB is suggestive of carcinoma.[49] Furthermore, the increasing use of thyroid ultrasound has led to the detection of a large number of nodules which previously would have been ignored. The population prevalence for thyroid nodules is around 5% by palpation, but 10% of 25 year olds and 55% of women aged over 70 have nodules on ultrasonography: only a small fraction of these will be malignant.[50] A detailed cost–benefit analysis for the investigation of thyroid nodules found incidentally on neck ultrasound has not been undertaken.

Thyroid ultrasound has an increasingly important role in thyroid cancer follow-up, with the recognition

BOX 60.6 Ultrasonographic features suggestive of (a) a malignant thyroid nodule, and (b) a benign thyroid nodule in decreasing order of specificity

- Microcalcification
  - Irregularity of the border of the nodule
  - Increased blood flow in nodule on colour-flow Doppler
  - Hypoechogenicity
  - Absence of a halo
- Diameter less than 1 cm (those less than 0.5 cm do not require further intervention)
  - Simple cyst with no solid component
  - Comet tail sign, due to colloid content
  - Honeycomb appearance

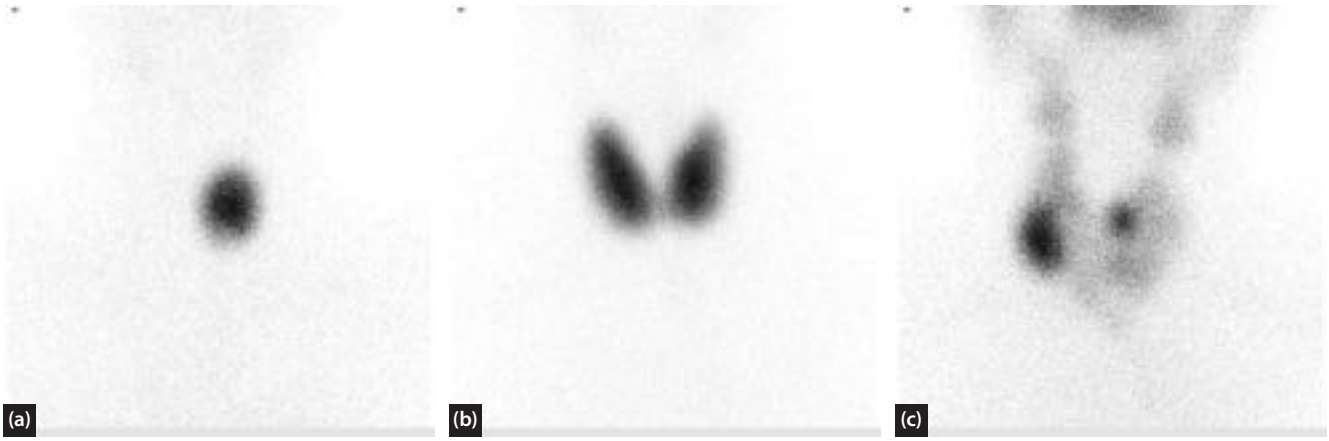


Figure 60.2 Thyroid ^{99m}Tc scintiscans. (a) Toxic adenoma; **(b)** Graves' disease; **(c)** multinodular goitre. Images courtesy of Colleen Brown, Sheffield Teaching Hospitals NHS Foundation Trust.

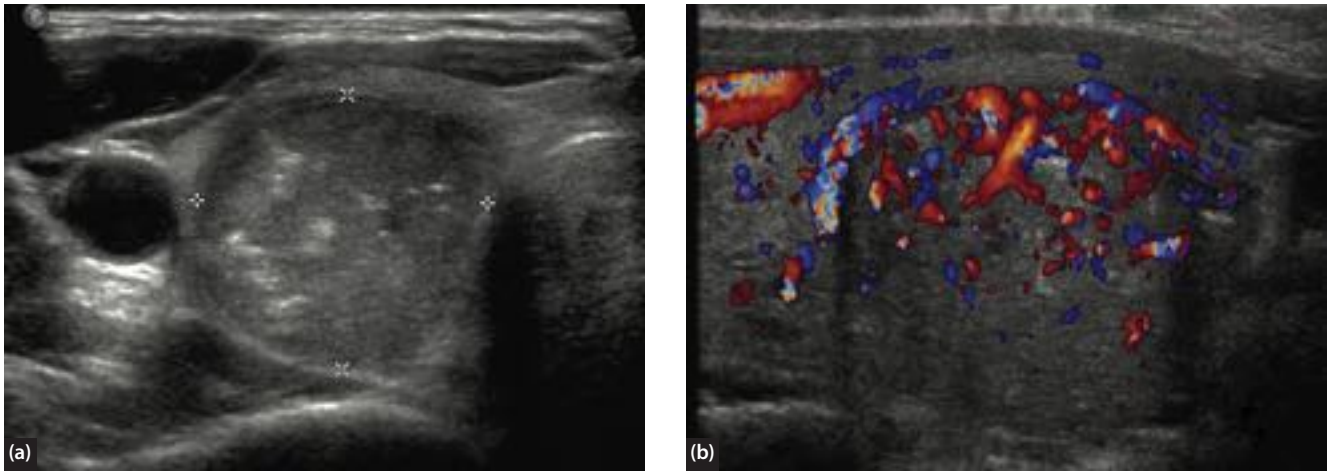


Figure 60.3 Thyroid ultrasound images of papillary carcinoma. (a) Microcalcification; **(b)** chaotic vascular pattern on colour-flow Doppler. Images courtesy of Dr Catherine Clout, Sheffield Teaching Hospitals NHS Foundation Trust.

that whole-body scintiscanning has low sensitivity. Measurement of serum Tg and cervical ultrasound is the best current method to detect recurrent disease in low-risk patients.[41, 50] Ultrasound elastography is a technique that assesses nodule consistency by measuring the amount of distortion produced by an external force. Although initial reports have been encouraging, based on the premise that malignant nodules are firm and thus have low elastic strain,[51] other studies have found no improvement over conventional ultrasound, even if the two are combined.[52] This technique is operator-dependent and at present elastography is inadequate to guide management of thyroid nodules.[53]

Other imaging techniques

Computed tomography (CT) and magnetic resonance imaging (MRI) have only an ancillary use to ultrasound in the investigation of thyroid disease.[47] Such scans are useful in the assessment of large goitres to determine whether there is any tracheal compression or substernal extension.[48] In the initial phase of acute thyroiditis, CT scanning is as good as ultrasound at demonstrating the inflammatory process but more accurate with regard to anatomical involvement; barium swallow imaging is superior to both in detecting a pyriform sinus fistula when the acute inflammatory process subsides.[54]

^{18}F-FDG-position emission tomography (PET) has generally been used to localize thyroid cancer recurrence in patients with raised Tg levels but no evidence of disease on whole-body scintiscans. However, its overall impact remains to be defined, and specificity and sensitivity figures are unclear.[41, 55] Non-malignant false-positive results from FDG-PET may be encountered with reactive lymph nodes, suture granulomas and muscle activity. Additional proposed uses for this technique include (i) the initial work-up of patients, although half of patients with inderminate nodules on fine needle aspiration biopsy and a positive FDG-PET result have benign lesions,[56] (ii) staging and follow-up of invasive Hürthle cell carcinoma, and (iii) categorization of risk in patients with known distant metastases.[41]

KEY POINTS

- Thyroid dysfunction can be diagnosed and managed by simple blood tests: a normal serum TSH level rules out primary thyroid dysfunction.
- Although modern tests for TSH, FT3 and FT4 are robust, occasional artefacts may be encountered, and the possibility of non-thyroid illness as an explanation for abnormal results should always be considered.
- Autoimmune thyroid disease can be diagnosed by the detection of serum TPO antibodies; robust immunoassays for TSH-receptor antibodies make these the test of choice to diagnose Graves' disease.
- Ultrasound has superseded scintiscanning for the structural evaluation of the thyroid and is recommended for the detailed investigation of thyroid nodules.

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CHAPTER 61

BENIGN THYROID DISEASE

Christopher M. Jones and Kristien Boelaert

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: hyperthyroidism, thyrotoxicosis, subclinical hyperthyroidism, Graves' disease, hypothyroidism, myxoedema, subclinical hypothyroidism, thyroiditis, subacute thyroiditis, Hashimoto's thyroiditis, goitre, thyroid nodule and multinodular goitre. Secondary search criteria included thyroid-stimulating hormone, thyroxine, triiodothyronine, antithyroid peroxidase, elastography and fine-needle aspiration cytology. Emphasis has been placed on pathogenesis, diagnosis and treatment with level 1 and 2 evidence reported wherever possible.

INTRODUCTION

Benign thyroid disease is commonly encountered by clinicians. The term encompasses thyroid hormone imbalance, abnormal enlargement of thyroid gland tissue and, less commonly, thyroid tenderness. These abnormalities constitute a significant burden within clinical practice, particularly in relation to the elderly, and often require significant biochemical, immunological, radiological and histological investigations in addition to thorough clinical assessment. Thyroid dysfunction encompasses deficient and excess thyroid hormone production, respectively hypothyroidism and hyperthyroidism, which together affect approximately 2% of women and 0.2% of men.[1] While it is clear that the sequelae of overt thyroid dysfunction affect nearly all body systems and that they are therefore associated with significant morbidity and mortality, the significance of subclinical thyroid dysfunction is yet to be fully elucidated. Enlargement of the thyroid gland, or goitre, whether generalized or focal, augments the burden imposed by thyroid disease and may affect up to 60% of the population, with higher frequencies seen in the elderly and women.[2] Although the majority of cases of thyroid enlargement may be managed conservatively, the need to first exclude malignant aetiology and the more intensive management of these patients pose significant challenges to the clinician.

HYPERTHYROIDISM

Definitions

Hyperthyroidism refers to hyperfunction of the thyroid gland and is defined by reduced levels of thyroid-stimulating hormone (TSH) and raised free T4 (fT4) and free T3 (fT3) concentrations. It leads to thyrotoxicosis, which is the clinical syndrome resulting from a biochemical excess of fT4, fT3 or both. Hence, biochemical tests of thyroid function may identify hyperthyroidism before it becomes clinically apparent, with a rise in fT3 and fall in TSH concentrations typically seen prior to a rise in fT4. **Thyrotoxicosis** may be a consequence of a disorder of the thyroid gland itself, which is referred to as primary disease, or may be secondary to abnormal production of TSH resulting from pathology of the anterior pituitary gland. **Subclinical hyperthyroidism** is diagnosed in patients for whom TSH levels fall below the normal reference range but who have normal fT4 and fT3 concentrations. This must be in the absence of disease of the pituitary or hypothalamus, ingestion of drugs that inhibit TSH secretion or the presence of non-thyroidal illness (**Box 61.1**).

BOX 61.1 Key definitions in thyroid hormone excess (hyperthyroidism)

Hyperthyroidism	*Hyperfunction of the thyroid gland (raised T4 and T3 with suppressed TSH)*
Thyrotoxicosis	*Clinical syndrome resulting from excess thyroid hormones*
Subclinical hyperthyroidism	*Normal T4 and T3 in the presence of low TSH*

Epidemiology

Hyperthyroidism is approximately ten times more common in women than in men within iodine-replete communities, affecting between 0.5% and 2% of the female population.[3] The Third National Health and Nutrition Examination Survey (NHANES III) reported the prevalence of clinically significant hyperthyroidism to be 2 per 1000, whereas the prevalence in older persons is reported between 0.4% and 2.0%.[4, 5] The reported annual incidence for men and women respectively varies between 0.4–0.8/1000 and 0.1/1000 per year; higher rates are seen in iodine-deficient areas.[6] Unlike for hypothyroidism, there is no documented increase in the probability of the development of overt hyperthyroidism with age.

Subclinical hyperthyroidism is more common and can be readily diagnosed following the introduction of sensitive assays for determining TSH concentrations. The incidence of subclinical hyperthyroidism is reported to increase with age. In a UK survey of 1210 persons aged over 60 years and registered within a single general practice, 6.3% of women and 5.5% of men were identified to have TSH levels below normal.[7] The overall prevalence of low TSH levels in the Colorado study of 25 862 individuals was 2.2%.[8] Of the 13 334 persons enrolled in NHANES III, only 0.8% of randomly selected individuals met criteria for subclinical hyperthyroidism, though this rose to 3% of those aged over 80 years.[4]

Aetiology

There are myriad causes of hyperthyroidism, as summarized in Table 61.1, alongside causes of thyrotoxicosis. The most common is Graves' disease, an autoimmune disorder in which antibodies are directed against and stimulate the TSH receptor. Toxic multinodular goitre is commonly seen and features one or more autonomous thyroid hormone-producing nodule(s) that cause thyroid hormone excess. Inflammation of the thyroid may also result in clinically important thyrotoxicosis, in addition to exogenous ingestion of thyroid hormones, the presence of ectopic thyroid tissue or aberrations of thyroidal autonomy. Each carries a specific clinical presentation and requires specific treatment strategies.

Clinical manifestations

Hyperthyroidism may be accompanied by a constellation of signs and symptoms, the breadth of which is attributable to the diversity of action of thyroid hormones. Apathetic or masked thyrotoxicosis may be seen in some patients who fail to develop any symptoms of thyroid excess whatsoever.[9] Older individuals may additionally demonstrate a paucity of symptoms though cardiovascular complaints are seen most frequently; it is therefore appropriate to adopt a low threshold for performing thyroid function testing in older persons.[10] There nevertheless exists a rough correlation between circulating thyroid hormone concentrations and symptom severity. The signs and symptoms of hyperthyroidism are summarized in Table 61.2.

SYMPTOMS

The symptoms of thyrotoxicosis result from both β-adrenergic overactivity and the intracellular action of thyroid hormones. Patients may complain of anxiety, poor

TABLE 61.1 Causes and classification of thyrotoxicosis and hyperthyroidism

	Thyrotoxicosis with hyperthyroidism	Thyrotoxicosis without hyperthyroidism
Common	Graves' disease Toxic multinodular goitre Solitary toxic adenoma	Silent (painless) thyroiditis Postpartum thyroiditis Subacute thyroiditis Exogenous thyroid hormone
Uncommon	TSH-secreting pituitary adenoma Iodine intake Radiographic contrast agents Iodine-containing drugs (amiodarone) Pituitary resistance to thyroid hormone Neonatal Graves' disease Hyperemesis gravidarum Struma ovarii Metastatic follicular thyroid carcinoma	Drug-induced thyroiditis (amiodarone, lithium, interferon-α) Acute infectious thyroiditis Radiation thyroiditis Infarction of thyroid adenoma 'Hamburger' thyrotoxicosis

TABLE 61.2 Clinical manifestations of hyperthyroidism

Symptoms	Signs
Weight loss	Sinus tachycardia
Anxiety	Atrial fibrillation
Agitation	Fine tremor
Irritability	Warm moist skin
Palpitation	Palmar erythema
Fatigue and weakness	Onycholysis
Breathlessness	Hair loss
Heat intolerance	Proximal myopathy
Sweating	Muscle wasting
Increased appetite	High output heart failure
Menstrual irregularity	Thyroid bruit
Hair loss	
Brittle nails	

concentration and irritability. They may report insomnia despite extreme fatigue, and a paradoxical fall in weight may be seen in the presence of increased appetite as a consequence of increased basal metabolic rate. Weight loss in conjunction with depression and agitation in this context has previously been termed 'apathetic hyperthyroidism'.

Heat intolerance and increased perspiration are common complaints. Stool frequency is also increased yet frank diarrhoea is rare. Oligomenorrhoea and infertility may occur in women, although amenorrhoea is seen only rarely. Men may report reduced libido and painful gynaecomastia.

SIGNS

Clinical findings include agitation, rapid speech, palmar erythema, the presence of a fine tremor and warm, moist skin. Hair may be fine and thin while sympathetic overactivity and thyroid orbitopathy contribute to lid retraction and lid lag. Examination of the neurological system may reveal a fine tremor of the outstretched hands, hyperreflexia and a proximal myopathy. Sinus tachycardia or atrial fibrillation (AF) is frequently noted on cardiovascular examination. Approximately 15% of older persons with new-onset AF have thyrotoxicosis, while a study of 40 628 patients with hyperthyroidism identified a prevalence of AF of 8.3%.[11] Consequently, new-onset AF warrants an assessment of thyroid status, particularly in older patients among whom AF is seen more commonly and in whom cerebral emboli or worsening cardiac failure may be readily precipitated by its development.[12]

Thyroid enlargement is commonly noted in patients with hyperthyroidism. There may be a single nodule in patients with an autonomously functioning adenoma or a nodular goitre in those with toxic multinodular goitre. A smooth goitre is seen in many patients with Graves' disease although the thyroid is impalpable in 30% of those with Graves' and toxic nodular hyperthyroidism.[3] Other features seen in hyperthyroidism include osteoporosis, signs of hypercalcaemia and shortness of breath. Signs relating to the excess production of thyroid hormones, including the development of goitre, may be less evident among older persons.

In rare instances, established or new-onset hyperthyroidism may present as an acute 'thyroid storm'. This potentially life-threatening condition should be considered in patients with a fever and altered mental state. It commonly comprises psychiatric disturbance such as agitation or psychosis coupled with hyperpyrexia, AF and congestive cardiac failure.[13] Patients may subsequently become comatose. This condition is commonly precipitated by stressors such as infection, surgery or childbirth.

Thyrotoxicosis may also very rarely be associated with periodic paralysis (thyrotoxic periodic paralysis; TPP), particularly among Asian populations and especially in Chinese and Japanese patients aged between 20 and 40 years.[14] Patients typically experience recurrent episodes of transient skeletal muscle weakness which initially affects the lower limbs prior to afflicting the truncal muscles and then all four limbs. Attacks may last 3–72 hours. Severe cases have been accompanied by total paralysis of respiratory, bulbar and ocular muscles. The hallmark of TPP is hypokalaemia, which is thought to result from the action of thyroid hormone on Na^+, K^+-ATPase activity. Treatment with intravenous potassium during an attack may therefore hasten muscle recovery and reduce the potential risk of cardiac arrhythmia. Prophylaxis against further attacks can be achieved using spironolactone or propranolol yet definitive treatment of hyperthyroidism remains the mainstay of management.

Diagnostic evaluation

A history and examination suggestive of thyroid overactivity requires further investigation prior to the initiation of treatment or further investigation. Laboratory investigations used in the workup of suspected thyrotoxicosis are shown in Table 61.3. The single most important test is the measurement of serum TSH. If TSH is within normal range, a diagnosis of hyperthyroidism can usually be ruled out. Rare cases in which thyrotoxicosis is caused by a pituitary lesion, such as a TSHoma, or syndromes of thyroid hormone resistance stand as the exception to this rule. In these instances serum TSH may be normal or slightly raised in association with raised fT3 and fT4 concentrations.

In most cases of hyperthyroidism the typical picture is of undetectable serum TSH with elevated serum concentrations of fT4 and fT3. A low TSH and a normal fT4 concentration should prompt fT3 measurement as 10% of cases of thyrotoxicosis are so-called 'T3 toxicosis'. This is most commonly seen in mild cases of toxic nodular hyperthyroidism (either a single autonomous nodule or a multinodular goitre) or early in relapse of Graves' disease. It is important to note that not all laboratories perform T3 assays unless specifically requested.

A low TSH is not specific for thyrotoxicosis. 'Non-thyroidal illness' or treatment with a variety of drugs may lower the TSH below the normal range, although it is still usually detectable in these circumstances. For these reasons it is preferable to measure the TSH in conjunction with serum fT4 and, in specific cases, fT3 as well (Box 61.2).

TABLE 61.3 Laboratory investigations in suspected thyrotoxicosis

Laboratory test	Findings	Comment
Thyroid function tests	Elevated free T4 and/or free T3 Suppressed TSH	Unless TSH-secreting pituitary adenoma or thyroid hormone resistance
Immunology	Raised TSH-receptor antibodies	Pathognomonic for Graves' disease
	Raised anti-TPO antibodies	Indicative of underlying thyroid autoimmunity
Biochemistry	Elevated alkaline phosphatase Elevated calcium	
Haematology	Normochromic normocytic anaemia	Long-standing cases
	Raised ESR	Subacute thyroiditis

BOX 61.2 Key considerations in TSH testing

Low TSH is not specific for thyrotoxicosis.

Measurement of serum fT4 should be undertaken if TSH is abnormal.

A low TSH and normal fT4 may mask T3 toxicosis.

The specific patterns seen in thyroid function tests (TFTs), as depicted in Table 61.4, are accompanied by non-specific changes in other laboratory tests. Hypercalcaemia is seen in approximately 10% of patients as a consequence of increased bone turnover and secondary suppression of parathyroid hormone.[15] Levels of alkaline phosphatase may increase and both a raised ESR and normocytic normochromic anaemia seen.

TSH-receptor (TSH-R) antibodies are analysed in the laboratory through binding assays or bioassays.[16] These respectively measure TSH-R levels through respectively quantifying either the degree to which radiolabelled TSH–TSH receptor binding is inhibited by the presence of immunoglobulins, or the effect immunoglobulins have on thyroid cell function. The routine use of TSH-R antibody testing is increasing for the diagnosis of Graves' disease and the presence of these antibodies acts as a specific indicator of the disease. Interestingly, high levels of TSH-R antibodies seen in patients with Graves' disease who are pregnant predict neonatal thyrotoxicosis.[17] The additional presence of thyroid peroxidase (TPO) antibodies is suggestive but not pathognomonic for Graves' disease.

THYROID SCINTIGRAPHY IN THE INVESTIGATION OF THYROTOXICOSIS

In cases in which the aetiology of thyrotoxicosis remains unclear despite history, examination and laboratory investigations, thyroid scintigraphy may be utilized. This technique analyses radioactive iodine uptake by the thyroid gland and can be used to differentiate between 'hot' and 'cold' areas of increased and decreased function respectively. In most hyperthyroid states uptake will be at the higher end of normal or raised and there are specific scintigraphic appearances associated with different conditions (Figure 61.1). Uptake is typically low in transient thyroiditis and in iodine-induced hyperthyroidism. Isotope imaging, typically with technetium, can be useful to differentiate between focal uptake in one or more autonomous nodules and diffuse uptake in Graves' disease, but it is less specific than iodide-uptake scans. Radioisotope scanning lacks specificity, with high values also seen in individuals who have a normal thyroid gland in addition to those with iodine deficiency and conditions such as Hashimoto's thyroiditis.

Specific disorders of thyroid hormone excess

GRAVES' DISEASE

In iodine-replete parts of the world, Graves' disease is the most common cause of thyrotoxicosis (Figure 61.2). First described in 1835, Graves' disease is a syndrome consisting of hyperthyroidism, moderate diffuse goitre, ophthalmopathy and dermopathy. In many patients, hyperthyroidism and goitre are the only features. It is more common in women than men at a ratio of greater than 5:1. Men are affected later and the disease may be more severe. Its peak incidence is in the twenties and thirties, but the disease can occur at any age, albeit uncommonly before puberty. Graves' disease is both more common and more likely to be complicated by ophthalmopathy in smokers, in whom the risk of Graves' disease is almost doubled.[18]

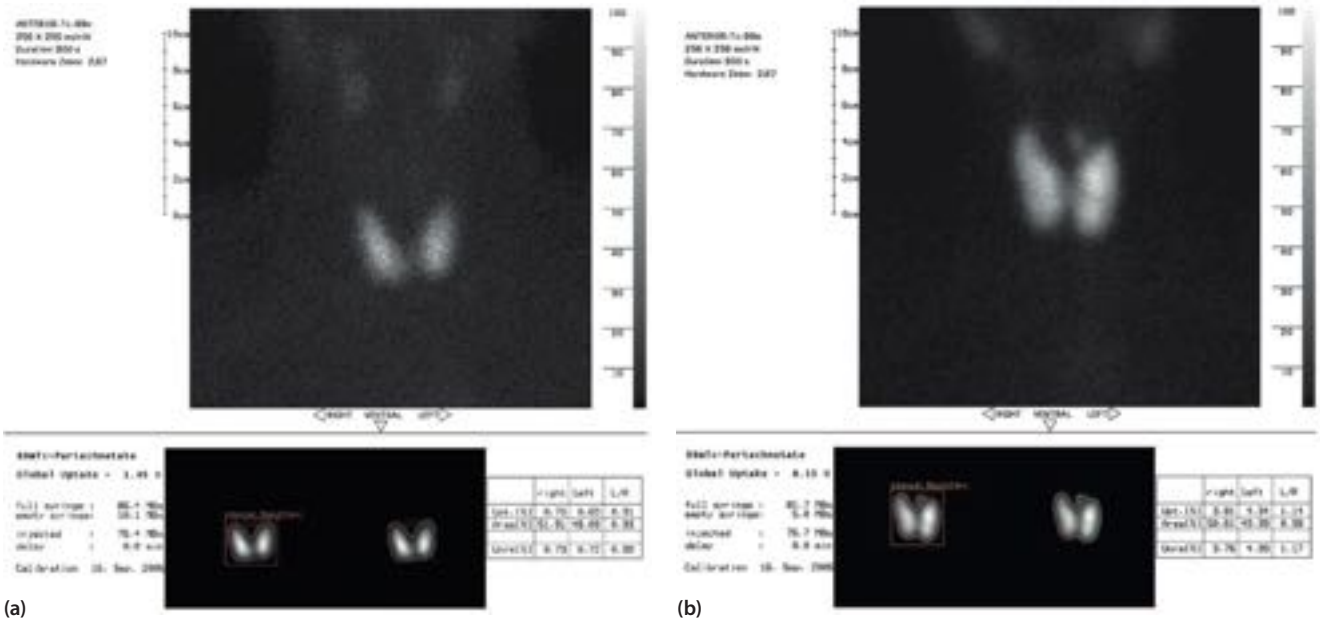
Pathogenesis

Graves' disease is an autoimmune condition characterized by the presence of circulating IgG oligoclonal autoantibodies directed against the TSH receptor within thyroid tissue (TSHR-Ab). These bind to the extracellular domain of the TSH receptor where they cause activation of intracellular cyclic AMP and thereby mimic the effect of pituitary TSH to stimulate thyroid hormone synthesis and secretion. Increased expression of fibroblast growth factor (FGF) contributes to enlargement of the gland resulting in

TABLE 61.4 Specific patterns of thyroid function tests

Suspected pathology	Specific diagnosis	TSH	T4	T3	TSH response to TRH
Hyperthyroidism	Primary hyperthyroidism	↓	↑	↑	N/A
	T3 toxicosis	↓	↔	↑	N/A
	Subclinical hyperthyroidism	↓	↔	↔	N/A
	TSHoma	↑/↔	↑	↑	N/A
	Amiodarone effect without overt thyroid dysfunction	↔	↑	↓	N/A
Hypothyroidism	Primary hypothyroidism	↑	↓	↓	↑
	Central hypothyroidism	↔/↓	↓	N/↓	↔/↓
	Resistance to thyroid hormone	↔/↑	↑	↑	↑
	Non-thyroidal illness	↔/↓	↔/↓	↓	↔/↓

Note: ↑: increased; ↓: decreased; ↔: normal.



(a) (b)

Figure 61.1 Scintigraphic appearances. (a) Normal thyroid; **(b)** Graves' disease with pyramidal lobe.

a diffuse swelling. Antibodies which specifically activate phospholipase A_2 are especially goitrogenic.[19]

The expression of CD80 and CD86 by dendritic cells and B cells may trigger Graves' hyperthyroidism by acting to co-stimulate infiltrating T cells.[20] These are targeted against antigens such as the thyrotropin receptor, which is presented to them by thyroid cells that express HLA class II molecules in response to interferon-γ production. The presentation of antigen and molecules such as CD40, CD54 and IL-6 by thyroid cells may later exacerbate the autoimmune process.[21] Cross-reactivity between these thyroidal antigens and antigens in orbital and extra-orbital tissues may explain the close relationship between Graves' disease and both ophthalmopathy and dermopathy. The thyrotopin receptor is additionally expressed in preadipocytes of orbital fibroblasts and has therefore been suggested as a possible cross-reactive antigen.[22, 23]

The aetiology of Graves' disease remains unknown. It runs in families and a concordance rate in monozygotic twins of 20% suggests a genetic contribution to its development, albeit with additional contribution from environmental factors responsible for promoting development of the disease. Graves' is well known to be associated with HLA-DR3 and HLA-DQA1*0501 in Caucasians, while HLA-DRB1*0701 is protective.[24] Environmental factors linked with the development of disease include life stress and subsequent activation of specific neuroendocrine pathways, female sex, steroids, smoking, dietary iodine intake and immune modulators such as interferon α.[25–27] Lithium may also promote Graves' hyperthyroidism via its immunologic sequelae.[28] Graves' disease has been associated with other diseases mediated by the immune system, including Type 1 diabetes, vitiligo (**Figure 61.3**), coeliac disease, pernicious anaemia and Addison's disease.

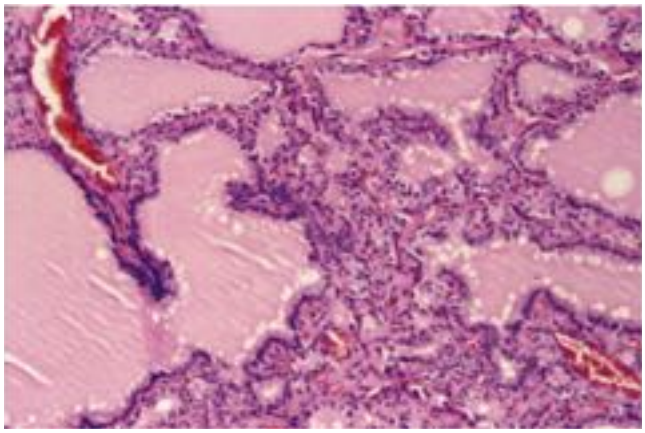


Figure 61.2 Graves' disease. A vascular gland displaying characteristic tortuous, hyperplastic follicles with blunt papillary infolding. The thyrocytes are columnar in outline and there is accentuated marginal vacuolation of stored colloid.



Figure 61.3 Vitiligo in hands of patient with Graves' disease.

Clinical manifestations and natural history

Although Graves' disease can occur rapidly over a few weeks, in most the onset is gradual and insidious. Patients exhibit many of the clinical features discussed above but may in addition have extrathyroidal manifestations such as ophthalmopathy (with exophthalmos and conjunctival oedema) and, rarely, dermopathy and acropathy.

A diffuse goitre is present in the majority of cases but its absence does not rule out Graves' disease, as the thyroid may be of normal size in around 3%.[15–18] The goitre is usually symmetrical, there may be an overlying palpable thrill and a bruit may often be heard. The thrill and bruit result from the increased blood flow to the thyroid.[15–18]

Graves' disease is usually treated with antithyroid medication in the first instance. While adequate therapy is given, the disease may be quiescent, but it can return if compliance diminishes or if drug dosage is inappropriately reduced. As with many autoimmune conditions, Graves' disease is sometimes self-limiting, although this is rare. Around 30% of patients experience lasting remission after treatment with antithyroid drugs.

Extrathyroidal manifestations of Graves' disease

Thyroid eye disease

Ophthalmopathy is common in Graves' disease. It is clinically apparent in approximately 50% of patients and may present prior to the onset of Graves' disease.[18] In 75% of those for whom eye disease is clinically apparent, eye signs appear within a year before or following the diagnosis of hyperthyroidism.[18] Even in the absence of clinical signs, imaging such as MRI has provided evidence of eye involvement in most patients (**Figure 61.4**). Approximately 90% of patients with thyroid eye disease also have Graves' disease.[29] The majority of the remainder have autoimmune hypothyroidism.

The ophthalmopathy seen in Graves' disease is characterized by swelling of the extraocular muscles, proliferation of periorbital fat and late fibrosis leading to muscle tethering.[30] The lesions develop due to an accumulation of glycosaminoglycans and a lymphocytic infiltration of the orbital and retro-orbital tissues. Patients who smoke are more likely to suffer eye disease of greater severity than non-smokers and hypothyroidism is an additional potentially exacerbating factor.[31, 32]

Patients with thyroid eye disease may complain of irritation in the eyes and the feeling of a foreign body. There may be excessive watering, especially in the wind. As the disease progresses, there is sometimes a change in physical appearance with periorbital oedema and/or a staring expression caused by exophthalmos and/or eyelid retraction. Eyelid retraction may give the false impression of proptosis, though both most often coexist. This may be bi- or unilateral and patients can complain of a feeling of pressure behind the eyes. Even in apparent unilateral cases, evidence of bilateral disease may be apparent on imaging. In severe cases the patient cannot close their eyes at night, leading to corneal ulceration and scarring. Apparent nerve palsies are also seen due to infiltration of the extraocular muscles with fat and fibrotic changes.

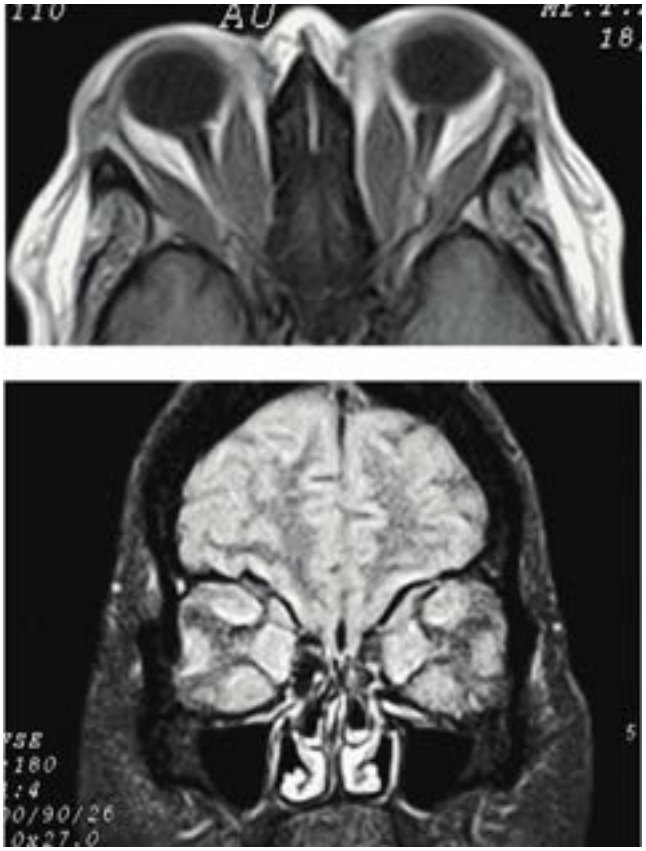


Figure 61.4 Thyroid eye disease. MRI orbits, showing enlarged extraocular muscles.



Figure 61.5 Patient with thyroid eye disease and optic neuropathy. (a) Pre-corrective surgery and **(b)** after surgical decompression. Note the upper lid retraction, corneal injection, periorbital fat deposition and proptosis pre-surgery.

Diplopia is noted in a significant proportion of patients and corrective surgery may be required (**Figure 61.5**).[33]

A rapid deterioration in visual acuity and loss of colour vision are ominous signs and may be caused by pressure on the optic nerve by swollen extraocular rectus muscles or sheer stretch of the optic nerve. Urgent treatment is required if permanent visual loss is to be avoided. Patients must also be referred urgently to an ophthalmologist if they develop strabismus or poor eye movement, or corneal ulceration or if their visual acuity is less than 6/18 (**Box 61.3**).[34]

BOX 61.3 Urgent referral criteria in thyroid eye disease

- Rapid deterioration in visual acuity
- Ocular nerve palsies
- Unacceptable cosmetic appearance
- Visual acuity of less than 6/18
- Decreased colour vision
- Corneal ulceration

The most frequently seen signs of thyroid eye disease include eyelid retraction and periorbital oedema. Lid lag also occurs frequently and in mild cases arises as a consequence of sympathetic overactivity, whereas in more significant instances is the result of Graves' ophthalmopathy. Exophthalmos is seen in up to a third of patients. Compression of the optic nerve at the apex of the orbit is rare but can result in visual loss.

Thyroid eye disease occurs in two phases: a dynamic phase and a quiescent phase. Unfortunately, even when Graves' ophthalmopathy is well-treated and quiescent, patients do not always achieve a return in physical appearance to their pre-morbid state. Mild to moderate thyroid eye disease often requires no treatment and may improve spontaneously. Local discomfort can be managed with artificial tears and elevation of the head of the bed to reduce oedema. Severe ophthalmopathy requires management in a multidisciplinary team with experienced ophthalmologists. High-dose glucocorticoids as well as other immunosuppressive agents and orbital radiotherapy can be used successfully in early and active disease, which will have beneficial effects in approximately two-thirds of patients.[35, 36] The chimeric anti-CD20 monoclonal antibody Rituximab acts to deplete B-cells and may also be of benefit in thyroid eye disease, though trials are ongoing.[36, 37] Ocular nerve palsies require treatment from an experienced ophthalmologist, either initially or after failure of glucocorticoid treatment.

Dermopathy

This occurs in 1–2% of patients with Graves' disease, almost always accompanied by severe eye disease.[38] Usually occurring over the shins and known as pretibial myxoedema, it may affect other areas of the body.[39] Dermopathy in Graves' disease also occurs at sites of trauma, thereby exhibiting the Koebner phenomenon.

The skin appears raised, oedematous, nodular and discoloured with a pink or brownish tinge (**Figure 61.6**).[40] It is characterized by a florid lymphocytic infiltrate and a build-up of glycosaminoglycans. Although not usually treated, fluorinated steroids may be used topically with occlusive dressings.[39]

Acropachy

This very rare condition occurs in less than 1 per 1000 patients. It presents as clubbing of the fingers with subperiosteal new bone formation seen on plain X-ray films.[41] Acropachy arises from glycosaminoglycan accumulation and is seen in association with dermopathy and ophthalmopathy. There is no treatment.



Figure 61.6 Pretibial myxoedema.

Laboratory diagnosis

The routine measurement of TSH-R antibodies for the diagnosis of Graves' disease is increasingly regarded to be both valid and reliable.[16] Anti-TPO antibodies are also commonly measured. Laboratory results otherwise typically identify raised serum fT4 and fT3 with undetectable serum TSH.

KEY POINTS

GRAVES' DISEASE

- Graves' disease is the most common cause of thyrotoxicosis in iodine-replete populations.
- It is more common in women than men.
- It is an autoimmune condition characterized by the presence of IgG anti-TSH receptor antibodies.
- Antithyroid peroxidase antibodies are present in 75% of patients.
- Ophthalmopathy, dermopathy and acropachy are important extrathyroidal manifestations.
- Antithyroid medication is used in most cases at least initially.

TOXIC MULTINODULAR GOITRE

Nodular thyroid disease predominates in the elderly and surpasses Graves' disease as the most common cause of hyperthyroidism in older persons living within iodine-replete areas.[42] In regions in which iodine is relatively deficient, toxic nodular thyroid disease is the most common cause of hyperthyroidism.[43] A toxic multinodular goitre (MNG) occurs when two or more autonomously functioning thyroid nodules secrete excess thyroid hormone. Its precise cause is not known but may relate to genetic change that occurs within specific nodules and thereby drives clonal expansion.[44] As a consequence of its long natural history, an elderly patient presenting with a toxic MNG may describe the presence of the goitre many years before the thyrotoxicosis develops.[45] Exposure to pharmacological doses of iodine, such as those found in contrast media, may also precipitate hyperthyroidism through the Jod Basedow effect.[46] This is commonly seen in areas of iodine deficiency.

Toxic MNGs are generally observed in an older patient group than those who present with Graves' disease and the degree of thyroid hyperfunction is typically less marked.

For these reasons, the classical clinical symptoms and signs of thyrotoxicosis may not all be present. It is the cardiovascular effects that predominate, including palpitation, AF and other tachyarrhythmias.[47] Patients with toxic MNG may also report the presence of a long-standing goitre. Compressive symptoms are a possible consequence of the presence of a MNG and include dysphagia to solids and dyspnoea that worsen at night.

KEY POINTS

TOXIC MULTINODULAR GOITRE

- This occurs in older patients.
- Thyroid hyperfunction is less marked than in Graves' disease.
- Cardiovascular symptoms predominate.
- Definitive treatment with radioiodine is required.

SOLITARY TOXIC ADENOMAS (PLUMMER'S DISEASE)

A single toxic adenoma is a benign tumour autonomously secreting sufficient thyroid hormone to suppress pituitary TSH secretion. Solitary adenomas tend to grow to at least 3 cm in diameter prior to causing overt hyperthyroidism.[48] They are a rare cause of thyrotoxicosis and account for only around 5% of cases.[48] A mutation in the TSH receptor gene occurs in 20–83% of cases.[49] Several point mutations of this gene have been identified, mostly in the transmembrane domain. These are somatic and result in TSH receptor activation and consequent autonomous thyroid hormone secretion. Other activating mutations have been identified downstream in the stimulatory G protein pathway linked to cyclic AMP production.[50, 51]

Subclinical hyperthyroidism, characterized by below-normal serum TSH and normal serum fT4 and fT3 concentrations, is often evident on biochemical testing.[52] It occurs early in the clinical history of a toxic adenoma as a consequence of negative feedback prompted by TSH receptor activation and the resultant autonomous production of thyroid hormones.[53] Patients with a toxic adenoma are often younger than those with a toxic MNG, and present in the fourth or fifth decade. There may be a history of a slowly enlarging neck mass and many will have a palpable nodule. The autonomously functioning tissue may nevertheless be diffuse and a palpable nodule will not therefore be apparent in all patients. The level of thyroid hyperfunction is less than that seen in Graves' disease and signs may thus be less florid.[52] Radionuclide scanning may be utilized to distinguish a solitary toxic adenoma from toxic MNG and Graves' disease. It typically demonstrates a focus of isotope accumulation with no other visible areas of uptake.

Management of hyperthyroidism

The initial approach to the hyperthyroid patient is to minimize symptoms (often with a beta-adrenergic blocking drug) and to reduce the synthesis of thyroid hormones. Overt hyperthyroidism necessitates effective therapy in all cases in order to reduce the risk of psychological, cardiovascular and skeletal sequelae. The principles of management are summarized in **Box 61.4**.

BOX 61.4 Principles of management of hyperthyroidism

Minimize symptoms (e.g. with the use of a beta-adrenergic blocking drug)

Treat hyperthyroidism to reduce risk of psychological, cardiovascular and skeletal sequelae:

- Thionamides
- Radioiodine
- Surgical resection

Three modalities of treatment exist: drug therapy, radioiodine treatment and surgery. Their relative indications, advantages and disadvantages are summarized in **Table 61.5**. It has been demonstrated that each of the three treatment modalities is as effective at reducing thyroid hormone concentration, with similar improvements seen in quality of life and patient satisfaction following their use.[54–56] Treatment selection therefore depends on the underlying aetiology, the preference of the clinician and patient factors. Service considerations often also play a role in determining treatment choice and include cost, local restrictions on the use of radioisotopes and the availability of a skilled surgical team.

Standard practice in Europe has been to favour antithyroid medication in patients under 40 years of age, with surgery reserved for patients who relapse.[57] In contrast, radioiodine therapy is not restricted to use in older patients within the USA and antithyroid drug regimens are consequently not commonplace. Radioiodine is considered first-line therapy in Graves' disease and toxic multinodular goitres yet its use, which is commonly associated with hypothyroidism, is not without controversy.[2, 32]

A long-term increase in all-cause and vascular mortality after treatment of hyperthyroidism with radioiodine has for instance been described, though this is probably due to an underlying diagnosis of thyrotoxicosis rather than a consequence of radioiodine therapy itself.[58] Induction of hypothyroidism after radioiodine treatment reduces this risk, perhaps because hypothyroidism is the best marker of reversal of adverse tissue effects. Fears about the development of cancer after radioiodine have not been realized, although Graves' hyperthyroidism itself might be associated with a slight increase in the absolute risk of thyroid cancer.[59–61]

There is consequently a lack of consensus regarding appropriate thyroid hormone replacement in patients rendered hypothyroid by radioiodine, and some evidence to suggest that antithyroid drugs may be safely used longer term for the management of relapsing and remitting hyperthyroidism.

PHARMACOLOGICAL MANAGEMENT

The thionamides (carbimazole, its active metabolite methimazole [not available in the UK] and propylthiouracil) are the most effective antithyroid drugs and represent the mainstay of drug treatment of thyrotoxicosis.[57]

TABLE 61.5 Specific indications, advantages and disadvantages of treatment modalities used in the management of thyrotoxicosis

	Treatment modality		
	Antithyroid drugs	**Radioactive iodine**	**Surgery**
Indications			
Graves' disease	✓	✓	✓
Toxic nodular hyperthyroidism		✓	✓
Pregnancy	✓		✓
Children	✓		✓
Significant ophthalmopathy	✓		✓
Advantages			
Definitive treatment		✓	✓
Non-invasive	✓	✓	
Outpatient therapy	✓	✓	
Low cost	✓	✓	
No exposure to radiation	✓		✓
Low risk of hypothyroidism	✓		
Relief of compressive symptoms		✓	✓
Histological diagnosis			✓
Disadvantages			
Permanent hypothyroidism		✓	✓
Worsening ophthalmopathy		✓	
Frequent follow-up	✓	✓	
Invasive			✓
Expensive			✓
Specifics	Low cure rates	Slow cure Radiation thyroiditis risk Need to defer pregnancy Radiation protection required	Risk of hypocalcaemia Scar Surgical complications

They act by blocking the synthesis of T4 and T3 early in their biosynthetic pathway by disrupting the organification and oxidation of iodide through inhibition of the thyroperoxidase enzyme. Propylthiouracil (PTU) additionally acts to inhibit the conversion of T4 to T3 but this is not thought to be of clinical relevance. Thionamides have also been associated with a possible immunomodulatory effect, although this is of doubtful clinical significance given that most patients relapse following drug withdrawal.[62] Carbimazole can be dosed as a once-daily preparation in order to improve compliance and results in fewer adverse effects than propylthiouracil.[63] It is therefore generally given in preference, with propylthiouracil reserved for use in pregnancy, women attempting to conceive or patients who have developed an adverse reaction (other than agranulocytosis) to carbimazole or methimazole.[64]

Dosage

All patients with hyperthyroidism require specialist referral and patients should be commenced on antithyroid drug treatment while they await further clinical review.[65] Carbimazole is available as 5 mg and 20 mg tablets and is usually given in a starting dose of 20–30 mg per day in a single dose. Treatment should usually begin at 30 mg in cases of severe disease (fT3 and fT4 levels more than twice the upper limit of the normal reference range). Propylthiouracil is given in divided doses, with a dose of 200 mg approximately equivalent to 20 mg carbimazole. Patients begin to feel an improvement at 10–14 days and fT4 and fT3 values return to normal levels over 4–6 weeks.

Side effects

Side effects are seen in 1–5% of patients taking thionamides and can occur with both carbimazole and PTU (Table 61.6). The most common side effect is pruritic rash, which can usually be managed conservatively. Occasionally, the rash necessitates a change from one drug to the other and cross-reactivity in this context is not typically a problem. Other relatively minor side effects include fever, urticaria and arthralgia.[57, 66]

TABLE 61.6 Side effects of thionamides

Severity	Side effects
Mild	Pruritic rash Fever Urticaria Arthralgia
Serious	ANCA-associated vasculitis Hepatitis Liver failure Agranulocytosis

A fever and sore throat in a patient taking thionamides requires measurement of full blood count.

More serious side effects are rare and include development of an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (typically associated with PTU) and hepatitis.[67, 68] Agranulocytosis is a serious side effect and occurs in 0.2–0.5% of patients.[67] This typically occurs in the first few weeks of treatment but may occur at any point during antithyroid drug therapy since it is an iodiosyncratic reaction. It is more common in patients taking high doses. For this reason it is essential that all patients are warned (preferably in writing) of the risk of agranulocytosis and that clear instructions are given to present urgently for a full blood count if they develop a fever or sore throat. The agranulocytosis is usually transient and resolves after thionamide withdrawal.

PTU can also result in fulminant hepatic failure, which can necessitate liver transplantation or lead to death. PTU-related acute liver failure occurs in an estimated 1 in 10 000 adults, although it is more commonly seen in children.[69] The US Food and Drug Administration has consequently issued a warning relating to the use of PTU, and its first-line use in adults and children is now not recommended unless the patient is in the first trimester of pregnancy, if side effects are reported with carbimazole or methimazole therapy, if radioiodine or surgery is not an option or in some instances of life-threatening thyrotoxicosis.[70]

The development of agranulocytosis, hepatitis or vasculitis is an absolute contraindication to the further use of thionamides.

Graves' disease

In cases of Graves' disease patients may be offered a full course of thionamide therapy in the hope of inducing remission. Treatment should be offered for a period of 12–18 months as shorter courses are associated with higher rates of relapse.[71, 72] Treatment duration is agreed with the patient at the outset, but at any point medication may be stopped if definitive therapy is preferred. Serum fT4 should be measured regularly, ideally every 4–6 weeks initially, then 8–12 weekly once control is achieved. Drug doses are titrated according to the serum concentration of fT4. Serum TSH may remain suppressed in the medium to long term in patients with Graves' disease due to delayed recovery of thyrotrophs. Most patients require a maintenance dose of 5–10 mg carbimazole and 50–100 mg PTU. Poor compliance should be suspected if larger doses are required.

Treatment efficacy

Remission rates with this regimen are less than 50%, but they may be higher in the elderly.[55–73] Relapse usually occurs within 3–6 months of thionamide withdrawal, in which case patients should be offered definitive treatment. Efforts to risk-stratify patients for their likelihood of relapse using markers such as goitre size, thyroid suppressibility, HLA status, the presence of TSH-receptor antibody and TSH response to thyrotropin-releasing hormone have been unsuccessful.

On a population basis, increased likelihood of remission is most strongly associated with age and sex.[73] Remission occurs in approximately 20% of men, compared to 40% of women, in addition to 33% of those less than 40 years of age compared to 48% of those aged over 40. A small goitre or one that shrinks during therapy also appears related to an increased risk of remission.[74] Once remission is achieved, cure is likely if the patient remains euthyroid for 6 months, although a slowly increasing proportion relapses with length of time of follow-up. Ninety per cent of relapses occur within 3 years. **Table 61.7** summarizes poor prognostic factors for relapse of medically treated Graves' disease.

Block and replace

Although most clinicians use thionamides alone to treat Graves' disease, some prefer the 'block and replace' regimen. This uses thionamides to block endogenous hormone production completely with hypothyroidism avoided in the long term by supplementing with exogenous thyroxine. The dose of thyroxine is then adjusted to maintain serum TSH within the lower reference range. Advocates of this regime suggest that it requires less monitoring and leads to better compliance. Remission rates are not, however, improved by standard block and replace therapy and there is no substantial evidence for any advantage of this regime.[75, 76] There is clear evidence of increased adverse effects, some of which are serious and are related to the higher doses of thionamides required.[75] This regimen is also contraindicated in pregnancy because thionamides cross the placenta more easily than T4, leading to the potential for foetal goitre and hypothyroidism.

Toxic multinodular goitre and toxic adenoma

Thionamides may be used in the short term in order to induce euthyroidism in patients with nodular disease but do not lead to remission or cure of thyrotoxicosis in

TABLE 61.7 Poor prognostic factors for relapse of medically treated Graves' disease

Factor type	Prognostic factor
Demographic	Male gender Age < 40 years
Clinical history	Repeated episodes of relapse Presence of a large goitre
Biochemical	Severe biochemical disease Greatly increased T3:T4 ratio High levels of TSH receptor antibodies

this context. Definitive treatment with radioiodine or surgery is therefore required. As the thyrotoxicosis is usually biochemically less severe than Graves' disease, the starting dose of thionamides may be smaller. If surgery or radioiodine is not appropriate, thionamides can be continued indefinitely.

Adjuncts to antithyroid drugs

Beta-adrenergic blockers are useful adjuncts to thionamides in the management of thyroid hormone excess. They act promptly to reduce symptoms such as tremor, palpitations and tachycardia. Their use is cautioned in the elderly where heart failure may be present. The most commonly used beta-adrenergic blocker is propranolol. Thyrotoxicosis may result in accelerated clearance of propanolol and higher doses of this drug may therefore be required.

Patients who develop AF are at risk of embolic complications. Anticoagulation with warfarin or a novel oral anticoagulant (NOAC) such as rivaroxaban or apixaban should therefore be considered, in accordance with the patient's CHA_2DS_2-VASc score and the specific licence of the NOAC. There have been no controlled trials of the use of anticoagulants in thyrotoxic AF but overwhelming evidence for their efficacy in other settings argues in favour of their use for as long as there are not clear contraindications. There is also no evidence for or against the preferential use of NOACs in this context. Approximately half of those with thyrotoxic AF will revert spontaneously to sinus rhythm and this typically occurs within 3 months of the initiation of antithyroid therapy. For those who remain in AF, joint cardiological management involving specific therapy to restore sinus rhythm may be considered when the patient is euthyroid. Chemical or electrical cardioversion is more likely to restore sinus rhythm in those whose AF is of short duration and in those who have no underlying heart disease.[77]

RADIOIODINE

Radioiodine is increasingly used both as first-line therapy in Graves' disease, for toxic multinodular goitre and in patients with Graves' disease for whom initial treatment with a course of thionamides has failed (**Box 61.5**).[32] It may also be used to induce shrinkage of benign goitres and in the management of autonomous thyroid nodules.[2] Permanent hypothyroidism results in most patients treated with radioiodine, though this may occur many years later. The incidence of hypothyroidism is dose-dependent.[78]

Administration

Radioiodine is administered orally as sodium ^{131}I in capsule form and can be given in the outpatient department. It is incorporated into thyroid tissue and acts principally through the emission of beta rays with a range of 0.5–2 mm. These penetrate into tissue and result in high absorbed doses of radiation within thyroid tissue while sparing the surrounding anatomy. Lasting thyroid tissue damage results but usually lags with maximum thyroid ablation occurring over 6 weeks to 4 months. Scintigraphic imaging may be employed following the administration of radioiodine as a result of emitted gamma rays in order to determine its distribution within thyroid tissue and to support dosimetry.

BOX 61.5 Radioiodine treatment

- Used in toxic multinodular goitres and Graves' disease
- Administered orally as a sodium ^{131}I capsule
- Thyroid tissue damage results from emission of beta rays
- Pre-treatment with thionamides and symptomatic relief usually required
- Side effects include radiation thyroiditis and exacerbation of ophthalmolopathy
- Long-term safety is proven but hypothyroidism is common
- Contraindicated in pregnancy, women who are breastfeeding and children

There is no national consensus regarding the most appropriate dose of radioiodine. The Royal College of Physicians of London recommend that the dose used should be enough to achieve euthyroidism with an acceptable risk of the subsequent development of hypothyroidism. Most centres will administer a fixed dose of 400–600 MBq, which is large enough to induce cure in the majority of patients.[79] Some centres give larger doses to men and those with large goitres in whom it is suggested that relative radioiodine resistance may be found. Larger doses may be preferable in the elderly, especially those with concomitant heart disease, to be certain of rapid resolution of hyperthyroidism.[80]

Many investigators have attempted to determine a method for calculating a radioiodine dose sufficient to cure hyperthyroidism without resulting in hypothyroidism. Postulated methods have involved assessment of the target volume mass, calculations of likely isotope uptake and assessment of isotope turnover.[81] These have not, however, been supported by prospective studies and it has been shown that the use of a calculated dose carries no advantages over a fixed dose in terms of outcome, but results in extra cost and inconvenience for the patient as a consequence of the planning required.

National radiation protection policies exist and include measures to avoid contamination of the home or workplace with radioiodine. They include avoidance of close contact with small children, avoiding sharing utensils and the recommendation to sleep alone.

Pre-treatment with antithyroid medication

Symptom relief may be achieved by beta-adrenergic blocking agents used peritherapeutically in patients undergoing radioiodine administration with coexistent AF. Pre-treatment with thionamides (preferably with carbimazole) should be administered unless the hyperthyroidism is very mild and radioiodine administered once biochemical euthyroidism is restored. This is because it may take 3–4 months for radioiodine to induce euthyroidism whereas thionamides act much more quickly.

There may be a temporary exacerbation of hyperthyroidism as the radiation damage causes follicular destruction and 'dumping' of preformed thyroid hormone into the circulation.[82] Thionamides may therefore be restarted temporarily following radioiodine administration in order to reduce the risk of radiation-related thyroiditis causing an exacerbation of hyperthyroidism, particularly in the elderly and those with cardiac disease.[83]

There is evidence to suggest that use of methimazole and PTU during radioiodine therapy impacts on radioiodine kinetics within the thyroid gland. Whichever thionamide is used, it should thus be discontinued 1 week before radiodiodine administration in order to reduce the risk of negative impacts on therapeutic outcomes.[84, 85] Most clinicians advise restarting thionamides after radioiodine administration, particularly in those with severe disease or who tolerate hyperthyroidism poorly. The antithyroid drug can then be tailed off according to measurements of serum fT4 concentration. In instances in which thionamide therapy is continued during radioiodine administration, success rates are reported to fall from over 90% to under 50%.

Follow-up

In the short term, clinical assessment of the patient should be carried out every 4–6 weeks. In addition to serum TSH, serum fT4 concentration should be measured. Measurement of TSH concentration alone may be misleading as it may be suppressed for many months after treatment and does not necessarily imply that relapse is imminent, especially if the patient is clinically euthyroid and the serum T4 concentration is normal. If biochemical hyperthyroidism persists after a 6-month period, it is likely that a second (and rarely a third) dose of radioiodine will be required. Hypothyroidism commonly results in these patients.

All patients who have received radioiodine require long-term biochemical follow-up. Effectively achieved with a computerized recall system, this is essential as the incidence of hypothyroidism is significant many years after treatment with radioiodine and, eventually, up to 90% may become hypothyroid. Annual measurement of serum TSH is appropriate.

Efficacy

Dependent on the administered dose, 50–70% of patients achieve euthyroidism and shrinkage of goitre around 2 months after therapy.[32] Around 15–20% of patients require a second dose 6–12 months after their initial treatment. A small proportion of patients require a third dose. Those treated with low-dose radioiodine, males, those with severe hyperthyroidism and those with a medium to large goitre are less likely to be cured after a single dose of radioiodine.[86]

Side effects and safety

Many patients are concerned about the concept of radiation treatment and perceive that there may be an increased risk of subsequent cancer. Radioiodine has been used for many years, with well-established efficacy. In terms of cancer, long-term safety has been well demonstrated.[32, 87, 88] The thyroid appears more sensitive to the effects of radiation in children and adolescents. Consequently, most paediatricians would avoid radioiodine in these cases.

Patients who have received radioiodine therapy may notice a sore throat or neck tenderness. This reflects radiation thyroiditis and is thought to occur in around 1% of cases. Symptoms are usually mild and transient. As a result of thyroid ablation, the main side effect of radioiodine treatment is hypothyroidism, although the percentage of patients who develop this during the first year varies according to the dose of radioiodine used. The risk of hypothyroidism with a dose of 600 MBq is around 60%. After the first year, the annual incidence is around 2–3% and seems to be dose-independent.

Radioiodine may worsen moderate to severe ophthalmopathy, particularly in smokers.[31, 89] Adjunctive administration of corticosteroids may ameliorate or even prevent the development of ophthalmopathy.[22] Most physicians delay administration of radioiodine until moderate or severe eye disease has been stable for 12 months. Those with mild eye disease are given radioiodine alongside a course of steroid prophylaxis.[22]

Contraindications

Pregnancy is an absolute contraindication to the use of radioiodine due to the risk of ablating foetal thyroid tissue. A pregnancy test is therefore necessary prior to administration of radioiodine and effective contraception required for 4–6 months after treatment in order to allow for resolution of the effects of transient gonadal radiation. Inadvertent pregnancies require close monitoring, although there is little evidence to suggest that birth defects are increased as a result of exposure to radioiodine during pregnancy. Exposure in early pregnancy is nevertheless associated with a theoretical potential late cancer risk due to foetal irradiation, and exposure after 14 weeks may result in thyroid ablation.

Radioiodine is also contraindicated in women who are lactating, in young children because of fears of increased risk of developing subsequent thyroid carcinoma, and in those who are unable to understand or comply with local radiation protection measures.

Use of radioiodine is associated with worsening of Graves' ophthalmopathy and its use is therefore relatively contraindicated in this group.[90] Radioiodine should not be used in patients with active thyroid eye disease, whereas steroid prophylaxis is recommended for patients with clinically apparent but stable eye disease.[91] Prophylactic steroid treatment is otherwise not recommended for patients who do not have evidence of thyroid eye disease because of the low absolute risk of developing eye disease after receiving radioiodine.[92] Routine steroid prophylaxis has, however, been recommended by consensus statement for smokers given radioiodine treatment, even in the absence of established eye disease, in light of this group's increased risk of complications with radioiodine.[93]

Specific applications of radioiodine

Graves' disease

Radioiodine is increasingly regarded as the treatment of choice in Graves' disease. In certain groups of patients, such as young women or those with mild disease, a course of thionamide therapy may be appropriate in an attempt to induce remission. However, in general radioiodine is considered first line, especially in those whom antithyroid medication is unlikely to result in a cure, such as young men.

Some clinicians target the therapeutic ideal of euthyroidism in patients with Graves' disease by using low-dose radioiodine. There are, however, a number of problems with this approach. Firstly, Graves' may recur in the thyroid remnant, resulting in recurrent hyperthyroidism. This uncontrolled hyperthyroidism results in a permanent reduction in bone density. Secondly, subclinical hyperthyroidism is a risk factor for AF. Many clinicians give radioiodine in a dose large enough to attain euthyroidism in the majority and to avoid recurrence, with a consequent greater risk of hypothyroidism. A dose of 4–600 MBq results in euthyroidism in 90% of cases but at the expense of around 70% hypothyroidism over 20 years.

Nodular thyroid disease

Radioiodine is an effective and definitive treatment option in toxic nodular thyroid disease. It can be used as first-line treatment in those who have mild biochemical hyperthyroidism and who tolerate it well. In the elderly, pre-treatment with a thionamide is necessary to rapidly relieve hyperthyroidism prior to administration of radioiodine.

Radioiodine is effective in achieving euthyroidism and, in those with autonomously functioning nodules, hypothyroidism is less common. The autonomously functioning nodule causes TSH suppression, which, in turn, suppresses surrounding thyroid tissue so that radioiodine is then preferentially taken up into the nodule with sparing of the rest of the gland. Radioiodine may also cause shrinking of nodular goitres with a reduction in thyroid size of 45% after 2 years.

Although around 90% are cured, those with large goitres or with severe hyperthyroidism may not achieve a cure with a single dose of radioiodine and a subsequent dose may be necessary after 6 months' treatment with antithyroid medication.

SURGERY

Although most experts agree that surgery has little part to play in the routine management of thyrotoxicosis, there are instances where partial or subtotal thyroidectomy may be regarded to be a safe and effective treatment for thyroid overactivity.

Indications for surgery

Indications for surgery are summarized within Table 61.8 and include patient preference, the presence of a cosmetically unacceptable goitre, severe ophthalmopathy, uncontrolled disease, poor response to antithyroid drugs and presence of a coexisting potentially malignant lesion.

TABLE 61.8 Indications for surgery

Indication	Notes
Patient factors	
Patient fear/rejection of radioiodine	
Radioiodine contraindicated	Pregnancy, breastfeeding mothers
Pregnancy with side effect to thionamides	
Pregnancy with severe uncontrolled disease	Radioiodine contraindicated
Clinical features	
Additional non-functioning nodule	If carcinoma cannot be excluded
Cosmetically unacceptable goitre	Radioiodine causes only slow shrinkage of goitre
Severe uncontrolled ophthalmopathy	Radioiodine may worsen ophthalmopathy
Local compressive symptoms	

Preparation

Thyroid surgery may result in the liberation of preformed thyroid hormone, which can lead to 'thyroid storm'. This rare, potentially life-threatening condition carries a mortality of up to 50% and is described in Table 61.9. Thorough preparation is required in order to avoid post-operative thyroid storm and significant cardiovascular complications.

Antithyroid drugs are routinely used prior to operative intervention in order to restore euthyroidism. Preoperative beta-adrenergic blockade may be required if euthyroidism has not been effectively achieved prior to surgery or if a patient is unable to take antithyroid medication due to serious side effects. Use of beta-adrenergic blockers may confer additional technical advantages for the surgeon by decreasing gland vascularity.

Lugol's iodine had traditionally been used in patients awaiting surgery in an effort to reduce iodide uptake and therefore inhibit thyroid hormone release, as well as reducing the vascularity of the thyroid gland. It is now avoided due both to the unpredictable response to its administration and to its potential for exacerbating, rather than improving, thyrotoxicosis.

Complications

Complications of thyroidectomy are relatively unusual, as there is universal agreement that those who perform such surgery should be experienced and perform it frequently.[94, 95] In order of importance, potential complications include bleeding, recurrent laryngeal nerve injury, hypocalcaemia secondary to parathyroid hypofunction or hungry bone disease, infection, thyroid storm, keloid formation and seroma (Box 61.6).

Bleeding into the operative site may result in airway compromise due to the development of a haematoma. Immediate clot evacuation and ligation of bleeding vessels

TABLE 61.9 Features and management of extremes of thyroid dysfunction, myxoedema coma and thyroid storm

Predisposing factors		Features/signs	Treatment	
			General measures	Specific measures
Myxoedema coma	Occurs in elderly patients with hypothyroidism who: • have withdrawn thyroxine • have a severe concomitant illness • are inactive, immobile or live in unheated accommodation	Coma Hypothermia Bradycardia Hyponatraemia Hypoglycaemia Hypotension	*Ideally HDU/ITU* Treat precipitating illness with antibiotics if necessary Slow rewarming (0.5 °C/h) Warm humidified oxygen or ventilation if necessary Monitor and treat arrhythmias Correct hypotension and electrolyte imbalance	T4 300–500 µg via NG tube, then 50–100 µg daily If no improvement T3 10 µg i.v. 8-hourly or 25 µg orally Hydrocortisone 50–100 mg 6–8-hourly unless hypocortisolism excluded
Thyroid storm	Develops in hyperthyroid patients with acute infection who: • are postpartum • have undergone thyroid or non-thyroid surgery • reactive iodine containing contrast agents • withdraw antithyroid medication	*Rare but life-threatening condition, significant mortality (up to 50%)* Severe signs of hyperthyroidism Fever/hyperpyrexia Alteration in mental state Tachycardia/tachyarrhythmia Vomiting and diarrhoea Multi-organ failure – cardiac failure, hepatic congestion with hyperbilirubinaemia and jaundice, dehydration and renal failure	*Best carried out in ITU* Cooling, fluid balance, antibiotics, respiratory support if necessary Correction of electrolyte imbalance Standard antiarrhythmic therapy Anticoagulation if in atrial fibrillation Chlorpromazine if agitated	PTU 300 mg 6-hourly via NG tube (PTU blocks T4 to T3 conversion) Potassium iodide 60 mg 6-hourly via NG tube (inhibits thyroid hormone release; start 6 hours after PTU. Propanolol 160–180 mg in divided doses or by infusion to block adrenergic manifestations Prednisolone 60 mg o.d. may also stop T4 to T3 conversion Plasmapheresis may be necessary in refractory cases

BOX 61.6 Complications of surgical thyroid resection

- Bleeding
- Recurrent laryngeal nerve injury
- Hypocalcaemia
- Infection
- Thyroid storm
- Keloid formation
- Seroma

is therefore required. Damage to the recurrent laryngeal nerve is also possible and vocal cords should be checked prior to surgery. Unilateral damage causing some hoarseness usually improves after a few weeks. Bilateral damage is rare but serious, as stridor develops soon after extubation. The ensuing airway obstruction necessitates a tracheostomy.

Damage to the parathyroid glands can occur and may be transient. It can follow a direct insult or an interruption of blood flow to the glands. The frequency and severity of damage increases with the extent of thyroid surgery and also correlates with the incidence of post-operative hypothyroidism. Transient hypocalcaemia may be seen post-operatively and the patient may be symptomatic with signs of neuromuscular excitability such as Chvostek's sign, Trousseau's sign and carpopedal spasm. Hypocalcaemia typically occurs 1–7 days post-surgery and repeated measurement of serum calcium concentration during this period is therefore mandatory, as is close clinical monitoring of the patient for relevant signs. Mild hypoparathyroidism is managed with oral calcium supplementation but more severe cases require intravenous calcium gluconate.

Effective pre-operative preparation means thyroid storm is now exceedingly rare. It should be managed in the intensive care setting with oxygen, cooling, sedation, PTU and the use of intravenous beta-adrenergic blockers and steroids. Aspirin may exacerbate the condition by causing an increase in free thyroid hormone levels and should be avoided.

Thyroid function in the post-operative setting

The relative degree of thyroid function following thyroidectomy depends on the volume of the thyroid remnant preserved. Thyroid function in the immediate post-operative period should include measurement of fT3, fT4 and TSH. Approximately 20% of patients who are initially hypothyroid will be euthyroid within 3–6 months of surgery. Permanent hypothyroidism tends to become apparent in the first 2 years after surgery. The rate of post-operative hypothyroidism is reported to be in the range of 2–48%, with recurrent hyperthyroidism seen in 0–15% of patients. Measurement of fT3 and fT4 may be necessary in patients who have been managed for post-operative hypothyroidism because their clinical state may not be accurately reflected by serum TSH.

Specific applications of surgery

Graves' disease

In most large centres the surgical treatment of choice in Graves' disease is a total thyroidectomy. In expert hands the recurrence rate with this procedure is less than 4% but at the expense of hypothyroidism, such that patients leave hospital taking levothyroxine therapy.

Nodular thyroid disease

Toxic nodular hyperthyroidism may be treated by thyroid lobectomy or excision of a single hot nodule. The adenomas are often easy to excise and there is very little risk of either recurrence or post-operative hypothyroidism. For patients with a toxic MNG, surgery is appropriate for those with compressive symptoms, such as dysphagia and upper airway obstruction, and for those with a cosmetically unacceptable goitre. Radioiodine may cause shrinkage of the gland and may be preferable in the high-risk patient, although the rate of shrinkage is relatively slow.

KEY POINTS

THYROTOXICOSIS

Clinical features

- Classical symptoms may not be present in the elderly.

Investigations

- Measure fT4, TSH and thyroid autoantibodies in suspected hyperthyroidism. fT3 and ESR may be useful.
- Ultrasound and nuclear medicine scans should be reserved for specialist use.
- Hyperthyroidism due to thyroiditis is often self-limiting. Treat with NSAIDs +/– beta blockers.

Treatment

- Initial management should consist of antithyroid drugs +/– beta blockers and endocrine referral.
- Thionamides: warn patients of side effects. 'Block and replace' or titration regimes may be used.
- Radioiodine: safe and effective. This is the first-line treatment in the elderly and those with cardiac dysfunction.
- Surgery: used in toxic multinodular goitre, compressive symptoms, Graves' disease, eye disease.

Subclinical hyperthyroidism

Subclinical hyperthyroidism is essentially a biochemical diagnosis, though it is increasingly associated with a number of potential complications. Its detection relies on sensitive assays of TSH and it is therefore only in recent years that our understanding of this condition has widened.

AETIOLOGY

The biochemical finding of low TSH with normal fT4 and fT3 may result from an exogenous source, as a consequence of treatment with thyroxine or a raft of other drugs, or from an endogenous pathology. These include nodular thyroid disease, undetected early Graves' disease or non-thyroidal illness. Exogenous subclinical hyperthyroidism is by the far the largest group with over 20% of patients taking thyroxine having low TSH values on at least one occasion.[8, 96]

COMPLICATIONS

Long-term survival appears to be affected by suppressed TSH, contributing to an increased mortality due to cardiovascular causes.[97] The transience of TSH reduction in patients with illness or drug therapy suggests that for these individuals subclinical hyperthyroidism is likely to be of little consequence. Potential complications of subclinical hyperthyroidism are therefore likely confined to those in whom TSH suppression reflects a minor degree of thyroid hormone excess.

A specific complication associated with subclinical hyperthyroidism is that of AF, with those aged over 60 years who have an undetectable TSH harbouring a threefold increase in relative risk.[98] Subclinical disease is also associated with reductions in bone mineral density and increased fracture risk, especially in postmenopausal women.[99, 100]

MANAGEMENT

The management of subclinical hyperthyroidism remains both complex and controversial. The prevailing consensus is that in those with persistent TSH suppression and evidence for underlying thyroid disease antithyroid treatment is warranted, particularly if the subclinical hyperthyroidism is associated with cardiac disease or AF.[101, 102] As these patients are usually elderly, radioiodine is the treatment of choice unless contraindications exist. There does, however, remain a paucity of evidence for a beneficial effect of this therapy in this setting and the results of relevant randomized controlled trials are awaited.

Practically, it is prudent to repeat TFTs on a 6-monthly basis in those who have endogenous subclinical hyperthyroidism where AF and osteoporosis may have been exacerbated by excess thyroid hormone treatment.[102]

KEY POINTS

SUBCLINICAL HYPERTHYROIDISM

Aetiology

- Some causes are related to thyroid disease and its management: thyroxine therapy, previous Graves' hyperthyroidism, Graves' ophthalmopathy, nodular goitre.
- Other causes relate to non-thyroidal illness: any significant illness, therapy with drugs such as glucocorticoids, iodine-containing compounds, pregnancy.

Investigations

- Findings show low TSH with normal fT4 and fT3.

Complications

- AF
- Osteoporosis

Management

- Antithyroid treatment may be warranted

Thyrotoxicosis in the absence of hyperthyroidism

Perhaps confusingly, thyrotoxicosis may present in the absence of hyperthyroidism. In these instances thyrotoxicosis results from thyroid hormone excess originating either from the thyroid gland as a consequence of a destructive lesion or from a source outside the thyroid. The absence of hyperthyroidism refers to thyrotoxicosis occurring despite there being no increased synthesis of thyroid hormones in the thyroid gland. Consequently, a low uptake of radioiodine is seen on scintigraphy.

DESTRUCTIVE THYROIDITIS

Thyroiditis refers to any inflammatory condition of the thyroid. It may be associated with transient thyrotoxicosis during its acute phase as a consequence of disruption to the normal architecture of the thyroid gland, which results in the release of T4 and T3 from the colloid.

Classification of thyroiditis

The classification of thyroiditis is confusing but may be divided into those processes in which pain and tenderness develop, and those that do not have pain as a predominant feature (Table 61.10). Generally, the former rarely result in permanent hypothyroidism but the latter often do. Subacute, painless and postpartum thyroiditis are generally associated with only mild thyrotoxicosis which lasts only a few weeks as a consequence of the restoration of normal thyroid architecture.

Subacute granulomatous/De Quervain's thryoiditis

Clinical features

De Quervain's, giant cell or subacute thyroiditis is an uncommon cause of transient thyrotoxicosis. The typical patient is female and aged between 40 and 60 years.[103] Presentation is with pain in the region of the thyroid, often (but not always) associated with swelling. This is associated with systemic symptoms such as fever, dysphagia and malaise. The pain is a striking feature, may radiate to the ear and is worse on turning the head. On examination there is often swelling of either thyroid lobe, which may be extremely painful to palpate. Signs of thyrotoxicosis may be present, such as tachycardia, tremor and irritability. There may also be fever. It can take 8 weeks for pain to resolve and a complete resolution is seen in 6 months.

Investigations

Laboratory tests show raised inflammatory markers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and there may be a normocytic normochromic anaemia.[104] Thyroid scintigraphy with ^{99m}Tc or $^{121/131}$I shows a complete absence of uptake, although this can also occur with thyrotoxicosis factitia and iodine-induced hyperthyroidism. Histology is characteristic and lends the condition its name, with multinucleate giant cells surrounding a central core of colloid. Initial TFTs show thyrotoxicosis with a suppressed TSH and an elevated serum fT4. This reflects destruction of the thyroid follicles by the inflammatory process and release of pre-formed thyroid hormone.

Clinical course

At 12–16 weeks there may be a hypothyroid phase during which the damaged tissue is unable to generate thyroid hormone. Most patients do not require treatment with thyroxine and most are ultimately euthyroid. Rarely, hypothyroidism may be permanent. Initially, thyroid autoantibodies may be positive but again this is often transient although some retain thyroid autoimmunity for life. The course of subacute thyroiditis is shown in Figure 61.7.

Management

Treatment is supportive. Non-steroidal anti-inflammatory drugs such as aspirin and indomethacin are effective analgesics, while beta-adrenergic blockers are useful if symptomatic in the thyrotoxic phase. Rarely, the severity may necessitate high-dose oral corticosteroids

TABLE 61.10 Classification of thyroiditis

Pain and tenderness	Diagnosis	Subcategories
Yes	Subacute granulomatous thyroiditis	De Quervain's Giant cell thyroiditis
	Infectious thyroiditis	
	Radioiodine-induced thyroiditis	
No	Subacute lymphocytic thyroiditis (silent)	Postpartum thyroiditis Drug-induced thyroiditis
	Chronic lymphocytic thyroiditis	Hashimoto's thyroiditis Postpartum thyroiditis
	Fibrous thyroiditis (Riedel's thyroiditis)	
	Amiodarone-induced thyroiditis	

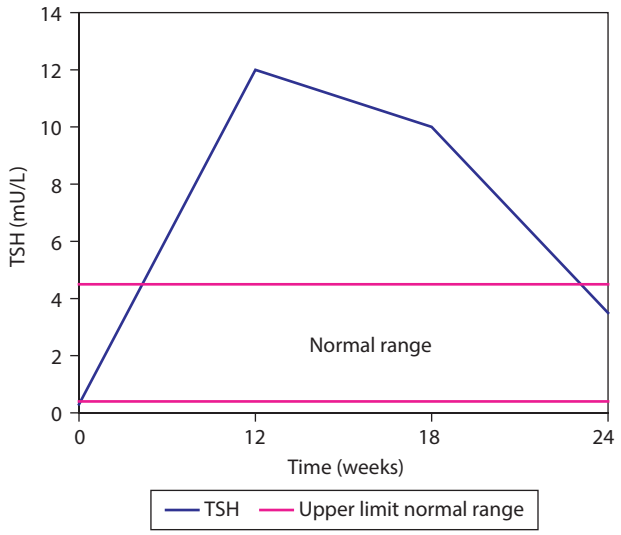


Figure 61.7 Typical course of subacute thyroiditis.

(e.g. prednisolone 30–40 mg daily) which are extremely effective in reducing the pain and swelling but must be withdrawn slowly over some months if the condition is not to recur.[105]

Aetiology

The female preponderance, seasonal incidence, geographical aggregation and raised inflammatory markers have led to a hypothesis of a viral aetiology.[106] Mumps virus, Coxsackie, influenza and adenoviruses have been implicated in the development of the disease although a viral role in the pathogenesis remains obscure.

Silent/painless thyroiditis

Painless thyroiditis can occur in the early stages of autoimmune thyroiditis. This may lead to mild biochemical hyperthyroidism and occasionally to symptomatic thyrotoxicosis. The thyrotoxicosis is generally mild and raised markers of inflammation are rarely found, in contrast to subacute thyroiditis. The thyroid is enlarged in approximately half of all patients and is not painful. Fine-needle aspirate reveals the changes associated with Hashimoto's disease and includes extensive lymphocytic infiltrate with plasma cells rather than multinucleate giant cells. Thyroid autoantibodies are often positive.

The duration of the thyrotoxic phase is around 8 weeks and symptomatic treatment with beta-adrenergic blockers may be required. There then follows a hypothyroid phase that can last for more than 6 months. In most patients, euthyroidism is eventually restored but permanent hypothyroidism is almost certain to develop over time.

Radiation-induced thyroiditis

Administration of large doses of radioiodine may result within 2 weeks in thyroiditis. There is usually a requirement only for simple analgesia and this condition tends to self-resolve within 2 weeks of its onset. Significant pain or swelling may necessitate the use of oral glucocorticoid therapy.

Iodine-induced thyrotoxicosis

Iodide-induced thyrotoxicosis (IIT) results from genetic change that leads to autonomous thyroid hormone production within sufficient numbers of thyrocytes to cause hyperthyroidism in the presence of an increased supply of iodine. This 'Jod Basedow' effect is often seen in patients with toxic MNGs in areas of iodine deficiency. It may also occur in the absence of pre-existing thyroid disease and generally resolves within 6 months. Iodine-containing contrast agents are a common source of excess iodine and confer a 0.3% risk of IIT within iodine-deficient areas.[107]

Amiodarone-induced thyrotoxicosis

Use of amiodarone may result in thyrotoxicosis by one of two ways. In patients with pre-existing thyroid disease, the high iodine content of amiodarone may induce thyrotoxicosis.[108] This is termed amiodarone-induced thyrotoxicosis (AIT) type 1. AIT type 2 arises when a destructive thyroiditis occurs as a consequence of the cytotoxic effect of amiodarone and its metabolite, desethylamiodarone. AIT is prevalent in iodine-deficient areas whereas in areas which are iodine-replete, amiodarone-induced hypothyroidism (AIH) predominates.

Withdrawal of amiodarone may result in an improvement for patients with both AIT type 1 and AIT type 2. Oral corticosteroid therapy may restore euthyroidism in those with AIT type 2 while thionamides are effective in AIT type 1. Antithyroid drugs may be given with potassium perchlorate, which inhibits thyroidal iodide uptake and consequently increases sensitivity to thionamide action.

HYPOTHYROIDISM

Definitions

Hypothyroidism refers to the insufficient production and secretion of thyroid hormones from the thyroid gland. It may occur due to a disturbance within the thyroid gland itself (**primary hypothyroidism**) or within the hypothalamic–pituitary–thyroid axis (**secondary hypothyroidism**).[109] The term **myxoedema** is not synonymous with hypothyroidism and refers to the accumulation of glycosaminoglycans occurring in severe hypothyroidism. These hydrophilic substances are deposited within the dermis, leading to induration of the skin and the characteristic facial features of hypothyroidism. The term **hypothyroxinaemia** may be used to refer to low serum fT4 concentrations in the presence of normal levels of TSH (**Box 61.7**).

BOX 61.7 Key definitions in thyroid hormone deficiency (hypothyroidism)

Hypothyroidism	*Insufficient production and secretion of thyroid hormone*
Primary hypothyroidism	*Pathology of the thyroid gland itself*
Secondary hypothyroidism	*Pathology of the hypothalamic–pituitary–thyroid axis*
Myxoedema	*Accumulation of glycosaminoglycans in the dermis*
Hypothyroxinaemia	*Low serum fT4 concentrations in the presence of normal TSH concentrations*

Epidemiology

Like hyperthyroidism and other autoimmune conditions, hypothyroidism is more common in women, amongst whom its prevalence is estimated at 2%.[1] This compares to 0.2% of men.[1] Incidence peaks in the 40–50 years age group so that prevalence in women aged over 65 rises to 5–10%.[97] Juvenile hypothyroidism is nevertheless not uncommon. Neonatal hypothyroidism, which if untreated results in severe intellectual impairment, occurs in around 1 in 4000 births and is routinely screened for in the postnatal period in the UK.[110]

Aetiology

The causes of hypothyroidism are outlined in Table 61.11. The most common cause in areas replete with iodine is chronic autoimmune hypothyroidism, otherwise termed Hashimoto's thyroiditis.[111, 112] Hypothyroidism may also be an iatrogenic phenomenon, resulting either from thyroidectomy, use of radioiodine therapy or external beam irradiation of the neck.[32, 112, 113] Worldwide, the most common cause of hypothyroidism is iodine deficiency.[114]

Clinical manifestations

Insufficiency of thyroid hormone affects almost every organ system in the body. The effects of hypothyroidism can be broadly categorized into those relating to the generalized slowing of all metabolic processes and those resulting from the tissue accumulation of glycosaminoglycans, as summarized in Table 61.12. Among other features, the slowing of metabolic processes results in fatigue, cold intolerance and weight gain. Characteristic features of hypothyroidism such as coarse dry skin, hair loss and doughy peripheral oedema relate to glycosaminoglycan accumulation. A low threshold for thyroid function testing is necessary, given that few patients have all signs and symptoms of hypothyroidism. There is, however, no consensus for routine screening of thyroid function.

SYMPTOMS

The onset of symptoms may be insidious and go unrecognized, such that severe myxoedema may result. The typical patient complains of lethargy and fatigue, and these complaints, plus the accompanying apathy and listlessness, mean that the ability to work is impaired. There may be a slow increase of weight despite a reduction in appetite and constipation is a common feature. Cold intolerance is typical with the patient wearing multiple layers of clothes at initial consultation.

Menstrual periods may be heavy and a desired conception elusive. Myopathy may cause difficulty in walking upstairs or rising from a chair, and numbness and paraesthesia in the hands may develop as carpal tunnel syndrome results from peripheral oedema. Occasionally, neuropsychiatric complications may result and 'myxoedema madness', though now largely confined to historical literature, was previously described.

SIGNS

There may be a husky voice incorrectly attributed to laryngitis but which actually results from oedema of the vocal cords. Women may complain of dry coarse hair and brittle nails. Peripheral and facial oedema is also seen, as is bradycardia, the presence of a goitre and slow-relaxing tendon reflexes. The rare but life-threatening condition of

TABLE 61.11 Causes of hypothyroidism

Primary			Secondary	
Associated with goitre (TSH raised, T4 low)	**Not associated with goitre (TSH raised, T4 low)**	**Self-limiting**	**Hypothalamic (TSH low, T4 low)**	**Pituitary (TSH low, T4 low)**
Hashimoto's thyroiditis (chronic thyroiditis) Iodine deficiency (affects 800 million worldwide) Inherited defects of biosynthesis Maternal transmission; e.g. antithyroid agents	Atrophic thyroiditis Iatrogenic; e.g. radioiodine, surgery, neck irradiation Congenital anomaly; e.g. thyroid agenesis Drug-induced; e.g. amiodarone, lithium, iodides, phenylbutazone	Transient thyroiditis; e.g. subacute or silent Postpartum thyroiditis Iatrogenic; e.g. overtreatment with antithyroid medication	Congenital; e.g. lack of TRSH Infiltrative; e.g. sarcoidosis, tuberculosis, primary or metastatic malignancy Infective; e.g. encephalitis	Congenital; e.g. lack of TSH Panyhypopituitarism; e.g. pituitary tumour, cranial irradiation, infection, inflammation

TABLE 61.12 Manifestations of hypothyroidism

	Clinical manifestations					
	General	**Skin**	**Gastrointestinal**	**Cardiovascular**	**Reproductive**	**Neurological**
Symptoms	Weakness/fatigue Decreased appetite Weight gain Coarse facial features Cold intolerance Peripheral oedema	Coarse, dry skin Pale skin/flush (peaches and cream) Loss/drying of hair	Decreased appetite Weight gain Constipation	Peripheral oedema	Menorrhagia Ovulatory failure Galactorrhoea	Slow/hoarse speech Intellectual impairment Carpal tunnel syndrome Neuropsychiatric problems
Signs	Characteristic facial features Goitre	Pale, cool skin Peripheral/facial oedema		Bradycardia		Slow-relaxing tendon reflexes Hoarse voice

myxoedema coma can occur in hypothyroidism, particularly in older patients, and can be precipitated by infection, trauma or cold.

Diagnostic evaluation

Thyroid function testing may help support clinical suspicion of hypothyroidism. Low serum fT4 concentration is the hallmark of reduced thyroid function.[115] This is usually associated with a raised TSH concentration, though this may be normal or low in secondary hypothyroidism. Concentrations of fT3 tend to be decreased but may be normal. Microsomal antibodies may be significantly raised in cases of autoimmune hypothyroidism. Other non-specific changes are seen, including a normochromic normocytic anaemia and an atherogenic lipid profile consisting of raised serum levels of cholesterol, triglycerides and low-density lipoprotein (LDL) in addition to lowered high-density lipoprotein (HDL). Reduced negative feedback from thyroid hormones and a consequent excess of thyrotropin-releasing hormone stimulates excess production of prolactin from the anterior pituitary gland so that serum levels may be raised. Laboratory investigations and findings are summarized in Table 61.13.

Ultrasound evaluation of the thyroid may provide support in determining the cause of hypothyroidism although should not be performed routinely. Low echogenicity and gross inhomogeneity are seen in autoimmune thyroiditis. Use of colour-flow Doppler may identify greater vascularity in autoimmune thyroiditis than in the atrophic variant of the disease. The identification of nodular tissue should raise suspicion of coexisting adenomas or malignancy.

Specific conditions associated with hypothyroidism

CHRONIC AUTOIMMUNE HYPOTHYROIDISM (HASHIMOTO'S THYROIDITIS)

Seen in 3.5 per 1000 women per year and fewer than 1 per 1000 men per year, this condition is in many respects the archetypal autoimmune disease.[116] In addition to occurring more commonly in females, it runs in families where Graves' disease may feature along with other autoimmune conditions, such as vitiligo, pernicious anaemia, rheumatoid arthritis and type 1 diabetes mellitus.[112] It is more common in older women yet it can occur in infants as young as 2 years of age and it is the major cause of hypothyroidism in children.

The pathogenesis of this condition is well understood.[117] Histology reveals diffuse lymphocytic infiltration of the thyroid gland and the presence of circulating thyroid autoantibodies, reflecting the direct cellular injury induced by cytotoxic T-cells and the role of humoral factors.

Although patients have high circulating antibodies to thyroid microsomes and to thyroglobulin, these are not thought to have functional activity. Histologically, the gland is infiltrated with lymphocytes and areas of follicular destruction and fibrosis may be evident.[117] Enlarged epithelial cells with oxyphilic changes in the cytoplasm and Askenazy cells are commonly found in this condition (Figure 61.8).

Initially, the thyroid hypofunction may be subclinical, but it may become overt with a rate of developing hypothyroidism of around 5% per year. A slowly growing goitre may have been found on examination or noted by the patient or a family member.

The typical goitre is moderate in size and smooth. Although both lobes are affected, the gland may appear asymmetrical. The presence of the goitre may predate the development of overt hypothyroidism and, generally, the goitre remains static or may decrease in size. Some patients present without a palpable goitre and are said to have atrophic autoimmune thyroiditis, which is thought to represent the end point of Hashimoto's thyroiditis.[111]

IATROGENIC HYPOTHYROIDISM

This may be seen as a consequence of surgery, treatment with radioactive iodine or external beam radiotherapy, such as that used in the management of head

TABLE 61.13 Laboratory investigations in suspected hypothyroidism

Investigation		Results in hypothyroidism	
		Primary	Central
Thyroid function	TSH	↑	↓/↔
	fT4	↓	↓
	fT3	↓/↔	↓/↔
Immunology		Positive thyroid microsomal autoantibodies	
Biochemistry		Raised serum cholesterol, triglycerides, LDL Lowered HDL	
Endocrine		Raised serum prolactin	
Haematology		Normochromic normocytic anaemia	

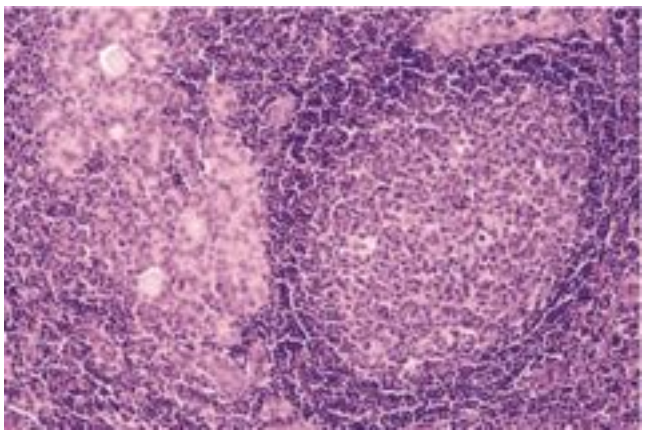


Figure 61.8 Histology of Hashimoto's thyroiditis. There is a dense interstitial lymphocytic infiltrate, with secondary germinal centre formation, enveloping small colloid-depleted follicles. These are lined with plump cuboidal oxyphil (Askanazy or Hürthle) cells possessing characteristic copious pink granular cytoplasm.

and neck malignancy. Hypothyroidism may occasionally result from overtreatment of hyperthyroidism with antithyroid medication, but with close monitoring this is not common.

Thyroidectomy

Hypothyroidism would become evident in all patients who have undergone total thyroidectomy at around 2–4 weeks without treatment. Thyroid hormone replacement should therefore be commenced in these patients prior to their discharge from hospital. Subtotal thyroidectomy may also result in hypothyroidism, with most patients becoming so within a year.

Radioiodine therapy

The majority of patients treated with 400–600 MBq of radioiodine will develop hypothyroidism.[18, 113] This may be transient, resulting from radiation thyroiditis some 4–6 weeks after treatment, or permanent. Sustained hypothyroidism may not ensue until months or even years after therapy.

External beam neck irradiation

Radiotherapy given to the neck may result in both hypothyroidism and an increased risk of thyroid malignancy, especially in children and adolescents.[113]

For patients who have had more than 25 Gy there may be a slow-onset dose-dependent development of hypothyroidism. Such patients should be carefully monitored for both the hypothyroidism, which can initially be subclinical, and for nodular thyroid disease which may herald a thyroid malignancy.

Tyrosine kinase inhibitor therapy

Small molecular tyrosine kinase inhibitors (TKIs) are used across a spectrum of disorders and have been associated with thyroid dysfunction.[118, 119] The vascular endothelial growth factor receptor (VEGFR) disruptor sunitinib has, for instance, been linked to both hypothyroidism and thyrotoxicosis. Other TKIs have also been implicated in thyroid dysfunction including Imatinib, which targets the Philadelphia chromosome in chronic myeloid leukaemia, and motesanib, which is used in differentiated thyroid carcinoma.[120]

IODINE DEFICIENCY

Iodine deficiency remains the most common cause of hypothyroidism and goitre worldwide.[43, 114] Iodine is present in the body in only minute amounts and must therefore be sourced from the diet. When iodine requirements are not met, thyroid hormone synthesis is impaired and goitre follows due to increased secretion of TSH, which is released to maximize utilization of available iodine and acts to stimulate the thyroid. Goitres may be present from young adulthood and can become sufficiently large to cause obstructive symptoms. Other iodine deficiency disorders include mental retardation and neonatal cretinism, a combination of intellectual impairment, ataxia, coarse facies and deaf mutism. This has a substantial effect on mental development.[121]

It is estimated that iodine intake is insufficient in 36.5% of school-age children and 35.2% of the general population worldwide. South-east Asia, Africa and the Western Pacific are the most affected by iodine deficiency whereas the addition of iodine to salt in the USA and, to a lesser extent Europe, results in sufficient dietary intake of iodine for the majority of the population. Mild-to-moderate iodine deficiency is nevertheless recognized in the United Kingdom, where salt iodization is not commonplace.[43] Diets high in goitrogens, such as cassava and some soya beans, can exacerbate complications of iodine deficiency.

NEONATAL HYPOTHYROIDISM

This is routinely screened for during the postnatal period in iodine replete regions.[109] It may be caused by inherited defects in thyroid hormone synthesis, transplacental transmission of anti-TSH antibodies causing transient neonatal thyroid underactivity or thyroid gland agenesis and dysgenesis.

CENTRAL HYPOTHYROIDISM

Lack of hypothalamic thyrotropin-releasing hormone or pituitary TSH may lead to hypothyroidism, although central hypothyroidism accounts for less than 1% of all cases of hypothyroidism. The commonest cause is a tumour in the hypothalamic or pituitary region and the surgery or radiotherapy used to treat them.[122] Such central causes may be distinguished from primary hypothyroidism by a normal or low-serum TSH concentration that is inappropriate given a low serum fT3 and fT4 concentration. Approximately a third of patients with central hypothyroidism display marginal elevation of TSH, which is bio-inactive.

Patients with a pituitary adenoma may have other features of hypopituitarism, such as hypogonadism and hypoadrenalism. These may mask the symptoms of thyroid hormone deficiency. Patients with central hypothyroidism should be referred for specialist consultation.

Management of hypothyroidism

Levothyroxine is the drug of choice for the treatment of hypothyroidism.[123, 124] It is absorbed from the upper small bowel with approximately 80% efficiency and is a prohormone which is deiodinated in peripheral tissues to the active hormone T3. T3 has a tenfold higher affinity than T4 for thyroid hormone receptors. Treatment is provided with the aim of returning the patient to a euthyroid state both clinically as judged from symptoms, and biochemically as judged from serum TSH estimations.

ADMINISTRATION OF LEVOTHYROXINE

At 7 days, the half-life of levothyroxine is long enough to allow for daily or even weekly dosing if compliance is an issue. The average daily dose is around 125 µg but variation exists and typical doses required to achieve

euthyroidism range between 100 µg and 150 µg. In those less than 50 years of age with no evidence of ischaemic heart disease, a moderate dose (1.6 mcg/kg or typically 100 µg) may be started immediately. In older patients, or those with known cardiac disease, a starting dose of 25 µg is prudent due to the risk of exacerbating or precipitating cardiac disease as a consequence of the rise in cardiac output associated with initiation of therapy. Increments of 25 µg can be added every 4–6 weeks until TSH concentrations are within the normal range.

Due to the long half-life of thyroxine, 4–6 weeks should elapse before measuring TSH concentration after initiating therapy or after dose adjustment. Once stable, serum TSH needs to be checked on an annual basis to ensure ongoing compliance.[109]

SPECIFIC CONSIDERATIONS WHEN PRESCRIBING THYROXINE

Central hypothyroidism

In those with central hypothyroidism, it is imperative that hypoadrenalism be excluded before initiating thyroxine therapy. An adrenal crisis may be precipitated if hypoadrenalism is not treated before thyroxine therapy is commenced. In central hypothyroidism, the serum TSH concentration is of no value in monitoring therapy, thus dose adjustments should be made on serum fT4 and fT3 concentrations alone, aiming to keep serum fT4 in the upper half of the reference range.

Elderly patients

Thyroxine therapy should be started at a dose of 25–50 µg daily and increased every 4 weeks until stable. Overtreatment, resulting in a suppressed TSH concentration, should be avoided due to the risk of precipitating AF.

Pregnant women

Women need more thyroid hormone during pregnancy and those with pre-existing hypothyroidism cannot increase T4 and T3 secretion in the same manner as women who do not have hypothyroidism. Hypothyroid women need around 40% more thyroxine in pregnancy and the dosage should be increased upon finding of a positive pregnancy test. Thyroid function tests should be monitored using pregnancy and gestation specific reference ranges preferentially. Repeat measurements should be undertaken 4-weekly during the first trimester and once per trimester thereafter. Most international guidelines recommend treating with levothyroxine to keep serum TSH below 2.5 mIU/L prior to and during pregnancy.[124–126]

T3 THERAPY

A minority of patients feel that their symptoms of hypothyroidism are not controlled on thyroxine therapy despite normal concentrations of TSH and T4. Some choose to take T3 in addition to or instead of thyroxine, although due to its rapid absorption and short half-life it must be taken three times a day and fluctuations in thyroid hormone levels exist. Current national and international guidance does not recommend the use of T3 monotherapy or T3/T4 combination therapy in the management of hypothyroidism based on the lack of evidence supporting these treatment strategies.[127, 128] Similarly, the use of desiccated thyroid extract is not advisable.[129]

KEY POINTS

HYPOTHYROIDISM

Clinical features

- Manifestations presented are those of the slowing of metabolic processes and tissue accumulation of glycosaminoglycans.

Investigations

- Low serum T4 and raised TSH is seen in primary hypothyroidism.
- Low serum T4 with normal or suppressed TSH are seen in central hypothyroidism.
- A pro-atherogenic lipid profile and a normochromic normocytic anaemia are seen in chronic disease.

Treatment

- Levothyroxine is the drug treatment of choice.
- A lower starting dose may be required in older patients.
- There is no evidence to suggest an advantage from T3 therapy.

Subclinical hypothyroidism

Subclinical hypothyroidism is a biochemical diagnosis made where a raised TSH is seen in conjunction with a normal fT4 concentration.

EPIDEMIOLOGY

It is common, affecting 7–8% of women and 2–4% of men. The prevalence rises with age to approximately 15% in women over 60.[130] It is also more common in those with other autoimmune conditions.

AETIOLOGY

Subclinical hypothyroidism may be endogenous or iatrogenic, resulting from either previous radioiodine treatment or surgical resection of the thyroid gland. Around 60% of women with subclinical hypothyroidism have positive antibodies to thyroid peroxidase.[131] Prospective studies have confirmed that those with both positive thyroid autoantibodies and elevated TSH concentrations are at risk of developing overt hypothyroidism at a rate of around 5% per year, although this figure is likely to be greater in older patients.

MANAGEMENT

Given the potential risks to bone and cardiovascular health of overtreatment with thyroxine, there remains controversy as to who should be treated and at what point.

Recent guidelines have highlighted evidence linking raised TSH and cholesterol but otherwise state that data for a clear benefit to treatment are lacking. Many clinicians would opt to treat in the presence of symptoms and serum TSH concentration of greater than 10 mU/L as well as positive antibodies, as a result of the high risk of progression to overt hypothyroidism. For asymptomatic patients with a modestly raised TSH (below 10 mU/L) or with a low or negative titre of microsomal antibodies, retest on a 6-monthly basis is advised.[132]

KEY POINTS

SUBCLINICAL HYPOTHYROIDISM

Aetiology

- This is an autoimmune condition.
- It is iatrogenic: previous radioiodine treatment, surgical resection.

Investigations

- Raised TSH with normal fT4 and fT3 is seen.

Complications

- These are unclear.
- There is a possible association between raised TSH and cholesterol.

Management

- Best practice is unclear: treat if serum TSH >10 mIU/L or during pregnancy.

THYROID DISEASE IN PREGNANCY

Thyroid dysfunction is relatively common in pregnancy, during which both overt and subclinical disease are associated with adverse outcomes.[125] Foetal development is dependent on maternal thyroid hormone delivered via the transplacental route until around 18 weeks of gestation, although maternal thyroid hormone transfer continues up to delivery. Thyroid hormones are known to influence foetal size and the maturation of tissues, in addition to uteroplacental development. The foetal brain additionally responds to thyroid hormones from 5 weeks of gestation. Euthyroidism is therefore essential throughout pregnancy in order to minimize risk to the foetus.

Physiological changes to the thyroid axis during pregnancy have been extensively described previously.[133] Maternal TSH is seen to decline during the first trimester but resolves to pre-pregnancy levels by the end of gestation. Maternal fT4 concentrations decline throughout pregnancy. Gestation-specific ranges, which are both population- and age-specific, should therefore be used by the clinician caring for a pregnant patient with thyroid disease.

Hyperthyroid states in pregnancy

The immunological changes associated with pregnancy and delivery can affect thyroid status in different ways. Those with pre-existing disease may find symptoms are aggravated or ameliorated at different times during the pregnancy.

Postpartum, around 5–10% of women develop thyroid dysfunction. The risk is higher in those who have positive thyroid antibodies, Type 1 diabetes mellitus (25%), a family history of thyroid disease or another coexisting autoimmune condition.[125] Of those who develop postpartum thyroid dysfunction, around one-third have postpartum thyroiditis. The remainder may present with either Graves' disease or Hashimoto's thyroiditis. In those with biochemical and clinical thyrotoxicosis developing later than 3–6 months postpartum, Graves' disease is more likely, and in these cases the hyperthyroidism will be sustained.[125]

Radioisotope uptake measurements are the investigation of choice and can help to distinguish between postpartum thyroiditis and Graves' disease. The distinction is important, as treatment choices differ according to the aetiology of thyroid dysfunction. Those with postpartum thyroiditis will show reduced uptake on scintigraphic scanning whereas those with Graves' disease will show elevated uptake. Breastfeeding should be avoided for 24 hours if ^{99m}Tc is used.

POSTPARTUM THYROIDITIS

This commonly presents with symptoms of thyrotoxicosis at around 12 weeks post delivery, followed by a period of hypothyroidism at around 3–6 months. Histologically, there is a destructive thyroiditis with a florid lymphocytic infiltrate seen at around 16 weeks in those who are antibody-positive. In some women, only the hypothyroid phase is evident and eventually there will be a return to a euthyroid state. Patients may be managed symptomatically with propranolol during the thyrotoxic phase if necessary. Treatment of the hypothyroid phase may be needed in around a third of women and T4 may be necessary for up to 12 months.[134]

Long term, patients who have experienced postpartum thyroiditis are at risk of further episodes in subsequent pregnancies. About 25% of women will develop permanent hypothyroidism, and recurrent postpartum thyroiditis is seen in up to 80% of subsequent pregnancies. Specialist monitoring and annual monitoring of TFTs are essential.

HYPEREMESIS GRAVIDARUM

Transient thyrotoxicosis may be seen in hyperemesis gravidarum. It is likely to arise as a consequence of the shared alpha subunit of beta-HCG and TSH, with high levels of HCG in hyperemesis gravidarum causing stimulation of the TSH receptor. Around 60% of women with hyperemesis gravidarum have a raised serum fT4 concentration with a suppressed serum TSH. Management is supportive and antithyroid medication should be avoided.

Thyrotoxicosis resulting from hyperemesis gravidarum may be distinguished from that occurring as a consequence of Graves' disease by a negative family history, a lack of any other autoimmune illness and negative thyroid

antibodies (anti-TSH-receptor antibodies in particular). Physical signs typically associated with Graves' disease, such as a diffuse goitre, will also be absent.

GRAVES' DISEASE

This accounts for around 90% of cases of thyrotoxicosis observed in pregnancy and around 1 in every 500 women are affected.[134] Graves' disease may contribute to menstrual irregularities, difficulties in conception and an increased rate of miscarriage. In those who do conceive, the recognition and effective management of Graves' is crucial given that untreated hyperthyroidism is associated with miscarriage, premature labour, low birthweight and pre-eclampsia.

Graves' disease may rarely develop *de novo* in pregnancy but diagnosis may be delayed as signs and symptoms may be wrongly attributed to physiological changes occurring in pregnancy, such as increased metabolic rate, increased cardiac output, heat intolerance and mood changes. Other symptoms may include hyperemesis gravidarum, muscle fatigue and, occasionally, cardiovascular problems such as pregnancy-induced hypertension or high output cardiac failure.

Treatment of thyrotoxicosis in pregnancy seeks to achieve rapid biochemical euthyroidism while alleviating symptoms.[92, 125, 126] Specific beta-adrenergic blocking agents may be used as adjuncts but the mainstay of treatment is antithyroid medication. Radioiodine cannot be used as it is contraindicated in pregnancy. Propylthiouracil is preferred to carbimazole in the first trimester as it is associated with fewer teratogenic effects. If antithyroid drugs are continued during the second and third trimester, carbimazole remains the drug of choice in view of fears of liver function abnormalities with propylthiouracil treatment. Antithyroid drugs are excreted in breast milk and babies from mothers taking doses of carbimazole of 20 mg daily or more while breastfeeding should have 4-weekly thyroid function testing.

The presence of circulating anti-TSH-receptor antibodies in pregnancy may result in foetal thyrotoxicosis due to transplacental transfer. Current guidance recommends the determination of TSH-receptor antibody concentrations at 20 weeks' gestation and close monitoring of those with significantly raised levels.[125, 135]

Joint management with the endocrinologist, obstetrician and paediatrician is important as there is a risk of foetal and neonatal thyrotoxicosis indicated by low birthweight, irritability and tachycardia.

Hypothyroid states in pregnancy

Overt hypothyroidism is associated with both anovulation and first trimester abortion. It is therefore unlikely to present at conception or during early pregnancy though it is seen in approximately 0.2–1% of women during the first trimester. If untreated during pregnancy, hypothyroidism confers a two- to threefold increased risk of spontaneous miscarriage, pregnancy-induced hypertension and pre-eclampsia, low birthweight (which is largely a consequence of prematurity) and perinatal mortality. There is additional data to link maternal hypothyroidism with an increased incidence of neurodevelopmental defects.[135]

OVERT HYPOTHYROIDISM

Pre-conception thyroid hormone replacement may offer protection against early pregnancy hypothyroidism. During pregnancy the requirement for thyroid hormone increases due to weight gain, transfer of T4 to the foetus and raised concentrations of thyroxin binding globulin. Gastrointestinal absorption is also known to decrease. An increased dose of thyroxine may be required as early as 4 weeks' gestation. Treatment should target the prevention of hypothyroidism and it is important patients are counselled prior to or during early pregnancy in order to ensure compliance with therapy. It is prudent to counsel women to double their dose of thyroxine on 2 days each week should they have a positive pregnancy test, given that a routine antenatal visit does not occur until 10–12 weeks of gestation.

Between 40% and 70% of patients will require further dose adjustment even following this empirical dose increase. Most clinicians would measure TFTs around 4–6 weeks' gestation, 4 weeks after any increase in dose of T4 and at least once per trimester. Levothyroxine dosage can be reduced to pre-pregnancy levels 2 weeks after delivery with TFTs reviewed after 6 weeks in order to ensure adequate thyroid hormone replacement. Dose adjustment of levothyroxine should be based on serum TSH as it demonstrates less inter-individual variation than fT4 concentrations. Some authors do, however, advocate the use of fT4 concentrations in light of the key role of T4 in determining foetal brain development. Ingestion of iron supplementation and antacid for gastroesophageal reflux may affect thyroxine absorption and further complicate dosing.

Obstetricians advocate managing pregnancies complicated by hypothyroidism as high risk. As such, aspirin is advised for pre-eclampsia prophylaxis in addition to uterine artery Doppler studies to screen for malplacentation. Routine observations should be undertaken frequently to assess for pre-eclampsia.

SUBCLINICAL HYPOTHYROIDISM

Rates of subclinical hypothyroidism in pregnancy are dependent on the iodine status of the population.[136] A recent meta-analysis of studies which included subclinically hypothyroid populations demonstrated a significant increase in risk of pregnancy loss (including miscarriages, stillbirths and perinatal deaths), pre-term delivery (OR 1.3; 95% CI 1.05–1.60), placental abruption (OR 2.16; 95% CI: 1.15–4.06) and breech presentation at term.[137] Raised serum TSH is also associated with breech presentation, reduced external cephalic version success rate and an increased incidence of neurodevelopmental defects.[138–141]

There is a paucity of evidence relating to the management of subclinical hypothyroidism either during pregnancy or in those attempting to conceive. Interestingly, treatment

of subclinical hypothyroidism favours increased live birth rates in subjects undergoing assisted conception. Many endocrine professional bodies advocate the use of levothyroxine therapy, ideally prior to conception, given that the risk ratio is highly favourable with the potential risk of hyperthyroidism minimized by regular monitoring of thyroid function. Recent ATA guidelines support treatment only in TPO antibody-positive women but are relatively undecided on the merits of treatment in TPO antibody-negative disease. The American Congress of Obstetricians and Gynecologists does not endorse recommendations for the treatment of subclinical hypothyroidism in pregnancy.

KEY POINTS

THYROID DISEASE IN PREGNANCY

- Joint management with an endocrinologist, obstetrician and a paediatrician is important.
- Hyperemesis may be associated with thyrotoxicosis.
- Graves' disease should be managed with pregnancy – propylthiouracil is preferable to carbimazole.
- TSH should be maintained at <2.5 mLU/L in hypothyroid women.
- Postpartum thyroiditis is common.

EUTHYROID GLANDULAR ENLARGEMENT

Classification

The term 'goitre' refers to a thyroid gland which exceeds the upper limit defined for normal volume. This may simply be described as 18 mL for women and 25 mL for men but assessment of thyroid size should also respect age-specific criteria for normal values. Thyroid enlargement may be diffuse or may result from the presence of one or multiple thyroid nodules. It may additionally occur in the context of euthyroidism, hypothyroidism or hyperthyroidism. This section will review the enlargement of the thyroid gland which commonly occurs in the absence of aberrant hormone concentrations.

Epidemiology

Enlargement of the thyroid gland is common. The Wickham Survey identified the presence of a palpable goitre in 15% of persons within an iodine-replete region and a visible goitre in 7%, supported by data from the US Framingham study that identified a 5–10% lifetime risk of developing a thyroid nodule.[6, 142] The prevalence of goitre is closely related to dietary intake of iodine. This is such that, while 35.9%of the 3941 participants without known thyroid disease in the Study of Health in Pomerania had a goitre in its first phase, goitre was significantly rarer in the 5-year follow-up as iodine intake increased.[143, 144]

The advent of high-resolution ultrasound has led to reported rates of goitre of between 19% and 67% in imaged individuals, even if the gland is normal on palpation. Higher frequencies have been noted in women and the elderly.[2]

Aetiology

Thyroid enlargement occurring in the absence of thyroid hormone excess or deficiency may be diffuse or nodular. The potential for malignancy is of concern, although thyroid cancer remains rare and accounts for only 1% of all new malignant disease.[145] Papillary and follicular thyroid cancers are together termed differentiated thyroid cancers and represent 72–85% and 10–20% of thyroid cancers respectively.[146] The remainder comprise of follicular (10–20%), medullary (1.7–35%), anaplastic (<1%) and other carcinomas (1–4%). Benign and malignant causes of nodular thyroid enlargement are summarized in Table 61.14.

Risk factors for the development of thyroid cancer include exposure to head and neck irradiation in infancy and childhood.[147] Increased rates of childhood papillary cancer have been noted in Belarus and Ukraine and are thought to reflect the Chernobyl nuclear reactor accident.[148]

Women are disproportionately affected by thyroid cancer with data suggesting a prevalence of 1.5%, which compares to 0.5% for men. Conversely, the presence of a thyroid nodule in a man is more likely to represent an underlying carcinoma.[2, 149] This is explained by the equal rates of thyroid carcinoma for men and women despite a 5–10 times greater prevalence of nodular thyroid disease in females. Those at the extremes of age are also at most risk of harbouring thyroid cancer.[149]

Survival rates are favourable with percentage cancer deaths of 0.21% and 0.3% for men and women respectively.[150] The incidence of thyroid cancer is rising rapidly and this is, at least in part, due to increased detection of

TABLE 61.14 Causes of nodular thyroid enlargement

	Malignant	
Benign	**Follicular or C-cell origin**	**Malignancy of other origin**
Follicular adenoma	Papillary carcinoma	Thyroid lymphoma
Hürthle cell adenoma	Follicular carcinoma	Malignancy metastatic to the thyroid
Colloid cyst	Hürthle cell carcinoma	
Simple/haemorrhagic cyst	Medullary thyroid carcinoma	
Lymphocytic thyroiditis	Anaplastic carcinoma	
Granulomatous thyroiditis		
Infectious processes		

incidental thyroid cancers.[150] Clinicians must increasingly respond to the challenge of identifying the minority of patients with thyroid cancer who require surgical intervention and additional therapies.

Clinical manifestations

Goitre development is asymptomatic in the majority of cases but is often visible once thyroid volume exceeds 40 mL. Patients may note that they have changed their collar size or stopped wearing necklaces. As many as 30–85% of patients are reported to develop mechanical compression of the trachea and/or the oesophagus but the majority remain asymptomatic.[151] In those who do develop obstructive sequelae, the location of the goitre may predict symptomatology. Retrosternal goitres often result in dysphagia, for example, whereas retrotracheal goitres are more commonly associated with dyspnoea.

Diagnostic evaluation

History and physical examination are key to the evaluation of suspected goitre and may suggest thyroid carcinoma in some instances.[149] History should focus on the presence of mechanical symptoms, the temporal nature of thyroid enlargement, the presence of risk factors for malignancy such as previous head and neck irradiation, and family history relevant to a potential hereditary cancer syndrome.

The neck and upper thorax must be assessed on examination and palpation undertaken to determine goitre size and the presence of nodularity. The presence of signs suggestive of excess or insufficient thyroid hormone should be noted, as should evidence of mechanical compression.[151]

Features which strongly suggest the presence of thyroid carcinoma include rapid enlargement during hormonal therapy, vocal cord paralysis, ipsilateral lymphadenopathy and the presence of a hard, fixed nodule (**Table 61.15**).[2, 149] These are, however, absent in the vast majority of cases and thyroid enlargement as a consequence of malignancy is indistinguishable from enlargement of benign aetiology in many cases. There is in addition considerable inter- and intra-observer variation regarding assessment of the size and morphology of the thyroid. A potential consequence is the increase in the use of ultrasound imaging to assess for and characterize thyroid nodularity.

Investigations in thyroid enlargement

LABORATORY INVESTIGATIONS

Recent guidelines published by both the American Thyroid Association (ATA) and the British Thyroid Association (BTA) advocate determination of the serum TSH concentration during the initial evaluation of a patient with a thyroid nodule.[152, 153] Thyroid function tests must also be utilized to exclude thyroid dysfunction. Raised TSH should result in assessment of fT4 to identify either subclinical or overt hypothyroidism. Similarly, measurement of fT3 and fT4 should be undertaken in the presence of a suppressed TSH in order to delineate overt from subclinical hyperthyroidism or T3 toxicosis.

However, while virtually all patients with thyroid carcinoma are euthyroid, TSH may be suppressed in cases of malignancy. Interestingly, TSH concentration is increasingly recognized as an independent risk factor for thyroid malignancy. In a study of 1500 patients investigated with fine-needle aspiration cytology (FNAC) following presentation with thyroid enlargement, an increased odds ratio for malignancy was noted in those with serum TSH >0.9 mU/L.[154] Subsequent analysis of 843 patients undergoing resection of likely thyroid malignancy confirmed an increased likelihood of thyroid cancer with higher serum TSH concentration.[155] Levels of serum TSH were also found to be greater in patients with advanced malignancy (stage III/IV disease) compared with those with stage I or II disease.[156]

Serum levels of thyroglobulin are influenced by the size of a thyroid gland and factors such as iodine intake. Routine assessment of serum thyroglobulin is therefore not recommended for the initial evaluation of thyroid nodules by both the ATA and the BTA as it is neither a sensitive nor a specific diagnostic test in this context.[152, 153] Serum thyroglobulin measurements either under TSH suppression or stimulated do, however, remain the gold-standard tumour marker in patients with proven thyroid cancer.

There remains considerable controversy over the measurement of other potential serum markers of thyroid malignancy. Antithyroid peroxidase measurements are, for instance, undertaken by more than half of clinicians, yet they are found in approximately 10% of the general population and may reflect a coexistent autoimmunity rather than directly relate to the thyroid nodule.[2] The immunometric calcitonin assay is a sensitive marker for

TABLE 61.15 Elements suggestive of thyroid carcinoma in a patient's clinical workup

History	Clinical examination	Imaging
Family history	Hard, fixed nodule	Hypoechogenicity
Male	Vocal cord paralysis	Solid nodule
Extremes of age	Ipsilateral lymphadenopathy	Microcalcification
Head and neck irradiation in infancy/childhood		Irregular margins
Previous radiation exposure		Increased intranodular flow
Compressive symptoms		Increased anterior–posterior dimension
Nodular enlargement during hormonal therapy		Invasion
		Lymphadenopathy

detection of medullary thyroid cancer, albeit with a high false-positive rate as a consequence of heterophilic antibodies. Calcitonin levels of greater than 10 pg/mL are very sensitive for the detection of medullary thyroid cancer and should elicit further investigation.[157] Despite evidence to suggest that use of calcitonin is cost-effective and a useful tool in the evaluation of thyroid nodules, its use is not widely recognized in the US and is more commonplace within Europe.[158]

DIAGNOSTIC IMAGING

The imaging modality used in the assessment of thyroid enlargement is at least partly dependent on the clinical scenario. There is a growing array of options for the clinician, including ultrasonography, scintigraphy, computed tomography (CT) scanning, magnetic resonance (MR) imaging and, most recently, positron emission tomography (PET).

Ultrasound

The most widely used imaging modality in the detection and evaluation of thyroid nodules is ultrasonography, which is now recommended routinely in the assessment of goitre by BTA, ETA and ATA guidelines.[152, 153] This non-invasive technique has the capacity to detect non-palpable nodules, in addition to permitting estimation of the size of goitres and nodules and allowing accurate guidance of fine-needle aspiration biopsy (FNAB).

A number of specific ultrasonographic changes are associated with malignancy, including hypoechogenicity, solid nodules, microcalcifications, irregular margins, increased intranodular flow, increased ratio of anterior/posterior dimensions in transverse and longitudinal views (more tall than wide), the presence of invasion or evidence of regional lymphadenopathy.

There are several retrospective case series that have together indicated a role for ultrasound imaging in reliably detecting malignancy.[159, 160] Consequently, radiologists may use a US (U) grading system (U1–U5) to predict malignancy and guide clinicians in deciding whether biopsy of a thyroid nodule is required.[152] The U classification system is depicted in **Table 61.16**. Ultrasound findings that represent a benign nodule (U1–U2) are regarded as not requiring FNAB unless the patient has a high risk of malignancy. Those that are equivocal (U3) or show a higher risk of malignancy (U4–U5) should lead to cytological assessment via FNAB.

Elastography may also be utilized and typically identifies diminished compressibility in malignant thyroid nodules.[161] Interestingly, neither the number of nodules nor their size is predictive of malignancy. The presence of multiple suspect ultrasonographic findings confers an 83–99% sensitivity and 56–85% specificity for thyroid malignancy.[161, 162] This high sensitivity may result in unnecessary investigations and intervention for clinically insignificant nodules. The low specificity continues to render ultrasound assessment of thyroid nodules inferior to FNAB for the diagnosis of malignancy.

TABLE 61.16 Ultrasound (U) classification of thyroid nodules

U classification	Nodule type	Ultrasound characteristics
U1	Normal	
U2	Benign	Vascularity, egg shell calcification, cystic change, iso-echoic or mildly hyper-echoic
U3	Indeterminate/ equivocal	Homogenous, hyper-echoic, equivocal echogenic foci, mixed or central vascularity, solid or halo
U4	Suspicious	Solid, hypo-echoic, peripheral calcification, lobulated outline
U5	Malignant	Solid, hypo-echoic, lobulated outline, intranodular vascularity, taller > wide, lymphadenopathy

Thyroid scintigraphy

Scintigraphy is of little value in the differentiation between benign and malignant nodular disease due both to its poor sensitivity and specificity. While this technique permits differentiation between 'hot' (functional) and 'cold' (non-functional) nodules, most malignant nodules trap isotope less well than normal thyroid tissue and thus appear cold, yet the risk of malignancy in cold nodules is nevertheless as high as 8–25%.[163] Both the BTA and the ATA have published guidelines stating that scintigraphy has no role in the routine management of the thyroid nodule.[152, 153]

Other imaging modalities

Use of CT and MRI provides high-resolution three-dimensional imaging of the thyroid gland but affords no advantage over thyroid ultrasound for the detailed assessment of thyroid architecture. They additionally afford little value in the differentiation between benign and malignant lesions.[164] The use of 2-deoxy-2-fluoro-D glucose (FDG-PET) has met with promise but is limited by both cost and availability. For patients with large goitres, flow volume loop assessment may be helpful.[151]

Suspicious nodules are now not uncommonly identified incidentally during FDG-PET imaging undertaken for a separate indication.[165] Effective workup of patients with incidentally identified focal hypermetabolic thyroid lesions on FDG-PET imaging is crucial, with approximately one-third of identified lesions likely to be malignant.[166]

FINE-NEEDLE ASPIRATION BIOPSY

FNAB is the gold-standard investigation in the evaluation of patients presenting with thyroid enlargement and provides both direct and specific information about the pathology of nodules.[152, 153] This inexpensive and easy-to-learn technique carries a low complication rate and is the preferred diagnostic tool by the majority of thyroidologists. It remains the investigation of choice in the

evaluation of thyroid nodules as advocated in new ATA guidance.[167]

Current BTA guidance recommends a combination of US and cytological findings in the diagnosis of thyroid cancer.[152] The BTA and ATA have additionally provided guidance for the classification of cytological aspirates, as summarized in Table 61.17.

In summary, under BTA guidance nodules with seemingly benign US characteristics in patients of usual or low risk of thyroid cancer can be discharged from follow-up with no requirement for routine follow-up ultrasound. In instances of benign (Thy2) cytology and benign ultrasound findings there is again no requirement for follow-up ultrasound. Repeat FNAB is, however, required if US findings are suspicious and the initial FNA result is Thy1, or if the previous FNAB result is Thy2.

Cystic lesions which repeatedly yield non-diagnostic aspirates require close observation and, particularly in if the nodule is solid, may necessitate surgical intervention. Surgery may also be offered to patients with benign cytology who belong to a high clinical risk group or who have pressure symptoms or rapid nodular growth.

TABLE 61.17 Cytological classification of fine-needle aspirates and action required

ATA classification (Bethesda System)		
Diagnostic category	**Cytological diagnosis**	**Management**
I	Non-diagnostic	Repeat US-guided FNA
II	Benign	Clinical follow-up
III	Atypia/follicular lesion of undetermined significance	Repeat FNA
IV	Suspicious	Surgical hemithyroidectomy
V	Suspicious	Near-total thyroidectomy / surgical hemithyroidectomy
VI	Malignant	Near-total hemithyroidectomy
BTA classification (RCPath Thy System)		
Diagnostic category	**Cytological diagnosis**	**Management**
Thy1	Non-diagnostic	US assessment +/– repeat FNAB
Thy2	Non-neoplastic	Correlate with clinical / US findings
Thy3	Neoplasm possible	
	Thy3a – Atypia (uncategorized)	Further US +/– repeat FNAB
	Thy3f – Atypia (possible follicular neoplasm)	Diagnostic hemithyroidectomy
Thy4	Suspicious of malignancy	Diagnostic hemithyroidectomy
Thy5	Diagnostic of malignancy	Surgical resection

Indeterminate cytology results are common and are reported in 15–30% of FNA specimens. Gender, nodule size and cytological features such as the presence of atypia may improve diagnostic accuracy but overall predictive values remain low. The use of molecular markers in refining the diagnosis of thyroid cancer is a rapidly expanding field and gene expression classifiers and mutation analysis panels are regularly in some US centres.[168] However, there is as yet insufficient evidence to recommend the routine use of molecular markers in the diagnosis of thyroid cancer.[152]

The risk of malignancy is similar in those with multiple thyroid nodules compared with those presenting with a single nodule. Since sonographic characteristics are superior to nodule size in identifying malignancy current ATA and BTA guidance recommends diagnostic ultrasound in those with multinodular thyroids. Fine-needle aspiration should be undertaken in those with suspicious features. If none of the nodules has a suspicious appearance, the likelihood of malignancy is low and it is reasonable to aspirate the largest nodule only.

KEY POINTS

THYROID ENLARGEMENT

AETIOLOGY

- Benign causes include follicular and Hürthle cell adenoma, colloid cyst, infectious processes and thyroiditis.
- Malignant causes include papillary, follicular, Hürthle cell, and anaplastic or medullary thyroid carcinoma.
- Malignancies may be metastatic to the thyroid.

Clinical features suggesting carcinoma in a patient with thyroid enlargement

- Clinical history: rapid tumour growth, vocal cord paralysis, male sex, age <20 or >60 years, history of head or neck irradiation, presence of compressive symptoms, family history of multiple endocrine neoplasia or medullary thyroid carcinoma.
- Examination: firm nodules, fixation to adjacent structures, regional lymphadenopathy.

Investigations

- High-resolution ultrasound is the diagnostic imaging modality of choice.
- Fine-needle aspiration biopsy is required for cytological assessment.

Management

- Cytological diagnosis of Thy1 and Thy2 will require at least one repeat.
- Cytological diagnosis of Thy3, Thy4 or Thy5 will likely necessitate surgical intervention.

Medical management of nodular thyroid disease

NON-TOXIC MULTINODULAR GOITRE

Surgery is the treatment of choice where there is evidence of moderate to severe compressive symptoms, where FNAC

of a dominant nodule is suspicious of malignant or where the patient prefers surgery for cosmetic reasons.

Radioiodine therapy

Medical treatment of goitre previously involved the use of suppressive thyroid hormone but this is now considered outdated.[169] Use of suppressive therapy necessitates acceptance of a state of subclinical hyperthyroidism and consequent increased risk of reduced bone mineral density and cardiovascular disease.[97] Its discontinuation often also results in the resumption of growth of thyroid nodules or goitres. Contemporary management therefore typically utilizes the administration of radioactive iodine in cases in which a patient has refused surgery or if age, frailty or comorbidities preclude operative intervention.

Reduction in goitre size may be as significant as 60% and may continue for years after treatment, although most shrinkage occurs soon after treatment. Favourable outcomes are more likely in patients with small goitres who are young, have a shorter history of goitre and who receive higher doses of radioiodine.

Approximately 75% of those with the largest goitres will achieve relief from dyspnoea, accompanied by a reported 36% increase in the cross-sectional area of the trachea.[170] These patients may require large doses of radioiodine and may require hospitalization and isolation as a requirement of radiation protection legislation. Alternatively, therapy may be fractionated over a course of a few months.

The use of radioiodine is not, however, without side effects. Hypothyroidism commonly results from its use and is more likely if multiple doses of radioiodine are administered. The prevalence varies according to the amount of radiation exposure, with figures quoted ranging between 8% and 40% at 1–2 years.[2] While uncommon, radiation thyroiditis may occur in 3–13% of patients and causes neck pain and tenderness. Graves' hyperthyroidism associated with the development of TSH receptor antibodies occurs in up to 5% of patients and is usually transient.

Goitre size may transiently increase following the administration of radioiodine. Some concern has been voiced previously that this might contribute to a deterioration in respiratory function in those with tracheal compression. This fear is not well substantiated within the literature with studies demonstrating only a small decrease in tracheal cross-sectional area after therapy with no increase in upper airways obstruction. The use of prednisolone peri- and post-radioiodine to minimize risks of tracheal compression has been advocated but there is no evidence base for this practice.

Recombinant TSH may be employed as an adjunct to radioiodine therapy.[171] Its use in this setting is aimed towards increasing the stimulus for radioiodine uptake into a goitre so as to maximize the effect per dose ratio. Preliminary data relating to the use of this adjuvant treatment are encouraging but evidence for efficacy in volume reduction is not yet available. Consequently, recombinant TSH is not widely used at present.[172]

SOLITARY NON-TOXIC NODULE

Treatment of a solitary toxic nodule is similar to the management of multinodular goitre.[173] Surgery remains the treatment option of choice in cases of suspected malignancy and for cosmetic effect. Suppressive therapy with thyroid hormones is not recommended for solitary nodules for reasons outlined previously in this chapter.

Radioiodine therapy

Nodules which take up iodine (hot nodules) may be managed with radioiodine. This simple treatment is safe and cost-effective for this purpose, with a single dose delivering a thyroid volume reduction of up to 40%. Hypothyroidism is seen in approximately 10% of patients at 5 years post-radioiodine, although its frequency is higher in those with pre-existing thyroid autoimmunity.

Aspiration

Approximately 10–15% of solitary thyroid nodules are cystic. Many will resolve over time and small cysts of less than 3 mL volume are managed with a conservative expectant approach. Larger cysts should be aspirated with FNAB performed on any residual nodule. Surgery may be considered in these cases as around 10% of large lesions may harbour thyroid cancer. Recurrence rates following aspiration are poor and may be as high as 80%.

THYROID INCIDENTALOMAS

This area of thyroid disease has gained growing importance as a consequence of the increasing recognition of previously unrecognizable thyroid nodules through various imaging modalities. Usually measuring less than 1.5 cm, these incidentalomas are often diagnosed during evaluation for non-diagnostic neck disorders and pose a management quandary for clinicians.[152, 153]

The Society of Radiologists in Ultrasound recently released a consensus statement which stipulated that highly suspicious ultrasonographic features, such as microcalcifications, should prompt a biopsy in nodules 1 cm or larger, other suspicious features such as solid consistency should prompt biopsy at 1.5 cm or larger and less suspicious appearances such as mixed solid and cystic consistency should be considered only if nodules measure 2 cm or larger.[159] These guidelines have, however, met with controversy as patients undergoing surgery for papillary cancers as small as <1.5 cm have been identified to have distant metastasis.[174] The revised British Thyroid Association Guidelines on the management of thyroid cancer do not take size into consideration when evaluating incidentalomas and suggest FNAB of nodules that are indeterminate or suspicious on ultrasound (U3–U5 categories).[152]

An alternative approach may be to observe small nodules, in the absence of features of malignancy, and to proceed to FNAB for larger or rapidly growing incidentalomas and those with features suggestive of malignancy, such as irregular margins and increased intranodular flow. Most will require US-guided FNAB as they will be

impalpable, and mixed radiological and clinical follow-up is advocated.

CONCLUSIONS

Thyroid dysfunction is common, affecting more than 2% of the population and is usually caused by autoimmune disease. Thyrotoxicosis is most commonly caused by Graves' disease, with other important causes including toxic nodular hyperthyroidism and thyroiditis. The mainstays of treatment of thyrotoxicosis—namely, antithyroid drugs, radioiodine, and surgery—have not changed for more than 60 years, although the evidence base directing treatment choices and modes of administration is improving. Importantly, there is a rapidly increasing evidence base that mild or subclinical hyperthyroidism is associated with serious consequences, especially cardiovascular effects and osteoporosis.

Worldwide iodine deficiency is the most common cause of hypothyroidism, although in developed countries this is usually caused by Hashimoto's thyroiditis, another autoimmune disease. A number of definitive treatment modalities for hyperthyroidism result in permanent hypothyroidism. Levothyroxine mono-therapy remains the standard of care for patients with hypothyroidism. Significant controversy continues to surround the long-term consequences and need for thyroid hormone replacement therapy in mild subclinical hypothyroidism. The management of thyroid dysfunction in pregnancy requires a coordinated multidisciplinary approach involving endocrinologists and obstetricians.

Thyroid enlargement and nodules affect up to 50% of the population and the challenge is to identify patients harbouring malignancy from the large majority who have benign disease. When thyroid dysfunction is excluded, the use of high-resolution ultrasound and fine-needle aspiration cytology are the most important diagnostic tools in this setting. A multidisciplinary approach involving thyroid surgeons, radiologists, nuclear physicists and endocrinologists are crucial for optimal management approaches in patients presenting with thyroid gland enlargement. If the presence of malignancy is excluded, often a conservative approach can be adopted. Treatment of suspected thyroid cancer usually involves surgery, whereas a conservative approach is usually adopted in those with benign thyroid enlargement. If there is significant compression, surgery or administration of radioiodine to shrink the goitre may be indicated.

FUTURE RESEARCH

Hyperthyroidism

- Investigation of novel and safe ways to modulate the underlying disease process in Graves' disease including immunological and other biological agents
- Further evaluation of the mechanisms of and risk factors for the development of severe side effects of the antithyroid drugs
- Determination of the long-term outcomes following treatment and their dependence on the treatment modalities employed
- Prospective randomized controlled trials assessing the indications for and outcomes following treatment of subclinical hyperthyroidism

Hypothyroidism

- Development of superior biomarkers of euthyroidism to supplement serum TSH measurements
- Mechanistic research on serum triiodothyronine levels, including effects of age and disease status, relationship with tissue concentrations, as well as potential therapeutic targeting
- Long-term outcome clinical trials testing combination therapy with T3/T4 or thyroid extracts
- Development of thyroid hormone analogs with a favourable benefit to risk profile
- Prospective randomized trials assessing the indications for and outcomes following treatment of subclinical hypothyroidism

Nodules

- Refinement of long-term follow-up strategies in patients with benign nodular thyroid disease
- Improvements in diagnostic accuracy of fine-needle aspiration cytology of thyroid nodules
- Identification of useful molecular markers diagnostic of thyroid malignancy
- Investigation of the role of elastography in the diagnosis of thyroid nodules

KEY POINTS

- Both overt and subclinical thyroid dysfunction are of clinical importance.
- Classical symptoms of thyrotoxicosis may not be present in the elderly.
- Levothyroxine is the mainstay of treatment in hypothyroidism with inconclusive evidence to indicate an advantage from T3 therapy.
- Thyroid disease in pregnancy requires a specialist-driven multidisciplinary approach.
- Thyroid cancer is rare but must be considered in cases of euthyroid glandular enlargement.
- High-resolution ultrasound, with or without fine-needle aspiration cytology, is used first-line in the investigation of euthyroid goitre.

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CHAPTER 62

MANAGEMENT OF DIFFERENTIATED THYROID CANCER

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: thyroid, cancer, carcinoma, management, radioiodine, as well as published guidelines from the British and American Thyroid Associations. Reference lists for selected papers were examined for further sources.

INTRODUCTION

The prognosis of differentiated thyroid cancer (DTC) is excellent for most patients. Patients with Stage I–Stage III disease have a 10-year survival rate of over 98%,[1] but the survival rate drops dramatically for patients with Stage IV disease, especially when gross local invasion or distant metastases are present in patients older than 45 years.

The management of DTC is mainly surgical, with adjuvant radioiodine ablation followed by TSH suppression in some cases. In the past almost all patients received similar treatment with a combination of all three therapeutic modalities. Over the past 5–10 years, however, a more personalized approach to treatment has been introduced. This tailors the specific treatment that a patient receives according to their individual requirements and risk of recurrence. The type and size of their tumour and the presence or absence of aggressive features such as lymph node metastases or aggressive histological features mainly determine stratified treatment. This change in treatment paradigms has also recently extended to the stratification of risk of recurrence following the completion of treatment, leading to variable follow-up requirements.

INVESTIGATIONS

The investigation of a patient with suspected thyroid cancer[1, 2] has been covered appropriately in Chapter 59. Briefly, this includes a detailed clinical history, which should in particular elicit a family history of thyroid cancer, previous neck irradiation and a history of Hashimoto's disease (predisposing to lymphoma). The diagnosis will have been obtained using a combination of high-resolution ultrasound scan (USS) and fine-needle aspiration cytology in most cases. Once thyroid cancer is diagnosed, ideally the extent of the disease should be further staged to assess tumour size, invasion of important central structures such as trachea and oesophagus, and the presence of nodal metastases and/or distant metastases (**Table 62.1**). This is undertaken using a combination of ultrasound of the neck, CT and/or MRI.

Use of iodinated contrast for CT scanning will impose some restrictions on the use of ablative radioiodine within 2 months of the scan due to the high concentration of iodinated contrast taken up by the thyroid, which may diminish the effectiveness of radioiodine.[1, 2] However, this is usually not a problem because the treatment period will include surgery and recovery from this in the first instance and in view of more recent evidence indicating that the clearance period for iodine in both thyroidectomized and euthyroid patients is only 4 weeks.[3] Importantly, subjects requiring radioiodine ablation are frequently intermediate-risk patients, in whom a small delay in this treatment will have little effect on outcome. Those patients with more aggressive thyroid cancer tend to have non-iodine avid disease or iodine-refractory disease in which case a

TABLE 62.1 TNM classification of thyroid cancer[58]

Primary tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤2 cm in greatest dimension limited to the thyroid
T1a	Tumour ≤1 cm, limited to the thyroid
T1b	Tumour >1 cm but ≤2 cm in greatest dimension, limited to the thyroid
T2	Tumour >2 cm but ≤4 cm in greatest dimension, limited to the thyroid
T3	Tumour > 4 cm limited to the thyroid, or gross extrathyroidal extension invading only strap muscles
T3a	Tumour > 4 cm limited to the thyroid
T3b	Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles) from a tumour of any size
T4a	Tumour of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, oesophagus or recurrent laryngeal nerve
T4b	Tumour invades prevertebral fascia or encases carotid artery or mediastinal vessels
Regional lymph nodes (cervical or upper mediastinal)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastases to Level 6/7 nodes unilateral or bilateral
N1b	Metastases to unilateral, bilateral or contralateral cervical (Levels 1, 2, 3, 4 or 5) or retropharyngeal nodes
Distant metastases	
M0	No distant metastases
M1	Distant metastases
Residual tumour	
RX	Cannot assess presence of residual primary tumour
R0	No residual primary tumour
R1	Microscopic residual primary tumour
R2	Macroscopic residual primary tumour

Note: TNM: tumour, node, metastasis.

delay in receiving radioiodine ablation is significant only in that it can increase time to other adjuvant modalities such as external beam radiotherapy.

TREATMENT

Over the past decade, a more evidenced-based approach to treatment and follow-up has been espoused by both the American Thyroid Association[2] and the British Thyroid Association.[1] This has resulted in the concept of treatment planning tailored to patients' individual needs. The introduction of personalized medicine has also extended to the need for and duration of TSH suppression as well as to follow-up strategies. Where there is no evidence or conflicting evidence, an open and frank approach with the patient is now recommended so that a full discussion of the potential benefits and risks of adjuvant treatment can be undertaken, leading to shared decision-making.

An assessment of both patient and tumour factors before and after surgery helps determine the extent of the thyroidectomy, the need for neck dissection, the need for radioiodine ablation and the requirement for post-treatment TSH suppression. In addition, the intensity of follow-up the patient requires can be predicted.

Extent of thyroidectomy

Thyroidectomy is the mainstay of treatment for thyroid cancers. In recent years there has been a move towards the more conservative hemithyroidectomy rather than total thyroidectomy. This has coincided with a decrease in the indications for radioiodine ablation. Generally speaking, for DTC, a total thyroidectomy is recommended for patients with tumours >4 cm in size and for patients with tumours where there is multifocal disease, bilateral disease, extrathyroidal spread or confirmed nodal or distant metastases. Additional factors that may warrant

bilateral surgery are older age (>55 years), a history of radiation exposure, familial differentiated thyroid cancer, adverse histopathological features and potential difficulties with follow-up.[4]

The evidence for doing a total thyroidectomy rather than a hemithyroidectomy for patients with low-risk papillary thyroid cancer (PTC) of <4 cm with no poor prognostic features is equivocal and conflicting. Careful review of the data indicates that, while there is a decreased risk of recurrence with total thyroidectomy, and while in the long term this may be a more cost-effective approach, the difference is small when compared with more limited surgery.[5–7] In these cases one should have a discussion with the patient regarding the benefits and risks of total thyroidectomy vs. hemithyroidectomy.

Patients with follicular thyroid cancer associated with any of the above poor prognostic features should be advised to undergo a total thyroidectomy.

If tumour is found during the operation to be encasing the recurrent laryngeal nerve (RLN), the clinician should aim to preserve the nerve if it was functioning pre-operatively. This may mean a small amount of disease is left on the nerve but this is acceptable in view of the functional detriments of vocal cord palsy, the gain in quality of life and, importantly, the fact that there is no survival benefit to be gained from nerve sacrifice.[8]

Pre-operatively, one should assess the trachea and the oesophagus radiologically, to identify the need for partial tracheal or oesophageal resection in order to achieve macroscopic tumour clearance. This is important because, unlike for RLN involvement, residual disease left at these sites leads to a significant decrease in survival.[9] Furthermore, careful pre-operative assessment allows determination of the need for input from a cardiothoracic surgeon.

Treatment of papillary thyroid microcarcinoma

Papillary thyroid microcarcinoma (PTMC) is defined as a tumour no greater than 1 cm in maximum diameter. In general this has an excellent prognosis with almost no mortality. A recent meta-analysis,[10] however, indicated that there are at least two types of PTMC – those found incidentally during histological evaluation post-operatively and those that are identified pre-operatively, either incidentally during radiological investigation or because they caused symptoms. Those patients who are diagnosed incidentally on histology have no mortality and almost no recurrence risk and therefore can be considered as cured and can be discharged to their GP. They should, however, undergo annual thyroid function test monitoring since hemithyroidectomy carries a medium- to long-term risk of hypothyroidism.

Those patients with lesions that were identified radiologically may have a slightly higher risk of recurrence. If there are no poor prognostic features (such as aggressive histology, extracapsular spread or lymph node metastasis), these patients can be followed up for 5 years in the same manner as patients with low-risk DTC and then be discharged to a lower-intensity setting. Any patient who has PTMC with aggressive features should be managed in the same way as a patient with non-low risk papillary thyroid cancer.

Neck dissection

There is no evidence of benefit from doing a prophylactic lateral neck dissection in patients with no overt lateral neck disease.[2] The evidence for potential benefits from prophylactic central neck dissection is unclear and conflicting, with some studies indicating improved outcomes[10, 11] while others do not.[12] In addition, some studies show no additional complications from central neck dissection, whereas others have shown that there is considerable added morbidity.[13–16] There is a suggestion, however, that central neck dissection may be of benefit in tumours >4 cm in size and in tumours with extrathyroidal extension, but the evidence is unclear. Prophylactic central neck dissection is not recommended in patients who have low-risk disease, or have tumours <4 cm in size with classical PTC and no extrathyroidal extension.

Once surgery is completed, TSH suppression should be undertaken with either thyroxine T4 (2 mcg/kg) or with Liothyronine (20 mcg t.d.s.) until the histopathology is available, and a decision can be made as to the need for adjuvant treatment.

Radioiodine ablation

Of all the treatments for thyroid cancer, the practice of radioiodine ablation has undergone the most radical change in recent years. The evidence of the American Thyroid Association Guidelines in 2009 heralded personalized evaluation and decision-making for radioiodine ablation, a decision that should be made at the multidisciplinary team discussion following surgical resection. For radioiodine ablation to be effective, a total thyroidectomy is required, and therefore patients who have had a hemithyroidectomy require a completion thyroidectomy prior to consideration of this treatment.

The benefits of radioiodine ablation have to be weighed carefully against the potential side effects. Positive effects include the possibility of improved survival, reduced recurrence and better monitoring with thyroglobulin in the long term. The downsides, however, include the inconvenience of being in an isolation ward and the requirement not to come into contact with adults and children for 14–25 days following radioiodine ablation. For younger female patients, the implications on pregnancy and breastfeeding must also be considered. Amenorrhoea/oligomenorrhea may occur for 4–10 months following radioiodine ablation, as the gonadal tissue is exposed to radiation via blood and excretion in urine and faeces. Current recommendations are to defer pregnancy for 6 months (BTA guidelines[1]) or 6–12 months (ATA guidelines[2]) following radioiodine treatment. Breastfeeding should be

discontinued at least 8 weeks prior to radioiodine administration to prevent excessive uptake by lactating breast tissue.[1] Male patients are advised to defer fathering a child for 4 months following treatment.[1]

Patients also sometimes complain of dryness of the mouth, swelling of the submandibular glands and feeling tired soon after the treatment. Xerostomia can increase with time. Finally, sperm banking is often offered to men, as infertility is possible.

Patients in whom radioiodine is indicated include those patients with tumours >4 cm or with gross extrathyroidal spread or distant metastasis. These patients will receive an ablative dose of radioiodine followed by a treatment dose. Patients for whom radioiodine is not indicated include those who have unifocal or multifocal tumours <1 cm in size which are histologically classed as papillary or follicular variant, or minimally invasive follicular cancer, with no angioinvasion or extension outside the thyroid capsule.

The difficulty arises in the group of patients who have intermediate features, as data regarding the benefits of radioiodine ablation are sparse. These include patients with tumours 1–4 cm in size. Those patients who have poorer prognostic features could be offered radioiodine ablation. The poor prognostic features include aggressive histology (tall cell or poorly differentiated or diffuse sclerosing PTC), widely invasive follicular thyroid cancer, extracapsular invasion, multiple involved lymph nodes or a high ratio of involved to non-involved nodes and large size of individual nodes that are involved.

Recently, two large randomized controlled trials (RCTs) have shown that a lower dose of 1.1 Mbq is as effective as a higher dose of 3.7 Gbq. The lower dose, however, had fewer side effects.[17, 18] Patients have to be prepared for radioiodine ablation by either recombinant TSH injection 5 days before treatment or by Levothyroxine withdrawal, which is more prolonged and has greater side effects. An iodine scan is undertaken 2–10 days after the treatment. This allows assessment of radioiodine uptake and whether uptake has occurred in areas outside the neck.

High treatment doses of radioiodine are recommended in patients who have gross residual disease or distant metastases. These patients may require repeat treatments every 6–12 months, especially those with disease not amenable to surgery.

Further details on radioiodine treatment are provided in Chapter 66.

External beam radiotherapy

Patients with gross evidence of local tumour invasion at surgery are candidates for external beam radiotherapy (EBRT), as are those with residual or recurrent tumour that is non-radioiodine avid. Intensity-modulated radiotherapy (IMRT) is the method of choice as it reduces damage to other surrounding tissues[19] and reduces toxicity. There is no clear-cut evidence as to the best timing of EBRT in relation to radioiodine remnant ablation. Detailed information on EBRT is provided in Chapter 66.

ASSESSMENT OF THE OUTCOMES OF TREATMENT

The post-radioiodine scan, carried out between 2 and 10 days after ablation, helps assess the uptake of radioiodine in the thyroid bed, as well as the extent of residual and metastatic disease. However, the main evaluation of success of treatment occurs 9–12 months afterwards. Evidence suggests that stimulated thyroglobulin measurements provide the most sensitive method of detecting recurrent or residual disease. Stimulated thyroglobulin should be undertaken along with high-definition ultrasound of the neck and thyroid gland. Together these are more accurate than undertaking a whole-body radioiodine scan.[20, 21]

An injection of recombinant TSH 9–12 months after surgery with a measurement of the thyroglobulin and thyroglobulin autoantibodies following this enables an assessment of disease activity. Stimulated thyroglobulin can also be undertaken using thyroxine withdrawal, but this causes more symptoms and takes more time.[22–24] A stimulated thyroglobulin of <0.5 mcg/L after TSH stimulation has been shown to predict disease-free status with 98–99% accuracy. A stimulated thyroglobulin of >2 mcg/L is highly predictive of persistent disease.[20, 25–28] It should be noted, however, that stimulated thyroglobulin can only be used in the absence of thyroglobulin antibodies and is most sensitive in patients who have had both total thyroidectomy and radioiodine ablation. Conversely, it can predict absence of recurrence with 95–99% accuracy.[29,30]

An unstimulated thyroglobulin of <0.1 mcg/L in the absence of thyroglobulin antibodies and a negative USS has a very high negative predictive value in low-risk patients and can be used as a cost-effective alternative to stimulated thyroglobulin.[31–33]

CT scanning should be used only if the measurement of serum thyroglobulin is unreliable or when the post-radioiodine ablation scan shows uptake beyond the neck.

FOLLOW-UP

Dynamic risk stratification produces three groups (Table 62.2): those with an excellent response, those with persistent disease, and those with equivocal or indeterminate response to treatment. Patients with an excellent response are defined as those who have had surgery and radioiodine ablation and in whom the stimulated thyroglobulin is <1 mcg/L, with a negative USS. Patients who have an excellent response can undergo a less stringent follow-up regimen with annual thyroglobulin assessments. Their TSH should be maintained in the low-normal range at 0.3–2.0 mU/L (Table 62.3). If they are disease-free after 5 years, consideration can be given to following them up in a less intensive setting, such as a nurse-led clinic.[2, 34–37] It should be noted that the appearance of thyroglobulin antibodies when they were previously absent, or their gradual rise, may indicate evidence of recurrent disease.

Patients with an incomplete response include those with a stimulated thyroglobulin >10 mcg/L or a

TABLE 62.2 Dynamic risk stratification following treatment for thyroid cancer[1]

Response	Criteria	Risk stratification	Follow-up
Excellent	*All of the following:* Suppressed and stimulated Tg <1 mcg/L Neck USS without evidence of disease Cross-sectional and/or nuclear medicine imaging negative (if performed)	High	6-monthly for first year Annually thereafter
Indeterminate	*Any of the following:* Suppressed Tg <1 mcg/L and stimulated Tg ≥1 and <10 mcg/L Neck USS with non-specific changes or stable sub-1 cm nodes Cross-sectional and/or nuclear medicine imaging with non-specific changes, not completely normal	Intermediate	More frequently depending on individual need
Incomplete	*Any of the following:* Suppressed Tg ≥1 mcg/L or stimulated Tg ≥10 mcg/L Rising Tg values Persistent or newly identified disease on cross-sectional and/or nuclear medicine imaging	Low	Investigate and more frequently depending on individual need

TABLE 62.3 Grading of TSH suppression[1]

Response	TSH suppression (mU/L)
Excellent	0.3–2.0
Indeterminate	0.1–0.5 (for 5–10 years)
Incomplete	<0.1 (indefinitely)

rising thyroglobulin concentration. They may have a neck USS that shows recurrence. If their ultrasound is normal, then they require a CT scan or MRI. In these patients where cross-sectional imaging is negative, a PET-CT scan should be undertaken. If this is still negative, then a ^{131}I scan should be undertaken. If there is evidence of surgically resectable disease in these patients, that should be undertaken. If there is no surgically resectable disease, then further radioiodine therapy can be offered. These patients should then have TSH suppression (<0.1 mU/L) indefinitely and should undergo close follow-up.

Patients with an indeterminate or equivocal response (stimulated thyroglobulin 1–10 mcg/L with non-specific changes on neck ultrasound) should be kept under close review with serial thyroglobulin measurements and ultrasound scans to attempt to detect recurrence at an earlier stage. The TSH should be maintained in the range 0.1–0.5 mU/L for at least 5–10 years.

BEST CLINICAL PRACTICE

- ✓ For appropriately selected low-risk patients, hemithyroidectomy may be appropriate surgical management.
- ✓ A small amount of disease may be left on a functioning recurrent laryngeal nerve without compromising survival.
- ✓ Prophylactic central neck dissection should be reserved for high-risk patients.
- ✓ Lateral neck dissection should only be undertaken in patients with overt lateral neck disease.
- ✓ Dynamic risk stratification should be undertaken for all patients who have had total thyroidectomy and radioiodine ablation to guide their follow-up and further management.
- ✓ Radioiodine ablation is indicated for high-risk cases and some selected intermediate-risk cases.

FUTURE RESEARCH

- ➤ Molecular profiling of tumours as an aid to risk stratification
- ➤ Methods of identifying high-risk radioiodine-resistant tumours early to escalate treatment and reduce recurrence
- ➤ The role of the immune response in thyroid cancer and how this may influence lateral neck dissection

KEY POINTS

- Differentiated thyroid cancer is rare but has a rising global incidence.
- Thyroid cancer remains a predominantly surgical disease.
- Personalized treatment based on the patient's individual disease and recurrence risks is now the mainstay.
- Management of all patients with thyroid cancer should be discussed in the context of a multidisciplinary team.

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CHAPTER 63

MANAGEMENT OF MEDULLARY THYROID CANCER

Barney Harrison

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: medullary thyroid cancer, MEN2, calcitonin and thyroidectomy.

INCIDENCE

Medullary thyroid cancer/carcinoma (MTC) is diagnosed in approximately 1000 people each year in the United States and 25–50 people per year in the UK and it is responsible for 5–10% of paediatric thyroid cancers. In patients with nodular thyroid disease screened for MTC the prevalence is reported as 0.4%–1.8% (see below).

PATHOLOGY

MTC arises from C-cells located in the middle and upper third of the thyroid gland, adjacent to or within thyroid follicles, between the follicular cell basement membrane and the surface epithelium. C-cells are of neural crest origin and produce calcitonin, calcitonin gene-related peptide (CGRP) and carcinoembryonic antigen (CEA).

The physiological role of calcitonin is unclear. In patients with metastatic medullary thyroid cancer, in whom calcitonin levels are grossly elevated, and after total thyroidectomy for benign disease when levels are low, no derangement of calcium homeostasis is apparent.

C-cell hyperplasia

C-cell hyperplasia (CCH) is defined as a multifocal (diffuse or nodular) quantitative increase in C-cells. Two types of CCH are described:

- **neoplastic:** typically nodular and diffuse and indistinguishable from invasive MTC cells
- **reactive/physiological:** typically diffuse, associated with hypercalcaemia, hyperparathyroidism, chronic lymphocytic thyroiditis and follicular thyroid tumours.

Medullary thyroid cancer

MACROSCOPIC

Sporadic tumours are usually solitary (90%) and unilateral. In familial disease, MTC is usually bilateral and multifocal.

CYTOLOGY

Cell morphology is variable, oval/round/spindle-shaped cells may be seen in clusters or as single cells with pleomorphic nuclei and eosinophilic cytoplasm. Eosinophilic extracellular material is amyloid.

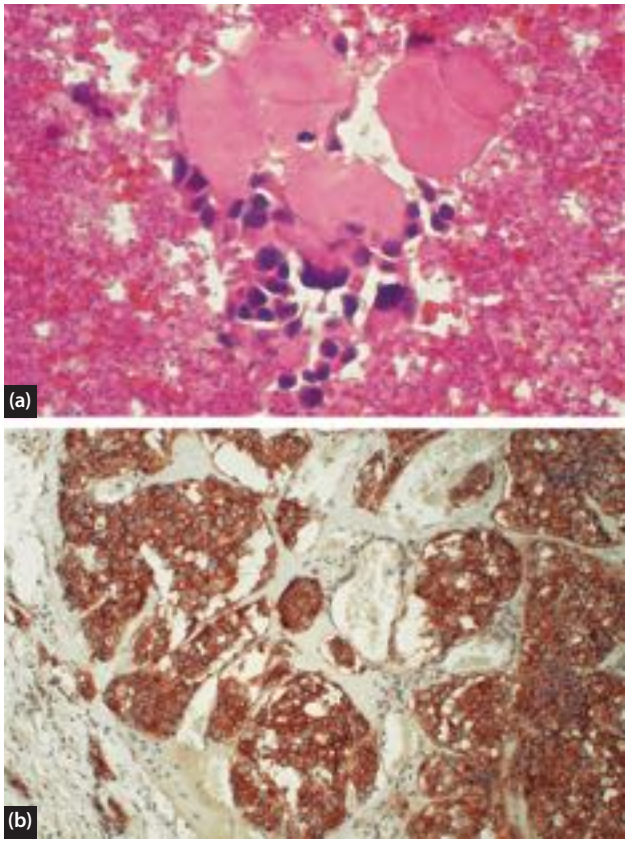


Figure 63.1 **(a)** MTC cytology from fine needle aspiration **(b)** MTC histology showing strongly positive immunohistochemical staining for calcitonin.

HISTOPATHOLOGY

Variants of classical MTC include papillary, follicular, squamous and oncocytic subtypes. Amyloid is seen in 80% of tumours on immunohistochemistry, and tumour cells stain positive for calcitonin (**Figure 63.1**), CEA and chromogranin A. Thyroglobulin staining is negative.

MTC is staged as described in the *AJCC Cancer Staging Manual*.[1]

HEREDITARY MTC

Genetically determined disease accounts for 25% of MTC cases. The three main clinical variants are all inherited as autosomal dominant disorders with age-related penetrance and variable expression:

- multiple endocrine neoplasia type 2A (MEN 2A): >50% of cases
- multiple endocrine neoplasia type 2B (MEN 2B): 5% of cases
- familial medullary thyroid cancer (FMTC).

The prevalence is estimated at 1 in 30000. MTC is expressed in almost all patients and is usually the first manifestation of the syndrome; the age at onset can be roughly predicted according to the genotype.

Gain of function germline and somatic mutations of the *RET* proto-oncogene (chromosome 10q11.2) are implicated in the pathogenesis of MTC. *RET* encodes a plasma membrane-bound receptor tyrosine kinase that is expressed by thyroid C-cells, cells of the adrenal medulla, autonomic nerve ganglia, colonic ganglia and parathyroid cells.

Germline mutations associated with MEN 2/FMTC are found in 7 of the *RET* gene's 21 exons. The codon mutations correlate with the MTC phenotype.[2]

The extracellular, codon 634 mutation (found in 85% of MEN 2A cases) induces a dimerization of the RET receptor which leads to abnormal cell growth, differentiation defects and cellular transformation. The intracellular, codon 918 mutation found in 95% of cases of MEN 2B is associated with receptor activation in the absence of receptor dimerization by alteration of kinase substrate specificity.

Somatic mutations of *RET*, usually at codon 918, are found in approximately 25% of sporadic MTC and linked with poorer prognosis.

CLINICAL FEATURES OF SPORADIC AND HEREDITARY MTC

Sporadic MTC presents usually in the fourth to sixth decade, MEN2A typically presents in the second or third decades, MEN2B in the first and second decades, and FMTC in the fourth and fifth decades. The sex ratio is almost equal.

A thyroid mass is normally the first indication of disease (>75%), cervical lymphadenopathy is a presenting feature in approximately 40–50% of patients. Around 10% of patients will have distant metastases, and symptoms include diarrhoea (the specific cause of which is unknown), flushing and bone pain. Rarely (<1%), ACTH/CRH production by MTC causes Cushing's syndrome[3] and is associated with poor prognosis.

Phaeochromocytoma is most frequently associated with *RET* codon mutations 634 and 918,[4] occurs in 50% of MEN 2 patients most commonly in the third and fourth decades and may be the presenting feature of MEN 2 in up to 25% of cases.

In patients with MEN 2A, hyperparathyroidism occurs in 20–30% of individuals with *RET* 634 mutations. The hypercalcaemia is often mild. Asymmetric parathyroid gland enlargement is likely and resection of only enlarged glands is recommended.[5]

Rare variants of MEN 2A with specific *RET* mutations are associated with Hirschsprung's disease and cutaneous lichen amyloidosis (brownish plaques of multiple tiny papules, usually in the interscapular area).

In FMTC, the age at onset of MTC is later than is seen in MEN 2A and MEN 2B; the phenotype is less aggressive. MEN 2B has a specific phenotype that may be apparent in infancy and progresses as the patient ages. There is a typical facial appearance with enlarged lips (**Figure 63.2**). Mucosal ganglioneuromas arise in the digestive tract – associated with abdominal distension, megacolon, constipation and diarrhoea. In infants, the colonic manifestations of MEN 2B may be confused with Hirschsprung's disease. Ganglioneuromas are seen on the conjunctivae, lips and tongue (**Figure 63.3**).



Figure 63.2 Typical facial phenotype of three unrelated MEN 2B patients.



Figure 63.3 Tongue of an 11-year-old MEN 2B patient showing typical ganglioneuromas.

Other manifestations include skeletal abnormalities such as Marfanoid habitus, joint laxity, pes cavus and pectus excavatum, and markedly thickened corneal nerves. Around 95% of patients have a mutation at codon 918, and 75% of patients are the index case (i.e. *de novo* mutations).

DIAGNOSIS OF MTC

The diagnosis of MTC in most cases will result from the investigation of patients who present with a thyroid or lymph node mass. Fine-needle aspiration cytology (FNAC) will result in a diagnosis in 50% of cases,[6] and the additional use of calcitonin assay of the fine-needle aspirate has high sensitivity and specificity for MTC diagnosis.[7] When necessary, targeted core needle biopsy avoids the need for open biopsy.

Routine measurement of basal calcitonin in patients presenting with nodular thyroid disease is recommended by some, to identify otherwise undetected MTC and lead to the potential benefit of better outcome. Basal hypercalcitonaemia will be evident in at least 1.5% of screened individuals but approximately 60% of those with a high basal calcitonin do not have MTC. The positive predictive value of an abnormal basal calcitonin greater than 100 pg/mL is 100%.[8] Recommendations on the use of routine calcitonin screening in patients with nodular thyroid disease in recent draft guidelines of the American Thyroid Association[9] and British Thyroid Association[2] (against) are at variance with European Thyroid Association guideline recommendations (in favour).[10]

PRE-OPERATIVE INVESTIGATIONS

Calcitonin

Serum calcitonin is a sensitive and accurate marker of MTC. False-positive serum calcitonin levels are recorded in patients with autoimmune thyroid disease, hypercalcaemia, foregut-derived neuroendocrine tumours and renal failure. Normal basal calcitonin levels are higher in neonates and children than adults.[11] MTC with normal basal serum calcitonin is described in less than 1% of patients, more often in those with advanced disease.[12]

Basal calcitonin should be measured in all MTC patients prior to surgery. The level of calcitonin is a good indicator of disease extent. Lymph node involvement may be found in patients with calcitonin as low as 10–40 pg/mL; distant metastasis and extra-thyroidal growth can occur with calcitonin levels of 150–400 pg/mL.[13]

In patients with potentially false-positive basal calcitonin levels, or when there is uncertainty about the histological diagnosis, a calcium stimulation test should be performed.[14] Basal calcitonin levels that are false positives (i.e. not MTC) do not respond significantly to calcium stimulation.

Urinary or plasma catecholamines / metanephrines

Biochemical testing for phaeochromocytoma (24-hour urine, or plasma for metanephrines and normetanephrines) is mandatory prior to surgery in all patients with a diagnosis of MTC. Phaeochromocytoma should be treated before the thyroid disease. Annual biochemical screening for phaeochromocytoma is warranted from the age of 11 years in carriers of *RET* codon mutations 918 and 634, and from the age of 16 in the remainder.[15]

Calcium

A serum calcium level should be obtained from all patients prior to surgery. Hypercalcaemia and high or inappropriate serum PTH will indicate the need for careful assessment of the parathyroid glands at the time of thyroidectomy and excision of enlarged glands. Age of commencement of screening for primary hyperparathyroidism is recommended as for phaeochromocytoma.[15]

RET mutation analysis

RET mutation analysis should be performed in all patients diagnosed with MTC. Your 'sporadic' patient may represent the index case of a previously undiagnosed MEN kindred. The prevalence of a germline *RET* mutation in patients with apparently sporadic MTC is reported as 7%.[16]

DNA-based testing will identify mutations in more than 95% of individuals with MEN 2A and MEN 2B and in about 85% of individuals with FMTC. When a patient with MTC is identified as carrying a *RET* mutation, genetic screening should be offered to first-degree relatives. Family members identified as gene-positive can be offered therapeutic, risk reduction or prophylactic surgery for MTC (see below).

Ultrasound

Neck ultrasound performed as a part of thyroid workup or to guide FNA can identify bilateral and or multiple thyroid lesions – suggestive of genetically determined disease, and enlarged or abnormal lymph nodes.

CT/MRI scanning

Cross-sectional imaging of the neck and mediastinum is required to identify tracheal/oesophageal invasion and mediastinal lymphadenopathy (**Figure 63.4**).

Systemic staging to include lungs, liver and axial skeleton (including bone scintigraphy) is appropriate in patients with extensive neck disease, symptoms of metastatic disease or a calcitonin >500 pg/mL.[17] Positive findings may restrict the extent of neck surgery.

Pre-operative laryngoscopy is essential in patients with proven or suspected MTC.

Staging

For staging of MTC, please refer to Chapter 58.

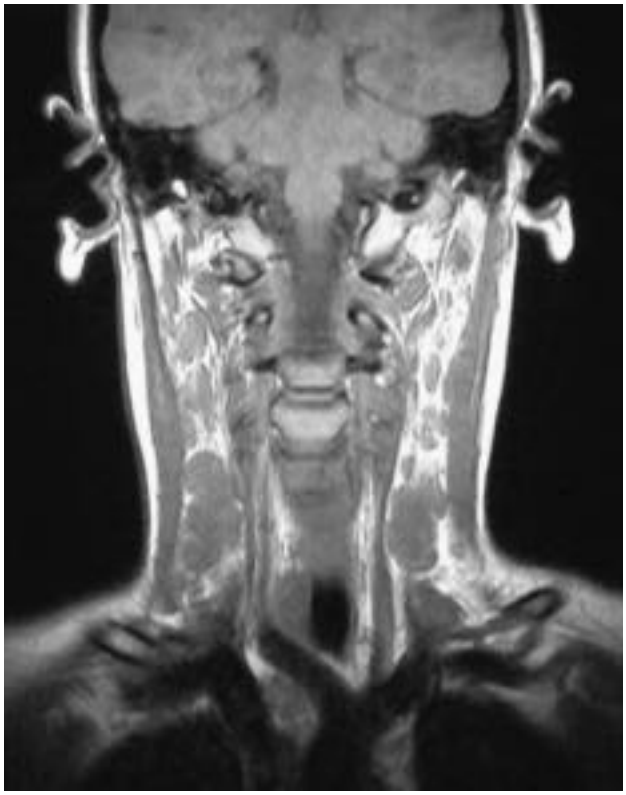


Figure 63.4 Magnetic resonance image showing bilateral cervical and infrabrachiocephalic lymphadenopathy in a 17-year-old MEN 2B patient following previous thyroidectomy.

SURGERY FOR MTC

The aims of surgery in patients with MTC are to remove all disease in the neck, produce biochemical and clinical cure and minimize the risk of locoregional relapse that might compromise the airway, oesophagus or recurrent laryngeal nerves. This requires total thyroidectomy and lymph node dissection in most patients. Surgery should be performed with the intention to preserve the recurrent laryngeal nerves, superior laryngeal nerves and parathyroid function.

Rationale for lymph node dissection in MTC

Node metastases are common (>75%) in patients with palpable MTC[18] and occur early in the disease. Lymph node involvement may be found when the basal calcitonin level is only minimally above the normal range:[13] the frequency can be predicted by tumour size and ranges from 17% (pT1) to 100% (pT4).[19] Node metastases in sporadic medullary microcarcinoma (1 cm diameter or less) have been reported to occur in 43% of patients.[20]

Ipsilateral lateral neck nodes may be involved in over 80% of cases and contralateral lateral nodes in over 50%.[21] The frequency of ipsilateral and contralateral lateral compartment node involvement reflects the degree of central compartment node positivity.[21] Skip metastases (negative central and positive lateral or mediastinal compartments)

are found in approximately 20% of patients. Mediastinal node disease is more likely to occur in patients with positive cervical nodes and extra-thyroidal extension; contralateral cervical or mediastinal lymph node involvement predicts an increased risk of distant metastases.[22]

The normal recommendation for the treatment of MTC is total thyroidectomy, although sporadic disease is usually unilateral and unifocal (80%). Total thyroidectomy and compartment-orientated node dissection is associated with improved survival and a reduced risk of recurrence.[23] Biochemical cure can be obtained in 95–100% of patients without lymph node metastases, and in 32–45% of patients with lymph node metastases.[24, 25] When fewer than 10 lymph nodes are involved, an undetectable calcitonin level is observed in 57% of patients.[25]

A reasonable approach to the primary surgical treatment of MTC without distant metastases includes the following:

- Clinically evident MTC: a minimum of total thyroidectomy and central neck lymph node dissection (levels VI-VII). Therapeutic selective lateral neck dissection should be performed if there is clinical or radiological evidence of nodal disease. Ipsilateral prophylactic selective lateral neck dissection (levels IIa–Vb) is advised if central neck nodes are involved as there is a high risk of lateral neck node disease. In the absence of overt central neck node disease, histological confirmation of node metastasis by intra-operative frozen section should be performed prior to prophylactic lateral neck dissection. Alternatively, a two-stage procedure may be performed. As biochemical cure is unlikely when node metastases are present in more than two lymph node compartments,[26] prophylactic bilateral lateral neck dissection is not recommended.
- Incidental MTC >1 cm diagnosed at hemithyroidectomy with elevated post-operative basal calcitonin: treat as above.
- Incidental micro MTC <5 mm (*RET*-ve) and normal post-operative basal calcitonin: completion thyroidectomy is not required.
- MTC >5 mm in diameter when the post-operative basal calcitonin is elevated, or when the basal calcitonin is normal and stimulated calcitonin levels are elevated: total thyroidectomy and central neck dissection.
- After previous surgery and five or fewer lymph nodes removed with calcitonin <1000 pg/mL: central and ipsilateral lateral neck node dissection as above should be considered.
- When pre-operative imaging identifies infrabrachicephalic mediastinal nodal disease and no evidence of distant metastases: mediastinal lymphadenectomy (via a trans-sternal approach) should be performed.

Patients with known distant metastases at diagnosis should be considered for total thyroidectomy and central neck lymph node dissection, and/or resection of enlarged mediastinal nodes to prevent subsequent compromise of the airway, recurrent laryngeal nerves and oesophagus. Survival may be prolonged in patients with disseminated disease.

FOLLOW-UP

Thyroid function and serum calcium should be monitored post-operatively, the former in conjunction with replacement doses of thyroxine to maintain normal TSH levels. After surgery, measurement of calcitonin levels should be delayed as the post-operative fall in levels may be delayed for up to 3 months.[27] All patients with MTC require lifelong review, and regular monitoring of calcitonin and CEA. Patients with MEN 2 require multidisciplinary follow-up (endocrinology/oncology/surgery) to diagnose, treat and monitor the other components of their syndrome.

PERSISTENT/RECURRENT HYPERCALCITONAEMIA AND RECURRENT MTC

Historically, patients have undergone less than optimal initial surgery, approximately 50% of patients having less than treatment guidelines recommend. Surgical treatment that is compliant with recognized guidelines is said to result in fewer reoperations and more biochemical cure.[28]

Residual/recurrent disease is diagnosed on the basis of clinical symptoms, signs or an elevated/rising calcitonin or CEA. Locoregional and distant metastases from MTC occur preferentially within the first 5 years.

When a patient presents with persistent or recurrent hypercalcitonaemia, there are three key issues for the surgeon:

- Was the initial surgery less that that recommended according to best practice?
- Is the source of calcitonin in the neck (residual thyroid or lymph nodes) or mediastinum and amenable to further surgery?
- Will further surgery result in cure or improved survival?

The fundamental issue is whether residual disease lies within the neck and is remediable by surgery. Reoperation in selected patients can result in normalization of calcitonin in up to 44% of cases. Biochemical cure is most likely to occur in those patients who have previously undergone inadequate first-time surgery and have serum calcitonin ≤1000 pg/ml or five or fewer nodes removed at previous surgery.[29]

Radiographic evidence of recurrent disease is unlikely when the calcitonin level is at or below 250 pg/mL.[23] In the 'absence' of metastases and when first-time neck surgery was less than adequate, reoperation should be considered for what is persistent disease. This will usually require compartment-orientated cervical node dissection. When localization studies identify recurrent locoregional disease after appropriate first-time surgery, reoperative surgery should also be performed. The presence of distant disease should not in isolation preclude surgery. The aim of surgery is not only to cure or significantly reduce disease bulk or symptoms but also to relieve or prevent future compression of the airway and oesophagus as well as involvement of the brachial plexus or recurrent laryngeal nerves.

LOCALIZATION OF PERSISTENT/ RECURRENT MTC

Diagnostic imaging studies in patients with persistent/ recurrent hypercalcitonaemia are used to identify surgically remediable locoregional disease that may put the patient at risk of airway or oesophageal compression. They also provide baseline criteria to facilitate entry of patients into clinical trials, and measurement of responses to systemic therapy.

In patients with elevated calcitonin levels following thyroidectomy, metastases are best detected when serum calcitonin levels are greater than 800 pg/mL. The most efficient detection of metastatic MTC consists of neck ultrasound, chest CT, liver MRI, bone scintigraphy and axial skeleton MRI.[30] FDG PET/CT identifies residual/ recurrent MTC in patients with progressive disease and suggests poor survival. F-DOPA PET/CT more accurately assesses the extent of residual MTC[31] with sensitivity of 80%,[32] but access to this latter scan is limited in the UK.

OUTCOME AND PROGNOSIS

Reported survival rates at 10 years range from 56%[33] to 96%[24] respectively. More than 50% of patients with sporadic MTC will die of their disease. Biochemical cure following surgery is associated with 97.7% survival at 10 years;[34] disease-specific survival for patients with micro MTC is reported as 96% at 10 years.[35] Children with medullary carcinoma thyroid have 5-year survival rates of 95%. Patients with advanced disease have a median survival of 8 years,[36] and a third of patients with systemic symptoms die within 5 years.[37]

When post-thyroidectomy calcitonin/CEA levels are raised, measurement of doubling times at 6-month intervals predicts outcome. Post-treatment calcitonin/CEA doubling times of less than 1 year[38] or more than 2 years[39] correlate with worse and better outcomes respectively.

NON-SURGICAL TREATMENT OF MTC

Adjuvant radiotherapy

Adjuvant radiotherapy has been found to be independently associated with a decreased survival although its use is inevitably confined to those patients with a worse prognosis. External beam radiotherapy is reported to reduce local relapse in high-risk patients and in those presenting with more advanced disease. It has not been shown to produce a survival benefit. It should be considered in those patients at high risk of locoregional recurrence.

Targeted biological therapy

The rationale for the use of tyrosine kinase inhibitors arises from the knowledge that nearly all patients with genetically determined MTC and approximately 50% of patients with sporadic MTC have germline or somatic *RET* mutations respectively. *RET* encodes a receptor for tyrosine kinase. Clinical benefit from treatment of patients with symptomatic progressive/metastatic MTC with Vandetanib and Cabozantinib is seen in more than half the patients, but toxicity is considerable and side effects common.[40]

Diarrhoea can be an extremely distressing symptom of widespread metastatic MTC and is often resistant to treatment with antimotility drugs. Somatostatin analogues may reduce symptoms, and chemoembolization of liver metastases may be effective.[41]

PROPHYLACTIC SURGERY FOR HEREDITARY MTC

Children and adolescents identified by *RET* screening to be at risk for the development of medullary thyroid cancer can be treated with prophylactic thyroidectomy before developing the disease. The timing of the intervention **and** the extent of surgery should be based on the affected codon, the age of the patient and the calcitonin level. Gene carriers with serum calcitonin less than 60 pg/mL who have undergone surgery appear to have intra-thyroidal MTC without evidence of nodal spread.[42]

The timing of thyroidectomy

Children with *RET* codon 918, 883, mutations (MEN 2B) have the **highest** risk from aggressive MTC – neoplastic transformation of C-cells occurs in the first year of life. Prophylactic thyroidectomy should be performed within the first year of life, preferably in the first 6 months.

Children with a *RET* codon 634 mutation have a **high** risk for MTC – neoplastic transformation of C-cells occurs in the first decade. Prophylactic thyroidectomy should be performed at 5 years of age, or earlier if the calcitonin level is elevated above 40 pg/mL.[13]

Children with other *RET* codon mutations are now recommended to undergo 6-monthly clinical examination, and measurement of serum calcitonin around the age of 5 years. With parents involved in decision-making, thyroidectomy may be delayed until later in childhood or the teenage years if calcitonin levels do not rise above the normal range. Although some national guidelines recommend the use of neck ultrasound in assessment of at-risk patients, it appears to be ineffective in identifying MTC in this patient group.[43]

The need for and timing of lymph node surgery

In ideal circumstances, risk reduction surgery – total thyroidectomy – should be performed before the onset of MTC thereby reducing the need for lymph node dissection, which is associated in children with an increased risk of hypoparathyroidism and recurrent laryngeal nerve injury. In reality, cases often manifest when it is likely or evident that MTC is already present and occult lymph node metastasis may have occurred.

It has been suggested that children from known kindred with highest-risk mutations (918, 883) should be considered for lymph node dissection at the time of prophylactic thyroidectomy in the first year of life. Because the risk of post-operative hypoparathyroidism is so high in these children, if parathyroid glands cannot be identified or preserved at surgery, it may be appropriate to avoid node dissection.

Children with MEN 2A with a mutation of codon 634 should undergo central neck dissection at the time of prophylactic thyroidectomy if the calcitonin level is greater than 40 pg/ml or when there is evidence of node metastasis on imaging.

Results of 'prophylactic' surgery

Previously reported outcomes of 'prophylactic' surgery should be interpreted with the knowledge that MTC was often present at the time of surgery; the intervention would have been better termed 'risk reduction' or indeed therapeutic. Until 2005 only 15% of the 275 reported 'prophylactic' thyroidectomies performed on *RET* 634 children were carried out before the age of 5.[44] Studies of outcome from **risk reduction** surgery in young patients up to the age of 21 years confirm that biochemical cure is possible and sustained at follow-up in the majority of individuals, but the highest chance of 'cure' results when age-appropriate prophylactic surgery is performed on individuals **at risk** of MTC.[45]

KEY POINTS

- Care for adult and paediatric MTC patients should be provided in a tertiary centre and treated according to the recommendations of the specialist MDT.
- All patients with MTC should be offered *RET* gene mutation analysis. If the patient is confirmed to have genetically determined disease, first-degree relatives should be offered genetic screening.
- Risk reduction/prophylactic surgery should be offered to gene carriers prior to the onset of malignant disease.
- All patients with proven or suspected MTC must have undergone biochemical testing to exclude phaeochromocytoma prior to neck surgery.
- Patients with MTC and an elevated basal calcitonin should undergo a minimum of total thyroidectomy and central neck lymph node dissection.

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CHAPTER 64

MANAGEMENT OF ANAPLASTIC THYROID CANCER/LYMPHOMA

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: anaplastic thyroid cancer and thyroid lymphoma.

INTRODUCTION

Apart from both being malignancies of the thyroid gland, the other similarity between anaplastic thyroid cancer and thyroid lymphoma is that for the majority of cases the role of surgery is limited to diagnosis and maintaining an airway. The majority of anaplastic thyroid cancer is advanced at presentation, either locally or distantly or both, and complete resection is rarely possible. In the majority of thyroid lymphomas with the exception of limited stage IE mucosa-associated lymphoid tissue (MALT) surgery is not curative and radiation with or without chemotherapy is the optimal treatment.

ANAPLASTIC THYROID CANCER

Anaplastic thyroid carcinoma (ATC) is at the extreme end of a continuum of dedifferentiation of follicular adenomas and differentiated thyroid cancer (DTC). In contrast to DTC, however, it occurs in older patients (median age 65). The female:male ratio (3:2) still is in favour of female patients but it is relatively more common than DTC in men. Unlike DTC and thyroid lymphoma it is a highly fatal cancer with a median survival of only 3–5 months. Given the appalling survival after diagnosis of the majority of patients with ATC, it is essential in any discussion of treatment that the potential risks and side effects of any treatment are discussed along with a discussion of best supportive care. Fortunately, ATC is rare in the US, accounting for less than 2% of all thyroid cancers.[1–2]

Patients usually present with rapid onset of locoregional symptoms in the background of a pre-existing thyroid goitre or mass. In a large review of over 3000 patients an enlarging neck mass occurred in 86%, also change in voice, swallowing and breathing in about a third of patients for each symptom.[1] Local pain was less common (approximately 15%). Extrathyroid extension is usual, local invasion occurring in up to 90% of cases and distant metastases are identified at presentation in 30–50%. Although the lung is the commonest site of metastasis (35%), metastases can occur in any part of the body. Given the aggressive nature of ATC, the UICC/AJCC staging is unique in that all patients are staged as stage IV: Stage IVa (confined to the thyroid), stage IVb (extrathyroid extension) and stage IVc (distant metastatic disease).[3] Along with extent of local invasion and presence of metastases, male gender, age above 60 and size of the primary (>5–7 cm) are associated with poorer survival.[2, 4, 5]

Imaging for staging should consist of CT head and neck, chest and abdomen and, when available, fluorine-18-labelled deoxyglucose positron emission tomography (FDG-PET) to assess local and distant disease. USS and MRI of the neck and a bone scan may also be of value.[6] As a third of patients have a change in voice at presentation, assessment of vocal cord function, airway adequacy and intral-uminal extension of tumour into the trachea, preferably by fibre-optic endoscopy, is essential. Once initial investigations are complete, stage of the tumour has been assessed and potential surgical

resectability has been determined, the options of treatment which require a multidisciplinary approach with surgical, medical oncology, and radiation oncology opinions along with best supporting care can be discussed with the patient and family.[7]

The morphological appearance of ATC can be very varied but spindle cells are the commonest, and giant cells and cells with squamoid differentiation can also occur. All, however, have numerous and often atypical mitoses.[8] Extensive necrosis, sometimes with inflammatory infiltrates, is common. The pathogenesis from differentiated thyroid cancer is shown in that 20% or more can coexist with areas of DTC. Surgical resection with negative margins and consequently survival is more likely in cases where ATC is only a small component.[9] A fine-needle aspiration may be diagnostic but often a core biopsy is required.

Treatment

See **Figure 64.1**.

SURGERY FOR POTENTIALLY RESECTABLE LOCOREGIONAL DISEASE

No more than 10% of patients have ATC confined to the thyroid; of these, ATC may be found incidentally.[9] In the majority of other patients, an assessment by an experienced surgeon is essential to assess whether a resection with either negative (R0) or microscopic margins (R1) is possible. In the recent guidelines on the management of ATC by the American Thyroid Association it was clearly stated that: 'Gross tumor resection, not debulking, is the goal of surgery.'[7] If the tumour is resectable, a total or near-total thyroidectomy with central and lateral lymph node dissection should probably be performed. Survival for patients with an R0 or R1 resection can result in long-term survival. However, it is important to balance the aggressiveness of the surgery with the quality of life and prognosis of a patient with ATC. An R0 or R1 resection should be performed only if surgical morbidity is minimal. Ablative surgery such as a total laryngectomy should be avoided.[7, 10] A tracheostomy, however, may be required if the patient is in acute airway distress or stridor.

ADJUVANT THERAPY

Following a successful resection, adjuvant therapy should be considered along the lines described below for unresectable ATC. Although there are no randomized controlled studies in the management of ATC, two population-based studies support the use of multimodality therapy and suggest that survival is improved. A large Surveillance, Epidemiology, and End Results (SEER)-based study of 516 patients found in a multivariate analysis that surgery combined with external beam radiotherapy (EBRT) was an independent predictor of survival.[11] In a smaller study from British Columbia, survival was better in patients who had more extensive surgery and had high-dose radiation with or without chemotherapy.[12] That these were population-based studies is important: a number of single institutional studies also support the use of multimodality therapy compared to mono therapy but they are all subject to bias as there is always an element of case selection with patients with less extensive disease, young age and better performance status potentially receiving more aggressive therapy.[9, 13–17]

The role of additional therapy after resection of an incidental ATC is uncertain. The ATA working group did not come to a consensus on whether to advise additional therapy in this situation. The role for neoadjuvant therapy for patients with unresectable disease is also uncertain. Although there have been a few reports recommending neoadjuvant therapy, the majority of patients remain unresectable. Rather than planned neoadjuvant therapy, the ATA guidelines recommend combined modality therapy for unresectable disease and, if the disease response is durable and distant metastases do not develop, then consideration of surgical resection.[7, 18–20]

UNRESECTABLE LOCOREGIONAL DISEASE

Data on outcome when a resection is not possible are mainly from single institutional reports and again subject to case selection bias, but patients with good performance status with no evidence of metastatic disease appear to have a better outcome following high-dose radiation with or without chemotherapy.[14] A response rate of 80% to radiation alone has been reported with suggestion of a dose response with higher doses resulting in a trend to improved survival but not tumour response.[21] To overcome the rapid growth rate of ATC and potential for tumour cell repopulation after radiation has commenced, the radiation may be hyperfractionated and accelerated with two fractions given a day, so that the overall treatment time is reduced. In addition, chemotherapy may be given concurrently in an attempt at radiation sensitization.[22] The most frequently prescribed chemotherapy agent in the past was doxorubicin. In a multimodality approach combining mostly doxorubicin with hyperfractionated radiation, a local control rate of 60% has been reported, but the 2-year survival rate was only 9%.[23] In contrast, the Mayo Clinic experience found no benefit in median survival, although more survived to 1 year (23%) when chemotherapy + radiation was compared with radiation alone (10%).[24]

Several more recent reports of other agents that are better established as head and neck cancer radiosensitization (cisplatin and taxanes) have suggested encouraging results with concurrent chemoradiation. In a report on 6 patients treated with intensity-modulated radiation therapy (IMRT) and docetaxel all patients had at least a partial response and 4 had a complete response.[25] In another report on 10 patients, 5 were alive and free from disease at 32 months with a median survival of 60 months. However, due to either metastatic disease or patient preference, only 10 out of 25 patients with ATC were treated on the protocol.[26] In a report of hyperfractionated radiation without chemotherapy the median survival was greater than with

conventional therapy (13.6 vs 10.3 months).[22] In contrast in another study, however, a hyperfractionated accelerated protocol with larger fraction size, no survival advantage was reported but there was significant toxicity.[27]

Typical radiation doses would be hyperfractionated 60–70 Gy in 40–45 fractions over 4–5 weeks or daily fractions such as 60–70 Gy in 30–35 fractions.

Most of the newer studies combining radiation and chemotherapy utilize IMRT. With this technique it is possible to generate concave dose distributions and narrow margined dose gradients so that normal structures can be spared while complex volumes are treated.[17, 28, 29] Despite modern radiation techniques, the toxicity from hyperfractionated radiation or concurrent chemoradiation can be significant and enteral nutrition with a feeding tube and growth factor support may be required, especially if large tumour volumes are treated. There has been no comparison of altered fractionation alone

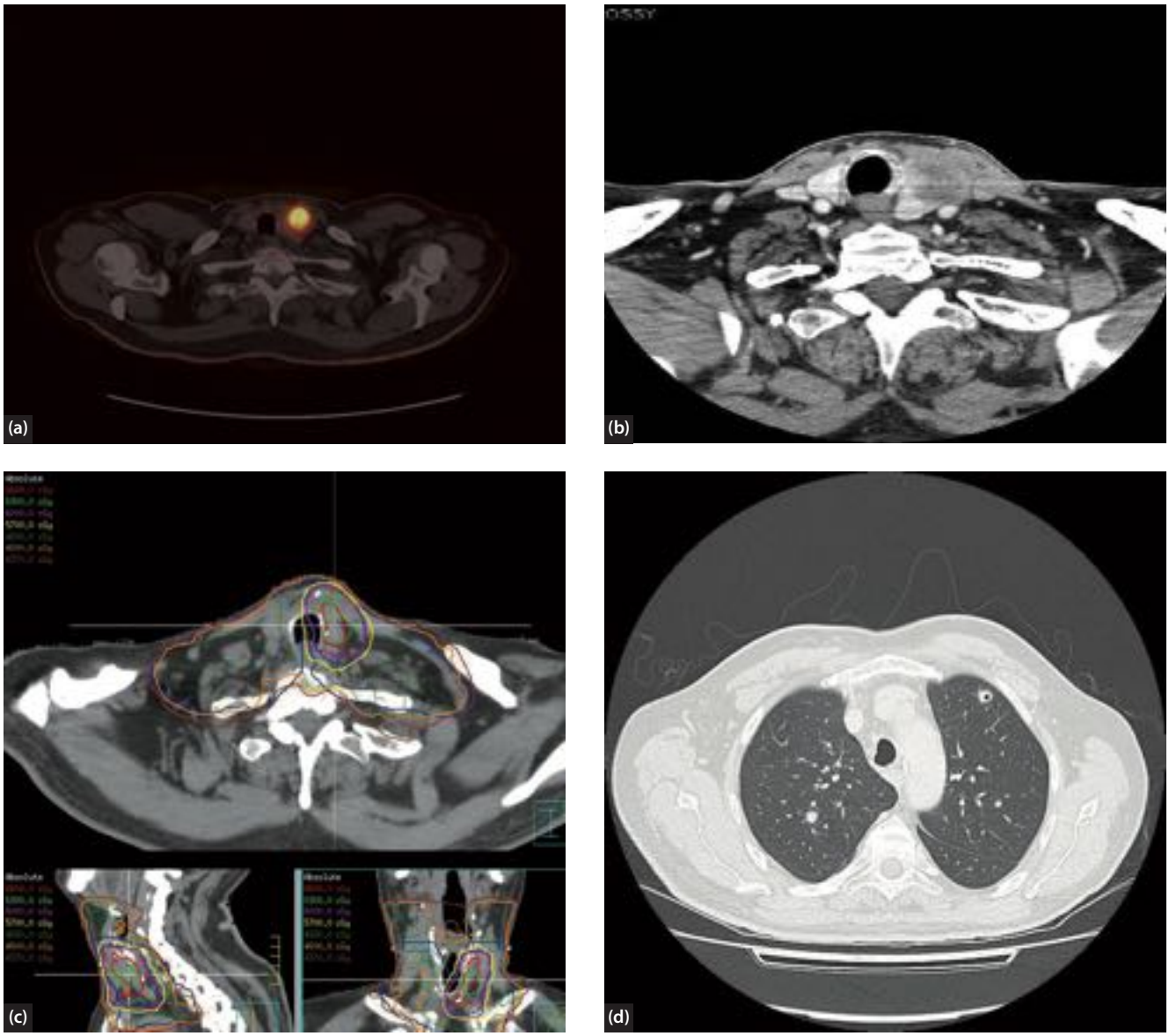


Figure 64.1 Anaplastic thyroid cancer. A 68-year-old man who had a long-standing history of a thyroid nodule that had increased in size. Fine-needle aspiration showed large and spindle cells and necrosis diagnostic of anaplastic thyroid. **(a)** Axial CT scans of his head and neck showed a 4 cm mass. There was no evidence of local invasion or lymph node involvement. **(b)** A PET scan showed uptake at the site of the lesion and nowhere else. He underwent surgical resection. Pathology revealed a 4 cm widely invasive anaplastic thyroid carcinoma. The tumour arose from a well-differentiated papillary carcinoma showing tall cell change but 70% of the total tumour volume was anaplastic carcinoma. There was extensive perineural invasion, and focal angioinvasion. The tumour infiltrated extrathyroidal skeletal muscle. **(c)** He received post-operative radiation therapy using an IMRT technique: 60 Gy in 40 fractions twice daily over 4 weeks was given to the post-operative site and concurrent 44 Gy in 40 fractions to the rest of the thyroid bed and adjacent nodal areas. **(d)** Within 2 months of completing his radiation he developed lung metastases which have progressed on paclitaxel.

compared to chemoradiation with standard or hyperfractionated radiation and the potential benefits remain unanswered especially when more aggressive therapy is associated with increased toxicity.[30]

There is no consensus whether there is any benefit in high-dose radiation with or without concurrent chemotherapy in patients with limited metastatic disease and otherwise good performance status, but it has been recommended in selected highly motivated patients.[7, 31] For patients of poor performance status who decline or who would not tolerate high-dose radiation, low-dose radiation may be of palliative benefit in controlling pain and possibly obstructive symptoms.[21] As noted earlier, radiation can result in an 80% response rate and, although higher doses of radiation resulted in improved survival, the response rate was no better. Palliative doses such as 20 Gy in five fractions (which may be repeated 4–6 weeks later) or 30 Gy in ten fractions may be of benefit in these patients.

METASTATIC DISEASE

In the presence of metastatic ATC, life expectancy is poor and therefore maintaining a good quality of life for as long as possible is imperative. Short 1–2-week courses of radiation as described above may control local symptoms. Unfortunately, ATC is not a chemosensitive disease and the response rates to systemic therapy are generally poor and short-lived. Currently, of the available chemotherapeutic agents the taxanes (paclitaxel or docetaxel), doxorubicin and cisplatin have the greatest clinical effect. Docetaxel (60 mg/m^2 i.v. every 3 weeks) can stabilize disease for a time and rarely results in a complete response.[25] There are several small reports on the use of molecular targeted agents. Antimicrotubular agents and kinase inhibitors occasionally result in a partial response or stable disease but more research is required.[2, 7, 32] Palliative radiation may be required for bone and lung metastases.[33]

KEY POINTS

ANAPLASTIC THYROID CARCINOMA

- Uncommon
- Poor survival (median 3–5 months)
- Best if incidental or R0 resection possible
- Often disseminated at diagnosis
- The role of surgery is for:
  - diagnosis
  - secure airway
  - resect to R0 or R1 if possible
- Local regional control important
- Multimodality treatment: surgery, radiation, chemotherapy
- Not chemosensitive but taxanes and molecular targeted agents show some promise
- Quality of life and palliative care are important
- Treatment guidelines:
  - American Thyroid Association – comprehensive
  - National Comprehensive Cancer Network – limited
  - European Thyroid Association – very limited

LYMPHOMAS

The management of non-Hodgkin lymphoma (NHL) in the thyroid gland is primarily influenced by the acuteness of the presentation, histology and the Ann Arbor stage.[6] A thyroid presentation occurs in only 1–2% of all patients diagnosed with lymphoma, and these are usually in stage IE (when the thyroid gland alone is involved) or stage IIE (when the cervical or superior mediastinum lymph nodes are involved additionally). The 'E' designations indicate that an extranodal organ (the thyroid gland) is involved as a primary site. The principle role for surgery is to establish the diagnosis of lymphoma[34] and to ensure a stable airway since thyroid lymphomas often present with a bulky mass with significant compression of the upper aerodigestive tract. A tracheostomy (temporary) may sometimes be necessary for tracheal lumen compromise if the patient presents with stridor. While fine-needle aspirate (FNA) may suggest lymphoma, it may be inadequate for subtyping the histology, in which case either core-needle biopsy or an open biopsy will be required. Optimal pathology interpretation involves immunophenotypic and sometimes special molecular studies, which can be done on cytology specimens if there is good cell yield. Special fixative and fresh tissue are necessary and therefore specific protocols for tissue retrieval and processing are required. If the FNA biopsy is diagnostic and able to subtype the lymphoma accurately, the therapeutic role of surgery is limited[34] as most patients are treated with chemotherapy, radiation therapy, or a combination of the two. In most cases a philosophy of functional preservation is followed. The need for the use of chemotherapy and/or radiation therapy is generally not diminished following surgical excision of lymphoma, except in the case of MALT lymphoma where a thyroidectomy if performed may be considered curative if there has been a complete excision.[35] However, aggressive surgical approaches that compromise function, including neck dissection and cosmesis, should be avoided.

Staging investigations should include CT scans of neck, chest, abdomen and pelvis and a FDG-PET scan. Thyroid scintigraphy tests with radioactive iodine or ^{99m}Tc are generally unhelpful. Blood work including complete blood count, lactate dehydrogenase (LDH) (which as a tumour marker for lymphoma usually correlates with the disease burden), liver function tests and creatinine should be done. A bone marrow aspirate and biopsy is standard. Approximately 90% will be found to have localized (stage IE or stage IIE) disease.[36] Advanced stages (stages III–IV) of lymphoma where there is documented lymphoma outside the thyroid gland and cervical lymph nodes are treated primarily with chemotherapy and will not be discussed further here. In these situations the thyroid involvement is considered secondary spread as part of disseminated lymphoma. For stage I–II presentations in the thyroid, the curative treatment approach involves radiation alone,

or combined modality therapy with chemotherapy followed by consolidation radiation.

Indolent lymphoma

The most common indolent lymphomas in the thyroid are **MALT lymphomas** (also known as extranodal marginal zone lymphomas), with **follicular lymphomas** being second most common;[36, 37] both are radiation-sensitive diseases. MALT lymphomas present with localized (stage IE–IIE) disease in 90% of cases,[38, 39, 41] involving the thyroid gland as a nodule or mass, occasionally diffusely enlarging the thyroid gland, usually non-bulky (<5 cm). It is almost always associated with pre-existing Hashimoto's thyroiditis and occasionally other autoimmune diseases which are predisposing conditions to the development of MALT lymphomas.[41] Cervical lymph nodes are involved in 20–30% of cases. Females are more commonly affected than males with a ratio of 3:1.[36]

Stage I and stage II MALT or follicular lymphomas of the thyroid gland are treated with involved-site radiation therapy (RT), covering the thyroid site and the immediate drainage lymph node regions (zones 3, 4, 5 and 6). If a total thyroidectomy was performed and the MALT lymphoma was localized within the thyroid gland and has been completely excised, no further therapy may be required and the patient should be carefully followed.[35] Local treatment is therefore highly successful, resulting in an excellent local control rate exceeding 95% and long-term disease-free survival of >90% for MALT lymphoma,[38, 39, 41, 42] and 50–60% for follicular lymphoma.[44, 45] Because of exquisite radiation sensitivity, low to moderate doses (24–30 Gy, fractionated over 2–4 weeks) has been the standard approach.

Aggressive histology lymphoma

Thyroid lymphoma with aggressive histology is the most common, accounting for 65–70% of cases.[36, 37, 45] It usually presents with a rapidly enlarging mass, sometimes growing to 10 cm or even larger when diagnosed. It can arise *de novo* or from pre-existing indolent lymphoma or Hashimoto's thyroiditis, recognized as histological transformation to aggressive disease with a poorer prognosis. There is a female predominance with typical presenting age of over 65 years.[37, 46] Cervical lymph nodes are commonly involved (20–50%).[45, 46] The most frequent histology is diffuse large B-cell lymphoma (DLBCL)[37] (**Figure 64.2**) for which standard therapy has been well established based on phase III clinical trials. Other types of aggressive lymphomas (e.g. T-cell lymphomas) rarely present in the thyroid and the management is based on a similar philosophy of treatment with combined modality therapy (CMT) and functional preservation.

Despite a presentation at an early stage (IE–IIE), the recognition of the high risk for occult systemic disease mandates the use of systemic immunochemotherapy to achieve the best cure rates.[37, 45, 46] Patients are treated with CMT, typically the CHOP-R regimen (cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab), with chemotherapy first for 3–6 cycles, followed by moderate dose radiation (30–40 Gy) 3–6 weeks later. In general, a cure rate ranging from 70–85% is achieved, depending on age, tumour burden and other prognostic factors such as performance status and LDH level.[46, 47] For the typical B-cell lymphomas, the addition of immunotherapy with anti-CD20 antibody (rituximab) in combination with chemotherapy improves the clinical outcome compared with CHOP alone[48–50] and is considered the standard approach. Because of the moderate radiation doses required (30–40 Gy), short-term toxicity is mild and serious long-term toxicity is rare, particularly with IMRT, with improved ability to further reduce the dose to uninvolved normal tissues. For stage IE patients treated with CMT, the radiation volume can be limited to the primary thyroid disease site, without intentional coverage of the drainage lymph nodes. For stage IIE patients, the coverage should include the thyroid site and the immediate drainage lymph node regions (typically bilateral zones 3, 4, 5 and 6).

Toxicity of treatment

When chemotherapy is required, the principle toxicities depend on the drugs used. For the CHOP-R regimen, the most common toxicities include nausea and vomiting, fatigue, alopecia, mucositis, myelosuppression, increased risk of infections and bleeding, neuropathy (vincristine), infusion-related reactions (rituximab) and prednisone-related side effects. More serious toxicities, such as cardiac failure, are fortunately rare. Standard management protocols including use of pre-medication, cardiac ejection fraction assessment and monitoring, and use of growth factor support minimizes these risks.

The toxicities of radiation therapy are moderate and significantly less severe than for treatments given for thyroid cancer, due to the lower total dose required for lymphoma. Short-term toxicity is mild and serious long-term toxicity is rare in virtually all head and neck tissues irradiated in the lower neck area. Xerostomia is not expected since the treated volume is generally below the level of the salivary glands. There is a significant risk of radiation-induced hypothyroidism (30% risk for a dose of 30–40 Gy).

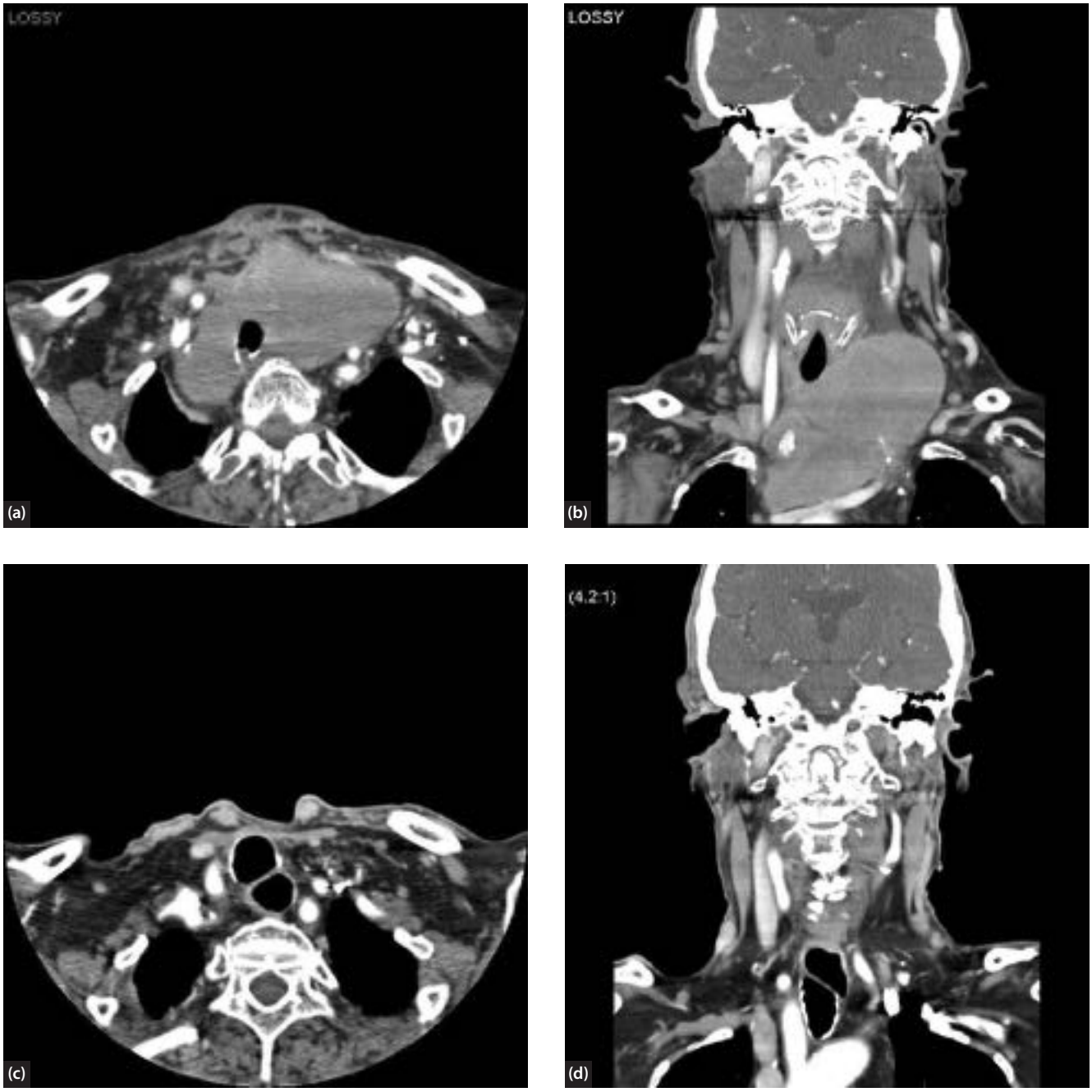


Figure 64.2 Lymphoma. An 82-year-old woman with a rapidly enlarging thyroid mass, with biopsy (right hemithyroidectomy) showing diffuse large B-cell lymphoma. There was significant residual disease involving the left lobe of the gland, right paratracheal area, and also lymphadenopathy in the left neck. Stage IIAE. Pre-treatment CT scans: **(a)** axial; **(b)** coronal. Treatment was with combined chemotherapy and radiation (CHOP-R × 6 cycles and 35 Gy) with curative intent. There was complete resolution of the disease 2 years post therapy. Post-treatment CT scans: **(c)** axial; **(d)** coronal.

KEY POINTS

Primary thyroid lymphomas

- Uncommon
- Usually localized
- The role of surgery is for:
  - diagnosis
  - secure airway
- Almost always B-cell lymphomas
- The MALT-type lymphoma has a high cure rate (>90%) with local therapy (surgery or radiation)
- Diffuse large B-cell lymphoma requires combined chemotherapy and radiation with long-term cure in 75% of patients

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CHAPTER 65

MANAGEMENT OF LOCOREGIONALLY RECURRENT DIFFERENTIATED THYROID CANCER

Iain J. Nixon and Ashok R. Shaha

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: thyroid cancer, recurrence, papillary thyroid cancer and follicular thyroid cancer.

INTRODUCTION

As differentiated thyroid cancer (DTC) becomes increasingly common, so does the challenge of managing patients with post-treatment evidence of recurrent disease. The appropriate management of such patients requires an understanding of the biology of DTC and the concept of recurrence versus persistent disease. Clinicians must also recognize the high potential for morbidity from salvage therapy and balance that against the benefit likely to be gained by their patients. In this chapter we will discuss recurrent DTC and outline an approach to management of this complex problem. The discussion will be limited to the surgical management of locoregional recurrence as systemic therapies for disseminated disease are discussed elsewhere.

RISK GROUP STRATIFICATION

Initial risk stratification systems for differentiated thyroid cancer focused on mortality.[1–3] Using these systems, patients can be classified as low, intermediate or high risk of death from disease. However, the majority of patients will fall into the low- and intermediate-risk groups with few fatalities. In 2009 the American Thyroid Association (ATA) recognized the importance of risk group stratification in recurrence prediction.[4] They published a system which again stratified patients in to low, intermediate and high risk of recurrence (**Table 65.1**).

Initial disease extent and the extent of primary surgical resection are important predictors of locoregional recurrence.[5] Those patients with advanced local disease or bulky nodal metastases have higher rates of recurrence than those with smaller lesions. Patients who have gross disease following surgery are clearly at high risk of disease progression.

Specific factors associated with locoregional recurrence include macroscopic extrathyroid extension, multiple or large volume nodal metastases, locally invasive disease and aggressive histological subtypes (insular, tall cell or poorly differentiated carcinoma). Other factors which can also predict poor outcome include advanced age, the presence of *BRAF* mutations and Tg doubling time.

A recent publication from the ATA recognized the importance of the status of the neck in predicting locoregional recurrence.[6] This work, which summarized the

TABLE 65.1 American Thyroid Association risk of recurrence stratification

	Regional metastases	Distant metastases	Extrathyroid extension	Surgical resection	Aggressive pathology	RAI uptake outside thyroid bed	
Low risk	Absent	Absent	Absent	Complete	Absent	Absent	Only low risk if all are true
Intermediate risk	Present	Absent	Microscopic	Complete	Present	Present	Intermediate **or high risk if any are true**
High risk		Present	Macroscopic	Incomplete			

TABLE 65.2 Level of risk associated with specific nodal metastatic features in papillary thyroid cancer (adapted from Randolph et al[6])

	Descriptor	Locoregional recurrence rate
Clinically N0 (cN0)	All patients	6%
	Young patients*	0%
	Older patients *	9%
Clinical N1 (cN1)	All patients	13–30%
	All patients*	19–42%
Pathological N1 (pN1)	All patients	7–14%
	All patients*	13%
Specific pN1 descriptors	<5 positive lymph nodes	3%
	>5 positive lymph nodes	19%
	>10 positive lymph nodes	21%
	Extranodal extension	15%

* Denotes that papillary micro carcinomas were excluded from these cohorts.

available literature at the time, demonstrated the importance of size and number of nodal metastases as well as the significance of extranodal extension (Table 65.2).

DEFINITION OF RECURRENCE IN DIFFERENTIATED THYROID CANCER

The approach to managing DTC has become increasingly standardized over the past 50 years.[4, 7–11] Recognition of the relatively indolent biology of the disease and the role of therapy has led to well-defined international treatment guidelines. However, over the same time period a significant change has taken place in relation to recurrent disease.

In the mid-20th century, clinicians followed their patients with clinical examination including palpation of the neck and visualization of the larynx. Investigations including chest X-rays would soon be surpassed by more advanced imaging including computed tomography (CT) scanning, magnetic resonance imaging (MRI) and ultrasound. Further progress with ever-improving imaging, particularly with the widespread adoption of high-resolution ultrasound, allowed clinicians to subject the central and lateral neck to increasing levels of scrutiny following initial therapy.

During the same period the introduction of serum thyroglobulin (Tg) measurement allowed a biochemical assessment of residual or recurrent tissue of thyroid origin. Improvements in the sensitivity of Tg assays have now allowed the detection of recurrence which is of such small volume that even the most advanced imaging systems cannot identify structural disease. In addition to measuring Tg in patients' serum, when structurally suspicious nodal disease is targeted for biopsy, cytology can be supported with thyroglobulin measurements in fine-needle aspiration biopsy specimens in order to confirm metastatic thyroid cancer.[12]

While our ability to identify biochemical and structural evidence of recurrent disease has improved, so too has our understanding of the biology of DTC. The majority of patients with DTC will have papillary thyroid cancer (PTC). This malignancy has a behaviour which does not conform to that of other head and neck malignancies. Groups who routinely dissect the regional lymph nodes in PTC report high rates (up to 40%) of histologically demonstrable metastatic lymph nodes, despite a lack of pre-operatively identifiable disease.[13] The more scrutiny such nodal dissections are subjected to, the higher the rate of demonstrable metastasis, with one group showing over 50% of nodal specimens to contain evidence of thyroid tissue in resected lymph node specimens by immunohistochemistry when conventional staining showed no evidence of thyroid cells.[14]

Unlike squamous cell carcinoma, however, where the presence of regional lymph node metastases is associated with a halving of survival, the impact of subclinical metastases in PTC has little impact on survival.[6] Indeed, the impact on recurrence has also be questioned.[15,16] So small is the perceived impact of occult nodal disease that no major international guideline now supports prophylactic lateral neck dissection in DTC and the tide is turning away from prophylactic central neck dissection also except in high-risk patients.[7,17]

In understanding recurrent DTC, therefore, the clinician must appreciate some critical distinctions. Structural recurrence which can be suspected based on clinical examination or imaging studies and supported by cytological sampling must be distinguished from biochemical recurrence alone. In addition, when disease is identified following initial therapy, a distinction must be drawn between likely persistent disease in the nodes of an untreated neck and truly recurrent disease which presents within the previously operated field. It should also be recognized that, when unresectable disease is identified either pre-operatively or following surgical exploration, progression of disease in that site presents another separate challenge for the disease management team.

Most recurrences are now detected by biochemical evaluation and/or ultrasound screening. Following initial therapy, a rising Tg tends to be an indication of recurrence which is generally in the lymph nodes of the neck. Although cross-sectional imaging and radioactive iodine (RAI) scans can be used to detect structural recurrence, ultrasound is usually the most convenient modality to assess the regional lymphatics. Positron emission tomography (PET) scanning can be useful, particularly for de-differentiating cancers which lose their radioactive iodine avidity. Such PET-positive, RAI-negative disease is more aggressive and associated with poor outcome. An outline for considering recurrent thyroid cancer is provided in Table 65.3.

MANAGEMENT OF RECURRENCE

The goals of managing recurrent disease in thyroid cancer should be considered prior to embarking on a course of management. The ultimate goals include removing recurrent disease and preventing further recurrence.[18] When considering these aims, one must also consider the goal of minimizing morbidity and negatively affecting a patient's quality of life. Indeed, if the decision is made to observe potentially recurrent disease, the goal of management is to prevent disease progression, with a particular focus on invasion of critical structures during follow-up.

Disease recurrence in the central neck may involve the nodal tissue, the thyroid bed or both. Local, thyroid bed recurrence is rare but, when it occurs, the anatomical location of disease presents a significant challenge in terms of surgical resection. Involvement of the recurrent laryngeal nerve (RLN) may be a presenting feature of the recurrence, and invasion of the larynx or trachea should be suspected based upon the relationship between the airway and the site of disease. Airway involvement can be categorized as by Shin et al. into tumour adherent to the perichondrium (stage 1), invading cartilage (stage 2), involving submucosa (stage 3) or involving mucosa (stage 4) (Figure 65.1).[19]

Pre-operative assessment of the airway is critical in managing thyroid cancer recurrence, particularly with regard to assessment of the function of the RLNs. If a tumour involves the oesophagus, unlike in primary disease where a plane can often be dissected between muscle and mucosa, scarring may require full-thickness oesophageal resection which will then mandate appropriate reconstruction with free tissue transfer or gastric pull-up. Following surgery, external beam radiotherapy should be considered as an adjunct as it has been shown to improve rates of local control in patients demonstrating gross extrathyroidal extension.[20–23]

A contrast should be made between visceral and nodal recurrence in the neck. Isolated nodal recurrence which does not involve the laryngopharyngeal complex should be carefully assessed prior to deciding to operate. Again the function of the RLNs, the size of the lesion and its

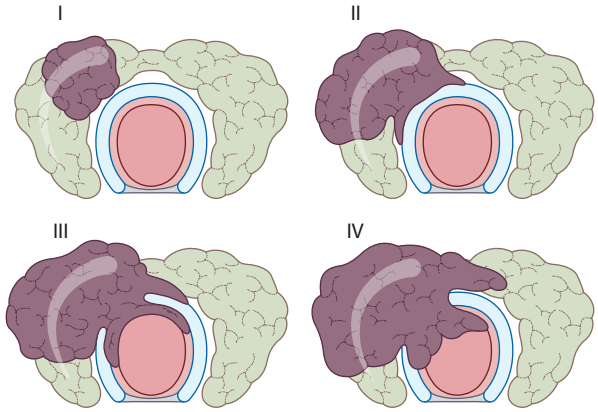


Figure 65.1 Shin classification of airway involvement with thyroid cancer.

TABLE 65.3 Types of differentiated thyroid cancer recurrence

Central compartment		Lateral neck		Distant
Thyroid bed	Central compartment lymph nodes	Levels I–V	Retropharyngeal and parapharyngeal nodes	Pulmonary > non-pulmonary metastases
Recurrence involving visceral structures	(Levels VI and VII)			

precise anatomical location should be determined. Small-volume nodal tissue which is distant from the nerve and airway may be safely followed. In contrast, rapidly enlarging nodes or disease in close proximity to the central neck viscera should be treated more aggressively in order to prevent extension into vital structures.

A compartment-orientated approach to a previously unoperated nodal field harbouring recurrence includes a level II–V selective neck dissection for lateral neck disease and levels VI–VII for central neck disease. However, for recurrence within an operated field, such an approach is likely to be associated with high morbidity and a more targeted approach may be reasonable.

Evidence relating to oncological outcomes following surgical therapy for recurrent DTC suggests that a significant number of patients can be 'cured'. However, the literature is difficult to interpret due to differences in definitions of cure (biochemical versus structural), the inclusion of patients of various risk groups in different studies and the differences in duration of follow-up. Nonetheless, groups report success rates of 25–90% of appropriately selected patients.[24–30]

For example, research from MD Anderson Cancer Center, USA, found that, of 210 patients with recurrent or persistent PTC who underwent comprehensive central compartment dissection, 71% of pre-operatively Tg positive had no evidence of post-operative disease and 66% had no measurable Tg at last follow-up (median 7.25 years). Those patients who did suffer recurrence were able to be surgically salvaged giving an overall 98% central compartment control rate and 10-year disease-specific survival of 99% for young patients and 78% for older patients. In this surgical series from a tertiary referral cancer centre the rate of hypoparathyroidism was 1% and new RLN palsy was encountered in 2%.[27]

A group from Ohio State University reported outcomes of 95 patients with recurrent or persistent PTC. They found that 27% of patients achieved a biochemical complete response following lymphadenectomy and 42% achieved a stimulated Tg of <2.0 ng/mL. Even those who did not achieve a complete response did have a significant reduction in Tg following initial and, if required, subsequent surgeries. None of these patients developed distant metastases or died of disease.[28]

It should be noted, though, that the senior authors of such publications are experienced, high-volume surgeons often working in tertiary referral centres. Such outcomes are unlikely to be achieved in less experienced hands.

Traditional surgical therapy has been the standard of care for structural disease following initial therapy in DTC. However, some groups have adopted an alternative approach including both ethanol and radiofrequency ablation of small-volume recurrences with apparently high rates of success. Although not widely practised, these treatment modalities are particularly attractive for low-risk patients with small nodes in a site amenable to a percutaneous approach.[31–34]

EVALUATION OF THYROGLOBULIN LEVEL

The introduction of routine Tg monitoring following treatment for DTC has resulted in a paradigm shift in such patients' management. Small-volume recurrences can now be identified prior to the development of structural disease. The identification of a rising Tg should prompt further imaging. In most circumstances, persistent disease is in the neck and ultrasonography will be the initial imaging modality of choice. If significant structural disease is encountered, surgical excision should be recommended.

If small-volume (<8 mm) suspicious nodes are identified, clinicians should proceed with caution. When one study observed 166 low-risk patients with abnormal lateral neck nodes, only 20% of patients demonstrated progression and 14% regressed.[35] Assessment of the potential disease extent and relationship to critical structures should guide further management in this situation. Small-volume nodes which are distant from the RLN may safely be monitored without the need for biopsy or intervention. If a decision is made to pursue such small-volume disease, even in experienced hands, identification of the nodes in question can be challenging and techniques such as charcoal tattooing and intra-operative ultrasound should be considered to aid localization.

When a rising Tg is encountered in the absence of any evidence of structural disease on imaging, surgery is not indicated. The role of RAI in this situation is controversial with some advocating empirical treatment in an attempt to address occult micrometastases. In general, however, this approach is not supported.[36]

COMPLICATIONS OF TREATMENTS

Rates of complication in the setting of revision surgery, particularly in a previously operated field, are higher than those following initial therapy.[37] Although common complications include injury to the RLN and temporary or permanent hypoparathyroidism when re-entering the central neck, revision lateral neck surgery is also associated with high rates of injury to the accessory nerve, the lower division of the facial nerve or the sympathetic trunk. Due to the relatively high rates of complication, the disease management team must develop a balanced approach and incorporate what they consider the best surgical intervention to control disease while minimizing rates of complication.

PRACTICAL TIPS IN THE MANAGEMENT OF RECURRENT THYROID CANCER

The management of recurrent thyroid cancer is complex and surgical intervention may be difficult due to

involvement or proximity of the structures in the central compartment. Thorough evaluation with cross-sectional imaging is very important. The decision about tracheal shave versus sleeve-resection of the trachea will directly depend on the tracheal involvement by recurrent tumour. A majority of the tumours can be easily shaved off the trachea, unless there is a direct submucosal or intra-luminal extension of the disease. The surgeon should be prepared to make these complex decisions intra-operatively for the best oncologic resection of the recurrent tumour.

The nodal recurrence in the central compartment and at level IV may be also a complex surgical undertaking, primarily related to complications of nerve injury and hypoparathyroidism. The operating surgeon should evaluate the extent of the disease and be prepared to manage the patient with a multidisciplinary approach. These patients will require lifetime follow-up.

A sub-centimetre recurrent tumour may be difficult to find and may present a higher risk of injuring the nerve. Generally these patients are secondary references to a cancer centre and involvement of the surgeon, endocrinologist and the multidisciplinary team is very critical. Patients should be warned of the complications of the surgical procedure and the appropriate decision-making should be undertaken for the best form of treatment. Patients should be informed that the thyroglobulin level may not be normalized after the surgery, or they may recur in the future, either in the same neck, quadrilateral neck or in the superior mediastinum. It is very important to have a best understanding with the patient, their family and the treating physicians. The first principal of surgery should be maintained – *Primum non nocere* – first do no harm.

CONCLUSION

Patients with recurrent differentiated thyroid cancer truly require multidisciplinary team management. Not only a surgeon and endocrinologist but nuclear medicine physician, radiologist, pathologist, cytologist and even oncologist must collaborate for optimal evaluation and overall control of disease. By balancing the risks of treatment against the chance of successful outcome, the disease management team must consider options from observation through limited resection to aggressive surgical therapy on a case-by-case basis.

KEY POINTS

- Recurrent thyroid cancer may be biochemical or structural.
- Careful assessment of recurrence should include cross-sectional imaging and endoscopy.
- Small volume nodal recurrence in areas without critical structures may be suitable for observation.
- Large-volume recurrence in high-risk areas (around the recurrent laryngeal nerve for example) should be managed surgically.
- The potential complications of revision surgery should be carefully weighed against the potential benefits on an individual patient basis.

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CHAPTER 66

NON-SURGICAL MANAGEMENT OF THYROID CANCER

Laura Moss

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: radioactive iodine, risk stratification, thyroglobulin, radiation protection and targeted therapy.

DIFFERENTIATED THYROID CANCER

There is limited prospective randomized controlled data relating to the management of differentiated thyroid cancer (DTC) as it is an uncommon disease with a long natural history. Many areas of thyroid cancer management remain controversial, including the indications for ablation using radioactive iodine (RAI, also called radioiodine), the optimal administered activity of radioiodine, the degree and duration of thyroid-stimulating hormone (TSH) suppression, as well as indications for external beam radiotherapy and optimal timing for initiation of targeted therapies for the treatment of metastatic disease. The recommendations in this chapter reflect common UK practice and advice from the British Thyroid Association (BTA) and American Thyroid Association (ATA) guidelines.[1, 2]

^{131}I treatment

Normal thyroid gland tissue and differentiated thyroid cancer can concentrate iodine from the circulation and ^{131}I (an unsealed radionuclide of iodine) is taken up in the same way as stable iodine in the diet.

In practice, it is very difficult to achieve complete surgical ablation of the thyroid gland and some residual tissue, known as the thyroid remnant, is inevitably present. As a rule, normal thyroid tissue within the remnant will preferentially take up the iodine compared to thyroid cancer tissue. Hence, if a large remnant is present post-operatively, the post-ablation whole-body radioiodine scan cannot be relied upon to exclude the presence of residual malignancy either locally in the neck or at distant sites as the iodine may be seen in the remnant only. Only when this remnant of normal thyroid tissue is ablated can you reliably expect to see any significant radioiodine uptake in regional and distant sites of differentiated thyroid cancer.

RADIOIODINE REMNANT ABLATION

Radioiodine uptake is usually seen in the thyroid bed following a total or near-total thyroidectomy. ^{131}I destruction of this residual tissue is called radioiodine remnant ablation (RRA).

RRA aids the detection and earlier treatment of persistent/metastatic disease by destroying normal thyroid tissue; it may destroy microscopic foci of cancer in the thyroid remnant, and aids interpretation of serum thyroglobulin (Tg) measurements during follow-up. Remnant ablation may reduce local recurrence and increase survival,[3, 4] although not all reported series support these findings.[5–8]

It is important to individualize patient management and to use radioiodine selectively by allocating patients to a risk category post-operatively (Table 66.1).

TABLE 66.1 Post-operative risk stratification for risk of recurrence of DTC[1]

Category of risk	Patient characteristics
Low risk	No local or distant metastases All macroscopic tumour has been resected, i.e. R0 or R1 resection No tumour invasion of locoregional tissues or structures The tumour does not have aggressive histology (tall cell, or columnar cell PTC, diffuse sclerosing PTC, poorly differentiated elements) or angioinvasion
Immediate risk	Microscopic invasion of tumour into the perithyroidal soft tissues (T3) at initial surgery Cervical lymph node metastases (N1a or N1b) Tumour with aggressive histology (tall cell, or columnar cell PTC, diffuse sclerosing PTC, poorly differentiated elements) or angioinvasion
High risk	Extrathyroidal invasion Incomplete macroscopic tumour resection (R2 resection) Distant metastases (M1)

The following is the British Thyroid Association's guidance on the indications for ^{131}I ablation.[1]

- **No indication for ^{131}I ablation**
  These patients are at low risk of recurrence or cancer-specific mortality.
  - Tumour <1 cm unifocal or multifocal, and on histology classical papillary or follicular variant or follicular minimally invasive without angioinvasion and no invasion of thyroid capsule.
- **Definite indications for ^{131}I ablation**
  - Tumour >4 cm.
  - Any tumour size with gross extrathyroidal extension (pT4).
  - Distant metastases present.
- **Uncertain indications for ^{131}I ablation**
  Patients in this category may or may not derive a benefit from ablation. Factors that may influence the decision on whether to proceed include:
  - large tumour size
  - extrathyroidal extension
  - presence of unfavourable histological cell type (tall cell, or columnar cell papillary thyroid cancer (PTC), diffuse sclerosing PTC, poorly differentiated elements)
  - widely invasive histology
  - multiple metastatic lymph nodes
  - resected metastatic lymph nodes large in size, high ratio of positive to negative nodes, extracapsular nodal involvement.

HIGH VERSUS LOW ADMINISTERED ACTIVITY OF ^{131}I FOR REMNANT ABLATION

Administered activities of ^{131}I of 1.1 GBq or 3.7 GBq show similar rates of successful remnant ablation,[10–13] although there is a trend towards higher success rates with higher administered activities.

Results from two large multicentre randomized trials[14, 15] have shown that 1.1 GBq of ^{131}I was as effective as 3.7 GBq in ablating the thyroid remnant, while adverse events were fewer in the 1.1 GBq group. In these studies all patients had undergone total thyroidectomy and had an R0 (no microscopic residual disease) resection. Most patients were staged pT1 N0 and pT2 N0. One of the trials[14] included patients with pT3 tumours, and patients with N1 disease, who were ablated successfully with 1.1 GBq. A recent meta-analysis found no difference in efficacy between 1.1 GBq and 3.7 GBq.[16]

^{131}I ADMINISTRATION PROCEDURE

Those prescribing radionuclide therapies in the UK must hold an appropriate Administration of Radioactive Substances Advisory Committee (ARSAC) certificate and the treatment must be given in appropriately designed areas.

Radioiodine is administered orally. Although it is available in liquid or capsule formulations, the latter is the preferred format as it is easier and safer to handle.

For successful remnant ablation to be achieved, the TSH level prior to the isotope administration must be elevated to >25–30 mU/L. This stimulates the sodium iodide symporter (membrane protein involved in active transport) and hence radioiodine uptake into thyrocytes. This can be achieved in two ways.

- **Recombinant human TSH injections (rhTSH, Thyrogen™):** These can be administered as an exogenous source of TSH and allow the patient to continue with thyroid hormones throughout the radioisotope treatment period. The benefit with using rhTSH is the avoidance of potential significant physical and psychological symptoms of hypothyroidism resulting from thyroid hormone withdrawal.[17, 18]
- **Thyroid hormone withdrawal:** If the period between surgery and RRA is expected to be longer than 4 weeks, patients should be commenced on thyroid hormone replacement. If liothyronine is commenced (usual dose 20 mcg tds), this should be withdrawn 14 days prior to radioactive iodine treatment. If levothyroxine is used, it should be substituted with liothyronine starting 28 days prior to radioactive iodine treatment and this is then stopped for the last 14 days prior to treatment. By swapping the thyroid hormones in this way, it is possible to reduce the length of time that the patient is rendered hypothyroid. If ^{131}I ablation can be performed approximately 4 weeks after surgery, there may be no need for thyroid hormone supplementation to be commenced in the immediate post-operative period but this might be associated with the development of unnecessary hypothyroid symptoms.

The decision whether a patient should receive ^{131}I remnant ablation after thyroid hormone withdrawal (THW) or after rhTSH injections depends on the current licensed

indications of use for rhTSH, the patient's comorbidities and the local availability of rhTSH injections.

The current licensed indications for rhTSH (Thyrogen™) use are as follows:

- With serum Tg testing with or without radioiodine imaging for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on thyroid hormone suppression therapy (THST). Low-risk patients with well-differentiated thyroid carcinoma who have undetectable serum Tg levels on THST and no rhTSH-stimulated increase of Tg levels may be followed up by assaying rhTSH-stimulated Tg levels.
- For pre-therapeutic stimulation in combination with a range of 1.1–3.7 GBq radioiodine for ablation of thyroid tissue remnants in patients who have undergone a near-total or total thyroidectomy for well-differentiated thyroid cancer and who do not have evidence of distant metastatic thyroid cancer.

Patient factors that would warrant rhTSH use in preference to THW include hypopituitarism, functional metastases causing TSH suppression, severe ischaemic heart disease, previous history of psychiatric disturbance precipitated by hypothyroidism, advanced disease and frailty.

Injections of rhTSH (0.9 mg) are given by deep i.m. injection into the buttock on days 1 and 2 with radioiodine being administered on day 3.

Possible rhTSH side effects include flu-like myalgia, mild nausea and headache. There is also the possibility of stimulating thyroid remnant tissue and metastases, resulting in local symptoms, and consideration should be given to prophylactic corticosteroids before use if residual neck disease or metastases are known to be present.

Serum Tg should be measured immediately prior to ^{131}I administration if THW preparation is undertaken or ideally on day 5 if rhTSH is used and local facilities are set up to handle radioactive samples.

Patients with pT1-2, N0 with R0 resection should receive 1.1 GBq. For patients with pT3 and/or N1 disease, the final choice of ^{131}I activity should be decided by the MDT on an individual case basis, taking all prognostic factors into consideration.

^{131}I therapy doses are usually in the range 3.7–5.5 GBq. Whole-body radioiodine scans are performed 2–10 days after giving radioiodine for ablation or therapy to determine the sites of radioiodine uptake and are more sensitive than diagnostic whole-body scans due to the higher administered activity of radiation used. The addition of SPECT CT to planar gamma camera imaging allows more precise anatomical localization of any iodine uptake demonstrated. The timing of the scan will depend on the administered activity of ^{131}I, the method of patient preparation (rhTSH versus thyroid hormone withdrawal) and the clinician's choice of the residual activity at which to image the patient.

Physiological ^{131}I uptake is seen in salivary tissue, genitourinary tract, gastrointestinal tract and sinuses. Hürthle cell lesions are generally poorly responsive to radioiodine treatment and in particular distant metastases are often resistant to radioiodine therapy.

A pre-ablation radioisotope scan is not routinely indicated, but it may be used to demonstrate the size of thyroid remnant. If a large remnant is seen, consideration of further surgery may be warranted. If further surgery is not appropriate, it may influence the activity of radioiodine that is administered and prompt the prescription of pre-medication with corticosteroids prior to RAI to limit radiation thyroiditis symptoms.

If a preablation scan is performed, a low administered activity of ^{99m}Tc pertechnate or ^{123}I are preferred to ^{131}I as they reduce the risk of stunning,[19, 20] which is the term used for the reduction in uptake of the ^{131}I therapy dose as a result of the pre-treatment diagnostic dose.

Thyroid hormones can be started 1–3 days after radioiodine administration if the patient has been withdrawn from hormones. If the patient has been given rhTSH, they can stay on thyroxine throughout the procedure.

Prior to radioiodine administration, the total body iodine pool should be reduced. A low daily intake of iodine can increase the effective radiation dose achieved with ^{131}I in the regions of interest.[21–23] There is little consensus on the degree and the duration of dietary iodine restriction, but duration of the diet is often 1–2 weeks.

Other sources of excess iodine (e.g. iodinated i.v. contrast and amiodarone) should be eliminated before proceeding with ^{131}I administration.

^{131}I TOXICITY

- Neck discomfort and swelling may be caused by an inflammatory response in the remnant, residual tumour or involved cervical lymph nodes. This is most likely to be seen when there is a large thyroid remnant present. Discomfort is usually adequately treated with simple analgesics. If the patient has only had a debulking procedure and gross residual thyroid tissue is present, prophylactic corticosteroids are advisable to minimize the pain and swelling associated with the inflammatory response and can be started just prior to RAI administration.
- Patients may experience an altered sense of taste, and nausea (although vomiting is uncommon and prophylactic antiemetics are not routinely indicated).
- Sialadenitis arises due to physiological uptake of ^{131}I and subsequent excretion from salivary tissue. This can be reduced by encouraging patients to drink liberal quantities of fluids. In the long term, it is possible for intermittent parotid swelling, which may be tender, to develop. This can often be managed by parotid duct massage and the use of post-meal sialogogues if there is no evidence of duct stenosis or calculus.
- Lacrimal gland dysfunction.
- Radiation cystitis. The risk may be reduced by maintaining a high fluid intake following radioiodine administration and during the isolation period.
- Gastritis.
- Bleeding/oedema in metastases.

- Bone marrow suppression. This reaches its peak 4–6 weeks after treatment. It is more likely in those patients who have extensive skeletal metastases or who have received prior external beam radiotherapy or chemotherapy.
- Gonadal tissue is exposed to radiation from radioiodine in the blood, urine and faeces.
- **Male fertility:** a temporary rise in follicle-stimulating hormone (FSH) and a reduction in sperm count may be seen. High cumulative doses (e.g. >14 GBq) may reduce fertility, and consideration should be given to sperm storage in high-risk cases where multiple therapeutic doses of ^{131}I are expected.[24]
- **Female fertility:** no significant difference in fertility rate, birth weights or prematurity rates have been documented. Temporary alterations in the menstrual cycle may last for 4–10 months in about a quarter of female patients. Increased risk of miscarriage may persist for up to 1 year following ^{131}I ablation/therapy.[25–29] The risk of impaired fertility may be reduced by maintaining a high fluid intake following radioiodine administration and for the duration of the isolation period. This is in order to dilute the urine and therefore reduce concentration of radioactive iodine in the bladder and hence exposure of gonadal tissues.
- If the patient has undergone thyroid hormone withdrawal, constipation is a common symptom of the hypothyroid state so laxatives may help in reducing radiation exposure to gonadal tissue.
- If miliary pulmonary metastases are present, the patient may be at risk of developing pulmonary fibrosis especially if a high cumulative activity of radioiodine is administered. Consideration of pulmonary function test monitoring and corticosteroids immediately before and during treatment may reduce this risk. The data available are, however, fairly limited.[30]
- An increased risk of leukaemia and second cancers in organs that concentrate ^{131}I (salivary gland, breast, bladder, colon) is seen, with the risk being highest with high cumulative activities of radioiodine, i.e. greater than 18.5 GBq, and after external beam radiotherapy. The risk of leukaemia is lower than reported in earlier series due to deliberate attempts to limit the total body dose and to increase the interval between radioiodine administrations, whereas the risk of second solid malignancy might be higher than previously thought.[31, 32]
- Good hydration, frequent micturition and regular bowel activity will help reduce the level of whole-body radiation.

Consideration should be given to the use of high-dose corticosteroids before radioiodine if there is bulky neck disease or metastatic disease.

RADIATION PROTECTION ISSUES

Before the administration of ^{131}I, pregnancy and lactation must be excluded. Following the administration of ^{131}I, pregnancy must be avoided for 6 months and male patients must avoid fathering a child for 4 months.[33]

During the patient's stay in the isolation room, visiting of family and friends must be restricted to non-pregnant adults. Visiting options vary between centres but often entail no direct entry into the patient's room, with visitors needing to stay in a designated area outside the room.

The patient's clothing must be washed separately on their return home, unless it is heavily soiled, when storage on the hospital site or disposal may be needed. The method of transport home may be determined by the patient's residual activity. For example, short-distance travel in a private family vehicle, unoccupied by children, may allow discharge home with a higher residual activity than a longer journey via public transport where exposure to other members of the public, particularly children, may occur. Once at home, the patient must double-flush the toilet, use separate cutlery and crockery, sleep alone, and restrict the time with and extend the distance between them and their contacts. The duration of the restrictions is individualized for each patient and is longer for prolonged and close contact with children and pregnant women than with non-pregnant adults. Timing of a patient's return to work will depend on the type of work undertaken, the work environment and the surrounding work personnel involved. The patient will be given dates on discharge home which advise how long radiation protection restrictions need to be followed for adults and a second longer date for children and pregnant (or potentially pregnant) women

TSH LEVEL

Following total thyroidectomy, thyroxine is required both to replace thyroid hormones no longer produced endogenously and to suppress TSH levels. The dosage tends therefore to be larger than that used for replacement purposes following thyroidectomy for a benign aetiology.

Thyroxine in these larger doses prevents the pituitary from being stimulated to produce TSH and hence prevents stimulation of any remaining thyroid tissue, whether normal or malignant, with the intention of reducing the risk of recurrence, tumour progression and death.

The degree of suppression has not been tested in prospective studies and, due to concerns regarding the effects of prolonged supraphysiological thyroxine doses in low-risk cases, there has been a recent move to relax the degree of TSH suppression in low-risk cases, aiming for a TSH within the lower part of the normal range.

The BTA Guidelines 2014 recommend the following:[1]

- Patients who have not received RRA do not require TSH suppression and the serum TSH should be maintained in the low–normal range.
- Following initial treatment with total thyroidectomy and RRA, and before evaluation of the patient's response to treatment after 9–12 months, TSH should be suppressed to below 0.1 mU/L in all patients.
- In patients with an excellent response to treatment for thyroid cancer, the serum TSH should be maintained in the low–normal range.

- In patients who have an indeterminate response, it is recommended that the goal of TSH suppressive therapy be adjusted to maintain serum TSH concentrations between 0.1 mU/L and 0.5 mU/L for 5–10 years.
- In patients with an incomplete response to treatment for thyroid cancer, the serum TSH should be suppressed below 0.1 mU/L indefinitely in the absence of specific contraindications.

When TSH is being suppressed, the free T4 (fT4) level is often seen to be above the upper limit of the normal range. Moderate elevation does not commonly result in symptoms or signs of 'hyperthyroidism'.

Thyroxine is taken once daily, usually in the morning, and on an empty stomach. A number of medications can interfere with the absorption of thyroxine, so it is advisable to leave a 2-hour gap between taking thyroxine and other medications, such as calcium supplements, antacids, iron and multivitamins.

THYROGLOBULIN

Thyroglobulin is a glycosylated protein which is a key substrate for biosynthesis and storage of thyroid hormones. It is secreted by normal and cancerous thyroid cells and its release is TSH-dependent. The diagnostic sensitivity of Tg is increased when the TSH level is elevated. The Tg level may be undetectable in 20% of cases in the presence of isolated lymph node metastases if it is measured while the patient is on TSH suppression therapy. The serum Tg level is more sensitive than ^{131}I whole-body scan (WBS) in detecting recurrent or metastatic disease.

Thyroglobulin autoantibodies (TgAb) interfere with the ability to accurately measure and follow Tg trends. The prevalence of thyroglobulin antibodies is higher in patients with differentiated thyroid cancer (DTC) than in the general population (up to 25% versus 10%).[34] There is evidence that measuring TgAb levels and trends is of value in monitoring patients with thyroid cancer if the Tg cannot be relied upon in the presence of the autoantibodies; a rising trend in TgAb levels may indicate disease relapse in a patient.[35–39]

In order to interpret the serum Tg level, it is necessary to know the TSH level and TgAb level.

Serum thyroglobulin is not useful as a diagnostic test pre-operatively because Tg is a product of normal thyroid tissue and can be markedly elevated by inflammatory thyroid diseases. It is therefore not specifically a serum tumour marker; however, if elevated in a patient who has previously been rendered athyroid by surgery and radioiodine ablation, it may indicate recurrent or metastatic differentiated tumour.

A serum Tg which starts rising over time while on suppressive thyroxine therapy is highly suggestive of tumour recurrence and needs further investigation. There is no need to measure Tg under TSH stimulation if the basal serum Tg is already detectable.[40–45]

FOLLOW-UP

There is some variation in practice relating to the timing and modalities used for assessing success of thyroid remnant ablation. Whole-body radionuclide imaging has largely been superseded by neck ultrasound and stimulated Tg assessment in many centres. Cervical ultrasound is a sensitive method for detection of residual disease in the thyroid bed or cervical lymph nodes. It is essential for the ultrasound to be performed by a highly skilled operator with knowledge of thyroid cancer behaviour and not as a routine investigation by a general ultrasonographer.

Diagnostic ^{131}I or ^{123}I scans can, however, provide useful information on the effectiveness of ablation and the need for further ^{131}I if uptake was seen outside the neck on the post-ablation whole-body scan and can be considered for patients with thyroglobulin antibodies.

A follow-up neck ultrasound scan and stimulated Tg should ideally be performed 9–12 months following ablation.[1] The results from these two investigations will be used to allocate patients to a treatment response group. This process is 'dynamic risk stratification' (**Table 66.2**).[46–48]

For low-risk cases, if initial follow-up serum Tg is undetectable under TSH stimulation conditions, subsequent long-term follow-up Tg assessments can be performed under TSH suppression conditions.[49]

If the follow-up neck ultrasound scan and stimulated Tg are within normal limits, the patient is kept on clinical follow-up with Tg monitoring. If the scan or the Tg is abnormal, a decision needs to be made on further management. This may be surgery if localized disease is identified in the thyroid bed or cervical lymph nodes or ^{131}I therapy. The usual administered activity of ^{131}I in this setting is 5.5 GBq[1] and this too will be followed up with repeat imaging and Tg assessment to assess response.

TABLE 66.2 Dynamic risk stratification: definitions of response to initial therapy of DTC (9–12 months after total thyroidectomy with R0 resection and subsequent RRA) (Adapted from American Thyroid Association[42, 43])

Excellent response	Indeterminate response	Incomplete response
All of the following are present: • Suppressed and stimulated Tg <1 µg/L • Neck ultrasound without evidence of disease • Cross-sectional and/or nuclear medicine imaging negative	*Any* of the following are present: • Suppressed Tg <1 µg/L and stimulated Tg ≥1 and <10 µg/L • Neck ultrasound with non-specific changes or stable subcentimetre lymph nodes • Cross-sectional and/or nuclear medicine imaging with non-specific changes, although not completely normal	*Any* of the following are present: • Suppressed Tg ≥1 µg/L or stimulated Tg ≥10 µg/L • Rising Tg values • Persistent or newly identified disease on cross-sectional and/or nuclear medicine imaging

The TSH stimulated Tg level may remain detectable at low levels after ^{131}I ablation. This could represent residual/recurrent cancer but in the majority of cases represents thyroid remnant. An expectant policy in low-risk cases is recommended with repeat TSH-stimulated Tg assessment at 6–12 month intervals. In many cases, repeat assessments will reveal a gradual decline in stimulated Tg to the point of no detection, when routine follow-up should then be commenced.

Thyroglobulin-positive, imaging negative disease

This is a not uncommon scenario seen in the follow-up of patients with differentiated thyroid cancer and there is uncertainty regarding optimal management.

When Tg is detectable, additional investigations aiming to localize the disease recurrence and offer specific therapy (in particular, surgical resection of the disease wherever possible) are indicated.

A possible imaging strategy is as follows:

1. Neck ultrasound/MRI of neck and mediastinum – the thyroid bed, cervical and mediastinal nodes are the most common sites of recurrence for PTC. *If negative:*
2. CT lungs – to look for micronodular lung metastases. Remember the potential for iodinated intravenous contrast to inhibit subsequent radioiodine uptake. *If negative:*
3. ^{99m}Tc isotope bone scan. MRI spine is more sensitive and may be considered if the bone scan is equivocal and the patient has localized symptoms. *If negative, consider proceeding with:*
4. ^{18}FDG-PET/CT imaging. TSH stimulation prior to positron emission tomography (PET) imaging has shown increased sensitivity in some studies.[50, 51] Patients with positive FDG-PET imaging have a reduced 3-year survival compared with those who are FDG-PET scan-negative. If PET imaging is positive, ^{131}I imaging is typically negative and the patient is radioiodine refractory. This is often referred to as the 'flip flop' phenomenon.

If imaging fails to identify sites of disease, there are two main approaches:

- continued monitoring until repeat imaging demonstrates recurrent disease or the patient becomes symptomatic
- empirical ^{131}I therapy.[52, 53]

The decision on whether to proceed with an empirical dose of ^{131}I needs to be made, bearing in mind the risk category of the patient and the rate of Tg rise. It is uncertain whether empirical ^{131}I treatment is beneficial in patients with raised serum Tg, compared to active surveillance. There is no evidence from randomized controlled trials for or against empirical ^{131}I. Proponents argue that a high proportion of patients will have positive post-therapy scans and/or thyroglobulin response and some may achieve cure. Opponents argue that some of these patients have minimal disease and hence radioiodine is unlikely to improve survival and that treatment is associated with acute toxicity. A meta-analysis showed that 50% of post-therapy scans will be positive and of these positive cases 60% will also show a fall in Tg.

Recurrent or metastatic disease

Between 5% and 20% of patients with papillary thyroid cancer relapse in the thyroid bed or cervical nodes, and surgery is the treatment of choice for such locoregional recurrence. Ideally, complete resection is recommended but, if this is not feasible, debulking is beneficial as this will facilitate greater radioiodine uptake in a smaller volume of disease. Distant metastases develop in 10–20% with pulmonary and bone accounting for the majority. If the patient has radioiodine-avid disease, repeated doses of radioiodine are indicated provided there is evidence of symptomatic, radiological or biochemical response.

Remission can be achieved in about two-thirds of patients with neck recurrence and one-third of those with distant metastases. Remission is more likely when a limited tumour burden is present.[54, 55]

Prognosis depends on the distribution and number of metastatic sites, tumour burden (microscopic foci are more likely to respond) and age at the time of diagnosis of metastases.[56, 57] If tumour takes up ^{131}I, then long-term survival is possible. The preferred treatment is repeated doses of ^{131}I with administered activities ranging between 3.7 GBq and 5.5 GBq at 6–12-month intervals.

Fixed administered activities of ^{131}I are generally used, but dosimetrically calculated activities are used in some centres.[58] There is no maximum limit to the cumulative administered activity of ^{131}I that can be used in the treatment of a patient with persistent disease. Normal bone marrow function is needed and reductions in the administered activity are required in the presence of renal impairment.

Extensive bony metastases are generally not curable by ^{131}I alone. For solitary or a limited number of bone metastases, external beam radiotherapy, resection or embolization with or without post-operative external beam irradiation may be associated with increased survival. Other potential treatments include thermal ablation and cement injection.

External beam radiotherapy

The use and role of radiotherapy in differentiated thyroid cancer is debated due to conflicting results in published series. There are no randomized controlled trials and the retrospective reviews often extend over several decades, resulting in considerable variation in extent of surgery and accuracy of staging investigations. Problems with selection bias are also encountered, as well as inappropriately short follow-up for a disease with a long natural history.

The published data are also often lacking with regards to the radiotherapy techniques and doses used, the acute and late toxicity and study end points. The long natural history of the disease means that drawing conclusions from any treatment intervention is difficult.[59–61]

External beam radiotherapy (EBRT) is infrequently used but the main indications are:

- gross local invasion with significant gross macroscopic residual
- residual or recurrent neck disease that fails to concentrate iodine and that is not amenable to surgery
- palliation of inoperable metastatic disease.

The area treated (target volume) generally includes the thyroid bed (in particular the tracheo-oesophageal groove) and draining lymph nodes (perithyroidal lymph nodes in the central compartment, paratracheal, pretracheal, superior mediastinum and cervical lymph nodes) in papillary and oncocytic follicular (Hürthle cell) cancers. Draining lymph nodes do not need to be irradiated in non-oncocytic follicular thyroid cancer unless there is confirmed nodal involvement.

Technical difficulties arise due to the irregular shape of the areas requiring treatment and their proximity to the spinal cord, which is more sensitive to the effects of radiotherapy than tumour tissue and is therefore a dose-limiting structure. Without careful attention to radiotherapy planning and delivery, the patient is at risk of radiation myelopathy. The anatomical relationship between the target area and the spinal cord makes it difficult to deliver a homogenous dose to the areas at risk with conventional radiotherapy techniques.

Intensity-modulated radiotherapy (IMRT) allows a better radiation dose distribution to the tumour while reducing the dose to radiosensitive organs close to the target areas.

During radiotherapy the patient is treated supine. Due to the proximity of the area for treatment to critical structures and the need to deliver treatment accurately and precisely over a number of weeks, an immobilization shell is required to keep the patient in a reproducible position.

The most common acute toxicities seen with external beam radiotherapy in this situation are mucositis with associated odynophagia, skin erythema, skin desquamation and laryngitis. If level I and II cervical lymph node areas need irradiating, taste changes, xerostomia and accelerated dental decay and a small risk of osteoradionecrosis of the mandible can arise.

It is possible that radiotherapy may reduce the uptake of radioiodine into residual thyroid tissue and therefore consideration should be given to administering radioiodine therapy before external beam radiotherapy. However, in practice, there may be a significant delay before the patient can be admitted to the isolation room for RRA and for some patients it may be advisable to proceed with external beam radiotherapy rather than delay both treatment modalities.

Targeted therapies

The principal indication for targeted treatments is progressive, symptomatic disease, refractory to conventional treatments. Efficacy for increased progression-free survival (PFS), but not overall survival, has been demonstrated for several agents. The agents demonstrating the most activity and clinical benefit to date are sorafenib and lenvatinib. A randomized phase 3 trial of sorafenib versus placebo resulted in a PFS benefit of 5 months for patients on sorafenib over those on placebo (10.8 versus 5.8 months; $p < 0.0001$).[62] Studies continue to evaluate the role of molecular profiling in determination of the most appropriate targeted agent.

Targeted therapy agents are administered orally and have a different toxicity profile compared to conventional chemotherapy. The common toxicities are:

- hypertension
- hand–foot skin reaction (palmar–plantar erythrodysaesthesia) and rash
- diarrhoea, constitutional symptoms such as anorexia and weight loss
- cardiac ischaemia
- increased risk of bleeding
- alopecia.

These agents should only be prescribed by a specialist and patients need to be closely observed especially during the initial weeks of therapy in order to detect early signs of toxicity. There is a high incidence of toxicity which will require treatment breaks and dose reductions.

Targeted therapy is a rapidly evolving area and information on current clinical trial activity can be found at the websites listed in ‘Key points’ below.

Chemotherapy

There are no data to support the use of adjuvant chemotherapy in the management of differentiated thyroid cancer and it is also not routinely used in the management of locally recurrent or metastatic disease. Its use has largely been superseded by targeted therapies. Published studies of chemotherapy have usually only included small numbers of patients and have often had a mixture of histological tumour types within the study population.

Doxorubicin is the most extensively studied agent in advanced thyroid cancer and the most frequently used drug, with a partial response rate of approximately 20–30% reported.[64–66] There is no clear evidence, however, that its use increases survival. Doxorubicin in combination with cisplatin has demonstrated a higher response rate but with additional toxicity and no improvement in outcome.

Childhood

Thyroid nodules are more likely to be malignant in children. Papillary carcinoma is the most common differentiated thyroid cancer seen, with 30–40% being

multifocal; 40–90% of patients are found to have involved cervical nodes at initial surgery.

Differentiated thyroid cancer tends to behave more aggressively in children younger than 10 years of age and the chance of recurrence is also higher.[67–70]

^{131}I ablation is generally indicated for all children and adolescents with differentiated thyroid cancers >1 cm following total thyroidectomy, and selective neck dissection is recommended for children with positive nodes. The dynamic risk stratification model has not been specifically validated in the setting of paediatric differentiated thyroid cancer but the same general principles should be considered when deciding on the pros and cons of radioiodine remnant ablation.

At presentation, 10–20% have lung metastases, while bone metastases are rare (<1%). Fewer than 10% will die as a result of their disease.

Management of differentiated thyroid cancer during pregnancy

If differentiated thyroid cancer is diagnosed during pregnancy, it is essential to consider the risk to both mother and foetus of both the cancer treatment options and the continuation of the pregnancy. Thyroid cancer discovered during pregnancy does not behave more aggressively than that diagnosed in a similar aged group of non-pregnant women. Women of childbearing age with thyroid cancer generally have an excellent prognosis, similar to that of non-pregnant women.

Thyroidectomy in the first trimester of pregnancy is associated with a very high risk of miscarriage, but it may be performed safely in the second trimester. Alternatively, surgery can be deferred until after the baby is delivered provided the patient is monitored and the thyroid cancer lesion remains stable. Suppressive doses of thyroxine are safe in pregnancy and may be considered until surgery is possible. The dosage of thyroxine will need to be increased during pregnancy.[71] Termination of pregnancy is rarely indicated.

It is advisable to stop breastfeeding at least 8 weeks and preferably 8 weeks prior to ^{131}I.

Follow-up

Frequency and type of follow-up depends on an individual's risk of recurrence.[1]

Patients who have undergone hemithyroidectomy for a low-risk cancer do not require TSH suppression.

Once the thyroid remnant has been ablated and following dynamic risk stratification the frequency of attendance will be decided in each case individually:

- Patients with excellent response should be followed 6-monthly for the first year, and annually thereafter.
- Patients with indeterminate or incomplete response should be followed up more frequently depending on individual need.

Follow-up should be lifelong for the following reasons:

- The disease has a long natural history.
- Late recurrences can occur, which can be successfully treated with a view to cure or long-term survival.
- The consequences of supraphysiological levothyroxine replacement (such as atrial fibrillation and osteoporosis) need monitoring, especially as the patient ages.
- Late side effects of ^{131}I treatment may develop.

Clinical trials

A list of websites where information on current clinical trials can be found is given in 'Key points' below.

MEDULLARY THYROID CARCINOMA

Surgery is the main modality of treatment for this disease and monitoring of serum calcitonin post-operatively is important in establishing whether biochemical control has been achieved.[72, 73] The calcitonin level of many patients, however, remains elevated after surgery and it is frequently difficult to locate the site of residual disease and determine whether it is local or at a distant site. Blood samples taken for calcitonin must be immediately stored in ice since rapid degradation occurs at room temperature and may give falsely low results. Carcinoembryonic antigen (CEA) is also commonly raised and can similarly be used to monitor progress and response to therapeutic intervention.

It is presumed that rendering a patient calcitonin-negative will give them an improved chance of long-term survival and cure. Many patients with a raised calcitonin level remain well with an excellent performance status for many years, whereas others become symptomatic over a much shorter interval. In a retrospective review of 65 patients,[74] calcitonin doubling time during follow-up was a significant predictor of survival in both univariate and multivariate analyses. A calcitonin doubling time greater than 2 years was associated with long-term survival, whereas patients with a doubling time of less than 6 months all died as a result of their medullary thyroid cancer. An online calcitonin and CEA doubling-time calculator can be found on the American Thyroid Association website (https://www.thyroid.org).

External beam radiotherapy

Due to a lack of prospective studies, the role of adjuvant radiotherapy to the thyroid bed and cervical nodes remains uncertain.[75–77] It is difficult to compare published series due to considerable differences in radiotherapy dose fractionation and eligibility criteria, and the relative rarity of the disease means that recruitment has been over very long periods of time. Reported series also often fail to report the associated toxicity and impact on quality of life of any treatment intervention.

Radiotherapy may be indicated in the following situations:

- post-operatively, when the disease was locally advanced at presentation and a macroscopic clearance has not been achieved
- multiple involved lymph nodes, especially if extracapsular spread is present
- bulky inoperable tumours
- palliation of distant metastases (e.g. bone).

Routine adjuvant radiotherapy in the post-operative setting has not been shown to improve survival.

METASTATIC MEDULLARY THYROID CANCER

Many patients' survival can be measured in years and, even in the presence of significant disease bulk, quality of life can often be good.

Distant metastases frequently involve the liver, lungs and the skeleton and may first come to light when the serum calcitonin level rises significantly. Occasionally, the first sign of the development of distant metastases may be when the patient starts to experience diarrhoea as a result of excess peptide release or symptoms related to excess hormone production. As well as experiencing frequent loose bowel actions often with urgency, wheezing and flushing are also possible. Cushing's syndrome may also rarely occur. These symptoms may respond to somatostatin analogue therapy (e.g. octreotide). Chemotherapy is rarely helpful and has largely been superseded by targeted therapies.

There is no curative treatment option. Treatment interventions are therefore usually reserved until the patient becomes symptomatic and/or develops significant radiological progression with accelerated calcitonin doubling times rather than at first presentation of asymptomatic radiologically diagnosed metastases or raised tumour markers.

Unlabelled somatostatin analogue therapy for diarrhoea

Diarrhoea can be a challenging symptom for some patients and, in the first instance, is usually managed with loperamide and/or codeine. If these agents fail, consideration can be given to the use of somatostatin analogue agents.

Somatostatin receptors can be found on medullary thyroid cancer cells and therefore blocking these receptors can result in a decrease in the amount of peptide and calcitonin released. However, a significant decrease in tumour mass is not seen and the aim of treatment is an improvement in symptoms – diarrhoea and flushing and quality of life. Unfortunately, any recorded benefits often seem to be short-lived.

If a patient responds favourably to a twice or three times daily subcutaneous administration of octreotide, a synthetic somatostatin analogue, with a reduction in diarrhoea frequency or severity, then they can be commenced on a monthly depot preparation. With prolonged use, there is a risk of tachyphylaxis developing with loss of symptomatic benefit. However, if symptom control deteriorates, it is important to consider if disease progression is the cause before attributing the change to tachyphylaxis. Octreotide and lanreotide have a different spectrum of somatostatin receptor blockade. Side effects of the somatostatin analogues include gastrointestinal disturbances, such as anorexia, nausea, vomiting, abdominal pain, flatulence, diarrhoea and steatorrhoea, and rarely with long-term use gallstones may occur. Abnormalities of glucose metabolism may also occur. Local reactions at the site of administration may be seen and rotation of the injection site is recommended.

Targeted radiolabelled therapies

Once metastatic disease has been established, imaging with ^{123}I metaiodobenzylguanidine (mIBG) or ^{111}In octreotide may demonstrate selective uptake at sites of known tumour relapse, thereby opening up the possibility of using similar agents as targeted radiolabelled therapies.

As medullary thyroid cancer is not derived from follicular cells, it does not accumulate radioiodine.

METAIODOBENZYLGUANIDINE (mIBG) THERAPY

Metaiodobenzylguanidine is a guanethidine derivative, structurally similar to noradrenaline. It is transported into neuroendocrine tumour cells by monoamine transport proteins and may be useful as a therapy in a small number of cases.

Approximately 30–40% of medullary thyroid cancers concentrate ^{131}I-mIBG, but histological tumour characteristics that reliably predict isotope uptake and hence suitability for therapy have not yet been defined.

Prior to treatment, care must be taken to prevent the use of drugs that may interfere with the uptake and retention of mIBG. The following are some examples, but not an exhaustive list: tricyclic antidepressants, phenothiazines, calcium channel blockers, salbutamol and opioids. Administered activities of ^{131}I-mIBG vary and treatment is often given at 2–3-month intervals for three cycles, depending on the patient's tolerance and the benefits observed.

The treatment is given in an isotope isolation room by intravenous infusion usually over a 1–2 hour period through a lead-shielded infusion system. Frequent blood pressure monitoring is required during the infusion and for a period of time afterwards, as unstable blood pressure can result. In practice, this is usually managed by slowing or interrupting the infusion, but in the case of a hypertensive crisis, intravenous alpha and beta blockers such as phentolamine boluses and an esmolol infusion may be required. These drugs should be prescribed in advance and should be available at the time of the mIBG administration.

Prophylactic antiemetics, such as ondansetron, are indicated prior to the infusion and should be continued for 72 hours afterwards. It is advisable to insert two cannulae to allow simultaneous i.v. fluids to be given to ensure good hydration in case the patient is unable to take adequate fluids orally as a result of nausea. It is possible that the

patient may experience diarrhoea, wheezing and flushing related to peptide and hormone release from the tumour. The patient remains in the isolation room for several days and will follow similar radiation protection procedures as described above under 'Differentiated thyroid cancer'.

Whole-body gamma camera imaging is performed preferably with SPECT CT just before the patient is discharged home to demonstrate the distribution and intensity of isotope uptake.

A full blood count (FBC) should be checked weekly for 6 weeks afterwards as myelosuppression, particularly thrombocytopenia, can occur. This is more likely if there is widespread bone marrow involvement or if the patient has received chemotherapy.

Response to treatment can be assessed in terms of symptom improvement, decreasing calcitonin levels or tumour regression on imaging. It is the former, however, which tends to dictate management decisions. Up to 60% of patients may derive symptom benefit and 30–80% may achieve disease stabilization. However, these data are derived from small series.[78–80] mIBG is traditionally reserved until patients become symptomatic from metastatic disease and it is unknown whether its use earlier in the natural history of the disease may be beneficial.

RADIOLABELLED SOMATOSTATIN ANALOGUE THERAPY

Somatostatin receptor imaging is reported to have a sensitivity of 50–70% in localizing medullary thyroid tumour.[81, 82]

Somatostatin analogues bound to ^{90}Yttrium or ^{177}Lutetium can therefore be used as therapy in those patients who demonstrate sufficient somatostatin analogue uptake within sites of tumour when compared to background physiological uptake. A subjective benefit may be seen after one or two treatments and this may be associated with a reduction in calcitonin/CEA and tumour stabilization. It is important to realize that a formal radiological assessment of response can be misleading. Often, overall tumour size remains static on cross-sectional imaging, even in the presence of significant radioisotope uptake, symptomatic response and biochemical response. Toxicity includes myelosuppression and nephrotoxicity. Pre-treatment with an amino acid infusion reduces binding of the somatostatin analogue to the renal tubules and hence reduces renal damage.

Other targeted therapies

Various vascular endothelial growth factors (VEGFs) and VEGF receptors (VEGFRs) are often overexpressed in MTC, both in tumour cells and in the supporting vascular endothelium.

Two agents are now licensed for the treatment of symptomatic inoperable locally advanced or metastatic medullary thyroid cancer:

- vandetanib[83–85] (Caprelsa™) which targets *RET*, epidermal growth factor receptors (EGFRs) and VEGFR
- cabozantinib[86] (Cometriq™) which targets *RET*, c-Met and VEGFR.

These agents have shown the potential to provide high rates of disease control (partial response and stable disease) with durable responses and a highly statistically significant improvement in PFS. These treatments are given orally on a daily basis for as long as tumour control persists.

Common acute toxicities include:

- photosensitivity
- palmar plantar syndrome, rash
- prolonged QTc interval and risk of sudden death
- hypertension
- fatigue, reduced appetite, diarrhoea, nausea, vomiting
- corneal deposits
- proteinuria, nephrolithiasis.

Short-term toxicity can be significant and often requires dose reductions or treatment withdrawal. Treatment should only be initiated by a specialist and close monitoring is required. Long-term toxicity needs to be investigated further and includes concerns over the potential for skin malignancy to develop.

Chemotherapy

This is rarely used now that targeted therapies have become available but it might rarely be considered for rapidly progressive and symptomatic metastatic disease.

There are no randomized controlled trials and no significant survival benefit has ever been demonstrated.

As medullary thyroid cancer is a neuroendocrine tumour (NET), chemotherapy regimens with activity in other NETs, such as carcinoids, have been suggested, such as 5-fluorouracil and streptozocin.

Clinical trials

A list of websites where information on current clinical trials can be found is given in 'Key points' below.

ANAPLASTIC THYROID CANCER

Patients with anaplastic thyroid cancer (ATC) have a very poor prognosis, with the median survival being 6 months from symptom onset.[87–89]

External beam radiotherapy

This tumour is the least radiosensitive of the thyroid tumours. Tumour response tends to be partial even with high doses and the majority of patients still die as a result of locally progressive disease. It is also very important to appreciate that patients may spend a very significant proportion of their remaining lives undergoing treatment and recovering from its significant toxicity.

Attempts have been made to improve response to treatment by intensifying the radiotherapy regimen by hyperfractionation (delivering more than the standard one fraction of radiotherapy per day) or by shortening the time period over which it is delivered (accelerated radiotherapy) and combining this with chemotherapy.[90–93] This intensification has in some series resulted in improved response rates but at the cost of increased toxicity and no increase in overall survival.[94]

Chemotherapy

There is no definitive evidence to demonstrate prolonged survival or improved quality of life for ATC patients treated with systemic therapy. Tumour regression can, however, be induced in some patients. Risks and potential benefits must be carefully considered in each case. The agents with the greatest clinical activity in metastatic ATC are the taxanes (paclitaxel or docetaxe), the anthracycline doxorubicin, and the platins (carboplatin and cisplatin).

Fosbretabulin, a prodrug of the antimicrotuble-disrupting agent combretastatin was assessed in the randomized phase II functional assessment of cancer therapy (FACT) trial. Unfortunately, the study closed prematurely due to slow patient recruitment but stable disease was seen in 27% with a median survival of 4.7 months and 23% of patients surviving 1 year.[95]

Clinical trials

A list of websites where information on current clinical trials can be found is given in 'Key points' below.

KEY POINTS

- Decisions on radioiodine remnant ablation should be individualized taking into account both patient and tumour factors.
- Administered activity of radioiodine in the ablation setting is dependent on the risk category.
- Recombinant human TSH should be used where possible in the radioiodine ablation setting to avoid hypothyroidism and reduced quality of life caused by thyroid hormone withdrawal.
- Degree and duration of long-term TSH suppression depends on the dynamic risk stratification outcome.
- Metastatic thyroid cancer may be low volume, slowly progressive and asymptomatic in many cases and an active surveillance approach is appropriate during this time.
- Information on current clinical trials can be found at the following websites:
  - https://www.ukctg.nihr.ac.uk/
  - https://www.clinicaltrials.gov/
  - https://www.cancer.gov/
  - https://www.centerwatch.com/
  - https://www.thyroid.org/

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CHAPTER 67

THYROIDECTOMY

Ricard Simo, Iain J. Nixon and Ralph P. Tufano

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: thyroidectomy, thyroid surgery, thyroid lobectomy, total thyroidectomyt, recurrent laryngeal nerve, thyroid cancer.

There is lack of substantive high-level evidence due to the intrinsic nature of the chapter. In most areas the evidence is at most level 2.

HISTORY OF THYROIDECTOMY

The first recorded thyroidectomy was attributed to Abdul Kasan Kelebis Abis in Baghdad in AD 500. The first in Europe was performed in Spain by another Arabic physician Abu Al-Qasim (El-Zahra 936–1013) and its record published in his book *Al-Tasrif* in AD 952.

In 1646 the first thyroidectomy using scalpels was performed. However the patient, a 10-year-old, died and the surgeon was imprisoned. During the subsequent two centuries surgery for the thyroid gland was hazardous due to the inability to adequately control bleeding, and the lack of antisepsis and anaesthesia. Most patients died and this surgery was extremely unpopular and even condemned by prominent physicians and surgeons. The mortality rate from thyroid surgery by 1850 was about 40%.

During the first part of the 19th century advances were made in the understanding of the function of the thyroid gland and the role of iodine. Two Swiss physicians, Johan Straub and Franciois Coindet, recommended the use of iodine to reduce the size and vascularity of goitres before surgery was undertaken.

The second half of the century saw two crucial developments that helped to usher in a new era of thyroid surgery: the discovery of anaesthesia and the introduction of antisepsis by Joseph Lister meant that surgery became much safer. These developments coincided with the arrival of Theodor Kocher and Albert Theodor Billroth.

Albert Theodor Billroth (1829–1894), one of the most prominent surgeons of his time, reduced his thyroidectomy mortality rate from 40% to 8% thanks to anaesthesia and antisepsis. However, thyroid surgery will always be associated with Theodor Kocher (1841–1917). While he was Chair of Surgery in Bern, he performed more than 5000 thyroidectomies. He was extremely meticulous and paid close attention to haemostasis. He was the first surgeon to systematically ligate the inferior thyroid artery, which reduced significantly the risk of haemorrhage. His mortality rate plummeted from 12.6% in 1870 to 0.2% in 1898. He introduced the collar incision, preserved the strap muscles whenever possible and pioneered anaesthesia and antisepsis for thyroid surgery. However, by removing the entire thyroid gland, many patients were left severely hypothyroid and Kocher described this as *chachexia struma priva*. This prompted him to study the physiology, pathology and surgery of the thyroid gland in great detail, which in 1909 earned him the Nobel Prize. It was from then on that he was acknowledged as the 'father of modern thyroid surgery'.

William S. Halsted (1852–1922) brought the Kocher surgical philosophy to the USA. He also introduced antisepsis and developed a new set of haemostats, which together with his meticulous technique made thyroid surgery very safe. Halsted also introduced the first residency programme at the John Hopkins Hospital in Baltimore where he was made Professor of Surgery. From this programme, many famous future thyroid surgeons were trained including Charles Horace Mayo, Frank Lahey and George Crile.

Further refinements to thyroid surgery were introduced by Thomas Peel Dunhill, Jan Mikuliz, Wolfler, Eugene Gley and Harold Floss who first introduced the use of motion pictures to teach thyroid surgery.

Thyroidectomy is now a common procedure with rates increasing year-on-year.[1] In contrast to early results, complications related to thyroidectomy are now uncommon, with the highest volume surgeons reporting the lowest risk of morbidity.[2]

Despite all of these developments, the principles of Kocher's surgical philosophy with meticulous surgical technique and exemplary attention to detail continue to serve as the cornerstone of thyroid surgery.[3, 4]

SURGICAL CONCEPTS

- **Total lobectomy (TL):** the removal of the one lobe, often performed with a thyroid isthmusectomy.
- **Thyroid isthmusectomy (TI):** the excision of the thyroid isthmus, often with the pyramidal lobe of the gland, a procedure that should be reserved for nodules in the isthmus which measure no more than 4 cm in diameter and do not encroach significantly on either lobe.
- **Subtotal thyroidectomy (ST):** the bilateral excision of more than one half of the thyroid gland on each side together with the isthmus. This technique is currently not recommended.
- **Near-total thyroidectomy or Dunhill's thyroidectomy (NTT):** the excision of 90% of the gland, leaving a small remnant of tissue on one side at the level of the Berry's ligament.
- **Total thyroidectomy (TT):** the excision of the entire thyroid gland.

Partial lobectomy, subtotal lobectomy and nodulectomy are confusing terms and are best avoided.

INDICATIONS AND EXTENT OF SURGERY

Thyroidectomy is a benchmark procedure for surgeons, and a thorough understanding of the indications for surgery results in the ability to select the most appropriate primary operation, which is critical to maintaining excellent outcomes. When selecting an appropriate thyroid procedure, the surgeon must first consider whether the surgery is for benign disease, malignancy or diagnostic purposes.

Excision of a nodule from the thyroid gland or 'nodulectomy' has been abandoned. The reasons for this include the bloody nature of the operation itself, but more importantly the high rates of recurrence of benign or malignant disease following surgery. Not only are recurrence rates high, but re-operative surgery for recurrence typically involves unacceptably high risks to both the recurrent laryngeal nerve (RLN) and the parathyroid glands. In addition, for malignant disease, unacceptable oncological outcomes have been associated with less than total thyroid lobectomy.

For most purposes, then, the complete removal of one entire thyroid lobe should be considered the minimum thyroid surgery performed by the modern surgeon.[5]

SURGERY FOR BENIGN DISEASE

Patients without evidence of malignancy may be considered for surgery either due to benign nodular thyroid disease causing compression or cosmetic concerns, or in the setting of hyperthyroidism.

Non-toxic multinodular goitres

In the event that nodular disease has resulted in compression of the trachea or oesophagus, surgical decompression should be considered. Pre-operative assessment is crucial. The surgeon must not only consider the site of compression, but the entire gland, as some patients will have bilateral multinodular disease.[6]

In patients with a single nodule which has enlarged sufficiently to cause compression, TL alone may be sufficient to relieve symptoms, while preventing the need for contralateral tracheoesophageal groove dissection, and therefore eliminating the chance of permanent hypoparathyroidism and bilateral vocal cord palsy. Post-surgical surveillance of the remaining thyroid remnant will be required, as will regular thyroid function tests as up to a third of patients will develop hypothyroidism during long-term follow-up.[7] The need for later thyroid hormone replacement is more common in those with a raised pre-operative thyroid-stimulating hormone level or thyroiditis.[8]

For those patients with bilateral multinodular goitre (MNG), TT is the operation of choice.[9] This removes all nodules and minimizes the chance of recurrence.

ST should only be considered in healthcare settings where an adequate supply of exogenous thyroid hormone cannot be ensured, and functioning thyroid tissue is preserved to maintain endocrine function.

Thyrotoxicosis

The choice of surgery for patients with hyperthyroidism will be related to the pre-operative findings in the gland as a whole. Analysis suggests that surgery for Graves' disease is successful, with total thyroidectomy the preferred option.[10]

For those patients with an autonomously functioning solitary nodule, TL alone may suffice. For those patients with multinodular disease or global glandular dysfunction (e.g. Graves' disease), TT should be recommended. Such an approach again reduces the chance of recurrent hyperthyroidism, and the need for reoperative surgery. Patients considered for such surgery must understand that they will require lifelong hormone supplementation.

'DIAGNOSTIC' SURGERY

This term is controversial but just under 30% of patients investigated for thyroid malignancy will have an indeterminate pre-operative diagnosis.[11] In this setting, each patient should be considered on an individual basis.

Those patients with uninodular disease, which would be adequately treated with TL alone in the setting of malignancy, should undergo TL.[12, 13] Those with multinodular disease should be considered for TT for ipsilateral diagnostic purposes and also to prevent the need for lifelong serial assessment of contralateral nodules.

Patients who have uninodular disease but are likely to require completion thyroidectomy in the event of a malignant diagnosis can be offered either diagnostic TL with completion thyroidectomy as a staged procedure, TT up front, or TL with on-table frozen section analysis with immediate completion if malignancy is confirmed.

Each approach has advantages and disadvantages. Clinicians must assess each case, including the clinical, biochemical, ultrasonographic and cytological features in order to make an individualized decision. A number of statistical models are available to assist in predicting the risk of malignancy within an individual thyroid nodule, which can be used in the clinical setting to aid decision-making and informed consent.[14]

SURGERY FOR MALIGNANT DISEASE

Many patients who undergo surgery for thyroid nodules do so with a biopsy-proven malignant lesion.[15]

For patients with T3 and above differentiated thyroid cancers (DTC), medullary carcinoma of the thyroid, poorly differentiated thyroid cancer, multinodular glands, multifocal cancer, evidence of extrathyroidal extension or overt nodal metastases, the majority of authors agree that TT is the procedure of choice.[16–20]

Patients with disease limited to the isthmus may have a TI lesion[21] but for the majority of patients with uninodular DTC, without extra thyroid extension or metastases, TL results in oncological outcomes equal to TT.[22, 23]

When considering the extent of surgery for thyroid cancer, the surgeon, endocrinologist, nuclear medicine physician and patient must all agree to the proposed treatment plan. Bear in mind that it is rare for a patient with DTC to die of disease following appropriate primary therapy, so a balance between maximizing outcome while minimizing morbidity must be achieved in every case.

CONSENT

The consent for thyroidectomy should include the explanation of the procedure, its rationale and the options of alternative treatments relevant to the condition. The potential complications should be discussed and should include the risks of general anaesthesia, scarring, infection, haemorrhage, injury to the external branch of the superior laryngeal nerve (EBSLN) and to the RLN, hypocalcaemia and hypothyroidism. In cases of large retrosternal goitre or invasive thyroid carcinoma, the risks of airway obstruction with the potential need for tracheostomy should also be discussed. If extensive intrathoracic goitre requires sternal split or lateral thoracotomy, all relevant complications such as injury to pleura and pneumothorax, pneumonia, and injury to phrenic nerves and the pericardium should be discussed.[8, 24, 25]

PRE-OPERATIVE CONSIDERATIONS

1. Evidence of clinical examination, cytological or histopathological analysis and adequate imaging should be available.
2. Laryngeal examination and pre-operative voice assessment with fibre-optic laryngoscopy should be performed on all patients.[26]
3. Patients should be euthyroid; in thyrotoxic patients adequate precautions should be taken to avoid the possibility of a thyroid storm.
4. Patients should be adequately consented.
5. Patients undergoing general anaesthesia should have a north-facing endotracheal tube so it does not interfere with the surgical field.
6. Local anaesthetic should be considered to help haemostasis while raising the flaps and to aid analgesia in the post-operative period.
7. Neuromonitoring and surgical aids such as loops, microscope, fine bipolar forceps, ligaclips and energy devices should be encouraged to facilitate surgery.
8. Mild hypotensive anaesthesia should be used but reversed before the procedure is completed.

SURGICAL TECHNIQUE FOR STANDARD THYROIDECTOMY

Position The patient should be in a supine position, with a soft shoulder support and a soft head ring to allow maximum extension of the neck and aid stabilization of the head during surgery (**Figure 67.1**).

Incision and incision planning

The classical Kocher collar incision consists of a transverse cervical incision in a skin crease placed halfway between the cricoid cartilage and the sternal notch. There is no one-size-fits-all rule for the incision placement, but the following aspects should be considered (**Figure 67.2**).

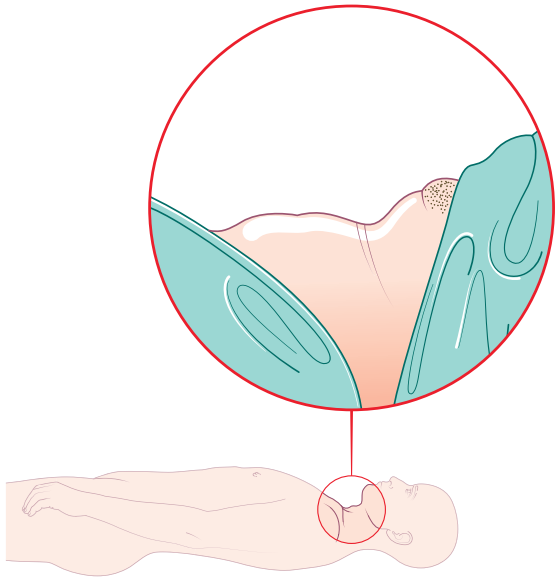


Figure 67.1 Position of patient undergoing thyroidectomy, demonstrating the supine posture with neck extension.



Figure 67.2 Typical Kocher incision 6 months after thyroidectomy.

- **Access:** The incision must be of adequate length to provide sufficient access to the superior, inferior and lateral aspects of the thyroid to ensure a safe dissection. Many surgeons prefer an incision as small as 3 cm and use retraction to move the incision in relation to the gland, exposing the areas of interest in sequence.
- **Cosmesis:** To avoid unnecessary attention drawn to the wound, it should be symmetrical across the midline. By placing the incision in a deep skin crease, the end result will be excellent, and in many cases this will outweigh the need for a small incision: it may be more cosmetically appealing to make a longer incision placed in a skin crease than a short incision between creases.
- **Secondary movement:** When planning the incision, breast size should be considered. In women with large breasts, significant inferior movement of the scar will occur over time. In this case, placing an incision higher in the neck will prevent the scar from migrating to an unsightly position in the presternal area.
- **Future procedures:** Particularly in high-risk patients with extrathyroid extension, for example, the surgeon should bear in mind the possibility that future access to the central and lateral neck may be required. An incision above the level of the cricoid cartilage can easily be extended along a skin crease to the level of the trapezius in order to access all levels of the neck if required at a later date. The modified extended Kocher incision is particularly helpful in this setting.[27]

Approach

Following the skin incision the tissues should be divided through the subcutaneous fat and the platysma. Traditionally, flaps are raised in the immediate subplatysmal plane up to a level above the thyroid cartilage and down to the suprasternal notch. The anterior jugular

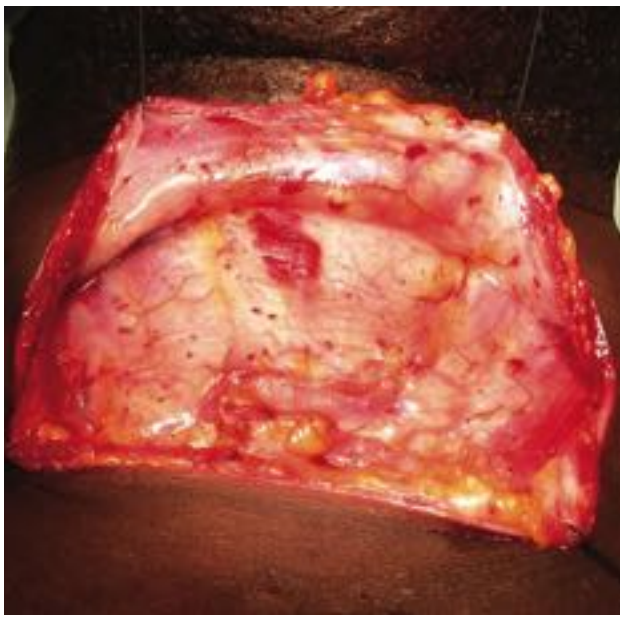


Figure 67.3 Subplatysmal flaps elevated.

veins should be identified and protected during this dissection as damage to these vessels during the early dissection can result in significant post-operative haemorrhage. The extent of dissection should be tailored to the gland in question. The exposure required for a small atrophic gland will be significantly less than for a retrosternal goitre (Figure 67.3).

When an extensive dissection is required, flaps should be raised over the sternomastoids, and indeed the muscle can be dissected from its fascial envelope to improve access to the lateral aspect of the gland. The most inferior tendinous insertions of the sternomastoid muscles are connected by ligamentous fibres which can be divided to improve access to an intrathoracic goitre.

Incision of the cervical fascia

The investing cervical fascia is then incised in the midline and opened to the level of the thyroid cartilage and to the level of the sternal notch. Care should be taken to identify any communicating vessels crossing the midline (Figure 67.4).

Thyroid isthmus (TI)

The TI is identified once the cervical investing fascia has been opened. In cases of performing a TL only, it can be divided early to help the mobilization of the gland or can be dealt with at the end of the procedure. The timing of the division will depend on the experience of the surgeon.

Division of the strap muscles

This is often necessary, especially in cases of large glands. This allows access and better visualization of the vascular pedicles, particularly the superior pedicles. Either the sternothyroid and/or the sternohyoid muscles can be divided. They should be divided in the upper third as this will prevent injury to the ansa cervicalis, which enters the muscles in their inferior aspect (Figure 67.5).

Dissection proceeds on one side initially. The sternohyoid should be separated from the sternothyroid and the medial aspect of the carotid sheath, with the ansa cervicalis identified laterally.

Lateral retraction of the sternohyoid muscle allows access to the sternothyroid muscle. This should again be grasped with atraumatic forceps. Medial traction on the thyroid gland allows dissection of the muscle from the surface of the gland. Attention should be paid to this plane, which is elevated close to the muscle. Evidence of extrathyroid extension at this point should alert the surgeon to the advanced local stage and will alter the approach to the gland. If extrathyroid extension into the straps is evident, the muscle should be excised by dividing above and below the gland.

Identification and division of the vascular pedicles

This is an essential step in thyroidectomy. Individual vessels should be carefully dissected, identified, ligated and divided. This is best done with a curved dissector such as a Lahey or a Mixter dissector. This will allow adequate haemostasis, reducing the risk of post-operative haemorrhage, and will reduce the risk of injury to the superior laryngeal nerve and of leaving large glandular remnants that invariably exist between the vessels.

The superior pole

Management of the superior pole is critical to achieving total removal of the thyroid lobe. Great care should be taken to identify and control the multiple vessels, which fan out from the superior pedicle to insert on the gland.

Traditional descriptions of identifying the superior thyroid artery and dividing distant to the gland should be discouraged as they increase the potential for damage to the EBSLN as it crosses to innervate the cricothyroid muscle. Instead, these vessels should be taken close to the gland, ensuring that the entire superior pole is dissected (Figure 67.6).

Some authors now consider identification of the EBSLN mandatory in all procedures. Most, however, prefer to take care to stay close to the gland rather than exploring the area to formally identify the nerve.

Having started the mobilization, the next step is identification of the superior parathyroid gland (PTG). This will be found adjacent to the posterior capsule of

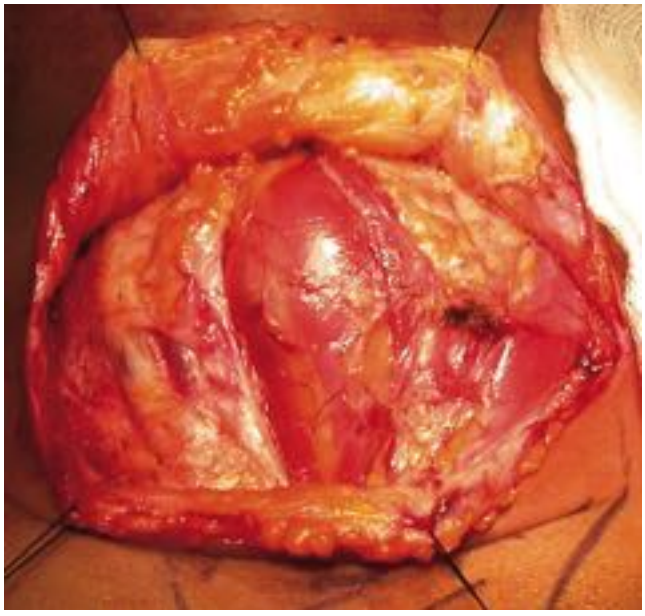


Figure 67.4 Incision cervical fascia, demonstrating the exposure of the thyroid isthmus.

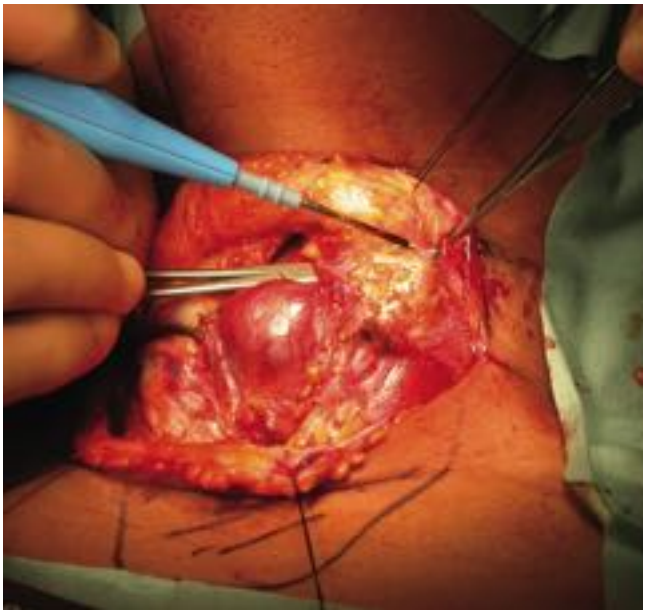


Figure 67.5 Division of the strap muscles using monopolar cutting diathermy.

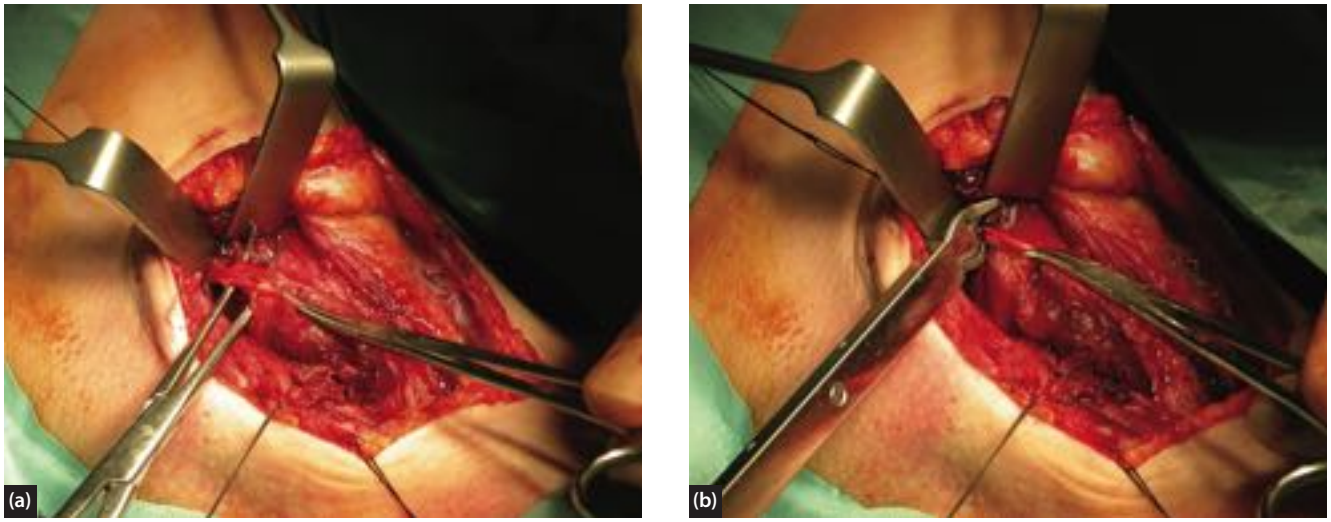


Figure 67.6 Identification, dissection and division of the superior vascular pedicle vessels.

the superior pole. The blood supply must be maintained, and the gland dissected off the thyroid in order to maintain function.

The lateral aspect

With the superior pole mobilized, attention can be turned to the lateral aspect of the gland. The surface of the gland is identified and dissected from the strap muscles. The dissection is done using a combination of sharp and blunt dissection to expose the whole length of the gland. At the lateral aspect of the gland the middle thyroid veins are ligated and divided to allow delivery of the gland and access to the paratracheal areas.

The fascia surrounding the gland is dissected and the thyroid is slowly mobilized, allowing visualization of the trachesophageal groove (**Figure 67.7**).

The inferior pole

With the superior and medial aspects of the gland mobilized, attention can be turned to the inferior pole.

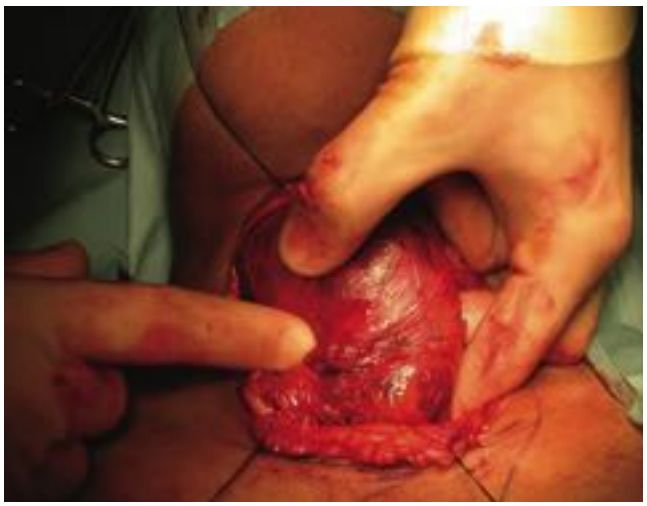


Figure 67.7 Mobilization of the lateral aspect of the gland.

By identifying the trachea, a safe plane of dissection can be developed which allows the inferior pole to be dissected from the trachea without jeopardizing the RLN.

External branch superior laryngeal nerve

The EBSLN should be identified whenever possible during the dissection of the superior pole.[28–30] This is done at the sternothyrolaryngeal or Joll's triangle, which is delineated by the superior thyroid pedicle and upper lobe of the gland, the cricothyroid muscle and the lower edge of the thyroid cartilage (**Figure 67.8**).

Recurrent laryngeal nerve

The position of the RLN varies depending on the side, as previously described in the anatomy section. Although most RLNs are single, up to 30% of nerves can branch before entering the larynx and this may lead to higher risk of injury (**Figure 67.9**).[31, 32]

- **Lateral approach:** The nerve is usually identified in the Beahrs triangle in the lower lateral part the neck. This triangle is defined by the inferior thyroid artery superiorly, the trachea medially and the common carotid artery laterally. This is safest way of identifying the recurrent laryngeal nerve (**Figure 67.10**).[33]
- **Superior approach:** The nerve can be identified at the level of the cricothyroid junction at its entry into the larynx. This approach can be very useful in cancer patients with extensive nodal disease, reoperative surgery, when other approaches have failed and when considering a non-recurrent laryngeal nerve. Once the nerve is identified, it should be dissected in a caudal direction, tunnelling the tissue surrounding the nerve with a mosquito fine-tip dissector (toboggan technique). The tissue above the tunnel is then diathermized with bipolar diathermy and divided (Figure 67.11).[33]



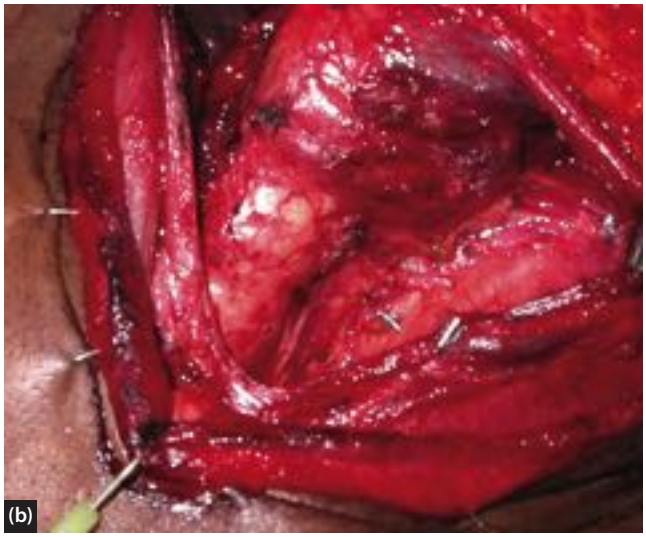


Figure 67.8 Identification of the SLN in the Joll's triangle.

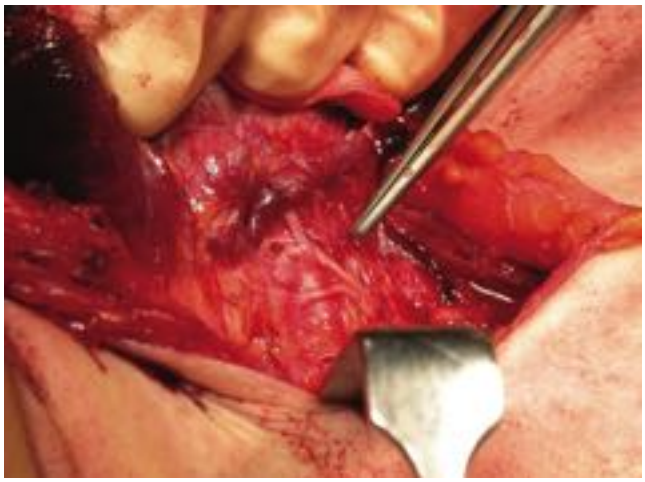


Figure 67.9 RLN demonstrating two extralaryngeal branches.



Figure 67.10 Identification of the RLN using a standard lateral approach.

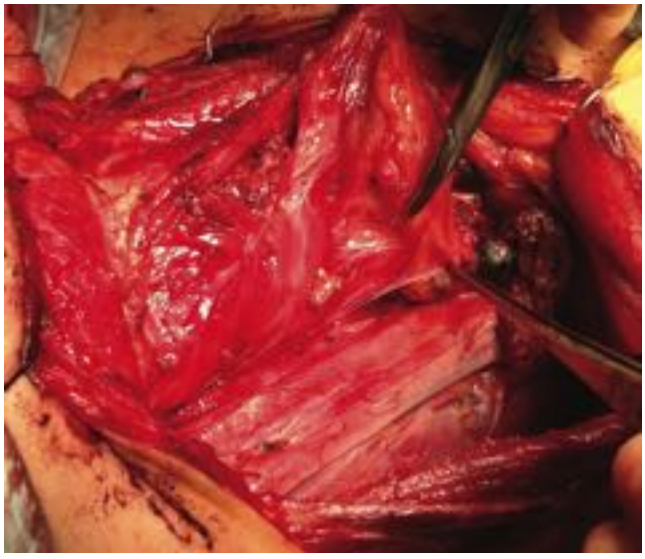


Figure 67.11 Identification of the RLN at the cricothyroid joint using a superior approach.

- **Inferior approach:** In large goitres or in revision surgery, an inferior approach can be used. This allows identification of the nerve in a virgin site (Figure 67.12).[33]

In every thyroidectomy, an attempt should be made to identify the nerve. Without this attention to detail, injury rates can be unacceptably high. Having identified the nerve, there is no need for it to be traced for any great distance. With experience, the surgeon will come to recognize the importance of the relationship between Berry's ligament and the nerve. In patients with a low Berry's ligament, which sits posterior on the trachea, the nerve will be in close proximity to the gland at this crucial point. In these cases the nerve must be carefully traced and the gland mobilized off the nerve. When Berry's ligament is high, the nerve is often quite laterally placed in comparison, and minimal dissection will be required. This minimizes the chance of inadvertent injury.

Around 2% of RLNs are non-recurrent and this is almost always present on the right. Pre-operative imaging

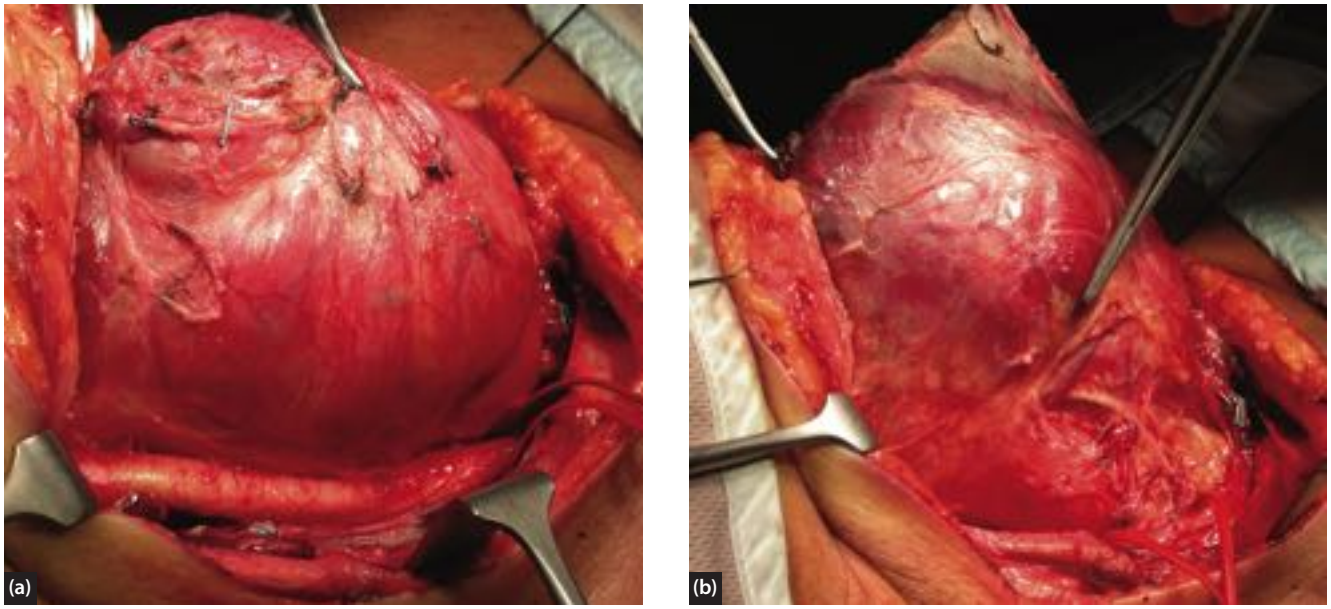


Figure 67.12 Identification of the RLN at the apex of the Beahrs triangle using an inferior approach.

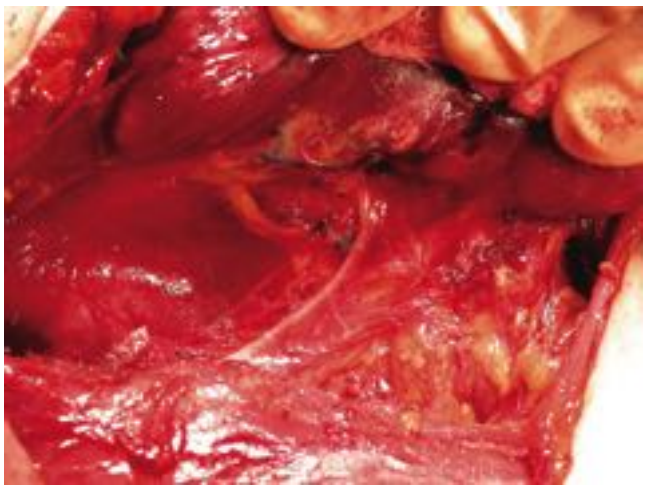


Figure 67.13 Non-RLN arising directly from the right vagus nerve.

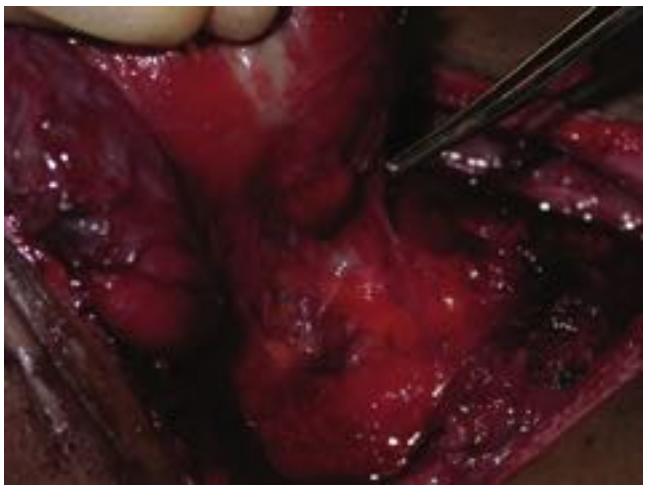


Figure 67.14 Typical position of the parathyroid glands once the right thyroid lobe has been mobilized, demonstrating the superior parathyroid gland in a superior-lateral position and the inferior parathyroid gland in an anterior-inferior position with the RLN crossing from a caudal to cranial position.

which identifies situs inversus, or more commonly a retroesophageal subclavian artery, may raise the index of suspicion. If the RLN cannot be identified in the traditional position, the surgeon must consider the possibility of a non-recurrent nerve. This structure will be running inferomedially from the vagus nerve and will be wide in comparison to a normal RLN (Figure 67.13).

RLN MONITORING

Recent technological advances have allowed surgeons to assess the integrity of the recurrent laryngeal nerve during thyroidectomy. Proponents of these techniques highlight the potential reduction in rates of iatrogenic injury and find the nerve monitor useful in the training of junior surgeons. Those who oppose the routine use of nerve monitors cite increases in operative time and cost as well as the lack of clear evidence of overall patient benefit. The topic remains controversial, and it is covered in detail elsewhere.

Management of the parathyroid glands

The parathyroid glands should be identified whenever possible. The position of the glands can be variable and 25% of the glands may not be in the position that the surgeon expects them to be (Figure 67.14). When the thyroid gland has been mobilized, the superior parathyroid gland should fall in a posterior position from the nerve and the inferior parathyroid gland in an anterior one. Once identified, the tissue handling needs to be very precise and delicate so the glands can be dissected with their blood supply preserved.

The superior glands are relatively uniform in their position. The inferior glands are traditionally described as ventral to the RLN in the region of the inferior thyroid artery. However, it is not uncommon for these glands to

be aberrant in position, and lie somewhere between the level of the cricoid to the thymus. Traditionally, 1% of parathyroids have been considered to be intrathyroidal, although with careful scrutiny of resected thyroid tissue this may be an underestimate.

Parathyroid glands rely on their blood supply to function, and it is critical that their nutrient vessels are preserved. The glands should be gently dissected from the thyroid, taking care not to cause traction or diathermy injury to their blood supply. In the event that a parathyroid is excised, or is considered non-viable, a sample should be sent for frozen section analysis and, on confirmation, the gland should be divided into around 12 pieces for implantation into a muscle. Often the sternomastoid muscle is used due to its convenience, although this view has recently been challenged.[34]

Berry's ligament

At this level the recurrent laryngeal nerve is at greatest risk. The ligament is dissected using fine and judicious bipolar diathermy. The blades of the bipolar should be resting on the thyroid gland and away from the nerve. Once the diathermy has been performed, the ligament is divided with a size 15 blade scalpel. This provides the best accuracy and reduces the risk of injury. It is important to note that the ligament is often very vascular and its thickness variable. It is therefore often necessary to dissect and divide the ligament in several steps until the perichondrium of the trachea is reached (**Figure 67.15**).

Pyramidal lobe

The pyramidal lobe should always be identified, dissected and excised together with the thyroidectomy specimen.

Having delivered the thyroid from Berry's ligament, the gland should be dissected off the anterior tracheal wall towards the midline. Great care should be taken at this point to identify any pyramidal tissue. If this is left behind, it will be evident on post-operative imaging and may result in the need for adjuvant RAI, or sampling to exclude the possibility of local recurrence. The pyramidal lobe tends to be a central structure, although it is not always immediately in the midline. It extends in the direction of the thyroglossal tract towards the hyoid, and should be divided as superiorly as possible (**Figure 67.16**).

Closure

1. **Wound wash.** Once the thyroidectomy is completed, the wound is washed with water or normal saline. Iodine-based solutions are best avoided, especially when performing surgery for thyroid cancer, as this may interfere with subsequent radioiodine ablation.
2. **Haemostasis.** Haemostasis is essential. To check for any bleeding points, the wound must be clean of clots. When this has been done, a Valsalva manoeuvre should be used at least twice to check for any bleeding.



Figure 67.16 Dissection of the pyramidal lobe.

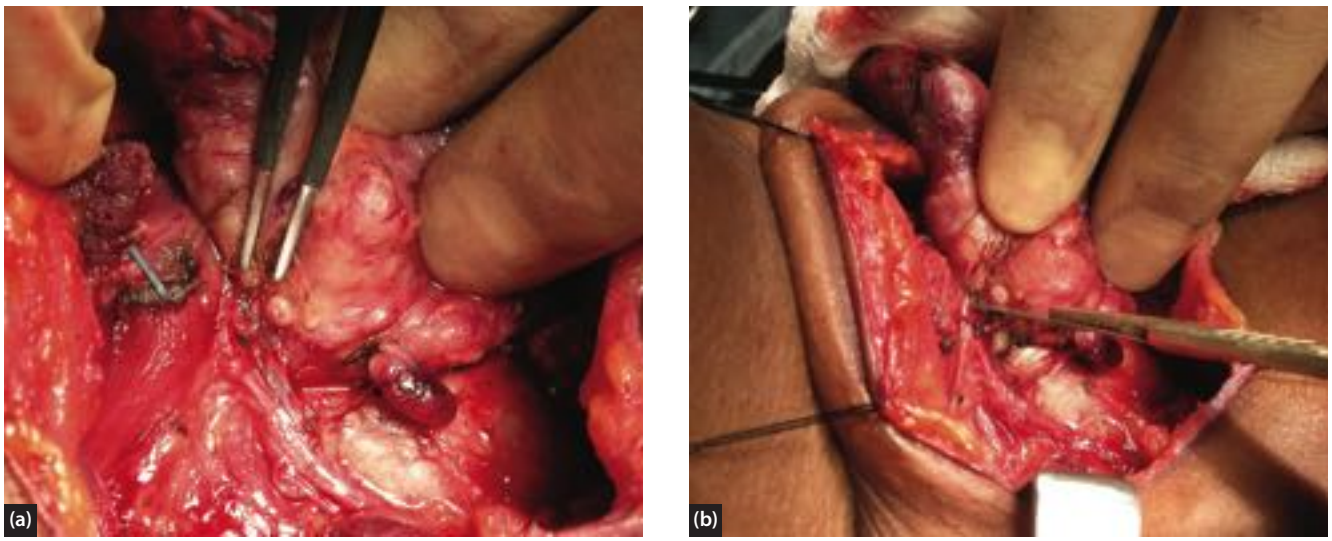


Figure 67.15 Management of the Berry's ligament using careful bipolar coagulation of the fine vessels followed by division of the ligament with a size 15 scalpel.

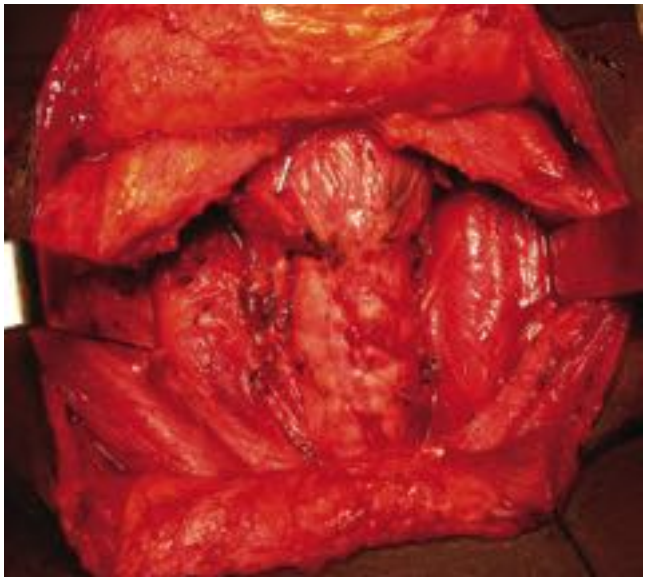


Figure 67.17 Post-operative appearance of a thyroid bed after total thyroidectomy, demonstrating the trachea, larynx, RLNs and parathyroid gland.

3. **Check the RLNs and parathyroid glands.** Once haemostasis is completed, the RLNs and the parathyroid glands should be checked to ensure that they are intact anatomically. If neuromonitoring is used, an EMG signal should be obtained and recorded (Figures 67.17 and 67.18).
4. **Drainage.** The need for drains should be considered on an individual patient basis. Many prospective, randomized trials have shown that drains do not reduce haematomas or seroma rates. Despite this, some units use suction drains, particularly when a significant dissection has resulted in a large dead space or the patient uses anticoagulation.[35]
5. **Subcutaneous tissues and skin closure.** The wound is closed in layers. The strap muscles should be approximated with an absorbable suture. Many surgeons now advocate only one suture to prevent trachea–cutaneous adhesion, while maintaining a connection between the deep central neck and the more superficial planes. The theory is that this may prevent the development of high lymphovascular pressure in the perilaryngeal tissue in the event of a hematoma, thereby reducing the risk of airway oedema and respiratory obstruction.



Figure 67.18 Specimen of a total thyroidectomy for thyroid cancer.

The platysma should then be re-approximated using an absorbable suture. The skin should then be closed with meticulous attention to detail to optimize wound healing. The technique (interrupted nylon, staples, subcuticular sutures, skin glue, etc.) is less important than the need to be precise and treat the skin edges with respect. The ideal closure will allow easy reopening in the event of haematoma.

POST-OPERATIVE CARE

- **Position.** Patients should be nursed head up in a 45 degree position for the first 4 hours before they can start mobilizing.
- **Venous thromboembolism (VTE) prophylaxis.** Patients undergoing thyroid surgery should have adequate VTE prophylaxis. As a general rule, anticoagulant VTE prophylactic agents should be commenced 24 hours from the procedure and continued until the patient is discharged.
- **Nursing.** Patients should be monitored in an adequate post-operative care facility or ward. An adequate pathway of monitoring and enhanced recovery should be instigated in all units dealing with thyroid surgery. Suture or staple removal forceps should be available at the bedside.
- **Steroid therapy.** The use of intravenous steroid therapy in the first 24 hours is a valuable adjunct to analgesia as an antiemetic and in one randomized controlled trial has shown to reduce the rate of RLN neuropraxia.[36]
- **Antibiotic prophylaxis.** This is not usually necessary. In complex cases with extensive dissection, ETE involving the airway structures or lateral neck dissection, prophylactic antibiotics up to three doses in 24 hours should be considered.
- **Analgesia.** Adequate analgesia is imperative. Opiates are preferred to non-steroidal analgesics to minimize the risk of post-operative bleeding.
- **Resume oral intake.** Patients can resume oral intake as soon as they are fully awake and have a normal diet 4 hours from completion of the procedure.
- **Mobilization.** Early mobilization should be encouraged.
- **Drain removal.** Monitoring of drainage volume should be every 8 hours. If the volume is less than 20 mL at 24 hours or 10 mL at 8 hours, the drain may be removed.
- **Removal of sutures or staples** – most surgeons use either staples or subcuticular sutures. Staples can be removed as early as 36 hours from completion of the procedure, and edges reinforced with Steri-Strip™ tapes for 7–10 days. This will ensure adequate healing and optimal cosmesis.
- **Calcium management.** This is addressed in Chapter 79 on the prevention and management of complications.
- **Post-operative vocal cord check.** A post-operative vocal cord check should be done as soon as possible after the surgery if RLN injury is suspected. If there is no suspicion of RLN injury, a post-operative vocal cord check can be done in the first post-operative appointment.[26]

KEY EVIDENCE

- Essential pre-operative investigations for thyroid surgery include clinical examination, thyroid function test, thyroid antibodies, ultrasound-guided FNAC, pre-operative voice assessment with fibre-optic laryngoscopy and, for established malignancy, appropriate cross-sectional imaging investigations.
- Thyroid lobectomy is the minimum procedure acceptable except for those nodules located in the isthmus or pyramidal lobe.
- During thyroidectomy the recurrent laryngeal nerves and parathyroid glands should be identified and preserved unless there is pre-operative evidence of involvement with locally invasive thyroid cancer.

KEY POINTS

- Evidence of clinical examination, FNAC, core needle biopsy and adequate imaging USS, CT or MRI should be available.
- Laryngeal examination and pre-operative voice assessment with fibre-optic laryngoscopy should be performed in all patients undergoing thyroid surgery.
- Patients should be euthyroid or in cases of thyrotoxicosis in which the thyroid function is abnormal adequate precautions should be taken to avoid the possibility of a thyroid storm.
- Patients should be adequately consented.
- Patient undergoing general anaesthesia should have a north-facing endotracheal tube so it does not interfere with the surgical field.
- Local anaesthetic should be considered pre-operatively to help haemostasis while raising the flaps and to aid analgesia in the post-operative period.
- Nerve monitoring should be used whenever possible.
- Surgical aids such as loops, microscope, fine bipolar forceps, ligaclips and harmonic knives are very useful and should be encouraged to facilitate surgery.
- Mild hypotensive anaesthesia should be used but reversed before the procedure is completed.
- Adequate incision and approach should be employed for the extent of the procedure.
- Surgery is the mainstay of thyroid cancer treatment and total thyroidectomy should be performed in the majority of patients.
- Level VI selective or central compartment neck dissection should be performed whenever indicated.
- Careful tissue handling is paramount as the thyroid gland is one of the most vascular glands in the body.
- The RLN should always be identified and preserved.
- The EBSLN should be identified whenever possible. This may only be possible in up to 60% of cases due to the position of the nerve in relation to the superior thyroid pedicle.
- Parathyroid glands should be identified and preserved whenever possible. If, however, a parathyroid gland is removed during surgery or its blood supply is lost, frozen section should be used to confirm the nature of the tissue and, if positive, the gland should be reimplanted in a pocket made in the sternocleidomastoid muscle.

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CHAPTER 68

SURGERY FOR LOCALLY ADVANCED AND NODAL DISEASE

Joel Anthony Smith and John C. Watkinson

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Surgery for recurrent disease: Locoregional recurrence 809
Surgery for distant disease 809
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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: well-differentiated thyroid cancer, advanced thyroid cancer, extrathyroidal spread, nodal disease, laryngotracheal invasion, oesophageal invasion and recurrent laryngeal nerve invasion.

Key evidence has come from the British Thyroid Association guidelines for the management of well-differentiated thyroid cancer, the American Thyroid Association guidelines for the management of well-differentiated thyroid cancer and the American Head and Neck Society Consensus statement.

INTRODUCTION

In the majority of cases, differentiated thyroid cancer (DTC) carries an excellent prognosis and behaves in an indolent manner.[1–3] However, in advanced disease, including direct spread beyond the thyroid capsule or extranodal spread, surgical management is challenging with higher associated morbidity and mortality.[1, 4] Surgery is well accepted as the primary modality of treatment of both primary and recurrent DTC although adjunctive therapies play an important role.[3, 5] Awareness of poor prognostic features pre-, intra- and post-operatively can aid in appropriate surgical planning and decision-making and there is a move towards patient-specific risk stratification in management strategy.[4] Treatment planning should be patient-centred and be made within the context of a multidisciplinary team setting (MDT).[3] When treating patients with advanced thyroid cancer, decision-making is the most important part of management, as often a balance must be struck between achieving clear margins and the potential morbidity of surgical intervention. Patients with residual thyroid cancer may survive for many years and be minimally symptomatic. As such, in DTC, leaving microscopic and sometimes macroscopic disease behind to preserve function may be the most appropriate course of action.

ADVANCED THYROID CANCER

Surgical management of advanced thyroid cancer includes:

- direct disease extension beyond the thyroid capsule (extrathyroidal spread)
- recurrent or residual disease in the thyroid bed and neck
- extracapsular nodal disease
- surgery for distant metastasis.

EXTRATHYROIDAL SPREAD

Spread of disease beyond the thyroid capsule into surrounding tissues represents a poor prognostic sign with significant potential for increased post-operative morbidity and early mortality.[6] Extrathyroidal extension (ETE) can be present at some level in up to 25% of patients and occurs in papillary and follicular disease with equal frequency although papillary thyroid cancer has a much greater incidence and is therefore more likely to be encountered.[2, 6–10] Extrathyroidal spread can range from minimal extension into surrounding strap muscles and fat (T3) to invasion of the laryngobronchial tree and prevertebral muscles (T4a/b).

Extrathyroidal spread occurs most commonly in those with other risk factors for adverse prognosis.[9, 11–12]

Residual and unrecognized disease is likely to represent the most common manifestation leading to local recurrence and macroscopic disease clearance is associated with higher survival.[2, 13] As such, early recognition of extrathyroidal spread with appropriate pre-operative planning is likely to minimize the risk of inadvertently leaving residual disease. Patient factors that increase the risk of extracapsular spread mirror the risk factors for detecting malignancy in a thyroid nodule and include extremes of age at presentation, size of primary tumour (>4 cm), advanced nodal disease or clinical evidence of distant metastases.[8–9, 11] Presentation with features of upper aerodigestive tract invasion including voice change, recurrent laryngeal nerve palsy, stridor and dysphagia should alert the surgeon to the need for careful clinical assessment of the aerodigestive tract including flexible laryngoscopy to assess vocal fold function as a well as bronchoscopy and oesophagoscopy if directed clinically.[14] In addition, patients with suspected aerodigestive tract invasion should have analysis of pre-operative imaging by a radiologist with a special interest in head and neck radiology, preferably within the context of the MDT such that surgery can be planned with the patient fully informed.

Histological factors that should alert the surgeon to a higher risk of ETE include poorly differentiated and unencapsulated histological subtypes associated with more aggressive disease such as diffuse sclerosing, solid and tall cell types.[9]

Once identified pre-operatively, management planning should be discussed in detail with the patient such that the appropriate resection boundaries and the morbidity associated with obtaining completely clear margins can be adequately understood.[3] The operative skills, experience and repertoire of the surgeon are important factors when obtaining clear surgical margins in patients with cancer spread beyond the thyroid capsule.[14–16]

Involvement of non-vital structures around the thyroid bed

The greatest chance of cure is obtained through macroscopic removal of disease with clear margins. This is the case primarily and for residual or recurrent disease where there is direct spread from the thyroid gland. Predicting extrathyroidal spread is important but not always possible and subtle involvement of local structures are often not identified on imaging.[2] If extrathyroidal spread involves the strap muscles or surrounding lympho-fatty tissue where en-bloc excision leads to little added morbidity, it is generally accepted that these structures should be excised as far as the disease progresses.[3, 17]

Involvement of the recurrent laryngeal nerve

In locally advanced thyroid cancer, the recurrent laryngeal nerve (RLN) can be involved to a greater or lesser extent in up to 60% of cases by direct cancer spread from the gland or by paratracheal lymph nodes.[6] RLN involvement can range from tumour abutting the nerve to partial or total encasement and direct invasion.[18] Evidence that nerve and functional voice preservation can be achieved without compromising local recurrence has led many to adopt a nerve-preserving technique, although large-scale trial data supporting this are not available.[17–19] Further, some studies suggest RLN function can return after tumour has been peeled off the nerve, even when extensively dissected.[20] RLN involvement, in the presence of a still-functioning nerve, is not usually possible to predict on radiological grounds. Most patients with RLN involvement or encasement have no predictive features. Where a pre-existing, ipsilateral cord palsy exists in the context of an encased nerve, most would advocate nerve excision.[17] In a functional ipsilateral vocal cord, with solitary RLN involvement, some would advocate removal as the balance of morbidity from a unilateral RLN palsy may outweigh the risk of leaving disease behind. Others, however, would aim to preserve the nerve while removing macroscopic disease on the basis that adjuvant treatment would be employed to reduce the risk of local recurrence.[17–19] Decisions such as these should be patient-specific. Where both RLNs are involved and functional pre-operatively, a more difficult decision has to be made, but most would advocate RLN preservation to avoid tracheostomy. The British Thyroid Association (BTA) recommends leaving one or both nerves in situ regardless of macroscopic disease and relying on non-surgical post-operative treatment modalities to achieve local control.[3] In addition, RLN monitoring is widely used in thyroid surgery and may aid intra-operative decision-making regarding nerve preservation.[21] This may be particularly helpful in the presence of an apparently functional nerve where nerve signal has been lost.[22] There is debate, however, on the ability of intra-operative nerve monitoring to predict voice outcome following thyroid surgery and large-scale prospective studies are needed to evaluate this further.[23, 24]

Where resection of the recurrent laryngeal nerve is anticipated, such as in the context of a pre-existing vocal fold paralysis, there is some evidence albeit from small studies that primary re-anastamosis of the RLN may improve voice outcome.[25] Such repair may involve end-to-end or cable graft repair. The skills of the operating surgeon may be a factor in whether this is achievable and donor nerve morbidity must be taken into account.

Involvement of the trachea and larynx

Oesophageal and pharyngeal involvement is rare in isolation, and normally occurs in association with involvement of the laryngobronchial tree.[2] When disease recurs, it is most likely to do so locally (70%).[26] Up to 50% of death from DCT is from direct invasion of the airway. The prognosis for those with locoregional recurrence is better than those with distal disease, however, and where locoregional control can be achieved, death is more likely from distant metastasis.[27] Treatment should therefore be directed towards macroscopic, local disease clearance.

Again, where resection is being considered, patient and tumour factors should be at the forefront of the decision-making process. Whether tumour breaches the inner lumen of the airway is the key to surgical planning and all patients with suspected airway invasion should undergo thorough pre-operative evaluation. Clinically, laryngoscopy and bronchoscopy should be performed if luminal spread is suspected. Imaging in the form of contrast-enhanced CT is specific if not particularly sensitive in detecting both tracheal and laryngeal invasion and MRI may add further information regarding laryngeal cartilage invasion.[28] Depending on the skills of the surgeon, the extent of resection may mandate involvement of other specialities or onward referral to tertiary care.

Where macroscopic disease invades the outer layers of the laryngobronchial tree, most agree it is acceptable to shave cartilage as far as macroscopic disease is seen and treat post-operatively with ^{131}I and/or external beam radiotherapy (ERBT).[29, 30] In tracheal invasion, local control rates as high as 95% have been reported when adopting such strategies, even with high rates of microscopically involved margins.[31] It is likely that post-surgical, adjuvant treatment reduces recurrence and improves survival in these circumstances.[29, 32] Where macroscopic disease excision necessitates entering the lumen of the airway, formal resection and reconstruction should be considered.[29, 33] Although this is likely to increase surgical morbidity from anastomotic breakdown, laryngotracheal stenosis and tracheostomy dependence, revision surgery for residual or recurrent disease is likely to be very challenging and carry significantly higher morbidity.[34–36] Options for segmental tracheal and laryngeal resection can be seen in **Figures 68.1–68.4**.[37]

As with tracheal involvement, where the outer layers of the larynx are involved, macroscopic resection of disease with preservation of the larynx is likely to achieve good rates of local control. Where disease spreads through the cartilage, consideration of partial or total laryngectomy should be made as leaving behind macroscopic disease is associated with a high risk of recurrence, regardless of post-operative treatment, and salvage surgery is again likely to involve high morbidity.[17] Often laryngeal preservation can be achieved, however, with good functional and local outcomes.[38] Again decisions should be made

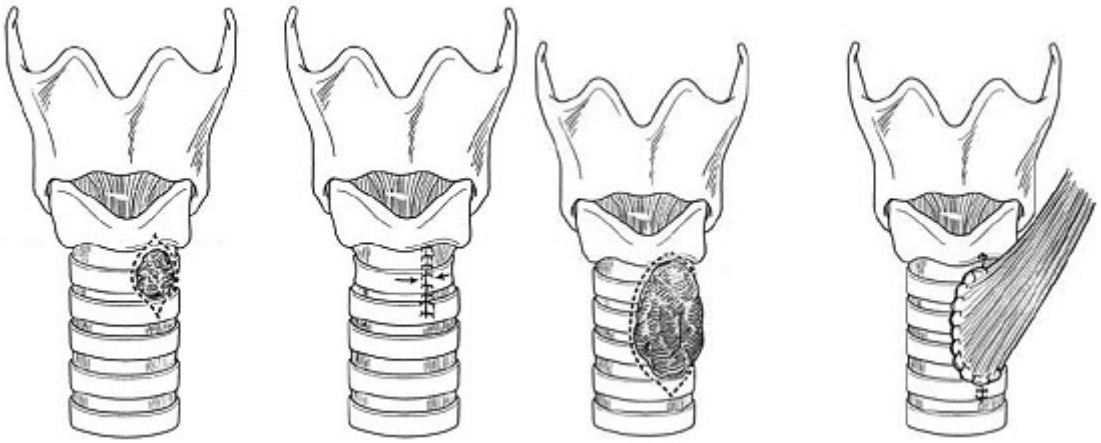


Figure 68.1 Options for tracheal resection and repair. A small defect can be closed primarily and a larger defect reconstructed with a local muscle flap.

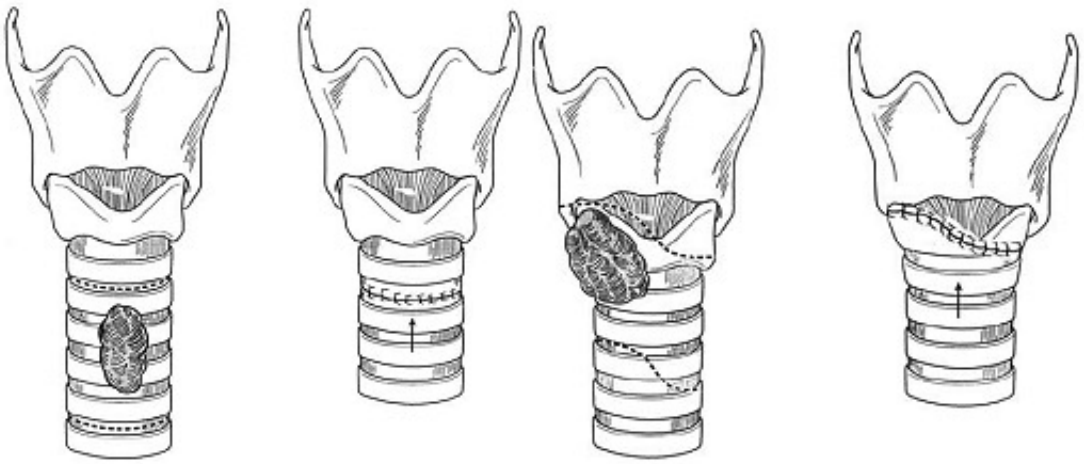


Figure 68.2 Segmental tracheal resection – with an end-to-end primary anastomosis and a stepped closure involving partial resection of the cricoid cartilage.

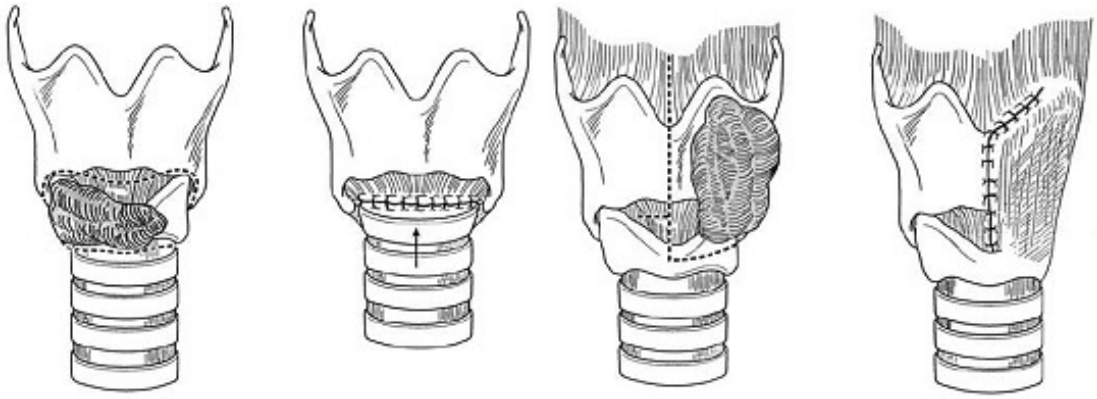


Figure 68.3 Total cricoid resection – with trachea to cricothyroid membrane anastomosis and vertical hemilaryngectomy.

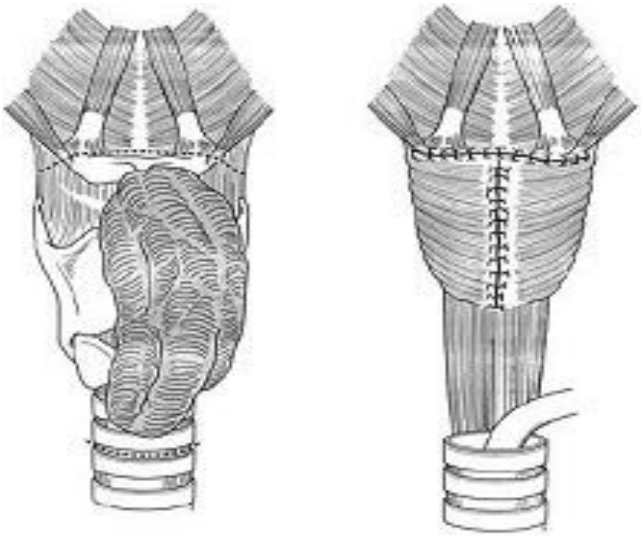


Figure 68.4 Total laryngectomy – for advanced disease extending across the midline.

with the patient at the centre of the discussion and including surgeons with the appropriate skill mix to complete the procedure.[39]

Involvement of the pharynx and oesophagus

Pharyngeal and oesophageal invasion are rare in thyroid cancer and most commonly occur from direct primary tumour extension rather than extranodal disease in the central compartment.[36] A history of true dysphagia should prompt a thorough evaluation of the aerodigestive tract although in most cases involvement is asymptomatic. This is in part because intra-luminal involvement is rare with extension most frequently involving the muscularis layer in isolation without submucosal or mucosal spread.[10] As such, endoscopic examination of the pharynx and oesophagus is often not predictive. As involvement is most likely due to direct spread, the position of the primary within the thyroid may give an important clue to the presence of invasion. MRI scanning is both sensitive and specific at predicting invasion and should be performed whenever invasion is suspected.[40]

Surgery to the pharynx and oesophagus will be dictated by the extent of involvement but should follow the principals of macroscopic disease resection. Where the lumen is breached, segmental resection is required which may be repairable by layered closure or by direct reanastomosis.[17] More extensive defects may require myofascial or myocutaneous reconstruction from pedicled local flaps, free microvascular tissue transfer or gastric pull-up procedures.

Involvement of the vascular compartment

Although rare, vascular involvement occurs and every effort should be made to recognize involvement in the preoperative phase.[41] Both the internal jugular vein (IJV) and common carotid artery can be involved by direct primary tumour spread although IJV compression and thrombosis is more commonly caused by extensive nodal disease.[42] Again, it is patients with high risk features who are more likely to present with vascular involvement. Clinical signs of arterial involvement are often minimal but major venous involvement should be suspected in the presence of facial flushing, oedema, venous congestion and unexplained headaches or vascular events. Where vascular involvement is suspected, extensive pre-operative evaluation should be performed as there is significant potential for morbidity and mortality if the IJV and or carotid has to be resected.[17] Imaging should be directed towards assessment of resectability and, if so, what structures would need repair. Combination imaging including ultrasound Doppler, MRI, MRA and CT angiography may be sufficient to evaluate intra-luminal involvement and distinguish thrombus from intra-luminal tumour.[42] Formal angiography may be required, however, in particular to assess the arterial supply to the circle of Willis if arterial resection is contemplated.

Ipsilateral IJV involvement can be resected with no recourse to reconstruction of the venous system. There is consensus, however, that in bilateral IJV resection, reconstruction with autologous vein graft should be considered, due to the significant morbidity associated with bilateral IJV excision.[17, 43] Most authors consider a completely encased carotid to be akin to inoperable disease although cases of carotid resection and are reported.[42]

Encasement up to 270 degrees is usually amenable to resection assuming the artery itself is not directly invaded. Where an attempt to resect disease that is advanced to that extent is being considered, careful consideration of the surgical morbidity and the likelihood of improving survival should be undertaken.

SURGERY FOR RECURRENT DISEASE: LOCOREGIONAL RECURRENCE

As with primary disease, recurrent disease should be managed surgically where possible and with curative intent.[13, 3] Local disease recurrence is most often seen in the thyroid bed with the central and lateral neck compartment less commonly affected. Patients with high-risk features are more likely to die from their disease and as such the case for surgical intervention for recurrent local disease is more clear cut.[3] In those with low-volume or low-risk disease, however, close clinical observation may be a better strategy.[3] Consideration should be paid to the position of the recurrence prior to any attempt at surgical excision as well as ^{131}I uptake status. Patients with locoregional recurrence have a better prognosis than those with distant disease, a reflection of the fact that recurrent disease is most likely enlarging residual disease rather than loss of disease control and that all modalities of treatment are still available. Where resection is undertaken, a complete clearance of the central compartment should be performed with invasion into local structures managed as previously discussed.[17]

Where disease recurs in the lymphatics, the central and lateral compartments are most commonly affected and disease can be confined to the nodes themselves or spread extranodally into the free tissue spaces of the neck. Where nodal compartments are macroscopically affected, the aim should be to clear all affected levels in their entirety, avoiding 'berry picking' at all times. In the lateral compartment clearing levels IIa to IV with level Vb if affected is considered the treatment of choice.[1] Where extranodal extension affects other structures such as the vascular compartment or neural structures, consideration of the balance between morbidity and increased survival should be made on a case-by-case basis.

Where nodal disease recurs in previously dissected nodal levels, a comprehensive dissection of the lateral neck should be considered in patients with high-risk disease. In previously operated levels, this may involve excision of the residual node, affected local structures and and scar tissue only. Again, a watchful waiting strategy may be adopted for those with low-risk recurrent disease.[3] Non-surgical treatments should be explored with ^{131}I uptake status as well as the possibility of EBRT for patients not amenable to surgery.

SURGERY FOR DISTANT DISEASE

Distant metastatic spread carries a poor prognosis, in part a representation of the disease process itself and in part due to the limitation of treatment modalities available, particularly surgery.[44] Distant spread is most common to the lung followed by bone, soft tissues and brain.[45] Although metastasis reduces life expectancy by 50%, the disease can progress slowly and may be relatively asymptomatic.[44] For many patients with distant metastases, including to mediastinum and lung, surgery is not considered an option and an assessment should be made as to whether metastases uptake iodine.[3] In these situations ^{131}I may be the treatment of choice with or without EBRT. For isolated or limited bony metastases in accessible places where morbidity is low, surgery may be considered, especially as ^{131}I is relatively ineffective at treating these lesions.[46] Selection should be on a case-by-case basis and multimodal treatment considered. Pain, weight-bearing positions, risk to neuronal structures and risk of other treatment modalities such as EBRT should be considered prior to or instead of surgery. Surgery may be considered first-line treatment for isolated cerebral metastases in patients with good performance status as greater long-term survival has been demonstrated.[3, 47, 48] Surgery for cerebral metastasis should be considered regardless of ^{131}I uptake and a decision made in conjunction with a neurosurgical team.

FUTURE RESEARCH

- Imaging modalities for the detection of early recurrence or residual disease
- Centralization of data and patients with advanced disease for the purpose of audit and research
- Randomized trials in the surgical management of locoregional recurrence and distant disease
- Biomarkers to predict subtypes more likely to recur
- Surgical technology to aid in monitoring intra-operative nerve function

KEY POINTS

- Where possible, individual patient and tumour factors (risk stratification) should be included in decision-making.
- Management should be patient-centred and made within the context of the MDT with consideration of non-surgical treatment where appropriate.
- Assessment and anticipation of advanced disease allows management decisions to be made in advance of surgery.
- Microscopic residual disease may not adversely affect long-term survival.
- A balance must be struck between extent of planned excision and associated morbidity, particularly when there is involvement of the upper aerodigestive tract.

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CHAPTER 69

MINIMALLY INVASIVE AND ROBOTIC THYROID SURGERY

Neil S. Tolley

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: robotic thyroidectomy, minimal invasive thyroid surgery (MIVAT).

INTRODUCTION

The principles for safe thyroid surgery were laid down by Kocher at the beginning of the 20th century. Until recently there has been little change to the technique he described, an approach to thyroidectomy that conferred him Nobel laureate in 1909. His incision is still eponymously used although this rarely reflects the incision that he performed.

The site of incision and scar is often a significant focus of patient anxiety when considering surgery. Studies have revealed that 71% of patients surveyed in a thyroid clinic would prefer not to have a neck scar given a choice, a view independent of sex and skin colour. Furthermore, validated scar assessments reveal that professionals rate the aesthetics of a scar more favourably when compared to patients.[1]

Until further advances in medical research permit an incision that is truly scarless, techniques will continue to evolve to minimize scarring. This will facilitate safe surgery through a smaller and cosmetically more desirable incision or for the incision to be placed at a site where the scar is unobtrusive and invisible.

MINIMALLY INVASIVE THYROIDECTOMY

Technological developments of the endoscope and energy sealing devices provided essential prerequisites to develop small incision thyroidectomy techniques. These are known by several euphemisms: minimally invasive video-assisted thyroidectomy (MIVAT) or Miccoli technique, minimally invasive thyroidectomy (MIT), endoscopic-assisted thyroidectomy (EAT) and, finally, the Henry technique. Endoscopic-assisted thyroidectomy more accurately describes these techniques in practice.

Paolo Miccoli in Pisa and Jean-François Henry in Marseille largely pioneered the techniques of minimal invasive thyroidectomy.

Miccoli technique

Miccoli described the open method (gas-less), where a 2–3 cm midline incision facilitates endoscopic dissection of the superior pole and its delivery into the neck. Dissection of the lower pole and completion thyroidectomy is then done in a conventional manner once the thyroid is delivered through the incision. It has the disadvantage of requiring both two competent assistants and video stacks. Nonetheless, it avoids the potential complications of insufflation and it is possible to perform a total thyroidectomy through a single incision.

Excellent visualization of structures such as the recurrent, external laryngeal nerves and the parathyroids is obtained. Its limitation, as in all minimal invasive techniques, is the size and nature of the lesion for which the technique is suitable. This equates to approximately 8% of a UK surgeon's practice.[1] Volume outcome data would indicate that only surgeons with a large thyroid practice would have sufficient numbers to hone and maintain the skills required to adopt this technique both safely and

responsibly. A steep learning curve exists requiring over 50 cases before a surgeon obtains expert status.[2] This on a background where 86% of the British Association of Endocrine and Thyroid Surgeons (BAETS) membership perform fewer than 50 thyroidectomies a year[3] is indicative of why few surgeons have adopted this technique in the UK.

MIVAT permits solitary nodules of 3 cm to be safely removed. Highly experienced and skilled surgeons in the technique have extended its application to selected Graves' and cancer patients. It is wise to avoid its use in patients with a history of thyroiditis, cancer or previous surgery. It is recommended that total thyroid lobe volume should not exceed 20 mL with nodules up to 3 cm being suitable, equating to a volume of 14 mL.

In the author's experience, if the small incision necessitates excessive traction (which it does), this can predispose to hyperpigmentation and hypertrophy of the scar. This is clearly undesirable given the reason for using this technique in the first place. Long-term cosmetic analysis of scars is therefore essential for adequate evaluation of minimally invasive techniques. Figure 69.1 shows the Miccoli instrumentation.

Henry technique

Virtually synchronous to the advent of Miccoli's technique was the insufflation method largely pioneered by Jean-François Henry in Marseille. This relies on the creation of three lateral ports along the anterior border of sternomastoid, two 3 mm ports for instrumentation and a 1 cm port for introduction of the insufflator endoscope. CO_2 at a pressure of 8 mmHg facilitates working space and achieves a bloodless field in which to dissect. It requires an assistant to hold and manipulate the endoscope while dissection proceeds with the other port instruments.

Dissection takes places completely within the neck and delivery of the thyroid lobe once completed is through the endoscope port. Indications for the technique replicate that of Miccoli. A total thyroidectomy is not possible by this method. Technically it is much more challenging than the Miccoli method and, while lending itself very well to parathyroidectomy, it has not been widely adopted for thyroid surgery. Figure 69.2 shows the Henry instrumentation.

Minimally invasive thyroidectomy – the evidence base

There have been many peer-reviewed publications and even meta-analyses on minimally invasive thyroidectomy. The meta-analysis of Radford contained only five studies with a low degree of freedom and study heterogeneity. It also included a series from Miccoli, the pioneer of the technique. The analysis of 318 patients concluded that complications were no higher and supported superior cosmetic outcomes at the expense of operative time. Scar cosmesis was studied in the early post-operative period only and validated scar assessment methods were not used.[4]

The literature gives clear guidance on the indications, methodology, safety and learning curves. It has been less clear on volume outcome metrics. The latter will assume greater prominence with the advent of revalidation and surgical outcomes being placed in the public domain. Long-term prospective cohort studies comparing conventional and MIT are regrettably lacking. However, a personal communication with JFH has suggested there may be little or no difference in scar satisfaction after 18 months once full healing has taken place.



Figure 69.1 The Miccoli range of instruments (gas-less) technique inclusive of suction dissectors, spatulas and specially designed retractors. A 30 degree 4 mm endoscope is used.



Figure 69.2 The range of instruments available for the Henry (gas) technique. Three ports are used and operative space is created by CO_2 insufflation.

Despite these reservations there is nonetheless a patient demand for this procedure. In the highly skilled such as Miccoli and Henry with high volume practices there is undoubtedly a niche for this technique. It is particularly attractive to those patients who have a tendency to hypertrophic scarring and possible keloid, although in the author's experience true keloid is very rare in thyroidectomy scars. However, because of the technical difficulty of achieving competency, steep learning curves and a regular supply of suitable cases, a large volume thyroid practice is essential. For this reason very few centres in the UK perform truly minimally invasive thyroidectomy.

SCARLESS IN THE NECK TECHNIQUES

Despite advances conferred by minimally invasive techniques they nonetheless have the disadvantage of leaving a scar in the neck. Although other endoscopic techniques have been employed, including a facelift approach,[5] the desire to avoid an incision in the head and neck has led to infraclavicular innovations. It is important that emphasis is placed on scarless in the neck rather than minimally invasive because the latter would not be an accurate description of any infraclavicular method.

Transaxillary and breast techniques were pioneered in the Far East particularly by Japanese and Korean surgeons. The cultural desire to avoid a scar in the neck from the negative feng shui in having a horizontal scar in the neck (denoting death) has been a significant driving force behind these innovations. Although technically demanding, the published literature shows that lobectomy or total thyroidectomy can be achieved safely.[6] These techniques are known as the axillo-bilateral-breast approach (ABBA) and bilateral axillo-breast approach (BABA) respectively.

There is not surprisingly a steep learning curve and a requirement to have a competent assistant working with 2D operative view in a confined operative space. Both gasless and insufflation techniques have been used, the latter potentially being complicated by hypercarbia, which can be a serious sequela of insufflation techniques.[7]

With the introduction of the da Vinci telerobot in the late 1990s, the next logical iteration was for this new technology to be used for thyroidectomy.

ROBOTIC-ASSISTED THYROIDECTOMY (RAT)

NASA had long considered the dilemma that would arise if an astronaut became ill in space. The concept of remote or 'tele' robotics was therefore spawned. The Ministry of Defence also declared an interest in developing the concept of bringing surgical expertise to the front line without placing the surgeon in danger. Patents for the technology were ultimately acquired and a system for commercial use developed by Intuitive (Sunnyvale, California).

The da Vinci telerobotic technology makes remote operating a reality with the feasibility of transatlantic surgery being published by Marescaux and colleagues in 2001.[8]

In head and neck surgery, pioneering work in the USA by Weinstein and colleagues in Philadelphia has led to robotics becoming the gold standard for the treatment of oropharyngeal tumours. In the UK, adoption has been frustratingly slow but this will change and a bright future is predicted for telerobotics in this domain of head and neck surgery.

The da Vinci system has also been used for both thyroid[9] and parathyroid[10] surgery. Lobe and colleagues published a lobectomy using the da Vinci with insufflation in 2005.[11] The present transaxillary technique, however, has been pioneered by Chung and other Korean surgeons.[6, 9, 12, 13] In 2013, Korean surgeons had experience in excess of 3000 patients. For reasons to be elaborated upon later, establishment of RAT has been tardy elsewhere in the world.

Chung and colleagues working at the Yonsei University in Seoul have published data on feasibility and learning curves supporting a superior cosmetic outcome and better post-operative swallow.[14, 15] They have also published data supporting its safe use in patients with papillary thyroid cancer. Noteworthy is that the mean size of tumour excised was only 8 mm and therefore fits into a microcarcinoma category.[16] Further studies are required before conclusions can be made with regard to safety in treating thyroid cancer.

A recent meta-analysis[17] supports its safety compared with conventional thyroidectomy (CT). Complications including cord palsy and hypocalcaemia rates were shown to be no different in this analysis. This study, however, has a low degree of freedom and high heterogeneity. There was also a heavy weighting of publications from pioneering units in Korea. Further prospective cohort studies are required before general conclusions can be made about the safety of RAT. There is inherent publication bias as complications of RAT tend not to get published.

Da Vinci telerobotics system

The da Vinci is a master–slave robot that has undergone five iterations from Standard, Xi to SP machines. The system consists of three components: the surgeon console, cart and video stack containing camera control units (charge-coupled devices, CCDs) and other hardware. As a master–slave device, movements of the robotic arms are controlled by the surgeon sitting remotely in the console.

The surgical cart engages with the patient through a process termed 'docking'. The cart has four arms, one holding an endoscopic camera with other arms being used for surgical instruments. In practice this equates to instruments in the right and left hands with fourth arm instrumentation serving as a surgical retractor or assistant.

Endoscopes are 8 mm or 12 mm and, unlike standard endoscopes that give a 2D view, images seen with the da Vinci are in 3D. This is brought about by the endoscope casing containing two endoscopes thereby replicating a truly 3D surgical experience. This gives the surgeon a

depth of field dimension to the operative field. The endoscope can be moved to alter magnification and also moved in various planes to avoid line of sight conflicts that accompany standard endoscopic methods.

Movement of instruments within the hand of a surgeon are restricted by anatomical limitations brought about by evolution. The human hand is able to adduct, abduct, supinate, pronate, flex and extend through a defined range of movements. This limitation is apparent during standard suturing and it limits what a surgeon can achieve in confined spaces where visualization is limited. These anatomical restrictions are overcome by the Endowristed capability of robotic instrumentation.

Robotic instruments are capable of moving through an arc of 270 degrees in both clockwise and anticlockwise directions. Clever algorithms within the system are finally able to remove natural human tremor, a process termed 'tremor-filtration'. Finally, motion-scaling permits the range of movement of instruments in the operative field to be scaled so that movements of the hands at the console can lead to smaller or larger movements at the patient interface. In essence this gives the surgeon 7 degrees of freedom and confers a capability of being equally dextrous with dominant and non-dominant hands.

The CCDs are able to transmit images of each endoscope to the right or left eyes when seen through the viewing binoculars. This replicates a truly 3D surgical experience. The Si has a screen resolution of 1080, a 30% improvement in quality compared to 720 in the S and 480 in the standard machines.

Fine control of the instrument jaws is brought about by movement of thumb with index and middle fingers that are inserted through the rings of the hand control, as shown in Figure 69.3.



Figure 69.3 The operating surgeon at the console controlling the robotic arms and instruments by the hand cradle.

Infrared sensors in the console stop any movement of the robotic instruments once the surgeon moves his head from the console as a safety measure. The development of dual consoles, bolt-on simulators and telestration aid both training and proctorship of robotic surgery.

Ethical considerations

The da Vinci is now routinely used for hemithyroidectomy, lobectomy, total thyroidectomy and level VI central compartment dissection. More recently, applications have extended to lateral compartment neck dissection through the axillary approach.[18]

A review of published literature from South East Asia shows that the majority of patients undergoing robotic surgery have had relatively small nodules, with the mean size of cancerous nodule removed 8 mm. Although median nodule size would have been more appropriate, it is clear that surgery is being undertaken on patients with small volume pathology. This has been confirmed by personal communication from several surgeons who have visited Korea.

A different healthcare system in association with screening of the thyroid, a variance in reimbursement tariff for robotic compared to conventional approaches (by a factor of five) combined with a national psyche for avoiding a neck scar have combined to create the perfect environment for advancing robotic thyroid surgery in Korea.

Ethical, safety and economic factors need to be considered before the introduction of new technology and surgical techniques. Surgeons practise in an environment of scrutiny with a medicolegal dimension that appears insatiable. However, without the adoption of innovation, advances which improve patient care will be stifled. The history of surgery abounds with examples of innovations that were initially resisted – some quite vehemently – anaesthesia, antisepsis, caps, gowns, gloves and even 'keyhole' surgical techniques to name but few. The environment in which RAT takes place in the Far East may not necessarily translate to a western European population. The body habitués of patients, cultural perception to neck scars and the health system in which doctors operate are very different.

The author received training in robotic surgery in 2007 before publication of RAT. To innovate and learn RAT unassisted has been a long and arduous journey involving cadaveric dissection in Paris, Strasbourg and Geneva. Furthermore, ethical permission was sought and finally granted after two submissions. Funding for prospective evaluation studies was obtained for the initial 50 patients. Obtaining recognition from private companies to recognize robotic head and neck surgery was another hurdle that had to be negotiated for fee-paying patients. Finally, peer perception of RAT had to be negotiated and addressed as we all work in an environment where to be considered maverick and an outlier confers professional risk.

There are thyroid-specific and generic considerations for RAT. My personal view is that RAT is suitable for hemithyroidectomy of nodules or nodular pathology of up to 6 cm and a total thyroidectomy, provided the



Figure 69.4 Keloid scarring on the upper arm following vaccination – a patient typically who may have valid reasons for avoiding a visible neck scar.

contralateral lobe is 'near' normal. I would counsel avoidance for cancer other than for microcarcinoma in the young and for Graves' disease. It is an attractive option for patients having a history of hypertrophic scarring (Figure 69.4) or those simply expressing a personal preference to avoid neck scarring. The approach should be avoided in obese patients with a BMI over 30, those with degenerative shoulder pathology and those with other significant comorbidity placing them in an ASA category greater than 2. The ideal patient, therefore, would be a thin, narrow-chested female with a thyroid nodule of up to 4 cm. Nodules of greater than 4 cm can be removed but are technically more challenging. Large cystic nodules can also be made suitable by aspiration at the time of surgery.

Consent

As for all surgery, informed consent should take place. It is my opinion that all consent but particularly RAT should be performed by the consultant. The literature supports that RAT is as safe as conventional surgery with the same risk of bleeding, infection, vocal cord palsy and parathyroid dysfunction. RAT, however, has the additional rare potential complication of brachial plexus dysfunction. The operation achieves the objective of translocation of an incision from neck to axilla at the expense of an increased operative time. The inpatient stay and time off work are identical.

Reservation of RAT regarding airway obstruction from a bleed is often a concern quite reasonably raised. It may come as a surprise that airway obstruction will not occur following a bleed from RAT simply because the potential space for a bleed to disseminate is so capacious compared to conventional thyroidectomy. In this respect it is safer than CT, although this would not be a cogent argument for the routine introduction of RAT.

Operative set-up

PRE-OPERATIVE CONSIDERATIONS

Teamwork is essential in the pre-operative preparation of the patient. On the arm of the side of surgery no identification bracelet, lines, blood pressure cuffs or ECG leads must be placed. I routinely use laryngeal nerve monitoring.

It is very important to mark the 5–6 cm axillary incision while the patient is awake, with the back of the patient's hand touching the central portion of the forehead, a position which I describe as an extended salute (Figure 69.5). In my experience this is the only technique that successfully identifies the best site for the incision. Otherwise, part of the incision can migrate to the upper arm or onto the anterolateral chest wall. I often extend the incision superiorly in a curvilinear fashion so it sits in a natural crease, which reduces tension and a tendency towards a hypertrophic and pigmented scarring. The axilla is not an environment well suited for healing because of its damp anaerobic nature but, with experience and correct planning, the incision heals well and becomes invisible (Figure 69.6).

At induction the patient is routinely given i.v. Augmentin and 4 mg Dexamethasone.

THEATRE SET-UP

Prior to transfer of the patient to the operating table it is important that all three components of the da Vinci are appropriately positioned. The cart is placed on the opposite side of the operating table (Figure 69.7) and is draped

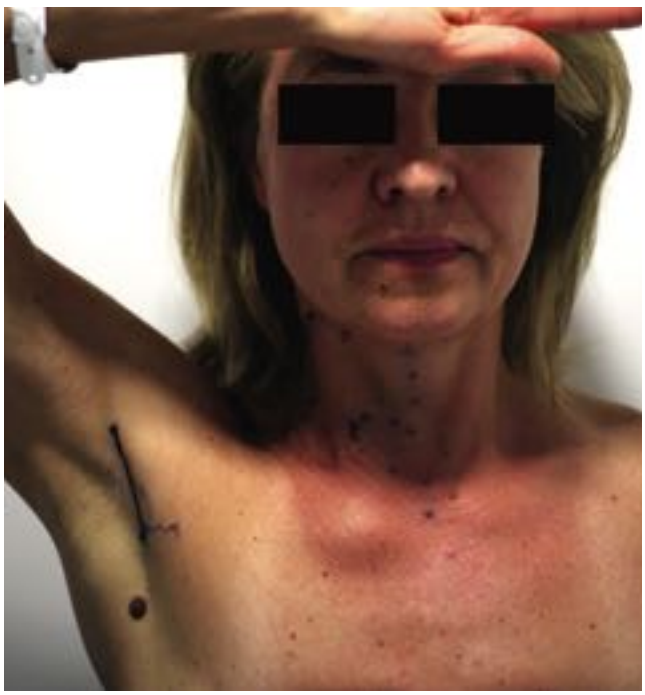


Figure 69.5 Marking of the incision immediately prior to surgery. This is of fundamental importance and is a vital component of pre-operative planning.



Figure 69.6 The same patient as in Figure 69.5, showing the axillary scar 9 months following surgery.



Figure 69.7 The cart is docked at right angles to the operating table, on the opposite side to the incision.

and correctly positioned before the patient is moved onto the operating table, thereby being ready for docking.

Contrary to CT, a shoulder roll is not placed under the shoulders as this has a tendency to overextend the neck and move the superior pole away from the robotic instruments. I place the patient's head and shoulders under a pillow so that there is adequate and comfortable support in a subtle 'sniffing the morning air' position. The head of the table is then dropped by about 20 degrees to widen the angle between the arm and the chest.

A special arm rest supports the arm, which is abducted and flexed with the forearm pronated so that the back of the hand rests on the central portion of the forehead. I stabilize this position with a Velcro coin attached to the hand and forehead. This movement has the effect of elevating and externally rotating the clavicle to that the distance between the incision site and thyroid gland is shortened. The positioning of the arm in this way is a modification to Chung's method where the arm is fully extended over the head. This puts the brachial plexus at risk and should never be used in my opinion. I have had no problems since I modified Chung's method of arm positioning.

Once completed, the incision site is infiltrated with 2% Xylocaine and 1:200000 adrenaline. Skin preparation and draping then take place while the surgeon scrubs.

The operation

PREPARATION OF THE ROBOTIC FIELD

The area to be dissected extends from the thyroid cartilage to sternal notch in a subcutaneous plane. The superior and inferior extent of the axillary incision is level with the thyroid and sternal notches respectively. An imaginary line in a horizontal plane connects the two with the area to be dissected being trapezoid-shaped.

Dissection extends medially in the subfascial and subcutaneous planes above pectoralis major and over the clavicle. The natural dehiscence between the sternal and clavicular heads of the sternomastoid is entered to get to the plane of the strap muscles. Dissection then extends under the strap muscles to access the thyroid gland. The surgical planes are then developed as in a standard CT. The lower insertion of the sternothyroid into the back of the manubrium and first rib is divided as is its superior attachment to the thyroid cartilage; this allows full access to superior pole structures. I routinely divide the omohyoid muscle as it extends over the internal jugular vein. Once the strap muscles have been separated off the thyroid gland to approximately a third of the contralateral thyroid lobe, dissection is complete. A modified retractor is then inserted (Chung, Kuppersmith, Modena or Imperial) and the robot docked.

DOCKING

The cart is docked at right angles to the operating table (Figure 69.7). All four arms can be placed through a single axillary incision or the fourth arm can be inserted through a periareolar incision. The last incision has little morbidity and the scar is invisible once it has healed.

The 30 degree down 12 mm stereoscopic endoscope is placed at an angle of 220 degrees and is inserted low laterally, extending high and upwards medially towards the thyroid gland. The fourth arm can then be placed under the endoscope, which functions as the assistant. Finally, the first and third arms, which carry the instruments for dissection and haemostasis, are positioned. The fourth assistant arm holds the 8 mm Prograsp, while the first and third arms hold a combination of 5 mm Maryland, Debakey and Harmonic shears.

THE PROCEDURE

It is my preference to identify the recurrent laryngeal nerve and parathyroid glands first by using Maryland and Debakey forceps. Once these have been clearly defined, I then swap the Debakey for the Harmonic shears. The shears use old CS14 harmonic technology that will

seal and transect vessels of up to 3 mm, which is adequate for RAT. As with all energy sealing devices, care must be taken when using this instrument close to the nerve.

Standard technique is to divide the superior pole vessels, identify the external branch of the superior laryngeal nerve then dissect the thyroid off the trachea and divide the isthmus as in a standard lobectomy. For a total thyroidectomy the approach is to divide the superior pole vessels first then dissect the thyroid off the trachea to help mobilize the remaining lobe. The inferior pole vessels and middle thyroid vein are then divided before identification and careful dissection of the nerve off the thyroid gland. This part of the operation often involves repositioning of the retractor, which has a tendency to slip. If a subtotal thyroidectomy is to be avoided, the contralateral thyroid lobe is required to be near normal in my opinion.

As in all thyroid surgery, haemostasis should be meticulous and a reversed Valsalva in the presence of normotension must be adhered to before closure. As in conventional surgery, I do not insert a drain and have found this to be unproblematic.

Closure of the incision is with 4-0 subcuticular Vicryl Rapide and Dermabond. An anterior chest wall compression dressing is applied overnight and patients are advised to wear a sports bra or vest for 2 weeks to provide light compression to the anterior chest wall. I routinely give antibiotics for 7 days. Follow-up is at 2 weeks, then 3, 6, 12 and 18 months as all patients are in a prospective study for long-term RAT evaluation.

CONCLUSION

RAT is an exciting technological development in thyroidectomy. It is here to stay but presently will have niche indications. It is not for every surgeon, hospital or patient in its present state of technological development.

Economically it is difficult to justify and lack of competition in the robotic market is hindering the expansion of robotic surgery. Training, proctorship and credentialing are factors of vital and fundamental importance to guarantee safety.

The use of RAT is technically challenging with a steep learning curve. It is still in an evaluation phase and incorporation of patients into long-term studies will assist this process. Robotic technology must be used sensibly, responsibly and ethically to ensure patient safety.

KEY POINTS

- The evidence base for minimal invasive and scarless in the neck techniques for thyroid surgery are outlines.
- This is an evolving field that will witness the indications, applications and approach for remote thyroid surgery change with advances in robotic technology.

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CHAPTER 70

SURGERY FOR THE ENLARGED THYROID

Neeraj Sethi, Josh Lodhia and R. James A. England

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: goiter, goitre, retrosternal, thyroidectomy, mediastinal, thyroid, intrathoracic. There are no randomized controlled trials comparing treatments for the enlarged thyroid. Evidence to support statements made in the chapter are level 2b at best.

INTRODUCTION

The term 'goitre' derives its etymological origins from the Latin 'gutter' meaning throat.[1] Today goitre can be used to describe any thyroid considered to be larger than normal. Prior to widespread salt iodination, Gerber found the average thyroid weight in women over 50 years was 80–90 g and in men 55–75 g.[2] The same study found 30 years after salt iodination the average thyroid weight reduced by approximately half. Pankow et al. reported that the average weight of thyroids in men aged 20–29 years was 16.4 g and 14.4 g for women, suggesting that subjects spending their entire life under the influence of iodinated salt are likely to have a smaller thyroid.[3] The upper limit of the normal thyroid gland in the iodine-replete population is considered to be 20 g.[4, 5]

In 1994, the World Health Organization (WHO) defined goitre as any palpably enlarged thyroid.[6] A number of geographically different radiographical studies in iodine-replete regions found the upper limit of the impalpable thyroid to be approximately 15 cm^3 in men and 12 cm^3 in women.[7–9]

In this chapter we discuss the clinical and radiological assessment and management of the enlarged thyroid. This includes both retrosternal goitre and goitre without intrathoracic extension.

TERMINOLOGY

The Swiss anatomist Haller first described the finding of a thyroid with intra-thoracic extension in 1749.[10] The first report describing removal of such a thyroid was by Klein in 1820.[11] Intra-thoracic, secondary intra-thoracic, substernal and cervicomediastinal are all terms that have been used synonymously with retrosternal. Up to ten definitions for these are found in the literature with the most commonly used being either (i) any goitre which extends below the thoracic inlet (with the patient in the surgical position) or (ii) any goitre where more than 50% of the gland is below the thoracic inlet.[12–21] Primary intrathoracic goitre is a distinct entity and describes a thyroid mass that originates from ectopic thyroid tissue in the mediastinum, rather than from cervical thyroid tissue.[22]

Large goitres without intra-thoracic extension comprise a group without a clear definition in terms of volume or weight. One study of 813 goitres divided patient groups by weight of gland after thyroidectomy and defined the huge goitre as heavier than 400 g.[23]

AETIOLOGY

Crile attributed goitre with intra-thoracic extension to neck musculature obstructing extra-thoracic growth and directing the goitre downwards.[14] In 1934, Lahey and Swinton discussed the potential role of negative intra-thoracic pressure and downward traction from swallowing.[24] These goitres tend to extend into the anterior mediastinum with only 10–15% growing into the posterior mediastinum.[25] The majority of these tend to be right-sided due to the great vessels impeding extension into the left thorax.[26] Primary intra-thoracic goitre is due to an abnormality of embryologic migration. A key point is that goitres with intra-thoracic

extension still derive their blood supply from the superior and inferior thyroid arteries, while primary intra-thoracic goitre is supplied by intra-thoracic vessels.[27, 28]

In accordance with the variation in terminology describing goitre with intra-thoracic extension, the incidence described in the literature varies from 0.2–45%.[16, 29] Using one of the most common definitions (where the majority of the goitre lies below the thoracic inlet) the incidence is up to 20%.[16, 25, 30] Primary intra-thoracic goitre represents less than 1% of all goitres and up to 12% of all mediastinal tumours.[31]

CLINICAL PRESENTATION

In goitre without intra-thoracic extension, the most common presenting symptom is an anterior neck mass. Compressive symptoms (dysphagia, cough, dyspnea, wheeze, stridor) occur in up to 17% of patients and are associated with increasing size of goitre.[32–34] In benign disease recurrent laryngeal nerve palsy at presentation is rare (0.7%).[35]

The goitre with intra-thoracic extension often presents without any palpable, or a barely palpable, neck mass with the majority of the thyroid bulk being in the chest.[1, 36] Approximately 40% of these can be asymptomatic. The most common presenting symptoms are secondary to airway compression, with acute distress occurring in up to 20%, followed by dysphagia.[16, 37, 38] Less common presentations include superior vena cava syndrome (venous distention of neck and chest wall, dyspnoea, facial oedema, upper limb oedema, plethora, cyanosis, papilloedema, cough, confusion), which can also lead to the development of downward oesophageal varices.[39–42] Pemberton's sign (facial congestion and cyanosis while elevating both arms) indicates increased thoracic inlet pressure due to a retrosternal mass.[43] Horner's syndrome due to direct compression of the sympathetic chain, chylothorax due to thoracic duct compression and transient ischaemic attacks secondary to thyrocervical steal have also been reported.[44–46]

Primary intra-thoracic goitre presents either as an incidental finding or with compressive symptoms similar to goitre with intra-thoracic extension.[28, 31]

INVESTIGATIONS

Biochemical assessment of thyroid function is necessary for management of all goitres. The majority are euthyroid, particularly goitres with intra-thoracic extension (80%).[1, 16, 39, 47] Up to 30% may have suppressed serum TSH levels without raised thyroid hormone levels (subclinical thyrotoxicosis).[48]

Ultrasound is highly sensitive and specific for evaluating morphology and measuring volume of accessible, extra-thoracic goitre.[49, 50] It cannot evaluate intra-thoracic goitre, except as an occasional adjunct in transluminal endobronchial fine-needle aspiration to aid pre-operative diagnosis of posterior mediastinal goitre.[51] CT remains the best imaging modality when evaluating the extent of intra-thoracic extension. As a basic rule, if it is not possible to palpate the distal extent of a thyroid goitre, a CT scan is necessary to assess its intra-thoracic extent.

CT allows assessment of the full inferior extent of the intra-thoracic goitre, as well as the shape and position of the goitre in terms of the mediastinal compartment.[52] A number of studies have examined CT findings as predictors of whether a thoracic approach is needed. Although CT is not a definitive predictor, it is more likely a sternotomy will be required if the goitre extends below the level of the aortic arch or there is evidence of extra-thyroid extension suggesting malignancy.[52–55] The risk of malignancy in goitres with intra-thoracic extension has been reported to be up to 11%.[39, 56] Factors that increase the likelihood of requiring a lateral thoracotomy are a goitre extending into the posterior mediastinum or a primary intrathoracic goitre that is primarily right-sided.[52]

Scintigraphy plays no role in the pre-operative evaluation of the biochemically euthyroid patient.[57] Indeed, intra-thoracic goitres often demonstrate limited iodine avidity despite their size (**Figures 70.1–70.4**).



Figure 70.1 Incidental plain chest X-ray abnormality suggesting a mediastinal mass due to primary intra-thoracic goitre.

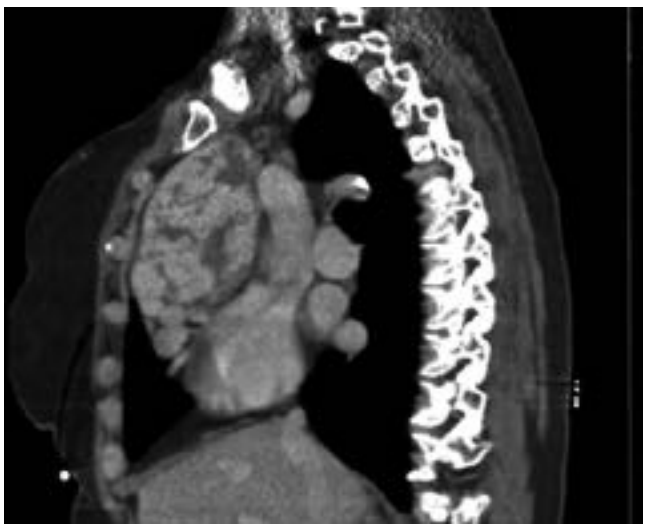


Figure 70.2 Confirmation of the mass as a likely primary intrathoracic goitre on parasagittal MR image.

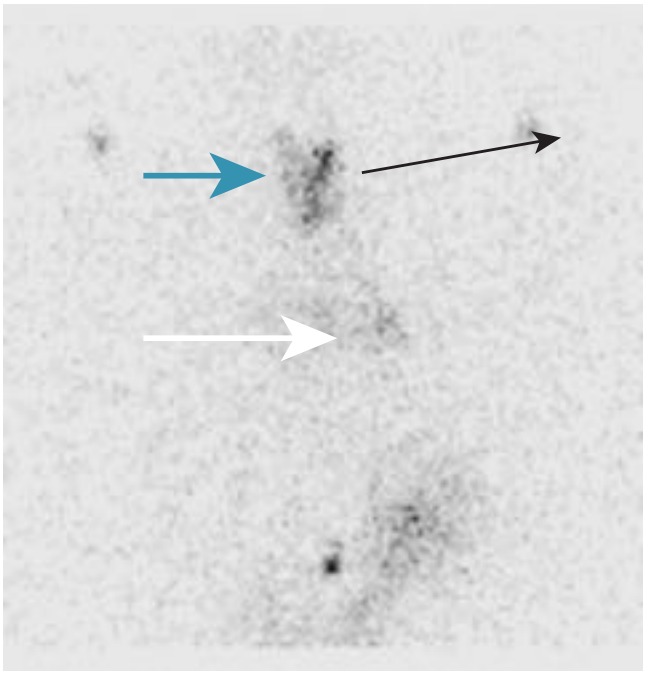


Figure 70.3 ^{123}I image demonstrating reduced iodine avidity often demonstrated by primary intrathoracic goitre (blue arrow demonstrates thyroid uptake in the neck; white arrow demonstrates uptake in the intrathoracic portion).



Figure 70.4 Removing the intra-thoracic goitre from the chest cavity preserving the innominate vein (arrow).

Objective assessment of respiratory compromise secondary to retrosternal goitre is difficult. The most common test performed is flow loop spirometry.[58] Obstruction secondary to goitre theoretically produces flow volume loops characterized by plateaus of flow during both forced inspiration and expiration.[59] However, studies have found that flow volume loop results correlate poorly with goitre weight, extent of tracheal narrowing or patient-reported symptoms.[60–63]

MANAGEMENT

When assessing the need for thyroidectomy in a patient with an enlarged thyroid and particularly retrosternal goitre, two questions need to be asked. First, will the patient benefit from the procedure and second are the surgical risks outweighed by the potential surgical benfits? The American Thyroid Association guidelines suggest that in the absence of lower airway disease, a patient will gain from retrosternal thyroidectomy from a respiratory perspective if the trachea is compressed by 35% or greater on axial CT imaging preoperatively.[64, 65] However, the American literature shows us that patients with retrosternal goitre are older, have more comorbidities, and a 73% increased risk of death during admission.[66]

In addition, patients undergoing sternotomy have a 25% risk of respiratory complications compared to a 2% risk for those who undergo a cervical approach only and the risk of deep sternal infection is cited as 1–5%, with sternal dehiscence carrying a 50% mortality rate.

A significant body of thyroid surgeons will cite the risk of spontaneous intragoitre haemorrhage leading to acute respiratory embarrassment as a reason to perform retrosternal thyroidectomy. However, Hsu tells us that in a retrospective group of patients presenting to the intensive care unit of Singapore General Hospital over a 15 year period with acute respiratory distress caused by mediastinal mass, only 1 of 19 was due to retrosternal goitre and this patient made a full recovery following surgery whilst admitted.[67] Perhaps therefore this risk, although real, is over exaggerated.

When assessing patients with retrosternal goitre therefore, it is important to remember that the majority comprise an older more frail patient subgroup.

NON-SURGICAL MANAGEMENT

No intervention

In the asymptomatic, euthyroid, benign goitre without intra-thoracic extension a conservative approach is appropriate.[68] A Scandinavian study followed up 261 patients with euthyroid goitre over 10 years.[69] Of these patients 21.8% required surgery due to worsening symptoms, 1.9% were diagnosed with carcinoma over the 10-year period and 5% developed thyrotoxicosis. Three patients died of their disease (two after developing anaplastic carcinoma and one with aggressive papillary carcinoma).

An operative approach is advocated by some as the only option to avoid the risks associated with bleeding or continued growth.[39, 70, 71] One of the largest series of thyroidectomies published included 1153 goitres with intra-thoracic extension or primary intra-thoracic goitre.

This found that they were at a higher risk of post-operative complications compared to goitres without intra-thoracic extension.[72]

Radioiodine therapy

In symptomatic patients who refuse or are unfit for surgery, radioiodine (^{131}I) therapy remains an option. This has been used in the treatment of hyperthyroidism for over six decades.[73] Conventional ^{131}I has been shown to reduce non-toxic goitre size by approximately 30–45% after 1–2 years in around 80% of patients.[74–77] The effect does diminish with increasing goitre size and approximately 10% of goitres will continue to grow.[74] In a small series conventional ^{131}I does appear to have the same effect on the intra-thoracic portion of goitres as the extra-thoracic portion.[78] Goitres causing compressive symptoms should not be considered for ^{131}I as it can induce an acute increase in size.[73] Other adverse effects of ^{131}I include radiation-induced thyroiditis, transient hyperthyroidism and long-term hypothyroidism (up to 58%).[73] The long-term risk of thyroidal or extra-thyroidal malignancy does not appear significant but is not definitively known.[79–82] Recombinant human TSH-augmented ^{131}I has been demonstrated to improve radioiodine uptake and increase volume reduction by 33–56% compared to conventional ^{131}I therapy.[83–85]

SURGERY

Anaesthetic considerations

Traditionally, the two primary anaesthetic concerns related to massive goitre were intubation difficulty and problems extubating due to tracheomalacia. A number of series have been published detailing the rate of difficulty intubating and/or the need for tracheostomy in patients with goitre.[86, 87] These suggest that the majority of patients with huge goitres with or without intra-thoracic extension can be intubated successfully using i.v. induction or awake fibreoptic intubation. In a report from an endemic goitre region, the rate of tracheostomy was not increased in goitres weighing >400 g compared to those <400 g.[23] As might be expected, there is a significant increase in the proportion of difficult intubations in huge goitres. Tracheomalacia is also reported to be a rare occurrence in iodine-replete regions (<1%) though it may be more common in endemic goitre regions (up to 33%) in the huge goitre with or without intra-thoracic extension.[23, 86, 88, 89] Treatment options for this include prolonged intubation, placement of supporting sutures, tracheal stenting and tracheostomy.[23, 42]

Another concern is sudden, post-induction cardiorespiratory collapse, which has been described in patients with mediastinal masses.[90] Cardiopulmonary bypass is the necessary option in this situation. The risk of requiring this may be more common in posterior mediastinal goitre and in those with extremely low tracheal compression where prophylactic tracheostomy is not beneficial.[91, 92]

Surgical considerations

The patient is consented ideally prior to the day of surgery. The aims of the operation should have been clarified by the operating surgeon and understood by both parties. Any imaging performed should be available in theatre. The important things to note on imaging are whether the thyroid extends into the posterior mediastinum, whether it extends behind the oesophagus and whether it extends between the trachea and oesophagus. Other significant factors include evidence of extra-thyroidal extension, and evidence of oesophageal or tracheal invasion. Careful study of the CT scan is necessary as tracheal invasion may be subtle but may make goitre delivery extremely difficult (**Figures 70.5** and **70.6**).

With retrosternal disease the likely necessity for cardiothoracic input should be identified pre-operatively. The overwhelming majority of retrosternal goitres are deliverable through a collar incision. However, it is foolhardy to perform such procedures in units where

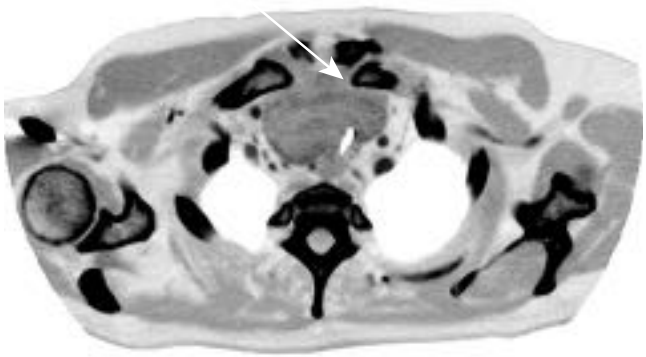


Figure 70.5 Axial CT scan of the chest demonstrating early invasion of the tracheal wall (arrowed) from a poorly differentiated thyroid cancer in the 10 o'clock position.

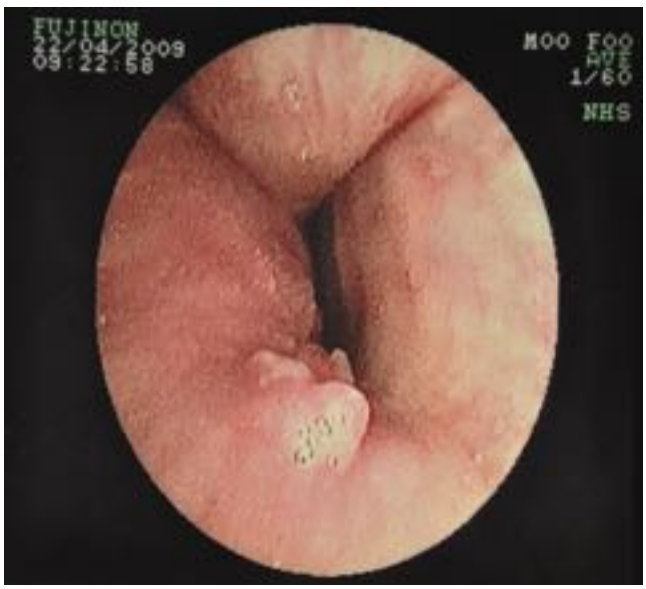


Figure 70.6 Tracheoscopic confirmation of the CT findings.

cardiothoracic expertise is not available. Cardiothoracic input is necessary in primary intrathoracic goitre and occasionally in malignant thyroid disease where the tumour has extended beyond the boundaries of the thyroid within the chest. In the latter instance the benefit of resection should be carefully discussed with the patient pre-operatively because often the patient has comorbidities and the procedure is palliative rather than curative, so a careful risk–benefit analysis should be considered. Rarely, thoracic access is necessary due to patient proportion. A short, obese patient may provide limited access through the neck to the thyroid. The majority of these patients have incidental retrosternal glands, which begs the question: just because the thyroid is retrosternal, will its removal confer significant benefit to the patient?

Extension of the goitre to the level of the carina has previously predicted the need for sternotomy.[13, 14] Thyroid weight greater than 800g has also been linked with the need for an extra-cervical approach, but this is a post-operative finding.[13, 15] The choice of which extra-cervical approach to take depends on whether access to either hemithorax or mediastinum is required.

In the infrequent situation where greater exposure is required, the option for a partial upper median sternotomy, anterior thoracotomy in the second or third space or video-assisted thoracoscopic approach may be sought. Given that the majority of thyroid masses lie anterior to the innominate vein, a median sternotomy or partial upper median sternotomy provides ideal exposure to the mass and bilaterally towards the pleura. In posterior mediastinal goitre a lateral thoracotomy may be considered. If there is asymmetry to the retrosternal extension, entering via the side with the majority of the mass is appropriate, although the aortic arch can limit access on the left, especially if there is suggested involvement of posterior mediastinal structures such as the trachea. In this situation a right-sided posterolateral thoracotomy is the incisional choice. In the rare situation that there is lateral extension into the upper thorax, a Dartevelle approach (**Figure 70.7**) would provide better control of the subclavian vessels, though this may limit exposure in the neck. Additionally, the use of video-assisted thoracoscopic surgery (VATS) has aided the excision of retrosternal goitres.

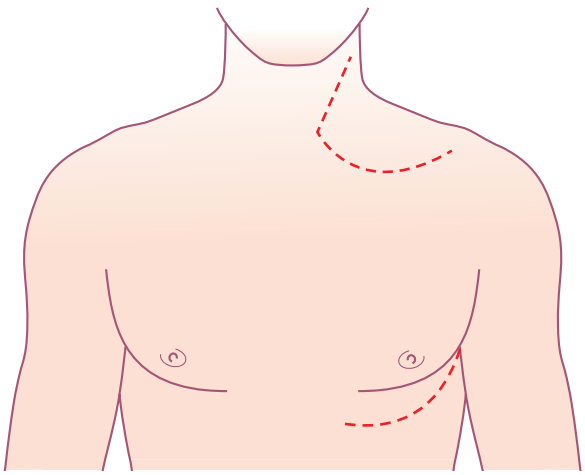


Figure 70.7 Dartvelle approach.

The patient is positioned 30° semi-supine with the right side slightly elevated. A double lumen tube allows for lung isolation. The possible approaches include a lateral camera position with medial utility ports allowing for retraction and dissection, or a subxiphoid camera position which can allow for visualization of both hemithoracic cavities. This approach provides good visualization from below and of the phrenic nerves, internal mammary vessels and great vessels. The mass is removed through the cervical incision. The subxiphoid approach limits visualization of the posterior mediastinum as the pericardium lies in the way.

Surgical procedure

A collar incision is made, normally extended to the membranous insertion of the sternomastoid muscles. A superior subplatysmal flap is raised and the flap extended laterally beyond the bodies of the sternomastoid muscles. In virtually every case, once the linea alba is divided to gain access to the thyroid isthmus, the strap muscles are divided. This is best performed superiorly as innervation of the straps is from inferior to superior.

The key to successful delivery of the retrosternal gland is to achieve mobility without excessive blood loss. A plane is therefore developed laterally between the thyroid lobe and the carotid sheath which may lie lateral to the cervical component of the gland, or anterior or posterior to the gland. An anteriorly placed carotid does not preclude thoracic delivery as lateral retraction will still enable delivery in the majority of cases. While the surgeon develops the plane, keeping on the gland surface, it is possible to assess the initial intra-thoracic extent of the gland, and indeed sometimes reach a finger to the inferior extent of the gland.

The next step is to devascularize the lobe. The superior thyroid pedicle is identified in the normal manner, retracted laterally from the cricothyroid muscle, to minimize risk of damage to the external branch of the superior laryngeal nerve, and divided vessel by vessel. The superior vessels are generally far larger in retrosternal glands so there is an increased need for ties or Ligaclips®. Once the pedicle is ligated, the mobility of the lobe is increased. Further blunt dissection laterally improves mobility further. This can be facilitated by placing a gauze swab on the lobe and digitally retracting the lobe out of the chest, the swab reducing slippage. A finger gently slid down the lobe into the mediastinum will give an indication of the extent of intrathoracic extension. Using these manoeuvres, the lobe can often simply be delivered from the chest. This becomes more difficult if the thyroid is particularly firm or if the central isthmic portion of the gland is enlarged pushing the trachea away from the manubrium as this reduces the potential of swinging the enlarged lobe in a superiomedial direction during extra-thoracic passage. In this circumstance it is often useful to palpate for the plane between the trachea and the lobe below the isthmus so that retraction from the chest can be performed both medially and laterally on the lobe.

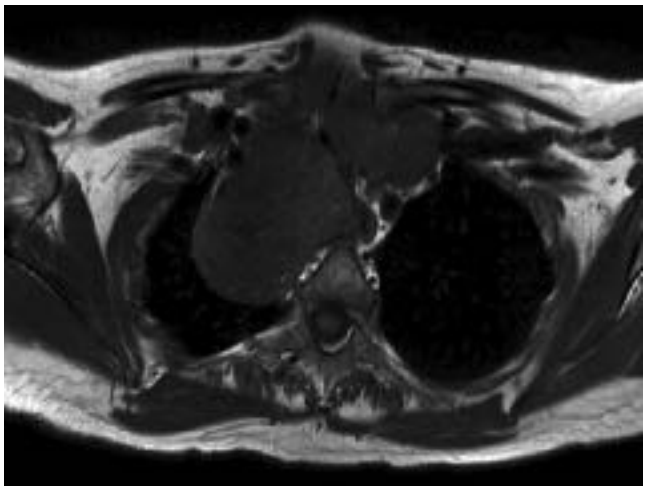


Figure 70.8 Axial MR demonstrating huge goitre with right posterior mediastinal component.



Figure 70.9 Delivery of right posterior mediastinal goitre through a cervical incision. The recurrent laryngeal nerve lies anterior to the goitre (arrow).

The search for the recurrent laryngeal nerve is generally performed once the lobe has been delivered from the chest as the nerve will lie deep to the lobe. However, in posterior mediastinal goitre this is not always the case and the nerve can lie anterior to the retrosternal portion. In this instance, therefore, the nerve needs identifying prior to lobe delivery (Figures 70.8 and 70.9). Continuous vagal nerve monitoring if available is a great advantage in such cases.

On completion of the operation the strap muscles are restored and often a drain is inserted to reduce the risk of haematoma formation in the mediastinal space.

In a study comparing morbidity of surgery for goitres with and without intra-thoracic extension Pieracci, Fahey and others found that those with intra-thoracic extension experienced significantly higher rates of recurrent laryngeal nerve injury (2.1%), post-operative bleeding (2.2%) and deep-vein thrombosis (0.5%).[68, 93–95] Multiple series suggest there is not necessarily a higher risk of permanent post-operative hypoparathyroidism following surgery for goitres with intra-thoracic extension.[68, 94, 96] Increasing size or weight of thyroid alone does not appear to be associated with an increased risk of intra-operative surgical complications.[23, 97–99]

KEY POINTS

- Surgery is performed on the enlarged thyroid to relieve obstructive symptoms, to manage thyroid overactivity, and to manage thyroid cancer or suspicious goitres.
- Pre-operatively the goitre should be assessed for function and extension. If the distal extent cannot be manually palpated, or if the goitre is an incidental intra-thoracic or retrosternal presentation, three-dimensional imaging should be obtained pre-operatively.
- Pre-operatively, the surgeon needs to know the extent of thyroid extension, whether the trachea or bronchi are compressed, and the relationship of the gland to the retro-oesophagus, and retropharyngotracheal area, beware the gland passing between the trachea and oesophagus. A significant isthmic retrosternal goitre is harder to deliver through the neck, and a patient's thoracic proportions should be considered.
- Surgeons should carefully assess imaging, paying particular attention to the integrity of the tracheal wall as tracheal invasion may be subtle.
- Surgery on large goitres, particularly with retrosternal extension, should involve an experienced thyroid anaesthetist.
- The thyroid will be deliverable through a collar incision in virtually every case but, if there is evidence of extra-thyroidal extension or primary intra-thoracic goitre, cardiothoracics should be alerted.
- When performing retrosternal thyroid surgery, the first part of the operation involves mobilizing the portion of the gland in the neck to facilitate thoracic delivery. During this phase it is not normally necessary to look for the nerve (except in posterior mediastinal presentation). Delivery is simplified by splitting the straps, dividing the isthmus, dealing with the upper pole, and digital dissection often both medial and lateral to the thoracic component at the level of the thoracic inlet.
- Retrosternal thyroid surgery should only be performed in a centre with cardiothoracic availability.
- In posterior mediastinal goitre be vigilant for the recurrent laryngeal nerve passing anterior to the thoracic portion of the goitre.
- When dissecting in the presumed tracheo-oesophageal groove, it is often worth inserting an oesophageal bougie to accurately locate the oesophagus and avoid mucosal transgression.
- Tracheomalacia is vanishingly rare in a first world economy but, if encountered, it will normally respond to extended intubation post-operatively.

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CHAPTER 71

CLINICAL EVALUATION OF HYPERCALCAEMIA

Mo Aye and Thozhukat Sathyapalan

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: hypercalcaemia, parathyroid hormone, primary hyperparathyroidism, familial hypocalciuric hypercalcaemia and hypercalcaemia of malignancy.

INTRODUCTION

Since the advent of the automated serum biochemistry analyser in the 1970s, mild to moderate hypercalcaemia has become a common incidental finding in clinical practice. Very high serum calcium (more than 3 mmol/L, 12 mg/dL), however, remains uncommon. Whenever hypercalcaemia is confirmed, a definitive diagnosis needs to be established. Primary hyperparathyroidism (PHPT) and malignancy are the two commonest causes of hypercalcaemia and account for more than 90% of cases.[1] Initial evaluation should be directed at distinguishing between the two.

INTERPRETATION OF SERUM CALCIUM

Before any further investigation, it is essential to make sure that the apparent hypercalcaemia is not a false-positive laboratory test result. Biologically relevant hypercalcaemia is due to an elevated ionized ('free') calcium concentration. Most standard laboratories measure total calcium rather than ionized calcium. Up to 45% of serum calcium is bound to protein, principally albumin. Increased protein binding can result in apparent elevation in serum total calcium concentration without any rise in the ionized calcium. This phenomenon is called 'pseudohypercalcaemia'. It may occur in those with hyperalbuminaemia from severe dehydration. Rarely, calcium-binding paraproteins in multiple myeloma present with pseudohypercalcaemia. Conversely, when albumin is low as in chronic illness, severe malnutrition or liver disease, serum total calcium may appear to be falsely low although ionized calcium is normal. If a laboratory is able to measure ionized calcium reliably, it would be preferable to measure it directly in clinical situations where serum albumin may be high or low.

Most laboratories will correct measured serum total calcium with respect to albumin, assuming normal albumin to be 40 g/L:

$$[Ca]_{adjusted} = [Ca]_{total} + \{0.02 \times (40\,g/L - [Alb]_{serum})\}$$

where:

$[Ca]_{adjusted}$: adjusted serum calcium, in mmol/L

$[Ca]_{total}$: measured serum total calcium, in mmol/L

$[Alb]_{serum}$: measured serum albumin concentration, in g/L.

With US units measuring calcium in mg/dL and albumin in g/dL, the correction formula is:

$$[Ca]_{adjusted} = [Ca]_{total} + \{0.8 \times (4\,g/dL - [Alb]_{serum})\}$$

A single, unexpected serum calcium reading should be repeated to confirm the diagnosis. If hypercalcaemia is detected in association with dehydration, calcium should be retested after correction of dehydration. Where cumulative results are available, previous calcium results should be reviewed to see if hypercalcaemia is acute or chronic. Chronic, stable, asymptomatic hypercalcaemia is likely to be benign, the commonest cause being PHPT. Familial hypocalciuric hypercalcaemia (FHH), an inherited condition characterized by a loss of function mutation of the calcium-sensing receptor (CaSR), may also present as chronic asymptomatic hypercalcaemia.

The degree of hypercalcaemia also may be useful diagnostically. Primary hyperparathyroidism usually presents with borderline or mild hypercalcaemia (serum calcium concentration often below 2.75 mmol/L, 11 mg/dL). Values above 3.25 mmol/L (13 mg/dL) are unusual in primary hyperparathyroidism, although they do occur, and are more common in patients with malignancy-associated hypercalcaemia.

CLINICAL EVALUATION

Mild to moderate hypercalcaemia is usually asymptomatic. Signs and symptoms of hypercalcaemia are non-specific and similar regardless of the cause. These include constitutional symptoms such as weakness, lethargy, intellectual weariness and depression.[2] Very severe hypercalcaemia both contributes to and is exacerbated by dehydration. Additional features should be sought in the clinical presentation to help uncover the underlying cause of hypercalcaemia.

An adult with asymptomatic hypercalcaemia probably has PHPT. Clinical features which favour this diagnosis include chronicity, modest elevation in serum calcium levels, slow or no progression of hypercalcaemia over time, normal physical examination and lack of obvious alternative diagnoses. Established end-organ damage such as osteoporotic fragility fractures, declining renal function and kidney stones may be surrogate features of chronicity and their presence may provide some reassurance that the underlying cause of hypercalcaemia is not neoplastic.

PHPT typically occurs in middle-aged or older women. A finding of high calcium in a patient outside this demographic group should prompt consideration of causes other than PHPT. Younger patients with hypercalcaemia may have a familial cause. Parathyroid cancer should be suspected in young men presenting with PTH-driven hypercalcaemia.

Although hypercalcaemia can be the first manifestation of malignancy, in most patients with malignancy-associated hypercalcaemia, the disease is not occult. Typically, features of underlying disease would have brought the patient to medical attention; hypercalcaemia is detected as an additional finding during further investigations. Rapidly progressive or very high serum calcium concentrations should raise concerns about malignancy. Breast, lung, colon and prostate cancers are the commonest solid organ tumours with skeletal metastases.[3]

TABLE 71.1 Causes of hypercalcaemia

Parathyroid hormone dependent

I. Primary hyperparathyroidism
   a. Solitary or multiple adenomas
   b. Parathyroid hyperplasia
   c. Parathyroid cancer
II. Tertiary hyperparathyroidism (end-stage renal failure)
III. Ectopic PTH secretion (very rare)
IV. Multiple endocrine neoplasia – MEN 1 and 2a
V. Inactivating mutations in CaSR or G proteins: familial hypocalciuric hypercalcaemia (FHH)
VI. Lithium therapy (alteration in CaSR function)

Parathyroid hormone independent

I. Neoplastic
   a. Osteolytic skeletal metastases
   b. Multiple myeloma
   c. Paraneoplastic syndrome (PTHrP mediated)
II. Chronic granulomatous disease (e.g. sarcoidosis)
III. Endocrine disorders
   a. Hyperthyroidism
   b. Acromegaly
   c. Hypoadrenalism
IV. Medications
   a. Thiazide diuretics
   b. Hypervitaminosis A or D
   c. Theophylline
   d. Teriparatide (human recombinant PTH 1-34)
V. Excessive calcium intake
   a. Milk-alkali syndrome
   b. Total parenteral nutrition
VI. Miscellaneous
   a. Immobilization
   b. Metaphyseal chondrodysplasia
   c. Congenital lactase deficiency

Clinical evaluation should include an enquiry about weight loss, change in bowel habit, examination of the respiratory system, breast examination in women and prostate examination in men. Multiple myeloma may present with hypercalcaemia alone.

Dietary calcium intake and medications (prescription and non-prescription drugs, herbal preparations, calcium and vitamin supplements) are important to diagnose drug-induced hypercalcaemia (Table 71.1). If possible, any medication that may be causing hypercalcaemia should be discontinued. With the exception of vitamin D excess, hypercalcaemia is generally mild in drug-induced hypercalcaemia. Diagnoses are not mutually exclusive. It is possible for thiazide diuretics to accentuate or unmask mild or incipient PHPT.

LABORATORY EVALUATION

Once hypercalcaemia has been confirmed, the next step should be to determine whether this elevation is PTH-driven. PTH mediates hypercalcaemia both in PHPT and FHH. All other causes of hypercalcaemia suppress PTH (Table 71.2).

TABLE 71.2 Differential diagnosis of hypercalcaemia

Condition	Total adjusted serum calcium	Ionized serum calcium	Phosphate	Parathyroid hormone (PTH)	Urinary calcium excretion	Vitamin D	Comments
Pseudohypercalcaemia	↑	⇔	⇔	⇔	⇔	⇔	May occur in presence of calcium-binding proteins other than albumin (e.g. in myeloma)
Primary hyperparathyroidism (PHPT)	↑	↑	⇔ or ↓	↑ or high-normal	High-normal or ↑	⇔ or ↓	Usually mild to moderate. More common in postmenopausal women May be hereditary, e.g. MEN 1 and 2a
Familial hypocalciuric hypercalcaemia (FHH)	↑	↑	⇔ or ↓	↑	Ca : creatinine excretion ratio <0.01	⇔	Autosomal dominant Usually presents with asymptomatic hypercalcaemia
Osteolytic skeletal metastases	↑↑	↑↑	⇔ or ↑	↓↓	↑ but routine measurement not needed	⇔	May present with very high calcium level, often over a short duration Clinical features of primary solid organ tumour usually predominates
Multiple myeloma	↑	↑	⇔ or ↑	↓	⇔ or ↑	⇔	Hypercalcaemia may be the first presenting clinical feature Usually has normal alkaline phosphatase
Paraneoplastic syndrome	↑	↑	⇔ or ↑	↓	⇔ or ↑	⇔	Raised PTHrP Features of malignancy may predominate
Vitamin D excess (oral ingestion, granulomatous disease, lymphoma)	↑	↑	↑ or ⇔	↓	⇔ or ↑	⇔ or ↑	1,25-DHCC raised in granulomatous disease and lymphoma

Serum parathyroid hormone (PTH)

ELEVATED OR MID- TO HIGH-NORMAL PTH

Hypercalcaemia with elevated PTH is likely to be PTH-driven. Elevated PTH in the setting of hypercalcaemia is most likely to be due to PHPT.[4] For reasons which are not clear, PHPT also appears to be more common in cancer patients than in the general population.[5, 6] PTH should still be measured even in patients with known malignancy who present with elevated calcium. Confirmation of PHPT in this situation could obviate a psychologically distressing and ultimately futile search for metastatic or paraneoplastic disease.

Parathyroid hormone levels should be interpreted in context. Physiologically, once hypercalcaemia is established, production of PTH from the parathyroid glands should be switched off. A PTH level within the upper half of the reference range despite hypercalcaemia is 'inappropriately elevated'; this picture is still consistent with PTH-driven hypercalcaemia and hence with the diagnosis of PHPT. It should also be noted that PTH levels rise with age. In a younger individual (age <45 years), the normative range is lower and narrower. PHPT in a young individual may show a PTH value that is within normal range for the population.[7]

However, with a PTH level within the upper end of the normative range, other diagnoses such as FHH should also be considered. PTH levels may be influenced by pre-analytic factors related to collection, storage and transit.[8] PTH should be repeated when the test results appear equivocal.

In chronic kidney disease, there is complex interplay of regulatory hormones (PTH, calcitriol and fibroblast growth factor 23 (FGF-23)). The characteristic biochemical picture is elevated PTH in response to high phosphate, low calcitriol (1,25 dihydroxycholecalciferol), with or without low serum calcium. Hypercalcaemia is relatively rare until relatively later stages of chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73 m^2 BSA). Hypercalcaemia in this situation may occur as a progression of compensatory ('appropriate') parathyroid hyperplasia to an autonomous overactivity of parathyroid glands. This is known as tertiary hyperparathyroidism. The diagnosis is relatively straightforward since the emerging trend would be well documented in a patient with progressive renal decline; most patients who develop tertiary hyperparathyroidism also have end-stage renal failure. Hypercalcaemia may be absent in those patients if they are on haemodialysis.

Hypercalcaemia may also be seen patients with adynamic bone disease, a form of chronic kidney disease mineral bone disorder (CKD-MBD) characterized by low bone turnover. In such patients, calcium elevation results from failure of the bone to take up calcium after an oral calcium load, such as calcium carbonate to treat hyperphosphataemia.[9] PTH in adynamic bone disease is only modestly elevated, typically (<11 pmol/L, 110 pg/mL) and may appear disproportionately low relative to the degree of renal dysfunction.

Following renal transplantation, the parathyroid hyperplasia subsides over a period of months to years. Sometimes, hypercalcaemia develops after successful renal transplantation as calcitriol production is restored before parathyroid hyperplasia has subsided completely.

SUPPRESSED PTH

PTH-independent causes should be considered if the PTH is low or within the lower half of the reference range. Serum intact PTH levels below 2.2 pmol/L (20 pg/mL) are highly suggestive of a non-PTH related cause.

Malignancy should be suspected if the hypercalcaemia is of short duration and especially if the calcium level is very high (>3 mmol/L). More often than not, the primary tumour is a solid organ tumour and the patient may present with clinical features attributable to the primary cancer. Hypercalcaemia may arise from direct lytic metastases from non-small cell lung cancer, breast cancer, renal cell carcinoma and gastrointestinal tumours. Skeletal symptoms such as bone pain and pathological fractures may be present. It is recognized, however, that hypercalcaemia and the extent of skeletal metastases are poorly correlated.[10]

In the absence of overt skeletal metastases, humoral hypercalcaemia of malignancy may arise from the action of tumour-derived humoral factors, such as PTH-related protein (PTHrP). PTHrP-related hypercalcaemia has been described in association with solid organ tumours, particularly squamous cell carcinoma of the lung and skin, head and neck tumours and renal cell carcinoma. PTHrP does not react with PTH assays. Humoral hypercalcaemia is accompanied by suppressed PTH levels on standard second- and third-generation PTH assays. Measurement of PTHrP is seldom justified in clinical practice as the underlying malignancy should be self-evident. Levels of PTH and 1,25DHCC are both suppressed appropriately.[11]

Hypercalcaemia occurs in as many as 30% of patients with multiple myeloma.[10] Anaemia, bicytopenia or pancytopenia may be accompanied by reversal of albumin–globulin ratio and impaired renal function. Alkaline phosphatase usually remains normal as osteoclastic bone resorption in myeloma is not accompanied by osteoblastic attempts at bone formation. A number of cytokines have been implicated, including tumour necrosis factor α (TNF-α), transforming growth factor β (TGF-β), interleukin-1 and leukaemia inhibitory factor. In the past, these humoral agents were collectively covered under a generic term 'osteoclast activating factor'. Elevated PTHrP has also been described in myeloma patients.

24-hour urinary calcium and urine calcium/creatinine excretion ratio

Urinary calcium should be measured routinely in suspected PHPT. The 2013 Fourth International Workshop consensus criteria lists calcium excretion of more than 10 mmol/day (400 mg/day) as one of the criteria for considering surgery in asymptomatic PHPT.

Familial hypocalciuric hypercalcaemia is rare in the general population but it is clinically important because the biochemical picture is indistinguishable from PHPT except for hypocalciuria.[12] The 24-hour urinary calcium is typically less than 5 mmol/day (200 mg/day) in FHH. Calculating urinary calcium/creatinine (Ca/Cr) excretion ratio is preferable to simply measuring 24-hour urinary calcium for excluding FHH. The ratio is calculated using paired serum and urinary calcium and creatinine samples, using the following formula:

$$\text{Ca/Cr excretion ratio} = \frac{\text{Urine calcium}\left(\frac{\text{mmol/L}}{\text{L}}\right) \times \text{Plasma creatinine}\left(\frac{\frac{\mu\text{mol}}{\text{L}}}{1000}\right)}{\text{Plasma calcium}\left(\frac{\text{mmol/L}}{\text{L}}\right) \times \text{Urine creatinine}\left(\frac{\text{mmol}}{\text{L}}\right)}$$

The Ca/Cr excretion ratio is less than 0.01 in approximately 80% of patients with FHH. In PHPT, the Ca/Cr excretion ratio is typically greater than 0.02.

When evaluating patients with apparent hypocalciuria, other factors which may cause hypocalciuria should also be considered and eliminated. These include vitamin D deficiency (<30 nmol/L, <12 ng/mL), very low calcium intake, treatment with thiazide drugs and lithium therapy.

In FHH, there may be a family history of hypercalcaemia as FHH follows an autosomal dominant pattern of inheritance. Patients with FHH have few, if any symptoms. Hypercalcaemia tends to be modest. PTH itself may be high-normal or just modestly elevated. Serum magnesium levels may also be raised. Hypocalciuric hypercalcaemia may be acquired as an autoimmune disorder and may be associated with antithyroid, antigliadin or antiendomyseal antibodies.

Vitamin D metabolites

Except in cases of obvious humoral hypercalcaemia of malignancy, serum vitamin D should be performed routinely in non-PTH dependent hypercalcaemia. An elevated 25-hydroxycholecalciferol [25(OH)D] is indicative of excessive ingestion of vitamin D. There is no agreement on the level of 25(OH)D at which hypercalcaemia typically occurs. Many experts define vitamin D intoxication as a value greater than 375 nmol/L (150 ng/mL).[13]

Parathyroid hormone catalyses the conversion of 25(OH)D to 1,25 dihydroxycholecalciferol (1,25-DHCC). With long-standing PHPT, it is common for the substrate 25(OH)D to become depleted. Serum calcium may drift lower with coexisting vitamin D deficiency with the true extent of hypercalcaemia being revealed only after vitamin D deficiency has been corrected.

Measurement of 1,25-DHCC is not required routinely but should be considered if the cause of hypercalcaemia is unclear. Extra-renal conversion of 25(OH)D to 1,25-DHCC occurs in granulomatous diseases and in lymphoma. A chest X-ray to look for malignancy or sarcoidosis may be helpful. Most patients with sarcoidosis or lymphoma generally have clinically evident pulmonary and extrapulmonary manifestations. In the absence of such clinical involvement, a thorough search for occult pulmonary, renal, hepatic, ocular and bone marrow granulomas is indicated.

PTH-independent hypercalcaemia associated with normal or low vitamin D metabolites may result from unsuspected stimulation of bone resorption (as in multiple myeloma, thyrotoxicosis, prolonged immobility, hypervitaminosis A), or unrecognized high calcium intake especially in the face of milk-alkali syndrome.

Serum phosphate

Parathyroid hormone is phosphaturic. A low phosphate level may occur in PHPT and in PTHrP-driven humoral hypercalcaemia. Vitamin D increases reabsorption of phosphate from renal tubules. Hypercalcaemia which occurs in association with vitamin D excess or in granulomatous diseases is associated with high or high-normal phosphate levels. Phosphate levels are variable in FHH.

Diagnostic imaging

Evidence of osteitis fibrosa on a bone film is very specific for primary hyperparathyroidism but is only seen in about 5% of cases. Radiographs of the skeleton are no longer recommended in view of the rarity of radiologically detectable bone disease. There is no role for high-resolution neck ultrasound, computed tomography or technetium ^{99m}Tc sestamibi (MIBI) scintigraphy in routine evaluation of suspected PHPT. These tests are useful only for pre-operative localization of confirmed disease.

Tests of other endocrine diseases

In most situations, hypercalcaemia occurring in association with other endocrine diseases is an ancillary finding. The clinical presentation is usually dominated by signs and symptoms of the underlying endocrine condition.

THYROID FUNCTION TESTS

Mild hypercalcaemia occurs in 15–20% of patients with thyrotoxicosis.[14] Hypercalcaemia persisting after control of thyrotoxicosis should be evaluated on its own merits, as there may be concomitant hyperparathyroidism.

EVALUATION OF ADRENAL FUNCTION

Hypercalcaemia is an occasional finding in adrenal insufficiency.[15] Possible contributory factors are: increased bone resorption, ECF volume contraction, haemoconcentration and increased proximal tubular reabsorption of calcium. Cortisol administration reverses hypercalcaemia within days. Again, persistence of hypercalcaemia despite treatment should prompt evaluation. Hypercalcaemia has also been described in central hypoadrenalism due to hypophysitis.[16]

EXCLUSION OF PHAEOCHROMOCYTOMA

PHPT occurs as part of multiple endocrine neoplasia (MEN 2a). Rarely, hypercalcaemia can be a feature of phaeochromocytoma itself due to humoral production of PTHrP.

Miscellaneous conditions

Other less common causes of hypercalcaemia due to increased bone resorption include Paget's disease of the bone, especially if the patient is immobilized, administration of oestrogen or a selective-oestrogen receptor modifier (SERM) to patients with breast cancer who have extensive skeletal metastases[17] and hypervitaminosis A (ingestion of more than 50000IU daily).[18] Retinoic acid causes a dose-dependent increase in bone resorption, resulting in overall incidence of hypercalcaemia of approximately 30%.[19, 20] Theophylline toxicity has been associated with mild hypercalcaemia.[21] In Jansen-type metaphyseal chondrodysplasia, a rare form of dwarfism, mutations in PTH or PTHrP receptor genes result in continuous activation of the receptor even with low PTH levels of PTH secretion.[22] The clinical picture is that of asymptomatic but significant hypercalcaemia with low phosphate and normal or low PTH.

KEY POINTS

- Primary hyperparathyroidism and malignancy are the two commonest causes of hypercalcaemia.
- Once hypercalcaemia is confirmed, the next step is to determine whether this elevation is parathyroid hormone driven by measuring parathyroid hormone.
- Parathyroid hormone levels will be raised or inappropriately normal in primary hyperparathyroidism and suppressed in malignancy related hypercalcaemia.
- In patients with familial hypocalciuric hypercalcaemia the urine calcium creatinine excretion ratio is typically less than 0.01.

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CHAPTER 72

INVESTIGATION OF HYPERPARATHYROIDISM

M. Shahed Quraishi

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: hyperparathyroidism, localization, invasive, non-invasive, imaging, intra-operative and sestamibi.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is the commonest cause of hypercalcaemia in the outpatient population. Over the last decade the advent of improved pre-operative imaging, intra-operative PTH monitoring (IOPTH) techniques and radioguided surgery has resulted in the development of various techniques of 'minimal access parathyroidectomy'. These have succeeded the classic 'four-gland bilateral exploration', with better outcomes.[1,2] Primary hyperparathyroidism is usually caused by a solitary adenoma (80–85%), hyperplasia (10–15%), double adenoma (2–5%) or parathyroid carcinoma (<1%).[3]

Pre-operative localization studies are useful in determining the appropriate surgical technique and approach; they should not be used as a diagnostic tool or as a factor to decide the need to operate and should be ordered only after a decision has been made to operate. Information gained contributes to reduced surgical time, reduced hospital stay, less risk of permanent hypoparathyroidism and use of local/regional anaesthesia.[4]

Several modalities can be used to image the parathyroid gland and can be categorized into:

- **non-invasive studies:** radiology/sonography-based imaging, nuclear medicine imaging
- **invasive techniques:** selective venous sampling (SVS), parathyroid arteriography, fine-needle aspiration.

NON-INVASIVE LOCALIZATION STUDIES

Ultrasonography

The neck is scanned with the patient in the supine position and head slightly extended to simulate the position during surgery. Usually sonography is performed with a 10 MHz or a higher transducer to provide gray scale and colour Doppler imaging in the transverse and longitudinal planes. Ultrasound (US) provides detailed anatomical information of the gland and structures adjacent to it. Techniques can be utilized to aid identification of enlarged parathyroid glands, which include rotating the neck away from the side being examined, gentle compression of the neck and asking the patient to swallow during the scanning.

The results are highly operator-dependent with sensitivity and specificity of US imaging in the ranges 51–96% and 90–98% respectively.[4–6] The sensitivity of glands >500 mg is 86% compared with 75% for glands <500 mg.[7] Factors that reduce the sensitivity of US are a background of concomitant multinodular thyroid, parathyroid hyperplasia and multiple adenomas. There seems to be no difference in US detection of adenomas due to serum calcium and PTH values.[8]

Attention is focused on the area posterior and inferior to the thyroid gland, medial to the carotid sheath and the tracheo-oesophageal grove. The superior parathyroid

glands are less commonly ectopic as compared to the inferior pair. Up to 20% of PAs are found at ectopic sites. The usual sites are the retro-oesophageal, retro- or paratracheal, superior mediastinum, within the carotid sheath, thymus tissue and adjacent to the hyoid bone. Scanning should be extended to the retromandibular area superiorly down to the clavicle/suprasternal notch if not found in the usual sites.

The classic enlarged parathyroid adenoma is greater than 1 cm and typically a homogeneously hypoechoic, ovoid, well-marginated, extrathyroidal solid lesion with a fat or connective tissue plane separating it from the thyroid gland. Parathyroid adenomas are typically highly vascular lesions, which on colour Doppler sonography reveal a peripheral vascular arc arising from a vascular pedicle on the superior or inferior pole of the adenoma (**Figure 72.1**). The main supply is from a branch of the inferior or superior thyroid artery. In comparison, normal lymph nodes have a central echogenic fatty hilum surrounded by hypoechogenic cortex with small hilar vessels and are typically kidney-shaped.

Larger adenomas may be multilobed, pear-shaped or complex with cystic/solid components. Other structures in the vicinity which may mimic PA are the oesophagus and the longus colli muscle. They are recognized on US imaging by identifying the striated muscles, position and their elongated structures. Parathyroid carcinomas may show cystic degeneration, calcification, heterogeneity with local invasion and local lymphadenopathy. Intra-thyroidal adenomas (**Figure 72.2**) may mimic thyroid nodules whereas thyroid nodules may appear like parathyroid adenomas (**Figure 72.3**). In Hashimoto's thyroiditis central compartment lymphadenopathy may make it difficult to identify parathyroid adenomas due to similar features.[9]

US-guided fine-needle aspiration and rapid PTH assay can help differentiate an adenoma from a lymph node, and it is utilized especially to evaluate patients before revision surgery.[10] If all four parathyroid glands are enlarged on ultrasound, the diagnosis may be PT hyperplasia; the glands may appear asymmetrically enlarged and individual hyperplastic glands may be difficult to distinguish from an adenoma. The advantages and disadvantages of US scanning are listed in **Table 72.1**.

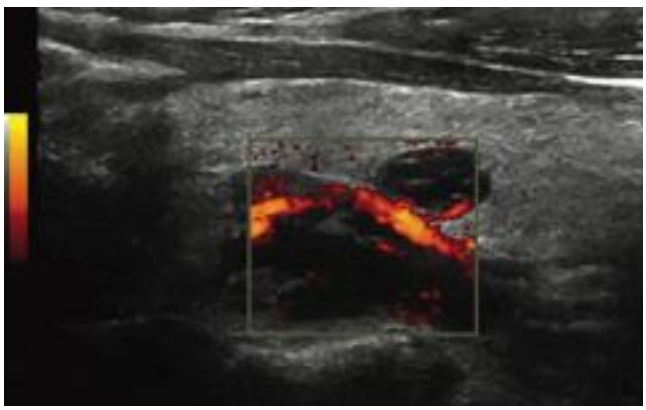


Figure 72.1 Colour Doppler sonography reveals a peripheral vascular arc arising from a vascular pedicle on adenoma.

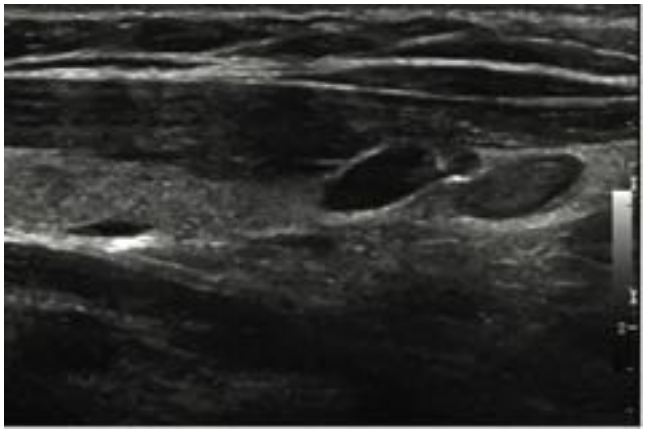


Figure 72.2 Intrathyroidal adenoma.

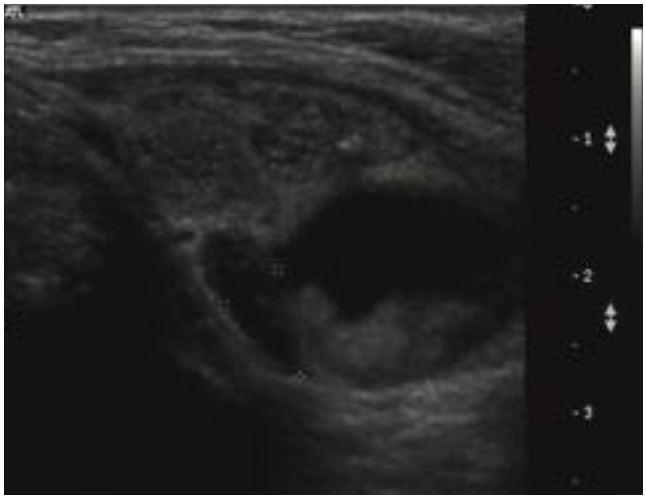


Figure 72.3 Multinodular goitre with parathyroid adenoma.

TABLE 72.1 Ultrasonography for parathyroid adenomas

Advantages	Pitfalls
Inexpensive	Operator-dependent
No radiation exposure	Ectopic or intra-thyroid adenomas missed
Non-invasive	Limited value in retro-oesophageal, paratracheal and mediastinal adenomas
Helpful in fine-needle biopsy	Difficult to differentiate between small adenomas and lymph nodes

For best results and interpretation of parathyroid sonography, well-trained and experienced personnel with a specialist interest are essential and lead to successful localization of the parathyroid adenomas in the surgical field.

Imaging using radioactive tracers

SESTAMIBI SCINTIGRAPHY

^{99m}Tc sestamibi was originally used for diagnostic cardiology and was accidentally found to be concentrating in parathyroid adenoma tissue.[11]

TABLE 72.2 Predictive factors for sestamibi scan

Positive	Negative
High oxyphil content (>20%)	Thyroid nodules
Vitamin D deficiency	Multigland disease
High PTH levels	Adenomas <600 mg
High calcium levels	Calcium channel blockers

Sestamibi diffuses passively through cell membranes and accumulates almost exclusively in mitochondria. High mitochondria content in oxyphilic cells in parathyroid adenomas is considered to be the reason for the excessive tissue uptake in PHPT.[12] A meta-analysis of 35 ultrasound and 14 sestamibi-SPECT studies had a pooled sensitivity of 76.1% and 78.9% respectively.[13]

Factors influencing sestamibi imaging include the following and are summarized in Table 72.2:

- **Calcium:** A higher calcium level is more likely to be observed in patients with positive sestamibi scans. In a study of 102 patients, a positive sestamibi scan was found in over 95% of patients with calcium over 11.3 mg/dL.[14] Other studies suggested that the severity of hyperparathyroidism has an influence on sestamibi scans, with positive scans in 64% of asymptomatic patients, in 83% with nephrolithiasis and in 100% of patients with severe bone involvement.[15]
- **PTH:** A high PTH level was directly related to the uptake ratio and positive scans, with almost 100% sensitivity when the PTH levels exceed 200 pg/mL.[16] This was not replicated by others[17] and PTH levels do not allow selection of candidates for pre-operative scanning.[18]
- **Vitamin D deficiency:** In a study of 421 patients with low cholecalciferol levels, positive scans were more likely in those who were vitamin D-deficient than in those with normal vitamin D.[19]
- **Calcium channel blockers:** The use of these interferes with the sestamibi uptake by parathyroid cells and reduces the sensitivity of ^{99m}Tc-MIBI parathyroid SPECT.[20]
- **Oxyphil content:** Adenomas with >20% oxyphil cell content are associated with a positive scan while small adenomas (<600 mg) and low oxyphil cells (<20%) are likely to give negative results.[21]
- **Multigland disease:** In a study of 123 patients, none of the 15 patients with multigland disease were identified pre-operatively. It is a major shortcoming of sestamibi scanning in identifying multigland disease.[22]
- **Thyroid disease:** In the presence of thyroid nodules, the sensitivity of sestamibi scanning is low (92% vs 53%).[23] However, a large retrospective study did not find any difference.[24]

Sestamibi scintigraphy is the imaging of choice for pre-operative localization of parathyroid adenomas. ^{99m}Tc sestamibi is taken up by the mitochondria of the salivary, thyroid and parathyroid tissue. In parathyroid adenomas the mitochondria-rich oxyphil cells retain the radiotracer for longer than in thyroid tissue.[25] It is a functional scan and provides limited anatomical details.

The patient should be positioned as on the operating table with a sandbag under the shoulders under the gamma camera. Dual phase planer images are taken 10 minutes after injection of ^{99m}Tc sestamibi and again 2 hours later to identify a focus of retained radiotracer consistent with a hyperfunctioning parathyroid gland. It is better at picking up mediastinal ectopic glands not identified in ultrasound imaging (Figure 72.4). It is also used to identify adenomas during radioguided surgery. The combination of sestamibi scans with 3-dimensional (SPECT) imaging, fusion with

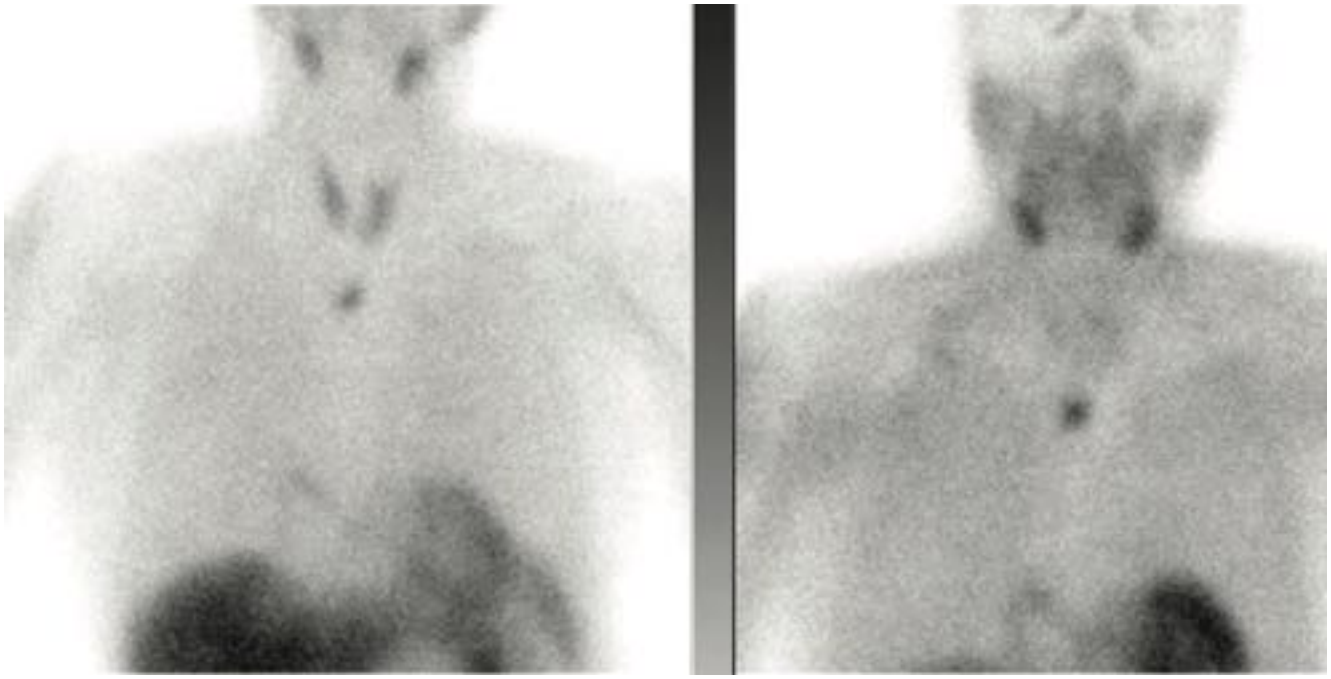


Figure 72.4 Sestamibi scan showing ectopic parathyroid in the mediastinum.

computed tomography (MIBI-SPECT-CT) and thyroid subtraction scans helps obtain better results.

SPECT

Sestamibi–single-photon emission computed tomography (SPECT-MIBI) provides multidimensional higher-resolution images, which helps to detect glands deep in the neck and improves detection of ectopic glands, hence aiding focused surgical techniques. Various studies have shown that SPECT (92–98%) improves the sensitivity of abnormal parathyroid gland in comparison to sestamibi scintigraphy (71–79%).[26, 27] Its sensitivity to identify multigland disease is, however, limited (**Figure 72.5**).

SPECT-CT FUSION

The addition of an integrated SPECT-CT scanner combines the gamma camera with a multidetector CT (**Figure 72.6**). The SPECT provides the functional information while the CT provides the anatomical information which facilitates surgical exploration.[28] A study using SPECT-CT revealed the exact position of the abnormal gland in 102 out of 116 patients (88%), while CT or SPECT-MIBI alone was predictive in 65% and 55% respectively.[29]

SUBTRACTION THYROID SCAN

Dual isotope subtraction scintigraphy is useful in identifying abnormal parathyroid glands in the presence of thyroid pathology. The patient is given a radiotracer which accumulates in thyroid and parathyroid (sestamibi) followed by a thyroid-specific radiotracer (radioiodine ^{123}I or technetium pertechnetate (^{99m}Tc pertechnetate).[30]

After taking images of both radiotracers, computer software is used to subtract the thyroid element from the combined thyroid parathyroid (sestamibi) image, revealing the parathyroid area (**Figure 72.7**). The limitation of this technique is that the image quality can be compromised due to motion artefact.

COMPUTED TOMOGRAPHY (CT)

Axial contrast-enhanced fine cuts (2.5–3 mm) through the neck will help localize PAs in 46–87% of cases,[31, 32] allowing accurate imaging for focused surgical techniques. This modality is available in most hospitals but it is a costly procedure with exposure to radiation. On routine use, studies have not found any advantage over ultrasound in identifying abnormal parathyroid glands. It is helpful in identifying ectopic glands in the mediastinum or

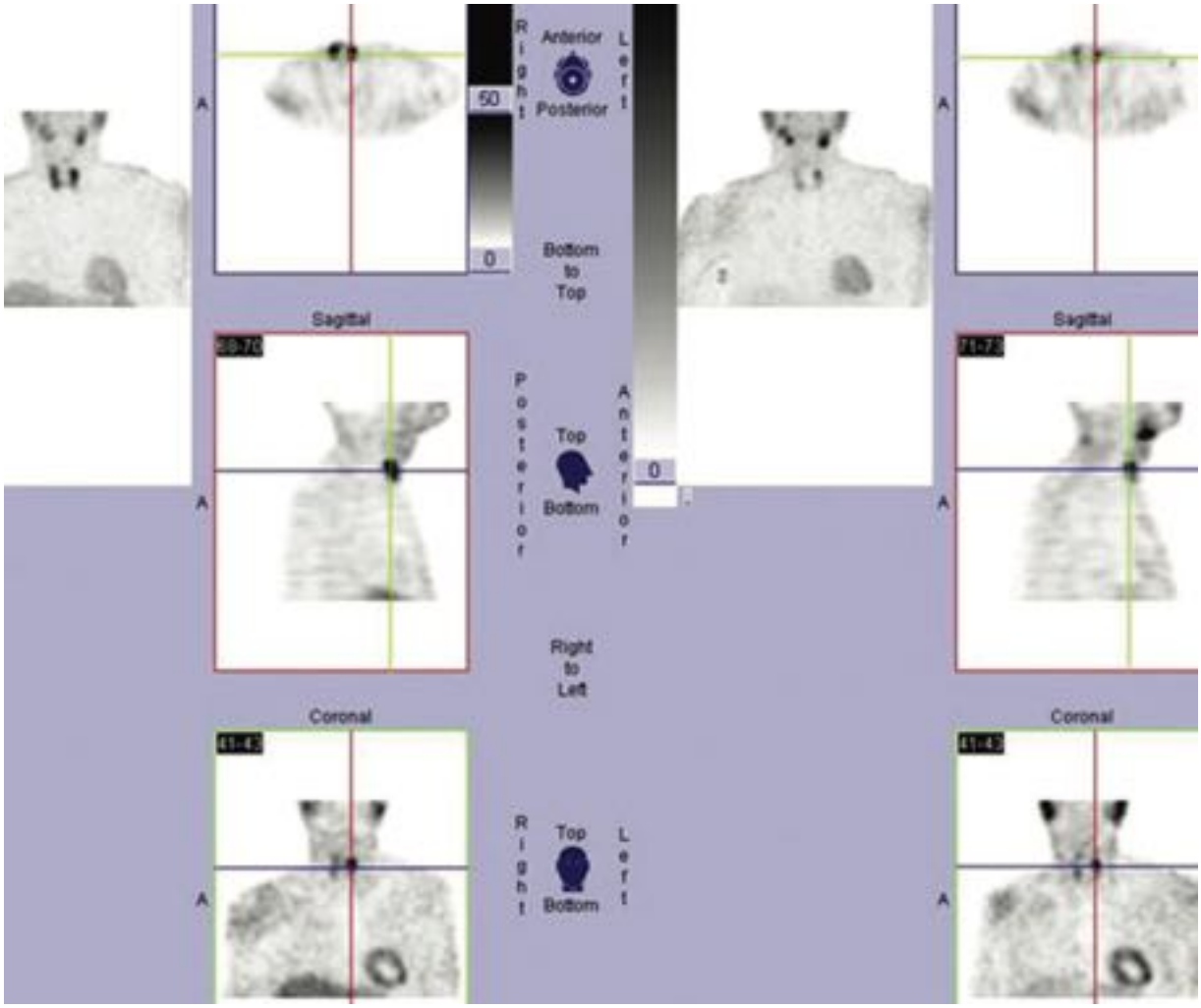


Figure 72.5 SPECT-MIBI.

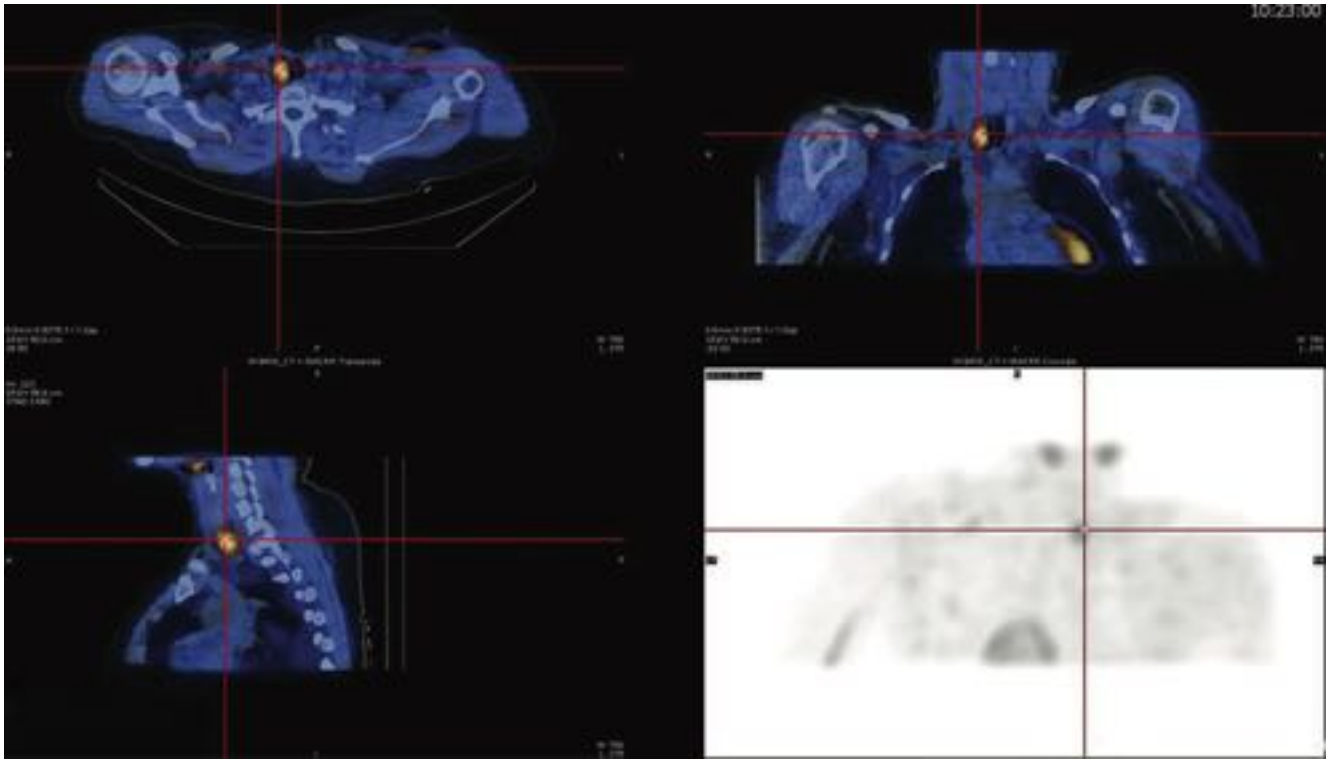


Figure 72.6 MIBI-SPECT-CT.

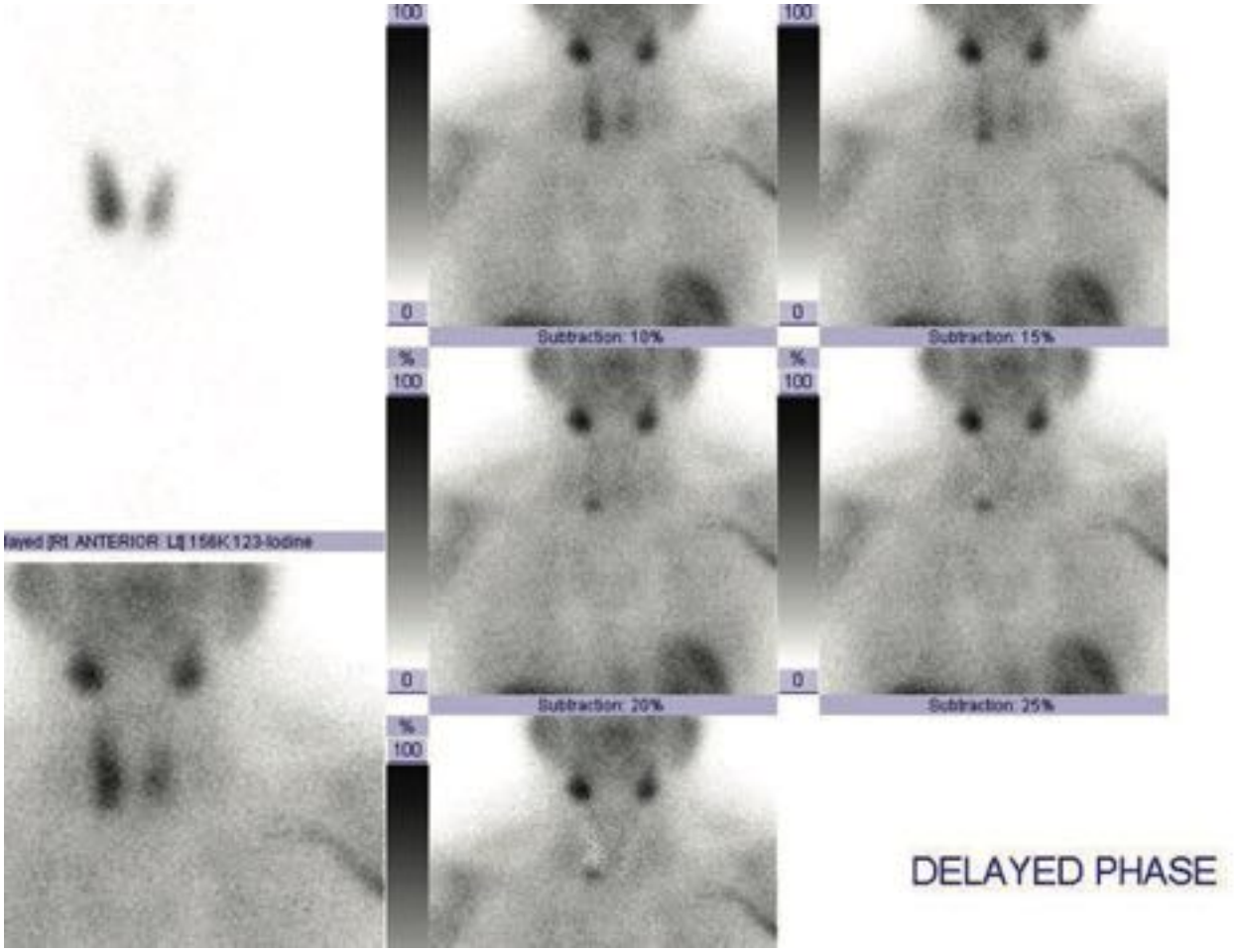


Figure 72.7 Dual isotope: Sestamibi/iodine 123, subtraction study.

trachea-oesophageal groove, especially in patients with a prior failed neck exploration and distorted tissue planes.[33]

Four-dimensional computed tomography (4D-CT) techniques utilize the characteristic of rapid contrast uptake and washout of parathyroid adenomas. The name is derived from an added dimension from the rapid changes of perfusion of contrast over time to 3D-CT. It provides both anatomical and functional data about the abnormal parathyroid glands. The image protocol for 4D-CT scans initially consists of an unenhanced scan followed by an intravenous bolus of non-ionic contrast (2 mL/kg with a maximum of 120 mL at 4 mL/second). Triple-phase 1.5 mm axial scans are repeated from the angle of the mandible to the carina at 30, 60 and 90 seconds after the administration of contrast.

Information from 4D-CT helps to localize ectopic glands (in the deep neck, mediastinum or laterally within the carotid sheath) or intra-thyroid parathyroid adenomas. Prior to the intravenous administration of contrast material, parathyroid adenomas demonstrate attenuation similar to that of muscle. Parathyroid adenomas tend to be hypervascular structures with variable contrast enhancement and early washout. A hypervascular soft-tissue mass near the expected location of the parathyroid glands is considered to represent a parathyroid adenoma (**Figure 72.8**). Ectopic glands may be seen, most commonly within the mediastinum. This helps to improve pre-operative planning in revision surgery in a scarred field with poor tissue planes and thus reduces operative morbidity.[34–36]

MAGNETIC RESONANCE IMAGING (MRI)

This modality is less commonly used than ultrasound and sestamibi scans for pre-operative localization but is still useful for evaluation of abnormal parathyroid glands due to its excellent anatomic detail. For revision surgery, it provides a non-invasive, radiation-free modality to localize abnormal parathyroid tissue. The reported sensitivity of MRI for abnormal parathyroid tissue ranges from 74% to 88%[37, 38] and images are not degraded by streak artefacts from surgical clips or previous surgery. However, compared to CT scans, MRI appears especially useful in detecting ectopic mediastinal glands, with sensitivities exceeding 80%.[39] Parathyroid adenomas are identified as soft-tissue masses in the expected location of the parathyroid glands. The most common tissue characteristics are intermediate to low T1-weighted images and high signal intensity on T2-weighted images.[40] The accuracy of MRI imaging of parathyroid disease is reduced in concomitant thyroid disease, which is present in up to 40% of patients with hyperparathyroidism.[41]

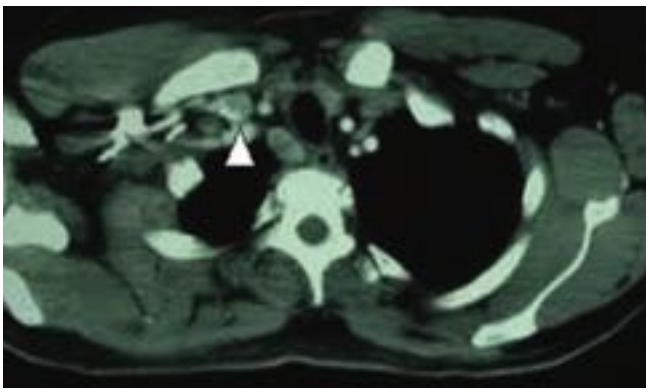


Figure 72.8 4D CT scan. (Courtesy: Dr F. Riffat.)

POSITRON EMISSION TOMOGRAPHY AND CT (PET-CT)

Studies of FDG-PET do not confirm that it is as good an imaging technique as MIBI and ultrasound for abnormal parathyroid glands.[42] In patients with initial diagnosis of hyperparathyroidism, the sensitivity of PET-CT for detection and localization of parathyroid adenomas is not as promising as previously thought.[43] While performance was better in secondary hyperparathyroidism, we believe that PET-CT cannot be recommended for PHPT localization although it may be useful for patients in whom other imaging modalities have failed to find the abnormal parathyroid gland.[44]

INVASIVE LOCALIZATION TECHNIQUES

Selective venous sampling

Selective venous sampling (SVS) is the most common invasive modality used for parathyroid localization and the accuracy is much better than large venous sampling. In patients with suspected residual parathyroid adenomas after unsuccessful surgery or in those where non-invasive methods are negative or conflicting, invasive localization techniques may be helpful. In these situations, SVS has a sensitivity of 75% compared to sestamibi (65%) or ultrasound (50%).[45] A 1.5–2-fold increase in PTH levels allows for identification of side (left vs. right) and region (cervical vs. thoracic). False positive results in SVS can be attributed to post-operative changes in venous flow due to ligatures or scarring.

Factors that need to considered with SVS include costs, expertise, radiation exposure and risks such as haematoma at catheter site, adverse reactions to contrast material and vascular accidents. With intact PTH assays, the sensitivity of SVS has been reported as high as 98%[46] and can be considered as the gold standard in patients with persistent or recurrent hyperparathyroidism and unhelpful non-invasive localization techniques.

Parathyroid arteriography

Selective arteriography was performed to localize adenomas in the past when other non-invasive techniques were not available, with varying results. Due to the risk of central venous system complications associated with this technique, it is rarely used. There may be limited benefit in post-operative patients with altered venous or fascial anatomy due to surgical sequelae.

Fine-needle aspiration

For revision surgery, CT or ultrasound-guided fine-needle aspiration (FNA) can be helpful in distinguishing parathyroid from non-parathyroid tissue.[47,48] Testing the sample for PTH levels is more sensitive than cytology as thyroid follicular cells may look similar to parathyroid tissue.

COMPLEX CLINICAL SETTINGS

Localization techniques in multigland disease patients such as multiple endocrine neoplasia (MEN) type 1, familial HPT, secondary or tertiary hyperparathyroidism are less accurate. Often the dominant hyperactive parathyroid(s) is prominent and other less active ones may be suppressed in the background. **Figure 72.9** shows the parathyroid localization flow charts for surgery in hyperparathyroidism used at the University of California, San Francisco.[49]

In a systematic review of more than 20 000 cases of solitary adenomas (SA), multiple gland hyperplasia disease (MGHD) and double adenomas (DA), ^{99m}Tc-sestamibi and ultrasound were 88.44% and 78.55% sensitive, respectively, for SA, 44.46% and 34.86% for MGHD, and 29.95% and 16.20% for DA.[50]

In minimal access parathyroidectomy one of the challenges is to identify the posteriorly placed superior adenoma. This not uncommonly placed in the trachea–oesophageal groove, retro-oesophageal area or adherent to the lateral oesophageal wall. It may erroneously be interpreted as an inferior gland in planar sestamibi scans but better identified in SPECT scans. Standard 10 Mhz ultrasound probes may give negative results in these cases due to poor penetration in glands placed in a deep plane.[51]

Hyperparathyroidism in pregnancy could limit the choices of imaging modalities. The first choice would be to try ultrasonography alone and consider surgery only in severe hyperparathyroidism with renal and/or bony complications. Ultrasound-guided FNA with PTH aspiration directly from the gland may be useful for confirmation.[52] If the need for further imaging is necessary, MRI and low-dose sestamibi with radiation shielding to the embryo may help.[53,54] Mild or moderate presentations are best deferred until pregnancy is over.

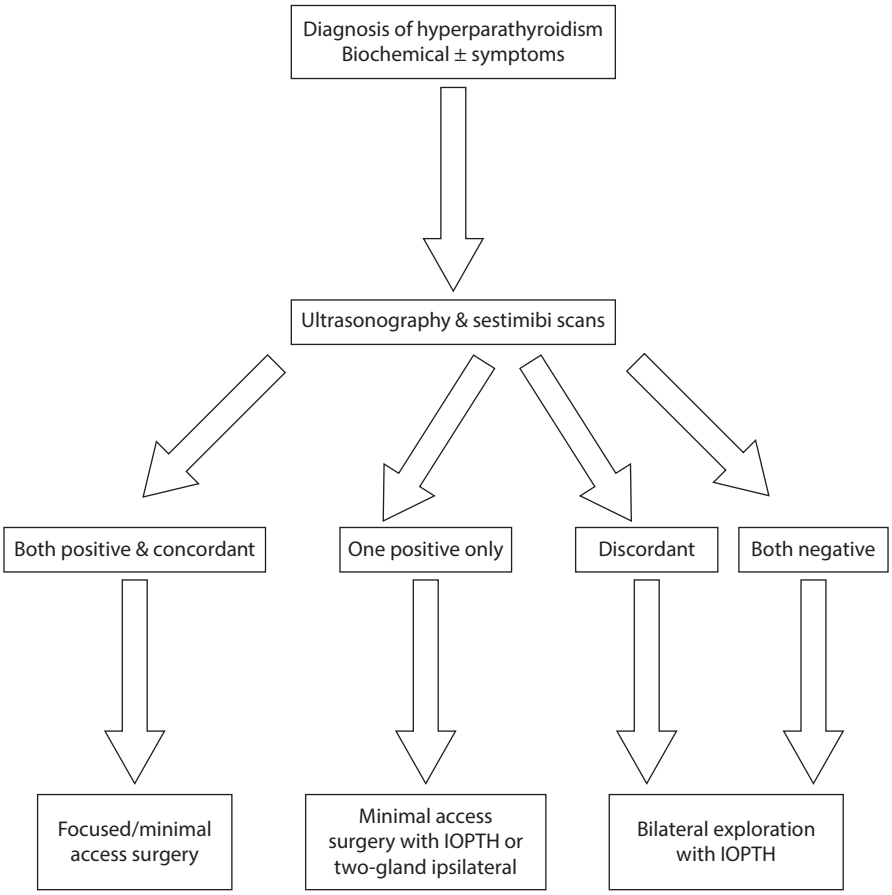


Figure 72.9 Parathyroid localization flow charts for **(a)** first-time surgery used at the University of California, San Francisco. (Modified from Randolph GW. *Surgery of the thyroid and parathyroid glands*, Figures 57.9 and 57.10.) [49] *(Continued)*

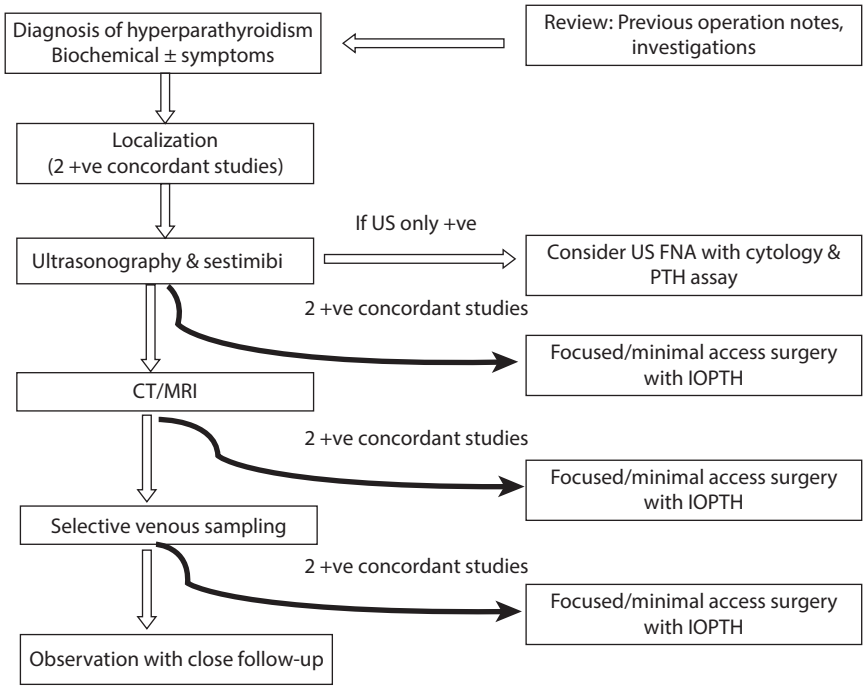


Figure 72.9 (Continued) Parathyroid localization flow charts for **(b)** revision surgery in hyperparathyroidism used at the University of California, San Francisco. (Modified from Randolph GW. *Surgery of the thyroid and parathyroid glands*, Figures 57.9 and 57.10.)[49]

KEY POINTS

- Minimal access, minimally invasive parathyroidectomy is now producing cure rates equal to the traditional four-gland bilateral exploration.
- This requires good localization studies, and non-invasive techniques such as ultrasound with sestamibi scans are quite often adequate to give satisfactory information to perform a focused surgical procedure as a day case.
- Invasive techniques are best reserved for revision surgery and negative imaging studies.
- The final choice of the pre-operative localization studies depends on local expertise, choice and final surgical outcomes.

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CHAPTER 73

MANAGEMENT OF HYPERPARATHYROIDISM

Neil J.L. Gittoes and John Ayuk

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: hypercalcaemia, parathyroidectomy, primary hyperparathyroidism, cinacalcet. Further relevant articles were obtained by manual screening of the reference lists of selected papers and contemporary textbooks.

CLASSIFICATION OF HYPERPARATHYROIDISM

Hyperparathyroidism literally means excess secretion of parathyroid hormone (PTH). In isolation, the term 'hyperparathyroidism' is of little value in informing clinical practice. For instance, hyperparathyroidism may occur as the result of autonomous hypersecretion of PTH causing hypercalcaemia; conversely physiologically appropriate hypersecretion of PTH may be seen in conditions where hypocalcaemia prevails. Thus the classification of hyperparathyroidism into primary, secondary and tertiary allows an aetiology-based approach to management. Typical biochemical features of primary, secondary and tertiary hyperparathyroidism are shown in Table 73.1.

Depending on specific underlying causes of secondary and susceptibility to tertiary, specific biochemical features will differ. This chapter will focus on the management of primary hyperparathyroidism (PHPT). Because secondary hyperparathyroidism (SHPT) has underlying medical causes, management of the range of conditions causing SHPT (e.g. vitamin D deficiency and chronic renal impairment) is beyond the scope of this chapter.

INTRODUCTION TO PRIMARY HYPERPARATHYROIDISM

PHPT represents a biochemical syndrome of inappropriate or unregulated hypersecretion of parathyroid hormone (PTH) by one or more of the four parathyroid glands in the absence of a recognized stimulus, leading to hypercalcaemia. Most cases are sporadic and caused by a single parathyroid adenoma (85–95%) or multigland disease (5–10%), with parathyroid carcinoma accounting for <1%.[1]

CHANGING CLINICAL PRESENTATION OF PHPT

PHPT was previously considered a relatively rare disorder, with clinical manifestations dominated by renal and/or bone disease. However, in modern times the diagnosis is most frequently recognized coincidentally on biochemical testing in patients evaluated for unrelated complaints. The annual incidence of PHPT is around 20 cases per 100 000, although the prevalence does vary depending on the populations studied and detection methods used.[2, 3]

TABLE 73.1 Biochemical features of primary, secondary and tertiary hyperparathyroidism

	Primary	Secondary	Tertiary
PTH	↑/↑↑	↑↑	↑↑↑
Calcium	↑	↓	↑/↑↑
Phosphate	↓/→	↓ – vitamin D deficiency ↑ – renal failure	↓/↑
Alkaline phosphatase	→/↑	→/↑	↑
Notes		Biochemistry differs according to underlying cause	

Classical skeletal complications (osteitis fibrosa cystica) are present in less than 5% of newly presenting patients and the incidence of renal stones has fallen to around 15–20%.[4] The latter, however, is still the most common complication of PHPT. More diffuse calcification may also be seen in the renal parenchyma (nephrocalcinosis) in association with hypercalciuria and a decline in renal function may be seen with long-standing PHPT.

Neuromuscular manifestations tend to be vague and include fatigue and subjective weakness, as opposed to a definable myopathy. Reduction in neurocognitive function that sometimes ameliorates following successful parathyroidectomy has been described.[5] Psychological and psychiatric symptoms are not in isolation regarded as indications for parathyroidectomy, however.[6]

Peptic ulcer disease and pancreatitis are associations of classical primary hyperparathyroidism. Pancreatitis is rarely seen nowadays because most PHPT is 'mild'. Peptic ulcer disease may be seen in patients who have PHPT in association with multiple endocrine neoplasia syndrome type 1 (MEN-1). Cardiovascular risk is increased in PHPT, particularly with respect to increased vascular stiffness.[7] There is an increased incidence of hypertension with PHPT, although the underlying mechanisms are not fully understood. Results of a number of recent studies suggest parathyroidectomy in hypertensive patients reduces systolic and diastolic blood pressure.[8, 9]

WHAT ARE THE INDICATIONS FOR PARATHYROIDECTOMY?

Parathyroidectomy is the only curative treatment for PHPT, with first-time cure rates exceeding 95% of cases.[10] In symptomatic patients or those with evidence of end-organ disease, such as low bone mineral density (BMD) or kidney stones, cohort studies have demonstrated that after successful parathyroidectomy BMD improves substantially and the incidence of kidney stones declines; cognitive function may improve and cardiovascular disease rates and premature death also appear to decrease.[11–14] For these reasons, if no contraindications exist, all patients with symptomatic PHPT or in whom there is evidence of end-organ disease should receive parathyroidectomy.

ASYMPTOMATIC PHPT

The clinical profile of PHPT has shifted from a symptomatic disorder with hypercalcaemia-related symptoms, kidney stones and overt bone disease to a symptomatically more mild condition, and there remains controversy concerning surgical intervention in patients with no clear clinical features. Some clinicians believe 'asymptomatic' patients with no complications can be managed non-surgically, while others believe virtually all patients with biochemical evidence of PHPT, irrespective of how mild, should undergo parathyroidectomy as there may be 'insidious' elements to chronic mild PHPT.[15]

IS ASYMPTOMATIC PHPT BENIGN?

Consequences of untreated asymptomatic PHPT

Developing robust clinical guidelines for the management of asymptomatic PHPT requires a clear understanding of the natural history of the disease. However, large-scale high-quality data in this area are lacking. A prospective study published in 1999 reported no significant change in serum calcium concentration, urinary calcium excretion and BMD after 10 years in 52 patients with asymptomatic PHPT who did not undergo parathyroidectomy.[16] The same group published 15-years follow-up data in the same cohort of patients, reporting a small but significant increase in serum calcium concentration compared to baseline, along with a 10% decline in BMD at one or more sites, although lumbar spine BMD remained unchanged.[17] In addition, there was progression of PHPT in 37% of patients over the 15 years of observation, to the point that criteria for surgery were met.

In a recent well-characterized cohort of 904 untreated patients with mild PHPT (median follow-up 4.7 years), serum calcium did not rise in the group but there was a significant rise in PTH concentration over the follow-up duration.[18] There was progression of PHPT in 121 patients (13%) and 26 (3%) underwent parathyroidectomy for progressive disease during the follow-up period. Baseline age (higher) and PTH concentration were markers for disease progression.[18]

Impact of asymptomatic PHPT on BMD and fracture risk

A small number of studies have prospectively examined bone density changes in treated and untreated asymptomatic PHPT. Studies have generally been short term over 1–2 years. A meta-analysis of such studies has shown small but significant loss of bone density in untreated PHPT, ranging from 0.6% to 1.0% per year.[19] Following parathyroidectomy, there was a rise in bone density, broadly similar to that observed in patients with mild PHPT who did not undergo parathyroidectomy but who were treated with antiresorptive medical therapies.[19]

In a randomized controlled trial of parathyroidectomy versus observation, 28 patients followed up without surgery were found to have a loss of BMD at the femoral neck (–0.4% per year) and total hip (–0.6% per year), but not at the spine or forearm.[20] In 25 patients managed surgically, following parathyroidectomy there was an increase in BMD of the spine, femoral neck, total hip and forearm. Similar findings were reported in two randomized controlled trials comprising 191 patients[21] and 50 patients[22] with asymptomatic PHPT randomized to surgery or observation. The trial of 191 patients reported a significant increase in BMD compared to baseline at the lumbar spine following surgery, with a similar trend at the femoral neck.[21] BMD remained stable in the observation group. At 1 year, the second trial observed a statistically significant change in lumbar spine and total hip BMD between the parathyroidectomy and observation groups.[22] There was no difference in distal radius BMD between the two groups.

In the prospective study of the natural history of asymptomatic PHPT over 15 years, a 10% decline in BMD at one or more sites was observed in patients managed without surgery, although lumbar spine BMD remained unchanged.[17] In patients who underwent parathyroidectomy, there was post-surgical improvement in BMD at all sites (lumbar spine, femoral neck and distal radius). BMD increased and remained above the 10% line for 15 years after surgery.

There are no controlled studies on the risk of fracture in asymptomatic PHPT patients. However, cohort and population studies suggest that fracture risk is increased up to 10 years before diagnosis and treatment of PHPT (relative risk up to 1.8), suggesting fracture risk may be increased in undiagnosed, asymptomatic PHPT patients.[13, 23] The impact of surgery on this potential increased fracture risk remains unclear.

Impact of asymptomatic PHPT on cardiovascular morbidity and mortality

Population and cohort studies have demonstrated that both serum calcium and PTH are independent risk factors for coronary artery disease in subjects *without* PHPT.[24, 25] A number of studies suggest patients with moderate to severe PHPT may have an increased risk of coronary artery disease that appears to decrease after successful parathyroidectomy.[26, 27] However, a small randomized study of 49 patients with mild PHPT demonstrated no significant differences in echocardiographic features at 2 years in untreated and parathyroidectomy patients.[28]

Increased peripheral vascular resistance is an independent marker of cardiovascular risk. A small number of studies have reported increased vascular stiffness in patients with mild PHPT.[29, 30] One study demonstrated that 15% of the variance in the difference between the second and first systolic peaks in the pressure waveform of the radial artery was uniquely accounted for by the presence of PHPT.[30] Interestingly there was a strong positive correlation between PTH and arterial stiffness and PHPT was a stronger predictor of arterial stiffness than traditional risk factors such as age, smoking and hypertension. This suggests that mild asymptomatic PHPT may represent a prominent risk factor for arterial stiffness, which in turn is a predictor of early cardiovascular pathology. The effect of successful parathyroidectomy on arterial stiffness is unknown.

A matched cohort study, using hospital episode statistics and mortality data, demonstrated that patients with mild PHPT had significantly worse cardiovascular outcomes, in terms of mortality and non-fatal events.[18] The risk of other comorbidities was also increased. These adverse outcomes were subsequently shown to be linked to high baseline PTH concentration but not baseline calcium.[31]

Mild PHPT and risk of malignancy

An almost twofold increased incidence of malignant tumours has been reported in patients with PHPT compared with matched controls.[32, 33] However, bias may be present due to a number of factors: some patients may have endocrine tumour syndromes that have PHPT as a feature; in addition, an underlying malignancy is often a prompt for biochemical testing during which incidental PHPT might be detected, and patients with hypercalcaemia detected unexpectedly are likely to undergo detailed assessments for underlying malignancy.[34] Long-term follow-up of patients with mild PHPT has also demonstrated a significant increased risk of malignancy compared to controls (hazard ratio and cardiac index: HR 2.18, CI 1.80–2.65).[35]

Impact of asymptomatic PHPT on neurocognitive function/quality of life

Neurological and neuropsychiatric symptoms have been described in classical PHPT,[36, 37] but it is less clear to what extent they are present (and are reversible) in milder forms of PHPT seen commonly today. Neurological and neuropsychiatric symptoms are especially difficult to define and investigate in mild PHPT. Some studies have demonstrated improvements in quality of life (QOL),[38–40] but others have not.[41, 42] Potential reasons for the inconsistent results include the observational nature of many of the studies, small sample sizes, the inclusion of subjects with symptomatic hyperparathyroidism, lack of appropriate control groups and testing at short intervals after parathyroidectomy.[6]

A number of randomized studies of surgery versus observation have been conducted in patients with mild PHPT that addressed aspects of neuropsychiatric function. In 53 patients randomized to surgery or observation, QOL scores measured using the SF-36 general health survey showed significant decline in five of the nine domains (social functioning, physical problem, emotional problem, energy and health perception) in patients followed up without surgery, but in only one of the nine domains (physical function) in the patients who had parathyroidectomy.[20]

These findings suggest a modest measurable benefit of parathyroidectomy in social and emotional role function. Psychological function as assessed by the Symptom Checklist-90 (SCL-90) scale did not change significantly in either group, except for a decline in anxiety and phobia in patients who had surgery in comparison with those who did not. More recently, in a cohort of 191 patients with mild PHPT randomized to medical observation or surgery, significantly lower QOL and more psychological symptoms were found compared with age- and sex-matched healthy subjects.[21] Both groups were similar at baseline, and no clinically significant changes in these parameters were seen during the 2-year observation period. Another randomized controlled trial of surgery versus observation in 50 patients assessed QOL and psychosocial well-being using Short Form health survey SF-36 and SCL-90 at baseline and after 1 year of follow-up.[22] A modest but significant beneficial effect on QOL (bodily pain, general health, vitality and mental health) was observed in the parathyroidectomy group compared with observation group. One study demonstrated increased anxiety and depression at baseline that did respond positively to parathyroidectomy.[43]

Overall, the findings of these studies are inconsistent and the available data remain incomplete on the precise nature and reversibility of neuropsychological symptoms following surgery for mild PHPT. However, some of the data support a modest beneficial effect of parathyroidectomy on QOL and psychological functioning.[6, 43]

Impact of asymptomatic PHPT on survival

A number of large population-based cohort studies have demonstrated that patients with PHPT appear to be at risk of premature death,[44, 45] with a 50% increase in mortality, predominantly due to cardiovascular disease. However, these data were not specifically derived from asymptomatic patients. A study that examined outcome in an unselected cohort of patients with predominantly uncomplicated, asymptomatic PHPT[46] found overall survival was not reduced, compared to age- and gender-matched controls. Although patients in the highest quartile of serum calcium levels had significantly worse survival than patients in the three lower quartiles, even in this group, compared to age- and gender-matched controls, there was only a trend towards reduced survival in the patients who did not undergo surgery. Based on these data, the authors concluded that the current practice of observing patients with uncomplicated mild PHPT does not compromise survival. However, a recent matched cohort study from Scotland found all-cause mortality was increased in patients with mild primary hyperparathyroidism, demonstrating a hazard ratio of 2.24 (CI 1.99–2.51), incorporating an increase in cardiovascular deaths (HR 2.67 [CI 2.21–3.23]) and cancer deaths (2.69 [CI 2.16–3.56]).[35] Cumulative survival was not linked to baseline calcium, but higher PTH concentrations at baseline did predict worse survival outcome.[31]

Thresholds for surgery in asymptomatic PHPT

Parathyroidectomy is the only cure for PHPT and should be recommended in all patients with symptomatic PHPT or evidence of end-organ damage such as low BMD or kidney stones. However, considerable controversy exists regarding the need for surgery in asymptomatic patients.[47] Emerging data on the natural history of asymptomatic PHPT have demonstrated that the chronic course of the disease may not be as benign as once considered.[15] A small but significant fall in BMD over many years, particularly at sites rich in cortical bone, can also be anticipated after 15 years of observation.[17] In addition, a number of randomized controlled trials of parathyroidectomy versus observation in patients with asymptomatic PHPT have demonstrated improvements in BMD, neurocognitive function and QOL.[20–22] Recent epidemiological data on adverse long-term outcomes in patients with mild untreated PHPT have caused a drift towards a lower threshold for parathyroidectomy. The National Institutes of Health (NIH) have developed consensus guidelines, most recently updated in 2009,[48] giving specific indications for when surgery is recommended in patients with asymptomatic PHPT (**Box 73.1**).

BOX 73.1 National Institutes of Health consensus guidelines for surgery in asymptomatic PHPT

- Age < 50
- Serum calcium > 0.25 mmol/L above upper limit of normal
- Renal
  - A. Creatinine clearance < 60 c/min
  - B. 24-h urine for calcium > 400 mg/d (> 10 mmol/d)
  - C. Presence of nephrolithiasis or nephrocalcinosis by X-ray, ultrasound, or CT
- Bone mineral density (by DXA):
  - A. BMD by DXA: T-score < –2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius
  - B. Vertebral fracture by X-ray, CT, MRI, or VFA
- Medical follow-up undesired or impractical

(Adapted from Bilezikian 2014)

The consensus guidelines also recommend a structured conservative follow-up protocol for patients who do not fulfil the guidelines for surgery (**Box 73.2**) and advice regarding hydration status and symptom recognition. It is in this situation that the potential benefits of a permanent cure need to be balanced against the risks of surgery. A particular concern is that mild disease will progress to disease fulfilling surgical criteria at a time when the patient's fitness for surgery has decreased.

BOX 73.2 Monitoring protocol for patients with asymptomatic PHPT (eGFR: estimated glomerular filtration rate)

Serum calcium annually

eGFR, annually; serum creatinine, annually. If renal stones suspected, 24-h biochemical stone profile, renal imaging by X-ray, ultrasound, or CT

Every 1–2 years (3 sites), X-ray or VFA of spine if clinically indicated (e.g., height loss, back pain)

(Adapted from Bilezikian 2014)

These guidelines do not overtly encompass the most recent epidemiological data and, on balance, making an individualized assessment of pros and cons of parathyroidectomy in individual patients is the authors' preferred stance.[34]

MEDICAL MANAGEMENT OF PHPT WITHOUT SURGERY

Although surgery is the only cure for PHPT, medical treatments can be considered for patients who do not fulfil criteria for surgery or those who are unsuitable for or decline surgery. Bisphosphonates and hormone replacement therapy (HRT) are treatment options for those individuals with PHPT for whom the primary goal is skeletal protection, while the calcimimetic cinacalcet effectively lowers serum calcium and PTH levels in PHPT; however, there is a dearth of data demonstrating positive end-organ outcomes.[49]

Intravenous and oral bisphosphonates may cause a transient reduction in serum calcium, but these are not effective in maintaining lower serum calcium levels in patients with PHPT in the long term.[3] However, they can prove useful in managing the bone disease associated with PHPT. Alendronate is the most extensively studied bisphosphonate in PHPT and has been shown to significantly increase BMD in the lumbar spine and femoral neck in patients treated for up to 2 years.[3, 50, 51] The findings of these studies suggest that bisphosphonates, in particular alendronate, may be useful in the treatment of bone disease associated with PHPT when parathyroidectomy is not recommended or possible. However, there are no data demonstrating that BMD changes reflect a reduced fracture risk. In one meta-analysis there was a similar positive effect on BMD with bisphosphonates compared to parathyroidectomy in patients with mild PHPT.[19] Quantitatively similar effects have also been demonstrated with HRT.[19]

Extracellular ionized calcium regulates PTH secretion via the calcium-sensing receptor (CaSR). Stimulation of the CaSR results in inhibition of PTH gene transcription, reduced PTH secretion and reduced parathyroid cell proliferation. Cinacalcet is an orally active calcimimetic, which acts by modifying the CaSR, causing downstream (calcium-like) effects without having true calcium effects peripherally. By mimicking the action of extracellular calcium on the CaSR, cinacalcet blocks PTH secretion. Studies in humans have demonstrated that cinacalcet lowers PTH levels and improves calcium/phosphate homeostasis in patients with primary and secondary hyperparathyroidism.[52, 53] A double-blind, randomized, placebo-controlled study reported normalization of serum calcium in 73% of patients treated with cinacalcet, compared with 5% of placebo-treated patients.[53] PTH decreased by 7.6% in the cinacalcet group, but increased by 7.7% in the placebo group. There were no significant differences in 24-hour urinary calcium levels between the cinacalcet- and placebo-treated patients. Hip and forearm BMD were in the osteopaenic range and remained unchanged throughout the study in both groups. An open-label extension of this study was recently reported, in which 45 subjects from both groups were treated with 30 mg or 50 mg of cinacalcet twice daily for up to 4.5 years.[49] Cinacalcet normalized serum calcium in all patients, and maintained eucalcaemia for the duration of the study. Plasma PTH levels reduced substantially, especially in the latter years, but did not normalize. Mean BMD remained in the normal range (Z-scores of –1 to +1) for the length of the study, with no improvements in BMD observed when expressed as mean change from parent study baseline at the spine, wrist, femoral neck and total femur. A review of studies on the use of cinacalcet in PHPT has confirmed these findings, reporting that cinacalcet effectively lowers serum calcium and PTH levels but does not alter bone turnover or increase BMD.[54]

Despite cinacalcet's beneficial effects on serum calcium and PTH levels in patients with PHPT, there are no data supporting beneficial effects on hard clinical endpoints of fractures (or changes in bone density), kidney stones or cardiovascular disease. QOL has been assessed in a study of 17 patients with persistent PHPT after parathyroidectomy or with contraindications to parathyroidectomy that were treated with cinacalcet;[55] using the SF-36 and Medical Outcomes Study (MOS) Cognitive Functioning scales, the authors found that cinacalcet treatment was associated with improved functional status and well-being in patients with intractable PHPT. The improvements in the Physical Component Summary and Mental Component Summary scores were comparable with the improvements observed in patients with PHPT following parathyroidectomy. This was a small trial, and the results need corroborating in larger studies. In 2008 cinacalcet was approved by the European Commission for the treatment of hypercalcaemia in patients with PHPT for whom parathyroidectomy is indicated on the basis of serum calcium levels but in whom parathyroidectomy is not clinically appropriate or is contraindicated. However, its high cost and lack of data showing improvements in BMD mean that cinacalcet cannot presently be advocated as an alternative to parathyroidectomy.

CONCLUSION

Parathyroidectomy offers the only potential cure for PHPT and should be recommended in all patients with symptomatic PHPT or with evidence of end-organ damage, where there is no obvious contraindication. However, considerable controversy exists regarding the need for surgery in asymptomatic patients. Recently published guidelines have outlined criteria for surgery in the management of asymptomatic PHPT, recommending structured follow-up for patients who do not fulfil these criteria. However, emerging data on the natural history of asymptomatic PHPT have demonstrated that the chronic course of the disease may not be as benign as once considered, with

significantly worse cardiovascular outcomes in terms of mortality and non-fatal events, as well as significantly increased risk of malignancy. This has led some clinicians to propose that virtually all patients with biochemical evidence of PHPT, irrespective of how mild, should undergo parathyroidectomy.

Presently there is no alternative medical therapy to parathyroidectomy that has proven efficacy in managing all aspects of PHPT. Alendronate has beneficial effects on BMD but has not been shown to reduce fracture risk or significantly lower serum calcium, while cinacalcet normalizes serum calcium but does not alter BMD.

Despite the high success rate, low morbidity and convenience of modern parathyroidectomy, patients need to be assessed on a case-by-case basis and important clinical considerations need to be balanced to determine whether parathyroidectomy is the best option for individual patients with mild asymptomatic PHPT (**Box 73.3**).

BOX 73.3 Factors influencing management of patients with mild PHPT

Favours conservative management	Favours parathyroidectomy
Old age	Young age
Short life expectancy	Long life expectancy
High operative risk	Low operative risk
Patient preference	Patient preference
Initial low fracture risk	Risk of worsening bone disease
	Risk of worsening renal function
	Neuropsychiatric features
	Cardiovascular risk*
	High baseline PTH*

(Adapted from Gittoes & Cooper 2010[34] and incorporating more recent data* from Yu et al. 2011[35])

KEY POINTS

- PHPT is caused by inappropriate/unregulated hypersecretion of parathyroid hormone by one or more of the four parathyroid glands.
- The clinical profile of PHPT has shifted to a symptomatically more mild condition.
- Skeletal complications, renal stones, neuromuscular manifestations, peptic ulcer disease and pancreatitis are now rarely seen in the context of PHPT.
- Parathyroidectomy is the only curative treatment for PHPT, and if no contraindications exist should be performed in all patients with symptoms or end-organ disease.
- Medical treatments can improve bone mineral density and normalize serum calcium, but have not been shown to improve long-term outcomes.
- Asymptomatic PHPT may have clinical sequelae, and specific indications exist for when surgery is recommended.
- Structured follow up is required for patients with asymptomatic PHPT who do not fulfil criteria for surgery.

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CHAPTER 74

MANAGEMENT OF PERSISTENT AND RECURRENT HYPERPARATHYROIDISM

David M. Scott-Coombes

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: recurrent, persistent, hyperparathyroidism and re-operation and localization.

'The second hardest decision in surgery is when to operate; the hardest decision is when to reoperate.'

Dr Claude H. Organ Jr, MD (1926–2005)

INTRODUCTION

Patients requiring reoperative surgery pose a significant clinical challenge for a number of reasons. Someone has already failed to cure the hyperparathyroidism, suggesting that this case is not 'straightforward'. That 'someone' could be a very good parathyroid surgeon – you or me. This heightens the likelihood of it being difficult and, if you were the surgeon who failed in the first place, it is challenging to encourage the patient to maintain their faith in you. Furthermore, the operative field is going to be more treacherous and so one needs all the help one can get to minimize complications and maximize success. When faced with this clinical challenge, it is wise to have a predetermined strategy.[1]

DEFINITIONS

Persistent hyperparathyroidism (HPT) is defined as the development of hypercalcaemia within 6 months of the first parathyroid operation, whereas hypercalcaemia presenting after an interval of 6 months is termed recurrent HPT. It is important to understand this distinction because it will give clues to help derive a successful outcome at the next operation, see **Boxes 74.1** and **74.2**.

INCIDENCE

How common is failure? Percentages for bilateral neck exploration and targeted surgery are the same in published data and national disease registries, with a failure rate in the order of 5%.[2]

REASONS FOR FAILURE

In two landmark publications investigating the reasons for failed parathyroidectomy from California (n = 102)[3] and Uppsala, Sweden (n = 69),[4] the percentage of distribution between persistent and recurrent disease is remarkably similar. Most (76%) reoperative surgery is for persistent disease. The main causes for failure are shown in **Table 74.1**. While cause of the majority of the failures were classified as 'ectopia', most ectopic tumours were in the neck in the classically recognized locations such as paraoesophageal and intrathymic.

Recurrent disease is very rare. In the Uppsala series it accounted for only 13 cases over 20 years. Most patients had hyperplasia and nearly all of them (89%) were diagnosed to have multiple endocrine neoplasia type 1 (MEN 1).

BOX 74.1 Clue number 1

Persistent HPT is a consequence of inadequate first-time surgery whereas recurrent HPT is a result of the underlying disease process.

BOX 74.2 Clue number 2

If no gland or a normal gland was excised at the original operation, then it is highly likely that the patient has single gland disease (**Table 74.2**).[13]

TABLE 74.1 Causes of failure in first-time parathyroidectomy[3]

Cause	%	Number
Tumour in ectopic position	53	54
Incomplete resection of multiple abnormal glands	37	38
Tumour in normal position (missed at previous operation)	7	7
Re-growth of partially resected tumour	3	3

TABLE 74.2 The outcome at the first operation is a guide to the underlying pathology[13]

First operation	Underlying pathology	(%)
No gland or normal gland excised	SGD	84
	MGD	11
	Unknown	5
Pathological gland excised	MGD	90
	Regrowth of partially resected adenoma	10

SGD, single gland disease; MGD, multiple gland disease.

Sporadic adenoma as a cause of recurrent disease was exceptionally rare in this series. Of the four cases, one had seeding at the time of the first operation, one recurred at 2 years after a partial resection and only two true second adenomas presented at 8 and 16 years after the first parathyroidectomy.

Another important factor contributing to success at the first operation is the experience of the surgeon. Preventable operative failures are more common in low volume (fewer than 50 cases per year) hospitals.[5]

MEN 1

Recurrent HPT is an inevitable outcome of surgery, even when performed to the highest standard, in patients with MEN 1.[6] There are a number of surgical options for patients with MEN-HPT (see Chapter 77) with recurrence rates reported to vary from 11% at 6 years[7] to 63% at 10 years.[8] National Registry data such as those from Scandinavia and the United Kingdom paint a worse picture than the published data, with persistent hypercalcaemia rates of 25% reported in Scandinavia and 17% in the UK.[9, 10]

STEPS TO SUCCESS

Step 1: Confirm the diagnosis

The clinician should start at the beginning in terms of establishing a biochemical diagnosis of HPT (see Chapter 72). Particular attention should be given to ensuring that there is no evidence of renal insufficiency, vitamin D deficiency, and familial hypercalcaemic hypocalciuria or paraneoplastic hypercalcaemia.

Step 2: Does the patient need further surgery?

Reoperation should only be considered if the patient has symptomatic hypercalcaemia or when there is evidence of progressive disease (nephrolithiasis or bone disease). The decision about whether to operate is determined by balancing the severity of the disease with the risks of surgery. The main complications of reoperative parathyroidectomy are hypoparathyroidism and recurrent laryngeal nerve injury. Both of these are more common in redo surgery. Hypoparathyroidism (2–20%)[11] is more common due to the increased rate of multiple gland disease and the fact that normal glands may have been removed at the first operation. RLN injury is more common (up to 6%)[4, 12] owing to the scarred operative field.

In addition, unlike first-time surgery, the decision to reoperate may be influenced by a successful localization result that would both facilitate a targeted approach and increase the likelihood of a successful outcome.

Step 3: Research

There is a need to thoroughly sift through all the evidence from the previous attempt to cure the patient. You might have to be prepared to be cynical about the operation note – is what was written an accurate reflection of what was done? If possible, a conversation with the previous surgeon may be helpful, more so if it was in the recent past. The aim is to try to identify clues that describe the boundaries of the previous exploration in order to establish the region(s) where scar tissue will be worst.

In the histopathology report, if parathyroid glands were removed, were they normal or abnormal? Take note not only of the histology but also the weight of the resected specimen.

Review all of the previous localization studies. It is worth while viewing the images **yourself** as sometimes a surgeon will be prepared to place more emphasis than the radiologist on an indeterminate finding.

Step 4: Localization

Parathyroid localization (see Chapter 72) is an essential step in reoperative surgery. The goal is to be able to perform a limited operative procedure targeted according to

the localization results in order to minimize risk to both recurrent laryngeal nerves. As stated, it may be that a decision about whether to proceed with surgery is taken once the results of the localization are known.

^{99m}Tc sestamibi (MIBI) scintigraphy and ultrasound are requested first. Non-invasive localization studies have become more successful in recent times compared with 20 years ago.[14] MIBI can be complemented with SPECT-CT coregistration to provide a three-dimensional image. Any lesions identified on ultrasound can be considered for aspiration for PTH. If these modalities are positive, it is reasonable to proceed to surgery.[13] Cross-sectional imaging with MRI or CT would be the next mode of imaging. Four-dimensional computed tomography is an emerging technique that explores the changes in perfusion of contrast over time to provide a new 'dimension'. Results have been promising for reoperative parathyroidectomy.[15]

As each localization studies fails, so the available procedures become more invasive. Angiography either by digital subtraction or conventional methods is the next technique to consider. In expert hands impressive results can be achieved.[16] However, these invasive studies can be associated with significant morbidity.[17] Selective venous sampling (SVS) of all patent superior, middle and inferior thyroid, thymic, brachiocephalic and vertebral veins (as well as a peripheral sample) attempts to 'regionalize' the tumour rather than precisely locate it. A gradient of at least twofold is considered significant.[18] Ligation of veins at the time of the first operation can lead to anomalous venous draining and give misleading results. Many Units use SVS in combination with angiography.

The Uppsala group has published the impact of localization on their practice.[19] Few patients underwent surgery before 1980. Between 1980 and 1990 localization was undertaken in one-third of patients, more between 1990 and 2000 (75%) and in all patients after 2000. Localization has had a profound impact on the ability to perform a targeted approach; 66% underwent bilateral neck exploration between 1962 and 1989, whereas since 1990 no fewer than 73% underwent a unilateral neck exploration.

Step 5: Surgery

PREPARATION

Reoperative parathyroid surgery is a difficult procedure and should be undertaken only by surgeons experienced in this field. The surgeon should be familiar with the anatomical variants that are a consequence of either embryology or migration of a pathological gland. Vocal cord examination by nasoendoscopy is mandatory. The patient must be thoroughly consented to the risk of complications including permanent and temporary nerve injury, haematoma/return to theatre as well as failure to find the abnormal gland(s).

OPERATION

The surgical strategy is influenced by the clues from previous surgery and the outcome of the localization studies (Table 74.3). It is advisable to set aside plenty of time in theatre to undertake the case and make sure that you have good assistance. The site of the surgical incision should be through the previous incision. Consider asking your radiologist to place a mark on the skin over the site of the presumed adenoma or perform an ultrasound in the operating room yourself. Obviously, if the localization places the gland in the mediastinum, then midline sternotomy, thoracotomy or thoracoscopy should be considered, especially if the tumour does not appear to be intra-thymic such that a cervical approach is contraindicated.

TABLE 74.3 Surgical strategy in reoperative parathyroidectomy

Expected pathology	Strategy
Solitary abnormal gland	Focused approach
Multiple glands	Bilateral approach
Carcinoma/parathyromatosis	En-bloc resection

The surgical approach to the deeper structures in the neck will be influenced by the previous operation and the localization result. For example, if the first-time operation was unilateral (targeted/minimally invasive) and the localization study identifies the gland to the contralateral side, a traditional midline approach will suffice. But if the previous operation was a bilateral exploration and/or the localization result is ipsilateral to the previous operation, then a lateral approach should be adopted. This is achieved by dissecting between the lateral edge of the sternohyoid (strap) muscle and the medial edge of the sternocleidomastoid muscle. In this area the tendon of omohyoid is encountered and divided. Immediately deep to this tendon is the middle thyroid vein (if not already divided) as it drains into the internal jugular vein. The carotid sheath is carefully retracted laterally and the tracheo-oesophageal groove is explored. The intention is to identify the recurrent laryngeal nerve (RLN) in previously unexplored territory and this is most likely to be in a caudal direction. Consideration should be given towards using the nerve monitor. A positional statement by the European Society of Endocrine Surgeons on modern techniques in parathyroid surgery did not recommend the routine use of neuromonitoring in first-time neck exploration but stated that it may be of value in reoperative surgery.[20]

Once the RLN has been located, a careful search for the abnormal gland is made. For the inferior gland, incise the strap lateral to the midline and follow the surface of the thyroid towards the thyrothymic ligament. For the superior gland, the intersection of the RLN with the inferior thyroid artery is the key area to start looking (see Chapter 77). Intra-operative ultrasound scanning (IOUS) has been reported to be helpful in identifying abnormal glands (normal glands are not identified) and results in shorter operative time in the hands of enthusiasts.[14] If an abnormal gland cannot be located, blind thyroid lobectomy should not be undertaken owing to

the rarity of the intra-thyroidal adenoma,[21] unless confirmed by IOUS.[14]

Once a gland has been located and excised, both frozen section and intra-operative PTH (ioPTH) assay will provide clues to success. The key information from the pathologist is to confirm that the excised tissue is 'parathyroid'. Localization tells you where to start and ioPTH tells you when to stop! While the literature is not unanimous, most evidence is that ioPTH helps to decide when the operation can be terminated and is an accurate predictor of cure.[19, 22] There is no real evidence, however, that it increases the success rate.

POST-OPERATION

As with all parathyroid surgery, the patient should be closely monitored for the development of a wound haematoma. Results from the UK national audit suggest that the rate of haematoma in redo parathyroidectomy more than doubles compared with first-time surgery (1.2% vs 0.5%).[10] Attention is also given towards the complications of RLN injury and hypocalcaemia. Post-operative nasoendoscopy should be undertaken routinely. The rate of permanent hypoparathyroidism (see Step 2) is between 5% and 11% in most series.[12, 14] A protocol for managing this complication should be written and available in the medical record. A suggested algorithm is shown in Table 74.4.

The serum calcium will provide biochemical evidence of surgical success. In expert centres success rates of over 95% are reported.[3, 19]

THE FUTURE

There are two reasons why some surgeons fear that reoperative surgery may become more common.

1. **Focused surgery** – does it lead to higher failure rates? The increased success of pre-operative parathyroid localization and the widespread adoption of ioPTH assay has led to an explosion in the use of a focused approach to first-time parathyroidectomy.[23] Critics of this approach are concerned that ioPTH is inaccurate in determining complete excision among patients with multiple gland disease.[24, 25] In a recent review of 845 cases of focused parathyroidectomy using ioPTH, with a failure rate of 2.9%, the main cause of operative failure was the inability of the surgeon to find the abnormal gland, not the failure to diagnose multiglandular disease.[26] In other words, the most common cause of failed parathyroidectomy remains the surgeon, and experience counts.[27]
2. **Mild disease.** A study that looked at outcomes in patients with double negative parathyroid localization found an alarmingly high rate of persistent hyperparathyroidism (13.3%).[28] It is telling that the median weight of adenoma was small (350 mg). Parathyroid localization is less reliable with smaller tumours[29] although ioPTH assay remains a valuable tool in patients with milder HPT.[30] Either the threshold for parathyroidectomy is being set too low or the wrong surgeon is undertaking this surgery.

TABLE 74.4 Algorithm for managing hypocalcaemia

Corrected plasma calcium mmol/L (mg/dL)	Symptomatic	Asymptomatic
>2.15 (8.6)	Milk	nil
2.00–2.15 (8.0–8.5)	Calcichew 1 g b.d.	nil
1.90–2.00 (7.6–8.4)	Calcichew 1 g t.d.s. 1-alfacalcidol 1 µg o.d.	Calcichew 1 g t.d.s.
1.80–1.90 (7.2–7.5)	Calcichew 1 g t.d.s. 1-alfacalcidol 1 µg b.d.	Calcichew 1 g t.d.s. 1-alfacalcidol 1 µg b.d.
<1.80 (<7.2)	Tetany: 10–30 mL i.v. calcium gluconate over 10–15 min*	Calcichew 1 g t.d.s. 1-alfacalcidol 1 µg t.d.s.

b.d., twice daily; t.d.s., three times per day; i.v., intravenous
* The cannula must be carefully sited to avoid extravasation.

KEY POINTS

- Reoperative parathyroidectomy is a challenging situation.
- The steps to success include careful pre-operative research and a skilled operative technique.
- Localization is mandatory and should be successful prior to contemplating a reoperation. ioPTH assay and neuromonitoring may be useful tools.
- There is a case for centralizing these cases in expert centres but, as with most other aspects of surgery; it is better to get it right the first time.

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CHAPTER 75

MANAGEMENT OF PARATHYROID CANCER

Pamela Howson and Mark Sywak

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: parathyroid and cancer, hypercalcaemia, parathyroid and tumour.

INTRODUCTION

Parathyroid carcinoma (PAC) is a rare cause of primary hyperparathyroidism which presents with clinical manifestations of severe hypercalcaemia. It was first described in 1904 by Swiss surgeon Fritz de Quervain who reported a non-functioning metastatic PAC, and Sainton and Millot were the first to describe a functioning metastatic PAC in 1933. Around 90% of PACs are functional and may present with a palpable neck mass which invades locally. Skeletal and renal complications are commonly present at presentation. Surgery remains the only effective treatment for primary tumours where en bloc resection is key. Medical therapies are critical for controlling hypercalcaemia. Germ-line DNA testing for the *HRPT2* mutation should be considered for patients who present with PAC.

INCIDENCE AND NATURAL HISTORY

PAC is a very rare malignancy accounting for less than 1% of cases of primary hyperparathyroidism in Europe and the United States, and up to 5% in Japan.[1–3] According to the Surveillance, Epidemiology and End Results cancer registry data, the annual incidence is 5.73 per 10 000 million. This represents a prevalence of 0.005% of all cancers.[4]

PAC occurs equally in males and females, unlike parathyroid adenomas, which have a female preponderance (3–4 : 1).[2] PACs present mostly in the fourth to fifth decades of life, which is a decade earlier than their benign counterpart. However, the age of diagnosis is in the range of 23–90 years old. There is no racial predisposition in PAC, whereas benign parathyroid tumours more commonly occur in the Western population.

PAC generally runs a slow but progressive course. Less than 8% of patients have lymph node or distant metastases at initial presentation. The mean time to recurrence is generally within 2–5 years of operation and takes the form of locoregional or cervical node involvement (30%), lung metastases (40%), liver secondaries (10%), or bone or brain deposits. Failure of treatment can result in death from hypercalcaemic-related end-organ damage within 14 months. In general, however, PAC tends to have a relatively indolent course because of the tumour's low malignant potential, with a 5-year survival of 86% and a 10-year survival of 35–79%.[2,4,5] A significant proportion of patients (25%) will be diagnosed with PAC after initial surgical treatment following review of histopathology or after developing metastatic disease.

AETIOLOGY AND MOLECULAR PATHWAYS

The pathogenesis of PAC is poorly understood with few known environmental or genetic causative agents. Animal models show that parathyroid glands are histologically resistant to X-ray damage at doses less than 5 Gy, but doses of 5–25 Gy cause oedema and hyperaemia, and higher doses cause severe damage with hyperplasia, cyst and adenoma formation and carcinoma.[6] Head and neck irradiation has been associated with the development of PAC.[7]

PAC has also been reported in patients with secondary and tertiary hyperparathyroidism.[8] End-stage renal failure can promote clonal expansion of cells within the parathyroid hyperplasia that progresses to parathyroid carcinoma. Chronic hypercalcaemia alone in the setting of renal failure has been postulated as a possible trigger for the development of PAC,[9] although the association is weak. An increased risk of PAC has also been associated with multiple endocrine neoplasia type 1 (MEN 1) and with autosomal dominant familial isolated hyperparathyroidism, which is due to mutations in the tumour suppressor genes *MEN1* and *CDC73* or the calcium-sensing receptor (*CaSR*) gene, resulting in the formation of one or more parathyroid adenomas.[2]

Interestingly, several oncogenes and tumour suppressor genes have been linked to PAC. Cyclin D1 or *PRAD1* (parathyroid adenoma 1) is an oncogene involved in cell cycle regulation and is located on chromosome 11q13.[10] It is overexpressed in 91% of PAC specimens and up to 61% of benign parathyroid tumours,[11] but the exact mechanism of carcinogenesis remains unclear. PAC also lacks the retinoblastoma tumour suppressor gene on chromosome 13.[12, 13] Retinoblastoma protein prevents excessive cell growth by inhibiting cell cycle progression, and hence its absence results in dysregulation of cell growth.

The *HRPT2* gene, which encodes the parafibromin protein, has attracted much attention in PAC. Most of the data on the genetics involved in this rare disease are derived from studying inherited disorders of primary hyperparathyroidism such as hereditary hyperparathyroidism-jaw tumour syndrome (HPT-JT). HPT-JT is an autosomal dominant disease characterized by fibromas of the maxilla and mandible and tumours of the parathyroid. In this condition 30% of the parathyroid tumours are PACs.[2] HPT-JT is associated with an inactivating germ-line mutation of the *HRPT2* gene on chromosome 1q25-q32. This is a tumour suppressor gene encoding the protein parafibromin which has anti-proliferative properties. However, it is also defective in sporadic PAC,[14] and parafibromin expression is decreased or absent in PAC, which may have significant implications for diagnosis and management. Kim and colleagues[15] showed that the loss of parafibromin expression was 94.4% specific for the diagnosis of PAC, and recurrences and metastases only occurred in cases with a loss of parafibromin. Moreover, it has been found that *HRPT2* gene mutation results in the upregulation of up to four proteins including histone H1 and H2, E-cadherin and amyloid BA4 precursor protein (APP).[16] Histone proteins are involved in gene repair mechanisms. E-cadherin is involved in cell–cell adhesion, and loss of function contributes to tumorigenesis by increased proliferation, invasion and metastasis. Its upregulation is indicative of the cell's loss of function in cell adhesion. APP is a functional neuronal receptor but its upregulation in PAC is of uncertain significance. Staining for these proteins provides a diagnostic marker for PAC.

CLINICAL PRESENTATION

To treat PAC effectively, the clinician should have a high index of suspicion prior to initial surgery so that an appropriate operative approach may be undertaken. This requires an awareness of the differences in presentation between primary hyperparathyroidism due to benign disease and cancer. Patients with PAC are typically younger than those with benign causes of hyperparathyroidism (fourth to fifth decades).[17] PAC occurs equally in both genders. Since 90% of PAC are functioning tumours, most manifest with symptoms similar to benign hyperparathyroidism, namely weakness, fatigue, anxiety and depression, bone pain, renal stones, abdominal pain, peptic ulcer disease and pancreatitis. However, bone disease and renal involvement are far more common in parathyroid malignancy, occurring in up to 80–90% of patients with PAC[18, 19] and the presence of both is strongly predictive of malignancy. Bone disease includes bone pain, osteopenia, osteoporosis, pathological fractures, osteitis fibrosa cystica, 'salt and pepper' skull and subperiosteal bone resorption. Renal involvement includes ureteric calculi, nephrocalcinosis or renal impairment. Acute pancreatitis, peptic ulceration and hypercalcaemic crisis occur in 12–18% of patients with PAC. These symptoms usually occur before local invasion by the tumour.

Around 50–70% of patients with PAC present with a palpable neck mass.[2, 20] This is extremely uncommon in benign disease, and can be associated with evidence of local invasion including recurrent laryngeal nerve palsy and dysphagia. Non-functioning tumours do not present with symptoms of hypercalcaemia and therefore are more likely to present with a palpable neck mass.

Serum calcium and parathyroid hormone are elevated in PAC, but the average calcium is much higher in PAC than in benign causes of hyperparathyroidism.[2, 18] Most patients with parathyroid adenomas have serum calcium levels within 1 mg/dL above the upper limit of normal; patients with PAC have serum calcium in excess of 3.5 mmol/L (14 mg/dL) and serum parathyroid hormone levels 10–15-fold greater than the normal range. A parathyroid hormone level 10 times the upper limit of normal carries a positive predictive value of 81% for PAC.[21]

Imaging of PAC differs to that for parathyroid adenomas due to a greater emphasis on the detection of locoregional tumour infiltration and distant metastasis. Neck ultrasound is a non-invasive and sensitive study for the detection of enlarged parathyroid glands. PAC are typically large (>15 mm), hypoechoic, lobulated, irregular lesions.[22]

Ultrasound has been shown to have a high accuracy in detecting parathyroid lesions 1 cm or larger.[23] Infiltration and calcification seen on ultrasound have a high positive predictive value for identifying parathyroid malignancy.[24] A meta-analysis of pre-operative localization techniques found that ultrasound had a sensitivity of 76% and a positive predictive value (PPV) of 93%.[25] Ultrasound can also be used to guide fine-needle aspiration (FNA) biopsy of neck lymphadenopathy, but FNA of the primary lesion should be avoided to prevent disruption of the primary tumour.[26] FNA is not useful in distinguishing benign from malignant parathyroid disease.[2]

^{99m}TC sestamibi scintigraphy is useful for localizing primary, recurrent and metastatic disease and to confirm ultrasonographic localization. The radiolabelled isotope has a particular affinity for parathyroid mitochondria.[20] It cannot, however, discriminate benign from malignant disease. Sestamibi has a high sensitivity of 79% and a PPV of 91% and continues to be the most useful imaging modality in benign and malignant causes of hyperparathyroidism.[25]

Four-dimensional computed tomography (4D CT) is increasingly used for parathyroid localization in hyperparathyroidism, particularly when ultrasound and sestamibi imaging are negative or indeterminate (**Figure 75.1**). It has a sensitivity and specificity of 82% and 92% respectively for the localization of parathyroid adenomas.[27, 28] Parathyroid glands have unique angiographic and perfusion characteristics[29] including a 'blush' following intra-arterial contrast used to distinguish abnormal parathyroid tissue. 4D CT uses non-contrast imaging to differentiate thyroid from parathyroid tissue, as well as an early post-contrast phase to determine a hypervascular gland, and a delayed post-contrast scan to detect altered enhancement or abnormal contrast retention.[30] However, 4D CT delivers a significant radiation dose despite dose reduction techniques (20–40 mGy per phase of imaging) and no study has elucidated its importance in PAC diagnosis or localization. Its use may be supported in determining infiltration pre-operatively if PAC is suspected and in reoperative surgery.

In circumstances of recurrence, ^{18}F-FDG PET CT has been used to detect locoregional recurrence or distant metastases.[31] MRI may also be useful for mediastinal recurrence.[32]

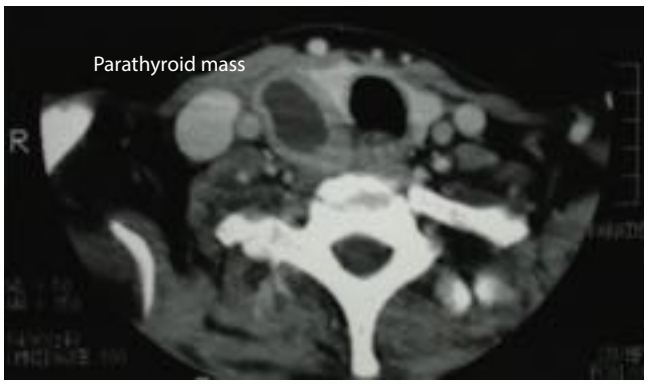


Figure 75.1 Neck CT axial image depicting large right parathyroid mass that proved to be a PAC causing tracheal deviation.

OPERATIVE FINDINGS AND SURGERY

Surgical resection is the main therapeutic modality for PAC, even in the presence of metastatic disease. Treatment of hypercalcaemia and correction of renal dysfunction is often necessary prior to surgical intervention. Hydration with saline, correction of electrolyte imbalance, diuretics and bisphosphonates are useful to optimize the patient's condition prior to surgery.

PAC can be difficult to diagnose intra-operatively but usually appears as a large, firm, grey-white mass with adherence to adjacent tissue and is often greater than 3 cm in maximal diameter (**Figure 75.2**). Parathyroid adenomas, in contrast, are smaller, softer and are reddish-brown or tan in colour.[3, 33] En bloc resection involves carefully removing the parathyroid lesion and resecting all adherent tissues with grossly clear margins. This will typically involve ipsilateral thyroid lobectomy and the adjacent level 6 lymphatic component. This approach frequently requires autotransplantation of the ipsilateral parathyroid gland where it appears macroscopically normal as well as cervical thymectomy. It is important not to rupture the capsule, as this increases the risk of seeding and recurrence.[34] PAC can also involve the overlying strap muscles, trachea, oesophagus and recurrent laryngeal nerve. In order to provide the best chance of cure these structures may require en bloc resection.[34, 35] Recurrent laryngeal nerve involvement is suspected pre-operatively if the patient has a hoarse voice and warrants resection in cases where its function is lost due to tumour infiltration or where it is involved circumferentially by malignancy. Sacrifice of a normally functioning nerve is generally not



Figure 75.2 Resection specimen of parathyroid carcinoma removed en bloc with adjacent thyroid tissue. The parathyroid carcinoma is adherent to the thyroid. (Photo courtesy of Prof Anthony Gill, Dept of Anatomical Pathology, Royal North Shore Hospital, Sydney Australia.)

required unless its preservation results in gross residual tumour remaining in the thyroid bed. Lymph node involvement is uncommon, occurring in only up to 8% of patients, and as a result comprehensive lymphadenectomy is usually not necessary except in the local area, level 6. Prophylactic modified radical neck dissection does not improve survival and is not typically performed at the primary surgical procedure. It may be of greater utility in reoperative cases.

In at least 25% of initial presentations PAC is diagnosed after primary surgery on histopathology or with the development of distant metastases.[36] In patients with PAC who undergo routine parathyroidectomy because cancer is not suspected, 50% or more will develop local recurrence.[7, 33] The mean time for recurrence in this population is 41 months and the mean disease-free survival time is 62 months.[7] Conversely, if detected before or during operation, then local recurrence rates are 10–33% and long-term survival improves significantly.[7]

The main issue of controversy is the management of PAC diagnosed after initial surgery on histology. O'Neill and colleagues[37] found that subsequent unilateral hemithyroidectomy and lymphadenectomy did not reveal any residual disease and therefore further radical surgery may not be warranted. This is supported by Fujimoto and colleagues[38] who recommended post-operative follow-up at 3-month intervals for PAC that had minimal invasion and low malignant potential as these tumours did not necessarily locally recur. Alternatively, it has been suggested that aggressive histopathological features of extensive capsular and vascular spread should prompt re-exploration and completion of resection.[39]

After initial resection, all patients require immediate monitoring and lifelong surveillance. In the early post-operative period, temporary hypocalcaemia may occur due to secondary uptake of calcium into bones (hungry bone syndrome) which requires treatment with supplemental calcium and vitamin D. PTH levels should also be checked post-operatively to ensure curative resection. Thereafter, PTH and corrected serum calcium are monitored every 3 months.[32] If these increase, sites of recurrence should be evaluated with sestamibi scintigraphy and anatomical imaging. If these imaging studies are inconclusive, selective venous catheterization and PTH measurement are recommended to regionalize the recurrence.[40]

Recurrence is most often locoregional and occurs within 2–3 years of the initial operation.[19, 34] For recurrent locoregional disease, cervical and/or mediastinal re-exploration with wide resection including thymectomy are indicated.[32, 34] Pre-operative vocal cord examination should be performed prior to reoperative surgery.[34] A reoperative neck is challenging due to scar tissue and distorted anatomical planes, but various techniques have been described to aid in re-resection. These include injection of methylene blue dye, which is selectively taken up by parathyroid tissue,[41, 42] or intravenous injection of technetium-99m 1 hour pre-operatively and subsequent use of the gamma probe intra-operatively to localize the recurrence.[43] The low incidence of PAC makes evaluation of these modalities difficult, but extrapolation of the experience with benign parathyroid disease suggests that methylene blue dye and the gamma probe offer little advantage to the experienced parathyroid surgeon. Intraoperative PTH testing, however, is useful in confirming resection of the target lesion.[43, 44]

Even for distant PAC metastasis, resection is advocated to provide palliative control of hypercalcaemia, which can be debilitating and life-threatening. Where possible, even small metastatic deposits should be considered for resection. The most common sites of distant metastatic PAC spread are to the lungs, liver and bone, and up to 30% of patients already have metastases at initial presentation.[45, 46] Radical resections which have provided symptomatic relief include liver or pulmonary wedge resections, bone and cerebral metastasis resections, and oesophageal resection with gastric transposition.[47–51]

HRPT2 germ-line DNA testing should be considered for patients presenting with apparently sporadic PAC. It is unclear whether genetic testing should be offered to at-risk relatives, but monitoring serum calcium levels offers a simple alternative to definitive DNA diagnosis.[14]

HISTOPATHOLOGY AND DIAGNOSIS

Schantz and Castleman[52] developed a set of criteria for the histopathologic diagnosis of PAC in 1973. These included the presence of a fibrous capsule or fibrous trabeculae, rosette-like cellular architecture, presence of mitotic figures, and capsular or vascular invasion. Stojadinovic and colleagues[53] added the presence of adjacent skeletal muscle invasion by tumour. This study found capsular and vascular invasion in 92% and 81% of PAC specimens respectively, and 19% had perineural invasion. However, the histological criteria are often equivocal and hence the World Health Organization (WHO) defined PAC in 2004 as those parathyroid lesions displaying vascular invasion, perineural space invasion, capsular penetration with growth into adjacent tissues and/or metastases (**Figure 75.3**).[54] While the presence of fibrosis is common, it was not consistent and not considered pathognomonic of PAC, and the trabecular growth only occurs in a minority of cases, with rosette formation a rare finding. In addition, the presence of coagulative necrosis, macronucleoli and mitotic activity greater than 5 mitoses per 50 high-power field is a diagnostic pathologic triad that reflects a high risk of malignant versus benign behaviour. A proliferation marker ki-67 greater than 5% is suggestive of malignancy.

There is generally no accepted staging system for PAC. Tumours tend to be classified as localized when confined to the parathyroid and local soft tissues or metastatic when distant metastases occur.

Since not all PACs exhibit the above diagnostic histopathologic criteria, markers have been sought to distinguish benign from malignant tumours. These include immunohistochemistry markers for ki-67, bcl2, cyclin D1, Rb, CaSR, although false negatives with these arose owing to the rarity of PAC.[55] The *HRPT2* tumour suppressor gene encodes the protein parafibromin. As mentioned previously, parafibromin is involved in apoptosis, inhibits G1 to S phase

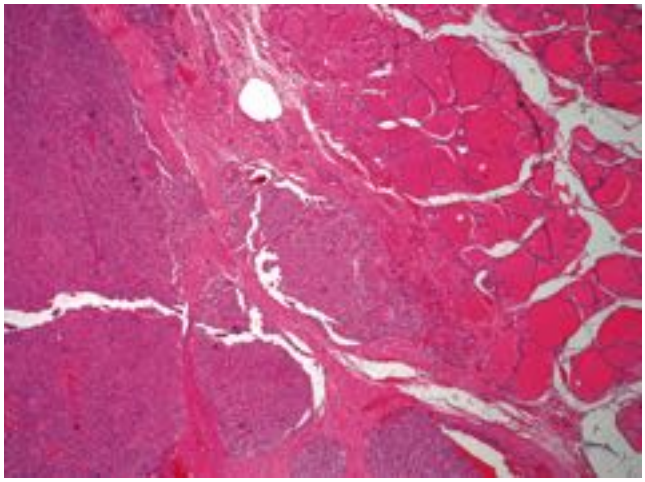


Figure 75.3 Histological section of parathyroid carcinoma invading into adjacent thyroid tissue. The presence of unequivocal invasive growth is the basis of the WHO 2004 criteria for the diagnosis of parathyroid carcinoma (*H&E, original magnification ×100*). (Photo courtesy of Prof Anthony Gill, Dept of Anatomical Pathology, Royal North Shore Hospital, Sydney Australia.)

of the cell cycle, regulates the wingless type (Wnt) pathway, and regulates growth factor expression.[56] Loss of the protein parafibromin will therefore increase cellular proliferation. It has been found that 77% of all PAC harbour mutations in the *HRPT2* gene[14, 57] in contrast to benign adenomata where the mutation is demonstrated in less than 1%.[58] Demonstration of the *HRPT2* mutation is therefore relatively specific for PAC. Tumours with inactivation of *HRPT2* will show loss of parafibromin staining on immunohistochemistry.[55, 59] The absence of nuclear staining for parafibromin is diagnostic of PAC or an HPT-JT-related tumour and is a useful adjunct to the traditional histological criteria for malignancy.[56] Another molecular marker called protein gene product (PGP 9.5) is used to complement parafibromin in the immunohistochemistry process, and this is upregulated in the majority of PAC.[55]

MEDICAL THERAPY

Hypercalcaemia

Medical control of hypercalcaemia is important preoperatively and also in cases of inoperable PAC. Hypercalcaemic crisis is a medical emergency and requires prompt intervention.[34] Aggressive fluid resuscitation with isotonic saline is required as patients become severely dehydrated due to nephrogenic diabetes insipidus and associated nausea and vomiting. Loop diuretics such as frusemide increase urinary calcium excretion and are effective once the patient is euvolaemic. Bisphosphonates (e.g. pamidronate, clodronate, etidronate) inhibit osteoclast-mediated bone resorption and cause apoptosis of osteoclasts and are critical in reducing serum calcium in PAC.[60] Intravenous pamidronate is infused slowly at a dosage of 60–90 mg and decreases calcium in 2–4 days.[2] The effect has a duration of 1–3 weeks but efficacy reduces with time.

Calcimimetic agents (e.g. cinacalcet) increase the sensitivity of parathyroid cells to the suppressive effects of high extracellular calcium by binding to calcium-sensing receptors on parathyroid cells.[2, 60] Cinacalcet is an oral agent given 30–60 mg daily with a rapid onset of action that reduces calcium within 48 hours and is generally well tolerated.

Other useful agents in PAC include calcitonin and plicamycin. Calcitonin inhibits osteoclast bone resorption and increases urinary excretion of calcium. Calcitonin can be used in conjunction with corticosteroids, which in isolation are useful in reducing hypercalcaemia.[61] Plicamycin is an antineoplastic antibiotic that transiently inhibits bone resorption but has toxic effects on the liver, kidneys and bone marrow. Gallium nitrate, octreotide and haemodialysis can also be used to reduce hypercalcaemia.[2, 34, 62]

Chemotherapy

Chemotherapeutic agents do not offer significant benefit to patients with PAC. There is no standard chemotherapy regime for PAC as there are no randomized trials to support its use. Several case studies involving the use of dacarbazine, fluorouracil, cyclophosphamide, methotrexate and doxorubicin[63, 64] have shown some success.

Radiotherapy

PAC has historically been considered radioresistant.[7, 34] However, the Mayo Clinic reports disease-free survival of 60 months in four patients who received post-operative radiotherapy[65] and this is supported by the MD Anderson experience of a lower local recurrence rate from 77% to 17% with adjuvant radiation.[35] Other case reports support findings that PAC may be a radiosensitive tumour.[66, 67] Given the lack of strong evidence for the routine use of external beam radiotherapy in PAC, it seems prudent to incorporate it when surgical options have been exhausted.

PROGNOSIS

PAC is generally a slow-growing cancer and the median overall survival is 14.3 years but can range from 1 month to more than 20 years.[4, 46, 68] Overall survival ranges from 85% at 5 years to 35–79% at 10 years.[2] As there is no widely accepted adjuvant therapy, complete surgical resection remains the mainstay of cure for both primary and recurrent disease.[40] En bloc resection results in 10–30% local recurrence and 90% long-term survival rates; incomplete resection results in a 50% recurrence rate and a mortality rate of 46%.[7] Other negative prognostic indicators include lymph node or distant metastases and non-functioning tumours. Tumour size is not a prognostic indicator.[46, 68] There is currently no prognostic staging system. Mortality from functional PAC is due to end-organ failure (e.g. renal failure) from uncontrolled hypercalcaemia.[39, 40]

Overall, PAC is a rare, slowly progressive malignancy, which requires medical control of hypercalcaemia, surgical resection and long-term follow-up. It is best managed in a multidisciplinary setting with clinicians experienced in the management of parathyroid disease. Expert histological assessment is critical as is an understanding of the genetic associations this rare cancer exhibits.

KEY POINTS

- Parathyroid cancer is a rare cause of primary hyperparathyroidism and typically presents with marked hypercalcaemia with corrected serum calcium greater than 14 mg/dL or 3.5 mmol/L.
- Parathyroid cancers typically present in the fourth to fifth decades of life and are distributed equally between males and females.
- Pre-operative treatment requires correction of metabolic and electrolyte disturbances with saline hydration, loop diuretics, bisphosphonates and calcimimetics.
- Surgery is the mainstay of treatment and the only curative modality.
- The surgical approach should incorporate four-gland parathyroid exploration with en-bloc resection of the tumour and involved structures to achieve complete removal.
- Mutations of the *HRPT2* tumour suppressor gene are strongly associated with the hyperparathyroidism-jaw tumour syndrome and parathyroid cancers.
- Parathyroid cancer is generally a slowly progressive malignancy with a 10-year disease-specific survival of 49–77%.
- Immunohistochemical staining for parafibromin and PGP 9.5 are useful adjuncts to histological diagnosis of parathyroid cancer.

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CHAPTER 76

BILATERAL PARATHYROID EXPLORATION

R. James A. England and Nick McIvor

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: bilateral exploration, four-gland exploration and parathyroid.

INTRODUCTION

Primary hyperparathyroidism (HPT) is only curable surgically. It is a common endocrine condition with approximately 100 000 new cases diagnosed annually in the United States.[1] Traditionally, the operative procedure of choice involves a search for all four parathyroid glands and the selective removal of any gland(s) judged enlarged by visual inspection. The principles of bilateral parathyroid exploration (BPE) have remained unchanged since their first description by Felix Mandl in 1926.[2]

More recently, improved localization techniques and the use of intra-operative parathyroid hormone level monitoring have led to a shift away from BPE towards more focused surgery, the often-labelled minimally invasive parathyroidectomy (MIP). This procedure enables ambulatory parathyroidectomy and parathyroidectomy under sedation or local anaesthesia. However, most parathyroid surgeons agree that MIP is only feasible for single-gland disease.

The traditional four gland exploration is therefore mainly for patients with suspected multigland disease, negative imaging and patients undergoing revision surgery. The significant incidence of such patients demands that a parathyroid surgeon has the ability to perform the traditional operation.

This chapter discusses the situations in which BPE is generally the preferred surgical option and the operative steps of BPE.

WHEN TO PERFORM BILATERAL PARATHYROID EXPLORATION

Cases where bilateral parathyroid exploration may be performed fall into four broad groups:

- suspected multigland disease
- parathyroid cancer
- failed pre-operative localization
- failed MIP.

Suspected multigland disease

Approximately 15% of primary HPT patients and all those with secondary HPT have multigland disease. Those with primary HPT having multigland disease include those with double adenoma, non-familial hyperplasia, and familial HPT.

PRIMARY HPT – DOUBLE ADENOMA / PRIMARY HYPERPLASIA

There is some debate as to whether double adenoma is a distinct entity. Some argue that double adenomas are rare and the distinction between adenoma and asymmetrical hyperplasia is difficult pathologically.[3] Hyperplasia can be localized within a gland and asymmetrical between glands.

It is not surprising therefore that there is poor correlation between surgeons and pathologists and even among pathologists themselves when interpreting hyperfunctioning glands.[4]

Clonal studies confirm that adenomas are monoclonal whereas hyperplastic glands and normal glands are polyclonal.[5] However, the likelihood of monoclonal growth occurring simultaneously in two separate glands should be low. Increased proliferative activity is reported in normal glands of some double adenoma patients, suggesting adenomas may arise in a background of hyperplasia.[6] Furthermore, clonal studies have confirmed monoclonal growth occurring within hyperplastic glands in both primary hyperplasia and renal hyperparathyroidism.[6–8] Thus the concept of double adenoma is supportable albeit probably in a setting of asymmetrical hyperplasia. The question remains as to how long a patient should be observed after removal of double adenomas to exclude the possibility of recurrence and/or diagnosis of hyperplasia. An interval of 5 years has been recommended.[3]

In primary HPT, therefore, the surgeon needs to know that double adenoma/primary hyperplasia exists, that imaging is unreliable in this situation,[9, 10] and that a small proportion of patients undergoing MIP will require BPE.

PRIMARY HPT – FAMILIAL

Familial HPT comprises approximately 10–20% of all HPT presentations is discussed further in other chapters.

The hereditary syndromes, most frequently caused by mutations within specific genes, include multiple endocrine neoplasia (MEN) familial HPT and non-MEN familial HPT. MEN HPT occurs in MEN 1 and MEN 2A. Non-MEN HPT includes familial hypocalciuric hypercalcaemia (FHH) and neonatal severe hyperparathyroidism caused by heterozygous and homozygous calcium-sensing receptor gene mutations respectively. Also included is familial isolated HPT for which no specific genetic mutation has thus far been identified, and hyperparathyroidism-jaw tumour syndrome (HPT-JT).[11]

A familial syndrome should be suspected in young patients (teens, 20s), those with a family history of HPT, and those with a previous history or family history of medullary carcinoma, phaeochromocytoma, insulinoma, carcinoid or pituitary tumour. Familial syndromes exist in an autosomal dominant pattern.

Traditional BPE is the procedure of choice in most of these patients with the exception of FHH, which requires no treatment.

MEN familial HPT

MEN 1 HPT MEN 1 is relatively rare, occurring in approximately 1 in 30 000 people. The *MEN1* gene, identified in 1997, is the only gene known to be associated with the syndrome.[12] Primary hyperparathyroidism is the most common clinical manifestation of multiple endocrine neoplasia type 1.[2] It represents approximately 2–4% of all PHPT, making it the most common form of inherited HPT. Clinically evident disease is present in 95% of carriers by 25 years of age, with all being affected by 50.[13] The severity of the condition mandates surgery is performed in most cases but the type of procedure performed varies. The aim of surgery has to be to control HPT, minimize HPT recurrence and avoid hypoparathyroidism. Because of the genetic nature of the condition, removal of only enlarged glands at surgery is not practised because recurrence rates are too high.

Currently, two surgical approaches tend to be practised: subtotal parathyroidectomy removing at least 3–3.5 glands, and total parathyroidectomy with autotransplantation. In both procedures transcervical thymectomy is advised as the thymus often contains ectopic and/or supernumerary parathyroid glands and may develop thymic carcinoids.[14]

Subtotal parathyroidectomy generally involves the removal of the three largest glands and part of the fourth, maintaining approximately 50 g of parathyroid tissue. In 20% of cases all four glands cannot be found and in this situation a three-gland parathyroidectomy is performed. Large series with long-term follow-up are sparse, but persistent HPT rates range from 0% to 33%, recurrence rates from 0% to 51% and hypoparathyroidism rates from 0% to 27%.[15–19]

Total parathyroidectomy aims to remove all functioning parathyroid tissue. Hypoparathyroidism is then avoided by reimplantation of approximately 50 mg of autologous parathyroid tissue harvested from the most macroscopically normal of the parathyroid glands removed.

The optimum surgical approach is debatable. A cohort study from the Netherlands concluded that the most effective surgical approach involved subtotal parathyroidectomy (SPTX) with bilateral transcervical thymectomy. This was because persistence/recurrence was statistically more frequent when thymectomy was not performed, but permanent hypoparathyroidism was much more likely following total parathyroidectomy (TPTX). However, due to the rarity of the condition, a sample size of 73 patients undergoing a variety of surgical procedures in a non-randomized fashion makes it hard to draw firm conclusions.[20] The conclusions obtained correlated with those from a previous meta-analysis searching Medline, Embase and Cochrane from 1966 to 2008 which resulted in the analysis of 12 studies comparing SPTX with TPTX. The analysis concluded that <SPTX (defined as <three gland resection) should not be preformed because of the high risk of persistent and recurrent disease. Also TPTX carried too high a risk of permanent hypoparathyroidism (67%). Once again, more caution should be observed, no RCTs were found and all data was retrospective. In addition, follow-up periods varied and the study group was from the same institution as the more recent Netherlands study.[21]

MEN 2A HPT The MEN 2A subtype constitutes 70–80% of cases of MEN 2. In MEN 2A the overriding concern is to manage medullary thyroid cancer (MTC) in a timely fashion, ideally operating on the patient prior to

malignant transformation, but after diagnosis or exclusion of phaeochromocytoma. MEN 2A hyperparathyroidism occurs in approximately 20–30% of MEN 2A patients and is generally mild or asymptomatic.[22] In the majority of cases, hyperplasia occurs prior to adenoma formation although at surgery a single adenoma may be found.[23] It tends to occur in the third decade of life, but generally before the age of 39.[24] Although hyperparathyroidism is associated with various *RET* codon mutations, it tends to occur primarily in association with the exon 11 codon 634 mutation, which accounts for 85% of patients with MEN 2A.[25]

Recommended surgery depends on whether the neck has previously been operated on as is frequently the case to manage/avoid medullary thyroid cancer. In the unoperated neck with diagnosed PHPT in MEN 2A, ATA guidelines suggest removal of either enlarged glands only, a 3–3.5-gland parathyroidectomy (subtotal) or total parathyroidectomy, all with forearm autograft. For patients who develop PHPT after thyroid surgery it is recommended that parathyroid surgery is directed by pre-operative imaging, again with forearm autograft unless a functioning graft already exists. Patients are controlled medically if there is a high risk of surgical mortality, recurrent disease after previous surgeries or limited life expectancy. All recommendations are grade C.[26] It is felt that the optimal surgical intervention should be individualized as the condition is mild and, indeed, often asymptomatic, and most series have significant numbers of permanent hyper- and permanent hypoparathyroid patients.[27, 28]

Non-MEN familial HPT

Severe neonatal hyperparathyroidism This is a very rare but life-threatening disease in neonates demanding urgent management. Total parathyroidectomy via BPE following medical stabilization with biphosphonate therapy is usually required within the first few months of life. The morbidity of permanent hypoparathyroidism has encouraged surgeons to autotransplant parathyroid tissue, with variable success.[29]

Hyperparathyroidism-jaw tumour syndrome HPT-JT is a rare autosomal dominant familial cancer syndrome. The condition comprises primary HPT, ossifying tumours of the maxilla and mandible and less commonly renal cysts and/or uterine tumours.[30] HPT is the commonest feature of this disease. In affected individuals HPT occurs in approximately 80% of cases. The HPT occurs at a young age (mean 32 years), and it has a high incidence of severe hypercalcaemia and 15% malignancy rate. Treatment comprises a protocol similar to the management of MEN 2A, where only macroscopically enlarged glands are removed, although all glands should be found and assessed because of the high cancer rate. Some advocate total parathyroidectomy to negate the cancer risk.[31] If a likely cancer diagnosis is made at surgery, then en bloc resection of tumour, ipsilateral thyroid lobe and adjacent involved tissue is performed.

SECONDARY/TERTIARY HPT

Parathyroid surgery in renal failure

With decreasing renal function there is an associated decrease in renal 1-alpha hydroxylase activity, with a resultant drop in calcitriol or vitamin D3 synthesis. This in turn decreases the stimulation of the vitamin D receptor on parathyroid cells, causing an increased production of PTH and secondary HPT.[32] This leads to extraskeletal calcification and cardiac disease, causing an increased risk of cardiovascular morbidity and mortality. Indeed, dialysis patients on multivariant analysis have a 30 times greater risk of cardiovascular mortality than the general population.[33]

Renal failure patients are treated to normalize biochemical parameters, minimize bone disease and prevent extraskeletal calcium deposition. Nephrologists use serum calcium, phosphate, vitamin D and PTH levels as surrogate markers of disease severity. Treatment involves replacing serum vitamin D and restricting phosphate in the diet; vitamin D replacement in renal failure patients has been shown to reduce the risk of mortality, particularly cardiac related mortality.[34] If phosphate restriction proves insufficiently effective, phosphate binders such as calcium acetate and aluminium hydroxide are prescribed. In addition, calcimimetic agents such as cinecalcet may be used. Its implementation has led to a reduction in fracture risk, hospitalization rates for cardiovascular disease and requirement of parathyroid surgery.[35]

The need for parathyroidectomy in renal hyperparathyroidism has fallen due to improved medical control, a retrospective US survey reporting a 30% decline in the 1990s.[36] Currently, 1–2% of these patients will undergo surgery annually, with 10% ultimately requiring parathyroidectomy.[37] The cut-off point for deciding on a surgical option is not well established. The National Kidney Foundation Kidney Disease Quality Outcomes Initiative (KDOQI) suggest that patients with PTH >800 pg/mL associated with hypercalcaemia and/or hyperphosphataemia, despite medical therapy, should be offered parathyroidectomy.[38] Uncontrolled renal HPT results in morbidity classically from pruritis, the severity of which has been directly correlated to intact PTH levels,[39] bone pain, fractures or calciphylaxis and increased mortality rates.[40] In addition, a survival benefit has been demonstrated in renal failure patients undergoing parathyroidectomy.[41]

The optimal operative strategy for these patients is debatable. The main options include total parathyroidectomy versus subtotal parathyroidectomy (a 3.5-gland parathyroidectomy), with or without autotransplantation. In addition, the practice of simultaneous transcervical thymectomy varies.

A recent international survey assessing surgical practice in the management of renal hyperparathyroidism primarily within Europe obtained analysable results from 86 different surgeons performing renal parathyroidectomy.[42] The survey suggests that 20.9% of respondents operated without any pre-operative imaging. When used, the most popular imaging modalities are ultrasound (36%) and sestamibi

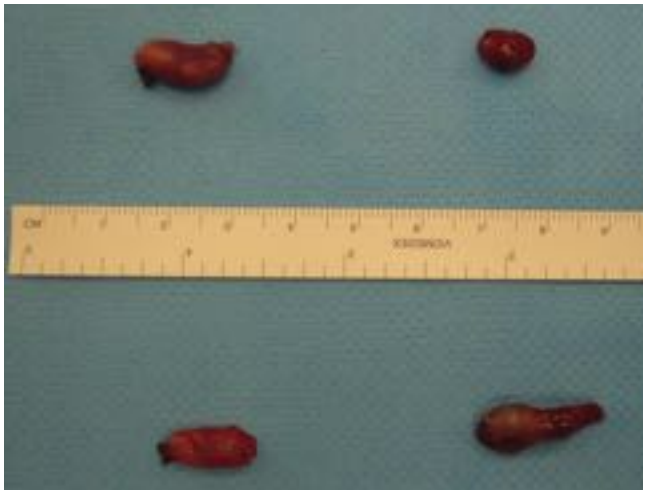


Figure 76.1 Four-gland parathyroidectomy specimen during renal parathyroidectomy in secondary hyperparathyroidism.

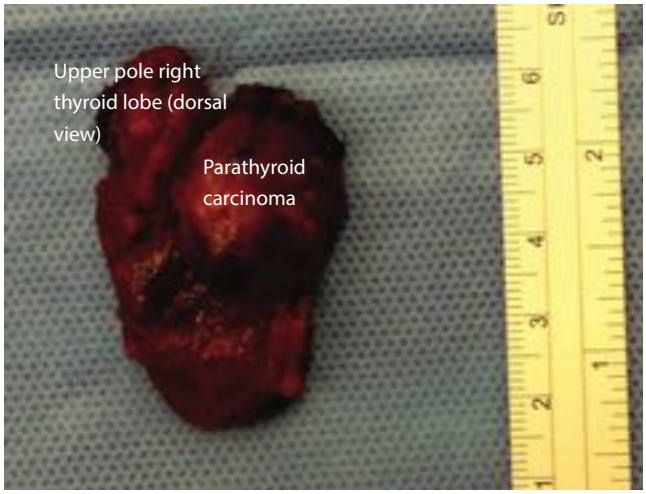


Figure 76.2 Right superior parathyroid carcinoma removed en bloc with right thyroid lobe.

scintigraphy (9.3%), with both in combination in 33.7%. Respondents reported that 98.8% perform subtotal or total parathyroidectomy, with or without immediate autotransplantation (Figure 76.1). In addition, 74.4% routinely perform transcervical thymectomy with 25.6% prepared to perform a transsternal exploration during initial surgery.

In the study, the practice of autotransplantation (AT) is extremely variable: 40.7% perform immediate AT while 36% do not. Smaller percentages tailor their practice to ioPTH results or dialysis techniques. The forearm is the implantation site of choice in 72.7% and the sternocleidomastoid in 16.4%. Graft function is assessed with serum PTH monitoring from grafted versus non-grafted forearms in 62.9% of cases, with 13.6% (n = 5) performing a temporary implantectomy ('Casanova test') and one using sestamibi scintigraphy (2.6%).

Parathyroid cancer

Parathyroid cancer is the cause of primary hyperparathyroidism in approximately 1% of cases. In advanced cases it has a high morbidity and mortality rate, mortality usually caused by intractable hypercalcaemia. If parathyroid cancer is suspected either pre-operatively or intra-operatively, the most likely way of achieving cure is through thorough surgical resection of the tumour and any involved surrounding tissue; the only appropriate surgical option is therefore BPE.

The involved parathyroid gland tends to invade immediately surrounding tissues including ipsilateral thyroid lobe, recurrent laryngeal nerve and ipsilateral strap muscles. If these structures are involved clinically, most surgeons advocate en bloc resection, avoiding breach of the tumour capsule to minimize risk of tumour seeding, with ipsilateral level 6 clearance if there is evidence of nodal involvement (Figure 76.2). Failure to perform en bloc resection or to clear the ipsilateral neck at revision surgery carries a significantly higher risk for local recurrence and death.[43, 44] Because of failure to make a correct clinical diagnosis at the time of first surgery and/or different management beliefs, en bloc resection only occurs in approximately 12% of cases with up to 86% of patients having inadequate resection at first surgery.[45, 46]

Failed pre-operative localization

Pre-operative sestamibi localization is negative in up to 20% of PHPT patients. This is reported to occur with increased incidence in multigland disease (32%). In a recent analysis of over 2600 patients with PHPT at a single institution, a curative operation was performed in 90.4 % with a negative MIBI compared to 97.5 % with localization (P<0.001).

4D-CT is an emerging technique that uses high-resolution CT images, multiplanar reformats and perfusion characteristics to identify abnormal parathyroid glands in patients with hyperparathyroidism. 4D-CT correctly identifies unilateral vs bilateral disease in 90% of patients, potentially reducing the need for BPE.[47]

Failed MIP

MIP may require conversion to BPE when there is failure to find a pre-operatively imaged gland or failure of ioPTH to drop to below 50% baseline at 10 minutes after adenoma excision, suggesting multigland disease.

This is especially significant in double adenoma. In a dual institution study of patients undergoing bilateral exploration, the ioPTH incorrectly indicated success after removal of the first adenoma in 55% of cases of double adenoma.[48] In comparison between the two groups, the authors found that the second adenoma was significantly smaller than the first in the false positive group (p = 0.03).

THE OPERATION OF BILATERAL PARATHYROID EXPLORATION

The patient is ideally consented before the day of surgery. The surgeon reviews the diagnosis, the indications for surgery and any imaging performed. The aims of the operation are defined. The incidence of adverse events should be

cited according to the surgeon's audited data. Specific risks include surgical failure and disease recurrence, recurrent laryngeal nerve damage and post-operative haematoma. The option of no surgery with its risks and consequences is discussed to enable an informed decision.

On the day of surgery, the neck is marked for level of incision by sitting the patient in a neutral position looking straight ahead. A surgical marker places a line at the bony soft-tissue junction at the level of the sternoclavicular joints.

The procedure is normally performed under general anaesthesia. The patient is intubated with a north-facing armoured endotracheal tube. The patient is placed in a supine position with 30 degrees of head elevation. Where possible, the neck is extended using a sandbag placed under the shoulders with the head stabilized on a headring.

The surgical field is prepared and draped. An incision of approximately 5 cm is made through skin and platysma. To optimize access, a subplatysmal flap is raised to approximately 1 cm above the cricoid cartilage and laterally superficial to the sternomastoid muscles. An inferior flap does not enhance surgical access. The strap muscles are separated at the linea alba. Occasionally, the linea alba is hard to identify as the muscle bodies are closely approximated. In this situation, the strap muscles are followed inferiorly towards the sternal notch as the muscles diverge caudally.

The plane between the deep straps and the thyroid lobe is developed from medial to lateral. The thyroid lobe is partially delivered from deep to the straps by lateral retraction of the ipsilateral strap muscles while the thyroid lobe is digitally retracted medially by the surgeon with a single layer of surgical gauze between the lobe and the middle finger. Fibrous bands are separated by the action of opening the surgical scissors in a medial to lateral direction. Bands that fail to divide are normally small blood vessels under tension which require bipolar diathermy. Once the lobe is adequately mobilized, a suture may be placed through the lobe in a cephalocaudal direction to enable the assistant to retract the thyroid out of the operative field. Simultaneously, the strap muscles and carotid sheath are retracted laterally so that the area directly surrounding the dorsal thyroid and tracheo-oesophageal gutter may be explored. A dry surgical field is vital as bleeding causes tissue discoloration and may create problems with parathyroid identification, especially with normal suppressed glands. Rinsing the wound with saline may help.

A successful search for the parathyroid glands requires a thorough knowledge of their surgical anatomy and embryology. The surgeon should understand the positions of parathyroid ectopia, which are mandated both embryologically and by the effects of increasing gland mass and deglutition.

The search should proceed in a methodical way. Ideally, no gland should be removed until all are visualized, but in a significant number of cases only one adenomatous gland and two suppressed/normal glands are found. In this situation it is acceptable to remove the enlarged gland, note the position of the identified normal glands and record the identity of the missing gland.

The superior gland is the more constant in position and generally lies on the posterior surface of the thyroid gland within 1 cm of the cricothyroid joint and posterior to the recurrent laryngeal nerve. As the thyroid lobe is retracted out of the neck and onto the trachea, its relationship with the nerve is inverted so the nerve lies deep to the superior parathyroid (**Figure 76.3**). An enlarged superior gland often works its way into a retropharyngeal/retro-oesophageal position by the combined actions of swallowing and gravity. It is found by identifying the inferior thyroid artery laterally, the recurrent laryngeal nerve inferomedially and entering the retropharyngeal space by mosquito dissection above the artery. Gentle soft-tissue dissection will identify the gland, which can be drawn out by gentle traction on its pedicle (**Figure 76.4**). If no gland is evident, the retropharyngeal compartment and the posteriomedial surface of the superior thyroid pole should be explored, the latter often requiring full mobilization of the pole by division of the superior vascular pedicle.

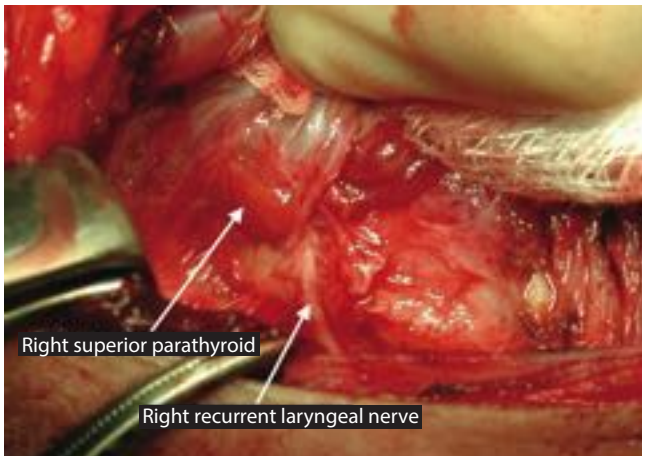


Figure 76.3 Demonstrating the inverted relationship between the right superior parathyroid and the right recurrent laryngeal nerve when the right thyroid lobe is retracted onto the trachea.

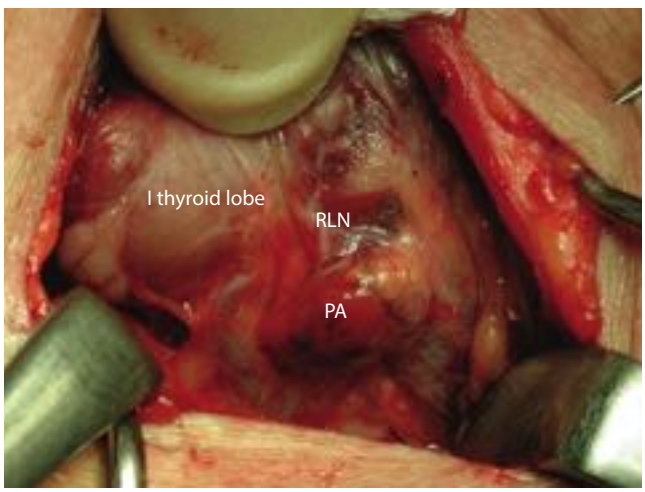


Figure 76.4 Left thyroid lobe retracted medially and enlarged left superior parathyroid adenoma (PA), having been delivered from the retro-oesophageal gutter, lying on top of the left recurrent laryngeal nerve (RLN).

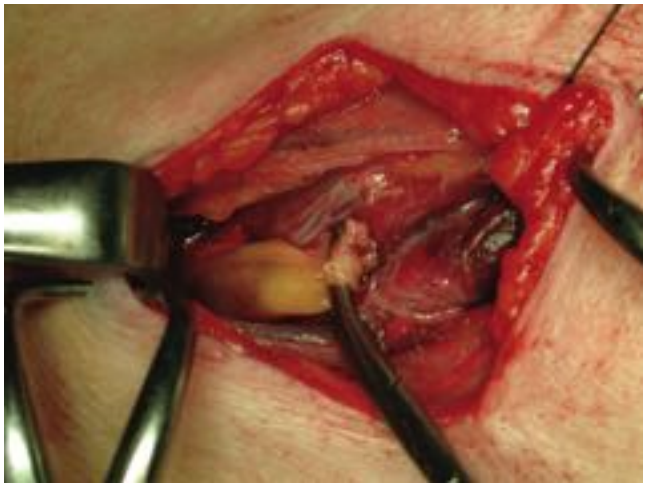


Figure 76.5 Left thymic remnant being delivered from the mediastinum and containing an ectopic inferior parathyroid adenoma.



Figure 76.6 Delivered thymic remnant containing ectopic adenoma.

The inferior gland is typically found near or within the thyrothymic tract, extending from the lower pole into the superior mediastinum, and it usually lies in a plane anterior to the nerve. Again, fascia is carefully dissected from the inferior pole out towards the recurrent laryngeal nerve. Progressive dissection into the thyrothymic tract will usually identify the gland. Further search for the inferior gland by delivery of the thymus into the neck is required only if an adenoma has not been identified on either side of the neck. This is to avoid devascularizing a normal but suppressed gland. If no gland has been found, the lower pole itself should be carefully inspected as a gland can often be found deep to the fascia compressed onto the thyroid.

Thymic delivery is effected by dissection inferiorly, anterior to the carotid artery, but medial to the recurrent nerve and lateral to the trachea at the level of the clavicle. The thymus continues as an extension of the thyrothymic tract and may be delivered from the chest by gentle and progressive traction on its capsule (Figures 76.5 and 76.6).

Surgical failure necessitates a thorough review of all dissected areas with documentation of clearly identified parathyroids and those missing. A 'second look' often identifies parathyroids which have changed colour due to devascularization or bruising.

If a superior gland, which is of 4th branchial arch origin, is missing, then inspection behind the hyoid, larynx, pharynx and within the carotid sheath at inferior thyroid artery level is performed. The possibility of an intrathyroidal gland must be considered, best identified with ultrasound. Hemithyroidectomy is performed only if there are good grounds for suspecting an intra-thyroidal adenoma. If an inferior gland is missing, the carotid sheath is explored from the level of the superior thyroid artery down to the sternoclavicular joint.

Failure after such a meticulous and sequential operation occurs in a small minority of patients. The possibility of an incorrect diagnosis must be considered. The surgeon must accept that the gland may be beyond the dissected field and that further imaging studies are required. Accurate operative documentation is essential. Before closing, blood may be taken for PTH assay from the upper IJV and lower IJV on each side as this may help narrow the subsequent search by suggesting the area of the rogue gland. Further surgery is then dictated by the severity of the hyperparathyroidism, positive imaging and patient consent.

KEY POINTS

- Bilateral parathyroid exploration (BPE) is normally reserved for multigland disease, familial disease, cases with negative imaging and revision surgery.
- When performing BPE, the surgeon should be aware of the embryology of the parathyroid glands and hence the most likely positions of ectopia for a missing gland.
- In 80% of cases, a gland on one side is symmetrical with that on the other, so finding the corresponding contralateral gland may aid the search for a missing gland.
- The dissection should be as bloodless as possible to avoid discoloration of surrounding tissues, which makes parathyroid identification difficult, particularly when glands are suppressed.
- The commonest position of an ectopic superior gland is retro-oesophageal, and an inferior intra-thymic.

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CHAPTER 77

MINIMALLY INVASIVE PARATHYROIDECTOMY

Parameswaran Rajeev and Gregory P. Sadler

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: parathyroidectomy, hyperparathyroidism and imaging.

INTRODUCTION

The surgical management of primary hyperparathyroidism has evolved from open neck exploration to minimally invasive surgery since the first successful parathyroidectomy was performed by Felix Mandl in Vienna in 1925. Minimally invasive parathyroidectomy (MIP) is now the treatment of choice for patients with sporadic hyperparathyroidism, with a parathyroid tumour localized by pre-operative imaging. The success of the technique is attributable to the improvements in pre-operative localization with sestamibi scanning and high-resolution neck ultrasound. This chapter describes the indications and technique of MIP in the management of sporadic primary hyperparathyroidism.

Primary hyperparathyroidism (HPT) is a common medical problem and is the most frequent cause of hypercalcaemia in the outpatient setting. The incidence of the disease has increased over the last decade worldwide,[1, 2] with the disease being more prevalent in women and with advancing age.[3, 4] Primary HPT is caused by a solitary adenoma in 80–85%, hyperplasia in 15–20%, usually in familial syndromes,[5] and carcinoma in less than 1% of cases.[6] Surgical extirpation of the gland is the mainstay of treatment in this condition.

Bilateral neck exploration has been considered the gold standard in the surgical management of primary parathyroid disease. However, with the emergence of improved pre-operative parathyroid localization with high-resolution ultrasound scan, sestamibi and SPECT scans, the technique of MIP has evolved.[7–9] The operation is performed under local anaesthesia (superficial cervical block) and intravenous sedation[10, 11] or general anaesthesia.[12]

The success of the procedure has been demonstrated in numerous studies with or without intra-operative PTH assay.[9, 10, 12, 13] The advantages of performing minimally invasive parathyroid surgery have been shown to be lower cost,[14] shorter operating time,[15, 16] shorter stay in hospital[12, 16] and improved cosmesis and patient satisfaction.[17] Technically, the operation is performed with a small incision measuring 2–3 cm on the neck and excludes the extrathyroidal approaches via the axilla or chest wall.

Surgical anatomy of the parathyroid glands

> *The success of parathyroid surgery must lie in the ability of the surgeon to know a parathyroid gland when he sees it, to know the distribution of the glands, where they hide, and also to be delicate enough in technique to be able to make use of this knowledge.*
>
> **Edward D. Churchill (1931)**[18]

This statement should fundamentally apply to all surgeons practising parathyroid surgery, more so in minimally invasive surgery. A thorough understanding of the embryology and anatomy is essential before performing the technique of MIP.

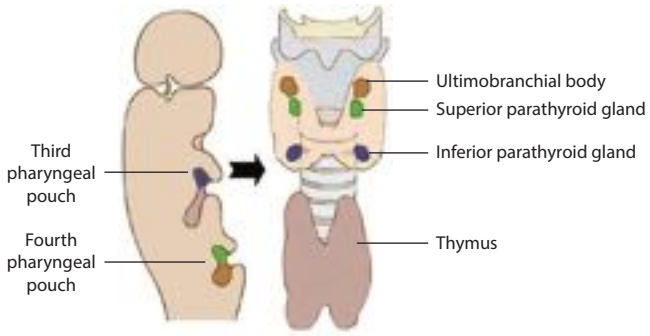


Figure 77.1 Diagram of normal pharyngeal organ development. The superior parathyroid glands and ultimobrachil body derive from the fourth pharyngeal pouch. The inferior glands originate from the third pharyngeal pouch along with the thymus. Reproduced with permission from Chen H, Senda T, Emura S, Kubo K. An update on the structure of the parathyroid gland. *Open Anat J* 2013; **5**: 1–9.[19]

Parathyroid glands are usually four in number and usually lie on the posterior surface of the thyroid gland, each with its own connective tissue capsule. The glands develop from the third and fourth pharyngeal pouches in the fifth week and descend to join the thyroid gland by about the seventh week of development. The inferior parathyroid gland arises from the superiorly located third pouch and the superior from the inferiorly located fourth pouch, as shown in **Figure 77.1**. This anatomical positioning of the parathyroid is linked to the development of the thymus. The thymus originates from the caudal portion of the third pharyngeal pouch and as it descends into the thorax, the inferior parathyroid usually accompanies it. The inferior parathyroid detaches from the thymus during the migration and takes its position on the posterior surface of the thyroid gland. Occasionally the inferior parathyroid moves with the thymus into the thorax and rests in an ectopic position.

The anatomical landmark that helps the surgeon in identifying the parathyroid gland intra-operatively is the inferior thyroid artery. The superior parathyroid glands are usually located within a circumscribed area about 2.5 cm above the intersection of the recurrent laryngeal nerve (RLN) with the inferior thyroid artery and the inferior glands located about the same distance below it. However, both the glands may be located outside the normal position and this is more commonly seen with the inferior parathyroid glands. Variations in the position of the superior glands include the upper thyroid pole in the posterior aspect of the neck, the retropharyngeal or retro-oesophageal space or rarely intra-thyroidally.[20, 21]

The inferior parathyroid glands have a wider distribution and may be located anterior, inferior or lateral to the inferior thyroid pole besides its conventional position. They may be seen in eutopic positions in the neck close to the thyrothymic ligament or within the cervical portion of the thymus or carotid sheath and, rarely, intra-thyroidally. They may also be located ectopically in the anterior mediastinum or in the aortopulmonary window.[20, 21]

It is not uncommon to confuse fat, accessory thyroid nodules or even lymph nodes with parathyroid glands. The parathyroid glands are usually vascular and bleed or bruise easily, unlike fat or thyroid tissue.[21] The glands are softer than thyroid tissue and lymph nodes. A simple technique to differentiate parathyroid from non-parathyroid tissue is to apply gentle pressure with a fine surgical instrument to the parathyroid glands; they appear to move inside their own capsule unlike non-parathyroid tissue.

INVESTIGATIONS FOR PARATHYROID DISEASE

The most important aspect in the use of minimally invasive parathyroid surgery is to establish the correct diagnosis and localize the disease accurately. Primary HPT can be differentiated from other forms of hypercalcaemia by careful history, physical examination and laboratory investigations. The disease has evolved from the classical symptomatic to asymptomatic form. Most patients today present with abnormal biochemistry results and do not have any manifestations of the disease.

The presence of the disease is confirmed biochemically with elevated calcium and parathyroid hormone levels, in the presence of normal renal function. It is important to measure vitamin D levels as the disease is characterized by low plasma levels of 25-hydroxyvitamin D and high plasma levels of 1,25-dihydroxyvitamin D. An autosomal dominant condition that mimics primary HPT is benign familial hypocalciuric hypercalcaemia (FHH), and this is excluded by measuring 24-hour urinary calcium excretion.

PRE-OPERATIVE IMAGING

> *The only localizing study indicated in a patient with untreated primary HPTH is to localize an experienced parathyroid surgeon.*
>
> **J.L. Doppman** [22]

For many years until the development of MIP, the role of pre-operative imaging was considered to be less important than the skill of the surgeon. Imaging in parathyroid disease has evolved over the last 60–70 years, with significant improvement in pre-operative localization. For MIP, it is essential to have a 'road map' of the anatomical location of the parathyroid gland and this is usually achieved by non-invasive modalities in the form of ultrasound and sestamibi scan, computed tomography (CT) and magnetic resonance imaging (MRI)[22] (**Figure 77.2**).[22] The invasive modalities are usually reserved for re-operative parathyroid surgery.

Imaging with sestamibi is the first-line investigation using the single-radioisotope technetium-99m (^{99m}Tc) sestamibi followed by high-resolution ultrasound scan. Recent studies have shown the combination of sestamibi with SPECT to be superior to single modality imaging [23, 24] and effective in detecting posterior glands.

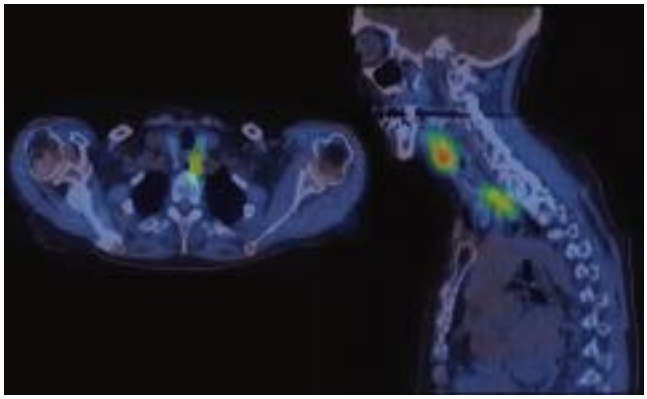


Figure 77.2 Sestamibi/CT functional overlay showing a left superior parathyroid adenoma. The tumour has dropped in the retro-oesophageal position and is not viewable on ultrasound scanning.

Ultrasound scanning (USS) has a complementary role to sestamibi and is useful in assessing the anatomy of the neck. It can easily differentiate parathyroid glands from thyroid nodules, which may be seen in up to 40% of patients. However, USS is operator-dependent and may miss smaller and deeper glands.

Where the scans are discordant, the current practice is to perform a CT or MRI scan for further confirmation of the adenoma. As a single modality, CT and MRI are of little use in localizing parathyroid adenomata for a minimally invasive approach. Their role is more in localizing ectopic disease or in the context of re-operative surgery.

INDICATIONS FOR MIP

The indications for MIP are no different from the conventional cervical exploration – symptomatic or asymptomatic patients fulfilling the established NIH criteria.[25] The technique is reserved for patients with uniglandular disease with concordant scans. Where there is discordance, absent imaging or negative scans MIP should not be performed. A scoring model for uniglandular disease has been developed by Kebebew et al[26] and includes: single site on sestamibi scan, single site on ultrasound, concordant localization, serum calcium >1 mg/dL above the upper normal limit, and PTH twice the upper limit of normal. The predictive value of the scoring system is 100% and therefore patients with a score of more than 3 should be offered MIP. Conditions that make patients unsuitable for MIP are listed in Box 77.1.

BOX 77.1 Contradictions to MIP

- Multiglandular disease
- Family history of MEN or familial hyperparathyroidism
- History of irradiation
- Previous neck surgery
- Chronic renal insufficiency
- Lithium therapy

OPERATIVE STEPS

Preparation and incision

The surgery may be performed under general anaesthesia or local anaesthesia with intravenous sedation (LA+IVS). All patients have a superficial cervical block with 20 mL of 0.25% Marcaine infiltrated on the involved side. Patients have an ultrasound scan on the morning of the surgery with pre-operative skin marking, and the image acts as the 'road map' to the adenoma (Figure 77.3). The patient is positioned on the table supine with slight neck extension by placing a gel pad or pillow behind the shoulder blades. The patient's head is supported in a gel donut and hyperextension is thereby prevented. The table is tilted 30 degrees in a reverse Trendelenburg position. The surgical site is prepped and sterile-draped from the chin to the sternal notch.

The skin incision is made according to the position of the adenoma that is pre-operatively marked by ultrasound. Either a medial or a focused lateral approach may be used to remove the adenoma. The medial approach is more suitable for a superficial inferior adenoma whereas the lateral approach is useful in picking a posterior inferior or a superior adenoma. We routinely use the focused lateral approach for superior and inferior adenomas. A 2–2.5 cm incision is placed along the skin crease overlying the medial border of the sternocleidomastoid muscle corresponding to the position of the parathyroid adenoma (Figure 77.3).

Once the skin incision is made, the platysma is divided gently by electrocautery and the subplatysmal plane is developed using blunt scissors. The medial edge of the sternocleidomastoid muscle is identified and the fascia divided superiorly and inferiorly. Any small vessel encountered is cauterized. The sternocleidomastoid muscle is retracted laterally and the lateral edge of the strap muscles is exposed. The plane below the muscles is entered and the strap muscles are retracted medially to expose the thyroid. By this technique, of medial retraction of straps and lateral retraction of the jugular vein underlying the sternocleidomastoid, most parathyroid glands are identified in the neck.



Figure 77.3 Incision for MIP, positioned over medial border of left sternomastoid (20 mm).

Exposure of the inferior parathyroid adenoma

The inferior parathyroid glands are usually seen at the inferior pole of the ipsilateral thyroid lobe or in or around the thyrothymic ligament. The adenomas are usually seen anterior to the RLN and inferior to the inferior thyroid artery. Once the plane between the straps and sternocleidomastoid is exposed, the thyroid is retracted medially and anteriorly. Using blunt artery forceps the parathyroid is circumferentially dissected free from the thyroid and the gland is gently lifted using vascular forceps, taking care not to fracture the parathyroid. Tributaries to the gland are clamped with a small haemostat and ligated. The gland is then excised and sent for histological evaluation. Adenomas located in the thyrothymic ligament or even in the thymus can be removed by this approach.

Exposure of the superior parathyroid adenoma

The superior adenoma is usually located in an area above the intersection of the inferior thyroid artery with the RLN, posteriorly in the retropharyngeal or in the retro-oesophageal space. The thyroid gland is retracted medially and the inferior thyroid artery is identified along with the RLN. In the case of large adenomas the artery may need dividing, as they lie usually posteriorly. Once the adenoma is identified, the dissection is performed in the avascular plane posterolaterally and, using the vascular forceps, the gland is gently mobilized, taking care not to injure the RLN. The pedicle, located posteromedially, is identified, clipped and divided. If the adenoma cannot be located in the positions described, one may need to consider that the adenoma may be intra-thyroidal. In this scenario, a decision for open-neck exploration is advised.

Once the adenoma is excised and haemostasis achieved, the wound is irrigated. The platysma and the skin are closed with subcuticular Vicryl Rapide, and Steristrips or glue applied to the wound.

Confirmation of cure

Most centres recommend the use of intra-operative PTH (IOPTH) levels to ensure that the adenoma is resected and also to assess cure. When this is achieved, the PTH levels fall to 50% of the pre-operative value at 10 minutes and this is predictive of cure in 98% of cases.[27]

COMPLICATIONS

The complications of MIP are rare in the best of hands and in centres of excellence. They are listed in **Box 77.2**.

BOX 77.2 Complications of MIP

- Recurrent laryngeal nerve palsy
- Bleeding
- Hypoparathyroidism (rare)
- Persistent disease
- Failure to cure

POST-OPERATIVE CARE

Patients are routinely prescribed analgesia and calcium supplementation on discharge. On discharge, irrespective of symptoms of hypocalcaemia and patients are generally advised to take calcium for a minimum of 24–48 hours post excision. While most of these cases are performed as day cases, patients are monitored for a minimum of 4–6 hours for any signs of haematoma. A patient leaflet on wound care is provided on discharge. Patients are reviewed in clinic at 4–6 weeks post-surgery, and calcium and PTH levels are checked to confirm cure.

KEY POINTS

- Confirm diagnosis of PHPT.
- Perform localization studies.
- Concordant studies: consider MIP.
- Ensure adequate exposure to perform operation safely.
- Establish protocol to manage post-operative hypocalcaemia and bleeding.

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CHAPTER 78

SURGICAL FAILURE AND REOPERATIVE SURGERY

Schelto Kruijff and Leigh Delbridge

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: parathyroid and reoperative parathyroid surgery.

BACKGROUND

General introduction

Primary hyperparathyroidism (PHPT) is a disease characterized by elevated serum calcium and parathyroid hormone (PTH) levels. It is a common disorder although multiple factors can influence its incidence such as regional influences, nutritional status, the availability of routine biochemical screening, sex (incidence higher in females), previous irradiation and age. Where the average incidence is 4.3/1000 in the United States, in women aged between 55 and 75 years the incidence can rise up to 21/1000.[1] It is most frequently caused by a single benign adenoma and is associated with a range of symptoms. The parathyroid glands play a key role in regulating the calcium homeostasis through an interaction between PTH, serum ionized calcium and vitamin D with the gastrointestinal tract, kidney and skin. Calcium is the single most potent activator of PTH release and, when its levels decrease, the calcium-sensing receptor (CaSR), situated on the parathyroid chief cells, is activated and stimulates the release of PTH.[2]

Historically, patients with hyperparathyroidism would present with advanced clinical features such as fractures, skeletal deformities, 'brown tumours', renal calculi and even kidney failure. After the discovery of the PTH and the introduction of routine biochemical screening with the auto-analyzer in the 1970s, a significant change took place such that most patients were diagnosed at an earlier stage, with an associated dramatic increase in presentations for surgery.

Historical perspective on surgical management

The only cure for PHPT is to surgically remove the hyperfunctioning parathyroid adenoma or adenomata (in the case of multigland disease) or to reduce the bulk of parathyroid tissue in patients with hyperplasia. The historical evolution of surgery for PHPT, as well as the surgical strategies after operative failure, can be considered in three distinct phases. The first phase was the 'learning curve'. While the first documented removal of a parathyroid adenoma by Bland-Sutton in 1910 was successful, he was certainly not aware of the pre-operative diagnosis.[3] Most of the early documented intentional parathyroid procedures in the 1920s were associated with failure for a variety of reasons that may still plague parathyroid surgeons today. In Vienna in 1925, Hirsch undertook a four-gland parathyroid exploration which turned out to be negative with no tumour found. The patient was subsequently diagnosed with fibrous dysplasia, which was the wrong diagnosis. Also in Vienna in 1925, Mandl performed the first initially successful intentional parathyroidectomy, although a number of years later the patient developed recurrent disease and died.[4] In 1927, Churchill performed a total of seven parathyroid explorations on the same patient before finally removing a large mediastinal adenoma. Unfortunately, his patient died post-operatively of renal failure, albeit cured of his hyperparathyroidism.[5]

The second phase was the open four-gland exploration approach. With an increasing understanding of

parathyroid anatomy and embryology over subsequent decades, open four-gland parathyroid exploration became the gold standard procedure for patients with hyperparathyroidism, providing cure rates in experienced hands of over 95% with minimal complications. In that phase, failure in the 5% of patients was largely related either to surgery being performed by an inexperienced surgeon, or to the presence of an ectopic parathyroid adenoma, usually located in a mediastinal position. Multigland disease was readily managed since all four parathyroid glands were routinely identified and any large glands removed.

The third and current phase of minimally invasive parathyroidectomy (MIP) was ushered in with the report of the first endoscopic parathyroidectomy by Gagner in 1996.[6] The initial techniques employed endoscopic assistance, but it soon became clear that a more direct approach via a 2 cm open mini-incision (either central or lateral) was feasible and much more direct.[7] The perceived advantages with a minimally invasive approach were patients with less post-operative pain, smaller scar and shorter hospital stay, and MIP has now become standard of care, with reported cure rates of over 95%, at least in the short term.[7] Unlike open four-gland parathyroid exploration, the most common cause of failure in MIP is the presence of multigland disease. Up to 15% of patients have historically been reported to have multigland disease present, which represents the number who, in theory, require more than one gland excised to achieve normocalcaemia.[8] However, with the advent of MIP, aiming at a pre-operatively identified parathyroid abnormality, a much higher frequency of solitary adenomas of 96% was found.[8] The extent of the pre-operative workup influences the number of observed solitary adenomas. Lee came to a supporting conclusion comparing the presence of multigland disease before and after the introduction of MIP and found that the incidence of multiple enlarged glands being removed dropped from 15% to 4%, although there was no documented change in the incidence of surgical failure. These findings indicate that many enlarged glands in patients with multigland disease do not contribute to hypercalcaemia.[9]

Numerous techniques have been introduced to minimize the risk of failure during MIP. The most widely utilized is the intra-operative measurement of serum PTH levels (IOPTH) first introduced by Irvin.[10] Many authors claim this reduces the risk of failure, although there are no convincing data to support this proposal. IOPTH works best when not required, when a single localized adenoma is removed at MIP, but it fails most often when most needed, especially in the presence of multigland disease. Therefore, we recommend IOPTH is not utilized, rather emphasis is placed upon high-quality concordant imaging for localization, providing a success rate of 98% as documented in our last published series of over 100 successive cases.[11] If a single abnormal gland cannot be localized, then open parathyroidectomy is still offered.

While short-term failure is no higher in patients having a MIP, there is increasing concern that long-term recurrence may be rising. For example, after having performed more than 17 000 parathyroid operations having, Norman has recently abandoned the unilateral MIP claiming that the procedure carries a 10-year recurrence rate of 4–6%.[12] He recommends that the only way to achieve 10-year cure rates of over 95% is to examine all four parathyroid glands.[12] The group claims that no diagnostic tool such as intra-operative PTH (IOPTH) is able to confirm with enough certainty that all the abnormal glands have been removed. They also argue that several studies have shown that 20% of patients have more than one abnormal, enlarged gland, and in 16% an initial IOPTH drop after removing one enlarged gland will still require the removal of additional tumours.[12–14] As previously noted, in general, the experience is that high-quality imaging, with appropriate selection for MIP based upon concordant localization studies (4D CT, sestamibi scan and ultrasound), is the most appropriate means of minimizing initial parathyroidectomy failure to around 2% (**Figure 78.1**). When that inevitably occurs, reoperative parathyroidectomy can still be undertaken (by experienced surgeons) with very high success rates and minimal complications (**Figure 78.2a,b**).[15]

Anatomy and embryology of difficult locations

The parathyroid glands are small tan brown organs which arise from the dorsal aspect of the pharyngeal pouch in the fifth week and descend in the direction of the caudal thyroid gland. They are soft, weigh 35–55 mg, and measure 2–7 mm in length.[15] Multiple shapes, ranging from leaf to bean form, are found.[16] Adenomas are usually oval, red-brown masses that can replace the normal parathyroid gland, although haemorrhagic and cystic lesions can also be seen. An adenoma can weigh anywhere from 50 mg to several grams. On histologic examination, parathyroid chief cells will be seen clustered around capillary networks.[16] Localization studies may help the surgeon locate any pathological glands; success in parathyroid surgery, however, is mainly based upon a thorough knowledge of

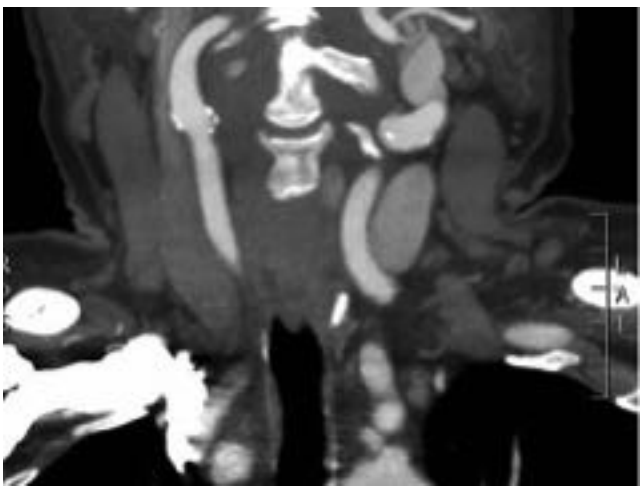


Figure 78.1 4D CT scan showing a left retropharyngeal undescended superior adenoma.

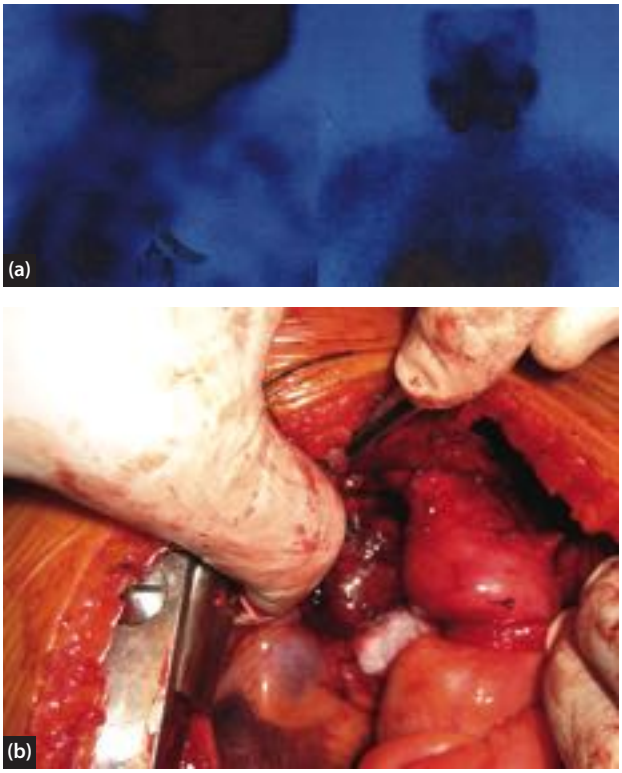


Figure 78.2 (a) Sestamibi scan of fifth ectopic adenoma in aorta pulmonary window. **(b)** Operative photo of removal of right inferior parathyroid adenoma in aorta pulmonary window.

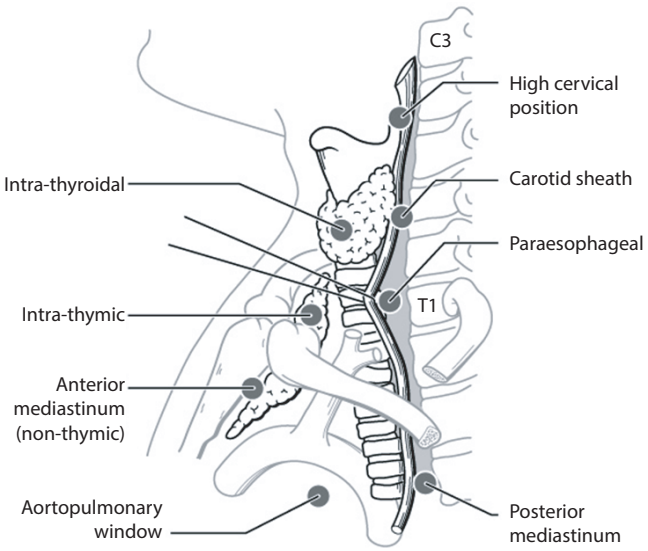


Figure 78.3 Common ectopic locations of missed parathyroid adenomas leading to surgical failure.

the anatomy and a thorough understanding of the embryology of the glands (Figure 78.3).

The first procedure is the golden opportunity to cure the patient. Reoperative surgery for failure is almost always a more challenging procedure due to loss of normal anatomical planes, as well as the presence of scarring and fibrosis that may obscure the classic appearance of both normal and abnormal parathyroid glands that experienced surgeons rely on.

LOCATION OF THE SUPERIOR PARATHYROID GLANDS (PIV)

The superior glands arise from the dorsal wing of the fourth pharyngeal pouch and descend in a caudal direction with the thyroid gland itself. Most superior parathyroid glands (PIVs) are located immediately adjacent to inferior cornu of the thyroid cartilage, close to the recurrent nerve, cranial to the branch of the inferior artery nerve. Exposure of the posterior aspect of the thyroid lobe is made by displacing the gland inwards and retracting the jugular–carotid bundle outwards. After this simple exposure, the superior glands are then found immediately superior to the junction of the recurrent laryngeal nerve and the inferior thyroid artery.[17]

These glands are closely associated with the recurrent nerve and so, when mobilizing them, especially with a minimal invasive approach, identification and dissection of the nerve are of vital importance. However, when the superior gland is abnormal, it tends to migrate posteriorly and downwards. Therefore, when it is not in immediate contact with the thyroid, it should be sought lateral to or behind the oesophagus, bearing in mind that the lower a superior descended gland travels the more posterior it becomes.

The origin of the pedicle is usually at the upper third of the thyroid lobe and can be located by simple traction on the pedicle. The superior parathyroid gland can also be situated just under the perithyroidal sheath, close to the posterior aspect of the lobe. Quite often a flattened parathyroid adenoma is located at the posterior aspect of the upper pole of the thyroid lobe which may easily be missed when one does not know where to look for it.

LOCATION OF THE INFERIOR PARATHYROID GLANDS (PIII)

Because of a longer descent, the inferior parathyroid glands (PIIIs) have a much higher variability in location when compared with the superior parathyroid glands; the inferior parathyroid glands arise from the dorsal aspect of the third pharyngeal pouch and, following the development of the thymus, they descend in a caudal-medial direction. Over 40% are situated at the posterior aspect of the thyroid lobe from the inferior thyroid artery to the lower pole of the lobe and along the thyrothymic ligament. PIII is very rarely situated posteriorly and becomes more anterior the lower it descends. Quite often these glands are located at the posterior aspect of the lower pole of the lobe, situated anterior to the recurrent nerve. The thyrothymic ligament is a common location for a gland and it can be situated at the thymic upper pole. It is important to remember that, in 80% of patients, the location of the inferior and superior parathyroid glands is symmetrical when compared with the glands on the contralateral side of the neck.[18]

Definitions of failure – persistent disease vs. recurrent disease

Persistent hyperparathyroidism is defined as the presence of an elevated serum calcium and inappropriately elevated

or non-suppressed serum PTH within 6 months of the initial surgical procedure; recurrent hyperparathyroidism is defined as the same biochemical scenario developing after at least 6 months of hypercalcaemia. Persistent PHPT (80–90%) is much more common than recurrent (10–20%) PHPT. While this definition is somewhat arbitrary, it acts to separate out those patients with multigland disease in whom hypercalcaemia appears subsequent to an initial successful operation, presumably since the second adenoma was present but inactive at the time of initial surgery. Even in the most experienced hands, persistent hyperparathyroidism following failure at initial surgery for PHPT will never reach zero although centres with a high turnover of cases should achieve an initial success rate of 95–98%.[13]

As noted, there is a conceptual difference between failure following an open parathyroidectomy, where this is largely due to either surgical inexperience or ectopic location, and failure after MIP, where this is largely due the presence of multigland disease in the neck that has not been identified on pre-operative localization studies. Recurrent hyperparathyroidism due to multigland disease may even develop after several years, often being associated with a familial disorder; in contrast, the development of a second adenoma is very rare and mostly seen in patients who have had previous irradiation.[19] Parathyroid carcinoma should also be considered in the differential diagnosis of failure and in some situations a recurrence corrects an original misdiagnosis for an atypical adenoma. Local recurrence can be a parathyroid carcinoma, although this can also be seen after capsular rupture of benign lesions (parathyromatosis).

INVESTIGATION OF PERSISTENT OR RECURRENT DISEASE (THE THREE 'R'S)

Before undertaking any second exploration in the neck for recurrent primary hyperparathyroidism it is of vital importance to understand fully the causes for the failure of the initial operation. The workup before any reoperative exploration should consist of 'the three R's'; **reconfirm** the diagnosis, **review** the operative and pathology reports, and **repeat** the imaging.

Reconfirm the diagnosis and reassess the patient

The diagnosis of PHPT can only be made again if other causes of hypercalcaemia are excluded. In the first place serum analysis and 24-hour urine should be repeated to look for raised PTH and calcium to confirm the diagnosis of PHPT. Elevated PTH with normal calcium can occur in up to 30% post-op due to hungry bone syndrome (secondary response to bone remineralization), low vitamin D levels, impaired renal hydroxylation of vitamin D-25 or decreased peripheral PTH sensitivity or an impaired renal function. Elevated calcium in the presence of suppressed PTH suggests a misdiagnosis such as bone metastases. A modestly elevated serum calcium and serum PTH can be seen in familial hypocalciuric hypercalcaemia (FHH), which mimics PHPT and is a well-recognized cause of failure in an index case. It is of crucial importance to assess a family history properly to be able to exclude FHH because the disorder is not cured by parathyroidectomy. FHH is caused by various mutations in the gene coding for the CaSR. The CaSR responds to serum calcium and mediates feedback inhibition of PTH release. A loss-of-function mutation results in a rising of the calcium threshold that triggers reduction of PTH secretion. Serum concentration of calcium is thus maintained at higher levels since more calcium is needed to trigger negative feedback. This results in hypercalcaemia, and since more calcium is sequestered in the serum, this often results in hypocalcuria.[20] FHH is excluded by demonstration of a 24-hour urinary calcium/creatinine ratio greater than 2%. A family history of PHPT should be sought in order to exclude not only FHH but also other familial endocrinopathies such as MEN 1 and MEN 2A.

Review the operative and pathology reports

It is important to consider factors that might have made the previous surgery difficult such as a very short neck, a coexisting multinodular goitre, or a poorly placed incision, in order to be able to form an operative strategy. It is then vital to obtain and review the operative and pathology reports to determine which parathyroid glands have already been identified or removed. Issues such as who performed the procedure (experience), what kind of procedure was performed (MIP or four-gland exploration) and what was removed (parathyroid normal or abnormal; fat; nodes) all need to be identified. In addition, more detailed information, such as the position of glands identified and/or removed and the time that was spent exploring the neck looking for sites of ectopic parathyroid to be explored, should be documented. Is there anything abnormal to be noted in the report such as thyroid nodules or lymph nodes that might have formed distracting conditions during surgery and the pathology reports should be assessed thoroughly?

Repeat the imaging

A reoperative procedure for PHPT without a positive localization study will most likely lead to a second failed procedure and is a potential recipe for disaster. Localization studies are mandatory although there is no consensus as to which provide the best information. Because the specificity and sensitivity for each method vary greatly, combined localization studies, commencing with the least invasive, are generally recommended.[21]

Our own recently published series showed that 4D CT had an accuracy of 91% in reoperative cases and is significantly more accurate than either sestamibi or ultrasound.[22] In another study it was reported that imaging before reoperation with sestamibi has a 59% identification rate,

ultrasound 36%, CT 41% and selective venous sampling 78%.[15] Non-invasive imaging studies (ultrasound, sestamibi, 4D CT) are the studies of first choice, with invasive procedures such as venous sampling and arteriography used only if non-invasive studies are inconclusive or conflicting. In evaluating venous sampling it is important to realize that the study does not image the abnormal parathyroid gland but rather provides information to the surgeon regarding the region where the parathyroid is located.[23] Sometimes image-guided fine-needle aspiration (FNA) with biochemical assessment of the diluted aspirate (not cytological examination) may help distinguish a parathyroid tumour from other structures. A recent report demonstrated that fewer patients now undergo invasive studies (56% versus 73%), which was attributed to improvements in imaging technology.[24] The anatomical diagnosis should ideally be established by a concordance of the results of at least two investigations. When used together, imaging techniques correctly identify abnormal glands in nearly 95% of cases.[25]

CONSERVATIVE OPTIONS

Although parathyroid surgery forms the only definite cure for PHPT, the risks and benefits of surgery need to be appropriately considered and discussed with the patient. When there is an urgent need to treat hypercalcaemia or surgery is contraindicated, or the patient decides against it, non-surgical alternatives are available.

For acute treatment of severe hypercalcaemia, intravenous saline solution loop, diuresis and bisphosphonates are recommended.[26] Subcutaneous calcitonin is also an option, but its efficacy is limited to the first 2 days. Cinacalcet is a calcimimetic drug and lowers PTH secretion by enhancing receptor sensitivity to extracellular calcium. Normocalcaemia can be achieved after 1 day of treatment, the response to cinacalcet can be persistent and it is generally well tolerated.[30] The drug has been shown to be effective in reducing or normalizing serum calcium levels in several groups of patients with PHPT, including patients with mild to moderate PHPT, parathyroid carcinoma, and in PHPT as a part of MEN type 1.[27] Cinacalcet at low dosages is well tolerated, but side effects are more frequent and severe when relatively high doses are needed to control hypercalcaemia. The most common adverse events are nausea, vomiting and paresthesias.[26] Cinacalcet may be of benefit in a wide spectrum of PHPT, offering a novel therapeutic option for the control of hypercalcaemia in PHPT patients who are not able to undergo parathyroidectomy. To what extent the reduction of serum calcium translates into a clinical benefit, particularly in patients with mild to moderate hypercalcaemia, is currently unknown.[28]

SURGICAL APPROACH

In a reoperative situation, a focused exploration is the goal, aiming to locate only the abnormal gland and remove it without disturbing normal glands, mostly positioned in scar tissue and easily damaged or devascularized. There is almost no role for a blind open four-gland exploration in the reoperative situation.

Operative strategy for previous failed open parathyroidectomy

If localization studies have provided a lateralization or a more specific regionalization, a focused re-exploration on the side of localization is performed. If the patient had a standard anterior approach through a cervical incision at the first operation, the same skin incision is used, followed by a lateral approach, in the plane lateral to the strap muscles and medial to the sternocleidomastoid muscle (SCM), rather than the standard approach between the strap muscles. This approach is preferred to avoid heavily scarred planes from the previous anterior neck exploration.

The dissection begins from the medial aspect of the SCM muscle, finding the plane medial to the internal jugular vein then continuing that down to the pre-vertebral fascia, which is often virgin, unscarred tissue. The thyroid lobe can then be identified. The recurrent laryngeal nerve should be identified at this stage using the inferior approach as described for reoperative thyroid surgery.[29] The nerve is located in the trachea-oesophageal groove below the plane of initial surgery and tracing it upwards. As the carotid sheath is retracted to the lateral side, the neck is explored superiorly to the level of the hyoid bone, inferiorly to the brachiocephalic vessels and posteriorly in the trachea-oesophageal plane.[29] Common missed positions of the inferior parathyroid are the inferior and posterior surface of the thyroid gland beneath a thin layer of the capsule, the thyrothymic ligament and the thymus tissue situated in the anterosuperior mediastinum. A parathymus (a parathyroid gland that remained undescended during embryological development) may leave an inferior gland, as high as the mandibular angle. An inferior adenoma positioned here is thus located more superior than the superior parathyroid gland.

During the thorough search along the embryological descent of the gland itself, we dissect towards the superior mediastinum and on the way open and explore the carotid sheath, removing a major portion of the thymus. For the search of the superior parathyroid, the superior pole vessels should then be ligated to facilitate exposure of the superior-posterior side of the thyroid and the trachea-oesophageal groove can be explored by entering this area immediately posterior to the inferior thyroid artery. The technique of palpating the posterosuperior mediastinum digitally can be used to exclude large adenomas that might have been missed in the initial operation. This superior adenoma would thus be situated inferior to the inferior parathyroid gland (PIII).[30, 31]

If the above strategy fails to locate any abnormal parathyroid tissue despite imaging having demonstrated a possible candidate lesion on that side, the contralateral side should not be blindly explored at the time. Bilateral reoperative surgery after a previous bilateral exploration

has the potential to lead to bilateral recurrent laryngeal nerve palsy and tracheostomy. Under these circumstances, surgery for the contralateral side should be deferred and reconsidered after further imaging.

Operative strategy for previous failed MIP

Minimal invasive unilateral exploration has now become the procedure of first choice for most first-time parathyroid procedures. In a reoperative situation after a unilateral-focused operation for the first operation, the approach should depend upon the initial incision placement and operative approach. For an adenoma localized to the same side as the initial procedure, if a lateral mini-incision approach was initially utilized, an anterior cervical approach should be considered instead of the lateral approach extending the scar to a classic Kocher incision. However, if a midline mini-incision or videoscopic approach was utilized initially, then a lateral approach second time around is preferable. Should the adenoma be localized to the contralateral side to the initial operation, a lateral mini-incision approach on that side is entirely appropriate.

Mediastinal exploration

Most mediastinal adenomas are located in the posterior mediastinum or in the anterior mediastinum just superior to the aortic arch and can usually be explored from the same cervical approach. Previous extensive cervical surgery (particularly if a cervical thymectomy had been attempted and the thymic tissue was disrupted) may prevent a cervical delivery and necessitate a median sternotomy. Likewise, a large adenoma lying below the aortic arch may not be deliverable and may require a sternotomy. An adenoma located deep in the middle mediastinal window requires a thoracotomy. Confident localization must be obtained before the surgeon proceeds to mediastinal exploration (**Figure 78.2a,b**). There is absolutely no role for blind mediastinal clearance in the futile hope of retrieving or devascularizing a non-localized tumour.

REVIEW: RESULTS AND POST-OPERATIVE COMPLICATIONS

Results

For patients with persistent or recurrent hyperparathyroidism, pre-operative localization studies and a focused surgical approach can result in a 95% success rate with a minimum of complications.[32] However, management of persistent or recurrent hypercalcaemia after failed initial surgery remains one of the greatest challenges in endocrine surgery. Neither the cure rates nor the complication rates of reoperative surgery have changed significantly over the last few decades despite the revolutionary development of imaging.

Although multigland disease is still the most important cause for primary failure, Thompson demonstrated that 40% of missed abnormal glands reside in a normal anatomical position.[33] Despite the success rates for reoperative surgery varying from 82% to 98%, the fact that most missed adenomas are located in abnormal anatomical positions challenges all surgeons to strive for a primary cure to prevent a patient having to face the risks of reoperation.[30]

The rates of persistent hyperparathyroidism after surgery vary considerably around the world, with some centres reporting rates as high as 24% and other centres in Europe and Australia rates as low as 2–3%. This, of course, may simply reflect referral pattern in these countries where most primary operations are performed by experienced endocrine surgeons.[32, 33] However, Lew reported a failure rate for reoperative parathyroid surgery of 2.9%, of which most failures (76%) were due to failure of the surgeon to locate the abnormal gland.[34, 35] Only 24% of missed adenomas in this study were caused by multigland disease.[35] Their group also concluded that the surgeon's judgement and experience are paramount, especially in these cases.

Complications

The most significant complication of reoperative parathyroid surgery is a recurrent laryngeal nerve injury, resulting in vocal cord paralysis. Despite the difficulty of dissecting in scarred tissue planes, the permanent nerve injury rate is exceptionally low in most published series, ranging from 0.4% to 4%, and the rates of permanent hypocalcaemia in reoperative parathyroid surgery have been reported to be in the range of 5–11% in the most recent series.[36–40] The use of intra-operative nerve monitoring was studied recently by comparing nerve injury rates. Since there was only one unintentional nerve injury in each group, the authors concluded that, although monitoring can be performed safely, it does not decrease the injury rate.[41] Careful dissection and visualization of the nerve remain the best protection against injury. However, if the surgeon decides to use intra-operative nerve monitoring, employing it routinely in these cases is more effective to gain more experience with the technique and to be able to make best use of it in the reoperative setting.

Permanent hypocalcaemia is the other significant complication of reoperative parathyroid surgery, where the normal glands may have been damaged, biopsied, or all three normal glands may even have been excised during the first operation.

SUMMARY

Patients with recurrent or persistent PHPT present a challenge, even for the experienced parathyroid surgeon. It is crucial to reconfirm the diagnosis, consider the risks and benefits of the reoperation, and review the operative notes and pathology reports and the results of localization tests. The success rates are high in the hands of an experienced surgeon who has excellent knowledge of the embryology

and anatomy of the parathyroid glands. The complication rate of recurrent laryngeal nerve injury and permanent hypocalcaemia is acceptable but considerably higher than during initial parathyroid operations. Most missed adenomas seem to be located in a normal anatomical position, which challenges all parathyroid surgeons to strive for a primary cure in the first operation and to prevent a patient needing to face the risks of reoperation.

KEY POINTS

- The only cure for PHPT is to surgically remove the hyperfunctioning parathyroid adenoma or adenomata.
- Unlike open four-gland parathyroid exploration, the most common cause of failure in MIP is the presence of multigland disease.
- High-quality imaging, with appropriate selection for MIP based upon concordant localization studies (4D CT, sestamibi scan and ultrasound), is the most appropriate means of minimizing initial parathyroidectomy failure.
- Persistent PHPT (80–90%) is much more common than recurrent (10–20%) PHPT.
- The workup before any reoperative exploration should consist of 'the three R's'; reconfirm the diagnosis, review the operative and pathology reports, and repeat the imaging.
- In a reoperative situation, a focused exploration is the goal, aiming to locate only the abnormal gland and remove it without disturbing normal glands.
- The most significant complications of reoperative parathyroid surgery are recurrent laryngeal nerve injury and permanent hypoparathyroidism.
- The success rates are high in the hands of an experienced surgeon who has excellent knowledge of the embryology and anatomy of the parathyroid glands.
- Most missed adenomas seem to be located in a normal anatomical position, which challenges all parathyroid surgeons to strive for a primary cure in the first operation and to prevent a patient having to face the risks of reoperation.

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CHAPTER 79

COMPLICATIONS OF THYROID AND PARATHYROID SURGERY AND HOW TO AVOID THEM

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: thyroid surgery, complications, haematoma, recurrent laryngeal nerve injury, oesophageal injury, tracheal injury, airway complications, hypoparathyroidism, hypothyroidism and thyroid storm. The evidence in this chapter is mainly levels 3 and 4. The clinical recommendations are mainly B and C.

INTRODUCTION

Complications in thyroid and parathyroid surgery are uncommon but significant when they occur. Averting the complications should begin pre-operatively with an assessment of risk factors for potential complications and a thorough discussion with the patient outlining the risk factors, treatment approaches and outcomes. Sound anatomical knowledge and meticulous surgical technique aid in minimizing complication risk. Post-operatively, close observation of the patient is the key to identifying and managing problems early and successfully, leading to a better overall outcome.

SEROMA

The incidence of seroma formation is low, occurring in 1–7% of cases. Seromas are more likely to occur after surgery for a large goitre or a total thyroidectomy. Post-operative neck swelling should be taken seriously and monitored for rapid enlargement or tenderness. In most cases, seromas are managed conservatively with observation and by reassuring the patient.[1] When seromas are painful or lead to tightness, aspiration of the fluid using sterile technique eases the patient's discomfort but may need to be repeated several times before reaccumulation of the fluid stops. Placing a drain into the dead space left after the surgery may also be helpful. If there is a concern of infection, the aspirated fluid should be sent for culture and antibiotics should be started. In the majority of patients, seromas resolve over 6–8 weeks with watchful waiting.[1]

INFECTION

Infection of the surgical site is quite rare in thyroid and parathyroid surgery, occurring in less than 1% in most cases series. These surgeries are considered clean by the Centers for Disease Control and the National Safety Network criteria for wound classification and do not require peri-operative antibiotics.[2] In certain instances, using a peri-operative antibiotic selectively may be reasonable given a patient's risk factors for potential infection.

Intra-operatively, if there is a break in sterility or another source of contamination such as entry into the

aerodigestive tract is identified, then antibiotics are warranted. Superficial wound infections are treated with local wound care and oral antibiotics. Deep wound infections are more serious: they require incision and drainage with wound culture, placement of a drain in addition to i.v. antibiotics and investigation for the source, which is often a missed aerodigestive injury.[3, 4] Cervical infections after thyroid and parathyroid surgery should never be underestimated and should be treated definitively and swiftly to prevent mortality from this complication.[5]

HAEMATOMA

Minimizing the risk of post-operative haematoma begins pre-operatively by identifying risk factors for each patient that contribute to an increased likelihood of a post-operative haematoma. Several articles have defined significant risk factors including male gender, older age, smoking, large thyroid, benign pathology, antiplatelet/anticoagulation therapy and Graves' disease.[6, 7] Obtaining a good history is important; hypertension and taking herbal supplements such as fish oil increase the risk of bleeding and potential haematoma formation.[8] Following surgery, hypertension, vomiting and excessive coughing or sneezing can induce haematoma formation.[8, 9]

Maintaining meticulous haemostasis intra-operatively, particularly at the end of the case, is essential. There are several thermal haemostatic instruments that can be used including monopolar cautery, bipolar cautery and vessel-sealing devices, none of which confers better haemostasis over another. Many surgeons utilize the Valsalva manoeuvre to identify and control any potential areas of bleeding prior to closure.[1] Drains do not decrease the rate of post-operative haematoma; in fact one study shows that a drain is a risk factor for haematoma. Drains should be used very selectively in this setting and, because they increase the risk of infection, antibiotics should be administered while the drain is in place.[10–13] Haemostatic agents may be used in the thyroid bed but they have not been shown to decrease the rate of haematoma. Most haematomas occur within the first 6–12 hours after surgery. However, a small percentage of haematomas form greater than 24 hours after surgery and up to 1–2 weeks afterwards.[6, 14] Haematomas can be superficial (above the strap muscles) or deep (below the strap muscles). As the haematoma expands, it causes venous and lymphatic congestion which exacerbates laryngopharyngeal oedema leading to eventual airway compromise. Decompressing and evacuating the clot is the first and most important manoeuvre in order to help alleviate airway narrowing. While the patient is awake, the incision is released and the strap muscles are incised to release pressure from the haematoma.[15] Securing the airway is paramount; placement of an endotracheal tube when necessary is preferred. If this is not possible, then an emergency tracheostomy may be needed. The patient is then returned expeditiously to the operating theatre for haematoma evacuation, identification and control of the bleeding source. After achieving complete haemostasis, the wound is closed again.[1, 15] Most patients who return to the operating room for haematoma evacuation recover well from this second procedure and are discharged the day after surgery.

RECURRENT LARYNGEAL NERVE INJURY

In the pre-operative setting, a thorough history and physical examination should be performed to identify any concurrent factors such as significant smoking history, lung cancer or reflux disease, affecting the voice quality of the patient. Pre-operative laryngoscopy should be performed on all patients to document baseline vocal cord function.[16, 17]

Intra-operative direct visualization of the recurrent laryngeal nerve (RLN) lowers the rates of temporary and permanent RLN injury rates and is considered the gold standard.[18–21] Intra-operative neural monitoring (IONM) is an important complement to visualization of the nerve. IONM have shown a trend towards lower RLN injury rates but statistical proof is lacking in part due to lack of adequate statistical powering of most studies. IONM aids in mapping the RLN, in assessing nerve function, and in identification of an injured nerve segment.[16, 22, 23] Having real-time monitoring allows the surgeon to change the technique or the amount of retraction that is causing harmful impact on the RLN.[16] When injury is suspected, identification of the injured segment, assessment of the injury and the possibility of repair should be explored. The RLN injury should be managed appropriately at the time of identification.[24, 25]

An analysis of 27 articles, reviewing more than 25 000 patients undergoing thyroidectomy, found the average post-operative vocal cord paralysis (VCP) rate was 9.8% and ranged from 0% to 18.6%.[26] Post-operative laryngoscopy should be performed to reliably document post-operative glottic function and for early identification of VCP to initiate appropriate management.[16] There are multiple methods for restoring voice quality in patients who have vocal cord dysfunction. In the first 3 months, cordal injections can enhance contact between the vocal cords and improve swallowing, voice and cough. If the injury is permanent, procedures like thyroplasty and medialization laryngoplasty can be performed.[27] These methods rely on placement of a structural implant to reapproximate the injured cord with the normal cord. Finally, reinnervation is another option that can be accomplished by mobilizing a functioning nerve, typically the ansa cervicalis to the distal RLN stump. It may take several months to regain voice function after this procedure.[27]

INJURY TO THE EXTERNAL BRANCH OF THE SUPERIOR LARYNGEAL NERVE

IONM can be very helpful in intra-operative identification of the external branch of the superior laryngeal nerve (EBSLN), as up to 20% of EBSLN are subfacial

and visually unidentifiable.[28] A precise surgical technique with careful superior pole dissection and ligation of the superior pole vessels on the gland itself is important.[29, 30] Understanding the anatomical variations of the EBSLN course is the best guide for protecting the nerve. With monitoring there is a standardized approach to identification and dissection of the EBSLN.[31]

Post-operatively, the surgeon should inquire about voice strength, pitch and fatigue. If the patient has any of these complaints, EBSLN injury should be suspected and a formal voice evaluation with videostroboscopy as well as speech therapy should be performed.[29]

HYPOPARATHYROIDISM

For patients with thyroid cancer, substernal goitre, Graves' disease and reoperation, hypoparathyroidism is a significant concern. Pre-operative Vitamin D, serum calcium and PTH evaluations are helpful in establishing a baseline for calcium homeostasis prior to surgery. If the vitamin D is low, replacement before surgery is helpful in order to decrease risk of symptomatic hypocalcemia secondary to lack of calcium absorption.[32]

Meticulous dissection with preservation of the parathyroid glands and their blood supply is required to avert hypoparathyroidism.[33] The standard method for preserving the parathyroid glands and their blood supply is capsular dissection. The glands are mobilized and reflected away from the thyroid gland while keeping their blood supply intact.[20, 21, 24] Disruption of parathyroid gland vascularity is the most common reason for post-operative hypoparathyroidism. If a parathyroid gland seems non-viable after surgical dissection, a portion may be sent for frozen section to confirm parathyroid tissue and the remainder can be autotransplanted into the sternocleidomastoid muscle.[35] Inadvertent removal of one or more parathyroid glands with the thyroid can also cause hypoparathyroidism.[36]

Post-operatively, serum calcium levels can be checked to determine the need for calcium supplementation. Some surgeons give post-operative calcium supplementation to all patients. Hypoparathyroidism can be temporary, less than 6 months post-surgery (8–30%) or permanent, more than 6 months post-surgery (1.7–3.5%).[19, 32] In the acute setting with serum calcium levels less than 1.75 mmol/L, i.v. calcium gluconate is administered to alleviate symptoms which can include paraesthesia, muscle cramps and spasms, twitching, tetany, seizures and cardiopulmonary dysfunction. If serum calcium is at least 2 mmol/L, then it is treated with oral calcium carbonate and vitamin D. For patients with a history of gastric bypass surgery or reflux disease, calcium citrate is used instead of calcium carbonate because it is better absorbed in these patients.[37] The starting dose of calcium is usually 500–1000 mg three times a day with upward titration if symptoms persist. For vitamin D administration, the most active form, 1,25-dihydroxy D3 (calcitriol), is used with a starting dose of 0.25 µg each day. Ionized calcium, phosphorous, PTH and vitamin D should be checked at regular intervals if the patient is not improving. The goal is to maintain a low-normal serum calcium with normal phosphorous levels and low urinary calcium excretion.[32] For patients with permanent hypoparathyroidism, maintaining calcium and phosphorous levels is more difficult and requires routine monitoring and changes to supplementation as needed. Urine calcium levels tend to increase over time and lead to renal insufficiency. Osteoporosis is also a concern for these patients because their bone resorption is decreased.[32] A new treatment option is recombinant PTH (rhPTH), an injectable synthetic human PTH administered subcutaneously once or twice a day.[38] It has been shown to maintain serum calcium levels, decrease phosphorous levels and decrease or eliminate the need for vitamin D supplementation. From a physiological standpoint, there is improved bone turnover and a decreased urinary calcium level.[38, 39]

AERODIGESTIVE INJURY

In patients with known thyroid cancer with a concern for tracheal or oesophageal invasion, a thorough workup including imaging and endoscopy should be completed pre-operatively. This is helpful for surgical planning and for avoidance of aerodigestive injury.

During surgery, inadvertent entry into the oesophagus or trachea is uncommon but, when it occurs, it is usually secondary to adherent tumour or lymph nodes.

Tracheal injuries can be small or large. Small injuries can be repaired primarily with absorbable sutures.[40] If primary closure is not possible, segmental tracheal resection may be performed or a tracheostomy tube placed. Oesophageal repair includes debridement of the tissues edges with two-layer closure of the mucosa and muscle separately. A strap muscle may be used to buttress the repair. A closed drainage system is placed, antibiotics and parenteral nutrition are started and the patient is kept nil by mouth for 7–10 days when a contrast swallow is done to check for a leak.[40–42] If there is no leak, a soft diet is introduced. Long-term complications from a leak include stricture and fistula, both of which require further workup and treatment.[42]

HYPOTHYROIDISM

Surgical hypothyroidism should be a point of pre-operative discussion for any patient undergoing thyroid surgery. Typically, the starting dose for levothyroxine is 1.6–1.8 mcg/kg/day and is titrated based on thyroid function tests thereafter. Patients with thyroid cancer may need a higher dose in order to suppress growth of cancer cells.[43]

For patients who have undergone lobectomy, there is a 15–50% risk of abnormal thyroid function after surgery with the need for levothyroxine. Hashimoto's disease, higher TSH or lower free T4 or a smaller remaining lobe increase the likelihood of requiring T4 supplementation.[44, 45]

Bloods should be checked 6–8 weeks after surgery because the half-life of levothyroxine is 7 days and it takes about this period of time to reach a steady level.[43, 46, 47]

HYPERTHYROIDISM

Patients with hyperthyroidism secondary to Graves' disease and less often toxic multinodular goitre or a toxic nodule are at risk for development of thyroid storm throughout the disease course. Usually an external source such as infection, surgery, trauma or increased iodine intake is the inciting factor for thyroid storm.[48] Multiple systems are affected in thyroid storm – cardiopulmonary, thermoregulatory, metabolism, neurological and gastrointestinal. It is quite rare to develop this extreme form of thyrotoxicosis but when it occurs, early recognition and prompt supportive treatment are essential for survival.[48] Pre-operatively the surgeon needs to discuss with the patient the risks of thyroid storm and the importance of compliance with medication up to the day of surgery. Thyroid function tests should be checked regularly prior to surgery to ensure that free T4 and free T3 levels remain within an acceptable range. If free T4 is above 20 pmol/L and the free T3 remains high, surgery is postponed until those levels decrease appropriately.[48]

In the operating theatre, a shift in vital signs alerts anaesthesia to the possibility of thyroid storm. Tachycardia, dysrhythmia (usually atrial fibrillation), high fever and respiratory changes are the most common symptoms.[48] Cooling the patient, administering a beta blocker and hydrocortisone are initiated to mitigate the associated symptoms. Concurrently, antithyroidal medication, PTU or carbimazole is also started to stop synthesis of new hormone and to prevent peripheral conversion of T4 to T3. Of note, most anaesthetists give a dose of Dantrolene in this situation because the symptoms of malignant hyperthermia and thyroid storm are difficult to differentiate.[48] Post-operatively, patients with thyroid storm need close monitoring and continuation of supportive care until thyroid hormone levels normalize and the patient is no longer symptomatic.

AIRWAY CONCERNS

Determining potential airway risk pre-operatively is the best way to minimize airway complications both during intubation and post-operatively. Recognizing patients who are at higher risk because of their disease extent, by a thorough pre-operative assessment recognizing shortness of breath, dysphagia and hoarseness helps guide anaesthesia and surgical planning.[49, 50] Patients with large goitres, substernal goitres and invasive cancers have a higher risk of airway complications. If there is concern for a substernal component or tracheal narrowing, neck and chest CT scan should be performed.[50] Anaesthetics should be consulted early in the workup of these patients so that a joint anaesthetic–surgical plan can be developed pre-operatively. In some instances, a planned tracheostomy may be considered if there is significant tracheal narrowing, a long-standing goitre or thyroid cancer. On the day of surgery, anaesthesia and surgery jointly decide the best approach based on the patient's pre-operative findings.[49, 51] Options include induction and traditional intubation or use of a glidoscope, awake fibreoptic intubation or planned tracheostomy. At the completion of the surgery, the surgeon and anaesthetist should discuss the likelihood of success with extubation.[51] The majority of patients can be safely extubated and will experience improvement in airway symptoms. Some patients may need prolonged intubation if there is concern for tracheomalacia, which is rare. In other cases, a tracheostomy may be done at the end of the surgery, because of intra-operative detection of significant tracheal narrowing or bilateral RLN injury.[1, 52] Any patient who has a difficult airway or airway complications at the time of surgery should be counselled in the post-operative setting about these difficulties and instructed to convey this information prior to future surgeries.

HYPERTROPHIC OR KELOID SCAR

During the pre-operative visit, a thorough history of prior operations and scar formation is key to having the best possible outcome for the surgical scar. All old scars should be examined for healing issues. In a patient with known keloid formation, a surgical as well as post-surgical plan is developed. The skin should be marked in the holding area just prior to surgery while the patient is still awake in order to find the most natural skin crease for the incision. In theatre, less is more for closing these incisions including use of suture and manipulation of the tissues. Steroid injections can also be employed prior to skin closure.[1] A tension-free closure also helps minimize scarring. Close follow-up for hypertrophy or keloid formation post-operatively and early plastic surgery or dermatology consultation are important so that advanced options for scar treatment can be explored in a timely manner. Post-operatively patients should be educated about sun exposure and use of sunscreen on the incision as well as use of over-the-counter scar care products to aid in minimizing scar formation.[1]

BEST CLINICAL PRACTICE

- ✓ Pre-operatively, a thorough history, physical examination and laryngoscopy can help identify risk factors that can increase the likelihood of intra-operative and post-operative complications and also provide the opportunity to discuss post-operative expectations with the patient.
- ✓ Intra-operatively a sound anatomical knowledge, meticulous surgery, avoidance of harmful manoeuvres and use of complementary technology such as nerve monitoring can help avert complications.
- ✓ Post-operative active surveillance for complications, especially in high-risk patients, and early identification with appropriate management of complications are of paramount importance.

KEY POINTS

- The post-operative course starts in the pre-operative setting with a detailed discussion about surgery, risks and benefits.
- Knowledge of the anatomy and excellent surgical technique are essential for positive outcomes.
- Early recognition of complications with applicable treatment offers better outcomes.

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CHAPTER 80

THYROID AND PARATHYROID SURGERY: AUDIT AND OUTCOMES

David Chadwick

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: thyroidectomy, parathyroidectomy, complications, hypocalcaemia, laryngeal nerve palsy and outcomes.

INTRODUCTION

Surgery of the thyroid and parathyroid glands is generally considered very safe. Mortality is minimal, so relevant outcomes relate mainly to the avoidance of specific surgical complications. These are reasonably well defined, and their incidence may depend to a large extent upon the operative skill of the surgeon, thereby providing an ideal opportunity for clinical audit.

OUTCOMES: ESTABLISHING THE MAGNITUDE OF RISK

Accurate knowledge of the frequency of surgical complications may be considered important for many reasons. These include: assistance in patient counselling and consent for surgery; use in surgical decision-making in selection of patients for surgery; identification of risk factors which influence complication rates, particularly if these can be modified to improve results; and provision of benchmarking data by which surgeons can be compared, with the aim of improving surgical performance.

The principal complications to be addressed, related to thyroid and parathyroid surgery, are the following:

- **Post-operative bleeding,** particularly that which requires re-exploration of the neck/evacuation of a haematoma, to protect the airway.
- **Hypocalcaemia,** secondary to the disturbance of parathyroid function. This may occur in the early post-operative phase, usually during the index admission, and may or may not require treatment. In a proportion of these cases, hypocalcaemia will be transient, as parathyroid glands recover their function, but a smaller proportion may progress to permanent hypoparathyroidism.
- **Recurrent laryngeal nerve (RLN) injury,** leading to vocal cord paralysis. As with hypocalcaemia, this may be transient, with recovery of function occurring over a variable time period, or permanent.
- **Persistent hypercalcaemia,** in surgery for primary hyperparathyroidism, where this outcome represents a failure to cure the disease.

Other complications exist, but estimates of their incidence are highly unreliable, due to considerable variation in their definition, perceived impact, detection strategies and geographical factors. For example:

- severe wound infection is rare, and the definitions of milder infection vary widely between studies
- evidence of superior laryngeal nerve injury may be subtle, and frequently is not actively sought
- some complications are simply extremely rare and also influenced by the nature of the presenting disease (e.g. tracheomalacia, chyle leak).

For this reason, the remaining discussion will focus on the principal complications of bleeding, hypocalcaemia and recurrent laryngeal nerve injury.

Estimates of the rates of these complications may derive from individual (often retrospective) case series reported in the medical literature or from large-scale prospective audits/registries designed to measure these outcomes.

Interpretation of the data from retrospective case series is prone to several difficulties. First, there may be issues of case selection bias. Even within a consecutive series, the rationale for the selected time period of study is often not stated, and clusters of complications either side of this time interval can significantly affect results, particularly in smaller series. Many publications do not explicitly record the degree of missing data, nor cases excluded from analysis or lost to follow-up.

Second, studies often vary greatly in the definitions of relevant complications, and in the strategy for their detection. This is particularly relevant for hypocalcaemia and recurrent laryngeal nerve palsy (RLNP). Calcium levels may be uniformly measured after surgery, but hypocalcaemia may be defined in several ways: for example, any result below the local reference range; a result below various other biochemical thresholds; the presence or absence of hypocalcaemic symptoms; the requirement for treatment with calcium and/or vitamin D supplements; or combinations of these variables. Such differences in definitions may result in widely disparate estimates of hypocalcaemia rate, even when applied to the same group of patients.[1] Early hypocalcaemia may also be avoided by the use of prophylactic calcium/vitamin D supplements, and protocols vary greatly between surgeons in this regard.

Likewise, the diagnosis of post-operative RLNP is dependent on the incidence and timing of post-operative laryngeal examination.[2–4] Voice changes after thyroidectomy are commoner than documented RLNP, but vocal cord palsy may also be asymptomatic and is often transient. Many surgeons do not routinely arrange post-operative laryngeal examination, and the available methods for performing such examinations differ in their accuracy. It is clear that routine laryngeal examination reveals much higher rates of RLNP than where vocal cord function is assessed solely on the basis of vocal symptoms and that the earlier in the post-operative course such examination occurs, the higher will be the rate of (at least transient) RLNP.[3, 4] For these reasons, rates of RLNP are extremely difficult to compare across retrospective case series.

For both hypocalcaemia and RLNP, the point at which the complication is described as 'permanent' is also variable. Recovery may occur beyond 12 months post-operatively, but data on very long-term follow-up are harder to obtain, and may be incomplete. Results at 6 months may represent a reasonable compromise, but this approach risks overestimation of truly permanent outcomes.

Third, results may be affected by variation in case mix, which is often poorly described. Relevant variables might include, for instance, re-operative versus first-time surgery, indication for surgery (e.g. malignant versus benign), and extent of thyroidectomy and of concomitant central compartment lymphadenectomy.

Fourth, there may be use of 'inappropriate denominators'. For instance, the rate of hypocalcaemia within a series of thyroidectomies will be influenced by the proportion of cases having bilateral surgery, as hypoparathyroidism will not usually result from unilateral dissection. The overall rate of hypocalcaemia will therefore be artificially low if unilateral lobectomies are included in the denominator. This is often inadequately described in published series. Similar considerations apply to recurrent laryngeal nerve injury, where the rate of RLNP per patient may differ significantly for a given rate per nerve at risk, because bilateral surgery carries twice the risk of injury to one or other nerve.

Finally, retrospective series are prone to publication bias, reflecting individuals' tendency only to publish 'good' results. Genuinely excellent outcomes might thus be reported from some highly specialized centres and represent an aspirational target, but these may not reflect more general, routine practice.

Regarding persistent hypercalcaemia after surgery for primary hyperparathyroidism (HPT), additional considerations apply in interpreting the available literature. Although historical series[5, 6] report cure rates of over 97%, there has been a resurgence of interest in recent years in performing targeted surgery, following localization studies such as sestamibi and ultrasound scanning. Such surgery may be performed via a mini-incision open method or by various endoscopic techniques. Recent case series, frequently reporting only targeted surgery, are therefore restricted to a subgroup of patients, with obvious abnormalities on imaging, who may potentially have larger adenomas and therefore be 'easier' to cure. Conversely, the limitations of pre-operative imaging in excluding multigland disease may reduce the cure rate in a proportion of targeted cases, while those with entirely negative imaging are possibly the most difficult to cure, in turn affecting the results of bilateral exploration.[7] Individual units' or surgeons' results may therefore be dependent not only on the quality of the surgery but on referral practices and case selection, and they can be reliably compared only if information on all their operated HPT cases is made available.

Despite these concerns, some estimate of risk can be made, and **Table 80.1** summarizes recent results from larger case series.

Prospective audits and registries may partly avoid some of these problems, as they may be able to apply more consistent definitions of relevant outcomes, remain contemporaneous and potentially collect uniform information on case mix and other factors which might influence outcomes. They also have the potential to study much larger numbers of patients than would be feasible in most single centres, thereby increasing the precision of any risk estimates.

The best-established national registries examining global results of thyroid and parathyroid surgery are the Scandinavian Quality Register[21] and the UK-wide Audit of the British Association of Endocrine and Thyroid Surgeons (BAETS).[22]

The Scandinavian Quality Register[21] was established in 2004 and receives data on thyroid, parathyroid and adrenal surgery, submitted from multiple centres across Sweden (and Denmark). Coverage is high, with participating units accounting for over 90% of the cases currently being performed in Sweden, and with a full spectrum of thyroid pathology being represented.

The BAETS National Audit[22] was initiated in 2000 and currently receives data on thyroid, parathyroid, adrenal and endocrine pancreatic surgery from BAETS members, via a standardized electronic pro forma. The distribution of pathology represented is similar to that of the Scandinavian Registry, although coverage within the UK is lower, at about 35% of thyroid cases (estimated from English Hospital Episode Statistics).

Results from both registries have been published in national reports[21, 22] and, as is apparent in Table 80.1, show rates of complications generally higher than the best results previously reported in the medical literature. It is likely, therefore, that they represent a more realistic assessment of the true rate of complications in routine practice, for the reasons alluded to above.

Even within large, specifically designed registries, however, difficulties remain in providing reliable estimates of risk. These include the following:

- **Data entry issues.** Registries and large prospective audits are dependent on entry of data by external agents, such as by hospital coding departments or individual members of a host specialty association. Such data may therefore be liable to incomplete case acquisition,

TABLE 80.1 Summary rates of complications in recent large case series and national registries

	Reference	Re-exploration for haemorrhage	Early RLNP	Permanent RLNP	Early hypocalcaemia*	Late/permanent hypocalcaemia*
Single centres	Burkey et al[8] (*n* = 13817) (Thyroid and parathyroid)	0.3%				
	Rosenbaum et al[9] (*n* = 1050) (Thyroid and parathyroid)	0.6%				
	Promberger et al[10] (*n* = 30142)	1.7%				
	Leyre et al[11] (*n* = 6830)	1.0%				
	Lee et al[12] (*n* = 2636)		0.7%	0.2%	35.3%	0.4%
	Efremidou et al[13] (*n* = 932)	0.2%	1.3%	0.3%	7.3%	0.3%
	Karamanakos et al[14] (*n* = 2043)	1.3%	1.7%	0.9%	27.8%	4.8%
	Hermann et al[15] † (*n* = 16443)		5.1%	1.4%		
	Erbil et al[16] † (*n* = 3250)		1.8%	0.3%	6.6%	0.3%
	Tartaglia et al[17] (*n* = 1636)	1.2%	1.9%	0.9%		0.8%
Multicentre studies and National Registries	Godballe et al[18] (*n* = 5490)	4.2%				
	Duclos et al[19] † (*n* = 3574)			2.1%		2.7%
	Baldassarre et al[20] (*n* = 119567)				9.0%	
	Scandinavian Quality Register[21] Thyroid (*n* = 13975) Parathyroid (*n* = 6113)	 2.0% 0.5%	 3.0% 3.0%	 1.1% 0.3%	 16%	 3.0%
	BAETS Audit Thyroid[22] (*n* = 26222) Parathyroid (*n* = 11923)	 1.1% 0.4%		 1.0%	 22.7%	 6.3% 2.5%
		Persistent hypercalcaemia (all primary HPT)				
	Scandinavian Quality Registry[21] Parathyroid	5.9%				
	BAETS Audit[22] Parathyroid	4.9%				

* Bilateral resections only
† Routine post-operative laryngoscopy

variations in how the definitions of index complications are applied, incorrect coding and data transposition errors.
- **Data quality issues,** in particular the possibility of duplicate entries, and the rates of missing data.[22] The latter are particularly liable to affect estimates of risk, as it is feasible that poorer outcomes may be more frequent within the cohort whose data on that outcome are missing.
- **Choice of a suitable period of analysis,** balancing the need to provide the most contemporaneous data against the advantages of greater patient numbers which might be provided by a longer time period of study. Comparisons between individual units' or surgeons' results may be especially prone to misinterpretation in this regard, due to the greater random variation existing around point estimates of risk with small patient numbers.

These considerations aside, it is likely that national registries provide the most realistic estimates of risk for the purposes of consent and provision of benchmarking data.

OUTCOMES: COMPARISON BETWEEN PROVIDERS

A natural use of audit and registry data is to compare surgical performance between surgeons or hospitals. This may be useful for individual surgeons, to reassure themselves that their practice is satisfactory, or to identify areas where performance might be improved, and so enhance the quality of care. Such considerations may also contribute significantly to surgeons' appraisal processes and, in the UK, to revalidation with professional regulatory bodies (General Medical Council). With appropriate refinement, such data may also assist patients and service commissioners in selecting hospitals or surgeons.

This issue has recently gained increasing attention in the UK, with the introduction of NHS England's Consultant Outcomes Publication process,[23] through which individual surgeons' outcomes for various subspecialty procedures have been made available in the public domain. For thyroid surgery, this was first made publically available in 2013, using data derived from the BAETS audit, via a web-based portal. These data have been updated annually since 2013.[24]

In addition to the above-mentioned problems, further difficulties exist in using audit data for this purpose, particularly issues of random variation and case mix.

Even when the overall risk of a surgical complication is known, the exact number of events observed in any given series of operations will be subject to some random variation. Statistical methods can help identify when the observed variation is within that expected by chance, and traditionally confidence intervals are calculated, outlining the limits beyond which chance is less likely to explain the observed variation. Selection of appropriate confidence limits, however, is difficult. Set too widely, they risk designation of all surgeons as 'within control limits', and so miss those whose performance may in fact be lower than average. Set too tightly, they risk inappropriate identification of surgeons as 'outliers', with the potential for damage to reputation and career.

With any operation, the risk of certain complications occurring may also be affected by case mix, for example variation in patient characteristics, such as age or comorbidity, or in surgical complexity. Surgeons taking on more complex cases might be expected to have a higher complication rate, even if their performance is no worse than the average.

In some surgical fields, the factors affecting results are well defined, allowing for risk adjustment, to allow for case mix. In endocrine surgery, however, there are no established, validated models for this purpose.

For thyroidectomy, factors identified from individual case series as potential confounders include:

- patient age and gender[10, 18, 25]
- extent of thyroid resection (lobectomy versus subtotal versus total thyroidectomy)[10, 14, 16, 18, 25]
- re-operative versus first-time surgery[10, 14, 16, 25, 26]
- malignant versus benign disease[14, 18, 26]
- Graves' disease versus other benign diseases[14]
- central neck dissection, in addition to thyroidectomy[27,28]
- goitre size and retrosternal versus cervical goitre[29, 30]
- surgeon caseload/experience[19, 31, 32]

As mentioned above, however, it is difficult to combine the results from these disparate studies into a unified mathematical model of risk-adjustment, and it is likely that only analyses from prospective registries will have the power and consistency of definition of relevant variables to do this. A preliminary, multivariate analysis from the BAETS dataset[33] has been a first step towards this, generating estimates of odds ratios for those factors most strongly affecting certain complications, namely:

- for bleeding: extent of thyroidectomy and patient age
- for early hypocalcaemia: Graves' disease, age, gender and level 6 node dissection
- for late hypocalcaemia: cancer diagnosis and particularly level 6 node dissection.

It must also be recognized that risk-adjustment models can only make allowance for those variables included within the original dataset, and that other, unrecorded, factors may influence results, for instance patient comorbidity or ethnicity[34, 35] or thyroid volume.[30]

There remains an urgent need to explore this issue further, if accurate comparison is to be made between surgeons, on the basis of registry data.

OTHER USES OF AUDIT DATA

Published registry data[21, 22] also provide interesting insights into:

- use and accuracy of pre-operative investigations, such as fine-needle aspiration cytology (FNAC)

- trends over time in the management of certain conditions, e.g. the gradual replacement of subtotal by total thyroidectomy for most benign conditions, or the increasing trend to perform pre-operative localization studies in first-time primary hyperparathyroidism
- management and staging of thyroid cancer, particularly variations in the extent of 'prophylactic' lymph node surgery
- rare diseases, including medullary thyroid cancer and parathyroid cancer
- trends in the use of technological innovations, such as a slow increase in intra-operative laryngeal nerve monitoring, more rapid increase in the use of vessel sealing devices, such as the Harmonic scalpel or Ligasure, and decreasing use of intra-operative PTH monitoring during parathyroidectomy.

CONCLUSION

Surgeons are coming under increasing scrutiny and they need to demonstrate that their outcomes are acceptable, for their own satisfaction in addition to meeting the needs of patients, commissioners and regulatory bodies. This is particularly pertinent to thyroid and parathyroid surgery, as outcomes are clearly under the direct influence of the operating surgeon, and publication of these outcomes is already occurring in the public domain.

Estimation of complication rates from published case series is highly problematic. Participation in national registries contributes to more accurate analysis of outcomes, and is recommended to all surgeons with an interest in thyroid and parathyroid surgery.

KEY POINTS

- Assessment of complication rates of thyroid and parathyroid surgery from published data is prone to many limitations.
- Large case series and national registries suggest the following range of risk estimates:
  - Re-operation for bleeding 0.2–4.2%.
  - Early/transient recurrent laryngeal nerve palsy 0.7–5.1%.
  - Persistent recurrent laryngeal nerve palsy 0.2–1.0%.
  - Persistent hypocalcaemia (bilateral thyroid resection) 0.3–6.3%.
- There is a need for validated risk-adjustment models to be developed, if outcomes are to be accurately compared between healthcare providers.

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CHAPTER 81

MEDICOLEGAL ASPECTS OF HEAD AND NECK ENDOCRINE SURGERY

Barney Harrison

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: thyroid, thyroidectomy, litigation, malpractice, informed consent and medicolegal.

INTRODUCTION

England and Wales have among the highest level of personal injury damages awards in the world, with an increasing frequency of claims. In England, the number of surgery claims received by the National Health Service Litigation Authority (NHSLA), which manages negligence and other claims against the NHS on behalf of its member organizations, rose by 66% from 2009 to 2013 with General Surgery representing 33.8% and Others – including ENT – 2.5%. Since 2011 the annual payments made by the NHSLA in respect of clinical negligence have exceeded a billion pounds per year.

Clinical negligence claims in 2013/14 were 11 945 compared with 10 129 in 2012/13. In 2013/14, 44% of clinical negligence claims were resolved without a payment and 79% of the small number of cases that were decided in court (historically less than 5%) were successfully defended at trial.

THE LAW

A successful claim of medical negligence is required to prove that:

- the treatment received fell below the reasonable/accepted standard of competence that a patient had a right to expect – **breach of duty of care**
- the patient suffered an injury or loss – **damage**
- it is more likely than not that the injury would not have occurred or been less severe if appropriate treatment had been given, i.e. there is a link between the breach of duty and the injury – **causation.**

The claim must be brought within a specific time after the injury – **period of limitation.**

Successful damages awards will reflect two elements:

- pain, suffering 'loss of amenity'
- financial loss and extra expenses caused by the injury.

THE LIKELIHOOD AND FACTS AROUND LITIGATION AND THYROID SURGERY

Legal systems around the world differ but, in general, cases that arise from medical negligence that end up in court are civil prosecutions. In relation to thyroid surgery the studies described below provide some insight into the likelihood and outcome of claims or prosecutions reaching court subsequent to thyroid surgery.

Europe

From England, the NHSLA recorded 17 claims related to thyroidectomy and vocal cord dysfunction between 1995 and 2005.[1]

A German report[2] reviewed outcomes of 75 thyroidectomy-related malpractice claims in which expert opinion was provided by a single 'witness' over a 15-year period. Unilateral vocal cord palsy was the cause of the action in 28%, bilateral vocal cord palsy in 29%, hypoparathyroidism (all patients requiring calcium and vitamin D) alone in 13%. In 37% of the cases more than one major complication occurred. The claimant was successful in 77% of bilateral RLN palsies, 24% of unilateral palsy and 25% in post-operative hypoparathyroidism.

A prior German study[3] found that between 1975 and 1998 thyroidectomy represented 1% of litigation cases. A successful claim was more likely if a second operation was necessary, if the goal of the operation had been missed, or if any kind of complication was followed by a fault in post-operative care.

USA

Three studies are based on data from the Physicians Insurers Association of America said to represent 60% of privately insured physicians in the United States and 25% of malpractice claims.

Over a 24-year period, approximately 2 585 000 thyroidectomies were performed. The authors[4] estimated from their study that 5.9 claims are filed per 10 000 thyroid operations. Of thyroidectomy-related claims, 11% went to trial and a third (2 per 10 000) resulted in an indemnity payment.

Between 1986 and 2007, 112 closed claims (claims made irrespective of whether dismissed, settled or went to trial) were identified involving iatrogenic vocal cord palsy.[5] Of these, 42% resulted from thyroid and parathyroid surgery. Failure to recognize the complication and consent issues were responsible for 36% and 19% of the claims respectively.

A review of 315 closed malpractice claims related to otolaryngology–head and neck surgery between 1978 and 2007 found that nerve injuries accounted for 20.3% of claims including the accessory (5.4%) and recurrent laryngeal nerve (3.5.%); 5.1% of claims related to thyroidectomy.[6]

Two studies from the USA have assessed thyroid-related claims that went to court, the cases identified by review of legal databases.

Of 30 thyroid-related post-verdict cases (1987–2000), 33% were associated with surgical complications.[7] In respect of nine RLN injuries, the claim related to lack of informed consent in seven cases. In six of eight cancer-related cases, the claim related to delayed diagnosis.

The second study identified 33 cases that went to court in relation to alleged negligence associated with thyroid surgery between 1989 and 2009.[8] Of these, 46% involved RLN injury (five bilateral, five unilateral, five unspecified), and 6% delayed diagnosis. The majority of the seven claims where the outcome favoured the plaintiff were filed because of a lack of informed consent.

Finally, a review of 81 spinal accessory nerve injury claims that went to trial (1985–2007) found that the causative procedure was lymph node biopsy (68%), and neck dissections in only 5%. Lack of informed consent and failure to diagnose the injury were the basis of the allegation in 21% and 20% respectively.[9]

CONSENT TO SURGERY

The importance of adequate informed consent prior to an intervention cannot be overstated, most importantly for best patient care and, secondly, as indicated above, your avoidance of undesired consequence if a claim of negligence is submitted.

In the UK, the General Medical Council document *Consent: patients and doctors making decisions together*[10] includes imperatives (as an overriding duty) with regard to providing information on diagnostic uncertainty, options for treatment, the potential benefits and risks. In addition the document recommends that it is your duty to ensure patients understand information and how this can be enhanced.

Further clarification on who may obtain consent, what should be discussed and how it should be recorded is provided in *Good surgical practice* published by The Royal College of Surgeons (2014).[11]

Risks will usually be 'side effects, complications, failure of an intervention to achieve the desired aim'. Additional information in the form of information leaflets can be useful, and is recommended, but should not be considered as a replacement for a thorough discussion with the patient.[12]

Historically if a claim for litigation arose in the UK, a legal test (*Bolam*) was applied to determine whether the conduct of a doctor could be supported by a responsible body of medical opinion. In the *Sidaway* judgment that followed it was for doctors to decide how much to inform a patient of the risks of a treatment. Since early 2015, following a judgment in the Supreme Court (*Montgomery* v. *Lanarkshire Health Board*), this no longer applies to the law on consent. It is now required that a doctor takes 'reasonable care to ensure that the patient is aware of any material risks involved in any recommended treatment and of any reasonable alternative or variant treatments'. A material risk is one to which a reasonable person would be likely to attach significance, i.e. a risk that might alter the particular patient's decision.

WHEN THINGS GO WRONG

In the UK, since 2014, NHS providers have been required to comply with a duty of candour. It places a legal duty on hospitals and other providers to inform and apologize to patients, or their families if there have been mistakes in their care that led to death, severe or moderate harm. The duty of candour legislation applies to all Care Quality Commission registered providers since 2015. This contractual statutory requirement is, of course, in addition to the ethical duty of a doctor to inform patients and their families when an incident has occurred.

Good surgical practice[11] emphasizes the requirement to inform patients as soon as possible of any harm that has occurred, to apologize and to offer reassurance.

A useful overview of the background and threshold levels at which disclosure should be applied can be found via the RCS website.[13]

A CLAIM ARISES...

The plaintiff's/defendant's solicitors will instruct an expert witness to provide a report on possible breach of duty and/or condition and prognosis. An expert witness should provide, from knowledge and experience, an independent and balanced opinion **for the court** (not the instructing lawyers) on the facts of a case, an explanation of 'technical' issues, a view on what is considered 'reasonable', and matters of causation (symptoms or condition) that have arisen as a result of damage.

Some of the typical issues on which an expert witness may be asked to provide an opinion in a thyroid/parathyroid medical negligence claim are discussed below with current relevant 'evidence'.

IMPACT OF A DELAY IN CANCER DIAGNOSIS

For patients with differentiated or medullary thyroid cancer there are staging and prognostic scoring symptoms that allow an opinion on outcome from the time of actual diagnosis. The expert, in relation to the impact of delay, is unlikely to be able to state (as is often asked) what might have been the prognosis at a previous point in time. The evidence base on the clinical significance of any delay in the diagnosis of thyroid cancer is very limited.

A study using data from the Korean Central Cancer Registry[14] assessed the impact of delay from thyroid cancer diagnosis to first curative treatment and found the small number of deaths in these patients precluded precise estimates. The lowest mortality was observed for patients who had surgery between 1 and 4 weeks after diagnosis but there was no clear pattern of increased risk found with delay of up to 12 weeks in thyroid cancer.

In a study cohort of 1355 patients with DTC,[15] factors influencing the prognosis of patients who died found that cancer mortality was 4% in patients who underwent initial therapy within a year, compared with 10% in the others. The 'delay' group had twice the cancer mortality at 30 years (6% compared to 13%).

In contrast, a study including 47 patients with a delayed diagnosis of differentiated thyroid cancer as a consequence of initial benign cytology – median delay 52 months; range 13–205 months – found no difference in 5-year disease-free survival when compared with a historical cohort of patients treated with 'immediate' surgery.[16]

FAILURE TO PERFORM A SECOND FNA OF A SUSPICIOUS THYROID NODULE

False negative thyroid FNA rates of <3%–10.2%[17, 18] are reported in patients subsequently confirmed as having thyroid cancer. As suspicious features on ultrasound are reported in 90% of patients with thyroid cancer **and** false negative FNA,[17] inadequate cytology (Thy1) or benign cytology (Thy2) in association with sonographic features of concern indicates at the very least a need for further FNA as recommended in the British Thyroid Association Guidelines.[19]

RECURRENT LARYNGEAL NERVE PALSY AND INTRA-OPERATIVE NERVE MONITORING

Risk factors for vocal cord palsy include Graves' disease, post-operative bleed, retrosternal, malignant, recurrent benign and malignant goitre, no identification of the recurrent laryngeal nerve.[20–23]

At thyroidectomy, intermittent intra-operative nerve monitoring (IONM) is useful for identification of the recurrent nerve and its branches, but loss of signal in at least one in three cases is not associated with post-operative nerve dysfunction. The limitation of intermittent IONM is that injury to the nerve from whatever cause is identified after the event. Implicit in its use is that IONM is carried out in the recommended manner.[24]

There are two key issues in the context of litigation.

- There is a lack of evidence that intermittent IONM is associated with a decrease in the risk of permanent vocal cord palsy at first time[25–28] and reoperative thyroidectomy.[28] Temporary nerve dysfunction in both operative scenarios appears to be reduced with IONM use.[25, 29]
- If nerve monitoring is used, what is the appropriate next step if there is loss of signal on the first side of a bilateral thyroid procedure? Continue with the second side or abandon the operation and await laryngoscopy? The risk of bilateral vocal cord palsy at thyroidectomy is variously reported as 1 to >3 per thousand cases.[30, 31] The next step will clearly depend upon the indication for surgery (benign vs malignant disease), the experience of the surgical team, the nature of the signal loss and familiarity with the technicalities of IONM. Two studies from the same unit[32, 33] propose staged thyroidectomy in this worrying scenario; both have limitations that affect the interpretation of their results.

The natural evolution from intermittent to continuous IONM and evolving technology may help resolve the limitations associated with its use.

APPROPRIATENESS OF AN INPATIENT STAY OF LESS THAN 24 HOURS AFTER THYROIDECTOMY IN THE CONTEXT OF NECK HAEMATOMA/HYPOCALCAEMIA

The instructing solicitors might enquire as to the safety of a less than 24 hour inpatient stay for a patient who developed neck haematoma after day-case surgery.

Risk factors for post-operative bleeding include reoperative surgery and bilateral procedures. Life-threatening neck haematoma that requires reoperation will occur in 0.6–2.1% of cases.[31, 34–37] Although most will occur within 6 hours of surgery, 20–37% will occur after 6–24 hours and 0–10% after 24 hours.[35, 36, 38]

An assessment of parathyroid function after completion or total thyroidectomy is mandatory. National specialist databases record post-operative hypocalcaemia rates of 21% (British Association of Endocrine and Thyroid Surgeons) after total thyroidectomy for MNG and, from Scandinavia, 6.4% patients required i.v. calcium after bilateral thyroidectomy.[34]

Post-operative measurement of serum calcium/PTH and/or routine calcium supplementation is used to identify and minimize risks of significant hypocalcaemia. Be aware that in patients who become hypocalcaemic, the lowest level of serum calcium is on or after the second post-operative day.[39,40] If a patient is discharged too soon, they may develop severe untreated hypocalcaemia.

EXPERIENCE OF THE SURGEON

There are an increasing number of publications to support the concept that high-volume thyroid surgeons have better patient outcomes than low-volume surgeons. This is reported for post-operative neck haematoma,[41,42] hypocalcaemia,[42,43] adequacy of thyroidectomy in patients with thyroid cancer[44] and RLN palsy.[22,42,43] There is, however, little consistency in what constitutes a high-, intermediate- or low- volume surgeon (**Table 81.1**).

Surgeon experience is particularly important in relation to paediatric cases.[45] Children whose thyroidectomy or parathyroidectomy was performed by a low-volume surgeon (<30 endocrine cervical per year) had more endocrine complications than those whose operation was performed by a high-volume surgeon (11% compared to 5.6%). Sosa[46] reported complication rates after thyroidectomy/parathyroidectomy in 1199 patients 17 years old or younger. Children had significantly higher endocrine-specific complication rates than adults after parathyroidectomy and thyroidectomy. Even when thyroidectomy is performed by high-volume surgeons, 7% of patients will require intravenous calcium[47] and post-operative hypocalcaemia is reported in 34% of children <10 years of age.[48]

TABLE 81.1 Variation in classifications of thyroid surgeon operative volumes

Author	Year	Low volume	Intermediate volume	High volume
Sosa[49]	1998	1–9 per year		>100 per year
Tuggle[45]	2008			>30 per year
Kandil[42]	2013	<10 in 10 years	10–99 in 10 years	≥100 in 10 years
Loyo[43]	2013	≤9 per year	9–23 per year	>23 per year
Dehal[41]	2014	<10 in 10 years	10–99 in 10 years	≥100 in 10 years
Adkisson[44]	2014	–		≥30 per year
Landerholm[50]	2014	–	<50 per year	–

KEY POINTS

- Ensure that thyroid function and serum calcium are normal prior to and after surgery. This is your responsibility unless someone else has agreed to take over these aspects of care.
- Ensure at the very least that the content and legibility of your clinical record, the consent form and the operation note would stand up to scrutiny by an 'expert' third party.
- The contents of an operation note should include that indicated in *Good surgical practice*. It would seem entirely appropriate and necessary in the context of thyroid/parathyroid surgery (for your potential benefit in a claim) to record findings related to the parathyroid glands and their preservation as well as the recurrent laryngeal nerves.
- Ensure that for complex patients (e.g. the non-compliant thyrotoxic patient) there is adequate peri-operative support from endocrinology colleagues.
- Post-operative laryngoscopy should be performed in a patient with post-operative voice symptoms.
- The defence of a claim will depend upon your statement of:
  - what you did – were you the appropriate surgeon?
  - why you did it – what were the indications for operation?
  - what your notes say
  - how you managed the complication(s).
- Be reassured that complications are not necessarily due to error.

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CHAPTER 82

CLINICAL EVALUATION OF THE PITUITARY PATIENT

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SEARCH STRATEGY AND EVIDENCE BASE

Data in this chapter may be updated by a Medline search using the keywords pituitary disease and pituitary adenoma and focusing on clinical features and ophthalmological assessment. The evidence in the chapter is mainly levels 3 and 4 but also with some level 2 evidence.

INTRODUCTION

The commonest lesion arising in the pituitary gland is a pituitary adenoma.[1] The clinical manifestations of pituitary adenomata may relate to their endocrine effects of hormone deficiency, hormone excess or a combination of both.[2] In addition there may be a physical effect related to a space-occupying lesion. Occasionally the presentation may be acute with infarction into a previously undiagnosed pituitary adenoma. Increasingly, with the widespread use of sophisticated imaging techniques, lesions within the pituitary gland may be identified before they become symptomatic, the so-called 'pituitary incidentaloma'.[3]

CLINICAL MANIFESTATIONS OF HORMONE DEFICIENCY

The syndrome of pituitary hyposecretion occurs when the mass effect of a lesion within the pituitary gland compresses the normal tissue leading to a reduction or absence of the normal secretion of pituitary hormones. This resulting hypopituitarism (**Figure 82.1**) affects the reproductive system most commonly.[4] Typically, women experience oligomenorrhoea or amenorrhoea with associated infertility; men commonly experience symptoms of hypogonadism, with increasing loss of libido and erectile dysfunction and associated infertility. There is a characteristic delayed onset of puberty in those adolescents affected.



Figure 82.1 Hypopituitarism.

A specific effect of growth hormone hyposecretion in children and adolescents may result in reduced growth velocity and short stature. Thyrotropin (TSH) deficiency leads to mild hypothyroidism with low but not absent levels of circulating T4 and T3. The thyroid is capable of low-grade autonomous secretion of thyroid hormones so symptomatically and biochemically central hypothyroidism is not as profound as primary thyroid failure. It is, however, often missed due to 'TSH-only' screening policies in primary care when a TSH can be normal but inappropriately so for the low levels of circulating T4 and T3.

Adrenocorticotropic hormone (ACTH) deficiency results in symptoms of lethargy, postural hypotension and electrolyte disturbance (hyponatraemia) but, again, this may not become manifest until the patient with a pituitary adenoma is placed under physiological stress with an intercurrent infection or illness and is unable to mount an appropriate cortisol stress response. Varying degrees and combinations of hormone insufficiency may be manifest in a patient with a pituitary adenoma and invariably present with insidious onset.

Prolactin (PRL) is a pituitary hormone related to the lactation response, with its own functional suppressive effect on pituitary luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which constitutes nature's own 'natural contraceptive'. It is under tonic inhibition from hypothalamic dopamine delivered down the pituitary stalk. As a result, anything interrupting the secretion of dopamine can cause an ambient rise in PRL, commonly between 1000 mU/L and 5000 mU/L (NR < 450), often referred to as 'stalk hyperprolactinaemia'.[5] PRL is therefore the last hormone to become deficient in the presence of a pituitary lesion. Clinically hypoprolactinaemia is significant only if it occurs in the postpartum period as part of Sheehan's syndrome. This is a vascular problem and not usually related to the presence of a pituitary adenoma.

Diabetes insipidus is a deficiency of one of the posterior lobe pituitary hormones, arginine vasopressin (AVP), previously known as antidiuretic hormone (ADH). Diabetes insipidus is much rarer at presentation in patients with pituitary adenomas whatever their size and, if present, alternative diagnoses, such as craniopharyngiomas, germinomas, metastases or inflammatory pituitary lesions (sarcoidosis, Generalized Polyangiitis, Langerhans cell histiocytosis) should be considered. Of course, surgical intervention is a recognized cause of diabetes insipidus which may be just transient or permanent following transphenoidal or transcranial surgery. The clinical effects of pituitary deficiency are shown in Table 82.1.

Pituitary hormones can be given pharmacologically (e.g. GH, AVP (DDAVP), LH (HCG) or FSH) or the end-organ hormone can be replaced (e.g. hydrocortisone, thyroxine, testosterone, oestrogen/progesterone) to ensure homeostasis titrated to normal physiological and clinical function.

TABLE 82.1 Pituitary hormone deficiency: modes of presentation

Hormone deficiency	Presentation
Hypogonadism (LH/FSH)	Amenorrhoea Infertility Erectile dysfunction Loss of libido
Hypoadrenalism (ACTH) (hypocorticosteroidism)	Malaise Hypotension Hypoglycaemia Hyponatraemia
Hypothyroidism (central (TSH))	Tiredness, lethargy, dry hair, dry skin
Growth hormone deficiency	Lethargy, reduced exercise capacity, central adiposity, reduced muscle mass, premature coronary artery disease, reduced bone density and short stature
AVP (ADH) deficiency	Diabetes insipidus (polyuria/polydipsia) Hypernatraemia Dehydration/coma

CLINICAL MANIFESTATIONS OF EXCESS HORMONE SECRETION

Excessive hormone secretion by a pituitary adenoma produces several classical clinical syndromes (Table 82.2).

Prolactinoma

The commonest type of secreting pituitary adenoma is the prolactinoma, accounting for approximately 40% of adenomas.[1] Prolactin is a peptide hormone that stimulates mammary tissue to produce milk. The hormone also counteracts the effects of dopamine, which is thought to be responsible for sexual arousal. This antagonist effect of PRL is thought to cause reduced libido and impotence.

Until the 1970s surgery was the mainstay of treatment for prolactinoma but, following the introduction of the dopamine 2 receptor agonist Bromocriptine, the majority of prolactinomas are now treated medically. Bromocriptine has a significant side effect profile in certain patients (nausea, nasal stuffiness, postural hypotension) and hence newer dopamine agonists such as

TABLE 82.2 Excess pituitary hormone secretion

Hormone in excess	Clinical manifestation
Prolactin (prolactinoma or stalk compression)	Galactorrhoea Amenorrhoea infertility and loss of libido
Growth hormone	Acromegaly
ACTH	Pituitary-dependent Cushing's disease
TSH (TSHoma)	Central thyrotoxicosis (rare)
FSH/LH (gonadotrophinoma)	Macrogonadism (extremely rare)





Figure 82.2 Clinical features of hyperprolactinaemia.

Quinagolide (non-ergot) and Cabergoline have become useful alternative drugs in the management of prolactinomas. Dopamine agonists will reduce PRL levels whatever the cause but in addition will cause significant tumour shrinkage and involution in true prolactinomas – often diagnostically so. Non-shrinkage of a pituitary lesion (on serial MRI) despite a good suppression of PRL means that the lesion is unlikely to be a true prolactinoma and the elevated PRL is due to 'stalk hyperprolactinaemia'. This may change management towards a more surgical approach.

Recent concern has been raised about the potential for Cabergoline to cause cardiac valvulopathy with long-term high-dose use.[6] The most recent analyses, however, reassure us that this is unlikely to occur in prolactinoma patients in the doses we use in endocrine practice.[7]

CLINICAL FEATURES

See **Figure 82.2** and **Table 82.3**.

The presenting features of a prolactinoma are related to hyperprolactinaemia, the mass effect of the tumour and other associated endocrine insufficiencies or more rarely pituitary apoplexy.

HYPERPROLACTINAEMIA

The features of hyperprolactinaemia in females and males are shown in **Table 82.3**. Osteoporosis occurs in both males and females as a result of oestrogen and testosterone deficiency, and bone density should be assessed appropriately as part of the initial and long-term management strategy.

TABLE 82.3 Clinical features of prolactinoma/hyperprolactinaemia

Patient gender	Clinical features
Female	Galactorrhoea Loss of libido Infertility Irregular menses Osteoporosis
Male	Loss of libido Gynaecomastia Infertility Osteoporosis

The tumour may present with features related to that of an expanding mass within the pituitary fossa, reduction in visual fields and/or acuity as a result of pressure on the under surface of the optic chiasm, or more rarely with involvement of cranial nerves within the cavernous sinuses (III, IV, VI). Headache may be present and is considered to be related to stretching of the overlying dura. Very large prolactinomas may present with hydrocephalus and deterioration in cortical brain function with lateral extension resulting in temporal lobe

symptoms which usually resolve with surgical resection or more commonly dopamine agonist-induced tumour involution.

DIFFERENTIAL DIAGNOSIS OF HYPERPROLACTINAEMIA

Hyperprolactinaemia is also associated with conditions other than pituitary adenomas (Table 82.4). In particular 'stalk compression' of the hypothalamic pituitary pathway by any form of mass lesion in the pituitary fossa may interrupt dopamine inhibition of prolactin-secreting cells resulting in hyperprolactinaemia as previously mentioned.

Acromegaly

Acromegaly is a disorder of adults as a consequence of the overproduction of growth hormone which results in significant changes to the patient's appearance over considerable time. If growth hormone excess occurs before fusion of the epiphyses in adolescence, the condition is known as pituitary gigantism.

The commonest underlying cause of acromegaly is that of a spontaneously occurring pituitary adenoma, although rarely it may be a result of a genetic syndrome such as multiple endocrine neoplasia type I (MEN I – along with parathyroid and pancreatic endocrine tumours), GSP mutations, McCune–Albright syndrome[8] or more recently familial acromegaly due to mutation in the aryl hydrocarbon receptor protein.[9]

Pituitary tumours occasionally co-secrete other hormones such as growth hormone and prolactin (somatomamotroph adenomas) occasionally with the additional secretion of TSH causing central hyperthyroidism. Co-secretion of prolactin often indicates a co-responsivity to the suppressive effects of dopamine agonists.

INCIDENCE

Acromegaly has an incidence of 3–4 per million per year with an incidence in the general population of approximately 60 cases per year. This condition affects all races and both sexes with patients typically presenting between the ages of 40 and 50 years.[10]

TABLE 82.4 Differential diagnosis of hyperprolactinaemia

Underlying cause	Differential diagnosis
Physiological	Pregnancy Breastfeeding Mental stress
Drugs	Drugs antagonizing the effects of dopamine including major tranquilizers (phenothiazines and haloperidol) Metoclopromide Domperidone and methyldopa and the combined oral contraceptive pill
Diseases	Chronic renal failure Hypothyroidism Bronchogenic carcinoma Sarcoidosis Idiopathic

CLINICAL FEATURES

Acromegaly has an insidious onset with features of bone and soft-tissue overgrowth. The initial features include changes in shoe size, ring size and coarsening of facial features (Figure 82.3). However, symptom onset is non-specific with sweating, lassitude and musculoskeletal pain resulting in a concomitant delay of diagnosis. The mean time to diagnosis is 8 years with a range of 6–10 years.[11]

Table 82.5 includes the features commonly associated with a diagnosis of acromegaly. Consideration of these should prompt further investigation.

Acromegaly is recognized as causing reduction in life expectancy by up to 10 years in those untreated.[11] Suppression of growth hormone levels to < 1 µg/L and normalization of IgF1 (age and sex adjusted), returns the death rate to that expected of the normal background population.[12] The increase in mortality is related to duration of symptoms prior to diagnosis, disease duration, increasing age and presence of complications at diagnosis.[13]

Reduction in morbidity and mortality relies upon prompt diagnosis and early investigation and treatment. General practitioners and primary care physicians should be alert to the possibility of agromegaly in patients presenting with coarse features, excess sweating, increased ring or shoe size and sleep apnoea,[14] resistant hypertension unresponsive to three or more agents and/or difficult-to-control diabetes.

Cushing's disease

Cushing's syndrome is the term applied to a wide group of disorders with symptoms and signs due to chronic exposure to excess glucocorticoid, irrespective of the underlying cause. The commonest cause is exogenous steroid treatment.

Cushing's disease is the term applied to Cushing's syndrome of pituitary origin (pituitary-dependent adrenal hyperplasia). The disease was described by Harvey Cushing in 1932 as pituitary basophilism.

Table 82.6 shows the causes of endogenous Cushing's syndrome and their approximate frequency.

AETIOLOGY

Cushing's disease often presents with non-specific symptoms which may be slowly progressive and therefore missed as a developing condition in primary care. The mean time to diagnosis after the first presenting symptom is 6 years.[15] Chances to diagnose are often missed in clinical consultations. Cushing's disease mimics common conditions such as obesity, poorly controlled diabetes and hypertension and consideration may not be given to its possibility by the treating doctor.



Figure 82.3 Clinical features of acromegaly.

TABLE 82.5 Features commonly associated with acromegaly

Disorder type	Feature(s)
Musculoskeletal	Macroglosia, enlargement of lips, hands and feet Prominent brow Prognathism, interdental separation Skeletal abnormalities – degenerative osteoarthritis Carpal tunnel syndrome and hearing loss
Cardiovascular	Hypertension Cardiomyopathy Arrhythmias Heart failure
Respiratory	Obstructive sleep apnoea
Metabolic	Diabetes mellitus Excess sweating
Gastrointestinal	Colonic polyps

TABLE 82.6 Aetiology of Cushing's Syndrome

Cause of Cushing's Syndrome	F:M	%
ACTH-dependent[a]		
Cushing's disease	3.5:1[b]	70
Ectopic ACTH syndrome	1:1	10
Unknown source of ACTH[c]	5:1	5
ACTH-independent	4:1	10
Adrenal adenoma	1:1	5
Adrenal carcinoma		<2
Other causes (PPNAD, AIMAH, McCune-Albright)		

Note: PPNAD primary pigmented nodular adrenal disease, AIMAH ACTH-independent massive adrenal hyperplasia.

[a] In women 9:1 ratio of Cushing's disease to ectopic ACTH
[b] Male preponderance in children
[c] Patients may ultimately prove to have Cushing's disease, ectopic CRH <1% of all cases of ACTH-dependent disease



Figure 82.4 Clinical features of Cushing's disease.

Untreated, Cushing's disease is associated with a 50% mortality rate at 5 years, commonly as a result of cardiovascular complications.[16] Significant morbidity results from irreversible organ damage over a prolonged period.

CLINICAL FEATURES OF CORTISOL OVERPRODUCTION

The features of excess cortisol exposure are well described – the typical central obesity, plethora and spontaneous purpura (Figure 82.4). However, it is important to realize that certain features are of more diagnostic value than others (Table 82.7).[17]

It is important to assess the use of exogenous glucocorticoid and in particular the use of inhalers and skin creams. Several photographs of the patient's appearance over a period of months to years may also indicate the developing changes in appearance associated with Cushing's disease.

TABLE 82.7 Clinical value of symptoms and signs of Cushing's disease

Clinical diagnostic value	Symptoms and signs
High	Skin atrophy Proximal myopathy and wasting Bruising Childhood growth arrest Osteoporosis
Medium	Oedema Striae Moon face Facial hirsuitism Labile mood
Non-specific	Buffalo hump Hypertension Diabetes mellitus Plethora Acne

NEURO-OPHTHAIMOLOGICAL FEATURES OF PITUITARY DISEASE

The relationship between the optic chiasm and pituitary gland is intimate with lesions expanding superiorly out of the pituitary fossa impacting on the chiasm.

Afferent visual pathway

The optic nerves transverse the orbit and pass through the optic canal where their dural sheath fuses to the wall of the canal. In up to 4% of patients the optic nerves may be dehiscent of bone as they traverse the lateral wall of the sphenoid sinuses.[18] The intra-cranial portion of the optic nerve passes superiorly and medially to form the optic chiasm. Chiasm is named after the Greek letter chi but in life more closely resembles the letter H. Within the chiasm 50% of the axons within each optic nerve decussate to run in the opposite optic tract to the centres higher in the brain.

The location of the chiasm relative to the pituitary gland varies. In the vast majority it lies directly above the pituitary fossa but in a minority of patients it may either be anterior (pre-fixed), or posterior to the pituitary (post-fixed) above the dorsum sellae. On average[19] it lies approximately 10 mm above the pituitary gland, although in a minority (14%) it may be as little as 2 mm above it.

Efferent pathways

Within the cavernous sinus on either side of the pituitary fossa lie the cranial nerves responsible for eye movements and papillary responses to light. Figure 82.5 shows the relationship of the oculomotor, trochlear and abducens nerves within the cavernous sinuses. The oculomotor is the nerve most frequently involved by pituitary adenoma expansion. Also within the cavernous sinuses lie the ophthalmic and maxillary divisions of the trigeminal nerve.

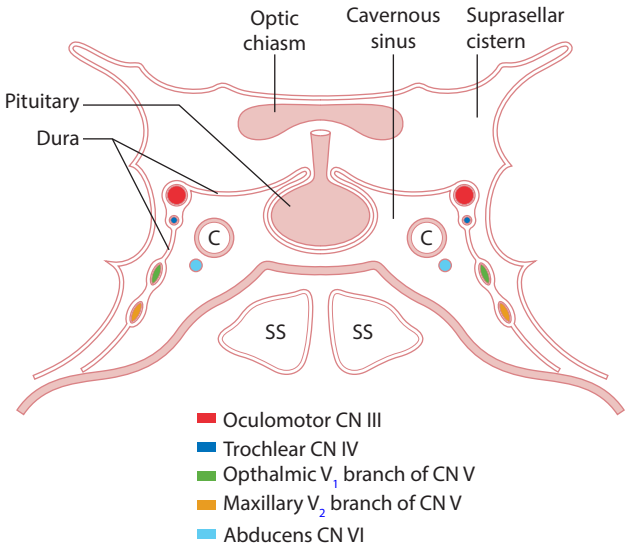


Figure 82.5 Cavernous sinus.

Ophthalmic presentations related to pituitary disease

The classic presentation of an expanding non-functioning pituitary tumour is a bitemporal hemianopia caused by compression of the axons within the chiasm (Figure 82.6). Typically a superior quadrantanopia occurs initially as the axons subserving the temporal visual fields are involved initially by the pituitary compression from below. It should be noted that visual acuity can also be affected. In addition, pituitary tumours do not always respect the midline and can give an asymmetrical visual field defect. A pre- and post-fixed chiasm would produce variable hemianopias, an important consideration when assessing the visual fields.

Clinically patients may not be aware of selective visual field loss, although with progression symptoms may become apparent, for example failing to notice the edges of a doorway when walking through it and bumping into it. Prolonged compression of the optic fibres results in atrophy of the optic disc noted on fundoscopy. More severe or generalized atrophy is associated with a poorer prognosis to visual recovery.[20]

Formal assessment of visual fields should be undertaken by a specialist technician to minimize operator dependency and ensure accuracy. Static perimetry techniques (Goldman visual field assessment) have largely been replaced by kinetic perimetry. The Humphrey visual field analyser (Figure 82.7) consists of a bowl-shaped background of set luminescence. The patient fixates on a central target and presses a button when a light stimulus in the periphery is perceived. Testing takes up to 30 minutes for both eyes and is largely automated, reducing margins for error.

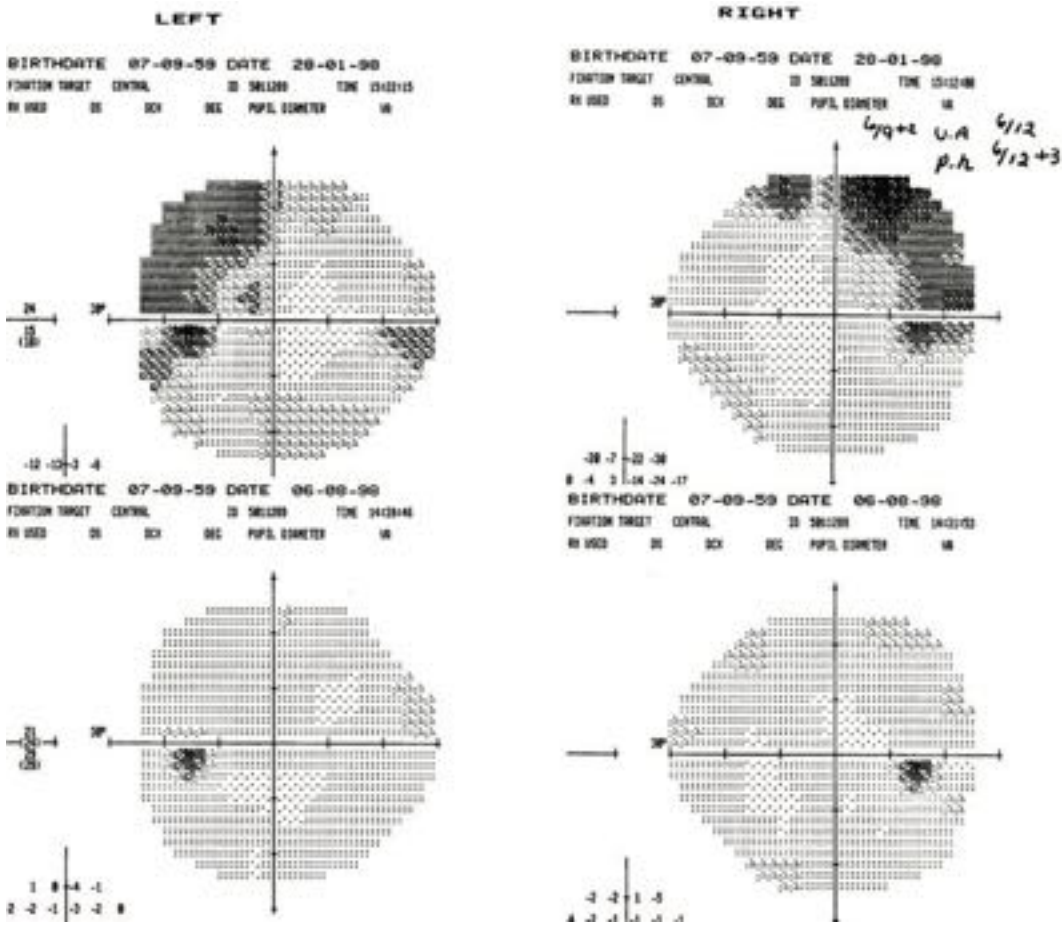


Figure 82.6 Bitemporal hemianopia.



Figure 82.7 The Humphrey visual field analyser.

Motor nerve involvement

Pituitary tumours also have a tendency to compress or invade the cavernous sinus as they expand. In the majority of cases this involvement is asymptomatic but pituitary apoplexy characteristically presents with severe headache and, on occasion, acute oculomotor nerve palsies and hemianopias with loss of acuity. However, all cranial nerves within the cavernous sinus may be involved with palsies potentially affecting III, IV and VI. There is a consequent diplopia and reduced range of ocular movement. Involvement of the sympathetic fibres may result in a Horner's syndrome and facial sensation may be disturbed by involvement of the ophthalmic and maxillary divisions of the trigeminal nerve. Visual field disturbances are much more common than those of ocular motor nerves but in each case formal assessment, documentation and management should be undertaken by a specialist neuro-ophthalmologist.

Vision following surgical decompression

All large series demonstrate a majority of patients experience visual improvement following surgery to macroadenomas with optic apparatus involvement. A study of 67 patients undergoing resection of adenomas compressing the visual pathway reported 88% showing improvement of visual function, despite half of those having significant optic atrophy.[21] Another study demonstrated normalization in 35% of eyes and improvement in 60%.[20] In keeping with most studies the duration and severity of visual field involvement directly affects prognosis for visual recovery. Recovery of vision can be equally dramatic with medical management of a macroprolactinoma with dopamine agonists. Radiotherapy treatment alone is rarely if ever used in this situation as it can pose an additional threat to the optic apparatus. Surgical debulking is invariably recommended prior to adjuvant radiotherapy.

TSHomas

Pituitary thyrotrophin-secreting adenomas (TSHomas) are extremely rare tumours causing hyperthyroidism by chronic stimulation of a normal thyroid gland. In the past 50 years approximately 50 cases have been reported in literature.[22]

Patients present with signs and symptoms of hyperthyroidism, commonly thyrotoxicosis and a goitre with a vascular bruit. The characteristics of this condition are centrally driven thyrotoxicosis with high levels of thyroid hormones in the presence of detectable and invariably elevated TSH and alpha subunit levels.

Gonadotrophinoma

These tumours are often indistinguishable from other non-functioning pituitary adenomas as they are usually 'silent' and not associated with excess secretion of LH and FSH. Therefore, they are usually detected upon histological analysis following operative intervention for a clinically and biochemically non-functioning pituitary macroadenoma.

Non-functioning adenomas

A systematic review of pituitary adenomas in 2004 reported an estimated prevalence of 16% in the population.[1] Non-functioning adenomas are the most common subgroup requiring surgical intervention.

Occasionally, apparently functionless pituitary adenomas will stain for ACTH in the absence of biochemical or clinical cortisol excess. It is important to note this category of pituitary adenoma, the so-called 'silent corticotrophinoma', as they are more prone to physical recurrence and require more assiduous post-decompressive surveillance and early recourse to external beam radiotherapy (EBRT) is often indicated.

True null cell adenomas are rare, accounting for less than 10% of non-functioning adenomas biopsied and examined histologically.

Non-functioning adenomas commonly present as expanding pituitary lesions (visual disturbance), as hypopituitarism or as lesions found incidentally on CT or MRI of the brain. The clinical manifestations of hypopituitarism and stalk compression have already been discussed.

These patients with non-functioning adenomas should be assessed for the loss of visual fields and visual acuity, as well as an assessment of pituitary hormone status. Management may involve serial MR imaging for small asymptomatic lesions, or a combination of surgery or radiotherapy for symptomatic lesions.

Pituitary apoplexy

This is an uncommon but well-described clinical presentation found in a small minority of pituitary adenomas.[23] It occurs as a result of either haemorrhage into or infarction of a pituitary adenoma and may be the presenting feature of a previously undiagnosed tumour.[24] The typical features are of a sudden severe headache mimicking subarachnoid haemorrhage, which may be associated with a deterioration in visual acuity or visual fields. Subsequently an acute loss of pituitary hormones may produce acute adrenal insufficiency or diabetes insipidus or the so-called 'triple response' of transient diabetes insipidus rapidly followed by a period of syndrome of inappropriate antidiuretic hormone (SIADH) and

hyponatraemia due to disordered AVP leakage with ultimate exhaustion of AVP stores and a return to diabetes insipidus.[25] It is important to recognize this phenomenon acutely and in the post-operative period as it requires close monitoring of serum and urine electrolytes/osmolalities and fastidious attention to fluid balance, fluid type and the timely use of fluid restriction or DDAVP® administration dependent on which phase the patient is going through.

Larger tumours are more prone to bleeding and more rapidly growing lesions may be at a high risk of apoplexy.[23] Initially, aggressive medical management is appropriate with high dose steroids both to replace the acute adrenal insufficiency and to provide anti-inflammatory effect if visual disturbance is minimal, provided there is close observation of the patient. Deterioration in symptoms or lack of spontaneous improvement indicates the need for surgical intervention.[26]

CONCLUSIONS

Lesions within the pituitary fossa generally present either with disturbance of pituitary hormone function or as a result of a mass lesion extending outside the pituitary fossa. Mass lesions most commonly result in deficiencies in the patient's visual field or more rarely with cranial nerve palsies.

All lesions within the sellar or parasellar areas require a comprehensive endocrine evaluation and, if there is a lesion approximating the optic chiasm or apparatus a specialist opthalmological assessment should also be made.

Endocrine assessment should continue in the post-treatment phase in order that any hormone deficiencies are corrected.

KEY POINTS

- All lesions involving the pituitary fossa should undergo a formal endocrinology assessment.
- The commonest secreting adenoma is a prolactinoma, the majority of which are managed medically.
- Untreated, acromegaly and Cushing's Disease are life shortening conditions.
- Macroadenomas may not produce a classical bitemporal field defect.
- Pituitary apoplexy is an emergency and may require surgical intervention.

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CHAPTER 83

INVESTIGATION OF PITUITARY DISEASE

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SEARCH STRATEGY

The information in this chapter is taken from standard UK endocrinology clinical practice. It reflects expert opinion (level 4 evidence) with regard to endocrinology tests currently performed in the UK.

Data in this chapter may be updated by a Medline search using the keywords: prolactin, IGF-1, ACTH stimulation test, dexamethasone suppression test, pituitary function testing, SIADH, diabetes insipidus, Cushing's disease, acromegaly, pituitary adenoma and hypopituitarism.

INTRODUCTION

The pituitary gland lies in the sella turcica which is situated in the middle cranial fossa at the base of the brain. It is linked functionally to the hypothalamus by the pituitary stalk. The anterior pituitary secretes growth hormone (GH), thyrotropin or thyroid-stimulating hormone (TSH), corticotropin or adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH), all of which are under positive stimulatory control, and prolactin (PRL) which is under the inhibitory control of dopamine. The posterior lobe releases arginine vasopressin (AVP, also called antidiuretic hormone) and oxytocin.

INVESTIGATING ANTERIOR PITUITARY DYSFUNCTION

The anterior pituitary hormonal secretion is regulated by hypothalamic releasing and inhibitory factors delivered via portal capillaries, and by negative feedback inhibition of the respective hormones secreted by the target endocrine glands such as the thyroid gland and adrenal cortex.

The presentation of anterior pituitary disease, most commonly associated with a structural lesion, may result from:

- local mass effects – causing headache, visual field defects and ocular nerve palsies
- pituitary hormone deficiencies – producing wide-ranging effects as a result of single or multiple deficiencies, with GH and gonadotropins (LH and FSH) usually affected first, followed much later by ACTH and TSH
- pituitary hormone hypersecretion – usually arising as a consequence of neoplastic proliferation of particular cell types within the gland.[1, 2]

Investigation includes:

- tests for hormone hyper- or hyposecretion, by measuring TSH and thyroxine, FSH/LH and testosterone or oestradiol and prolactin – dynamic testing is required for the ACTH/cortisol axis and determination of GH deficiency or excess
- imaging – MRI is the modality of choice for radiological assessment
- neuro-ophthalmological evaluation, including assessment of visual acuity and visual fields.[3]

Investigating anterior pituitary hormonal hypersecretion

Pituitary masses may present with a typical clinical syndrome resulting from hypersecretion of one or more anterior pituitary hormones. Alternatively, they may present through compression of surrounding structures such as the optic chiasm or the adjacent normal pituitary, causing hypopituitarism. Functional pituitary tumours can produce a complex picture of combined hormonal excess and/or deficiencies.

LABORATORY INVESTIGATION

The presenting clinical features of functional pituitary adenomas (e.g. acromegaly, Cushing's syndrome) guide the laboratory studies. However, for a sellar mass with no obvious clinical features of hormone excess, laboratory studies are geared towards determining the nature of the tumour and assessing the possible presence of hypopituitarism. When a pituitary adenoma is found incidentally on MRI scan, the initial hormonal evaluation will be guided by the history and clinical examination to look for signs of hormone excess including: (i) prolactin; (ii) insulin-like growth factor- 1 (IGF-I); (iii) 24-hour urinary free cortisol and/or overnight oral dexamethasone (1 mg) suppression test; (iv) α-subunit, FSH and LH; and (v) thyroid function tests (free T4 and TSH). Additional hormonal evaluation may be indicated based on the results of these tests (**Table 83.1**). Pending more detailed assessment of hypopituitarism, 8 a.m. cortisol and testosterone levels, and thyroid function tests usually identify patients with pituitary hormone deficiencies that require hormone replacement before further testing or surgery.[4]

Diagnosis of hyperprolactinaemia

Basal morning PRL levels should be measured to assess hypersecretion. It may be necessary to measure prolactin levels on different occasions when clinical suspicion is high. Since prolactin may be elevated as a stress response in a random sample, cannulated prolactin levels with samples taken through a cannula at 60-minute intervals after insertion to reduce this stress response can be helpful.[5] In patients with markedly elevated PRL levels (>2000 mU/L), results may be falsely lowered because of assay artefacts (the high-dose hook effect); sample dilution is required to measure these high values accurately, but it is rare with modern assays. Falsely elevated values may be caused by aggregated forms of circulating PRL, which are biologically inactive (macroprolactinemia).[6] Hypothyroidism should be excluded by measuring serum TSH and T4 levels.

Diagnosis of acromegaly

Age- and gender-matched serum IGF-I levels are elevated in acromegaly. Consequently, an IGF-I level provides a useful laboratory screening measure when clinical features raise the possibility of acromegaly. Due to the pulsatility of GH secretion, measurement of a single random GH level is not useful for the diagnosis or exclusion of acromegaly and does not correlate with disease severity. The diagnosis of acromegaly is confirmed by demonstrating the failure of GH suppression to <1 μg/L within 1–2 hours after a 75 g oral glucose load.[7] PRL is elevated in approximately a quarter of patients with acromegaly. Thyroid function, gonadotropins and sex steroids may be reduced because of tumour mass effects. Since most patients will undergo surgery with glucocorticoid coverage, tests for ACTH reserve in asymptomatic patients could be deferred until after surgery.[8]

Diagnosis of Cushing's disease

The diagnosis of Cushing's syndrome is based on laboratory documentation of endogenous hypercortisolism.[9] Measurement of 24-hour urine free cortisol is often used as the screening test, ideally two collections with measurement of creatinine that should not differ by more than 10% to indicate adequacy of collection. Alternatively, the failure to suppress plasma cortisol after an overnight 1 mg dexamethasone suppression test can be used to identify patients with hypercortisolism. However, this test has a false positive rate of 2% in the normal population, 13% in obese subjects and 23% in hospital inpatients and is not favoured by many clinicians. A low-dose dexamethasone suppression test is also used to confirm hypercortisolemia, which has a higher sensitivity of 98% for screening Cushing's syndrome. This is done by administering 0.5 mg of dexamethasone 6 hourly for 48 hours at 9 a.m., 3 p.m., 9 p.m. and 3 a.m., and should lead to complete suppression of cortisol to <50 nmol/L in normal subjects with serum cortisol measurement at baseline and 48 hours. As nadir levels of cortisol occur at night, elevated midnight samples of cortisol are suggestive of Cushing's syndrome and this test will require admission to hospital. More recently, however,

TABLE 83.1 Baseline tests to evaluate pituitary hormone hypersecretion

Disorder	Tests	Comments
Acromegaly	Serum IGF-I	Interpret IGF-I relative to age- and gender-matched controls
	Oral glucose tolerance test with GH obtained at 0, 60 and 120 min	Normal subjects should suppress growth hormone to <1 μg/L
Prolactinoma	Serum prolactin	Prolactin levels can be higher in patients who take medications including antidepressants, antipsychotics and antiemetics as well as some over-the-counter medications and homeopathic remedies MRI of the pituitary if prolactin significantly elevated (<2000 mU/L)
Cushing's disease	24-hour urinary free cortisol	Ensure urine collection is total and accurate ideally with 2 × 24-hour samples with measurement of creatinine that should not differ by more than 10%
	Dexamethasone (1 mg) at 11 p.m. and plasma cortisol measured at 8 a.m.	Normal subjects suppress to <1.8 μg/dL (< 50 nmol/L)
	ACTH assay	Distinguishes adrenal adenoma (ACTH suppressed) from ectopic ACTH or Cushing's disease (ACTH normal or elevated) after biochemical confirmation of hypercortisolemia

midnight salivary free measurements have been used which are simpler. Basal plasma ACTH levels often distinguish patients with ACTH-independent (adrenal or exogenous glucocorticoid) from those with ACTH-dependent (pituitary, ectopic ACTH) Cushing's syndrome.[10] Mean basal ACTH levels are about eightfold higher in patients with ectopic ACTH secretion compared to those with pituitary ACTH-secreting adenomas. However, extensive overlap of ACTH levels between these two disorders (ectopic ACTH versus pituitary ACTH-secreting adenoma) precludes using ACTH to make the distinction.[11]

If the investigations are highly suggestive of pituitary Cushing's disease, then pituitary MRI with gadolinium enhancement is undertaken but it is often not sensitive enough to detect small (<2 mm) pituitary ACTH-secreting adenomas. In this case, bilateral inferior petrosal sinus ACTH sampling before and after corticotropin-releasing hormone (CRH) administration may be required to distinguish a pituitary lesion from ectopic ACTH-secreting tumours that may have similar clinical and biochemical characteristics.[12] Simultaneous assessment of ACTH concentrations in each inferior petrosal vein and in the peripheral circulation provides a strategy for confirming and localizing pituitary ACTH production. Sampling is performed at baseline and 2, 5 and 10 min after intravenous bovine CRH (1 μg/kg) injection. An increased ratio (>2) of inferior petrosal to peripheral vein ACTH confirms pituitary Cushing's syndrome. After CRH injection, peak petrosal-to-peripheral ACTH ratios of ≥3 confirm the presence of a pituitary ACTH-secreting tumour when there is unequivocal endogenous hypercortisolemia. The sensitivity of this test is >95%, with rare false-negative results encountered in patients with aberrant venous drainage. Petrosal sinus catheterizations are technically difficult, and about 0.05% of patients develop neurovascular complications.

Most ACTH-secreting pituitary tumours are <5 mm in diameter, and about half are undetectable by sensitive MRI. The high prevalence of incidental pituitary microadenomas diminishes the ability to distinguish ACTH-secreting pituitary tumours accurately by MRI.

Diagnosis of TSH-secreting adenomas

TSH-producing macroadenomas are rare but are often large and locally invasive when they occur. Patients usually present with thyroid goitre and hyperthyroidism, reflecting overproduction of TSH. Diagnosis is based on demonstrating elevated serum free T4 levels, inappropriately normal or high TSH secretion, and MRI evidence of a pituitary adenoma.[13] The commonest cause of elevated FT4 and normal or high TSH is failure to comply with treatment for hypothyroidism and taking thyroxine supplementation a few days prior to thyroid function tests. It is, however, also important to exclude other causes of inappropriate TSH secretion, such as resistance to thyroid hormone, an autosomal dominant disorder caused by mutations in the thyroid hormone β receptor and resistance to thyrotopin.[14] The presence of a pituitary mass and elevated α-subunit levels are suggestive of a TSH-secreting tumour.

Diagnosis of non-functioning and gonadotropin-secreting pituitary adenomas

Clinically non-functioning tumours often present with optic chiasm pressure and other symptoms of local expansion or may be incidentally discovered on an MRI performed for another indication.[15] Menstrual disturbances or ovarian hyperstimulation rarely occur in women with large tumours that produce FSH and LH. More commonly, adenoma compression of the pituitary stalk or surrounding pituitary tissue leads to attenuated LH and features of hypogonadism. PRL levels are usually slightly increased due to stalk compression. Most non-functioning tumours respond poorly to medical treatment, but these can be given an empirical treatment with a dopamine agonist, unless decompression of the chiasm is warranted if prolactin levels are raised.

Free α-subunit levels may be elevated in 10–15% of patients with non-functioning tumours. In female patients, peri- or postmenopausal basal FSH concentrations are difficult to distinguish from tumour-derived FSH elevation.

Testosterone levels are usually low, despite the normal or increased LH level, perhaps reflecting reduced LH bioactivity or the loss of normal LH pulsatility. Because this pattern of hormone levels is also seen in primary gonadal failure and with ageing, the finding of increased gonadotropins alone is insufficient for the diagnosis of a gonadotropin-secreting tumour. For non-functioning and gonadotropin-secreting tumours, the diagnosis usually rests on immunohistochemical analyses of resected tumour tissue, as the mass effects of these tumours usually necessitate resection.[16] Although acromegaly or Cushing's syndrome usually present with unique clinical features, clinically unapparent somatotroph or corticotroph adenomas can be excluded by a normal IGF-I value and normal 24-hour urinary free cortisol levels.

MAGNETIC RESONANCE IMAGING

Sagittal and coronal T1-weighted magnetic resonance imaging (MRI), before and after administration of gadolinium, allows precise visualization of the pituitary gland with clear delineation of the surrounding structures. Adenoma density is usually lower than that of surrounding normal tissue on T1-weighted imaging, and the signal intensity increases with T2-weighted images. The high phospholipid content of the posterior pituitary results in a 'pituitary bright spot'.

Sellar masses are commonly encountered as incidental findings on MRI, and most of these are incidentalomas. In the absence of hormone hypersecretion, these small lesions can be safely monitored by MRI, which is performed annually and then less often if there is no evidence of growth. Resection may be considered for incidentally discovered macroadenomas, as about one-third become invasive or cause local pressure effects. If hormone hypersecretion is evident, specific therapies are indicated. When larger masses (>1 cm) are encountered, they should also be distinguished from non-adenomatous lesions including meningiomas (associated with bony hyperostosis), craniopharyngiomas (usually calcified and hypodense) and gliomas (hyperdense on T2-weighted images).

OPHTHALMOLOGICAL EVALUATION

Visual field assessment that uses perimetry techniques should be performed on all patients with sellar mass lesions that abut the optic chiasm. Bitemporal hemianopia or superior bitemporal defects are classically observed, reflecting the location of these tracts within the inferior and posterior part of the chiasm. Homonymous cuts reflect postchiasmal lesions and monocular field cuts prechiasmal lesions.

HISTOLOGICAL EVALUATION

Immunohistochemical staining of pituitary tumour specimens obtained at transsphenoidal surgery confirms clinical and laboratory studies and provides a histological diagnosis when hormone studies are equivocal and in cases of clinically non-functioning tumours.

Investigating anterior pituitary hormonal hyposecretion (hypopituitarism)

The clinical manifestations of hypopituitarism depend on which hormones are lost and the extent of the hormone deficiency. Biochemical diagnosis of pituitary insufficiency is made by demonstrating low levels of trophic hormones in the setting of low target hormone levels (**Table 83.2**).[1] For example, low free thyroxine in the setting of a low

TABLE 83.2 Tests of pituitary sufficiency: dynamic pituitary hormonal testing

Hormone	Test	Blood samples	Interpretation
Growth hormone[19]	Insulin tolerance test: Regular insulin (0.05–0.15 U/kg i.v.)	–30, 0, 30, 60, 120 min for glucose and GH	Glucose <40 mg/dL (2 mmol/L); GH should be >3 µg/L (5 mU/L)
	Glucagon stimulation test: 0.5–1.5 mg of glucagon i.m.	0, 30, 60, 90, 120, 150, 180, 210, 240 min for GH	Peak GH should be >3 µg/L (5 mU/L)
	GHRH test: 1 µg/kg i.v.	0, 15, 30, 45, 60, 120 min for GH	Normal response is GH >3 µg/L (5 mU/L)
	L-arginine test: 30 g i.v. over 30 min	0, 30, 60, 120 min for GH	Normal response is GH >3 µg/L (5 mU/L)
	L-dopa test: 500 mg p.o.	0, 30, 60, 120 min for GH	Normal response is GH >3 µg/L (5 mU/L)
ACTH	Insulin tolerance test:[18] Regular insulin (0.05–0.15 U/kg i.v.)	–30, 0, 30, 60, 120 min for glucose and GH	Glucose <40 mg/dL (2 mmol/L); cortisol should increase by >7 µg/dL (180 nmol/L) or to >20 µg/dL (550 nmol/L)
	Glucagon stimulation test: 0.5–1.5 mg of glucagon i.m.	0, 30, 60, 90, 120, 150, 180, 210, 240 min for cortisol	Cortisol should increase by >7 µg/dL (180 nmol/L) or to >20 µg/dL (550 nmol/L)
	CRH test: 1 µg/kg CRH i.v. at 8 a.m.	0, 15, 30, 60, 90, 120 min for ACTH and cortisol	Basal ACTH increases two- to fourfold and peaks at 20–100 pg/mL
	Metyrapone test:[20] Metyrapone (30 mg/kg) at midnight	Plasma 11-deoxycortisol and cortisol at 8 a.m.; ACTH can also be measured	Plasma cortisol should be <4 µg/dL to ensure an adequate response Normal response is 11-deoxycortisol >7.5 µg/dL or or ACTH >75 pg/mL
	Standard ACTH stimulation test: ACTH 1-24 (Cosyntropin), 0.25 mg i.m. or i.v.	0, 30, 60 min for cortisol and aldosterone	Normal response is cortisol >21 µg/dL and aldosterone response of >4 ng/dL above baseline
	Low-dose ACTH test: ACTH 1-24 (Cosyntropin), 1 µg i.v.	0, 30, 60 min for cortisol	Cortisol should be >21 µg/dL
	3-day ACTH stimulation test consists of 0.25 mg ACTH 1-24 given i.v. over 8 hours each day	0 and 72 hours for cortisol	Cortisol should be >21 µg/dL
TSH	Basal thyroid function tests: T4, T3, TSH	Basal tests	Low free thyroid hormone levels in the setting of TSH levels that are not appropriately increased
	TRH test: 200–500 µg i.v.: 0, 20, 60 min for TSH and PRL		TSH should increase by >5 mU/L unless thyroid hormone levels are increased. Evoked prolactin response indicates lactotrope integrity
LH, FSH	Basal LH, FSH, testosterone, oestrogen		Basal LH and FSH should be increased in postmenopausal women Low testosterone levels in the setting of low LH and FSH
	GnRH test: GnRH (100 µg) i.v.	0, 30, 60 min for LH and FSH	In most adults, LH should increase by 10 IU/L and FSH by 2 IU/L Normal responses are variable
Multiple hormones	Combined anterior pituitary test: GHRH (1 µg/kg), CRH (1 µg/kg), (or insulin stress test or glucagon stimulation test), GnRH (100 µg), TRH (200 µg) are given i.v.	–30, 0, 15, 30, 60, 90, 120 min for GH, ACTH, cortisol, LH, FSH and TSH	Combined or individual release hormone responses must be elevated in the context of basal target gland hormone values and may not be uniformly diagnostic

or inappropriately normal TSH level suggests secondary hypothyroidism. Similarly, a low testosterone level without elevation of gonadotropins suggests hypogonadotropic hypogonadism.

Provocative tests may be required to assess pituitary reserve.[17] GH responses to insulin-induced hypoglycaemia, arginine, l-dopa, growth hormone-releasing hormone (GHRH) or growth hormone-releasing peptides (GHRPs) can be used to assess GH reserve. Corticotropin-releasing hormone (CRH) administration induces ACTH release, and administration of synthetic ACTH (cosyntropin – Cortrosyn) evokes adrenal cortisol release as an indirect indicator of pituitary ACTH reserve.

ACTH reserve is most reliably assessed during insulin-induced hypoglycaemia.[18] However, this test should be performed cautiously in patients with suspected adrenal insufficiency because of enhanced susceptibility to hypoglycaemia and hypotension. Insulin-induced hypoglycaemia is contraindicated in patients with active coronary artery disease or seizure disorders. The glucagon stimulation test is also used for dynamic pituitary function testing and can be used safely when insulin is contraindicated.

INVESTIGATING POSTERIOR PITUITARY DYSFUNCTION

The neurohypophysis, or posterior pituitary gland, is formed by axons that originate in large cell bodies in the supraoptic and paraventricular nuclei of the hypothalamus. It produces two hormones: (i) arginine vasopressin (AVP), also known as antidiuretic hormone; and (ii) oxytocin. AVP acts on the renal tubules to reduce water loss by concentrating the urine. Oxytocin stimulates postpartum milk letdown in response to suckling.

AVP deficiency causes diabetes insipidus (DI), characterized by the production of large amounts of dilute urine. Excessive or inappropriate AVP production predisposes to hyponatremia if water intake is not reduced in parallel with urine output.

Deficiency of AVP secretion: diabetes insipidus

Decreased secretion or action of AVP causes diabetes insipidus and is characterized by the production of abnormally large volumes of dilute urine. The 24-hour urine volume is >50 mL/kg body weight and the osmolarity is <300 mOsmol/L. The polyuria produces symptoms of urinary frequency, enuresis, and/or nocturia, which may disturb sleep and cause mild daytime fatigue or somnolence. It is also associated with thirst and a commensurate increase in fluid intake (polydipsia). Clinical signs of dehydration are uncommon unless fluid intake is impaired.

INVESTIGATION

When clinically suspected, a 24-hour urine should be collected on an *ad libitum* fluid intake to confirm polyuria. If the volume exceeds 50 mL/kg per day, polyuria is present. If the osmolarity is >300 mOsmol/L, the polyuria is due to a solute diuresis and the patient should be evaluated for glucosuria or other less common causes of excessive solute excretion. However, if the 24-hour urine osmolarity is <300 mOsmol/L, the patient has a water diuresis and should be evaluated further to determine which type of DI is present.

Except in the rare patient who is clearly dehydrated under basal conditions of *ad libitum* fluid intake, the evaluation should begin with a fluid deprivation test. The test should be started in the morning and water balance should be monitored closely, with hourly measurements of body weight, plasma osmolarity and/or sodium concentration, and urine volume and osmolarity.

If fluid deprivation does not result in urine concentration (osmolarity >300 mOsmol/L, specific gravity >1.010) before body weight decreases by 5% or plasma osmolarity/sodium exceeds the upper limit of normal, the patient has severe pituitary or severe nephrogenic DI. These disorders can usually be distinguished by administering desmopressin (DDAVP, 0.03 µg/kg s.c. or i.v.) and repeating the measurement of urine osmolarity 1–2 hours later. An increase of >50% indicates severe pituitary DI, whereas a smaller or absent response is strongly suggestive of nephrogenic DI.

The differential diagnosis of DI may also be facilitated by MRI of the pituitary and hypothalamus. In most healthy adults and children, the posterior pituitary emits a hyperintense signal in T1-weighted midsagittal images. This 'bright spot' is almost always present in patients with primary polydipsia but is invariably absent or abnormally small in patients with pituitary DI. It is usually also small or absent in nephrogenic DI, presumably because of high secretion and turnover of vasopressin. A normal bright spot virtually excludes pituitary DI, is unlikely in nephrogenic DI, and strongly suggests primary polydipsia.

Excess AVP secretion: syndrome of inappropriate ADH secretion

Excessive secretion or action of AVP results in the production of decreased volumes of more highly concentrated urine. If not accompanied by a commensurate reduction in fluid intake or an increase in insensible loss, the reduction in urine output results in excess water retention with expansion and dilution of all body fluids. In some patients, excessive intake results from inappropriate thirst. If the hyponatremia develops gradually or has been present for more than a few days, it may be largely asymptomatic. However, if it develops acutely, it is almost always accompanied by symptoms and signs of water intoxication that may include mild headache, confusion, anorexia, nausea, vomiting, coma and convulsions, and it could be lethal.

AETIOLOGY

Hyponatremia and impaired urinary dilution can be caused by a primary defect in the regulation of AVP secretion or

action or can be secondary to a recognized non-osmotic stimulus such as hypovolemia, hypotension, nausea or glucocorticoid deficiency. The primary forms are generally referred to as syndromes of inappropriate ADH secretion (SIADHs). They have many different causes, including ectopic production of AVP by lung cancer or other neoplasms; eutopic release by various diseases or drugs; and exogenous administration of AVP, desmopressin or large doses of oxytocin.

SIADH is a diagnosis of exclusion that can usually be accomplished with routine historic, physical and laboratory information. In a patient with hyponatremia, the possibility of simple dilution caused by an osmotically driven shift of water from the intracellular to the extracellular space should be excluded by measuring plasma glucose and/or plasma osmolarity. Normal results of liver function tests, lipids and glucose concentration exclude rare causes of artifactual pseudohyponatraemia (hyperproteinaemia and hyperlipidaemia) or hyperosmolar hyponatraemia, where water moves from the intracellular to the extracellular compartment (in severe hyperglycaemia).

SIADH needs to be confirmed by results of paired serum and urine samples: serum hyposmolality must be <275 mOsm/kg (normal range: 275–295 mOsm/kg), and urine osmolality >100 mOsm/kg and sodium ≥30 mmol/L, in the absence of hypovolaemia, hypervolaemia, adrenal or thyroid dysfunction and use of diuretics.[21, 22] Paired serum and spot urine samples need to be sent for osmolality and sodium to confirm both hyponatraemia and SIADH. Serum osmolality measurement is not necessary when there is an obvious contributory cause. It can confirm true hyponatraemia (<275 mOsmol/kg) and rules out the rarer hyperosmolar hyponatraemia and pseudohyponatraemia (serum osmolality ≥275 mmol/L).[23]

Urine osmolality (normal range 300–900 mOsm/kg) is needed to confirm SIADH but it also helps in differentiating it from two other conditions. By definition, SIADH is an incomplete suppression of antidiuretic hormone (urine osmolality >100 mOsm/kg); a spot urinary osmolality <100 mOsm/kg indicates appropriate complete suppression. Complete suppression of antidiuretic hormone is seen in psychogenic polydipsia (history of mental illness) and malnutrition (history of heavy alcohol consumption).[24]

Urinary sodium concentration is helpful when the cause of hyponatraemia is not apparent from the history and examination or when SIADH is suspected. In euvolaemic hyponatraemia (including SIADH), the urinary sodium is ≥30 mmol/L.[22, 25] Hypervolaemic hyponatraemia should be apparent clinically; because of the reduced effective circulating volume, the kidney concentrates the urine (>100 mOsm/kg) and conserves sodium (<30 mmol/L; but it can be higher when the patient is taking diuretics).[22] The clues to hypovolaemia in the history include obvious fluid loss (through diuretics, for example) or third space fluid loss, when fluid with high sodium content is sequestered in a body space, as occurs in burns patients. The urinary sodium concentration in all hypovolaemic hyponatraemia is <30 mmol/L except when the kidney is the site of the loss, for example with diuretic use, salt-losing nephropathy, or mineralocorticoid deficiency.[26]

When the fluid status is difficult to determine clinically, low serum concentrations of urea and uric acid indicate SIADH, and a raised concentration of urea is more likely to reflect hypovolaemia.[24]

KEY POINTS

- Pituitary adenomas can cause local mass effects as well as hyper- or hyposecretion of pituitary hormones.
- Magnetic resonance imaging of the pituitary is the modality of choice for imaging pituitary pathology.
- Visual field assessment using perimetry techniques should be performed on all patients with sella mass lesions that abut the optic chiasm.
- The initial hormonal evaluation of a pituitary adenoma will be guided by the history and clinical examination for evidence of hormone insufficiency or excess.
- Biochemical diagnosis of pituitary insufficiency is made by demonstrating low levels of trophic hormones in the setting of low target hormone levels. Provocative tests may be required to assess pituitary reserve.
- Dynamic pituitary function testing is required for testing the integrity of the ACTH/cortisol axis and determination of GH deficiency or excess.
- Water deprivation testing can be useful for the diagnosis of diabetes insipidus.

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CHAPTER 84

PRIMARY PITUITARY DISEASE

Christopher M. Jones and John Ayuk

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: pituitary, adenohypophysis, neurohypophysis, adenoma, macroadenoma, non-functioning adenoma, prolactin, prolactinoma, growth hormone, acromegaly, adrenocorticotrophic hormone, Cushing's disease, Cushing's syndrome, thyroid-stimulating hormone and gonadotrophins. Secondary search criteria included epidemiology, aetiology, management and pathogenesis. Particular focus has been placed on the epidemiology, aetiology and management of key disorders of the pituitary with level 1 and 2 evidence reported wherever possible.

INTRODUCTION

Disease of the pituitary gland may result in a broad spectrum of clinical phenotypes.[1,2] This is perhaps unsurprising given the function of the pituitary as the 'conductor of the endocrine orchestra'. Consisting of both an anterior and a posterior portion, respectively termed the adenohypophysis and the neurohypophysis, the pituitary lies immediately below the hypothalamus.

Anterior pituitary (adenohypophysis)

FUNCTION

The anterior pituitary secretes thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), growth hormone (GH), prolactin (PRL) and the gonadotrophins follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (Table 84.1). Their secretion is subject to marked clinical rhythms and varies widely between the different hormones. Gonadotrophin release is, for instance, well recognized to follow a 28-day cycle in women, where it is critical for ovulation and implantation. ACTH follows a circadian rhythm and normal GH secretion is pulsatile, with more pulses secreted during sleep. Knowledge of these fluctuations is important, both for the recognition that isolated measurement of pituitary hormones or their downstream mediators may be misleading and because loss of a recognizable rhythm may indicate disease, such as in Cushing's disease. Interestingly, seasonal rhythms are known to impact on pituitary hormone synthesis in other species but are unlikely to be of significance in humans.

ANATOMY

The anterior portion of the pituitary may be divided into three constituent parts. The largest of these is the pars anterior, which constitutes approximately 80% of gland volume.[3] A smaller contribution to pituitary mass is made by the pars intermedia, which is well developed in the foetus, and the pars tuberalis, which forms from an upward extension of the anterior wall of the gland and wraps around the lower end of the pituitary stalk.[3]

FUNCTION AND FEEDBACK

Secretion of hormones from the pituitary gland is controlled by the hypothalamus. For the hypophysiotrophic cells of the anterior gland, this regulation is derived by

TABLE 84.1 Principle pituitary hormones and their regulators, secreting cell and action

	Pituitary hormone	Abbreviation	Secreting cell	Downstream target	+ve feedback	–ve feedback	Effects
Anterior pituitary	Adrenocorticotrophic hormone	ACTH	Corticotrophs	Adrenal gland	CRH	Cortisol	Corticosteroid secretion
	Growth hormone	GH	Somatotrophs	Liver Adipose tissue	GHRH	IGF-1 Somatostatin	Growth Modulation of lipid/carbohydrate metabolism (effects modulated by insulin-like growth factor 1; IGF-1)
	Luteinizing hormone	LH	Gonadotrophs	Gonads	GnRH Ostrogen	Sex steroids Inhibin (FSH)	Reproductive system development Gametogenesis
	Follicle-stimulating hormone	FSH					
	Prolactin	PRL	Lactotrophs	Breast	TRH	Dopamine	Lactation
	Thyroid-stimulating hormone	TSH	Thyrotrophs	Thyroid	TRH	T4 and T3	Thyroid hormone (T4 and T3) synthesis and release
Posterior pituitary	Oxytocin		Supraoptic and paraventricular nuclei (hypothalamus)	Myoepithelial cells (uterine) Prefrontal cortex	Cervix stretch Suckling		Supports lactation Uterine contraction Emotional bonding
	Antidiuretic hormone	ADH		Liver Kidney Brain Vasculature	Reduced plasma volume/osmolality Angiotensin II Cholecystokinin	Atrial natriuretic peptide	Regulate water retention Induce vasoconstriction

Note: CRH: corticotrophin-releasing hormone; GHRH: growth hormone-releasing hormone; GnRH: gonadotrophin-releasing hormone; TRH: thyrotrophin-releasing hormone; IGF-1: insulin-like growth factor 1; T4: thyroxine; T3: triiodothyronine.

neural stimuli and feedback from circulating hormones, whether these are secreted by the anterior pituitary itself (such as growth hormone (GH)) or a target organ (such as thyroxine). Active hormones influence pituitary hormone production both by directly exerting feedback on anterior pituitary cells and, more significantly, by inducing the synthesis of neurohormones by hypophysiotrophic neurons, which are then transported down their axons and released into the pituitary portal circulation, from where they are carried to target cells in the anterior pituitary.

These neurohormones will have either a stimulatory or an inhibitor effect on the cells of the anterior pituitary gland. Stimulatory neurohormones include gonadotrophin-releasing hormone (GnRH), thyrotrophin-releasing hormone (TRH), corticotrophin-releasing factor (CRF) and GH-releasing hormone (GHRH). The inhibitory neurohormones include somatostatin, which inhibits the release of GH, and dopamine, which inhibits prolactin release.

PITUITARY GLAND VASCULATURE AS IT RELATES TO TESTS FOR NORMAL FUNCTION

The pituitary gland arterial blood supply derives from the superior and inferior hypophyseal arteries, both of which are branches of the internal carotid artery. The superior hypophyseal arteries supply a plexus which is closely associated with the median eminence of the hypothalamus and the axons of the hypophysiotrophic neurons within the hypothalamus. These vessels then form a pituitary portal circulation, which runs down the pituitary stalk into sinusoids in the anterior pituitary. The venous drainage of the gland is into the cavernous sinuses. These are venous lakes, which contain the last part of the internal carotid arteries, and cranial nerves III, IV, V and VI. They are connected across the midline by a variable array of intercavernous connecting veins and they drain into the superior and inferior petrosal sinuses. The venous connections are of importance when considering inferior petrosal sinus sampling as a method of locating secreting adenomas.

Posterior pituitary (neurohypophysis)

The posterior pituitary sits in continuity with the hypothalamus and secretes oxytocin and antidiuretic hormone (ADH, otherwise known as vasopressin).[3] These are released from the axons of supraoptic and paraventricular neurons that run through the pituitary stalk from the hypothalamus. Granules of oxytocin and ADH are stored at the distal end of these axons and are released into the systemic circulation when stimulated to do so.

KEY POINTS

PITUITARY GLAND STRUCTURE, FEEDBACK AND FUNCTION

Structure

- The pituitary gland is formed of both an anterior portion (itself split into three constituent parts) and a posterior portion.
- Pituitary venous drainage is into the cavernous sinuses.

Feedback

- Release of pituitary hormones is governed by hypothalamic input and systemic feedback.

Function

- The pituitary gland is the 'conductor of the endocrine orchestra' – responsible for coordinating metabolism, growth and reproduction.

THE SPECTRUM OF PITUITARY DISEASE

There are a wide range of pathologies of the pituitary gland, the clinical manifestations of which reflect the complexity of a diverse organ formed of two constituent parts and various different cell types. Broadly, anterior pituitary diseases include congenital hypopituitarism and isolated growth hormone deficiencies, in addition to the development of functioning and non-functioning pituitary adenomas. This chapter will focus on clinical presentations arising from the development of anterior pituitary adenomas. Disease of the posterior pituitary tends to be acquired and will also be discussed, albeit in less detail.

CONGENITAL PRIMARY HYPOPITUITARISM

A large number of genes have now been associated with congenital hypopituitarism. Mutations seen in genes encoding specific cell types or hormone subunits generally give rise to isolated pituitary hormone deficiencies; mutations in genes responsible for early pituitary development result in combined hypopituitarism. A complete outline of congenital hypopituitarism is beyond the scope of this chapter but key disorders and – where known – their underlying genetic aetiology are discussed.

Congenital combined pituitary hormone deficiency

Recessive mutations of the chromosome 5q gene *PROP1* underlie the majority of cases of combined pituitary hormone deficiency, accounting for approximately 50% of familial cases.[4] The deficiency in hormone production resulting from mutations of *PROP1* is variable but generally accounts for growth hormone, TSH and prolactin deficiency. More significant deficiency of these same hormones occurs with mutations of the chromosome 3p gene *POUIFI*, though TSH deficiency may present later in childhood and is in some instances preserved.[5]

Combined pituitary hormone deficiency may also arise as part of a syndrome, as is the case in septo-optic dysplasia, Rieger's syndrome and holoprosencephaly.[6] Septo-optic dysplasia carries an incidence of approximately 1:10 000 and both sporadic and familial cases have been described with *HESX1*, *SOX2* and *SOX3* implicated in the pathogenesis of this disorder.[7] Hypoplasia of both the pituitary and optic nerve is seen as a consequence, in addition to defects of the midline forebrain. This commonly results in neurological defects. Visual impairment and variable endocrine deficiencies – the most common of which are isolated GH deficiency and combined TSH and ACTH deficiency – are also seen.

Reduced levels of GH have also been noted in the autosomal dominant condition Rieger's syndrome, which encompasses a constellation of craniofacial and eye abnormalities. Conversely, holoprosencephaly is more commonly associated with posterior hormone deficiency and diabetes insipidus. Mutations in the sonic hedgehog (SHH) pathway are thought to result in this condition, which is characterized by a failure of the prosencephalon (the embryonic forebrain) to develop into two hemispheres.[8]

KEY POINTS

CONGENITAL COMBINED PITUITARY HORMONE DEFICIENCY

- This may occur as part of a syndrome or independent of non-pituitary clinical features.
- Mutations in *PROP1* and *POUIFI* are responsible for most non-syndromic cases.
- Syndromic causes include septo-optic dysplasia, holoprosencephaly and Rieger's syndrome.

Congenital isolated pituitary hormone deficiency

Congenital isolated hormone deficiencies are rare but both familial and sporadic cases of specific anterior and posterior pituitary hormone deficiencies have been reported.

ISOLATED GONADOTROPHIN DEFICIENCY (HYPOGONADOTROPHIC HYPOGONADISM)

One of the most fascinating forms of isolated hormone deficiency is that of isolated GnRH-deficiency (IGD). This may be sporadic or of X-linked, autosomal dominant or autosomal recessive inheritance.[9] It is characterized by hypogonadism, which itself results from LH and FSH deficiency and is thus alternatively termed hypogonadotrophic hypogonadism (HH).

IGD may occur alone or in association with a loss of sense of smell (anosmia). Kallmann syndrome refers to the association of anosmia with IGD. This accounts for approximately 60% of subjects with IGD and affects approximately 1:10000 males and 1:40000 females.[10] Around three quarters of patients with Kallmann syndrome exhibit olfactory bulb agenesis on neuroimaging.[11]

Patients with IGD may present early in life or during adulthood. When present at birth, IGD is associated with the development of a micropenis and cryptorchidism.[9] Later in life patients with IGD demonstrate evidence of hypogonadism, the most notable clinical consequence of which is limited development of secondary sexual characteristics. 'Scratch and sniff' tests can be used to formally test for anosmia. Treatment is targeted towards both stimulating gametogenesis with pulsatile GnRH or combined gonadotrophins and inducing secondary sexual characteristics with gonadal steroids. A number of causative genes have been mapped for Kallmann syndrome and normosmic IGD,[12] as summarized in **Box 84.1**.

ISOLATED GH DEFICIENCY

Congenital deficiency of GH occurs in every 1:4000–1:10000 births and may have a familial component.[13] Four distinct forms have been characterized. In type IA congenital isolated GH deficiency large homozygous mutations in the GH-encoding *GH1* gene result in exceptionally low levels of GH, even on provocation. Antibodies are generated against GH on treatment so that the adult's final height is low. Smaller mutations in either *GH1* or *GHRH* are seen in type IB isolated GH deficiency, in which a similar but milder GH deficiency is seen.

Congenital isolated GH deficiency type II is an autosomal dominant disorder in which patients present with short stature.[14] It is now recognized that this condition arises as a result of a splice site mutation in intron 3 of the *GH1* gene. This produces a mutant 17.5 kDa molecule containing a deletion between amino acids 32 and 71 (the Del32-71-GH deletion), which has a dominant negative effect and prevents secretion of wild-type GH. As a consequence, supplementation with GH is generally an effective treatment for this condition.

BOX 84.1 Isolated GnRH deficiency (IGD)-associated genes. These account for approximately 50% of all cases of IGD

Kallmann syndrome

KAL1

Normosmic IGD

KISS1
KISS1R (GPR54)
TAC3
TACR3
GNRHR
GNRH1

Kallmann syndrome and normosmic IGD

KAL1
FGFR1
PROKR2
PROK2
CHD7
FGF8

Type III isolated GH deficiency is X-linked and may be associated with agammaglobulinaemia. Its pathogenesis is yet to be fully elucidated.[15]

KEY POINTS

CONGENITAL ISOLATED GROWTH HORMONE DEFICIENCY

Type Ia

- Autosomal recessive
- GH undetectable
- Anti-GH antibodies raised against exogenous GH

Type Ib

- Autosomal recessive
- GH low but no anti-GH antibodies raised

Type II

- Autosomal dominant
- Short stature – effectively managed with GH replacement

Type III

- X-linked
- Associated with agammaglobulinaemia
- Causative gene not yet known

ISOLATED TSH DEFICIENCY (CENTRAL HYPOTHYROIDISM)

Central hypothyroidism describes underactivity of the thyroid gland resulting from insufficient TSH stimulation. It is rare, affecting around 1:50000 live births, and both sporadic and familial cases have been described.[16] There are existing programmes already in place to screen for hypothyroidism, such as the 'blood spot' test used within the UK NHS. In the absence of this, infants may present with non-specific symptoms and failure to thrive. In cases of established central hypothyroidism, hormonal assays reveal low free thyroxine (fT4) with inappropriately normal or low TSH levels.

ISOLATED ACTH DEFICIENCY

ACTH deficiency is generally associated with other pituitary hormone deficiencies and isolated ACTH deficiency is vanishingly rare, with only a few cases reported to date. Symptoms may vary from failure to thrive to signs of acute adrenal insufficiency.[17]

ACQUIRED PRIMARY HYPOPITUITARISM

Aetiology

Hypopituitarism may arise in later life through a variety of aetiologies which include tumour growth, radiotherapy, pituitary infarction, pituitary gland infiltration, trauma and infection.[18] These are summarized in **Table 84.2**.

TABLE 84.2 Causes of acquired hypopituitarism

Category	Examples
Neoplasia	Non-functioning pituitary adenomas Functioning pituitary adenomas Parapituitary tumours Craniopharyngioma Meningioma Metastatic deposits Chordoma Glioma
Iatrogenic	Radiotherapy Pituitary Cranial Nasopharyngeal Surgery (see Trauma)
Systemic disease	Sarcoidosis Haemochromatosis Langerhans cell histiocytosis Granulomatosis with polyangiitis (Wegener's disease) Lymphocytic hypophysitis
Infection	Tuberculosis Pituitary abscess
Vascular	Subarachnoid haemorrhage Pituitary apoplexy Sheehan's syndrome
Trauma	Traumatic brain injury Direct pituitary trauma (e.g. surgery)

PITUITARY APOPLEXY AND SHEEHAN'S SYNDROME

Overview

Pituitary apoplexy refers to a medical emergency in which infarction of the pituitary gland occurs due to haemorrhage or ischaemia. Predisposing factors include radiotherapy, coagulation disorders, the use of anticoagulants and a reduction in intra-cranial pressure.[19] Pituitary infarction due to postpartum haemorrhage has also been described and is termed Sheehan's syndrome.[20]

Clinical assessment

Pituitary apoplexy should be considered in all patients presenting with a sudden-onset headache, vomiting, visual impairment, meningism and reduced consciousness. This constellation of symptoms may be accompanied by second, third, fourth and/or sixth cranial nerve palsies.

Patients with pituitary tumours should be considered at risk of apoplexy and should be provided with information regarding relevant signs and symptoms. In those who are not known to harbour pituitary adenomas, a detailed history is required to identify symptoms of pituitary dysfunction.[19] Subsequent clinical examination should focus on the cranial nerves and visual fields for confrontation. More formal assessment of the visual fields can be undertaken using the Humphrey visual field analyser or Goldmann perimeter and can be undertaken once the patient is clinically stable.

Endocrine workup

In all patients suspected to have pituitary apoplexy, blood samples should be sent to assess electrolytes, renal function, liver function, full blood count and clotting. Assessment of anterior pituitary hormones and their downstream mediators is also required and should include cortisol, fT4, prolactin, TSH, IGF1, GH, LH, FSH and gonadotrophins.[21]

Diagnostic imaging

An urgent MRI or dedicated pituitary CT should be performed in patients with suspected apoplexy.[21] High signal will be seen on both T1- and T2-weighted MRI images.

Management

The first priority in managing a patient with pituitary apoplexy is to ensure haemodynamic stability. Empirical steroid therapy is used in patients who are haemodynamically unstable, demonstrate reduced visual acuity or who have a reduced consciousness level. It is recommended that a 100–200 mg bolus of hydrocortisone is used as initial therapy, followed by either continuous intravenous infusion of hydrocortisone or 6-hourly intra-muscular injections.[21]

In patients who are not haemodynamically unstable, steroid treatment is considered in those for whom 9 a.m. serum cortisol is less than 550 nmol/L. Patients with mild, stable or improving symptoms can be managed conservatively; in cases with severe or progressive visual impairment or altered mental state, early surgery provides the optimal chance for neurological recovery. The decision on whether to proceed to surgery must be taken by a multidisciplinary team with appropriate expertise in endocrinology, ophthalmology and neurosurgery. If conservative management is elected for and a new visual deficit arises, decompressive surgery should be reconsidered.

KEY POINTS

PITUITARY APOPLEXY

- Pituitary apoplexy is a medical emergency in which infarction of the pituitary gland occurs.
- It should be considered in all patients with sudden-onset headache, meningism, reduced consciousness and visual impairment.
- Pituitary hormones should be assayed.
- Urgent MRI or focused pituitary CT should be undertaken in all patients suspected of pituitary apoplexy.
- Use empirical steroid therapy if the patient is haemodynamically unstable.
- Early surgery may support recovery in patients with severe or progressive symptoms.

LYMPHOCYTIC HYPOPHYSITIS

This rare chronic inflammatory condition of the pituitary most commonly presents in late pregnancy or in the first postpartum year.[22] It is considered to be autoimmune in

origin and antipituitary antibodies have been implicated in its pathogenesis. A lymphoplasmacytic infiltrate is seen and causes variable destruction, oedema and fibrosis of the pituitary parenchyma with resultant mass effects and hypopituitarism. Corticosteroids may play a role in the management of this condition but its natural history is yet to be determined. Spontaneous recovery has been reported.

Investigations

Biochemical and imaging tests used in cases of suspected hypopituitarism are complex and discussed in Chapter 83. Briefly, these investigations are employed both to identify and determine the extent of hormone deficiency, and to elucidate the cause of the hormone deficiency. Biochemical analyses to identify hypopituitarism include both the assessment of basal hormone levels and dynamic testing. Additional investigations such as angiotensin-converting enzyme (ACE), ferritin, hCG and aFP may be required to identify an underlying cause for the hypopituitarism, and imaging with MRI is mandatory. In some instances biopsy may be required to determine the aetiology of an underactive pituitary gland.

Anterior pituitary hormone replacement

Table 84.3 summarizes the clinical features associated with adult-onset anterior pituitary hormone deficiency.

GROWTH HORMONE DEFICIENCY AND REPLACEMENT

Clinical features of GH deficiency

Adult-onset growth hormone deficiency occurs in 1/10 000 persons. It is specifically associated with a triad of poorer skeletal health, increased cardiovascular risk and impaired quality of life (QOL).[18, 23] Patients with GH deficiency most frequently report reductions in their energy and vitality, and manifest greater emotional liability, impaired socioeconomic performance and poorer relationship-building than matched control subjects.[24]

TABLE 84.3 Clinical features associated with adult-onset anterior pituitary hormone deficiency

Hormone deficiency	Symptoms and signs
Gonadotrophins (LH and FSH)	Male: Loss of secondary sexual hair, erectile dysfunction, testicular atrophy
	Female: Anovulatory cycles, oligomenorrhoea, amenorrhoea
Prolactin	Inability to lactate
Growth hormone	Poor skeletal health, increased cardiovascular risk, impaired quality of life
ACTH	Addisonian features without hyperpigmentation
TSH	Weight gain, cold insensitivity, constipation, dry skin, hair loss, fatigue
ADH	Polyuria, polydipsia

Given the vital role of GH in lipid, protein and carbohydrate metabolism, it is perhaps unsurprising that GH deficiency is associated with increased cardiovascular risk. This is specifically conferred by a cacophony of changes that include increased central fat deposition, decreased lean mass, increased total and low-density lipoprotein cholesterol, increased triglycerides, a reduction in insulin sensitivity and hypertension.[25] Endothelial dysfunction has also been reported, as has an increase in inflammatory markers, the development of microvascular abnormalities and changes in cardiac size and function.[26]

A reduction in bone turnover is a further consequence of GH deficiency and bone mineral density falls as a consequence. There are in addition reports of a resultant increase in the risk of radiologically diagnosed vertebral fractures and clinically identified non-vertebral fractures. GH deficiency is also seen to negatively impact on exercise capacity, renal function and the maintenance of healthy skin.[25]

Rationale for GH replacement

There is no evidence to date to conclude that GH replacement eliminates the excess mortality seen in instances of GH deficiency and the degree to which GH replacement should be administered remains controversial.[25, 27] In many countries universal replacement is provided to all patients with deficiency in order to counter the deleterious clinical features outlined above. For a number of European countries, however, GH replacement is provided only to those with impaired QOL or reduced bone mass. Guidelines published by the UK National Institute for Health and Care Excellence (NICE) in 2003 restrict GH to patients with severe GH deficiency (GH < 9 mU/L) and impairment of QOL (defined as a QOL–Assessment of Growth Hormone Deficiency in Adults (AGHDA) score of greater than or equal to 11).[28]

Treatment and monitoring

In paediatrics GH is generally administered at a dose based on each patient's body weight and surface area. A similar approach in adults resulted in a number of side effects, including significant fluid retention, and this dosing strategy is consequently not commonly used. Management of adult GH deficiency instead relies on dose titration.[25] Respective starting doses of 0.2 mg/day and 0.3 mg/day are recommended for males and females, though this dose should be reduced to 0.1 mg/day in older patients. Serial IGF-1 measurements are then used to monitor GH replacement with a target of the middle-upper end of the age-matched IGF-1 range. In the steady state IGF-1 levels should be repeated at least annually. Repeat measurements are nevertheless required 6 weeks after each dose change. Close monitoring of markers of HbA1c, lipids and bone mineral density are also required during treatment with GH.

GH replacement cannot be continued in cases of active malignancy, in patients with idiopathic intra-cranial hypertension and in patients with proliferative retinopathy as a consequence of diabetes mellitus.

KEY POINTS

ISOLATED GH DEFICIENCY

- Isolated GH deficiency is associated with poor skeletal health, impaired quality of life and increased cardiovascular disease.
- There is no absolute evidence for a reduction in mortality following GH replacement.
- Guidelines differ. Current UK NICE guidelines advocate treatment if quality of life is impaired.
- Dose titration is required to establish the correct GH regime.
- GH replacement may be contraindicated in certain circumstances.

THYROID-STIMULATING HORMONE DEFICIENCY AND REPLACEMENT

Once-daily thyroxine is sufficient for hormone replacement in central thyroid hormone deficiency.[29] Given that TSH is deficient, it cannot be used to identify the optimal replacement dose. This should instead be estimated based on clinical assessment and measurement of circulating (free) thyroid hormone levels, which are conventionally recommended to be in the middle or upper part of the albeit rather broad normal range. It is important that fT4 levels are taken prior to ingestion of thyroxine on the day of sampling.

GONADOTROPHIN DEFICIENCY AND REPLACEMENT

Oestrogen and testosterone replacement are respectively the usual method of sex hormone replacement for males and females with gonadotrophin deficiency. Gonadal steroid replacement will not, however, induce fertility. Patients who are seeking to conceive must therefore receive gonadotrophin therapy.[23]

Therapy in males

Testosterone replacement is required by males with gonadotrophin deficiency both to relieve the symptoms of hypogonadism (such as a reduction in libido) and to counter the long-term consequences of hypogonadism (such as osteoporosis). A link between testosterone deficiency and cardiovascular disease has been postulated but is far from proven. When given as replacement, testosterone may be administered via the transdermal route as a gel or patch, as an intra-muscular depot or as oral therapy. Patient preference, pharmacokinetics, treatment burden and cost should be considered in choosing between administration routes when initiating testosterone therapy.

The Endocrine Society has published guidelines for the management of adult men receiving testosterone therapy.[30] These advise that patients are evaluated within 3–6 months of treatment initiation in order to assess both response to treatment and the presence of adverse effects. Serum testosterone levels should be monitored at 3–6 months after treatment initiation and kept within the mid-normal range.

Baseline assessment and regular reassessment of haematocrit is required as excess androgen replacement is known to cause polycythaemia. Bone mineral density assessment is also advised within 2 years of testosterone replacement initiation in patients with osteoporosis or previous low trauma fracture. Prostate-specific antigen (PSA) levels also require regular monitoring in patients for whom initial levels exceed 0.6 ng/mL. The adverse sequelae of testosterone replacement remain uncertain and further research is required to conclude whether there is any association with increased prostate volume and a greater burden of cardiovascular disease.

Induction of spermatogenesis can occur with both gonadotrophin injections and subcutaneous pulsatile infusions of GnRH. Patients should be aware that this induction of spermatogenesis takes at least 3 months and may require over a year of therapy.

Therapy in females

Oestrogen is required by women of premenopausal age and may be administered as oral or transdermal therapy. The risks postulated for the use of hormone replacement therapy (HRT) in postmenopausal women are not thought to apply to the premenopausal setting.

Gonadotrophin injections and subcutaneous pulsatile infusions of GnRH are successful treatments for both hypothalamic gonadotrophin deficiency and primary pituitary disease. Ultrasound monitoring is required to assess ovarian response.

ACTH DEFICIENCY AND REPLACEMENT

Glucocorticoids are generally required in instances of ACTH deficiency. Strategies for effective glucocorticoid replacement are discussed elsewhere in this book and apply to this setting.

EMPTY SELLA SYNDROME

Empty sella syndrome (ESS) refers to a rare condition in which the sella turcica – a saddle-shaped depression of the sphenoid bone that forms the pituitary fossa in which the pituitary gland ordinarily sits – appears on radiological imaging to be partially or completely filled with cerebrospinal fluid.[31] This occurs as a consequence of the herniation of the suprasellar subarachnoid space into the intrasellar space, with resultant compression of the pituitary gland. Both primary and secondary forms of ESS have been described.

In primary ESS weakness of the diaphragma sella or increased intra-cranial pressure is thought to promote arachnoid membrane herniation. This most commonly occurs in obese women and both hypertension and headache are common concomitant features. Hypopituitarism is uncommon and management is supportive. ESS is considered to be secondary in instances in which it follows pituitary radiation, surgery, infection or infarction. Clinical findings in cases of secondary ESS commonly include visual abnormalities and symptoms reflecting loss of pituitary function.

PITUITARY ADENOMAS

Benign tumours arise within the pituitary gland and have been recognized in as many as one in four persons in post-mortem and radiological studies. Only a small proportion of these are clinically apparent. These result in considerable morbidity both as a consequence of the production of excess pituitary hormone and through mass effect from compression of surrounding structures.

Definitions

Pituitary adenomas are benign neoplasms which do not typically metastasize and which may be categorized into those that produce hormones and those that fail to efficiently secrete their gene product.[32] These are respectively termed 'functioning' and 'non-functioning'. Functioning adenomas may arise from any one (or more) of the anterior pituitary cell types and are commonly categorized by their cytodifferentiation. While the majority produce a single hormone, 1–30% express more than one hormone and are described as plurihormonal.

Pituitary tumours are additionally classified by size, with those exceeding 1 cm in diameter termed macroadenomas and those less than 1 cm in diameter referred to as microadenomas.

Pathophysiology

There has been considerable interest in pituitary tumourigenesis and a number of potential subcellular therapeutic targets have been delineated.[33] Our understanding of the development of pituitary adenomas nevertheless remains incomplete. A number of mechanisms have been implicated in pituitary tumourigenesis, including tissue plasticity and the dysregulation of both transcription and the cell cycle through a number of specific tumour-initiating and tumour-promoting factors.

Although no single initiating factor has been identified as pathognomonic for pituitary adenoma pathogenesis, these tumours are monoclonal and intrinsic molecular events are thus thought to lead to pituitary tumourigenesis. These early events are recognized to include epigenetic changes and increasing pituitary chromosome instability. Despite this, pituitary adenomas are invariably benign and their mitotic activity remains at relatively low frequency with key mutations found in common malignancies (such as p53 mutations) only rarely found. Proliferative restraint may be conferred by mechanisms required to ensure the tissue plasticity required by the pituitary gland to maintain physiological homeostasis. **Box 84.2** summarizes key molecular mechanisms implicated in pituitary tumour pathogenesis.

BOX 84.2 Key molecular mechanisms implicated in pituitary tumour pathogenesis

Oncogene activation: e.g. GNAS, CCND1, HMGA2, FGFR4 and H-Ras

Tumour suppressor gene inactivation: e.g. AIP, MEN1, PPKAR1A, Rb and BRG1

Cyclin mutation: e.g. the CCNB2 cyclin and CDKN2A cyclin-dependent kinase inhibitor

Securin overexpression: PTTG has been found to be overexpressed in pituitary tumours

An understanding of the growth of pituitary adenomas is also important for delineating symptoms relating to their mass effect. Extension of pituitary adenomas outside of the pituitary fossa may occur in a superior, inferior or lateral direction (**Table 84.4**).

Investigations

BIOCHEMISTRY

Biochemical evaluation of pituitary function involves both direct assessment of hormone levels and dynamic testing. This is discussed in more detail below.

IMAGING

Imaging of the pituitary is covered in more detail in Chapter 83. In summary, imaging may be used to identify both intrinsic and extrinsic pituitary abnormalities in suspected adenomas (**Figures 84.1–84.4**).[34, 35]

The identification of an intrinsic lesion within a normal-sized pituitary in a patient with clinical features of a functioning adenoma may, however, be misleading because there is a significant background prevalence of asymptomatic pituitary adenomas in the general population. Concluding in a systematic review published in 2004, Ezzat and colleagues, for instance, identified an overall prevalence of pituitary adenomas of 16.7% (14.4% in autopsy studies and 22.5% in radiological studies).[36]

TABLE 84.4 Extrinsic pituitary adenoma spread

Direction of extrinsic pituitary spread	Expected symptoms	Notes
Superior, into the suprasellar cistern	Visual field defects: superior temporal quadrantanopia, bitemporal hemianopia	Most common direction of spread
Lateral, into the cavernous sinus	Usually asymptomatic	
Inferior, into the sphenoid sinus	Usually asymptomatic Possibility of CSF rhinorrhoea or meningitis	May result in a connection between the CSF spaces and the nose

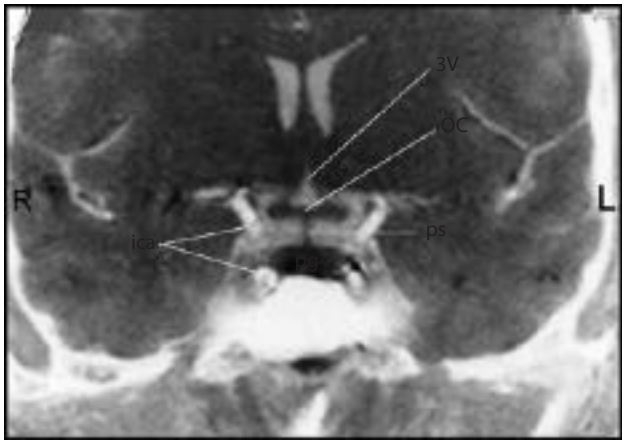


Figure 84.1 Normal pituitary gland. 3V, third ventricle; ica, internal carotid artery; oc, optic chiasm; pg, pituitary gland; ps, pituitary stalk; ss, sphenoid sinus.



Figure 84.2 T1-weighted MR scan without contrast showing a left-sided microadenoma as a hypointense area. a, adenoma; n, normal pituitary; ss, sphenoid sinus.

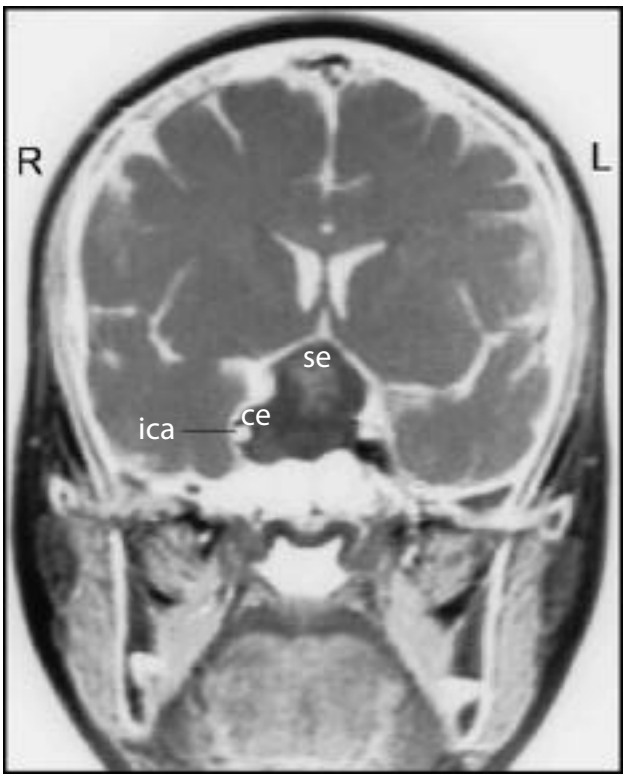


Figure 84.3 Macroadenoma of the pituitary with suprasellar extension and extension into the right cavernous sinus. ce, cavernous sinus extension; ica, internal carotid artery; se, suprasellar extension.

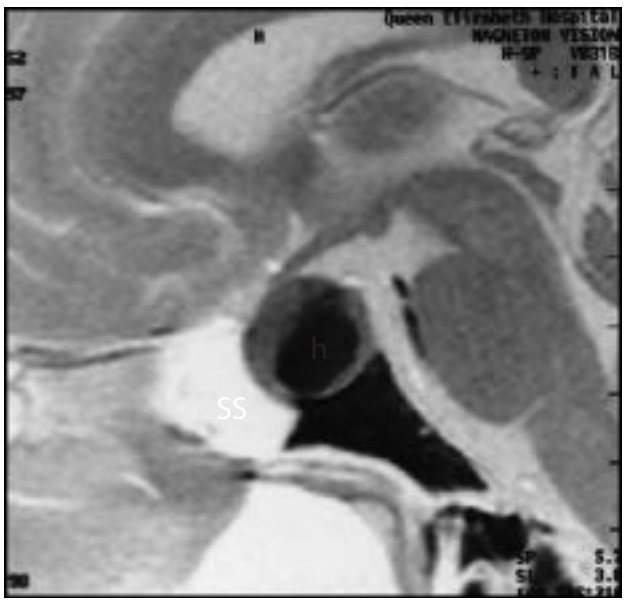


Figure 84.4 Sagittal T1-weighted MRI showing haemorrhage into a macroadenoma. H, area of haemorrhage; ss, sphenoid sinus.

A more recent review authored by Karavitaki in 2012 reported a prevalence of 78–94 cases/100 000 inhabitants.[37] It is also apparent that small functioning adenomas may not be visible on imaging.

Imaging is also used to provide information on invasion or displacement of adjacent structures if a tumour extends out of the pituitary fossa (termed an extrinsic pituitary abnormality).

VISUAL FIELD ASSESSMENT

Pituitary tumours result in visual field defects in some, but not all, patients.[38] When present, the typical visual field abnormality is a bitemporal superior quadrantanopia or hemianopia, but this will depend on the position of the optic chiasm in relation to the pituitary. The earliest detectable abnormality is loss of perception of a red target.

In most cases the visual field impairment is reversible if detected and treated early. It is thus imperative that all patients with pituitary tumours who complain of visual disturbance are referred for an ophthalmologist's opinion and visual field testing. Similarly, visual field assessment is vital pre- and post-operatively in patients with a macroadenoma that abuts the optic nerves or chiasm, even if there are no ocular symptoms.[38]

Functioning pituitary adenomas

PROLACTINOMA

Prolactin

Human prolactin is a protein consisting of 199 amino acids. It has similarities with GH and, though its predominant and most active form is a monomer, it also circulates as a dimer and polymer. Serum assessment of prolactin level is a reliable measure of this hormone and is used for both the diagnosis of prolactinoma and to monitor the effect of treatment. Circulating levels are higher in women than in men.

Prolactin regulation occurs via neural and feedback pathways to the hypothalamus and anterior pituitary. Inhibitory factors – PIF – and releasing factors are involved in the control of prolactin release. The main PIF is dopamine. Around 12–28% of cells in the normal anterior lobe produce prolactin. The control of secretion is complex and a wide range of factors and conditions influence prolactin secretion.

The main site of action of prolactin is the mammary gland where it acts to prepare for milk production and to maintain it.

Prolactin excess

Physiologically high levels of prolactin are to be expected during pregnancy and lactation. Pathological causes of hyperprolactinaemia include autonomous secretion of prolactin by a pituitary prolactinoma and loss of PIF from the hypothalamus. Levels of prolactin may be very high in prolactinomas and can exceed 10 000 mU/L. It is important to note that non-functioning adenomas may cause a moderate rise in prolactin levels of up to approximately 2000 mU/L.[39] This is likely a consequence of a loss of PIF due to stalk compression by the adenoma. Prolactin may also be elevated in GH-secreting adenomas as it can be produced in excess along with GH.[39]

Clinical features Physiological and pathological hyperprolactinaemia provide negative feedback on the hypothalamo-pituitary axis and suppress the release of GnRH. Clinical sequelae of hyperprolactinaemia include galactorrhoea. Amenorrhoea may also occur in women as a consequence of reduced gonadotrophins.[39, 40] Men are usually relatively asymptomatic but low gonadotrophin levels may reduce the secretion of testosterone, causing loss of libido.[40] Importantly, prolactinomas may cause few symptoms and no pituitary macroadenoma should be assumed to be non-functioning unless serum prolactin is less than 2000 mU/L.

Management Dopamine agonists, such as bromocriptine and cabergoline, are the first-line treatment for prolactinomas.[40, 41] Serum prolactin levels can be used to monitor their effect, as can neuroimaging. It is expected that prolactin levels will fall and that the tumour will shrink with dopamine agonist therapy but neither is guaranteed. Surgery or radiotherapy may be used in patients intolerant of or resistant to dopamine agonist therapy, and serum prolactin levels would again be used to monitor the result of either of these interventions.[42]

KEY POINTS

PROLACTINOMA

- Prolactin has an important role in preparing for lactation.
- Prolactin is physiologically raised during lactation and in pregnancy.
- Mild hyperprolactinaemia may occur in stress, with use of antidopaminergic drugs and in pituitary stalk compression.
- Prolactinomas can cause very high levels of prolactin and may result in galactarrhoea or amenorrhoea.
- Dopamine agonists are first-line treatment.

SOMATOTROPH ADENOMAS (SOMATOTROPHINOMAS)

Growth hormone

Also known as somatotrophin, GH is a single-chain 191 amino acid protein synthesized by somatotrophic cells, which contribute approximately half of the cells of the anterior pituitary. GH acts either directly on cells when it binds to GH receptors, or indirectly when it triggers the production of insulin-like growth factors (IGFs), which are mainly synthesized in the liver. IGF-1 is the most important of the IGFs and its mean concentration reflects that of GH over time. Concentrations of both GH and IGF-1 can be measured in serum but, because normal secretion of GH is pulsatile and the hormone has a short half-life in circulation, unlike IGF-1 which has a long half-life, the concentration of IGF-1 is a very useful indicator of mean GH output.

The pulsatile release of GH means that the volume secreted may be varied by the frequency or the amplitude of its pulses. When considering the diurnal rhythm, output is highest during slow-wave sleep. Over a lifetime, output is highest during adolescence and decreases with age. A random GH is normally less than 5.5 mU/L.

GH is anabolic and stimulates protein synthesis. It is essential for normal growth and protein metabolism. It also induces lipolysis and is secreted during hypoglycaemia, raising energy from body stores. Conversely, hyperglycaemia suppresses GH output. GH is also known to antagonize insulin, which is why acromegaly (excess of GH) may induce the onset of diabetes mellitus or make it worse.

Growth hormone excess: acromegaly

Excess GH results from the development of a functioning somatotroph adenoma.[43] If this occurs prior to closure of the epiphyseal plate, the result is gigantism. Excess GH after epiphyseal plate closure is referred to as acromegaly.

Clinical features The clinical features that characterize acromegaly derive largely from GH/IGF-1 excess but may also reflect excess prolactin, given that it is co-secreted in approximately 30% of tumours.[44] Common signs and

TABLE 84.5 An overview of the symptoms, signs and complications of acromegaly

Symptoms	Signs	Complications
• Sweating • Arthralgia • Headaches • Increased shoe size • Increased hand size • Preoccupation with appearance can result from physical changes	• Musculoskeletal • Enlargement of the hands and feet • Myopathy • Osteoarthritis • Deepening of the voice • Coarsening of the facial features • Jaw growth and macroglossia • Obstructive sleep apnoea commonly seen • Soft-tissue swelling • Carpal tunnel may result	• Metabolic syndrome • Hypertension • Insulin resistance • Ischaemic heart disease • Cerebrovascular disease • Congestive cardiac failure • Visual field defects • Obstructive sleep apnoea • Colonic polyp formation

symptoms of acromegaly are summarized in Table 84.5, as are the complications of this condition.

Diagnosis Random estimation of serum GH levels is unreliable as a consequence of its pulsatile release. Current Endocrine Society guidelines propose measurement of the downstream GH mediator IGF-1 in patients with features or conditions typically associated with acromegaly and in patients with a pituitary mass.[45] Acromegaly should subsequently be confirmed by identification of a lack of GH suppression to less than 1 µg/L in the presence of hyperglycaemia following on oral glucose load.[44] It is important to measure other pituitary hormones in view of potential pan-hypopituitarism. Serum calcium is also worth assessing as hypercalciuria may result from the stimulation of renal 1α-hydroxylase by GH. MRI demonstrates a pituitary tumour in 98% of cases following biochemical diagnosis.

It is important to screen for conditions associated with acromegaly following diagnosis. This should include evaluation for hypertension, multinodular thyroid enlargement, diabetes mellitus, osteoarthritis, sleep apnoea and cardiovascular disease. Patients should also be screened for colonic neoplasia.

Management First-line treatment for most patients is transsphenoidal surgery.[46] Endoscopic approaches are increasingly employed to improve the success of this procedure, recurrence rates for which currently stand at 6% at 5 years.[47] Specific complications of surgical intervention include hypopituitarism, transient mild syndrome of inappropriate antidiuretic hormone (SIADH – see 'Postoperative pituitary function' below) and CSF leak. Surgery should be considered even in those patients for whom cure is not expected (such as in the case of large invasive macroadenomas), because it improves cure rate with medical management.[48]

Radiotherapy is rarely used as a primary treatment for somatrotroph adenomas but may be employed if transsphenoidal surgery is unsuccessful.[49, 50] GH levels fall slowly after radiotherapy and may not return to normal for many years after treatment, meaning that adjunctive medical treatment is usually required and must be monitored at least annually. Side effects of radiation treatment include a risk of hypopituitarism and an approximate 2% increase in the incidence of second tumours within the radiation field. Newer approaches to radiation therapy include intensity-modulated radiotherapy (IMRT) and stereotactic radiosurgery (SRS).[51]

Three broad classes of drugs are used in the medical management of acromegaly.[50] Long-acting somatostatin analogues suppress GH secretion in approximately two thirds of patients with acromegaly, with symptomatic improvement common. Tumour volume reduction is seen in a significant proportion of patients managed with somatostatin analogues.[52, 53] Side effects include colic, diarrhoea and the development of gallstones.

Dopamine agonists also lower GH and IGF-1 levels but do not usually return these hormones to normal levels. Cabergoline is known to be more effective than bromocriptine and restores IGF-1 to normal in approximately one third of acromegalic patients.[54] Finally, for those patients who do not respond to somatostain analogues, pegvisomant is indicated. This acts by inhibiting GH receptor functional dimerization. IGF-1 should be used to monitor response to this therapy and has been reported to return to normal in more than 90% of patients.[55, 56]

KEY POINTS

FUNCTIONING SOMATROTROPH ADENOMA

- Acromegaly results from GH excess occurring after closure of the epiphyseal plate.
- Profound changes in physical appearance occur in untreated GH excess.
- Failure to suppress GH during a 75 g oral glucose tolerant test and elevated IGF-1 confirm the diagnosis of acromegaly.
- Transsphenoidal surgery is first-line therapy.
- There are long-term consequences to GH excess, including the metabolic syndrome and increased risk of colonic polyposis.

CORTICOTROPH ADENOMAS (CORTICOTROPHINOMAS)

ACTH

ACTH is a 39 amino acid peptide. It is derived from a large precursor protein which is found in the corticotrophic cells of the anterior and intermediate lobes of the pituitary, in some neuronal cell groups, in peripheral chromaffin cells

and some immune cells. In the anterior pituitary, 6–10% of cells are corticotrophs.

ACTH usually has a short circulating half-life and it is more usual to assay plasma cortisol levels and 24-hour urinary free cortisol production to screen patients for Cushing's syndrome. Both can be reliably measured. In normal subjects, plasma cortisol levels are highest in the morning and lowest at night. In Cushing's syndrome, this rhythm is absent and both plasma cortisol and urinary free cortisol levels are elevated.

Normal ACTH output is regulated by CRF and vasopressin. These two potentiate each other, but CRF output is suppressed by high circulating levels of glucocorticoids, whereas vasopressin is not. ACTH acts mainly on the adrenal cortex which secretes glucocorticoids, mineralocorticoids and androgens.

ACTH excess: Cushing's syndrome and Cushing's disease

Clinical features These are outlined in Table 84.6. They may gradually worsen over a period of years prior to a formal diagnosis being established.

Diagnosis Establishing a diagnosis of Cushing's syndrome is complex as a consequence of the diurnal rhythm of cortisol release. Endocrine Society guidelines advise testing for Cushing's syndrome in patients with early-onset features such as osteoporosis and hypertension, and patients with progressive symptoms typical of Cushing's syndrome. The first aim in investigating Cushing's syndrome is to confirm elevated cortisol. The underlying cause must then be clarified.

Is this Cushing's syndrome? Circulating glucocorticoid levels and 24-hour urinary free cortisol can be measured by routine laboratory assays. Investigations commonly employed to screen for excess cortisol secretion are outlined in Table 84.7. Two late-night salivary cortisol measurements may also be used for initial testing.

Physiological causes of hypercortisolism should be ruled out prior to confirming Cushing's syndrome. These include alcohol dependence, morbid obesity, poorly controlled diabetes mellitus, physical stress and pregnancy.

TABLE 84.6 Symptoms and signs of Cushing's syndrome

Symptoms	Signs
Mood disturbance	Change in facial appearance – 'moon facies'
Impairment of short-term memory	Development of striae
Loss of libido	Hirsutism
Irregular menstrual cycles	Easy bruising
	Weight gain & centripetal fat distribution
	Proximal myopathy
	Hypertension
	Osteoporosis/osteopenia
	Impaired glucose tolerance

TABLE 84.7 Investigations used to screen for Cushing's syndrome[57]

Test	Comments
24-hour urinary free cortisol	This is a useful screening test but should not be used in isolation for diagnosis because of a significant false negative rate.
Circulating glucocorticoid levels	Levels are measured by routine laboratory assays. Normal plasma cortisol levels are subject to large diurnal variation and the precise levels will depend on the laboratory used. In our institution, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK, normal levels are 180–550 nmol/L at 09:00 and <130 nmol/L at 00:00. Loss of diurnal rhythm is a feature of Cushing's syndrome.
Overnight dexamethasone suppression test	Dexamethasone is administered at midnight and serum cortisol assayed at 09:00. Plasma cortisol is effectively suppressed in normal subjects but not in patients with autonomous ACTH secretion.

What is the underlying cause? Once cortisol excess has been confirmed, its aetiology must be identified in order to differentiate Cushing's disease from Cushing's syndrome.[57, 58] This must be defined if treatment is to be appropriate and effective. Raised cortisol levels may be a consequence of excess production from the adrenal glands themselves, as in an adrenal adenoma or carcinoma, or due to excessive stimulation of the adrenal cortex by overproduction of ACTH, secreted from the pituitary or an ectopic source. The commonest cause of Cushing's syndrome is excess ACTH from the pituitary (70%), termed Cushing's disease.

The following investigations and results are used to determine the underlying cause of Cushing's syndrome:

- **ACTH:** If the source of excess glucocorticoids is adrenal, the plasma ACTH level will be suppressed.
- **Hypokalaemic alkalosis:** This is a feature of Cushing's syndrome due to ectopic ACTH, but not of Cushing's disease.
- **The high-dose dexamethasone suppression test:** This is used to differentiate between a pituitary source and an ectopic source of ACTH. While there are several variations of this test, the broad approach of this investigation is to exploit the differential sensitivity of feedback with increasing doses of dexamethasone between different causes of ACTH-dependent Cushing's syndrome. At low doses of 0.5 mg four times a day, for instance, the powerful glucocorticoid dexamethasone will suppress secretion of ACTH in normal subjects but not in subjects with autonomous ACTH secretion. However, pituitary secretion of excess ACTH is not totally autonomous, and so high doses of dexamethasone (2 mg four times a day) will suppress ACTH output from the pituitary. Conversely, ectopic sources of ACTH are more autonomous and suppression will not occur with either low- or high-dose dexamethasone.

TABLE 84.8 The dexamethasone suppression test

	Normal	Pituitary Cushing's	Ectopic Cushing's
Low-dose dexamethasone	Suppression of plasma cortisol and UFC	No effect	No effect
High-dose dexamethasone	Suppression of plasma cortisol and UFC	Suppression of plasma cortisol and UFC	No effect

A common approach to this test is to administer 2 mg dexamethasone orally every 6 hours for 48 hours. Serum cortisol is assessed prior to and following the administration of dexamethasone. Unfortunately, this test is not invariably accurate because 10–20% of ACTH-secreting pituitary adenomas do not suppress on high dose whereas 50% of ACTH-secreting bronchial carcinoid tumours show some suppression on high dose. It is therefore important to have additional evidence of a pituitary adenoma before concluding that the cause of Cushing's syndrome is a pituitary adenoma as opposed to an ectopic source of ACTH. This test is summarized in Table 84.8.

- **CRF test:** If CRF is administered, ACTH levels will rise in normal subjects. This response is exaggerated in Cushing's disease but is typically absent if the source of ACTH is ectopic. However, once again this test is not foolproof. Up to 10% of pituitary adenomas do not respond to infused CRF as would be expected and a few ectopic ACTH-producing tumours do respond by secreting more ACTH.
- **Metyrapone test:** This is a sensitive test of ACTH reserve but is now used less frequently given the wide availability of ACTH assays. Briefly, metyrapone blocks glucocorticoid metabolism and should therefore result in a rise in ACTH. This response is usually exaggerated in Cushing's disease, but not if the source of ACTH is ectopic.[59]
- **Inferior petrosal sinus sampling:** This is an invasive test used to define the source of excess ACTH, usually in instances in which pituitary MRI is normal or equivocal.[60] Given that Cushing's disease results from a microadenoma in more than 90% of cases, it is postulated that MRI identifies a causative lesion in only one third to two thirds of cases.[61] Inferior petrosal sinus sampling is regarded as the 'gold standard' for the diagnosis of Cushing's disease.[62] It may also predict adenoma lateralization, although it is usually accurate in only two thirds of patients, and holds out the prospect of localizing the source of ACTH within the pituitary itself.

This is an invasive technique, requiring cannulation of both inferior petrosal sinuses under radiographic control via the femoral vein. With the catheters in place, samples can be taken for hormonal assay. After baseline samples are taken to assay the pituitary hormone levels from each side, CRF is administered intravenously and further samples are taken to measure the effect on pituitary hormone output. High levels of ACTH in blood obtained from IPSS are strongly indicative of a pituitary source of ACTH. A differential between the levels of ACTH in the IPS and peripheral sample is further evidence of a pituitary source. If this is combined with a CRF test, a rise in the ACTH levels can be demonstrated with CRF. This raises the sensitivity of the test to 95%. Although there are large venous connections between the cavernous sinuses, the venous blood between the two may not mix very much.[63] If there is a marked difference in the ACTH levels between the two sides, without a similar asymmetry in the levels of the other pituitary hormones (prolactin, GH, FSH, LH), tumours can be localized by this technique.

Management This section refers only to the management of Cushing's disease. The first-line approach in most instances is selective adenomectomy via transsphenoidal surgery. Delayed normalization of cortisol levels following this procedure is not uncommon and complications of surgery are high as a consequence of patients' poor preoperative performance status.[64] Up to 25% of patients will develop a recurrent adenoma.[65]

Second-line treatment generally involves the use of radiotherapy.[64] Control of cortisol levels will not occur for a number of years (mean period of 2 years) and may induce hypopituitarism.

Medical management of Cushing's disease is often required during radiotherapy to control cortisol levels. Medical therapy is also indicated in instances in which surgery fails to control cortisol output or to treat acute, potentially life-threatening disease complications such as opportunistic infections, psychosis and severe hypertension.[66] Approaches include pituitary-directed treatments such as somatostatin analogues, administration of adrenal blocking drugs including mitotane and ketoconazole, and in a proportion of patients use of glucocorticoid antagonists such as mifepristone. Combination therapy is often required.

Bilateral adrenalectomy was previously favoured as the treatment of choice for Cushing's disease and may still be indicated if pituitary surgery, radiotherapy and medical treatment fail to control cortisol levels.[67] A laparoscopic approach can be used to reduce morbidity. An important complication of bilateral adrenalectomy is Nelson's syndrome.[68] This describes the rapid enlargement of a pituitary lesion as a consequence of the loss of negative feedback from high cortisol levels following adrenalectomy. It presents with visual and ocular effects, in addition to hyperpigmentation as a consequence of high circulating levels of ACTH. Prophylactic radiotherapy can be used to minimize the risk of this complication.

KEY POINTS

CORTICOTROPH ADENOMA

- Cushing's disease results from a functioning corticotroph adenoma.
- Hypercortisolaemia results in mood disturbance, loss of libido, change in facial appearance, proximal myopathy, weakened skin, easy bruising and a raft of other signs.
- Investigations into suspected Cushing's syndrome should first identify hypercortisolaemia and subsequently locate the source of the hypercortisolaemia.
- Inferior petrosal sinus sampling is essential when there is doubt about the origin of ACTH-dependent Cushing's syndrome.

TSHOMA

TSH

TSH induces release of both T4 and, to a lesser extent, T3. Most T4 is converted to T3 within the peripheries. In cases of primary hyperthyroidism, negative feedback from fT4 and fT3 results in inhibition of TSH release.

TSH excess

TSH secreting adenomas are rare and represent only a very small percentage of functioning adenomas.[69, 70]

Clinical features Patients may present with features of hyperthyroidism but on investigation for this will be identified to have inappropriately normal or elevated TSH levels.

Establishing a diagnosis Thyroid function tests are a key first-line investigation. If a TSHoma is suspected following thyroid function testing, an MR scan of the pituitary gland should be undertaken. Tumours may be micro- or macroadenomas.

Management Surgical excision, radiotherapy and medical treatment are all options for the management of TSHomas. These tumours respond well to somatostatin analogues.[69] They can, however, be more aggressive than standard pituitary adenomas and long-term biochemical and imaging follow-up is therefore appropriate. Radiotherapy can be considered if surgical cure is not possible.

GONADOTROPHINOMAS

These seldom present as functioning tumours. The diagnosis of a gonadotrophinoma is usually made on immunohistochemical analysis of non-functioning adenoma tissue following surgery.

FSHOMA

FSH

FSH is secreted by the gonadotrophin cells of the anterior pituitary and shares an alpha-subunit with LH, TSH and HCG. The specific actions of FSH, conferred by its beta-subunit, include stimulating germ-cell maturation, initiation of follicular growth in females and regulation of androgen-binding production from Sertoli cells in males. FSH secretion is enhanced by activin and reduced by inhibin.

FSH excess

FSH-secreting adenomas are seen more commonly in men and premenopausal women but are nevertheless rare.

Clinical features FSH-secreting pituitary adenomas are usually asymptomatic. Clinical features in male patients generally relate to tumour mass effect and the development of hypogonadism. An association between FSHoma and macroorchidism has also been reported, particularly in prepubertal males.[71] Development of an FSHoma in a premenopausal woman can result in ovarian hyperstimulation syndrome. This manifests as abdominal bloating secondary to increased ovarian size or the accumulation of ascites. FSH-secreting adenomas arising in postmenopausal women are invariably asymptomatic and present a significant diagnostic challenge.

Establishing a diagnosis Measurement of FSH is key in women.[72] In premenopausal women, elevated serum oestradiol with inappropriately high FSH is indicative of an FSHoma. LH is usually normal or suppressed, differentiating the clinical picture from that of polycystic ovarian syndrome. In postmenopusal women, a raised FSH may represent an FSHoma and warrants further investigation, with a higher index of suspicion confirmed by concomitant suppression of LH. Pituitary MRI is required to assess for a macroadenoma and this may often be the first-line investigation in men, who generally present with mass effect, though FSH should also be assessed.[72] Ultrasonography may additionally be employed in premenopausal women and in men in order to respectively identify ovarian cysts and macroorchidism.

Management Management requires multidisciplinary team input. Options include watchful waiting, surgery and radiotherapy.[73] Medical therapy is not generally effective for gonadotroph adenomas.

Non-functioning pituitary adenomas

These do not present with overt hormone excess and are instead characterized by the consequence of a space-occupying lesion spreading out of the pituitary fossa. They may be associated with partial or complete hypopituitarism. This classically involves a progressive loss of pituitary hormone secretion with gonadotrophins (LH and FSH) affected first, followed by GH, TSH and ACTH. Children may present with cessation of growth or delayed puberty.[74]

Diagnosis of non-functioning adenomas relies on both neuroimaging and the biochemical assessment of pituitary function. Prolactin should also be assessed but may be elevated in non-functioning pituitary adenomas. It is essential both that any hormone deficiency is corrected and that asymptomatic functioning adenomas are identified, particularly in the case of prolactinomas as medical management may render surgery unnecessary.

PITUITARY CARCINOMA

Pituitary carcinoma accounts for less than 0.1% of all tumours and is most commonly ACTH- or prolactin-secreting, though a significant proportion are non-functioning.[75] These tumours are more likely to be p53 positive. By definition, pituitary carcinomas feature evidence of metastatic disease. Metastases are more likely to be systemic (to liver, bone, lungs and the lymphatic system) than craniospinal. Mass effects predominate and surgery forms the mainstay of management. There is some evidence for the use of chemotherapy but data from controlled trials are lacking. Favourable responses have been reported with use of the alkylating agent Temozolomide.[76] Palliation may otherwise be afforded through medical management with dopamine agonists for malignant prolactinomas, and from the use of radiotherapy. Prognosis is poor and most patients die within a year.[75]

FAMILIAL PITUITARY TUMOUR SYNDROMES

Familial pituitary tumours are rare and account for less than 1 in 20 pituitary adenomas. They are nevertheless recognized to occur as part of multiple endocrine neoplasia type 1 (MEN 1), multiple endocrine neoplasia type 4 (MEN 4), Carney complex and familial isolated pituitary adenomas.

Multiple endocrine neoplasia type 1

MEN 1, alternatively known as Wermer's syndrome, is characterized by dermal tumours (including lipomas, lentiginosis and angiofibromas) in addition to tumours of the parathyroid, pancreas and pituitary. This occurs as a result of mutations in the *MEN1* gene and genetic analysis is recommended in patients with a strong family history and recurrent neoplasia in the organ distribution described above.[77]

Multiple endocrine neoplasia type 4

MEN 4 has only recently been described and occurs as a consequence of mutations in the *CDKN1B* tumour susceptibility gene.[78] The number of patients with MEN 4 remains low and there are consequently not yet guidelines in place for the management of patients with MEN 4. Pituitary adenomas are the second most common tumour type occurring in patients with *CDKN1B* mutations.[77]

Carney complex

Pituitary adenomas are seen in approximately one in five patients with this rare autosomal dominant condition.[79] Other tumours seen include myxomas of the breast, skin and heart, in addition to adrenal testicular and thyroid tumours.

Familial isolated pituitary adenomas

Familial isolated pituitary adenomas (FIPAs) represent 2% of all pituitary adenomas.[80] Around one in five cases of FIPA are thought to result from mutations of the aryl hydrocarbon receptor-interacting protein (AIP) gene, which causes pituitary adenoma predisposition of variable penetrance. Gigantism is a particular feature of AIP mutations and germline *AIP* mutations have been shown to correlate with the development of large pituitary adenomas.

POST-OPERATIVE PITUITARY FUNCTION

In functioning adenomas, successful surgery should correct the excess hormone secreted by the adenoma. It may, however, additionally render the patient deficient in other pituitary hormones and is unlikely to restore hormone levels which were deficient pre-operatively.

Hormone assays are used to assess the results of treatment. In microadenomas a resolution of the hormonal excess and persistently normal or low levels of that hormone indicate a cure and are a more accurate method of assessing the results of treatment than imaging. It is essential to test for all the pituitary hormones because the patient may develop a deficiency of any of them. If the pituitary is irradiated, the onset of hypopituitarism may be gradual. Lifelong follow-up is important, as recurrence or hypopituitarism can occur years later.

Patients should be advised that they may experience headaches following their procedure, that they must double their hydrocortisone dose if they are unwell and that they should not discontinue their medication without prior discussion with a health professional. Importantly, patients should also be advised not to drive following surgery until their vision is reassessed and to avoid sporting activities for 6–12 weeks.

FUTURE RESEARCH

There are a number of promising areas of future research in pituitary disease. Advances in genetically engineered mouse models and DNA sequencing technology may provide insight into mechanisms underlying tumour pathogenesis and invasiveness, leading to personalized genetic characterization and tailored treatments.

Chemokines (signalling proteins secreted by cells) have been identified as novel regulators of normal and tumour pituitary cell function; studies targeting chemokine networks may reveal novel therapeutic approaches for managing pituitary tumours.[81]

The role of tyrosine nitration in pituitary disease has also been studied; elucidation of mechanisms and biological functions of tyrosine nitration in pituitary tumourigenesis could potentially provide biomarker targets for novel pharmacological agents.[82]

KEY POINTS

- The pituitary gland plays an important role in regulating reproduction, metabolism and growth.
- Production of pituitary hormones is subject to marked cyclical rhythms, necessitating dynamic testing to diagnose some pituitary hormone excesses or deficiencies.
- Hypopituitarism may be congenital or acquired, and may feature isolated or combined hormone deficiencies.
- Benign pituitary adenomas are common, though many do not present clinically. They may be functioning or non-functioning.
- In functioning adenomas, clinical characteristics are determined by the effects of the excess hormone.
- Extrinsic growth of a pituitary adenoma can result in visual field impairment, or rarely CSF rhinorrhoea and meningitis.
- Management of post-operative pituitary hormone deficiencies requires specialist multidisciplinary team input led by an experienced endocrinologist.

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CHAPTER 85

SURGICAL MANAGEMENT OF RECURRENT PITUITARY TUMOURS

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: pituitary tumours, pituitary surgery, revision pituitary surgery, recurrent pituitary tumours and functional pituitary adenomas.

INCIDENCE OF RECURRENT PITUITARY TUMOURS

Recurrence of pituitary adenomas after traditional microsurgical removal is not uncommon. In the relevant literature, recurrence rates for pituitary adenomas vary between 7% and 21%.[1] Similarly, it is clear that regrowth after incomplete tumour removal is a very likely event, being reported in 39–75% of cases.[2–9] Risk factors for recurrence include incomplete resection at the initial surgery, frank invasion of the cavernous sinus, tumour type and strong expression of pituitary tumour transforming gene.[10–12] Gross total removal rates after endoscopic endonasal approach (EEA) removal of primary non-recurrent pituitary adenomas have been reported to be high, in the range of 77–96%.[13–16] In a meta-analysis of endoscopic surgery for pituitary adenomas, Tabaee and colleagues reported the overall gross total resection rate to be 78%.[17] The main factor limiting total resection was frank invasion of the cavernous sinus.[17]

Cavallo et al. noted a recurrence rate of 9% (59 of 635) of pituitary adenomas. After retrospectively analysing the patients who recur, they noticed that at primary surgery 38.9% of them (23 of 59 patients) had a lesion with negative predictive factors, such as a cavernous sinus invasion, high labelling index or young age at diagnosis.[18]

Surgery for recurrent tumours is indicated in the presence of mass effect or systemic effects of persistent hormonal hypersecretion, as observed in Cushing's disease and acromegaly/gigantism. Small recurrences confined to the lateral cavernous sinus region must be considered for radiation treatment.

PRE-OPERATIVE EVALUATION

In addition to the necessary clinical and diagnostic information used to indicate revision surgery, additional information should be sought in order to improve the safety and efficiency of subsequent surgery. Accordingly, the aims of the pre-operative evaluation are:

- to identify sequelae of the previous procedure that may hinder the efficient creation of a sinonasal corridor (e.g. significant sinonasal scarring or the presence of a foreign body used for the previous reconstruction)
- to develop an understanding of the reconstructive options available
- to identify any contraindications to surgery, such as active, untreated infection
- to identify sequelae of the previous procedure that may increase the risk of subsequent procedures (e.g. pseudoaneurysm).

Office-based nasal endoscopy is useful to guide the surgical planning, particularly in the setting of revision surgery. This allows the surgeon to assess the sinonasal cavity for surgical approach and reconstructive options, as well as to rule out sinonasal sequelae and the presence of infection. First, nasal endoscopy provides the surgeon with the necessary information to determine what form of reconstruction was performed prior to the revision (i.e. free graft or nasoseptal flap, NSF). Furthermore, careful inspection of a potential NSF will guide reconstructive options, in the event that a large cerebrospinal fluid (CSF) leak requiring vascular reconstruction occurs during the surgery. During the conventional transseptal approach with a microscope, there is risk of septal perforation or compromise of the sphenopalatine artery (SPA) or posterior septal artery, which supply the nasoseptal flap (Hadad-Bassagasteguy flap).[19] Therefore, in patients who have been operated on in this fashion previously, alternative flaps or other techniques will need to be considered in the event that a vascularized reconstruction is necessary (see 'Reconstruction options' below).

Meticulous radiological assessment is crucial when planning a revision pituitary surgery, particularly when dealing with recurrent functional microadenomas. Dedicated magnetic resonance imaging (MRI) of the sellar and parasellar regions can demonstrate tumour location, status of the medial cavernous sinus wall, distance of the lesion to the optic apparatus, signs of stalk deviation and degree of scarring tissue the surgeon may expect to find.

Any patient who underwent a previous transsphenoidal procedure must be considered for a vascular study in order to evaluate the internal carotid arteries (ICAs). It is very important to rule out the presence of pseudoaneurysm from previous cavernous sinus manipulation particularly if the same skull base team did not perform the original surgery. Furthermore, imaging such as computed tomography angiography (CTA) can be very helpful in ruling out previous vascular complications and can be used in the image guidance system localizing the ICAs, which may be completely exposed out of their canal due to the previous surgery. The CTA is also useful in determining the presence of buttress materials left during the previous procedure.

Complete endocrine evaluation is always necessary before any pituitary procedure in order to establish the patient's baseline and to rule out or confirm pre-operative hormonal deficits. This evaluation includes assessment of the following hormones:

- prolactin
- growth hormone (GH)
- insulin-like growth factor 1 (IGF-1)
- cortisol
- adrenocorticotrophic hormone (ACTH)
- thyroid-stimulating hormone (TSH)
- free triiodothyronine (T3)
- total thyroxine (T4)
- testosterone
- luteinizing hormone (LH)
- follicle-stimulating hormone (FSH).

Patients with hypopituitarism require appropriate replacement to avoid peri-operative complications, particularly if their cortisol levels are found to be low. Conversely, if cortisol levels are normal, the patients do not receive a steroid stress dose during anaesthetic induction to prevent confusion in the immediate post-operative lab values. Diabetes insipidus (DI) must be ruled out and addressed properly when present; the anaesthesiology and post-operative care teams must be aware of this condition and maintain the use of desmopressin when it is detected before surgery.

Patients with tumours causing compression of the optic apparatus must also be evaluated by ophthalmology. As with the endocrine assessment, this seeks to establish a baseline for post-operative comparison. If the patient has no objective visual deficit but the original tumour presented with optic compression, the ophthalmological evaluation is also required.

INTRA-OPERATIVE IMAGING NAVIGATION AND POSITIONING

In the setting of revision surgery, pre-operative imaging plays a critical role; this is in part due to the close relationship to important orbital and intra-cranial structures. Transsphenoidal approaches to the sella demand a high degree of surgical precision and an accurate understanding of the pertinent anatomical relationships.[20] This task can be challenging in patients with altered anatomy and poor anatomical landmarks, frequent in those patients who have had previous surgery or who have disease invading or engulfing the surrounding structures.[21, 22]

Both osseous and neurovascular structures may serve as important landmarks during transsphenoidal approaches to the sella. Hence, both computed tomography (CT) and MRI have their advantages and disadvantages: CT scans are generally optimal for identifying bone integrity and bony landmarks, while MRI is more suited for soft-tissue differentiation. The CT can also provide additional surface points during surgery and thus increase navigation accuracy.

The authors find that intra-operative navigation is especially useful during revision surgery, where normal anatomical structures may be distorted and, as mentioned above, there is a need to rule out previous vascular complications.[23, 24] In this setting, we resort to MRI navigation with the intent to better define the interface of tumour and normal anatomy fused with CTA, which can demonstrate more clearly the bony formation and changes caused by the previous procedure and the vascular structures. Ideally, fusion of the two modalities allows for discrimination of the tumour not only with surrounding soft tissue but also with the ICA and other vessels for more complex tumours, such as the relationship with the basilar artery and anterior circulation. That said, the surgeon often finds the tumour/gland interface to be misleading and must rely on direct observation during dissection to achieve optimal resection rates. These tumours may expand superiorly to

the suprasellar space, laterally to the cavernous sinus or inferiorly to the clivus. Information regarding key anatomical landmarks can be provided by the intra-operative image guidance system and are valuable in order to achieve safe tumour removal.[25]

Prior to setting up the intra-operative navigation system, the surgical team must decide if there is a need to fix the head of the patient. The authors typically use a three-pin Mayfield head clamp when there is cavernous sinus invasion (because electromyographic monitoring precludes the use of paralytics) or if there is more than 180 degrees of internal carotid encasement.[26] In cases where intra-operative monitoring is not necessary, the patient's head rests on a horseshoe head holder (**Figure 85.1a**). In these cases, a mask attached to a transmitter is placed on the face of the patient (**Figure 85.1b**) covered by clear drapes during the entire procedure, which is tracked by the optic system and allows dynamic image guidance (**Figure 85.1c,d**).

Finally, the authors always prepare the abdomen and the lateral thigh for a potential fat or fascia lata graft respectively (or in a high-risk patient, for the possibility of harvesting muscle to patch an injured artery) (**Figure 85.1e**).

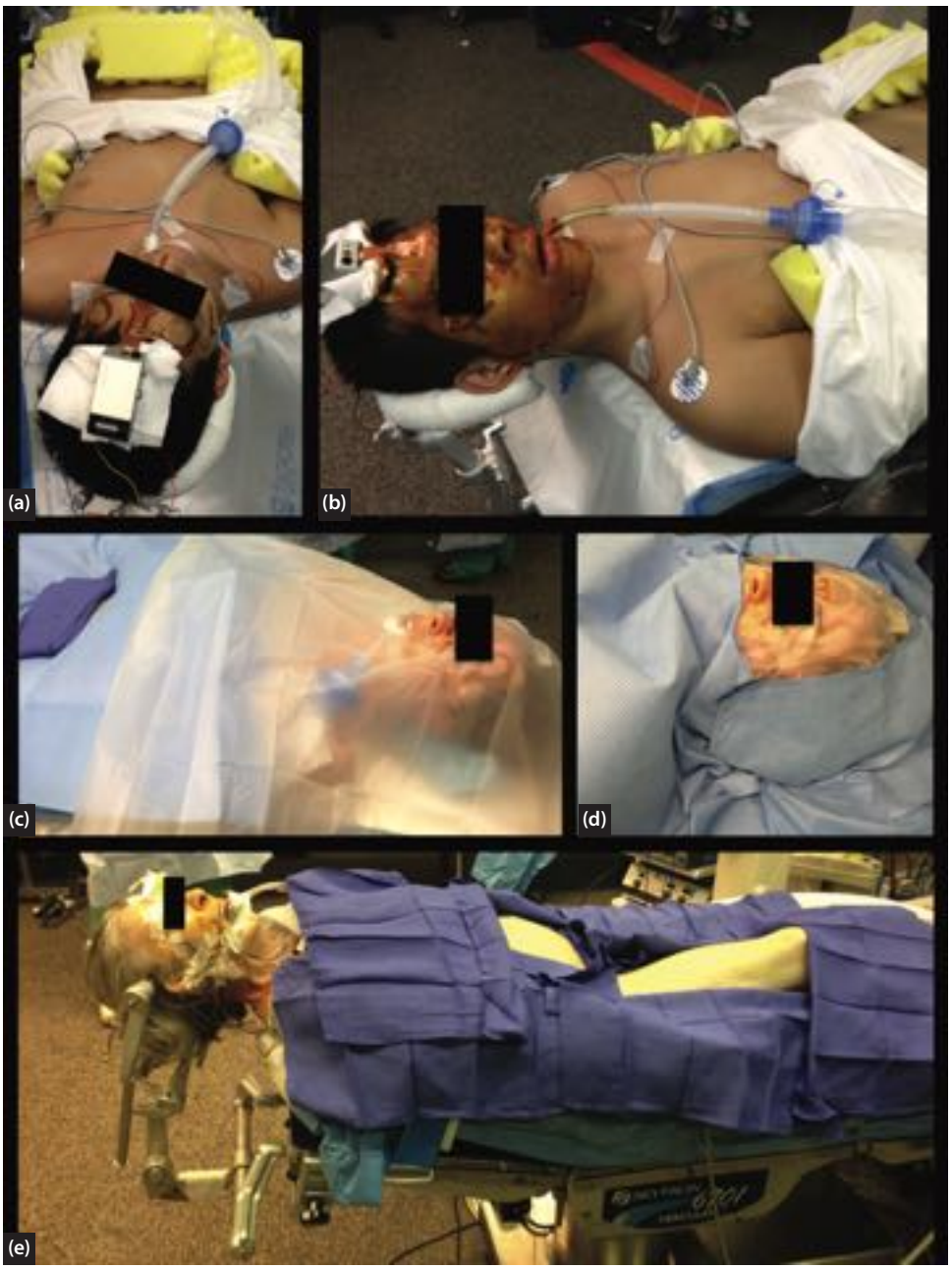


Figure 85.1 Patient and image guidance positioning. (a,b) The patient is supine with the head slightly tilted to the right, resting on a horseshoe head holder. The navigation mask and transmitter are placed on the patient's face; the abdomen has been prepared. **(c,d)** The patient's face is covered with transparent sterile drapes and surrounded by standard drapes. **(e)** In this case both the abdomen and thigh were prepped; the head is secured on a Mayfield head holder and the navigation transmitter is attached to it.

TECHNICAL PEARLS FOR TUMOUR REMOVAL

Recurrent tumours must first be distinguished between secreting or non-secreting; this classification carries implications during the procedure itself regarding the goals of surgery (total resection versus debulking). Appropriate workup is performed as outlined in previous chapters to establish the endocrine profile of the lesion. Functional tumours, such as those seen in the setting of Cushing's disease, acromegaly/gigantism and hyperprolactinemia, on average have a higher recurrence rate than non-functional tumours (15–30% versus 10% respectively).[27]

The first and foremost surgical pearl is to maximize the exposure of the sphenoid sinus and sella. A recent study demonstrated that the lack of exposure during initial tumour removal was a significant cause for recurrence.[28] For this reason, the sphenoid keel must be completely removed or drilled down to expose the sphenoid floor; this manoeuvre provides the necessary working angle for the cranial to caudal exposure. Removing all bony septations within the sphenoid sinus maximizes horizontal exposure, thus, providing access from lateral wall to lateral wall with clear visualization of the lateral opticocarotid recesses (LOCR), when is present (**Figure 85.2a**). We favour the use of a high-speed drill for the removal of septations in lieu of rongeurs because the drill provides more control. These inter- and intra-sinus septations often end on a dehiscent ICA and their removal with a blunt forcep or rongeur may fracture the ICA canal and lacerate the vessel.[29]

When drilling down the face of the sella, enough bone must be removed as to expose the 'four blues'.[30] These represent the walls of the cavernous sinus laterally and the intercavernous sinuses superior and inferiorly (**Figure 85.2b**). The authors typically drill the face of the sella until its wall is very thin, and then use a Kerrison rongeur as a dissector to separate and then lift the bone off the dura, avoiding the urge to bite the bone with the rongeur. This technique helps to avoid an inadvertent internal carotid injury as well as tears in the cavernous sinus wall. Bone that does not fracture with a gentle pull from the Kerrison rongeur indicates the need for further drilling. In addition, drilling of the sellar floor and the surrounding bone provides the ability to retract the internal carotid artery laterally and the use of a cotton tip applicator[31] to manipulate the tumour from below.

Once the bone is satisfactorily removed, one frequently encounters the material that was previously used for reconstruction; most often this is a fat graft that turns into dense scar. Typically, fat becomes too fibrous to remove with a two-suction technique; thus, the authors typically use dissectors and true-cutting instruments to separate and remove the fibrosis. During this phase of dissection, CTA-based image guidance is helpful to define those areas of the ICA that became dehiscent from previous exposures. If there is bone protecting the ICA, sharp dissection can be used to separate the tissues safely.

Once the dura of the sella is well exposed, a feather blade (Mizuho; Tokyo, Japan) is used to make the incision, usually starting in the centre of the sella and carrying it down vertically. The dura is separated from the underlying gland or tumour with a ball probe, avoiding separating the two layers of dura. The incision is then extended laterally towards the cavernous sinus using 45° angled microscissors, both superior and inferiorly. The superior cuts must be performed parallel to the sphenoid floor, so as to avoid violation of the arachnoid membrane of the diaphragm sellae and a subsequent CSF leak. A dissecting instrument is then used to explore the tumour and identify landmarks, including the medial wall of the cavernous sinus and the diaphragm sellae. The use of navigation and endonasal acoustic Doppler sonography probes (Mizuho; Tokyo, Japan), to confirm intra-operative anatomy, is prudent in all revision cases.[32]

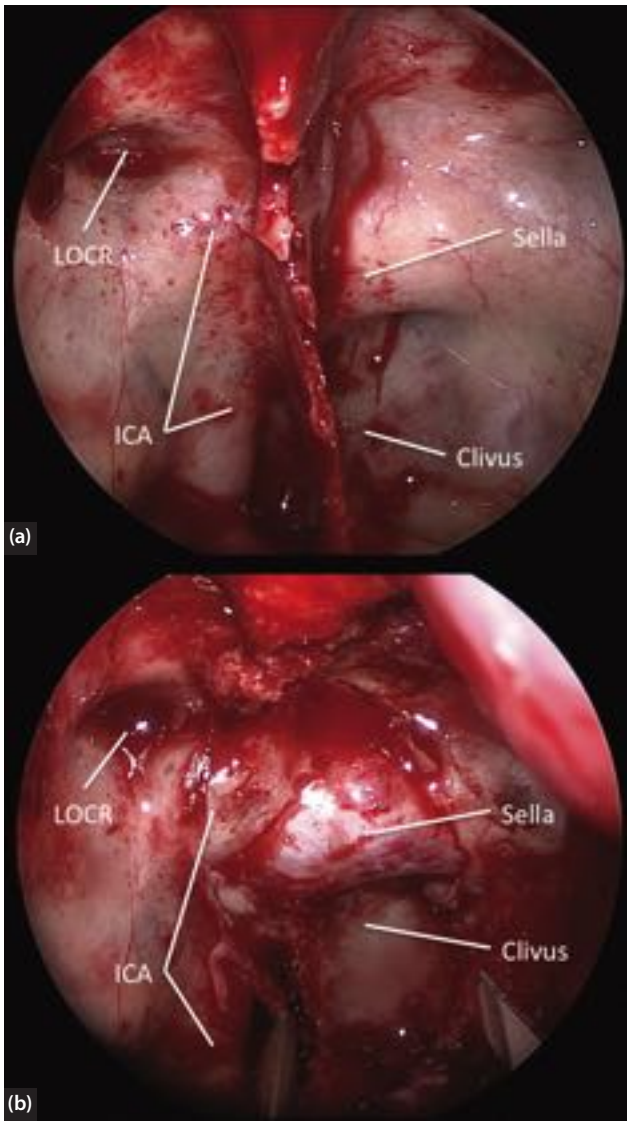


Figure 85.2 Exposure for resection of a pituitary microadenoma. (a) The sphenoid sinus has been entered; observe the bony landmarks and the relation between the septation and the right ICA. **(b)** The face of the sella has been removed, from ICA to ICA and from superior to inferior intercavernous sinuses. Note the proximity between the ICAs, narrowing the operative corridor. ICA, internal carotid artery; LOCR, lateral opticocarotid recess.

Tumour consistency dictates the instrumentation choices. Tumours that are soft are dissected and debrided using a two-suction technique. More fibrous tumours require the use of microscissors or a side-cutting power instrument (Myriad, NICO Corporation; Indianapolis, Indiana). The authors find that the ultrasonic aspirators currently available are aggressive and may inadvertently draw neurovascular structures into the instrument.

If a solid or extremely fibrous tumour is encountered but it is not invading the cavernous sinus, an extracapsular dissection is attempted, provided that the lesion is of reasonable size. Extracapsular dissection is safer than powered instrumentation and the surgeon can define the landmarks and planes for dissection while freeing the tumour from the surrounding structures. It is crucial to find the compressed pituitary gland early during this dissection in order to avoid extracapsular resection of the gland along with the tumour and consequent panhypopituitarism. The dissection must take place between the pituitary gland and tumour interface. If the lesion is very large, it can be debulked before these manoeuvres are employed.

A cotton tip applicator is a practical and relatively atraumatic retractor that decreases the risk of damaging the arachnoid membrane and producing a CSF leak while retracting the descending diaphragma sellae. More importantly, this manoeuvre greatly assists in identifying the tumour–gland interface, exposing the plane of dissection.[31, 33]

RECONSTRUCTION OPTIONS

Rescue flap

A rescue flap is elevated in most patients undergoing an endoscopic endonasal resection of a pituitary adenoma.[34] In this setting, the rescue flap allows the mobilization of the pedicle from the face of the sphenoid, therefore allowing for a wide sphenoid opening without compromising the blood supply to the nasoseptal flap. The rescue flap technique avoids the donor site morbidity associated with a nasoseptal flap.[35] A rescue flap harvest begins by incising the mucosa over the rostrum of the sphenoid sinus from the lateral wall of the nose at the level of the sphenoid ostium, carrying the incision over the sphenoid rostrum, and then anteriorly into the nasal septum mucosa (for approximately one third to half of the septum following the sagittal plane). Recently, the authors have incorporated an additional inferior incision as a modification to the original description, to increase the pedicle inferior mobility.[36] At the end of tumour resection, if a nasoseptal flap is not needed, absorbable packing reapproximates the pedicle to the bony rostrum.

Endoscopic reconstruction with free tissue grafts

Free tissue grafts are commonly used to reconstruct skull base defects after an EEA for a recurrent pituitary adenoma. Typically, they are used to reconstruct small to moderate (i.e. less than 1 cm), low-flow CSF leaks; however, in revision cases, there may not be a middle turbinate from which to harvest a graft if an EEA was performed at the time of primary resection. In this scenario, a variety of techniques such as a 'bath plug' repair or inlay–onlay strategy with acellular dermis or fascia lata may be employed. Regardless of which reconstructive tissues are employed, a multilayer technique and complete defect coverage are critical to achieve a dependable reconstruction.

First, a subdural or epidural inlay graft of collagen matrix (Duragen, Integra Life Sciences) or fascia lata is placed; this helps to stop (or at least reduce) the flow of CSF and decrease the dead space. Collagen matrix is pliable and soft, thus allowing for its safe manipulation around neurovascular structures. This subdural or epidural graft should extend beyond the dural margins, ideally 5–10 mm in all directions. If the graft is placed in the subdural space, a subsequent inlay graft of acellular dermis or fascia lata is placed in the epidural space (between the dura and the skull base). Occasionally, the bony edges are not adequate to support an inlay graft; the graft is then placed extracranially as an onlay (on the nasal side of the defect). It is critical that the edges of the defect are meticulously denuded of mucosa to allow for revascularization of the graft and to avoid mucocele formation.

Once the in- and onlay grafts are in place, a free tissue graft is applied if one is available. Healing of free mucosal grafts (i.e. take) is excellent; however, they are limited by size and the fact that they can only be used as onlay grafts. If a mucosal graft is not available, the reconstruction is bolstered with a free fat graft, typically harvested from the abdomen, or a free fascial graft, which can be fascia lata or temporalis fascia. The final layer consists of non-adherent packing such as absorbable gelatin sponge squares and expandable sponge packing or the balloon of a Foley catheter to further bolster the reconstruction. Any nasal packing is removed 3–5 days after the procedure.

Nasoseptal flap takedown

Increasingly, we have encountered patients who have had prior NSF placement for reconstruction. Although the authors generally do not use a nasoseptal flap for the reconstruction of a CSF leak associated with pituitary surgery (since the success rate with free tissue grafts is excellent), they do try to reuse the flap in patients who have had one previously. This manoeuvre has been termed 'the nasoseptal flap takedown technique'.[37]

The edges of the flap and the nasal mucosa can usually be clearly defined; however, the longer the period after the first surgery, the more difficult this delineation becomes. Once this interface is identified, the edges of the flap can be followed down to its pedicle (usually found overlying the pterygoid wedge). This pedicle must be preserved during the second surgery. The edges of the flap are mobilized centripetally using the sharp end of a Cottle elevator, thus exposing the underlying bony edges of the prior surgical defect. The nasoseptal flap is then elevated in a distal to proximal fashion towards the pedicle. Any soft-tissue structure that was exposed as part of the primary

operation will heal and adhere to the undersurface of the flap (periosteal side) and therefore commonly requires a two-surgeon, four-hand sharp dissection. The pedicle is then mobilized from the underlying bony pterygoid wedge, and the flap is stored in the nasopharynx. Once the extirpative portion of the case is complete, the flap is repositioned over the defect.

There are some specific limitations of the nasoseptal flap takedown that do not apply to primary nasoseptal flap skull base reconstructions: its shape is defined by the healing process over the defect (as it heals and contracts, the flap conforms and moulds itself to the defect); it is less pliable and will retain the shape of the previous defect; it tends to migrate out of the nasopharynx into the surgical field due to increased stiffness and fibrosis. These must be kept in mind when the takedown is performed.

A case illustration of a 45-year-old female who presented with a recurrent adenoma is shown in Figures 85.3 and 85.4.

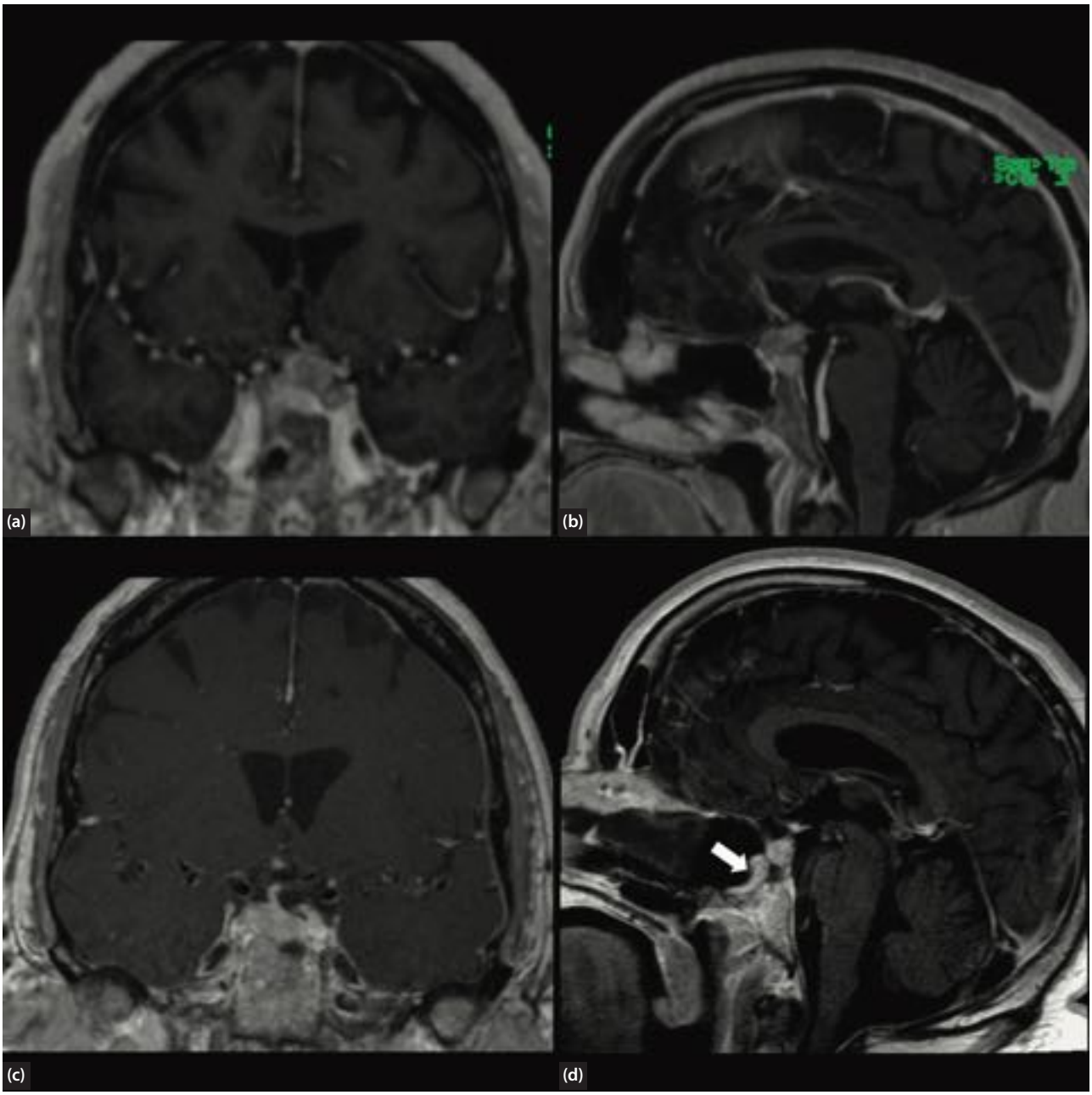


Figure 85.3 Case illustration 1. This 45-year-old female presented with a recurrent adenoma expanding into the suprasellar space and abutting the optic chiasm; her initial surgery was performed endonasally elsewhere. Pre-operative coronal **(a)** and sagittal **(b)** contrast T1-weighted MR imaging reveals the tumour on the superior left portion of the sella; the gland is seen inferiorly and to the right. Note the relation of the lesion to the optic chiasm. Post-operative coronal **(c)** and sagittal **(d)** contrast T1-weighted MR imaging confirms a thorough resection of the tumour with decompression of the optic apparatus; note the enhancing nasoseptal flap (white arrow).

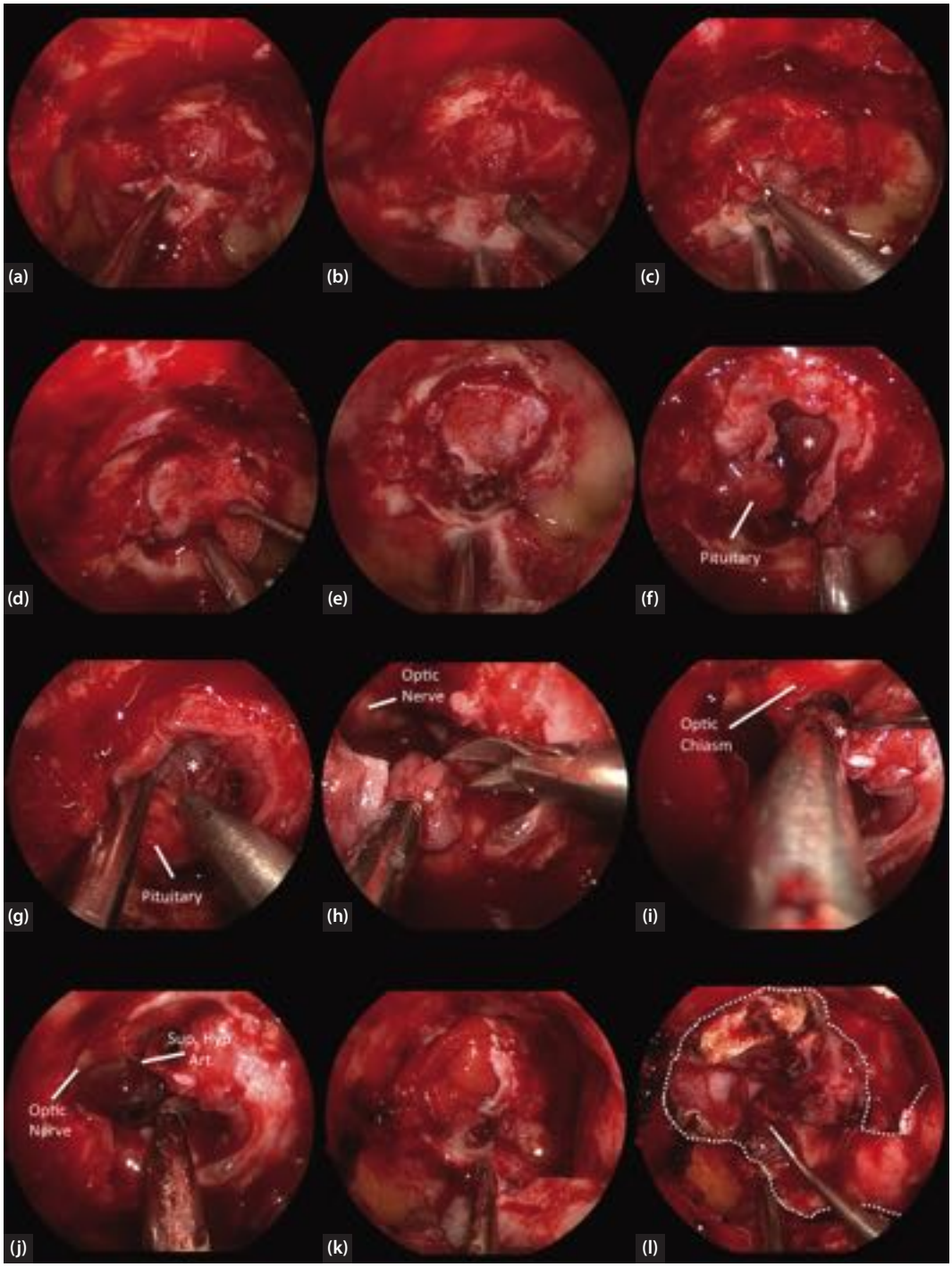


Figure 85.4 Case illustration 2. Stepwise depiction of the case illustration surgery shown in Figure 85.3. **(a)** Sphenoid sinus exposure; note the poor definition of the surgical landmarks. **(b)** The sellar bony opening is expanded with the use of a high-speed drill. **(c)** Scar tissue is displaced by blunt dissection and rongeur removal. **(d)** The Cottle dissector is used to elevate the buttress material employed in the previous surgery from the underlying dural replacement. **(e)** The sella is outlined, from ICA to ICA and from superior to inferior intercavernous sinuses. Note the dural replacement. **(f)** The dura has been opened and the pituitary gland and tumour (*) are visible. **(g)** The double-suction technique is employed to debulk the lesion (*). **(h)** Sharp dissection enables safe removal of the tumour (*) from the optic apparatus. **(i)** The last tumour remnants (*) are separated from the optic chiasm with a fine dissector. **(j)** Final view after tumour removal, prior to reconstruction; the right superior hypophyseal artery (Sup. hyp. art) has been preserved. **(k)** The dural defect is plugged with a collagen matrix replacement. **(l)** A left nasoseptal flap, raised during the approach, is applied over the defect (dotted line). Observe the pedicle arising from the left sphenopalatine foramen.

POST-OPERATIVE MANAGEMENT

All patients submitted to an endonasal endoscopic resection for a recurrent pituitary tumour are sent to an intermediate care unit after surgery where specific monitoring for DI and hypotension secondary to acute hypocortisolism can take place. If the patient is already on desmopressin and/or steroid replacement pre-operatively, these are maintained and rigorous electrolyte surveillance is performed. If pituitary function is normal before surgery, patients are monitored clinically and with prolactin and cortisol serum levels the morning after the procedure. If hypocortisolism is detected, steroid replacement is instated. If new onset DI is observed and the patient is awake and coherent, oral fluid replacement with water is encouraged. If sodium levels remain stable after the initial 48 post-operative hours, it is likely that the posterior gland recovers function and there will be no permanent DI. Otherwise, if desmopressin is initiated, the patient must be challenged by the endocrinologist with increasingly lower doses to determine whether function is still present or is permanently gone.

Patients with Cushing's disease are observed more closely, with ACTH levels checked during and after surgery and cortisol sampling every 6 hours for the initial post-operative 48 hours. This period of time is usually sufficient to determine whether steroid levels will drop enough to cause symptoms ('crashing'). If cortisol levels drop below 5 mcg/dL, steroid replacement is initiated regardless of the patient's clinical status.

Patients with acromegaly or gigantism do not require specific measures other than cortisol and prolactin sampling the morning after surgery. Long-term remission is assessed with GH and IGF-1 levels, typically in an endocrinology clinic within the first 6 weeks after the operation.

Whether and which nasal packing is necessary is determined by the reconstructive technique. As previously mentioned, packing is kept in place for the initial 3–5 days after the procedure. For the first 24 hours, the same antibiotics given during anaesthetic induction (typically cefepime and vancomycin, when needed) are maintained. An oral broad-spectrum antibiotic is used after that for as long as the packing is in.

All patients are seen at the otolaryngology clinic within the first week of discharge; the nasal packing is removed and endoscopy is used to assess healing and debridement of crusting. The degree of crusting will ultimately determine the frequency of visits the patient must endure during the recovery period for nasal hygiene.

CONCLUSION

In summary, recurrent pituitary adenomas are an excellent indication for an endoscopic endonasal approach. The wide-field visualization afforded by the endoscope allows a superior level of safety where the surgeons can observe the key sphenoid landmarks. As with any reoperation, there is a need for adequate preparation before the procedure and adequate planning for surgical resection and reconstruction. Intra-operative image guidance plays a crucial role in avoiding complications, particularly of the vascular kind.

KEY POINTS

Pre-operative management and planning

- Meticulous radiological investigation with head CTA and pituitary MRI is required.
- Assess pituitary function.
- Assess visual function.
- Conduct endonasal evaluation with office endoscopy (rule out infection, assess reconstruction options).

Image guidance

- Fusion between CTA and MRI increases accuracy.
- CT bone window can be used to provide additional reference points.

Intra-operative management

- Bone removal and exposure are paramount to adequate tumour resection.
- Image guidance and acoustic Doppler sonography help to avoid vascular injuries.

Skull base reconstruction

- The rescue flap minimizes nasal morbidity while securing the flap pedicle.
- Free tissue grafting is effective for the majority of CSF leaks after pituitary surgery.

Post-operative management

- Endocrine function and electrolyte levels must be closely monitored.
- Clinic visits are key to preventing excessive crusting and infection.

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CHAPTER 86

ADJUVANT TREATMENT OF PITUITARY DISEASE

Andy Levy

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: adjuvant treatments for pituitary tumours.

OVERVIEW OF PITUITARY ADENOMAS

The incidence of clinically overt pituitary adenomas is around 15–20 per million per year. Fifty to sixty percent are microadenomas and these, by definition, regain trophic stability after a period of deregulated post-induction growth. A further proportion of pituitary macroadenomas grow slowly or not at all and may not require intervention if bioactive hormone secretion is not a feature. Overall, approximately one third of pituitary adenomas require surgical intervention at least once, and as their prevalence is relatively high – 2.5 cases per 10 000 – pituitary adenomas constitute the third most common intra-cranial tumour requiring neurosurgical intervention. Occult pituitary adenomas are more common still, with histological evidence of pituitary adenomas at the time of death from unrelated causes in 11–14% of the population.[1, 2]

Approximately 50% of newly diagnosed pituitary adenomas are prolactinomas. Endocrinologically inactive adenomas account for 30%, somatotrophinomas for 15–20%, corticotroph adenomas for 5–10% and thyrotroph adenomas for less than 1%.[3] Limited dural invasion is fairly typical in all macroadenomas and slow expansion over a period of years expected. Aggressive expansion, requiring repeated surgery and adjuvant treatment is atypical, and frank metastatic spread is exceptionally rare.[4]

Non-specific symptoms

Headaches typically associated with pituitary adenomas are non-specific, variable in their characteristics and insidious in onset. They can mimic classical migraine, tension headaches, sinusitis and various causes of facial pain. Analgesics, tricyclic antidepressants at low dose, verapamil and beta-blockers can sometimes be helpful, as can a trial of withdrawing dopamine analogues if possible (e.g. bromocriptine). Headaches caused by haemorrhage that originates within a pituitary mass (pituitary apoplexy) or haemorrhage following pituitary infarction (e.g. in some cases of Sheehan's syndrome) are characteristic of meningeal irritation and tend to start abruptly. Headaches can be cured by transsphenoidal surgery or precipitated by the same.

PRIMARY TREATMENT

With the exception of prolactinomas, first-line treatment for pituitary adenomas that hypersecrete or cause mass effects remains transsphenoidal decompression. This remains the case if the lesion extends into the suprasellar cistern although, if the diaphragma is substantially intact, a pterional or subfrontal approach is sometimes preferred. Outcomes depend critically on the skill of the operator, but even the most gifted and experienced surgeons are rarely able to fully excise a pituitary macroadenoma.

Meningitis and damage to visual apparatus or vascular structures is rare with standard or endoscopic surgery, but longer-term problems of hypopituitarism, impaired olfaction or gustation and a tendency to sinusitis if the nasal septum is damaged or displaced are more common. Endoscopic transsphenoidal surgery requires more generous access and has a higher risk of CSF leakage.

WHY IS ADJUVANT TREATMENT NEEDED?

Most clinically significant pituitary disease results from sporadic pituitary adenoma formation. Complete excision of a pituitary adenoma of any description is far from a universal surgical outcome. Approximately 30% of non-functioning pituitary macroadenomas increase in size to some extent within 5–10 years of the original surgical intervention[5] and micro-invasion of surrounding structures is common.[6] Certainly for endocrinologically inactive macroadenomas the aim of primary surgical intervention is debulking rather than attempted complete excision as this addresses immediate issues of space occupation and seems in many cases to discourage remnant growth. Even in optimistic series, clinically significant residual tumour tissue is present in at least 20% of cases.[7] After surgery for tumour recurrence, almost 40% of patients experience a sustained remission,[8] yet up to 60% of functioning pituitary macroadenomas remain biochemically active after primary treatment[9, 10] and, particularly for these, adjuvant treatment may be required.

Recognition of the benign nature of the vast majority of pituitary adenomas, technical advances in transsphenoidal surgery, particularly more effective and comfortable ways to close the bony deficit in the pituitary fossa and sphenoid, nagging concerns about potential long-term side effects of radiotherapy and improved screening with the ready availability of high-quality (and X irradiation-free) MRI has made watchful waiting the norm.

If the adenoma extends laterally into a cavernous sinus, proximal to the carotid syphon and cranial nerves without any danger of impingement on the optic apparatus, other treatments are likely to be first line.

PROLACTINOMA

A dopaminergic drug, typically cabergoline (0.25–1 mg once or twice a week) or bromocriptine (2.5–10 mg daily) is first-line treatment for prolactinomas. Although dopamine agonists are not teratogenic, current best practice at the time of writing, with no clear rationale, is to stop dopamine analogues when pregnancy is confirmed. Symptomatic tumour regrowth during pregnancy is unusual. The convenience and excellent side-effect profile of the long-acting, ergot-derived D2 agonist cabergoline made it the preferred treatment in most cases until 2007 when (along with pergolide) an association with valvular heart disease was described[11, 12] At the low doses used for prolactinoma rather than Parkinson's disease, the same association has not been demonstrated in pituitary disease[13, 14] and echocardiographic screening is not generally considered necessary.

Microprolactinoma

Where drug treatment is not first-line owing to side effects or costs, microadenomectomy in symptomatic premenopausal women may be curative if a suitably skilled and experienced surgeon is available. If fertility is not required and galactorrhoea is not an issue, oestrogen replacement may be a satisfactory alternative to a dopamine agonist. Postmenopausally, it may be perfectly appropriate to offer no specific treatment other than reassurance. Microprolactinomas occasionally spontaneously resolve (about 7% overall, increasing to almost one third after a pregnancy) but change little in size in response to dopamine analogues.

Macroprolactinoma

It is rare for surgical decompression alone to bring prolactin output from a macroprolactinoma into a range when no further treatment is required. Biopsy is rarely required to confirm the diagnosis, but very occasionally surprisingly large prolactinomas release very modest amounts of prolactin and are mistaken for endocrinologically inactive macroadenomas that are assumed to be restricting portal dopamine flow by compressing the pituitary stalk. Surgery may be appropriate, however, if the patient's compliance with tablet treatment is poor or if the patient is intolerant of dopamine analogues, usually because of psychoses or intractable nausea and dysphoria. Prolactinomas are rarely resistant to dopamine analogues but occasionally response times are relatively prolonged.

Unless accompanied by haemorrhage and altered blood or cystic degeneration, 90% of macroprolactinomas can be expected to shrink with dopamine analogue treatment,[15] to the extent that, if the sphenoid bone has been eroded, a CSF leak may result. A small proportion of macroprolactinomas involute completely after long-term dopamine analogue treatment and treatment can be cautiously withdrawn without tumour recurrence.

The second generation alkylating chemotherapeutic agent temozolomide, related to the imidazotetrazines used primarily for grade IV astrocytomas (i.e. glioblastoma multiforme) and sometimes for oligodendrogliomas, has been used successfully for exceptionally rare and resistant cases of malignant pituitary adenomas including a case of malignant (i.e. metastatic) prolactinoma.[16] Anecdotally, a useful effect of temozolomide has been reported in approximately two thirds of 16 pituitary carcinomas and 30 aggressive pituitary adenoma cases.[17]

SOMATOTROPHINOMA

Even in the hands of experienced surgeons, primary transsphenoidal decompression of somatotroph adenomas in isolation has only a 50:50 chance of achieving immediate

and longer-term biochemical remission. At least one third of post-operative patients have persistent disease despite additional medical therapy.[18] Even if the GH response to a glucose load meets the current criterion of 'cure', i.e. GH suppression to <1 mcg/L after a 75 g oral glucose load, a further post-operative cohort continues to experience subtle symptoms that significantly impair quality of life, associated with a normal or only modestly elevated IGF1. Persistent disease is associated with an approximately fourfold increased risk of colorectal carcinoma and with widespread arthralgia and arthritis, impaired glucose tolerance, hypertension, carpal tunnel syndrome, sweating, obstructive sleep apnoea and dysmorphophobia, all of which contribute to a 30% increase in all-cause mortality[19] and all of which need individual and specific management irrespective of ongoing pituitary function or dysfunction.

Somatostatin analogues

Evidence for a beneficial effect of somatostatin analogue treatment before pituitary surgery is inconsistent and unconvincing. In the event that surgery and sometimes repeated pituitary surgery does not secure remission, or when surgery is inappropriate owing to comorbidity, infirmity, technical difficulty (i.e. tumour remnants are out of reach) or because it does not concord with the patient's wishes, long-acting somatostatin analogues are typically the adjuvant treatment of first choice. Somatostatin analogues are reasonably well tolerated, although they produce variable abdominal cramping and bloating that diminishes over time but may recur for a short time after each injection. Accumulation of biliary sludge resulting from reduction in gallbladder motility is rarely a problem. A modest degree of remnant tumour shrinkage (typically by about one third volume (10–50%) in a third to a half of cases[20–22] probably results from a reduction in the size of individual somatotroph cells and hence in overall tumour size rather than an absolute reduction in somatotroph cell numbers. Circulating growth hormone and IGF1 levels drop fairly rapidly into the reference range in about 50% of cases, and typically the efficacy of treatment becomes more pronounced over time such that, after about 5 years, most patients have circulating GH levels within the 'normal range'. Doses are titrated up if control is not achieved after several months' treatment, but over time it may be possible to reduce the dose or increase the dosing interval further.[23] Long-term treatment has significant economic costs and can over time become irksome for patients for whom uncomfortable and socially disruptive injections are a life sentence. For many patients who are not put into remission by initial surgery, somatostatin analogues are used until such time as fractionated radiotherapy takes effect.

Newer long-acting and broad spectrum somatostatin receptor ligand with high affinity to receptor subtypes 1,2,3 and 5 (pasireotide) and chimeric somatostatin and dopamine receptor agonists – dopastatins[24] (BIM-23A760[25]) – have yet to show any particular advantage in terms of comfort or control.[26]

Growth hormone receptor antagonists

Pegvisomant is a growth hormone (GH) antagonist with a half-life of greater than 70 hours delivered as a daily or weekly subcutaneous bolus.[27, 28] It interferes with growth hormone signalling and by so doing produces a high rate of normalization of insulin-like growth factor 1 in patients with somatotroph adenomas, including those in whom somatostatin analogues alone are insufficient to gain control of hormone secretion.[29, 30] Used in isolation, reduced feedback inhibition results in a concurrent increase in circulating growth hormone levels by about 75%. Concerns that tumour growth may accelerate if pegvisomant is used in patients without concurrent somatostatin analogues or prior radiotherapy have not been substantiated, at least during the first 3 years of treatment,[31] although increases have been reported in around 2% of cases.[32] The prohibitive costs of these analogues and side effects, particularly liver function abnormalities that affect approximately 25% of patients, albeit transient, mean that its place in acromegaly management alone and in combination with somatostatin analogues has yet to be established.[33]

Dopamine receptor agonists

Cabergoline, a second-generation long-acting dopamine agonist, reduces GH to within the reference range in a quarter to a third of patients with acromegaly[34, 35] and reduced IGF1 to within the reference range in one third,[36] an effect that is additive to that of somatostatin analogues[36] and independent of prolactin levels.[37] Despite these data, controversy persists, with groups reporting no effect of cabergoline but efficacy with quinagolide,[38] and others contending that bromocriptine has no effect and cabergoline only modest efficacy in fewer than 10% of patients as an adjunct to treatment with somatostatin analogues.[19]

Conventional fractionated radiotherapy

Radiotherapy is no longer an automatic adjunct to pituitary tumour surgery owing to the ease and safety of follow-up with MRI and computerized visual fields, and the expectation that remnant growth will be minimal and predictable. Nevertheless, it remains a useful and safe but relatively slow-acting treatment in selected patients in whom progression of unresectable tumour or excess hormone secretion persists.[39] In patients who have yet to complete their families the significant ongoing risk of hypopituitarism over the first 8–10 years is a further contraindication, given the expense of ovulation induction and restoration of male fertility using exogenous gonadotrophins.[40] External beam radiotherapy is remarkably safe, but long-term effects of external beam radiotherapy on cerebral vasculature and on the induction of secondary brain tumours within the radiation field, which amounts to a 2–4% risk at 20 years, is a more significant concern in young patients.[41, 42]

Early side effects of radiotherapy are generally limited to tiredness during the latter stages of treatment and for several weeks after treatment, and occasionally headaches

and transient loss of a small amount of scalp hair, particularly with the older linear accelerator protocols using just three trans-cerebral windows.

Stereotactic radiosurgery

Stereotactic or gamma knife radiosurgery for acromegaly allows radiotherapy to be delivered in one rather exhausting and uncomfortable day for the patient rather than fractionated over several weeks. Somatotrophinomas are not the pituitary adenoma subtype most amenable to Gamma knife radiosurgery owing to their size when they tend to come to treatment.[43] In patients who for the most part have already failed conventional treatment with surgery, conventional fractionated stereotactic radiotherapy and drugs, local tumour control is typically achieved in 37–100% and hormonal control in 17–82% within 2–3 years. New pituitary hormone deficiency occurs in 33–40% of patients over this time[44–48] but otherwise side effects are minimal.[49]

CORTICOTROPHINOMA

Corticotroph adenomas are typically microadenomas at diagnosis and extension beyond the confines of the sella is unusual. Nevertheless, even in the most optimistic published series, pituitary surgery alone fails to induce remission in Cushing's disease in 10–30% of cases and as many as 10% of patients are still obviously affected in the long term. If surgical remission is achieved, there remains a significant, persistent and unpredictable tendency to relapse that affects almost one third of patients by 10 years.

Depending on the clinical circumstances, disease that clearly persists immediately after attempted transsphenoidal microadenomectomy may be addressed by a further, more radical transsphenoidal clearance often within hours or days of the first approach. If preservation of pituitary function, in particular fertility, is a priority and no obvious microadenomatous remnants are visible on pituitary imaging, laparoscopic bilateral adrenalectomy rather than pituitary radiotherapy or a further transsphenoidal approach may be preferred. Nelson's syndrome, disinhibition of corticotroph remnant growth following bilateral adrenalectomy owing to reduced glucocorticoid feedback, is rare, particularly so if very little corticotroph adenoma tissue is present in the fossa, and there is no established rationale for prophylactic pituitary radiotherapy in these circumstances. Although lifelong treatment with glucocorticoids and mineralocorticoids is required, cure is immediate and the morbidity of the procedure itself low.

Many different groups of drugs have been proposed as useful in Cushing's disease, including metyrapone, mitotane, ketoconazole, etomidate, aminoglutethimide, trilostane, mifepristone, sodium valproate, dopamine D2 agonists, reserpine, serotonin antagonists, somatostatin receptor agonists, Bexarotene (a retinoid targeted to retinoid X receptors), the NF-kappaB inhibitor parthenolide, PPAR-gamma receptor ligands and Lapatinib, a tyrosine kinase inhibitor that interrupts the human epidermal growth factor receptor 2 (HER2) pathway.

In practical terms metyrapone, a steroid 11β-hydroxylase inhibitor that has been available in Europe for the last 50 years (500 mg–4 g daily in divided doses) is a reliable, reversible inhibitor of adrenal cortisol synthesis and secretion. It is sometimes used to improve overall metabolic and tissue status prior to transsphenoidal surgery or occasionally to help determine whether more invasive treatment of mild hypercortisolaemia is likely to yield symptomatic benefit. Metyrapone is also exploited as an interim adjunctive therapy while waiting for pituitary radiotherapy to reduce corticotroph function or as sole treatment in the longer term if patients are unable or unwilling to tolerate surgery, as its effects are not subject to tachyphylaxis. The drug should not be used in pregnancy or during lactation, but otherwise significant side effects are few, other than gastrointestinal upset and mild hirsutism.[50] Even if hypocortisolaemia is avoided, the effects of a rapid fall in circulating cortisol levels to within normal limits may for some patients result in depressed mood, arthralgia and in the slightly longer term by disappointment that weight loss is not sustained and that dyslipidaemia, hypertension and impaired glucose tolerance may continue to need specific treatment. Failure of the phenotype to completely regress even after full biochemical remission contributes to a significantly reduced quality of life in the long term and demoralizing recognition that, despite biochemical remission, the perceived pre-morbid 'self' may be very slow to re-emerge.

Ketoconazole, an imidazole derivative used to treat mycoses by inhibiting fungal sterol synthesis, is also used when physical treatments such as transsphenoidal surgery are inappropriate or have failed or the effects of radiotherapy are awaited. Although unlicensed for this indication in the UK, ketoconazole is believed to be effective in reducing circulating cortisol levels in up to 70% of cases – an endpoint that does not equate with remission.[51]

Mitotane is a hepatotoxic, neurotoxic and teratogenic adrenal cytotoxic agent that is highly persistent in the body and generally reserved for unresectable, metastatic or relapsed adrenal cortical carcinoma. It has been used in Cushing's disease (i.e. pituitary-dependent Cushing's syndrome) as first- or second-line treatment[52] but is slow to induce remission, not well tolerated, requires monthly plasma level monitoring and, even if effective in the short term, does not prevent recurrence of the disease in most patients over a median of 13 months.[52]

Etomidate is an intravenous inducing agent that at sub-anaesthetic doses (0.1 mg/kg per hour) powerfully inhibits adrenal 11β-hydroxylase.[53] It has a very rapid onset of action and can be easily titrated against circulating cortisol levels in a high dependency setting.[54] For patients in whom metyrapone or ketoconazole is ineffective in controlling severe hypercortisolaemia, etomidate as a continual infusion is uniquely effective and can be used to rapidly suppress otherwise intractable neuropsychiatric symptoms and give tissues time to recover from high-level cortisol exposure prior to bilateral adrenalectomy.

Centrally acting drugs such as sodium valproate, cabergoline and cyproheptadine are rarely effective. The broad spectrum somatostatin receptor agonist pasireotide shows only partial efficacy in a minority of patients and is associated with significant side effects such as impaired glucose tolerance and frank diabetes[55] in the majority. Mifepristone, a synthetic steroid inhibitor of progesterone receptors used as an emergency contraceptive, is also a powerful type 2 glucocorticoid receptor antagonist. It is approved by the FDA as a therapy to diminish the metabolic effects of hypercortisolaemia in Cushing's syndrome.

Even in remission, patients with a history of corticotroph adenoma have an increased standardized mortality ratio compared to age-matched controls.

THYROTROPH ADENOMA

Debulking transsphenoidal adenomectomy is the primary treatment of choice for thyrotroph adenomas. Even if primary surgical treatment restores euthyroidism in this rare secretory subtype (which accounts for less than 1% of pituitary tumours coming to surgery), external beam radiotherapy to the pituitary bed is often strongly considered as early adjuvant treatment as thyrotroph adenomas have a particular propensity to recur and as, if they do, the presence of thyrotoxicosis, which would be a significant additional surgical risk, can only be directly controlled at the expense of further disinhibition of thyrotroph function. Somatostatin analogues are effective in suppressing thyrotrophin release but tumours typically escape control over time.

PITUITARY CARCINOMAS

The limited dural invasion often seen in pituitary adenomas explains the occasional persistence of symptoms of excess hormone secretion even in the presence of an apparently empty sella. Pituitary carcinoma presenting as metastatic pituitary disease, however, is fortunately rare, constituting less than 0.2% of pituitary adenomas.[56] Over the last 50 years fewer than 150 have been reported in the literature, 36% of which were prolactinomas and 30% corticotroph adenomas.[57] The correlation between behavioural characteristics and mitotic markers such as *p53* mutation and Ki-67 is too weak to allow pre-emptive treatment and the diagnosis only becomes apparent when repeated imaging discloses aggressive trophic characteristics and metastatic spread. In addition to debulking and radiotherapy, the orally active second-generation alkylating agent temozolomide has been used in cases of aggressive pituitary adenomas and pituitary carcinomas having previously been reserved for malignant glioma. In a recent series of 44 patients, three cycles of treatment (200 mg/m^2 daily for 5 days every 28 days) produced a response rate of around one third of patients, with reduction in tumour volume, or more typically, reduction in the rate of tumour progression. It is of some interest that, at the time of writing, several patients who have received ipilimumab, a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) monoclonal antibody used to treat metastatic melanoma, have rapidly developed anterior pituitary failure presumably of autoimmune origin. Whether this could be used in extremis in pituitary carcinoma has not yet been explored.[58]

ENDOCRINOLOGICALLY INACTIVE ADENOMAS AND GONADOTROPHINOMAS

No specific management options are available after surgery and radiotherapy, although agents such as dopamine analogues have been tried. *In vitro*, the dopamine–somatostatin chimeric compound BIM-23A760 has been shown to have very modest antiproliferative actions,[59] but any medical therapy for endocrinologically inactive pituitary adenomas is a triumph of optimism over evidence. Endocrinologically inactive pituitary adenomas are sensitive to radiotherapy and trophic stasis or tumour shrinkage after a medium of 12.5 Gy delivered by stereotactic radiosurgery (gamma knife) controls tumour size in at least 90% of patients, with reduced risks of secondary tumour induction and cerebral vasculopathy compared to standard fractionated radiotherapy.[60, 61]

CRANIOPHARYNGIOMA

At one time craniopharyngioma was thought to be relatively radioresistant, and some centres withhold radiotherapy after primary surgery pending an evaluation of further growth even when initial decompression has been relatively modest.[62] Aggressive attempts to resect craniopharyngioma are associated with significant morbidity, and experimental therapies such as intracystic P32, bleomycin or yttrium-90 have not gained acceptance.[63, 64]

KEY POINTS

- Surgical outcomes of pituitary adenoma treatment continue to depend very heavily on the innate skill of specialist surgeons.
- In adults, LINAC remains a very effective and safe treatment that reduces significant craniopharyngioma and pituitary tumour space occupying-recurrence 5-fold.
- A significant minority of non-cystic macroprolactinomas involute completely after prolonged dopamine agonist treatment.
- In acromegaly, quality of life depends primarily on attention to the management of obstructive sleep apnoea, arthritis, orthodontic problems, dysmorphophobia and cardiovascular risks.
- Metyrapone is a reliable and safe inhibitor of adrenal cortisol synthesis and secretion in the medium if not long term.

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Section 3
Rhinology

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CHAPTER 87

ANATOMY OF THE NOSE AND PARANASAL SINUSES

Dustin M. Dalgorf and Richard J. Harvey

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed and Medline search using the following keywords: paranasal sinuses, maxillary sinus, ethmoid sinus, frontal sinus, nasal cavity, nasal bone, nasal cartilages, nasal mucosa, nasal septum and turbinates. Evidence presented in this chapter is Levels 3 and 4 while recommendations are Grace C.

INTRODUCTION

This chapter outlines the embryological development of the nose and paranasal sinuses, neurovascular and anatomical structures of the external nose, nasal cavity and nasal septum. A surgically relevant approach to the paranasal sinus anatomy is discussed with a focus on fixed anatomical landmarks and the concept of the horizontal and vertical components of the paranasal surgical box. The anatomical descriptions and surgically relevant anatomical concepts are based on standard text, peer reviewed journals referenced in the bibliography and the author's personal experience.

DEVELOPMENT OF THE NOSE AND PARANASAL SINUS

Traditional teaching of paranasal sinus anatomy focused on embryological development and pathways of pneumatization with limited clinical application. These descriptions are included for completeness but the emphasis in this chapter is on the surgically relevant anatomy

External nose and nasal cavity

The nose develops from a number of mesenchymal processes around the primitive mouth during the fourth week of gestation. Collections of neural crest cells undergo proliferation and form the nasal placodes. Sinking of the nasal placodes leads to formation of the nasal pits which further deepen to form the nasal sac. Adjacent mesoderm cells proliferate to give rise to the medial and lateral nasal prominences of the frontonasal process which surround the nasal pit and sac to eventually become the nares (Figure 87.1).

The maxillary processes grow anteriorly and medially to fuse with the medial nasal prominences and frontonasal process to close off the nasal pits and form separate nasal cavities. The primitive nasal cavity and mouth are initially separated by the bucconasal membrane. This membrane gradually thins as the nasal sacs extend posteriorly and

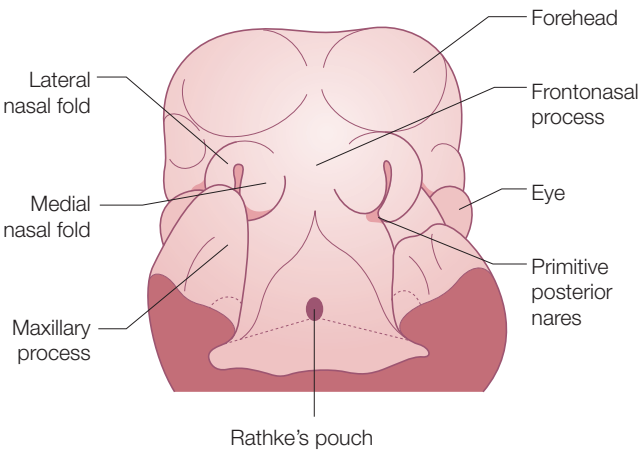


Figure 87.1 Embryological development of the primitive nose and palate during fusion of the maxillary process to the lateral and medial nasal prominences.

BOX 87.1

Failure of the bucconasal membrane to break down during embryological development results in choanal atresia

eventually breaks down to form the choanae. Failure of this membrane to break down results in choanal atresia.

The frontal and maxillary processes fuse to give origin to the lateral two thirds of the upper lip, superior alveolar ridges and palatal shelves. The medial nasal prominences fuse with the maxillary process to form the philtrum and medial crus of the lower lateral cartilages. The lateral nasal prominences form the nasal bones, upper lateral cartilages and lateral crus of the lower lateral cartilages.

Palate and nasal septum

The septum develops from the posterior midline growth of the frontonasal process in the root of the oral cavity and extends posteriorly to the opening of Rathke's pouch. The primitive or primary palate begins to form anteriorly with fusion of the maxillary and frontonasal processes. As the nasal cavities enlarge, the palatal processes, derived from lateral maxillary mesoderm, grow medially towards each other and the nasal septum. Initially, the palatal processes are vertically oriented and lateral to the tongue (Figure 87.2). Further growth of the jaw and oral cavity enables the palatal processes to migrate medially towards the midline and fuse (Figure 87.3). The fusion begins along the posterior margin of the primitive palate and progresses from anterior to posterior to form the secondary palate. Partial notching of the posterior hard palate represents an incomplete fusion of the secondary palate and may indicate a submucus cleft. A midline dehiscence in the fusion of the primary and secondary palate forms the incisive foramen.

Maxillary sinus

The maxillary sinus is the first sinus to appear between the 7th and 10th weeks of gestation. The maxillary sinus appears as a shallow groove expanding from the primitive ethmoidal infundibulum into the mass of the maxilla. Expansion and absorption results in a small sinus cavity present at birth. Rapid growth of this cavity occurs during childhood until age seven followed by gradual enlargement, reaching its final size by age 17–18 years. Growth may continue beyond this period with extensive pneumatization involving the entire hard palate (Figure 87.4).

Any disruption or abnormality in the development of the maxillary sinus may result in maxillary sinus aplasia or hypoplasia. Maxillary sinus hypoplasia is present in up to 10% of CT scans.[1] Radiographic diagnostic criteria for maxillary hypoplasia include: (1) enlargement of the vertical orbit, (2) lateral position of the infraorbital

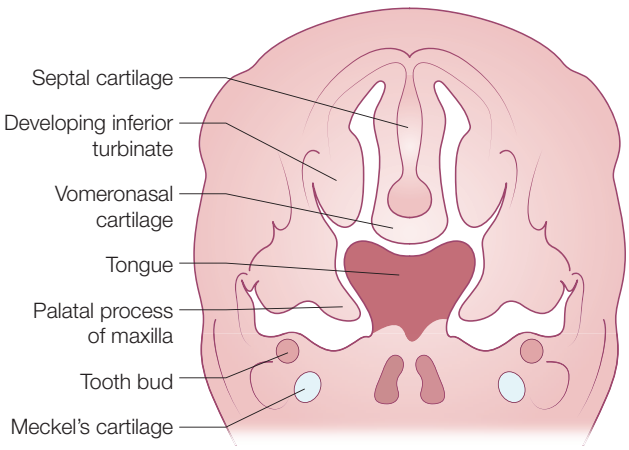


Figure 87.2 Section through the developing palate of a 20 mm human foetus. The palatal shelves are positioned vertically due to occupation of this space by the tongue.

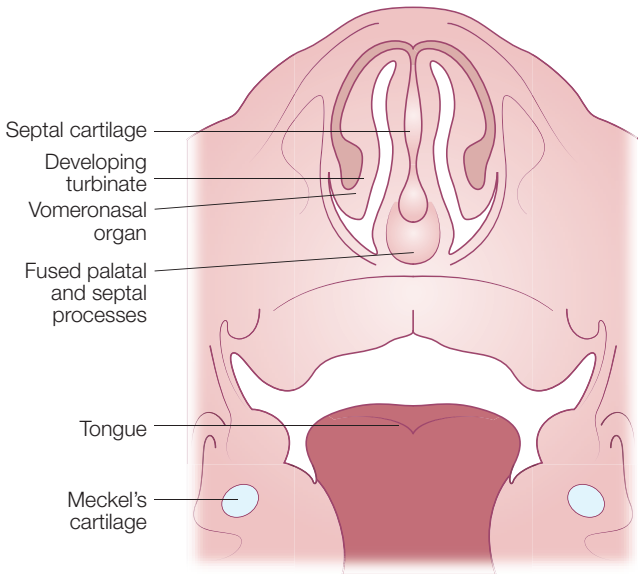


Figure 87.3 Section through the developing palate of a 48 mm human foetus. With further growth of the oral cavity to accommodate the tongue, the palatal shelves are able to migrate medially into a horizontal position and begin to fuse in an anterior to posterior direction.



Figure 87.4 Coronal CT of extensive maxillary sinus penumatization into the hard palate (arrows) with evidence of maxillary sinus dysfunction (left greater than right).

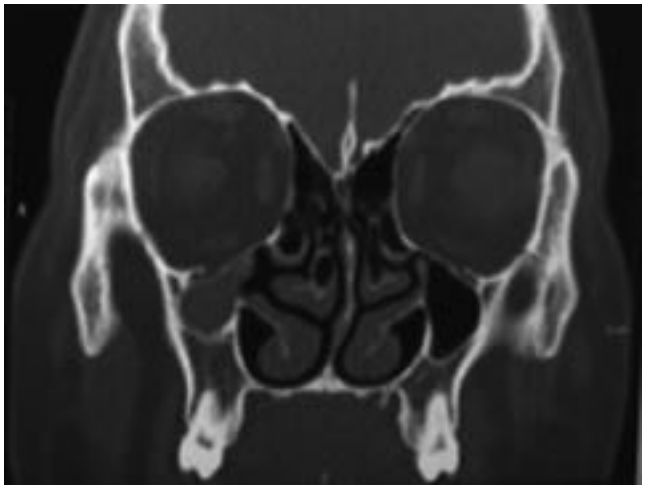


Figure 87.5 Coronal CT demonstrating maxillary sinus hypoplasia on the right side and maxillary sinus atelectasis on the left side.

neurovascular canal, (3) elevated canine fossa, (4) enlargement of superior orbital fissure and (5) enlargement of pterygopalatine fissure (Figure 87.5).[2]

Ethmoid sinus

During the 9th and 10th weeks of gestation, a series of folds called ethmoturbinals that are separated from each other by corresponding grooves appear in the lateral wall of the nasal capsule. Fusion of these folds leads to the development of crests, each with an ascending and descending portion. All permanent ethmoidal structures are present at birth and develop from these crests and the furrows between them. As a result, acute sinusitis in children often involves the ethmoid cavity which can extend laterally through the lamina papyracea causing orbital complications.

BOX 87.2

The ethmoid structures are present at birth and acute sinusitis involving this cavity can extend laterally and result in orbital complications.

Understanding the basic embryology of the four or five ethmoturbinals defines a series of lamella that must be removed in order to pass from the anterior of the sino–nasal cavity to the sphenoid sinus. In order from anterior to posterior, these lamella include: FIRST: agger nasi (ascending portion) and uncinate process (descending portion), SECOND: bulla ethmoidalis, THIRD: basal lamella of the middle turbinate, FOURTH: superior turbinate and FIFTH: supreme turbinate if present.

Sphenoid sinus

The sphenoid sinus begins to develop in the twelfth week of gestation as an evagination from the sphenoethmoidal recess. A small sphenoid sinus is present at birth with progressive enlargement starting at age three during pneumatization of the sphenoid bone. Three pneumatization patterns have been described with reference to the sella turcica.[3] These pneumatization patterns are important for surgical planning of transphenoid approaches to pituitary tumours. These include sellar (90%), pre-sellar (9%) and conchal (1%) type pneumatization patterns (Figure 87.6). The sellar type is most common and describes sphenoid pneumatization posterior to the sella turcica. The presellar type describes sphenoid pneumatization up to the anterior sella and the conchal type describes a shallow bowl with minimal sphenoid pneumatization and trabecular bone between the sinus and sella. The sphenoid sinuses can also pneumatize laterally into the pterygoid root resulting in the presence of a lateral sphenoid recess (Figure 87.7). This pneumatization pattern results in exposure of the neurovascular structures surrounding the sphenoid sinus.

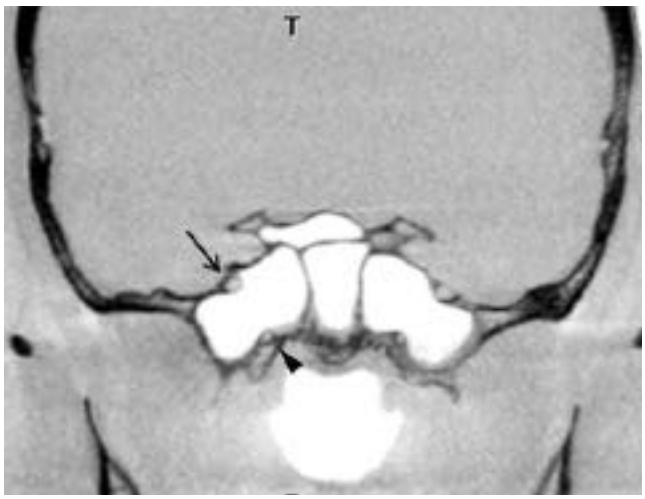


Figure 87.7 Coronal CT of sphenoid sinus. Lateral sphenoid recess (asterisk), maxillary division of trigeminal nerve (arrow), vidian nerve (arrow head).



Figure 87.6 Sphenoid sinus pneumatization patterns. Midline sagittal CT indicating the **(a)** sellar **(b)** pre-sellar and **(c)** conchal types of sphenoid sinus pneumatization patterns.

The lateral recess pneumatization pathway occurs between the second trigeminal division and the vidian nerve.

BOX 87.3

The three different sphenoid sinus pneumatization patterns are described with reference to the sella turcica and include: sellar (90%), pre-sellar (9%) and conchal (1%) type. These pneumatization patterns are important for surgical planning of transphenoid approaches to pituitary tumours.

Frontal sinus

The frontal sinus is the most variable sinus in terms of size and shape. Pneumatization of the frontal bone begins during the 16th week of gestation originating from the anterior ethmoid complex. At birth, the frontal sinuses appear only as a small blind pocket that is difficult to distinguish from the anterior ethmoid air cells on imaging. With gradual pneumatization, the frontal sinuses are seen in most radiological studies by the age of 8 years. Significant frontal pneumatization does not occur until early adolescence and continues until 18 years of age. Although still developing, the relative proportions of the frontal sinus have reached adult ratios by age 10–12 years and just prior to the second growth spurt.

EXTERNAL NOSE

Skin and muscles of the external nose

The thickness of the skin and soft tissues of the nasal bridge vary according to individual skin type and anatomical location. Over the dorsum and sides of the nose, the nasal skin is thin and loosely adherent to the underlying framework. The nasal skin becomes thicker and more adherent towards the nasal tip and alar cartilages where it contains numerous sebaceous glands. The elasticity and mobility of the skin over the nose also varies according to the quality of the collagen fibers anchoring the skin to the underlying structures.

The extension of the facial SMAS (subcutaneous musculoaponeurotic system) layer continues over the nose as numerous muscles of the external nose which function to compress, dilate, depress or elevate the nostrils and nasal tip. These muscles are all supplied by branches of the facial nerve. The nasal elevators include the procerus, levator labii-superioris alaeque nasi, and anomalous nasi muscles. The depressors include the alar nasalis and depressor septi nasi muscles. Compressor muscles include the transverse nasalis and compressor narium minor. The dilator naris anterior muscle acts as a minor dilator.

The subcutaneous tissue of the nose is made up of four layers: superficial fatty, fibromuscular, deep fatty and periosteal layers. The superficial fatty layer is directly connected to the dermis. The fibromuscular layer comprises the nasal SMAS. The deep fatty layer lies deep to the SMAS and contains the neurovascular system. The deepest layer is the periosteum and perichondrium. During external approach rhinoplasty, dissection deep to the third layer minimizes post-operative scarring and retraction because the neurovascular and SMAS structures are preserved.

BOX 87.4

Dissection deep to the third layer of the nose (deep fatty layer) minimizes post-operative scarring and retraction because the neurovascular and SMAS structures are preserved.

Vestibule

The nasal vestibule is the anterior most aspect of the nasal cavity and serves as the entry point from the external nares into the nasal cavity. The vestibule is demarcated by the limen nasi located at the caudal border of the lower lateral cartilage. The limen nasi is the location where the marginal incision is made during external approach rhinoplasty. It is lined by keratinizing stratified squamous epithelium, and coarse hairs called vibrissae, sebaceous glands and sweat glands. A layer of mucous typically covers the outer surface of the vibrissae which functions to filter airborne particles during inspiration. It is important to note that only a small part of the alar rim is composed of cartilage from the lateral crus, the majority is composed of fibrofatty tissue.

Nasal cartilages

While much focus is placed on the internal septal and turbinate anatomy, the anterior third of the nasal passage has a critical functional role and can greatly influence nasal airflow. The nasal cartilages consist of hyaline cartilage that attach to the bones of the anterior nasal aperture to form the skeletal framework of the external nose. These cartilages include the upper and lower lateral cartilages, septum and sesamoid complex.

The lower lateral cartilage is divided into medial, intermediate and lateral crus that form the natural arch of the nasal ala. The upper lateral cartilages are trapezoid shaped cartilages that attach to the dorsal septum in the midline, nasal bones cranially at the rhinion and lower lateral cartilages caudally via the scroll area.

The relationship and architecture of these cartilages form the external and internal nasal valves which are critical to nasal airflow. The external nasal valve is comprised of the septum medially, alar rim (lateral crus, sesamoid complex and fibrofatty tissue) laterally and nasal sill inferiorly (Figure 87.8). Anatomical abnormalities or compromise in the structural integrity of these components can cause external valve narrowing, stenosis or dynamic valve collapse that is exacerbated during inspiration.

The internal nasal valve, in normal development, is the narrowest portion of the nasal cavity and is bounded by the septum medially, caudal edge of the upper lateral cartilage and head of the inferior turbinate laterally and nasal floor inferiorly (Figure 87.8). The apex of the internal nasal valve is approximately 10–15 degrees in Caucasians and wider in non-Caucasian populations. Changes in the relationship of any structure within this space can cause symptoms of nasal obstruction.

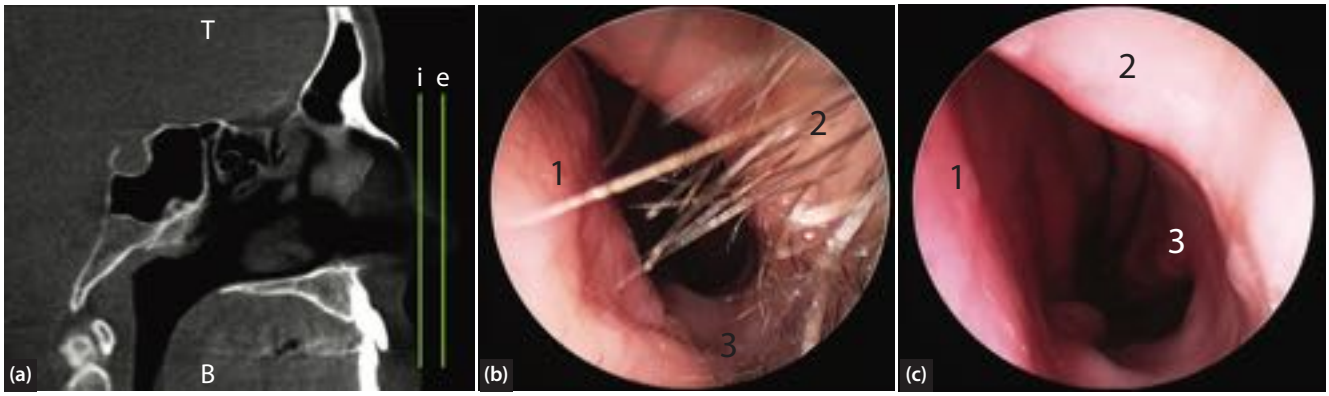


Figure 87.8 Nasal valves **(a)** Midline sagittal CT scan with green line indicating the relative positions of the external (e) and internal (i) nasal valves. **(b)** Endoscopic view of the left external nasal valve including (1) septum (2) alar rim (comprised of lower lateral crus, sesamoid complex and fibrofatty tissue) and (3) nasal sill. **(c)** Endoscopic view of the left internal nasal valve including (1) septum (2) caudal edge of upper lateral cartilage and (3) head of inferior turbinate.

BOX 87.5

The structures of the external and internal nasal valve are critical to nasal airflow with the internal nasal valve representing the narrowest portion of the nasal cavity. The internal nasal valve is bounded by the septum medially, caudal edge of the upper lateral cartilage and head of the inferior turbinate laterally and nasal floor inferiorly.

Blood supply

Arterial supply to the external nose has both external and internal carotid artery contributions. Branches of the facial artery supply the alar region and include the angular and superior labial arteries. The angular artery and its lateral nasal branch supply the nasal side wall and ala. The superior labial artery gives rise to a columellar branch that supplies the nasal sill and columella and a septal branch that supplies the anterior nasal septum. The ophthalmic artery gives rises to a dorsal nasal branch which anastomoses with the lateral nasal branch of the angular artery to supply the dorsum and nasal side wall. The nasal dorsum and nasal side wall also receive vascular supply from the external nasal branch of the anterior ethmoid artery and infraorbital artery respectively. There are rich anastomoses between these vessels on each side and between right and left sides of the nose.

The venous networks do not parallel the arterial supply but correspond to territories termed arteriovenous units. The frontomedian area drains to the facial vein and the orbitopalpebral area drains to the ophthalmic vein. The facial vein originates as the angular vein located at the inner canthus. The angular vein forms as the confluence of the supratrochlear and supraorbital veins. The upper lip and nose are considered the danger area of the face because infections in this region may be transmitted in a retrograde fashion intracranially to the cavernous sinus. This phenomenon can occur because the facial vein communicates through a valveless venous system with the cavernous sinus via the ophthalmic vein.

KEY POINTS

- The upper lip and nose are considered the danger area of the face because infections in this region may be transmitted in a retrograde fashion through a valveless venous system to the cavernous sinus.

Nerve supply

A working knowledge of the neural supply to the external nose has clinical value when performing a nerve block to this region during procedures such as rhinoplasty or closed reduction of nasal fractures (Figure 87.9). The supratrochlear and infratrochlear branches of the ophthalmic nerve supply the skin of the nasal root, bridge and upper portion of the side wall of the nose. The infraorbital branch of the maxillary nerve supplies the remaining skin of the nasal side wall. The external nasal branch of the anterior ethmoid nerve exits between the nasal bone and upper lateral cartilage to supply the skin over the dorsum and nasal tip.

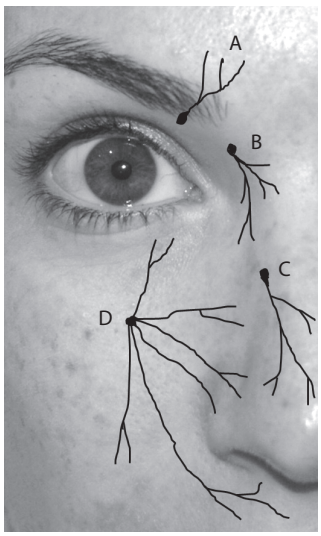


Figure 87.9 External nasal innervation (A) supratrochlear nerve (B) infratrochlear nerve (C) anterior ethmoid nerve (D) infraorbital nerve.

Lymphatic drainage

The lymphatic drainage of the external nose is directed towards the submandibular, submental and facial nodes. Drainage of the external nose is often bilateral and drainage to the parotid region may be possible.

Nasal cavity

The nasal cavity extends from the external nares to the posterior choanae, where it becomes continuous with the nasopharynx. The nasal cavity is divided into two passage ways by the nasal septum. Each side consists of a floor, roof, lateral and medial (septum) wall. The nasal floor is concave from side to side, flat anteroposteriorly and horizontally oriented. The anterior three-quarters are comprised of the palatine process of the maxilla and the posterior one-quarter by the horizontal process of the palatine bone. Approximately 12 mm behind the anterior aspect of the nasal floor is a slight depression which corresponds to the incisive canal. The incisive canal contains terminal branches of the nasopalatine nerve and greater palatine artery. The roof of the nasal cavity is formed by the skull base and slopes downward anteroposteriorly. This is important to recognize during endoscopic sinus surgery as dissection progresses posteriorly towards the sphenoid sinus.

The superior aspect of the nasal cavity including the superior septum, superior turbinate and upper aspect of the middle turbinate is lined by olfactory epithelium. With the exception of the vestibule, the remainder of the nasal cavity is lined by respiratory epithelium. The respiratory epithelium of the nasal cavity is continuous with the mucosal lining of the entire upper and lower airway system.

BOX 87.6

Three different types of epithelium within the nasal cavity consist of squamous (nasal vestibule), olfactory (superior septum, superior turbinate and upper aspect of the middle turbinate) and respiratory (remainder of nasal cavity) epithelium.

Nerve supply

Innervation of the nasal mucosa includes both autonomic and sensory components. The autonomic nervous system regulates the degree of vascular tone, turbinate congestion and nasal secretions present in the nose. Nasal secretion is regulated by the parasympathetic nervous system. Presynaptic parasympathetic fibers travel along the vidian nerve (contribution from the greater superficial petrosal (parasympathetic) and deep petrosal (sympathetic) nerves) and synapse within the sphenopalatine ganglion to innervate the nasal mucosa via postsynaptic fibers. Vascular tone and turbinate congestion is regulated by the sympathetic nervous system. Post-synaptic sympathetic fibers pass through the sphenopalatine ganglion and terminate in the nasal mucosa. The ophthalmic and maxillary divisions of the trigeminal nerve provide the sensory innervation to the nasal mucosa. Trigeminal nerve fibers also pass through the sphenopalatine ganglion and transmit sensations of pain, temperature and touch. The lateral wall of the nose and turbinates are supplied by the posterolateral nasal nerves from V2 arising from the sphenopalatine foramen and the ethmoidal nerves arising from V1. Although an artery supplies the inferior turbinate posteriorly, the neural innervation is from the lateral wall nerves continuing caudally.

BOX 87.7

The parasympathetic nerve regulates nasal secretions, sympathetic nerve regulates vascular tone and turbinate congestion, and the trigeminal nerve controls nasal cavity sensation.

NASAL SEPTUM

The nasal septum serves many functions, including separation of the nasal airway into two nasal cavities, support of the nasal dorsum, and maintenance of the nasal tip and forms part of the nasal valves. Deviation of the nasal septum can lead to significant nasal airway obstruction and cosmetic deformity. The nasal septum consists of a bony, cartilaginous and membranous portion (**Figure 87.10**).

The bony portion is comprised of the perpendicular plate of the ethmoid bone, vomer, maxillary crest and palatine bone (**Figure 87.10**). The perpendicular plate of the ethmoid forms the upper one-third of the nasal septum. It is continuous superiorly with the cribriform plate and crista galli and abuts a variable amount of the nasal and frontal bones. Posteriorly the perpendicular plate articulates with the sphenoid crest, posteroinferiorly with the vomer and anteroinferiorly with the septal cartilage. The vomer forms the posterior and inferior nasal septum and articulates by its two alae with the sphenoid rostrum creating the vomerovaginal canals through which the pharyngeal branches of the maxillary artery travel. The inferior border of the vomer articulates with the nasal crest formed by the maxillary and palatine bones. The anterior border articulates with the septal cartilage and the posterior edge of the vomer forms the posterior free edge of the septum.

The cartilaginous portion of the nasal septum is composed of the septal or quadrilateral cartilage (**Figure 87.10**). The quadrilateral cartilage is bound firmly by collagenous fibers to the nasal bones, perpendicular plate of the ethmoid and vomer. The septal cartilage is continuous with the upper lateral cartilages towards the bridge of the nose. A projection of the septal cartilage called the sphenoidal process or septal tail extends posteriorly between the vomer and perpendicular plate of the ethmoid. The septal tail can serve as an additional source of cartilage to harvest especially during revision rhinoplasty. The inferior attachment sits within the nasal crest of the maxilla and is bound by looser connective tissue creating a pseudoarthrosis. This joint allows mobility of the septal cartilage base during flexion thereby reducing the risk of fracture or dislocation with trauma. The membranous septum is a segment of connective tissue between the caudal portion of the septal cartilage and columella.

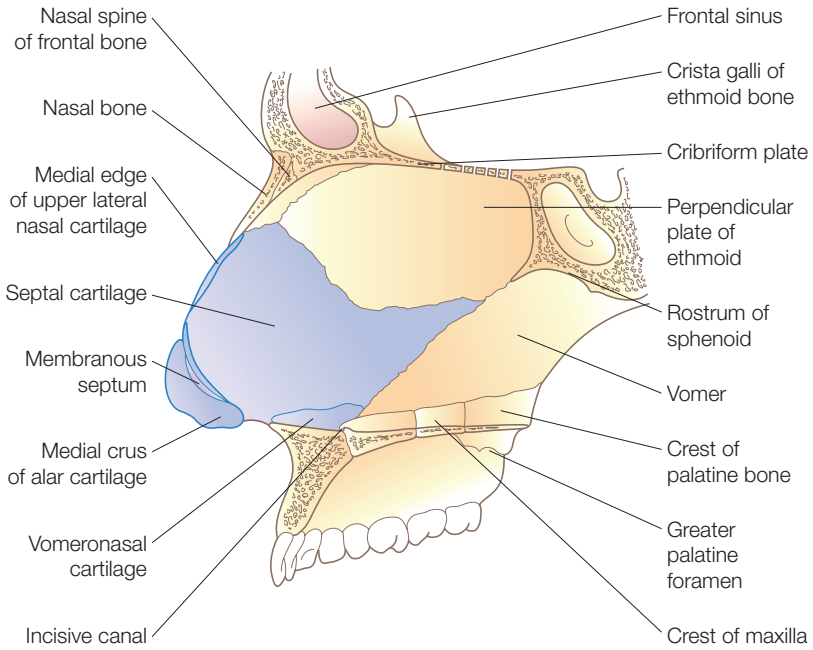


Figure 87.10 The cartilaginous and bony components of the nasal septum.



Figure 87.11 Coronal CT of septal swell body (arrow).

The nasal septal swell body is a widened region of the anterior nasal septum located anterior to the middle turbinate at the internal nasal valve (Figure 87.11).[4] Histological analysis of this tissue demonstrates an increased amount of venous sinusoids and fewer glandular elements compared to adjacent septal mucosa.[4] The high proportion of venous sinusoids suggests the capacity to alter nasal airflow in a similar manner to the inferior turbinates.

Blood supply of the nasal septum

Both the external and internal carotid arteries contribute to the vascular supply of the nasal septum (Figure 87.12). The external carotid artery branches supplying the septum include the sphenopalatine and greater palatine arteries (branches of the internal maxillary artery). The sphenopalatine artery supplies the posteroinferior septum by a branch called the posterior septal artery. The posterior septal artery is the basis of the nasoseptal mucosal flap which is the workhorse for endoscopic skull base reconstruction. The greater palatine artery enters the nasal cavity through the incisive canal to supply the anteroinferior portion of the septum. The septal branch of the superior labial artery (branch of the facial artery) contributes to the vascular supply of the caudal septum and columella. The internal carotid artery branches supplying the septum include the anterior and posterior ethmoid arteries (branches of the ophthalmic artery). The anterosuperior and posterosuperior portions of the nasal septum receive vascular supply from the anterior and posterior ethmoid arteries respectively.

The anterior ethmoid artery, posterior septal artery and septal branch of superior labial artery contribute to Kisselbach's plexus which is located along the anterior nasal septum at Little's area (Figure 87.12). This region is formed by the anastomosis of these arteries which terminate as a rich vascular bed of long capillary loops. Kisselbach's plexus is the most common location of epistaxis due to its rich vascular supply and susceptibility to injury from such factors as turbulent airflow and digital trauma.

BOX 87.8

Kisselbach's plexus is the most common location of epistaxis due to its rich vascular supply (confluence of the anterior ethmoid, posterior septal and septal branch of superior labial arteries) and susceptibility to injury from turbulent airflow and digital trauma.

The venous system drains via the sphenopalatine vessels into the pterygoid plexus posteriorly and into the facial

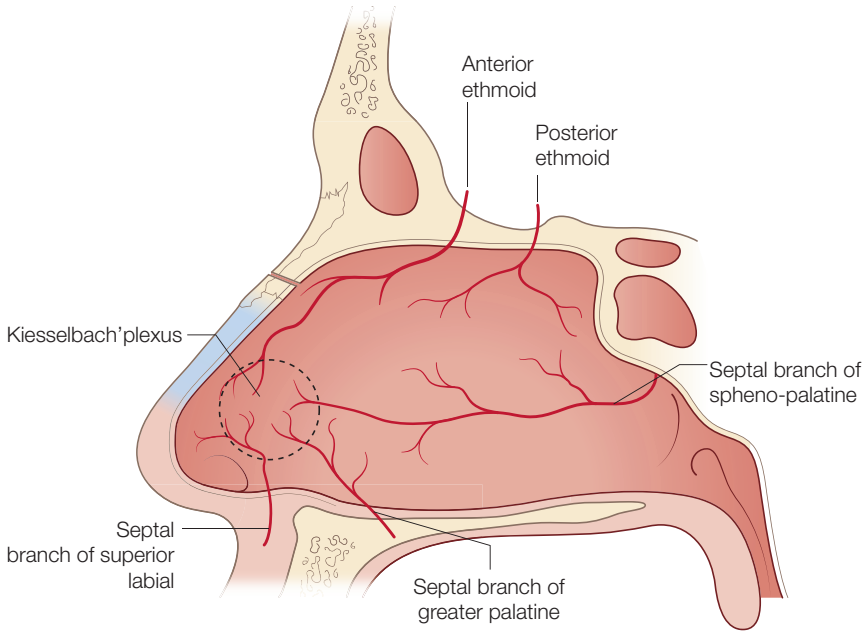


Figure 87.12 Vascular supply of the nasal septum.

veins anteriorly. Superiorly, the ethmoidal veins communicate with the superior ophthalmic system and there may be direct intracranial connections through the foramen caecum into the superior sagittal sinus.

Lateral nasal wall and turbinates

The inferior, middle and superior turbinates are internal structures found along the lateral nasal wall. The middle and superior turbinates arise from extensions of the ethmoid bones whereas the inferior turbinate is an embryologically independent osseus structure. The space between the lateral nasal wall and inferior, middle and superior turbinates is called the inferior, middle and superior meatus respectively. Each meatus is associated with the connection between a specific anatomical structure and the nasal cavity along a series of well-defined drainage pathways. The lacrimal duct drains into the inferior meatus approximately 1 cm posterior to the head of the inferior turbinate. Although not considered a true valve, the opening of the nasolacrimal duct is called Hasner's valve which is formed by small folds of mucosa. The middle meatus forms the common drainage pathway of the maxillary, anterior ethmoid and frontal sinus into the nasal cavity. The superior meatus forms the common drainage pathway of the posterior ethmoid air cells.

Turbinates are structures filled with vascular channels and venous sinusoids which serve to warm and humidify air and modify nasal airflow resistance. The turbinates continuously dilate and constrict under sympathetic control in response to environmental conditions. A process occurs every 0.5–3 hours in a normal physiological phenomenon known as the 'nasal cycle' resulting in alternating congestion and decongestion of the nasal cavities. Turbinate hypertrophy is a common cause of nasal obstruction in which the turbinates are either chronically congested or hypertrophied due to allergic or non-allergic triggers as part of an inflammatory rhinitis conditions.

BOX 87.9

The nasal turbinates continuously dilate and constrict every 0.5–3 hours in a normal physiological phenomenon known as the 'nasal cycle'.

Blood supply of the lateral nasal wall

Both the internal and external carotid arteries supply the lateral nasal wall. The sphenopalatine artery contributes the majority of the arterial supply to the turbinates and lateral nasal wall (**Figure 87.13**). It enters through the sphenopalatine foramen which lies just inferior to the horizontal attachment of the middle turbinate. The sphenopalatine foramen is formed by the sphenopalatine notch of the palatine bone in articulation with the sphenoid bone. The crista ethmoidalis is a small crest of the perpendicular plate of the palatine bone located anterior to sphenopalatine foramen and serves as a consistent and reliable landmark to identify this vessel during endoscopic dissection.[5] The sphenopalatine artery commonly branches lateral to the crista ethmoidalis with many variations in the branching pattern. In one cadaver study, 97% of specimens had two or more branches of the sphenopalatine artery medial to the crista ethmoidalis.[6] It is critical that the surgeon is aware of these variations and controls all branches to ensure successful endoscopic ligation of the sphenopalatine artery for epistaxis. If more proximal vascular control is required, the internal maxillary artery can be ligated in the pterygopalatine or infratemporal fossa by removal of the posterior wall of the maxillary sinus.

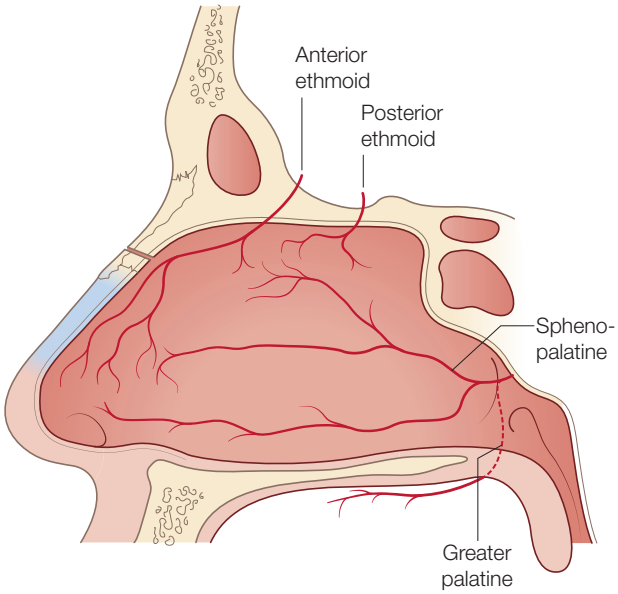


Figure 87.13 Vascular supply of lateral nasal wall.

BOX 87.10

The crista ethmoidalis is a small crest of the perpendicular plate of the palatine bone located anterior to sphenopalatine foramen and serves as a consistent and reliable landmark to identify the sphenopalatine artery during endoscopic dissection. There are often two or more branches of the sphenopalatine artery medial to the crista ethmoidalis.

A small area along the anterior aspect of the lateral nasal wall is supplied by a branch of the facial artery. The inferior part of the lateral nasal wall adjacent to the palate is supplied by the greater palatine artery. The internal carotid artery contribution is via the anterior and posterior ethmoid arteries (branches of the ophthalmic artery) which supply the superior lateral wall. The anterior ethmoid artery traverses three compartments of the head during its course from the orbit to the olfactory fossa and into the nasal cavity. After branching from the ophthalmic artery in the orbit, the anterior ethmoid artery passes between the superior oblique and medial rectus muscles through the anterior ethmoid foramen. This portion is easily identified on pre-operative coronal CT imaging. The anterior ethmoid artery travels through the ethmoid cavity obliquely in a posterior to anterior direction either within the bone of the skull base or a mucosal mesentery. The artery traverses intra-cranially into the olfactory fossa through the lateral lamella of the lamina cribrosa. After entering the intra-cranial cavity, it gives off anterior meningeal branches before re-entering the nasal cavity through the cribroethmoidal foramen. Within the nasal cavity, it divides into the anterior and posterior nasal arteries. The anterior and posterior nasal arteries each give rise to lateral and medial branches that supply the lateral nasal wall and nasal septum respectively.

The anterior ethmoid artery is more difficult to access surgically, with only 20% of arteries found within a mesentery that can be successful clipped via a transnasal approach.[7] Endoscopic removal of the lamina papyracea allows identification of the anterior and posterior ethmoid arteries between the periobita and skull base. Alternatively, an external approach via a modified Lynch incision can be used. There is considerable overlap between the internal and external carotid arterial systems on each side and between sides of the nasal cavity which can complicate attempts at arterial ligation in the management of epistaxis.

BOX 87.11

The anterior ethmoid artery is more difficult to access endoscopically as it is only found within a mesentery that can be ligated in a small portion of cases. An external approach using a modified Lynch incision is often the preferred method of ligation.

PARANASAL SINUSES

Anatomy of the paranasal sinuses can be divided into anatomy that has surgical relevance and descriptions that are academic in nature.

Surgical anatomy of the paranasal sinuses

Traditional descriptions of paranasal sinus anatomy focus on pneumatization patterns of air cells with corresponding clefts and spaces. Such descriptions are academic and have little clinical relevance to modern endoscopic sinus surgery. Although an understanding of sinonasal anatomy is critical to ensure safe and complete endoscopic sinus surgery, the concept of pneumatization pathways and development is highly variable and often distorted by disease or prior surgery. Endoscopic sinus surgery is an exercise of anatomical dissection around fixed anatomical landmarks. Akin to traditional mastoid surgery, the sinus surgeon must identify certain key anatomical landmarks in order to delineate the limits of dissection. These landmarks must be based on fixed anatomical structures rather than variable anatomy that can be distorted or absent from disease processes or prior surgery. The goal of surgery is to identify these landmarks early during the procedure in order to provide orientation for the remainder of the operation. These consistent anatomical landmarks include: (1) the maxillary sinus, (2) the orbit from the maxillary sinus roof / orbital floor and medial orbital wall (lamina papyracea) and (3) skull base identified posteriorly by the sphenoid sinus. These defined anatomical limits establish the boundaries of the paranasal surgical box including the horizontal and vertical components of this box.[8] The concept of the paranasal surgical box forms the basic framework of endoscopic sinus surgery (Figure 87.14).

The boundaries of the horizontal portion of the paranasal surgical box include the middle turbinate medially,

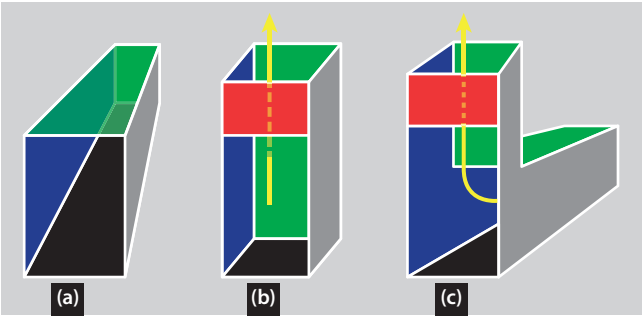


Figure 87.14 Schematic diagram of the right paranasal surgical box. **(a)** Horizontal component of the right surgical box with limits of dissection including medial orbital wall (blue), middle turbinate (grey), skull base (green), sphenoid sinus (yellow). **(b)** Vertical component of the right surgical box with limits of dissection including medial orbital wall (blue), middle turbinate (grey), skull base (green), anterior nasal beak (red). **(c)** Combined schematic diagram of the horizontal and vertical components of the paranasal surgical box.

medial orbital wall (lamina papyracea) laterally, floor of nose inferiorly and skull base superiorly (Figure 87.15).[8] The boundaries of the vertical portion of the paranasal surgical box include the middle turbinate and intersinus septum medially, lamina papyracea laterally, nasofrontal beak anteriorly and skull base posteriorly (Figure 87.16).[8]

Upon completion of the maxillary antrostomy (or any maxillary sinus opening), identification of the maxillary sinus roof/orbital floor exhibits the first key anatomical landmark (Figure 87.17). This landmark first provides the location of the orbit and then provides a safe working distance from the skull base during identification of the sphenoid sinus whether via the natural ostium or not (Figure 87.18).[9,10] Although conceptually the floor of orbit should be below the skull base, anatomical studies have demonstrated that the maxillary sinus roof / orbital floor was below the level of the skull base (lowest portion of the cribriform plate) in 100% of cases with an mean distance of 10.1 ± 2.7 mm.[9] This landmark was also found to be below the level of the sphenoid planum in 100% of cases with a mean distance of 11.0 ± 3.7 mm and located at approximately 50% the height of the sphenoid.[9] As a surgical rule, staying below or at the level of the maxillary sinus roof / orbital floor as dissection proceeds posterior will avoid the skull base. Although a well-pneumatized maxillary sinus reduces the height of the posterior ethmoid cavity and may lead to poor surgical trajectory and skull base injury this surgical rule still applies.

The ethmoid bulla is attached to the medial orbital wall (lamina papyracea) laterally. With the orbital floor on view, removal of the ethmoid bulla enables identification of second key anatomical landmark (Figure 87.19). Identification of where the floor turns vertically to become the medial orbital wall enables safe exposure of the entire orbital axis and delineation of the lateral boundary of the paranasal surgical box (Figure 87.19).

The third key landmark is the sphenoid sinus/posterior skull base (Figure 87.20). The maxillary sinus roof/orbital floor landmark is used as a reference to mark the level of the sphenoid ostium. Any dissection medial to the orbital axis and below or at the level of the orbital floor will allow safe entry into the sphenoid. While structures such as the superior turbinate are incredibly useful in defining the medial boundary of dissection for the ethmoid cavity, this

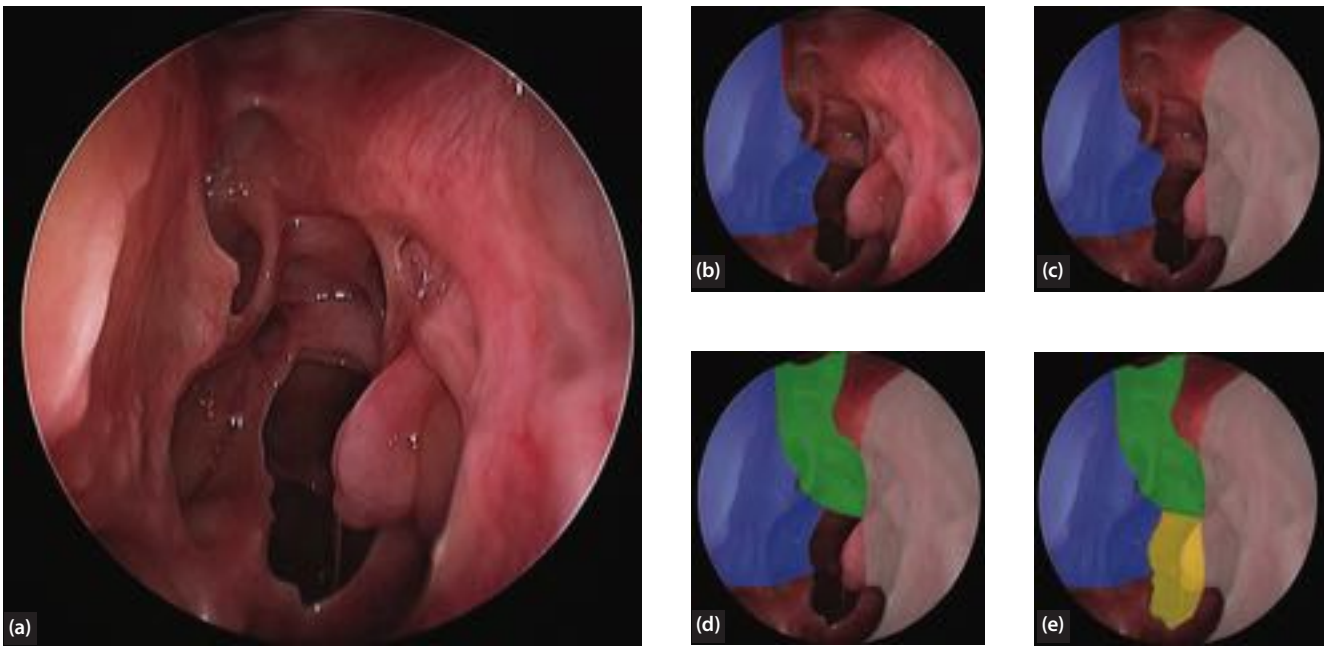


Figure 87.15 (a) Endoscopic view of the right horizontal component of the paranasal sinus surgical box with the medial, lateral, superior and inferior limits of dissection visible with a single position of the endoscope. The lateral, medial and superior boundaries of the horizontal surgical box are indicated as **(b)** medial orbital wall (blue) **(c)** middle turbinate (grey) **(d)** skull base (green) respectively. **(e)** Sphenoid sinus (yellow) serves as an important landmark to identify the skull base at its most posterior position.

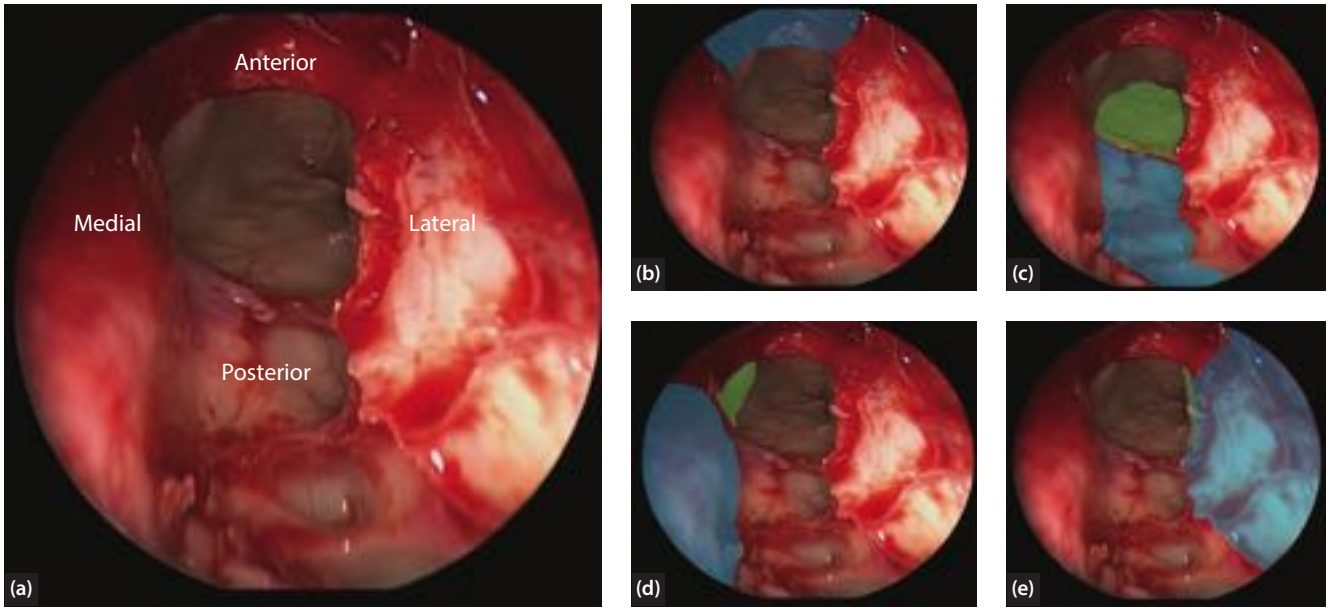


Figure 87.16 (a) Endoscopic view of the left vertical component of the paranasal sinus surgical box with anterior, posterior, medial and lateral limits of dissection visible with a single position of the endoscope. The anterior, posterior, medial and lateral boundaries of the vertical surgical box are indicated as **(b)** nasal beak (blue) **(c)** skull base (blue) and posterior table of frontal sinus (green) **(d)** middle turbinate (blue) and frontal intersinus septum (green) **(e)** medial orbital wall (blue) and supraorbital roof (green) respectively.

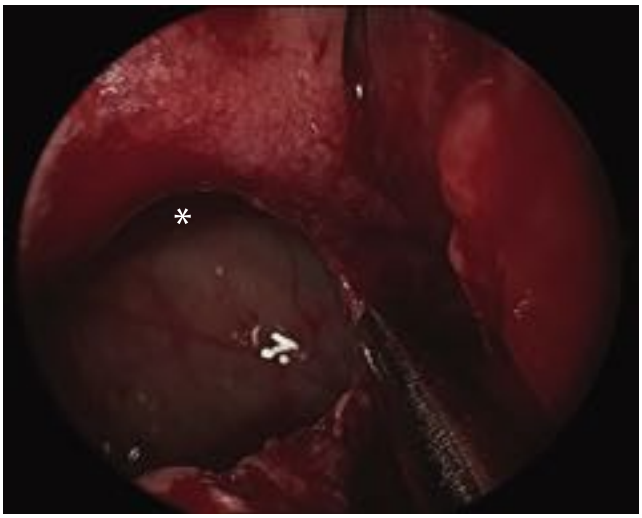


Figure 87.17 Maxillary sinus roof/orbital floor landmark. Endoscopic view of right maxillary sinus antrostomy. Asterisk indicates the position of the right maxillary sinus roof/orbital floor which serves as the first surgical landmark during endoscopic sinus surgery.

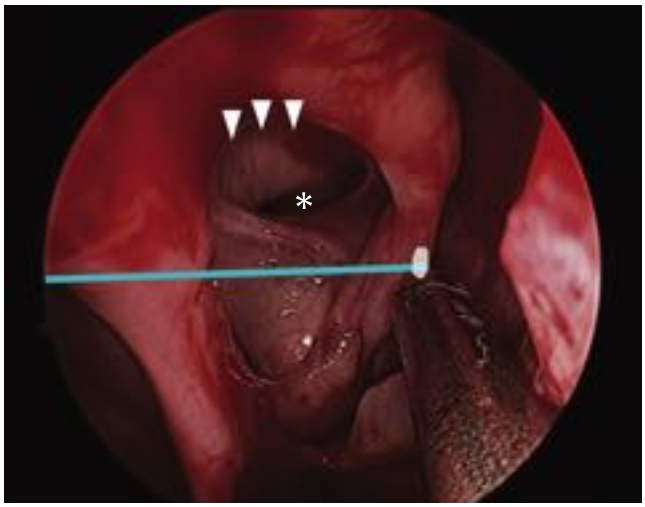


Figure 87.18 Endoscopic view of right maxillary sinus antrostomy after removal of anterior ethmoid cells and basal lamella. Line indicates the horizontal relationship between the maxillary sinus roof / orbital floor landmark and position of the sphenoid ostium. White oval indicates the relative position of the sphenoid ostium. Application of this landmark will ensure safe and easy identification of the sphenoid sinus and avoids mistaking a posterior ethmoid cell or Onodi cell (asterisk) for the true sphenoid sinus. Note that within the Onodi cell is the presence of an exposed optic nerve (arrow heads).

structure cannot be relied upon as it is often removed by pathology or previous surgery. Opening of the sphenoid ostium and removal of the anterior sphenoid wall enables clear visualization of the posterior skull base. The skull base slopes downwards from anterior to posterior, thus, the posterior skull base is at its lowest height within the horizontal portion of paranasal surgical box at the level of the sphenoid sinus (Figure 87.20). The sphenoid can be widely opened laterally as the orbital axis (and thus the lateral limit) is previously identified. Once the posterior skull base is identified, all four limits of dissection of the horizontal portion of the paranasal surgical box are defined (Figures 87.14 and 87.15) and all cells within the confines of these boundaries must be removed.

Performing a complete dissection of the horizontal portion of the paranasal surgical box serves to define the limits of dissection for the vertical portion of the box (Figures 87.14 and 87.16). The limits of dissection that

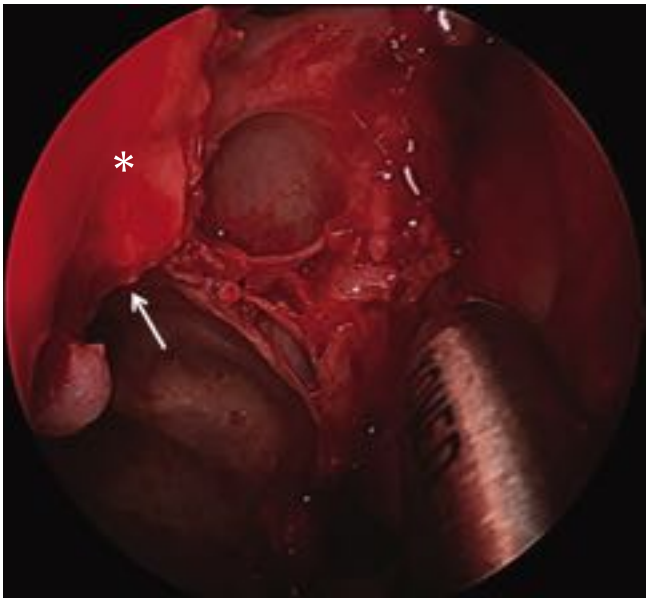


Figure 87.19 Endoscopic view of right anterior ethmoid sinus cavity. The position of the right medial orbital wall (asterisk) is identified after removal of the ethmoid bulla. The transition from the orbital floor to the medial orbital wall is clearly delineated (arrow).

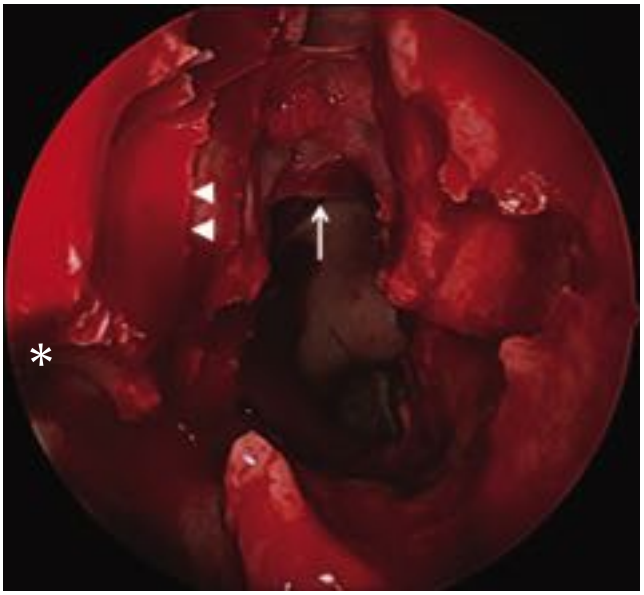


Figure 87.20 Endoscopic view of right sphenoid sinus cavity. The position of the posterior skull base (arrow) is identified after removal of the anterior wall of the sphenoid sinus. The positions of the orbital floor (asterisk) and medial orbital wall (arrow heads) landmarks are visible with a single position of the endoscope.

are defined during the complete sphenoethmoidectomy include the medial orbital wall laterally, middle turbinate medially and skull base posteriorly. These limits are extended superiorly to define the boundaries of the vertical portion of the surgical box and all cells within the confines of these boundaries are removed (Figure 87.14).

BOX 87.12

- Endoscopic sinus surgery is based on the identification of key fixed anatomical landmarks including the orbital floor, medial orbital wall, sphenoid sinus and posterior skull base.
- These landmarks help to define the anatomical limits of dissection during surgery and establish the boundaries of the paranasal surgical box including the horizontal and vertical components of this box.
- The horizontal component of the paranasal surgical box includes the medial orbital wall laterally, middle turbinate medially and skull base posteriorly. These limits are extended superiorly to define the boundaries of the vertical component of the paranasal surgical box which includes the middle turbinate and intersinus septum medially, lamina papyracea laterally, nasofrontal beak anteriorly and skull base posteriorly.

DEVELOPMENTAL AND FUNCTIONAL ANATOMY OF THE PARANASAL SINUSES

The paranasal sinuses are paired structures lined by ciliated pseudostratified columnar respiratory epithelium identical to that in the lower airway. The cilia beat in a coordinated fashion to carry the mucous blanket which traps particles from the sinus into the nose through a series of well-defined pathways. The paranasal sinuses are divided into anterior, posterior and sphenoid compartments that serve as functional units based on these drainage pathways. The anterior functional unit is comprised of the maxillary, anterior ethmoid and frontal sinuses. These sinuses drain into the nose through the osteomatal complex in the middle meatus. The posterior functional unit is comprised of the posterior ethmoid sinus and drains into the nose through the superior meatus. The sphenoid functional unit is comprised of the sphenoid sinus and drains through the sphenoethmoid recess located medial and posterior to the superior turbinate. Although the anterior and posterior ethmoid cavities share a common name, they are completely separate functional entities with different drainage pathways and embryologic origins.

The concept of the sinonasal compartment or functional unit has clinical relevance during endoscopic sinus surgery. Once a compartment is entered with surgical instrumentation, all diseased mucosal cells within the compartment must be completely dissected in order to remove obstructive phenomenon, avoid leaving behind disconnected cells from the surgical cavity, prevent mucocele formation, re-establish post-surgical mucociliary function that is free of recirculation effects, and enable maximal delivery of topical therapy. The ultimate goal of surgery (whether limited or extensive) is the creation of a new functional sinus cavity.

Anterior functional unit

BOX 87.13 Uncinate process and maxillary sinus

- The uncinate process is a sickle-shaped bone which attaches inferiorly to the inferior turbinate and palatine bone and anterosuperiorly to the lacrimal bone.
- The posterosuperior attachment will be discussed later along with the frontal sinus.
- The true maxillary ostial opening is covered by the uncinate process and cannot be viewed endoscopically in a sinus cavity that has not been previously opened surgically.
- The uncinate, together with a fold of mucosa called the anterior and posterior fontanelle cover the opening to the maxillary sinus. Accessory ostia may be present in the fontanelle that can be mistaken for the true maxillary ostium.
- Failure to correctly identify the true ostia and connect it with the common sinus cavity may result in a phenomenon known as mucous recirculation. During recirculation, mucous is directed towards the natural opening along the mucociliary drainage pathway and re-enters the sinus through the accessory ostium.

ETHMOID BULLA

The ethmoid bulla is the largest and most consistent anterior ethmoid air cell. It attaches to the lamina papyracea laterally and has variable attachments to the skull base and basal lamella creating a series of clefts and spaces within the middle meatus that are well described, but have little clinical significance. The reader is referred to the consensus document produced by the Anatomic Terminology Group for a detailed description of anatomic terminology and nomenclature.[11] A variant of normal anatomy in this region is called a Haller cell. A Haller cell is an infraorbital anterior ethmoid cell that pneumatizes into the maxillary sinus and may cause obstruction of the maxillary sinus ostium. Complete removal of the ethmoid bulla is critical to define the medial orbital wall as a landmark.

MIDDLE TURBINATE

The complex shape of the middle turbinate is divided into three segments according to the sagittal, coronal and axial planes to which it is oriented. The sagittal segment attaches to the skull base at the lateral lamella. The coronal segment creates the basal lamella which separates the anterior ethmoid (those cells draining in the middle meatus) and posterior ethmoid (draining via the superior meatus) cavities. There is no natural connection between these two cavities. This partition is often not smooth due to posterior projections of the anterior ethmoid air cells and anterior projections of the posterior ethmoid air cells. The safe working distance from the skull base established by the maxillary sinus roof/orbital floor is used as a reference point to proceed through the basal lamella and enter the posterior ethmoid cavity.[9] The axial segment of the middle turbinate attaches to the lateral nasal wall and is the entry point of a terminal branch of the sphenopalatine artery.

FRONTAL SINUS

The vertical portion of the paranasal surgical box defines the anatomical limits of dissection of the frontal recess. The boundaries of the vertical portion of the paranasal surgical box include the intersinus septum and middle turbinate medially, lamina papyracea laterally, nasofrontal beak anteriorly and skull base posteriorly (**Figures 87.14** and **87.16**). Successful identification of these anatomical limits of the surgical box and removal of all cells within its confines ensures complete dissection of the frontal recess. To define the limits of the vertical portion of the paranasal surgical box, one must consider the various cells that may encroach on this space from the anterior, posterior, medial and lateral directions.

Agger nasi, posterosuperior uncinate process and frontal ethmoid cells

Anterior structures encroaching on the frontal recess include the agger nasi, lateral uncinate process and frontal cells (**Figure 87.21**). The agger nasi is the anterior-most ethmoid air cell and its medial border is formed by the uncinate process.[12] The degree of pneumatization of the agger nasi influences the position of the superior uncinate process and thickness of the bony nasofrontal beak.

The uncinate process can insert into the medial orbital wall, skull base or middle turbinate. Recent studies have demonstrated that the uncinate has multiple attachments in more than 50% of cases rather than a single attachment pattern (**Figure 87.22**).[12, 13] Classic teaching that describes three distinct attachments of the uncinate process which determines the direction of the frontal sinus drainage pathway is neither surgically relevant nor accurate (**Figure 87.22**). The uncinate process inserts onto the medial orbital wall in 85% of cases.[13] Thus, the frontal recess drainage pathway is medial to the uncinate process in 85% of cases. An uncinate process with an isolated attachment to either the skull base or middle turbinate (without attachment to the medial orbital wall) occurs in only 15% of cases.[13] This attachment pattern leads to a surgically obvious frontal drainage pathway located lateral to the uncinate process that is easily identified at the time of surgery. The surgical rule holds true that the frontal recess is medial to the remnant uncinate process or 'vertical bar' in 85% of cases[14] with the other uncinate attachments representing easy surgical arrangements.

BOX 87.14

The uncinate process inserts onto the medial orbital wall in 85% of cases resulting in a frontal recess drainage pathway that is medial to the uncinate.

Frontal cells represent cells of the first ethmoturbinal that pneumatize above the agger nasi towards the frontal sinus. According to the Kuhn classification, a type 1 frontal cell is a single frontal ethmoidal cell above the agger nasi and below the frontal sinus floor, type 2 is a tier of

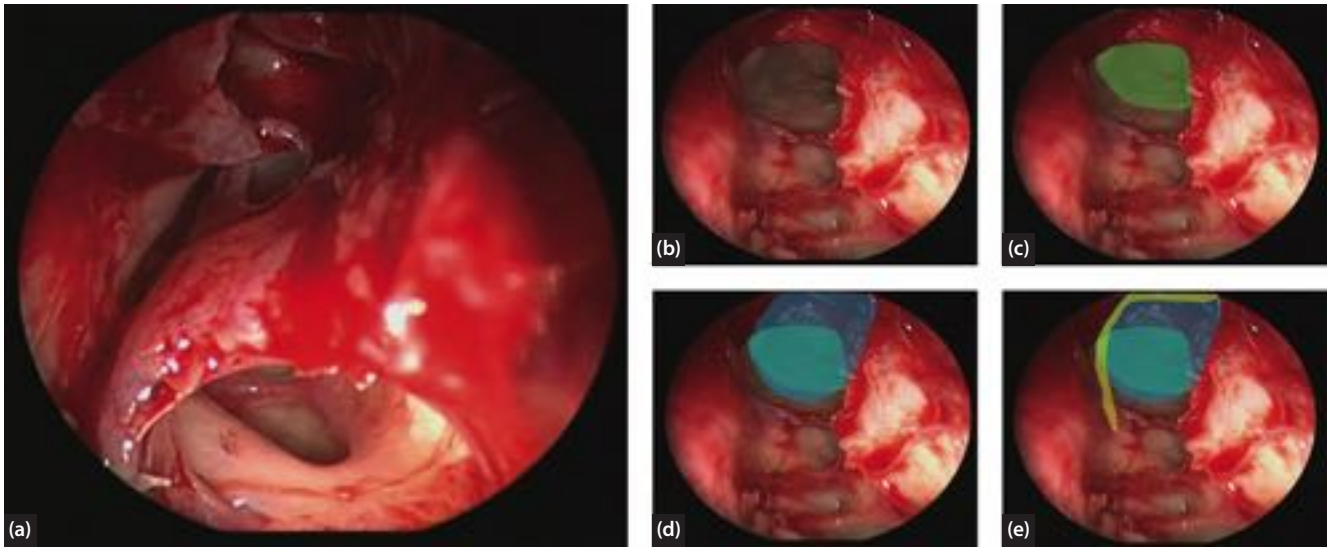


Figure 87.21 Anterior structures encroaching on the frontal recess depicted by a series of onlay diagrams. **(a)** Left frontal recess with all cells intact prior to surgical dissection, **(b)** left Draf 2A frontal sinusotomy with removal of all cells encroaching on the frontal recess. The relative positions of the anterior cells are superimposed including: **(c)** frontal cells (green), **(d)** agger nasi (blue), **(e)** superior uncinate process (yellow).

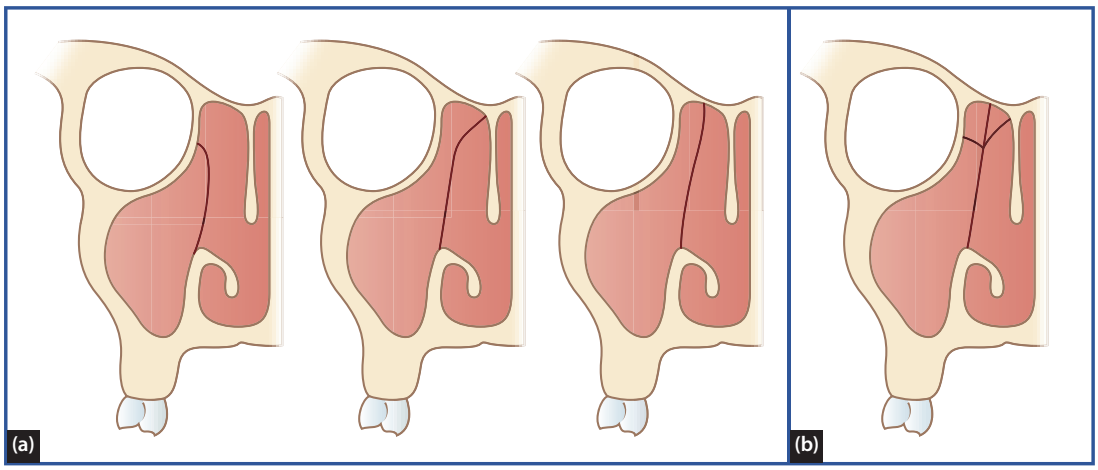


Figure 87.22 Schematic diagram of the uncinate process with different arrangements of its superior attachment. **(a)** Classic teaching describes 3 distinct attachments to the medial orbital wall, middle turbinate and skull base respectively which determines the direction of the frontal sinus drainage pathway. This description is not accurate. **(b)** The uncinate process has multiple attachments in greater than 50% of cases rather than a single attachment.

cells above the agger nasi, type 3 is a cell pneumatizing into the floor of the frontal sinus and type 4 is an isolated frontal ethmoid cell within the frontal sinus. Using multiplanar reconstructed imaging, Wormald further modified this classification to more accurately describe type 3 cells as frontal ethmoidal cells that fill less than 50% of the frontal sinus and type 4 cells as filling greater than 50% of the frontal sinus.[15] These classifications of frontal cells are primarily to ensure that the surgeon's view of a large frontal recess cell lumen will not be mistaken for the true frontal sinus. Identification of these frontal cells on preoperative imaging prevents false assumption of completion sinusotomy (see Chapter 99 on the frontal sinus).

Supraorbital ethmoid and suprabulla cells

Posterior structures encroaching on the frontal recess include supraorbital ethmoid cells, suprabulla cells and the ethmoid bulla (**Figure 87.23**). Supraorbital ethmoid cells are anterior ethmoid air cells that extend superiorly and laterally over the orbital roof.[16] These cells are recognized on imaging giving the appearance of a septated frontal sinus on coronal view and a cell located posterior and lateral to the frontal sinus on axial view.[16] Supraorbital ethmoid cells have three clinically significant features relevant to the frontal recess: (1) they can cause obstruction of the frontal recess, (2) they can be falsely mistaken for the true frontal sinus leading to incomplete surgical dissection and (3) they are associated with a low position of the anterior ethmoid artery within a mesentery because these cells pneumatize downward from the skull base behind the artery.[17] The supraorbital ethmoid cell also creates a very narrow orbitocranial cleft posteriorly that can be very challenging to operate within.[18] Suprabulla or frontal bulla cells are pneumatized extensions above

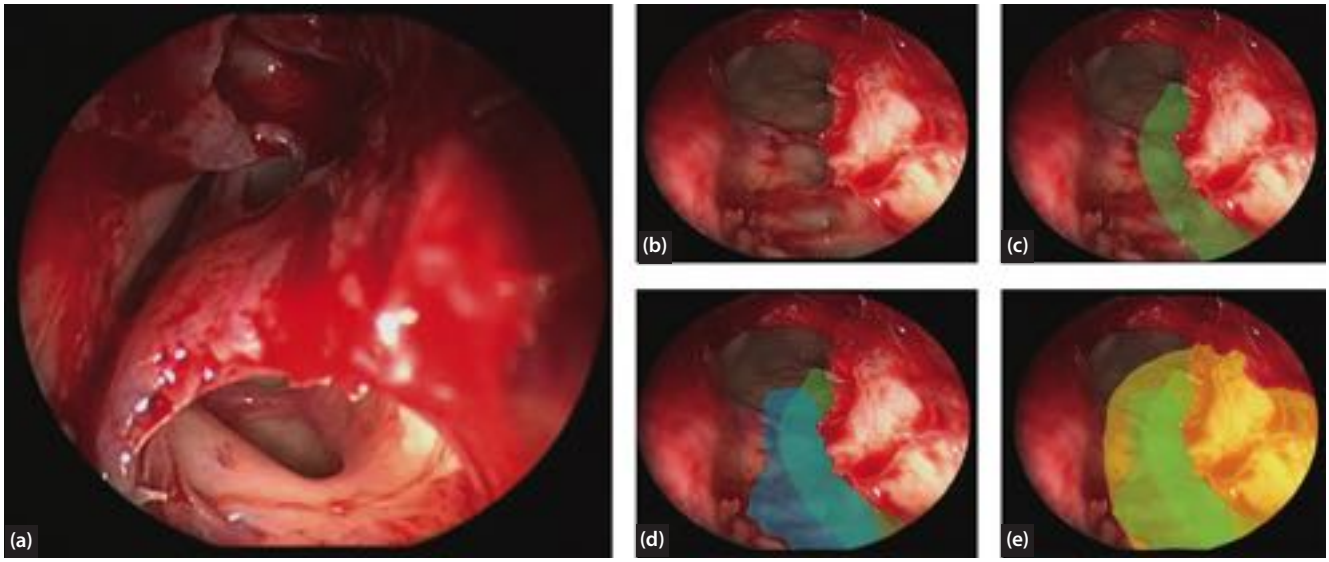


Figure 87.23 Posterior structures encroaching on the frontal recess depicted by a series of onlay diagrams. **(a)** Left frontal recess with all cells intact prior to surgical dissection, **(b)** left Draf 2A frontal sinusotomy with removal of all cells encroaching on the frontal recess. The relative positions of the posterior cells are superimposed including: **(c)** supraorbital ethmoid cell (green), **(d)** suprabulla cell (blue), **(e)** ethmoid bulla (yellow).

the ethmoid bulla up the skull base and on the posterior table of the frontal sinus. These cells can become quite large and mistaken for either the skull base or posterior table of the frontal sinus. Failure to recognize these cells on pre-operative imaging will also result in incomplete surgical dissection of the frontal recess.

BOX 87.15

- Supraorbital ethmoid cells have significant features relevant to the frontal recess as the can: (1) cause obstruction of the frontal recess, (2) be falsely mistaken for the true frontal sinus leading to incomplete surgical dissection and (3) be associated with a low position of the anterior ethmoid artery within a mesentery placing this artery at risk of injury during surgery.
- Suprabulla cells pneumatize up the skull base and failure to recognize these cells pre-operatively will result in incomplete surgical dissection of the frontal recess.

Medial structures encroaching on the frontal recess include intersinus septal cells and medially inserting uncinate process. Intersinus septal cells represent pneumatization of the frontal sinus septum. Lateral encroaching structures include frontal cells, agger nasi and a lateral uncinate process attachment.

Posterior functional unit

The posterior functional unit is comprised of the posterior ethmoid air cells with drainage into the superior meatus. A variant of normal anatomy in this region is a lateral and posterior pneumatization of a posterior ethmoid cell called an Onodi cell (Figure 87.18). Onodi cells pneumatize over the optic nerve exposing this critical structure to injury during surgery. These cells can also be mistaken for the true sphenoid sinus leading to incomplete surgery. Application of the maxillary sinus roof/orbital floor landmark identifies the level of the sphenoid ostium and enables complete dissection of the sphenoid sinus.

BOX 87.16

Onodi cells pneumatize over the optic nerve placing the optic nerve at risk for injury during surgery. An Onodi cell can be identified on the coronal view CT sinus as giving the appearance of a horizontal septation within the sphenoid sinus.

Sphenoid functional unit

The sphenoid functional unit is comprised of the sphenoid sinus which drains into the sphenoethmoid recess. Identification of the sphenoid sinus enables the surgeon to determine the level of the posterior skull base at its lowest position. The sphenoethmoid recess is the space between the superior meatus and septum. The supreme turbinate may be seen here. The sphenoid ostium opens behind the superior turbinate and is neither medial nor lateral to it.[19] Complete removal of the anterior sphenoid wall laterally enables the surgeon to identify the medial orbital wall at its posterior position. The main structures associated with the sphenoid sinus include the optic nerve, carotid artery and sella turcica where the pituitary gland is located. The pneumatization pattern of the sphenoid sinus can be variable. The different types include sellar (90%), pre-sellar (9%) and conchal (1%) pneumatization patterns (Figure 87.6). The sellar type describes sphenoid pneumatization posterior to the sella turcica. The pre-sellar type describes sphenoid pneumatization up to the anterior sella and the conchal type describes a shallow bowl with minimal sphenoid pneumatization and trabecular bone

between the sinus and sella. The sphenoid sinuses can also pneumatize laterally into the pterygoid root resulting in the presence of a lateral sphenoid recess (Figure 87.7).

CONCLUSION

The paranasal sinuses represent some of the most variable human anatomy. An understanding of the developmental and functional anatomy is critical to understand patterns of disease and pathophysiological events in the sinuses. However, it is an understanding of the anatomical boundaries of paranasal sinuses that are critical for the surgeon to avoid major complications. Ensuring the ostia are incorporated into the common surgical cavity provides the basis for a functional post-surgical cavity rather than discreet identification of their location.

BEST CLINICAL PRACTICE

- ✓ The paranasal sinuses represent some of the most variable in human anatomy.
- ✓ Although a knowledge of the developmental and functional anatomy is critical to understand patterns of disease and pathophysiological events in the sinuses, they are often of limited assistance during surgery.
- ✓ The anatomical boundaries of the paranasal sinuses are critical for the surgeon to avoid major complications. Variable clefts, pneumatization patterns and features that are easily distorted by pathology and prior surgery are not good guides for a surgeon.
- ✓ Ensuring complete surgical dissection with ostia incorporated into the common surgical cavity provides the basis for creating a new functional neo-sinus cavity post-operatively.

FUTURE RESEARCH

- ➤ Understanding the epithelial dysfunction with intrinsic mucosal inflammation, local microbial colonization and mucociliary dysfunction as the contributing factors in patients with chronic sinus inflammation is still evolving.

KEY POINTS

- Identify key fixed anatomical landmarks to delineate the limits of dissection of the paranasal sinus surgical cavity (box) for safe and complete endoscopic sinus surgery.
- The main structures are the orbit and skull base. These are defined by (1) maxillary sinus roof (orbital floor) (2) medial orbital wall (3) sphenoid sinus roof (skull base) and (4) the lateral sphenoid wall (orbital apex).
- Paranasal sinuses are divided into anterior, posterior and sphenoid compartments that serve as functional units based on mucociliary drainage pathways.
- Once a compartment is surgically entered, all mucosal cells within the compartment must be completely dissected to create a new functional neo-sinus cavity.

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CHAPTER
88

OUTPATIENT ASSESSMENT

Martyn L. Barnes and Paul S. White

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SEARCH STRATEGY

Data in this chapter may be updated by PubMed MeSH searches using the following keywords: otolaryngology, diagnosis, nose and outpatients, as well as selected subheadings e.g. 'otolaryngology/diagnosis'[Majr]. Several thousand articles were identified, almost all too specific in context to guide this short overview chapter. Notable exceptions are cited. See also the future research comments.

INTRODUCTION

Rhinology is an increasingly broad sub-speciality in which outpatient assessment is adjusted to suit each individual case. This chapter explores basic rhinologic history taking, clinical examination, nasendoscopy and the use of patient reported outcome measures (PROMs). Interpretation and use of more specialist assessments such as rhinometry, facial pain and lacrimal testing are described in their respective chapters. Investigations are described in their respective chapters, for example 'Measurement of the Nasal Airway' and 'Radiological imaging in rhinology and skull base surgery'.

The aim of an outpatient assessment is to reach a diagnosis in order to guide management. In many patients this may be clear from the history alone.

HISTORY TAKING

This is best initiated by characterizing the index nasal symptom(s), noting duration, periodicity, nocturnal variation, seasonal effects, laterality, association with trauma or prior surgery, and whether there are any alleviating or provoking factors. The enquiry should cover the presence of nasal obstruction or congestion, facial pain, hyposmia, anosmia, rhinorrhoea and post-nasal discharge. Secondary symptoms such as sneezing, itch, epiphora, taste disturbance and dry mouth should be elicited where appropriate. Understanding the symptoms and their associations is not only useful diagnostically, but also helps to create a picture of the level of quality-of-life impairment suffered. The character of any nasal discharge can give clues to an acutely infective (mucopurulent) versus chronic rhinosinusitis or inflammatory origin. Increasing unilateral nasal obstruction associated with epistaxis (often minor) or facial pain and swelling suggests neoplasia and indicates the need for urgent assessment.

It is important to enquire about allergies, hay-fever, exposure to animal dander, asthma (or more general respiratory symptoms), and aspirin hypersensitivity. A previous history of nasal trauma may suggest nasal obstruction resulting from septal fracture or dislocation causing obstruction or failure of support to the internal nasal valve. Surgical procedures such as rhinoplasty, alar base reduction, and cleft palate surgery may all be associated with similar restrictive changes on the nasal airway.

Many systemic diseases have nasal manifestations. Granulomatosis with polyangiitis (previously Wegener's granulomatosis) is a systemic vasculitis in which nasal obstruction is associated with diffuse crusting of the nasal mucosa. Other conditions such sarcoidosis, Churg-Strauss vasculitis and Bechet's syndrome have a similar presentation. Cocaine abuse and habitual nose picking can cause septal crusting, septal perforation, and saddle deformity all of which have the potential to cause nasal impairments. Immunodeficiencies and ciliary defects are also commonly associated with nasal pathology.

A history of cigarette smoking is relevant as it may potentiate allergic rhinitis, and vasomotor rhinitis is

sometimes seen as a cause of nasal obstruction during smoking cessation.

The psychological aspects of the history are important to address. Many rhinologic symptoms relate to stress, anxiety, and psychosomatic manifestations. Directed enquiry into work and home situations will often elicit a patient's own concerns to this end.

Previous and current therapeutic trials of medication and their efficacy should be recorded. Many drugs exacerbate nasal symptoms, especially common are those with anti-muscarinic effects, such as anti-prostatic medications, anti-epileptics, antidepressants, antipsychotics, antihistamines, and drugs for Parkinson's. Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen in patients who have Samter's triad (nasal polyposis, asthma and NSAID intolerance) can trigger non-infective rhinitis and rhinosinusitis. Nasal obstruction associated with vasomotor rhinitis is a side effect of a number of drugs, including antihypertensives (such as beta blockers and calcium channel blockers), sedatives, phenothiazines, antidepressants, oral contraceptives and drugs used to treat erectile dysfunction. Overuse of sympathomimetic decongestant nasal sprays can cause rhinitis medicamentosa.

PATIENT REPORTED OUTCOME MEASURES (PROMs)

Contemporary practice should include the evaluation of the full-patient presentation. This process is simplified by the routine use of PROMs – questionnaires that aim to capture and quantify the bulk of symptomatology and disease impact. These should be supplemented and validated by direct questioning and inviting patients to discuss other ways in which they have been affected. When patients complete forms prior to the appointment, the administrative burden is minimized and the exercise will add to the efficiency and efficacy of the history taking process. Capture of these data (ideally digital) should facilitate research, audit, and service evaluation.

The following are selected examples of the more prevalent and well-validated patient reported outcome measures that may be useful in a rhinology clinic (Table 88.1).

EXAMINATION

Nasal Structure / Aesthetics

A full facial aesthetic assessment should be performed in patients with external deformity or cosmetic concerns. Examination of the external nose should begin with careful inspection and palpation of the nasal bones and alar cartilages. The detail should include an evaluation of skin type, skin scars, soft-tissue envelope thickness, integrity of the upper and lower lateral cartilages, nasal tip support, tip configuration, nares shape and integrity of the external and internal nasal valves. These factors can offer useful information on the more subtle causes of nasal dysfunction such as nasal valve insufficiency. Abnormalities of relevance to function as well as cosmesis include saddle deformity, septal deviation and deficiencies of the upper or lower lateral cartilages.

Functional assessment / anterior rhinoscopy

Nasal patency is assessed through anterior rhinoscopy – examination of the anterior nose using a Thudicum's speculum and head light illumination. First the patient is asked to breathe normally through their nose, noting any difficulty or noise. A thumb is used to gently occlude each nostril in turn and assess unilateral patency, remembering that many normal subjects are unable to breathe comfortably through a single nasal airway.

The degree of alar margin or 'external nasal valve' collapse is observed on normal and on forced inspiration, again noting that some dynamic narrowing is normal. The inferior turbinates should be evaluated for congestion, mucosal thickening and the presence of exudate.

TABLE 88.1 Select examples of the more prevalent and well-validated patient reported outcome measures that may be useful in a rhinology clinic

Instrument	Domain Focus	PubMed Citations	Licensing
Sinonasal Outcomes Test (SNOT-22)[2]	Sinonasal	59	See wustl.edu website.[3] Contact Jay Piccirillo (+1-314-362-8641)
Glasgow Benefit Inventory (GBI)[4]	Change in Generic QoL (Benefit)[a]	129	Free for non-commercial use. Contact maa@ihr.gla.ac.uk
Rhinasthma[5]	The Unified Airway	17	No details provided. Contact canonica@unige.it
Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)[6]	Allergic Rhinitis	140	No details provided. Contact jill@qoltech.co.uk
SF-36[7]	Generic QoL	12K+	See Qualitymetricwebsite.[8] Contact info@qualitymetric.com

[a] As a benefit inventory, the GBI can be used on a single occasion (e.g., at post-operative follow-up) in order to assess the effects of an intervention – a significant administrative advantage. The Sinosasal Outcome Test-22 Questionnaire version 4 is the domain (rhinology) specific instrument recommended by the Clinical Audit and Practice Advisory Group of ENT-UK[1] based on a PubMed search conducted on July 2013 PubMed citations prior to 2009 publications.

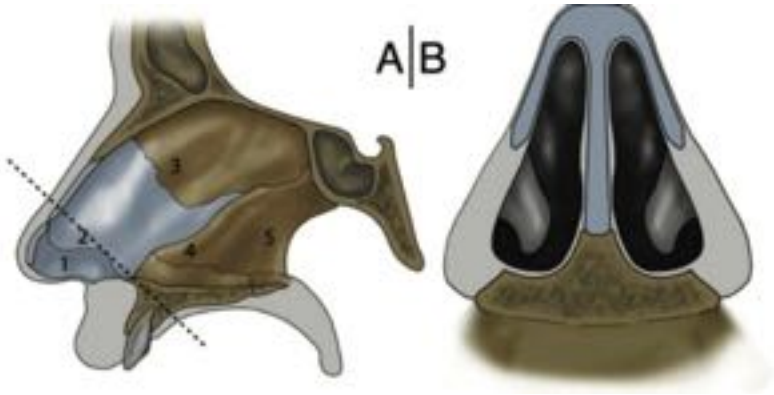
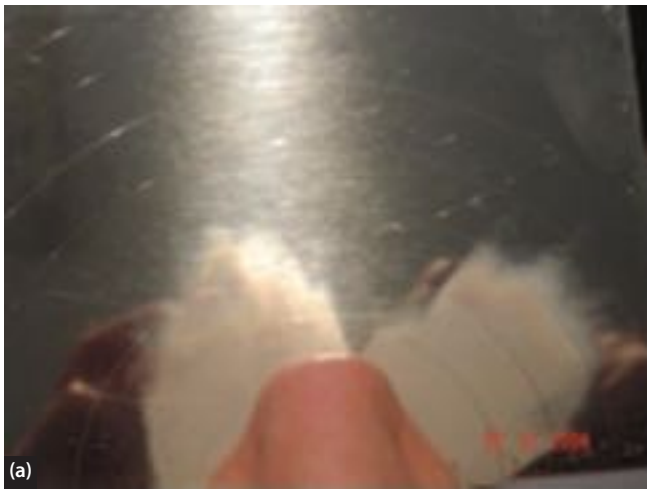


Figure 88.1 Cottle's areas of the nasal septum and the internal nasal valve region (dotted line). Deviations of the nasal septum can be classified by location and by severity. Locations include, 1 – Caudal septum, 2 – Internal nasal valve, 3 – High mid septum, 4 – Low mid septum, 5 – Posterior septum. Severity is graded 0 – No deviation, 1 – Minimal, 2 – Less than 50% lateralized, 3 – More than 50% lateralized, 4 – Fully lateralized (mucosal contact with lateral wall). This figure is released by SurgTech Ltd. (see www.SurgTech.net). They are available free of charge for anyone to use with certain provisos (see www.surgtech.net/terms). http://www.surgtech.net/Rhino/Exam/

The area between the inferior turbinate head, upper lateral cartilage and the nasal septum is the narrowest part of each nasal airway, termed the 'internal nasal valve' (**Figure 88.1**). The cross-sectional area of this space should be assessed at rest, on normal and forced inspiration. Any restriction may be due to septal deformity, turbinate engorgement or internal valve collapse. The latter may be static or dynamic due to upper lateral cartilage deformity or weakness respectively. Static internal nasal valve collapse is associated with an acute 'valve angle' at the junction of the septal and upper lateral cartilages (less than 15°). Poor septal support can also result in a shallow valve height, with nasal restriction despite an even more obtuse angle (more than 15°). Septal obstruction elsewhere in the nose can be classified and graded as shown in **Figure 88.1**.

Simple tests such as the peak nasal inspiratory flow, nasal vapour condensation, or nasal valve splinting tests can be helpful adjuncts to confirm the clinical evaluation of nasal patency (**Figure 88.2**).

Cottle's manoeuvre (testing for improvement in nasal patency with lateral traction on the alar) tends to improve all nasal airways and is not advocated as a usefully discriminant test. Other clinical tests can be helpful – internal



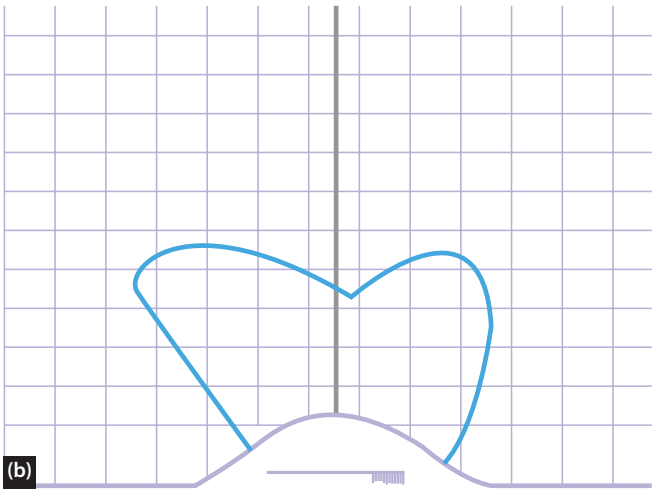






Figure 88.2 Nasal patency tests. (a,b) A vapour condensation test can be performed with a metal tongue depressor or a Glatzel calibrated mirror and gives a ready reckoning of relative flow. **(c)** A peak nasal inspiratory flow (PNIF) meter can evaluate overall nasal patency (normally more than 100 $L min^{-1}$ in an adult). **(d)** Splinting tests on the external and internal nasal valve can confirm anatomical deficiencies.

TABLE 88.2 Nasendoscopy Technique

First Pass – Front to back
The endoscope is passed along the nasal floor, visualizing the septum and inferior turbinate. In the post-nasal space, the eustachian cushion and orifice, and the fossa of Rosenmüller are seen. Any mucopurulent post-nasal drainage can be noted. On withdrawal, the inferior meatus and, where possible, Hasner's valve are inspected.
Second Pass – Medial to the middle turbinate
Passing the endoscope medial to the middle turbinate, the sphenoethmoid recess, superior turbinate, and slit-like opening of the sphenoid ostium are visualized. The olfactory cleft is seen more anteriorly. Head repositioning may be required, and an angled endoscope is recommended.
Third Pass – The middle meatus
Retracting, rotating the view laterally, and rolling the endoscope into the middle meatus will medialize the turbinate to expose any middle meatal mucopurulence accessory ostia or other pathology. The hiatus semi-lunaris, bounded by the uncinate and ethmoid bulla can be seen, as well as the membranous fontanelles and any associated accessory ostia. An angled endoscope is recommended.

valve collapse may respond to a trial of *Breathe-Right*® strips®. Similarly, nasal vestibule stents such as France's alar dilators®, AirMax Nasal splints®, or Max-Air Sinuscones® can have a positive effect on both valve areas.

Nasendoscopy

This is a necessary investigation for all patients referred for a specialist investigation of nasal or paranasal sinus disease. It is best performed after the application of decongestant (often combined with a local anaesthetic).The effect of the vasoconstriction on the turbinate mucosa will give a useful indication of the reversibility of any congestion. Endoscopic evaluation using a three-pass technique (Table 88.2) should enable visualization of the inferior meatus, middle meatus, superior meatus, spheno-ethmoidal recess, olfactory cleft, septal areas, and the nasopharynx. Narrow diameter (2.5–3.0 mm) angled endoscopes (30–45°) confer greater opportunity to look around corners into each narrow nasal meatus. Patient confidence is enhanced by initiating the examination with passes though the more patent parts of the airway, for example, on the side opposite to any septal deviation. Conditions causing severe obstruction of the anterior airway such as a dramatic septal deviation or large polyps may preclude endoscopy beyond this level, but the clinical relevance will be obvious. Examples of the endoscopic anatomy, and common pathologic and findings are provided in Figures 88.3 and 88.4.

Endoscopic nasal biopsy

Any nasal masses should be evaluated for colour, consistency, vascularity and origin. Bilateral nasal polyps need not be biopsied unless the mucosal appearance is unusual, however, it is a sensible precaution to obtain histopathology in all primary polypectomy cases. Other endonasal masses can often be biopsied in a clinic situation, but the possibility of a vascular nature (e.g. juvenile angiofibroma) or meningo(encephalo)coele must be considered based on the appearance, location and apparent margins. In such cases, a CT with contrast or MRI scan may prevent significant complications. If a biopsy is still required, it may be best performed in the operating theatre. In all cases, preparations should be made to address any epistaxis following biopsy.

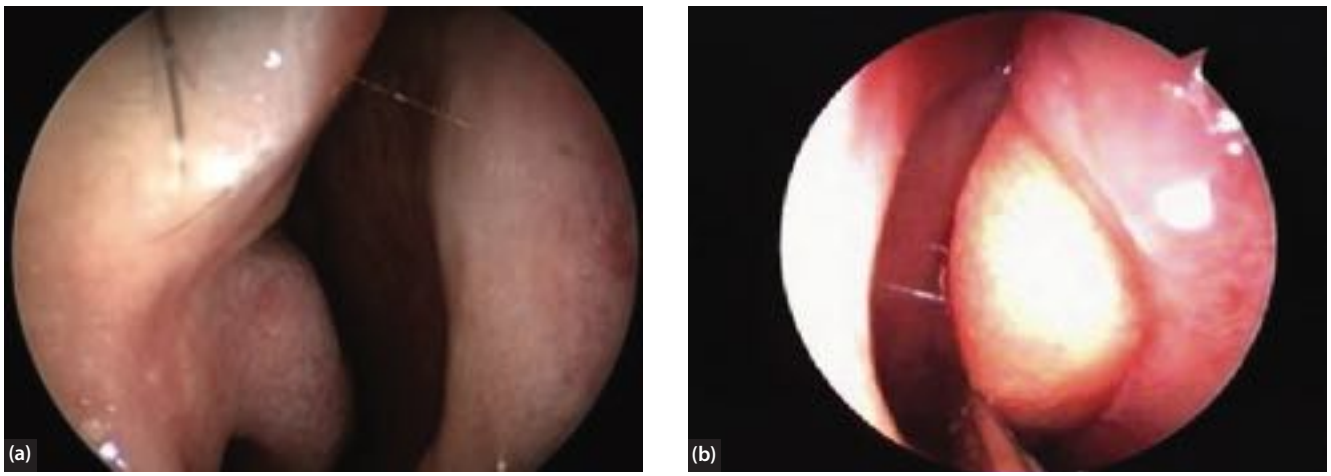


Figure 88.3 Stills of endoscopic anatomical findings. (a) Endoscopic view of the right internal nasal valve. **(b)** Endoscopic view of right middle meatus. *(Continued)*





Figure 88.3 (Continued) Stills of endoscopic anatomical findings. **(c)** Endoscopic view of right middle meatus, showing the uncinate process, hiatus semilunaris and ethmoidal bulla. **(d)** Endoscopic view of the right side of the nasopharynx.







Figure 88.4 Stills of common endoscopic pathological findings. **(a)** Left inferior turbinate hypertrophy in allergic rhinitis. **(b)** Right nasal polyp. **(c)** Severe crusting of the right inferior turbinate and septum in granulomatosis with polangitis.

BEST CLINICAL PRACTICE

- ✓ Systematic approach to history and examination based on presenting concerns.
- ✓ Appropriate PROMs used to record presentation and clinical progress - patient completed.
- ✓ Formally recorded benefits for surgery and other interventions.

FUTURE RESEARCH

- ➤ Rarely do we formally study our greatest tool – the medical history and examination.
- ➤ In the future, the coming together of medical informatics, the electronic patient record, patient reported outcome measures, and innovative (largely patient led) data collection techniques applied to routine clinical practice will bring together a wealth of data we currently fail to recognize and interpret. This will give us greater opportunities to improve our understanding of the patient symptom journey, diagnostic implications, and the effect our interventions truly have on this. It may also trivialize clinician involvement. Such changes seem some way off yet – a good start would be a 'Rhinology' MeSH term.

KEY POINTS

- Well-developed skills in clinical history and examination are key to efficiently arriving at the correct diagnosis and implementing appropriate management in all our patients.
- PROMs have become an integral component of patient assessment.
- Nasal endoscopy is a necessary investigation for all patients referred for a specialist rhinologic assessment.

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CHAPTER 89

PHYSIOLOGY OF THE NOSE AND PARANASAL SINUSES

Tira Galm and Shahzada K. Ahmed

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed and Medline search using the following keywords: nasal obstruction, nasal mucosa, nasal blood flow, nasal cycle, nasal cilia, olfaction, nasal valve and autonomic nervous system.

INTRODUCTION

To understand the pathological process affecting the nose and the paranasal sinuses, it is important to have an understanding of the normal physiological functions of the nose.

The nose is a complex organ that forms an important part of the face and has multiple functions. Anatomically, the nose may be considered to have an external and internal component. The internal component forms the nasal cavities. The external component is prominent, pyramidal with an apex at the tip whose base is attached to the forehead. The nose projects downward with two perforated apertures, the nostrils, which are separated by the columella. The external nose is made up of cartilaginous and bony parts. The cartilaginous part consists of lower lateral cartilages and upper lateral cartilages both of which are in pairs. Fibrous tissue connects the cartilages. The internal nose is divided by the nasal septum into left and right chambers. The entrance of the internal nose: the nasal vestibule is lined by skin, and it contains appendages. The rest of the nasal entry is lined by respiratory mucosa and olfactory epithelium. Each cavity consists of a floor, roof, lateral and medial walls.[1]

The principal physiological function of the nose is to humidify and warm inspired air, as well as to remove noxious particles from the air, thus protecting the delicate distal lower respiratory tract. The nose also serves as a sense organ, housing the olfactory apparatus that allows individuals to smell substances for pleasure and defence purposes. These functions are highly dependent on the anatomical structure of the nose. The vomeronasal organ (VNO) is the peripheral sensory organ of the accessory olfactory system and is located either at the base of the nasal septum in humans or in the roof of the mouth in most amphibians, reptiles and mammals. The VNO role is to detect pheromones and other chemical signals that initiate innate behavioural response between individuals of the same species. These chemical communications facilitate social interactions such as sexual relationships.

The nasal mucosa is the first part of the airways to come in contact with the external environment, with an adult inspiring up to an estimated 10 000 litres of air daily. The nasal mucosa is very vascular containing arterioles, arteriovenous anastomoses and venous sinusoids, with a large surface area of 150 cm^2.[2] During normal breathing the nose contributes up to 50% of the resistance of the entire airway, with any change in this resistance playing a significant role to the total respiratory function.[3] These vital properties allow the nasal airway to play an important role in the normal homeostasis of the body.

THE ROLE OF PARANASAL SINUSES

The paranasal sinuses are air filled cavities found in the maxilla, sphenoid, ethmoid and frontal bones. They develop from an outgrowth of the nasal cavity, and hence pathology affecting the nose also affects the paranasal sinuses. Development of the paranasal sinuses vary, with ethmoid and maxillary sinuses being present at birth and the frontal sinuses developing by the age of six, however they can also be absent. The degree of development of the sphenoid sinus differs considerably.

The physiological role of the paranasal sinuses is uncertain, but a number of possible functions have been suggested.

This includes the following:

- Providing a physical buffer against injury to the face
- Vocal resonance
- Reduction of skull weight
- Humidification
- Heat insulation
- Air conditioning

NASAL BLOOD FLOW

Nasal blood flow plays a crucial part in the normal physiological function of the nose.

It can be determined using temperature change, colour change, photoelectric plethysmography, and laser Doppler techniques (**Figure 89.1**). There can be various combinations of blood flow based on the balance between arteriovenous shunting, arterial airflow as well as venous pooling. The main clinical variations include hyperaemia, reduced arterial perfusion and ischemia. Arteries and arterioles cause resistance while venules and sinusoids give capacitance. The nose has an abundant blood supply, from branches of both the internal and external carotid arteries. A rich vascular bed composed of predominantly arteriovenous anastomosis and venous sinusoids supply the nasal mucosa. The venous sinuses form the erectile tissue that is located on the anterior nasal septum and the inferior turbinates. They have the ability to expand and shrink, which has an impact on the nasal resistance and nasal airflow.[4] Animal studies have shown that venous pressure has a greater impact on the nasal airway resistance, with nasal resistance increasing by 1.2–1.3% per mmHg of venous pressure increase.[5]

NASAL MUCOSAL VESSEL CAPACITANCE

Two main mechanisms, the hydrostatic pressure of blood and the autonomic nervous system influence nasal mucosal vessel capacitance. The change in hydrostatic pressure affects the filling pressure of vessels, where increase in pressure expands the venous sinusoids. The autonomic

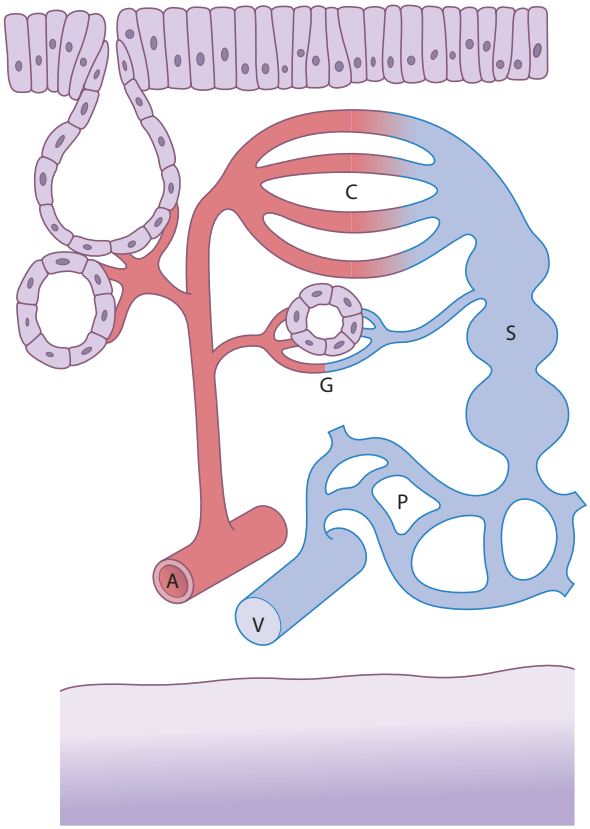


Figure 89.1 Schematic representation of the blood supply of the turbinates. A, arteriole; V, venule; C, capillaries; G, interstitial glands; P, venous plexus; S, venous sinusoids.

nervous system controls the activity of smooth muscle found in the walls of the arteriovenous anastomoses leading to changes in nasal blood flow. Other factors which also influence nasal blood flow include medication, temperature and humidity.[6]

AUTONOMIC NERVOUS SYSTEM

The nose is innervated by parasympathetic and sympathetic fibres, which have a profound impact on nasal physiological function. The parasympathetic fibres originate in the midbrain, with the post-ganglionic fibres travelling in the maxillary branch of the trigeminal nerve and providing secretomotor supply to the mucous glands in the nasal mucosa. The primary neurotransmitters are acetylcholine, which induces serous secretion and vasoactive intestinal peptide which causes vasodilation of the blood vessels of the nasal mucosa. The sympathetic innervation to the nose starts from the thoracic spinal nerves, with pre-ganglionic fibres synapsing in the cervical sympathetic ganglion. The post-ganglionic fibres travel alongside the internal carotid artery. Sympathetic fibres predominantly innervate smooth muscle in the walls of arterioles and sinusoids. The primary neurotransmitter is noradrenalin, which has the opposite effect on the nose, causing a reduction in secretomotor activity of mucous glands and causing vasoconstriction of the blood vessels. Drugs may mimic the effects of sympathetic and

TABLE 89.1 Drugs acting on the nasal mucosa

Drug Group	Mode of action	Example
Sympathomimetics and their antagonists	Compounds act on alpha 1 receptors and cause vasoconstriction	Adrenalin and noradrenaline analogues Cocaine blocks uptake of noradrenalin in nerve endings. Also acts as a local anaesthetic Drugs used for hypertension such as beta-blockers
Parasympathomimetics and their antagonists	Compounds act to cause vasodilation and increase nasal secretions	Pilocarpine causes vasodilation and watery secretions Ipratropium bromide blocks muscarinic receptors, thus preventing acetycholine from binding
Antihistamines	Predominantly block H^1 receptors. Histamine is found mainly in mast cells and causes vasodilation and increases plasma leaking from capillaries	Antihistamines
Local anaesthetics	Inhibit Na channel influx therefore reduce the rate of depolarization/repolarization.	Lignocaine

parasympathetic nerve supply. Table 89.1 gives an overview of drugs frequently used and their mode of action on the nose.

EPITHELIUM-CILIARY FUNCTION

There are three types of epithelium in the nose. First, there is squamous also referred to as the transitional epithelium that consists of the vibrissae, sweat glands, and nasal vestibule (sebaceous glands). Second, there is the pseudostratified columnar epithelium that covers two-thirds of the posterior nasal cavity. This epithelium contains ciliated as well as non-ciliated columnar cells, basal cells as well as mucin secreting goblet cells. The nasal epithelium is located on the lamina propria and basement membrane, which are served by capillaries that facilitate fluid flow through to the nasal mucosa. Finally, there is the olfactory neuroepithelium that forms the superomedial portion of the superior turbinate, nasal root and superior septum. There are various types of cells in the olfactory epithelium but the more common are Bowman glands and ducts, bipolar receptor cells, sustentacular cells and microvillar cells. Cilia are located on the surface cells of the respiratory tract. Their role is to push mucus backwards towards the nasopharynx.

The ultrastructure of all cilia remains the same; however, nasal cilia are somewhat short. The surface membrane of a cilium encloses an organized ultrastructure. The nine outer-paired microtubules enclose a single inner pair of microtubules. The outer pairs of microtubules are linked to one another by nexins and to the inner pair of microtubules by central spokes. In addition, outer pairs of microtubules have both outer and inner dynein arms that are made up of an ATPase. There are two layers of nasal mucus film, the lower layer that is more watery and cilia move freely, and the upper viscous layer. Importantly, there are small hooks on the tips of the cilia to facilitate their movements once they enter the viscous layer.

At body temperature, cilia beat frequency ranges from 7 to 16 Hz. The frequency usually remains constant when the temperatures are between 32 and 40 °C. The cilia can beat rapidly in a propulsive stroke or slowly during the recovery phase. Notably, the propulsive period is characterized by the cilium straightening while the tip points to the viscous layer. The recovery phase sees the cilium bending over in the aqueous layer. During this process, adenosine triphosphate (ATP) is converted to adenosine diphosphate (ADP) using the enzyme ATPase that is found at the dynein arms. This magnesium ion (Mg^{2+}) dependent reaction produces energy. Motion occurs whenever there is sliding of the outer pair microtubules against one another. The mitochondria located near the cell surface next to cilia's basal bodies generate the ATP.[7]

Metachronous movement of cilia propels the mucus blanket backwards, thus only those (cilia) that are at right angle to the direction of the flow form the phase. Cilia that are in the flow-direction are out of phase until the cycle completes. From the front of the nose, mucus flows posteriorly. Thereafter, mucus from the sinuses and from the lateral wall joins together with most passing through the middle meatus. The majority of mucus then passes around the Eustachian orifice before it is swallowed.

The nose is a constantly changing environment where slight fluctuations can affect the function of cilia. Dry conditions stop ciliary action and at temperatures below 10 °C and temperatures above 45 °C, ciliary movement stops. Isotonic saline preserve the activity of cilia, however, if the solutions are 5% above and 2% below the normal isotonic saline conditions, paralysis occurs. Likewise, potassium ions do not affect ciliary function except when the levels become non-physiological.[8] Furthermore, cilia can beat above pH 6.4 as well as function in a slightly alkaline medium of up to pH 8.5 for a prolonged period. Infections in the upper respiratory tract can cause damage to the epithelium and the function of cilia also deteriorate with age.[9]

EFFECT OF SMOKING ON THE NOSE

Tobacco contains hundreds of noxious chemicals and when smoked can irritate the lining of the nose resulting in increased nasal secretions and congestion caused by impairment of mucociliary clearance. Smoking causes a reduction in the number of cilia and change in mucous viscosity. Studies have shown that eight hours after exposure to tobacco smoke the efficiency of mucociliary clearance had reduced, with heavier smokers having more marked impact.[10]

NASAL AERODYNAMICS

Knowledge of the aerodynamic behaviour of the nasal airway provides an aid to the decision-making process of medical and surgical management of pathological processes affecting the nose.

At rest the normal inspiratory flow rate in an adult ranges between 5 L/min to 12 L/min and has a pressure change of 50 Pa between the nostrils and the nasopharynx. During exercise the flow rate increases with a correspondent drop in pressure, where the flow rate can increase to as much as 150 L/min.[11]

Fluid dynamic experiments of the nose (**Figure 89.2**) have shown that nasal flow is laminar as it enters the nasal vestibule, with no mixing of the different air layers at low velocity.

The velocity of the air increases as it passes through the nasal valve, the narrowest site of the upper respiratory tract. At this point turbulent flow is observed in the nasal cavity, with different air layers swirling together. The change from laminar to turbulent flow is paramount as it allows the velocity of the air to reduce, thus allowing prolonged contact of inspired air with the nasal mucosa and therefore allowing the nose to perform its vital functions.

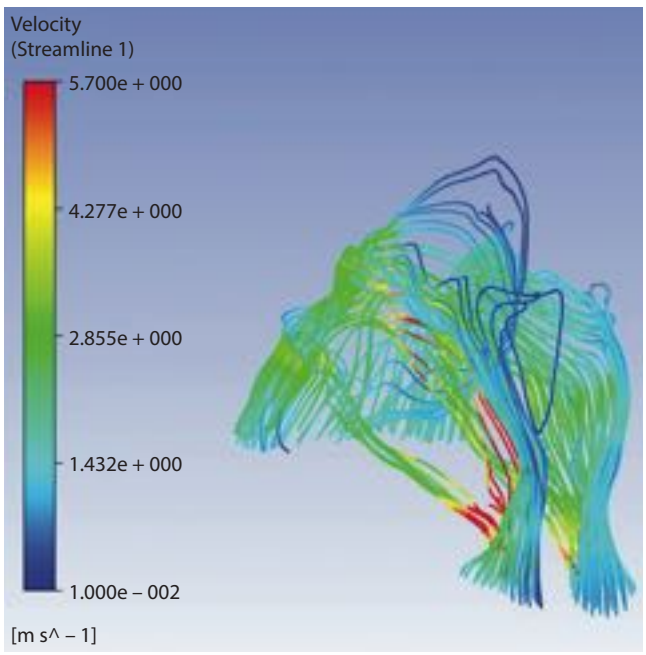


Figure 89.2 Velocity streamlines.

Septal deviation and turbinate hypertrophy can cause a reduction in the cross-sectional area of the nasal mucosa and thus also affect nasal function.[12, 13]

NASAL CYCLE

The nasal cycle is a well-recognized physiological activity whereby each side of the nose alternates the phases of congestion and decongestion.[14] Vascular activity produces the changes, especially the volume of blood in capacitance vessels (venous sinusoids). The changes are cyclical and occur every 4 to 12 hours with the changes being constant for each person. The nasal cycle can be demonstrated in up to 80% of adults, however, it is not easy to demonstrate in children.[15]

The physiological significance of the nasal cycle is not clear. However, resistance and airflow leads to increased cyclical secretions in the side that is experiencing the greatest flow. Several factors affect the nasal cycle; these include exercise, pregnancy, hormones, infections, allergy, fear, emotions and sexual activity. The autonomic nervous system regulates many of the changes. Notably, vagal over activity can lead to congestion while high levels of CO_2 present in inspired air that is produced as a result of rebreathing may reduce the nasal resistance. Hyperventilation reverses the situation.[16] Nasal congestion may also occur due to drugs that block the action of the noradrenaline. Antihistamines also produce anticholinergic effects that can halt parasympathetic activity. This results in increased sympathetic tone that improves the nasal airway. Hormonal changes seen in puberty also affect the nasal mucosa.

NASAL RESISTANCE

Nasal resistance plays a crucial role in preventing the collapse of the lower respiratory tract, notably the lungs, with nasal resistance contributing up to 50% of the total airway resistance. As nasal airway resistance is increased, it causes an increase in negative intra-thoracic pressure and in turn enhances pulmonary ventilation. Mathematically, resistance of nasal airflow is equal to the pressure of the nasal flow divided by flow rate. Nasal air flow is affected by the radius of the nose. Based on laminar flow equations, a decrease in the nasal radius can cause a four-fold decrease in nasal air flow (see Chapter 90, Measurement of the nasal airway). The presence of laminar and turbulent flow in the nasal passageway is vital to the physiology of air exchange. Nasal airway resistance is achieved through three key components. These include the nasal vestibule, the nasal valve and the inferior turbinates.

Nasal vestibule

The nasal vestibule is composed of a compliant wall that can collapse in response to the negative pressure caused by inspiration thus increasing nasal resistance. A flow of 30 L/min is the limiting rate during inspiration at which nasal airway collapse occurs at the nasal

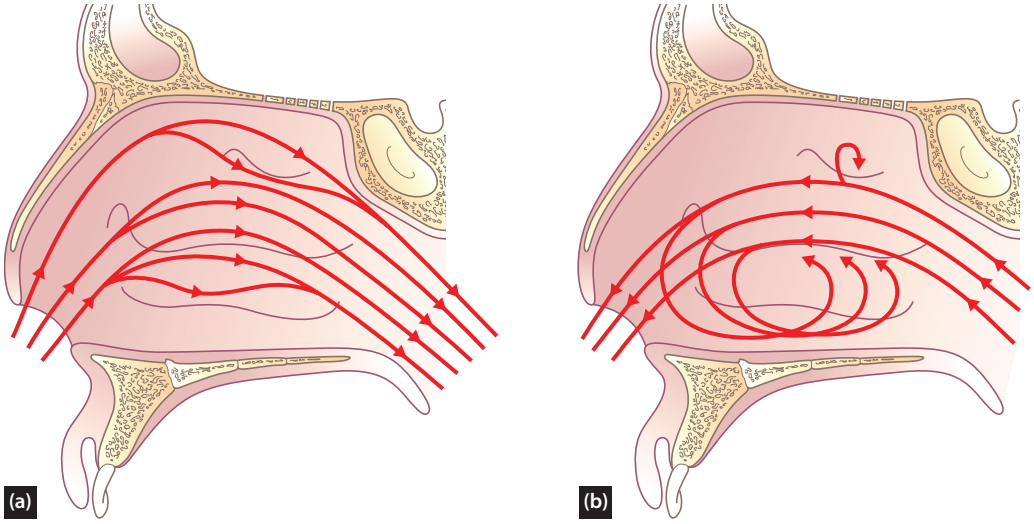


Figure 89.3 (a) The direction of inspiratory airflow. **(b)** The direction of expiratory airflow.

vestibule (Figure 89.3a). However, this airway collapse can be prevented by activation of the ala nasi muscle during inspiration. Contraction of this muscle results in a change of the shape of the vestibule which leads to a reduction in air flow turbulence without affecting the cross-sectional area. Paralysis of ala nasi, as seen in facial nerve palsy, causes the nasal vestibule to collapse during inspiration and hence increase nasal resistance. During exercise the ala nasi muscle contracts, which increases the radius of the nasal cavity and hence reduces nasal resistance.[17]

Expiration has the opposite effect, as the positive pressure within the vestibule increases the radius of the nose and in turn improves nasal airflow (Figure 89.3b).

Internal nasal valve

This is the narrowest part of the nasal airway and helps to direct the airflow upward and backward across the anterior part of the inferior turbinate. It is found approximately 2 cm posterior to the anterior nares and has a cross-sectional area between 55–83 mm^2. The size of the inferior turbinate (an erectile tissue) and position of the nasal septum determines the dimensions of nasal valve.

The nasal valve is bound superiorly by the caudal end of upper lateral cartilages and septum medially. The inferior boundary is the nasal floor, laterally is the bony piriform aperture with the adjacent fibrofatty tissue and posteriorly is the head of the inferior turbinate. The nasal valve makes a significant contribution to upper airway resistance and produces the most turbulent airflow.[12] During quiet respiration, the velocity of the anterior valve ranges from 12 to 18 m/sec. The nasal valve is often referred as the internal nasal valve. Therefore any change in the size of the inferior turbinate and deviation of the septum at this level has an impact on the nasal valve. The nasal valve plays a key role clinically, and the treatment of the components that make up the nasal valve area can have a marked impact on nasal airway resistance.

The Cottle maneuver is used to assess the narrowing of the nasal valve area at rest. The test is conducted by lateralizing the soft tissue and the nasal vestibule. It is considered positive if it improves nasal airflow. Swelling of the inferior turbinate has a profound effect on nasal resistance. Consequently, treatments that aim to reduce the size of the inferior turbinate have a significant effect on the nasal resistance as opposed to that of the nasal surgery that removes septal spurs.

Inferior turbinate

The turbinates of the nose can swell and recede, thereby reducing the dimensions of the nasal cavity contributing to nasal airway resistance. The inferior turbinates are part of the nasal valve area and they help the change of laminar inspired air into turbulent flow. The large surface area and extensive blood supply of the inferior turbinate increases the interaction of inspired air with nasal mucosa which enables the nose to carry out its functions more effectively.[18]

Pathological processes causing enlargement of the inferior turbinate by only a small incremental increase of 1–2 mm have been shown to lead to a significant reduction in the nasal airflow velocity down to 0.42 m/s when compared to 0.89 m/s in the normal healthy nose.[19]

NASAL FUNCTION

The nose has various physiological functions. Respiratory functions include heat exchange, filtration, humidification, nasal neurovascular reflexes and voice modification. Olfaction functions are stimulus pathways and there is trigeminal input.

Heat exchange

The temperature of inspired air can range from –50 to 50 °C. Since various racial groups live in different

environments, the nose has evolved to suit different local conditions.

Filtration

The turbinates organize the pattern of airflow, enabling the nose to exhale all of the inspired air to the airstream. This happens fairly slowly around and along the ciliated turbinates. In the process, heat and energy is emitted into the inspired airstreams thereby saturating the airborne particles as well as micro-organisms. Eventually, the particles and micro-organisms become heavier, sinking into the mucosal layer where they are processed using enzymes and immune system cells.

Olfaction

Sense of smell plays an important role in protection from danger, such as fire. It is also central in forming positive and negative memories affecting individual psychological wellbeing, socialization and interpersonal relationships, with dysfunction leading to a poor quality of life (see Chapter 110. Abnormalities of Smell).

DEFENCE MECHANISMS OF THE NASAL MUCOSA

The nose has a role in protective mechanisms to prevent noxious substances entering the lower respiratory tract. This defence mechanism can be divided into mechanical and immunological defence.

Mechanical defence

The nose is able to protect the lower airway by removing particles of approximately 30 µm or upward such as pollen in inspired air. The velocity of the inspired air drops significantly after the nasal valve. As turbulence increases, so does the deposition of particles. Particles with irregular shapes resist change to the greatest extent because they have a larger surface area. Vibrissae only stop the largest particles. Mucociliary flow is the main mechanical defence of the nasal mucosa because it physically cleans inspired air. The mucociliary transport system is made up of cilia of the respiratory epithelium as well as a mucous blanket. The latter consists of a deeper layer where ciliary motion occurs as well as a superficial thicker gel layer. Viscoelastic properties enable it to trap larger particles. This mechanical defence is predominant and expels filtered particles and debris into the nasopharynx and oropharynx as well as elimination through sneezing and coughing.[20]

Immunological defence

Mucus consists of compounds that are able to neutralize antigens through innate mechanisms, learned, and adaptive immunological responses. Immunoglobulin A (IgA) and immunoglobulin E (IgE) are found on the surface, and they act whenever the mucosa is breached. In most cases, bacterial allergens are destroyed, but there are other viruses and bacteria that require the activation of the cell-mediated immune responses. IgA is the main immunoglobulin in secretions and has distinctive characteristics. IgA has two subgroups, namely IgA_1 and IgA_2. IgA_1, with a monomeric structure, is frequent in serum while IgA_2, with a dimer structure, is common in nasal secretions.[21] Immunoglobulin A constitutes 70% of the total proteins in nasal secretions.

EFFECT OF PREGNANCY ON THE NOSE

Pregnancy induced rhinitis (PIR) is a common problem, and has an incidence of around 22%. PIR has been defined as nasal congestion that is not present before pregnancy, but manifests itself in the second or third trimester, lasting 6 or more weeks with no known allergic cause, which then resolves completely within 2 weeks of delivery.[22] The cause of PIR is still under debate as is the impact of pregnancy hormones on the nasal mucosa. Studies have shown that during pregnancy there is a decrease in mucociliary clearance and increase in nasal resistance, with oestrogen having possible role in inducing histamine receptors on epithelial cells.[23, 24]

BEST CLINICAL PRACTICE

- ✓ Pregnancy induced rhinitis (PIR) is a common problem, and has an incidence of around 22%.
- ✓ PIR has been defined as nasal congestion that is not present before pregnancy, but manifests itself in the 2nd or 3rd trimester, lasting 6 or more weeks with no known allergic cause, which then resolves completely within 2 weeks of delivery.[22]

FUTURE RESEARCH

- ➤ Nasal morbidity, unlike in disorders affecting the other senses, is difficult to quantify, yet conditions such as sinusitis are chronic and affect a significant percentage of the population.
- ➤ Continued basic science research is desperately needed that may lead to a better understanding of the physiology of nasal function to ultimately help in better treating common nasal complaints.

KEY POINTS

- The principal physiological function of the nose is to
  - humidify and warm inspired air
  - remove noxious particles from the air
  - also serves as a sense organ
- The nose has an abundant blood supply, from branches of both the internal and external carotid arteries.
- The venous sinuses form the erectile tissue that is located on the anterior nasal septum and the inferior turbinates.
- Smoking causes a reduction in the number of cilia and change in mucous viscosity.
- The nasal cycle is a well-recognized physiological activity whereby each side of the nose alternates the phases of congestion and decongestion.[14]
- Nasal resistance plays a crucial role in preventing the collapse of the lower respiratory tract, notably the lungs, with nasal resistance contributing up to 50% of the total airway resistance.

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CHAPTER 90

MEASUREMENT OF THE NASAL AIRWAY

Ron Eccles

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: rhinomanometry, acoustic rhinometry, nasal peak inspiratory flow and human. The data were supplemented by further searches and use of a personal database. The evidence in this chapter is not aimed at any specific treatments, only methods to measure the patency of the nasal airway, and based on a range of studies that include randomized clinical trials of Level 1 evidence.

INTRODUCTION

Nasal obstruction is one of the most common complaints presenting to ENT surgeons, but treatment is usually initiated without any objective measurement of nasal airflow or nasal patency. Pneumologists have access to useful normal ranges for lung function, whereas rhinologists have not established generally accepted ranges for normal nasal patency.

Establishing a normal range of nasal patency is confounded by several factors related to nasal physiology. First, the nose is directly exposed to the external environment and acts as an air conditioner to protect the lungs from infection and variations in environmental conditions, whereas the lungs operate as part of the internal environment at a constant temperature of 37 °C in a sterile environment. Second, the nose is subject to spontaneous changes in nasal patency associated with the 'nasal cycle', with spontaneous congestion and decongestion of the large veins found in the nasal epithelium.[1] The direct exposure of the nose to the external environment and the spontaneous changes in nasal patency associated with the nasal cycle make normal or 'physiological' nasal patency unstable and difficult to define.[2]

'Anatomical' nasal patency is the nasal patency measured after decongestion of the nasal blood vessels by application of a topical nasal decongestant or by standard exercise. Anatomical nasal patency is a useful measure for the nasal surgeon as it is determined solely by the hard tissues of the nose such as cartilage and bone.[3]

Measures of nasal obstruction usually involve measurement of nasal airflow or an assessment of the cross sectional area of the airway. The nasal airway can be considered as a simple tube, and measurement of the airflow through the tube and its driving pressure, by means of rhinomanometry, can provide a measure of nasal patency. The prime factor determining nasal patency is the cross sectional area of the nasal airway and this can be measured by means of acoustic rhinometry. Rhinomanometry provides a functional measure of nasal patency, whereas acoustic rhinometry provides an anatomical measurement of cross sectional area or nasal volume. Rhinomanometry and acoustic rhinometry are the major techniques used for measuring the nasal airway but other techniques such as measurement of nasal peak inspiratory flow can also provide useful measures of nasal patency.

This section will discuss the most commonly used measurements of nasal patency and their relevance to research and clinical practice in rhinology.

RHINOMANOMETRY

Rhinomanometry normally provides a measure of nasal resistance to airflow and measures of nasal patency in units of nasal airflow may be further calculated from

this parameter. Nasal resistance to air flow is calculated from two measurements: nasal airflow and trans-nasal pressure.[4] Both these parameters are measured by means of differential pressure transducers (manometers) and this is why the study of nasal pressure and flow is termed 'rhinomanometry', since manometry involves the measurement of pressure. Nasal airflow can be measured by means of a flow head that usually consists of a mesh resistance inside a tube. The pressure difference across the mesh generated by airflow through the tube is used to measure airflow. Trans-nasal pressure can be measured by relating the pressure at the posterior nares to that at the entrance of the nostril, which will normally be atmospheric pressure or nasal mask pressure.

Active rhinomanometry involves the generation of nasal airflow and pressure with normal breathing. Passive rhinomanometry involves the generation of nasal airflow and pressure from an external source, such as a fan or pump, to drive air through the nose.

Active rhinomanometry can be divided into anterior and posterior methods according to the location of the pressure-sensing tube. In active anterior rhinomanometry, the pressure-sensing tube is normally taped to one nasal passage. The sealed nasal passage acts as an extension of the pressure-sensing tube to measure pressure in the posterior nares. With this method, nasal airflow is measured from one nostril at a time and the pressure-sensing tube is moved from one side of the nose to the other. Therefore, nasal resistance is determined separately for each nasal passage and the total resistance is then calculated by summing the values as shown in the formulae below.

In active posterior rhinomanometry as shown in Figure 90.1, the pressure-sensing tube is held in the mouth and detects the posterior nares pressure when the soft palate allows an airway to the mouth.

Total nasal airflow can be measured from both nasal passages simultaneously. The right and left nasal airflows can be measured separately by taping off one nostril at a time. Total nasal resistance can be determined directly from the total nasal airflow and trans-nasal pressure with this method. A disadvantage of this method, when compared with the anterior method, is that not all subjects can obtain an airway around the soft palate into the mouth. With some training of subjects it is possible to obtain satisfactory results from about 90% of subjects.

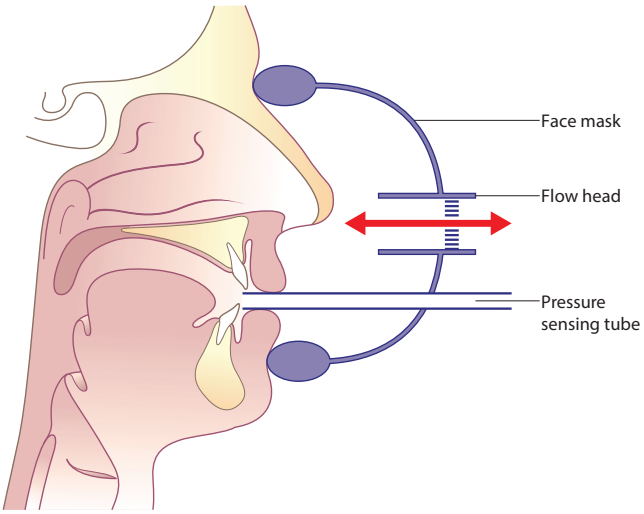


Figure 90.1 The technique of posterior rhinomanometry. This involves a pressure-sensing tube in the mouth that detects the changes in pressure in the posterior nares, and a flow head to measure nasal airflow.

Passive rhinomanometry involves the direction of an external flow of air through the nose and out of the mouth. The method may involve either measurement of a driving pressure at a constant flow or measurement of the flow at a constant pressure. Passive rhinomanometry is particularly useful if it is necessary to separate the upper and lower airways for experimental work.

Active anterior rhinomanometry, using surgical tape to seal a pressure-sensing tube into the nasal passage, is one of the most commonly used methods for clinical determination of nasal resistance and it is recommended by standardization committees,[5,6] but posterior rhinomanometry has been used successfully in clinical trials on nasal surgery and nasal decongestants.[7–9]

Nasal airway resistance can also be measured by use of a head-out body plethysmograph (displacement type) and with this method the flow head is located on the side of the body-box and the pressure-sensing tube is passed along the floor of the nasal cavity. This method has the advantage that the nose is unimpeded by any mask.[10]

When making measurements of nasal airway resistance it is important to take several measurements with repositioning of the mask between measurements. This is to control for air leaks around the mask that are a common source of error. A single measurement of nasal airway resistance is unreliable and a standard operating procedure should be implemented to prevent investigator bias when gathering data.[4]

Nasal resistance to air flow may be calculated from the following equation:

$$R = \frac{\delta P}{V}$$

R = resistance to air flow/cm H_2O/litre per second or Pa/cm^3 per second
δP = trans-nasal pressure, in cm H_2O or Pa
V = nasal air flow, in litre/s or cm^3/s

This equation is a compromise that has been generally accepted by rhinologists and it does not take into consideration the separate components of laminar and turbulent air flow.[5,6]

A plot of the dynamic relations of trans-nasal pressure and flow on an x/y plotter shows a curvilinear relationship for the $\frac{\delta P}{V}$ plot. Nasal airflow increases with increase of trans-nasal pressure, but at higher pressures there is a limitation of flow due to the increased frictional effects of turbulent airflow. The flow-limiting effect of nasal alar collapse is only apparent during rapid or close to maximum inspiratory manoeuvres.

The curvilinear relationship between trans-nasal pressure and flow means that one cannot simply determine

nasal resistance from the slope of the graph, as would be the case with a straight-line relationship. The slope of the $\frac{\delta P}{V}$ plot varies along its length and, therefore, it is not possible to describe the whole curve with a single numerical value for resistance. It is, however, possible to define the resistance at any given sample point along the curve and this has been the solution recommended for a standardized measurement of nasal resistance.[5,6]

The positive or negative pressure at the posterior nares results in airflow through both nasal passages. The right and left nasal airflows are normally asymmetrical due to the nasal cycle and therefore a single pressure value may relate to two different airflows. It is, therefore, sensible to standardize nasal resistance by measuring both nasal airflows at the same sample pressure point rather than by measuring trans-nasal pressures at the same sample flow point.

Unilateral nasal airflow measured at a sample pressure point of 150 Pa and bilateral nasal airflow measured at 75 Pa are recommended.[5] Other parameters may be calculated from the pressure flow curve but these are not in general use and are not generally accepted.[6] The Asian population cannot always achieve the higher sample pressure of 150 Pa during normal quiet breathing, and the lower sample pressures of 100 and 50 Pa, respectively, are generally accepted for nasal resistance measurements in Japan.

The lower nasal pressures in the Asian population compared to Caucasians is due to smaller body size and smaller lung volume.

Total nasal resistance to air flow can be either determined directly using the posterior method of rhinomanometry or it can be calculated by combining the two separate values of nasal resistance for the two nasal passages as shown in the formula below:

$$\frac{1}{R(total)} = \frac{1}{r(left)} + \frac{1}{r(right)}$$

The reciprocal of total resistance is equal to the sum of the reciprocals of left and right resistance.

When quoting values for total nasal resistance it should be stated whether the value was obtained by measurement of total nasal air flow using posterior rhinomanometry, or whether the air flows of the nasal passages have been measured separately.

Normal nasal airflow

As discussed above, nasal patency in health is unstable and may be even more variable in disease, therefore it is difficult to give any normal range. The variability in nasal patency is especially marked for unilateral patency as it is normal for one nasal passage to be obstructed and the other quite patent as a normal phase of the nasal cycle. However, total nasal patency is more stable because of the reciprocal relationship between the two nasal passages.[1]

In adult subjects free from signs of nasal disease mean total resistance has been reported to be around 0.23 Pa cm^3 s with a range of 0.15–0.39 Pa cm^3 s.[11] As a routine screening procedure in our laboratory we normally consider a total nasal resistance to airflow of 0.3 Pa cm^3 s as an upper limit of the normal range. Cole considers any total airway resistance greater than 0.25 Pa cm^{3}s as obstructed.[10] Nasal resistance is at a maximum in the infant at around 1.2 Pa cm^3 s,[12–13] declines to the adult value at around 16–18 years of age and then shows only a slow decline with increasing age.[14] In a study on healthy male volunteers a relationship between age and nasal resistance was reported, with resistance declining with increasing age from 0.6 Pa cm^3 s (age 5–12 years) to 0.29 Pa cm^3 s (age 13–19 years) and 0.22 Pa cm^3 s (age >20 years) in males.[15] The relationship between age and nasal resistance was similar in females but in general nasal resistance was lower in females than males.[15]

If the nose is decongested by exercise or application of a topical decongestant then this eliminates any physiological variation in resistance and allows one to investigate the anatomical factors influencing resistance. Studies by Broms[16] have provided a table of predictive values for height and nasal resistance in the decongested nose that are useful in assessing the extent of any deviation from normality in patients with nasal skeletal stenosis.

Total nasal resistance gives an overall measure of nasal function but it is a very crude measurement, as it provides no information about the separate nasal passages. Rhinologists have a dilemma when assessing nasal function as the nose consists of two separate dynamic airways. However, it is not very informative to quote the mean of unilateral resistance when measured over several hours because this mean value will have a large standard deviation due to the instability of unilateral resistance. The range of unilateral nasal airway resistance in a group of healthy volunteers when recorded over a 6–8 hour period has been shown to vary from 0.36 to 1.36 Pa cm^3 s[17] and 0.28–0.63 Pa cm^3 s.[18] This indicates that there is often almost a fourfold change in unilateral resistance associated with the spontaneous congestion and decongestion of the nasal venous sinuses.

One way to overcome the dilemma of spontaneous changes in unilateral nasal resistance is to decongest the nose prior to assessment. This solution is of use to the surgeon whose main interest may be in assessing the extent of any nasal anatomical problem,[16] however one study reports that nasal patency after decongestion is not always reproducible over several months in healthy subjects[19] but it is reported to be stable over shorter periods of 12 hours.[4] However, decongestion of the nose is of no use in studying nasal physiology and pathophysiology as it is the spontaneous changes in unilateral resistance that are of interest to the physiologist and clinician. One solution is to quantify the extremes of unilateral resistance or the amplitude of the unilateral changes in resistance that occur over a period of several hours. This approach has been used to determine the unilateral changes in resistance and to assess the efficacy of nasal surgery.[7] The disadvantage of unilateral nasal measurements is that in order to assess the amplitude of changes in unilateral nasal resistance it is necessary to make measurements

over several hours. The advantage of unilateral measurements are that they give a comprehensive assessment of the dynamic nose rather than the crude snap shot that is provided by a single measure of total resistance.

ACOUSTIC RHINOMETRY

Acoustic rhinometry has been developed from methods previously used to measure lower respiratory tract resistance. The method consists of generating an acoustic pulse from a spark source or speaker and the sound pulse is transmitted along a tube into the nose. The sound pulse is reflected back from inside the nose according to changes in the local acoustic impedance which are related to the cross sectional area of the nasal cavity. The reflected sound is detected by a microphone, which transmits the sound signal to an amplifier and computer system for processing into an area distance graph.

The cross sectional area measurements obtained with acoustic rhinometry correlate very well with area measurements made by computed tomography scans, and nasal airway resistance measured by rhinomanometry, but the accuracy of acoustic rhinometry is unreliable in the posterior part of the nose, especially when the nasal passage is congested.[20]

Acoustic rhinometry is also subject to artefacts caused by noise and breathing.[21] The volume of the nasal cavity (e.g. between 2 and 5 cm depth into the nose) can be calculated from the cross sectional areas across a measured distance into the nose, and nasal volumes are often used to study the effects of medical and surgical treatments.

A major advantage of the technique of acoustic rhinometry is that it provides a measure of nasal cross sectional area and volume along the length of the nasal passage, unlike rhinomanometry that is limited to measuring the effects of the narrowest point of the nasal airway on nasal airflow. Technical specifications for standard operating procedures for acoustic rhinometry have been standardized as regards the accuracy and repeatability of measurements and the acquisition of data.[22]

Normal values for acoustic rhinometry

Normal values for acoustic rhinometry have the same limitations described above for rhinomanometry, due to the spontaneous changes in nasal patency associated with the nasal cycle. The normal adult value for minimum cross sectional area for a nasal passage is quoted as 0.7 cm^2 with a range of 0.3–1.2 cm^2 and this increases on decongestion to 0.9 cm^2 with a range of 0.5–1.3 cm^2.[23]

The volume of the nasal cavity, between 2 and 5 cm depth into the nasal passage, has been reported to be 3.71 cm^3 (3.58–3.84) in school children aged 9–11 years and 5.44 cm^3 (5.21–5.67) in adults, after decongestion.[24]

The diagnostic value of acoustic rhinometry has been investigated by Lenders and Pirsig (1990), who could distinguish various deviations of nasal structure, such as valve stenosis, septal deviation, turbinate hypertrophy and tumour masses.[25]

The accuracy of acoustic rhinometry like rhinomanometry is dependent on the interface between the equipment and the nose. For example, the cross sectional area of the nasal vestibule is susceptible to distortion if a tube is inserted into the nose. Mispositioning of the nasal tube and air leaks are just as likely to give spurious measurements with acoustic rhinometry as face mask leaks with rhinomanometry, but with care the technique of acoustic rhinometry provides reproducible data.

PEAK NASAL FLOW

The peak inspiratory or expiratory airflow through the nose associated with maximal respiratory effort can be used as a measure of nasal conductance. The measurement is effort dependent and is less sensitive than rhinomanometry or acoustic rhinometry in determining small changes in conductance.[26] Expiratory measurements are likely to cause expulsion of nasal secretions into the measuring instrument, and inspiratory flow measurements are likely to cause nasal alar collapse and flow limitation. Simple peak flow instruments such as the Wright, mini-Wright, and Youlten flow meters are often used to measure peak nasal inspiratory flow (PNIF) with the use of a face mask. However, the use of more sensitive spirometers can improve the accuracy and reproducibility of nasal measurements,[27] and reliable measurements can be made with standard pulmonary spirometry equipment.[28] Measurement of PNIF may be useful for the assessment of large changes in nasal conductance such as those associated with nasal challenge and nasal decongestion,[29] and for this type of work the measurement of PNIF compares well with rhinomanometry for the assessment of nasal patency.

Normal values for peak nasal inspiratory flow

Normal values for PNIF have been reported in both adults[30] and children aged 6–11.[31] Normal values for PNIF in a healthy adult Caucasian population have been described as related to age, sex and height with PNIF declining with age and being greater in males than females.[30] Mean PNIF in adult males was 143 L/min, and 122 L/min in females.[30]

SUBJECTIVE MEASUREMENTS

Nasal sensations are important in the study of nasal disease, as it is the patient's perception of nasal sensations (symptoms) that is of primary concern to the patient. However, the clinician in the assessment and treatment of nasal disease is mainly concerned with restoring normal nasal function to the nasal airway by reducing nasal obstruction by medical or surgical means. The clinician has various objective measures of nasal function such as rhinomanometry and acoustic rhinometry but the problem is that these objective measures of nasal function do not always correlate with the patient's own assessment of nasal sensations such as the sensation of nasal airflow.[32]

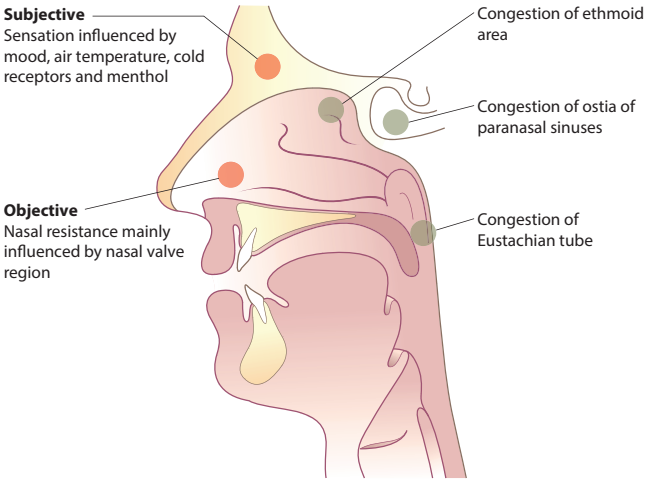


Figure 90.2 Factors that influence the patient's perception of nasal airflow and relationship to objective and subjective measures of nasal obstruction. *Objective measurements* are mainly determined by the cross sectional area of the nasal valve region at the tip of the inferior turbinate. *Subjective measurements* are influenced by the stimulation of cold receptors in the airway and the patient's perception of obstruction may be influenced by menthol and mood. Congestion in the ethmoid area, ostia of paranasal sinuses and Eustachian tube cause a perception of congestion and pressure that is unrelated to any change in nasal airway resistance as these areas are distant from the nasal valve.

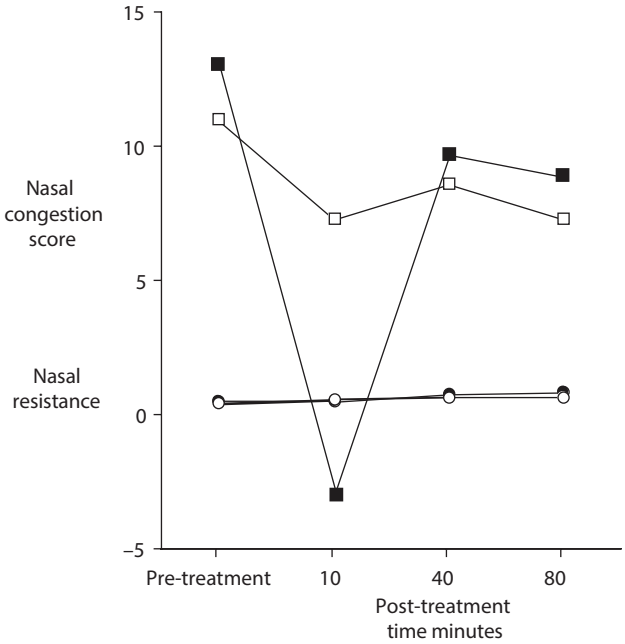


Figure 90.3 The effects of ingestion of an 11 mg l-menthol lozenge on subjective sensation of nasal congestion and nasal resistance to airflow in human volunteers with common cold. The subjective sensation of nasal congestion, measured on a 100mm visual analogue scale, was significantly reduced 10 min. after ingestion of the lozenge but nasal airway resistance as measured by rhinomanometry was unaffected. Shaded symbols represent the values for the menthol treated group and the open symbols represent the mean values for the placebo treated group.[34]

The reason for the lack of correlation between the perception of nasal airflow and nasal resistance as measured by rhinomanometry may be because the resistance to nasal airflow is primarily determined by the nasal valve area, whereas the symptoms of nasal obstruction may be influenced by other areas of the nose as well as the nasal valve area, as illustrated in Figure 90.2.

Congestion in the ethmoid region may cause contact of ethmoid surfaces and a sensation of pressure and obstruction that would have little or no effect on nasal airway resistance. Similarly, pressure changes in the middle ear and paranasal sinuses may cause a sensation of nasal obstruction and pressure without any effect on nasal airway resistance. Another factor that may explain the lack of correlation between objective and subjective measures of nasal obstruction is that the nasal airway consists of two parallel airways and the total nasal conductance may be near normal even if one nasal passage is completely obstructed. Subjects with nasal obstruction associated with acute upper respiratory tract infection have a total nasal airway resistance that is close to normal yet they still complain of nasal obstruction because one nasal passage may be severely congested whilst the other is patent.[17] Objective and subjective unilateral measures of nasal obstruction have been shown to have a much better correlation than combined bilateral measures for the two nasal passages indicating that the nose should be assessed as two separate organs rather than a single combined airway.[33]

Studies on the effects of menthol on nasal sensation of airflow clearly demonstrate the lack of any correlation between objective measures of nasal airway resistance and subjective measures of airflow.[34] In patients with nasal obstruction associated with common cold, ingestion of a menthol lozenge causes a great improvement in the sensation of nasal airflow without any change in nasal airway resistance, as shown in Figure 90.3. This is because the menthol vapour causes an increase in the sensitivity of cold receptors that detect nasal airflow, and a perception of nasal decongestion, without any objective change in nasal resistance.

Subjective scores of nasal symptoms provide the main outcome criteria for clinical trials on new treatments for rhinitis yet our knowledge of the factors influencing the perception of symptoms is still very superficial.

MEASUREMENT OF THE NASAL AIRWAY BY THE RHINOLOGIST

The rhinologist may be interested in measuring the patency of the nasal airway for two reasons: first to assess the severity of any nasal obstruction and select patients for medical and/or surgical treatment and second to assess the efficacy of any treatment in increasing nasal airflow. There is a large literature on the assessment of medical and surgical treatments aimed at improving nasal airflow and only two examples will be given here to demonstrate the usefulness of rhinomanometry in assessing patient response to surgical or medical treatments of nasal obstruction.

The efficacy of nasal surgery as a treatment for chronic nasal obstruction was demonstrated by measuring changes

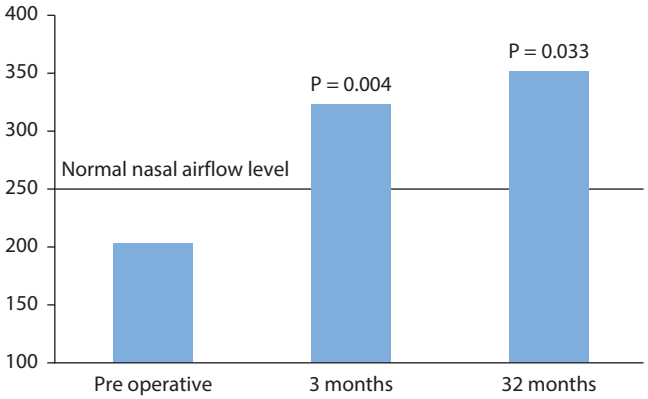


Figure 90.4 The effect of Coblation inferior turbinate surgery on total nasal conductance of airflow pre-operatively, at 3 months and 32 months follow-up. The Y axis is nasal airflow patency cm^3 sec as measured by posterior rhinomanometry. The line represents normal level of airflow in health in health. P values relate to comparison with preoperative airflow.[35]

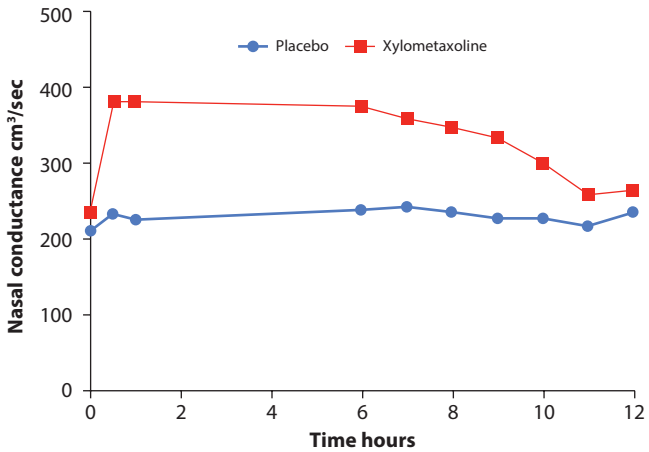


Figure 90.5 Effects of xylometazoline and placebo nasal sprays on nasal conductance in subjects with nasal congestion associated with common cold. The figure demonstrates the reproducibility of the mean nasal conductance measurements over a 12 hour period in the placebo treatment group (n = 29). The sensitivity of rhinomanometry is demonstrated by the significant increase in mean nasal conductance over 10 hours after treatment with xylometazoline (n = 32).[9]

in nasal airflow by posterior rhinomanometry before and after Coblation inferior turbinate reduction surgery at 3 and 32 months post-operatively as illustrated in Figure 90.4. The mean baseline nasal conductance was 248.6 cm^3/s (range 2.5–614.8), which improved significantly (p = 0.033) to 342.1 cm^3/s (range 166.7–500) at 32 months post-operatively.[35]

The efficacy of medical treatment of acute nasal obstruction associated with common cold was demonstrated by measuring changes in nasal airflow before and after treatment with a topical nasal decongestant, xylometazoline as illustrated in Figure 90.5. The decongestant effect of xylometazoline was significantly greater than placebo, as shown by the nasal conductance at 1 hour (384.23 versus 226.42 cm^3/s; p < or = 0.0001).[9]

BEST CLINICAL PRACTICE

✓ Nasal surgery for the treatment of nasal obstruction should be guided by objective measurement of nasal airway patency pre- and post-operatively

FUTURE RESEARCH

- The major deficiency in our knowledge concerning measurement of the nasal airway is that there is no generally accepted standard measurement to assess the degree of obstruction of the nasal airway.
- Rhinomanometry is generally accepted as the 'gold standard' for the assessment of nasal obstruction but this technique is only available in research centres and is not generally used in the clinic. Even when rhinomanometry is used, there is a choice between various techniques such as anterior and posterior, and various sample pressures (75 Pa for posterior, and 150 Pa for anterior) that make it difficult to compare results from different laboratories.
- Standardization of rhinomanometry was attempted in 1984[5] but little progress has been made since then. The new recommendations for standardization of rhinomanometry and acoustic rhinometry add little more than mathematical modelling to the older standardization recommendations.[6]
- The introduction of acoustic rhinometry was initially proclaimed as a method that would replace rhinomanometry but this has not taken place as the technique is not quicker or more reproducible than rhinomanometry.
- A major problem in measuring the nasal airway is the lack of any generally accepted reference tables for nasal patency related to age, height, sex and race etc. and future research is needed to provide some reference values for the rhinologist for each of the methods described above.[2]
- Measurements of the nasal airway will be restricted to research laboratories unless a cheap and portable instrument is developed for use in the clinical setting and some progress has been made in establishing the use of the much cheaper and easily used peak flow meter to measure nasal obstruction in adults and children.[30–31]

KEY POINTS

- Objective and subjective measurements of nasal conductance do not correlate well for bilateral measures but do correlate for unilateral measures
- The spontaneous changes in unilateral nasal resistance associated with the nasal cycle cause great variability in physiological nasal airflow
- Subjective measurements are important as they relate directly to symptoms
- Decongestion of the nose eliminates the effects of the nasal cycle and allows the measurement of anatomical nasal airflow
- Acoustic rhinometry provides anatomical rather than functional measurements of the nasal airway
- Rhinomanometry is generally accepted as the 'gold standard' for measurement of nasal airway resistance
- Acoustic rhinometry and rhinomanometry in their current forms have not found a routine place in the day to day assessment of patients in the rhinology clinic.

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CHAPTER 91

ALLERGIC RHINITIS

Quentin Gardiner

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SEARCH STRATEGY

Data and recommendations in this chapter are taken from the ARIA 2008 update and 2010 revision, and may be updated by a Medline search using the keywords: allergic rhinitis, allergic rhinosinusitis and allergic rhinoconjunctivitis linked with aetiology, presentation, epidemiology, prevalence, allergen avoidance, treatment, immunotherapy, children, pregnancy and surgery.

INTRODUCTION

Allergic rhinitis is characterized by inflammatory changes in the nasal mucosa caused by exposure to inhaled allergens. It is a common disease, affecting between 0.8 and 39.7% of the world population[1] (depending on location) with prevalence in Western Europe of 23%. It causes significant disability and is often poorly managed. There may be co-morbidities with other organs being involved, commonly the eyes causing allergic conjunctivitis and the lungs with allergic asthma. Indeed, these diseases are increasingly considered to be a single entity, with a spectrum of respiratory allergic response, termed the unified allergic airway. They have a common epidemiology, pathophysiology, and in many cases, treatment approach.

Allergic rhinitis and allergic rhinoconjunctivitis are caused by an inflammatory response to an allergen to which the patient has already been exposed. In this abnormal response the individual has produced allergen specific immunoglobulin E (IgE) which binds to mast cell surface receptors. Subsequent allergen exposure causes this receptor/IgE complex to trigger mast cell degranulation with the release of preformed mediators. This inflammatory mediator release includes not only histamine, but also other granule contents (serine proteases, heparin), and newly synthesized eicosanoid mediators (leukotriene C4, prostaglandin D2, thromboxane and PAF).

For further details please see Chapter 14, 'Allergy: basic mechanisms and tests'.

These inflammatory mediators cause the classic symptoms of allergic rhinitis: nerve irritation causing sneezing and itching, loss of mucosal integrity causing rhinorrhoea and vascular engorgement causing block. Histamine drives the majority of acute nasal symptoms such as sneezing and itching with leukotrienes and prostaglandins being involved in longer term symptoms such as block.

DEFINITION

Rhinitis is defined clinically as having two or more symptoms of anterior or posterior rhinorrhoea, sneezing, nasal blockage and/or itching of the nose during two or more consecutive days for more than one hour on most days.[2]

Allergic rhinitis is diagnosed when these symptoms are caused by allergen exposure leading to an IgE mediated reaction. Allergic rhinitis is subdivided into intermittent (IAR) or persistent (PER) disease and the severity into mild or moderate/severe (**Figure 91.1**).

These definitions are not interchangeable with the terms seasonal and perennial and were introduced to relate the patient's symptoms, rather than an allergen, to a diagnosis.[4] In one large study of people with allergic

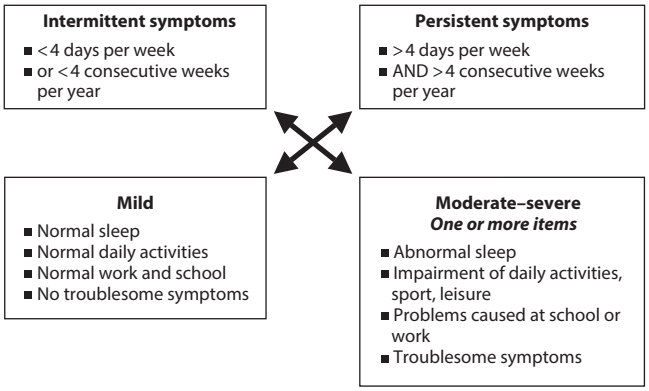


Figure 91.1 Classification of allergic rhinitis. Reproduced with permission.[3]

rhinitis, 10% were classified as having mild intermittent rhinitis, 14% mild persistent rhinitis, 17% moderate/severe intermittent rhinitis and 59% moderate/severe persistent rhinitis; therefore approximately 75% of patients will be diagnosed as having a persistent rhinitis and 25% intermittent.[5] Whether the disease is classified as mild or moderate/severe depends on the effect on the patient's social life[6,7] work/school[8–10] and sleep.[11] Sleep disturbance is common in patients with moderate/severe allergic rhinitis[12] and may lead to daytime sleepiness.[13] This is also linked to problems with learning at school[14] and examination success in children[15] and time off work and loss of productivity in adults.[16]

Patients with non-allergic rhinitis may have similar symptoms[17] which are discussed in other chapters – infectious rhinitis, occupational rhinitis, drug-induced rhinitis, hormonal rhinitis, irritant rhinitis, tobacco mucositis, persistent non-allergic rhinitis with eosinophilia (NARES) and idiopathic (vasomotor) rhinitis. The diagnosis of an allergic rhinitis is made by correlating the allergic symptoms and history with diagnostic tests demonstrating allergen-specific IgE, whether by skin prick testing or by measuring specific IgE levels in the blood (RAST).

PREVALENCE

The prevalence of allergic rhinitis varies widely around the world. The International Study on Asthma and Allergy in Childhood (ISAAC 1)[1] and its follow–up (ISAAC 3)[18] showed the prevalence of rhinoconjunctivitis to vary between 0.8% and 39.7% in different populations (**Figure 91.2**).

Countries with a low prevalence of asthma (<5%) such as Indonesia, Romania and Greece had a low prevalence of allergic rhinitis. Conversely, countries with a high prevalence of asthma (>30%) such as the United Kingdom, Australia and New Zealand had a high prevalence of rhinitis (15–20%).

There has been a steep increase in the prevalence of allergic rhinitis over the last 40 years,[19,20] though this may now be slowing.[21] The reasons for this increase are uncertain. Children who live on farms and have contact with livestock are less likely to develop allergic rhinitis than their urban peers[22,23] suggesting a possible protective effect of microbial exposure. Larger family size, more frequent infections and unhygienic contact may all be protective – the hygiene hypothesis.[24] This suggests

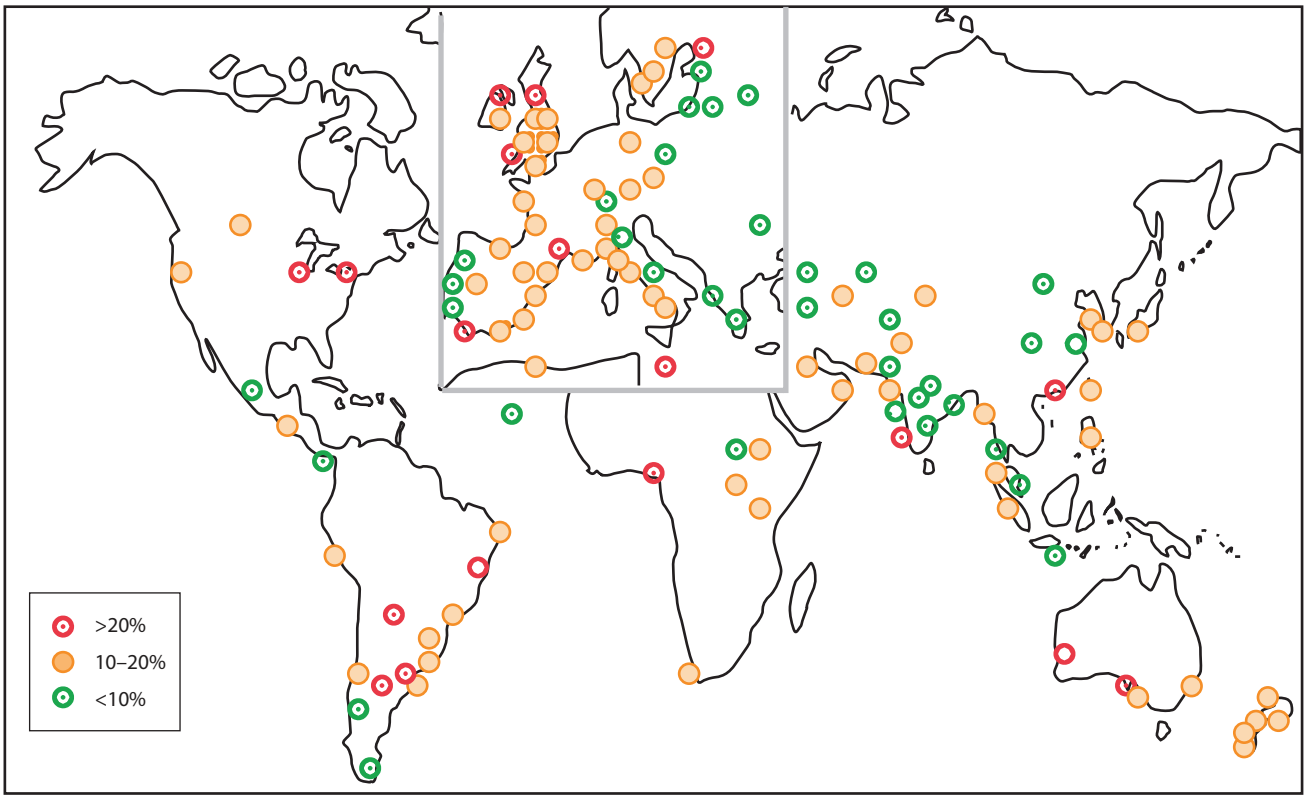


Figure 91.2 Prevalence of allergic rhinitis worldwide, 13–14 year olds. Reproduced with permission.[1]

that reduced exposure to infective agents reduces the Th1 response and leads to an overdrive of the Th2 immune response leading to excessive production of IgE and consequent atopy. There are however some uncertainties about this concept.[25] Chronic parasitic disease (for example with worms) is also protective, possibly because of the production of blocking antibodies (IgG4).[26] Eradication of worm infestation increases skin reactivity to aeroallergens.[27]

All these reasons suggest that an urbanized, Western lifestyle promotes the development of allergic disease. The link with helminth infection may also point the way to future treatment options.

NATURAL HISTORY

Genetic factors are certainly involved in the aetiology of allergic rhinitis. Having parents who are atopic may increase the risk of a child having an allergic disease by 3–6 times.[28] Exposure to an allergen is also required before sensitivity develops therefore environmental factors are also important. Pollen-induced allergic rhinitis is uncommon before the age of 2 years suggesting that exposure over two seasons is required for sensitization.[29] The 'atopic march'[30] in children refers to the sequential development of allergic diseases, often starting in infants with atopic eczema then the development of allergic rhinitis and finally allergic asthma.[31] Several studies have shown that adult-onset asthma is more likely to occur in patients with allergic rhinitis than in those without, usually increasing the risk by a factor of three,[32] though whether allergic rhinitis is an earlier manifestation of allergic disease in patients who will go on to develop asthma or whether the nasal disease itself causes asthma is unclear. Remission of symptoms may occur over time. One study showed that although the overall prevalence of allergic rhinitis increased from 12.4% in 1992 to 15% in 2000 in keeping with the worldwide increase, 23.1% of patients who had allergic rhinitis in 1992 no longer had symptoms in 2000.[33] Symptoms of rhinitis generally become less severe with age and skin prick testing shows less reactivity in the elderly.[34]

KEY POINTS

- Allergic rhinitis is an IgE mediated disease
- In Western societies it is common (>20%)
- It is often associated with other allergic diseases such as allergic conjunctivitis and asthma
- It may have significant negative effects on sleep, work and study
- Patients with allergic parents are more likely to be allergic
- Lack of helminth infection may be important in development of disease
- Allergic disease is often less severe in the elderly

PRESENTATION

Most patients will be referred from general practice with two or more symptoms of anterior or posterior rhinorrhoea, sneezing, nasal blockage and/or itching of the nose. Young children may simply present with block. Other complaints such as itchy eyes, pharyngeal itch, hearing loss due to otitis media with effusion, atopic eczema, asthma, loss of smell, chronic cough, snoring, fatigue, sore throat and halitosis may occur.[35, 36] Unilateral symptoms, mucopurulent rhinorrhoea, thick post-nasal discharge, epistaxis, pain and anosmia are not usually associated with allergic rhinitis and should prompt further investigation.

The history is crucial. When symptoms started, how long they last and when they occur will allow determination of likely long-term atopy, whether the problem is persistent or intermittent and the possible allergens. Ask direct questions regarding symptoms suggestive of asthma such as wheeze or cough. A family history of atopy is important as it makes the diagnosis of allergy more likely.

Symptoms of rhinitis, conjuctivitis, cough and wheeze during the summer months suggest grass pollen sensitivity; waking with a blocked nose might be linked to house dust mites in the bed. The main presenting symptoms and their severity should be determined. Does the nasal block cause problems with sleep or work?

Ask about the character of the nasal discharge. A coloured discharge suggests infection whereas the discharge is usually clear in allergy. Does the block switch from side to side? This is common in patients with mucosal inflammation and less likely with anatomical abnormalities alone such as septal deviation.

More direct questions should be asked regarding endocrine problems that may cause rhinitis (hypothyroidism) and medication (the combined oral contraceptive pill may cause congestion). Specific questions may be helpful in patients with seasonal symptoms. Tree pollen allergy (birch particularly) may be associated with oral allergy syndrome which causes swelling or tingling of the lips when eating uncooked fruits and vegetables such as potatoes, carrots, cherries, celery, apples, pears, plums, peaches, parsnip, kiwi, hazelnuts and apricots and is found in approximately half the patients with birch pollen sensitivity.[37] It may also be reported with other pollen sensitivities.

EXAMINATION

A general examination of the patient may reveal other signs of atopic disease such as eczema or allergic conjunctivitis and sometimes an allergic crease may be seen on the patient's nose.

Examination of the nose should always be performed, if only to exclude causes other than allergy. Anterior rhinoscopy will allow an assessment to be made of the colour and state of the nasal mucosa and to see whether it is swollen and causing obstruction. It may be oedematous, blue or pale in colour and covered in thin mucus, but this is not always the case. In children a blocked nose with normal nasal mucosa may suggest adenoid enlargement. Endoscopic examination will allow polyps and other nasal disease to be excluded. In severe or atypical presentations (especially in the presence of cartilage or mucosal loss,

cosmetic changes, systemic illness or refractory bleeding) exclusion of other inflammatory or neoplastic diseases is important.

A history suggesting asthma such as wheeze or nighttime cough may necessitate examination of the chest or referral to a respiratory physician.

DIAGNOSIS

For many patients, a clear history that fits with allergic rhinitis and a corresponding nasal examination will allow a diagnosis to be made confidently, though in specialist practice skin prick tests will normally be carried out as part of the standard workup. If there is diagnostic uncertainty, or if the consequences of a possible allergy are important (such as a pet allergy), then allergy testing should be performed. This will normally be either a skin prick test (SPT)[38] or measurement of specific IgE in the blood (often referred to as radioallergosorbent testing or RAST[39] (see Chapter 14).

Skin prick testing is usually the preferred option as it allows the patient to see the results directly and gives time for patient education about avoidance measures if required.

The method of skin prick testing involves the use of a small lancet to introduce an allergen into the skin. If the patient is sensitized to the allergen then IgE sensitized mast cells will degranulate and cause a wheal and flare reaction in the skin. Negative (saline) and positive (histamine) controls are also used to rule out dermographism and non–reactivity respectively. If the negative control shows a reaction or the positive control shows no reaction then blood IgE levels should be measured. If an oral antihistamine has been taken in the preceding 7–10 days then the positive control may not react. A positive reaction is noted by a wheal size 2 mm or greater than the negative control. In the United Kingdom the main four allergens that should be tested for are grass pollen, house dust mite, cat and dog but the prevalence of sensitivities varies around the world with cockroach sensitivity common in tropical countries. Patients with particular exposure can have various other allergens tested depending on their history (for example exposure to horses or moulds). It should be noted that a positive skin test shows atopy but it does not necessarily mean that the patient has a clinically relevant reaction to that allergen. The reaction has to be correlated with the patient's symptoms. Approximately 25% of adults have a positive reaction on skin prick testing but only 10–15% are symptomatic (though some patients with positive tests will go on to develop allergic disease in the future).[40]

RAST testing is usually reserved for patients who require a diagnosis but where SPTs are unavailable or inappropriate. A blood sample is taken and radio- or enzyme-labelled anti-IgE is added to the serum. A positive result is shown by an IgE level of 0.35 kU/l or greater. As for SPTs, a positive result may not necessarily be clinically relevant.

Nasal allergen challenge is the gold standard of allergy diagnosis but it is infrequently required or available. It may be useful where the history is suggestive of a particular allergen being responsible for symptoms but the skin prick tests are negative. An allergen is applied to the nasal mucosa, or the patient exposed to an airborne allergen, and subjective measurements made (symptom scores) as well as objective measurements (sneeze count, peak nasal inspiratory flow, rhinomanometry, pulmonary peak flow, etc.).[41] This method of testing can also be used in patients suspected of having salicylate intolerance using lysine aspirin applied to the nose and is a possible substitute for an oral salicylate challenge. Nasal challenge testing is complex and has the risk of inducing anaphylaxis and is therefore is used only in specialist centres.

Various other methods of determining sensitivity are also described including the measurement of inflammatory mediators such as histamine, PGD2, leukotrienes, kinins and tryptase in blood or nasal secretions, nasal cytology and histology and measurement of nitric oxide in exhaled air.[42] None of these methods are generally used in clinical practice.

Symptoms of asthma may indicate the need for respiratory assessment with pulmonary function tests and reversibility with a bronchodilator.

KEY POINTS

- The history and symptoms are crucial in diagnosis.
- The timing of symptoms will often lead to diagnosing the allergy.
- Nasal examination is mainly to exclude other causes.
- In severe or atypical presentations (especially in the presence of cartilage or mucosal loss, cosmetic changes, systemic illness or refractory bleeding) exclusion of other inflammatory or neoplastic diseases is important.
- Ask about asthma symptoms (wheeze and cough).
- Skin prick testing is useful particularly in persistent allergic rhinitis where the cause may not be clear.

TREATMENT

- The prevention of allergic rhinitis
- Methods of reducing allergen exposure
- Pharmacological treatment of allergic rhinitis (see also Chapter 28)
- Immunotherapy for allergic rhinitis
- Surgical treatment
- Complementary therapies

The prevention of allergic rhinitis

Various areas have been examined to determine if sensitization can be reduced in infancy – no definite triggers have been found but recommendations have been made on the available evidence. It has been advised that children should breastfeed for at least the first three months after birth,[43] that there is no benefit in having a reduced antigen diet for the mother in pregnancy and during lactation[44] and that parents should not smoke in pregnancy or near children, although no definite link with allergy has been found.[45] There was also limited evidence of benefit in reducing exposure to house dust mite but no benefit in not exposing children to furry pets.[46]

REDUCING ALLERGEN EXPOSURE

As the clinical effects of allergic rhinitis are caused by allergens it would seem logical that reduced exposure would benefit symptoms. The major allergens to be found indoors are house dust mite, cat, dog and other furry animals, cockroach and moulds. Outdoors the main allergens are airborne pollens which vary during the year and depend on local conditions. In Europe tree pollen is found during the spring, grass and weed pollens during the summer and various mould spores during the summer and autumn. In North America ragweed sensitivity is a common problem but this is not found in Europe. Tropical areas will have less seasonal variation.

METHODS TO ACHIEVE ALLERGEN REDUCTION

House dust mite allergen reduction aims to reduce the amount of mite allergens in the home:

- Wash bedding regularly (every 1–2 weeks) at 55–60 °C to kill mites (washing with cold water removes 90% of mite allergens; washing at 55–60 °C kills mites)
- Wash pillows and duvets in hot water (55–60 °C) and encase pillows and mattresses with protective coverings that have a pore size of 6 µm or less
- Sufficient ventilation of dwellings to decrease humidity; aim to reduce indoor relative humidity to below 50% and avoid damp housing conditions.

Reproduced with permission of the WHO.[47]

ADDITIONAL STRATEGIES

- Use a good quality vacuum cleaner (if possible, one fitted with a HEPA filter)
- Use a damp duster when dusting and cleaning surfaces
- Replace wall to wall carpets with linoleum or wooden floors which can be wiped clean
- Remove/reduce curtains and soft furnishings in the bedroom
- Replace fabric-covered seating with leather or vinyl
- Remove soft toys from the bedroom; wash them at 55–60 °C or freeze them (in a kitchen deep-freezer) to kill house dust mites
- Exposure of mattresses, rugs and carpets to direct strong sunlight (for more than 3 hours) kills mites and can be used in appropriate regions.

Pollen avoidance provides mechanical barriers to pollen contact.

- Keep windows closed at peak pollen times
- Wear glasses or sunglasses to help prevent pollens entering the eyes
- Consider wearing a mask over nose and mouth to prevent inhalation of pollens at peak time
- Use air-conditioning where possible
- Install car pollen filters where possible

Pet allergen avoidance reduces the amount of pet allergen indoors.

- If possible, find another home for the pet and do not introduce new animals into the home. If the pet is not removed from the home then:
  - Exclude pets from bedrooms and if possible keep pets outdoors
  - Vacuum carpets, mattresses and upholstery regularly
  - Change clothes before going to school or work if you have had contact with any animal (e.g. horse/cat/dog).

Cockroach allergen avoidance involves removing the cockroaches, eliminating the places and conditions in which they can live and removing all allergens.

- Eradicate cockroaches with appropriate insecticidal bait
- Seal cracks in floors and ceilings
- Enclose all food
- Do not store waste in the home
- Scrub floors with water and detergent to remove allergens.

Mould allergen avoidance aims to prevent mould from growing and mould spores from becoming airborne during mould removal.

- Use dehumidifiers in the home if relative humidity is consistently high (above 50%)
- Ensure heating, ventilation or air-conditioning systems are properly maintained
- Use 5% ammonia solution to remove mould from bathrooms and other contaminated surfaces
- Replace carpets with hard flooring and replace wallpaper with paint
- Repair indoor water damage immediately.

Unfortunately despite these measures it is very difficult to achieve significant allergen reduction or elimination and clinical benefit from these strategies has been limited. For example a study looking at the results of using impermeable covers on mattresses and pillows demonstrated a reduction in dust mite allergen to 30% of the initial level, but found no evidence of clinical benefit.[48]

Table 91.1[49] summarizes the evidence of efficacy for some of these measures. Although the evidence base for recommending allergen reduction is poor it may nevertheless benefit some patients and a trial of avoidance may be useful.

Food allergy

It is very unusual for food allergy to cause isolated nasal symptoms, although the nose may be involved in more generalized systemic reactions. Foods such as peanuts, nuts, shellfish, fish and fruits such as strawberry may be involved. Milk and egg allergy is more common in younger children but usually resolves by 4–6 years old.

TABLE 91.1 Effect on allergen levels and evidence of clinical benefit

Measure	Evidence of effect on allergen levels	Evidence of clinical benefit
House dust mites		
Encase bedding in impermeable covers	Some	None (adults): evidence A Some (children): evidence B
Wash bedding on a hot cycle (55–60 °C)	Some	None: evidence A
Replace carpets with hard flooring	Some	None: evidence A
Acaricides and/or tannic acid	Weak	None: evidence A
Minimize objects that accumulate dust	None	None: evidence B
Vacuum cleaners with integral HEPA filter and double-thickness bags	Weak	None: evidence B
Remove, hot wash or freeze soft toys	None	None: evidence B
Pets		
Remove cat/dog from the home	Weak	None: evidence B
Keep pet from main living areas/bedrooms	Weak	None: evidence B
HEPA-filter air cleaners	Some	None: evidence B
Wash pet	Weak	None: evidence B
Replace carpets with hard flooring	None	None: evidence B
Vacuum cleaners with integral HEPA filter and double-thickness bags	None	None: evidence B

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Skin prick testing or IgE levels can confirm a true allergy but may give false positive results, therefore should be targeted at specific allergens rather than having a screening role. Avoidance of allergenic foods may be difficult (particularly in the case of peanut allergen which may be found in many processed foods) and suitable substitutes must be found to avoid dietary insufficiency and consequent malnutrition.

True food allergy should not be confused with oral allergy syndrome where there is cross-reactivity with a pollen allergen and which is relatively common.

Pharmacological treatment of allergic rhinitis

The basic summary of recommendations for treatment according to the ARIA guidelines[50] are shown in Figure 91.3.

The effects of the various medications used are summarized in Table 91.2.

The most widely used and effective medications to treat allergic rhinitis are oral or topical antihistamines and topical nasal steroids.

It should be stressed that these medications aim to achieve improved symptom control and are not a cure for allergy. They generally need to be taken for as long as there is allergen exposure causing symptoms. Symptom control is better for patients with intermittent allergic rhinitis if they start treatment prior to exposure to the allergen to which they are sensitized. For example, patients with grass pollen allergy should be advised to start treatment a month before the pollen season starts to try to avoid the development of symptoms and nasal inflammation and to stop treatment at the end of the season.

In keeping with the idea of the unified allergic airway, treatment for asthma may also be required, whether this be long-term or to manage wheeze only during the peak pollen season (peak seasonal wheeze). Treatment of the nose with topical steroids reduces asthma symptoms[51] and treatment of the lungs may reduce nasal symptoms[52] therefore symptom control will be better if both nose and lungs are assessed and treated together in symptomatic patients.

ANTIHISTAMINES

The symptoms of running, sneezing and nasal and eye itching are histamine driven and antihistamines are the first-line treatment for these symptoms in patients who have no problem with nasal obstruction. They have little effect on nasal blockage.[53] The older first-generation antihistamines (chlorphenamine, diphenhydramine) are rarely used now due to their sedative effects, though ketotifen may still have a role with some additional effect as a mast cell stabilizer. Second generation oral antihistamines such as loratadine and cetirizine are non-sedating, safe for long-term use and can be used for children. They have a rapid onset of action (usually less than an hour) and will give symptom reduction on a once daily dosing. Antihistamines give better symptomatic control when used regularly rather than on an as required basis.[54] Topical antihistamines (for example azelastine) may be used intranasally to achieve rapid symptom control and can be combined with a topical nasal steroid. It has the disadvantages of having a bitter taste that some patients

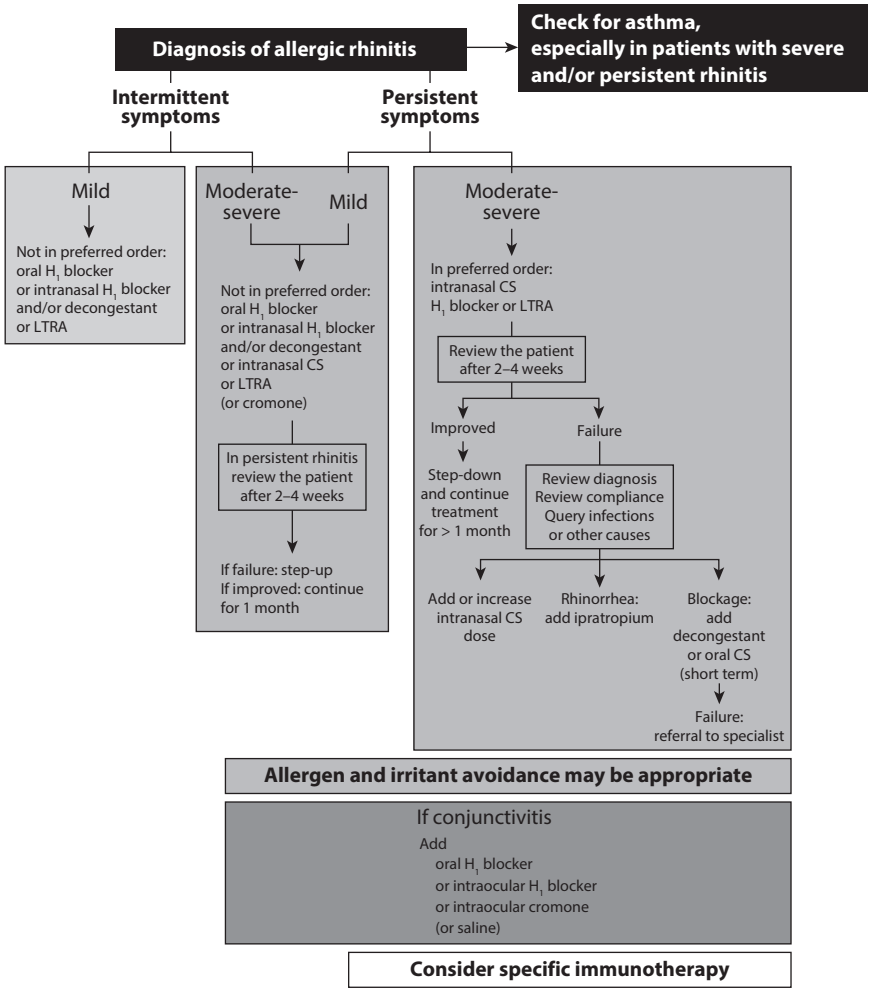


Figure 91.3 Allergic rhinitis management (algorithm of the ARIA update recommendations 2008). Reproduced with permission.[50]

TABLE 91.2 Pharmacological treatments and their effects in allergic rhinitis

	Itch/sneezing	Discharge	Blockage	Impaired smell
Sodium cromoglicate	+	+	+/–	–
Oral antihistamines	+++	++	+/–	–
Ipratropium bromide	–	+++	–	–
Topical decongestants	–	–	+++	–
Topical corticosteroids	+++	+++	++	+
Oral corticosteroids	+++	+++	+++	++
Antileukotrienes	–	++	+	+/–

dislike and needs twice daily dosing. Azelastine eyedrops may also be useful in reducing ocular symptoms.

Antihistamines alone may control symptoms adequately in some patients though many will require the addition of a topical nasal steroid.

INTRANASAL GLUCOCORTICOSTEROIDS

Glucocorticosteroids are the most effective treatment for allergic rhinoconjunctivitis.[55] Topical use in the form of a spray or drops is preferred to oral use to reduce side effects, although occasionally oral steroids may be useful. Intra-nasal application allows a high concentration of the active drug to be delivered to the nasal mucosa with minimal systemic absorption. The drugs reduce all symptoms of allergic rhinitis and ocular symptoms and are the first-line treatment of choice in patients who complain of nasal block.[56] As steroids have an effect on the production of pro-inflammatory mediators within the cell nucleus their effect is slow to occur and long lasting. Most steroids will not have an appreciable effect on symptoms for several hours or days and it can take two weeks for full benefit to be noticed. Patients should be warned of this as some will give up on treatment if it does not work rapidly.

Side effects of intra-nasal steroids are few but include epistaxis. This may be caused by incorrect use of the spray delivery system causing trauma as there is no evidence of nasal mucosal atrophy even with long-term use.[57] The systemic bioavailability of these drugs is low. Minor growth retardation has been noted in children treated with intranasal beclometasone[58] but this has not been shown with fluticasone[59] or mometasone.[60] These drugs are generally relatively cheap and in many countries can be bought without prescription.

SYSTEMIC GLUCOCORTICOSTEROIDS

Oral steroids may occasionally be useful in patients with severe symptoms to allow reduction of mucosal swelling and subsequent use of topical medication or to cover a short period when symptom control is particularly bad. Prednisolone 20–40 mg/day is normally sufficient[61] but oral steroids may cause serious side effects so their use should be considered carefully and length of treatment be kept as short as possible. For this reason depot injectable steroids, while effective at symptom control, are not recommended as once injected their effects cannot be stopped.[62]

LEUKOTRIENE RECEPTOR ANTAGONISTS (LTRAS)

Cysteinyl leukotrienes are a family of eicosanoid inflammatory mediators (LTC4, LTD4 and LTE4) produced in leukocytes, mast cells, eosinophils, basophils and macrophages by the oxidation of arachidonic acid by the enzyme arachidonate 5–lipoxygenase. Their effects are to cause bronchoconstriction, increase vascular permeability and attract inflammatory cells and as such are involved in the processes underlying asthma and allergic rhinitis.[63] In the UK montelukast (a leukotriene receptor antagonist) is licensed for the treatment of allergic rhinitis associated with asthma. In studies it was found to be as effective as loratadine in reducing nasal symptoms but less effective than a topical nasal steroid.[64] Combined use of cetirizine and montelukast was shown not to improve symptom control above each drug individually in one study[65] but to be more effective when combined in another.[66] There is a significant variation in responsiveness to LTRAs and a closely monitored trial of treatment may be useful in some patients. It now has a place in the updated ARIA treatment guidelines (**Figure 91.3**).

SODIUM CROMOGLICATE

Sodium cromoglicate nasal spray has modest effects on rhinitis symptoms but must be used four times daily, which limits compliance.[67] It has no side effects and can be used on young children.[4] Cromoglicate eye drops can be effective against ocular itching.[68]

DECONGESTANTS

Topical (e.g. xylometazoline) and systemic decongestants (e.g. pseudoepedrine) are available and have a place in allergic rhinitis management. The topical decongestants are more effective and have a more rapid onset of action. They reduce nasal obstruction and may allow access of a topical steroid into an otherwise obstructed nose. The disadvantage is of rebound vasodilation when their use is stopped leading to a worsening of symptoms and of rhinitis medicamentosa with longer term use. A maximum length of treatment of 7–10 days therefore is advised. Systemic decongestants may also have side effects such as insomnia, tachycardia and tremor.[4]

IPRATROPIUM

Topical ipratropium bromide spray is effective at controlling watery rhinorrhoea and can be a useful addition to a topical steroid if rhinorrhoea is not being well controlled.[69] Side effects are infrequent but include prostatic symptoms and worsening of glaucoma.[4]

NASAL DOUCHING

Saline nasal douches may help with symptom control[70] and can physically remove an allergen from the nasal mucosa. If pollen levels are high regular douching may be of benefit.

Immunotherapy

Immunotherapy (sometimes called desensitization) is a method of inducing tolerance to an allergen and therefore reducing unwanted symptoms. It can reduce the symptoms of allergic rhinitis, offer long-lasting reduction of symptoms (even when treatment has stopped) and can prevent the progression of allergic disease.[71] It involves repeated exposure of the patient to the allergen usually, but not always, with a gradual increase in allergen dose. It can be given subcutaneously by injection (SCIT) or sublingually in drops or tablets (SLIT). Studies have shown similar efficacy for SCIT and SLIT.[72] It is effective in reducing symptoms in adults and older children[71] though the results are less clear for children under five.[73] There are several guidelines regarding the selection of patients and treatment protocols, one of which is published by the British Society for Allergy and Clinical Immunology.[74]

Immunotherapy use in the UK is limited but it is widely used elsewhere. Patients considered are those who have severe symptoms but whose response to standard medical treatment has been unsatisfactory, or those patients who have unacceptable side effects from their medication.

This group may be larger than generally supposed with up to 40% of patients in UK general practice stating that symptom control of their rhinitis was poor.[75] The diagnosis of an IgE mediated response should be confirmed by skin prick tests or measurement of IgE levels before treatment and correlated with the patient's history to ensure the correct allergen is used. The main allergens used in Europe are for the main causes of allergic rhinitis – house dust mite, grass pollen, cat, dog and tree pollen. These extracts are all available in standardized doses. Treatment is usually continued over a 3-year period to achieve a long lasting tolerance after treatment has stopped.[76]

Recent exposure of the nose to allergen may lead to asymptomatic eosinophil infiltration and a pro-inflammatory mucosal environment – a concept known as priming. Such changes are likely to be reflected in the bone marrow also, with an increased production of allergy-associated cellular and biochemical mediators which are effective systemically. This can cause a patient who has specific IgE to an allergen but no clinical allergy to be 'primed' and who will subsequently react clinically to an allergen to which they would not normally react.[77] For example a patient with IgE to dog and grass pollen may not normally have an allergic response to either but if exposed to dog will then show an allergic response to grass pollen later in the season. This explains why immunotherapy treatment for one allergen may have a beneficial effect for others.

EFFICACY

With good patient selection immunotherapy can be very effective. In a study of patients with grass pollen sensitivity treated with SCIT, over the peak pollen season mean symptom and medication scores were 32% and 41% lower respectively than those in a placebo group,[78] and these results or better have been replicated in many other studies.[79] Immunotherapy for older children with allergic rhinitis also reduces the risk of developing allergic asthma later in life[80] and of developing new allergies.[81]

PROCEDURE AND SIDE EFFECTS

With SCIT there is usually an updosing phase of between 2 and 4 months when the dose of allergen is gradually increased to the maintenance dose. This maintenance dose is then injected every 4–6 weeks for a 3-year period. SLIT may be updosed or, in some treatment protocols, the patient starts with the maximum dose and continues with this daily for 3 years. Giving the patient a product to which they are known to be sensitized carries the risk of side effects. These are usually transient redness and itching around an injection site, or oral itching, and can be reduced by pre-treatment with an oral antihistamine. Very occasionally patients may suffer a generalized reaction such as urticaria, bronchoconstriction or anaphylaxis and resuscitation facilities with adrenaline must be available.[71] Almost all reactions will occur within 30 minutes of treatment therefore patients should be observed for an hour after injection. SLIT should be taken under medical supervision for the first dose but can then be taken by the patient at home if they do not react severely.

ANTI-IgE ANTIBODY (OMALIZUMAB)

Omalizumab is a monoclonal antibody that binds to circulating IgE preventing it from binding to mast cells and causing degranulation.[82] Omalizumab reduces all nasal symptoms and improves asthma control[83] but has the risk of causing anaphylaxis and is expensive. It is administered by monthly injection. Currently it is recommended only for patients with severe allergic asthma with or without rhinitis symptoms.

Surgery

Surgery cannot cure allergy but can give relief of nasal blockage if other methods fail. Reduction of submucosal fibrotic tissue on the inferior turbinates that has developed due to long-standing inflammatory changes may improve the airway and allow access for topical nasal steroids.[84] If the nose remains congested even after the application of a decongestant in clinic then surgery should be considered as the mucosal swelling may be fixed. Polypoidal mucosa may also be found in some patients with severe allergic rhinitis and occasionally this needs to be removed.

Complementary treatments

Trials of homeopathy, acupuncture and herbal remedies have not shown any evidence of beneficial effect in allergic rhinitis[85] but many patients use them and are satisfied with the results.

KEY POINTS

- Although allergen avoidance seems logical there is minimal evidence of beneficial effect.
- Food allergies do not present with isolated allergic rhinitis.
- Antihistamines and topical nasal steroids are the main treatments for allergic rhinitis.
- Antihistamines work better if used regularly rather than on demand.
- Leukotriene receptor antagonists may be useful.
- Immunotherapy is highly effective but access to treatment is limited.
- Reduction surgery to the inferior turbinates may be of use occasionally.

CHILDREN WITH RHINITIS

Allergic rhinitis is the most prevalent allergic disease in children[86] and can have significant effects on the child's quality of life. It may exacerbate other allergic disease such as asthma.[87] Younger children may get frequent episodes of acute infective rhinitis in a year and it can be difficult to differentiate these from allergy. If the episodes last more than 2 weeks and are associated with other allergic symptoms such as itching then allergy should be considered. In children with nasal obstruction but healthy nasal mucosa and clear anterior nares then adenoidal hypertrophy may be present.[88]

Skin prick testing may be performed on young children, though some will not tolerate it. It can be done on the skin of the back rather than the forearm if the child is afraid of the lancet.

The treatment algorithm is similar to that for adults but it may be more difficult to get a child to use a nasal spray. As many of these children also have asthma, however, they may be used to using an inhaler. Oral non-sedating antihistamines are the standard first-line treatment but a trial of a leukotriene receptor antagonist should also be considered if a nasal spray is not tolerated or if the steroid load is excessive. Fluticasone (from 4 years old)

and mometasone and triamcinolone (from 6 years old) have low systemic bioavailability and are the steroids of choice.[89] As with adults depot steroids are not recommended. Growth should be monitored if the child is already using steroids (such as an inhaled steroid for asthma or steroid creams for eczema) although there is no evidence of an effect on the hypothalamic-pituitary-adrenal axis with normal doses.[90] Beclometasone has been associated with growth retardation and is not recommended for children.[58] SCIT is generally not recommended for children under 5 years, though SLIT may be used increasingly in the future. Its efficacy in young children is, however, still uncertain.[73, 91]

PREGNANCY

Rhinitis of pregnancy is relatively common and probably caused by high levels of oestrogen. It may occur in women without any past history of rhinitis, allergic or otherwise. Symptoms of allergic rhinitis may also be exacerbated during pregnancy, probably by the same cause. Although topical nasal steroids with low bioavailability are relatively safe, hypertonic saline douches or occasional use of topical decongestants may be preferable. The condition is self-limiting and resolves rapidly following childbirth.

BEST CLINICAL PRACTICE

- ✓ Advice to reduce allergen exposure in high-risk families has not been shown to be effective in reducing prevalence of allergy.
- ✓ Avoidance of parental smoking during pregnancy and childhood is probably important, though evidence is lacking.
- ✓ Breastfeeding is recommended.
- ✓ Although allergen avoidance is desirable, it is frequently expensive, time-consuming, impracticable or, in the case of pollens, not feasible.
- ✓ Recent trials and a meta-analysis have failed to demonstrate efficacy of house dust mite avoidance or reduction methods in adult patients with persistent rhinitis and asthma.
- ✓ Patients with allergic rhinitis and /or asthma who are sensitive to cats and dogs should be advised to remove the animals, not replace them, or at a minimum keep them out of the bedroom.
- ✓ Food allergy almost never causes isolated nasal symptoms.
- ✓ Antihistamines all rapidly relieve itching and sneezing but have minimal effect on block.
- ✓ Antihistamines appear to be more effective if used regularly.
- ✓ Topical glucocorticoids are the most effective treatment for rhinitis, especially if started prior to allergen exposure.
- ✓ There is no difference in efficacy between the various topical glucocorticoid preparations, but fluticasone and mometasone have the lowest systemic bioavailability and therefore should be considered in paediatric practice or patients having inhaled or cutaneous steroids.
- ✓ Specific immunotherapy is highly effective and may prevent development of future allergic disease.

FUTURE RESEARCH

- ➤ Should allergen avoidance methods be used by parents to prevent the development of allergy in children? What effect does this have?
- ➤ Should occupational allergen avoidance methods be used?
- ➤ Should patients with allergic rhinitis and/or conjunctivitis use antihistamines, glucocorticosteroids, antileukotrienes, cromones, decongestants or ipratropium bromide? What is the relative effect of these medications? Can decongestants be used long term if used with a nasal steroid? For what period and how regularly should they be used?
- ➤ Should allergen specific immunotherapy be used in patients with allergic rhinitis? What is the effect of subcutaneous and sublingual specific immunotherapy?
- ➤ Do complementary and alternative treatments for allergic rhinitis have an effect?
- ➤ Should medications for allergic rhinitis be used in patients with concomitant asthma for the treatment of symptoms of asthma?
- ➤ What is the role of helminths in the development of allergic disease?

KEY POINTS

- Allergic rhinitis is best considered in the context of the unified allergic airway, or even as a systemic disease.
- Diagnosis is based on the symptomatic presentation, exposure and evidence of allergen sensitization.
- The disease has a strong association with asthma and an underestimated prevalence, cost and impact on quality of life.
- The mainstay of contemporary treatment are avoidance of allergen, oral or topical antihistamines and topical corticosteroids, but immunotherapy has a re-emerging role.

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CHAPTER 92

NON-ALLERGIC PERENNIAL RHINITIS

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline and Embase searches using the keywords: rhinitis, vasomotor rhinitis, non-allergic rhinitis, NANIPER, occupational rhinitis, drug-induced rhinitis, NARES, drug therapy and surgery.

INTRODUCTION

Although rhinitis is a cause of widespread morbidity, medical treatment costs, reduced work productivity and lost school days, the disease is often trivialized. Non-infectious rhinitis can broadly be subdivided into two subclasses, allergic and non-allergic rhinitis, depending predominantly on whether or not an allergic aetiology is implicated. Whilst allergic rhinitis has been extensively investigated and the underlying mechanisms are relatively well understood, there is comparatively little information on non-allergic rhinitis. The term 'non-allergic rhinitis' is commonly applied to a diagnosis of any nasal condition in which the symptoms are identical to those seen in allergic rhinitis but an allergic aetiology has been excluded. These non-allergic aetiologic entities can broadly be classified as:

- idiopathic rhinitis (also referred to as vasomotor rhinitis, or non-allergic non-infectious perennial rhinitis (NANIPER));
- non-allergic occupational rhinitis;
- hormonal rhinitis;
- drug-induced rhinitis; and
- other forms (non-allergic rhinitis with eosinophilia syndrome (NARES), rhinitis due to physical and chemical factors, food-induced rhinitis, emotion-induced rhinitis, atrophic rhinitis).[1, 2]

Unlike allergic rhinitis there are no specific diagnostic tests for non-allergic rhinitis, and diagnosis is made on the basis of rhinitis symptoms in the absence of identifiable allergy (by allergy testing), structural abnormality, immune deficiency, sinus disease or other causes.

Ninety-five percent of normal subjects without rhinitis complaints have been shown to sneeze up to four times a day and to blow their noses up to four times a day, as an average over 2 weeks.[3] This would suggest that five or more sneezes and/or nose blowing per day may possibly be indicative of nasal disease. Whilst it is difficult to readily diagnose non-allergic rhinitis, it has been suggested that in patients with perennial non-allergic rhinitis this condition persists for greater than 9 months each year and produces two or more symptoms, including hypersecretion, blockage, sneezing and post-nasal drip.

Although there are some studies of the prevalence of non-allergic rhinitis amongst the rhinitic population, large variations (ranging from around 20 to 50%) have been reported,[4, 5] presumably due to difficulties in definition and diagnosis of the disease. It is evident that the incidence of positive skin tests to inhalant allergens is far greater than the incidence of rhinitis symptoms in large cross-sectional epidemiological studies. This also implies that rhinitis symptoms in a patient with a positive skin test are not necessarily caused by the allergen, suggesting that the contribution of non-allergic rhinitis to the total number of rhinitis patients may be substantially greater than hitherto estimated. A survey of nearly 1000 rhinitis patients seen in 18 allergy clinics in the USA showed that 23% of the patients had pure non-allergic rhinitis and, importantly, 34% of the patients were diagnosed with

'mixed' rhinitis (a combination of allergic and non-allergic rhinitis),[6, 7] a group not considered in the other studies. Furthermore, both non-allergic and mixed rhinitis occur more frequently in adults than in children, may be more common in females and are more likely to be perennial than seasonal. More recently, the survey was extended to include more than 22 000 practitioners, each of whom contributed ten patients with rhinitis to the survey. The interim results of the survey indicated that as many as 70% of these patients have mixed rhinitis, with only 9% having the non-allergic rhinitis component alone.

PATHOPHYSIOLOGICAL CONSIDERATIONS

Non-allergic rhinitis, allergic rhinitis and post-infectious rhinitis have nasal hyper-reactivity to various stimuli (for example odours, position, temperature, histamine, etc.) in common, which consequently does not allow differentiation between allergic and non-allergic causes. Unlike patients from some subgroups of non-allergic rhinitis (particularly drug-induced, hormone-induced and NARES) and patients with allergic rhinitis for whom the aetiology is well defined, the aetiology and pathophysiology for the majority of patients with non-allergic non-infectious rhinitis are largely unknown. Although the term 'vasomotor' implies increased neuronal efferent traffic to the blood vessels supplying the nasal mucosa, this has never been proved.[1] Some mechanistic studies have suggested that the functional abnormality in NANIPER may be associated with an imbalance between the sympathetic and parasympathetic nervous systems, which leads to an imbalance in neuronal control of the end organs in the nose.[8] Indeed, nasal provocation with capsaicin, which specifically stimulates afferent nerve fibres, has been shown to result in a dose-dependent leukocyte influx, albumin leakage and glandular secretion in patients with allergic rhinitis[9] and to be efficacious in the treatment of NANIPER.[10] However, reports on the underlying mechanisms are conflicting. Whilst some studies have suggested that capsaicin induces neurogenic inflammation in patients with allergic rhinitis, possibly as a consequence of abnormal nociceptor function, this has been shown not to be the case in NANIPER.[11] Forced expiration through the nose has been found to significantly increase nasal airway resistance, but not mucous production or sneezing, within the first minute in NANIPER patients and not in non-rhinitic controls, suggesting that mechanical stimulation may also be an important mechanism in NANIPER patients.[12] However, in view of the fact that sympathetic stimulation leads to vasoconstriction and parasympathetic stimulation leads to nasal congestion, it is likely that the imbalance is biased towards parasympathetic stimulation since rhinorrhoea is the predominant complaint in this condition.[8]

Review of the limited data available for idiopathic rhinitis, which comprises the largest group of patients with non-allergic rhinitis, has indicated that several pathologic mechanisms, including non-IgE-mediated inflammatory responses, C-fibre stimulation, parasympathetic hyper-reactivity and/or sympathetic hyporeactivity, and glandular hyper-reactivity, might play a role in these patients.[13] However, it is not clear whether these mechanisms operate separately or in combination in the same patient, and whether these mechanisms may be caused by different aetiological entities.

Some attempts have been made to develop diagnostic tools for this condition. Assessment of skin reactivity to a variety of vasomotor agents, including Papaverine, Methacholine, Histamine and Compound 48/40, has demonstrated that the frequency of pathological skin reactivity to Papaverine, but not the other three agents, is significantly increased in patients with perennial non-allergic rhinitis, compared with healthy subjects.[14] This suggests that Papaverine-induced skin reactivity may be a useful diagnostic tool for non-allergic rhinitis. A dose–response study has shown that histamine-induced total nasal resistance follows a model exponential curve, suggesting that it may be possible to classify non-specific nasal hyper-reactivity in allergic and non-allergic subjects as a function of the regression b coefficient of the empirical equation used in reactivity classes.[15] Methacholine tests may be able to differentiate idiopathic rhinitis subjects from controls, but only in those suffering from rhinorrhoea as the main symptom. Recently, cold dry air (CDA) challenge has been suggested to differentiate best between controls and idiopathic rhinitis patients.[13] However, none of these tests is suitable to differentiate the non-allergic idiopathic from other forms of rhinitis, nor has any been demonstrated to be superior to a simple case history.

TYPES OF NON-ALLERGIC RHINITIS

Idiopathic rhinitis

Idiopathic rhinitis is characterized primarily by symptoms of nasal blockage, rhinorrhoea and sneezing, although the prevalence of sneezing, conjunctival symptoms and pruritis is lower than that in allergic rhinitis. Although the subjects have traditionally been classified as either 'runners' (those with predominantly rhinorrhoea) or 'blockers' (those with predominantly nasal congestion and blockage), many patients suffer from more than one type of these symptoms, therefore making it difficult to subdivide the patients into these groups. The aetiology is unknown in most cases and the disease is thought to be triggered mainly by irritants and changes in atmospheric conditions.[16] Among patients with chronic symptoms, the percentage with a non-allergic aetiology increases progressively with age and reaches >60% beyond the age of 50 years, therefore suggesting that functional abnormality in this condition may be associated with the ageing process in the nasal mucosa.[16]

Non-allergic occupational rhinitis

Occupational rhinitis, as the term implies, may be defined as rhinitis caused by exposure to airborne agents present in the work place. These agents elicit predominantly sneezing, nasal discharge and/or blockage and may act via

both immunologic (IgE-mediated) and non-immunologic mechanisms. The non-immunologic triggers are often irritant or toxic small molecular weight compounds such as aldehydes, isocyanates, aircraft fuel and jet stream exhaust, solvents, etc.,[1, 8, 17] or may be physical (long-term exposure to cold air). Whilst the specific mechanisms underlying the effects of these irritants and toxic agents have not been fully elucidated, it is possible that damage and/or stimulation of the epithelial cells and neurons by the irritants may lead to proinflammatory mediators and neuromediators, which may predispose the nasal mucosa to inflammation and infection, subsequently resulting in the symptoms of rhinitis. Indeed, a study investigating the effect of airborne exposure to the non-allergenic microbial agents endotoxin and beta(1,3)-glucan in compost workers has reported that concentrations of total cells (predominantly neutrophils), myeloperoxidase (MPO), IL-8, nitric oxide (NO) and albumin were significantly higher in compost workers than in controls.[18] Similarly, occupational exposure to vanadium pentoxide, a constituent of fuel oil ash and a known respiratory irritant, has been shown to significantly increase the number of polymorphonuclear cells in nasal lavage of boilermakers.[19]

HORMONAL RHINITIS

Hormonal rhinitis is often associated with pregnancy in particular, although puberty is also known to induce the symptoms of rhinitis.[1, 8] A large multicentre study has indicated that the cumulative incidence of pregnancy rhinitis was 22%, and in women who were smokers this was significantly increased with a relative risk enhancement of 69%.[20] Neither asthma nor rhinitis were, apparently, risk factors for pregnancy rhinitis. In contrast, only 2% of patients with non-allergic rhinitis may be afflicted by rhinitis due to hypothyroidism or acromegaly.[21]

Oestrogens cause vascular engorgement, not only in the female genital tract, but also in the nose, leading to nasal obstruction and/or nasal hypersecretion. Beta-oestradiol and progesterone have been shown to increase the expression of histamine H_1 receptors on human nasal epithelial cells and mucosal microvascular endothelial cells,[22] and to induce eosinophil migration and/or degranulation, in marked contrast to testosterone, which decreases eosinophil activation and viability.[23] Compared with pregnancy rhinitis, the evidence linking hypothyroidism with nasal pathology is sparse, and the reported increase in nasal secretion associated with thyroid disease is anecdotal.[1]

DRUG-INDUCED RHINITIS

Several commonly employed medications, such as aspirin, other non-steroidal antiinflammatory drugs (NSAIDs), beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, methyldopa, oral contraceptives, psychotropic agents and nasal topical decongestants (Oxymetazoline, Naphazoline, Xylometazoline) may induce symptoms of rhinitis when they are administered either topically or systemically. The symptoms may be either predictable, as would be the case for known side effects of particular drugs, or unpredictable, based on individual hypersensitivity to certain drugs, in particular aspirin, which commonly exacerbates rhinitis and asthma. However, intolerance to aspirin and/or NSAIDs predominantly produces rhinorrhoea, which may be either isolated or part of a complex involving hyperplastic rhinosinusitis, nasal polyps and asthma.[1] In contrast, intolerance to ACE inhibitors, methyldopa or oral contraceptives, which is less common than aspirin intolerance, leads predominantly to nasal blockage.[1] Whilst persistent overuse of the topical nasal vasoconstrictors also leads to nasal decongestion by a mechanism involving a rebound effect following withdrawal of these drugs, excessive use of these agents may also lead to nasal hyper-reactivity and hypertrophy of the nasal mucosa, a condition known as 'rhinitis medicamentosa'.[1, 8]

OTHER FORMS OF RHINITIS

NARES

The term NARES was originally introduced by Mullarkey and colleagues, who characterized the condition on the basis of a presence of greater than 20% eosinophils in nasal smears of symptomatic patients with perennial sneezing attacks, a profuse watery rhinorrhoea, nasal pruritis, incomplete nasal obstruction and occasional loss of smell.[1, 4, 7, 8] In addition to these symptoms, a marked feature of the disease is the lack of evidence of allergy, as indicated by negative skin prick tests and/or absence of serum IgE antibodies to specific allergens.

The prevalence of NARES has been shown to range between 13 and 33% in patients with non-allergic rhinitis.[21, 24] Although the specific aetiology of NARES is not clear, in view of the features shared by this syndrome and the triad (nasal polyposis, intrinsic asthma and intolerance to aspirin) and because NARES patients frequently develop nasal polyps and asthma later on in life, it has been suggested that NARES may be an early expression of the triad.[24] Indeed, in approximately 50% of NARES patients without a history of respiratory symptoms, bronchial responsiveness is associated with an increase in the number of sputum eosinophils, but not with an increase in the number of nasal eosinophils.[25] Some investigators have suggested that NARES is a variant of vasomotor rhinitis, and referred to the condition as 'perennial intrinsic rhinitis'.

Rhinitis due to physical and chemical factors

Nasal symptoms similar to those of rhinitis can be induced by physical and chemical factors in individuals with sensitized nasal mucous membranes.[2] Cold, dry air has been shown to lead to a condition known as skier's nose, in which rhinorrhoea features prominently. Exposure to chemicals, particularly air pollutants derived from cigarette smoke and liquid petroleum fuels, have also been

shown to directly exacerbate symptoms of rhinitis in non-allergic individuals,[2] although their effects have generally been extensively investigated and well documented in the lower airways of allergic individuals.[26] Little information is available on the acute or chronic effects of air pollutants on the nasal mucosa.

Food-induced rhinitis

Few studies have documented that certain foods and alcoholic beverages can induce non-allergic rhinitis, although the underlying mechanisms are largely unknown. Hot and spicy foods, in particular, which contain capsaicin, lead to a watery rhinorrhoea termed 'gustatory rhinitis', probably as a result of the capsaicin stimulating the sensory nerves to release neuropeptides and tachykinins.[1, 2] In contrast, alcoholic beverages are thought to induce symptoms as a result of vasodilation. Dyes and preservatives, as well as sulphites, appear to play a role in a very few cases, whereas some foods may contain clinically relevant concentrations of histamine or other biogenic amines.

Emotionally induced rhinitis

Although not studied extensively, emotional factors such as stress and sexual arousal have been documented to affect the nose, likely as a result of autonomic stimulation.[2, 27] In patients suffering from post-coital rhinitis, anxiety appears to be a predominant feature, which leads to worsening of their disease.[27]

Atrophic rhinitis

Primary atrophic rhinitis is a condition that occurs predominantly in women and is characterized by progressive atrophy of the nasal mucosa and underlying bone of the turbinates.[1, 2] This leads to the formation of thick crusts, which leave a constant foul smell (ozaena) in the nose.[1, 2] Furthermore, the nasal cavities are enlarged and there is the sensation of nasal congestion. Although the precise aetiology of this condition is not clear, it has been suggested that this may be a result of infection with *Klebsiella ozaenae* and other bacteria. However, primary atrophic rhinitis is distinct from secondary atrophic rhinitis, which develops directly as a result of granulomatous nasal infections, chronic rhinosinusitis, excessive nasal surgery, trauma and irradiation.

Differential diagnosis

Allergic rhinitis is the major disease to differentiate from non-allergic rhinitis and may be excluded by appropriate allergy tests. However, the possibility of a local IgE production within the nasal mucosa may account for some cases where skin prick tests or IgE antibodies to common allergens are not positive. Several other conditions, including polyps, sinusitis, congenital and acquired anatomical abnormalities (e.g. nasal septal deviation, adenoid hypertrophy, hypertrophy of nasal turbinates, choanal atresia), benign and malignant tumours, granulomas, ciliary defects and cerebrospinal rhinorrhoea,[1, 2] are known to mimic symptoms of non-allergic non-infectious rhinitis and therefore have to be excluded by careful examination in order to make the correct diagnosis. Anatomical nasal abnormalities block the flow of nasal secretions and lead to rhinorrhoea, post-nasal drip and nasal blockage. In children, congenital choanal atresia can lead to reduced nasal airflow, resulting in nasal blockage. Tumours are not very common in the nasal passages, but when established and growing rapidly they often lead to unilateral nasal obstruction, bleeding and pain. Rhinorrhoea and nasal congestion, in the absence of pruritis, are also characteristic features of nasal mastocytosis, an extremely rare condition, in which eosinophils are absent and tests for IgE-mediated disease are negative.

Diagnosis as a step-wise approach

In daily clinical practice, the diagnosis of non-allergic rhinitis and its subgroups is mainly based on a thorough case history, followed by the step-wise exclusion of possible differential diagnoses, as follows.

If the case history is suggestive of clinically relevant non-infectious rhinitis:

- check possible stimuli, severity and duration of disease;
- check drug use (systemic and topical), exposure at work place, hormonal status (pregnancy, hypothyroidism, acromegaly) and involvement of other organs (asthma, hormonal status);
- exclude other nasal disease (rigid nasal endoscopy);
- exclude allergy: skin prick test, serum IgE-antibodies to the most frequent inhalant allergens, and ultimately nasal provocation testing in selected cases;
- exclude chronic rhinosinusitis (nasoendoscopy +/– computed tomography (CT) scan);
- perform nasal cytology (eosinophilia), and if shown to be positive then perform oral Aspirin challenge.

Therapy for non-allergic perennial rhinitis

First, an evaluation of the severity of the disease should be performed to confirm the need for therapy, in connection with counselling on how to avoid non-specific stimuli. In case of drug-induced, food-induced or occupational rhinitis, specific avoidance measures are employed as first-line therapy.

Several treatments (pharmaceutical, non-conventional and surgery) have been employed for idiopathic non-allergic rhinitis.[28] Intra-nasal anticholinergics (Ipratropium Bromide) may be useful in patients with nasal secretion as the predominant symptom, whereas nasal decongestants should be avoided or limited to 10 days. Topical steroids and antihistamines are the two main classes of drugs employed, of which only Fluticasone Propionate, Budesonide, Beclomethasone and Azelastine, respectively, have been approved by the Food and Drug Administration (FDA). Azelastine nasal spray has been

found to be more effective than placebo for control of rhinorrhoea, post-nasal drip, sneezing and nasal congestion in most patients, although its effect on nasal congestion was rather marginal.[29] The efficacy of intra-nasal steroids in patients with vasomotor rhinitis has been inconsistent. Furthermore, whilst the topical nasal steroids are more frequently used for treatment of more severe symptoms, they are mostly useful in patients in whom an inflammatory pathogenesis is a prominent feature of their disease, for example NARES. Recent evidence suggests that in patients who do not respond to treatment with nasal steroids, treatment with non-conventional therapies such as silver nitrate, botulin toxin and particularly intra-nasal capsaicin may be beneficial. Studies in patients suffering from NANIPER have demonstrated that intra-nasal capsaicin leads to a significant and long-term reduction in clinical VAS scores, compared with placebo.[10] In another study, treatment once daily for 5 weeks with intranasal capsaicin was also shown to significantly improve all symptoms and produce a larger vascular response throughout a 6-month follow-up period in patients suffering from severe chronic non-allergic rhinitis with nasal vasoconstrictor abuse.[30] In cases where nasal obstruction is resistant to medical treatment and if the inferior turbinate is hyperplastic, surgical intervention to reduce the size of the turbinate by various procedures has been shown to be useful. Endoscopic transnasal vidian neurectomies have also been performed by excision, diathermy and cryotherapy, and have produced results with varying degrees and duration of success.[31–33]

Recent interest in intranasal capsaicin prompted a Cochrane Review that included 302 patients with idiopathic non-allergic rhinitis.[34] Whilst the quality was judged to be low to moderate there was sufficient evidence that capsaicin was superior to both placebo and Budesonide. Studies were of variable follow-up ranging from 4 to 38 weeks. Given the limited treatment options for non-allergic rhinitis and good safety profile[35] Capsaicin represents a reasonable therapeutic choice.

Small scale non-powered studies have shown therapeutic potential for intra-nasal Botulinum toxin for non-allergic rhinitis.[36–38] Symptoms of nasal obstruction, discharge, sneezing and itching all improved, though the duration of improvement was limited to 2–3 months.

CONCLUSION

Despite increasing evidence for the various forms of non-allergic rhinitis, many of these conditions are often underrated and trivialized, primarily due to the paucity of information on the causative factors, the underlying mechanisms and/or the absence of specific diagnostic tests. Furthermore, there are differences in opinion amongst clinicians and researchers regarding classification of disease and in conditions such as occupational rhinitis, in particular, the situation is further compounded as a consequence of legal and financial compensatory implications, for both employers and employees alike. To date, no specific diagnostic test is available, and clinical diagnosis is based on case history and exclusion of other disease. Despite these difficulties, however, recent evidence suggests that relevant diagnostic tools and specific information regarding the mechanisms underlying some of these conditions is more forthcoming and should therefore lead to a better overall understanding and management of these conditions in the future.

BEST CLINICAL PRACTICE

- ✓ Wherever possible, the treatment should take into account the aforementioned subgroups of non-allergic perennial rhinitis.
- ✓ In idiopathic rhinitis, antihistamines and topical steroids are the two main classes of drugs for treatment. Topical steroids are to be preferred if an inflammatory pathogenesis is suggested.
- ✓ Intra-nasal capsaicin is supported by a better evidence base than intra-nasal Botulinum toxin but both treatments remain outside widespread clinical use.
- ✓ Surgery is an option in patients with persistent nasal obstruction not improved by medication.

FUTURE RESEARCH

- ➤ There is a marked lack of diagnostic tools/procedures for determining each type of these conditions.
- ➤ There is a marked lack of controlled trials for determining diagnosis.
- ➤ Epidemiological studies on prevalence of different types of non-allergic rhinitis are required.
- ➤ Research on mechanisms underlying these conditions is needed.

KEY POINTS

- Approximately half of rhinitis patients may suffer from non-allergic rhinitis.
- There are no specific diagnostic tests for non-allergic rhinitis.
- A thorough case history is the best diagnostic tool available and should focus on drug intake, work exposure and hormonal status to subdivide the condition into subgroups.
- As the symptoms are quite non-specific, the differential diagnoses have to be excluded.

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CHAPTER 93

OCCUPATIONAL RHINITIS

Hesham Saleh

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search and an Embase search using the key words: rhinitis, occupational rhinitis, rhinitis and occupation, air pollutants and occupational, occupational disease, occupational accident, occupational allergy, occupational exposure, occupational hazard, occupational health, occupational medicine, occupational safety, work environment, industrial medicine, industry, industry and industrial phenomena, work and disability.

INTRODUCTION

Occupational rhinitis (OR) is an inflammatory disease of the nose, which is characterized by intermittent or persistent symptoms (i.e. nasal congestion, sneezing, rhinorrhoea, itching), and/or variable nasal airflow limitation and/or hypersecretion arising out of causes and conditions attributable to a particular work environment and not to stimuli encountered outside the workplace.[1] Symptoms usually manifest in weekdays and abate during weekends and holidays. When exposure has been prolonged the condition may become irreversible and symptoms persist.[2, 3] OR frequently coexists with asthma and conjunctivitis, and it has been documented that occupational rhinitis precedes the development of occupational asthma especially when high molecular weight compounds (HMW) are involved (see below).[1, 3, 4] Occupational rhinitis is commoner than occupational asthma and most reports show that it tends to occur two to four times more frequently. [1, 3, 5]

The prevalence of occupational rhinitis is unknown. Studies have dealt primarily with occupational asthma with less work on rhinitis. It has been estimated that 2–5% of all patients with asthma in the United States have work-induced asthma.[1] It is possible that the incidence of occupational rhinitis is underestimated due to failure to diagnose and because, unlike asthma, it is not a life-threatening condition. Workers may be reluctant to report symptoms for this reason as well as for fear of job loss, loss of seniority, or fear of repercussions from co-workers.[1] A variety of cross-sectional studies of populations from diverse occupations exist but, because of the different methodologies used, interpretation of data is difficult. Furthermore, data from epidemiological studies are lacking. Information from the Finnish Institute of Health showed that 20% of all cases of rhinitis were occupational in origin.[7] The same study also showed that the number of cases more than doubled between 1987 and 1991. Another study, utilizing the Finnish Register, showed that the incidence of occupational rhinitis is higher in men than women (60% and 40% respectively). Also a gender difference exists for the age at which occupational rhinitis develops. Men have the highest incidence at the age range of 25–29 years, after which the incidence gradually declines. In women, the incidence of occupational rhinitis gradually increases and peaks between 40 and 44 years of age.[4] It has been suggested that this difference is related to the fact that men and women are engaged in different jobs and hence exposed to different kinds of causative agents.[8]

More than 200 chemicals and organic dusts have been implicated as a cause of occupational rhinitis and asthma.[1] The pathological effects of these are either due to an allergic reaction or irritation of the nasal mucosa. Well-documented causative agents include laboratory animals

such as rats, mice and guinea pigs, grains (bakers), storage mite (agricultural workers), wood dust, particularly hard wood such as western red cedar (furniture manufacturers), guar gum (workers in the food processing and carpet industry), *Bacillus subtilis* enzymes (detergent manufacturing workers), persulphate salts (hairdressers), latex and chemicals such as acid anhydrides, isocyanates, platinum salts, glues and solvents.[1, 3, 6] Symptoms may develop after a latency period of 2 months to 18 years in the case of allergic occupational rhinitis.[1, 6] This observation does not apply to irritant occupational rhinitis which can develop on immediate exposure.

RISK FACTORS

Risk factors for developing occupational rhinitis include exposure (intensity and duration), atopy and smoking.[6] Most reports on exposure have focused on intensity, and associations have been confirmed in laboratory animal workers, wool textile mill workers and bakery workers amongst others.[3] Duration of exposure has seldom been studied. Other studies have shown an association between atopy and specific sensitization to high molecular weight agents in grain elevators, fish and seafood workers, bakers, workers exposed to latex, coffee and others. Although smoking is known to induce the release of inflammatory mediators and to cause mucosal changes, its impact on occupational rhinitis is yet to be shown. The current evidence on this matter is still inconclusive as some studies show higher risk of occupational rhinitis in smokers and some do not.[3, 6, 9]

PATHOGENESIS

The nose is the first portal of entry to the respiratory tract and is exposed to a constant stream of air. Materials that accompany the air stream tend to impact on the mucus surface as a function of their aerodynamic equivalent diameter (AED).[10] Approximately 80% of those that have an AED of more than 9 µm, 50% of those with 2–9 µm AED and 40% of material with less than 2 µm stick to the nasal wall. Highly soluble materials such as ammonia, sulphur dioxide, and formaldehyde also deposit in the upper airway. Smaller particles and less water-soluble gases generally pass to the lower airways.[8] According to the nature of the offending agent, occupational rhinitis may be allergic or irritant.

Allergic occupational rhinitis

Allergic occupational particles may trigger an IgE-mediated (Type 1) immune response. A late-phase response may also develop 4–6 hours after the initial reaction.[8] The causative agents are classified into high molecular weight compounds (HMWC), such as animal and vegetable proteins, and low molecular weight compounds (LMWC), such as isocyanates and anhydrides. IgE dependant mechanisms, that can be assessed through skin prick test and specific IgE levels have been demonstrated with most high molecular weight compounds (HMWC).[3, 8] Low molecular weight compounds (LMWC) can also produce specific IgE antibodies by acting as a hapten to form hapten-protein conjugate. However, an IgE-mediated mechanism has been elicited only rarely with LMWC. **Table 93.1** shows a number of HMWC and **Table 93.2** shows LMWC implicated in allergic occupational rhinitis with the related occupations.[1, 3, 6]

Irritant occupational rhinitis

Non-allergic, irritant chemicals may trigger the release of substance P and other inflammatory mediators from sensory C-fibres after binding to chemoreceptors on their surface.[11, 12] This sequence, known as neurogenic inflammation, leads to vasodilatation, oedema, and other manifestations of inflammation. The patients complain of burning, stinging or painful sensation in the nasal passages in addition to nasal congestion and rhinorrhoea.[1] Delayed response does not occur in cases of irritant rhinitis.[8] Existing evidence shows the release of substance P in the nose with exposures to nicotine, capsaicin, ether, and formaldehyde. Chronic irritant rhinitis requires protracted exposure to one or more irritating chemicals. However, in reactive upper airways dysfunction syndrome (RUDS) rhinitis results from an acute exposure to high concentrations of a respiratory irritant, and persists after the exposure.[12] **Table 93.3** shows a number of agents implicated in irritant occupational rhinitis with the related occupations.[1, 6]

Corrosive reactions may also occur due to excessive concentrations of irritating and soluble chemical gases. Substances implicated in causing corrosion are ammonia, hypochloric acid, vinyl chloride, organic sulphur containing compounds, acrylamide, cyanide, nitriles and organophosphoside compounds.[1] Disorders of olfaction may occur a result of rhinitis or as a direct effect of irritants on the olfactory receptors and their central connections.[13] Anosmia and hyposmia have been reported after single high-dose exposure to sulphuric acid, hydrogen selenide, phosphorus oxychloride and a mixture of pepper and cresol.[8] Other case reports of olfactory disorders present workers chronically exposed to low levels of chemicals such as benzene, benzol, cadmium, carbon disulphide, ethyl acetate, formaldehyde, hydrazine, menthol, solvents, and oil of peppermint.[8, 14] However, olfactory disorders in occupational rhinitis are otherwise under-investigated.

Similar to other patients with allergic and non-allergic rhinitis, patients with occupational rhinitis may manifest nasal hyperreactivity to non-specific environmental agents such as changes in temperature and humidity, exposure to tobacco smoke and strong odours.[1] The prevalence of this entity is, however, unknown.

HIGH RISK OCCUPATIONS

Data from the Finnish Register of Occupational Diseases identified furriers, who are exposed to different kinds of animal epithelium, as the highest risk group for developing occupational rhinitis. Livestock breeders and bakers were the occupations following in rank.[4] Other commonly

TABLE 93.1 High molecular weight compounds (HMWC) causing allergic occupational rhinitis

High molecular weight compounds	Occupation
Animal proteins (rats, mice, guinea pigs, rabbits, hamsters)	Laboratory animal workers, pet shop owners, veterinarians, farmers
Other animal derived allergens (pig)	Swine confinement workers
Grain dust	Grain elevators
Flour, alpha amylase	Bakery workers
Bacillus subtilis	Detergent workers
Enzymes (papain, trypsin, pancreatic extracts, lactase)	Pharmaceuticals
Wool	Wool textile workers
Insects (locust, fruit fly)	Laboratory workers
Arthropods	Laboratory workers
Mites (storage, red spider)	Bakers, farmers, grain elevators, food processors
Mould spores	Librarians
Latex	Healthcare workers
Guar gum/vegetable gum	Food processors, carpet workers, printing
Green coffee bean	Coffee production
Tea	Tea workers
Dried fruits	Dried fruit workers
Tobacco leaf	Tobacco workers
Cayenne peppers	Hot pepper workers
Pollens	Gardeners, greenhouse workers
Sunflower pollen	Bakers, agricultural workers
Soybean dust	Farmers, food processors
Saffron flower	Saffron workers
Cocoa	Packers
Garlic	Food workers
Milk proteins (alpha Lactalbumin, casein)	Chocolate manufacturing, tannery
Fish, prawn, crab	Food processors
Bird proteins	Poultry breeders, farmers
Raw poultry	Food processors
Cow dander	Dairy farms

TABLE 93.2 Low molecular weight compounds (LMWC) causing allergic occupational rhinitis

Low molecular weight compounds	Occupation
Diisocyanates (toluene diisocyanates, diphenyl-methan diisocyanates)	Painters, urethane mould workers
Anhydrides (trimellitic anhydride, methyl tetrahydrophtalic anhydride, pyrotomellitic anhydride)	Epoxy resin production, plastics, electric condenser workers, chemical workers
Wood dust (western red cedar, several other woods	Furniture making, carpentry
Colophony	Electronics, welders
Metals (platinum, nickel, chromium)	Platinum refinery, metal processing or plating
Drugs (psyllium, senna, spiramycin)	Healthcare workers, bulk laxatives factory workers, pharmaceuticals
Chemicals (reactive dyes, carmine, polyamide, polyester, para-amide)	Reactive dye product producers, synthetic fibre workers
Cotton	Farmers, cotton mill workers
Persulphates	Persulphage product manufacturers, hairdressers
Solvents and organic dust	Shoe manufacturing
Azo dyes	Textile dying
Chlorine	Pulp and paper production

TABLE 93.3 Causative agents of irritant occupational rhinitis

Irritant substance	Occupation
Ammonia, nitrogen dioxide, hydrogen sulphide	Agricultural workers
Smoke	Firefighters
Cooking vapour	Food service workers
Glutaraldehyde, formaldehyde	Healthcare workers
Inorganic acid vapours	Laboratory workers
Sulphur dioxide	Power plant, oil refinery workers
Solvent vapours	Printers, painters
Zinc chloride smoke	Military personnel
Chloride, chlorine dioxide, hydrogen sulphide	Pulp mill workers
Oxides of nitrogen, ozone, diesel exhaust	Traffic wardens, lorry drivers, railroad workers
Asphalt vapours, polycyclic aromatic hydrocarbons	Roofers, pavers
Metallic oxide fumes	Welders
Talc	Pharmaceutical workers, cosmetic manufacturers

reported occupations include farmers, food-processing workers, wood workers, detergents manufacturers, animal laboratory workers, hairdressers and healthcare workers.

Bakers

A large number of cross-sectional studies show that work-related symptoms of rhinitis and sensitization are common among bakery workers. Work-related rhinitis has been shown in 18% to 29% of workers and specific sensitization in 10% to 38%.[3] The offending agents are wheat and cereal flours, cereal amylases, fungal amylases, storage mites contaminating wheat flour and others such as baking additives.

Farmers

The prevalence of occupational rhinitis in farmers is unknown. However, a variety of agricultural exposures have been associated with rhinitis. These include grain farming and handling, livestock breeding, feed manufacture and handling, dairy farming, tea farming, cotton, flax, and hemp processing and organophosphorous pesticides.[15] Storage mites, present in storage hay have been described as a cause of barn allergy. A number of reports on grain elevator workers showed prevalence of sensitization in 9% to 28%.[3]

Food processing workers

It has been suggested that the food industry accounts for the largest number of cases of occupational rhinitis.[3] Cases of occupational rhinitis due to guar gum are well documented. It is obtained from the seeds of the tree *Cyamopsis tetragonoloba*, and used as a food additive as well as a laxative and a colour fixing agent in the carpet industry. The prevalence of symptoms in workers is, however, less well documented. Symptoms related to other plant-related allergens such as soybean, coffee bean, garlic, cinnamon and hot peppers have also been reported.[1] Occupational rhinitis has also been correlated to fish and seafood proteins. Prevalence of symptoms of 5% to 25% in fish factory workers has been reported.[3]

Wood manufacturers

Hard woods, often of tropical origin, are well-known factors in causing work-related symptoms. Plicatic acid, found in western red cedar, has been suggested as the causative agent of rhinitis in carpenters and furniture manufacturing workers.[3, 16] Symptom prevalence figures are less well documented. Oak, beech and pine have also been implicated.[16] Soft woods, used in joiner shops, have been less reported than hard woods in relation to rhinitis.[16]

Detergent manufacturers

Biological enzymes are used extensively in the detergent industry as well as pharmaceutical and food industries. *Bacillus subtilis* enzymes and lactase have been commonly implicated in occupational rhinitis.[1, 3, 6] Prevalence rates of occupational rhinitis from 7% to 16% have been reported in workers. Specific sensitization ranged from 22% to 52%.[3]

Animal laboratory workers

Laboratory workers are one of the groups most commonly affected with occupational rhinitis.[1] It has been suggested that proteins from virtually any mammalian species may induce an allergic response in human beings.[1] Rats are the most commonly implicated but mice, guinea pigs, rabbits and hamsters are also known to cause occupational rhinitis.[1, 3] Immunological substances implicated include saliva, urine, dander and serum. Previous reports demonstrate symptom prevalence of 10% to 33% and specific

IgE antibodies to animal protein in 6% to 46% of workers. Recent evidence suggests a trend towards a progressive decline in the prevalence, which may be due to the reduction of exposure since the early 1980s.[3, 17]

Healthcare workers

Concern has been raised about latex allergy in healthcare workers and patients due to the extensive use of latex gloves. Rubber latex is a naturally occurring cytoplasmic exudate obtained from the tree *Hevea brasiliensis*.[18] It is used extensively in the manufacture of surgical gloves and other medical devices (drains, bag and valve masks, mouth gags and bandages are some examples).[19] Aerosolized particles of latex proteins are carried in the cornstarch used to powder the gloves and may remain airborne for hours.[19, 20] Significant quantities of airborne latex have been measured in areas using powdered latex gloves.[20] These proteins have been implicated in causing rhinitis, asthma and anaphylaxis.[18–20] Exposed personnel may also develop contact dermatitis as a reaction to the chemical accelerators and preservatives that are added to latex to improve its physical property.[19] Anaphylaxis most often affects patients during open surgery due to mucosal absorption, and has been reported in those who have had multiple surgical procedures and in patients with spina bifida.[18] However, anaphylactic reactions were also reported during gloving and inhaling latex in the workplace.[18] Healthcare workers with regular latex exposure have been reported to have symptom prevalence rates of 3% to 17%.[21] Specific skin tests have been shown to be positive in 5% to 20% in contrast to prevalence in the general population of less than 1%.[18]

Other substances that may cause occupational rhinitis in healthcare workers include formaldehyde and drugs such as psyllium, senna and spiramycin.[3] Formaldehyde is also used widely in industry in addition to its use as a sterilizing agent in medicine. It is toxic at high doses and can induce irritant reaction. It is also been suggested that it can act as a hapten and cause an IgE mediated reaction.[22]

Other occupations

Workers reported to have occupational rhinitis in other occupations have been referred to in **Tables 93.1–93.3**.

EFFECTS OF AIR POLLUTION

In the first half of the 20th century dramatic episodes of severe pollution, caused by sulphur dioxide (SO_2) derived from coal combustion, occurred in the Western world. Regulations to decrease the use of coal in homes and industry were set and other fuels like petrol and gas substituted coal. The by-products of petrol consumption in transport and industry, however, have replaced the decline of coal-associated pollution. Exhaust fumes consist of oxides of nitrogen, namely nitric oxide (NO) and nitric dioxide (NO_2), ozone (O_3), particulate matter (PM) and volatile organic compounds (VOCs).[23] Much of the research done on pollution has been on its effects on the lower airway. However, epidemiological studies suggest an association between pollution and rhinitis.[9] Laboratory studies have shown that exposures to NOx, O_3 and diesel exhaust particles result in the release of inflammatory mediators in the nasal mucosa.[24] A link between high levels of environmental pollutants and increased prevalence of allergy has also been suggested.[9] Whether this would have an impact on allergic occupational rhinitis remains to be examined.

Certain occupations such as traffic wardens, railroad workers and lorry drivers may be exposed to high levels of pollution that result in high prevalence of symptoms of rhinitis.[25]

SICK BUILDING SYNDROME

Sick building syndrome (SBS) is described as the high prevalence of eye, nose and throat irritation, fatigue and headache among office workers temporally associated with time at work and characterized by an absence of abnormal physical findings and laboratory results.[8] It is a diagnosis of exclusion as multiple causative agents have been implicated. More than 300 volatile organic compounds (VOCs) were identified as indoor pollutants causing SBS. They originate from building materials, combustion fumes, cleaning compounds, paints and stains in addition to tobacco smoke. It has been suggested that workers in buildings with mechanical ventilation and air conditioning have a higher risk of SBS symptoms than workers in naturally ventilated buildings.[26, 27]

DIAGNOSIS

Diagnosing occupational rhinitis can be difficult. A combination of history, examination and investigation will aid the diagnosis. Nasal provocation test (NPT) with the suspected agent is particularly central to secure the diagnosis.

History

The patients present with a variable number of symptoms including nasal obstruction, anterior rhinorrhoea, postnasal discharge, crusting, disturbed sense of smell and taste and epistaxis.[2] A detailed history of the patient's complaint in addition to occupational history is essential to aid the diagnosis. Development of symptoms during the working week with improvement at weekends and holidays provide the clue for diagnosis. However, history in itself is not sufficient for diagnosis and could be feigned by workers claiming compensation. The history can be further compounded by the presence of symptoms of rhinitis due to atopy in allergic patients. In patients with protracted exposure, the symptoms may continue during absence from work further complicating matters.[1] The difference in presentation between allergic and irritant occupational rhinitis should be also borne in mind. In allergic patients, rhinitis may take longer to develop

and may be manifested by a delayed response a few hours after exposure. On the other hand, patients with irritant rhinitis may develop the symptoms instantly on exposure and do not have a delayed response.[1] A history of eye, throat, skin and chest symptoms should be elicited. It is important to enquire about smoking and drug history including over-the-counter decongestants, substance abuse and other drugs known to cause nasal symptoms such as aspirin, alpha-blockers, beta-blockers, antidepressants and ACE inhibitors. Enquiries should be made on history of atopy in the patient and first-degree relatives.[1, 2] An enquiry about problems of the sense of smell and taste should also be made.

A detailed occupational history includes the patient's account of a typical working day, the nature of chemicals, duration and intensity of daily exposure and use of protective masks.[8] A substance information sheet or an engineer's report may also be required particularly in medico-legal cases. Other work factors such as type and efficiency of ventilation, history of accidents and spills, and effects on co-workers should also be considered.[2, 6] A site visit has been recommended if the history of work conditions is unhelpful.[1]

Examination

The physical findings in occupational rhinitis are non-specific. Nasal examination should include description of mucosal changes, nature of secretions, crusting, epistaxis, ulceration and perforation. These are particularly important in medico-legal cases.[1] Crusting and epistaxis are commoner in irritant rhinitis. Eye inspection for conjunctivitis and oral cavity/oropharynx examination for ulceration should also be done. Chest examination for signs of asthma is important as well as inspection for dermatitis, which occurs in latex allergy.

Investigations

The skin prick test is useful in allergic occupational rhinitis for most HMW and some LMW agents. It is also be helpful in diagnosing suspected atopy. However, sensitization to an occupational agent is not sufficient to diagnose occupational rhinitis, because it only indicates an immunological response and not necessarily a clinical syndrome.[3] Skin prick tests have been used extensively in cross-sectional studies to assess sensitization to a specific agent. Sensitivity and specificity have been evaluated with differing results.[3] Measuring serum specific IgE has also been used in a number of studies. The sensitivity and specificity is probably less than that of the skin prick test but a combination of both tests may enhance sensitivity and specificity.[1]

A secure diagnosis cannot be made without a nasal provocation test (NPT).[1, 6] This is more conclusive when performed in controlled conditions in the laboratory with known agents. Carefully graded exposure to increasing doses of the suspected agent in specialized ventilated environmental chambers is the best method. Difficulties arise when dealing with unknown or multiple agents.[3] On these occasions a workplace provocation test may be an option.[1, 3] Unfortunately, no standardized method for nasal provocation is yet recommended and the test is time consuming. The test must be accompanied by an objective measure of the nasal response such as acoustic rhinometry or rhinomanometry.[4, 28] Nasal inspiratory flow rate measurement (NIPF) is also useful with nasal provocation. It can be also be used by the patient to measure fluctuations of the nasal airway during the working week.[3] Other measures such as collecting nasal lavage for analysis of cells and inflammatory markers and brush biopsies have been used with nasal provocation. They are generally more suitable for research situations and have been used extensively in various trials.[3] Exhaled nitric oxide measurement has also been used in clinical trials but not in routine clinical practice.[29]

When an olfactory disorder is suspected and in medico-legal cases, olfaction should be tested using one of the commercially available tests such the University of Pennsylvania Smell Identification Test (UPSIT).[2]

MANAGEMENT

The best management approach for occupational rhinitis is prevention. In established cases avoidance methods should be instituted and medical therapy may be tried. Immunotherapy may have a part to play in treating severe cases of allergic occupational rhinitis.

Prevention

Primary prevention in the workplace may be effective and should always be considered.[1] Environmental control measures are undertaken by recognizing potentially sensitizing allergens and controlling the point source of any mucosal irritant. Enclosing previously open operations and automating hand operations should be considered. Masks, gloves and protective clothing should be used and ventilation improved.[1, 6] It has been suggested that applicants for high-risk jobs should be screened for atopy by history taking and skin prick test. However, this has not been shown to be efficient, particularly when the marker of susceptibility (e.g. atopy) is prevalent in the general population.[1]

In workers with established diagnosis certain avoidance measures may be effective. For example, laboratory workers who become sensitive to rats generally react to rat urinary protein rather than epithelium. It has been suggested that it may be possible for them to perform surgery on rats, if the cage containing the rats – which is soaked with urine – is kept out of the laboratory. In healthcare workers sensitive to latex the use of powder-free gloves by all co-workers has been shown to reduce symptoms and allow allergic patients to continue their work.[18] Non-latex gloves are available and may be used as an alternative for sensitive individuals. In some occupations where preventive measures are ineffective, relocation of the worker or even changing jobs may be recommended.

Medical therapy

Medical therapy of occupational rhinitis is similar to that of non-occupational allergic rhinitis and should be instituted according to evidence-based guidelines.[30] Antihistamines, sodium cromoglycate, topical corticosteroids, anticholinergic spray and saline douches have all been used.[1, 6] Systemic steroids have also been suggested in severe cases. Treatment may be most effective in allergic occupational rhinitis.[1] However, no studies on the efficacy of these medications in occupational rhinitis are available at present. The choice of agent is often based on trial and error according to efficacy and frequency of side effects. Sedating antihistamines affect work productivity adversely and second-generation antihistamines are preferred. Patients may use them regularly when they have chronic symptoms or periodically before an expected exposure to an allergen.[1]

Immunotherapy

Studies have reported some improvement in symptoms during immunotherapy with purified rodent proteins, wheat flour extracts, and natural rubber latex.[31] Fear of severe reactions with continued exposure to the offending antigen at the same time of the administration of immunotherapy have precluded its use.[1] Furthermore, many of the offending antigens are not available for treatment. However, where alternative jobs are not a consideration, the risks of treatment should be balanced against the benefits.[1]

FUTURE RESEARCH

- Epidemiological studies are required to detect incidence and prevalence in various populations.
- Longitudinal studies should be conducted to document the natural history of the condition.
- The impact of occupational rhinitis on the quality of life of affected workers needs to be studied.
- Characterization of the clinical features and pathophysiology of non-allergic occupational rhinitis.
- More studies of the role of atopy and smoking in the development of occupational rhinitis are needed.
- The agreed diagnostic test, nasal provocation, should be standardized and other tests such as exhaled nitric oxide measurements should be further investigated.
- Randomized controlled trials should be designed to identify the best possible therapy.

KEY POINTS

- The prevalence of occupational rhinitis in the general population is still unknown.
- Occupational rhinitis is either allergic or irritant.
- Occupational rhinitis frequently coexists with asthma and conjunctivitis.
- Exposure, atopy and smoking are risk factors.
- History of work-related symptoms with improvement in weekends and holidays is typical.
- Nasal provocation is the main diagnostic test.
- Prevention is the best approach.
- Medical therapy is similar to that for other types of rhinitis.

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CHAPTER 94

RHINOSINUSITIS: DEFINITIONS, CLASSIFICATION AND DIAGNOSIS

Carl Philpott

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: rhinosinusitis, rhinitis, sinusitis, classification and differential diagnosis and by reference to the European position paper on rhinosinusitis and nasal polyps.

RHINOSINUSITIS AND RHINITIS DEFINITIONS

The European position paper on rhinosinusitis and nasal polyps (EPOS) has now defined rhinosinusitis as a diagnosis made on clinical grounds based on the presence of characteristic symptoms, combined with objective evidence of mucosal inflammation (Table 94.1).[1]

This has been widely accepted internationally, although alternative classifications and guidelines have been produced, such as by the American Academy of Otorhinolaryngologists/Head & Neck Surgeons (AAOHNSF) Rhinosinusitis Task Force Committee.[2] The most recent international guidelines have supported the EPOS definition, confirming the need for objective evidence to confirm the symptom profile (ICORS).[3] The defining symptoms and signs listed in the EPOS 2012 document apply to both adults and children and can be further qualified in terms of severity by use of a visual analogue score for the question 'how troublesome are your symptoms of rhinosinusitis?' (**Table 94.2**). In practice, the severity is often defined by individual responses on Patient Reported Outcome Measures (PROMs) such as the SNOT-22 with recent consensus statements considering minimum scores for surgical candidates.[4]

Rhinosinusitis can then be further defined as acute or chronic based on duration of symptoms: acute being less than 12 weeks duration and chronic being greater.[1,5] Within acute rhinosinusitis (ARS), further distinctions can be made on a timeline basis such that a common cold

TABLE 94.1 Clinical definition of rhinosinusitis[1]

Diagnostic criteria for rhinosinusitis	Symptoms should be correlated by either endoscopic and/or radiological findings
Primary symptoms (requires at least one to be present, but if both present it is sufficient to make diagnosis on the basis of symptoms)	Nasal blockage/obstruction/congestion Nasal discharge (anterior/posterior)
Additional symptoms (may also be present and at least one is needed if only one of the primary symptoms is present)	Facial pain/pressure Olfactory dysfunction Hyposmia/anosmia
Duration	>10 days, <3 months = acute >3 months = chronic
Endoscopy (*any of these*)	Nasal polyps Mucopurulent discharge (middle meatus) Oedema/mucosal obstruction in middle meatus
CT scan findings (*as well as or instead of* endoscopic *findings*)	Mucosal changes within the ostiomeatal complex and/or sinuses

TABLE 92.2 Visual Analogue Scores (VAS) for rhinosinusitis symptoms[3]

Severity	VAS scale (10 cm line)
Mild	0il
Moderate	4od
Severe	8eve

BOX 94.1 Additional symptoms or signs for acute bacterial rhinosinusitis[1]

At least three of the following should be present:

- Discoloured discharge (unilateral predominance)
- Severe local pain (unilateral predominance)
- Fever (>38°C)
- Elevated ESR/CRP
- 'Double-sickening' – deterioration after initial milder phase of illness

(acute viral rhinosinusitis) will last for less than 10 days and acute post-viral rhinosinusitis will last between 100 days and 12 weeks in duration. ARS is considered to be bacterial (ABRS) if at least three of the symptoms in Box 94.1 exist.[1]

For a diagnosis of recurrent acute rhinosinusitis, there must be symptom-free episodes between the clinical events. Chronic rhinosinusitis (CRS) is phenotypically divided into those cases with polyps (CRSwNPs) and those without (CRSsNPs) based on endoscopic findings. This division has also been broadly based up the pathophysiological themes within these two main subgroups which is discussed further below. Allergic fungal rhinosinusitis (AFRS)[6–8] is a smaller subgroup, believed to represent 10% of those with CRSwNPs, and is discussed in Chapter 96. A proportion of patients with CRSwNPs also fall into a unique subset, characterized by coexistent asthma and aspirin sensitivity known as Samter's triad or aspirin exacerbated respiratory disease (AERD).[8] AERD is believed to account for approximately 15% of CRSwNPs, classically manifest by severe nasal and/or respiratory symptoms following ingestion of salicylates, and there may be considerable overlap with AFRS-like cases.[9]

Finally, in all cases of CRS, some patients may experience acute exacerbations with worsening of symptoms for short periods, which may be triggered by viral URTIs.

Despite all the above definitions, there remain areas of uncertainty as not all patients adhere to the diagnostic symptoms and in primary care settings, diagnosis is often based on symptoms alone as the equipment to perform suitable nasal examinations is lacking. Rhinosinusitis should be distinguishable from rhinitis but inevitably there will be overlap. Rhinitis can broadly be categorized into allergic and non-allergic types, with the former now defined as persistent or intermittent according to the WHO committee Allergic Rhinitis In Asthma (ARIA) (Figure 94.1).[10, 11] Rhinitis is defined as the presence of at least two of the following: nasal blockage, rhinorrhoea (clear), sneezing or itching. Other varieties of rhinitis is discussed further in Chapters 91–93. Clinicians need to also be mindful that systemic diseases can manifest themselves in the nose, as is discussed further below.

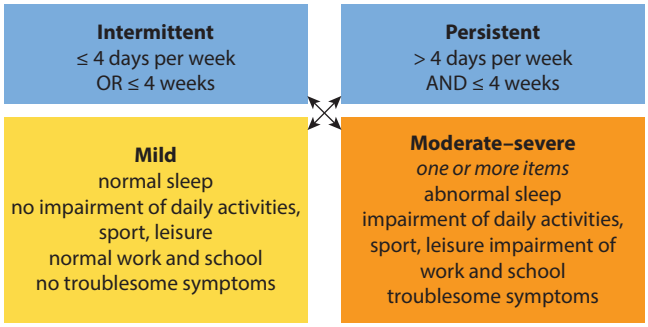


Figure 94.1 ARIA classification.[9]

EPIDEMIOLOGY AND SOCIOECONOMIC IMPACT

ARS is a very common condition and based on the current literature, prevalence rates vary from 6 to 15% with a prevalence of recurrent ARS estimated at 0.035%.[1] In a 3-year case-control study of the Dutch population, van Gageldonk-Lafeber estimated that annually, 900 000 individual patients consulted their primary care physician for acute respiratory tract infection.[12] This high volume of patients then receives a variable response from medical practitioners in terms of treatment.[13–15] Given that the proportion of bacterial causes amongst all ARS is believed to be as little as 0.5–2.0%,[16] this results in over-prescribing of antibiotics as found by a Danish study, where diagnostic certainty was found to be 70% based on symptoms and limited examination and where penicillin V was the preferred agent of choice.[17] German healthcare data over 1 year showed that 6.3 million separate diagnoses of ARS were made and in conjunction with this 8.5 million prescriptions were provided.[18]

CRS represents a significant disease burden worldwide, affecting at least 11% of the population[19] and consequently carrying with it a substantial economic burden to healthcare systems, to patients and to the economy from loss of productivity in the workplace.[18, 19] In fact 'sinusitis' was cited as one of the top ten most costly physical health conditions to American businesses in 1999,[20] as it has an increasing incidence in middle age with a significant socio-economic impact and impairment of quality of life.[21, 22] As a disease entity in the UK its prevalence is greater than ischaemic heart disease (3.7%), diabetes (4%), chronic obstructive pulmonary disease (1.5%), heart failure (<1%) and stroke (<1%) and equivalent to that of peripheral vascular disease, arthritis and back pain, several of which have been shown to have a lesser impact on patients' quality of life than CRS.[23] Patients with CRS also have a 5–17% prevalence of asthma as shown by a recent European study. This figure is higher in secondary care cohorts.[22, 25]

In the EPOS 2012 document stated: 'The overview of the currently available literature illustrates the paucity of accurate information on the epidemiology of CRSsNPs and CRSwNPs, especially in European countries, and highlights the need for large-scale epidemiologic research exploring their prevalence and incidence.'[1] A recent UK study has shown that CRS affects the social spectrum equally and that poor socioeconomic status does not

appear to be a risk factor for CRS,[22] but there remains a need for larger scale studies that may also examine the natural history of the disease.

There are about 2.7 million outpatient consultations for ENT disorders per year in England and Wales and sinonasal disease is thought to account for at least 120,000 visits per year).[26] Failure of medical treatment usually leads to an operation being offered with over 40,000 nose and sinus operations performed per year in England and Wales;[26] based on current tariffs this is an estimated £30 million spent each year. Furthermore, in patients who undergo surgery, the UK Sinonasal audit revealed a surgical revision rate of up to 20% within 5 years[27] and also a ten to fifteen fold variation in surgical practice around the UK;[28] the cost of this revision surgery is estimated at £15 million per year.[25]

There are no published estimates of cost of healthcare and productivity losses for patients with CRS in the UK. Previoius findings from the USA estimate that patients with CRS spend more than $500 each year on healthcare and miss an average of 5.67 workdays per year versus 3.74 days per year for patients without CRS,[29] suggesting a significant disease burden on both the healthcare system and on individuals that is equal to or exceeds that for diseases that are thought to be more serious. An earlier study found that the overall yearly economic cost was $1500 per patient[30] and that estimated healthcare expenditures attributable to CRS and common comorbidities were close to $5.78 billion in 1996 excluding out-of-pocket expenditures or time off work for patients. Bringing this up to date, yearly estimated costs for CRS in the USA now exceed $60 billion.[31, 32] Another USA study concluded that the direct costs associated with CRS are higher than the background costs due to increased clinic visits and prescriptions, as well as significant productivity losses.[33] Surgical treatment for CRS certainly appears to influence drug costs,[34, 35] but this may depend on the level of intervention. There is also increasing evidence that earlier surgical intervention may reduce the prevalance of late onset asthma.[36]

DIAGNOSTIC AIDS

As stated above, EPOS 2012 has included the need for endoscopic or radiological findings to confirm the evidence from a patient's history and the flow diagrams within the EPOS document can be used to guide clinicians as to when to implement the latter. Thus rigid nasal endoscopy and CT scanning of the sinuses are at the present time the gold standard investigations for CRS. Endoscopy allows the clinician to assess the nose for the presence of polyps, mucopus discharge or middle meatal oedema. Furthermore the endoscope can be used to accurately sample any mucopus for microbiological analysis.[37] In cases of suspected allergic or eosinophilic fungal/mucinous rhinosinusitis, a fungal smear and culture should be requested, although diagnostic yield from such samples can be hugely variable depending on local laboratory resources and techniques.[33] CT scanning should be considered mandatory for all cases where surgical intervention is planned.[28]

There are a number of adjuncts beyond endoscopy, radiology and microbiology that may aid diagnosis or perhaps the differential diagnosis, although they may also give more specific information about the aetiology or presence of concurrent disease and predict response to treatment.

These include:[38]

- Allergy testing – skin prick testing or RAST
- Nasal brushings for cytology
- Nasal biopsy for exclusion of neoplasia, to look for granulomas/vasculitides or to examine for evidence of eosinophilia and fungal hyphae
- Blood tests – full blood count (serum eosinophilia), ANCA (Wegener's granulomatosis), ACE (sarcoidosis)
- Olfactory testing:
  - Psychophysical (threshold (quantitative) and iscrimination/identification (qualitative))
  - Olfactory event-related potentials (OERPs) (objective)
- Physiological testing
  - Peak inspiratory nasal flow
  - Rhinomanometry
  - Acoustic rhinometry
  - Mucociliary clearance (saccharin test)
- Ciliary function testing
  - Ciliary beat frequency
  - Ciliary beat pattern analysis
  - Electron microscopy
- Patient reported outcome measures/symptom scores – these include the Sinonasal Outcome Text (SNOT),39 Rhinosinusitis Outcome Measure (RSOM-31),40 Chronic Sinusitis Survey (CSS), 41 and other validated questionnaires.

ACUTE RHINOSINUSITIS

ARS is a very common condition that is predominantly managed in primary care and hence rarely seen by hospital specialists unless complications occur. As stated above, the primary cause of ARS is viruses[34] and only 0.5–2.0% of patients are believed to develop ABRS. Current EPOS guidelines for primary care therefore suggest the use of symptomatic relief, nasal douching and decongestants with consideration given to the use of topical steroids depending on severity. Cases with the features listed in **Box 94.1** or where duration has been greater than 10 days are more likely to benefit from antibiotics. Predisposing factors to ARS include anatomical factors (e.g. Haller/infra-orbital ethmoid cells, conchae bullosa), allergy, smoking and poor mental health. Whilst there is evidence in some of these factors to support the contrary, both anatomical and allergy factors have a reasonable weight of evidence in the literature.[1]

The viruses most commonly implicated in ARS include rhinoviruses (50%), influenza and parainfluenza viruses, adenovirus, respiratory syncytial virus and enterovirus.[42] If bacteria do become implicated the organisms most commonly see are *S. pneumoniae* (27%), *H. influenzae* (44%), *M. catarrhalis* (14%) with other organisms sometimes seen including *S. pyogenes* and *S. aureus*. The proportion of

these organisms has changed in recent years with vaccination schemes.[43] Pathophysiological mechanisms relating to viral agents include cell invasion of the respiratory epithelium leading to inflammatory changes including mechanical changes, epithelial damage and activation of humoral and cellular defences. In bacterial cases, this is largely a superinfection following an initial viral insult where epithelial disruption has already occurred and there has been an associated decrease in ciliated cells and increase in goblet cells which eventually cause sinus ostial obstruction. The accumulating mucus causes an initial increase in the intra-sinus pressure followed quickly by negative pressure due to the lack of ventilation. This then sets up a vicious cycle of further congestion, mucus retention, impaired gas exchange and pH balance and largely prevents clearance of inflammatory products and debris leading to an ideal medium for bacteria to flourish.

TABLE 94.3 Complications of ABRS

Orbital	Intra-cranial	Osseous
Pre-septal cellulitis	Subdural empyema	Pott's puffy tumour (subperiosteal abscess of frontal sinus)
Orbital cellulitis	Meningitis/ encephalitis	Maxillary osteomyelitis (in infancy)
Subperiosteal abscess	Intra-cerebral abscess	
Orbital abscess	Epidural abscess	
	Superior sagittal sinus thrombosis	
Cavernous sinus thrombosis		

Most cases will be self-limiting with complications of ARS exceedingly rare; an estimated 2–4 cases per million of the population per year. This was perhaps thought to be due to the high rate of antibiotic use but there is evidence to suggest that in cases where complications have occurred, this has not been prevented by prior use of oral antibiotics.[44] Complications of ARS can be subdivided into orbital (60–75%), intra-cranial (15–20%) and osseous (5–10%) (Table 94.3). In orbital cellulitis, 90% are secondary to ABRS. A national survey in the UK found 78 cases of complications relating to ABRS over a 1-year period.[44] A review of the literature on complications shows that the mortality rate varies between 2 and 19%.

CHRONIC RHINOSINUSITIS

Please refer to Figure 94.2.

At the present time CRS is largely subcategorized into cases with polyps (CRSwNPs) and cases without polyps (CRSsNPs). The clinical definition has been outlined above but relates to a heterogeneous group of patients that fall loosely within one of these two subgroups.[1] The reason for this coarse subcategorization is the apparent themes within the pathophysiology of these two groups. CRSwNPs is characterized by an intense oedematous stroma in the sinonasal epithelium, with albumin deposition, pseudocyst formation and subepithelial/perivascular inflammatory cell infiltration. It appears to be associated with a typical T-helper 2 cell (TH_2) skewed eosinophilic inflammation, with high interleukin (IL-5) and eosinophil cationic protein (ECP) concentrations in the polyps. By comparison, CRSsNPs is characterized by fibrosis, basement membrane thickening, goblet cell hyperplasia, subepithelial oedema,

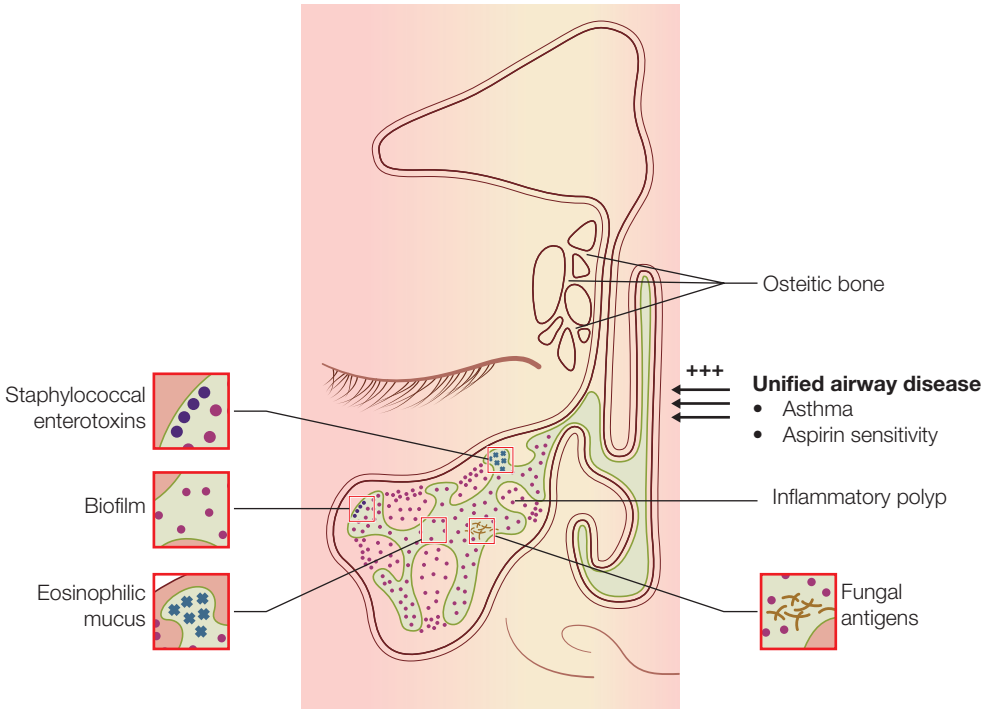


Figure 94.2 Aetiological mechanisms proposed for CRS.

and mononuclear cell infiltration. It exhibits a T-helper 1 cell (TH_1) milieu, with increased levels of interferon gamma (IFN-γ) in inflamed sinus mucosa and low ECP/myeloperoxidase ratios.[45] This basic division into the two subgroups does however represent a gross oversimplification of a heterogeneous disease. These categories can therefore be further divided as discussed below (Tables 94.4 and 94.7). The various aetiological mechanisms that have been proposed for CRS are summarized in Figure 94.2.

Polypoidal chronic rhinosinusitis

It is important that 'nasal polyposis' is not considered a diagnosis, merely a description of a pathological endpoint of sinonasal disease, hence why the term chronic rhinosinusitis with nasal polyposis is used to denote the most common manifestation of polyps; other examples of nasal polyps will include antrochoanal polyps and reactive polyps such as may be seen around other inflammatory focus such as a fungal ball or inverted papilloma. The clinician finding nasal polyps inside the nose should always ask why they have formed, although the answer may not always be readily apparent. The classifications below provide a useful framework around which to base the potential aetiology of nasal polyps.

LOCALIZED NASAL POLYPOSIS (CRSWNPS – LOCALIZED)

Please refer to Figure 94.3. A unilateral nasal polyp should always be viewed with suspicion, especially in older patients and in anyone exposed to wood dust. It may represent a benign entity such as an antro-choanal polyp or be part of a tumour such as an inverted papilloma or sinonasal malignancy. A unilateral polyp may occur as a result of a prior inflammatory event, predisposing to sinus ostia obstruction, hypoxia and subsequent bacterial infection. Microbiology sampling in clinic should be performed if appropriate but computed tomography and biopsy of the polyp are indicated in order to decide on the medical and surgical treatment strategy to pursue. Caution should be advised with performing a biopsy of any polyp that arises superiorly within the nose, or from the back of the nose in a juvenile male patient.

TABLE 94.4 Classification for the finding of nasal polyps

Polypoid CRS		
Localized	Reactive polyp(s)	Inflammatory
		Neoplastic
Diffuse (CRSwNPs)	Host	Anatomical e.g. poor OMC function, aspirin sensitivity (AERD)
		Atopy
	External agent	Staphylococcus superantigen
	Combined host/external agent interaction	Allergic fungal rhinosinusitis and its related derivatives
Systemic	Cystic fibrosis, Churg/EMRSexternal	

DIFFUSE NASAL POLYPOSIS (CRSwNP – DIFFUSE)

A number of recognized mechanisms appear to have a role in polyp formation, although this is by no means fully understood and there may well be crossover between them. These include bacterial (super-antigen response), fungal sensitization, and atopy. These may be associated with biofilm formation or frank eosinophilia, both exacerbating and propagating the inflammatory process. When severe bilateral nasal polyposis is present with aspirin sensitivity and asthma, the possibility of AERD and hence salicylate desensitization therapy should be considered. CT scanning will further elucidate a pansinus opacification typical of AFRS/AERD (Figure 94.4), (double density signs) or show less marked disease consistent with atopy and superantigen cases. In cases of suspected AFRS/AERD, thick granular

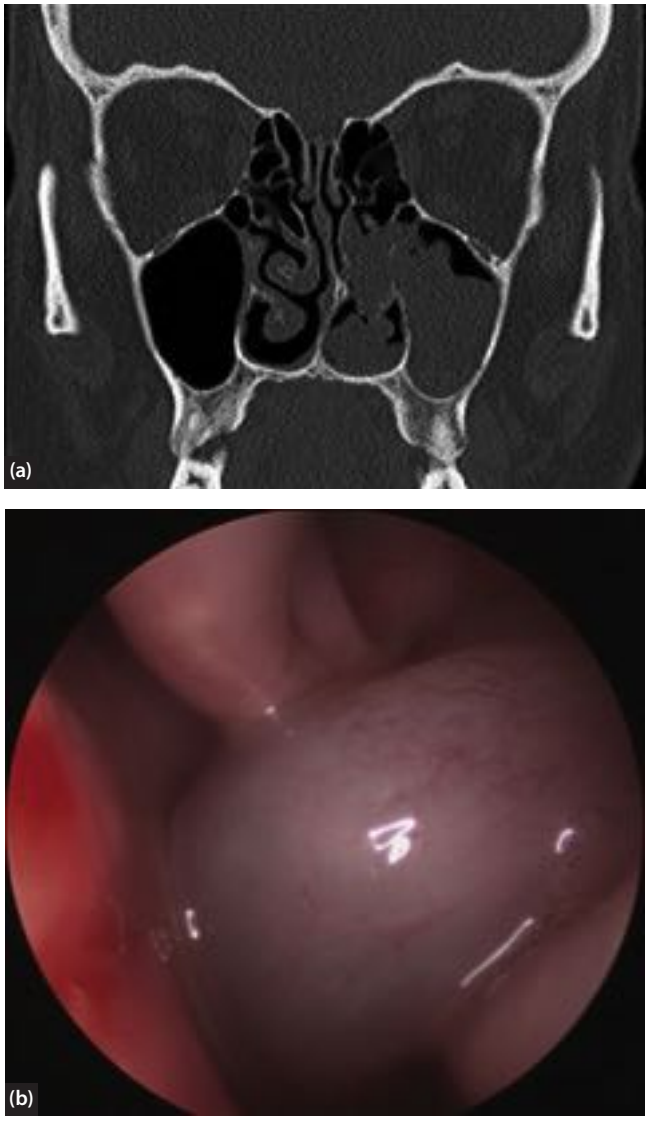


Figure 94.3 (a) Radiological and (b) endoscopic appearance of an antro-choanal polyp.

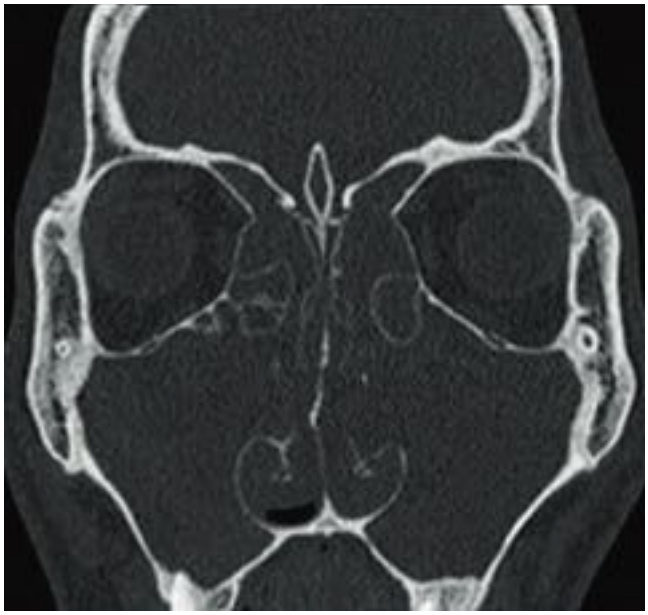


Figure 94.4 Pan-sinus opacification consistent with AFRS and AERD cases.

(eosinophilic) mucin will usually be found at initial presentation, during surgery or sometimes in the post-operative period. Less viscous mucus will perhaps suggest bacterial superantigen aetiology.

Bacterial superantigens, fungal antigens and allergic allergens have all been suggested as mechanisms driving T-cell activation, IgE and IL5 production resulting in subsequent tissue eosinophilia. Lack of consistency in studies suggests that each of these pathogens cannot be solely responsible, and the pathogenesis is likely to represent a multifactorial interaction. Also Asian studies have identified a predominantly TH_1 cell and TH_{17} pattern within polyp tissue[46] and in cystic fibrosis, patients exhibit a neutrophilia.[45] These observations highlight the apparently heterogenous nature of biochemical pathways that ultimately result in the clinical phenotype of CRSwNPs.

Furthermore some cases show polyps confined to the OMC on CT scanning indicating poor OMC function perhaps with narrowing features such as Haller cells. All cases should have appropriate mucus samples sent for routine and/or fungal cultures with fungal smears in the latter case. Both gram positive and negative bacteria have been cultured from the nasal cavity of CRSwNPs patients, the latter of which are rarely cultured from healthy subjects.[47–49] However, it is uncertain as to whether identification of a specific bacterium represents infection, or simply colonization. Data on biofilms in CRSwNPs is lacking but some recent evidence suggests up to 75% of cases may elicit biofilm;[50] clearly further evidence is needed to confirm this.

The super-antigen hypothesis proposes that non-invasive *S. aureus* in the nasal mucosa of CRS patients secretes exotoxins, which produce a localized eosinophilic inflammatory response as studies have shown exotoxin, specific super-antigen IgE, eosinophils and markers of eosinophilic inflammation are higher in cases of CRSwNPs compared to CRSsNPs.[51, 52] To counter this hypothesis is the evidence that there are differing levels of *S. aureus*



Figure 94.5 CRSwNPs with marked osteitis.

(65%), superantigen-specific IgE (50%) and T-cell changes (33%)[53, 54] suggesting that the superantigens may have a role in some cases of CRSwNPs patients, but not all. Tissue eosinophilia can be a useful marker of severity and may help predict severity in these patients.[55]

Much of the evidence around fungal hypotheses is muddied by the difficulties in proving fungal organisms are present and with studies that do not carefully select cases more likely to represent fungal aetiology leading to the conclusion that fungi are mere bystanders and antifungals do not work.[56] Studies have demonstrated a high frequency of both fungi and eosinphilic mucin in CRS patients compared to control subjects suggesting a unique, T-cell driven hypersensitivity to fungi, independent of IgE mediated/atopic pathways.[57] This is supported with evidence that peripheral blood mononuclear cells and eosinophils of CRS patients react to Alternaria fungal extracts, in contrast to controls.[47] However a T-cell receptor mediated hypersensitivity response to fungal antigen has yet to be definitively elucidated and it is possible that a non-specific protease-based reaction to Alternaria is occurring.

The role and significance of osteitis in CRS is currently unclear, although may explain why some cases are resistant to standard oral treatment regimens. In CRSwNPs, osteitis may act as a marker of severity and has been shown to occur significantly more often in revision cases[58, 59] (**Figure 94.5**).

NASAL POLYPOSIS SECONDARY TO SYSTEMIC DISEASE

Two main systemic conditions should be considered in the presence of diffuse nasal polyposis: Churg-Strauss Syndrome (CSS) and cystic fibrosis (CF). Up to 76% of CSS cases demonstrate nasal polyps and ANCA positivity should alert the clinician to the underlying vasculitis characterized by necrotizing inflammation of the vessel wall, particularly of small arteries, arterioles, capillaries and venules.[60] Although newborn screening for CF will pick up most cases, any doubt in a child presenting with diffuse nasal polyposis in conjunction with total opacification of the sinuses as well as hypoplastic

sinuses (typically frontal and sphenoid), should be followed up with a sweat test. Nasal endoscopy demonstrates polyp formation in up to 45% of adults with cystic fibrosis (CF), although most will show radiological evidence of disease.[61] Polyps from children with CF have a significantly lower eosinophil count than patients with 'typical' adult onset CRSwNPs.[62] However, there have also been studies to demonstrate significant overlap in eosinophil concentrations between groups.[63] Absent mucociliary clearance exhibited in primary ciliary dyskinesia results in recurrent bacterial infections and CRSwNPs in approximately 40% of patients.[64]

NON-POLYPOIDAL CHRONIC RHINOSINUSITIS (CRSsNPS)

It is worth noting here that some cases of CRSsNPs may be classified as CRSwNPs due to polypoid change around obstructed sinus ostia, rather than representing more diffuse polyps seen in other cases of CRSwNPs. Careful consideration of the relevant treatment paradigms should therefore be given in conjunction with relevant radiological findings. However, it is also likely, given the insidious nature of CRS, that some cases appear as CRSsNPs at first presentation but eventually develop nasal polyposis.

Localized CRSsNP (isolated sinus disease and odontogenic disease)

Anatomical variation may predispose a patient to isolated inflammation in only one of the sinuses (**Figure 94.6**) as a post-obstructive phenomenon.

Infundibular opacification has been shown to be associated with maxillary sinus disease in approximately three-quarters of cases in a series of 100 prospectively evaluated CT scans,[65] suggesting that anatomic variants such as infra-orbital ethmoid cells, concha bullosa, and narrow nasal cavity secondary to deviated nasal septum correlated with mucosal thickening, particularly in the maxillary sinus (**Figure 94.7**).



Figure 94.6 Localized CRSsNPs.

Preceding events may include an allergic or viral exacerbation, leading to obstruction of the sinus ostia, with secondary bacterial infection. Depending on the attachment of the uncinate process, some cases may also involve the frontal and anterior ethmoid sinuses on that same side and endoscopy typically reveals a bulging uncinate process where the infection appears to be 'walled-off' in the anterior sinuses. Microbiology sampling of mucopus should be performed in conjunction with surgical drainage and aeration as medical therapy typically fails but these patients tend not to need any sustained post-operative medical treatment. In approximately 10% of these cases the cause will be odontogenic.[66] Therefore, all unilateral cases should include an oral examination and a careful review of the maxillary sinus floor on the CT scan to look for signs of an oro-antral fistula.[67] Involvement of oral maxillofacial colleagues will be beneficial at an early stage where odontogenic aetiology is suspected to enable optimization of management.[68]

DIFFUSE NON-POLYPOIDAL CRSsNP

CRSsNPs is histologically characterized by fibrosis, goblet cell hyperplasia, basement membrane thickening, subepithelial oedema and mononuclear cell infiltration (**Figure 94.8**).

It accounts for about 45% of the cases seen in secondary care[22] but presents a lower surgical burden than CRSwNPs.[25, 55] Remodelling is a dynamic process in both health and disease that balances extra-cellular matrix (ECM) production and degradation, which is regulated by diverse mediators among which TGF-β takes a central role. Indeed, the up-regulation of the TGF-β signalling pathway in patients with CRSsNP and its down-regulation in patients with CRSwNPs on the protein level are reflected by oedema formation and a lack of collagen production in patients with CRSwNPs and excessive collagen deposition associated with



Figure 94.7 Infundibular disease due to anatomical narrowing.

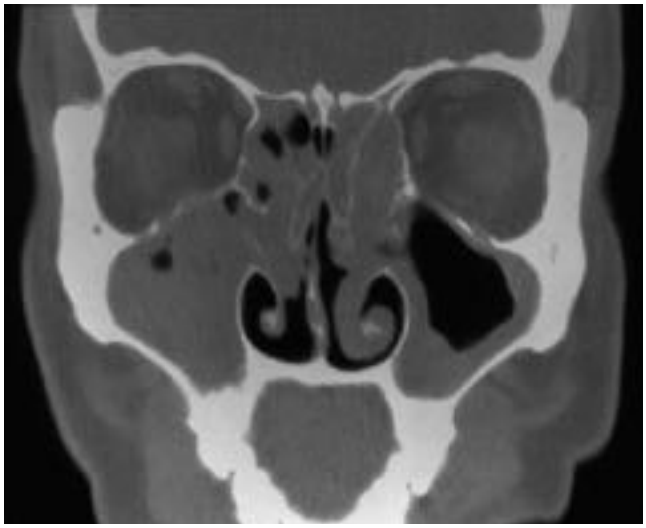


Figure 94.8 Coronal CT image demonstrating diffuse pansinusitis and mucosal thickening, indicative of severe CRSsNPs.

fibrosis in patients with CRSsNPs.[56] CRSsNPs is also distinct from CRSwNPs immunologically, characterized by a TH_1 milieu with increased levels of IFN-γ in the inflamed sinus mucosa and low ECP/myeloperoxidase ratios.

Much like CRSwNPs, bacterial colonization of the paranasal sinuses in CRSsNPs has a similarly uncertain significance.[69] While identifiable bacteria are comparable between the two subtypes,[47–49, 69, 70] *S. aureus* colonization appears to be more statistically significant in patients with CRSwNPs (63.6%) compared to controls, which is not apparent in CRSsNPs patients (27.3%),[52] however, the organism is identified as the most common pathogen in CRS patients as a whole, especially post-operatively.[71] This former observation has thus largely rejected the superantigen hypothesis in CRSsNPs. Conversely, reports on biofilms are more abundant in CRSsNPs patients, with detection rates ranging from 28.6 to 100%.[72–76] Multiple bacterial species have been identified, including *P. aeruginosa, S. aureus, S. pneumonia, H. influenza* and *M. catarrhalis*. Again, their overall relevance in the context of disease pathogenesis remains incompletely defined, but biofilms are thought to be at least partially responsible for a subset of recalcitrant CRSsNPs cases. The same can be said for the clinical significance of fungal pathogens isolated from CRSsNPs patients.

The significance of OMC obstruction in the context of CRSsNP is more clear-cut than the polypoidal variant. In the latter, OMC obstruction may be a 'barometer' of overall disease burden, in that increasing Lund-Mackay scoring is associated with OMC involvement overall.[77]

SYSTEMIC CONDITIONS CAUSING RHINOSINUSITIS

The systemic conditions likely to manifest with nasal polyps have been discussed above in the section on CRSwNPs. This section will therefore focus on other systemic conditions that give rise to CRS or should perhaps be considered as a differential diagnosis for CRS.[78,79] Granulomatous diseases to consider include granulomatosis with polyangiitis (GPA) formerly known as Wegener's Granulomatosis and sarcoidosis.[80] Clues to the diagnosis may be derived from blood tests including Anti-nuclear cytoplasmic antibody (ANCA) and angiotensin converting syndrome (ACE) which if elevated may need corroboration with tissue biopsy and other imaging. These conditions typically manifest with intranasal crusting and the former can be locally destructive with erosion of sinus lamellae and septal cartilage, the latter giving rise to a characteristic saddle-nose deformity. Ciliary dyskinesias represent another group of disorders that will manifest with rhinosinusitis.[81] Primary ciliary dyskinesia is often associated with situs inversus and known in this circumstance as Kartagener's syndrome. Patients often present in adolescence and may have a prior history of otitis media with effusion; they may also suffer with bronchiectasis.[82] Ciliary dyskinesias will show delayed mucociliary clearance times and require investigation at specialist centres, of which there are three in the UK.[83] Clear rhinorrhoea, especially unilaterally, should always prompt investigation for a CSF leak, initiated by collecting nasal fluid to test for β-2 transferrin. Tumours will typically present with unilateral symptoms such as blockage or bleeding but inverted papillomas may sometimes be found amongst bilateral CRSwNPs, hence it is important to send material for histology during any surgery to remove polyps, especially the first time, if there is any index of suspicion. Tumours may also present when they cause secondary infection by sinus ostial occlusion.

Rhinosinusitis may also be a presenting or secondary feature of patients with immunodeficiencies (e.g. HIV[84]) or who are immunocompromised by systemic treatment for other disorders (e.g receiving immunosuppressive drugs for organ transplantation). In those cases, patients require endoscopic retrieval of mucopus where possible, as unusual organisms may be found.[85] Immunodeficiency should always be considered a possibility in patients who appear not to respond to standard medical and surgical care for CRS[86, 87] and in cases of recurrent ARS. Common variable immune deficiency (CVID), selective IgA deficiency, IgG subclass deficiency, and specific antibody deficiency are all possible immunodeficiencies that can be detected in cases of CRS.[88] Refractory cases of CRS have been shown to have low IgG in 18%, low IgA in 17% and low IgM in 5%[89] with both IgA and IgG deficiencies postulated as potential contributory factors for patients failing medical therapy for CRS.[90] In children, where a higher index of suspicion accompanies the onset of CRS, IgG_3 subclass deficiency has been reported in association with the presence of nasal polyposis.[91] Another study looking at 245 CRS patients failing prolonged antibiotic therapy found that about 8% had an IgG deficiency[92] with IgG_3 deficiency being implicated as the most common Ig deficiency in the wider group of patients with CRS[93] and IgG_2 in cases of recurrent ARS.[94] Certainly there is a role for screening for immunodeficiency in CRS patients refractory to standard treatment.[88, 95]

A list of differential diagnosis and key diagnostic features is found in **Table 94.5**. This is by no means exhaustive but does provide a guide to other conditions that should be considered.

TABLE 94.5 Systemic conditions causing rhinosinusitis or possible differential diagnosis

Congenital	Cystic fibrosis	Abnormal sweat test CFTR gene mutation on chromosome 7
	Primary ciliary dyskinesia	Abnormal mucociliary clearance and cilial ultrastructure
	Primary immunodeficiencies (CVID, SCID, hypo/dys–gammaglobulinaemias	Low/absent antibodies
Infectious/inflammatory	HIV	Positive ELISA for HIV
	Sarcoidosis	Elevated ACE CXR signs (hilar lymphadenopathy)
	Tuberculosis	Acid-fast bacilli Mantoux test positive
	Granulomatosis with polyangitis (Wegener's)	cANCA positive Leukocytoclastic vasculitis on biopsy
	Eosinophilic granulomatosis with polyangitis (Churg-Strauss Syndrome)	pANCA positive
Neoplastic	Haematological malignancies	Abnormal FBC/bone marrow
	Sinonasal malignancies	Biopsy positive Radiological changes
Iatrogenic	Atrophic rhinitis	Excessive crusting following radical nasal surgery
	Chemotherapy/immunosuppression	Relevant drug history
Metabolic	Malnutrition	Low BMI

FUTURE RESEARCH

- The EPOS paper[1] and more recently the European Forum for Research and Education in Allergy and Airway Disease (EUFOREA)[96] have carefully detailed where future research efforts need to be directed and hence the tables below summarize this.
- There is clearly much work to be done, above all, in understanding the complexities of this heterogeneous disease and perhaps in the future separating patients out into distinct groups based on cytokine profiling, allowing personalized medical treatment for individual patients.[97]
- Through the characterization of CRS phenotype subsets, well-defined endotype groups should become distinguishable.
- Continual identification of specific disease subgroups, genetic changes and biomarkers as directed by good epidemiological studies will be valuable undertakings for future research, particularly in the context of implementing novel treatment strategies and the overall prognosis of the condition.

BOX 94.2 EPOS 2012 Aetiological Research Priorities

Future research should consider the role of:

- Socioeconomic status
- Severity staging with respect to QoL
- Prognostic symptoms in primary care
- Endotyping and phenotyping – including how to assess this and the impact upon management and outcomes
- Osteitis (long-term study and RCT of treatment options)
- Purulence in assessing response to treatment
- Childhood events, smoking and AR as risk factors
- Psychological, neurological, GORD risk factors
- Genetic profiling on susceptibility to disease and therapeutic response
- CRSsNPs pathophysiology

Future research should further investigate:

- Olfactory disorders, headache, facial pain
- The development of new classifications based on endotypes and phenotypes
- Better understanding of inflammatory pathways including TGF-β, T-cells, dendritic cells, microbiomes and search for new and clinically applicable biomarkers
- The pathogenesis of 'allergic' fungal rhinosinusitis and AERD.
- Understanding of the link between CRSwNPs and lower airway disease.
- The natural history of CRS and epidemiology studies.

BOX 94.3 EPOS[1] and EUFOREA[96] research priorities for CRS management

- Improve professional education and efficient dissemination of evidence-based guidelines to optimize outcomes and reduce referral rates to secondary care.
- Conduct a large prospective placebo controlled study of long-term antibiotic treatment in a well-defined CRS population, exploring effects on the patient's quality of life, immune system, microbiota of the airway as well as the health economic impact.
- Seek better local therapies for immunomodulation.
- Conduct an RCT on oral steroids versus surgery on the long-term outcomes of CRSwNPs.
- Conduct an RCT studying the effects of oral corticosteroids on olfactory function in CRSwNP.
- Conduct multicentre RCTs on surgery versus no treatment for patients with CRSwNPs to establish the natural course of disease.
- Conduct RCTs on minimal versus more extensive endoscopic sinus surgery.
- Investigate the effect of early surgical intervention on CRSwNPs to see if it alters the course of the disease.
- Better tools for the diagnosis and differential diagnosis of facial pain in assessment of rhinosinusitis symptoms and examination in CRS.
- To establish whether treatment of CRS affects outcomes of comorbid lower airways disease (eg asthma, COPD)
- To undertake further RCTs studying the effects of surgery and medical treatment on the lower airways (lung function/QoL/symptoms) in CRSwNP and concomittant asthma.
- Demonstrate whether the relative frequency of different symptoms and signs in CRSwNPs and CRSsNPs predict a differential response to different therapies.
- Cost effectiveness of biological treatment versus surgery.
- Socioeconomic impact of implementation of phenotyping and endotyping into care pathways.

KEY POINTS

- Rhinosinusitis is a common disease with CRS affecting an estimated 10% of the population worldwide.
- Most ARS is not bacterial and requires symptomatic relief only.
- CRS is a heterogeneous disease with differing phenotypes and endotypes; the latter have yet to be clearly determined.
- CRS presents a significant burden on healthcare resources but guidelines exist for its medical and surgical management.
- Where other clues are present, consideration must be given to other systemic causes for sinonasal disease.
- Due to the relative paucity of evidence, more clinical trials are needed to determine the most effective treatment strategies for the various forms of CRS.

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CHAPTER 95

NASAL POLYPOSIS

Louise Melia

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: nasal polyps, chronic rhinosinusitis with nasal polyps, cystic fibrosis, asthma, aspirin exacerbated respiratory disease, eosinophilic granulomatosis with polyangiitis, Young's syndrome, intranasal corticosteroids, systemic corticosteroids and endoscopic sinus surgery.

INTRODUCTION

Nasal polyps represent the end stage local manifestation of chronic inflammatory disease of the sinonasal tract. The condition is a distinct subgroup of chronic rhinosinusitis, chronic rhinosinusitis with polyps (CRSwNP). Despite the prevalence of polyps, the long history of recognition and extensive research and literature, their aetiology remains elusive and poorly understood. In the last few decades numerous studies have tried to determine the exact pathogenesis of this disease and although many have shown factors thought to be related and associated, none have come to a definitive conclusion about causation. CRSwNP can significantly affect quality of life, and places significant financial burden on society, directly as a result of outpatient appointments, prescriptions, investigations and hospitalization, and indirectly as a result of missed work days and decreased productivity at work. Despite adequate treatment CRSwNP runs a chronic and recurrent course. Nasal polyps continue to be a challenge for rhinologists treating patients with this chronic disease and for those searching for a cause.

Definition

Nasal polyps are best thought of as 'chronic rhinosinusitis with nasal polyps' (CRSwNP), and European guidelines define these conditions clinically as:

- inflammation of the nose and paranasal sinuses associated with two or more symptoms, one of which should be nasal blockage/obstruction/congestion or nasal discharge:
  - +/– facial pain/pressure
  - reduction or loss of smell

and either

- endoscopic evidence of
  - polyps and/or
  - mucopurulent discharge from the middle meatus or oedema, mucosal obstruction primarily in the middle meatus

and/or

- CT changes:
  - mucosal changes within the osteomeatal complex and/or sinuses[1]

Morphologically nasal polyps are oedematous grape-like protrusions most often originating in the upper part of the nose around the osteomeatal complex on the lateral wall. The surface epithelium tends to be smooth and consists of pale translucent tissue which distinguishes them from the more vascular mucosa of the nasal cavity. Polyps can vary widely in size and should be considered a bilateral condition. Rare cases of unilateral polyps should only be diagnosed once all other more likely pathologies have been reliably excluded.

INCIDENCE AND PREVALANCE

The annual incidence of CRSwNP is between 1 and 20 per 1000 population.[2] This incidence declines after 60 years of age. In the normal population the prevalence is between 1 and 4% in adults and 0.1% in children. Nasal polyps are more common in males (2–4:1). There is no racial predilection. Certain systemic diseases, as mentioned below, carry a much higher incidence of nasal polyps.

CLINICAL PRESENTATION

Clinical presentation is variable and depends on the extent of polyp disease. Small polyps may not produce symptoms and may be identified incidentally during rhinoscopic examination, whilst larger polyps may cause significant symptoms. In general, patients with nasal polyps will present with various symptoms that have generally persisted over months to years, progressing from mild nasal congestion with a watery rhinorrhoea to a persistent nasal obstruction associated with hyposmia or anosmia, as well as a thicker post nasal discharge and very occasionally headaches. Epistaxis is not associated with benign polyps and may suggest a more serious pathology in the nasal cavities. Massive polyps or a single large polyp that obstructs the nasal cavities or nasopharynx can cause chronic mouth breathing and obstructive sleep symptoms. Rarely, proptosis, hypertelorism and diplopia can result from alterations in the craniofacial structure. Generally, because of their slow-growing nature, massive polyposis does not cause neurological symptoms or pain, even if they extend into the intracranial cavity (Figure 95.1).

PATHOGENESIS

Polyps arise in the presence of inflammation that may be initiated by a number of factors, resulting in dysregulated interaction between the sinus epithelium and the lymphoid system.[3] Histologically, they consist of loose connective tissue, inflammatory cells and fluid, and are usually covered by pseudostratified, columnar, ciliated epithelium (Figure 95.2). Polyps form when oedematous connective tissue stroma ruptures and herniates through the basement membrane.[4]

Despite a growing body of evidence that bacteria, fungi, allergens, and superantigens play a prominent role in the pathophysiology of nasal polyps the exact cause remains unknown.

In the last decade, research has revealed unique cytokine and cellular inflammatory profiles that may contribute

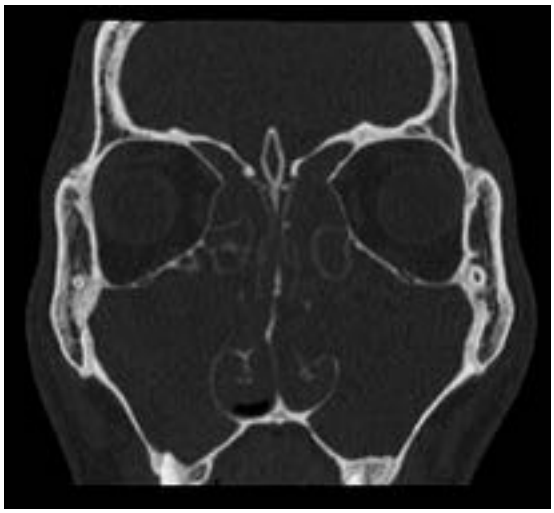


Figure 95.1 Coronal CT image showing complete opacification of sinuses secondary to nasal polyps.

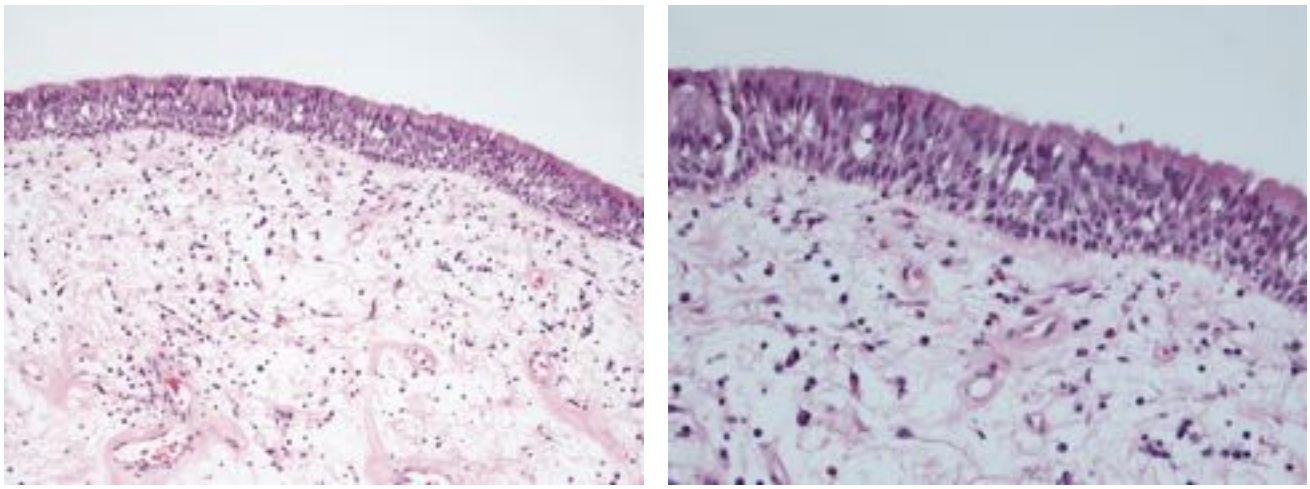


Figure 95.2 Photomicrographs of a simple inflammatory nasal polyp (magnifications of X250 and X400).

to nasal polyps. Approximately 80% of nasal polyps in Western countries are characterized by a robust T-helper 2 response, eosinophilic infiltration[5, 6] decreased T regulatory function,[6] and an abundance of IL-5 cytokine.[7, 8]

Allergy

It is not yet completely clear whether there is an increased risk for the development of nasal polyps in allergic patients, and the evidence in the literature is conflicting. Only 0.4–4.5% of patients with allergic rhinitis have nasal polyps,[9–11] which is similar to the normal population. However, nasal polyps have been shown in 25.6% of patients with allergy compared to 3.9% in a control population.[12] The prevalence of allergy in patients with nasal polyps has been shown to vary from 10%[13] to 64%.[14] Elevated levels of immunoglobulin E (IgE) and positive skin tests to inhalant allergens have been determined in the majority of patients with nasal polyps[10, 15] and association has been found between levels of both total and specific IgE and eosinophilic infiltration in nasal polyps. In patients with nasal polyps however the total serum IgE levels are only partially correlated to local tissue IgE levels and local eosinophilic inflammation.[16] The highly increased local tissue IgE levels in nasal polyps are often polyclonal and independent of total serum IgE levels or allergy skin prick test responses[17] and it has recently been demonstrated that mucosal polyclonal IgE is functional by inducing mast cell degranulation independent of serum IgE levels.[18]

Bacteria

A link between bacterial colonization and nasal polyps has been postulated, but remains unproven. Examination of microbial organisms in the nasal cavity has revealed the presence of a diverse flora, consisting mostly of aerobic and anaerobic bacteria. These include gram-negative organisms such as *Moraxella catarrhalis, Haemophilus influenzae*, *Prevotella* species, *Enterobacter* species, and *Pseudomonas* species.[19, 20] Gram-positive organisms include streptococci, coagulase-negative staphylococci, and *Staphylococcus* aureus.[21] It is believed that the main species involved in the exacerbation of nasal polyps is *Staphylococcus aureus* which harbours genes coding for enterotoxins.[16, 22–25]

In one study, 42.5% of *Staphylococcus aureus* strains isolated from nasal polyp patients and controls harboured at least one classic enterotoxin gene.[26] The secreted toxins coded for by these genes behave as superantigens, which, unlike conventional antigens, do not need processing.[23–28] Superantigens induce the activation of numerous T-cell clones and a massive secretion of cytokines, and therefore have the ability to activate as much as 20% of the body's T cells, compared with only 0.001–0.0001% for regular antigens.[29, 30] In CRSwNP this is characterized by an increased eosinophilic inflammation and formation of IgE antibodies.[31] The formation of bacterial biofilms on the sinus mucosa has also been suggested to be responsible for chronic rhinosinusitis.[32, 33] Biofilms are bacteria enclosed within a self-developed matrix of polysaccharides which renders the bacteria inaccessible to antimicrobial agents. Clinically, cases of nasal polyps with the presence of biofilms may be associated with a more severe form of the disease and worse postoperative outcome.[34, 35]

ASSOCIATED DISEASES

The prevalence of CRSwNP is around 7% in patients with asthma, compared to 4% of the general population,[36] and increases to 30–60% in patients with aspirin exacerbated respiratory disease (AERD).[37] Chronic inflammation and allergic fungal sinusitis have also been considered to be potential risk factors for nasal polyps, and the association between genetic variations and chronic rhinosinusitis suggests that genetic polymorphisms could be related to nasal polyps development.[38, 39]

Asthma

The link between the upper and lower airways has been reported since the beginning of 1800s, with both being lined by the same pseudostratified ciliated columnar epithelium. In patients with nasal polyps 30–71% have been shown to have asthma,[10, 40] and there is a direct association between asthma severity and the presence of nasal polyps.[41] Of patients with late-onset asthma, 10–15% develop nasal polyps, with patients generally developing asthma first, then polyps within 9–13 years. This occurs faster in patients with aspirin-induced asthma, about 2 years from the onset of symptoms.[42] Asthma and nasal polyps share the same basic features of eosinophilia, mucus cell hyperplasia, oedema, thickened basal membrane and increased pro-inflammatory mediators, for example cysteine leukotrienes.[43–45]

The relationship between upper and lower airway pathology is further corroborated by the improvement in lower airway disease that is observed when nasal polyps are effectively treated.[46]

Aspirin-exacerbated respiratory disease (AERD, *Samter's Triad*)

The combination of bronchial asthma, nasal polyposis and aspirin sensitivity is also well described in the otolaryngology literature. It was first described by Wimal in 1922 and then formally recognized as a triad of clinical manifestations by *Samter* et al. in 1967.[47] Its prevalence is reported to be as high as 0.3% in the general population and between 5 and 10% of the adult asthmatic population.[48] The prevalence of patients with nasal polyps, asthma and aspirin sensitivity increases over 40 years of age, and these patients are normally non-atopic. The currently accepted pathophysiology behind aspirin sensitivity syndrome lies in the inhibition of cycle-oxygenase in the arachidonic acid pathway. By blocking cycle-oxygenase, the arachidonic acid is shunted into lipoxygenase and there is an increased production of leukotrienes. The subsequent decreased prostaglandin E2 leads to mast cell instability with release of histamine. The combination of increased histamine

release and increased leukotriene causes increased vascular permeability, leakage from the vascular system and oedema. It is thought that this cycle of inflammation and oedema results in the formation of polyps.[49] The nasal polyps associated with AERD/*Samter's* Triad are often very extensive, with significantly higher radiological CT scores than non-AERD patients with nasal polyps.[48] They can be difficult to treat and have a higher rate of recurrence. One cohort study of 549 patients with nasal polyposis found the polyp-free rates at 5 years following FESS for failed medical treatment to be 84% for control patients, 55% for patients with asthma and 10% for patients with AERD. At 10 years these rates dropped to 78% and 45% for the control patients and the patients with asthma. 100% of those with AERD had already recurred.[50]

Allergic fungal rhinosinusitis

Allergic fungal rhinosinusitis (AFRS) was first reported in 1976.[51] It is a type 1 hypersensitivity reaction to fungal antigens in which patients usually present with unilateral or bilateral nasal polyps. Approximately 80% of patients with fungal sinusitis have nasal polyps.[36] Theories on pathogenesis include hypersensitivity and T-cell mediated reactions as well as a humoral immune response. Treatment is largely surgical, with a strong role for oral corticosteroids and an emerging role for immunotherapy. Antifungals, both systemic and topical, currently have a limited role in treatment, although this area needs further study.[52] In 1994, Bent and Kuhn published their diagnostic criteria centred on the histologic, radiographic, and immunologic characteristics of the disease (**Table 95.1**).[53] Patients must meet all the major criteria for diagnosis, while the minor criteria serve to support the diagnosis and describe individual patients but are not used to make a diagnosis. The major criteria include a history of type I hypersensitivity by history, skin testing, or *in vitro* testing; nasal polyposis; characteristic computed tomography (CT) scan findings with soft tissue differential densities; the presence of eosinophilic mucin without fungal invasion into the sinus tissue; and a positive fungal stain of sinus contents removed at the time of surgery. The minor criteria include a history of asthma, unilateral predominance of disease, radiographic evidence of bone erosion, fungal cultures, presence of Charcot-Leyden crystals in surgical specimens, and serum eosinophilia. A wide variety of fungi have been isolated from the sinuses of patients with chronic rhinosinusitis and as fungal detection techniques improve, so does the sensitivity to detect them, with some studies demonstrating fungal presence in almost 100% of patients, both controls and CRS patients.[54] Therefore the only features that appear to be unique to AFRS are type 1 hypersensitivity and the characteristic CT findings.

TABLE 95.1 Bent and Kuhn Classfication of Allergic fungal rhinosinusitis[53]

Major	Minor
Type I Hypersensitivity	Asthma
Nasal polyposis	Unilateral disease
Characteristic CT findings	Bone erosion
Eosinophilic mucin without invasion	Fungal cultures
Positive fungal stain	Charcot-Leyden crystals
	Serum eosinophilia

Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations of a gene on chromosome 7. The gene prevalence is approximately 1:25 in the Caucasian population and it currently affects 9000 people in the UK.[55] CF patients have thick, tenacious mucus secondary to a mutation in the CF transmembrane conductance regulator chloride channel that affects mucociliary transport.[56] Although the majority of CF patients do not report sinonasal symptoms, CRS is prevalent,[57] with nasal polyps present in up to 86% of patients.[58] In CF CRS, inflammation is neutrophil driven with IL-8 being the primary cytokine.[59, 60] Sinus cultures typically grow *Staphlococcus aureus* or *Pseudomonas aeruginosa*.[61, 62] Examination of CF patients with nasal polyps usually reveals bilateral polyposis with thick rhinorrhoea and facial deformities such as hypertelorism.[63] In addition to nasal polyps, CT scan findings include hypoplasia of the frontal or sphenoid sinuses as well as demineralization and medial displacement of the uncinate process.[59, 64–67]

Mucocele formation is not uncommon in CF, and therefore the presence of mucoceles in a child should raise suspicion for CF.[68, 69]

Primary ciliary dyskinesia

Primary ciliary dyskinesia (PCD) is a rare autosomal recessive disease in which abnormal or absent beating of cilia hinders normal mucociliary clearance. The commonest presentations are in the upper and/or lower respiratory tracts, with mucus retention and recurrent infection leading to nasal polyposis and/or bronchiectasis.[70] Kartagener's syndrome is a clinical variant of PCD and is a triad of chronic sinusitis, bronchiectasis and situs inversus. Twenty-seven per cent of patients with Kartagener's syndrome have nasal polyps (**Figure 95.3**).[36]

Young's syndrome

Young's syndrome is a rare disease consisting of three components: obstructive azoospermia, bronchiectasis and sinus disease. Although it is a recognized cause of male infertility and is well known in the field of infertility,[71] the exact nature and natural history of the sinus disease component is not widely understood. The prevalence of Young's syndrome remains unknown. In the 1980s, the syndrome was reported to affect one in 500 males and was described as being more common than cystic fibrosis.[72] However, in the last 20 years only a handful of case reports have been published on this syndrome.[73–75] A reduction in the use of mercury in Europe and the USA has been cited as a potential reason for this decline. Mercury exposure in



Figure 95.3 Chest radiograph showing dextrocardia.

childhood is likely to be the only aetiological factor identifiable in Young's syndrome, with a history of mercury intoxication seen in 10% of Young's syndrome patients in one series.[76] Mercury inhibits enzymes containing sulphydryl by reacting with thiols to form mercaptides. Mercaptides are thought to inhibit glycolysis, which is necessary for the normal function and energy supply of sperm and cilia.[77]

EGPA (Churg Strauss)

Previously known as Churg Strauss syndrome, this entity has now been recognized by the 2012 revised nomenclature for vasculitides as eosinophilic granulomatosis with Polyangiitis (EGPA). It is a systemic small-vessel vasculitis associated with asthma and eosinophilia, and is traditionally described to evolve through a prodromic, allergic phase characterized by asthma and rhinosinusitis, an eosinophilic phase hallmarked by peripheral eosinophilia and organ involvement, and a vasculitic phase with clinical manifestations due to small-vessel vasculitis.[78] These phases partially overlap and may not appear in such a defined order, although asthma and rhinosinusitis only rarely arise after the vasculitic manifestations.[79] Criteria for classification from the American College of Rheumatology[80] consist of the following:

- asthma
- eosinophilia of >10% in peripheral blood
- paranasal sinusitis
- pulmonary infiltrates, sometimes transient



Figure 95.4 Chest radiograph showing pulmonary infiltrates.

- histologic evidence of vasculitis with extravascular eosinophils
- mononeuritis multiplex or polyneuropathy
- if ≥4 criteria are present, sensitivity is 85%, and specificity is 99.7%.

The typical case that should raise suspicion of EGPA is that of a patient with adult-onset asthma and a history of rhinosinusitis, who develops pronounced eosinophilia and lung infiltrates. Eosinophilia may occur in straightforward asthmatic patients but is usually mild (<10%); likewise, lung infiltrates due to bronchial plugging by mucus and superimposed infection may complicate asthma, but they are uncommon. Nasal polyps affect approximately 50% of patients with EGPA and consistently recur after surgery in patients not receiving immunosuppressive therapy (**Figure 95.4**).[81]

Genetics

Despite many previous attempts to explain disease pathogenesis, the exact genetic mechanisms underlying the development of nasal polyps remain unclear. Suggestion for a potential genetic basis to nasal polyps is afforded by degree of inheritability suggested from family and twin studies as well as the existence of chronic rhinosinusitis and nasal polyps in simple mendelian diseases. Associations between chronic rhinosinusitis and polymorphisms in over 30 genes have been published, however, studies of monozygotic twins have not shown both siblings to always develop polyps, indicating that environmental factors are also likely to play a role in the development of nasal polyps.[82–85]

DIAGNOSIS

Anterior rhinoscopy is the first step to diagnosis, but is inadequate alone and cannot exclude polyps. Rod Lens nasendoscopy after topical decongestant is needed for

diagnosis, as well as identifying discharge, crusting or scarring secondary to previous surgery. Plain sinus radiographs are insensitive[86–88] and should not be used to diagnose polyps. CT scanning with coronal sections is the investigation of choice for assessing the extent of the disease and detailing the anatomy before surgery.[89–91] Magnetic resonance imaging may be helpful to differentiate from tumour, or if intracranial extension of disease is suspected. History for features of systemic disease should be taken, including lower airway symptoms, and tests for factors associated with nasal polyps can be performed. The effects of treatment on nasal obstruction and polyp masses can be documented objectively via nasal inspiratory peak flow,[92] rhinomanometry,[93] acoustic rhinometry,[94] olfactory tests and symptom scoring (**Figure 95.5**).[95]

CLASSIFICATION

Endoscopic and CT-based staging systems are used to determine the extent of disease within the nose and sinuses, and facilitate both medical communication and evaluation of therapeutic responses. The clinical staging system and endoscopic scoring systems are based on the assumption that the polyp grows from the middle meatus down towards the floor of the nose (**Table 95.2**).[96, 97] The radiological staging system includes all sinuses and the osteomeatal complex bilaterally. Various radiological staging systems have been described. The Lund–Mackay system gives a score of 0–2 depending on the absence, partial or complete opacification of each sinus system and of the osteomeatal complex on computed tomography scanning. A maximum score of 12 per side can be achieved (**Table 95.3**).[98] The Lund-Mackay score increases with increasing grade of polyposis.

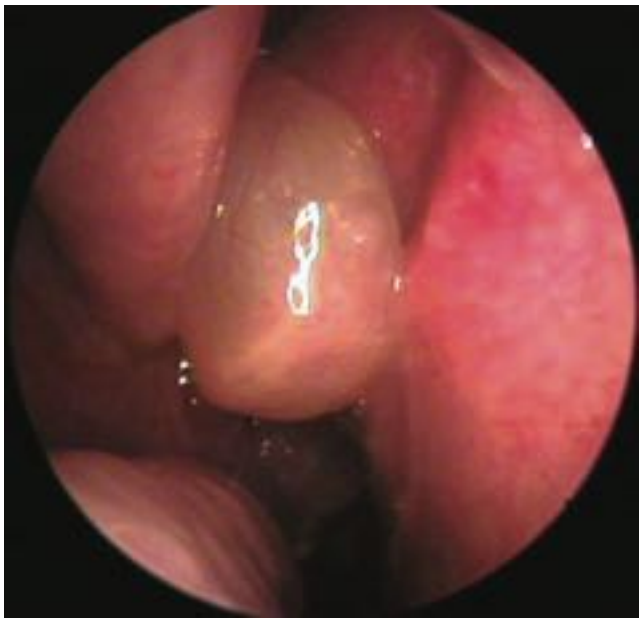


Figure 95.5 Endoscopic view of a nasal polyp.

MANAGEMENT

Treatment aims to eliminate symptoms and nasal polyps, re-establish nasal breathing and olfaction, prevent recurrence and improve patients' quality of life. Treatment can be divided into medical and surgical.

Medical

All patients should have a trial of medical therapy first, unless histology is required. Medical treatment consists mainly of topical and systemic corticosteroids, which are thought to affect eosinophil function directly by reducing both eosinophil viability and activation,[99] and indirectly by reducing the secretion of haemotactic cytokines by nasal mucosa and polyp epithelial cells.[100] Intranasal corticosteroids (INCS) have been shown to be more effective than placebo at improving nasal airflow, reducing polyp size and decreasing rate of recurrence.[1] The effect on sense of smell is poor when compared to systemic steroids, which may be due to the sprays being unable to reach the olfactory mucosa because of oedema. Nasal drops are more effective than sprays and have a significant positive effect on sense of smell, however, they are relatively potent topical steroids, and may be used initially, although not for longer than 2 months at one time unless under specialist supervision, or for longer than 4 months in one

TABLE 95.2 Endoscopic staging of nasal polyps[96]

Polyp	0 = absence of polyp 1 = polyps in middle meatus only 2 = beyond middle meatus
Oedema	0 = absent 1 = mild 2 = severe
Discharge	0 = no discharge 1 = clear, thin discharge 2 = thick, purulent discharge
Scarring	0 = absent 1 = mild 2 = severe
Crusting	0 = absent 1 = mild 2 = severe

TABLE 95.3 Radiological staging of CRS[98]

Paranasal sinuses	Right	Left
Maxillary 0,1,2		
Anterior ethmoid 0,1,2		
Posterior ethmoid 0,1,2		
Sphenoid 0,1,2		
Osteomeatal complex 0*, 2*		
Total points to each side		

0 = no abnormalities, 1 = partial opacification, 2 = complete opacification
0* = not occluded, 2* = occluded

12-month period, as they can be absorbed systemically. Larger polyps may require systemic corticosteroids,[101] for example prednisolone 0.5 mg/kg each morning for 5–10 days. Maintenance therapy with topical corticosteroid spray is recommended as these may have lower bioavailability than drops and are less likely to be administered incorrectly.

It is recommended that patients are started on sprays, drops or systemic steroids depending on their initial presentation and examination findings. On review, a decision can be made whether to continue with medical treatment, request further investigations or consider surgical intervention.[1] Antihistamines only help if allergy is present,[102] and leukotriene inhibitors may help patients with coexisting asthma and/or aspirin sensitivity.[103–105]

Common side effects of intranasal corticosteroids include local irritation and epistaxis. Potential adverse events related to the administration of intranasal corticosteroids are effects on growth, ocular effects, effects on bone and effects on the hypothalamic pituitary-adrenal axis. Cases of adrenal suppression and Cushing's syndrome from systemic absorption have been reported, but are rare.[106] Measurement of salivary cortisol is a useful, non-invasive and economical test for monitoring patients using intranasal corticosteroids.[107] There is evidence that a 3-month course of a macrolide antibiotic can help nasal polyps.[108] Macrolides have been shown to increase mucociliary transport, reduce goblet cell secretion and cause accelerated apoptosis of neutrophils, all of which would reduce the symptoms of chronic inflammation. However, acute cardiac toxicity is an increasingly recognized potential adverse effect of antimicrobial drug treatment and several agents of the macrolide class of antibiotics are known to interfere with the delayed rectifier potassium current, which results in accumulation of potassium ions in cardiac myocytes and thereby delays cardiac repolarization. Evident on an electrocardiogram as a prolongation of the QT interval, this mechanism is thought to underlie an increase in the risk of torsade de pointes, a potentially fatal arrhythmia, with macrolides. A recently published large cohort study has found a significantly increased risk of cardiac death associated with clarithromycin. No increased risk was seen with roxithromycin.[109] Nasal douching provides symptomatic benefit, and should be used with sterilized or distilled water to avoid contamination.

Surgical

Surgical management is considered for patients who have failed to respond to maximal medical treatment and for those with complications.

Functional endoscopic sinus surgery aims to improve sinus ventilation and drainage as well as removing polyps. The extent of surgery varies with the extent of disease, the surgeon's individual practice and available technology. Functional endoscopic sinus surgery has been used for many years to treat sino-nasal conditions and permits a better view of the surgical field, allowing more precise clearance of the inflammatory change than conventional surgery. It may be associated with fewer complications and lower recurrence rates.[110, 111]

Patients being treated for polyp disease derive the greatest benefit from functional endoscopic sinus surgery, and those whose main preoperative symptom is nasal obstruction or headache report higher benefit. Coexistent asthma, allergic rhinitis or aspirin intolerance does not decrease the benefit of sinus surgery in patients with polyps.

Postoperatively, patients should be treated with nasal douching and intranasal or systemic corticosteroids, and compliance with this treatment will influence the long term efficacy of surgery. There is good evidence that postoperative use of topical nasal steroids reduce the rate of polyp recurrence.[112]

SUMMARY

Nasal polyps are a chronic disease of the upper respiratory tract that form as an end result of severe inflammation in the nose and paranasal sinuses and are considered to be a subgroup of chronic rhinosinusitis. Although not life-threatening, they can cause severe symptoms with a significant impact on quality of life. Nasal polyps arise in patients with chronic inflammation resulting from many different pathologies and why certain patients develop polyps remains unknown. Extensive research has resulted in a greater understanding of this disease, with evidence that bacteria, fungi, allergens, and superantigens play a prominent role in the pathophysiology of nasal polyps. However the exact cause remains elusive. The annual incidence of nasal polyps is between 1 and 20 per 1000 population. Certain systemic diseases are associated with a much higher incidence of CRSwNP with a prevalence of around 7% in patients with asthma and up to 30–60% in patients with aspirin exacerbated respiratory disease.

Anterior rhinoscopy is the first step to diagnosis, but cannot exclude polyps. Rigid nasendoscopy after is required for diagnosis. CT scanning with coronal sections is the investigation of choice for assessing the extent of the disease and detailing the anatomy before surgery.

A combined treatment strategy involving both medical and surgical management is recommended for long-term control because of the chronic and recurrent nature of the disease, with treatment aiming to eliminate nasal polyps and rhinitic symptoms, re-establish nasal breathing and olfaction, prevent recurrence and improve patients' quality of life. Medical treatment consists mainly of intranasal

BEST CLINICAL PRACTICE

- ✓ Initial medical treatment with topical intranasal corticosteroids
- ✓ Clinical review allows adjustment of medical therapy, planning of further investigations and reduces need for surgery
- ✓ Consider surgery in patients who have failed to respond to maximal medical therapy
- ✓ Unilateral nasal polyps are tumours until proved otherwise

and systemic corticosteroids, thought to affect eosinophil function by reducing both eosinophil viability and activation, and by reducing the secretion of chemotactic cytokines. This improves nasal airflow, reduces polyp size and decreases the rate of recurrence. Surgical management should be reserved for patients who have failed to respond to maximal medical treatment.

KEY POINTS

- Nasal polyps can cause severe symptoms and can have a significant impact on quality of life.
- Although known to be associated with chronic inflammation the exact aetiology remains elusive.
- Nasal polyps are associated with many chronic conditions including asthma, aspirin exacerbated respiratory disease and cystic fibrosis.
- Nasal polyps can be easily diagnosed with anterior rhinoscopy and nasendoscopy.
- Combined medical and surgical treatment is recommended for long-term control of symptoms.
- Unilateral nasal polyps should be treated as suspected malignancy until biopsy proves otherwise.

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CHAPTER 96

FUNGAL RHINOSINUSITIS

Eng Cern Gan and Amin R. Javer

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed and Medline search using the following keywords: fungal rhinosinusitis, fungal ball, mycetoma, allergic fungal rhinosinusitis, invasive fungal rhinosinusitis.

INTRODUCTION

Fungal rhinosinusitis (FRS) can be categorized into two broad groups; invasive and non-invasive.[1] This is based on the presence or absence of fungus in the tissue (mucosa, blood vessel or bone) respectively.[2]

NON-INVASIVE FRS

SAPROPHYTIC FUNGAL INFECTION

Saprophytic fungal infection refers to visible fungal colonization of mucus crusts seen within the nose and paranasal sinuses on nasoendoscopy (**Figure 96.1**).[3, 4] These patients are usually asymptomatic or may present with a foul smelling odour.[2] The proposed mechanism is dysfunction in mucociliary transportation from surgery leading to crust formation. The crust then acts as a platform for growth of fungal spores.[3] It has been suggested that saprophytic fungal infections may be precursors to fungal balls if left untreated.[3] Endoscopic cleaning of the infected crust with or without continued self-irrigation with saline is usually the only treatment required.[3]

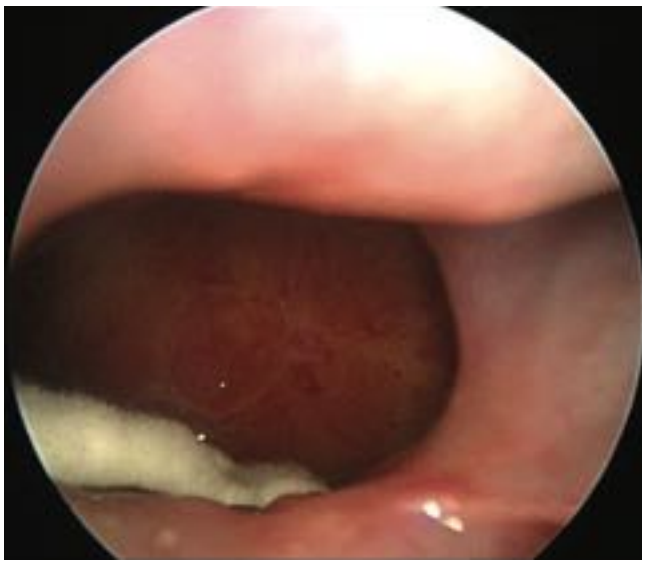


Figure 96.1 Saprophytic fungal infection where visible fungus is seen growing on mucosal crust.

FUNGAL BALL

A fungal ball is a dense accumulation of extramucosal fungal hyphae, usually within one sinus, most commonly the maxillary sinus.[2] Although the most common organism in a fungal ball is *Aspergillus*, the cultures are often negative and other fungal species have also been identified.[2] Fungal balls are seen more commonly in immunocompetent, middle-aged and elderly females, often with a history of previous dental procedure, especially dental fillings.[2]

The diagnosis of fungal ball is based on the following features: radiological findings of sinus opacification often with areas of hyperattenuation, cheesy or clay-like debris within the sinus (**Figure 96.2a and 96.2b**), accumulation of fungal hyphae without evidence of tissue fungal invasion seen microscopically, non-specific chronic inflammation of the sinus and the absence of eosinophil predominance, granuloma or allergic mucin.[1]





Figure 96.2(a–b) (a) Image guidance system (IGS) CT images of a left maxillary sinus fungal ball showing areas of hyperattenuation. **(b)** A centrally located calcification within a completely opacified left maxillary sinus from a fungal ball. The calcification is due to metabolic deposits of calcium within the fungal concretions.

The management involves a wide opening of the involved sinus and complete removal of the fungal debris. Examination of the involved sinuses with angled scopes is crucial to ensure complete surgical extirpation. Subsequent regular surveillance in the clinic is necessary. Oral or topical antifungals are not necessary.

FUNGUS-RELATED EOSINOPHILIC FRS INCLUDING ALLERGIC FUNGAL RHINOSINUSITIS (AFRS)

Introduction

AFRS is a non-invasive fungal sinusitis resulting from an allergic and immunologic response to the presence of extramucosal fungal hyphae in the sinuses. It was first recognized as an upper airway manifestation of allergic bronchopulmonary aspergillosis (ABPA) in the 1970s.[5] Although *Aspergillus* was the presumed pathogen in the first few early case series, subsequent case series showed that dematiaceous fungi such as *Bipolaris*, *Curvularis* and *Alternaria* were more common.[6]

Epidemiology

The prevalence of FRS amongst chronic rhinosinusitis (CRS) patients who undergo surgery is between 12 and 47%.[7, 8] Of this, AFRS is the most common form, accounting for between 56 and 72% of patients with FRS.[7, 8] The typical AFRS patients are young immunocompetent adults.[9] The mean age at presentation is between 21 and 33 years old.[10] There is a higher male to female ratio of between 1.5 and 2.6 to 1.[10] Wise et al. found that AFRS patients also have a lower socioeconomic status and a higher African American ratio compared to CRS patients.[10]

Pathophysiology

Although it has been over 30 years since AFRS was first described, the underlying pathophysiology remains unknown and controversial. A number of popular theories have evolved. Manning et al. proposed a mechanism derived from the ABPA model.[11] Based on studies demonstrating raised fungal-specific IgE antibodies and IgG antibodies in AFRS patients, it is believed that an atopic host exposed to fungi resulted in antigenic stimulation by a combination of Gell and Coombs type I and type III hypersensitivity.[11, 12]

While the immunologic theory proposed by Manning et al. is supported in the literature, it fails to explain the unilateral or asymmetric nature of AFRS, the persistence of a raised IgE level after prolonged fungal immunotherapy and the failure of a rise in specific IgG levels resulting from the formation of IgG-blocking antibodies following fungal immunotherapy.[13] An alternative theory was later proposed by Panikou et al.[14] Their landmark but non-peer-reviewed paper stated that fungi were present in

the nasal secretions of 96% (202 patients) of consecutive CRS patients and 100% (14 patients) of healthy volunteers with no sinus disease. Elevated total and specific IgE levels were not prevalent amongst the AFRS patients and not significantly different to that of the control group. Hence, they rejected the role of an IgE-mediated reaction in the pathogenesis of AFRS. Rather, eosinophilic chemotaxis in response to extramucosal fungi was the hallmark of the inflammatory reaction in AFRS. The term **eosinophilic fungal rhinosinusitis** (EFRS) was introduced. Similarly, the term **eosinophilic mucin** was suggested as a replacement for **allergic mucin** to emphasize the importance of eosinophils in the pathophysiology of AFRS. However, the eosinophilic theory does not explain the triggering factor for eosinophil chemotaxis.

In 2000, Ferguson performed a literature review and concluded that there may be two different disease processes in play: allergic and non-allergic fungal rhinosinusitis.[15] The term **eosinophilic mucin rhinosinusitis** (EMRS) was used to describe non-allergic fungal sinusitis. These patients were felt to have histological features similar to AFRS but without the presence of fungus. The underlying mechanism was believed to be a systemic dysregulation of immunologic controls resulting in upper and lower airway eosinophilia. By recognizing EMRS and AFRS as two separate entities with a similar phenotypic endpoint, the treatment strategies for these patients can be formulated according to their pathogenesis. Antifungal agents and fungal immunotherapy should theoretically benefit only AFRS and not EMRS patients.[15]

Diagnostic criteria

In 1994, Bent and Kuhn described a diagnostic criteria for AFRS based on 15 consecutive AFRS patients.[16] They found 11 important clinical features, 5 of which were present in all 15 patients. These 5 features were termed major criteria and the remaining 6 features as minor criteria. All 5 major criteria were necessary to define AFRS while the minor criteria were considered supporting features (Box 96.1). These criteria set the benchmark for diagnosis of AFRS for many years with minor variations proposed over the years.

There exists a subgroup of patients who do not meet all five major criteria but behave like AFRS patients and respond to AFRS treatment strategies (previously known as **atypical AFRS**). We have therefore adopted the Bent and Kuhn criteria with minor modifications to be more inclusive. An elevated IgE level is not always present in all AFRS patients and may fluctuate within the normal range as the disease stage changes.[9, 17] We currently utilize the following five major criteria to diagnose patients with AFRS (Box 96.2).

BOX 96.1 Bent and Kuhn Diagnostic Criteria for AFRS

Major criteria	Minor criteria
• Evidence of type I IgE–mediated hypersensitivity • Nasal polyposis • Characteristic CT findings • Eosinophilic mucus • Positive fungal smear	• Asthma • Unilateral predominance • Radiographic bone erosion • Fungal culture • Charcot-Leyden crystals • Serum eosinophilia

BOX 96.2 St Paul's Sinus Center Diagnostic Criteria for AFRS

Major criteria
• Immunocompetent patient • Presence of nasal polyposis • Characteristic CT findings • Presence of allergic mucin • Positive fungal cultures or the presence of fungal hyphae on fungal staining

Clinical presentation

Although there are no pathognomonic symptoms for AFRS, clinical suspicion should be high when one encounters a young patient with uni- or bi-lateral nasal polyposis with thick, sticky yellow/green mucus, characteristic double density sign on CT and who responds to oral steroids. Often, the symptoms are subtle and similar to that of chronic sinusitis with nasal polyposis.[18] On nasoendoscopy, inspissatted thick yellow or brown peanut-butter like mucus may be seen among the polyps (Figure 96.3a–c).

Investigation

IMMUNOLOGIC TEST

Patients with AFRS have an elevated IgE level. In a long term follow-up of AFRS patients by Marple et al. the total IgE levels were found to be between 50 and >1000 IU/ml. The average total IgE level was about 550 IU/mL. Because of the wide range of total serum IgE levels in AFRS patients, it is not useful as a screening tool.[19] However, total serum IgE level may be useful in monitoring clinical activity in the management of AFRS.[17] An *in-vivo* (skin prick) or *in-vitro* (RAST) test can be utilized to demonstrate fungal specific IgE as a diagnostic criteria for AFRS.[20, 21]

IMAGING – COMPUTED TOMOGRAPHY (CT) AND MAGNETIC RESONANT IMAGING (MRI) SCANS

AFRS patients have typical features that are present on an unenhanced CT and enhanced MRI scans of the paranasal sinuses (Box 96.3).[22, 23]

CT without contrast is the imaging of choice in suspect patients. The focal or diffuse areas of hyperintensity seen on CT are due to calcium and manganese deposits in the necrotic debri of the fungus and allergic mucin.[22] This results in a 'double density' or rail-track sign, (Figure 96.4). The optimum setting in the bone protocol



Figure 96.3(a–c) Clinical appearance of AFRS. **(a)** Nasoendoscopic picture of the left nasal cavity of an AFRS patient with allergic mucin covering a nasal polyp. **(b)** Allergic mucin is being suctioned out from the left sphenoid sinus. **(c)** Gross appearance of allergic mucin.

BOX 96.3 Characteristic findings of AFRS on CT and MRI scans of the paranasal sinuses

CT features	MRI features
• Heterogenous signal intensities within the paranasal sinuses filled with allergic mucin ('double density sign') • Expansion of the paranasal sinuses/nasal cavity • Unilateral or asymmetric disease load • Bony erosion	• T1 weighted images – central areas of hypointensity with peripheral enhancement • T2 weighted images – central areas of hypointensity or signal void with peripheral enhancement

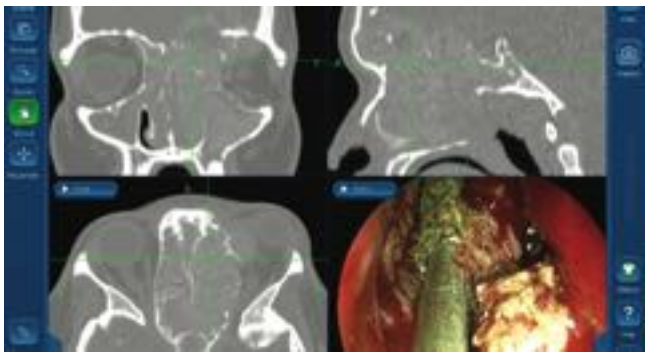


Figure 96.4 IGS CT images of a patient with extensive AFRS. There is a large erosion of the left skull base with intra-cranial extension as well as erosion of the left lamina papyracea. There is complete opacification of all sinuses with heterogeneity in signal intensity that is most obvious in the left maxillary sinus ('double density' sign).

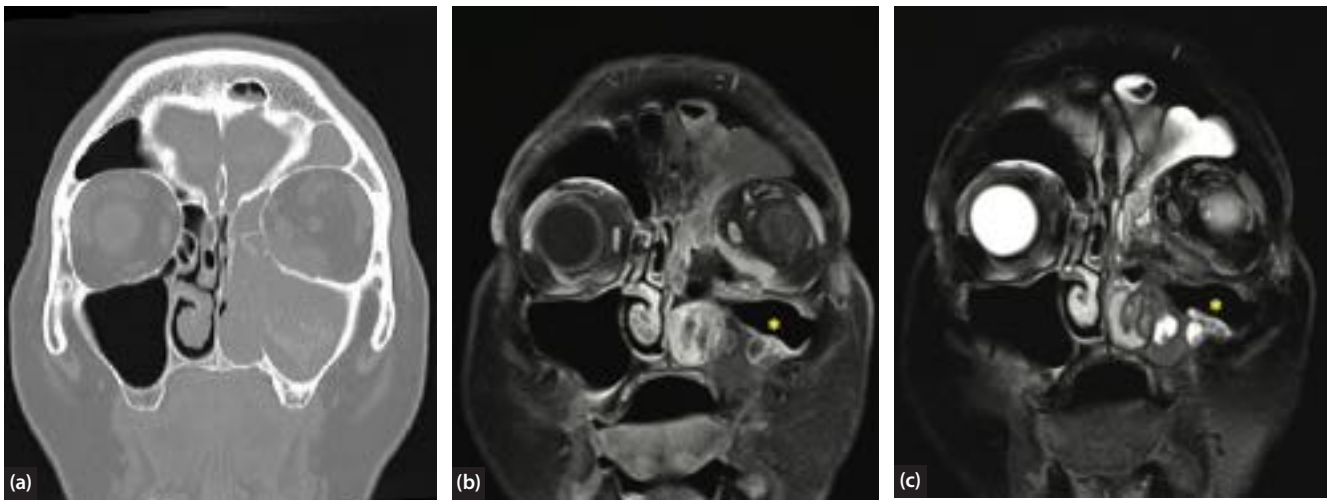


Figure 96.5(a–c) Radiographic imaging of a patient with chronic invasive fungal rhinosinusitis with fungal concretions in the left maxillary sinus. **(a)** Coronal cut of a CT scan showed complete opacification of the left maxillary sinus with areas of hyperattenuation, suggestive of fungal concretions. **(b & c)** Coronal cut of a T1–weighted MRI **(b)** and T2–weighted image **(c)** of the same patient showing a signal void (asterisk) from the fungal concretions in the left maxillary sinus. The signal void is due to heavy metals (iron, magnesium and manganese) within the fungal concretions.

to accentuate this sign is a window width of ~2000 House unit (HU) and centred at ~–250/–200.[24]

MRI of the paranasal sinus with intra-venous gadolinium contrast can be considered when the diagnosis of AFRS is uncertain or if there are concerns with rare intra-cranial or intra-orbital complications. The protein content and viscosity of the secretion will determine the signal intensity seen on MRI. In fungal infections, the consistency of the secretion usually results in a low intensity on T1 and a much lower intensity to signal void on T2 (**Figure 96.5**a–c).[22] This is due to higher concentration of iron and manganese as well as calcium deposits within the fungal concretions.[23]

HISTOLOGY

The hallmark of AFRS is the presence of allergic mucin. Grossly, it is thick, tenacious and highly viscous in consistency.[18] Hence, the terms 'peanut butter' and 'axle-grease' are often used to describe the characteristic appearance of the mucus. Histologically, allergic mucin consists of an eosinophilic mucin with necrotic eosinophils, inflammatory cells, Charcot-Leyden crystals (the by-product of eosinophil) and fungal hyphae (**Figure 96.6**a).[25] As fungal hyphae are infrequent and scattered within allergic mucin, their detection is difficult unless specific stains with a silver stain such as Grocott's or Gomori's methamine silver (GMS) stain are performed (**Figure 96.6**b).[18]

FUNGAL CULTURE

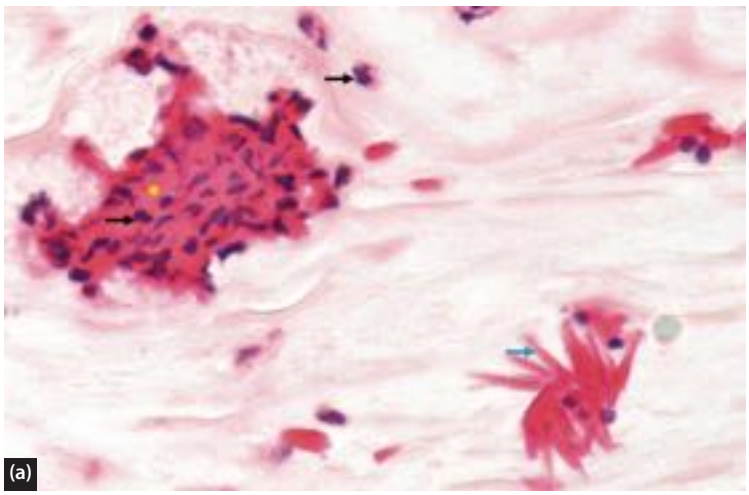
A positive fungal culture provides supporting evidence in the diagnosis of AFRS. However, its absence does not exclude the diagnosis of AFRS. The presence of a positive fungal culture in AFRS patients ranged from 49 to 100%, depending on the culture method used.[6, 12, 14, 26, 27] In our institution, positive fungal cultures were obtained in 64% of AFRS patients using a modified Mayo Clinic fungal culture technique. Likewise, a positive fungal culture does not confirm the diagnosis of AFRS. The histological identification of allergic mucin is still the most reliable marker for the diagnosis of AFRS.[18]

Management

Once a diagnosis of AFRS has been established, patients are enrolled into a committed long-term management program with regular and long-term follow-up considered critical to the success of the treatment. A combination of surgery with a comprehensive post-operative medical regimen to keep the disease under control is almost always required.[28]

SURGICAL TREATMENT

Unlike the management of classical CRS, surgery is usually the first line treatment in the management of AFRS. Meticulous and complete endoscopic sinus surgery is the gold standard for the surgical extirpation of polypoid disease and allergic mucin in an attempt to restore ventilation and drainage of the sinuses.[9] Removal of allergic mucin and fungal debris eliminates the antigenic factor that incites the disease in an atopic host. Surgery also provides wide access for surveillance, clinical debridement and application of topical medication. In our center, functional endoscopic sinus surgery (FESS) for AFRS patients is routinely carried out with image-guidance system (IGS). We feel that the use of IGS allows complete removal of diseased cells in the sinuses and minimizes the risk of complications from distorted anatomy.



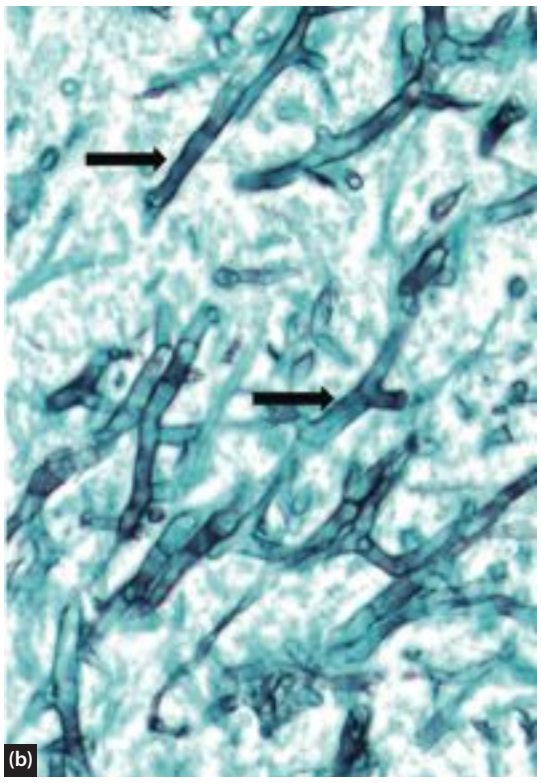


Figure 96.6(a–b) Histology of allergic mucin and fungal hyphae. (a) H&E stain of allergic mucin showing eosinophils (black arrows), eosinophil aggregate (yellow asterisk) and Charcot-Leyden crystals (blue arrow) on a mucinous background. **(b)** Fungal hyphae (black arrows) with 45° branching and septation typical of *Aspergillus sp*. (GSM stain). Slides are courtesy of Dr Blair Walker, Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, Canada.

ENDOSCOPIC STAGING OF MUCOSAL DISEASE POST-SURGERY

Regular follow-up and accurate documentation of the sinonasal mucosa of AFRS patients after surgery is critical to monitor disease status and response to adjunctive medical treatments. Kupferberg et al. devised a 4-stage system for endoscopic follow-up in these patients post-surgery (Table 96.1).[30] However, the Kupferberg staging system lacks sensitivity, often resulting in patients remaining in the same endoscopic stage despite having improved symptomatically and endoscopically. In 2010, Philpott et al. introduced a new endoscopic staging system for AFRS. The Philpott-Javer system[30] is a validated mucosal staging system that was derived from modifications made to the Kupferberg system. Such a system is much more sensitive and allows for much better tracking of disease control post-operatively (Figure 96.7).

TABLE 96.1 Kupferberg post-operative endoscopic staging system for AFRS

Stage	Endoscopic finding
I	Normal mucosa
II	Mucosal oedema/allergic mucin
III	Polypoid oedema/allergic mucin
IV	Sinus polyps and fungal debris

Medical treatment

SYSTEMIC MEDICATIONS

I. Corticosteroids

Oral steroids are useful in the perioperative period of patients with AFRS. In the pre-operative period, a short course of coritcosteroids reduce intra-operative bleeding

Sinus Cavity	Right	Mucin	Left	Mucin
Olfactory cleft	0-9	1	0-9	1
Frontal	0-9	1	0-9	1
Ethmoid	0-9	1	0-9	1
Maxillary	0-9	1	0-9	1
Sphenoid	0-9	1	0-9	1
Total	50		50	
Bilateral total	100			

Grading	State of Mucosa
0	No oedema
1-3	Mucosal oedema (mild/moderate/severe)
4-6	Polypoid oedema (mild/moderate/severe)
7-9	Frank polyps (mild/moderate/severe)



Figure 96.7 A clinic poster for the Philpott-Javer endoscopic staging system for AFRS.

and size of the polyps.[13] In a prospective comparative study by Landsberg et al, AFRS patients who received oral steroids pre-operatively showed greater radiologic and endoscopic improvement compared to CRSwNP patients.[31]

In the post-operative period, the corticosteroids regimen was initially derived from the protocol used in treatment of ABPA.[32] In a 4-year follow-up study of 11 AFRS patients by Kuhn and Javer, a reduction in IgE and mucosal disease post-operatively were seen in patients who were on steroids. They found that in order to prevent recurrence, a minimum of 6 months of normal sinus mucosa while on steroids is necessary before steroids can be slowly discontinued.[17] A 6-month post-operative regimen of tapering corticosteroid therapy was proposed by Kuhn and Javer, including the use of high-dose intranasal corticosteroids.[29]

Systemic steroids, although beneficial in the perioperative period, are not without adverse side effects. Although long-term oral corticosteroid may be necessary in some patients, its use should be judicious and limited to short courses in the perioperative period and in acute exacerbations of AFRS to suppress growth of recurrent polyps.[33]

II. Antifungals

Oral antifungals are considered a viable treatment option for patients with recalcitrant AFRS. They are also used as a steroid-sparing medication, allowing some patients to be weaned off from long-term oral corticosteroid therapy.[34] Early reports by Bent and Kuhn on the efficacy of oral antifungals in AFRS patients showed mixed to poor results.[35] However, subsequent retrospective case series showed that oral itraconazole (200–400 mg daily) has potential benefits as a steroid sparing alternative and in prolonging time to disease recurrence.[34, 36, 37] Oral itraconazole is associated with risk of elevated liver enzymes, congestive heart failure, nausea, rash, headache, malaise, fatigue and oedema (Janseen Pharmaceutica, Beerse, Belgium). Asymptomatic transaminitis is not uncommon (4–19%)[34, 36] and cessation of treatment is usually sufficient for the elevated liver enzymes to revert back to normal. It appears that a subset of AFRS patients seem to respond to antifungals. Future RCTs are needed to identify the ideal candidate and to assess the efficacy, safety and optimal dosage and regime for oral antifungals in the treatment of AFRS.

TOPICAL MEDICATION

I. Corticosteroid

Topical corticosteroids are used as standard treatment for patients with AFRS. They are most effective in the post-operative period when open sinus cavities and middle meati allow access to the paranasal sinuses. The benefit of topical over systemic steroid lies in the ability of topical steroid to achieve the highest drug concentration in the target tissue (sinonasal mucosa) without the undesirable systemic side effects.[38] Although studies on the efficacy of intra-nasal steroids in AFRS patients are lacking, their benefits have been well established in CRS patients with nasal polyposis.[39] An evidence-based review with recommendations based on Grade A evidence by Rudmik et al. provided a strong recommendation for the use of standard topical nasal steroids for the management of CRS.[40] Standard topical nasal steroids are metered-dose topical steroid solutions that have been approved for use in the nasal cavity by the U.S. Food and Drug Administration (FDA). These include metered-dose nasal sprays such as mometasone furoate, fluticasone propionate, fluticasone furoate, budesonide, beclomethasone dipropionate monohydrate, ciclesonide, flumisolide and triamcinolone acetonide.[40]

The use of budesonide administered as drops, atomized sprays or through low volume saline rinses have gained popularity in the treatment of AFRS patients. These are 'non-standard' topical nasal steroids and are not FDA approved for application in the nasal cavity. Other 'off-label' non-standard topical steroids that have been used in the sinonasal cavity include low-volume solutions such as intra-nasal dexamethasone ophthalmic drops (0.1%), prednisolone ophthalmic drops (1%) and ciprofloxacin/dexamethasone otic drops (0.3/0.15).[40] Non-standard topical nasals steroids have the advantage of delivering higher volume and/or high concentration of steroids into the sinonasal cavity. In the treatment of post-operative refractory CRS patients, topical budesonide (Pulmicort Respules) via the Mucosal Atomization Device (MAD; Wolfe-Tory Medical, Salt Lake City, UT) resulted in improvements in both physician and patient global assessments and also reduction in the use of oral prednisolone (**Figure 96.8**).[41]



Figure 96.8 Pulmicort nebule and the MAD syringe.

The main concern of non-standard topical nasal steroids sprays is systemic absorption resulting in unwanted systemic side effects. In post-surgical CRS patients, Sachanandani et al. demonstrated that budesonide nasal irrigation (2.5 mg of budesonide diluted in 5 ml of normal saline in each nasal cavity) for 30 days improved clinical symptoms of CRS without hypothalamic-pituitary-adrenal (HPA) axis suppression.[42] A prospective study was conducted in our centre to determine if application of high dose budesonide (1 mg of Pulmicort Respules twice a day) via the MAD over 2 months causes HPA suppression and results in an increase in plasma cortisol and detection of plasma budesonide. The result of the ten patients subjected to high dose budesonide delivered via the MAD did not show any evidence of HPA suppression nor any elevation of plasma cortisol or presence of plasma budesonide.[43] Hence, the use of topical budesonide delivered via the MAD looks promising as an effective and safe adjunct in the treatment of AFRS.

At our centre, AFRS patients are instructed to use budesonide rinses (2 ml of 0.5 mg/ml Pulmicort Respules in every 60 ml of normal saline) in the immediate post-operative period. After 3 weeks post-operatively, the budesonide is delivered through a MAD (1 ml in each nostril). Patients are taught to apply the spray in the Mygind position (**Figure 96.9**). We favour the Mygind position as it is supported by our recently completed study on post-FESS cadaveric heads. Our study showed superior distribution of fluorescein within the ethmoid and frontal sinuses and the frontal recess when the head was placed in the lateral-head-back (LHB) position compared to the vertex-to-floor (VTF).[44]



Figure 96.9 Application of Pulmicort through the MAD in the Mygind position.

II. Antifungals

In CRS, topical antifungals have been deemed ineffective in a number of meta-analyses and systemic reviews.[40, 45–48] As AFRS is a different disease entity resulting from an immunologic hyperreaction to extramucosal fungus,[11, 12] topical antifungals should hypothetically reduce the immunologic reaction of an atopic host by decreasing the antigenic load. In a RCT of 50 AFRS patients by Khalil et al., the fluconazole nasal spray arm had the best recurrence rate (10%) followed by combined oral itraconazole and topical fluconazole (14.3%), fluconazole nasal irrigation (28.6%), oral itraconazole alone (66.7%) and control (75%).[49] Although results from this RCT appeared promising, larger RCTs will be required to establish the role of topical antifungals in the management of AFRS.

III. Immunotherapy (IT)

In ABPA, IT has been avoided due to the possibility of an immune complex-mediated reaction developing from the IgG produced by IT.[50] As opposed to ABPA, the fungal antigenic stimulus can be removed surgically in AFRS patients. Surgical removal of fungal debris and allergic mucin in AFRS patients has also been shown to decrease allergen-specific IgE levels for fungal antigen.[11] Hence, it can be argued that fungal IT after surgery may potentially provide benefit rather than harm in the management of AFRS.[50]

A literature review by Hall and deShazo in 2012 revealed ten studies on fungal IT in AFRS patients.[50] In most studies, there were improvements in clinical outcomes. No major systemic reactions, nor evidence of worsening of disease in patients treated with fungal IT were reported. The only side effects reported were minor local reaction. Although the results of fungal IT appeared promising, the lack of RCT warrants better-designed research to establish the efficacy and safety of fungal IT in the treatment of AFRS.

Adjunctive treatment

MANUKA HONEY

Manuka (*Leptospermum scoparium*) honey from New Zealand is the most therapeutically potent honey.[51] It has been shown to be active against a broad spectrum of gram-positive and gram-negative bacteria.[52] The principal active ingredient responsible for the antibacterial property in Manuka honey is methylglyoxal (MGO).[53] MGO is present in Manuka honey at a concentration of up to 100-fold that of conventional honey.[53] In an *in vitro* study by Alandejani et al., Manuka honey at a concentration of 33% v/v was shown to be effective in eradicating methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* (PA) biofilms.[54] In fact, conditions that rapidly induced antibiotic resistance did not cause bacterial resistance to honey.[55]

At St Paul's Sinus Centre, our early experience with Manuka honey irrigation (**Figure 96.10**) in AFRS patients refractory to surgery and post-operative oral and intranasal steroids showed a partial response to Manuka honey with 21% of patients showing mucosal improvement after treatment with Manuka honey irrigation in one nostril.[56] It appears that there is a subgroup of AFRS patients who do respond well to Manuka honey irrigation. In our recently completed RCT (unpublished) comparing post-FESS patients treated with either Manuka honey or saline solution for 3 months, we found a cytokine signature of up-regulated interleukin (IL)-1b, IL-4, IL-6 and



Figure 96.10 Manuka honey preparation and the power rinse bottle for sinus irrigation.

IL-12 in the sinonasal mucosa of patients who responded to Manuka honey treatment. This preliminary result looks promising and larger studies to confirm the result of this study will be warranted.

Future treatment strategy

ANTI-IMMUNOGLOBULIN E (IGE) THERAPY

Omalizumab (Xolair) is a humanized monoclonal anti-IgE antibody that has been used as an adjuvant treatment in severe atopic asthma, allergic rhinitis and CRS with nasal polyposis.[57, 58] In the only randomized double-blind placebo-controlled trial on omalizumab therapy on nasal polyps and asthma patients, Gevaert et al. demonstrated that there was significant improvement in total nasal endoscopic polyp scores, CT findings, airway symptoms and quality of life scores after 16 weeks of omalizumab treatment.[59] These improvements were seen irrespective of the presence of allergy. Omalizumab therapy has also been shown to be effective in ABPA patients.[60] Given the pathophysiological similarity between ABPA and AFRS, the use of omalizumab in AFRS patients should be explored. At our centre, seven patients with refractory AFRS and raised IgE levels with moderate or severe asthma underwent subcutaneous omalizumab injections (mean number of injections = 7.57; mean dosage = 287 mg; mean follow-up period = 9.7 months). They had improved sinonasal symptoms and endoscopic scores and were less dependent on corticosteroid and antifungal treatments.[61] We are excited about the outcome of this study which we hope will pave the way for a double blind RCT to determine the efficacy of this drug.

INVASIVE FRS

ACUTE (FULMINANT) INVASIVE FRS

Acute or fulminant invasive FRS is a life-threatening disease present usually in immunocompromised patients with impaired neutrophilic response. These patients include those with uncontrolled diabetes mellitus, acquired immunodeficiency syndrome (AIDS), iatrogenic immunosuppression, organ transplantation and haematological malignancies.[62] This condition is characterized by the presence of hyphal invasion of sinus tissue and a time course of less than 4 weeks.[3, 4] Histological features include mycotic infiltration of blood vessels, vasculitis with thrombosis, tissue infarction, haemorrhage and acute neutrophilic infiltrate.[1] *Aspergillus* species and the fungi in the order of mucorale (e.g. *Rhizopus*, *Rhizomucor* and *Mucor*) are the most commonly implicated species.[1]

The inability to mount a host response to invasive fungal disease in immunocompromised patients can make the diagnosis of this disease entity difficult, especially in the early stages.[63] Although common reported clinical symptoms include fever, cough, crusting of the nasal mucosa, epistaxis and headaches,[1] a high index of suspicion of this disease entity should be present in any immunosuppressed patients with localizing sinonasal symptoms. Often, fever of unknown origin that has failed to respond to 48 hours of broad-spectrum intravenous antibioitcs may be the initial presenting symptom.[64]

In the early stages, nasoendoscopic findings may be as subtle as the presenting symptoms. Alteration in mucosal appearance such as a discoloration, granulation and ulceration are the most consistent physical findings.[65] There are no pathognomonic features for invasive FRS on imaging and a CT scan is the initial radiologic investigation of choice (**Figure 96.11**). Compared to AFRS, invasive FRS tends to have more focal bony erosions, lacks expansion of the sinuses, has more limited sinus disease and has more disease outside of the sinuses than within when there is intra-orbital or intra-cranial extension.[23]

Without early treatment, rapid progression of disease with 50–80% mortality rates from intra-orbital and intracranial complications have been reported.[64] Improvement of the host immune response is paramount for survival. Surgery is necessary to halt or slow progression of the disease (allowing time for bone marrow recovery), to reduce fungal load and to provide a tissue culture.[64]

Prior to definitive identification of the causative fungi, empirical treatment with intravenous amphotericin B, a broad-spectrum antifungal agent, has been recommended.[66] Once a causative fungal species has been identified, the use of the triazoles (fluconazole, itraconazole and variconazole) can be considered.[63, 66] The triazoles are effective in the treatment of invasive FRS without the associated nephrotoxicity seen in standard amphotericin B.[66] However, the triazoles lack effectiveness against the *Mucorales* species and their presence should be ruled out before its use is considered.[1, 63]



Figures 96.11 Intra-operative IGS images of the sphenoid sinus of a patient with invasive FRS. The fungal disease has eroded the infero-posterior wall of the sphenoid sinus (which is formed by a pneumatized clivus).

GRANULOMATOUS INVASIVE FRS

This disease entity is defined by invasive fungal infection lasting more than 12 weeks.[4] It is usually of gradual onset and is seen more commonly in Sudan, India, Pakistan and Saudi Arabia.[1] The causative agent is almost exclusively *Aspergillus flavus*.[1] Patients are typically immunocompetent and the predominant clinical features include proptosis with an enlarging mass in the cheek, nose, paranasal sinus and orbit.[1, 63] CT findings are not different to that of chronic invasive FRS although they have a tendency for multiple sinus involvement.[67] The distinguishing feature from chronic invasive FRS is histological findings of fungal tissue invasion and a granulomatous reaction with considerable fibrosis. This is evident from the presence of non-caseating granulomas with foreign body or Langerhans-type giant cells, occasional vasculitis and sparse hyphae.[1, 4, 63] Treatment includes complete surgical removal and antifungal agents.

CHRONIC INVASIVE FRS

Chronic invasive FRS is a slowly destructive disease with a time-course of more than 12 weeks duration. Patients are usually immunocompetent or have subtle abnormalities in the immune system from diabetes mellitus, chronic low dose corticosteroid use and AIDS.[4, 63] The most common fungi implicated is *Aspergillus fumigatus*.[4] The clinical picture of chronic invasive FRS is similar to that of granulomatous invasive FRS. The ethmoid and sphenoid sinuses are most commonly involved.[4] On histology, chronic invasive FRS demonstrates invasion of fungi into the sinonasal mucosa with a dense accumulation of fungal hyphae, occasional vascular invasion, and chronic or sparse inflammatory reaction.[1, 4] There is no difference in the prognosis or the management of both chronic invasive and granulomatous invasive FRS.[4] For the occasional patients with invasive FRS with a time line between 4 and 12 weeks, the term subacute invasive FRS has been recommended.[4]

CONCLUSION

In summary, FRS is an uncommon but important part of the disease spectrum of CRS. Although there are certain clues from clinical and radiological findings, histology is key in distinguishing the different subtypes of FRS. Obtaining the correct diagnosis is crucial as each disease entity differs in the optimal management strategy. Antifungal agents are usually not required in the management of non-invasive FRS but are part of the first line treatment in invasive FRS.

BEST CLINICAL PRACTICE

- ✓ In the management of AFRS, endoscopic sinus surgery is required to decrease antigenic stimulation from the fungus; drain and ventilate the paranasal sinuses; and provide access to the surgeon for clinical surveillance, debridement and application of topical medication.
- ✓ Post-operative oral steroids and standard topical nasal steroids are recommended to maintain a healthy sinus cavity in the medical management of AFRS.
- ✓ Non-standard topical nasal steroid (e.g. budesonide), oral antifungals and immunotherapy are options in cases of refractory AFRS.

FUTURE RESEARCH

- ➤ There is insufficient evidence for the use of topical antifungals in the management of AFRS or invasive FR and more research in this area is required
- ➤ Omalizumab therapy may be a potential treatment option for the management of refractory AFS. The safety and effectiveness of this treatment modality should be explored in randomized controlled trials

KEY POINTS

- FR is categorized into non-invasive and invasive groups depending on the absence or presence of fungus within the sinonasal tissue respectively.
- AFRS is the most common type of FR.
- In medically fit patients with FR, endoscopic sinus surgery is indicated to remove fungal load and ventilate the involved paranasal sinuses.
- Intravenous antifungal agents and reversal of the immunocompromised status of the host are paramount in the management of invasive FR.

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CHAPTER 97

MEDICAL MANAGEMENT FOR RHINOSINUSITIS

Claire Hopkins

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SEARCH STRATEGY

The author consulted the suite of Cochrane reviews on chronic rhinosinusitis (www.cochrane.org/news/suite-cochrane-reviews-chronic-rhinosinusitis) to underpin the recommendations in this chapter.

MEDICAL MANAGEMENT OF ACUTE RHINOSINUSITIS

INTRODUCTION

Acute rhinosinusitis is common, affecting 6–15% of the population each year. The vast majority of cases are viral, with bacterial infection estimated in less than 2% of cases; however there is significant overlap, with viral infection triggering inflammatory changes that facilitate secondary bacterial infection. Most cases resolve spontaneously within 10 days, and the incidence of complications is very low. Medical treatment may be antimicrobial or anti-inflammatory, with an aim of reducing the infective and inflammatory load to both reduce the severity and duration of illness, to prevent recurrence and complications, or reducing symptom severity alone.

REDUCTION OF INFECTIVE LOAD

Inappropriate antibiotic use is a significant threat to public health in terms of increasing resistance, yet antibiotics are prescribed in over 80% of outpatient visits in the United States for acute rhinosinusitis (ARS),[5] and ARS is the fifth most common indication for antibiotic treatment. Although the majority of ARS is viral, antibiotics are often both expected by patients and prescribed by physicians.[1–4]

The majority of studies and meta-analyses have shown little benefit from antibiotics in most patients with ARS.[5–8] The most recent systematic review, published by the Cochrane Collaboration in 2012, included 10 trials with a total of 2450 adult participants.[9] Irrespective of antibiotic usage, 47% of participants were cured after one week and 71% after 14 days. Five more participants per 100 had shortened time to cure between 7 and 14 days if they received antibiotics instead of placebo (number needed to treat = 18). Purulent secretion resolved faster with antibiotics (odds ratio (OR) 1.58 (95% CI 1.13 to 2.22)), (NNT = 11, three trials). However, 27% of the participants who received antibiotics and 15% of those who received placebo experienced adverse events (OR 2.10) (number needed to treat to harm NNTH = 8, seven trials). Therefore, while there was a small beneficial clinical effect with antibiotics, there was also an increased risk of adverse effect.

While there are limitations with the evidence (there is often marked heterogeneity of patients, different diagnostic criteria applied, and most studies conducted in subspecialty clinics, rather than primary care), current evidence supports restricting antibiotic usage in uncomplicated ARS.

DIFFERENTIATING BACTERIAL FROM VIRAL ARS

If those with bacterial infection can be identified, a more selective approach to antibiotic prescribing may be applied. The gold-standard for confirmation is a positive bacterial culture from a maxillary sinus aspirate. However, this requires specialist care, and incurs patient morbidity. Endoscopically guided middle-meatal cultures have been shown to have good specificity but lower sensitivity when compared with direct aspiration. Symptomatic selection alone is unreliable, unilateral facial pain and nasal purulence have a positive predictive value of 40% and 50% only for positive bacterial culture. When a combination of 3 out of 4 of nasal purulence, purulence in the post-nasal space, high fever (>39C) and raised ESR are used, specificity may be increased to 80%.

Choice of antibiotic if indicated

Where a decision to treat with antibiotics has been made, due to the presence of complications or in severe infection, the choice can be based on culture results, or local resistance to common classes. A Cochrane review comparing different classes of antibiotics found no significant difference between penicillins or non-penicillins (cephalosporins, macrolides) or between non-penicillins and amoxicillin-clavulate. Prolonged courses (10–14 days) do not significantly increase cure rates, thus a short course of narrow-spectrum agents may reduce the risk of increasing antibiotic resistance.

Role of treatment in preventing complications

The incidence of complications of ARS is low. Of those cases of complicated ARS reported to a UK audit, 50% had received antecedent antibiotic treatment. When comparing the prevalence of complicated ARS is countries with widely differing rates of antibiotic prescribing, there seems to be little difference; in the Netherlands, with the lowest rates of antibiotic usage, the prevalence is reported at 3 per million population per annum while in the US it is 2.7–4.3 per million. Thus antibiotic usage does not seem to prevent the development of complications.

Reduction of inflammation

Studies of topical glucocorticoids have demonstrated some benefit for the relief of symptoms in both viral and bacterial ARS. A meta-analysis of three studies, with ARS diagnosed by symptoms and confirmed by radiologic or endoscopic studies, found that adult participants receiving INCS were more likely to have resolution or improvement of symptoms than those receiving placebo (73% versus 66.4%; risk ratio (RR) 1.11).[10] Higher doses of INCS had a stronger effect on improvement or complete relief of symptoms. When used as an adjunct to antibiotic therapy in the treatment of ABRS, a meta-analysis of placebo-controlled trials suggests that 15 patients would need to be treated with intra-nasal glucocorticoids to improve clinical symptoms in one patient.[11] As the risk of adverse events with short-term usage INCS is low, INCS can be recommended in ARS.

Similarly, meta-analysis supports a role for systemic steroid treatment as adjunctive treatment.[12] Four RCTs with a total of 1008 adult participants met our inclusion criteria. Acute sinusitis was defined clinically in all studies, with radiological confirmation in three. All participants received oral antibiotics and were assigned to either oral corticosteroids or the control (placebo in three trials and non-steroidal anti-inflammatory drugs in one). In all trials, participants treated with oral corticosteroids were more likely to have short-term resolution or improvement of symptoms than those receiving the control treatment: at Days 3 to 7, risk ratio (RR) 1.4; risk difference (RD) 20% and at Days 4 to 10 or 12, RR 1.3, RD 18%. An analysis of the three trials with placebo as a control treatment showed similar results but with a lesser effect size: Days 3 to 6: RR 1.2, RD 12% and Days 4 to 10 or 12: RR 1.1, RD 10%.

Symptomatic improvement

There is limited evidence to suggest that nasal decongestants may have a small beneficial clinical effect in reducing nasal congestion, but not overall duration of ARS.

There is little evidence that saline therapies assist in symptom relief. Low-volume saline sprays may assist in mucus and crusting but there is evidence that high-volume irrigations are poorly tolerated in the setting of acute inflammation and are currently not recommended.[13] A randomized study comparing hypertonic with isotonic saline found no difference between groups in terms of severity or duration of symptoms, but higher adverse events (local discomfort) associated with hypertonic saline.

Medical management in complicated ARS

The management of complications of ARS will often require surgical intervention to address the complication itself, but will also require ongoing medical management to treat the underlying sinus infection. Where possible, choice of antibiotic should be culture directed, and are usually be given intravenously, followed by an oral course on discharge. There are no randomized trials of the medical management of complicated ARS; however, in many published case series, decongestants are given. There is little evidence regarding the use of systemic steroids in such cases, but they are often given to reduce cerebral oedema associated with intra-cranial complications, and are likely to be more beneficial than detrimental.

Prevention of ARS

There is a growing body of evidence identifying allergic rhinitis as a predisposing factor for ARS. It would be reasonable to assume that optimal medical management of

AR may reduce the risk of ARS, but there are no studies to confirm or refute this. A recent systematic review found only a weak association between laryngeal reflux and ARS. Therefore, there does not appear to be any role for antireflux medication. One study has evaluated the benefit of INCS at the onset of symptoms of a common cold in reducing the risk of developing post-viral rhinosinusitis, and found no benefit.

MEDICAL MANAGEMENT OF CHRONIC RHINOSINUSITIS

INTRODUCTION

'The treatment of chronic rhinosinusitis is primarily medical, with surgery reserved for those who fail a trial of maximal medical therapy', is a commonly quoted approach in the management of CRS. However, what maximal medical therapy entails, and how to define those who fail to respond is perhaps more controversial than it may appear. This chapter hopes to address this and summarize current evidence.

OVERVIEW OF THE PATHOPHYSIOLOGY OF CRS

Chronic rhinosinusitis is a heterogenous group of several phenotypes, and is likely to represent the end-point of multiple aetiologies, rather than a single disease process. In some cases, sinonasal disease is a manifestation of systemic disease; examples include vasculitides, cystic fibrosis, sarcoidosis and cilial motility disorders. Medical treatment in these groups is usually directed at systemic disease management, where possible. CRS may also occur as a direct result of focal abnormalities; a foreign body, fungal ball, odontogenic infection or very rarely, an anatomical obstruction. Medical management plays no significant role in first-line management in this group, and treatment is usually surgical correction of the focal abnormality. Medical treatment may be required to facilitate normalization of the sinonasal mucosa post-operatively. These groups of *secondary* CRS will not be considered further in this section.

Primary CRS refers to the vast majority of patients that present to otolaryngologists with unexplained inflammation of the upper airway. It is common to find lower airway disease as part of a broader respiratory condition but not as a result of systemic disease. In these patients, with *primary* CRS, there is an interaction of intrinsic mucosal inflammation, local microbial community and mucociliary dysfunction, with each factor being of varying importance in individual patients.[14] Considerations of these three factors will help direct medical therapy in these patients; the aim will be to reduce inflammation, reduce bacterial load and optimize ciliary function by removing mucus. Chronic rhinosinusitis may be subcategorized by the endoscopic assessment of the middle meatus, if necessary after decongestant; polyps presenting to the middle meatus or nasal cavity is defined as *CRS with polyps* (CRSwNP), CRS *sine (without) polyps* (CRSsNP) is used when no polyps are visible on endoscopy, accepting that there may be polypoid change within the sinuses. While there is increasing recognition that CRSwNP and CRSsNP are opposing ends of a spectrum, there remains overlap between the conditions, and many studies to date have not separated according to phenotype. It is acknowledged that there is a move away from phenotyping the disease, and greater endotyping of the mucosal condition is anticipated.[15–16] Greater distinction occurs when separating the eosinophil dominated (or Th2 skewed) CRS group. This better defines the inflammatory process and often referred to as eosinophilic CRS (eCRS). However, little distinction occurs in routine clinical practice beyond phenotype. Therefore this review will combine both groups, but will highlight where medical therapies differ in efficacy.

TREATMENT TARGETING INTRINSIC MUCOSAL INFLAMMATION

Mucosal inflammation is the defining feature of CRS; it may be intrinsic, as in those with asthma and aspirin sensitivity, or occur as a result of local infection or environmental exposure. Glucocorticoids have formed the mainstay of medical therapy for CRS, while long-term macrolides, doxycycline and other novel approaches also target the inflammatory pathway.

Intra-nasal corticosteroids

There are many studies supporting the role of topical corticosteroids. For CRSwNP, 40 studies (3624 patients) met the inclusion criteria for a recent Cochrane review.[17] The primary outcomes were sino-nasal symptoms, polyp size and polyp recurrence after surgery. When compared to placebo, topical corticosteroids improved overall symptom scores (standardized mean difference (SMD) −0.46; $P < 0.00001$; seven trials, $n = 445$) and had a higher proportion of patients whose symptoms improved (responders) (risk ratio (RR) 1.71, $P = 0.0002$; four trials, $n = 234$). Topical corticosteroids also decreased the polyp score (SMD −0.73; $P < 0.00001$; three trials, $n = 237$) and had a greater proportion of patients with a reduction in polyp size (responders) (RR 2.09; $P < 0.00001$; eight trials, $n = 785$) when compared to placebo. Topical corticosteroids also prevented polyp recurrence after surgery (RR 0.59; $P = 0.0004$; six trials, $n = 437$). However, there is a significant amount of heterogeneity in the included studies. Some of these showed very little or no benefit. Subgroup analyses by sinus surgery status helps to explain this heterogeneity, revealing a greater benefit in reduction of polyp score when topical steroid was administered in patient groups who had undergone previous sinus surgery (SMD −1.19) compared to patients who had never had surgery (SMD −0.13; $P < 0.00001$). There was no

difference between groups in terms of adverse events. In CRSsNP, the number of studies available smaller, and the risk of bias greater, but a beneficial effect for INCS is found; ten studies (590 patients) met the inclusion criteria for meta-analysis.[18] The primary outcome was sino-nasal symptoms. When compared to placebo, topical steroid improved symptom scores (SMD −0.37; P = 0.002; five trials, *n* = 286) and had a greater proportion of responders (risk ratio 1.69; P = 0.002; four trials, *n* = 263). Even with a limited number of studies, heterogeneity was present and subgroup analyses of patients who had received sinus surgery versus those who had not was not significant (P = 0.35). However, only the sinus surgery group had a positive effect on meta-analysis. Subgroup analyses by topical delivery method revealed more benefit when steroid was administered directly to the sinuses than with simple nasal delivery (P = 0.04). There were no differences between groups for quality of life and adverse events.

Intra-nasal corticosteroids have an excellent safety profile, with the systemic bioavailability for second-generation compounds (mometasone and fluticasone) less than 1%[12] There is a low incidence of adverse events, with nasal irritation and epistaxis the most common, and are safe for long-term use. Studies show no evidence of nasal mucosal atrophy with long-term use,[19] or growth retardation in the paediatric population.[20] Patient education regarding delivery techniques and the need for compliance is essential (**Figure 97.1**).

In summary, INCS are beneficial in CRSwNP and CRSsNP, and the risk of adverse events low. However, the effect size is often very small and penetration into previously unoperated sinuses is limited, and there may be a greater response to topical therapy after surgery, utilizing direct delivery to the sinuses.

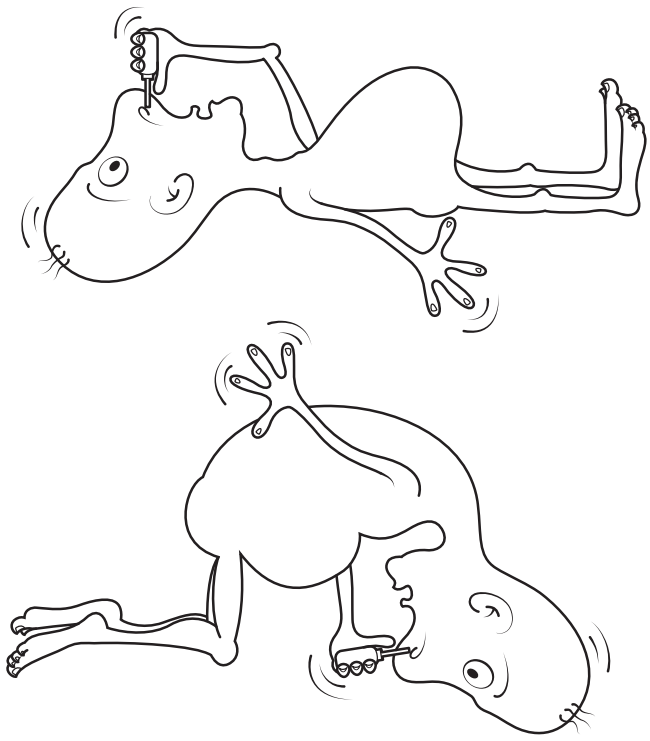


Figure 97.1 Correct application for nasal drops. (a) Head back position. **(b)** Head down position.

Systemic corticosteroids

In contrast, there is a relative paucity of comparative data for the efficacy of systemic corticosteroids. In CRSsNP, there are no RCTs, or studies evaluating systemic steroids alone: instead all case series supporting the use of systemic steroids combine therapy with antibiotics and INCS, and are at best level 4 or 5.[21–22] In CRSwNP, three trials (166 patients) were suitable for inclusion in systematic review,[23] and showed a short-term benefit of a short (2- to 4-week) course of oral steroids of variable doses and duration when compared to placebo. There was an objective reduction of polyp size and a subjective improvement of nasal symptoms and quality of life. There was no report of significant adverse effects of treatment with a short course of steroids. Therefore, for short periods, when the risk of adverse event is small, systemic steroids can be recommended for the treatment of CRSwNP. There are no studies to inform us as to the optimum interval between repeated courses of systemic steroids, and use should be weighed up against potential adverse events and discussed with individual patients. However, deriving a plan from best evidence may suggest that a course should last at least as long as the life-span of a tissue eosinophil, have a total or maximal dose below that reported in most case series of serious adverse event from systemic steroid and be infrequent enough to protect against long-term risks of osteoporosis and posterior subcapsular cataract formation. This is further discussed later in this chapter.

Immunomodulatory antibiotics

Long-term macrolide antibiotics are used for their anti-inflammatory effects, based on their efficacy in lower airways disease. They target markers including IL-8, IL-4, IFNγ and TNFα, and have a predominant effect on neutrophil-mediated inflammation. Open label studies have demonstrated improvement in symptoms. There are two prospective randomized controlled trials, one published after a Cochrane review on the topic. The first study included only CRSsNP and showed a significant effect of roxithromycin on symptom scores and IL-8 levels, with greater efficacy in patients with normal IgE levels. A subsequent study has found no effect; however this study included both CRSwNP and CRSsNP, and therefore it is likely that this study included more patients with elevated IgE than the first.[24]

Long-term use of macrolide antibiotics is associated with increasing levels of macrolide resistance, and gastrointestinal side effects are relatively common. Therefore use should be directed at those patients most likely to benefit (i.e. CRSsNP, normal IgE levels), and further studies are required.[25]

Doxycycline has been investigated for a potential anti-inflammatory role. In a PCRCT, a 20-day course of doxycycline was shown to reduce levels of myeloperoxidase,

eosinophil cationic protein, matrix metalloproteinase-9 in CRSwNP patients, and had a moderate and sustained effect on polyp size over a 12-week period.[26] The clinical impact of this effect, while present at 90 days, is likely to be of minimal clinical benefit. The difference between corticosteroid and the doxycycline was dramatic, but simple withdrawal of the corticosteroid at 20 days prevents sustained benefit. Doxycycline may be an adjunct in the eCRS subgroup while macrolides may assist in the non-eCRS patient.

Leukotriene receptor antagonists

Montelukast, a leukotriene receptor antagonist has been investigated in studies primarily as an adjunct to steroid treatment inpatients with CRSwNP and asthma. There is one positive single-blinded placebo controlled cross-over study with methodological problems, that shows benefit over placebo, while three other randomized trials were negative for change in polyp scores, although there were some benefits on some symptoms including sneezing and facial pain.[27] Most studies found greater benefit in patients with associated nasal allergy. There is the definite possibility of leukotriene receptor antagonists assisting with concomitant allergic rhinitis symptom control in these patients and may be the mechanism of effect as many of these patients have both conditions. This is also the basis of some benefit seen and reported by studies on immunotherapy and CRS.[28]

Novel immunoregulation

Direct targeting of the inflammatory pathway is possible using monoclonal antibodies. In two recent small PCRCTs, omalizumab (anti-IgE) has been shown to significantly reduce both symptom scores and polyp size,[29] and mepolizumab (anti-IL-5) has a significant effect on polyp size.[30] High cost, risk of anaphylaxis and need for subcutaneous injection are limiting factors in widespread application of such treatments at present. Many other anticytokine and antichemokine agents have been trialled in asthma and lower airway disease.[31] The respiratory epithelium is likely to co-ordinate the inflammatory process in eCRS with many mediators enacting a pro-inflammatory response.[32] It is highly likely that 'downstream' inhibition of a single agent may be suboptimal as redundancy of inflammatory pathways is present, and while one may be inhibited, others may persist. This is likely to explain why some of these medications have an effect but are not a panacea of treatment.

Aspirin desensitization

Aspirin sensitivity is usually associated with nasal polyposis and asthma (Samter's triad). Patients often have extensive polyposis, with high rates of recurrence after both medical and surgical treatment. Immune tolerance may be achieved and maintained by regular administration of aspirin, either orally or intra-nasally.

Tolerance is achieved by giving incrementally increasing dosages of oral aspirin until several hundred milligrams per day are tolerated. Used in this fashion, there is evidence of significant improvement in many parameters affecting both nose and chest, and has been found to be beneficial in patients with Samter's triad,[33–34] but comes with a significant risk of gastrointestinal side effects. More recently, doses as low as 100 mg have been used, and a placebo controlled randomized trial has shown a reduction in polyp recurrence in trial patients.[35] In the event of polyp recurrence requiring surgical intervention, oral aspirin is normally discontinued, and therefore desensitization must be repeated.

Lysine aspirin, a soluble from, is used for diagnosis of aspirin sensitivity by nasal or bronchial challenge and topical nasal desensitization. In a double-blind, placebo-controlled crossover study, topical lysine aspirin was associated with a reduction on cysteinyl leukotriene receptors, however, there was no significant clinical effect.[36]

TREATMENT AIMED AT REDUCING MICROBIAL LOAD

Treatment aimed at reducing microbial load or eradicating pathogens from the sinuses assumes that these play a role in causing or propagating CRS. Bacteria may play a role in acute infective exacerbations. Bacterial capsules and exotoxin may trigger an inflammatory response, while superantigens (predominantly Staphylococcal) and fungi may induce eosinophilic inflammation. The organisms isolated from patients with CRS differ from those in ARS, with *Staphylococcus aureus*, *S. epidermidis*, and anaerobic and Gram-negative bacteria predominating. Some, such as *S. epidermidis* are likely to be innocent colonizers. Polymicrobia is common. *S. aureus* may be isolated in up to 50% of CRSwNP, and MRSA is being increasingly grown, with more than 40% *S. aureus* cultures in the US now resistant to methicillin. Anaerobes are identified in 14–93% cultures, and may be involved in acute exacerbations.

Culture directed short-term antibiotics may be of use during acute exacerbations of CRS, but there are no studies evaluating effect on short courses on long-term symptom control. Long-term macrolides are discussed above, and are used predominantly for an anti-inflammatory effect.

Doxycycline has been compared with oral steroids in a placebo-controlled RCT in CRSwNP, and was found to have a moderate, but more sustained effect when compared with methylprednisolone. While doxycycline reduced post-nasal drip, it had no effect on nasal congestion, anosmia or rhinorrhea. Therefore it may be considered as an adjunct in treatment of CRSwNP but needs further evaluation.

While topical antibiotics have been shown to reduce bacterial colonization in animal studies, there is no evidence in the current literature that topical antibiotics are beneficial in the treatment of CRS. There have been three placebo-controlled RCTs, two in patients without previous surgery, one in difficult to treat CRS.[37] In all three there was no additional benefit of topical antibiotic compared to the placebo arm of nasal irrigation alone.

Even more recent trials of mupirocin, as an antistaphylococcal, delivered post-surgically in large volume irrigation, demonstrated little effect on patient outcomes. They are not therefore currently recommended.

Biofilms, both bacterial and fungal, have been demonstrated within the sinuses of patients with CRS, and their presence is associated with more severe disease and recalcitrance to surgical therapy. Systemic antibiotics are relatively ineffective against biofilms; topical antibiotics and surfactants may be more beneficial, but are likely to penetrate the sinuses only after surgery, and therefore will play a limited role in the treatment of the pre-operative patient with CRS.

The role of antifungal agents in the treatment of CRS has caused much controversy since the Mayo clinic made a patent application for the topical application of antifungals in patients with CRS in the late 1990s. However, the encouraging results of open label studies have not been repeated in randomized trials. A Cochrane meta-analysis identified 5 PCRCTs evaluating topical treatment, and one comparing systemic treatment with placebo.[38] Symptomatic response rates were better, and adverse event rate was lower in the placebo arm in all studies. These studies were conducted on groups of patients with CRSwNP (2), CRSsNP (1), and a mixed group of both (2 without previous surgery, 1 with). Therefore in any of these patients there is no evidence to support the use of antifungals. There are no randomized trials assessing antifungal agents in the treatment of selected patients with allergic fungal sinusitis, except for one PCRCT demonstrating reduced recurrence rates up to 9 months after surgery in patients treated with topical fluconazole when compared with itraconazole of placebo.[39]

TREATMENT AIMED AT IMPROVEMENT IN MUCOCILIARY CLEARANCE

Normal mucociliary clearance is dependent upon both ciliary function and the mucus blanket. Saline irrigation can improve mucociliary clearance by the removal of mucus, infected crusts and pro-inflammatory agents. Eight studies were eligible for inclusion in a Cochrane meta-analysis in 2007,[40] which demonstrated benefit from saline irrigation both when used as sole modality treatment and as an adjunct, albeit less efficacious than intranasal steroid. Large volume irrigation appears to have a greater impact on mucus management than simple sprays on RCT.[41] A subsequent RCT published in 2012 found hypertonic saline irrigations and saline spray alone had a comparable response rate to patients treated with hypertonic saline irrigation and INCS.[42] Studies directly comparing isotonic and hypertonic saline have not reported symptomatic outcomes, but suggest some benefit of hypertonic saline in terms of radiological improvement, at the cost of higher rates of local adverse effects. One small cross-over randomized trial demonstrated greater effectiveness of saline irrigation with xylitol compared with saline alone.[43]

As irrigation is generally well tolerated, it can be recommended for use in patients with CRS. As with other topical treatments, patients should be instructed on correct techniques for irrigation (**Figure 97.2**).

Mucoactive agents

Amphiphatic molecules possess the ability to be soluble in both water and organic solutions. They form the basis of surfactants. This effects both the solution and remaining molecular load behaviour at air–surface interfaces.[44] Pulmonary surfactant greatly improves the efficiency of mucocilial clearance by reducing adhesiveness of mucus to the respiratory epithelium. Acute respiratory distress of the newborn is the case example of the requirement of such agents in respiratory function. Surfactants can have both mucoactive properties and antimicrobial properties. Chemical surfactants can interfere with microbial cell membrane permeability and cause membrane disruption. These agents are often classified as cationic, anionic or zwitterioninc (possessing non-adjacent positive and negative charges) based on the charge of the hydrophilic domain present in these molecules. Cationic surfactants possess the most antimicrobial properties but are also the most irritating.[45]



Figure 97.2 Technique for nasal irrigation.

Commercial agents such as detergents, soil wetting agents, paints, antifogging solutions and ski wax are all examples of surfactants. The combination of PEG-80 sorbitan laurate, cocamidopropyl betaine and sodium trideceth sulfate (Johnson & Johnson Baby Shampoo®) has been shown to have both antibiofilm forming properties at 1% solution and clinical efficacy in managing refractory CRS patients.[45] Surfactants may not be a direct therapy for aggressive polypoid mucosal change that is dominated by inflammatory Th2 response but they are useful for treating crusting, thick mucus and chronic bacterial mucosal colonization.

Delivery of medical therapy

Cadaveric studies have documented poor penetration of topical therapies into the sinuses, particularly the frontal and sphenoid sinuses.[46] ESS can improve delivery, but only if ostial enlargement and the extent of surgery are sufficient to do so; the minimum ostial size is 4 mm to achieve maxillary sinus penetration, and retention of the uncinate in minimally invasive techniques is likely to act as a barrier to penetration.[47] Therefore, in the pre-operative state, topical therapies reach only the nasal cavity, potentially treating nasal polyps, oedema at the ostiomeatal complex and any associated turbinate hypertrophy. In order to treat the sinus mucosa, systemic therapy must be employed. In the post-operative state, topical therapy plays a greater role in managing disease control. Studies in humans support the data from these studies with less than 0.1% of solution making the maxillary sinus.[48]

The delivery device is important, with aerosol sprays achieving poor penetration beyond the anterior third of the nose. The most effective delivery devices are the positive pressure, high-volume irrigation bottles or Neti pots, which can penetrate all sinuses in a post-operative patient following wide sinus surgery or frontosphenoethmoidectomy (**Figure 97.3**).[49]



Figure 97.3 Combining local topical corticosteroid into a delivery device (such as an irrigation bottle with a volume > 100ml) makes an enormous difference to the distribution of local therapy. When combined with a wide post-surgical cavity, the ability to control the sinus mucosa is vastly different than simple nasal sprays and without prior surgery. This shift in transitioning a patient from relying on systemic medication to delivery treatment to the sinuses to a local-based therapy has dramatically changed the outcomes for patients with chronic conditions.

ASSESSMENT OF THE RESPONSE TO MEDICAL TREATMENT

As the aim of treatment for CRS is to reduce the symptom load and impact on quality of life, these subjective symptoms need to be quantified to allow repeated measures in order to evaluate response to therapy. There are several validated disease specific quality of life measures for use in CRS. Knowledge of scores in the normal population and the minimum clinical important difference facilitates detecting improvement (**Table 97.1**). Alternatively a VAS scale may be used.

Response to treatment should be considered as relief of the symptoms of CRS to the point that they are no longer present or bothersome.[13] If this is maintained, with or without ongoing medical therapy, then disease can be considered as controlled. This concept of disease control is well defined for asthma, but has been largely neglected in CRS until the recent EPOS guideline (**Table 97.2**); however, the proposed table needs to be data driven. Recent publication has suggested a refinement of this to focus on nasal obstruction, endoscopic evidence of oedema and mucus production and systemic medication use as either corticosteroid or antibiotics.[50] A proposed NOSE system was proposed (Nasal Obstruction, Systemic Medication, Endoscopy).

Control of disease is both to prevent infective exacerbations and control baseline symptoms. 'Normal' mucosa on endoscopy is the reference point but even this is not associated with 'no' nasal symptoms as many will have rhinitis reactions to account for some disease burden.

Usually 4–8 weeks should be allowed before considering treatment to have failed in patients with established CRS. If there has been improvement but incomplete resolution, a further period of ongoing medical treatment is recommended, although this is rarely with systemic corticosteroids. Persistent evidence on either endoscopy or CT of active mucosal inflammation is associated with

TABLE 97.1 Summary of outcome instruments and their key properties

Instrument	Items/ Domains	MID	Normal	Completion time (min)
Adult Acute Rhinosinusitis				
SNOT-16	16/1			5
Adult Chronic Rhinosinusitis				
RSOM-31	31/7			20
SNOT-16	16/1			5
SNOT-20	20/1			5–10
SNOT-22	22/1	8.9	7	5
RSDI	20/1	10.4		5
Rhinoqol	17/3			5–10
CSS	6/2	9.8		5
FNQ	12/1			<5
SNAQ-11	11/1			<5



Figure 97.4 Poorly controlled CRS requiring ongoing medical treatment and likely revision surgery.

TABLE 97.2

	Controlled	Partly controlled	Uncontrolled
Blockage	-	Present	3 or more
Rhinorrhoea		Mucopurulent	
Facial pain		Present	
Smell		Impaired	
Sleep		Disturbed	
Nasendoscopy		Diseased	
Systemic medication		Required in last 3 months	

a high rate of relapse even in the asymptomatic patient (**Figure 97.4**).[51] Where patients are asymptomatic, treatment can be withdrawn in the presence of normal endoscopy and or CT. Where endoscopy remains abnormal, the patient should continue with saline irrigation and intranasal corticosteroid and counselled on the potential need for future therapy.

Where there has been no response, the history and examination findings should be reviewed to ensure both the correct diagnosis, and to exclude symptom amplifiers that may be less amenable to standard treatment – for example, coexisting depression may lead to higher levels of symptoms for a given disease burden. Secondary CRS should be considered, and assessment of the full respiratory system undertaken, including testing for secondary eosinophilic disorders, vasculatides and immunodeficiencies where appropriate. Smoking cessation should be strongly encouraged. If there is no response, and surgical treatment is being considered, a CT scan should be performed, even with positive endoscopy, as an aid to surgery and exclusion of other diagnoses (fungal ball, AFS, neoplasia) if not already performed.

Any patient with unilateral polypoid disease, where there is a suspicion of malignancy, the presence of associated neurological or orbital symptoms or atypical features should not be considered for a trial of maximum medical therapy. They require urgent radiological imaging, followed by surgery and histological examination where indicated.

WHEN DOES A MEDICAL THERAPY ONLY APPROACH FAIL?

The question of when to be more aggressive in therapy for CRS is a common question. The dictum of a trial of conservative medical therapy before surgery in every case is false. Both fungal ball and AFS are examples where initial surgery is required. Especially in CRSwNP, there is little basis to the concept of either medical or surgical treatment alone, as combined therapy is critical to control disease.[52] Thus, what is being achieved from intervening surgically? There will be CRSsNP patients in whom the mucosal oedema, basement membrane thickening and fibrosis are causing ostial occlusions, which cannot be resolved medically and are leading to persistent disease. However, this concept is not true for CRSwNP, eCRS or eosinophilic subtypes.[53, 54] Simply operating to 'unblock' or 'ventilate' the sinus is not an endpoint supported by evidence. Access for topical therapies is critical as a goal of surgery for CRS patients, and thus allows a patient to switch from relying on systemic therapies to local treatments.[52]

Failure is defined by patient-focused outcomes rather than evidence of mucosal inflammation. Those patients who have a high symptom burden despite treatment, or go on to have infective exacerbations, are failures. The benefits of repeated courses of systemic treatment need to be weighed against the risk of adverse events. We would consider the need for more than two courses of systemic treatment per year indications that medical-only treatment has failed. Greater frequency may expose patients to deleterious effects of systemic corticosteroid use.[55] Each course is recommended for 14–21 days as this best equates to the lifespan of a tissue eosinophil.[56] An accumulative dose less than 290–1000 mg is recommended, with a maximum of 30–40 mg daily, as this is the range in which significant complications and medicolegal complaints occurred.[57] Those patients that fail to derive sufficient benefit from pre-surgical medical treatment and fulfil the diagnostic criteria for CRS, in whom an alternative diagnosis is not found, and who have confirmation of mucosal disease on CT, should be considered for surgery.

Patients with complete nasal obstruction due to nasal polyps, where there has been no reduction in size following initial medical treatment, are unlikely to be able to achieve access to topical treatment. In the van Zele study,[26] symptomatic improvement was maximal shortly after completing prednisolone, and the benefit had significantly waned by 12 weeks. It may be worth considering surgical intervention at an earlier point in such patients.

MEDICAL TREATMENT POST-SURGERY

Allowing a transition to effective local or topical therapy is a critical role for surgical intervention. With this aim, surgery is often complete, wide and designed to remodel the paranasal sinus to a common cavity that can be managed. Hypersecretory mucus can be easily removed and anti-inflammatory therapy effective delivered.[52] This is especially true for CRSwNP, where local ostial obstruction is unlikely to play a major role in the perpetuation of the disease process.[53, 54]

Although nasal polyps or the presence of asthma might identify these inflammatory patients, they are still often missed. A structured histopathology of sinus tissue using defined criteria for eosinophilic CRS or greater than 10 eosinophils per high power field (>10 per hpf) will reveal an additional 20% of CRSsNP to be classified as eCRS (**Figures 97.5, 97.6**).[58] The diagnosis of eCRS has prognostic implications. eCRS is associated with greater clinical and radiological severity,[58, 59] higher risk of asthma[59] and higher risk of polyp recurrence when compared to non-eCRS.[60] Serum eosinophilia, while associated with eCRS and predictive of asthma,[59] is not predictive of the localized inflammatory processes[61] and was less sensitive for eCRS.[58] Surgery provides an ideal opportunity to make this disease distinction.

Corticosteroid irrigations are the mainstay of topical anti-inflammatory therapy post-ESS.[52–62] They are delivered in large-volume positive pressure saline irrigations. These treatments are often mislabelled as 'high dose' or 'high concentration' but neither of these is true. The delivered steroid dose is mostly in a more diluted form than

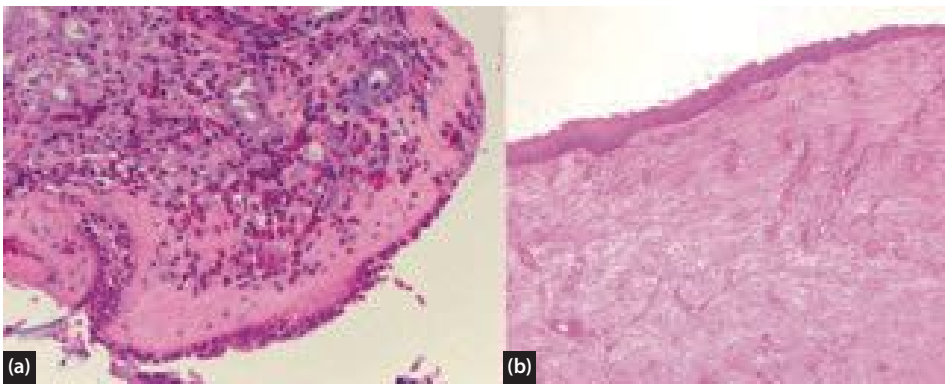


Figure 97.5 (a) Tissue eosinophilia is a marker of more severe disease and generally corticosteroid sensitive. **(b)** Significant subepithelial fibrosis is a feature of long-term tissue remodelling and likely portends a poor prognosis similar to studies on tissue remodelling and in asthma.

Chronic Rhinosinusitis Histopathology Report	
Tissue	
Overall degree of inflammation	Absent / mild / moderate / severe
Eosinophil count	<10 / 10–100 / >100 per hpf
Neutrophil infiltrate	Absent / focal / < 20 / > 20 per hpf
Inflammatory predominance	Lymphocytic / lymphoplasmocytic / lymphohistiocytic / neutrophilic / eosinophilic/ other
Basement membrane thickening	**<7.5 µm / 7.15–15 µm / >15 µm**
Sub-epithelial oedema	Absent / mild / moderate / severe
Hyperplastic / papillary change	Absent / present
Mucosal ulceration	Absent / present
Squamous metaplasia	Absent / present
Fibrosis	Absent / partial / extensive
Mucin	
Fungal elements	Absent / present
Charcot-Leyden Crystals	Absent / present
Eosinophil aggregates	Absent / present

Figure 97.6 An example of routine efforts to improve histopathologic profiling in CRS during routine clinical care. The structured outline provides simple information on eosinophilic inflammatory activity, eosinophil activation (aggregates and Charcot-Leyden crystals), neutrophilic infiltrate and tissue remodelling (squamous metaplasia, fibrosis and basement thickening). Simple algorithms such as corticosteroids for eosinophilic disease and potential macrolide therapy for neutrophilic predominant patients are possible with just a little pathologic assessment.

simple sprays and the total residual delivered is usually less than 5% making the exposure to the patient less than simple spray therapy.[63] They are effective since they actually deliver the pharmaceutical to the sinus mucosa. Studies have shown no effect on serum cortisol,[64] urinary cortisol or the adrenocorticotropin hormone stimulation test.[65]

SUMMARY

Medical therapy is the mainstay of management for rhinosinusitis.

For acute infections, antibiotics are rarely required and treatment is largely supportive, except in the presence of complications.

For chronic disease, reducing mucosal inflammation is a cornerstone of treatment. Intra-nasal corticosteroids are the first line of treatment. Systemic steroids, immune-modulatory drugs and novel monoclonal antibodies may be used in carefully selected cases. Antibiotics may be of benefit in acute infective exacerbations. Endoscopic sinus surgery plays an adjunctive role in facilitating delivery of topical medications when standard delivery approaches have failed.

KEY POINTS

- Medical therapy should have a 3-way goal of reducing inflammatory load, normalizing microbial community and restoration of mucocillary function.
- Medical therapy to the paranasal sinus is primarily via the systemic route in the unoperated patient.
- Systemic corticosteroid is effective, but use is usually limited to 2 courses a year, of 2–3 weeks duration and often less than 30–40mg maximal daily dose as a reducing course.
- There is little evidence of ostial obstruction as a cause of CRSwNP or the eosinophilic subgroup.
- Surgery, while potentially curative for some, is more commonly utilized to enable long-term local or topical therapy to control disease.
- Corticosteroid irrigations are a common effective delivery mechanism in the post-surgical patient. Their use is similar to that of a prophylactic inhaler for asthma patients.

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CHAPTER 98

SURGICAL MANAGEMENT OF RHINOSINUSITIS

A. Simon Carney and Raymond Sacks

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the following keywords: rhinosinusitis, sinusitis and surgery, restricted to English language and abstract publication. A secondary literature review of reference lists from keynote papers and relevant book chapters was also undertaken.

INTRODUCTION

As the mucosa of the paranasal sinuses are in direct continuity with that of the nasal cavity, the term 'rhinosinusitis' has now been recognized as the correct description of a disease defined as: 'inflammation of the nose and the paranasal sinuses characterized by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip): +/– facial pain/pressure +/– reduction or sense of smell'.[1]

Rhinosinusitis of less than 12 weeks with complete resolution of symptoms is termed acute rhinosinusitis (ARS) with chronic rhinosinusitis (CRS) developing at or after 12 weeks of symptoms without complete resolution.[1]

There are many exacerbating factors, which can cause or influence the severity of rhinosinusitis. These include (but are not restricted to): asthma, aspirin exacerbated respiratory disease (AERD), cystic fibrosis and immunodeficiency.[1–4]

A comprehensive history of surgery for the management of rhinosinusitis is beyond the scope of this chapter; however, it is fair to say that the advent of antibiotics and the rigid endoscope have both completely revolutionized the indications and surgical techniques for operative management of rhinosinusitis.[5]

The aetiological causes of both ARS and CRS remain controversial, incompletely understood and subject to continued speculation.[6] It is becoming increasingly apparent that surgical indications and techniques for the management of rhinosinusitis depend, to a greater or lesser degree, on the belief by the individual surgeon or local surgical community in these various aetiological theories. For example, in countries where osteo-meatal complex (OMC) obstruction is seen as paramount for disease causation, simple middle meatal antrostomy and anterior ethmoidectomy ('mini-FESS') may be considered as standard of care; whereas, in countries where surgery is predominantly seen as optimizing the environment for the application of topical medical therapies, a more complete fronto-spheno-ethmoidectomy ('full-house FESS') is deemed as a more appropriate primary procedure.[7, 8]

With new technological developments, minimally invasive options such as balloon sinus dilatation are now available[9] and yet at the other end of the spectrum, extensive 'nasalization' of all the paranasal sinuses is now possible using high powered drills, haemostatic agents and computer navigation systems.[10]

In this chapter, we will examine the literature surrounding this complex area and attempt to present it in an evidence-based manner.

DIAGNOSIS

The diagnosis of both ARS and CRS depends on an accurate history and clinical examination of the patient. Whilst nasal endoscopy and CT scanning are critical in confirming the diagnosis, these are usually only available

through an ENT specialist or allergist. CRS is subdivided into disease with nasal polyps (CRSwNP) and without (CRSsNP).[1] Bilateral nasal polyps are required for a diagnosis of CRSwNP.[1] It can further be subdivided by histological phenotypes such as eosinophilic or neutrophilic CRS, which is now recognized to influence both the medical (both pre- and post-operative) and surgical management of the patient.[11]

In the specialist setting, rigid nasal endoscopy can be used to visualize the osteo-meatal complex in patients. It can also aid the collection of sinus secretions for microbiological analysis.[1] Whilst the presence of pus, erythema and oedema can be valuable positive findings, endoscopic findings remain extremely subjective and there is little evidence they alter outcomes.[1, 12–14]

Radiology

Due to the poor resolution, high false positive and false negative results, plain sinus x-rays are no longer recommended for the investigation of either ARS or CRS.[1] The advance in CT scanning technology has meant it is now possible for high resolution CT images to be rapidly obtained with a very small radiation dose. CT scans should ideally be reconstructed into three planes (coronal, axial and para-sagittal).[15] The use of laptop-based computer programs such as OsiriX, and the routine availability of images on CD-ROM, has now made further manipulation of CT images possible on an individual patient basis.[16]

SURGICAL OPTIONS

Indications for surgery

ACUTE RHINOSINUSITIS

Medical management remains the mainstay for ARS with antibiotic therapy being reserved for patients with severe disease, especially with the presence of high fever or severe (unilateral) facial pain.[1] In rare cases, ARS may progress to complications involving the orbit, the cranium or frontal bone. Where sub-periosteal and intra-orbital abscess, epidural or subdural abscesses, meningitis and/or intra-cranial sinus thrombosis, surgical options may then enter the management algorithm.[17] A good principle is that where the ARS complication is managed medically (e.g. meningitis), the ARS may be managed medically as well; whereas when a complication is to be managed surgically (e.g. orbital or intra-cranial abscess, Pott's puffy tumour), then simultaneous surgical drainage of the affected sinuses should be considered.[18]

CHRONIC RHINOSINUSITIS

There is a huge amount of evidence on the medical management of CRSwNP and also CRSsNP.[19] Well produced guidelines such as the EPOS2012 document[1] have concluded that topical steroids and nasal irrigation should be tried by primary care physicians for at least 4 weeks before considering a referral to an ENT specialist. If the diagnosis is clinically confirmed and maximal medical therapy has not improved symptoms, a CT scan is then indicated. The CT findings not only enable assessment of the presence of residual disease that could be addressed by surgery but also provide the surgeon with the ability to recognize the presence of anatomical risk factors for the development of CRS and to facilitate surgical planning. There are multiple factors which need to be considered before a decision to undertake surgery is reached;[20] these include i) patient factors; such as general cardio-respiratory health, anticoagulation treatment and social factors, ii) facility factors; such as access to (and the availability of) appropriately trained personnel and acceptable equipment levels for the type of surgery being considered and iii) economic factors; which include cost both to the individual and to the relevant healthcare system.

Appropriate informed consent must be obtained from all patients when considering surgery and this consent must include an honest discussion of the natural history of their condition,[21] the risks and sequelae of surgical complications,[22] the potential for recurrent disease,[23] the usual need for ongoing medical management and always the option of continuing non-surgical management.[24]

SURGICAL PROCEDURES

Anaesthesia for sinus surgery

Although it is entirely possible to do most forms of endoscopic sinus surgery under local anaesthetic, it is common practice for patients to have a general anaesthetic in many Western countries.[1, 25] Whilst the use of laryngeal mask anaesthesia has not yet been universally accepted, it is the authors' view that, unless there are significant increased risks of laryngeal soiling (significant laryngopharyngeal reflux, obesity or other medical factors), laryngeal mask anaesthesia is generally preferred over endotracheal intubation.[26] The use of volatile inhalation agents has declined and with the increasing availability of short acting opiates such as Remifentanil, many surgeons prefer total intravenous anaesthesia (TIVA). With TIVA there is a very small but real risk of awake anaesthesia and therefore the use of bispectoral index (BIS) monitoring is recommended to avoid this potentially serious medicolegal complication. The evidence regarding TIVA and an improved surgical field remains controversial.[27] Whilst some authors claim that there is significant benefit from TIVA,[28] the use of sevoflurane (at low concentration only) and remifentanil combined probably provides just as good a surgical field and avoids the need for BIS monitoring. Mean arterial blood pressure (MAP) is determined by the following equation: MAP = heart rate (HR) x stroke volume (SV) x systemic vascular resistance (SVR). In order to optimize the surgical field, hypotensive anaesthesia is desirable. Our evidence-based recommendation is to maintain a systolic MAP of approximately 90 mmHg, which is best achieved by maintaining the HR at approximately 60 beats per minute.[25, 27, 28] Volatile agents, which achieve hypotension by reducing SVR, can paradoxically cause a deterioration of the surgical field due to vasodilatation of the nasal microvasculature. Further discussion

on anaesthesia for sinus surgery can be found in several good review articles.[25, 29, 30]

Surgical position

There is good evidence that the surgical field is optimized by placing the patient in the reverse Trendelenberg position.[31] Many surgeons remain concerned about the effect of head elevation and its potential reduction in cerebral blood flow (CBF) and oxygenation. Whilst physiological studies have confirmed that CBF does vary with head elevation, the cerebral perfusion pressure remains constant at elevations of between 0 and 30°.[31]

Intranasal preparation

There is evidence that transpalatal injection of the greater palatine canal decreases intra-operative blood loss during sinus surgery[32] but despite the evidence, the technique has failed to break through it into routine clinical practice. This may be due to the fact that whilst head elevation has been demonstrated to produce a 38.3% reduction in nasal blood flow, injection of the greater palatine canal only produces a reduction of 4.7%.[31, 32]

Topical decongestion in the form of cocaine and adrenaline, +/– sodium bicarbonate ('Moffat's solution') soaked on neuro-patties, ribbon gauze or pledgets remains most commonly used[33] although a randomized controlled trial has shown that the use of co-phenylcaine (ENT Technologies, Victoria, Australia) which is a combination of lignocaine 5% and phenylephrine 0.5%, is just as effective.[34] There are many legal restrictions on the use of cocaine and in many countries it is simply not possible for ENT surgeons to use cocaine and other alternatives are therefore required. Oxymetazoline alone is utilized in many centres with effective results.[35] Local anaesthetic infiltration of the middle turbinate, nasal septum and frontal process of the maxilla is then commonly performed. 1–2 mls of 1% lignocaine with 1 in 80 000 adrenaline is typically utilized.[35] It is always important to be aware of the total dose of cocaine, lignocaine or other local anaesthetics that are given both topically and intra-mucosally. Toxic reactions from overdose have been reported and the use of adrenaline will frequently cause a rise in heart rate with a corresponding temporary deterioration in the operative field (which may be greater than the gained benefit of the vasoconstrictor effect). Rather than immediately proceeding to surgery, it is therefore preferable to allow a period of time for topical and injected vasoconstrictors to establish their local effect, whilst allowing their systemic effect to dissipate.

Functional endoscopic sinus surgery (FESS) for rhinosinusitis

GENERAL PRINCIPLES

Recent CT scans of the patient's sinuses are mandatory and should be available to the surgeon throughout the operation.[36] If scans are available in traditional x-ray film format, these can be placed on a mobile viewing box adjacent to the surgeon. It is increasingly common for images to be provided in electronic format (DICOM-viewers). In this case, a large plasma screen TV or monitor can be placed adjacent to the surgeon and multiple images displayed on the screen simultaneously. It is important that a member of the theatre team is computer skilled to change the displayed images, if required. It is difficult for a surgeon to remember the multiple anatomical nuances of each individual patient and without the presence of images during surgery, increased complications may occur. If intra-operative image navigation is available, some surgeons regard this as an adequate replacement for the above but it is the personal preference of the authors to have standard images available at all times, in case of equipment failure or poor registration of the image navigation system.

EYE PREPARATION

Traditionally, the eyes have been left open with lubrication but many surgeons now accept limited or even complete taping of the eye, still allowing rapid access to the globe but providing for better corneal protection. There have been several medicolegal cases whereby corneal abrasions have resulted in successful lawsuits.[37]

SURGICAL TECHNIQUES[36, 38]

i) Uncinectomy

The free edge of the boomerang-shaped uncinate process can be identified in most cases by the use of a Freer's elevator. The use of a sickle knife on the interior portion of the uncinate is to be discouraged as orbital penetration can easily occur.[37] Either adult or paediatric back-biting forceps are readily available which allow for safer uncinate incision (**Figure 98.1**).

Superiorly on the uncinate process, the orbit is relatively more protected by the hard bone of the frontal process of the maxilla.[36] A sickle knife can be used safely in this area although a back-biter remains an acceptable alternative. The uncinate process can then be removed using

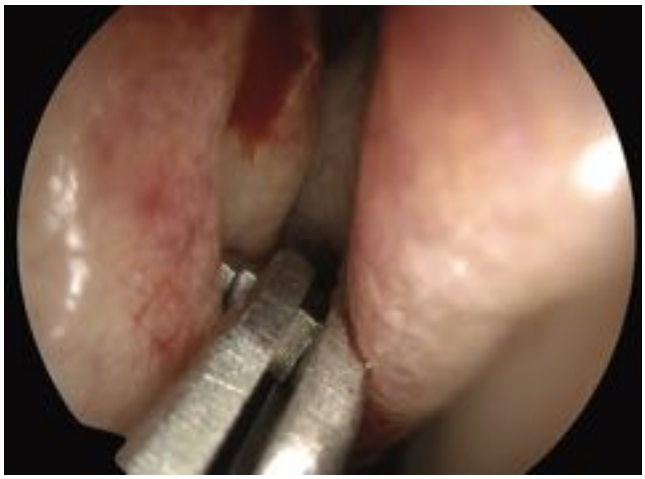


Figure 98.1 A paediatric back-biting forcep is used to perform the inferior uncinectomy incision.



Figure 98.2 Dissecting out the bone of the horizontal process of the uncinate.

angled through-biting forceps or can be dislocated forward using a double right-angled ball probe and then cautiously removed with the microdebrider or through-biting forceps. Any rough edges can be removed using a 2 mm Kerrison's punch.[38] It is always important to then address the horizontal part of the uncinate which extends inferior to the natural ostium of the maxillary sinus. The bone of the horizontal portion can be dissected free from the mucosa (**Figure 98.2**) and the natural ostium can simply be stretched open with an angled probe or sucker, without removing any mucosa. For more advanced disease (or in revision cases), it may be necessary to remove mucosa to create a large middle meatal antrostomy.

ii) Removal of the ethmoidal bulla

The natural ostium of the ethmoidal bulla sits posteromedial to the anterior face. The ostium can be located by several methods; a double right angled ball probe or 45° antral curette can then be used to fracture the anterior face forwards (**Figure 98.3**). A microdebrider can then be used to remove the bulla, aiming for complete removal



Figure 98.3 A double right-angle ball probe is inserted into the natural ostium of the bulla ethmoidalis (medial) then the anterior face is fractured anteriorly.

of partitions between the lamina papyracea and the middle turbinate. When removing the bulla superiorly, it is important to recognize the location of the anterior ethmoidal artery. Although commonly located in the suprabullar recess, on rare occasions, the artery can sit within the anterior wall of the bulla and be damaged by inadvertent use of the microdebrider in this area. If present, other anterior ethmoidal cells can be removed in a similar manner. The use of through-biting instruments is preferred to standard Blakesley-Wells forceps as the latter can tear mucosa and leave exposed bone in the final sinus cavity.

iii) Posterior ethmoidectomy

The ground lamella of the middle turbinate defines the junction between the anterior and posterior ethmoid sinuses. After reference to the CT scan, the ground lamella should be perforated in the infero-medial quadrant. This avoids inadvertent injury to the skull base or lamina papyracea. Once the posterior ethmoid is opened, the roof of the maxillary sinus can be used as a guide to the superior limit of dissection within the posterior ethmoid. Anatomical studies have shown that the antral roof will always be below the skull base and allow for safe passage to the sphenoid sinus.[38, 39] A microdebrider, Kerrison's punch or through-biting instruments can be used to remove the partitions between the posterior ethmoid cells. Care should be taken in the posterior ethmoid as the optic nerve may traverse through an Onodi cell and the surgeon should always be aware of their exact surgical location at all times.

iv) Sphenoidotomy

The natural sphenoid ostium is located in the sphenoethmoidal recess, medial to the superior turbinate and at the height of the antral roof. It is not always possible to pass an endoscope medial to the superior turbinate to identify the ostium and part of the middle turbinate can be resected with a back-biting forceps, entering the superior meatus and locating the forward projection of the superior turbinate from within the posterior ethmoid cavity. The inferior third of the superior turbinate can then be resected in order to gain access to the sphenoethmoidal recess. If the sphenoid ostium can still not be located using this method, an artificial opening to the sphenoid can be made through the posterior ethmoid and then extended medially to incorporate the natural sphenoid ostium. Again, if accessing the sphenoid through the posterior ethmoid cavity, perforating the ground lamella of the superior turbinate should always be done in the infero-medial portion to avoid accidental injury to the skullbase.

v) Frontal sinus surgery

The Agger nasi cell is key to all approaches to the frontal recess.[36] In a small percentage of patients it may be absent but it is a good landmark in the vast majority of cases. Using a Kerrison's punch in the axilla of the middle turbinate (**Figure 98.4**), the anterior portion of the Agger nasi can be removed.[38]

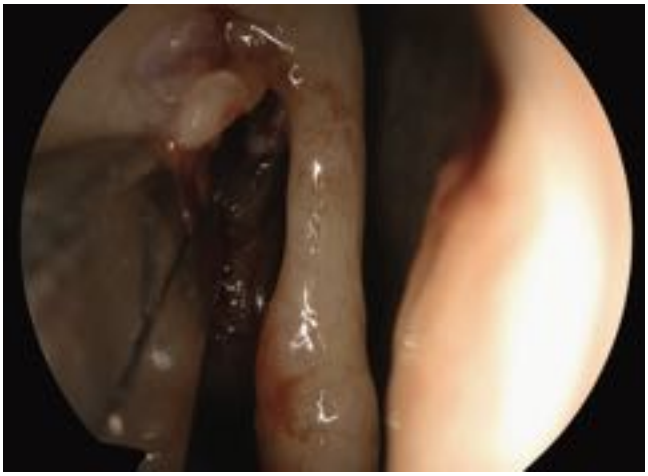


Figure 98.4 A 2 mm 450 forward-angled Kerrison's punch is used to raise the axilla of the middle turbinate and improve access to the Agger nasi and the frontal recess.



Figure 98.5 Exposure of the frontal recess by removing the posterior wall and roof of the Agger nasi cell.

Curettes and angled instruments can then be used to remove the posterior wall and roof of the Agger nasi to expose the frontal recess (**Figure 98.5**).

Although mucosal flaps have been advocated for this approach,[36] the authors no longer regularly utilize axillary flaps as adhesions can easily be prevented using other methods and regular post-operative review. Once the Agger nasi has been removed, any remaining fronto-ethmoidal cells can be removed using through-biting instruments, curettes or angled microdebrider blades. Care must be taken to avoid a circumferential injury to the mucosa in this area as this will undoubtedly result in stenosis of the frontal recess and recurrent frontal sinusitis. When dissecting the frontal recess, the position of the anterior ethmoidal artery needs to be identified and maintained in the surgeon's mind at all times. Any inter-sinus septal cells or supraorbital ethmoid cells may also need to be addressed and these generally require the use of angled endoscopes and curved microdebrider blades. Advanced frontal instrumentation such as a giraffe forceps or 3.5 mm Hosemann punch (**Figure 98.6**) may greatly facilitate surgery in this area.[38]

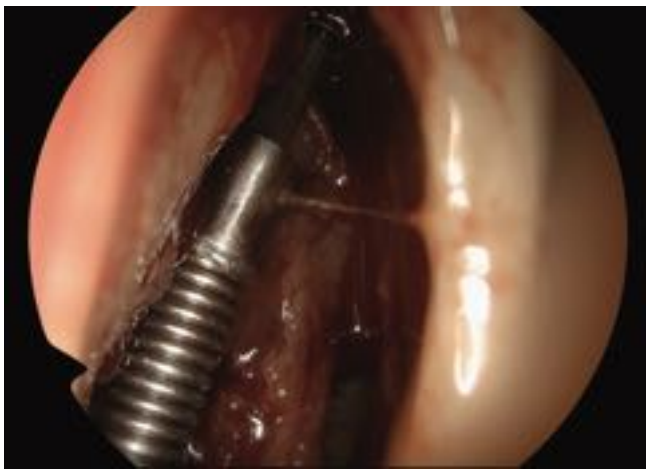


Figure 98.6 Use of a Hosemann punch to facilitate removal of Kuhn cells in the frontal recess. It is critical to avoid circumferential mucosal injury in this location.

POST-OPERATIVE MANAGEMENT

It is critical to see patients regularly in the immediate post-operative period. Although surgeons routinely perform debridement of the sinus cavity in several countries, there is controversy as to whether this is absolutely necessary. Randomized controlled trials have shown no difference in outcomes between patients who receive regular toilet of their sinus cavities versus those that do not.[40]

Most surgeons routinely use high volume saline irrigations to clean the nose of mucopus, blood clot and other tissue.[1] Although the choice of solution is largely an individual one, a recent randomized controlled trial demonstrated improved outcomes using Ringer's lactate solution, when compared to either isotonic or hypotonic saline solution.[41] However, the cost of pre-made irrigation sachets needs to be offset against any potential benefit. There is no evidence that the use of prophylactic post-operative antibiotics improves outcomes following routine endoscopic sinus surgery.[1] If mucopus is found at the time of surgery, a swab should be taken and targeted antibiotic treatment should then be prescribed. Institutional guidelines may now prevent the surgeons from prescribing routine prophylactic antibiotics unless infection is identified at the time of surgery. In the case of severe disease (and usually in most cases of CRSwNP) a 10 day course of oral Prednisolone can be given. It is the authors' practice to use 25 mg prednisolone daily for 10 days without tapering. However, individual surgeons will have their own preferred steroid regimes. It is important to remember that eosinophils can last up to 3 weeks in the tissues and if there is extensive eosinophilic disease (usually in the case of CRSwNP), it may be logical to use an extended course of steroids for 3 weeks or longer.[38] In this case, the steroid dose will need to be tapered off to avoid an Addisonian crisis. It is the authors' practice to see patients 7–10 days following surgery then weekly if there are any concerns or fortnightly if not. At 6 weeks, one would expect the sinus cavity to be fully healed and at that

stage, routine nasal steroids and less frequent irrigations can be continued until review at 3 months. It is important to emphasize to patients with severe disease that they may need to be on topical steroid sprays or irrigations for some time (and in some cases, e.g. eosinophilic CRS, for an indefinite period) to prevent recurrence of their nasal polyps.

SURGICAL COMPLICATIONS

In the hands of experienced clinicians, reported complications are rare. Analysis of the literature reveals a range of significant complications between 0.3 and 22.4% (median 7.0%).[22] Although the majority of these are minor and do not result in any adverse outcome to the patient, damage to the orbit or skull-base can be severe and result in significant morbidity and mortality. Excessive bleeding and poor visualization of the operative field is associated with an increase in complication rates. When a bloody field is encountered, if this cannot be controlled, it is always safer to abandon the procedure and plan elective second stage surgery. Continuing with surgery without proper visualization can result in a catastrophic outcome. A recent meta-analysis from Australia has demonstrated that the use of intra-operative image guidance does significantly reduce the incidence of complications.[42] Such equipment however is costly and in the UK and Australia, surgeons would not routinely use intra-operative image guidance for primary, uncomplicated sinus surgery.

Avoiding complications

A proper pre-operative history will identify if the patient is taking significant medication (e.g. warfarin, clopidogrel or aspirin). There are many other drugs and homeopathic preparations that can also effect bleeding. NSAID's, fish oil and vitamin preparations are amongst those often missed. Correct interpretation of the CT scans will alert the surgeon to any presence of any high risk anatomical features which might increase the chance of damage to the orbit or cribriform plate. Dehiscence of the lamina papyracea, angulation of the vertical lamella of the cribriform plate and congenital defects in the skull base and over the carotid artery can all be identified pre-operatively.

HAEMORRHAGE

Knowledge of the anatomical location of the major branches of the sphenopalatine artery and anterior ethmoidal artery will prevent injury in the first instance. Aggressive resection of the horizontal part of the middle turbinate and extending the sphenoid ostium inferiorly will damage two of the major branches of the SPA. Identification and avoidance of the anterior ethmoidal artery should be performed in all cases where the bulla is elevated up to the skull base or the frontal recess is dissected. Small bleeding vessels can usually be controlled with topical vasoconstrictors (1 in 80 000 adrenaline, with or without cocaine). Larger vessels can be controlled with dedicated suction bipolar diathermy. Caution must be used if monopolar diathermy is considered as heat dissipation can damage surrounding structures, including the optic nerve.[43] In cases of diffuse mucosal bleeding, topical haemostats such as Surgiflo or Floseal can be utilized to good effect. Very rarely, formal ligation of the SPA[36] or exploration of the orbit for clipping of the anterior ethmoidal artery may be required. Direct bipolar diathermy of the anterior ethmoid artery is rarely required and may be problematical, owing to the presence of varying degrees of bone thickness over the artery.

ORBITAL INJURY

The orbit can be damaged with the first incision of a sickle knife through the inferior portion of the uncinate process (**Figure 98.7**). Other high risks areas are when performing a middle meatal antrostomy where there is a long thin infundibulum. If orbital fat is exposed, it is essential that the surgeon recognizes this immediately. No repair of the defect is usually necessary and the eye should be routinely checked to identify any intra-orbital haemorrhage. Any proptosis should be regarded as significant and decompression of the orbit by removing the lamina papyracea and incising the orbital periosteum may be required, with or without a lateral canthotomy and/or cantholysis.[36]

If a surgeon fails to recognize they have exposed orbital fat and continues manipulation in this area, damage to the medial rectus or other ocular muscle can occur. The use of the microdebrider has been associated with an increased risk of damage to the medial rectus muscle. If damage to the ocular muscles is suspected, an ophthalmological opinion should be obtained although there is usually little that can be done to repair a transected muscle and late oculoplastic surgery may never restore normal movement to the damaged eye.[37]

OPTIC NERVE INJURY

The optic nerve can be damaged due to intra-orbital haematoma (see above) or direct injury from within the



Figure 98.7 An orbital haematoma caused by a breach of the lamina papyracia during sinus surgery.

posterior ethmoid or sphenoid. It is most at risk if the optic nerve is on a mesentery within an Onodi cell. If injury to the optic nerve is suspected during a surgical procedure, steroids should be given and an urgent ophthalmological consultation should be obtained as soon as possible.

CSF LEAK

If the skull base is damaged during sinus surgery, a CSF leak can be created (**Figure 98.8**). The estimated prevalence of this is 0.5% of sinus surgical cases.[37] The area at greatest risk is surrounding the vertical lamella of the cribriform plate. If this lamella is at an angle (rather than vertical) it is more easily damaged, especially with angled instruments or microdebrider blades. Again, a bloody surgical field increases the risks of CSF leak.

Often a CSF leak can be identified immediately and can be repaired without any long-term morbidity to the patient. Repair of CSF leaks has been covered elsewhere in this book but options include fat plugs, artificial materials or homografts with or without covering mucosal grafts. The use of fibrin glue has greatly facilitated the closure of CSF leaks.

CAROTID ARTERY INJURY

The internal carotid artery can be damaged during sphenoid surgery, especially if there is a bony dehiscence over the artery. Pre-operative identification of such a dehiscence will reduce the chance of such complications arising. A carotid injury can be catastrophic and devastating. It can be extremely difficult to manage due to the high volume of exuding blood, which will obscure the operative field. The anaesthetist must commence immediate haemostatic resuscitation and the sphenoid packed. Although direct carotid artery repair (with either a J-suture or muscle pack) has been advocated,[44] placement of an endovascular stent is an effective alternate treatment option.

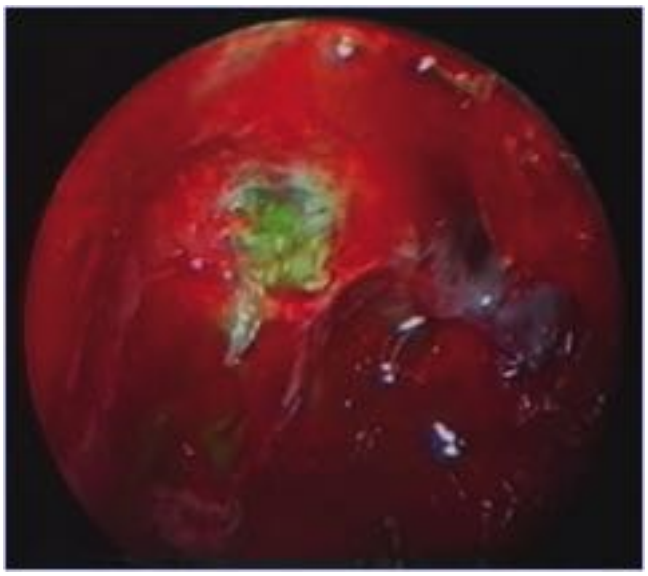


Figure 98.8 Iatrogenic CSF leak caused by damage to the skull base during FESS.

EVIDENCE BASED SURGERY FOR CHRONIC RHINOSINUSITIS

Whilst most surgeons would feel that sinus surgery benefits the vast majority of their patients, critical analysis of the literature reveals that this is not always the case. Owing to the phenomenon of cognitive dissonance,[45] surgeons will always be reminded of their successes and psychologically repress their failures. There have been few randomized controlled trials (RCT) looking at surgery for chronic rhinosinusitis. The Cochrane collaboration continues to update its analysis of evidence behind surgery for CRS and have only found six RCT's in this area and excluded three of them.[46] One trial compared twelve patients undergoing endoscopic middle meatal antrostomy with seventeen patients undergoing inferior meatal antrostomy. The trial showed no difference between the groups but was poorly powered and poorly designed.[47] A second study looked at patients undergoing FESS versus antibiotics and again found no difference between the two groups.[48] The third and best study randomized ninety patients to medical treatment (long-term antibiotics, intra-nasal corticosteroids and saline irrigations) or FESS. Whilst both treatments had significant benefit to the patients, there was no significant difference between the medical and surgical arm.[49]

In patients with CRSwNP, thirty-one patients were randomized to receive FESS on one side after oral and topical steroids. Whilst surgery provided additional benefit in some patient symptom scores, there was no difference in post-operative smell between the two groups.[50] The RCT evidence does demonstrate more benefit for patients with CRSwNP than CRSsNP.[51] Other non-RCT data provides more support for surgery, especially in patients who have failed medical management.[51] The Royal College of Surgeons of England performed the national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis in 2000. This audit looked at over 3000 patients and found that patients with CRSwNP did better following surgery than patients with CRSsNP. Three point six percent had revision surgery within 12 months and 11.8% within 36 months.[52] A 5-year follow-up study published in 2009[53] revealed that 19% of patients had undergone revision sinus surgery during a 5-year post-operative period. Revision rate was 21% in patients with CRSwNP compared to 15% with CRSsNP.

Recently, studies have evaluated the implications of tissue eosinophilia on post-operative outcome. Eosinophilic CRS has been shown to be of greater clinical severity as well as having a higher recurrence of disease following surgery.[54] One recent study also showed that 'full-house' FESS with post-operative steroid irrigations significantly reduces the risk of recurrence in CRSwNP.[55]

Whilst several clinical factors have been shown to decrease baseline quality of life (QOL) scores (including; asthma, ASA status, depression, and female gender), few of these factors appear to correlate with

poorer outcomes post-operatively.[56] Asthma and ASA status have been demonstrated to influence clinical outcome post-ESS.[57] One trial showed that patients with asthma or higher ASA generally had worse endoscopy scores post-operatively but showed greater symptom improvement than those without asthma.[58] Depression, whilst having no effect on objective measures, demonstrated greater degrees of improvement on QOL scores.[59] Patients who had undergone previous FESS had worse post-operative endoscopy scores although their degree of symptom improvement was similar to that seen in primary surgical patients.[60] Although contrary to established conceptions, neither smoking nor allergy has been shown to affect post-surgical outcomes following FESS.

These QOL studies have been reviewed well in several published articles.[60]

In conclusion, although there is little RCT evidence to demonstrate the benefit of FESS over medical treatment, there is a large amount of level 2 and level 3 data demonstrating that FESS is safe and produces significant symptom and QOL improvement for patients with both CRSwNP and CRSsNP.

Balloon sinuplasty

Balloon dilatation of either the maxillary, frontal and/or the sphenoid sinus ostia is an alternative technique that is increasingly being performed, especially in North America. It is a highly controversial topic and yet there is a large amount of evidence that balloon dilatation can maintain patency of the sinus ostia with 80.5% patency at 6 months, 85.1% at 1 year and 91.6% at 2 years.[61] However, cadaveric studies have shown that, when the maxillary sinus 'ostium' is dilated, the true ostium may be missed and a false ostium created in the posterior fontanelle. These findings have been confirmed by a clinical study performed in Austria.[9] There are significant health care costs with the disposable balloons used for most sinus dilatations, although reusable balloons are now entering the marketplace, which should reduce costs in the future. Small RCTs have shown balloon dilatation to be non-inferior to FESS[62] and a non-randomized trial has shown balloon dilatation to produce lower sinonasal outcome test (SNOT-20) scores compared to conventional FESS at three months.[63] Larger and more robust trials are certainly required to establish which patients should be treated with this new treatment modality and at what stage during their disease progression.[64]

RHINOSINUSITIS IN CHILDREN

The management of children with rhinosinusitis remains controversial. There is a large body of evidence to support the use of adenoidectomy alone as a first-line treatment and to reserve any form of endoscopic sinus surgery for rare and resistant cases.[1] In a meta-analysis and systematic review of adenoidectomy in paediatric CRS, 50–80% of children with CRS improved following adenoidectomy alone.[65] Whilst there does not appear to be any evidence that endoscopic sinus surgery produces any deleterious effects on mid-facial growth, it is widely accepted that conservative treatment should be pursued with all medical management options exhausted before surgery is considered in this patient age group.[1] There may be a role for surgery in patients with cystic fibrosis and immune deficiencies to provide better access for topical irrigations and medications to control their disease although fortunately, such cases remain in the minority treated by most paediatric rhinologists.

CONCLUSIONS

The advent of endoscopic sinus surgery has largely replaced external approaches to the sinuses with some exceptions relating to disease involving the lateral frontal sinus or pre-maxilla. Outcomes of FESS surgery in patients with CRSwNP and CRSsNP remain excellent where medical management has failed, however there is little evidence for endoscopic sinus surgery over medical management as a primary treatment. When significant extra-sinus complications are associated with ARS, and surgical intervention is indicated, most cases can be managed endoscopically. It should always be remembered that FESS does carry a risk of significant and severe complications and rare mortality. Good patient selection, meticulous operative technique and post-operative care remain critical to optimize patient outcomes.

FUTURE RESEARCH

- Better evidence about the best treatment regimes for 'maximal medical therapy' prior to consideration of FESS is required.
- The relative benefits of aggressive 'full-house' FESS versus conservative 'mini-FESS' need to be ascertained.
- Balloon sinus dilatation remains an intervention where further clinical trials would clarify its role in current management algorithms.
- More research is necessary to provide an adequate evidence-basis for post-FESS medical management regimes.

KEY POINTS

- FESS is an effective technique for patients with both CRSwNP and CRSsNP when medical management has failed.
- Revision rates for FESS are generally between 10–20% over a 5-year period, more so in patients with CRSwNP.
- Good pre-operative planning, surgical technique and post-operative follow-up have been demonstrated to produce optimal outcomes.
- FESS has been demonstrated to improve the effective medical management of patients with eosinophilic CRS.
- CRS remains a mucosal disease and ongoing medical management is typically required to prevent recurrent symptoms despite adequate FESS.

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CHAPTER
99

THE FRONTAL SINUS

Salil Nair

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search (as well as PubMed) using the following keywords: frontal sinus, Draf, Lothrop, frontal sinus drill out, osteoplastic flap, osteoma focusing on anatomy, diagnosis, outcomes, management and surgical strategy. The evidence in this chapter is mainly levels 3/4 with some level 2 evidence. The clinical recommendations are predominantly B and C.

INTRODUCTION

The frontal sinus is arguably the most complex of the paranasal sinuses. It demonstrates great variability in size and septation and is rarely symmetrical. In up to 5% of the population this sinus is absent or rudimentary.[1]

ANATOMY

An overview of the anatomy of the paranasal sinuses is covered in Chapter 87. This section refers specifically to the complex anatomy of the frontal recess and frontal sinus.

The frontal sinus ostium drains into an hourglass shaped space termed the frontal recess. Previously, this was incorrectly termed the frontonasal duct but it is not a tubular structure. The frontal recess is a three-dimensional space which communicates with the ethmoidal infundibulum within the middle meatus. In essence the ventilation and drainage of both the maxillary and frontal sinuses pass through narrow complex clefts and spaces before they reach the middle meatus. These clefts and spaces are part of the anterior ethmoid air cells. A normal healthy frontal sinus is therefore dependent on the health of the anterior ethmoids.

Only in the frontal sinus is mucus actively transported inwardly. This is along the frontal intersinus septum, laterally along the roof and back medially along the floor. Less than 60% exits the sinus in any given circuit. Hence, there is a significant recirculation of mucus.[2]

THE FRONTAL RECESS

The frontal recess is bound anteriorly by the agger nasi and the frontal process of the maxilla, the frontal beak. The thickness of the frontal beak depends on the pneumatization of the agger nasi and the presence of frontoethmoidal cells. In general, but not invariably, the greater the number of cells and pneumatization present the smaller the beak and the wider the frontal ostium.[3] The medial border of the frontal recess is the superior attachment of the middle turbinate, the lateral lamella of the cribriform plate, the height and angle of which can vary considerably. The lateral and posterior boundaries are formed by the lamina papyracea and the upward continuation of the anterior face of the bulla, respectively. If the bulla lamella is absent superiorly, a suprabulla space will communicate directly with the frontal recess. In this situation the anterior ethmoidal artery is not protected by the bulla lamella and may be at risk during dissection of the frontal recess. The anterior ethmoidal artery, traversing the skull base

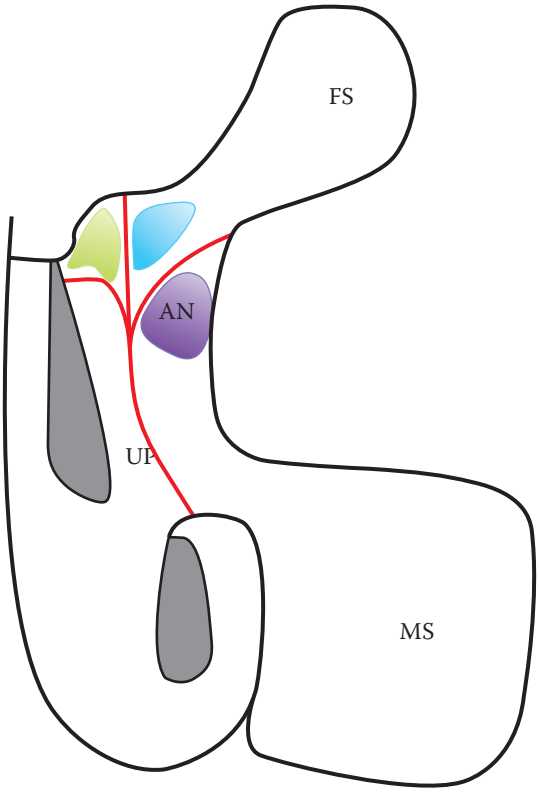


Figure 99.1 Attachments of the uncinate process (UP). Note the presence of frontal ethmoidal cells may alter the attachment of the uncinate process to the skull base, middle turbinate or a combination of these (AN, Agger nasi; FS, Frontal sinus; MS, Maxillary sinus).

from laterally posteriorly to medially anteriorly, is more likely to lie in a mesentery when the olfactory fossa depth is greater than 4 mm.[4] Superiorly, the frontal recess communicates with the frontal sinus but posterior to this, the roof is formed by the fovea ethmoidalis.

Both the agger nasi and uncinate process are key structures in understanding the frontal recess. The agger nasi cell is present in over 90% of patients.[5] The crescent shaped uncinate process attaches inferiorly to the inferior turbinate but superiorly it can attach to the lamina papyracea (33%), skull base (10%) or middle turbinate and a combination of these (57%) (**Figure 99.1**). When present, the medial, posterior and even superior walls of the agger nasi cell are often attached or intimately related to the superior aspect of the uncinate process (**Figure 99.2**).[6]

There are many complex anatomical variations within the frontal recess. Building a three-dimensional image of the various cells is crucial to understanding the anatomy and safe dissection in this area. This has been elegantly described by Wormald et al. in numerous articles and texts.[3, 7, 8]

The simplest configuration within the frontal recess is the presence of an agger nasi cell only. In this instance the uncinate process, curving around the agger cell, would most likely attach directly to the lamina papyracea. Following an uncinectomy and viewed from below, the superior cut end of the uncinate resembles 'a vertical bar'. Access to the frontal sinus is medial to the vertical bar.[9]

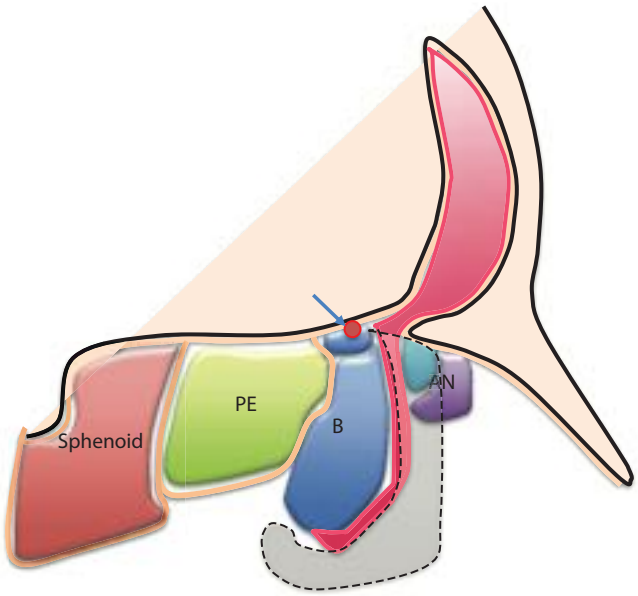


Figure 99.2 The lateral nasal wall. The uncinate process is outlined in a black dotted line. Note its relationship with the agger nasi (AN), B (bulla) and PE (posterior ethmoid). Arrow highlights the anterior ethmoidal artery.

Accessory cells in the frontal recess

The array of cells within the frontal recess can be complex and confusing. In an attempt to provide clarity, Bent and Kuhn proposed an early classification of these cells.[10] This has since been modified.[3] The most recent classification describes the various cells as anterior or posterior, and medial or lateral, with respect to the frontal recess.[11]

Frontal ethmoidal cells are frequently present and classified 1 to 4 (**Table 99.1**). These are anterior ethmoidal cells that are in contact with the frontal process of the maxilla, the anterior limit of the frontal recess. They sit above the agger nasi cell and are described by their number and degree of extension into the frontal sinus. Recently, a more simplified classification has been proposed. The IFAC (International Frontal Sinus Anatomy Classification), primarily describes these accessory cells based on their location and relationship with the agger nasi and ethmoid bulla.[12] Anterior cells are termed supra agger cells and if extending into the frontal sinus are called supra agger frontal cells (SAF). Supra bulla cells are posterior cells and similarily if these extend into the frontal sinus are called supra bulla frontal (SBF) cells. When multiple or large they can obstruct ventilation of the frontal sinus (**Figure 99.3**). Being able to *read* the configuration of these cells, and how it affects the outflow tract is an important step in dissecting the frontal recess. In general, frontal ethmoidal cells tend to push the frontal sinus drainage pathway either posteriorly and/or medially (**Figure 99.4**).

In order to build a three-dimensional understanding of the frontal recess, CT images in the coronal, axial and parasagittal planes are required. In **Figure 99.5** the coronal CT image depicts bilateral frontal cells (**a**). If one merely looked at image (**b**), the frontal ethmoidal cell on the left

TABLE 99.1 Classification of frontal sinus and recess cells

Cell type	Description	Significance	Best CT view
Anterior*			
Agger nasi	A cell that sits anterior to, or directly above to the origin of the middle turbinate	Push the drainage pathway of the frontal sinus medial, posterior or posteromedially	Coronal, Sagittal
Frontal ethmoidal	Anterior lateral ethmoid cells above the agger nasi cell (in contact with the frontal process of the maxilla)		
Type 1/SAC	Single cell above the agger nasi cell – supra agger cell (SAC)	Tend to push the drainage pathway posteriorly	
Type 2/SAC	Tier of cells above the agger nasi cell		
Type 3/SAFC	A frontal cell that pneumatizes into the frontal sinus – supra agger frontal cell (SAFC)		
Type 4/SAFC	A frontal cell that pneumatizes into the frontal sinus and extends by more than 50% of the vertical height of the sinus (**Figure 99.6**)	Removal of these cells will often require an extended frontal sinus procedure	
Posterior*			
Supra bulla	Cell above the bulla not pneumatizing into the frontal sinus	May contain the anterior ethmoid artery	Sagittal
Frontal bulla or supra bulla frontal cell (SBFC)	A cell pneumatizing forward from the bulla or suprabulla space. These 'crawl' along the skull base. Posterior wall of the cell is the skull base.	They tend to push the frontal sinus drainage pathway anteriorly	Coronal, Axial
Supraorbital ethmoid	Pneumatization of the orbital plate of the frontal bone. Posterior wall is the skull base	Give the impression that one has entered the frontal sinus. They open posterior and lateral to the frontal ostium. Associated with anterior ethmoid artery in a mesentery	
Medial*			
Intersinus or frontal septal	Cell based medially in the anterior ethmoid region or pneumatizing the interfrontal sinus septum	Tend to push the drainage pathway laterally	Coronal, Axial

* Refers to EPOS anatomical terminology classification.[11] Supra agger frontal cell (SAFC), based on the IAFC (International Frontal Sinus Anatomy Classification), is an anterior lateral ethmoidal cell that extends into the frontal sinus (T3 cell) whereas a large SAFC can significantly pneumatize into the frontal sinus (T4 cell).[12]

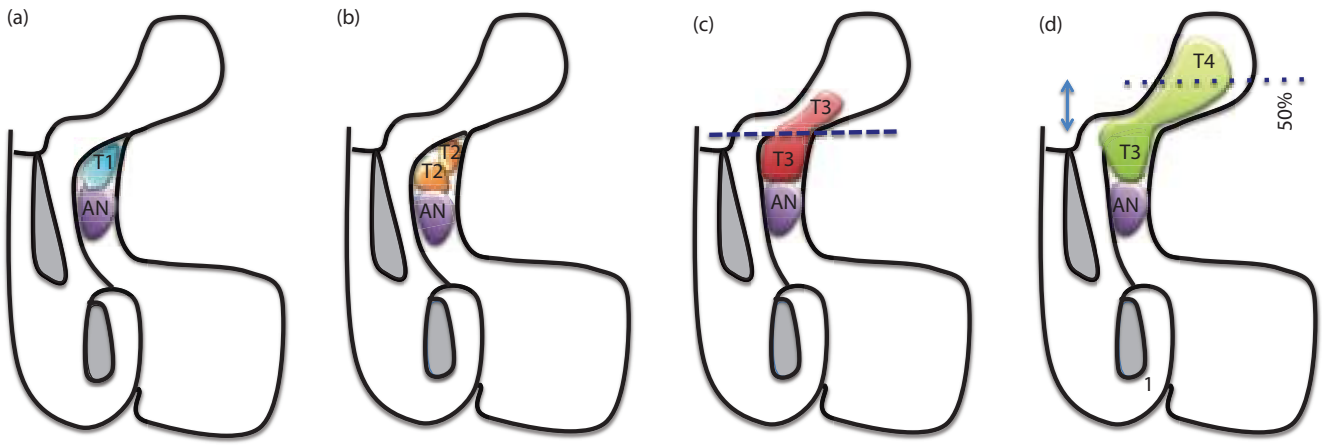


Figure 99.3 Frontal ethmoidal cells. A type 1 or Supra Agger cell (SAC), a single cell sitting above the aggger nasi **(a)**. Multiple supra cells, but not entering the frontal sinus **(b)**. Any cell extending beyond the floor of the frontal sinus (hashed line) is at least a type 3 cell or supra agger frontal cell (SAFC) **(c)**. In **(d)** a cell extending beyond 50% of the height of the sinus (dotted line), is termed a type 4 cell or large SAFC.

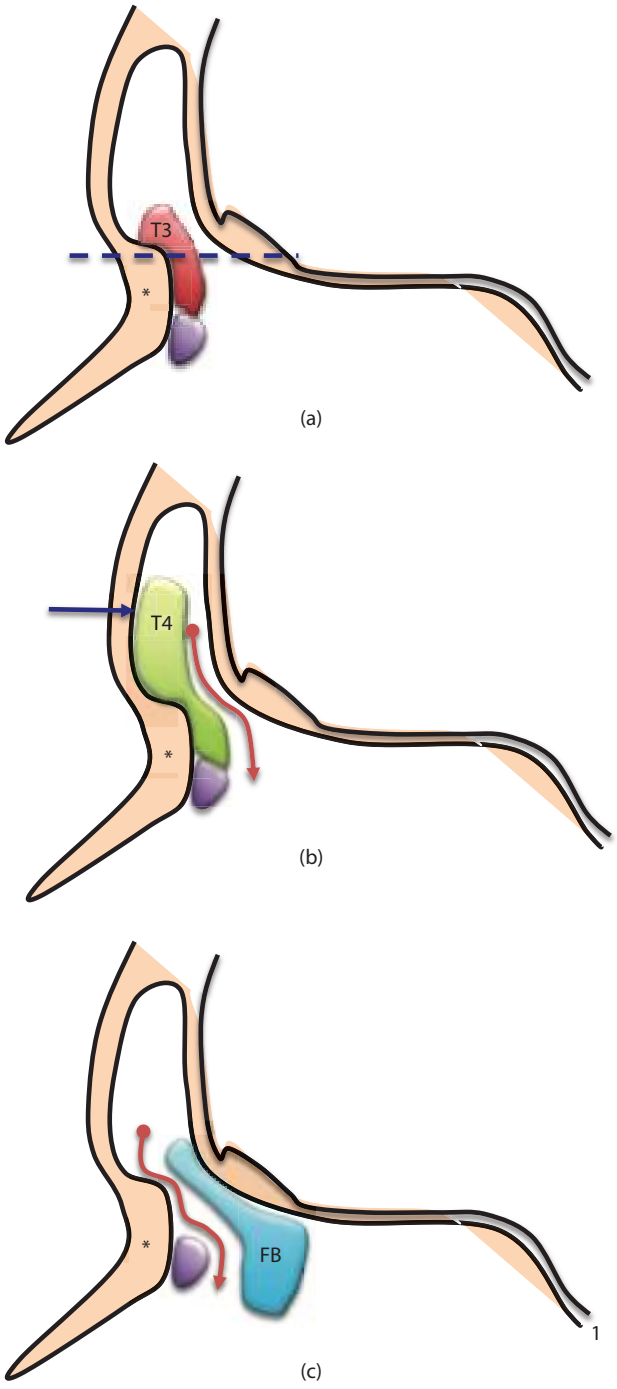


Figure 99.4 Parasagittal views. In **(a)**, a type 3, or small supra agger frontal (SAF) cell pushes above the floor of the frontal sinus (dotted line). In **(b)** a type 4, or large supra agger frontal (SAF) cell extends above 50% of the height (solid arrow) of the frontal sinus. In **(c)** a frontal bulla (FB), or supra bulla frontal (SBF) cell pneumatizes forward from the bulla. It is not in contact with the frontal process of the maxilla or frontal beak (*). The red arrows indicate the drainage pathway of the frontal sinus, which is anterior to the frontal bulla cell and posterior to the frontal ethmoidal cell.

side would have been identified incorrectly as a type 1 cell sitting above the agger nasi cell. However, 'walking' forwards through the images one can identify the same cell

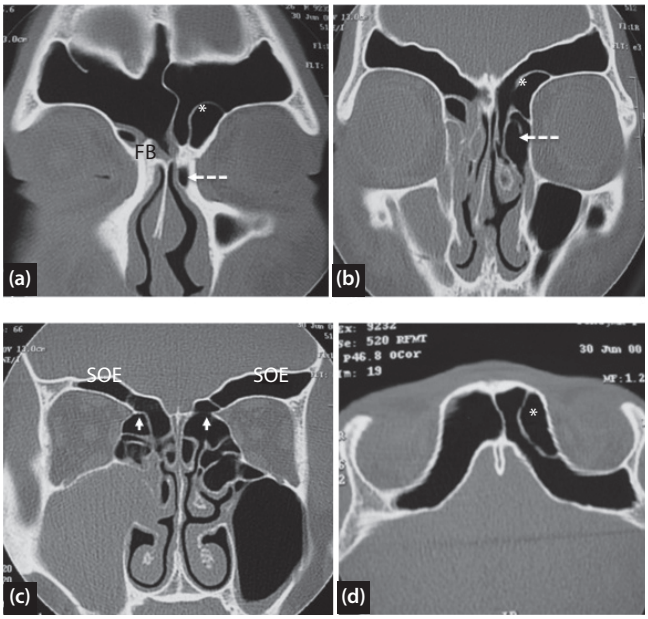


Figure 99.5 In the coronal CT scans **(a)** and **(b)**, the frontal beak (FB), agger nasi cell (dotted arrow) and type 3 cell can be seen (*). Pneumatization of the orbital plate of the frontal bone, the supraorbital ethmoids (SOE), produces a curious 'double lamina' effect of the orbital roof. The anterior ethmoidal artery (solid arrow) is seen traversing the space in a mesentery **(c)**. Axial image identifying the type 3 cell within the frontal sinus **(d)**.

extending superiorly into the frontal sinus, thus making this a type 3 cell. The drainage pathway is best studied in the axial images, and in this case is medial to the type 3 cell (**d**). It is through these pathways that one can dissect the frontal recess and remove obstructing cells.

Type 4 cells are rarely isolated within the frontal sinus and usually pneumatize from the frontal recess. They can be extensive (**Figure 99.6**) and cause disease by direct obstruction of the outflow tract or be diseased themselves. In most instances, it is not possible to completely remove these cells via a standard frontal sinus approach and an extended procedure such as a modified endoscopic Lothrop may be required.

In approximately 65% of Caucasian patients, the orbital plate of the frontal bone can be extensively pneumatized, resulting in supraorbital ethmoid cells (SOEC) (**Figure 99.5c**). An ethnic variation does exist with the incidence being much lower in east Asia.[13] SOEC can present a number of surgical challenges. Firstly, the anterior ethmoidal artery is more likely to be present in a mesentery and hence susceptible to injury.[4] Secondly, a greater proportion of the orbit and skull base are exposed within the surgical field. Finally, it is easy to mistake the opening of the supraorbital cells as that of the frontal sinus. The former tends to open more posteriorly and laterally.

Cells can pneumatize forward from the bulla itself (frontal bulla cells) or above the bulla (suprabulla cells). These 'crawl' along the skull base and if large enough can push the frontal sinus drainage pathway anteriorly (**Figure 99.4**). Large frontal bulla cells can appear as isolated cells within the frontal sinus and be mistaken for a type 4 cell on a coronal CT scan image. They are readily

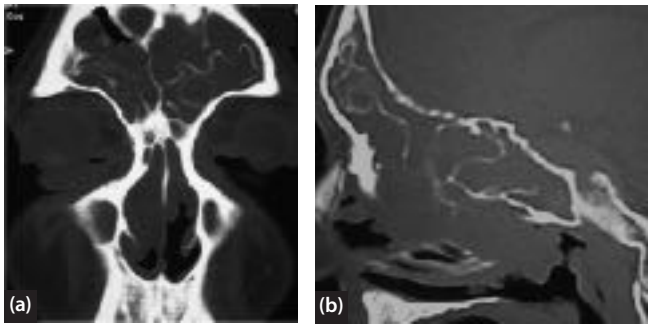


Figure 99.6 Extensive bilateral type 4 cells **(a)** coronal view and **(b)** parasagital.

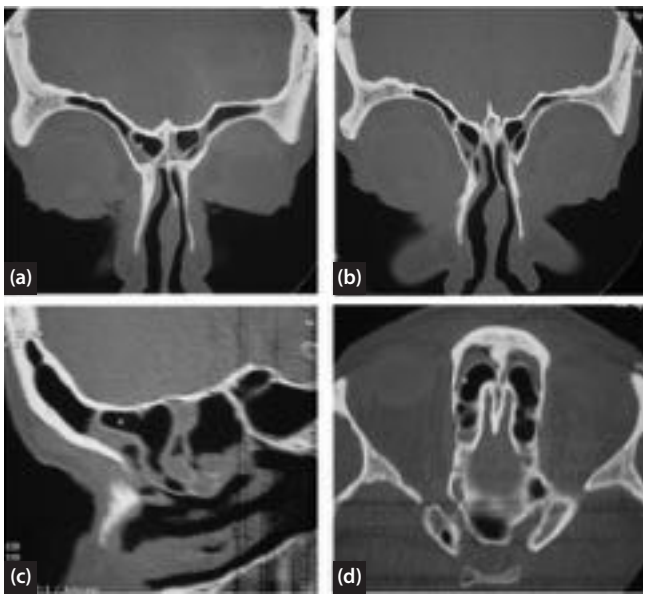


Figure 99.7 Frontal bulla cells. (a) CT image shows cells within the frontal sinus (*). These cells are present in the frontal recess and closely applied to the skull base **(b)**. The parasagittal view confirms forward pneumatisation of the bulla **(c)**. Note the mucosal thickening and frontal sinus drainage pathway anterior to the frontal bulla cells **(d)**.

distinguished from frontal ethmoidal cells as they are not in contact with the frontal process of the maxilla or the frontal beak. Instead they hug the skull base and are best identified on the axial and parasagittal CT sections (Figure 99.7). On coronal CT images supraorbital ethmoid cells are found lateral to the frontal sinus, whereas frontal bulla cells are medially placed.

As the name indicates, frontal intersinuus septal cells arise from the frontal sinus septum. These tend to push the drainage pathway laterally and ultimately drain into the frontal recess on that side (Figure 99.8). According to the most recent classification proposed by the EPOS (European position paper) group, an intersinus septal cell is therefore a medial frontoethmoidal cell.[11]

Diagnosis

A carefully taken clinical history is indispensible. This is particularly important with frontal sinus symptoms

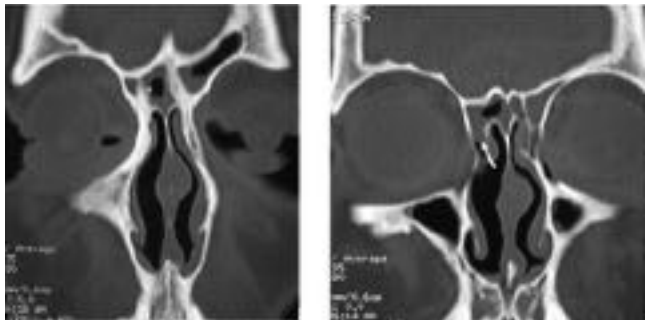


Figure 99.8 Interfrontal sinus septal cells (*). Drainage pathway (solid arrow).

where often a diagnosis of headache has been mislabelled as frontal sinusitis. Sinus headaches are uncommon. An excellent review on the subject by Jones explains that the vast majority of people presenting with symmetrical frontal headache have a tension type headache. Unilateral, episodic headaches are vascular in origin.[14] The headache history is important to try and characterize the symptoms and exclude frontal sinusitis.

A history of facial trauma, previous sinonasal surgery and comorbidities such as asthma and aspirin sensitivity are relevant.

Most patients would undergo a full otorhinolaryngological examination. Rarely inspection of the forehead might reveal a swelling which may or may not be tender. Painful percussion is suggestive of acute frontal sinusitis or even osteomyelitis, so called Pott's puffy tumour. A painless swelling may indicate a mucocoele.

Endoscopy

Although anterior rhinoscopy is routinely performed, the accepted gold standard is nasal endoscopy. Traditionally, 4 mm rigid endoscopes have been used to examine the nose. However, smaller 3 mm endoscopes provide very similar optics and tend to be better tolerated by most patients. Narrower 2.7 mm and 1.9 mm endoscopes are available but compromise image quality and are less robust. Despite the use of narrow endoscopes, access to the middle meatus may be difficult. In patients who have had previous surgery an angled endoscope (30° or 45°) is useful in examining the frontal recess. In addition, a flexible nasendoscope can be navigated into the frontal sinus for inspection purposes.

Imaging

Plain sinus X-rays are inadequate for the routine diagnosis and management of frontal sinus disease. They are useful in providing a template of the frontal sinus when considering an osteoplastic flap procedure. The recommended view is an occipitofrontal sinus plain X-ray.

Ultrasonography is not routinely used for imaging of the paranasal sinuses. Scintigraphy is useful in diagnosing osteomyelitis of the frontal bone. It is helpful in assessing the extent of disease and for follow-up purposes.

COMPUTER ASSISTED TOMOGRAPHY (CT)

Clinical history and nasal endoscopy are essential in managing patients with frontal sinus symptoms but this must be complemented by imaging. CT is the first choice of radiological imaging for sinus disease and is essential for planning surgery. In pre-operative planning, coronal sinus images are most frequently used due to better correlation of radiological and clinical findings during surgery. However, studies have demonstrated that parasagittal views are very helpful in not only identifying the complex cells within the frontal sinus but also the drainage pathways.[15, 16] Ideally, CT images should be available in coronal, axial and parasagittal planes. Although Zinreich et al.[17] proposed a protocol for CT imaging of the sinuses, most institutions will have developed their own preferred technique. Current low dose spiral and multidetector CT scanners are able to acquire images quickly and reformat axial images into coronal and parasagittal planes. The need to acquire direct coronal images is no longer necessary and the effective dose of paranasal sinus CT can be reduced to the order of a chest radiograph.[18] Advantages of axial scanning include improved patient comfort during scanning and avoidance of dental artifacts. Furthermore, raw data from thin section axial scanning can be used for intra-operative computer assisted navigation, if available. Excellent detail can be achieved with contiguous axial cuts of 0.6 mm thickness. A satisfactory compromise might be to use thin-collimation contiguous, 1 mm thickness axial slices. Scan should be reconstructed in the axial, coronal and sagittal planes using both soft-tissue and high resolution algorithm bone windows with a reconstruction thickness of 3 mm or less.[19] The standard bone window/level settings range between 1500–2000/300 Hounsfield units (HU) and 450/50 HU for soft tissue windows . Many centres have access to picture archiving and communication systems (PACS), which allow the end user to easily alter the window settings. This is particularly helpful in fungal ball and chronic fungal sinus disease, where soft tissue window settings may demonstrate double densities associated with calcification and eosinophillic mucin, respectively.

MAGNETIC RESONANCE IMAGING (MRI)

MRI offers excellent soft tissue detail but no bony definition. It is very useful in differentiating tumour from retained secretions. Tumours tend to enhance with T1-weighted gadolinium enhanced scans while fluids do not. Mucus and secretions tend to avidly enhance on T2-weighted images. MRI is very helpful in assessing the dual interfaces between the nasal cavity, and the orbit and the intra-cranial cavity.[20] Enhancement of the lamina papyracea or dura may indicate tumour involvement. Indeed, dural thickening of greater than 2 mm, loss of the hypointense zone and nodular enhancement are highly predictive of dural invasion by malignancy.[21] MRI is particularly useful in assessing patients with ongoing symptoms, who have previously undergone an osteoplastic flap with obliteration. The scans can helpfully distinguish mucocole formation from fat necrosis and infection.[22, 23] It is recommended that in cases of unilateral sinus disease, both CT and MRI are routinely performed. The two imaging modalities are complementary in diagnosing tumours such as inverted papilloma and fungal disease. The characteristic appearances of fungal disease are an iso- or hypo-attenuated signal on T1-weighted images and a signal void on T2-weighted images.[24]

CONGENITAL FRONTOBASAL MALFORMATIONS

Nasal dermoids, cysts and fistulae

Rarely, the frontal sinus can be involved in congenital abnormalities of the skull base. This may be secondary to craniofacial dysostosis or persistence of embryonic remnants. Congenital midline nasal lesions include nasal dermoids, encephaloceles and gliomas. The nasal dermoid is the least rare of these, and is an uncommon midline developmental anomaly. Unlike other craniofacial dermoids, these lesions can present as a cyst, a sinus or a fistula (**Figure 99.9a**) and may have an intra-cranial extension (**Figure 99.9b**).[25] The incidence is estimated at between 1:20,000 and 1:40,000 live births.[26] These fistulas may extend from the skin to the frontal bone, leading to pressure atrophy and narrowing of a frontal sinus if it is developed. Progressive enlargement of the nasal dermoid can cause local infection, meningitis and brain abscesses.

Typically, nasal dermoids present as a midline mass anywhere from the base of the columella, along the dorsum to the glabellar region. They are non-compressible and can discharge sebaceous material.[27]

Pathogenesis

Sessions[25] was the first to coin the term *nasal dermal sinus cyst* to include all the lesions containing ectoderm and mesoderm located in the nose. Briefly, as the neuroectodermal tract recedes, dermal attachments can be drawn in along its course. As the dura mater recedes from the prenasal space it may pull nasal ectoderm upward and inward to form a sinus or a cyst.[28]

Imaging

Imaging is a critical component in the evaluation of nasal dermoids given the associated risk of intra-cranial extension. CT and MRI provide complementary information. For CT, fine cut multiplanar, contrast enhanced imaging is optimal. On CT imaging, the presence of a widened foramen caecum and bifid crista galli do not necessarily indicate intra-cranial extension. However, a normal foramen caecum and crista galli rule out intra-cranial disease.[28]

Surgery

The following principles are important when considering the ideal surgical approach: permit access to a midline cyst

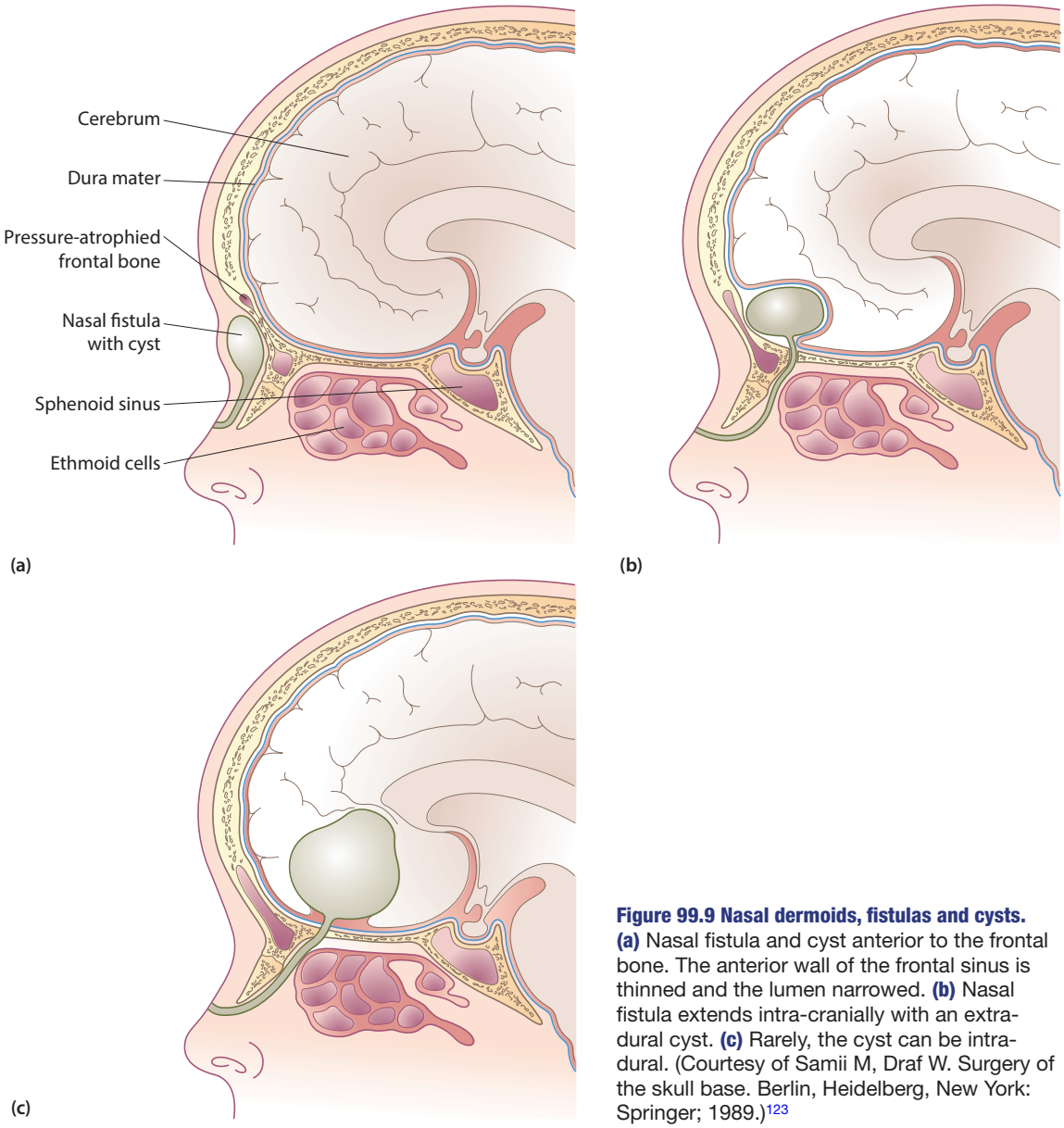


Figure 99.9 Nasal dermoids, fistulas and cysts. **(a)** Nasal fistula and cyst anterior to the frontal bone. The anterior wall of the frontal sinus is thinned and the lumen narrowed. **(b)** Nasal fistula extends intra-cranially with an extra-dural cyst. **(c)** Rarely, the cyst can be intra-dural. (Courtesy of Samii M, Draf W. Surgery of the skull base. Berlin, Heidelberg, New York: Springer; 1989.)[123]

and allow access for medial and lateral osteotomies; allow access to the skull base; facilitate reconstruction of any resulting nasal deformity and finally have a cosmetically acceptable scar.[27] The midline vertical approach is commonly used for extra-cranial lesions although some favour an external rhinoplasty approach for better cosmesis. The latter can be combined with a direct excision if necessary.[29] When there is evidence of intra-cranial extension, a combined approach with the neurosurgical team is recommended. Endoscope assisted excision of extra-cranial dermoids using bilateral intercartilagenous incisions have been described. Recent publications have suggested that it may be feasible to endoscopically access some intra-cranial dermoids.[30]

Although the recurrences following surgery are low, they can occur many years later. Long-term follow-up is therefore essential.

INFLAMMATORY CONDITIONS OF THE FRONTAL SINUS

Acute frontal sinusitis

Acute rhinosinusitis (ARS) is sudden in onset and often follows an upper respiratory tract infection (URTI). It is defined as an increase in symptoms after 5 days or persistent symptoms after 10 days with less than 12 weeks duration. It is estimated that only 0.5% to 2% of viral URTI are complicated by bacterial infection, although the true incidence is unknown due to the difficulty in clinically distinguishing bacterial from viral infections. The prevalence rates for ARS vary from 6% to 12%.[31]

Acute frontal sinusitis occurs as part of a generalized acute rhinosinusitis. In most cases ARS resolves without complication or the need for antibiotic treatment.

Mild symptoms are effectively managed with intra-nasal corticosteroid monotherapy or in conjunction with antibiotics (see Chapter 97, 'Medical Therapy for Rhinosinusitis'). Although topical nasal decongestants are often used, there is little evidence to suggest any effect in relieving ostial oedema. However, they may provide symptomatic relief of nasal congestion. Isotonic and hypertonic saline nasal douches are effective in alleviating symptoms.[31]

Extrasinus complications of acute frontal sinusitis are relatively rare in the current antibiotic era. Nonetheless, in some patients acute frontal sinusitis may become complicated. This is most commonly seen in young adolescent men.[32, 33] The frontal sinus is the most common sinus associated with intra-cranial infection. Clinically, patients may present with a persistent severe headache, frontal or periorbital swelling, altered mental status or meningeal signs. The possible complications are outlined in **Table 99.2**.

The general management of the complications of rhinosinusitis are discussed elsewhere (see Chapter 101, 'Complications of Rhinosinusitis'). If culture results are unavailable, antibiotic therapy should target the common organisms which include *H. Influenzae, S. pneumonia, S. pyogenes* and *alpha haemolytic streptococci*.[34] Despite antibiotic therapy, there is not an insignificant incidence of morbidity and occasionally mortality estimated between 5% and 15%.[35]

CT is the imaging modality of choice. Multiplanar imaging of the brain, orbit and sinuses with contrast enhancement is necessary as the incidence of concomitant complications is significant. In one study, approximately 24% of patients aged 7 or older attending theatre for surgical intervention of an orbital complication also had an intra-cranial complication.[36] Evidence of intra-cranial or orbital involvement requires a multidisciplinary approach.

As mentioned above the surgical management is covered elsewhere. In brief, neurosurgical complications may require a craniotomy. Traditionally, the frontal sinus can be trephined and irrigated via a small infrabrow approach and the placement of a drain. An alternative approach has been described which involves performing a 'mini' frontal sinus trephine.[37] The disadvantage of this method is the difficulty in establishing irrigation via the small trephine port. Orbital abscesses not responding to maximal medical therapy require surgical drainage. A classical Lynch-Howarth approach is favoured.

Increasingly, orbital complications such as subperiosteal abscesses and acute complicated frontal sinusitis are being managed endoscopically. In the acutely infected state, dissection of the frontal recess can be very challenging and requires a significant level of advanced endoscopic skills. However, the role of endoscopic frontal sinus surgery in the initial management of intra-cranial complications of sinusitis remains unclear. In a recent 6 year retrospective review of 23 patients, ESS did not appear to influence the need for neurosurgical intervention, even with lesions less than 1 cm.[38]

Chronic frontal sinusitis

Although much work has improved our understanding, the aetiology and pathogenesis of chronic rhinosinusitis (CRS) is still described as multifactorial. The bacteriology of CRS differs from that of ARS with a higher prevalence of anaerobic organisms. Chronic rhinosinusitis with (CRSwNP) or without (CRSsNP) may cause obstruction of the frontal sinus outflow tract and lead to chronic frontal sinusitis. The current mainstay of treatment for CRS involves medical therapy.[31] The majority of patients respond to a combination of antibiotics, nasal irrigations, intra-nasal and if necessary oral steroids therapy. The optimal management is discussed in Chapter XX (The management of CRS). However, despite maximal medical therapy some patients may have persistent symptoms. As in CRS, the diagnosis of frontal sinusitis is based on symptoms (frontal pressure or headache), clinical findings and CT imaging. In these patients, surgical intervention may be necessary. However, despite surgery a proportion of patients may continue to suffer with frontal sinus symptoms and develop recalcitrant chronic frontal sinus disease. This may be related to persistent disease or scarring and stenosis secondary to surgery.

The frontal recess is a complex space and anatomical variations, inflammation and scarring may play an important role in the aetiology of chronic frontal sinusitis. The relative contribution of each of these factors to chronic frontal sinusitis requiring surgical intervention has not been well quantified. A number of retrospective studies have examined the impact of accessory cells within the frontal recess and the development of frontal sinusitis. One study has reported that the presence of suprabulla cells, supraorbital ethmoid cells, frontal bulla cells and recessus terminalis was significantly associated with frontal sinusitis.[39] In another study, the prevalence of frontal sinus mucosal thickening was increased in patients with type 3 and 4 frontal ethmoidal cells.[40] Other studies suggest that although scarring, retained agger and frontal cells may contribute to anatomical obstruction, the ongoing mucosal inflammation is the most important factor leading to frontal sinusitis.[41–44]

TABLE 99.2 Complications of acute frontal sinusitis

Local (frontal sinus)	Orbital	Intra-cranial
Mucocele Pyocele Osteomyelitis (Potts puffy tumour)	Orbital cellulitis (including subperiosteal, intra-orbital abscess)	Meningitis Epidural abscess Subdural empyema Intra-cerebral abscess Superior sagittal sinus thrombosis Cavernous sinus thrombosis

FRONTAL SINUS SURGERY

Despite advances in medical and surgical therapy, chronic frontal sinusitis remains a difficult disease to manage. Over the years, the surgical management of frontal sinus disease has evolved from open obliterative procedures to endoscopic mucosal sparing techniques. Although extensive and complex frontal sinus pathology can be managed endoscopically there remains a definitive role for open procedures such as the osteoplastic flap.

There are no simple guidelines for the management of chronic frontal sinusitis. Prior to considering any surgery it is wise to review the clinical history, imaging and indications. Underlying conditions such as diabetes, immune disorders and aspirin exacerbated respiratory diseases need to be identified.[45]

In the past, treatment of chronic frontal sinusitis was directed towards the sinus itself. However, contemporary management is based on the understanding that the problem most often involves the drainage pathway, the frontal recess rather than the sinus. The principles of surgery are to relieve obstruction that may lead to inflammatory changes. Mucosal preservation is important as mucosa regenerating over bare bone lacks effective cilia.[46]

There is much debate regarding the philosophies of managing the frontal sinus in CRS. These range from minimal invasive sinus techniques (MIST) where following an uncinectomy transitional spaces are opened, to addressing an obstructed frontal recess irrespective of patient symptoms.[7, 47] Most rhinologists would agree that the best surgical approach to the frontal sinus is a graduated one (Table 99.3).

Numerous descriptions and approaches to the frontal sinus have been described. Not only is this confusing but it makes it difficult to draw meaningful comparisons from the published literature. The most widely accepted classification is that described by Draf and his colleagues although this has waned in popularity, as it too can be open to interpretation.[48] The classification describes increasingly aggressive approaches to the frontal sinus. The general rule would be to choose the least invasive approach to achieve the desired outcome. In some cases, the least invasive may necessarily be quite extensive. The surgery needs to be tailored to the individual needs of each patient and depends on various factors such as previous surgery and extent of disease.

The choice of surgical procedure used to manage recurrent frontal sinus disease will depend on a number of factors outlined in Table 99.4. The surgeon needs to take into account the extent and completeness of the previous surgery, the anatomy of the frontal sinus and the overall burden of disease. An assessment of the surgical complexity based on the anatomy alone is available in Table 99.5.

In an attempt to better define the extent of surgery to the frontal recess and sinus, an international panel of

TABLE 99.3 Graduated approach to frontal sinus surgery

Graduated approach to frontal sinus surgery	
No exploration	No disease
Balloon sinuplasty	May have a role in certain situations with limited disease
Draf type I (frontal sinusotomy), ethmoidectomy*	Removing cells within the frontal recess, following an FESS
Draf type IIa and b*	Remove cells extending into the frontal sinus and resect bone between the lamina papyracea and middle turbinate (a) or nasal septum (b)
Draf type III, modified endoscopic Lothrop (MEL), Frontal sinus drillout*	Resection of the floor of the frontal sinus, superior nasal septum and interfrontal sinus septum
Osteoplastic flap + MEL Osteoplastic flap with obliteration	Above and below approach Removal of all mucosa within the sinus and obliteration with fat
Riedel's procedure Cranialization	Removal of the anterior table of the frontal sinus Removal of sinus mucosa and the posterior table of the frontal sinus

* A frontal sinus mini trephine may be used as an adjunct to these procedures.

TABLE 99.4 Factors influencing the surgical approach

	Considerations	Surgical options
Patient	Compliance issues and significant comorbidities	Simple FESS with minimal manipulation of the frontal recess
	Asthma, aspirin sensitivity	Comprehensive clearance of frontal recess If recurrent disease see below
Anatomy	Preserved landmarks, minimal previous surgery, no complex cells	Draf type I procedure
	Poor landmarks, osteoneogenesis, multiple revision procedures, thick frontal beak, complex frontal cells	Draf type (modified endoscopic Lothrop)
Pathology	Chronic frontal sinusitis with or without polyps. No previous surgery	Draf type I procedure
	Recurrent disease, ASA with polyps, eosinophillic mucin CRS, tumours, lateral mucoceles. Recalcitrant	Draf type (modified endoscopic Lothrop)
	Complicated frontal sinusitis with erosion of the posterior table, anterior table osteitis, tumours extending laterally	Draf III or an osteoplastic flap approach. Combined approach

TABLE 99.5 The International classification of complexity of frontal sinus surgery

	Wide AP diameter (≥10 mm)	Narrow AP diameter (9–6 mm)	Very narrow AP diameter (≤5mm)
Cells below ostium (AN, SAC, SBC)	Less complex (Grade 1)	Moderate complexity (Grade 2)	High complexity (Grade 3)
Cells encroaching into the ostium (SAFC, SBFC, SOEC, FSC)	Moderate complexity (Grade 2)	High complexity (Grade 3)	Highest complexity (Grade 4)
Cells extending significantly into the frontal sinus (SAFC, SBFC, SOEC, FSC)	High complexity (Grade 3)	Highest complexity (Grade 4)	Highest complexity (Grade 4)

AP refers to the frontal ostium anterior-posterior (AP) diameter as measured from the frontal beak to the skull base at its narrowest distance on the parasagittal CT scan. Classification of the cells is in accordance to the International Frontal Sinus Classification[12]: AN (Agger Nasi), FSC (frontal septal cell), SAC (supra agger cell), SAFC (supra agger frontal cell), SBC (supra bulla cell), SBFC (supra bulla frontal cell), SOEC (supra-orbital ethmoid cell). Data from Wormald PJ, Bassiouni A, Callejas CA, et al. The International Classification of the radiological Complexity (ICC) of frontal recess and frontal sinus. *Int Forum Allergy Rhinol*. 2016.[123]

TABLE 99.6 Extent of frontal sinus surgery (EFSS). A comparison between the Draf frontal sinus surgery classification and a new proposed international classification of extent of frontal sinus surgery

Draf classification[124]	International classification of the extent of EFSS[12]	Tissue/Bone removal
	0 – No bone or tissue removal. Balloon dilatation	No Tissue removal
Draf 1 – Ethmoidectomy and removal of cells below the frontal sinus	1 – Removal of cells in the frontal recess not directly obstructing the frontal ostium	Removal of cells
	2 – Removal of cells obstructing the ostium but not extending through the ostium	
Draf 2a – Enlargement of the frontal ostium between the lamina papyracea (LP) and the middle turbinate (MT)	3 – Removal of cells extending through the frontal ostium (no widening of the frontal ostium)	
	4 – Removal of cells extending through the frontal ostium with enlargement of the ostium (bone removal, usually frontal beak)	Removal of bone
Draf 2b – Enlargement of the frontal ostium from the LP and the nasal septum	5 – Enlargement of the frontal ostium from the LP to the nasal septum	
Draf 3 – Bilateral enlargement of the frontal ostia, resection of the superior nasal septum, floor of the frontal sinus and inter-sinus septum	6 – Bilateral enlargement of the frontal ostia into a common ostium, with resection of the superior nasal septum, inter-sinus septum and floor of the frontal sinus	

experts have proposed a new classification (Table 99.6). The aim is to standarize terminology and provide a framework which should allow better comparison of surgical outcomes.[12]

No frontal recess exploration

Unfortunately, it is not uncommon for frontal sinus obstruction to occur as a result of surgery.[41, 43] In the absence of positive CT scan findings and clinical symptoms the frontal sinus or recess should not be explored. Unnecessary instrumentation in a healthy recess can result in mucosal injury and adhesion formation.[49]

Balloon sinuplasty

Introduced in 2006, balloon sinuplasty is proposed to be a minimally invasive approach to the management of CRS involving the frontal sinus. The technique introduces a balloon over a guide wire, which may be illuminated, to confirm its position in the frontal sinus. Once in place, spanning the ostium, the balloon is dilated with a controlled inflation device. In theory, this gently enlarges the ostium by effecting microfactures of the surrounding bone and compressing the soft tissue. Soft tissue injury is suggested to be minimal but the rate of synechia formation is reportedly at least equal to that seen with conventional endoscopic sinus surgery (ESS). Complications include inability to cannulate the sinus, and CSF leak.[50, 51] Although it is a safe and well tolerated procedure, the evidence in support of its use as an alternative to standard ESS techniques is limited.[31, 52, 53] In many instances balloon dilation is combined with ESS and is termed a hybrid procedure.

Draf type I (ethmoidectomy and frontal sinusotomy)

This is the commonest primary procedure performed for chronic frontal sinusitis and in many cases is sufficient.[54] As the least invasive procedure the aim is to clear obstructing disease **inferior** to the level of the frontal ostium – the frontal recess. The key step is performing a complete ethmoidectomy. This includes removal of any anterosuperior ethmoid cells, the agger nasi and uncinate process (Figure 99.10). This approach is best limited to when there



Figure 99.10 A Draf type I frontal sinusotomy with removal of the agger and anterior ethmoid cells in the frontal recess cells.

is only minor pathology in the frontal sinus. It may not be sufficient in cases where the patient suffers from significant nasal polyposis associated with aspirin intolerance and asthma.

Draf type II frontal sinusotomy

Where a more conservative surgical approach has failed an extended frontal sinus procedure may be required. In a Draf type II approach, cells extending into the frontal sinus are removed (Figure 99.11). If the frontal ostium is widened from the lamina papyracea to the middle turbinate this is called a type IIa approach. This may be possible by using a Kerrison or Hajek-Kofler punch. Extending this opening beyond the middle turbinate to the nasal septum is a type IIb approach. This involves removing the anterior end of the middle turbinate and drilling the floor of the sinus to the midline. The indications for a Draf type IIb are limited but may be used to address unilateral frontal ostium osteoneogenesis, inverted papilloma, osteomas or medially placed frontal mucoceles. A recent study has suggested using a Draf type IIb approach for addressing contralateral inaccessible frontal sinus disease. Although short-term patency was good, larger patient numbers and longer follow-up data are required before this can be recommended.[55]

Draf type III (modified endoscopic lothrop)

Also known as a median drainage procedure or frontal sinus drill-out, the operation was first described by Lothrop in 1914 as an external procedure.[56] Draf described an intranasal microscopic approach while others described a similar endoscopic technique.[57, 58] The modified endoscopic Lothrop procedure (MELP) has recently gained popularity as a minimally invasive alternative to frontal sinus obliteration. The possible indications for a MELP are highlighted in Table 99.7.

The procedure consists of creating a large common drainage pathway for the paired frontal sinuses by resecting the upper nasal septum, the frontal intersinus septum

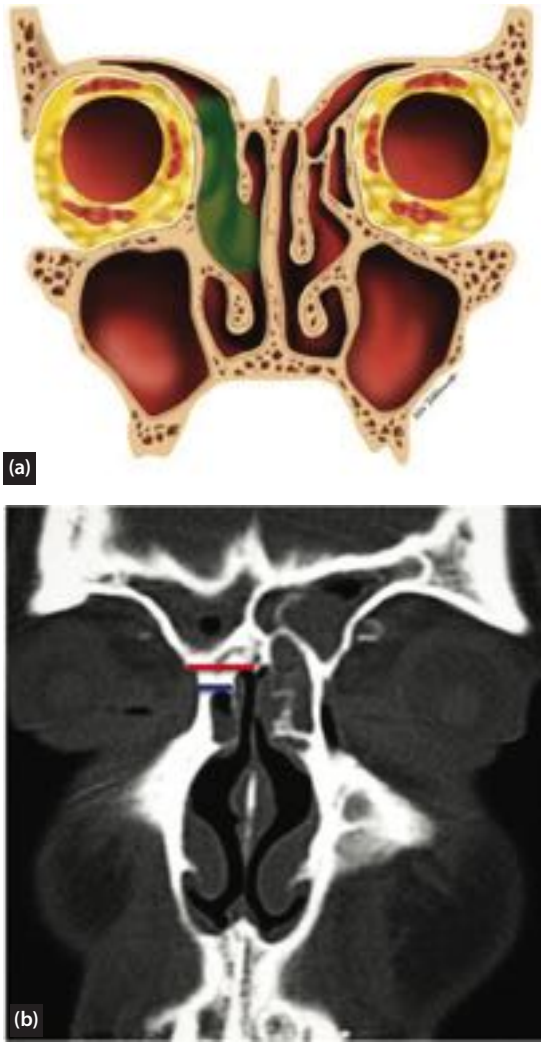


Figure 99.11 The Draf type II, with removal of cells extending into the frontal sinus **(a)**. The coronal CT highlights the extent of bone removal **(b)**. Type IIa involves widening of the ostium from the lamina papyracea to the middle turbinate (blue line) and IIb extending this to the nasal septum (red line).

and the floor of both frontal sinuses (Figure 99.12). The procedure is technically demanding as useful landmarks are often absent and the operative field is narrow. A septectomy performed early allows the surgeon to work more freely in the narrow confines. The use of frontal mini trephines helps with early identification of the frontal ostium and hence the posterior limit of dissection. The use of computer assisted navigation may improve efficacy and safety but is no substitute for sound surgical training and anatomical knowledge.[59]

Drilling commences from one frontal recess and proceeds across the midline to the contralateral recess. A small area of skin is often exposed bilaterally just above the axilla of the middle turbinate and demarcates the lateral extent of dissection. To obtain the maximum possible opening it is necessary to drill down the anterior projection of the skull base. In order to do this safely, it is helpful to identify the first olfactory neurons, which are found by peeling back the mucosa between the middle

turbinate and the nasal septum. The fibres can be seen to arise just posterior to a linear groove through a small bony opening. When this is performed on both sides the so-called 'frontal T' results (Figure 99.13). The long limb corresponds to the posterior aspect of the septectomy (the perpendicular plate of the ethmoid) and the horizontal limbs to the posterior margin of the frontal sinus floor resection. A summary of the essential steps of the procedure is outlined in Box 99.1.

In certain situations when access to the frontal sinus is blocked (osteoma or osteoneogenesis) or the anatomy is grossly distorted, one can use a midline approach. Rather than drilling from lateral to medial a transeptal approach can be used. This involves finding the 'frontal T' early and drilling immediately superiorly to enter the floor of the frontal sinus in the midline. This is relatively safe as one is drilling away from the skull base. Drilling then proceeds from medial to lateral in an 'inside to outside' fashion.

Complications of the MELP include injury to the skin and nasal bones, orbital injury, damage to the skull base and CSF leak.

TABLE 99.7 Utility of the modified endoscopic Lothrop procedure (MELP)

Potential indications for a MELP	
Chronic frontal sinusitis	Refractory to previous endoscopic surgery
CRS with nasal polyps, asthma, aspirin exacerbated respiratory disease	Controversial, but may be indicated as a primary procedure
Allergic fungal disease	Includes eosinophilic mucin CRS, fungal sinusitis
Mucoceles	Large frontal mucoceles, even those extending beyond the mid-pupillary line[22]
Salvage osteoplastic flap	'unobliteration' of the frontal sinus[23]
Frontal osteoma	Grade I and II. Less suitable for grade III and IV with significant posterior table erosion and lateral extension[111]
Inverted papilloma	Extending into the frontal sinus. May require an accessory port in to the sinus[72]
Frontal sinus trauma	Closure of CSF leaks
Cranionasal resection	As part of a skull base resection for anterior cranial fossa tumours
Alternative to OPF with obliteration	Preservation of a functioning sinus, able to survey for recurrent disease, improved cosmesis, decreased morbidity, shorter hospital admission, lower cost[125]

Reasons for failure of frontal recess and sinus surgery

Despite careful pre-operative planning and maximum medical therapy, surgery in the frontal recess can fail. The commonest causes for failure include.

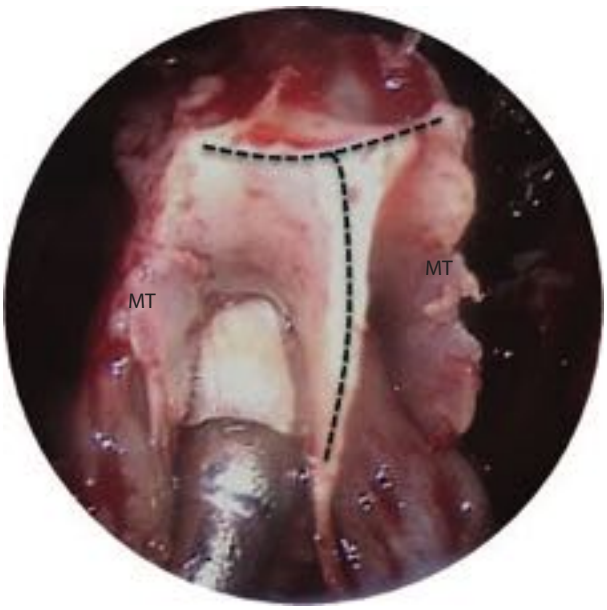


Figure 99.13 The 'frontal T'. An intra-operative view with the olive tip suction on the first olfactory neuron. The vertical limb of the dotted line is the posterior margin of the septectomy (perpendicular ethmoid plate). Horizontal limb is the posterior margin of the frontal ostium and joins the two amputated ends of the middle turbinate (MT).

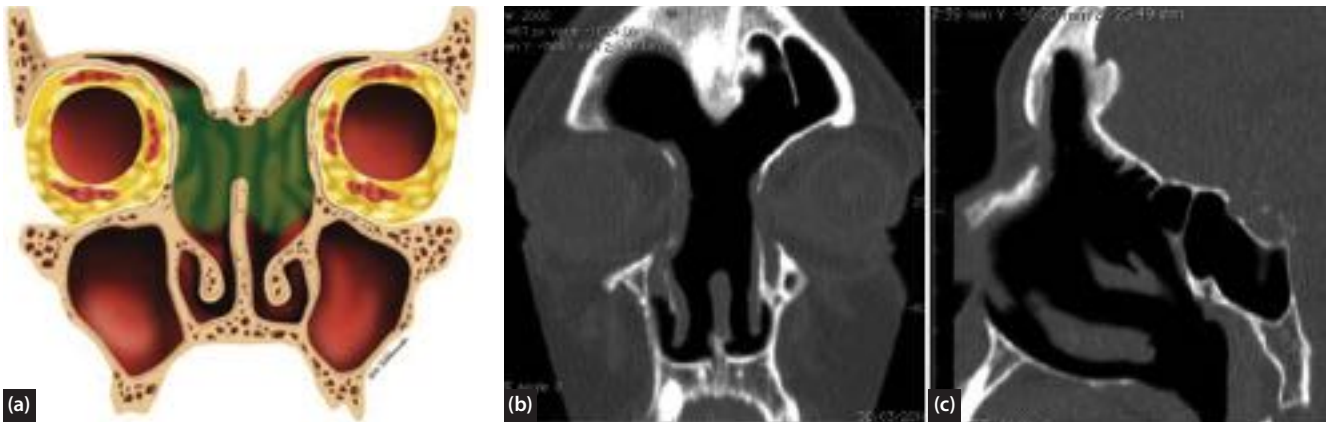


Figure 99.12 The Draf type III or modified Lothrop. Note the widening of the frontal ostium from lamina to lamina **(a)**, the reduction of the frontal intersinus septum **(b)** and the beak **(c)**.

BOX 99.1 Summary of operative steps for the MELP

ESSENTIAL STEPS OF A MODIFIED ENDOSCOPIC LOTHROP (DRAF TYPE III) PROCEDURE

1. Complete sphenoethmoidectomy
2. Clear frontal recess and identify frontal ostium. Frontal mini trephines may be required. If no access consider midline, trans-septal approach
3. Create septal window. At least 2 x 2 cm. Posterior limit is anterior end of middle turbinate. Inferior limit, to allow visualization of contralateral middle turbinate axilla. Superiorly to the nasal vault
4. Trim anterior end of middle turbinate to skull base.
5. Dissect mucosa posteriorly between middle turbinate and nasal septum to identify first olfactory neuron
6. Drilling commences in an anterior, superior and lateral direction from the frontal ostium through the axilla of the middle turbinate. Small area of skin may be exposed laterally.
7. As drilling extends superiorly, it is easier to drill from the contralateral side via the septal window
8. Reduce frontal intersinus septum and frontal beak to join the two sides together
9. Try to preserve mucosa over posterior aspect of frontal ostium
10. Lower bone over anterior projection of the skull base to primary olfactory neuron

ONGOING MUCOSAL DISEASE

Persistent or recurrent nasal polyps frequently obstruct the sinuses. Patients with eosinophilic CRS presenting with polyps fare less well. Similarly patients with asthma and nasal polyps are likely to require revision surgery.[60]

INCOMPLETE DISSECTION WITH RETAINED UNCINATE PROCESS AND RESIDUAL CELLS IN THE FRONTAL RECESS

This can impede drainage and exacerbate ongoing mucosal inflammation.[40, 61]

LATERALIZATION OF THE MIDDLE TURBINATE

Whether partial resection of the middle turbinate predisposes to frontal sinusitis is unclear. However, the incidence of lateralized middle turbinates in revision surgery is high (36–78%).[61, 62] The frontal sinus rescue procedure was described to address frontal recess stenosis secondary to middle turbinate lateralization. Mucosa is dissected from the turbinate and the stump trimmed back to the skull base. The medial mucosa is discarded and the lateral mucosa from the sinus is draped over the denuded stump.[63]

SCARRING AND SYNECHIA

Meticulous attention to detail can help to minimize unnecessary trauma and subsequent scarring. However, synechia and scarring are very common findings in revision frontal sinus surgery but may not always be symptomatic.[60, 62]

OSTEONEOGENESIS

Failure to preserve mucosa results in scarring and osteoneogenesis.[64] The incidence of osteoneogenesis is higher in patients that have undergone sinus surgery. It may occur secondary to a combination of factors such as persistent mucosal inflammation, ongoing infection and surgical trauma. The ongoing osteitis promotes mucosal inflammation and oedema and may contribute to frontal recess stenosis.[65]

Outcomes for endoscopic frontal sinus surgery

Although trials providing high level of evidence are not available, there are a number of well organized prospective studies that have shown endoscopic sinus surgery (ESS) is safe and effective in managing patients with CRS (with and without polyps) when medical therapy has failed.[31] The evidence of effectiveness for various frontal sinus procedures is less well documented.

Most studies define success as objective endoscopic evidence of frontal sinus patency. Subjectively however, despite a patent recess some patients will continue to complain of ongoing symptoms.[66] This mismatch between patient reported outcome measures and clinical or radiological findings poses a challenge in both selecting the ideal candidate for frontal sinus surgery and reporting results. A recent review of the literature has identified at best, level 3 evidence in support of the clinical efficacy of frontal sinus surgery, the main issues being the relative short follow-up periods and the different surgical techniques performed for various indications.[67] Early patency rates of 90% at 12 months, falling to 68% after 72 months, have been reported.[60] Others report a 90% patency rate in non-eosinophilic CRS, dropping to 85% in eosinophilic CRS, over an average follow-up period of 46 months.[68] A recent study with a shorter follow-up reported a high overall ostial patency rate of 92% with symptom resolution in 78% which was unaffected by asthma, EMCRS and smoking when assessed individually but additive when combined together.[69]

There has been much comparison in the literature between the osteoplastic flap procedure (OPF) with obliteration and the MELP. The OPF with obliteration has a reported success rate as high as 93% at 8 years but is not without complications (see 'The osteoplastic flap procedure' below).[70] A systematic review and meta-analysis of the safety and efficacy of the MELP reports an overall patency rate of 95.9%. An overall failure rate of 13.9% is quoted with 80% of those failing undergoing a revision MELP and the remainder an osteoplastic frontal sinus obliteration.

The osteoplastic flap procedure

The OPF procedure was developed to manage chronic frontal sinus disease refractory to procedures such as the external frontoethmoidectomy, which were associated with high failure rates.[71] Obliteration with fat was introduced later and popularized by Goodale and Montgomery. Although the OPF with fat obliteration is reported to be

the gold standard treatment with success rates over 90% it does have a long-term failure rate of up to 25%.[72] In addition, it is associated with significant morbidity. These include CSF leaks, persistent forehead numbness, severe headaches without evidence of recurrent disease, frontal bossing, supraorbital neuralgia, mucocele formation, donor site complications after abdominal fat harvesting and difficulties with post-operative surveillance.[70, 73, 74] In a graduated approach to frontal sinus surgery some might consider this the final step, as the frontal sinus is rendered non-functional. Others would argue that it is a safe and effective procedure in carefully selected patients.

Without question, the OPF approach offers unparalleled access to the frontal sinus and is indicated when wide exposure is necessary (**Table 99.8**). However, the role of frontal sinus obliteration for the surgical treatment of frontal sinus abnormalities is much more controversial.[71, 75–77] In a large series, based in a tertiary setting performing over 700 frontal sinus procedures in a 3-year period, less than 2% of cases were managed by an OPF with obliteration.[78] In the current endoscopic era, the indications for obliteration are dwindling. The ability to tackle pathology from above via an OPF approach and simultaneously endoscopically restore ventilation from below has offered an alternative to obliteration. Traditionally, obliteration was suggested for fractures of the anterior table of the frontal sinus involving the outflow tract. Currently however, one might consider repairing the fracture, monitoring with imaging and perhaps endoscopically intervening at a later stage if necessary.[79]

Without obliteration

An OPF can be performed through a number of approaches. Coronal, brow and mid forehead incisions have all been used to expose the anterior table of the frontal sinus. Zigzag coronal incisions are better camouflaged in male pattern baldness. A combination of local anaesthesia (Lignocaine 1%), vasoconstrictors (adrenaline 1:1000), steroid (Adcortyl 5 mg) and Hylase (I,500 iu) aid dissection and minimize bleeding. An incision is made down to the periosteum. Using a combination of blunt and sharp dissection the scalp flap is elevated to the supraorbital ridge and over the root of the nose. The flap is pulled caudally on both sides, leaving behind the periosteum and the bone, thus preserving the supraorbital and supratrochlear vascular nerve bundles. The next step is to precisely define the extent of frontal sinus pneumatization. Conventionally, a 6-foot Caldwell view (occipitofrontal view) X-ray was used as a template to mark out the margin of the frontal sinus. CT-generated frontal sinus templates are virtually identical to the Caldwell radiograph-derived templates and may obviate the need for additional imaging.[80] As an alternative, transillumination can be used to outline the extent of the sinus. When available, surgical navigation has been shown to be more accurate and may reduce the risk of inadvertent intra-cranial entry.[81] Others have developed 3D models of the frontal sinus using pre-operative CT data from which an accurate template is produced (**Figure 99.14**).[82]

The periosteum is incised 1.5 cm outside the frontal sinus margin (or template) and elevated to the margin of the sinus where an osteotomy is performed. An alternative is to entirely elevate the pericranium with the skin flap.[83] An oscillating saw angled at 30° towards the frontal sinus provides an opening with a large surface area for easier fixation of the bone lid. The bony incision is carried to the supraorbital ridge on both sides. When opening the frontal sinus bilaterally, the intersinus septum must be separated from the anterior frontal sinus wall with an angled chisel. The fracture and elevation of the bony lid is undertaken

TABLE 99.8 Relative indications for an osteoplastic flap procedure. (*) May consider frontal sinus obliteration

Possible scenarios	Pathology
Wide exposure of the frontal sinus necessary and endoscopically inaccessible anatomy	Large osteomas Inverted papilloma with significant lateral extension Malignant tumours Far lateral mucoceles in a well-pneumatized sinus
Failed endoscopic procedures for chronic frontal sinusitis	Where maximal medical therapy and MELPs have failed (*)
Extensive frontal bone osteomyelitis	Unresponsive to medical therapy and ESS
Extensive neo-osteogenesis of the frontal recess	May occur secondary to failed endoscopic sinus surgery, facial fractures, frontal bone osteomyelitis (*)
Diseased small underdeveloped sinuses	Anterior-posterior distance less than 8 mm making a MELP difficult (*)
Frontal sinus fractures	Anterior and posterior table fractures, CSF leaks and those involving the frontal sinus outflow tract

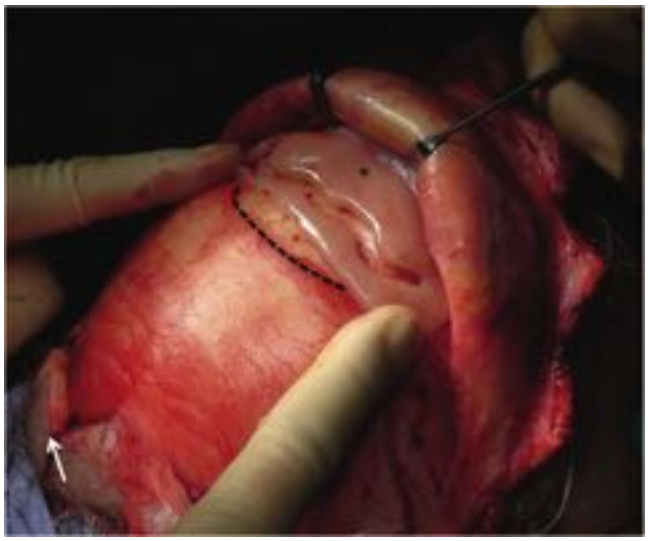


Figure 99.14 Marking out the osteotomy incision during an osteoplastic flap procedure. The template shown (*) was created from a 3D model and provides a guide for the bony osteotomy. Note the cute edge of the periosteum approximately 1.5 cm posterior to the incision site (dotted line) and the zigzag coronal skin incision (white arrow). (Courtesy of Mr A Sama.)

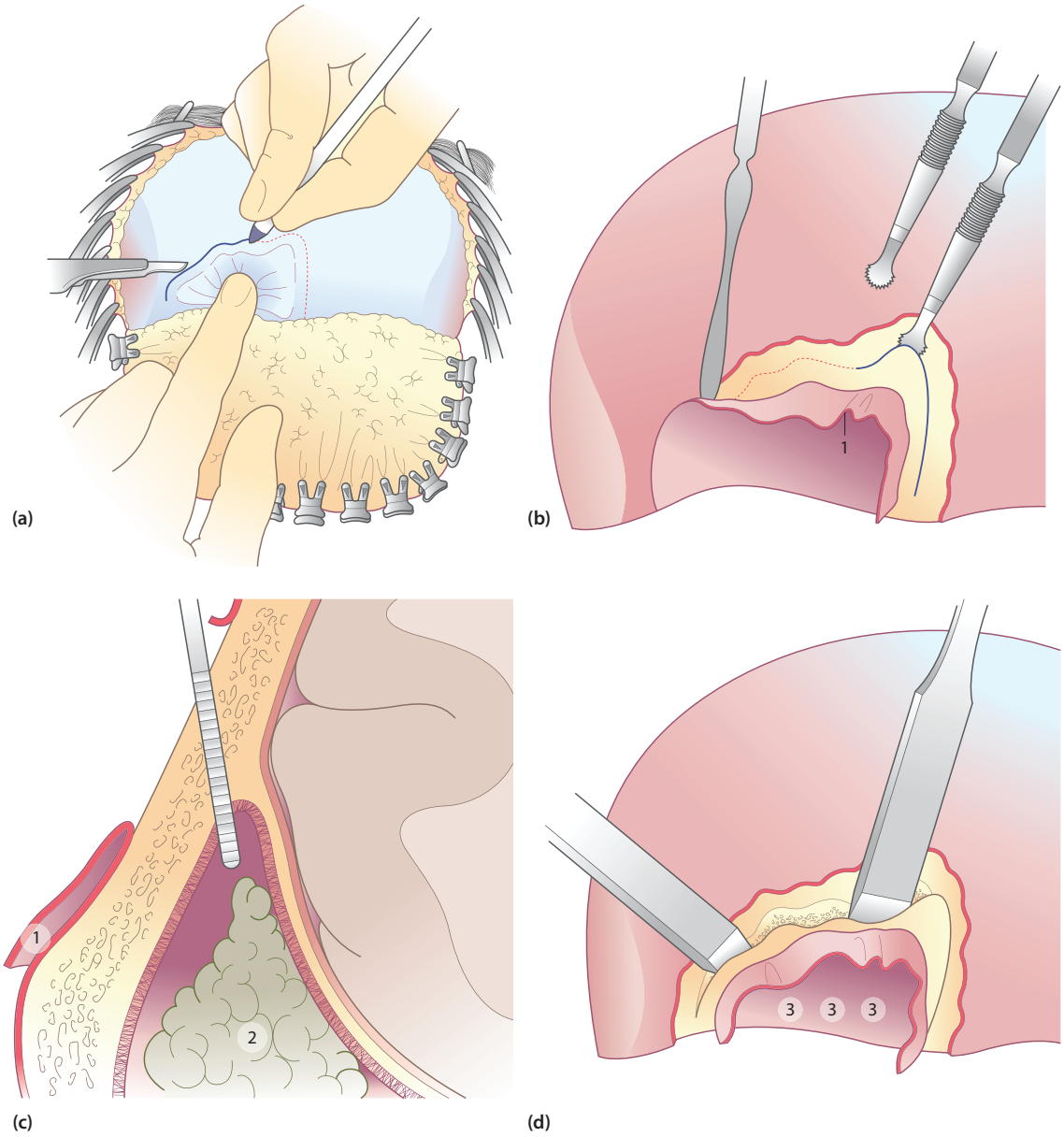


Figure 99.15 Technique of the osteoplastic frontal sinus operation. **(a)** The periosteal incision is marked approximately 1.5 cm outside the template. **(b)** The periosteum is elevated just beyond the osteotomy site. The bone flap is created with a drill/saw corresponding to the limits of the frontal sinus. **(c)** An oblique incision through the bone enlarges the area for replacement of the bony flap. **(d)** Elevation of the frontal sinus anterior wall with two broad chisels. This ends in a fracture of the frontal sinus floor just posteriorly of the supraorbital ridge. (1: periosteum, 2: pathology, 3: drill holes for fixation.) *(Continued).*

with a wide osteotome. Ideally the bone lid hinges on the periosteal flap, although in practice this is rarely possible. The pathology is now accessible (Figure 99.15).[84]

On completion, the bone lid is replaced and the periosteum is sutured. Often the periosteum may not be intact and the bone lid will need securing with mini plates. The scalp wound is closed over a closed-suction drain.

With obliteration

If obliteration is being considered, its success depends on the complete removal of all mucous membrane elements. The use of a diamond burr on the inner cortex of the sinus helps to exenterate mucosal invaginations and promotes neovascularization. The frontal ostium is plugged with fascia, or oxidized cellulose (Surgicell®, Ethicon, Inc., Somerville, NJ).[49] Obliteration is usually performed with fat harvested from the abdomen but alternatives include a vascularized pericranial flap, cancellous bone, muscle and alloplastic material. Monitoring the sinus post-obliteration is an issue. MRI is most useful but it can be difficult to distinguish fat necrosis from mucocele formation and recurrent disease.[75]

Above and below approaches

Endonasal procedures may be combined with external procedures such as an osteoplastic flap or trephine

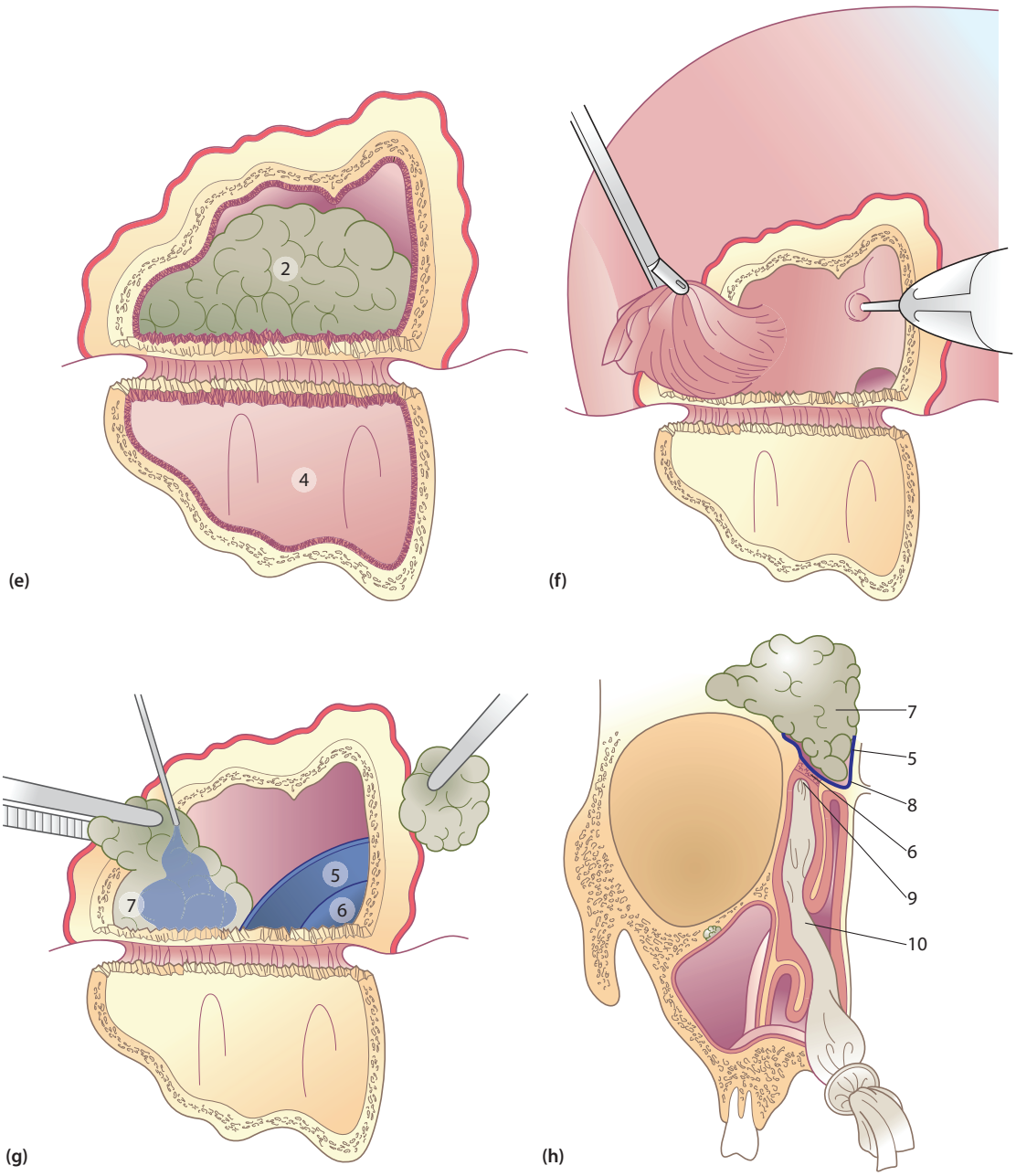


Figure 99.15 (Continued) Technique of the osteoplastic frontal sinus operation. **(e)** Appearances after down fracturing of anterior wall of frontal sinus. **(f)** The mucosa is completely removed and using the operation microscope, the internal table drilled with the burr. **(g)** After blockage of the ostium, frontal sinus drainage by inverting the mucosa, covering the cartilage with preserved fascia or galea-periosteum and fixing with fibrin glue, the frontal sinus is filled with pieces of fat. These are made to cohere with fibrin glue. Finally, the bony flap is replaced and closure of the wound begins. **(h)** Situation at the end of the operation: (1) Elevated galea-periosteum; (2) pathologically altered mucosa frontal sinus; (3) drill holes; (4) bony flap hinged on periosteum (anterior wall of the frontal sinus); (5) preserved fascia; (6) cartilage; (7) transplanted fat with fibrin glue; (8) fibrin glue; (9) resorbable sponge; (10) rubber finger packs. (Redrawn from Draf W. Surgical treatment of the inflammatory diseases of the paranasal sinuses: indication, surgical technique, risks, mismanagement, and complications, revision surgery (Reproduced with permission from Die chirurgische Behandlung entzuendlicher Erkrankungen der Nasennebenhoehlen: Indikation, Operationsverfahren, Gefahren, Fehler und Komplikationen, Revisionschirurgie). *Arch Otorhinolaryngol* 1982; **235**: 133–205 (Kongressbericht 1982).

(see 'Frontal sinus trephination' below). This combined approach has meant that where some sinuses would have been obliterated in the past it may not be necessary to do so now. The approach may be used when pathology in the frontal sinus outflow tract cannot adequately or safely be addressed by an endonasal approach alone. A MELP can be combined with a frontal trephine or OPF to remove tumours such as inverted papilloma with lateral attachments. The obvious advantage of this is to retain a functioning sinus that is endoscopically accessible and can be monitored by imaging. Medially based osteomas, neo-osteogenesis of the frontal recess, posterior table CSF leaks and encephaloceles can be managed by the 'above and below' approach.[46, 75–78]

Frontal sinus trephination

Trephination of the frontal sinus is a procedure that is normally performed in cases of complicated acute frontal sinusitis not responding to medical management, but it can have a role in chronic frontal sinus disease.[85]

In the acute setting, a small incision (1–1.5 cm) is made below the medial eyebrow and supraorbital rim down through the periosteum. The periosteum is elevated and a drill is used to make a small window at the junction of the floor and anterior wall of the frontal sinus. The sinus is irrigated and a drain placed *in situ*.

A modified frontal trephine technique, the mini trephine (Medtronic, Jacksonville), is useful during surgery for chronic frontal sinus disease. The landmarks are identified in **Figure 99.16**. The use of fluorescein stained saline to irrigate the trephine can aid in dissection of the frontal recess pathway. One must always aspirate prior to irrigation and be cautious when a dehiscence of the orbit is present. Indications include any situation where the frontal sinus outflow tract is difficult to detect, for irrigation of the sinus intra- and post-operatively and as an adjunct to more complex frontal sinus procedures. A pre-operative CT scan to define the depth and extent of pneumatization of the frontal sinus is essential. Complications such as intracranial penetration with CSF leak, periorbital trauma and incision related infection have been reported.[86–88]

External frontoethmoidectomy

This historical procedure, which was associated with a high failure and complication rate, has been replaced by endoscopic approaches to the frontal sinus.[84] The operation was conceptually flawed as it was designed to remove the bony support of the frontal recess. As a result scarring and fibrosis obstructed the outflow tract. It was performed via an external, slightly curved incision (Lynch) made halfway between the nasal dorsum and the medial canthus. The indications for a Lynch incision today are to externally access the anterior ethmoidal artery, in the drainage of periorbital abscesses and if extended superolaterally, to trephine the floor of the frontal sinus.

Cranialization of the frontal sinus

Frontal sinus cranialization for refractory chronic frontal sinusitis is rarely performed. Cranialization has a role in procedures requiring a craniotomy. Performed in conjunction with the neurosurgeons, the commonest indicaton is for extensive fractures of the frontal sinus, particularly the posterior table. Other indications include tumours and osteomyelitis.

Using a coronal incision a midfrontobasal craniotomy can be used.[89] The posterior wall and floor of the sinus are removed. Mucosa of the frontal sinus outflow tract is inverted into the nasal cavity and sealed with fascia or a strip of pericranium and fibrin glue. The success of the procedure relies on meticulous removal of the entire frontal sinus mucosa and drilling the sinus with a diamond burr. Dead space between the anterior wall and dura can be filled with fat or a vascularized pericranial flap.[90] Complications include dural injury with CSF leak, bone flap necrosis, frontal lobe trauma and intra-cranial mucocele formation.

Riedel's procedure

Riedel's procedure involves removing the floor, anterior wall of the frontal sinus and its entire mucosal lining.

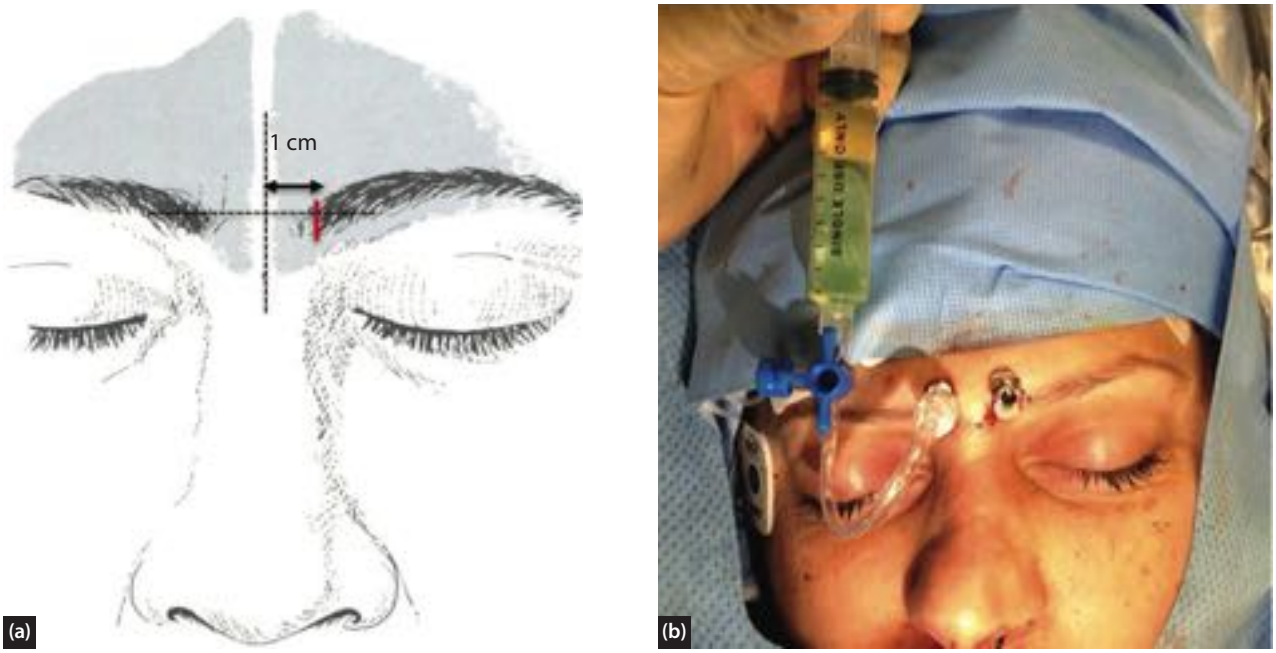


Figure 99.16 (a) Frontal mini-trephine landmarks. The incision can be hidden in the medial aspect of the eyebrow or if necessary in a vertical crease. However, given the possible anatomical variations, careful evaluation of the imaging is essential in every case to avoid inadvertent injury and to help select the safest distance from the midline for frontal sinus trephination.[87] **(b)** Fluorescein tinted saline is injected via the trephine during a MELP.

Although it is rarely performed, it does have a role in a small proportion of patients where frontal sinus drainage cannot be established and frontal sinus obliteration has failed. These include patients who have osteomyelitis or tumours involving the anterior wall of the frontal sinus. The main criticism of the procedure is the cosmetic defect, which can be reduced by chamfering the supraorbital ridge and smoothing out the margin of the sinus to a gentle curve. As the mucosa within the sinus is removed recurrent complications are uncommon.[91]

TUMOURS

Sixty percent of sinonasal tumours arise in the maxillary sinus, 20% arise in the nasal cavity, 5% in the ethmoid sinuses, and only 3% in the sphenoid and frontal sinuses. Fifty-five percent of sinonasal malignancies are carcinomas, squamous cell carcinomas being the commonest. Tumours of the ethmoid sinus and superior nasal vault are usually adenocarcinomas.[92] As it is with chronic frontal sinus disease, tumours of the frontal sinus present a significant challenge in diagnosis and management. Although tumours originating within the frontal sinus are rare, extension into the sinus is not.

Imaging

The aim of imaging is to provide reliable information on the nature of the tumour (benign vs. malignant), map its extent and point of origin, and distinguish concomitant inflammatory reactions. MRI best achieves this. Multiparametric MRI imaging, using a combination of apparent diffusion coefficient and time-signal intensity curve techniques, may help differentiate benign and malignant sinonasal diseases.[93]

CT is often requested as the initial investigation for sinonasal symptoms and it provides useful bony detail particularly in fibro-osseous lesions.

General principles of tumour surgery of the frontal sinus

Ideally, it is preferable to remove a frontal sinus tumour using the most minimally invasive technique. Tumour characteristics (benign or malignant), site, involvement of adjacent structures (dura and orbit), and local expertise determine the surgical approach. Management decisions should be made within a multidisciplinary team including head and neck surgeons and neurosurgery when appropriate. As with chronic frontal sinus disease a stepwise approach is recommended:

- Endonasal (including modified Lothrop procedures)
- Osteoplastic flap (bi-coronal incision, mid forehead, brow)
- Above and below (endoscopic and frontal craniotomy)
- Subcranial, subfrontal and transcranial.

The midfacial degloving approach provides excellent access to bony structures of the midface and posterior parts of the anterior skull base but less satisfactory access to the frontal sinus. Generally, with OPF approaches for tumour removal, frontal sinus obliteration should be considered a contraindication given the inability to detect subsequent tumour recurrence.

Endoscopic considerations

When considering an endoscopic approach, experience in dealing with inflammatory diseases and endonasal duraplasty is mandatory. The endoscopic modified Lothrop procedure (MELP) provides excellent access to the frontal sinus when managing chronic frontal sinus disease but its utility in tumour disease has some limitations. In tumour surgery it is necessary not only to visualize the site of the lesion but also to instrument that area with curettes and drills. The degree of the frontal sinus pneumatization is an important factor. The better the pneumatization, the wider the radius of action of the instrument. The following general guidelines for operating on tumours of the frontal sinus are useful:

1. Lesions not extending beyond a sagittal plane through the lamina papyracea are accessible endoscopically. Lesions extending beyond this may be accessible depending on the anterior-posterior dimension of the floor of the frontal sinus and the intercanthal distance.[94]
2. Tumours arising from the medial quarter of the orbital plate of the frontal sinus may be accessible via a MELP alone or with the aid of an external trephine. (**Figure 99.17**).
3. Lesions originating in the lower third of the posterior wall of the frontal sinus are usually accessible via an endoscopic approach.
4. In general, tumours arising from the anterior wall of the frontal sinus are difficult to access endoscopically.[84] Those arising low down may be accessible via a MELP.
5. A narrow anterior-posterior dimension of the floor of the frontal sinus (<10 mm) can limit endoscopic access and favour open or combined approaches.[95]
6. Superior reach within the sinus may not be possible in well pneumatized sinuses.[96]
7. The junction of the anterior and posterior wall in the most lateral part of the frontal sinus may be too narrow to admit a drill. Similarly, supraorbital ethmoid cells may limit lateral access for tumour removal.[97]

BENIGN TUMOURS

Inverted papilloma

Inverted papilloma (IP) are relatively uncommon benign epithelial tumours of the nasal cavity. They are locally aggressive, have a tendency to recur and are associated with malignancy. Histologically, the tumour is characterized by epithelium inverting into the stroma with a distinct and intact basement membrane. Human papilloma virus has been implicated in the pathogenesis. Viral DNA has been found in the adjacent normal appearing

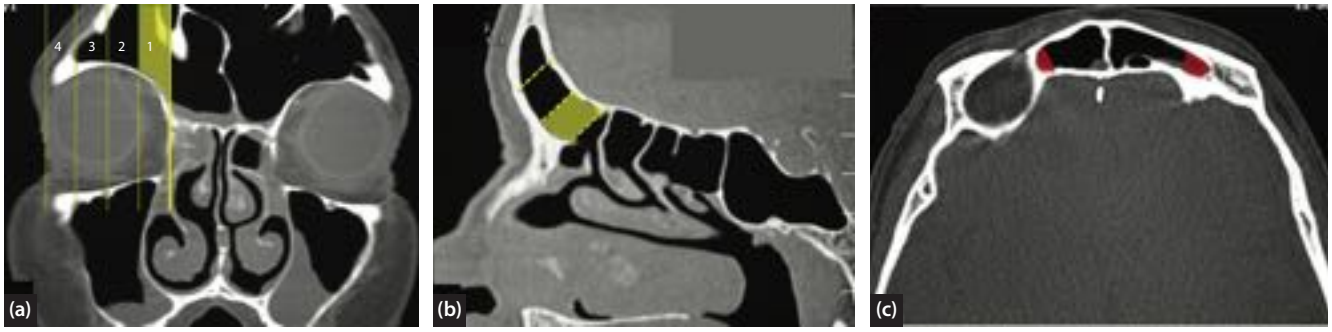


Figure 99.17 (a) Coronal CT demonstrating orbital zones. Zone 1: medial quarter of the orbit (yellow highlight); Zone 2: outer margin of Zone 1 to the midorbital point; Zone 3: laterally from midorbital point to halfway between the midorbital point and the lateral aspect of the orbit; Zone 4: the lateral-most quarter. (Modified with permission.)[97] **(b)**. Parasagittal CT scan. Lesions which originate from the lower third (yellow area) of the posterior or anterior wall of the frontal sinus may be accessible endoscopically.[84] **(c)** Axial CT scan. The lateral junction of the anterior and posterior walls may be inaccessible due to their narrowness (red area).

tissue and may account for the associated recurrence rates although in many cases this is due to residual disease. The incidence of IP in normal bilateral nasal polyps is rare (<1%). As multiple sites within the paranasal sinus may be involved, localization of the origin is not always easy. The commonest sites of origin are the ethmoid region (48%), lateral nasal wall and maxillary sinus (28%) with the frontal sinus accounting for only 2.5%.[98] Bilateral frontal sinus involvement is not uncommon (16%).[99]

Although CT is the primary mode of imaging, MRI is complementary and recommended. Particularly in the frontal sinus when tumour can obstruct the outflow tract, MRI is very useful in distinguishing mucus from papilloma. Focal hyperostosis on CT imaging is a common finding in patients with IP but may be helpful in identifying the site of origin.[100, 101]

Surgical strategy

The success of surgery is dependent on defining the extent of disease, identifying the site of tumour origin and attachments and fully extirpating all affected tissue. This includes removal of the underlying mucoperiosteum and burring the bone. Within the frontal sinus, the narrow confines and proximity to the anterior skull base and orbit makes this a challenge. This is reflected by the higher recurrence rates (22%) than would be expected for endoscopic management of IP in other locations (3%).[99]

The OPF procedure offers a wide exposure of the frontal sinus, and has traditionally been the preferred approach. The modified Lothrop procedure combined with angled instruments and endoscopes offers similar access and is a valid alternative.[102] Generally, tumours originating medially or from the lower third of the posterior wall of the frontal sinus can be accessed by a frontal sinusotomy or Draf type II approach. Those arising laterally or along the anterior wall will require an extended endoscopic approach or an OPF. A summary of the suggested surgical strategy can be found in **Table 99.9**.

Extended approaches such as a MELP can be augmented by an external trephine, which can provide an additional port for instruments or endoscopes. The relative accessibility is highlighted in **Figure 99.17**.

TABLE 99.9 Suggested surgical strategy for frontal sinus inverted papilloma

Site of origin within the frontal sinus	Surgical approach options
Unifocal, attached to MW or lower AW/PW. Multifocal as above	Draf type IIa/b MELP
Unifocal or multifocal, attached to superior AW, superior PW or LW	OPF, MELP possibly with external trephine
Lateral to midpoint of orbit	OPF, MELP with external trephine

Anterior wall: AW; posterior wall: PW; medial wall: MW; lateral wall: LW; osteoplastic flap: OPF; endoscopic modified Lothrop procedure: MELP.[102]

A recent systematic review suggests that more aggressive primary approaches may facilitate better disease control.[99] Patients should be followed up for a minimum of 3 years. Where tumour removal was performed via a MELP, direct surveillance can be performed. When this is not possible an MRI is recommended.[103]

Fibro-osseous lesions

Fibrous dysplasia, ossifying fibroma and osteoma are a group of benign bony abnormalities that can affect the paranasal sinuses. They lie along a continuum from least to the most bony content.[104]

OSTEOMAS

Osteomas are the most common benign tumour of the paranasal sinuses, with a prevalence of 3%. These slow growing tumours occur most often in the ethmoid followed by the frontal sinuses.[105] There are three main theories regarding the aetiology of osteomas: developmental, traumatic and infectious. The developmental theory suggests that reactivation of embryonic stem cells leads to uncontrolled bone formation. The traumatic and infectious theories propose an inflammatory process as the initiating factor for bony tumour formation.[103] Histologically 3 types are found: ivory or compact, mature or cancellous

and mixed. Their attachment may be broad based or occasionally via a stalk.

CT imaging is the investigation of choice with osteomas appearing as homogenous, dense, well-circumscribed lesions. MRI is recommended when extra sinus involvement is suspected.

Most osteomas are asymptomatic. The commonest reported clinical symptoms are headache or a sensation of pressure. However, these symptoms may be non-sinogenic and one must be cautious in attributing them to the presence of an osteoma.[14]

Surgical strategy

Small asymptomatic osteomas do not require surgery. Conservative management with watchful waiting and interval imaging is recommended.[106] The following guidelines are useful indicators for surgery:

- Symptomatic patients (chronic rhinosinusitis and mucoceles secondary to obstruction, facial deformity, orbital or neurological complications)
- Tumours occupying more than 50% of the frontal sinus
- Continued growth on serial CT imaging
- Tumours obstructing the frontal recess
- Tumours extending outwith the paranasal sinuses (orbital and intra-cranial)

Surgical approaches can be classified as external, endoscopic or a combination of both (above and below). The osteoplastic flap approach with or without fat obliteration has been the gold standard as it provides excellent access and visualization (**Figure 99.18a–c**) but it is not without morbidity (see above). Recently, there has been a trend towards an entirely endoscopic approach such as a Draf IIb (**Figure 99.19a–c**) or modified endoscopic Lothrop procedure (MELP/Draf III).

When combined with an OPF procedure, the MELP aims to maintain long-term patency of the frontal neo-ostium by avoiding obliteration. There is some debate as to the limits of the endoscopic approach. Some of these limitations are discussed above under 'Endoscopic considerations'. Other important factors include the extent of intra-cranial extension, significant orbital involvement and erosion of the posterior or anterior wall of the frontal sinus.[95, 107] A grading system for osteomas is outlined in **Table 99.10**. Conventionally mostly grade I and II tumours were removed endonasally. With the advances in endoscopic instrumentation and surgical skill, many grade III and grade IV can be managed endoscopically.[108–110] Tumours extending beyond a vertical plane through the lamina papyracea are accessible endoscopically. However, access to tumours arising lateral to the midpoint of the orbit may be limited.[97] Tumours extending through the anterior table of the frontal sinus are best managed by an external approach. Although large osteomas filling the sinus may be managed endoscopically, the operative duration is likely to be much shorter via an open approach. Clearly, the surgical strategy needs to be based on the individual's anatomy. Variables such as the degree of frontal sinus pneumatization, interorbital width (distance between both lamina papyracea) and A-P dimension of the floor of the frontal sinus are important considerations in determining the most appropriate approach.[94, 111]

Gardner's syndrome

The syndrome consists of a triad of multiple osteomas, colorectal polyps, skeletal abnormalities and supernumerary teeth. The disease is autosomal dominant and carries a 100% risk of malignant transformation of the colonic polyps by the age of 40. Patients usually present in their second decade with rectal bleeding, pain and diarrhoea. As early diagnosis is important, all patients presenting with frontal sinus osteomas should have a thorough systemic enquiry.[104]

Fibrous dysplasia

Fibrous dysplasia (FD) is a slow growing, tumour-like lesion of bone. It occurs when normal cancellous bone is replaced by abnormal fibrous tissue. The fibrous tissue replaces the spongiosa and fills the medullary cavity with poorly calcified trabeculae (**Figure 99.20**). This genetic disease is a result of a mutation in the *GNAS1* gene located on chromosome 20q13, which normally codes for the alpha subunit of the stimulatory G-protein.[112, 113]



Figure 99.18 Osteoplastic approach for the removal of a large frontal sinus osteoma. Elevation of the bone flap **(a)** and **(b)** reveals the osteoma (*) filling the left frontal sinus **(c)**; the right frontal sinus outflow tract is indicated with a white arrow.

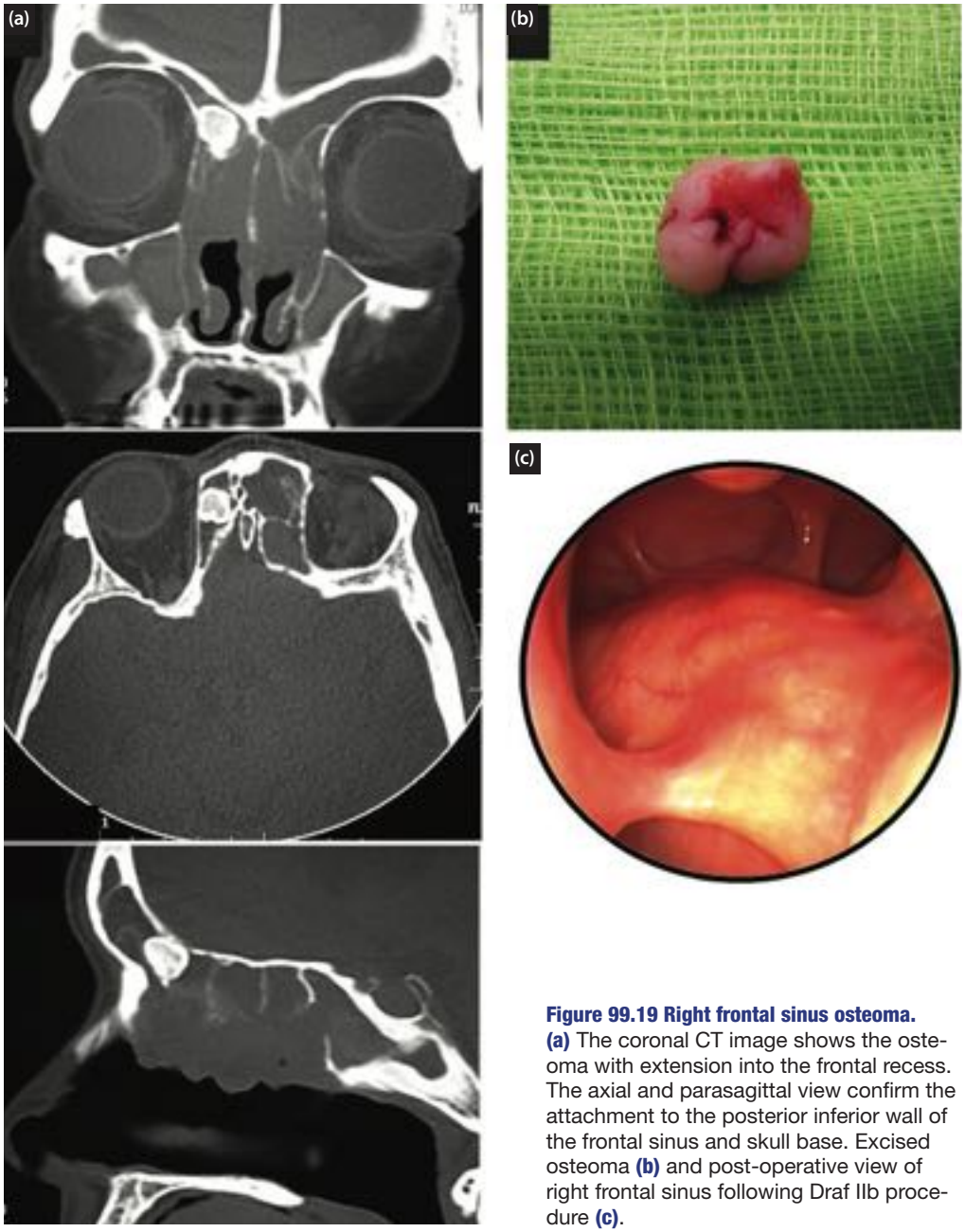


Figure 99.19 Right frontal sinus osteoma. **(a)** The coronal CT image shows the osteoma with extension into the frontal recess. The axial and parasagittal view confirm the attachment to the posterior inferior wall of the frontal sinus and skull base. Excised osteoma **(b)** and post-operative view of right frontal sinus following Draf IIb procedure **(c)**.

TABLE 99.10 Frontal sinus osteoma grading system. The grading system highlights three variables: The location of attachment of the base, the relationship of the lesion to a virtual sagittal plane through the lamina papyracea and the A-P width of the frontal recess

Grade	Description
I	Base of attachment is posterior–inferior along the frontal recess. Tumour is medial to a virtual sagittal plane through the lamina papyracea. Anterior–posterior diameter of the lesion is less than 75% of the anterior–posterior dimension of the frontal recess.
II	Base of attachment is posterior–inferior along the frontal recess. Tumour is medial to a virtual sagittal plane through the lamina papyracea. Anterior–posterior diameter of the lesion is greater than 75% of the anterior–posterior dimension of the frontal recess.
III	Base of attachment is anterior or superiorly located within the frontal sinus AND/OR Tumour extends lateral to a virtual sagittal plane through the lamina papyracea.
IV	Tumour fills the entire frontal sinus.

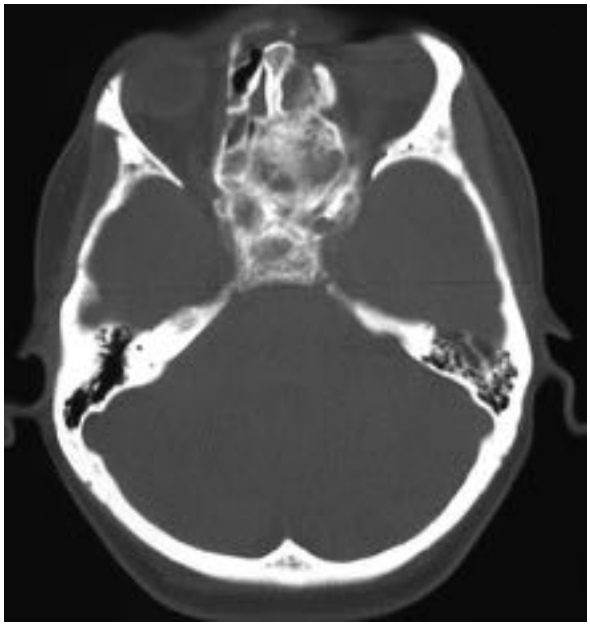


Figure 99.20 Extensive fibrous dysplasia (FD) involving the ethmoid and sphenoid sinus. The patient had previously undergone surgery for FD involving the left frontal sinus.

Most cases (75%) are diagnosed before the age of 30 and tend to stabilize after the patient reaches skeletal maturity.[104, 114] Two forms are present:

- Monostotic (80%) – Craniofacial involvement occurs in up to 25% of cases with the maxilla and mandible most commonly affected. Although monostotic FD in the long bones does not cross the joint line, it can cross bony sutures in the maxillofacial skeleton.
- Polystotic (20%) – various areas of the skeleton can be affected with craniofacial involvement present in 40% to 50% of cases. Polyostotic FD, endocrine hyperfunction (such as precocious puberty and/or hyperthyroidism) and café-au-lait spots are components of McCune-Albright syndrome. This rare condition primarily affects females.

FD has a low rate of malignant transformation occurring in 0.5% of polyostotic forms and in 4% of lesions with McCune-Albright syndrome.

Patients with the monostotic form are frequently asymptomatic, often diagnosed incidentally. Polyostotic FD can present early with manifestations of bone pain and deformity. Both variants can lead to symptoms of vascular or neurological compression. Craniofacial disease can present as headaches or facial asymmetry. Sphenoid and frontal sinus FD may lead to optic nerve compression and mucocele formation respectively.

CT and MRI are helpful in establishing the diagnosis but if there is any doubt a biopsy is recommended. On CT imaging, lesions appear fairly homogenous with a 'ground glass' appearance. As the lesion scleroses, 'cotton wool' areas appear. MRI helps evaluate the soft tissue component and can distinguish it from other lesions such as meningiomas and bone cysts. FD tends to display an intermediate signal on T1-weighted images and is hypointense on T2-weighted images.[104]

Surgical strategy

Most studies recommend conservative management. Medical treatment is limited to symptomatic relief. Bisphosphonates are useful in reducing the incidence of fractures and bone pain. Asymptomatic patients with monostotic FD can be observed. Endoscopic sinus surgery can provide symptomatic relief by improving sinus drainage pathways.[115] In more severe cases and those with cosmetic deformity, local controlled resection and recontouring may be feasible depending on symptoms and location. Paranasal sinus lesions causing sinusitis or optic nerve compression may be managed endoscopically, ideally with the aid of computer assisted navigation.[84, 103] The rate of malignant transformation to an osteosarcoma is low, at 0.5%, but any painful, rapidly growing lesion should raise suspicion. There is no role for radiotherapy in treating FD.[115]

Ossifying fibroma

The nomenclature surrounding ossifying fibroma (OF) is diverse and confusing. Broadly, OF can be classified into 3 categories:[116]

1. Ossifying fibroma
2. Cemento-ossifying fibroma (COF)
3. Aggressive psammomatoid ossifying fibroma (APOF) or juvenile-aggressive OF.

These benign tumours can have differing biologic behaviour. Histologically, lesions consist of 2 main components: fibrous stroma and bone elements. APOF lesions consist of irregular bony spicules within a cellular fibrous stroma. Classically, this resembles cementum or calcified 'psammomatoid bodies'. COF lesions have similar histologic features with cementum-like material present throughout the lesion.

Clinically, lesions are often asymptomatic but can present with proptosis, diplopia, epiphora, facial swelling, nasal obstruction, epistaxis and headaches. Endoscopically they appear as smooth mucosally covered masses. This locally destructive tumour occurs most commonly in the facial skeleton affecting the mandible in 75% of cases. When arising outside the mandible, OFs appear to affect the ethmoid and maxillary sinuses most frequently. Similarly, APOFs most commonly affect the ethmoid sinus followed by the maxillary sinus, orbit and frontal sinus. Multiple sinus involvement is not uncommon. COF most commonly present in the maxillary and ethmoid sinus and rarely in the frontal and sphenoid sinus.[116]

All three variants display similar features on CT. Sharply circumscribed round lesions with an eggshell rim and central radiolucency are typical of OF. APOF and COF have a thicker bony rim and a central ground glass appearance. MRI features are similar to fibrous dysplasia with a low to intermediate signal on T1-weighted

imaging and variable intensity on T2-weighted imaging. An endoscopic biopsy may be required to confirm the diagnosis.

Treatment strategy

If OF is suspected on imaging, a biopsy is recommended to confirm the diagnosis. For paranasal sinus disease this may be achieved endoscopically. The role of biopsy is to exclude malignant pathology such as sarcoma. Ideally, treatment should be complete surgical excision but this is dependent on the site and symptoms. Evidence would suggest that a more conservative approach might be acceptable where there are little or no symptoms.[115, 117] Surgical resection may be achieved by an endoscopic approach, with more extensive disease requiring a combined approach including craniofacial resection. Recurrence rates for APOF, COF and OF are low.[103, 104, 117]

MALIGNANT TUMOURS INVOLVING THE FRONTAL SINUS

Primary malignant tumours of the frontal sinus are very rare. Squamous cell carcinoma is the commonest tumour, affecting the maxillary sinus in up to 30% and the frontal sinus in less than 1%. Other primary tumours include adenocarcinomas and non-epithelial malignancies such as lymphomas. Mostly the frontal sinus becomes involved by direct extension of tumour from adjacent sites. Metastasis of malignant tumours to the frontal sinus is rare. Along with tissue biopsies, CT and multiparametric MRI are helpful in establishing the diagnosis, extent of disease and in particular orbital and dural involvement.[118]

The comprehensive management of sinonasal malignancy is covered elsewhere in this book. However, the principles of surgery are twofold: complete resection of the tumour by the least invasive approach. It would appear that more important than 'en bloc' resection is to achieve negative tumour resection margins.[103]

Malignant tumours of the nasal cavity and other paranasal sinuses, which have not led to major bone destruction and are just reaching the frontal sinus, may be operated on via the endonasal route.

More extensive tumours of this type, or primary malignant frontal sinus tumours, may be approached by the subcranial technique, according to Raveh et al.[119] through a coronal incision, without shaving the hair, sometimes in combination with midfacial degloving, if the lower sinuses are involved. The subcranial approach also allows management of malignancies with skull base or even intradural involvement.

To summarize, there is a stepladder of three surgical techniques: (1) endonasal; (2) midfacial degloving; (3) subcranial approach,[119] which has proved to be very efficient when dealing with malignant tumours of the nasal cavity and the paranasal sinuses, including the frontal sinus and the anterior skull base. The great advantage of all these approaches is the avoidance of visible scars, a fact much appreciated by the patients. The lateral rhinotomy is generally reserved if exenteration of the orbit is needed simultaneously.

OTHER CONDITIONS

Frontal pneumosinus dilatans

Pneumosinus dilatans refers to an abnormally large aerated sinus. This uncommon condition can affect all the paranasal sinuses but has a predilection for the frontal sinus. When associated with the frontal sinus, aeration extends beyond the normal margin of the frontal bone. Characteristically, the walls of the sinus are of normal thickness and there is no evidence of erosion. It is unlike a pneumocele where the aerated sinus is associated with a thinning of its wall and this can be focal or generalized.[120]

AETIOLOGY

A number of theories have been put forward but the pathophysiology remains poorly understood. These theories include: (a) mucocoele growth and spontaneous rupture, (b) a one-way valve mechanism, (c) hormonal influences affecting bone resorption and (d) congenital defects.[121] The mechanism most favoured is that of a one-way valve.

CLINICAL FEATURES AND INVESTIGATIONS

The condition usually presents between the 2nd and 4th decade and has a male preponderance. Most patients are asymptomatic but bony expansion can result in frontal bossing. Less common pressure-related symptoms include diplopia, headache or intra-cranial symptoms.

Pneumosinus dilatans has been shown to be associated with a number of pathological conditions such as planum meningiomas, arachnoid cysts, fibrous dysplasia, acromegaly and prolonged cerebrospinal fluid shunting. Recently, an association with congenital polyosteotic fibrous dysplasia (McCune Albright syndrome) has been reported.[121]

CT imaging is the investigation of choice.

MANAGEMENT

It is important to address any pathology within the sinus or obstructing ventilation of the sinus. If this cannot be achieved endoscopically then an open approach may be required. In patients with functioning ostia the cosmetic deformity is the main issue. This can be corrected by direct, full thickness, resection of horizontal bone strips of the anterior wall of the sinus. Plating of the bone fragments is not required if the galea-periosteum remains attached.[122]

BEST CLINICAL PRACTICE

- ✓ Trial of optimum medical therapy prior to any surgical intervention is important.
- ✓ Recording of outcome data is essential.
- ✓ Post-operative care should include regular saline douches and debridement as necessary.
- ✓ Mucosal preservation during surgery is important. The use of pedicled flaps in more extensive surgery such as the modified Lothrop aids healing and reduces post-operative crusting.
- ✓ The modified Lothrop procedure aims to provide maximal ventilation and facilitate removal of eosinophilic mucin and osteitic bone.
- ✓ Consider more extensive surgery in the following scenarios:
  - ✓ AERD is associated with higher incidence of frontal neo-ostium stenosis.
  - ✓ Asthma (associated with a higher rate of surgical revision).
  - ✓ CRSwNP revision rate higher.
  - ✓ Osteoneogenesis.
  - ✓ Greater burden of disease, Lund McKay score > 16.
  - ✓ Frontal ostium opening on anteroposterior dimension (sagittal CT view) < 4mm.

FUTURE RESEARCH

- ➤ Which patient groups might benefit from more extensive primary frontal sinus surgery?
- ➤ Method of targeted delivery of local steroid and antibiotic therapy within the frontal sinus.
- ➤ Effect of alternative therapies on chronic sinus disease.

KEY POINTS

- The anatomy of the frontal recess is variable and complex. A detailed knowledge of the anatomy is vital when operating within this area.
- One should approach this area with caution. Meticulous attention to detail and careful dissection is key.
- An *all or nothing* approach is suggested.
- It is important to address any disease in the frontal recess/sinus when managing patients with Chronic Rhinosinusitis. Failure of surgery can often be attributed to unaddressed disease within the frontal recess and sinus.
- Incomplete or inadequate surgery in the frontal recess can lead to iatrogenic disease and persistence of symptoms.
- The greater the disease burden as noted by the preoperative Lund-McKay (LM) CT score, the more extensive the surgery required.
- The incidence of more extensive frontal sinus surgery is higher in patients with Asthma and AERD (Aspirin exacerbated respiratory disease)
- Patients with frontal sinus disease may not have *specific* frontal sinus symptoms
- Headache as the predominant symptom without any other significant symptoms of sinusitis is unlikely to be sinogenic in origin.

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CHAPTER 100

MUCOCELES OF THE PARANASAL SINUSES

Darlene E. Lubbe

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SEARCH STRATEGY

A PubMed search was conducted to support the data in this chapter using the Medical Subject Headings (MeSH) paranasal, maxillary, frontal, ethmoid, sphenoid sinus and mucocele. The chapter will focus on the etiology and surgical management of mucoceles. The evidence in this chapter is mainly level 2b.

DEFINITION

A mucocele is an epithelium-lined mucus-filled sac within one of the paranasal sinuses with expansion of the sinus cavity and remodelling of the sinus walls. It forms secondary to obstruction of the outflow tract of the involved sinus together with an inflammatory process within the sinus.[1] It is lined by pseudostratified or low-columnar epithelium in contradistinction to a cyst that has a distinct separate membrane. Where bony erosion has taken place, the mucocele's epithelium is often fused with dura or orbital periosteum.

SITE OF DEVELOPMENT

The frontal, ethmoid, maxillary and sphenoid sinuses are involved in descending order of frequency (**Table 100.1**).[2] Frontal sinus mucoceles are probably more common because of the complex and narrow drainage pathway of the frontal sinus that is easily obstructed.[2–3] Mucoceles can form in any other aerated structure such as a concha bullosa of the middle (**Figure 100.1**) or superior turbinate. Obstruction of the nasolacrimal duct can also cause a lacrimal sac mucocele/dacryocele.



Figure 100.1 Mucocele within a concha bullosa.

TABLE 100.1 Aetiopathogenesis of mucoceles

Series	Number of cases	Prior sinus surgery	Prior trauma	Spontaneous	CRS without surgery	Tumours
Bockmühl et al.[2]	255	66%	14%	17%	2%	1%
Devars du Mayne et al.[7]	68	75%		15%	7%	
Khong et al.[5]	28	86%	7%			
Nakanishi et al.[6]	24	87.5%		12.5%		
Lund et al.[1]	48			92%	2%	

AETIOLOGY

Sinus surgery is now the leading cause (66–86%)[4–6] of mucocele formation following surgery mostly for chronic sinusitis and nasal polyposis.[2, 7] The interval between surgery and subsequent mucocele formation can range between 1 and 19 years and depends on the location of the mucocele, with frontal and sphenoid mucoceles developing earlier than maxillary sinus mucoceles. Surgery in the region of the frontal recess during functional endoscopic sinus surgery can cause circumferential injury to the frontal sinus outflow tract with subsequent stenosis and mucocele formation. External fronto-ethmoidectomy/Lynch-Howarth operation is a leading cause of mucoceles because of loss of lateral bony support of the frontal recess which causes herniation of the periorbital tissue into the frontal sinus outflow tract. In a large series by Bockmühl et al, 78% of mucoceles following sinus surgery was associated with the Lynch-Howarth and/or Caldwell-Luc operations versus 1.5% after endonasal surgery.[2]

A significant incidence of mucoceles has been reported following endoscopic repair of skull-base fractures in children. In one study 50% of patients developed mucoceles after repair of skull-base defects with a middle turbinate overlay patch.[8] Only 10–14% of mucoceles are secondary to trauma and 15–17% develop spontaneously; the mean interval between head injury and mucocele formation is 9 years.[7] Any benign or malignant tumour can lead to mucocele formation but the incidence in the literature is low and ranges from 1% to 5% (**Table 100.2**).

PATHOGENESIS

It is thought that in order for a mucocele to form two factors are essential: an obstructed sinus outflow tract and an inflammatory process within the sinus. Osteolytic cytokine-IL-1 and tumour necrosis factor are present within the epithelial lining of mucoceles; it has been postulated that this cytokine may be the responsible for the bony erosion in expanding mucoceles.[1]

CLINICAL FEATURES

Bony erosion leads to expansion of the sac beyond the sinus cavity into the cranial cavity or orbit. Symptoms depend on the sinus involved. A visible mass is often seen on the forehead (**Figure 100.2a** and **b**), medial canthus or in the gingivobuccal sulcus or cheek. Ophthalmologic symptoms are more common than rhinological and neurological symptoms.[9] The most common ophthalmologic complaints are periorbital swelling, pain and exophthalmos (**Figure 100.3**). Displacement of the orbital contents can lead to limited ocular mobility, visual disturbance and diplopia.[4, 9] Optic neuropathy has been reported in up to 18% of patients who present with ophthalmologic symptoms and is due to direct compression of the optic nerve in the posterior ethmoid and sphenoid sinuses.[9] A mucocele within a concha bullosa may present with nasal obstruction and/or secondary sinusitis. Epiphora and a cystic swelling in the medial canthus suggest the presence of a dacryocele.

Radiology

Computed tomography (CT) findings suggestive of a mucocele are a homogeneous, isodense lesion within an expanded sinus with bony remodelling of the sinus walls (**Figures 100.2c** and **3**). Contrast enhancement only occurs with a pyocele. A bony defect of the lamina papyracea and/or superomedial part of the orbital rim is often seen in fronto-ethmoidal mucoceles.[10] The globe may be displaced laterally and/or inferiorly with evidence of proptosis on axial images. The sac can cause erosion of the posterior table of the frontal sinus and compression of the intracranial contents. It can be difficult to differentiate maxillary sinus mucoceles from other benign or malignant lesions.

TABLE 100.2 Site of involvement

Series	No. of mucoceles	Frontal	Fronto-ethmoidal	Ethmoid	Spheno-ethmoid	Sphenoid	Maxillary
Lee et al[4, 10]	82	45%		28%		18%	9%
Bockmühl et al[2]	290	43%	8%	14%		10%	25%
Har-El et al[11]	108	61%		16%	6%	11%	6%

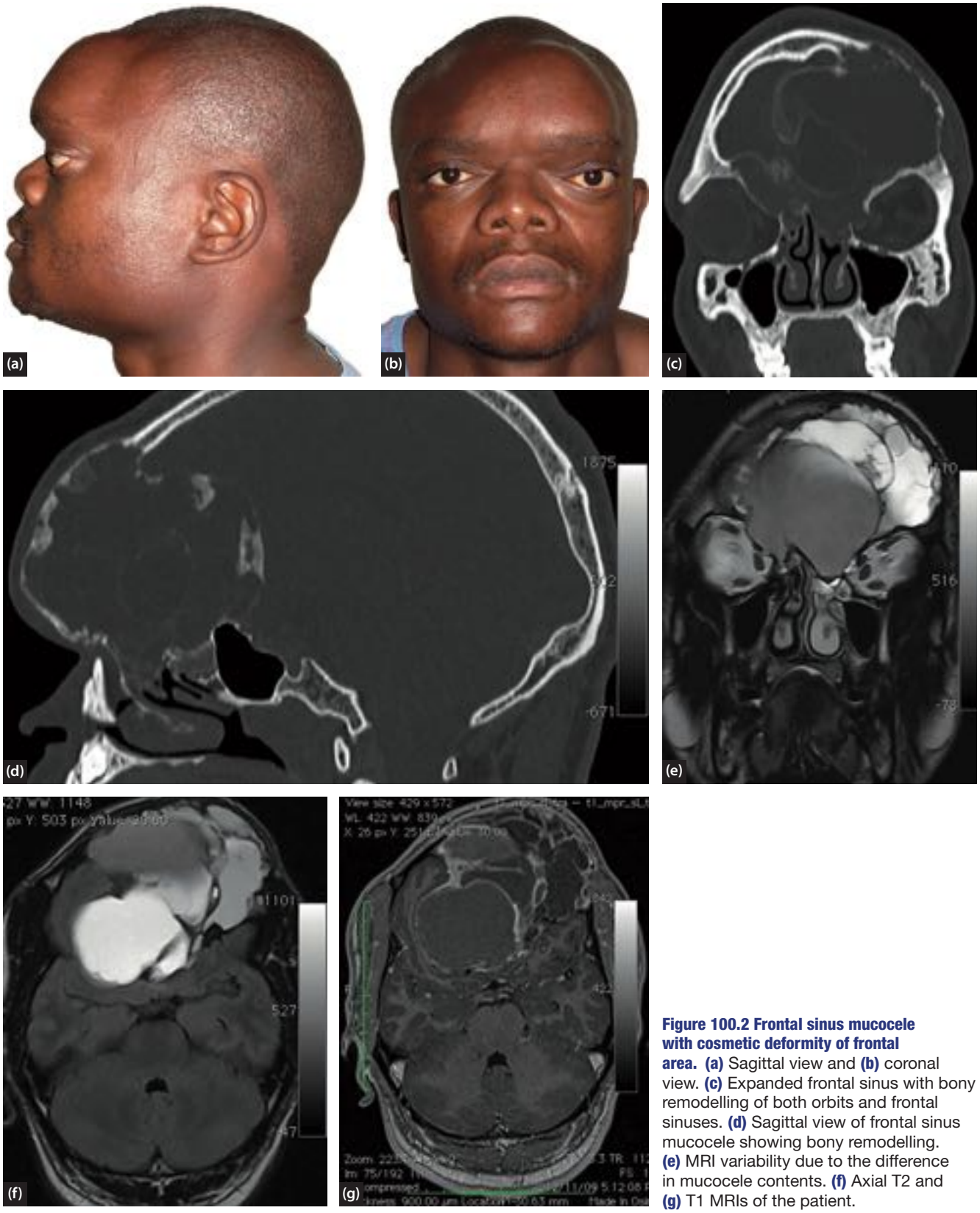


Figure 100.2 Frontal sinus mucocele with cosmetic deformity of frontal area. **(a)** Sagittal view and **(b)** coronal view. **(c)** Expanded frontal sinus with bony remodelling of both orbits and frontal sinuses. **(d)** Sagittal view of frontal sinus mucocele showing bony remodelling. **(e)** MRI variability due to the difference in mucocele contents. **(f)** Axial T2 and **(g)** T1 MRIs of the patient.

Magnetic resonance imaging (MRI) should be considered in cases of significant bony erosion of the posterior table of the fontal sinus or the orbital lamina papyracea, in order to delineate the mucocele from adjacent soft tissue e.g. cerebral tissue. It should also be recognized that MRI can be misleading due to the variability of mucocele content (Figures 100.2e and 2f). Mucoceles generally have a high-water content and are hyperintense on T1; pyoceles have higher protein content and greater variability of signal intensity on both T1- and T2-weighted images (Figure 100.2e to 2g).



Figure 100.3 (a) Displacement of the left eye secondary to a frontal sinus mucocele. **(b)** Coronal CT scan of the patient.

Differential diagnosis

1. Benign or malignant tumours
2. Allergic fungal sinusitis/Other fungal disease
3. Cholesterol granuloma (rare).

SURGICAL MANAGEMENT

Treatment is to widely marsupialize the sac to provide permanent ventilation and sinus drainage and to relieve pressure on vital structures. Cosmetic deformities often settle with time as bony remodelling takes place.[11]

Fronto-ethmoidal mucoceles

Wide marsupialization is essential whether by endoscopic and/or open technique. Endoscopic surgery with wide marsupialization/nasalization is the first line of treatment for simple mucoceles but a modified endoscopic Lothrop procedure (MELP) is often required for more complex frontal sinus mucoceles.[5, 11] Good results have been reported with endoscopic techniques with recurrence rates ranging from 0 to 25%.[7, 11] The MELP is especially useful where there is loss of lateral support in the frontal recess due to bony erosion/previous removal of the superior aspect of the lamina papyracea. Combined approaches are often required for laterally located mucoceles as thick bony septations might not allow for endoscopic techniques alone (**Figure 100.3b**). Whilst the Lynch-Howarth approach can be used to access laterally located frontal sinus mucoceles and to assist with the drilling down of bony septations, the approach is associated with risk of long-term frontal outflow obstruction. An osteoplastic frontal flap in combination with a MELP may be required for those mucoceles lying far laterally in the frontal sinus. Transorbital neuroendoscopic surgery (TONES) – and specifically the superior eyelid approach – allows for an alternative, less invasive approach to address pathology of the lateral frontal sinus. Stenting remains controversial; most authors do not advocate the use of stents to maintain patency except in smaller unilateral marsupializations.[6, 11, 12] If a stent is placed, it is important that it is loose fitting to prevent circumferential pressure necrosis that could eventually lead to stenosis.

Obliteration of the frontal sinus has a high success rate (93%) but a major complication rate in excess of 20%.[12] A contraindication to frontal sinus obliteration is extensive erosion of the posterior table of the sinus due to the inability to remove the normal respiratory epithelium on dura.[12] Obliteration has, therefore, largely fallen out of favour.

Maxillary sinus mucoceles

It is important to allow for wide drainage of the maxillary sinus into the nasal cavity; a wide middle meatal antrostomy will usually suffice. A partial medial maxillectomy with preservation of the lacrimal system may be required to gain access to laterally located mucoceles.[11] The Caldwell-Luc approach is only offered in centres where endoscopic surgery is not an option.

Sphenoid sinus mucoceles

A wide sphenoidotomy and intra-nasal marsupialization are all that is required for sphenoid sinus mucoceles.

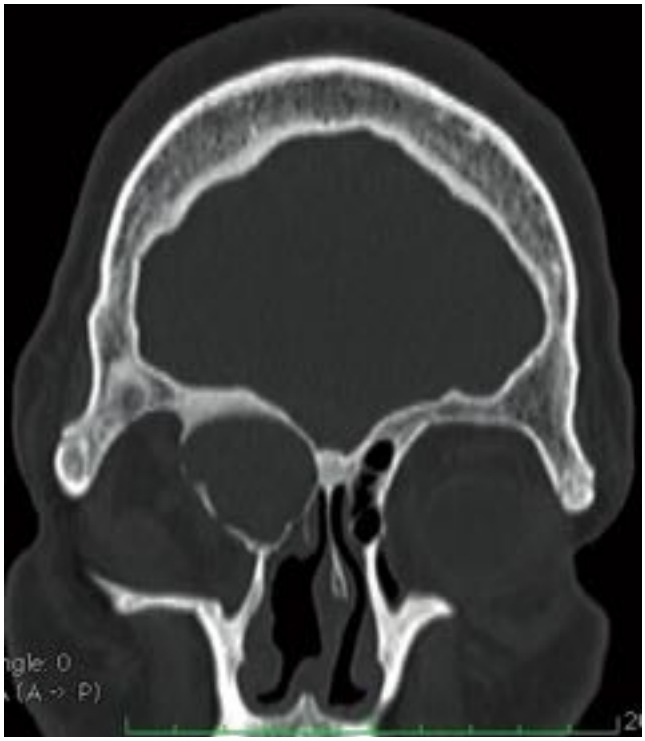


Figure 100.4 Homogeneous, isodense lesion within an expanded ethmoid sinus with bony remodelling of the sinus walls.

No attempt is made to remove the lateral sphenoid sinus mucosa as bony erosion place the internal carotid artery or optic nerve at risk of injury.

Other mucoceles

Mucoceles that have formed within a concha bullosa require resection of the lateral aspect of the concha bullosa. Dacryoceles are managed by endoscopic dacryocystorhinostomy.

COMPLICATIONS

Great care needs to be taken when decompressing a large, tense frontal mucocele that displaces the frontal lobe of the brain (**Figure 100.2c** and **d**) as sudden expansion of the cranial contents can disrupt the dural vessels and cause a subdural haematoma, or disrupt the dura and cause a cerebrospinal fluid (CSF) leak. Close post-operative monitoring is therefore essential in such patients. Because recurrence can occur decades later, long-term follow-up is required.

BEST CLINICAL PRACTICE

- ✓ CT is the imaging modality of choice and must be performed pre-operatively.
- ✓ Wide endoscopic marsupialization is the first line treatment for simple mucoceles.
- ✓ MELP is a good alternative to obliteration procedures.
- ✓ Combined approaches may be required with laterally located frontal sinus mucoceles.
- ✓ Long-term follow up is required to assess the need for further surgery to correct cosmetic deformities and to ensure patency of the marsupialized sac

FUTURE RESEARCH

- ➤ The pathogenesis of idiopathic mucoceles needs to be further investigated to ascertain if factors exist that make certain people more susceptible to mucoceles.
- ➤ Although cosmetic deformities can settle with time as bony remodelling takes place, no studies have been done to assess the long-term cosmetic outcome with marsupialization alone.

KEY POINTS

- Sinus surgery is now the leading cause of mucoceles.
- Wide marsupialization is required for all mucoceles.
- Bony remodelling can take place after surgery and cosmetic deformities will improve with time.

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CHAPTER 101

COMPLICATIONS OF RHINOSINUSITIS

Stephen Ball and Sean Carrie

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search along with BMJ evidence using the keywords: rhinosinusitis, complications, orbital cellulitis, intra-cranial, cavernous sinus thrombosis and Pott's puffy tumour.

DEFINITION

Complications of rhinosinusitis result from progression of acute or chronic infection beyond the paranasal sinuses, potentially causing significant morbidity from either local or distant spread.

EPIDEMIOLOGY

Epidemiological studies estimate an incidence of three complications from rhinosinusitis per million population per year; approximately one in every 12,000 acute rhinosinusitis episodes,[1] although this probably underestimates the disease burden. Most complications tend to occur in children and young adults, who typically experience six to eight upper respiratory infections per year.[2] Rhinosinusitis occurs in 5–10% of these infections[3] with the majority of complications originating from frontal and ethmoid sinus infections. Complications of rhinosinusitis are more accentuated in children and adolescents because of their thinner, more porous bony septa and sinus walls, open suture lines and larger vascular foramina.

CLASSIFICATION

Complications of rhinosinusitis are generally classified as orbital, intra-cranial, bony or chronic.

Complications may be caused by either local progression or distant spread via the bloodstream. Local progression is typically through areas where the surrounding bone is thin such as the porous lamina papyracea, where there is a direct anatomical connection[6, 7] or through osteitic bone. Direct routes of spread occur through neurovascular foramina such as the infraorbital canal, or via the valveless diploeic veins of Breschet of the frontal, ethmoid and sphenoid bones. The venous drainage of the sinus mucosa is via these diploeic veins,[8] which communicate with the dural venous plexus, the absence of valves facilitates retrograde spread of infection. Local complications of rhinosinusitis can be specific for the individual sinus groups and may best be discussed relating to their presumed anatomical sinus of origin. However, isolated sinus infections are rare and usually simultaneous infection is present in more than one sinus group.

Frontal

Anterior spread of acute frontal sinusitis through the outer table of the skull may cause a boggy subperiosteal abscess and osteomyelitis. This condition is commonly referred to as Pott's puffy tumour, following its description by Sir Percival Pott in 1760.[9] Posterior spread of infection can cause acute intracranial complications such as subdural empyema, meningitis, cerebritis and intracranial abscess. Subdural empyema is the most common intracranial complication of sinusitis, and the most common cause of subdural empyema is frontal sinusitis.[5] Spread of infection inferiorly can lead to orbital cellulitis.

Ethmoid

Orbital cellulitis is by far the most frequent acute complication of ethmoid sinusitis. It can vary in degree and severity and is typically graded with the Chandler classification.[10] This clinically useful classification (**Table 101.1** and **Figure 101.2**) also helps to guide the overall management of the patient although its lack of sensitivity and specificity means it has been superseded by the current availability of CT scanning. It is also important to note that orbital cellulitis can present at any stage of the Chandler classification and the disease does not necessarily progress in a chronological order i.e. a stage 2 can progress directly to stage 5 bypassing the steps in between and so on.

Maxillary

Isolated maxillary rhinosinusitis rarely gives rise to acute complications. Acute cheek swelling usually results from complications of dental disease, though there may be an associated secondary maxillary rhinosinusitis.

Sphenoid

Isolated sphenoid sinusitis is rare, but complications can result in meningitis[12] or cavernous sinus thrombosis by direct spread.[13] In cavernous sinus thrombosis infection may spread through veins from the paranasal sinuses and orbit to the cavernous sinuses as thrombophlebitis or by septic emboli. Bacteria themselves are pro-thrombotic, the thrombus provides good conditions for growth and bacteria within the thrombus are shielded by the outer layers from antibiotics which they can later re-infect.[14] In cases arising from acute sinusitis the sphenoid and ethmoid sinuses are the most common source.[14] Intracranial complications can also occur following a skull base fracture through the sphenoid sinus.

CLINICAL PRESENTATION

Any of the complications described above may present with a good history or obvious signs of preceding rhinosinusitis. However, it is not uncommon for the rhinosinusitis itself to be 'occult' or asymptomatic. In children it is more likely that there will be no prior history of rhinosinusitis, with the complication often being the first presentation.

ORBITAL COMPLICATIONS

It is estimated that 3% of sinusitis cases will progress to orbital cellulitis[7] with 60–85% of orbital cellulitis cases being secondary to sinusitis.[15,16] The remainder are caused by processes such as dacryocystitis or facial infection.[16] In the pre-antibiotic era death or blindness occurred in up to 20% of patients.[7]

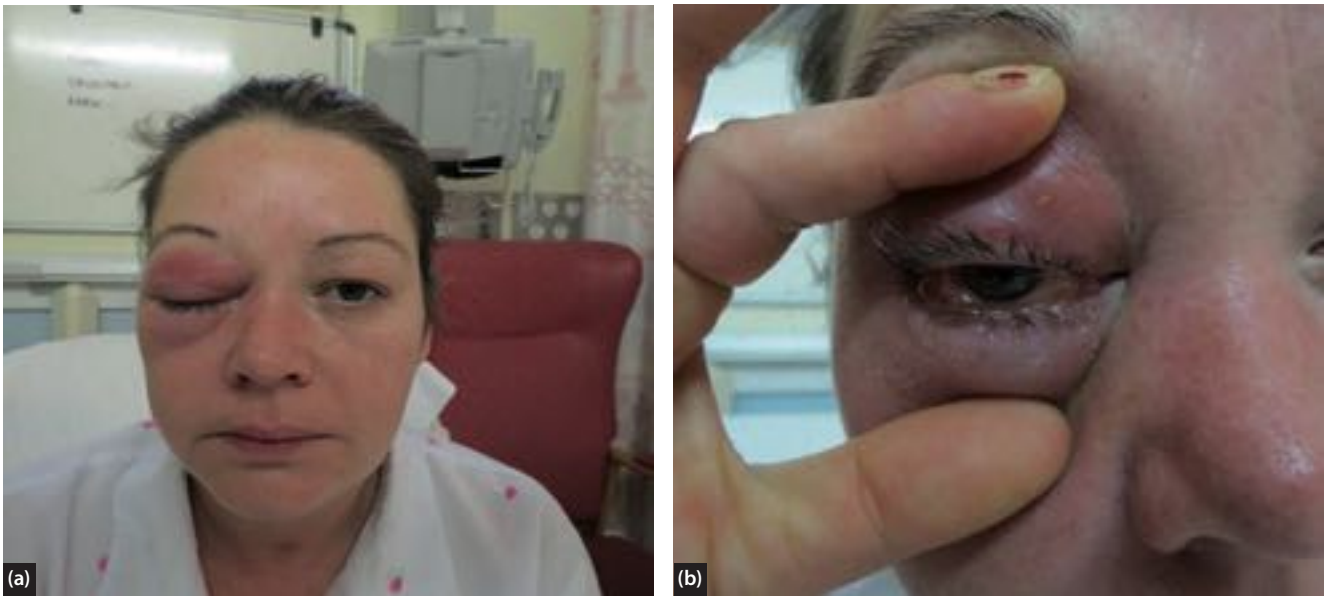


Figure 101.1 Right orbital cellulitis, Chandler classification stage 2; postseptal cellulitis. It is important to open the eyelids to fully examine the eye & vision. Here we see chemosis typical of orbital cellulitis, there was no visual defect, diplopia or relative afferent pupillary defect.

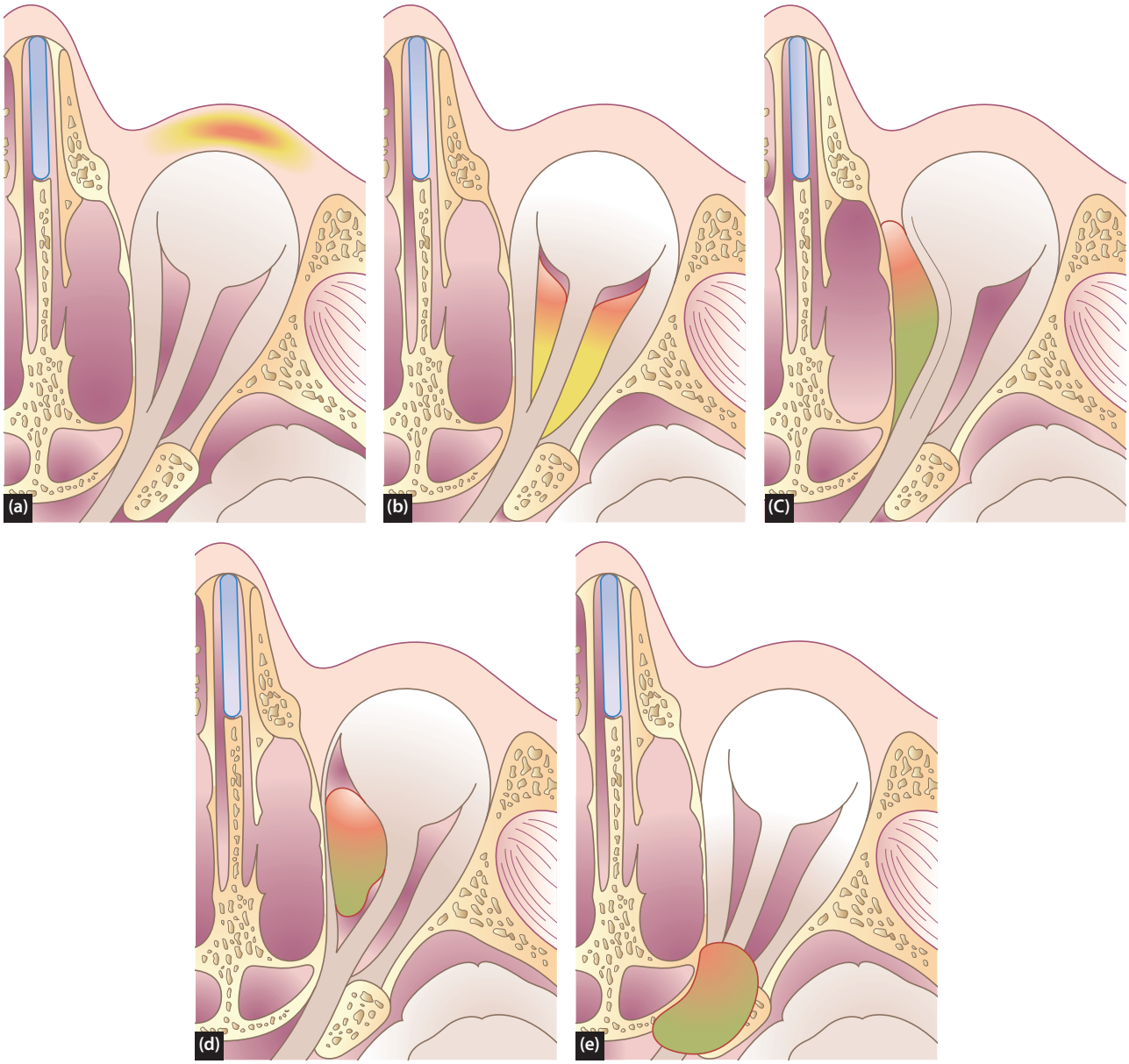


Figure 101.2 Various orbital complications on axial projection: **(a)** preseptal inflammation; **(b)** orbital cellulitis; **(c)** orbital cellulitis with subperiosteal (extra periosteal) abscess; **(d)** orbital cellulitis with intra-periosteal abscess; **(e)** cavernous sinus thrombosis. Red and yellow shading indicate inflammation/cellulitis, and green shading indicates pus. Redrawn from [11], with permission.

TABLE 101.1 Complications of rhinosinusitis, figures in brackets indicate relative frequency

Orbital[4]	Intracranial[5]	Bony	Chronic
Preseptal cellulitis (50%)	Sub dural empyema (38%)	Osteomyelitis & Pott's puffy tumour	Mucocele & pyocele
Postseptal cellulitis or orbital cellulitis without abscess (35%)	Intracranial abscess (30%)		
Subperiosteal abscess (15%)	Extradural abscess (23%)		
Orbital abscess (<1%)	Meningitis (2%)		
Cavernous sinus thrombosis	Cavernous or sagittal sinus thrombosis (2%)		



Figure 101.3 Pre-operative clinical photograph from an adolescent male with cavernous sinus thrombosis secondary to rhinosinusitis. Note the bilateral periorbital signs of oedema, cellulits and subtle left VIth cranial nerve palsy.

The onset is noted by swelling around the eye. Oedema results from congestion of veins draining the eyelid and can be present when the infection is still confined to the sinus. Cellulitis from untreated sinusitis represents stage 1 of the disease with local spread of inflammatory elements to the lid. Postseptal cellulitis (stage 2) is confined to the orbit but has extended through the orbital septum, potentially with intraconal involvement. Patients will have eyelid swelling, chemosis and proptosis, potentially with impaired extraocular muscle function and diplopia (**Figure 101.1**). Postseptal cellulitis typically results from transmitted pressure from the sinus to orbital veins with leakage of inflammatory elements into the orbit. It is difficult to clinically differentiate postseptal cellulitis from subperiosteal abscess (stage 3), CT scanning is mandatory here and reflects the fact that the classification system pre-dates the ready availability of scanning.

Orbital cellulitis is far more common in children (50% under 6 years)[17] and young adults (76–85% under 20 years).[18,19] Visual problems are a late sign, but may be present if the problem is stage 2 (postseptal cellulitis) or beyond. Specific enquiries should be made regarding diplopia, visual acuity and colour vision; signs which indicate compromised optic nerve function. At stage 5 (cavernous sinus thrombosis) signs of chemosis, periorbital oedema, proptosis, progressive opthalmoplegia, visual impairment and symptoms including headache and trigeminal parasthesia will be present (**Figure 101.3**).[20] In the case of orbital infection, cavernous sinus thrombosis will result from septic thrombophlebitis of the superior ophthalmic vein. Initially signs may be unilateral; bilateral disease propagates via the intercavernous sinuses.[21] Published mortality from cavernous sinus thrombosis is high at between 14% and 79% and up to half of patients experience morbidity including residual cranial nerve palsies and blindness.[14, 21] Animal experiments have demonstrated that visual loss may be irreversible if retinal ischaemic time exceeds 100 minutes.[22] Superiorly located orbital subperiosteal abscesses with severe frontoethmoiditis may indicate an increased potential for intracranial suppuration and should be aggressively evaluated.[23]

EXAMINATION

Clinical endoscopic examination of the nose should be performed to help determine the site and extent of disease. In the case of orbital cellulitis, a formal assessment of the degree of chemosis, range of eye movements, degree of proptosis, relative afferent pupillary defect, visual acuity (using a Snellen chart), colour vision (using Ishihara plates) and inspection of the optic disc should be made. This should ideally be carried out by an ophthalmologist. This assessment should be repeated at least twice daily and where there is increasing concern, 4–6 hourly monitoring of the full range of eye movements, visual acuity and colour vision should be undertaken with regular temperature and pulse measurements. For intracranial complications a full neurological examination should be completed. The possibility of occult intracranial complications should always be considered, even in a patient with a normal neurological examination. If intracranial complications are found, neurosurgical opinion is required. Multidisciplinary involvement is important but leadership of care should be clear and preferably by an experienced ENT surgeon.

INVESTIGATIONS

Rhinosinusitis can cause complications in different sites simultaneously. In one series the frequency of developing both intracranial and orbital complications was 5.4%, which rose to 13–24% for those who required surgical intervention to drain orbital disease.[23] Investigations should therefore be used to confirm the diagnosis, extent and any occult complications.

Radiological

There is currently a wide range of techniques available for imaging the paranasal sinuses and surrounding structures. The aim of these investigations is to:

- confirm the diagnosis of the complication
- define the extent and site of the complication
- help plan treatment including surgical approach
- confirm that there is no other covert complication present
- Monitor the response to treatment.

Contrast enhanced computed tomography (CT) is advised as first-line imaging because of its superiority in demonstrating bony anatomy and pathology of the orbit and sinuses with its speed and ease of examination. MRI provides outstanding soft tissue detail without radiation

TABLE 101.2 Chandler stages

Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Preseptal cellulitis	Postseptal cellulitis or orbital cellulitis without abscess	Subperiosteal abscess	Orbital abscess	Cavernous sinus thrombosis/abscess
Inflammation does not extend beyond the orbital septum (where the medial orbital periosteal reflection attaches to the medial eyelid at the tarsal plate).	Inflammation extends into the tissues of the orbit.	There is abscess formation deep to the periosteum of the orbital bones, typically at the lamina papyracea from ethmoid sinusitis.	There is abscess formation within the orbit which has breached the periosteum.	The inflammatory process has extended into the cavernous sinus which thromboses and may progress to abscess formation.

exposure. It should be noted that CT scanning may miss up to 50% of early stage intracranial complications. A low threshold for MR imaging is advised if there is any clinical suspicion of intracranial involvement.

The diagnosis of the complication should be apparent from the clinical appearance. If there is full ocular movement and normal colour vision, no immediate radiological investigation is indicated unless there is concern about intracranial pathology. Imaging should be undertaken to confirm the presence and site of suspected abscess prior to surgical drainage. Plain X-rays have no role as they are unable to define anything but the grossest orbital abnormalities. The investigation of choice is high-resolution triplanar axial, coronal and sagittal CT scanning. This will give the greatest chance of picking up small abnormalities, which may be missed with uniplanar scans. Although magnetic resonance imaging (MRI) will define abnormalities in the orbit, there is no evidence that it is more accurate than CT[24] and the lack of bone definition for planning surgery makes it of limited value for first-line imaging. Ultrasound also will not demonstrate surgical anatomy and has high false positive and negative rates.[24, 25]

Radiological findings

It is important to be familiar with the interpretation and analysis of triplanar imaging when managing patients with complications of rhinosinusitis as it aids the planning of surgical intervention. We would recommend, where possible, jointly reviewing the imaging with an experienced radiologist. Below are some of the common signs to look out for each stage of the Chandler classification.

1. **Preseptal cellulitis** – eyelid swelling and thickening of the preseptal tissues with possible posterolateral extension to the temporal fossa. Importantly, CT will not distinguish between oedema, preseptal cellulitis and allergy.
2. **Postseptal cellulitis** – the findings as above often with induration of the extraconal, intraconal and retrobulbar fat without abscess.
3. **Subperiosteal abscess** – CT scans show a typical lenticular rim-enhancing collection adjacent to the lamina papyracea with a fat plane between it and the displaced medial rectus muscle (**Figure 101.4**). Lateral deviation and proptosis of the globe may be visible on axial images. Sightthreatening complications of optic neuritis or optic nerve ischemia may also be present without radiological signs. Subperiosteal abscess secondary to frontal sinusitis typically forms an abscess superiorly with anteroinferior globe displacement.[16]
4. **Orbital abscess** – Scans may show multiple rim-enhancing orbital abscesses with surrounding cellulitis and a resultant proptosis.
5. **Cavernous sinus thrombosis** – It is important to note that in the early stages CT scans appear normal. CT and MR venography are complementary in the diagnosis of cavernous sinus thrombosis.[27] There may also be thickening and increased signal intensity in the extraocular muscles in T2-weighted MRI.[28]

TABLE 101.3 Risk factors for simultaneous orbital and intra-cranial complications[23]

Risk factors for intracranial infection in children admitted for orbital complications of acute rhinosinusitis[23]
Male
Age 7 years and older
Failure to improve after appropriate therapy
Changes in neurologic status
Frontal sinus opacification on CT
Superior or lateral position of orbital abscess
Need for surgical intervention to drain orbital abscess

Haematological investigations

The place of haematological investigations is three-fold:

1. to help identify any serious underlying disease process such as a haematological malignancy;
2. aid in assessment of fitness for surgery;
3. monitor the patient's response to treatment.

Other investigations

- Blood cultures
- Sinonasal/abscess pus culture ideally from initial nasal endoscopy

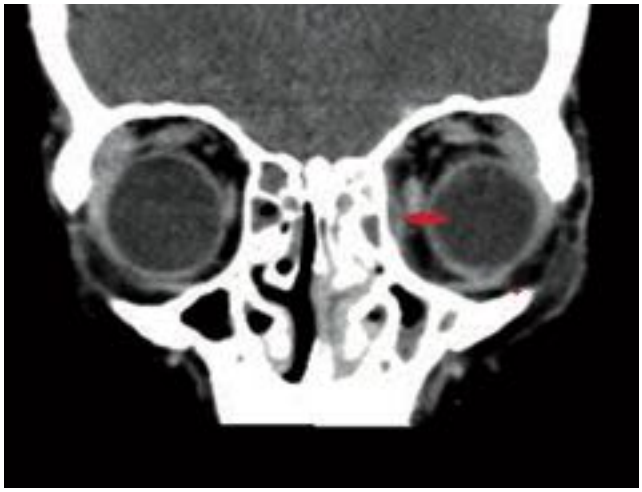


Figure 101.4 Coronal CT scan showing left maxillary and ethmoid sinusitis with associated medial orbital subperiosteal abscess (red arrow) and displacement of the globe.

- Urinalysis for diabetes mellitus, potentially causing immunocompromised
- Clinical observations. The simple regular monitoring of temperature should not be forgotten, any persisting infection may result in sustained or 'spiking' pyrexia requiring further clinical and radiological investigation.

TREATMENT

Medical

Almost all patients with complications of rhinosinusitis require admission for observation and treatment. Unless an abscess is demonstrated by radiological or other investigation, non-surgical management of rhinosinusitis complications is normally first choice. The exception is when vision is affected by pressure on the optic nerve from surrounding inflammation without abscess formation.

The aim of medical management is to control and eliminate both the disease process of the complication and of the primary rhinosinusitis. Antibiotics form the mainstay of medical treatment, but expert opinion suggests decongestant medications such as xylometazoline aids the resolution of acute rhinosinusitis by reducing mucosal oedema, although the evidence is inconclusive.[26] Selection of antibiotics is typically made on clinical grounds prior to identification of any organism or before culture-specific sensitivities are known. Broad-spectrum antibiotics are advised for severe complications of sinusitis to cover the likely organisms including *S. pneumonia*, *S. anginosus* and other *Streptococcus* species, *H. influenzae*, *S. aureus*, *Moraxella catarrhalis* and anaerobic bacteria (*Prevotella*, *Porphyromonas*, *Fusobacterium* and *Peptostreptococcus* species).[19, 29–31]

Polymicrobial and anaerobic isolates are more common in patients older than 15 years of age and in patients with intracranial complications.[29, 32] *Streptococcus anginosus* species represent some of the most frequently cultured organisms from either orbital or intracranial complications and have a tendency towards abscess formation.[33, 34] Complications, especially intracranial, are often one-off events due to highly pathogenic organisms. There will be marked local variation in causative organisms and sensitivities, therefore liaison with microbiology colleagues is recommended. An initial regime of intravenous cephalosporin with metronidazole would be an appropriate first choice until case-specific cultures and sensitivities are known. In patients with antibiotic sensitivities, other appropriate antibiotics should be selected in accordance with local microbiology policies.

The evidence base for systemic corticosteroid use is lacking in complications of rhinosinusitis. The risk of direct pressure from inflammation may possibly be reduced though this needs to be balanced against the immunosuppressive action and side effects of the steroids. In general, the use of systemic steroids is not recommended unless there is evidence of pituitary insufficiency in cavernous sinus thrombosis.

In the absence of abscess formation or reduction in visual signs medical management should initially be implemented for the first 24 hours, with frequent monitoring as described previously (**Figure 101.5**). If there is no significant clinical improvement in the first 24 hours of medical treatment, surgical intervention should be considered. Also, if at any point there is any clinical deterioration, urgent repeat imaging with a view to emergency surgical intervention is likely to be required. For orbital complications, intravenous antibiotic administration should continue until clinical improvement is well established and only then should oral medications be substituted. Evidence for how long oral antibiotics should be continued is limited, though 14 days of culture directed antibiotics is often appropriate. In the early stages of cerebritis, appropriate antibiotic administration can prevent intracerebral abscess formation.[35] Once a brain abscess has formed, surgical drainage combined with a prolonged antibiotic course of 4–8 weeks is recommended.[29]

CAVERNOUS SINUS THROMBOSIS

Prolonged broad-spectrum antibiotics must be given for at least 2 weeks beyond clinical resolution as bacteria sequestered within the thrombus may not be killed until the dural sinuses have started to recanalize.[14] Relapse and recurrence of meningeal and ocular signs have been reported up to 6 weeks after recovery and cessation of antibiotics[14] and follow-up for at least 6 months is advised.[26] Surgery is indicated only to drain any non-draining sinus infection or abscess collection.[14] There remains no consensus for the use of anticoagulation; proponents suggest that anticoagulants prevent thrombus propagation and have anti-inflammatory properties.[36, 37] Those against hypothesize that thrombus formation walls off infection and prevents its spread, with anticoagulants increasing the risk of intracranial bleeding in an already inflammatory environment. If anticoagulation is to be used rapidly reversible agents such as unfractionated heparin infusion should initially be used[14] aiming for an activated partial thromboplastin time (APTT) between 1.5–2,[38] switching to low-molecular weight heparins once the condition has improved.

Surgical

The surgical treatment of patients with complications of rhinosinusitis can be divided into procedures necessary to manage the complication and surgery for the rhinosinusitis. Often these are performed at the same time and may involve joint working with neurosurgeons in the case of intracranial suppuration.

The surgery required for acute complications of rhinosinusitis is often similar to that used for managing chronic rhinosinusitis. The principles of draining any pus and establishing ventilation of the sinuses remain. Where complications have arisen from acute rhinosinusitis it is likely that the operative field will be inflamed and very haemorrhagic, potentially making endoscopic surgery much more difficult than in the presence of chronic rhinosinusitis alone.

Knowledge of the likely sinus origin of the orbital complication is important in planning any surgical treatment. In ethmoid sinusitis orbital abscesses are typically medial to the globe, and in frontal sinusitis abscesses often form more superiorly within the orbit. A relatively large study of 240 patients identified patients with proptosis but normal eye movements and visual acuity are likely to require surgery, whereas infections with cellulitis alone are likely to settle with medical management.[18] Adolescent patients also appear more likely to develop complications requiring surgical intervention.[32]

The debate about the best approach to drain orbital collections remains a current controversy. Advocates of endoscopic surgery suggest that endoscopic ethmoidectomy with removal of the lamina papyracea and pernasal drainage of the orbital abscess is appropriate. The advantages of an endoscopic approach include avoiding facial scarring, ventilating the sinuses endonasally by operating on the osteomeatal complex, less post-operative orbital oedema, a shorter hospital stay and the absence of possible wound complications such as stitch abscesses.[39] More traditional external orbitotomy also has its proponents, and unless the surgeon is very familiar with endoscopic sinus surgery, it is more appropriate to use an external approach. If performing endonasal drainage the surgeon must be prepared to convert to external drainage if required and it is advised that patients and relatives are appropriately consented prospectively for both approaches. The external approach is also advised for abscesses that are not situated medially within the orbit adjacent to the lamina papyracea. The external approach uses a conventional Lynch–Howarth approach for an external ethmoidectomy, allowing an assistant to help keep the operative field clear whilst the subperiosteal abscess is drained. Occasionally, the orbital abscess will lie away from the lamina papyracea, especially if associated with frontal rhinosinusitis. As the abscess may lie in the roof of the orbit or further laterally, it is essential to obtain a CT scan preoperatively to define the position of any orbital collection and plan surgical treatment. Drainage of the abscess can be maintained with surgical drains either into the nasal cavity fixing to the septum or externally through the medial canthal incision. The evidence for performing concurrent surgical ethmoidectomy at the same time as draining the abscess is limited, as opposed to relying on medical treatment to deal with the rhinosinusitis and only draining the

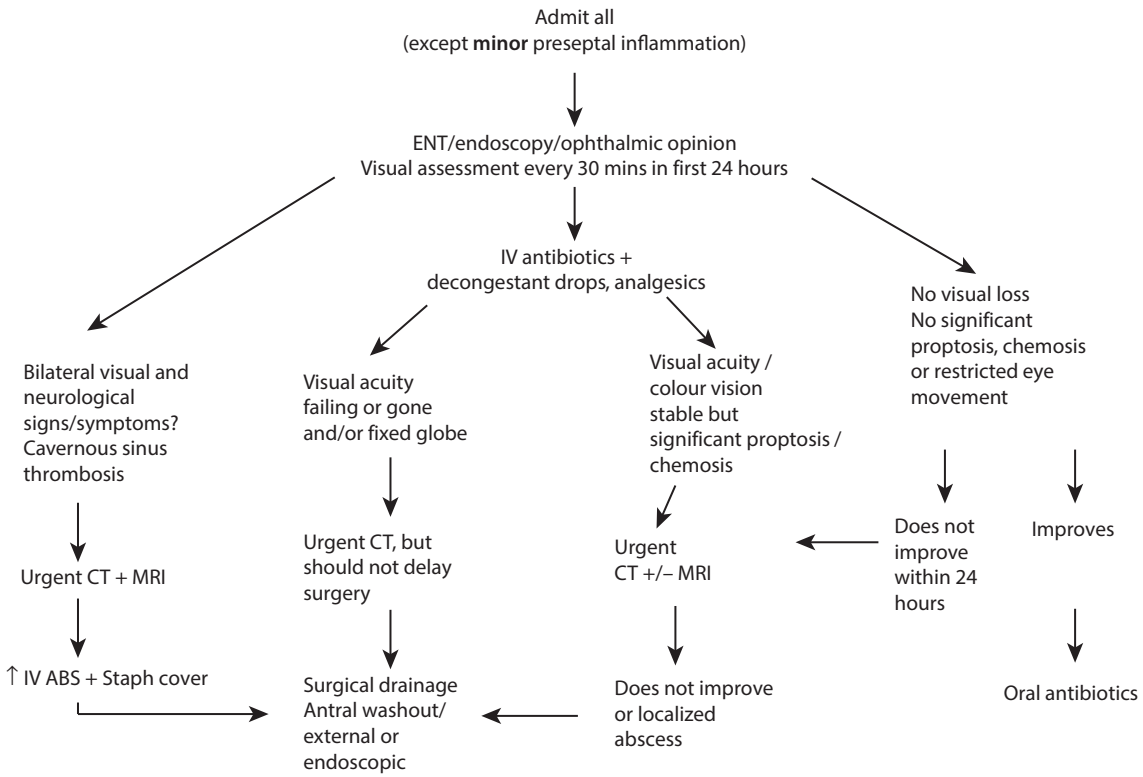


Figure 101.5 Management algorithm for orbital complications.

orbital collection surgically. However, the authors would advocate undertaking a maxillary washout or antrostomy and limited ethmoidectomy to allow all areas of pus to be drained. There are some early reports regarding possible medical management of carefully selected patients with small medial subperiosteal abscesses,[40] though at present we would advocate draining any orbital collection surgically with concurrent medical management.

Prognosis of orbital complications

If prompt treatment is carried out with adequate monitoring of patients, the prognosis for the return of normal vision is excellent. However, there is a small but significant risk of diplopia following surgery.[41] Provided the patient's presentation is not delayed and there is effective teamworking with ophthalmologists, paediatricians where appropriate, and otorhinolaryngologists ensuring prompt surgical intervention if non-surgical management fails, full recovery of eye function should occur.

INTRACRANIAL COMPLICATIONS

Brain abscess

Brain abscess can occur as a complication of either local or distant spread. The frontal sinuses are the most common source followed by the ethmoid, sphenoid and maxillary sinuses.[23] Haematogenous spread is the most likely mechanism of distant spread. It is estimated that 40–60% of brain abscesses arise from paranasal sinus infections.[42] The total reported incidence of intracranial complications from acute rhinosinusitis is between 3% and 17% of hospitalized sinusitis patients.[42, 43]

Subdural empyema

Subdural empyema is one of the commonest intracranial complications of rhinosinusitis, typically from haematogenous spread.[5] The brain is clearly more exposed as the infection is beyond the protective dura mater and allows the possibility of thrombosis of the dense network of veins in this space. Serious neurological injury can occur if not treated rapidly and aggressively with combined medical treatment and neurosurgical drainage to decompress the brain and evacuate the empyema. Subdural empyemas present with meningeal irritation and neurological signs such as seizures or focal deficits.

Extradural empyema

Extradural empyemas tend to be less symptomatic as the brain is protected by the dura mater. The signs are less marked and specific and are often only present when the collection reaches a size to cause mass effect.

Brain infarction

Cerebral ischaemia and infarction are rare vascular complications of sinusitis from either dural venous thrombosis secondary to adjacent empyema, or cavernous carotid artery occlusion.[28]

CLINICAL PRESENTATION

Early symptoms are often non-specific such as headache, fever, seizure, drowsiness, diplopia (VIth cranial nerve palsy) eye pain and nausea.[5] There may not be a preceding history of acute rhinosinusitis and clinical examination will not always identify suppuration from the paranasal sinuses. Adolescent and young adult males are more commonly affected which may be due to the vascularity of the diploeic system in this age group.[23] Frontal lobe abscesses are the most common intracranial abscess location. There may be specific neurological symptoms if there is a well-defined intracranial abscess including acute pain and possible loss of consciousness associated with meningitis. Some authors advocate scanning all patients with acute frontal rhinosinusitis or orbital cellulitis to exclude such serious complications, which may initially be clinically 'silent'.[13, 42]

INVESTIGATIONS

MRI scanning has been shown to be superior to CT in the diagnosis of intracranial complications and is the investigation of choice for the diagnosis of suspected intracranial extension.[24] The example in **Figure 101.6** demonstrates the presence of a small subdural frontal abscess apparent on MR imaging but not visualized by a contrast enhanced CT scan.

As soon as an intracranial complication is detected, joint management of the case with neurological or neurosurgical colleagues is mandatory. If possible, surgery to drain affected paranasal sinuses should be undertaken synchronously with any neurosurgical operative intervention. If synchronous paranasal sinus surgery is to be undertaken, CT scanning is desirable to demonstrate the bony anatomy of the paranasal sinuses, provided any delay incurred in scanning is compatible with the patient's clinical condition. Intracranial complications may be relatively silent and a high index of suspicion should be maintained (**Figure 101.7**). Intracranial complications may also develop after the initial presentation and any change in neurological status should merit consideration for repeat imaging.

TREATMENT

For medical treatment see earlier in the chapter. The surgical treatment of intracranial complications will inevitably involve neurosurgical expertise. As far as the otorhinolaryngologist is concerned, discussion needs to take place as to whether the sinus surgery will be done at the same time as any neurosurgical procedure. There is unfortunately little evidence to help decide whether these should be done as separate procedures but, as with orbital cellulitis, it is the authors' practice to undertake the surgery for the complication at the same time as for the underlying rhinosinusitis. Intracranial complications are most likely to arise

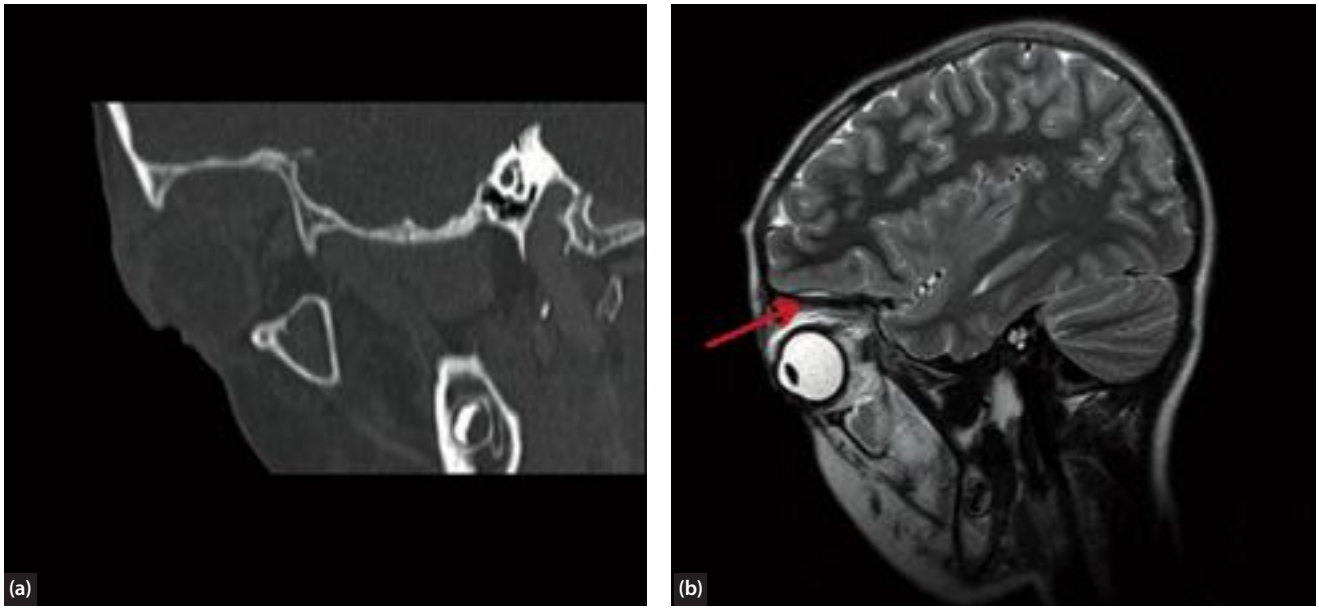


Figure 101.6 Contrast enhanced sagittal CT scan of a child with acute sinusitis and headache. **(a)** No intracranial pathology was identified to account for the symptoms. An MRI scan of the same child **(b)** highlighted a small subdural frontal abscess (arrow illustrates pathology).

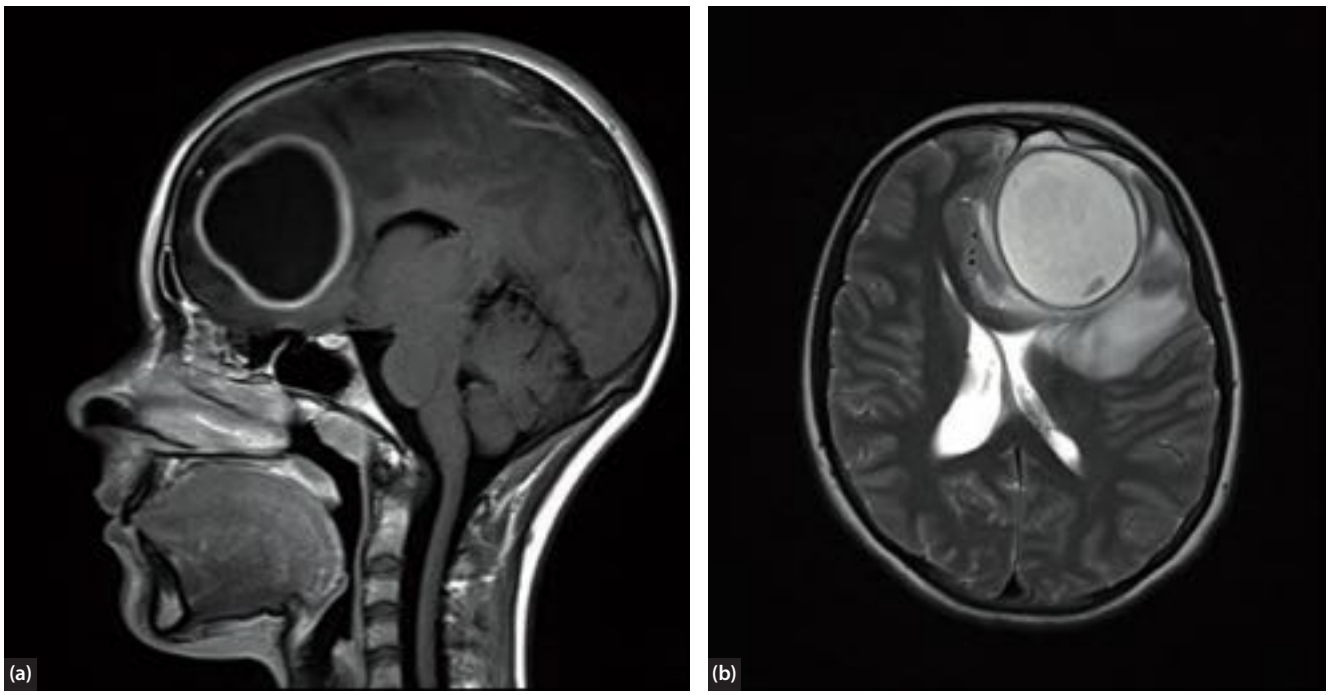


Figure 101.7 MRI images of a large frontal intracerebral abscess secondary to rhinosinusitis.

from frontal rhinosinusitis as opposed to the remaining paranasal sinuses, and endoscopic frontal surgery is likely to be challenging and potentially dangerous. In the acute setting, it is better to undertake a temporary frontal drainage procedure concomitantly with surgery for the intracranial condition. A frontal sinus trephine procedure with placement of an external drain is most commonly used, although endoscopic balloon sinuplasty has been used to drain acute frontal sinus collections pernasally[44] and may become more popular in future. Any definitive frontal sinus surgical procedure can be deferred until the patient has fully recovered from treatment of the complication.[45]

Prognosis from intracranial complications

The increased availability of scanning has no doubt led to earlier diagnosis and better outcomes.[46] Published mortality rates vary between 0 and 25%[5, 30] Unsurprisingly,

mortality varies according to the specific complication and increases with age and decreased level of consciousness on presentation.[31, 42] Persistent morbidity such as hemiparesis, epilepsy, altered cognitive function and cranial nerve palsies are reported in between 11% and 40% of cases.[5, 30, 43] Early recognition of complications and multidisciplinary treatment is essential for the best possible outcome.

BONY COMPLICATIONS

Pott's puffy tumour

In the 18th century Percival Pott described the case of a patient with a pericranial abscess related to trauma. The area, he noted, was 'swollen and puffy'. The term Pott's puffy tumour is now used to describe a subperiosteal cellulitis or abscess of the frontal bone associated with frontal oeteomyelitis and presenting with headache, swelling and, on occasion, a discharging frontal fistula (**Figure 101.8**). The infection can spread posteriorly giving rise to intracranial sepsis either by erosion of the posterior table or more likely by septic thrombophlebitis via the diploeic veins.[47] The reported rate of coexistent intracranial complications is high between 29% and 60%, though not all are present on initial imaging[47, 48] which suggests prompt cross-sectional imaging and treatment are paramount. Both Gallagher and Jones[48, 49] noted a preponderance of Streptococcus anginosus infection in series of such patients, where positive cultures were obtained.

Management requires drainage of pus from the frontal sinuses, achieved either endoscopically or conventionally through a frontal sinus trephination via an incision in the superomedial aspect of the orbit. In the absence of a subperiosteal or intracranial abscess, further surgery may not be necessary acutely. Prolonged antibiotic therapy, ideally culture-directed, for 6–8 weeks covering both aerobic and anaerobic organisms is recommended by the authors. Once the acute phase has subsided the patient should be re-evaluated to determine if a frontal sinus drainage procedure is required for long-term management. This can be undertaken endoscopically or externally through an osteoplastic frontal flap, or in combination (see Chapter 99 Frontal Sinus). However, as these infections rarely recur, in general, patients can be reassured this an unlikely occurrence.

A limited subperiosteal abscess may be drained through a Lynch Howarth brow incision. However, this does not allow adequate inspection of the frontal bone to assess for necrotic bone. An alternative is to perform a spectacle incision providing good exposure to the frontal sinus but resulting in a scar, which may not be acceptable cosmetically. A bicoronal scalp incision and flap provides excellent access to assess the whole frontal sinus enabling removal of diseased bone. This procedure is of such significant complexity that the inexperienced rhinologist should not undertake it.

Associated intracranial complications necessitate prompt neurosurgical intervention. This is typically performed through a bifrontal craniotomy enabling drainage of intracranial pus and removal of necrotic bone.[50] Complete removal of the posterior table will require frontal sinus cranialization. Extensive osteomyelitis of the anterior table may necessitate a Riedel's procedure[51] with removal of the anterior wall and floor of the frontal sinus allowing the forehead skin to collapse onto the posterior table. Whilst this causes a significant cosmetic

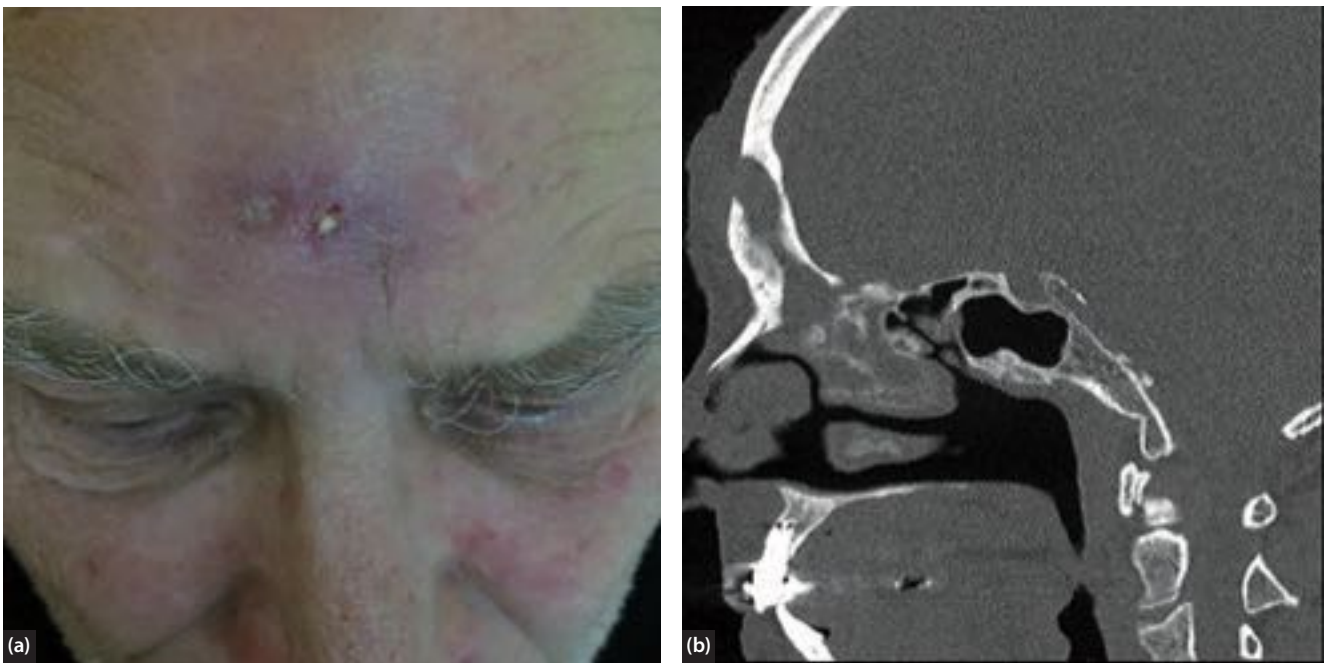


Figure 101.8 Clinical photograph **(a)** & sagittal CT scan **(b)** through the frontal sinus showing Pott's puffy tumour; a discharging frontocutaneous fistula from the subperiosteal collection, frontal sinusitis with osteomyelitis and bone erosion of the anterior frontal sinus wall.

deformity, reconstruction with split calvarial bone or alloplastic materials can be undertaken at a later stage when all infection has resolved.[52]

CHRONIC COMPLICATIONS

Chronic complications of rhinosinusitis usually result from chronic rhinosinusitis. As with acute complications, the nature of the complication depends on the particular sinus or group of sinuses involved. Mucoceles are chronic, slowly expanding lesions in any of the sinuses that may result in bony erosion and can extend beyond the sinus (see Chapter 100, Mucoceles). It is unusual for chronic rhinosinusitis to cause orbital cellulitis or intracranial complications unless there is an infective exacerbation.

ACKNOWLEDGEMENTS

We would like to acknowledge the previous work of Mr Robert Slack and Mr Richard Sim. This is an updated and revised chapter based initially on their work from the seventh edition. Additional acknowledgement must be made to Professor Nick Jones for his helpful advice and critical reading of the manuscript.

FUTURE RESEARCH

- There is continued controversy as to whether surgery for orbital abscess complications is best undertaken endoscopically or externally. The availability of local expertise often determines the preferred approach, though it may be possible for carefully designed clinical trials to provide more evidence.
- The numbers of patients presenting with complications of rhinosinusitis is relatively small, the symptoms can be varied and the time required to begin treatment is very short. This makes it very difficult to design studies that would result in level 1 or 2 evidence. Consequently the evidence presented here is mostly based on retrospective case series data.
- There is also little information to suggest why some individuals should develop complicated sinus disease when similar organisms are isolated from patients with uncomplicated disease. Bony sinus anomalies that narrow anatomically important areas such as the osteomeatal unit (OMU) which may predispose to sinusitis are seen with similar frequency in children, adults[49] and asymptomatic individuals making their significance unclear.[50] However, when specific measurements of OMU calibre are made, no significant difference between children and adults exists implicating additional mucosal immune mechanisms which require further investigation.[51]

BEST CLINICAL PRACTICE

- ✓ Careful, repeated clinical observations with a low threshold for repeat imaging if there is deterioration in clinical condition.
- ✓ Radiological investigations of choice are CT with MRI for suspected intracranial pathology.
- ✓ Broad-spectrum antibiotics with streptococcal and anaerobic cover form the mainstay of medical treatment.
- ✓ Surgical treatment is normally required for resolution in patients with abscess formation.
- ✓ Cultured *Staphylococcus aureus* should not be dismissed as a contaminant.
- ✓ A multidisciplinary approach is essential to ensure optimal outcome.

KEY POINTS

- The major complications of rhinosinusitis are orbital and intracranial infections, of which orbital complications are the more common.
- The incidence of complications is greatest in children and young adults.
- The speed of initiating treatment and confirming the diagnosis can greatly reduce the morbidity and extent of intervention required.
- Multidisciplinary care involving ENT surgeons with ophthalmology, paediatric and neurology/neurosurgical input as required is a standard of care

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CHAPTER 102

THE RELATIONSHIP BETWEEN THE UPPER AND LOWER RESPIRATORY TRACT

Nigel K.F. Koo Ng and Gerald W. McGarry

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: rhinitis, allergic rhinitis, sinusitis, nasal polyps, asthma, occupational, chronic obstructive pulmonary disease, hypersensitivity, allergens, bronchial hyperreactivity, nasal mucosa, bronchi, biopsy, nasal provocation tests, bronchial challenge tests, airway remodelling, quality of life, disease management, anti-allergic agents, anti-asthmatic agents, steroids, leukotriene antagonists, anti-IgE antibodies (omalizumab), immunotherapy and nasal surgery.

INTRODUCTION

The close relationship between the upper respiratory tract (nose and paranasal sinuses) and the lower respiratory tract (tracheobronchial tree) is something that is manifestly observed by all practising rhinologists. Whilst it can be observed in a number of rare conditions such as granulomatosis with polyangiitis, this close relationship is most striking in the conditions of asthma, rhinitis and nasal polyposis (**Table 102.1**). The relationship between the upper and lower respiratory tract is so evident in rhinitis and asthma that these conditions may be viewed as ends or parts of a respiratory inflammatory spectrum. Most patients with asthma also have rhinitis[1] and treatment of coexisting rhinitis may improve asthma. The concept of 'one airway, one disease' and the 'unified airway' in which the upper and lower airways act as a whole unit has been proposed, with rhinitis and asthma representing manifestations of the same inflammatory process.[2, 3] However, there are also differences between rhinitis and asthma and not all patients with rhinitis have asthma.[4]

EPIDEMIOLOGICAL RELATIONSHIP BETWEEN RHINITIS AND ASTHMA

There is strong epidemiological evidence both from cross-sectional and longitudinal studies that rhinitis and asthma are related. The two conditions often coexist in the same patients, with rhinitis occurring in over 65% of allergic asthma patients and in over 80% of patients with non-allergic asthma.[1] In the Copenhagen Allergy Study,[5] between 40–50% of allergic rhinitis patients had allergic asthma and the risk of allergic asthma was up to 300 times higher in allergic rhinitis patients than those without allergic rhinitis.

It is not only allergic rhinitis however that is associated with asthma; there is also an association between non-allergic rhinitis and asthma. Rhinitis has been shown to be an independent significant risk factor for asthma in both atopic and non-atopic individuals.[6] There is also an association between asthma and chronic rhinosinusitis, irrespective of smoking behaviour.[7] Sixty percent of chronic rhinosinusitis patients have associated lower airway disease (24% asthma, 36% small airway disease).[8]

TABLE 102.1 Examples of disease which affect the upper and lower airways

Asthma
Rhinitis
Chronic rhinosinusitis
Sarcoid
Granulomatosis with polyangiitis
Cystic fibrosis
Ciliary dyskinesias

RHINITIS AND NON-SPECIFIC BRONCHIAL HYPERRESPONSIVENESS

Many patients with allergic rhinitis who do not have asthma symptoms demonstrate bronchial hyperresponsiveness, a key feature of asthma.[9] They showed increased bronchial sensitivity to stimuli such as methacholine (a parasympathomimetic agent) or histamine. In those with seasonal rhinitis and allergy to pollen, the degree and prevalence of bronchial hyperresponsiveness is significantly greater during the pollen season compared to outside this period.[10] Those with perennial rhinitis have a higher risk of bronchial hyperresponsiveness compared to those with seasonal rhinitis.[11, 12]

Patients with allergic rhinitis and bronchial hyperresponsiveness are at greater risk of developing asthma than those with normal bronchial challenges.[13] However, not all patients with allergic rhinitis have increased bronchial hyperresponsiveness and there are large differences in the extent of airway responsiveness exhibited in asthma and rhinitis.

CAUSATIVE AGENTS IN RHINITIS AND ASTHMA

Asthma and rhinitis share many common risk factors. Some of the agents inducing asthma and rhinitis such as allergens and aspirin[14] are well known to affect both the upper and the lower airways. This is compatible with the concept of a 'unified airway', although many studies have shown some differences in the genetic and environmental risk of these two conditions suggesting that there is an element of specificity for each condition.[15]

Bacterial enterotoxins, by acting as a superantigen, may play a role in the development and/or severity of asthma and allergic rhinitis.[16] In a mouse model of allergic asthma, application of *Staphylococcus aureus* enterotoxin B to the nose or to the bronchus each resulted in a more severe bronchial eosinophilic inflammation.[17] It has also been shown that there is increased *Staphylococcus aureus* colonization in the nose and specific IgE antibodies against *Staphylococcus aureus* enterotoxins in patients with nasal polyps.[18]

Upper respiratory tract viral infections, often caused by rhinovirus, are strongly associated with asthma exacerbations in children and adults[19, 20] Experimental induction of upper respiratory tract rhinovirus infection in allergic rhinitis patients has been shown to increase airway hyperreactivity and late asthmatic reactions after allergen challenge.[21] However, rhinovirus also has the ability to infect the lower respiratory tract and induce a pro-inflammatory response, suggesting that rhinovirus-mediated asthma exacerbations may result from a direct lower respiratory tract reaction.[22]

The most common precipitants of occupational asthma can all induce occupational rhinitis. Although rhinitis and asthma are closely related, the relationship in occupational disease is less well known. Occupational rhinitis, however, is often associated with occupational asthma, and this association is significantly greater with high molecular weight agents compared to low molecular weight agents.[22] As patients with occupational rhinitis can often go on to develop occupational asthma, cessation of allergen exposure in occupational allergic rhinitis is important to try to prevent asthma.

RHINITIS AS A RISK FACTOR FOR ASTHMA

There are many studies which support rhinitis as a risk factor for asthma both in children and adults.[6, 23–26] Physician-diagnosed allergic rhinitis in infancy has been shown to be independently associated with doubling the risk of asthma by 11 years old.[27] In another study, allergic rhinitis in childhood was found to be significantly associated with a two- to seven-fold increased risk of asthma in pre-adolescence, adolescence, or adult life.[28] Furthermore, the risk of childhood asthma persisting to middle age was three times higher in children with allergic rhinitis compared to those never having allergic rhinitis.[28]

In adults, a study of college students found that the risk of developing asthma over a 23-year period was significantly higher in those diagnosed with allergic rhinitis compared to those without (10.5% vs. 3.6%).[29] A 15-year prospective study of Finnish twins found that patients with 'allergic rhinitis including hay fever' were more likely to develop asthma by four times if male and six times if female compared to patients without allergic rhinitis.[30] Some have found the prevalence of asthma to be associated to the severity and duration of rhinitis with the highest prevalence in patients with moderate/severe persistent allergic rhinitis[31] whereas others report no correlation between the Allergic Rhinitis and its Impact on Asthma (ARIA) categories of rhinitis and the prevalence of asthma.[32]

Allergic rhinitis usually precedes asthma and the term 'The Allergic March' has been used to describe the progression of allergic nasal disease in the upper airway to the lower airway. It is not clear, however, whether allergic rhinitis causes asthma or whether allergic rhinitis is just an earlier clinical manifestation of allergic disease in atopic patients who would in any case develop asthma. Children with atopic eczema have significantly greater risk of developing asthma and allergic rhinitis than those

with non-atopic eczema[33] and it has been suggested that the allergic march may begin even earlier with eczema[34] leading to rhinitis and then asthma.

The increased risk of asthma is not just limited to allergic rhinitis but is also found with non-allergic rhinitis.[15] It has been reported that rhinitis increased the risk of asthma in both atopic and non-atopic patients by about three times.[6] It appears that rhinitis and asthma are not just linked because they share atopy as a common risk factor.

INFLAMMATION OF THE UPPER AND LOWER RESPIRATORY TRACT IN RHINITIS, ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Similarities and differences between nasal and bronchial inflammation in asthma and rhinitis

There are many anatomical and physiological similarities between the upper and lower airways. They are both lined by pseudostratified ciliated columnar epithelium on a continuous basement membrane (**Figures 102.1a** and **102.1b**). Throughout the submucosa there are mucous glands, blood vessels, structural cells (fibroblasts), some inflammatory cells (monocytic cells, lymphocytes and mast cells) and nerves. There are also significant differences however, between the upper and lower respiratory tracts. The nasal mucosa is highly vascular with an extensive subepithelial capillary and arterial system and venous cavernous sinusoids. Vascular dilatation can result in increased upper airway resistance and subsequent nasal obstruction. In contrast, bronchoconstriction is due to the contraction of airway smooth muscle which is present from the trachea to the bronchioles, rather than changes in the vasculature.

Inflammation is a key component in the pathogenesis of rhinitis and asthma and studies have shown a similar inflammatory infiltrate (eosinophils, mast cells, T-lymphocytes and cells of the monocytic lineage) involved in the inflammation of the nasal and bronchial mucosa. There also appears to be similar pro-inflammatory mediators (histamine, cysteinyl leukotriene), T-helper 2 (Th2) cytokines (interleukin IL-4, IL-5, IL-13 and granulocyte-macrophage colony-stimulating factor), chemokines (RANTES and eotaxin) and adhesion molecules in the inflammation of the upper and lower airways in rhinitis and asthma. Airway smooth muscle is important in the pathogenesis of asthma not only by causing bronchoconstriction but may also be involved by increased proliferation and the expression and secretion of a variety of proinflammatory mediators and cytokines.[35, 36] In patients with both rhinitis and asthma, the degree of inflammation in the upper and lower airways may be different. Greater eosinophilic inflammation has been found in the bronchi compared to the nose in untreated asthmatic patients with rhinitis.[37] Epithelial shedding and basement membrane thickening are key features of airway remodelling in asthma and have also been found in sinonasal specimens of patients with chronic rhinosinusitis.[38] The extent of epithelial shedding and reticular basement membrane thickening however are greater in the bronchi than in the nose in patients with both asthma and rhinitis.[37]

Nasal and sinus inflammation in asthma and chronic obstructive pulmonary disease

Eosinophilic infiltration of the nasal mucosa has been demonstrated in patients with asthma irrespective of the presence of nasal symptoms,[39] further supporting the hypothesis that asthma and rhinitis are clinical manifestations of the same disease. There is also a strong association between chronic rhinosinusitis and asthma, with a higher

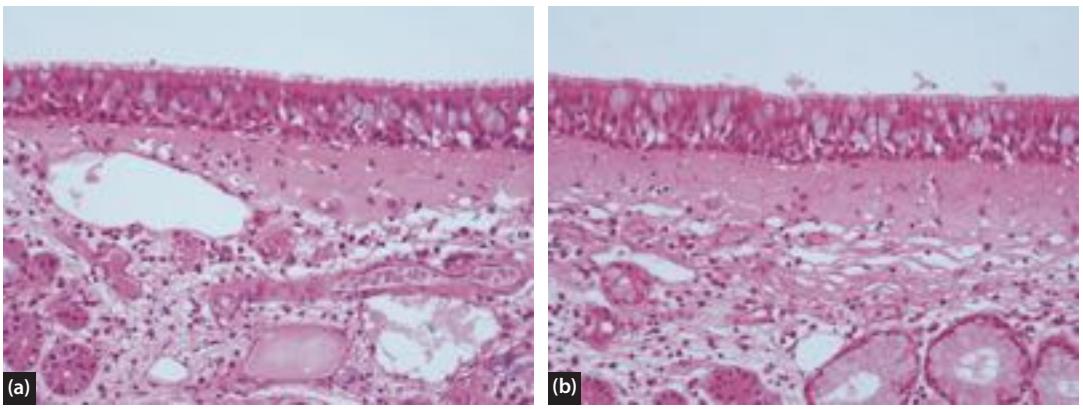


Figure 102.1 **(a)** Photomicrograph of nasal mucosa showing ciliated pseudostratified columnar epithelium on the surface with underlying basement membrane and lamina propria. The lamina propria contains prominent dilated, thin walled vascular channels some of which are filled by red cells or pink, flocculent protein rich material derived from plasma. A few mucosal glands are present towards the left. A light scattering of chronic inflammatory cells is seen in the mucosa. H&Ex200. **(b)** Photomicrograph of lower respiratory mucosa showing ciliated pseudostratified columnar epithelium on the surface with underlying basement membrane and lamina propria. The lamina propria contains a few mucosal glands towards the bottom of the image. No prominent vascular channels are present. A light scattering of chronic inflammatory cells is seen in the mucosa. H&Ex200.

rate of nasal polyps in asthmatic patients compared to non-asthmatics.[40] The triad of aspirin sensitivity, asthma and nasal polyps in aspirin-induced asthma is considered a separate clinical syndrome and found in about 10% to 15% of asthmatics.[41]

Patients with asthma often also have radiological evidence of sinusitis.[42, 43] The frequency of abnormal CT scans has been reported to be similar in patients with mild to moderate asthma (88%) compared to those with severe steroid dependent asthma (100%).[44] However, the extent of sinonasal involvement is greater in the latter, as based on clinical symptoms and CT.

The relationship between the upper and lower airways in patients with COPD has been much less extensively studied than in asthma. Some have found no significant difference in the prevalence of rhinitis in patients with COPD compared to those without[45] and an association between COPD and the upper respiratory tract has not been widely appreciated. There is, however, increasing evidence that upper airway disease may be related to COPD.[46] Some studies have reported increased upper airway symptoms and nasal inflammation in patients with COPD.[47–51] There is a need for further research in this area including the impact of treatment of the upper airway in patients with COPD.[52]

Bronchial inflammation and remodelling in rhinitis

In non-asthmatic patients with allergic rhinitis, there appears to be remodelling in the lower airways similar, although less marked, to that in asthma.[53] Studies of the bronchial mucosa in non-asthmatic allergic rhinitis patients and atopic non-asthmatics have shown an increase in the thickness of the basement membrane and in eosinophils, compared to normal individuals.[54, 55] Natural exposure to pollen in non-asthmatic patients with seasonal allergic rhinitis, results in increased lymphocytes, eosinophils and IL-5 expression in the bronchial mucosa.[56] Nasal allergen challenge in patients with seasonal allergic rhinitis shows increased sputum eosinophils and bronchial responsiveness to methacholine with inflammation of the bronchial and nasal mucosa.[57, 58]

Bronchial challenge of rhinitis patients leads to bronchial and nasal inflammation

In allergic non-asthmatic patients, endobronchial allergen challenge causes bronchial constriction and inflammation, with an increase in inflammatory cells recovered by bronchoalveolar lavage.[59] Endobronchial allergen challenge not only causes bronchial symptoms in non-asthmatic allergic rhinitis patients but also affects the nose, inducing nasal symptoms and inflammation resulting in reduced pulmonary and nasal function.[60] It has been shown that there is an increase in the number of eosinophils in the challenged bronchial mucosa and in the blood. In the nose, there is also an increase in eosinophils as well as eotaxin-positive cells in the nasal lamina propria with enhanced expression of IL-5, after bronchial challenge.[60]

POSSIBLE MECHANISMS OF INTERACTION BETWEEN THE UPPER AND LOWER RESPIRATORY TRACT

The nose plays a crucial role in warming, humidifying and filtering air before it enters the lower airways. Impairment in nasal function can therefore impact on the lower airways. Nasal obstruction can lead to increased oral breathing, reduced filtered air and increased exposure of the lower airways to allergens. Bypassing the nose also results in colder air being delivered to the lower airways, which can also trigger bronchoconstriction in asthmatic patients.[61] Although aspiration of nasal contents can occur in neurologically impaired patients, it is not thought to be responsible for the nasobronchial interaction under normal circumstances.[62]

The upper and lower airways not only interact via their anatomical connection but there may also be neural reflexes and systemic mechanisms.[63] A nasobronchial reflex has been proposed although there has been controversy as to whether it exists with limited evidence to support its presence.[61] A double-blind randomized study of nasal challenges in asthmatic patients with allergic rhinitis and in controls found that methacholine increased lower airway resistance but this could be blunted by pre-medication of phenylephrine to the nasal mucosa.[64] The implication is that the effect was through systemic absorption rather than a nasobronchial reflex. More recently it has been shown that nasal allergen provocation rapidly induces bronchial hyperresponsiveness by substance P binding to the neurokinin 1 receptor with an increased number of substance P-positive pulmonary nerves.[65] However, the precise interactions between the upper and lower airways are yet to be fully understood.

There is increasing evidence that the upper and lower airways are connected via a systemic route. Following local allergen challenge, there is high and rapid absorption of allergens in the nasal and bronchial vasculature.[66] There is also an increase in eosinophils in the blood and airway tissues as well as bone marrow eosinopoiesis.[58, 60, 67, 68] Increased serum IL-5 levels occurs after allergen exposure[69] and appears to play a critical role in allergic airways eosinophilia and eosinopoiesis in the bone marrow.[61, 70–73] In addition, it has been suggested that there is '*in situ* haemopoiesis' with basophils/mast cells and eosinophils accumulating in allergic tissue from in situ growth and differentiation of progenitors, stimulated by soluble haemopoietic factors derived from mucosal cell populations.[74]

MANAGEMENT IMPLICATIONS

As rhinitis and asthma often coexist, a combined approach is recommended to manage the airways. The presence of disease in the lower airways can affect the results of investigations of the upper airways such as peak nasal inspiratory flow (PNIF) (**Figure 102.2a**). Although objective measures of nasal patency are not widely used in routine clinical practice, PNIF is reported to be the best validated technique for the evaluation of nasal flow through the nose[75]



Figure 102.2 **(a)** Peak nasal inspiratory flow being measured. **(b)** Peak expiratory flow being measured.

and is quick, simple and cheap to use. It may be particularly helpful in evaluating children and adolescents with allergic rhinitis due to the subjective nature of the clinical information and the possibility that they may underestimate their symptoms.[76] However PNIF is affected by lower airway function[75] and has been reported to positively correlate with peak expiratory flow (PEF) in healthy children and adults (**Figure 102.2b**).[77, 78] PEF has been shown to be predictive of PNIF and low values of PNIF may be reflective of poor lower airway function rather than representing nasal obstruction.[78] Pulmonary function tests (particularly spirometry and PEF), in contrast objective tests of nasal patency are much more commonly used and can be helpful in confirming the diagnosis in asthma.[79]

Treatment of rhinitis may reduce morbidity from asthma and patients with asthma should be assessed for rhinitis and vice versa.[15] A retrospective cohort study of 4 944 patients with both allergic rhinitis and asthma (without any evidence of COPD) found that those treated for allergic rhinitis had a significantly lower rate of asthma-related emergency department visits or hospitalizations compared to those not treated.[80] Another retrospective study of 13 844 patients with asthma found that treatment with intra-nasal steroids of nasal conditions significantly reduces exacerbations of asthma leading to emergency department visits[81] although it has also been reported that there may be bias in such an observational study.[82]

Treatment options for rhinitis and asthma include pharmacological agents, immunotherapy and surgery for chronic rhinosinusitis. Although treatment regimes are well established for each individual condition, optimal management for coexisting rhinitis and asthma is still not agreed. Questions remain as to whether each condition should be treated separately or concurrently and which therapies should be used.[83]

Medical management

Drugs for rhinitis and asthma can be given via local (intra-nasal or inhaled (intra-bronchial)), oral and parenteral routes. Topical glucocorticosteroids to the nose and bronchi are a highly effective treatment for rhinitis and asthma. Intra-nasal glucocorticosteroids administered for rhinitis have been reported to improve asthma symptoms and to reduce asthma exacerbations leading to emergency department visits.[81, 84–87] However, not all studies have shown an improvement in asthma with intra-nasal glucocorticosteroids in patients with rhinitis and asthma.[88, 89]

The effect of inhaled intra-bronchial glucocorticosteroids on the nasal airway has been less well studied. However, one study reported that orally inhaled budesonide in patients with seasonal allergic rhinitis without asthma caused clinically significant anti-inflammatory effects in the whole airway.[90] This included the nasal mucosa which was not directly exposed to the drug with reduced seasonal eosinophilia both in the circulation and in the nose with a reduction in nasal symptoms. Oral glucocorticosteroids are also highly effective in asthma and rhinitis although its long-term use is limited by side effects.

H1-antihistamines are an important part of the treatment for allergic rhinitis. Some studies have also shown an improvement in asthma with oral antihistamines[91–93] although others have not and they are not currently recommended for the treatment of asthma.[94] Anti-leukotrienes have also been found to be effective in improving allergic rhinitis and asthma.[92, 95–101] The clinical response, however, is highly heterogeneous and they are generally considered as second line or add-on treatments.[79, 102, 103]

The anti-immunoglobulin E monoclonal antibody omalizumab has been shown to be a safe and effective additional treatment in moderate to severe asthma in children and adults. By binding with free IgE, it inhibits the release of mediators and production of cytokines from mast cells and it has also been found to be effective in allergic rhinitis. In patients with concomitant allergic asthma and persistent allergic rhinitis, there is a clinically significant improvement in both asthma and rhinitis with omalizumab.[104] The ability to reduce IgE levels irrespective of allergen specificity means that the role of omalizumab in allergic disease is potentially huge; it has also been used in combination with immunotherapy.

Specific Immunotherapy

Immunotherapy is a technique that involves progressive incremental exposure to causative allergens in order to modulate the immune response and achieve clinical tolerance to the allergens. It may be administered via a subcutaneous (SCIT) or a sublingual (SLIT) route and both have been reported to be effective in allergic disease. Serious complications such as

anaphylactic reactions are uncommon, although are a major limitation of immunotherapy. SLIT is considered to be much safer than SCIT although less effective.[105]

Immunotherapy is reported to be effective in asthma and allergic rhinitis with improvements in symptoms and medication use.[105–109] However, it has also been highlighted that the quality of reporting of most immunotherapy trials is low[110] and there are many questions about immunotherapy that remain unanswered. Nevertheless, immunotherapy has shown promising results. It appears that immunotherapy in children sensitive to a single allergen can alter the natural history of allergy and prevent development of new sensitizations.[111–113] There is also some evidence, although limited at present, that immunotherapy has the potential to prevent the development of asthma in children with allergic rhinoconjunctivitis.[114–117] There is a need for further research in immunotherapy, which may not only have a therapeutic role but may also prevent and alter the natural course of allergic disease.

Surgical management

In addition to improving nasal symptoms, endoscopic sinus surgery (ESS) may also improve asthma in patients with chronic rhinosinusitis and asthma. Studies have shown improved asthma symptoms and control with a reduction in the use of inhalers, systemic medications and hospital admissions for asthma following ESS in chronic rhinosinusitis patients.[118-125] The positive effect on asthma has also been shown to continue long term following ESS,[126] with an improvement in severity of asthma, frequency of attacks and use of asthma medication, at an average follow-up of 6.5 years after surgery in one study.[127] Benefit in children with asthma and chronic sinusitis following ESS has also been reported, with a significant reduction in hospitalizations for asthma, school days missed and symptom scores in asthma and sinusitis.[128]

Lung function tests following ESS in patients with asthma and chronic rhinosinusitis have shown improvement in some studies[120, 122, 129, 130] whilst others have found no improvement.[119, 128, 131] Some have also not found any significant improvement in asthma following ESS in patients with chronic rhinosinusitis with and without nasal polyps.[132, 133] The reported difference in outcomes may be due to the heterogeneity and relatively small numbers of subjects and also to differences in outcome measures in these studies.[52]

The first randomized prospective study comparing medical and surgical treatment of chronic rhinosinusitis with and without polyps in asthmatic patients found subjective and objective improvements in asthma in both treatment groups.[134] However, overall asthma control was better maintained in the medically treated group and medical treatment was also superior to surgery in the subgroup of patients with nasal polyps.

The presence of asthma has been reported to negatively affect the outcome of ESS on the upper airway.[130, 135] Others, however, have found that asthma only has a negative impact on outcome in those with the most extensive sinonasal disease.[136] Furthermore, some report that asthma does not negatively affect outcome after ESS.[137, 138]

QUALITY OF LIFE AND COSTS IN ASTHMA AND RHINITIS

Asthma and allergic rhinitis results in poorer quality of life, demonstrated by the European Community Respiratory Health Survey,[139] a population-based study of young adults, using the SF-36 questionnaire. They found that patients with both asthma and allergic rhinitis had more physical limitations than patients with only allergic rhinitis, but there was no difference between these two groups for aspects related to social/mental health. Patients with allergic rhinitis but not asthma were more likely to have problems with social activities, daily activities as a result of emotional problems, and poorer mental well-being compared to patients with neither asthma nor rhinitis. There were too few patients with asthma without rhinitis to study although it appears that impairment in social life in asthmatics may be related to nasal symptoms.

More recently, however, it has been reported that allergic rhinitis does not seem to further impair health-related quality of life or only has a minor impact in asthmatic patients. Health-related quality of life (based on the SF-36 questionnaire) is markedly reduced in patients with asthma with or without allergic rhinitis, compared to those with allergic rhinitis alone, without any significant difference between those with asthma alone and those with both diseases.[140, 141] Other studies however, have shown that quality of life is worse in patients with asthma and allergic or non-allergic rhinitis compared to those with asthma alone.[142–144]

Rhinitis and asthma are global health problems that cause significant morbidity with loss of productivity and have massive direct and indirect costs. Worldwide, it is estimated that there are 500 million people with allergic rhinitis, 300 million people with asthma and also hundreds of millions of people with non-allergic rhinitis/rhinosinusitis.[79, 145] Although a global problem, there is geographical variation in the prevalence of rhinitis and asthma which tends to be lower in rural communities or low- to middle-income countries compared to Western developed countries.[15] Rhinitis increases asthma costs particularly in children and young adults and those with coexisting asthma and allergic rhinitis have been found to have higher medical care costs by an average of 46% compared to those with asthma alone.[146]

SUMMARY

The upper and lower respiratory tracts are intimately related as demonstrated by the similarities between rhinitis and asthma. Most patients with asthma have coexisting rhinitis whilst many rhinitis patients have asthma and an even greater number demonstrate non-specific bronchial hyperresponsiveness. Rhinitis and asthma are not only linked because they share atopy as a common risk factor; both allergic and non-allergic rhinitis are risk factors for asthma. Inflammation is a key component in the pathogenesis of both rhinitis and asthma and in many respects they appear to be manifestations of the same disease, representing a continuum of disease.

Airway smooth muscle present from the trachea to the bronchioles not only causes bronchoconstriction in asthma but may also be involved by increased proliferation and the expression and secretion of a variety of proinflammatory mediators and cytokines.[35, 36] The difference between rhinitis and asthma may therefore be due to an epithelial-mesenchymal trophic unit[147] in rhinitis whereas in asthma there is an epithelial-mesenchymal-muscular trophic unit. Although the precise interactions between the upper and lower respiratory tracts are not yet fully understood, it is clear that optimal management of patients with rhinitis and asthma requires an integrated upper and lower airway approach.

As rhinitis and asthma often coexist, a combined approach is recommended to investigate and treat the upper and lower airways. Studies strongly support the 1999 World Health Organization workshop 'Allergic rhinitis and its impact on asthma' (ARIA)[1] and the 2008 update,[145] which recommended that:

- Patients with persistent allergic rhinitis should be evaluated for asthma by history, chest examination and, if possible and when necessary, assessment of airflow obstruction before and after bronchodilator;
- History and examination of the upper respiratory tract for allergic rhinitis is performed in patients with asthma;
- Proposal of a strategy combining the treatment of both the upper and lower airway disease in terms of efficacy and safety.

Although there are some recommendations in the treatment of coexisting allergic rhinitis and asthma in the ARIA 2008 update[145] and 2010 revision,[148] further research is required in this area.

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BEST CLINICAL PRACTICE

- ✓ H1-antihistamines are effective in rhinitis.
- ✓ Intra-nasal corticosteroids are effective in rhinitis.
- ✓ Intra-nasal corticosteroids are inconstantly effective in asthma.
- ✓ Intra-nasal corticosteroids may reduce asthma exacerbations.
- ✓ Anti-leukotrienes are often effective in rhinitis and asthma.
- ✓ Anti-IgE monoclonal antibody is effective in both rhinitis and asthma.
- ✓ Allergen-specific immunotherapy is effective in both rhinitis and asthma.

FUTURE RESEARCH

- ➤ More prospective studies should assess the relationship between rhinitis and asthma.
- ➤ More studies are needed to assess nasal and bronchial inflammation in patients with asthma and COPD.
- ➤ Nasal remodelling is poorly understood.
- ➤ More studies are needed to understand the mechanisms of interaction between the upper and lower respiratory tract.
- ➤ Further large pivotal clinical trials are needed to assess whether the treatment of one target organ may improve outcome measures of the other target organ and to assess the specific impact of the different pharmacological agents, immunotherapy and surgery on the whole airway.

KEY POINTS

- The close relationship between the upper respiratory tract and the lower respiratory tract is something that is manifestly observed by all practising rhinologists, demonstrated by the similarities between rhinitis and asthma.
- Rhinitis and asthma may be viewed as ends or parts of a respiratory inflammatory spectrum.
- Most patients with asthma also have rhinitis and many patients with rhinitis have asthma.
- Allergy is associated with rhinitis and asthma.
- Allergic and non-allergic rhinitis are risk factors for asthma.
- Asthma and rhinitis share many common risk factors.
- There are many anatomical and physiological similarities between the upper and lower airways although there are also differences.
- There is a similar inflammatory infiltrate in the upper and lower airways in rhinitis and asthma.
- Bronchial challenge of rhinitis patients leads to nasal inflammation. Nasal challenge induces bronchial inflammation.
- The upper and lower airways not only interact via their anatomical connection but there may also be neural reflexes and systemic mechanisms.
- Treatment of rhinitis may reduce morbidity from asthma and patients with asthma should be assessed for rhinitis and vice versa.
- A combined approach is recommended to treat the upper and lower airways in patients with rhinitis and/or asthma.

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CHAPTER 103

NASAL SEPTUM AND NASAL VALVE

Shahram Anari and Ravinder Singh Natt

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: septoplasty, rhinoplasty, septorhinoplasty, functional rhinoplasty, nasal valve surgery, turbinate surgery and paediatric.

INTRODUCTION

Nasal breathing is the normal path of respiration in human beings. Nasal airway passage accounts for approximately half of the total airway resistance and this resistance is required for optimal respiratory physiology.[1] Nasal airway patency or its resistance can be measured by objective and subjective tools.

Rhinomanometry measures trans-nasal airflow and pressure during respiration to determine nasal airway resistance. Nasal cycle and mucosal pathology play a part in these measurements and would make the results based on one rhinomanometry reading less reliable or reproducible. Taking objective measurements before and after nasal decongestants can help distinguish between mucosal hypertrophy and structural deformity as the cause of nasal obstruction.[2] Acoustic rhinometry determines the nasal cross-sectional area and nasal volume through the analysis of reflected sound pulses within the nasal cavity but the nasal airflow is not included in this method and therefore the effects of dynamic collapse can be missed. Inaccurate placement of the probes during the measurements can also lead to erroneous results.

Due to the inherent problems with the objective measures, subjective tools are more commonly employed in the clinical and research settings. Visual analogue scale appears to be a simple and adequate tool to measure the nasal patency subjectively. The Nasal Obstruction Symptom Evaluation (NOSE) scale is a validated tool for nasal obstruction in adults. The five domains each score 0 (no symptoms) to 4 (severe symptoms) and the result is multiplied by 5 producing a maximum score of 100.[3]

From a practical point, the current technology cannot accurately determine the level or cause of nasal obstruction; clinical examination remains the mainstay of clinical diagnosis.

The nasal airway is composed of two nasal cavities, each with a medial and a lateral wall as well as a floor. The nasal cavity and its elements are referred to in a three-dimensional structure and we follow the terminology demonstrated in **Figure 103.1** in this chapter.

1. **Medial nasal wall:** This is mainly formed by the nasal septum which in itself is composed of bony, cartilaginous and membranous parts. The columella forms the most caudal part of the medial wall.

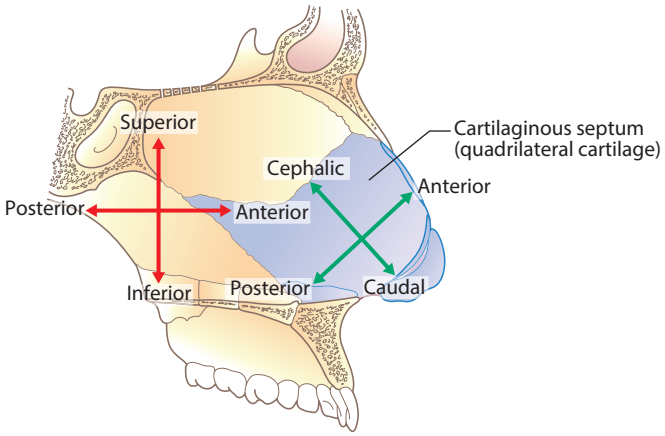


Figure 103.1 Terminology used in nasal and septal orientation. Red arrows refer to the nasal cavity; green arrows refer to the nasal septum.

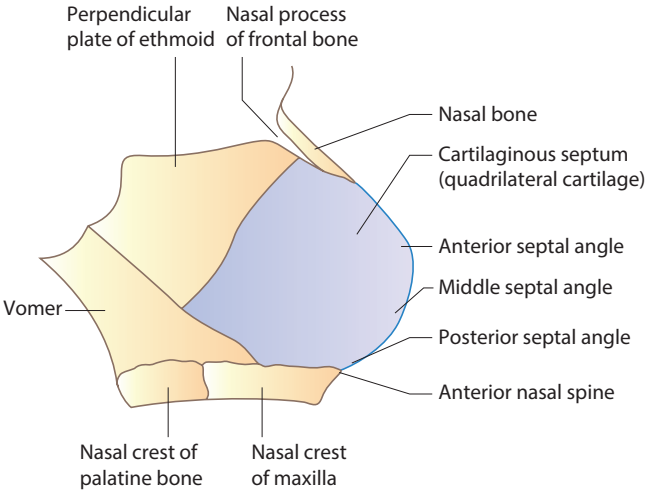


Figure 103. 2 Nasal septal anatomy and its terminology.

2. **Lateral nasal wall:** This is formed by the turbinates, fibrofatty tissue and cartilages (sesamoid cartilages, accessory cartilages, upper lateral cartilage and the lateral crus of the lower lateral cartilage).
3. **Nasal floor:** This wall is formed by the floor of the nasal cavity and the nasal vestibule sill.

The elements involved in the nasal airway could have an adverse effect on the nasal airway patency. These elements are mainly incorporated in the nasal septum and the nasal valve areas and it is essential that they are carefully assessed during clinical examination.

NASAL SEPTUM

ANATOMY

The nasal septum is divided into bony, cartilaginous and membranous parts (from cephalad to caudal). The bony septum is mainly formed by the perpendicular plate of ethmoid and vomer. The palatine bones and maxillary crest form the most posterior parts of the bony septum (Figure 103.2). The cartilaginous septum (i.e. quadrilateral cartilage) is not an isolated cartilage and in fact is in unison with the upper lateral cartilages forming one cartilaginous unit.

AETIOLOGY

Nasal obstruction can be caused by septal deflection which can be developmental or secondary to trauma. In some cases, the trauma occurs in childhood and the patient does not necessarily remember the incident.

DIAGNOSIS

An L-shaped strut of septum measuring approximately one centimetre in width is required to support the external nasal skeleton (Figure 103.3). Deviation at the nasal septum L-strut needs to be differentiated from the obstruction caused by the rest of the septum, as it will have implications on the management.

Septal examination should include inspection as well as palpation. During inspection, the position of deviation should be mapped in relation to the L-strut. Nasendoscopy will allow inspection of the anatomy in the neutral position and it also allows inspection of the elements that are not visible in anterior rhinoscopy; this at times can reveal adenoid tissue, mucosal abnormalities, nasal polyps or choanal pathology which can cause nasal obstruction.

Nasal airflow can be demonstrated by misting of the examination mirror or metal tongue spatula but this technique needs to be used with caution. Absence or reduction of the misting can be suggestive of a structural blockage but a satisfactory amount of misting does not necessarily indicate a patent nasal airway as perceived by the patient. This will be discussed further in the examination of the nasal valve.

Palpation is used to feel for attachment of the septum to the anterior nasal spine and to feel for fracture lines. In patients who have undergone septal surgery in the past, gentle palpation of the septum with an applicator (e.g. Jobson Horne probe) might indicate the areas deficient of cartilage.

During assessment, a decision is to be made as to whether the septal deflection is the sole cause of nasal obstruction. Nasal valve and mucosal elements need to be taken into consideration. The history of constant nasal obstruction points to an anatomical blockage whereas the intermittent obstruction points to the mucosal elements

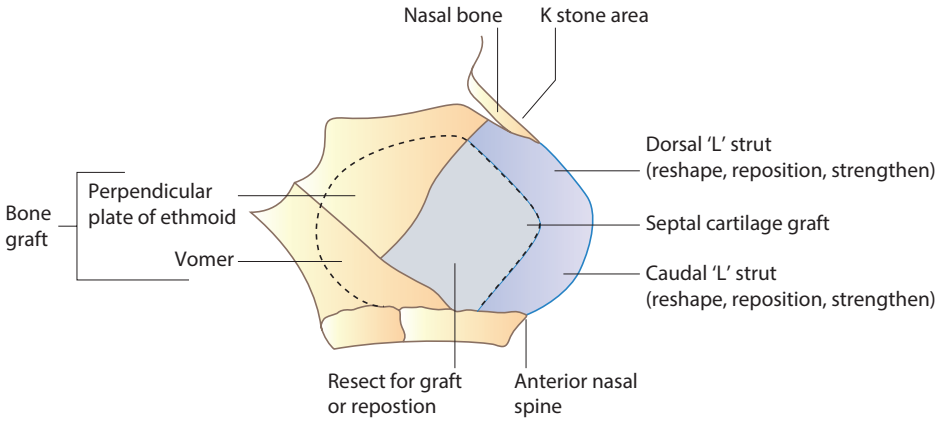


Figure 103.3 Septal cartilaginous L-strut with a minimum 10 mm width is preserved for structural support. The rest of the bony and cartilaginous septum can be used as grafts.

to be at least partially to blame. Significant improvement in nasal obstruction after application of topical nasal decongestants indicates the role of mucosal elements in nasal obstruction. Intermittent nasal obstruction, especially one that changes sides, can be due to nasal cycle. Patients who have had complete nasal obstruction might complain of this phenomenon after their successful nasal airway surgery. If the patient notices obstruction in the lateral decubitus, then the engorgement of turbinates on the dependent side or the collapse of the lateral nasal wall (i.e. nasal valve elements) on the opposite side can be blamed.

TREATMENT

Septal deviation can be present due to the inherent bend of the septal cartilage or as a result of septal tilt due to deviated bony septum. In cases where the septum is inherently straight, the septal tilt may be corrected by addressing the bony attachments; when the cartilage is inherently deformed, special techniques are employed.

Most septal deviations involve the caudal and dorsal L-strut to some degree but in cases where the obstruction does not involve the L-strut, the offending segment can be excised through submucosal resection (SMR).

SUBMUCOSAL RESECTION

In this technique, the L-strut is not addressed therefore a Killian incision for approach would suffice. A Killian incision is placed about 1 cm cephalad from the caudal end of the septum (**Figure 103.4**). At this point the perichondrium is less adherent to the underlying cartilage and the flap can be raised more easily. If the deviation is situated further cephalad, the incision for access can be made close to the offending segment.

The deviated part of the septum is freed from its peripheral cartilaginous and bony attachments. The *in-situ* bony deviation can be in-fractured to put the bony septum in midline or it can be excised conservatively. Bony septum is an invaluable source of graft material for septal reconstruction; therefore the excision should be done conservatively. The harvested septum can then be used as a graft or it can be straightened and reinserted in its place. It can be secured to the remaining septum by sutures to avoid migration; some authors prefer to secure it by inserting bilateral intra-nasal splints.

SEPTOPLASTY

In most cases of septal deviation, the septal L-strut is involved. SMR is not effective in these cases as it cannot address the caudal and dorsal struts. Septoplasty techniques are needed to address these problems and the approach should provide access to the L-strut.

Hemitransfixion incision is designed to provide access to the whole septum including the caudal L-strut. The incision is placed at the caudal edge of the septum. The length of the incision depends on the access required (**Figure 103.4**). If access is required to the whole of caudal arm of the L-strut then a full hemitransfixion is used. However, if access is not required for the most posterior parts of the septum, then a partial hemitransfixion would suffice. If access is required to the floor of the nasal cavity then an extended hemitransfixion incision is used.

Generally, raising the mucosal flap on the concave side would be enough to allow access for excision of septal cartilage and bone, to detach the septal osseocartilaginous junction, to score the concave side and apply other relevant techniques. It also reduces the chance of septal perforation by keeping the opposite mucosa intact. In certain conditions, both mucosal flaps are raised, especially when the surgeon would like to keep the sutures in the mucosal envelope or in cases where access to both sides of the septum is required (e.g. S-shaped septal deformity).

Caudally, the perichondrium is adherent to the septal cartilage and care must be taken to identify the actual plane of dissection at the subperichondrial level. This can be achieved by scoring the area to find the desired plane.

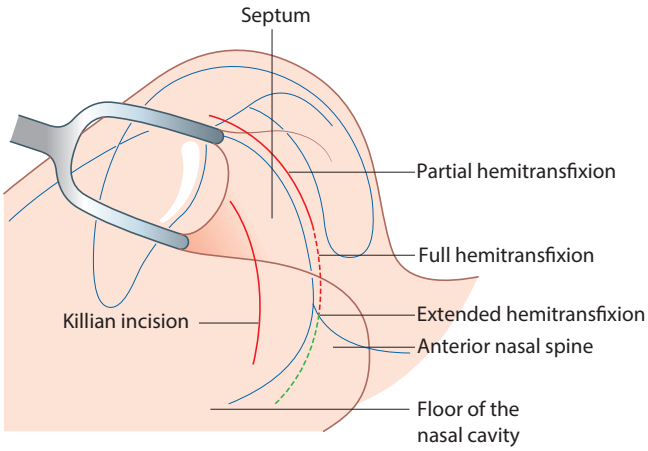


Figure 103.4 Placement of different incisions for approach to the septum.

If the flap is raised at the correct plane, minimal to no bleeding is encountered. The extent of the flap elevation depends on the plan of surgery. The flap can be raised as far cephalically as possible to have access to the perpendicular plate of ethmoid for harvesting bony grafts. Often it is easier to raise the flap anteriorly as far cephalically as possible and then to change direction more posteriorly and raise the flap from cephalic position caudally (i.e. back to front) by the help of a Pennington septum elevator (Figure 103.5).

When the bony osseocartilaginous junction between the quadrilateral cartilage and the bony septum is reached, this junction is disarticulated to gain access to the opposite side of the bony septum. Care must be taken not to perforate the mucosa on the other side when raising the mucosal flap from the opposite side of the bony septum. Often the disarticulation is not enough to allow the cartilaginous septum to return to midline and a sliver of bone or cartilage needs to be removed. The excision should be planned carefully to remove the bony or cartilaginous pieces as usable grafts rather than excising them piecemeal. Disarticulation of the quadrilateral cartilage from the maxillary crest is required to allow the septum to move to midline; often a sliver of bone or cartilage needs to be removed. The 1 cm of bony-cartilaginous junction at the L-strut is left undisturbed if possible but often this area requires special attention.

If access is required to the floor of the nasal cavity then an extended hemitransfixion is applied (Figure 103.4).

Pennington Septum Elevator, Double-Ended

Catalog#	Description	Length	Width 1	Width 2
20–246*	Right and left	8-1/4″ (210 mm)	4 mm	4.5 mm

*Miltex® Brand



Figure 103.5 Pennington septum elevator.

This would allow raising a tunnel underneath the septal spur which reduces the chance of mucosal tear over the spur (Figure 103.6). Raising the flap over a spetal spur can be challenging as the perichondrial fibres of the cartilaginous septum and the periosteal fibres of the maxillary crest are interwoven. To reduce the chance of mucosal tear, two techniques can be employed.

BACK TO FRONT TECHNIQUE (CEPHALAD TO CAUDAL)

In this technique, the flap is raised more anteriorly at the caudal septum and raised towards the cephalic position; the direction of dissection is then moved posteriorly and the flap is raised from the cephalic position caudally. This way the plane of dissection is at the correct subperiosteal level initially and then continues at the subperichondrial level reducing the chance of mucosal tear.

FRONT TO BACK TECHNIQUE

In this technique, the mucoperichondrial flap is raised over the quadrilateral cartilage and the bony septum; this constitutes the anterior tunnel over the spur. Then another subperiosteal tunnel is raised posterior to the septal spur which constitutes the posterior tunnel (Figure 103.6). The mucosa left attached to the most prominent part of

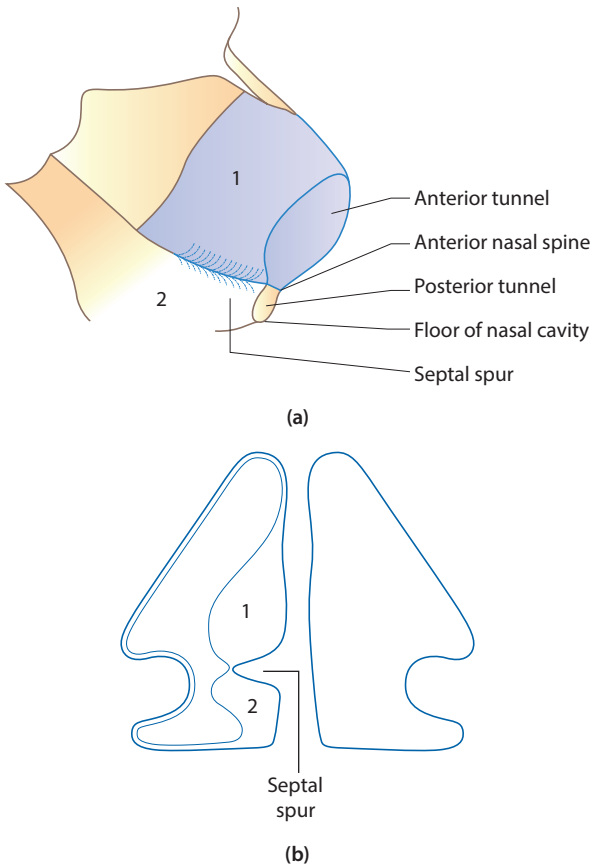


Figure 103.6 Anterior **(1)** and posterior **(2)** tunnels are raised to reduce the chance of mucosal tear over the septal spur.

spur is then addressed by sharp dissection without the tension of the mucosa on either side.

SEPTOPLASTY TECHNIQUES

In septoplasty, the attention is more on reconstruction rather than excision. The excision alone can be performed as SMR on the body of the septum but deviations of the L-strut require special reconstructive techniques.[4]

The deviated septum can be addressed by 1) Cutting techniques, 2) Grafting techniques, 3) Suturing techniques, and 4) Relocating techniques. The techniques can be used alone or in combination.

The surgical techniques described here are not exhaustive; the techniques and the choice of equipment and sutures are those of the senior author's (SA) who has found them reliable and reproducible.

CUTTING TECHNIQUES

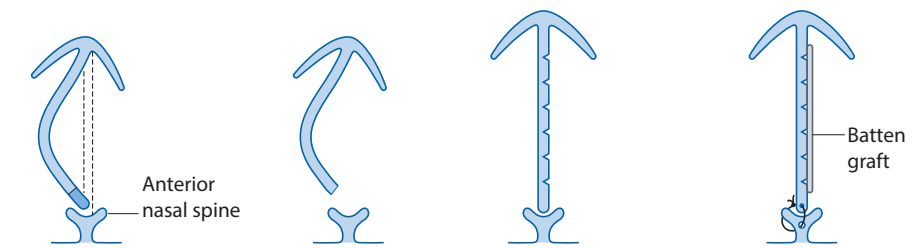
Scoring of the septal cartilage on the concave side allows the septum to become straight, eliminating the deviation. The septum will be kept in position by the scar tissue in grooves created by scoring on the concave side; therefore, the septum should be kept in position, free of any tension until the scar tissue is set in place. This technique is not wholly reliable as under-scoring or over-scoring can result in unsatisfactory results. Also, if the flap is only raised on the concave side, the result of warping might be delayed due to the effects of attached perichondrium on the other side. For these reasons, it will be more predictable if the scored segment is splinted against a batten graft. In S-shaped septal deformities, the scoring needs to be done on the concave segments on both sides; hence the need for raising bilateral mucoperichondrial flaps. If the septum is fractured, the fractured line needs to be weakened by scoring or cutting through to allow the septum to return to midline; in this instance the concomitant grafting technique (splinting) is recommended.

Caudal septal deviation or dislocation is often addressed by excising the excess cartilage at the caudal arm of the L-strut. In the swinging door technique, an appropriate amount of caudal L-strut is excised to allow the septum to return to the midline.[5] The septum then needs to be secured to the midline again; this can be achieved by suturing the septum back to the anterior nasal spine or its periosteum. To apply sutures to the anterior nasal spine, a hole is made in the bone using a strong hypodermic needle or using a drill with a Fissure burr. The septum is then secured in place with 4 x 0 PDS sutures. Scoring technique is used to correct the convexity but the septum is splinted with a graft in order to avoid unsatisfactory results due to under-scoring or over-scoring (**Figure 103.7**).

Often the deviation at the dorsal L-strut of the quadrilateral cartilage is because of deviation of the bony attachment to the perpendicular plate of ethmoid. In these cases, the osseocartilaginous junction needs to be disarticulated all the way through (and sometimes encroaching into the last 1–1.5 cm). Traditional teaching warns us of septal collapse if this segment is disturbed; however this is simply not true. The quadrilateral cartilage of the septum is attached to the upper lateral cartilages and as long as this attachment and the attachment of the upper lateral cartilages to the nasal bones are intact and the bones are secure and stable, the septum will not collapse. If the bony cartilaginous junction at the dorsal L-strut needs to be disarticulated fully, it should be clearly documented in the operative notes for future operations.

GRAFTING TECHNIQUES

Often the deviated septum can be kept in a straight line if it is splinted against a graft. Both septal cartilage and septal bone (from perpendicular plate of ethmoid or from vomer) can be used for this purpose. The perpendicular plate of ethmoid is stronger and thinner compared to the septal cartilage.[6, 7] The technique involves harvesting a suitable piece of perpendicular plate of ethmoid which is then thinned down using a large diamond burr (e.g. 5 mm diamond burr). The graft is then perforated using a Fissure burr and it is splinted against the concave side of the septum (**Figure 103.8**). Care must be taken to position the bony strut a few millimetres from the septal edge so that it is not felt by the patient and it does not cause obstruction for dorsal reconstruction (e.g. spreader grafts). Often the septum is scored to



(a) Excess septal length in deviated position

(b) Excess septum excised

(c) Scoring, straightening and lengthening of the septum

(d) Septum fixed to anterior nasal spine

Figure 103.7 Swinging door technique is a reliable method in dealing with anterior septal deviations: **(a)** Septal convexity to the right has resulted in excess caudal septal length, **(b)** The excess length of the septum is excised, **(c)** The height of septum is restored after scoring of the concave side, **(d)** The weakened septum is splinted against a batten graft and secured to the midline.

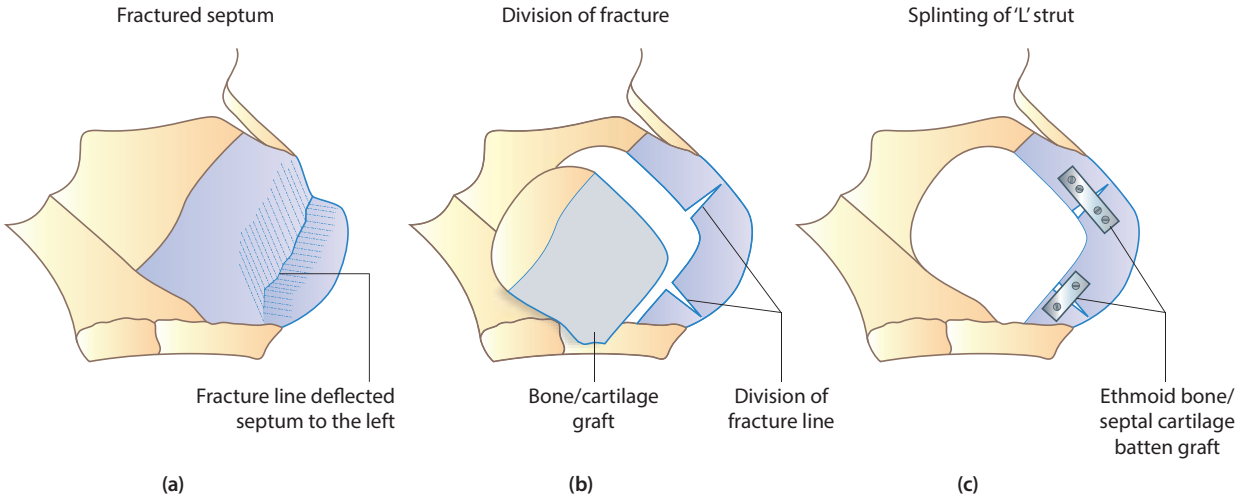


Figure 103.8 Septal bony grafts form the perpendicular plate of ethmoid are used to splint the deviated or fractured parts of the cartilaginous septum: **(a)** Left septal deviation with a vertical fracture line is demonstrated, **(b)** The graft is harvested from the body of septum and the fracture line on the L-strut is cut through and divided, **(c)** The septum is splinted with an ethmoid bone graft.

make it more pliable to conform to the straight ethmoid bone. A fine absorbable or non-absorbable suture is used to secure the graft to the septum (e.g. 5×0 PDS®). This technique is more reliable than scoring alone as it eliminates the chance of residual deviation or over-correction due to underscoring or overscoring. A graft made from the septal bone can cause rigidity to the caudal septum; a side effect less noticeable if the batten graft is fashioned from the cartilaginous septum.

The deviation of the dorsal L-strut can be corrected by spreader grafts too. The concave part of the dorsal septum is scored to weaken the septum and to allow it to return to the midline; it is then splinted by spreader grafts and secured in place by sutures (e.g. 5×0 PDS®). For this particular technique, external approach provides better access of visualization however spreader grafts can be inserted through endonasal approach too.

SUTURING TECHNIQUES

A mattress suture can be used to control the septal curvature.[8] In this technique, the septum is first scored (preferably underscored) just enough to make it pliable so it can be shaped and kept in shape by fine sutures. The entrance and exit sutures are placed on the convex side and the knot is incrementally tightened until the desired position and shape is achieved. A fine non-absorbable suture (e.g. 5×0 Prolene®) is used for this purpose and bilateral mucoperichondrial flaps are raised so that the suture is covered by the septal mucosa.

RELOCATING TECHNIQUES

These techniques are used when the septum is dislocated off the midline and it only requires reinsertion onto the maxillary crest. The septum needs to be secured in its midline position and this is achieved by suturing the septum either onto the periosteum of the anterior nasal spine or to the actual bone by drilling a hole onto it. Fine absorbable or non-absorbable sutures can be used for this purpose. At times other surgical techniques such as scoring and grafting are required to keep the septum in midline.

Often a deviated caudal septum can be improved by door-stop technique where the septal cartilage is dissected free along the maxillary crest and is relocated over the nasal spine which acts as a door stop and secures the caudal septum in a straighter position.[9]

SPECIAL SEPTOPLASTY CONSIDERATIONS

There are special cases related to septoplasty which deserve to be discussed separately.

Endoscopic septoplasty

This technique can be used to improve visualization particularly of more cephalic septal deformities. It also allows minimal access dissection to reach isolated deviated parts of the septum (more relevant in revision cases). Endoscopic septoplasty can be used concomitantly along with sinus surgery. It is also an effective teaching tool.[10]

External approach septoplasty

Most septoplasty techniques can be performed through the endonasal approach; in certain situations especially where the dorsal L-strut deformity is concerned, the external approach septoplasty can improve surgical access. External septorhinoplasty is also favourable in complex septal reconstructive cases such as extracorporeal septoplasty.

Extracorporeal septoplasty

In cases of a severely fractured and deformed septum, the correction and reconstruction can be achieved through an extracorporeal technique.[11] In this method, the septum (both cartilaginous and the bony segment) is excised in one piece as intact as possible. This requires detachment of the cartilaginous septum from upper lateral cartilages and its attachment to the maxillary crest posteriorly. The septum is then measured and a template is made to represent the new septum. Now two different techniques can be employed:

1. **Re-orientation**: The new L-strut is harvested from a straight section of the excised septum and it is re-inserted in place.
2. **Reconstruction**: The septum is reconstructed by a variety of techniques (as described before) and then reinserted in its place. In cases of fractured septum, the fracture line is cut through or weakened to straighten the septum and then the septum is splinted against a graft as previously described. In cases where the septum is broken into many pieces, the segments of septum are splinted against a sheet of thinned down perpendicular plate of ethmoid or a PDS sheet (like a jigsaw puzzle). A fine absorbable or non-absorbable suture (e.g. 5x0 PDS®) is used to secure the pieces of septum to the ethmoid bone graft or the PDS sheet.

The neo-septum is then reinserted into its position. A Fissure burr is used to make a groove onto the maxillary crest for the septum to rest on. A hole is also made onto the anterior nasal spine so that the septum is secured caudally (e.g. 4×0 PDS®). The second point of fixation is to the upper lateral cartilages (e.g. 5×0 Prolene® or PDS). For further security, the neo-septum can be secured to the nasal bones at the K-stone area.

Paediatric septoplasty

There remains controversy about the optimal age and extent of septal surgery in the paediatric population. However, studies have demonstrated that septal surgery performed in children as young as 6 years old provides long-term satisfactory outcomes.[12, 13] Delaying operation on children with deformed nasal skeleton and septal deformities can adversely affect nasal and facial growth and it prolongs patients' suffering from nasal blockage.[12]

Surgeons have addressed septal deformity in children with a range of techniques from closed reduction of septal deviation to the extracorporeal technique through an external approach septorhinoplasty.[12, 14]

The most important aspect of surgery is to resect the cartilage conservatively and to avoid disrupting the endochondral ossification plates if possible. Excision should be kept to minimum and any excised segment should be reinserted after remodelling.[12]

Evidence from cleft rhinoplasty and septal surgery is used by those advocating surgical intervention in earlier years and justifying more extensive surgery, however, it is wise to avoid over-enthusiastic septal surgery in early years especially if the nasal blockage is unilateral delaying the definitive surgery to later teen years and early adulthood.

NASAL VALVE

The nasal valve is the narrowest portion of the nasal airway. Failure to properly address the nasal valve at primary surgery has been the cause of persistent nasal obstruction in a large proportion of failed septoplasties.[15] The nasal valve is the area caudal to the nasal bones and it is unique in two aspects: 1) It contains the narrowest section of the nasal airway (i.e. internal nasal valve), and 2) It contains a mobile collapsible segment (i.e. lateral nasal wall and its contents).

The nasal valve has traditionally been divided into two 3D-areas: 1) Internal nasal valve, and 2) External nasal valve. This division is arbitrary as in reality there is no clear line between them and they are connected to each other through the lateral nasal wall soft tissues (e.g. at the scroll area).

ANATOMY

The described boundaries of nasal valves have not been consistent in the literature. For the purpose of this chapter, we describe each nasal valve with the following three walls (**Figure 103.9**).

Internal valve

- **Medial wall**: septum
- **Lateral wall**: caudal end of the upper lateral cartilage (ULC), anterior part of the inferior turbinate
- **Nasal floor**: floor of the bony aperture.

External valve

- **Medial wall**: septum, columella
- **Lateral wall**: lateral crus of the lower lateral cartilage (LLC), fibrofatty alar lobule
- **Nasal floor**: nasal sill.

The lateral nasal wall weak triangle contains the sesamoid cartilages and lies between the defined boundaries of the two valves forming part of their lateral walls. There is no universal term for this part of the nasal wall and different terms have been used interchangeably (e.g. weak lateral triangle, external lateral triangle).

Nasal valve angle refers to the angle between the caudal edge of the ULC and the septum, and it is measured at 10–15 degrees in Caucasian Leptorrhine noses (i.e. long narrow noses mostly seen in white individuals as opposed

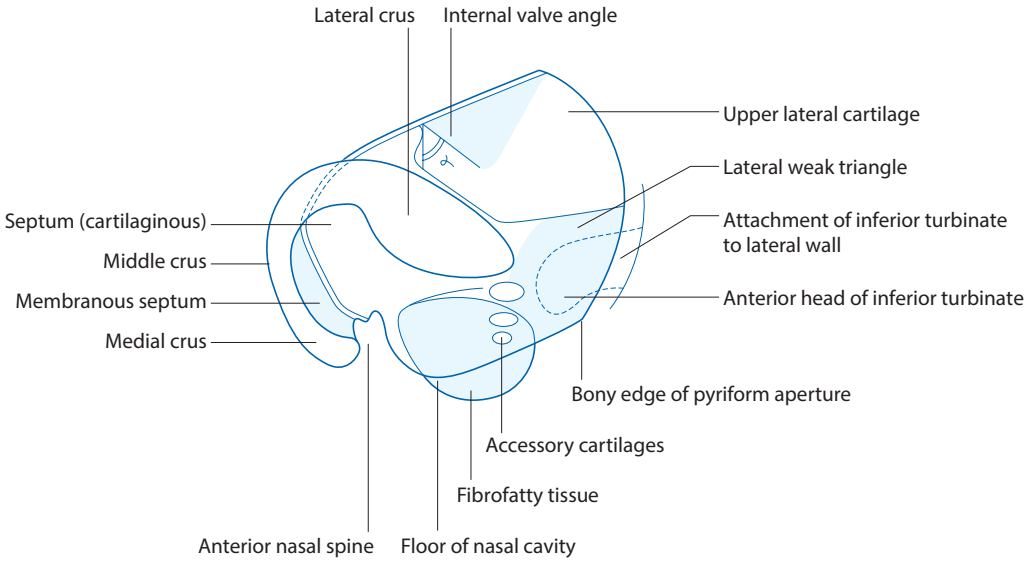


Figure 103.9 The elements incorporated in the nasal valve walls are demonstrated.

to the flat broad Platyrrhine noses seen in the black population). More acute internal nasal valve angles can be associated with nasal blockage and result in dynamic external valve collapse.

AETIOLOGY

The obstruction at the nasal valve can occur due to:

- **Static narrowing**: the nasal airway is narrowed or blocked secondary to deformed anatomy (e.g. congenital, developmental, traumatic or iatrogenic).
- **Dynamic collapse**: in this situation, the nasal airway is patent at rest and in expiration but the lateral wall collapses due to increased intra luminal negative pressure during inspiration. Dynamic collapse follows Poiseuille's principle and the Venturi effect (See Volume 2, Chapter 28) and the surgeon needs to understand the interplay between the nasal airflow, nasal wall resistance and the cross-sectional area of the nasal valve. To address the dynamic collapse, the surgeon needs to increase the cross-sectional area of the nasal airway on the collapsing side and/or strengthen the weakened lateral nasal wall. Also, increasing the airflow on the opposite side will help reduce the excessive flow on the collapsing side, improving the dynamic collapse.

Anatomical narrowing of the nasal valve is caused by the elements in the nasal valve walls.

Medial wall

1. **Septum**: anterior septal deviation or caudal dislocation can narrow the nasal valve area.
2. **Columella**: widened columella is caused by prominent footplates or prominent soft tissue (e.g. depressor septi nasi muscle). Asymmetry, dislocation and deviation of the footplate can narrow the external nasal valve.

Lateral wall

1. **ULC**: anatomical narrowing of the internal valve angle, sequela of lateral osteotomy (e.g. pinched bony nose and medialized ULC).
2. **Lateral crus of LLC**: Its configuration and alignment (e.g. cephalic position) can predispose to nasal obstruction.
3. **Fibrofatty tissue (alar lobule and lateral nasal wall weak triangle)**: Its medialization usually follows weakened or medialized cartilaginous support (e.g. aggressive cephalic trimming, facial palsy).
4. **Inferior turbinate**: Mucosal swelling or bony prominence.

Nasal floor

1. **Soft tissue stenosis**: Developmental or iatrogenic (i.e. secondary to alar base surgery)
2. Bony aperture stenosis is a rare condition but it can be corrected surgically.

DIAGNOSIS

A thorough nasal examination is essential in diagnosing the cause of nasal blockage. Attention to nasal septal deformity as well as the nasal valve area is paramount. In many cases of dynamic external valve collapse, the internal valve is the culprit.

Misting of the examination mirror or a metal tongue spatula on nasal expiration does not equate with a patent nasal airway as it is perceived by the patient. In fact, lack of misting on the spatula test is a more reliable method to demonstrate nasal blockage; in these cases if the lack of misting persists despite adequate decongestion, it confirms static structural obstruction. Misting test relies on nasal expiratory flow and it can therefore miss the dynamic collapse which only occurs on inspiration.

A nasal speculum can be used to examine the anterior nasal cavity; however, the nasal airway and the valve area should be examined by an endoscope to assess the anatomy

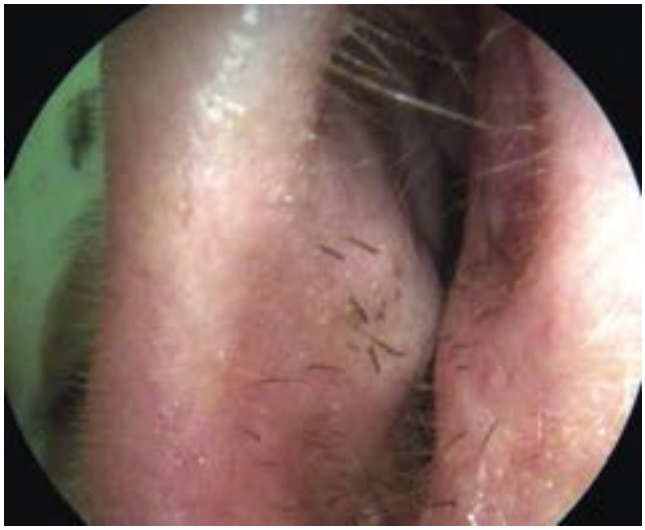


Figure 103.10 The nasal airway and the nasal valve should be inspected in its neutral position. Nasal speculum can distort the anatomy and can hide the culprit. (Reprinted with permission from Anari S. Nasal Valve Surgery. *ENT News & Audiology* 2013; **22**(3): 44–6).



Figure 103.11 Cottle's manoeuvre is not a specific test for the external valve. The internal valve is also affected via its attachments to the external valve elements; **(a)** Internal valve angle in resting position, **(b)** Opening of the internal nasal valve angle during Cottle's manoeuvre. (Reprinted with permission from Anari S. Nasal Valve Surgery. *ENT News & Audiology* 2013; **22**(3): 44–6).

in its neutral position. Using a nasal speculum can distort the anatomy and can obscure the culprit (Figure 103.10). Nasal airway should be assessed at rest as well as inspiration and expiration; it should also be re-examined after nasal decongestion. Considerable improvement in nasal blockage after decongestion highlights the role of mucosal congestion in nasal obstruction. Treatment of the allergic elements and addressing the inferior turbinates should be part of the management plan in these cases.

Manipulation of the elements on the lateral nasal wall is required to identify the cause of the nasal valve blockage. Cottle's manoeuvre (i.e. gently pulling the cheek laterally) increases the cross-sectional area of the nasal valve however it is not a specific test as it lateralizes elements incorporated in the lateral walls of both the external and the internal nasal valves (Figure 103.11). Also, a person with normal nasal airway would generally perceive increased nasal patency with Cottle's manoeuvre. Perhaps a negative Cottle's test is more informative suggesting that the cause of the nasal blockage does not rest in the lateral nasal wall.

A more precise way of examining the lateral nasal wall is by modified Cottle's manoeuvre where a soft-tipped instrument (i.e. Jobson Horne probe) is used to assess the structures internally. The probe can be used to lateralize each element very conservatively to assess patient's perception of nasal patency improvement during inspiration.

TREATMENT

Nasal valve dilators (e.g. Breathe Right® or Nozovent®) (Figure 103.12) and nasal steroid medications play a part in the non-surgical management of nasal valve obstruction.

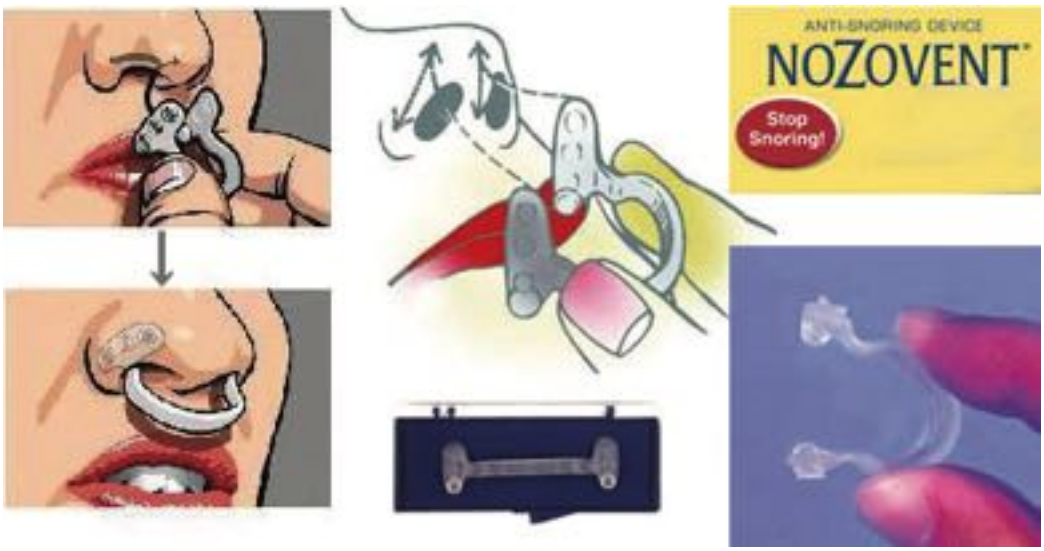


Figure 103.12 Nozovent.

The surgical techniques are divided into: 1) Cutting techniques (incision and excision); 2) Suturing techniques; 3) Grafting techniques; and 4) Relocating techniques.

The following list of surgical techniques is not exhaustive but the senior author has found them to be effective. The techniques are aimed at each of the offending segments.

Septum

The techniques to address the deviated septum have already been described in the previous section of this chapter.

Upper lateral cartilage

CUTTING TECHNIQUES

In cases where the internal nasal valve is narrow, excision of a few millimetres of the caudal ULC can increase the valve angle. This is based on the principle that the angle between the septum and upper lateral cartilage increases when moving cephalad. This can be achieved through external rhinoplasty as well as endonasal approach. If the length of the ULC is reduced, the excess mucosa needs to be trimmed to prevent obstructing the angle.[16]

SUTURING TECHNIQUES

The ULC can be flared using a suture connecting them to each other (Figure 103.13). This allows increase in the internal nasal valve angle. The knot needs to be tied incrementally to achieve the beneficial effect but to avoid undesirable aesthetic changes.[17] This technique can be used along with spreader grafts to maximize the benefit.

Suspension sutures can be used to improve the internal valve area (Figure 103.14). A non-absorbable suture is used to anchor the ULC to the adjacent bony structures (e.g. orbital rim or frontal process of the maxilla).[18] To improve the efficacy of this technique, the midfacial and nasal soft tissues need to be extensively undermined and the sutures should be placed without tension.

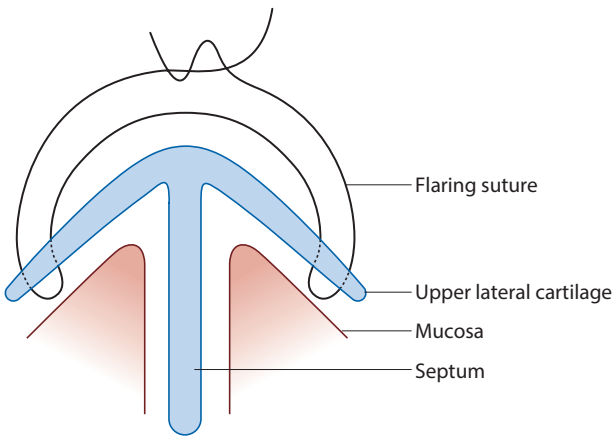


Figure 103.13 Flaring suture is used to splay the upper lateral cartilages and to open up the internal nasal valve angle and the cross sectional area of the internal valve.

GRAFTING TECHNIQUES

Spreader grafts are used to reconstruct the dorsal 'T' junction between the ULC and septum (Figure 103.15). Their use is both for functional and aesthetic purposes although some argue the magnitude of their functional advantage. These grafts can be inserted through the endonasal and external approach.[19]

Butterfly grafts can be taken from the septum or conchal cartilage and they saddle the dorsum to open up the midnasal vault and internal valve. They could have an undesirable aesthetic effect causing the supra-tip fullness. To reduce the supra-tip fullness, a hosting groove can be carved on the septal dorsum.[20]

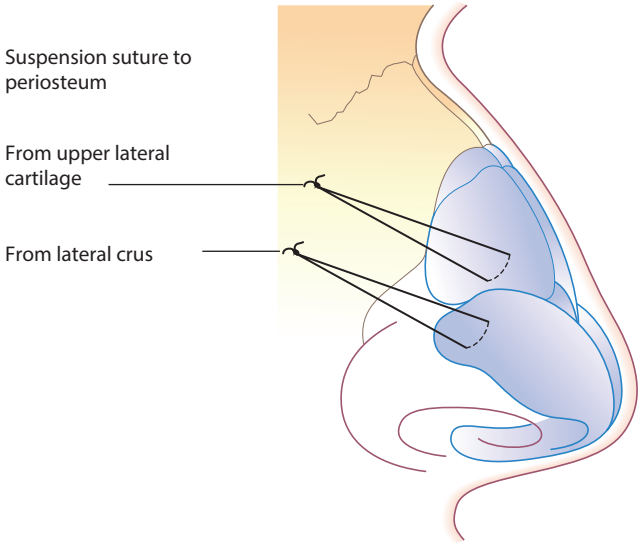


Figure 103.14 Suspension sutures can prevent the collapse of the lateral nasal wall.

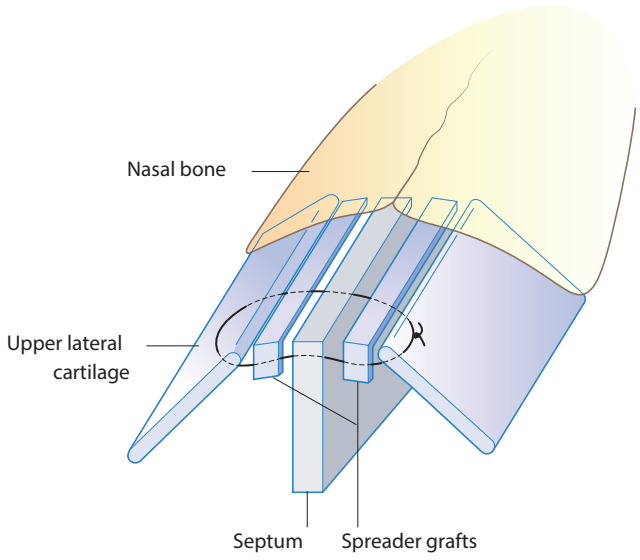


Figure 103.15 Spreader grafts are placed between the upper lateral cartilages and the septum to reconstruct the dorsal septal 'T' segment.

Lateral crus of LLC

CUTTING TECHNIQUES

In cases of nasal tip ptosis (e.g. ageing nose), lateral crus trans-section and overlap (i.e. lateral crural overlay) results in improvement in nasolabial angle and air flow dynamics.[21, 22]

SUTURING TECHNIQUES

Mattress sutures are used to control the lateral crus curvature.[8] Cases of extreme convexity which result in invagination of the crus into the nasal vestibule can be corrected this way (**Figure 103.10**). The domal formation sutures can result in straightening of the lateral crus too.

Spanning sutures have been designed for nasal tip refinement but as they alter the tilt of the lateral crus, they increase support for the nasal side wall too. This is essentially a mattress suture securing the two lateral crura together. This suture is very powerful and it should be used to keep the crura in the desirable position; too much tension on the suture can have adverse effects and could lead to alar retraction.[23]

Alar expansion sutures are essentially mattress sutures designed to splay the lateral crura and improve the valve area. The tension on these sutures should be controlled as they can cause alar retraction.[24]

Lateral crus suspension sutures are used to support the lateral nasal wall (**Figure 103.14**). These are similar in principle and method of execution to suspension sutures used for ULC.[18]

GRAFTING TECHNIQUES

The lateral crus strut graft or alar strut graft is often a septal graft that is secured between the vestibular skin and the defective lateral crus and it may rest over the bony piriform aperture for further stability (**Figure 103.16**).[25] In some cases, a shorter version of the graft (the so-called mini-strut) is inserted underneath the lateral crus to strengthen it and to bring the severely convex or concave lateral crus to a more straightened configuration.

The alar batten graft is usually taken from the septal or conchal cartilage and placed in a subcutaneous pocket over the point of maximum collapse of the lateral nasal wall (**Figure 103.16**). This graft can be positioned cephalad, caudal or on the lateral crus and can extend over the bony piriform aperture for further stability.[26]

Spanning grafts straddle the dorsal septum and they are attached to the lateral crura keeping them in the desired orientation and position. If required, a groove on the dorsal edge of the septum can host the graft preventing supratip fullness.[23]

At times, an extremely convex or concave lateral crus can be completely excised from its bed and reinserted on the opposite side. Also the strip of cephalic trim can be used to splint the remaining lateral crus strip and reduce the excessive curvature; these techniques are described in a variety of names and fashions (e.g. turn-in flap, turnover grafts, flip-flop grafts etc.).

RELOCATING TECHNIQUES

A cephalically-positioned lateral crus can lead to reduced support for the lateral nasal wall which can lead to external valve collapse. Reorientation of the lateral crus can be achieved by elevating the lateral crus from its original bed and reinserting it into a more caudal and posterior position (**Figure 103.17**). The lateral crus is repositioned on its own or with the added structural support of a strut graft usually taken from septum. This technique has been described both through the endonasal and external approach but the latter is technically less challenging.[27]

Fibrofatty tissue

GRAFTING TECHNIQUES

Non-anatomic grafts (such as alar rim grafts or lateral wall grafts) are used to strengthen the collapsible lateral nasal wall (**Figure 103.16**). The grafts should be carved thin enough to cause little aesthetic disfigurement and yet they need to be strong enough to increase lateral nasal wall strength.

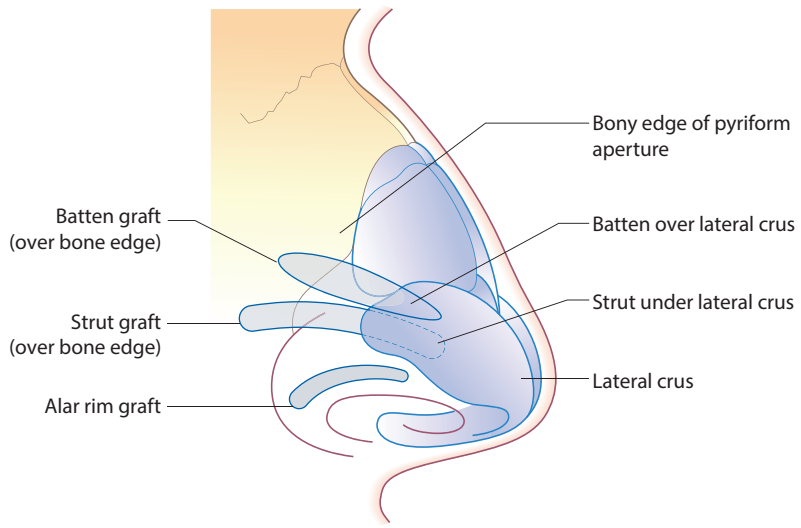


Figure 103.16 Position of alar strut, batten and rim grafts to support the lateral nasal wall from collapse.

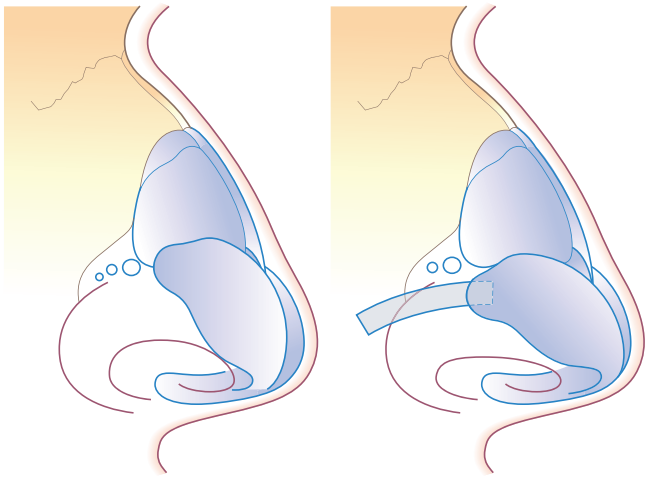


Figure 103.17 Repositioning of the lateral crus: **(a)** Lateral crus of the lower lateral cartilage is in its cephalic position (i.e. malposition). In this position, there is less support for the lateral nasal wall and the lateral nasal wall is prone to collapse on inspiration, **(b)** the lateral crus is repositioned into its orthotopic position with the help of a lateral crus strut graft. The lateral nasal wall has greater support in this position.

They are usually inserted in tight subcutaneous pockets over the maximum point of nasal wall collapse.

SUTURING TECHNIQUES

Lateral nasal wall suspension sutures are used to improve the narrowing in this segment.[28] Often the sutures are applied to the upper lateral cartilage or the lateral crus of the lower lateral cartilage and as a result the lateral nasal wall lateralizes (**Figure 103.14**). When the sutures are applied to the cartilage rather than the fibrofatty soft tissue, the result seems to last longer.

Inferior turbinates

Inferior turbinate enlargement can be compensatory on the opposite side of nasal obstruction or it can be part of the inflammatory nasal condition (e.g. allergic rhinitis).

The surgical techniques aim to reduce the size of inferior turbinates by reducing the conchal bone or the submucosal expansile venous plexus (See Chapter 105).[29] Cryosurgery, laser cautery, submucous electrocautery, linear mucosal diathermy, microdebridement of the submucosal venous plexus and radiofrequency have been used to address the dynamic mucosal element of the inferior turbinate engorgement. Radiofrequency-assisted turbinate reduction surgery has been suggested to cause minimal disruption to nasal function.[30]

In cases of bony enlargement, the conchal bone is reduced while preserving the mucosa. Turbinate outfracture can improve the nasal airway with minimal trauma to the nasal lining, however the anterior head of the inferior turbinate – which plays an important part in the nasal valve area – is not easily amenable to lateralization.

Nasal sill/vestibule

CUTTING TECHNIQUES

Z-plasty is performed to improve the nasal valve narrowing.[31] This technique is to address the stenosis at the internal valve angle mostly caused by inappropriate septo(rhino)plasty incisions and closure techniques.

GRAFTING TECHNIQUES

Composite skin and cartilage grafts harvested from the pinna concha can be used to improve the stenosis at the internal valve angle or the nasal sill (depending on the source of stenosis).

Columella

Widening of the columella can narrow the nostril size and result in external nasal valve narrowing. Widening of the columella or a protruding footplate can be addressed by excising, relocating or suturing techniques.[32] Grafting techniques (e.g. columella strut graft) can improve the nasal droopy tip and improve nasal airflow dynamics; this is a commonly performed step in treatment of the ageing nose.

DRESSING AND SPLINTS IN NASAL AIRWAY SURGERY

The use of post-operative nasal packing remains a varied practice. Careful dissection and minimal trauma during surgery makes risk of bleeding minimal and obviates the need for nasal packing which would save the patient the discomfort of subsequent nasal pack removal. Septal quilting sutures have demonstrated a greater reduction in post-operative haematoma complications and have improved patient satisfaction in comparison with nasal packing.[33, 34]

Some surgeons use septal splints to prevent adhesions especially when septal mucosal lacerations are present and concomitant turbinate surgery has been performed. Some use septal splints as an extra support for the septum especially when extensive reconstructive surgery has been performed.[35]

Most surgeons protect the outer nasal skeleton after external septoplasty and nasal valve surgery by applying an external splint. Thermoplastic splints or Plaster of Paris can be applied without the need to pinch the nasal skeleton – an action that is best avoided if suturing or grafting techniques of nasal valve surgery have been employed.

COMPLICATIONS

Complications may arise from septal surgery but they are mostly due to poor surgical planning and operative techniques. These include bleeding, infection, saddle deformity, nasal tip depression, septal perforation, adhesion, septal haematoma, septal abscess, sensory changes including upper dental anaesthesia and upper incisors teeth discolouration.[34, 36]

Certain aspects of nasal surgery may not necessarily be considered as complications but more as anticipated side effects; they should be discussed with patients (e.g. rigidity of the septum and nose after certain techniques especially bone grafting techniques; aesthetic changes associated with nasal valve surgery).

CONCLUSION

Septum and nasal valve both play important parts in the nasal airway. The result of nasal airway surgery is dependent on the correct diagnosis and execution of the relevant techniques related to the offending segment of the nasal airway.

The patient must also be informed that almost all of the above nasal valve techniques will result in some aesthetic change to their nose. The option of surgical treatment should be discussed with this side effect in mind. When patients decline major nasal valve surgery which could result in noticeable aesthetic changes, a combination of septal surgery, turbinate surgery and minor nasal valve surgery can achieve comparable results with minimal aesthetic changes.[37]

BEST CLINICAL PRACTICE

- ✓ In most cases of septal deviation, the septal L-strut is involved. SMR is not effective in these cases as it cannot address the caudal and dorsal struts; septoplasty techniques are needed.
- ✓ In certain situations, especially where the dorsal L-strut deformity is concerned, external approach septoplasty can improve surgical access.
- ✓ Certain aspects of nasal surgery may not necessarily be considered as complications but more as anticipated side effects.
- ✓ Nasal valve dilators (e.g. Breathe Right® or Nozovent® (**Figure 103.12**) and nasal steroid medications play a part in the non-surgical management of nasal valve obstruction.
- ✓ The most important aspect of paediatric septal surgery is to resect the cartilage conservatively and to avoid disrupting the endochondral ossification plates.
- ✓ In cases of severely fractured and deformed septum, the correction and reconstruction can be achieved through an open approach septorhinoplasty with the septum *in situ* or through extracorporeal techniques.[11]

FUTURE RESEARCH

Studies on nasal airway surgery are often observational or retrospective. Variations in the causes of nasal obstruction, the surgical procedures performed and the outcome measures used to measure the change have added to the complexity of analyzing the evidence. It is often impossible to analyze the effects of one particular procedure in a study as often multiple procedures are used simultaneously in nasal airway surgery.

Nasal mucosal swelling, whether in its physiological form (i.e. nasal cycle) or in its pathological form (i.e. rhinitis), adds to the complexity of measuring the effects of surgical intervention. The same problem exists when employing objective measures such as rhinomanometry to measure the effect. There is a need for an objective tool to measure the nasal airway resistance and to identify the level of obstruction taking into account the nasal airflow. This tool should be able to measure nasal flow and resistance during nasal breathing to be able to detect the dynamic elements of nasal obstruction.

The subjective elements of nasal obstruction add to the complexity of analyzing the effects of surgical interventions as the lack of correlation between the subjective and the objective tools have been shown before in the literature.

Like other aspects of surgical practice, it would be very difficult and often unethical to conduct randomized controlled trials to produce the high level evidence for nasal airway surgery.

Future studies on surgical techniques need to have improved designs and their cohort needs to be comparable. Ideally only one surgical procedure needs to be performed so the effect can be measured solely on that particular procedure. Like any surgical study, the operator dependant factors play a part in the results and this needs to be taken into account when designing any study.

Tissue engineering is a rapidly developing field and further advances in this field would be very much welcomed by rhinoplasty surgeons who are always in need of cartilage for nasal support and nasal valve surgery.

KEY EVIDENCE

Several studies demonstrate a consistent benefit for nasal valve repair. Nasal airway surgery benefits are measured by patient-reported outcome measures (PROM) which are more clinically relevant than objective measures.

KEY POINTS

- Nasal airway surgery requires attention to the nasal septum as well as nasal valve areas.
- Correct diagnosis is essential in choosing the correct surgical technique.
- The patient's nasal airway should be examined in the neutral position using an endoscope.
- The nasal expiratory misting test can miss the dynamic elements of nasal obstruction.
- The nasal speculum can distort the anatomy and can hide the culprit.
- Cottle's manoeuvre is not a specific test for the external nasal valve.
- The nasal airway should be examined before and after topical decongestion to assess the effect of mucosal swelling on it.
- Most nasal valve procedures will have an aesthetic effect and the patient should be warned of these prior to the operation.
- Patient-reported outcome measures appear to be more clinically relevant than the objective measures.
- Nasal obstruction can be caused by septal deflection which can be developmental or secondary to trauma.
- In septoplasty, the attention is more on reconstruction rather than excision.
- Complications may arise from septal surgery but they are mostly due to poor surgical planning and operative techniques.
- There remains controversy about the optimal age and extent of septal surgery in the paediatric population.

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CHAPTER 104

NASAL SEPTAL PERFORATIONS

Charles East and Kevin Kulendra

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search restricted to English papers using the keywords: septum, perforation, and reconstruction from a medline search as well as textbooks of otolaryngology published in English literature and local Audits.

INTRODUCTION

Definition: through and through defect or defects of the nasal septum. The exact prevalence of septal perforations is unknown as many perforations are asymptomatic, but in a general otolaryngology practice the clinician will encounter several patients with septal holes each year. Younger and Blokmanis[1] cite an incidence of just over 1%, which makes the condition relatively common. It must be remembered that racial traditions and fashion dictate that perforations in various parts of the body are a part of normal life and the anterior nasal septum is no exception. The majority of perforations involve the anterior quadrilateral cartilage of the septum. Kuriloff[2] has provided an extensive list of the local and systemic causes (**Table 104.1**). Currently, the most common cause of perforation in the UK is probably local trauma, although in a significant percentage, no clear history exists attracting the label of 'idiopathic'. The trauma is frequently self-induced or iatrogenic following surgery to the nasal septum or nasal instrumentation. Injuries to the cartilagenous skeleton of the nose may result in perforation through a compound fracture of the quadrilateral cartilage in the absence of any external deformity. Recreational drugs, for example crack or cocaine snorted nasally, are becoming increasingly common as a cause of septal necrosis.[3] The prevalence of chronic specific infections producing perforations is small, but there are a significant number of inflammatory conditions which should be excluded, particularly if the history does not give an easy clue to the aetiology.

SYMPTOMATOLOGY

The principle symptoms associated with perforations are crusting, epistaxis and whistling. Other symptoms include a feeling of dryness, emptiness in the nose or a general feeling of discomfort. In a series of 69 septal perforations, Brain[4] showed that 62.4% were completely free from any symptoms. Size and position of the hole had a direct bearing on the presence of symptoms. Anterior perforations and large perforations where the anterior margin is in front of the nasal valve appear to be the most troublesome. This probably relates to the relatively slow mucociliary clearance from the anterior septum, low humidity in the anterior nares compared to controls[5] and the loss of mucosa, all contributing to dryness and crusting. The accumulation of large crusts around the margin of the perforation produces a sensation of blockage. With large stable perforations, patients may feel the nose is empty or complain of 'blockage', even when nasal airflow is greater than average. These features may be due to turbulence of airflow in the nasal vestibule, although there is little evidence to support this. Huge perforations produce a common nasal cavity resulting in rhinolalia and an inability to

TABLE 104.1 Aetiologies of nasal septal perforations

Traumatic causes	Surface irritants	Infections	Neoplastic	Inflammatory
Nasal surgery	Cocaine insufflation	Syphilis	Melanoma	Sarcoidosis
Nose picking	Cocaine adulterants	Typhoid	Adenocarcinoma	Crohn's disease
Septal cauterization (bilateral)	Heroin inhalation	Diptheria	Squamous cell carcinoma	Dermatomyositis
Nasal packing for epistaxis	Decongestant nasal sprays Intra-nasal corticosteroids	Tuberculosis	Metastatic carcinoma	Rheumatoid arthritis
Septal hematoma/abscess	Lime, cement, glass, salt, dust	Rhinoscleroma	Lymphoma	Relapsing polychondritis
Cryosurgery	Tar and pitch	Lepromatous leprosy		Granulomatosis with polyangiitis (GPA)
Intubation (nasogastric/tracheal)	Fumes (chromic/sulfuric acid)	Leishmaniasis		Systemic lupus erythematosus
Desiccation (ozena, deviated septum)	Arsenicals, mercurials	Mucor		
Radiation	Calcium nitrate, cyanide	Rhinosporidiosis		
Stab and gunshot wounds	Phosphorus, sodium carbonate	Alternaria		
Foreign bodies (button batteries)	Copper-smelting fumes	Actinomycosis		
		Aspergillosis		
		Histoplasmosis		
		Cryptococcosis		
		Coccidioidomycosis		
		Paracoccidioidomycosis		
		Candidiasis		

clear secretions.[2] Nasal mucosal cooling is associated with increased sensation of patency but this does not correlate with clinical observation in patients with nasal perforations whose intra-nasal temperature rises after successful closure.[5]

Inflammation in the perforation margin leads to recurrent epistaxes, often triggered when the crust separates or is removed. Epistaxis can be quite significant from the sphenopalatine vessels. Large areas of mucosal deficit, particularly where there is cartilage exposure, prevent normal mucus clearance, contributing to localized infection and more inflammation. The local inflammation in the nose is often perceived as a generalized sense of discomfort, felt internally and over the nasal bridge. Over time, necrosis of septal cartilage will lead to enlargement of the hole in 'active perforations', sometimes to such a size that surgical closure is impossible.

CLINICAL ASSESSMENT

A full history is necessary when investigating septal perforations to cover the wide range of aetiologies. Principally, it is important to identify episodes of nasal trauma, cautery or surgery and, in particular, a history of substance abuse. Though patients may often deny it, aggressive nasal self-toilet with digital trauma or tissues will convert an inflamed mucous membrane to an ischaemic crusty area which ulcerates – the so-called 'pick ulcer'. Continued attempts to remove the crust invariably lead to cartilage exposure, cartilagenous necrosis and subsequent perforation.

An overall assessment of the external and internal nasal skeleton should be made together with nasal endoscopy. Endoscopy is the best method to assess the margins and state of the residual septum. Measurement of the dimensions of the hole is performed by introducing a small paper ruler into the contralateral airway and reading the scale through the hole. Saddle deformities, deviations of the nose or septum, columella retraction and intra-nasal adhesions are commonly seen and may require reconstructive rhinoplasty techniques to correct if surgery is contemplated. Nasal questionnaires using a linear visual analogue scoring system may be used as a measure of symptom severity. Although not essential in routine clinical practice, they do provide subjective assessment for comparing pre- and post-treatment symptoms and are a basic measure of outcome (**Figure 104.1**). Other outcome measures via validated questionnaire have been used to measure patient benefit from surgical repair.[6]

Nasal septal perforation questionnaire

NAME:

Please mark you own score by marking a line at the appropriate point.

0 = No symptoms, **10** = Worst symptoms.

		1	10
1	Crusts/scabs		
2	Nose bleeds		
3	Whistling		
4	Nasal discomfort		

Please mark the appropriate point for your symptoms in Questions 5 and 6

5	My nose feels empty		My nose feels blocked
6	Can clear secretions easily		Can't clear secretions at all

Figure 104.1 Nasal septal perforation questionnaire.

SPECIAL INVESTIGATIONS

Because of the wide range of aetiologies for septal perforation, history-taking is crucial. Any signs of inflammation around a perforation, however, should prompt investigation of other anatomical areas in the head and neck, as well as investigations for systemic inflammatory conditions. Nasal perforations may be the first sign of various granulomatous disorders, including Wegener's granulomatosis, and occur with a variety of collagen disorders including relapsing polychondritis, systemic lupus erythematosus (SLE) and dermatomyositis. Of the infective causes, the clinician is guided by the health of the patient, but tuberculosis and syphilis should be excluded. A full blood count, erythrocyte sedimentation rate (ESR), urea and electrolytes, urine analysis, C-ANCA, treponemal investigations, ACE titres and a chest X-ray, together with a nasal swab, provide an adequate baseline. Other symptoms of inflammation in the respiratory tract, for example cough, middle ear effusions, an arthritis or skin rash, should prompt referral to a clinical immunologist.

There is little evidence that extensive investigations for patients with healed, stable and asymptomatic perforations contribute to a change in the management, particularly where the aetiology is clear. Routine biopsy of septal perforations to exclude vasculitis has been suggested,[6,7] but biopsy rarely reveals anything other than chronic inflammation and is not usually sufficient for a specific diagnosis. Indeed, biopsy may convert an inactive perforation to an 'active state', resulting in significant enlargement of the hole. The role of routine biopsy in idiopathic perforations has recently been questioned. In two retrospective series, septal biopsy was shown to be non-specific for Wegener's and was only of value in those perforations with an irregular margin which were clinically malignant.[8,9] It is clear that the diagnosis of Wegener's or its reactivation cannot be reliably inferred from biopsy of the nasal septum alone. Practically, therefore, perforations should be biopsied if there is an unexplained aetiology, with persistent inflammation, or if the perforation is irregular. Specimens should be examined for mycobacteria and fungi, and with immunocytochemistry to exclude a neoplasm.[2]

PREVALENCE OF SEPTAL PERFORATIONS

The prevalence of septal perforations following nasal septal surgery shows wide variation and has been reported as between 1.4% and 25%. The prevalence appears higher after submucous resection operations (17–25%) than the more conservative septoplasty procedures (1.4–5%).[10] The use of nasal splints during septal surgery is known to produce a higher incidence of perforation.[11] Splinting is unnecessary in the majority of routine septal surgery unless established adhesions are being treated. Recent retrospective reports[12] have suggested an association between nasal steroid sprays and the development of nasal perforation. It is known that all steroid sprays can cause inflammation over the caudal septum, by direct irritation or their initial vasoconstrictor activity, particularly if there is a septal deviation which takes the brunt of the spray jet. Patients should be directed to use the spray with the opposite hand to the nostril being treated, minimizing the impact on the septum. Any ulceration after starting steroid spray use should be allowed to heal by withdrawing the medication.

MANAGEMENT

The majority of septal perforations are asymptomatic and require no specific treatment.[4] The more anterior the lesion, the more likely it is to cause symptoms. This probably relates to accessibility by the patient to pick at the nose, but may also be related to fast airflow producing drying in the region of the internal nasal valve. The management can be divided into three groups.

PREVENTION

In a series of 50 perforation repairs at the Royal National Throat, Nose and Ear Hospital, 60% had a previous history of septal surgery. Meticulous attention to technique is required in elevating the mucoperichondrial flaps in the correct plane, particularly avoiding overlapping bilateral mucosal tears. Starting the dissection on the easier (usually the concave) side to raise one intact flap first, and using an autograft of cartilage or ethmoid plate to support any tears, is good practice. The mucoperichondrium over large spurs is often very thin, and tears may be inevitable. However, when the spur is removed, there will be a relative excess of mucosa which can be repaired with absorbable sutures. Quilting sutures in the septum after surgery should be tied loosely to allow for post-operative oedema. The authors have seen perforations caused by individual sutures tied tightly in the septum which resulted in ischaemic necrosis. Septal inflammation or ulceration should be treated by withdrawing the source of the irritation and promotion of healing, for example by eradication of pathogenic bacteria, avoidance of aggressive cleaning and use of mucosal protectants (petroleum jelly, sesame seed sprays). Antiseptic silicon barrier creams over 6–8 weeks will stabilize the mucosa in the majority of cases. In recalcitrant inflammation, thin reinforced silastic sheeting can be sutured to cover the caudal septum. If there is a large area of cartilage exposure, however, this still may not be sufficient to prevent progression to perforation. When a septal ulcer heals, the scar produced may leave a persistent area of squamous metaplasia which never reverts to a mucosal surface. Periodic and regular use of barrier creams may be necessary or the regular application of sesame seed oil which has a longer duration of effect than simple saline douching.

NON-SURGICAL

This, essentially, is aimed at reducing the drying effect in the nasal mucosa to alleviate crusts and epistaxis. Alkaline nasal douches, proprietory saline sprays and petroleum-based ointments are commonly used. There are no studies of the effectiveness of this type of regimen, but many patients adopt a twice daily ritual of douching and ointment application. It is usually obvious within 6–8 weeks whether this will be effective in maturing the margins of a perforation.

OBTURATION

The principle of obturation is to cover the inflamed mucosal margin. In 2002, Meyer[13] cited the use of septal obturators in the management of perforations. Inert sheeting (usually silastic) was placed to prevent drying and encourage epithelialization over the cartilage/bony septum to create a mature mucosal edge. Evidence suggests that patients do derive benefit from the use of nasal obturators, but opinion on their usage and effectiveness is divided. Facer and Kern,[14] in a retrospective study of 73 patients, reported 72.8% of obturators remained in place, but 27.4% of buttons were removed or were extruded. Brain[4] described the long-term outcome of 102 patients with medium or large holes (1 cm perforations or larger). He described a good result in 44.4 and 32.4%, respectively. The main benefit from obturation appears to be the control of whistling and epistaxis. Often, crusting and nasal discomfort remain a problem.[6, 15] The feeling of obstruction is improved when crusting is reduced, but the bulk effect of an obturator may increase blockage, particularly in anterior perforations with a narrow nasal valve. Poorly tailored silastic may irritate the mucosa, particularly with anterior holes close to the membranous septum. Patient interference and movement of the mobile membranous septum against the edge of the obturator can lead to granuloma formation. It is often for these reasons that patients request removal of the obturator.

SURGICAL

Enlargement of a nasal septal perforation to prevent whistling was described by Jackson and Coates in 1922,[16] but there is little evidence to support its routine use in clinical practice. One retrospective article of widening of the perforation and posterior edge repair in larger holes (15–50 mm) evaluated the pre- and post-operative symptom scores obtained by a linear visual analogue questionnaire. Benefit was reported for the symptoms of crusting and epistaxis and overall nasal discomfort with a significant reduction in mean scores. This technique appears to offer some value for patients with persistent inflammation who could not retain a nasal obturator and who were deemed unsuitable for surgical repair.

SURGICAL REPAIR OF SEPTAL PERFORATIONS

The plethora of techniques for septal perforation repair described over the years attest to the fact that there is still a challenging technical problem for the nasal surgeon, although reliable surgical techniques with good outcomes have been published in the last 15 years. The variety of repairs may be classified as:

- Free grafts:
  - simple or composite autografts
  - allografts

- Pedicled flaps:
  - local nasal mucosal
  - buccal mucosal
  - composite septal cartilage and mucosa
  - composite skin/cartilage
- Rotation/advancement of mucoperichondrial or mucoperiosteal flaps.

Combinations of techniques have been employed in many small reports. In the larger series of observational outcomes of perforation repairs, two factors emerge that appear to have an important bearing on a successful outcome, to achieve closure in 80–90 % of cases. The first is that there is sufficient residual mucosa in the nasal fossa which can be mobilized and transposed allowing direct suturing of the mucosal defect (**Figure 104.2**).

The second is the routine use of a connective tissue interposition graft to support the repair. Bilateral mucosal flaps with the main blood supply derived from the sphenopalatine vessels form the basis of most techniques. Grafts have been reported using temporalis fascia,[17] mastoid periosteum, cranial periosteum, cartilage (septal, auricular, rib) perichondrium and bone (either locally or from rib or the iliac crest).[18, 19] Small defects can be closed with bipedicled flaps, by making relieving incisions either superiorly or inferiorly.[20] Larger holes up to about 2 cm require larger flaps which are pedicled only posteriorly based on the sphenopalatine vessels, and are effectively transposition/rotation flaps.[1, 20–23] Even if complete bilateral mucoperichondrial suturing of the hole is not possible, the use of a connective tissue graft between the leaves allows for epithelialization on the side of incomplete closure, as long as the flaps are protected from drying out and the reconstruction does not get infected. In the presence of any dehiscence of the sutured mucosal defect, it appears that epithelialization occurs more reliably over fascia than cartilage or bone. Reports using acellular dermal allografts[24, 25] instead of fascia appear to give similar success rates. The allografts are expensive, but it must be remembered that donor site morbidity from fascia is not a major issue and the repair is entirely the patient's own tissue. The use of other collagen xenografts may be an alternative. The primary author has used at least two layers of either temporalis or temporoparietal fascia, if necessary with a sandwich of cartilage as a composite graft where there is little supporting remaining quadrilateral cartilage (**Figure 104.3**), for the last 6 years with a current success rate of 87%.

Auricular cartilage, which is a useful graft, is often curved and care should be taken anterosuperiorly at the internal valve because any excess thickness at this level risks post-operative nasal block, requiring revision surgery. Where this may be a problem, a combined approach by raising an anteriorly based turbinate flap endoscopically either alone or with mobilization of mucosa from the floor and upper nose will often allow a tension free repair of the hole without the need for a cartilage graft between the layers. The patient should be counselled that a second usually minor procedure to divide the pedicle of the flap may be required at about 3 months if restriction of breathing is still present.

The nasal fossa is a contaminated area and therefore antibiotic prophylaxis is important. There are no studies as to the ideal length of the course, but the development of sepsis can have a potentially devastating effect on the residual cartilage producing a saddle deformity. Currently, the authors give a 10-day course and supplement this with topical antibacterial ointment.

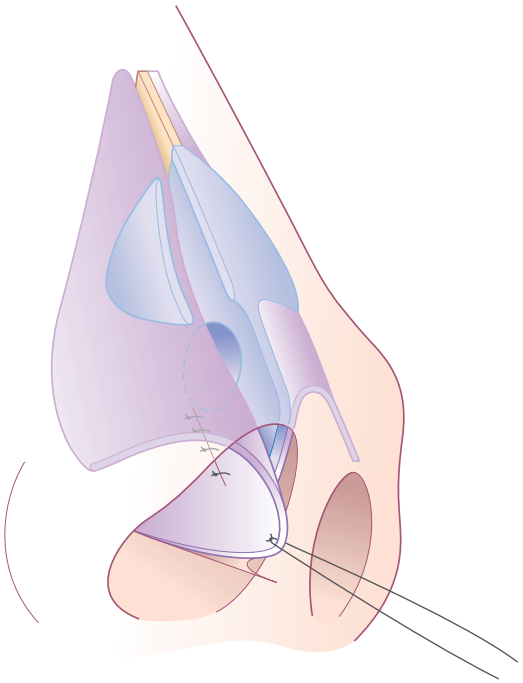


Figure 104.2 Extensive mobilization of the mucosal lining allows a round hole to be closed with sutures in a straight line.

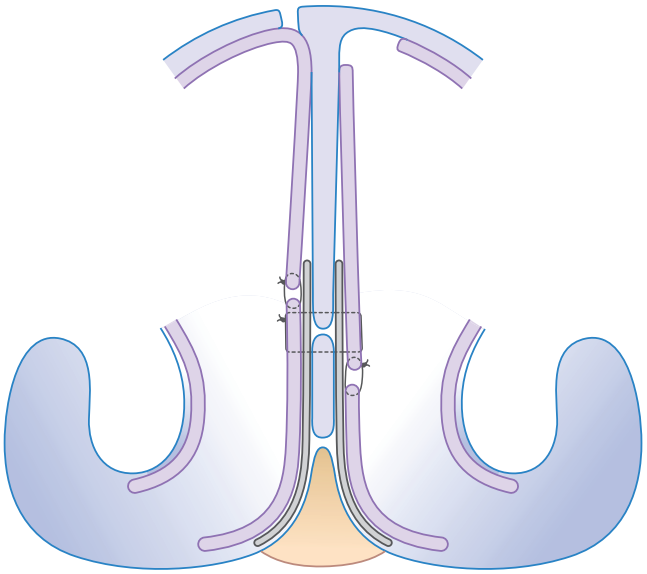


Figure 104.3 Bilateral mucosal flap repair with staggered mucosal rotation/transposition flap closure and connective tissue interposition graft. The fascia should extend to the nasal floor to cover any secondary defect inferiorly.

There is an anatomical limit to the amount of septal mucosa which can be transposed and this is directly inverse to the size of the septal hole. Large perforations (larger than 2.5 cm), particularly with a large vertical dimension as opposed to horizontal linear holes, still pose a problem. However, by extensive undermining along the nasal floor and inferior meatus inferiorly and under the upper lateral cartilage superiorly, substantial flaps may be created. The careful atraumatic elevation of flaps is technically demanding, particularly if the mucoperichondrium is inflamed, atrophic or there is a significant spur of the septum. The surgeon has four options for the approach.

Endonasal[17]

This approach is limited principally by nostril size and position of the hole. Design of the endonasal flaps is critical in this approach due to the limited access. Broad-based elevations via hemitransfixion incisions and bipedicled flaps preserving anterior and posterior blood supplies with horizontal relieving incisions together with interposition grafts should give very good results for small holes (up to 0.5 cm).

Endoscopic

An anterior pedicled turbinate flap is raised to include the mucosa of the medial and inferior surfaces, reflected forwards and sutured to the margins of the septal perforation following submucosal mobilisation.[18] Bilateral flaps provide a more secure repair although if the pedicle remains bulky, a second procedure to divide the attachment may be required. Unilateral septal flaps based on the anterior ethmoid vessels and including mucoperiosteum from the nasal floor can be transposed forward and sutured on one side to the margins of the hole.[19] The opposite side epithelializes over several weeks and disturbance of the valve is minimal.

External rhinoplasty

Approach via a trans columella approach[21] or a columella-philtrum incision: The external approach or its modification by sectioning the columella below the medial crural footplates and connecting to a transfixion and intercartilagenous incisions provides excellent exposure of the septum and lower dorsum, particularly if concomitant rhinoplasty is required and especially when additional grafting is needed to the nasal valve or dorsum. Alar crease incisions only provide limited additional unilateral access and should not be combined with the transcolumella approach because of the risk of ischaemia to the columella flap. It is possible to design larger flaps through this approach and suturing of the mucosal hole is definitely easier than by the endonasal approach. The use of medially based pedicled buccal mucosal flaps have limited use for larger perforations, but are useful to repair secondary deficiencies of the membranous septum when the mucosa has been mobilized to close very anterior holes.

Mid-face degloving approach[26]

This is an extensive dissection of the face which has been employed for very large holes (>2 cm). Used purely as an approach with standard rotation transposition mucosal flaps, it appears to offer little benefit over an external approach for successful closure but with a higher complication rate (vestibular stenosis, 20%). Variation of the technique by employing tissue expansion of the mucosa and skin grafting to the nasal sill appear to improve the success rate and reduce the incidence of nasal vestibular stenosis. Tissue expansion is achieved along the nasal floor using a small (1 × 3 cm) expander over 6–8 weeks with a total volume of 4–7 mL. This technique has the advantage of generating more lining for easier mucosal closure, but the extensive relatively traumatic dissection must be weighed against the degree of benefit to be gained by the patient. Reported success in this series was 18 out of 22 patients with holes from 2 cm to 4 cm diameter.

Although there is evidence of good technical success in surgical repair of the perforated septum for small–medium sized holes, objective evidence of patient benefit following surgical closure is limited. Lindemann et al.[5] have shown improvements in nasal physiology particularly in end-inspiratory humidity and a reduction in symptom scores for epistaxis and nasal dryness.

BEST CLINICAL PRACTICE

- ✓ Meticulous attention to technique in the execution of septal surgery with adequately supported repair in the event of mucosal tears.
- ✓ Referral to specialist rhinologist/facial plastic surgeon for repair of small- to medium-sized holes.

FUTURE RESEARCH

- ➤ More supporting evidence of outcome measures including general health status is needed to confirm the benefits of surgical repair.
- ➤ Tissue engineering with the possibility to produce cartilage sheets and stable collagen as implants, which are guaranteed free from infection, will remove the need for a donor site.

KEY POINTS

- More than half of perforations are asymptomatic and do not require treatment.
- Trauma is the most common cause of septal perforation.
- Small to medium holes can be closed reliably by surgery.

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CHAPTER 105

MANAGEMENT OF ENLARGED TURBINATES

Andrew C. Swift and Samuel C. Leong

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SEARCH STRATEGY

Data in this chapter may be updated by a search using the keywords: turbinates, nasal surgical procedures, nasal obstruction and nasal procedures.

MANAGEMENT OF ENLARGED TURBINATES

Introduction

The inferior turbinates are dynamic structures that form a crucial part of the normal functional nose. However, they are structures that are relatively easy to access. They have been recognized as a cause of nasal obstruction and therefore subject to numerous operative techniques to either reduce their size or excise them completely.[1] Various surgical techniques of turbinate reduction or destruction have been described since the middle of the 19th century. Despite a declining trend in England (United Kingdom), inferior turbinate reduction surgery remains a commonly performed procedure in ENT practice (**Figure 105.1**). Contemporary otorhinolaryngological literature states that the evidence base for the multitude of techniques for turbinate reduction is weak and that surgeons empirically offer surgery where the predominant symptom is nasal obstruction.[2] In fact, there is currently no ideal surgical procedure and most techniques offer only short-term benefit.[3] Paradoxically, most specialist rhinologists who devote a major part of their practice to conditions of the nose perform surgery to the inferior turbinate infrequently.

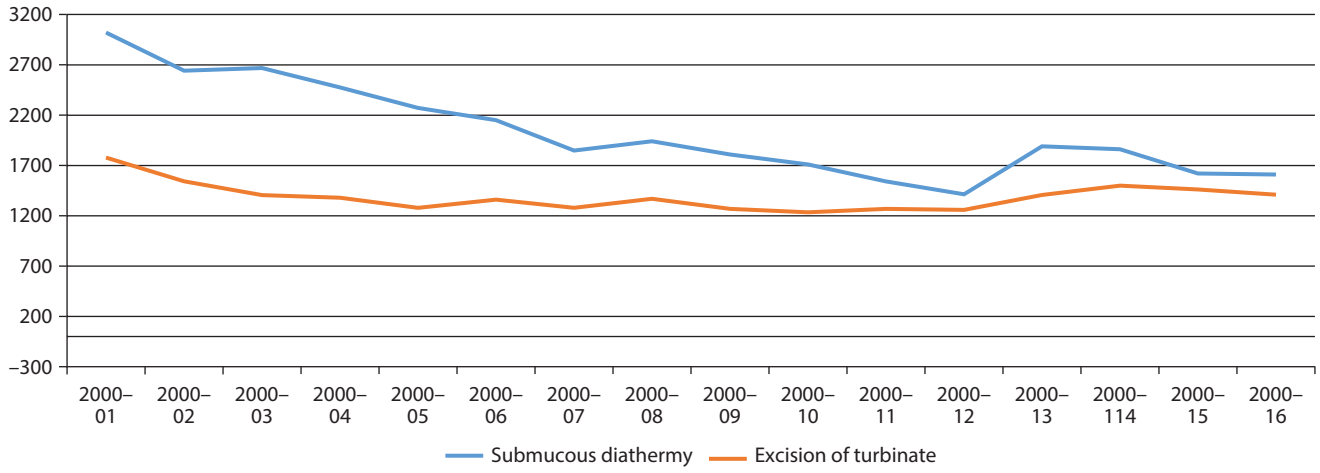


Figure 105.1 Trends in adult turbinate surgery in England from financial year 2000 to 2016. E04.1 = Submucous diathermy to turbinate of nose. E04.2 = Excision of turbinate of nose NEC. (Source: Hosptial Episodes Statistics, http://content.digital.nhs.uk

History of turbinate surgery

Operative techniques to reduce the size of the inferior turbinates have been practiced since 1845. The first technique to be described was electrocautery: at the time this was being used for a wide variety of non-nasal medical complaints, justified by the misconception of nasal reflex neurosis. Hol and Huizing[4] described 13 techniques of interior turbinate reduction up to the present day.

Anatomy of the inferior turbinates

The inferior turbinate consists of a supporting cancellous conchal bone, named after the Greek for scroll, covered by specialized erectile mucosa.[5] The turbinate is attached along the inferolateral aspect of the nasal cavity, extending from the interior nasal valve to just anterior to the Eustachian tube. The conchal bone is firmly attached to the inferomedial surface of maxilla. The adjacent maxilla is very thick anteriorly and becomes thin in the midsection of the nose. The conchal bone is not a completely straight structure but curves superiorly reaching its highest point in the mid nasal cavity. The nasolacrimal duct opens into the superior aspect of the inferior meatus just between the thick anterior bone and the thin section in the mid part of the nose. The entrance of the nasolacrimal duct is protected by Hasner's valve.

From the applied point of view, these anatomical points are important to appreciate: during antral washout the trochar is passed into the inferior meatus below the turbinate to puncture the lateral wall of the nose into the maxillary sinus. The superior part of the attachment of the inferior turbinate is thin in the midsection of the nose and puncture is generally easy.

The blood supply is from the lateral branch of the sphenopalatine artery that enters the posterior aspect of the turbinate. Sensation is supplied by the trigeminal nerve; sympathetic nerves travel along the feeding arterial blood vessels; the parasympathetic supply also travels along the vascular supply but travels along the vidian nerve before entering the nose through the sphenopalatine foramen.

Physiology in health

The inferior turbinate is an important functional component of the normal nose. It warms inspired air and maintains linear rather than turbulent airflow within the nose.[6] The turbinate is covered by a functional ciliated pseudostratified respiratory mucosa that is supported by a lamina propria, below which is a vascular layer rich in venous sinusoids (**Figures 105.2a** and **105.2b**).

The normal inferior turbinate is a dynamic structure that varies in size according to the degree of congestion. The latter is determined by the control of blood flowing through the specialized erectile tissue. This change is governed by the autonomic neural supply: the sympathetic nerves induce reduction of blood flow and a decrease in volume whilst the parasympathetic supply congests the erectile tissue of the turbinate. The degree of congestion varies in a cyclical manner in a healthy nose every few hours and is coordinated so that when one side is congested the other is constricted. This phenomenon is known as the nasal cycle: it can be demonstrated in about 80% of humans but the purpose is unknown.[7]

Definition of an enlarged inferior turbinate

Operations to reduce the size of the inferior turbinate are generally based on the fact that it is enlarged. However, in clinical practice, this is usually a subjective assessment and diagnosis is normally made by exclusion criteria when dealing with the sensation of nasal obstruction. Various terms are used to describe this enlargement and there is a lack of standardization.[8] The various terms include hypertrophic, congested, hyperplastic, and engorged turbinates.

In practice, gross congestion of both inferior turbinates in a patient with severe rhinitis may be obvious. However, it is important to appreciate that congestion may reflect stages of the nasal cycle. It is therefore important to consider the effect of spraying a topical decongestant onto the inferior turbinates before accepting the fact that the inferior turbinates are chronically congested.

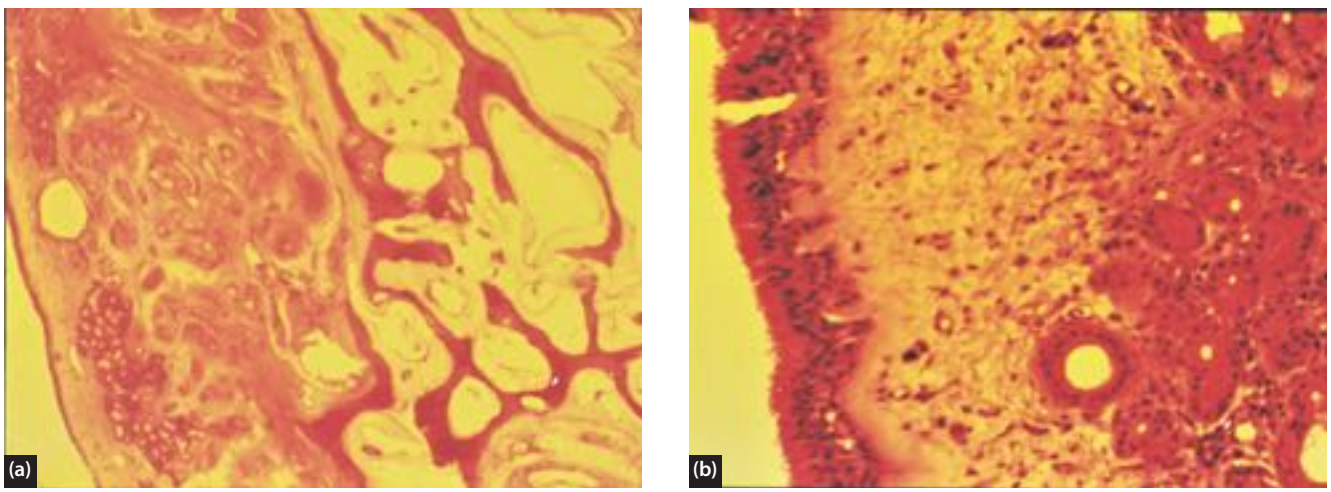


Figure 105.2 Histology IT1 **(a)**; Histology IT2 **(b).**

Histological studies of bilaterally enlarged inferior turbinates have shown dilated congested venous sinuses, subepithelial inflammatory cell infiltration, fibrosis of the lamina propria, and dilatation of mucous gland ducts.[5] Other changes include an increase in pseudostratified surface epithelium, goblet cells and mucous gland acini. Histology of inferior turbinates from patients with non-allergic perennial and allergic rhinitis has shown degenerative change and fibrosis in the lamina propria in the non-allergic group whereas the allergic turbinates showed gross tissue oedema.[9] In patients with septal deviation and contralateral inferior turbinate enlargement, an additional finding has been a two-fold increase in the bony concha compared to cadaver controls.

It is of note that the medial aspect of the mucosa is thickest in an enlarged turbinate.[10] It has been suggested that surgery should therefore be targeted to the mucosa over the medial aspect of the turbinate and the inferior section that is rich in vascular sinusoids.[11]

Pathogenesis of inferior turbinate enlargement

Whilst assessing a patient with enlarged inferior turbinates, it should be helpful to categorize the enlargement according to a classification proposed by Hol and Huizing.[4, 12] The individual categories are judged according to clinical features as follows:

1. Compensatory hypertrophy
2. Protruded turbinate
3. Hyperplasia of the turbinate head
4. Hyperplasia of the whole turbinate
5. Hyperplasia of the turbinate tail.

Compensatory hypertrophy of the inferior turbinate is seen when the nasal septum is deviated to the opposite side, and the turbinate seems to fill the empty space. **Protrusion** is where the turbinate extends more medially into the nasal cavity than expected. It may be more apparent on the coronal CT images when the conchal bone may be seen to make a less acute angle with the lateral nasal wall. Hyperplasia of the turbinate head and whole length of the turbinate may both occur with chronic rhinitis. Should the head enlarge, the turbinate may enlarge anteriorly and obstruct the nasal valve. Hyperplasia of the posterior end is said to occur in patients with chronic sinusitis and post-nasal discharge.

In patients with rhinitis, the effect of the nasal cycle is accentuated; patients may become aware of the cycling effect on their sensation of nasal obstruction that may become significantly worse whilst in the supine position due to nasal reflexes. In patients with severe forms of rhinitis or significant rhinosinusitis, the inferior turbinates may become chronically enlarged. This effect becomes even more so should the patient self-medicate with xylometazoline to try and decongest the nose.

Sarcoidosis is an unusual disorder that may cause quite severe inferior turbinate enlargement and should be considered if the turbinates do not respond to normal topical treatments for rhinitis.

Clinical features

Patients with enlarged inferior turbinates will invariably present with nasal obstruction. The complete nasal symptom complex together with nasal examination and endoscopy will normally lead to the correct clinical diagnosis of allergic or non-allergic rhinitis or chronic rhinosinusitis. The anterior head of the congested inferior turbinates may appear as a red swelling or be pale and purplish: the latter is typically associated with severe allergic rhinitis (**Figure 105.3**). The swollen anterior end is easily visible on examination of the nose and in primary care this is often mistaken for an inflamed nasal polyp.

Ideally, the nose should be examined before and 10 minutes after mucosal vasoconstriction: chronically congested inferior turbinates normally do not reduce in size but remain large. This is important to note if turbinate surgery is being considered.

Imaging is not normally required unless surgery is being considered for rhinosinusitis. However, when available, helpful information about the turbinates may be demonstrated. CT is the best imaging modality (**Figure 105.4**), although MRI may also yield useful information (**Figure 105.5**).

Physiological evaluation of the inferior turbinates

Nasal obstruction is a subjective symptom that has a complex pathophysiological mechanism that is not yet fully explained.[13] It is not an uncommon phenomenon to find discordance between reported severity of nasal obstruction and clinical findings. It is thus important to measure the degree of obstruction in order to monitor the effects of surgery and audit the effectiveness of medical/surgical intervention. This can be done with a visual



Figure 105.3 Gross enlargement of the right inferior turbinate in allergic rhinitis.



Figure 105.4 Multi-planar CT sinus: enlarged inferior turbinates.

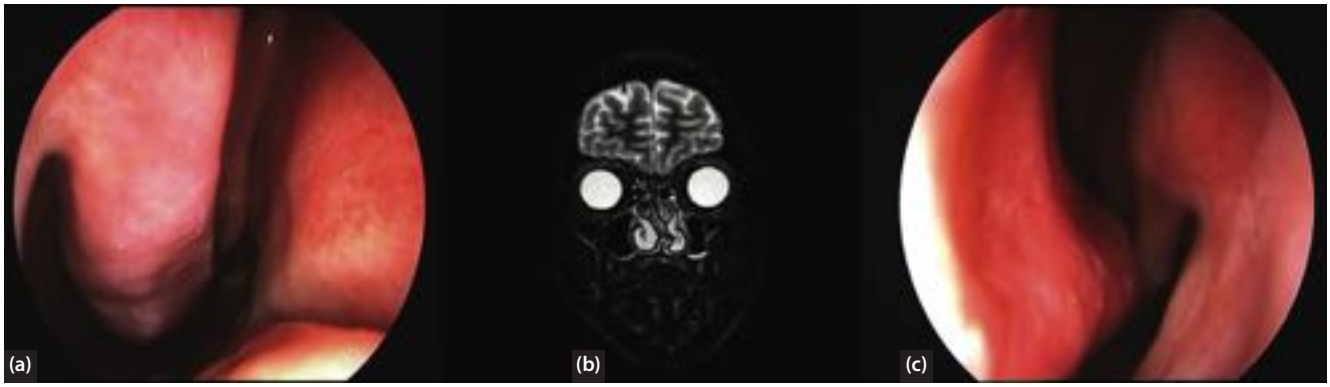


Figure 105.5 Enlarged right inferior turbinate and septal deviation to the left: endoscopic view and MRI appearance.

analogue scale and the 22 question Sino-Nasal Outcome Test (SNOT-22).

A few departments will have access to physiological measuring techniques (Figure 105.6) such as acoustic rhinometry, anterior rhinomanometry and rhinospirometry. These tools can demonstrate the degree of obstruction, the difference between each side of the nose and the change with nasal surgery. In the research setting measurements can be obtained before and after vasoconstriction, but in the clinical setting, this is not practical, and mucosal vasoconstriction should be induced in all cases. An overall assessment of the degree of nasal obstruction can also be obtained by measuring the peak nasal inspiratory flow using a specific nasal spirometer.

MEDICAL TREATMENT FOR THE ENLARGED INFERIOR TURBINATE

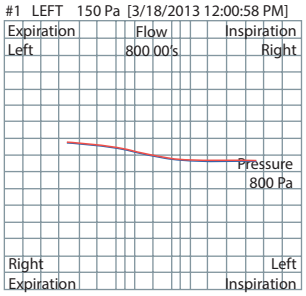
Firstly, rhinitis medicamentosa due to chronic abuse of vasoconstrictor agents should be sought and excluded. If present, the patient should be counselled on inducing factors and that their nose will become more obstructed until recovery starts to occur.

There is no contention amongst ENT specialists that the first line of treatment for enlarged inferior turbinates is medication. Topical nasal steroids are the mainstay of treatment for both allergic and non-allergic rhinosinusitis. However, prolonged once/twice daily treatment for at least 3 months is necessary, with reassurance that topical nasal steroids are safe to use every day. Topical steroids are often combined with oral antihistamines, antibiotics and saline in the treatment of chronic rhinosinusitis.[14]

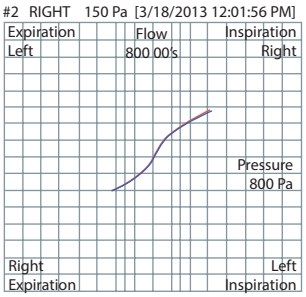
However, should medical intervention fail to provide good control, the option of surgery needs to be considered.

SURGICAL MANAGEMENT FOR THE ENLARGED INFERIOR TURBINATE

Surgery should ideally be restricted to patients with a significant symptomatology in whom operative intervention is likely to be effective. However, this is an area where there may be much diversity in opinion and practice with regard to the management of the inferior turbinate. As previously stated, it is paradoxical that specialist rhinologists operate on the inferior turbinate infrequently, but turbinate surgery is still a common procedure in the generality of the speciality. The explanation for this diversity is that with perceived enlargement of the turbinate it is very tempting to just reduce the size of the turbinate and this will generally result in an improved nasal airway. However, without addressing the driving forces for the condition, it is likely that any beneficial effect from inferior turbinate surgery will be short-lived. On the other hand, if underlying chronic rhinosinusitis is identified and corrected by

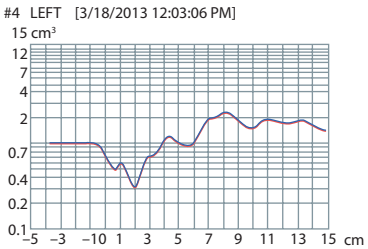


Standard	Inspiration	Expiration
Mean resistance	5.980	4.337
Max deviation	1.444	0.000
Respirations	3	1

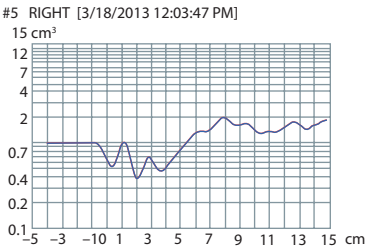


Standard	Inspiration	Expiration
Mean resistance	0.865	0.930
Max deviation	0.053	0.059
Respirations	4	4

(a)

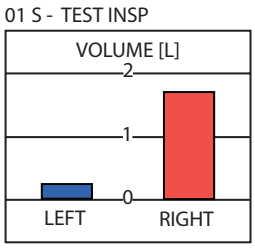


LEFT	Area	Distance
First minimum	0.30	2.07
Second minimum	N/A	N/A
MCA	0.30	2.07
Volume (0-5)	3.44	

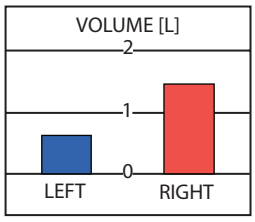


RIGHT	Area	Distance
First minimum	0.39	2.07
Second minimum	0.47	3.80
MCA	0.39	2.07
Volume (0-5)	3.16	

(b)



	Result
Left volume	–0.2473 L
Right volume	–1.0708
NPR	–0.75
Time	10.02 s
Outcome	Y



	Result
Left volume	–0.6574 L
Right volume	–1.152 L
NPR	–0.38
Time	10.02 s
Outcome	Y

(c)

Figure 105.6 Nasal physiology. Investigations in a patient with a large left inferior turbinate **(a)** Anterior rhinomanometry showing increased resistance and low flow on the left hand side of the nose. **(b)** Acoustic rhinometry consistent with significant obstruction in anterior nasal cavity. **(c)** Rhinospirometry: partitioning effect shows marked preference for right nasal airway.

endoscopic sinus surgery, with or without septal deformity surgery, the turbinate will often respond in a positive way without the need for turbinate reduction surgery.

As well as the diversity of opinion as to when to operate on the inferior turbinate, there is also a wide range of different operations and techniques, each with their own proponents.

It is not realistic to expect that this situation will ever become standardized, but it may be possible to modify the way that surgeons perceive the inferior turbinate.

Perhaps the most important aspect to consider when operating on the inferior turbinate is to preserve the mucosa and maintain the mucociliary transport.

A simple system of classifying turbinate operations is proposed in **Box 105.1**.

It may be necessary to excise the inferior turbinate for access during tumour surgery such as removal of an angiofibroma or inverted papilloma within the maxillary sinus. Resection may also be necessary in treating malignancy such as adenocarcinoma or melanoma. The inferior turbinate has been utilized as a pedicle graft in the closure of septal perforations or as a free graft source for repairing dural defects in the anterior skull base.

Individual techniques

The authors recommend that ideally inferior turbinate reduction should be restricted to submucosal mucosal preservation techniques where at all possible to minimize the risk of complications. However, acknowledgement is given to the fact that alternative techniques such as mucosal reduction by a microdebrider is safe and effective in experienced hands.

It is also acknowledged that some techniques require specific technology that may be expensive and it is unlikely that any one department will have a choice of all of the possibilities.

All techniques require mucosal vasoconstriction to minimize bleeding during the procedure. Performing the surgery under endoscopic control facilitates precision surgery with minimal collateral damage.

BOX 105.1 Simple system of classifying turbinate operations

Mucosal preservation surgery

- Lateralization by outfracture
- Mini-microdebrider surgery
- Radiofrequency
- Coblation
- Turbinoplasty
- Submucosal diathermy

Mucosal destructive reduction surgery

- Superficial cautery
- Chemocautery with chromic acid or trichloric acid
- Cryosurgery
- Laser surgery
- Direct microdebrider mucosal reduction

Turbinate excision procedures

- Partial
- Subtotal
- Posterior end

MUCOSAL PRESERVATION SURGERY

The two simplest low-cost techniques are lateralization by outfracture and submucous diathermy.

Lateralization

Lateralization by outfracture can be done by simply using an elevator to mobilize the concha by infracture, and then pushing the whole turbinate laterally. Although this probably results in the least improvement in the airway of the various techniques, it is very low risk, but can often be used as an adjunct to septal surgery or endoscopic sinus surgery to facilitate access to the nose. An alternative that may give a more effective result is to create a submucosal tunnel and outfracture the concha in segments via this tunnel.

Submucosal diathermy

Submucosal diathermy (SMD) is performed by passing an insulated Abbey™ needle along the length of the inferior turbinate in 2–3 different passes, and applying the diathermy at 70 W, as the needle is withdrawn. SMD is monopolar diathermy that generates intense heat at the electrode tip. This causes tissue destruction, inflammation and fibrosis. Initially, the nose is likely to feel more blocked until healing has occurred. There is a risk of extensive tissue destruction following excessive diathermy and the necrotic inferior turbinate will slough and crust over a prolonged period.

Classically, it is said that SMD will only be effective in patients that demonstrate good pre-operative turbinate reduction after applying a topical decongestant. Short-term results are good but this effect is often not maintained in the long term.

SUBMUCOSAL TECHNIQUES REQUIRING SPECIFIC TECHNOLOGY

Turbinate reduction can be achieved very effectively with a mini-microdebrider. A submucosal tunnel is created through a small incision of the anterior end of the turbinate (**Figure 105.7**). The erectile tissue can be reduced over the medial and inferior part of the turbinate by partial resection with a 2 mm diameter oscillating mini-microdebrider blade. Post-operative nasal packing is not necessary. This technique is effective, carries minimal risk, and the microdebrider can be controlled to preserve all of the overlying mucosa.

Submucosal microdebrider reduction has been combined with a procedure to divide the posterior nasal nerve at the sphenopalatine foramen. This procedure is known as functional inferior turbinosurgery (FITS) and aims to interfere with the autonomic control and reduce turbinate sensation.[15]

Coblation® techniques utilizes a narrow electrode or wand that creates low temperature plasma of 85 degrees and effectively dissolves tissue and later induces fibrosis. Radiofrequency (RF) has also been used with good effect and utilizes high frequency alternating current to generate heat and ablate tissues.

All of the submucosal techniques allow for precise surgery that can be performed under endoscopic control. Reports suggest the techniques are effective and can be repeated if needed.

Turbinoplasty

This technique is designed to preserve functional mucosa over the surface of the turbinate whilst achieving substantial reduction in the volume of the turbinate. The turbinate is initially in-fractured and an incision made over the anterior head and along the inferior margin (**Figure 105.7**). The mucosa is elevated from both sides of the bony concha. The concha is then resected in varying degrees. The lateral mucosa is removed with a microdebrider and the medial mucosa placed so that it lies laterally and forms a 'neoturbinate'. The anterior end of the turbinate is typically reduced and moved away from the nasal valve by this technique. Support dressings are then placed in the nose.

Mucosal destructive reduction surgery

Some of these procedures will destroy the specialized mucosal surface of the turbinate and may cause long-term crust formation and underlying infection with prolonged healing. It has been suggested that there is very little to justify some of these techniques in modern day surgery.[1]

Turbinate excision techniques

These are much more radical techniques than the techniques described above.

Radical subtotal resection of the turbinate operation includes resection of the mucosa and bony concha along the length of the inferior turbinate (**Figure 105.8**). This operation can be painful and has a much greater chance of damaging the lateral branch of the sphenopalatine artery and cause heavy epistaxis. It also carries long-term risks of crusting and the empty nose syndrome (*vida infra*).

To reduce the risk of significant complications and improve the airway at the region of the nasal valve, the operation of partial resection was devised. The enlarged anterior head and anterior third of the inferior turbinate are excised (**Figure 105.9**). The line of resection is first crushed to limit bleeding. Angled scissors are then used to excise the required section of turbinate. This can be done utilizing a headlight but an endoscope gives greater precision.

Enlargement of the posterior end of the inferior turbinate is occasionally seen. Such cases often have irregular polypoid mucosa over the inferior turbinate and local resection may be appropriate. Historically this was done using a specific snare developed in the days where large posterior ends were seen with the aid of a post-nasal mirror. A more controlled way of doing this now is to use a microdebrider under endoscopic control.

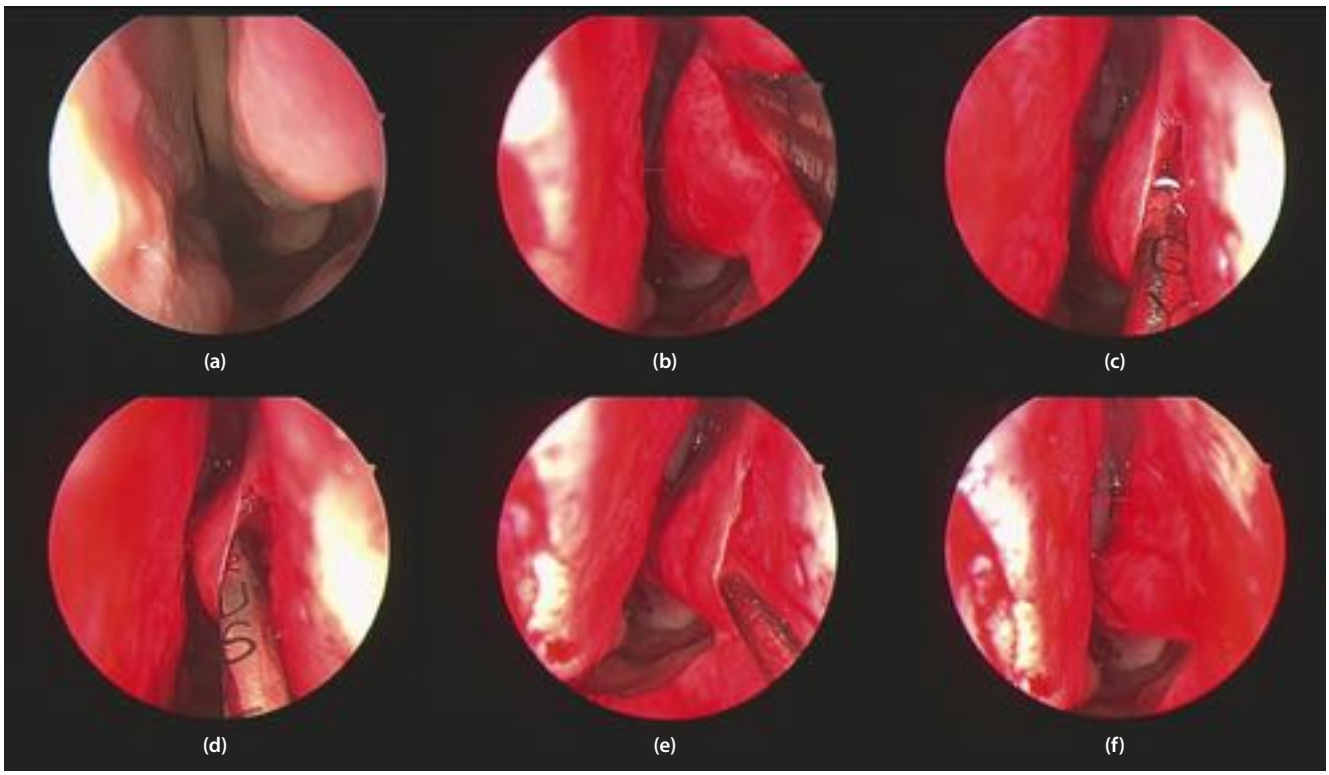


Figure 105.7 Submucosal turbinate reduction with mini-microdebrider blade. (a) Decongested left inferior turbinate **(b)** anterior turbinate incision **(c-e)** submucosal placement of microdebrider blade **(f)** replacement of mucosa against concha.

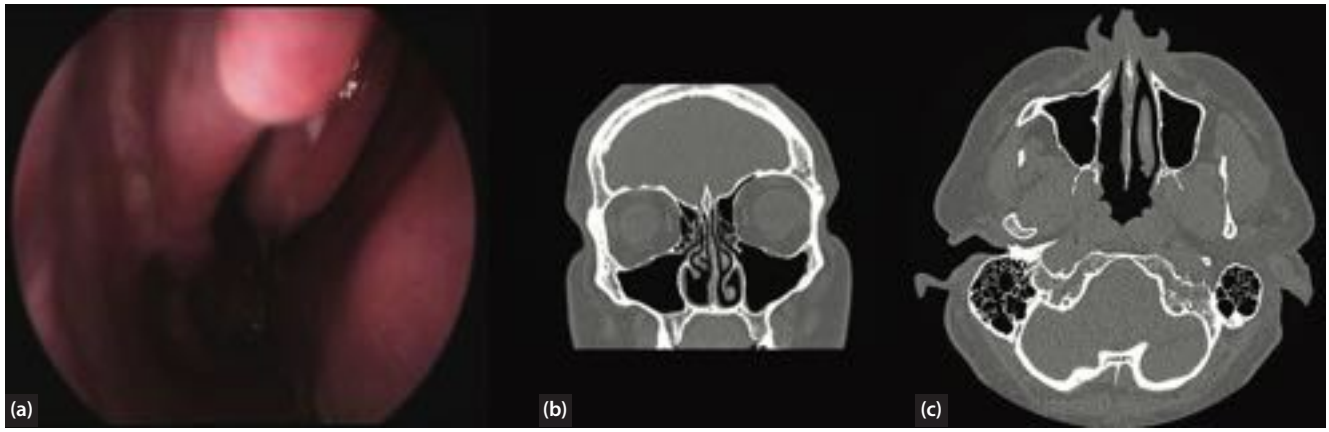


Figure 105.8 Appearance of radical excision of right inferior turbinate: endoscopic view and CT scan images.



Figure 105.9 Partially resected turbinate.

Laser surgery

Lasers can be used to reduce the size of the inferior turbinate by excision, vaporization or coagulation. They can be used under local anaesthesia as a day-case or office procedure. Several types have laser have been described and their action is dependent on the particular properties of the laser according to the wavelength. Several surgical laser techniques have been described: these vary widely from limited spot applications to the turbinate head through to spot applications, mucosal excision or vaporization of the anterior section or whole length of the turbinate.

The properties of the CO_2 laser favour tissue cutting and vaporization. Normally, a microscope, micromanipulator and angled mirrors to divert the beam onto the turbinate are required. The light energy is absorbed by water causing significant tissue heat to a depth of 4 mm but with limited collateral tissue damage. Long-term benefit and improved results compared to electrocautery have been described.[16]

The neodymium-yttrium aluminium garnet (Nd-YAG), potassium titanyl phosphate (KTP), and argon-ion lasers can all be transmitted down a flexible fibre which makes them suitable to be used under endoscopic control. They are absorbed by haemoglobin and coagulate to a limited depth. The holmium yttrium aluminium garnet (Ho-YAG) is primarily absorbed by water but is able to remove bone as well as soft tissue.[17]

Although reports suggest that laser therapy is effective, the long-term results are in general less certain.[10]

Direct microdebrider mucosal reduction surgery

Direct debridement of the inferior turbinate is utilized as an effective means of relieving nasal obstruction in patients with gross inferior turbinate hypertrophy secondary to allergic or non-allergic chronic rhinitis. The mucosa is debrided down to periosteum along the medial aspect and inferior edge of the anterior two-thirds of the inferior turbinate. Bleeding is minimal as long as the periosteum is undisturbed. Healthy normal mucosa regenerates within 6–12 weeks following surgery and mucociliary clearance problems have not been observed.

TURBINATE SURGERY IN SPECIFIC CLINICAL SITUATIONS

Rhinosinusitis and endoscopic sinus surgery

In most patients undergoing endoscopic sinus surgery for chronic rhinosinusitis, there is no need to perform inferior turbinate surgery. Chronic rhinosinusitis will induce mucosal congestion of the nasal mucosa and inferior turbinates. Following endoscopic sinus surgery and post-operative medication, the degree of mucosal inflammation within the sinuses should significantly improve, with the benefit of reduction in the secondary congestion of the turbinates. Should inferior turbinate surgery still be deemed necessary, the authors would suggest that this is restricted to a mucosal preservation technique of surgery.

Septal deviation

Compensatory enlargement of the inferior turbinate is often observed on the opposite side to a septal deflection. It would therefore seem logical that turbinate reduction surgery would be indicated at the time of septal surgery. Formal study of this dilemma has, however, shown a positive effect from submucous unilateral turbinate reduction as shown by acoustic rhinometry and patient self-assessment at 6 months following surgery.[18]

Histological studies have shown that enlargement of the inferior turbinate on the contralateral side to a septal deviation may be due to an increase in the size of the conchal bone as well as an increase in mucosal thickness.[4] This would favour submucosal conchal resection and turbinoplasty in such cases.

Although these research findings are of interest, not all studies support the concept of simultaneous turbinate reduction and it is of note from clinical experience that most septal corrective surgery is performed without inferior turbinate reduction and patients generally have a satisfactory outcome.[19] The potential risk of bleeding and adhesion formation also needs to be taken into account in deciding on whether to include turbinate reduction with septoplasty.

Septorhinoplasty

Some surgeons will routinely excise the inferior turbinates at the time of doing septorhinoplasty to maximize the chance of improving nasal obstruction. However, this will increase the potential for heavy bleeding post-operatively and is probably not going to result in any significant long-term advantage.

Sleep disordered breathing

There is a cogent argument to maximize the nasal airway in patients with sleep-disordered breathing, particularly when there may be a problem of compliance with CPAP due to nasal obstruction. This is an instance where there may be a tendency for surgeons to be radical in their approach to the inferior turbinate and to excise both turbinates whilst also correcting septal deformity. However, there is a lack of evidence to support a policy of radical excision in this group of patients and a more conservative approach is recommended. Most studies do support mucosal preservation turbinate reduction techniques as an adjunct to septal surgery for snoring, although none have demonstrated significant decrease in the apnoea-hypopnoea index of obstructive sleep apnoea patients.[20]

Inferior turbinate surgery in children

Most children with nasal obstruction have rhinitis or adenoid enlargement. Rhinitis is mostly allergic and generally improves following treatment with anti-allergic medication and allergen avoidance. Should significant nasal obstruction persist and inferior turbinates remain large, there may be a case for turbinate reduction surgery. Children with sleep disordered breathing and obstructive sleep apnoea may benefit from inferior turbinate surgery.[21] A recent comparison of adenotonsillectomy with and without microdebrider-assisted inferior turbinoplasty has shown improved results in the children who underwent turbinate reduction.[22]

A recent survey of turbinate reduction techniques in the USA showed that 80% of surgeons combined turbinate surgery with another procedure such as adenotonsillectomy, septal surgery and sinus surgery, and the most popular techniques are now the microdebrider and coblation®.[23]

COMPLICATIONS

Inferior turbinate surgery is not without risk and consent for surgery should include a discussion about complications and their subsequent management.

The most immediate significant risk is severe haemorrhage, particularly after turbinate resection.

Procedures that are destructive to the mucosa may be followed by prolonged nasal crust formation that can take several weeks if not months to improve.

Long-term risks include nasal adhesions or synechiae between the turbinate and the septum. Visual change and blindness is rare but has been reported from the use of monopolar diathermy at the posterior end of the turbinate.

The danger of performing radical resection of tissue within the nasal cavities was recognized many years ago as a cause of ozaena and mucosal atrophy. Huizing suggests that too radical turbinectomy should be considered as a 'nasal crime'.[12] Patients undergoing radical resection risk developing chronic infected smelly crusting within the nose. Fortunately, this condition is rarely seen following inferior turbinate reduction surgery in modern otorhinolaryngology.

However, total resection of the inferior turbinate does carry a risk of inducing the 'empty nose syndrome (ENS)' in which the patient complains of nasal obstruction in the absence of an obstructive cause (**Figure 105.9**).[24] The pathophysiology is unclear but probably involves altered nasal receptor sensitivity, associated with humidity and conditioning of inhaled air; neuropsychological factors have also been suspected. Visible dryness or crusting are normally not seen. Should ENS occur after inferior turbinate resection, inserting a submucosal Medpor (Porex Surgical Inc) implant to effectively create a neo-turbinate has recently been described as a successful means of management.[25]

OUTCOMES

Benefit from turbinate surgery would ideally be defined as improvement in both objective and subjective measurements of nasal airflow. Despite overwhelming data supporting the efficacy of turbinate surgery, of 93 studies reporting positive results, most were case series of retrospective reviews: only 14 reported acoustic rhinometry

results and 12 had rhinomanometric data[26] (evidence level 4 and 5). There have been few comparative studies and no systematic reviews of outcomes comparing the efficacy of different surgical techniques.[2] Furthermore, there is currently no specific quality of life assessment tool for turbinate reduction surgery.

In the largest randomized study to date, submucous resection and lateralization of the inferior turbinate resulted in sustained long-term improvement in nasal airflow and mucociliary clearance when compared to other surgical techniques (**Figure 105.10**).[27] Furthermore, over a fifth of patients in this series experienced atrophic rhinitis following radical turbinectomy.

A long-term study on a cohort of 341 patients who had submucous resection of the turbinate reported that 91.3% were symptom free at 10-year follow-up.[28] Rhinomanometric data demonstrated over 90% improvement of nasal airflow compared to the initial baseline and this was sustained at long-term follow-up.

Although newer surgical techniques such as Coblation® and radiofrequency ablation do not have long-term data yet, early results suggest that these techniques appear to offer promising short-term improvement in nasal airflow (**Figure 105.11**).[29–31] RCT data are unusual but a recent study has shown a definite reduction in turbinate enlargement and subjective improvement in nasal obstruction after bipolar radiofrequency volumetric tissue reduction (RFVTR) compared to placebo at 6–8 weeks.[32]

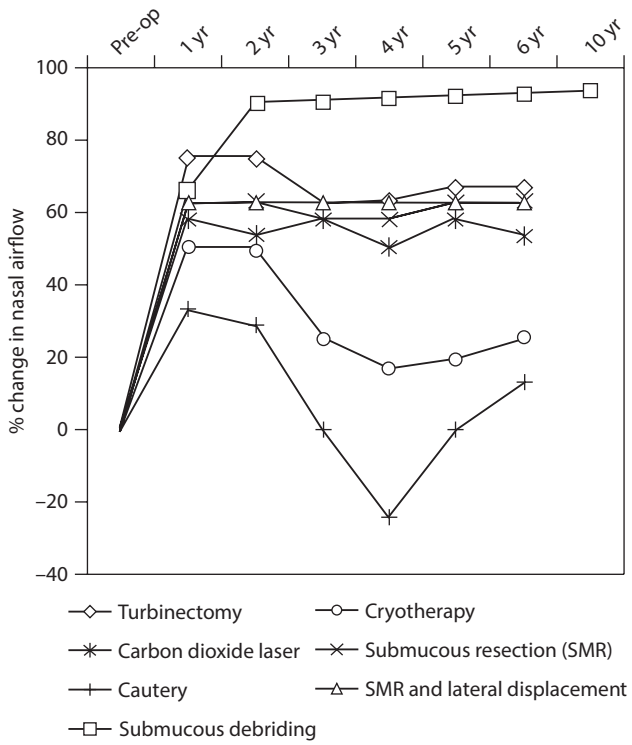


Figure 105.10 A comparison of long-term results between different surgical techniques based on average change in nasal airflow. Data for turbinectomy, carbon dioxide laser, cautery, cryotherapy, SMR and lateral displacement were derived from Passali et al.[27] The submucous debriding data was derived from Yañez and Mora.[28]

RECENT RESEARCH ON THE INFERIOR TURBINATE

Computational fluid dynamics (CFD) is a numerical simulation application that enables the visualization of flow factors (velocity, pressure, vector, streamline and vortices) under variation flow conditions and has been used in the aerospace industry and civil engineering. Although computational fluid dynamic studies (CFD) remain an experimental tool in rhinology, CFD has enabled detailed study and understanding of nasal physiology. A three-dimensional nasal cavity is constructed from either MRI or CT scans before CFD simulations are performed by a supercomputer. The physiological effects of modelling septal perforation, deviation and enlarged inferior turbinates have been studied extensively using CFD simulations.[6]

It has been demonstrated that despite a small increment of 1–2 mm in the overall dimensions of the inferior turbinate, a significant change in the air pressure around the nasal valve region occurs: nasal airflow is reduced and there is redistribution of airstreams to the upper parts of the nasal cavity.[33] The resultant negative pressure in the nasopharynx and reduced flow rate have been postulated to adversely affect the function of the surrounding muscles and mobility of the soft palate: the latter are common etiological factors for Eustachian tube dysfunction, snoring and obstructive sleep apnoea.[34]

Although CFD simulations have yet to be performed on actual post-operative cases, it is possible to simulate outcomes following turbinate surgery. Partial turbinectomy, especially when the enlarged turbinate is reduced by a third, result in the return of near-normal airstreams and aerodynamics (**Figure 105.12**).[35] In contrast, radical turbinectomy causes an alteration of nasal aerodynamics akin to that observed in atrophic rhinitis.[36] Also, excision of the lower third of the inferior turbinate lowers the ability to heat inspired air by 11.7% due primarily to inducing turbulent airflow.

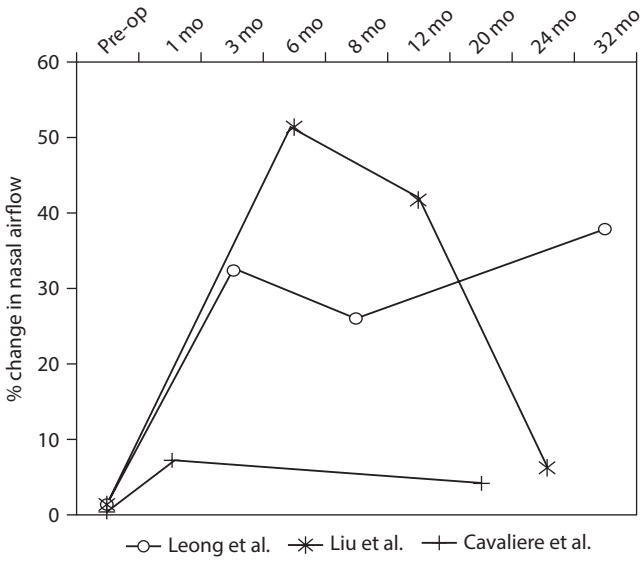


Figure 105.11 Average change in nasal airflow after Coblation® inferior turbinate reduction surgery. Data derived from Leong et al.[29] Liu et al.[30] and Cavaliere et al.[31]

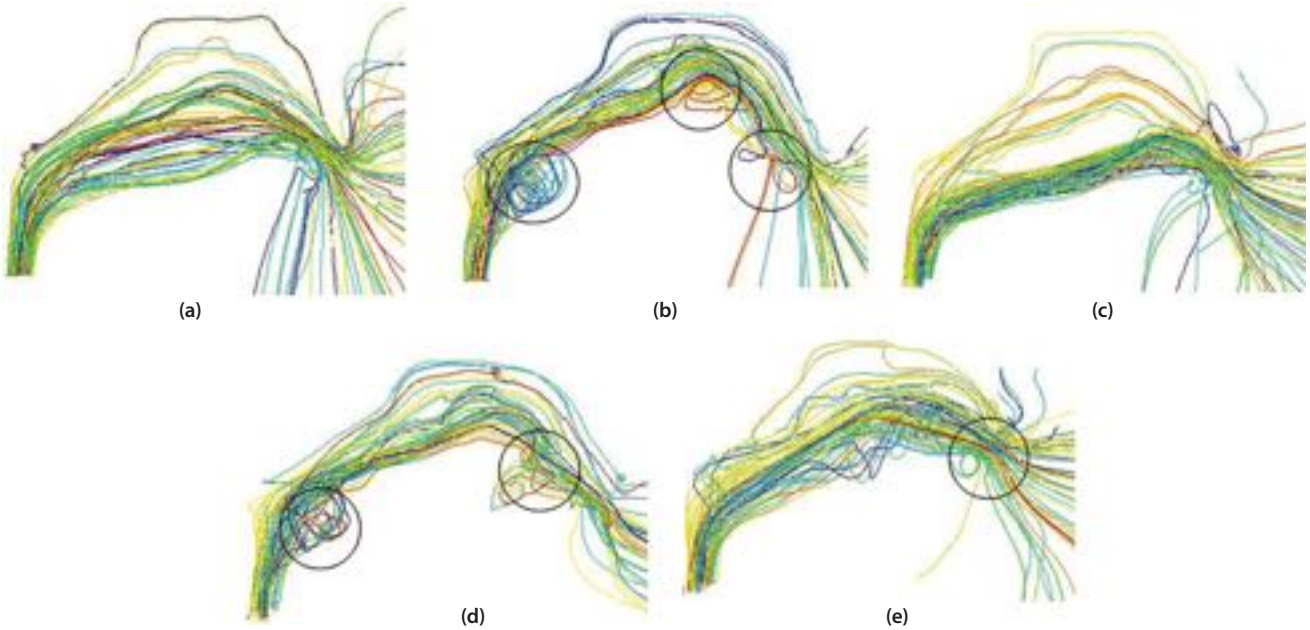


Figure 105.12 Comparison of the velocity streamlines in the nasal cavity with an inspiratory airflow rate of 17.4 L/min. The vortex areas are circled. **(a)** Healthy nasal cavity. **(b)** Enlarged inferior turbinates causing nasal obstruction. **(c)** Lower third of the inferior turbinate excised. **(d)** Head of the inferior turbinate excised. **(e)** Radical inferior turbinate resection. (With permission from Prof. D-Y Wang, National University of Singapore.)

BEST CLINICAL PRACTICE

- ✓ Warn patients and document the risk of nasal crusting post-operatively. Include the possibility of long-term recurrence of nasal obstruction and possible revision surgery in the consent process.
- ✓ Always seek information about over-the-counter self-medication for the nose and consider the possibility of rhinitis medicamentosa.
- ✓ Re-examine the inferior turbinates again 10 minutes after applying a topical decongestant to assess the effect of vasoconstriction.
- ✓ Nasal endoscopy is strongly recommended before listing patients for inferior turbinate surgery.
- ✓ Consider a sinus CT scan if there is a suspicion of chronic rhinosinusitis in patients with chronically large inferior turbinates.
- ✓ Inferior turbinate surgery can result in heavy epistaxis. Check patients are not taking anticoagulants and utilize more conservative turbinate reduction techniques in preference to more aggressive techniques.

FUTURE RESEARCH

- ➤ There is a need for RCTs to compare different techniques of inferior turbinate reduction surgery after failed medical treatment. Comparisons should clearly separate allergic from non-allergic groups and restrict groups to adults or children. Trials should include short and long-term outcome data and review complications as well as clinical effectiveness.
- ➤ The clinical entity of the 'empty nose syndrome' needs clarification. Aetiology, diagnosis and management issues need to be investigated.

KEY POINTS

- Surgery of the inferior turbinate should be deferred until the patient has undergone an adequate trial of normally-effective medication.
- Large inferior turbinates may reflect an underlying allergic rhinitis. Consider effective conservative management regimes, including allergen identification and prevention, prior to committing to surgery.
- Always consider and exclude co-existent chronic rhinosinusitis prior to operating on enlarged inferior turbinates.
- Great caution should be exercised with regard to turbinate surgery in children. Inferior turbinate surgery is best avoided if at all possible.
- Beware of excessive resection of the inferior turbinates: this can induce chronic crusting and a sense of nasal obstruction.

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LINKS TO NATIONAL GUIDANCE DOCUMENTS

Radiofrequency tissue reduction for turbinate hypertrophy – guidance (IPG495) Source: National Institute for Health and Care Excellence – NICE – 25 June 2014, https://www.nice.org.uk/guidance/ipg495

Powered microdebrider turbinoplasty for inferior turbinate hypertrophy – guidance (IPG498) Source: National Institute for Health and Care Excellence – NICE – 23 July 2014, https://www.nice.org.uk/guidance/ipg498

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CHAPTER 106

EPISTAXIS

Gerald W. McGarry

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SEARCH STRATEGY

Data in this chapter may be updated by multiple searches using the keywords: epistaxis, aetiology, management, treatment and therapies, arterial supply, venous drainage and key clinical areas. Main articles, RCTs and systematic reviews were searched. Results were augmented by a manual search through major references and texts. Many older references are cited because of their quality and value which has stood the test of time. Indeed newer publications frequently, simply repeat (often without acknowledgment) the findings of much earlier works and so in these cases I have used the original publication as the reference.

BACKGROUND

Epistaxis is defined as bleeding from the nose. This simple definition belies the difficulties associated with one of otolaryngology's commonest and most difficult to treat emergencies. The historical literature contains numerous references to epistaxis and its antiquity is reflected in the fact that the simplest treatment for a nose bleed (pinching the ala nasi) is called the Hippocratic technique.

While extensive review of the history of epistaxis is beyond the scope of this book, much of the historical literature remains relevant and students of this subject are advised to review the writings of Morgagni who even predicted nasal endoscopy in 1761![1]

SURGICAL ANATOMY OF THE NASAL VASCULAR SYSTEM

It is vital that the surgeon responsible for managing patients with epistaxis has a sound understanding of the nasal vasculature. The surgical anatomy of this system has in recent years been revisited by those who raise nasal mucosal flaps in skull base surgery and the reader is advised to read some of the articles on that subject to help consolidate understanding of this crucial area.[2]

Arterial supply

The internal and external carotid arteries supply the nose via branches which anastomose extensively within the lateral wall, septum and across the midline. On the anterior septum an arterial plexus was identified as a frequent site of haemorrhage by James Little in 1879 and the same plexus was described one year later by Kiesselbach.[3] As a result of these descriptions, the area most frequently implicated in epistaxis is known as Little's area or Kiesselbach's plexus. In the posterior nasal cavity, the vessels are larger than those in Little's area and can more easily be traced to their external or internal carotid origin.

EXTERNAL CAROTID ARTERY

The external carotid artery supplies the nasal cavity via facial and maxillary branches. The facial artery supplies the most anterior part of the septum (nasal septal rami of

superior labial artery), the vestibule (lateral nasal artery) and a small area of the nasal cavity (ascending palatine artery). The maxillary artery supply is via sphenopalatine and greater palatine branches. The greater palatine artery supplies the anteroinferior part of the nasal floor and septum.

The sphenopalatine artery is the most important supply to the nasal cavity. It enters through the sphenopalatine foramen and immediately divides into posterior septal and posterior lateral rami.[4] The posterior lateral division gives the inferior and middle turbinate arteries. These vessels were studied in detail by Burnham in 1935 and his work remains the definitive reference on this subject.[5] Burnham described how the inferior and middle turbinate arteries run in bony tunnels within the turbinates. Shaheen postulated that these bony conduits could reduce the likelihood of the arteries being involved in epistaxis.[6] The posterior septal branch of the sphenopalatine artery runs medially across the face of the sphenoid to the posterior part of the septum then takes an undulating course anteroinferiorly in the muco-perichondrium. Its terminal branches anastomose in Little's area.

INTERNAL CAROTID ARTERY

The internal carotid contributes the anterior and posterior ethmoidal branches of the ophthalmic artery. The anterior ethmoidal artery, after arising in the orbit, runs under the superior oblique muscle to the anterior ethmoidal canal in which it traverses the ethmoid and nasal cavities. It terminates in the region of the ethmoid fovea in a meningeal branch and a larger branch to the nasal roof, olfactory cleft and superior turbinate. The posterior ethmoidal artery is smaller than the anterior ethmoidal artery and is present in only 80% of individuals.[7] Like the anterior vessel, this artery runs medially but this time passes above the superior oblique muscle to enter the posterior ethmoidal foramen situated 5 mm anterior to the optic canal and 10/15 mm behind the anterior ethmoidal foramen. Within its canal, the posterior ethmoidal artery is accompanied by the sphenoethmoidal nerve and a branch of the nasociliary nerve. This vessel also divides into a terminal meningeal branch and a branch to the posterosuperior nasal cavity, olfactory sulcus and sphenoethmoidal recess.

INTERNAL AND EXTERNAL CAROTID TERRITORIES

The nasal cavity is the location of the principal internal-external carotid artery anastomoses in the head and neck. There has been debate over the relative importance of each supply to the nasal cavity. Shaheen showed that the area supplied by the ethmoidal arteries was much smaller than had previously been thought. His findings were supported by observing; sphenopalatine branches to the superior meatus and superior turbinate, the comparatively narrow calibre of the ethmoidal arteries and the fact that the larger of the two ethmoidal arteries, the anterior, is absent in as many as 14% of cadaver dissections.[6] The view that the middle turbinate marks a watershed between internal and external carotid circulations is erroneous as the arteriolar anastomotic network allows varying directions of flow to occur. Compensatory anastomotic flow for example via the facial arteries is thought to explain re-bleeding events which may occur following ligation or embolization.[8]

Venous drainage

The veins follow the arteries within the mucosa. The exception is the periarterial venous cuff surrounding the intra-osseous portions of the inferior and middle turbinate arteries. The veins of the lateral wall drain through the sphenopalatine foramen into the pterygoid venous plexus and to the internal jugular vein. Anteriorly, drainage is via superior labial and greater palatine veins to the facial vein and ultimately the external jugular system. Of particular note clinically is the retro-columellar vein running 2 mm behind and parallel to the columella. This vein is in a particularly superficial area and is a common cause of venous epistaxis in children.

Key clinical areas

WOODRUFF'S PLEXUS

The role of Woodruff's plexus (WP) in epistaxis was at one time frequently discussed, especially in the North American literature.[9, 10] Woodruff (1949) described a plexus of prominent blood vessels lying just inferior to the posterior end of the inferior turbinate (**Figure 106.1**).[11] He commented on how this plexus was a frequent site of adult epistaxis and described 14 cases of bleeding from this area. Many authors describe WP as a frequent source of so-called 'posterior' epistaxis despite the absence of any numerical evidence to support this. Shaheen in 1967 attempted to study and define WP but was unable to identify the plexus in nasal ethmoidal blocks.[6] A more recent study with endoscopic photography and anatomical micro-dissection confirmed that the plexus does indeed exist but showed it to be a venous plexus and thus very unlikely to be important in epistaxis.[12]

LATERAL WALL OR SEPTAL BLEEDING?

There is general acceptance that overall the vast majority of epistaxis occurs from Little's area but there is debate on the relative importance of various other sites. Some suggest that WP is important and others nominate the septum or other regions of the lateral wall as prime sites. Numerous studies using various methods and examination techniques have produced diverse findings.[10, 13–16] For example, Shaheen failed to find any lateral wall bleeding while Wurman did not report any septal bleeding.[10, 16] Sixty percent of bleeding points identified by el-Simily were septal whereas 62% of those found by Rosnagle were on the lateral wall.[17, 18] In a

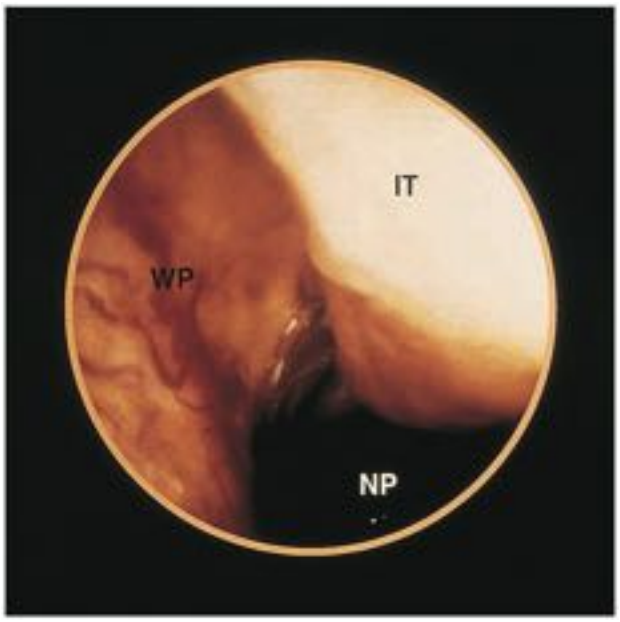


Figure 106.1 Endoscopic photograph of Woodruff's plexus (right). IT: inferior turbinate, WP: Woodruff's plexus, NP: nasopharynx.

study of 50 patients with adult primary *posterior* epistaxis, McGarry identified the bleeding point in 94% (6% not located despite endoscopy), 70% bled from the septum and 24% from the lateral wall. There was no side predilection (50% left nostril and 48% right, 2% bilateral).[19] These findings support the observation that posterior, like anterior, epistaxis is predominantly septal in origin (Figure 106.2).

ANTERIOR ETHMOIDAL ARTERY IN ENDOSCOPIC SINUS SURGERY AND IN TRAUMATIC EPISTAXIS

Detailed knowledge of this vessel is essential for surgeons carrying out endoscopic sinus surgery and for those planning its ligation for epistaxis. The artery is frequently encountered in a mesentery just below the skull base between the ethmoid fovea and the lamina papyracea. Inadvertent damage to the mesentery can lead to troublesome bleeding from the artery. Transection of the vessel during sinus surgery can result in retraction of the bleeding end into the orbit with subsequent pressure haematoma and risk of visual loss. In patients with orbito-ethmoidal fractures, severe and often intermittent epistaxis can occur due to damage to this vessel and in such cases open ligation may be the only option to control the bleeding. The vessel can be ligated as a treatment for epistaxis via an external (medial canthal) approach or endoscopically (trans-ethmoidal). The open approach via a medial orbital incision is the most reliable and preferred method and the artery may be clipped, bipolared or ligated without entering the bulbar fascia (Figures 106.3 and 106.4).

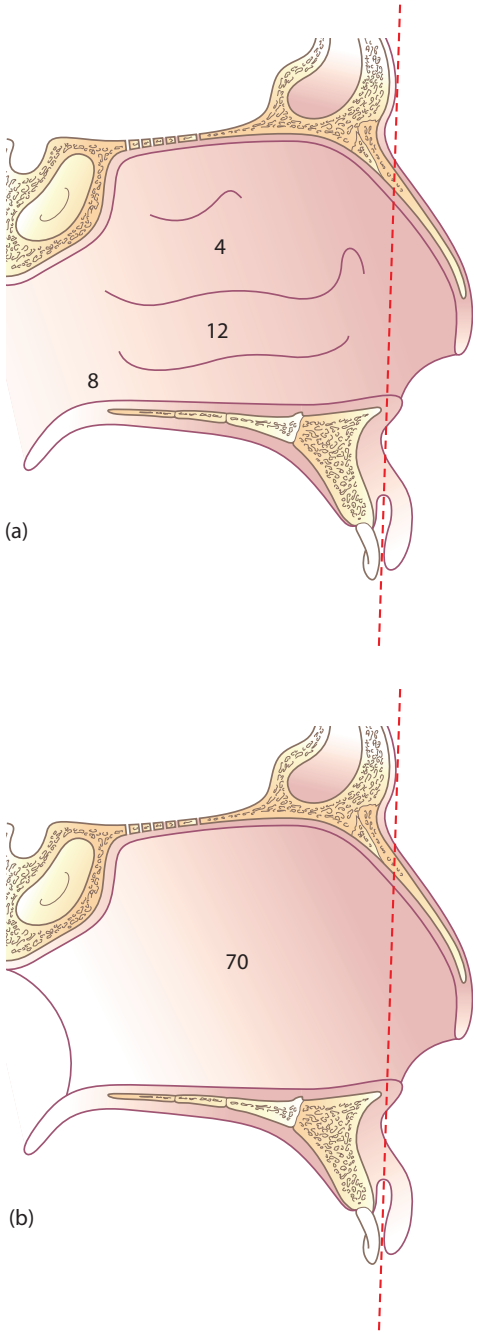


Figure 106.2 Diagram of sites of bleeding in posterior epistaxis. **(a)** lateral nasal wall, **(b)** septum. Numbers are percentages (6% not located).

SURGICAL ANATOMY OF THE SPHENOPALATINE FORAMEN

The sphenopalatine foramen is the portal for the major arterial supply of the nasal cavity. Lateral to the foramen lies the pterygopalatine space. The foramen is formed by a U-shaped notch in the vertical portion of the palatine bone which is closed posterosuperiorly by the sphenoid bone. The foramen transmits the sphenopalatine artery, vein and the nasal palatine nerve (maxillary division of

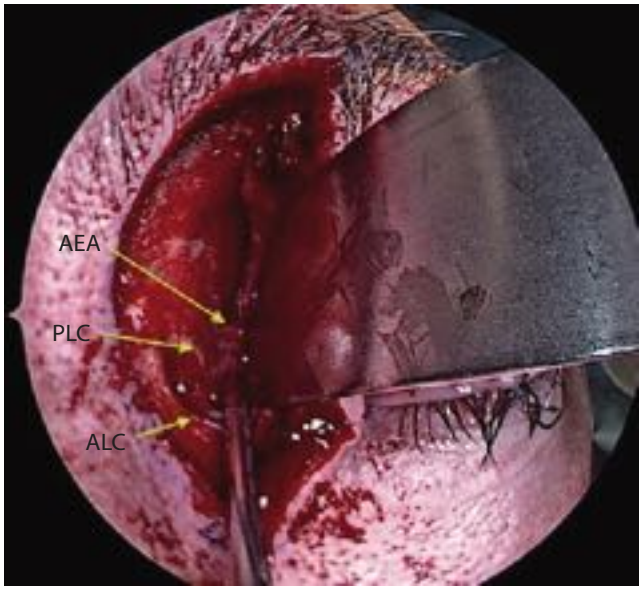


Figure 106.3 Open approach to ligate left anterior ethmoidal artery. ALC: anterior lacrimal crest, PLC: posterior lacrimal crest, AEA: anterior ethmoidal artery.

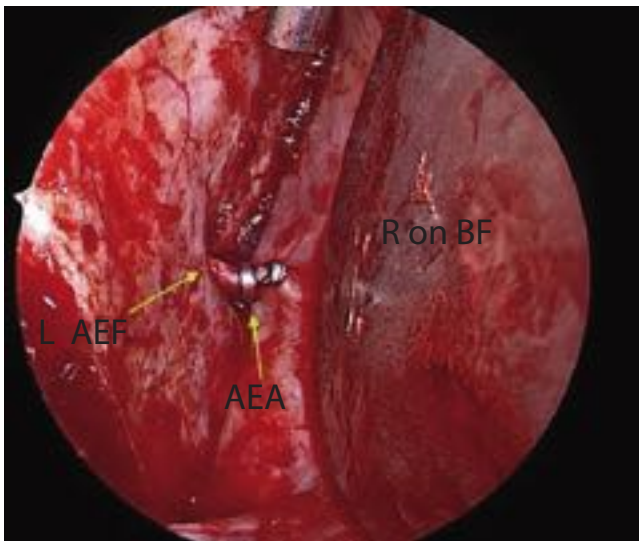


Figure 106.4 Operative field in ligation of anterior ethmoidal artery (left). RonBF: retractor on bulbar fascia, LPEF: lamina papyracea and anterior ethmoidal foramen, AEA: anterior ethmoidal artery with titanium clips applied.

the trigeminal nerve). Clinically this foramen is the key to the procedure of endonasal endoscopic sphenopalatine artery ligation (ESPAL). Surgical localization of the foramen can be difficult. Bolger et al. studied a small bony projection which lies anterior to the foramen in 96% of cases.[20] This landmark is called the crista ethmoidalis and its recognition during surgery may help in finding the foramen. The crista is variable in size but consistent in its position anterior to the artery and so it is a key landmark for the endoscopic surgeon (See Figure 106.8).

SURGICAL ANATOMY OF THE BLOOD SUPPLY OF THE INFERIOR TURBINATE

Severe secondary epistaxis is a serious complication of inferior turbinectomy. Understanding the vascular supply of the inferior turbinate may help in both the avoidance and the management of this complication. At its origin, the inferior turbinate artery runs anteroinferiorly in the submucosa where it is vulnerable to damage during radical turbinectomy. On reaching the inferior turbinate, it divides into three parallel branches each of which run in bony tunnels within the substance of the turbinate. These tunnels with their peri-arterial cuff of fibrous tissue and venous elements may prevent the artery constricting following turbinectomy and may predispose to post-operative haemorrhage.[4, 14]

Attempts to control haemorrhage following turbinectomy should be directed towards the posterosuperior aspect of the inferior turbinate where pressure or bipolar to the submucosal segment of the artery should prove effective.

CLASSIFICATION OF EPISTAXIS

Clinical classification

Traditionally, epistaxis has been classified on the basis of presumed aetiology and publications include long lists of factors thought to cause the condition.[21] As most cases are idiopathic and since case-control evidence does not exist for most of the putative aetiological factors, a causation-based classification is inappropriate.

A clinical classification based on the clearly observed patterns of presentation of epistaxis is more useful.

Adult or childhood epistaxis

There is a pronounced bimodal distribution in the age of onset of epistaxis. The condition is common in childhood, becomes less common in early adult life and then peaks in the sixth decade. Thus, while it can occur at any time in life, this variation with age is sufficiently pronounced to classify epistaxis as **childhood** (less than 16 years) or **adult** (greater than 16 years).

Primary or secondary

Between 70% and 80% of all cases of epistaxis are idiopathic, spontaneous bleeds without any proven precipitant or causal factor.[22] This type of bleeding can be classified as **primary** epistaxis. As our understanding of the aetiology advances, the number of cases of true primary epistaxis will decrease but, at present, this definition encompasses the majority of cases.

A small proportion of cases are due to a clear and definite cause such as trauma, surgery or anti-coagulant overdose and can be classified as **secondary** epistaxis. The distinction between primary and secondary epistaxis is

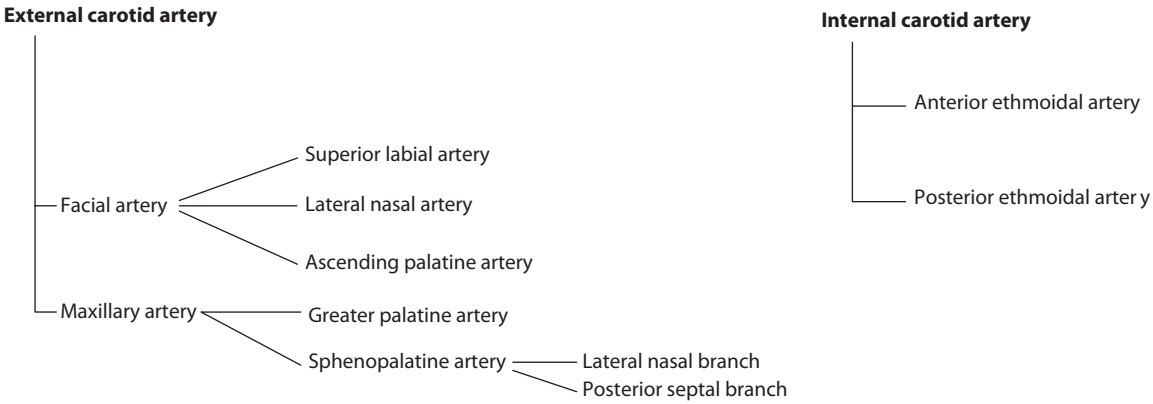


Figure 106.5 Schematic of blood supply to nasal cavity.

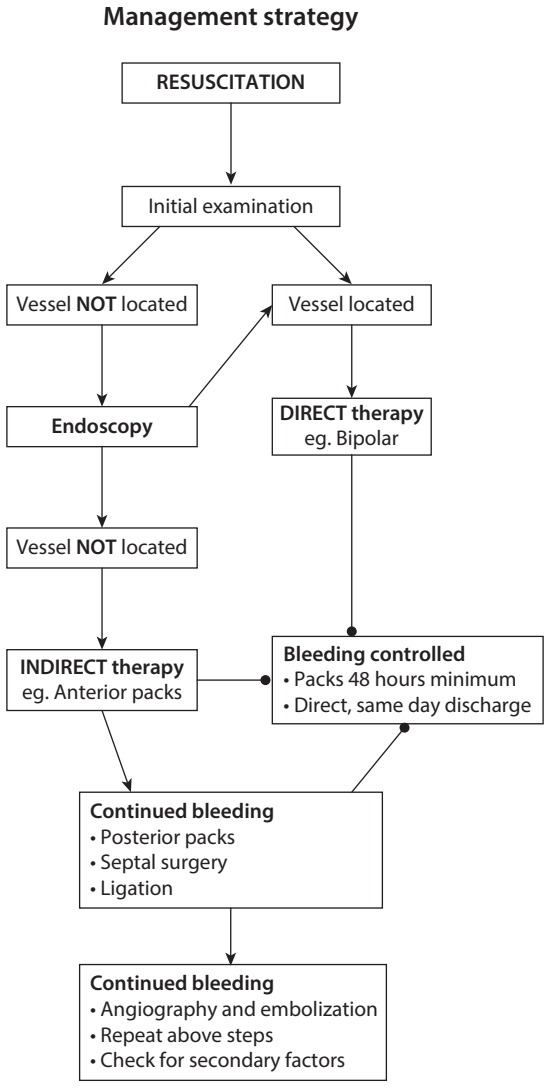


Figure 106.6 Management algorithm.

more than academic as the management of each type is quite different, e.g. techniques used to control primary epistaxis are unlikely to be successful for a secondary epistaxis due to coagulopathy.

Anterior and posterior epistaxis

The terms anterior and posterior epistaxis are frequently used but the definitions are imprecise and inconsistent and really not very useful. Pearson attempted to standardize the term posterior epistaxis as a bleeding point which cannot be located despite examination with a headlight, vasoconstrictors and suction.[9] While this is a clinically useful definition, modern techniques of examination and endoscopy, are likely to see true posterior bleeds moving further and further back! Attempts to define anterior epistaxis as bleeding from Little's area are problematic, due to the lack of a precise definition of Little's area. To standardize the use of the term 'posterior epistaxis' and 'anterior epistaxis', the author proposes that their use be restricted to the following:

- **Anterior epistaxis** – bleeding from a source anterior to the plane of the piriform aperture. This includes bleeding from the anterior septum and rare bleeds from the vestibular skin and mucocutaneous junction. These should be the bleeds where the clinician will easily locate the bleeding point and management should be simple.
- **Posterior epistaxis** – bleeding from a vessel situated posterior to the piriform aperture, i.e. from within the nasal cavity. This allows further subdivision of these posterior or nasal cavity bleeding points into lateral wall, septal and nasal floor bleeding. These are the bleeds that will challenge the clinician the most.

Further descriptive classification based on the severity and frequency of the bleeding can also be used, e.g. whether recurrent (usually minor and non-life-threatening) or acute, severe. It is of interest that for adults at least, the severity of an epistaxis is inversely proportionate to its frequency. That is, recurrent primary epistaxis tends to be minor, non-life-threatening and often easily managed whereas acute, severe epistaxis is often a one-time event resulting in hospitalization and carrying a high morbidity.

For the remainder of this chapter, the clinical syndromes of adult epistaxis are discussed. Childhood epistaxis is discussed elsewhere in this textbook (Table 106.1).

TABLE 106.1 Classification of epistaxis

- **Primary:** no proven causal factor
- **Secondary:** proven causal factor
- **Childhood:** <16 years
- **Adult:** >16 years
- **Anterior:** bleeding anterior to piriform aperture
- **Posterior:** bleeding point posterior to piriform aperture

ADULT PRIMARY EPISTAXIS

Demography

Adult primary epistaxis is the variant that challenges otolaryngologists the most. The condition can occur at any age but is mainly a disease of the elderly. Between 7% and 14% of adults have epistaxis at some time or other but only 6% of cases are seen by otorhinolaryngologists.[23, 24] The peak presentation is the sixth decade and most large case series reveal a slight male predominance (55 male, 45 female).[15, 25] Most cases are minor, self-limiting or easily managed anterior bleeds but nevertheless a significant number require admission to hospital. The annual rate of admission to otolaryngology units in the northern UK with adult epistaxis is 30 per 100,000 per annum.[26] In Scotland, epistaxis is the commonest reason for adult admission to an ENT ward.[27] Fewer than 10% of hospitalized patients require a general anaesthetic procedure to secure haemostasis.[28] It is not surprising that such a common haemorrhagic condition of elderly patients is associated with significant morbidity and mortality. After head and neck cancer, epistaxis stands out as a prominent cause of mortality in ENT patients.

Aetiology

By definition the aetiology of primary epistaxis is unknown but there are clear suggestions that systemic factors may be important (Table 106.2).

CHRONOBIOLOGY

The frequency of admission is greatest in the autumn and winter months.[28, 29] This seasonal variation correlates with fluctuations in environmental temperature and humidity.[30] A chronobiological rhythm is also observed at the circadian level where onset of bleeding and hospital admission show a biphasic pattern with peaks in the morning and late evening.[31, 32] There are strong parallels between the circadian rhythms of primary epistaxis and those observed in subarachnoid haemorrhage.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAID)

Adult pattern epistaxis is associated with the use of NSAID. Patients are more likely than controls to consume NSAID. The NSAID used include prescribed and self-administered compounds especially aspirin. The action of non-steroidal anti-inflammatory drugs is mediated via an anti-platelet aggregation effect due to altered platelet membrane physiology.[33–35]

ALCOHOL

Similar aetiological associations to those of NSAID have been found with alcohol. Epistaxis patients are more likely to consume alcohol than matched control patients and are more likely to have consumed alcohol within 24 hours of

hospital admission than other emergency admissions. The use of alcohol by epistaxis patients is associated with a prolongation of the bleeding time despite normal platelet counts and coagulation factor activity. Once again, the effects of NSAID and alcohol mirror those reported in subarachnoid haemorrhage.[36, 37]

HYPERTENSION

This has long been considered a cause of epistaxis. However, a number of large studies have failed to show a causal relationship between hypertension and epistaxis.[38] Attempts to correlate epistaxis with secondary effects of hypertension or with the severity of hypertension have proved inconclusive.[39] Even if not causal, elevated blood pressure is observed in almost all epistaxis admissions. This apparent hypertension in acute admissions may be a result of anxiety associated with hospital admission and the invasive techniques used to control the bleeding.

SEPTAL ABNORMALITIES

Septal abnormalities are common and depending on the definition used between 1% and 80% of the population have a significant deviation.[40] Given such a high prevalence, the perceived association between epistaxis and septal abnormalities could be coincidence. One study found an association between septal deviation and *recurrent* epistaxis in young subjects.[41] There is no clear case control evidence of an association between septal abnormalities and adult epistaxis.

Management

In order to be effective the management of adult epistaxis should follow an incremental sequence of interventions (**Figure 106.6**). The theoretical ideal treatment requires identification of the bleeding point and direct control of the bleeding, at source. First, the patient must be resuscitated, bleeding slowed, the nasal cavity examined and a treatment plan established.

RESUSCITATION

Given the high prevalence of coexistent cardiovascular disease, prompt and effective resuscitation is required. Sixty-five percent of cases are referred from an accident and emergency department and thus many will already have had some form of therapy.[28] First aid by pinching the ala nasi (the Hippocratic technique) is supported by the frequency with which the anterior part of the septum is the source of bleeding. Otorhinolaryngologists should ensure medical students, nurses and other team members are fully aware of the precise technique for compression of the nostrils. In one study of Accident and Emergency staff, only 43% of trained medical and nursing staff could correctly demonstrate the Hippocratic technique.[42] Recent surveys of junior doctors show that nothing much has changed and there is still poor understanding of initial management of epistaxis![43] History and examination will help in assessing the amount of blood lost. In all but the most minor of bleeds intravenous access is established and baseline blood estimations are taken. A detailed history should be taken, looking for predisposing factors. Routine coagulation studies in the absence of a positive history are not indicated.[15, 44]

TABLE 106.2 Summary of aetiological evidence of adult primary epistaxis

- **Weather:** proven association
- **NSAID:** proven association
- **Alcohol:** proven association
- **Hypertension:** no association
- **Septal deviation:** no association

ASSESSMENT

The patient should be assessed in a semi-recumbent position and nursing assistance is mandatory. Everyone involved should wear protective visors and clothing as blood aerosol contamination is common, especially when inserting nasal packing.[45] Basic equipment includes: couch or reclining chair, headlight, suction, vasoconstrictor solutions (lignocaine and pseudoephedrine solution has now widely superseded cocaine solutions) and a selection of packs, tampons and cautery apparatus. All specialist ENT units should also have access to rod lens nasal endoscopy equipment and bipolar electrodiathermy.

DIRECT OR INDIRECT THERAPIES

Treatment may be divided into direct (bleeding point specific therapies) or indirect treatments. Indirect treatments are those that do not require identification of the bleeding point. Direct treatments are logically and theoretically superior and, therefore, a committed search for the bleeding vessel should always be undertaken.[9]

DIRECT MANAGEMENT

There has been a slow but steady uptake of direct strategies throughout the UK. Despite this, however, a minority of cases admitted to otolaryngology units in the UK are managed by direct control of the bleeding point.[28] The reluctance to use direct approaches may be due to a perceived difficulty in locating bleeding points, but probably also reflects the fact that over 70% of cases are managed by the most junior members of the specialty.[27] Anterior epistaxis is usually very straightforward to identify and treat and over 90% of cases can be controlled with silver nitrate cautery or bipolar. The use of packing for primary anterior epistaxis is unwarranted and should be strongly discouraged.

Posterior epistaxis can occur from the lateral wall, floor or septum. As previously discussed there is evidence to support the septum as the principal locus. Systematic examination with a headlight will identify most bleeding points. Once identified, bleeding points can be directly

controlled with bipolar diathermy, chemical cautery (difficult in posterior bleeds), electro-cautery or direct pressure from miniature targeted packs.[46]

Endoscopic control

Failure to locate the bleeding point on initial examination is an indication for examination with a rod lens endoscope. Endoscopy identifies the source of posterior epistaxis in over 80% of cases.[26, 10, 14, 46] Endoscopy enables targeted haemostasis of the bleeding vessel using insulated hot wire cautery or modern single fibre bipolar electrodes.[26] Success rates for immediate control by endoscopic guidance are consistently reported in the 90% range.[26] Monopolar diathermy should not be used in the nasal cavity as there have been reports of blindness due to current propogation.[47]

Adoption of direct (including endoscopic) management strategies has been shown to facilitate out-patient management and to significantly reduce in-patient stay (**Figure 106.7**).[26]

Indirect therapies

Failure to find the bleeding point is an indication for use of one of numerous traditionally favoured indirect strategies.

Nasal packing

Packing can be anteriorly or posteriorly placed. Anterior packing has been the mainstay of treatment for centuries. Skills required for accurate packing are difficult to acquire and with modern techniques of nasal surgery, less frequently encountered in a surgeon's training.

Ribbon gauze impregnated with petroleum jelly or Bismuth Iodoform Paraffin paste (BIPP) is inserted the entire length of the nasal cavity in attempt to tamponade the bleeding. Once inserted, the packs are left *in situ* for between 24 and 72 hours.[48] Continued or re-bleeding with packs *in situ* is observed in up to 40% of cases.[49] Complications of packing include; sinusitis, septal perforation, alar necrosis, hypoxia and myocardial infarction. Packing is usually considered an indication for antibiotic cover but the evidence base for this is lacking.



Figure 106.7 Single fibre bipolar unit for direct management of epistaxis.

Modern and now more frequently used variations on anterior packing include special tampons (Merocel® and Kaltostat®) and balloon catheters (Brighton or Epistat). Balloons and tampons are favoured by non-specialists as first-line therapy but are associated with similar complications and re-bleed rates to packing. If over inflated, balloons will prolapse anteriorly and posteriorly with the risk of hypoxia and alar necrosis.[50] There is no evidence of greater efficacy for packs compared to balloons or tampons.

Persistent bleeding or re-bleeding is an indication for further examination of the nasal cavity and renewed search for the bleeding point. There is no clear, universally agreed definition of failed packing but patients who continue to bleed should proceed to surgical management sooner rather than later. In the author's institution the agreed protocol is that all admitted epistaxis patients should be haemostased within 24 hours of admission. If this has not been achieved a rhinologist should be summoned to review the case. Patients should not be left on a ward with blood oozing from nasal packs or tampons while on-call teams change shift!

Hot water irrigation

Irrigation of the nasal cavity with water at 50 °C has been proposed as an alternative to packing. Although this technique has seen little use in the UK, Stangerup reports similar levels of success comparing the hot water technique to anterior packing and balloon tamponade.[49, 51] Up to one third of patients find the technique difficult to tolerate and so use of specialized irrigation catheters is recommended. The exact mechanism of action of this treatment is unclear but may, paradoxically, involve reflex vasodilatation and reduction in nasal lumen dimensions.[52]

Systemic medical therapy

Tranexamic acid and epsilon aminocaproic acid are systemic inhibitors of fibrinolysis. Tranexamic acid has been shown to reduce the severity and risk of re-bleeding in epistaxis at a dose of 1.5 g three times a day. Tranexamic acid does not increase fibrin deposition and so does not increase the risk of thrombosis. Pre-existing thromboembolic disease is a contraindication. At present antifibrinolytics are best reserved as adjuvant therapy in recurrent or refractory cases. There has been a recent increase of interest in this drug and it may become more important in managing secondary bleeds due to novel anticoagulants.[53]

Topical haemostatic agents

Topical thrombin compounds have been marketed for operative field haemostasis in surgery. The use of these compounds in epistaxis is attractive to those looking for a simple fix. Compounds such as Floseal (Baxter Healthcare) have been used and results have been variable with some authors finding no real benefit.[54] In the author's experience these agents can only be considered an additional tool for the management of difficult (especially secondary) bleeds

and should never replace the main aim of identifying and directly treating the source of the bleeding.

Surgical management

If the techniques described above fail, surgical intervention is required. Endoscopic diathermy of the bleeding point under anaesthetic may control the bleeding but if the vessel still cannot be controlled (or even located) indirect surgical therapy is indicated. Surgical management for continued epistaxis consists of:

- Posterior packing
- Ligation techniques
- Septal surgery techniques
- Embolization techniques.

POSTERIOR NASAL PACKS

Posterior packing should be viewed as largely obsolete but in extreme cases or where no specialist rhinologist is available it may be indicated. It can, in extremis, be carried out under local anaesthetic but general anaesthesia is preferable. Nasopharyngeal tamponade is achieved using special gauze packs inserted transorally and positioned by means of tapes passed from the posterior choana to the anterior nares bilaterally. These posterior 'Bellocq' packs are secured against anterior gauze packing. The securing tapes are tied over padding positioned to protect the columella from pressure necrosis. An easier and perhaps kinder alternative is to insert a Foley urethral catheter (size 12 or 14) along the floor of the nasal cavity until the nasopharynx is reached. The Foley catheter is inflated with 15 ml of water, pulled forward to engage in the posterior choana and anterior packing is then inserted. The Foley catheter needs to be secured anteriorly taking care not to cause pressure over the columella. Posterior packing causes considerable pain and may cause hypoxia secondary to soft palate oedema. Sinusitis and middle ear effusions are common. More serious complications include necrosis of the septum and columella. Antibiotics and opiate analgesia are necessary. Once they have been placed, posterior packs should be left in position for a minimum of 48 hours or at least until a rhinological surgeon can attend to the patient.

LIGATION TECHNIQUES

Ligation is reserved for intractable bleeding where the source cannot be located or controlled by the techniques described above. Knowledge of the blood supply of the nasal cavity and the likely sources of epistaxis will inform the choice of ligation technique (**Figure 106.5**).

Ligation should be performed as close as possible to the likely bleeding point thus the hierarchy of ligation is:

- Sphenopalatine artery
- Internal maxillary artery
- External carotid artery
- Anterior /posterior ethmoidal artery.

Endonasal endoscopic sphenopalatine artery ligation (ESPAL)

ESPAL conforms to the ideal of controlling the bleed as close as possible to its nasal source. The sphenopalatine artery is the main supply of the nasal cavity and thus the most logical target for ligation. Modern endoscopic techniques have seen an increase in popularity of this procedure and it has now largely replaced all other ligations as the procedure of choice. The operation has been performed with an operating microscope but much more commonly using modern endoscopic techniques. Under general or local anaesthetic, an incision is made approximately 8 mm anterior to and under cover of the posterior end of the middle turbinate. The incision is carried down to the bone and a mucosal flap is elevated posteriorly until the fibroneurovascular sleeve arising from the sphenopalatine foramen is identified. The foramen can be difficult to identify but its location is signalled by the crista-ethmoidalis.[20] Once the main vessel is identified, it can be ligated using haemostatic clips (**Figure 106.9**) and divided or coagulated using bipolar diathermy (**Figure 106.8**). In some series success rates for this procedure have reached almost 100%.[55] Complications including re-bleeding (anastomoses), infection and nasal adhesions are generally less common than with other procedures.

Internal maxillary artery ligation (IMAL)

This was more frequently used prior to the development of ESPAL procedures. The artery is exposed

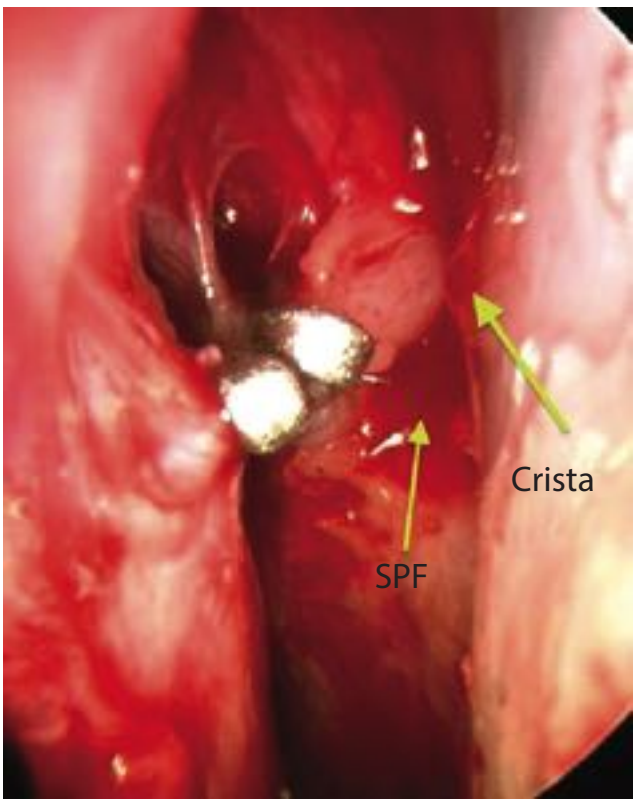


Figure 106.8 Haemostatic clips applied to main trunk of sphenopalatine artery (left) in procedure of ESPAL. Crista: crista ethmoidalis, SPF: sphenopalatine foramen.



Figure 106.9 Rotatable ligation clip applicators suitable for ESPAL.

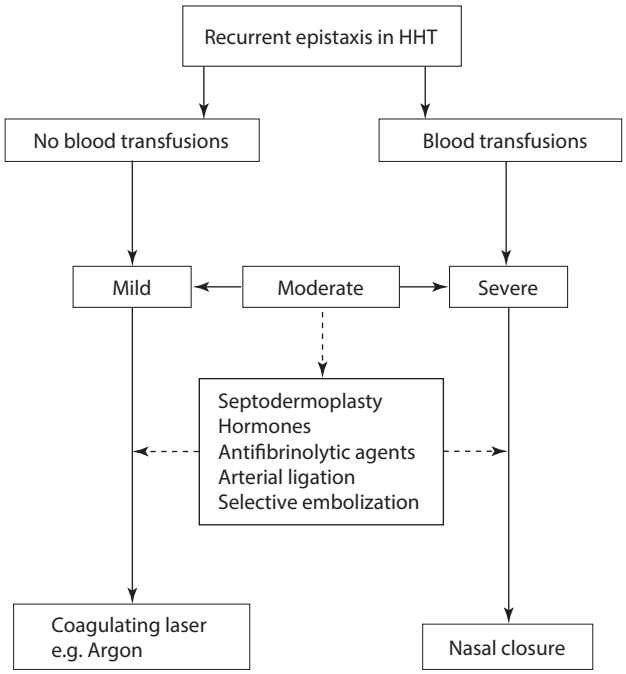


Figure 106.10 The management of HHT. From Lund and Howard, *Am J Rhinol* with permission.[68]

trans-antrally via anterior (sublabial) or combined anterior and medial (endoscopic) techniques. In the traditional sublabial approach an antrostomy is formed taking care to preserve the infra-orbital nerve. The mucosa of the posterior wall of the antrum is then elevated and a window is made through into the pterygopalatine fossa. The branches of the internal maxillary artery are identified pulsating within the fat of the fossa and are carefully dissected out prior to clipping with haemostatic clips. The proximal internal maxillary artery, descending palatine and sphenopalatine branches are all clipped and ideally divided. An endoscopic variation of this technique uses a middle meatus antrostomy as an instrument port with a 4 mm endoscope is inserted through a small canine fossa antrostomy.[56] Trans-antral ligation controls haemorrhage in 89% of cases and is comparable to embolization in both cost and efficacy.[57] Endoscopic trans-antral ligation of the internal maxillary artery can also be carried out via a middle meatus antrostomy and is occasionally required when control of a damaged sphenopalatine artery is lost during ESPAL. Complications include: sinusitis, damage to the infra-orbital nerve, oro-antral fistula, dental damage and anaesthesia and rarely ophthalmoplegia and blindness.

External carotid artery ligation (ECAL)

ECAL represents a step further away from the nasal source of bleeding. Nevertheless, the relative technical ease of this procedure justifies its use in extreme cases and by non-rhinologists. This procedure can be carried out under local or general anaesthetic using either a skin crease incision or a longitudinal incision parallel with the anterior border of the sternomastoid. The carotid bifurcation is identified and the external carotid confirmed, double checked for arterial branches and then ligated in continuity. Some authors advocate anterior and posterior ethmoidal artery ligation as an adjuvant to this procedure. In one study, external carotid artery ligation secured haemostasis in 14 out of 15 patients.[58] Complications include wound infection, haematoma and neurovascular damage.

Anterior/posterior ethmoidal artery ligation (EAL)

Given the minimal contribution of these arteries to the nasal blood supply, their ligation is best reserved as an adjuvant to one of the procedures described above or in cases of confirmed ethmoidal bleeding (e.g. ethmoidal fracture, iatrogenic tear). The arteries are approached by a medial canthal incision which is carried down to the bone of the anterior lacrimal crest. Periosteal elevators are then used to elevate and laterally retract the bulbar fascia. The anterior ethmoidal artery is seen as a fibro-neurovascular mesentry running from the bulbar fascia into the anterior ethmoidal foramen. The vessel is clipped and divided and dissection is continued to identify the posterior artery which is located approximately 12 mm behind. Endoscopic trans-ethmoidal ligation of the anterior ethmoidal artery has been described. The popularity of ligation of these vessels in primary epistaxis possibly reflects the technical ease of the open procedure rather than any logical reason for ligating vessels with such a small contribution to the nasal blood supply (**Figures 106.3** and **106.4**).

SEPTAL SURGERY

When epistaxis originates behind a prominent septal deviation or vomero-palatine spur, septoplasty or submucosal resection (SMR) may be required to access the bleeding point. Some authors have advocated septal surgery as a primary treatment for failed packing. The rationale is that by elevating the mucoperichondrial flap for septoplasty or SMR, the blood supply to the septum is interrupted and haemostasis secured. In one study a strategy involving SMR and re-packing was found to be more effective and economic than ligation in patients who had failed with

packing, however, this was prior to widespread adoption of ESPAL techniques.[59]

EMBOLIZATION

Embolization under angiographic guidance has been shown to control severe epistaxis in between 82% and 97% of cases.[57, 60, 61] Under local anaesthetic, transfemoral Seldinger angiography is used to identify the bleeding points and display the nasal circulation. It is essential to exclude arteriovenous malformations, aneurysms and fistulae prior to embolization. Once the bleeding vessel is identified, a fine catheter is passed into the internal maxillary circulation and particles (polyvinyl alcohol, tungsten or steel microcoils) are used to embolize the vessels. The ipsilateral facial artery is also embolized in order to prevent re-circulation. Complications include skin necrosis, paraesthesia, cerebrovascular accident and groin haematomas.

Embolization is of similar efficacy to ligation techniques and, therefore, choice will depend on local expertise, availability and experience. The risks of embolization mean that is should be reserved for failed ligations or where no rhinological surgical expertise is available.

Adult recurrent epistaxis

Recurrent bleeding is more commonly seen in children. When recurrent bleeds occur in adults, secondary epistaxis is most likely. Bleeding is usually minor and troublesome rather than life-threatening and it is uncommon to see bleeding by the time the patient presents. A full and detailed history and examination should identify factors such as aspirin use, liver disease or bleeding from the margins of a septal perforation. Rarely nasal tumours present with recurrent blood-stained discharge which should be distinguished from epistaxis per se. Patients using topical nasal medications (particularly steroid sprays) frequently report minor recurrent bleeds.

If a bleeding point can be identified cautery is used but often no single vessel can be identified and an area of vestibulitis is found. Evidence for the efficacy of topical antiseptic creams is available from paediatric studies and it is likely (but unproven in adults) that chlorhexidine and neomycin creams may reduce the frequency of bleeding. An area of debate is what to do when aspirin being used for cardiovascular prophylaxis is responsible for recurrent bleeds. If there is a history of cardiovascular disease or vascular graft surgery then aspirin should not be discontinued, otherwise temporary cessation of aspirin may be required to allow the recurrent bleeding to settle.

SECONDARY EPISTAXIS

Epistaxis is commonly observed in patients with coagulopathy secondary to liver disease, leukaemia or myelosuppression. In such cases, treatment of the epistaxis demands close liaison with haematologists and physicians. The following causes of secondary epistaxis deserve special mention.

Trauma

Post-traumatic nasal haemorrhage does not conform to the normal pattern of epistaxis and its origin and severity is almost infinitely variable. Persistent bleeding can occur from the ethmoidal arteries following fronto-ethmoidal fracture. In this case the vessels may be lacerated, incompletely divided or even held open by fractures through their bony mesentries. Severe haemorrhage refractory to packing should be managed by open approach ligation.

Catastrophic bleeding has been reported after head injuries due to delayed rupture of an internal carotid artery pseudo-aneurysm. Thus persistent or unexpectedly severe bleeding even some time after a head injury should be seen as an indication for CT scanning and angiography.[62]

Post-surgical

Bleeding can occur after almost any nasal surgery and is seldom difficult to manage. An exception is the severe haemorrhage which occurs in between 3% and 9% of inferior turbinectomies.[63] As previously discussed bipolar to the main branch of the inferior turbinate artery will usually secure haemostasis. Anterior subtotal turbinectomy may carry a reduced risk of post-operative bleeding.[63]

Iatrogenic damage to the anterior ethmoidal artery during endoscopic sinus surgery should be managed by bipolar of the vessel. Retraction of the vessel into the orbit can give rise to a tension haematoma of the orbit and is a surgical emergency (see elsewhere).

Massive and usually fatal epistaxis can result from damage to the internal carotid artery during posterior ethmoid or sphenoid sinus surgery. The bleeding is usually uncontrollable but packing, angiography and embolization may be tried.

Warfarin

Patients on warfarin constitute between 9% and 17% of epistaxis admissions.[27, 64] Bleeding may be due to overdose or loss of control but can also occur in patients whose INR is within the therapeutic zone. With warfarin, direct therapies seldom work and packing may be required. Bleeding is often from multiple sites and attempts at instrumentation lead to further mucosal damage and bleeding. After resuscitation, anterior packs should be gently inserted and the haematology team consulted. With large areas of bleeding or oozing fibrin glue has been used as a haemostatic dressing.[65] When deciding to reduce, stop or even reverse warfarin, the medical history and the severity of the epistaxis must be considered. If the INR is within the therapeutic range and treatment seems to be controlling the bleeding it may be safe to continue the warfarin.[64]

New oral anticoagulants: TSOACs

New target specific oral anticoagulants such as Rivaroxiban and Dabigataran are seeing increased use throughout the healthcare system. As a result numbers of secondary epistaxis cases in patients on these medications

are being seen in our ENT units. Unlike vitamin K antagonists the reversal of these new agents is often difficult to achieve and can be incomplete. Siegal has written a useful paper on the subject.[66]

When dealing with epistaxis in patients on these compounds ENT surgeons are advised to liaise at the earliest opportunity with the local haematology team. In addition to discussing with haematologists about anticoagulant reversal it is important that no steps are taken to stop or reverse agents without first clarifying the indication for the medication. Liaison with cardiologists may be required to avoid catastrophic complications (e.g. stent occlusion) as a result of withholding antiplatelet or anticoagulant medication for what may even after all prove to be a very minor epistaxis.

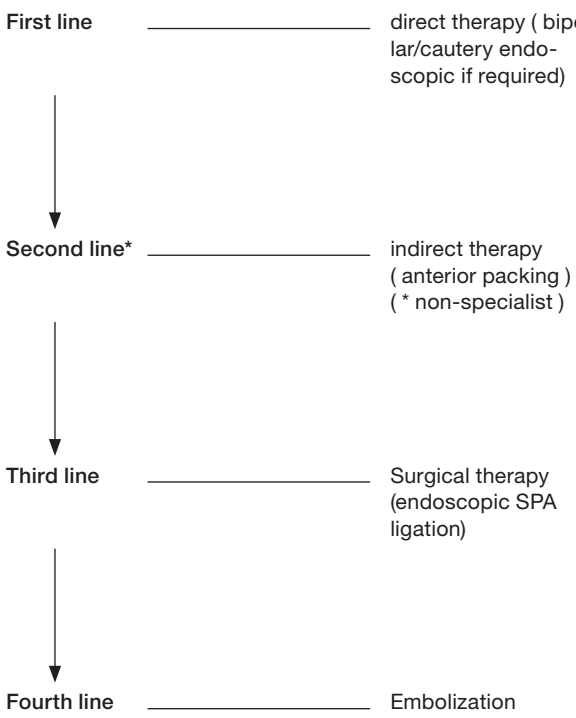
Hereditary haemorrhagic telangiectasia

Hereditary haemorrhagic telangiectasia (HHT) or Osler-Weber-Rendu disease is an autosomal dominant condition affecting blood vessels in skin, mucous membranes and viscera. Penetrance is variable but reaches 97% by age 50 years and occasional atavistic cases are observed. The genetic abnormality has been located to chromosome 9q (HHT1) and chromosome 12q (HHT2). The classical features are telangiectasia, a-v malformations and aneurysms. Recurrent epistaxis occurs in 93% of cases.[67] Management involves packing, cautery, antifibrinolytics, systemic or topical oestrogens, coagulative lasers, septal dermoplasty, ligation and embolization and as a last resort permanent surgical closure of the nostrils (Young's operation). Laser photocoagulation has become a popular therapy and the NdYAG, Argon and KTP532 lasers have all been used with some success. Large multicentre comparisons of these treatments have not been conducted and due to the relative rarity of the condition this situation is likely to persist. **Figure 106.10** is an algorithm for management of this condition.[68] A recent study showed that the disability produced by Young's operation was more than offset by an improved quality of life due to reduced bleeding. Trials of systemic, topical or locally injectable Bevacizumab have produced conflicting results and at present the efficacy of this drug in HHT is unproven.[69]

Tumours

Nasal tumours seldom present as epistaxis in isolation. More commonly tumours produce blood-stained discharge with other nasal symptoms (unilateral obstruction, pain, swelling). The risk, albeit small, of missing a tumour is another good reason for using nasal endoscopy in epistaxis cases. Juvenile nasopharyngeal angiofibroma (JNA) and haemangiopericytoma (HPC) are rare vascular tumours which can present with recurrent or severe epistaxis in association with nasal obstruction. Treatment of JNA and HPC is mainly surgical but may include pre-operative embolization and are dealt with elsewhere in this textbook.

BEST CLINICAL PRACTICE



[Grade C]

FUTURE RESEARCH

- Publications still consistently fail to classify epistaxis or define the study population. Thus studies involve heterogenous groups of patients and different types of epistaxis making comparisons difficult. As result level 1 and 2 evidence is scarce.
- Multicentre comparisons of treatment and management strategies still do not exist.
- Basic research is required to identify initiating and aetiological factors.

KEY POINTS

- Direct bleeding point specific approaches are superior to indirect nasal packing strategies.
- Epistaxis secondary to drugs or coagulopathy requires management of the underlying cause.
- Endoscopic ligation of the sphenopalatine artery is the ligation of choice.
- The endoscope has revolutionized the treatment of epistaxis.

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CHAPTER 107

NASAL AND FACIAL FRACTURES

Dae Kim and Simon Holmes

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: nasal fracture, maxillofacial injuries, mandibular fractures, maxillary fractures, orbital floor fractures, nasoethmoid fractures and frontal sinus fractures, focusing on diagnosis, surgery, management and complications.

NASAL FRACTURES

INTRODUCTION

Treatment of nasal fractures was first recorded 5000 years ago during the early Pharonic period in Ancient Egypt. The Edwin Smith papyrus describes repositioning of deviated nasal bones with the fingers or elevators, the insertion of splints and the application of external dressings.[1] Just as then, nasal fractures are still very common. Isolated fractures of the nasal pyramid account for about 40% of all facial fractures. Furthermore, fractures of the nasal bones are often sustained along with other fractures of the facial skeleton. Delays in management can result in significant cosmetic and functional deformity that is often a cause for subsequent medicolegal action. The management of fractures of the nose is an important part of everyday ear, nose and throat (ENT) practice.

EPIDEMIOLOGY AND AETIOLOGY

Relatively little force is required to fracture the nasal bones, as little as 25–75 lb/in.[2] It is perhaps not surprising that young men are twice as likely to sustain a fractured nose as women. Subsequent refracture rates of 5% have been reported.[3] The peak incidence is in the 15–30-year age group when assaults, contact sports and adventurous leisure activities are more common.[4] In childhood, accident-prone toddlers not infrequently fracture their noses as well and these are often of a greenstick nature. Compound and comminuted fractures are more common in the elderly who are prone to falls.

CLASSIFICATION AND PATHOPHYSIOLOGY

Nasal fractures have been classified in a number of ways, for example, by the nature of injury, the extent of deformity and the pattern of the fracture.

Nature of injury

Most fractures result from laterally applied forces (> 66%). In a series reported by Illum et al. fractures following frontal injuries accounted for only 13%.[5] Greater force is required to fracture the nose with a blow directed from the front as the nasal cartilages behave like shock absorbers.

Extent of deformity

A five-point grading system has been developed for the extent of lateral deviation of the nasal pyramid:

- **Grade 0:** bones perfectly straight
- **Grade 1:** bones deviated less than half of the width of the bridge of the nose
- **Grade 2:** bones deviated half to one full width of the bridge of the nose
- **Grade 3:** bones deviated greater than one full width of the bridge of the nose
- **Grade 4:** bones almost touching the cheek.

Pattern of fracture

Nasal fractures can also be subdivided into three broad categories that characterize the patterns of damage sustained with increasing force. This classification has some practical utility as each category of fracture requires a different method of treatment.

CLASS 1 FRACTURES

Class 1 fractures are the result of low–moderate degrees of force and hence the extent of deformity is usually not marked. The simplest form of a Class 1 fracture is the depressed nasal bone. The fractured segment usually remains in position due to its inferior attachment to the upper lateral cartilage which provides an element of recoil. The nasal septum is generally not involved.

In the more severe variant, both nasal bones and the septum are fractured. The fracture line runs parallel to the nasomaxillary suture ipsilateral to the side of the applied force to a point approximately two-thirds along the length of the nasal bone, where the bone becomes much thicker. The fracture line then connects across to the contralateral side and runs parallel and just below the dorsum. The cartilaginous septum is fractured approximately 0.5 cm below the dorsum and this aspect of the injury may extend posteriorly into the bony septum, through the perpendicular plate of the ethmoid and skull base. This fracture was first described by Chevallet and bears his name (Figure 107.1).

Class 1 fractures tend not to cause gross lateral displacement of the nasal bones and may not even be perceptible. Deformity generally results from a persistently depressed fragment, which is often due to impaction of the flail segment beneath the residual nasal bone. In children, these fractures may be of the 'greenstick' variety and significant nasal deformity may only develop at puberty when nasal growth becomes accentuated.[6]

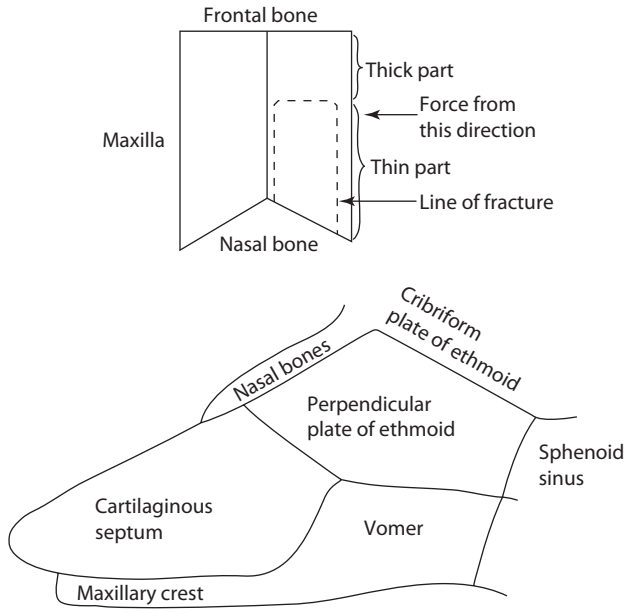


Figure 107.1 The distal part of a nasal bone is half the thickness of the proximal part. When it fractures, the nose is apparently deviated but the impression of deviation is optical (Chevallet fracture). It is important to recognize this injury. The edges of the stable segment can often be palpated. Figure courtesy of AGD Maran.

CLASS 2 FRACTURES

Class 2 fractures are the result of greater force and are often associated with significant cosmetic deformity. In addition to fracturing the nasal bones, the frontal process of the maxilla and septum are also involved. However, the ethmoid labyrinth and adjacent orbital structures remain intact (see Class 3). The pattern of deformity is determined by the direction of the force applied. A frontal impact tends to comminute the nasal bones and cause gross flattening and widening of the dorsum; while a lateral impact produces a high deviation of the nasal skeleton.

What may appear to be a simple dislocation of the quadrangular cartilage from the bony septum is in reality a complex 'C-shaped' fracture that extends from the quadrangular cartilage beneath the nasal tip, posteriorly through to the perpendicular plate of the ethmoid, to the anterior border of the vomer and then forward through the lower part of the perpendicular plate of the ethmoid into the inferior part of the quadrilateral cartilage. This pattern of fracture was first described by Jarjavay and bears his name (Figure 107.2).

As a rule of thumb, if the nasal dorsum is deviated laterally greater than half the width of the nose (Grade 2 or greater fracture), then a septal fracture must also be present. Septal fracture-dislocations tend to happen at points of weakness. They are where the quadrangular cartilage inserts into the cartilaginous dorsum, the bony septum and the maxillary crest. Both the nasal bone and septal fractures need to be reduced together in order to achieve a satisfactory cosmetic result.

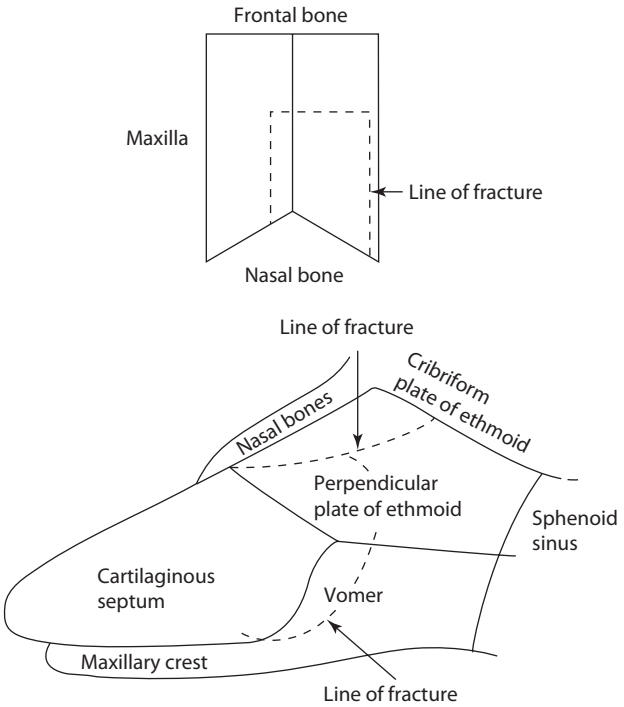


Figure 107.2 A Class 2 nasal fracture involves the thicker proximal portion of the nasal bone. It results in true deviation and also fracture of the perpendicular plate of the ethmoid and quadrilateral cartilage (Jarjavay fracture). Figure courtesy of AGD Maran.

CLASS 3 FRACTURES

Class 3 fractures are the most severe nasal injuries encountered and usually result from high velocity trauma. They are also termed naso-orbito-ethmoid fractures and often have associated fractures of the maxillae. The external buttresses of the nose give way and the ethmoid labyrinth collapses on itself. This causes the perpendicular plate of the ethmoid to rotate and the quadrilateral cartilage to fall backwards. These movements cause a classic, 'pig-like' appearance to the patient, with a foreshortened saddled nose and the nostrils facing more anteriorly, like the snout of a pig. There is also telecanthus, which may be exaggerated further by disruption of the medial canthal ligament from the crest of the lacrimal bone.

Two categories of naso-orbito-ethmoid fractures have been recognized by Raveh.[7] In type I, the anterior skull base, posterior wall of the frontal sinus and optic canal remain intact. In type II, there is disruption of the posterior frontal sinus wall, multiple fractures of the roof of the ethmoid and orbit that may extend posteriorly to the sphenoid and parasellar regions. Multiple dural tears, cerebrospinal fluid leaks (CSF), pneumocranium and cerebral herniation may complicate this type of injury. (The management of this type of nasal fracture is covered later in this Chapter).

CLINICAL PRESENTATION

History

It is prudent to establish how and when the injury was sustained, not only for medicolegal purposes but also because there is a limited period of time during which simple reduction is possible. There will almost certainly be some degree of nasal obstruction associated with the injury, but complete obstruction and persisting pain might indicate the presence of a septal haematoma. Enquiry should be made about any obvious change in the shape of the nose and of previous injuries or past nasal surgery. The patient may have a recent photograph that could be helpful to establish their claim.

Other injuries may also be present and may have been overlooked. Diplopia, visual disturbance and epiphora suggest orbital trauma. Loose teeth, an altered bite or trismus indicate the need for a dental opinion. The onset of watery rhinorrhoea and loss of the sense of smell, though uncommon, signal possible skull base damage and the need for a more detailed evaluation. Finally, it is worth enquiring about their leisure pursuits and any occupational hazards that might influence any decision to correct the deformity.

Key issues to consider when determining history include:

- details of how and when the injury was sustained
- nasal obstruction
- change in appearance
- anosmia; hyposmia; watery rhinorrhoea
- visual disturbance; diplopia; epiphora
- altered bite; loose teeth; trismus
- occupation; leisure pursuits.

Examination

The importance of clear and complete records of the clinical examination cannot be overemphasized. What is and what is not a new injury can be difficult to determine at a later date when litigation is contemplated. Inspect the nose for any external deformity. This may be extremely difficult in the acute situation when swelling may hide an underlying abnormality. A second inspection a few days later may be necessary. Gently palpate the nasal bones for a step deformity and make note of any surgical emphysema that could suggest a more serious injury. Make a detailed record of soft-tissue lacerations. Inspect the nasal cavities and check for the presence of a septal haematoma or deviation. A thorough general ENT/head and neck examination must also be completed.

Key issues to consider when examining a patient include:

- deviation, depression, step deformities
- mobility, crepitus, specific areas of point tenderness
- generalized swelling and specific bruising
- skin and mucosal lacerations
- septal fracture/haematoma/abscess/perforation.

INVESTIGATIONS

Unlike other fractures, nasal X-rays are not required to make the diagnosis or aid subsequent reduction. In a prospective study undertaken by Logan et al., it was concluded that X-rays were not cost effective.[8] Their only possible utility is proof of injury in subsequent litigation. If there is

clinical evidence of a more serious facial injury computerized tomography (CT) scan should be acquired. Samples of any watery rhinorrhoea must be collected in those with suspected CSF leak and tested for b2 transferrin.

TREATMENT

The indications for surgical intervention in the acute phase are significant cosmetic deformity and nasal obstruction caused by a septal haematoma. However, a very significant number of patients (up to 80%) do not require any active treatment; many do not have a nasal fracture and, in those that do, the fracture may not be displaced.[4] Soft-tissue swelling can produce the misleading appearance of a deformity which disappears as the swelling subsides. Reassurance is all that these patients may require. Topical vasoconstrictor drops are helpful to alleviate congestion and obstructive symptoms. A reexamination about 5 days later is prudent where there is uncertainty about the need for reduction.

Many patients will have a pre-existing nasal deformity caused by a previous incident. Manipulation of the nose will, at best, only return it to its most recent appearance. Patients that fall into this category may be better advised to consider a formal rhinoplasty when everything has settled down some months later. Others will be at continued risk of further injury because of an occupational hazard, sport or leisure activity. It is better to advise this group of patients to undergo a definitive septorhinoplasty when the risk of further injury no longer exists.

The timing of surgical assessment and subsequent reduction is crucial as there is a narrow window of opportunity to correct the deformity. Failure of referral or timely referral is a common cause of litigation in nasal injuries. Patients should be seen quickly, certainly within the first few days and no later than one week. Patients with a suspected septal haematoma should be seen urgently at the first possible opportunity. The optimal time for clinical assessment is around 4 days, by which time much of the oedema will have subsided and any underlying deformity become apparent. Review at 4 days allows sensible planning for reduction of the fracture on an elective operating list within the next 2 to 3 days, if it is to be reduced under a general anaesthetic. By 7 days, the bony abnormality will be easily palpable and still movable. Further delay makes effective reduction less likely and sometimes impossible without making osteotomies. In children, healing can take place even more quickly and earlier intervention is indicated.

Those patients for whom treatment is considered unnecessary should be given the contact details of the ENT clinic lest deformity become apparent over the ensuing weeks.[4]

Anaesthesia

Reduction of a fractured nose can be performed under local or general anaesthesia. Many studies have shown reduction of nasal fractures under local anaesthesia to be perfectly adequate and acceptable.[9, 10]

Local anaesthesia has several advantages but the injections can be painful and the associated distortion of soft tissues can hinder accurate assessment of the reduction and the literature is divided over the influence on outcomes. In a retrospective analysis of 324 patients, Courtney et al. found a higher number of patients seeking a septorhinoplasty when the initial reduction was performed under local anaesthetic (17.2%) than general anaesthetic (3.2%).[3] On the other hand, Ridder et al. found that there was no significant difference in overall success rate.[11]

Local anaesthetic can be used as a combination of external infiltration with internal application of topical preparations. Lignocaine is injected along the nasomaxillary groove, infraorbital nerve in its foramen and around the infratrochlear nerve. Jones and Nandapalan recently reported the use of topical EMLA (prilocaine and lignocaine) cream or AMETOP (amethocaine) gel to the external nose instead of infiltration.[12] They found less discomfort when the manipulation was carried out using the topical, local anaesthetic preparation compared with local infiltration. They achieved similar cosmetic and functional results.[12] Within the nose, sprays, injections, pastes or packs coated with local anaesthetic are all acceptable, using combinations of cocaine, lignocaine, adrenaline and phenylephrine. The vasoconstrictive element helps to reduce any bleeding associated with mucosal tears from instrumentation during the reduction, but must be used cautiously in hypertensive patients or those with cardiovascular disease.

There are easily identifiable groups of patients who are not suitable for reduction under local anaesthesia. Children and patients with low pain thresholds or significant anxiety states are better admitted for general anaesthesia. Likewise, attempts at reduction of fractures where there has been delay in presentation are better performed under general anaesthetic.

Methods of reduction

Closed techniques for nasal reduction have traditionally been used. The general principle of any fracture reduction is to mobilize the fragments first by increasing and then decreasing the degree of deformity. An initial slight increase in deformity away from the side of the blow to disimpact the fragments, followed by steady movement back towards and often slightly beyond the midline is usually required. Generally, this can be achieved by firm digital pressure. Sometimes instruments are necessary, particularly in those where there has been delay. Various elevators and forceps have been developed specifically for this purpose, such as Freer, Hills and Howarth elevators and Ashe and Walsham forceps (**Figure 107.3**). The instrument is held so that the index finger of the dominant hand is placed along the instrument in the line of the nose. In this way, the depth that the instrument must be inserted into the nasal cavity is easily gauged and inadvertent damage to the orbit avoided (**Figure 107.4**).

All Class 1 and most Class 2 fractures can be reduced with these techniques. In some Class 2 fractures, closed reduction alone may not achieve a satisfactory result as the final position of the nasal dorsum reflects the deformity of the underlying septum.[1, 13–15] At least 50% of



Figure 107.3 Instruments used in nasal fracture manipulation. **(a)** Howarth's elevator; **(b)** Ashe's forceps (septum); **(c)** Walsham's forceps (nasal bones).



Figure 107.4 Determining depth of insertion of instrument into nasal cavity.

these fractures remain displaced because of overlapping segments of the fractured perpendicular plate of the ethmoid or septal cartilage, which can only be repositioned by open reduction. Occasionally, the bones are fixed, especially if the fracture is old, and osteotomies are necessary to release the fragments before manipulation. These should be performed cautiously to avoid the risk of extension into the orbit or, even worse, intra-cranially.[16]

Splints or packs may be necessary, depending on the stability of the reduction and the surgeon's preference. A splint or plaster applied to the nasal bridge maintains, to some extent, the position of the nasal bones and prevents accidental displacement. Splints are usually kept in place for about 7 days. It is advisable to refrain from contact sports for at least 6 weeks.

Very occasionally, open reduction techniques may be desirable or required to provide optimal results, despite the increased time and effort involved. Verwoerd identified the following indications for open reduction:[15]

- bilateral fractures with dislocation of the nasal dorsum and significant (pre-existent or recent) septal deformity
- infraction of the nasal dorsum
- fractures of the cartilaginous pyramid, with or without dislocation of the upper laterals.

For depressed tip or flail lateral fractures that are unstable despite closed reduction techniques, Kirschner (K) wires can be used. The wire is inserted under fluoroscopic guidance into the depressed fragment as well as neighbouring uninvolved bone (maxilla or frontal bone), and the wires are screwed together externally to maintain the position. The external wire can be covered by dressings or plaster to protect the wires from disruption and the patient from injury. The wires are removed after 2 weeks.

Some authors advocate a more aggressive approach to the treatment of acute nasal fractures which includes some 'rhinoplasty' techniques, such as release of upper lateral cartilages, hump removal and camouflaging cartilage grafts.[17] Incorporation of these more advanced techniques into the management of the fractured nose requires expertise, more instrumentation and more operating time and this may not always be feasible or desirable.

Management of the nasal septum

Septal fracture is often missed and is a major reason for poor functional and cosmetic results. Kim et al. found that 46.9% of nasal fractures have a concomitant septal fracture.[18] If a significant septal fracture-dislocation is present, it is wise to reduce this at the same time as the nasal bones. In fact, a satisfactory reduction of nasal bones is often not possible without improving the position of the septum. An often-quoted aphorism, 'where goes the septum, so does the nose' is not far from the truth.

Septal reduction can sometimes be performed with Ashe's forceps, but often requires a Killian or hemitransfixion incision, elevation of mucosal flaps to expose the

cartilage and bone fragments, and replacement and/or removal of cartilaginous and bony fragments, as in a standard septoplasty. Quilting sutures prevent a dead space from forming and a haematoma from collecting.

COMPLICATIONS

Poor cosmetic result

Attempts to reduce deformity are not always successful. Factors which contribute to an unsatisfactory cosmetic result include:

- extent of the injury
- time delay in surgical reduction
- poor surgical technique
- unrecognized and untreated septal fracture
- pre-existing nasal deformity
- post-operative trauma (in recovery room or subsequently)
- scarring and fibrosis.

Unfortunately, it is not uncommon for the shape of the nose to change over time due to subsequent scarring and fibrosis, loss of tip or dorsal support, or hump formation. Some patients inevitably require a septorhinoplasty despite apparent adequate reduction. It is wise to wait at least 6 months after the injury before embarking on septorhinoplasty to allow the fractures to heal, the oedema to settle completely so the underlying nasal skeleton is evident, and for any fibrosis to develop.

Nasal obstruction

Post-operative nasal obstruction is also common and there are many causes that include:

- valve obstruction
- collapse of upper lateral cartilages and depressed nasal bones
- septal deviation
- widened septum (haematoma)
- tip ptosis.

These causes need to be considered and addressed at a subsequent septorhinoplasty.

Epistaxis

Epistaxis at the time of injury may be impressive but is usually relatively brief. Occasionally, fractures involving the nasoethmoidal complex can cause laceration to the anterior ethmoidal artery. This may result in repeated, brisk and significant haemorrhage that only stops once the fracture has been reduced. Very occasionally, prolonged packing or ligation of the artery is required. Bleeding can also be troublesome at the time of reduction, particularly if instruments are used. Preparation of the nose with vasoconstrictive agents helps to minimize this blood loss.

Septal complications

A submucoperichondrial bleed not infrequently complicates nasal fractures. While most septal haematomas are relatively limited, some may strip the mucoperichondrium over an extended area and deprive the underlying cartilage of its source of nutrition. This can lead to cartilage necrosis and ultimately nasal deformity. Septal haematomas present with an acute unilateral or bilateral nasal obstruction and, on inspection, there is a reddish-purple, fluctuant swelling of the caudal septum. A deviated septum can be confused with a septal haematoma. Gentle pressure on the bulging area will ascertain that it is fluctuant if a collection is present. Untreated, an abscess may develop and the patient becomes very unwell with a fluctuating fever and severe facial and cranial pain. Rarely, cavernous sinus thrombosis or other forms of intra-cranial sepsis can ensue.

The haematoma or abscess must be drained as soon as possible. This can be performed under local or general anaesthetic, either by using needle aspiration or preferably an incision. Often the collection will have become organized and so impossible to aspirate. In this situation, a small window of mucoperiostium should be excised ensuring there is no corresponding defect on the contralateral side which could predispose to a perforation. Once drained, quilting sutures from one side through cartilage to the other are inserted to eliminate the dead space. Packs or splints can be used to provide gentle pressure on the septum. The patient must be reexamined within 48 hours to establish that the collection has not recurred. The management of a septal abscess is similar, but with the addition of appropriate antibiotic therapy.

Septal perforations may also develop after nasal fractures, usually as a result of septal haematomas and their surgical treatment. Loss of cartilaginous septal support can also lead to a saddle nose deformity, as well as columellar retraction and a broadened septum.

KEY POINTS

- Nasal fractures are common and awareness of the basic principles of management ensures good outcomes.
- All significant nasal injuries should be assessed within a few days if there is cosmetic deformity and within 24 hours if nasal obstruction is evident to exclude a septal haematoma.
- It is important to assess each patient carefully and be vigilant over potential complications.
- Document all details carefully in case of subsequent litigation.
- Not all referred patients actually have fractures and even some with fractures do not need surgery.
- Most cases can be reduced adequately with closed techniques, unless the fractures are complex or a significant septal fracture-dislocation is present.
- There are no significant differences between the outcomes of local versus general anaesthesia: more important predictors of outcome include pre-existing deformity, severity of injury, delay in assessment and poor surgical technique.
- Residual cosmetic deformity and nasal obstruction are relatively common complications and it is wise to counsel patients about these from the outset.
- A formal septorhinoplasty can be performed in cases of poor outcome, best performed at least 6 months after the injury.

BEST CLINICAL PRACTICE

- ✓ Prompt medical review within 24–48 hours of all significant nasal injuries, with urgent ENT referral if a septal haematoma or if a Class 3 fracture is present.
- ✓ Exclusion of related injuries to face, orbit, jaws and central nervous system (CNS) at initial assessment and appropriate specialist referral if present.
- ✓ ENT assessment at 4 to 5 days if cosmetic deformity or nasal obstruction are present.
- ✓ Closed reduction at 7 days, or open reduction if more complex.
- ✓ Review 7 days post-operatively with removal of external nasal splint.
- ✓ No contact sports for at least 6 weeks post-operatively.

FUTURE RESEARCH

- ➤ More prospective studies are required comparing closed and open reduction techniques.
- ➤ More prospective studies are needed to compare nasal bone reduction with nasal bone reduction and septoplasty.
- ➤ Studies need to be undertaken to determine whether a more aggressive approach to the initial management of nasal fractures (such as open reduction, septoplasty, 'rhinoplasty techniques') will prevent subsequent septorhinoplasty.

FACIAL FRACTURES

INTRODUCTION

Injuries to the face are common and account for 10% of all accident and emergency department attendances. Aesthetically, first impressions of a person in terms of their intellect, ability, trustworthiness and even sexual orientation are influenced by facial appearance. Functionally the facial skeleton provides support to the muscles of facial expression and these in turn act as the sphincter that protects the eyes and make the mouth competent. The facial skeleton holds and supports the eyes in the optimum position for binocular vision and the orbital margins provide additional protection for the globes. Historically the success of facial fracture management was judged entirely on the final dental occlusion. While it is important to ensure that a normal bite is achieved, it is just one of the criteria that define today's standard of care. Equally important is the restoration of both the vertical and transverse facial dimensions. This can be achieved by extended craniofacial bone exposure and the use of rigid and semi-rigid internal fixation. In addition, meticulous attention to the repair of soft tissues injuries ensures the best possible cosmetic result.

KEY POINTS

- Maxillofacial trauma is extremely common. Ten percent of all accident and emergency attendances are related to facial injuries.
- Immediate assessment of the airway is essential.
- Most facial fractures are managed by semi-rigid internal fixation through extended subperiosteal exposure of the fracture.
- Wiring of the jaws is no longer the standard of care.
- Cerebrospinal fluid (CSF) rhinorrhoea and retrobulbar haematoma should be excluded in all middle-third facial injuries.

AETIOLOGY

Fractures of the nose, mandible and middle third of the face are usually caused by road traffic accidents, physical violence, falls, attempted suicide, and sporting injuries (Figure 107.5). Most injuries are low energy and heal predictably. Higher-energy injuries cause gross comminution of the bones and do not heal as well. It is important to ascertain the exact mechanism of injury not only for medicolegal reasons, but also to ensure that an adequate screening examination is undertaken to detect other injuries and so that a prognosis on the likely stability of any repair can be given.

KEY POINTS

- Successful outcome involves restoration of pre-morbid facial proportions, dental occlusion and accurate soft tissue repair.
- Road traffic accidents, interpersonal violence, attempted suicide and sports injuries are the most common cause of facial fractures.
- The mechanism of injury will provide insight on the possible degree and extent of the injury and the methods that will be necessary for repair.



Figure 107.5 A true panfacial fracture. Green arrows – mandibular symphysis : Yellow arrows – right mandibular condyle (left hidden): Red arrows – right Le Fort 2 : Light blue arrows – Le Fort 1.: Dark blue arrows – Le Fort 3 : Black arrows – Naso orbitothmoid : Purple arrows – Parasagittal midline split maxilla.

PRIMARY CARE

The initial survey

Maxillofacial injuries endanger the airway and can cause profuse haemorrhage. Associated neck injuries are common and should always be suspected and excluded. Advanced trauma and life-support protocols dictate that a rapid and accurate primary survey should be undertaken in the following sequence:

1. **Airway**. Evaluate and secure the airway, while maintaining alignment of the neck in case there is an unstable cervical spine injury.
2. **Breathing**. Make sure that there is adequate ventilation.
3. **Circulation**. Control sources of blood loss.
4. **Disability**. Assess the level of consciousness and neurological dysfunction.
5. **Exposure.** Ensure that all other injuries are identified.

The establishment of a safe airway and effective ventilation is essential so that hypoxia and carbon dioxide retention is prevented and the resultant post-traumatic cerebral oedema minimized. Oral or nasal bleeding, posterior displacement of the tongue secondary to mandibular fractures or the result of postero-inferior displacement of the maxilla in middle-third injuries may further compromise the airway. It may be necessary to reduce these fractures immediately and place temporary bridal wires around dentoalveolar segments to increase bony stability. Although the correct surgical procedure for the rapid relief of acute upper airway obstruction is often a cricothyroidotomy, there is occasionally merit in performing an immediate tracheostomy if it can be conducted swiftly and safely. Haemorrhage from facial fractures can be torrential and demands immediate attention. The use of anterior and posterior nasal packs has been abandoned in favour of the epistat (Figure 107.6). It is important to remember that any injury to the upper middle third of the face is likely to have shattered the anterior skull base.



Figure 107.6 Epistat in anatomical model. Palpation of the posterior balloon in the nasopharynx ensures no intra-cranial intubation.

Inadvertent intubation of the anterior cranial fossa through the cribriform plate or medial wall of the orbit is a distinct possibility and should be borne in mind when attempting to pass any tube through the nose. Intense shock should not be attributed to a facial injury until abdominal, pelvic, orthopaedic or thoracic causes have been excluded. Use of the Glasgow Coma Scale will alert the clinician to impending intra-cranial complications. Immediate neurosurgical advice should be obtained if the patient's conscious level deteriorates. CSF rhinorrhea must be suspected in any high-level nasoethmoid or maxillary fractures. This demands prophylactic antibiotic therapy to prevent meningitis. Tetanus prophylaxis should be administered in any non-immune patient.

Principles of primary management

Once the primary survey of the injury has been completed, a secondary survey is carried out to exclude other injuries and to categorize the extent of the facial injury. The soft tissues of the face are carefully scrutinized and any lacerations or cuts noted together with the proximity to relevant anatomical structures including the eyebrows, conjunctival margins, nasal aperture and the vermillion border of the lips. Facial nerve function should be documented and the integrity of the parotid duct assessed. Visual acuity and ocular movements are recorded. Any orbital injury may be complicated by a retrobulbar haemorrhage and retinal detachment, both of which are preventable and treatable causes of permanent blindness.

A full hard-tissue examination is conducted by palpating the orbital margins, zygomatic projection, nasal skeleton and mandibular outline. If conscious, the patient is asked whether their bite is comfortable and if it feels normal, and if there is any numbness. A full dental examination is necessary so that any fractured or missing teeth that may have been inhaled are identified and accounted for. Finally, the dental occlusion and maxillary or mandibular instability is formally assessed and documented.

Radiographic evaluation

All major trauma patients should have chest, cervical spine and pelvic X-rays as soon as possible. The selection of X-rays of the facial skeleton is discussed later, but it is certainly worth including the facial skeleton on any computerized tomography (CT) scan that might be required for a patient with multiple injuries. Early detection of these injuries greatly simplifies their management. The timing of any maxillofacial intervention is controversial. Historically, it was usual to await resolution of any facial swelling before the assessment process began. Patients might wait for 5 to 7 days before surgery was considered. With modern-day techniques, there is a trend to fix facial fractures earlier. This policy avoids the so-called double insult of accidental and surgical trauma. Swelling can be reduced by nursing the patient in the head-up position with ice packs, together with a single

dose of dexamethasone. Facial wounds should be cleaned and lacerations closed as soon as possible, if necessary under local anaesthesia.

Any facial fracture that communicates with the oral cavity through the periodontal ligament of teeth should be regarded as compound and parenteral prophylactic antibiotics given.

BEST CLINICAL PRACTICE

- ✓ Maxillofacial fractures can endanger the airway.
- ✓ Be aware of associated cervical spine injuries.
- ✓ Consider tracheostomy at the outset in patients with extensive trauma.
- ✓ Close soft tissues injuries as soon as possible.
- ✓ CT scans of the head and facial bones help to define the extent of both facial and cerebral injuries.
- ✓ Do not forget to give tetanus prophylaxis.
- ✓ Exclude cervical spine injuries.
- ✓ Check visual acuity in all patients with middle-third facial injuries lest they have a retrobulbar haemorrhage.

MANDIBULAR FRACTURES

Introduction

The mandible is a parabolic-shaped bone with a complex articulation that consists of paired synovial joints – the temporomandibular joints – and movements that are, in part, guided by the dental occlusion. Satisfactory rehabilitation of the fractured mandible requires accurate reduction, adequate fixation and mobilization. The traditional method of treatment was immobilization of the fracture with intermaxillary fixation (IMF) (Figure 107.7). More recently, it has been realized that the advantages of such treatment in terms of cost and simplicity were far outweighed by a number of disadvantages. At the outset, there were always concerns about the airway lest it became compromised by soft-tissue swelling or vomiting. The period of immobilization was uncomfortable and inconvenient for the patient as it imposed dietary restrictions.[19, 20] Furthermore, the use of wires placed the surgeon and nursing staff at risk of needlestick injuries.[21] To make matters worse, the fixation achieved by this method was often inadequate, particularly if the dentition was incomplete or in bad repair (Figure 107.8).

The widespread use nowadays of miniplates and extended subperiosteal exposure of the craniofacial skeleton to achieve fixation means that there are now few indications for closed reduction of any facial fracture. In this way, correct anatomy and occlusion is restored.[22, 23] One further and very significant advantage of not using IMF is that in severely injured patients a tracheostomy might be avoided.

Surgical anatomy

The mandible will fracture when subjected to direct and indirect force. Stereotypical fracture configurations are recognized that are determined by the direction and magnitude of the applied force and whether the teeth are in or out of occlusion at the time. Fractures happen at points of potential weakness where the bone is relatively thin (Figure 107.9). The angles of the mandible may be weakened by unerupted wisdom teeth, the parasymphysis by the long root of the lower canine and the condylar neck by its slender anatomy. It is also common for the mandible to fracture in more than one place,

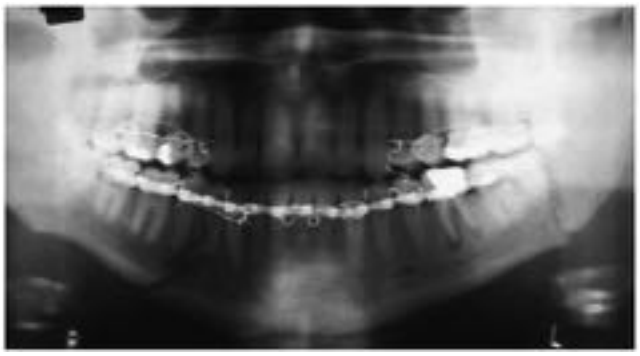


Figure 107.8 This fracture of the angle of the mandible has been managed inappropriately by intermaxillary fixation – the posterior segment of the left mandible is not controlled. The molar tooth in the line of the fracture should be extracted and an alternative form of fixation applied.



Figure 107.7 Eyelet wires fastened to the dentition and interconnected is the simplest form of intermaxillary fixation.

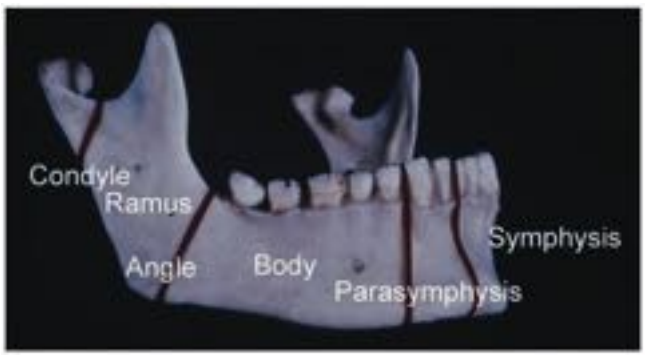


Figure 107.9 Lines of weakness in the mandible that determine the pattern of fractures in the mandible.

for example, the parasymphysis (site of direct violence) and condylar neck (site of indirect violence). It is obviously sensible to look carefully for more than one fracture. Displacement of the fracture depends on a variety of factors, the most important of which are the pull of attached muscles.

Signs and symptoms

The signs and symptoms produced by mandibular fractures are determined by the site of the fracture.

Fractures of the body, angle and symphysis are associated with:

- a step deformity palpable either externally or intraorally
- asymmetry of the lower dental arch and derangement of the occlusion
- pain and paradoxical movement and crepitus on distraction of the fractured segments
- haematomas in the buccal sulcus or floor of the mouth
- blood-stained saliva
- anaesthesia of the lower lip.

Fractures of the condylar neck are associated with:

- tenderness over the temporomandibular joint
- trismus
- deviation of the jaw towards the injured side on opening the mouth
- inability to move the mandible to the side opposite the fracture
- deviation of the jaw to the fractured side at rest with an anterior open bite secondary to gagging of the molar teeth in fracture dislocation
- symmetrical anterior open bite in bilateral fractures of the necks of the condyles.

Closed reduction techniques

As stated previously, the use of IMF plays a much smaller role in modern maxillofacial surgery. Simple mandibular fractures can be held in normal occlusion and plated without much difficulty.[24] Nevertheless, IMF still has a part to play in two groups of patients. First, those with undisplaced fractures and no neural deficits who want to avoid more complex surgery and, second, those with unilateral condylar fractures. In the emergency room, a simple tie wire placed around the teeth either side of a displaced fracture can reduce pain, bleeding from bone ends and make nursing easier in the hours and days before a planned open reduction and internal fixation.

THE INTACT DENTAL ARCH

There are several methods of applying wire to an intact dental arch to provide IMF. Perhaps best known are eyelet wires. This is very simple but is only possible in those situations where there are two adjacent teeth in contact. The main disadvantage is that it is difficult to combine eyelet wires with elastic traction and it can be awkward to thread wire through tight interdental contact points, particularly in an awake patient. A simple and ingenious modification is the Leonard button (**Figure 107.10**), an eyelet wire with a small metal disc instead of a loop.

THE INCOMPLETE DENTAL ARCH

Arch bars

An arch bar is a strip of metal that is wired to each jaw using several individual teeth. The bar may be prefabricated using a model made from a pre-operative dental impression (**Figure 107.11**), or may be made at the time of surgery by adapting a pre-formed pattern. Arch bars can span short gaps within each jaw, but will not cope with large gaps or when there is no posterior tooth. Their main advantage is that they provide a relatively simple means of stabilizing more complex fractures and at the same time provide indirect fixation.

Intermaxillary bone pins

A rapid method of intermaxillary fixation has been described.[25] A mono-cortical screw is placed through the mucosa between the canine and first premolar on each side and jaw. The screws are then wired together or connected with elastic bands. It is important to ensure that



Figure 107.10 The Leonard button – a simple device that facilitates intermaxillary fixation by either wire or elastic bands.



Figure 107.11 Intermaxillary fixation has been achieved by the use of preformed arch bars connected by elastic bands.

the path of the screw enters bone and avoids the roots of teeth. These specially designed screws are brittle and care must be exercised when inserting them lest they break.

External fixation

The use of rigid and semi-rigid fixation has diminished the need for external fixation. External fixation is now only indicated for those patients with gross tissue loss as might be seen in the theatre of war and for those with pathological fractures, particularly when the patient is too unwell to undergo extensive surgery. A number of methods have been described and are in current clinical use. By far the simplest is the placement of cortical screws and then connecting them with an external bar made of acrylic. We have found that a mini-Pennig orthopaedic fixator provides an elegant means of stabilizing fractures (**Figure 107.12**), as well as avoiding pin tract problems, and the need for constant tightening and adjustment.

Internal fixation

ACCESS

Intra-oral incisions

Wherever possible, bone plates should be placed through an intra-oral approach. Mucogingival incisions are made so that the resultant flap includes the periosteum. It is essential that a sufficient cuff of mucosa is raised so that the plate is completely covered after closure. Care must be taken to avoid inadvertent damage to the mental nerve in the anterior region.

Extra-oral incisions

External incisions are used for the lower border of the mandible and condylar neck. Lower border plates are ideal when there is gross comminution or tissue loss. They are also preferable in fractures of grossly resorbed edentulous mandibles.[26] In these situations, it is better to use bicortical screws and thicker plates that can provide superior fixation. The incision is made two finger-breadths below the lower border of the mandible in order to avoid damage to the mandibular branch of the facial nerve. The incision is deepened through the platysma muscle and then blunt dissection exposes the lower border of the mandible. Condylar neck fractures are approached through a retromandibular incision while higher condylar neck fractures are better exposed through a pre-auricular incision.[27]

PRINCIPLES OF MANDIBULAR FIXATION

The zones of tension and compression mentioned earlier dictate the ideal position and plate configuration around a fracture site. In simple mandibular fractures, monocortical 2 mm plates provide adequate fixation because of the phenomenon of load sharing between the fracture and the osteosynthesis. In the anterior mandible, two plates are used while posteriorly one plate is usually sufficient[28] and in both situations 6 mm long screws are used. The placement of plates in the region of the mental nerve can be technically demanding (**Figure 107.13**). In complicated fractures where there is gross comminution, tissue loss or infection, a load-bearing osteosynthesis with rigid internal fixation and bicortical screws are required.

CONDYLAR NECK FRACTURES

There is no topic more controversial in maxillofacial trauma than the management of condylar fractures. The 'gold standard' management of most displaced mandibular fractures is reduction and internal fixation. There is just one exception – fractures of the condyle. In the case of condylar fractures, functional adaptation, neuromuscular rehabilitation and altered condylar mechanics may compensate for the deficiencies of IMF in terms of accuracy of reduction. Bilateral displaced condylar neck and high-intra-capsular fractures generally have poor outcomes and are better managed by an open reduction.[29] Several factors determine the best approach to the condyle. These include the position of the fracture, available skin creases, tissue laxity and last but not least, the experience of the operator.



Figure 107.12 A mini-Pennig wrist fixator used to provide external fixation.



Figure 107.13 Fixation of a fracture in the parasymphyseal region of the mandible using plates. The lower plate has been manipulated beneath the mental nerve.

A retromandibular incision provides the most direct and simple approach to the ramus and subcondylar region, albeit that the surgeon must be careful not to damage the facial nerve. An additional pre-auricular incision can be usefully employed with higher condylar neck fractures. In recent years, there has been enthusiasm for endoscope-assisted repair techniques that are technically difficult to perform but avoid large facial scars.[30, 31] Once exposed, the fracture is reduced and fixed with miniplates.

KEY POINTS

Mandibular injuries

- Mandibular injuries are often multiple.
- IMF following closed reduction is no longer acceptable practice for the majority of mandibular injuries.
- Most fractures are treated with non-compression miniplates.
- The management of condylar neck fractures is controversial.
- Endoscopic techniques may have a role in the management of certain mandibular fractures.

Signs and symptoms of mandibular fractures include:

- bony step deformity;
- deranged occlusion;
- pain;
- sublingual haematoma;
- blood-stained saliva;
- mobile teeth in the fracture line;
- anaesthesia of the lip;
- trismus.

Signs and symptoms of condylar neck fractures include:

- tenderness over the temporomandibular joint (TMJ);
- trismus;
- lateral open bite;
- anterior open bite.

FRACTURES OF THE MAXILLA

Introduction

Fractures of the midfacial skeleton can be subdivided into lateral (zygomatic) or central (maxillary, nasal, nasorbito-ethmoid) fractures. The symptoms and signs of maxillary injuries depend on the level of the fracture (Figures 107.14 and 107.15). The classical features of a midfacial fracture are circum-orbital ecchymosis (panda facies), facial oedema and emphysema, lengthening of the face and an anterior open bite. Not all of these signs need be present. An infra-orbital nerve sensory deficit is not uncommon in higher fractures and bruising at the junction of the hard and soft palate is frequently present.

Surgical anatomy

The bone of the midfacial region is generally very thin and offers little resistance to anterior and lateral forces.



Figure 107.14 Severe multilevel Le Fort fracture with typical 'panda eyes'. An epistat has been inserted to arrest haemorrhage.

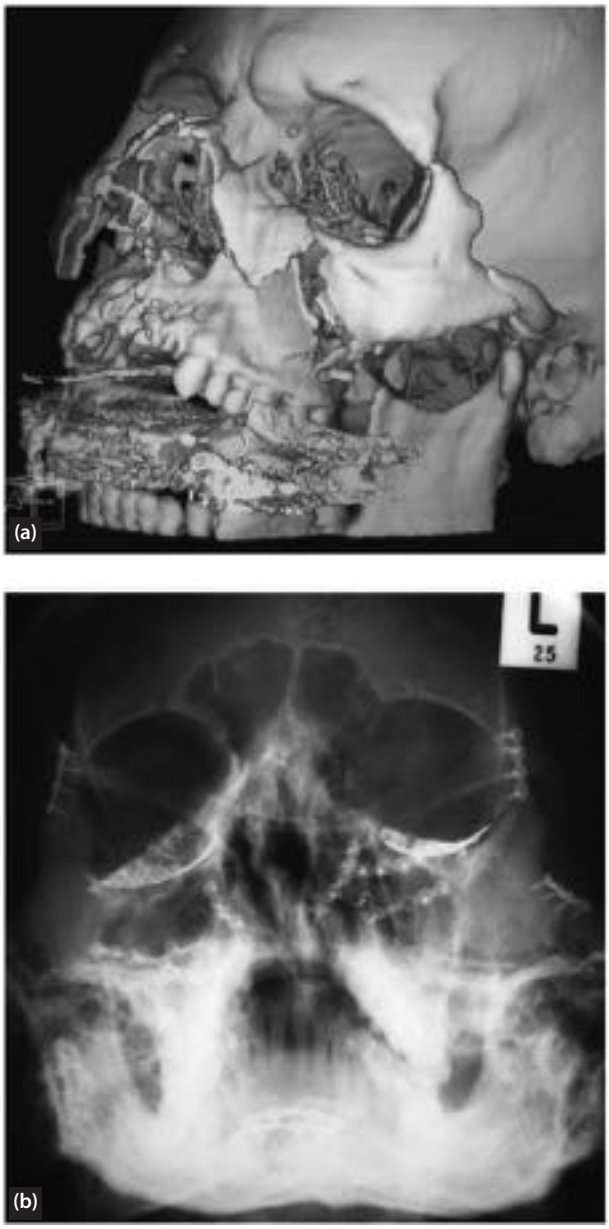


Figure 107.15 (a) 3D CT reconstruction demonstrating vertical, horizonal and transverse disruption to the entire craniofacial skeleton. **(b)** Post-operative view, note bilateral titanium orbital floor reconstruction.

Le Fort[32] described three levels of midfacial fracture (Figure 107.16):

1. **Le Fort 1** This fracture runs above the floor of the nasal cavity, through the nasal septum, maxillary sinuses and inferior parts of the medial and lateral pterygoid plates.
2. **Le Fort 2** This is a fracture which runs from the floor of the maxillary sinuses superiorly to the infraorbital margin and through the zygomaticomaxillary suture. Within the orbit, it passes across the lacrimal bone to the nasion. The infraorbital nerve is often damaged by involvement in this fracture.
3. **Le Fort 3** This represents a disconnection of the facial skeleton from the cranial base. The fracture traverses the medial wall of the orbit to the superior orbital fissure and exits across the greater wing of the sphenoid and zygomatic bone to the zygomaticofrontal suture. Posteriorly, the fracture line runs inferior to the optic foramen, across the lesser wing of the sphenoid to the pterygomaxillary fissure and sphenopalatine foramen. The arch of the zygoma is also broken.

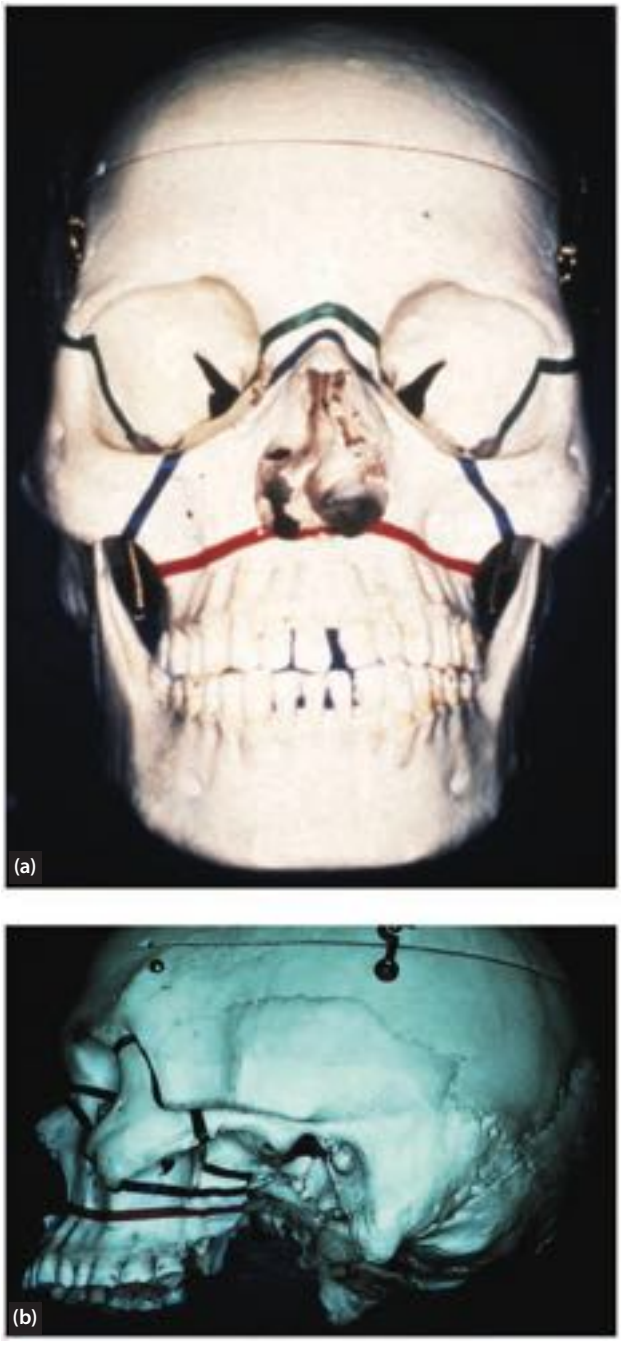


Figure 107.16 (a) and **(b)** The Le Fort injuries: red, Le Fort 1; blue, Le Fort 2; green, Le Fort 3.

While the Le Fort classification is attractive and accurate for low-energy injuries, in high-energy injuries there are very few instances of pure Le Fort fractures and most configurations involve multiple Le Fort levels,[33] together with zygomatic and nasal/nasoethmoid components. Authors have described thickened areas of bone between the maxilla and skull base which act as buttresses.[34] In essence, these thickened areas of bone provide a strategy for reconstruction[34, 35] and are key areas for osteosynthesis.

Signs and symptoms

Middle third facial fractures produce the following symptoms and signs:

- epistaxis
- circumorbital ecchymosis
- facial oedema
- surgical emphysema
- lengthening of the face
- infraorbital anaesthesia.

Principles of management

EMERGENCY TREATMENT

Midfacial fractures can easily compromise the airway with torrential epistaxes and posterior impaction of the maxilla. The bleeding can be arrested by using epistats or anterior and posterior nasal packs. If retroposition of the maxilla is a problem, it can be pulled forwards using the index and middle finger placed behind the patient's soft palate.

REDUCTION

The maxilla is mobilized by a combination of digital pressure and traction on arch bars or interdental wires. The position of the maxilla is 'eye-balled' with reference to the bony buttresses and dental occlusion. This can be difficult when the bone fragments are comminuted or the dentition is mutilated. Rowe maxillary disimpaction forceps can prove invaluable if the maxilla is impacted.

FIXATION

Modern management of the fractured maxilla parallels that of the mandible.[31] Internal fixation with

1.3 or 1.5 mm, low-profile miniplates placed along the buttresses provides very satisfactory stabilization of the fractured segments. Access to fractures of the anterior and lateral maxilla can be achieved through a gingivobuccal incision ensuring that there is an adequate cuff of unattached mucosa to isolate the plates from the mouth at closure. The posterior limit of the incision should be no further than the first permanent molar to preserve a good blood supply. The buccal fat pad may be avoided by angling the scalpel blade or cutting diathermy at 45° to the gingival cuff. Subperiosteal elevation with preservation of the infraorbital nerve allows reconstruction of the paranasal and zygomatic buttresses. The infraorbital rim needs to be reduced and fixed in Le Fort 2 maxillary fractures, nasomaxillary fractures, zygomatic injuries and orbital floor repairs. A number of skin incisions can be used (Table 107.1) all of which have advantages and disadvantages.

KEY POINTS

Maxillary fractures

- Maxillary fractures may involve the orbits.
- They may disrupt the occlusion.
- Internal fixation has replaced external fixation for the majority of maxillary fractures.
- Most high-energy maxillary fractures are not pure Le Fort injuries and are also comminuted.
- Haemorrhage may be arrested with anterior and posterior nasal packs or epistats.

ZYGOMATIC COMPLEX FRACTURES

Surgical anatomy

The body and processes of the zygomatic bone make up the lateral middle third of the facial skeleton. Blows to this part of the face are common and may cause either a depressed fracture of the entire zygomatic bone or a fracture of the zygomatic arch (Figure 107.17). These injuries were originally termed 'tripod fracture' because of the disruption of the three commonly recognized articulations:

1. fronto-zygomatic
2. infraorbital rim
3. zygomaticomaxillary buttress.

In fact, there are two further articulations worthy of consideration:

1. zygomatic arch;
2. zygomaticosphenoid.

The lateral middle third of the face provides support and protection for the globe of the eye. Accurate anatomical reduction of such fractures is important for facial appearance, optimum function of the eye, and because of its close proximity to the coronoid process, for opening and closing the mandible.

Signs and symptoms

The lateral aspect of the face is best examined from the front, above and behind the patient. It will be swollen and bruised. A subconjunctival haemorrhage is almost invariably present in fractures of the zygomatic body (Figure 107.17). Even if the eyelid is closed by oedema, it is essential that the eye is examined and its acuity recorded. Eye movements may be restricted, particularly in upward gaze if there is an orbital floor dehiscence and blow-out of the orbital contents (Figure 107.18). The zygomatic prominence may be difficult to assess initially because of soft tissue swelling but, once this has decreased, reduced projection will become more obvious. A step deformity of the infraorbital margin may be palpable and the frontozygomatic suture may be tender to touch. In arch fractures, there is often a palpable depression and limited mouth opening. Finally, the sensation of the cheek may be altered



Figure 107.17 Typical appearance of a patient with a fractured zygoma. A slight depression of the cheek is clearly visible and he has a subconjunctival haemorrhage.

TABLE 107.1 Orbital access

Incision	Advantage	Disadvantage
Transconjunctival	Good exposure, aesthetic	Slight risk of entropion
Transconjunctival with cantholysis	Excellent exposure	Risk of lid malposition
Transconjunctival with transcaruncular extension	Excellent exposure of medial orbit wall	Technically difficult
Lower eyelid	Straightforward to execute	Risk of increased sclera show, ectropion Visible scar
Infraorbital	Rapid, minimal increased scleral show	Poor cosmesis



Figure 107.18 Reduced ocular movement and enophthalmos associated with an orbital floor injury.

if there has been damage to either the zygomaticotemporal or zygomaticobuccal nerves.

Imaging

Whilst most fractures are visible on 15 and 30° occipitomental X-rays, CT scanning is increasingly becoming standard of care particularly if there are signs of diminished ocular motility. Hess charting should be obtained in all cases with subjective diplopia.[36]

Management

Minimally displaced fractures may be managed conservatively with a full explanation to the patient and instructions not to blow their nose for a period of 2–3 weeks. It is prudent to review the patient after 10 days when much of the swelling will have resolved to make sure that no active intervention is required. Displaced fractures require reduction with or without fixation. Reduction may be achieved in a number of ways. The precise method will depend on the surgeon's preference and the configuration of the fracture. Each method has its advocates and offers certain advantages over others (Table 107.2).

GILLIES TEMPORAL APPROACH

The hair is shaved just anterior to the ear and both infraorbital margins are exposed for comparison. Following infiltration with local anaesthetic and adrenaline solution, a small incision is made down to the superficial temporal fascia. The fascia is then incised and an elevator is passed down on the temporalis muscle so that its tip lies just under the fracture. The bone is then elevated.

POSWILLO HOOK

The point of application of the hook is the intersection of a line drawn vertically from the lateral orbital margin and a horizontal line drawn from the inferior margin of the nose. The hook is inserted through a stab incision and the zygoma lifted back into position.

INTRA-ORAL OR KEEN APPROACH

A mucogingival incision is made in the buccal sulcus in the molar/premolar region. An elevator may be passed behind the zygomatic body to elevate the fracture.

Diastasis at the frontozygomatic suture and high-energy injuries are typically unstable. Closed reduction does not allow examination of the articulations of the zygoma. Minor discrepancies may be missed and only come to light some days later.

In reality, surgical exposure of the relevant articulations together with experience ensures good outcomes for the overwhelming majority of patients. The zygoma may be plated at the frontozygomatic suture, infraorbital margin, zygomatic buttress and zygomatic arch. Wound closure is extremely important. Optimal draping of the soft tissues requires meticulous closure of the periosteum over the plates. Some surgeons 'hitch' the deep tissues to superior tissues to provide further support.[37]

TABLE 107.2 Zygomatic complex fractures – advantages and disadvantages of surgical approaches

Approach	Indication	Advantage	Disadvantage
Gillies	Medially displaced body fractures, zygomatic arch fractures	Elevating site distant from fixation site	Requires skin incision, may be conspicuous in the bald patient
Dingman	Medially displaced body fractures	Uses common skin incision to that of frontozygomatic access	May be difficult to plate frontozygomatic suture and elevate simultaneously Incision may become stretched
Poswillo hook	Posteriorly displaced fractures Not arch fractures	Good mechanical advantage, quick, only one suture required	Access point of hook is prominent on the lateral cheek prominence and may be noticeable
Keen	Medially displaced fractures, arch fractures	Avoids cutaneous scars	Does not address displacement at the frontozygomatic suture Elevation and plating at this site are difficult simultaneously Theoretical contamination of the fracture site with oral microorganisms
Coronal	Laterally displaced arch fractures	The only approach for this rare fracture	Extensive surgical exposure

Post-operative care

The patient is instructed not to blow their nose and, for the first 12 hours, they should be closely observed for signs or symptoms of a retrobulbar haemorrhage. Increasing pain, proptosis, ophthalmoplegia, diminishing visual acuity and a palpable increase in ocular pressure should alert the attendant to this and indicate the need for urgent exploration and evacuation of any haematoma. Most long-term complications relate to malunited fractures. It is important to realize that early accurate anatomical reduction provides the best results. Secondary reconstruction is difficult because of bony remodelling and fibrosis in the overlying soft tissues.[38, 39]

KEY POINTS

Retrobulbar haemorrhage can involve:

- decreased visual acuity;
- diplopia;
- ophthalmoplegia;
- proptosis;
- tense globe;
- dilated pupil;
- loss of direct light reflex.

BEST CLINICAL PRACTICE

Management involves:

✓ dexamethasone 4 mg/kg bolus, 2 mg/kg, 6-hourly;
✓ acetazolamide 500 mg i.v.;
✓ mannitol 20%, 200 mL;
✓ finally, remove the sutures and consider surgical decompression by a lateral cathotomy.

ORBITAL FLOOR FRACTURES

Introduction

The form and function of the globe depends on the integrity of the bone and soft tissue of the orbit. Blunt trauma to the globe[40] or adjacent bone can lead to a fracture of the thin bone of the orbital floor.[41]

Signs and symptoms

The cardinal signs of an orbital floor fracture are enophthalmos and hypoglobus (depressed pupillary level). Enophthalmos is most apparent when the contralateral eye is normal. Other signs include supratarsal hollowing, hooding of the eye, narrowing of the palpebral fissure width and an infraorbital nerve deficit. A small fracture of the orbital floor can lead to a trap door phenomenon. If the orbital fat or inferior oblique muscle becomes trapped in the fracture configuration, then interference with muscular function results in diplopia on upward gaze (Figure 107.18).

Imaging

CT imaging with axial, coronal and sagittal reformatting provides best standard of care

BEST CLINICAL PRACTICE

Ophthalmology review

✓ Assessment of visual acuity is mandatory. Retrobulbar haemorrhage causing loss of sight is a rare occurrence but is treatable and should be sought in every orbital injury.
✓ Hess charting allows comparison of the visual fields of each eye. Post-operative charting can be used to assess the quality of repair.
✓ Hertel exophthalmometry gives an objective analysis of the position of the globe. It has limited value in acute trauma.

Management

Significant orbital floor injury requires exploration and repair. The approach will be determined by the size and position of the blow-out fracture. All soft-tissue components should be mobilized and supported by a graft. Various grafts and materials have been used for this purpose. polydimethylsiloxane (PDS) are readily available and most suited for smaller defects. Titanium alloplasts, either prefabricated or custom-made using CAD-CAM technology are extremely useful especially when there are concomitant zygomatic complex fractures.[42]

NASO-ORBITO-ETHMOID COMPLEX FRACTURES

Definition and classification

Naso-orbito-ethmoid (NOE) fractures involve the anatomical confluence of the nose, orbits and ethmoids. This is a complex area and these injuries are often overlooked. Reconstruction at a later date is extremely difficult. The most useful classification of these injuries was devised by Markowitz et al.[43] who defined them in terms of their attachment to the medial canthal ligaments (Table 107.3).

TABLE 107.3 Classification of naso-orbito-ethmoid complex fractures

Classification	
Type I	Single large central fragment bearing the canthal ligaments
Type II	Fragmentation of the central fragment, medial canthal ligaments attached to bone
Type III	Comminution of the central fragment with no bone attached to canthal ligaments

Signs and symptoms

Loss of nasal projection and tipping up of the end of the nose are common features of these injuries (Figure 107.19). Splaying of the nasal root and telecanthus indicates gross comminution. There is usually blunting of the canthal angle and movement of the medial canthus can be elicited by displacement of the lateral palpebral ligament.

Management

Type I fractures can be stabilized using miniplates. Surgical access is through a coronal flap, intra-orally and lower eyelid incisions may be required. Type II and III fractures are also repaired with miniplates, but require a transnasal canthopexy to reduce the telecanthus and hold the position of the medial canthal ligaments. This is accomplished by means of plates and/or a wire. The lacrimal integrity should be assessed pre- or peri-operatively and stented primarily if damaged.

UPPER FACIAL THIRD FRACTURES INVOLVING THE FRONTAL SINUS

Fractures involving the frontal sinus may lead to deformity and be complicated by infection. These injuries are classified according to the involvement of the anterior and/or posterior table and whether or not there is damage to the nasofrontal duct.[44] The principal aims of treatment are to leave the patient with a safe and functional sinus and with no cosmetic deformity. Fractures of the anterior table may be treated conservatively if there is no cosmetic deformity, while displaced fractures require reduction and fixation. Fractures of the posterior table demand a neurosurgical opinion and may need an obliterative procedure or cranialization with obliteration of the frontonasal recess and its lining.[45, 46] Persistence of the epithelial lining with inadequate drainage predisposes to mucocoele formation.[47]



Figure 107.19 Patient with a naso-orbito-ethmoid fracture with typical loss of nasal projection and tilting of the nasal tip.

Soft tissue injuries

Accurate repair of soft tissue injuries including skin and fascia layers is mandatory for optimum results. Facial wounds should be closed as soon as possible provided they are clean. Meticulous debridement with antiseptic solution is essential. Grit from the roads can tattoo wounds badly and be a real problem and are best removed using a sterile nylon scrubbing brush.

Experience with cutaneous malignancy demonstrates that sizeable areas of tissue loss can be dealt with primarily, so some selective removal of poorly viable wound margins would appear to be sensible. It is crucial to ensure that any underlying bony injury is repaired to enable correct support and soft tissue draping.

The facial nerve and parotid duct are frequently damaged in significant soft-tissue injuries. The facial nerve is easiest to find and repair in the first 48 hours, while the peripheral branches can still be stimulated. Epineural repair provides the patient with the best chance of a good recovery.

Identification and alignment of key landmarks such as the vermillion border of the lip, eyebrow, alar margin of nose, ear and eyelids is essential for a good cosmetic result. Similarly, the use of deep sutures (4/0 vicryl or equivalent) to take tension out of the wound and to avoid dead space together with appropriate skin sutures (5/0 or 6/0 monofilament) produces the best results. Shelved lacerations should be managed by placing sutures with a bigger 'bite' on the more depressed side, and triangular edges by the 'corner stitch' technique. Sutures are best supported by steristrips and removed after 4–7 days. Chloramphenicol eye ointment can be applied to the wound 4 times daily for one week.

The patient should be instructed in wound care and told to avoid direct sunlight on the wound for one year.

PAEDIATRIC FACIAL INJURIES

Fortunately, serious maxillofacial injuries in this age group are uncommon. Minor injuries, particularly soft tissue and dentoalveolar are, however, frequent. The treatment concepts and protocols are similar to adult patients.[48]

Soft tissue injuries

Minor soft-tissue injuries are managed in the same way as adult patients. Consideration should be given to the use of resorbable sutures to avoid unnecessary general anaesthesia for suture removal. Cyanoacrylate glue can be used with care but not in the presence of substantial connective tissue damage.

Injured anterior teeth

Dental injuries to the upper anterior teeth are extremely common, but their management and prognosis is

extremely complex. The optimal treatment protocol is determined by a number of factors that relate to the type of tooth fractured, the presence and level of any root fracture, the vitality of the pulp and the state of development of the root. It is essential that an expert opinion is sought from a maxillofacial surgeon or paedodontist. Fractured teeth can be temporarily repaired, exposed pulps capped with calcium hydroxide based pastes and mobile teeth splinted to adjacent teeth. Anterior permanent teeth that have been avulsed should be reimplanted at the first available opportunity and splinted. If the reimplantation is delayed, the tooth should be kept moist in the mouth of the patient or parent. Alternatively, the tooth could be stored in a glass of milk.

Fractures of the facial bones

As stated previously, the principles of reduction and fixation of facial bone fractures in children are the same as for adults. Plates should be placed using short screws to avoid damaging developing tooth germs and all mandibular metal work removed after 3–6 months so that it does not interfere with growth. Fractures of the condyle are usually treated conservatively as there is an immense capacity for remodelling and any intervention might damage the growth centre.[49] Fronto-naso-ethmoid injuries differ in their fracture pattern because the development of the frontal sinus may not be complete. Any extensive dissection of the medial canthal area may lead to excessive subperiosteal bone formation and therefore repairs in this area should be supported by acrylic buttons in the immediate post-operative phase.[50]

BEST CLINICAL PRACTICE

Paediatric dental injuries

- ✓ Consider whether the injury might be non-accidental.
- ✓ Reimplant avulsed teeth as soon as possible.
- ✓ Use short screws and take care not to damage unerupted teeth.
- ✓ Remove plates 3–6 months after surgery.
- ✓ Manage condylar fractures conservatively.

FUTURE RESEARCH

- ➤ The controversy on the virtues of open and closed management of condylar neck injuries will persist. The management and outcomes of intra-capsular fractures may well become revolutionized by alloplastic materials.

KEY POINTS

Soft tissue injuries

- Accurate repair of soft tissue injuries including skin and fascia layers is mandatory for optimum results.
- It is crucial to ensure that any underlying bony injury is repaired to enable correct support and soft tissue draping.
- Identification and alignment of key landmarks such as the vermillion border of the lip, eyebrow, alar margin of nose, ear and eyelids is essential for a good cosmetic result.

Paediatric Facial Injuries

- Fortunately, serious maxillofacial injuries in this age group are uncommon. Minor injuries, particularly soft tissue and dentoalveolar are, however, frequent.
- The treatment concepts and protocols are similar to adult patients. The principles of reduction and fixation of facial bone fractures in children are the same as for adults.
- Fractures of the condyle are usually treated conservatively as there is an immense capacity for remodelling and any intervention might damage the growth centre.

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CHAPTER 108

CSF LEAKS

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using keywords: CSF leak, CSF rhinorrhoea, spontaneous CSF leak, skull base repair and intrathecal fluourescein.

INTRODUCTION

Few procedures reflect the tremendous benefits of endoscopic techniques in quite the same way as the endoscopic closure of CSF leaks. Although the ultimate chance of success may in some measure depend on the aetiology of the leak,[1] remarkable results of 90% success rates at the initial attempt with success rates up to 97% with revision have been published.[1, 2] Despite these impressive figures there continues to be isolated enthusiasm for open approaches in some neurosurgical centres. Some published neurosurgical series have success rates as low as 60% with predictable sequelae from brain retraction and sacrifice of the olfactory nerves, to say nothing of the coronal flap and frontal craniotomy. Recent neurosurgical publications have recommended open approaches in the face of adverse prognostic factors such as prior radiation or elevated intra-cranial pressure.

Although rhinorrhea can be a socially troubling symptom, the principal motivation for repair of CSF leaks is to reduce the risk of meningitis or other intra-cranial complications. The incidence of meningitis in patients with an active CSF leak has been quoted as 10% year on year[3, 4] although a more recent study suggested that the incidence may be as low as 0.3% per year per active leak per person.[5] Daudia et al. found that in 11 patients with 190 years of active leaks 21 developed meningitis resulting in an overall risk of 19% although most occurred in the first year of the leak.[5]

The repair of a newly diagnosed CSF leak is not an absolute surgical emergency and time can be taken to properly work-up and investigate the patient. During this time the simple advice of telling the patient not to blow their nose or to sneeze 'with their mouth open' and not to use CPAP needs to be reinforced. Nonetheless, because of the risk of meningitis, surgical repair should be performed at the earliest reasonable opportunity. Even today meningitis is associated with a definite mortality rate. Few studies have followed patients with repaired leaks over the long term. A publication from the Mayo Clinic[6] identified recurrence of leaks in a group of 21 patients at an average of 50.8 months after corrective surgery. The longest interval to recurrence in this group of patients was 28 years.

In patients with a history of a CSF leak it is worth checking their pneumococcal antibody titres and recommending vaccination with a 23-valent polysaccharide PNC vaccine or a 7-valent conjugate PNC vaccine if it is low.

In recent years, the spectrum of leaks seen in major centres has changed significantly. Most of the leaks seen

today are either 'spontaneous' or what might be termed 'anticipated'. The 'anticipated' category of leaks comprises those seen after anterior skull base or sellar or parasellar tumour resection. In these patients, the bony defect is often substantial and this has required a reappraisal of reconstructive techniques.

While a variety of classification systems of CSF leaks exist, perhaps the most useful is the time-honoured system of classification by aetiology. CSF leaks can be considered as congenital, spontaneous or post-traumatic. Post-traumatic leaks can be further divided into those associated with head trauma, those seen as a complication of sinus surgery and those seen as a part of skull base surgery. A small number of patients with tumours also present with CSF leaks.

HEAD TRAUMA

CSF leaks are quoted as occurring in perhaps 2% of head injuries and 12% to 30% of skull base fractures.[8] Most CSF leaks occur as a result of blunt trauma. They may present as CSF otorrhea, CSF oto-rhinorrhea or CSF rhinorrhea. The conventional viewpoint is that most traumatic CSF leaks will heal with conservative treatment including bedrest. Insertion of a lumbar drain may sometimes be required. It is likely that only the sinus mucosal aspect of the defect closes as the dura does not regenerate. This produces a relatively fragile closure and work by Bernal-Sprekelsen et al.[9] has suggested a substantial continuing risk of meningitis in these patients. The authors suggest that this 'mono-layer of protection' may be eroded by either the pulsatile effect of the brain or by inflammation within the nose.[9] With the widespread availability of endoscopic closure, performed with statistically small risks, this conservative management paradigm might be challenged, changing towards a more active interventionist policy.

Massive head trauma with complex comminuted and displaced fractures of the skull base can be incredibly difficult to treat. Open approaches may be of value for these patients. The decision to proceed with an open approach is sometimes made easier by the presence of intra-cranial injuries requiring attention or significant fractures of the posterior wall of the frontal sinus. Free tissue transfer has been reported as being helpful in carefully selected groups.[10] In massive 'egg-shell' fractures of the sphenoid sinuses, fat obliteration can be considered, leaving the treatment of possible subsequent mucoceles that may develop to a secondary procedure.

CONGENITAL CSF LEAKS

Congenital CSF leaks in association with encephalocele or meningoencephaloceles are uncommon. These are well diagnosed on MRI and this scan is recommended when sinus opacity is demonstrated adjacent to a skull base defect. Brain tissue contained within the encephalocele is invariably non-functioning and can be removed as part of the surgical procedure. Congenital abnormalities of the inner ear such as the Mondini Dysplasia may present with substantial CSF leaks where the CSF has only briefly transversed the perilymphatic space. Such leaks, in addition to presenting as hearing loss or recurrent meningitis, may also present with CSF otorrhea or CSF oto-rhinorrhea (Figure 108.1).



Figure 108.1 Coronal CT scan of meningo – encephalocele medial to and eroding the left middle turbinate.

CSF LEAKS ASSOCIATED WITH TUMOURS

Tumours causing substantial erosion of the skull base may present with CSF rhinorrhea. Occasionally where tumour shrinkage occurs, for example during induction chemotherapy, CSF leaks may also occur. The closure of the CSF leak is part of the surgical treatment of the tumour and for the closure to be successful it is important for the margins of the CSF leak to be clear of tumour, particularly in malignant disease. Persisting CSF leaks in the face of residual untreated tumour may present a considerable challenge. A study by Boudreaux and Zins[11] described open treatment of CSF leaks in 14 high-risk patients. Nine of the 14 patients had malignant brain tumours. A success rate of 85% was reported.

SPONTANEOUS LEAKS

A good deal of recent interest has centered on 'spontaneous CSF leaks' sometimes described as 'idiopathic'. The association of spontaneous leaks with middle-aged

women with a raised body mass index is now well known. These leaks are thought to represent a variant of benign intra-cranial hypertension.[12] These patients have a generally elevated intra-cranial pressure, this diagnosis being made on lumbar puncture after surgical repair. It is not possible to measure this pre-operatively as the persistent leak reduces the pressure although there may be radiological features of increased intra-cranial pressure such as an empty sella, enlarged ventricles or diffuse erosion of the skull base.[1] When the CSF is actively draining – for example, perhaps at the time of lumbar puncture for fluorescein installation prior to repair, the intra-cranial pressure is often reduced. It is thought that the elevated intra-cranial pressure is due to poor CSF resorption by the arachnoid villi.[12] This increased intra-cranial pressure with associated pulsatile forces produces thinning of bone that is most evident in the weakest areas of the skull base. Herniation of the meninges and brain, often with CSF leakage, most often occurs in the lateral recess of a well pneumatized sphenoid, in the area of the lateral lamella of the cribriform and in the ethmoid roof. These may be multiple sites of weakness of the skull base.

Imaging and diagnosis are similar to other varieties of CSF leaks. In cases of multiple cranial base defects, intrathecal fluorescein can be helpful in localizing the exact location of active leakage. Identification of 'spontaneous' as the likely aetiology of the leak pre-operatively is helpful in counselling the patient.[1] Spontaneous leaks are most likely to recur and the success rates for endoscopic closure are worse than for other aeteologies.[1] In one study, 21% of spontaneous leaks recurred, going up to 46% if there were radiological signs of a raised intra-cranial pressure compared to 2% if the leak was not spontaneous.[1] With spontaneous leaks there can be re-leakage at the site of repair but there can be multiple areas of weakness of the skull base and with untreated underlying elevated intra-cranial pressure other areas may break down and leak.

Areas of substantial skull base dehiscence may benefit from additional reinforcement with a bone or cartilage graft. This is sometimes easier said than done with a thin bony skull base and difficulty in finding a reliable 'edge'. CSF leaks in the lateral recess of well pneumatized sphenoid sinuses may be best approached by the transantral transpterygoid approach described by Bolger.[13] Post-operatively, the elevated intra-cranial pressure may be helped by oral acetazolamide. Selected patients may benefit from shunting. Success with employing a gastric bypass for morbid obesity has also been described.[12]

CSF LEAKS COMPLICATING SINUS SURGERY

A rate of serious complications in the order of 0.5% or less is generally quoted for endoscopic sinus surgery (**Figure 108.2**). CSF leaks diagnosed intra-operatively or post-operatively would be included in this category of serious complications.

A publication by Bachmann et al.[14] looked at the incidence of occult cerebrospinal fluid fistulae during sinus surgery. They found a 3% incidence of occult leaks utilizing the beta-trace protein assay. They had reviewed 69 consecutive patients, 'all-comers', undergoing surgery at the hands of an experienced surgeon in a tertiary referral centre. None of the patients with occult leaks displayed any symptoms or sequelae out to the follow-up period of 6 months. The authors speculated that occult leaks may be more common than previously thought and that small leaks may self-heal. The important caveat to be included with this study is that these patients need to be followed long term to examine the likelihood of delayed meningitis.

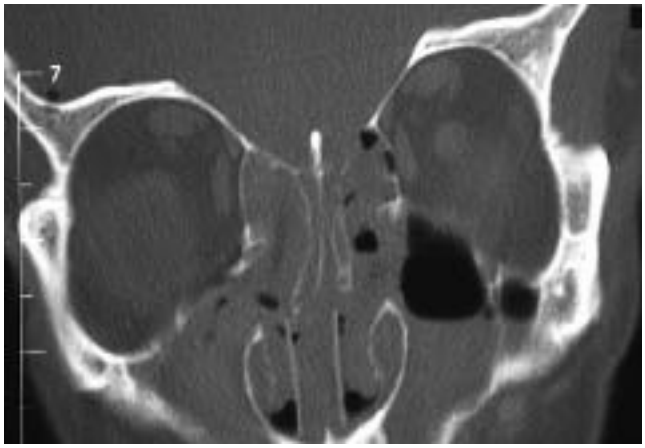


Figure 108.2 Coronal CT scan image revealing left skull base injury, clinically presenting with a CSF leak, complicating endoscopic sinus surgery.

Some of the details of CSF leaks complicating sinus surgery are covered in the complications chapter of this book. Image-guided surgery, while indisputably helpful in individual cases, has not reduced the likelihood of complications in large case series. Powered instrumentation, the other great technological advance in sinus surgery in recent times, has changed the scale of complications, making brain parenchymal injury more likely than eminently treatable CSF leaks. With brain parenchymal injuries has come the need to exclude significant intra-cranial adverse vascular events.

As a general rule, CSF leaks complicating sinus surgery, diagnosed intra-operatively should be repaired under the same anaesthetic. Local intra-nasal tissue can be used for the repair with generally good results. The most likely anatomical sites for CSF leaks complicating sinus surgery are the very thin bone of the lateral lamella of the cribriform plate, the area of the anterior skull base where it is weakened by the anterior ethmoid neurovascular bundle and posteriorly where there may be confusion as to the exact anatomical relationship between the last posterior ethmoidal cell and the sphenoid sinus.

In unusual circumstances, a decision can be made not to repair the CSF leak under the same anaesthetic. Where the degree of surgical disorientation is such that attempts at repair might result in further damage such as an orbital or brain parenchymal injury, an argument can be made for referring these patients to specialist centres for closure. The wound can be carefully packed with particular care being exercised during the 'wake-up' from anaesthesia.



Figure 108.3 Plain skull film demonstrating pneumocephalus complicating the use of positive airway pressure. Permission pending from Kopelovich J, et al. *J Clinical Anesthesia* 2012 Aug; 24(5): 415–18.

It is crucial that the patient does not receive positive pressure mask ventilation after extubation for fear of substantial pneumocephalus developing (**Figure 108.3**).

CSF leaks complicating sinus surgery may also become evident in the post-operative period. Any complaint of clear rhinorrhea post-operatively needs to be taken seriously and investigated vigorously. The appropriate investigation of such leaks will be dealt with later in the chapter.

REPAIR OF SURGICALLY-INDUCED SKULL BASE DEFECTS

Endoscopic approaches to the anterior skull base and sellar and parasellar regions are increasingly employed for the treatment of a variety of pathological processes. Small defects can be repaired in the same way as defects of other aetiologies. For larger defects, free-fat grafts can be successfully employed. More recently, interest has focused on the use of vascularized tissue flaps. The idea of CSF leak repair utilizing vascularized septal or turbinate flaps is not new. Yessenow and McCabe reported excellent success rates utilizing this tissue in transnasal, extracranial, non-endoscopic repair of CSF leaks nearly 30 years ago.[15]

Most reports have focused on posterior septal flaps. The so-called 'Hadad-Bassagasteguy' flap utilizes septal mucoperiosteum and mucoperichondrium based on the nasoseptal artery. Kassam et al.[16] reported its general utility in 75 patients undergoing endonasal endoscopic cranial base surgery. Harvey et al.[17] reported on the experience of two skull-base centres over a 12-month period comprising 30 patients. They related using a variety of flaps including the posterior septal flap as well as inferior turbinate and nasal floor flaps. They emphasized technical aspects relating to the flap including avoiding injudicious initial posterior septectomy, decisions regarding a concomitant hemi-transfixion or Killian septal incision and careful preservation of the flap during surgery. They also emphasized the use of multi-layer skull base reconstruction initially supported by an inflated Foley catheter balloon.[17]

INVESTIGATION OF CSF LEAKS

A story of clear rhinorrhea, sometimes tasting salty and often posturally provoked, with an appropriate antecedent history is clinically suspicious for a CSF leak. Such patients must be investigated vigorously. As compelling as such a history appears, these patients do not always end up having CSF leaks as shown by Bateman and Jones in 9 patients presenting with highly suggestive histories.[18] Further investigation is therefore required. Endoscopic examination of the nose may be unrevealing but is part of the initial work-up.

The next goal is to obtain fluid for testing. Ideally this can be obtained at the office visit, sometimes with postural provocation (**Figure 108.4**). When this is unsuccessful we will sometimes have patients run up stairs in an effort to increase intra-cranial pressure and produce drainage or strain on a closed glottis. If this fails, patients are given vials to take home to catch fluid for testing. In the United States the beta-2-transferrin test is widely available and the most commonly used. A downside of the test is that it may only be performed in certain major centres and thus it may take a few days to get a result. The beta-2-transferrin test provides excellent sensitivity, specificity and positive and negative predictability in the diagnosis of CSF leaks.[19] A concomitant serum value enhances its utility. Occasional false positives have been reported in certain liver diseases or hereditary disorders of protein metabolism. It has been suggested in some European



Figure 108.4 Collection of posturally provoked CSF rhinorrhea.

studies that beta-trace protein is an even better test than beta-2-transferin in detecting CSF leaks.[19]

IMAGING FOR DIAGNOSIS OF CSF LEAKS

The clear majority of CSF leaks can be diagnosed using beta-2-transferrin testing and reformatting of ultra-fine cut CT scan images of the sinuses. The coronal scan is most helpful in examining the ethmoid roof but other views are useful in diagnosing leaks at other anatomical sites. These images are most often obtained as part of planning for image-guided surgery. Details of a bony defect may be seen or an area of opacification or an air fluid level in an adjacent sinus. In the situation where there is an opaque sinus adjacent to a skull base defect an MRI scan should be performed to help diagnose a possible encephalocoele or meningocoele. Where a defect is not visualized in the sinuses, a CT examination of the temporal bones should be considered to exclude CSF oto-rhinorrhea in difficult to diagnosis cases.

In some centres MRI cisternography is performed if fine cut CT scans and beta-2-transferrin testing do not provide a diagnosis. A variety of technical modifications of the MRI enhance its ability to detect the area of the leak.[20] More commonly in cases where the diagnosis is unclear, CSF contrast studies are considered (**Figure 108.5**). This may utilize radiographical contrast such as iohexol or alternatively a radio-active tracer. These investigations require the patient to be actively leaking at the time of the study. As they need an intrathecal contrast agent of one sort or another, these tests are associated with a slightly greater risk than non-invasive studies. Radionucleide cisternography involves intrathecal administration of a tracer via a lumbar puncture followed by imaging once the tracer has had an opportunity to make its way to the skull base. Strategically placed nasal pledgets are also used. It is our practice to cut these pledgets into different shapes as this helps to identify their position in the nose after they come out. Radioactive tracers of different half lives can be considered. Localization of CSF leaks by Gadolinium-enhanced MRI cisternography has also been described. Gadolinium is injected into the subarachnoid space. This is an 'off-label' use of gadolinium in the United States and requires a separate consent. Aydin et al.[21] found this technique useful in 43 of 51 patients. No neurological sequelae were seen from the injection.



Figure 108.5 Intrathecal contrast CT study revealing left skull base defect.

CONTROVERSIES IN REPAIR

INTRATHECAL FLUORESCEIN

It is my practice to use intrathecal fluorescein as part of the repair of all CSF leaks planned as a discrete procedure. Separate consent is obtained for the intrathecal use of fluorescein as its use via this route is not approved by the FDA. There is at least a theoretical advantage to giving this while the patient is awake and a German publication describes employing intrathecal fluorescein the afternoon before surgery.[22] In this publication, fluorescein is administered without CSF withdrawal to minimize CSF displacement.[22]

As a practical matter in the United States fluorescein is mostly administered in the operating room after induction of general anaesthesia. Our neurosurgical colleagues perform a lumbar puncture and insert a lumbar drain. Ten cc's of the patients CSF is withdrawn and this is mixed with 0.1 cc of 10% fluorescein suitable for injection. The mixture is then re-injected slowly over 10 minutes timed by the clock. The patient is placed slightly head down and sufficient time is allowed for the fluorescein to equilibrate throughout the subarachnoid space. The nose is closely examined with zero degree and angled telescopes and sites of leakage are disclosed by the bright green colour of the fluorescein. Usually the light of the telescope is sufficiently broad spectrum to achieve this – occasionally a blue light filter is helpful. The intrathecal fluorescein is of use, firstly in diagnosing a CSF leak, secondly in disclosing its exact location and thirdly, by its absence, providing evidence of success of the repair (**Figure 108.6**).

Complications of fluorescein's intrathecal use have been reported.[22] The most common complication cited has been seizures but in general this has been associated with use of the wrong formulation of fluorescein, occipital application, a higher than recommended dose or rapid bolus injection. Other complications have been attributed to the simultaneous use of intrathecal radiographical contrast material. Citing these concerns,



Figure 108.6 Intra-operative slow re-injection of patient's CSF mixed with fluorescein.

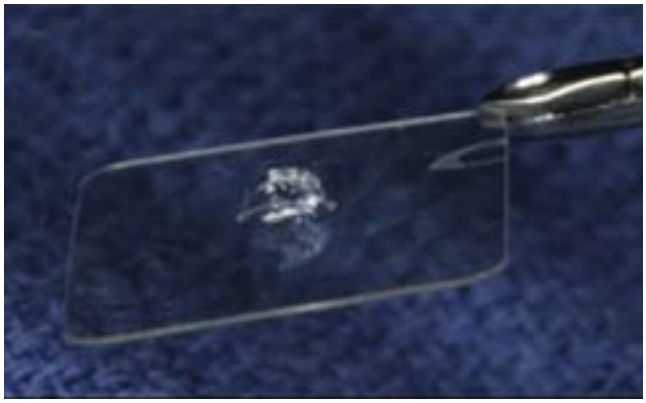


Figure 108.7 Bioabsorbable transparent plate. 'Handle' provides for ease of manipulation. Permission pending from Potter, NJ, et al. *Laryngoscope* 2015; **125**(6): 1313–15.

Zuckerman and Del Gaudio[23] described excellent success rates in 42 CSF leaks repaired without using intrathecal fluorescein or indeed lumbar drains. They relied on high-resolution CT and intra-operative image guidance for leak identification. The use of topical 5% fluorescein applied intra-operatively to the surgical site has also been described.[24] This can also be used as an office-based diagnostic test. The authors recommend skin testing the patient with fluorescein eye drops to rule out allergy the day prior to the procedure.[24]

LUMBAR DRAINS

The routine use of lumbar drains in elective CSF leak repair is controversial. Our practice is to use one when intrathecal fluorescein has been employed. The drain is placed at the time of initial lumbar puncture and then 'closed' and re-opened immediately prior to repair. Lumbar drains can be associated with important complications and their use requires specialist nursing management. In our hospital, patients with lumbar drains are managed on the neurosurgical floor.

We feel that the reduction in intra-cranial pressure afforded by the lumbar drain offers an extra measure of insurance for the repair. Certainly, however, series of successful repair without lumbar drains of selected patients with CSF leaks have been described.[23]

TECHNICAL ASPECTS OF THE REPAIR

Whatever preferences and prejudices a surgeon might have regarding specific aspects of the surgical repair, evidence can be found in the literature to support that view. Successful repair of CSF leaks requires identification of the exact site of leakage. This may require considerable dissection in difficult to find leaks. In contrast to routine endoscopic sinus surgery where mucosal preservation and avoidance of scarring is of paramount importance, in cases of CSF leak repair, scarring incited by mucosal stripping helps form a dense repair. No literature exists favouring one graft material over another and therefore the choice is largely based on surgeon preference, ease of manipulation, cost etc. Likewise no literature exists regarding the use of onlay versus underlay grafts. In general, free grafts have been preferred to vascularized flaps for smaller defects because of technical ease of manipulation and obviation of the potential for contraction with healing. Recent interest in closing large defects associated with skull base surgery has favoured pedicled flaps.[16, 17] While bone or cartilage grafts are helpful in medium- sized defects they have not been used for large repairs or generally in small defects. There is some evidence to support the use of fibrin glue to reinforce the closure. In a pig model, Almeida et al.[25] showed that fibrin glue enhanced closures had superior graft adherence and higher 'burst pressures'. Neurosurgical authors[26] have recommended dural sealants as an adjuvant to surgical repair in high-risk patients. A concern is that these 'sealant' materials may add to the cost of the surgery without significantly improving success rates. Potter et al.[27] have described the use of bio-absorbable plates as part of the surgical repair of CSF leaks in patients with an elevated BMI. Dloughy et al.[27] described young age and elevated BMI as independent variables predictive of post-operative CSF leakage after endoscopic pituitary surgery. Potter et al.[28] recommended use of semirigid bio-absorbable plates as part of the surgical repair of CSF leaks in patients with an elevated BMI, describing a significant reduction in leak rates after pituitary surgery following their use (**Figure 108.7**).

We place a 'break-layer' of Gelfoam® under the area of repair and then place a Merocel® pack. The Gelfoam® isolates the repair from shearing forces when the pack is removed. As mentioned earlier in the chapter, inflated catheter balloons[17] may provide temporary structural support after major skull base repairs.

CONCLUSION

Remarkable progress has been made in the endoscopic treatment of CSF leaks. Advances have occurred both in pre-operative imaging and diagnosis as well as in technical refinements of the surgical closure. Areas of interest in the future might include a better understanding of patients with spontaneous leaks and advances in the reconstruction of significant skull base defects from endo-nasal craniotomies.

KEY POINTS

- Endoscopic repair is treatment of choice.
- Beta-2 transferrin or Beta-trace protein are highly accurate diagnostic tests.
- High-resolution CT scans are needed in all cases.
- Intrathecal fluourescein helps in difficult cases.
- Precise layered closures give best results.

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CHAPTER 109

GRANULOMATOUS CONDITIONS OF THE NOSE

Joanne Rimmer and Valerie J. Lund

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: granulomatous disease, Wegener's granulomatosis, granulomatosis with polyangiitis, sarcoidosis, Churg Strauss syndrome, cocaine-induced midline destructive lesion, nose and paranasal sinuses. The evidence is mainly levels 2/3 with some level 4 randomized trials. The clinical recommendations are predominantly grades C with some B and D.

INTRODUCTION

A granuloma is an organized collection of macrophages, known as epithelioid cells, which fuse to form multinucleated giant cells. This histological configuration is encountered in a number of infective, inflammatory and neoplastic conditions of the nose and sinuses (Table 109.1) and is also seen in various conditions in which vasculitis plays a role. Vasculitis may be primary or secondary and is further classified according to the size of vessel affected (Table 109.2).

Whilst many of these conditions are systemic, they may be limited to the upper respiratory tract or present with otorhinolaryngological symptoms; the ear, nose and throat (ENT) surgeon must therefore maintain a continuous low threshold of suspicion to establish the diagnosis at the earliest opportunity.

SARCOIDOSIS

Sarcoidosis is a systemic granulomatous condition of unknown aetiology which may affect any part of the body, but most frequently involves the lungs and intra-thoracic lymph nodes, in over 90% of cases.[3] It has a global incidence of 6–16 per 100,000 population per annum but there is significant geographical variation, with 64 cases per 100,000 in Scandinavia.[4] It is 10–20 times more common in African-Americans (36.5–81.8 per 100,000) than Caucasians (1.2–19 per 100,000). Besnier first used the term 'lupus pernio' to describe cutaneous lesions in 1889, but it was Boeck who recognized the more generalized nature of the condition 10 years later.[5, 6]

Age and sex

Sarcoidosis is a condition of young adults with a peak onset between the third and fourth decades. It is slightly more common in women than men.[7]

Aetiology

The aetiology of sarcoidosis remains unknown, but theories suggest an immunological response to an unidentified antigen in genetically predisposed individuals.[8] The antigens may be infectious or environmental, and possibilities include mycobacteria, fungi, chemicals such as beryllium and zirconium, pine pollen and peanut dust.[9] There are abnormalities of both the cell-mediated and humoral immune systems.[4] Macrophages and T-cell activation lead to release of cytokines including tumour necrosis factor (TNF), with resultant granuloma formation.[10]

TABLE 109.1 Granulomatous conditions affecting the nose and sinuses

Infective		Inflammatory	Neoplastic
Bacteria			
Tuberculosis	*Myobacterium tuberculosis*	Sarcoidosis	Extranodal NK/T-cell lymphoma
Leprosy	*Myobacterium leprae*	Granulomatosis with polyangiitis (Wegener's)	
Rhinoscleroma	*Klebsiella rhinoscleromatis*	Eosinophilic granulomatosis with polyangiitis (Churg Strauss)	
Syphilis	*Treponema pallidum*	Cocaine-induced midline destructive lesion	
Actinomycosis	*Actinomyces israeli*	Giant cell granuloma	
Fungal[a]			
Aspergillus	*Asp. fumigatus, flavus, niger*	Eosinophilic granuloma	
Zygomycosis	*Conidibolus coronatus*	Cholesterol granuloma	
	Rhizopus oryae		
Dematiaceae	*Curvularia*		
	Alternaria		
	Bipolaris		
Rhinosporidiosis	*Rhinosporidiosis seeberi*		
Blastomycosis	*Blastomyces dermatitidis*		
	Cryptococcus neoformans		
Histoplasmosis	*Histoplasma capsulatum*		
Sporotrichosis	*Sporotrichum schenkii*		
Coccidioidimycosis	*Coccidioides immitis*		
Protozoa			
Leishmaniasis	*Leishmania spp.*		

Source: Modified from reference[1], with permission.
[a]Covered in Chapter 96, Fungal rhinosinusitis.

TABLE 109.2 Primary vasculitis according to vessel size

Large, medium and small blood vessels	Medium and small blood vessels	Small blood vessels	Miscellaneous conditions	Secondary vasculitis
Takayasu arteritis	Polyarteritis nodosa	Microscopic polyangiitis	Buerger's disease	Infection-related vasculitis
Giant cell (temporal) arteritis	Eosinophilic granulomatosis with polyangiitis (Churg Strauss)	Schönlein–Henoch syndrome	Behçet's disease	Serum sickness or drug hypersensitivity-related vasculitis
Granulomatous angiitis of the central nervous system	Granulomatosis with polyangiitis (Wegener's)	Cutaneous leukocytoclastic angiitis	Kawasaki disease	Hypocomplementemic urticarial vasculitis
				Vasculitis associated with rheumatic connective tissue diseases
				Vasculitis associated with other systemic diseases
				Malignancy-related vasculitis
				Post-transplant vasculitis
				Pseudovasculitic syndromes (myxoma, endocarditis, Sneddon syndrome)

Source: Reprinted from reference[2], with permission.

Clinical features

Sarcoidosis is a multisystem disease; the reported distribution of clinical manifestations tends to reflect the bias of the treating physician. It primarily affects the lower respiratory tract but may involve almost any organ or system in the body (Table 109.3). It involves the upper respiratory tract in up to 18% of cases.[11] Sinonasal sarcoid is reported in 1–4%, more frequently than previously realized, and it is generally agreed that nasal manifestations are almost always part of chronic multisystem sarcoid.[12] Nasal symptoms commonly include obstruction, crusting, bleeding or facial pain (Table 109.4). A staging system for sinonasal involvement has been described to help tailor treatment: stage I is reversible involvement of the nose alone; stage II is moderate but potentially reversible disease of the nose and/or limited sinus involvement; and stage III is severe, irreversible and extensive sinonasal disease.[4]

The nasal mucosa often has a rather characteristic granular appearance, sometimes referred to as a 'strawberry skin' because of the tiny pale granulomas against hypertrophic erythematous mucosa. This is generally very friable and there may be ulceration, crusting and adhesions. The anterior nasal septum is most often affected and may perforate, particularly if traumatized by surgery. The nasal bones may be involved by a process similar to the dactylitis seen in the fingers; patients may present with a soft-tissue mass or expansion of the nasal bridge. This may be associated with thickening and purplish discoloration of the overlying skin known as lupus pernio (Figure 109.1), which is a cutaneous manifestation of chronic systemic sarcoid.[3] Facial pain is experienced by one in five patients with nasal sarcoid.[12] There may be hyposmia due to mechanical obstruction of the olfactory cleft by crusting or fibrosis or as a result of direct neuropathy.

Salivary gland enlargement is seen in 5–10% of cases, more rarely associated with facial palsy and uveitis when it is termed uveoparotid fever or Heerfordt's syndrome.[8] The larynx is involved in 1–5% of cases, most commonly the supraglottis (85%), with symptoms of cough, hoarseness, dysphagia and more rarely stridor.[13] Tracheal involvement is rare but bronchial sarcoid is common. Chronic progressive pulmonary fibrosis occurs in 25% of cases of chronic pulmonary sarcoid.[3]

TABLE 109.3 Frequency (%) of clinical involvement of extrapulmonary organs in sarcoidosis

Extrathoracic sites	Percentage
Peripheral nodes	73
Skin	32
Liver	21
Eye	21
Spleen	18
Bone	14
Salivary glands	6
Joints	6
Heart	5
Nervous system	5
Kidneys	4
Nose and mouth	3
Lacrimal glands	3
Skeletal muscle	1
Larynx	1
Stomach and intestine	1
Uterus	1

TABLE 109.4 Incidence (%) of symptoms in patients with nasal sarcoidosis

Symptom	Percentage
Nasal stuffiness and obstruction	88
Crusting	63
Blood-stained discharge	37
Purulent discharge	30
Facial pain	22
Mucoid discharge	15
Anosmia	4

Source: Reproduced with permission from the ©ERS 1988.[12]

Diagnosis

No test is pathognomonic for sarcoidosis. Diagnosis therefore relies on a combination of clinical features, imaging, histology, biochemical and serological testing and the exclusion of other granulomatous diseases. Previously the most reliable investigation, the Kveim test has been withdrawn in the UK for unproven health and safety reasons.[14] It involved intra-dermal injection of splenic tissue from a patient with sarcoidosis, with biopsy of the resulting skin nodule. The classic histological appearance is that of a non-caseating granuloma with central epithelioid cells



Figure 109.1 Typical appearances of nasal lupus pernio.

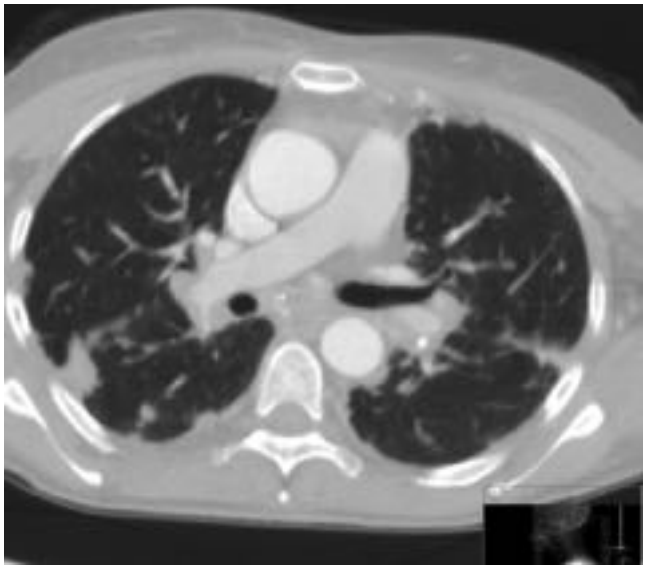


Figure 109.2 Axial CT scan showing typical pulmonary infiltrates in systemic sarcoidosis. (Courtesy of Dr Timothy Beale.)



Figure 109.3 Coronal CT scan showing sclerosis and osteolysis of the nasal bones associated with a soft tissue mass in nasal sarcoid.

surrounded by lymphocytes and fibroblasts. Biopsy should target potentially affected tissue such as the lung, skin and lymph nodes; lip biopsy of minor salivary glands can be useful.[8] Biopsy of nasal mucosa is only of use if it appears abnormal, when over 90% of samples are positive; random biopsy of macroscopically normal mucosa is negative in 92%.[12]

Serum angiotensin converting enzyme (ACE) is elevated in up to 85% during active disease, but this is non-specific as it is also elevated in other conditions such as tuberculosis, leprosy and primary biliary cirrhosis.[15] Serum and urinary calcium levels are elevated in approximately 15% of cases.[4]

Imaging of the lower respiratory tract shows varying degrees of pulmonary involvement, which allow staging of the disease (**Figure 109.2**). Stage I is bilateral hilar lymphadenopathy, stage II is hilar lymphadenopathy and pulmonary infiltrates, stage III is pulmonary infiltrates alone and stage IV is pulmonary fibrosis.[16] Bronchoscopy will allow biopsy. Plain X-rays of the nasal bones may show rarefaction or punctate osteolysis in up to one quarter of cases and this, together with soft tissue changes, may also be seen on computerized tomography (CT) scanning (**Figure 109.3**).[17] CT will also demonstrate secondary involvement of the sinuses though will not distinguish between active disease and secondary infection. Bilateral lacrimal gland enlargement may also be seen.

Magnetic resonance imaging (MRI) of the brain may show granulomatous involvement of the basal meninges.

Treatment

Sarcoidosis has a variable clinical course that often correlates with the mode of presentation; an acute onset with arthritis and erythema nodosum is usually self-limiting, whilst a more insidious onset with lupus pernio and sinonasal involvement tends to be more chronic.[18] Up to two-thirds of patients will spontaneously remit, generally those with stage I and II pulmonary disease, while 10–30% follow a chronic course with relapses despite systemic therapy.[19] Some patients require no treatment at all, but international guidelines suggest systemic or intra-lesional steroid treatment for life-threatening disease or if critical organs are involved.[20] Despite a lack of controlled studies, steroids remain the mainstay of treatment for severe disease, with the addition of agents such as methotrexate to reduce the steroid dose if required. Hydroxychloroquine has been used for cutaneous and sinonasal sarcoidosis, although the response rate is less than 50% and there is a risk of ocular toxicity.[21] Lupus pernio may respond dramatically to medical treatment.[22] There has been recent interest in TNF-alpha inhibitors such as infliximab and etanercept.[23]

Nasal symptoms may be helped with topical treatment including intra-nasal steroids, glucose and glycerine drops, and nasal douching. Surgery has a limited role, particularly in the presence of active disease, although endoscopic sinus surgery can be undertaken to remove obstructing lesions or for secondary bacterial infection, with success in selected cases.[24] Septal surgery should be avoided if possible as an increased rate of septal perforation has been reported.[3] Symptomatic laryngeal disease that fails to respond to systemic treatment may be treated with transoral laser and intra-lesional steroid injections.[25]

GRANULOMATOSIS WITH POLYANGIITIS (WEGENER'S)

Granulomatosis with polyangiitis (GPA) is a systemic condition characterized by granulomatous inflammation of the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels with focal or proliferative glomerulonephritis.[27] GPA was formerly known

as Wegener's granulomatosis, after Wegener's article on rhinogenic granulomatosis in 1939, but has been renamed as part of a move towards a vasculitis terminology based on pathology.[28, 29] GPA classically involves a triad of upper airway, lung and renal disease, but limited or localized forms of the condition have been reported in up to 30% of cases.[30] Thus, the true incidence of the condition is difficult to determine. Whilst up to 1967 only 138 unequivocal cases had been recorded in the literature, the incidence is now estimated to be 10–15 per million per year with a prevalence of up to 5 per 100,000 population in Europe.[30–32]

Age and sex

The mean age at diagnosis is 40–50 years.[33] The age of presentation in our own cohort ranges from 15 to 78 years (n = 180 patients), although it has been reported in younger children. Cabral's paediatric series reported a median age at diagnosis of 14.2 years (range 4–17 years).[34] Men and women are equally affected, although in children there appears to be a female preponderance.[34, 35] GPA is predominantly a Caucasian disease (over 90%).[26]

Aetiology

GPA appears to be an autoimmune disease, given its strong association with antineutrophil cytoplasmic antibodies (ANCA). *In vitro* studies have shown that ANCA binds to and activates neutrophils, which then release oxygen radicals, inflammatory cytokines and lytic enzymes and adhere to and kill vascular endothelial cells.[36] ANCA may also induce immune complex formation.[26] In GPA, cytoplasmic ANCA (c-ANCA) are specific for proteinase-3 (PR3), an endogenous peptide. There is evidence that a mimic peptide may be introduced via an exogenous infective agent such as *Staphylococcus aureus*.[36] This theory is supported by the higher rate of chronic nasal *S. aureus* carriage in patients with GPA, in whom it is associated with more frequent relapses.[37]

Clinical features

Any part of the body may be affected and in generalized disease there is often associated general malaise, disproportionate to the clinical findings. Limited forms of the disease are now well recognized; the European Vasculitis Study Group classified GPA as 'localized' (respiratory tract involvement only with no features of systemic vasculitis), 'early systemic' or 'generalized' disease.[38] In the USA, 'limited' GPA refers to systemic non-life threatening disease rather than truly localized forms.[39] Whilst many of these cases may progress to generalized disease, there is some evidence that a subset (approximately 5%) will remain localized.[40] The frequency with which different sites are involved, both at presentation and subsequently, varies with the interest and specialty of the reporting physicians.[41] Duration of symptoms before a diagnosis is made remains highly variable and can be more than one year.[42]

The head and neck is the most common site of involvement at presentation, in 73–93% of cases.[33, 43] The nose and sinuses are involved in more than 80%, with symptoms including nasal obstruction, crusting, discharge and bleeding. In addition, patients may complain of facial pain.[42] Destruction of the intra-nasal structures may follow, including the septum, turbinates and sinuses with formation of a single large cavity. While there is intranasal destruction of bone and cartilage in some patients with GPA, leading to septal perforation and a characteristic nasal collapse, there are none of the gross destructive changes of the midfacial skin seen in NK/T-cell lymphomas and basal cell carcinomas.

Approximately one-third of patients develop otitis media with effusion with associated conductive hearing loss due to eustachian tube dysfunction, and more rarely pain and suppuration. Sensorineural hearing loss also occurs in 35%.[43] Facial nerve paralysis has been recorded in 8–10%.[44]

Subglottic or upper tracheal stenosis occurs in 16% of cases, although it is 5 times more common if GPA presents in childhood.[45] It may present as progressive dyspnoea on exertion or as acute airway obstruction. Localized GPA requires exclusion in an adult presenting with an apparently idiopathic subglottic stenosis.[46]

Oral symptoms are rare but ulceration may be seen and 'strawberry' gingival hyperplasia is said to be pathognomonic.[47]

Ocular manifestations, including conjunctivitis, dacryocystitis and episcleritis, occur in approximately 50% of patients at some point.[43] Approximately, 2% develop proptosis from a granulomatous mass within the orbit (**Figure 109.4**). Visual loss occurs in up to 8%, usually from optic nerve ischaemia due to inadequately treated retro-orbital disease.

Necrotizing vasculitis in the lungs causes cough, haemoptysis and pleuritic pain. The pulmonary lesions often cavitate and can usually be seen radiologically. Over 75% of patients develop renal involvement; early treatment is vital since damage is irreversible.[43] Cutaneous manifestations include ulceration and nodules, and both polymyalgia and polyarthritis have been described. Neurological sequelae include meningitis, mononeuritis multiplex and neuropathy of cranial nerves.[26]

Diagnosis

The ANCA test, first described by van der Woude in 1985, has significantly improved the diagnosis of GPA and other vasculitides.[48] There are two main staining patterns: c-ANCA, 90% of which are PR3-ANCA; and perinuclear (p-ANCA), 90% of which are specific for myeloperoxidase (MPO-ANCA).[49] In general, patients with GPA have c-ANCA, whereas p-ANCA tends to occur in other conditions, such as microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Using combined immunofluorescence and enzyme-linked immunosorbent assay techniques, the sensitivity and specificity of c-ANCA are 91% and 99% respectively; the sensitivity falls to 60% with localized disease.[50] C-ANCA is positive

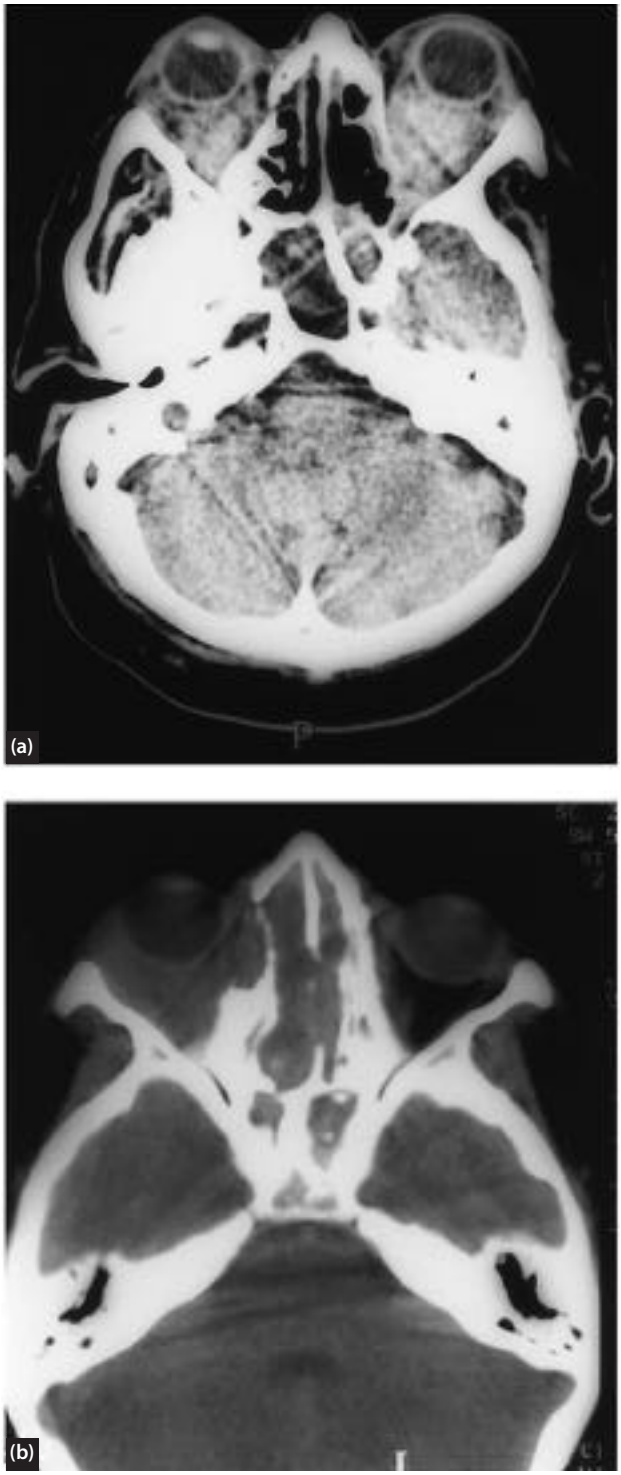


Figure 109.4 (a) and (b) Axial CT scans showing sclerosis and opacification of the nasal cavity associated with widespread infiltration of the orbit in GPA.

in over 90% of patients with generalized active disease and titres have been shown to correlate well with disease activity.[51] However, 10% of patients with GPA have a positive p-ANCA result and up to 20% may be ANCA-negative; in localized disease this figure may rise to 30%.[26] In addition, there may be false-positive c-ANCA results with cocaine abuse.[52] Other blood tests should therefore also be requested, including a full blood count, erythrocyte sedimentation rate, c-reactive protein, serum urea and creatinine and serum ACE. Urinalysis and chest X-ray should be performed. Tissue biopsy may be helpful in ANCA-negative patents where suspicion remains high, but is non-diagnostic in up to 50% of head and neck specimens.[26] Paranasal sinus biopsies tend to yield more positive results than nasal specimens.[53] The main histological features are granulomatous inflammation, vasculitis and necrosis.

The American College of Rheumatology proposed a clinical classification in 1990 to distinguish GPA (Wegener's) from other vasculitides (**Table 109.5**).[54] The Chapel Hill Consensus added PR3-ANCA to the definition in 1994.[55]

CT and MRI may show characteristic features (**Figure 109.5**). In a series of 74 patients, over 90% showed

TABLE 109.5 1990 American College of Rheumatology criteria for the classification of Wegener's granulomatosis*

Criteria	Definition
Nasal or oral inflammation	Painful or painless oral ulcers or purulent or bloody nasal discharge
Abnormal chest X-ray	Nodules, fixed infiltrates or cavities
Abnormal urinary sediment	Microscopic haematuria with or without red cell casts
Granulomatous inflammation on biopsy	Histologic changes showing granulomatous inflammation within the wall of an artery or in the peri- or extravascular area (artery or arteriole)

* For classification purposes, a patient shall be said to have Wegener's granulomatosis if he/she has satisfied any two or more of these four criteria. This rule is associated with a sensitivity of 88.2% and a specificity of 92.0%.



Figure 109.5 Coronal CT showing typical appearances of Wegener's in the nose with septal destruction hyperostosis and opacification of the sinuses together with orbital infiltration.

non-specific mucosal thickening in the nasal cavity or paranasal sinuses, 62% showed evidence of bone destruction and 78% had new bone formation in the walls of the sinus cavities.[56] In addition, the orbit was affected in 37%. Whilst the diagnosis of systemic GPA is made clinically, in a patient without a history of previous sinonasal surgery the combination of bone destruction and new bone formation on CT is virtually diagnostic, especially when accompanied on MRI by a fat signal from the sclerotic sinus wall, so-called 'tramlining'.[57] These findings can be helpful in localized sinonasal GPA, where the clinical diagnosis is uncertain and the c-ANCA test may be negative. Imaging of the chest may show nodules, progressive cavitation or fibrosis. Imaging of the larynx should be considered in any patient with symptoms suggestive of subglottic stenosis.

Treatment

Untreated, GPA is a lethal disease with a mean survival of 5 months.[58] Rapid diagnosis remains of great importance since a fulminating course with a fatal outcome can occur in as little as 48 hours. The introduction of systemic corticosteroid treatment improved mortality rates to 50%.[32] However, it was the combination of oral cyclophosphamide with corticosteroids that improved remission rates to 93%.[59] Despite this, over half of patients will have at least one relapse, and the potential side effects of cyototoxic treatment are not insignificant.[33] Treatment regimes today aim to induce remission and then maintain it, whilst minimizing side effects, and the European Vasculitis Study Group (EUVAS) has undertaken several controlled trials to inform treatment algorithms.[60]

Remission-induction therapy is typically with a combination of high-dose steroids and cyclophosphamide or methotrexate.[26] The usual daily dose of cyclophosphamide is 2 mg/kg, to a maximum of 200 mg per day. There is significant morbidity associated with long-term cyclophosphamide treatment, with side effects including alopecia, haemorrhagic cystitis, opportunistic infections and malignancies; leukaemia and lymphoma are 11 times more likely, and there is a 33-fold increase in the risk of bladder cancer.[61] Strategies to reduce these adverse effects include shorter treatment durations and the use of intermittent 'pulsed' cyclophosphamide. Several randomized trials have shown that pulsed therapy is as effective as oral treatment in achieving remission, but it is associated with a higher relapse rate.[62] Methotrexate, an antimetabolite, has been shown in randomized trials to be an effective alternative to cyclophosphamide in inducing remission in patients with limited and less severe GPA.[63] More recently rituximab, an anti-CD20 monoclonal antibody, has been shown to be as effective as cyclophosphamide in inducing remission.[64] The multicentre randomized double-blind RAVE (Rituximab for ANCA-Associated Vasculitis) trial also suggested that rituximab may be superior in relapsing disease.

High-dose glucocorticoids are an essential part of remission–induction treatment, and prednisolone is initially given at a dose of 0.5–1 mg/kg daily, to a maximum of 80 mg per day; this can then be tapered over the course of several months before stopping completely where possible.[65] Patients may require further courses of glucocorticoids to manage disease exacerbations and relapses. The side effects of long-term systemic therapy are well known, including osteoporosis, diabetes, hypertension, proximal myopathy, weight gain and cataracts.

Remission-maintenance therapy aims to keep GPA quiescent with minimal treatment morbidity. Methotrexate can be used, with similar relapse rates compared to long-term cyclophosphamide treatment.[66] These patients should receive folic acid supplementation to prevent folate deficiency. Azathioprine is an alternative immunosuppressive agent with less morbidity than cyclophosphamide, and a randomized controlled trial showed equivalent remission control.[67] Both methotrexate and azathioprine may be used as monotherapy to maintain remission, but are also given as steroid-sparing agents to reduce the dose of prednisolone required by some patients.

Multiple controlled trials have been undertaken in an effort to try and find less toxic but equally effective immunosuppressive agents. Mycophenolate mofetil, a purine synthesis inhibitor, has shown promise in this area but a large multicentre randomized controlled trial showed a higher relapse rate when compared with azathoprine.[68] Leflunomide, a T-cell inhibitor that targets purine synthesis, appears to be well tolerated and effective in remission maintenance.[69] Deoxyspergualin, an immunomodulatory agent which inhibits lymphocyte differentiation, appears to be effective in maintaining remission and reducing steroid requirements.[70] Tumour necrosis factor antagonists, such as infliximab and etanercept, have shown less promising results. A multicentre placebo-controlled trial of etanercept plus standard therapy showed no benefit compared to placebo.[72]

The possible association between GPA relapses and *S. aureus* infection in the nose prompted trials of long-term antibiotic treatment, namely trimethoprim-sulphamethoxazole (co-trimoxazole), with mixed results. A double-blind placebo-controlled trial showed that relapse rates were reduced compared to controls.[72] However, another randomized trial reported that co-trimoxazole did not maintain remission as effectively as methotrexate.[73]

Whatever treatment is used, patients require regular monitoring for both treatment side effects and disease activity. Serial monitoring of c-ANCA can be useful; it frequently becomes negative when the disease is under control but this is not always the case, particularly in localized forms.

Topical nasal treatment such as douching, intra-nasal steroids and nasal lubricants may be helpful for symptomatic relief of crusting and bleeding. Surgery is generally reserved for cases that are refractory to medical treatment, or for complications of GPA.[26] Endoscopic sinus surgery is rarely helpful in improving symptoms, but may be undertaken in selected cases. Endoscopic dacryocystorhinostomy has been reported to improve epiphora, but should be avoided in active disease.[74] Septal perforation repair is not recommended but the use of a silastic septal button

can be beneficial. Augmentation rhinoplasty to correct a saddle-nose deformity should be deferred until the disease has been in remission for at least one year. A series of 13 patients in remission from Wegener's reported a 92% overall success rate from dorsal augmentation without reactivation of disease.[75] Grommets are best avoided if possible, because of the risk of chronic otorrhoea; hearing aids are a better option to treat both conductive and sensorineural hearing loss.[44] It has been said that 50% of patients with subglottic stenosis will require a tracheostomy at some point, but recent studies suggest that conservative treatment may avoid this in most cases. Conservative laser surgery combined with endoluminal balloon dilatation and intra-lesional steroid injection appears to give satisfactory results.[76]

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (CHURG STRAUSS)

In 1951, Churg and Strauss described a syndrome of allergic angiitis and granulomatosis, a rare systemic vasculitis which has more recently been named 'eosinophilic granulomatosis with polyangiitis' (EGPA).[77, 78] The Chapel Hill consensus defined it as 'eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, associated with asthma and eosinophilia.'[55] It is the rarest of the ANCA-associated vasculitides, with an estimated annual incidence of 0.5–4 per million in Europe, although may be underestimated.[31] However, in asthmatics this incidence rises to 67 per million.[79]

Age and sex

The mean age at diagnosis is 50 years (range 4–75 years).[80] Both male and female preponderances have been reported, but overall there appears to be no significant difference.[79, 81, 82]

Aetiology

The aetiology remains unknown but it may be an autoimmune disease mediated by Th2-cells which activate both eosinophils and neutrophils.[83] Direct eosinophilic infiltration and the release of cationic proteins and cytokines then cause tissue injury.[80] High levels of eosinophils and immunoglobulin E (IgE) in vessels and tissues also suggests a direct role in the development of the vasculitis, possibly an allergic response to an unknown allergen. EGPA has been reported to occur after treatment with the leukotriene receptor antagonist zafirlukast.[84] However, this appears to relate to the unmasking of vasculitis by the reduction in systemic steroid treatment that zafirlukast allowed, rather than be a true causative effect.[85] Other suggested precipitants include vaccination, desensitization therapy and inhalation of various aeroallergens, which all support an allergic aetiology.[86]

Clinical features

Asthma occurs in approximately 99% of patients, and is characteristically late-onset; in 83% of cases it precedes the vasculitis by an average of 8 years.[87] Sinonasal symptoms are present in up to 93%, and have been reported to worsen prior to diagnosis in 28% of patients.[81, 88] Allergic rhinitis and chronic rhinosinusitis with nasal polyps occur in up to 75% of cases.[82] Patients frequently complain of nasal obstruction, rhinorrhoea, anosmia and sneezing, as well as crusting and epistaxis to a lesser degree; nearly half may have undergone previous nasal surgery before the diagnosis is made.[81]

Neurological symptoms are common, with mononeuritis multiplex in up to 76% and peripheral polyneuropathy in approximately one-quarter of cases.[89] Central nervous system involvement is less common, but is the second commonest cause of death.[90]

Cutaneous symptoms including papules and nodules occur in up to 50% of cases. Cardiac involvement is less common but is the major cause of mortality, usually from granulomatous myocarditis.[79]

Three clinical phases of EGPA have been described, although they do not necessarily follow each other consecutively.[90] The first, prodromal, phase may persist for several years, and is characterized by adult-onset asthma and upper respiratory tract inflammation. Phase two is characterized by peripheral eosinophilia, usually with pulmonary infiltrates and eosinophilic gastroenteritis. The third phase is that of the systemic vasculitis, including constitutional symptoms, neurological and cutaneous involvement.[80]

Diagnosis

Diagnosis is based on the typical clinical features with a peripheral eosinophilia of greater than 10% of the white cell differential, plus tissue biopsy. Histology shows necrotizing vasculitis, extravascular necrotizing granulomas and tissue eosinophilia, but it is rare to see all three features on one biopsy.[82] ANCA is positive in 40–75% of cases, typically p-ANCA specific for MPO but occasionally c-ANCA is seen.[80, 86] There is evidence that ANCA modulates the phenotype, with a more vasculitic disease in ANCA-positive patients.[87] The French Vasculitis Study Group series reported significantly more peripheral neuropathy, ENT and renal involvement in patients with a positive p-ANCA, as well as less frequent cardiac pathology.[78] There was a higher relapse rate in ANCA-positive cases but significantly reduced mortality.

Chest X-ray usually shows transient peripheral infiltrates, but pleural effusions are seen in up to 10% of cases.[79] Sinonasal imaging shows non-specific widespread opacification consistent with chronic rhinosinusitis with polyps, and patients are perhaps more likely to develop frontoethmoidal mucocoeles.[61] The American College of Rheumatology clinical criteria for the classification of EGPA includes pulmonary and sinus radiological abnormalities (**Table 109.6**).[91]

TABLE 109.6 1990 American College of Rheumatology criteria for the classification of Churg Strauss syndrome*

Criteria	Definition
Asthma	History of wheezing or diffuse rales on expiration
Eosinophilia	Eosinophilia >10% on white blood cell differential count
Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy
Pumonary infiltrates, non-fixed	Migratory or transitory pulmonary infiltrates on radiographs
Paranasal sinus abnormality	History of acute or chronic paranasal sinus pain or radiographic opacification of the paranasal sinuses
Extravascular eosinophils	Biopsy including artery, arteriole or venule, showing accumulations of eosinophils in extravascular areas

*For classification purposes, a patient shall be said to have Churg Strauss syndrome if he/she has satisfied any four or more of these six criteria. This rule is associated with a sensitivity of 85% and a specificity of 99.7%.

The differential diagnosis includes parasitic and fungal infections, eosinophilic pneumonia, idiopathic hypereosinophilic syndrome and other vasculitides.

Treatment

Treatment is primarily with high-dose systemic steroids, which are tapered when possible. Those with organ or life-threatening disease, or those requiring persistently high doses of steroids may require treatment with cyclophosphamide to induce remission.[88] Methotrexate has also been used for both induction and maintenance of remission, and azathioprine and mycophenolate mofetil may be helpful as steroid-sparing agents.[79] Interferon-alpha has been successful in treating refractory cases.[92] Overall remission rates are high (91%) but over 25% relapse either within the first 3 months or much later, after 5 years.[86] Survival has improved with the advent of corticosteroid and immunosuppressive treatment, with mortality similar to that of the normal population.[88] Sinonasal symptoms should be treated with topical nasal steroids, douching and endoscopic sinus surgery as required, which may be multiple times.[81]

COCAINE-INDUCED MIDLINE DESTRUCTIVE LESION

Cocaine use via intra-nasal inhalation is known to cause mucosal inflammation. Septal perforation has been reported in approximately 5% of chronic users, but more aggressive midfacial destruction has also been noted.[52] Such cocaine-induced midline destructive lesions (CIMDL) can mimic localized or systemic GPA as well as neoplasia.

Aetiology

Cocaine is the trigger but patients who develop CIMDL appear to be predisposed to produce ANCA. Nearly 90% have a positive p-ANCA against human neutrophil elastase (HNE), which may increase apoptosis and the local inflammatory response to injury.[52]

Clinical features

Patients complain of chronic nasal obstruction and bleeding, with change in shape of the nose and nasal regurgitation as the lesion progresses to destroy the nasal framework and in particular the palate; this is more common than in GPA patients where it occurs only rarely. There are rarely systemic symptoms. Not all patients will admit to cocaine use. Examination confirms a variable degree of destruction of the septum, turbinates, lateral nasal wall and floor (**Figure 109.6**).

Diagnosis

The differential diagnosis includes infections, GPA and neoplasia, and these must be excluded. Whilst the majority of patients with CIMDL will have a positive HNE-ANCA, over 50% of patients will also have a positive PR3-ANCA. This makes differentiation from limited GPA more difficult, but studies have shown no evidence of HNE-ANCA positivity in either normal controls or patients with GPA.[93] Histology is often very similar to that of GPA, with vasculitis and fibrinoid necrosis, so may not be helpful unless it confirms GPA.[52] Urine, blood and hair can be tested for cocaine if necessary.

Treatment

There is no role for immunosuppression, and patients must stop using cocaine to prevent further progression. Conservative treatment includes nasal douching, debridement of necrotic areas and topical or systemic antibiotic therapy. Surgical correction of septal perforation or nasal deformity should not be attempted until the patient has been clear of cocaine for at least 6–12 months.

EOSINOPHILIC GRANULOMA

This is a clonal proliferation of Langerhans cells associated with a heterogeneous inflammatory infiltrate of eosinophils, histiocytes, lymphocytes, plasma cells and neutrophils. It is now regarded as a neoplastic condition with a variable clinical course.[94, 95] It is also considered a manifestation of histiocytosis-X and is sometimes referred to as Langerhans cell histiocytosis or Langerhans granulomatosis.

Age and sex

A wide age range from infancy to over 80 years has been recorded, but about 85% of cases are detected in the first

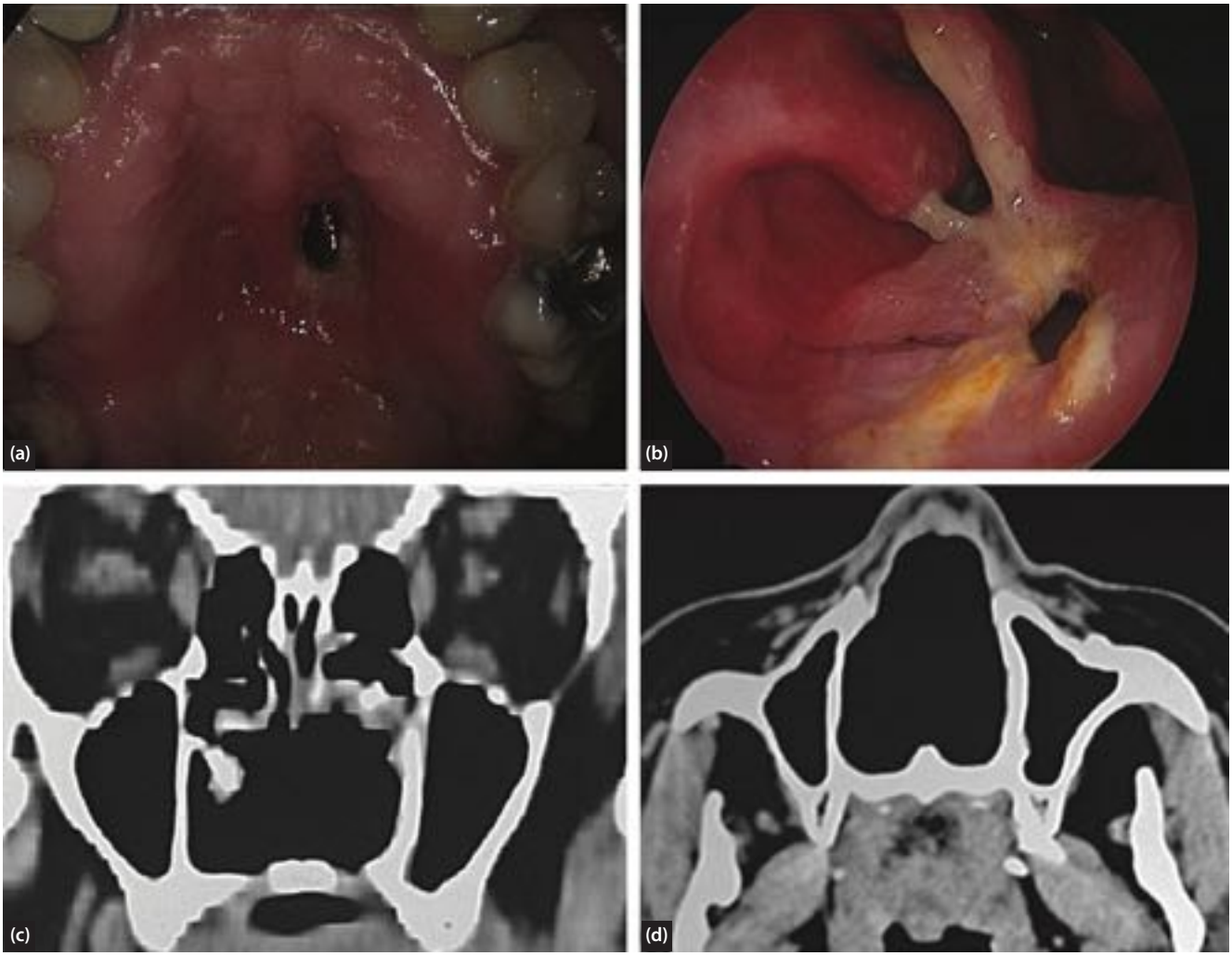


Figure 109.6 Cocaine-induced midline destructive lesions. **(a)** Oral endoscopy showing a 1cm hard palate perforation with regular margins; **(b)** Nasal endoscopy showing extensive destruction of the nasal septum and inferior turbinate as well as the hard palate perforation; **(c)** Coronal and **(d)** axial CT showing extensive destruction of the septum and turbinates (Courtesy of Dr Matteo Trimachi).

three decades of life; 60% are young children. Males are affected twice as frequently as females.

Clinical features

Whilst all organs may be affected, eosinophilic granuloma predominantly occurs in bones. The skull is a common site of involvement, in particular the temporal, frontal and parietal bones. The usual presentation is a painful swelling of the involved bone, often for many months, associated with cervical lymphadenopathy. Mandibular lesions produce toothache, gum ulceration and loose teeth, whereas involvement of the temporal bone may simulate acute mastoiditis.

Diagnosis

Radiological evaluation shows punched-out bony lesions and radiolucent areas around the teeth. Lesions in the skull often show bevelled margins due to angulated destruction of the cortical bone. Macroscopically, the lesions are soft and yellow or red-brown in colour; biopsy material is best obtained by curettage. Microscopically, the Langerhans cells are mixed with other inflammatory cells. The cytoplasm of the Langerhans cells may be eosinophilic and Charcot–Leyden crystals may be found in ordinary histiocytes. There is intense osteoclastic activity at the periphery of the granuloma due to prostaglandin and cytokine production by the Langerhans cells.[96] During the healing phase of the granuloma, the stroma becomes increasingly fibrotic.

Treatment

Treatment depends on whether or not the eosinophilic granuloma is localized and/or solitary. Solitary, or 'type II disease', is at least five times more common than polyostotic disease. Some solitary lesions will spontaneously regress. With unifocal disease a combination of curettage/excision and radiotherapy is usually curative, provided that no new lesions develop within the first year. A proportion of patients will develop a generalized disease with hepatosplenomegaly, lymphadenopathy, skin lesions and further osseous lesions, so called 'type I disease'.

The course of this can be rapid with a poor prognosis; additional chemotherapy has been advocated in these circumstances. At present, the most effective chemotherapy regime appears to be etoposide and steroids given for periods of 12 months or more dependent on the response.[97] Alpha interferon and bone marrow transplantation have also been used successfully.

GIANT CELL GRANULOMA

Granuloma-like aggregates of giant cells in a fibrovascular stroma characterize this benign condition otherwise referred to as 'giant cell reparative granuloma' or 'giant cell reaction of bone'. It was first described by Jaffe in 1953 in the jaws, although other craniofacial sites have been reported.[98]

Age and sex

These lesions commonly occur in children and young adults, with a female to male preponderance of 2:1.

Clinical features

Pain and swelling over the affected bone are the most common symptoms, but diplopia, hearing loss, vertigo and tinnitus have also been reported. The maxilla and mandible are most commonly affected followed by the sphenoid and temporal bones.[98, 99] Bilateral symmetrical involvement of the jaws by giant cell granulomas is seen in cherubism, a rare inherited childhood condition (**Figure 109.7**).[100]

Diagnosis

CT shows expansile lytic lesions with a 'soap bubble' centre and well-demarcated edges. Histologically, the granuloma has a cellular fibroblastic stroma containing aggregates of giant cells. These cells are smaller and have fewer nuclei than in a true giant cell tumour. The lesions are benign despite the presence of mitoses, which may cause the inexperienced pathologist difficulties. To add to the confusion, the microscopic appearance of giant cell granulomas is indistinguishable from that of the solid variant of aneurysmal bone cysts. Biochemical investigations (serum calcium, phosphate and alkaline phosphatase) should be undertaken to distinguish it from the brown tumour of hyperparathyroidism.

Treatment

Curettage alone is associated with recurrence in 15% of cases and excision should be undertaken where possible.[99]

CHOLESTEROL GRANULOMA

This is a rare granulomatous foreign body reaction to cholesterol crystals precipitated in the tissues, and has also been referred to as a chocolate cyst or orbital cholesteatoma.

Age and sex

In 6 cases managed by the senior author, the age ranged from 31 to 89 years (mean 59 years) with a male preponderance of 5:1.

Aetiology

It is presumed to result from haemorrhage due to trauma, but there must also be abnormal ventilation and drainage of the involved sinus.[101]

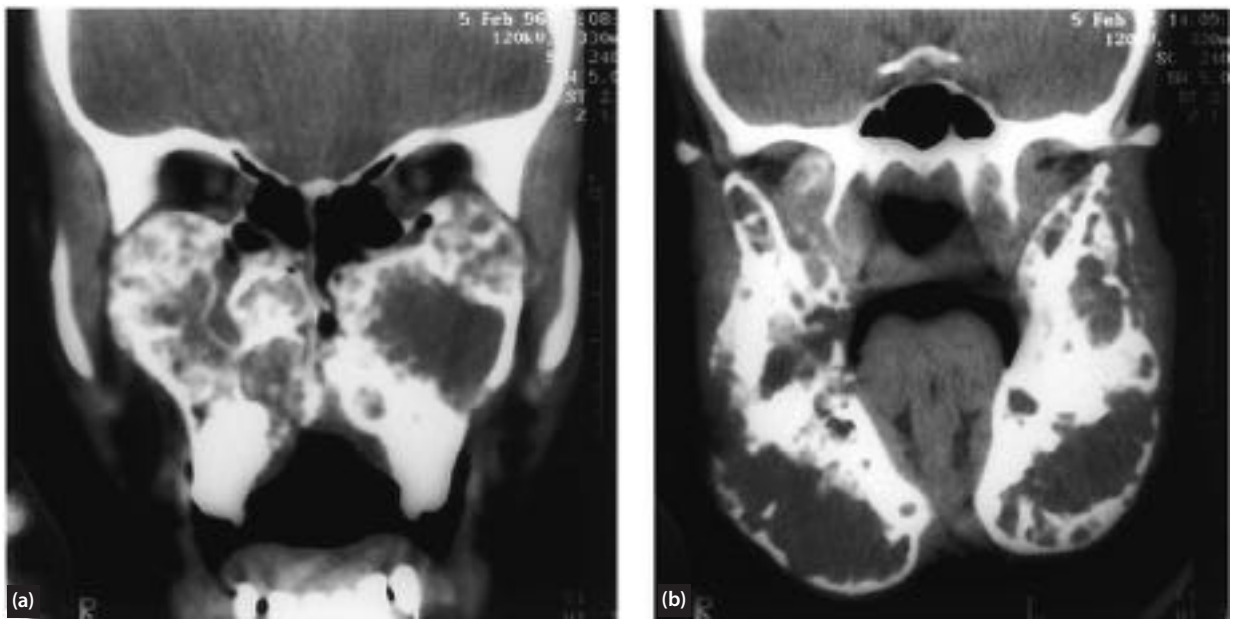


Figure 109. 7(a) and (b) Coronal CT scans of upper and lower jaw showing typical appearances of cherubism.

Clinical features

Although more common in the ear, these lesions may affect the maxillary or frontal sinuses, producing bony expansion, cosmetic deformity and displacement of adjacent structures, such as the globe. The differential diagnosis includes a mucocele and a dermoid or epidermoid cyst.

Diagnosis

Typical CT appearances are of a cyst-like expansion of the sinus that does not enhance with contrast. A very high signal is produced on all MRI sequences.

Histologically, it has a characteristic appearance of granulation tissue containing foreign body-type giant cells surrounding clefts created by the cholesterol crystals.[102]

Treatment

Surgical drainage and marsupialization is required, by whichever approach facilitates complete removal of the granulation tissue to prevent recurrence.[103, 104]

GRANULOMATOUS NEOPLASIA – EXTRANODAL NK/T-CELL LYMPHOMA

Many terms, most notably 'midline lethal granuloma', have been used to describe the condition now known to be an extranodal NK/T-cell lymphoma, nasal type (ENKTCL).[105, 106] It is included in this chapter for completeness due to this historical nomenclature. This rare non-Hodgkin's lymphoma (NHL) causes destruction of the midface and was the subject of great pathological debate. Now recognized as a distinct entity by the WHO, it is most common in south-east Asia and South America.[106]

Age and sex

NK/T cell lymphoma may occur at almost any age from the first to the ninth decade, but is most common in the fifth or sixth decades. A male preponderance has been reported.[107]

Aetiology

ENKTCL appears to be caused by the Epstein-Barr virus.[108]

Clinical features

ENKTCL usually arises in the nasal cavity and spreads to involve adjacent structures including the orbits, oral cavity, skin and paranasal sinuses. The intra-nasal granulomatous mass initially causes symptoms of obstruction, discharge and bleeding. Progressive destruction of the nasal skeleton and overlying skin occurs (**Figure 109.8**).

Diagnosis

Early diagnosis is important, as the prognosis for widespread disease is much worse. Good quality representative biopsy material from tissue beneath the slough and crust is essential. Histologically, the infiltrates are polymorphic and atypical cells may to be arranged in a necrotizing angiocentric growth pattern. The tumour consists of neoplastic T-lymphocytes with a significant inflammatory infiltrate.[109] Immunohistochemistry is usually positive for CD56, CD2 and cytoplasmic CD3.[106] Granulomas and giant cells are not present in T-cell lymphomas; thrombosis and necrosis are, however, common findings. Imaging and bone marrow biopsy are also required for staging purposes.



Figure 109.8 ENKTCL affecting the midface with **(a)** early ulceration and **(b)** significant central destruction.

Treatment

This is an aggressive tumour but tends to have a dramatic response to radiotherapy, which is therefore the recommended treatment for localized disease.[110] The role of chemotherapy has not yet been established, but may be given in addition for recurrent or disseminated disease.[111] Local recurrence rates range from 31–67%, with an overall 5-year survival rate of 38–45%.[106]

BEST CLINICAL PRACTICE

- ✓ The sensitivity and specificity of c-ANCA in GPA are 91% and 99% respectively.
- ✓ Pulsed cyclophosphamide therapy is as effective as oral treatment in achieving remission in GPA, but it is associated with a higher relapse rate.
- ✓ Rituximab is as effective as cyclophosphamide in inducing remission in GPA and may be superior in relapsing disease.
- ✓ Methotrexate and azathioprine have shown similar relapse rates compared to long-term cyclophosphamide treatment for GPA.
- ✓ Subglottic stenosis due to granulomatous disease can be satisfactorily treated with conservative laser surgery combined with endoluminal balloon dilatation and intra-lesional steroid injection.

FUTURE RESEARCH

- ➤ The aetiology of these conditions remains obscure and requires further investigation.
- ➤ It is uncertain whether all cases with limited GPA progress to systemic disease or what triggers this progression.
- ➤ The sensitivity of c-ANCA requires refinement, particularly in limited forms of GPA.
- ➤ Further multicentre controlled trials are required to inform treatment with newer, less toxic medications for these rare conditions.

KEY POINTS

- Many patients with systemic granulomatous conditions present first to ENT surgeons. It is important to maintain a low threshold of suspicion in order to make an early diagnosis and avert more severe systemic disease.
- Any patient with blood-stained discharge and crusting in the nose has a granulomatous condition until proven otherwise.
- No one test is completely reliable and a combination of clinical findings combined with diagnostic investigations is required.
- Secondary or tertiary referral may be required to diagnose and manage the condition.
- Management should be multidisciplinary.
- A range of medications is available, of which steroids combined with cytotoxic drugs are the most frequently used.
- Patients on long-term systemic steroids should be monitored for complications.
- Surgery is generally reserved for refractory cases or complications of disease.

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CHAPTER 110

ABNORMALITIES OF SMELL

Richard L. Doty and Steven M. Bromley

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: olfaction, smell, anosmia, dysosmia, phantosmia, age, odour identification, psychophysics, odour threshold, odour discrimination, presybyosmia, head trauma, olfactory epithelium, olfactory bulb and UPSIT.

INTRODUCTION

The ability to detect environmental chemicals is a primary function of the nose. A proper functioning sense of smell allows a person to discriminate between thousands of largely organic, low-molecular mass, volatile compounds and provides information regarding: (1) the safety of a substance or environment (e.g., spoiled food, leaking natural gas); (2) the aesthetic properties of everyday objects (e.g., rose, dirty laundry); and (3) elements of basic communication (e.g., mother/infant interactions). When combined with gustatory and somatosensory stimuli, the sense of smell determines the flavours of foods and beverages, and aids the process of digestion by triggering normal gastrointestinal secretions. Moreover, the olfactory system contributes significantly to a person's quality of life. Among 750 patients presenting to our centre with largely olfactory problems, more than 68% experienced altered quality of life, 46% described changes in appetite or body weight, and 56% reported influences in daily living or psychological well-being.[1] Loss of smell can result in significant psychological disruption and even generate feelings of physical and social vulnerability and victimization.[2] The importance of smell is also emphasized by the consequences of its loss in those who depend on it for their livelihood (e.g., cooks, homemakers, firefighters, plumbers, wine merchants, chemical plant workers, etc.). Loss of smell can also adversely affect nutrition, especially in the elderly and, importantly, has been associated with longevity. In a recent longitudinal study of over a thousand non-demented older persons, mortality risk was nearly two and a half times higher in those with low than with high odour identification test scores after adjusting for sex, age, education and other variables.[3]

Although otorhinolaryngologists are often the first physicians that patients with smell complaints visit, some patients find themselves making repeated appointments to multiple physicians until their olfactory problem is adequately addressed. Unfortunately, olfactory health is generally disregarded by physicians. This is beside the fact the abnormalities of smell are ubiquitous. There are at least 2.7 million (1.4%) adults in the United States with olfactory dysfunction; presumably similar numbers exist world-wide.[4] Also, most patients who complain of decreased 'taste' function actually have an unrecognized impairment of smell.[1] Diminished 'taste' is typically due to loss of flavour sensations derived from retronasal stimulation of the olfactory receptors, rather than impairment of taste-mediated sensations, *per se*.[3] Importantly, a patient's lack of olfactory function can be an early sign of a number of serious disease states, including nasopharyngeal carcinoma, Alzheimer's disease, Parkinson's disease, frontal meningiomas, multiple sclerosis, and sinus infections.[5, 6] While some patients initially present to their physicians with a frank complaint of smell impairment, others can be completely unaware of their dysfunction, making routine clinical assessments of olfaction imperative.

The necessity of the physician to properly evaluate for abnormalities of smell function is also supported in the medicolegal arena, with claims of accidental and iatrogenic smell disturbance often resulting in substantial financial awards. Routine clinical quantitative measurement of smell function can now be easily performed in the office setting, allowing a physician to:

- validate and characterize a patient's olfactory complaint
- identify patients who might be malingering
- quantify and document known presurgical smell impairment
- longitudinally, follow the course of smell function in the midst of a therapeutic intervention or during recovery from previous loss.

This chapter summarizes important aspects of olfactory anatomy and physiology, describes the common olfactory disorders encountered in clinical practice, and provides current practical techniques for the evaluation and management of smell disturbance.

ANATOMY AND PHYSIOLOGY

The nose: Structure in relation to smell

The human nose contains two independent nasal passages that are dynamic conduits that subserve both respiration and olfaction. The nasal cavities not only warm and humidify inspired air, but they help to eliminate most airborne pathogens and environmental pollutants – a number of which can be toxic to the olfactory system.[7] The olfactory neuroepithelium exists within a small region of nasal mucosa (said to be ~2 cm^2) in the upper recesses of the nasal chambers lining the cribriform plate and sectors of the superior turbinate, middle turbinate, and septum (**Figure 110.1**).[8] The olfactory cleft, an opening of approximately 1 mm wide that sits 7 cm deep to the nostril, harbours the majority of the olfactory neuroepithelium which is difficult to observe even by modern endoscopic techniques.[9] While most of the air stream coming into the nose is shunted through the passages around the inferior and medial turbinates and along the septal wall, only 10–15% of the air reaches the olfactory neuroepithelium.[10] Thus, minor changes in nasal architecture and airflow can result in substantial air-flow blockage to olfactory regions without much impairment in nasal respiratory ability.[7,11] For example, relatively small polyps located in the superior meatus can deflect incoming air currents away from the olfactory cleft, resulting in smell impairment.[11] On the other hand, too patent an airway, as seen with excessive turbinate removal, can improperly shunt air away from the olfactory cleft, resulting in at least some deterioration in olfactory acuity.[12] It is important to remember that while chronic rhinosinusitis can lead to swelling of the mucosa and a mechanical conductive block, there is evidence for local inflammatory toxicity to the olfactory neuroepithelium that may not be alleviated with surgical intervention.[13] A significant amount of retronasal airflow from the nasopharynx occurs during swallowing and deglutition. This retronasal route is vital to the production of flavour from swallowed foods – adding *smell* to both *taste* and *touch*.



Figure 110.1 CT scan of paranasal sinuses and associated nasal structures. The * is within the right maxillary sinus, below the right eye. The inferior portion of the middle turbinate is indicated by the white arrowhead and the inferior turbinate by the circle. Note the attachment of the middle turbinate to the cribriform above. A short fat white arrow is in the left anterior ethmoid sinus and points to the anterior ethmoidal neurovascular bundle as it emerges from the left orbit and courses along the roof of the ethmoid. The central small open arrow is located in the anterior cranial fossa directly above the bony crista galli. The long thin arrow situated with the olfactory cleft points to the cribriform plate. The five-pointed star in the right olfactory fossa is adjacent to the vertical lamella of the cribriform plate. From: Lanza DC, Clerico DM. Anatomy of the human nasal passages. In: Doty RL (ed) Handbook of olfaction and gestation. New York: Marcel Dekker, 1995, p. 60. Copyright © 1995 by Marcel Dekker, Inc.

The human nasal passage is intermittently affected, at least in some individuals, by the 'nasal cycle'. This cycle, an autonomic ultradian rhythm of periodic alternating side-to-side nasal turbinate engorgement and disengorgement, is said to occur in 80% of the normal population with a cycle frequency ranging from 40 minutes to 4 hours.[7] The nasal cycle itself, which is less frequent in the very young and the very old, does not appear to affect overall olfactory sensitivity in the normal nose; however, intermittent engorgement in the context of a pre-existing structural distortion can result in a noticeable, albeit transient, blockage of a nasal passage (e.g., when turbinate adhesions are present).

Four neural systems within the human nose

Most land mammals have four major specialized neural systems within the left and right sides of the nose:

- The main olfactory system (Cranial Nerve I or CN I).
- The accessory olfactory system (i.e., the vomeronasal system).

- The trigeminal somatosensory system (CN V)
- The nervus terminalis or terminal nerve (CN 0).[14, 15]

While CN I mediates common odour sensations (e.g., vanilla, rose, chocolate), CN V mediates both chemical and non-chemical stimuli in the form of somatosensory sensations (e.g., irritation, burning, cooling, tickling, touch). CN V is also responsible for inducing reflexive responses, such as secretions of mucus and halting of inhalation, that help to prevent or minimize chemically-induced or thermally-induced damage to the linings of the nose and lungs. The vomeronasal system is non-functional in humans; while a rudimentary vomeronasal tube is present on each side of the septum with an opening into the human nose, it has no centrally-projecting nerve and humans do not possess an accessory olfactory bulb, the target of such a nerve. CN 0 was discovered after the other cranial nerves had been named, and consists of a loose plexus of ganglionated nerves that, in most mammals, is in close proximity to the vomeronasal organ and nerve. Its neurons are immunoreactive to the peptide hormone gonadotropin-releasing hormone (GnRH), implying a yet-to-be characterized association with endocrine processes. It has been suggested by some that CN 0 may be a vestige of an ancient nerve whose function was lost or superseded by other parts of the nervous system, although this argument is weak, given that it is so well conserved among a wide range of vertebrates, including humans.

Olfactory neuroepithelium and neural transduction

Before neural transduction can begin, odourants must (a) enter the nose during either active (e.g. sniffing) or passive (e.g., diffusion) processes, (b) pass through the olfactory cleft, and (c) move from the air phase into the largely aqueous phase of the olfactory mucus. During mastication, odourants from the oral cavity actively move into the nasal cavity via the nasal pharynx (retronasal direction). Mucus is important in that it ensures a moist and protective environment for the olfactory neuroepithelium, and aids in dispersing odourants to the olfactory receptors. From the mucus, odourous chemicals either diffuse or are transported by specialized proteins (termed odourant binding proteins) to the receptors.

The olfactory neuroepithelium has an ultrastructure of variable uniformity and, contrary to many textbooks, cannot be discerned reliably from the surrounding respiratory epithelium by the naked eye. It is a pseudostratified columnar epithelium, supported by a highly vascularized lamina propria. Throughout life, islands of respiratory-like epithelial metaplasia appear within the epithelium, presumably as a result of cumulative viral, bacterial, and other insults.[14] In the adult, at least six distinct classes of cells – defined morphologically, biochemically, and functionally – can be identified within the neuroepithelium (**Figure 110.2**).

- The *bipolar sensory receptor neuron* is derived embryologically from the olfactory placode, is of CNS origin, and extends odourant receptor-containing cilia into the mucus.
- The *supporting* or *sustentacular cell* insulates the bipolar receptor cells from one another, regulates mucus production, transports molecules across the epithelium, and detoxifies and degrades odourants.
- The *duct cell of Bowman's glands* secretes most of the mucus within the olfactory receptor region.
- The poorly understood *microvillar cell* is located at the surface of the epithelium and, like the supporting cell, sends tufts of microvilli into the nasal mucus.
- The *horizontal (dark) basal cells*, one of two main classes of stem cells within the basement membrane of the epithelium.
- The *globose (light) basal cells*, a multipotent basal cell that can give rise to neurons and non-neuronal cells, including the horizontal basal cells.[14]

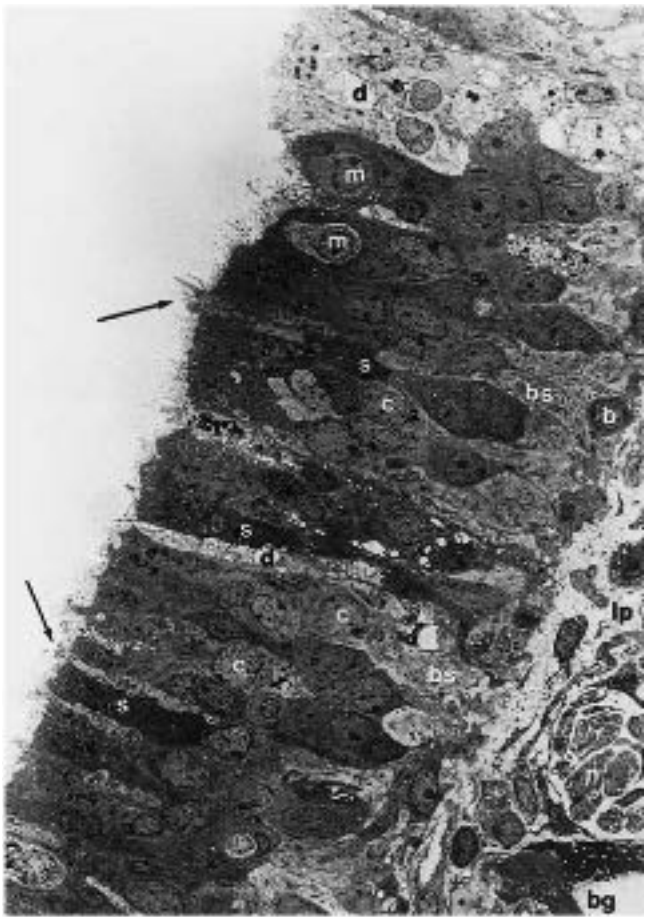


Figure 110.2 Low-power electron micrograph (× 670) of a longitudinal section through a biopsy specimen of human olfactory mucosa taken from the nasal septum. Four cell types are indicated: ciliated olfactory receptors (c), microvillar cells (m), supporting cells (s) and basal cells (b). The arrows point to ciliated olfactory knobs of the bipolar receptor cells. d = degenerating cells; bs = base of the supporting cells; lp = lamina propria; n = nerve bundle; bg = Bowman's gland. Photo courtesy of David T. Moran.

The number of olfactory receptor cells exceeds that of any other sensory system except vision; collectively, the surface area of the cilia is quite large – exceeding 20 cm^2 in the human.[15] Seven domain transmembrane olfactory receptors, which reflect the expression of the largest known vertebrate gene family (on the order of 1000 genes or pseudogenes, accounting for ~1% of all expressed genes), are found on the 10–30 cilia that project into the nasal mucus from each of these cells.[16] Approximately 6 million receptor cell axons ultimately coalesce into 30–50 fascicles, termed the olfactory fila, which traverse the cribriform plate and pia matter to synapse with second-order neurons within the glomeruli of the olfactory bulb. The olfactory receptor neurons primarily use the neurotransmitter glutamate to excite OB neurons, while dopamine appears to be a necessary modulator of olfactory nerve input.[17] The process of actually transforming the chemical energy of receptor binding into a neural signal – signal transduction – requires a complex cascade of events, some of which involves activation of G proteins (e.g., that of an olfactory-specific subtype, G_{olf}) and various second-messenger enzymes.[18, 19]

It is important to recognize that the olfactory nerve cells, as well as the proximal extraneural spaces, can serve as conduits for the movement of viruses and exogenous agents from the nasal cavity into the brain. This was recognized many years ago as a major route of polio viruses into the brain, leading to programmes to cauterize the olfactory epithelium of school children with zinc sulphate in Toronto and other major cities to avert contracting polio during epidemics. This 'olfactory vector' route has been proposed as a potential explanation for both the olfactory loss and the aetiology of some forms of common neurodegenerative diseases, such as Alzheimer's disease and idiopathic Parkinson's disease,[20] although evidence for this hypothesis in these cases remains largely circumstantial.

The olfactory bulb and central projections

The olfactory bulbs are complex structures located on the ventral surface of the frontal lobes directly over the cribriform plate. The first synapse of the incoming bipolar olfactory receptor cell neurons occurs within spherical structures making up a distinct layer of the bulb – the glomeruli. A given receptor projects to only one glomerulus, and any given glomerulus appears to receive most of its input from a restricted region of the epithelium. The main afferent second-order neurons are termed mitral and tufted cells. A considerable amount of convergence of information occurs at the level of the glomeruli. The mitral and tufted cells, in turn, send collaterals that synapse within the periglomerular and external plexiform layers, resulting in 'reverberating' circuits in which negative and positive feedback occur. The apical dendrites of the mitral and tufted cells are influenced by interneurons and centrifugal fibres, most of which are GABAergic or dopaminergic.[21]

It is generally believed that the olfactory system is unique among sensory systems in that information from the sensory receptors is sent directly, and primarily ipsilaterally, into cortical regions without synapsing in the thalamus. However, some cortical projections from primary to secondary (i.e. orbitofrontal) cortex do ultimately relay through the thalamus, and there are some contralateral projections via the anterior commissure. The latter arise largely from pyramidal cells of the anterior olfactory nucleus (AON; a structure whose cells are primarily in the rostral olfactory peduncle). Higher order brain regions in addition to the AON that are targeted by the mitral and tufted cells of the bulb include (from rostral to caudal):

- The piriform cortex.
- The olfactory tubercle.
- The entorhinal area.
- The amygdaloid cortex (a region contiguous with the underlying amygdala).
- The corticomedial nuclear group of the amygdala.

There is a rich supply of centrifugal fibre projections from sectors of the olfactory cortex and other central structures to the olfactory bulb which modify and control olfactory input.[21, 22] Structures involved in centrifugal activity include the AON, piriform cortex, lateral entorhinal cortex, regions of the amygdala, raphe nuclei, locus ceruleus, and regions of the hypothalamus.[22] Third-order projections occur, in a reciprocal fashion, to numerous regions, including the mediodorsal nucleus of the thalamus, the posterior and medial hypothalamus, the hippocampus, and the orbitofrontal cortex, the latter of which also receives second-order projections. Areas of the cortex that result in smell perception when stimulated include the pre-piriform and intermediate piriform cortices. Lesions of the olfactory system anterior to the olfactory trigone (including the neuroepithelium, fila, bulb, and tract) can result in total lack of smell on the affected side. However, lesions within olfactory structures more posterior to the olfactory trigone do not typically cause complete loss.[22, 23]

OLFACTORY DISORDER CLASSIFICATION

Olfactory disorders are classified according to standard schemata. It is important to differentiate between a patient's chemosensory complaint and the findings of objective testing, which are not always in congruence. *Anosmia* refers to an inability to detect qualitative olfactory sensations (i.e., absence of smell function); *Partial anosmia* defines an ability to perceive some, but not all, odours; *Hyposmia* or *microsmia* refers to decreased sensitivity to odours; *Hyperosmia* reflects increased sensitivity to common odours; *Dysosmia* (sometimes termed cacosmia or parosmia) is distorted or perverted smell perception

to odour stimulation; *Phantosmia* is a dysosmic sensation perceived in the absence of an odour stimulus (a.k.a. olfactory hallucination); and *Olfactory agnosia* refers to an inability to recognize an odour sensation, even though olfactory processing, language, and general intellectual functions are essentially intact, as in some stroke patients. Other less commonly used terms include *Heterosmia* – a condition where all odours smell the same, *Presbyosmia* – a decline in smell sense with age, and *Osmophobia* – a dislike or fear of certain smells. Presbyosmia is less specific than the other terms noted above (e.g., it does not distinguish between anosmia and hyposmia) and is laden, by definition, with the notion that it is age *per se* that is causing the age-related deficit. Olfactory dysfunction can be either bilateral or unilateral (sometimes termed binasal or uninasal), and bilateral testing usually reflects the better functioning of the two sides of the nose.

CLINICAL EVALUATION OF SMELL FUNCTION

History

Proper assessment of a patient's smell function requires:

- A detailed clinical history
- Objective quantitative olfactory testing
- A thorough physical examination emphasizing the head and neck with appropriate brain and rhinosinus imaging.

It is important to recognize that patients frequently confuse 'taste problems' with true smell loss, and that many deny any olfactory disturbance until formal testing proves otherwise. Several focused questions can help establish the nature of the olfactory disturbance. Was olfactory functioning previously normal? Does the patient have a problem with smell, taste, or both? What is the timing of onset, duration of impairment, and pattern of occurrence? *Sudden olfactory loss* can be consistent with possible head trauma, ischaemia, infection, or a psychiatric condition. *Gradual loss* may indicate a progressive and obstructive lesion in or around the nasosinus region, particularly if the loss is unilateral. *Intermittent loss* may suggest an inflammatory process in association with nasal and sinus disease. Is the problem seasonal, suggesting an allergic seasonal rhinitis? Is there a history of precipitating antecedent events, such as head trauma, viral upper respiratory infections, chemical or toxin exposures, and nasosinus surgeries? Does the patient have any nasal discharge that is mucous-appearing (e.g., allergy), purulent (e.g., infection), or clear (CSF rhinorrhea after trauma)? Does the patient use drugs of abuse, such as intra-nasal cocaine, ethanol, or tobacco? Each of these substances has been associated with some form of olfactory impairment; for example, chronic alcoholism can result in significant impairment in smell discrimination[24] and cigarette smoking results in a loss of olfactory ability that is proportional to the cumulative smoking dose.[25] Cessation of smoking can result in improvement in olfactory function over time.

It is essential to determine all medications used by the patient since many reportedly cause smell and taste disturbance. For example, smell or taste loss or disturbances are reported in the Physicians' Desk Reference (PDR) as a potential side effect of hundreds of medications.[26] Does the patient have comorbidities that can contribute to smell impairment, such as renal failure, liver disease, hypothyroidism, diabetes, or dementia? Delayed puberty in association with anosmia (with or without midline craniofacial abnormalities, deafness, and renal anomalies) suggests the possibility of Kallmann's syndrome or some variant thereof. Is there a recent history of epistaxis, discharge (clear, purulent or bloody), facial numbness or weakness, nasal obstruction, allergies, headache or irritation (i.e., signs that may have localizing value)? A positive family history suggests a genetic aetiology. A history of headache which can suggest sinusitis, migraine, or intra-cranial tumour should be sought. Are smells present without an obvious stimulus? A simple partial seizure, or aura, may not be obvious and other signs of ictal activity should be explored (e.g. limb shaking, difficulties with speech, unresponsiveness, automatisms, loss of consciousness, and déjà vu). Given the strong relationship of Alzheimer's disease and idiopathic Parkinson's disease to smell impairment, one should also look for memory- and parkinsonism-related complaints in older patients. A physician should also be aware of pending litigation and the possibility of malingering since olfactory loss is a compensatable injury. Malingering is readily detected in most patients by forced-choice olfactory testing. Malingerers frequently perform more poorly than expected on the basis of chance on such tests.[27]

Physical examination and evaluation

Patients complaining of smell disturbance typically require a general assessment of the head and neck and more detailed otolaryngological and neurological examinations. Are there any signs of trauma such as healing wounds, scarring or distorted nasal or skull architecture? Inspection of the nasal passages can begin with a simple nasal forceps examination to view the peripheral nasal cavity for signs of polyps, congestion, deviation of septum, or inflammation. However, this method is limited, and often nasal endoscopy, employing both flexible and rigid scopes, is needed to ensure thorough assessment of the olfactory meatal area. A deviated septum, *per se*, does not imply a smell disturbance since the olfactory cleft can remain patent; however, the additional presence of polyps, masses, adhesions of the turbinates to the septum may adequately obstruct airflow. Rarely, foreign bodies can be present, particularly in the context of a psychiatric disturbance. Nasal mucus membranes must be examined for colour, surface texture, swelling, inflammation, exudate, erosion, ulceration, epithelial metaplasia, and atrophy.

The presence of mucopus above the eustachian tube orifice suggests posterior ethmoid and/or sphenoid sinus disease. However, mucopus below the eustachian tube implies involvement of the osteomeatal complex. A pale mucous membrane suggests allergy, usually as a result of oedema within the lamina propria. Atrophy of the lamina propria is suggested by unusual spaciousness, dryness and crusting, as is seen in atrophic rhinitis. Exposures to environmental or industrial pollutants can result in metaplasia within the epithelium, in addition to swelling, inflammation, exudates, erosion, and ulceration.

The neurological evaluation should focus on cranial nerve function, with particular attention to the optic nerve (CN II), trigeminal nerve (CN V), and the facial nerve (CN VII). Visual acuity, visual field, and optic disc examinations aid in the detection of possible intra-cranial mass lesions resulting in increased intra-cranial pressure (papilloedema) and optic atrophy, especially when considering Foster Kennedy syndrome (described below). General sensation over the face should be done (e.g., cotton, pin-prick, temperature). The nasal tickle, performed by using cotton to tickle the inside of one nostril, is also useful since an asymmetric withdrawal response suggests impairment of trigeminal fibres within the nose. The face should be symmetrical and full strength, with intact taste on the anterior two-thirds of the tongue bilaterally. Signs of frontal lobe injury and memory impairment may also aide in the diagnosis.

Biopsy of the olfactory epithelium is occasionally helpful. However, the interpretation of such biopsies is complicated by sampling issues and the fact that metaplasia of respiratory-like epithelium occurs throughout the olfactory epithelia in persons with no olfactory problems. Some laboratory tests, such as blood serum tests, may also be helpful in evaluating for underlying medical conditions suggested by history and physical examinations, such as infection, nutritional deficiencies (e.g. B6, B12), allergy, diabetes mellitus, and thyroid, liver, and kidney disease.[3] Contrary to many textbooks, there is no proven efficacy of zinc or vitamin A treatments in cases where frank deficiencies are lacking.

Quantitative olfactory testing

Several standardized and practical psychophysical tests have been developed over the last several years, including a number of brief self-administered tests ranging from the 3-item Pocket Smell Test™ to the 40-item University of Pennsylvania Smell Identification Test or UPSIT.[28] The UPSIT is commercially known as the Smell Identification Test™ and is the most widely used olfactory test, having been administered to more than one million patients worldwide (**Figure 110.3**).[29] The UPSIT can be self-administered in 10 to 15 minutes by most patients in the waiting room, and scored in less than one minute by non-medical personnel. Available in more than 30 different languages, this test consists of four booklets containing 10 microencapsulated ('scratch and sniff') odourants apiece. Test results are in terms of a percentile score of a patient's performance relative to age- and sex-matched controls, and olfactory function can be classified on an absolute basis into one of six categories: normosmia, mild microsmia, moderate microsmia, severe microsmia, anosmia, and probable malingering. Since chance performance is 10 out of 40, very low UPSIT scores reflect avoidance, and hence recognition, of the correct answer, allowing for determination of malingering. The reliability of this test is very high (test-retest $r = 0.94$).

Although most olfactory problems are bilateral, and bilateral testing reflects the better functioning side of the nose, in some instances, unilateral testing is warranted.[23] To accurately assess olfaction unilaterally, the naris contralateral to the tested side should be occluded without distorting the patent nasal valve region. Such occlusion not only prevents air from entering the olfactory region from the naris (orthonasal stimulation), but prevents active movement of odour-laden air into the occluded side from the rear of the nasopharynx (retronasal stimulation). An easy way of doing this is to seal the contralateral naris using a piece of Microfoam™ tape (3M Corporation, Minneapolis, MN) cut to fit the naris borders. The patient is instructed to sniff the stimulus normally and to exhale through the mouth.



Figure 110.3 The four booklets of the 40-odorant University of Pennsylvania Smell Identification Test (UPSIT; commercially known as the Smell Identification Test™). Each page contains a microencapsulated odorant that is released by means of a pencil tip. This test, which has been administered to ~ 400,000 patients since its development, is the most widely used olfactory test in the world, with English, French, German, and Spanish versions available. The UPSIT is considered to be the "eye chart for the nose." Photo courtesy of Sensonics, Inc., Haddon Hts., NJ 08035 USA. Copyright © 2000 by Sensonics International.

While, in most cases, olfactory dysfunction can be adequately characterized by the UPSIT, some physicians employ, alone or in combination with the UPSIT, a smell threshold test. A commonly employed test employs phenyl ethyl alcohol as the odourant and establishes the threshold employing a staircase procedure.[30] Thresholds determined using this procedure are similar in principle to audiometric thresholds using the von Bekesy procedure. Like the UPSIT, threshold testing can be done either bilaterally or unilaterally.

The recording of olfactory event-related potentials (OERPs) is available in some specialized medical centres as an additional means of assessing the integrity of the olfactory system. Using brain electroencephalography (EEG), the test consists of discerning synchronized brain activity recorded from overall EEG activity following brief presentations of odourants. Unfortunately, OERP testing requires complex, specialized and expensive equipment capable of delivering well-delineated 'square wave' odourant pulses into the nose within the background of continuously flowing warmed and humidified air. Although OERPs can be useful in some cases in detecting malingering, and are generally sensitive to alterations in olfactory function due to a wide range of causes, unlike their visual and auditory counterparts, they are *unable* to discern where in the pathway the anomaly exists that is causing the problem.

Imaging studies

There are multiple ways of medically imaging patients with smell disturbance. Plain radiographs are rarely useful due to an inability to capture details of the osteomeatal complex. Computed tomography (CT), on the other hand, has proven to be the most useful and cost-effective technique to assess sinonasal tract inflammatory disorders, and is superior to magnetic resonance imaging (MRI) in the evaluation of the bony structures (e.g. ethmoid, cribriform plate, olfactory cleft). In particular, coronal CT scans are useful in evaluating paranasal anatomy. MRI is better to evaluate soft tissue, and is the technique of choice to image the olfactory bulbs, tracts, and cortical parenchyma. Positron emission tomography (PET), single-proton emission computed tomography (SPECT), and functional MRI (fMRI) presently have limited usefulness outside of research institutions.

CAUSES OF SMELL DISTURBANCE

There are a number of known aetiologies, many non-mutually exclusive, for olfactory disturbance (Table 110.1). The majority of cases of presumably permanent chronic anosmia or hyposmia are due to prior upper respiratory infections, head trauma, and nasal and paranasal sinus disease – most causes reflecting permanent damage to the olfactory neuroepithelium.[1] **[Level 1 evidence]** Despite extensive evaluations, a substantial proportion remains idiopathic.

TABLE 110.1 Reported agents, diseases, drugs, interventions and other aetiologic categories associated in the medical or toxicologic literature with olfactory dysfunction. Note that categories are not mutually exclusive

Air Pollutants & Industrial Dusts	
Acetone	Formaldehyde
Acids (e.g. sulfuric)	Grain
Ashes	Hydrazine
Benzene	Hydrogen selenide
Benzol	Hydrogen sulphide
Butyl acetate	Iron carboxyl
Cadmium	Lead
Carbon disulphide	Nickel
Cement	Nitrous gases
Chalk	Paint solvents
Chlorine	Paper
Chromium	Pepper
Coke/coal	Peppermint oil
Cotton	Phosphorus oxychloride
Cresol	Potash
Ethyl acetate	Silicone dioxide
Ethyl & methyl acrylate	Spices
Flour	Trichloroethylene
Drugs	
Adrenal steroids (chronic use)	Propylthiouracil
Amino acids (excess)	Thiouracil
Cysteine	Antivirals
Histidine	Cardiovascular/hypertensives
Analgesics	Gastric medications
Antipyrine	Cimetidine
Anaesthetics, local	Hyperlipoproteinaemia medications
Cocaine HCl	Artovastatin Calcium (Lipitor)
Procaine HCl	Cholestyramine
Tetracaine HCl	Clofibrate
Anticancer agents (e.g., methotrexate)	Intra-nasal saline solutions with:
Antihistamines (e.g., Chlorpheniramine malate)	Acetylcholine
	Acetyl, b-methylcholine
Antimicrobials	Menthol
Griseofulvin	Strychnine
Lincomycin	Zinc sulfate
Macrolides	Local Vasoconstrictors
Neomycin	Opiates
Pencillins	Codeine
Streptomycin	Hydromophone HCl
Tetracyclines	Morphine
Tyrothricin	Psychopharmaceuticals (e.g., LSD, psilocybin)
Antirheumatics	Sympathomimetics
Mercury/gold salts	Amphetamine sulphate
D-Penicillamine	Fenbutrazate HCl
Antithyroids	Phenmetrazine theoclate
Methimazole	
Endocrine/Metabolic	
Addison's disease	Hypothyroidism
Congenital adreanl hyperplasia	Kallmann's syndrome
Cushing's syndrome	Pregnancy
Diabetes mellitus	Panhypopituitarism
Froelich's syndrome	Pseudohypoparathyroidism
Gigantism	Sjögren's syndrome
Hypergonadotropic hypogonadism	Turner's syndrome

(Continued)

TABLE 110.1 ***(Continued)*** Reported agents, diseases, drugs, interventions and other aetiologic categories associated in the medical or toxicologic literature with olfactory dysfunction. Note that categories are not mutually exclusive

Infections – Viral/Bacterial	
Acquired immunodeficiency syndrome (AIDS)	Fungal
Acute viral rhinitis	Influenza
Bacterial rhinosinusitis	Rickettsial
Bronchiectasis	Microfilarial
Lesions of the nose/Airway blockage	
Adenoid hypertrophy	Nasal Polyposis
Allergic rhinitis	Rhinitis medicamentosa
Perennial	Structural abnormality
Seasonal	Deviated septum
Atrophic rhinitis	Weakness of alae nasi
Chronic inflammatory rhinitis	Vasomotor rhinitis
Hypertrophic rhinitis	
Medical Interventions	
Adrenalectomy	Influenza vaccination
Anaesthesia	Laryngectomy
Anterior craniotomy	Oophorectomy
Arteriography	Paranasal sinus exenteration
Chemotherapy	Radiation therapy
Frontal lobe resection	Rhinoplasty
Gastrectomy	Temporal lobe resection
Haemodialysis	Thyroidectomy
Hypophysectomy	
Neoplasms – Intra-cranial	
Frontal lobe gliomas and other tumours	Paraoptic chiasma tumours
Midline cranial tumours	Aneurysms
Parasagital meningiomas	Craniopharyngioma
Tumours of the corpus callosum	Pituitary tumours (esp. adenomas)
Olfactory groove/cribriform plate meningiomas	Suprasellar cholesteatoma
	Suprasellar meningioma
Osteomas	Temporal lobe tumours
Neoplasms – Intra-nasal	
Neuro-olfactory tumours	Leukemic infiltration
Esthesioepithelioma	Nasopharyngeal tumours with extension
Esthesioneuroblastoma	Neurofibroma
Esthesioneurocytoma	Paranasal tumours with extension
Esthesioneuroepithelioma	Schwannoma
Other benign or malignant nasal tumours	
Adenocarcinoma	
Neoplasms – Extranasal and Extracranial	
Breast	Lung
Gastrointestinal tract	Ovary
Laryngeal	Testicular
Neurologic	
Amyotrophic Lateral Sclerosis	Familial dysautonomia
Alzheimer's disease	Guam ALS/PD/Dementia
Cerebral abscess (esp. frontal or ethmoidal regions)	Head trauma
	Huntington's disease
Down syndrome	Hydrocephalus

(Continued)

TABLE 110.1 ***(Continued)*** Reported agents, diseases, drugs, interventions and other aetiologic categories associated in the medical or toxicologic literature with olfactory dysfunction. Note that categories are not mutually exclusive

Neurologic	
Korsakoff's psychosis	Syringomyelia
Migraine	Temporal lobe epilepsy
Meningitis	Hamartomas
Multiple sclerosis	Mesial temporal sclerosis
Myesthenia gravis	Scars/previous infarcts
Paget's disease	Vascular insufficiency/anoxia
Parkinson's disease	Small multiple cerebrovascular accidents
Refsum's syndrome	
Restless Leg Syndrome	Subclavian steal syndrome
Syphilis	Transient ischemic attacks
Nutritional/metabolic	
Abetalipoproteinemia	Trace metal deficiencies
Chronic alcoholism	Copper
Chronic renal failure	Zinc
Cirrhosis of liver	Whipple's disease
Gout	Vitamin deficiency
Protein calorie malnutrition	Vitamin A
Total parenteral nutrition w/o adequate replacement	Vitamin B6
	Vitamin B12
Pulminary	
Chronic obstructive pulminary disease	
Psychiatric	
Anorexia nervosa (severe stage)	Malingering
	Olfactory reference syndrome
Attention deficit disorder	Schizophrenia
Depressive disorders	Schizotypy
Hysteria	Seasonal affective disorder

In general, loss of olfactory function can be subdivided into two classes: (a) *conductive or transport impairments* from obstruction of the nasal passages (e.g., chronic nasal inflammation, polyposis, etc.); and (b) *sensorineural impairment* from damage to the olfactory neuroepithelium, central tracts, and connections (e.g., viruses, airborne toxins, tumours, seizures, etc.). In some circumstances, it is difficult to classify an olfactory disorder into one of these classes, since blockage of airflow to the receptors and damage to the receptors or other elements of the olfactory neuroepithelium can be simultaneously involved. Chronic rhinosinusitis, for example, can produce damage to the olfactory membrane in addition to blocking airflow, and altered membrane function can, over time, lead to degeneration within the olfactory bulb, a central structure. Although we are currently able to treat many causes of olfactory disturbance due to conductive factors or inflammation of the olfactory epithelium, most olfactory disorders due to sensorineural factors remain untreatable.

In most cases, hyperosmia reflects a patient's heightened response to an odour, rather than an increased ability to smell, *per se*. This problem has been reported in some conditions associated with a change in hormone

balance, such as in pregnancy and Addison's disease (adrenal-cortical insufficiency), as well as head trauma, migraine, drug withdrawal, epilepsy (intericatal period), multiple-chemical sensitivity, and psychosis. While hyperosmia is relatively rare, dysosmia is more common. Usually dysosmia reflects dynamic alterations of degeneration or regeneration within the olfactory neuroepithelium over time, and it is not uncommon for patients who eventually develop anosmia to report having experienced weeks of dysosmia preceding the experience of anosmia. Dysosmia implies an olfactory system that is intact at least to some degree, as total smell loss does not typically accompany most cases of dysosmia.[1] Severely debilitating, long-lasting, and intractable chronic dysosmias have been treated by surgical ablation of regions of the olfactory neuroepithelium, or by surgical removal of a diseased olfactory bulb or bulbs.[31] Olfactory hallucinations or phantosmias can occur from a problem anywhere along the olfactory neural pathways, from the nose to the cortex. Sometimes they are associated with ictal epileptiform activity (e.g., simple partial seizures), nasal sinus disease (e.g., infection), and head trauma. If someone believes a smell is present (hallucination) and persistently gives this smell personal reference to outside events, despite contradicting evidence, this patient may suffer from *olfactory reference syndrome* – a depression-related disorder. In some cases, there may be a pathological correlate in the form of right hemispheric lesions.[32] Olfactory agnosia is an extremely rare phenomenon, although it appears to be less commonly investigated than visual and auditory agnosia. It is associated with lesions of the right inferior temporal lobe and often linked to prosopagnosia (agnosia for familiar faces).

The more common disorders or entities associated with olfactory impairment are discussed in more detail below, beginning with the more frequent ones.

Upper respiratory infection

Upper respiratory viruses, such as those associated with the common cold and influenza, are considered the most common aetiology of permanent olfactory loss in man. Other infectious causes that have been reported include hepatitis, herpes simplex encephalitis, and variant Creutzfeldt-Jacob disease. It is not clear what predisposes someone to viral-induced smell dysfunction or the precise mechanisms behind it. Often the smell-affecting respiratory illness is described as being more severe than usual. In a study of olfactory biopsies of 4 patients with anosmia and 11 patients with hyposmia due to a viral illness, Jafek and colleagues[33] noted that patients with anosmia had markedly reduced numbers of receptors and those receptors were abnormal compared to those patients with hyposmia. Given the ability of the olfactory neuron to regenerate, spontaneous recovery of some smell function is theoretically possible over a prolonged period; however, complete recovery is less likely the longer the patient has the loss and is likely inversely related to the degree of dysfunction. In general, it is necessary to exclude other aetiologies prior to making a diagnosis of post-viral anosmia. HIV-infected patients are said to show an early impairment in odour thresholds and a later decline in odour identification and discrimination function which appears to parallel a general reduction in cognitive abilities.[34]

Head trauma

Head trauma often results in smell loss, particularly where rapid acceleration/deceleration of the brain occurs (i.e. coup/contrecoup injury) (**Figure 110.4**). Blunt trauma to the occiput has been found to produce greater olfactory loss than trauma to the front of the head.[35] Following head trauma, the loss of smell is usually, but not always immediate, although it may take a while for the patient to recognize the presence of the dysfunction. In some cases, months can pass before the smell loss is apparent to the patient. Common mechanisms include disruption from shearing forces of the olfactory fila through the sinonasal tract, and direct contusion and ischaemia to the olfactory bulb and frontal and temporal poles. Fracturing of the cribriform plate is not a prerequisite for smell loss. The prevalence of olfactory loss following head trauma is around 15% and, on average, is proportional to the severity of the injury.[35,36] As would be expected, such prevalence is much higher in patients referred to specialized smell and taste centres for evaluation and treatment. For example, among 268 patients evaluated at our centre who had experienced head trauma, 66.8% had anosmia, 20.5% hyposmia, and 13% had normal smell function. MRI images may reveal damage to the olfactory bulbs, tracts and areas of the temporal and frontal lobes.[36] Animal research shows that intra-cranial haemorrhage and ischaemia can lead to degeneration of the olfactory epithelium without transection of the olfactory nerves.[37] **[Level 1 evidence]** Iatrogenic trauma, such as surgery, can cause smell impairment and has been seen with such procedures as sinus surgery and laryngectomy.[38]

Nasal and sinus disease

While the olfactory impairment that follows a viral syndrome or head trauma can be classified as *sensorineural*, the dysfunction that results from nasal and sinus disease is usually considered *conductive* – in other words, there is impaired air flow to the olfactory receptors. Theoretically, any inflammatory or obstructive process in the nose can result in a disturbance of smell function, with common examples being allergic rhinitis, rhinosinusitis, nasal polyposis, intra-nasal tumours and previous nasal surgery. In the evaluation of 240 patients with allergic rhinitis, Rydzewski and colleagues found that 21.4% of patients had smell impairment and there was a significant correlation between olfactory thresholds and levels of eosinophils in the blood and nasal discharge.[39] Treatments in the form of surgery (e.g., excision of polyps) or medication (e.g., administration of topical or systemic steroids) may improve olfactory function in some cases; however, complete return is not typical. Thus, while chronic rhinosinusitis

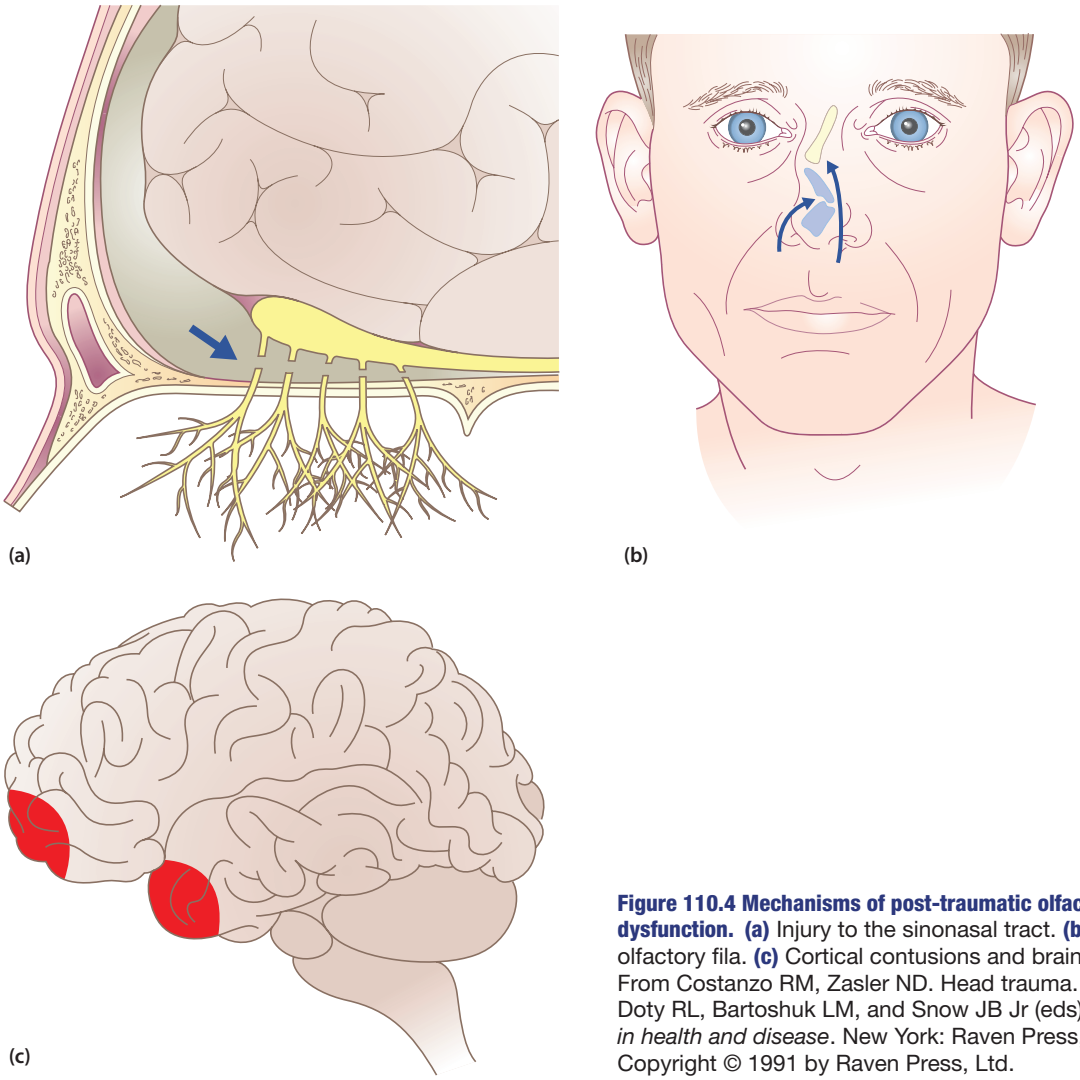


Figure 110.4 Mechanisms of post-traumatic olfactory dysfunction. (a) Injury to the sinonasal tract. **(b)** Tearing of the olfactory fila. **(c)** Cortical contusions and brain hemorrhage. From Costanzo RM, Zasler ND. Head trauma. In: Getchell TV, Doty RL, Bartoshuk LM, and Snow JB Jr (eds) *Smell and taste in health and disease*. New York: Raven Press, 1991, p. 713. Copyright © 1991 by Raven Press, Ltd.

can result in nasal airflow blockage, there is also a component of direct toxicity to olfactory neurons and impaired ciliary motility resulting in abnormal clearance of mucus. These combined factors make any one treatment modality limited. In one study, it was found that systemic steroids can temporarily reverse conductive olfactory impairment in 83% of patients while topical steroids helped in only 25% of patients – making systemic steroids a useful diagnostic tool.[40] The severity of histopathological changes within the olfactory mucosa of patients with chronic rhinosinusitis is positively related to the magnitude of olfactory loss, as measured by the UPSIT.[41] Biopsies from the neuroepithelial region of patients with nasal disease are less likely to yield olfactory-related tissue than biopsies from controls.[42] Anosmic rhinosinusitis patients generally exhibit a more pathological epithelium (e.g., disordered arrangement of cells and increased islands of respiratory epithelium) when compared to non-anosmic patients with rhinosinusitis.[43] Excessive dryness of the nasal mucosa – as seen in atrophic rhinitis, Sjögren's syndrome, and repeated nasal surgery – can cause olfactory dysfunction, since a moist receptor environment aids chemoreception and transduction.

Tumours and mass lesions

A number of tumours in and around the olfactory bulbs or tracts can cause olfactory disturbance. Examples include olfactory groove meningiomas, frontal lobe gliomas, and suprasellar ridge meningiomas arising from the dura of the cribriform plate. Due to the olfactory nerve's close location to the roof and medial wall of the orbit, as well as the optic nerves and tracts, structural lesions affecting smell may also affect vision. Also, olfactory tumours may extend into the frontal lobes resulting in symptoms of dementia and possibly the release of primitive reflexes (e.g., grasping, snout, and glabellar). Mass lesions need not be in the olfactory tracts to cause smell impairment. Ishimaru and colleagues[44] identified two patients with hyposmia from tumours to the right frontal lobe; the hyposmia reversed with craniotomy and tumour resection. Mass lesions around the olfactory region can result in a *Foster-Kennedy syndrome*, which consists of: (a) ipsilateral anosmia, (b) ipsilateral optic atrophy, and (c) contralateral papilledema secondary to raised intra-cranial pressure.[45] *Pseudo* Foster-Kennedy syndrome has been reported in patients with increased intra-cranial pressure who had previous

unilateral optic atrophy.[46] Similarly, tumours in central regions of olfactory processing (e.g., mesial temporal lobe) can also potentially affect smell. Headache often accompanies a complaint of smell loss when the aetiology is a mass lesion. Lymphoma has been known to infiltrate into olfactory areas and cause dysfunction. Similarly, granulomatous diseases – such as syphilis, sarcoidosis, SLE, and Wegener's granulomatosis – often result in anosmia. In patients suspected of having a neoplasm, neuroimaging is essential.

Neurodegenerative diseases

Olfactory deficits have been described in a number of neurological disorders (**Table 110.1**). Importantly, olfactory dysfunction may be the first clinical sign of Alzheimer's disease (AD) and idiopathic Parkinson's disease (PD). Smell testing is useful in identifying persons who have PD, as well as those who either have, or are at risk for having, AD. In PD, bilateral olfactory deficits occur before the onset of most of the classical neurological signs and symptoms and are unrelated to disease stage, use of anti-parkinson medications, duration of the illness, and severity of the symptoms, such as tremor, rigidity, bradykinesia or gait disturbance.[5, 6] Measurement of smell function can be useful to distinguish PD among the other disorders that share many non-olfactory symptoms and signs, such as progressive supranuclear palsy, multiple-system atrophy, parkinsonism induced by the proneurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and essential tremor.[6, 20] In a male patient suspected of PD, based on history and physical who is less than 60 years of age, an UPSIT score of 31 carries a 91% sensitivity and 88% specificity of correctly diagnosing patient suspected of having PD.[6] In a woman suspected of PD, who is less than 60 years old, an UPSIT score of 33 carries a 79% sensitivity and 85% specificity.[6]

With regard to AD, Graves and colleagues[47] found that olfactory dysfunction in the presence of one or more APOE-e4 alleles was associated with a very high risk of subsequent cognitive decline, and smell testing identified persons who came to exhibit later cognitive decline better than did a global cognitive test. Devanand and colleagues[48] found that patients with mild cognitive impairment scored lower on the UPSIT than did the controls, and that patients with low UPSIT scores (<34) were more likely to develop AD than the other patients. When low UPSIT scores were accompanied by a lack of awareness of olfactory deficits on the part of the patients, they found that this predicted the time to development of AD. UPSIT scores from 30 to 35 showed moderate to strong sensitivity and specificity for diagnosis of AD at follow-up. In later life, individuals with Down syndrome show similar clinical and pathological changes to AD patients and have lower performance on a modified UPSIT compared to controls matched on mental age. However, it is not clear whether this is due to AD-related pathology, *per se*, as Down syndrome children as young as 12 years old exhibit smell dysfunction.[49] **[Level 1 evidence]**

The olfactory loss associated with multiple sclerosis is directly proportional to the number of MS-related demyelinating lesions in central brain regions associated with olfactory processing (e.g., inferior middle temporal lobe and periorbital frontal cortex).[50] **[Level 1 evidence]** Olfactory function actually increases and decreases as the plaque numbers increase and decrease.[51] Therefore, knowledge of a patient's UPSIT score largely predicts the plaque load in the olfaction-related regions. **[Level 1 evidence]**

Schizophrenia is associated with significant deficits in olfactory threshold sensitivity and odour identification.[52] **[Level 1 evidence]** The fact that there is an inverse correlation with UPSIT scores and disease progression suggests that there may be progressive neurodegenerative changes within olfactory-related pathways and smell testing can be used as a marker of disease progression.[52]

Epilepsy and migraine

Olfactory auras, also described as hallucinations, are rare but frequently associated with seizures and headaches. Olfactory auras consist of sudden unexplained sensations of smell that are usually unpleasant (although not always) and are rarely isolated events.[53] In epilepsy, mesial temporal lobe structures involved in the usual processing of odour information – such as the amygdala and hippocampus – have been implicated as the generators of ictal olfactory sensations (simple or complex partial seizures) that often evolve into secondarily generalized seizures.[54] Common aetiologies include mesial temporal sclerosis and tumours.[54] Some cases of epilepsy have been associated with hyperosmia during the inter-ictal period, although most patients with long-standing epilepsy and intractable seizure activity, such as candidates for temporal lobe resection, are hyposmic.[53] The effect of migraine on smell function is less understood. The concept of certain smells provoking or exacerbating a migranous headache – osmophobia – may exist similar to that of photophobia or phonophobia.

Other causes and considerations

Less than 5% of patients who present to a specialized centre for smell and taste disorders have a chemosensory disturbance that can be directly attributed to an exposure of a toxic compound.[1] There are numerous chemical agents that have been reported to affect smell function, including acrylates, cadmium, benzene, formaldehyde, solvents and nickel dust, among others (**Table 110.1**).[55] Tobacco smoking results in diminished olfactory ability as a function of cumulative smoking dose, and importantly, smoking cessation can result in improvement in olfactory function over time.[25] Medications are also a common cause of smell disturbance and should be considered early, especially in the context of a new drug therapy (**Table 110.1**).[56]

Several endocrine disorders evidence disorders of smell. For example, Kallmann's syndrome, or hypogonadotropic hypogonadism, is an X-linked or autosomal recessive neuronal migrational disorder associated with anosmia

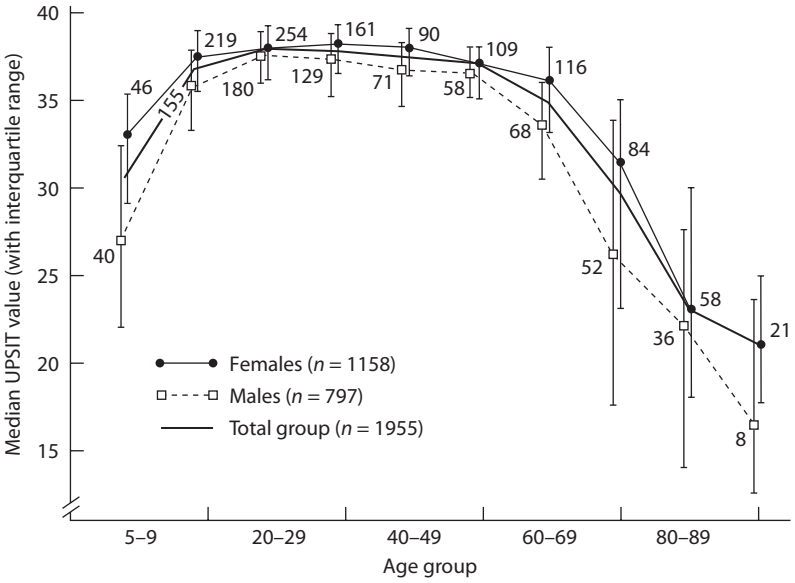


Figure 110.5 Scores on the University of Pennsylvania Smell Identification Test (UPSIT) as a function of age and gender in a large heterogeneous group of subjects. Numbers by data points indicate sample sizes. From Doty RL, Shaman P, Applebaum SL, et al. Smell identification ability: changes with age. *Science* 1984; **226**: 1441–3. Copyright © 1984 by the American Association for the Advancement of Science.

(aplasia of the olfactory bulb) and hypogonadism (pituitary involvement). **[Level 1 evidence]** Similarly, patients with septo-optic dysplasia (de Morsier's syndrome) can have hyposmia, visual symptoms, and precocious puberty.

Age-related deficits in smell function are well documented and decreased smell function is present in most elderly patients, including ones who are healthy and taking no medications (**Figure 110.5**).[57] Under the age of 65 years, approximately 1% of the population has major difficulty smelling. Between 65 and 80 years, this increases remarkably, with about half of the population exhibiting at least some decrement in the ability to smell. Over the age of 80, this figure rises to nearly 75%.[54] Despite the association with age, the complaint of smell loss should never be attributed simply to age, as often an accumulation of damage over the years is the culprit and a single event, such as a bad cold, can be the precipitating factor. In general, the age-related changes in smell function are reflected not only in damage to the olfactory receptors but related decreases in number of glomeruli within the olfactory bulb.[58] Whether age-related factors increase the susceptibility of the epithelium to damage from exogenous agents is not clear. What is clear, however, is that smell loss in older persons adversely affects the quality of life. Chemosensory loss has been implicated as a cause – particularly in the elderly – of malnutrition, weight loss, and worsening of a medical illness.

TREATMENT OF SMELL DISORDERS

The most effective treatments available are those for *conductive* anosmia, where there is an obstruction of airflow through the nose to the olfactory neuroepithelium. As noted above, the typical causes of mechanical obstruction include nasal sinus disease, including inflammation, and intra-nasal neoplasms. After diagnosis is confirmed using tools such as nasal endoscopy and CT scanning of the sinuses, the next appropriate course of action may include topical or systemic steroids. Conductive and sensorineural olfactory loss are often distinguishable using a brief course of systemic steroid therapy since patients with conductive impairment often respond positively to the treatment, although long-term systemic steroid therapy is not advised. Topical nasal steroids are often ineffectual in returning smell function because the steroid fails to reach the affected regions in the upper nasal passages. Increased efficacy presumably occurs when the nasal drops or spray are administered in the head-down Moffett's position.[40] Proper allergy management is essential and may require the use of an antihistamine. When a bacterial infection is suspected (e.g., infectious sinusitis), a course of antibiotics should be used. Surgery should be considered for: (1) very large and medically-refractory polyps; or (2) situations where a malignant neoplasm is suspected. Importantly, pre- and post-intervention olfactory testing should be performed to establish intervention efficacy, as well as to screen for subsequent slow relapse that is characteristic of most conductive disorders. In cases where rheumatological granulomatous disease is suspected, such as Wegener's granulomatosis or sarcoidosis, further immunomodulation using agents such as cyclophosphamide or methotrexate may be necessary.

Sensorineural impairment of olfaction is typically more difficult to manage, and the prognosis for patients suffering from long-standing total loss due to upper respiratory illness or head trauma is poor. The majority of patients who recover smell function subsequent to trauma do so within 12 weeks of injury.[35] Patients who quit smoking typically have dose-related improvement in olfactory function and flavour sensation over time.[25] Central lesions, such as CNS tumours that impinge on olfactory bulbs and tracts can often be resected with significant improvement in olfactory function. When epilepsy or migraine is suspected, a course of anti-epileptic or anti-migraine medications might prove beneficial. Medically-refractory epilepsy resulting in olfactory disturbance can be successfully treated with surgery. For

example, Chitanondh[59] reported successful treatment of 7 patients with seizure disorder, olfactory hallucinations, and psychiatric problems by stereotactic amygdalotomy, concluding 'stereotactic amygdalotomy has a dramatic effect on olfactory seizures, auras, and hallucinations. It is a safe surgical procedure and can be done without neurological deficit'. In patients with multiple sclerosis, immunomodulatory therapies, including interferon beta and occasional steroids, is the mainstay of treatment. When depression or psychosis is suspected, a course of an anti-depressant and appropriate psychiatric referral may be necessary.

Medications that induce distortions of olfaction can often be discontinued and replaced with other types of medications or modes of therapy. In addition to direct effects on the olfactory system, the side-effects of many medications is to detrimentally dry the nasal mucosa (e.g., anti-cholinergics). Dopaminergic and cholinergic therapies do not improve the olfactory dysfunction seen in Parkinson's disease, and there is no evidence that neuroleptics alter the olfactory loss of patients with schizophrenia. Despite the fact there are advocates for zinc and vitamin therapies, there continues to be no strongly compelling evidence that these therapies work except in cases where frank zinc or vitamin deficiencies exist.

In patients with complete anosmia, supportive measures are necessary to protect them from further harm; thus

- Smoke and carbon monoxide detectors need to be installed and properly working
- When possible, electric appliances should be used instead of gas appliances
- Expiration dates for food products should be scrutinized and old food items checked by someone with normal smell function or discarded
- A balanced diet – particularly in the elderly – must be kept to prevent weight loss and malnutrition. Adding flavour enhancers (e.g., monosodium glutamate, food colouring, chicken or beef stock) to foods can also help with their appeal.

A physician needs to be cognizant of medicolegal ramifications in his or her evaluation and management. In cases of personal injury malingering is not uncommon, and may be distinguished from true anosmia by the pseudo-disappearance of trigeminal function or unusually low UPSIT test scores (i.e., those below chance responding), suggesting active avoidance of the correct answer. When queried on a standardized questionnaire, malingerers were found to minimize factors that might be otherwise associated with their chemosensory complaint. For example, relative to non-malingerers, malingerers reported significantly fewer allergies, dental problems, cigarettes smoked, surgical operations, nasal sinus problems, and use of medications. They also reported significantly more putative symptom-related psychological duress, interference with daily activities, weight loss, decreased appetite, and taste loss. Litigation involvement was found to be higher in malingerers than non-malingerers. Age, sex, education, and length of written symptom descriptions did not differentiate malingerers from non-malingerers.[27]

PROGNOSIS

Spontaneous recovery of function appears to vary depending on the severity of the disturbance. Thus, for patients whose odour identification ability is less severe (e.g., UPSIT scores above 25), prognosis for complete recovery is much better than for those with complete anosmia. In one study, for example, odour identification tests were administered to 542 patients complaining of smell dysfunction on two occasions separated from one another by 3 months to 24 years.[60] The percentage of anosmic and microsmic patients exhibiting statistically significant change in function, as defined by 4 UPSIT points, was 56.72% and 42.86%, respectively. However, only 11.31% of anosmic and 23.31% of microsmic patients regained normal age-related function over time. Age, severity of initial olfactory loss, and the duration of dysfunction at the first test occasion were significant predictors of the amount of change. Interestingly, aetiology, sex, time between the two test administrations, and initial smoking behaviour were not strong predictors.

Given such factors, an important part of management for many patients is to use quantitative olfactory testing and establish the true degree of olfactory loss so that some

FUTURE RESEARCH

In general, the medical community needs to become better educated regarding the importance of the chemical senses for the well-being and everyday function of human beings, and to realize that accurate assessment of these senses is critical for (a) establishing the validity of a patient's complaint, (b) distinguishing between complaints of taste and olfactory dysfunction, and (c) monitoring the efficacy of treatment regimens. The basis of the olfactory loss in the earliest stages of a number of neurodegenerative disorders, including Alzheimer's disease and idiopathic Parkinson's disease, needs elucidation, as gene therapy and other therapeutic modes may be of future value in reversing not only the olfactory dysfunction, but other elements of these diseases. There is dire need to establish the mechanisms involved in olfactory cell degeneration and regeneration, as well as in the production of appositional bone growth in the region of the foramina of the cribriform plate, which may be an age-related process. A greater understanding of these and related phenomena, such as the nature of inflammation associated with rhinosinusitis, may ultimately lead to topical or systemic treatments that can mitigate smell dysfunction secondary to damage to the olfactory receptor cells or closure of the foramina of the cribriform plate.

estimate or prognosis can be given. Importantly, age- and sex-related normative data allows one to put into perspective a patient's overall problem. For example, many older patients find it rather therapeutic to know that, while his or her smell function is not what it used to be, it still falls above the average of his or her peer group.

KEY POINTS

- The olfactory system contributes significantly to a person's quality of life.
- A patient's lack of olfactory function can be an early sign of a number of serious disease states, including nasopharyngeal carcinoma, Alzheimer's disease, Parkinson's disease, frontal meningiomas, multiple sclerosis, and sinus infections.
- Too patent an airway, as seen with excessive turbinate removal, can improperly shunt air away from the olfactory cleft, resulting in at least some decrement in olfactory acuity.
- A significant amount of retronasal airflow from the nasopharynx occurs during swallowing and deglutition. This retronasal route is vital to the production of flavour from swallowed foods – adding *smell* to both *taste* and *touch*.
- Throughout life, islands of respiratory-like epithelial metaplasia appear within the epithelium, presumably as a result of cumulative viral, bacterial, and other insults.
- The number of olfactory receptor cells exceeds that of any other sensory system except vision; collectively, the surface area of the cilia is quite large – exceeding 20 cm^2 in the human.
- The olfactory nerve cells, as well as the proximal extraneural spaces, can serve as conduits for the movement of viruses and exogenous agents from the nasal cavity into the brain.
- It is essential to determine all medications used by the patient since many reportedly cause smell and taste disturbance.
- Several standardized and practical psychophysical tests have been developed over the last several years, including a number of brief self-administered tests ranging from the 3-item Pocket Smell Test™ to the 40-item University of Pennsylvania Smell Identification Test or UPSIT.
- The majority of cases of presumably permanent chronic anosmia or hyposmia are due to prior upper respiratory infections, head trauma, and nasal and paranasal sinus disease – most causes reflecting permanent damage to the olfactory neuroepithelium.
- A number of tumours in and around the olfactory bulbs or tracts can cause olfactory disturbance.
- Olfactory deficits have been described in a number of neurological disorders. Importantly, olfactory dysfunction may be the first clinical sign of Alzheimer's disease (AD) and idiopathic Parkinson's disease (PD).
- The olfactory loss associated with multiple sclerosis is directly proportional to the number of MS-related demyelinating lesions in central brain regions associated with olfactory processing (e.g., inferior middle temporal lobe and periorbital frontal cortex).
- Schizophrenia is associated with significant deficits in olfactory threshold sensitivity and odour identification.
- Under the age of 65 years, approximately 1% of the population has major difficulty smelling. Between 65 and 80 years, this increases remarkably, with about half of the population exhibiting at least some decrement in the ability to smell. Over the age of 80, this figure rises to nearly 75%.
- *Sensorineural* impairment of olfaction is typically more difficult to manage, and the prognosis for patients suffering from long-standing total loss due to upper respiratory illness or head trauma is poor.

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CHAPTER 111

DISORDERS OF THE ORBIT

Nithin D. Adappa and James N. Palmer

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: orbital anatomy; nasolacrimal system; epiphora; endoscopic dacrocystorhinostomy; thyroid eye disease; Graves' ophthalmopathy; orbital decompression; optic nerve decompression; silent sinus syndrome; orbital pseudotumor; orbital neoplasm; and orbital tumour. The evidence in this chapter is mainly levels 3 and 4. The clinical recommendations are predominantly B and C.

INTRODUCTION

Given its intimate relationship to the paranasal sinuses, a thorough understanding of the orbit is essential for the otorhinolaryngologist. We are faced with a wide variety of orbital conditions due to the general proximity of the sinonasal cavity as well as the surgical corridor the sinuses provide (Box 111.1). The most common conditions include epiphora, thyroid eye disease, optic nerve compression, imploding maxillary sinus, pseudotumor, and orbital neoplasms.

BOX 111.1 Differential diagnosis of orbital pathology

Infectious
- Bacterial
- Fungal

Inflammatory
- Graves' orbitopathy
- Granulomatous disease
- Pseudotumor

Neoplastic
- Benign
  - Fibro-osseous
  - Neural
  - Vascular
- Malignant
  - Lymphoma
  - Epithelial
  - Non-epithelial
  - Metastatic

Traumatic

Other
- Epiphora

RELEVANT SURGICAL ANATOMY

Orbital anatomy

The orbit is a quadrilateral pyramid, with its base facing forwards, laterally and slightly inferiorly (Figure 111.1). The orbit contains the globe, extraocular muscles, nerves, vessels and other associated structures including the lacrimal apparatus. The average volume in the adult Caucasian orbit is 30 ml.[1] The orbit receives contribution from 7 distinct bones: maxillary, zygomatic, ethmoid, lacrimal, sphenoid, frontal, and palatine bones all of which make unique contributions to each orbital wall.

Medial wall

The medial wall is most relevant to otorhinolaryngologists due to the proximity of the paranasal sinuses. From an anterior to posterior direction, the boney contribution of anterior lacrimal crest originates at the frontal process of the maxilla. The lacrimal bone makes up the second one half of the lacrimal sac fossa and the posterior lacrimal crest. The lamina papyracea (arising from ethmoid bone) makes up the majority of the medial orbital wall. The paper-thin bone overlies the ethmoid sinuses.[2] The anterior and posterior ethmoid foramina are found in the superior aspect of the orbit along the fronto-ethmoidal suture line. The anterior ethmoid foramen is a useful

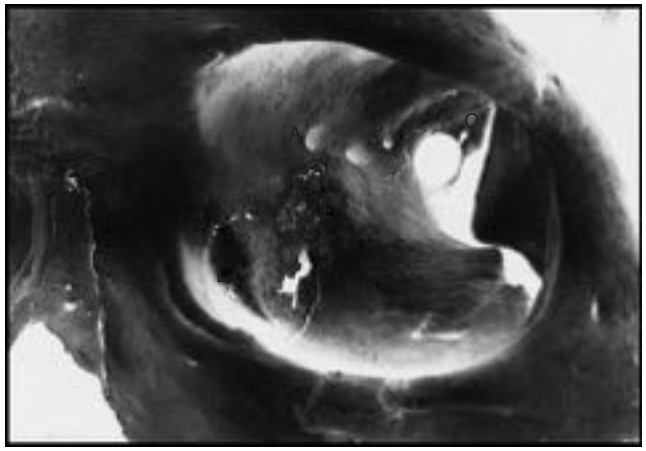


Figure 111.1 The orbit. A, anterior ethmoidal foramen, P, posterior ethmoidal foramen, O, optic canal, E lamina papyracea, M, maxilla, L, lacrimal bone.

landmark and is identified 20–25 mm posterior to the anterior lacrimal crest and the posterior ethmoid foramen is 30–35 mm posterior to the anterior lacrimal crest.[3] The thick bone of the sphenoid body forms the most posterior portion of the medial orbital wall adjoining the optic canal.

Superior wall

The roof of the orbit is formed primarily by the frontal bone.[2] The superior margin has a supraorbital notch or foramen with its respective nerves and vessels.[4] The trochlea is a connective tissue sling anchoring the tendinous portion of the superior oblique muscle to the orbital wall and the trochlear fovea, a small depression lying close to the superomedial orbital margin.[4]

Inferior wall

The floor is formed by the orbital surface of the maxilla, the zygomatic and the palatine bone. At approximately the midpoint of the orbit floor runs the infraorbital groove containing the maxillary division of the trigeminal nerve (V2) leading to the infraorbital foramen. Medial to the infraorbital nerve, the orbital floor is relatively thin and fractures more easily than the lateral aspect.[4]

Lateral wall

The zygomatic process of the frontal bone, the orbital surface of the zygoma and the greater wing of the sphenoid form the lateral wall. These bones join at the zygomaticosphenoid suture line, creating the thickest boney wall. The lateral tendons all attach to the lateral tubercle, which is found 3–4 mm posterior to the lateral orbital rim.[4]

Orbital contents

The orbit is lined by the fibrous periorbita. It is attached to bone at the orbital margin, suture lines, the trochlear fossa, fissures, the lateral tubercle, the anterior lacrimal crest, and perforating vascular foramina. Other than these locations, the periorbita is loosely attached and easily dissected. The globe and other orbital tissue structures are surrounded by orbital fat, which cushions the globe and facilitates in orbital movement. This is further aided by orbital connective tissue septae that slide over each other for smooth movement.[5]

Nasolacrimal system

The nasolacrimal drainage system consists of the superior and inferior canaliculi which feed into the common canaliculus, lacrimal sac and subsequently the nasolacrimal duct.[6] The system begins at the punctum of each eyelid where the canaliculi initially run at 90° to the lid margin for 1–2 mm before running parallel with the lid margin. After 10 mm they join to form the common canaliculus. The common canaliculus angles inferiorly and forward for 3–5 mm before entering the lacrimal sac. The nasolacrimal duct exits from the inferior portion of the lacrimal sac and continues in an inferior direction for approximately 12 mm before entering the nose 10–15 mm behind the anterior end of the inferior turbinate and 16 mm above the floor of the nasal cavity at Hasner's valve. The lacrimal bone that attaches inferiorly with the base of the inferior turbinate forms the posterior wall of the bony canal and the frontal process of the maxilla forms its anterior boundary.

The lacrimal sac is protected in the concavity of the lacrimal fossa of the medial orbital wall. The fossa is formed anteriorly by the harder frontal process of the maxillary bone and posteriorly by the softer lacrimal bone. The frontal process forms the anterior lacrimal crest and the remainder of the anterior portion of the fossa.

Epiphora

Epiphora from nasolacrimal system obstruction is either anatomic (70%) or functional (30%).[7] This includes complete blockages anywhere from the lacrimal punctum to the nasal cavity. Functional obstructions, on the other hand, are a result of either significant narrowing within the lacrimal system that delays normal lacrimal flow or a failure of the lacrimal pumping mechanism. Dacrocystorhinostomy (DCR) is performed to relieve epiphora resulting from an obstruction of the nasolacrimal system.

The majority of nasolacrimal system obstruction is unknown. Idiopathic obstruction is seen more frequently with increasing age and demonstrates a female preponderance. Less common causes include surgical trauma, facial trauma, granulomatous conditions such as Wegener's granulomatosis and sarcoidosis, malignancy, infections, and radiation exposure. It should be noted that while a significant number of patients suffer nasolacrimal injury after FESS (up to 15%), actual obstruction resulting in epiphora is very rare.[8]

ENDOSCOPIC DACROCYSTORHINOSTOMY

Indications

A DCR is indicated when there is a symptomatic distal obstruction of the nasolacrimal duct that is not relieved by probing and syringing. It is not indicated when the obstruction is in the canaliculi or puncti as the endoscopic DCR will not bypass these areas.

Pre-operative evaluation and studies

A thorough history and physical examination is essential to aid in identification of the site of obstruction. The patient should be questioned on history of radiation, neoplasm, midface trauma, systemic diseases, sinonasal disease and ocular conditions.

Syringing and probing the nasolacrimal system can aid in identification of the site of obstruction. Inability to flush through the inferior canaliculus indicates obstruction at the site of the punctum or inferior canaliculus whilst reflux of saline through the other canaliculus indicates a distal obstruction. Probing with a Bowman lacrimal probe also helps identify the level of obstruction. Nasal endoscopy is also useful to exclude anatomic abnormalities that may interfere with an endoscopic approach.

An ophthalmologist will often perform a fluorescein dye disappearance test in the office. Fluorescein is applied to the eye and after 10–15 minutes a bluelight filter is used to attempt to identify fluorescein runoff into the nose. Radiographic tests include a dacrocystogram, which can identify diverticula, stenosis, strictures, dacryoliths or a tumour. Dacryoscintigraphy uses radionucleotide. ^{99m}Tc also may be helpful when identifying for a functional obstruction when there is free flow on a syringe test along with an abnormal fluorescein dye disappearance test. Computed tomography (CT) is generally not indicated unless there is suspicion for neoplastic etiology or history of midface trauma requiring further evaluation.

Surgical procedure

Create a posteriorly based mucosal flap

The initial goal is to expose the lacrimal bone and frontal process of the maxilla. Initially a superior incision should be made horizontally 10 mm above the axilla of the middle turbinate. This incision should extend from 2–3 mm posterior to the axilla and run forwards for approximately 10 mm onto the frontal process of the maxilla. The blade should then be turned vertically and a cut made on the frontal process of the maxilla from the superior incision to just above the insertion of the inferior turbinate. Finally, a cut is made horizontally and the inferior mucosal incision made form the insertion of the uncinate to join the vertical incision.

Elevation of the mucosal flap

Elevation is best accomplished with a suction freer. It is critical to stay on the bone to avoid losing the surgical plane in the transition from the hard bone of the frontal process of the maxilla to the softer lacrimal bone (Figure 111.2).

Remove lacrimal bone

A round otologic knife can be used to flake off the lacrimal bone overlying the posterior portion of the lacrimal sac.

Removal of frontal process of the maxilla

This bone is much harder and overlies the anterior aspect of the lacrimal sac. This can be accomplished with a kerrison punch or a DCR drill bur. The sac should be exposes fully by removing all bone up to the mucosal incisions. The sac will form a prominent bulge into the nasal cavity (Figure 111.3).



Figure 111.2 Elevation of posteriorly based mucosal flap over left nasolacrimal crest.

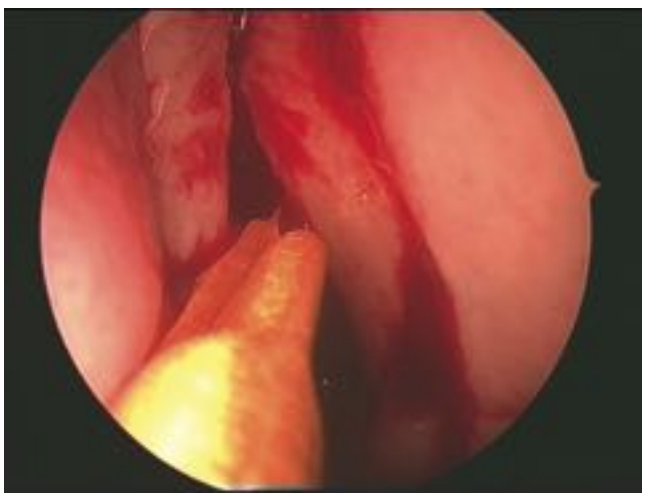


Figure 111.3 Resection of left anterior lacrimal crest with kerrison punch.

Expose the agger nasi cell

By exposing the agger nasi cell, the mucosa of the lacrimal sac will be able to lie against the mucosa of the agger cell, allowing for a wider marsupialization of the lacrimal sac.

Marsupialize the lacrimal sac

Insert a lacrimal probe through the inferior canaliculus (Figure 111.4) and tent the lacrimal sac up with the probe. Make a vertical incision with two subsequent horizontal incisions on the superior and inferior portion of the sac to create the widest possible anterior and posterior flaps. Once the sac is marsupialized, it should be lying flat on the lateral nasal wall (Figure 111.5).

Reposition the mucosal flap

Cut the mucosal flap so only a superior and inferior limb are present and reapproximate this over the bone at the bone–lacrimal sac junction at both the superior and inferior aspects of the lacrimal sac flaps.



Figure 111.4 Probing of the inferior canaliculus.

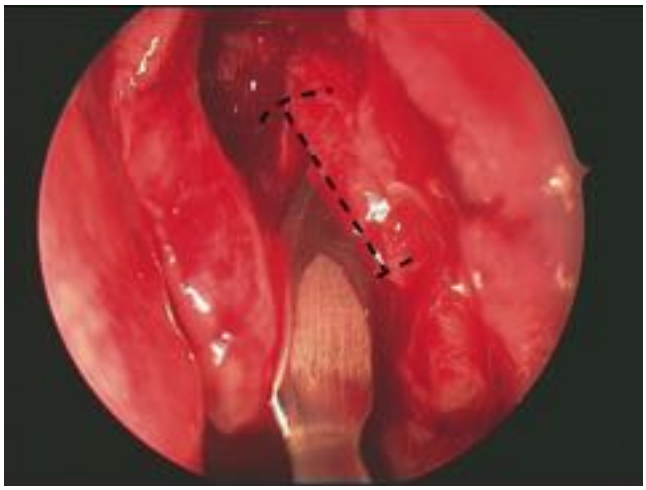


Figure 111.5 Incision of the left lacrimal sac. Then create an anterior and posterior flap, incisions should be made along the dotted lines.

Pass the Crawford silastic tubes

The lacrimal tubes are inserted into the superior and inferior punctae and passed into the nasal cavity. They can be secured by tying the tubes together. Place a small piece of gelfoam along the mucosal flaps to hold them in place.

Post-operative management

Patients are discharged on saline sprays, 7 day course of oral antibiotics, and topical antibiotic eye drops for 2 weeks. Patients are endoscopically evaluated with removal of crusting at 2 weeks. Crawford tubes are removed at 4–6 weeks and the lacrimal system is checked for patency using the fluorescein dye disappearance test.

Complications

Complications demonstrated in endoscopic DCR are similar to those reported in endoscopic sinus surgery including epistaxis, occurring in 2% of patients.[9, 10] Other possible complications of the procedure include obstruction and subsequent rhinosinusitis of the frontal or maxillary sinus, orbital penetration with damage to the extraocular muscles, cerebrospinal fluid leak and orbital haematoma.

THYROID EYE DISEASE

Introduction

Thyroid eye disease (Graves' ophthalmopathy) is an incompletely understood autoimmune disease with infiltration of T lymphocytes and macrophages into the orbital tissue as well as an increased glycosaminoglycan deposition with subsequent enlargement of orbital fat and extraocular muscles.[1, 11, 12] The increased volume in the fixed boney orbit impairs venous drainage resulting in chemosis and periorbital edema. This ultimately leads to increased retrobulbar pressure and enlargement of extraocular muscles potentially leading to loss of vision. The increased volume may result in significant proptosis and possible globe subluxation, exposure keratitis, or corneal ulceration. Approximately 50% of patients who have thyroid eye disease will develop orbital manifestations.[13]

Thyroid eye disease has two phases; an inflammatory phase and a burnt-out phase. The inflammatory phase typically lasts from 6 months to 3 years. During this phase, inflammation, fibrosis, and adipogenesis occur resulting in the changing ocular findings.[14] The burnt-out phase is defined as a period of disease where the ocular findings do not progress during a minimum of 6 months.

Conservative treatment options include eye lubrications, eyelid taping, and patching for the patients with dryness and diplopia, as well as controlling thyroid function. In the inflammatory stage, corticosteroids, immunosuppressants, orbital irradiation, and surgical decompression may also be necessary to improve symptoms and reduce optic nerve compression. Subsequently, in the burnt-out stage, lid surgery, strabismus surgery, and orbital decompression may be required.[14]

ENDOSCOPIC ORBITAL DECOMPRESSION

Indications

Indications for orbital decompression include compressive optic neuropathy, exposure keratitis, diplopia, and cosmesis. Both external and intra-nasal decompression has previously been described. Otorhinolaryngologists typically perform an endoscopic approach only or in conjunction with other approaches.

Pre-operative evaluation and studies

Given the wide variety of procedures possible with varying degrees of decompression, careful discussion with the ophthalmology team is critical for understanding the degree of decompression necessary. In general an endoscopic decompression is indicated for patients with moderate to severe thyroid eye disease. It may be performed in conjunction with an open approach for the orbital floor and lateral wall if further decompression is necessary. The procedure is generally utilized for thyroid orbitopathy but can also be used as a corridor to gain access to orbital tumours, biopsy of indeterminate orbital lesions, or palliative therapy for malignant tumours causing visual symptoms.[15]

A complete ophthalmology examination is necessary prior to the procedure. This includes evaluation of the degree of proptosis, assessment of eye movements and diplopia, measurement of visual acuity, and colour vision. Preoperative consent must include discussion of risks including permanent double vision and need for strabismus surgery.

A CT scan evaluating the orbits and sinuses is required to review relevant anatomy. Typical findings include a greater than two-fold enlargement of extraocular muscle bodies, sparing the tendinous portions. The medial and inferior rectus muscles are most commonly involved although all muscles may be enlarged (**Figure 111.6**).[16] The surgeon should identify the middle turbinate attachment, location and course of the anterior ethmoid artery, and the presence of an onodi cell as the optic nerve may course through the lateral aspect of the cell.

Surgical procedure

Perform a maxillary antrostomy, complete ethmoidectomy and sphenoidotomy

During sinus surgery, it is important to completely resect the uncinate process. In addition, we advocate resection of the middle turbinate for improved exposure and decreased risk of adhesions. During dissection, special attention should be made to identify all ethmoid cells have been removed along the lamina papyracea. The maxillary antrostomy should be as large as possible to allow for ideal exposure during decompression.

Resection of medial orbital wall bone

The orbital wall should be penetrated in a controlled fashion. Typically a j-curette or Freer elevator can be used. Care should be taken to perform this gently to avoid trauma to the periorbita. The fragments can be freed from the periorbita with the j-curette or Freer elevator and subsequently removed with Blakesley forceps. Take care not to penetrate the periorbita at this time as prolapsing fat will make surgery more difficult. All bone should be resected superiorly up to the ethmoid roof, inferiorly to the orbital floor, anteriorly to the maxillary line and posteriorly to

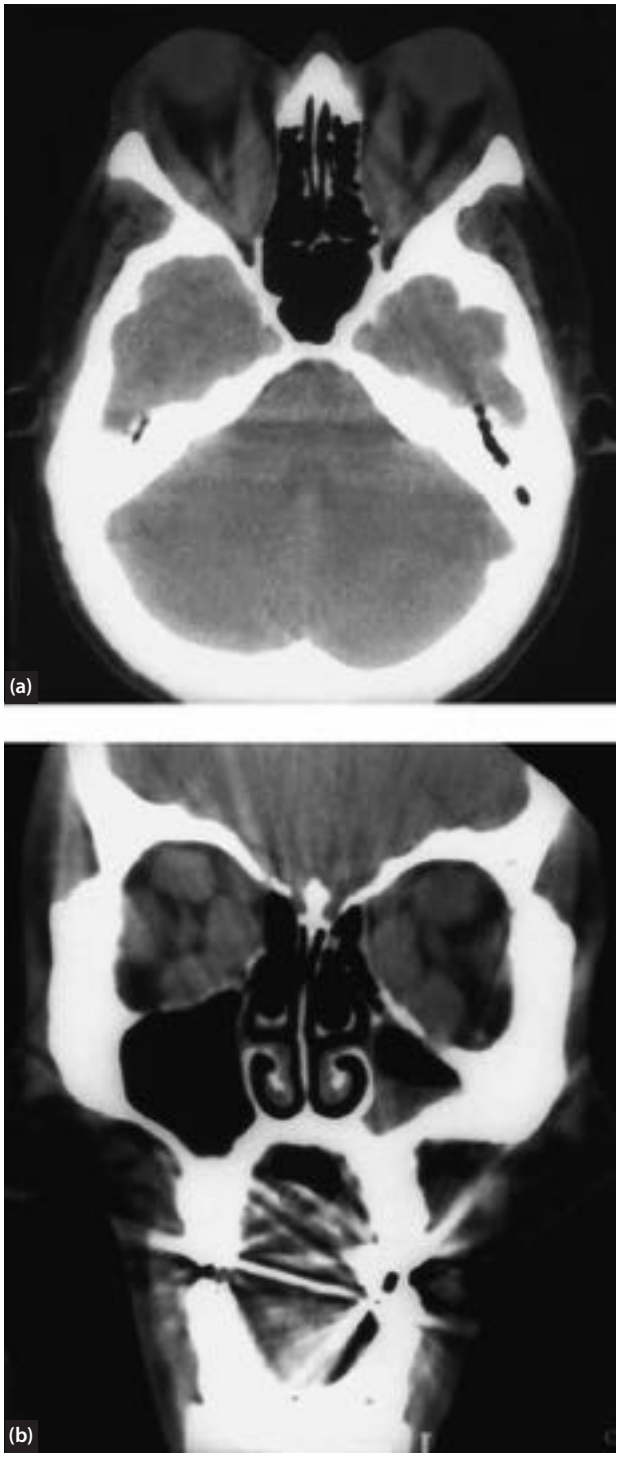


Figure 111.6 (a) Axial and **(b)** coronal CT scans in thyroid eye disease showing the classical 'Coca Cola' bottle sign of auto-decompression (axial) and compression of orbital apex due to enlarged extraocular muscles.

the face of the sphenoid sinus. Care should be taken when removing bone superiorly to avoid skull base injury that may produce either a cerebrospinal fluid leak or ethmoidal vessel injury.

Down fracture of the orbital floor

Start by elevating the periorbita off the medial orbital floor. Use a spoon curette to down fracture the medial aspect of the orbital floor. The bone of the orbital floor is significantly thicker than the medial orbital wall and requires increased force. The bone often fractures in one large piece at the infraorbital canal junction. Note that if the down fracturing is not performed bilaterally, there is an increased risk for post-operative diplopia, especially in the horizontal plane.

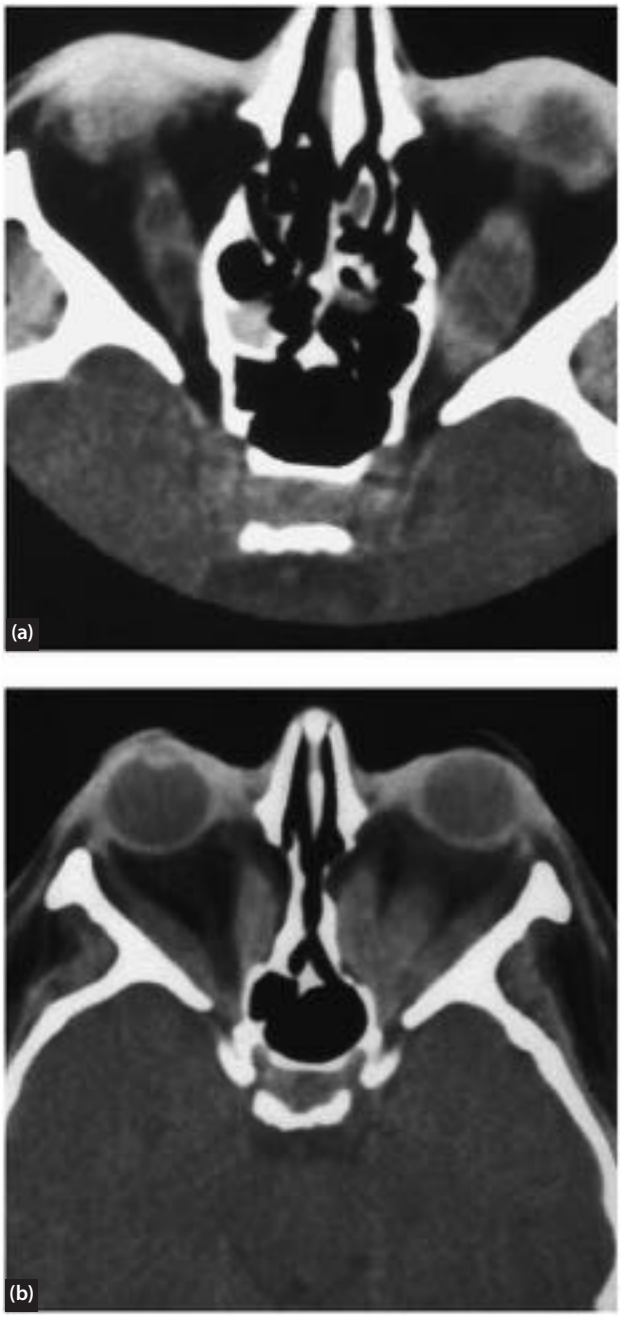


Figure 111.7 (a) Axial and **(b)** coronal CT scans of patient with thyroid eye disease before and after endoscopic decompression.

Incision of periorbita

The incision should begin at the posterior limit of the decompression and follow a posterior to anterior direction to prevent prolapsing orbital fat from obstructing visualization. A series of parallel incisions should be made in this fashion. In patients without optic neuropathy, a fascial sling can be left in place overlying the medial rectus to prevent diplopia.[17] A curved seeker can be used to gently dissect the remaining fibrous bands between fat lobules.

Prolapse of orbital fat into maxillary and ethmoid sinuses

If done completely, a significant amount of fat will prolapse in the sinuses. The eye may be balloted to confirm fat herniation and allow further prolapse.

Post-operative considerations

It is critical prior to extubation and in the immediate post-operative period to have a clear discussion with the anaesthesia team. This potentially will avoid aggressive post-extubation mask ventilation, which can result in orbital subcutaneous emphysema. Expect large amounts of post-operative swelling, oedema, and erythema. Our patients are typically observed overnight and discharged on broad-spectrum antibiotics and instructed to start nasal irrigations. Patients should avoid nose blowing for 2 weeks to prevent subcutaneous emphysema or even prolapse of the globe.

Results

Post-operative diplopia is frequently encountered with 15–63% of post-operative patients reporting new-onset or worsening diplopia.[15, 18–22] In most cases, this is temporary and resolves spontaneously over weeks to months. Strabismus surgery will be considered in 8–10 months following decompression if diplopia persists.

The average ocular recession from endoscopic decompression ranges from 3.2–5.1 mm reduction of proptosis with an inferior and medial wall decompression.[17, 19, 23] Concurrent lateral decompression provides an additional 2 mm of recession.[19] Post-operative deterioration of visual acuity is demonstrated in less than 5% of patients.[24–26]

OPTIC NERVE COMPRESSION

Optic nerve compression is a rare entity requiring decompression. The optic nerve may be decompressed for a number of indications.

Endoscopic optic nerve decompression

Traumatic optic neuropathy is the most common indication for endoscopic or open optic nerve decompression.

Unfortunately, success rates are limited for this procedure.[27–30] Traumatic optic neuropathy was initially felt to be secondary to vascular compromise from external compression resulting in injury to the optic nerve. More recent investigation has favoured the theory that manual compression results in a conduction block and focal demyelination leading to compressive optic neuropathy.[31]

Benign or malignant tumours of the skull base can occasionally compress the orbital apex. Meningiomas of the skull base, in particular, produce a hyperostotic reaction with mass effect from the soft tissue component that may directly impact the orbital apex. Benign fibro-osseous lesions or sinonasal tumours can in a similar fashion result in compression of the apex or the optic nerve itself.

Many different approaches have been described for optic nerve decompression including transorbital, transantral, extra-nasal transethmoid, intra-nasal microscopic, and craniotomy approaches. We believe the endonasal approach is superior as it offers a number of advantages over other approaches such as preservation of olfaction, quick recovery period, lack of external scars, and excellent intra-operative visualization. However, the ideal approach should be dictated by the pathology and its location.

PRE-OPERATIVE CONSIDERATIONS AND STUDIES

A thorough ophthalmologic history and physical examination should be performed. A fine cut CT scan of the sinuses and orbit should be evaluated for optic canal compression, fracture, or bone displacement and sinus anatomy for endoscopic considerations. An MRI of the orbits should also be considered for evaluation of the optic nerve and orbital contents.

PROCEDURE

Perform a complete ethmoidectomy and sphenoidotomy

Pay special attention to removing all boney partitions off the lamina papyracea. Additionally, open up the sphenoidotomy maximally, especially laterally. Identify the optic nerve, carotid artery and the opticocarotid recess (**Figure 111.8**). Image guided surgery is ideally employed here.

Fracture the lamina papyracea in posterior ethmoid region

As in orbital decompression, eggshell fracture and remove bone of the lamina in the posterior ethmoids. Again, pay special care not to penetrate the periorbita.

Drill down the bone of the optic strut

Use a diamond drill with copious irrigation to avoid thermal injury to the optic nerve. Drill along the nerve, not across it. As the bone thins, gently flake it away. The amount of decompression depends on the pathology. For cases of traumatic optic neuropathy and thyroid eye disease, the optic nerve should be decompressed for a distance of 1 cm posterior to the face of the sphenoid sinus (**Figure 111.9**).[32] Further decompression of the nerve can



Figure 111.8 Silent sinus syndrome with inferior collapse of orbital floor associated with maxillary sinus outflow obstruction.

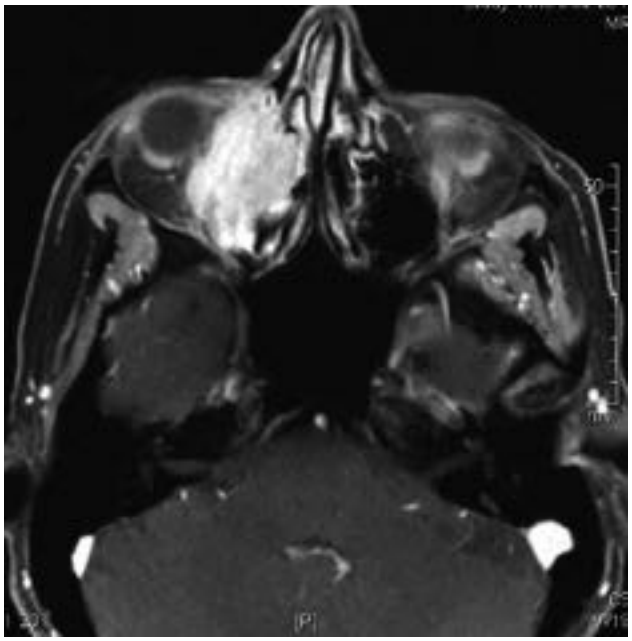


Figure 111.9 Axial T1-weighted post-contrast MRI demonstrating a large infiltrative orbital mass. It was initially reported to be an aggressive malignant neoplasm. Subsequent biopsy demonstrated orbital pseudotumor.

be created with incision of the sheath itself. If this is to be performed, the incision should be in the superomedial quadrant as the ophthalmic artery may lie in the inferiomedial quadrant of the optic nerve sheath in approximately 15% of cases.[33] The incision should be made from

a posterior to anterior direction and which includes the release of the tendinous ring of Zinn. Be prepared for a possible CSF leak which can be closed with a mucosal flap.

POST-OPERATIVE CONSIDERATIONS

Close communication with the ophthalmologic team is critical. They will aid in serial eye examination and help guide the generally required high dose oral steroids. Additionally, antibiotics and gentle saline rinses are recommended. To minimize intra-conal pressures, nasal packing is not utilized following the procedure, and the patient should be instructed on avoiding nose blowing and straining post-operatively.

Imploding maxillary sinus

Imploding maxillary sinus or silent sinus syndrome is believed to originate from obstruction of the osteomeatal complex of the paranasal sinuses leading to hypoventilation of the maxillary sinus. This enclosed cavity in certain settings is thought to undergo air resorption, thus creating a suction effect of subatmospheric pressure within the maxillary antrum.[34–36] The development of a pressure vacuum within the sinus, in turn, results in the accumulation of mucous into the antrum, subclinical inflammation and eventual collapse of the maxillary sinus through attenuation of the maxillary bony side walls. The hallmark of the disease is lack of traditional chronic sinusitis symptoms. Instead patients present with enopthalmos, occasionally with double vision as well.

Diagnosis is typically confirmed though CT imaging, demonstrating maxillary atelectasis and decreased height of the orbital floor (**Figure 111.8**). Treatment for imploding maxillary sinusitis is correcting the underlying pressure system of the maxillary sinus. Although historically this was done with a Caldwell-Luc, it is now treated with an endoscopic maxillary antrostomy. Depending on the severity of bone resorption, the patient may also require surgical intervention to restore height to the orbital floor. This can be done as a single procedure or in a staged fashion.

Orbital pseudotumor

Orbital pseudotumor, or idiopathic orbital inflammation, is a diagnosis of exclusion. The exact etiology of this condition is unclear, but it should be in the differential diagnosis of orbital pathology as it comprises 10% of orbital lesions.[37] The clinical signs include proptosis, diplopia, pain, eyelid swelling, ptosis and chemosis. Similar lesions can arise elsewhere in the head and neck including the pterygopalatine and infratemporal fossae.

Pseudotumor presents as a nonspecific orbital mass on CT and/or MRI (**Figure 111.9**).[37] Diagnosis is one of exclusion, most commonly ruling out lymphoma. Most clinicians should have a low threshold for biopsy if the clinical course is not typical of pseudotumor. Histology generally demonstrates polymorphous inflammatory infiltration of T and B cells, plasma cells, eosinophils, neutrophils and a variable degree of fibrous tissue proliferation.[38]

Treatment of orbital pseudotumor is typically medical, most commonly with oral steroids, but is also treated with radiotherapy, chemotherapy or immunosuppression for refractory cases. Surgical intervention is only considered to establish a diagnosis, or for emergent treatment of compressive symptoms as a temporizing measure.

Orbital neoplasms

Orbital neoplasms can broadly be divided into benign and malignant lesions. Otorhinolaryngologists participate as part of a multidisciplinary team in treatment. Benign neoplasms most commonly consist of fibro-osseous lesions, neural lesions, and vascular lesions, while malignant neoplasms are generally divided into epithelial, non-epithelial, lymphoma, and metastatic.

Benign neoplasm

FIBRO-OSSEOUS LESIONS

Benign fibro-osseous lesions affecting the optic nerve and orbit are similar to lesions dealt with in the paranasal sinuses. These lesions are primarily fibrous dysplasia, ossifying fibromas, and osteomas. Fibrous dysplasia is either monostotic or polyostotic fibrous dysplasia (**Figure 111.10**). Asymptomatic lesions are observed with surveillance imaging. Those resulting in orbital or optic nerve compression require surgical intervention. Conversely, ossifying fibromas are aggressive and can be locally destructive, in these cases, early resection



Figure 111.10 Axial CT scan with right-sided fibrous dysplasia with encroachment of the optic nerve.

is recommended. Finally, osteomas are benign, osseous lesions presenting with slow growth. They have an increased incidence along the frontoethmoidal suture line and accordingly may encroach on the orbit. Similar to fibrous dysplasia, if asymptomatic, these can be observed with surveillance imaging.

NEURAL

Neural-derived neoplasms of the orbit and orbital apex most commonly consist of gliomas, neurofibromas, schwannomas, and meningiomas. As with most orbital lesions, presentation is dependent on tumour pathology and position within the orbit. Neurofibromas and schwannomas tend to present more anteriorly within the orbit, and meningiomas and gliomas are often retrobulbar. Optic nerve meningiomas are of special significance as removal or even biopsy of these lesions can cause damage to the blood supply of the optic nerve resulting in visual loss. Typically optic nerve meningiomas are treated conservatively unless the patient develops visual loss.

VASCULAR

Vascular lesions include lymphangioma, orbital varices and arteriovenous malformations. Complete surgical resection for vascular lesions is often not feasible, but orbital apical decompression often may plays a role in management. Non-encapsulated lesions, or lesions that infiltrate critical orbital structures should only be decompressed if they are causing optic neuropathy.

Malignant neoplasms

EPITHELIAL

Primary epithelial tumours of the orbit are very rare. When present, they generally involve the lacrimal gland. Lacrimal gland tumours range from pleomorphic adenoma to aggressive neoplasms such as adenoid cystic and squamous cell carcinoma.[39] Open surgical resection is often the treatment of choice as endoscopic access with clear margins is often challenging.

NON-EPITHELIAL

The most common non-epithelial neoplasm is rhabdomyosarcoma. It typically presents in childhood and should be considered on the differential in any child presenting with progressive proptosis. Other sarcomas such as liposarcoma and leiomyosarcoma, although rare, can present in the orbit.

LYMPHOMA

Lymphoma typically presents as a painless enlarging mass. Surgical intervention, as with lymphoma of other areas, consists of biopsy only. Ultimate treatment depending on tumour type and stage consists of radiation therapy and/or chemotherapy.[39]

METASTATIC

Metastatic neoplasm must be considered in the differential for any orbital lesion. The most common are neuroblastoma, leukaemia, breast carcinoma, lung carcinoma, and prostate carcinoma.

CONCLUSION

Otorhinolaryngologists must have a thorough understanding of the wide variety of pathology that occurs in the orbit due to the close proximity of the paranasal sinuses. This is relevant both in terms of paranasal sinus involvement of orbital lesions as well as treatment corridors through the nose. Most of these lesions are best treated by a multidisciplinary team for optimal outcomes.

KEY POINTS

- A thorough understanding of the orbital anatomy is essential for otorhinolaryngologists given the close proximity to the paranasal sinuses.
- Optimal results in endoscopic DCR require both knowledge the site of obstruction as well as optimal surgical steps to ensure patency.
- Traumatic optic neuropathy is the most common indication for endoscopic optic nerve decompression. Unfortunately, success rates are limited for this procedure.
- There is a wide variety of orbital neoplasms and accurate diagnosis and workup are necessary to identify the correct treatment plan.
- Treatment of orbital pathology requires a close working relationship between ophthalmologists and otorhinolaryngologists.

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CHAPTER 112

DIAGNOSIS AND MANAGEMENT OF FACIAL PAIN

Rajiv K. Bhalla and Timothy J. Woolford

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SEARCH STRATEGY

A systematic search of the available literature was performed using Medline, Embase, Cochrane library and NHS Evidence. Search terms included facial pain, sinusitis, neuropathic pain, migraine, trigeminal autonomic cephalalgia, neuralgia, persistent idiopathic facial pain, referred pain, and medication- or analgesia-dependency headache, focusing primarily on diagnosis and management.

INTRODUCTION

The diagnosis of facial pain is complex, requiring a holistic approach to the patient. Individuals are often convinced or have been convinced, either by reading the internet or by their family doctor, that their facial symptoms have underlying sinus aetiology. Additionally, there may be a strong psychological component to the onset, severity, exacerbation and prolongation of symptoms. These consultations have a propensity to be difficult and are usually time-consuming. However, time invested at an initial consultation is often time well invested, particularly if patients are helped to understand the underlying mechanism of their pain if sinus pathology is not the cause. This chapter examines the presentation and subsequent management to the otolaryngologist of patients with the symptom of facial pain, and includes an extensive discussion on medical and adjuvant therapies currently used to treat diseases that are not isogenic in aetiology.

BACKGROUND

Reaching the correct diagnosis in patients with facial pain is challenging because many patients come with fixed ideas about the cause of their pain. The majority are convinced they have sinusitis, a not unreasonable view because the diagnosis has often been confirmed by their general practitioner or other specialists. A proportion of patients have already undergone unsuccessful nasal or sinus surgery. If all cases of facial pain are assumed to be sinogenic in aetiology, those with other conditions will not receive the correct medical treatment and unfortunately, many patients will continue to be subjected to inappropriate surgery.

The majority of painful stimuli from the face are transmitted to the spinal tract of the brain stem via afferents in the trigeminal nerve. Pain afferents from the VIIIth, IXth and Xth cranial nerves also relay in the spinal tract. Facial pain from deep structures tends to be a dull, poorly localized ache because the afferent nerves innervating them are unmyelinated. Facial skin is supplied by myelinated nerves that produce a sharper pain. Various neurophysiological models have been proposed to explain the nociceptive inputs causing tension headache and migraine, and suggest pathogenesis similar to that of fibromyalgia and irritable bowel syndrome, conditions that frequently coexist. Experimental studies suggest that increased excitability of the central nervous system generated by repetitive and sustained pericranial myofascial input may be partly responsible, along with widespread changes in brain function and connectivity.[1, 2] By extrapolation, facial pain is likely to be caused by central sensitization of the trigeminal nucleus by myofascial, vascular or supraspinal input, with exacerbations or provocation of pain induced by supraspinal inhibition of the trigeminal nucleus by

psychological influences.[3] To add to this, surgery, trauma and inflammation may promote nociceptive stimulation of the trigeminal caudal nucleus and initiate pain.

There are many different ways of dividing the subsections in the ensuing descriptive text. However, from the perspective of the otolaryngologist the most important differentiation, perhaps, is between facial symptoms of sinogenic aetiology and those that are not. Hence, the chapter is divided accordingly, with great emphasis on the decision to operate and perhaps more important to avoid surgery. The chapter also furnishes the reader with comprehensive differential diagnoses for the patient that presents with the symptom of facial pain. In truth, the diagnoses, aetiological hypotheses and management options have not changed greatly over the last 10 years. An individual presenting with facial pain represents an extremely common encounter in both specialist rhinology and general otolaryngology out-patient clinics. A thorough grounding in what is and what is not sinus-related, understanding from where this information arises, and starting with a broad and holistic perspective in any new or complex follow-up consultation is of paramount importance to ensure that effective interventions are implemented where indicated, and withheld when they are not.

SINOGENIC FACIAL PAIN

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[4] Unfortunately though, discriminating between *pain* caused by sinusitis and *pain* caused by other pathologies is, perhaps, conceptually too difficult for the large majority of our patients and why, perhaps, we often hear ourselves asking questions such as, 'Describe the pain to me' and, 'What do you mean by pain?'

Pain in sinusitis that is not acute or complicated is probably a misnomer. Enough evidence now exists to suggest that sinusitis per se does not cause *pain* but instead, may be associated with other more vague symptoms. Patients may complain of pressure, fullness or throbbing in the distribution of the paranasal sinuses or at the vertex of the head. Symptoms may be bilateral or unilateral, particularly if individual sinuses are affected by pathology. Examples include pathology such as pyomucocele of the maxillary antrum, or fibrous dysplasia or osteoma of the ethmoid sinus causing secondary obstruction of drainage pathways, or mucocele of the sphenoid sinus (**Figures 112.1** and **112.2**). Exacerbation of these symptoms on bending forwards is not, however, diagnostic or suggestive of rhinosinusitis.[5] Furthermore, symptoms may be acute, recurrent acute (moderated by repeated short courses of antibiotics) or chronic. Associated with these symptoms may be nasal congestion and/or hyposmia, although these symptoms may be difficult for the patient to recall, particularly if the underlying diagnosis is of recurrent acute sinusitis. Clarification often requires some gentle probing. More readily detectable are the endoscopic signs of polyposis and obstruction of outflow drainage pathways, and mucosal disease (**Figure 112.3**). However, these signs are frequently subtle and may, therefore, be missed. It is also highly relevant that over 80% of patients with endoscopic evidence of purulent secretions have no headache or facial pain.[6] Moreover, if surgery is performed in cases where facial pain is the dominant symptom without firm clinical evidence of rhinosinusitis, not surprisingly, a significant proportion of these patients continue to complain of facial pain post-operatively.[7]

- Management of rhinosinusitis is initially medical, with imaging reserved for failed maximal medical therapy, complications of rhinosinusitis, or suspicion of malignancy.
- Surgery should be targeted, as good correlation between symptoms, signs and radiological findings.

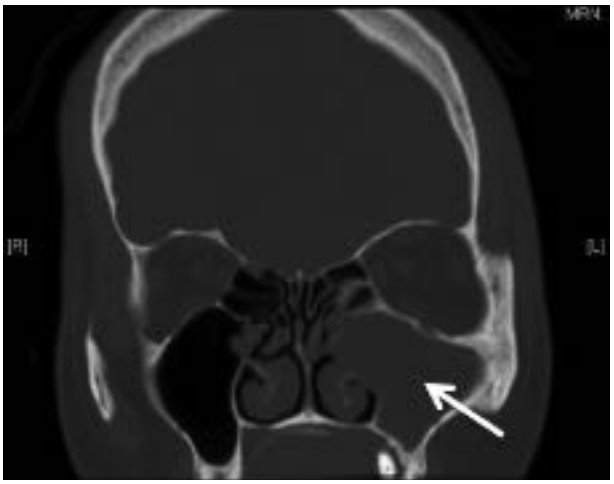


Figure 112.1 Coronal CT image depicting a left antral pyomucocele (arrow).



Figure 112.2 Coronal CT image depicting a left sphenoid mucocele (arrow).

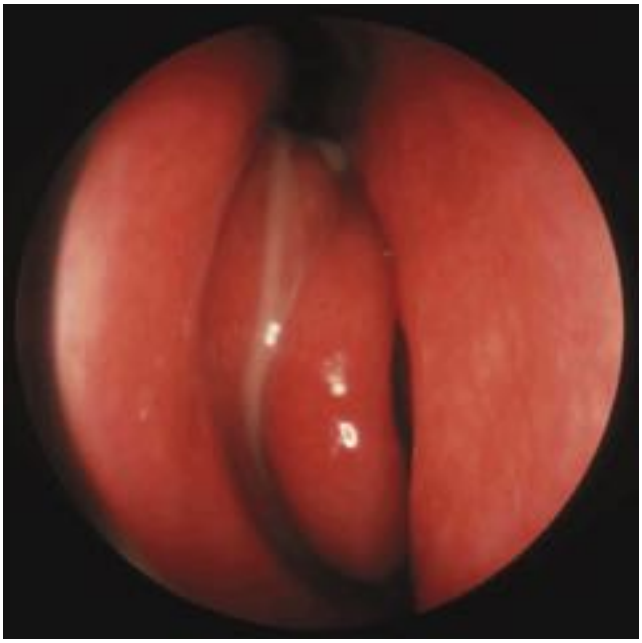


Figure 112.3 Endoscopic digital photograph showing rhinosinusitis with associated purulent discharge in the right middle meatus.

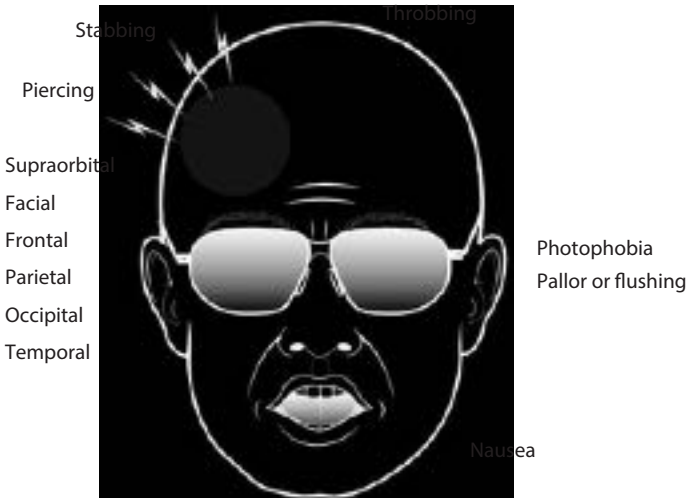


Figure 112.4 The features of migraine.

NON-SINOGENIC FACIAL PAIN

The primary headaches

These are headache disorders not caused by another condition. Each is worth considering in the context of an otolaryngology out-patient setting since they are not infrequently encountered in both specialist rhinology and general situations. Some rhinologists will be very comfortable with the medical management of these headache disorders and will have a thorough understanding of the mechanisms of drug actions and their side effects; some rhinologists will rely heavily on a partnership with a neurologist and/or a colleague with a special interest in pain management. Either approach is acceptable. Not covered in this section are primary headache disorders of the stabbing, cough (precipitated by valsalva), exertional (onset during or immediately after exercise), sexual activity, thunderclap (maximum intensity reached within a minute), hypnic (waking patient from sleep), or new daily-persistent (intractable headache that persists daily for at least 3 months) subtypes.[8] Suspicion should prompt a referral to a neurologist with an interest in headache, for an informed second opinion.

MIGRAINE

Migraine is characterized by recurrent, often unilateral, moderate to severe headaches, which may be associated with a number of symptoms attributable to the autonomic nervous system (Figure 112.4). The headache is described as pulsatile or throbbing, and may be severe enough to force the sufferer to bed in a darkened and quiet room as the pain is generally aggravated by physical activity or sensory stimulation. It may last between 2 and 72 hours.

In classical migraine, accounting for 25% of cases, the associated autonomic symptoms may include one or more of nausea, vomiting, photophobia, and phonophobia. Up to one-third of classical migraine sufferers may describe prodromal aura: a transient visual (scintillating scotoma, which is an area of partial alteration in the field of vision that flickers with zigzagging lines resembling fortifications or walls of a castle), sensory (olfaction or taste), or language or motor disturbance (pins-and-needles or numbness), which signals that the headache will soon occur.[9] Common migraine sufferers experience the same throbbing headache and nausea but without the aura associated with classical migraine.

Although previously believed to be a neurovascular disorder, the mechanism for migraine is now believed to be a disorder of the brain itself.[10] Cortical spreading depression is a wave of intense depolarization that starts in the occipital lobe, propagates through the brain and is followed by a period of suppressed activity. Consequent activation of the trigemino-vascular system causes the release of neuropeptides (e.g. calcitonin gene-related peptide, substance P) from peripheral trigeminal nerve endings. It is these neuropeptides that are thought to play a role in causing and maintaining the headache. The pulsating quality of migraine is thought to be caused by a process of peripheral sensitization. The condition runs in families in approximately two-thirds of cases, is more common in women and sufferers may describe triggers, which can be encountered up to 24 hours prior to the onset of an attack.[11–13] Some examples of triggers include stress, hunger, fatigue, hormonal changes, foodstuffs containing tyramine (aged cheeses, smoked fish, cured meats, some types of beer), monosodium glutamate, indoor air quality and lighting, although the evidence base for all of these is poor.

Over 90% of self-diagnosed and doctor-diagnosed sinus headaches meet the International Headache Society criteria for migraines and yet 60% receive an antibiotic prescription.[5] Furthermore, over 40% of migraine sufferers had at least one unilateral nasal symptom of congestion,

rhinorrhoea or ocular lacrimation, redness or swelling during an attack, which can confuse the picture somewhat. However, these episodes do not last longer than 72 hours and endoscopic examination during an acute episode yields no evidence of purulent secretion.

Main aspects of treatment for acute migraine

- Trigger avoidance
- Acute symptomatic control
- Pharmacological prevention.

Medications are useful if used early in an attack. For mild to moderate symptoms simple analgesics, such as non-steroidal anti-inflammatory drugs (NSAIDs) or the combination of acetaminophen, acetylsalicylic acid and caffeine, are recommended for initial treatment in acute attacks.[14] Ibuprofen provides effective relief of symptoms in about half of people and diclofenac has also been found to be effective, both prescribed either with or without metoclopramide.[15, 16] Triptans (e.g. sumatriptan, naratriptan, rizatriptan, zolmatriptan) may help individuals with moderate to severe symptoms or those with milder symptoms who do not respond to simple analgesics, and are effective in up to 75%.[14, 17] Most side effects are mild, such as flushing, but they are not recommended for people with cardiovascular disease due to rare cases of myocardial ischaemia.[14] Unfortunately though, they may cause medication-overuse headaches if used for more than 10 days per month. Older medications, such as ergotamine and dihydroergotamine, remain as effective as triptans in the management of acute migraine, are less expensive, and are associated with side effects that are typically benign.[18]

Preventative measures in migraine include medications, nutritional supplements and lifestyle alterations. Prevention is recommended in those that have headaches for more than 2 days a week, cannot tolerate the medications used to treat acute attacks, or those with severe attacks that are not readily controlled. Options for medical prevention include anti-epileptic drugs (e.g. topiramate, sodium valproate), beta-blockers (e.g. propanolol, metoprolol), beta-adrenergic receptor antagonists (e.g. timolol), and antidepressants (e.g. amitriptyline, venlafaxine).[19, 20] It is important, however, to appreciate the side effects and contraindications for each before prescribing. Furthermore, it is often reassuring for patients to know that the doses of antidepressants prescribed to treat headaches and facial pain are somewhat lower than those used in the management of depression.

Botulinum toxin type A, administered intra-muscularly to between 31 and 39 sites around the head and back of the neck, has been found to be useful in those with chronic migraines (15 or more headache days per month of which at least 8 days are with migraines) but not those with episodic ones (0 to 14 headache days per month).[21, 22] The treatment is endorsed by the National Institute for Health and Clinical Excellence.[23] Evidence for effective control of other facial pain conditions using botulinum toxin is scarce, although it has also been used for headaches of tension origin.

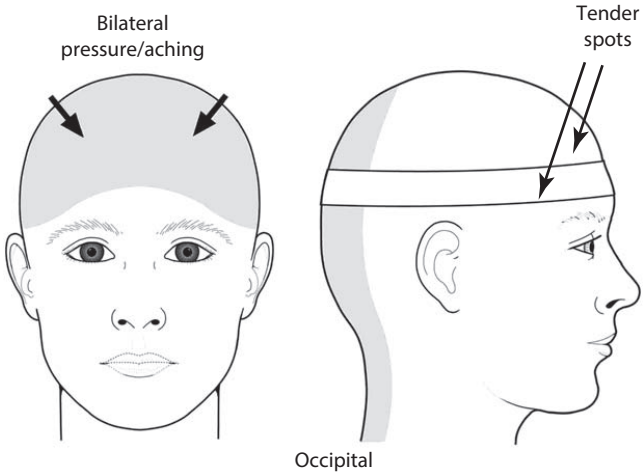


Figure 112.5 The characteristics of tension-type headache.

TENSION-TYPE HEADACHE

This is a headache that can vary in intensity in the same individual, but is usually symmetric and non-pulsatile in nature. The feeling is of tightness, pressure or constriction (vice-like) that may be confined to a small area at the glabella or extend across the whole forehead and into the temporoparietal scalp, often with a tightness or tenderness in the occiput and related trapezius (**Figure 112.5**). There is often some hyperaesthesia of the skin in the area giving the impression to the patient they have sinusitis, and tender trigger points can often be identified in the neck and shoulder areas. Clearly, the aggregate of symptoms suggests an underlying association with stress and tension, but depression and anxiety may also contribute.[3] Furthermore, although many analgesics are being taken, the patients say they offer little relief and, in fact, analgesic-dependent headaches (see below) can complicate the picture. Despite extensive investigation, the underlying pathophysiology remains a matter of speculation, with peripheral muscular and central nervous system components both likely involved. Pericranial myofascial mechanisms are probably of importance in episodic tension-type headache, whereas sensitization of central nociceptive pathways and inadequate endogenous anti-nociceptive circuitry seem to be more relevant in chronic tension-type headache.

Relaxation training, stress management and counselling have been shown to be beneficial in the management of chronic (continuous or last for more than 15 days per month) tension-type headaches although these are, perhaps, therapeutic measures that could be implemented for all non-sinogenic headaches including, for example, temporomandibular joint disorders.[24] Amitriptyline is also effective in the management of tension headache and mid-facial segment pain (see below). Dosing begins at 10 mg, taken once daily at night, and increased in increments of 10 mg every 6 weeks until the pain is controlled. Rarely, 50 mg is needed. The main side effect is sedative, which enhances quality of sleep but may cause a 'hangover' effect the following morning. Tolerance to this effect usually develops after a few days. Treatment should be continued for at least 6 weeks before judging its effect, and should

be continued for 6 months if it has helped. Alternatively, a triptan may be of value when there is overlap between headaches caused by tension and migraine.

CLUSTER HEADACHE AND OTHER TRIGEMINAL AUTONOMIC CEPHALALGIAS

The trigeminal autonomic cephalalgias are a group of primary headache disorders that include cluster headache, paroxysmal hemicrania, and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/cranial autonomic features (SUNCT/SUNA).[25] Trigeminal autonomic cephalalgias are generally characterized by relatively short-lasting attacks of severe pain and lateralized associated features including pain, cranial autonomic symptoms and where present, migrainous symptoms, such as photophobia. Key for the otolaryngologist when diagnosing a trigeminal autonomic cephalalgia is the consideration of underlying pituitary or pituitary-region pathology, since the posterior hypothalamus is crucial in the pathophysiology of these headaches.[26] Although the syndromes share much in their pathophysiology and investigation paths, their treatment is distinct, so that accurate differentiation is important for optimal management. Due to the associated autonomic symptoms, there is a great propensity for the presentation to be confused with sinus pathology, causing misdiagnosis and subsequent mismanagement. It is of great value if such patients are managed in conjunction with a neurologist and/or colleague with a special interest in pain management.

Cluster headache

Cluster headaches are excruciating unilateral headaches of extreme intensity affecting the frontal and temporal regions, extending over the cheek and even into the teeth. There is often associated lacrimation, rhinorrhoea and nasal obstruction, symptoms that have led to misdiagnosis of sinusitis. The pain is typically lancinating or boring/drilling in quality, and is located behind the eye or in the temple (**Figure 112.6**). Descriptions range from a red-hot poker inserted into the eye or a spike penetrated from the top of the head, behind one eye, and radiating down the neck. Men are more often affected than women, primarily between the ages of 20 and 50 years. The duration of the common attack ranges from as short as 15 minutes to 3 hours or more with a rapid onset and without preliminary signs that are characteristic of a migraine. 'Side shifting' between cluster periods and bilateral headache have been described.[27] Clusters of headaches often continue for several weeks followed by months or years of remission. The intense pain in cluster headache is caused by dilation of blood vessels creating pressure on the trigeminal nerve. The aetiology of this process is, unfortunately, not fully understood but is, perhaps, due to an abnormality in the hypothalamus. Preventive treatment is always indicated for cluster headaches, to be started at the first sign of a new cluster cycle. Oxygen therapy, triptans, calcium-channel blockers (e.g. verapamil), and systemic corticosteroids have been found to be effective at managing cluster headaches.

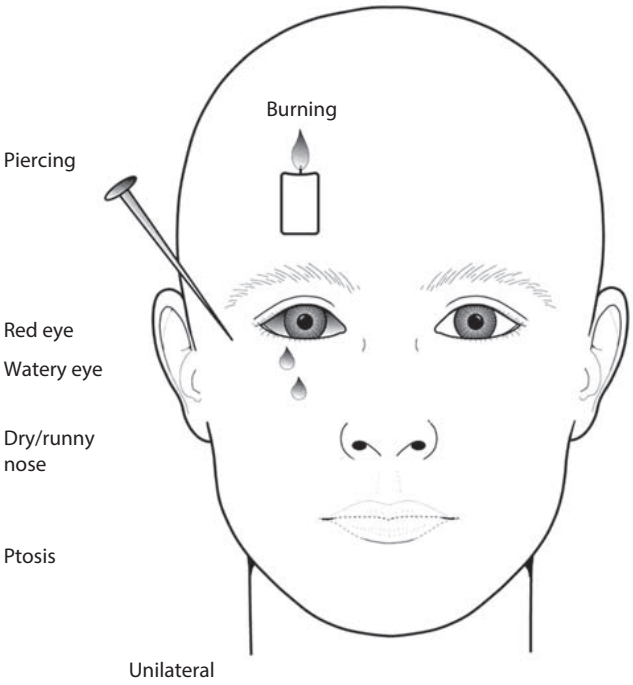


Figure 112.6 The features of cluster headache.

Paroxysmal hemicrania

This is a severe debilitating unilateral headache affecting usually the periorbital and frontotemporal regions, with an average age of onset of 30 to 40 years. Attacks are usually short-lasting, ranging from 2 to 45 minutes, and frequent, happening more than 5 times a day. Trigeminal autonomic symptoms may include nasal congestion, rhinorrhoea and lacrimation, lending itself to diagnostic confusion. The majority of patients with paroxysmal hemicrania respond to indomethacin within 24 hours. In cases where indomethacin fails to work, other drugs that have been suggested include calcium-channel blockers, naproxen, carbamezapine, and sumatriptan.

SUNCT/SUNA

Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform attacks with cranial autonomic features (SUNA) have the shortest attack duration and the highest attack frequency. They are typified by severe, brief, unilateral attacks that usually occur in the distribution of the trigeminal nerve. SUNA differs from SUNCT in that autonomic symptoms are less prominent. Possible effective preventive drugs are carbamazepine, lamotrigine, gabapentin, and topiramate. At present, the drug of choice for SUNCT seems to be lamotrigine, whereas SUNA may better respond to gabapentin.[28]

Hemicrania continua

This is also a strictly unilateral headache causing moderately severe pain, without side-shift, with exacerbations that can include cranial autonomic symptoms as part of the phenotype (e.g. conjunctival injection, lacrimation,

nasal congestion, rhinorrhoea, ptosis, or miosis). The headache is daily and continuous, without pain-free periods, and lasts for more than 3 months. The condition occurs more often in women and tends to present first in adulthood. Its diagnosis requires response to indomethacin but where side effects are an issue, other treatments may include gabapentin, topiramate, radiofrequency ablation of the supraorbital nerve, nerve blocks or botulinum toxin.

NEURALGIAS CAUSING FACIAL PAIN

Trigeminal neuralgia

Trigeminal neuralgia is characterized by paroxysms of brief but severe pain followed by asymptomatic periods without pain, although a constant dull ache may persist in some patients.[29] The pain is often described as stabbing or lancinating, burning, pressing, crushing, exploding or shooting, and patients may describe a trigger area on the face so sensitive that touching or even air currents may trigger an episode. Individual attacks usually affect one side of the face at a time, lasting from several seconds to a few minutes and may repeat up to hundreds of times throughout the day. The pain also tends to occur in cycles with remissions lasting months or even years. Vascular (arterial and venous) compression of the trigeminal nerve roots has emerged as the likely cause in most cases, with the superior cerebellar artery, the anterior and posterior inferior cerebellar arteries, and the superior petrosal vein including several of its tributaries most often implicated.[30] Such compression can injure the protective myelin sheath of the nerve and cause erratic and hyperactive nerve functioning. Diagnosis should be prompt as the longer a patient suffers with trigeminal neuralgia, the more difficult it may be to reverse the neural pathways responsible for pain. Magnetic resonance imaging should be performed to exclude multiple sclerosis or posterior fossa pathology. The anticonvulsant carbamazepine is the drug of choice for management. Gabapentin, lamotrigine and topiramate are useful as second-line agents. Percutaneous radiofrequency thermo- or chemical rhizotomy of the Gasserian ganglion is a valuable intervention in some cases, whilst stereotactic radiotherapy may offer relief of symptoms for others, although the effectiveness tends to decrease with time. Microvascular decompression produces satisfactory relief of trigeminal neuralgia symptoms in the majority of well-selected cases.

Post-herpetic neuralgia

This is pain following a herpes zoster infection, and is defined as pain recurring or continuing at the site of shingles after the onset of the rash. Up to 50% of elderly patients that have had shingles may develop post-herpetic neuralgia though fortunately, most recover during the first year. Antiviral agents help curtail the pain of acute shingles and they may also reduce the risk of subsequent post-herpetic neuralgia. Various medical treatments may be helpful, particularly carbamazepine or gabapentin with or without a tricyclic antidepressant.[31] However, management of distressing pain in these cases is often the remit of a pain specialist.

Post-surgical / traumatic neuralgia

The external portion of the nose is highly innervated by branches of the ophthalmic and maxillary divisions of the trigeminal nerve including the nasociliary nerve, external nasal nerve, infratrochlear nerve, anterior ethmoidal nerve, and infraorbital nerve. As these nerves are located on the external portion of the nose just deep to the skin, they can be easily traumatized with any impact to the nose, either following trauma or after surgery.[32] The pathophysiology is unclear and may be a central, due to neuroplasticity within the trigeminal nucleus producing spontaneous firing of neurones and reverberating circuits, or a peripheral phenomenon, perhaps due to direct neural damage with fibrosis or neuroma formation, or neural entrapment. Callous formation or post-traumatic focal inflammation may exacerbate the problem.

Removal of prosthetic pressure (e.g. from spectacles), drugs to treat neuropathic pain (amitriptyline, gabapentin, or pregabalin), infiltration with local anaesthetic and corticosteroid, nerve decompression and ultimately, nerve section may offer some symptom relief. These patients often suffer a degree of psychological distress following injury or are dissatisfied with the result of their surgery, and it is not uncommon for symptoms to be exaggerated if associated with ongoing litigation. It should be borne in mind that correction of an aesthetic abnormality is unlikely to alleviate pain and caution should be observed when managing such patients. Furthermore, there is the added risk of worsening the pain syndrome or causing new pain to develop after surgical intervention.

Sluder's neuralgia and 'contact point pain'

The theory that implicates mucosal contact points within the nose as a cause of headache or facial pain has, unfortunately, become firmly entrenched in otolaryngology folklore.[33] The findings have been used by some to support the notion that mucosal contact points within the nasal cavity can cause referred pain, even though the original studies did not describe contact point-induced headache or facial pain. High-quality studies now exist to support the view that the majority of people with contact points experience no facial pain.[34] Although Sluder's description of sphenopalatine ganglion neuralgia described a collective group of neuralgic, motor, sensory and gustatory symptoms and signs including facial pain, he did not actually describe the presence of contact points, which is all the more confusing as to why his theory has been extrapolated by some to include mucosal contact with the lateral nasal wall as a cause for facial pain.[35] Moreover, there is nowhere else in the body where mucosa-to-mucosa contact causes pain. It seems probable that the majority of case series in the

literature that describe surgery for anatomical variations (septal spur, concha bullosa, a paradoxically curved middle turbinate, a superior turbinate touching the septum, or a large ethmoid bulla) in patients with facial pain that responded to surgery result from the effect of cognitive dissonance or from surgery altering neuroplasticity within the brainstem sensory nuclear complex.[34] Benefit is more often partial than complete and relatively short-lived. Further prospective, randomized and blinded trials with a minimum follow-up period of 12 months are required to assess the place of contact point surgery.

DENTAL PAIN

Painful teeth

A frequent source of referral to a specialist rhinology clinic is the patient with vague maxillary or piriform aperture pain that has been assessed in an oral or maxillofacial surgery clinic and radiological investigation has identified mucosal thickening in the maxillary antrum. It is important to note that maxillary retention cysts are an extremely common finding in one-third of patients with no sinus complaint. Most will either shrink or remain unchanged over time.[36] Surgery is rarely indicated. True dental pain can often be elicited by percussing the offending tooth, although pain originating from pulp disease may be poorly localized causing misdiagnosis. This pain rarely crosses the midline but radiation to the opposite jaw (e.g. maxilla to mandible) and surrounding structures may further confuse the picture. In contrast, dentino-enamel defects will produce a sharp, well-localized pain often caused by a lost or cracked filling. Once the periodontium is involved the pain becomes localized to the affected tooth, which throbs and is tender to percussion.

Temporomandibular joint disorder

This is not an uncommon presentation in otolaryngology clinics, where muscular hyper- or parafunction may produce acute or chronic pain in the pre- or periauricular areas, deep otalgia, and tenderness in the temporoparietal and cervical regions of the scalp. Clinical findings may include scalloping of the buccal mucosa in cases of bruxism, tenderness in the muscles of mastication or in the temporomandibular joint itself, and smoothed contours of the pre-molar and molar dentition. Other causes include malocclusion, mal-alignment following dental restorative procedures, stress and anger, excessive chewing (e.g. gum), and degenerative joint disease. Treatment includes joint rest, non-steroidal anti-inflammatory analgesia, correction of aetiological factors, and an occlusal splint (e.g. biteguard) worn at night or, sometimes, longer duration can relieve inflammation in a tender joint. Use of a 'one-size-fits-all' splint can worsen symptoms in some people and so these should be custom made. Physiotherapy, temporomandibular joint injection with corticosteroid and local anaesthetic or botulinum toxin, and low-dose amitriptyline may be useful in some resistant cases.

Phantom tooth pain

Patients with unrelenting pain in the teeth, gingival, palatal or alveolar tissues often see multiple dentists and have multiple irreversible procedures performed and still have their pain. Common diagnoses include atypical odontalgia, persistent orodental pain, or if teeth have been extracted, phantom tooth pain.[37] One possibility is that these pain complaints are due to a neuropathic alteration of the trigeminal nerve, but more likely is a diagnosis of persistent idiopathic facial pain (see below). Treatment may include pharmacological medications that suppress nerve activity. The common medications used for atypical odontalgia and phantom tooth pain include gabapentin, tricyclics, topical anaesthetics and opioids.

OTHER CAUSES OF FACIAL PAIN ENCOUNTERED BY THE OTOLARYNGOLOGIST

Mid-facial segment pain

This is a type of tension headache that affects the midface (**Table 112.1** and **Figure 112.7**).[38] The diagnosis can be challenging as patients and their family practitioner are often convinced the symptoms are due to rhinosinusitis. However, dubious endoscopic evidence of rhinosinusitis should prompt the clinician to refute this diagnosis in support of a neurological cause. The mechanism behind tension pain and its management have been described above.

Analgesia-dependency headache or medication-overuse headache

Many headache sufferers, particularly tension-type, mid-facial segment pain and migraine, can get into a cycle of taking an excessive amount of analgesics in spite of the fact that they have little effect. Dull, diffuse and band-like headaches, usually starting in the early morning, are suggestive of drug-induced or analgesic-dependent headaches. The drugs most often used are acetaminophen,

TABLE 112.1 Criteria comprising mid-facial segment pain

- A symmetric sensation of pressure or tightness. Some patients may say that their nose feels blocked even though they have no nasal airway obstruction.
- Involves the areas of the nasion, under the bridge of the nose, either side of the nose, the peri- or retro-orbital regions, or across the cheeks. The symptoms of tension-type headache often coexist.
- There may be hyperaesthesia of the skin and soft tissues over the affected area.
- Nasal endoscopy is normal.
- Computerized tomography of the paranasal sinuses is normal (note a third of asymptomatic patients have incidental mucosal changes on CT).
- There are no consistent exacerbating or relieving factors.
- There are no nasal symptoms (note that approximately 20% of most populations have intermittent or persistent allergic rhinitis, which may occur incidentally in this condition).

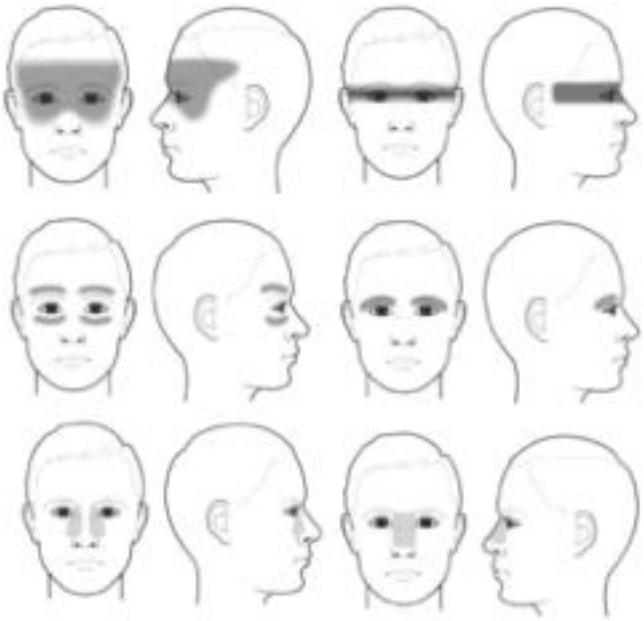


Figure 112.7 Facial map of the patterns of distribution of mid-facial segment pain.

caffeine, non-steroidal anti-inflammatory medications, codeine, ergot alkaloids, and pyrazalone derivatives.[39] On stopping analgesics, headaches disappear or decrease by more than 50% in two-thirds of patients, but withdrawal may be problematic as symptoms can take several weeks to disappear. Positive predictors for successful treatment are migraine as the primary headache, chronic headache lasting less than 10 years, and the regular intake of ergotamine. The underlying mechanisms behind analgesia-dependency headache remain unknown.

Myofascial pain

This is characterized by chronic pain caused by multiple trigger points in the neck, jaw or ear, and is five times more common in post-menopausal women (Table 112.2). The condition has many features in common with temporomandibular joint dysfunction, with tender points identifiable in the sternomastoid and trapezius muscles. Aetiological factors include malocclusion and poor deltopectoral posture, but stress and tiredness have a tendency to amplify the symptoms. Chronic myofascial pain may be helped by applying local heat, ultrasound therapy and often massage to relieve trigger point tenderness. Other pharmacological treatments are similar to temporomandibular joint disorders.

TABLE 112.2 Clinical features of a myofascial trigger point

- focal point tenderness
- reproduction of pain on trigger point palpation
- hardening of the muscle upon trigger point palpation
- pseudo-weakness of the involved muscle
- referred pain
- limited range of motion following approximately 5 seconds of sustained trigger point pressure

Cervical spine degenerative disease and cervicogenic headache

Cervicogenic headache is recognized as a referred pain in the head and by muscular association, to the face.[40] Primary sensory afferents from the cervical roots C1 to C3 converge with afferents from the occiput and trigeminal afferents on the same second-order neuron in the upper cervical spine. Consequently, the anatomical structures innervated by the cervical roots C1 to C3 are potential sources of cervicogenic headache. Pain may originate from different muscles and ligaments of the neck, from intervertebral discs and particularly, from the atlanto-occipital, atlanto-axial, and C2/C3 zygapophyseal joints. Treatment may include simple analgesia, physiotherapy, complementary therapies such as acupuncture or massage, cervical epidural corticosteroid injection, local botulinum toxin injection, radiofrequency ablative therapy, and surgery. Severe cases should be managed in conjunction with a spine specialist.

Temporal arteritis

This is an inflammatory vasculitis of the temporal artery. The condition usually presents to the rheumatologist or vascular surgeon but in the rare instance that an affected patient does present to an otolaryngology clinic, it is essential that a prompt diagnosis is made. Delay can, unfortunately, render a patient blind due to disease progression and involvement of the ophthalmic artery. Loss of vision in both eyes may occur very abruptly. Women over 55 years are most commonly affected, presenting with headache, fever, jaw or tongue claudication, and visual disturbance. The temporal area may be tender, with prominence of the temporal arteries, which may be thickened. Diagnosis is confirmed by raised erythrocyte sedimentation rate and a minimum 1 cm length biopsy of the temporal artery, which shows giant cells infiltrating the tissue, intimal hyperplasia and fragmentation of the internal elastic lamina. Unfortunately, a negative biopsy result does not definitely rule out the diagnosis. High-dose corticosteroids (prednisolone 1mg/kg/day) must be started as soon as the diagnosis is suspected, even before biopsy confirmation, if there is a strong clinical suspicion that the condition is present.

Pain caused by tumour

Although tumours rarely present with facial pain, nearly 80% of patients with head and neck cancers experience facial pain related to their tumour or treatment.[41] Constant or progressive dull or gnawing pain, particularly if associated with other suspicious symptoms or neurological signs should alert the clinician. A past history of malignancy may raise the possibility of metachronous tumour or metastasis. A thorough examination of the head, neck and upper aerodigestive tract along with appropriate radiological imaging is mandatory to exclude the possibility of underlying tumour. Occasionally, tumours may have a long natural history of growth, such

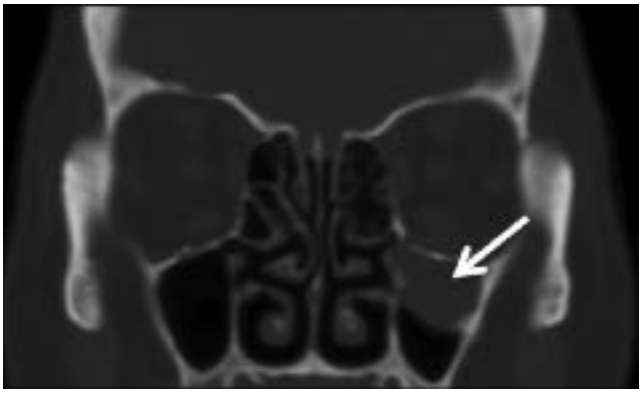


Figure 112.8 Coronal CT image showing a recurrent left infraorbital schwannoma (arrow) causing chronic facial pain.

as a neuroma, and pain may have been present for several years (Figure 112.8).

Patients with neoplasia of the paranasal sinuses, benign or malignant, often present with advanced disease. Unilateral nasal obstruction, bloody or discoloured nasal discharge, a proptosed or displaced globe, facial paraesthesia or swelling, and a loose tooth or ill-fitting denture may represent advanced disease. Pain is usually a late feature.

PERSISTENT IDIOPATHIC FACIAL PAIN (ATYPICAL FACIAL PAIN)

This warrants special mention in its own right. A diagnosis of exclusion only, patients are all too easily labelled as suffering *atypical* facial symptoms when actually, a thorough understanding of alternative causes, mechanisms and symptoms, and appropriate management lends itself to a happier outcome for both the patient and attending otolaryngologist. It is described as a persistent facial pain that does not have the classical characteristics of cranial neuralgias and for which there is no obvious cause.[9] The diagnosis is possible if the facial pain is localized, present daily, and throughout all or most of the day and by definition, neurological and physical examination findings in persistent idiopathic facial pain should be normal. Both the incidence and pathophysiology of the condition are unknown, and it is seen primarily in older adults.[42] The pain does not usually stay within the anatomical boundaries of the trigeminal nerve distribution. It may move from one part of the face to another between different consultations and other symptoms, such as 'mucous moving' in the sinuses, are often described. A number of patients have such completely fixed ideas about their condition that they will not be convinced otherwise, whatever the weight of evidence to the contrary.[5] Pain is often disproportionately described in dramatic terms in conjunction with an excess of other unpleasant life events. Many of these patients have a history of other pain syndromes and their extensive records show little progress despite various medications and investigations. They have often undergone previous sinus or dental surgery and may be resentful about their treatment. Significant psychological disturbance or a history of depression may exist with the suggestion that they are unable to function normally as a result of their pain. Some project a pessimistic view of treatment, almost giving the impression they do not wish to be rid of the pain that plays such a central role in their lives.

The management of such patients is almost always challenging and confrontation is nearly always counterproductive. A good starting point is to reassure the patient that you recognize that they have genuine pain and an empathic consultation with an explanation should be conducted. Drug treatment revolves around a gradual build-up to the higher analgesic and antidepressant levels of amitriptyline (75 to 100 mg) at night. Second-line treatment includes gabapentin and carbamazepine. Patients should sympathetically be made aware that psychological factors may play a role in their condition and referral to a clinical psychologist or psychiatrist may be helpful. Attempts have also been made to further separate idiopathic facial pain syndromes according to topographical criteria. Pain clearly localized in the eye (idiopathic ophthalmodynia) or in the nose (idiopathic rhinalgia) has been described.[43] Whether all such focal syndromes are topographic variants of persistent idiopathic facial pain or independent disorders remains a topic for discussion.

HISTORY TAKING IN FACIAL PAIN

In an effort to draw together the breadth of descriptive text provided in this chapter, an approach to taking a thorough and accurate history is now presented since this is the crux to making a correct diagnosis in a patient that presents with facial pain. It may not be possible to make a correct diagnosis at the first visit, particularly if the patient has seen a number of physicians previously and is emotionally charged. Retaking a history at a subsequent consultation in conjunction with the evidence provided in a symptom diary may further clarify the situation.

In attempting to make a diagnosis, it is helpful to broadly classify symptoms into sinogenic and non-sinogenic in aetiology. Sinus-related symptoms (Table 112.3), coupled with endoscopic evidence of disease, should be readily substantiated. Non-sinogenic causes can be broadly classified as primary headache disorders (migraine, tension and cluster), neuralgias, pain caused by tumours, and others (mid-facial segment pain, dental, analgesia-dependency and persistent idiopathic facial pain). It is useful to have a mental algorithm to plan questions and to use these to work through a diagnostic checklist of possible conditions.

- **Where is the pain and does it radiate anywhere?**
  Asking the patient to localize pain can be extremely useful in differentiating sinogenic from other causes of pain, and may differ from information contained in the referral letter. Bilateral facial pain is commonly, although not exclusively, mid-facial segment pain. Migraine, cluster and other trigeminal autonomic headaches, and temporomandibular joint disorders tend to be unilateral. The manner in which the patient outlines

TABLE 112.3 Definitions of headache caused by rhinosinusitis and the diagnosis of rhinosinusitis

International Headache Society definition of headache due to rhinosinusitis[9]	European Position Paper on Rhinosinusitis and Nasal Polyps 2012 definition of rhinosinusitis in adults[5] Is it the latest now?
A. Frontal headache accompanied by pain in one or more regions of the face, ears or teeth and fulfilling criteria C and D B. Clinical, nasal endoscopic, CT, and/or MRI imaging and/or laboratory evidence of acute or acute-on-chronic rhinosinusitis C. Headache and facial pain develop simultaneously with onset or acute exacerbation of rhinosinusitis D. Headache and/or facial pain resolve within 7 days after remission or successful treatment of acute or acute-on-chronic rhinosinusitis	Rhinosinusitis in adults is defined as: • inflammation of the nose and the paranasal sinuses characterized by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip): • ± facial pain/pressure • ± reduction or loss of smell • and either • endoscopic signs of: • nasal polyps, and/or • mucopurulent discharge primarily from middle meatus and/or • oedema/mucosal obstruction primarily in middle meatus and/or • CT changes: • mucosal changes within the ostiomeatal complex and/or sinuses

their pain, and the gestures used, can inform the examiner of the emotional significance of the symptom.

- **Is the pain continuous or intermittent?**
  Sinogenic pain and migraine are unlikely to be continuous or present on a daily basis. Pain of this character is more likely to represent tension headache, mid-facial segment pain, analgesia-dependency headache or atypical facial pain. Constant and predominantly unilateral pain, particularly if it is progressive, may be due to a tumour and this possibility must be considered.
- **What is the character of the pain?**
  Vascular pain tends to be throbbing in nature, with cluster headaches being particularly severe. Mid-facial segment pain, like tension headache, is often described as pressure or band-like pain. Trigeminal neuralgia may cause intense stabbing pain that is initiated by a trigger.
- **What precipitates or is associated with the pain?**
  Sinogenic pain is associated with adverse rhinological symptoms, but should be differentiated from trigeminal autonomic symptoms. Migraine may have preceding aura and is often associated with nausea. Trigger factors, such as certain foods, withdrawal of stress and sleep disruption, are well recognized. Cluster headaches are frequently triggered by alcohol and wake the patient. The pain of temporomandibular joint disorder is exacerbated by chewing, and that of trigeminal neuralgia and myofascial pain is provoked by trigger points.
- **What relieves the pain?**
  Sinogenic facial pain almost always responds to medical treatments such as topical decongestion, either short or long term, and antibiotics. Patients with migraine will retreat to a quiet and darkened room to lie down, which helps them to cope with their symptoms. Although mid-facial segment pain may initially respond to simple analgesics, the benefit is usually short-lived.
- **What effect does the pain have on daily life?**
  Patients with persistent idiopathic facial pain often describe their pain in dramatic detail as severe and unrelenting despite sleeping well and living a relatively normal life. In contrast, some patients with this condition are unable to work and blame the pain for a breakdown in a close relationship. Severe crippling pain that wakes the patient, often a man, is typical of cluster headache.

BEST CLINICAL PRACTICE

- ✓ A careful and meticulous history is key to accurate diagnosis of facial pain, acknowledging that most patients will not have sinogenic pain.
- ✓ Examination must include nasendoscopy to assess the sinus drainage pathways, lateral nasal wall and visible anterior skull base, particularly when the patient is either symptomatic or in pain. A normal endoscopic examination in such circumstances makes the diagnosis of sinogenic pain extremely unlikely.
- ✓ Plain sinus X-rays should not be used. Computed tomography should be reserved for cases of failed maximal medical therapy, complications of rhinosinusitis, or where there is suspicion of malignancy. Non-pathological sinus mucosal thickening is common in asymptomatic patients and management based only on radiological findings, without clinical correlation, will result in unnecessary surgery.
- ✓ Non-sinogenic facial pain should be managed medically, with complementary therapies, using cognitive behavioural therapy and rarely, with surgery if decompression or nerve section is considered. Caution should be observed if consideration is given to offering endoscopic sinus surgery or nasal plastic surgery to manage facial pain.
- ✓ A multidisciplinary approach to managing chronic non-sinogenic facial pain offers the best outcome for the patient.

FUTURE RESEARCH

- ➤ Neural pathophysiology in rhinosinusitis remains poorly understood.
- ➤ Neural pathophysiology in non-sinogenic facial pain also remains poorly understood.
- ➤ Although the psychological aspects of facial pain are well recognized, well-designed epidemiological studies to assess the incidence of anxiety-depressive disorders in patients with facial pain do not exist. Understanding this association may help to drive forward targeted therapy in such individuals.
- ➤ Future studies should focus on investigation of the source of peripheral nociception, the role of descending pain modulation, and the development of animal models for headache and facial pain to support the pathophysiologic importance of central sensitization in these conditions.

KEY POINTS

- Fundamental to the accurate diagnosis of facial pain is a comprehensive and detailed history.
- Management of patients with chronic facial pain can be time-consuming and complex.
- Facial pain may be exacerbated by an underlying psychological predilection, such as stress, depression or anxiety, or by a litigious motivation.
- Surgery for facial pain is rarely beneficial and may, conversely, either exacerbate or cause *de novo* pain.
- Rhinosinusitis, unless acute or associated with complications, does not usually cause pain.
- Genuine sinogenic pain may be complicated by non-sinogenic pain of multifactorial aetiology.
- Normal clinical examination and radiology does not usually suggest rhinosinusitis and often does not warrant surgery. Recurrent acute sinusitis moderated by antibiotic therapy may be the exception.
- Incidental sinus mucosal thickening on computed tomography does not automatically indicate that facial pain is sinogenic in aetiology.
- Many headache disorders may have associated trigeminal autonomic symptoms such as lacrimation, nasal congestion and rhinorrhoea.
- Many patients with chronic facial pain that is not sinogenic in aetiology benefit from drugs to manage neuropathic pain.
- It is useful to manage patients with chronic facial pain in a multidisciplinary team with neurology, pain specialty, psychology, oculoplastic and neurosurgical colleagues.

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CHAPTER 113

JUVENILE ANGIOFIBROMA

Bernhard Schick

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SEARCH STRATEGY

Data in this chapter may be updated by a search on PubMed and Medline which will enable the reader to identify latest information on this condition using the following keywords: nasopharyngeal neoplasms, angiofibroma, adolescent, and child', supplemented by the author's personal bibliography.

INTRODUCTION

Juvenile angiofibroma (JA) is a unique tumour presenting almost exclusively in adolescent males. The tumour is rare, with an incidence of e.g. 0.4 cases per 1 million inhabitants per year in Denmark.[1] A higher incidence has been reported in Southern Europe and even more in Asia. Although tumour biology is still not completely understood, the knowledge about JAs is increasing and the tumour is well-defined clinically. Consideration of the clinical tumour characteristics is of utmost importance in the diagnosis and treatment of JAs.

Therapeutic options for JAs include surgery, radiotherapy and, in rare cases, chemotherapy. Tumour resection is the therapy of choice. Various surgical techniques have been described previously, ranging from endonasal surgery and mid-facial degloving to approaches using skin incisions, e.g. lateral rhinotomy or infratemporal approaches. At the current time, and in the hands of experienced sinonasal surgeons, endoscopic resection has been proven to allow successful treatment of most JAs[2] based on a precise knowledge of the clinical findings.

CLINICAL FINDINGS

The tumour usually arises from the lateral wall of the posterior nasal cavity close to the sphenopalatine foramen and the pterygoid base (**Figure 113.1a**). Due to its early submucosal expansion towards the nasopharynx, it has frequently been termed 'nasopharyngeal angiofibroma'. Due to this location nasal obstruction and nasal bleeding may be symptoms presented by the adolescents. Although the tumour is histopathologically classified as a benign lesion, bony erosions of the pterygoid, the clivus and the sphenoid sinus floor are common hallmarks of JAs. Bony destruction of the sphenoid sinus floor is followed by tumour extension into the sphenoid sinus. Here the tumour may fill the sinus space almost completely without infiltrating the mucosa. Furthermore, the tumour may grow along the central skull base towards the foramen lacerum. In such cases, assessment should be made of the presence, or not, of tumour tissue posterior to the pterygoid plates.

It is important to consider that JAs spread along natural foramina and fissures. Tumour tissue may extend laterally through the sphenopalatine foramen into the pterygopalatine fossa and further into the infratemporal fossa. In this case, a widened sphenopalatine foramen and an anterior displacement of the posterior maxillary sinus wall are typical radiological findings (**Figure 113.1b**).

Finger-like tumour processes may be encountered in the infratemporal fossa. A further lateral extension or tumour growth beyond the maxillary sinus will present as facial swelling. The orbit may be reached via the inferior orbital fissure causing proptosis and/or optic nerve compression with visual disturbance. Intra-cranial tumour spread is observed in advanced stages mainly through the roof of the infratemporal fossa and in some cases via the superior orbital fissure. In cases of intra-cranial tumour growth, JAs are mainly located in the extradural space. Dural infiltration or even brain involvement are rare events.

Blood supply of this highly vascular tumour needs to be evaluated carefully in order to diagnose and treat

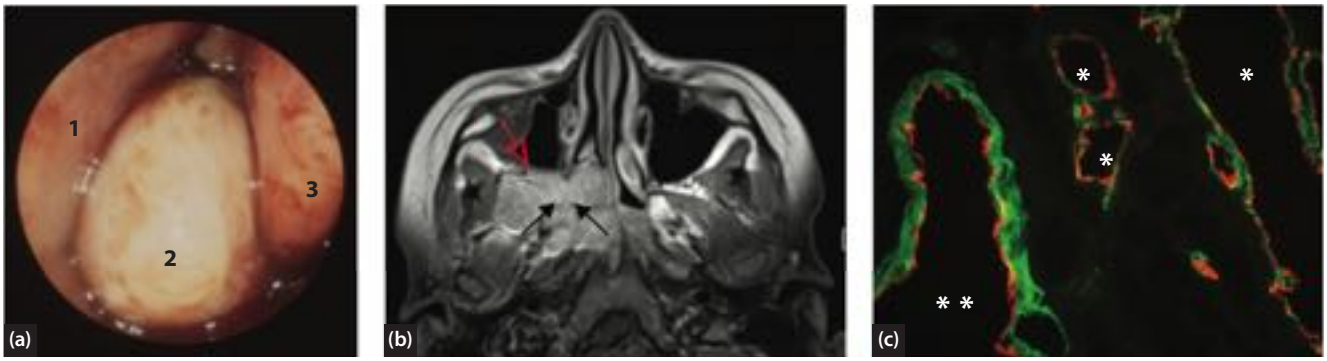


Figure 113.1 (a) Endoscopic view of a juvenile angiofibroma (JA) in the left posterior nasal cavity (1 = nasal septum, 2 = tumour, 3 = inferior turbinate). **(b)** MRI of a juvenile angiofibroma (arrows) after application of contrast medium showing an enlarged sphenopalatine foramen (black arrows) and anterior displacement of the posterior maxillary sinus wall (red arrow). **(c)** Staining of a juvenile angiofibroma (JA) with antibodies against laminin (vascular wall, green) and the endothelial cell marker CD31 (red) demonstrates irregularly shaped vessels lined by endothelial cells only (*) in the vicinity to vessels with a regular vascular wall architechture (**).

JAs successfully. The diagnosis is based on the typical clinical and radiological findings.[3] Tumour biopsy should be avoided due to the risk of severe bleeding. In its early stages, the tumour is supplied by the sphenopalatine and maxillary arteries. In advanced stages, further branches of the external carotid artery (ECA), such as the ascending pharyngeal artery, contribute to tumour blood supply. Besides the internal carotid arteries (ICAs), the vertebral arteries have to be considered as additional feeders, especially in large JAs. In view of this, a careful angiographic evaluation of ipsilateral and contralateral ECAs and ICAs is strongly recommended in all JAs, and should be accompanied by an examination of both vertebral arteries in advanced tumour stages. Pre-operative superselective embolization of this highly vascularized tumour has attracted great attention and is recommended by most authors. Some surgeons do not ask for pre-operative embolization as they close the feeding vessels before tumour removal and have found it wise to detect possible tumour remnants by bleeding, as well as to avoid site effects of embolization e.g. brain infarction. In addition, a cell saver can be used during surgery to avoid allogenic blood donation. As well as defining the tumour feeders in JAs, the vascular tumour architecture deserves special attention, especially as the surgeon is able to reduce blood loss by respecting the unique structure of JAs.

TISSUE ARCHITECTURE

JAs are benign fibrovascular tumours with characteristic irregularly-shaped vessels, which may be lined by endothelial cells only (**Figure 113.1c**) or show an incomplete vascular wall architecture. Therefore, the surgeon is faced with profuse bleeding when opening these non-contractible pathological vessels during dissection of the tumour. The extreme variability in the amount of fibrous tissue and vessel density within JAs is of outstanding importance for the surgeon. The highest density of vessels, in particular those with the characteristic irregular shape, is found below a pseudocapsule at the tumour surface. Thus, the surgeon should always dissect along the pseudocapsule in order to avoid severe bleeding. Towards the centre of the tumour, the amount of fibrous tissue increases, while vessel density decreases. Based on the clinical findings and the specific vascular architecture, JAs have been defined as vascular malformations rather than true neoplasms.[4] Recently published genetic and molecular findings have supported this theory.[5]

JUVENILE ANGIOFIBROMA AND THE FIRST BRANCHIAL ARCH ARTERY

It has been proposed that the tumour origin is based on an incomplete regression of the first branchial arch artery.[6] This theory is especially attractive, as it is able to explain different aspects of JAs:

Firstly, during embryological development, the first branchial arch artery finally recedes close to the pterygoid base and sphenopalatine foramen regions. Secondly, vascular remnants of this artery are incorporated into the sphenopalatine and maxillary arteries themselves. Thus, both the proximity of tumour origin to the sphenopalatine foramen and its main blood supply from the sphenopalatine and maxillary arteries in early stages of JAs can be explained by the 'branchial arch artery' theory. The fact that this embryological vessel is connected to the C4-segment of the ICA deserves special attention in this context: persistent vascular remnants of the first branchial arch artery contacting the ICA are able to account for the observation of a vascular supply from the ICA, despite an anatomical distance between this vessel and the JA. Furthermore, the 'branchial arch artery' theory elucidates the common finding of residual tumour at the pterygoid base and clivus and explains why it is necessary to drill the bone in this specific location in order to remove tumour remnants at the site of origin.[2, 7]

ENDOSCOPIC RESECTIN: SURGICAL CONSIDERATIONS

Endoscopic resection of JAs follows tumour management principles by keeping the specific characteristics of this

unique tumour in mind. Basically, the strategy of endoscopic resection takes the following considerations into account:

1. Opening of the maxillary sinus and exposure of its posterior wall are performed early during surgery. The size of the tumour dictates the size of the medial maxillectomy. The bony posterior wall of the maxillary sinus is removed with 'through cutting' punches or drills avoiding trauma to the periosteum in the pterygopalatine fossa before resection of the bone is completed. Following incision of the periosteum, the sphenopalatine and maxillary arteries are identified and clipped or coagulated. Early control of the main feeding vessel is of great value to assist further tumour resection. An alternative in early JAs is to push the tumour gently in a medial direction out of the pterygopalatine and infratemporal fossae and to identify the main feeding vessel by this manoeuvre. In cases where an extended access to the maxillary sinus does not allow exposure of the lateral tumour border within the infratemporal fossa in advanced JAs, the tumour can be pushed medially with a finger placed externally at the lateral border of the maxillary sinus below the jaw.
2. Resection of the posterior nasal septum is advised to widen the access in endoscopic tumour removal and to define tumour margins at the nasal septum.
3. The anterior sphenoid sinus wall is removed in order to expose the tumour within the sphenoid sinus. For this purpose, a bilateral opening of the sphenoid sinus is usually necessary.
4. Finally, the tumour is dissected directly off the pterygoid base and pterygoid canal regions and the clivus. Troublesome venous bleeding from the bone can be managed at this stage with drilling, chemical haemostatic agents or fine endosurgical diathermy.
5. It is of utmost importance to drill at the pterygoid base and the clivus at the end of surgery in order to avoid residual tumour.
6. Endoscopic dissection should always follow the pseudocapsule in order to avoid injury of the tumour at the surface. Finger-like extensions of the tumour can be gently pulled out along the pseudocapsule

INDICATION AND LIMITATION OF ENDOSCOPIC SURGERY

Endoscopic resection of JAs using the nostrils as natural openings is an ideal option to treat the majority of tumours successfully. Nevertheless, the endonasal approach should not be applied in a dogmatic sense. It depends on the personal experience of the surgeon to determine whether endoscopic tumour resection is appropriate in a particular JA. Each surgeon should feel free to convert to an open approach during surgery if the endoscopic resection cannot be performed in a particular situation. From the author´s point of view, indications and limitations of endoscopic JA surgery will change for every surgeon with increasing experience in this field.

In general, the endoscopic resection can be used to remove JAs limited to the nasal cavity, the nasopharynx, the sphenoid sinus and the pterygopalatine fossa. With increasing experience, a surgeon might be able to perform an endoscopic resection of JAs which extend into the infratemporal fossa and to the space posterior to the pterygoid plate. With increasing experience, a surgeon will be able to remove tumour tissue from the orbit and the parasellar region in primary surgery. Generally, an endoscopic tumour resection is not recommended in situations of broad skull base infiltration, extensive blood supply from the internal carotid artery, encasement of the internal carotid artery and brain infiltration.[2]

Due to the importance of preserving neurovascular function, the surgeon may be forced to leave residual tumour in areas around the optic nerve, the cavernous sinus, the internal carotid artery and the dura, independent of the surgical approach selected. In cases of revision surgery for residual tumour, the surgeon should be very careful about selecting an endonasal approach, as the limitatons for endocopic approaches are different compared to primary surgery. If the residual tumour is potentially adherent by fibrosis to important neurovascular structures, it may not possible to tease out tumour tissue as one can in primary surgery. Careful radiological follow-up of residual tumour adjacent to delicate neurovascular structures assists in monitoring potential tumour growth. Nicolai has demonstrated that residual tumour does not necessarily expand when assessed on serial MR imaging.[2]

BEST CLINICAL PRACTICE

- ✓ Tumour biopsy should be avoided due to the risk of severe bleeding.
- ✓ The surgeon should always dissect along the pseudocapsule in order to avoid severe bleeding.
- ✓ The endoscopic resection can be used to remove JAs limited to the nasal cavity, the nasopharynx, the sphenoid sinus and the pterygopalatine fossa.
- ✓ An endoscopic tumour resection is not recommended in situations of broad skull base infiltration, extensive blood supply from the internal carotid artery, encasement of the internal carotid artery and brain infiltration.
- ✓ Juvenile angiofibromas can be mobilized along the pseudocapsule, but are firmly fixed at the clivus and the pterygoid base.
- ✓ Dissect strictly along the pseudocapsule and avoid entering the tumour surface, as this will result in severe bleeding due to the high-density of irregularly-shaped vessels at the surface.
- ✓ Finger-like tumour extensions can be teased out gently in most cases during primary surgery.
- ✓ Knowledge of the tumour arterial feeders is essential for the surgeon, as these need to be controlled during tumour resection.

- ✓ Always check carefully for tumour extension posterior to the pterygoid plate, as residual tumour can easily be left at this point.
- ✓ Drilling of the pterygoid base and the clivus is of the utmost importance in order to avoid residual tumour at the site of tumour origin.
- ✓ Endoscopic resection has been found to be a valuable alternative to external approaches for the successful management of most juvenile angiofibromas.
- ✓ With increasing experience, endoscopic management allows the surgeon not only to resect small, but also intermediate JAs.

KEY POINTS

- At the current time, and in the hands of experienced sinonasal surgeons, endoscopic resection has been proven to allow successful treatment of most JAs[2] based on a precise knowledge of the clinical findings.
- It is important to consider that JAs spread along natural foramina and fissures.
- The surgeon may be forced to leave residual tumour in areas around the optic nerve, the cavernous sinus, the internal carotid artery and the dura, independent of the surgical approach selected.
- Tumour origin is close to the sphenopalatine foramen and the pterygoid canal; bony destruction at the pterygoid base and the clivus is frequently observed.
- Widening of the sphenoplataine foramen and anterior displacement of the posterior maxillary sinus wall are typical radiological findings.
- Tumour spread takes place along natural foramina and fissures.
- The maxillary/sphenopalatine arteries are the main tumour feeders. However, the surgeon should always bear in mind that further tumour feeders may arise from the internal carotid artery.
- Tumour diagnosis is based on the typical signs on CT, MRI and angiography. A biopsy should not be performed due to the risk of severe bleeding.
- Irregularly-shaped vascular spaces, which may have an endothelial lining only, embedded in a fibrous stroma are the reason for potential profuse tumour bleeding.
- JAs are proposed to be vascular malformations originating from vascular remnants of the first branchial arch.

ACKNOWLEDGEMENTS

The author thanks Julia Dlugaiczyk, MD for a critical reading of the manuscript and valuable suggestions.

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CHAPTER 114

ENDOSCOPIC MANAGEMENT OF SINONASAL TUMOURS

Alkis J. Psaltis and David K. Morrissey

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SEARCH STRATEGY

This chapter is based on and supported by a detailed search strategy encompassing PubMed, Medline and the Cochrane Library. Searches utilized a combination of keywords associated with the endoscopic management of sinonasal tumours. These keywords included but were not limited to: paranasal sinus, endoscopy, sinonasal tumours, benign sinus lesions, malignant sinus lesions, endoscopic field control, endoscopic access, image guidance, vascular, orbital and intra-cranial extension and injury.

INTRODUCTION

With the advent of the endoscope and its early application to the management of inflammatory sinonasal conditions, surgeons identified significant advantages of endoscopic endonasal surgery over open approaches. Increasing endoscopic experience and advances in instrumentation and imaging technology have led to a natural evolution and expansion of endoscopic endonasal surgery to now commonly include the management of benign and malignant sinonasal tumours. The scope of this chapter is to provide the reader with a general overview of the approach to the endoscopic management of sinonasal tumours. Tumour specific management can be found in other chapters dedicated to the individual pathologies.

EVIDENCE BASE FOR ENDOSCOPIC MANAGEMENT OF SINONASAL TUMOURS

As surgical experience with the endoscopic resection of sinonasal tumours increases, so has the body of evidence supporting its role.[1] Systematic reviews and large case series now support the endoscopic approach as a favourable treatment option for the management of benign tumours, including most cases of sinonasal inverted papilloma,[2–5] juvenile nasal angiofibroma[6–8] and osseous tumours such as osteomas,[9, 10] ossifying fibromas[11] and fibrous dysplasia.[12, 13]

The application of endonasal endoscopic techniques to the management of malignant sinonasal tumours has been more controversial.[14–16] Early concerns raised included the violation of the oncologic principle of en bloc resection, the ability to deal with vascular complications and the difficulty associated with defect reconstruction. Evidence is now emerging however that refutes such concerns, with large case series showing reduced morbidity,[17] improved vascular control,[18] better quality of life outcomes[19] and equivalent survival outcomes to open approaches. These findings have led to the support of the endoscopic approach for the management of sinonasal tumours by a recently published European Position Paper.[20] Malignant pathologies successfully treated via endoscopic techniques include squamous cell carcinoma, adenoid cystic carcinoma, adenocarcinoma, aesthesioneuroblastoma, sinonasal undifferentiated carcinoma and sinonasal melanoma.[15, 17–24]

SINONASAL TUMOUR EPIDEMIOLOGY

Tumours involving the sinonasal cavity are considered rare entities. They can arise from any of the structures comprising the paranasal sinuses or can involve the sinuses by direct extension from adjacent structures. Consequently, these tumours encompass a large and diverse group of lesions (**Table 114.1**). The most commonly reported benign lesion is a sinonasal osteoma, with a radiological incidence of 1%. Ossifying fibroma, fibrous dysplasia and inverted papilloma are the next most commonly reported

TABLE 114.1 Summary of sinonasal tumours by tissue of origin

Tissue of origin	Benign lesions	Malignant lesions
Epithelial	• Inverted Papilloma • Oncocytic Papilloma • Exophytic Papilloma • Respiratory Epithelial Adenomatoid Hamartoma (REAH) • Salivary Gland Adenomas	• Squamous Cell Carcinoma • Sinonasal Undifferentiated Carcinoma (SNUC) • Lymphoepithelial Carcinoma • Adenocarcinoma • Salivary Gland Carcinomas • Mucoepidermoid • Adenoid Cystic Carcinoma • Acinic cell Carcinoma
Neuroendocrine		• Carcinoid
Soft tissue	• Myxoma • Leiomyoma • Haemangioma • Schwannoma • Meningioma • Neurofibroma • Angiofibroma • Haemangiopericytoma	• Fibrosarcoma • Rhabdomyosarcoma • Angiosarcoma • Malignant Peripheral Nerve Sheath Tumour
Bone and cartilage	• Fibrous Dysplasia • Osteoma • Osteoblastoma • Chondroma • Ameloblastoma	• Chondrosarcoma • Osteosarcoma • Chordoma
Haematological and lymphatic		• Lymphoma • Langerhans cell Histiocytosis
Germ cell tumours	• Dermoid cyst	• Teratoma Sinonasal yolk sac tumour
Neuroectodermal tumours		• Esthesioneuroblastoma

benign lesions of the paranasal sinuses.[20] Sinonasal malignancies are less common with an estimated incidence of 0.5–1/100 000.[25] They account for around 1% of all malignancies and 3– 5% of all head and neck cancers.[20,23] Primary epithelial tumours are the most common type of sinonasal malignant tumour, with squamous cell carcinoma the most common subtype followed by adenoid cystic carcinoma and adenocarcinoma. Of the less common non-epithelial tumours, lymphoma is the most commonly reported tumour.[20]

DIAGNOSIS AND PRE-OPERATIVE PLANNING

Evaluation of sinonasal masses should commence with a complete history and physical examination. In addition to a focused otorhinological examination, a complete cranial nerve assessment should be performed on all these patients. Table 114.2 highlights concerning features that should be looked for on clinical examination.

Endoscopy

Nasal endoscopy forms an integral part of the rhinological assessment. Although large masses may create difficulty with respect to performing a complete endoscopic assessment, it is important to obtain as much information pre-operatively as possible. Documentation of the likely site of origin, as well as involvement or destruction of the septum, lacrimal system, orbit, palate, nasopharynx and skull base is important and may provide useful information regarding the likely pathology, endoscopic resectability and access or approach required. Although biopsy may be performed at the time of endoscopic assessment, we recommend review of the relevant radiological investigation. This may avoid catastrophic complications including torrential bleeding or CSF leak (Figure 114.1).

Radiology

Radiological investigations in the form of computed tomography (CT) and magnetic resonance imaging (MRI) are critical in management of sinonasal tumours. Imaging not only helps characterize the tumour and assess the local and regional extension but also aids in the planning of surgery and adjuvant treatments. High resolution CT scans with contrast and slice thickness of 1 mm should be performed in all patients. CT scan permits superior assessment of osseous margins of the skull base and sinus walls which are less effectively demonstrated on MRI. Specific features to assess on CT scan and their clinical implications are shown in Table 114.3.

MRI provides inherently superior soft-tissue resolution and multiplanar capabilities, rendering it superior for the assessment of soft-tissue masses and extension of infectious or malignant processes outside the confines of the paranasal sinuses. MRI facilitates the differentiation of retained secretions and haemorrhage from the tumour mass and allows a better appreciation of the tumour margin and its interface with normal tissue and critical structures. MRI of the paranasal sinuses must include

TABLE 114.2 Concerning features on clinical examination

Clinical finding	Reason for concern
Conductive hearing loss/Middle ear effusion	Obstruction/invasion of eustachian tube
Visual change/loss **Visual field change** **Diplopia/Ophthalmoplegia** **Pain on eye movement** **Chemosis/Orbital displacement**	Optic nerve involvement Intra-cranial extension, optic chiasm compression Involvement of intra-orbital contents
Clear rhinorrhea	Dural/Intra-cranial involvement with CSF leak
Facial paraesthesia	Compression/invasion of the maxillary or infraorbital nerve
Loose teeth **Dental paraesthesia**	Invasion of the alveolar process and dental roots
Facial asymmetry	Possible involvement of facial soft tissues
Oronasal or Oroantral fistula	Erosion of the nasal floor or maxillary sinus floor
Palpable cervical nodal disease	Possible metastatic spread
Reduced neck range of motion	Paraspinal muscle involvement

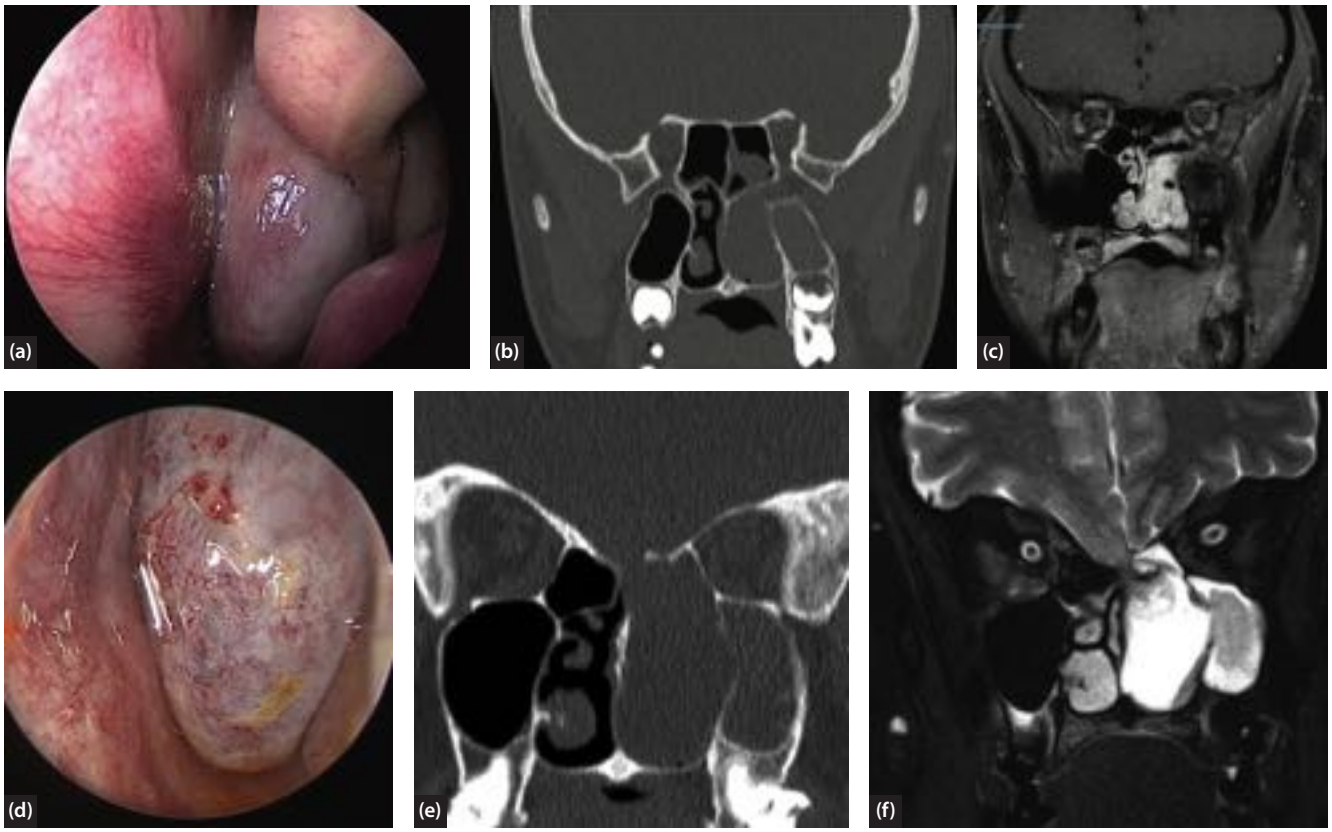


Figure 114.1 Highlights the importance of obtaining imaging prior to the biopsy of a nasal lesion. **(a)** Endoscopic Image of left juvenile nasal angiofibroma resembling a simple benign nasal polyp in the sphenoethmoidal recess. **(b)** Coronal CT scan of left juvenile nasal angiofibroma showing characteristic expansion of the sphenopalatine foramen and **(c)** an MRI T1 with gadolinium contrast demonstrating the extensive vascularity of the juvenile nasal angiofibroma with the presence of flow voids as well. **(d)** An endoscopic image of a large left sided encephalocele presenting a left sided nasal mass. **(e)** CT and **(f)** MRI coronal images of the left encephalocele showing the clear intra-cranial origin and skull base defect. Although the pathology is suspected from the CT, MRI is needed to confirm the diagnosis prior to surgery.

high resolution (1 mm) T1- and T2-weighted images of the sinonasal cavity, orbit, skull base and the adjacent intracranial compartment. Understanding the advantage of each sequence and a systematic approach to the evaluation of the images can be extremely useful to the surgeon in understanding the characteristics of the tumour. The use of gadolinium chelate contrast agents with fat saturation increases the sensitivity of the contrast enhancement, thereby improving the detection of local disease extent and the presence of disease beyond the paranasal sinuses such

TABLE 114.3 Radiological features on CT and their possible implications

Feature	Potential clinical implication
ORBIT	
Breech of lamina papyracea **Loss of orbital fat planes** **Involvement of extra-ocular muscles**	May indicate involvement of orbit and the need for orbital exenteration.
SEPTUM	
Erosion of septum	Important implications for surgical access and repair. Lesions crossing midline will require a septectomy and binasal approach. Gross septal involvement may preclude the use of the nasoseptal flap.
SKULL BASE	
Asymmetrical or low lying	Increase risk of inadvertent entry and CSF leak during surgery
Position of anterior ethmoid arteries	Mesentery suspended arteries are at increased risk of injury
Skull base defect	Suggestive of intra-cranial extension of sinonasal pathology or intra-nasal extension of intra-cranial pathology
SPHENOID SINUS	
Extent of pneumatization	Laterally pneumatized sinuses may place the carotid at risk
Onodi cells	May contain optic nerve and be confused with sphenoid sinus
Location of sphenoid septations	Septations may be closely related to carotid artery and optic nerve, requiring great care when removing.
PARANASAL SINUS	
Osteitic changes	Possible site of tumour origin
Widened bony foramina	Perineural invasion of tumour Nerve sheath tumour
Tumour calcification	See to varying degrees with aesthesioneuroblastoma, chondroma, chondrosarcoma, osteoma, ossifying fibroma and osteosarcoma
Expansion of paranasal sinus / fossae	Tends to indicate the presence of a mass within the space

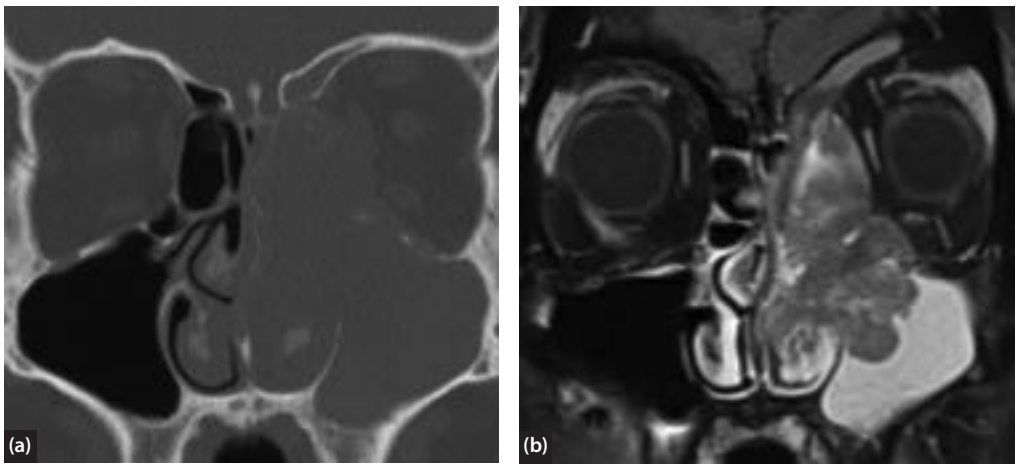


Figure 114.2 Coronal CT and MRI of a sinonasal tumour. Although the CT would suggest involvement of the extra-ocular muscles, the MRI demonstrates clear preservation of the fat plane. The MRI also facilitates a differentiation of tumour from retained secretions seen in the maxillary sinus. These images highlight the importance of obtaining both a CT and MRI for skull base tumours.

as dural involvement or perineural spread. Figure 114.2 demonstrates the complementary features of CT and MRI in the work-up of skull base tumours.

Clinical Positron Emission Tomography (PET) relies on the preferential uptake of 18-fluorodeoxyglucose (18-FDG) by tumour cells that exhibit a higher density of GLUT1 glucose transporters. When combined with CT it can improve tumour localization, although the increased 18-FDG avidity in areas of sinonasal inflammation or infection can confound its utility in the paranasal sinuses. In the evaluation of these tumours its usefulness is predominantly confined to the detection of distant metastases.

Biopsy

Pre-operative endoscopic-guided biopsies should be taken prior to performing the definitive surgical procedure. Biopsies should typically be performed after reviewing the relevant radiology to exclude vascular lesions or prolapsed meningo-encephaloceles. Whenever possible,

multiple deep biopsies from the centre of the tumour should be taken to gain a representative sample and avoid sampling the non-specific and necrotic superficial aspects of the tumour. Tissue should always be sent both fresh, and in formalin fixative, to allow both routine histopathology and flow cytometry. Tumour histopathology will help direct management and intra-operative decision-making.

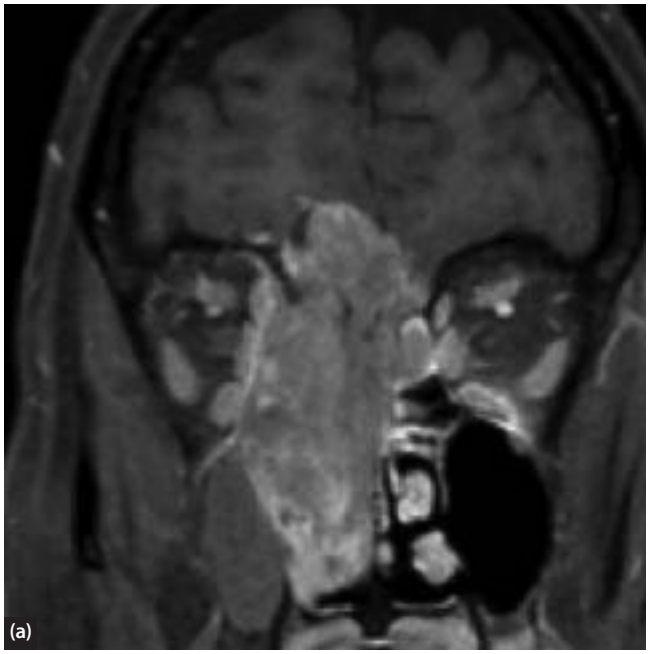
Multidisciplinary planning meetings

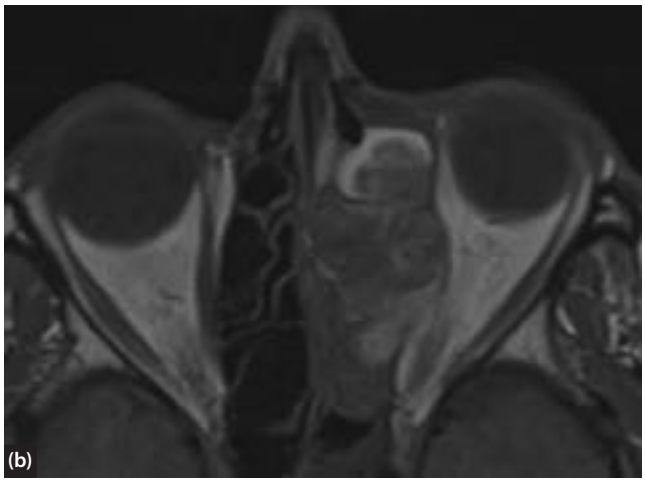
All patients with malignant and complex pathology should be presented to a multidisciplinary team, comprising of surgeons, radiologists, medical and radiation oncologists and allied health professionals. Treatment recommendations made by the team should not only take into account the pathology of the tumour but also the age, health and functional status of the patients, as well as their level of home support. Although complete oncological clearance is the ultimate goal of any treatment, this may not be possible without causing significant morbidity to the patient. Patients and families should be informed of all the different treatment options discussed at tumour board meetings to enable informed consent to be made.

PRINCIPLES OF ENDOSCOPIC MANAGEMENT OF SINONASAL TUMOURS

Case selection

As experience with endoscopic cranial base surgery increases, so have the limits of what is considered endoscopically resectable. Dura, the olfactory bulbs and lamina papyracea can all be safely resected as can the entire anterior cranial base from the cribiform plate to the planum sphenoidale. Transclival approaches allow resection of tumours from the nasopharynx, clivus and the odontoid process, with the inferior limit of endoscopic resectabilty considered the nasopalatine line.[26] Endoscopic medial maxillectomy provides access to the pterygopalatine and infratemporal fossa, while the petrous temporal bone, Meckel's cave and middle cranial fossa can be accessed via the transpterygoid approach. Relative contraindications to an entirely endoscopic approach include the involvement of skin and subcutaneous tissue, the nasolacrimal sac, carotid artery, the anterior table of the frontal sinus and extensive dural and brain involvement (**Figure 114.3**). Like all forms of surgery, endoscopic endonasal surgery is associated with a steep learning curve. It is recommended that surgeons considering performing oncological surgery first become proficient in the surgical management of sinonasal inflammatory disease, before progressing to benign and eventually malignant tumours. Surgeons should use simpler cases to improve their familiarity with the endoscopic anatomy as well as the ergonomics involved in endoscopic surgery. The latter takes on greater importance when a second surgeon becomes involved.





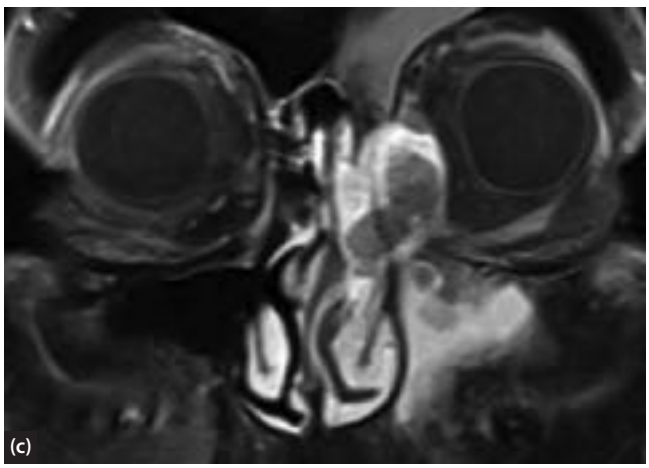


Figure 114.3 Demonstrates relative contraindications to a purely endoscopic resection. **(a)** shows gross intra-cranial involvement necessitating a combined endoscopic and anterior craniofacial approach; **(b)** shows frank invasion of the extra-ocular muscles with loss of preservation of the orbital fat planes and **(c)** shows involvement of the lacrimal apparatus and the anterior soft tissue structures.

Optimizing the surgical field

Poor visualization due to excessive bleeding has been shown to be associated with an increased risk of intra-operative complications.[27–30] Strategies to improve the surgical field include proper patient positioning, regulation of haemodynamic parameters, adequate topicalization and the use of electrocautery. Studies suggest that positioning a patient in 15–20° of reverse Trendelenberg can increase venous drainage without compromising cerebral perfusion. Similarly, the use of total intravenous anaesthesia to maintain a mean arterial blood pressure of approximately 60 mmHg and a pulse rate below 70 bpm has also been shown to decrease surgical bleeding without affecting cerebral blood flow, provided a patient does not have underlying cardiovascular disease. Pre-operative topicalization of the nasal cavity with local anaesthetic infiltration and patties soaked in vasoconstricting agents is also useful as is the intra-operative use of haemostatic agents such as Gelfoam® and Floseal®, along with the use of warm saline irrigations and cautery.[30] Although suction monopolar cautery is extremely useful in tumour debulking, it should be avoided near the skull base and orbit due to the theoretical risk of heat and electrical current transmission to vital structures.

Image guidance technology

Image guidance technology is considered a useful aid when performing endoscopic skull base surgery. It provides the surgeon with enhanced anatomical localization and the current literature suggests that its use may decrease surgical disorientation, improve surgical completeness and potentially lower complication rates.[31, 32] The incorporation of CT/MRI fusion is also thought to provide valuable information with regard to the extent of tumour resection and the clarification of boundaries between the tumour and normal adjacent soft tissues and neurovascular structures.[33]

Principles of oncologic resection

The complete resection of a tumour with as little morbidity as possible is the primary goal of any oncological surgery. Although traditional surgical paradigm dictates that this be performed in an en bloc manner, the anatomical confines of the nasal cavity prevent this for the vast majority of endoscopic tumour resections. Fortunately, despite filling the nasal cavity, many sinonasal tumours have a small, well-defined area of origin or tissue invasion. Provided en bloc excision of this site is performed, ideally with a cuff of normal surrounding tissue, the remainder of the tumour can be selectively debulked down to attachment points, without compromising the completeness of resection or increasing the risk of recurrence.[34]

Surgical access techniques

Prior to debulking the tumour, the initial steps of the procedure are aimed at improving surgical access. The purpose of this is twofold. Firstly it will allow the surgeon more room for instrumentation and improve the vectors needed to approach the peripheral aspects of the tumour and secondly, it will allow early identification of tumour-free zones that can serve as margins or the limits of the resection.

IMPROVING LATERAL ACCESS

Lateral sinonasal tumours, including those involving the maxillary sinus and pterygopalatine or infratemporal fossae have historically proven difficult to access endoscopically. The introduction of angled endoscopes and instrumentation as well as the development of various approaches has meant that many of these tumours can now be resected entirely endoscopically. To access such tumours, surgeons must not only consider the lateral extent of these tumours, but the likely vectors required for instrumentation. Tumours confined to the nasal cavity with no extension beyond the infra-orbital nerve can usually be managed through the ipsilateral nostril, while those extending outside this zone will require additional lateral access. Lateral access can be improved through a transeptal approach often combined with removing varying amounts of the medial maxillary wall.

Transeptal approach

Although various transeptal approaches have been described, they are all variations of the concept of non-opposing septal incisions described by Douglas et al.[35] This procedure allows use of the contralateral nostril for instruments or endoscopes thereby increasing the horizontal plane of access. The additional advantage it confers is that it allows a second surgeon to be involved to provide retraction and additional instrumentation when required. Although septal perforation is a risk of this approach, it can be reduced by preserving rather than resecting septal cartilage, and ensuring that the mucosal incisions on either side of the septum are not opposing (**Figure 114.4**).

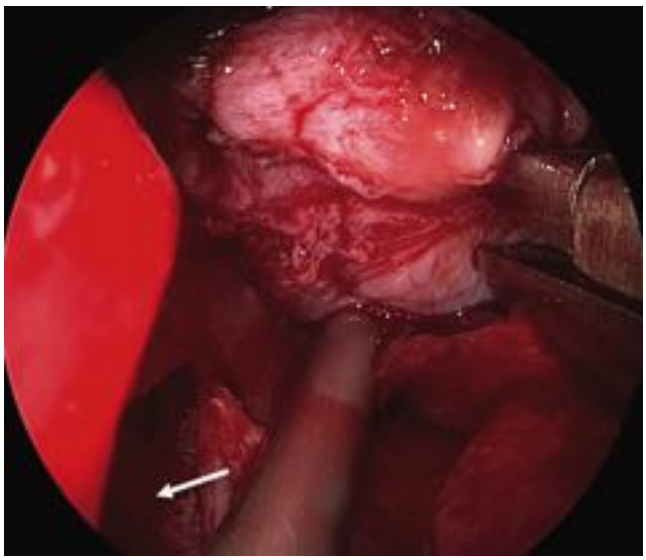


Figure 114.4 This image demonstrates the utility of the trans-septal approach. Here a patient with a Juvenile Nasal Angiofibroma has the mass manipulated via an instrument in the contralateral nostril placed through the transeptal incision (arrow) and the ipsilateral nostril.

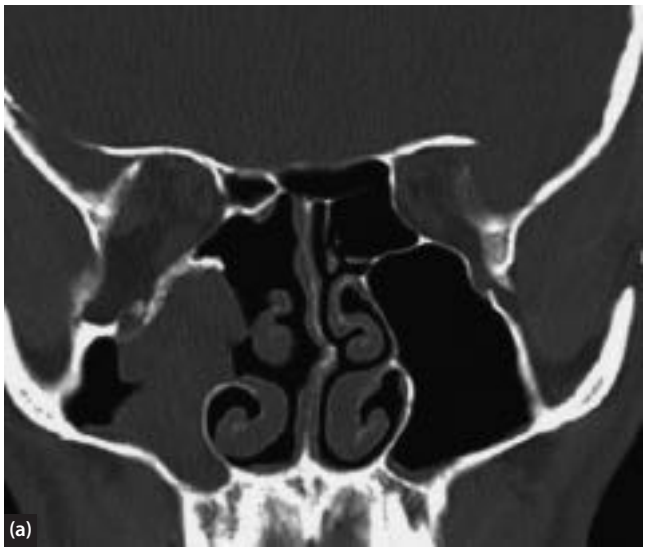
Transmaxillary approaches

Surgery for lesions involving the maxillary sinus typically commences by performing a routine uncinectomy to identify the natural maxillary ostium. Depending on the size and location of the tumour, the antrostomy can then be enlarged accordingly. Posteriorly based lesions, including those extending into the pterygopalatine fossa, located medial to the infra-orbital nerve can usually be accessed with a mega-antrostomy. Lesions located lateral to the infra-orbital nerve or those involving the infratemporal fossa require more extensive resection of the medial maxillary wall. A modified medial maxillectomy allows preservation of the lacrimal duct by extending the mega-antrostomy inferiorly below Hasner's valve to the piriform aperture. This approach allows inferiolateral access to the maxillary sinus (Figure 114.5).

For more superiorly based lesions, a total medial maxillectomy is needed with transection of the nasolacrimal duct. Although this approach confers an inherent risk of epiphoria, this can be minimized with clean sharp transection of the duct followed by probing and splaying the duct open. The anterolateral area of the maxillary sinus is considered the most difficult to access endoscopically. The pre-lacrimal approach as described by Zhou et al[36] is a modification of the Denker's procedure, that allows direct access to this area, with reduced alar retraction, collapse and risk to the canine root. In this procedure, following reflection of the soft tissues and mucosa of the anterior aspect of the inferior turbinate, osteotomies are used to remove a small buttress of bone at the junction of the antero-medial walls of the maxillary sinus, adjacent to the pre-lacrimal recess, with the nasolacrimal duct visualized and left intact. Through this window, the surgeon has direct access to the entire maxillary sinus including the anterior and lateral walls. Tumours can be carefully removed from these regions and sites of origin/attachment can be directly addressed (Figure 114.6).

IMPROVING POSTERIOR ACCESS

Binasal access provides the key to addressing tumours involving the nasopharynx, sphenoid sinus, pituitary fossa and the infratemporal and pterygopalatine fossae. The creation of an adequately sized posterior septectomy affords such access. Through this septal window,



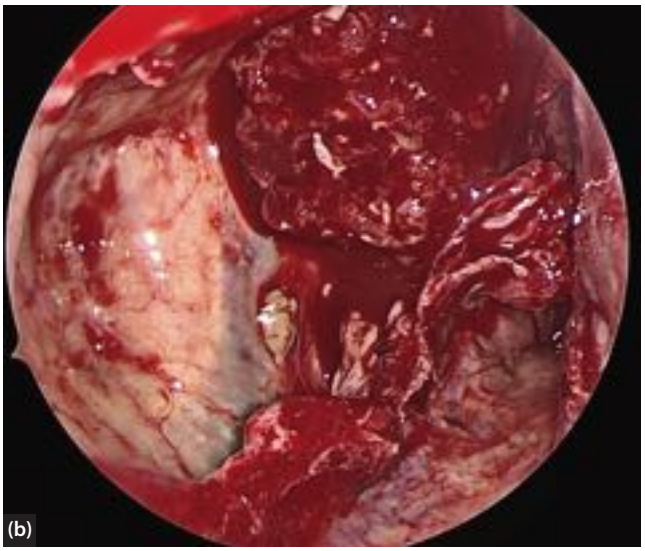




Figure 114.5 (a) Coronal CT of the sinuses showing a right maxillary inverted papilloma arising from the roof of the maxillary sinus medial to the infra-orbital nerve. The area of osteitis often indicates the site of origin; **(b and c)** demonstrate the site of origin of the inverted papilloma prior to **(b)** and after **(c)** it has been removed, drilled down and cauterized to reduce the chance of recurrence. The black arrow indicates the infraorbital nerve.

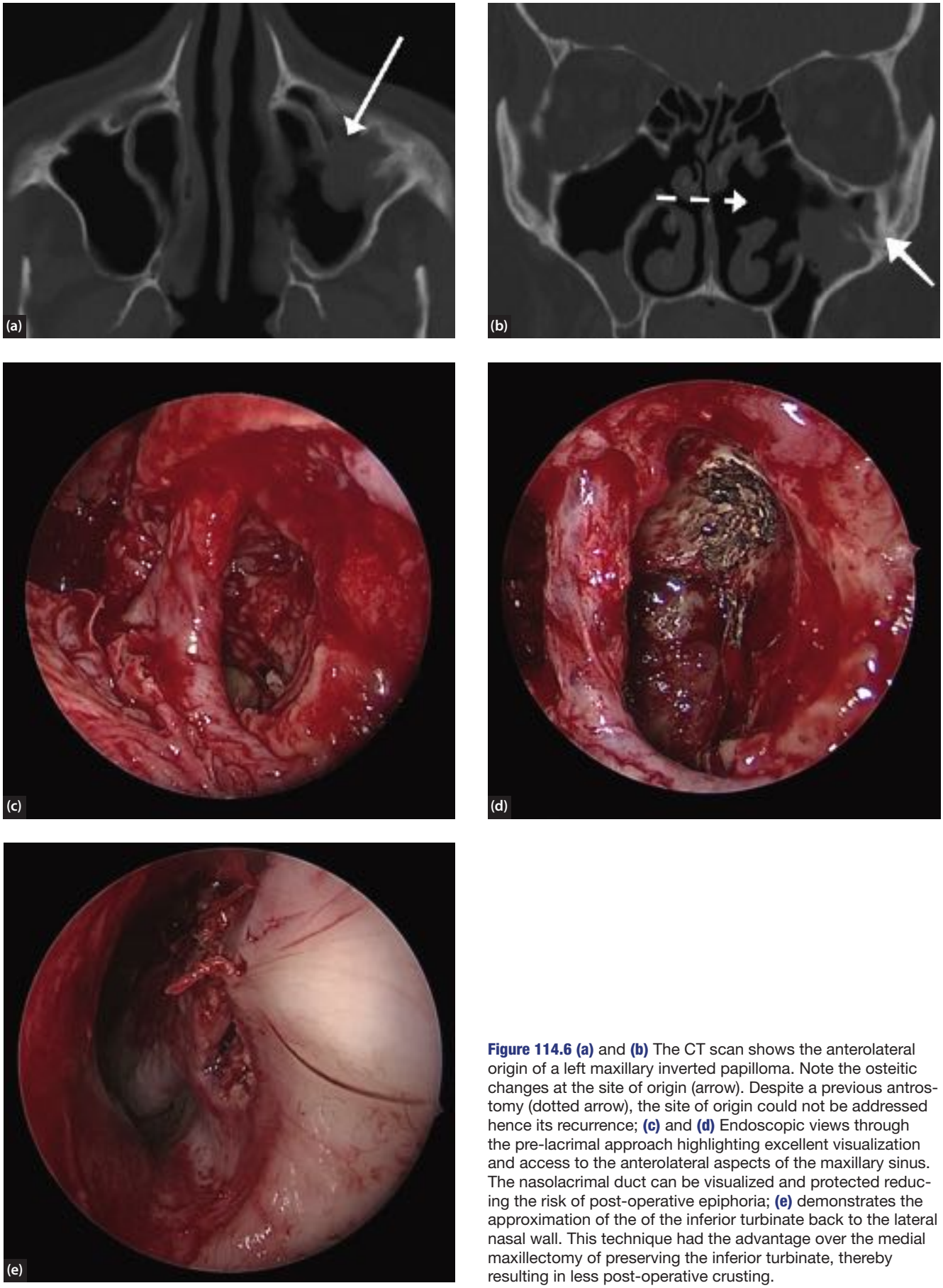


Figure 114.6 (a) and **(b)** The CT scan shows the anterolateral origin of a left maxillary inverted papilloma. Note the osteitic changes at the site of origin (arrow). Despite a previous antrostomy (dotted arrow), the site of origin could not be addressed hence its recurrence; **(c)** and **(d)** Endoscopic views through the pre-lacrimal approach highlighting excellent visualization and access to the anterolateral aspects of the maxillary sinus. The nasolacrimal duct can be visualized and protected reducing the risk of post-operative epiphoria; **(e)** demonstrates the approximation of the of the inferior turbinate back to the lateral nasal wall. This technique had the advantage over the medial maxillectomy of preserving the inferior turbinate, thereby resulting in less post-operative crusting.

a two-surgeon team can utilize an endoscope and up to three surgical instruments to reach the aforementioned posterior regions.

Posterior septectomy

Before performing a posterior septectomy, the surgeon must consider whether a nasoseptal flap will be required for reconstruction. This flap is based on the posterior septal artery, a branch of the sphenopalatine artery, and runs just below the sphenoid ostium to supply the majority of the septal mucosa. If a CSF leak is anticipated, the nasoseptal flap is typically raised before performing the septectomy and then stored either in the nasopharynx or in the maxillary sinus. If a leak is not anticipated, the surgeon must still take care to preserve the pedicle in case a flap may be required later. At this stage, the sphenoid ostia are located on either side and enlarged superiorly to the skull base and laterally to the lamina papyracea. Wide exposure allows visualization of the bony landmarks of the internal carotid artery and optic nerves and avoids inadvertent injury. With this exposure, the surgeon can then perform an appropriately-sized septectomy depending on the access required. For sellar lesions, a limited septectomy may be all that is necessary and this typically involves removing the posterior and inferior aspect of the septum with powered instrumentation or retrograde forceps. The septal window should extend anteriorly enough to enable complete visualization of the entire surgical field and limit contralateral instrument clash. An even larger septectomy will be required for surgery involving the middle cranial fossa, clivus and infratemporal fossae. Where possible, surgeons should attempt to preserve at least 1.5 cm of postero-superior septal mucosa in the region of the olfactory cleft for preservation of smell and taste (**Figure 114.7**). Obviously in the case of malignant tumours, surgical clearance of the tumour takes precedence but patients

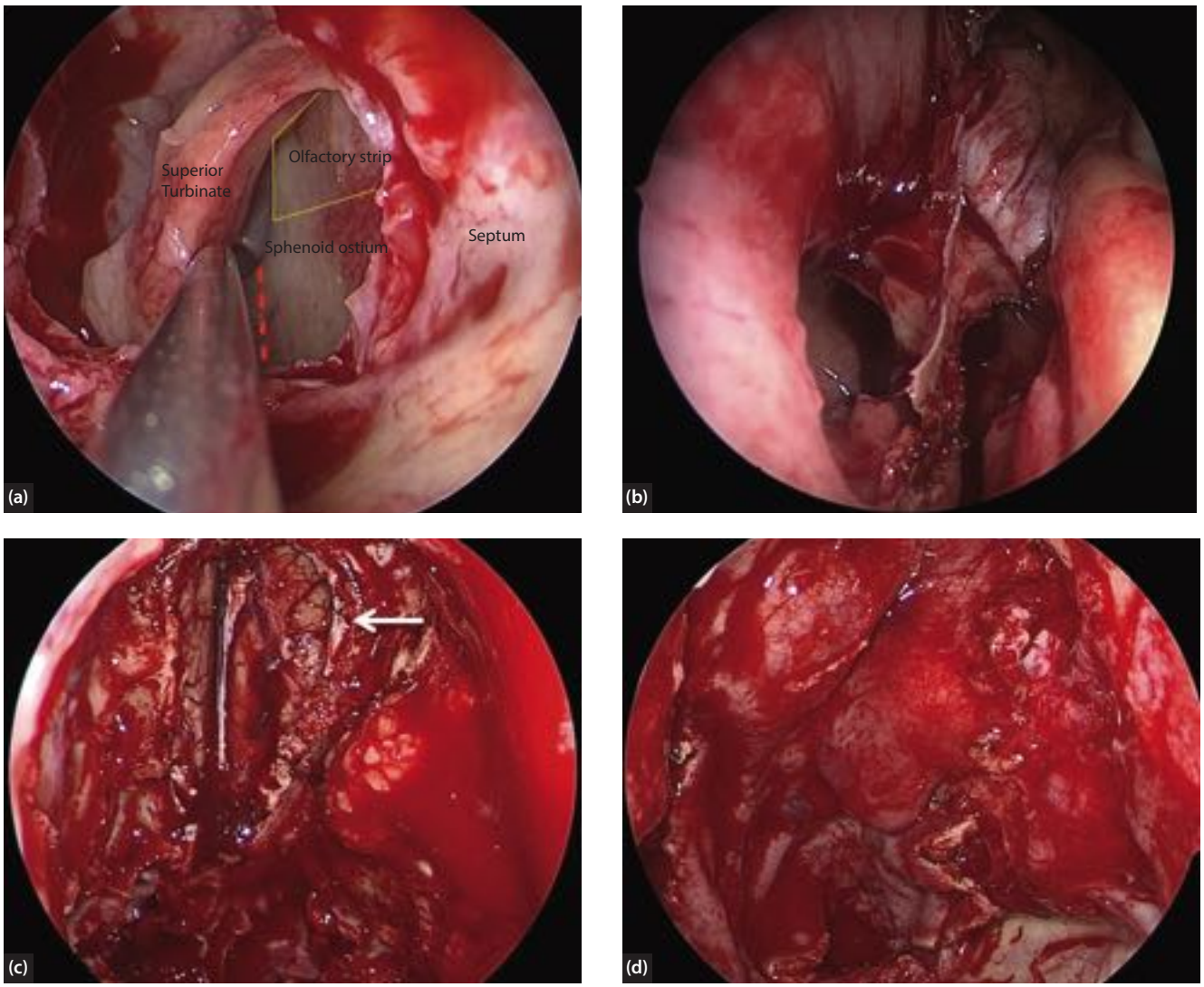


Figure 114.7 (a) Shows an endoscopic view of the nasal cavity and septum via the transethmoid approach. Highlighted in yellow is the olfactory strip that needs to be preserved when harvesting the flap. The red dotted line is the area of the vascular predicle supplying the flap. This should not be violated; **(b)** demonstrates the right nasoseptal flap reflected into the post nasal space. **(c)** shows a skull base defect of the anterior cranial fossa following resection of an aesthesioneuroblastoma. The white arrow represents the edge of the skull base defect and **(d)** shows reconstruction of the defect with a large nasoseptal flap.

should be warned pre-operatively of the possible loss of function of these senses.

IMPROVING SUPERIOR ACCESS

All aspects of the anterior skull base can be accessed endoscopically allowing the complete endoscopic resection of sinonasal tumours with intra-cranial extension. The anterior ethmoid artery provides a useful landmark when planning surgery for these lesions. If the intracranial component lies posterior to these vessels, targeted resection of the posterior skull base can usually provide adequate access for tumour removal. If however, the intracranial extent of the tumour lies anterior to the level of the anterior ethmoid arteries, an endoscopic modified lothrop procedure (EMLP) will typically be required to access the anterior aspect of the tumour. The EMLP also improves lateral access to lesions within the frontal sinus. Through a superior septectomy, surgeons can use the contralateral nostril to reach lesions well beyond the frontal recess and even beyond the mid-pupillary line. This not only avoids the need for external incisions, but also increases the ease of post-operative surveillance. The surgical site can be directly visualized endoscopically, reducing the need for as frequent imaging.

Tumour resection

Once appropriate access has been created, the tumour can then be debulked in a controlled manner down to its site of attachment. Debulking can be performed using various instruments including powered micro-debriders and radio-frequency ablation wands. Specimen traps should be applied to instruments, so that all of the tumour removed from the patient can be sent for histopathological analysis. Following debulking of the tumour, the site of attachment is usually visualized. The management of this region depends on numerous factors, including the age and functional state of the patient, the histology of the tumour and the location and extent of the attachment. Where possible, attainment of clear surgical margins should be attempted. Frozen sections taken from the margins of the tumour field have been shown to be reliable for ensuring complete resection of most sinonasal tumours, with the exception of mucosal melanoma and adenoid cystic tumours.[37] In addition to these frozen specimens, surgical margin specimens should also be sent in formalin fixative for formal histopathological analysis. Careful orientation of specimens and close discussion with the histopathologists should be undertaken for all specimens, to aid in the generation of an accurate histological report and to avoid errors such as the air-tumour interface being erroneously reported as a positive margin.

Whilst the ultimate goal of surgery is a complete oncological resection of the tumour, the nature of the tumour and the characteristics of the individual patient may, on occasion, necessitate a degree of compromise. Benign tumours may be appropriate for sub-total resections with post-operative surveillance where there is significant risk to critical structures or in the elderly frail population. Malignant tumours may also be palliated in this fashion while limiting morbidity from the resection.

Reconstruction

Sinonasal tumour resection may result in a defect in the skull base. If the dura remains intact, and the defect is small, it may be left alone, but large defects and all breaches of the dura should be repaired to avoid meningoencephalocele formation and ascending meningitis.

Small defects (< 1cm) in the dura mater are typically amenable to a 'Bath Plug' type repair as described by Wormald.[38] Larger defects, however, will usually require multi-layer closure with an underlay of autogenic material such as tensor facia lata harvested from the thigh or dural substitutes (e.g. Duragen®, Integra Life Sciences, Plainsboro, New Jersey USA), followed by an overlay which may be a free-mucosal graft or in most cases a vascularized flap. The most commonly employed vascularized flap is the Hadad nasoseptal flap,[39] described in the previous section, but inferior and middle turbinate flaps have also been successfully used. For very large defects (> 3 cm), reinforcement of the repair site with a rigid buttress of septal cartilage or titanium mesh is also thought necessary, prior to coverage with the mucosal flap, to minimize the risk of encephalocele formation.

Complications of endoscopic techniques

Endoscopic approaches to sinonasal tumours share the minor and major complications seen in endoscopic sinus surgery. Surgeons who wish to perform endoscopic skull base surgery must make themselves familiar with these complications and their management. A thorough understanding of the surgical and radiological anatomy of the sinuses and skull base and the attendance of skull base courses may help to minimize their frequency and severity. Of all the complications, major vascular injury is one of the most serious and anxiety provoking. Through animal wet labs, Valentine and Wormald have developed and evaluated several techniques for controlling such injuries, including the use of the muscle patch.[40] They showed that the application of crushed muscle to the site of a major arterial bleed could primarily control the bleed in all cases while maintaining vascular patency. This led to reduced blood loss and overall improved survival.[41] A follow-up study by the same group highlighted the benefits of surgeons undergoing training in this technique before undertaking complex skull base cases.[41]

POST-OPERATIVE CARE AND TUMOUR SURVEILLANCE

Once the initial perioperative period is complete, the role of the surgeon moves to one of surveillance for recurrence. Surveillance is performed with regular endoscopic examinations and serial imaging. Performance of an early post-operative CT or MRI scan within 3–6 months post-surgery provides a baseline that can be referenced,

should the patient develop clinical features suggestive of recurrence.

CONCLUSION

Published data now support the use of endoscopic techniques for the management of appropriately selected benign and malignant tumours of the paranasal sinuses. The decision to undertake such a resection should ultimately be made by a multidisciplinary team that has considered the patient, the pathology in question and the skill set of the endoscopic skull base team. With appropriate training and surgical planning, complications can be minimized and outcomes can become more predictable.

FUTURE RESEARCH

➤ New technology and increased experience continues to advance the field of endoscopic sinus and skull base surgery. Although still in early development, real-time intra-operative imaging, 3-dimensional endoscopes and remotely controlled robotic instrumentation hold promise in their application to this field. Such technology may one day further improve the safety and oncological results of endoscopic skull base procedures.

KEY POINTS

- The operating surgeon must understand the anatomy of the paranasal sinuses and the nature of the pathology to be managed.
- A comprehensive history and examination with review of radiology and biopsy specimens will enable a safe and effective plan to be formulated for the endoscopic approach to sinonasal tumours.
- The surgeon must be aware of the limitations of his or her individual endoscopic skills and the capabilities of the other teams involved to ensure that case selection is appropriate.
- Endoscopic skills and equipment are rapidly evolving, thus surgeons must remain current in their knowledge and skill development to undertake this complex surgery.

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CHAPTER 115

SURGICAL MANAGEMENT OF PITUITARY AND PARASELLAR DISEASES

Philip G. Chen and Peter-John Wormald

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the following keywords: pituitary adenoma, pituitary gland, transsphenoidal pituitary resection, sella, transsellar approach and endoscopic skull base surgery.

INTRODUCTION

History

For years, the surgical approach to the central skull base has been a challenge for surgeons given its relatively inaccessible location. A number of pathologies occur in this region and examples include pituitary adenomas, meningiomas, chordomas, germ cell tumours, and epidermoid cysts.

Sir Victor Horsley is credited with performing the first removal of a pituitary tumour in 1889, using a craniotomy with transfrontal route.[1] Shortly thereafter, Herman Schloffer[2] (1907) utilized a transfacial-transsphenoidal approach to the pituitary fossa, and he was followed by Oskar Hirsch[3] (1909) who used a transnasal transseptal route. Another pioneer of the transnasal route was Harvey Cushing but he eventually abandoned it for open surgery.[2, 4] Pituitary surgery continued to evolve through the 1950s as notable surgeons such as Gerard Guiot realized the merits of the transsphenoidal approach.[5] In the 1960s, James Hardy took advantage of the increasing availability and visualization provided by use of the operative microscope to perform the first microsurgical pituitary surgery via a transsphenoidal route.[6] This became the standard approach for pituitary and sella surgery.

In the early 1990s technological advances in optics, digital cameras, light sources, and monitors afforded surgeons a high-resolution view that was sufficient to safely perform intra-nasal surgery without external incisions. With growing experience in endoscopic sinus surgery, efforts began to expand use of the endoscope to assist in skull base surgery. In 1992, Jankowski published the first description of a fully endoscopic transnasal technique for the pituitary gland.[7]

Microscopic approaches

The transition from open approaches to microscopic was accepted, as there was no brain retraction, decreased wound breakdown, shorter hospitalization, and no scar. The sublabial-transseptal microscopic approach is time tested and has been the standard of care for years. A sublabial incision is made followed by elevation of the septal mucosa off the septal cartilage and bones. The quadrangular cartilage is fractured laterally and bony septum removed followed by removal of the bony sphenoid face. The resulting microscopic view is straight into the sella. A variation is the transseptal approach with a hemitransfixion incision using a self-retaining retractor between the mucosal flaps. While effective, the microscopic view is limited by the speculum with an inability to visualize lateral extension of tumour.

Transition to endoscopic approaches

The use of the rigid endoscope in lieu of the microscope was initially met with resistance by some surgeons. Nonetheless, endoscopic approaches have rapidly gained popularity as experience has grown, and outcomes appear at least as favourable as microscopic approaches.[8, 9] Proponents of an endoscopic transsphenoidal approach

to the pituitary and surrounding structures suggest that benefits over microscopic surgery include decreased pain and damage to the nasal mucosa, an improved panoramic view, and good mobility with angled views. Furthermore, there is no external incision or associated numbness which occurs with the sublabial approach. The wide angle provided by the endoscope allows the critical landmarks and tumour to be seen in the same field of view, even in regions which are difficult to see and access (**Figure 115.1**). This is especially helpful when tumour extends beyond the limits of the sella turcica, with an improved ability to remove these tumour extensions and decrease the risk of residual or recurrent diease.[9–11]

Endoscopic surgery of the sellar region requires two surgeons. One surgeon holds the endoscope to provide the second surgeon an optimal view to perform the surgical dissection bimanually. Skilled endoscopic sinus surgeons have a vast experience in the approach to and operating within the sphenoid sinus and can provide fast and efficient access to the sella and skull base. Neurosurgeons with experience in pituitary surgery understand the surgical technique and complexities of operating in this region. Together, these two surgeons form an experienced team that can safely access and remove tumours of the sellar and parasellar regions. These teams should initially gain experience in the endoscopic management of pituitary tumours and learn the nuances of having two to three instruments and an endoscope in the sphenoid simultaneously. This creates challenges for the team in learning how to best prevent the crossing of instruments as well as access to tumour extensions especially in challenging areas. For this learning curve in endoscopic skull base surgery, Snyderman and colleagues described a categorization of cases into five levels of difficulty.[12] With regard to surgery of the sellar and parasellar regions, level II cases have pathology confined to the sella. Level III cases exhibit extrasellar extension but also remain extradural, while intra-dural dissection elevates complexity to level IV out of V.

Pituitary tumours make up the vast majority of endoscopic transsellar surgery,[13] but additional skull base pathologies within the sella turica and parasellar region can be addressed in a similar fashion.[14] Other pathologies include lesions such as Rathke cleft cysts, craniopharyngiomas, fibrous dysplasia, chordomas, chondrosarcomas, epidermoid cysts, and meningiomas.

PRE-OPERATIVE ASSESSMENT

History and physical examination

Prior to embarking upon any surgery, it is critical that the surgeons understand the patient's pathology, extent of disease, neurological deficits, concurrent head and neck disease, and other co-morbidites. A comprehensive history should always be obtained with a full head and neck examination. Special attention should be paid to the cranial nerves which pass through the cavernous sinus. Visual status such as acuity, visual fields, and gaze restrictions may be best performed by an ophthalmologist. Inclusion of rigid nasal endoscopy is also warranted to determine whether sinonasal disease or anatomic obstructions are present which would need to be addressed during surgery. Particularly when pituitary tumour surgery is to be performed, an endocrinologist should be involved in the patient's care, and the patient's hormonal status and pituitary function should be determined prior to surgery.

Imaging

Radiographic imaging is critical to preparing for skull base surgery, and details of skull base and sellar region imaging are covered in detail elsewhere in this text. The primary goal of the otolaryngologist is to gain wide transnasal access to the sella (**Figure 115.2**). All patients require

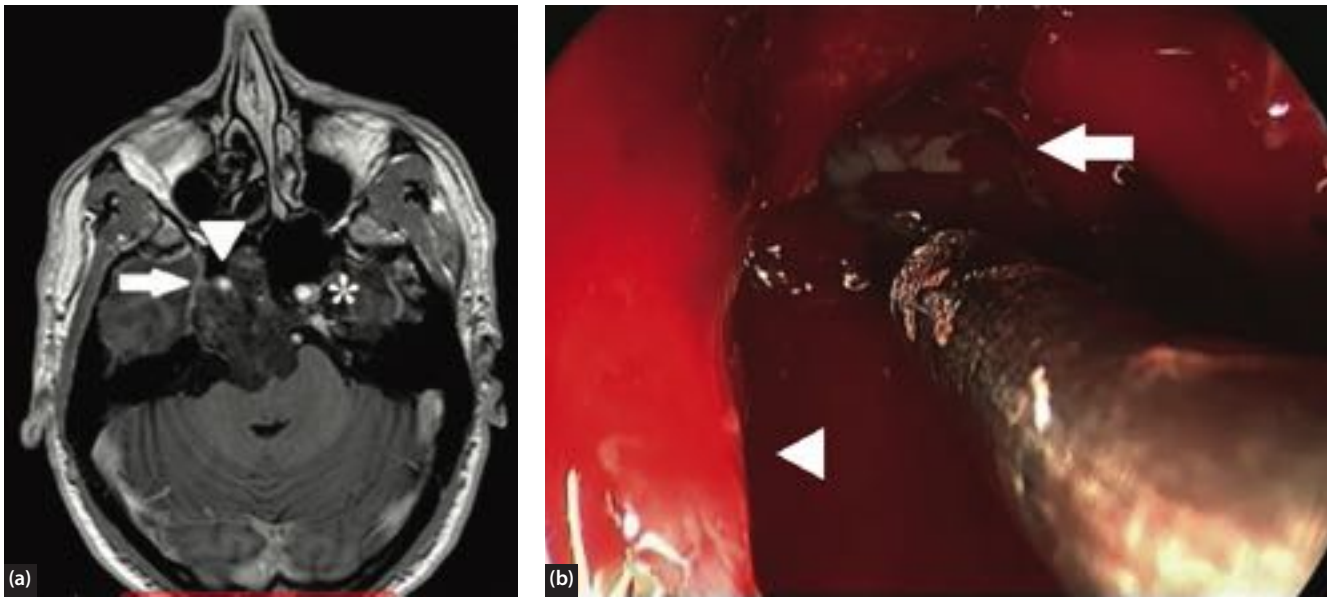


Figure 115.1 (a) MRI chordoma axial labelled. **(b)** Residual tumour.

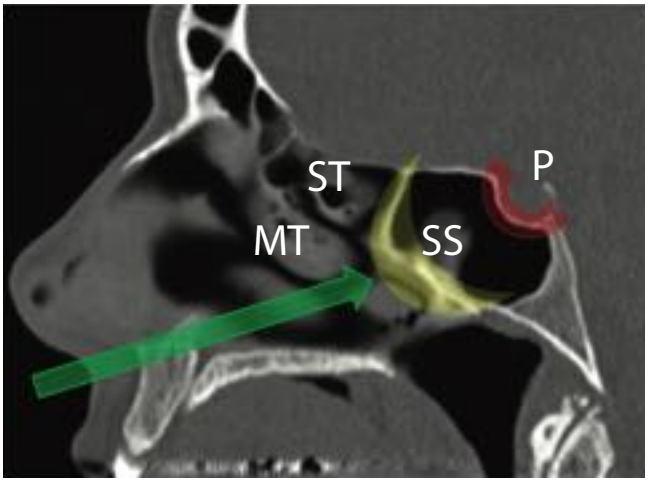


Figure 115.2 CT sella approach.

a computed tomography (CT) scan of the sinuses. Bone windows are helpful to determine presence of tumour invasion or bony remodelling. Further, review of CT scans helps delineate sinonasal disease, septal deviation (which helps with planning of a nasoseptal flap), sinus aeration, access to the sphenoid sinus, and anatomical variations such as Onodi cells, sphenoid intersinus septa, and the course of the carotid artery and optic nerve as well as potential areas of dehiscence (**Figure 115.3**). If there is additional concern about the carotid artery, a CT angiogram is indicated.

In addition to CT, an MRI with image guidance navigation (IGN) protocol should be obtained. This assists with pre-operative planning by differentiating tumour mass from obstructed mucus/fluid. Further, MRI is superior to CT in providing information about tumour morphology and whether dural enhancement or invasion is present. Image guidance is routinely used for all skull base cases, and this practice is widespread at large skull base centres.[15, 16] IGN is never a substitute for thorough understanding of the patient's individual anatomy, but rather should confirm the surgeons' anatomical knowledge. It may be especially helpful for revision cases, challenging anatomy, resident teaching, expanded transsphenoidal approaches, and when extrasellar extension is present.[16] Additional benefits have been reported including improved accuracy, reduced morbidity, and shorter duration of intensive care stays.[17] However, there is associated set-up time and the systems require some practice to become familiar with them. The surgeons must know the limitations of IGN and realize the system is not always accurate.



Figure 115.3 (a) CT intersinus septum carotid opt cor. **(b)** CT intersinus-septum carotid artery.

ENDOSCOPIC TRANSSPHENOIDAL APPROACH TO SELLA

Pre-operative considerations

Optimizing the nasal cavity for an endoscopic approach is an important first objective of the surgery. This includes assessing the CT scan for the need to remove the lateral wall of a concha bullosa or in some cases, the entire middle turbinate. Septal deviations and need for a septoplasty is evaluated. The transsphenoidal approach can be expanded to transplanum, transclival/transodontoid, and transpterygoid approaches as dictated by the size, type, and extent of the tumour.

The operating theatre is set up for a two-surgeon approach, and usually this is best accomplished by turning the table so that the anaesthetist is at the foot of the patient. The patient should be catheterized for accurate fluid balance management, especially with the risk of diabetes insipitus during pituitary tumour removal. We have found that lumbar drains are not routinely required even if a CSF leak is created during surgery. This prevents the potential complications associated with lumbar drains. Routine broad spectrum prophylactic antibiotic cover is given and the nose is decongested as for sinus surgery with topical and local vasoconstrictive agents. A surgical

preparation of abdomen or thigh as a graft donor site is performed. We prepare the abdomen to harvest fat and rectus abdominis fascia in most pituitary tumours, but prepare the right thigh for fat and fascia lata when larger defects are anticipated (craniopharyngiomas, meningiomas, chordomas, etc.). Image guidance is set up usually with a scuba head strap for the electromagnetic IGN system and then the patient is registered.

The head of bed is placed in the reverse Trendelenburg position to decrease venous congestion and bleeding in the operative field. Instruments include the standard sinus and endoscopic skull base instruments, a high-speed drill, bipolar forceps, and an endoscopic ultrasonic aspirator.

Surgical technique

The first step in the surgery is optimizing the nasal cavity. Anatomical obstructions are addressed, such as performing septoplasty and removal of concha bullosa. Eliminating these obstructions improves access and passing of instruments from both sides of the nose. This decreases the risk of striking instruments against the septum which increases bleeding, damages mucosa, and slows surgery. In extended pituitary approaches (substantial opening of the arachnoid mater), a septal flap should be raised.[18] If one is unsure whether a pedicled septal flap will be required, then the vascular pedicle of the flap should be preserved on one side. This is accomplished by placing an incision from the lower edge of the natural ostium of the sphenoid and carrying this incision anterior and horizontal for about 3–4 cm. A suction Freer is used to mobilize this flap to the level of the posterior bony choana (**Figure 115.4**). This will allow the anterior face of the sphenoid to be widely opened while allowing the mobilized mucosa with the posterior nasal artery to be preserved. This ensures that should a septal flap be needed for reconstruction of the skull base or for closure of a large CSF leak, that the flap can still be raised and utilized.

Access to the sella should be created bilaterally to increase the working space for the binasal two-surgeon approach. Wide access yields improve visualization and allows space for the endoscope to be placed out of the way of the suction and dissecting instruments during surgery. The middle corridor of the nasal passage is widened by lateralizing the middle turbinates to expose the sphenoethmoidal recess and superior turbinate. The inferior half of the superior turbinate is removed flush with the face of the sphenoid sinus (**Figure 115.5a**). In many patients, the sphenoid ostium is clearly identified medial to the superior turbinate at the junction of the lower third and upper two-thirds of superior turbinate.[19] If the natural ostium is not visible the blunt end of the 4 mm microdebrider blade can be used to measure 12 mm from the posterior choanae.[20] A blunt Freer elevator is used to palpate the sphenoid face and identify the ostium. Entry with a Freer has a low risk of injuring the critical structures housed within the sphenoid sinus. The sphenoid ostium is widened and the posterior ethmoids opened so the sphenoid ostium can be widened to the lamina papyracea (**Figure 115.5a**). The final size of the sphenoidotomy should be from septum to lamina laterally, and from the roof of sphenoid to the floor of the sphenoid vertically. The Hajek-Koffler and Kerrison punches are ideal to for this purpose. While the bites are aggressive enough to make rapid progress, the biting mechanism minimizes the risk of inadvertently damaging the optic nerve and carotid artery (**Figure 115.5b**). At this point the mucosa of each side of the sphenoid should be elevated from medial to lateral leaving the lateral mucosa still attached to the bone (**Figure 115.5c**). This provides two mucosal flaps that can be used to reconstitute the anterior face of the pituitary fossa at the end of surgery. However, these mucosal flaps are removed if a pedicled septal flap is utilized.

To maximize access and to prevent the posterior edge of the septum being pushed into the endoscope thereby limiting visualization, a posterior septectomy is performed. This can be completed with the microdebrider, scalpel, or large backbiting forceps. If the microdebrider is used, care is taken to protect the pedicle of the septal flap and therefore the septectomy is only performed above the previously mobilized pedicle. Usually about 1–1.5 cm of the posterior edge of the septum is removed (**Figure 115.5d**). Intersinus septations are carefully removed using a rongeur or diamond drill, being conscious that septations frequently veer towards the carotid artery and/or optic nerve (**Figure 115.5f**). Septations are removed flush with the face of the sella. The medial[21] and lateral opticocarotid recesses are identified along with the anterior genu of the carotid arteries and both optic nerves (**Figure 115.5f**). Confirmation of these structures is obtained by using the image guidance suction probe. These limits define the planned bony exposure of the sella and identification reduces the likelihood of damaging them during the bone removal.

In most patients with a pituitary macroadenoma, the sellar face will be soft due to tumour expansion and pressure on the bone. A Freer elevator is used to gently fracture the bone giving an edge for placement of the 2 mm forward biting Kerrison punch. Alternatively, if the bone is hard (often seen with microadenomas), a diamond burr is used to "eggshell" the bone so it can be gently fractured

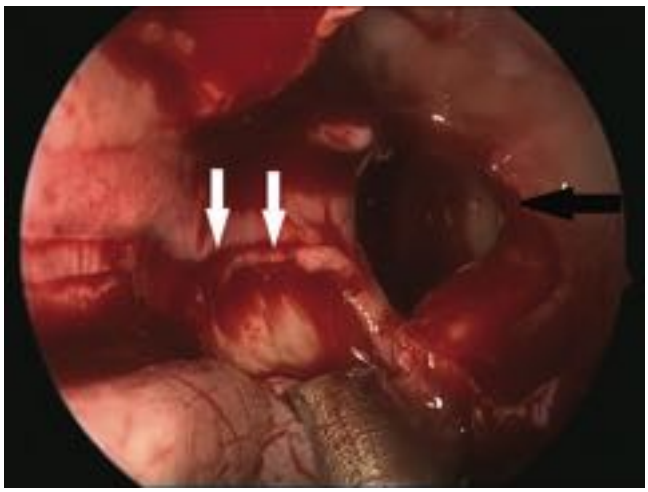


Figure 115.4 Septal flap.

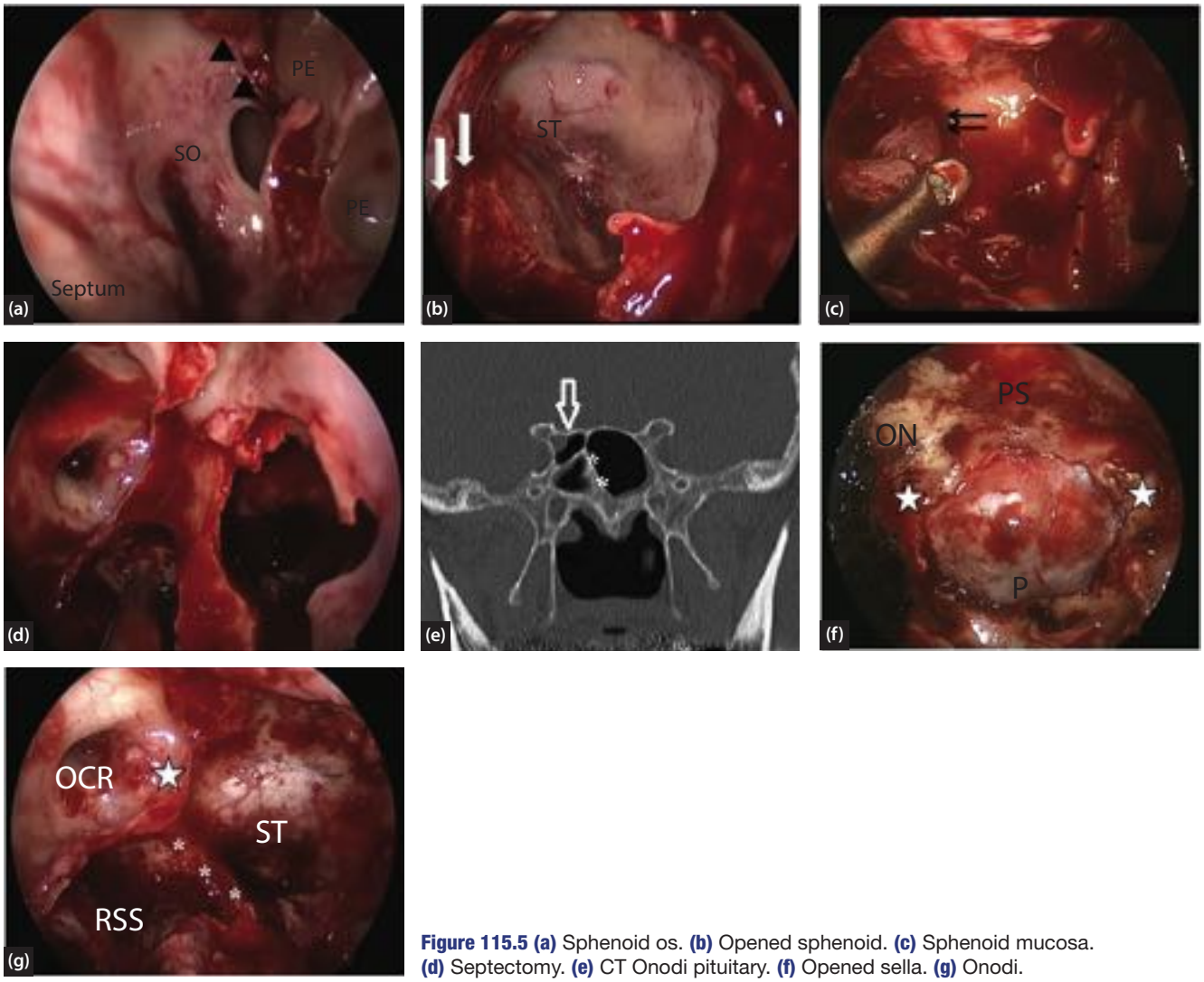


Figure 115.5 (a) Sphenoid os. **(b)** Opened sphenoid. **(c)** Sphenoid mucosa. **(d)** Septectomy. **(e)** CT Onodi pituitary. **(f)** Opened sella. **(g)** Onodi.

and removed. The Kerrison punch is used to remove the bone off the dura exposing the underlying dura from one cavernous sinus to the other and from the pituitary fossa floor to just below the tuberculum sella (Figure 115.5f). Once bone removal is complete the surgeon must be able to easily pass instruments below the pituitary fossa and from one sphenoid wall to the other. Creating this large space allows significant freedom of movement for the instruments without the bony walls of the sphenoid limiting access to any part of the sellar or parasellar region.

The dura is opened with a retractable blade or a number 11 blade in a U-shaped incision placed a few millimetres medial to each cavernous sinus and joined at the floor of the sella. This produces a superiorly based U-shaped flap which gives the best possible exposure of the fossa (Figure 115.6a). Cruciate incisions are no longer used as the visualization after such an incision is poor compared to the U-shaped incision.

In patients with macroadenomas the tumour should be immediately apparent and tissue is taken and sent for histology (Figure 115.6b). In patients with microadenomas, the MRI scan and image guidance can be helpful in identifying the tumour. An attempt is made to complete an extracapsular resection of these tumours thereby improving the chances of complete resection. Tumours have varying consistency from soft to firm, and the best instruments for removal will depend on the consistency. They may remain confined to the sella turcica or may extend into the parasellar and suprasellar regions. In cases of parasellar extension, a 30° angled endoscope is very useful to access tumour under vision and appreciate the full extent of the disease. This visualization is paramount to ensuring comprehensive removal, and achieving such views is not possible with microscopic approaches. Figure 115.1b is an example of a tumour that has grown laterally and behind the cavernous segment of the carotid artery. This extension would have been impossible to see with the microscope. It has been established that extrasellar extension is a risk factor for persistent disease;[22] thus, we aggressively chase tumour extensions in secreting tumours. However, our philosophy regarding extrasellar extension in cases of non-secreting adenomas is to resect what is relatively easy to remove without putting the patient at undue risk.

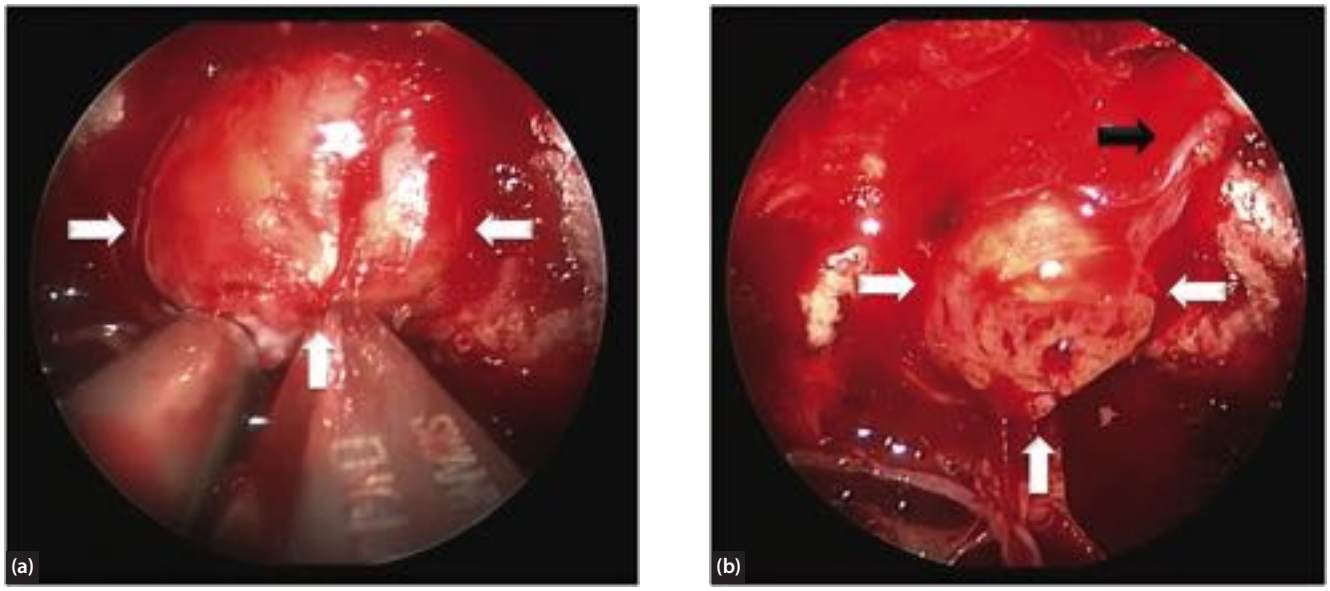


Figure 115.6 (a) Dural incision. **(b)** Tumour exposed.

After complete tumour removal, haemostasis is ensured using Gelfoam paste (made up of Gelfoam® powder (Pfizer Inc, New York, NY) and saline) and pressure from neuropathies. The pituitary fossa is gently filled with the paste and the dura placed over the paste. The sphenoid mucosal flaps are placed over the dura, secured with Surgicel® (Ethicon, Somerville, NJ) and fixed with a layer of fibrin glue. No packing is placed in the sphenoid sinus.

If a cerebrospinal fluid (CSF) leak is created during tumour removal, the diaphragm sellae defect is identified and a small triangle of fat placed into the defect ensuring cessation of the leak. An additional small piece of fat is placed in the sellar fossa with a layer of fascia over the fat. The dura and sphenoid mucosa are draped over the fascia followed by Surgicel® and fibrin glue. A layer of Gelfoam® is then placed over the glue followed by a ribbon gauze pack soaked in bismuth iodoform paraffin paste (BIPP) or antibiotic ointment. This is removed on day 3 post surgery. For large CSF leaks or in patients who have had an extended approach with a defect in the arachnoid mater, the pedicled septal flap is raised.[18] The fascia (or dural substitute such as DuraGen™ (Integra LifeSciences Corp., Plainsboro, NJ)) is placed as an underlay intra-cranial graft with the pedicled septal flap placed over this graft onto the bone of the defect. The edges of the flap are secured with Surgicel® and fibrin glue and the repair covered with Gelfoam® and the sinus packed with ribbon gauze soaked in BIPP for 3 to 7 days depending on the size of the defect.

SURGICAL APPROACH FOR PARASELLAR (CARVENOUS SINUS) EXTENSION

Parasellar extension beyond the pituitary fossa is initially dealt with as above. In some cases, tumour may extend anterior to the carotid before entering the cavernous sinus (Figure 115.7a). As per our philosophy, such tumour extensions are only addressed in secreting tumours as the risks outweigh the benefits in benign non-secreting tumours.

When lateral access is required, bone anterior to the anterior genu of the cavernous carotid artery is very gently removed. It is often safest to perform osteotomies with a 2 mm diamond burr on this bone and then to use a blunt hook to dissect the carotid from this bone before fracturing this bone (osteotomies control the fracture points) and removing it to expose the carotid artery. After complete

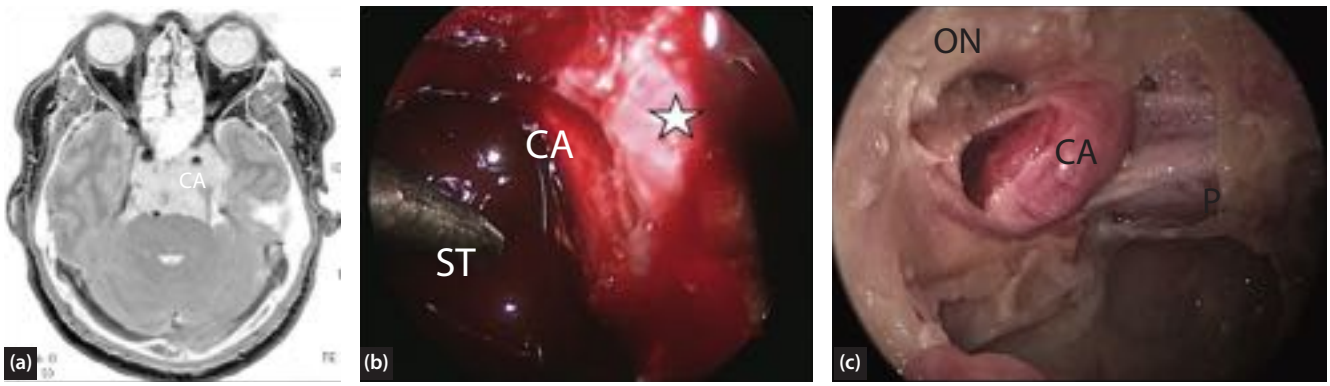


Figure 115.7 (a) MRI tumour encase L carotid. **(b)** Lateral to carotid intraop. **(c)** Far lateral approach.

exposure of the anterior genu of the artery, the cavernous sinus can be approached from anterior and lateral to the carotid (**Figures 115.7b** and **115.7c**). Post-tumour removal, the exposed carotid artery should be covered by the pedicled septal flap.

COMPLICATIONS

Delayed complications

The most common complication is CSF leak. Our philosophy is not to limit tumour resection because of fear of creating a CSF leak. We feel that we can successfully deal with any CSF leak at the end of the surgery. However, a post-operative CSF leak is a complication, and while this does occur the accepted rate of post-operative CSF leaks should be less than 5%. We use a multilayer closure including use of fibrin glue and a sphenoid sinus pack to maximally bolster the skull base repair and prevent a post-operative leak. Currently our post-operative CSF leak rate is under 5% with this protocol. Should a post-operative CSF leak occur, the patient is kept on bedrest and a lumbar drain is placed. If, despite these measures, the leak does not cease within 24 hours the patient returns to theatre for a formal closure. Other more common complications include mucosal scarring, hyposmia or anosmia, nasal crusting, and sinusitis.

Immediate complications

Immediate complications other than CSF leak include vision damage and both venous and arterial bleeding. The pre-operative imaging is very useful in preventing devastating complications; therefore, anatomical variations such as an Onodi cell (sphenoethmoidal cell) should be identified pre-operatively (**Figures 115.5e**, **115.5f**). The Onodi cell pneumatizes lateral and superior to the sphenoid sinus and the optic nerve often runs within it. Failure to identify this ahead of time places the optic nerve at risk. Similarly, the medial location of the carotid artery (**Figure 115.1a**) or an intersinus septum that attaches to the carotid artery is identified on imaging (**Figures 115.3a** and **115.3b**).

Carotid artery injury is a devastating complication with up to 30% of patients having neurological sequelae and an approximate 20% mortality rate.[23] Carotid injury is one of the most challenging endonasal situations requiring both calmness and skill from both surgeons.[24] Recently, an animal model has been created by our group to provide skull base surgeons with a realistic model where techniques of how to manage high-flow bleeding can be taught and these surgical skills can be practised. This model almost exactly replicates both significant cavernous sinus and carotid artery bleeding.[25] We have used this model to assess the best way to handle such a complication and recommend the use of crushed muscle as a patch on the bleeding vessel as the quickest, safest, and most effective way to handle such a complication.[26]

CONCLUSION

The endoscopic transsphenoidal approach is a safe and effective means to remove many tumours within the sellar and parasellar regions of the central skull base. With improvements in technology, combined with greater surgical experience, the boundaries of safe and effective endoscopic removal of tumours will continually be pushed with the goal of improving patient care.

KEY POINTS

- The endoscopic approach to stellar and parasellar lesions has benefits over the microscopic approach including angled visualization and a dynamic, mobile view. However, this approach requires two surgeons and the image is only in two dimensions.
- An endoscopic skull base surgery team consisting of a neurosurgeon and otolaryngologist should be formed to perform these cases. They should start on easier pathologies before advancing to more difficult cases such as laterally based tumours and those that are adjacent to critical structures.
- Wide nasal access is critical to facilitate visualization and complete tumour removal, which is best accomplished with a binaural approach.
- It is important to salvage the posterior nasal artery so that a nasoseptal flap can be used to cover this defect if a cerebrospinal fluid leak is encountered.

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CHAPTER 116

EXTENDED ANTERIOR SKULL BASE APPROACHES

Carl H. Snyderman, Paul A. Gardner, Juan C. Fernandez-Miranda and Eric W. Wang

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SEARCH STRATEGY

Data in this chapter may be updated by Medline and PubMed searches using the following keywords: anterior skull base, craniopharyngioma, endoscopic endonasal surgery, meningnioma, nasal dermoid, pituitary adenoma and sinonasal malignancy.

INTRODUCTION

A paradigm shift has occurred in skull base surgery over the last two decades with the introduction of endoscopic techniques for sinus surgery. Endoscopic techniques have been widely adopted for surgery of the pituitary gland and endoscopic endonasal surgery (EES) has been extended to include extrasellar regions of the ventral skull base. EES encompasses parasellar regions for the treatment of sellar pathology that extends to the cavernous sinus and suprasellar area, as well as the anterior cranial base.

The primary principle of EES is not endoscopic visualization but rather utilization of the endonasal corridor to provide optimal access with the least morbidity for the patient. For many tumours that are bounded by the neural and vascular structures of the cranial base, the endonasal corridor allows complete resection while minimizing manipulation of uninvolved cranial nerves, blood vessels, and brain tissue. In comparison to the microscope, the endoscope provides superior visualization with the capability of panoramic views and angled visual pathways. EES is team surgery, requiring the coordination of two specialties to achieve operative goals. Skull base team surgery is a dynamic process that results in enhanced visualization, increased efficiency, and improved communication and problem-solving.

CLASSIFICATION OF APPROACHES

Endonasal approaches to the ventral skull base are classified based on their orientation in sagittal and coronal radiological planes relative to the sphenoid sinus (Table 116.1).[1] The sphenoid sinus is the epicenter of endonasal skull base approaches since it is often the starting point for endoscopic skull base experience (pituitary surgery) and it is the location of critical anatomical structures (optic nerves, internal carotid arteries). Sagittal plane surgical modules extend from the frontal sinus to the sella, and from the sella to the upper cervical spine (C1/2). Coronal plane modules extend laterally, in correspondence with each cranial fossa (anterior, middle, and posterior).

The anterior cranial base extends from the sella to the frontal sinus in the midline plane and laterally across the orbital roof. Discrete sagittal plane modules include transfrontal, transcribriform, and transplanum approaches. These can be combined to provide complete access to the anterior cranial fossa for large intra-cranial tumours or excision of sinonasal malignancy that involves the skull base. For example, an endonasal resection of an aesthesioneuroblastoma includes transfrontal (Draf 3 frontal sinusotomy), transcribriform, and transplanum modules. Lateral margins of the anterior cranial base may be extended to the midline of the orbits by removal of the medial orbital roofs.

TABLE 116.1 Classification of endonasal approaches to the skull base

Sagittal plane
Transfrontal
Transcribriform
Transplanum (suprasellar)
Transsellar
Transclival
Superior: Posterior clinoid
Middle: Mid-clivus
Inferior: Foramen magnum
Transodontoid (craniovertebral junction)
Coronal plane
Anterior (anterior cranial fossa)
Supraorbital
Transorbital
Middle (middle cranial fossa)
Medial cavernous sinus
Medial petrous apex
Suprapetrous (middle fossa, lateral cavernous sinus)
Infratemporal skull base
Posterior (posterior cranial fossa)
Transcondylar
Infrapetrous
Parapharyngeal space

INDICATIONS

Pathologic processes may arise from intra-cranial, cranial, or extracranial structures and include a diversity of benign and malignant pathologies (Table 116.2). Isolated transfrontal approaches are primarily performed for inflammatory sinus disease (chronic frontal sinusitis, mucocele) and benign tumours (osteoma). The intracranial component of a nasal dermoid can be removed by following the tract through the foramen cecum, anterior to the crista galli.

Isolated transcribriform approaches are used for meningoencephaloceles that typically involve the lateral lamella of the cribriform. Rarely, tumours may arise from the olfactory nerves (olfactory schwannoma, olfactory hamartoma, aesthesioneuroblastoma). The most common indication for a transcribriform approach is for olfactory meningioma or sinonasal malignancy with skull base involvement. A transcribriform approach is usually combined with transfrontal and transplanum approaches to obtain adequate access and resection margins.

TABLE 116.2 Indications for endoscopic endonasal surgery (by surgical approach)

Transfrontal	chronic sinusitis, mucocele, osteoma, nasal dermoid
Transcribriform	meningoencephalocele, olfactory groove meningioma, olfactory schwannoma, olfactory neuroblastoma, sinonasal malignancy
Transplanum (suprasellar)	Pituitary adenoma, craniopharyngioma, meningioma
Transellar	Pituitary adenoma, Rathke's cleft cyst, craniopharyngioma
Supraorbital	osteoma, meningioma, sinonasal malignancy

Sellar pathology includes primary pituitary adenomas (functioning and non-functioning) and Rathke's cysts. Large macroadenomas may extend to the suprasellar area and require a combined transsellar-transplanum approach for exposure and removal. A combined approach is also used for craniopharyngiomas and tuberculum meningiomas.

A supraorbital approach augments transcribriform and transplanum approaches by providing access to the roof of the orbit and associated dura. Usual indications for a supraorbital approach include a dural tail for meningiomas and dural margins for sinonasal malignancy.

For patients with sinonasal malignancy, oncological principles can be preserved with EES.[2] The goal of surgery is complete oncological resection with the least morbidity. With such cases, the endoscope is only a surgical tool and resection margins should not be compromised in order to perform an endoscopic resection. Although it is often promoted, en bloc resection is not achievable with an 'open' approach in many patients, due to proximity of the tumour to critical neural and vascular structures and fracturing of the tumour specimen. There is also abundant evidence that en bloc resection is not necessary as long as final resection margins are negative (e.g., inverted papilloma, Moh's surgery for skin cancer, and laser resection of pharyngeal and laryngeal squamous cell carcinoma). For sinonasal malignancy that involves the cribriform plate with risk of intra-cranial extension along olfactory filia to the olfactory bulb, bilateral wide resection of the anterior cranial base is recommended including dura, olfactory bulbs, and olfactory tracts.[3] Potential benefits of endoscopic surgery include better visualization of resection margins with better local control, no transgression of normal tissue planes with risk of tumour seeding, absence of frontal lobe manipulation, and faster recovery with early institution of adjunctive therapies.

A wide variety of sinonasal neoplasms are suitable for EES if properly selected. These include olfactory neuroblastoma (aesthesioneuroblastoma), neuroendocrine carcinoma, sinonasal undifferentiated carcinoma (SNUC), squamous cell carcinoma, adenocarcinoma, adenoid cystic carcinoma, and melanoma. Operability is determined by the biological behaviour of the tumour (diagnosis), stage (extent), and patient factors (age, medical co-morbidities). Surgery is generally preferred as the first treatment option for resectable tumours that do not have a high risk of distant metastases. Brain invasion is not necessarily a sign of inoperability. If a pial or cortical margin of brain tissue can be removed to achieve a negative margin without sacrificing major cerebral vasculature, then the tumour is operable. If there is tumour involvement of cerebral vessels, then the goal of surgery is no longer cure but palliation. Such patients usually receive radiochemotherapy first and surgery is reserved for salvage treatment of residual disease. For tumour with aggressive biological behaviour and increased risk of metastases (SNUC, melanoma), systemic therapy (chemotherapy, immunotherapy) is considered first. Even though the prognosis remains poor for cure of mucosal melanoma, EES is considered for local control.

The endoscope provides additional treatment options in patients with malignancy. In addition to performing a

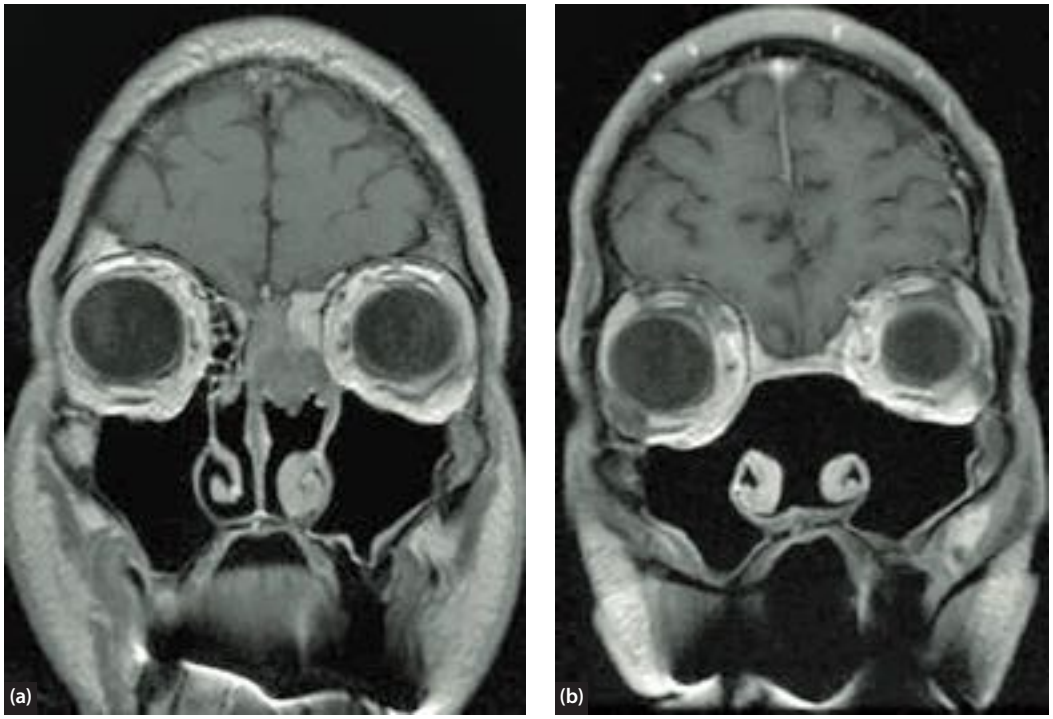


Figure 116.1 Pre-operative (a) and post-operative **(b)** MRI of a complete oncological resection of an adenocarcinoma of the left olfactory cleft with cranial base involvement.

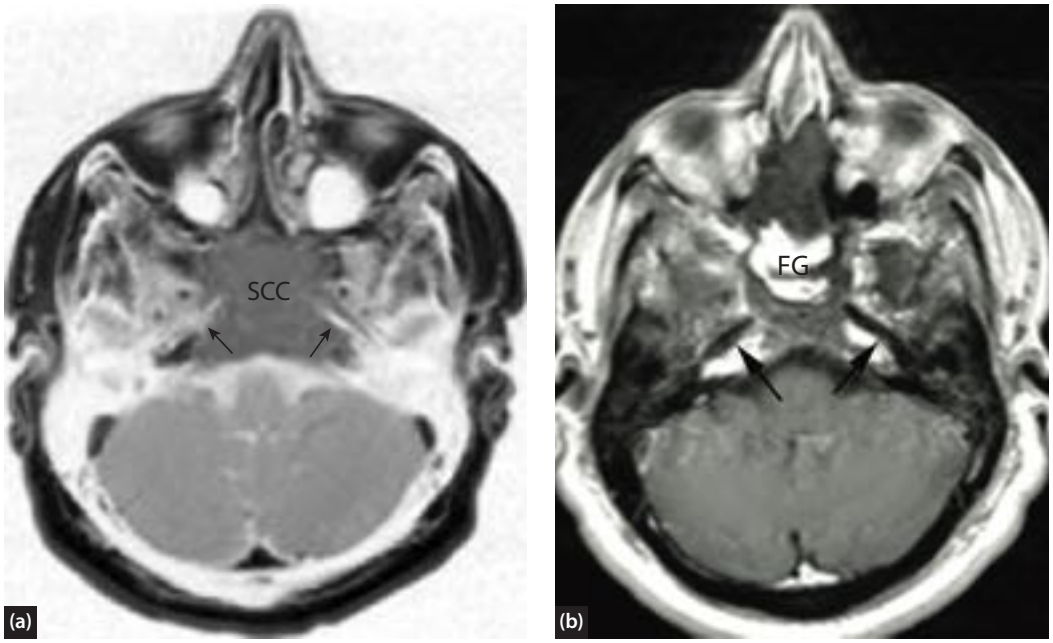


Figure 116.2 Debulking of unresectable squamous cell carcinoma of nasopharynx prior to radiochemotherapy. The patient presented with a VIth nerve palsy that resolved with surgery. **(a)** Pre-operative MRI with tumour encasement of both internal carotid arteries (arrows). **(b)** Post-operative MRI with fat graft (FG) and residual tumour surrounding the internal carotid arteries (arrows). The patient had a complete response to radiochemotherapy and remains disease-free more than 10 years later.

complete oncological resection (Figure 116.1), debulking of tumour prior to radiochemotherapy (Figure 116.2) may be considered in order to relieve symptoms such as bleeding, infection, pain, or compression (brain, orbit, cranial nerves). In addition, potential benefits of debulking prior to radiotherapy include accurate assessment of tumour margins and areas of invasion, modification of radiation ports to spare uninvolved tissues (optic nerves), and improved therapeutic response. The endonasal approach is ideal for palliation of symptoms in patients with unresectable recurrences (Figure 116.3). The morbidity of EES is minimal in such cases and affords the opportunity for multiple outpatient surgeries. Palliative surgery may also be considered for prevention of complications related to continued tumour growth (e.g., visual loss).

Pre-operative planning

The pre-operative evaluation of patients with tumours involving the cranial base starts with a detailed history and thorough physical examination. Presenting symptoms are often minimal and non-specific. Sellar and suprasellar tumours may present with headache, endocrine dysfunction, or visual loss. Intra-nasal tumours may present with

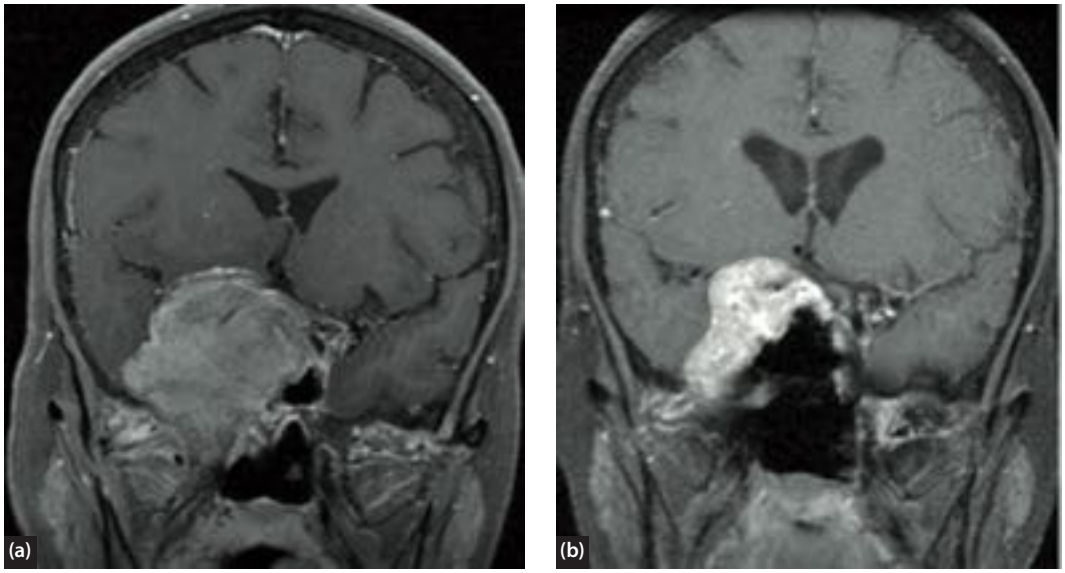


Figure 116.3
(a) Unresectable olfactory neuroblastoma with complete encasement of the right orbital apex and cavernous sinus. **(b)** Palliative EES with limited resection of residual tumour was performed to limit spread of tumour to the uninvolved eye and preserve vision (MRI is 2 years following radiochemotherapy and 1 year following surgery).

nasal obstruction, olfactory loss, epistaxis, or rhinorrhea. Tumours that extend laterally to the orbit may cause diplopia from displacement or invasion of orbital tissues. Intra-cranial tumours are often silent but subtle changes in personality and memory loss may become evident with further questioning.

Physical examination includes nasal endoscopy to assess the location and extent of tumour. Origination medial to the middle turbinate is typical of olfactory neuroblastoma. Coexistent sinus pathology may include infection, mucocele formation, and nasal polyposis. Olfaction may be assessed using available 'scratch and sniff' tests (Sensonics, Inc, Haddon Heights, NJ). Assessment of orbital function includes examination of extraocular motility and visual acuity. Visual field testing can provide evidence of early visual compromise and topographic data (tumour location relative to the chiasm). If there is concern about brain function, neurocognitive testing of executive functions can be performed. Pre-operative testing of visual and brain function is valuable for comparison with postoperative function.

Radiological imaging is essential for proper diagnosis as well as surgical planning. Both computed tomographic (CT) scan and magnetic resonance imaging (MRI) are obtained in many cases due to complementary information. CT is better for demonstrating bone erosion and sinus anatomy and MRI is better for delineating soft-tissue invasion and differentiating tumour from obstructed secretions. Scans are obtained using a skull base format with intra-operative navigation in mind. CT angiography is useful for identification of the internal carotid artery (ICA) or anterior cerebral arteries both pre-operatively and intra-operatively using navigation.

SURGICAL TECHNIQUES

EES is performed in an operative suite that is dedicated to endoscopic procedures. The room is organized around the patient with multiple monitors for viewing endoscopic images. The operative set-up is as shown in Figure 116.4. Following induction of anaesthesia, the head is immobilized with 3-point fixation in a Mayfield clamp. This allows precise positioning of the head for endoscopic access and facilitates intra-operative navigation. It also prevents inadvertent movement of the head during periods of critical dissection. The head is extended to increase anterior access and slightly rotated and laterally flexed to align the surgical corridor with the surgeon. Intra-operative navigation is registered and neurophysiological monitoring electrodes are placed. Cortical function (brain ischaemia) is monitored during every case using somatosensory-evoked potentials. If dissection of cranial nerves (III, IV, VI) is anticipated, electromyographic (EMG) monitoring of extraocular muscles is performed.

The nasal mucosal tissues are decongested with pledgets soaked in 0.05% oxymetazoline and the nasal vestibule and midface are prepped with betadine solution. Antiseptic rinses of the nasal cavity are not used due to

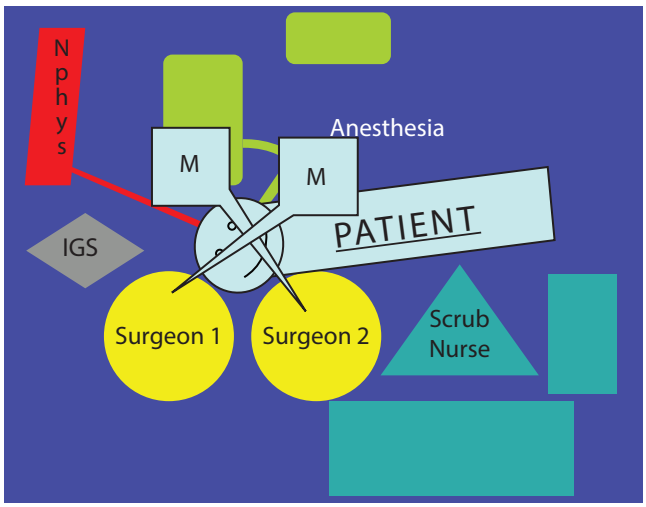


Figure 116.4 Operating room set-up. IGS: image-guidance system; M: monitor; NPhys: neurophysiology.

their deleterious effects on mucociliary function. A third-generation cephalosporin antibiotic is administered intravenously for perioperative prophylaxis.

Standard equipment for endonasal surgery includes a full set of endoscopic sinus surgery instruments including frontal sinus instruments, endoscopic bipolar electrocautery with exchangeable tips, endonasal drill with 4 mm coarse (hybrid) diamond bits, an array of angled Frazier and Fukushima suctions, pistol-grip extended microscissors and fine-tip extended dissectors for microvascular dissection. A nerve stimulator is used to aid identification of cranial nerves and a Doppler probe is used to identify and measure blood flow in major vessels.

Surgical approaches

TRANSFRONTAL APPROACH

The transfrontal approach provides access to the skull base anterior to the cribriform plates. It includes the floor of the frontal sinuses and the foramen cecum and crista galli in the midline. With drilling of the 'beak' of the frontal bone, the majority of the posterior table of the frontal sinus is accessible. Key landmarks and limits of the transfrontal approach are noted in Table 116.3.

A Draf 3 frontal sinusotomy is the foundation for the transfrontal approach (Figure 116.5). The nasofrontal recess is identified bilaterally by following the uncinate process and opening the anterior ethmoid air cells. The anterior ethmoid artery is identified at the posterior limit of the nasofrontal recess. The anterior tip of the middle turbinate is resected to the first olfactory fibre. The mucosa and periosteum of the olfactory sulcus can be elevated to assist in identification of the anterior margin of the cribriform plate and olfactory fibres. A superior septal window is created between the nasofrontal recesses to provide binarial access and improved angles for instrumentation. With visualization of the frontal sinuses on both sides, the floor of the frontal sinuses is then drilled in a curvilinear fashion anterior to the crista galli. Additional bone is drilled anteriorly in the midline (frontal beak) to increase access superiorly. Intersinus septations are drilled as necessary to provide a wide drainage pathway.

TABLE 116.3 Key landmarks and limits of the transfrontal approach

Key landmarks	
	Foramen cecum
	Crista galli
	Frontal sinus
Limits	
	Anterior: anterior table frontal sinus
	Posterior: posterior table frontal sinus
	Medial: crista galli
	Lateral: lacrimal fossa
	Superior: posterior table midpoint

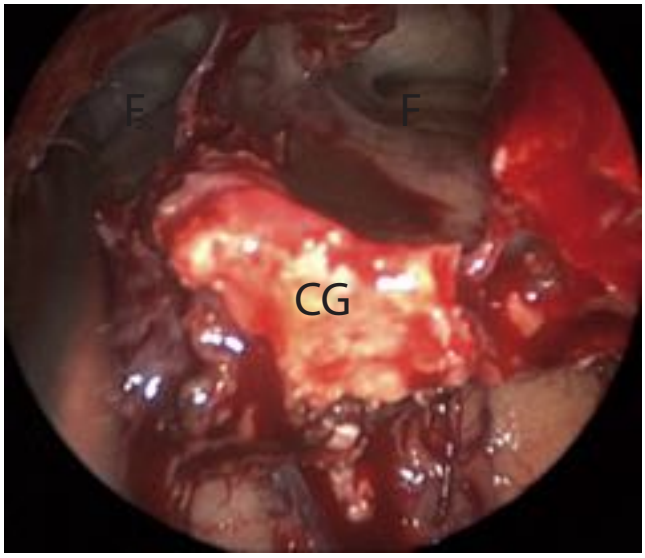


Figure 116.5 Draf 3 frontal sinusotomy for resection of sinonasal malignancy. CG: crista galli; F: frontal cell.

The posterior table of the frontal sinus is thinned with a drill and then elevated with dissecting instruments to expose the dura. The crista galli can be exposed in the midline and partly removed by drilling.

CASE EXAMPLE: NASAL DERMOID

A 5-year-old boy presented with a history of recurrent inflammation of the nasal dorsum despite prior transcutaneous excisions of a dermoid cyst of the nasal dorsum. A well-healed scar of the nasal dorsum was present without active inflammation. Nasal endoscopy revealed swelling of the superior nasal septum. CT and MRI demonstrated swelling of the superior nasal septum with a sinus tract extending through the foramen cecum to a small intra-cranial but extradural collection (Figure 116.6). Following frontal sinusotomy, the septal portion of the dermoid cyst was opened and contents were removed. The sinus tract was followed through the skull base by drilling the surrounding bone. The sinus tract was resected to the surface of the dura without a CSF leak. The defect was left open to the nasal cavity to prevent recurrence.

TRANSCRIBRIFORM APPROACH

A transcribriform approach provides access for tumours that arise from the cribriform plate area such as olfactory neuroblastomas and olfactory groove meningiomas. It is also a common site for meningoencephaloceles with spontaneous CSF leaks. A transcribriform approach is often combined with transfrontal and transplanum approaches for complete resection of the anterior cranial base in patients with a sinonasal malignancy. Key landmarks and limits of the transcribriform approach are noted in Table 116.4.

A Draf 3 frontal sinusotomy may be necessary to provide access to the anterior limit of the cribriform plates and also avoids problems with post-operative obstruction

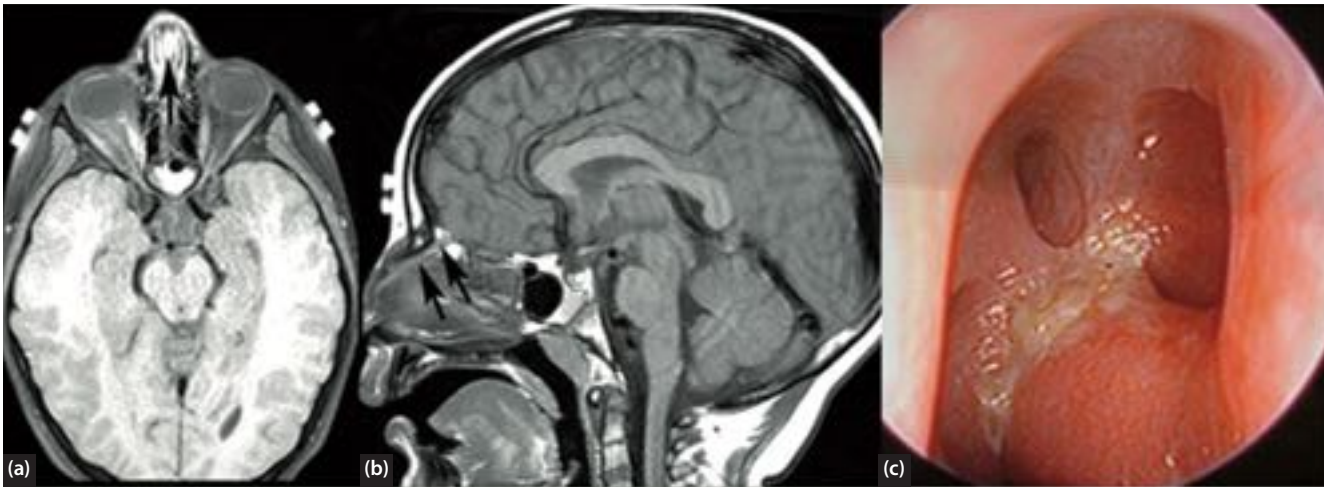


Figure 116.6 Pre-operative axial **(a)** and sagittal **(b)** MRI demonstrate a dermoid cyst extending from the superior nasal septum (arrow) through foramen cecum (arrows) to the surface of the dura. **(c)** Endoscopic view of healed defect of superior septum following surgery.

TABLE 116.4 Key landmarks and limits of the transcribriform approach

Key landmarks	
	Crista galli
	Olfactory filia, olfactory bulbs
	Lateral lamella
Limits	
	Anterior: frontal sinus
	Posterior: planum, posterior ethmoid artery
	Medial: crista galli
	Lateral: orbit

of the frontal sinuses. Bilateral ethmoidectomies are performed and the middle turbinates are resected. It may be necessary to debulk large intra-nasal tumours first in order to delineate the margins of the tumour and expose the area of skull base involvement (Figure 116.7a). Devascularization of intra-nasal tumours can be achieved by bipolar electrocautery of the tumour surface and ligation of feeding vessels. The anterior and posterior ethmoidal arteries may be identified where they cross the skull base lateral to the tumour. The paired vessels diverge from each other as they pass medially. The anterior ethmoidal artery is located between the 2nd and 3rd ethmoid lamella just posterior to the nasofrontal recess. Navigation can also be used to locate the artery; it exits the orbit in a coronal plane that is tangential to the posterior surface of the globe. The anterior and posterior ethmoidal arteries are best transected on the orbital side of the skull base. The lamina papyracea is partially removed and the orbital periosteum is dissected from the orbital roof. The periosteum is tethered where the vessels enter the foramina. The vessels are cauterized with bipolar electrocautery prior to transection. It is important to leave a small stump for cauterization so that the vessel does not retract into the orbit and cause a retro-orbital haematoma.

The bone of the skull base is then thinned with the drill and elevated to expose the dura to the margins of resection. If dural margins are important, it is helpful to elevate the dura from the orbital roof; this makes it easier to resect additional dural margins later, if needed. The dura is incised laterally with a retractable sickle knife and the incisions are extended with micro-scissors, taking care to avoid injury to cortical vessels. In the midline anteriorly, it is necessary to detach the dura from the crista galli. The base of the crista galli is removed with the drill prior to dural opening so that the attachment of the falx can be cauterized and cut once the dura is open (Figure 116.7b). Transection of the falx is directed posteriorly towards its free edge. This releases the dural specimen anteriorly and the remaining posterior dural cuts can be made. Additional intra-cranial tumour is dissected as needed.

CASE EXAMPLE: OLFACTORY SCHWANNOMA

A 12-year-old male presented with headaches and altered personality. Imaging revealed a large intra-cranial tumour arising from the olfactory area (**Figure 116.8**). A bilateral transcribriform approach was performed with complete intra-dural excision of the tumour. Histological examination confirmed an olfactory schwannoma.

TRANSPLANUM APPROACH

A transplanum approach provides access from the cribriform plates anteriorly to the tuberculum posteriorly (Figure 116.9). The planum forms the roof of the sphenoid sinus and is bounded by the optic canals posterolaterally. Most commonly, an isolated transplanum approach is used for access to intra-cranial tumours such as meningiomas. It may be combined with a sellar and suprasellar approach for suprasellar lesions such as pituitary tumours and craniopharyngiomas. Meningiomas that extend into the optic canals can be completely removed by decompressing the optic canals medially out to the optic strut.

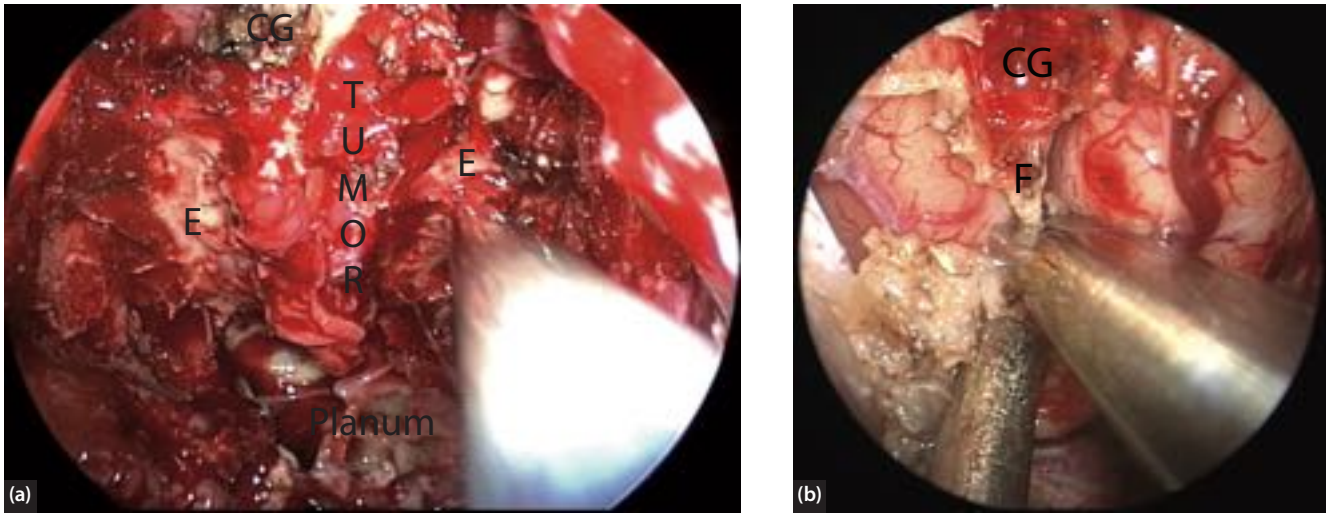


Figure 116.7 (a) The tumour is debulked and surrounding bone landmarks of the skull base are exposed. CG: crista galli; E: ethmoid roof. **(b)** The falx (F) is transected to release the dural specimen anteriorly. CG: site of crista galli.

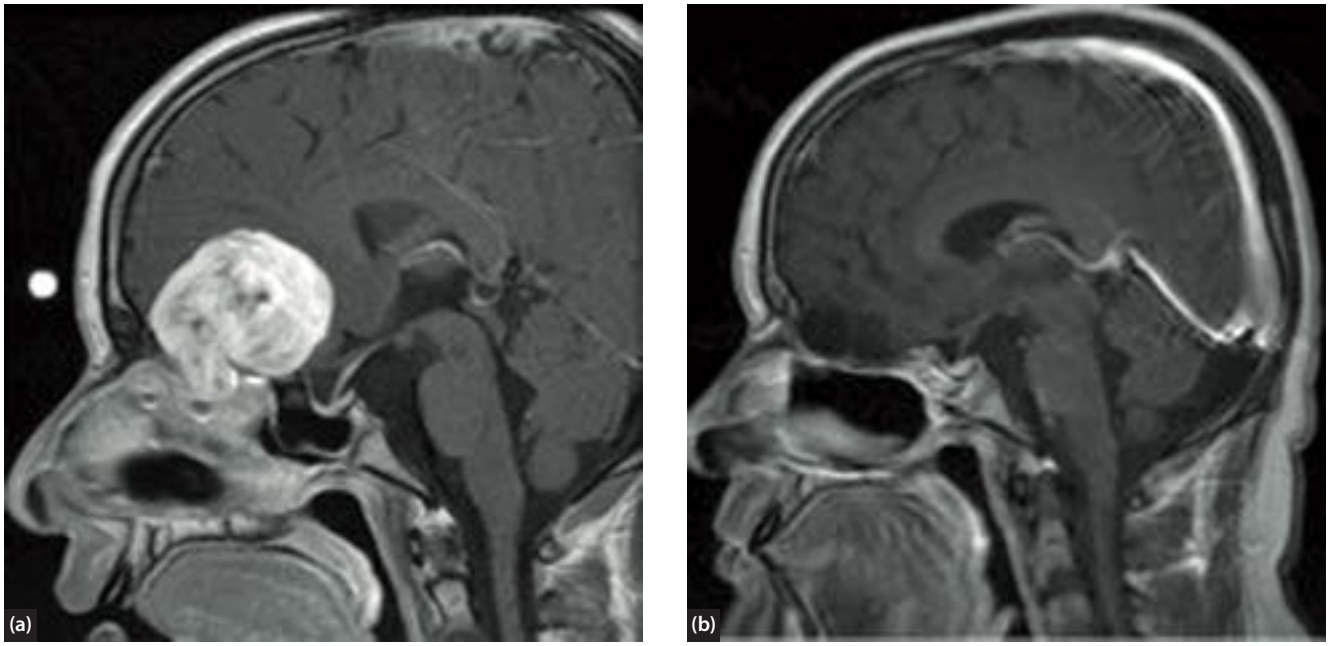


Figure 116.8 Pre-operative **(a)** and post-operative **(b)** MRI of olfactory schwannoma in a 12-year-old boy removed using a transcribriform approach.

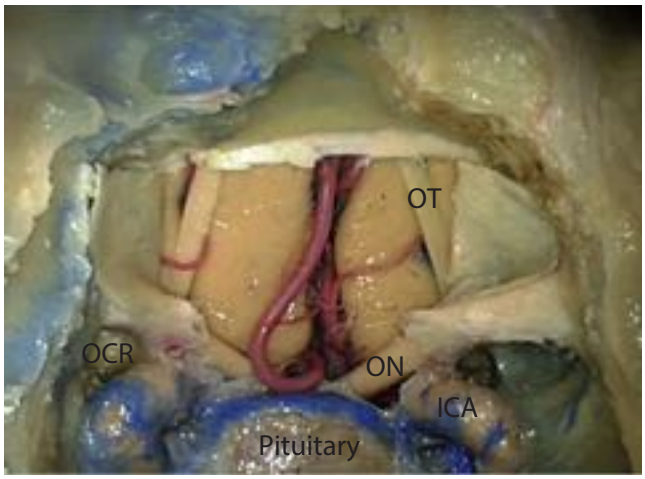


Figure 116.9 Anatomical dissection of a transplanum approach demonstrating key landmarks. ICA: internal carotid artery; OCR: optic-carotid recess; ON: optic nerve; OT: optic tract. The transplanum approach is bounded by the cribriform plates anteriorly.

Key landmarks and limits of the transplanum approach are noted in Table 116.5.

Bilateral ethmoidectomies and a wide sphenoidotomy are necessary to provide visualization of the planum. The rostrum of the sphenoid is resected to provide binarial access. It is important to avoid aggressive resection of the septal attachment superiorly due to risks of olfactory injury or cerebrospinal fluid leak from the cribriform plates. The sphenoid sinus landmarks are identified and mucosa is stripped from the bone. The posterior ethmoid

TABLE 116.5 Key landmarks and limits of the transplanum approach

Key landmarks	
	Posterior ethmoid artery
	Olfactory tracts
Limits	
	Anterior: cribriform plate
	Posterior: superior intercavernous sinus
	Posterolateral: optic canals
	Lateral: orbital apex

arteries are variable in location and diameter but are generally found near the junction of the planum sphenoidale and roof of ethmoid sinus. The foramina are approximately 4–7 mm anterior to the optic canal.

The bone of the planum is outlined with the drill and fragments of bone are dissected from the underlying dura in an anterior to posterior direction. Posteriorly, the optic canals are kept in sight. If tumour dissection from the optic canals is necessary, a 3 mm coarse diamond bit is used to thin the overlying bone. Copious irrigation is used to prevent thermal injury to the optic nerves. The thinned bone is carefully elevated with fine dissectors to avoid compression of the optic nerves. The posterior ethmoid arteries are cauterized and transected on the orbital side of the bone. Excessive bone removal beyond the anterior margin of the tumour should be avoided so that normal brain tissue does not descend and obstruct the view.

The dura is incised with a retractable sickle knife and the incisions are extended with micro-scissors, taking care to avoid injury to cortical vessels. Tumour dissection is performed using standard microsurgical techniques with internal debulking followed by extracapsular dissection. If the dura is incised to the optic canals, care should be taken to identify and preserve the ophthalmic artery, which is often inferior and medial to the optic nerve as it branches from the ICA (Figure 116.10).

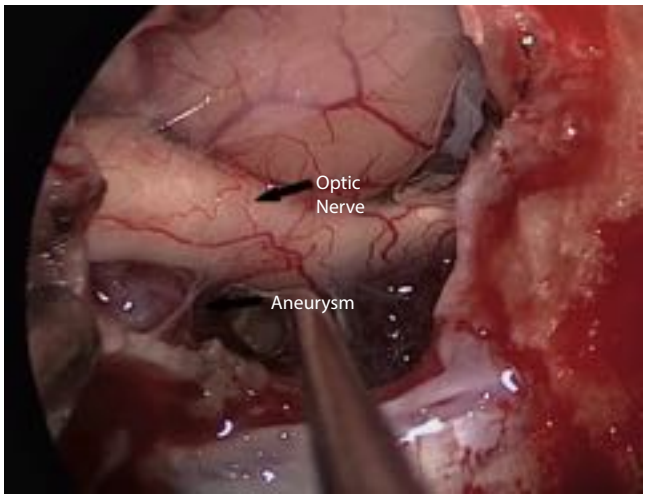


Figure 116.10 Intra-operative view of an aneurysm arising from the right ophthalmic artery.

CASE EXAMPLE: MENINGIOMA

A 45-year-old female presented with headaches and vision loss. MRI revealed a large suprasellar tumour with compression of the optic chiasm and tumour extension into the optic canals (Figure 116.11). Gross total excision was achieved using a transplanum approach. The dura of the optic canal was opened medially just above the optic nerve and tumour was dissected without injury to the ophthalmic artery.



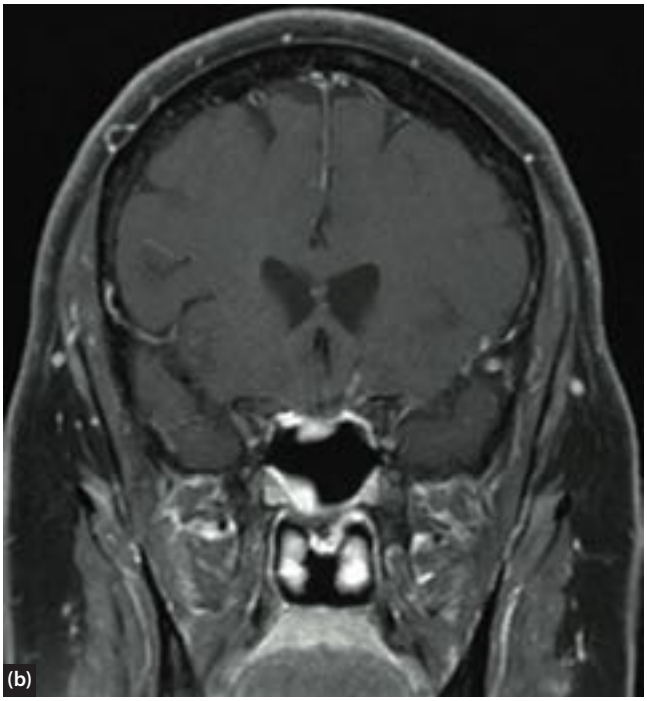


Figure 116.11 Pre-operative **(a)** and post-operative **(b)** MRI of a planum meningioma. GTR was achieved using a transplanum approach with decompression of the optic canals.

SUPRAORBITAL APPROACH

The supraorbital approach is a coronal plane approach that provides access to the orbital roof. The maximal limit of exposure is the mid-sagittal plane of the orbit. This approach is used to remove tumour-involved bone (osteomas, meningioma) and to chase dural margins for sinonasal malignancy or meningiomas. It is often combined with transcribriform or transplanum approaches. The supraorbital approach is bounded anteriorly and posteriorly by the ethmoidal arteries. Key landmarks and limits of the supraorbital approach are noted in Table 116.6.

Following a complete sphenoethmoidectomy, the medial wall of the orbit is removed to the level of the skull base. The anterior and posterior ethmoidal arteries are identified and transected following cauterization. Periorbital is then dissected from the orbital roof to the mid-plane of the orbit. Access is greater in the middle and posterior orbit due to the trajectory of the surgical corridor. A binarial approach with a superior septal defect greatly enhances the exposure for instrumentation and minimizes contact of powered instrumentation with the orbital tissues. While the orbital tissues are protected with a suction or retracting instrument, the medial orbital roof is drilled and removed with rongeurs to the margin of resection. Posteriorly, removal of bone can extend to the anterior clinoid and facilitate 270° decompression of the optic canal.

CASE EXAMPLE: SINONASAL MALIGNANCY

A 52-year old man presented with nasal obstruction and a unilateral nasal mass involving the skull base with dural thickening over the medial orbit (**Figure 116.12a**). Biopsy confirmed a diagnosis of undifferentiated carcinoma and resection of the tumour and skull base was performed, including removal of the medial wall of the orbit. The initial dural incision did not provide an adequate resection margin (**Figure 116.12b**) and additional bone was removed from the orbital roof (**Figure 116.12c**) to achieve a negative dural margin.

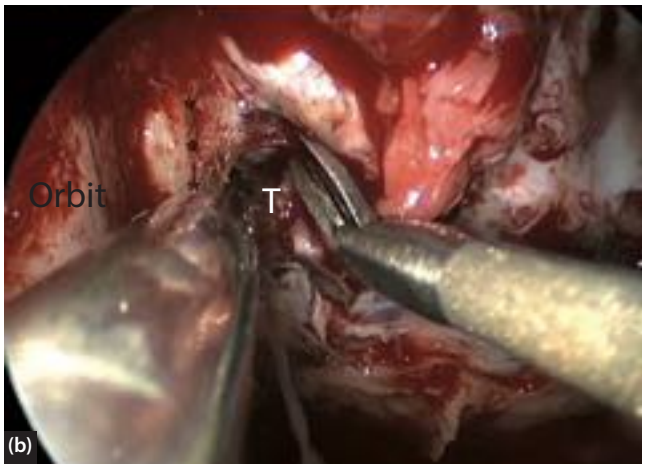
SUPRASELLAR APPROACH

A suprasellar approach is combined with transsellar and transplanum approaches to gain access to suprasellar pathology. The most common indications include pituitary macroadenomas with suprasellar extension, craniopharyngiomas, and meningiomas. It is bounded by the

TABLE 116.6 Key landmarks and limitations of the supraorbital approach

Key landmarks	
	Anterior and posterior ethmoid arteries
Limits	
	Anterior: frontal sinus
	Posterior: optic canal
	Superolateral: midplane of orbit





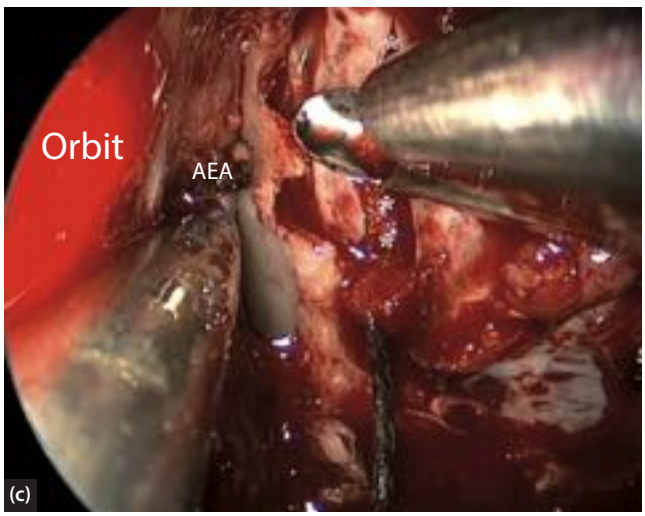


Figure 116.12 (a) Pre-operative MRI demonstrating intra-cranial extension of tumour (arrow). **(b)** Intra-operative view of initial dural incision with exposure of tumour (T). The edge of the resected bone is highlighted with asterisks. **(c)** Additional bone is removed from the orbital roof with retraction of orbital contents. The initial dural incision is highlighted with asterisks. AEA: anterior ethmoid artery.

optic chiasm superiorly and pituitary stalk or membrane of Lillequist posteriorly. Key landmarks and limits of the suprasellar approach are noted in Table 116.7.

Following a wide sphenoidotomy with opening of posterior ethmoid air cells, the landmarks of the sphenoid sinus are identified (Figure 116.13). This includes the sella, optic canals, lateral optic-carotid recess, and parasellar ICA. The medial optic-carotid junction or recess (mOCR) is an important landmark where the ICA courses medially before it passes under the optic nerve. The medial clinoid is a small bony projection below the medial OCR that provides a medial point of attachment of the dural rings next to the anterior genu of the cavernous ICA. In some cases, this can be calcified to form a complete ring around the ICA.

The bone of the sella is first thinned with the drill and removed to the margins of the cavernous sinus superiorly and laterally. Bone rongeurs are used to lift the thinned bone rather than bite the bone due to risk of injury to the ICA, especially at the medial optic-carotid junction. Anteriorly, the bone of the posterior planum is thinned with the drill until dura is exposed. The tuberculum strut (bone between the optic canals) is then disconnected laterally with a drill just medial to the optic canals (Figure 116.14). Then the entire tuberculum strut can be dissected free as a single piece of bone.

TABLE 116.7 Key landmarks and limitations of the suprasellar approach

Key landmarks	
	Optic canals
	Tuberculum
	Ophthalmic arteries
Limits	
	Anterior: planum sphenoidale
	Lateral: optic canals, paraclinoidal ICA

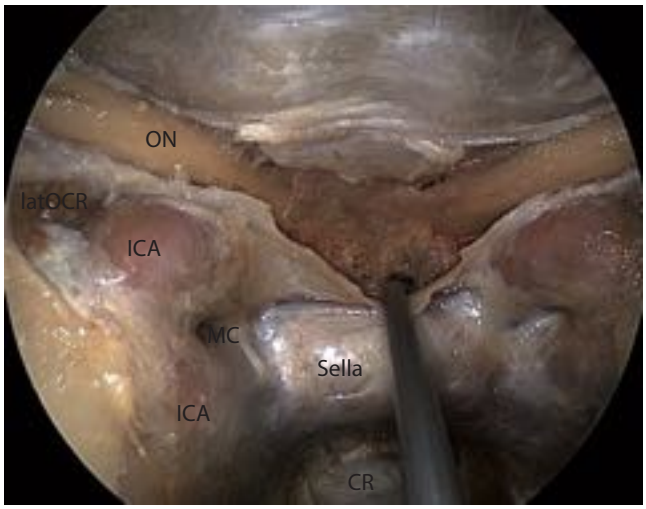


Figure 116.13 Key landmarks of the suprasellar approach. CR: clival recess; ICA: internal carotid artery; latOCR: lateral optic-carotid recess; MC: middle clinoid; ON: optic nerve.

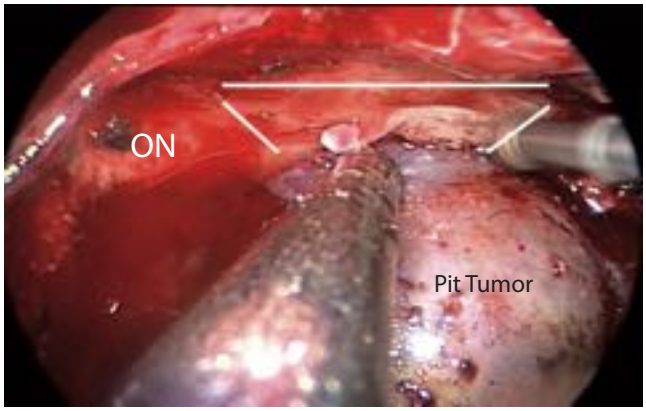


Figure 116.14 The bone cuts (lines) for a suprasellar approach for resection of a pituitary tumour (Pit Tumour) with suprasellar extension are shown. The lateral cuts are made with the drill medial to the optic nerve (ON) canals. Removal of the tuberculum allows descent of the suprasellar component of the tumour.

The dura is then incised above and below the superior intercavernous sinus (SIS). The location of the optic chiasm should be ascertained from pre-operative imaging in case it is prefixed or displaced anteriorly by tumour. The SIS is then cauterized with bipolar electrocautery and transected. Bleeding from the cut edges is controlled with application of Floseal® or Surgifoam®. Dural cuts are extended as necessary to the margins of the tumour.

CASE EXAMPLE: CRANIOPHARYNGIOMA

A 44-year old man presented with progressive vision loss, headache and fatigue. Imaging showed a heterogeneous, partially cystic suprasellar lesion involving the pituitary stalk and elevating the optic chiasm (Figure 116.15). Hormonal evaluation revealed hypogonadism, hypothyroidism and borderline adrenal insufficiency. The patient underwent an endoscopic endonasal suprasellar approach with complete resection of the tumour that was histologically confirmed to be a craniopharyngioma. The tumour extensively involved the pituitary stalk, which was transected as part of complete removal. The patient's vision improved significantly post-operatively and he was treated with oral replacement for panhypopituitarism with the new addition of diabetes insipidus.

Reconstruction (nasoseptal flap, pericranial flap)

Prior to dural reconstruction, it is imperative to have good haemostasis. Bipolar electrocautery is used for bleeding dural edges and small arterioles. Cavernous sinus or venous bleeding can be controlled with application of haemostatic materials such as Surgifoam® or Floseal®. Mild oozing from the surface of the brain or residual tumour can be controlled with copious irrigation of warm saline (40°C).[4] It may take 10 minutes or more of continuous irrigation to confirm that all bleeding is controlled.

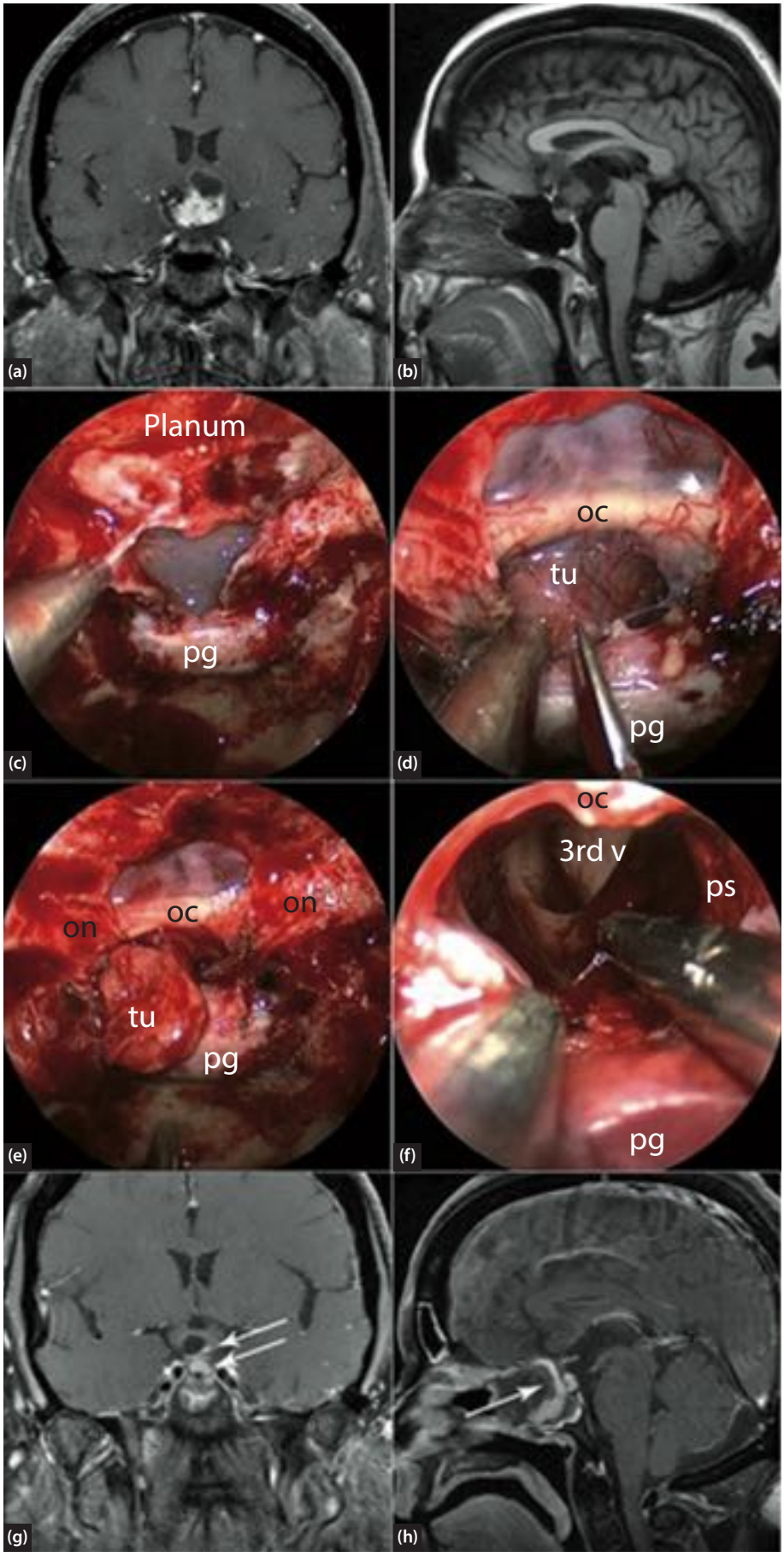


Figure 116.15 Craniopharyngioma. Pre-operative, intra-operative and post-operative images of a suprasellar craniopharyngioma with intraventricular extension that underwent GTR with EES. **(a, b)** Pre-operative MRI demonstrates a mixed solid and cystic suprasellar tumour that invades the floor of the 3rd ventricle. **(c)** Intra-operative view with a 0-degree endoscope after bony resection of the planum, tuberculum and anterior wall of the sella with exposure of the pituitary gland (pg). **(d)** After opening the suprasellar arachnoid, the optic chiasm (oc) is identified and the solid compartment of the tumour (tu) is visualized between the optic chiasm and the pituitary gland (pg). **(e)** The tumour (tu) is dissected and removed from the suprasellar cistern. The dura over the optic nerves (on) remains intact. **(f)** A closer view with the 0-degree endoscope provides direct visualization of the 3rd ventricle (3rd v), the floor of which was eroded by the tumour. Having removed the tumour, the pituitary stalk (ps) is identified with deviation to the left. The optic chiasm (oc) and pituitary gland (pg) remain intact. **(g, h)** Post-operative MRI with contrast confirm GTR of the craniopharyngioma. The pituitary stalk can be seen on the coronal image (upper arrow) deviated to the left, just above the pituitary gland (lower arrow). The linear contrast-enhancing area on the sagittal MRI (arrow) represents the vascularized nasoseptal flap that was used for skull base reconstruction and the enhancing spot behind the flap is the intact pituitary gland.

Reconstruction of dural defects of the anterior cranial base is ideally performed using vascularized tissue.[5] Although small dural defects are effectively repaired using a variety of techniques and materials, the use of vascularized tissue is associated with significantly lower post-operative CSF leak rates for larger defects. Local vascularized flaps include middle turbinate, inferior turbinate, and nasal septal flaps, all of which are based on terminal branches of the sphenopalatine artery. Regional vascularized flaps include pericranial and temporoparietal fascial flaps. Of these, the nasal septal flap and pericranial flap offer the best coverage and are preferred for reconstruction of large defects of the anterior cranial base.

The nasal septal flap[6] is raised at the beginning of the procedure to preserve the vascular pedicle. The superior incision runs parallel to the skull base approximately 1 cm below the skull base. If there are concerns about tumour involvement of the septum, clear margins are assessed by frozen section or reconstruction with a pericranial flap is considered. The inferior incision runs from the posterior choana along the posterior edge of the nasal septum to the junction of the nasal septum and nasal floor. If a wider flap is needed, the nasal floor can be incorporated into the flap. The anterior incision connects the superior and inferior incisions at the junction of the septal mucosa and skin of the nasal vestibule. It is important to include the most anterior-superior septal mucosa that is anterior to the attachments of the middle turbinate in order to harvest a maximal flap. After the flap is elevated from the underlying septal cartilage, it is displaced into the nasopharynx during the remainder of the procedure.

When it is time to repair the dural defect, an inlay fascial graft is placed between the brain and the dura. The septal flap is then transposed to cover the entire defect. All surrounding mucosa should be removed so that the entire flap is in contact with bone or dura. If the flap is not long enough, the reach of the flap can be extended by drilling the sphenoid floor or filling the clival recess with autologous fat grafts. The margins of the repair can also be augmented with onlay fascia grafts placed under the flap or fat grafts placed over the edges of it as needed. The donor site on the anterior nasal septum is covered with a free mucosal graft when available, and Silastic® nasal splints are placed.

An extracranial pericranial flap provides maximal vascularized tissue for reconstruction.[7] After the intradural fascial graft is placed, the flap is harvested using a bicoronal scalp incision. The scalp is elevated to the level of the nasion and supraorbital rims with preservation of the supraorbital neurovascular bundle on one or both sides. The bone at the level of the nasion is then drilled to create a window (approximately 2.0 cm × 0.5 cm) into the nasal cavity that is below the level of the skull base (**Figure 116.16**). The pericranial flap is then dissected from the scalp in a subgaleal plane and passed through the bony defect into the nasal cavity. Rotation of the flap is facilitated by sacrificing the vascular pedicle on one side. Endonasally, the flap is spread out to cover the dural and bony margins of the defect. If possible, the flap pedicle is displaced to one side to prevent obstruction of the drainage pathway of the Draf 3 frontal sinusotomy. Care should be taken to ensure the proximal flap is in contact with the anterior aspect of the skull base defect or the bone of the posterior table of the frontal sinus.

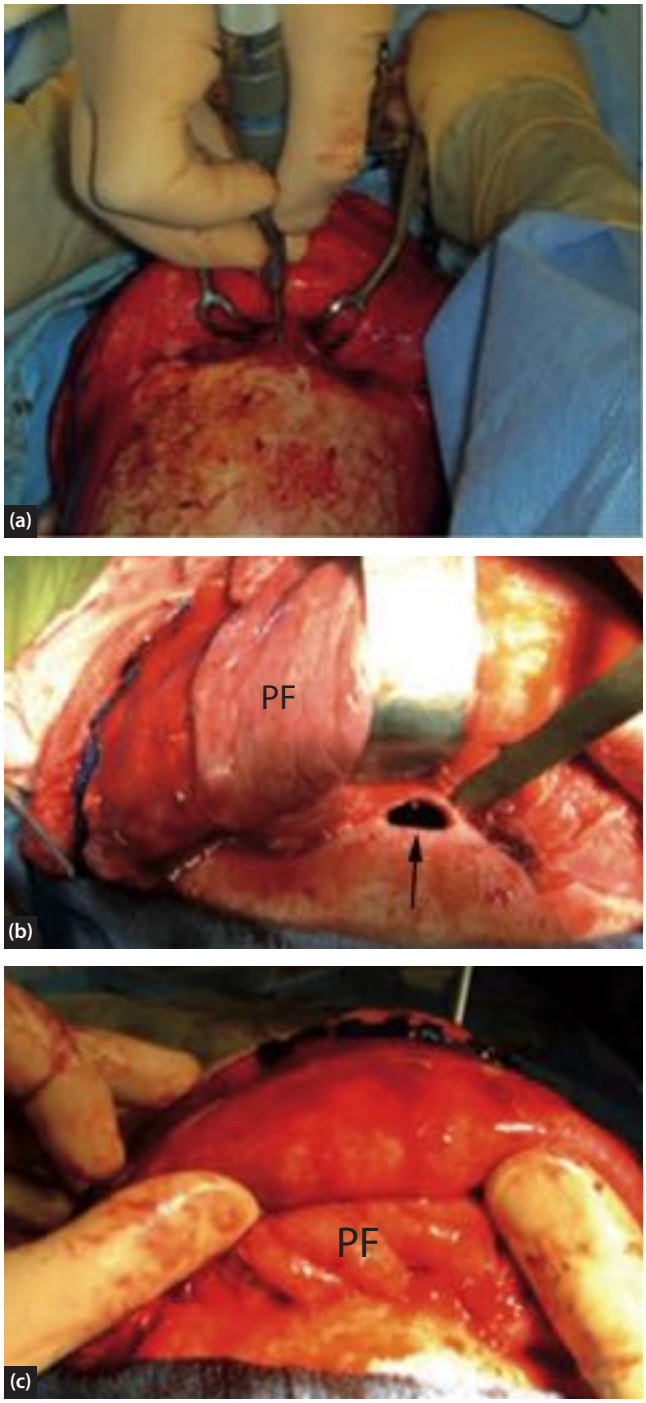


Figure 116.16 An extracranial pericranial flap requires drilling **(a)** of a bone window (arrow) at the nasion that extends from orbit to orbit below the level of the skull base **(b)**. The pericranial flap (PF) is pedicled on one or both supraorbital vessels and passed through the bone window into the nasal cavity **(c)**.

The reconstructive flap is then covered with layers of Surgicel®, tissue glue, and Gelfoam®. Support of the reconstruction is provided by a Foley catheter inflated with saline or Merocel® tampons. Tampons are preferred

for large anterior defects and when the optic nerves are exposed and susceptible to compression.

CASE EXAMPLE: PERICRANIAL FLAP

A 79-year-old female underwent EES for an olfactory neuroblastoma. Because of septal involvement by the tumour, reconstruction of the anterior cranial base defect with a nasoseptal flap was not possible (**Figure 116.17**). An extracranial pericranial flap was harvested using a bicoronal scalp incision and was passed into the nasal cavity inferior to the skull base using a bony window at the level of the nasion and covered the defect widely, including the medial orbits. The post-operative course was not complicated by a CSF leak and sensory and motor function of the frontal scalp was preserved.

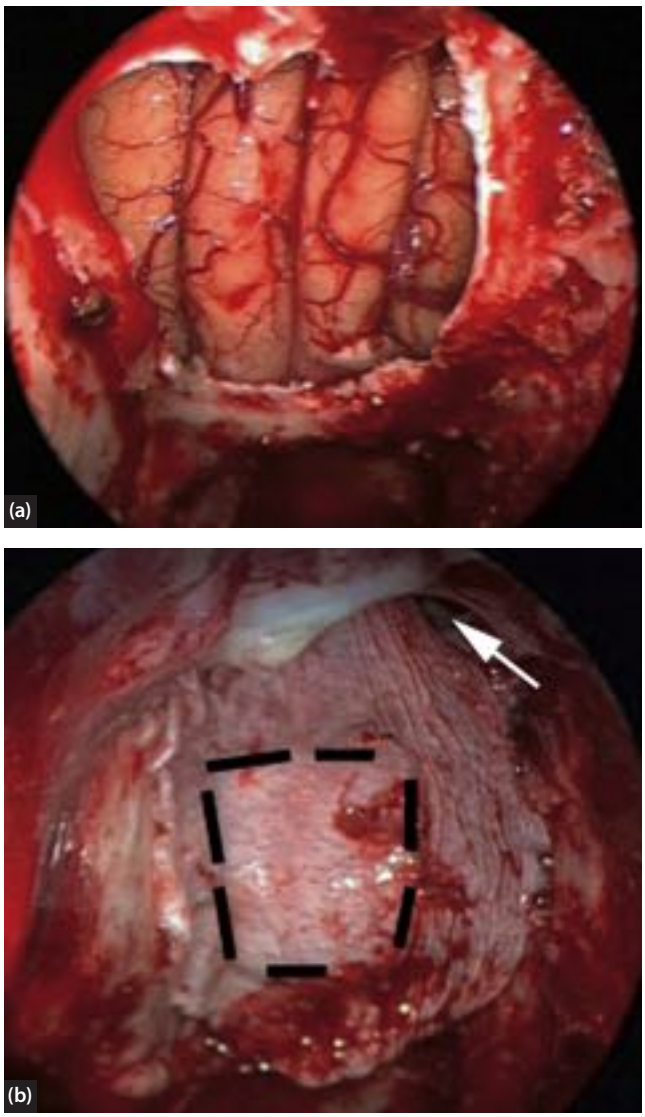


Figure 116.17 A nasoseptal flap was not available for reconstruction of this dural defect. (a) Following endoscopic endonasal excision of an aesthesioneuroblastoma. **(b)** An extracranial pericranial flap provided ample coverage of the defect (original dural defect outlined). Note drainage pathway (arrow) for the frontal sinuses to the side of the flap pedicle.

Post-operative care

Patients are monitored for signs of intra-cranial complications and a CT scan of the brain is performed within 8 hours to look for evidence of intra-cranial haemorrhage or tension pneumocephalus. Visual outcomes are assessed if dissection included the optic nerves/chiasm. If a suprasellar approach is performed, patients are also at risk for diabetes insipidus and are managed in conjunction with the endocrinology service. Antibiotic prophylaxis is continued for the duration of nasal packing. After 24 hours, patients can be switched to an oral cephalosporin (Ceftin). Lumbar drainage is used in patients with significant arachnoidal dissection (i.e. high-flow leaks), but there is limited evidence to support this practice.

Nasal packing is removed in 5–7 days; this can be done in the outpatient clinic. Nasal splints are maintained for 1 week if a pericranial flap is used and for 3 weeks if a septal flap is used. This facilitates mucosalization of the septum. Nasal irrigations with saline are performed daily and periodic endoscopic debridement of the nasal cavity is performed until healing is complete.

OUTCOMES

We have successfully treated several nasal dermoids with intra-cranial extension (extradural) through foramen cecum using an endonasal approach. Review of the literature demonstrates minimal data regarding endoscopic endonasal resection of nasal dermoids.[8] The initial experience is positive, however, and suggests that equivalent outcomes can be achieved with these techniques.

Oncological outcomes for sinonasal malignancy are limited. A meta-analysis of 23 studies (361 patients) of treatment for aesthesioneuroblastomas demonstrated a higher published survival rate for endoscopic surgery when compared to open surgery, even when stratifying for year of publication. Although endoscopic series had similar follow up, they had earlier stage (Kadish) disease, suggesting a treatment bias. Data are even more limited for other sinonasal malignancies such as squamous cell carcinoma, adenocarcinoma, and sinonasal undifferentiated carcinoma. Early results suggest that comparable results can be achieved using endoscopic techniques.

The optimal approach for olfactory groove meningiomas remains controversial, but there is a role for EES for debulking large tumours in the elderly and avoiding frontal lobe retraction. In a review of 44 patients who underwent EES for olfactory groove meningiomas (unpublished data), 55% underwent gross total resection, 16% near total and 30% subtotal. In 16 patients, tumours were removed in two stages, both to allow tumour descent/ collapse and as part of the endoscopic learning curve. Overall, the CSF leak rate was nearly 40%, but this decreased throughout the series as reconstructive techniques evolved. As a result, 6.8% of patients suffered post-operative meningitis. As experience improved, the gross total resection rate increased to almost 70% in the last 3 years. No patients had worsening of vision and 64% of those with preoperative visual impairment improved.

Suprasellar meningiomas often present with visual impairment. In a review of 75 patients with suprasellar meningiomas, visual impairment was the most common presenting symptom in 81%. Following EES, complete resolution or improvement of visual symptoms was seen in 86% of patients with deterioration in only 4% (2 patients). These results compare favourably to the literature for open approaches and suggest that preservation of small vessels of the optic chiasm are better visualized and preserved with EES. Gross total resection (GTR) was achieved in 79%. GTR was limited by large tumours (>3 cm), multilobulated tumours, and those with vascular encasement but not by optic canal involvement. CSF leak was the most common complication in 25% of patients but has decreased to 16% since the introduction of the nasoseptal flap for reconstruction.

Craniopharyngiomas are well suited for an endonasal approach. We performed a retrospective review of 64 patients (47 adults, 17 children) with craniopharyngioma who underwent EES.[9] The most common presenting symptom in adults was visual loss (81%); headache was most common in the paediatric population (65%). Resection >95% was achieved in 72% of patients; the resection rate was significantly better in the paediatric population. Of those patients presenting with visual impairment, vision was improved or normalized in 86%. In patients with normal pituitary function (n = 24), new pituitary deficit occurred in 14 (58%). Other than pituitary dysfunction (hypopituitarism and diabetes insipidus), CSF leak was the most common complication (23%) but decreased to 11% following introduction of the nasoseptal flap for reconstruction. Treatment options for recurrent disease (34% of patients) included repeat EES in 55% of recurrences. With the goal of gross total or near total resection, EES can be employed for the treatment of every craniopharyngioma regardless of the location, size and extension (excluding purely intra-ventricular tumours) and can provide acceptable results, comparable to traditional craniotomies. This surgical technique is not limited to adult patients, actually showing higher resection rates in the paediatric population.

In patients undergoing EES of the skull base, excellent QOL scores are noted using the anterior skull base questionnaire.[10] One area of relative deficiency is in specific symptoms, such as olfactory loss. Limited data suggest that QOL is superior to open transcranial approaches for tumours involving the anterior cranial base. Nasal morbidity has been assessed in the endonasal surgical group using the SNOT-22 questionnaire, a validated instrument.[11] The use of a nasoseptal flap for reconstruction had a limited negative impact. As expected, increasing nasal morbidity (decreased QOL) has been noted in the expanded (non-transsellar sagittal plane and coronal plane) surgical modules compared to transsellar surgery.[12]

COMPLICATIONS

Complications may be categorized in multiple ways, by location, type, or time period. Intra-operative complications are rare and depend on the type and extent of pathology and the surgical approach.[13, 14] The most serious intra-operative complications are injuries to the optic nerves or carotid arteries. Meticulous surgical technique, familiarity with endoscopic anatomy, and good visualization are key factors in avoiding injury. With a transcribriform approach, the frontopolar vessels are at particular risk and the dura should be initially incised laterally to avoid injury. Visual loss may result from direct trauma to the optic nerves or from loss of vascular supply (branches of superior hypophyseal arteries).

Post-operatively, the most common complication is CSF leak. Potential risk factors include the size and location of the dural defect, patient factors (prior treatment, obesity), reconstructive technique (materials, vascularized flap, packing), and perioperative care (patient activity, lumbar drain, debridement). Most leaks are small and are related to insufficient coverage by the reconstructive tissues. In most cases, endoscopic repair supplemented by a lumbar spinal drain is successful. Intra-cranial infection is rare and is usually associated with a post-operative CSF leak. Prompt repair of CSF leaks and limited use of lumbar spinal drains is encouraged to limit the risk of infection.

Sinonasal complications include sinusitis, epistaxis, synechiae, chronic crusting, cosmetic deformity, and loss of olfaction. Delayed epistaxis is usually due to a branch of the sphenopalatine artery. A saddle-nose deformity can result from loss of septal support. Even if the olfactory nerves are preserved, some loss of olfaction is common and may be due to altered airflow patterns, mucosal oedema and crusting, post-operative irradiation, or direct damage to the olfactory epithelium or olfactory tracts. Fortunately, QOL studies demonstrate that overall sinonasal morbidity is low.

KEY POINTS

- The anterior cranial base from the frontal sinus to the sella and from orbit to orbit is accessible using EES.
- These techniques can be applied to a wide variety of lesions including meningoencephaloceles, benign tumours (nasal dermoids, meningiomas, craniopharyngiomas, pituitary adenomas) and malignant tumours (sinonasal malignancy) with preservation of microsurgical and oncological principles.
- Many of the challenges of endonasal surgery have been solved and large dural defects can be reconstructed effectively using vascularized flaps.
- Oncological and functional outcomes are comparable or superior to other approaches with the potential for decreased morbidity.
- Proper training in endoscopic techniques and adherence to the principles of team surgery is necessary to avoid complications and achieve superior outcomes.

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CHAPTER 117

IMAGING IN RHINOLOGY

Gregory O'Neill

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: sinonasal, paranasal, and diagnostic imaging with cross-referencing from the papers thus identified.

INTRODUCTION

Modern imaging has come to occupy a pivotal role in the pre-/post- (and intra-) operative depiction of patient anatomy and disease localization in the sinonasal region, and can, on occasion, provide insights into pathology. The principal modalities used in sinonasal imaging are CT and MRI, and their role (as outlined in the examples that follow) is frequently complementary. PET-CT, a technique combining anatomical information with metabolic information (by virtue of uptake of the glucose analogue ^{18}F-FDG), is increasingly utilized in head and neck cancer imaging in general (for example, in the investigation of the unknown primary), although its role in sinonasal imaging is still emerging.

Plain film imaging is now largely obsolete (except in the context of trauma or, perhaps on the rare occasion when an AP frontal sinus radiograph may be used in template planning for osteoplastic flap surgery). In one study, comparing plain radiographs and coronal CT scans in a paediatric population with recurrent sinusitis, there was an almost 75% discordance between plain film and CT findings.[1] Plain radiographs are neither necessary nor sufficient to either exclude or confirm sinus disease. This advice may be modified, however, in healthcare systems where access to modern cross-sectional imaging is limited.

IMAGING MODALITIES – TECHNICAL ASPECTS

Computed tomography (CT)

Multi-detector row CT (MDCT) enables a patient to be rapidly scanned in the supine position, resulting in submillimetre slices that can be reformatted, in high resolution, in axial, coronal or sagittal planes.

The main drawback with CT is that it involves ionizing radiation. Radiation dose to the lens of the eye is a specific concern in relation to sinonasal imaging and work has focused on the potential for reducing the dose of radiation whilst still maintaining diagnostically satisfactory images.[2]

With CT, high-attenuation ('white') bone contrasts against low attenuation ('black') air and intermediate ('grey') soft tissue and fluid. In terms of providing contrast between different soft tissues or fluid, intravenous iodinated contrast can be of assistance, to some extent, although MRI is superior and usually to be preferred (particularly in the assessment of neoplastic disease where contrast between tumour and secretions/inflamed mucosa is desirable).

Magnetic resonance imaging (MRI)

Having the advantage of no ionizing radiation and superior soft tissue contrast, the imaging sequences employed

usually involve a combination of T1- and T2-weighted images with Gadolinium contrast agents being employed to assess complications of inflammatory disease or to assess spread of neoplasms (particularly to assess perineural tumour spread and dural invasion).

Note that in comparison to CT, no (or very little) contrast is seen on MRI between air and cortical bone (both low signal, or 'black', thus CT more optimally depicts the intricacies of bony anatomy), between cortical bone and fast-flowing blood (for example, between the wall of the sphenoid and the internal carotid artery), or between air and dessicated secretions (both signal voids on T2-weighted images, see below). Thus, there are pros and cons to both CT and MRI and frequently both are needed – particularly in assessing disease involving the skull base.

A particular feature of MR imaging of the paranasal sinuses is the effect that increasing viscosity and protein concentration within secretions has on T1-weighted and T2-weighted images signal intensities – a source of potential confusion. As protein concentration (or viscosity) increases, the signal intensity on T1-weighted images (which for water is low to intermediate) increases and then falls (becomes bright and then dark). For T2-weighted images (starting with bright 'water' signal) there is a gradual decrease in signal intensity[3] (**Figures 117.1** & **117.2**).

At the extreme end of the spectrum, with markedly viscid and dehydrated secretions, a signal void is produced on all imaging sequences.[4] If MRI is the initial investigation then this could be mistaken for air, although a clue to the presence of dessicated secretions may be the finding of expansion of the affected sinus (a mucocele) (**Figure 117.3**). CT will clarify by demonstrating intermediate or high attenuation contents ('grey') within the sinus (as opposed to air which would appear 'black').

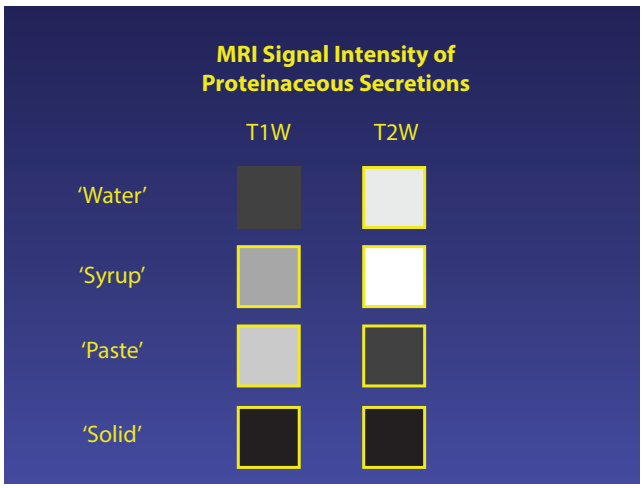


Figure 117.1 MRI of sinus secretions. Note, as the concentration of sinus secretions increases the signal intensity on T1-weighted images goes from intermediate to high to low, whereas on T2-weighted images the signal intensity progressively decreases.

Positron-emission tomography/ computed tomography (PET-CT)

A technique fusing the anatomical information of CT with metabolic information provided by uptake of the glucose analogue ^{18}F-FDG (fluoro-deoxy-glucose) and predicated on tumour (or inflammatory) tissue having increased metabolism and thus increased glucose uptake in comparison to normal tissue. As indicated, its potential role in sinonasal imaging is gradually being appreciated but we will return to this topic towards the end of this chapter.

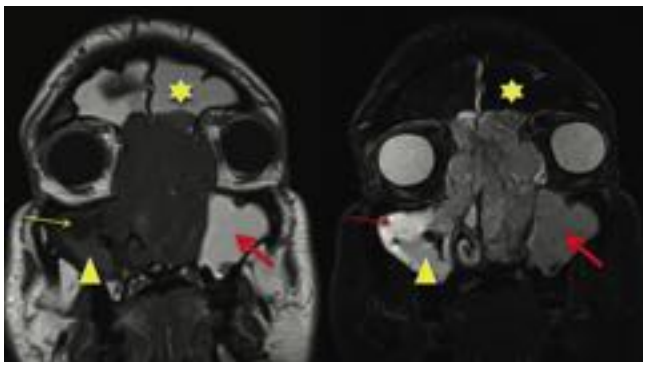


Figure 117.2 MRI of sinus secretions (olfactory neuroblastoma). A large nasal cavity olfactory neuroblastoma causing obstruction of the frontal and maxillary sinuses (T1-weighted image on left, fat-suppressed T2-weighted image on right). Note the differing signal intensities of secretions in the affected sinuses depending on their concentration. Mucosa lining the right maxillary sinus (arrows) is of a similar signal intensity to the aqueous humour (equates to water) in the globe above. Within the right maxillary sinus (arrowheads) the concentration of secretions begins to increase and, as a result, the signal begins to increase on T1-weighted images and decrease on T2-weighted images. Compare with the left maxillary sinus (large arrows) where, as the concentration increases still, the signal on T1-weighted becomes markedly high whilst continuing to reduce (although remaining fairly high) on T2-weighted images. With increasing thickness/concentration of secretions in the frontal sinuses (stars), the signal remains high on T1-weighted images but has now dropped out on T2-weighted images.

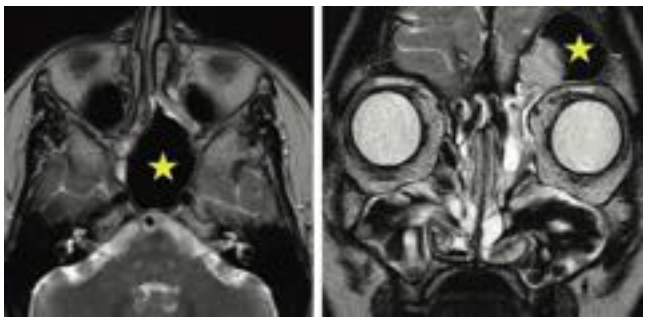


Figure 117.3 Mucoceles containing signal voids. Dessicated secretions can produce a signal void that can be confused for an air-filled sinus, particularly on T2-weighted images. The expansion of the sinus walls hints at a mucocele and in both cases CT confirmed an opacified sinus.

IMAGING – APPLICATIONS

Depicting anatomy

Sinonasal anatomy is subject to tremendous variation and is virtually unique to any one individual such that plain radiographic and, more recently, CT assessment of sinus anatomy are well-recognized techniques for victim identification in forensic investigation.[5]

Some anatomic variants are relevant in terms of potential risk of surgical complications: for example, asymmetry of the anterior skull base (in particular the fovea ethmoidalis) or the presence of an Onodi cell (or sphenoethmoidal cell–a posterior ethmoid cell projecting posteriorly and lateral to, or more commonly above, the sphenoid sinus to be related to the optic nerve).[6]

There are also a number of anatomic variants which have a close relationship to the drainage pathways of the paranasal sinuses. It is controversial as to whether any of these (other than maybe nasal septal deviation) have an aetiologic role in the development of sinusitis.[7] However, an understanding of these variants remains necessary to safe and effective sinus surgery. The reader will be familiar with most anatomic variants including the concha bullosa (pneumatized middle turbinate) and the Haller cell (an air cell located below the ethmoid bulla, inferomedial to the orbit).

More complex are the variants of anatomy occurring in the frontal recess region. This area is of particular concern as this is a difficult area to operate in and as the frontal sinus is an area prone to sinusitis recurrence following FESS.[8]

In understanding frontal recess anatomy, it is useful to start with the basic template of frontal sinus, frontal sinus ostium, frontal sinus drainage pathway, agger nasi cell and ethmoid bulla (**Figure 117.4**). To this template we can consider the various potential frontal recess cells in three groups: medial, anterior and posterior. The medial group consists of the interfrontal sinus septal cell which is best seen on coronal images and easily appreciated as an air cell arising within the interfrontal sinus septum.

The anterior group of frontal cells are classified into types 1 to 4 (**Figure 117.5**).[9] Note that in Kuhn's original classification a type 4 cell is an isolated cell in the frontal sinus. However, Wormald[6] has modified this classification describing both type 3 and 4 cells as frontal cells which pneumatize through the frontal sinus ostium and extend cephalad to a height either less than (type 3) or more than (type 4) 50% of the height of the frontal sinus.

The posterior group consists of the suprabullar cell and the frontal bullar cell, the differentiating characteristic of the latter being that it extends beyond and above the frontal sinus ostium in contradistinction to the former (**Figure 117.6**).

Also belonging to the posterior group, and the hardest cell to illustrate conveniently in a single image (requiring study of both coronal and axial images), is the supraorbital cell.[10] The opening is usually found anterior to the canal for the anterior ethmoidal artery and it extends laterally to pneumatize the orbital plate of the frontal bone, its distinction from the frontal sinus made clear on axial images, where a bony septum can be seen between the two.

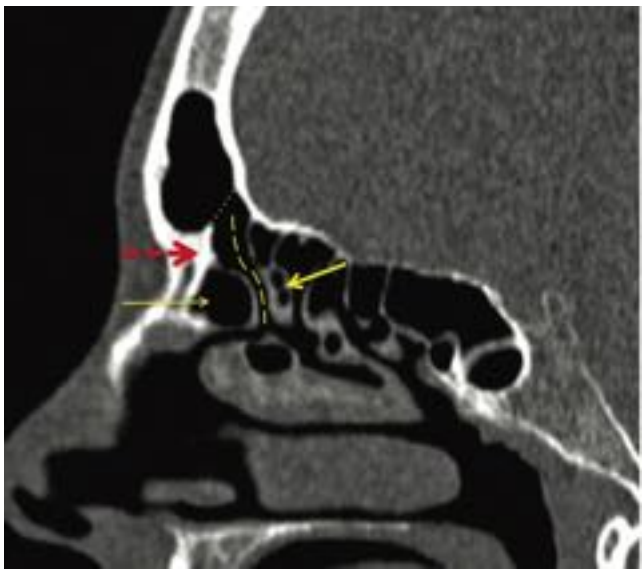


Figure 117.4 Typical frontal recess anatomy as demonstrated in parasagittal section. Frontal sinus ostium (dotted line) runs from frontonasal beak (interrupted arrow) anteriorly to anterior skull base posteriorly. Frontal sinus drainage pathway (dashed line). Note wide superior compartment leading into narrow inferior compartment. Agger nasi cell (small arrow). Ethmoid bulla (large arrow). (Note small suprabullar air cell).

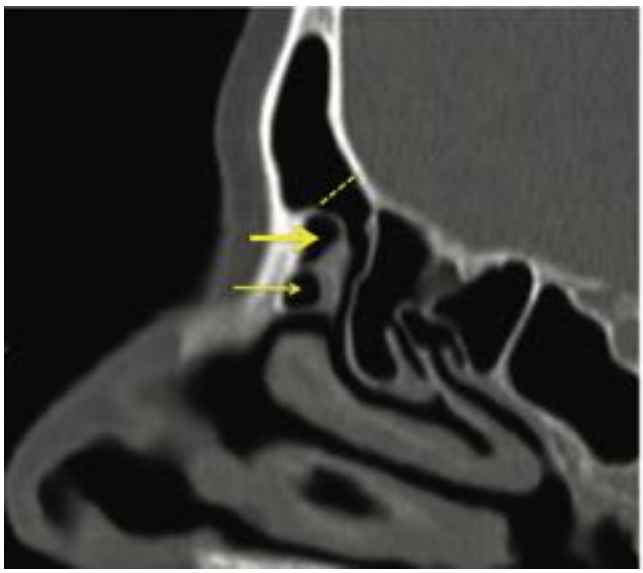


Figure 117.5 Type 1 frontal cell. Type 1 frontal cell (large arrow) sitting above agger nasi cell (small arrow). Note relationship to frontonasal beak. Note the frontal sinus ostium (interrupted line). In a type 2 configuration there are two cells above the agger nasi cell but below the frontal sinus ostium. In type 3 and type 4 configurations a large frontal cell extends through the ostium into the frontal sinus for a variable distance of either <50% (type 3) or >50% (type 4) of the height of the frontal sinus.

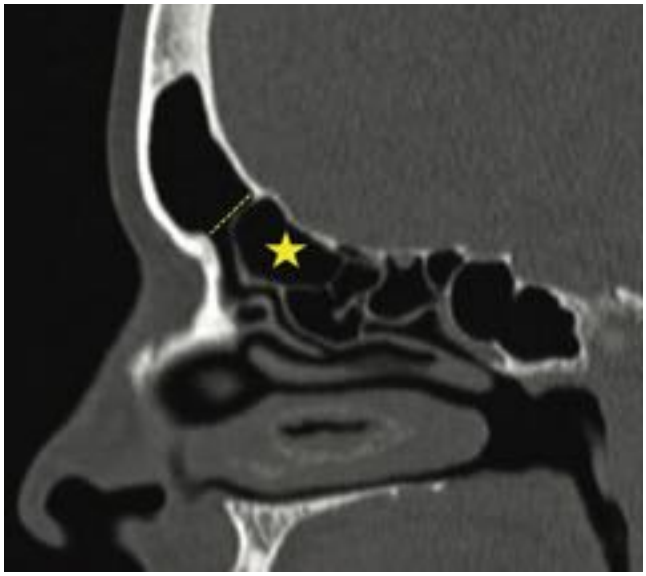


Figure 117.6 Suprabullar cell (star). Note relationship to anterior skull base and frontal sinus ostium (dashed line). A frontal bullar cell extends above the dashed line into the frontal sinus.

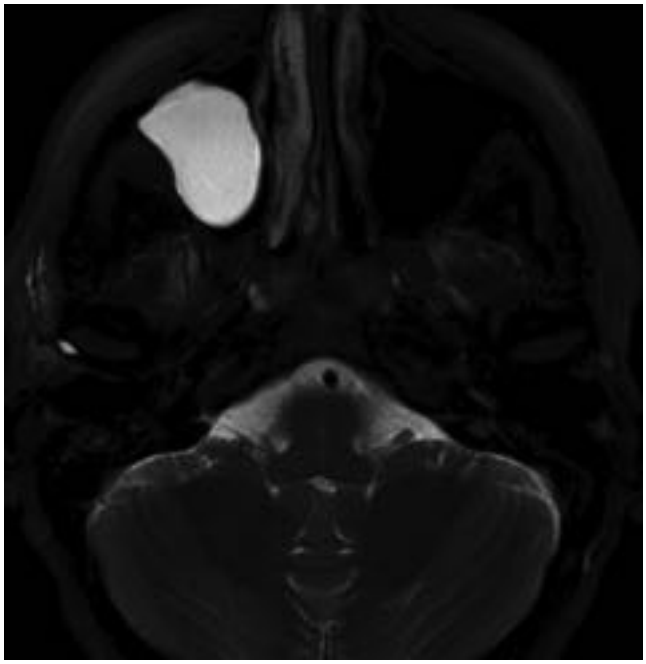


Figure 117.7 Maxillary sinus retention cyst. High signal on T2/fat-saturated images. Typically smooth outlined, 'dome-shaped' lesion.

Sinus inflammatory disease

INCIDENTAL FINDINGS

Mucosal thickening, fluid-filled sinuses and retention cysts are common findings in asymptomatic patients imaged for other reasons: for example, patients undergoing MRI of the head/brain for neurological symptoms,[11] or of the internal auditory meati,[12] or cone-beam CT for orthodontic patients.[13] It has been said that incidentally found mucosal thickening up to 3 mm is of no clinical significance and that in the ethmoid sinuses 1–2 mm of mucosal thickening occurs in 63% of asymptomatic patients.[14] The concept of an 'incidental' Lund score, with 0–5 considered 'normal', has also been suggested.[15] As regards retention cysts (recognized as dome-shaped, smoothly marginated opacities on CT with high (fluid) signal on T2-weighted MR; **Figure 117.7**), the natural history is that the majority either regress or remain unchanged.[16]

The relevance of these incidental findings depends on correlation with clinical findings.

RHINOSINUSITIS (TYPICAL)

The diagnosis of rhinosinusitis is largely a clinical/endoscopic one. Whilst a negative CT is useful to rule out rhinosinusitis and provoke the search for an alternative diagnosis (particularly where the predominant symptom is facial pain[17]), the role of CT when sinusitis is diagnosed is largely one of demonstrating the bony anatomy prior to surgery and defining disease extent (**Figure 117.8**). Disease extent can be quantified through the use of one of a number of staging systems of which the Lund-Mackay system[18] is perhaps the best known. CT acquisition is also needed

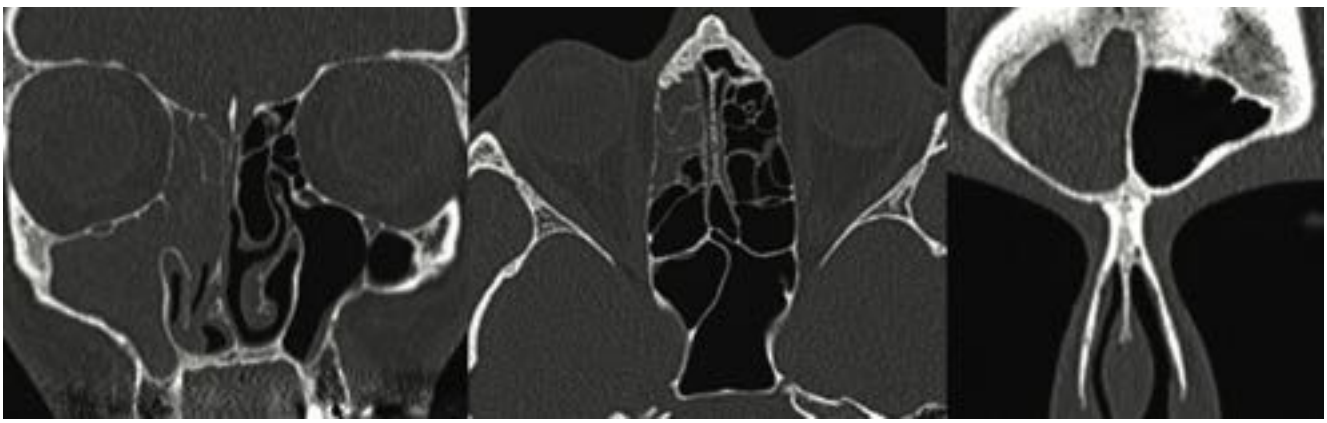


Figure 117.8 Rhinosinusitis. OMU pattern. A case of rhinosinusitis conforming to an ostiomeatal unit pattern of disease involving frontal, maxillary and anterior ethmoid sinuses. Whilst this pattern of disease suggests obstruction at the level of the middle meatus, the CT appearance of the affected sinuses is non-specifically bland.

where the operating surgeon employs a surgical navigation system in theatre.

In terms of diagnostic information, whilst sinus wall sclerosis serves as a pointer to chronicity of disease, the plain CT imaging findings are, for the most part, banal. CT (and MRI) become of more crucial use diagnostically in the investigation of the complications of sinusitis, particularly subperiosteal orbital abscess and intra-cranial infective complications.

FUNGAL SINUSITIS

Fungal sinusitis is a disparate group, with disparate imaging features (**Figure 117.9**), which can be classified into invasive and non-invasive forms:

Invasive (IFS)

Acute invasive fungal sinusitis (AIFS) AIFS usually occurs in immunocompromized patients and is a rapidly progressive, potentially fatal condition. Findings on CT such as bone erosion and mucosal thickening may be subtle.[19] The finding of extrasinus extension (or perisinus soft tissue infiltration)[20] is described as an early and characteristic finding suggesting AIFS (with MR said to be more sensitive in this regard).[21] However, a larger retrospective review[22] found that the commonest early findings on CT in this condition were severe, unilateral, nasal mucosal inflammatory changes (marked mucosal thickening or complete nasal cavity opacification) and that these were found much more frequently, and earlier, than osseous erosion or extra-sinus extension. More recently, the finding on post-contrast MRI of foci of non-enhancement in the nasal cavity (the so-called 'black turbinate' sign-non-enhancing devitalized tissue contrasting with the typical mucosal enhancement normally seen in sinusitis, **Figure 117.9**) has been described in two patients with mucormycosis.[23] In the correct clinical context this finding has the potential to alert the radiologist and surgeon to the correct diagnosis.

Chronic invasive fungal sinusitis (CIFS) Affected patients are usually immunocompetent or have a mild degree of immunocompromise (such as diabetics).

Chronic granulomatous invasive fungal sinusitis (CGIFS) CGIFS usually occurs in Africa (Sudan) or South Asia, is usually caused by *Aspergillus* species, and occurs in immunocompetent individuals. It is considered by some not to be a separate entity but to be a subset of chronic invasive fungal sinusitis.

On CT, chronic (granulomatous) invasive fungal sinusitis tends to display homogeneous soft tissue opacification with no focal hyperdensities (in contrast to allergic fungal sinusitis). Disease tends to be limited in extent or unilateral, sinus expansion is not a feature, focal bony erosion is limited to areas of extra-sinus extension and the burden of disease is often more outwith the sinuses (for example, intra-orbital) than within.[24]

Non-invasive

Allergic fungal sinusitis (AFS) Typically, affected patients are immunocompetent with a history of atopy. A characteristic finding at endoscopy is the presence of so-called 'allergic mucin'.[19]

The typical imaging findings at CT are those of unilateral or bilateral opacification of multiple sinuses, with sinus expansion, bony erosion of the sinus walls, and areas of intra-sinus high attenuation (due to heavy metals, calcium and inspissated secretions).[25]

An important point to note is that whilst AFS is classified as non-invasive (in histopathological terms), advanced disease with sinus expansion and bony erosion can result in extensive intra-cranial and/or intra-orbital 'invasion' with an aggressive appearance on imaging which can mimic malignancy.

Also, it should be noted that the presence of intra-sinus high attenuation is not specific to AFS but can be seen with dessicated secretions in chronic rhinosinusitis. In this case the imaging features of sinus expansion and bony

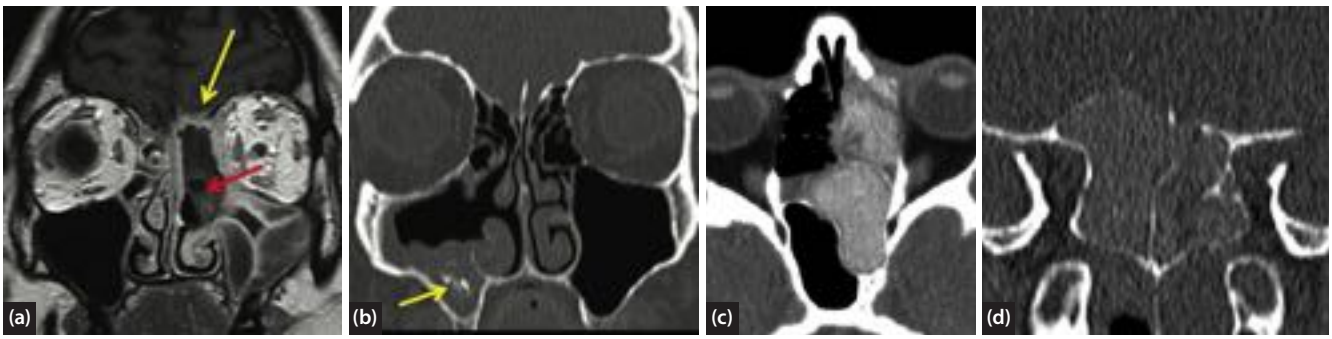


Figure 117.9 Fungal sinusitis. (a) is a case of acute invasive fungal sinusitis (mucormycosis) with cribriform plate extension and dural enhancement as demonstrated on MRI. Note also the non-enhancement of the left middle turbinate and adjacent ethmoid air cells (the so-called 'black turbinate' sign) due to the presence of devitalized tissue. Compare with the normally enhancing right middle turbinate. **(b)** is a case of non-invasive mycetoma or 'fungal ball' on plain CT. The 'ball'-like nature of this condition containing punctate hyperdensities is difficult to appreciate on a non-contrast CT where there is no discrimination with the adjacent inflamed mucosa. **(c)** is a case of allergic fungal sinusitis with the ethmoid sinuses filled with high attenuation material and with expansion of the sinus causing lamina papyracea remodelling. More typically allergic fungal sinusitis is diffuse and bilateral as in **(d)** where there is remodelling of the skull base in the region of the sphenoid. Part **(a)** is reprinted from The Otolaryngologist, Vol **1**(1), Fraser L, McGarry W. Core knowledge and literature review, p. 5. 2006 Copyright with permission from Rila Publications Ltd, London.

thinning point to the former whereas the latter is more characterized by thickening and sclerosis of sinus walls.

The MR appearance is typically low to signal void on T2-weighted image (due to heavy metals and dessicated secretions) and more variable on T1-weighted image.[19]

Fungal ball/ mycetoma A fungus ball is a tangle of fungal hyphae within a sinus, but with no allergic mucin (compare with AFS) and no evidence of submucosal invasion (compare with IFS).[19] Affected individuals tend to be older and immunocompetent.

Typically a single sinus is involved, and on a non-contrast CT, an iso- to hyper-attenuating soft tissue mass is seen, frequently containing punctate or nodular calcifications. In contrast the inflamed mucosa lining the sinus is hypo attenuating on CT, hyper intense on T2-weighted image MRI and demonstrates contrast enhancement.

The fungus ball is low signal on T1-weighted and T2-weighted images as it contains little or no free water. Contained calcifications or heavy metals (iron and manganese)[26] produce a characteristic signal void on T2-weighted image.[27]

Granulomatous inflammation

Covering a range of disorders, this subset is characterized by the common imaging features of nasal septal perforation and destruction of the midline sinonasal skeleton including turbinates and hard palate.

The differential diagnosis for septal perforation and mid-face destruction not only includes the various granulomatous disorders but also neoplasia (for example, squamous cell carcinoma), infection (leprosy, syphilis, tuberculosis, actinomycosis, rhinoscleroma) and cocaine misuse (**Figure 117.10**).



Figure 117.10 Cocaine-induced nasal cavity destruction. Note the mucosal thickening accompanying destruction of the right inferior turbinate and lower aspect of right middle turbinate. Unusually the process is unilateral and the nasal septum is not involved.

Of the granulomatous disorders, Wegener's granulomatosis has a particular propensity for involvement of the nasal cavity and paranasal sinuses.

The early features of the disease may be non-specific (mucosal thickening, sinus opacification) but with disease progression, bony destruction occurs involving nasal septum and turbinates initially. Neo-osteogenesis (to the extent of sinus obliteration) is also a feature on CT, and one which is exacerbated by surgery.[28]

On MRI, as on CT, the early manifestations of sinonasal Wegener's may be non-specific and indistinguishable from sinusitis. In the later stages granulomatous inflammation is depicted as low-signal intensity lesions, best depicted on T2-weighted images. Orbital involvement may occur.[29]

The imaging features of cocaine misuse are similar to Wegener's but at initial presentation the extent of mid-face destruction is usually greater (perhaps reflecting a delay to presentation).[30]

Sarcoidosis shares similar imaging features with other granulomatous disorders, but a feature which is said to be characteristic is the finding of soft tissue nodules on the septum or turbinates.[31]

NK (natural killer cell)/T-cell lymphoma (formerly known as lethal midline granuloma) shows a tendency to spread as a thin sheet of tumour enveloping turbinates and septum[32] and may extend into the nasopharynx[32] or paranasal sinuses.[33] Nodal involvement is not usual. Interestingly, a recent study has shown a majority in their cohort presenting as unilateral nasal cavity disease.[33] However, the imaging findings are not diagnostic and the finding that is most characteristic for this disease is Southeast Asian ethnicity.[32, 33]

Miscellaneous

The imaging features of a miscellaneous group that includes antrochoanal polyp and silent sinus syndrome are virtually diagnostic (**Figure 117.11a** and **117.11b**). In the maxillary sinuses, a possible odontogenic cause of sinusitis (**Figure 117.11c**) should always be considered and one should consider also odontogenic cysts (**Figure 117.11d**) in the differential diagnosis of the 'opacified maxillary sinus'.

Sinonasal neoplasms

It is rare (if ever) that imaging will be able to definitively diagnose a sinonasal lesion without the referring clinician ultimately having to make recourse to biopsy. Conversely, however, the radiologist and clinician must be alert to those occasions when it is mandatory *not* to perform a biopsy (for example highly vascularized tumours, sphenoid sinus internal carotid artery pseudoaneurysm).[34]

But for the most part, the purpose of imaging the sinonasal neoplasm is to delineate the extent of the tumour, both in terms of differentiating tumour from secetions or mucosa (**Figure 117.12**) within the sinonasal compartment (where MRI is of particular use), and in terms of defining extent outwith the sinonasal compartment.

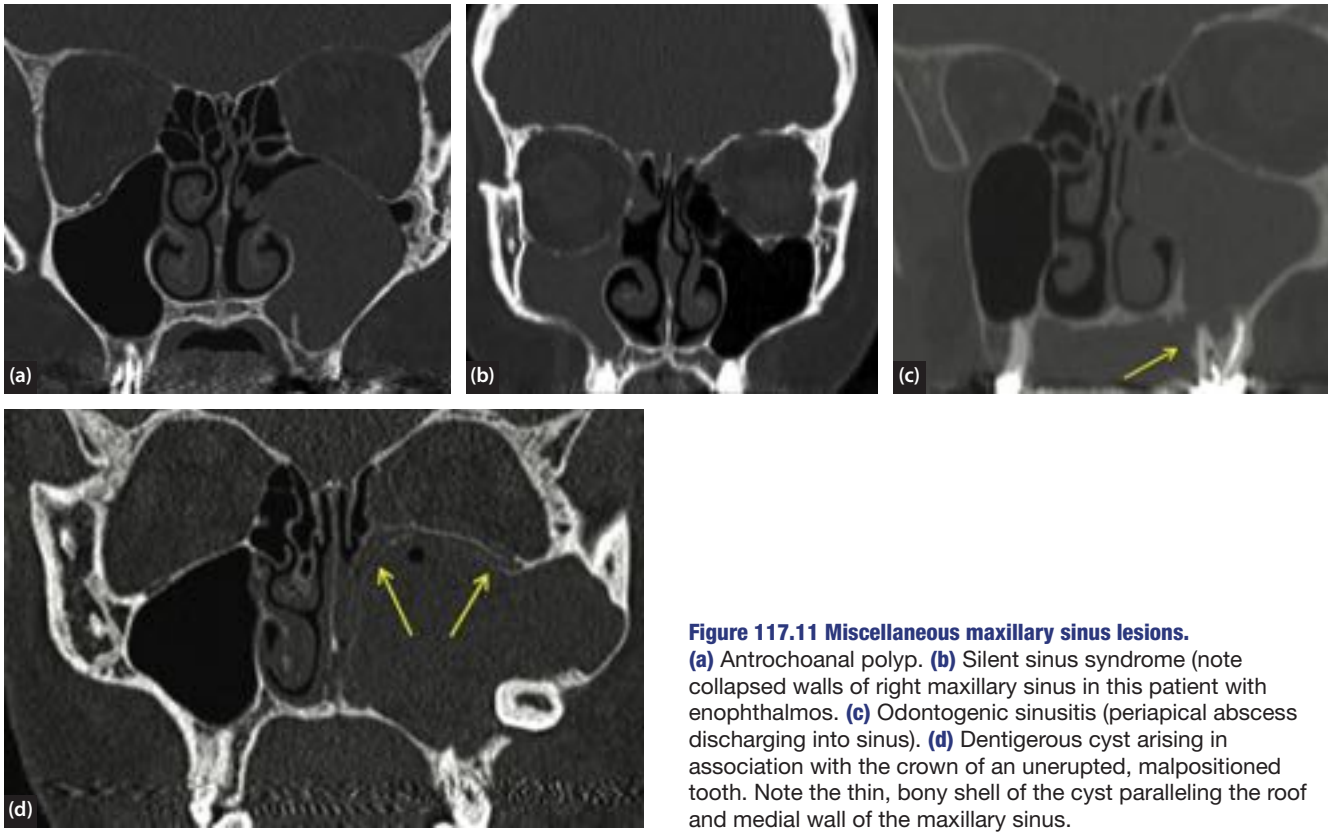


Figure 117.11 Miscellaneous maxillary sinus lesions. **(a)** Antrochoanal polyp. **(b)** Silent sinus syndrome (note collapsed walls of right maxillary sinus in this patient with enophthalmos. **(c)** Odontogenic sinusitis (periapical abscess discharging into sinus). **(d)** Dentigerous cyst arising in association with the crown of an unerupted, malpositioned tooth. Note the thin, bony shell of the cyst paralleling the roof and medial wall of the maxillary sinus.

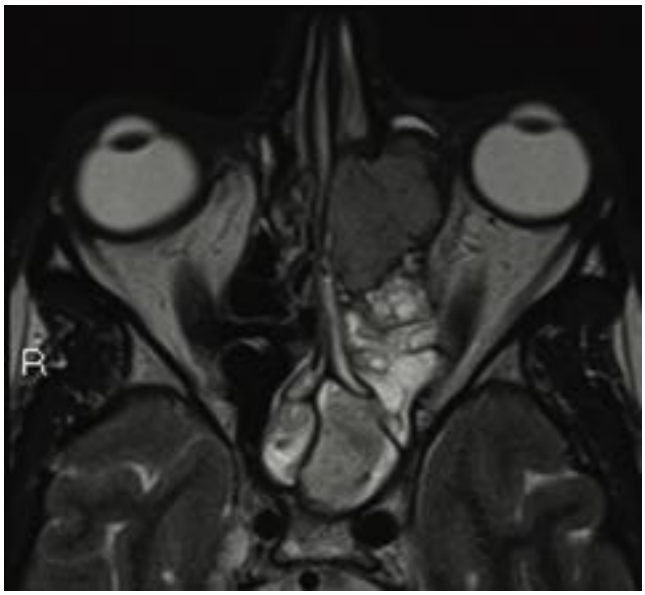


Figure 117.12 Tumour vs. obstructed secretions. MRI sharply defines the extent of this tumour in the anterior ethmoid sinus contrasting with obstructed secretions in the posterior ethmoids and sphenoid.

SPECIFIC TYPES OF NEOPLASMS

Inverting papilloma

A unilateral mass commonly originating in the lateral nasal wall and involving middle meatus and maxillary sinus, although less commonly the site of origin will be the maxillary sinus itself, the anterior ethmoid sinus or, rarely, the sphenoid, frontal or posterior ethmoid sinuses. Though benign, these lesions commonly recur and are associated with squamous cell carcinoma. CT features include internal calcification, and bony erosion or bowing. Focal hyperostosis (**Figure 117.13c**) is a finding which has been said to correlate with the site of origin of this neoplasm – a finding which has potential relevance in planning the extent of surgery needed to achieve extirpation.[35] On MRI a characteristic convoluted, cerebrifrom pattern (**Figure 117.13a** and **117.13b**) is said to be highly suggestive of this diagnosis, with the concomitant finding of necrosis suggesting a coexistent focus of carcinoma.[36]

Sinonasal carcinoma

These include the common squamous cell carcinoma and the less common adenocarcinoma. Neither have specific imaging characteristics and the purpose of imaging is to define tumour extent.

Adenoid cystic carcinoma is given particular attention because of its poor prognosis, in part because of its propensity for perineural spread. However, this mode of tumour extension will be more frequently encountered in squamous cell cancer simply because the latter is much more common. Thus imaging of all forms of carcinoma must include post-contrast MR sequences with particular care given to examining the cranial nerves (**Figure 117.14**), pterygopalatine fossa, skull base foraminae and the intracranial compartment.

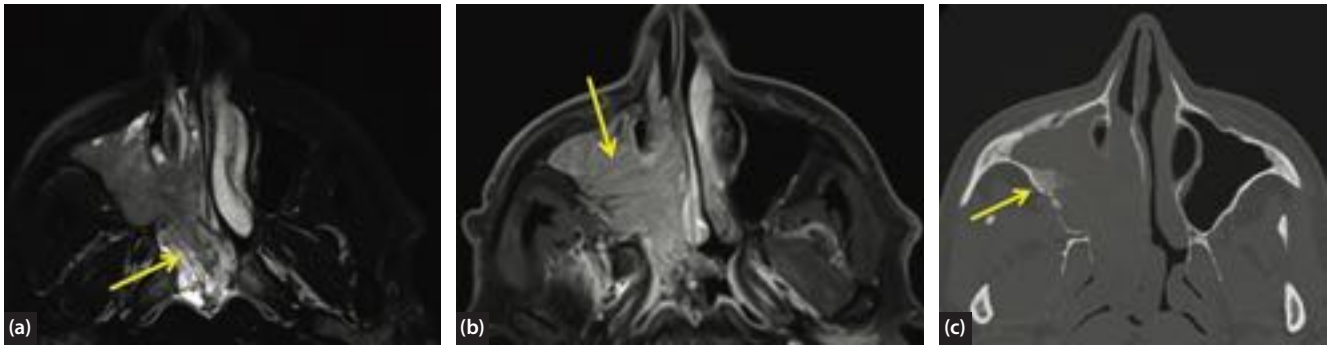


Figure 117.13 Inverted papilloma. Note the striations ('cerebriform' pattern) visible on T2 FS **(a)** and post-contrast **(b)** MRI and the focus of hyperostosis in the lateral wall of the maxillary sinus on CT **(c)** suggesting the site of origin of this growth.

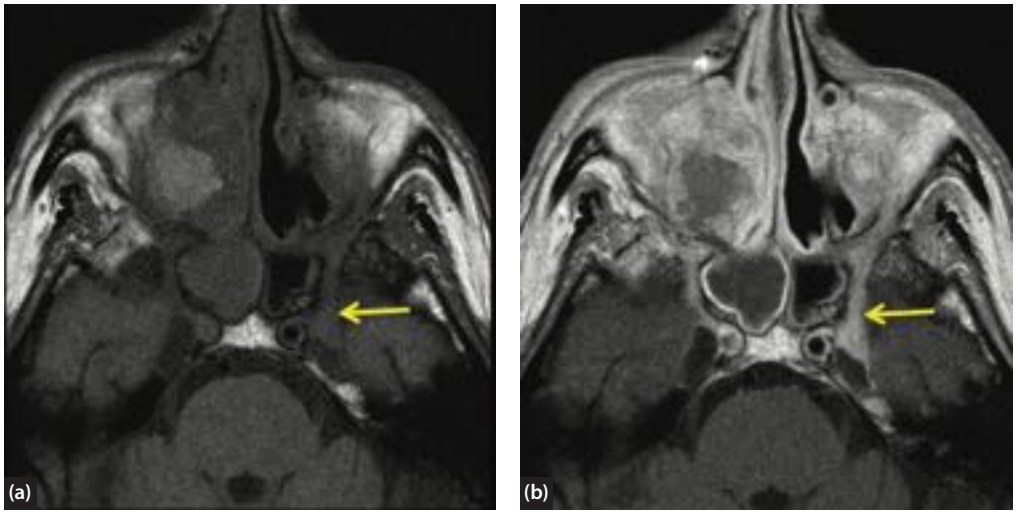


Figure 117.14 Perineural tumour spread (recurrent SCC). Note enhancement of left maxillary nerve (also right). **(a)** Pre-contrast; **(b)** post-contrast.

Sinonasal melanoma

Sinonasal melanoma is infrequent and whilst these lesions may demonstrate high signal on T1-weighted images, presumably because of the paramagnetic effect of melanin[37] or haemorrhage,[38] a number may be amelanotic in which case the imaging features are non-specific.

Bone and cartilage tumours

In contrast to the non-specific imaging features of sinonasal disease in general, imaging (in particular, CT) of lesions arising from bone or cartilage plays a central diagnostic role in concert with pathology.

Benign lesions include osteoma, which can appear as dense cortical bone or ground-glass,[39] and fibro-osseous lesions (fibrous dysplasia or ossifying fibroma). Fibro-osseous lesions are readily recognizable on CT although biopsy may still be required to refine the diagnosis. In contrast, the MRI appearance of fibrous dysplasia can be misleading and may be a trap for the unwary (**Figure 117.15**).

Of the malignant lesions primarily arising from bone, chondrosarcoma is perhaps the most common in the paranasal sinus region and can be suggested on CT by matrix calcification (**Figure 117.16a**) and on MRI by high signal on T2-weighted image (as a result of a high matrix water content) and by curvilinear septal enhancement on post-contrast images (**Figure 117.16b** and **117.16c**).[40, 41]

Vascular lesions

These include haemangioma, haemangiopericytoma, angiomatous polyp and the juvenile nasal angiofibroma (JNA). The clues to the vascular nature of a nasal mass include the finding of flow voids and avid enhancement with contrast (**Figure 117.17**). The location of the lesion is an important feature of the JNA, which characteristically expands the pterygopalatine fossa.

Lymphoma

T cell lymphomas characteristically affect the nasal septum (see above) whilst B cell lymphomas typically arise in the maxillary sinus with an epicenter close to the lateral sinus wall and tumour on either side of the sinus wall.[39]

Neuroendocrine tumours

This is a group of tumours including olfactory neuroblastoma (**Figure 117.2**) and sinonasal undifferentiated carcinoma (SNUC) which tend to arise in the superior nasal fossa but which otherwise frequently have non-specific imaging features.

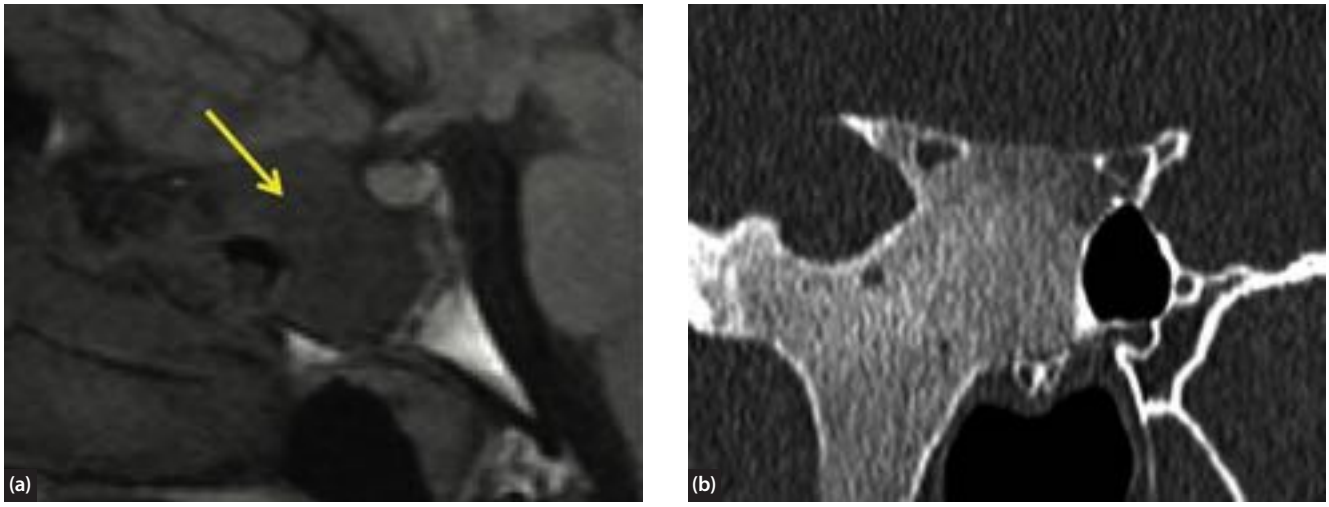


Figure 117.15 Fibrous dysplasia. (a) On MRI it is very easy to confuse fibrous dysplasia (in this case involving sphenoid) with tumour. **(b)** On CT the diagnosis is straightforward.



Figure 117.16 Chondrosarcoma. (a) Note calcified matrix of a chondrosarcoma of the nasal septum. **(b)** Internal septal enhancement on post-contrast MRI. **(c)** High signal on T2-weighted image resulting from high water content of chondroid matrix.



Figure 117.17 Juvenile angiofibroma. Note flow voids ('black dots' and curved black lines) within this brightly enhancing tumour indicating that this is a highly vascularized lesion.

Predicting dural invasion

Skull base invasion by (with or without intra-cranial extension of) a sinonasal malignancy has important implications in assessing the feasibility and extent of surgical resection and in deciding between an endoscopic or open approach to the tumour. Whilst CT is important to assess the integrity of the bony skull base owing to the contrast between bone and soft tissue, MRI becomes essential for assessing tumour relationship to dura and brain parenchyma.

Whilst a tumour with clear evidence of intra-cranial extension associated with brain oedema on MRI is generally considered to imply that the tumour has breached the leptomeninges to involve the brain parenchyma (Figure 117.18),[42] the use of MRI in predicting earlier degrees of dural invasion has also been studied. Pial enhancement, nodular dural enhancement and dural thickening of more than 5 mm have been found to be predictive of dural invasion. A linear pattern of enhancing dura was more commonly associated with, or interpreted as, reactive inflammation adjacent to tumour.[42] Further, where linear dural enhancement is separated from tumour by a thin hypointense zone this suggests reactive inflammation. In contrast, areas where tumour cannot be

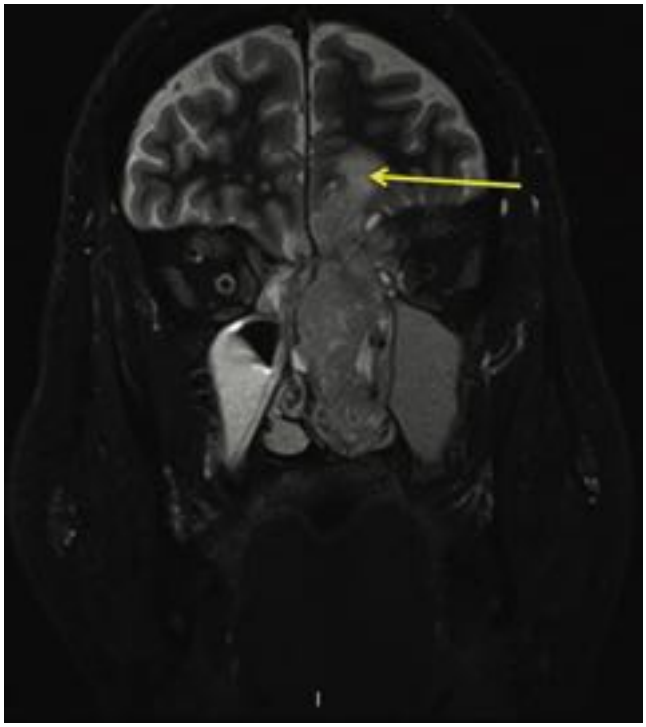


Figure 117.18 Brain parenchymal invasion. Vasogenic oedema in the left frontal lobe implies that this tumour (an olfactory neuroblastoma) has transgressed the dura and is now invading brain.

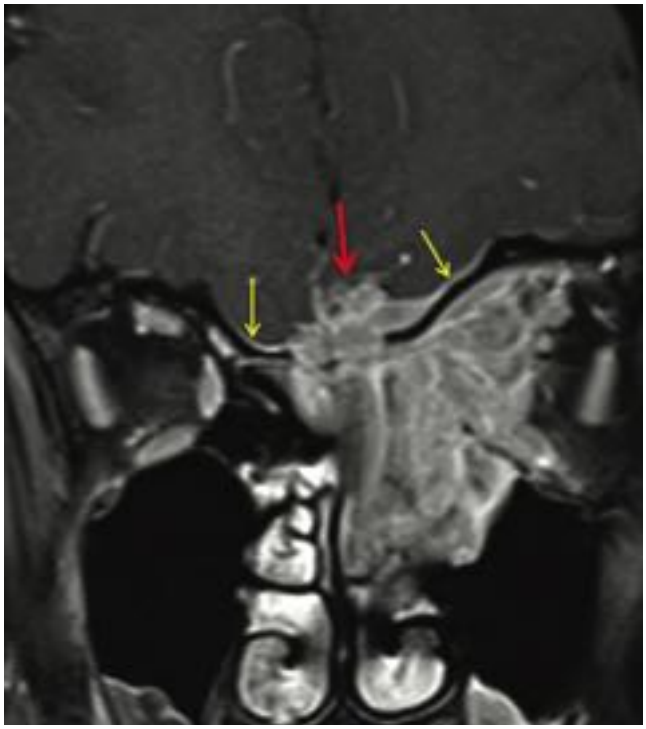


Figure 117.19 Alveolar rhabdomyosarcoma. Note the thin linear dural enhancement (yellow arrows) representing reactive inflammation interrupted by nodular tumour tissue, indistinguishable from enhancing dura. This corresponds to the nodular enhancement described by Eisen[42] or the focal interruption of linear dural enhancement by tumour as described by Ahmadi[43, 44] and is a marker for dural invasion.

visually separated from enhancing dura, or where there is a focal interruption of linear dural enhancement by tumour (**Figure 117.19**), suggest dural invasion.[43, 44]

CSF leaks

CSF rhinorrhoea is most commonly post-traumatic in origin (frequently post-surgical), less commonly non-traumatic (tumours, infection or congenital lesions), and occasionally spontaneous. In most cases, non-contrast CT of the skull base is the only imaging investigation required to identify a skull base defect (**Figure 117.20**).[45]

MRI should be performed in cases where a skull base defect found on CT is associated with opacification in the nasal cavity or sinus below the defect, to exclude an encephalocele or meningoencephalocele (**Figure 117.21**).

More advanced techniques include non-contrast MR cisternography (heavily T2-weighted with fat suppression), which relies on the detection of a continuous, bright CSF column from the subarachnoid space to the nasal cavity or sinus below[46] or, in cases where there remains a diagnostic dilemma, then more invasive cisternography (radionuclide or CT) may be considered.

MR cisternography using intrathecal Gadolinium has been used to detect CSF leaks with reported success,[47] however, its widespread acceptance has been delayed (partly due to a lack of FDA approval) and some have sounded caution regarding the lack of data confirming an absence of neurotoxicity over the long-term.[48]

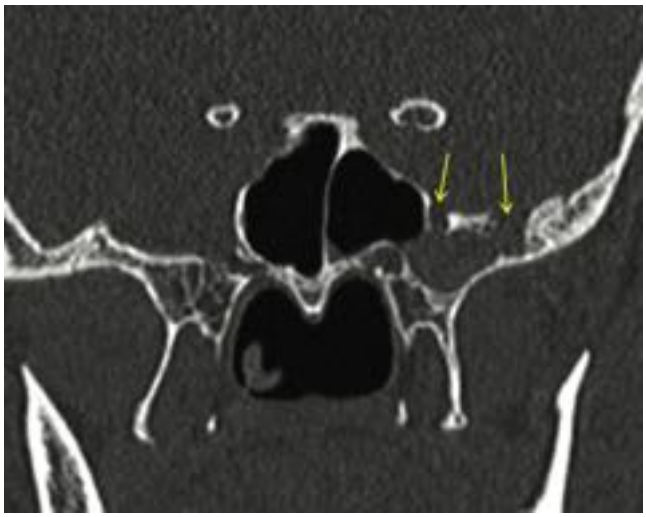


Figure 117.20 Arachnoid granulations. Spontaneous CSF fistula. Arachnoid granulations (yellow arrows) eroding roof of sphenoid sinus with fluid noted in the sinus below. Note extent of lateral pneumatization of the sinus. Non-contrast CT is frequently the only investigation needed to identify the site of a CSF leak.

An alternative to cisternography is the use of intrathecal fluorescein injection coupled with the endoscopic detection of fluoroscein-stained CSF leaking through a skull base defect (**Figure 117.22**).

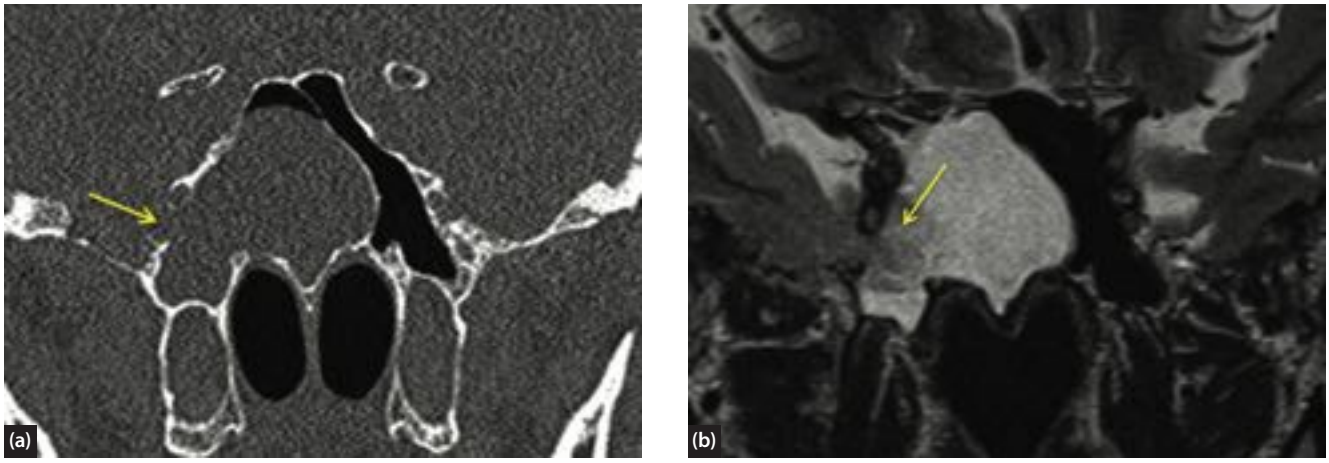


Figure 117.21 Encephalocele. (a) Note the defect in the lateral wall of sphenoid and the contiguous opacification within the sinus on this non-contrast CT. MRI is mandatory subsequent to this. **(b)** Note herniating brain tissue through the defect. The converse situation, the finding of a sinus 'polyp' or fluid adjacent to the skull base on MRI, may require a subsequent CT to more clearly depict the bony defect.



Figure 117.22 Endoscopic detection of CSF leak following intrathecal injection of fluoroscein. Note skull base defect with fluoroscein leakage adjacent to tip of probe. (Courtesy of Gerry McGarry).

IMAGING – NEW DEVELOPMENTS

The roles of PET-CT and DWI (diffusion-weighted imaging) are as yet not clearly defined but are beginning to emerge.

PET-CT

As sinonasal malignancies are rare, and are heterogeneous in terms of pathology, the role of PET-CT has been slow to emerge. Where PET-CT has been used in the staging or re-staging of sinonasal malignancy it has been seen to have a role in altering treatment course, particularly in the detection/exclusion of distant metastases (where consistently high negative predictive values have been demonstrated).[49, 50] However, caution should be exercised regarding the number of false positive studies (24%),[50] which may lead to unnecessary interventions (biopsies), and with regard to the occasional false negative study (for example, in intra-cranial disease where the normal metabolic activity of the brain may obscure disease).

It is unlikely that PET-CT will obviate the need for conventional imaging (in particular, MRI – although PET-MRI has been shown to be feasible), it is being more frequently used as an important adjunct – especially in the settings of advanced disease (where the finding of distant metastases may avoid major, potentially mutilating surgery) and in recurrent disease (where the effects of treatment, residual masses and recurrent disease are difficult to differentiate on conventional imaging).

In the setting of sinonasal papillomas PET-CT has been explored for its potential in identifying co-existent malignancies but with disappointing results.[51]

PET-MRI

This development has so far only been explored in terms of its feasibility but has the potential to improve soft-tissue contrast and reduce radiation exposure compared with PET-CT. Whole body imaging is feasible using this technique although the technique is not widely available and its role remains uncertain.[52]

Diffusion-weighted imaging (DWI)

Essentially, this is an extension of MRI predicated on the degree to which free water molecules diffuse in tissues. In general, the more cellular the tissue the less extracellular space available for water to diffuse. The degree to which diffusion occurs in tissues can then be expressed in terms of the apparent diffusion coefficient (ADC). The more cellular the tissue the lower the ADC and therefore it might be hoped that measuring the ADC of a tumour might help distinguish benign tumours from, usually more cellular, malignancies. Unfortunately, the picture is complicated by factors such as tumour necrosis and the presence

of keratin, collagen or debris. A considerable overlap in ADC values has been observed between benign sinonasal tumours and malignancies[53] although other observers report improved differentiation between inflammation, benign lesions and malignancy through the use of ADC mapping (a visual map of ADC values assigned to individual pixels rather than an overall ADC)[54] particularly if interpreted alongside the analysis of time-signal intensity curves generated from dynamic contrast-enhanced MRI (DCE MRI).[55]

Cone beam CT

A low-cost, compact technology used widely in dental practice, as yet the image quality (particularly soft-tissue contrast) does not compare with conventional CT. However, the potential for significant radiation dose-reduction exists and its role in sinonasal imaging could include intra-operative imaging (for example, assessing adequacy of resection).[56]

CONCLUSION

Modern cross-sectional imaging plays a central role in the diagnosis and assessment of sinonasal disease. Whilst MRI and CT are the key imaging modalities it is likely that the use of PET-CT will continue to expand as its role becomes clearer, particularly in the setting of sinonasal malignancy.

This is a complex area, both in terms of the anatomy of the sinonasal region and anterior skull base and in terms of the heterogenous pathologies presenting here. Increasingly therefore, there is a need for increased subspecialization by dedicated head and neck radiologists working closely with head and neck surgeons in the best interests of this patient group.

BEST CLINICAL PRACTICE

- ✓ Radiologists should work closely with clinicians and pathologists in an MDT setting.
- ✓ Radiologists should aim to subspecialize in this challenging area.
- ✓ Audit results.

FUTURE RESEARCH

- ➤ New techniques are being developed in CT to reduce radiation dose whilst maintaining high-quality images.
- ➤ Anticipated developments in cone beam CT are expected to include improved image quality and potentially intra-operative use.
- ➤ The role of Diffusion-weighted MRI is expected to be refined.
- ➤ Advancements in PET MRI are expected.

KEY POINTS

- There is virtually no role for plain radiography in the investigation of sinus disease.
- Radiation to the eyes is a particular concern with CT.
- CT and MRI differ in the contrast demonstrated between different tissues. Thus these two modalities are often complimentary.
- Sinus anatomy is subject to extreme variability between individuals.
- Mucosal thickening, fluid-filled sinuses and retention cysts are common incidental findings.
- In inflammatory disease, imaging is useful to exclude sinusitis as a cause of symptoms, to provide an anatomical roadmap to the surgeon, and to provide diagnostic information.
- In neoplastic disease, the purpose of imaging is to alert the surgeon when not to perform a biopsy and to delineate the extent of the tumour in relation to secretions and inflammation, and spread outwith the sinonasal compartment.
- The role of PET CT is an evolving one but it is of particular use in staging cancer patients with advanced disease and in detecting recurrence.

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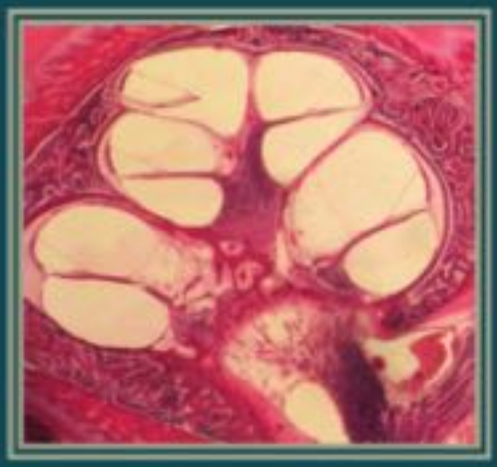
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The Ear
Skull Base

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Foreword

The eighth edition of *Scott-Brown* signals the beginning of a new and exciting era for ear, nose and throat surgeons, and also the end of 10 years of very hard work undertaken by John Watkinson and Ray Clarke, the Editors-in-Chief, their team of subeditors and, not least, the publishers. Whatever subspeciality the current generation of trainees decides to follow, they will all have to read and refer to *Scott-Brown* in order to complete their education and gain accreditation. It will be a constant companion and guide throughout their professional lives.

When asked to write the foreword for this edition, I was immediately reminded that I had read John Ballantyne and John Groves's third edition as a trainee, bought the fourth edition as a senior registrar, written chapters for Alan Kerr and Philip Stell in the fifth edition, edited the *Basic science* volume of the fifth edition and was ultimately Editor-in-Chief of the seventh edition. As each edition takes about 10 years to produce, that makes me very old indeed. John and Ray have one final task as Editors-in-Chief: to recommend their successors to the publishers. That was made easy for me as both of them had proved themselves more than capable with the previous edition, and the eighth edition is now their masterpiece. They can enjoy the next 10 years as thousands of surgeons worldwide recognize and thank them for their industry.

This edition reflects the continued expansion of our speciality into fields that Scott-Brown himself could never have imagined. It lays the groundwork for the current generation to make their contribution that will, no doubt, be prompted by technological developments, an evidence base of what is wise and what is not, together with the experience gained by teamwork with other clinicians in today's multidisciplinary approach to patient care.

Simply looking at the table of contents it is clear to see that our role in endocrine surgery has increased dramatically over the last 10 years. The thyroid and parathyroids now account for 30 chapters. How would Scott-Brown have viewed that when the tonsils and adenoids justify just one chapter each, and the sore throat has a mere passing reference? Times have certainly changed and ENT surgery has grown up. We have reflected on our past practices, and the evidence base for our management protocols that was emphasized in the previous edition of *Scott-Brown* has been taken to heart.

I hope that this edition will find its way into every medical library in the world and onto every ENT surgeon's bookshelf. It will serve and guide surgeons throughout the English-speaking world, whether they live in high- or low-income countries. It is said that the tragedy of getting old is that we feel young. Reading these volumes makes me wish that I had my time all over again.

Michael Gleeson



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Preface

When we were asked to head up the editorial team for this, the eighth edition of *Scott-Brown*, we were mindful of Michael Gleeson's towering achievement in bringing the seventh edition to fruition. Michael delivered a much-loved text – conceived in the early post-war years when antimicrobials, the operating microscope and the National Health Service were all in their infancy – in an entirely new format that befitted modern surgical scholarship. Authors, editors and readers alike had become acutely conscious of the need to quote high-quality evidence to guide clinical decisions; the concept of grading clinical recommendations – and, by implication, acknowledging gaps in the evidence base of our practice – was born. Recognizing the enormity of Michael's contribution led us into the trap that has befallen every editor who has come before us; we grossly underestimated the task ahead. We had misjudged the pace of change. What began as an 'update' of some outdated chapters became a complete rewrite to reflect the advances that marked the decade between editions, but we were determined to keep the text to a manageable size. In the end, we have 330 chapters, but with a slightly smaller page count than the seventh edition.

The basic science knowledge that underpins our clinical practice is no longer focused just on anatomy and physiology; genetics, molecular biology, new techniques for auditory implantation, information technology, new medical therapies for many old disorders together with seismic changes in endoscopic technology and in medical imaging have transformed our specialty. Today's head and neck surgery would have been unrecognizable to the early authors and editors. Surgical oncologists have recourse to completely different treatment strategies than did their predecessors and now work as part of multidisciplinary teams. They deal with different disease patterns and vastly changed patient expectations. Thyroid and parathyroid surgery has become almost exclusively the domain of the otolaryngologist. Surgery of the pituitary fossa has come within our ambit, as has plastic and reconstructive surgery of the head and neck as well as aesthetic facial surgery. Neurotology, audio-vestibular medicine, rhinology and paediatric otolaryngology are accepted subspecialties, each with its own corpus of knowledge and skills and each warranting a sizeable section of this text. Contemporary otolaryngology is now a collection of subspecialty interests linked by common 'stem' training and a shared passion for looking after patients with disorders of the upper respiratory tract and the head and neck.

There is a view that a single text – even a multivolume tome of this size – cannot cover the entire knowledge base of modern clinical practice. The subspecialist will, of course, need recourse to supplementary reading. The pace of change shows no sign of slowing down, but there is still a need for a comprehensive working text embracing the whole spectrum of our workload. That was the task we set our authors and section editors; we think they have done our specialty proud.

In the new 'digital' editorial world authors create manuscripts on personal computers. They transmit chapters, figures, amendments and revisions across continents and time zones with a few keystrokes. The bulky packages containing grainy photographic prints and the reams of paper with closely-typed and heavily scored text that accumulated on authors' and editors' desks are a distant memory. References, guidelines and systematic reviews are all available online; the editorial 'red pen' has been replaced by a cursor on the screen. This 'new age' has enabled us to look ever further for expertise. We are proud to have enlisted the support of authors from more than 20 countries for this edition. *Scott-Brown* always enjoyed particular affection and respect in Asia, Australia, Africa and the Middle East. It has been a joy to welcome authors in increasing numbers from many of these parts of the world. We are now a truly global specialty and the eighth edition fully reflects this.

What has not changed is the huge time commitment authors and editors need to make. That time now has to be fitted into an increasingly pressurized work environment. Revalidation, mandatory training, more intense regulatory scrutiny, expanding administrative burdens and ever-expanding clinical commitments leave little time for scholarship. Our section editors are all busy clinicians. They have generously given their time, first instructing authors, cajoling them and then editing their chapters, virtually all of which have been completely rewritten since the last edition. Each author was chosen because of his or her specific clinical and scientific expertise and none has disappointed. Authors and section editors receive no reward other than the satisfaction of knowing that they have made a contribution to teaching and learning in a specialty that has given us all so much professional satisfaction. We are profoundly grateful to them and hope that their endeavours spur the next generation of otolaryngologists to carry on this noble tradition. *Scott-Brown* simply wouldn't happen without this generous and dedicated commitment, unstintingly and graciously given.

It is impossible to produce a book like *Scott-Brown* without the contribution of many individuals working behind the scenes. We would like to express our gratitude to our Publishers, Taylor and Francis, and to the staff who have worked on this project from its early days in 2011 to publication in 2018. In particular we would like to mention Cheryl Brandt who with good humour and patience helped to reel in many of the 330 chapters. Miranda Bromage joined the team in 2016 and her publishing experience and enthusiasm for medical education have helped guide this new edition through its final phases to publication. Finally, we are indebted to Nora Naughton who has dedicated so much more than just her extensive publishing skills to this project. Nora's meticulous attention to detail, combined with her warmth and wisdom have encouraged us all at the end of this endeavour.

We are truly 'passing on the torch' of a huge amount of accumulated knowledge and wisdom; it is this that gives us, the Editors-in-Chief, the greatest pleasure.

Read on and enjoy, our thoughts are yours.

RWC
JCW

I wish to acknowledge the love, happiness and inspiration that have been passed on to me by both my parents and grandparents. I recognise and value the friendship of my dear friend Ray Clarke who has been with me all the way on this rewarding and worthwhile endeavour. I would specifically like to thank Esme, Helen and William, without whom none of this would have been achievable. Their love and support has helped guide me through the years leading up to the publication of this tome, and my final thanks go to Angela Roberts and Sally Holden for their typing and editing skills.

JCW 2018

Thanks to my wife Mary for her patience and support. My parents, Emmet and Doreen Clarke, both sadly died during the preparation of this book. They would have been proud to have played a part in such a scholarly enterprise.

RWC 2018



Black Hut on the River Test – Pastel by W G Scott-Brown – circa 1970. Reproduced by kind permission of Mr Neil Weir, who was presented with the original by the artist.

A Tribute to Bill Scott-Brown



Walter Graham ('Bill') Scott Brown. 1897–1987

Walter Graham ('Bill') Scott-Brown was twenty-three when he arrived at Corpus Christi College Cambridge in 1919. One of the generation of young men whose entry to university and the professions was delayed by their participation in the First World War, he had joined the Gunners in 1915 as an 18-year-old. He considered himself blessed to have survived – although wounded – when so many of his contemporaries never returned from the Front. In those early post-WW1 years the medical school at St Bartholomew's ('Barts') in London was keen to attract 'gentlemen'. To this end a series of scholarships – 'Shuter's scholarships' – was established to lure those with humanities degrees from Oxford and Cambridge into medicine. It was via this scheme that the young Scott-Brown qualified MB, BCh in 1925. By now married to Margaret Bannerman, one of the very few women medical graduates of her generation, the two established a general practice in Sevenoaks, Kent. His work here involved looking after children with poliomyelitis, which was then commonplace, and his MD thesis was on polio-related bulbar palsy. It earned him the Copeman Medal for research from the University of Cambridge. While working in general practice, Bill pursued his interest in the then fledgling specialty of otolaryngology, securing fellowships from London and Edinburgh. Postgraduate training was haphazard; there were no structured programmes or even junior posts, so the young Scott-Brown was fortunate to be awarded a Dorothy Temple Cross Travelling Fellowship. Mrs Florence Temple Cross had set up these awards (now administered by the Medical Research Council) in memory of her daughter, who died in 1927 aged thirty-two. They were made available to young physicians to help them travel to overseas centres specifically to study tuberculosis, then rampant and one of the commonest causes of death in young adults. The young Scott-Brown visited the leading pioneers of the day in Berlin, Vienna, Budapest, Stockholm, Copenhagen, Madrid and Venice. Here he developed his considerable endoscopy skills. He reported that his first bronchoscopies were done on a Venetian street entertainer who, for a few coins, would inhale sundry objects that the doctors would then dexterously retrieve from his main stem and segmental bronchi – without of course any anaesthesia!

Times were lean on Scott-Brown's return. Margaret ('Peggy') was now a popular and well-established GP who supported him as his private practice developed. Eventually he secured appointments at East Grinstead, the Royal National and Royal Free Hospitals. He had a thriving Harley Street practice and was the favoured otolaryngologist of the aristocracy. His reputation was such that he become laryngologist to the Royal family, was appointed Commander of the Victorian Order and was a particular favourite of the then Princess Royal, HRH Mary the Countess of Harewood.

By 1938 he was wealthy enough to purchase a farm in Buckinghamshire where he bred prize-winning shorthorn cattle. Ironmongery and blacksmith work were hard to come by during the war years, so Scott-Brown prided himself on his ability to make his own agricultural implements, cartwheels and farm wagons in a makeshift forge he himself established on the farm. He would while away endless hours here at weekends following a busy week in London. An accomplished fly fisherman, he was part of the exclusive Houghton Club whose members fished the River Test in Hampshire, where he numbered aristocrats including the Prince of Wales among his circle.

Scott-Brown's celebrated textbook came about in the early 1950s, when he became ill with jaundice and heart trouble. He was advised to rest, and took 6 months off work. Not satisfied with editing what has become the standard UK textbook, he took up painting as well. He became a celebrated artist whose work is still prized in many private collections. One of his pastels is reproduced on the preceding page.

Bill Scott-Brown lived to be 90. He died in July 1987, six weeks after his beloved Peggy and just as the fifth edition of the celebrated textbook that still bears his name was going to press. His legacy lives on in the pages of this book, and we are proud to continue the tradition of scholarship and learning which he established all those years ago.

We would like to thank Martin Scott-Brown for his help in compiling the biography above.

John C. Watkinson and Raymond W. Clarke
London, 2018

Acknowledgements

We acknowledge our debt of gratitude to the many authors who have contributed to previous editions of Scott-Brown's Otorhinolaryngology, and in particular to authors from the seventh edition, published in 2008. We are also grateful to Neil Bateman who helped with the initial planning of the Paediatrics section.

Chapter 10, **Management of the hearing impaired child,** contains some material from 'Investigation management of deaf child' by Sujata De, Sue Archbold and Ray Clarke. The material has been revised and updated by the current author.

Chapter 28, **Stridor,** contains some material from 'Acute laryngeal infections' by Susanna Leighton. The material has been revised and updated by the current author.

Chapter 31, **Acquired laryngotracheal stenosis,** contains some material from 'Jugular foramen lesions and their management' by Kees Graamans. The material has been revised and updated by the current author.

Chapter 97, **Imaging of the temporal bone,** contains some material from 'Anatomy of the skull base and infratemporal fossa' by Charlie Huins. The material has been revised and updated by the current author.

Chapter 106, **Non-vestibular schwannoma tumours of the cerebellopontine angle,** contains some material from 'Evaluation of the skull base patient' by Ranit De and Richard M Irving. The material has been revised and updated by the current author.

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Abbreviations

2D	two-dimensional
3D	three-dimensional
4D	four-dimensional
5-HT	5-hydroxytryptamine
A	adenine; *or* anterior
AABR	automated auditory brainstem response
AAHL	age-associated hearing loss
AAOHNS	American Academy of Otolaryngologists/ Head and Neck Surgeons
ABC	aspiration biopsy cytology
ABCDE	airway, breathing, circulation, disability and exposure
ABG	air–bone gap
ABI	auditory brainstem implant
ABR	auditory brainstem response; *or* acoustic brainstem-evoked response
ABRS	acute bacterial rhinosinusitis
AC	air conduction; *or* alternating coupled; *or* auditory cortex; *or* acquired cholesteatoma
ACC	adenoid cystic carcinoma; *or* American College of Cardiology
ACD	acoustic hearing devices
ACE	angiotensin-converting enzyme
aCGH	array comparative genomic hybridization
ACh	acetylcholine
ACHD	acoustic hearing devices
AchR	acetylcholine receptor
ACT	Aid for Children with Tracheostomies; *or* acceptance and commitment therapy
ACTH	adrenocorticotrophic hormone
AD	Alzheimer's disease; *or* autosomal dominant
ADD	attention deficit disorder
ADH	antidiuretic hormone
ADHD	attention deficit hyperactivity disorder
AEP	auditory evoked potentials
AF	atrial fibrillation; *or* anterior fontanelle
AFP	alphafetoprotein
AFRS	allergic fungal rhinosinusitis
AHI	apnoea/hypopnoea index
AI	apoptotic index
AICA	anterior inferior cerebellar artery
AIDS	acquired immunodeficiency syndrome
AIED	autoimmune ear disorders
AJCC	American Joint Committee on Cancer
ALD	assistive listening device
ALPS	autoimmune lymphoproliferative syndrome
ALR	auditory late responses
ALS	advanced life support; *or* amyotrophic lateral sclerosis
ALSPAC	Avon Longitudinal Study of Parents and Children
ALTB	acute laryngotracheobronchitis
ALTE	apparent life-threatening event
AMA	American Medical Association
AMEI	active middle ear implant
AML	acute myeloid leukaemia; *or* anterior malleal ligament
AN	acoustic neuroma; *or* auditory neuropathy; *or* audiovestibular nerve
AN/AD	auditory neuropathy/auditory dyssynchrony
ANCA	antineutrophil cytoplasmic antibody
ANSD	auditory neuropathy spectrum disorder
AOAE	automated otoacoustic emission
AOM	acute otitis media
AP	anteroposterior; *or* action potential
APD	auditory processing disorder
APHAB	Abbreviated Profile of Hearing Aid Benefit
APLS	Advanced Paediatric Life Support
APMET	aggressive papillary middle ear tumour
APTT	activated partial thromboplastin time
APUD	amine precursor uptake and decarboxylation
AQP2	aquaporin 2
ARHL	age-related hearing loss
ARNSHL	autosomal recessive non-syndromic hearing loss
ARS	acute rhinosinusitis
ARSAC	Administration of Radioactive Substances Advisory Committee
ART	acoustic reflex threshold; *or* advanced rotating tomograph; *or* antiretroviral therapy
a-SCC	anterior semicircular canal
ASD	autistic spectrum disorders
ASHA	American Speech-Language-Hearing Association
ASPO	American Society of Pediatric Otolaryngologists
ASSR	auditory steady state response
AT	ataxia telangiectasia; *or* auditory therapy *or* training; *or* autotransplantation

ATD ascending tract of Deiters
ATN auriculotemporal nerve
ATP adenosine triphosphate
AV apical vesicles; *or* arteriovenous
AVF arteriovenous fistula
AVM arteriovenous malformation
AVP Amplatzer vascular plug; *or* arginine vasopressin
AVPU alert, voice, pain, unresponsive
aVOR angular VOR

BAAP bone-anchored auricular prosthesis
BAC bacterial artificial chromosome
BAHA bone-anchored hearing aid
BAO-HNS British Association of Otorhinolaryngologists – Head and Neck Surgeons
BAPO British Association for Paediatric Otolaryngology
BC bone conduction
BC-FMT bone conduction floating mass transducer
BCG Bacillus Calmette–Guérin
BCHA bone conductor hearing aid
BCHD bone conduction hearing device
BCHI bone conducting hearing implants
BCI bone conduction implant
BET balloon Eustachian tuboplasty
BiPAP bilevel positive airway pressure
BKB Bamford-Kowal-Bench
BLEC benign lymphoepithelial cysts
BLEL benign lymphoepithelial lesions
BLS Basic Life Support
BM basilar membrane
BMI body mass index
BMP bone morphogenetic protein; *or* bone morphogenic protein
BNOE benign necrotizing otitis externa
BOA behavioural observation audiometry
BOR brachio-oto-renal
BP blood pressure
BPPV benign paroxysmal positional vertigo
BPV benign paroxysmal vertigo; *or* benign positional vertigo
BRBNS blue rubber bleb naevus syndrome
BRUE brief resolved unexplained event
BS Behcet's syndrome; *or* brain stem
BSA British Society of Audiology
BTE behind the ear
BTK B-cell antigen receptor; *or* Bruton's tyrosine kinase
BTO balloon test occlusion

CAD caspase-activated DNase
CAGE cerebral air gas embolism
CAM2 a prescription rule for amplification. It is the second version of a rule devised by Dr Moore and colleagues at Cambridge University
CAMHS child and adolescent mental health service
cAMP 3',5'-monophosphate; *or* Cyclic AMP
CAMREST Cambridge method for loudness restoration
CANS central auditory nervous system
CANVAS cerebellar atrophy, neuropathy, vestibular arreflexia syndrome
CAP compound action potential; *or* category of auditory performance; *or* College of American Pathologists
CAPD central auditory processing disorder
CAT combined approach tympanoplasty
CBCT cone beam CT
CBNS congenital bony nasal stenosis
CBT cognitive-behavioural therapy
CC congenital cholesteatoma
CCA common carotid artery; *or* congenital canal atresia
CCD charge-coupled device
CCR chemokine receptor
CCSS Childhood Cancer Survivor Study
CCT Consonant Confusion Task
CCW counter-clockwise
CDC Centers for Disease Control and Prevention
CDP computerized dynamic posturography
CEA carcinoembryonic antigen
CERA cortical evoked response audiometry
CF cystic fibrosis; *or* characteristic frequency
CFRT conformal radiotherapy
CFTR cystic fibrosis transmembrane conductance regulator
CFU colony-forming unit
CGH comparative genomic hybridization
CH congenital haemangiomas
CHA conventional hearing aids
CHABA Committee on Hearing, Bioacoustics, and Biomechanics
CHAMP cochlear hydrops analysis masking procedure
CHAOS congenital high airway obstruction syndrome
CHARGE coloboma, heart defects, atresia choanae, retardation of growth, genital anomalies and ear abnormalities
CHAT Childhood Adenotonsillectomy Trial
CHD congenital heart disease
CHL conductive hearing loss
CI cochlear implantation; *or* cardiac index; *or* confidence interval; *or* concha inferior

CIC completely in canal
***cis*-DPP** cis-dichlorodiammine platinum II
CISS constructive interference in steady state
CJD Creutzfeldt–Jakob disease
CL cleft lip
CM capillary malformation; *or* concha media; *or* cochlear microphonic; *or* cricothyroid muscle
CMAP compound muscle action potential
CMCC congenital midline cervical cord/cleft
CMT Charcot–Marie–Tooth; *or* combined modality therapy
CMV cytomegalovirus
CN cranial nerve; *or* cochlear nuclei; *or* cochlear nerve; *or* congenital nystagmus
CNAP cochlear nerve action potential
CNLDO congenital nasolacrimal duct obstruction
CNS central nervous system
CNV copy number variations
CO_2 carbon dioxide
COM chronic otitis media
COMT catechol-O-methyltransferase
COR conditioned orientation reflex
COSI Client Oriented Scale of Improvement
COWS cold-opposite-warm-same
COX-2 cyclo-oxygenase 2
CP cleft palate; *or* cuticular plate
CPA cerebellopontine angle
CPAP continuous positive airway pressure
CPO cleft palate only
CRH corticotrophin-releasing hormone
CRIDE Collaboration for Research in Deaf Education
CRM canalith repositioning manoeuvre
CROS contralateral routing of signal *or* sound
CRP C-reactive protein; *or* canalith repositioning procedure
CRS chronic rhinosinusitis; *or* congenital rubella syndrome
CS corticosteroid
CSD chronic subjective dizziness
CSDD cervical spine degenerative disease
CSF cerebrospinal fluid
CSOM chronic suppurative otitis media
CT computed tomography; *or* conventional thyroidectomy
CSSD cervical spine degenerative disease
CTME carcinoid tumour of the middle ear
CTR cricotracheal resection
CTSIB Clinical Test of Sensory Integration and Balance
CUSA cavitational ultrasonic surgical aspirator
CVA cerebrovascular accident
CVID common variable immune deficiency
CW clockwise
CWD canal wall down
CWU canal wall up

DACI direct acoustic cochlear implant
DACS direct acoustic cochlear stimulation
dB decibel
dBEML decibel effective masking level
dBHL decibel hearing level
dB SPL decibel sound pressure level
DCR dacryocystorhinostomy
DDHS Direct Drive Hearing System
DFO deferoxamine mesylate
DHE dihaematoporphyrinether
DHI dizziness handicap inventory
DM diabetes mellitus
DNA deoxyribonucleic acid
DNSI deep neck space infection
DO distraction osteogenesis
DoH Department of Health
DP directional preponderance
DPOAE distortion product otoacoustic emission
DPTA diethylenetriamine penta-acetic acid
DQ drooling quotient
DSA digital subtraction angiography
DSFS Drooling Severity and Frequency Scale
DSL desired sensation level
DSS disease-specific survival; *or* Department of Social Security
DTI diffusor tensor imaging
DTPA diethylene triamine pentacetic acid
DVN descending vestibular nuclei
DWI diffusion-weighted image
DW-MRI diffusion-weighted magnetic resonance imaging

E exposure
EA episodic ataxia; *or* early antigen
EABR electrical auditory brainstem
EAC external auditory canal; *or* external acoustic canal
EAM external auditory meatus
EANONO European Academy of Otology and Neurotology
EAS electric acoustic stimulation
EBV Epstein–Barr virus
ECA external carotid artery
ECAP electrically evoked compound action potential
$ECCO_2R$ extracorporeal carbon dioxide removal

ECG electrocardiogram
ECLA extracorporeal lung-assisted
ECLS extracorporeal life support
ECM extracellular matrix
ECMO extracorporeal membrane oxygenation
ECog electrocochleography
ECPR extracorporeal cardiopulmonary resuscitation
EE external frontoethmoidectomy; *or* excitation–excitation
EEA endoscopic endonasal approach
EEG electroencephalography; *or* electroencephalogram
EES endoscopic ear surgery
EFS event-free survival
EGF epidermal growth factor
EGFR epidermal growth factor receptor
EI excitation–inhibition
ELISA enzyme-linked immunosorbent assay
ELS European Laryngological Societies
ELST endolymphatic sac tumour
EMFA extended middle fossa approach
EMG electromyography
EML effective masking level
ENG electronystagmography
ENoG electroneurography
ENT ear, nose and throat
EO eosinophilic oesophagitis
EOR extra-oesophageal reflux
EORD extra-oesophageal reflux disease
EORTC European Organisation for Research and Treatment of Cancer
EP endolymphatic potential
ES embryonic stem; *or* endolymphatic sac
ESID European Society for Immunodeficiencies
ESPO European Society of Pediatric Otorhinolaryngology
ESR erythrocyte sedimentation rate
ESS endoscopic sinus surgery; *or* Epworth Sleepiness Scale; *or* empty sella syndrome
ET essential thrombocytosis; *or* endotracheal tube; *or* Eustachian tube
ETD Eustachian tube dysfunction
ETT endotracheal tube
ETV endoscopic third ventriculostomy
EU European Union
EUA examination under anaesthesia
EVAS enlarged vestibular aqueduct syndrome
EXIT extrauterine intrapartum treatment

F0 fundamental frequency
FAO far advanced otosclerosis
FAAF four alternative auditory feature
FBC full blood count
FDA Food and Drug Administration (USA)
FDG fluorodeoxyglucose; *or* 2-[18F] fluoro-2-deoxy-D-glucose; *or* F18-fluoro-2-deoxy-D-glucose
FDG-PET 2-[18F] fluoro-2-deoxy-D-glucose–positron emission tomography; *or* fluorine-18-labelled deoxyglucose positron emission tomography
FDT fluorescein disappearance test
FEES fibreoptic endoscopic evaluation of swallowing
FESS functional endoscopic sinus surgery
FGF fibroblast growth factor
FIESTA fast imaging employing steady-state acquisition
FIG6 a prescription rule for amplification, named after the figure in an article on which it was based
FiO_2 fraction of inspired oxygen
FLAIR fluid attenuated inversion recovery
fMRI functional magnetic resonance imaging
FMT floating mass transducer
FN facial nerve
FNA fine-needle aspiration/aspirate
FNAC fine-needle aspiration cytology
FNS facial nerve schwannoma
FOAR fronto-orbital advancement and remodelling
FT fibrous tissue
FTA-ABS fluorescent treponemal antibody test

GABA gamma-aminobutyric acid
GABHS group A beta-haemolytic streptococcus
GAS Goal Attainment Scaling
GCS Glasgow Coma Scale
G-CSF granulocyte-colony stimulating factor
GDNF glial cell-derived neurotrophic factor
GERD gastrooesophageal reflux disease
GGF geniculate ganglion fossa
GHABP Glasgow Hearing Aid Benefit Profile
GI gastrointestinal
GLUT-1 glucose transporter-1
GMC ganglion mother cell; *or* General Medical Council (UK)
GN glossopharyngeal nerve
GOR gastro-oesophageal reflux
GORD gastro-oesophageal reflux disease
GP general practitioner
GRADE Grading of Evidence, Assessment, Development and Evaluation

GSA general sensory afferent
GSPN greater superficial petrosal nerve
GVA general visceral afferent
GVE general visceral efferent

H2 histamine receptor type 2
HA hydroxyapatite
HAART highly active antiretroviral therapy
HADS Hospital Anxiety Depression Scale
HAPI Hearing Aid Performance Inventory
HAT hearing assistance technology
HB House–Brackmann
HBOT hyperbaric oxygen therapy
HCG human chorionic gonadotrophin
HDU high dependency unit
HES Hospital Episode Statistics
HHIE Hearing Handicap Inventory for the Elderly
HHT hereditary haemorrhagic telangiectasia
HI hearing impaired
Hib Haemophilus influenzae type b
HIF hypoxia inducible factor
HINTS head impulse, nystagmus characteristics, test for skew
HIT heparin-induced thrombocytopenia; *or* head-impulse test
HIV human immunodeficiency virus
HJB high jugular bulb
HL hearing loss; *or* hearing level; *or* hairy leukoplakia; *or* Hodgkin lymphoma
HLA human leukocyte antigen
HM history of migraine; *or* hemifacial microsomia
HME heat and moisture exchanger
HPV human papillomavirus; *or* human herpes virus 8
HR hazard ratio
HRCT high-resolution computed tomography
h-SCC horizontal semicircular canal
HSF heat shock factors
HSMN hereditary sensory-motor neuropathy
HSP heat shock protein
HSV herpes simplex virus
HSV-1 herpes simplex virus type 1
HSV-2 herpes simplex virus type 2
HT hydroxytryptamine
HTA hyalinizing trabecular adenoma; *or* Health Technology Assessment
HVDT health visitor distraction test
Hz hertz

IAC internal auditory canal
IAM internal auditory meatus
IC inferior colliculus; *or* immunochemistry
ICA internal carotid artery
ICAM-1 intercellular adhesion molecule 1
ICD International Classification of Disease
ICHD International Classification of Headache Disorders
ICP intracranial pressure
ICTD intracranial tumour diameter
ICU intensive care unit
ICVD international classification of vestibular disorders
IDT infant distraction test
IFN interferon
Ig immunoglobulin
IgA immunoglobulin A
IgE immunoglobulin E
IGF-1 insulin-like growth factor 1
IgG immunoglobulin G
IgM immunoglobulin M
IHAFF International Hearing Aid Fitting Forum
IHC immunohistochemistry; *or* inner hair cell
IHS International Headache Society
IJV internal jugular vein
IL-1 interleukin-1
ILD inter-ear latency difference; *or* interaural intensity level difference
IMRT intensity-modulated radiation therapy
IMSPAC imitative test of speech pattern contrast perception
INC interstitial nucleus of Cajal
INO internuclear ophthalmoplegia
iNOS inducible nitric oxide synthase
INR international normalized ratio; *or* interventional neuroradiology
IPD invasive pneumococcal disease
IQ intelligence quotient
IRS insulin receptor substrate; *or* Intergroup Rhabdomyosarcoma Study
ISJ incudostapedial joint
ISMAR Innsbruck Sensory Motor Activator and Regulator
ISO International Standards Organization
ISSNHL idiopathic sudden sensorineural hearing loss
ISSVA International Society for the Study of Vascular Anomalies
IT inferior turbinate; *or* intratympanic
ITDs interaural time differences
ITE in the ear
ITT intention to treat analysis

IUCC International Union against Cancer
i.v. intravenous

JB jugular bulb
JCIH Joint Committee on Infant Hearing
JNA juvenile nasopharyngeal angiofibroma
JOF juvenile ossifying fibroma
JORRP juvenile recurrent respiratory papillomatosis

KADS keratinocyte attachment destroying substance
KO keratosis obturans; *or* keratizing obturans
KMS Kasabach–Merritt syndrome
KTP potassium titanyl phosphate

LA lymphangioma; *or* left anterior
LADD Lacrimo-auriculo-dento-digital
LARP left anterior–right posterior
LCH Langerhans' cell histiocytosis
LDH lactic dehydrogenase
LDL low-density lipoprotein; *or* loudness discomfort level
LED light-emitting diode
LGOB loudness growth in octave bands
LI language impairment
LINAC linear accelerator
LMA laryngeal mask airway
LOCHI long-term outcomes from childhood hearing impairment
LOH loss of heterozygosity
LP lamina papyracea; *or* lichen planus; *or* lymphocyte predominant; *or* left posterior; *or* levator palatini
LPI long process of incus
LPR laryngopharyngeal reflux
LRST lateral reticulospinal tracts
LSCC lateral semicircular canal
LSP language service professional
LTB laryngotracheobronchitis; *or* laryngotracheobronchoscopy
LTR laryngotracheal reconstruction
LTV long-term ventilation
LVA large vestibular aqueduct
LVAS large vestibular aqueduct syndrome
LVN lateral vestibular nuclei
LVOR linear vestibulo–ocular reflex
LVST lateral vestibulospinal tract

M metastases; *or* microphone; *or* mastoid
MAF minimum audible field
MAIS Meaningful Auditory Integration Scale
MAP minimum audible pressure
MAPK mitogen-activated protein kinase
MARD migraine anxiety-related dizziness
MBCT mindfulness-based cognitive therapy
MBL mannose-binding lectin
MCF middle cranial fossa
MCL maximum comfortable level
MCP-1 monocyte chemotactic protein-1
MDCT Multidetector computed tomography
MDT multidisciplinary team
ME middle ear
MEA middle ear adenoma
MEG magnetoencephalography
MEI middle ear implants
MEK MAPK/extracellular signal related kinase
MELAS mitochondrial encephalopathy, lactic acidosis and stroke-like episode
MEN multiple endocrine neoplasia
Men C Meningococcus C
MERI Middle Ear Risk Index
MET middle ear transducer; *or* mechanoelectrical transduction
MF middle fossa
MGB medial geniculate body
MHC major histocompatibility complex
MIBG metaiodobenzylguanidine; *or* iodine-123-metaiodobenzylguanidine
MIP-1a macrophage inflammatory protein-1a
MLC multi-leaf collimator
MLF medial longitudinal fascicle *or* fasciculus
MLR middle latency response
MLTB microlaryngotracheobronchoscopy
MMP-2 metalloproteinase-2
MMP-9 metalloproteinase-9
MMA middle meningeal artery
MMR measles, mumps and rubella
MOTT mycobacteria other than tuberculosis
MPS mucopolysaccharoidoses; *or* massive parallel sequencing
MR magnetic resonance
MRA magnetic resonance angiography
MRC Medical Research Council (UK)
MRI magnetic resonance imaging
MRL minimal response level
mRNA messenger ribonucleic acid
MRS Melkersson–Rosenthal syndrome; *or* magnetic resonance sialography
MRSA methicillin-resistant *Staphylococcus aureus*
MRST medial reticulospinal tracts

MRV migraine-related vestibulopathy
MS multiple sclerosis
MST maximal stimulation test
MTC medullary thyroid carcinoma
mtDNA mitochondrial DNA
mTHPC meso-tetra (hydroxyphenyl) chlorin
MVN medial vestibular nuclei
MVST medial vestibulospinal tract

N nodal
NADP nicotinamide adenine dinucleotide phosphate
NADPH reduced form of nicotinamide adenine dinucleotide phosphate
NAI non-accidental injury
NAL National Acoustic Laboratories (Australia)
NAM nasoalveolar moulding
NBN narrow-band noise
NBCA n-butyl-2-cyanoacrylate; *or* N-butylcyanoacrylate
NEAME neuroendocrine adenoma of the middle ear
NESSTAC North of England and Scotland Study on Tonsillectomy and Adenoidectomy in Children
NET nerve excitability test; *or* neuroendocrine tumour
NFκB nuclear factor kappa B
NF1 neurofibromatosis type 1
NF2 neurofibromatosis type 2
NFA non-functional adenoma; *or* nasofrontal approach
NG nasogastric
NH normal hearing; *or* neurophypophysis
NHL non-Hodgkin lymphoma
NHS National Health Service (UK)
NHSP Newborn Hearing Screening Programme
NI nervus intermedius
NICE National Institute for Health and Care Excellence (UK)
NICH non-involuting congenital haemangiomas
NICU nonimmunological contact urticaria; *or* neonatal intensive care unit
NIH National Institutes of Health (USA)
NIHL noise-induced hearing loss
NIL noise immision level
NMDA N-methyl-d-aspartate; *or* National Minimum Data Set (UK)
NNT number needed to treat
NO nitric oxide
NO_2 nitric dioxide
NOD-2 nucleotide-binding oligomerization domain-containing protein 2
NOE naso-orbito-ethmoid
NP nasopharynx; *or* nasopharyngeal
NPA nasopharyngeal airway
NPC nasopharyngeal cancer; *or* nasopharyngeal carcinoma
NPH nucleus prepositus hypoglossus
NPTA National Prospective Tonsillectomy Audit (UK)
NPV negative predictive value
NRT neural response telemetry
NSAID non-steroidal anti-inflammatory drug
NSC National Screening Committee
NSRAN nonsyndromic recessive auditory neuropathy
NTHi non-typeable *Haemophilus influenzae*
NTM non-tuberculous mycobacteria
NU-CHIPS Northwestern University Children's Perception of Speech

OAE otoacoustic emission
OAVS oculoauriculovertebral spectrum
OCS otic capsule sparing
OCT optical coherence tomography
OCV otic capsule violating
OHC outer hair cell
OKN optokinetic nystagmus
OM occipitomental; *or* otitis media
OMC osteomeatal complex
OME otitis media with effusion
OMENS orbit, mandible, ears, nerves and soft tissue
OMIM Online Mendelian Inheritance in Man
ONSM optic nerve sheath meningiomas
OOPS Ossiculoplasty Outcome Parameter Staging
OPG orthopantomogram; *or* osteoprotegerin
OR occupational rhinitis
ORL otorhinolaryngology
OSA obstructive sleep apnoea
OSAS obstructive sleep apnoea syndrome
OSPL output sound pressure level
OTOF otoferlin
OVAR off-vertical axis rotation
oVEMP ocular vestibular evoked myogenic potentials
OWN oval window niche

P phosphate; *or* posterior; *or* promontory
PACU post-anaesthesia care unit
PAIG Paediatric Audiology Interest Group
PAM postauricular muscle artefact
PAMR postauricular myogenic response

PANQOL Penn Acoustic Neuroma Quality of Life
PaNSTaR Paediatric and Neonatal Safe Transfer and Retrieval (PaNSTaR)
PBI primary blast injury
p-BPPV persistent benign paroxysmal positional vertigo
PBT proton beam therapy
PC Paediatric cholesteatoma; *or* processus cochleariformis
PCA patient-controlled analgesia
PCD primary ciliary dyskinesia
PCHI permanent childhood hearing impairment
PCP planar cell polarity
PCR polymerase chain reaction
PCTR partial cricotracheal resection
PCV7 heptavalent pneumococcal conjugate vaccine
PD Parkinson's disease
PDB Paget's disease of bone
PDH prevention to deafness and hearing impairment
PDL pulsed dye laser; *or* paediatric long
PDS polydimethylsiloxane
PDT photodynamic therapy
PEACH Parents' Evaluation of Aural/Oral Performance in Children
PEG percutaneous endoscopic gastrostomy
PET polyethylene terephthalate; *or* positron emission tomography; *or* patulous (branching) Eustachian tube
PEWS paediatric early warning scores
PFAPA periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis
PFS progression-free survival
PI pulsatility index; *or* performance-intensity
PI3K phosphotidyinositol 3
PICA posterior inferior cerebellar artery
PICANet Paediatric Intensive Care Audit Network
PICS Paediatric Intensive Care Society
PICU paediatric intensive care unit
PID primary immunodeficiency
PIHA partially implantable hearing aid
PIP peak inspiratory pressure
PIVC parietoinsular vestibular cortex
PLF congenital perilymphatic fistula
p.o. by mouth
POGO prescription of gain and output
PORP partial ossicular replacement prosthesis
POSTA Preschool Obstructive Sleep Apnoea Tonsillectomy Adenoidectomy
PP palatopharyngeus
ppeSPL peak-to-peak equivalent sound pressure
PPG pterygoplatine ganglion
PPI proton pump inhibitor; *or* patient and public involvement
PPPD persistent postural-perceptual dizziness
PPRF parapontine reticular formation; *or* paramedian pontine reticular formation
PPV phobic positional vertigo; *or* positive predictive value; *or* pneumococcal polysaccharide vaccine
PROM patient-reported outcome measure
PRRs pattern recognition receptors
PRS persistent rhinosinusitis; *or* Pierre Robin sequence
PSA prostate-specific antigen; *or* pleomorphic salivary adenoma; *or* persistent stapedial artery
p-SCC posterior semicircular canal
PSG polysomnography
Psol parasolitary nucleus
PSP progressive supranuclear palsy
pSPL peak Sound Pressure Level
PT prothrombin time
PTA pure tone audiometry; *or* peritonsillar abscess
PTS permanent threshold shift
PTSD post-traumatic stress disorder
PVA polyvinyl alcohol
PVC polyvinyl chloride
PVP pause vestibular position; *or* position vestibular pause
PVRQOL Paediatric Voice-related Quality of Life

QOL quality of life
QTF Quebec Task Force

RA retinoic acid; *or* right anterior
RAAS renin-angiotensin-aldosterone system
RALP right anterior–left posterior
RANKL regulation of nuclear factor κB ligand
RAST radioallergosorbent test
RCPCH Royal College of Paediatrics and Child Health
RCS Royal College of Surgeons of England
RCT randomized controlled trial
RDI respiratory disturbance index
REAG real-ear aided gain
REAL Revised European American Lymphoma
RECD real ear to coupler difference
RED rigid external distractor
REFTL reference equivalent force threshold level
REIG real-ear insertion gain
REM rapid eye movement
RET rearranged during transfection

RETSPLs reference equivalent sound pressure levels
REZ root entry/exit zones
RI resistance index; *or* reflux index
RICH rapidly involuting congenital haemangiomas
RIMLF rostral interstitial nucleus of the medial longitudinal faciculus
RION radiation induced optic neuropathy
RIP raphe interpositus
RMS root mean square; *or* rhabdomyosarcoma
RMHA remote microphone hearing aids
RNA ribonucleic acid
RNP ribonucleoprotein
RNS reative nitrogen species
ROS reactive oxygen species
RP rapid prototyping; *or* right posterior
RPR rapid plasma regain
RR relative risk; *or* respiratory rate
RRI relative risk of improvement
rRNA Ribosomal ribonucleic acid
RRP recurrent respiratory papillomatosis
RS retrosigmoid
RSV respiratory syncytial virus
rTMS repetitive low-frequency transcranial magnetic stimulation
RW round window

SAD supraglottic airway device; *or* specific antibody deficiency
SAL sensorineural acuity level
SALT speech and language therapist
SCA superior cerebellar artery
SCBU special care baby unit
SCC squamous cell carcinoma *or* cancer; *or* semicircular canal
SCDS superior canal dehiscence syndrome
SCID severe combined immunodeficiency
SCM sternocleidomastoid
SCN severe congenital neutropenia; *or* solid cell nests; *or* Suprachiasmatic Nucleus
SCUBA self-contained underwater breathing apparatus
SEM scanning electron microscopy
SENTAC Society for Ear, Nose and Throat Advances in Children
SF-36 Medical Outcome Study Short-Form 36-Item Health Survey
SGS subglottic stenosis
SHML sinus histiocytosis with massive lymphadenopathy
SIDS sudden infant death syndrome
SIGN Scottish Intercollegiate Guidelines Network
SIMEHD semi-implantable middle ear electromagnetic hearing device
SiN speech reception in noise
SISI short increment sensitivity index
SL sensation level
SLE systemic lupus erythematosus
SLP superficial lamina propria
SLT speech and language therapist
SMD space and motion discomfort
SMHL sinus histiocytosis with massive lymphadenopathy
SNHL sensorineural hearing loss
SNP single-nucleotide polymorphism
SNR signal-to-noise ratio
SNRI serotonin–noradrenaline (norepinephrine) reuptake inhibitors
SNVs single nucleotide variants
SP substance P; *or* summating potential
SPD spatial processing disorder
SPECT single photon emission computed tomography
SPITE surgical, prosthetic, infection, tissue, Eustachian
SPL sound pressure level
SqCC squamous cell carcinoma
SR stereotactic radiation
SRS subacute rhinosinusitis; *or* stereotactic radiosurgery
SRT speech recognition threshold; *or* speech reception threshold; *or* stereotactic radiotherapy
SSC superior semicircular canal
SSCD superior semi-circular canal dehiscence
SSD single-sided deafness
SSEP somato sensory evoked potential
SSG split skin graft
SSNHL sudden sensorineural hearing loss
SSP steady state potential
SSPL saturation sound pressure level
SSRI selective serotonin reuptake inhibitor
ST superior turbinate; *or* subtotal thyroidectomy; *or* sinus tympani
SUV standardized uptake value
SVA special visceral afferent
SVE special visceral efferent
SVN superior vestibular nuclei; *or* superior vestibular nerve
SVS selective venous sampling
SVV subjective visual vertical

T thymine; *or* tumour; *or* telecoil
T3 triiodothyronine

T4 thyroxine
TARGET Trials of Alternative Regimens in Glue Ear Treatment
TB tuberculosis; *or Mycobacterium tuberculosis*
TBI traumatic brain injury
^{99m}Tc technetium-99m
TCF tracheocutaneous fistula
TDT tone decay test
TEOAE transient evoked otoacoustic emission
TFI Tinnitus Functional Index
TGF transforming growth factor
TGF-α transforming growth factor alpha
TGF-β transforming growth factor beta
TGF-β1 transforming growth factor beta 1
Th T helper
THI transient hypogammaglobulinaemia of infancy; *or* tinnitus handicap inventory
TIA transient ischaemic attack
TICA totally implantable cochlear amplifier
TIVA total intravenous anaesthesia
TLR toll-like receptors
TM transmastoid; *or* tympanic membrane; *or* tectorial membrane
TMC1 transmembrane channel-like gene 1
TMJ temporomandibular joint
TMM test and tubomanometry
TN trigeminal neuralgia; *or* trigeminal nerve
TNF tumour necrosis factor
TNF-α tumour necrosis factor alpha
TNM tumour, node, metastasis
TOAE transient evoked otoacoustic emission
ToD teachers of the deaf
TOE transoesophageal echocardiography; *or Trichophyton*, *Oidiomycetes* and *Epidermophyton*
TOF tracheo-oesophageal fistula
TORCH toxoplasmosis; other (such as syphilis, varicella, mumps, parvovirus and HIV); rubella; cytomegalovirus; herpes simplex
TORP total ossicular replacement prosthesis
TORS transoral robotic surgery
TP tensor palatine
TPHA *Treponema pallidum* haemagglutination assay; *or* treponemal haemagglutination
TPMT thiopurine-5-methyltransferase
TPN total parenteral nutrition
TRH thyrotrophin-releasing hormone
TRT tinnitus retraining therapy
TSH thyroid-stimulating hormone; *or* thyrotrophin
TSS transitional space surgery
TT thrombin time; *or* total thyroidectomy; *or* tensor tympani
TTEABR transtympanic electrical auditorybrainstem
TTS temporary 'threshold shift'

UICC International Union Against Cancer
UHL unilateral hearing loss
UNHS universal newborn hearing screening
UNICEF United Nations Children's Fund
URTI upper respiratory tract infection
US ultrasound; *or* ultrasonography
uVD unilateral vestibular deafferentiation

VACTERL vertebral defects, anal atresia, cardiac defects, tracheo-oesophageal fistula, renal anomalies and limb abnormalities
VAS visual analogue scale; *or* visual analogue score
VATS video-assisted thoracoscopic surgery
VBRT Vestibular balance rehabilitation therapy
VCA viral capsid antigen; *or* vestibulocochlear artery
VCR vestibulocollic reflex
VDRL Venereal Disease Research Laboratory
VEGF vascular endothelial growth factor
VEGFA vascular endothelial growth factor A
VEMP vestibular-evoked myogenic potential
VFSS videofluoroscopic swallowing study
VHI Voice Handicap Index
VHIT video head impulse test
VHL Von Hippel–Lindau
VM venous malformations; *or* vestibular migraine
VMA vanillylmandelic acid
VN vestibular nuclei; *or* vagus nerve
VNG videonystagmography
VOG video-oculography
VOR vestibulo-ocular reflex
VORP vibrating ossicular prosthesis
VORS vestibulo-ocular reflex suppression
VP ventriculoperitoneal
VPI velopharyngeal insufficiency
VR vestibular rehabilitation
VRA visual reinforcement audiometry
V-RQOL voice-related quality of life; *or* Voice-related Quality of Life Questionnaire
VS vestibular schwannoma; *or* vibrant soundbridge
VSB vibrant soundbridge
VSM velocity storage mechanism
VSR vestibulospinal reflex

VT	ventilation tubes
VV	visual vertigo
vWD	von Willebrand disease
VZV	varicella zoster virus
WAD	whiplash-associated disorder
WBC	white blood cell
WDT	word discrimination threshold
WES	whole exome sequencing
WGS	whole genome sequencing
WHO	World Health Organization
WIPI	Word Intelligibility by Picture Identification test
WRS	world recognition scoring
WVA	wide vestibular aqueduct

Section 1
Paediatrics

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CHAPTER 1

INTRODUCTION TO PAEDIATRIC OTORHINOLARYNGOLOGY

Raymond W. Clarke

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Developing ENT services for children 5
Training the otorhinolaryngologists of the future 6
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SEARCH STRATEGY

The author's personal bibliography formed the basis for this chapter. Some material is reproduced from '*Clarke's Paediatric otolaryngology – practical clinical management*'.[1]

HISTORY OF PAEDIATRIC OTORHINOLARYNGOLOGY

Laryngology

Otorhinolaryngologists have been caring for children since the specialty began. Diphtheria, epiglottitis and laryngeal tuberculosis were commonplace in children throughout the 19th and early 20th centuries. Victorian and Edwardian laryngologists such as Morell Mackenzie and Sir Felix Semon in London had large paediatric practices and dealt with these often-fatal upper respiratory tract pathologies. Semon was laryngologist to the British Royal family and undertook tonsillectomy on the grandchildren of Queen Victoria, making tonsillectomy a fashionable intervention in the drawing rooms of the aristocracy.[2–4]

Gustav Killian pioneered suspension laryngoscopy in Freiburgim Breisgau at the beginning of the 20th century and the technique was soon taken up for children. Chevalier Jackson (**Figure 1.1**) in Philadelphia established a reputation throughout the United States and beyond for his skills at tracheobronchoscopy. A brilliant teacher, he illustrated his work in his own hand and was probably the single most important figure to popularize airway endoscopy in children on both sides of the Atlantic.[5–7]

Sophisticated diagnostic and therapeutic procedures in children are only possible because of the huge advances made in improving the survival and care of small babies. Joseph O'Dwyer (New York) is credited with the first successful emergency endotracheal intubation in a child in 1884 (**Figure 1.2**), but the technique was associated with a high mortality. Long-term nasal endotracheal intubation as an alternative to tracheotomy was popularized only from the 1960s onwards; paediatric otolaryngologists are acutely aware of the debt they owe to paediatricians and anaesthesiologists. Wilson published the first English-language textbook of paediatric otorhinolaryngology (ORL) in 1955 (**Figure 1.3**) and wrote of emergency tracheotomy in children: 'these are desperate cases at best, and it may be a comfort to remember that the worst thing which can happen is that the patient will die. This is unfortunately a likely event in any case.'[8]

The pioneering work of British physicist Harold Hopkins in the design of 'rod-lens' telescopes (**Figure 1.4**)

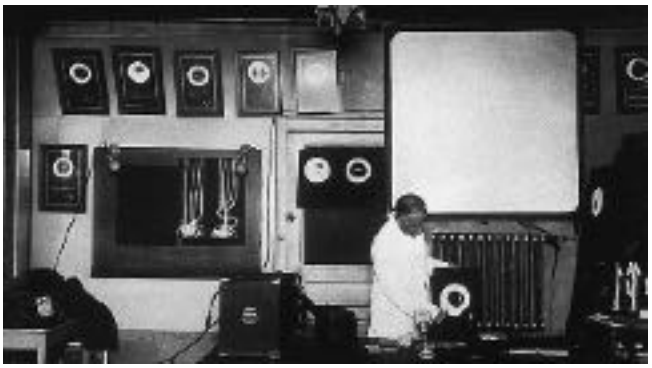


Figure 1.1 Chevalier Jackson. Reproduced by kind permission of the John Q. Adams Center for the History of Otolaryngology – Head and Neck Surgery, American Academy of Otolaryngology – Head and Neck Surgery Foundation, 2007. All rights reserved.

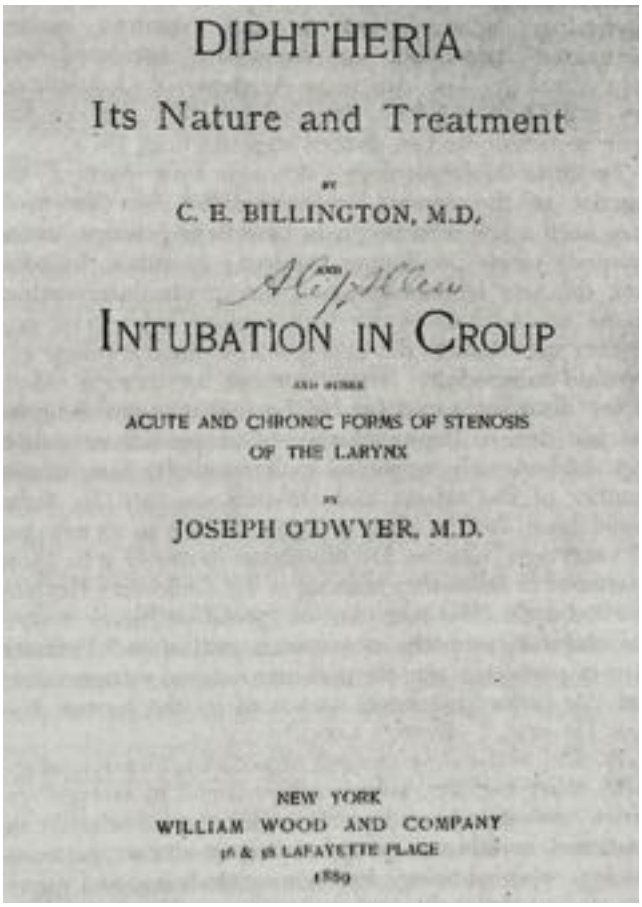


Figure 1.2 Joseph O'Dwyer paper 1865.

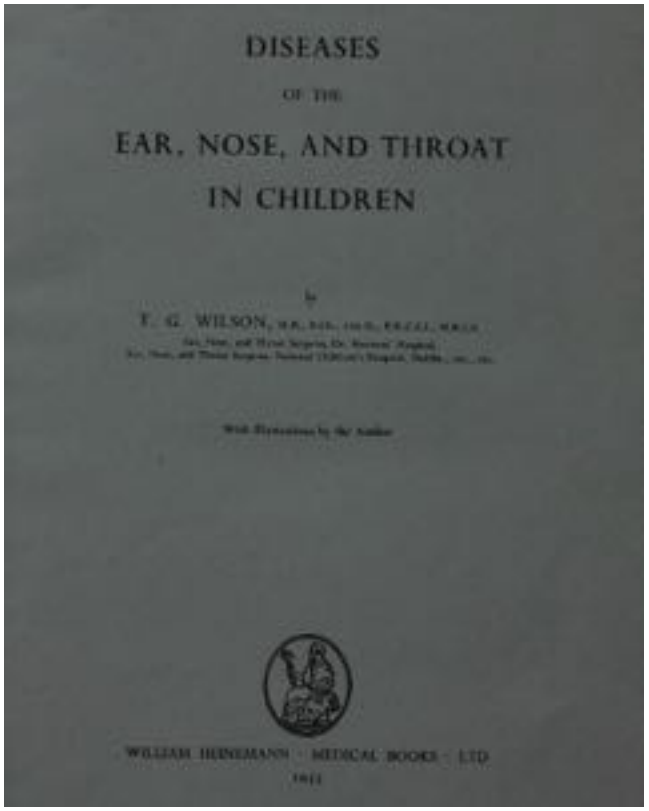


Figure 1.3 Frontispiece of Wilson's textbook (1853).[8]



Figure 1.4 Paediatric airway endoscopy using Hopkins rod lens.

moved paediatric airway surgery to new levels.[9] Modern-day airway endoscopy in children is a highly skilled – and safe – undertaking and the fear and trepidation that surrounded tracheostomy in children is a distant memory.

Otology and audiology

Mastoid surgery in children was popularized by Sir William Wilde (1815–1878). Wilde described otitis media with effusion – 'strumous otitis', recognizing its association with Eustachian tubal dysfunction.[10, 11] He advocated tympanocentesis as a treatment and pioneered the use of the myringotome (**Figure 1.5**). He was an early advocate for the recognition and education of the deaf child, but the profession of audiology really began in the 1920s when audiometers became available. Edith Whetnall in London established a network of clinics which became a model for the assessment and treatment of hearing-impaired children; her 1964 textbook *The Deaf Child* was the standard work for many years.[4]

Cochlear implantation, developed in the 1970s and refined and improved upon throughout the next 30 years, has transformed the lives of hearing-impaired children and their families in the developed world.

The assessment and rehabilitation of the hearing-impaired child has advanced greatly in recent years, and paediatric audiology is an important and growing medical specialty.

Societies and associations

Gatherings of otolaryngologists with an interest in ORL in children took place in Eastern Europe from the beginning of the 20th century. In the United States the Society for Ear, Nose and Throat Advances in Children (SENTAC) (https://sentac.org/) met in 1973. The American Society of Pediatric Otolaryngology (ASPO) (htpp://aspo.us/) was founded in 1985. The European Working Group in Pediatric ENT was founded in 1977 and later became the European Society of Pediatric Otorhinolaryngology (ESPO) (http://www.espo.eu.com/), a forum for discussion and advances in paediatric ORL through international

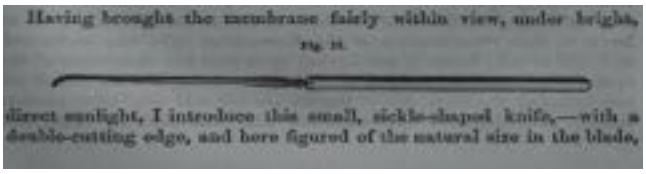


Figure 1.5 Wilde's myringotomy knife as illustrated by Wilde in *Practical observations on aural surgery: and the nature and treatment of diseases of the ear.*[10]

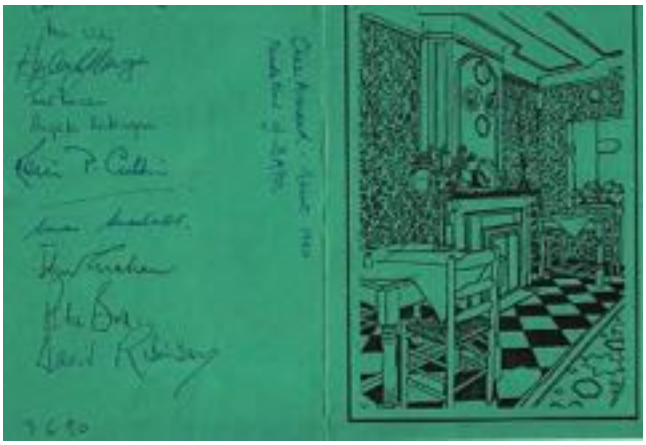


Figure 1.6 Menu from Ghent 1990, foundation of BAPO.

meetings and via its journal the *International Journal of Pediatric Otolaryngology*. The British Association for Paediatric Otolaryngology (BAPO) (https://www.bapo.co.uk/) was formed in 1991. The idea for a British society came about at a meeting of colleagues attending the international congress at Ghent in 1990. Surviving mementos include a signed menu from the Chez Armand restaurant (**Figure 1.6**) (John Graham FRCS, personal communication)!

DEVELOPING ENT SERVICES FOR CHILDREN

Advocating for children

ORL is the specialty with the biggest paediatric surgical workload. It is important that ORL clinicians are to the fore in driving service changes forward to best serve children, families and the next generation of specialists. Up to 30–50% of our workload involves the care of children. Otolaryngologists have, and must maintain, an important role as strong advocates for children.

The philosophy and thinking that influences how we care for children has undergone a radical transformation in recent years. Doctors are no longer seen as infallible. Parents are well informed and expect full participation in decision-making. They expect that their child will be treated in an environment that serves the needs of the child and family and that carers and other staff are fully trained not only in delivering health care, but also in the principles of looking after children and families. There is a growing expectation that service organization should be driven not by the needs of professionals but by the needs of children and families. These legitimate expectations put an onus on us as doctors and planners when setting up services for children. Despite the desirability of treating children close to home, children with unusual or complex conditions or who are in need of highly specialized intervention will have their care best delivered in one of a small number of more specialized settings, where resources and skills are concentrated.

Hospitals that undertake the care of children need to commit to exemplary standards, with the involvement of senior staff in ensuring that the specific requirements of children are met.[12] In a hospital with several otolaryngologists on staff, one should ideally be designated as lead for paediatrics so that he/she can advocate for children at the highest level and can coordinate management, transfer and referral of children with complex needs who may need treatment in a specialized centre. Well-established liaison networks and good communication with specialist centres, paediatricians, community paediatric services, social services, parents and advocacy groups are a cornerstone of good paediatric practice.

Organizing clinics and theatre

Children are best seen in a designated children's clinic rather than in a mixed adult and children's setting.

The clinic setting should be 'child-friendly' with suitable toys, papers and pens and facilities for parents and siblings (see Chapter 2, The paediatric consultation). Similarly, it is nowadays accepted best practice that surgical lists should be planned so as to permit 'children only' lists rather than mixed adult and child surgery.[12]

Theatre staff looking after children need to be suitably trained and in particular the anaesthesiologist should be competent in paediatric anaesthesia with a sufficient workload and throughput to maintain his/her skills in the peri-operative care of children. Children under the age of 3 years will usually require more specialized anaesthetic care. The professional associations that govern anaesthesia in different jurisdictions have their own recommendations with which anaesthesiologists will generally be familiar. If at all possible and provided it is safe, children should be admitted and discharged on the same day ('day' surgery or 'ambulatory care').

Children are best looked after in a children's ward rather than in a mixed ward with adults, again with appropriately trained and accredited nursing staff. Provision should be made for parents, who will usually wish to stay with the child overnight.

If children require overnight nursing care – for example, following adenotonsillectomy for obstructive sleep apnoea (OSA) – experienced paediatric ear, nose and throat (ENT) nurses are usually best placed to look after them. A small number of children will need more thorough monitoring and supervision, perhaps with one-to-one nursing care, or admission to a high dependency unit (HDU) or, exceptionally, to a paediatric intensive care unit (PICU).

TRAINING THE OTORHINOLARYNGOLOGISTS OF THE FUTURE

The diagnosis and management of ORL conditions in children forms an essential part of the syllabus for all ENT surgeons in training. Examinations in ORL – including the European Board Examination[13] – put much emphasis on this, and in general otolaryngologists are well trained in the principles of looking after children with common disorders of the upper respiratory tract.

Although subspecialization in ORL is largely 'system' (otology, head and neck surgery, rhinology) rather than age-based, a growing number of otolaryngologists now choose to undertake advanced training in a fellowship programme in one of the major children's hospitals with a view to taking a special clinical interest in the care of children. In addition to basic and fellowship training, all of us who care for children need to have up-to-date knowledge and skills in topics such as child protection, prescribing for children, analgesia and paediatric resuscitation, and continue to maintain and refresh our knowledge and skills.

BEST CLINICAL PRACTICE

- ✓ Clinicians caring for children and young people should undertake a level of paediatric clinical activity that is enough to maintain minimum competencies.
- ✓ Children should be treated safely, as close to home as possible, in an environment that is suited to their needs, with their parents' involvement in decisions, and with the optimal quality of care.
- ✓ Where theatre scheduling permits, children should have their surgery performed on a dedicated children's operating list.

FUTURE RESEARCH

- ➤ There is an increasing trend to centralize children's surgery. Otolaryngologists must ensure they are to the fore in local service planning.
- ➤ ENT surgeons need to take a strong advocacy role to make for better services for children.
- ➤ Training in the generic skills required to care for children is essential to ORL practice.
- ➤ Training in paediatric emergencies should be encouraged for all ORL practitioners who look after children.

KEY POINTS

- Paediatric otorhinolaryngology is as old as the specialty of otolaryngology itself.
- The pathophysiology and natural history of disease may be very different in children.
- Looking after children is an integral part of the work of an ORL specialist.
- Developments in medicine, anaesthesia and intensive care have brought about a need for increasingly specialist care for children with ORL disorders.
- The improvements in endoscopy brought about by the discoveries of Harold Hopkins transformed paediatric airway care.

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FURTHER INFORMATION

American Society of Pediatric Otolaryngology (ASPO): htpp://aspo.us/

British Association for Paediatric Otolaryngology (BAPO): https://www.bapo.co.uk/

European Society of Pediatric Otorhinolaryngology (ESPO): http://www.espo.eu.com/

Society for Ear, Nose and Throat Advances in Children (SENTAC): https://sentac.org/

CHAPTER 2

THE PAEDIATRIC CONSULTATION

Raymond W. Clarke

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SEARCH STRATEGY

Data for this chapter are mainly drawn from the author's personal bibliography. The websites of the General Medical Council (GMC) (http://www.gmc-uk.org/), the Royal College of Surgeons of England (RCS) (https://www.rcseng.ac.uk/), the Department of Health (DoH) (https://www.gov.uk/government/organisations/department-of-health), General Medical Council: http://www.gmc-uk.org and the National Institute for Health and Care Excellence (NICE) (https://www.nice.org.uk/) were also consulted.

INTRODUCTION

Children and their parents will often vividly remember their encounters with a doctor. The child's first contact with medical staff and hospitals sets the scene for subsequent visits. A good paediatric consultation is more than a forum for making a diagnosis and planning management; it is an opportunity to familiarize the child and family with the hospital, the clinic, and the members of the team who will look after them during one or more admissions and outpatient visits. For the doctor, it is often the beginning of a rapport with a family who may need to see you many times over the ensuing years. Attention to a few details makes for a far better experience. It is worth putting time, effort and preparation into making the exchange as pleasant and productive as possible for the child and family.[1–4]

The principles that make for a satisfactory and worthwhile visit to the otorhinolaryngology (ORL) department apply to both adults and children, but some features of the children's clinic are unique. The decision to seek advice will have been made not by the patient but by the parent(s) or carer. The older child will express her views; with babies and young children you are essentially looking after a family rather than a patient. The history, the diagnosis, the discussion of management options, and the decision-making are 'by proxy' and will usually involve the parents – sometimes alone, and sometimes in consultation with the child.

BUILDINGS AND FACILITIES

The clinic experience for the family starts well before they see you. Easy road access, car parking, a bright friendly environment with adequate outlets for food and drinks, baby-feeding facilities, wheelchair-friendly access and an environment where children and parents feel safe and welcome contribute greatly to parental and child satisfaction with their visit. Planning modern children's hospitals and facilities is a highly skilled and complex endeavour. It requires close liaison between the architects and their design team, clinicians, hospital staff, children and their advocates, and planning authorities (**Figure 2.1**).

Despite their small size, children need proportionately more space than adults. Seating has to be comfortable and suitable for all ages. Wheelchair access is essential as are spaces for breastfeeding, well-equipped bathrooms and facilities for changing of babies' clothes. A bright spacious waiting room well stocked with toys, pens, paper, crayons and computer games and able to



Figure 2.1 Foyer of Royal Liverpool Children's Hospital.



Figure 2.2 Waiting room with toys.

withstand the rough and tumble that is inevitable in a group of children will make for a far happier experience than a cramped facility (**Figure 2.2**).[5] Children become bored and fractious if they wait too long or have not got enough space.

Play therapists are invaluable and, if the hospital authorities can be persuaded to hire a professional entertainer, better still.

An examining room should be able to accommodate not just the patient, doctor and nurse but two parents, one or more siblings, sometimes in 'Moses baskets' or pushchairs, and often a grandparent. In the case of many of the children with special needs who make up a sizeable proportion of referrals to an ORL service, there may be a need to accommodate a wheelchair, oxygen cylinders and the various bits and pieces the parents carry for tracheotomy care and gastrostomy management. Ideally, an examining room should have a small play area as well where the child and siblings can occupy themselves while the mother gives the history and the doctor can quietly observe the child. The physical environment must be safe for the child, with no spirit lamps, sharp instruments or corners. Discreetly put away instruments other than those in frequent use. Small children will be frightened at the sight of an array of picks and hooks. Handwashing facilities are mandatory. An operating microscope is nowadays essential, either in the room or nearby. Endoscopy – both flexible and rigid – is now so frequently performed in an outpatient setting in children that it can be regarded as a standard requirement in a paediatric ORL clinic. A range of scopes – with facilities for safe storage – and ideally a monitor and a high-specification image capture system with a printer are nowadays mandatory.

Audiological testing rooms should be adjacent to the clinic so that the child can easily move from one to the other.

STAFFING CHILDREN'S CLINICS

Paediatric clinics need more nursing support than general ENT clinics.[6] Reception staff and care assistants with the training and expertise needed to deal with parents and children make for a far better clinic experience. Best practice is that a registered children's nurse should be available 'to assist, supervise, support and chaperone children'[1, 2] but arrangements will vary in different jurisdictions and in different healthcare settings. Staff numbers need to be sufficient not only to support the working of the clinic, but also to ensure the safe supervision of patients and their siblings while parents are preoccupied.

Audiological professionals are an integral part of paediatric ENT practice; a fully registered audiology technician with facilities for audiometry and tympanometry should be available for all children's ENT clinics.

Other professionals may be needed depending on the nature of the clinic: a speech and language therapist (SALT) for voice disorders or cleft palate, or specialist audiological personnel for children with bone-anchored hearing aids (BAHAs) or cochlear implants (CIs).

Trained specialist nurses who liaise with families in the community – for example in supporting home tracheostomy care – greatly enhance the clinical experience for parent and child. Some units arrange a 'preadmission' clinic so that when a child is scheduled for surgery she can

have her pre-op checks in advance of the day of admission. A dedicated nurse usually runs these clinics, and it can be useful for the family to meet her/him at the first clinic visit so that they can plan ahead.

PREPARING FOR THE CONSULTATION

Ideally, the children's clinic must be separate from the adult clinic. If it is not possible to have a clinical area and a set of consulting rooms that are used exclusively for children throughout the working week, they should be scheduled for a dedicated paediatric session; children should no longer be seen in a 'mixed' adult and paediatric setting. It can be very uncomfortable for children and families if they are allocated the same clinic and have to share a waiting room with a group of adult patients.

Adolescents may feel uncomfortable surrounded by hordes of small children and need to have their particular needs catered for. Some hospitals have separate clinics for adolescents planned for after school times, and teenagers usually appreciate a separate ward or section of a ward if they need inpatient care.

There is much to be said for running separate clinics for some categories of patients. These may include 'special needs' clinics and clinics where multidisciplinary input is required, for example audiology, cleft palate and plastic surgery. Plan the optimum organization of time and space in such clinics to strike a balance between making the most efficient use of time by all concerned and the need to ensure you do not overtire or overwhelm the child by asking her to see too many adults in one room at one time.

A visit to the hospital is a routine event for the doctor. It is a major episode in the life of the child and parent.

Remember that the parent/carer is likely to have had to make arrangements in advance of their visit. They may have had to book time off work, childcare for siblings, a day off school for the child, and transport for the trip.

Take time to read the case-notes – often electronic nowadays – including the results of investigations if applicable, and learn the child's name before the consultation starts. If the child has a chronic medical condition or a syndrome, read up on it in advance if you can. This is relatively easy nowadays as so much information is available online. Parent and child will appreciate continuity and, if a child needs to be seen for repeat visits, it is ideal if the same doctor sees them each time.

Make sure parents or children do not feel rushed in clinic; if you have to hurry them along, the clinic has not been properly planned. If family members do not speak the same language as the doctor and clinic staff, an interpreter will be needed, and this should be arranged well in advance of the visit.

It is not the author's place to advise on dress code; suffice to say that your best tailored suit and crisp, freshly pressed shirt will neither impress the average 8-year-old nor continue to look crisp at the end of a busy morning with a succession of spirited children!

THE HISTORY

Welcome the family and greet the child by name. Make eye contact and start by introducing yourself. Introductions should include others in the room; ask permission for medical/nursing students to be present and for them to examine the child. Multidisciplinary clinics can be particularly intimidating as several specialists are present. It is good practice for all to wear a name badge and many hospitals will demand this. Establish who is with the child – it may be a parent, a carer or a grandparent. Be clear on who is going to give you the history and make sure the child gets an opportunity to speak if she is old enough. Doctors are taught to take very focused histories, but in a paediatric setting it is often better to ask an open question, such as 'What are your worries about Kirsten?', than to steer the parent down a particular set of symptoms.

Good consultation skills can be taught, learnt and improved upon with constructive feedback and should be an important part of training and assessing surgeons as they progress towards independent practice.

Many doctors regard themselves as good communicators because they can explain illnesses and procedures in easy-to-follow terms, but of course communication is a two-way street. Listening – without interruption – can be more useful than talking. It is essential that the parent – usually the mother – feels that her account has been carefully listened to and understood before you probe with more direct questions. Watch the child, look at the mother's facial expressions, note how she interacts with the child and pick up as much information as you can from both verbal and non-verbal clues.

Listen well and talk less until it is clear that the parent feels you have the full picture.

If the parents offer to show you the child's growth chart, a record of their visits to the doctor, diary entries, photographs or short video clips, make sure you look at them. The parents will feel any record of their child's health is important and they may give you much information, for example about the child's overall development or, in the case of video clips, the child's sleep pattern. The birth and perinatal history may be important, and particularly with airway pathology it is helpful to ask the mother about the delivery, whether the baby was term or premature, whether there were any concerns about breathing and feeding as a newborn and in particular

whether there was any airway intervention such as an endotracheal tube or a period in the special care baby unit (SCBU).

EXAMINATION

Begin the examination as soon as the child comes into the room. Note the child's gait, breathing pattern and state of alertness. Once they have had a chance to settle in the clinic room, young children are usually happy to be examined. Smaller children are best examined sitting on their mother's knee.

For the ENT examination explain in an age-appropriate way what is going to happen; don't persist if the child is fractious or struggling.

It is not appropriate to restrain an older child for the purpose of an elective clinical examination, but the mother/father can gently but firmly hold a baby or toddler to facilitate otoscopy, examination of the nose and examination of the neck (Figure 2.3).

Most children will tolerate otoscopy; if there is wax or debris, it is usually possible to remove it by suction to get a better view. Use the biggest speculum that will comfortably fit in the ear canal. If you need a better view, use the microscope, which should be as well tolerated as a standard otoscope. Thin otoendoscopes with high-quality cameras and viewing monitors are becoming more widely available and represent a good opportunity to record findings, to facilitate better explanations of pathology to parents and to use as an aid to teaching.

A good way to start a nasal examination is to assess the nasal airway using a cold metal spatula to look for the pattern of condensation (Figure 2.4). Children do not like the Thudicum's speculum; you can get a good view of the nasal cavities by elevating the tip of the nose and looking with a good light source (Figure 2.5) but high-quality modern endoscopes have made rhinoscopy far easier and better tolerated. Although some surgeons like to use a local anaesthetic spray, the author has not found this useful and in general, if a child will not tolerate a nasendoscope, she will tolerate a spray even less; get the best view you can using a headlight.



Figure 2.3 Examining a child.

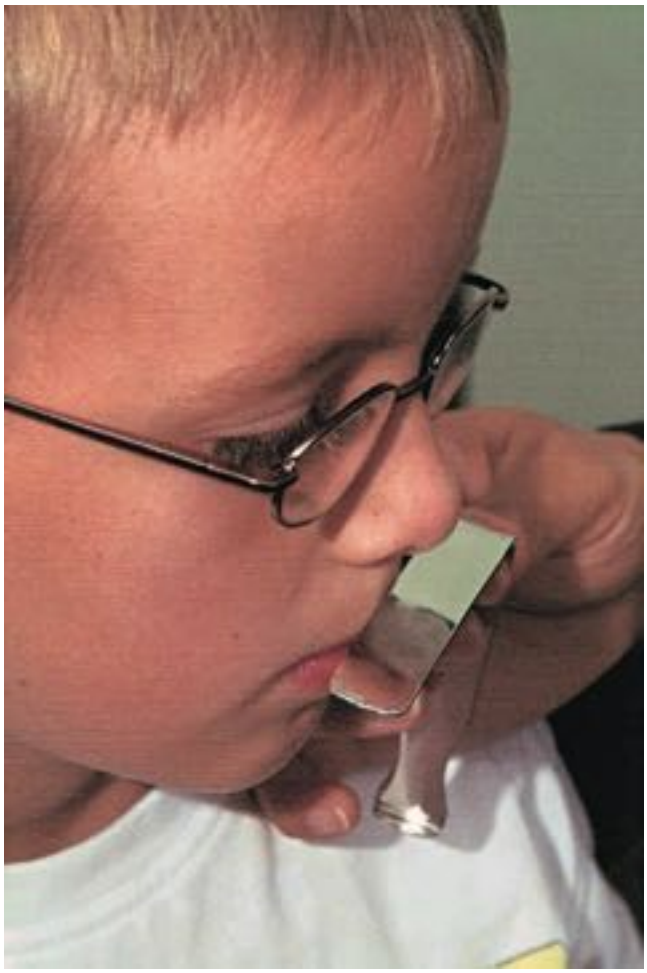


Figure 2.4 The spatula test.



Figure 2.5 Nasal examination.

Examine the pharynx with a standard headlight. Children dislike tongue depressors; the author very rarely uses one. You can get a good view of the nasopharynx using a telescope with an angled lens carefully placed between the tonsils.

Examining the larynx can be difficult, but flexible transnasal endoscopy will give you a very good view in a

cooperative older child, or in the case of a baby who is gently but firmly held by the mother. As with nasendoscopy, the author has not found local anaesthesia very helpful. You may be able to see the vocal cords with an angled-lens rigid telescope but, if a child is anxious or distressed and you have to get a view of the larynx, then arrange admission for a general anaesthetic.

Neck examination should focus on observation for lumps, bumps, sinuses and asymmetry, gently palpating to assess for lymph nodes. 'Lymphadenopathy' is probably a misnomer in children as some degree of lymph node enlargement is physiological and should cause no alarm.

INVESTIGATIONS

Few if any investigations are needed for most common ENT presentations in children.

Pure-tone audiometry (provided the child is old enough) and tympanometry are essential components of a full ENT examination. Radiological imaging may be needed depending on the pathology, and ultrasonography is increasingly used to quickly assess neck swellings. Some ENT surgeons are now skilled at getting good ultrasound images in clinic. If the child needs blood tests, then she should have local anaesthetic cream (e.g. EMLA™ cream, an emulsion containing lidocaine and prilocaine) before being sent for phlebotomy. Photography can be useful – for example, for facial and neck lesions – and close liaison with a skilled medical photography department will make for a better paediatric ENT service.

MANAGEMENT PLAN

The parents have come to see you to hear your opinion on their child's condition and to discuss a management plan with you. This part of the consultation is vital and must never be rushed. Explanations should be straightforward and easy to understand, involving the child where appropriate. Models, diagrams, printed and audiovisual material can aid this process greatly. For many interventions, such as tonsillectomy, adenoidectomy and insertion of tympanostomy tubes, there will be more than one management option and it is important that each is discussed in an open and honest way. This sometimes means doctors have to admit doubts and uncertainties and these are best explained without embarrassment so that a way forward can be agreed by consensus. The treatment will be a matter for negotiation between the otolaryngologist and the mother and/or child and questions should be encouraged. Some parents see the ORL consultation as a means to confirm a treatment option they have already decided on with their family doctor (e.g. tonsillectomy for recurrent sore throats). Others are reluctant to consider any surgery, but all will greatly appreciate an informed discussion and an honest presentation of the evidence for current practice focused on the specific needs of their child. In general, parents appreciate a discussion with the senior clinician, but this needs to be balanced with the need for residents and juniors to see patients and improve their diagnostic and consultation skills.

PAEDIATRIC MEDICAL ASSESSMENT

ENT surgeons are not typically trained medical paediatricians; if you are seeing a significant number of children, you will come across conditions that are best diagnosed and dealt with by paediatrician colleagues. Some knowledge of these conditions can help early detection and referral so that parents and children are offered skilled support as soon as is practicable. Attention deficit hyperactivity disorders (ADHD), autistic spectrum disorders (ASD), and a variety of 'functional' disorders may well present first to the otolaryngologist.

ADHD

Every clinician will be familiar with the child who fidgets, won't sit still, and seems to have a poor attention span. Parents will often volunteer that the child is 'hyperactive' or disruptive. In extreme cases this may constitute a behavioural syndrome termed attention deficit hyperactivity disorder (ADHD). This condition is now thought to affect 3–4% of children worldwide. They occasionally present with suspected hearing loss or poor sleep patterns.

The defining features of ADHD are hyperactivity, impulsivity and inattention, but these characteristics are distributed in varying degrees throughout the population.

ADHD diagnostic criteria vary somewhat, but the core feature of the diagnosis is that symptoms are associated with 'at least a moderate degree of psychological, social and/or educational or occupational impairment'. ADHD is not a categorical diagnosis; it should only be made with great care following a thorough assessment by a skilled and experienced paediatric team.[7] A diagnosis of ADHD has serious potential implications; it is generally a persisting disorder. Most affected children will go on to have significant difficulties in adulthood, including continuing ADHD, personality disorders, emotional and social difficulties, substance misuse, unemployment and involvement in crime. Management can be very taxing, involving social and educational services, the family doctor and his/her team, specialist paediatricians and, of course, the child's family.

Autistic spectrum disorders

Autism was once thought to be an uncommon developmental disorder but is now estimated to occur in at least 1% of children. Healthcare personnel need to be aware of some of the features so as to facilitate early diagnosis and intervention. The characteristic features are impairment in reciprocal social interaction and social communication,

TABLE 2.1 Some features of autistic spectrum disorders (ASD) in preschool children

Aspect	Examples
Language	Delayed speech development Frequent repetition of set words and phrases
Responding	Not responding to their name being called Rejecting cuddles
Interacting	Unaware of other people's personal space Intolerant of people entering their personal space Avoiding eye contact
Behaviour	Repetitive movements Playing with toys in a repetitive way Getting upset if there are changes to normal routine

combined with restricted interests and rigid and repetitive behaviours. In recognition of the great heterogeneity of autism, the term 'autistic spectrum disorder' (ASD) is now more commonly used. The list of possible symptoms is very large but some key features are shown in Table 2.1.

Otolaryngologists may suspect that a child referred for a hearing or speech assessment has an ASD. The diagnosis needs to be made with great care and warrants a full assessment by an experienced team.[8] If ASD is confirmed, families and the child or young person themselves can experience a variety of emotions, including shock and worry about the implications for the future. Some have a profound sense of relief that others agree with their concerns. Skilled diagnosis is important: it can offer an understanding of why a child or young person is different from their peers, open doors to support and services in education, health and social care, and provide a route into voluntary organizations and contact with other children and families with similar experiences. All of these can improve the lives of the child or young person and their family.

Children with ASD may present to the ENT clinic with language delay or suspected hearing loss.

Given the frequency of the condition, many children who present to the ENT clinic will have a background history of ASD and it is important to be aware of the diagnosis because of its very common association with comorbidity. ASD is strongly associated with a number of coexisting conditions. Approximately 70% of people with autism also meet diagnostic criteria for at least one other (often unrecognized) psychiatric disorder that further impairs their psychosocial functioning. Intellectual disability (intelligence quotient [IQ] below 70) occurs in approximately 50% of young people with autism. Deafness and other sensory impairments are more common and may be difficult to recognize.

Children with ASD need particularly sensitive care and attention if they are admitted for surgery.

Some children with ASD find the company of other children distressing and they are especially likely to become upset if they have to wait too long. In general they should be assessed early by the anaesthesiologist, considered for a sedative – 'pre-med' – scheduled early on the operating list, and discharged as soon as they are fit. Day surgery is preferable unless there are very good medical reasons to keep the child in overnight.

Functional disorders

Just as in adult medicine, children present to the ENT clinic with symptoms for which no organic pathophysiological explanation can be found despite a thorough examination and in some cases extensive investigation. The term 'functional disorders' is often used to emphasize that, although no structural or anatomical abnormality can be demonstrated for example on imaging, endoscopy or microscopy, there may be physiological dysfunction.

ENT symptoms in children may include:

- earache
- tinnitus
- hearing loss
- dysphagia
- neck pain
- balance disorders
- dysphonia
- stridor (very occasionally).

Terms such as 'medically unexplained', 'psychogenic', 'stress-related', 'psychosomatic' and 'hysterical' were used in the past but have been abandoned as they were unhelpful, became derogatory and implied a certain amount of 'blame' on the part of the patient.

Functional disorders are not the same as factitious or feigned illness; it is hugely counterproductive to make the child or parent feel that they are not believed.

The symptoms are very real to the patient and can cause great distress, which can be exacerbated if they are treated in an insensitive or judgmental way.

Take a full history, examine the child thoroughly, arrange investigations as needed – including audiometry, imaging and endoscopy – and formulate a diagnosis. If you suspect a functional basis for the symptoms, enquire into issues such as school, relationships with siblings, friends and family and whether there has been any change in home circumstances. Parental disharmony, bullying at school and the trauma of the physiological and psychological changes of puberty and adolescence can all have an impact on health and well-being, with somatic symptoms coming to the fore. An experienced clinician will need to strike a balance between a thorough investigation to rule out an organic aetiology and a more minimal approach focusing on history, examination and reassurance. A sensitive and thoughtful explanation of the findings to parent and child will allay fears and make for a good rapport for follow-up visits.

There is often a background history of environmental or psychological stress, but dealing with a certain amount of anxiety, uncertainty and insecurity is all part of

growing up. Children can – consciously or unconsciously – describe symptoms that bring about some 'secondary gain' for them, such as time off school, increased parental attention in the event of a new sibling, and the benefits associated with being perceived as 'sick'. Functional disorders are distinct from true malingering or feigned symptoms, although these do very occasionally present as well. It is difficult to know on the basis of a single consultation whether there is any significant psychological morbidity; too-early referral to a psychological support service can be counterproductive.

Many functional disorders are short-lived and should not be 'over-medicalized.'

It is the author's practice in most circumstances to reassure the family that the majority of these symptoms are transient and rarely need intensive intervention. Bear in mind that depression, pathological anxiety and rarely overt psychosis do occur in children, and skilled psychiatric help will be needed in some circumstances. Referral protocols vary but most children's hospitals will have a child and adolescent mental health service (CAMHS) team, who will see and assess children at short notice. Many hospitals will have specific policies covering this type of scenario; clinicians should ensure they have the appropriate training for the setting in which they work. Management must be tailored to the individual child and family and prognosis varies greatly.

CONSENT AND PARENTAL RESPONSIBILITY

It goes without saying that every medical intervention requires the informed consent of the patient. What is different in the case of young children is that they may not have the capacity and understanding ('competence') to weigh the benefits and risks of an intervention, and consent will usually need to be given on their behalf. It is wise to involve the child whenever possible. The interests of the child must, of course, take precedence over the wishes of others, even parents, and the law in almost all jurisdictions recognizes this, but clinicians will want to respect the legitimate concerns of parents, carers or legal guardians. The legalities that govern these processes vary in different jurisdictions and healthcare settings but the principles are broadly similar.

Once children reach the age of 16 years they are deemed legally 'competent' in the UK.

Reaching the age of legal competence means children are responsible for decisions relating to consent themselves, but it is of course wise to involve parents if at all possible in major decisions in the young. If a young person up to the age of 18 years is not 'competent' – for example, due to learning disability, reduced consciousness, or severe illness – then a parent or person with 'parental responsibility' (see below) can give consent for them, but over the age of 18 years in UK law a parent cannot give consent on behalf of a young person. This causes difficulties in the case of young adults with learning disabilities, many of whom remain under the care of children's hospitals. In these cases the clinician must make the decision on the young person's behalf, ideally with the written agreement of another senior clinician and with the full approval of the parent.

A child under the age of 16 years may well be able to understand the implications of a treatment strategy. In UK law such a child who has 'sufficient understanding and intelligence' to enable him or her to understand fully what is proposed is deemed 'Gillick competent' or as it is sometimes known 'Fraser competent'.[9] The decision as to whether a child fulfils the criteria for 'Gillick competence' rests with the clinician, hence teenagers undergoing, for example, tonsillectomy may give their own consent. The issues around consent in children can cause great sensitivity and are fraught with medicolegal pitfalls. If in any doubt, seek the advice of one or more senior clinicians.

In the case of a child who is not 'competent', consent has to be sought from and given by a person with 'parental responsibility.'

'Parental responsibility' is usually held by one or both of the parents. The situation varies in different jurisdictions but in England and Wales 'parental responsibility' is automatically given to the mother, and to most fathers. A father will have parental responsibility if he is married to the child's mother or listed on the child's birth certificate (after a certain date, which varies in jurisdictions). Fathers who do not have parental responsibility can get it via an agreement with the mother or they can apply for it through the courts. Grandparents, foster parents and others who look after children do not have parental responsibility unless special legal arrangements have been made. Consent from one parent is legally valid but it is best to obtain consent where applicable from both. A written record of consent, signed by the doctor and the parent, is an important document and, although not legally mandatory, in general an invasive intervention should not proceed without it. Verbal consent for surgery is possible – and in many circumstances entirely reasonable. If, for example, a newborn baby needs urgent surgery, very often the mother will be recovering in the maternity unit. The surgeon should speak to her by telephone, explain the natural history of the condition, the implications of treatment, the consequences of not treating, and the timing of treatment. It is good practice to get another healthcare professional (e.g. a nurse) to confirm with the mother that she understands and agrees with what is being proposed and to record the exchanges in the case notes.

It may be necessary in emergency scenarios to proceed without consent – for example when a child needs urgent

intervention following an accident and the person with parental responsibility is not immediately available.[10–13]

A recent UK legal judgement – the 'Montgomery' case – has moved the focus of consent more towards the specific needs of the individual patient. This follows the guidance of the General Medical Council[11, 12] but makes even more explicit the need for doctors to take reasonable steps to ensure that **patients are aware of any risks that are material to them**. This puts a greater onus on us as surgeons not only to communicate the benefits and risks of interventions but to judge the individual needs and perceptions of our patients/parents and to customize our discussion of management options to those varying patient/parent views.[14, 15]

Consent in children causes great sensitivity. Make sure you are familiar with the Department of Health guidelines,[10] the findings of the 'Montgomery' case,[14] the advice of the General Medical Council[11–13] and the guidance of the surgical Royal colleges.[15] Trainee surgeons in particular are advised to seek the advice of senior colleagues in the event of any uncertainties.

FUTURE RESEARCH

- Department of Health (DoH): https://www.gov.uk/government/organisations/department-of-health
- General Medical Council (GMC): http://www.gmc-uk.org/
- National Institute for Health and Care Excellence NICE): https://www.nice.org.uk/
- Royal College of Surgeons of England (RCS): https://www.rcseng.ac.uk/

KEY POINTS

- A visit to the hospital is a routine event for the doctor. It is a major episode in the life of the child and parent.
- Children should be seen in appropriately staffed, dedicated children-only 'child-friendly' clinics.
- Audiological professionals and audiological testing facilities are an integral part of children's ENT clinics.
- Autistic spectrum disorders (ASD) are increasingly common and may present to the otolaryngologist.
- Make sure you are familiar with the procedures governing consent in children in your healthcare setting.

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CHAPTER 3

RECOGNITION AND MANAGEMENT OF THE SICK CHILD

Julian Gaskin, Raymond W. Clarke and Claire Westrope

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SEARCH STRATEGY

Data in this chapter are taken from the Advanced Paediatric Life Support (APLS) manual and the websites and publications of the General Medical Council, the National Institute for Health and Care Excellence (NICE), and the Paediatric Intensive Care Society (PICS), supplemented by the authors' personal bibliographies and their experiences as clinicians and teachers.

INTRODUCTION

Children under the care of otolaryngologists are mostly looked after in an outpatient or planned inpatient setting, and are in good general health. Very ill children – sometimes with complex and multisystem diseases – are typically cared for by paediatricians and their teams, but the otolaryngologist will often participate in shared care. Every doctor who looks after children will, from time to time, be presented with an emergency situation; children who are apparently well can deteriorate very quickly.

Doctors who deal with children also need to be aware that children are vulnerable to harm and abuse and that we have a duty of care to recognize and act if we have any concerns about such abuse or maltreatment.

This chapter outlines some of the general principles that underpin the care of the very sick child, and highlights some of the features of child abuse that may present in an ORL clinic.

A short book chapter is, of course, no substitute for structured learning and experience. ORL training programmes now recognize this and both otolaryngologists-in-training and established practitioners will need to complete formal 'hands-on' training courses in the principles of resuscitation and in 'child protection'.

THE 'NORMAL' CHILD

The aphorism that 'children are not small adults' conveys important lessons, not least that the physiology of the child and their responses to illness may be very different from those in adults. Children have lower physiological reserves; they can deteriorate with alarming rapidity. Doctors who work largely with adults may not always appreciate, for example, the widely varying baseline observations in children, and their changes with age (**Table 3.1**). Fluid requirements are, of course, also very different in children (**Table 3.2**).

An awareness of the normal parameters is essential, as deviations away from these allow the clinician to recognize them at the earliest opportunity. Ongoing assessment and monitoring can facilitate early detection of change and prompt life-saving intervention.

RECOGNIZING THE SICK CHILD

The way we approach recognizing and managing seriously ill patients nowadays has largely been shaped by the principles developed in Basic and Advanced Life Support courses (BLS and ALS).[1, 2] Courses and teaching modules

TABLE 3.1 Normal range at different ages for children's weight, respiratory rate, pulse rate and systolic blood pressure (adapted from APLS manual[1])

Age	Weight (kg)	Respiratory rate (RR) (breaths/minute)	Pulse/minute	Systolic blood pressure (mmHg)
Birth	3.5	25–50	120–170	65–105
1 year	9.0	20–40	110–160	70–95
4 years	16.0	20–30	80–135	70–110
10 years	32.0	15–25	70–120	80–120

TABLE 3.2 Fluid requirements in normal healthy children (adapted from APLS manual[1])

Body weight	Fluid per day (mL/kg)
First 10 kg	100
Second 10 kg	50
Each subsequent kg	20

focused on the needs of healthcare personnel looking after sick children developed from the early 1990s as the Advanced Paediatric Life Support (APLS) system, which teaches a structured and reproducible set of skills applicable across specialty, language, cultural and geographical boundaries.[1] APLS teaching materials are produced and regularly updated by a multidisciplinary team of paediatric emergency physicians, anaesthetists, surgeons and paediatricians. Much emphasis is given to the care within the first hour, the so-called 'golden hour', which governs the trajectory of subsequent management. With important, easy-to-remember initial steps, the right order of resuscitation can begin to help avert a sick child deteriorating, or even worse, dying.

Prioritizing bodily systems has helped clinicians and those first on the scene to deal with complex situations in the best possible way. A structured approach concentrates on different systems of the body in an order that generally allows the most important problems to be assessed and dealt with first before moving on. These systems include the **respiratory**, **circulatory** and **central neurological** systems. They can be remembered as:

A – Airway
B – Breathing
C – Circulation
D – Disability (central neurological system)
E – Exposure (temperature, rash, bruising).

The respiratory system – airway and breathing

In the initial assessment of a sick child, the airway and breathing must be considered first. A blocked or reduced airway has to be addressed as a matter of extreme urgency as this impacts quickly on all of the organ systems. Signs to be observed include **apnoea**, **stertor** and **stridor**. As the child's ribcage is soft and pliable, sternal and intercostal **recession** and **'tracheal tug'** (indrawing of the suprasternal tissues) can often be seen if a child is working hard to breathe.

The respiratory rate must be measured. This will vary according to the child's age (see Table 3.1). If a child is tachypnoeic, this may be due to airway or lung pathology, or a metabolic acidosis (trying to 'blow off' carbon dioxide). A slowing respiratory rate is not always a comfort; it may be due to fatigue or cerebral depression and can be a preterminal sign.

Respiratory noises can help to define the level of airway narrowing, but this is not specific enough to make a definite diagnosis. If the noise is a low-pitched, snoring-type sound ('stertor'), then obstruction is usually at the level of the nasopharynx or oropharynx. 'Stridor' – generally a higher-pitched noise, (although the two terms are used imprecisely) – is often inspiratory but can also be biphasic (inspiratory and expiratory), and is classically brought about by obstruction in the larynx. This can be the supraglottis, glottis or subglottis but stridor can also be due to narrowing of the trachea or even the main bronchi. Biphasic stridor is particularly ominous and suggests severe airway compromise. Obstruction in the lower airway or in the distal bronchial tree will usually produce **wheeze**, which is more pronounced on expiration. All these respiratory noises are normally more pronounced in the presence of good airflow. In a preterminal state when the airflow is reduced, there may not be an obvious respiratory noise, despite significant obstruction within the airway. Beware the stridulous child who becomes quiet. Gasping is almost invariably a late sign of a severely hypoxic, exhausted child.

A child with severe airway obstruction will often adopt a position – usually when lying down – with the neck extended. This is called an 'opisthotonic' position and is aimed at trying to open the upper airway maximally due to obstruction. Other signs to look for in the assessment of airway compromise include flaring of the nostrils as an infant tries to increase the intake of air during inspiration.

Inspection, palpation and auscultation of the chest can reveal important signs too. Chest expansion can be a very sensitive sign when making an assessment of the amount of air passed during inspiration and expiration. The same goes for auscultation, where reduced air entry can be evaluated. If air entry is unequal across the lungs, this may point to pathology affecting one lung, such as a pneumothorax or a bronchial foreign body. A 'silent chest' is another late sign in a child that may be about to have a cardiopulmonary arrest.

Simple measurement of the pulse can inform the clinician of the presence of tachycardia associated with hypoxia. However, this is also likely if the child is anxious or pyrexial. Bradycardia is an ominous preterminal sign.

Monitoring equipment such as a pulse oximeter may be of additional support as it can help give a measure of the arterial oxygen saturation. Pulse oximetry should be used as an adjunct; guard against false reassurance if other clinical signs do not support a good read-out from the pulse oximeter. It is important to realize that there is often a time delay of a few seconds before the oxygen saturation registers; the true oxygen saturation in the patient's arterial blood may be lower than the reading suggests. Conversely, a low reading may relate not only to a patient's low oxygen levels but can occur in hypothermia, severe shock or if there is poor contact with or interference from the sensor.

In severe hypoxia, expect to see skin pallor due to vasoconstriction. Cyanosis is a late and highly ominous sign. In a child without an underlying cardiac condition it is extremely serious, suggestive of severe respiratory compromise; if due to hypoxia it suggests that the child is close to a respiratory arrest.

The circulatory system (C)

After airway and breathing, circulation needs to be assessed next. One of the first signs is the pulse rate, measured either by palpation (better centrally via a larger artery such as one of the carotid or femoral arteries) or with pulse oximetry (again, bearing in mind its limitations). Normal ranges of pulse rate can be seen in Table 3.1, varying with age. Tachycardia will often be seen in shock, where a decreased stroke volume (amount of blood pumped from the left ventricle in a beat) leads to release of catecholamines such as adrenaline. Bradycardia is a late sign of impending cardiac arrest. Weak pulses, particularly centrally, can be a sign of very poor perfusion as blood pressure is usually maintained until severe shock develops. Blood pressure readings are not as useful because systolic blood pressure is usually well maintained in a shocked child. Once hypotension has supervened, a cardiac arrest is highly likely.

Capillary refill is a much earlier sign of circulatory compromise. This should be assessed centrally, ideally on the sternum, where digital pressure is applied to the skin for 5 seconds and then released. The resultant blanched skin colour change should usually return to normal within 2 seconds. If this is prolonged, it is a sign of poor skin perfusion but is also suggestive of potential underlying poor perfusion to other organs. Although fever does not affect this sign (which is therefore very useful in assessing a child with septic shock), a cold environment does, so the ambient temperature needs to be taken into account.

Other signs of poor circulation relate to the effects on other organs. The skin can show obvious changes such as cold peripheries but also mottling. Poor perfusion will affect the conscious state and cause reduced urinary output and increased respiratory rate.

The central neurological system – disability (D)

A formal assessment using the Glasgow Coma Scale (GCS) used in adult patients is often very difficult to transfer over to a child. A quick way of assessing the conscious level in a child is using the acronym AVPU to signal progressively decreasing conscious level:

- **A**lert
- responds to **V**oice
- responds to **P**ain
- **U**nresponsive.

If the child in unresponsive to verbal stimulus but does respond to painful stimulus, this would equate to a GCS of 8 or less. Ways to measure response to painful stimuli can be to exert pressure over key points of the body, such as the sternum or supraorbital ridge. Subsequent sounds, localization to the painful stimulus or seeing if the eyes open can then be recorded.

Observing the posture of the child can be helpful. Often, hypotonia ('floppy' child) is present if the child has had a significant neurological insult. Sometimes there are specific positions a child will adopt depending on the location of intracranial pathology. Flexed arms and legs is known as a decorticate posture and extended arms and legs is known as a decerebrate posture, which is usually in keeping with a more severe injury. With meningitis, there may be neck stiffness.

The reaction of the pupils to a light stimulus can reveal important information related to the function of the central neurological system. Dilated pupils, or pupils that are unequal or unresponsive to light, may point toward serious neuropathology.

There may also be signs of abnormal central neurological function in the respiratory and circulatory systems, with altered breathing patterns, hyperventilation or apnoea. Brain herniation can cause a vasopressure response with hypertension and bradycardia.

Exposure (E)

A full assessment of the sick child involves stripping the patient down to look at the skin for bruising related to injury or rashes related to infection or allergy, which may dictate the need for investigations such as blood cultures, CT imaging and lumbar puncture (provided there is no evidence of raised intracranial pressure). It is also important to check the temperature and reassess all the signs again such as respiratory rate, pulse rate and so on.

With this simple but highly effective order of assessment, using airway, breathing, circulation, disability and exposure (ABCDE), the correct priorities are set to ensure that important features in the recognition of the sick child are not missed.

EARLY MANAGEMENT

Following the structured approach of assessing a seriously ill child, resuscitation and treatment is required. This follows the same systematic format.

Airway

Suctioning of secretions, removal of intra-oral foreign bodies or debris, a chin lift and jaw thrust are the immediate measures to free the airway. This is likely to overcome any oropharygeal obstruction. If the airway obstruction is not resolved by such simple manoeuvres, an **adjunctive airway** may be required. This may be in the form of a nasopharyngeal airway (NPA), an oropharyngeal or 'Guedel' airway or a laryngeal mask airway (LMA). If the airway cannot be maintained by one of these measures, endotracheal (ET) intubation will be needed. This could be via the nose (nasotracheal) or mouth (orotracheal). Externally, a tracheostomy can be formed, or in a dire emergency situation a cricothyroid puncture.

Nebulized adrenaline and intravenous steroids such as dexamethasone may all help to improve upper airway obstruction (see Chapter 28, Stridor).

If an airway foreign body is likely and the child is *in extremis,* then immediate transfer to an operating theatre for removal of the object using a ventilating bronchoscope can be life-saving. An oropharyngeal foreign body may need to be immediately engaged and removed with Magill forceps.

Breathing

Once the airway is secured, breathing needs to be efficacious. This requires there to be no intra-cerebral compromise of the respiratory centre and no abnormality of the lungs or musculature surrounding the lungs. Emergency treatment to aid breathing would be by applying high-flow oxygen via a facemask with a reservoir bag, or direct attachment to an endotracheal tube if the child has been intubated. Bag-valve ventilation ('bagging') can also be performed and works by introducing positive pressure. Investigations may include a chest radiograph, arterial blood gases or blood cultures, but stabilizing the airway and ensuring the child is breathing safely is by far the highest priority.

Circulation

Supporting and reversing inadequate circulation requires intravenous cannulation and administration of intravenous fluids in the first instance. However, if intravenous cannulation is not readily achievable, particularly in hypovolaemic shock where peripheral venous access may be difficult due to vasoconstriction, intra-osseous access will be required. Intra-osseous fluids can be infused effectively to reverse a circulatory deficit in children. Replacement of blood in the presence of significant blood loss may also be needed. Primary investigations are blood tests in the form of a full blood count, urea and electrolytes, clotting screen and a group and save/cross match. An electrocardiogram is also needed. If septic shock is suspected, blood cultures and intravenous antibiotics are required.

Disability

Rapid assessment using the AVPU stimulus test above will help ascertain if intubation is necessary to protect the airway. A child with responses only to painful stimulus or a child who is unresponsive (**P,U**) meets this criterion. Any patient with a neurological deficit must have their glucose level checked (don't ever forget glucose – **DEFG**). If blood glucose levels are found to be abnormal, they can be reversed with intravenous treatments. Seizures or convulsions can be treated with benzodiazepines. Signs of raised intracranial pressure are likely to require CT scanning and specialist input from neurology or neurosurgical teams.

Adequate analgesia – including the use of opioids where safe and appropriate – is an important part of the early management of the sick child.

Exposure

Septicaemia may cause a purpuric rash. Meningitis may cause a non-blanching purpuric rash, along with other signs of meningism. Intravenous antibiotics are then needed immediately. Anaphylaxis may cause an urticarial rash and angio-oedema, particularly around the lips and oropharynx. In such cases, adrenaline given via nebulizer and intra-muscularly is often immediately helpful, with intravenous steroids and intra-muscular antihistamines later on in the resuscitation period.

SAFE TRANSFER

Once the seriously ill or injured child has been appropriately resuscitated and stabilized, the next step in their care may involve some form of transfer to another hospital unit. Inter-hospital transfer will be needed if the level of care or expertise cannot be delivered at the first location where the child is seen. Reasons for this may include the need for specialist teams such as neurosurgery for intra-cerebral complications, paediatric ENT surgery for complex airway issues such as foreign body inhalation or laryngeal stenosis or even because of a lack of available facilities and staff within that hospital's intensive care unit. Wherever the destination or whatever the indication, the principles remain the same.

Resuscitation as described earlier needs to have taken place prior to transfer. It is essential to have good teamworking and communication throughout the whole process. From an ENT viewpoint this may require securing the airway jointly with the anaesthetist and could even mean a tracheostomy or cricothyroidotomy in an extreme airway emergency, although nowadays this is very rarely needed. Urgent treatment should not be delayed waiting for transfer or for a retrieval team to arrive. If endotracheal intubation is required and achieved, one of the

greatest concerns would be accidental displacement or dislodgement and it is essential that endotracheal tubes and tracheostomy tubes are carefully secured.

The principles of safe transfer have been refined by guidance from the Paediatric and Neonatal Safe Transfer and Retrieval (PaNSTaR) group[3] who, following the lead of APLS, have created the acronym **ACCEPT** to help focus thinking around safe transfer:

- **Assessment:** Before making a transfer a formal assessment needs to be undertaken by the transfer team. Continuous monitoring and reassessment will also be required.
- **Control:** The one in overall charge of the transfer needs to take control of identifying and allocating key tasks.
- **Communication:** Good communication between the current, transfer and receiving teams needs to take place, along with the child's family.
- **Evaluation:** Ensure that the transfer is appropriate.
- **Preparation and packaging:** Ensure appropriate preparation of the child, equipment and personnel has taken place, mindful of the limitations when providing medical care in a mobile setting.
- **Transportation:** The mode (road or air) and effects of that mode of transport to medical care need to be fully considered.

'Retrieval' teams are an increasingly important part of networked care for children. Teams may include paediatricians, anaesthetists, intensive care physicians, nurses and paramedics and a paediatric otolaryngologist. These teams have particular training needs including ongoing attention to maintaining their skills, and the otolaryngologist will often have a key role in the team.

PAEDIATRIC INTENSIVE CARE

Paediatric critical care describes the care of children who need an enhanced level of observation, monitoring or intervention which cannot safely be delivered in general wards.[4] Paediatric intensive care unit (PICU) staff look after children and young people whose conditions are life-threatening and who need constant close monitoring and support from equipment and medication to restore/maintain normal body functions. This includes care of children requiring intubation and ventilation, single- or multiple-organ support and continuous or intensive medical and nursing supervision. This also includes routine planned post-operative care for surgical procedures and during some planned medical admissions.

Three levels of such care are now widely accepted:

- **Level 1 Basic critical care:** A child, for example, with mild upper airway obstruction needing nebulized adrenaline would be managed here.
- **Level 2 Intermediate critical care:** This includes care of a child with an NPA, and early care of children with a newly fashioned tracheostomy. A level 2 unit (often referred to as a high dependency unit or HDU) would usually manage a child needing non-invasive ventilation such as CPAP.
- **Level 3 Advanced critical care:** This is often referred to as a paediatric intensive care unit (PICU). Such a unit would have a high ratio of nurses to children and be able to provide mechanical ventilation, in addition to other forms of organ support.

Cross-specialty working between ENT surgeons and PICU is essential in the care of critically ill children. Examples include post-operative management of a child after upper airway surgery, acute management of the difficult airway, acute upper airway obstruction, diagnosis and management of upper or lower airway malacia and multispecialty working for establishing and maintaining long-term ventilation (LTV) in patients with severe respiratory disease.

Strategies used in PICU are aimed at restoring and maintaining normal body functions. In essence, this is done by providing adequate oxygen and energy supplies to all organs and tissues to maintain their function. Oxygen is delivered to the body via respiration and delivered to the tissues by being carried in the blood (mostly via haemoglobin) and so normal tissue function is dependent on adequate oxygen supply to the lungs (ventilation) and adequate blood supply to the tissues (cardiac output and circulation). The principles of ventilation are largely generic, regardless of the large variety of underlying pathologies leading to the child needing ventilation. Ventilation ensures adequate pulmonary oxygen supply and carbon dioxide removal, but it may cause injury to the lungs by barotrauma/volutrauma and alveolar collapse, or by direct oxygen toxicity. Regardless of whether the lungs are normal or diseased, a 'lung-protective' ventilator strategy should be used. Pressure, volume and oxygen settings can be minimized and mild or 'permissive' hypercapnia and hypoxia is now accepted. In PICU PIP (peak inspiratory pressures) ≥30 cm H_20, expiratory tidal volumes ≥10 mL/kg and inspired oxygen concentration (FiO_2) ≥60% are all associated with ventilator-induced lung injury.

PICANet (Paediatric Intensive Care Audit Network) reports indicate that around 40% of admissions in the UK are planned (34% post-surgery) and 60% are for unplanned emergency care. The top three indications for admission to PICU are cardiovascular (28.6%), respiratory (26%) and neurological (11%). Around 65% of admissions require invasive ventilation and 15% non-invasive ventilation. PICU mortality rates remain low (<4%).[5]

If a child in PICU has signs of inadequate cardiac output (e.g. low blood pressure, evidence of poor perfusion, decreased urine output), this can be supported in a number of ways. It may simply involve restoration of intravascular volume (either with i.v. fluids or blood/blood products) or additional support with drugs that increase cardiac output. Inotropes (e.g. adrenaline) increase myocardiac contractility and heart rate; vasopressors (e.g. noradrenaline/vasopressin) increase systemic vascular resistance (e.g. in vasodilatory shock). Lusitropes (e.g. milrinone) aid diastolic relaxation of the heart so that it will contract better (Starling's law) and cause peripheral vasodilation increasing blood supply to the tissues.

Other therapies available in PICU replace the function of acutely injured organs in the short term until they recover or in the longer term until a more definite therapy option is found. Examples of this are total parental nutrition (TPN) and continuous renal replacement therapies (dialysis).

While maintaining/restoring normal function using the above strategies it is important to treat the underlying condition (e.g. antibiotics for infection, surgical intervention), keep the patient comfortable using sedation and analgesia if required, and ensure the patient's safety by preventing hospital-acquired harm and delivering high-quality care at all times.

For the very seriously injured/ill child in whom usual PICU therapies are not restoring or maintaining normal cardiac or respiratory function, but in whom the underlying condition is considered to be reversible, the use of extracorporeal life support (ECLS) strategies should be considered. Extracorporeal life support is a general term to describe prolonged but temporary support of heart and lung function using mechanical devices. Device applications require a combination of vascular access catheters, connecting tubing, a blood pump, a gas exchange device (oxygenator), a heat exchanger, measuring and monitoring devices, and systemic anticoagulation.

There are various subtypes of ECLS (with varying degrees of overlap) including:

- ECLA – extracorporeal lung-assisted systems
- ECMO – extracorporeal membrane oxygenation: a high-flow ECLS to replace lung and/or heart function, the term used synonymously with ECLS
- $ECCO_2R$ – extracorporeal carbon dioxide removal
- ECPR – extracorporeal cardiopulmonary resuscitation (emergency cardiac support in cardiac arrest).

The principle of these techniques is that blood is drained from the circulation and reinfused back after passing through the extracorporeal circuit where it is oxygenated and carbon dioxide is removed.

These are highly specialized techniques available only in a few designated centres.

MONITORING AND RECORDING

A child's medical condition can change very quickly; a previously 'well' child can become very ill in a short space of time. Careful monitoring and recording of simple physiological measurements such as pulse and temperature can alert staff early that a child is becoming dangerously ill, and may prompt early life-saving intervention. If parents or nursing staff feel a child has deteriorated, that in itself should be enough to prompt a careful medical review. There has been increasing emphasis on 'paediatric early warning scores' (PEWS) in recent years[6, 7] and most hospitals now have policies and protocols that guide staff on the need for a rapid response. There is no universally agreed PEWS system, so for now clinicians will need to familiarize themselves with the system in use in the setting in which they work. The important issue for doctors looking after children – particularly doctors who are less familiar with paediatric practice – is to be aware of the need to seek specialist advice if in any doubt.

RECOGNIZING 'SEPSIS'

Children may develop a life-threatening, rapidly progressive, exaggerated inflammatory response to infection, leading to impaired organ function. This has come to be known as 'sepsis' and has been the subject of much attention in recent years.[8, 9] There is a significant mortality (25%). Children at particular risk are the very young (infants under 1 year), those with a history of recent trauma including surgery, children with immune dysfunction and children with indwelling medical devices such as lines and catheters.

Whenever a patient presents with symptoms or signs raising the possibility of infection, sepsis should be considered. It is a time-critical emergency and warrants immediate intervention with completion of the 'sepsis six' within an hour, shown in **Box 3.1**.

BOX 3.1 The 'sepsis six' (NICE guidelines)[9]

1. High-flow **oxygen** via facemask
2. Blood **investigations** including blood culture (ideally before antibiotics) and blood gas
3. **Antibiotics** – broad-spectrum, intravenous (or parenteral) according to local guidance and taking account of patient's microbiology, given at maximum recommended dose within an hour of recognition of sepsis
4. **I.V. fluid** bolus – if signs of fluid depletion (including raised lactate)
5. **Lactate** measurement – repeated regularly if raised (>2 mmol/L)
6. **Fluid balance** monitoring

CHILD PROTECTION

Every professional involved in the care of children needs to be aware of the potential for children to be subject to abuse or neglect.

This can take the form of physical, emotional, or sexual abuse and may be perpetrated by family members, by friends and acquaintances or by professionals who come in contact with the child. Professional regulatory bodies – e.g. the General Medical Council (GMC) in the UK – expect doctors working with children and young people to be especially conversant with the features of abuse and neglect and to act upon any concerns they have.[10] Arrangements for raising such concerns vary in different healthcare settings and in different jurisdictions but the principles are essentially the same.

You should be familiar with the main presentations in your area of practice that can be caused by abuse and with the strategy for seeking appropriate advice and support.

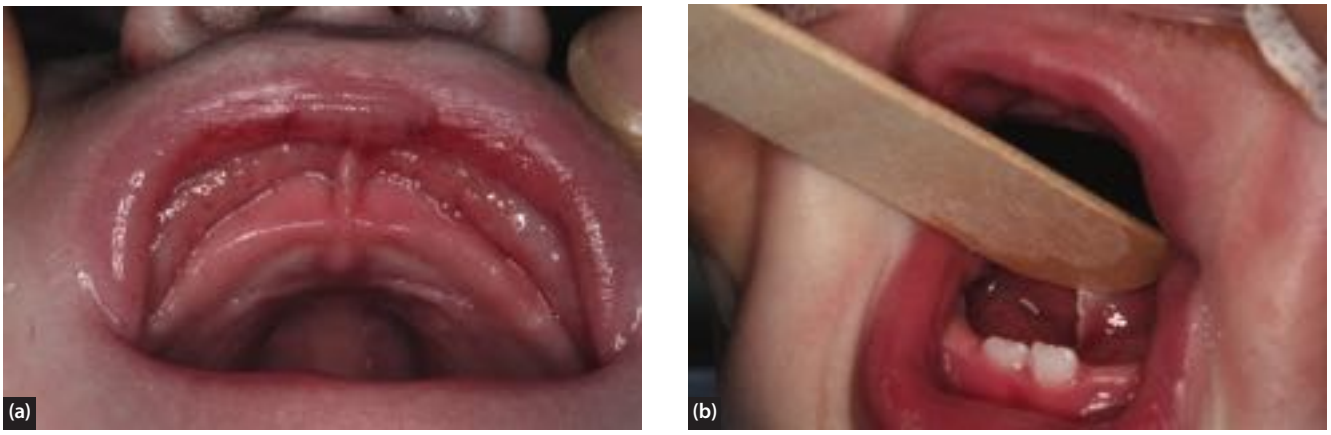


Figure 3.1(a) Tear of the labial frenulum with ulceration of the labial mucosa, **(b)** healing tear of the lingual frenulum.

Most children's hospitals will have a 'child protection' team who can be contacted for advice in confidence. Anecdotal evidence would suggest that few ENT surgeons make a diagnosis of child abuse, but it is essential that they are aware of it as a possible explanation for some unusual presentations. Up to 75% of children who suffer physical abuse have injuries to the head and neck (**Figures 3.1a, b and 3.2**). Some ENT presentations that may be linked with child abuse are shown in **Box 3.2**. If you suspect that a child's symptoms may be due to abuse or neglect, seek advice from an experienced colleague. Most children's hospitals have a designated team headed up by a paediatrician 'child protection lead' who has the expertise and sensitivity to give advice and support to you as a concerned clinician, and where necessary to explore the issue with the parents. This is clearly an area where great sensitivity and delicacy are needed. An accusation of abuse or neglect can have devastating consequences for the child and family.

BOX 3.2 Some possible non-accidental injuries in the head and neck

Tears to the lingual frenulum
Bruises to the cheeks, lips, gums
Nasal injuries
Injuries to the pinna, especially 'pinch' marks (**Figure 3.2**)
Auricular haematomas
Traumatic perforation of the eardrum
Maxillofacial fractures
Dental trauma
Injuries to the palate, e.g. due to forceful feeding
Bruising to the neck

A very small number of parents deliberately bring about symptoms and signs of disease in their child in an attempt to gain attention from healthcare personnel. ENT examples include ear injuries, blocked tracheostomy tubes and deliberate smothering. This is a serious psychiatric condition (Munchausen Syndrome by Proxy) and needs urgent and expert management.



Figure 3.2 Bruising of the ear. 'Pinch' marks as seen on the upper aspect of the pinna are said to be pathognomonic of non-accidental injury.

A small number of children may, for various reasons, be best looked after outside their family setting, for instance by social services or the local authority. They may be placed in a designated care setting or with an alternative family (foster family). Arrangements will vary in different healthcare settings, but in general these children ('looked-after children', or 'children in care') need particularly vigilant medical attention. They will usually have a named social worker and close liaison with her/him is important in ensuring continuity of medical management, especially if they require surgery, investigations or repeat follow-up visits.

BEST CLINICAL PRACTICE

- Retrieval teams are increasingly important in paediatric care, and otolaryngologists may be key members of the team.
- Beware impending 'sepsis' in a child. It warrants immediate intervention.
- Be aware of the potential for children to be subject to abuse or neglect.

FUTURE RESEARCH

- ➤ Paediatric critical care is a recognized and expanding medical specialty, with the potential for ever better care and outcomes for very seriously ill children.
- ➤ Early warning scores for sick children are being harmonized with the potential for more widely accepted guidelines on early intervention for the sick child.
- ➤ 'Retrieval' of sick children and transfer to PICU is an increasingly important part of the work of specialized children's hospitals.

KEY POINTS

- Children who are apparently well can deteriorate very quickly.
- Biphasic stridor suggests severe airway obstruction.
- Bradycardia and cyanosis are ominous signs in a child with airway obstruction.
- Beware the stridulous child whose breathing becomes quiet – she may be close to cardiac arrest.
- Cross-specialty working between ENT surgeons and PICU is essential in the care of critically ill children.

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CHAPTER 4

ANAESTHESIA FOR PAEDIATRIC OTORHINOLARYNGOLOGY PROCEDURES

Crispin Best

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SEARCH STRATEGY

Data in this chapter are based on the author's personal bibliography of key papers on paediatric anaesthesia and on his extensive experience in clinical practice. The website of the Association of Paediatric Anaesthetists of Great Britain and Ireland (APA) http://www.apagbi.org.uk is a good source of information on guidelines and current best practice relating to anaesthesia in children.

INTRODUCTION

The purpose of this review of anaesthesia for paediatric otorhinolaryngology (ORL) procedures is not to produce a definitive text for the expert anaesthetist working in a tertiary centre; rather it is to give a flavour of the techniques and pitfalls associated with the specialty. Guidance on patient selection and pre-operative preparation is discussed and some aspects are considered in greater detail.

Paediatric ORL surgery covers a whole range of conditions from the apparently simple such as the insertion of grommets to complex airway reconstruction. Even simple cases need advance planning. Any treatment episode for a patient is a cooperative effort between all the professionals involved. Only if the team works together will optimum conditions be provided to treat each condition quickly and effectively. From the moment the patient presents, no matter how 'routine' the case may be, this principle must be foremost in the minds of all. In the case of the shared airway (vide infra), this is even more critical.

Once the patient has been diagnosed, assessed for surgery and anaesthesia and their procedure scheduled, there must be a briefing of all staff at the beginning of the session to ensure that all are fully informed of what is proposed, and that everything is required for full pre-, peri- and post-operative care. More complex cases may require detailed advanced planning.

If in doubt, discuss the case with the anaesthetists well in advance of the day of surgery.

PATIENT SELECTION

The reason why families attend an ENT clinic is to seek an opinion for treatment for their child. If surgery is planned, anaesthesia and peri-operative care is a vital part of this process. It is important that whoever sees the patient in clinic is aware of what aspects of the medical history the anaesthetist needs to know. This can be broadly broken down into problems resulting from the condition itself, and associated conditions – both congenital and acquired. These need to be considered in the light of what treatment is proposed.

ORL conditions of anaesthetic relevance

Patients with obstructive sleep apnoea may need special nursing care and present challenges for post-operative management (see Chapter 27, Paediatric obstructive sleep apnoea).[1]

Any patient presenting with stridor or other symptoms of airway obstruction will be a source of particular concern to an anaesthetist. These patients can cause huge problems on induction of anaesthesia and can potentially lead to that most acute of emergencies the

'can't intubate, can't ventilate' scenario. Preparation and planning will prevent most of these dramas.

Associated conditions

CONGENITAL

There are many congenital conditions that may need special consideration in a child undergoing a general anaesthetic. These range from the obvious ones affecting the airway directly, such as laryngotracheal obstruction, to conditions affecting the child's general health, such as myotonic, neurological or cardiac conditions. Sometimes more than one condition coexists, for example Down syndrome in which patients have abnormal tissues, neck instability with cardiac anomalies such as atrial or ventricular septal defects. Some conditions improve with age, for example Pierre Robin sequence or Goldenhar syndrome, as the micrognathia associated with both improves with age. Some get worse, for example Treacher Collins syndrome and the mucopolysaccharidoses such as Hurler syndrome.[2]

It is also useful to know in advance if the patient has any conditions such as attention deficit hyperactivity disorder (ADHD) that may influence behaviour (see Chapter 5, The child with special needs). Children with autistic spectrum disorders (ASD) need to be identified well in advance of surgery. Many struggle with disturbance of their routine and are best having surgery on a day admission basis, preferably first on the list and with early discharge so that they can get back to their normal surroundings as soon as possible.

ACQUIRED

These conditions will be what patients usually present with, for example subglottic stenosis after prolonged endotracheal intubation, laryngeal webs and recurrent respiratory papillomatosis. Knowledge of what caused the problem and what has been done previously makes anaesthesia less of a challenge.

Drug history

Children fortunately do not tend to be the victims of the polypharmacy that afflicts the modern elderly adult. It is useful to document drugs that affect the heart, lungs and nervous system so that we can ensure that long-term conditions continue to be treated. Several of these may directly affect the conduct of the anaesthetic, including beta-blockers, vasodilators and diuretics.

Nature of procedure

Many ENT operations are considered 'routine'. Procedures such as adenotonsillectomy and insertion of drainage tubes into the middle ear are the bulk of the operative work of a department and children undergoing this type of surgery will not ordinarily need any special anaesthetic considerations unless the patient has any of the associated factors outlined above, or unless they have significant obstructive sleep apnoea (OSA). Other procedures (e.g. microlaryngoscopy and bronchoscopy) may be considered 'routine' in a tertiary referral centre. Which children need to be discussed individually in advance of surgery will depend on the experience of the surgeon and anaesthetist and on what is done in that particular unit.

Where do we operate?

The surgeon assessing the patient needs to consider where the procedure should be carried out. This depends on the nature of the case, the experience and practice of the team and the peri-operative facilities available on site, including nursing care and the availability of ventilatory support. Some cases are best suited to a tertiary referral centre and, if in any doubt, the staff at these institutions will be pleased to discuss the case with any referring clinician.

More detailed planning

It may be necessary to involve other disciplines in the care of cases which are difficult in themselves (e.g. major airway reconstructions) or where the patient has significant comorbidities. It is the practice in our institution to have a multidisciplinary meeting once a month where surgeons, anaesthetists, intensivists, specialist nurses and any other disciplines necessary meet and discuss forthcoming cases in detail. In this way PICU and HDU beds can be booked in advance, and ward and anaesthetic staffing rosters can be planned.

If in doubt, discuss the case with the anaesthetists.

PRE-OPERATIVE ASSESSMENT

It is becoming common practice for children and their parents or carers to attend a pre-operative assessment clinic before any operative procedure. It should be borne in mind that attending hospital with a child is in itself disruptive for both child and family, so ideally the patient should attend the pre-operative assessment clinic on the same day that they are seen by the surgeon.

Pre-op clinics are typically conducted by an experienced and suitably trained children's nurse. At this clinic the staff can take a history, examine the child and help prepare them for the procedure. This may include the provision of written and illustrated materials, which the family can peruse at home. It should be emphasized that, useful though these leaflets can be, they are no substitute for a proper interview with the anaesthetist. Any material used should also be prepared in conjunction with the anaesthetic department in order to reflect current practices and guidelines. If any problems are detected at this clinic, there should be a prompt communication with both surgeon and anaesthetist to aid planning. It is pointless for a patient to attend such a clinic if they then present on the day with something which should have been dealt with earlier.

ADMISSION

Whether a patient is admitted on a day-case basis (ambulatory care) or for overnight stay depends on local policies, geography and the nature of the operation. Many hospitals now carry out tonsillectomy, adenoidectomy, microlaryngoscopy and bronchoscopy and other similar procedures on a day-case or '23-hour' basis.[3] Irrespective of the time the patient stays in hospital, several things must happen before the operation commences.

PREPARATION AND ANAESTHETIST'S VISIT

The patient's weight and temperature must be checked. This allows the calculation of drug doses and early warning of any infections that may be present. The operating surgeon must see the patient, obtain consent for the procedure if this has not already been done, and mark the site of the operation if appropriate. The anaesthetist will see the patient, check the patient's general condition and confirm their suitability for anaesthetic. Careful note will be taken of any infection, especially of the respiratory tract. An active symptomatic respiratory tract infection causes a large increase in anaesthetic problems and these children should have their procedures delayed for 2 weeks until they have recovered. The anaesthetist will also explain the induction of anaesthesia to the patient and family and deal with any concerns they may have. In addition, they will discuss the post-operative period, especially with regard to analgesia.[4]

Fasting guidelines

It is very important that the patient is adequately fasted for the procedure (Table 4.1). Nothing ruins the anaesthetist's day like the appearance of a wave of vomit coming towards the airway on induction of anaesthesia. Compliance with guidelines can be patchy; parents sometimes misunderstand instructions or for one reason or another do not give accurate information, so detailed questioning may be necessary.[5]

Premedication

Some patients may require 'premedication' to reduce anxiety. As all the commonly used agents are sedative, they are almost always contraindicated in any patient who has an obstructed airway for any reason. If one is to be used, it must be **only** on the expressed instructions of the anaesthetist performing the procedure. Anticholinergics are sometimes given to dry up secretions and militate against the bradycardic effects of volatile anaesthesia. It is not our practice to use them as we find that we have more problems post-operatively with patients being unable to clear sticky secretions. They are, however, always drawn up ready for use in an emergency. Local practices will vary according to anaesthetic preference.

As always, if in doubt, discuss the case with the anaesthetists.

TABLE 4.1 Fasting guidelines

Food/drink	Fasting time (hours)
Clear fluids*	2
Breast milk	4
Formula or cow's milk	6
Pastes and solids	6

* Clear fluids include diluting juice but NOT natural fruit juices.

ANAESTHESIA

Briefing

Any operation is a cooperative venture. Before any operating list is started, the full team must assemble and there must be a thorough briefing given where all members can discuss the cases of the day. This will ensure that the list is correct, treatment plans can be finalized and the availability and operability of any specialized equipment that may be necessary can be checked. This is in line with the WHO recommendations on surgical safety, which also include a checklist to be completed before every individual case is started (Figure 4.1).[6]

Basic principles

There are few occasions in anaesthesia and surgery where the surgeon and anaesthetist work so closely together as in paediatric ENT procedures. Many of these involve a shared airway, and it must be accepted that, in the case of any deterioration in the condition of the patient, the anaesthetist must be allowed instant and full access to the patient to deal with the immediate problem. The surgeon's role in this circumstance is to provide assistance to the anaesthetist, which may extend in life-threatening circumstances to the provision of an emergency surgical airway. It therefore follows that any surgeon undertaking an operating list that includes patients likely to need emergency care **must** be capable of performing such a procedure. Unlike the adult situation, cricothyroid membrane puncture on children is difficult and has a high failure rate irrespective of how it is done, so *in extremis* a surgical cricothyrotomy or tracheostomy may need to be carried out urgently.[7]

Technique

The choice of anaesthetic technique will be largely dependent upon the type of operation being performed, the nature of the patient and any specific requests from the surgeon to assist with the operation. The well-known anaesthetic triad of 'anaesthesia, analgesia and relaxation' can be obtained in a number of different ways. Similarly, whether the patient should breathe spontaneously or be ventilated and whether they should be intubated or not will be covered in 'Spontaneous respiration vs endotracheal intubation and paralysis' below.

World Health Organization

SURGICAL SAFETY CHECKLIST (FIRST EDITION)

Before induction of anaesthesia ▶▶▶▶▶▶▶▶▶ Before skin incision ▶▶▶▶▶▶▶▶▶▶▶▶▶ Before patient leaves operating room

SIGN IN

☐ **PATIENT HAS CONFIRMED**
- IDENTITY
- SITE
- PROCEDURE
- CONSENT

☐ **SITE MARKED/NOT APPLICABLE**

☐ **ANAESTHESIA SAFETY CHECK COMPLETED**

☐ **PULSE OXIMETER ON PATIENT AND FUNCTIONING**

DOES PATIENT HAVE A:

KNOWN ALLERGY?
☐ NO
☐ YES

DIFFICULT AIRWAY/ASPIRATION RISK?
☐ NO
☐ YES, AND EQUIPMENT/ASSISTANCE AVAILABLE

RISK OF >500 ML BLOOD LOSS (7 ML/KG IN CHILDREN)?
☐ NO
☐ YES, AND ADEQUATE INTRAVENOUS ACCESS AND FLUIDS PLANNED

TIME OUT

☐ **CONFIRM ALL TEAM MEMBERS HAVE INTRODUCED THEMSELVES BY NAME AND ROLE**

☐ **SURGEON, ANAESTHESIA PROFESSIONAL AND NURSE VERBALLY CONFIRM**
- PATIENT
- SITE
- PROCEDURE

ANTICIPATED CRITICAL EVENTS

☐ **SURGEON REVIEWS:** WHAT ARE THE CRITICAL OR UNEXPECTED STEPS, OPERATIVE DURATION, ANTICIPATED BLOOD LOSS?

☐ **ANAESTHESIA TEAM REVIEWS:** ARE THERE ANY PATIENT-SPECIFIC CONCERNS?

☐ **NURSING TEAM REVIEWS:** HAS STERILITY (INCLUDING INDICATOR RESULTS) BEEN CONFIRMED? ARE THERE EQUIPMENT ISSUES OR ANY CONCERNS?

HAS ANTIBIOTIC PROPHYLAXIS BEEN GIVEN WITHIN THE LAST 60 MINUTES?
☐ YES
☐ NOT APPLICABLE

IS ESSENTIAL IMAGING DISPLAYED?
☐ YES
☐ NOT APPLICABLE

SIGN OUT

NURSE VERBALLY CONFIRMS WITH THE TEAM:

☐ **THE NAME OF THE PROCEDURE RECORDED**

☐ **THAT INSTRUMENT, SPONGE AND NEEDLE COUNTS ARE CORRECT** (OR NOT APPLICABLE)

☐ **HOW THE SPECIMEN IS LABELLED** (INCLUDING PATIENT NAME)

☐ **WHETHER THERE ARE ANY EQUIPMENT PROBLEMS TO BE ADDRESSED**

☐ **SURGEON, ANAESTHESIA PROFESSIONAL AND NURSE REVIEW THE KEY CONCERNS FOR RECOVERY AND MANAGEMENT OF THIS PATIENT**

THIS CHECKLIST IS NOT INTENDED TO BE COMPREHENSIVE. ADDITIONS AND MODIFICATIONS TO FIT LOCAL PRACTICE ARE ENCOURAGED.

Figure 4.1 WHO Surgical Safety Checklist (from http://whqlibdoc.who.int/publications/2009/9789241598590_eng_Checklist.pdf6).

Equipment

In addition to the full range of anaesthetic equipment that should be present in all locations where anaesthetics are given, there are several features that should receive extra attention (**Figure 4.2**). Although any child when anaesthetized may have a 'difficult' airway, this is much more likely in a situation where the patient is being anaesthetized for the investigation of just such a condition. Although every theatre suite should have a difficult intubation trolley containing emergency equipment, there is a case for duplication of this provision where elective airway work is being done. Specific items may be a matter for personal choice, especially with regard to equipment such as types of laryngoscope blade, for example. Recent reviews[8, 9] have emphasized the need for training and a common approach to any problems.

As well as the more traditional endotracheal tubes and face masks, the use of the laryngeal mask has proved invaluable in some cases of the difficult airway. Once one of these is in place, if the airway needs to be secured further, a fibre-optic intubation can be performed through the mask using a guide wire and airway exchange catheter, and the laryngeal mask removed.[10] This kind of procedure is complex and ideally should be planned in advance.

In addition to the traditional range of anaesthetic laryngoscopes, the anaesthetist may also have recourse to a number of newer video and fibre-optic devices (**Figure 4.3**).[11, 12] To a large extent, which is to be used is a matter of personal preference, however it is important for every unit to choose only one, and become expert in its use during routine cases. An emergency is no time to learn how to use an unfamiliar piece of equipment.

'Can't intubate, can't ventilate'

This is a situation every anaesthetist dreads and, as mentioned above, the surgeon may be called upon to assist in obtaining an airway. **NEVER FORGET the option of waking the patient up. The case can then be planned for another time in the light of what has happened.**



Figure 4.2 Basic set of equipment for paediatric airway anaesthesia. Included are face mask with a soft seal, different types of anaesthetic laryngoscope, endotracheal tube and laryngeal mask, Guedel airways, Magill forceps and an intubating bougie.



Figure 4.3 McGrath videolaryngoscope. This is one of the more effective types of videolaryngoscope, enabling a view of the larynx when conventional methods may not be adequate.

Assistance

The anaesthetist must have a trained assistant. This may be an experienced operating department assistant or nurse or another anaesthetist. Irrespective of who this person is, they must be familiar with local policies and guidelines, have a good knowledge of the available equipment and how it is used, and have taken part in the pre-operative briefing.

POST-OPERATIVE CARE

There is little point in proceeding with complex anaesthesia and surgery if facilities do not exist to care for the patients post-operatively. The post-anaesthesia care unit (PACU) must be staffed to a defined level of competence, and there must be equipment available in the unit to deal with any emergency, including emergency drugs and an anaesthetic machine. More complex cases may require the services of a high dependency or intensive care unit. The basic rule is never to start a case unless you have the facilities to finish it. The Association of Anaesthetists of Great Britain and Ireland has published general recommendations for organization and staffing.[13] If an emergency case has to be done where appropriate facilities do not exist, the anaesthetic team must recover the patient. Patients should not be discharged from the PACU until the anaesthetist/recovery staff are sure that the patient is fully conscious, is appropriately hydrated, is not in pain and has had appropriate analgesia prescribed as well as full instructions to

the ward on post-operative care. A handover sheet, which can be filled out by staff, is very useful for this purpose.

When patients are discharged, they should be provided with information sheets particular to their procedure, containing contact details for the institution should they have any problems.[14]

NEVER start a new case until the last patient is safe.

SPECIFIC OPERATIONS

Tonsillectomy and adenoidectomy

This is probably the commonest operation performed by the ENT surgeon. Surgical options are 'cold steel' dissection, or the use of the coblator or harmonic scalpel systems. Anaesthetically, the choice of airway management is to use either an endotracheal tube (ETT) or a laryngeal mask airway (LMA). The ETT is more secure than an LMA and is easier for the surgeon to keep out of the way in placing a Boyle Davis gag. However, the LMA is quicker and easier for the anaesthetist to place. The choice will depend ultimately upon surgical and anaesthetic preference. It important never to compromise an airway merely for convenience's sake.

Another discussion is whether to admit these patients as day cases (by which is meant early morning admission and evening discharge) or for an overnight stay. This will depend upon local facilities, patient population and patient preference, among other things. Analgesia must be effective no matter what system is chosen. A useful review covers this subject in more detail.[15]

Antiemesis can be helped with dexamethasone,[16] ondansetron or a combination of the two. Remember that patients can swallow a little blood during the operation, which can often lead to a vomit afterwards. This is of no consequence if small and not repeated.

Post-operative analgesia in our institution is provided by regular oral ibuprofen, with paracetomol as required. We do not give any form of oral opiate as a take-home drug; instead, patients are asked to contact us if they have any problems.

Airway examination and treatment

There is no doubt that the treatment of a compromised paediatric airway is one of the most challenging procedures to face any operative team, particularly for the anaesthetist. Not only will the patient have to be kept safe, but also there is little point in the child having an anaesthetic unless the surgeon is able to do the procedure. Safety is paramount. Surgery will not proceed until the anaesthetist is satisfied that the patient is in a fit state for that to happen. It **must** be remembered that waking the patient up again if the airway cannot be adequately secured is always an option. Recent reviews have emphasized the importance of training and a considered approach.[17, 18]

Patients will present with a variety of conditions, both congenital and acquired, which will be covered in other chapters of this book.

SPONTANEOUS RESPIRATION VS ENDOTRACHEAL INTUBATION AND PARALYSIS

The basic principle of paediatric airway anaesthesia is to keep the patient breathing. This sounds almost too obvious to state, but it must be remembered that all anaesthetic agents of whatever type depress respiration and reduce muscle tone such that a patient who, when awake, is capable of maintaining their own airway promptly loses it when anaesthetized. Additionally, in some cases such as mediastinal tumours the patient may be impossible to intubate in an emergency, making rescue very difficult if they have a respiratory arrest. A careful gas induction using sevoflurane in oxygen is the preferred method for anaesthetizing these patients. The airway is being constantly observed as the patient becomes anaesthetized and the process is gradual and controllable. Intravenous access, if not gained beforehand to avoid upsetting the patient, can be gained as soon as possible and the airway is under constant control.

Unlike the adult situation where the bulk of examination is for tumour or infection, the majority of paediatric patients present with disorders of breathing requiring further investigation. If they are intubated and paralysed, tracheo- or laryngomalacia may not be seen due to the pressure effects of insufflated gas. Similarly, if the patient is intubated for ventilation, the pressure of the endotracheal tube may squash pathology such as tracheal haemangiomata, making them impossible to see.

The ideal situation for both diagnosis and treatment of airway problems is the spontaneously breathing patient maintaining their own airway. This can be achieved either by using a volatile anaesthetic agent in oxygen or by the use of total intravenous anaesthesia (TIVA). Whichever method is used depends upon anaesthetic and institutional preference.

The use of a volatile agent has the benefit of simplicity in that the patients control their own depth of anaesthesia. If they become 'light', they breathe up and get deeper; if 'deep', the respiratory rate slows down, thereby lightening the anaesthetic. TIVA can be quite labour-intensive, as the rates of the infusions may have to be constantly adjusted according to circumstance. This takes the anaesthetist's attention away from the airway at what may be a crucial time.

The larynx is also sprayed with lidocaine to decrease the response to instrumentation, although care must be taken to ensure the patient is anaesthetized deeply enough to avoid temporary laryngospasm when this is done. Oxygenation can be obtained by means of a nasal airway attached to an Ayres 'T' piece anaesthetic circuit. If the patient is to be ventilated, they are better intubated. Jet ventilation, frequently used in adults, carries significant risk of barotrauma in small children although some centres use it successfully.[19] This is not our practice, as we believe the disadvantages far outweigh any benefits. Finally, a dose of dexamethasone is given to patients to try to reduce any oedema that may affect the airway post-operatively. The evidence for this is scanty but most experienced airway anaesthetists feel that this is of value.[20]

In summary, a logical approach with a high degree of safety is a gas induction of anaesthesia with sevoflurane or halothane (if available) in oxygen, the establishment of intravenous access if not already present, getting the patient deep enough to spray the larynx with lidocaine and the nose with xylometazaline, and maintenance of anaesthesia with spontaneous respiration using insufflated volatile with oxygen via a nasal airway. This has the added benefit of leaving instrumentation of the airway to the surgeon, as the anaesthetic has not affected the airway appearance.

Once the patient is stable on the operating table, any surgical examination and intervention can take place.

Micro-laryngoscopy and bronchoscopy

Examination of the airway is essential to diagnosis and treatment. There are a variety of methods including suspension laryngoscopy, examination with a Hopkins rod and bronchoscopy.

Suspension laryngoscopy is used for detailed examination of the larynx and associated structures (**Figure 4.4**). Great care must be taken not to overextend the neck, especially with conditions such as Down syndrome where there is a pre-existing instability. The mechanical advantage of the wheel used to adjust the suspension is enormous; the anaesthetist must watch this closely and stop the surgeon if the neck is moved too far.

The bronchoscope has a side arm for the attachment of the anaesthetic circuit and the delivery of gases (**Figure 4.5**). It also has side holes along the shaft to allow ventilation of both lungs when the instrument has been passed down one bronchus. When the surgeon first places the instrument, it must be passed down to the carina or these side holes may still be in the pharynx, preventing proper ventilation and control of the airway.

At every stage of the examination the surgeon must check with the anaesthetist that the patient is stable and well oxygenated. Communication is key; there must be a constant dialogue between the two. During any examination the anaesthetist must ensure that, when the surgeon is assessing the airway, the patient is not subjected to any degree of positive pressure from the anaesthetic circuit. This may distend the trachea or bronchi and make airway collapse much less apparent. However, positive pressure can be applied on demand to assess how much a collapsed airway can open.

Removal of airway foreign body

The approach here is the same as above, except that grasping forceps may be used either on their own with the aid of a Hopkins rod or through a bronchoscope. The preferred method is to have the patient breathing spontaneously as some feel that positive-pressure ventilation may force bits of the object further into the respiratory tree and the paralysed patient will, by definition, have periods of apnoea when examination and retrieval are taking place. However, jet ventilation can be used as long as the astute anaesthetist is aware of potential problems.[21]

Laser surgery

Laser surgery is covered in more detail in a review.[22] Safety is the prime consideration, and the laser must never be used unless staff are properly trained in its use and all appropriate precautions are taken.

Reconstruction of the airway

There are a large number of procedures that can be carried out for reconstruction of the airway, ranging from a cricoid split to full tracheal reconstruction under cardiopulmonary bypass. The principles, however, are exactly the same as above, i.e. scrupulous attention to the airway and good communication with the surgeon. If we take the example of an anterior laryngotracheal graft, the procedure may be as follows.



Figure 4.4 Laryngoscope and suspension. This illustrates the lever formed by the laryngoscope with the arm of the suspension system. The wheel at the top, which is used for adjusting the extension and flexion of the head on the neck, has a considerable mechanical advantage and damaging overextension could result.



Figure 4.5 Bronchoscope. Note the side holes towards the end of the 'scope, and the plastic mount for attaching the anaesthetic 'T' piece. This one is prepared for laser surgery, with a Hopkins rod and YAG laser fibre *in situ*, which reduces the bore of the system considerably, making it even more important to keep gas leakage as low as possible.

Pre-operatively the patient is breathing normally, albeit partially obstructed. In this case the patient will be orally intubated with a smaller than normal-sized ETT. The surgeon will then make a tracheostome for the duration of the operation through which the anaesthetist will ventilate the patient, and the patient will then have a nasal ETT placed at the end of the procedure. The tip of the ETT can be positioned under direct vision by the surgeon before the tracheal incision is closed. The patient remains intubated for some days post-operatively, with the head in a neutral position to allow time for the trachea to heal.

Tracheostomy

A paediatric tracheostomy differs from the adult in technique, as a vertical slit is made in the trachea after placing two lateral support sutures. Anaesthetic technique will depend upon why the patient is having the procedure. A stoma for a patient who requires one for chronic ventilation is very different from one who is undergoing the procedure for an acute airway problem. The anaesthetist, who may have to sit at the head of the patient manually supporting the airway, must guide the surgeon. Once the surgeon has identified the trachea and made a vertical slit, the endotracheal tube will be slowly withdrawn under direct vision until the tracheostomy tube can be inserted.

Post-operative care is key; the stay sutures remain in place and are stuck to the chest with tape while a track forms. This will enable a replacement tube to be placed in the event of the first one being displaced or falling out.

Ear operations

GROMMETS

The commonest operation and one of the simplest. Beware this illusion. The patient is still fully anaesthetized and asleep is asleep. The anaesthetist will probably use a laryngeal mask airway. The surgeon must check that the patient is fully prepared before starting: a myringotomy is highly stimulating and the patient suddenly moving as the incision is made could be disastrous.

MIDDLE AND MAJOR EAR OPERATIONS

The requirement seen in adult surgery for induced hypotension during the procedure is not necessary in children. Children have a lower resting blood pressure than adults, and modern anaesthetic agents can produce a good operating field for the surgeon without recourse to beta-blockers or vasodilators. Placing the patient a little 'head up' to reduce venous pressure and ventilating the patient to normocapnia is often all that is necessary. The use of nitrous oxide is a little more controversial: some believe it increases the pressure in the middle ear, some that it makes no difference, and evidence can be found in the literature for both positions. Ultimately, this is a question of operator preference and should be discussed with the anaesthetist beforehand.

Nasal surgery

ADENOIDECTOMY

Adenoidectomy is either a single procedure or carried out in conjunction with the placement of grommets and/or tonsillectomy. Again, the choice of how to maintain the airway is a matter of discussion between surgeon and anaesthetist.

REDUCTION OF NASAL FRACTURE

This ostensibly simple operation can be fraught with danger: the nasal bone may have to be refractured in order to get a good result and this can occasionally result in a torrential haemorrhage. The anaesthetist is best advised to use a laryngeal mask airway and place a throat pack before the surgeon proceeds. No one wants to have to deal with an unprotected airway rapidly filling up with blood.

Head and neck

This can range from a 'lumpectomy' to the excision of branchial or thyroglossal cysts. Operations common in adults, such as total laryngectomy, are fortunately extremely unusual in children. The anaesthetist will ensure that the airway is protected by placing an endotracheal tube. A laryngeal mask airway is not secure enough when the head is fully draped, as the head position may be changed during the procedure to improve surgical access.

KEY POINTS

- The airway must be protected at all times. If there is any problem whatsoever, the anaesthetist must instantly be given as much access as required.
- Good communication is crucial. Never start a procedure until there has been a full briefing of all involved staff. This is the time to plan for any problems, not when they occur.
- Never forget that the patient can always be woken up again, to come back another day. Do not persist in the face of adversity.
- Finally, if in any doubt, discuss the case with the anaesthetist.

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CHAPTER 5

THE CHILD WITH SPECIAL NEEDS

Kate Blackmore and Derek Bosman

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: special needs, cerebral palsy, disability, prematurity, neurodisability, Down syndrome, hearing loss, cochlear implant, obstructive sleep apnoea, laryngomalacia, tonsillectomy/adenoidectomy and aryepiglottoplasty.

INTRODUCTION

While the majority of paediatric otolaryngology deals with routine work in the well child, there is a significant part of the workload for the paediatric otolaryngologist that deals with children with special needs. The incidence and survival of very preterm infants has increased dramatically over the last few decades and with this comes increased morbidity.[1, 2] Children with special needs are prone to the usual childhood otolaryngological problems but they are also predisposed to specific problems mainly related to airway difficulties and hearing loss. The whole approach to treating a child with special needs is different and requires special consideration.

TERMINOLOGY

An **impairment** describes a pathological process (e.g. cerebral palsy) and a **disability** is the consequence of an impairment. A **handicap** is a disability of body or mind which interferes with the ability to lead a normal life or to benefit from a normal education.[3] Although terms such as handicap and disability are used commonly in the medical literature, they can be upsetting to parents, and doctors should be sensitive to this.

Special needs is an umbrella underneath which a diverse range of needs often caused by a medical, physical, mental or developmental condition or disability can be categorized. It can include cognitive difficulties, physical or sensory difficulties, emotional and behavioural difficulties, and difficulties with speech and language. This term seems to be more commonly acceptable to parents.

GENERAL CONSIDERATIONS

Hospital appointments

The clinical environment in which children with special needs are seen is important. The consulting room needs to be large enough to accommodate wheelchairs and equipment along with room for the carers.

It is paramount that these families are not kept waiting for long periods in the outpatient department as this can cause great difficulties and distress for the child. Child-friendly waiting areas and the presence of play therapists can help minimize distress and upset during outpatient consultations.

Ideally, hospital appointments should be kept to a minimum. Children with multiple comorbidities will see many different specialties, resulting in frequent trips to the hospital. The disruption to the child's routine can be significant. Specialist clinics that bring clinicians and allied healthcare workers together offer a great advantage to both the clinicians and the family, for example a tracheostomy clinic

bringing together ENT, respiratory paediatricians and speech and language therapists.

Clinicians should also not forget the cost implications of multiple hospital appointments. A recent cross-sectional study in the UK revealed that children with multiple comorbidities are more commonly born to families in the lower socioeconomic groups so that economic challenges may compound the difficulties of looking after a child with complex needs.[4]

Whether within a specialist clinic or not, the time required for an adequate consultation is significantly longer than for typically developing children without complex needs and multiple morbidities and this should be acknowledged when planning clinics and operating lists. Histories are more complex, examination is more challenging and discussions regarding treatment, particularly potential surgery, require more detailed explanation and planning.

Communication

Good doctor patient/parent communication has been shown to result in improved patient knowledge, better adherence to treatment, decreased surgical morbidity and greater satisfaction with care.[5, 6] This is especially true when treating children with special needs. Good, clear communication with the parents/carers, the child and any healthcare professionals involved with the child is paramount.

PARENTS/CARERS

In assessing children with complex problems it is often tempting to used closed questioning to control the duration of the consultation. Parents perceive this approach as showing a lack of interpersonal interest and ultimately it will result in a suboptimal consultation. Parents have greater trust in doctors who allow them to tell their whole story, express their concerns and listen to their ideas.[5, 6]

Parents of children with multiple comorbidities or complex problems will be 'experts' in their children and want, rightly, their views and concerns to be addressed in any decision-making. Decisions about care and management should be part of a family-centred process in the majority of cases.

It is also important to recognize that the parents' priorities for their child may not reflect your own. For example, parents of a child with a tracheostomy may be keen for early decannulation, or conversely may be reluctant to consider decannulation as they are nervous about losing the security of what they perceive as a 'safe' airway.

Parents commonly report that doctors do not give enough information with regard to their child's surgery or health status, particularly in the context of chronic or terminal illness.[5, 6] While we may feel that we have covered all the essential information in explaining, for example, a surgical procedure, its complications and recovery time, it is some of the more minor points that can be important to the parents: how much hair will be removed, the site of the intravenous cannula, how long until their child can eat. In children with special needs these seemingly minor issues can be particularly important and it is essential that the doctor takes the time to answer all the parents' questions.

PATIENT/CHILD

Children should be involved in as much of the consultation as possible. They should be given information in a way they can understand it, given choices about their care and asked their opinion. Children will often understand more than has been assumed.[6] This was shown in Bluebond-Langner's study of terminally ill children in which children as young as 3 years were aware of their diagnosis and prognosis despite not being told by an adult.[7]

While involving the patient may be more difficult in a child with special needs, it is important that any child who has the ability to understand and process the information is given the opportunity to do so. Increased understanding will heighten confidence, decrease fear and improve the level of trust between the child and their parent/doctor. However, this has to be undertaken with the agreement of the parents – giving too much information may be severely detrimental to a child with special needs.

Again, where possible, understanding the child's priorities regarding their health care and what they deem to be important for improving their quality of life should not be underestimated.

COLLEAGUES

Children with special needs will often be under the care of many different specialties and it is vital that there is clear communication between everyone in the healthcare setting. All involved clinicians and allied healthcare workers should be copied in to letters from outpatient consultations and inpatient attendances. This clear communication ensures that everyone involved is aware of the child's current health status and treatment plans. It also allows for the potential coordination of multiple procedures under a single general anaesthetic (e.g. blood tests and tooth extraction), which will decrease the amount of undue stress on the child.

PROGNOSIS, PALLIATION AND QUALITY OF LIFE

Full discussion of this issue is beyond the scope of this chapter but it is important that we take time to consider some areas that we will have to address during our work with children.

The significant advances in neonatology over recent years have dramatically increased the survival of extremely premature babies.[8–11] There was a 44% increase in the number of extremely premature babies admitted to the neonatal intensive care units in the UK over the 10-year period from 1995 to 2006,[10] although evidence suggests that the long-term morbidity, particularly neurodisability,[9] of the survivors has remained unchanged.[10]

Because of the advances we have seen in neonatology, doctors are increasingly likely to have to make difficult decisions about whether to start or continue invasive life-sustaining treatment with the known risk of a poor long-term prognosis. Withholding or withdrawing life-sustaining treatment in a neonate, or indeed a child of any age, is extremely difficult and often highly charged and emotive. While advances in technology make it increasingly possible to sustain life, this may only increase pain and suffering to the child and their family. It is essential that the healthcare team has allowed enough time to gather information about the child's condition and other relevant problems before any discussions or decisions on whether further treatment is appropriate can be made.[3] Decisions should never be rushed.

The Royal College of Paediatrics and Child Health document *Withholding or withdrawing life sustaining treatment*[3] gives guidance on the circumstances when withholding or withdrawing treatment should be considered. The guidelines advise that, if the future life of the child will be 'impossibly poor', then it would be reasonable to withhold treatment. In a child whose life is already 'impossibly poor' and there is no sign that this will improve in the foreseeable future, then it would be reasonable to consider withdrawing treatment.

In situations where withholding or withdrawing treatment is deemed the most appropriate course of action, this should be discussed with the family at an early stage. The family must be given all the information they require, along with enough time to be able to understand and process it. They should also be given the opportunity to seek a second opinion if they wish. The consent of the parents is important for the final decision to be made, but the ultimate responsibility lies with the healthcare team. This may help lessen the guilt that some parents/carers feel following decisions in these situations.[3]

Reaching a decision to withdraw or withhold treatment does not mean cessation of care. The provision of palliative care to provide pain relief, alleviation of other symptoms (e.g. airway distress) and also support the emotional, social and spiritual needs of the child and their family is paramount.[3]

In situations where withdrawal of treatment is not appropriate but there is an expected progressive morbidity, communication with the family, and the child if appropriate, is again extremely important. When discussing prognosis and long-term morbidity, doctors have a tendency to 'medicalize' outcomes and list potential complications and morbidities with percentages of likelihood. While this is obviously an important area, it is imperative that the quality of life the child and family may have is discussed, including the capacity for happiness, and the good and the bad that go along with caring for a child with multiple comorbidities. The positive aspects of what life ahead may look like need to be considered; do not simply dwell on the potential problems.[12]

What makes a 'good quality of life' is a difficult philosophical question to which there would be no unanimous answer. Many people with severe functional limitations consider they have a life of high quality and are happy to be living it while an observer may not rate it so highly. Do those living with disabilities have a more positive view of their life because they have never known an alternative?[13] Do they find more value in things that able-bodied individuals value less?[14] Whatever the answer, it is important that we do not judge the quality of life of those with several functional limitations on the same basis as we view our own lives. Our priority should be to provide a high quality of care to children with disabilities and provide support for their families.

THE EAR AND HEARING LOSS

Hearing loss

Children with hearing loss who have additional disabilities make up a significant proportion of the hearing-impaired paediatric population and they can be a challenging group to manage. It is estimated that 2–4% of neonates in the neonatal intensive care unit will have a significant bilateral hearing loss.[15] The underlying cause for sensorineural loss is probably multifactorial, with risk factors such as low birthweight, low Apgar score, hyperbilirubinaemia, ototoxic medication and mechanical ventilation all being well documented.[16] It has also been reported that low birthweight babies often have central auditory processing problems, with difficulty discriminating speech and poorer auditory recognition than that of term neonates.[17, 18]

Hearing loss may also be conductive or have a conductive element to it. This is often seen in children with Down syndrome or craniofacial abnormalities, and it has been associated with ventilator-dependent children.[19]

Hearing loss is associated with delayed speech development and learning at school[20] so it is imperative that these children are picked up by audiological services at the earliest opportunity. In the past, children with multiple comorbidities have been overlooked with regard to improving their hearing simply because of the difficulty in obtaining accurate audiometry. Testing using auditory brainstem responses (ABRs) has allowed detection of hearing loss to be more accurately assessed in children with multiple problems.

Fitting of hearing aids at an early stage, regardless of neurological or mental status, has been shown to improve auditory behaviours in a significant proportion of children with multiple disabilities.[21] However, there will be a number that do not improve or simply cannot tolerate wearing the aids. There may also be difficulties fitting the aid in a congenitally narrow external meatus, or increased problems with wax impaction or recurrent otitis externa as a result of the mould.

Cochlear implantation in children with profound hearing loss and other disabilities was a controversial issue in the earlier days of implantation. There is increasing evidence that children with additional disabilities can benefit greatly from a cochlear implant.[22–26] This group of children may not achieve the same outcomes with regard to open set speech recognition as those with no other disabilities

but in the majority of cases they have improved speech perception and communication abilities.[22] Being able to predict the outcomes of surgery in children with additional disabilities is obviously much more difficult and parents must have realistic expectations of surgery.

Middle ear disease

OTITIS MEDIA WITH EFFUSION

Otitis media with effusion (OME) is common in the paediatric population and the associations with speech and language delay in early childhood and poor behaviour have been well reported.[27–29] Children with multiple disabilities are often already predisposed to language deficits and behavioural and learning difficulties.

Children with craniofacial abnormalities are more susceptible to OME due to the presence of a small nasopharynx and Eustachian tube anomalies, and there should be a heightened awareness when seeing these children.

Diagnosis can be difficult as examination is often challenging, particularly in the presence of wax impaction or anatomical changes such as narrow external canals in children with Down syndrome. If obtaining hearing thresholds with age-appropriate audiometry and tympanometry is not possible, it may be necessary to undertake ABR under a general anaesthetic. This would also allow any necessary ear toilet and thorough examination of the tympanic membrane/attic plus the insertion of ventilation tube if appropriate. Controversies regarding ventilation tube insertion in children with Down syndrome will be discussed in Chapters 6, The child with a syndrome and 13, Otitis media with effusion.

CHOLESTEATOMA

Cholesteatoma in a child with special needs is a difficult situation often requiring a general anaesthetic to confirm the diagnosis. Computed tomography (CT) of the temporal bone will aid planning of the surgical approach and identify and any anatomical variants. There is no single correct approach to surgery and each case has to be assessed individually. Open mastoid surgery has the advantage that, hopefully, only one surgical procedure is required and any residual disease will be visible on examination. However, open cavities often require regular aural toilet, particularly in the early post-operative period, and the child may not tolerate this. The family may also find keeping the ear dry difficult to achieve, and swimming may be an important part of the child's therapy.

Undertaking a combined approach tympanoplasty would avoid these problems but may require multiple surgeries to exclude recurrence, particularly as audiometric testing may not be possible as an observation tool. The associated comorbidities of the child, however, may make multiple general anaesthetics unviable.

Recent studies reveal that diffusion-weighted magnetic resonance imaging (MRI) of the temporal bones is becoming a useful tool for detecting residual and/or recurrent cholesteatoma. This technique is increasingly showing a high positive predictive value for detection of cholesteatoma and may reduce the number of second-look procedures in canal wall-up surgery.[30, 31] One drawback in paediatric patients with special needs is that it will almost certainly have to be undertaken under general anaesthetic.

THE UPPER AERODIGESTIVE TRACT

Children with complex physical comorbidities, particularly neurological, will frequently have respiratory problems and feeding difficulties. There may be a number of contributory factors which may have an overall cumulative effect.

Feeding, aspiration and gastro-oesophageal reflux

Oromotor skills are often dysfunctional in those with neuromuscular pathologies.[32–34] Children with cerebral palsy in particular may have difficulty coordinating swallowing with ventilation. The resultant 'turn taking', alternating between breathing and swallowing, can lead to aspiration of solids and fluids at mealtimes.[33]

Gastro-oesophageal reflux is also more common, and often more severe, in children with cerebral palsy or other neuromuscular disorders. The reason for this is unknown but it is hypothesized that it may be due to increased intra-abdominal pressure caused by the spasticity of the abdominal muscles. Altered peristalsis combined with dysfunctional oesophageal sphincters can then result in aspiration of refluxed material.[33]

Coughing and choking during feeding will draw attention to the possibility of aspiration, particularly when associated with recurrent lower respiratory tract infections, but often in children with comorbidities aspiration is silent.[33–35] While these children may struggle during mealtimes, they rarely show signs of aspirating.

The consequences of aspiration are also varied, with some children tolerating recurrent episodes with no sequelae. More commonly, recurrent aspiration results in lower respiratory tract infections, which may ultimately lead to lung fibrosis in severe and unrecognized cases. Diagnosing silent aspirators is more difficult and they often go unrecognized until malnutrition or respiratory complications occur.[34]

Treatment of aspiration ranges from positional/postural feeding positions and feed thickeners to tube feeding via a nasogastric tube or gastrostomy. Tube feeding has been associated with a higher mortality than in those fed orally but whether this is a result of the parenteral feeding rather than a reflection of the underlying comorbidities is not known.[36, 37] Tube-fed children are still at risk of reflux and aspiration even in those who have had a fundoplication at the time of gastrostomy.[38] Children with a tracheostomy appear to have some protection from the complications of tube feeding and this may be due to the ability to undertake regular suctioning, application of oxygen and nebulizer and positive-pressure ventilation.[39]

Obstructive sleep apnoea (OSA)

Children with craniofacial anomalies, Down syndrome and neuromuscular disorders are all at increased risk of obstructive sleep apnoea (OSA). With the multitude of other problems that this population of children may have, OSA is often overlooked or simply felt to be 'normal for him/her' by their parents/carers. Given the association with disrupted sleep, irritability and behavioural problems, failure to thrive and at the severe end of the spectrum pulmonary hypertension and right heart failure, it is vital that there is a high index of suspicion.

Predisposing factors may relate to anatomical abnormalities such as midface hypoplasia in the craniofacial disorders and hypotonia of the pharyngeal musculature in the neuromuscular disorders. In some cases (e.g. Down syndrome) it may be a combination of both. Other documented associations are seizure disorders, gastro-oesophageal reflux, increased oral secretions and obesity.[40, 41]

Management of OSA in children with complex problems should be undertaken in a multidisciplinary approach. Sleep disorder problems are common in this group of children and it is difficult to be assured of a correct diagnosis of OSA from clinical examination alone. Polysomnography is the gold standard for diagnosis and will aid in selection of children who are appropriate for surgical intervention.

Management should be undertaken in a stepwise approach, eliminating simple factors like bacterial or allergic rhinitis as a first line. Although in the general paediatric population over 80% of cases of OSA will be effectively treated by adenotonsillectomy alone,[42] the same cannot be said for those with additional comorbidities, particularly if there is a neuromuscular element.

Most would agree that the aim is to avoid a tracheostomy where possible and first-line surgical management of removal of the tonsils and adenoids, even if only mildly enlarged, is the general approach. Whilet adenotonsillectomy may not completely resolve the obstructive symptoms, it may allow the consequent use of a nasopharyngeal airway or continuous positive airway pressure (CPAP) to maintain an adequate airway.

The implications of anaesthesia in children with other comorbidities and the increased risks of complications following surgery need to be considered and any decision to proceed with surgery made within the multidisciplinary team. Parents should be counselled accordingly.

Other surgical approaches that have been shown to improve OSA in some circumstances but are rarely helpful in routine practice include uvulopharyngopalatoplasty,[43–45] mandibular advancement,[46] tongue base reduction and hyoid suspension.[44] Distraction osteogenesis may have a role in some children with craniofacial anomalies (see Chapter 19, Craniofacial anomalies).

The management of OSA in children with complex problems should not be rushed but it is also imperative in some circumstances to act early, for example if there is concern about impending pulmonary hypertension. Some disorders, such as the mucopolysaccharidoses, are progressive and delaying intervention may result in a lost opportunity.

Laryngotracheal disease

Stridor in children with multiple comorbidities may be multifactorial and/or multilevel. It is often simply, but incorrectly, attributed to the underlying neuromuscular problems associated with the child's diagnosis. Where possible, a flexible nasolaryngoscopy in the clinic will allow a dynamic assessment of the upper airway to the level of the vocal cords. There should be a high index of suspicion of multilevel disease, and a full airway assessment under general anaesthetic may be required.

When underlying airway pathology is found it must be remembered that children with complex comorbidities, particularly neuromuscular, often do not respond as well to treatment as an otherwise well child would be expected to. Laryngomalacia is a good example of this. While most cases of laryngomalacia do not require surgical intervention, for those that do supraglottoplasty has a high success rate.[47] Patients with comorbidities, however, tend to have a worse outcome.[48] Children with cardiac abnormalities have been found to have a significantly higher failure rate following supraglottoplasty, which may be related to respiratory rate, an increased work of breathing or associated developmental problems.[49] However, it is children with neurological comorbidities who do particularly badly with laryngomalacia, many requiring revision surgery[49–51] and a significant proportion requiring tracheostomy.[49, 52] This may be due to a difference in underlying pathophysiology in laryngomalacia associated with neuromuscular disorders. Rather than being due to overly pliable cartilage, the underlying problem is more likely due to laxity of the soft tissue of the supraglottis. This results in an excess of redundant soft tissue, which prolapses into the airway, and ultimately the underlying cartilage will also be involved.[53]

SURGERY IN THE CHILD WITH SPECIAL NEEDS

Undertaking surgery in a child with special needs requires careful consideration and planning. Multiple comorbidities may affect decision-making and sometimes a more conservative or aggressive approach is undertaken compared with what would be required in an otherwise well child. In some cases it may not be possible to undertake a full assessment of the child other than under a general anaesthetic. While it is certainly not a standard approach, in these cases decisions as to the surgical procedure may need to be made 'on the table'. This has implications for consent and often requires the surgeon to speak to the family while the child is under anaesthetic.

It is essential that there is a dedicated pathway for children admitted for surgery with special needs and that all involved specialties are aware of the impending surgery and admission.

Hospital admission and surgery in children with complex medical problems or learning disabilities are often associated with high levels of anxiety in both the patient and parent. In order to minimize distress it is imperative that communication, planning with the family and pain management are undertaken on an individual basis.

Children with special needs often have a very strict daily routine and alterations to this can cause significant distress. Trying to accommodate the child in a side room where possible will help avoid excessive noise disturbance and will make it easier for the parent to care for their child.[54] Where possible, having the child first on the theatre list will help reduce fasting time and the anxious wait for surgery.

Surgical pre-assessments enable the child and parent/carer to visit the ward and theatre complex prior to surgery and allow the family to familiarize themselves with the department. This may help decrease anxiety on the day of surgery and help highlight any potential problems prior to admission.

Anaesthetics can be challenging but assessment by the anaesthetist prior to admission will help prepare for a smooth patient journey. Sedative premedication may help settle the child prior to the anaesthetic and may aid with cooperation. It may not be possible to insert cannulae until the child is anaesthetized and these may need to be removed as early as possible after the procedure.

Pain management in children who are unable to express pain through the usual verbal or behavioural routes can be difficult, and standard approaches are often unhelpful. Parents often recognize specific signs when their child is in pain, such as change in vocalization, altered facial expression, change in usual posture and reduced responsiveness to stimuli.[55] These can often be very subtle findings that would be apparent only to the parent/carer who knows the child well. Health professionals need to work closely with the parents in assessing pain levels in order to be able to manage the child's pain appropriately.

Many of these children require a 'step up' of services when surgical procedures are undertaken, such as a high dependency unit bed post-tonsillectomy in a child with OSA and spastic cerebral palsy. It is also important, however, to try to discharge them home as soon as it is safe to do so. This will allow them to be in a more familiar environment and to return to their usual routine. In some situations it is preferable to discharge before all the usual criteria have been met (e.g. passing urine, eating).[56]

BEST CLINICAL PRACTICE

- ✓ Examination of a child with special needs can be difficult and it may be necessary to proceed to examination under general anaesthetic in order to gain a diagnosis.
- ✓ There is increasing evidence that children with additional disabilities can benefit greatly from cochlear implantation.
- ✓ Stridor in children with complex comorbidities may be multilevel and multifactorial.
- ✓ Obstructive sleep apnoea is often overlooked in children with complex comorbidities. Management should not be undertaken without careful consideration and planning, but some disorders are progressive and treatment needs to be undertaken without untimely delay.

KEY POINTS

- The survival of preterm babies has dramatically increased over recent years but the long-term morbidity has remained unchanged.
- Children with special needs require a more detailed evaluation which takes longer.
- Specialist clinics that bring together health professionals offer a great advantage to both the clinicians and the family.
- It is essential to ensure good communication with all the health professionals involved in the care of a child with special needs.
- Surgical outcomes are often less successful in the child with special needs than for other children.

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CHAPTER 6

THE CHILD WITH A SYNDROME

Thushitha Kunanandam and Haytham Kubba

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SEARCH STRATEGY

Data in this chapter may be updated by an OVID search using the keywords: Trisomy 21 (Down syndrome), Turner's syndrome, 22q11 deletion (velocardiofacial syndrome and Di George sequence), mucopolysaccharidosis, CHARGE and Pierre Robin, each of which was cross referenced with search term such as otolaryngology, airway, otology, larynx and nose.

INTRODUCTION

The subject of syndromes can be a confusing mess of eponyms, acronyms and gene deletions. In this chapter, we will try to get to grips with the terminology, what to do when faced with a child who is known to have a particular syndrome, when to suspect a syndrome that has not been diagnosed yet, and finally what the general otolaryngologist needs to know about some of the commoner syndromes in paediatric otolaryngology practice. Many of the syndromes will be covered in other chapters.

DEFINITIONS

A **syndrome** is a well-characterized constellation of major and minor anomalies that occur together in a predictable fashion, and for which a single underlying cause is known or suspected. The syndrome is a descriptive term for the collection of clinical features and often carries the name of the person who first described it (such as Down syndrome) or a description of the clinical features themselves (often as an acronym, such as CHARGE, or a simple list, such as velocardiofacial syndrome) while the **disease** is a way to describe the same entity in terms of its underlying cause (such as trisomy 21, which is the cause of Down syndrome, or 22q11 deletion, which is the cause of velocardiofacial syndrome).

A **sequence** occurs when a single developmental anomaly causes a chain of effects on nearby or related structures. For example, in the Pierre Robin sequence, the small mandible causes the tongue to fall back obstructing the pharynx (glossoptosis) and also to sit high in the oral cavity, preventing the palatal shelves from fusing, leading to a U-shaped cleft palate. These features are all directly related and can be considered as one. Thus, the Pierre Robin sequence may be found as one feature of Treacher Collins syndrome. Another example of a sequence would be an absent thymus leading to impaired T-cell immunity with recurrent ear infections (Di George sequence, which often occurs as a part of velocardiofacial syndrome).

In an **association**, a number of clinical anomalies appear together more often than would be expected by chance alone but no underlying genetic cause has been identified. An example would be the VACTERL association (vertebral defects, anal atresia, cardiac defects, tracheo-oesophageal fistula, renal anomalies and limb abnormalities). Once the genetic cause is known, the association becomes a syndrome. CHARGE is one such example, where what used to be known as CHARGE association is now more properly referred to as CHARGE syndrome since the cause has been identified as a mutation in the gene *CHD7*.[1]

GENERAL APPROACH TO THE CHILD WITH A SYNDROME

There are a few syndromes that occur commonly enough in otolaryngology practice that the otolaryngologist should probably know something about them. There are considerably more syndromes, many thousands in fact, that are so rare that the otolaryngologist may see them once in a lifetime. When faced with a syndrome you have never heard of, there is no shame in admitting the fact and no need to panic. Two minutes with any internet search engine will usually fill in most of the blanks. A more detailed literature search can be done at leisure for selected complex patients if required.

The best source of information, however, is usually the parents. For the rare syndromes they are usually the most experienced people in the room and you should not be afraid to use their expertise. In order to establish a good rapport with parents, it is not necessary to pretend to be the world's greatest expert in some rare syndrome that you looked up on the internet two minutes before; it is very important, though, to handle the family with sensitivity and respect. They will often be frequent hospital attenders who are under the care of many specialists and are therefore very 'medicalized'. They can be exquisitely sensitive to language so always remember that the child comes first and the syndrome second: you are dealing with 'a child who has Down syndrome', not 'a Down's kid', and certainly not 'a Down's'. Thankfully, old-fashioned terms like 'mongol' are long gone.

Parents can be very sensitive to any suggestion that their child is being treated less well than others because of their syndrome. A common cause of misunderstanding is in saying that a certain treatment 'is not worthwhile' because you think it is unlikely to work, which the parents hear as 'because the child is not worth treating'.

Ultimately, the syndrome is only ever of secondary importance. You are there to treat the child and to manage the same conditions that you always do. Whatever the syndrome, you are going to look at ear health and hearing, airway problems and recurrent infections, and you are going to be very careful with the cervical spine if the child is having an operation.

A child can present to the ENT clinic in one of two ways. Many children with enter the clinic with an underlying diagnosis of a syndrome already established, likely to be common in those with a characteristic phenotype. There are, however, a group of children who will present through ENT clinics with what would be considered common presentations and where there is a 'hidden syndrome'. In these cases the ENT surgeon is quite often an early opportunity to aid diagnosis. Naturally, this pathway can be more complicated and will also have to be handled incredibly sensitively.

Common presentations to ENT clinics include ear infections, hearing concerns and airway issues. These three presentations are often very common in children with syndromes as much as with the otherwise typically developing population of children. Coupled with an index of suspicion and additional features, this can be the path to early diagnosis.

SYSTEMATIC APPROACH TO THE CHILD WITH A SYNDROME

As some of the common ENT conditions can be associated with certain syndromes, this is a good basis upon which to assess and manage children with any syndrome. The approach can then be adapted to each specific syndrome and child.

Systematic management mainly involves assessment of otological manifestations and airway manifestations.

Otological manifestations

A history of recurrent acute otitis media (AOM) can be common in children with syndromes. Of course, ear infections are extremely common in all children. About half of all children have had an episode of AOM before their first birthday, increasing to 80% by their third birthday.[2] Most are managed in the community without seeing an otolaryngologist. In the UK, specialist referral is usually only requested for those with recurrent episodes of infection. During the consultation, the question inevitably arises as to whether the repeated infections are due to some underlying cause. Parents very often suspect some kind of systemic immune problem and for most the answer is 'no'. However, the otolaryngologist should be aware that among these many children with ear infections are a small number with specific syndromes that might not yet have been diagnosed.[2] In particular, a female child of short stature with a history of ear infections should make one alert to the possibility of Turner syndrome.

As well as infective problems, there are several types of hearing problem noted in children with syndromes. It is important to recognize these issues early and give consideration to the management options. Children with syndromes may have learning difficulties and additional support needs and addressing any hearing difficulties early on will help to reduce any potential handicap. Audiological screening can be a useful means of identifying problems and intervening early, although testing in this population can have its own challenges.

Conductive hearing loss can be common, particularly otitis media with effusion (OME). Although the management of this condition can mirror that in the typical childhood population, occasionally adjustments should be made for the underlying syndrome. For example, in children with Down syndrome, hearing aids are recommended in preference to ventilation tube insertion. However, in children with a cleft palate and a middle ear effusion, ventilation tube insertion is highly recommended. The high incidence of middle ear problems can lead to the development of cholesteatoma in these children and this should be kept in mind.

Sensorineural hearing loss should also be diagnosed early and treated appropriately. Hearing amplification options should be fully considered for each case, including standard hearing aids through to cochlear implantation. Children with craniofacial syndromes may present

some practical difficulties due to their head shape and/or behaviour, for example with respect to the wearing of hearing aids. Soft band and bone-anchored hearing aids may be more suitable options. In terms of cochlear implantation, again the anatomy may make surgery more tricky and there are naturally additional anaesthetic considerations to deal with for many of these children. Both these factors require surgery of this nature to be performed in specialist implant centres in tertiary level paediatric hospitals.

One should also remember to consider the cosmetic aspect under 'otology' management in terms of microtia. Again, these children should be managed in a multidisciplinary setting taking into account the hearing and cosmetic components. These settings should allow for an informed discussion on the merits of surgery in terms of auricular prostheses or auricular reconstruction.

Airway manifestations

Airway management in children with syndromes can be exceptionally challenging. Craniofacial abnormalities in particular can lead to great anxiety regarding airway management when the children present to other services for elective or 'routine' surgery: the anaesthetist may have to deal with a difficult intubation scenario in addition to a potentially more complicated peri-operative and post-operative period. Airway manifestations can also present as neonatal emergencies at birth, such as in bilateral choanal atresia or severe micrognathia.

In managing the airway, the level of obstruction should be considered with an awareness that this could be at the nasal level, nasopharynx, tongue base or at the level of the larynx/trachea/bronchi. Formal airway endoscopy (MLB) will allow for complete assessment of the level(s) of obstruction and exclude any other airway anomalies.

Adenotonsillar surgery can often be undertaken to help alleviate obstruction at the naso- and oropharyngeal level. The degree of adenotonsillar hypertrophy is not always clearly related to the degree of obstruction and no doubt the situation is much more complex with neurological and muscular tone often confounding the situation. Pre-operative assessment by means of sleep studies can be useful in assessing obstruction and certainly useful in guiding post-operative recovery.

Nasopharyngeal airways can be extremely useful airway adjuncts. Their use is indicated where the pathology relates to tongue-base collapse and micro/retrognathia as, for example, seen in Pierre Robin sequence (PRS). Often there can be symptomatic improvement as the child grows and a nasopharyngeal airway is a successful temporizing measure. However, in some situations formal surgery is required in the form of mandibular distraction or midface advancement.

Finally, tracheostomy may be required in some children with significant airway obstruction. The implications of a tracheostomy must be carefully considered for the child and the family. The procedure itself may also be more complex due to unusual airway anatomy, such as a tracheal sleeve.

WHEN TO SUSPECT THERE MAY BE A SYNDROME

Among the many children presenting on a daily basis to the otolaryngology clinic, there are a few whose symptoms are due to an underlying genetic condition. In most cases the underlying syndrome is obvious and has already been diagnosed, such as the child with Down syndrome. There are some syndromes, however, whose features may be subtler and easily missed. For some, the first presenting features may be in the ears, nose or throat and the otolaryngologist may be the first doctor to see the child and therefore the first to have the opportunity to spot the underlying diagnosis. This is an important opportunity to make potentially a huge difference to the child and family as making the correct diagnosis can affect not only the management of the otolaryngological condition but also of many other body systems.

The commonest clinical situation where this chance to make an early diagnosis occurs is in the child with recurrent AOM. It is very worthwhile looking out for a few underlying syndromes that might not have been diagnosed yet, specifically common variable immunodeficiency, Turner syndrome, mucopolysaccharoidosis and 22q11 deletion. The latter three have characteristic facies (which are often subtle) and mucopolysaccharoidosis and Turner also have short stature as a feature. All are discussed further below. Immunodeficiency is discussed in Chapter 7, Management of the immunodeficient child.

It is important that the ENT surgeon has knowledge of some of the less common genetic disorders in order that appropriate and timely referral for specialist management can be made.

SPECIFIC SYNDROMES

Down syndrome

Down syndrome is a common and easily recognizable disorder with familiar phenotype and genotype (trisomy of all or a critical portion of chromosome 21). This syndrome easily demonstrates the ear, nose and throat problems that can need to be considered in managing a child with any syndrome.[3]

The most common ENT reasons for referral in children with Down syndrome are OME, sleep-disordered breathing and laryngomalacia. The possibility of atlantoaxial subluxation in this group of children should mean that any surgical procedure involves very careful handling of the neck. Immunological aspects of the disease can lead to ventilator tube otorrhoea, persistent rhinorrhoea and recurrent upper respiratory tract infections. Endotracheal intubation can be difficult and often the child will need a smaller diameter ET tube than her age would suggest. There is an increased mortality in this group of children (×6 throughout infancy and ×17 until age 9 years) compared to age-matched controls.[4]

Otological aspects of the disease include the following:

- persistent otitis media with effusion – hearing aids should normally be offered to children with Down syndrome who have hearing loss due to OME[5]
- narrow and waxy ear canals – ventilator tube otorrhoea and early extrusion can be more common
- conductive hearing loss secondary to ossicular anomalies
- sensorineural hearing loss with increased labyrinthine dysplasia – inner ear dysplasia is common in children with Down syndrome
- increased incidence of cholesteatoma
- anatomical abnormalities of the facial nerve – tympanomastoid surgery can be especially challenging.

Hearing screening with behavioural testing throughout early childhood should be carried out to establish near-normal hearing with the use of amplification or ventilation tube insertion. Cholesteatoma should be suspected in continuously discharging ears.

Airway aspects of the disease include:

- obstructive sleep apnoea – relative adenotonsillar hypertrophy, upper airway obstruction as part of craniofacial condition including hypoplasia of pharynx and maxillary arch with nasal obstruction, sometimes generalized muscle hypotonia ('floppy baby')
- tracheobronchomalacia – increased incidence in this population and there may be a need for ventilation with/without tracheostomy and continuous positive airway pressure (CPAP)
- synchronous airway anomalies can be seen including a tracheal bronchus, subglottic stenosis and tracheo-esophageal fistula.

Annual screening for OSA until age 3–5 years is recommended. It is important to realize that, even after adenotonsillar surgery, there is a greater than 50% finding of residual OSA that will likely need medical intervention (e.g. CPAP). These children are unsuitable for day-case adenotonsillectomy and they will often require high-dependency care post-operatively.[6, 7]

Turner syndrome

Turner syndrome (TS) is characterized by the complete or partial loss of one X chromosome. TS is surprisingly common, affecting 1 in 2000 females, although perhaps only half have been formally diagnosed and are known to medical services. Some are diagnosed at birth due to characteristic features such as oedematous feet, while others are diagnosed in adolescence due to growth failure and delayed puberty. The vast majority of girls with TS present to otolaryngologists in their early years with recurrent AOM and OME, and for many this occurs long before the diagnosis of TS has been made.[8] Progressive mid-to-high tone sensorineural hearing loss is common in school years and early adulthood. Cholesteatoma is also not infrequent.[9] Early diagnosis can make a huge difference to these patients as it enables the detection of heart anomalies, which are commonly present, as well as growth hormone treatment for short stature. Suspicion is key: consider TS in any girl with ear problems and short stature, and refer on to an endocrinologist if concerned. If she is the shortest girl in her school class, think, 'could this be Turner syndrome?'

22q11 deletion syndrome

22q11 deletion syndrome encompasses the clinical conditions previously termed velocardiofacial syndrome and Di George syndrome which are now known to be different manifestations of the same genetic defect. A variety of clinical features can occur but not in every child.[10] Common features include submucous cleft palate, congenital heart anomalies, absent thymus with impairment of T-cell immunity (Di George sequence) and characteristic facial features. The ENT clinical features result from abnormal development of structures derived from the third and fourth pharyngeal pouches. The first presentation to medical services may well be with recurrent episodes of AOM due to the impaired T-cell immunity. Another presentation to the otolaryngologist is with a congenital glottic web which is almost always diagnostic of 22q11 deletion (see Chapter 30, Congenital disorders of the larynx, trachea and bronchi).[11, 12] Again, the phenotypic profile is highly variable and awareness and suspicion are key. If there is suspicion of 22q11, full ENT assessment including laryngoscopy should be performed and referral to a geneticist and cardiologist initiated.[13]

Mucopolysaccharoidoses

The mucopolysaccharoidoses (MPS) comprise a group of conditions that result from the deficiency of lysosomal enzymes causing the accumulation of glycosaminoglycans in tissues. Head and neck structures are frequently involved early and the otolaryngologist may see children before the onset of systemic disease.[14] Features commonly include recurrent otitis media, mixed hearing loss, upper airway obstruction +/– obstructive sleep apnoea and coarse facial features. Due to the non-specific clinical features, diagnosis is frequently delayed but early diagnosis is essential, particularly in Hunter syndrome, where enzyme replacement therapy is now available.[15] MPS is also associated with intubation difficulties and may pose a significant anaesthetic risk. OSA is extremely common, with a prevalence of up to 90%, and patients may benefit from adenotonsillectomy.[16] Suspicion of MPS should prompt specialist referral, and confirmation is with urinary glycosaminoglycan measurement and enzyme assays.[14]

CHARGE syndrome

CHARGE syndrome is an autosomal dominant genetic disorder typically caused by mutations in the chromodomain helicase DNA-binding protein-7 (*CHD7*) gene.[1, 17, 18] The acronym 'CHARGE' denotes the non-random

association of coloboma, heart anomalies, choanal atresia, retardation of growth and development, and genital and ear anomalies, which are frequently present in various combinations and to varying degrees in individuals with CHARGE syndrome.[19]

Neonatal presentation:

- small for gestational age
- dysmorphic features
- respiratory distress/cyanosis
- swallowing/feeding difficulty
- failed newborn hearing screen
- inability to pass nasogastric tube.

Choanal atresia is membranous or bony, and bilateral in over 50% of cases, usually presenting in the newborn period with a cyclical pattern of respiratory distress. This can be a threat to life because infants cannot establish mouth breathing. Of all features of CHARGE syndrome, choanal atresia (when bilateral) is the most easily ascertained and requires early surgical correction. When associated with other anomalies (e.g. cyanotic heart disease, tracheoesophageal fistula and/or atresia), prognosis is poor. Unilateral atresia may present as persistent nasal discharge in early childhood.

External ear malformations are seen in 90–100% of patients. Ears may be small, simple, low-set, and/or cup-shaped; a protruding helix may be unravelled.

Vestibular or cochlear defect leads to sensorineural deafness. Middle ear problems cause conductive hearing loss and are commonly due to ossicular malformations, stapedius tendon abnormality, or serous effusion. CT scan of the temporal bone demonstrates partial or complete semicircular canal hypoplasia.

Syndromes discussed elsewhere

Syndromic craniosynostosis (Pfeiffer, Apert, Crouzon and Saethre–Chotzen syndromes) are discussed in Chapter 19, Craniofacial surgery.

Syndromes causing deafness (such as Pendred, Waardenburg and Usher, as well as many others) are discussed in Chapter 10, Management of the hearing impaired child.

KEY POINTS

- Far too many syndromes have been described for anyone to be familiar with them all, but a few common ones should be well-known to any paediatric otolaryngologist.
- Be careful with the words you use in front of parents as they are often very sensitive to anything that sounds like a lack of respect for the child.
- Regardless of the nature of the syndrome, the role of the otolaryngologist will most often be to address issues of hearing, recurrent infections and airway obstruction, whilst always being careful with the cervical spine.
- Some children presenting with common otolaryngological problems may have an underlying syndrome that has not yet been diagnosed. Be alert to any features that may allow you to make the diagnosis.

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CHAPTER 7

MANAGEMENT OF THE IMMUNODEFICIENT CHILD

Fiona Shackley

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: immunodeficiency, otitis media, sinusitis, mastoiditis, otolaryngological disease, ENT, nasopharyngeal colonization, hypogammaglobulinaemia and HIV.

INTRODUCTION

The infant nasopharynx becomes colonized with microorganisms from shortly after birth.[1] There is a consequent constant balance of host, microbial and environmental factors that allow individuals to be colonized with potentially infectious organisms or allow microorganisms to breach host defence to cause local or systemic disease.[2] In the young child with an immature immune system, recurrent respiratory tract infection, particularly otitis media, is common. Studies carried out prior to the widespread introduction of pneumococcal conjugate vaccines indicate that 83% of children will have suffered one episode of otitis media by 3 years of age and 46% will have had at least three episodes.[3] Recurrent infections of the upper respiratory tract are also common in children with primary immunodeficiency (PID). ENT specialists may be the first clinicians to see a child with an immune defect and have a key role in identifying these children. This is also the case for children with HIV infection who may present to an ENT specialist before their diagnosis has been confirmed. Early diagnosis and commencement of treatment for both primary and acquired immune deficiency improves long-term outcome.[4, 5] Unfortunately, identifying the children who need further investigation can be difficult, although other features including failure to thrive, absence of or excessive lymphadenopathy, dysmorphic features and skin problems should raise concerns.[6] Some children with minor immune defects may only become symptomatic because of other associated features including allergic tendency, GOR and Eustachian tube dysfunction.[7, 8]

PRIMARY IMMUNODEFICIENCY

Children born with a reduced immune system, or the tendency to develop a reduced immune system over time, are classified as having PID.[9] Ascertainment of the true incidence of these conditions is difficult. An estimate from a US telephone survey indicated a prevalence of PID in the US of 1:2000.[10] Over 60% of these immune problems relate to antibody production.[10, 11] Antibody plays an essential role in the process of opsinophagocytosis,[12] destroying common organisms in ear and sinus disease including *Streptococcus pneumoniae*, non-typable *Haemophilus influenzae* and *Moraxella catarrhalis*. These are clearly children or adults who may have seen an otolaryngologist before the diagnosis is considered.

Identifying children with immune deficiency

Several guidelines are available to help clinicians identify children with immune deficiency. The Jeffrey Modell '10 warning signs of infection'[13] indicate that immunodeficiency should be considered in any child with more than four new ear infections in one year; more than two episodes of severe sinusitis pneumonia, infections that do

not respond to routine antibiotics, failure to thrive or a family history of immunodeficiency. Consequent studies using these risk indicators have shown that, particularly for antibody deficiency, it can be very difficult to differentiate the immunologically normal and abnormal child in the absence of features such as poor growth or family history.[14] The current ESID guidelines, while not giving a threshold for ENT infections that might indicate the need to investigate, do give clear pathways for appropriate investigations.[6]

Transient hypogammaglobulinaemia of infancy

All children rely on transplacental transfer of maternal antibodies during the last trimester of pregnancy, which helps protect them over the first 6 months of life while the infant's antibody production becomes adequate.

In some children, there appears to be a delay in this maturational process resulting in low IgG, which can be associated with a reduced IgA and IgM. Transient hypogammaglobulinaemia of infancy (THI) is a diagnosis of exclusion and a definitive diagnosis is only possible over time when the problem resolves. In paediatric series this is the commonest form of symptomatic antibody deficiency.[15, 16] The pathogenic process behind THI is not understood. A small number of children continue to have problems with infections and persist in having low antibody levels or fail to make adequate response to their routine immunizations. The majority are reported to improve by the age of 4 years although in some children the IgG remains low into late childhood.[16, 17]

Hypogammaglobulinaemia is common in preterm infants who may not be symptomatic although routine prophylactic immunoglobulin is not recommended.[18] Also, high levels of cord blood pneumococcal-specific antibodies did not seem to provide sufficient protection for Aboriginal infants who are known to be at increased risk of early otitis media illustrating the fact that low antibody levels alone may not be the sole explanation for recurrent ENT infections in early infancy.[19]

If low immunoglobulin levels are identified, it is important to be sure that there is not a more significant underlying immune defect present.[6]

IgA deficiency/ IgG subclass deficiency and specific antibody deficiency

IgA deficiency is present in around 1 in 600 blood donors.[20] Most individuals with IgA deficiency are completely well and, in many children, the deficiency is transient. Some people do suffer more frequent infections including ear and sinus disease and occasionally develop progressive antibody deficiency.[21] This is more likely if they have an associated IgG subclass deficiency, particularly IgG2, or specific antibody deficiency (SAD). Activity against pneumococcal capsular polysaccharide appears best mediated by the IgG2 subclass which young children may be poor at generating. IgG2 deficiency is commoner in some series of children with recurrent otitis media.[22] However, asymptomatic IgG2 deficiency is also well documented.[23] Quality of antibody production can be assessed by looking at protective levels of antibody following immunizations. A group of individuals has been described who have reduced ability to make antibodies to polysaccharides, a key component of the capsular wall in some organisms. Poor polysaccharide responses are normal in children under 2 years but are also seen in some older children and adults where it will be labelled as SAD. While definitions of this condition are available,[24–26] the introduction of routine pneumococcal conjugate vaccine immunizations and lack of access to standardized assays to assess response adds controversy to diagnosis of this condition.[27, 28]

Common variable immune deficiency

In combined adult and paediatric data common variable immune deficiency (CVID) is the commonest symptomatic antibody deficiency[29] defined by a reduced IgG (beyond the age of 4 years), a history of infections and often inadequate response to immunizations.[9] A proportion of children with CVID may initially have been labelled as THI but continue to be symptomatic and have low IgG levels in later chidlhood. In a recent paediatric series, 88% of children with CVID had recurrent respiratory tract infections, 78% otitis media and 78% sinusitis.[30] Around 10% of individuals with CVID[31] have an identifiable gene defect but the cause for the majority of CVID remains unclear. There are two peaks of onset, in mid-childhood and early adulthood. Delay from symptoms to diagnosis and treatment is usually around 4–5 years.[30, 32] These are clearly the type of children who may have seen an otolanyngologist before the diagnosis is considered.

X-linked agammaglobulinaemia

A small group of children, predominantly boys, who present with severe infection and a paucity of lymphoid tissue will have X-linked agammaglobulinaemia. Due to defects in the *BTK* gene, affected boys fail to manufacture mature B-cells and consequently make no or very little IgG. While some of these children suffer serious life-threatening infections, recurrent otitis is the commonest infection identified prior to diagnosis.[33] In a small number of patients, deletions in the terminal portion of the *BTK* gene may extend to involve the deafness dystonia protein gene resulting in sensorineural deafness.[34] These children are differentiated from THI and CVID patients initially on the basis of extremely low IgG, IgA and IgM or absent B-cell numbers. Consequent protein and molecular studies confirm a *BTK* defect in most children. In a small number of individuals there are autosomal recessive conditions that result in a similar phenotypes affecting both boys and girls.[35] Boys with X-linked agammaglobulinaemia usually present at 6–18 months of age but diagnosis may be delayed till

later in childhood in 10–15%, unfortunately sometimes after children have already sustained lung and ear damage. Bruton's use of regular immunoglobulin infusions was the start of what is a key treatment for children with antibody deficiency.[36]

Other conditions that may mimic antibody deficiency

X-linked hyper IgM syndrome may present like CVID with absent or low IgG and IgA but normal or elevated IgM.[37] The defect in CD40 ligand results in T- and B-cell functional problems. Hyper IgE syndrome[38] and DOK 8 deficiency[39] are both associated with eczematous skin problems, raised IgE and recurrent infections, again particularly otitis media. Wiscott–Aldrich syndrome, due to mutations in the WASP cytoskeletal protein, also often presents with severe eczema, thrombocytopaenia and ear infections.[40] These children are at increased risk of opportunistic infection and may require bone marrow transplant in addition to immunoglobulin replacement.

TREATMENT OF ANTIBODY DEFICIENCY

Children with antibody deficiency, THI and SAD with mild infections may be managed with prophylactic antibiotics including amoxicillin, azithromycin and cotrimoxazole.[41, 42] There is very little trial evidence to support this but practice has been based on studies from otitis media.[43] For more severe immunodeficiency, and certainly X-linked agammaglobulinaemia, or in children where antibiotic prophylaxis alone does not control infections, immunoglobulin replacement can be given either as an intravenous infusions 0.4–0.6 g/kg every 3–4 weeks or a weekly subcutaneous infusion which can be easily given at home and is well tolerated by children. There is good evidence that adequate immunoglobulin replacement improves long-term outcome.[44, 45]

Phagocyte abnormalities

Due to the key role of neutrophils in phagocytosis, ENT infections are also frequently seen in children with reduced neutrophil numbers and function. In infancy, neutropaenia may be consequent to a number of known molecular defects but is also seen in conjunction with some metabolic conditions including glycogen storage disease. These children can be at risk of life-threatening sepsis but otitis media, oral ulceration and abscesses are also common.[46, 47] The commonest cause of neutropaenia in our practice in young children is benign autoimmune neutropaenia or alloimmune neutropaenia. Recurrent otitis media can be a frequent problem in these children and severe mastoiditis or adenitis may be a presenting feature.[48] A blood count will identify children with persistent neutropaenia who can then have consequent genetic or autoimmune studies to define the cause. Congenital neutropaenia usually requires treatment with granulocyte-colony stimulating factor (G-CSF) to increase neutrophil numbers but may require bone marrow transplant. Autoimmune neutropaenias can often be managed with antibiotic prophylaxis and prompt treatment of infections.[47]

Defects in the neutrophil oxidative burst pathway are well described, resulting in chronic granulomatous disease. These children can develop deep-seated infections, sometimes with unusual organisms including *Serratia species, Burgholdheria cepacia* and fungal infections.[49] These may cause severe adenitis, mastoiditis or sinusitis.[50] This should always be considered in children with particularly severe disease who may present to ENT teams for acute surgical intervention. Unlike with many other immune defects, these children may not have problems early in infancy and can present in late childhood with an unusual infection. Management is with long-term prophylactic antibiotics and antifungals and, with an appropriate donor, bone marrow transplant has been very successful. Most cases are X-linked but AR forms also occur.

Children with defects in leucocyte adhesion molecules may also present in infancy with severe otitis and mastoiditis.[51] One of the key laboratory findings that may alert an ENT surgeon to this defect is the presence of a very high WBC. Consequent questioning may reveal a history of delayed cord separation.

Other innate immune system defects

Deficiencies in the compliment system are more likely to present with septicaemia than recurrent ear or sinus infections.[52] However, deficiency in mannose-binding lectin (MBL), which facilitates complement activation, is relatively common in the population[53] and may, particularly in conjunction with other immune system abnormalities or Eustachian tube dysfunction, contribute to recurrent ear and sinusitis infections.[54, 55] No specific treatment options are available apart from prompt antibiotic treatment.

IMMUNE DEFICIENCY IN OTHER PAEDIATRIC SYNDROMES

Di George or velocardiofacial syndrome,[56] CHARGE (coloboma, heart defects, atresia choanae, retardation of growth, genital anomalies and ear abnormalities)[57] and Down syndrome[58] are all linked to an increased risk of ear infections through facial structure and palatal abnormalities but are also at risk of immune deficiency which, in the case of 22q deletions, may be quite severe. Clinicians should have a lower threshold for considering immune deficiency in children with dysmorphic syndromes. Children with developmental delay and associated microcephaly may have a defect in DNA repair or chromosome stability. Immune deficiency is a recognized complication of many

of these conditions,[59] the most notable being ataxia telangiectasia where recurrent otitis media is a well-recognized common complication.[60]

Autoimmune lymphoproliferative syndrome

Autoimmune lymphoproliferative syndrome (ALPS) is an uncommon group of conditions associated with defects in the apoptosis pathway. The degree of immune deficiency associated with this condition is variable but children can present in infancy and early childhood with persistent, sometimes, massive cervical adenopathy.[61]

MHC Class 1 deficiency

Rarely older children may present with sinusitis, nasal polyposis and bronchiectasis due to MHC Class 1 deficiency.[62]

Severe combined immune deficiency

Children with these severe immune defects will not usually present to the ENT team at diagnosis, as the majority will suffer severe generalized infections in early life.

INVESTIGATIONS FOR PID

The European Society for Immunodeficiencies (ESID) guidelines provide a helpful pathway indicating initial screening test for children with recurrent ENT infections should include FBC, and measurements of IgG, IgA and IgM.[6, 9] Perisistent or recurrent neutropaenia may indicate a congenital or autoimmune neutropaenia requiring further genetic and autoantibody testing. If low immunoglobulins are identified, lymphocyte subsets should be carried out particularly to ensure the child has adequate B-cell numbers. Responses to routine immunizations should also be evaluated including Hib, tetanus and *Pneumococcus*. For children who have had pneumococcal conjugate vaccine, measurement of pneumococcal serotypes if available should be carried out rather than total pneumococcal antibodies. Children with low vaccine responses should be offered booster immunizations and the response reassessed in 4–6 weeks. Looking at children's response to Pneumovax is recommended by some guidelines but lack of access to standardized tests to assess the response can limit the clinical utility of this. If symptoms are persistent, IgG subclasses, MBL and complement studies CH50 APCH50 are recommended. Children with other features to suggest a more fundamental immune defect including failure to thrive, family history, severe eczema, abnormal lymphadenopathy or dysmorphic features should be discussed with the local immunology service as further investigation is likely to be indicated. In the context of features suggesting SCID, including lymphopaenia, the local paediatric team should be urgently alerted.

IMPACT AND USE OF IMMUNIZATIONS

The introduction of routine infant immunization with pneumococcal conjugate vaccines in many developed countries since 2000 has had a significant impact on invasive pneumococcal disease[63] but has also reduced otitis media[64] and the need for surgical intervention with tympanostomy tubes.[65] There is evidence that pneumococcal strains present in the older pneumococcal polysaccharide vaccine (PPV) but not current conjugate vaccines are now causing more otitis media[66] but there is no evidence unfortunately that giving additional doses of either conjugate or PPV to children with recurrent otitis media reduces infections.[67, 68] There is also some concern that repeated doses of PPV may result in blunting of the immune response.[28]

HIV/ACQUIRED IMMUNE DEFICIENCY

HIV is estimated to affect 3.4 million children worldwide.[69] Rates of new infections in children have dramatically reduced worldwide through treatment interventions that prevent mother-to-child transmission. The majority of children with HIV acquire infection from their mothers before birth, during delivery or during breastfeeding. Without control of maternal infections with highly active antiretroviral therapy (HAART), and infant prophylaxis, mother-to-child transmission was around 25%.[70] With appropriate maternal and infant medication, advice against breastfeeding or control of maternal virus while breastfeeding and, where indicated, Caesarean section, it is anticipated that transmission can be reduced to less than 2% worldwide and is already less than 1% in some developed countries.[71]

ENT complications

Many children become symptomatic over the first 2 years of life but others may be well into late adolescence.[72] In this group of children parotid enlargement may be a common feature and may be the initial presentation to ENT services. Otitis media and chronic suppurative complications are common, with a trend to increasing ear infections over time as the child's immune system fails.[73]

Conductive hearing loss as a consequence of ear infections can have significant impact on a child's well-being and development. In addition, HIV-infected children appear to be at increased risk of sensorineural deafness, tinnitus and vestibular symptoms, highlighting the importance of audiological assessment in all HIV-infected children.[74] Access to HAART has had a significant impact on children's survival and may have led to a decrease in the number of children with ENT manifestations of HIV.[75, 76] HIV-infected children will still, however, suffer from ENT-related problems and potentially require surgical intervention including tympanostomy tubes

and myringoplasty. Infectious cervical lymphadenitis with common and opportunistic organisms including tuberculosis and atypical mycobacteria may also present neck swelling to ENT specialists.

Who and how to test

UK national guidelines for HIV testing list recurrent and troublesome ear infections and chronic parotitis as clinical indicators for HIV testing in children.[77] While routine testing of all children with recurrent ear infections may not be indicated, HIV testing in children with chronic parotitis is recommended irrespective of there being no other apparent risk factors. HIV should also be considered if a child is found to have significantly raised immunoglobulins when being investigated for a PID.[6] Unexplained lymphadenopathy is an indication in adult but not paediatric UK guidance but is a well-described feature, though the clinical appearance may be difficult to differentiate in infected and uninfected children.[78]

Any trained heath professional should be able to obtain consent for HIV testing.[77] However, HIV testing a child adds the additional complexity of the implications the test result may have for the family, particularly if the parents themselves are unaware of their own underlying diagnosis. Usually local paediatric or infectious disease colleagues are happy to be involved. The significant stigma, guilt and concern around disclosure can make it extremely difficult for parents to agree to testing. Parental refusal to have HIV testing may then become a child protection issue requiring involvement from social care and the court system.[79] Wherever possible, however, healthcare staff should work with families to encourage them to have testing carried out and engage with ongoing clinical input voluntarily.

Initial screening for children over 18 months of age is by HIV serology and p24Ag, which should then be repeated and include a DNA PCR and RNA viral load. Children under 18 months of age require testing using DNA or RNA PCR.[80] A CD4 count may be arranged with the confirmatory testing but CD4 count alone should not be used as a surrogate for HIV testing in families who will not consent to testing.

TABLE 7.1 ENT features and staging (adapted from PENTA)[80]

Clinical stage WHO or CDC	ENT features in children
Mildly symptomatic WHO 1 and 2; CDC A	Recurrent otitis media +/– chronic otorrhoea Recurrent sinusitis Chronic parotitis
Moderate to severe symptoms WHO 3 and 4; CDC B and C	Oral candidiasis Oesophageal candidiasis Extrapulmonary TB Atypical mycobacterial disease Necrotizing gingivitis Recurrent oral HSV Oral hairy leukoplakia Lymphoma/Kaposi sarcoma

When to treat

A variety of guidelines is available to indicate when it is appropriate to commence children on antiretroviral treatment based on a combination of symptoms and CD4 count. A number of common ENT presentations are seen in the relatively well HIV-infected child who may not yet need to be on medication unless associated with a low CD4 count. Other conditions that may present to ENT are key indicators themselves of the need to start treatment (**Tables 7.1** and **7.2**).

Families need significant support with compliance with HAART. Most children show rapid improvement in their CD4 count and immune reconstitution over the first few months of treatment. However, for some children the residual damage caused by recurrent ear and chest infections may mean they continue to have problems that need ongoing input from the ENT team.

TABLE 7.2 Age-specific thresholds to start treatment (adapted from PENTA)[80]

	Under 12 months	1–3 years	3–5 years	Over 5 years
Clinical stage	Start all	CDC B or C WHO 3 and 4	CDC B or C WHO 3 and 4	CDC B or C WHO 3 and 4
CD4 count	Start all	CD4 < 1000 (25%)	CD4 < 500 (20%)	CD4 < 350

KEY POINTS

- Children with primary or acquired immunodeficiency will commonly present with ENT problems.
- Clinical features may not differentiate immune-deficient children from normal children.
- Simple baseline investigation can screen out a number of severe immune defects.
- Close working between ENT teams and the local paediatric immunology/infectious disease services should be encouraged.

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CHAPTER 8

HEARING SCREENING AND SURVEILLANCE

Sally A. Wood

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search for relevant articles published in English, using the following keywords: infant or newborn and hearing screening and hearing impairment.

INTRODUCTION

Any discussion of screening must be grounded in an understanding of the principles of screening as a public health exercise and an understanding of the epidemiology of the condition of interest, in this case moderate–profound permanent childhood hearing impairment (PCHI). This chapter starts with an outline of the key definitions and principles of screening, before proceeding to review evidence on the epidemiology of permanent childhood hearing impairment. The case for newborn screening and the current performance of the newborn hearing screening programme in England is summarized. The need for surveillance in the preschool years is reviewed and the school entry screen is briefly discussed.

PRINCIPLES AND DEFINITIONS

Screening

Screening is a public health service in which members of a defined population who do not necessarily perceive they are at risk of or already affected by a disease or complications are asked a question or offered a test, to identify those individuals who are more likely to be helped than harmed by further tests or treatments to reduce the risk of a disease or its complications.[1] In the UK the National Screening Committee (NSC) assesses the evidence for the introduction of national screening programmes and monitors the effectiveness and quality of these programmes in the English NHS.

Screening is ethically different from clinical practice; in screening the individual has not presented with a symptom or concern but is offered a test. When you treat an ill person, they have the possibility of benefit as well as the risk of harm. In screening some people who do not have the condition may experience the harm but have no benefit. Screening is not an infallible process and in all screening programmes there are inevitably individuals who fail the screen but do not have the condition (**false positives**), and individuals who pass the screen but do have the condition (**false negatives**). Thus there is an added ethical imperative to ensure that the screening programme does more good than harm.[2] The most likely potential harms from newborn hearing screening are related to parental anxiety for the parents of babies who fail the screen but do not have an impairment (false positives) and the ability of audiology services to make a correct and timely assessment in screen positives.

The principles that a screening programme should satisfy have been identified by Wilson and Junger[3] (1–10 below) and expanded by Haggard and Hughes[4] (11–14) in their review of screening for hearing impairment in children.

1. The condition (hearing impairment) should be an important health problem.

2. There should be an accepted treatment, i.e. an acceptable means of habilitation for those identified by the screen.
3. Facilities for assessment, diagnosis and treatment should be available.
4. The hearing impairment should be recognizable at an early stage.
5. There should be a suitable test for use as the screen.
6. The test should be acceptable to the parents and to the child.
7. The natural history of the condition should be known and understood.
8. There should be an agreed policy on who to treat.
9. The cost of case finding (including all consequential costs of the screening programme) should not be disproportionate to overall healthcare costs of care for the hearing-impaired child.
10. Case finding should be seen as a continuing process.
11. The incidental harm should be small compared to the overall benefits.
12. There should be guidelines on how to explain results to parents with appropriate support.
13. All hearing screening arrangements should be reviewed in the light of changes in demography, epidemiology and other factors.
14. Cost and effectiveness of hearing screening should be examined on a case-type basis to maximize the effectiveness and benefit for each type before considering overall costs, effectiveness and benefits.

There are a number of key definitions relevant to screening programmes which should be used in the quality assurance and audit of any screening programme. These measures are defined in Table 8.1 and described below.

Coverage is the proportion of the eligible population who complete the screen.

Screen positive/fail (A+B) is a screening result that is greater than or equal to a specified cut-off level. True positives (A) are those who fail the screen and have the condition. False positives (B) are those who fail the screen and do not have the condition.

Screen negative/pass (C+D) is a screening result that is less than the specified cut-off level. True negatives (D) are those who pass the screen and do not have the condition. False negatives (C) are those who pass the screen and have the condition. Screening programmes attempt to reduce false negatives to a minimum, while keeping false positives within manageable service levels. The aim of a screen is to refer on a manageable proportion of the population for further (diagnostic) tests, that proportion being likely to contain as many of the true cases in the population as possible.

Sensitivity (A/(A+C)) is the proportion of individuals with the target condition in the population who are correctly identified by the screen. The term can be applied to a screening test, or to the screen as a whole (if, as is the case with newborn hearing screening, the screen consists of more than one test) or to the screening programme as a whole. **Programme sensitivity** is the proportion of the subjects in the whole population with the specified condition (impairment) who are detected by the screening programme. It is a function of the screen sensitivity and the coverage achieved by the screen programme.

Specificity (D/(B+D)) is the proportion of individuals without the target condition in the population who are correctly identified as such by the screen. As with sensitivity, the term specificity may be applied at the level of test, the screen or the programme. **Programme specificity** is a function of specificity and coverage.

Positive predictive value (PPV) (A/(A+B)) is the proportion of individuals with a positive test result who have the target condition.

Yield is the number of cases identified by a screen. The yield is sometimes expressed as the number of cases identified via the screen per 1000 individuals screened, thus allowing comparison with published prevalence figures, and acting as a surrogate for sensitivity (since sensitivity can only be established in retrospect, once all false negative and missed cases have been found). The yield of a screen is affected by coverage and sensitivity, and affects the cost per case identified. The **incremental yield** is the number of true cases referred by a screen when any true cases that would have been or were identified by preceding screening, surveillance programmes or responsive services are excluded.

Incidence is the number of new instances of the condition (impairment) occurring during a certain period (e.g. a year) in a specified population. Thus, in an average-sized health community with 5000 births per year, an incidence of between five and ten cases of congenital permanent childhood hearing impairment of moderate or greater degree might be expected.

Prevalence is the total number of individuals who have a given disease or condition (impairment) at a given point in time per population figure (e.g. per 1000 live births). Davis et al.[5] have suggested a figure of 1.12 per 1000 for congenital permanent bilateral hearing impairment of moderate or greater degree.

Haggard and Hughes extended the screening criteria to include costs and cost-effectiveness as

TABLE 8.1 Measurement of screen performance

Screen outcome	Condition present	Condition absent	Total
Fail (positive)	A: true positive	B: false positive	A+B
Pass (negative)	C: false negative	D: true negative	C+D
Total	A+C	B+D	A+B+C+D

important issues for screening programmes (points 9 and 14 above). **Cost-effectiveness** analysis measures costs per unit of health gain.

Lost to follow-up is a measure of the percentage of screen positives that fail to enter follow-up. This is usually measured at a specific point in time.

Surveillance

The concept and practice of child health surveillance has been extensively discussed in the literature.[6,7] It is generally recognized to include a partnership between parents, children and health professionals in which parents are empowered to make use of services and expertise according to their needs. Ongoing surveillance for childhood hearing impairment is of considerable importance:

- Newborn hearing screens will not find all those with permanent hearing loss, because of late onset and progressive hearing loss.
- Any screening programme will miss some true cases.
- Mild permanent hearing loss will not be identified by the screen.
- Surveillance is a more justifiable approach to identification of children with persistent otitis media with effusion (OME) than a screening programme.

EPIDEMIOLOGY: PREVALENCE AND RISK FACTORS

Terminology and definitions

In the sections that follow, hearing impairment is categorized as mild, moderate, severe or profound on the basis of hearing threshold in dB HL (hearing level) averaged over the frequencies 0.5, 1.0, 2.0 and 4.0 kHz for the better hearing ear as follows:

- Mild 21–39 dB
- Moderate 40–69 dB
- Severe 70–95 dB
- Profound >95 dB.

This categorization is widely used in the literature.[5] It is slightly different from that adopted by the British Society of Audiology.[8] The World Health Organization has recently defined an alternative classification.[9]

Permanent childhood hearing impairment (PCHI) includes hearing impairment that results from a structural abnormality in the outer ear, middle ear as well as sensorineural hearing loss. The term congenital is used to denote hearing impairment that is present at, or very soon after, birth. While this is not a strictly accurate use of the term, it has been commonly used as a functional definition. Acquired hearing impairments are considered to be (i) postnatally acquired PCHI (e.g. as a sequela of meningitis or head injury); (ii) progressive hearing impairments usually diagnosed following ongoing progression of the impairment post diagnosis; (iii) impairments that are considered to be late-onset, with no evidence of progression but with some evidence of previously normal hearing.

Congenital permanent bilateral hearing impairment

The quality of published studies on the prevalence of PCHI is variable, with many studies marred by lack of clarity on case definition, uncertain methodology and incomplete case ascertainment. Of the better studies, those of Fortnum and Davis[10] and Fortnum et al.[11] are probably the most extensive and reliable. Fortnum and Davis report the results of a retrospective ascertainment of all cases of permanent bilateral hearing loss of moderate or greater degree in children born in the UK's Trent health region between 1985 and 1993. Based on the birth cohorts for 1985–1990, the prevalence of moderate to profound congenital permanent bilateral hearing impairment was 1.12 (95% CI 1.01–1.23) per 1000 live births as shown in Table 8.2. Acquired impairment was estimated at 0.21 per 1000. Prevalence is presented per 100 000 for ease of interpretation.

In a later study Fortnum and colleagues[11] reported prevalence rises from 0.91 per 1000 (95% CI 0.85–0.98) for the 3-year-old cohort to 1.65 per 1000 (95% CI 1.62–1.68) for the 9-year-old cohort, where it levelled off. The authors conclude that there are more late-onset and progressive permanent childhood hearing impairments than previously suspected. However, this prevalence was arrived at by including an adjustment for under-reporting based on data for the relatively small subgroup that had received cochlear implants. To date there are no longitudinal population studies that confirm this rise in prevalence. More recently Watkin and Baldwin[12] have shown a prevalence of 1.51 (95% CI 1.11–1.92)/1000 at the end of the first year in primary school (i.e. at age 6 years). Some of the children in their study had moved from countries outside the UK without newborn hearing screening and four had acquired a PCHI following meningitis. For Australian children Ching et al.[13] reported a similar prevalence of 1.57/1000 at age 16 years.

Irrespective of the true increase in prevalence over childhood these data support the use of newborn hearing

TABLE 8.2 Prevalence of PCHI[10]

	Severity (dB HL)	Prevalence per 100 000	95% CI
Congenital	40–69 (moderate)	64	56–73
	70–94 (severe)	23	19–29
	≥95 (profound)	24	20–30
Acquired	40–69 (moderate)	9	7–12
	70–94 (severe)	5	3–8
	≥95 (profound)	7	5–10

screening for the identification of the 1.12 (or thereabouts) congenital cases per 1000 births.

Risk factors

Risk factors for permanent congenital hearing loss are well established (Joint Committee on Infant Hearing, JCIH).[14] Davis and Wood[15] showed that babies admitted to a neonatal intensive care unit for more than 48 hours were 10.2 (95% CI 4.4–23.7) times more likely to have a permanent hearing loss (greater than 50 dBHL in this study) than those who did not undergo intensive care. Fortnum and Davis[10] showed that prevalence was increased 14-fold for children with a family history of early permanent childhood deafness. Babies with craniofacial anomalies associated with hearing impairment (e.g. cleft palate) are also at high risk for hearing loss. The large-scale Wessex study[16] reported that, of 25 000 newborns screened, 8.1% fulfilled high-risk criteria. The three major risk factors are:

- history of treatment in a neonatal intensive care unit (NICU) or special care baby unit (SCBU) for more than 48 hours
- family history of early childhood deafness
- craniofacial anomaly (e.g. cleft palate) associated with hearing impairment.

About 60% of congenital bilateral permanent hearing impairment of moderate degree or greater is associated with one or more of these three risk factors, in the proportions 29.3% NICU, 26.7% family history and 3.9% craniofacial anomaly.

Acquired and late-onset permanent bilateral hearing impairment

Acquired hearing impairment is one which, on the basis of case history, was not considered to be present and detectable using appropriate tests at or very soon after birth. Meningitis is the most common causes of acquired hearing impairment in children.[5] There remains a lack of evidence about the prevalence of progressive or late-onset impairments. Any newborn hearing screening programme will, of course, not identify these cases; other means of finding them are required.

Unilateral permanent hearing loss

Previous studies have suggested a prevalence of around 1 per 1000 in school-age children for unilateral impairment although prior to newborn hearing screening it was difficult to estimate how much of this was congenital. In the Newborn Hearing Screening Programme (NHSP) in England all babies that are screen positive, whether unilaterally or bilaterally, are referred for immediate follow-up. The rationale for this is to increase the sensitivity for bilateral PCHI rather than to identify unilateral PCHI per se. However, this has provided data on the prevalence of unilateral PCHI at 0.61 per 1000 screened.[17, 18] Such early identification does lead to issues about optimal management of unilateral PCHI.[19]

Mild hearing loss

Prevalence of mild hearing loss has been difficult to ascertain. Estimates based on clinical populations are biased as those with difficulties arising from a mild loss present to clinical services whereas those not experiencing difficulty do not. Hence population data are needed to estimate prevalence. Hall et al.[20] assessed hearing in children at age 7, 9 and 11 years as part of the ALSPAC (Avon Longitudinal Study of Parents and Children) study. They reported on prevalence of mild PCHI on the basis of consistent findings at all three test occasions. This methodology reduced the likelihood of a one-off assessment in a child with normal hearing but poor concentration being recorded as a case of mild PCHI. They found a prevalence of 0.4% for mild bilateral sensorineural hearing loss and 0.1% for bilateral high-frequency hearing loss giving an overall prevalence of 0.5% (CI 0.4, 0.8) at age 11 years. This is lower than commonly reported estimates from the USA[21] but similar to estimates from Australia.[22]

Auditory neuropathy spectrum disorder

Auditory neuropathy spectrum disorder (ANSD) is the label applied to clinical audiological test findings that indicate normal outer hair cell function as evidenced by the presence of otoacoustic emissions (OAEs) and/or the cochlear microphonic response and absent or severely abnormal auditory brainstem response (ABR). In earlier literature this was termed auditory neuropathy (AN); the new terminology was adopted in 2008.[23] This combination of test results suggests relatively normal activity in the outer hair cells but disruption of transmission at some point from the inner hair cells along the neural pathway to the brainstem. In some cases, neural firing may be occurring but with a lack of synchrony, so that no clear ABR is recordable. In some cases dys-synchrony may arise due to delayed maturation or myelination of the auditory pathway. The true prevalence of ANSD is not yet determined. It has been reported that up to 10% of all children with confirmed PCHI have auditory neuropathy. It is a condition found predominantly in the NICU population and it is considered relatively rare in the well-baby population.[23]

Temporary childhood hearing impairment

Temporary childhood hearing impairment due to otitis media with effusion (OME) is extremely common, with a point prevalence of 20% and a period prevalence in the under 5-year-olds of 80%.[4] The major risk factors are season, passive smoking, bottle-feeding, upper respiratory tract infections, admission to NICU as a newborn, day care and siblings having had OME. Refinement of risk factor analyses has indicated season, passive smoking, siblings having had OME and snoring and

mouth-breathing as the best indicators for persistence.[24] The TARGET (Trials of Alternative Regimens in Glue Ear Treatment) studies indicate effects of persistent OME on hearing difficulties, speech/language delay, disturbed sleep patterns, behaviour and (consequent on these) parental and child quality of life (see Chapter 13, Otitis media with effusion).[24]

THE RATIONALE POSITIVE FOR NEWBORN HEARING SCREENING

In this section, we will consider newborn screening mainly with respect to PCHI of moderate to profound degree.

The critical review (1997) of newborn hearing screening carried out as part of the UK's Health Technology Assessment programme[5] reviewed the evidence on the epidemiology, age at identification and intervention for PCHI, the performance of screens and services that were in place at the time and views of parents and appraised the options for detection of PCHI. The review concluded by recommending the introduction of universal newborn hearing screening for PCHI of moderate or worse degree in the better ear. Below is a brief summary of some of the evidence.

Outcomes

There is good evidence that outcomes in a number of domains are affected by bilateral moderate to profound PCHI. In most cases this is a severity-dependent effect, with greater effects for more severe impairments; there are, however, very great individual differences, with some children performing at levels appropriate to their age and others performing very poorly. These differences are not always a function of severity but will be a result of a range of intrinsic and extrinsic factors. One such factor is the age at identification, as well as habilitative support provided. The evidence of compromised outcomes associated with congenital PCHI comes from studies looking at communication skills,[25] literacy,[26] behaviour,[27] educational achievement,[28] mental health, [29] family dynamics[30] and quality of life.[27]

Age of identification

Prior to the introduction of universal newborn hearing screening the UK had a universal 8-month screen for childhood hearing impairment carried out by health visitors in community clinic settings and known as the health visitor distraction test (HVDT). With the introduction of newborn hearing screening this has been phased out; there is good evidence that it had poor sensitivity, poor specificity, high refer rate, low yield and was not cost-effective in terms of cost per case found.[5] The retrospective study of permanent childhood hearing impairment greater than or equal to 40 dBHL in children born between 1985 and 1993 and resident in Trent health region showed that the median ages at referral, confirmation of the impairment, prescription of hearing aids and fitting of hearing aids were, respectively, 10.4, 18.1, 24.4 and 26.3 months.[10] While much of the delay was clearly due to delays in the assessment process after referral, nonetheless the median age of screen referral for children with congenital hearing loss was little short of 1 year.

Benefits of early identification and intervention

There have been many observational studies that have reported benefits from earlier identification and intervention for PCHI[31, 32] but no true RCTs that address the question of whether universal newborn hearing screening (UNHS) results in earlier identification of PCHI, earlier intervention and improved outcomes. The only quasi RCT of the effect of newborn hearing screening on age at identification of PCHI and outcomes is the Wessex trial.[33] This study showed that birth during periods of UNHS was associated with confirmation of PCHI by 9 months of age and in turn this was associated with better receptive language scores but not with better speech at age 8 years.[33, 34] In 2008 the UNHS Task Force concluded that infants identified with PCHI through universal newborn screening have earlier referral, diagnosis and treatment than those identified by other means.[35] They concluded that the data from studies on language outcomes at school age strengthen the case for newborn screening but caution that effective methods of referral, follow-up and treatment are needed to maximize the effectiveness of newborn screening. Since then two population studies have confirmed that UNHS results in earlier identification and intervention and improved outcomes at age 3–5 years[36] and 7–8 years.[37] A further study found outcomes at age 3 years to be only weakly related to age at hearing aid fitting but for cochlear implant users the age at switch-on was significantly associated with better outcomes.[38]

The evidence around mild PCHI is equivocal. In a population study to determine the prevalence and effects of slight/mild sensorineural hearing loss in school children Wake et al.[22] concluded there was no strong evidence for adverse effects on language, reading, behaviour or health-related quality of life in children who are otherwise healthy and of normal intelligence. They did caution that further research is necessary to determine whether children with bilateral PCHI at the upper end of the slight/mild range experience adverse effects at the population level and, if so, whether they might gain more benefit than harm from systematic intervention. However, the optimal form of systematic intervention, including the role and benefits of amplification, remains to be determined.

Assessment and management

Some aspects of audiological assessment are easier in the first few months of life: for example, electrophysiological tests such as the auditory brainstem response, and habilitative procedures such as real ear measurements for hearing aid fittings can more readily be carried out during periods

of natural sleep. Perhaps more importantly, the earlier that parents and services know about the child's hearing impairment, the earlier decisions can be made about management including fitting of appropriate hearing aids, referral for cochlear implant, choice of communication methodology and provision of family support. In order to realize these advantages, screening and assessment must be viewed as the initial steps in a seamless family- and child-centred service with a multidisciplinary focus.

Costs

Bamford et al.[17] compared the NHS costs of NHSP (newborn) and HVDT (at 8 months of age) and concluded that NHSP appears to be a cost-effective strategy for hearing screening when compared to HVDT screening.

Cost-effectiveness

It has been argued that UNHS will have paid for itself within 10 years in terms of the long-term savings made in special education and social interventions. However, in a systematic review of cost-effectiveness Colgan et al.[39] identified only one study that found that UNHS could be cost-effective if early intervention leads to a substantial reduction in future treatment costs and productivity losses. Longitudinal data do not yet exist.

Parental wishes

Parents' views on the desirability and timing of newborn hearing screening received some attention in the literature prior to the widespread introduction of newborn hearing screening. Surveys show that around 80–90% of parents of children with permanent hearing impairment would have wanted it for their children if it had been available to them when their child was born.[40] It is also known that early identification tends to avoid the parental anxiety and anger that may be associated with delayed detection.[40, 41] Newborn hearing screening is widely accepted; data for the English programme show that less than 0.1% of families decline the screen.[18]

NEWBORN HEARING SCREENING

Case definition

While many North American screening programmes[42, 43] include babies with permanent mild and unilateral hearing impairments in their target group, the Newborn Hearing Screening Programme in England aims to identify all children with a moderate–profound PCHI in the better hearing ear.[17] As a by-product, the screen will also identify a number of babies who have unilateral and in some cases mild permanent hearing impairments, as well as temporary hearing impairments. The consequences of delay in identification are not well established in these infants, and optimal management is not clearly known. However, this is lack of evidence for effects rather than evidence of no effects, and research is needed to identify best practice for the early management of congenital permanent mild and unilateral hearing impairment as well as early management for temporary hearing impairments.

Current screening tests

The tests available for newborn hearing screening are automated otoacoustic emissions (AOAEs) using either transient or distortion product otoacoustic emissions or automated auditory brainstem response (AABR). Otoacoustic emissions reflect the activity in the outer hair cells of the cochlea, while AABR measures the neural response from the brainstem. Both types of test are available in portable hand-held screening instruments that employ automated detection algorithms to determine the presence or absence of a response and thus screening staff are not required to make any judgements about the response. Most screening programmes use a two-stage protocol (either OAE followed by AABR if required or two-stage AABR). The OAE is quick, minimally invasive and consumable costs are relatively low compared with AABR. The disadvantages are that it can be affected by the presence of fluid/debris in the outer or middle ear and will also miss neonates with auditory neuropathy. However, auditory neuropathy is predominantly found in the NICU/SCBU population and thus AABR is the method of choice in the NICU/SCBU population.

In the English NHSP screening is carried out using standard techniques and protocols[44, 45] and with equipment that has been approved for use within the programme. There are separate protocols for well babies and babies who have spent 48 hours or more in NICU/SCBU.

Well babies follow a two-stage two-technology protocol; the first stage is a transient AOAE screen, with a maximum of two attempts, followed by an AABR screen if required. A pass in both ears using AOAE, or a pass in both ears on AABR, constitutes an overall screen pass. **Babies cared for in NICU or SCBU for more than 48 hours** undergo a transient AOAE screen and an AABR screen. Those that fail the AABR screen in one or both ears are considered to be screen referrals and are referred for audiological assessment. Babies that pass the AABR screen in both ears and fail the AOAE screen in both ears are included in the risk-factor group and receive a follow-up at 8 months.

The most commonly used model in the English NHSP is a hospital-based screen employing a team of dedicated screeners performing the screening tests on newborns in the maternity unit before discharge. This is backed up by a recall clinic for the babies missed by the initial screen. In some areas a community-based screening model is used for well babies, with screening performed in the home or at local clinics.

Newborn hearing screening is also implemented in Wales, Scotland and Northern Ireland. These programmes also fall under the remit of the UK NSC. The details of their implementations differ in some respects from the English programme. Details can be found via the NSC website.[1]

High-risk screening

The high proportion of cases with risk factors led, in the early 1990s, to the widespread introduction of high-risk or targeted newborn screening in which attempts were made to screen all those babies (around 10% of the birth cohort) with risk factors, in order to achieve early identification for the 60% of true cases of congenital permanent impairment. However, in practice there are a number of difficulties with high-risk newborn hearing screening. The use of the family history risk factor is difficult to implement effectively[46] and thus the proportion of the target population identified by at risk screening was rarely above 40%.[5] Barker et al.[47] carried out a population audit of the effectiveness of stand-alone NICU screening compared with NICU screening as part of a universal screen and showed better performance in the latter case as measured by screening coverage, age of detection, loss to follow-up and positive predictive value of a refer result. More importantly, some 40–50% of babies born with permanent hearing loss demonstrate no risk factors. Numerous studies agree that around half of all affected infants have no risk factors at birth and thus would be missed by even the best-performing high-risk newborn hearing screening.[5]

Performance of universal newborn hearing screening

The NHSP in England was fully implemented in April 2006. Since then coverage has gradually improved and for the 2015/16 birth cohort 98.1% of babies completed screening by 4 weeks corrected age and 99.2% by 3 months. The refer rate has been relatively constant at 2.5% with 0.5% referring bilaterally. The yield for bilateral PCHI has been shown to be 1.01/1000 and the median age of identification for those screened by the programme is currently around 7 weeks.[18]

Parental anxiety

The prospect of the parental anxiety that might be engendered as a result of newborn hearing screening and in particular around false-positive results had been a cause for concern prior to the implementation of the screen. During implementation the NHSP in England developed a number of processes for ensuring high levels of information for mothers/parents, including a national screener-training programme, training and information sessions for other professionals, plain English information leaflets and DVDs for parents and informed parental consent to the screen. The detailed evaluation of Phase One of the English programme[17] indicated that, although referral for diagnostic tests has a small but significant effect on mothers' emotional well-being in the first 3 weeks after screening, the effect is below the cut-off for clinical concern. This small but significant emotional distress following recall for diagnostic tests after the screening is no longer evident at 6 months. The evaluation further concluded that ensuring good knowledge of possible reasons for referral seems to be protective against anxiety and newborn hearing screening does not cause more emotional distress than a test conducted some months later in infancy.[17] In the years since full implementation of the newborn screen in England parental anxiety has not emerged as a significant cause for concern.

Lost to follow-up

Lost to follow-up is an important consideration; there is little point in running a screening programme if the families of screen-positive babies are not willing to engage with diagnostic services and early intervention programmes. In the United States only slightly more than half of the infants who refer on newborn hearing screening receive follow-up.[48] In the English screening programme follow-up rates are much better; 87% of screen referrals have entered follow-up by 4 weeks and 95% by 6 months of age.[18, 49] Clearly there is a different context with services free at the point of use and a national programme and information system to track babies through screening and follow-up and record audiology results.

Quality assurance

There is an ethical duty within a screening programme to ensure not only a good quality screening service but also that good quality follow-up services are in place. The NHSP in England developed quality standards that include the screening pathway but also the follow-on diagnostic, medical, habilitation, early intervention and family support services.[50] These standards have been used as the basis for a national quality assurance programme. The quality and effectiveness of audiology services responsible for the electrophysiological assessment for babies that refer from newborn screening is pivotal to achieving early identification and intervention. Rigorous protocols and guidelines for these early assessments have been extensively developed alongside the implementation of the screening programme.[44]

THE SCHOOL-ENTRY SCREEN

Although there is a long history of school-entry hearing screening in the UK dating back to the 1950s, there has been little systematic evaluation of the benefits and there remains confusion about its aims and definition of the target condition. Apart from referring children with progressive and acquired permanent hearing loss that have not been picked up by parental observation and responsive services, the school-entry screen also has the potential to identify children with mild and unilateral hearing loss, as well as high-frequency hearing loss and other hearing losses with unusual configurations.

A Health Technology Assessment (HTA) review in 2007[51] found that a school-entry hearing screening is widely implemented, coverage is around 90% (in state schools), referral rates are high (8%), methods and referral criteria are highly variable and there is poor recording of data and little audit or quality assurance. The review concluded that, while screening for PCHI at school entry meets all but three of the requirements for

a screening programme, screening for temporary hearing impairment fails to meet at least six.

The current NSC policy acknowledges that, with the introduction of newborn screening, most cases will be identified before school entry; however, there will be some cases that were missed or have developed after the test. The current recommendation is that screening for hearing impairment in school-age children should continue while further research is undertaken.[1]

SURVEILLANCE

Surveillance for childhood hearing impairment is of considerable importance:

1. Newborn hearing screens will not find all those with preschool permanent hearing loss because of acquired, late-onset and progressive hearing impairment.
2. Any screening programme will miss some true cases.
3. Children with mild hearing loss and some with high-frequency hearing loss will not be identified by the screen.
4. Infants and children move in from countries where newborn hearing screening is not available.
5. Surveillance is a more justifiable approach to identification of children with persistent OME than a screening programme.

In an effort to identify children in category 1 above, many newborn hearing screening programmes have historically adopted regimes of targeted surveillance for babies who pass the screen and have certain risk factors. More recently, some programmes have questioned whether this is a useful service model.[52, 53] A recent analysis of data from English NHSP[54] showed that much of this risk factor-based surveillance is not effective and is now only recommended for babies that pass the screen with the following risk factors:

- syndrome (other than Down) associated with a hearing loss
- NICU with refer in both ears at OAE and pass in both ears at AABR
- craniofacial anomaly
- Down syndrome
- congenital infection.

Audiological assessment should always be carried out following recovery from meningitis, extracorporeal membrane oxygenation (ECMO), skull fracture and hyperbilirubinaemia.[55] Routine audiological monitoring should be offered to specific groups of children with a high risk of otitis media with effusion including children with Down syndrome and cleft lip and palate.[56, 57] Surveillance policies should encourage services to be highly responsive to parental or professional concern about a child's hearing or their development of auditory, vocal or communicative behaviour; where concern is identified, an age-appropriate audiological assessment should be carried out. The importance of ongoing surveillance by health visitors, family doctors, community health teams, as well as parents (reinforced by appropriate checklists such as those given to parents shortly after the birth of their child), should not be underestimated.

Otitis media with effusion has a high prevalence between 1 and 7 years of age. Screening for either the pathology or the consequent hearing impairment fails to meet the criteria for screening programmes outlined above because of its fluctuating nature, high remission rate and uncertainties over treatment.[58, 59] However, it can have an important impact on children's lives and development in persistent cases. Some sort of surveillance system needs therefore to be in place for identifying and intervening with those 5–10% of cases that have OME with a persistence or severity likely to interfere with development. It has been shown that the use by family doctors of a simple checklist and a training video significantly improves the positive predictive value of their referrals.[24]

FUTURE RESEARCH

- More evidence is needed on the medium- and long-term outcomes for children identified with PCHI and on the predictors for better outcomes.
- Further research is needed concerning the prevalence, aetiology, outcomes, diagnostic and habilitative options for children with auditory neuropathy spectrum disorder.
- Currently, some children with mild and unilateral hearing impairment will be identified as a by-product of newborn hearing screening for permanent bilateral hearing impairment of ≥40 dB HL. More research is needed about the prevalence, effects, outcomes and habilitative options for these children.
- There is evidence to show that progressive and acquired permanent childhood hearing impairment is more prevalent than previously thought. Confirmatory population-based prevalence data are needed together with continued assessment of the evidence on the risk factors to inform surveillance programmes.
- The school-entry screen requires a more extensive evidence base to enable evaluation of its effectiveness.

KEY EVIDENCE

- At least 1 in 1000 children is born with permanent bilateral hearing impairment ≥40 dB HL.
- If permanent bilateral congenital hearing impairment is identified before 6 months of age and habilitation started soon thereafter, the adverse effects are lessened.
- The prevalence of permanent bilateral hearing impairment ≥40 dB HL increases through childhood although the final prevalence figure is not yet certain; parents and professionals must continue to be appraised of this and surveillance systems and responsive services must be in place.
- Newborn hearing screening of all babies is the most cost-effective method of delivering early identification of congenital permanent hearing impairment of at least moderate or greater degree.
- More evidence is required on the outcomes for children with permanent mild or unilateral hearing impairment, and on alternative approaches to management.
- The evidence for school-entry screening is equivocal.
- Identification of persistent OME cases depends upon good surveillance systems in primary care and responsive services.

KEY POINTS

- Newborn hearing screening of all babies is the most effective and cost-effective way to identify congenital hearing loss.
- Audiology and screening services must work together to ensure rapid follow-up of screen referrals. This facilitates accurate audiological assessment. Such rapid follow-up, together with good-quality information, minimizes family anxiety.
- Audiology services must maintain and develop expertise in early audiological assessment techniques to enable early confirmation (or otherwise) of PCHI in babies referred from newborn hearing screening.
- Good quality services for true-positive cases based upon informed choices for parents are central to screening programmes at any age, but particularly for newborn screening.
- Management of true-positive cases involves close cooperation between health, education and social services.
- A surveillance programme must be in place to help identify late-onset and acquired hearing losses, backed up by fast responsive services.
- Parents and professionals in primary care need to be alert to the presence of persistent OME in some children.

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CHAPTER 9

HEARING TESTS IN CHILDREN

Glynnis Parker

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: audiometry/child and hearing test/child. Further information was accessed on the websites of the British Society of Audiology (BSA) (http://www.thebsa.org.uk/) and the American Speech-Language-Hearing Association (ASHA) (http://www.asha.org/).

INTRODUCTION

It is essential that suspected hearing loss in young children is promptly investigated. Accurate assessment of hearing is fundamental to diagnosis, investigation and rehabilitation. The techniques applicable to adults and older children are often inappropriate for the young child and for the older child or adult with special needs, particularly learning disability. Skilled testing by trained personnel in a suitable test environment is essential. The focus of this chapter is on those tests that require skilled observation and recording of the child's 'functional' responses to speech or 'non-speech' sound stimuli – often referred to as behavioural hearing assessments. The more complex evaluations utilized for pre- and post-assessment of children undergoing cochlear implantation are explored elsewhere (Chapter 11).

Effective assessment includes involving the family in a culturally and linguistically appropriate manner, providing a clear, sensitive explanation of the procedures and outcomes, supported by written information as available. A thorough assessment may require multiple sessions.

ELECTROPHYSIOLOGICAL TESTING

Key developmental age: 0–6 months, up to adult if appropriate

Electrophysiological techniques including otoacoustic emission (OAE), auditory brainstem response (ABR) and cortical evoked response audiometry (CERA) are discussed in Chapter 8, Hearing screening and surveillance, and Chapter 52, Evoked measurement of auditory sensitivity. These methods are mainly employed in newborn screening (see Chapter 8) and diagnostic testing of infants in the first 6 months.[1–4] They can also prove of value in children of any age when behavioural testing has failed to produce reliable results, in particular those with severe learning or communication difficulties.[5] Accurate assessment may require sedation or general anaesthesia. Electrophysiological techniques are also used to confirm hearing thresholds, for example, prior to cochlear implantation or where non-organic factors are suspected. While electrophysiological testing has the advantage of being objective in terms of the child's response, behavioural and

speech discrimination testing remain the only functional measures for assessing the complete auditory system.

BEHAVIOURAL OBSERVATION AUDIOMETRY

Key developmental age: 0–6 months

In behavioural observation audiometry (BOA), changes in activity are observed in response to a sound stimulus. Response behaviours include eye widening, eye blink (auropalpebral reflex), alteration in sucking response, arousal from sleep, startle or shudder of the body or definite movement of the arms, legs or body. From 4–7 months, lateral inclination of the head towards the sound or a listening attitude or stilling may be observed. The test is usually performed with the child cradled in the parent's lap or in an infant seat. The child's attention may be lightly engaged in front by a distractor. The sound stimulus may be presented for <2 seconds, in a horizontal plane, 15 cm from the child's ear, out of peripheral vision, or delivered via insert earphones. The distractor observes evidence of a response. A range of sound stimuli may be employed, including voice or noisemakers but ideally calibrated narrow-band, warble tones or ling sounds.[6,7]

Reliability as a diagnostic test is obviously a concern. A wide variability in judgement of response between testers due to misinterpretation of random movements and a tendency to underestimate hearing thresholds has been demonstrated.[8] Attempts have been made to reduce observer bias by use of video recording of the procedure and scoring the playback without knowledge of the sound or no sound trials.[9]

The use of BOA in infants under 6 months has been largely superseded by the availability of electrophysiological techniques. However, soundfield BOA may be of particular value in the verification of aided responses in infants, or in infants with a diagnosis of auditory neuropathy spectrum disorder when ABR is a poor indicator of functional hearing levels (see Chapter 69, Auditory neuropathy spectrum disorder and retrocochlear disorders in adults and children). It has the merit of allowing parents to participate in the assessment and witness their child's responses, leading to better understanding and acceptance of their child's hearing loss. BOA may have a continuing role in the assessment of older children with learning disabilities who have not reached an appropriate developmental stage for other means of assessment.

VISUAL REINFORCEMENT AUDIOMETRY

Key developmental age: 5-36 months

Visual reinforcement audiometry (VRA) incorporates the principle that young children can be trained by operant conditioning to produce a localizing turn to a visual stimulus in response to a sound stimulus. A technique of conditioned orientation reflex (COR) audiometry was initially described by Suzuki and Ogiba[10] and was further developed by Liden and Kankkunen[11] who introduced the term 'visual reinforcement audiometry'. Further developments and modifications to the technique have been described.[12,13] VRA is now established as a standard technique within the test battery for hearing assessment in preschool children and is generally suitable for infants once they have reached the developmental stage of being able to sit unsupported or with minimal support, i.e. at 5–7 months. VRA has largely replaced the use of the infant distraction test (see below) as it has become more widely available and has been demonstrated to generate more auditory-evoked head turns than an unrewarded sound stimulus and delays habituation so that the assessment is more likely to be completed.[14] The method is described with reference to the British Society of Audiology: Recommended procedure – Visual Reinforcement Audiology[15] and Widen et al.[16]

Test arrangement

The test room should be sound-treated to ensure low levels of ambient noise (ISO 8253),[17] which should be verified using a sound level meter. It should be adequately sized (recommended minimum of 6 m × 4 m), ideally with the ability to dim the lighting to permit enhancement of the illuminated vision reward. It may be partitioned to provide an observation area with a one-way window, with access to a communication system between the rooms, such as a radio link. A suitable arrangement is shown in **Figure 9.1**. If, however, this facility is not available, it is still possible to perform the test within one room, provided the tester operating the audiometer minimizes the distraction to the child and does not provide any additional clues. The child is seated on the parent's lap or on an infant seat or chair in front of a low table, with the parent seated slightly behind. A second tester may sit on the other side of the table or adjacent to the child to provide low-level play activity. For soundfield testing, the loudspeakers should be placed at 90° from the child and at the same height as the child's head at a distance of at least 1 m from the ear. Frequency-specific calibration of the sound signal from a test point equivalent to the child's head position is essential. Alternatively, a calibrated signal may be presented via insert earphones using foam tips or the child's own ear moulds, if available. This has the advantage of potentially providing more precise ear-specific response thresholds and even offers an opportunity to introduce masking by appropriate presentation of narrow-band noise in the contralateral ear. This is particularly valuable in amplification selection and setting.[18] A standard bone conductor may also be used in conjunction with VRA to differentiate between a conductive and sensorineural hearing loss.

Visual reinforcers are generally placed adjacent to or above each speaker. Facility should exist to move the reinforcer closer to the child to enhance reinforcement if indicated by visual ability or developmental status.

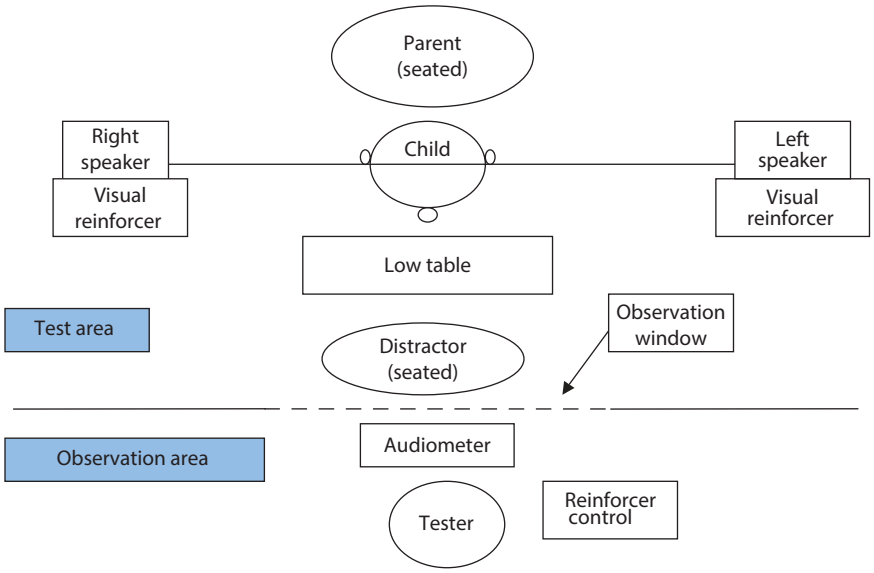


Figure 9.1 Test arrangement for visual reinforcement audiometry.

The reinforcer acts as a reward and therefore increasing the attractiveness or appeal to the child and introducing variety is likely to sustain interest and reduce habituation. Commercially available reinforcers include toys with eyes that light up and puppets in darkened glass cabinets which illuminate and dance. Monitors showing appropriate video displays can also be effective.[19, 20] The reinforcer is generally remotely activated by the tester as required.

Test method

Using the arrangement as described above, the first task must be to establish the conditioned response. Having drawn the child's attention to the front by gentle play activity on the table, a suprathreshold auditory signal should be presented concurrently with the visual reward. Appropriately calibrated frequency modulated (warble) tones, ling sounds or narrow-band noise (NBN) stimuli may be employed via soundfield, insert earphone, headphone or bone conductor, according to the clinical priority. For example, for a child with probable near-normal hearing, one might start with a 2 kHz warble tone at 60–70 dBHL, presented for 2–3 seconds. The child may turn to locate the sound (orientation response) and thereby view the activated reinforcer but, if necessary, the child's attention should be directed towards it. This sequence is repeated several times. The sound stimulus should then be presented alone and the reinforcer only activated after the child has produced an appropriate turning response. Praising the child and making it a game will further help to reinforce the response. If this can be reliably repeated two or three times, operant conditioning has been established. Children under 1 year or those with learning difficulties may take longer to successfully condition. If it appears that the initial auditory stimulus may be inadequate, this can be cautiously increased or a different frequency or vibrotactile stimulus used. NBN stimuli may be more effective in initially establishing the conditioned response,[21] but Thompson and Folsom[22] demonstrated that in VRA, unlike distraction testing, the complexity of the signal, including the bandwidth, had no effect on response rate once the child had been correctly conditioned.

Once the child has demonstrated successful conditioning, the aim is to establish the minimal response level (MRL) for each frequency, as prioritized by the clinical situation, bearing in mind that the child's cooperation may fail at any time. A typical order of stimulus presentation could be: 2 kHz – 500 Hz – 4 kHz – 1 kHz or 1 kHz – 4 kHz – 500 Hz – 2 kHz. Additional frequencies may be included if clinically relevant, for example 0.25 kHz, 3 kHz, 6 kHz, 8 kHz. A flexible descending/ascending (10 dB down, 5 dB up) principle, similar to that used in pure tone or play audiometry (see below), should be applied, although the increments and decrements in intensity (i.e. the steps up and down) may be increased to hone in on the response threshold. The duration of the signal is usually 2–3 seconds. One reliably obtained MRL is more valuable than a number of 'maybes'. Variable inter-trial intervals and 'no sound' control trials should be included to verify a true response and particular scrutiny is required in the event of frequent 'checking behaviour'.[23] If the child becomes bored and less responsive, it may be appropriate to recondition the child using suprathreshold stimuli and/or change the stimulus type or visual reward or, indeed, have a short break. Children generally respond well to praise and encouragement – the assessment should be a fun and enjoyable experience for the child and parent while maintaining objective accuracy. The outcome of each valid presentation and 'no sound' trial should be recorded in chart form, specifying the sound source, frequency range and intensity. A tick or a cross may be used to indicate whether a response was observed The MRL is regarded as the quietest level at which two out of three clear responses were recorded for each particular sound stimulus. The ability to localize the sound source correctly may be assessed, for example using a soundfield high- and low-frequency NBN

stimulus 30 dB above the MRL: difficulty with localization may indicate an asymmetric hearing loss although the converse does not necessarily apply.

Relevant observations which may affect the test reliability, such as alertness or cooperation of the child or subject-generated noise, should be recorded and taken into consideration when interpreting the results of the assessment. Responses recorded on soundfield testing are approximately +10 dB relative to adult thresholds and MRLs down to at least 25 dBHL on soundfield testing are generally regarded as compatible with satisfactory binaural hearing.[24, 25] Correction factors using insert earphones have been estimated for infants with normal hearing assessed by VRA relative to adult thresholds and are currently recommended as +15 dB at 0.5 kHz and 1 kHz and +5 dB at 2 kHz and 4 kHz.[15] Primus[26] found test–retest reliability to be good with 50% repeatability within 10 dB. Widen et al.[16] demonstrated that MRL for at least four frequencies were successfully recorded in more than 90% of over 3000 infants aged 8–12 months, tested using VRA.

THE DISTRACTION TEST

Key developmental age: 6–18 months

The test is based on the principle that the normal response observed when sound is presented to an infant is a head turn to locate the source of sound. The test is suitable at 6–18 months, corresponding to the stage when the child can sit erect unsupported and perform head turns in a horizontal plane. An appropriate allowance should be made for prematurity. Habituation is increasingly likely to occur after 12 months, although the technique may prove to be useful in older children with learning or communication difficulties where other methods have been unsuccessful.

The infant distraction test was first described by Ewing and Ewing in 1944,[27] but was subsequently modified by McCormick[28] who placed particular emphasis on the use of frequency-specific, calibrated sound stimuli. For many years the distraction test was used as a tool for screening for hearing impairment in infants around 7–9 months, but such programmes have generally been withdrawn in favour of electrophysiological screening in the newborn period[1, 2] (Chapter 8, Hearing screening and surveillance). The use of distraction testing by audiologists has also been largely discontinued in favour of VRA.[14] Nevertheless, it remains a valuable diagnostic technique when used by trained, experienced testers in appropriate settings when other methods are unavailable, unsuitable or unsuccessful. The test is described with reference to McCormick[29] and guidelines published by the British Society of Audiology.[30]

Test method

The test environment is similar to that used for VRA. Two testers are required, one to present the sound stimuli out of vision and the other to control the infant or child's attention in the forward direction (the distractor). The latter should be responsible for directing the test. The arrangement is shown in **Figure 9.2**. The child sits on the parent's knee, facing forward and erect, lightly supported around the waist. The distractor directs the attention of the child to a simple activity usually performed on a low table. Suitable examples include spinning a brightly coloured object, showing a small toy or blowing bubbles. In the classic distraction test described by McCormick,[29] the item is covered by the hands which maintain a fine attention control by moving the fingers slightly. The sound stimulus is presented by the second tester, half a second after the item is covered. The distractor observes the child's response.

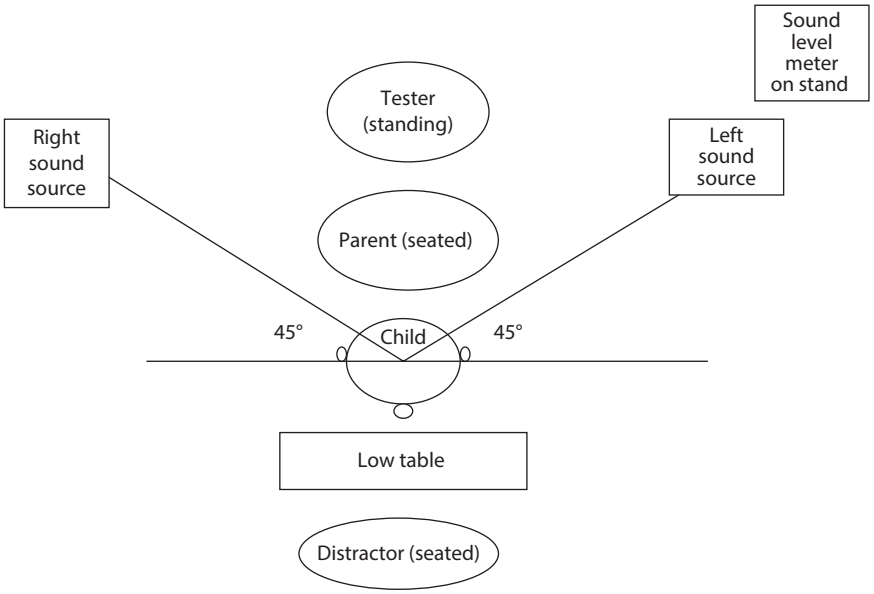


Figure 9.2 Test arrangement for the distraction test.

The second tester should be positioned strictly out of the child's visual field, which can be assumed to extend at least 90° to either side of the child's midline. The sound stimulus should be presented in the horizontal plane to the ears at an angle, set back 45° between 1 m and 15 cm from the child's ear. The shorter distance increases the head shadow effect, thereby increasing the sound stimulus on one side relative to the other. Evidence of asymmetric hearing levels may be indicated by a difference in response thresholds or difficulty in localizing the sound source. Particular care must be taken when presenting the sound close to the ear to avoid visual or tactile clues. The sound stimulus should continue up to 10 seconds if there is not an immediate response. During this interval, the distractor should maintain the fine attention control at the front until a response is observed.

The normal response expected is a full head turn in the direction of the sound. This may be rewarded by a smile or vocal praise or gentle touch from the second tester. Some warble tone generators incorporate a flashing light, which can be activated in response to the turn, providing an incentive to the child and thereby acting as a 'response reinforcer'. The child's attention should then be brought back to the front by the distractor.

A wide range of sound stimuli can be used to elicit a response, including voice (e.g. unforced 'S' = high frequency, or hum = low frequency), musical toys, calibrated high-frequency rattle, NBN or warble tones. Pure tones should be avoided due to the potential creation of standing waves, resulting in unpredictable sound levels. Responses to any sound stimulus may be valid, provided the intensity and the frequency spectrum, as delivered at the level of the ear, can be established. A sound level meter should be employed to check the intensity of the stimulus by accurately reproducing the sound and the distance from the ear. Although it has been demonstrated that infants are more likely to respond to wide-band sounds, this will inevitably provide less information regarding frequency-specific hearing as required for diagnosis and possible amplification prescription. Sound generators delivering calibrated narrow-band and frequency-modulated warble tones have been demonstrated to be effective at eliciting a response and are therefore generally preferred.[22]

Initially, a sound stimulus is presented which is anticipated to be likely to be suprathreshold, for example at 70 dB(A) in a child with probable normal hearing. A sound is then presented at the anticipated minimal response threshold, for example 30 dB(A). The intensity for sound-field testing is generally measured on the dB(A) scale, but this can be converted to dBHL if required, particularly for hearing aid prescription fitting – in practice the only correction factor required to the nearest 5 dB is +5 dB at 4 kHz.[17, 30]

There is no prescribed order for frequency and intensity of sound presentations. The number of reliable responses elicited by distraction testing may be limited, particularly in children over 12 months who may habituate to the test. It is therefore important to prioritize and focus on those thresholds which would be most valuable for each clinical situation but normally aim to include high-, mid- and low-frequency information. This, however, may need to be balanced against the benefit of varying the order and side of presentation simply to sustain the child's interest.

Variable intervals between presentations and control 'no sound' trials are essential for the validation of response thresholds in a distraction test and a scoring system should be employed in the same manner as for VRA (see above). Tactics such as increasing the interest of the distracting activity and/or maintaining that activity while the sound/no sound is presented may avoid 'clueing in' the child. This may be particularly helpful in children over 1 year. Evidence of visual, tactile or even olfactory clues must also be considered and addressed. The MRL is regarded as the quietest level at which two out of three clear responses are recorded for each particular sound stimulus. The MRL for distraction testing may be worse than for VRA and clinical judgement is required in interpreting the results.[14] Other observations such as the ability to localize the sound source correctly or any concerns about the test reliability should also be recorded.

TEST METHOD PITFALLS IN BOA, VRA AND DISTRACTION TESTING

Table 9.1 lists the most commonly encountered pitfalls in BOA, VRA and distraction testing and possible measures to avoid them.

PERFORMANCE TESTING (PLAY AUDIOMETRY)

Key developmental age: 2–5 years

The performance test was first described by Ewing and Ewing[27] as a transitional technique suitable for children from 2.5 years and in some cases younger, until cooperation with pure tone audiometry can be achieved. It follows the simple principle that the child is conditioned to wait for a sound and then to respond with a play activity. The test method is described with reference to McCormick.[29]

Test method

The child should be seated on a low chair adjacent to the parent in an uncluttered room with low levels of ambient noise.[17] A toy is placed on a low table in front of the child (Figure 9.3). Toys which involve a simple repetitive activity are most suitable, such as the classic 'men in a boat', balls on sticks, or pegs in a board. The conditioning sequence starts with the tester engaging the child's attention by holding the response item (e.g. the wooden man) poised waiting in front of the child. After a few seconds, a suprathreshold sound stimulus is presented and the tester responds by an appropriate activity, such as placing the man in the boat. This sequence is repeated several times,

TABLE 9.1 Pitfalls encountered in behavioural observation audiometry, visual reinforcement audiometry and distraction testing

Pitfalls	Avoidance measures
Attempting conditioning to sub threshold stimuli	Cautiously increase intensity of stimulus until a response is elicited
Visual, tactile, olfactory clues from parent, distractor or second tester	Critical observation of all parties 'No sound' control trials
'Checking' responses by child	Critical assessment of responses 'No sound' trials, if necessary take a break, or sustain distraction activity
Loss of interest in test, suprathreshold responses	Vary the sound stimulus Exchange roles of distractor or second tester Use broader band or more interesting sounds
Inaccurate estimation of frequency and intensity of stimulus	Use calibrated sound sources Measure accurately with sound level meter, trying to reproduce conditions
Extraneous noise, leading to false responses or only suprathreshold response	Use a sound-treated room with ambient noise <30 dB(A) Observe other auditory clues, e.g. clicking switch on warbler 'No sound' control trials



Figure 9.3 The performance test.

often supported by gestures such as a stop sign using the palm of the hand and a cupped hand to the ear to indicate listening. This has the advantage of avoiding dependence on spoken language. The child is then offered the response item and guided to wait and perform the task as shown. Vocal praise and possibly clapping should be used to reinforce a correct response. The number of repetitions required to successfully condition the child will depend on their age, developmental status and willingness to cooperate and in particular their ability to inhibit the response until the signal is detected. It may be necessary to increase the intensity of the signal or initiate conditioning using a vibrotactile stimulus.

Once the child has been successfully conditioned to perform the test without guidance, a flexible descending/ascending technique as described for pure tone audiometry (see Chapter 51, Psychoacoustic audiometry) can be applied to determine the MRL. While the MRL should be determined by a two correct responses out of three method, using the 10 dB down, 5 dB up technique, it may be appropriate to ascend and descend in larger steps to hone in on the threshold, as described for VRA (see above). The interval between presentations must be randomly varied to avoid a predictable rhythm. 'No sound' trials should be included. It may be necessary to reinstruct the child by guiding a few responses when the stimulus is changed or if the child appears to have lost concentration. It may also be necessary to introduce several changes of activity to sustain interest. This provides the tester with an opportunity to be adaptable and inventive and is part of the joy of audiology! Examples might include knocking the man off the table, flicking a small ball into a 'goal', or banging a drum. The aim is to be fun enough to motivate the child while being accurate enough to provide valid responses.

In the original description of the performance test, the signal used was a voiced 'go' (low frequency), or a sibilant 's' (high frequency).[27] When using voiced signals, it is essential that the face is totally outside the child's visual field and the mouth is shielded to prevent any awareness of air movement. The tester should therefore adopt a position similar to that described for distraction testing. Frequency-modulated warble tones with stimulus duration of 1–3 seconds are now the preferred option, providing low-, mid- and high-frequency-specific signals delivered by means of portable soundfield noise generators, loudspeakers, insert earphones (using the child's own ear moulds if available) or bone conductor, used in a similar arrangement to that described for VRA. The technique is particularly useful for recording aided soundfield responses. Whatever the signal, it is essential that the test conditions are reproduced accurately to calibrate the intensity delivered to the child's ear. The sequence of presentation should be determined by the clinical priority but would typically be 1 kHz–2 kHz–4 kHz–0.5 kHz then possibly 8 kHz, 0.25 kHz, 3 kHz and 6 kHz as indicated.

PURE TONE AUDIOMETRY

Key developmental age: 3 years onwards

The techniques employed in performance testing (play audiometry) naturally lead into pure tone audiometry as the child matures. This progression should be adapted to the individual child's ability and cooperation and to

the clinical priority. It may be possible, for example, to introduce a bone conductor before a child will tolerate headphones or, alternatively, a child who is accustomed to wearing hearing aids may comply with insert earphone audiometry via their ear moulds, as a progression from VRA. Insert earphones have the advantage of increasing transcranial attenuation reducing 'crossover' and of reducing the effect of ear canal collapse which may occur with supra-aural headphones. Again, it is important to sustain interest and concentration by the appropriate use of toys and praise.

The recommended procedures for pure tone audiometry[31] based on the Hughson and Westlake descending/ascending technique using 10/5 dB steps should be flexibility adapted (see Chapter 51, Psychoacoustic audiometry). There is no standard for the interpretation of results in children. Nielsen and Olsen[32] reported that it was possible to obtain at least six ear-specific air conduction thresholds from virtually 75% of 3-year-olds. An MRC multicentre otitis media study which examined a cohort of over 15 00 children found that there was only an improvement of 0.1 dB for bone conduction thresholds for each month of increase in age between 3 and 6 years. It was concluded that, by the age of 3 years, it should be possible to record hearing thresholds close to adult levels, if the child has conditioned adequately to the test.[33] The introduction of standard masking techniques, where appropriate, will depend on the child's cognitive developmental level and cooperation, but these may not be reliable until the age of 7 years.

AUDITORY SPEECH PERCEPTION TESTS

The ability to discriminate speech signals may be a valuable measure of functional hearing in children with normal to moderate degrees of impairment and is also increasingly used in the evaluation of more severely affected children supplied with hearing aids or cochlear implants. The test batteries developed for use in these latter situations are discussed elsewhere (see Chapter 51, Psychoacoustic audiometry). The tests described below represent a selection from a wide range available and are for use in more general clinical situations.

THE COOPERATIVE TEST

Linguistic developmental level: 18–30 months

The cooperative test is another test originally described by Ewing and Ewing[27] and requires the child to discriminate three different simple instructions, for instance having been handed a small toy, asked to 'give it to Mummy' or 'give it to teddy' or 'give it to baby'. Starting at a suprathreshold level, the voice is then dropped and visual clues removed by covering the mouth. A child with normal hearing may discriminate the instruction at 35–40 dB(A). This technique has been largely superseded by the more effective methods of assessing behavioural hearing thresholds such as VRA and by the more complex speech discrimination tests described below, but it may have some value if equipment and facilities are limited. It can obviously be adapted to suit different cultures and languages.

SPEECH DISCRIMINATION TESTS

Linguistic developmental level: 30 months onwards

A wide range of speech discrimination assessments are available and may be valuable in verifying hearing thresholds and in assessing the effectiveness of hearing aids or auditory implants.[34, 35] The choice of test will depend on the child's age, stage of linguistic development and home language and may be influenced by non-auditory factors such as access to language, specific language impairment and cognitive level.[36, 37] Several generations of toy and picture tests have been progressively developed and refined for the younger child including the Stycar test,[38] the Word Intelligibility by Picture Identification test (WIPI),[39] Northwestern University Children's Perception of Speech test (NU-CHIPS),[40] the Manchester picture test,[41] and the McCormick toy test,[42] which is widely used in the UK. This employs seven pairs of similar sounding nouns such as spoon/shoe or cup/duck, each represented by a small easily recognizable toy, placed on a table in front of the child in a quiet room, i.e. a closed-set assessment. Using live voice, the child is asked to 'show me the … spoon', etc. Having established an understanding, the voice level is dropped and visual clues removed by covering the mouth. The word discrimination threshold (WDT) is taken as the quietest level at which the child correctly identifies 80% of the toys including the paired consonants. For a child with normal hearing, this would be expected to occur at ≤40 dB(A). A digitized recorded version of the test is available which utilizes a small loudspeaker to deliver the instruction at variable intensities and this has been further developed to incorporate a scoring system using the ascending and descending principle to calculate the WDT, both in quiet and in the presence of a broadband noise signal. For children aged 2-5 years, a WDT at or less than 35 dB(A) in quiet is regarded as satisfactory, based on 71% correct responses for six reversals. The choice of words can be adapted for English as an additional language.[43, 44]

Further closed-set or 'forced-choice' speech test packages are available which examine more specific elements of consonant or vowel discrimination in quiet or in noise. In the Consonant Confusion Task (CCT)™, for example, the child is presented with nine sets of cards, each showing four pictures representing monosyllabic words containing the same vowel but different consonants such as cow/house/owl/mouse. The child is asked to point to the target word that they hear, presented at a calibrated level. Two of the four words in each set are repeated to reduce predictability. The percentage of correct responses can be calculated for each level and may be particularly valuable in verifying the effectiveness of a hearing aid programme.[45, 46] Other examples include the four alternative auditory feature (FAAF) test,[47] the imitative

test of speech pattern contrast perception (IMSPAC),[48] and the 'plurals test' which specifically assesses the ability to detect the word-final fricatives /s/ or /z/.[49]

Similar assessment tools are available in alternative languages.[50, 51]

Older children who have acquired appropriate linguistic skills, generally from around the age of 6–8 years may be compliant with formal speech audiometry, using open set tasks whereby they listen and repeat a word or sentence presented at a calibrated level in quiet or in noise to a single ear or binaurally. Original examples include the AB word list described by Arthur Boothroyd in 1968[52] and the BKB (Bamford-Kowal-Bench)[53] sentence list, which are widely used in children and adults and are described in Chapter 51, Psychoacoustic audiometry.

Monitoring tools using parental observation of auditory behaviour and language development are increasingly used to assess progress in children supplied with hearing aids and cochlear implants. Examples include LittlEARS® Auditory Questionnaire[54] for children under developmental age of 2 years and subsequently the Parents' Evaluation of Aural/Oral Performance in Children (PEACH)™ questionnaire.[55, 56]

HEARING ASSESSMENT IN CHILDREN WITH COMPLEX NEEDS

Approximately 30% of hearing-impaired children have an additional disability.[57] Children with global developmental delay have a particularly increased risk of hearing impairment and hearing assessment is therefore advocated for this group of children in addition to routine hearing screening.[58] However, this may be challenging and techniques must be appropriately adapted. For a child with complex needs, the test most suited to their developmental level rather than chronological age should be selected. Clear, simple demonstrations of conditioning tasks may require multiple repetitions to achieve understanding. In children with motor delay or physical disabilities, such as cerebral palsy, the required response must be tailored to the child's capability. In VRA, for example, it may be necessary to bring the visual reward closer and to accept an eye glance response. In distraction testing, a partial head turn, eye glide or stilling may be judged as an acceptable response provided it is reproducible and validated by 'no sound' trials. For performance testing and pure tone audiometry, the conditioning task may need to be modified, such as knocking a toy brick off a table with hands or feet, hitting a drum or observation of a reproducible body movement such as wriggling toes.

Visually impaired children are more likely to respond to familiar sounds or if the response is reinforced by a tactile reward such as puffs of air on the cheek.[59] The use of brightly illuminated reinforcers in a darkened room may facilitate VRA in the partially sighted.[15] Assessment of hearing in a child with autistic spectrum disorder may present a particular challenge, due to the characteristic self-directed behaviour and lack of shared attention, making interaction with the tester difficult, although the repetitive nature of performance testing may particularly appeal to some. Fear of the unfamiliar test room and staff may be addressed by building confidence over a number of visits. Pre-preparing the child by explanatory booklets or a personalized 'social story' may reduce the anxiety.[60, 61] Many children with autistic spectrum disorder have sensory processing issues resulting in sound sensitivity and care must be taken to provide reassurance and avoid distress.[62]

If the outcome of behavioural hearing assessment for a child with complex needs proves to be inconclusive, consideration should be given to objective electrophysiological measurement, which may require sedation or anaesthesia.[5]

BEST CLINICAL PRACTICE

- ✓ Be age-appropriate: use the test technique that is most suited to the child's age, developmental status and willingness or ability to cooperate.
- ✓ Be specific: know what you are testing. Calibrate the frequency and intensity of the sound stimulus.
- ✓ Be valid: reproducibility and use of 'no sound' trials are essential. Avoid other clues. Children can make good cheats.
- ✓ Be adaptable: non-standard techniques may be best in non-standard children.
- ✓ Be fun: children easily get bored and frightened. Their cooperation is required. Use toys and smiles – make it a game.

FUTURE RESEARCH

The only level 1 evidence and grade A recommendations cited in this chapter relate to the use of electrophysiological testing (ABR, OAE) for screening and diagnostic assessment in infants under 6 months of age.[1] Other test methods are essentially descriptive, having been progressively modified, based on expert experience and summarized in guidelines.[7, 15, 16, 30, 31, 35] While specific elements of the test protocols have been subjected to small-scale controlled studies,[12, 19–22, 43] the only large-scale studies available examine the feasibility of obtaining response thresholds using a test protocol, rather than its sensitivity or specificity.[16, 33] There is clearly a difficulty in performing blind controlled trials of obviously differing techniques. There are also no subject-specific definitive response thresholds available for comparison. Reliance is placed on intra- and inter-test/retest reproducibility, as an indication of accuracy.[8, 14, 16, 18, 23–26, 32, 36, 43, 54] Comparison of behavioural test response thresholds with subsequent pure tone audiometry thresholds cannot take account of fluctuating hearing levels during the intervening months or years.

There are therefore inherent challenges in conducting large-scale controlled trials. In the UK, emphasis has more recently been placed on establishing guidelines for good practice, promoting training and availability of equipment with the aim of improving equity of service.

KEY POINTS

- Accurate testing of hearing is essential in the diagnosis and management of childhood hearing loss.
- Testing and accurate assessment of the test results requires considerable skill and expertise.
- A 'menu' of tests is available depending on the child's age, the availability of expertise and the purpose of the test.
- More than one test method may be needed.
- Testing children with complex needs can be particularly challenging.

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FURTHER INFORMATION

American Speech-Language-Hearing Association (ASHA): http://www.asha.org/.
British Society of Audiology (BSA): http://www.thebsa.org.uk/.

CHAPTER 10

MANAGEMENT OF THE HEARING IMPAIRED CHILD

Chris H. Raine, Sue Archbold, Tony Sirimanna and Soumit Dasgupta

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: aetiology, deafness, hearing loss or hearing impairment, and child. The websites of the various associations shown in Box 10.1 are useful sources of information in this rapidly changing field.

INTRODUCTION

This chapter focuses on the general principles of the management of a child with stable or progressive sensorineural hearing loss including auditory neuropathy spectrum disorder (ANSD) (see Chapter 69, Auditory neuropathy spectrum disorder and retrocochlear disorders in adults and children).

Permanent childhood hearing impairment (PCHI) is defined as a confirmed permanent bilateral hearing impairment ≥40 dBHL (hearing level) averaged over the frequencies of 0.5, 1, 2 and 4 kHz in the better hearing ear. A PCHI can be conductive, sensorineural or mixed. The onset of hearing loss may be pre-natal, peri-natal or post-natal. The aetiology may be congenital or acquired.

The hearing loss may occur before (pre-lingual deafness) or after the child has acquired the ability to speak (post-lingual deafness). This distinction has important implications for education and management. Early identification and appropriate audiological, medical and educational intervention will help maximize the child's potential. Identifying and understanding the consequences of associated medical conditions, impairments and disabilities is also extremely important to provide the best opportunity for the child and the parents to make informed choices and plans for the future.

Earlier identification with universal newborn hearing screening (Chapter 8, Hearing screening and surveillance) is now practised in many developing -and most developed- countries. Improved audiological assessment techniques have provided a unique opportunity to confirm the exact nature and extent of the hearing loss within 8 weeks of birth, leading to very early habilitation with precise amplification and with diagnostic verification using well-developed and internationally

BOX 10.1

British Association of Paediatricians in Audiology www.bapa.uk.com[1]
British Association of Audiovestibular Physicians www.baap.org.uk[2]
British Society of Audiology http://www.thebsa.org.uk[3]
Genetics home reference http://ghr.nlm.nih.gov[4]
Hereditary hearing loss homepage http://hereditaryhearingloss.org[5]
NHS Modernising Children's Hearing Aid Service www.psych-sci.manchester.ac.uk/mchas[6]
NHS Newborn Hearing Screening Programme http://hearing.screening.nhs.uk[7]
The World Health Organization (WHO) www.who.int[8]
National Deaf Children's Society www.ndcs.org.uk[9]
British Association of Teachers of the Deaf www.batod.org.uk[10]

agreed techniques. Improved knowledge and understanding of aetiologies has made it possible to provide better information on the nature of the hearing loss, preventing deterioration in some cases and aiding identification of other system involvement, for example, retinitis pigmentosa in Usher syndrome and enlarged vestibular aqueduct in Pendred syndrome. Early confirmation of hearing loss, early amplification, early assessment of benefit from hearing aids, early understanding of important medical and aetiological factors, and early cochlear implantation have all led to much better audiological, educational and longer-term outcomes. This progress depends on multidisciplinary working, agreed professional guidelines, and the involvement of families and those with a hearing loss themselves.

The terms 'deafness' and 'deaf' are used in this chapter to cover moderate, severe and profound hearing loss. This is not to imply that mild hearing losses should be ignored. The severity of hearing loss or deafness may not necessarily have a direct relationship with disability (see WHO definition of impairments, activity limitations, and participation restrictions). These terms are discussed in a chapter on the special needs child (Chapter 5, The child with special needs).

According to the WHO[11] there are 466 million people worldwide with disabling hearing loss, i.e. hearing loss greater than 40 dB in the better hearing ear in adults (432 million) and a hearing loss greater than 30 dB in the better hearing ear in children (34 million). The majority live in the middle- and low-income countries of South Asia, Asian Pacific and sub-Saharan Africa.

CLASSIFICATION AND MEASURES OF HEARING LOSS

Although dBHL is an internationally agreed measure, there are differences in the classification and categorization of hearing loss between various organizations. It is important to describe which classification is employed and the frequencies used to average so that comparison can be made.[12–16] Classification of hearing losses by hearing thresholds is shown in **Table 10.1**.

TABLE 10.1 Four commonly used systems

dB HL	WHO	NHSP	BSA[13]	ASHA[12]
Normal	≤25	≤20	<20	–10 to 15
Slight	26 to 40			16 to 25
Mild		21 to 39	20 to 40	26 to 40
Moderate	41 to 60	40 to 69	41 to 70	41 to 55
Moderately severe				56 to 70
Severe	61 to 80	70 to 94	71 to 95	71 to 90
Profound	≥81	≥95	>95	>90

WHO World Health Organisation; NHSP Newborn Hearing Screening Programme; BSA British Society Audiology; ASHA American Speech-Language Hearing Association.

EPIDEMIOLOGY

The incidence of a child born with a PCHI is typically quoted as 1 per 1000 births. Fortnum et al.[17] reported an adjusted prevalence of 1.07/1000 and this may rise to 2.05/1000 amongst children 9 years or older,[17] as PCHI may present well after birth as a result of late onset congenital progressive or non-progressive hearing loss, either conductive or sensorineural. According to the NHS Newborn Hearing Screening Program (UK) from December 2012 to December 2013, the incidence of confirmed *bilateral* PCHI was 0.76%, while the figure for *unilateral* loss was 0.46%. About one third of all children with PCHI have severe to profound sensorineural hearing loss (SNHL). About one third of children with sensorineural PCHI will have a simultaneous vestibular weakness. Figures are considerably higher in developing countries.

AETIOLOGY

Hearing loss in a child may be present at birth ('congenital') or may develop after birth ('acquired'). Management of a child with confirmed PCHI requires a holistic approach for optimal audiological care with supporting services for the child and the family and also appropriate medical management, which includes offering and arranging necessary investigations to determine the aetiology. Most children with a PCHI have a SNHL. Those children who have a purely conductive hearing loss may have some congenital conditions, such as ossicular abnormalities and bilateral aural atresia. (Chapter 12, Congenital middle ear abnormalities) Some may have a mixed hearing loss, many have a fixed loss but others have a progressive hearing loss. In children, especially during the first 5–6 years of life, acute otitis media (AOM) and middle ear effusions ('glue ear') are common with a much greater prevalence than PCHI. Children with PCHI especially with craniofacial abnormalities are also vulnerable to AOM and to middle ear effusions, making their hearing loss temporarily worse. This is even more important in those who have unilateral hearing loss as their ability to hear is significantly compromised during such episodes (see Chapter 13, Otitis media with effusion and Chapter 14, Acute otitis media).

Infections causing a hearing loss include congenital conditions such as rubella and cytomegalovirus (CMV), and acquired childhood infections such as mumps, measles, meningitis and chronic otitis media. In the developed world, deafness from meningitis is declining because of HiB and Meningitis C vaccination and over half of children with PCHI have a genetic cause for their deafness.[18]

The causes of PCHI are shown in **Table 10.2**.

Genetic causes

Hereditary or genetic hearing loss results from aberrations in the coding function or processing of human DNA. In the Western world genetic factors are now thought to be responsible for over half the cases of congenital SNHL but with more genetic tests becoming available, and the pressure to perform them, this proportion is expected to

TABLE 10.2 Causes of permanent childhood hearing impairment

Causes of hearing impairment		
Congenital disorders		
Genetic	Syndromic	Autosomal recessive
		Autosomal dominant
		X-linked
		Mitochondrial
	Non-syndromic	Autosomal recessive
		Autosomal dominant
		X-linked
		Mitochondrial
Non-genetic	Congenital rubella syndrome	
	Cytomegalovirus First-trimester maternal infections (viral or bacterial)	
	Congenital syphilis Toxoplasmosis Hyperbilirubinemia Low birth weight Birth asphyxia Drugs during pregnancy, such as aminoglycosides, some antibiotics, anti-epilileptic drugs, cytotoxic drugs, antimalarial drugs, and diuretics. Maternal substance abuse e.g. alcohol, recreational drugs Maternal endocrine disorders e.g. diabetes mellitus, thyroid dysfunction 'Third window' disorders (see text, aetiology often unknown, may be congenital or acquired)	
Acquired causes		
Perinatal	Hypoxia	
	Hyperbilirubinemia	
Postnatal	Infections	Chronic otitis media
		Herpes Meningitis
		Mumps
		Measles Toxoplasmosis Varicella
		HIV
	Ototoxic drugs	
	Trauma / noise exposure	
	Neoplastic disease Foreign bodies in ear canal Immune system disorders	
Idiopathic		

rise significantly.[8, 19, 20, 21] About 70% of children with PCHI are considered to be non-syndromic (**Figure 10.1**) and the remaining 30% have one of a large variety of syndromic conditions.[22] Genetic hearing loss is mainly of monogenic phenotype. The majority ≈80% are autosomal recessive typically presenting pre-lingually, and some 20% are autosomal dominant, more typically presenting as progressive or post-lingual[23] with about 1% with X-linked or mitochondrial inheritance in which the trait is passed through the maternal lineage (see Volume 1, Chapter 2, Genetics in otology and neurotology).[24]

The gene mutations related to non-syndromic hearing loss are currently reported on web pages such as http://hereditaryhearingloss.org[5] and http://ghr/nlm.nih.gov.[4] Identification is labour intensive and expensive but with advancement in techniques new platforms are being applied.[25] Screening with Sanger sequencing for *GJB2* mutations is commonly performed, as they account for about 20% of autosomal recessive non-syndromic hearing loss (ARNSHL) for families in Northern Europe. Mutations in the pendrin gene *SLC26A4* are the next most frequent cause of ARNSHL.[21] The carrier

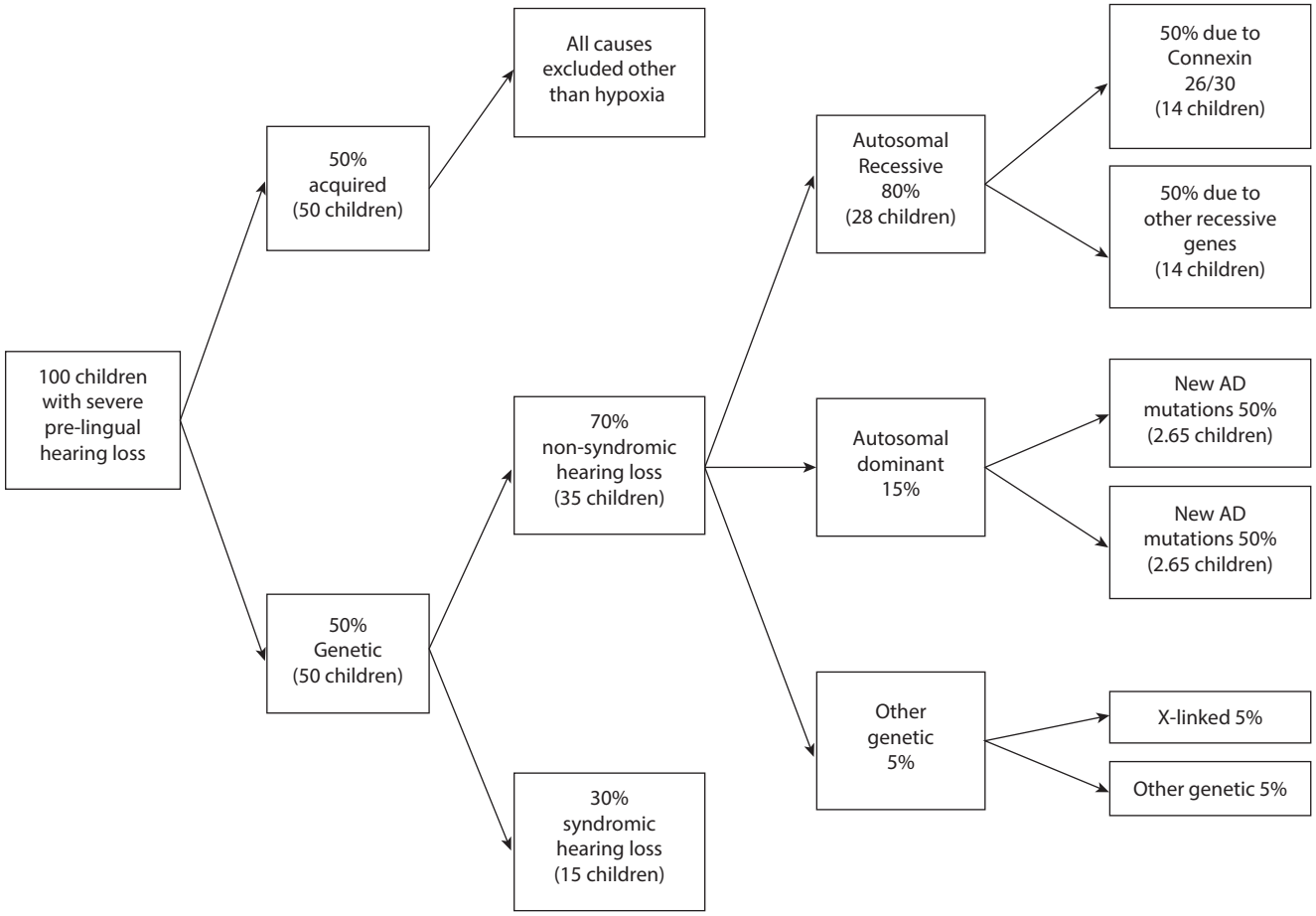


Figure 10.1 Aetiology of hearing loss in children.

rate in the general population for a recessive deafness-causing *GJB2* mutation is about one in 33.[26] Syndromic SNHL is found in conditions such as Pendred syndrome, Branchio-oto-renal syndrome, Usher syndrome and Waardenburg syndrome, amongst others.[19, 20] Conductive hearing loss is commonly encountered in Down syndrome and Treacher Collins syndrome likely to be due to the craniofacial abnormality encountered in these syndromes.

Congenital infection causing hearing loss

Maternal infections are still responsible for a significant proportion of acquired hearing loss, especially in developing countries, although vaccination has greatly reduced the incidence. The distribution of genetic hearing losses are shown in **Figure 10.1**.

Cytomegalovirus (CMV)

Congenital CMV, a herpes virus, is now the most common cause of non-hereditary SNHL in the developed world.[27, 28] CMV infection occurs in about 1% of pregnancies and 40% of affected mothers pass the virus on to the baby. In the UK congenital CMV affects 0.3–0.5% live births, but the incidence varies from 0.2% to 2.2% in other parts of the world.[28–30] Maternal infection within the first trimester is associated with greatest risk.[31] The hearing loss can be of delayed onset giving challenges in predicting which children with congenital CMV infection will develop hearing loss and whether or not the loss will continue to deteriorate.[32] About 30–50% have a unilateral hearing loss that may progress to a bilateral SNHL, so audiological monitoring is important.

Congenital rubella syndrome (CRS)

CRS is probably the most important cause of congenitally acquired hearing loss in countries with no rubella vaccination programme. CRS occurs when there is maternal infection with the rubella virus in the first trimester of pregnancy. It leads to a number of abnormalities in the child including deafness, ocular defects (cataracts, glaucoma), cardiovascular anomalies (patent ductus arteriosus, pulmonary artery stenosis and ventricular septal defects), central nervous system problems (microcephaly, global retardation) and characteristic skin changes (**Figure 10.2**).[33]

The WHO has recommended vaccination against rubella.[34] Two approaches have been suggested: prevention of CRS only, through immunization of adolescent girls and/or women of childbearing age; and elimination of rubella, as well as CRS through universal vaccination



Figure 10.2 Congenital rubella with characteristic skin rash. The child was profoundly deaf. Courtesy of J Verbov, Emeritus Professor of Paediatric Dermatology, Royal Liverpool Children's Hospital, Alder Hey.

of infants and young children.[35, 36] This latter is the norm in most developed countries where CRS deafness is almost unknown.[37]

Syphilis

Syphilis is caused by the bacterium *Treponema pallidum*. It is a common infection in much of the developing world and has recently re-emerged in parts of the developed world. The main route of transmission is sexual contact, but syphilis can also be transmitted from an infected mother to her baby (congenital syphilis). Congenital infection can occur at any stage during pregnancy, but the highest likelihood of damage to the fetus is when infection occurs and is untreated during the first or second trimesters. During primary syphilis, the rate of vertical transmission in untreated women is 70–100%; this drops to 10–40% in the latent stage of the disease. The poorest prognosis is for an infant infected during the first or second trimester by a mother in the primary or secondary stages of disease. Hearing loss is a late feature of congenital syphilis and often appears as one of a group of signs known as 'Hutchinson's triad'. These include inflammation of the cornea giving it an opaque appearance, which leads to loss of vision, peg-shaped upper incisors (Hutchinson's teeth) and VIIIth cranial nerve deafness. Hearing loss is the least common component of Hutchinson's triad and occurs in around 3% of children with late congenital syphilis. It typically appears when the child is 8–10 years of age, although occasionally it may be delayed until adulthood. Onset is sudden and damage to the cranial nerve is thought to result from a persistent and ongoing inflammatory response to the infection. Loss of hearing may be unilateral or bilateral and initially involves higher frequencies, with normal conversational tones affected later.[38] Syphilitic hearing loss is uncommon.[39] Congenital syphilis can be treated with high-dose penicillin, but is best prevented by identification and eradication of the infection in the mother. Pre-natal screening for syphilis is commonplace in developed countries and is the main priority for prevention of the disease in developing countries.[38]

Toxoplasmosis

A systematic review on neonatal toxoplasmosis showed that the use of anti-parasitical therapy initiated early showed very encouraging results in preventing SNHL. Children with congenital toxoplasmosis that had no treatment, partial treatment, delayed onset of treatment, or compliance issues should undergo annual audiological monitoring until able to reliably self-report hearing loss.[40]

ACQUIRED CAUSES

While the frequency of infections has dropped with the introduction of vaccines, a concomitant improvement in the survival rates of pre-term babies has increased the proportion of babies with hearing loss related to perinatal events, including stays in the neonatal intensive care unit (NICU). Pre-term and low-birth-weight infants are particularly susceptible to factors such as hypoxia and hyperbilirubinaemia. Davis and Wood[41] showed that babies admitted to a NICU for more than 48 hours were 10.2 (95%, confidence interval 4.4–23.7) times more likely to have a permanent hearing loss (greater than 50 dBHL in this study) than those who did not undergo intensive care.

Hypoxia is associated with apnoea, difficult delivery, low Apgar scores and use of ventilation. It is known to be associated with neurodevelopmental deficits, but the exact mechanism of hypoxia-related hearing loss is unclear. Although most believe that brain cells are more susceptible to hypoxia than the hair cells in the inner ear, there is some emerging evidence that apoptosis of hearing cells can occur without any injury to brain cells.[42]

Hyperbilirubinemia is an independent risk factor for SNHL in infants. High levels of unconjugated bilirubin have been associated with neuronal damage. The auditory brain nuclei and the inferior colliculi are often the first

part of the brainstem to be involved, often leading to hearing abnormalities.[43] These infants are more often than not nursed on a NICU, where they may receive ototoxic drugs, such as aminoglycoside antibiotics (e.g. gentamicin, tobramycin and amikacin) and diuretics (e.g. furosemide). Aminoglycoside-induced and non-syndromic deafness have been shown to have a genetic susceptibility and the pathogenic mitochondrial 12S rRNA. A1555G mutation was identified as the primary factor underlying the hearing loss in many familial as well as in genetically unrelated cases; also see ototoxicity in acquired causes of hearing loss.[44, 45]

Other causes of permanent acquired hearing loss include bacterial meningitis, chronic otitis media, mumps, measles, trauma, ototoxic drugs and head injury.

Meningitis

The most common cause of acquired PCHI is childhood bacterial meningitis. The risk of developing significant sensorineural impairment after bacterial meningitis has been estimated at approximately 10%.[46–49] but this varies depending on the organism. In the developed world Haemophilus influenza B (HiB) and Meningococcus C (Men C) vaccinations have led to significant reduction in these infections.

All patients should have early audiological assessment after an episode of meningitis. Patients identified with severe to profound loss should be 'fast tracked' for an assessment by a cochlear implant centre to minimize delay as ossification of the cochlear duct can make implantation difficult or even impossible (see Chapter 94, Cochlear implants).

Measles

Measles is a highly infectious viral illness, which presents acutely with high fever, running nose, characteristic Koplik's spots on the buccal mucosa and a distinctive generalized maculopapular rash (**Figure 10.3**). It occurs worldwide but its incidence has reduced significantly in developed countries since the introduction of an effective vaccine in 1968. It is predominantly a disease of infants and young children and occurs mostly after the age of 6 months. Globally, measles is the leading cause of vaccine-preventable child deaths.

Measles has been reported as a major aetiological factor for mild to moderate bilateral hearing loss in deaf children. As it was known that mucous membranes all over the body were affected, the observed hearing loss was previously thought to be conductive and attributable to suppurative otitis media, chronic perforation and mastoiditis, but SNHL occurs as well.

The WHO and United Nations Children's Fund (UNICEF) have emphasized primary prevention of measles in its global campaign against the prevailing childhood illnesses in the developing world for several decades. Immunization for measles can be administered as a single vaccine or as the triple MMR (measles, mumps and rubella) vaccine.



Figure 10.3 Child with maculopapular rash characteristic of measles. Courtesy of J Verbov, Emeritus Professor of Paediatric Dermatology, Royal Liverpool Children's Hospital, Alder Hey.

Mumps

Mumps, caused by infection with the mumps virus, is a non-suppurative enlargement of the salivary glands, particularly the parotids (see Chapter 39, Salivary glands). The infection may be subclinical in up to one third of the cases and in these the first presentation may be the appearance of complications. SNHL as a result of mumps is mostly unilateral and severe to profound, although bilateral loss has been described. The incidence of mumps-related SNHL has been reported as 0.5–5/100,000.[50]

Ototoxicity

'Otoxicity' refers to pharmacological agents that can cause a hearing loss with or without a vestibular loss usually at the cochlear level. The mechanism of action is by their action on the apoptotic pathway of cochleovestibular hair cells where generation of reactive oxygen species is a rate limiting step. The agents implicated are the aminoglycoside group especially gentamicin and tobramycin, chemotherapeutic agents especially the platinum derivatives cisplatin and carboplatin, vinca alkaloids, cyclophosphamide and methotrexate, anti-malarials including chloroquine, diuretics especially frusemide and ethacrynic acid, and iron chelators like desferrioxamine. These agents are not infrequently used in the paediatric population especially in cystic fibrosis, cancers and in paediatric haematological conditions. Chemotherapy ototoxicity monitoring protocols with subjective and objective assessment of hearing and vestibular function is required

to adjust therapeutic dosage. Genetic susceptibilities are reported with both gentamycin and cisplatin ototoxicity.[51]

Autoimmune ear disorders (AIED)

Autoimmune ear disorders can either be primary or secondary. Primary AIED affects only the cochleovestibular apparatus and the hearing loss is non-syndromic with autoantibodies directed only against the inner ear whilst secondary AIED affects multiple organs being part of the wider connective tissue disorder spectrum including rheumatoid and juvenile arthritis, the inflammatory bowel disorder group and for that matter any autoimmunity disorder.[52] The exact prevalence or incidence of AIED in children is unknown. The hallmark of this condition is a sudden SNHL with variable vestibular involvement which is responsive to steroids. Hearing can be salvaged during the acute phase within a critical time frame of 72 hours but in many presentations, this time period may be exceeded leading to a permanent irreversible hearing loss. Diagnosis is still a matter of controversy and inflammatory markers may not be raised especially in primary AIED. Therefore, all children presenting with sudden SNHL should receive a diagnostic and therapeutic steroid administration and a full workup of autoimmune markers.

Third window disorders

A condition involving the bony labyrinth may lead to a mixed hearing loss and can mimic other conditions. These conditions are called third windows and examples include semicircular anal dehiscences, enlarged vestibular aqueducts, X-linked gusher syndromes and dilated internal auditory meati (see Chapter 48, Physiology of hearing). Usually the vestibular system is also affected; therefore, a full vestibular quantification is necessary. In the paediatric population, this is not well researched but is now recognized as a condition which can often be missed.[53]

NEWBORN HEARING SCREENING

It has been shown that early diagnosis of PCHI has an important bearing on outcome. Several studies have demonstrated that children whose hearing losses were identified by 6 months of age demonstrated significantly better receptive and expressive language skills than did children whose hearing losses were identified after the age of 6 months.[54–56]

Prior to introduction of the newborn hearing screen in England and other countries within the UK, infant distraction test (IDT), first used in 1960s, was used as a hearing screening test until early 1990s. It was usually carried out by health visitors at the age of nine months within the community. IDT had neither high sensitivity nor specificity. As a result, a large number of children with normal hearing were referred for further investigations. More worryingly, almost one quarter of children born deaf were not identified until they were over 3.5 years of age.[57, 58] These concerns led to a Health Technology Assessment[59] of hearing screening in England and subsequently setting up of a newborn hearing screening programme (NHSP). As a result of universal neonatal screening in England, the median age of detection of PCHI is now 10 weeks.[60]

Currently, in England, all children are screened with automated otoacoustic emissions (AOAE) as close to the time of birth as possible by a trained operator with over 95% of babies having the hearing screen completed by 4 weeks of birth in hospital hearing screening programmes and within 5 weeks of birth in community newborn hearing screening programmes. AOAE screen is sensitive to hearing losses from 1 to 4 kHz while automated auditory brainstem response (AABR) detects hearing loss in the 2–4 kHz frequencies of more than 40 dBHL. The result of the screen is either a 'pass' or 'refer'. In addition, all NICU babies have AABR screen in addition to AOAE screen. This is because there is a higher incidence of children with permanent hearing loss (including auditory neuropathy, the latter estimated to be 0.9%) whose AOAE test would give a 'pass' result. Normally, a 'well' baby who passes the AOAE screen in both ears would be discharged so anyone in this group with ANSD(see Chapter 69, Auditory neuropathy spectrum disorder and retrocochlear disorders in adults and children) will be missed at this stage. Fortunately only 5–7% of all ANSD patients come from the 'well baby' population. On the other hand babies from NICU will have both AOAE and AABR screening tests and therefore anyone with a moderate or greater cochlear or neural hearing loss (up to the brainstem) should be identified by the NICU screen protocol.

In some babies the hearing loss could be progressive, and may develop after birth. As passing a hearing screen at or soon after birth can give a false sense of security to parents and professionals alike, it is extremely important to be vigilant so that any future suspicion of hearing loss is investigated promptly. In most countries there is some form of targeted follow-up of the babies with a risk factor, who passed the neonatal hearing screen.

More information on screening can be found in Chapter 8, Hearing screening and surveillance.

Unilateral hearing loss (single-sided deafness)

Screening has also resulted in early detection of unilateral permanent hearing loss. In the past, unilateral hearing loss (UHL) was considered to have little impact on speech and language development; this is not the case.[61] The yield for permanent unilateral moderate or greater hearing loss in the NHSP in England is 0.64 (95%, CI 0.37–0.91) per 1000 screened.[60] UHL can also be acquired as a result of trauma, infection, ototoxicity, metabolic disorders and surgery. UHL results in an inability to hear binaurally (from both sides), leading to difficulty in hearing speech in noise and poor localization of sound. Further, with frequent middle ear infections or effusions in the early years, those with a UHL may be at a greater risk of suffering with periods of significant hearing difficulties. School children with UHL may have increased rates of grade failures, need additional educational assistance and may

show behavioural issues in the classroom.[61] A unilateral conductive loss arising from atresia (absence of the external ear canal) has also been shown to have an impact on academic performance.[62]

It is unclear if children always 'catch up' as they grow older.[61, 63]The impact of UHL on language development and educational performance varies considerably but it needs to be kept in mind.[64] It is important to assess these children on an individual basis and make available appropriate support if needed, but many children can be managed expectantly.

Current practice is that UHL is investigated to identify progressive pathology or conditions that might affect the other ear, e.g. dilated vestibular aqueducts. Audiological management of children with UHL includes regular monitoring of their educational performance and maintenance of their technology by their teachers supported by specialist advisory teachers of the deaf (ToD), and environmental modifications including minimizing background noise and reverberation in the classroom and preferential seating nearer the teacher. More recently an increasing number of children with UHL have been fitted with and benefited from various hearing devices including contralateral routing of signal (CROS) hearing aids, bone conducting hearing implants (BCHI)) and FM devices such as iSense (see Chapter 93, Bone conduction hearing aids).[64–67]

Progressive hearing loss

Some children have normal hearing or only a mild loss at birth, but develop progressive hearing loss with time. Prevalence of permanent SNHL almost doubles by the second decade of life.[17] This group includes those with progressive as well as post-natally acquired hearing loss, highlighting the importance of continuing vigilance.

In countries where universal neonatal hearing screening has not yet been established, identification of children with PCHI is still dependent on parental or teacher suspicion, locally arranged behavioural screening programmes or questionnaires and preschool screening. In a questionnaire-based study in Nigeria, only 12% of parents of a child with hearing loss suspected hearing difficulty by the age of 6 months. Parental suspicion occurred mostly at 12–24 months, compared with 8–14 months in developed countries. The most common mode of detection was a child's failure to respond to sound (49%).[68] Since this study Nigeria has started a newborn hearing screening programme leading to early detection of hearing loss in that country.[69]

Progressive hearing loss may be due to genetic or environmental causes. In some syndromes such as Pendred syndrome, the hearing loss is typically progressive. Non-syndromic hearing loss related to a variety of known and unknown mutations can also be fluctuant or progressive.[70] Some infections such as congenital CMV and occasionally congenital syphilis can cause late-onset or progressive hearing loss. Similarly, children who contract bacterial meningitis, viral infections such as mumps and measles, chronic otitis media, suffer trauma including noise exposure or ototoxicity (e.g. aminoglycosides, platinum drugs) require audiological assessments. Early detection of hearing loss in these groups is based upon surveillance of at-risk groups (e.g. children undergoing chemotherapy) and parent/teacher/medical staff suspicion.

This group poses a challenge, as neonatal screening will not identify them and school entry screening no longer takes place in the UK. Identification of these cases therefore is dependent upon a high degree of suspicion in children with known associated syndromes, careful surveillance and prompt assessment in response to parent or teacher concern regarding hearing or speech and language development.

THE NEWLY DIAGNOSED DEAF CHILD AND FAMILY

For the majority of parents, having a child with hearing loss is completely unexpected; about 95% of deaf babies are born to hearing families.[71]

Parents remember with clarity the day they were told their baby was deaf, and cumbersome inexpert handling of this scenario can have profound adverse long-term effects. An experienced empathic team that works in a coordinated way with the family and can present a knowledgeable and non-partisan approach to the various options and resources available makes for the best outcome for parents and child. Now the diagnosis is likely to take place very early in the child's life while parents are adjusting to being parents and it is even more important that time is made available for them and that they are supported in the early days.

Parents may experience a range of emotions following diagnosis of hearing loss, including shock, confusion, depression, anger and guilt.[72] The presence of a child with hearing loss has often been linked with psychosocial stress in the parents and other family members,[73] but better information regarding screening and rehabilitation help families to deal with the trauma. The degree of hearing loss does not seem to influence the parents' reactions. In fact, stress levels were found to be higher in the parents of children with less severe hearing loss.[74] This might be because the child with a less severe hearing loss may at least sometimes respond to some sounds, which can delay the parents' adjustment to the hearing loss and confuse the diagnosis. Parents and healthcare professionals are faced with a series of dilemmas and challenges when it is established that a child is deaf. Parents will have questions regarding the reason for the hearing loss, prospects for development of the child – especially speech and future communication – and educational needs. Many of these questions cannot be answered straight away but parents are often required to make decisions without having time to take in the information they have been given before they have been able to adjust to having a child with hearing loss. Ensuring that parents and child develop effective early communication skills is vital to support language development.

The impact of the diagnosis on parents and family can remain in the long term when the further implications on education, social life and self-esteem become apparent. It is therefore vital that the process of screening and diagnosis is carried out by experienced multi-professional teams and that parents and family have continuing support.

Meeting other families has been found to be useful and the National Deaf Children's Society[9] provides helpful services and resources, as does SoundSpace.[75]

Medical management

While appropriate and optimum amplification along with early support is essential to achieve the best audiological outcome, deafness is a symptom rather than a definitive diagnosis, and it is important to identify the underlying cause and associated conditions, if any, as these may need their own management. A holistic approach often leads to better overall outcomes. for the child and family.

Medical management consists of a developmental assessment and identifying coexisting medical conditions as well as carrying out an extensive investigation into finding the cause of the deafness. It is therefore essential for every audiology team to have an appropriately trained medical practitioner, preferably at consultant level, to provide this aspect of care and support for children diagnosed with a hearing loss, and for their families. Investigating aetiology is an important and integral part of the management of a child with hearing loss at any age primarily to answer two questions:

1. How might the hearing loss evolve? This, in turn, alleviates uncertainty.
2. Is there a genetic factor for patients and parents/carers? They can be counselled from a genetic point of view.

In the UK, national guidelines for investigating the aetiology of PCHI were developed by the British Association of Audiological Physicians[2] in conjunction with the British Association of Paediatricians in Audiology[1] and are available on those two websites. It is recommended that core investigations are offered to the parents of all children with a newly diagnosed SNHL, while 'additional' investigations are dictated by individual circumstances and the findings of core investigations (Table 10.2). Parents may not wish to pursue investigations at such an early stage, the results of which in many cases may have no immediate impact on the management of the child and the family, but it is essential that healthcare professionals are aware of the baseline investigations and can discuss the rationale behind various tests so parents can make an informed choice.[2] These guidelines are not always fully implemented.

The aims of aetiological investigations are:

- to try to provide reasons for the deafness for parents
- to identify conditions that may affect audiological and medical management
- to provide better advice to parents with regard to best management of associated conditions
- to assist the family in making educational and management decisions for the child
- to inform genetic counselling
- to inform epidemiological research.

The recommendation is that patients should undergo core investigations with additional investigations as dictated by the clinical scenario.

History

A detailed and careful history of the pregnancy, perinatal period and birth and the post-natal period including

TABLE 10.2 Core investigations for all cases of bilateral severe to profound sensorineural hearing loss

Investigation	
Paediatric history	Detailed history of pregnancy delivery and postnatal period. Developmental milestones including speech and language and motor milestones, pre- and postnatal noise exposure, history of ototoxic medications, head injuries, ear disease, meningitis, viral illness and immunization status
Family history	Deafness or risk factors associated with hearing loss in first- and second-degree relatives
Clinical examination	Inspection and physical measurement of craniofacial region, assessment of the neck, skin and nails, limbs, chest and abdomen. Developmental examination
Audiology	Age-appropriate assessment including tympanometry. Audiometry on first-degree relatives
Imaging	Magnetic resonance imaging of inner ears and/or computed tomography of petrous temporal bones.
Electrocardiograph	
Urine for microscopic haematuria and for CMV DNA PCR in neonatal congenital hearing losses	
Connexin 26 and 30 mutations testing with access to clinical genetics service for counselling	
Ophthalmic assessment	
Referral to clinical geneticist	
Vestibular investigations	
CMV serology	

infections and medication is invaluable. Wherever possible, maternity and birth-related notes should be examined. Note details of drugs used, if appropriate with doses, duration and the blood levels of any potentiating medication. If jaundiced, blood levels of unconjugated bilirubin levels and the baby's condition at the time e.g. acidosis etc. should be noted. A history of hypoxia should be explored in great detail including length of ventilation, blood gases, metabolic evidence of hypoxia and evidence of any other neurological effects including memory and learning difficulties. It is important to note that, although hypoxia alone does not cause isolated sensorineural loss, there is recent evidence that cochlear cell death can occur without evidence of hypoxic brain injury.[42] Family history of hearing loss, speech and language delay and medical conditions should be explored.

Clinical examination

All children with hearing loss of unknown cause should be evaluated for features associated with syndromic deafness. Important features include branchial cysts, sinuses, fistulae and pits, pre-auricular appendages and pits, telecanthus, heterochromia iridis, white forelock, pigmentary anomalies, high myopia, pigmentary retinopathy, goitre and other craniofacial anomalies, palatal abnormalities e.g. cleft palate, submucus cleft, high-arched palate and abnormalities of teeth etc. It is also useful to look for any dysmorphism in the immediate family.

Audiology

Skilled audiological testing must be performed to assess the severity of the hearing loss and to determine whether it is conductive, sensorineural or mixed. This is discussed in detail in Chapter 9, Hearing tests in children. This should include ear specific hearing thresholds with ear and bone conduction as appropriate and testing for neural involvement e.g. ANSD where appropriate as per NHSP) protocols.[76, 77]

Imaging

The aetiology of profound hearing loss in children is multifactorial. Cross-sectional imaging is extremely useful in the detection and management of congenital abnormalities. Generally computed tomography (CT) including 3D reconstruction would be useful for exploring conductive hearing losses, inner ear bony dysplasia and large vestibular aqueduct syndrome. It is also of use to define facial nerve anatomy, integrity of the ossicular chain and dimensions of the internal auditory canal. MRI scans are more likely to detect abnormalities primarily involving the membranous labyrinth, and lesions of the central auditory pathway in the internal auditory canal, cerebellopontine angle, brainstem and cerebral cortex.[78–80] Bamiou et al. reported that about 28% of children with profound and/or progressive hearing loss and/or craniofacial abnormalities have an abnormal CT scan whereas, the child's gender, consanguineous parents, or family history of SNHL were far less likely to be associated with CT abnormalities.[81]

Dilated vestibular aqueduct was significantly correlated with the presence of progressive SNHL. At least 40% of children with large vestibular aqueduct (LVA) will develop profound SNHL. An interesting meta-analysis by Spencer et al.[82] reported on the linear relationship of hearing loss to LVA duct diameter. The identification of LVA should raise the suspicion of Pendred syndrome and thyroid abnormality but it also occurs in Branchio-oto-renal syndrome (BOR).[19, 20, 83] Patients with LVA are at risk of progressive deafness after minor head trauma. Identifying this anomaly influences management as it prompts a search for treatable thyroid function anomalies and parents can be counselled with respect to the dangers of incidental head trauma.[73]

Imaging can highlight characteristics of congenital syndromes such as BOR, CHARGE, X-linked and Waardenburg syndromes. In later life, inner ear infections, inflammatory conditions, trauma and tumours come to the fore.[8]

Studies of unilateral SNHL strongly support the need for imaging. Abnormalities on CT imaging have been detected in between 28% and 66% of sequential observations (**Figure 10.4**). There is a slightly higher yield of radiological abnormalities with increasing severity of hearing loss and a significantly higher imaging yield with unilateral than with bilateral SNHL.[81, 85–87]

Imaging modalities and techniques are discussed in Volume 1, Chapter 57, Imaging in head and neck endocrine disease and Volume 2, Chapter 97, Imaging of the temporal bone.

Blood tests

Although routine blood tests such as full blood count (FBC), thyroid function tests, erythrocyte sedimentation rate (ESR), syphilitic blood tests, cholesterol and triglyceride levels, urea and electrolytes are carried out, abnormalities are rarely related to the cause of the hearing loss.[85] The use of these blood tests is dependent on clinical suspicion of various conditions although some tests may be used as generalized screening tests e.g. inflammatory markers. **Table 10.3** lists these tests.

URINALYSIS

Simple testing for proteinuria and haematuria can identify renal disease and can be found in Alport syndrome.

TABLE 10.3 Additional investigations

Investigations
Haematological and biochemical tests
Serological test for congenital rubella and other infections e.g. syphilis, toxoplasma etc.
Thyroid tests
Immunology tests
Metabolic screen blood and urinalysis
Renal ultrasound
Chromosomal analysis

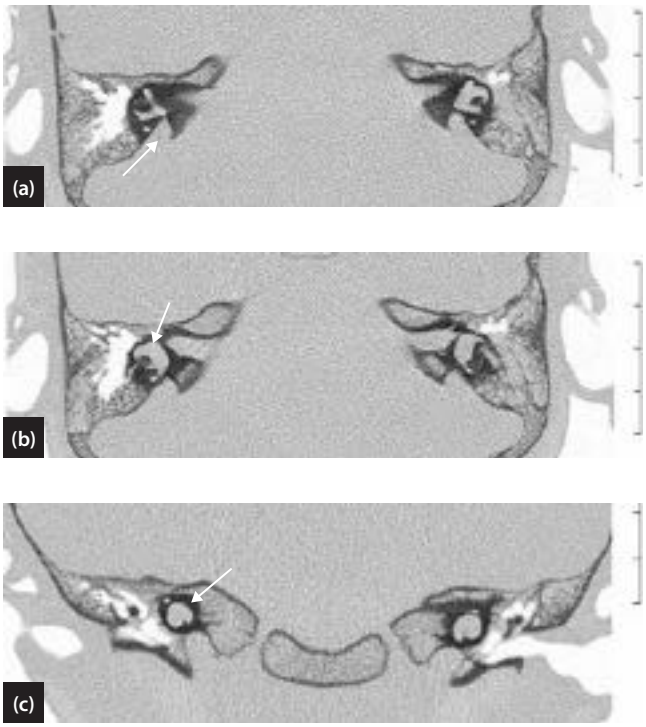


Figure 10.4 Typical appearances of a Mondini deformity in a child with bilateral severe sensorineural deafness. Axial high resolution CT scan through **(a)** dilated vestibular aqueducts and **(b)** a more inferior slice that shows bilateral dysplastic vestibules. **(c)** Coronal image through the abnormal cochlea showing typical Mondini abnormality with incomplete formation of the apical and middle turns of the cochlea. Images kindly supplied by D Saunders, Consultant Neuroradiologist, Great Ormond Street Hospital, London, UK.

SEROLOGY

Universal neonatal screening will detect less than half of all SNHL caused by congenital CMV infection[88] as the hearing loss in a large proportion of children with congenital CMV is progressive.[89] Laboratory testing has to be carried out in neonatal samples within 3 weeks of life for diagnosing congenital CMV. This presents difficulties as after 3 weeks of age, virus isolation could be due to acquired infection, which is not usually associated with adverse outcomes although there are a few publications suggesting extremely pre-term and immunocompromised babies can be susceptible to hearing loss from post-natally acquired CMV.[90, 91] Previous studies[28, 92, 93] have shown that dried blood spots on Guthrie cards collected at birth for the screening of metabolic disorders have proved a valuable tool for retrospective demonstration of CMV DNA for diagnosing congenital infection after months or even years of life. However, as the sensitivity of this test in symptomatic babies is around 90%, absence of CMV DNA in the dried blood spot does not necessarily exclude congenital infection. Infants who are born to sero-immune mothers are not completely protected from SNHL, although their hearing loss is often milder than that seen in CMV-infected infants following primary maternal infections. Late-onset and progressive hearing losses occur following congenital CMV infection and CMV-infected infants should be evaluated regularly to provide for early detection of hearing loss and appropriate intervention. Fluctuating hearing loss that is not explained by concurrent middle ear infections is another characteristic of CMV-related hearing loss in children.[32] Consideration for targeted screening and appropriate early treatment to reduce long-term morbidity is a potential option.[94, 95]

Rubella-specific IgG and IgM synthesized by the fetus are detectable at birth in CRS. However, since maternally derived rubella-specific IgG is also present in infants' sera, laboratory diagnosis of CRS is almost invariably made by detection of rubella-specific IgM responses. This response is detectable in almost 100% of CRS cases up to age 3 months with the most sensitive antibody-capture assays. The response declines progressively to less than 50% at 12 months and is rarely detectable after 18 months. It is therefore suggested that there is value in testing for CRS only if the deafness is identified within the first 6 months of life.[96]

OPHTHALMOLOGICAL ASSESSMENT

A comprehensive ophthalmic assessment is required as deaf children are heavily reliant on the sense of vision in order to develop efficient communication skills and explore the world around them. Any ophthalmic disorder needs to be recognized as soon as possible to optimize language development (spoken or sign, or both). These disorders may be correctable (such as myopia) or treatable (such as cataract). Those children with non-correctable and non-treatable visual disorders, like retinitis pigmentosa in Usher syndrome, require multiple environmental adaptations and appropriate support services and information.[97]

ELECTROCARDIOGRAM (ECG)

Deafness and electrocardiographic changes (prolongation of the Q-T interval and inversion of the T wave) with a clinical picture of syncopal attacks and sudden death, were described as a distinct syndrome by Jervell and Lange-Nielsen in 1957.[98] The syndrome is inherited as an autosomal recessive trait. This syndrome should be sought in children with syncope or a family history of it, especially those with congenital deafness.[99] Cardiologic control is required. The auditory and language outcomes after cochlear implantation in this syndrome are no worse than those in patients with non-syndromic sensorineural deafness.[100]

GENETIC SCREENING

The disorder DFNB1, caused by mutations in the *GJB2* gene (which encodes the protein connexin 26) and the *GJB6* gene (which encodes the protein connexin 30), accounts for about 50% of ARNSHL. The carrier rate in the general population for a recessive deafness-causing *GJB2* mutation is about one in 33 although this can vary according to racial background.[101] It is current practice

that the families of all children with bilateral PCHI are offered genetic screening for these two mutations. Establishing a molecular diagnosis of *GJB2*-related deafness is important clinically since these children can avoid some of the other aetiological investigations (although it must be remembered that dual pathology could exist) and usually are not at increased risk for medical comorbidity. In general, bony abnormalities of the cochlea are not part of the deafness phenotype and developmental motor milestones and vestibular function are normal.[102] The hearing loss associated with *GJB2*-related deafness can vary from mild to profound although most have a symmetrical severe to profound SNHL.[103] The diagnostic yield of *GJB2* screening is significantly higher in patients with severe to profound SNHL than in all other groups.[85]

There have been significant developments in genetic screening. Screening for the mitochondrial gene mutation *A1555G* (that makes individuals susceptible to aminoglycoside ototoxicity) is offered to patients who have developed hearing loss following exposure or to those individuals who are more likely to have repeated exposure to such antibiotics. If the gene is identified and subsequent administration of aminoglycosides restricted, then the severity of aminoglycoside-induced hearing loss can be limited. Also, as the gene is inherited from the mother, genetic screening to those members of the family and also restricting the use of aminoglycosides in maternal relatives will also limit the likelihood of hearing loss caused by these drugs. Hereditary Hearing loss[5] aims to give an up-to-date overview of the genetics of hereditary hearing impairment for researchers and clinicians working in the field.

SUPPORT AND EDUCATION

With the introduction of newborn hearing screening, the development of more effective hearing technologies including digital aids, implantable devices and wireless technology, and greater understanding of the implications of hearing loss on the development of communication, language and cognition, the opportunities and expectations for deaf children have changed dramatically. New communication technologies such as remote captioning, Skype and Facetime enable deaf young people to be supported in education in new ways. This has had great implications for all those involved with deaf infants, children and young people and their families, including audiologists, medical practitioners, speech and language therapists, teachers of the deaf and educational psychologists.

Early intervention

Following the introduction of newborn hearing screening, and the routine fitting of hearing aids in the first few months of life, and implantable devices in the first year of life, speech and language therapists and teachers of the deaf are involved with deaf infants and their families providing early intervention services at a very early stage. At this time the family may be faced with coming to terms with the diagnosis and new terminology and technology, while dealing with a young baby in their family. The consensus statement for Family Centred Early Intervention[104] provides useful guidelines, recommending the provision of:

- early timely and equitable intervention
- family provider partnerships
- informed choice and decision making
- family, social and emotional support
- family infant interaction
- use of assistive technology and supporting means of communication
- qualified providers
- collaborative teamwork
- progress monitoring
- programme monitoring

They provide guidance under each section and helpful resources, with the emphasis on family-centred services. These requirements place a great responsibility on the team providing the early intervention, particularly as we know its effectiveness has a positive long-term impact on outcomes in terms of language and education for the deaf infant. Early intervention is a strong predictor of later outcomes.[105, 106]

Hearing technology

See Chapters 54, Hearing aids, 55, Beyond hearing aids: An overview of audiological rehabilitation, 93, Bone-conduction hearing aids and 94, Cochlear implants for a comprehensive description of the rapidly changing available technology. Interventions include digital hearing aids, implantable devices (cochlear implants, bone-conduction hearing implants on softband for young children, middle ear implants), and assistive technologies such as FM systems and wireless technology.

The earlier that hearing aids or implantable devices are provided for a deaf child, the more effective they are known to be in the long term.[106] The early intervention team is key to their acceptance and use on a daily basis. For the family of a young deaf infant, adapting to the use of this technology can be challenging when coming to terms with the diagnosis and the implications of hearing loss. The technology itself may be complex to deal with in a family setting with a young baby and it is important that the audiology service liaises closely with those working with the family to ensure that there is a shared understanding of the implications of the hearing loss and expectations of the technology. The technology is changing constantly including sophisticated programmable hearing aids, electro-acoustic implants for those with high-frequency losses, middle ear and brainstem implants and developing techniques. Much information is available on websites and it is essential that all in a position of advising families keep up to date with current practice. Meeting other families and young people using the technology is helpful, and useful resources, including DVDs, are available from www.ndcs.org.uk[9] and from www.earfoundation.org.uk.[107]

The education of deaf children

The impact of childhood hearing loss on communication and language development and hence on educational outcomes and educational decisions has long been recognized as significant, and how to overcome it the source of much controversy with little in the way of evidence.[108] The seminal work of Conrad[109] showed that half of deaf children leaving school had speech that was 'difficult to understand' and had a median reading age of 9 years. Little changed with regard to educational outcomes until comparatively recently. With the rapid growth of hearing technologies, their earlier use, and more sophisticated assistive devices to address the problems of listening in noise and over distance, the impact of hearing loss on language and education has changed considerably in recent years.

Deaf children and young people represent challenges for researchers: they are a particularly heterogenous population with many variables to account for, including aetiology, age at diagnosis and amplification, cognitive ability, socioeconomic status, parental support, communication preference and educational management. Cochlear implantation has added more variables, including device used, age at implantation, surgical technique, generation of device and programming strategy. The impact of profound deafness on communication is readily apparent, but even a mild or moderate, or unilateral hearing loss which may not be so apparent can have an educational impact, with delayed language and a disadvantage in the classroom.[61, 110–113] A mild—moderate hearing loss impacts on the development of language and reading skills and hearing in one ear makes listening in noise and the localization of sound challenging, impacting on the ability to participate in the classroom.[113] A conductive, long-lasting hearing loss can also have a significant impact on access to the curriculum in the classroom; its fluctuating nature can exacerbate the difficulties it causes in listening in the classroom. In spite of this, the impact is often not recognized or addressed: for example, only 68% of deaf educational services are reported to support children with a conductive loss.[112]

Early identification, followed by early amplification has been shown to improve auditory abilities and hence language outcomes,[115] and the comprehensive LOCHI (Long-term outcomes from childhood hearing impairment) in Australia has demonstrated the benefits of early amplification.[116] The study showed that early intervention, maternal education, the absence of additional difficulties and oral communication in early intervention were linked to higher language scores. Early cochlear implantation has long been shown to be a predictor in producing language growth comparable to hearing peers[116–118] and is linked to improved spoken language acquisition, speech intelligibility, educational outcomes and greater participation in mainstream education.[119, 120]

More recent studies of educational outcomes show the positive impact of early cochlear implantation on educational outcomes including literacy; the study of Mayer et al.[121] found that of 33 young people aged 9–16, 75% were within the normal range for reading comprehension, when compared with hearing peers. Mayer and Trezek[122] reviewed the literacy outcomes for deaf students with cochlear implants with encouraging results.

However the picture remains complex. The National Deaf Children's Society, commenting on the Department of Education's report on children's grade attainment in 2015, pointed out that in spite of an increase in the numbers of deaf children achieving five GCSEs (41.1%), almost two thirds (58.9%) were failing to achieve the government's expected benchmark of five GCSEs at grade A*–C (including English and Maths), compared to just 35.8% of other children with no identified special educational need (from www.ndcs.org.uk).[9]

In spite of the progress made following early detection and intervention, hearing loss still has an educational impact. It impacts negatively on the more subtle areas of language development such as pragmatic skills.[105, 123, 124] Together with challenges in acquiring world knowledge, there remain challenges for deaf children in some higher order reading skills, such as inferencing skills, impacting on later educational attainments.

Schools and language teaching

Specialist education for deaf children was established long ago, with large schools for deaf children in many countries in the latter half of the nineteenth century and children taught according to the prevailing philosophy in the school, whether orally or using sign language. During the second half of the twentieth century more deaf children were educated in integrated settings, with their hearing peers, supported by improved technology, such as the fitting of FM systems which enabled teachers to use a microphone to aid communication with the deaf child (**Figure 10.5**) (Chapter 54, Hearing aids) and overcome the issues of background noise and distance, coupled with the political will to include more children with disabilities in mainstream education. Now the terms 'inclusive education' and 'least restrictive environment' are used internationally and supported by the legal requirement in most developed countries for deaf children to have an individual education programme with their needs identified.



Figure 10.5 A teacher of the deaf using an FM microphone.

More information on the history of deaf education can be found at www.batod.org.uk.[10]

Children with hearing loss may be educated in mainstream schools with or without support, in a special class or resource base in a mainstream school, in a specialist school for the deaf, or in a school which specializes in children with other difficulties, such as visual impairment, or language difficulties. The majority of deaf children are now in mainstream schools, where there may be challenges for access to the expertise and management necessary to overcome the impact of deafness and to fully utilize the technological and communication support available today.

The comprehensive CRIDE (Collaboration for Research in Deaf Education) 2015 report for the UK, available from www.batod.org.uk)[125] reveals that:

- 65% of deaf children are in mainstream provision
- 6% are in resource bases in mainstream
- 2% are in schools for the deaf
- 10% are in other special schools
- 15% are educated at home.

Whether to use a signed or oral approach has long been contentious. The Milan conference of 1880 concluded that the deaf were to be taught by oral means with the 'uncontestable superiority of speech over sign' and thus began 100 years of the dominance of oral education over sign – at a time when useful hearing could not be provided. The 'oral' view was challenged strongly by the reports of poor linguistic and educational outcomes[125] and by the increasing voice of the deaf community, promoting its own culture and language. Sign language is silent, with a grammar of its own and cannot be used with spoken language, and an interest in sign bilingual programmes where sign language is used independently of spoken language grew. To summarize, communication choices used with deaf children can be categorized in three major groups:

- oral/aural alone;
- those approaches using speech and sign (total or simultaneous communication);
- sign bilingualism.

There is increasing evidence that the new technologies of implantation and of earlier identification are changing some of these educational decisions.[126] There appears to be an increasing percentage of deaf children in the UK using spoken language. The CRIDE[125] shows that 87% of deaf children use spoken English or Welsh, with 2% using British or Welsh Sign Language and 8% using spoken English with signed support. The lack of empirical evidence for sign bilingualism and the better outcomes in terms of spoken language from early diagnosis and cochlear implantation than were predicted have been recognized.[126] While the evidence for the best method to support the development of improved educational outcomes remains contentious, an oral input, rather than a sign bilingual one, is most effective in producing spoken language outcomes.[116, 129] This may be provided with signed support for spoken language, for those who may need some visual support, either prior to implantation or in specific situations.[130]

Whatever the educational placement of the child it is important to ensure that the child's educational and social needs are met. Medical and audiological services have the goal of improving hearing and general health; for the educator there may be differing goals – those of literacy and numeracy and of social and emotional wellbeing. With regard to social and emotional wellbeing, there is no evidence to show that the advent of cochlear implantation has had an adverse effect on young people's wellbeing. Several studies show that young people with implants have a flexible view of their identity, as being both deaf and hearing, and have mental health status on a par with their hearing peers[131] and most do not relate to deaf culture as in the past.[132]

With the huge impact of today's technology on educational outcomes and management by providing useful hearing from an early age, it is vital that the technology supporting the child's access to the curriculum is used effectively; the acoustics in schools are often poor, the technology can be difficult to manage, particularly in a mainstream setting, and there may be considerable discrepancy between the child's functioning in the clinic and in school. Much of classroom learning takes place in group settings, which can be challenging for hearing aid or implant users, and the problem of signal to noise ratio (SNR) can be difficult to overcome. The acoustics of the educational setting need careful consideration, and a clinician involved in the fitting of hearing aids or implants should ensure that the child's teacher or classroom assistant understands the technology, can carry out simple trouble-shooting and has access to spares to ensure that the child is not without their amplification during the day. Accessories such as radio hearing aid systems (or FM), or the developing wireless, streaming systems or sound field systems are increasingly common, but need to be managed in the classroom rather than in the clinic. Children and young people are unlikely to use their equipment if it is not functioning properly, and the growing complexity of the technology demands increasing competence from teachers and increasing liaison with the audiology clinic. Communication technology is increasing in effectiveness too — remote captioning on tablets is available for use in school, college and work, and communication systems such as Skype and Facetime make lectures and meetings more widely accessible to deaf children and young people.

An additional challenge for deaf education in today's technological era is the growing number of deaf children with additional difficulties, and often very complex needs. CRIDE[125] reports that 21% of deaf children have an additional difficulty. Vestibular dysfunction is also very common in this group of children, and often overlooked. For these children it is even more important to ensure that today's audiological and communication technologies are available. It has been shown that they may not be referred for cochlear implantation in a timely fashion[133, 134] and parents reveal that education and the management of

audiology technology in schools which are not specialist schools for the deaf is a particular issue.[133] These are children for whom access to hearing can be particularly important, although the outcomes may not include the acquisition of spoken language and ones who present challenges for cochlear implant teams.[134]

Educational services for deaf children have a particular responsibility in times of challenging financial constraints and also of developing and changing technologies to ensure that children are monitored for changing hearing needs. For example, those with progressive hearing loss, and those for whom their hearing aids may not be sufficient and who should be referred for cochlear implant or bone-conduction hearing system. This responsibility involves training mainstream teachers in the monitoring of children and young people in the classroom and providing them with information about what changes in behaviour may be significant and where and how referrals should be made.

Support into further education and the world of work

Teachers of the deaf are now responsible for young people with hearing loss until the age of 25, and therefore now working in further and higher education settings and supporting young people into the workplace. The transition to further education and into the workplace is challenging, but it is essential that support is continued there and that young people learn to advocate for themselves and ensure whatever communication and hearing technology they require.

A report by Ng[135] revealed that these young adults have little or no communication or technology support as they enter work, and little knowledge of what is available to them. The continued positive impact of early diagnosis, intervention and today's technology require support into adulthood, to ensure long-term benefit.

Worldwide, the role of the teacher of the deaf is being challenged in these changing times. Teachers are likely to be involved with deaf children early in infancy and with their families, and require quite a discrete set of skills to effectively support parents and child at this vital time. With today's technologies, the educational needs of deaf children and young people are more subtle than they were previously, when they were more obvious. Teachers of the deaf work in a greater range of educational settings, with a greater range of deaf children than before, at a time where services are financially challenged. New ways of working enable education and audiology to be linked efficiently via Skype sessions, with the programming of cochlear implant systems in schools, and data logging on hearing aids and implants providing information to the clinic about what is happening in everyday life. There is a greater than ever need for collaboration between education and ENT and audiology departments to ensure that the benefits of today's technologies can be realized in education.

BEST CLINICAL PRACTICE

- ✓ All children with PCHI should have a full history and clinical examination, with audiological testing as appropriate to the child's age. Families should be offered aetiologiocal investigations to include imaging, genetic testing and other investigations as per published guidelines, followed by appropriate management of associated conditions and skilled genetic counselling.
- ✓ Optimum initial management is with early fitting of binaural hearing aids.
- ✓ If hearing aids are not appropriate early referral should be made for assessmnt of otological implants including cochlear implantation.
- ✓ Clinicians involved in the fitting of hearing aids or implants should ensure that the child's teacher of the deaf understands the technology, can carry out simple trouble-shooting and has access to spares to ensure that the child is not without their amplification during the day.
- ✓ Although the optimum management strategy for single-sided deafness is unknown, the child's teachers should be made aware of this condition.

FUTURE RESEARCH

- ➤ Vaccination programmes, particularly for measles and rubella, will have an important influence on reducing the incidence of PCHI in the developing world.
- ➤ Hearing aid technology continues to improve. These technological improvements need to be accompanied by wider worldwide distribution and availability of hearing aids.
- ➤ Establishing techniques for making a precise diagnosis in genetic deafness, with research into analysis of identified genetic abnormalities to inform focused genetic counselling and may ultimately facilitate therapeutic interventions.
- ➤ Imaging techniques continue to improve and are helping to facilitate more precise anatomical diagnosis.
- ➤ There is a need for further population studies on the effect of single-sided deafness and for a rational approach to management and surveillance for these children.
- ➤ Implementation of the 2016 WHO resolution[136] by governments and international public health legislators would greatly improve detection, prevention and treatment of childhood hearing loss.

KEY POINTS

- One infant per thousand is born with permanent deafness or hearing impairment that significantly affects language and social development. a further one per 1000 develops permanent deafness during childhood.
- Early identification and habilitation and optimal audiological and medical management leads to better life chances for the child.
- The benefits of universal screening are now widely accepted as best practice.
- Approximately half of permanent childhood hearing impairment is caused by genetic factors.
- Neonatal screening programmes have brought about earlier diagnosis, but some children with progressive hearing loss will not be detected unless surveillance is carried out during childhood.
- Unilateral hearing loss is detected much earlier as a result of universal screening.
- There is better understanding of optimum management of unilateral hearing loss to include active classroom management and amplification.
- Improved imaging and advances in genetic testing have meant that a precise aetiological diagnosis can be made in an increasing proportion of deaf children.
- A diagnosis of deafness has profound psychological and social implications for both the parents and the child.
- Patients who have had meningitis should have early audiology assessment.
- Initial management is usually with hearing aids but early referral for otological implants should be considered.
- Educational support is an essential part of the management of a deaf child and his/her family.
- Liaison between audiology and educational services is vital to ensure the technology is fully utilized in school.

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CHAPTER 11

PAEDIATRIC IMPLANTATION OTOLOGY

James Ramsden and Payal Mukherjee

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: paediatric, cochlear implant, middle ear implant, auditory brainstem implant, bone conducting implant, BAHA and focusing on diagnosis, surgery and management. The evidence in this chapter is mainly levels 3/4. The clinical recommendations are predominantly B and C.

INTRODUCTION

Paediatric hearing implants have become a routine part of the rehabilitation of deaf children. Cochlear implantation is one of the most dramatic and life-changing medical innovations of the 20th century. Bone-conducting hearing aids are an important tool for restoring hearing to deaf children if conventional hearing aids are ineffective, and middle ear implants are now starting to be used in specific indications in children. Developments in the field are driven by three main forces: technological progress, greater surgical confidence, and psychophysiological understanding of early language development. This chapter reviews the current boundaries for the clinical use of auditory stimulators to establish hearing in deaf children.

The auditory rehabilitation of prelingually deaf children has been revolutionized by cochlear implantation.[1] To date, more than 150 000 children have received cochlear implants, with often spectacular results. Cochlear implants provide access to sound that enables development of speech, language and literacy as well as attendance in mainstream education for many deaf children and is established as an effective and cost-effective intervention.[2]

Implantable hearing aids for children include two broad groups: 'electric hearing' with cochlear implants, and 'acoustic hearing' with bone-conduction implants (of which there are several types). For the great majority of children with profound sensorineural hearing loss (SNHL), the implant of choice is a cochlear implant.

COCHLEAR IMPLANTS

Cochlear implants are auditory implantable prostheses that electrically stimulate the spiral ganglion cells of the cochlear nerve directly in circumstances when the cochlear hair cells themselves do not function effectively to give adequate speech intelligibility. An implant consists of an external device with a microphone/processor and an internal device to stimulate the cochlear nerve. With improving technology, the indications for cochlear implantation are continually widening (see Chapter 94, Cochlear implants).

The first attempt to implant a cochlear implant (CI) was made in 1957 by Djourno and Eyries in Paris using a single-channel device.[3] These devices established that hearing could be achieved, but these early recipients used their implants largely in concert with lip-reading. In 1961, William House (otologist), John Doyle (neurosurgeon) and James Doyle (physicist) began work to implant a single-channel device. House's work continued into the 1970s, leading to the production of a 3M manufactured single channel device which was the first US Food and Drug Administration (FDA) approved model in 1984, and eventually to the Nucleus 22, which was the world's first commercial multi-channel CI with FDA approval.

The technology continued to improve with more widespread application of the product and greater confidence in its use. It was finally FDA approved for use in children in 1990. At this stage it was only approved for use for children above 2 years of age, but the age limit

was reduced to 18 months in 1998 and then further to 12 months in 2000. Since then, CIs have been routinely placed in children as young as 6 months, although in an anomaly the licence has never been amended to children below 12 months.

Design of implants

Although there are differences between devices, a basic arrangement is common with all the main manufacturers. There are four parts to the internal component: a magnet, a receiving induction coil (placed together to locate the outer transmitting coil by magnetic attraction), a processor and an electrode (**Figure 11.1**). A return electrode is also present, although this is usually incorporated in the housing of the processor unit.

An external processor is worn which communicates by induction with the internal receiver and also transmits power to activate the internal unit. There are various designs of the external processor to accommodate the different needs of users, but all have a microphone (or often two), and a speech processor, which employs a coding strategy to convert sound into electrical stimulation by the electrode. Various filters and coding strategies are used to give a variety of programs, optimized for speech, direction, music and so on. There is a magnet which holds the processor to the internal magnet, and a transmitter to send the signal by induction across the skin.

The number of active stimulating positions on the intracochlear electrodes varies from 12 to 22 according to the design of the implant. There are common themes to the types of intracochlear electrodes, although this is a field with relatively rapid development.



Figure 11.1 Internal part of cochlear implant (Cochlear N512).

POSITION WITHIN THE SCALA TYMPANI

The ideal position of the electrode is within the scala tympani where it sits close to the neural elements. Disruption of the basilar membrane by traumatic insertion or displacement into the scala vestibuli causes complete loss of residual hearing and may lead to worse outcomes.[4] Electrodes can be modiolar hugging (e.g. Cochlear Contour), Midscala (e.g. Advanced Bionics Midscala electrode) or lateral wall (e.g. MED-EL FLEX electrode).

SIZE

The cross-sectional size of the electrodes is reducing, mainly to improve the ease of insertion and to avoid trauma to the inner ear structures. The current electrodes allow preservation of residual hearing in many cases and may improve long-term cochlear health.

PLUGS, WINGS AND EXTRAS

MED-EL form electrodes have plugs to sit in the cochleostomy to help seal the cochleostomy and prevent cerebrospinal fluid (CSF) escape in abnormal anatomy with CSF 'gushers'. Other electrodes have wings to help positioning of the device (e.g. Cochlear Hybrid and EAS electrodes). Intracochlear positioners were tried in early devices, but these appeared to cause increased rates of bacterial meningitis and are no longer used.[5]

Custom-made electrodes for abnormal cochlear anatomy such as common cavities as well as split arrays used for ossified cochleas are also available.

Guidelines and funding

Prior to 2009, public funding in the UK allowed access for children to unilateral CI. However, in 2009, NICE published new guidelines which established that all eligible children were to receive bilateral simultaneous CI.[6] These guidelines were reviewed in 2011 after a multicentre audit and left unchanged.[2]

Given that binaural hearing skills are acquired early, there has been a preference for early implantation. This allows children rapid development of hearing and speech understanding by reducing deafness duration, maximizing the opportunity of early plasticity of the auditory system.[7] Children receiving a second implant several years after their first have demonstrated more significant asymmetries in brainstem and cortical function than those with a delay of less than 1 year or those implanted simultaneously.[8] These children have demonstrated poorer speech scores in the second ear compared to the first, stronger ear.

With the recognition of the benefits of bilateral and simultaneous cochlear implantation for children, a consensus was reached in 2010 by the Working group of European CI surgeons who released the European Bilateral Paediatric Cochlear Implant consensus statement. This stated that any infant or child who is an unambiguous CI candidate should receive bilateral simultaneous CI as soon as possible after the definitive

diagnosis is made and that surgery should be atraumatic to preserve cochlear function. Currently, more than 25% of children implanted before the age of 3 years have received bilateral implants worldwide whereas in children older than 3 years it is most likely that bilateral implants are inserted in a sequential manner.[7]

Prelingual deafness

Prelingually deafened children have not had the opportunity to organize the same cortical pathways as hearing children. Such deficits in maturation of the auditory cortex of prelingually deafened infants can be counterbalanced if hearing is introduced early. Animal models demonstrate a sensitive period of adaptation within the second to sixth months of life.[9] Similar outcomes have been noted in CI candidates in children. Prelingually deafened children implanted just prior to their teens show a delay in the development of normal morphology of cochlear-evoked potentials and prelingually deafened adults with CI do not achieve open-set speech discrimination.[10]

Thus there is a window or critical period of development during which it is important for these children to function at the same level as their hearing counterparts. With the introduction of newborn hearing screening (see Chapter 10, Management of the hearing impaired child), there has been an increased opportunity to diagnose these children early and therefore to implant them before 12 months of age. Parallelling this, there has also been an increased development of clinical and surgical skill, improved technology and a wider awareness of the benefit of speech understanding of implanted children, which have led to an increase in the number of children undergoing implantation prior to 12 months of age.[11]

Children implanted earlier have quicker language acquisition, earlier binaural skills, better language skills and can even develop along the normal path for language development.[12] Furthermore, data exist that early implantation increases the proportion of children in mainstream school and increases the cost utility of CIs significantly.[13]

Surgery in these young children is safe,[14–16] but barriers exist to early implantation. These include delays in scanning children, protracted behavioural audiology, parental concerns and waiting for surgery, but usually the greatest delay is referral from audiology/paediatric services for cochlear implantation. Newborn hearing screening, which exists in the majority of developed countries, identifies almost all of the children with congenital severe/profound hearing loss, but there is sometimes a reluctance to refer to cochlear implant centres without extended hearing aid trials and reassessment, which causes significant delays.[17]

Evidence does not yet exist that implantation below 6 months of age continues to improve outcomes further, and there is surgical concern that simultaneous implantation in very young infants carries a risk of bleeding which may be significant. Very early implantation (less than 6 months of age) is not yet a standard in paediatric implant surgery.

Postlingual deafness

Postlingual deafness in children is often due to meningitis or head injury. The outcome depends on the duration of deafness but most children who have had a period of hearing do well with CI. Recent changes in candidacy, however, have allowed other groups of postlingually deaf patients to benefit from CI. Children with auditory neuropathy spectrum disorder (ANSD) fall into this category and there is extensive ongoing work to understand this disorder better.[18, 19]

Partial deafness

An increasing number of studies have confirmed that partial deafness, most commonly high-frequency hearing loss with residual low-frequency natural hearing, is effectively treated in children with cochlear implantation.[20, 21] These children are hard to aid with conventional hearing aids because of the 'ski-slope' nature of the hearing loss. They may have limited ability to hear consonants and fricative sounds[20] though they have good low-tone hearing, which is important to appreciate music.[22] It is possible to implant with an approximately 90% chance of preserving useful hearing using a variety of electrodes.[23] Soft atraumatic electrode arrays and careful surgery are required to preserve the hearing.[24] There is an incidence of late loss of hearing a few months after the surgery, and it is usual to lose around 10–20 dB of hearing. There are speech processors that are designed to stimulate the high-frequency hearing using the electrical implant, and low-frequency hearing can be boosted with an acoustic hearing aid – combined in a single processor. This approach still allows access to interaural level and timing differences which facilitates localization of sound and binaural effects to increase speech understanding in background noise, compared to a conventional CI without low-frequency residual hearing. Once the residual hearing is below 80 dB this approach is ineffective as the residual hearing is no longer aidable – so, assuming a hearing loss due to the implant, it means that this 'hybrid' strategy is usually not attempted if the pre-operative low-frequency hearing is less than 60 dB HL.

A concern in children is that they will lose the residual hearing eventually during the natural process of ageing in the cochlear, a process which often occurs early in individuals with hearing loss. However, the modern hearing preservation electrodes are full or near full length and will function well even if the residual hearing is lost.

Single-sided deafness

Although the concept of cochlear implantation to restore bilateral hearing in adults is quite well established,[25] the value of using CROS (contralateral routing of sound) aids, bone-conducting aids or CIs is much less clear in children. Unilateral hearing loss in children results in educational deficits. Children with unilateral hearing loss are at increased risk of grade failures (24–35% vs

3% in normal-hearing children) and are more likely to require educational assistance (12–41%). Compared to normal-hearing siblings, these children have lower oral language scores, a 4.4 times risk of requiring an educational plan and a 2.5 times risk of having speech therapy.[26] Functional MRI scans have demonstrated neuroanatomical differences in auditory regions between single-sided deaf children and normal-hearing controls, but also in attention and executive control areas, and these children have a much higher incidence of behavioural problems[27] see Chapter 10, Management of the hearing impaired child.

CROS hearing aids are very poorly tolerated in children. Bone-conducting hearing aids (BCHAs) are more accepted, but the majority of children with single-sided deafness do not use them. A bone-conducting aid corrects the head shadow effect but does not give interaural level or timing differences to allow binaural hearing. Consequently, there are only modest improvements with a BCHA in localization or speech-in-noise comprehension. A CI will allow access to interaural level differences and will improve localization and speech in noise compared with BCHA, especially in situations where noise is presented to the normal-hearing ear and speech to the implanted ear. Interestingly, adults with unilateral CIs report a reduction in tinnitus; in children with hearing loss, tinnitus is often present but is rarely a major clinical problem.

There are only a few published reports of cochlear implantation in children with unilateral hearing loss.[28] However, it appears that this is as well tolerated by children as by adults who have had a sudden SNHL,[25, 29] and studies of prelingually unilaterally deaf children are underway. Early results are promising and this may be a viable treatment in the very near future. However, there may be additional issues to consider when treating congenital profound hearing loss in one ear. Animal studies indicate that, if unilateral deafness develops early and especially if it is congenital, then a period of time exists after which there is a shift in the cortical processing in preference of the hearing ear, which will influence the outcome of the second deaf ear if implanted.[30] The recommendation therefore from the animal work is to minimize the period of monaural stimulation as much as possible. Further data are necessary, investigating both short- and long-term implications of CI in single-sided hearing in children.

There will be additional prognostic factors to consider in children in addition to those in adults, such as whether the ear has ever heard, the presence of any malformations in the cochlea, the status of the nerve, the optimal window of time to implant, other comorbidities and their influence and so forth. As with bilaterally deaf children, minimizing the duration of deafness and early implantation will probably be very important in achieving good outcomes. However, significant questions remain about the cost-effectiveness of this treatment, and about the acceptability of a unilateral CI in older children and teenagers who may not wish to wear a hearing device for a unilateral disability.

Bilateral implantation

Bilateral CIs improve hearing for children with bilateral deafness beyond that which can be realized with a unilateral CI.[31] The aim in children is to promote important auditory processing that normally occurs when listening with two ears. Binaural hearing skills are normally acquired very early on; by 6 months of age, children with normal hearing show consistent lateralization of sounds by turning their heads. This means that small differences in interaural timing and level differences are detected and perceived by the auditory pathways. Speech comprehension in noise and localization are compromised when sound is heard from only one side or through only one CI but can be improved with bilateral CIs in both adults and children.[32]

Children receiving a sequential bilateral implant with an interval of several years have demonstrated significant asymmetries in brainstem and cortical function compared with those with a delay of less than 1 year or simultaneous implantation.[7] These children have demonstrated poorer speech scores in the second ear compared to the first, stronger ear.[33]

A most telling outcome of bilateral cochlear implantation is that children with two implants almost universally wear both devices and demand to have any equipment breakdowns (depleted batteries, broken components or device failures) repaired. Children and families also report improved hearing in the 'real world' even when outcomes measured in the audiological sound booth are minimal, which probably reflects the increased complexity of most listening situations beyond the quiet test environment.[34, 35]

Nevertheless, there are still many children around the world who receive a single implant or sequential implants. The main reason for this is financial. A number of children have residual hearing in the unimplanted ear and can benefit from bimodal (CI + hearing aid) amplification. There are also surgical concerns about bilateral simultaneous implantation (although there is no evidence to suggest a higher complication rate)[14, 36] and about possible vestibular dysfunction.

Assessment

Assessment for candidacy needs to be conducted in a specialized multidisciplinary team. In the UK the audiological guidelines for implant candidacy as per guidelines set by NICE[6] include severe to profound deafness (defined by thresholds of 90 dB or worse at frequencies of 2 kHz and 4 kHz without amplification) that preclude the child from attaining adequate speech, language and listening skills appropriate to age, developmental stage and cognitive ability with optimal acoustic amplification.

As with adults, assessment in children involves a battery of sound detection and speech perception tests, though the latter are somewhat limited in infants and in prelingual profound deafness. Preceding implantation, children undergo electrophysiological testing in the form of an auditory brainstem response (ABR) to obtain the true thresholds of the child. This may be acoustic and, if necessary, also

electric. In cases of auditory neuropathy, children may have an absent or abnormal ABR and thus otoacoustic emissions. Electrocochleography (ECoG) or eABR may also form part of the general battery of investigation for assessing candidacy for a CI. Aided thresholds and behavioural tests are important as well as speech perception tests but are conducted in an age- and disability-appropriate manner. Similarly, a hearing aid trial is offered to those children who may benefit from a trial or whose candidacy may be ambiguous, such as in the setting of ANSD.

In addition to the audiological factors that play a central role in candidacy, many other factors influence the outcome of children and thus a multidisciplinary assessment is very important.

Screening

Newborn hearing screening is now the accepted standard of care in most countries.[37] The National Health Service (NHS) Newborn Hearing Screening Programme (NHSP) was commissioned by the Department of Health in 1997 following a National Institute for Health Research (NIHR) Health Technology Assessment report which showed that a large number of deaf children were not being identified. Between 2001 and 2006 universal newborn hearing screening (UNHS) was implemented in England, Scotland, Wales and Northern Ireland and it is now estimated that, between 2006 and 2011, 74% of eligible children between 0 and 3 years had been implanted and 94% by age of 17.[38]

Medical assessment and imaging

A detailed history and examination should be conducted to evaluate the cause of the hearing loss, including prenatal and perinatal history to assess for risk factors some of which include TORCH infections (toxoplasmosis, other [syphilis, varicella-zoster, parvovirus B19], rubella, cytomegalovirus [CMV] and herpes infections), teratogens, prematurity, low birthweight, low APGAR scores, hyperbilirubinaemia, sepsis, meningitis and the administration of ototoxic medications. Other aspects of medical evaluation include a detailed family history, assessment for the presence of syndromes, immunization status and the presence of other otological disease which also involves the use of dedicated imaging of the temporal bone and knowledge of the status of the cochlear nerve.

Genetic hearing loss

The incidence of congenital hearing loss in the UK equal to or worse than 40 dBHL is somewhere in the order of 1 in 1000 children, with nearly 60% of these children having a genetic cause of deafness. It is estimated that 70% of genetic causes of hearing loss is non-syndromic and of these nearly 80% are inherited in an autosomal recessive manner.[39] The other 20% constitutes autosomal dominant, X-linked and mitochondrial DNA variant abnormalities. Although numerous loci of abnormalities have been characterized, the most common defect – constituting nearly 50% of all non-syndromic hearing loss – is a mutation in connexin 26 which codes for a gap junction protein beta 2.[40]

Syndromal deafness is less common and, although there are over 400 syndromes associated with hearing loss,[41] some common ones include Pendred, Usher syndrome and Jervell and Lange-Nielsen which are inherited in an autosomal recessive manner. Autosomal dominant syndromes include Stickler, branchio-oto-renal and Waardenburg syndrome.

Neurofibromatosis type 2, which can present later in childhood, is characterized by bilateral vestibular schwannomas (VS). Until recently, the presence of a schwannoma was considered a contraindication for CI. However, recent studies have reported successful outcomes of CI in untreated but stable VS, or in VS that has been stable following radiotherapy. When the tumour is growing and/or cochlear nerve preservation in not possible, an auditory brainstem implant (ABI) is another option.[42] (See Chapter 102, Surgical management of vestibular schwannoma, for more information).

Acquired hearing loss

Some of the causes of acquired hearing loss are outlined above. Although many such forms cannot be distinguished from genetic causes in young children, a thorough history may help provide helpful information, such as a history of prenatal infection with toxoplasmosis, syphilis, rubella, cytomegalovirus or herpes (TORCH microorganisms), and/or a perinatal history of prematurity, low birthweight, low Apgar scores and hyperbilirubinaemia.

Cytomegalovirus (CMV) is particularly interesting as early treatment with valganciclovir can prevent further hearing loss, or in a few cases bring about recovery in hearing. The optimum duration of treatment is not yet known, although 6-week to 6-month courses have been used. Early treatment appears to be more effective than later treatment.[43]

Meningitis, temporal bone trauma and rarely autoimmune inner ear disease may cause profound hearing loss and subsequent cochlear ossification. There have been reports of strategies that may be utilized to overcome partial and total ossification of the cochlea, including drilling out the basal turn, scalae vestibuli insertion and even the insertion of short or split electrodes. These procedures are, however, uncommon and therefore not well trialled and may risk damaging the neural elements. Nevertheless, they help emphasize the importance of a thorough medical and radiological evaluation in a multidisciplinary setting to inform the patient of the likelihood of success of implantation and also of the medical and psychosocial hurdles that lie in the path of postoperative rehabilitation.

Congenital malformations

About 20% of congenital SNHL can be attributable to inner ear malformations. Development in modern imaging and clinical experience has led to improved diagnosis and management of these disorders with respect to

cochlear implantation. The two main difficulties in surgery with malformations are CSF gusher and facial nerve abnormalities. Balanced with these is also a higher risk of meningitis with inner ear malformations with or without cochlear implantation.[44] Malformations were first divided into five main abnormalities: Michel deformity (labyrinthine aplasia), cochlear aplasia, common cavity, cochlear hypoplasia and incomplete partition. Minor adjustments have been recommended based on radiological differences of these abnormalities, subclassifying incomplete partition into three further categories depending on degree of severity. Type 2 incomplete partition, first described by Carlo Mondini, consists of a normal size cochlea with deficiency of the apical part of the modiolus and the corresponding interscalar septum. Together with a minimally dilated vestibule and a large vestibular aqueduct, a Type 2 incomplete partition forms the triad called the Mondini deformity. Incomplete partition Type 3 was reported in X-linked deafness.[45] In cochlear hypoplasia the normal cochlea turns do not form fully.

Pre-operative imaging therefore plays a very important role. An MRI not only is important in confirming the presence of a cochlear nerve in the presence of pre-lingual deafness, but will also show the turns of the cochlea and the anatomy of the vestibule. Furthermore, in cases where a CT scan may identify a narrow internal auditory canal, an MRI is also important to confirm that the nerve is present and not hypoplastic, especially when associated with certain syndromes such as CHARGE (coloboma, heart defects, atresia choanae, retardation of growth, genital anomalies and ear abnormalities). An absent cochlear nerve is a contraindication for CI. A finding of a hypoplastic cochlear nerve needs to be assessed individually, which may involve further imaging or an electrically evoked ABR.

High-resolution computed tomography (HRCT) helps to display the anatomy of the mastoid and the facial nerve as well as identify any malformations in the cochlea, the internal acoustic canal and other ear malformations. Altered facial nerve course is seen particularly in cochlear hypoplasia and common cavity. A hypoplastic cochlea may make for a difficult electrode insertion through a facial recess, as the round window may not be found in the usual area or the flatter profile of the promontory may mislead the surgeon. In these cases, alternate approaches such as a transmastoid labyrinthotomy, canal wall-down with a blind sac closure of the external ear canal or even a transcanal approach or insertion through the oval window may need to be employed.[46] Identifying the malformations also helps with the choice of electrode. Where the exact location of the neural tissue is not known, for example in a common cavity, an electrode with complete contact rings is likely to be more beneficial whereas in a hypoplastic cochlea, a shorter electrode may need to be used. Alternatively, in incomplete partition Type 2 all types of electrodes may be used.

Although there has been debate over which modality (MRI or CT) is more important in children, most implant teams utilize both CT and an MRI in the pre-operative planning of a CI as they each have their advantage and in the setting of malformations provide complementary information. It is important that these take place early in the workup of these patients to help guide them towards appropriate rehabilitation.

Auditory neuropathy spectrum disorder

First described in the mid-1990s,[47] auditory neuropathy is a hearing disorder characterized by the presence of outer hair cell function (evidenced by the presence of intact evoked otoacoustic emissions and/or cochlear microphonics) but abnormal or absent auditory brainstem response. However, due to the multifaceted nature of the aetiology of this condition and the recognition that the abnormality is not localized to the cochlear nerve, but may involve other defects such as inner hair cell/synapse or a synchronization of the signals being transmitted, the terminology was expanded to auditory neuropathy spectrum disorder (ANSD).[48]

Although the prevalence varies between studies and is difficult to quantify accurately, it has been estimated to be present in up to 1 in 10 children with permanent hearing loss.[49] The manifestation of this disorder involves difficulty hearing in noise, fluctuating sensitivity and speech perception scores not consistent with the level of residual hearing on the audiogram.

The aetiology can be multifactorial including genetic, congenital and acquired causes. Risk factors for ANSD include extreme prematurity (<28 weeks gestation), hyperbilirubinaemia reaching exchange transfusion levels, low birthweight or intrauterine growth restriction, and other neurological conditions such as hypoxic ischaemic encephalopathy and intraventricular haemorrhage (likely to occur in prolonged ventilation and sepsis). Genetic causes include Freidrich's ataxia, Charcot–Marie–Tooth disease and non-syndromic conditions such as DFNB9/*OTOF*.[50]

The electrophysiological tests constitute definitive diagnosis but, due to the heterogeneous manifestations of the ANSD, the recommended habilitation approach and choice of assisting device (whether it be a hearing aid or CI) remains controversial. The approach in children suffering with ANSD therefore has been to address patients on their own individual needs. Children with ANSD with cochlear nerve hypoplasia on MRI have worse CI outcomes and those with an absent cochlear nerve are unsuitable for CI.[51] Similarly, children who exhibit an atypical or absent ECAPs (electrically evoked compound action potentials) during implantation are also associated with poor outcomes.[52] Therefore, though a significant proportion of children will benefit from CI, some will benefit from amplification and some others who have bilateral cochlear nerve deficiency will not benefit from either intervention. Reasons for this heterogeneity with CI may be associated with their other comorbidities or with the failure of the electrical stimulus from CI to create adequate neural synchronization of signals. Thus a stepwise approach in a specialized multidisciplinary team is crucial to help guide the habilitation of these complex patients.

Chronic suppurative otitis media

Chronic suppurative otitis media (CSOM) was previously considered a contraindication to cochlear implantation. More recently, surgeons have applied a staged technique, in clearing the disease in the first stage and then performing an implant a few months later when the ear is dry. It is important to eradicate the source of any biofilms prior to the insertion of the CI. Some surgeons prefer to obliterate the mastoid cavity at the same time as the first operation, but the risk of future development of cholesteatoma remains and follow-up is made difficult due to the artefact created by a CI while using a diffusion-weighted MRI scan. In the presence of a dry, stable cavity, a blind sac closure and CI may be undertaken as a single stage.

Surgery

In most cases, cochlear implantation may be safely performed as a day-case[16] although in infants it is often sensible to admit overnight, especially if the surgery is in the afternoon.

INCISION

A postauricular approach with a small incision is preferable. The optimal incision for access has evolved over time. The general principles of the incision, irrespective of individual preferences, are that the incision should not be placed near the receiver/stimulator, to prevent skin breakdown and extrusion and also to ensure that blood supply to the region is not compromised. More complications relating to the skin are associated with a history of previous radiotherapy to the area.

APPROACH

Subperiostial flaps are raised and the mastoid exposed. A small cortical mastoidectomy is performed with a posterior tympanotomy. The round window should be identified and the surgically important landmarks include the incus short process, the facial nerve, chorda tympani nerve, incudostapedial joint and round window membrane.

RECEIVER/STIMULATOR PACKAGE

A bony recess which is specific to the device intended is drilled. The cortical bone is very thin in young children and at times the entire thickness of the cortical bone may be removed to the level of the dura to accommodate the receiver/stimulator and minimize skin complications. There are various ways to secure the electrode to prevent electrode migration, including drilling holes and tying sutures over the electrode or securing it with bone wax.

ROUND WINDOW VERSUS COCHLEOSTOMY

With the advent of electroacoustic stimulation in patients with residual low-frequency hearing there has been much interest in examining whether a round window perforation or cochleostomy is preferable. The advantage of a round window approach is that a small perforation can be made by a needle in the round window which helps seal the entry site of the electrode into the cochlea. Furthermore, there is no need for intracochlear drilling. A cochleostomy should be placed inferior to the round window. This involves meticulous drilling with exposure of the endosteum, which needs to be removed with a small hook thereby minimizing the trauma to the cochlea and preventing the entry of bone dust or blood into the cochlea. Both techniques have been shown to preserve low-tone hearing, and to minimize cochlear trauma. 'Soft surgery' may also minimize scar formation within the cochlea if the child needs revision surgery in the future.

Once the electrode has been inserted, the electrode entry is packed with fascia or periosteum at the site of entry to prevent leak of perilymph. In the case of residual hearing it is important not to overpack the middle ear as it may cause a degree of conductive hearing loss of the residual hearing frequencies.

NEURAL RESPONSE TESTING

Most units in the UK perform intra-operative testing to confirm electrode integrity and measure impedance.

BILATERAL SURGERY

This requires bilateral facial nerve monitoring. Care must be taken to plan the placement of the devices at the same level behind the ear so there is symmetry when the patient wears the external device.

POST-OPERATIVE RADIOGRAPH

A post-operative X-ray (Stenver's view) helps to confirm electrode insertion, identify potential tip foldover, and give a reference for the correct placement of the electrode in the cochlea should there be future problems. If required, radiographs, fluoroscopy and/or image guidance may also be used intra-operatively in cases of expected difficulty such as revision cases or congenital malformations.

Complications

Complication rates in paediatric cochlear implantation are in the order of 10% with major complications constituting < 3%. Malformations of the cochlea make for a higher incidence of complications.[14, 36, 53]

INFECTIONS

Wound infections constitute nearly half of all complications in children and a course of peri-operative antibiotics is important to minimize this.

FACIAL NERVE INJURY

With the use of facial nerve monitoring facial nerve paresis in a paediatric population is rare, though a rate of chorda tympani nerve injury between 5% and 20% has been reported.[54]

CSF FISTULA

This is rare and can occur early or late with an incidence of 1%. Secondary meningitis may occur but is extremely rare. It is important to pack the cochleostomy adequately to prevent this, especially in the presence of an enlarged vestibular aqueduct.

DEVICE FAILURE

The rate of device failure of contemporary CIs has been reported as <1%. Late device failure is difficult to predict and may even be difficult to diagnose in the setting of a developmentally delayed child or one with numerous comorbidities.

CHOLESTEATOMA

Secondary cholesteatomas, though rare, have been reported. It is important to stabilize any ear disease prior to embarking on cochlear implantation. Early retraction pockets may be repaired by cartilage tympanoplasty. Secondary cholesteatomas may need a radical mastoidectomy with blind sac closure and removal of all squamous epithelium but the inability to monitor the cavity for recurrence is a drawback.

POST-OPERATIVE MRI

If necessary for the patient, an MRI can be conducted in the presence of CI using a 1.5 Tesla MRI scanner. If the magnet of the receiver stimulator is left *in situ*, an ovoid void is created of approximately 60 mm × 100 mm in size compared to 35 mm × 55 mm size if the magnet is removed. The image quality is inferior in the immediate region of the void surrounding the receiver/stimulator but the rest of the image is of high quality. Tight head bandaging is recommended to avoid movement of the receiver/stimulator. Pain and discomfort during scanning can be alleviated by the injection of local anaesthetic to the area of the receiver/stimulator prior to head bandaging. Occasionally, movement of the internal magnet occurs, but this can usually be corrected by replacement of the magnet at a later stage.

MED-EL now have a rotating magnet design which allows the magnet to move within the implant to align with the magnetic field. This allows use of a 3T MRI and reduces the risk of discomfort and dislodgement of the magnet. However, the artefactual degradation of the image on the ipsilateral head is still present.

Post-operative rehabilitation

Specialist multidisciplinary support including audiologists, speech therapists and educators is crucial to the successful rehabilitation of implantation. Patients are typically seen at 2–4 weeks for 'switch on' and ongoing follow-up and support are required to enable optimal use of the implant and for acquiring appropriate speech and language development.

There is no doubt that there are multiple benefits from CI in children. After only 1–4 years of implantation, paediatric patients can demonstrate speech and language skills equivalent to their hearing counterparts. Prognostic factors influencing outcome include age at implantation, age of onset, residual hearing, use of hearing aids, other comorbidities, family support, post-operative rehabilitation and consistent use of the implant. Despite the best support and rehabilitation, in certain children, especially those with complex needs, it is more important to measure outcome with a quality-of-life measure than with traditional measures of outcome. In these children, it may be unrealistic to expect the development of oral language and therefore it will not accurately reflect the benefit that CI can give in providing the awareness of sound in the life of a child who is already deprived of many other psychological, sensory and social inputs.[55]

Extended candidacy

Different criteria for candidacy have been adopted in different health economies. In the UK the NICE (National Institute for Health and Care Excellence) guidelines determine candidacy: for children this is 90 dB hearing loss at 2 kHz and 4 kHz, with evidence of delayed speech and language development. However, children with hearing above these thresholds benefit from cochlear implantation in certain circumstances. There are numerous reports of children with asymmetric hearing loss benefiting more from the implanted side than the hearing aid side.[55] Furthermore, the outcomes after cochlear implantation in around 80% of children with hearing thresholds of 80–90 dB are better than can be achieved with hearing aids. This raises the possibility that current guidelines are too restrictive, and that a wider range of severely deaf children could be offered CIs, especially as residual hearing can usually be preserved allowing hybrid electroacoustic stimulation in both ears.[56]

Future technologies

The technological advancement of auditory implants continues apace and, in fact, it is likely that any report on this will be out of date within a few months, and certainly within several years. The following current areas of development look to be fruitful.

ELECTRODE DESIGN AND INSERTION

There are a number of electrodes developed by commercial implant companies which allow hearing preservation and deep insertion into the cochlea for 'complete cochlea coverage', and custom electrodes for anomalies in cochlea anatomy. Insertion forces appear to be crucial to maintain a healthy cochlea for long-term health of the inner ear, as well as hearing preservation. Robotic insertion to reduce these forces further is an active area of research interest with promising early studies.

NEUROTROPHINS AND GENE THERAPY

A CI is a promising conduit for delivering growth factors directly or by gene therapy techniques, as well as electrical stimulation to prolong and increase neural response. Recent animal studies have shown great promise in animal models, but these have not yet been translated to human trials.[57]

TOTALLY IMPLANTABLE IMPLANTS

Adults implanted with totally implantable devices have found outcomes limited by the subcutaneous microphone.[58] Newer devices may use the ossicular chain as a microphone for middle ear stimulation, and the translation of this technology to CIs is inevitable.[59] However, at this point, no totally implantable CIs have been used in children.

IMPROVED PROCESSING STRATEGIES

Sound processing strategies to improve the appreciation of music and to allow speech discrimination in background noise are actively being developed and released. Bidirectional microphones to determine sound direction, and communication between bilateral cochlea implants, along with automatic programmes that especially suit children, give better outcomes and are often retrospectively available to previous versions of CIs.

IMPROVED USER EXPERIENCE

Already, CI processors are routinely available which are compatible with add-on devices by Bluetooth™, or Wi-Fi signals. The processors are water-resistant, and in some cases waterproof, to allow swimming and showering while hearing. Off-the-ear solutions to minimize the visibility and improve the comfort of the processors are also helpful to some patients, although CIs still use significant power and so battery size can limit the size of devices. Finally, data logging and feedback to audiologists to help with tuning and remote management of devices to save on clinic visits can make life easier for patients and their families.

AUDITORY BRAINSTEM IMPLANTS

Auditory brainstem implants (ABI) are auditory prostheses designed to provide electrical stimulation directly to the cochlear nucleus in the absence of a functional cochlear nerve (**Figure 11.2**). First used in 1979 by William House and William Hitselberger after removal of an acoustic neuroma, their use has been mainly reserved in the setting of NF2.[60] Colletti et al first reported their use in a paediatric setting.[61] Use in prelingually deaf children remains primarily in those children in whom CI is contraindicated, for example in complete labyrinthine aplasia or congenital malformations with cochlear nerve hypoplasia or aplasia. In postlingual deafness, an ABI may be indicated in tumour or non-tumour patients. Tumour patients include patients affected with NF2 or bilateral VS whereas non-tumour patients include those with bilateral severe cochlear ossification (which may be secondary to meningitis), gross cochlear destruction from otosclerosis, other surgical conditions precluding CI, and fractures through the IAC causing cochlear nerve avulsion or unmanageable facial nerve stimulation post CI.[62]



Figure 11.2 Schematic diagram of ABI placement on auditory nuclei. The insert shows the panel of electrodes.

Long-term results are still pending but audiological outcomes are not seen to parallel CI. Open-set speech discrimination only occurs in occasional cases and therefore a CI where possible should always be the first option. Furthermore, a CI is easier and safer to implant, with a much lower risk of life-threatening complications. Prior to considering a paediatric ABI, therefore, very careful radiological assessment and electrophysiological testing (e.g. eABR) is crucial. In the setting of prelingual deafness, outcome will depend on early intervention and therefore it is important to identify candidates through newborn screening and subsequent medical and radiological assessment.

The optimal age for elective intracranial surgery is 18–24 months, but in some experienced centres the minimum age for an ABI can be regarded as low as 1 year. Earlier intervention carries the risk of hypovolaemia through CSF and blood loss, poorly formed lateral recess size and higher risk of brain swelling post-op but delayed intervention loses the benefit of cortical plasticity. Parents and carers need to be counselled prior to embarking on surgery that for prelingual recipients programming and rehabilitation is a lot more intensive that for CI and the results are not as good.

BONE-CONDUCTION HEARING IMPLANTS

Children with malformations of the external and middle ear or children who cannot use air-conduction hearing aids may be aided by bone-conduction hearing implants

(BCHIs). Surgical reconstruction of congenitally abnormal ears is performed in some centres but even in successful cases an air–bone gap of 20–30 dB may remain. Consequently, bone-conduction hearing aids have become widely used and with time, the indications, surgical techniques and number of available devices have continued to evolve.

Indications

Current indications for use of bone conduction devices in a paediatric setting include:

- conductive hearing loss
- congenital causes such as atresia or microtia
- acquired causes such as chronic otitis media or ossicular pathology
- chronic discharging ear (such as CSOM or recurrent otitis externa)
- unilateral mixed or profound hearing loss
- failure of the child to tolerate a conventional hearing aid.

Bone-anchored hearing aids

The first bone-anchored hearing aid (BAHA) was implanted in Sweden in 1977[63] and became commercially available in 1987. These hearing aids function by transmitting sound through bone via an osseointegrated abutment (Figure 11.3).

AGE OF IMPLANTATION

The US Food and Drug Administration have set a minimum age for paediatric use at 5 years. However, the minimum age for implantation is debated and there is no fixed worldwide guideline. In 2005 an international consensus was issued regarding bone-conduction hearing aids which recommended that surgery should not be undertaken prior to the age of 2–3 years. This was to allow the skull thickness and conditions to reach a minimum thickness to fit the fixture and allow osseointegration.[64]

Though successful implantation has been reported in a child as young as 14 months, the complication rate is inversely proportional to the age of implantation.[65] It is important to stimulate hearing as early as possible, and therefore in children too young for implantation the use of a bone-conduction hearing aid via a Softband™, which holds the hearing aid to the skin of the scalp via a metal or elastic headband, is advocated from about the age of 3 months.



Figure 11.3 Diagram of percutaneous bone-anchored hearing aid with titanium fixture in the bone (1), abutment (2) attaching to the fixture and hearing aid (3) (placed later and removable by patient).

SURGICAL CONSIDERATIONS

In the past BAHA surgery on children was staged, but tissue-preserving single-stage implants mean this is no longer necessary. The linear insertion technique eliminates the need for a skin flap. More recently, changes in device design have enabled preservation of soft tissue which both decreases the complication rates and also significantly reduces surgical time. However, in children a longer time to osseointegrate is recommended to compensate for the thinner calvarium.

COMPLICATIONS

Despite the advantage of the bone-conduction hearing technology, major short- and long-term complications of the percutanous implants in children include soft-tissue complications and fixture loss. Classification of soft-tissue complications are staged by Holger, ranging from 0 to 4, with 0 being reaction free skin around the implant and 4 being overt infection requiring implant removal. These complications seem to affect children more than adults and are associated with a higher rate of fixture rate loss (up to 14% over 15 years) in the paediatric population.[66] A much higher rate of fixture loss occurs when the shorter 3 mm fixture is placed, and so a 4 mm fixture should always be used. This involves depressing the dura during the implantation in all but the largest children.

CURRENT DEVICES AND RECENT MODIFICATIONS

Cochlear

In 2010, Cochlear introduced changes to the osseointegrated titanium fixture which included a wider base (4.5 mm versus 3.75 mm) for increased stability, smaller treads at the implant neck to improve load distribution and a Tioblast™ coating for faster osseointegration to the BI300 system. In 2012, it further modified the abutment with a hydroxyapatite coating (BA400) which

eliminated the need for soft-tissue reduction. The abutment sizes became longer to adapt to the thickness of the skin. Challenges in a paediatric setting include accommodating for growth and increases in soft-tissue thickness especially during puberty. The abutment is available in various lengths and may be changed to adapt to the child's growing needs.

A new transcutaneous system, the BAHA Attract, uses a magnet to secure the BAHA. While a major advantage in a paediatric setting is eliminating the soft-tissue complications of a BAHA, disadvantages include problems with future MRI scans and possible dampening of the signal through the skin.

Ponto

Oticon Medical introduced the Ponto in 2009, which is another bone-anchored hearing system. Similar to the Cochlear BAHA system, it comprises an implant, percutaneous abutment and external processor and – similar to the Cochlear BA400 system – has long abutments available which enable tissue-preservation surgery. The results are comparable and it is a well accepted option for a bone-conduction hearing device.

Middle ear implants

Middle ear implants, in selected patients, offer an option of hearing rehabilitation in conductive, mixed or SNHL. A worldwide consensus regarding the application of the vibrant soundbridge (VSB) found it is viable for use in children and adolescents if they have adequate anatomy to place the VSB, but each case and each treatment option should be weighed on its individual advantages and disadvantages.[67] The floating mass transducer may be connected to the incus long process, stapes remnant or round or oval window.[68, 69] The patient should be counselled about surgical issues and MRI compatibility and the risk of dislocation of the device with future MRI.

Bone Bridge

A transcutaneous bone-conduction hearing aid, which is indicated in conductive or mixed hearing loss as well as single-sided hearing – the Bone Bridge – was released by MED-EL corporation in September 2012. The device consists of an external audio processor and an internal bone-conduction implant. The internal component has an internal receiver coil, a magnet, a demodulator and a bone-conduction floating mass transducer (FMT) that is secured to the bone by two titanium screws. The power to drive the FMT and sound energy are transmitted transcutaneously via an inductive link to the internal coil, processed by the demodulator and then relayed to the BC-FMT, which then tranduces the signals into mechnanical energy. Osseointegration of the titanium screws is not thought to be crucial.

CONCLUSION

New devices continue to be introduced and current technology continues to evolve. With time, new indications continue to arise in the treatment of paediatric deafness. Despite the rapid introduction of new technology, it is important that the introduction and application of this into patient care be conducted in a rigorous evidence-based manner. To achieve this, it is essential that good collaboration continues between clinicians and industry and, most importantly, that regular and thorough feedback is obtained from patients and caregivers regarding the influence of new developments on their quality of life.

FUTURE RESEARCH

- ➤ Current areas of development in cochlear implant technology are discussed above.
- ➤ Fully implantable bone conducting devices will avoid skin complications in future but must increase gain to be suitable for all patients.
- ➤ The optimum rehabilitation of the child with single-sided deafness is still in evolution and awaits stronger evidence of benefit.

KEY POINTS

- Auditory implants can rehabilitate children with conductive and sensorineural hearing loss.
- Early, preferably bilateral, rehabilitation improves outcomes.
- Identification and rapid assessment of deaf children is essential.
- The technology is advancing quickly and should result in better outcomes in the future.

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CHAPTER 12

CONGENITAL MIDDLE EAR ABNORMALITIES

Jonathan P. Harcourt

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SEARCH STRATEGY

Data in this chapter may be updated by a search of the Guidelines databases on www.library.nhs.uk, the Cochrane library and TRIP databases using the keywords: congenital, middle ear and ossicle. This was supplemented by a PubMed search using the keywords: congenital and middle ear or ear, ossicle.

INTRODUCTION

Conductive hearing loss in children is usually acquired. The most common aetiology is otitis media with effusion (OME) but it may be the result of chronic otitis media (mucosal or squamous). In the presence of severe congenital deformity of the external ear, associated abnormalities of the ossicular chain are common but in isolation they are rare and often have a delayed diagnosis, particularly if unilateral.

A variety of non-ossicular congenital middle ear abnormalities may also be associated with ossicular deformities. They may be symptomatic in themselves or be important aspects of other middle ear conditions and surgery. They include:

- persistent stapedial artery
- anomalous course of the facial nerve
- congenital perilymphatic fistula
- high jugular bulb
- aberrant internal carotid artery.

Definition of congenital ossicular abnormalities

Congenital ossicular fixation and defect is defined as a malformation affecting the ossicular chain, present at birth, which leads to a dysfunction of the ossicular mechanism due to immobility or discontinuity of the ossicular chain.

Major malformations involve both the tympanic cavity and the external ear (ear canal and pinna) and are described as congenital aural atresia or microtia. In association with these conditions, in either sporadic cases or as part of a syndrome such as Treacher Collins or Goldenhar, there may be a variable degree of ossicular abnormality and there may also be associated inner ear dysplasia.

Minor malformations affect the ossicular chain alone and the tympanic membrane and ear canal are normal.

CLASSIFICATION OF CONGENITAL OSSICULAR ABNORMALITIES

There have been many published classifications based on individual surgeons' series.[1] Cremers' classification describes the largest published series of operated minor congenital ear anomalies (104 cases).[2] It has been modified by Tos[3] and seems to be the most inclusive and descriptive of all the published schemes (**Table 12.1**).

Minor malformations are divided into four main groups, each of which may be subdivided: isolated stapes ankylosis, ankylosis with other ossicular anomaly, isolated ossicular anomaly, and aplasia or severe dysplasia of the oval or round windows.

TABLE 12.1 Cremers' classification of minor congenital anomalies of the ossicular chain in 144 operated ears (modified by Tos) (reproduced from Tos,[3] with permission)

Class	Main anomaly	Subclassification	% ears operated (*n* = 144)
1	Isolated congenital stapes ankylosis (or fixation)	1. Footplate fixation a. Normal stapedial arch b. Monopodial stapedial arch c. Monocrural stapedial arch 2. Stapes suprastructure fixation a. Elongation of the pyramidal eminence b. Stapes - pyramidal process bony bar c. Stapes - facial canal bony bar d. Stapes - promontory wall bony bar e. More than one bony bar	30.6
2	Stapes ankylosis associated with another congenital ossicular chain anomaly	1. Incus and/or malleus deformation or aplasia of the long process of the incus 2. Bony fixations of the malleus and/or incus	38.2
3	Congenital anomaly of the ossicular chain but mobile stapes footplate	**Discontinuity of the ossicular chain** Aplasia of the long process of the incus Dysplasia of the long process of the incus	15.3
		Epitympanic fixation Malleus Anterior Superior Lateral Incus body Superior Lateral Medial Short process of the incus In incudal fossa **Tympanic fixation** Of the malleus handle Of the long process of the incus	6.3
4	Congenital aplasia or severe dysplasia of the oval or round window	**Aplasia**	6.9
		Dysplasia	
		Crossing (prolapsed) facial nerve Persistent stapedial artery	2.1 0.7

INCIDENCE OF CONGENITAL OSSICULAR ABNORMALITIES

Bergstrøm[4] reported that out of a group of 687 children with congenital hearing loss, only eight (1.2%) were found to have isolated middle ear anomalies. There is no systematic report of absolute incidence though Thringer et al.[5] reported the incidence of conductive hearing loss, severe enough to require amplification, to be 0.6:1000. These cases were all bilateral. The incidence of unilateral cases is unclear.

Cremers and Teunissen's series[2] does provide a relative incidence with stapes ankylosis with another associated ossicular chain anomaly being the most common finding (38%) with isolated stapes ankylosis being the other largest group (30%). Isolated anomaly of the ossicular chain was found in 22% and aplasia or severe dysplasia of the oval or round windows in 10%.

In a Japanese surgical series, Hashimoto et al.[6] reported a much higher rate of incudostapedial joint defects, either in isolation or with stapes fixation, making up nearly 50% of cases.

The majority of Cremers' cases were sporadic although in 25% they were part of a recognizable congenital syndrome including branchio-oto-renal, hemifacial microsomia, Klippel–Feil, Crouzon and Pfeiffer syndromes.

CLINICAL PRESENTATION OF CONGENITAL OSSICULAR ABNORMALITIES

Children with bilateral ossicular abnormalities will often present at a similar age to children with OME because of poor hearing performance and speech delay. It is not unusual that the children are managed with one or more sets of ventilation tubes before the diagnosis is made. The observation of a conductive hearing loss, normal tympanic membrane and normal middle ear pressure should lead to the general diagnosis.

INVESTIGATION OF CONGENITAL OSSICULAR ABNORMALITIES

Audiometry

There is an average threshold of approximately 50 dB, producing a flat air conduction line, with no low-frequency bias as with otitis media. There is an average air-bone gap (ABG) of 35 dB at 0.5-2 kHz, either due to Carhart's effect or because of the presence of an underlying sensorineural hearing loss. Tympanometry usually demonstrates a normal middle ear pressure with reduced compliance due to fixation of the ossicular chain.

Imaging

High resolution computed tomography (CT) scanning remains the primary imaging modality though complementary magnetic resonance imaging (MRI) studies may demonstrate associated labyrinthine and internal auditory meatal abnormalities. CT virtual endoscopy may offer a further mode of presenting the images for pre-operative surgical planning although currently it fails to image satisfactorily the stapes suprastructure.[7]

Exploratory surgery

The diagnosis may only be made during a tympanotomy, but an interesting alternative to lifting the tympanic membrane is to attempt to visualize the ossicles via Eustachian tube and middle ear endoscopy.[8] The innate risk of damage to the ossicles and extent of view with this technique is not yet well defined.

PRINCIPLES OF MANAGEMENT

As with all cases of hearing loss, children and adults with congenital ossicular abnormalities need to be managed with thought to their overall hearing performance and requirements.

In the presence of a bilateral moderate hearing loss due to a maximal or near-maximal conductive hearing loss, some form of auditory rehabilitation should be recommended. For the majority, this will mean a conventional unilateral or bilateral air conduction hearing aid. With minor malformations there should be a stable external ear canal as a platform for amplification. If the patient develops local complications in the external ear canal, such as recurrent or chronic otitis externa, a bone-anchored hearing aid (BAHA) would be a suitable alternative.

Unilateral cases are less well defined in terms of best management. In the presence of ipsilateral tinnitus, amplification may act as a tinnitus masker. A hearing aid may improve the patient's hearing performance in background noise and optimize sound localization. The positive benefits need to be weighed against the potential morbidity of a conventional hearing aid, which includes the occlusion effect, otitis externa and the body image issues involved in wearing hearing aids, particularly among children and adolescents.

Surgery for congenital ossicular abnormalities should only be undertaken by dedicated otologists with experience of complex middle ear reconstruction. When the diagnosis has been made in childhood, consideration for surgery should be preceded by an adequate trial of amplification. Whatever middle ear surgery is contemplated, but particularly with stapedotomy, there is a significantly higher risk of delayed sensorineural hearing loss due to sporadic episodes of acute otitis media in children under 10 years of age. By this time it may be appropriate to involve the child in the decision-making process or to wait until adolescence or adulthood to allow the patient to come to their own decision regarding surgical treatment.

A pre-operative CT scan would be a mandatory investigation to attempt to identify the ossicular abnormality, but also to visualize any other middle or inner ear abnormality such as an anomalous facial nerve, congenital cholesteatoma, aberrant vascular structures or labyrinthine dysplasia.

MANAGEMENT OF SPECIFIC CONGENITAL OSSICULAR ABNORMALITIES

Isolated stapes ankylosis

Tos[3] subdivided Cremers' basic classification to separate stapes ankylosis into two main groups, depending on whether the footplate or suprastructure is fixed (see **Table 12.1**). In 20% of cases the suprastructure may be abnormal, with one crus being absent (monocrural) or there being no recognizable crura but instead a single strut (monopodial).[9]

Congenital stapes ankylosis at the level of the footplate was first described by Shambaugh[10] in 1952. He emphasized the clinical contrast to otosclerosis, in particular that the margins of the congenitally fixed footplate and the annular ligament are difficult to visualize since the footplate bone blends into the bone of the surrounding otic capsule.

The pathological processes leading to stapes footplate fixation are unclear. Lindsey et al.[11] concluded from a temporal bone study that fixation occurs due to failure of the annular ligament to differentiate from the lamina stapedialis. This leads to continuous ossification from the otic capsule to the footplate. Nandapalan and Tos[12] argue, however, that the cause is a subsequent ossification of the already-formed annular ligament, around 16 weeks of gestational age, because any arrest of development at this stage would be likely to cause a more widespread inner ear abnormality.

An ossified stapedial tendon may develop because of a failure of its precursor to form a tendon and instead become cartilaginous like the neighbouring precursor of the pyramidal eminence.[12] This subsequently becomes ossified, fixing the stapes. The other rare forms of fixation of the stapes suprastructure are probably caused by the

persistence of the contact between the developing stapes and Reichert's cartilage, which is usually lost as the stapes forms.

Surgery for congenital stapes footplate fixation

Pre-operative scanning may demonstrate labyrinthine dysplasia, any degree of which should alert the surgeon to an increased risk of inner ear damage. In particular, a dilated fundus of the internal auditory meatus (IAM) should be sought. This is a feature of X-chromosome-linked progressive mixed deafness with perilymphatic gusher.[13] The dilation of the IAM is associated with a defect allowing communication of cerebrospinal fluid (CSF) with the labyrinthine, which is released through a stapedotomy and leads to a high rate of sensorineural hearing loss. The high perilymph pressure may be the cause of the apparent conductive element of the hearing loss, which may mask the principal sensorineural nature of the raised air conduction thresholds. A previously reported association with a 'patent cochlear aqueduct' has been shown to have no histological basis in temporal bone studies.[14] The aqueduct is normally patent and cases of so-called 'widely patent' ducts seem to relate to a flaring on the medial aspect of the duct as it enters the jugular foramen. There is little variation in the duct as it passes through the otic capsule.

The surgical technique is similar to otosclerotic stapes ankylosis. A common feature of congenital fixation is the presence of thick anterior and posterior crura. To reduce the risk of inner ear damage these may be vaporized with a KTP laser.[15] This may also be used to aid the formation of a stapedotomy as the footplate is often thick.

Reported outcomes of surgery from specialist centres for isolated congenital fixation of the stapes nearly match the outcomes in the literature for adult series for otosclerosis, with more than 70% closure of the ABG to 20 dB or less.[6, 16] However, excellent results, with an ABG of less than 10 dB, seem less common than with surgery for otosclerosis.[17] Rates of inner ear damage are also comparable.

Surgery for stapes suprastructure fixations

In the very rare cases where the footplate is mobile but the suprastructure is fixed, removal of the bony bar can be achieved using a CO_2, argon, potassium titanyl phosphate (KTP) or erbium laser or with a microdrill. Traditionally, this has been achieved with a curette or by fracturing with good results.[12]

Isolated non-stapes middle ear anomalies

There is a large variety of described anomalies among case reports in the literature and these represent the different subclasses in Table 11.1. In addition, the stapes itself, though mobile, may be dysplastic.

The surgical management is by appropriate tympanoplasty. If there is attic fixation, then a separate atticotomy is necessary to expose the problem and allow surgical treatment. If there is a bony bar, this can be relieved by laser, microdrill or curette. A similar approach is used with fixation of the malleus handle by an atretic plate. With the absence of the long process of the incus, an interposition prosthesis is indicated.

Stapes ankylosis associated with other deformities

The potential anomalies are as described when found in isolation. Stapedotomy is again indicated but it may be necessary to consider a mobilization of the ossicular chain if there is epitympanic fixation or a malleovestibulopexy following removal of the head of the malleus.[6] Though surgery is difficult in cases of a deformed incus or fixations of the incus and malleus in the attic, reported results are good.[17]

Congenital aplasia or severe dysplasia of the oval and round windows

The stapes crura are usually poorly developed and do not reach the region of the footplate and may be embedded in the facial nerve. In such cases the course of the facial canal is often anomalous.

With such a severe abnormality preventing conduction of sound energy into the inner ear and particularly with the risk of a facial palsy with an anomalous facial nerve, auditory rehabilitation with hearing aids or a BAHA may be most appropriate. The potential surgical solutions have significant drawbacks. A fenestration procedure would leave a cavity requiring long-term care. A neo-oval window operation, in which a *de novo* entrance into the labyrinth is either drilled on the promontorial or even on the rostral side of the Fallopian canal, has a high risk of inner ear damage.[2]

NON-OSSICULAR CONGENITAL MIDDLE EAR ABNORMALITIES

Persistent stapedial artery

The stapes forms around the stapedial artery, leading to formation of the obturator foramen. By 10 weeks of development the artery atrophies, leaving a patent foramen underneath the arch of the stapes. If persistent, it arises from the petrous internal carotid artery (ICA), traverses Jacobsen's canal for a short segment, exits at the promontory, passes through the stapes obturator foramen and enters the Fallopian canal close to the cochleariform process. The persistent stapedial artery (PSA) passes anteriorly, exiting the canal at the geniculate ganglion, and passes into the extradural space of the middle cranial fossa, where it gives rise to the middle meningeal artery. In the presence of a PSA, the foramen spinosum is usually

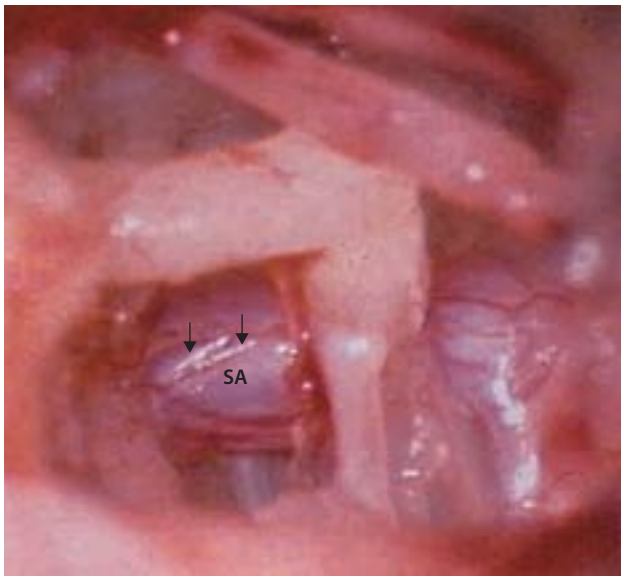


Figure 12.1 Finding during stapes surgery – a persistent stapedial artery (PSA).



Figure 12.2 Stapes may be normal and mobile, even in the presence of a bifurcated facial nerve.

absent and the ICA may have an aberrant course due to its collateral formation secondary to a segmental agenesis of the ICA.[18]

A PSA may present as a vascular mass within the middle ear,[18] found either during otoscopic examination of the ear or during middle ear exploration, but is often asymptomatic or the cause of pulsatile tinnitus and has no relationship to conductive hearing loss.

It may also present as a chance finding during stapes surgery (Figure 12.1). It is unclear whether the discovery of a PSA during a stapedectomy indicates a congenital fixation or is coincidental in cases of otosclerotic stapes ankylosis.

Traditional teaching has been that the presence of the artery is an absolute contraindication to stapedectomy, partly as it was thought that damage to the artery would lead to ischaemic damage to the facial nerve. Govaerts et al.,[19] however, reported 12 cases, including two of their own, in which the outcome of surgery was satisfactory. In three cases the artery was damaged or clipped without any post-operative complications.

Anomalous course of the facial nerve

The Fallopian canal may show dehiscence or have an anomalous course within any part of its course within the temporal bone. This has great surgical significance and may be a hazard in all forms of tympanomastoid surgery. An abnormal course is particularly common with microtia or with dysplasia of the oval and round windows and there should be a high index of suspicion in any surgery for congenital conductive hearing loss and the use of the facial nerve monitor is highly recommended.

The Fallopian canal arises from the otic capsule and the second branchial arch and a theory of the cause of an anomalous facial nerve is a failure of fusion of the two. As there is a relatively high association with other ossicular abnormalities other than of the stapes, a local teratogenetic effect may also be responsible.

Rohrt and Lorentzen[20] classified facial nerve displacement in the middle ear into four groups:

- facial nerve partially obliterates the stapes footplate
- bifurcation of the facial nerve
- facial nerve rests on the footplate with deformed stapes or oval window
- facial nerve rests on the promontory.

Although these abnormalities are often found in association with stapes fixation, it may be normal and mobile, even in the presence of a bifurcated facial nerve (Figure 12.2).

Congenital perilymphatic fistula

Congenital perilymphatic fistula (PLF) is an abnormal communication between the middle and inner ear. It may be associated with:

- microfissures around the oval and round windows
- labyrinthine or IAM dysplasia.

The diagnosis is controversial as there is no reliable preoperative test which identifies the condition and management is based on the suggestive diagnosis of a child presenting with progressive or fluctuating sensorineural hearing loss, possibly associated with vertigo. Weber et al.[21] define the intra-operative diagnosis as being based on the identification of clear fluid which reaccumulates with anaesthetic Valsalva or Trendelenburg manoeuvre. Beta-transferrin positive samples are consistent with CSF being a constituent of the leak and this will be a feature of some but not all cases of PLF, usually associated with

labyrinthine or IAM dysplasia. This is not a real-time test during the surgical procedure and is very specific but not very sensitive for PLF, which may not contain CSF.[22]

In view of the difficulties of diagnosis, Weber et al.[21] suggest the policy of packing temporalis muscle around the oval and round windows in all suspected cases. This is based on the observation that packing does not seem to cause any significant complications (such as a subsequent conductive hearing loss) and he argues that it may be beneficial despite no confirmation of a PLF. In his series of 160 ears with suspected PLF there was a greater than 90% rate of stabilization or improvement in hearing in both PLF-positive and PLF-negative cases, though he acknowledges that in other series there is a similar outcome in nearly half of cases without packing.

High jugular bulb

A high jugular bulb (HJB) is usually asymptomatic and discovered as an incidental finding on otoscopy or during middle ear surgery. It can cause heavy bleeding from accidental puncture while lifting a tympanomeatal flap or even inserting a ventilation tube.

The jugular bulb can be defined as 'high' if it reaches the level of the inferior bony annulus and is often covered by thin bone or is dehiscent. In the presence of a plethoric mass within the tympanic cavity, the differential diagnosis will include HJB, aberrant ICA, a PSA and a glomus tympanicum tumour.

An HJB can be associated with hearing loss. If it includes a medial portion impinging on the cochlear or vestibular aqueduct, a connection with vestibular symptoms and a sensorineural hearing loss has been suggested. There may be a more direct association with a conductive hearing[23] loss due to interference with the ossicles, contact with the tympanic membrane and obstruction of the round window niche.

Major surgery to occlude or reroute an HJB is unlikely to be justified by symptoms alone, though there are occasional reports of intrusive pulsatile tinnitus associated with an HJB. It is possible to consider endovascular occlusion in the rare case of persistent haemorrhage, when tympanic cavity surgery is contraindicated.[24]

Aberrant internal carotid artery

This may be associated with other vascular abnormalities such as a PSA and likewise present as a vascular middle ear mass. Associated symptoms include pulsatile tinnitus, which may be objective, and hearing loss. In approximately 20% of cases it is bilateral.[25]

An aberrant ICA is an important differential diagnosis of a glomus tympanicum tumour, which can be resolved by CT scanning. Brisk bleeding, hemiparesis, aphasia, deafness, Horner syndrome and intractable vertigo may result if the vessel is unintentionally injured.[25]

BEST CLINICAL PRACTICE

- ✓ Unless deafness is bilateral, management can be conservative.
- ✓ If there is bilateral hearing loss, auditory rehabilitation will be required.
- ✓ Surgery is difficult with uncertain outcomes and best considered only by those with specific training and experience.
- ✓ Surgery may be best deferred until children can participate in the process of informed consent.

FUTURE RESEARCH

- ➤ The incidence, aetiology and pathogenesis of congenital ossicular abnormalities is poorly understood.
- ➤ The role of otoendoscopy in the diagnosis and management of these conditions needs to be better defined.
- ➤ Developments in middle ear implantation may render corrective surgery almost redundant.

KEY POINTS

- Congenital abnormalities of the middle ear may occur in association with major malformations such as microtia.
- Isolated malformations are rare but include anomalies of the ossicular chain and the middle ear vasculature.
- Diagnostic delay is common. Deafness due to ossicular pathology is often misdiagnosed as otitis media with effusion. It is not unusual for children to have repeated ventilation tubes before the correct diagnosis is made.

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CHAPTER 13

OTITIS MEDIA WITH EFFUSION

Peter J. Robb and Ian Williamson

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SEARCH STRATEGY

Data in this chapter may be updated by searches in The Cochrane Library, Medline, Google Scholar and PubMed, using the keywords: adenoid, adenoidectomy, biofilm infection, gastro-oesophageal reflux, otitis media, otitis media with effusion, ventilation tubes. References from selected articles were reviewed after reading the abstract and included where relevant.

DEFINITION

Otitis media with effusion (OME) is the accumulation of mucus within the middle ear and sometimes the mastoid air cell system. Persistence of the fluid for the condition to be described as chronic is normally taken as 3 months or longer.[1] In children, OME may present with hearing loss, but also delayed speech and language development, poor social behaviour and, in younger children, difficulties with balance. There is sometimes a clearly defined history of preceding respiratory tract infection and otalgia with an episode of acute otitis media. The condition is widely known among both doctors and the general public as 'glue ear'. Approximately 80% of all children will have had a single episode of OME before the age of 3 years and 40% will have three or more episodes.[2] In the USA, the cost of managing all forms of otitis media is estimated at US$5 billion (£3.2 bn, €3.7 bn) annually.[3]

When childhood OME is preceded by an episode of acute otitis media, however, this typically follows a viral upper respiratory tract infection, associated inflammation and infection of the adenoid, secondary bacterial infection with a cascade of inflammatory mediators,[4] upregulation of mucin genes and effusion from the middle ear mucosa. In many children with OME there is no clear history of acute otitis media. Research currently in progress indicates a genetic inheritance of susceptibility to OME, causing impaired middle ear oxygen metabolism.[5] It is likely that ventilating the middle ear establishes a higher oxygen tension in part, inhibiting bacterial biofilm activity.

AETIOLOGY AND PATHOGENESIS

Histology

The Eustachian tube and anterior mesotympanum are lined by ciliated, pseudostratified columnar respiratory epithelium. The mucosa contains both goblet cells and mucus-secreting glands.[6] Inflammation of the epithelium and production of a serous or mucus effusion results in OME. In established OME, the flat cuboidal middle ear mastoid mucosa may be replaced by thicker pseudostratified mucus-secreting epithelium with varying degrees of specialization, such as the development of cilia. Goblet cells are frequently present and sometimes mucus-secreting glands are formed. The ciliary lining would appear to be less efficient at moving the secretions into the nasopharynx than normal.[7] The submucosa is oedematous and inflamed with dilated blood vessels and an increased number of macrophages, plasma cells and lymphocytes.

CHARACTERISTICS OF THE EFFUSION

The effusion varies in composition but is predominantly made up of the glycoprotein mucin. Also present in the effusion are secretory immunoglobulin A (IgA), lysozyme, interleukins and other inflammatory cytokines. Rheological adhesiveness and poor mucociliary transportability are characteristics of the effusions and the behaviour of the mucosa predicting persistence of the effusion and the need for surgical drainage and middle ear ventilation.[8, 9]

Microbiology

Positive bacteriological cultures of middle ear aspirate of OME fluid in children (more than 2 months' duration) produces the anticipated range of respiratory bacteria, including *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Branhamella* (*Moraxella*) *catarrhalis*.[10] However, 66% of the cultures were negative using traditional culture techniques, and no pathogens were cultured from fluid that had been present for at least 6 months. In contrast, using polymerase chain reaction techniques (PCR), 36% of middle ear mucosal biopsy specimens demonstrated intracellular *Streptococcus pneumoniae*.[11] The authors concluded this as important supporting evidence as a mechanism for bacterial persistence. Biofilms, which are communities of sessile bacteria, resistant to disruption and with a low metabolic rate, are embedded in a matrix of extracellular polymeric substances of their own synthesis. These communities may adhere to a foreign body or a mucosal surface with impaired host defence.[12] They are increasingly implicated in chronic inflammatory conditions such as OME. Biofilms were demonstrated in 92% of middle ear mucosal specimens of patients undergoing ventilation tube surgery for OME.[13] High-grade biofilm formation is also found on adenoid samples removed at surgery, supporting a role for adenoidal biofilm in the aetiology of OME. Adenoidal size is not correlated with biofilm formation, supporting the hypothesis that inflammation associated with the biofilm rather than adenoidal size per se blocking the Eustachian tube is the critical factor.[14] The contribution of biofilm formation in the middle ear and adenoid and the pathogenesis of OME is not yet completely understood, but it is likely that the biofilm is a secondary bacterial effect following viral respiratory tract infection, contributing to inflammation and mucus production. It is possible that those with a genetic defect of middle ear oxygen metabolism are predisposed to persistent OME with all its clinical manifestations.

Craniofacial abnormalities

OME occurs in nearly all infants and children with a cleft palate, and surgical repair of the cleft does not appear to reduce the incidence. The palatine muscles controlling Eustachian tube opening remain deficient through loss of decussating muscle fibres across the midline of the soft palate. In this group, OME has an incidence of at least 20% of 10-year-olds.[15] Children with a bifid uvula do not appear to have a higher incidence of OME[16] although, if adenoidectomy is combined with insertion of ventilation tubes, a sub-total removal should be performed under direct vision to reduce the potentially higher risk of velopharyngeal insufficiency.

It is unlikely that there is any correlation between dental malocclusion and OME.[17] While the incidence and persistence of OME in Down syndrome is well recognized, there is little evidence to clarify the factors contributing to the natural history of OME in those with Down syndrome.

Allergy

There is conflicting evidence on the importance of atopy and allergy in the pathogenesis of OME in childhood. In a validated questionnaire study of 89 children, with OME confirmed at the time of ventilation tube insertion, no difference in prevalence of allergic symptoms was found between the OME and reference group. Symptoms of nasal obstruction were significantly more prevalent, but this might represent adenoidal hyperplasia rather than allergic rhinitis.[18] In contrast, of 209 children with a history of OME extensively assessed in a specialist allergy clinic, 89% had evidence of allergic rhinitis, 36% had asthma and 24% eczema.[19] In addition to clinical history and examination, the assessment was based on nasal smears and skin prick testing, with blood eosinophil count and total immunoglobulin E (IgE) in a randomly selected subset. Such a study setting is subject to referral or spectrum bias. The worldwide prevalence of allergic rhinitis is 20%. The higher 89% figure reported in this study points towards a likely allergic component in many referred children with OME because of the strength of the association.[20] Furthermore, children with OME with a family history of allergy are more likely than controls to have a positive finding of rhinovirus in the middle ear cavity, indicating a link between viral respiratory tract infection and allergy predisposing to middle ear disease.[21]

Gastro-oesophageal reflux

The role of gastro-oesophageal reflux in the pathogenesis of OME in childhood is unclear, although it is known that, during swallowing, fluid can travel from the nasopharynx via the Eustachian tube into the middle ear. Gastro-oesophageal reflux is common in children, occurring in up to two-thirds of infants at 4 months of age, but decreasing thereafter.[22] Pepsin was first identified in middle ear effusions in 2002.[23] (Bile acids have also been identified in samples of middle ear fluid in children with OME.)[24] Biochemical analysis of middle ear fluid in OME suggest that pepsin is present in approximately 80% of samples at a level 1000 times higher than serum levels.[25] Mucosal damage is postulated to be mediated by the proteolytic activity of pepsin.

Pepsinogen immunoreactivity in adenoid tissue of children with OME has been found to be significantly higher than matched controls with no history of OME.[26] In this study, pepsinogen was detected in 84% of middle

ear effusions. *Helicobacter pylori*, confirmed by PCR assay, has been detected in middle ear effusions in 9/55 (16.3%).[27] An animal study concluded *H. pylori* did not per se cause a middle ear effusion, but rather contributed to the inflammatory process in the presence of middle ear fluid.[28] Gastro-oesophageal contamination of the middle ear appears not to correlate with symptomatic gastro-oesophageal reflux disease (GORD).[29]

The evidence in favour of a role for gastro-oesophageal reflux in the cause and/or persistence of OME is accumulating, but the relation between cause and effect, if any, is not fully understood. A systematic review of 242 studies (of which 15 met the inclusion criteria) concluded there is insufficient evidence to recommend antireflux treatment for otitis media with effusion.[30]

EPIDEMIOLOGY

The epidemiology of OME has been extensively studied in many countries. The studies include cohorts of children followed up at regular intervals for periods between birth and approximately 10 years of age. Most such studies are not designed or inadequately control for confounders (risk factors/effect modifiers). The background prevalence of OME is very high, making long-term effects difficult to evaluate with children frequently switching between having the condition and being clear of the condition. The prevalence of a condition is the number of true cases identified in a carefully estimated population (that might become cases) either over a fixed period or at any time point. Case ascertainment can be quite variable so tympanometry is recommended for larger studies (see 'Diagnosis' below for test characteristics). Such prevalence data are useful as an indicator of the potential clinical workload and the scale of the problem to children, their families and society. The incidence and remission rate of a condition measure the chances or rate of developing the condition and its clearance over a defined time frame respectively, which because of the chronic relapsing/remitting nature of the condition adds much value to the picture of the natural history, knowledge of which should help guide management decisions. In childhood OME, the two main determinants of the prevalence and incidence rates are the age of the child and the season of the year. When considering the evidence in this area there are many case-cohort level 2b studies to report from, but most of the larger well-conducted methodological studies are not recent.

Association with age

Zielhius et al.[31] reviewed a total of 23 studies that all used tympanometry as one of the diagnostic instruments to give age-specific prevalence rates up to 10 years of age. The background prevalence is bimodal with the first and largest peak found in approximately 20% of children aged 2 years. This is around the time when many children extend their social contacts, at playgroup or nursery school for example. Thereafter, the prevalence shows a dip with a second peak of approximately 16% in 5-year-olds, when most start attending a primary school. A study using a diagnostic algorithm of tympanometry combined with otoscopy in an attempt to improve precision, suggested that the early peak is most likely occurring around 1 year of age.[32] By the age of 8 years, the background prevalence in UK schoolchildren fell to 0–6% depending on time of year, whereas 5-year-olds had a higher season dependent range of 13–20%, 6-year-olds 8–13% and 7-year-olds 4–10%.[33]

Association with season of the year

In temperate climates, the effect of the season on the prevalence of OME has been recognized for many years, with around twice as many children being diagnosed with OME in the winter as in the summer months.[33–37] The most likely reasons for seasonal variation are the increased frequency of upper respiratory and ear infections in the winter, including the effects of seasonal influenza, and the greater chance of passing on infections between children because of the closer household contact in cold weather. If these factors are controlled for by analysis, however, the effect of season is no longer as evident,[38] but is demonstrated in other studies.[39, 40]

Little data exist for the effect of season from countries in non-temperate climates. The background prevalence of OME in Mediterranean children[41, 42] and subtropical countries[43, 44] does not appear to be very different from those in temperate countries but no independent effects for season are available. One study based in the northern tropical country of Vietnam showed increase in seasonal prevalence of OME from 3% to 11% when comparing the dry April with the December chilly rainy season.[45]

Risk factors for OME

The identification of the clinically most important risk factors is a key aspect of child health and clinical management because of the potential wide-scale benefit if these are able to be addressed, such as by strategic use of vaccines. Any identified risk factors cannot be assumed to apply equally to all age groups, for example breastfeeding effects may be greatest in the youngest cohorts. On *a priori* grounds, the risk factors for persistence of OME may well be different from the risk factors for its actual occurrence (incidence). Also one needs to consider the behavioural and clinical expression of the biological features including hearing impairments such as poor speech, or schoolwork that might be expected to relate more to how long the fluid has been present, and additional risk factors for 'disability' such as poor communicating styles.

When comparing evidence from risk factor studies it should be noted that potential factors are often inconsistently evaluated in the literature and heterogeneous, due to design issues, different populations, lack of agreement about what they are, and how to measure them uniformly and reliably. Often such studies have too few subjects with a particular characteristic to evaluate it reliably: for example, there are not many 5-year-old children who do

not go to school in the UK. A multivariate analysis can control for potential confounding variables. If low socioeconomic group is a mooted factor, for example, is it the small house, the number of siblings, the smoking, the junk food or the lack of a maternal university education and a car that makes the difference? It is unlikely to be all of these. Interim surgery in some risk factor cohort studies may complicate the analysis and interpretation, as it is clearly an important effect modifier of the outcome. It is deemed very likely that the risk factors for the occurrence of unilateral and bilateral OME will be the same. This premise has been experimentally confirmed by Engel et al.[40] That is why, in randomized clinical trials of children with OME, children rather than ears should be the unit of analysis for the primary outcome (because the ears are not independent variables).

Risk factors can be of interest in helping to understand why some individuals are more prone than others to suffer from a condition. Many journals prefer these presented as relative risk (RR) as easier to comprehend, although odds or hazard ratios may be used. In any specific individual, the number of risk factors present can be used as an approximate estimate of the risk of developing the condition. Usually, however, the relative risks for any single factor are only small (around two) and, to date, combinations of risk factors have not provided a sufficiently good or reliable guide for referral or interventions, although some factors may be modified.

Acute otitis media

In the age most studied, i.e. 0–2 years, recurrent episodes of acute otitis media (AOM) are frequent and this is likely to be the largest single group for developing persistent ear effusions. Each acute episode increases the reported odds ratio of developing OME by 12 (95% CI 6, 25) but this risk level no longer remains after 3 months.[46] Hence, the known risk factors for AOM, such as prematurity, frequent upper respiratory infections and non-breastfeeding, will apply in such clinical situations (OME preceded by AOM).[47] Studies of children in this age group that do not report the important frequency of AOM must also be considered less than optimal for clinical use in OME. There is no evidence that any medical management of AOM, including antibiotics, makes any difference to the chances of developing subsequent OME.[48]

Risk factors found in addition to AOM in a multivariate analysis confirm the increasing effect of age up to 2 years but also the effect of having siblings and a family history of them having OME.[38] Another study that otoscopically assessed family members of children with OME rather than just relying on historical reports found that 32% of siblings and 19% of parents were classified as otoscopically affected.[49] Other multivariate studies have suggested that, in addition to the number of siblings, attendance at day care with four or more other children up to 3.5 years of age can approximately double the risk (CI 1, 3).[39, 50] An international systematic review of risk factors found that the main risk factors for otitis media in populations were: attending day care, number of siblings, smoking, not breastfeeding, low birthweight and socioeconomic status.[51] Some of these factors are potentially modifiable (e.g. the number of children in day-care settings could be reduced to lessen this risk), but for most parents availability, convenience and cost are limiting determinants.

Genetic factors

In a same-sex twin/triplet prospective cohort study, Casselbrandt et al.[52] looked at sets where the zygosity was known. In children who had OME during the first 2 years of life, there was greater concordance in monozygotic sets in both the number and duration of OME episodes than in dizygotic sets. The magnitude of the effect of heredity in comparison to other risk factors for OME was not investigated. More recent work in mouse mutant models of chronic otitis media (COM) where hypoxia in microenvironments is known to be aetiologically important has demonstrated upregulation of hypoxia inducible factor (HIF) and vascular endothelial growth factor A (VEGFA).[53] This paves the way for targeted therapeutic interventions in future studies, although transferability of mouse-model findings to humans requires some caution and fuller evaluation.

Race

Whether the prevalence of OME is truly different in different races requires control for many other factors. When factors including socioeconomic group and child contacts are controlled for in a multivariate analysis, the prevalence in black children is no different from white children.[54] Chinese children may have a lower overall prevalence, but a multifactorial analysis has not been reported.[44]

Gender

Some multivariate studies report the risk of developing OME to be no different between boys and girls.[39, 40, 55] Some studies report a higher risk in boys[46, 49] and others a higher risk in girls.[38] It must be concluded that there is likely to be little difference, if any, in the background risk for boys compared to girls, with most epidemiological studies showing comparable base rates.

Smoking

For public health reasons, parental smoking has frequently been reported as a risk factor for the occurrence of OME. However, in one multivariate analysis when other factors had been controlled for, no effect of parental smoking was detected[40] but in another study it was found present for smokers of up to 20 cigarettes per day.[39] A large, more recent epidemiological study noted a temporal decline in consultations for otitis media, which was attributed to an increase in smoke-free households.[56]

Duration and recurrence of episodes

One large study of 1328 children aged 1–2 years showed the duration of episodes in individual ears was very skewed; the median duration of effusions was 3 months

or less, but the 95th percentile was at 12 months. Half of affected ears had resolved after 3 months. However, around 50% of the ears that resolved had a further episode.[57] What happens in individual infants rather than in ears has been well documented by Paradise et al.[54] in a large cohort (n = 2253) followed up from 2 months of age to 6, 12, 24 months of age, who found that 49%, 79% and 91% of infants respectively had had at least one episode of OME.

Hogan et al.[58] followed up 95 full-term infants monthly for 3 years. Overall, infants were twice as likely to develop unilateral as opposed to bilateral OME. One month later, in infants with a unilateral effusion, the majority (50%) had resolved, a minority (20%) had become bilateral and the other 30% remained unilateral. In those with bilateral effusions at the start, the majority (60%) remained bilateral 1 month later. In the others (40%), bilateral resolution was more frequent than unilateral resolution (in a ratio of 3:1).

An older cohort of 856 British children aged 5–8 years was screened three times a year (approximately every 4 months) for 3 successive years.[33] In a subsample of 67 ears with B tympanograms and with three consecutive screens, the resolution rates (to a non-B) at 4, 8 and 12 months were 52%, 78% and 91% respectively. The overall recurrence rate for this community study was quite low at 7%. A more detailed monthly study of 7-year-old Danish pupils (n = 387) reported the mean overall duration of an ear episode to be 1.8 months with 12% lasting more than 6 months.[59] Ears first diagnosed to have OME between September and February persisted longer than those first diagnosed between March and August.

Risk factors for persistence

Three studies have been identified that have followed up children to identify risk factors that might be used to predict those who are more likely to have persistent bilateral OME. One study was carried out in primary care and followed up children of 6 months or older for 3 months.[60] Another study was of children aged between 3 and 7 years referred from primary care with suspected OME and seen at secondary care on average 13 weeks later.[61] The third study was of children of the same age identified at secondary care to have bilateral OME with an associated hearing impairment in both ears of at least 20 dB hearing loss. These children were followed up for 3 months to identify those in whom the OME persisted bilaterally with the same degree of impairment.[62–64]

In these three studies, which all followed up the children for 3 months, the persistence rates of bilateral OME were 56%, 35% and 51% respectively. All studies identified the second half of the year (July–December) as a major risk factor, with odds ratios of between two and three. In primary care, whether a child has frequent or upper respiratory symptoms at the time of assessment is also an important determinant of persistence. In secondary care, the degree of associated hearing impairment predicted persistence. The only factor that might have had an influence and has the potential to be modified was whether the mother smoked, and this was a significant multivariate factor in the secondary care study.[61] In all three studies, the magnitude of the effect of any factor singly or in combination was insufficient to predict with reasonable certainty those likely to persist or resolve.

Clinical summary of best epidemiological evidence

The prevalence of OME in childhood is age-dependent, with two peaks in the distribution, one centred around 1–2 years of age and the other around 3–7 years of age.

In temperate countries, twice as many children have OME in the winter as in the summer. The increased frequency of upper respiratory infections and close contact with other children during the winter months contribute to this association.

Under 3 years of age, episodes of AOM, contact with other children and heredity are factors that increase the risk of occurrence. Unilateral OME is twice as common as bilateral OME. Those with a propensity to develop OME have more frequent episodes rather than longer episodes. Bilateral OME is more likely to persist than unilateral OME. In primary care, children with bilateral OME and a history of upper respiratory infections are more likely to persist. In secondary care, children with bilateral OME seen in the second half of the year (July–December) with a hearing impairment of 30 dB HL in both ears are more likely to persist.

None of the factors for persistence singly or in combination are sufficient to negate a requirement for a 3-month period of active monitoring before considering surgery.[65]

DIAGNOSIS

History

Parental recognition of hearing loss in their child is perhaps surprisingly only poorly correlated with OME. In a population-based study of 117 children with OME and 159 controls, parental suspicion of their child's hearing loss in the affected group was only 19.7%.[66] Furthermore, parents of children with OME tend to underestimate the severity of the hearing loss and overestimate their child's quality of life when assessed with the validated OM-6 questionnaire.[67] When parents were reassessed after surgical treatment of their child's OME, there was a significant response-shift bias for both hearing loss and quality of life. Indeed, many parents report concerns other than hearing loss, including poor speech and language development and signs of difficulties with balance. When balance was formally tested, one study reported improvement in balance with practice, but less so in those children with OME until after ventilation tube insertion.[68] In a case-control study, the post-surgery treatment group had a statistically significant decrease in sway velocity compared to the control group.[69] Children attending day care or nursery also may cause their carers or teachers concern, because of inattention and behavioural problems.[70] Difficulty taking part in group activities due to the hearing loss associated

with OME actually reflects an underlying impaired ability to process speech in noise which is more noticeable in this context than in one-to-one situations with primary carers.[71]

Taking a history, it is important to confirm a normal pregnancy, delivery and neonatal period and that neonatal hearing screening was performed and reported as normal. A very small number of children may pass neonatal hearing screening and have or develop sensorineural hearing loss during early childhood. It is important to be aware of the possibility of OME coexisting with a mixed hearing loss. Children with comorbidities (e.g. Down syndrome, cleft palate) are more commonly affected by OME, and this is usually more persistent.

Examination

OTOSCOPY

In some children, otoscopy may not be possible, either because the child is unable to cooperate or because the view is obscured by wax. In primary care, sodium bicarbonate or olive oil eardrops are often prescribed to soften and encourage dispersal of the wax. In second-tier community clinics and in secondary care, tympanometry and audiometry will usually provide sufficient additional information on the level of hearing loss, with or without wax obscuring the view of the tympanic membrane (**Figure 13.1**).

Otomicroscopy

In a study of 81 children (155 ears) using otomicroscopy with myringotomy under local anaesthesia as the reference standard, otomicroscopy showed better diagnostic agreement with myringotomy than otoscopy or tympanometry.[72] While not applicable to the outpatient clinic setting, intra-operative otomicroscopy performed by a specialist otolaryngologist in the anaesthetized child prior to myringotomy achieves greater diagnostic accuracy than pneumatic otoscopy and tympanometry. The overall accuracy of otomicroscopy was 94.1%.[73]



Figure 13.1 Normal right tympanic membrane. (Image courtesy of Mr Michael Saunders.)

Pneumatic otoscopy

When performed by trained specialists, the sensitivity of pneumatic otoscopy ranges from 85% to 93% and its specificity from 71% to 89%. However, these calculations omitted up to 20% of the children in whom pneumatic otoscopy was not possible.[74] Including these children alters the sensitivities and specificities dramatically. The sensitivity and specificity of pneumatic otoscopy, even where practicable, would be markedly poorer in practitioners whose skills have not been validated.[75] In contemporary practice, many clinicians will rely on a combination of otoscopy and tympanometry when assessing small children.

TUNING FORK TESTS

In a study of 58 children, aged between 2 and 11 years, the Rinne and Weber tuning fork tests poorly predicted conductive hearing loss in children with OME compared with pure tone audiometry. The results were independent of the child's age.[76] Tuning for tests should not be relied on to assess conductive hearing loss.[77]

FREE-FIELD VOICE TESTING

In primary care, audiometry is seldom available, particularly for younger children. In children over the age of 3 years, the sensitivity of modifications of the voice test administered by experienced examiners (e.g. use of pictures to point at or two-syllable words) is 80–96% and the specificity is 90–98%.[78] However, these outcomes are unlikely to be achieved when carried out by less experienced examiners in a primary-care setting.

Investigations

TYMPANOMETRY

For more than 30 years, tympanometry using an automated impedance meter (see Chapter 51, Psychoacoustic audiometry) has been widely available as a method of detecting OME. While an acoustic seal is sometimes difficult to achieve, bilateral tympanograms are generally obtainable in 98% of children between the ages of 3.5 and 7 years,[79] in 90–94% of infants 2–11 months of age[80] and 78–88% of infants 12–24 months of age.[81]

A modification of the Jerger classification is the most commonly used in clinical practice.[31, 82] This uses compliance and pressure as the numerical parameters, presented visually as a compliance curve (**Figure 13.2**).

Comparing the finding of middle ear fluid at the time of myringotomy, soon after tympanometry, a type B tympanogram is frequently associated with OME; a type A is infrequently associated with OME and a type C falls in between.[84] This study did not, however, subdivide type C tympanograms as type C_1 or C_2.

Overall, a number of level 1 evidence studies conclude that a type B tympanogram compared with all other types of tympanogram has a sensitivity of between 56% and 73% and a specificity of between 50% and 98% in detecting OME confirmed at the time of myringotomy.[84–86] Compared with

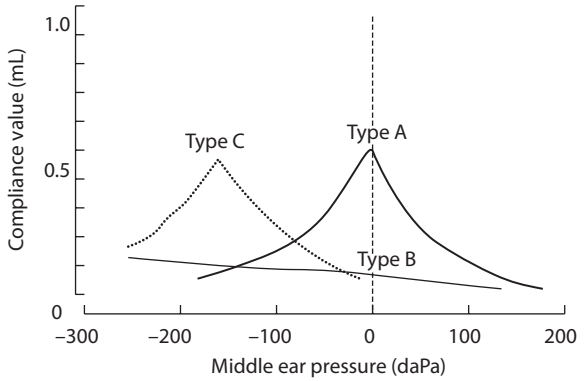


Figure 13.2 Tympanogram trace types.[83] A, peak between +200 and –99daPa; C, peak between -100 and -399daPa (further subdivided into C1, peak between –100 and –199daPa; C2, peak between –200 and –399 daPa); B, no observable peak between +200 and –600 daPa (Image courtesy of Mr Michael Saunders.)

all other types, a type B plus C_2 has a greater sensitivity of between 73% and 99%, and a specificity of between 40% and 74%.[87–90] The reasons for such a wide range of values are unclear and can be only partly explained by the differing proportion of ears with OME (sample bias). When nitrous oxide is omitted from general anaesthesia at the time of myringotomy (excluding the risk of a 'false dry tap'), the sensitivity and specificity of a Jerger type B trace predicting middle ear fluid is 0.73 and 0.84 respectively.[91]

Tympanoscopes

Automated, hand-held tympanoscopes (screening tympanometers) have the advantages of portability and lower cost and are particularly suited for primary care. In a primary care setting, when this equipment is used by trained operators,[92, 93] and a type B tympanogram is classified with a type C_2 tympanogram, the sensitivity and specificity (100% and 75%) is comparable to conventional impedance bridge tympanometry.[94, 95]

TYMPANOMETRY IN COMBINATION WITH OTOSCOPY

The diagnostic predictability of otoscopy and tympanometry, when in agreement, can be referenced against the findings at myringotomy.[96] When otoscopy suggests OME and is associated with a type B tympanogram, the combined sensitivity is 98%. When otoscopy suggests no OME and is combined with a type A tympanogram, the specificity is 98%. However, in this study the findings were in agreement in only 44% of ears. In the 56% where the results were not in agreement, another indicator of OME such as audiometry would be required to confirm the diagnosis. A combined otoscopy and tympanometry sensitivity and specificity were calculated for those otoscopy and tympanometry determinations in agreement, revealing both sensitivity and specificity above 90%.

ACOUSTIC REFLEXES

Measuring the acoustic reflexes in association with classification of tympanometry as peaked/non-peaked substantially lowered its specificity while adding little to the sensitivity, and it is therefore not recommended.[97, 98]

AUDIOMETRY

Audiometric assessment is mandatory for all children referred to secondary care with a suspected hearing impairment. While all children in the UK will have an objective neonatal hearing assessment, this does not guarantee continuing, normal hearing throughout childhood because some will develop sensorineural hearing loss. If a hearing loss is diagnosed in the absence of OME, this should be pursued with further hearing assessment, including bone-conduction thresholds and objective electrical response audiometry. Approximately 1% of children will have a previously undiagnosed congenital, sensorineural hearing loss[97] and a smaller number a postnatal hearing loss from *in utero* infection (e.g. cytomegalovirus).

Conventional air and bone conduction testing is the preferred method as it tests each ear separately and can quantify any conductive component present. In children over 3.5 years of age, air and bone conduction thresholds are obtainable in the majority of children (95% and 92% respectively) on the first occasion. Age, rather than the method of audiometry, is the main determinant of whether thresholds are obtainable. Even if the child's concentration is poor, the results on average are only 5 dB poorer and can still be used to guide management.[99]

Evidence from a small study of 31 children compared high-frequency hearing between 14 who had experienced no more than three episodes of bilateral OME and those who had experienced at least four episodes. There was an increase in hearing thresholds with increasing frequency, higher than those normally clinically tested (9 kHz to 18 kHz) and poorer high-frequency hearing in the group who had a history of four or more episodes of OME.[100]

Air–bone gap

The presence of an air–bone gap of at least 10 dB is a poor predictor of concurrent OME. It was only when the air–bone gap was greater than 30 dB that the dry tap rate reduced to 4% (1 of 27).[101]

Carhart notch in the bone-conduction thresholds

As OME is a conductive hearing loss, it is associated with a Carhart notch in the bone-conduction thresholds around 2 kHz. (By definition, the notch has to be 10 dB or greater between 0.5 kHz and 4 kHz as any lesser dips could be due to test/retest error.) Accurate bone-conduction thresholds are required and, in younger children, this may not be possible. In children older than the typical age group for OME, a Carhart notch was present in 48% of children with OME whose mean age was 9 years.[102] In those able to perform bone-conduction audiometry, the positive predictive value of a Carhart notch in diagnosing fluid at myringotomy was 97% and the negative predictive value was 87%.[103]

Diagnosis and management of OME

Confirmation of the diagnosis of childhood OME is based on a combination of otoscopy, tympanometry and audiometry. Otoscopy should be attempted in all children, not just to diagnose OME but also to confirm or exclude other ear pathology (Figure 13.3). Pneumatic otoscopy may be of added value where there is uncertainty, but it is limited in predictive value by the experience of the examiner and the cooperation of the child.

In a general secondary care setting, where audiological testing of younger children is not available, children under the age of 4 years should be referred to a community paediatric audiology (second tier) clinic for age-appropriate hearing assessment, combined with tympanometry. Children of 4 years of age and above, in the absence of cognitive or behavioural comorbidity, can be assessed in a general hospital paediatric ENT clinic, with both audiometry and clinical assessment on the same visit. When OME is confirmed, active monitoring of hearing over a 3-month period is recommended.[104] The benchmark for hearing loss due to bilateral OME is hearing in the better ear of 25–30 dB HL or worse, averaged at 0.5, 1, 2 and 4 kHz. Tympanometry will typically demonstrate probability of effusion in cases of reduced middle ear compliance, with Jerger type B or C_2 traces.

As well as applying strict audiometric criteria, it is also important to make a child-centred assessment as to how the child's hearing loss may affect their quality of life. Where the impact of the hearing loss, although less than 25–30 dB HL is judged to have a significant impact on the child's development, social skills or educational attainment, more active management is appropriate.

Having excluded a sensorineural hearing loss with audiometry, it is reasonable thereafter to use tympanometry alone to identify those children with persistent hearing impairment due to OME. Taking 25 dB HL in the better-hearing ear as the level requiring detection, limiting audiometry to those with a bilateral type B reduces audiology workload by 50% but detects 90% of such impaired children. Limiting audiometry to those with bilateral type B or C_2 tympanograms reduces the workload to 69% of the sample yet detects 95% of the children with hearing impairment due to OME.[79]



Figure 13.3 Right tympanic membrane: OME fluid and bubbles. (Image courtesy of Mr Michael Saunders.)

OUTCOMES OF CHILDHOOD OME

Natural history

The natural history is very important, as outlined above, and can help guide management in both primary and secondary care. Hogan found that the effusions in children under 3 years of age with a propensity to have bilateral OME lasted on average 10 weeks, albeit the children were likely to have a further episode within 11 weeks.[58]

The UK MRC (Medical Research Council) TARGET (Trial of Alternative Regimens in Glue Ear Treatment) study is also an invaluable source of natural history information in those children referred to secondary care aged between 3 and 7 years of age. A total of 3831 children of this age were referred because of suspected OME. The techniques for correctly diagnosing and detecting OME across primary care are currently less than adequate, with reliance predominantly based on subjective histories. When screened at the trial clinic, only 34% satisfied the criterion for further study of having bilateral OME associated with a hearing impairment of at least 20 dB HL in both ears.[62–64] This cohort underwent a 12-week watchful waiting period, following which 49% of children no longer met the bilateral OME hearing criterion, i.e. only 51% of the hospital cohort persisted. At that stage, children with persistent OME were randomized and, in those who had non-specific medical management, only 49% remained persistent 3 months later.[65] In summary, children referred into the TARGET study waited on average 13 weeks to be seen, underwent a watchful waiting period of 3 months and then waited a further 3 months for surgery, by which time in 92% the hearing impairment associated with their OME had resolved. Thus, even in secondary care, the vast majority of children with bilateral OME resolve spontaneously over a 9-month period, although the OME might recur.

OTOPATHOLOGY

Addressing the natural history of OME and possible progression to cholesteatoma, the best evidence comes from a large study of 964 children, screened for OME every 3 months between the ages of 2 and 4 years. The children were subsequently re-examined with otoscopy at between 7 and 8 years of age.[106]

The findings indicate that attic retractions are a disease effect of OME, with an incidence of approximately 14% in the most severely affected children (Figure 13.4). The proportion of these retractions that progress to cholesteatoma remains unknown. There is no evidence that the risk of attic retraction is altered by the insertion of ventilation tubes. Tympanosclerosis and atrophy of the pars tensa are also disease effects of OME. The risk of these is increased by the insertion of ventilation tubes to more than 45% and approximately 70% respectively. Long-term pars



Figure 13.4 Attic retraction. (Image courtesy of Mr Michael Saunders.)

tensa retractions (approximately 15%) are more likely to be due to insertion of ventilation tubes than by the disease process itself.

CONDUCTIVE HEARING IMPAIRMENT

There is a widely variable hearing loss due to OME. In a series of 385 children aged between 2 and 11 years with bilateral OME confirmed by a diagnostic algorithm including pneumatic otoscopy, tympanometry and reflexes, the hearing loss in the better-hearing ear varied from 0–4 dB HL to 50–54 dB HL.[107]

Overall, the mean threshold in the better ear was 21 dB HL (s.d. 10). In 54% of those with bilateral OME the pure-tone average in the better ear was better than 20 dB HL.[107] The mean threshold in the poorer-hearing ears was 31 dB HL (s.d. 13). The speech reception or speech awareness thresholds in infants in this study were of a similar distribution. This might suggest that many children with bilateral OME in this study had an insufficient hearing impairment to cause 'significant' disability warranting such intervention, although significance remains difficult to define. In the same study, the authors describe a group of children with unilateral OME. In these children, the mean threshold in the better ear was 11 dB HL (s.d. 7) and 23 dB HL (s.d. 10) in the poorer ear, indicating these are a potentially significant group who may experience hearing disadvantage on occasions.

While there is no predictable difference in the hearing levels in ears from a serous effusion compared with those with a mucoid effusion,[108] those children with recurrent OME have an effusion with a different rheological profile, with fluid that has higher frictional adhesion.[8]

Sensorineural hearing impairment

There is no high-level evidence indicating that OME is associated with sensorineural hearing impairment in the short term.[109] However, the previously noted study[100] described sensorineural hearing loss above the clinically tested frequency range (>9 kHz) in children with recurrent episodes of OME. High-frequency sensorineural damage above 8 kHz has also been reported in a case series of children with OME who had been operated on and followed up for between 3 and 5 years.[110]

Long-term hearing impairment

In children followed from birth to 18 years of age, those who had otitis media (both acute and OME) produced air-conduction thresholds 4 dB HL poorer on average and bone-conduction thresholds poorer on average by 2 dB than those who had not had otitis media.[111] In this clinically heterogeneous group, it is not possible to know if the poorer thresholds were the result of infection, OME or surgical intervention.

SPEECH AND LANGUAGE

Normal childhood speech and language development is a multifactorial process, dependent on many factors including the age of the child, the ethnic background and verbal communication at home, particularly from the primary carer. Hearing impairment, including that from OME, is likely to impede normal speech and language development. Assessment of speech and language is complicated by it having many components, including speech reception, speech and sound production, expressive language and cognitive understanding.

In comparison to the profound effect on speech and language development a severe sensorineural hearing loss would be expected to produce, the mild to moderate conductive hearing loss associated with OME in the first 2–3 years of life should result in a much smaller effect. In a meta-analysis of 14 studies, the authors concluded that the impact of OME in early childhood on later speech and language development was very small, and of uncertain clinical relevance.[112] However, the authors cautioned generalizing the findings, instead recommending child-centred individual management in the context of other variables, including attention to language skills, development and the general supportiveness of the child's environment. Prospective cohort studies suggest an impact of otitis media, related to the number of days with bilateral fluid during the first 2–3 years of life. However, follow-up of these children when they are 7–8 years of age suggests that, by then, the children have caught up with their non-affected peers.[113] Overall, while the data suggest a mild effect on speech production in early childhood,[114–116] evidence looking at receptive language, using speech reception in noise (SiN) rather than pure tone audiometry, shows that 40% of children with the poorest pre-treatment SiN scores achieved high benefit from insertion of ventilation tubes. The authors concluded that SiN is a better tool than pure tone audiometry to predict benefit from surgical intervention. There appear to be small but significant long-term effects on sound discrimination in children with a history of OME.[117, 118] If there are measurable lasting effects, from current evidence these seem to predominantly affect receptive language. Treating OME in very young children appears to have no significant effect on speech and language development in the short term.[119, 120]

COGNITION

The influence of OME as one of many interrelated variables affecting a child's intellectual development is difficult to determine. Cohorts of children can be grouped as to how much OME they have had and this is correlated to a particular outcome, having controlled for demographic and environmental factors. The effect of OME as an independent factor for academic development is probably small compared with the more influential demographic, social and economic factors. If there is an effect, this has been reported as generally small.[118, 121] While these studies conclude that any negative effect has disappeared by the age of 7–8 years, a birth cohort of 200 was reviewed as older children, during their teens. A history of OME in early childhood was associated with a deleterious effect on reading ability.[122] A further study[123] reviewing a larger cohort of the same group[124] concluded a lower IQ in the OME group, after adjustments for covariates, persisting at least until the age of 13 years.

BEHAVIOUR

Behaviour can be assessed using questionnaire reporting by parents or teachers. These give a global behaviour measure and can also score the various components of behaviour. The widely used Rutter Children's Behaviour Questionnaire[125] is subdivided into antisocial, neurotic, hyperactive and inattentive behaviour scores.

In a randomized, controlled trial, 55% of 3-year-old children with bilateral, 3-month persistent OME had abnormal overall Rutter scores, compared with 10–15% of unselected 3-year-olds.[126] There is also evidence that, even when a child with a history of early OME has reached the age of 13 years, they performed less well than non-OME children for neurotic and inattention traits. By 15 years of age, the OME group scored less well in the total behaviour score and specifically for inattentive and hyperactive behaviour.[122, 123]

BALANCE

While OME is one of the most common causes of balance disturbances in young children,[127] only about 30% of parents of children with OME report that they are concerned about their child's balance. When formally tested, 61% of children with OME have objectively defective motor proficiency; these symptoms resolve following insertion of ventilation tubes.[126, 127]

QUALITY OF LIFE

Quality of life (QOL) is a multidimensional concept reflecting general valuation of health states, also important as a child- or parent-centred measure of outcome in routine contexts. Only relatively recently have specific ear-related QOL measures been developed. The MRC Multi-centre Otitis media Study Group has produced the OM8-30 functional health status measure, which has been impartially evaluated, with favourable recommendation[128] and mapped onto generic QOL.[129] For routine patient-reported outcome measure (PROM) applications emphasizing QOL, a short-form easy-to-use measure, the OMQ-14, has recently been developed from the OM8-30. This uses two databases, from UK secondary[130] and primary[131] care trial cohorts, to define the 14 items from OM8-30 best reflecting QOL. Facets covered by the OMQ-14 questions include four main profile areas: (i) recurrent AOM, (ii) reported hearing difficulties, (iii) behaviour and parental QOL, and (iv) speech and language. Clinical research currently being performed using these measures is suggesting that such estimates of child- and parent-centered outcomes in 'the real world' are of considerable practical use. This is partly because hearing level, although an important assessment and outcome, demonstrates only low correlation with QOL. Short questionnaire measures have great potential to become a useful routine aspect of individual clinical assessment, alongside their current research use as an evaluation of interventions for OME.[132]

MANAGEMENT

Counselling and hearing tactics

Parents of children with OME are often misinformed about many aspects of the condition. In particular, they can have over-pessimistic views about its severity and be over-optimistic about the merits of surgery. At their first visit to the general practitioner or the specialist, time has to be spent explaining that, in general, OME is a benign condition with a high spontaneous recovery rate with no serious long-term sequelae. In most children, the main concern will be the hearing. It should be explained to the parents that the impairment associated with OME is very variable in degree and duration and mild or moderate at most.

It is important that all parents of children with OME receive appropriate general counselling about the natural history and relative benign nature of the condition. Those in contact with the child, including any minder or teacher, should be made aware that hearing-related disability can be minimized by adopting hearing tactics, including the following:

- Get the child's attention before starting to talk.
- Reduce the background noise as much as possible (e.g. turn off the television).
- Face the child so that they can see you talk to encourage lip reading.
- Speak in a normal voice in volume, speed and emphasis, as close as possible to the child.

Leaflets such as *Glue ear: A guide for parents* offered to parents could reinforce the above messages.[133]

Medical management

Medical management would potentially be of greatest benefit if it could speed the resolution of an episode of OME. Hence, randomized controlled trials carried out in

primary care settings would be those most appropriate to consider using resolution of OME as the outcome. Such studies need to define their target populations to exclude non-cases, etc. Some trials followed up children for just 1–2 weeks after therapy. However, if any treatment is effective after 1–2 weeks, then follow-up for the recommended watchful waiting period of 12 weeks is necessary to see if it is of benefit in the longer term, and might be used to reduce the proportion of children being considered for surgery.

NASAL TOPICAL STEROIDS

A Cochrane systematic review[134] identified several studies of topical nasal or oral steroids versus placebo.[131, 135, 136] The review, which included a sizeable UK study of nasal steroids versus placebo from UK primary care, concluded that there is evidence for no benefit from topical intranasal steroids.

SYSTEMIC STEROIDS

Considerable concern has been expressed about the use of oral steroids being given to children for a non-life-threatening and spontaneously resolving condition. Consequently, such treatment would have to be highly effective in the long term before it could be recommended. The review that included 12 studies in total and 945 patients[134] did, however, find some evidence to suggest that oral steroids are effective in the short term (2 weeks), and when combined with antibiotics.[137, 138] Systemic steroids cannot be recommended at present for childhood OME.[139]

ANTIBIOTICS

A Cochrane review based on 23 trials mostly from secondary care and 3027 subjects has suggested that antibiotics are unlikely to be beneficial.[140] There was evidence to show that antibiotics had no statistically significant benefit in the short term. Because trials were very heterogeneous, meta-analysis was not attempted. In the longer term there appeared to be slight benefit from use of antibiotics but there are some concerns about the generalizability of these data, and the disadvantages of antibiotics: rashes, diarrhoea, antibiotic-associated colitis, anaphylaxis, thrush and antibiotic resistance are increasingly well known, making them unsuitable for longer-term use. In particular, the Chief Medical Officer for England and Wales has highlighted antibiotic resistance as a major public threat to health.

NASAL DECONGESTANTS

A systematic review and meta-analysis of four trials (n = 1202) found that antihistamine/decongestants had no significant effect on the resolution rate of OME.[141] Nasal decongestants are not recommended for use in childhood OME.

MUCOLYTICS

A systematic review of six randomized controlled trials of S-carboxymethylcysteine published before 1993 could not demonstrate that they had an effect.[142] A later trial also showed no significant effect.[143] Because of a non-significant trend for increased benefit in these small, biased trials, a larger well-designed study is merited.

Other non-surgical approaches

AUTOINFLATION

A systematic review of autoinflation for the treatment of glue ear in children identified eight studies with 702 participants.[144] Pooled estimates found non-significant improvement in tympanometry at less than 1 month (relative risk of improvement (RRI) 1.47, 95% CI 0.69–3.13) and non-significant improvement at more than 1 month (RRI 1.22, 95% CI 1.00–1.49). A composite measure of tympanometry with audiometry showed a significant improvement at more than 1 month (RRI 1.74, 95% CI 1.22–2.50). Because of the low cost and absence of reported adverse effects, it was concluded that autoinflation was worth considering while awaiting natural resolution, and that primary care was a good setting for further studies. Some concerns have been raised though about the age at which the method can be performed reliably in children, and this also requires further evaluation. Currently autoinflation appears the most promising non-surgical management to augment active monitoring (watchful waiting).

HOMEOPATHY

No randomized controlled trials have been identified. A small, non-blinded study showed homeopathy to be of no benefit.[145]

Surgery

MYRINGOTOMY AND INSERTION OF VENTILATION TUBES

Myringotomy with aspiration of middle ear fluid but without insertion of a ventilation tube (grommet, tympanostomy tube) is ineffective surgical management of OME.[146] The incision closes within a few days and the effusion usually recurs.

Ventilation tubes of different materials are available, although in the UK, Teflon® grommets are typically used. Titanium-, gold- or silver oxide-coated ventilation tubes are intended to inhibit biofilm formation, although *in vitro* evidence indicates this is only the case if the material is coated with antibiotic.[147] Using scanning electron microscopy, some biomaterials, such as ionized, processed silicone, appear more resistant to biofilm formation, reducing the incidence of plugging of the tube and post-operative otorrhoea.[148]

Standard pattern ventilation tubes (e.g. Shepard, Shah – **Figure 13.5**) stay *in situ* for a shorter period than longer-term T-tube designs (**Figure 13.6**), but the longer a tube stays *in situ*, the higher the chance of complications, including plugging of the lumen, infection, thinning and collapse of the tympanic membrane with possible retraction and permanent perforation.[149] Up to 55% of Shepard



Figure 13.5 Right tympanic membrane Shah grommet *in situ*. (Image courtesy of Mr Michael Saunders.)



Figure 13.6 Right tympanic membrane T-tube *in situ*. (Image courtesy of Mr Michael Saunders.)

ventilation tubes have extruded within 6 months of insertion;[149, 150] in the same period, approximately 10% of T-tubes will have been extruded.[148]

In the future, both biofilm formation with infective complications and persistent perforation may be reduced or abolished by a currently experimental biodegradable, absorbable ventilation tube manufactured from poly-bis (ethylanate) phosphazene.[151]

Surgical technique

Site To maximize the duration of placement and minimize damage or perforation, the preferred insertion site of the ventilation tube is anteroinferior through a circumferential or radial incision. Insertion of the ventilation tube posterosuperiorly is not recommended because of the risk of damaging the ossicular chain. The ventilation tube inserted via a radial or circumferential incision does not influence the extrusion rate.[152] Placement of the grommet anteroinferiorly compared with placement posteroinferiorly lengthens the time a Shepard ventilation tube remains *in situ* (80% versus 45% at 6 months and 30% versus 15% at 12 months).[153] A tube placed anteriorly is also associated with a reduced but non-significant reduction in persistent perforation compared to a tube placed posteriorly in the tympanic membrane (1.8% versus 3.7%).[153]

Surgical aspiration While usual practice is to aspirate middle ear fluid through the myringotomy prior to insertion of ventilation tubes, there is no evidence to support this. Hearing levels 3 months following insertion of a ventilation tube were the same independent of aspiration.[155, 156] A literature review of the topic concluded aspiration produced increased rates of tympanosclerosis, secondary to trauma and bleeding of the tympanic membrane. Noise from persistent aspiration may lead to permanent noise-induced hearing loss.[157] Aspiration causing bleeding from the tympanic membrane may encourage subsequent biofilm infection of the ventilation tube.[158]

Topical preparations Ear drops can be used at the time of insertion of ventilation tubes to reduce the risk of tube blockage with blood and mucus, and to minimize local infection during the early post-operative period (see 'Complications of ventilation tubes' below).

ADENOIDECTOMY

Surgical techniques

In the UK, blind curettage adenoidectomy continues to be the most used technique. Digital palpation and blind curettage is used in 79.2% of cases, while only 8.1% use suction coagulation under direct vision.[159] It is surprising that curettage remains popular suffering the disadvantages of a blind procedure with unpredictable bleeding, poor access to choanal adenoid and risk of trauma to the Eustachian cushions. In contrast, suction diathermy affords direct vision with minimal blood loss[160] (mean 4 mL versus 50 ml L), haemostasis and negligible risk of post-operative haemorrhage.[161] Suction diathermy is also effective in performing partial adenoidectomy, leaving a ridge of adenoidal tissue at the inferior part of the nasopharynx, reducing the risk of velopharyngeal insufficiency in those children where this is likely after removal of the adenoid.[162] Other direct vision techniques include Coblation® and microdebrider, which have the disadvantage of high unit cost for adenoidectomy alone. KTP laser is associated with a high risk of nasopharyngeal stenosis,[163] which has not been reported using gold laser for adenoidectomy.[164] All single-use instrument techniques have the advantage of abolishing the potential risk of infection transmission[165] (see Chapter 26, The adenoid and adenoidectomy).

SURGICAL OUTCOMES

Hearing outcomes of ventilation tube insertion

The Cochrane systematic review of 'grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children'[166] concluded that the benefits of

grommets appear small and the effects on hearing diminish during the first year after surgery.

From the trials reviewed, grommets were beneficial in the first 6 months. At 3 months, the mean hearing was 12 dB better in those receiving grommets, falling to 4 dB at 6–9 months. Using pure tone audiometry as a surrogate for disability due to hearing loss fails to address the potentially complex disadvantage the developing child suffers during the period of untreated hearing loss. While the review reports no proven effects on language, speech development, behaviour, cognitive or quality of life, there is some trial evidence to support effects in these domains from published data.[113–123]

Uncertainties remain as the evidence collected in the review cannot entirely resolve discrepancies between analysed trial data on the one hand and parental and clinical observation of a beneficial treatment effect observed in practice on the other. This may be in some part due to a lack of validated and reliable child and parent-centred measures, lacking in many of the trials (with perhaps hitherto some overreliance on hearing level), while also duly acknowledging discrepancies arising from lack of control for placebo effects and other biases inherent in clinical practice.

The remaining challenge is to identify those children for whom intervention is needed and helpful.[167] Does a return to normal pure-tone audiometry after 12 months of hearing loss from OME equate to absence of disability during the same period? In considering data from randomized controlled trials, the effect of intervention may appear reduced in an intention to treat analysis (ITT), when the rate of transfer from control to intervention group is high (contaminates the control group with the intervention effect). However ITT does control for attrition bias and is the most appropriate and robust analysis when evaluating effectiveness and cost-effectiveness in the NHS setting.

The UK MRC TARGET multicentre study looked at the effect of ventilation tubes alone or with adjuvant adenoidectomy on child-centred outcomes. Children aged between 3.5 and 7 years, with bilateral OME, persistent over a 12-week 'watchful waiting' period and associated with a hearing impairment in both ears of 20 dB HL or poorer were eligible for inclusion. They were randomized to one of three arms: no-surgical management, bilateral ventilation tubes (Shepard) or bilateral ventilation tubes with adjuvant adenoidectomy. In the non-surgical group, hearing improved with time, mainly due to the natural resolution of the OME. Children randomized to have ventilation tubes had a marked improvement of 12 dB 3 months following surgery compared with the non-surgical group. In both ventilation tube groups, the hearing at 3 months does not become 'normal' (i.e. 0 dB HL). If one excludes the small number of ears in which the ventilation tube is non-functioning, there is still an air–bone gap of 13 dB.[168] At all other post-operative visits, when a tube was functioning, the air–bone gap was of a similar magnitude and, as the middle ear space was well-ventilated, was considered due to effusion and oedema around the ossicular chain.

The difference in hearing between the two surgical groups and the non-surgical group became almost negligible at 12 months. The reason for the deterioration in the hearing levels over time in those with a ventilation tube was due to a combination of two factors. First, the proportion of tubes that become non-functioning increased with time, though children were eligible to have them reinserted if the hearing entry criteria were satisfied at that time. The other reason was that, in ears where the ventilation tube has extruded and the OME has resolved, there is still a small but material conduction deficit of approximately 14 dB.[168] The reason why those in the non-surgical arm improved over that period was mostly due to the natural spontaneous resolution rate of the OME combined with a much smaller contribution from those who switched management arms to surgery.

TARGET demonstrated the improvement in hearing from ventilation tubes averaged over the first year was 5.7 dB. In the second year, the difference between the two groups became negligible. Hence, when averaged over 2 years, the benefit of ventilation tubes is reduced to 3.1 dB. A more recent individual data meta-analysis of four trials that randomized children to ventilation tubes or watchful waiting confirmed the benefit of short-term ventilation tube at 6 months but not at 12 months, with a magnitude of difference of 4.5 dB.[169]

In this same study, the meta-analysis from seven trials randomized 1232 children with persistent bilateral OME for 12 weeks to ventilation tubes or non-surgical management. The only factor predictive of a better hearing outcome at 6 months was attendance at day care with an impairment of 20–25 dB in both ears. Those not attending day care had no benefit (>1 dB) at 6 months. No effect of age, sex or socioeconomic group was evident. In three trials which randomized children 'by-ear', those with a binaural hearing level of >25 dB HL benefited by 10 dB at 6 months compared with the 4 dB of those with lesser hearing thresholds. These data suggest that, when the aim is improvement in the hearing, then younger children at day care and those with binaural hearing thresholds poorer than 25 dB HL and persistent over at least 12 weeks will benefit most.

Non-hearing outcomes are discussed in 'Outcomes of childhood OME' above.

Outcomes of adenoidectomy

The role of the adenoid in OME has been discussed above. Chronic inflammatory change in the mucosa of the Eustachian tube and middle ear secondary to biofilm infection of the adenoid rather than physical obstruction of the Eustachian tube is the likely cause, and removing this is how adenoidectomy is beneficial in the management of OME. Adenoidectomy reduces the need for reinsertion of ventilation tubes.[170, 171] At the time of writing, UK guidance[104] does not yet include the recommendation for adjuvant adenoidectomy. While clinicians recommended this for the 2011 NICE guideline update, the guideline was not changed. The US guideline does not recommend adjuvant adenoidectomy until the second insertion of ventilation tubes;[171] this might be appropriate guidance for the younger age group, given the role of the adenoid in laying down immune memory, discussed above.

Hearing In the TARGET trial, adenoidectomy at the time of insertion of ventilation tubes doubled the benefit and extended better hearing through the second year following intervention, reducing the need for repeat insertion of ventilation tubes, with an absolute risk reduction of 21%.[130]

Upper respiratory tract symptoms Adjuvant adenoidectomy confers the additional benefit of improved respiratory health over a 2-year period following surgery (Haggard MP, 2005, personal communication).

COMPLICATIONS OF VENTILATION TUBES

Operative

The most common operative complication is displacement of the ventilation tube into the middle ear, in 0.5% of cases. The tube should be retrieved if damage can be avoided. If not, the inert nature of the tube means that significant further problems are unlikely to occur. Efforts should be made to retrieve the tube at the time, but failure to remove it seldom causes problems. Posterosuperior myringotomy must be avoided as this risks damage to the ossicular chain and incudostapedial joint. Very rarely, a high dehiscent jugular bulb may be pierced by an inferiorly placed myringotomy.

Early post-operative

Aspiration at the time of surgery is unlikely to prevent blockage of the lumen of the ventilation tube.[156, 157] Early infection around the ventilation tube occurs in 9% of ears.[172] Topical antibiotic steroid drops at the time of surgery can reduce the incidence to 1%. Although likely to be safe in clinical practice,[173] aminoglycoside drops carry the potential risk of both ototoxicity and vestibulotoxicity and should be avoided. Quinolone antibiotic eardrops are a safer alternative and, although widely used worldwide, are currently unavailable in the UK. Quinolone eye drops (e.g. ofloxacin) are commonly used for this non-licensed indication.

Otorrhoea Otorrhoea in association with a ventilation tube *in situ* may follow an acute upper respiratory tract infection or can be the result of a chronic biofilm infection of the ventilation tube itself. Post-operative otorrhoea is the most common complication with a reported incidence of 10–50% (**Figure 13.7**). A Cochrane review failed to find good quality evidence to support a meta-analysis. While oral amoxicillin clavulanate combined with daily aural toilet was significantly more effective than placebo and daily aural toilet, no significant benefit could be shown for topical aminoglycoside preparations compared with each other or with oral steroids and oral antibiotics.[174] In a randomized, double-blind, controlled trial, topical ciprofloxacin drops were superior to topical saline and systemic antibiotics in managing ventilation tube otorrhoea. Failure rates were 23%, 58% and 70% in the groups treated with topical ciprofloxacin, topical saline and oral amoxicillin respectively.[175] A randomized, blinded parallel group study compared ciprofloxacin–dexamethasone ear drops with no treatment following ventilation tube insertion. In the treatment group, otorrhoea was observed in 4.95% of patients, compared to 39.39% of the untreated group ($p < 0.0001$).[176]



Figure 13.7 Right tympanic membrane with infected grommet. (Image courtesy of Mr Michael Saunders.)

Granulation tissue secondary to infection occurs in approximately 1%, and is similarly managed with topical preparations. Chronic infection of the ventilation tube may require removal of the tube (in approximately 4% of ears).[172] Ofloxacin as a topical antibiotic is preferable to ciprofloxacin, minimizing the risk of antibiotic resistance in a systemically used antibiotic.

Late post-operative

Hearing loss A study of 224 children following grommet insertion concluded that 25 years after surgical treatment for OME hearing was no different to age- and gender-matched controls. Neither myringotomy alone nor insertion of ventilation tubes resulted in a significant difference in long-term hearing level, compared to a gender-matched normative data set. Where myringosclerosis was present in ears following grommet insertion, there was a small associated loss (4–5 dB) in the high-frequency range. Where pars tensa atrophy occurred after grommet surgery, the long-term change in hearing was limited to an overall loss of 3–4 dB.[177]

Myringosclerosis ('tympanosclerosis') The most common structural complication after ventilation tube surgery is myringosclerosis, occurring more often with long-term tubes. Hyaline degeneration of the collagen tissue in the fibrous layer of the pars tensa is visible otoscopically as localized white patches or plaques (**Figure 13.8**). These do not occur in the absence of a history of otitis media. The frequency of myringosclerosis increases with the frequency of OME with an increased risk if a ventilation tube has been inserted.[166] While there was difference between short- and long-term tubes in this review, a later systematic review concluded that myringosclerosis was more common with long-term tubes.[178] This review



Figure 13.8 Myringosclerosis 'tympanosclerosis'. (Image courtesy of Mr Michael Saunders.)



Figure 13.9 Perforation. (Image courtesy of Mr Michael Saunders.)

also concluded no hearing impairment resulted from the presence of myringosclerosis.

Tympanic membrane perforation When a ventilation tube extrudes, the initial pars tensa perforation usually heals. A perforation may then subsequently reoccur at the same site due to a subsequent episode of AOM and, again, will normally heal spontaneously. Perforation is seen in between 1% and 6% of ears that have had a ventilation tube and in 1% of ears that have never had a ventilation tube inserted; perforation occurs more commonly in treated ears, and more often with long-term ventilation tubes (**Figure 13.9**).[179]



Figure 13.10 Pars tensa atrophy. (Image courtesy of Mr Michael Saunders.)

Pars tensa atrophy and retraction Thinning and retraction of the tympanic membrane are complications of persistent OME. In children initially referred with bilateral OME, pars tensa retraction to the incus or promontory (Sade grade 3/4) occurs in 8% of the better- and 10% of the poorer-hearing ears.[63] These retractions were not associated with a history of longer ear problems. Followed up over a 12-week watchful waiting period, they resolved in 69% of the better and 65% of the poorer ears. The OME had also resolved in 14% of the better and 10% of the poorer ears with a pars tensa retraction, respectively.

Pars tensa atrophy (**Figure 13.10**) also occurs in approximately 3% and retraction to the incus or promontory in 2% of ears in 7–8-year-old children in whom there is no history of OME. This incidence is similar to that in children with transient episodes of OME. However, the incidence of atrophy, but not of retraction, increases to approximately 9% in those with persistent OME. In those who still have a ventilation tube *in situ* for their OME, the incidence of atrophy increases to approximately 68% and retraction to approximately 14%. It could be argued that this increase in ears with a ventilation tube still *in situ* is because these are more persistent cases, rather than because of the ventilation tube itself. This is in part supported by the fact that the incidence is the same with short- and long-term tubes.[173] It can be concluded that ventilation tubes do not prevent the occurrence of atrophy or retraction and should not be inserted for that reason alone. Cholesteatoma is uncommon enough to make it difficult to draw clear conclusions about the effect of ventilation tube insertion on the incidence of this condition.[178]

Swimming and water contamination A meta-analysis concluded that for bathing and swimming, but not diving, ear protection does not or only slightly reduces otorrhoea in children following ventilation tube insertion.[178]

Hearing aids

Hearing aids can be used in children with persistent OME, to avoid repeated surgery, or where parents wish as their preferred initial management. Repeated visits for new ear moulds, maintenance of the aids and replacement of lost aids suggest this option might be time- and cost-intensive for both parents and providers. There is very limited published data on the subject. In a small case series,[179] hearing aids were acceptable to the majority of parents and gave aided thresholds with a mean of 17 dB, in the same range as expected of ventilation tubes. The main concern is potential noise trauma, as up to 13% of children become dependent on the aids and wish to continue to use the aids after the OME has resolved.

The Softband® bone-conduction aid incorporates a bone-anchored hearing aid in a headband. In a small prospective, non-randomized questionnaire study of 11 children aged between 6 and 15 years, half the children found daily listening situations to be mostly easy. All of the children used the Softband® at school. This is an older age group than those typically presenting with OME, but this small study indicates the need for a larger trial to assess the potential benefit of this non-invasive treatment of OME.[180]

Management of OME in children with related comorbidity

Even after surgical repair, children with a cleft palate have a high incidence of OME that in some is a persisting condition. Hearing aids rather than ventilation tubes are usually recommended to maintain near-normal hearing without the complications associated with repeated ventilation tube insertion or long-term tubes.[181] Similar constraints apply to the management of OME in children with Down syndrome, where there might also be a sensorineural component to the hearing loss.[182]

BEST CLINICAL PRACTICE

In primary care

OME should be suspected in children with 'ear-related concerns' who may have recently recovered from an episode of acute otitis media or are suffering from recurrent bouts.

- ✓ All children should have routine otoscopy to help confirm OME and distinguish it from AOM or COM. However, even with good training, otoscopy is unlikely to be sufficiently sensitive or specific to reliably make the diagnosis of OME on its own. Tympanometry with training of staff is likely to be more accurate in diagnosing if effusions are present.
- ✓ Free-field voice testing is a valid assessment of hearing in a primary care setting. Hearing-related QOL can also be estimated using the OMQ-14 (short form) questionnaire.
- ✓ No medical therapy (including antibiotics, topical nasal steroids, systemic steroids, nasal decongestants and mucolytics) has been proven to be clinically effective. Alternative and complementary therapies have not been shown to be effective in the management of OME either. In older children, autoinflation might be beneficial.
- ✓ It is important that all parents of children with OME receive appropriate general counselling about the natural history and nature of the condition. This includes advice regarding hearing tactics.
- ✓ If there is concern regarding the hearing in any child, referral for hearing assessment is indicated. For children under the age of 4 years, initial referral is to community paediatric audiology. In children aged 4 years and older, hearing assessment can be performed in a general paediatric ENT clinic. Active monitoring (watchful waiting) with audiometry can be continued in secondary care.

In secondary care

- ✓ Otoscopy, tympanometry and pure-tone air-conduction thresholds should be assessed in all children referred with suspected hearing impairment at their first clinic visit. Non-masked bone-conduction thresholds are generally obtainable in children over the age of 4 years. This will aid management of those with OME and detect previously undiagnosed sensorineural hearing loss.
- ✓ Primary carers of all children with OME should receive appropriate general counselling about the natural history and nature of OME.
- ✓ The hearing levels associated with the child's OME should be discussed with the parents and advice about hearing tactics given to help the parents mitigate any disability.
- ✓ Children with OME whose hearing thresholds do not satisfy the hearing criterion of 25 dB HL bilaterally should be followed up 12 weeks later with repeat audiometry.
- ✓ Where hearing loss of 25 dB HL or poorer in both ears persists after 12 weeks of active monitoring, discuss options for further management, including insertion of ventilation tubes with adenoidectomy, hearing aids or continued surveillance.
- ✓ While the risk of ototoxicity with topical aminoglycoside preparations is small, for the treatment of infected otorrhoea and where bacterial sensitivities allow, use quinolone ear drops when a grommet is patent or there is a tympanic membrane perforation.

FUTURE RESEARCH

- ➤ Different impact of OME and elevated hearing thresholds in children with different intellectual ability.
- ➤ Possible benefits of surfactant in the management of adenoidal biofilms.

KEY POINTS

- In children, the prevalence of OME is bimodal with the first and largest peak at 2 years of age (~20%) and the second peak at around 5 years of age (~16%).
- For each episode, resolution without treatment of the OME is the most likely outcome.
- The effect of hearing impairment on speech, language, cognition and behaviour may produce measurable changes long after the OME has resolved.
- Attic retractions are an OME disease effect with an incidence of approximately 14% in the most severely affected children. The proportion of these retractions that progress to cholesteatoma is unknown. There is no evidence that the risk of developing an attic retraction and the potential to develop a cholesteatoma is altered by the insertion of ventilation tubes.
- The benefit of ventilation tubes in children under 3 years of age with significant language, development or behaviour problems requires investigation. In children over the age of 3 years, the binaural hearing average is used as a surrogate of behaviour and for impact upon quality of life.
- All children with hearing thresholds of 25 dB or poorer in both ears should have their hearing documented over a 12-week watchful waiting period before any decisions regarding surgery are made.
- If ventilation tubes are to be inserted, adenoidectomy is effective adjuvant treatment, extending the period of benefit to the hearing of short-term ventilation tubes up to 2 years and reducing the proportion of children eligible for reinsertion of short-term tubes from around 50% to 25%. This effect is likely to be greatest in the oldest children. (Adenoidectomy in children under the age of 3 years might impact negatively on immune system development.)

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CHAPTER 14

ACUTE OTITIS MEDIA

Peter A. Rea and Natalie Ronan

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SEARCH STRATEGY

Data in this chapter may be updated by searches of Medline and the Cochrane Controlled Trials Register, using the keywords acute otitis media. Reference lists were reviewed for further articles, and authors of recent presentations contacted personally for their reference lists.

INTRODUCTION

For such a common childhood infection, acute otitis media (AOM) remains something of an enigma. It is hard to diagnose accurately and on existing evidence, as opposed to custom and tradition, there is still a high level of uncertainty over how it should best be treated. This is against a background of increasing bacterial resistance to antibiotics. There is plenty of evidence in the literature of the relative frequencies of viral and bacterial pathogens in AOM, but this is often of little help to the clinician on the spot in an individual case. Some of the epidemiological evidence is also relatively 'soft', since it is based on the flawed premise that AOM can accurately be diagnosed from the history and otoscopy alone, unsupported by tympanometry or tympanocentesis. In this chapter the authors have tried to thread their way through the often conflicting evidence about the practical management of AOM at the same time as covering what is known of the pathology, epidemiology and complications of this commonest of childhood illnesses.

Many areas of uncertainty, insufficient evidence and limited information about AOM remain. For this reason we have indicated Level 1 and Grade A evidence in the chapter. Even a meta-analysis, the supposed gold standard of evidence, is only as good as the studies it covers. It must be remembered that the prevalence of otitis media with effusion (OME), 'glue ear', only began to be widely appreciated after the development of the twin tools of universal hearing screening and the tympanometer, in the 1960s and early 1970s respectively. The accuracy of correct reporting of cases of AOM lags behind that of OME mainly because the essential presence of fluid in the middle ear is not confirmed by tympanometry and audiometry in the majority of large population studies of AOM.

DEFINITION

Acute otitis media (AOM) may be defined clinicopathologically as inflammation of the middle ear cleft of rapid onset and infective origin, associated with a middle ear effusion and a varied collection of clinical symptoms and signs. It is synonymous with acute suppurative otitis media. It normally develops behind an intact tympanic membrane but may include acute infections arising in the presence of ventilation tubes or existing tympanic membrane perforations. The requirement to confirm a middle ear effusion, and the nature of the symptoms and signs, vary between authors.[1, 2]

The literature supports four broadly defined subgroups of AOM:

1. **Sporadic** episodes occurring as infrequent isolated events, typically occurring with upper respiratory tract infections (URTIs)

2. **Resistant** AOM: persistence of symptoms and signs of middle ear infection beyond 3–5 days of antibiotic treatment
3. **Persistent** AOM: persistence or recurrence of symptoms and signs of AOM within 6 days of finishing a course of antibiotics
4. **Recurrent** AOM: either 3 or more episodes of AOM occurring within a 6-month period, or at least 4–6 episodes within a 12-month period (no consensus has been reached on the latter).

Groups 2 and 3 appear similar at first glance and this distinction may be questioned. It is included to maintain some consistency with the wider literature.

Grading of the severity of an episode has been attempted and has merit both clinically and for research. Pyrexia from 37.5 °C to 39 °C, vomiting and severity of otalgia have been used.[3, 4]

DIAGNOSIS

Diagnosis is based on the combination of often non-specific symptoms, evidence of inflammation of the middle ear cleft, and by some authors by the additional confirmation of a middle ear effusion. Diagnostic difficulty has affected the quality of research into AOM. There may well not be a clear history of a crescendo of otalgia in a coryzal child, followed by rapid symptomatic relief associated with tympanic membrane perforation and associated blood-stained otorrhoea. The difficulty in establishing clear diagnostic guidelines has been highlighted in an analysis of 80 studies of AOM.[5] In diagnosing AOM only 52.5% of the studies cited middle ear effusions, 32.5% included symptoms and signs of inflammation and 2.5% considered the rapidity of onset. Clinicians recognize this difficulty. A large multinational study rated clinicians' diagnostic certainty in children under 1 year of age at only 58%, rising to 73% in those over 31 months.[6]

Symptoms

Diagnosis by symptomatology alone is inaccurate because of the young age of most patients, and the non-specific nature of the symptoms. One third of children may have no ear-related symptoms. Two-thirds may be apyrexial.[7] Symptoms suggestive of AOM include rapid onset of otalgia, hearing loss, otorrhoea, fever, excessive crying, irritability, coryzal symptoms, vomiting, poor feeding, ear pulling and clumsiness (Table 14.1). AOM most commonly develops 3–4 days after the onset of coryzal symptoms. The otalgia will settle within 24 hours in two-thirds of children without treatment.[9] The otorrhoea, if present, is mucopurulent and may be blood-stained. Symptomatic relief is obtained without treatment in 88% by day 4–7. The hearing loss, caused by the middle ear effusion, occurs early in the illness and may persist at greater than 20 dB for 1 month in over 30%, and 2 months in 20% of children.

Signs

The child may appear unwell, and may rub his or her ear. The diagnosis is often confirmed, rightly or wrongly, by an attempt at otoscopic assessment of the tympanic membrane. However, a poorly functioning otoscope, the moving target of a child's head, the narrow ear canal of an infant, the natural redness of the tympanic membrane of a screaming child, wax, and above all the inaccuracy of an untrained (or even trained) eye straining to interpret a two-dimensional image, all combine to make otoscopy an imprecise art. Since trained observers have been shown to have only an 85% accuracy in otoscopic diagnosis,[10] it would not be surprising for a sensible primary care physician to rely more on history and the general aspect of a child than on otoscopic findings. With these reservations, diagnosis may be supported by otoscopic assessment of tympanic membrane **colour**, **position** and **mobility**. In AOM the tympanic membrane is usually opaque. It is most commonly yellow, or yellowish pink in colour, being red in only 18–19%.[7, 10] The position of the tympanic membrane reliably predicts AOM only when it is bulging. Hypomobility of the drum demonstrated by pneumatic otoscopy has been shown to aid diagnosis[10] and is felt essential in some countries,[1] though others including the Dutch[2] take a more pragmatic view and do not include this in their diagnostic criteria. Should the drum be perforated, or a ventilation tube be *in situ*, mucopurulent otorrhoea will be seen.

Investigations

Tympanometry may be used to establish the presence of a middle ear effusion but is not usually available. Tympanocentesis and culture of middle ear effusion have been used in a number of studies assessing diagnostic

TABLE 14.1 Relation of reported symptoms to presence of AOM in 302 children under 4 years of age (reprinted from Heikkinen and Ruuskanen,[8] with permission)

Symptom	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Earache	60	92	83	78
Restlessness	64	51	46	68
Rhinitis	96	8	41	74
Cough	83	17	40	61
Fever	69	23	38	53

accuracy of clinical signs, and establishing the organisms prevalent in a community. It is rarely required to make the diagnosis, though may be considered in high-risk children such as the immunocompromised, an unwell neonate, those that fail to respond to conventional treatment, and children who are seriously ill or have complications of AOM. Taking a bacterial swab of persistent otorrhoea following perforation is recommended. Nasopharyngeal swabbing for bacterial culture has been assessed but the correlation with middle ear organisms has been too weak to recommend it clinically.[11]

Specific investigation may be prompted by recurrent AOM not responsive to conventional treatment. Both iron-deficiency anaemia and white blood cell disorders have been associated with AOM, so a full blood count is indicated. Immunoglobulin assay may be appropriate: IgA, IgG (with subclasses) and IgM are typically assessed. Children with recurrent infection of ventilation tubes may also merit investigation for primary ciliary dyskinesia, particularly if nasal and pulmonary symptoms coexist.

Differential diagnosis

Pain may be referred from tonsillitis, teething, temporomandibular joint disorders, or simply be the result of an uncomplicated URTI. In a screaming child the tympanic membrane may well appear red. Diagnostic confusion may occur with acute mastoiditis, OME, otitis externa, trauma, Ramsay Hunt syndrome and bullous myringitis. Very rarely AOM may be the first indication of serious underlying disease such as Wegener's granulomatosis or leukaemia.

AETIOLOGY

Microbiological, anatomical and environmental factors combine with altered host defence mechanisms to predispose to infection. Genetic predisposition to recurrent AOM is being cited increasingly in the literature.

Infective agents

AOM results from infection of the middle ear cleft. Both viral and bacterial infections are implicated. These infections may occur in isolation or combination.

VIRUSES

Clinically, it is apparent that AOM is commonly associated with viral upper respiratory tract infections. As our ability to identify these improves, the role of viruses in the aetiology of AOM is becoming clearer. Increasing use of polymerase chain reaction assays for respiratory viruses suggests 60–90% of cases of AOM may be associated with viral infection.[12] In one study a specific viral cause of URTI was shown in 41% of children with AOM.[13] The viruses most commonly associated with AOM vary between studies, but in decreasing frequency include: respiratory syncytial virus (RSV), influenza A virus, parainfluenza viruses, human rhinovirus and adenoviruses. This heterogeneity is important when considering vaccination against viruses as a prophylactic measure.

The mechanism by which they give rise to AOM is likely to vary between viruses.

Viral material has been demonstrated in the middle ear aspirates of children with AOM in 48–71% of cases.[12] The viral material may either arrive passively along the Eustachian tube along with other nasopharyngeal secretions, or actively invade the middle ear cleft possibly by haematogenous spread. These alternative routes of entry are suggested by the wide variation in rates of isolation of specific viral strains in the middle ear during systemic infection, ranging from 4% to 74% of cases dependent upon the specific virus. If all arrived passively, similar rates of isolation would be expected. This implies that some viruses may be actively invading the middle ear cleft, and may be contributing directly to mucosal inflammation. Respiratory syncytial virus invaded the middle ear most frequently.[13] In contrast, those arriving passively appear to cause AOM by virtue of their action on the Eustachian tube, on bacterial adherence and on host immunity.

There is good clinical and animal evidence that viral infection affects Eustachian tube function.[12] At a cellular level there is release of multiple inflammatory mediators from cells within the nasopharynx. Ciliated epithelial cells numbers decline, mucus production increases in the Eustachian tube, and negative middle ear pressure results. This is likely to predispose to AOM.

Alteration of host immunity has been documented after viral infections, increasing susceptibility to bacterial infections. Cell-mediated immunity has been shown to be affected by RSV infection and neutrophil function altered by influenza viruses. In a study of children with bronchiolitis caused by RSV, 62% developed AOM. Bacteria were isolated from the middle ear in all these children.

The ability of bacteria to colonize and adhere to the nasopharyngeal epithelium appears to be increased by certain viral infections. Increased colonization by pathogenic bacteria may predispose to AOM.

Viral and bacterial infections coexist in the middle ear cleft in AOM in as many as two-thirds of cases where viruses have been identified. This is important as clinical studies show that children who have both viruses and bacteria in their middle ear are very much more likely to have a poor response to antibiotics when compared to those with bacteria only (33% versus 3% failure respectively, in one study[14]). Why this should be is unclear, but it may be related to the greater concentrations of inflammatory mediators in ears in which both bacteria and viruses are present.

BACTERIA

Streptococcus pneumoniae (pneumococcus) is the most common bacteria isolated from the middle ear in AOM, and it has been reported in 18–55% of cases. There are, however, some 90 serotypes. *Haemophilus influenzae* has been isolated in 16–37%, and *Moraxella catarrhalis* in 11–23% of cases.[15] Less frequently reported

are *Streptococcus pyogenes* in up to 13% of cases and *Staphylococcus aureus* in up to 5%.[16]

In persistent or recurrent bacterial AOM, repeat culture of middle ear aspirates has failed to grow pathogenic bacteria in 30–50% of patients, implying that inflammation may persist despite the eradication of the infecting organism. The role of biofilms is the subject of intensive study at present. The spectrum of organisms is similar to that in isolated episodes. In the 1980s *H. influenzae* was the most common organism identified in persistent or recurrent AOM, but this has been replaced by drug-resistant pneumococcus. After antibiotic treatment for recurrent AOM it is now estimated that 50% of *H. influenzae* are beta-lactamase producing. A similar proportion of pneumococci are penicillin-resistant.[16] Penicillin resistance in pneumococci results from decreased penicillin-binding protein on the bacterial cell walls so reducing the affinity for penicillin-related drugs, but this means that resistance may often be overcome by increasing drug dosage. This is not the case with beta-lactamase producing organisms. Most *M. catarrhalis* are now beta-lactamase producing.

Studies on HIV-positive children suggest a similar spectrum and prevalence of infecting organisms as occurs in immunocompetent children, except where the child is severely immunosuppressed where a higher percentage of *Staphylococcus aureus* has been reported.

Routes of spread of infection

Three potential routes are described: the Eustachian tube, tympanic membrane perforations or grommets, and haematogenous.

The Eustachian tube is traditionally assumed to be the main route by which organisms reach the middle ear, though there are relatively few studies to confirm this. It is speculated that negative middle ear pressure may facilitate the movement of bacteria up the Eustachian tube.[17] Circumstantial evidence is also gained from similarities in organisms cultured from the postnasal space and the middle ear cleft in AOM. Whether anatomical or physiological differences predispose to AOM is unclear. Studies of American Indians, who are prone to otitis media, suggest their Eustachian tubes are shorter, straighter and more patulous than in whites, but also that they have a low passive tubal resistance.[18] Research has found no difference in tubal dimensions in otitis prone and non-prone children. However, altered tubal function may play a role. Specifically, otitis-prone children have been shown to have significantly poorer active tubal function (muscular opening function).

Pathogen entry through tympanic membrane perforations or ventilation tubes is most commonly associated with water exposure.

Haematogenous spread is inferred from the evidence provided by studies of viral identification in the blood and middle ear described previously. It was shown that the wide variation in rates of identification of specific viral strains from the middle ear could not be explained by passive Eustachian tube transport alone.[12]

Risk factors

GENETIC FACTORS

There is growing evidence that recurrent AOM is largely genetically determined. It is likely that many genes are involved. There are numerous studies suggesting a familial association. A meta-analysis of risk factors has shown that, when one family member had had AOM, the risk increased for other family members (relative risk 2.63).[19] Racial differences are well described, with increases in American Indians, Inuits and Australian Aboriginals. However, environmental factors, such as poor economic status, may contribute to the increased risks in these groups. The most powerful evidence comes from twin studies, in particular comparison of monozygotic and dizygotic twins in whom the occurrence of AOM was compared.[18] Many immune-related mechanisms, which are likely to have a genetic basis, have been proposed. Certain HLA classes have been shown to be significantly associated with increased risk of AOM. Maternal blood group A is reported to an independent risk factor (relative risk 2.82). Atopy has also been associated with increased risk of developing AOM. **[Level 1, 2 and 3 evidence]**

IMMUNE FACTORS

Our understanding of the immune response to AOM remains incomplete. However, a number of specific associations have been identified which suggest that certain defective or immature pathways may predispose to infection. Low levels of IgG2 subclasses have been reported in several studies to be more common in otitis-prone children. Those with IgG2 deficiency were shown to be three times more likely to develop post-ventilation tube insertion otorrhoea, for example. Delayed maturation of anti-pneumococcal antibodies (IgG1 and IgG2 were studied) does appear to predispose to AOM. This may explain in part why children grow out of AOM as immunity matures.

Defective complement-dependent opsonization has been associated with recurrent AOM and diarrhoea in infancy.[18] This is caused in some examples by low concentrations of mannose-binding protein which acts as an opsonin. This appears to be a common defect with over 20% of children with recurrent AOM affected in some studies. This may be particularly important in infancy when the antibody repertoire is limited.

Aberrant expression of critical cytokines such as tumour necrosis factor and interleukins, resulting in suboptimal host defence, has been postulated as a cause for persistent infection. Expression of mucin genes, at least nine of which have been identified, may differ in those predisposed to AOM. Middle ear mucosa expresses specifically the *MUC5B* gene. Mucin genes regulate the production of mucin. Limited evidence is beginning to emerge that overexpression may alter the mucociliary transport system.[18]

A number of studies of children with HIV infection have yielded conflicting results. Advanced disease associated with low CD4 counts does seem to be associated with an increased incidence of AOM.

ENVIRONMENTAL FACTORS

There are many reports on the relative contribution of environmental factors. These are important as it may be possible to modify them. The most important is almost invariably stated to be day-care attendance outside the home. The larger the number of children in the group, the greater the risk. Day care outside the home carries a relative risk (RR) for AOM of 2.45, compared to a risk of 1.59 for children cared for in their own home. The incidence of AOM appears to follow that of seasonal URTIs in the winter months. Breastfeeding for 3 months is protective (RR 0.87). Use of a pacifier (dummy) carries a relative risk of 1.45.[19] Poor socioeconomic status associated with poor housing and overcrowding has been reported to be associated with AOM (e.g. overcrowding: RR 5.55 in a Greenlandic population). Passive smoke exposure from parental smoking is weakly associated (RR 1.0–1.6). There is more limited evidence to support the role of dietary factors, in particular cow's milk allergy, in predisposing to AOM. [Level 1 evidence]

Syndromic associations

Syndromes associated with abnormalities of skull base anatomy are well recognized as being associated with chronic middle ear disease, but less is published on associations with AOM. Children with Turner syndrome do suffer more frequent episodes of AOM. Down syndrome predisposes to middle ear disease including AOM. In cleft palate there is only a minor increase reported. Certainly Eustachian tube dysfunction in these groups predisposes to middle ear effusion, but it is not clear whether it is this dysfunction or an increase in risk secondary to subtle immunological factors that predisposed to infection. No increase is found in children with primary ciliary dyskinesia if grommets are not inserted, or cystic fibrosis.

A direct association between iron-deficiency anaemia, and the degree of anaemia, and frequency of AOM has been reported.

EPIDEMIOLOGY

AOM is one of the commonest illnesses of childhood. It accounts for about 25% of all prescriptions for children under 10 years of age in the USA, for example. Its incidence appears highest in the first year of life, more specifically the second 6 months of life in most studies, and gradually reduces with increasing age. This progression was shown by Strangerup[20] who reported an incidence of a first episode of AOM in 22% in the first year of life, 15% in year 2, and 10% in year 3, falling to 2% by year 8 (**Figure 14.1**). Epidemiological studies have been compromised by difficulty in achieving accuracy in diagnosis when large numbers of children are being assessed, hence there are wide variations in reported numbers. Incidences of over 60% are stated in some reports of infants up to age 1 year. By age 3 years some 50–70% of all children will have had at least one episode of AOM, and at least 75% by age 9 years.

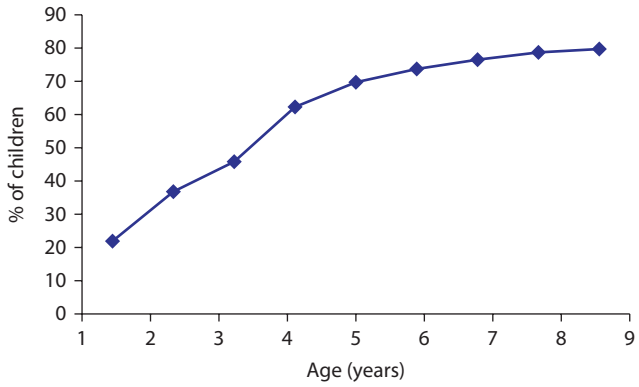


Figure 14.1 Cumulative incidence of acute otitis media (i.e. how many children have had at least one episode in their life). (From Strangerup and Tos,[20] with permission.)

The incidence of AOM certainly varies with the seasonal incidence of viral upper respiratory infections. There are reports that it is increasing over a period of years. Possible reasons include increased day nursery attendance, and changes in diagnostic awareness.

Recurrent AOM has been reported in 5% of children under 2 years of age. Others have reported that by age 3 half of children will have had at least three episodes. An important indicator of future problems is a first episode before 9 months of age: these children have a 1 in 4 risk of developing recurrent AOM.

In the first 2 years of life AOM occurs bilaterally in 80% of cases. After 6 years of age it is unilateral in 86%.[20]

MANAGEMENT OPTIONS

Most children with AOM will get better quickly and without treatment. Some will not. A very small number may develop potentially serious complications. Current debate questions whether and for whom treatment is required, and the role of prophylactic strategies. As serious complications are rare, it can be difficult to obtain high-quality evidence of how effective are prophylaxis and the treatment of episodes of AOM in preventing such complications.

Management of acute episodes

CONSERVATIVE TREATMENT

Most children will benefit from simple analgesics and antipyrexials, in a quiet supportive environment. Paracetamol and ibuprofen are most commonly used in the UK. There is limited experimental animal evidence showing that ibuprofen provides additional benefit by reducing mucosal inflammation when taken in combination with amoxicillin.

MEDICAL TREATMENT

Antibiotics

Uncertainty over the use of antibiotics is reflected in wide variations in usage between countries, ranging from 31%

in the Netherlands to 98% in the USA.[9] There is, however, an increasingly good evidence base for the most appropriate management in children over 2 years of age. In children under 2 the evidence base is weaker.

A recent meta-analysis has addressed the efficacy and safety of antibiotic treatment in children with AOM. Two-thirds of children were shown to recover within 24 hours regardless of treatment. However, antibiotics did have a small beneficial effect on subsequent pain levels, with one third experiencing less pain after 2–3 days and one quarter having reduced pain at 4–7 days. Antibiotics also reduced the number of patients exhibiting abnormal tympanometry at 2 weeks and 2 months, although there was no difference at 3 months. The number of tympanic membrane perforations and contralateral otitis episodes were also reduced in those receiving antibiotics. No effect was demonstrated on late AOM recurrence. However, the occurrence of adverse effects such as vomiting, diarrhoea and rash was significantly increased in the treatment group.[21]

The same review examined the effectiveness and safety of immediate antibiotic treatment against an initial observational approach. No differences were seen between groups in terms of pain, persistence of abnormal tympanometry, tympanic membrane perforations or AOM recurrence, but again the incidence of adverse effects was increased in the immediate treatment group, equating to an adverse event for 1 in every 14 children treated.

Attempts have therefore been made to try to identify a subgroup of children who may benefit from immediate antibiotics. Treatment benefit appears to be most marked in children aged less than 2 years, those with bilateral AOM and those with AOM and otorrhoea. Using short-term symptomatic outcome markers at day 3 has shown that immediate antibiotics may also benefit those children presenting with higher temperatures (>37.5 °C) or vomiting (NNT = 3–6).[4]

The optimum length of a treatment course if commenced has also been addressed in a meta-analysis. Short (less than 7 days) and long (more than 7 days) courses were compared. Risk of treatment failure at 1 month was higher with short courses of antibiotics (absolute difference of 3%) although had no benefit in the longer term. This difference was not observed when using ceftriaxone or azithromycin. In addition, gastrointestinal side effects were reduced when using azithromycin or short-acting antibiotics.[22] In the presence of a tympanic membrane perforation or ventilation tubes, AOM may be treated equally successfully with oral or topical antibiotics. The potential ototoxicity of topical aminoglycoside ear drops in these cases is well recognized and dose-dependent, therefore prolonged topical treatment should be avoided.

Generally, most institutions recommend initial treatment with paracetamol and ibuprofen in uncomplicated cases, with antibiotics to be prescribed if the symptoms worsen or persist for 3–4 days. Immediate antibiotics should, however, be considered if the child is systemically unwell, suffers from significant comorbidities including immunodeficiencies, craniofacial abnormalities or Down syndrome, or if they are under 2 years of age with bilateral AOM, recurrent AOM or tympanic membrane perforation.[2] The usual antibiotic of choice is a 5-day course of amoxicillin, with erythromycin or clarithromycin offered in allergic cases. Guidelines must, however, be adapted to suit local experience, for example in regions of the world with a high incidence of complications of AOM where all patients may be regarded as high risk. **[Level 1 evidence]**

Clinical recommendations for the use of antibiotics in children are summarized in **Box 14.1**.

BOX 14.1 Clinical recommendations for use of antibiotics in children

- Under 6 months of age
- Under 2 years of age with recurrent episodes
- Failure to improve after 2 days of 'watchful waiting'
- More severe symptoms including pyrexia or vomiting, irregular course, or any sign of a complication
- All 'high-risk' children including those with Down syndrome, craniofacial abnormalities, congenital inner ear abnormalities, immunodeficiencies
- Failure to improve after 2–3 days' treatment should lead to change of antibiotic
- Where national guidelines recommend all episodes should be treated

Which antibiotic?

This should be determined by national recommendations. Amoxicillin remains the first choice in most centres, but at higher than previously recommended doses (80 mg/kg/day) if drug-resistant pneumococci are common in a particular country or region, with macrolides for penicillin-sensitive patients. For persistent or resistant episodes, national policies should be sought depending on the prevalence of beta-lactamase producing organisms, and culture results if available. Options include amoxicillin-clavulanate or cefuroxime axetil orally, or intramuscular ceftriaxone (US Centre for Disease Control and Prevention).

Antihistamines and decongestants

A meta-analysis of the use of oral or intranasal antihistamines and/or decongestants concluded that their use could not be supported, and that medication side effects were higher when they were used together. While combining the two treatments was shown to slightly reduce persistent AOM at 2 weeks (NNT = 10.5), the result may have been biased by the design of the studies.[23] **[Level 1 evidence]**

SURGICAL TREATMENT

Surgery has a limited role in the treatment of an uncomplicated episode of AOM. Myringotomy was practised in the pre-antibiotic era, and indeed was continued until the late 1980s in some countries as a first-line treatment for AOM. However, there are now a number of good studies showing that myringotomy plus antibiotics offers no advantage over antibiotics alone. Myringotomy alone has a worse outcome than either of the antibiotic groups.[24]

Myringotomy is reserved for severe cases where complication is present or suspected, to relieve severe pain, or when microbiology is strongly required. [Level 1 evidence]

Management of *recurrent* acute otitis media

ALTERATION OF RISK FACTORS

It may be possible to alter many of the environmental risk factors discussed previously (Box 14.2). Parents should be reassured of the benign natural history of AOM, as these children have been shown to be more demanding than those without recurrent disease, and their mothers more anxious about their care. The most readily modifiable risk factor is exposure to other children. AOM increases with the number of children in day care, the length of time a child spends in day care each week, how young a child is when introduced into day care, the presence of children under 2 years of age in the day-care setting, and having a sibling in day care. Advice should include sitting a child semi-upright if bottle-fed, and avoiding passive smoke inhalation. Restricting the use of pacifiers particularly after infancy should be recommended for otitis-prone children. The mother may be advised to continue breastfeeding for at least 6 months after future pregnancies, and increasing vitamin C intake and avoiding alcohol in the third trimester, both of which have been weakly associated with AOM. The role of food allergies, in particular cow's milk, is still unclear. No effective role has as yet been shown for homeopathic remedies.

BOX 14.2 Modifiable risk factors to discuss with parents

Reduce exposure to other children, e.g. in day-care nursery setting.

Avoid passive smoking.

Sit semi-upright if bottle-feeding.

Avoid the use of pacifiers.

In future pregnancies breastfeed for at least 6 months, and avoid alcohol and increase vitamin C intake in the third trimester.

MEDICAL PROPHYLAXIS

Antibiotics

Antibiotic prophylaxis has the potential to cause problems but can be considered for recurrent AOM. Many organisms need to be covered so a broad spectrum drug is required, although there is no consensus in the literature as to which preparation is superior. Studies of prophylaxis of recurrent AOM invariably treat each individual recurrence with additional antibiotics. Trials therefore compare antibiotic prophylaxis versus placebo between acute episodes. The natural history of recurrent AOM is reassuring. Over 50% of children having no treatment between attacks will not suffer a further episode in the following 6 months. Indeed, only 1 in 8 continues to suffer recurrent AOM (i.e. three or more episodes) during the trials, if treated only for acute episodes. Meta-analysis does, however, show a modest benefit of antibiotic prophylaxis, equating to a reduction of 1.5 episodes per 12 months of antibiotic treatment given, which is about half that expected from the natural history. This suggests that one child would require 8 months of treatment to prevent one episode. However, this effect does not appear to promote longer-lasting benefit after cessation of therapy, and clearly treatment would need to be weighed against the cost of therapy, possible adverse effects and the potential for contribution to bacterial resistance, as well as the potential for masking ongoing active disease.[21]

While the routine administration of prophylactic antibiotics is largely not recommended on the basis of the meta-analysis described above, most trials exclude 'high-risk' children, who are often most in need of treatment. There may therefore be a place for its use in the management of high-risk children with recurrent AOM, despite the absence of specifically targeted studies.

Those studies that assessed the length of time a child has OME in association with AOM showed that, while antibiotic prophylaxis may reduce the incidence of AOM, it does not reduce the length of time with OME. Therefore, ventilation tubes should be considered for those prone to OME. [Level 1 evidence]

Xylitol

Xylitol is a commonly used sweetener that inhibits pneumococcal growth and the attachment of pneumococci and *Haemophilus* to nasopharyngeal cells. As such, it is a recognized prophylaxis for AOM when administered via chewing gum or syrup. A meta-analysis of limited data revealed significant treatment effects, reducing the incidence of AOM in healthy children attending day care by 25% when given at a dose of 8.4 g/day split into five doses,[25] although this effect was lost when the dose was reduced.[26] The very large quantities that must therefore be consumed and associated compliance issues, as well as lack of information with regards to duration of treatment required and long-term effects of consumption, mean that its use cannot yet be recommended.

Zinc

Zinc is a micronutrient found in a variety of foods and is essential for immune function and resistance to infection. It has been demonstrated to have a beneficial effect in the prevention and treatment of pneumonia and other respiratory conditions, and one study has suggested that zinc levels may be lower in children who experience recurrent AOM than in healthy controls. A meta-analysis examining the efficacy of zinc supplementation on frequency of episodes of AOM in children aged 1–5 years living in low- to middle-income countries showed mixed outcomes with no significant overall effect demonstrated.[27] However, there was limited evidence from one small trial that zinc may reduce otitis media in a cohort of infants being treated for malnutrition.

Vaccination

Vaccines have been used effectively against most common childhood infections caused by single specific organisms such as mumps, measles and rubella. The concept of vaccinating against AOM therefore is an attractive one that is being actively explored. Potential obstacles include the wide range of causative organisms, both bacterial and viral, the varied serotypes, technical difficulties in producing an effective immune response, obtaining an immune response before 6 months of age, parental resistance to multiple vaccination, and the possibility that the successfully targeted pathogens will simply be replaced by others.

Vaccination against viruses

Since 60–90% of episodes are initially associated with viral infections (see above), viral vaccination seems the most logical first step. AOM secondary to infection by the measles virus is now relatively uncommon in industrialized countries, for example.

Influenza A vaccination is currently the only commercially available preparation for the prophylaxis of viral upper respiratory tract infections. However, despite early promising results depicting associated reduced episodes of AOM in vaccinated children, a recent meta-analysis suggests that this reduction is small and that the benefits of vaccination for this purpose may not justify the use.[28] In laboratory-confirmed cases of influenza infection, the use of neuroramidase inhibitors such as oseltamivir has been shown to reduce the incidence of AOM in children aged 1–5 years (risk difference -0.14).[29] However, this is at the expense of increased side effects such as vomiting, and the use of oseltamivir for both treatment and prophylaxis should be carefully considered before commencement. **[Level 1 evidence]**

Respiratory syncytial virus vaccines are yet to demonstrate significant protection against lower respiratory tract infection, and currently recombinant monoclonal antibodies such as palivizumab remain the only way to treat severe respiratory disease secondary to RSV infection.[30] No trials are currently underway assessing a role in AOM.

Parainfluenza virus vaccines are not yet commercially available. Results from Phase 1 trials, however, demonstrate relative safety and immunogenicity in adults and seropositive children although proved insufficiently immunogenic in seronegative children,[31] and the impact on AOM has yet to be explored.

Vaccination against bacteria

Vaccination against *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae* and *Moraxella catarrhalis* is made difficult by the low immunogenicity of the polysaccharide capsule of these bacteria in young children and infants. Success against *Haemophilus influenzae* type b (which causes epiglottitis and meningitis) using a polysaccharide-protein conjugated vaccine provides one potential solution.

Streptococcus pneumoniae vaccination is particularly challenging because of the 90 different serotypes of the bacteria. However, as only a small number of these cause most pneumococcal AOM, and it has been shown that anticapsular antibodies can prevent pneumococcal AOM, progress has been made. Early attempts with unconjugated pneumococcal polysaccharide vaccines proved unsuccessful in children under 2 years of age. However, polysaccharide-protein conjugate vaccines allowed for an improved immunological response (immunogenic as young as 2 months) and a heptavalent pneumococcal conjugate vaccine (PCV7) was introduced in 2001.

Since the introduction of PCV7 into childhood vaccination schedules, the global burden of pneumococcal diseases in children has significantly reduced. The Centers for Disease Control and Prevention (CDC) reported a 77% reduction in overall invasive pneumococcal disease (IPD) rates and a 98% reduction in PCV7 serotype disease in children aged under 5 years compared with the pre-PCV7 era.[31] In addition, rates of outpatient attendance for recurrent AOM in children under 2 years reduced by 43%, with a 42% reduction in AOM-associated prescriptions in studies in the USA, and the insertion of ventilation tubes for AOM reduced by 16% and 23% in two states.[32] Furthermore, a global reduction in microbial resistance in vaccine serotypes, a reduction in nasal carriage of vaccine serotypes and a reduction in antibiotic resistant serotypes has also been noted.[31]

However, following the introduction of PCV7, the overall serotype distribution altered globally with an observed increase in non-vaccine serotypes. Subsequently, higher-valent pneumococcal conjugate vaccines became available and PCV13 (Prevenar 13®) became part of the UK Childhood Vaccination Schedule in 2010, currently administered at 2, 4, 6 and 12–15 months of age. A decline in IPD was consequently noted in the UK in the additional vaccine-related serotypes with a sustained decline in the original serotype related disease.[31] However, vaccines that confer species-wide protection against multiple bacterial pathogens by utilizing an antigen common to all known types of pneumococci would potentially be able to prevent early bacterial colonization and subsequent recurrent AOM and may prove more successful in the future.

These results are encouraging, but a recent meta-analysis demonstrated that, although PCV7 showed modest beneficial effects on recurrent AOM in healthy infants with a low baseline risk, there appeared to be no benefit in preventing further episodes in high-risk infants and older children who already had a history of AOM,[33] suggesting that prevention of early episodes is critical. Further studies assessing the impact of multivalent PCVs on AOM are ongoing, as are trials into maternal immunization strategies with respect to the benefit to the infant. **[Level 1 evidence]**

Since routine immunization against *Haemophilus influenzae* type b (Hib) was introduced, there has been a marked change in the predominant invasive serotype to non-typeable *Haemophilus influenzae* (NTHi), and the intrinsic heterogeneity of NTHi has led to challenges in

the development of a further successful vaccine. Phase 3 trials have now concluded into the efficacy of a 10-valent pneumococcal vaccine utilizing *Haemophilus influenzae* protein D conjugate (PHiD-CV). Protein D is a lipoprotein of *Haemophilus influenzae* and has produced protection against NTHi in rat and chinchilla models. While efficacy was demonstrated against a broad range of pneumococcal diseases including AOM and showed non-inferiority of PHiD-CV in comparison to PCV7, strong evidence of any additional protective efficacy against NTHi otitis was lacking and several other protein antigens remain under investigation.[34] **[Level 1 evidence]**

Moraxella catarrhalis vaccine research is at a preclinical stage, but the possibility of using surface proteins as vaccine candidates is currently being explored.

Special attention should be drawn to children with or awaiting cochlear implants. Concern has been raised about a potential increased risk of pneumococcal meningitis, although whether it is implant-related or reflects inner ear abnormalities in many of these children is unclear. Most children will receive PCV13 through the Childhood Immunisation Schedule, and it is recommended that children with cochlear implants receive an additional single dose of pneumococcal polysaccharide vaccine (PPV23) after they reach 2 years of age. If the vaccines were not received, or the child was treated with PCV7 only, catch-up doses are recommended up to the age of 18 years. Hib conjugate vaccine is also recommended for all children up to the age of 5 years.[35]

Immunoglobulins

The importance of immunological immaturity in the occurrence of recurrent AOM has been emphasized. However, therapeutic administration of immunoglobulin has produced variable results in clinical trials, and more recent data have contraindicated the dogma that otitis-prone children exhibit specific humoral immunodeficiencies.[36] As such, prophylactic treatment with immunoglobulins has failed to gain momentum.

Benign commensals

Previous data considered whether spraying benign commensals (alpha streptococci) into the nose to recolonize the nasopharynx following antibiotics might reduce AOM by inhibiting the growth of pathogenic bacteria. A significant reduction in recurrent disease and subsequent OME was reported, although failure rates remained high in both groups.[37] However, a separate smaller study, which did not pre-treat with antibiotics, showed no difference and no subsequent research has been performed in this area to date.

SURGICAL PROPHYLAXIS

In contrast to the large number of trials comparing antibiotic treatments, there are relatively few addressing surgical prophylaxis. Surgery is potentially attractive, however, in that it may reduce problems of antibiotic resistance and also treat subsequent OME.

Ventilation tubes

A meta-analysis of five trials concluded that the presence of ventilation tubes versus no tubes yielded a relative decrease in episodes of AOM of 56%, equivalent to an absolute reduction of 1.0 episode per child per year.[38] The effect occurred mostly in the first year of follow-up, presumably as this covered the period when the tubes were in place. Of equal importance is the reduction in the prevalence of OME by 115 days per child-year. Overall 79% were reported to have an improved quality of life. Side effects included recurrent otorrhoea in 7% and chronic otorrhoea in 4%. Other studies have shown a higher incidence of tympanosclerosis and focal areas of tympanic membrane atrophy of questionable significance in the ventilation tube groups.

These findings need careful interpretation. One of the studies compares antibiotic prophylaxis with amoxicillin to tubes to placebo.[39] The amoxicillin group had a significant reduction in episodes of AOM; the tube and placebo group did not. However, when AOM occurred in the placebo group, it was more distressing than when otorrhoea occurred with AOM in the group with tubes in place. Also over a 2-year period the surgical group had 26 and 61 days fewer with OME than the antibiotic and placebo groups respectively.

It is difficult to draw conclusions about the role of ventilation tubes. On the evidence available, they may be considered for children with recurrent AOM but no persistent effusion, in whom medical strategies have failed. There may be a greater role for them in preference to, or following failure of, medical prophylaxis in the child with recurrent AOM and persistent OME. **[Level 1 evidence]**

Adenoidectomy and adenotonsillectomy

The limited evidence base for best practice is most striking when considering adenoidectomy. The theoretical advantage of disrupting possibly pathological biofilms is appealing. Two papers are particularly worth discussing, both with a cohort of children from Pittsburgh. Randomization methods have been questioned in these studies, as has follow-up. The first concluded that adenoidectomy may be beneficial in children who had previously had ventilation tube insertion and suffered subsequent AOM. AOM was reduced by 31% relative to the control group in a 2-year follow-up (or 0.32 episodes per child-year), and subjects spent 42% less time with OME. Additionally, the need for further tubes was reduced by 50%.[40]

The second trial was of children who had not previously had ventilation tube insertion. Considering children without overt adenotonsillar disease, a modest reduction in the number of episodes of AOM was recorded in the first year after surgery from 2.1 to 1.4 following adenotonsillectomy, but not adenoidectomy. Similarly, OME was reduced from 30 to 19 days in year 1 in the adenotonsillectomy group, and to 22 days in the adenoidectomy group. The effect was not apparent after the first year. Dropout from the trial was particularly high in the adenoidectomy group, and the results should

be viewed cautiously. For children with adenotonsillar symptoms no AOM benefit was reported from adenotonsillectomy. The authors concluded the risks of surgery were not warranted in children who had not previously had ventilation tube insertion.

In summary, there is little evidence to support adenotonsillectomy. Adenoidectomy may be considered in those children who have failed medical therapy and had further AOM following ventilation tube insertion. The presence of OME increases the benefit of adenoidectomy.

KEY POINTS

Clinical recommendations for prophylaxis of recurrent acute otitis media

- Modify environmental risk factors.
- Consider antibiotic prophylaxis over the winter months, particularly if there is no background middle ear effusion.
- Vaccination against *Streptococcus pneumoniae* is available.
- Immunoglobulins may have a role in specific deficiencies.
- Consider ventilation tube insertion in the presence of persistent middle ear effusions between acute episodes.
- Consider adenoidectomy in children who have previously had ventilation tubes inserted but have further recurrent episodes of AOM.

OUTCOMES

An episode of AOM may:

- resolve rapidly with or without antibiotics
- prove resistant to first-line antibiotics
- persist or recur shortly after a course of antibiotics has finished
- subsequently recur
- progress to tympanic membrane perforation or other complication of infection.

Here we consider the medium- and long-term consequences of infection: the natural history of AOM, middle ear effusions, auditory functioning, and speech and language development.

Natural history

Data come from the control arms of randomized controlled trials, and hence usually exclude high-risk children, complicated cases, and those under 2 years old. Without antibiotic treatment, symptomatic relief from pain and fever occurs in about 60% of children within 24 hours of diagnosis, in over 80% by day 2–3, and 88% by day 4–7.[9, 41] These data do not equate with complete resolution – for example, otorrhoea may still be present without pain or fever – and only 73% reach the stage of complete resolution by day 7–14. In all studies those with resistant or persistent disease will have received antibiotic treatment.

For recurrent AOM the prognosis is also generally favourable. Following study entry, and with only acute episodes treated, recurrence rates fell to 0.13 episodes per child per month in the subsequent 6–24 months – about 1.6 episodes per year. Indeed, over half had no further attack in the following 6 months, and only 1 in 8 continued to satisfy the diagnostic criteria for recurrent AOM.[41] Other work has shown that, even in early recurrences of infection 3–4 weeks after a previous episode, a new organism is usually involved. Caution should be attached to these findings: though pooled numbers are large, high-risk children and those with baseline OME were generally excluded.

MIDDLE EAR EFFUSIONS

Middle ear effusions are an important outcome of AOM. Looking again at those children randomized to placebo, pooled data show rates of OME of 63% 2 weeks after AOM, 40% at 1 month and 26% at 3 months. Antibiotics did not appear to have any effect.[9, 41]

AUDITORY FUNCTIONING

What little work has been done on short-term audiometric outcomes suggests about 1 in 3 children will have an air–bone gap greater than 20 dB at 1 month after infection, and 1 in 5 at 3 months. There is limited evidence to suggest that AOM may reduce long-term audiometric thresholds. Several studies following cohorts of children have reported small but significant loss of very high-frequency hearing (11–16 KHz) in those with many episodes of AOM. There is a suggestion that this may be more a consequence of disturbed middle ear mechanics than cochlear damage. The significance for auditory functioning as the child grows older is not established.

SPEECH AND LANGUAGE DEVELOPMENT

It is difficult to separate the literature on AOM and OME outcomes. Little is written on speech production or reception. In children with OME a significant effect seems to occur in the early years of life on expressive language development but not receptive language. A small number of studies point to persisting effects on expressive language in school-age children. There is little evidence showing different cognitive development in school-age children with a history of otitis media in the first 3 years of life. There are suggestions that poor behavioural traits may be commoner by school age, but more work is required before conclusions are drawn.

COMPLICATIONS

Extracranial complications

TYMPANIC MEMBRANE

Tympanic membrane perforation is considered a complication of AOM. It is the commonest complication of infection

and is reported in 0–10% of episodes. Perforation is associated with a purulent or bloody otorrhoea and immediate relief of pain. It typically occurs in the posterior half of the pars tensa, and is associated with loss of the fibrous middle layer of the drum. This may predispose to future posterior retraction pockets. Four outcomes of perforation may result:

- In most cases the perforation heals spontaneously and the infection resolves.
- The infection may resolve but the perforation may persist. This may predispose the ear to future AOM or chronic suppurative otitis media.
- The perforation and otorrhoea may persist, manifesting as chronic suppurative otitis media. 'Chronicity' is generally deemed to have occurred by 3 months.
- A further complication may arise.

Haemophilus influenzae is the dominant otopathogen cultured in AOM with tympanic membrane perforation (followed by *Streptococcus pneumoniae*, then *Moraxella catarrhalis*). In an animal model, addition of dexamethasone to topical treatment with antibiotic drops significantly impaired short-term healing of perforation (at 4 weeks). The location and size of the perforation correlates to the resulting degree of sound conduction impairment, with larger perforations and those located in the anteroinferior quadrant leading to a larger conductive deficit.[42]

The long-term outcomes were assessed in a cohort of otitis-prone children followed up from 3–14 years of age. By the end of the study 7% had collapse of the posterior superior tympanic membrane, chronic suppurative otitis media, or central perforation.[43] Scarring or tympanosclerosis was present in 27%, though several studies report that ventilation tubes increase this risk.

ACUTE MASTOIDITIS

Four classes of mastoiditis are defined. During episodes of **acute otitis media** infection and inflammation may naturally extend into the mastoid cavity and be visualized radiologically. This is not associated with the typical signs of acute mastoiditis and is not considered a complication of AOM.

Infection may spread to the mastoid periosteum by emissary veins: **acute mastoiditis with periosteitis**. At this stage no abscess is present but the postauricular crease may be full, the pinna may be pushed forward, and there may be mild swelling, erythema and tenderness of the postaural region.

When **acute mastoid osteitis** develops, the infection has begun to destroy the bone of the mastoid air cells, and a subperiosteal abscess may develop. Signs may be similar to those when periosteitis is present. A subperiosteal abscess develops most commonly in the postauricular region. A zygomatic abscess may develop above and in front of the pinna. A Bezold abscess may result from perforation of the medial mastoid cortex, tracking down sternomastoid to the posterior triangle. Pus tracking down peritubal cells may result in a retropharyngeal or parapharyngeal abscess.

A fourth stage may be reached, **subacute ('masked') mastoiditis**, in incompletely treated AOM after 10–14 days of infection. Signs may be absent but otalgia and fever persist. This stage can also progress to serious complications.[3]

In the pre-antibiotic era mastoiditis was a common and serious complication of AOM. In a study in 1954 the control group were reported to have developed mastoiditis in 17% of cases.[9] In some developing countries rates of 5% are still quoted. In the 1970s it was estimated that 0.004% of cases of AOM resulted in surgery for mastoiditis. Many papers reported a drop in the incidence of pneumococcal mastoiditis following the introduction of the pneumococcal conjugate vaccine, however the incidence subsequently rose to parallel pre-PCV7 levels, postulated to be secondary to an increase in replacement serotypes. A recent paper showed, however, that the levels of pneumoccocal mastoiditis did not drop again as expected with the introduction of PCV13.[44] The current incidence is estimated to be around 1.2–6.1 cases per 100 000 inhabitants in developed countries.[45]

Acute mastoiditis is a disease of childhood. A large multicentre study found 28% to be in children less than 1 year of age, 38% 1–4 years, 21% 4–8 years, 8% 8–18 years, and 4% over 18 years old.[46] This higher incidence in younger children reflects the peak ages for AOM. Children under 2 years of age also show more distinct clinical signs of mastoiditis and higher inflammatory markers than older children, but they exhibit a more rapid improvement of symptoms, with lower rates of complications and surgery.[47]

Traditional teaching was that acute mastoiditis is preceded by 10–14 days of middle ear symptoms. However, in many papers the short length of middle ear symptoms prior to presentation is noteworthy. For example, in one large study about 32% had 1–2 days of symptoms, 34% had 3–6 days, 26% 7–14 days, and 8% over 14 days.[46] Prior antibiotic treatment of the infection is common, reported in 22–55% of children. Studies have shown that, despite reducing overall prescription rates for AOM, the incidence of acute mastoiditis has remained stable, with no significant difference demonstrated in prior antibiotic use between those who developed a subperiosteal abscess and those who did not.[48] It is therefore clear that antibiotics do not fully protect against mastoiditis.

Symptoms are of otalgia and irritability in most children. Diagnosis usually rests on the presence of postauricular swelling, present in 80–95% of cases, and protrusion of the pinna, seen in 95–100%.[49] Postauricular erythema and tenderness are also usually present and typically sited over MacEwen's triangle (on palpation through the conchal bowl). Pyrexia is reported in around 81% but is less common in those treated with antibiotics. Otorrhoea is present in only about 30%. Clinically, a red or bulging tympanic membrane will often be seen. A normal drum is reported in a very variable proportion of cases, but certainly does not exclude the diagnosis, and is believed to result from resolution of the mesotympanic infection following antibiotic treatment while the osteitis in the mastoid progresses. Sagging of the posterior wall of the

external auditory canal, resulting from subperiosteal abscess formation, should be looked for but is quoted as an uncommon finding. Few patients will have a 'full house' of the classic signs, and 22% may have no clinical symptoms prior to protrusion of the ear.

A somewhat different incidence of organisms has been identified from those gained from culture in AOM. Around 20% of samples do not grow bacteria. *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the most commonly reported in order of decreasing frequency. *Haemophilus influenzae* is less commonly reported, and *Moraxella catarrhalis*, *Proteus mirabilis* and Gram-negative anaerobes rarely. *Fusobacterium necrophorum* is also being increasingly implicated. Clinical features may vary in accordance with the pathogen isolated. *Streptococcus pneumoniae* appears to lead to more severe symptoms and a higher incidence of mastoidectomy, *S. pyogenes* causes less otalgia and *Pseudomonas aeruginosa* particularly affects children with ventilation tubes, with a less aggressive clinical course.[50]

Recommended investigations vary between institutions. A full blood count, CRP and blood cultures are often obtained. A CT scan of the mastoid is recommended when intracranial complications are present or suspected (though MRI may be more helpful in identifying specific intracranial pathology), when mastoidectomy is to be performed, and in those not improving on antibiotic treatment. A CT scan may show evidence of osteitis, abscesses and intracranial complications.

Differential diagnosis includes AOM, otitis externa, furunculosis and reactive lymphadenopathy. Rarely, undiagnosed cholesteatoma, Wegener's granulomatosis, leukaemia and histiocytosis may first present with AOM, hence tissue should be sent for histology if mastoidectomy is performed.

Although simple mastoidectomy represents the most reliable and effective surgical method to treat acute mastoiditis, a more conservative approach consisting of adequate parenteral antibiotic coverage with or without myringotomy is being increasingly adopted for children suffering from uncomplicated acute mastoiditis. The antibiotic of choice is generally a third-generation cephalosporin, or an aminopenicillin combined with a β-lactamase inhibitor. If *Pseudomonas aeruginosa* is suspected, treatment should include ciprofloxacin, piperacillin or fosfomycin.[45] Cases where there is a suspicion of intracranial complication and those not responding to conservative treatment should undergo cortical mastoidectomy. This may be combined with myringotomy with or without ventilation tube placement, and culture of the aspirate. This can be challenging surgery for the less experienced as the mastoid is often full of granulations and the facial nerve superficial in the young child. There is no uniformity in the literature as to the appropriate duration of observation prior to proceeding with surgery, with authors recommending periods in the wide range of 24–72 hours. The presence of a subperiosteal abscess, an unwell child, or a deteriorating clinical picture should prompt more rapid intervention. If in doubt, it is our recommendation to intervene to prevent complication, and sooner rather than later.

A most important message is that intracranial complications from acute mastoiditis develop in 6–17% of cases, and many of these may develop during hospitalization. Although acute mastoiditis may be less common than in the past, its severe complications still occur.

PETROSITIS

Infection may extend to the petrous apex. The classic features of Gradenigo's triad (VI nerve palsy, severe pain in the trigeminal nerve distribution and middle ear infection) are not always present. Patients commonly present with other intracranial complications. Historically, the treatment has been surgical, with a minimum of drainage of the mastoid and, in some centres, decompression of the petrous apex. Resolution of the sixth nerve palsy follows a variable course, from almost instant recovery to taking up to 6 weeks. However, more recently many patients have been successfully managed conservatively with administration of parenteral antibiotics, and most would now reserve surgery for those not responding to conservative management. Sixth nerve palsy resolution with conservative treatment can take up to 3 months.[51]

FACIAL NERVE PALSY

In the pre-antibiotic era it was estimated that acute lower motor neuron facial palsy complicated 0.5% of episodes of AOM. It is now quoted at 0.005%.[52] Most are related to bacterial infection, with one review suggesting the majority are secondary to *Staphylococcus aureus*, but case reports with viral AOM exist. The pathophysiology in most cases is a neuropraxia secondary to oedema or nerve compression, or to bacterial toxic metabolites in the setting of a congenitally dehiscent facial nerve. About four out of five children present with a partial paralysis. The case series in the literature report that about 80% of palsies respond well to ventilation tube insertion and intravenous antibiotics. The remainder undergo cortical mastoidectomy. Corticosteroids are also often used although there is no strong evidence base to support their use. Advice is conflicting about when and in whom mastoidectomy is required and the role of facial nerve decompression, although as recovery is generally so good, a more conservative approach without facial nerve decompression seems appropriate.

Some authors would advocate early electrophysiological testing in all patients with a complete paralysis as recovery in these cases can be more variable, with surgical intervention limited to those who fail conservative treatment or exhibit poor electrophysiological testing.[53] Most children achieve rapid restoration of normal facial function, with a mean time to complete recovery of 4 months. Those with a total paralysis at presentation have a recovery stretching over many months.

Sixth nerve palsy in the absence of petrositis has also been reported. It is speculated this may stem from phlebitis spreading along the inferior petrosal sinus from the lateral sinus.

LABYRINTHITIS

Round window permeability changes during acute infection are important as these may allow entry of bacterial toxins. There is some experimental evidence that permeability can be increased by streptococcal toxins. Preformed channels for bacterial entry may also exist, such as surgical or congenital perilymph fistulae. These may allow infection to spread directly to the subarachnoid space causing meningitis. Particular concern arises in children with congenital inner ear abnormalities, and those with cochlear implants.

Three types of labyrinthitis are recognized. **Perilabyrinthitis** is not associated with AOM. **Serous labyrinthitis** is inflammation of the labyrinth without pus formation, characterized by sensorineural hearing loss and vertigo, usually in a non-toxic patient. There may be an additional conductive loss secondary to the presence of fluid. Typically there is complete and rapid recovery of auditory and vestibular function.

Suppurative labyrinthitis may result from spread of infection from the mastoid or middle ear and may raise the suspicion of an anatomical defect or immune deficiency. Severe vertigo, nausea, vomiting, nystagmus and permanent hearing loss result. The nystagmus may exhibit various patterns, possibly due to differential effects on inner ear function by toxic or inflammatory mediators, however direction-fixed, irritative-type is the most common observed pattern.[54] Suppurative labyrinthitis is rare, and diagnosis is usually made based on clinical and audiometric findings. MRI, if performed, may demonstrate contrast enhancement of the labyrinth and there is some evidence to suggest the degree of enhancement correlates to both subjective symptoms and objective assessment of nystagmus. CT is not helpful in diagnosis but may help to delineate underlying anatomical abnormalities.[53]

The treatment of cases presented in the literature ranges from ventilation tube insertion and aggressive antibiotic use, to tympanomastoidectomy and cochleotomy. Resolution of the vertigo may take weeks to months to occur, demonstrating contralateral vestibular system compensation rather than recovery of function of the affected ear. Longer-term complications of suppurative labyrinthitis may include labyrinthitis ossificans, caused by fibrous or bony replacement of the labyrinth. The administration of steroids during the initial phase of the illness may help prevent the development of this complication.[53]

Intracranial complications

In the pre-antibiotic era intracranial complications of AOM were more common and mortality rates of over 75% are presented. Published mortality rates from intracranial complications now average about 5% in industrialized countries. Estimates of the incidence of intracranial complications vary significantly in the literature, with figures ranging from 0.04% to 17.6%.

The most common symptoms associated with an intracranial complication include fever, otalgia, cephalgia and reduced general condition as well as altered mental status. In other words, do not ignore the child with a headache, pyrexia and ear infection. In half of cases there may be signs only of AOM, and not mastoiditis. Frequently two or more complications coexist. Early diagnosis is important for improving outcomes. As the clinical picture in some cases may not differ from that of acute mastoiditis in terms of signs, symptoms and inflammatory indices, the clinician should always remain alert to the possibility of an otherwise asymptomatic intracranial complication and maintain a low threshold for performing imaging studies. CT with intravenous contrast is the usual imaging technique of choice for patients with acute mastoiditis as this also provides a road map for surgery. MRI is the preferred imaging modality in the presence of suspicion of intracranial complications, as it is superior to CT in the identification of intracranial suppurative lesions, meningeal enhancement and extradural granulation tissue. However, the difficulty in children under 7 years of age is that they are likely to require a general anaesthetic for this so a discussion with the parents regarding the risk and reward of different imaging modalities may be required. MR venography may be utilized to demonstrate the degree of patency of the associated venous sinuses.

Seven classical intracranial suppurative complications of AOM are described:[3] meningitis, extradural abscess, subdural empyema, sinus thrombosis, cerebritis, brain abscess and otitic hydrocephalus.

MENINGITIS

Meningitis is usually cited as the commonest intracranial complication of AOM, accounting for 54–91% of cases. In contrast, studies assessing aetiology of meningitis are conflicting. One of the largest recent studies found no association between bacterial meningitis and AOM, while another found an antecedent history of AOM in 29%,[55] though this does not equate to a causal relationship. The earliest symptoms are headache, fever, vomiting, photophobia, irritability and restlessness, with fullness of the anterior fontanelle in children under 22 months of age. Diagnosis is usually made on the clinical presentation, with a lumbar puncture demonstrating white blood cells and low glucose in the CSF. Special mention has already been made of possible associations between congenital inner ear malformations such as cochlear dysplasia and cochlear implants, and meningitis. Younger children, average age 2 years, are most commonly infected.

Studies focus almost exclusively on bacterial aetiologies. The rate of *Haemophilus influenzae* type b meningitis has dropped dramatically since vaccination was introduced. *Streptococcus pneumoniae* is the causal agent in a greater proportion because of this reduction.[55] A second intracranial complication should be looked for in any infant with meningitis with MRI scanning and the presence of a lung focus has been identified an as independent prognostic factor for an unfavourable outcome.[56] Myringotomy may help establish the infective agent if evidence has not been obtained from lumbar puncture.

Treatment is medical and should comprise a third-generation cephalosporin with consideration given to the

addition of vancomycin to cover for resistant strains. Some papers suggest that addition of dexamethasone may reduce potential neurological sequelae, although this appears to have no effect on audiological outcome which can affect 16% of children.[57] If mastoid surgery is required, it is usual to wait for an improvement in the medical condition of the child first if possible.

EXTRADURAL ABSCESS

This is the next commonest intracranial complication. It is more commonly associated with chronic disease. Pus collects between dura and bone, usually after bone erosion. If this lies in the posterior fossa medial to the sigmoid sinus, it is termed an extradural (epidural) abscess; if it is within the split of dura enclosing the sigmoid sinus, it is called a perisinus abscess. It may be discovered only at mastoidectomy, but may be suspected in the patient with persistent headache and fever, or severe otalgia. Treatment is surgical drainage.

SUBDURAL EMPYEMA

A collection of pus between the dura and arachnoid membranes is termed a subdural empyema. It is rare. It develops by direct extension of infection or thrombophlebitis. In addition to headaches and pyrexia, focal neurological signs, seizures and signs of meningeal irritation may be present. Paranasal sinusitis is reported to be a much commoner cause than AOM. Surgical drainage of the abscess through burr holes or craniectomy may be indicated. Mastoidectomy may sometimes be required, though many cases cited in the literature were treated medically.

SIGMOID SINUS THROMBOSIS

This has an estimated incidence of 0–2.7%[58] and most commonly results from erosion of the bone over the sinus from mastoiditis, and may also be associated with other complications. However, it occurs in association with otitis media alone in 43% of cases. Infected thrombus develops within the sinus and may then extend proximally and distally to the internal jugular vein and superior vena cava, entering the systemic circulation and causing septicaemia. In addition to headache and otorrhoea, a spiking pyrexia may develop. Griesinger's sign is mastoid tenderness and oedema secondary to thrombophlebitis of the mastoid emmisary vein. The presence of specific neurological signs and symptoms is significantly correlated with hypoplasia of the contralateral venous sinus and may be absent in up to 50% of children. The presence of *Fusobacterium necrophorum* dictates a more aggressive and prolonged clinical course. MRI is the imaging of choice showing an acute clot as isodense on T1 and hypodense on T2, with a subacute clot becoming hyperintense on T1. The addition of MR venography will demonstrate lack of flow and increase the sensitivity of the diagnosis especially in the early stage.

Management options described in the literature invariably include the use of systemic broad-spectrum antimicrobials. Non-pneumococcal streptococcal, anaerobic and staphylococcal species are commonly implicated and therefore ceftriaxone, metronidazole or clindamycin are commonly used.[59]

The surgical approach varies dramatically in the literature from myringotomy with ventilation tube placement, to mastoidectomy with or without delamination of the sigmoid sinus, needling of the sinus or thrombectomy. Internal jugular vein ligation and craniotomy have also been described.

The use of post-operative anticoagulation also varies between institutions, with duration ranging from 6 weeks to 6 months. Only one study reported an episode of a subsequent non-life-threatening intracranial haemorrhage, with no other complications related to the treatment identified in any of the other studies, leading to the conclusion that anticoagulation was safe if administered correctly.[60] The current British Society of Haematology guidelines for the management of paediatric cerebral venous sinus thrombosis recommends that anticoagulation should be commenced if there is no associated intracranial haemorrhage. This recommendation is, however, based on a non-significant trend in the anticoagulated group towards better survival and cognitive outcome, and the recommendation is not specific to venous sinus thrombosis of otological origin.[58] At least one series has shown unusually high rates of prothrombotic factors in children with otogenic venous sinus thrombosis, and it has therefore been suggested that anticoagulation may be used selectively in appropriately screened individuals, with a lower threshold for treatment in those in whom there is evidence of thrombus extension, such as Lemierre's syndrome.[59] A multidisciplinary approach with the involvement of paediatricians, haematologists and the infectious diseases team is recommended. In non-anticoagulated cases, it is recommended that further imaging is performed to look for evidence of extension of thrombus.

A recent systematic review into the management of otogenic paediatric cerebral venous sinus thrombosis found that 92% of patients underwent some form of surgery. Just over two-thirds of these patients underwent 'conservative surgery', most commonly mastoidectomy with decompression of the bony covering of the venous sinus. The remainder underwent a more extensive operation, usually mastoidectomy with thrombectomy, with IJV ligation performed in just 6%. Anticoagulation was the treatment for 59%, and a non-life-threatening bleeding-related complication such as post-operative haematoma was reported in 7%. A good outcome was reported in 79%. For those undergoing follow-up scans, complete recanalization was observed in 51% overall occurring up to 5 months later (47% of those who had been anticoagulated and 55% of those who had not).[58] Conservative surgery with anticoagulation is the most common treatment modality administered at present, although the low level of evidence available hinders the development of truly evidence-based guidelines.

FOCAL OTITIC ENCEPHALITIS (CEREBRITIS)

Focal inflammation and oedema of brain tissue may occur independent of or in association with any suppurative complication of AOM. Intensive antibiotic treatment is required.

BRAIN ABSCESS

Brain abscesses are more commonly associated with chronic ear disease but may occur in association with AOM and its complications. They form a larger proportion of complications in developing countries. They develop in both the temporal lobe and cerebellum. In the setting of acute mastoiditis, the most common causative organism is *S. pneumoniae* or other non-pneumococcal *Streptococcus* species.[59] Persistent headaches are the commonest symptom. Initial symptoms may be of encephalitis, but these often settle as the abscess organizes over days or weeks. Eventually, signs of raised intracranial pressure, focal neurology and infection develop. Investigations include CT imaging followed by lumbar puncture if safe.

Patients should undergo treatment with broad-spectrum antibiotics and mastoidectomy to remove the infective foci. In the early stages of cerebritis neurosurgical drainage may be avoided, but it will be required if the abscesses are expanding. Brain abscesses carry a potentially high mortality rate, though in industrialized countries the few large series now quote rates of below 10%. One large review found the mortality from otogenic causes, at 3.8%, was much lower than from other causes. The presence of morbidity such as sensorineural hearing loss, vestibular dysfunction and neurological sequelae varies from 20% to 79% and is reduced with early intervention and treatment.

OTITIC HYDROCEPHALUS

This is a complication of AOM manifesting as raised intracranial pressure in the absence of any space-occupying lesion, and without obstruction to the flow of CSF. Benign intracranial hypertension is a synonym. The aetiology is obscure. Headache is the predominant symptom and may be associated with drowsiness, vomiting, visual disturbance and diplopia, with signs of papilloedema and abducens nerve palsy on examination. It is commonly associated with sigmoid or transverse sinus thrombosis and so MRI/MRV are important investigations. Lumbar puncture will show raised CSF pressure, but normal CSF composition.

A number of medical treatments may be tried such as corticosteroids, mannitol, diuretics and acetazolamide and liaison with a paediatric neurologist is recommended.

CONCLUSION

It can be seen from this chapter that there are deficiencies in our current knowledge of both the diagnosis and aetiology of AOM, and uncertainties in management strategies. We have, however, been able to describe a number of potentially exciting developments that have occurred in the past few years. 'Future research' below summarizes what we feel this chapter should be able to report on when the next edition is being prepared.

BEST CLINICAL PRACTICE

- ✓ AOM is one of the commonest illnesses of childhood. Accurate diagnosis is notoriously difficult. A high index of suspicion is required in the unwell child.
- ✓ The clinician should distinguish between sporadic, resistant, persistent or recurrent AOM as management strategies differ. **[Grade A]**
- ✓ Two-thirds of children recover within 24 hours with or without treatment, so a period of watchful waiting may be reasonable in uncomplicated AOM. **[Grade A]**
- ✓ Antibiotics should not be withheld in severe or irregular infections, should be given if a child fails to improve within 2–3 days of the onset of AOM, and should be given in sufficiently high doses. **[Grade A]**
- ✓ Pyrexia (>37.5 °C), severe otalgia, vomiting, age under 2 years, and 'high-risk' children have all been used as indicators to use antibiotics sooner rather than later.
- ✓ Practitioners should be aware of local bacterial antibiotic resistance patterns, and prescribing policies. Broad spectrum antibiotics are not generally required as first line therapy. **[Grade A]**
- ✓ In otherwise healthy children over 2 years of age, 5 days antibiotics are usually adequate. **[Grade A]**
- ✓ For persistent or resistant AOM it should be noted that while pneumococcal drug resistance can usually be overcome by increased antibiotic doses, *Haemophilus* may be beta-lactam producing, so broader spectrum antibiotics may be required.
- ✓ Modifiable risk factors should be discussed with parents. These include nursery attendance, parental smoking, breast feeding, and the use of pacifiers.
- ✓ In the management of recurrent AOM, 8 months of antibiotic prophylaxis would on average be needed to prevent one episode of AOM. This strategy may be preferred in the absence of effusions between episodes of AOM. **[Grade A]**
- ✓ Ventilation tube insertion reduces the number of episodes of AOM by over 50%. This option may be preferred when effusions persist between episodes of AOM. **[Grade A]**
- ✓ Additional adenoidectomy may further reduce the number of episodes of AOM. **[Grade A]**
- ✓ The benefits of tonsillectomy on episodes of AOM are not sufficient to warrant its use in the management of recurrent AOM. **[Grade A]**
- ✓ Vigilance should be maintained for complications of AOM, the commonest symptoms being persistent pyrexia and headache.

FUTURE RESEARCH

- Greater standardization and reproducibility of diagnostic criteria is required to compare trials.
- The role of biofilms in the aetiology and treatment of middle ear infection is under intensive study.
- As most children appear to recover without treatment, better characterization of those who may have initial antibiotic treatment withheld is needed.
- Trials should be set up to study high-risk groups of children who are currently excluded from most studies: those with conditions predisposing them to acute otitis media; and children under 18 months of age. These are the children likely to benefit most from our intervention.
- Vaccination has been shown to be beneficial. Broadening the role for vaccination is likely over the next decade.
- The number and quality of trials of surgical intervention do not allow confident guidance to be given as to the long-term benefits, or consequences, of ventilation tube insertion.
- More data are required on the long-term consequences of recurrent infection in terms of altered audiometric thresholds, quality of life, and language and cognitive development.

KEY POINTS

- Acute otitis media is one of the commonest illnesses of childhood.
- Diagnosis can be difficult, particularly in very young children.
- Management recommendations vary widely between countries.
- A range of modifiable risk factors should be addressed.
- Evidence is emerging to support new prophylactic strategies.
- Intracranial complications are still seen despite prior antibiotic treatment.
- Do not ignore the child with AOM, headache and pyrexia.

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CHAPTER 15

CHRONIC OTITIS MEDIA

William P.L. Hellier

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the following keywords: chronic otitis media, chronic suppurative otitis media, cholesteatoma, paediatric, children, residual cholesteatoma and reccurent cholesteatoma.

INTRODUCTION

Traditionally, the term chronic suppurative otitis media (CSOM) describes chronic middle ear (ME) disease and is defined as 'chronic inflammation of the middle ear and mastoid cavity, which presents with recurrent ear discharge or otorrhoea through a tympanic membrane perforation'.[1] Chronic inflammation and changes within the ME cleft are, however, not necessarily associated with a non-intact eardrum. The term chronic otitis media (COM) is a better term to encompass the varied pathology seen as a result of chronic ME inflammation. COM was previously considered a direct result of acute otitis media. It is now suggested that, although COM can certainly be precipitated by an acute infection with or without tympanic membrane perforation, it may occur without episodes of acute otitis media.

Histologically, the findings in COM are similar to the initial changes in acute otitis media (AOM) with mucosal and submucosal inflammation (see Chapter 14, Acute otitis media). Continuing inflammation leads to a submucosal infiltrate with histiocytes, lymphocytes and other mononuclear cells, increasing vascularity, and an increase in mucous-secreting goblet cells. The chronic inflammation can lead to osteitis with bone destruction in or around the ME cleft. The ear responds with attempts at healing and repair. This can lead to the florid vascular granulation tissue that may form aural polyps, and the formation of new bone. Inflammation or infection can spread outside the middle ear or temporal bone leading to the complications of COM.

If the ongoing inflammation does resolve, either due to the body's response or because of medical or surgical intervention, the changes left by the chronic inflammation may persist. Submucosal scarring and fibrosis, increased mucous-producing cells, bony erosion or new bone growth, perforation or thinning of the tympanic membrane and changes in the labyrinth can all be seen. It is useful, therefore, to divide COM into **active COM** (ongoing chronic inflammation) and **inactive or healed COM**, where the chronic inflammation has resolved due to time or medical/surgical intervention but sequelae may still be present.

COM causes a variety of pathological changes that are recognized clinically. Generally, COM can be divided into **COM with cholesteatoma** and **COM without cholesteatoma**.

COM without cholesteatoma includes tympanic membrane changes including perforation, tympanosclerosis, thinning or atrophy of the drum, ossicular changes including erosion or fixation and the mucosal changes as described above. These conditions and their treatment are dealt with in Chapter 83, Chronic otitis media. This chapter will consider COM with cholesteatoma.

COM WITH CHOLESTEATOMA

Muller in 1838 first used the term 'cholesteatoma' describing what he thought was a neoplastic lesion with keratin flakes appearing to look like cholesterol crystals. Despite its 'oma' suffix, cholesteatoma is not a true neoplasm, even taking account of the propensity for the keratin epithelium to accumulate and invade the middle ear and mastoid and to erode the temporal bone. A recent consensus definition is: 'Cholesteatoma is a mass formed by keratinizing squamous epithelium in the middle ear and/or mastoid, subepithelial connective tissue and by the progressive accumulation of keratin debris with/without surrounding inflammatory reaction'.[2]

Paediatric cholesteatoma can be divided into congenital and acquired types.

Congenital cholesteatoma

Congenital cholesteatoma (CC) is 'an expanding cystic mass with keratinizing squamous epithelium located medially to the intact tympanic membrane, assumed to be present at birth but usually diagnosed during infancy or in early childhood in patients with no prior history of otorrhea, perforation, or previous ear surgery'.[2] The most accepted aetiology for the cause of CC is the persistence of epidermoid cell rests found in the anterior part of the epitympanum.[3] These rests are thought to usually regress but, if they persist and grow, squamous epithelium accumulates in the ME space forming a CC. Most CC seems to arise from the anterior ME[4] as a defined sac of epithelium, which would fit with this theory. CC is also found purely arising in the posterior ME or elsewhere in the temporal bone, so there may be other cell rests or there may be another pathogeneses. CC can also be found in the ME as free keratin epithelium with no defined sac.[5]

Petrous apex cholesteatomas, with cholesteatoma in the deep temporal bone with no obvious connection to the ME, are also thought to be caused by congenital rests of epithelium. They represent a different spectrum of disease and are discussed elsewhere (see Chapter 108).

To make a diagnosis of CC most definitions describe that there should be no history of AOM or tympanic membrane perforation, and the drum should be intact. However, AOM is common in the paediatric population, and it has been suggested that infrequent episodes of AOM should not exclude the diagnosis of CC. Late diagnosis of a CC can occur if there are few symptoms in the early stages. An extensive CC can become infected, leading to breakdown of the drum and a perforation, which is seen at the initial presentation. It can therefore be difficult in an older child to be sure whether their cholesteatoma is congenital or acquired.

There have been a number of staging systems suggested for CC, based on the extent of spread of keratin epithelium in the ME. Potsic[6] described a four-point staging system according to the degree of cholesteatoma spread in the ME, from his experience with treatment of 160 CCs:

Stage I	Single quadrant, no ossicular involvement or mastoid extension
Stage II	Multiple quadrants: no ossicular involvement or mastoid extension
Stage III	Ossicular involvement: includes erosion of the ossicles and surgical removal for eradication of disease; no mastoid involvement
Stage IV	Mastoid extension (regardless of findings elsewhere).

The stage of the CC at presentation was directly related to the risk of residual disease post-surgery (see later), and to the degree of initial hearing loss. There are other CC staging systems, such as the one described by Nelson.[4]

Acquired cholesteatoma

Acquired cholesteatoma (AC) in children is similar to adult disease in terms of its definition and aetiology. AC is not present at birth but develops with keratin epithelium invading the middle ear and temporal bone. Acquired cholesteatomas may be classified as being primary or secondary.

Secondary acquired cholesteatoma may develop due to ingrowth of keratin epithelium associated with a tympanic membrane perforation as a result of acute perforation or due to ear trauma of various types. More severe trauma, such as temporal bone fractures, can lead to keratin implantation within the ME or mastoid. Iatrogenic implantation of squamous epithelium can also occur after surgery. Any procedure where the ME is entered, even grommet insertion, can allow keratin epithelium to be left in the ME and the development of cholesteatoma.

The exact pathogenesis of **Primary acquired cholesteatoma** is debated, but four main mechanisms are proposed:

- the metaplasia theory
- the retraction theory
- the immigration theory
- the basal hyperplasia or papillary ingrowth theory.

A number of these factors working together may be responsible for cholesteatoma formation (e.g. retraction and basal hyperplasia).[7] These are discussed in more detail in Chapter 82, Acute otitis media and otitis media with effusion in adults.

The most commonly accepted theory is the retraction theory, which postulates that there is ingrowth of the squamous epithelium of the eardrum into the middle ear due to retraction of either a normal or an atrophic tympanic membrane.

Retraction of either the pars tensa or pars flaccida can occur, and this process is thought to be a sequel of dysfunction of the regulation of middle ear pressure. When the squamous epithelium in the retraction can no longer migrate out and 'self-clean', keratin debris builds up in the middle ear leading to slow invasion.

There are a number of theories regarding failure of the maintenance of normal middle ear pressure. The most widely accepted is that there is dysfunction of the Eustachian tube, leading to hypoventilation of the ME and a negative ME pressure. This negative ME pressure acts on either a normal or, if there has been AOM

or COM, an atrophic or thinned tympanic membrane, causing it to retract and allow cholesteatoma formation. Experimental animal models have shown that obstruction of the Eustachian tube causes drum retractions.[8] Children who have a cleft palate are found to have a higher incidence of cholesteatoma.[9, 10] Children are well recognized to have relatively poor Eustachian tube function, witnessed by their high rates of AOM and OME.

Epidemiology

The exact incidence of cholesteatoma in children is hard to know precisely and may vary between different races. A number of series from a variety of countries give different figures. A Danish study[11] gives the incidence as 8–15 per 100 000 person-years between 1977 and 2010. Earlier studies estimated incidence in the USA as 6 per 100 000 children.[9] Other studies have estimated the incidence as between 3 and 15 cases per 100 000 children.[12–15] Caucasians and African populations seem to have the highest cholesteatoma prevalence of all, with a low rate in non-Indian Asians and the Inuits.[16–18]

In approximately 7–10% of children there may be bilateral cholesteatomas at presentation, or contralateral cholesteatoma may develop during follow-up.[19, 20]

Congenital cholesteatoma has been calculated to make up approximately 10–28% of paediatric cholesteatoma, with 2–3% being bilateral (**Figure 15.1**).[4, 6, 21, 22]

Nelson et al.[4] found that children with CC tend to present earlier (5.6 +/– 2.8 years) than those with acquired cholesteatoma (9.7 +/– 3.3 years). Other authors have found a mean age for surgery for paediatric cholesteatoma to be around 10 years.[23, 24] Most studies on the epidemiology of paediatric cholesteatoma are based on surgical series.



Figure 15.1 Axial CT scan in a 5-year-old child. Arrows show mastoid opacification on both sides due to bilateral cholesteatoma, with erosion of the lateral semicircular canal on the left.

There is some evidence[10, 25] that the use of ventilation tubes may lead to a decrease in the incidence of paediatric cholesteatoma, probably due to the improvement of Eustachian tube dysfunction (ETD) and reducing the negative ME pressure that may cause the tympanic membrane retraction process.

DIFFERENCES BETWEEN PAEDIATRIC AND ADULT CHOLESTEATOMA

There are many similarities between adult and paediatric cholesteatoma: the nature of the disease process, the microscopic pathological findings and certain options for treatment. There are differences in terms of cholesteatoma origin (especially in CC), the areas of the temporal bone affected, temporal bone anatomy, some treatment limitations, the rates of residual and recurrent disease and the extent of ongoing Eustachian tube dysfunction. CC more commonly arises from the anterior middle ear, and therefore will often completely fill the ME cleft, including the Eustachian tube orifice, before spreading to the attic and mastoid. Paediatric cholesteatoma (PC) in general seems to spread more extensively through the temporal bone than in adult disease on average, with more involvement of the peri-labyrinthine cells and petrous apex.

There have been suggestions that PC is more aggressive than adult cholesteatoma, but there is no definitive proof that this is the case. The paediatric temporal bone is often more pneumatized than the adult's, so it is possible that the pathways through which cholesteatoma can invade are more open and the process of spread is easier,[26–29] leading to more extensive disease at presentation. Some studies have reported a greater inflammatory response in PC than in adult cholesteatoma, with an increased expression of various markers including metalloproteinases and certain antibodies.[28, 30–34] Greater inflammation, if present, may well lead to more bone erosion and spread of the squamous epithelium.

When compared to adult cholesteatoma, PC does not seem to invade the petrous labyrinth in as many cases. The rate of lateral semicircular canal (LSCC) fistula is less than in adults, as is erosion of the Fallopian canal and exposure of the facial nerve.[28, 35–39] Ossicular erosion due to cholesteatoma, however, seems to be more common in children.

In the child, the function of the Eustachian tube is often poor. Middle ear disorders such as AOM and OME are far more common in children than adults. The immaturity of the ET and the negative ME pressure it produces is one of the likely aetiological factors for the development of cholesteatoma. In adults, once a cholesteatoma has been surgically treated, aeration of the ME can improve, and this can reduce the potential for further retraction and recurrent cholesteatoma. In the child, however, immaturity of ET function may often continue even after the cholesteatoma has been removed by surgery. This is one of the factors that could explain the continuing ME problems and

greater incidence of recurrent cholesteatoma after surgery in the paediatric population (see below). ETD may slowly improve with age but some children may experience a long period with ME pressure dysfunction. With this in mind, the follow-up of children with cholesteatoma should be for many years, as late recurrence is always a possibility.

One of the most obvious differences between children and adults is their ability to tolerate interventions and procedures. Young children may not allow their ears to be examined under the microscope, or permit aural toilet or post-operative microsuction. Many children, if treated gently and kindly, will allow treatment in the outpatient setting. However, a child does not always understand why they need what is often an uncomfortable treatment and may be unable to tolerate it.

The surgeon treating PC is often working 'against the tide' of Eustachian tube dysfunction in a patient who may not allow easy access to their ear, may not tolerate certain procedures and who may need multiple general anaesthetics. This must be borne in mind when treating PC, and when planning both the surgical approach and the need for long follow-up care. These factors, in many surgeons' opinions, make PC a more difficult condition to treat than adult disease.

Diagnosis

The symptoms and signs of cholesteatoma in an adult are usually straightforward. A history of ear discharge often with hearing loss, and on examination a tympanic membrane retraction filled with keratin debris. In children these symptoms and signs are often present but, especially in younger children or in children with congenital cholesteatoma, these symptoms may not be classic and the ear is often difficult to examine.

Younger children with CC may present with hearing loss alone, which at this age is usually suspected to be OME. Unless the drum is adequately viewed with a modern, well-illuminated otoscope or a microscope, the classic appearance of white keratin behind an intact tympanic membrane may be missed (**Figure 15.2**). If the CC is unilateral, and the other ear has normal hearing, symptoms may not become apparent until quite late, as the ear will be dry and pain-free for some years, and the diagnosis may be made only when the eardrum breaks down and the hearing is assessed and found to be poor on one side, or other complications ensue.

Many children with acquired cholesteatoma (**Figure 15.3**) will present with ear discharge and possible hearing loss. However, as discussed above, it may not be possible to perform microsuction to visualize the drum and make the diagnosis. Discharge from a chronic TM perforation after AOM is more common than cholesteatoma in children, and in both conditions florid granulation tissue and possible aural polyp formation will need treatment before the two can be distinguished. This will usually need aural toilet and antibiotic/steroid eardrops, which the child may not allow.

Making the diagnosis and visualizing the drum can therefore take time and a number of outpatient appointments. Dry mopping of the ear can be used, but with care microsuction even in younger children is possible. The use of antibiotic/steroid ear drops will reduce the inflammatory response and allow a view of the TM. In some children who will not allow access to the ear, however, an examination under general anaesthesia (EUA) is needed to thoroughly toilet the ear, remove an aural polyp if present, and see the exact pathology. In children with congenital cholesteatoma, an EUA is often needed, as it is important to perform a myringotomy to establish if the

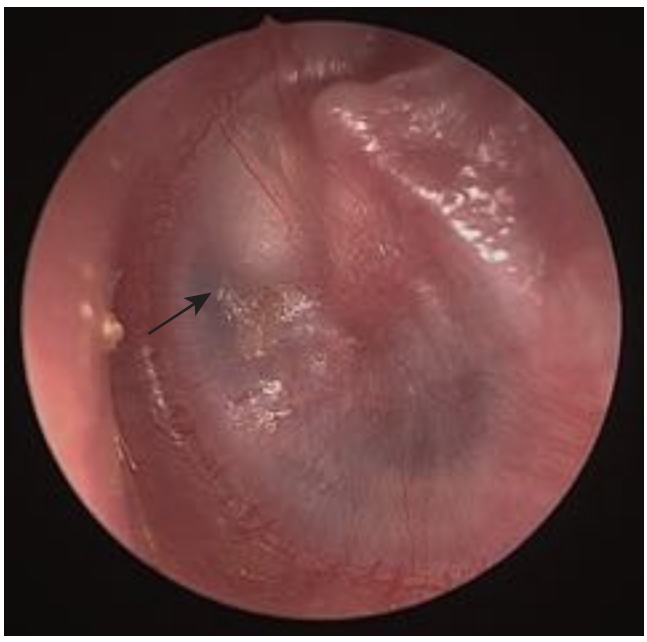


Figure 15.2 Endoscopic photo of a left ear in a 2-year-old child. Arrow indicates white cholesteatoma sac in anterior superior ME behind an intact TM.

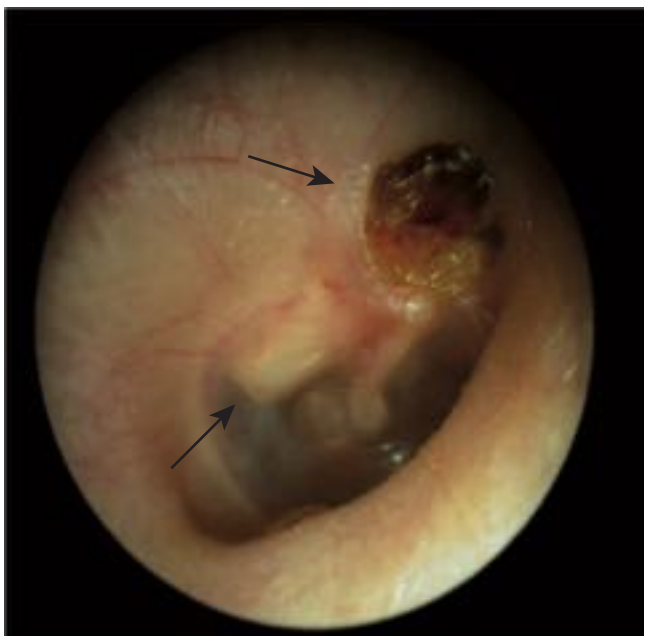


Figure 15.3 Endoscopic photo of the right ear. Thick arrow shows oxidized keratin of the cholesteatoma in the attic. The thin arrow shows the cholesteatoma sac in the posterior ME.

white appearance behind the drum is cholesteatoma, due to an unusually coloured middle ear effusion or another pathology.

MICROBIOLOGY

The bacteria cultured in paediatric COM with cholesteatoma are similar to those in adult disease. Studies show that in children with cholesteatoma *Pseudomonas aeruginosa*, *Proteus mirabilis* and *Staphylococcus aureus* are the most common isolates. Other bacteria can be found but make up a much smaller percentage of the cultures.[40] Any medical treatment used before or after surgery should therefore be targeted to treat these organisms.

IMAGING

Although children can present a difficult problem when it comes to imaging, especially in the under 8–10 years age group, knowledge of the anatomy of a child's temporal bone and the possible extent of the cholesteatoma is vital. Many children will, with the right encouragement, stay still enough for a scan to be performed, but some younger children will need a short general anaesthetic. This should be performed with great care, causing as little distress as possible, particularly as it is likely that the child will need a number of further anaesthetics in the course of their treatment for cholesteatoma, and a good experience at this stage will make the ongoing care far easier for the surgeon.

As discussed above, PC can be extensive at the time of presentation and may have spread around the bony labyrinth (**Figure 15.4**) or into the petrous apex. A computed tomography (CT) scan will give information about cholesteatoma extent but also visualization of any erosion of the bony labyrinth, facial nerve or dural plate that may be incipient or have occurred (**Figure 15.5**). CT scanning allows assessment of the degree of pneumatization of the temporal bone, the height of the middle fossa tegmen and the position of the sigmoid sinus.

Knowledge of the anatomy of the ear and mastoid and the nature of the disease spread allows the surgeon to anticipate potential intra-operative hazards and to plan the exact surgical approach that will be most appropriate to the individual, their temporal bone anatomy and their cholesteatoma.

CT scanning will give good information about the bony anatomy, with an estimation of cholesteatoma extent. This is therefore the main imaging modality. MRI scanning can be used but, because it takes longer and as it occurs in a confined space, it is not so well tolerated by children without general anaesthesia. It gives good soft-tissue differentiation so it can be helpful if there has been dural plate erosion to examine for intracranial cholesteatoma spread or complications, but it has a more limited role in the pre-operative workup. The use of MRI is becoming greater in the post-operative stages where it can be used for the assessment of potential residual cholesteatoma after surgery where a canal wall up procedure or a blind sac closure of the external canal has been performed. MRI can be used in the same way as it is for adult cholesteatoma[41] (see Chapter 97, Imaging of the temporal bone).

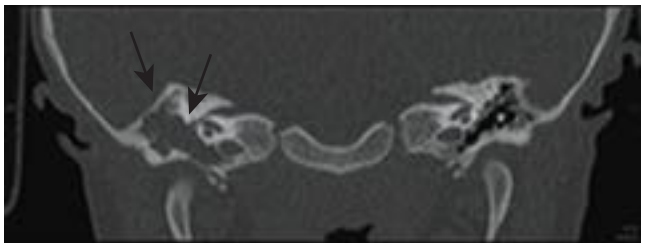


Figure 15.4 Coronal CT scan of a 5-year-old child. The arrow indicates extensive congenital cholesteatoma eroding the anterior attic and the 1st genu of the facial nerve.

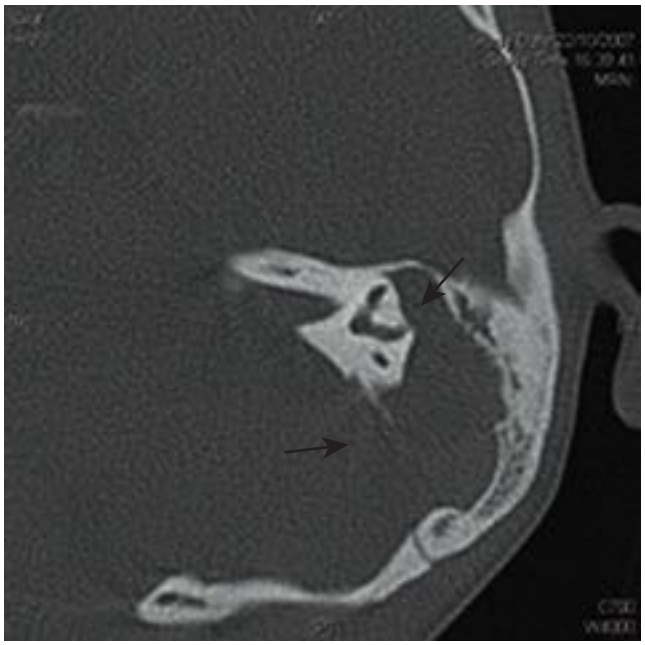


Figure 15.5 Coronal CT of a 5-year-old child. The arrow indicates extensive congenital cholesteatoma eroding the anterior attic and the 1st genu of the facial nerve.

Treatment

NON-SURGICAL TREATMENT

The risk of an intracranial complication of COM has been estimated to be in the order of 1 in 10 000 every year.[42] In an elderly, medically infirm adult with cholesteatoma there is a case for conservative/medical non-surgical treatment to keep the disease under control, as it may not cause a serious complication in their lifetime. A child who develops cholesteatoma at the age of 10 and who may live to 80 will have a risk of intracranial complications in the region of 1 in 140 per year throughout their lifetime. Surgery is therefore the treatment of choice for children with cholesteatoma. There are some exceptions, including children with other significant pathology who cannot tolerate general anaesthesia such as those with major cardiac disease, but this is very uncommon.

Medical therapy with antibiotic/steroid ear drops, combined with microsuction in those children who will tolerate it, can reduce any infective element of the cholesteatoma

and help to remove accessible keratin epithelium. If there is a waiting list for surgery, medical therapy can be used to help to control the erosive process until surgery occurs.

RATIONALE OF SURGERY IN PAEDIATRIC CHOLESTEATOMA

Parents of children with cholesteatoma usually initially hope that surgery will stop the discharge and smell from the ear, and return the hearing to normal. The paediatric otologist's first job after diagnosis is to help the parents and child understand that the primary role of surgery is to:

- remove all original cholesteatoma squamous epithelial matrix
- prevent further erosion and complications
- give a dry, watertight ear
- give an ear that will be self-cleaning
- prevent the occurrence of recurrent cholesteatoma.

A secondary role of surgery is to improve hearing, but only once the primary aim of a dry, stable, disease-free ear has been achieved. It is important that parents understand that it is not possible to return truly normal hearing, and that the aim is to restore the best possible hearing in an ear that will never be 'normal'.

The parents also need to understand that paediatric cholesteatoma represents a difficult disease process in a patient who is not always cooperative with the treatment. Children do not always understand the rationale for what may be uncomfortable medical and surgical procedures. Rates of both residual and recurrent cholesteatoma are higher in children than in adults, and there is commonly the need for a number of surgeries. Parents should be counselled that the diagnosis of cholesteatoma means not a 'one-stop operation' but rather a number of procedures with a prolonged period of follow-up.

SURGICAL APPROACHES FOR PAEDIATRIC CHOLESTEATOMA

The surgical approaches for PC are no different from those for adult disease. They can broadly be divided into the traditional 'canal wall down (CWD)' surgery – modified radical mastoidectomy or for very extensive disease subtotal petrosectomy, sometimes combined with obliteration or closure of the external ear canal – and the less invasive 'canal wall up (CWU)' approaches as follows, sometimes using endoscopic techniques:

- tympanotomy/tympanoplastic surgery
- atticotomy +/– reconstruction
- canal wall up mastoidectomy/combined approach tympanoplasty.

Many of the factors that influence the surgical technique are the same in children and adults – the extent of the cholesteatoma, whether long-term follow-up can be assured, if any complications have occurred, and the anatomy of the temporal bone. The child's age, their ability to tolerate microsuction or outpatient procedures, and parental choice need also to be considered. The ideal operation for PC is tone that removes all the cholesteatoma, gives a stable self-cleaning ear and heals quickly with minimum post-operative care.

Each surgical technique has pros and cons. The decision on the exact approach must be balanced, taking into account all the factors outlined above. The surgeon who operates upon PC must have the ability to perform a wide range of procedures for cholesteatoma.

Canal wall up versus canal wall down surgery in children

A review by Osborn in 2012 of 542 procedures for paediatric cholesteatoma found 89% of cases underwent CWU surgery and 10% CWD surgery initially.[43] Over the follow-up period, ultimately 14% of the cohort received a CWD procedure. The most common reasons contributing to the decision to perform a CWD operation were disease-related: 56% showed extensive/aggressive disease with erosion of the canal wall (**Figure 15.6**) or the need to remove attic bone. Anatomical reasons accounted for 43% (poor mastoid pneumatization, low tegmen, anterior sigmoid).

CANAL WALL UP SURGERY

Canal wall up (CWU) surgery endeavours to remove all the cholesteatoma but to retain the canal wall and a middle ear closed at the level of the original tympanic membrane. This can be achieved by operating via the canal in the case of localized ME choleasteatoma, with removal of some of the medial canal with an atticotomy or bony marginectomy and then reconstructing the defect and repairing the drum, or by a combined transmastoid and transcanal approach (often called a combined approach tympanoplasty (CAT) or a canal wall up mastoidectomy with tympanoplasty). The philosophy of these approaches is to leave an ear with a normal external canal and a stable reconstructed tympanic membrane.

The benefits and downsides of these CWU approaches in the child, if successful, are given in **Box 15.1**.

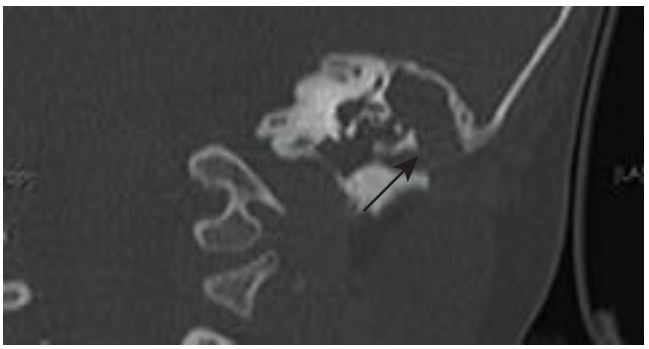


Figure 15.6 Coronal CT scan in an 8-year-old child. Extensive cholesteatoma filling the left mastoid and middle ear, with erosion of the external ear canal (arrow).

BOX 15.1 Benefits and downsides of CWU surgery in children

Benefits	Downsides
Normal ear canal and reconstructed tympanic membrane which does not need to be kept dry	The possible need for a 'second look' operation
Rapid healing as only a small area needs re-epithelialization	The possibility of recurrent cholesteatoma from the reconstructed tympanic membrane
Ear packing usually needed only once after surgery and removed in the outpatient clinic	Technically more demanding surgery
Able to use a normal hearing aid if hearing outcome not satisfactory	
Should not need ongoing microsuction to clean ear	

CANAL WALL DOWN SURGERY

In canal wall down (CWD) mastoidectomy or modified radical mastoidectomy the ear canal wall and the attic scutum are removed to give access to the middle ear, mastoid and attic and to clear the keratin epithelium. CWD surgery gives better intra-operative access to all areas of the ear. The surgical cavity formed is grafted to hopefully allow the migratory epithelium of the tympanic membrane remnant to grow around the cavity. Ideally this creates a bony cavity covered by a dry migratory squamous lining, with the remaining ME and Eustachian tube sealed off from the outside world. However, not every ear heals as well as can be hoped, and a proportion of mastoid cavities may continue to discharge or be wet, for a number of reasons. The 'wet ear' rate may be as low as 5%, but it can be far higher. In the child a wet mastoid cavity that is hard to access and clean presents a very difficult management problem. Males and Gray called this a 'mastoid misery', and many of these discharging cavities will need revision surgery.[44]

The benefits and downsides of the CWD approach in the child are given in Box 15.2.

RESIDUAL AND RECURRENT CHOLESTEATOMA IN CHILDREN

Childhood cholesteatoma has much greater rates of residual and recurrent disease than that seen in adults.[45] **Residual cholesteatoma** is the keratin epithelium that the surgeon failed to remove at the initial operation, so that it grows back (Figure 15.7). **Recurrent cholesteatoma** occurs when squamous epithelium begins to grow again into the middle ear cleft at a new site, either with invagination of the reconstructed tympanic membrane or through a weakness in the reconstruction (Figure 15.8). The term **recidivism** is sometimes used, combining residual and recurrent cholesteatoma. This can confuse as residual cholesteatoma occurs due to inadequate clearance of the initial disease and is therefore purely related to surgical



Figure 15.7 Endoscopic photo of a child's left ear, one year after CWU surgery for attic cholesteatoma. Arrow indicates residual cholesteatoma pearls under grafted attic area.

BOX 15.2 Benefits and downsides of CWD surgery in children

Benefits	Downsides
One major operation	A larger mastoid cavity
A cavity that can easily be inspected	If the cavity does not heal well, a discharging ear
Reduction of volume of middle ear and mastoid, so the Eustachian tube has less to ventilate, hopefully leading to a reduction in recurrent cholesteatoma	In an uncooperative child, often several general anaesthetics
	Often the cavity needs to be kept dry, as cold water can stimulate a caloric effect, so swimming may be restricted
	Sometimes difficult to use a hearing aid in a cavity
	After ME inflammation (common in the child) a cavity can be become unstable and discharge



Figure 15.8 Endoscopic photo of right ear some years after CWU surgery for attic cholesteatoma. The attic has been reconstructed with cartilage but there is recurrent retraction cholesteatoma posterior to this (arrow).

technique, whereas recurrent cholesteatoma may occur due to inadequate surgical reconstruction but is caused by the underlying process that drives cholesteatoma formation (such as Eustachian tube dysfunction), which may continue in the child even after surgery.

It would seem logical that, with the challenges of more difficult surgical access, CWU surgery would have a greater incidence of residual disease than CWD. There may be a trend towards this, but in CWD surgery there are still significant rates of residual cholesteatoma in children. These high residual rates are probably related to the greater extent of the initial disease, often in a well-pneumatized temporal bone.

Residual cholesteatoma rates in the literature for children after surgery range from 6% to 43% in CWU surgery[27,43,46–49] and from 6% to 38 % in CWD surgery.[43,50–52] It seems that rates of residual cholesteatoma can be reduced with the use of modern techniques and the increasing use of the laser and otoendoscope[53] (see Chapter 87, Otoendoscopy).

Recurrent cholesteatoma in CWU would be expected to be more common than in CWD, where there is a reconstructed tympanic membrane and larger ME cleft for re-retraction to occur. However, recurrent retraction and cholesteatoma formation does occur with CWD surgery in children, with epithelial pockets insinuating themselves into the temporal bone. This process can occur slowly over many years after both CWU and CWD operations and is probably a reflection of the ongoing Eustachian tube dysfunction in the child. A long period of post-operative follow-up is needed for any child who has had surgery for cholesteatoma.

In CWU surgery, cholesteatoma recurrence in children at 5 years post-operatively has been found by some reviews to be 17–25%.[49,52,54] More recently, techniques of obliteration of the mastoid in CWU surgery have shown lower rates of recurrence (3%),[46] and it is possible that reducing the volume of the middle ear and mastoid that the Eustachian tube has to ventilate may help reduce the recurrence rate. Cartilage reinforcement of the reconstructed drum may also help prevent recurrent cholesteatoma (**Figures 15.9** and **15.10**).

In CWD surgery recurrence rates of 7–25% are described at 5 years[43,51,54,55] but some retraction pockets in a mastoid cavity may form recurrent cholesteatoma up to 13 years after the initial surgery.[51] Other studies have found ongoing recidivism at up to 25 years post-operatively.[56]

Paediatric cholesteatoma represents a difficult disease process with higher rates of post-surgery residual and recurrent disease when compared to adults. This is in a patient who may not tolerate outpatient intervention so well and may not keep their ear dry as requested. There are a number of surgical options but, whichever technique



Figure 15.9 Endoscopic photo of a child's right ear. Arrow indicates cartilage reconstruction of the attic defect after CWU surgery for attic cholesteatoma.

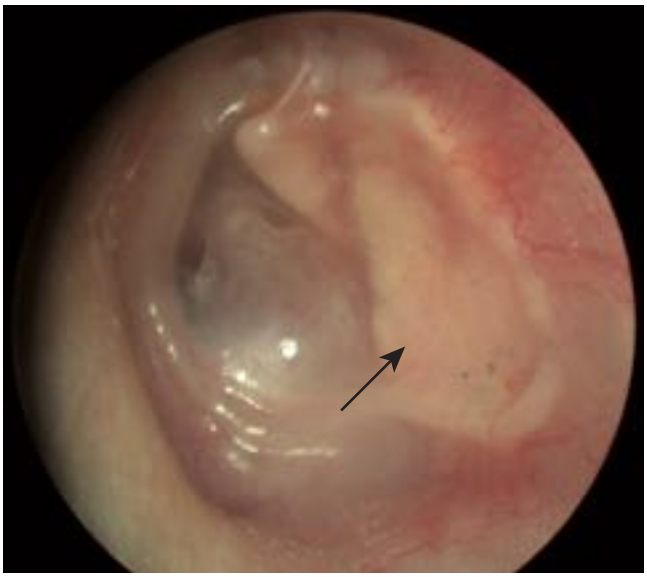


Figure 15.10 Endoscopic photo of the left ear. Posterior tympanic membrane reconstruction with cartilage (arrow) after CWU surgery for posterior pars tensa cholesteatoma.

is chosen, the surgeon will need to use meticulous care to ensure that all the existing cholesteatoma is removed.

In paediatric cholesteatoma over the last 10 years many surgeons have moved away from CWD surgery because of the problems associated with managing a mastoid cavity in children – the potential for 'mastoid misery'.

COM WITH CHOLESTEATOMA IN CHILDREN WITH OTHER SYNDROMES

Children with Down syndrome have an increased incidence of cholesteatoma possibly related to poor Eustachian tube function and midface hypoplasia.[57] Diagnosis of cholesteatoma in this group can be difficult as they often will have small external ear canals and may have learning difficulties. The anatomy of the ear is also challenging with small external canals, poor mastoid pneumatization and often a low mastoid tegmen. Access to the middle ear via the mastoid for a CWU procedure can be very limited and CWD surgery may need to be considered.[58] The facial nerve in children with Down syndrome can run in a more superficial or abnormal course. Care must be taken with mastoid surgery in these children, with the path of the intratemporal bone facial nerve identified on the imaging pre-operatively and the facial nerve monitor used to aid its identification intra-operatively. Careful thought is needed when choosing the operative approach and discussing outcomes with the parents.

Children with craniofacial syndromes, and also di George syndrome (22q11.2 deletion), similarly have a higher risk of cholesteatoma, probably again due to poor palatal and Eustachian tube function. If the child has microtia or a very narrowed external auditory canal with or without these syndromes, it can be difficult to assess the state of the tympanic membrane. An increased suspicion of the presence of COM with or without cholesteatoma should be borne in mind in these cases.

BEST CLINICAL PRACTICE

- ✓ Children with ear disease often need a number of procedures so gentle care is important to prevent a child becoming afraid and adverse to treatment.
- ✓ Imaging of the temporal bone in paediatric cholesteatoma is valuable to gauge disease spread, anatomy and to plan the surgical approach.
- ✓ Cholesteatoma surgery in children requires the surgeon to have the ability to perform a variety of otological approaches.
- ✓ Tympanomastoid surgery can be especially challenging in syndromic children.
- ✓ Residual and recurrent cholesteatoma is greater than in adults and long-term follow up is needed in children.

KEY POINTS

- Paediatric cholesteatoma is thought to be more aggressive than its adult counterpart.
- Children may not tolerate outpatient treatment or microsuction of the ears.
- Paediatric cholesteatoma is a surgical disease. Conservative treatment is very rarely appropriate.
- Canal wall up (CWU) techniques are increasingly preferred in children.
- Endoscopy and use of the laser may reduce the risk of residual cholesteatoma post surgery.

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CHAPTER 16

MICROTIA AND EXTERNAL EAR ABNORMALITIES

Iain Bruce and Jaya Nichani

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: microtia, congenital canal atresia, preauricular sinus, preauricular appendage and unilateral hearing loss.

INTRODUCTION

Abnormal development of the external ear can affect hearing, communication, education, cosmesis and increase the risk of recurrent infections. Our understanding of the consequences of unilateral hearing loss (UHL) upon childhood development continues to expand. While many children with unilateral hearing loss develop normally, some children experience negative effects upon development. The management of the cosmetic consequences of microtia should not occur in isolation, but in combination with the rehabilitation of hearing loss resulting from congenital canal atresia (CCA). Failure to manage cosmesis and hearing loss in combination can result in delayed intervention for hearing loss and/or the compromising of reconstructive options and ultimate outcome.

ANATOMY OF THE EXTERNAL EAR

The pinna, external auditory canal and outer epithelial layer of the tympanic membrane constitute the external ear.

Pinna

The **pinnae** are paired structures with a cartilaginous framework. The inferior part of the pinna (**lobule**) does not have a cartilaginous framework and is only supported by a fibrofatty matrix. The **helix** is the outermost cartilaginous curvature of the pinna. The curve of the **antihelix** runs inside and parallel to the curve of the helix. The antihelix divides superiorly to forms two crura: the **superior crus** and the **inferior crus**. The depression between the two crura is called the **triangular fossa**. Anterior to the antihelix is the concave depression called the **concha**. The conchal bowl is subdivided into the **cymba concha** superiorly and the **concha cavum** inferiorly. The elevation of cartilage anterior to the entrance of the external ear canal is called the **tragus**. The **antitragus** is the inferior-most prominence of the antihelix curvature opposite the tragus, and the gap between the tragus and the antitragus is called the **intertragal notch**. The cartilage of the pinna is continuous with the cartilaginous ear canal, thereby fixing it to the temporal bone along with muscles and ligaments (anterior, posterior and superior ligaments). The intrinsic muscles of the pinna are poorly developed; the extrinsic muscles (anterior, posterior and superior) may be well developed in some individuals.

External auditory canal

The **external auditory canal** (EAC) extends from the concha cavum to the tympanic membrane. It comprises a cartilaginous framework in its outer one-third and a bony canal in the medial two-thirds. The skin and the subcutaneous tissue lining the cartilaginous ear canal contain hair

follicles and glandular structures, whereas the bony canal is covered by a tightly adherent layer of epidermis. The external ear canal is 3–4 cm in length, with the anterior part of the canal being longer and more curved than the posterior canal.

Size and position of the external ear

At birth the anatomical landmarks of the pinna are fully formed. Subsequently, it grows to reach adult size by 8–10 years of age, measuring approximately 60 mm in length. Generally, the superior margin of the pinna lies in line with the eyebrow, and the lower limit of the lobule is in line with the base of the nasal septal columella.[1] It is inclined approximately 15–20° posteriorly and protrudes 15–20 mm from the scalp.

EMBRYOLOGY OF THE EAR

External ear

At 5 weeks of gestation, five paired structures (1, 2, 3, 4 and 6 **pharyngeal arches**) are visible externally, lying close to the developing neural crest. Each pharyngeal arch has an internal endodermal pouch, an external ectodermal cleft and a mesenchymal core which gives rise to an associated named blood vessel, nerve, muscle and cartilage. The external ear develops from the first two pharyngeal arches.[2]

Six nodular swellings called **hillocks of His** develop from the first and second arches, three on either side of the first pharyngeal cleft. Growth, differentiation and fusion of these hillocks result in formation of the pinna. The tragus, helix and cymba concha develop from the hillocks arising from the first arch, while the concha cavum, antihelix and antitragus arise from the hillocks of the second arch. The developing pinna is initially located in the neck and, by 20 weeks of gestation, it ascends to reach its normal location.[3]

The EAC develops from deepening of the first pharyngeal cleft. The first pharyngeal pouch deepens to contact the first cleft. As the embryonic connective tissue proliferates between the first pouch and the first cleft, the contact between the two developing structures is lost and the **meatal plate** develops. The meatal plate starts to canalize between 21 and 28 weeks, forming the inner two-thirds of the EAC. The innermost portion of the meatal plate contributes to the outer layer of the tympanic membrane.

Middle ear

The first and second pharyngeal arches and the first pharyngeal pouch contribute to the development of the middle ear. The middle ear and the inner layer of the tympanic membrane develop from the first pharyngeal pouch. The ossicles develop from the first two pharyngeal arches (malleus and incus from the first arch and the stapes from the second arch).

Inner ear

At week 4 of gestation surface ectodermal cells of the neural plate differentiate into sensory cells and form the **otic placode**. The developing otic placode lies close to the embryonic hindbrain, which contributes to the development of the vestibulo-cochleo-facial ganglion complex. The otic placode invaginates and forms the **otic vesicle**, which gives rise to the membranous labyrinth. The bony labyrinth forms from the periotic mesoderm.

Facial nerve

The facial nerve originates from neural crest cells. The neural crest cells arising from the hindbrain are closely related to the developing pharyngeal arches. The neurons of the first three branchial arches are derived from the neural crest cells (rhombomeres) and form cranial nerves V, VII and IX. The development of these cranial nerve nuclei occurs around the fourth week of embryogenesis and is complete by 16 weeks. Ossification of the Fallopian canal continues into the late foetal period. As the development of the facial nerve and the second arch are closely linked, abnormalities of the facial nerve are often associated with a malformed stapes.

DEVELOPMENTAL ANOMALIES OF THE EXTERNAL EAR

Preauricular sinus

The opening of a preauricular sinus is found in front of the helix, leading into a sinus tract lined with squamous epithelium (Figure 16.1). The tract lies in the subcutaneous tissues lateral to the temporalis fascia superiorly and parotid fascia inferiorly, and with a tortuous and branching course. The terminal portion of the tract is adherent to



Figure 16.1 Left preauricular sinus.

the cartilage of the helix. Preauricular sinuses are postulated to develop from defective or incomplete fusion of the hillocks of His during auricular embryogenesis. An alternative theory suggests that isolated or localized folding of ectoderm during auricular embryogenesis is the cause of preauricular sinus formation.[4]

Preauricular sinuses occur sporadically or may be inherited. Sporadic abnormalities are generally unilateral and bilateral preauricular sinuses are more likely inherited. Preauricular sinuses may be associated with several syndromes, most notably branchio-oto-renal syndrome. It has been suggested that preauricular sinuses may be linked with anomalies in the region of chromosome 8q11.1-q13.3.[5] Renal anomalies are commonly associated with external ear anomalies, particularly preauricular sinuses, with these patients often investigated using renal ultrasound to detect concurrent renal abnormalities. To aid selection of patients for renal ultrasonography, the following criteria have been suggested:[6]

- maternal history of gestational diabetes
- family history of ear anomalies or hearing loss
- associated craniofacial abnormalities
- associated cardiac abnormalities
- associated gastrointestinal abnormalities
- associated limb abnormalities.

The authors suggest that a preauricular sinus, or any other external ear abnormality, associated with any of the above findings is an indication for a renal ultrasound.

INDICATIONS FOR SURGERY

The decision to operate is usually influenced by the frequency and severity of infective episodes, chronicity of sinus discharge and the development of unsightly overlying skin inflammation (**Figure 16.2**). Incision and drainage should be avoided in acute infections due to the risk of sinus disruption and seeding, and less likely facial nerve injury. Acute infections are best treated with intravenous antibiotics and in severe cases needle aspiration with microbiology culture of the aspirate.[7]

SURGICAL TECHNIQUE

Several techniques have been suggested for excising preauricular sinuses including curettage, microdissection and wide local excision. When selecting a surgical technique, the fact that the sinus may branch extensively and be adherent to the pinna cartilage must be taken into consideration. Curettage is no longer routinely performed due to high recurrence rates and unsightly scarring. Microdissection techniques rely upon identification of the extent of the sinus and its branches, with lacrimal probes and methylene blue being used to delineate the sinus. The 'supra-auricular' approach involves identification of the plane of the temporalis fascia and dissection of the soft tissue between this plane and the helix of the pinna, remaining posterior to the parotid fascia, and without a formal attempt to identify the extent of the sinus and its branches.



Figure 16.2 Left preauricular sinus with inflammation of the overlying skin.

The resultant wide local excision is considered to give the lowest recurrence rate. Care must be taken to avoid facial nerve injury in revision cases and when skin and soft-tissue inflammation is extensive.[7]

Preauricular appendages

Preauricular appendages result from abnormalities of embryogenesis of the external ear[8] and may be unilateral or bilateral, solitary or multiple. These appendages have a fibrofatty core and often contain a cartilaginous component. They are usually found along a line drawn from the tragus to the angle of the mandible, reflecting origin from the first branchial arch. An increased risk of associated permanent hearing loss has been suggested in infants with preauricular appendages (**Figure 16.3**).[9]

INDICATIONS FOR SURGERY

Operating upon preauricular appendages is undertaken to improve cosmesis and facial symmetry. Surgery is usually undertaken after 1 year of age. Preauricular appendages associated with microtia may be operated upon to improve facial symmetry while waiting for the child to reach an age when ear reconstruction is considered.

SURGICAL TECHNIQUE

Appendages may contain a deeply extending cartilaginous core that may be more extensive than apparent from examination of the external component. Care must therefore be taken when resecting the deep components of

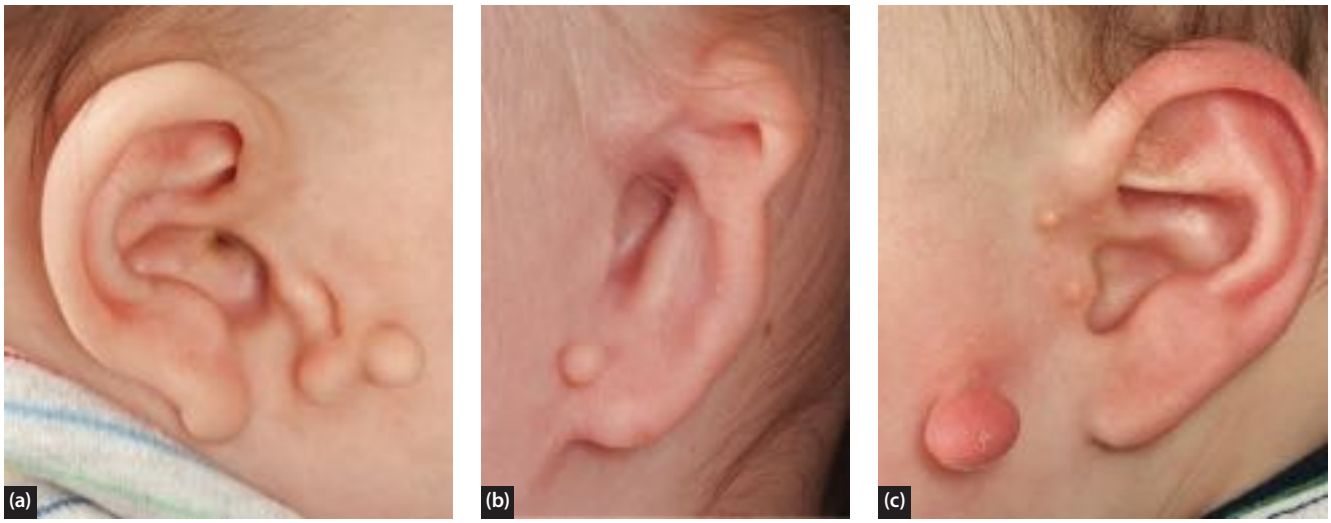


Figure 16.3 Preauricular appendages. **(a)** Associated with a mildly dysplastic right pinna; **(b)** associated with microtia of the left pinna; **(c)** associated with an otherwise normally developed pinna.

the appendage, due to the potential for inadvertent facial nerve injury. Often complete excision of the skin and soft-tissue components is undertaken with partial resection of the superficial part of the cartilaginous core.

MICROTIA

Microtia is a congenital abnormality in which the pinna (auricle) is malformed (see Figure 16.3b). This malformation, or underdevelopment, may be associated with congenital canal atresia or canal stenosis. The incidence of microtia has been reported to be 1 in 10000 and environmental and genetic factors are suggested aetiological factors.[10] CCA often accompanies significant microtia. Results following surgical correction of CCA (canaloplasty) are often disappointing, with a significant risk of chronic discharge and the persisting requirement for amplification. Children with canal stenosis, and those who have undergone canaloplasty, are at risk of developing a canal cholesteatoma and require regular monitoring and interval radiological surveillance.

Grading of microtia and CCA

Several attempts have been made to grade microtia and CCA in a clinically relevant manner, based on clinical, surgical and radiological characteristics (Table 16.1).[11–14] High-quality digital images of the external ear and face often prove more useful as a record of pre-operative appearance and for surgical planning. The pinna malformation may range from mild dysplasia (Figure 16.4) to complete lack of development of the external ear (anotia).

Clinical assessment of children with microtia

A multidisciplinary team is best placed to assess a child with microtia and any associated EAC atresia or stenosis. Attention to the following aspects of clinical and audiological assessment is required.

CLINICAL ASSESSMENT

This involves assessing the general health of the child, with respect to any comorbidity that may affect their management. Some children will also benefit from a psychological assessment, focused on coping with any anxiety associated with their condition and its management. Key points to be considered during assessment are:

- unilateral or bilateral microtia
- size of the microtic ear and its location
- development of the contralateral pinna in unilateral microtia
- hairline
- site and size of a remnant lobule
- presence or absence of normal skin separating the remnants of the microtic ear – this may suggest a superficial course of the facial nerve and caution is exercised during reconstruction to avoid damage to the superficially placed facial nerve
- presence of a stenotic ear canal
- growth and development of the mastoid bone
- space between the temporomandibular joint (TMJ) and the mastoid tip
- presence or absence of facial asymmetry (e.g. hemifacial microsomia in Goldenhar syndrome) (Figure 16.5)
- facial nerve function.

AUDIOLOGICAL ASSESSMENT

Children with microtia and canal stenosis/atresia will usually have a conductive hearing loss (CHL). A small proportion of these children may also have an underlying sensorineural hearing loss (SNHL). It is important to establish ear-specific bone conduction thresholds in early

TABLE 16.1 Examples of grading systems for microtia and congenital canal atresia

	Grading system	Description			
Microtia	Marx[11] *Based on clinical appearance*	**Grade 1** Smaller pinna, but all features of a normal pinna are recognizable	**Grade 2** Some features of a normal pinna are recognizable	**Grade 3** Rudiment of soft tissue and cartilage ('peanut')	**Grade 4** Absent pinna and ear canal
	Weerda[12] *Based on surgical management*	**1st degree dysplasia** Most structures of a normal pinna are recognizable (minor deformities)	**2nd degree dysplasia** Some structures of a normal auricle are recognizable	**3rd degree dysplasia** None of the structures of a normal pinna are recognizable	**Anotia** Absence of external ear
		Surgical definition: Reconstruction does not require the use of additional skin or cartilage	*Surgical definition:* Partial reconstruction requires the use of some additional skin and cartilage	*Surgical definition:* Total reconstruction requires the use of skin and large amounts of cartilage	
CCA	Weerda[13] *Based on clinical appearance*	**Type A** Marked narrowing of EAC with an intact skin layer	**Type B** Partial patency of the lateral EAC with an atretic medial meatal plate		**Type C** Complete atresia of the EAC
	Jahrsdoerfer[14] *Based on radiological appearance*	**Parameter** Stapes present Oval window open Middle ear space Facial nerve normal Malleus/incus complex present Mastoid well-pneumatized Incus/stapes connection Round window normal Appearance of external ear **Rating** 10 9 8 7 6 ≤5			**Points allocated** 2 1 1 1 1 1 1 1 1 **Surgical candidate** Excellent Very good Good Fair Marginal Poor	

infancy to enable appropriate management decisions. Management of bilateral CHL in children with bilateral CCA is of fundamental importance to normal speech and language development. In children with unilateral hearing loss, there is emerging evidence to support early intervention, as discussed below.

Management of significant microtia

The multidisciplinary team delivering care should be able to offer both hearing rehabilitation and all types of pinna reconstruction. Most commonly, children with microtia have three options regarding cosmesis: no intervention, autologous ear reconstruction using cartilage, and bone-anchored auricular prosthesis (BAAP). A proportion of children and young people with significant dysplasia will prefer to keep their 'special ear' and refuse intervention.

AUTOLOGOUS EAR RECONSTRUCTION

This requires two to four surgical procedures dependent upon the technique used (see Vol 3, Chapter 96, Partial and total ear reconstruction). The predominant principles of this procedure include construction of a cartilaginous framework, soft-tissue cover and projection of the reconstructed pinna. Autologous rib cartilage is harvested and used to carve the new cartilage framework. Timing of



Figure 16.4 Dysplastic left pinna in a girl with CHARGE syndrome.



Figure 16.5 Unilateral right microtia in a boy with Goldenhar syndrome. He has right hemifacial microsomia and a left epibulbar dermoid.

surgery will depend on availability of requisite amount of cartilage (8–10 years), and the child's ability to cooperate with the demands of surgery.

The risk of resorption and extrusion of the framework is lower in autologous cartilaginous frameworks as compared to frameworks made from artificial materials.

BONE-ANCHORED AURICULAR PROSTHESIS

A specialist prosthetist is critical in the surgical planning, production of an appropriate prosthesis, and aftercare of older children and young people fitted with bone-anchored auricular prostheses (BAAPs). A BAAP necessitates removal of the vestigial ear (including the lobule), therefore precluding subsequent autologous ear reconstruction if the recipient was dissatisfied with the BAAP. The surgeon and prosthetist must agree the position of the two osseointegrating fixtures. The choice of single- or two-stage surgery is made in the same way as for BAHA insertion. Following osseointegration, a gold retention bar is attached to the abutments, with the prosthetic ear clipping onto this bar. Reasons for opting for a BAAP include patient preference, failed autologous ear reconstruction and significant comorbidities precluding autologous ear reconstruction. The cosmetic outcome of an auricular prosthesis is closely linked to the experience of the prosthetist, with an experienced prosthetist able to add fine contouring and closely match skin colour. However, despite this, some patients prefer a reconstructed pinna that is made from their own tissues. Recurrent soft-tissue inflammation and traumatic fixture loss may complicate the use of percutaneous abutments, as encountered in percutaneous BAHA.

UNILATERAL HEARING LOSS IN CONGENITAL CANAL ATRESIA

Consequences of unilateral hearing loss in children

Traditionally, the presumption has been that UHL would not adversely affect speech and language and academic attainment, if the hearing thresholds in the contralateral ear were within the normal range. However, this assumption is now being challenged, with increasing evidence suggesting that significant numbers of these children could perform better with appropriate management and support.

The work of Lieu and colleagues has described and demonstrated the impact of UHL during childhood, with resultant underperformance in speech, language and cognition in children and young people. Regarding educational performance, a review of UHL (mild to profound severity) in children found a rate of 22–35% for repeating at least one grade and a rate of 12–41% for receiving educational assistance.[15] Lieu also demonstrated in a prospective 3-year longitudinal cohort study of 46 children aged



Figure 16.6 Child with Treacher Collins syndrome and microtia with CCA. The child is wearing a BAHA on a softband and has a tracheostomy *in situ*.

6–12 years with permanent UHL that parents and teachers reported persistent behavioural problems and academic weaknesses or areas of concern in approximately 25% of the cohort.[16] A further case control study of 20 young people (12–17 years) with UHL demonstrated that UHL was associated with a negative effect on standardized language scores and IQ persisting into adolescence. Sibling controls helped to ameliorate any bias resulting from socioeconomic, environmental and genetic factors. The authors also describe children with UHL having difficulty with listening in background noise and sound localization.[17]

Accepting the evidence for the potential negative impact of UHL upon development, the question remains as to the timing of the intervention: before or after the onset of clinically apparent underperformance. Gordon et al. have postulated the existence of aural preference syndrome, in which single-sided deafness in early childhood reorganizes the developing auditory pathways in favour of the hearing ear, and to the detriment of the cortical representation of the deaf ear. They recommend early intervention to secure functioning in the impaired auditory pathway and for restoring (or enabling) binaural hearing.[18] Early intervention would also be supported by the Fischer and Lieu study in which the cohort of young people had not closed the developmental gap with their siblings by adolescence.[17] In broad agreement with the concept of early intervention, the recently developed UK Care Standards for the Management of Patients with Microtia and Atresia[19] advocate the fitting of a bone conduction hearing device (BCHD, e.g. BAHA softband) in infants with microtia and CCA (**Figure 16.6**).

Managing hearing loss in congenital canal atresia

Central to the management of UHL in microtia with CCA is the expectation that in approximately 90% of cases the underlying cochlea function is maintained.[20] Secondly, transcranial attenuation is greater in early infancy, due to the stepwise fusion of the cranial bones during childhood. Therefore, infants and young children will have less transcranial transmission of signal from a BCHD than older children and adults. Also, it is possible to obtain accurate ear-specific bone conduction thresholds in early infancy, despite an inability to mask in a conventional manner in the absence of an external auditory canal.

SYNDROMES ASSOCIATED WITH EXTERNAL EAR ABNORMALITIES

Certain syndromes can be associated with abnormalities of the external ear (**Table 16.2**).[7] Understanding of the manifestations of these conditions is necessary as some may also be associated with other head and neck abnormalities, including abnormalities of the middle and inner ears, and craniofacial abnormalities. Involvement of other body systems (e.g. congenital heart disease (CHD) in a child with Down syndrome) may also be important when planning any surgical intervention under general anaesthesia. Knowledge of cognitive impairment is of critical importance when assessing the likely impact of hearing loss upon development and educational performance.

TABLE 16.2 Syndromes commonly associated with microtia and external ear abnormalities (adapted from Bruce[7])

Syndrome	Description	Chromosomal abnormality	External ear abnormality	Middle and inner ear abnormality
Treacher Collins (Figure 16.6)	Results from abnormal development of structures derived from the first and second pharyngeal complexes	*TCOF1* gene mutations	Bilateral microtia CCA	Ossicular abnormalities
Goldenhar (Figure 16.5)	Heterogeneous disorder associated with hemifacial microsomia, epibulbar dermoid, CHD and vertebral abnormalities	Cause unclear; several chromosomal abnormalities have been described	Unilateral microtia Preauricular appendages	Ossicular abnormalities Abnormal facial nerve anatomy
CHARGE (Figure 16.4)	**C**oloboma, **H**eart defects, **A**tresia choanae, **R**etarded growth and development, **G**enital abnormalities, **E**ar abnormalities	*CHD7* gene mutations	Dysplastic pinnae	Various middle and inner ear abnormalities Facial nerve palsy
Branchio-oto-renal	Branchial cleft abnormalities, ear abnormalities and renal malformations	*EYA1*, *SIX1* and *SIX5* gene mutations	Preauricular sinuses or tags	Ossicular abnormalities WVA Malformed cochlea and vestibular apparatus
Down	Multisystem involvement	Trisomy 21	Small, low-set pinnae Narrow EAC	Hypoplastic mastoid IAC stenosis Vestibular malformations

CCA, congenital canal atresia; CHD, congenital heart disease; WVA, wide vestibular aqueduct; EAC, external auditory canal.

KEY POINTS

- When managing a child with microtia and congenital canal atresia (CCA), consideration should be given to both cosmesis and hearing rehabilitation.
- Cosmesis and hearing should be managed together by a multidisciplinary team.
- In CCA cochlear function is usually normal.
- All children with CCA should undergo regular assessment of hearing, speech and language and educational performance.
- Some children with CAA benefit from a bone conduction hearing device (BCHD).
- Early fitting of BCHD in infants and young children with CCA may be advantageous.
- Bone conduction implants (BCI) should only be inserted in close cooperation with an ear reconstruction service, to prevent inadvertent negative impact upon reconstructive options.

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CHAPTER 17

DISORDERS OF SPEECH AND LANGUAGE

Suzanne Harrigan and Andrew Marshall

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: communication, language, speech, developmental milestones, speech and language therapy.

INTRODUCTION

We live in a world where communication is vital. Modern technologies, including the internet and mobile devices, mean that we can communicate with many more people and across greater distances than at any time in history. In the developed world, jobs that require interaction with others are more prevalent than they were in the last century; the office for national statistics in the UK reports that approximately 71% of men and 92% of women are now employed within service industries, where the skills of interpersonal communication are essential. So, in order to succeed and thrive, both in education and the workplace, the children of the 21st century require a level of spoken language and, in turn, literacy that can be achieved only through exposure to a rich and vibrant language learning environment. For those children who, for whatever reason, fail to develop adequate speech, language and communication skills, the future can be bleak, with a significant percentage of them running the risk of poor attainment levels at school and potentially slipping into antisocial behaviour. Bryan identified high levels of speech, language and communication difficulties within the young offender population.[1] Ironically, however, there appears to be a lack of awareness about the importance of speech and language development in the general population. In a report from the Communication Trust[2] as many as 50% of children were identified as having problems with speech and language on school entry. It is therefore essential that all professionals who come into contact with children are familiar with the developmental milestones for speech and language acquisition in order to intervene both medically and from a multidisciplinary perspective.

This chapter aims to provide the reader with a brief summary of childhood speech and language acquisition, with a particular focus on the first 5 years of life, when the foundations of language for learning and literacy are established. Some of the obstacles that may delay or hinder the developmental process will also be discussed and the 'red flags' that may indicate the presence of speech and language difficulties will be highlighted to ensure that ENT professionals are aware of these warning signs and act in a timely manner, rather than falling into the 'wait and see' trap that often occurs.

A WORD ABOUT TERMINOLOGY

Before looking at the developmental milestones, it is worth considering the terminology used to describe communication, language and speech development.

Pragmatics: using and understanding language in different situations
Verbal skills: understanding and using spoken language
Non-verbal skills: communicating using signs, gestures and body language

Expressive skills: getting a message across, verbally or non-verbally

Comprehension or receptive skills: understanding of language

Voice skills: volume, quality and pitch, which can be used to convey changes in meaning through intonation

Speech: pronouncing sounds and words. Speech and language therapists assess children's speech production in terms of the child's articulation – the physical capability to produce sounds, or phonology, i.e. the child's ability to use a range of sounds contrastively within the rules of the spoken language used.

MILESTONES FOR SPEECH, LANGUAGE AND COMMUNICATION DEVELOPMENT

This section will describe the stages in the development of speech, language and communication over the first 5 years of a child's life (summarized in Table 17.1). However, there is considerable evidence that the process of learning about voices and communication begins before birth, as the mother's speech patterns, particularly prosody (patterns of stress and intonation), are readily available to the baby in the womb. This means that hearing babies arrive in the world with a range of auditory experiences.[3, 4] Babies with hearing losses have therefore already experienced a period of auditory deprivation, despite the earlier identification of hearing problems in babies and management of childhood hearing loss.

Figure 17.1 illustrates the stages in the normal development of speech and communication in the first 5 months.

Birth to 3 months

Babies are born with a desire to communicate and are skilled at getting others to communicate with them. Newborn babies love looking at the human face and will try to copy facial movements. They have different cries for different physical states, so parents quickly begin to differentiate between a hungry cry and a cry of pain. As babies approach the age of 3 months, they are already becoming social beings, with the development of the social smile and laughter. Hearing babies startle to loud sounds and are particularly interested in and calmed by the sound of friendly voices, particularly their parents'. This emphasizes the need for babies with hearing losses to be provided with appropriate amplification as soon as possible, to capitalize on these early listening opportunities.

6 months

As babies grow and start to develop head control, their vocalizations become louder and more purposeful, and babble starts to develop at around the 6-month stage. Babies at 6 months are very sociable and interactive;

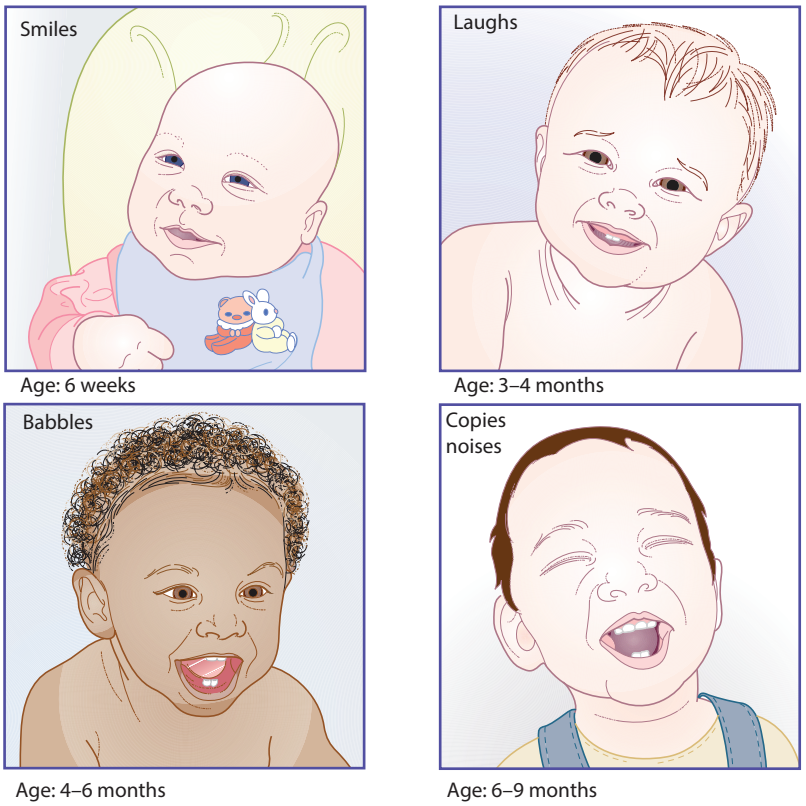


Figure 17.1 Stages in the development of speech and communication in the first 9 months.

TABLE 17.1 Stages of speech and language development in a child up to 5 years of age

Age	Listening and attention	Understanding	Speech sounds and talk	Social skills
Up to 3 months	Turns towards a familiar sound Startled by loud noises	Recognizes parent's voice Often calmed by familiar friendly voice, e.g. parents	Frequently cries, especially when unhappy or uncomfortable Makes vocal sounds, e.g. cooing, gurgling	Gazes at faces and copies facial movements, e.g. sticking out tongue Makes eye contact for fairly long periods
3–6 months	Watches face when someone talks	Shows excitement at sound of approaching voices	Makes vocal noises to get attention Makes sounds back when talked to Laughs during play Babbles to self	Senses different emotions in parent's voice and may respond differently, e.g. smile, quieten, laugh Cries in different ways to express different needs
6–12 months	Locates source of voice with accuracy Focuses on different sounds, e.g. telephone, doorbell, clock	Understands frequently used words such as 'all gone' and 'bye-bye' Stops and looks when hears own name Understands simple instructions when supported by gestures and context	Uses speech sounds (babbling) to communicate with adults; says sounds like 'ba-ba', 'no-no', 'go-go' Stops babbling when hears familiar adult voice Uses gestures such as waving and pointing to help communicate At around 12 months begins to use single words, e.g. 'mummum', 'dada', 'tete' (teddy)	Enjoys action rhymes and songs Tries to copy adult speech and lip movements Takes 'turns' in conversations (using babble)
12–15 months	Attends to music and singing Enjoys sound-making toys/objects	Understands single words in context, e.g. cup, milk, daddy, when the object was there Understands more words than they can say Understands simple instructions, e.g. 'kiss mummy', 'give to daddy', 'stop'	Says around 10 single words, although these may not be clear Reaches or points to something they want while making speech sounds	Likes being with familiar adults Likes watching adults for short periods of time
15–18 months	Listens and responds to simple information/ instructions, e.g. 'Ben, put on shoes', 'Mohammed, give to daddy'	Understands a wide range of single words and some two-word phrases, e.g. 'give me', 'shoe on' Recognizes and points to objects and pictures in books if asked Gives named familiar objects to adult, e.g. coat, car, apple, book	Still babbles but uses at least 20 single words correctly, although may not be clear Copies gestures and words from adults Constant babbling and single words used during play Uses intonation, pitch and changing volume with 'talking'	Simple pretend play Plays alone, although likes to be near familiar adult Although increasingly independent, happiest when near familiar adult
18 months–2 years	Focuses on an activity of their own choice but finds it difficult to be directed by an adult Use of child's name beginning to help them to attend to what the adult says, e.g. 'Sarah, eat sandwiches', 'Ali, put coat on'	Understanding of single words develops rapidly during this stage: between 200 and 500 words are known Understands more simple instructions, e.g. 'get mummy shoes', 'get your bricks', 'tell dad tea's ready'	Uses up to 50 words Begins to put two or three words together Frequently asks questions, e.g. the name of people and objects (towards 2 years of age) Uses speech sounds p, b, m, w	'Pretend' play developing with toys, such as feeding a doll or driving a car Becomes frustrated when unable to make self understood – this may result in tantrums Follows adult body language including pointing, gesture and facial expressions

(Continued)

TABLE 17.1 Stages of speech and language development in a child up to 5 years of age

Age	Listening and attention	Understanding	Speech sounds and talk	Social skills
2–3 years	Beginning to listen to talk with interest, but easily distracted Listens to talk addressed to him/herself, but finds it difficult if prompts are not provided, e.g. use of name, 'stop and listen'	Developing understanding of simple concepts, including in/on/under, big/little Understands phrases like 'put teddy in the box', 'get your book, coat and bag', 'draw a big brown dog' Understands simple 'who', and 'what' and 'where' questions but not 'why' Understands a simple story when supported with pictures	Uses 300 words, including descripting language, time, space, function Links four or five words together May stutter or stammer when thinking what to say Able to use pronouns (me, him, she), plurals and prepositions (in, on, under) Has problems saying speech sounds l/r/w/y, f/th, s/sh/ch/dz/j	Holds a conversation but jumps from topic to topic Interested in other's play and will join in Expresses emotion towards adults and peers using words, not just actions
3–4 years	Enjoys listening to stories Still finds it difficult to attend to more than one thing at a time, so can't easily listen to a speaker while still carrying on an activity; has to switch attention between speaker and task	Understands questions or instruction with two parts: 'get your jumper' and 'stand by the door' Understands 'why' questions Aware of time in relation to past, present and future, e.g. 'Today is sunny, yesterday was rainy. I wonder what the weather will be like tomorrow?' (towards 4 years)	Uses sentences of four to six words, e.g. 'I want to play with cars', 'What is that thingy called?' Uses future and past tense, e.g. 'I am going shopping', 'I walked home' May continue to have problems with irregular words, e.g. 'runned' for 'ran', 'swimmed' for 'swam' Able to remember and enjoys telling long stories or singing songs Has problems saying r, j, th, ch and sh	Understands turn-taking as well as sharing with adults and peers Initiates conversations Enjoys playing with peers Able to argue with adults or peers if they disagree – uses words, not just actions
4–5 years	Attention is now more flexible – the child can understand spoken instructions related to a task without stopping the activity to look at the speaker	Able to follow simple story without pictures Understands instructions containing sequencing words; 'first … after … last' Understands adjectives: soft, hard, smooth, etc. Aware of more complex humour, laughs at jokes that are told	Uses well-formed sentences, e.g. 'I played with Ben at lunchtime' but there may still be some grammatical errors Easily understood by adults and peers, with only a few immaturities in speech sounds, e.g. 'th', 't' and three-consonant combinations 'scribble' Frequently asks the meaning of unfamiliar words and may use them randomly	Chooses own friends Generally cooperates with playmates Able to plan construction and make-believe play activities, e.g. building models from Lego Takes turns in longer conversations Uses language to gain information, negotiate, discuss feelings/ideas and give options

Reproduced with permission from I Can.[5]

they can easily express their likes and dislikes through their facial expressions and vocalizations. At around this age, babies begin to understand that they can use their voices to attract the attention of their caregivers and they engage in vocal turn-taking with their carers. Hearing babies are beginning to gain meaning from what they hear at this stage – they can anticipate the arrival of a familiar person from hearing their approaching voice and they can make sense and respond appropriately to different tones of voice – so they can tell the difference between happy and angry voices, for instance. They may also respond to their name being called, and they may start to respond to 'no'.

At 6 months, babies enjoy exploring everything they can lay their hands on and most objects tend to go into the mouth. This is a particularly difficult stage for parents of young hearing-aid users as encouraging 6-month-olds to wear their hearing aids is challenging to say the least. All professionals need to support parents through this stage.

Warning signs are difficult to spot at this early age, but all professionals should be aware of the signs of possible communication difficulties. A baby of 6 months old who does not startle to loud sounds, engage in eye contact or smile back when being spoken to, or seems to lack interest in faces, may need to be seen by a paediatrician for developmental assessment.

9 months

At 9 months a baby's babbling is more advanced, with strings of both canonical babble (where the same consonants and vowels are reduplicated [*bababa*]) and non-canonical or variegated babble (where new and different consonants are introduced to the babble stream [*badabada*]). Babies with hearing are now beginning to understand familiar words and phrases, such as 'wave bye-bye', and they may even be making some early word attempts, where babble patterns such as 'mama' and 'dada' are beginning to be associated with the relevant people.

Babies at this age are starting to point to objects, which draws the adults' attention to the object and makes you name them. This is an important marker for communication development; babies who fail to develop pointing may be at risk of developmental disorders such as autistic spectrum disorder and they need to be carefully monitored.

Other important communication markers to look out for at 9 months are the child's ability to gain your attention and respond to noises. Babies who are failing to do these things, certainly by 12 months of age, may need further investigation.

12 months

Babies become toddlers around their first birthday and are also becoming great communicators! One-year-olds can understand many words and gestures and will respond accordingly. They can also initiate conversations themselves to express their wants and needs. Babies at 12 months will have a small number of words (around ten), although they will not pronounce them clearly and may only be understood by those closest to them. Intelligible speech is not something that should be expected at a year.

18 months

At 18 months toddlers are developing strong personalities and it is at this stage that there is enormous variability in children's language development. Some at this age have an extensive vocabulary and are already stringing words together into short phrases; others will still have only a small handful of words, and yet would still be classed as functioning within normal limits. Crucially, children's understanding of words and phrases is important at this age; 18-month-olds should be able to follow simple requests and point to pictures in a book and to body parts, and children who are not yet able to do this will need careful monitoring and possible referral to speech and language therapy services.

2 years

The 2-year-old's greatest achievement is their language development. A 2-year-old will have an average vocabulary of around 60 words and some two-word combinations, and they will understand many more. They will enjoy naming everything they see, and will repeat everything that they hear. At this time, adults need to focus on the meaning behind the message rather than the children's grammar and speech sounds as there will still be many errors.

It is between the ages of 2 and 3 years that speech, language and communication difficulties become more apparent, and early referral to speech and language therapy services is vital. Children of this age should be referred if:

- the child prefers to point or show what they want rather than to say it
- single words are not yet being combined into phrases or sentences
- they seem slow to follow instructions and prefer to wait to be shown what to do rather than be told
- adults, and particularly close family members, find it hard to understand what they say, either because their speech is unclear, or the language they use is confused.

3 years

A 3-year-old will be developing an understanding of the simple concepts of size, colour and position. They will also enjoy simple stories and be able to answer simple questions such as 'who…?' and 'what…?' They will have a rich and varied vocabulary of approximately 300 words, which they will be linking together into sentences of four or five words. Grammatical development will also be progressing, with children of this age starting to use grammatical markers for plurals, and grammatical words such as pronouns. Three-year-olds often stammer when talking, but this is a developmental stage which passes quickly. Their speech intelligibility is improving, although they will still struggle with certain speech sounds, or blends of sounds.

4 years

At 4 years of age, children use much longer sentences and are beginning to indicate past and future tenses, although they are likely to struggle with irregular tense constructions, so may say 'swimmed' instead of 'swam', for example. They will still have difficulties producing some speech sounds. A 4-year-old will need speech and language therapy assessment if:

- they are struggling to understand and retain language around concepts
- they are finding it difficult to talk in longer sentences, by failing to organize words into the right order or not having the vocabulary to express what they want to
- they miss out words within a sentence, for instance 'boy play ball' rather than 'the boy is playing ball'
- they are not using the right speech sounds or they miss out some sounds altogether
- they seem to have developed a stammer or dysfluent speech has persisted.

5 years

Five-year-olds are confident and competent communicators who use well-formed sentences and are easily understood by others. They are interested in language and words; they will frequently ask what words mean and are developing a verbal sense of humour.

SPEECH, LANGUAGE AND COMMUNICATION DIFFICULTIES: CAUSES AND PREVALENCE

Speech, language and communication needs may be the most common disability in children under the age of 5, with the range of estimates of prevalence across the UK population between 2% and 25%, depending on the data collection methods used and the criteria applied.[6] The speech, language and communication needs of preschool children can be many and varied, ranging from a child who presents with mild speech difficulties, to a child with no communication skills at all. These difficulties may arise as a consequence of other conditions, so children with sensory impairment, learning disabilities, physical needs or developmental disorders are far more likely than their peers to have problems communicating. However, significant numbers of children present with speech and language difficulties where there are no other factors present. Although for the majority of these children their problems may be relatively minor and easily remediated, a proportion of them will experience persistent and complex communication problems which will need specialist support for a prolonged period if they are to progress to their full potential.

An important distinction to make at this point is the difference between a language and/or speech **delay** and a true **disorder**. Speech and/or language delay is defined as 'a delay in speech and/or language development compared with controls matched for age, sex, cultural background and intelligence'.[7] The extent of the delay can vary from being fairly minor to severe and debilitating, particularly if associated with other conditions such as learning disability.

Learning difficulties

Around 2 million people in the UK have a learning disability. Mencap states that 'a learning disability is a reduced intellectual ability and difficulty with everyday activities – for example household tasks, socialising or managing money – which affects someone for their whole life. People with a learning disability tend to take longer to learn and may need support to develop new skills, understand complicated information and interact with other people'.[8]

Speech, language and communication difficulties are found in children and adults with all levels of learning difficulties, from mild through to severe and profound; the more significant and severe the learning disability, then the more likely it is for the communication difficulty to be severe, with approximately 80% of people with severe learning difficulties not acquiring speech.

Physical impairment

Children with physical impairments including cerebral palsy are likely to present with speech, language and communication difficulties. Speech in particular is often affected because of the difficulties in motor control and planning, but individuals with physical disabilities may also present with learning difficulties and sensory impairments, which can further exacerbate their communication difficulties. It is also important to mention that physical impairments of the vocal tract can cause speech difficulties. In particular, cleft palate, which is the most common congenital craniofacial abnormality, affecting about 1 in 600 live births, can cause atypical speech development and problems with resonance that can persist without specialist support and treatment.

Autistic spectrum disorder

Autism is a lifelong condition that affects how a person communicates with, and relates to, other people. It also affects how they make sense of the world around them. Autism is a spectrum disorder, which ranges from mild to profound, and communication difficulties, particularly in the areas of social communication and interaction, are crucial diagnostic indicators. The National Autistic Society suggests that approximately 700 000 people in the UK have ASD, which is 1 in every 100 people.

Sensory impairment

Childhood hearing loss is, of course, familiar to professionals working within ENT and it can have a considerable impact on communication, educational attainment, employment opportunities and quality of life. Deafness may be congenital or acquired, temporary, permanent or fluctuating and may range from a mild difficulty, where individuals may struggle a little to follow speech in noisy environments, through to a profound loss, where speech is inaccessible even with the most powerful hearing aids, and cochlear implantation may be necessary.

Over the past two decades, great advances have been made in hearing technologies, meaning that even profoundly deaf children can access spoken language in ways that were only dreamt of 50 years ago. However, there is certainly no room for complacency. Hearing technologies, although excellent, do have their limitations, especially in less than optimal acoustic conditions, and despite earlier identification of hearing loss thanks to newborn hearing screening programmes both in the UK and worldwide, a significant number of deaf children are still struggling to develop speech and language. The reasons for this are multifaceted and some of these will be beyond the control of professionals; a high percentage

(around 40%) of deaf children will have additional difficulties which may affect their ability to learn.[9] However, the importance of early and appropriate amplification is certainly something that ENT professionals need to consider.

The evidence for the importance of early cochlear implantation for the best spoken language outcomes in profound hearing loss is unequivocal, meaning that early referral to cochlear implant teams should be a priority for all ENT doctors. Many children implanted before 18 months of age show a similar rate of language development as their hearing peers. Those implanted after 3 years of age may struggle to catch up,[10] and it is recognized that a proportion of children will remain language-delayed when compared to hearing peers.[11] It is important to note, however, that children with cochlear implants consistently show a higher level of language attainment than profoundly deaf children using hearing aids (see Chapter 94, for further details).

It is worth noting here that children with visual impairments may also experience difficulties with communication. Children with visual impairments may follow a different developmental path to typically developing children, particularly in the area of social communication, as the early interactive skills of eye contact and shared attention may have been lacking. It is also very common for visual impairments to co-occur with other disabilities, meaning that these children's communication needs can be extremely complex.

Language disorders

Language disorders are identified when a child presents with a language score on standardized tests two standard deviations from the child's age and where there is no neurological, sensory, developmental or physical impairment that could account for the poor performance.[12] Language disorders can therefore be accurately diagnosed only by a process of exclusion and it is vital that thorough and comprehensive assessments are carried out to rule out the presence of other difficulties. This group of children is a significant one, with studies suggesting that 5–7% of children starting school have such a disorder. The most commonly used term to describe this condition is developmental language disorder (DLD), and children with DLD may have difficulty in only one or in a combination of language and speech areas. There is no single known cause of DLD, with both intrinsic and extrinsic factors playing a part.[13] However, genetics are known to have an influence, with evidence of strong family histories for DLD. More boys than girls present with DLD, with studies estimating ratios of around 3:1.

Speech sound disorders are distinguishable from speech delays because the children present with unusual or idiosyncratic patterns of speech production that do not follow normal developmental patterns. Children with speech sound disorders may also continue to use immature patterns for much longer than expected and may be resistant to therapeutic intervention. These children will have restricted and distorted sound systems and will have problems producing connected speech. It is important that any structural factors that may be causing or contributing to speech sound problems are investigated and ENT professionals may be asked to assess these children to check for issues such as palatal function and carry out a thorough examination of the head and neck.

HYPERNASAL SPEECH

In hypernasal speech (rhinolalia aperta) the velopharyngeal sphincter remains open or partly open during speech and air escapes into the nasal cavity. Causes include palatal paralysis (e.g. cerebral palsy), cleft palate, submucous cleft, adenoidectomy, and craniofacial surgery such as midfacial osteotomy. Placing a cold steel spatula under the nostrils and observing the misting pattern as the child speaks is a useful clinical test for the condition. Some nasal escape is normal during 'nasal' sounds such as *mm*, *nn* and *ng*, but misting when the child speaks a phrase with no nasal sounds (e.g. 'Katie's sister was six yesterday') is suggestive of palatal dysfunction. In established cases, there may be compensatory nasal grimacing as the child attempts to correct the nasal escape. Velopharyngeal insufficiency and submucous palatal clefts are discussed in Chapter 18, Cleft lip and palate.

HYPONASAL SPEECH

Hyponasal speech (rhinolalia clausa) can be caused by septal deviation, nasal polyps, gross turbinate hypertrophy, adenoids or a space-occupying nasopharyngeal lesion. The spatula test shows no escape when the child is asked to speak words with 'nasal' sounds; for example, 'Mummy and nanny are mending' will be pronounced 'Bubby and daddy are bedding'.

Tonsils, adenoids and speech

Tonsillectomy may affect the 'timbre' or resonance of the singing voice and, in the case of children who sing, it is wise to inform them and their parents of this. Adenoidectomy causes transient velopharyngeal sphincter dysfunction in about 5% of cases. This can cause troublesome rhinolalia aperta. In a small minority (0.01%) this may be long-standing.[14, 15]

Children with submucous palatal clefting – where the only external sign may be a bifid uvula (**Figure 17.2**) – should have adenoidectomy with extreme caution if at all. Partial adenoidectomy, under direct or endoscopic vision and preserving a buttress of tissue around the lateral margins, may preserve the velopharyngeal closure mechanism.[16]

Hyponasal speech due to large adenoids rarely constitutes an indication for adenoidectomy on its own. Usually there will be an independent indication for surgery, such as airway obstruction. Adenoids regress and parents should be made aware of this when giving informed consent if adenoidectomy is offered to improve the child's speech.



Figure 17.2 Bifid uvula – often associated with submucous cleft palate, causing rhinolalia aperta.



Figure 17.3 Tongue tie.

Tongue tie

Tongue tie (ankyloglossia) is characterized by tethering of the anterior part of the tongue to the floor of the mouth by a short lingual frenulum (Figure 17.3). It is usually asymptomatic but may restrict tongue mobility in the newborn and give rise to difficulties with breastfeeding. Many parents present for treatment as they are concerned about the appearance of the tongue or about the potential for the condition to interfere with activities such as licking the lips and kissing. The condition tends to improve as the child gets older. There is no evidence to link tongue tie with speech and language disorders. Nevertheless, parents often request treatment. If treatment is required, a simple division of the frenulum is adequate. In the newborn, this can be undertaken without anaesthesia but older children require a general anaesthetic.

ROLE OF THE SPEECH AND LANGUAGE THERAPIST

Speech and language therapy aims to help all children and adults to communicate as well as possible. All speech and language therapists (SLTs) practising in the UK are trained to at least graduate level and are registered with the Health Professionals Council. There are around 10 000 speech and language therapists working in the UK. Many of them are employed by the NHS, but some work for education authorities, for charities or in independent practice.

All SLTs understand how children's language, speech and communication develop, the difficulties that can arise, and how to help. Specialist therapists with more knowledge and experience of working with complex cases or specific conditions may also be employed, to help the local therapists plan appropriate interventions for the child and, in some cases, to see the child themselves for therapy. ENT professionals may come into contact with these specialist SLTs in fields such as deafness, where they are mainly involved in supporting children with severe to profound hearing losses, in cleft palate teams and in supporting children with voice problems.

Broadly, SLTs take responsibility for the assessment, diagnosis and treatment of children with speech, language and communication needs, and they may also be responsible for the assessment and treatment of swallowing disorders, if appropriately trained. The type of speech and language therapy a child receives will depend on many factors, including the child's needs and age, and the causes and severity of the problem(s). Therapy packages may include group or individual sessions, or assessment and advisory sessions with programmes of work being carried out by the family or school staff. All speech and language therapists are expected to work closely and collaboratively with other agencies and professionals who support the child, in particular those working in education who see the children frequently and are well placed to support the child's speech, language and communication needs in everyday settings.

For preschool children in particular, the parents will be the main focus of SLT support, as parents are always the child's first teachers, certainly as far as speech and language development is concerned. Research has shown that parents use on average over 12 000 words every day with their normally developing 2-year-olds and that the parents of the best talkers talk significantly more.[17] Interestingly, work carried out by the Lena Research Foundation showed

that the level of parental education does not predict the amount the adult speaks to the child, but gender and birth order does seem to have an effect, with girls being spoken to more than boys and firstborns hearing more talk than their younger siblings.[18] SLTs therefore play a major role in raising awareness of the importance of talking to children, and working with parents of young children with speech, language and communication needs to ensure that true progress happens within the home, not in the clinic.

The easy-to-use 'progress checker' on the Talking Point website[18] is helpful for ENT professionals in the process of deciding when to refer a child to speech and language therapy services. Other useful organizations/websites are listed below in 'References' and 'Further information'.

KEY POINTS

- Communication, speech and language difficulties can occur in isolation, or with associated conditions.
- Left untreated, speech, language and communication difficulties can have pervasive and long-term effects on the individual, including low academic attainment and offending behaviour.
- All ENT professionals should understand developmental milestones for speech and language acquisition, to ensure appropriate and timely referral to Speech and Language Therapy services.

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FURTHER INFORMATION

British Stammering Association: support for people who stammer. https://www.stammering.org/

Cleft Lip & Palate Association: for children affected by cleft lip and palate. https://www.clapa.com/

The Communication Trust: a consortium of over 50 not-for-profit organizations which champion the needs of those with speech, language and communication problems. http://www.thecommunicationtrust.org.uk/

I Can: UK charity for children with speech, language and communication needs. http://www.ican.org.uk/

Mencap: supporting those with a learning disability. https://www.mencap.org.uk/

National Deaf Children's Society: supporting children with all levels of hearing impairment. http://www.ndcs.org.uk/

Talking Point: information about children's communication. http://www.talkingpoint.org.uk/



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CHAPTER 18

CLEFT LIP AND PALATE

David M. Wynne and Louisa Ferguson

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the following keywords: cleft lip, cleft palate, velopharyngeal dysfunction, Pierre Robin sequence, otitis media with effusion and sleep disordered breathing.

INTRODUCTION

Cleft lip and cleft palate are the commonest form of orofacial clefting. Patients with a cleft of the lip or palate have multiple ENT problems and can present to the otolaryngologist with airway, hearing, speech or nasal issues. This chapter aims to describe the epidemiology and aetiology of cleft lip and palate, and the principles of treatment, particularly in regard to ENT-related issues.

CLEFT TYPES AND CLASSIFICATION

Orofacial clefts are generally classified by laterality and extent of the defect. Cleft lip is defined as a cleft of the structures anterior to the incisive foramen, also known as the primary palate (Figure 18.1). Cleft lip can be complete (involving the alveolus), incomplete or microform. It can also be unilateral or bilateral, and may or may not involve the palate. Cleft palate is clefting of the secondary palate and may be incomplete or complete, bilateral or unilateral, or submucous.[1] Cleft lip ± palate (CL±P) and isolated cleft palate/cleft palate only (CPO) are unique in both their aetiology and epidemiology.

Various classification systems have been devised over the years to try to account for the variability in clefting of the lip and palate. Veau's 1931 classification[2] is commonly utilized (Table 18.1), although it is incomplete since it makes no provision for isolated cleft lip.

In the 1950s Kernahan and Stark proposed an embryologically based system centred on clefting in relation to the

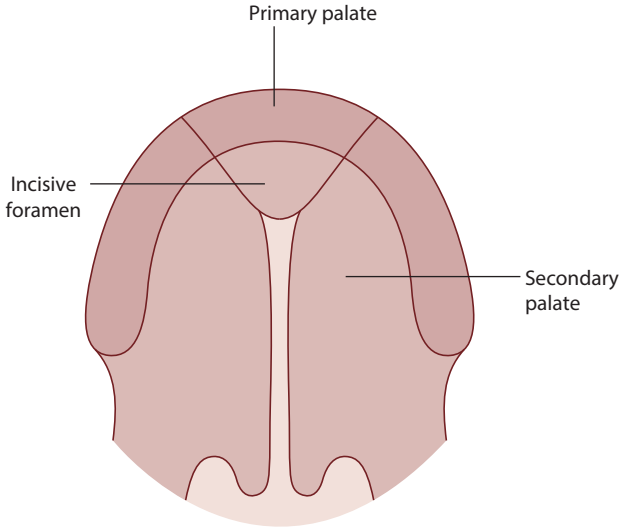


Figure 18.1 Primary palate anterior to the incisive foramen. Secondary palate, posterior to the incisive foramen.

TABLE 18.1 Veau's 1931 classification of cleft lip and palate[2]

Group	Description
Group I (A)	Defects of soft palate only
Group II (B)	Defects involving the hard palate and soft palate, extending not further than the incisive foramen
Group III (C)	Defects from the soft palate to the alveolus (usually involving the lip)
Group IV (D)	Complete bilateral clefts

incisive foramen. This was modified by Kernahan in 1971[3] who proposed a system based on the intraoral view of the palate. A 'Y' diagram representing the cleft is marked from 1 to 9, with the relevant areas marked dependent on the extent of the clefting (Figure 18.2).

The LAHSHAL system is commonly utilized in the UK (Figure 18.3). It involves recording the cleft status starting on the right-hand side and working from the lip back to the soft palate and then forward again on the left and marking each area as complete (C), incomplete (I) or no cleft (X). The areas are subdivided into lip, alveolus, hard palate and soft palate.

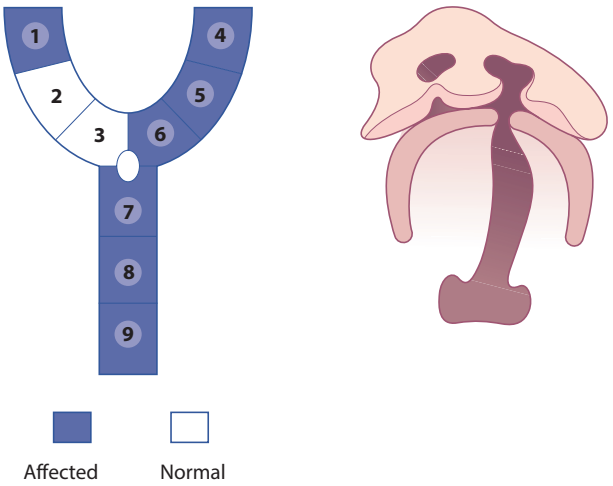


Figure 18.2 Kernahan's striped 'Y' classification. 1, 4, lip; 2, 5, alveolus; 3, 6, hard palate anterior to incisive foramen; 7, 8, hard palate; 9, soft palate; 0, incisive foramen.

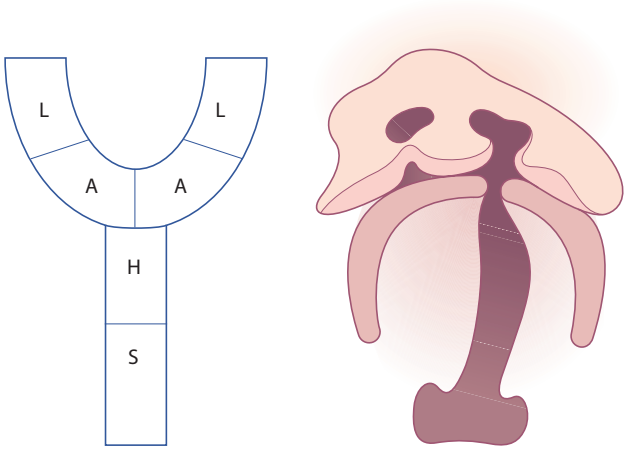


Figure 18.3 LAHSHAL – anatomical paraphrase of cleft lip, alveolus and palate. A, alveolus; H, hard palate; L, lip; S, soft palate.

EPIDEMIOLOGY

Cleft lip and cleft palate are the commonest form of orofacial clefting. CL±P and isolated cleft palate are two separate entities in terms of both aetiology and epidemiology. The overall incidence of orofacial clefting is between 1 in 600 and 1 in 750, which amounts to around 1000 new cases a year in the UK.[1] CL±P incidence varies with ethnicity and race. The Asian population have the highest incidence with approximately 2 per 1000. The white population have an incidence of 1 in 1000 and the lowest incidence is in the Afro-Caribbean population, which has an incidence of 0.3 per 1000 live births.[1,4] CL±P is more common in males and 80% are unilateral, with a left to right ratio of 2:1.[1] Isolated cleft palate is not affected by race and has an overall incidence of 1 in 1500. Cleft palate alone is twice as common in females.[5] The typical distribution of orofacial clefts is cleft lip and palate 46%, cleft palate only 33% and cleft lip alone 21%.[6]

AETIOLOGY AND GENETICS

Orofacial clefts may be syndromic or non-syndromic. Most orofacial clefts are non-syndromic and occur as an isolated anomaly. CPO is more commonly associated with a syndrome than CL±P, with a recent systematic review estimating around 50% for CPO 30% for CL±P.[7] There are now over 400 syndromes associated with CPO and CL±P in the London Dysmorphology Database,[8] with some of the more common syndromes listed in Box 18.1.

The most frequent interstitial deletion in humans is del(22)(q11.2), with an estimated prevalence of 1 per 4000 live births.[9] This deletion is associated with a wide phenotypic spectrum including the Di George and velocardiofacial phenotypes. Approximately half of the cases of 22q deletion will have a palatal abnormality, most commonly submucous cleft palate or CPO. These children can also

BOX 18.1 Common syndromes associated with CPO and CL±P according to the London Dysmorphology Database[8]

Syndromes associated with CPO	Syndromes associated with CL±P
22q deletion syndromes	Van der Woude syndrome
Treacher Collins	Trisomy 21
Stickler syndrome	
Apert syndrome	
Trisomy 21	
Goldenhar	

BOX 18.2 Risk factors associated with CL/P[9]

Maternal age
Maternal smoking
Maternal obesity (BMI>30)*
Prepregnancy diabetes*
First trimester heavy alcohol consumption
Medications (anticonvulsants, folate antagonists, retinoic acid)*
White non-Hispanic race*
Sex*

**Also associated with CPO.* Data from Watkins et al. 2014.[9]

have non-cleft velopharyngeal dysfunction due to a deep post-nasal space secondary to a wide skull base angle. Any patient with a palatal defect, and any other manifestation of 22q11 (cardiac malformation, neurodevelopmental delay, immunodeficiency) should be screened, as prevalence can be as high as 40%.

Non-syndromic clefting is multifactorial and is influenced by both genetic and environmental factors. Non-syndromic clefting may have a known or unknown cause. Variants of the *IRF6* gene (interferon regulatory factor 6) can cause a Mendelian type inheritance, notably Van der Woude syndrome, but variants of *IRF6* have also been implicated in non-syndromic orofacial clefts.[7] Genome-wide association studies have provided insights into the genetic background of non-syndromic CL±P and contributing genes include aberrations in *TGF-b3*, *NAT 1TBX22*, *MSX1* and *FGFR*.[9–12]

Environmental factors which contribute to facial clefting are varied, and many are still under evaluation (**Box 18.2**). Alcohol consumption, particularly in the first trimester, is known to be a risk factor.[13, 14] Maternal smoking also increases the risk of orofacial cleft,[15–19] with a population-attributable risk of up to 20%.[15, 19] Anticonvulsant drugs[20–22] increase risk of cleft palate and positive associations with maternal corticosteroid use in pregnancy have also been reported in the literature, although this is less clear-cut.[23] Low B-complex vitamins, folic acid deficiency[24] and maternal obesity[25] also have some links to clefting, although further research is needed to define these risks more clearly.

If a primary relative has a facial cleft the chances of the child having a cleft, in the absence of a defined syndrome, is 3.5%.[26] This decreases with secondary and tertiary relatives. For parents who already have a child with an orofacial cleft, the risk of a subsequent child having a cleft is around 2–5%.

EMBRYOLOGY

An understanding of the embryology responsible for the development of the cranium and face is important as it allows us to understand why CL±P and CPO are different entities. The five main prominences responsible for development of the face are the frontonasal prominence, the paired right and left maxillary prominences and the right and left mandibular prominences. Incomplete or aberrant timing of fusion of the frontonasal and maxillary prominences results in cleft lip and/or palate (**Figure 18.4**). The frontonasal prominence is split into medial and lateral nasal prominences by development of a nasal pit on the ventrolateral aspect of the frontonasal prominence. Formation of the lip occurs between the fourth and sixth weeks of gestation when the bilateral maxillary prominences fuse with the medial nasal prominence to form the lip and alveolus. The secondary palate begins to form during the sixth week of development as the palatine shelves, which are outgrowths from the maxillary prominences, advance obliquely downward to lie horizontally over the tongue. The palatine shelves fuse with the previously formed primary palate and then from anterior to posterior the palatine shelves fuse in the midline, so that by week 12 the palate is intact. Failure of any of these processes can result in clefting (**Figure 18.5**).

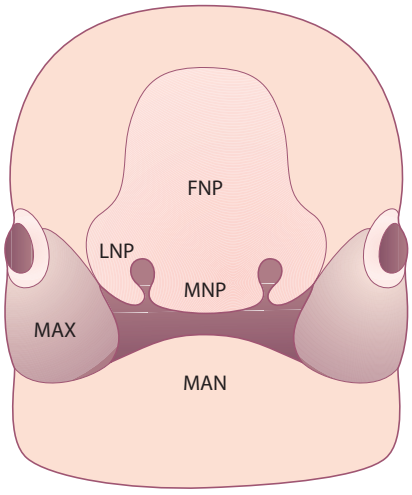


Figure 18.4 Development and fate of the facial processes. Representation of a 30–32-day-old human embryo showing the development of the facial processes. FNP, frontonasal process; MAX, maxillary process; MAN, mandibular process; MNP, medial nasal process; LNP, lateral nasal process.

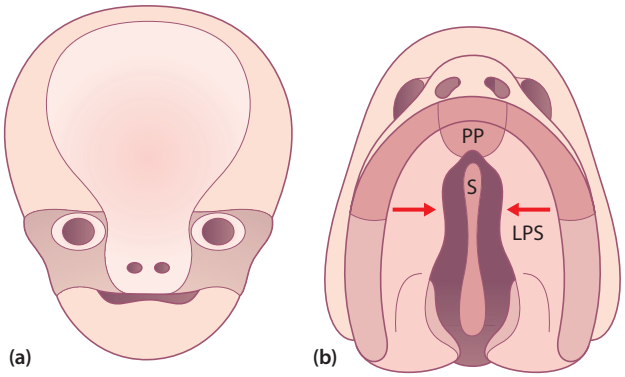


Figure 18.5 Representation of 7-week-old embryo showing the fate of the facial processes. (a) Frontal view; **(b)** ventral view of primary and secondary palate. LPS, lateral palatal shelf; PP, primary palate; S, nasal septum.

FUNCTIONAL ANATOMY

Anatomical anomalies of the lip, palate, septum, external nose and other midline structures can affect patients with a cleft lip and plate.

Lip

Integrity of the lip and oral sphincter is important for normal function of the mouth. A defect in the lip results in abnormal insertion of orbicularis oris and loss of continuity of the vermilion border, both of which have to be addressed in cleft lip repair in order to allow long-term return to form and function. The mucocutaneous area of the lip is well defined into three regions: there is the cutaneous skin of the upper lip and philtrum, an intermediate area of dry mucosa known as the vermilion and an internal area of moist mucosa.[27] The orbicularis oris normally forms a full sling under the mucosal covering, however aberrant muscle due to the cleft results in insertion of the orbicularis oris into the dermis and nasal ala on the cleft side and insertion into the columella on the non-cleft side (Figure 18.6).

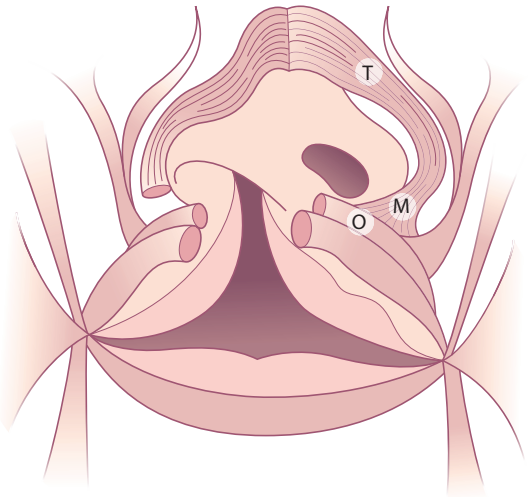


Figure 18.6 Nasolabial muscle ring in unilateral cleft lip. M, myrtiform head of nasalis muscle; O, oblique head of orbicularis oris; T, transverse head of nasalis muscle.

Nose

Abnormality of insertion of the orbicularis oris contributes to the nasal deformity seen as part of cleft lip. By inserting into the nasal alar base there is outward splaying of the lower lateral cartilage, which results in the alar base on the cleft side sitting more lateral and inferior than it should. This results in a differing shape and position of the lower lateral cartilage on the cleft side, with shorter medial crus and longer lateral crus, and a classically flattened and wider dome on the cleft side. The columella is shortened and the anterior cartilaginous septum deviated to the non-cleft side, due to the unopposed pull of the orbicularis oris on the columella. This allows bowing of the septum onto the cleft side more posteriorly and, along with the reduction in the nasal valve area due to lower lateral cartilage abnormalities, the overall nasal airway is restricted. Nasal airflow resistance is known to be higher in patients with CL±P by around 20–30%.[28, 29]

Palate

Clefts of the palate are associated with bony and soft-tissue abnormalities. Adequate closure of the velopharyngeal port for speech and swallowing is the aim of palate repair. The primary velar muscles are the levator veli palatini, palatopharyngeus and palatoglossus (Figure 18.7). The levator

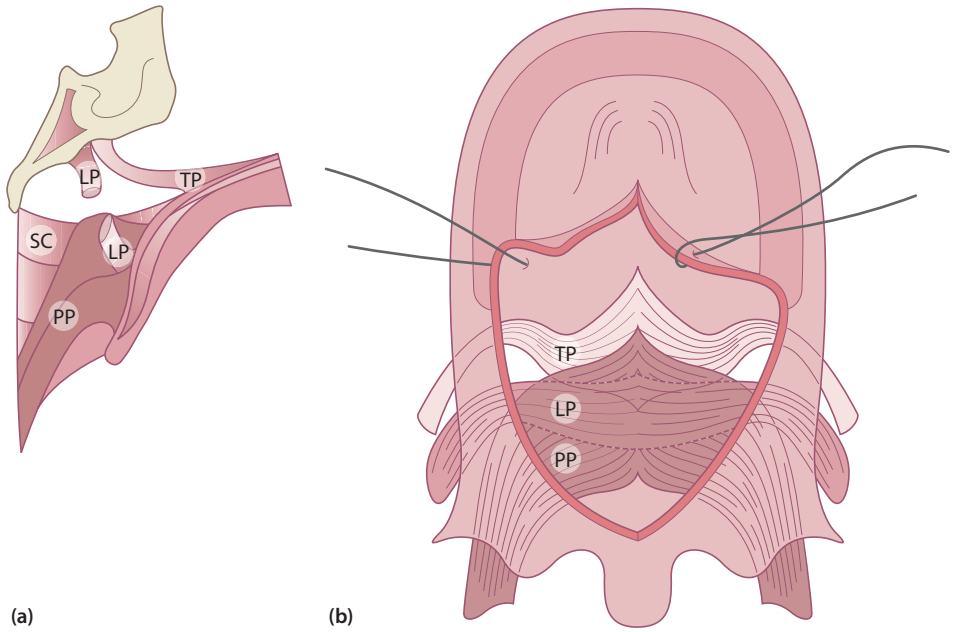


Figure 18.7 Velum muscles. **(a)** Sagittal view from midline; **(b)** inferior view. LP, levator palatini; PP, palatopharyngeus; SP, superior constrictor; TP, tensor palatine.

veli palatini muscle is the primary elevator of the palate. It originates from the medial part of the Eustachian tube and from the petrous temporal bone and runs anteriormedially to enter the middle third of the velum between the two heads of palatopharyngeus to join with its partner from the opposite side, and form the levator sling. In patients with a cleft palate the levator veli palatini no longer has this transverse orientation, but instead the muscle is longitudinally orientated and inserts into the bony cleft margin and posterior palatine bones. The palatoglossus and palatopharyngeus arise from the back of the palatal aponeurosis and maxillary tuberosity. The palatoglossus is a thin sheet of muscle that extends to form the anterior tonsillar pillar. The palatopharyngeus is a more substantial muscle that is split into two heads by the insertion of the levator veli palatini and runs down to form the posterior tonsillar pillar and inserts into the thyroid cartilage and pharyngeal aponeurosis. The palatopharyngeus and palatoglossus act as depressors and, along with the levator veli palatini, these muscles act to lengthen the velum. The final muscle to consider is the tensor veli palatini, whose primary function is opening of the Eustachian tube. Its fibres originate from the sphenoid spine, scaphoid fossa and lateral lamina of the Eustachian tube cartilage,[30] and form a tendon which winds round the pterygoid hamulus and spreads into a fibrous aponeurosis in the anterior third of the soft palate.

ENT ISSUES

Airway

All children are obligate nasal breathers for the first few months of life. This is due to the high position of the infantile larynx that gradually descends. In the neonate the anterior epiglottis can often be easily seen in the oral cavity behind the soft palate. This superior position of the larynx allows the infant to suckle.

There are many congenital anomalies associated with cleft lip and palate, and one of the most commonly seen in ENT is Pierre Robin sequence (PRS). In PRS micrognathia and glossoptopsis may result in upper airway obstruction (Figure 18.8).

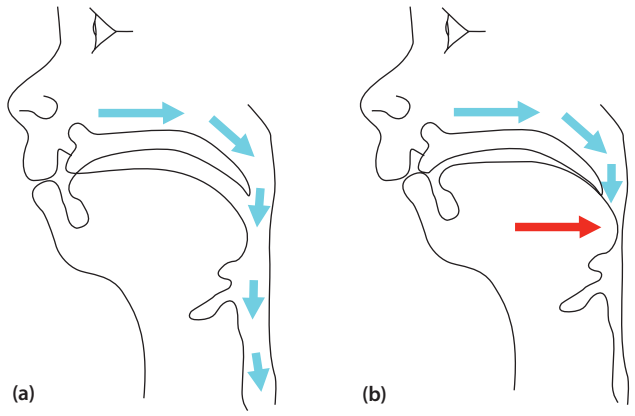


Figure 18.8 Diagrams showing **(a)** normal airway in an infant; **(b)** where retro-position of the mandible has resulted in the tongue blocking the airway.

NEONATAL PERIOD

Upper airway obstruction can happen immediately following delivery or can develop progressively over weeks or months of life. The Royal College of Paediatrics and Child Health (RCPCH) respiratory subgroup recommends that all children with craniofacial disorders including PRS undergo overnight oximetry, preferably in combination with measuring CO_2, within the first 4 weeks of life.[31] Children with PRS may have worsening obstruction between 4 and 8 weeks of age, and reassessment may be required during that time. Otherwise, further studies should be performed at 3–6-monthly intervals during the first year of life, and thereafter according to clinical symptoms. Often children with PRS have their palate surgery delayed until around 18 months of age to allow their airway obstruction to improve.

Treatment options for airway obstruction in these children, depends on the severity of symptoms. The options can be divided into two main subgroups, non-surgical and surgical, as listed in Box 18.3.

POST-OPERATIVE PERIOD

Any airway issues tend to happen within 24–48 hours of surgery. They are usually associated with palatal surgery or pharyngoplasties but on occasion can occur following lip repair or anterior rhinoplasty. Children are often placed in an HDU following primary lip and palatal surgery to allow careful monitoring in the early post-operative period. This allows close monitoring of the child and early intervention if the child develops any signs of respiratory distress.

LONG-TERM SLEEP-DISORDERED BREATHING

All cleft children have the same risk as other children with regard to sleep-disordered breathing and obstructive sleep apnoea (e.g. secondary to adenotonsillar hyperplasia). They may, however, be at higher risk due to their anatomical abnormalities being corrected and narrowing the nasopharynx.

A pharyngoplasty is performed to reduce the nasopharyngeal airway to help prevent nasal escape during speech. This has the potential detrimental effect of increasing the likelihood of apnoeic episodes. Careful pre-operative discussion and patient evaluation within the multidisciplinary team setting should be undertaken to discuss the risks versus benefits of such a procedure. The complications of chronic obstructive sleep apnoea (OSA) include hypoxemia, hypercarbinemia, neuropsychiatric problems and decreased cognitive function. In severe cases the chronic obstruction can result in pulmonary hypertension and cardiac failure. There is also a link between OSA in childhood and adult hypertension.

BOX 18.3 Treatment options for airway obstruction

Non-surgical	Surgical
Nasopharyngeal airway	Tongue–lip adhesion
CPAP	Tracheostomy
	Mandibular distraction

Hearing loss

As in all children, hearing loss in CL±P patients can be conductive, sensorineural or mixed.

Otitis media with effusion (OME) is almost ubiquitous with CL±P. Approximately 97% of cleft children are thought to have had an episode of OME by the age of 2,[32] with the incidence reducing with increasing age.[33] The aetiology behind the increased incidence of OME is thought to be due to Eustachian tube dysfunction secondary to the malposition of the tensor veli palatini muscle, as mentioned previously.

In the recent past this has led to the 'routine' insertion of ventilation tubes at an early age, usually at the time of palatal repair. However, as more data have been collected about the incidence and prevalence of the otological sequelae of OME, a much more selective approach has been introduced. Recent systematic reviews[32, 34] have shown there was insufficient evidence to determine if early ventilation tube placement had any benefit on either hearing or speech development, and that further studies in this area are warranted. Currently in the UK the Cleft Collective research group is undertaking the MOMENT trial (The Management of Otitis Media with Effusion in Children with Cleft Palate) to try to acquire more guidance on the optimum management of OME in CL±P patients.[35] As we know, not all episodes of OME will result in a hearing loss or damage to the middle ear. Current recommendations in the UK are found in NICE60.[36] Essentially, a persistent CHL associated with OME in excess of 25–30 dBHL or OME affecting a child's developmental, social or educational status should be offered treatment. The treatment options should include ventilation tube insertion or provision of hearing aids. Primary ventilation tube insertion is only recommended after careful ENT/audiology assessment in children with a cleft palate.

In the UK cleft care is closely audited and minimal standards of care have been agreed. Routine hearing testing is taken at 6 months, and 1, 2, 3, 4, 5, 10 and 15 years of age. Ensuring adequate hearing thresholds allows normal verbal communication to develop. This is important in the CL±P population as learned 'cleft type' speech cannot be corrected at an older age.

Long-term middle ear disease has also been reported to be higher in the cleft population due to persistence of Eustachian tube dysfunction following palatoplasty. Retraction pockets and subsequent development of cholesteatoma has been found to be higher in the cleft population[37–41] and ongoing otologic assessment in these patients is important.

MANAGEMENT

Care of a child with a cleft lip or palate is a complex, highly specialized and lifelong undertaking. Deficiencies of speech, facial growth, cosmetic appearance, hearing and dental problems require that this care is addressed in a multidisciplinary setting in order to allow adequate attention to all aspects of care and subsequently improve outcomes.[42] Input is needed from a cleft surgeon, otolaryngologist, paediatric dentist, specialist nurse, speech therapist, psychologist, audiologist, orthodontist, geneticist and paediatrician.

During the management of children with a cleft lip and palate, areas to be addressed are:

- speech
- hearing
- appearance
- dental growth and hygiene
- psychosocial health.

Diagnosis

Prenatal diagnosis of cleft lip and palate has allowed around 75% of children to be picked up as early as 13–16 weeks' gestation by ultrasonography.[43] Isolated cleft palate cannot be as easily detected prenatally, but the role of prenatal foetal MRI in further diagnosing palatal clefting may become more frequent in the future.[43] Following diagnosis, the parents should be referred antenatally to the cleft team so that appropriate support can be provided. Advice can be given on feeding, expectations of treatment protocols and details of parental support groups. After birth the specialist cleft nurse will make contact within the first 24 hours to give support and help establish feeding. Children with a cleft lip and palate may be able to breastfeed with help, or the use of specialized bottles (Haberman) may be more helpful, as the ability to create a vacuum to suckle milk is reduced.

Surgical management

Surgical management of cleft lip and plate is complex and tailored to the individual deformity present. There are numerous techniques across the world to deal with orofacial clefts and the detailed surgical steps of each procedure are beyond the scope of this chapter. The principles of surgical management are covered. Table 18.2 summarizes the timings of surgical management options.

TABLE 18.2 Surgical management from birth to adulthood

Age	Procedure
3–6 months	Primary lip ± nose repair ± hard palate
9–12 months	Palate repair ± ventilation tubes
4–5 years	Secondary speech surgery (if required)
8–10 years	Alveolar bone graft (if required)
15–18 years	Secondary rhinoplasty
16 years +	Orthognathic surgery (if required)

PRESURGICAL ORTHOPAEDICS AND NASOALVEOLAR MOULDING

Nasoalveolar moulding (NAM) is a form of presurgical infant orthopaedics designed to reduce the severity of the cleft deformity and move the nasal alar cartilages into a more favourable position. Attempts to reduce the severity of the cleft are not a new phenomenon and various devices have been used in the recent past. NAM involves using an oral plate, which is individually moulded with nasal stents attached, to try to achieve these aims. The device is fitted as soon after birth as feasible and is worn fulltime. It is regularly adjusted to alter the shape and length of the nasal cartilages and columella. The research on whether NAM successfully achieves these outcomes remains inconclusive,[44] although some studies show positive results,[45–47] particularly in improving nasal symmetry in the unilateral cleft lip and palate patients.[48] Randomized controlled trials at a national level are lacking and, although NAM is gaining support particularly in North America, it is yet to be incorporated into routine UK practice.

LIP REPAIR

Repair of the cleft lip aims to address both functional and cosmetic problems. In the UK the lip is generally repaired when the child is 3–6 months of age, along with the hard palate and primary nasal surgery, dependent on requirements. Neonatal lip repair is performed in some centres, although no firm evidence of aesthetic or functional benefit yet exists.[49, 50] The aims in both unilateral and bilateral cleft lip repair are similar: to achieve primary muscle continuity and reconstruct the lip elements to give a symmetrical-appearing Cupid's bow with the minimum of scarring. The importance of reconstructed musculature in achieving optimal results is well reported and should be adequately addressed at the time of lip repair.[51–56]

Bilateral cleft lip is a more severe deformity than unilateral and achieving muscle continuity across the projected premaxilla can be a challenge. The use of lip adhesion (taping of the lateral lip segments to the premaxillary segment) and single-sided staged surgery have been advocated in an attempt to facilitate lip repair, but neither of these approaches is supported in the literature. There are multiple approaches to reconstructing the skin of the lip, the Millard repair and its modifications, and the Fisher repair being the two most commonly practised in the UK.

PALATE REPAIR

Hard palate

Timing of palatal closure is variable between centres, and there is a trade-off between early palatal closure to help speech, and delaying hard palate closure to improve facial growth. In the UK it is common practice to close the hard palate with a vomerine flap at the time of lip repair in a complete cleft lip and palate, or close with the soft palate repair in an isolated cleft palate patient.

Soft palate

The aim of palatoplasty is to reorientate the palatal muscles in order to achieve lengthening and improve movement of the palate in order to create adequate velopharyngeal closure. There are various surgical options available to the cleft surgeon, each of whom will have their preference. The intravelarveloplasty, popularized by Sommerlad, involves radical dissection of the velar muscles and reorientation to a transverse position to recreate the anatomical levator sling.[57] The nasal and oral mucosa are dissected from the muscles and repaired over the newly formed sling to close the cleft (**Figure 18.9**).

The Furlow palatoplasty uses a double opposing Z-plasty technique to lengthen and reorientate the muscles. This method results in posterior repositioning of the velar muscles, albeit with a degree of asymmetry, and results in some degree of palatal lengthening. Both techniques have been shown to have good speech outcomes[58, 59] and there has been no difference found in audiological outcomes between the techniques.[60]

NASAL SURGERY

Nasal surgery in a patient with a cleft lip and palate aims to improve aesthetics and nasal airflow, in a timely fashion but with the minimum of disruption to facial growth. Cleft nose deformity is characterized by an asymmetric nasal tip, deviated septum and asymmetry of the nasal bones. Timing of nasal surgery is somewhat controversial. Given the complexity of cleft nasal deformities, definitive rhinoplasty is often reserved until adolescence and completed facial skeletal growth, however evidence has shown that stable long-term results with limited growth disturbance can be achieved with primary rhinoplasty.[61–64]

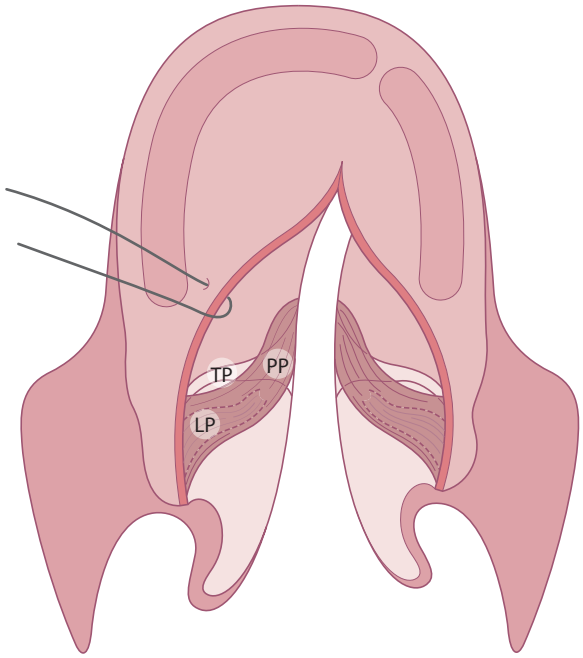


Figure 18.9 Cleft palate muscles. LP, levator palatini; PP, palatopharyngeus; TP, tensor palatini.

ALVEOLAR BONE GRAFTING

Some children will require alveolar bone grafting as a secondary procedure to stabilize the alveolar arch and allow eruption of the lateral incisor and canine into an optimal position. There is good evidence that secondary alveolar bone grafting produces consistently good results.[65, 66] Timing of the bone graft is usually determined by the development of the canine tooth, although earlier bone grafting may be indicated to support the eruption of the lateral incisor. There is no evidence that secondary bone grafting has a detrimental effect on facial growth when performed between 9 and 11 years of age. This is in contrast with primary bone grafting carried out before 2–3 years of age where evidence from retrospective case series suggests that these early bone grafts were associated with significant growth impairment.[67, 68]

SPEECH AND VELOPHARYNGEAL INSUFFICIENCY

Velopharyngeal insufficiency (VPI) can occur in children with a repaired cleft palate, those with a submucous cleft and in children without any obvious palatal abnormalities. It can also occur after adenoidectomy, with a reported clinically significant incidence of between 1 in 1500 and 1 in 3000. Stigmata of a submucous cleft are bifid uvula, zona pellucida and hard palate notch, all of which should be examined for at the time of adenoidectomy. VPI occurring after adenoidectomy will spontaneously resolve in about 50% of cases.[69] In order to achieve intelligible speech, the palate must be able to seal against the posterior pharyngeal wall and close off the nasopharynx. If this is impaired, nasal emissions and hypernasal speech can ensue. Around 20% of cleft palate children have persistent speech disorder following surgery, falling into the worst category of intelligibility.[70]

Treatment for velopharyngeal insufficiency includes speech therapy and palatal or pharyngeal surgery, dependent on the degree of VPI, underlying aetiology and age of the patient. In children with a submucous cleft, management is indicated only if symptoms of VPI occur. Assessment of VPI is best performed in a multidisciplinary environment. Examination of the mouth, concentrating on the integrity and movement of the soft palate and the tonsils, which rarely if hypertrophied may be interfering with palatal closure. Nasal examination and assessment of nasal patency should be performed. Standardized tests to assess articulation and intelligibility are performed by speech and language therapy.[70]

Flexible nasoendoscopy is fast becoming the investigation of choice to assess velopharyngeal port closure objectively. Speech videofluoroscopy is also widely used by many teams and can be an alternative if nasoendoscopy is not tolerated. Both investigations provide information and so far research has not shown superiority of one over the other,[71] although nasoendoscopy may provide a closer correlation with VPI severity.[72]

Management decisions come down to underlying symptoms and the size and location of the velopharyngeal gap. Palatoplasty may be indicated to treat VPI, either as a re-repair where there is evidence of anterior insertion of the levator muscles, or in the case of a submucous cleft. It is mainly used where the velopharyngeal gap is small[73, 74] and has been shown to have a lower morbidity than a pharyngoplasty.[75] Pharyngoplasty involves altering the shape of the velopharyngeal port in order to allow closure on speech. This can be done either by using flaps from the midline of the pharyngeal wall or by employing medial transposition of flaps from the lateral pharyngeal wall. Both types of pharyngoplasty have been shown to improve speech outcomes, with the possibility of achieving normal resonance in up to 85% of cases. The main downside to pharyngoplasty is the associated increased risk of sleep apnoea, and this must be discussed with the patient and their family pre-operatively.

KEY POINTS

- Clefts of the lip and palate are common congenital birth anomalies.
- Aetiology is multifactorial. Known associations are with maternal smoking and alcohol and antenatal anticonvulsants.
- Prenatal screening for cleft lip and palate is now routinely available in many centres.
- Management of patients with cleft lip and palate requires a multidisciplinary approach to ensure the best outcomes.
- Otitis media with effusion is a significant problem in cleft palate children and further research is required to identify best practice for management.

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CHAPTER 19

CRANIOFACIAL SURGERY

Benjamin Robertson, Sujata De, Astrid Webber and Ajay Sinha

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: craniofacial, craniosynostosis, OAVS, Treacher Collins, Apert, Crouzon, Pfeiffer, encephalocele, distraction osteogenesis, facial cleft, scapocephaly, trigonocephaly, brachycephaly and plagliocephaly.

INTRODUCTION

Craniofacial surgery is the medical specialty that diagnoses and manages complex congenital and acquired conditions of the craniofacial skeleton and associated structures. Patients with such conditions vary in their development and phenotypic presentation. Traditionally, these were thought of as congenital conditions but the term can be all-encompassing.

Due to the complexity of patients with craniofacial conditions, their treatment is required to take place in a multidisciplinary unit. Table 19.1 shows the specialties that comprise the multidisciplinary team (MDT) with their roles.

Treatment often lasts from the perinatal period, well into adolescence and often into early adulthood.

Owing to the complexity and heterogeneity of craniofacial anomalies there is no universal classification system. Many classification systems have been proposed, based on embryology, aetiology, anatomical location, morphology and genetics. In England, the National Commissioning Group recognizes six categories of patient:[1]

- craniofacial clefts
- craniofacial dysostosis
- craniosynostosis
- encephalocoele
- overgrowth, undergrowth or dysraphia associated with unilateral or bilateral orbital dystopia or displacement
- any other complex anomaly where referring specialists feel that the expertise present within the service would substantially benefit the treatment of the condition.

There are multiple other conditions of the craniofacial region that, although not specified in this classification, are often treated in these units due to the expertise of the clinicians involved. Currently in England and Wales, there are four units commissioned to treat the above conditions:

- Alder Hey Children's Hospital, Liverpool
- Birmingham Children's Hospital
- Great Ormond Street Hospital, London
- Oxford University Hospital.

The aim of this chapter is to describe the more commonly encountered groups of craniofacial anomalies, to outline the principles of their management and to review the role of the ENT surgeon in managing these patients. The genetic contribution to these conditions will also be discussed.

TABLE 19.1 The craniofacial team

Discipline	Role
Maxillofacial surgery	Surgical correction of deformity
Plastic surgery	Surgical correction of deformity
Neurosurgery	ICP, hydrocephalus, associated abnormalities, combined surgical treatment of the condition
Ophthalmology	ICP, acuity and motility, corneal protection
ENT (+ audiology)	Airway + nasal problems, hearing and middle ear disease
Anaesthetist	Experience of paediatric craniofacial and neurosurgical anaesthesia Access to paediatric intensive care unit (PICU)
Genetics	Diagnosis, associated conditions, risk of future siblings having the condition, risk of patient passing on the condition to his/her children
Speech and language therapist	Speech and language, feeding, general developmental milestones
Psychologist	Parental anxiety, preparation for operations, intervention for older patients, coping strategies, cognitive assessment
Paediatrician	General development, associated abnormalities
Orthodontist	Craniofacial growth and development, dental condition and occlusion
Specialist nurses and coordinators	Coordinating day-to-day activities/ advice/wound management

CRANIOSYNOSTOSIS

Craniosynostosis is the premature fusion of one or more sutures of the skull. This can occur as **primary** or **secondary synostosis**. The differentiation is paramount as treatment options differ greatly. In order to understand the pathophysiology of craniosynostosis, normal skull growth must be considered.

Normal skull growth

The stimulus for growth of the cranium comes from the expanding brain, which grows rapidly in the first 2 years of life, doubling in weight in the first year and achieving 90% of its adult size by the age of 2 years. This rapid brain growth has to be accommodated by a concomitant expansion in volume of the skull. The cranial vault consists of the frontal, parietal, temporal and occipital bones, which are separated from each other by the cranial sutures (metopic, sagittal, coronal and lambdoid). These sutures allow gradual displacement of the individual bones, allowing the brain to expand. In order to avoid large gaps developing between the bones as the expansion proceeds, new bone is deposited at the free margins of the bones adjacent to the sutures. Bone resorption and deposition also take place on the inner and outer surfaces of the calvarial bones to produce changes in their curvature and thickness.

The patent cranial sutures therefore allow for growth to take place in response to the stimulus of the growing brain and, unlike the epiphyseal plates of the long bones, cranial bones do not have intrinsic growth potential. The sutures only remain patent while brain growth is taking place. If brain growth ceases, cranial growth ceases, and the cranial sutures will be replaced by bone, resulting in fusion – a normal phenomenon once growth is complete.

Classification

Premature fusion of calvarial sutures has a variety of underlying causes, broadly divided into primary and secondary craniosynostosis.[2]

Secondary craniosynostosis is uncommon, but may be seen in microcephaly, where there is a lack of underlying brain growth, in some haematologic (polycythaemia, thalassaemia) and metabolic abnormalities (rickets, hyperthyroidism), and may be drug-induced (retinoic acid).

Primary craniosynostosis is much more common than secondary craniosynostosis. It can be classified on the basis of the number of sutures involved (single-suture, multiple or total), the site of the involved suture(s) (metopic, coronal, sagittal, lambdoid) and whether it is an isolated condition (non-syndromic) or associated with other malformations (syndromic). Primary craniosynostosis constitutes a significant workload in craniofacial units.

Incidence

Primary non-syndromic craniosynostosis occurs in approximately 1:2000 live births. Of the non-syndromic craniosynostoses, sagittal synostosis is the most common, accounting for approximately 60% of cases. In cases of non-syndromic craniosynostosis there is a male predominance with male to female ratios of 4:1 in sagittal synostosis and 3:1 in metopic synostosis. Of the syndromic craniosynostoses, Crouzon syndrome has the highest incidence, with 1:25 000 live births[3] and Apert syndrome in 1:60 000 live births.[4]

Aetiology

Craniosynostosis is aetiologically heterogeneous.[4] Both non-syndromic and syndromic craniosynostoses result from an interaction between genetic factors, molecular and cellular events, mechanical and deformational forces and secondary effects of each of these on normal growth and development. Premature fusion of the sutures may take place alone or, in syndromic craniosynostosis, with other anomalies. Most cases of isolated craniosynostosis are sporadic. However, familial cases do occur and a positive family history can be found in 14.4% of coronal, 6% of sagittal and 5.6% of metopic synostosis cases, but very rarely in lambdoid synostosis.[5–9] For isolated, single-suture synostosis with unaffected parents, the recurrence risks range from 1% in sagittal synostosis to 5% in coronal and metopic synostosis.[10]

Chromosomal abnormalities may also cause craniosynostosis, particularly in patients with other anomalies or problems with growth or development. Teratogens may also be causative, as in the case of sodium valproate and trigonocephaly. The syndromic craniosynostoses are usually genetically determined, often occurring as new mutations. There is an increasing recognition that some of the so-called isolated non-syndromic synostoses also have a genetic basis.

Genetics of craniofacial anomalies

The vast array of genetic conditions causing craniofacial anomalies precludes an exhaustive discussion of their genetics in this text. However, it is appropriate to discuss the more common conditions and encourage a low threshold for the involvement of the clinical genetics team in the management of patients with craniofacial anomalies. Clinical geneticists can contribute to both diagnosis and counselling of affected individuals and also their families. Interested readers are encouraged to consult the texts of Gorlin et al.[11] and Cohen and MacLean[4] for more extensive details on craniofacial anomaly syndromes.

When considering the aetiology of craniofacial anomalies, it is helpful to consider their aetiology in terms of **malformations** (e.g. genetic syndromes, teratogens), **deformations** (e.g. positional plagiocephaly) and **disruptions** (e.g. amniotic bands). Some craniofacial anomalies are multifactorial.

Genetic testing is not indicated in patients with isolated sagittal or metopic synostosis in whom there are no associated abnormalities or concerns about growth or development, and no significant family history. However, coronal synostosis, even when isolated, warrants analysis of at least *FGFR3* for the Pro250Arg mutation (see 'Muenke syndrome', or *FGFR3*-associated coronal synostosis syndrome below) and possibly analysis of the *TWIST* gene (see 'Saethre–Chotzen syndrome' below).

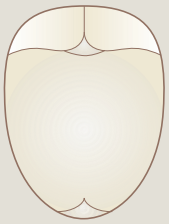
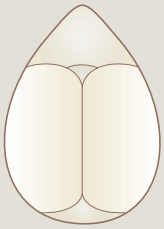
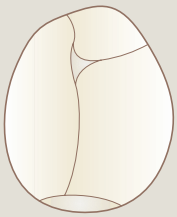
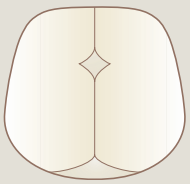
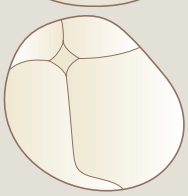
Genetic testing by DNA analysis of specific genes is available only for syndromes where the causative gene has been identified. This facilitates diagnosis and also counselling of family members, particularly when a parent may be a gene carrier with a very mild phenotype. Chromosomal analysis should be considered in any patient with complex or multiple abnormalities, or in whom there are concerns regarding a child's growth or development. Informed consent should be obtained prior to any genetic testing, especially as abnormal results may have implications for other family members as well as the child. Failure to identify a genetic abnormality in a syndromic patient does not, however, rule out a genetic cause for their condition, and involvement of a clinical geneticist is essential.

Prenatal diagnosis by genetic analysis of chorionic villus sample or amniotic fluid may be available for conditions in which the causative genetic abnormality is known. Prenatal ultrasound scanning later in pregnancy may reveal abnormal craniofacial contour or associated skeletal or systemic abnormalities in syndromic conditions; however, the premature sutural fusion of isolated craniosynostosis is much more difficult to detect.

Pathogenesis and consequences

Premature suture fusion results in inhibition of skull growth in a direction perpendicular to the affected suture. Despite this localized failure of skull growth, the brain continues to grow, and expands in different directions, where expansion can be accommodated by normal (patent) sutures, producing compensatory changes at a distance from the abnormal suture and usually parallel to it.[12] In the latter half of the last century, Moss[13] postulated that the cranial base was the site of abnormal physical stresses, and that these could be transmitted to the dura of the cranial vault, resulting in suture fusion. Whatever the underlying mechanism, the restriction of growth perpendicular to the fused suture, and the compensatory changes elsewhere in the cranium, may result in a reduction in cranial volume (and hence raised intracranial pressure (ICP)) and a change in shape (resulting in characteristic changes dependent on the suture or sutures involved) (**Table 19.2**).

TABLE 19.2 The craniosynostoses. Affected sutures and resultant head shapes. The anterior aspect of the skull (the forehead) is towards the top of the table

Shape of skull	Suture affected	Name
	Saggital	Scaphocephaly
	Metopic	Trigonocephaly
	Unilateral coronal	Frontal plagiocephaly
	Bilateral coronal	Brachycephaly
	Unilateral lambdoid	True posterior synostotic plagiocephaly

Clinical assessment and imaging

The history may be of a baby with an abnormal head shape, present at birth, gradually becoming worse. Examination reveals the characteristic head shape with ridging of the affected suture.

Plain films may allow assessment of sutural patency and the overall morphology of the skull. All sutures are usually easily visible in the normal growing skull, with the exception of the metopic suture, which normally fuses early. A prematurely fused suture may be sclerotic or may not be visible at all. The abnormal shape of the head will be apparent, and skull base abnormalities not apparent on clinical examination may be seen (e.g. the 'harlequin eye' appearance of the sphenoid ridge in coronal synostosis). Computed tomography (CT), especially when reconstituted via a 3D format, provides even more detail of the morphology of the skull (**Figure 19.1**). In addition, a CT scan allows evaluation of the intracranial contents although magnetic resonance imaging (MRI) is a more useful modality for assessing intracranial anatomy and pathology.

Raised intracranial pressure

It is logical to think of raised ICP developing as a result of failure of cranial expansion in the presence of continuing pressure from the growing brain. However, the relationship is complex, and other factors have been implicated. Raised ICP is not directly related to a decrease in intracranial volume,[14] and venous hypertension has been identified as a result of a significantly narrower jugular foramen (6.5 mm versus 11.5 mm) in complex and syndromic patients with raised ICP.[15]

The reported incidence of raised ICP in patients with craniosynostosis shows wide variation, and there is variability in the threshold for diagnosis in reported studies, with values of 15 mmHg or 20 mmHg chosen.[16] Reported incidence in mixed cohorts of non-syndromic and syndromic patients vary from 17% to 92%.[14, 17–19] Studies that have compared the incidence of raised ICP in non-syndromic and syndromic patients have shown a higher incidence in syndromic patients (approximately 50%) compared with non-syndromic patients (approximately 25%).[20, 21]

Diagnosis may be difficult because the classic clinical features of raised ICP are often absent. Thus, the child's development, in particular the acquisition of normal developmental milestones, vision, reading and language comprehension, motor skills, and general behaviour are important, and may require detailed specialist investigation, including ophthalmological assessment. Changes in visual-evoked potentials have been shown to be early indicators of raised ICP.[22, 23]

Plain skull films may show the classic 'copper-beaten' appearance of chronically raised ICP (**Figures 19.2**) but the absence of changes does not exclude raised ICP.[24] CT or MRI scanning may be helpful but, in cases where clinical assessment is equivocal, invasive ICP monitoring may be indicated, using either a traditional ICP monitor or, more recently, parenchymal fibre-optic transducers, which have been shown to be reliable as recorders of ICP and are associated with a low rate of complications.[20]

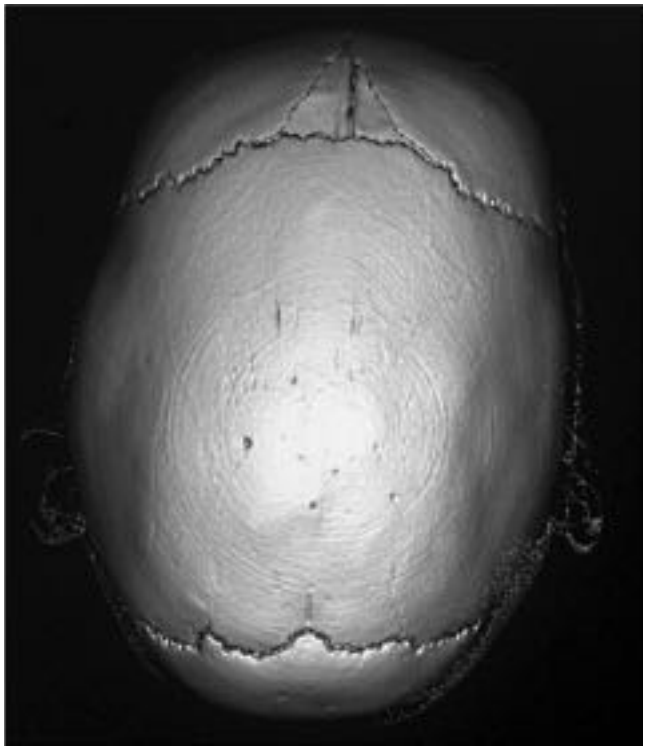


Figure 19.1 3D CT scan of patient with scaphocephaly. Note the absence of sagittal suture.

Hydrocephalus

Hydrocephalus is characterized by enlargement of the cerebral ventricles due to obstructed outflow of cerebrospinal fluid (CSF) somewhere along its path from the lateral ventricles, through the interventricular foramina, third ventricle, cerebral aqueduct, fourth ventricle and subarachnoid space to the sites of absorption. Hydrocephalus can occur in up to 20% of patients with craniosynostosis. It may be associated with chronic venous hypertension and hindbrain herniation, particularly in multisutural synostosis.

Differential diagnosis

Not all abnormal head shapes are due to craniosynostosis, and accurate diagnosis is essential since the management of non-synostotic head shape abnormalities is non-surgical. The bones of the skull in early life are relatively soft and deformable, rendering the head susceptible to alteration in shape for a variety of reasons. Non-synostotic causes of abnormal head shape include intrauterine and birth canal moulding, assisted delivery (e.g. Ventouse), intracranial abnormalities and postnatal deformational forces on the growing skull due to external pressure on the head or to uneven muscle tension in the muscles attached to the skull base.

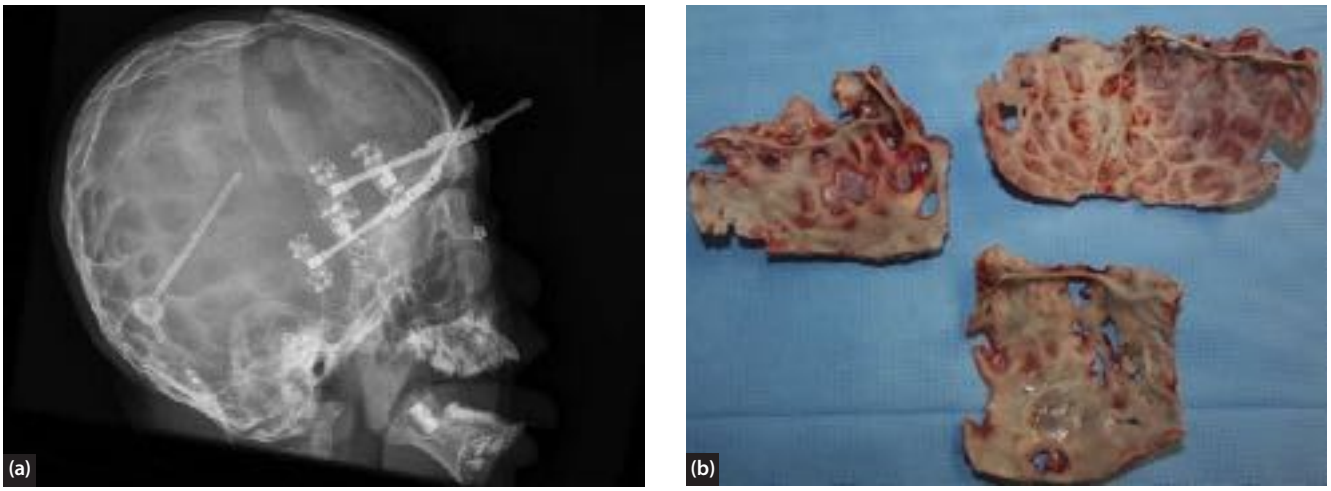


Figure 19.2 **(a)** Skull CT of a patient with raised ICP showing 'copper beating', treated with a shunt and undergoing distraction osteogenesis of the forehead. **(b)** Copper beaten bone shows indentation of underlying brain tissue.

Intrauterine, birth canal and assisted delivery moulding will be present at birth but improve fairly quickly. Intracranial abnormalities will present at birth but persist. Postnatal deformational changes are not present at birth, develop gradually and, if the cause is removed, will improve. This is in contrast to craniosynostosis, which is usually apparent at birth and progresses with growth. Diagnosis is usually possible based on the history and examination alone, but confirmation of the patency of sutures can be confirmed by plain radiographs or CT scan if needed.

The most common presentation of non-synostotic abnormalities of head shape is **occipital plagiocephaly**. This is usually due to deformational or positional plagiocephaly. The incidence of deformational plagiocephaly has significantly increased since 1992 when the National Institute of Child Health and Human Development at the US National Institutes of Health advocated and encouraged infants to sleep on their backs/supine to reduce the risk of sudden infant death syndrome (SIDS). This, combined with prematurity or potentially a delay in the ability to hold one's own head, may predispose a child to either symmetrical or asymmetrical flattening of the occiput. Other causes include abnormal head posture due to torticollis, vertebral abnormalities or ocular squint.

Clinically, there is flattening at the back of the head, often with anterior translocation of the ear on the affected side and an element of frontal bossing. Unfortunately, this condition tends to develop quickly. The natural history of this is that it tends to self-correct but may take a number of years. There is the propensity to have a mild element of asymmetry but with the combination of self-correction and increase in hair length and thickness, it is seldom noticeable. There is no surgical intervention warranted for correction of this. Orthotic firms have advocated the use of corrective helmets but the evidence to support this is currently lacking and thus the costs must be borne by the family.

General principles of surgical management of craniosynostosis

The indications for surgery are prevention and/or treatment of raised ICP, correction of significant cosmetic deformity and prevention of future skull shape deformity (or skull normalization) by allowing normal growth to take place. Essentially this allows the normalization of skull deformities and treats the raised ICP which results from a craniocerebral misproportionation.

The general principles of surgery for the craniosynostoses are to remove the cause by excising the affected suture, correct the existing deformity by reshaping the affected area of the cranium and moving it into the position it would have been in had it grown normally. This leaves an expanded intracranial volume, with a space between the dura and the repositioned bone, into which the brain can expand, thus relieving raised ICP if present. It also corrects the aesthetic deformity. Leaving a gap in the region of the excised suture, which will mimic a normal suture, should allow future growth to take place by movement of the bone in response to continued brain growth.

Timing of surgery is important. Early surgery has the advantage that ICP is normalized without delay, and the deformity may be less severe since it has had less time to develop. However, early surgery may be followed by reossification at the site of the excised suture (restenosis), with a re-emergence of the condition requiring further surgery. The timing of surgery is therefore a balance between operating too early with the risk of restenosis and operating too late when there may be prolonged raised ICP, the deformity is greater and its correction may require more extensive surgery because of lack of future brain growth and, thus, capacity for skull remodelling in response to brain growth. Another factor which must be considered is that surgery results in a significant risk of moderate, and sometimes severe, blood loss. Lastly, consideration should be given to minimizing the potential risks of undertaking a general anaesthetic on the developing brain.[25]

Major craniofacial surgery carries significant risks and complications, and a dedicated team familiar with all aspects of the management of these patients is a prerequisite for surgery to be performed. This will include a dedicated ward and theatre with appropriately trained staff, a paediatric anaesthetist and HDU/PICU facilities.

SINGLE-SUTURE NON-SYNDROMIC CRANIOSYNOSTOSIS

Most commonly, patients present with fusion (or partial fusion) of only one suture. Currently, apart from coronal synostosis, there is little evidence to state that single-suture fusion is commonly due to a Mendelian genetic change.

Sagittal synostosis (scaphocephaly)

With an incidence of approximately 1:4200–8500,[26, 27] sagittal synostosis is the most common form of craniosynostosis. Approximately 6% of cases of sagittal synostosis are familial, mostly transmitted as an autosomal dominant condition.[8] The remaining cases are sporadic and at least a proportion are likely to have multifactorial aetiology, including genetic and environmental factors. The recurrence risk to a couple with a child affected by sagittal synostosis in the absence of a family history of the condition is approximately 2%.[8]

It is usually noted at birth for its elongated skull length but the phenotypical presentation varies depending on the ensuing skull growth in the first 18 months of life. The presentation includes a relatively long, slender skull shape and often a midline sagittal ridge, corresponding to the sagittal fusion. Various or all aspects of the suture may become fused, each giving a different presentation. From a frontal perspective, the child may have significant frontal bossing, an elevated hairline and bitemporal pinching. Posteriorly, an excessive occipital bullet may develop. There may also be a middle 'saddle' deformity.

Various treatment regimes have been advocated and each unit will have their standardized technique. Depending on the age at presentation of the patient, a passive operation (including variations of strip craniectomy/microbarrel staving/spring distraction) may be performed. Older children often undergo a total calvarial vault remodelling (TVR) which addresses all the compensated growth deformities that occur. We advocate a strip craniectomy and microbarrel staving passive procedure if we are able to perform the operation safely prior to 6 months of age. If not, our patients undergo a TVR based on a modified Melbourne protocol at 12–18 months of age.[28]

Unicoronal synostosis (frontal plagiocephaly)

Unilateral/unicoronal or frontal plagiocephaly has an incidence of approximately 1 in 11 000.[4, 29] It has the most varied single-suture variation with both cranial and facial components. Cranially, this often presents with a retruded forehead and brow on the affected side, with a relative orbital dystopia (upwards on the affected side) due to the lack of anteroinferior growth secondary to the fused (or partially fused) coronal suture.

Facially, this then translates into a deviated face, expressed most significantly with a facial and nasal twist towards the affected side. There may also be a maxillary and eventually mandibular cant develop and, probably most functionally importantly, strabismus or a squint may develop. One of the aims of treatment is to obviously minimize these effects.

Bilateral coronal synostosis (brachycephaly)

Bicoronal synostosis is the most likely of all of the single-suture synostoses to have a Mendelian genetic basis.[30] Genetic testing should be offered to all patients with coronal synostosis. Testing can include the mutation hot spots in *FGFR1*, *FGFR2* and *FGFR3*, as well as full analysis of the *TWIST1* and *TCF12* genes.

Approximately 8–15% of patients with non-syndromal coronal synostosis have a family history of the condition. A positive family history is seen more often in patients with bicoronal synostosis.[7, 26] Empiric recurrence risk to a couple with a child with coronal synostosis and no family history of the condition is 5%, although genetic testing should ideally be offered in order to provide a family-specific recurrence risk.[7]

Metopic synostosis (trigonocephaly)

Traditionally thought to be the third most common form of synostosis, metopic suture fusion has over recent years seen a large increase in incidence.[31]

Between 5% and 10% of cases of metopic synostosis have been found to have a positive family history.[9] The incidence of learning disability and other developmental problems (especially expressive speech delay) is higher in patients with metopic synostosis than with other single-suture synostoses. This is at least in part due to the higher incidence of chromosomal copy number variants (CNVs) in patients with metopic synostosis. Suggestive features should therefore prompt detailed chromosomal analysis in patients with metopic synostosis, such as array comparative genomic hybridization (aCGH) studies. Environmental factors, such as exposure to teratogens during pregnancy, are a well-described cause of metopic synostosis.[32] Many cases are thought to be due to a combination of genetic and environmental factors. The empiric recurrence risk to a couple with a child with metopic synostosis with no known cause is 5%.[9]

Clinically, a wedge-shaped forehead typically ensues from premature closure of the frontal bones at the metopic suture. This prevents lateral growth of the frontal bones. This is combined with supraorbital recession and often hypotelorism, decreased interorbital and intercanthal distances. Children will often also develop wider parietal eminences due to compensated growth posterior to the fused frontal bone.

Correction of metopic (trigonocephaly) and coronal (anterior plagiocephaly/brachycephaly) is usually by means of a fronto-orbital advancement and remodelling (FOAR) (**Figure 19.3**). Individual unit protocols vary, but our institution will usually correct this from 12 to 18 months of age.

Tessier[33] originally described this procedure and it is now the mainstay for treatment of these conditions. It allows a conformational change of the forehead (and anterior cranial fossa) to take place, as well as allowing the anterior placement of the neo-forehead in order to increase the skull volume to minimize the risks of raised ICP. At the same time, the bifrontozygomatic width may be altered to correct the relative hypotelorism that ensues secondary to trigonocephaly. Conversely, this can be narrowed for patients with bicoronal synostosis.

The procedure is carried out with the patient supine. A coronal flap is raised. The forehead is then removed. This is designed by selecting bone that may subsequently facilitate a neo-forehead to be created. Techniques vary between institutions but usually this is carried out as a bilateral procedure (even for unicoronal synostosis). This then allows access to the anterior cranial fossa. The supraorbital bar is removed, protecting the frontal lobes of the brain and the eyes and optic nerves. This supraorbital bar is then corrected and remodelled to an ideal shape, allowing the neo-forehead to be attached to this. The construct is then usually replaced in an advanced position (subsequently creating an increased skull volume) and usually attached by resorbable plate fixation.

Lambdoid synostosis

Lambdoid synostosis has an incidence of only about 3% of craniosynostosis. A positive family history is rarely seen in patients with lambdoid synostosis and recurrence risks are low.[5]

The diagnosis of lambdoid synostosis is dependent on history (usually present at birth), examination (a trapezoid head shape when viewed from above compared to a parallelogram in deformational plagiocephaly, an inferiorly and posteriorly situated ear – see **Figure 19.4**) and radiologically (CT scan +/– 3D reconstruction).

Treatment of lambdoid synostosis rarely involves surgery. The risk of raised ICP is low and, once covered by hair, the negative aesthetic element of this is often minimized. If the deformity continues to cause a significant aesthetic concern or raised ICP becomes evident, a vault remodelling is usually undertaken.

SYNDROMIC CRANIOSYNOSTOSIS

It is estimated that there are over 500 different syndromes[35] that have craniofacial anomalies. From a craniosynostosis syndromic point of view, the vast majority of these patients, though, are due to the conditions outlined below. These syndromes are thought to develop through an interaction of genetic factors, molecular and cellular events, mechanical and deformations forces and secondary effects of each of these on normal growth and development.

Crouzon syndrome

Described in 1912 by a French neurosurgeon, this syndrome affects the face and cranium and occurs in 1:25 000 live births. Crouzon syndrome is characterized by craniosynostosis and maxillary hypoplasia with shallow orbits causing ocular proptosis. There is often bicoronal synostosis (brachycephaly) but occasionally the sagittal suture may also be affected. The main abnormality is an underdeveloped midface which results in prolapse of the globes ('exorbitism'), hypoplasia of the malar bones, retromaxillism and a resultant

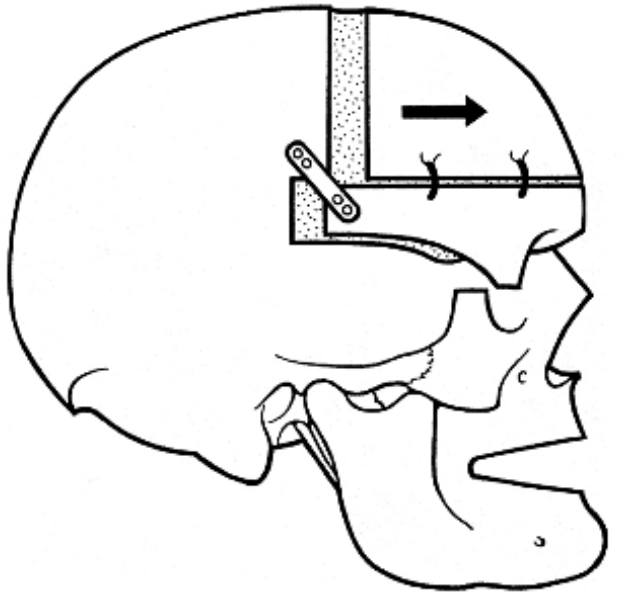


Figure 19.3 Fronto-orbital advancement surgery.

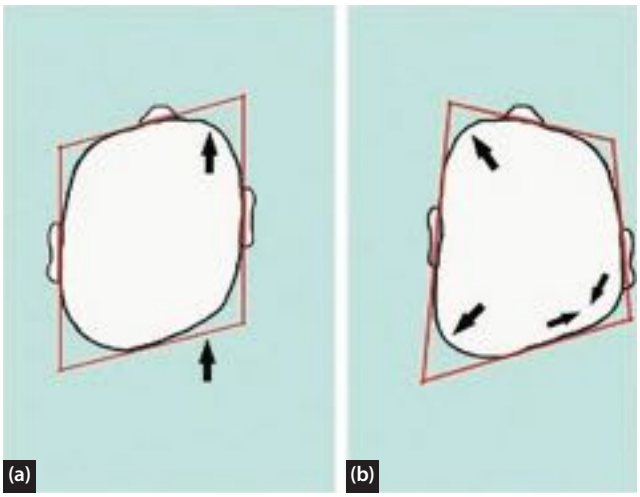


Figure 19.4 Differences between positional and true lambdoid synostosis. Positional moulding **(a)** produces a parallelogram-shaped head and the ear moves anteriorly on the affected side. Unilambdoid synostosis **(b)** produces a trapezoid-shaped head and the ear moves posteriorly towards the affected suture.

malocclusion (Figure 19.5). Anomalies of the middle ear and atresia of the external auditory canal may give rise to a conductive hearing loss. Abnormalities are usually confined to the craniofacial region although there may be systemic anomalies.[4] Intelligence is usually normal. Crouzon syndrome is caused by mutations in *FGFR2* and is autosomal dominant, although new mutations frequently arise.[29] The severity of this condition is extremely variable, even within the same family, and therefore a mildly affected parent may only be diagnosed after the birth of a more severely affected child. Severity may vary from a barely noticeable degree of proptosis and midfacial hypoplasia to, more rarely, cloverleaf skull.

Apert syndrome

Described in 1906 by Apert, this syndrome has an incidence of 1:60 000 live births. Apert syndrome is caused by mutations in *FGFR2*; two-thirds of cases have the mutation Ser252Trp while the remaining one-third have the Pro253Arg mutation.[36] There is an autosomal dominant pattern of inheritance although most cases of Apert syndrome occur without a family history as a result of new mutations and there is a link with advanced paternal age.[37] The main features of this condition include craniosynostosis (usually bicoronal), abnormal midfacial development and fusion of the digits of the hands and feet (syndactyly) (Figure 19.6). Abnormalities of the midface and cranium are evident at birth, with brachycephaly and midface retrusion causing an anterior open bite (malocclusion). Cleft soft palate or bifid uvula is present in 30% of cases. Fixation of the stapes footplate may cause a conductive hearing loss. There may be other associated malformations and intellectual ability may vary from normal to significantly impaired.[38]

Pfeiffer syndrome

First described in 1964, Pfeiffer syndrome is similar to Crouzon syndrome and is characterized by craniosynostosis and midfacial hypoplasia with shallow orbits. Additional features of Pfeiffer syndrome include broad thumbs and broad great toes. Severity of craniofacial anomalies can vary from mild midfacial hypoplasia to a cloverleaf skull (Figure 19.7). Coronal sutures are most commonly affected, with resultant brachycephaly. Other features may include skeletal anomalies such as fusion of the elbow joint, solid cartilaginous trachea and choanal stenosis or atresia. Three clinical or phenotypical subtypes have been suggested depending on the extent of associated features[4] and there is some evidence for a genotype–phenotype correlation for some mutations.[39] Pfeiffer syndrome is caused by mutations in *FGFR1* and *FGFR2*, in some cases the same mutations that can cause Crouzon syndrome.[7, 40, 41] Inheritance is autosomal dominant although many cases arise as a result of new mutations. Intelligence varies from normal to mild learning difficulties, although central nervous system abnormalities may occur in severe cases.[11]



Figure 19.5 Crouzon syndrome.

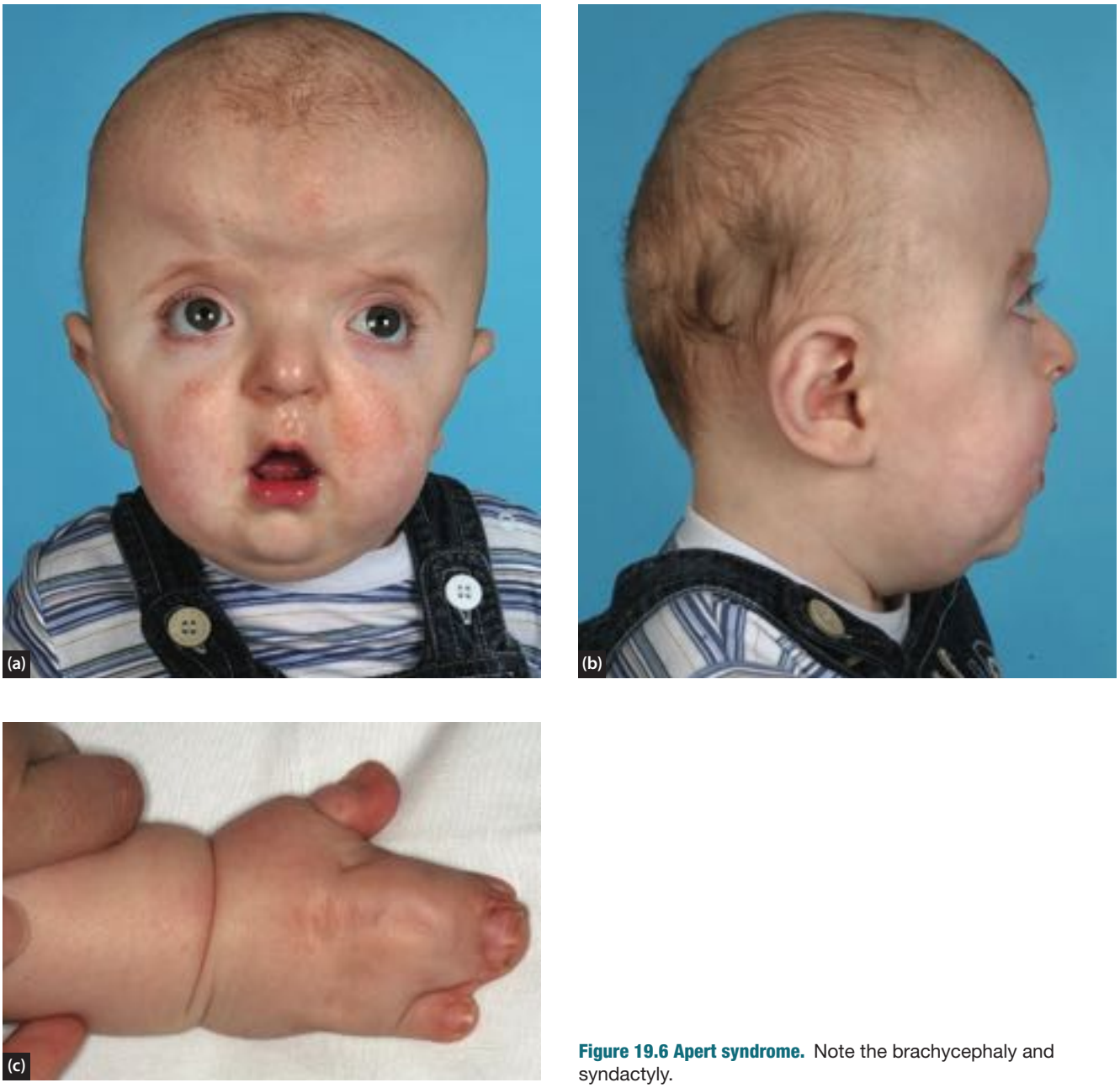


Figure 19.6 Apert syndrome. Note the brachycephaly and syndactyly.

Muenke syndrome

This autosomal dominant condition is associated with unilateral or bilateral coronal synostosis and a variety of minor anomalies. The cause is a specific mutation of *FGFR3*, the Pro250Arg mutation.[42] The phenotype this causes is extremely variable, even within the same family, and includes coronal synostosis, macrocephaly without synostosis, ptosis and minor anomalies of the hands and feet. Intelligence is usually within normal limits although learning difficulties, usually mild, may be present. The effect of the mutation may be so mild in some family members that they are unaware that they harbour a mutation. Genetic testing can be used to clarify their carrier status.

Saethre–Chotzen syndrome

Saethre–Chotzen syndrome was first described in 1931. This is an extremely variable autosomal dominant condition, although abnormalities may be milder than in other syndromic craniosynostosis conditions. Because of this, a mildly affected parent may not be aware that they also have the condition until after their more obviously affected child is diagnosed. The most commonly affected suture is the coronal suture and the craniofacial abnormalities are frequently asymmetric. Associated features may include ptosis, a low anterior hairline, small ears with a prominent horizontal crus, mild cutaneous syndactyly and broad thumbs and great toes. Mutations in the gene *TWIST1* cause Saethre–Chotzen syndrome but the phenotype has



Figure 19.7 Pfeiffer syndrome. Note the bulging temporal region, turricephaly, retruded midface and tracheostomy.

also been seen in association with the Pro250Arg mutation in *FGFR3* and with *TCF12* mutations.[43–45]

TCF12

Mutations in the *TCF12* gene are a recently identified and common cause of coronal synostosis affecting 10% of patients with unicoronal synostosis and 32% of those with bilateral synostosis, occasionally with additional sagittal involvement. Some patients have features consistent with Saethre–Chotzen syndrome, such as syndactyly, but with negative *TWIST1* analysis.[45] This is consistent with the fact that the *TCF12* and *TWIST1* proteins have been shown to interact.[45, 46] Most patients have isolated coronal synostosis with no additional features. A minority of patients with developmental delay, a learning disability or autism have been described but the majority have normal development and educational attainment.[45]

Craniofrontonasal syndrome

This condition is characterized by craniosynostosis which is usually coronal, frontonasal dysplasia, curly or frizzy hair, sloping shoulders and ridged nails. As part of the frontonasal dysplasia there is hypertelorism, a broad nasal bridge and, occasionally, a bifid nasal tip. There may also be skeletal anomalies such as joint hyperextensibilty, scoliosis and broad toes. Mutations in the gene *EFNB1* are causative.[47] The inheritance is X-linked dominant whereby females are more severely affected than males.

Carpenter syndrome

Carpenter syndrome is a very rare autosomal recessive condition characterized by craniosynostosis, which may affect all sutures causing a cloverleaf skull, and also polysyndactyly (accessory digits with fusion of the digits) and brachydactyly (shortened digits). Mixed hearing loss may also occur. Patients may have obesity and may show learning difficulties.[48] The causative gene has been identified as *RAB23*.[49]

Kleeblattschädel anomaly (cloverleaf skull)

This describes a trilobar skull and is usually caused by pansynostosis involving the coronal, lambdoid and metopic sutures, with bulging of the brain through open sagittal and sometimes squamosal sutures. The prognosis is often, but not universally, poor. Cloverleaf skull is a non-specific anomaly and may be an isolated defect or part of wider syndromes. As such, the aetiology of cloverleaf skull is varied. It may be seen in patients with certain chromosomal abnormalities or be a feature of syndromes such as Pfeiffer, Apert, Crouzon and Carpenter.

MANAGEMENT OF SYNDROMIC CRANIOSYNOSTOSIS

The aim of cranial management for syndromic craniosynostosis is similar to non-syndromic craniosynostosis. Primarily, it is to prevent or manage the raised intracranial

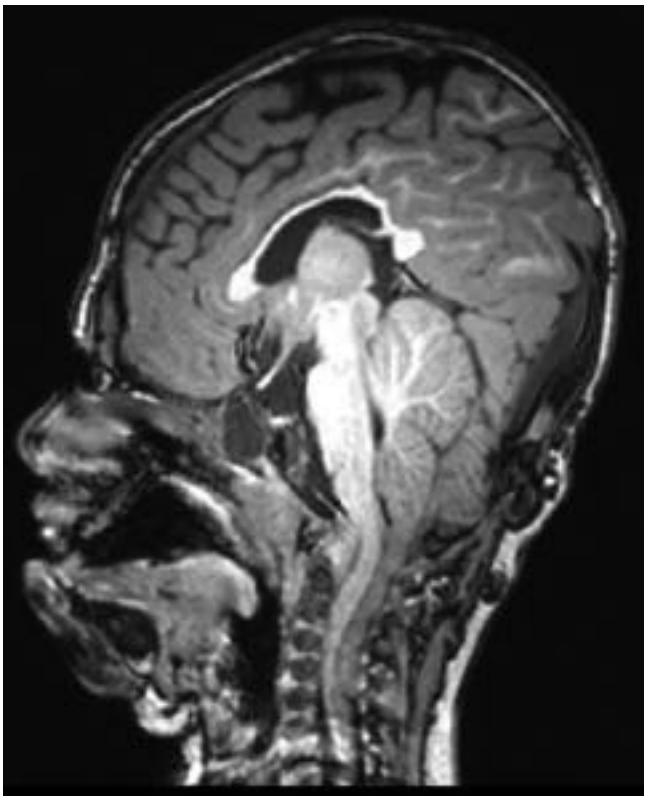


Figure 19.8 MRI scan showing a child with Crouzon syndrome with significant tonsillar herniation below the foramen magnum. Bicoronal synostosis has resulted in a significant brachycephaly deformity resulting in decreased posterior cranial fossa volume and a cramped cerebellum.

pressure that is synonymous with these conditions and to normalize the skull shape and morphology. Prior to this, though, various other factors will need to be addressed. Initially, this will include airway management, feeding and eye protection. Other comorbidities (e.g. cardiac/renal/respiratory systems) may require investigation and correction. Imaging is essential and CT brain and MRI spine and brain scans are routinely performed. In addition, support of feeding, speech and language and psychological needs is ensured by regular surveillance and input as required.

Airway

Respiratory problems may be central or peripheral. Central apnoeas may be related to a Chiari malformation and/or to raised ICP (**Figure 19.8**). An MRI must always be performed as part of a routine imaging series. More commonly, respiratory problems are secondary to obstruction, with reports of 40–83% of children being affected with obstructive sleep apnoea (OSA).[50]

Causes of obstruction in syndromic craniosynostosis are multilevel but include congenital bony nasal stenosis (CBNS) (**Figure 19.9a**), choanal atresia, nasopharyngeal narrowing, a crowded or narrow oropharynx, a thick long soft palate, subglottic stenosis, tracheal stenosis and tracheal cartilage sleeve. CBNS is caused by 3D hypoplasia of the maxilla, leading to narrowing of the nasal passages along their length. In addition, raised ICP can result in compromised neuromuscular control of airway patency.[50]





Figure 19.9 (a) CT scan showing congenital bony nasal stenosis (CBNS). **(b)** A child with Apert syndrome and CBNS managed with a nasopharyngeal airway (NPA).

CBNS and choanal atresia, particularly if bilateral, require treatment shortly after birth. Management options include dilatation with or without stenting, nasopharyngeal airways (NPAs), positive pressure ventilation using masks (non-invasive) and tracheostomy. The choice of modality is based upon a number of factors including a full airway assessment, other comorbidities geographical location, and facilities for follow-up and support and parental choice.

Dilatation and NPA insertion has been shown to be a successful first-line management option in the majority of patients (**Figure 19.9b**).[51] An NPA has the advantage over a stent of bypassing the narrow nostril but also the narrow nasopharynx and possibly the long thick soft palate. An NPA is required for 2–48 months. Carers and parents have to undergo training and demonstrate competency in managing the NPA after discharge from hospital.[52] Parents prefer management with an NPA compared to a tracheostomy.[53]

Positive pressure ventilation might be required either instead of or in addition to NPAs and other surgical interventions. Nasal continuous positive airway pressure (CPAP) using a mask has been found to be beneficial in a number of these patients, although fitting of the mask onto a retruded maxilla or a hypoplastic midface can be a challenge.

Adenotonsillar hypertrophy may contribute to ongoing obstructive symptoms and patients should be monitored for this. Although adenotonsillectomy as a treatment modality for OSA is less successful than in the general population, improvements – either symptomatic or on polysomnography (PSG) or both – are seen in up to 60% of patients. Cleft palate is a common finding in patients, particularly with Apert syndrome. A cleft palate or submucous cleft is no longer an absolute contraindication to adenoidectomy. With good visualization techniques, an inferior ridge can be left behind to enable palate–pharyngeal apposition.

Patients should be monitored both clinically and with PSG to detect severity of OSA, and early investigation and intervention is advocated. The frequency of surveillance PSG is to be determined on an individual case-by-case basis. Frequent sleep studies will often be undertaken to determine the level and severity of instruction.

Midface advancement surgery has variable effects upon upper airway obstruction. There are some reports of very successful outcomes of early midface advancement surgery in terms of decannulation or avoiding the need for a tracheostomy[54] while other reports are less positive.[55] In the authors' unit, there is generally an improvement in subjective and objective measures of OSA following midface advancement but not always sufficient to enable decannulation and/or discontinuation of CPAP.

Tracheal anomalies might also contribute towards airway obstruction in syndromic craniofacial patients. *FGFR2* syndromes such as Crouzon, Pfeiffer and Beare–Stevenson syndrome are associated with an abnormality of the trachea known as 'tracheal cartilaginous sleeve'.[56] This is a malformation in which individual tracheal arches are not formed. There is a continuous tracheal cartilaginous piece composed of a vertically fused C- or O-shaped cartilage. This might extend from the level of the subglottis down to the bronchi. When the cartilage is C-shaped, the pars membranacea is often notched posteriorly, giving the appearance of a keyhole.[57] Respiratory problems occur as a result of the reduced calibre and the reduced compliance of the trachea. Premature death occurs in almost all patients with this abnormality but a tracheostomy appears to offer a survival advantage. A tracheostomy will be more challenging to perform. Because of the rigidity of the trachea and the absence of rings, it may be necessary to cut a window rather than a vertical slit as is more common in paediatric tracheostomies. As the sleeve trachea causes narrowing, it might be necessary to select a tracheostomy tube with a smaller diameter than might be expected for age.

Post-operatively, these children are more susceptible to granulations related to trauma from suction (**Figure 19.10**). This is managed by using a shorter tracheostomy tube in order to avoid the end abutting on the abnormal ends of the C-shaped cartilage. In addition, topical application of steroids, regular attention to the 'granulomas' and education of carers with regard to suction help minimize the impact of these 'granulomas'. Nevertheless, they are a cause of significant morbidity and mortality in this group of patients.

Tracheostomy may be required either as a short-term solution, for instance to cover a surgical procedure perioperatively (e.g. midfacial advancement), or as a long-term

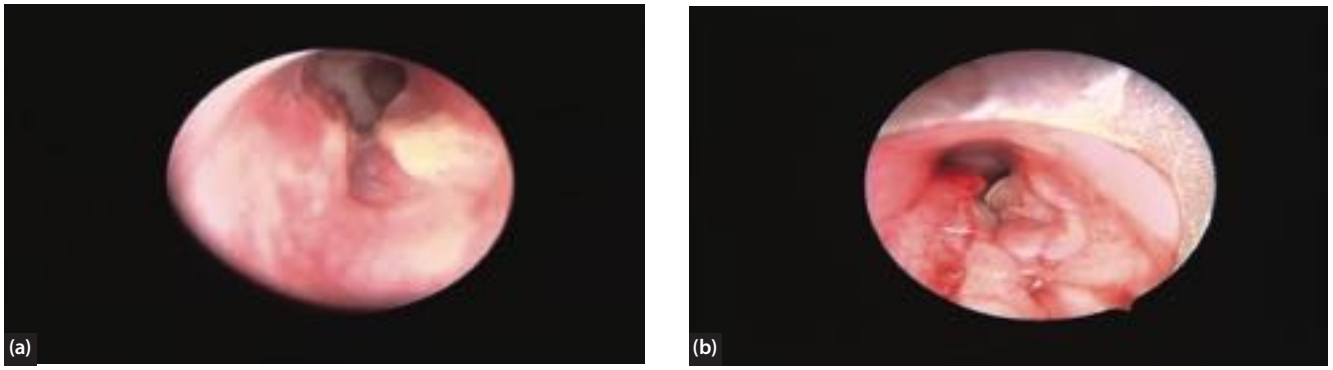


Figure 19.10 **(a)** Keyhole-shaped tracheal abnormality in Pfeiffer syndrome. **(b)** The same trachea with granulation secondary to trauma from suction. (Images courtesy of Ms M. Wyatt, Consultant Paediatric ENT surgeon, Great Ormond Street Hospital, London).

airway solution. Because the airway obstruction in these children is multilevel, a combination of approaches is required to optimize the airway. Ultimately, if these are not successful, a tracheostomy may be the safest approach.

Visual considerations

Due to both restriction of anterior frontal bone growth and midfacial hypoplasia, exorbitism (decreased orbital volume/capacity) often results. This can range from simple exorbitism with complete soft-tissue eye protection to dislocation (with or without reduction) or complete ocular exposure. Corneal abrasions are not uncommon in this situation.

Early ophthalmological assessment is imperative. Education for the family on globe reduction may be required and potentially surgical intervention (tarsorrhaphy) may be indicated.

Regular fundoscopy assessments are also mandatory to establish if raised ICP is present. Papilloedema, optic atrophy and progressive optic nerve dysfunction may accompany raised ICP. Uncorrected refractive effort, strabismus, ptosis and corneal abrasion can lead to amblyopia, potentially causing permanent visual disability if not identified and corrected.

Intracranial pressure

The mainstay of cranial surgery for syndromic craniosynostosis has been in the attempt to increase the intracranial volume, and thus control intracranial hypertension, while at the same time normalizing the head shape and thus improving the patient's overall appearance.[58] Without treatment, both visual and neurological deterioration may result. In addition to craniocerebral disproportionation, raised ICP in syndromic craniosynostosis can be influenced by venous hypertension, OSA and hydrocephalus.

As the most common cause of raised ICP is craniocerebral disproportionation, vault remodelling is intended to address this. Initially, especially for brachycephalic patients or bicoronal synostosis, a suturectomy or posterior vault expansion is advocated.[59]

Role of CSF diversion

Ventricular dilatation is a rare occurrence in non-syndromic craniosynostosis and in such cases hydrocephalus, if noted, is attributable to any coexisting disorder. However, it is a common feature of syndromic craniosynostosis and seen in nearly half the cases.[60] While non-progressive ventriculomegaly is seen commonly in Apert syndrome, it seldom requires CSF diversion. On the contrary, in Crouzon and Pfeiffer syndrome, ventriculomegaly is progressive and requires CSF diversion in most cases, despite early posterior vault expansion procedures. Patients with Saethre–Chotzen and Muenke syndrome are seldom affected by hydrocephalus.

The etiology of hydrocephalus is multifactorial: crowded posterior fossa , venous outlet obstruction and increased CSF outflow resistance are the commonest explanations.[60] The multifactorial nature of the problem is confirmed by the fact that, despite posterior vault expansion, a significant proportion of cases end up needing a shunt placement for progressive ventriculomegaly.

The options in terms of CSF diversion are limited to insertion of a ventriculoperitoneal (VP) shunt. Special precautions have to be taken to avoid shunt overdrainage as excess CSF shunting will lead to worsening of pre-existing venous hypertension (pseudotumour state). The authors recommend the use of a programmable shunt valve with inbuilt antisiphon device to obviate this problem. In the authors' experience, there is a very limited role for endoscopic third ventriculostomy (ETV) for CSF diversion. We have carried out ETV in a small number of cases with moderate ventriculomegaly post posterior vault expansion procedures in patients with subtle clinical and ophthalmological symptoms and signs of raised ICP. However, the default option for CSF diversion for hydrocephalus in syndromic craniosynostosis is insertion of a VP shunt with a programmable shunt valve with an inbuilt antisiphon device.

In our experience, the incidence of shunt infection and ventricular catheter blockage are higher in syndromic craniosynostosis, as are other shunt-related complications because of the associated problems of feeding, airway obstruction, frequent chest infections and progressive craniocerebral disproportion in these cases.

Cranial surgery for syndromic craniosynostosis

If the posterior vault size and shape is satisfactory, a fronto-orbital advancement and remodelling (FOAR) is performed[61] which both increases the volume of the skull and allows a conformational change or normalization of skull shape. Timing of this procedure varies depending on the individual institution's protocol. We will usually operate when the child is 12–18 months of age. This balances the risk of developing raised ICP if surgery is performed at a delayed stage against the risk of restenosis if the procedure is performed too early. Unfortunately, this is seldom the case and most patients will undergo a number of procedures. In our institution, depending on the severity of the craniosynostosis, a suturectomy will usually be performed. This allows continual skull growth and expansion with minimal shape deformities. This is usually only a short term measure, however, as most syndromic patients have a 'pro-ossification' genetic change and, as a consequence, the sutures will often re-fuse. Therefore, a posterior vault expansion is usually undertaken. This utilizes internal distraction devices to increase the posterior vault. It is only after the posterior vault is corrected/normalized that we address the forehead.

Midface advancement surgery for syndromic craniosynostosis

Midface advancement surgery is indicated to attempt to improve the airway in order either to avoid the need for non-invasive ventilation or a tracheostomy or to remove

dependence upon such a modality. However, outcomes of this procedure in terms of the airway are somewhat variable and unpredictable. Apart from the airway, the main indication for midface advancement surgery is to normalize appearance.

Timing of surgery to the midface is a matter of debate. In the UK, surgery is usually delayed until the age of 5–6 years, or older, prior to the child starting secondary education. This delay is intended to allow growth of the child so that their weight increases, as does the circulating blood volume. Midface surgery often results in significant loss of blood volume, with much of the haemorrhage not directly amenable to local control.

The type of surgery is dictated by the pattern of the deformity. There are three basic operations available.

1. The **Le Fort III osteotomy** involves advancement of all midfacial structures inferior to the frontal bone, i.e. nose, zygomas and maxilla en bloc. This requires a bicoronal flap for access to the nasal root, orbits and zygomatic bones and osteotomies of the nasal root, medial orbital walls, orbital floor, lateral orbital wall, frontozygomatic suture and pterygomaxillary complex. This allows mobilization of the midface. Internal fixation and bone grafts may be used to ensure satisfactory healing and stability. Due to the potential issues with achieving adequate advancement, however, this procedure is usually performed by distraction osteogenesis and a rigid external distractor (RED) frame now (see below).
2. Where midface hypoplasia is associated with hypertelorism, a **facial bipartition** may be carried out. It essentially involves a Le Fort III osteotomy to advance the midface and excision of a V-shaped segment of bone from the midline, creating two independent hemifacial segments, which can then be brought together to reduce the interorbital distance.
3. A **monobloc procedure** involves advancement of the forehead and midface at the same time by combining a Le Fort III procedure with FOAR.

See also ‘Distraction osteogenesis’, below.

Distraction osteogenesis

Conventional surgery involves osteotomy, mobilization and bone movement at one operation. Bone grafting and internal fixation are required to ensure healing and stability and to prevent relapse. This has the advantage of completing treatment at one operation. However, where the required bone movement is large (e.g. greater than 10 mm in the midface) or there is significant scarring of surrounding soft tissues (e.g. cleft or multiply operated patients), the desired movement may be difficult or impossible to achieve. There is also the risk of infected dead spaces (between the neoforehead and dura) in monobloc procedures due to the communication between the intracranial contents and the nasal commensal flora. The alternative of using distraction osteogenesis can be utilized to overcome these difficulties.

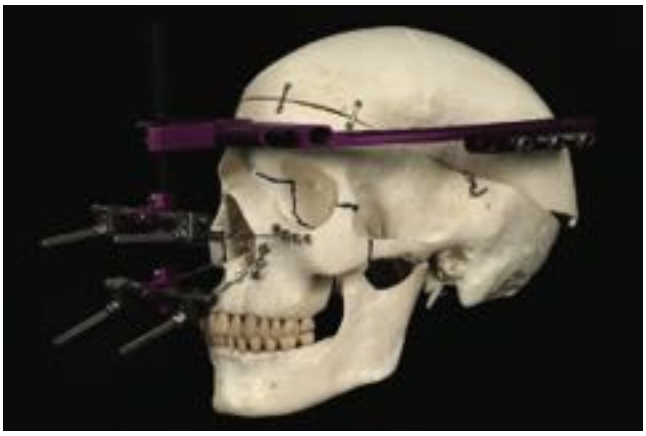


Figure 19.11 Distraction osteogenesis with a RED frame (KLS Martin RED Frame). The procedure is a craniofacial disjunction. The base of the skull is separated from the orbits/nasal bones/maxilla and underlying structures. After ensuring mobilization of these structures, titanium plates are usually secured to the nasal piriform and infraorbital region and percutaneous wires are secured to the RED frame. Progressive distraction is then commenced over the next week. The benefit of this procedure is that it allows growth of the bone as well as allowing soft-tissue expansion.

Distraction osteogenesis (DO) involves initial osteotomy, ensuring complete separation of bony segments, without mobilization or advancement, and application of an internal or external distraction device (e.g. RED frame), which is activated after a 1-week latent period and produces a movement of 1 mm per day. This allows gradual adaptation of a surrounding soft-tissue envelope, as well as osteogenesis within the osteotomy gap, allowing for greater movements without the need for bone grafting or internal fixation. Once the desired movement has been achieved, the distractors are left *in situ* for a further a period of two to three times the activation phase to allow consolidation of the newly formed bone.

Distraction therefore has the advantage of being able to produce larger movements without the requirement for bone grafts or internal fixation. The disadvantages are that the treatment is prolonged, the patient has to tolerate the distraction devices, and a second operation is often required for distractor removal. In most craniofacial patients, the advantages of distraction outweigh the disadvantages compared with conventional surgery and therefore the majority of midface advancements are now carried out using distraction (see **Figure 19.11**).

COMPLICATIONS OF CRANIOFACIAL SURGERY

Blood loss

Infants have a small absolute blood volume and there may be appreciable sudden haemorrhage, in particular from the cerebral sinuses. Blood loss varies with the timing and extent of the surgery. In a simple suture release, blood loss is in the region of 100 mL. Blood transfusion is not uncommon for

infants undergoing this surgery and for older children having more extensive procedures. Risk of viral or bacterial transmission is low but the consequences are potentially devastating. Avoiding transfusion is not always possible but, provided the intravascular volume is maintained, then patients can tolerate low haemoglobin levels.[62, 63]

The combined data of the NHS Designated Craniofacial Units reports approximately 75–85% of patients will require a blood transfusion per fronto-orbital advancement. Usually, this is due not to torrential bleeding but to the accumulation of mild ongoing losses from a prolonged procedure. Routinely, autologous blood recovery systems are used to minimize this, along with the use of relative hypotensive anaesthesia and utilization of tranexamic acid.

Air embolism

A major danger in craniofacial surgery is ingress and embolization of air through the circulation. This can occur at any stage during surgery, from inserting large-calibre central lines, raising a scalp flap or opening into the major sinuses. In anticipation of blood loss and air embolization, arterial and central venous lines are routinely used with a number of peripheral lines. A significant air embolism may result in hypotension, bradycardia and cardiac arrest. The highest risk occurs during elevation of the bone off the dura and preventative strategies are used to minimize this.

Cerebral oedema

All measures should be taken to avoid cerebral oedema. Positioning the patient correctly, ensuring correct endotracheal tube positioning and maintaining the correct intravascular fluid replacement are all vital. There should be minimal brain retraction and handling, particularly in cases of pre-existing raised ICP as this predisposes the patient to developing cerebral oedema. In many cases the use of systemic steroids (e.g. dexamethasone) may be useful in minimizing cerebral oedema.

Dural tear

Craniofacial operations such as suturectomy and vault expansion are essentially extradural procedures. In certain circumstances, for example repeat surgery or when 'copper beating' of the inner table of the skull is present, it may be impossible to avoid tears of the dura mater. The distorted anatomy must also be kept in mind and revision of pre-operative scans is imperative. Usually, small incidental tears are simply sutured closed and reinforced with fibrin glue. Larger tears may require dural grafting or formal repairs with the use of a patch.

CSF fistula

Cerebrospinal fluid leak is uncommon but will take place if a dural tear is not either recognized or adequately repaired. CSF can then leak through the scalp wound or, perhaps more commonly, leak into the nose and present as CSF rhinorrhoea. Often this is transient, lasting a few days and sealing spontaneously. Intra-operatively, it may be beneficial to perform a brief Valsalva manoeuvre in the attempt to identify any CSF (or blood) leaks. Obvious fistulae that fail to resolve must be treated. Of more concern are those that persist unnoticed and lead to infection or meningitis at a later date.

Infection

Infection can occur, particularly in cases involving communication with the paranasal sinuses, and result in meningitis, intracerebral abscess or subdural empyema. Chronic infection can also manifest as lost bone graft or implants. Post-operative infections are treated aggressively with systemic antibiotics and local debridement, with the attempt to preserve the bone flaps at all costs.

Intracerebral/subdural haematoma

Haematoma can present in the early post-operative phase with unexpected signs of raised ICP or 'lateralizing' signs.

Blindness

Surgery around the optic apex and skull base has the potential to damage the optic nerves or tracts. In particular, hypertelorism procedures and monobloc midfacial advancement carry a risk to these structures but all patients (and parents) must be informed and consented on this. Post-operative strabismus may also occur and regular ophthalmological assessments must be performed.

Restenosis

The aim of much cranial vault surgery is to release the prematurely fused sutures, thereby allowing unimpeded brain growth. The gaps created gradually ossify. Occasionally, premature restenosis takes place, and with continued brain growth there is a rise in ICP. This tends to happen more commonly in syndromic craniosynostosis than in non-syndromic cases. Saethre–Chotzen patients have a high incidence of reoperation for craniocerebral disproportionation.[64]

The potential for reossification declines with increasing age of the child (as rapid cerebral growth minimizes). In children over 1–2 years of age large bony defects of the skull vault may not close entirely. In some cases it is necessary to repair these defects using a split calvarial bone switch procedure at a later time.

HEMIFACIAL MICROSOMIA/OAVS

Gorlin et al.[65] and Beleza-Meireles et al.[66] suggested the term oculoauriculovertebral spectrum (OAVS) as a combined definition encompassing the overlapping diagnoses of hemifacial microsomia, first and second branchial arch syndrome, otomandibular dysostosis, facioauriculovertebral syndrome and Goldenhar syndrome.

TABLE 19.3 Vento's 1991 OMENS classification of oculoauriculovertebral spectrum (OAVS)

Aspect	Involvement
Orbit	
O_0	Normal orbit and position
O_1	Abnormal orbital size
O_2	Abnormal orbital position
O_3	Abnormal orbital size and position
Mandible	
M_0	Normal mandible
M_1	The mandible and glenoid fossa are small with a short ramus
M_2	The mandibular ramus is short and abnormally shaped
M_{2A}	Glenoid fossa is in anatomically acceptable position with reference to the opposite TMJ
M_{2B}	TMJ is inferiorly, medially and anteriorly displaced, with severely hypoplastic condyle
M_3	Complete absence of ramus, glenoid fossa and TMJ
Ear	
E_0	Normal ear
E_1	Mild hypoplasia and cupping with all structures present
E_2	Absence of external auditory canal with variable hypoplasia of the concha
E_3	Malpositioned lobule with absent auricle; lobular remnant usually inferiorly and anteriorly displaced
Facial nerve	
N_0	No facial nerve involvement
N_1	Upper facial nerve involvement (temporal and zygomatic branches)
N_2	Lower facial nerve involvement (buccal, mandibular and cervical branches)
N_3	All branches of the facial nerve affected. Other cranial nerves included
Soft tissue	
S_0	No obvious soft tissue or muscle deficiency
S_1	Minimal subcutaneous / muscle deficiency
S_2	Moderate – between the two extremes – S1 and S3
S_3	Severe soft tissue deficiency due to subcutaneous and muscular hypoplasia

OAVS is usually a sporadic condition. Multiple theories have been put forward to try to explain the aetiology but it is likely to be a multifactorial condition due to varying combinations of genetic and environmental (including teratogenic) factors. Rare cases (fewer than 1%) may be due to a mutation in the recently identified *MYT1* gene.[67]

Traditionally thought to have only a unilateral involvement, there is a small subset of those (around 10–25%) who are affected bilaterally. The phenotypical presentation, however, is usually different from left to right when this occurs.

Boys are three times more commonly affected than girls.[11]

Classification

Vento et al.[68] proposed the classification 'OMENS' (and OMENS-plus) to address the craniofacial aspects of OAVS (Table 19.3).

O – Orbit/orbitozygomatic[69]
M – Mandible – Kaban-modified,[70] Pruzansky classification[71]
E – Ear – Meurman,[72] modified Marx classification
N – Nerve (specifically facial nerve CN VII)
S – Soft tissue

Clinical diagnosis

The most striking feature of OAVS is the facial asymmetry that ensues from the involvement of the first and second branchial arches. This will usually be portrayed by a deviated chin point and subsequent dental malocclusion and/or orbital malpositioning (Figure 19.12).

As OAVS (or 'OMENS-plus'), has extracranial features, these should be investigated to rule out any other associated conditions. Vertebral anomalies should be looked for and investigated. A renal ultrasound and echocardiogram should also be performed to rule out renal and cardiac (e.g. tetralogy/ventricular septal defect or atrial septal defect/patent ductus arteriosus) concerns.

Orbit and orbitozygomatic involvement may vary from orbital and zygomatic malpositioning, micro- or anophthalmia, and epibulbar dermoids.

Ear deformity occurs in up to 95% of affected individuals.[73] Half of these will usually present with microtia. Associated hearing loss depends upon the development of the external auditory meatus and the middle ear. Hypoplasia of the middle ear with fusion or absence of the ossicles may occur (see Chapter 12, Congenital middle ear



Figure 19.12 Child with OAVS. Note the asymmetry and abnormal pinna.

abnormalities and Chapter 16, Microtia and external ear abnormalities).

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Neuromuscular deficiencies involve the facial and trigeminal nerves, with hypoplasia or absence of masticatory muscles and/or muscles of facial expression. There is facial weakness in approximately 12% of patients[50] and, more rarely, other cranial nerves may be involved. Soft-tissue asymmetries are partly related to hypoplasia of the masticatory and facial muscles, but other tissues such as salivary glands may be absent.

Management

Management is aimed at addressing each individual component of the classification. This will obviously involve a MDT for the extracranial components. Treatment regimes are similar to all syndromic craniofacial patients with airway protection or establishment, eye protection and feeding as the initial priorities. Hearing assessment soon follows. After this, assessment of mandibular function and the establishment of a ramal–condyle unit will take place. Ear deformities may be corrected by prostheses or autologous reconstruction. Facial nerve procedures will vary depending on the extent of the involvement. Eventually, corrective orthognathic surgery and soft-tissue balancing procedures may be undertaken to minimize the stigmata of the condition. This may be in the patient's late teenage years. Throughout the entire treatment period, regular ophthalmological assessments are required.

TREACHER COLLINS SYNDROME (MANDIBULOFACIAL DYSOSTOSIS)

Treacher Collins syndrome (otherwise known as mandibulofacial dysostosis) is characterized by the absence or hypoplasia of the zygomatic bones, eyelid abnormalities and mandibular hypoplasia and microtia (see Chapter 16).

Aetiology

Unlike hemifacial microsomia, Treacher Collins syndrome is an autosomal dominant condition, although approximately 50% of cases have no family history and therefore represent new mutations. Its incidence is approximately 1:50 000 live births.[74] Severity is very variable and other family members may be very mildly affected. Intelligence is usually normal. Treacher Collins syndrome is caused by mutations in the gene *TCOF1*.[75]

Clinical manifestations

The palpebral fissures may be down-slanting, with colobomas of the lower eyelid and eyelash/follicle malformations being common. A hypoplastic midface with poorly developed or absent zygomas, associated with mandibular hypoplasia, results in a very characteristic facial appearance (**Figure 19.13**). The mandibular hypoplasia might be severe enough to cause significant upper airway obstruction. Features are bilateral and often symmetrical. The difficulties in both intubation and treatment that arise are due to a steep occlusal plane angle (of both the maxilla and the mandible), often dental crowding, and significant retrognthaia of the mandible. Therefore the chin point is rotated in a clockwise direction towards the larynx/trachea (**Figure 19.14**).

Bilateral ear abnormalities including hypoplasia, microtia or anotia, hypoplasia or atresia of the external auditory meatus, middle ear anomalies and associated hearing defects are common. Inner ear function is usually unaffected leading to a conductive hearing loss. There is cleft palate in 35% of cases.

Management

Management of the airway in the neonate is required to overcome respiratory obstruction associated with



Figure 19.13 Treacher Collins. Abnormalities of zygomatic bones, ears, eyelids and mandible. Note the tracheostomy.

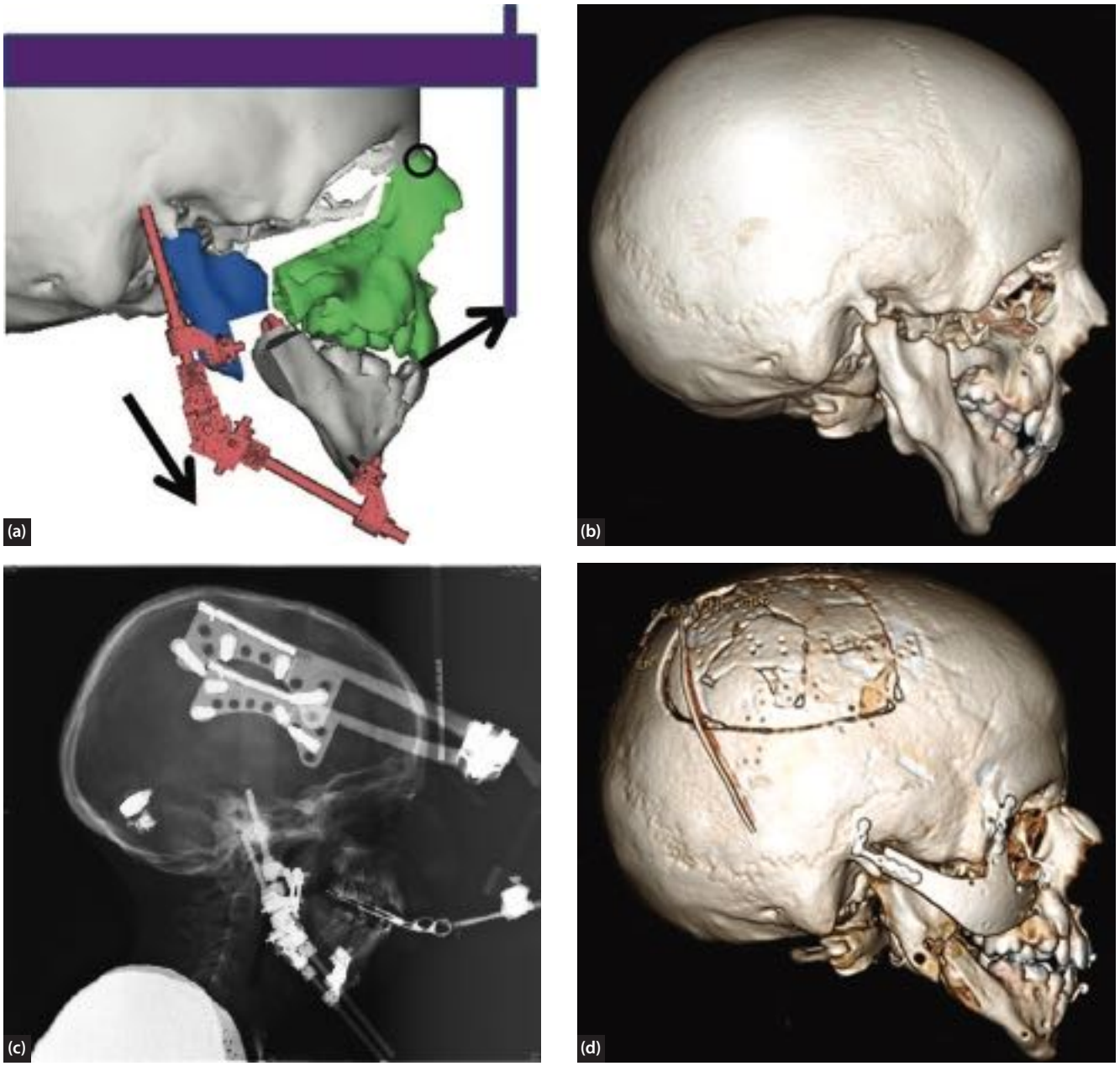


Figure 19.14 **(a)** Combination distraction osteogenesis allowing for lengthening of the mandible and rotation of the maxilla–madibular plane angle (by use of a nasion cerclage wire and traditional rigid external distraction to correct the occlusal plane). Image © Dr Richard Hopper MD. **(b)** Pre-operation. Steep mandibular occlusal plane angle with vertical mandibular growth pattern resulting in reduced retroglossal airway space. **(c)** Active distraction phase with combination RED (rigid external distractor) frame and mandibular distraction. **(d)** Post-operative 3D CT showing significant change in pogonion (chin point), normalization of occlusal plane angle and dentition. Calvarial onlay grafts used to reconstruct hypoplastic zygomatic arches. Photographs courtesy of Dr Richard Hopper MD, Seattle, Washington.

mandibular hypoplasia or choanal atresia. Early feeding difficulties may also need to be addressed. Further management may include repair of cleft palate, provision of bone-conducting hearing aid followed by a bone-anchored hearing aid, and close monitoring and intervention for speech and language development. Eyelid abnormalities may need surgical correction, hypoplastic or absent zygomas may be reconstructed, usually using calvarial bone grafts or alloplastic onlays, and mandibular deficiency can be corrected with conventional osteotomies or distraction osteogenesis (see **Figure 19.14**). Distraction techniques allow for both lengthening of the mandible in an AP direction (which addresses both the retrognathia and sometimes dental crowding) and, when combined with traditional osteotomies of the maxilla, rotation of the maxillomandibular complex in an anticlockwise direction. The latter addresses the occlusal plane and allows elevation of the chin point in a superior–anterior vector, in the hope to increase the retroglossal airway space as well as normalizing the bony skeleton and soft tissues.

ENCEPHALOMENINGOCOELE

Encephalomeningocoele represents a herniation of meninges with or without associated brain tissue, through a bony defect of the calvarium. They are a congenital anomaly representing one end of the spectrum of neural tube defects. Its diagnosis is based on the finding of either meninges and CSF (meningocoele) or nervous tissue (encephalocoele) beyond the confines of the calvarium.

The incidence of encephalocoele is reported to be as high as 1:3000 live births in South East Asia and as low as 1:10 000 live births in North America.[76]

Aetiology

Encephalocoeles may be isolated or associated with other anomalies.When other problems coexist, causes include chromosomal abnormalities, single gene disorders, teratogens and disruptions such as amniotic bands. The primary abnormality in the development of an encephalocoele is a mesodermal defect that develops when the surface ectoderm fails to separate from the neuroectoderm. This results in a defect in the calvarium and dura. Within the calvarium itself there may be failure of bone formation or pressure erosion from expanding intracranial contents. The aetiology of isolated cases is thought to be multifactorial, with both genetic and environmental factors playing a part. The widespread use of folic acid prior to conception and during pregnancy aims to reduce the frequency of neural tube defects in the general population. After the birth of an affected child, the use of high-dose folic acid prior to and after conception is recommended for subsequent pregnancies.[77]

Diagnosis

Detailed imaging is required for any nasal mass in the neonate prior to biopsy since anterior encephalocoeles may be confused with dermoids, neurofibromas and teratomas. Investigations may include an MR scan demonstrating a mass with intracranial connection and a CT scan demonstrating a bony defect in the calvarium (see **Figure 19.15** and Chapter 23, Neonatal nasal obstruction).

Classification and treatment

There are various classification systems for encephalocoele, based on the contents of the sac, site of the swelling, location of the skull defect and whether the swelling is

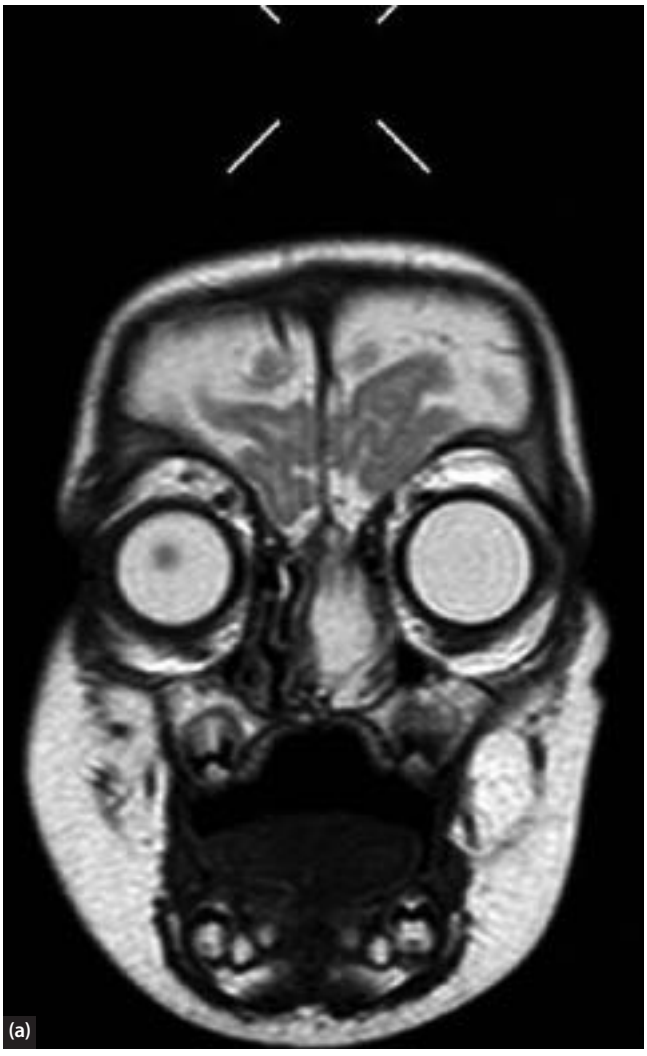




Figure 19.15 **(a)** MRI T2-weighted image of frontoethmoidal encephalocoele. Note the hypertelorism. **(b)** MRI-STIR TSE showing frontoethmoidal encephalocoele.

overt or occult. The most commonly applied system is that relating to the location of the cranial defect.

Encephalocoeles are classified as vault encephalocoeles and basal encephalocoeles based on their location in relation to vault and base of the skull. They are further subclassified as anterior (or sincipital) encephalocoeles and posterior (or occipital) encephalocoeles.

ANTERIOR ENCEPHALOCOELES

Anterior encephalocoeles have been studied extensively by Suwanwela.[78] Mahapatra further classified anterior encephaloceles[79] as follows:

A. Frontoethmoidal group
   i. Nasofrontal
   ii. Nasoethmoidal
   iii. Nasoorbital
B. Transethmoidal–nasopharyngeal
C. Transorbital
D. Transsellar–transphenoidal
E. Interfrontal (transmetiopic)
F. Anterior fontanelle

The commonest clinical presentation is swelling at the root of the nose, hypertelorism and nasal obstruction. Rare presentations are a leaking encephalocele and even with overt meningitis.

MRI of the brain and spine is the investigation of choice not only to define the lesion but also to identify associated anomalies of the entire central nervous system. Common associated anomalies are agenesis of the corpus callosum (15%), cortical dysplasia (5%) and hydrocephalus in as high as 20% of the cases.[79] CT with fine bone slices is used to define the bony defect and to better plan the bony/soft-tissue repair.

Basal encephaloceles (transethmoidal–nasopharyngeal, transphenoidal) have been at times mistaken for skull base lesions/tumours and biopsied, causing a surgical emergency in the process with CSF leak and meningitis.

Treatment

The frontoethmoidal group of encephalocoeles are managed through a bicoronal incision and craniotomy of the frontal bone and orbital bar in order to expose the neck of the encephalocoele. The neck is defined and incised to expose the contents (mainly gliotic brain). The neck is transected and repaired using dural graft. Though one-stage repair of encephalocele and correction of hypertelorism is practised by some centres around the world, our usual practice is to do a two-stage repair and defer the correction of the hypertelorism to a much later date once the upper facial growth is deemed to be complete.

The commonest post-operative complication is the development of CSF leak and hydrocephalus, which may necessitate insertion of a VP shunt in as many as 15–20% cases.

Both open and endoscopic modalities of treatment have been proposed. The recent development of endoscopic transnasal techniques has allowed the repair of these unique lesions in a minimally invasive manner as a joint neurosurgery–ENT procedure. The technique differs from the standard transcranial approach as the fundus of the encephalocoele is encountered first and the neck later. The sac of the encephalocoele sac is reduced in size with the help of cautery and the contents removed or replaced intracranial before the neck of the encepholocoele is encountered and transected. The authors' usual practice is the use of fascia lata and autologous fat to repair the skull defect and buttress the repair with a lumbar drain for a minimum of 5 days.

POSTERIOR ENCEPHALOCOELES

Vault encephalocoeles can vary greatly in size from being just a tiny skin blemish in the midline (cephalocoeles) to giant encephalocoeles. Large posterior encephalocoeles can present with difficult delivery because of their size, which can be at times giant (e.g. the size of the encephalocoele bigger than the size of the baby's head).[80]

Cephalocoele is often associated with venous anomalies such as vertical embryonic positioning of the straight sinus, splitting of the superior sagittal sinus, vein of Galen elongation, along with tenting of the tentorium.[81]

Treatment

Surgical management is primarily necessary where there is a risk of infection through communication of the lesion with the intracranial space or of rupture, or for cosmetic purposes. Surgical excision is curative in the majority of the vault encephalocoeles. Good pre-operative assessment of the venous sinus anatomy in relation to the lesion is useful in preventing serious vascular damage.

Giant encephalocoeles require semi-elective excision for fear of rupture and CSF leak and also to facilitate baby care and positioning in the cot. In the post-operative period more than 50% develop hydrocephalus and require VP shunt insertion. Associated secondary Chiari malformation and secondary sutural synostosis may require further treatment.

Prognosis

A significant percentage of the children who undergo repair of encephalocoeles will face growth, development and learning challenges and will require long-term follow-up in order to address these issues. Outcome for treated anterior encephalocoeles tends to be better than occipital encephalocoeles, with figures as low as 4 of 65 with long-term intellectual impairment.[76]

CRANIOFACIAL CLEFTS

A craniofacial cleft happens as a result of a failure of fusion of the various embryonic processes from which the craniofacial complex is formed. The exact incidence of craniofacial clefts is not known but can be estimated to be approximately 2 : 100 000 live births.[82]

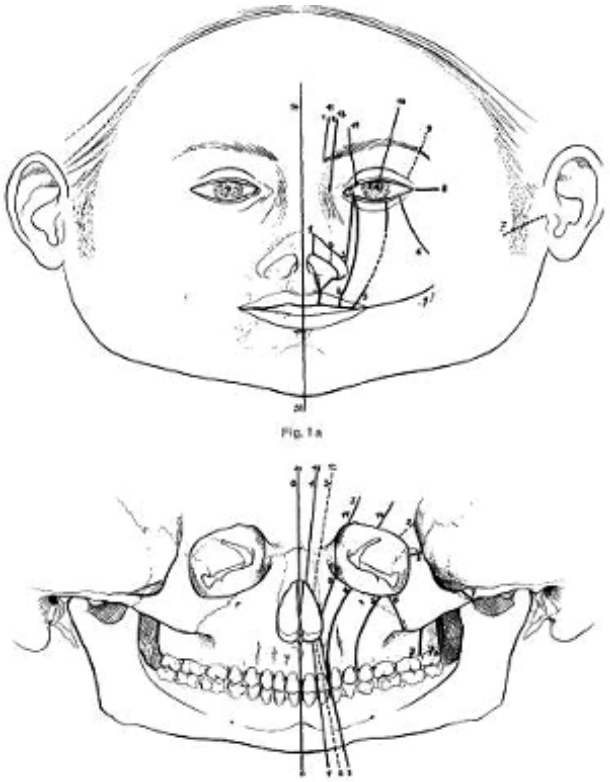


Figure 19.16 Tessier clefts. Reprinted from Tessier P. Anatomical classification of facial, craniofacial and latero-facial clefts. J Maxillofac Surg 1976; **4**: 69–92, with permission from Elsevier.[83]

Aetiology

The interplay of hereditary and environmental factors is complex and with few total cases is yet to be elucidated in detail. The majority of craniofacial clefts occur sporadically. Many factors have been implicated in the formation of craniofacial clefts, including drugs (e.g. anticonvulsants, corticosteroids and chemotherapeutic agents), radiation, infection, amniotic bands and metabolic disturbances during pregnancy. Craniofacial clefts may also be seen as part of wider syndromes such as Goldenhar syndrome.

Classification

Tessier[83] classified facial clefts according to their relationship with the orbit, nose and mouth. Numbering the clefts from 0 to 14 allowed the lower numbers to relate to the facial clefts and the higher numbers the cranial extensions (**Figure 19.16**) (see Chapter 18, Cleft lip and palate).

Clinical features

The clinical features are variable depending on the type of cleft. Clefts affecting the interorbital area result in hypertelorism and orbital dystopia (see **Figure 19.17**).



Figure 19.17 Facial cleft. Pre-operative **(a)** and post-operative **(b)** views.

Management

Surgical treatment will depend upon the site, size and severity of the cleft. The extent of the cleft can be variable, ranging from a notch in the soft tissues or soft-tissue deficiency to a severe cleft affecting skin, bone and brain.

Treatment will usually involve reconstitution of the layers, replacement of missing anatomical structures and normalization of secondary distortions.

FUTURE RESEARCH

- Technological advances have allowed the implementation of endoscopic instruments in the attempt to perform a relatively smaller craniofacial operation. The most common situation is currently to perform an endoscopic strip craniectomy for scaphocephaly combined with helmet therapy to achieve the desired morphological head shape change. Advocates of this technology and these techniques state that there is a smaller incision and also less blood loss intra-operatively. The converse argument, however, is that, if there is an intra-operative complication such as massive blood loss or dural tears/air emboli, surgical access is limited and significant blood is lost prior to being able to control it.
- Spring-assisted cranioplasty has been utilized in a number of conditions. Originally introduced by Lauritzen,[34] the procedure involves inserting an omega-shaped spring, made of stainless steel wire, usually after a osteotomy has been performed. The spring is then inserted and a constant force is applied across the osteotomy site. This technique shows great promise and has a proven track record from a safety point of view. Some criticism, though, has been received from not being able to modify the direction of expansion, sometimes a compromised aesthetic outcome and they require a second procedure to remove them.
- Mandibular distraction in children with mandibular hypoplasia to improve airway. Classically, this has been utilized in Pierre Robin sequence in an attempt to improve airway obstruction and prevent the need for tracheostomy, but there is growing evidence to suggest that most forms of significant mandibular retrognathia will benefit from distraction osteogenesis.[84] The procedure can be repeated in severe cases.
- High-resolution 3D imaging has allowed for the introduction of computer-assisted surgery. Detailed scans are imported into a proprietary program which allows manipulation of the 'bones'. Pre-surgery osteotomy cuts can be simulated by the computer, predicting the outcome of the operation. This then allows cutting guides to be fabricated intra-operatively and patient-specific plates to created. The significant benefits of this include an increase in speed of the operation and a predictable outcome that is visualized prior to surgery.

KEY POINTS

- Craniofacial surgery is undertaken in designated centres, with access to MDTs and critical care facilities.
- Children with syndromic craniosynostosis have a high incidence of airway problems, including OSA.
- Some children with severe craniofacial disorders will need long-term tracheostomy.
- Children likely to develop OSA should be monitored both clinically and with PSG to detect severity of OSA and to plan early investigation and intervention.
- Microtia is an important feature of many craniofacial disorders, particularly OAVS/hemifacial macrosomia and Treacher Collins syndrome
- Detailed imaging is essential for any nasal mass in the neonate prior to biopsy.
- Families of children with craniofacial disorders should be offered a consultation with a clinical geneticist.

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CHAPTER 20

BALANCE DISORDERS IN CHILDREN

Louisa Murdin and Gavin A.J. Morrison

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SEARCH STRATEGY

A number of search strategies were employed for this chapter. Using dizziness, vertigo, paediatric/pediatric/child and the major conditions as keywords, the following databases were consulted: Embase, Ovid Medline (R) and Journals @ Ovid full text subset.

INTRODUCTION

Young children do not usually complain of vertigo; history and diagnosis can be elusive. Owing to this, the pattern of symptoms in the very young has a wide differential diagnosis. Once middle ear disease and congenital or hereditary sensorineural conditions have been excluded, a large percentage will have dizziness associated with migraine. Posterior fossa neurological disease should be considered; in older children, adult causes of vertigo may be seen. Reassurance that the prognosis is favourable, and antihistamines such as cinnarizine or, if appropriate, antimigraine treatments are usually effective.

Estimates of prevalence of vestibular disorders in children suggest that the experience of vertigo is not especially rare. In one community-based study of children aged 1 to 15 years, 8% had experienced vertigo and in 23% of these it was severe enough that it interfered with activity.[1]

MATURATION OF THE VESTIBULAR SYSTEM

The otic capsule develops early in gestation between the fourth and twelfth weeks of intrauterine life. As the vestibular system is phylogenetically older than its auditory counterpart, each stage in development is in advance of the auditory system and therefore less vulnerable to environmental insult. The semicircular canals have formed from the utricular portion of the otic vesicle by the 30 mm stage, while the cochlear duct has two and a half coils by the 50 mm stage.[2] The vestibular nerve myelinates by 16 weeks *in utero*. By 24 weeks there is even a primitive vestibulo-ocular reflex present.

After birth, at 4 months of age, the baby can tilt its head to keep it vertical. It is the first sensory system to develop. Vestibular function is present at birth. Full-term babies demonstrate a 'doll's eye response'. When the baby is rotated, eye and head deviation is seen in the direction opposite to the direction of rotation. This is akin to the nystagmus seen in adults on rotation, but without the saccadic fast phases that have not yet matured at this age. Maturation of the vestibulospinal and vestibulo-ocular reflexes continues so that responses are maximal at 6–12 months of age.

Beyond this, responses decline, as part of normal motor development, to reach adult values around 10–14 years of age. Bithermal caloric responses can be made in 9-month-old babies if necessary, to measure the vestibulo-ocular reflex. Vestibular nystagmus in children, however, tends to be of a lower frequency and greater amplitude. Maximum slow-phase velocity readings are often similar to those in adults, but the normal ranges for the canal paresis and directional preponderance calculations are wider than those seen in adults.

Infantile reflex responses and motor milestones

The Moro response comprises a sudden bilateral extension of the upper limbs evoked by sudden jarring of the cot or dropping the head backwards by a few centimetres. This response is present in normal children at birth, and disappears by the sixth month. The secondary inherent responses are righting responses and protective reactions. From 4 months, the infant will tilt the head to maintain it vertical if the trunk is tilted laterally through 30° (head-righting reflex). The ages of sitting unsupported, crawling and walking bear some relation to vestibular function but also depend upon neurodevelopment. Vision also plays an important part in postural control.

ASSESSMENT OF THE DIZZY CHILD

Symptoms of vertigo in children

Childhood vertigo results from a mismatch of information from the three different sensory systems: vestibular, visual and proprioceptive. Vertigo, however, is much more difficult to recognize in babies and children than in adults; younger children are not able to describe what they are experiencing and may present with other behavioural symptoms. Parents or carers may report seeing the child suddenly cry out and drop to the floor or cling to the legs of adults, pallor, sweating, vomiting, screaming, lying face down in the cot and showing reluctance to be moved.[3] Interestingly, children born with a congenital lack of normal vestibular function often have no balance disturbance at all although they may have mildly delayed motor milestones. Vision remains by far the most important sense for locomotor and balance acquisition.

It is helpful to direct the history taking with a number of principal and most likely diagnoses in mind. In the paediatric age group the principal conditions to consider are:

- benign paroxysmal vertigo of childhood
- migraine associated vertigo
- epilepsy
- central causes of ataxia and loss of balance
- vestibular neuronitis
- BPPV
- adult causes, e.g. Menière's disease.

A more complete list is given in **Box 20.1**.

The presentation of vertigo varies quite dramatically according to the age of the child. While it is possible for 2-year-olds to experience acute vertigo, young children cannot describe this and may even present with torticollis. If there is a delay in motor milestones, children may present with poor balance or falling; this can also be associated with simple conditions such as 'glue ear'. By 5 years of age, short-lived dizzy episodes can be described, the common cause being benign paroxysmal vertigo (BPV) of childhood. By the teenage years, migrainous vertigo, psychogenic vertigo and the adult vertiginous conditions are much more common.

BOX 20.1 Causes of childhood vestibular symptoms

Conditions with hearing loss	Conditions with normal hearing
OME	Motion sickness
Suppurative ear disease	BPV of childhood
Cholesteatoma with fistula	Basilar migraine
Temporal bone trauma	Seizure disorders
Barotraumatic perilymph fistula	BPPV
Menière's disease	Post-traumatic vertigo
Post-traumatic vertigo	Viral labyrinthitis or neuronitis
Enlarged vestibular aqueduct syndrome	Posterior fossa tumours
Other congenital temporal bone anomalies, e.g. CHARGE association	Cardiac causes: syncope and arrhythmias
Dehiscent superior semicircular canal syndrome	Acute poisoning
Drug-induced ototoxicity	Multiple sclerosis and Lyme disease
Congenital syphilis	CNS infections: Coxsackie A and B, echovirus encephalitis or HIV infection
Herpes zoster oticus	Meningitis: viral or bacterial
Congenital CMV infection	Chiari malformations
Metabolic conditions: Hurler syndrome, hypothyroidism	Hereditary cerebellar ataxias
Usher syndrome	Acute cerebellar ataxia

History taking

It is helpful to establish the nature of the dizziness, whether it is true vertigo, loss of balance or a light-headed faint feeling. The duration and periodicity can be useful guides, as may precipitating factors such as head or neck injury.

The presence of frequent headaches and whether they occur with vertigo or at other times is important. Associated vomiting may be an indication of an acute true vertigo, a migraine phenomenon or the presence of raised intracranial pressure. Associated hearing loss, otalgia or otorrhoea are important. It can be helpful to categorize childhood dizziness into conditions with normal hearing and those with associated deafness (see **Box 20.1**).

A neurological history is essential, specifically if there is anything to suggest temporal lobe seizures, visual or olfactory hallucinations. The developmental history, in terms of the motor milestones, or any regression should be ascertained. The presence of a recent pyrexial illness, the drug history both current, past and, indeed, *in utero* can be important, and various sorts of poisoning should be borne in mind in the child who becomes acutely ill with vertigo and may have ingested something while playing. In the ill, febrile child a range of serious infectious diseases should be considered. In a slightly older child, it may

be more apparent that the problem is one of fainting or hyperventilation, or that there are cyanotic attacks or palpitations in association with the dizziness.

The family history is relevant, especially one of maternal migraine, familial sensorineural deafness or neurofibromatosis type 2 (NF2).

Examination of the dizzy child

Much of the paediatric vestibular examination can be carried out through observation of the child from the waiting area, moving into the consulting room. The routine paediatric examination will include otoscopy. Facial nerve function, tongue movements and the gag reflex should be checked. It is important to look at eye movements. This should include a cover test to check for strabismus and latent nystagmus, and, in particular, to search for nystagmus both with and without visual fixation. Head-shaking nystagmus can also be used effectively in children to unmask a unilateral peripheral vestibular deficit. Smooth pursuit, saccades and optokinetic nystagmus can be elicited using visually attractive targets. The standard clinical balance assessments can be undertaken, such as Romberg's test, Untenberger's stepping test and the tandem heel–toe gait. It is helpful to make this fun for the child by introducing games, such as hopping and kicking a football, to assess balance function better. Head thrust testing can be helpful in diagnosing a unilateral peripheral deficit. Dix-Hallpike positional testing should also be undertaken (see Chapter 62, Evaluation of balance).

Neurological examination of the limbs should be undertaken to seek signs of spasticity, myopathy, sensory neuropathy or other causes of gait abnormality. Rotation testing is easily carried out on an office chair with the child on the parent's lap. Cerebellar ataxia is seen on heel-toe tandem gait with dysmetria, but with normal ranges of lower limb motion and unchanged gait velocity and stride length. Characteristically, gait is wide based with dys-synergia and dysrhythmia, and balance is poor.[4]

Investigations

Audiometry is mandatory. This should comprise a pure tone audiogram or alternative threshold assessment, such as visual reinforcement audiometry, if the child's age or development demands it. Objective testing with brainstem auditory-evoked responses may be indicated. Tympanometry should also be undertaken.

Routine blood tests to exclude anaemia or other blood dyscrasias are worthwhile. The white cell count and inflammatory markers (erythrocyte sedimentation rate – ESR- or C-reactive protein) may give a clue to an infective condition which could have led, for example, to cerebellar encephalitis. Serology should exclude congenital syphilis, and human immunodeficiency virus (HIV) disease might be considered.

Depending on the history and the level of concern, other investigations might include formal rotation testing, bithermal caloric testing with videonystagmography or electronystagmography recordings. Vestibular evoked myogenic potentials (VEMPs) have also been successfully recorded in children and babies.[5] Ocular VEMPs are also suitable to record in children over 2.[6]

Imaging the head and inner ears with magnetic resonance (MR) scanning and/or a high-resolution computed tomography (CT) scan for the bony labyrinth and temporal bones will be indicated in selected children. For example, reassurance that there is no space-occupying lesion in a child with headaches and vertebrobasilar migraine, or defining an enlarged vestibular aqueduct in association with sensorineural hearing loss could be important. If the diagnosis is clinically obvious, however, it is unnecessary to undertake brain scanning.

Where the history indicates it, referral for an electroencephalogram (EEG) and neurological opinion or for an electrocardiogram and cardiac review may have to be considered.

CAUSES OF CHILDHOOD VESTIBULAR SYMPTOMS

The diagnostic flow chart (**Figure 20.1**) summarizes the diagnostic process in managing the child with vestibular symptoms. The conditions are discussed in more detail below.

VESTIBULAR CONDITIONS WITH NORMAL HEARING

Box 20.1 lists most of the conditions that can present with childhood vertigo, dizziness or balance problems. Although the differential diagnosis is extensive, in over half the children who present to the paediatric otolaryngologist with dizziness or disequilibrium, the cause will be otitis media with effusion (OME or 'glue ear'), BPV of childhood or dizziness as a migraine phenomenon.[7] A further study indicates the most common causes for vertigo in children to be migraine in 31% and BPV of childhood in 25%.[8] Other less frequent causes include trauma with deafness, delayed endolymphatic hydrops, benign positional vertigo and, more rarely, cerebellopontine angle tumour, seizures, acute vestibular neuritis or juvenile rheumatoid arthritis. In this study, abnormalities were found in hearing in 24%, in positional testing in 5%, in 11% of bithermal caloric tests, and in 65% on rotational chair testing.[8]

Motion sickness

Motion sickness is caused by a conflict in the kinetic input, often with an excessive vestibular stimulation. Girls are more commonly affected than boys and it tends to settle at puberty. Interestingly, motion sickness can occur in people with blindness, but can also be caused by purely visual stimulation. There is an association with migraine and vestibular dysfunction.[9]

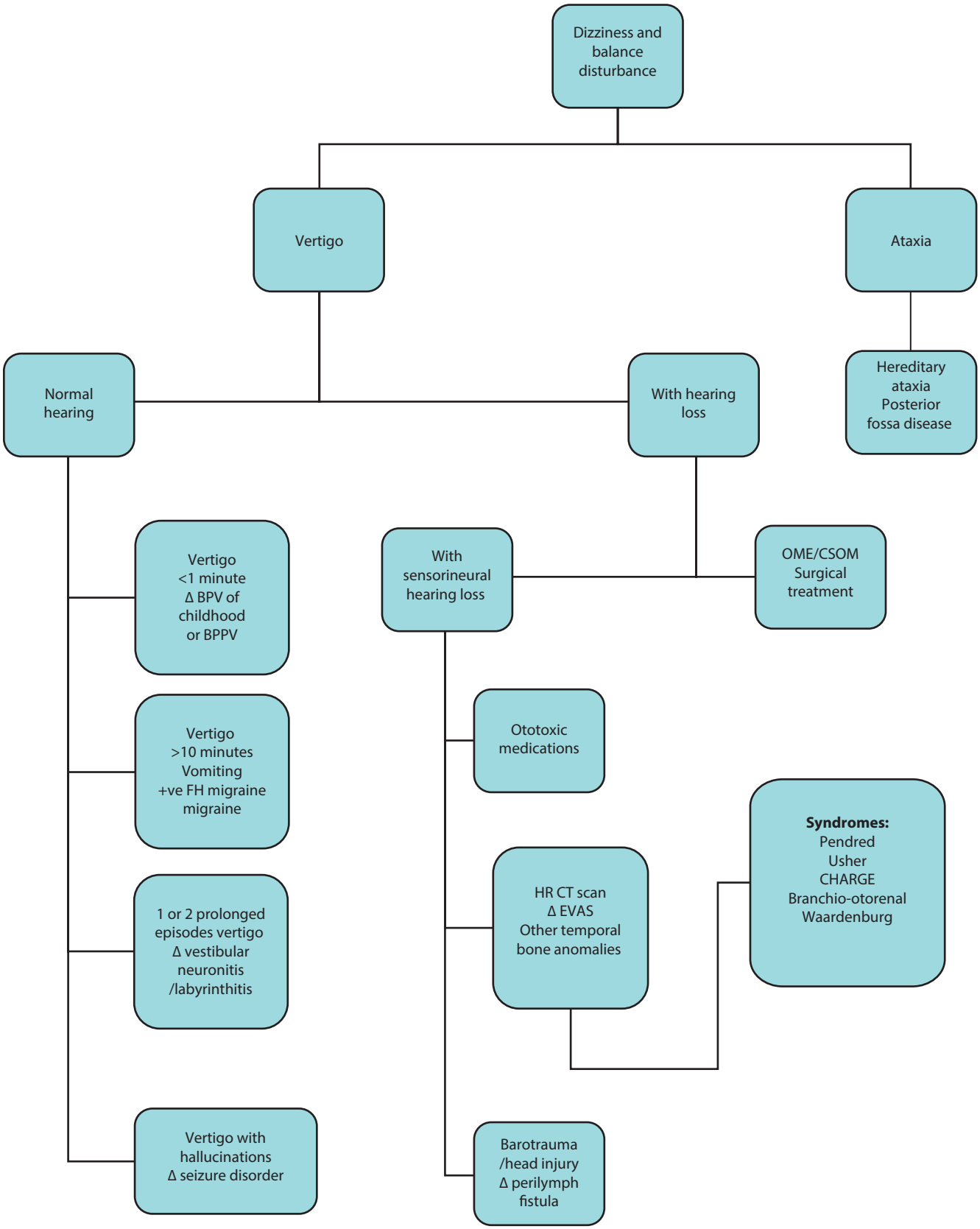


Figure 20.1 Diagnostic flow chart for balance disturbances in children.

Benign paroxysmal vertigo of childhood

Benign paroxysmal vertigo of childhood is not a positional vertigo and is quite different from benign paroxysmal positional vertigo (BPPV). It occurs in children who are aged 4 or over, with no obvious precipitating factors. It is a very frequent cause of paediatric dizziness, being found in 35% of children with dizziness in one series.[10] The child experiences short-lived acute vertigo for 30–60 seconds. He or she may fall or hold onto something suddenly and cry, becoming anxious, pale and sweaty and frequently vomiting. There is then a rapid return to complete normality a few minutes later. Nystagmus is present during attacks which are recurrent and variable in frequency, but interictal neurological examination is normal.[11] Attacks can continue in older children but usually subside. Half of these children go on to develop migraine in adolescence. Most have a family history of migraine. Caloric abnormalities are quite likely to be present if recordings are made.

A related condition that presents in a slightly younger age group is benign paroxysmal torticollis. Torticollis is not related to vertigo, however. There is a suggestion that creatinine kinase levels are likely to be elevated in BPV of childhood, and measurement may be helpful in diagnosis.[12]

BPV has a very favourable long-term prognosis. In one study the condition had resolved by about 8 years of age, and on long-term follow-up 21% had developed migraine but none had any vertigo or balance disorder.[13] The differential diagnosis of a child or baby presenting with marked torticollis is large and varied and should include congenital torticollis, paroxysmal torticollis with vertigo, mastoiditis or neck abscess, skull base tumour and neurological extrapyramidal spasmodic torticollis or psychogenic spasmodic torticollis.

Migraine and vertigo

Migraine is a common multifactorial neurovascular disorder. Several mutations have been discovered for rare forms of migraine; one within *CACNA1A* on chromosome 19p13, a gene encoding for part of a neuronal calcium channel codes mutations for familial hemiplegic migraine type 1 and also in episodic ataxia type 2. Genome-wide association studies have been carried out for more common forms of migraine; however, these are genetically complex with many different contributory genetic variations.

The prevalence of migraine in children and adolescents over periods between 6 months and lifetime is 7.7% (95% CI 7.6–7.8). Migraine presents differently in children when compared to adults, with shorter headaches that are more likely to be bilateral.[11] Vestibular migraine is a subtype of migraine present in the Appendix of the most recent International Classification of Headache Disorders (ICHD) classification. Basilar-type migraine is diagnosed when other symptoms attributable to the posterior circulation are present and ascribed to aura phenomena. Migraine is identified as a primary diagnosis in around 25% of those children presenting with dizziness. Headache need not be present with all attacks of dizziness. In one study into migraine-related vestibulopathy, common vestibular test abnormalities included a directional preponderance on rotational testing, unilateral reduced caloric responsiveness and vestibular system dysfunction patterns on posturography.

If dietary triggers are identifiable, they can be avoided, but there is no evidence that cutting out foods such as cheese or chocolate reduces frequency of migraine, and restricting children's diets is unlikely to be productive; in some cases it has been the cause of malnutrition.[14] Fasting, by contrast, is a proven trigger so encouraging regular meals and snacks is prudent. If attacks are occurring more than once a week, prophylaxis and prescribing prophylactic antimigraine medications may be considered as an option. Symptomatic relief has also been provided using anti-motion sickness medications, vestibular rehabilitation and pharmacotherapy directed at any associated anxiety.[15] Associated headache can be treated acutely in children over 12 years old with triptans.[16] Some more recent evidence supports selected use in 6–12-year-olds.[14] Electroencephalographic changes are seen during and shortly after a migraine attack but fully resolve in time. EEG, carried out within 4 hours of the onset of symptoms (initial stage), shows a diffuse polymorphic subdelta–delta activity. EEG, performed 16 hours after the onset of symptoms, shows delta–theta activity predominant over the occipital regions.[17]

Videonystagmography studies in children with migraine, undertaken during spontaneous nystagmus, gaze nystagmus, eye-tracking test, optokinetic and positional nystagmus and caloric testing, showed that all patients with migraine had abnormalities in vestibular testing. Analysis of the results suggested a mainly central localization of vestibular dysfunction.[18]

Vestibular neuronitis

Vestibular neuronitis presents as it does in adults, with acute severe vertigo, nausea and often vomiting but normal hearing. Characteristic nystagmus is seen during acute attacks. Children recover more quickly from this disorder than do adults. Half of patients can have repeated episodes, although within a few years attacks become progressively less severe and are likely to cease. Treatment is with vestibular rehabilitation, which in children takes the form of games (ball games, picking up of toys on the floor, and rapid head movements with gaze fixation on fixed targets).[19]

Benign paroxysmal positional vertigo

While in adults BPPV most commonly occurs spontaneously or follows vestibular neuronitis sometime previously, in children it is rare and BPPV is more likely to occur following a head injury or marked whiplash injury. The characteristic nystagmus seen in adults has been documented in children.[20] It has a good prognosis. In one study on children's temporal bones in Boston, 12.7% of paediatric temporal bones examined had basophilic deposits, many of them with otoconial crystals in the semicircular canals. That is much higher than the incidence in children

who had any vertigo symptoms, a temporal bone finding mirrored for this condition in adults.[21] The exact pathogenesis of BPPV is not yet fully explained.

Post-traumatic vertigo

The complaint of dizziness and headaches quite commonly follows head injury in children. The relatively high incidence of these persistent post-traumatic symptoms in children and adolescents presents a diagnostic challenge. It is often difficult to differentiate between functional complaints generated by psychological trauma or compensation seeking and an organic aetiology.[22]

Seizure disorders

Recurrent unprovoked seizures due to epilepsy are either generalized or localized (focal). Seizure disorders can give rise to vertigo in two ways: first, in the aura of a generalized (grand mal) fit; second, as vertiginous epilepsy or vestibulogenic epilepsy. In temporal lobe or occipital lobe focal epilepsy there may be transient loss of consciousness or amnesia; the child may describe the sensation of movement and may have visual or auditory hallucinations. There may be motor or emotional components. Convulsive epilepsies are generally unmistakable. Absence epilepsies may be recognized by the provocation of an episode during hyperventilation. Complex partial seizures in children can be difficult to distinguish from behavioural problems, shuddering attacks, paroxysmal vertigo, breath-holding spells, cardiogenic syncope, night terrors and movement disorders, such as paroxysmal kinesigenic choreoathetosis.[23]

A comparison of the elementary visual hallucinations of 50 patients with migraine and 20 patients with occipital epileptic seizures showed that in epileptic seizures they are predominantly multicoloured with circular or spherical patterns as opposed to the predominantly black and white linear patterns of migraine. This simple clinical symptom of elementary visual hallucinations may be helpful in distinguishing between classic or basilar migraine and visual partial epileptic seizures, particularly in children.[24] Referral to paediatric neurology is required if vertiginous epilepsy is suspected.

Psychogenic (conversion reaction) vertigo

Psychogenic dizziness should be diagnosed after excluding organic pathology. Sometimes seen in adolescents, more commonly girls, it is said to occur in children who are put under parental pressure to achieve. Recurrent fainting episodes can be seen in adolescence, when the possibility of a cardiac cause should be considered. In surdocardiac syndrome, for example, there is a prolonged QT interval, fainting and a risk of sudden death.

Psychogenic vertigo as a conversion reaction can be seen alone or in association with psychogenic hearing loss. The discrepancy between symptoms and findings in audiometric or vestibular tests is the essential clue for reaching a diagnosis of a conversion disorder. Referral to a psychiatrist may be necessary because many patients have problems in school or at home, and recovery may take a long time.[25]

Miscellaneous conditions with normal hearing

There are a number of other conditions which can mimic vertigo that are worth considering in the infant or child with unusual symptoms. These include toddler breath-holding attacks.

POISONING

In a child with dizziness, nausea and vertigo, among other symptoms, acute poisoning from plants, chemicals or drugs should be considered.

ATAXIA

Ataxia and other primarily neurological, hereditary or degenerative conditions are rare. They are discussed in a separate section (see 'Persistent imbalance and ataxia: central disorders' below).

VESTIBULAR CONDITIONS WITH ASSOCIATED HEARING LOSS

Otitis media with effusion and chronic suppurative ear disease

Glue ear may be detected in the clumsy child with poor balance who is more prone to falls than his siblings or peers. Chronic suppurative otitis media (CSOM) with perforation and infections can influence general balance and CSOM with cholesteatoma carries the possibility of a fistula to the lateral semicircular canal or oval window accounting for dizziness or leading to suppurative labyrinthitis.

Menière's disease

Childhood or adolescent onset of Menière's disease, although uncommon, is well documented. In one series, sporadic Menière's disease began in childhood in less than 3%, although, in the less common familial Menière's disease in more than 9%, no doubt due to the phenomenon of anticipation. The clinical features are indistinguishable from those in adults; however, early onset tends to be associated with more aggressive disease and a likelihood of relatively early bilateral involvement.[26, 27]

Associated temporal bone abnormalities and hearing loss

In numerous conditions and syndromes there is sensorineural hearing loss with temporal bone anomalies. In only a small number of these conditions are children likely

to present with vestibular symptoms. Vision remains the most important special sense in acquiring balance. Children with bilateral vestibular impairment may be delayed somewhat in motor development but rarely present with vertigo. Not surprisingly, in conditions where there is abnormal or absent vestibular development and visual loss, children are more likely to present with balance disturbances. Children with Usher syndrome have vestibular hypofunction and may therefore have balance difficulties when vision is also impaired.

In CHARGE association (see Chapter 23, Neonatal nasal obstruction) there are frequently abnormalities, for example a primitive otocyst, and such children may have absent semicircular canals and an aberrant facial nerve. A study from Ann Arbor researched patients with severe sensorineural hearing loss and agenesis of the semicircular canals. Most had CHARGE syndrome, some were non-syndromic, and one had Noonan syndrome. They did not present with vertigo.[27] X-linked hereditary deafness is another example in which vestibular symptoms are uncommon despite vestibular hypofunction. Vestibular hypofunction may be present in Down syndrome.

Enlarged vestibular aqueduct syndrome

Enlarged vestibular aqueduct syndrome is a rare congenital anomaly; vestibular disturbance is uncommon but is seen in 4% of children. Fluctuant and progressive sensorineural hearing loss is the norm and is bilateral in 87% of cases. A vestibular aqueduct radiologically wider than 1.5 mm at its midpoint or wider than 2 mm at the operculum is defined as enlarged.[28] Most patients maintain stable hearing in at least one ear over a 4-year period. It can occur in non-syndromic conditions but is also found in 50% of patients with Waardenburg syndrome (types 1 and 2), in which there may be significant widening of the vestibular aqueduct at its midpoint together with other temporal bone anomalies.[29] These children tend to have profound or severe hearing loss. Up to 30% of children with Waardenburg syndrome have vestibular impairment and some experience episodic vertigo. Enlarged vestibular aqueduct syndrome is also seen in Pendred and the branchio-otorenal syndromes, often with an associated Mondini deformity in the former. Patients with enlarged vestibular aqueduct syndrome may show an autosomal recessive inheritance (see Chapter 10, Management of the hearing impaired child).[30]

Avoidance of head injuries is recommended but this may not influence the progression of deafness. The pathogenesis is ill-understood. Surgery to occlude the vestibular aqueduct remains controversial. Conservative management is advised.

The patent cochlear aqueduct

The cochlear aqueduct at its narrowest portion is 0.14 mm wide. It widens as it opens into the posterior fossa with a very variable size at this point. The late Peter Phelps, who had extensive experience in the histopathology of temporal bones, stated that his study of 1400 normal temporal bones and 29 with dysmorphic labyrinths had failed to show a dilated cochlear aqueduct, and he believed that sensorineural deafness attributed to this, in fact, related to defects at the fundus of the internal auditory canal (Phelps P, personal communication).

Dehiscent superior semicircular canal syndrome

Dehiscent superior semicircular canal syndrome has been described. It can be demonstrated on high-resolution CT scanning. Typically, vertigo or oscillopsia is evoked by loud noises or by stimuli that result in changes in middle ear or intracranial pressure. The Tullio phenomenon (vertigo in response to sound) and Hennebert's sign (a positive fistula test with a normal middle ear) may therefore be found. Three-quarters of patients also experience chronic dysequilibrium – often the most debilitating symptom.[31] The condition may also present with an apparent conductive hearing loss. Evoked eye movements, by Valsalva manoeuvre against pinched nostrils, tragal compression or sounds over 100 dB at 500–2000 Hz, produce vertical and torsional components. Surgical repair via the middle fossa approach is successful. Radiologically, dehiscence in children is fairly common (27.3% of children under 2), but the degree to which this correlates with clinical symptoms is unclear.[32]

Perilymph fistulae

Perilymph fistulae in children are usually seen in association with temporal bone anomalies and pre-existing severe or total hearing loss in the affected ear. They may present with recurrent meningitis or with cerebrospinal fluid (CSF) behind the tympanic membrane. Perilymph fistulae can arise directly from blunt trauma to the middle ear or from temporal bone fractures and, iatrogenically, after ear surgery for CSOM or poststapedotomy. More rarely, marked barotrauma may lead to a fistula from the round or oval windows. In all these situations surgical exploration to seal the fistula is indicated. Spontaneous perilymph fistula in the normal temporal bone, however, is probably almost never seen.

In the late 1980s there was a vogue for clinically diagnosing a spontaneous perilymph fistula in children and adults who presented with symptoms of hearing loss, vertigo and sometimes tinnitus. These patients were subjected to surgical exploration of the middle ear with sealing of the apparent fistula. In general, the hearing outcomes from surgery did not seem to correlate with the finding of a fistula and, indeed, it can be very difficult at surgery to be sure if there is any real perilymph leak. To address some of the problems inherent in the diagnosis and treatment of perilymph fistulae, records of patients operated on at the House Ear Clinic over 12 years were reviewed retrospectively. Eighty-six patients were surgically explored for fistulae during this period. Thirty-five (40.7%) fistulae were found and 51 ears were patched whether fistulae were found or not. Of the 80 patients who were seen

for follow-up, 35 (43.8%) were subjectively better and 45 (56.2%) were the same. Although the number of fistulae found and the number of patients improved were similar, the composition of the two groups was different. On the basis of audiometric results, improvement in hearing happened in only 18.7% of patients. None of the demographic factors or diagnostic tests was predictive of either the presence of a fistula or the therapeutic outcome.[33]

Another retrospective study by Bluestone et al. on patients undergoing perilymph fistula repair compared pre- and post-operative hearing levels, vertiginous complaints and recurrences. In 92% of ears there was either stabilized or improved hearing and in 3% a decrease was noticed, but this was much later and believed not to be related. The results were similar, however, in the non-perilymph fistula ears, of which 95% had stabilized or improved hearing and, again, 3% had a much delayed decrease. Of the children with vertiginous complaints before surgery, 91% were improved or stable. Only one child felt somewhat worse, but, as with hearing loss, this was later than 6 months after the surgery.[34]

In yet another series of cases operated on for suspected perilymph fistula, ears with a surgically demonstrated fistula and sensorineural hearing loss had either flat or downward-sloping audiograms. At follow-up, vestibular symptoms were found to be eliminated or improved in 96% of cases with surgically demonstrated fistulae and in 68% of cases in which no fistula was detected at tympanotomy, but hearing improved significantly in only one ear (4%) of the former group and in five ears (20%) of the latter group.[35]

To conclude, perilymph fistulae can be a cause of hearing loss, vertigo or tinnitus and these symptoms may be fluctuant and possibly progressive. There is currently no good diagnostic test for a small fistula. In the paediatric population the most frequent cause is a congenital fistula. Severe or profound hearing loss is, in this instance, always associated with temporal bone anomalies when a perilymph/CSF leak may be present with fluid behind the tympanic membrane. A defect in the stapes and continuity with the fundus of the internal auditory meatus is one such example. This can be found with a true Mondini deformity, in which case some hearing from the basal turn of the cochlea is possible. These cases will require surgical exploration and closure of the leak, not to improve or restore hearing but in an attempt to prevent subsequent meningitis.

Traumatic perilymph fistulae with normal temporal bone anatomy are rare. They are described following head injury and penetrating injury to the middle ear with or without temporal bone fracture, but diagnosis is difficult.[36] A persistent perilymph fistula following ear surgery requires re-exploration. Severe barotrauma can also produce a fistula from the round window or oval window. Clinical suspicion will lead to the decision to explore the ear surgically. More obvious bony erosion with fistula is not infrequently encountered in the presence of cholesteatoma. Exploration and closure of the fistula is indicated. Spontaneous perilymph fistula, in the absence of head injury, direct injury or barotrauma can be virtually discounted.

Drug-induced vertigo or imbalance

Ototoxic medications, in particular aminoglycosides, can cause marked vestibular dysfunction with acute vertigo at the time of administration or poor balance, ataxia and motor delay. These drugs might have been administered systemically prenatally to the mother or in postnatal life, but occasionally topically in the presence of a chronic perforation or grommets. Fortunately, however, hearing loss from systemic aminoglycosides given to an infant is unusual. Some degree of vestibular loss may be more common and underdiagnosed. Streptomycin and gentamicin are more selectively vestibulotoxic. In one study, children who had previously been treated with streptomycin commonly showed delay in walking.[37]

Antimalarials such as mefloquine, which is cleared only slowly from the body, can cause dizziness or hearing loss. Platinum-based cytotoxic agents can cause ototoxicity, usually high-tone hearing loss and tinnitus rather than dizziness.

Miscellaneous conditions with hearing loss

Infectious aetiologies such as congenital cytomegalovirus (CMV) infection can include sensorineural hearing loss with vestibular symptoms and metabolic diseases such as Hurler syndrome can be seen with a retrocochlear type of hearing loss and vestibular impairment. Herpes zoster oticus can occur in children.

PERSISTENT IMBALANCE AND ATAXIA: CENTRAL DISORDERS

Toddlers may present with imbalance and a delay in motor development, or with a subsequent deterioration in vestibular function. They can have falls, fear of the dark, abnormal gait and vomiting. Primary developmental delay with motor delay and poor balance suggests a congenital or early acquired neurodevelopmental disorder, while regression of balance and locomotor function that was previously acquired indicates the need to exclude a space-occupying lesion such as meningioma or medulloblastoma. A family history of NF2 would raise suspicion. Any severe illness or even major surgery in a baby or smaller child will not infrequently lead to temporary loss of previously acquired skills such as the ability to walk.

ATAXIA

Ataxia is a common mode of presentation of cerebellar, posterior column and vestibular disease in children. The aetiology of ataxia covers a broad range, from infections to rare hereditary metabolic diseases. The importance of recognizing potentially reversible conditions such as vitamin E deficiency and Refsum's disease has been stressed.[38]

Hereditary cerebellar ataxia

Hereditary cerebellar ataxia presents with a slowly progressive ataxia although a posterior fossa tumour must be excluded by imaging. Cerebellar disorders display a variety of inherited and sporadic causes. Advances in genetics have led to the successful classification of over 20 forms of autosomal dominant and recessive cerebellar ataxia with variable phenotypes and have shed light on the underlying pathophysiology of many of these disorders. Successful disease-modifying or symptomatic treatments for these conditions, thus far, have remained limited.[39]

Refsum's disease

Refsum's disease is a disorder of lipid metabolism with pigmentary retinopathy, demyelinating neuropathy, ataxia and hearing loss. There is progressive difficulty in walking which develops between the ages of 4 and 7 years. In some cases the site of the hearing abnormality in Refsum's disease may be 'post-outer hair cells'.[40]

Charcot–Marie–Tooth disease

The most common hereditary degenerative condition is Charcot–Marie–Tooth disease. Inheritance is autosomal dominant. Perineal muscle atrophy is usual, congenital sensorineural deafness is present in some cases and there can be vestibular weakness. These children develop spinal scolioses and pes cavus.[41]

Acute cerebellar ataxia

Acute cerebellar ataxia occurs, usually in the first 3 years of life, in a child who was previously normal. It follows a viral febrile illness a few weeks beforehand. There is sudden ataxia, and the condition may take a number of months to resolve or leave some permanent sequelae. Neuroimaging should be considered in all children with new-onset ataxia.[42]

Chiari malformations

Type 1 Chiari malformation is characterized by cerebellar tonsil herniation through the foramen magnum. Children most commonly present with bilateral vocal cord paralysis and associated upper airway obstruction but they can also present with positional vertigo and a central type of nystagmus. The condition can be more severe and associated with syringomyelia, in which case there can be neurological improvement after foramen magnum surgical decompression. Type 1 may present to otolaryngologists.

Type 2 Chiari malformation is the same as type 1, except that in addition there is a non-communicating hydrocephalus and lumbosacral spina bifida. Type 3 can have any of these features but with cervical or occipital bifida. Children with types 2 and 3 have widespread neurological abnormalities and are unlikely to attend ENT clinics.

Miscellaneous conditions

Demyelination can present in post-pubertal children, in which case vertigo is quite commonly seen. NF2 with posterior fossa meningiomas or vestibular schwannoma are occasionally seen in children, and other intracranial posterior fossa lesions such as medulloblastoma may present with ataxia and vomiting.

Infectious causes

Infectious causes include Lyme disease. Viral infections include meningitis, Coxsackie A and B and echovirus; they can involve the central nervous system with vertigo, nystagmus and cerebellar signs. HIV infection is another possible cause. Bacterial infections include primary meningitis, labyrinthitis as a complication of meningitis or CSOM and tertiary or congenital syphilis.

TREATMENTS FOR VERTIGO

Medical treatments

The causative condition should be treated directly if possible. The mainstay of treatment, however, is usually an explanation to the parents and the child and reassurance.

Symptomatically, vestibular sedatives can be helpful. Antihistamines such as cyclizine or cinnarizine can be taken for more prolonged attacks. Hyoscine patches have been advocated and domperidone is helpful for associated sickness. Use should be limited to acute attacks rather than for chronic symptoms.

Dopamine antagonists including phenothiazines such as prochlorperazine are effective vestibular suppressants. However, there is a greater risk of extrapyramidal side effects when using phenothiazines, especially in children. They should be avoided in babies under 10 kg. Should these medications lead to extrapyramidal effects such as oculogyric crisis, it can be treated acutely with the antagonist, procyclidine, by injection.

HT3 antagonists such as ondansetron are powerful antiemetics, which block serotonin binding at vagal afferents in the gut and in the regions of the central nervous system (CNS) involved in emesis, including the chemoreceptor trigger zone and the nucleus tractus solitarii. Although principally used in post-operative nausea and vomiting or with cytotoxic drug therapy, they may have a role in the vertiginous child, especially if vomiting.

Attacks of vestibular migraine can be treated with domperidone, cinnarizine or cyclizine for nausea, vomiting or dizziness. Serotonin 5-HT1B/1D receptor agonists such as sumatriptan may be useful in management of headaches. Rizatriptan is reported to be more effective than other drugs of this class and other simple analgesics.[14] Preventative measures, if necessary, would be those currently recognized – pizotifen or propanolol – and if those fail, a neurologist might prescribe the full range of antimigraine medications available to use in adults.[16] Topiramate and flunairizine have randomized double-blind placebo-controlled trials in

children that support their use, and there are open label studies in favour of sodium valproate.[14]

Menière's disease may be treated with betahistine, a low-salt diet and possibly diuretics or intermittently by dehydration therapy such as glycerol taken orally. Surgery may occasionally be indicated in severe variants of the disease.

The seizure disorders are usually well controlled with anticonvulsants under the paediatric neurologist's guidance.

Physical treatments for vertigo

If there is benign positional vertigo, the Epley manoeuvre (see Chapter 64, Benign paroxysmal positional vertigo) can be employed successfully. Other vestibular rehabilitation exercises for children who have suffered unilateral labyrinthine damage might be helpful in achieving full central compensation and in speeding recovery.

Surgery for vertigo

Surgery relates to that indicated for specific underlying conditions. Unilateral glue ear with poor balance can be corrected by insertion of grommets (preferably bilaterally, the contralateral ear as a prophylactic measure).

If there is a perilymph fistula from barotrauma, middle ear or mastoid disease, or following surgery, that should be explored and closed. Likewise, suppurative ear disease and congenital or acquired cholesteatoma will require tympanomastoid surgery.

A perilymph/CSF fistula from congenital temporal bone anomalies should be closed surgically in an attempt to prevent future meningitis.

Childhood-onset Menière's disease tends to run an aggressive course with debilitating bilateral disease later in life. Destructive surgery is not advised at an early stage although endolymphatic sac decompression and drainage may have a role.

BEST CLINICAL PRACTICE

- ✓ A full history, neurotological examination and audiometry are required in assessing any child with vertigo.
- ✓ Middle ear disease and congenital sensorineural conditions with vestibular deficits should be excluded.
- ✓ Posterior fossa disease must be excluded where there is ataxia.
- ✓ In some cases, a full blood count, inflammatory markers, glucose, creatinine kinase, thyroid function and special serological tests are helpful.
- ✓ High-resolution CT scanning of the temporal bones and an MR brain scan are often indicated for dizziness with hearing loss.
- ✓ An MR brain scan is indicated for ataxic conditions.
- ✓ Special vestibular tests including bithermal caloric stimulation and rotational chair testing can be helpful in reaching a diagnosis and planning treatment.
- ✓ Referral to a paediatric neurologist is recommended if the diagnosis of a seizure disorder or basilar-type migraine is considered probable.
- ✓ Treatment should comprise explanation and reassurance about the condition and symptomatic medical treatment for the vertigo.
- ✓ Surgical treatment is recommended for significant balance disturbance with OME and for CSOM with cholesteatoma as well as for a persistent perilymph fistula from other causes.

FUTURE RESEARCH

- ➤ The value of bithermal caloric tests, videonystagmography and rotational chair tests has not been demonstrated in the varied paediatric population with vertigo.
- ➤ The benefit of vestibular rehabilitation exercises overencouraging straightforward everyday activities has not been studied in children's treatment regimens.
- ➤ Motion sickness has been subject to observational studies and effects of drug treatments but further research into aetiology and other treatments could be profitable.
- ➤ The role and efficacy (if any) of HT3 antagonists such as ondansetron in the management of childhood vertigo has not been studied.

KEY POINTS

- Vertigo results from a mismatch of three different sensory inputs for balance, i.e. vision, proprioception and the vestibular system.
- Presentation of balance disorders in children differs from that in adults; very young children cannot complain of vertigo.
- Fifty percent of cases of childhood dizziness and imbalance are caused by one of the three most common causes: BPV of childhood, migraine or OME.
- Neurological disease is a rare cause of vertigo in children but must be recognized.
- Adult causes of vertigo are seen in older children/adolescents.
- The mainstay of treatment is reassurance; symptomatic control with medication such as cinnarizine or antimigraine treatments is usually effective.

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CHAPTER 21

FACIAL PARALYSIS IN CHILDREN

S. Musheer Hussain

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Embryology and applied anatomy of the facial nerve 231
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Acquired facial paralysis 234
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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the following keywords: facial paralysis, otitis media, congenital facial paralysis, ear trauma, facial nerve injury, granulomatosis with polyangitis, Bell's palsy and parotid surgery. The focus was restricted to neonates and children.

INTRODUCTION

Bell's palsy remains the most common aetiology for facial paralysis in children[1] although it is much less common than in adults. In their study of 170 patients aged from birth to 18 years May et al.[2] found the following aetiology for facial paralysis: Bell's 42%, trauma 21%, infections 13%, congenital 8% and neoplasm 2%.

Bell's palsy in children is considered to have a better prognosis than in adults, regardless of treatment.

EMBRYOLOGY AND APPLIED ANATOMY OF THE FACIAL NERVE

Knowledge of the embryology and developmental anatomy of the facial nerve allows for a clear understanding of the various anomalies and clinical presentations of disorders of the facial nerve.

By the third week of embryonic development the facioacoustic crest is visible on the dorsolateral aspect of the hindbrain just cranial to the otic placode. The otic placode forms the otocyst, giving rise to the membranous labyrinth in the fourth week and the facial nerve becomes distinct. The geniculate ganglion has formed by the fifth week (Figure 21.1). The facial nerve divides into its main trunk, descending into the second branchial arch and the chorda tympani, which being the pretrematic branch curves cranially into the first branchial arch (Figure 21.1).

A pretrematic branch of a cranial nerve is one that supplies the arch preceding the arch to which the cranial nerve belongs. The chorda tympani and the main trunk of the facial nerve are equal in size at this stage. Malformations of the branchial arches are associated with anomalies of the chorda tympani such as elongation of the posterior canaliculus, reduplication and low position of the nerve.[3–4]

The facial nucleus is formed by neuroblasts in the pons, with the sixth nerve nucleus in close proximity. As the brain develops and the pons expands, the sixth nucleus ascends so that the facial nerve fibres have to whirl round the sixth nucleus forming an internal genu. Clinically, therefore,

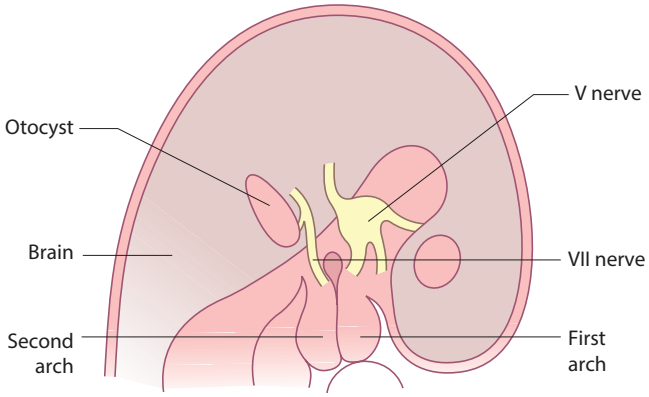


Figure 21.1 Line diagram of the fetal head at 5 weeks, showing the facial nerve.

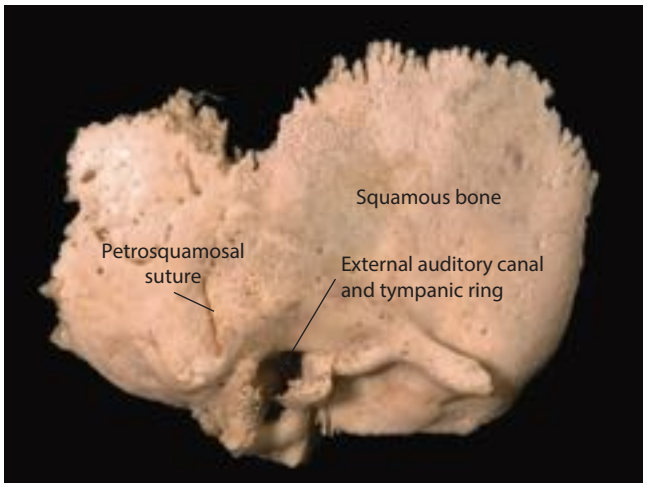


Figure 21.2 Neonatal temporal bone.

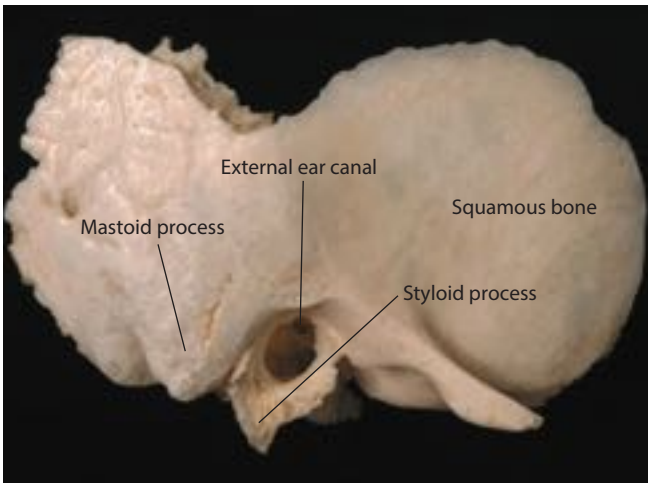


Figure 21.3 Temporal bone of a 1-year-old child.

an inflammatory or vascular event in this part of the brain will necessarily involve both these nerves. In developmental anomalies such as Moebius syndrome there is agenesis of the facial nucleus and among other defects there is also agenesis of the sixth nucleus.[5]

The geniculate ganglion has a separate origin from the facial nerve.[6] It is well defined by the seventh week and gives rise to the sensory roots that form the nervus intermedius. As the main facial trunk descends down the second branchial arch there is caudal movement of the first arch due to rapid expansion, producing the horizontal segment and the first and second genu of the vertical nerve with the greater superficial petrosal nerve acting as an anchor. Proctor and Nager's seminal papers[7, 8] describe the many variations encountered in the vertical segment of the facial nerve including a bipartite nerve, an anteriorly displaced nerve or one with a posterior hump. Failure to appreciate an anomaly of the facial nerve during surgery can have serious consequences.[9–12] Conditions related to malformations of the first or second arch such as Treacher Collins and Goldenhar syndromes will usually mean that the facial nerve is abnormal too.

At birth the normal temporal bone has no mastoid process and an incomplete tympanic ring. The 'U-shaped' tympanic ring has nodular prominences on each arm, which separate the annulus from the future external canal and the foramen of Huschke (**Figure 21.2**). By the end of the first postnatal year these processes fuse, lengthening the canal (**Figure 21.3**). The foramen usually closes some time later. The chorda tympani and the facial nerve may exit through the stylomastoid foramen in the newborn. The mastoid process and external auditory canal are undeveloped so the nerve is very superficial.

The mastoid process develops and reaches adult proportions by the age of 12 years. In neonates and small children the second genu of the facial nerve is more acute and courses more laterally. The most common variation in the course of the facial nerve canal involves the tympanic segment; the bony wall may be dehiscent in 35–55% of the population particularly above the oval window.[7, 8, 13, 14] Acute suppurative otitis media in neonates and children may therefore present with facial paralysis from neuropraxia or bacterial infiltration of the nerve sheath within an enclosed middle ear. Dehiscence of this segment of the facial nerve may be associated with a persistent stapedial artery in its course from the tympanic cavity to the middle cranial fossa where this becomes the middle meningeal artery.[15, 16] The foramen spinosum is absent on the side of the persistent stapedial artery on plain X-ray or CT.

On leaving the stylomastoid foramen the facial nerve enters the parotid gland in a more anterior location than in the adult, as the parotid gland is smaller and more anteriorly placed.[17] The nerve divides into two main divisions and these give rise to branches that supply the face and the upper neck muscles. The lower division of the facial nerve in young children runs very superficially over the angle of the mandible and can be damaged by a skin incision during surgery.

Surgery of the parotid region in children requires an understanding of the differences between adult and child facial nerve topography (**Table 21.1**).

DIAGNOSIS

This is discussed in general terms in this section. Individual conditions are covered under separate headings.

History taking and examination

A detailed clinical assessment is important in the diagnosis of facial paralysis. There may be good muscle tone so that it is difficult to identify the paralysis until the child cries. Associated symptoms that teenagers with facial paralysis may volunteer will not be available in a younger child. Careful attention to the mother's story will be rewarding.

Examination should include careful assessment of each branch of the facial nerve and whether the paralysis is complete or incomplete. The forehead wrinkles are absent and the eyebrow droops in lower motor neuron paralysis. The lower lid tends to fall away from the globe with tears

TABLE 21.1 Differences in the anatomical relationship of the facial nerve in adults and children

Feature	Child	Adult
Mastoid process and tympanic ring	Absent mastoid process and incomplete tympanic ring. The chorda tympani may exit through the stylomastoid foramen with the main trunk in the neonate	Mastoid process present and tympanic ring is complete by adolescence. The chorda tympani exits separately and proximal to the stylomastoid foramen
Second genu of facial nerve	Second genu of the facial nerve is more acute and more lateral	Second genu of the facial nerve is less acute and more medial
Position of nerve trunk	Nerve trunk on exit from the stylomastoid foramen is more anterior and lateral	Parotid is more posteriorly placed and the nerve trunk is less anterior and deeper
Position of nerve	Nerve very superficial over the angle of the mandible	Nerve less superficial over the angle of the mandible

collecting in the eye and spilling onto the face. The cheek may sag and the nasolabial fold may be lost. Speech may change as plosives are distorted with air blowing out on the paralysed side. The appearance of the non-paralysed side of the face is also characteristic as unbalanced muscle action accentuates the difference. The House Brackmann grading is limited but has the advantage of being widely known and may be used in children. Otoscopy is usually possible in even the smallest baby and signs of inflammation should be looked for in the head and neck. Other anomalies of the head and neck and the cranial nerves are noted.

Investigations

IMAGING

Imaging of the facial nerve in children may be useful in delineating the site of neural injury. Indications include persistent paralysis, trauma and suspected nerve involvement in systemic diseases.

MRI is the only modality that demonstrates the facial nerve comprehensively from the pons to the parotid gland; with gadolinium enhancement it is capable of showing inflammatory changes. CT makes it possible to see bony detail and is ideal when facial nerve involvement is in the middle ear cleft.

ELECTROPHYSIOLOGICAL TESTS

Electrophysiological tests allow objective assessment of function. Eavey et al.[18] found that 95% of children can be successfully tested with electroneurography (ENoG). Waveform amplitude and morphology were consistent with adult values except in infants. The most clinically helpful use of this test is to objectively assess facial nerve function, once spontaneous motion is lost in acquired paralysis or if it had never been seen in congenital paralysis. The authors maintain that the test is not an absolute predictor for return of function but that the added data when used with clinical information make assessment of prognosis more rational.

Glassock and Shambaugh[19] recommend a muscle biopsy in neonates with facial paralysis when the electromyography is silent. If muscle is found early, reanimation is advisable.

CONGENITAL FACIAL PARALYSIS

Syndromic and non-syndromic forms of developmental facial paralysis occur. These may be unilateral or bilateral, complete or incomplete. Prognosis is poor.[20, 21] Craniofacial anomalies associated with the first and second arch derivatives are common in this form of facial paralysis.

Nerve exploration is unrewarding in this situation.[22] Reanimation may be considered. There is a wide range of procedures for reanimation; the most desired neural tissue source for rejuvenation of the paralysed face is direct reanastomosis or interpositional grafting. Carr et al.[23] reviewed 186 children with congenital facial paralysis (60% male and 85% with bilateral paralysis) and found 29 in whom reanimation was performed (24 females and 5 males). All 5 males and 9 females had unilateral isolated facial nerve paralysis. Fourteen females had bilateral paralysis; only half of these were isolated. Other involved cranial nerves included abducens, hypoglossal, oculomotor and trochlear. The cranial nerve least likely to be involved was the accessory nerve, suggesting that this may be a reliable donor for reanimation procedures. As previously stated, early reanimation is advised by Glassock and Shambaugh[19] if muscle is found on biopsy in neonates with facial paralysis when electromyography is silent.

Moebius syndrome

Moebius syndrome is a rare cause of facial paralysis in neonates. It is characterized by the absence or underdevelopment of the sixth and seventh cranial nerves. It may be unilateral or bilateral. Agenesis of the facial nucleus is suspected, hence the sixth nerve involvement. Other cranial nerves may also be involved. Autism and mental retardation may be seen in a third of these patients.[5]

Goldenhar syndrome

Goldenhar syndrome (oculo-auriculo-vertebral dysplasia) is a wide spectrum of congenital anomalies that involves structures arising from the first and second branchial arches.[24] Involvement of the internal auditory meatus and the eighth nerve has been reported[25] as well as progressive hearing loss.[26]

Asymmetric crying facies

Congenital asymmetric crying facies is an uncommon condition caused by congenital hypoplasia or agenesis of the depressor anguli oris muscle on one side of the mouth. Although the functional deficit is small, the anomaly may be associated with cardiovascular, head and neck, musculoskeletal, respiratory, gastrointestinal, central nervous system or genitourinary anomalies in 45% of cases.[27]

CHARGE syndrome

The acronym CHARGE is used to describe specific congenital birth defects in children: **c**olobomata, **h**eart defect, **a**tresia of the choanae, **r**etarded development, **g**enital hypoplasia, and **e**ar anomalies and hearing loss. Facial nerve dysfunction has been noted in 38% of patients,[28] and an aberrant course may interfere with cochlear implantation.[29] Many children with the CHARGE association also have feeding and swallowing difficulties, and facial paralysis and pharyngeal in-coordination may be important diagnostic indicators of CHARGE association.[30]

Familial facial paralysis

Familial congenital facial paralysis has been reported in three male members from three generations in a family.[31] The paralysis becomes more pronounced with every successive generation.

Widening of the facial canal

Widening of the facial canal has been reported as a cause of multiple ipsilateral facial palsy in a child of 13 months.[32] The child had recurrent fever and facial palsy and the facial nerve appeared thickening in the widened canal, said to be the result of pressure from inflammation and oedema.



Figure 21.4 (a) Facial paralysis in a neonate caused by acute otitis media; **(b)** the state of the eardrum.

ACQUIRED FACIAL PARALYSIS

Infections

ACUTE OTITIS MEDIA

Acute otitis media in neonates and children gives rise to facial paralysis (**Figure 21.4a**). This is usually incomplete but the paralysis may progress in the first 2–3 days of onset. There is suppuration in the middle ear behind an intact tympanic membrane, which may appear red and bulging (**Figure 21.4b**). The child may be toxic but is typically not unwell. In some cases where antibiotics have been given, the signs of acute inflammation may not be pronounced.

The underlying pathology may be an erosion of the bony Fallopian canal or congenital dehiscence and nerve inflammation. Spread along structures such as the stapedial tendon, chorda tympani or posterior tympanic artery has been suggested. Moreano et al.[14] studied 1000 temporal bones and noted at least one facial canal dehiscence in 56% of temporal bones with the most common site of dehiscence being the oval window area. They introduced the concept of micro-dehiscence of the facial canal and found this in one third of the temporal bones. The most common pathogen in middle ear cleft infections in children is pneumococcus[33] (80%). A wide myringotomy and systemic antibiotics is the initial treatment. If mastoiditis is suspected, a CT scan and a cortical mastoidectomy may be needed. There is usually full recovery of facial nerve function.

CHRONIC OTITIS MEDIA

Facial paralysis in chronic otitis media is very uncommon. Sheehy et al.[34] report 11 cases of facial paralysis out of 1024 patients with chronic middle ear disease and cholesteatoma. Complications of chronic middle disease including facial paralysis are more common in the developing world.[35]

LYME DISEASE

This multisystem disease is caused by the tick-borne spirochaete *Borrelia burgdorferi*.[36] The incubation period is

1–4 weeks before a skin lesion appears. Ipsilateral or bilateral facial paralysis may appear weeks or months later in 11% of cases.[37] A report from Connecticut, an endemic area, describes Lyme disease as the cause of over 50% of facial paralysis in children.[38] Serological tests with ELISA (enzyme-linked immunosorbent assay) to detect IgG and IgM antibodies are used for diagnosis. Doxycycline is the oral antibacterial of choice, while amoxicillin and cefuroxime are alternatives that may be preferred in young children. Tick avoidance has long been the mainstay for preventing Lyme disease.[39]

VIRAL INFECTIONS

Recrudescence of *Herpes zoster* virus in the geniculate ganglion leads to the classical syndrome of Ramsay Hunt. The disease is uncommon in children. Hato et al.[40] in a retrospective study of 52 children with Ramsay Hunt syndrome found that facial paralysis was milder, complete recovery of the function more likely (79%) and associated cranial neuropathies less common in children than in adults. The timing of vesicle appearance tended to be delayed in children. The disease was rare in preschool children but relatively more common in older children. Treatment with oral or intravenous acyclovir and prednisolone has been recommended.[41–43]

Facial paralysis has been noted in Epstein–Barr virus infection and this may be bilateral in 40% of cases.[44] Facial palsy is an early ENT manifestation of HIV infection and is seen in 11% of cases.[45]

TUBERCULOSIS

The presence of facial paralysis with purulent otorrhoea that does not respond to conventional antibiotics should alert the physician to the possibility of tuberculosis. Antituberculous chemotherapy early in the disease may reduce the need for radical surgery[46, 47] and complications of otitis media.[48] CT scan is reported to be of value in the diagnosis of facial paralysis due to tuberculosis.[49]

Traumatic

BLUNT TRAUMA

Perinatal trauma

Birth-related trauma is a known cause of facial paralysis. The incidence of facial palsy in the newborn is 1.8 in 1000, the majority associated with forceps delivery.[50] In their report on neonatal facial paralysis, Smith et al.[51] found 74 out of 95 cases to be secondary to trauma associated with pregnancy and delivery. The diploic bone of the infant mastoid process, the paper-thin bone covering the facial nerve and the very superficial position of the marginal mandibular branch over the mandible all add to the problem. The pressure of the mother's sacrum on the infant facial nerve may also contribute.

In differentiating between congenital and perinatally acquired facial paralysis, the history and physical examination usually suffice. A history of forceps delivery, a baby weighing over 3.5 kg, a primipara mother, prolonged labour and the absence of associated craniofacial anomalies point to perinatal trauma as the cause. The presence of bruising of the side of the face and the mastoid region are suggestive of birth trauma, as are other complications associated with birth.

Electrophysiological tests may be used to aid diagnosis; voluntary action potentials on electromyography (EMG) indicate muscle innervation. EMG performed after 10 days of paralysis will show fibrillation or polyphasic potential in traumatic cases and absent electrical activity in congenital facial paralysis.[52] A CT scan may show a concealed fracture of the temporal bone.

Temporal bone fracture

An injury to the skull may cause temporal bone fracture. The fracture may be longitudinal or transverse or a combination of both. Classically, longitudinal fractures cause conductive hearing loss whereas transverse fractures usually cause irreversible sensorineural deafness. A third of fractures are transverse and these have associated facial paralysis in 50% of cases. Longitudinal fractures are more common and, although the incidence of facial paralysis is less (20%), longitudinal fractures cause more facial paralysis than transverse fractures. As discussed under embryology, the greater superficial petrosal nerve in the region of the geniculate ganglion tethers the facial nerve. In head injury the sudden deceleration creates a shearing force on the facial nerve leading to damage. Lee et al.[53] reviewed 72 children with temporal bone fractures ranging from 6 months to 14 years of age, with a bimodal distribution with peaks at 3 years and 12 years of age. The most common causes of fractures were motor vehicle accidents (47%), falls (40%), biking accidents (8%) and blows to the head (7%). Common presenting signs and symptoms[53] include hearing loss (82%), haemotympanum (81%), loss of consciousness (63%), intracranial injuries (58%), bloody otorrhea (58%), extremity fractures (8%) and facial nerve weakness (3%). The diagnosis of temporal bone fractures is best made clinically and radiographically.

The early care of temporal bone fractures is directed towards the treatment of CSF otorrhoea and immediate-onset facial paralysis. The delayed care is primarily concerned with hearing rehabilitation.[55]

Another classification[56] of temporal bone fractures is based on otic capsule sparing (OCS) and otic capsule violating (OCV) fractures. The otic capsule is spared in 90% of fracture and is a predictor of the absence of sensorineural hearing loss. However, conductive hearing loss or facial paralysis cannot be predicted by the OCS/OCV classification.

Surgical exploration as an option remains controversial, with no randomized controlled study. It does seem reasonable, however, to explore when nerve entrapment is suspected or where the integrity of the nerve is compromised.

PENETRATING TRAUMA

Injury to the face may damage the facial nerve or one or more of its branches. This may be the result of falling

onto a sharp object or a dog bite. The wound needs to be explored and the degree of damage established. This will allow repair with the functioning distal branches in a clean wound. Local control of infection should precede repair in a contaminated wound.

IATROGENIC TRAUMA

Ear surgery

Mastoid surgery in children caries a higher risk of injury to the facial nerve, even in experienced hands. This is due to the absence of the mastoid process in small children and the superficial position of the facial nerve, which is at risk from a low incision. The operating space within the mastoid cleft is small and, if in addition an anomaly is encountered, the problems multiply. The injury may not be identified at the time of surgery and may become obvious when the patient is awake.[57] The commonest site of injury is the tympanic segment and the second genu of the nerve.[58, 59]

Anomalies of the facial nerve encountered in patients with congenital malformation of the middle ear include displacement of the nerve and lack of bony cover.[10] A low-lying tegmen in a sclerotic mastoid is particularly serious and requires skill to protect the nerve at the second genu when drilling in this restricted area. The presence of granulating disease in revision surgery may obscure the usual landmarks and put the nerve at risk. Erosion of the bone by cholesteatoma and its spread to the supra tubal recess[59] puts the geniculate ganglion and the first genu of the facial nerve at risk of injury during disease clearance in the anterior attic. In patients with atresia or stenosis of the external canal the facial nerve may be damaged in its vertical segment due to the vertical segment being relatively lateral to the tympanic annulus. Intra-operative monitoring is advisable.

Injury to the facial nerve and the chorda tympani are recognized complications of cochlear implantation surgery.[60–62]

Parotid surgery

The superficial course of the facial nerve in infants and the underdevelopment of surrounding structures mean that the standard techniques for identification of the facial nerve trunk in adults could jeopardize the nerve in children. An alternative technique for identifying the facial nerve has been proposed by Farrior et al.[17] Anatomic dissections demonstrate that the facial nerve trunk can be consistently found in a triangle formed by the sternocleidomastoid muscle, posterior belly of the digastric muscle and the cartilaginous ear canal. As in the adult, the nerve canal can be identified in the mastoid cavity and followed into the neck. Unlike in the adult, it is inadvisable to use retrograde dissection of the marginal mandibular branch to find the trunk. If surgery is considered for non-tuberculous mycobacteria (NTM) of the intraparotid and adjacent lymph nodes, very careful dissection is required to preserve the facial skin and the nerve (**Figure 21.5**) (see Chapter 37, Cervicofacial infections).

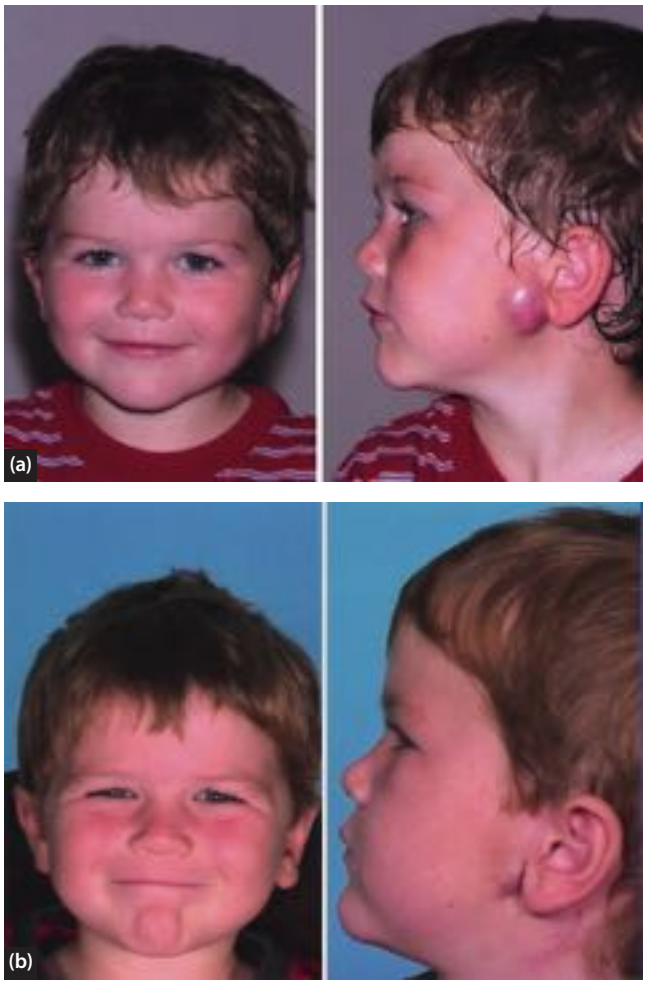


Figure 21.5 Non-tuberculous mycobacteria (NTM) of the parotid. (a) Presurgery; **(b)** 1 week after surgery with preservation of the facial nerve.

Branchial cleft sinus and fistula excision

The variable relationship of the branchial cleft sinus and fistula with the facial nerve makes the nerve vulnerable to injury during surgery. Very careful dissection with intra-operative monitoring is required. D'Souza et al.[63] reviewed the available English, French and German literature between 1923 and 2000 and found 158 cases with fistulae and sinuses. The fistulous tracts were more likely to lie deep to the facial nerve compared with sinus tracts. Lesions with openings in the external auditory meatus were associated with a tract superficial to the facial nerve. Younger children were more likely to have a deep tract with consequent increased risk of facial nerve damage. The fistula may be found anywhere along the anterior border of the sternocleidomastoid muscle.[64]

Solares et al.[65] in their report on ten patients with a mean age of 9 years found seven lesions medial to the

facial nerve, two lateral and one between branches of the facial nerve. (See also Chapter 41, Cysts and sinuses of the head and neck.)

Neoplasms

In children the two commonest causes of facial paralysis from malignancy are leukaemic infiltration of the temporal bone[66, 67] and rhabdomyosarcoma of the head and neck.[68–70] An intracranial tumour may present with facial palsy. Levy et al.[71] describe a case of acute mastoiditis and facial paralysis in a 5-year-old girl where the diagnosis of leukaemic infiltration of the middle ear cleft was made only after surgery and histological examination. Chemotherapy or combined chemo- and radiotherapy are the treatment of choice in known leukaemic patients without symptoms of superimposed infection of the ear or the mastoid process. Surgical management is restricted to cases in which tissue for histological diagnosis is required or drainage of acute infection is needed. A T-cell lymphoblastic lymphoma in the middle ear has been reported,[72] presenting with headaches, hearing loss and facial palsy in an 11-year-old that responded to intensive chemotherapy.

In the Durve et al.[68] series of 14 patients the median age at presentation of rhabdomyosarcoma was 4.5 years with a mean time of onset of symptoms to diagnosis of 21 weeks. Symptoms mimicked those of chronic otitis media, delaying diagnosis. The histological subtype was embryonal in 13 patients and alveolar in 1. All patients underwent multimodality treatment; the 5-year disease-free survival rate was 81%. Facial paralysis was the commonest regional post-treatment morbidity (8/14).

The presence of facial paralysis and lymphadenopathy or a mass with aural discharge, hearing loss and aural polyp should prompt urgent investigation and biopsy.

Benign neoplasm of the facial nerve is very rare in children. Facial paralysis from an intracranial neoplasm is uncommon.

IDIOPATHIC FACIAL PARALYSIS

Bell's palsy

Bell's palsy is the commonest cause of facial paralysis during childhood (42%).[2] It is an acute unilateral lower motor neuron facial paralysis diagnosed by exclusion. It is essential that otoscopy is normal, that there is no middle ear infection and that the hearing is not impaired. There is a body of opinion that attributes Bell's to infection by herpes virus due to a reactivation of latent *Herpes simplex* virus within the geniculate ganglion though the evidence for this is uncertain. There is a family history of Bell's palsy in a small number of patients and occasionally a viral prodrome.

Steroids are advocated in the acute stage for adults, with good evidence from a large randomized controlled trial to support this.[73] There is little evidence either way for children, however, and since the recovery rate is so high in children regardless of treatment (90%), it has been suggested that steroid administration is not required in children.[74]

Melkersson–Rosenthal syndrome

In Melkersson–Rosenthal syndrome, episodes of facial paralysis begin in early childhood or adolescence, predominately in the second decade of life. There is swelling of the lips, palatal mucosa and face, and the tongue is fissured.[75] The facial weakness usually takes a recurring course and is seen in 20% of cases. A conservative approach is usually recommended. A preliminary report suggesting facial nerve decompression for recurrent facial paralysis in Melkersson–Rosenthal syndrome has recently been further substantiated.[76–79]

Granulomatosis with polyangiitis

Granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis) is a systemic disease characterized by the classical triad of vasculitis, necrosis and granulomatous inflammation usually of the upper and lower respiratory tract and the kidneys. Primary otological presentation occurs in 20–25% of patients[80] and this includes facial paralysis.[81] A high index of suspicion, ESR, cANCA and histopathology help diagnose this condition. Combination therapy with corticosteroids and cyclophosphamide is given and cotrimoxazole may be used in the long term to reduce remissions.[82]

Hypertension

Hypertension is a rare cause of facial paralysis in children. Misdiagnosis may lead to serious consequences, as reported by Aynaci and Sen[83] in a case of a hypertensive child with facial paralysis. Bell's palsy was suspected and steroids were given, resulting in hypertensive pontine haemorrhage. Recurrent alternating facial paralyses have been reported in a child with hypertension. Antihypertensive treatment and control lead to cessation of further relapse.[84] A recent systematic review of facial palsy in patients with hypertension found 26 cases, of which 23 were children.[85] The palsy is usually unilateral and may recur in a quarter of cases.

CONCLUSION

The management of facial palsy in children includes treatment for eye exposure, smile asymmetry, drooling and lack of labial function and synkinesis. Free tissue transfer dynamic restoration is the preferred method for smile restoration[86] in this population. The outcomes are apparently better than in adults.

BEST CLINICAL PRACTICE

- ✓ MRI is the only imaging modality that demonstrates the facial nerve comprehensively from the pons to the parotid gland; with gadolinium enhancement it is capable of showing inflammatory changes.
- ✓ Electroneurography is a useful adjunct to clinical findings in predicting recovery from facial nerve palsy.
- ✓ In facial palsy secondary to acute otitis media optimum management is wide myringotomy and systemic antibiotics.
- ✓ Congenital and acquired facial paralysis in the neonate can be differentiated on the basis of examination supplemented as required by electrophysiologic investigations.
- ✓ It is standard practice to have facial nerve monitoring during parotid and tympanomastoid surgery in children with a high incidence of anatomical abnormalities of the facial nerve, e.g. Down syndrome, craniofacial anomalies.
- ✓ Retrograde dissection of the marginal mandibular branch of the facial nerve to find the trunk is particularly unreliable in children.

FUTURE RESEARCH

- ➤ The treatment for facial paralysis in children remains largely empirical; randomized controlled trials may help answer some of the questions. In view of the small number of cases and the generally good prognosis, multicentred trials with sufficiently large numbers of cases are required.
- ➤ The currently available monitoring systems for facial nerve function during surgery lack total reliability and are limited in scope.

KEY POINTS

- The commonest cause of facial paralysis in children is Bell's palsy.
- Knowledge of the embryology and developmental anatomy of the facial nerve allows for a clear understanding of the various anomalies and clinical presentations of disorders of the facial nerve.
- There are important anatomical differences between the topography of the facial nerve in adults and children.
- These differences and the confined surgical space can make tympanomastoid surgery and surgery of the parotid region in children particularly challenging. Surgeons operating in children must be extra vigilant to avoid iatrogenic facial palsy.
- The management of facial palsy in children includes treatment for eye exposure, smile asymmetry, drooling and lack of labial function and synkinesis.

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CHAPTER 22

EPISTAXIS

Mary-Louise Montague and Nicola E. Starritt

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SEARCH STRATEGY AND EVIDENCE BASE

A literature search was conducted for systematic reviews and randomized controlled trials and guidelines with the focus on management of childhood epistaxis. The core search terms used for Medline, Embase, and the Cochrane Database of Systematic Reviews were epistaxis and nosebleeds and were limited to children 0–18 years. The guidelines databases on www.evidence.nhs.uk, NICE Clinical Knowledge Summaries and BestBETS (Best Evidence Topics) were also searched.

INTRODUCTION

Epistaxis, from the Greek *epistazō*, 'to bleed at the nose', is a common problem in children although it is rarely severe and seldom requires hospital admission. Most episodes resolve spontaneously and can be managed at home or in the community setting. Recurrent frequent nosebleeds can, however, cause distress and anxiety to children and their parents and can be disruptive to sleep, school and sporting activities. It is this group of children who are most frequently referred for assessment and treatment to an otolaryngologist along with children presenting with severe acute bleeding and those children in whom an unusual aetiology is suspected.

EPIDEMIOLOGY

There is a bimodal distribution in the incidence of epistaxis, with peaks occurring in children under 10 years and adults over the age of 50 years. In childhood, as in adulthood, it is more common in males than females. It peaks between the ages of 3 and 8 years, and becomes much less common after puberty. Up to 60% of children will have had at least one nosebleed by the age of 10 years.[1] A cross-sectional study of 1218 children aged 11–14 years reported that 9% had frequent episodes of epistaxis.[2] The incidence of recurrent childhood epistaxis is highest in the winter months in northern climates. This mirrors the seasonal increase in viral upper respiratory tract infections and low relative indoor humidity associated with central heating use.[3] The presentation of epistaxis under the age of 2 years is rare and should prompt consideration of either an underlying coagulation disorder or non-accidental injury.[4, 5]

ANATOMY

In children anterior bleeds are by far the most common type, accounting for more than 90% of epistaxis.[6] They originate from Little's area on the anterior nasal septum either from Kiesselbach's plexus, a richly vascular arterial anastomosis just under the thin overlying nasal mucosa, or from retrocolumellar veins. Kiesselbach's plexus is formed by the anastomoses of the septal branches of five arteries: anterior and posterior ethmoidal arteries, sphenopalatine artery, greater palatine artery and the superior labial artery. Little's area therefore receives arterial supply from both the external and the internal carotid arteries.

PATHOGENESIS

The precursor to epistaxis in children is most commonly local dryness and crusting over Little's area (**Figure 22.1**).



Figure 22.1 Endoscopic view of nasal septal crusting seen in children with recurrent epistaxis.

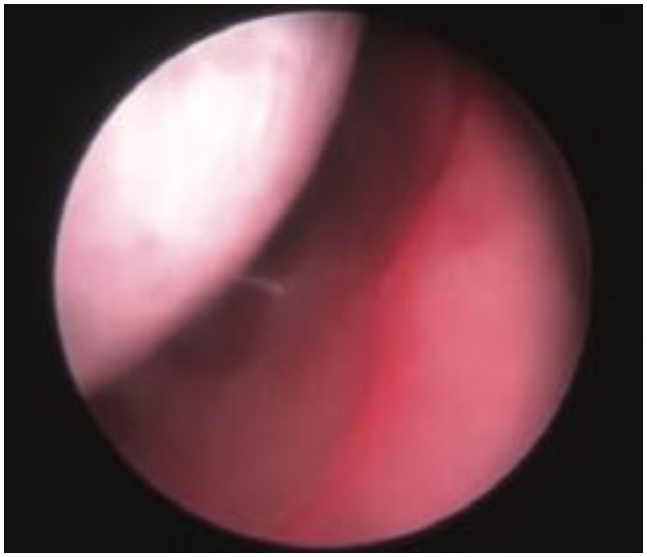


Figure 22.2 Endoscopic view of prominent septal vessels seen in children with recurrent epistaxis.

Most cases were historically labelled as idiopathic but recent evidence has led to the hypothesis that colonization of the nasal cavity by *Staphylococcus aureus* may contribute by causing low-grade inflammation.[7] Release of inflammatory mediators in response to more prolonged inflammation is thought to lead to neovascularization of the nasal septal mucosa. This may give rise to the frequently seen vessels on Little's area (Figure 22.2) which have been shown histologically to be thin-walled arterioles and capillaries with a surrounding inflammatory infiltrate.[8]

AETIOLOGY

Recurrent childhood epistaxis is usually attributed to digital trauma. Other common causes include allergic, viral and bacterial rhinitis and foreign bodies. Table 22.1 illustrates the range of local and systemic aetiologies one needs to consider in children.

TABLE 22.1 Local and systemic aetiologies of epistaxis in children

	Aetiology	Examples
LOCAL	Trauma	Nose picking or rubbing Blunt trauma or facial fractures Foreign body
	Inflammation	Upper respiratory infection Allergic rhinitis Vasculitis
	Anatomical	Septal deviation Septal perforation
	Neoplasms	*Benign* • Polyps • Pyogenic granuloma • Haemangioma • Juvenile nasopharyngeal angiofibroma • Inverted papilloma *Malignant* • Rhabdomyosarcoma • Nasopharyngeal carcinoma • Lymphoma
	Intranasal drugs	Steroids Decongestants Cocaine
SYSTEMIC	Bleeding disorders	*Coagulopathies* • von Willebrand Disease • Haemophilia *Platelet disorders* • Idiopathic thrombocytopenic purpura • Glanzmann thrombasthenia • Bernard–Soulier syndrome *Myeloproliferative disease* • Leukaemia • Thrombocytopenia
	Vascular abnormalities	Hereditary haemorrhagic telangiectasia (Rendu–Osler–Weber syndrome)
	Liver disease	
	Antiplatelet drugs	Aspirin Non-steroidal anti-inflammatory drugs
	Other drugs	Anticoagulants Valproic acid
	Parasitic infection	Dengue haemorrhagic fever

Tumours, such as juvenile nasopharyngeal angiofibroma (JNA) and rhabdomyosarcoma, are rare causes of epistaxis that can be both dramatic and difficult to control. JNA is a benign vascular hormonally sensitive tumour which arises in the lateral nasopharynx and occurs only in adolescent males. Although benign, it can cause severe problems through local invasion of adjacent structures.[9] Rhabdomyosarcoma is a rare malignant tumour occurring in young children presenting with severe intermittent epistaxis. It causes nasal obstruction with or without mucopurulent or bloody nasal discharge, often with signs of Eustachian tube dysfunction such as unilateral middle ear effusion. It can also present with pain and cranial

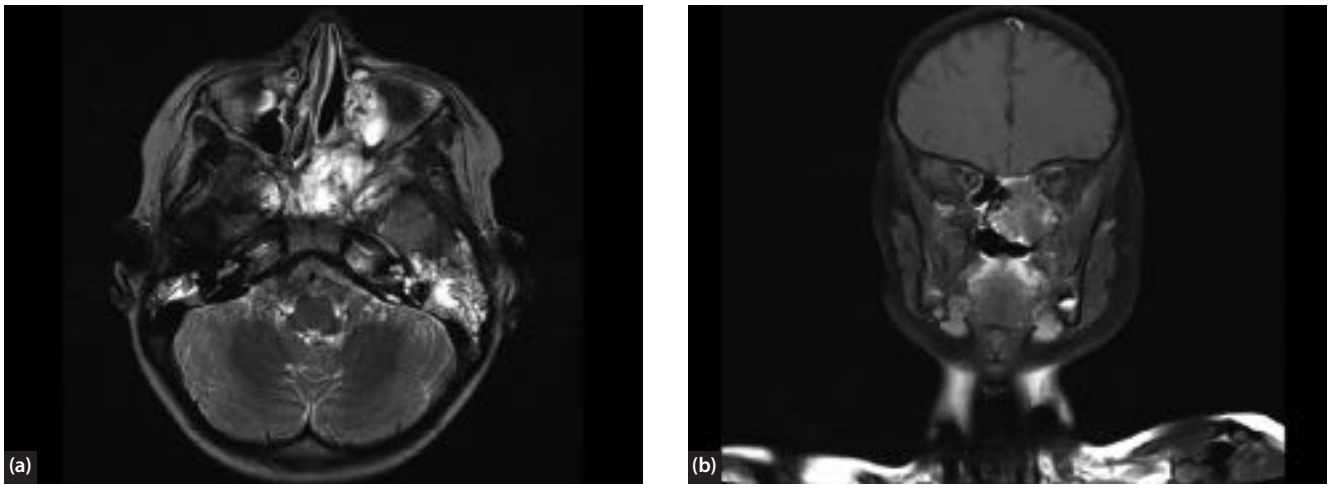


Figure 22.3 (a) Axial MRI and **(b)** coronal MRI showing nasopharyngeal rhabdomyosarcoma displacing the parapharyngeal fat space laterally. Opacification of right middle ear and mastoid air cells is also seen.

neuropathies (**Figure 22.3**). Nasopharyngeal carcinoma is fortunately rare in children. Approximately 50% present with epistaxis. It is often accompanied by a neck mass or neck pain.[10]

Primary and acquired coagulopathies are less common causes of nosebleeds in children but may present with recurrent or extremely refractory epistaxis. Von Willebrand disease (vWD) is the most commonly identified inherited coagulopathy with a prevalence of 5–10% in children with recurrent epistaxis when full coagulation studies including tests for vWD are performed.[2, 11] The haemophilias (factors VII, VIII, IX or XI deficiency) are much less common. Acquired coagulopathies are a rare cause of epistaxis in children in comparison to adults. They include various liver diseases with consequent depletion of clotting factors. An acquired form of vWD has also been described in children receiving valproic acid for epilepsy.[12]

Hereditary haemorrhagic telangiectasia (HHT) (Rendu–Osler–Weber syndrome), an autosomal dominant disorder of blood vessel walls characterized by extensive mucocutaneous telangiectasias, also causes recurrent epistaxis in more than 90% of those affected. Nosebleeds present at a mean age of 12 years and progressively worsen with age.[13] Gastrointestinal bleeding and pulmonary arteriovenous malformations can occasionally occur in childhood.

Nosebleeds often occur in children with thrombocytopenia either secondary to chemotherapy or a haematological disorder. It is rare, however, for haematological disorders to present with epistaxis as the primary symptom in children. Although rare, Glanzmann thrombasthenia, in which the platelet glycoprotein IIb/IIIa complex is either deficient or dysfunctional, is the commonest of the genetic platelet disorders.

ASSESSMENT

The assessment of children with recurrent epistaxis should begin with a careful history and physical examination.

History

The history should include the frequency, duration and laterality of the bleeding. Most epistaxis is bilateral, although one nostril may be more severely affected. One should also enquire about associated nasal and systemic symptoms and any precipitating factors including trauma. Past medical, family and drug histories and review of systems should also be covered.

UNILATERAL NASAL SYMPTOMS

When epistaxis is unilateral and accompanied by foul-smelling nasal discharge in a young child, a foreign body must be presumed present until proven otherwise. Having excluded a nasal foreign body, unilateral epistaxis should raise suspicion of a more serious local cause in the nose such as angiofibroma in a teenage boy or rhabdomyosarcoma in a younger child. Other 'red flag' symptoms include unilateral nasal obstruction, pain and facial swelling.

ALLERGIC RHINITIS

Nasal itch and blockage along with watery rhinorrhoea and sneezing are suggestive of allergic rhinitis.

SYSTEMIC SYMPTOMS

Bleeding from other anatomical sites or a history of easy bruising may indicate an underlying bleeding disorder. Symptoms of fever, arthralgia and weight loss may point to a diagnosis of vasculitis such as Granulomatosis with polyangiitis (Wegener's Granulomatosis), which may manifest in adolescence with epistaxis.

FAMILY HISTORY

A family history of bleeding disorders (e.g. HHT, haemophilia) should be enquired about. Often no definitive condition is identified but a positive family history of prolonged bleeding after surgery or dental extraction may warrant onward referral for haematological investigations.

DRUG HISTORY

Nosebleeds may be more frequent or more difficult to control in children taking certain medications, particularly anti-inflammatory agents (aspirin, ibuprofen) and anticoagulants (e.g. children with complex congenital heart disease or thromboembolic disease). Incorrect application of topical steroid sprays for rhinitis resulting in nasal septal trauma may be complicated by epistaxis.

ALLERGY HISTORY

A history of nut or soya allergy becomes pertinent if prescription of a topical antiseptic cream containing arachis (peanut) oil is being considered. There is a possible relationship between allergy to peanut and allergy to soya and it should not be used in children with soya allergy either.[14]

Clinical examination

Clinical examination focuses on the nose but complete ENT, head and neck and general examination of the child are also required. Younger children feel more secure sitting on a parent's knee. Initial assessment can be made with the child looking upwards by gently elevating the tip of the nose with a thumb allowing inspection of the nasal vestibule, anterior nasal septum, and anterior portion of the inferior turbinate illuminated by a headlight. Anterior rhinoscopy can also be performed with a well-illuminated otoscope with a large speculum.

The most common findings are crusting (two-thirds of children) and visible vessels (40–50% of children) on the anterior septum.[15, 16] Hallmarks of allergic rhinitis may be present including a transverse nasal skin crease ('the allergic salute'), and periorbital markers such as 'allergic shiners' and 'Dennie–Morgan lines'. Pale or bluish nasal mucosa and turbinates are also typical in allergic rhinitis. A nasal foreign body should be excluded. Distortion of nasal anatomy, an intranasal mass, polyps or cervical lymphadenopathy should raise the suspicion of tumour and also prompt a screen for cranial nerve palsies.

Rigid nasendoscopy is not tolerated well by children and, if a more posterior view of the nasal cavity and nasopharynx is required, a fine 2.2 mm flexible nasendoscope can be used after application of topical anaesthetic and vasoconstricting agent. Given the low yield of nasal endoscopy findings in younger children in particular, routine use is probably not warranted.[17] As the diagnosis of a nasal mass is most likely in adolescent males, nasal endoscopy should continue to be routine in their assessment.

Stigmata of systemic causes of bleeding, such as bruising, petechiae, cutaneous or mucocutaneous telangiectasia, should be looked for. Pallor may indicate significant blood loss or anaemia. The jaundiced child may have liver disease with a secondary coagulopathy.

In some circumstances, if an adequate view cannot be obtained or the child is not sufficiently cooperative, examination under general anaesthesia may be required.

INVESTIGATIONS

No consensus exists on the standard laboratory workup for paediatric epistaxis with clinician judgement largely guiding outpatient investigations. The routine use of blood testing is not advantageous from a healthcare cost perspective as there is such a low yield of significant findings.[17] Observational studies suggest that laboratory tests should be considered for children with prolonged (i.e. more than 30 minutes) or severe bleeding despite appropriate application of pressure, in children under the age of 2 years, and when the history and physical findings are suggestive of a bleeding disorder, malignancy, liver or other systemic disease.

Laboratory tests may include a full blood count (FBC) with differential white cell count and platelet count, and a coagulation screen comprising prothrombin time (PT) and activated partial thromboplastin time (APTT). The international normalized ratio (INR) should be checked if the child is receiving anticoagulants. Children found to have abnormalities should be referred for investigation to a paediatric haematologist. Further laboratory tests may include factor assays, von Willebrand factor and platelet function assays.

When tumour is suspected on the basis of history and examination including nasendoscopy, the diagnosis is usually confirmed by contrast-enhanced MRI. CT is often complementary. In the case of JNA a vascular-enhancing nasopharyngeal mass is seen (**Figure 22.4a,b**). Intranasal biopsy of JNA, which is a highly vascular tumour, should be avoided because of the risk of life-threatening bleeding. Selective digital subtraction angiography (DSA) elegantly demonstrates the vascular supply and allows pre-operative embolization of feeder vessels (**Figure 22.5a,b**). Post-embolization surgical resection is the treatment of choice.

When tumour is suspected, multidisciplinary review and discussion are essential between paediatric otolaryngologist, oncologist and radiologist to ensure that appropriate laboratory tests, imaging and histopathological specimens are obtained.

MANAGEMENT

Epistaxis in children can present either as an acute spontaneous episode or as chronic recurrent intermittent episodes of bleeding. The management of both scenarios is outlined.

Management of acute episodes of bleeding

It is unusual for acute epistaxis in children to need urgent transfer to hospital for resuscitation, most responding to direct pressure over the soft cartilaginous part of the nose (alae nasi) for 10–15 minutes (the Hippocratic method) (**Figure 22.6a,b**). Urgent transfer to hospital should be arranged if the bleeding is not responsive to pressure.

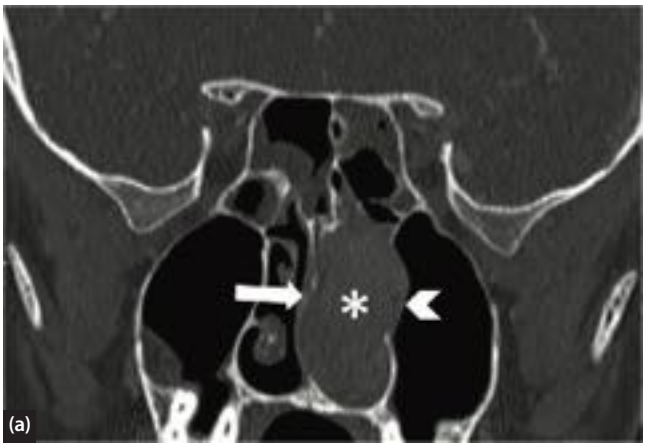
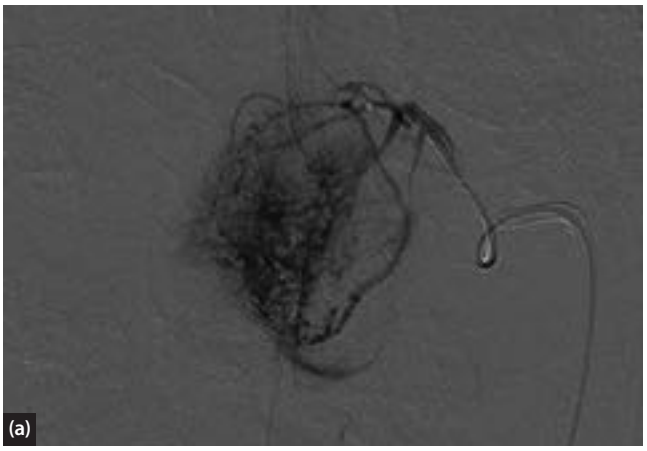




Figure 22.4 (a) Coronal CT. Juvenile nasopharyngeal angiofibroma (asterisk) extending into the choana with obstruction of the left nasopharynx, bowing of the vomer to the right (arrow) and bowing of the medial wall of the left maxillery antrum (arrowhead). **(b)** Axial CT. Bone windows showing erosion of the vomer (thick arrow), destruction of the pterygoid (arrowhead) and extension into the pterygopalatine fossa (thin arrow). Images courtesy of Dr S Goodwin, Consultant Paediatric Radiologist, Royal Hospital for Children, Glasgow.



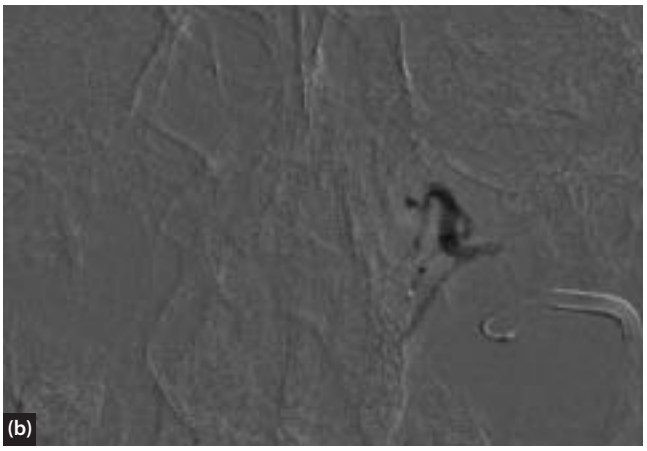


Figure 22.5 (a) Pre- and **(b)** post- embolization DSA demonstrating hypervascular tumour blush which has reduced significantly post-embolization of the distal left internal maxillary artery. Images courtesy of DR S Goodwin, Consultant Paediatric Radiologist, Royal Hospital for Children, Glasgow.

Initial assessment in the emergency department focuses on the child's airway, breathing and circulation. In a haemodynamically unstable child an effort should be made to assess blood loss, secure intravenous access and send venous blood for FBC, coagulation screen and blood group and save followed by fluid resuscitation. If the child is haemodynamically stable at presentation, laboratory blood tests do not need to be requested routinely. A careful history is taken from the parent or carer. The nasal cavity is examined, gently looking for a bleeding point anteriorly.

If the bleeding stops with first aid measures, a topical antiseptic cream (e.g. containing chlorhexidine hydrochloride 0.1% and neomycin sulfate 0.5%) can be applied and continued twice daily for up to 2 weeks to minimize crusting. If there is a history of peanut, neomycin or soya allergy, mupiricin ointment can be prescribed twice daily for 1 week as an alternative. Most acute nosebleeds in children respond to simple pressure and do not require referral to otolaryngology services.

Examination of the child who continues to bleed despite nasal pressure can be difficult. The oropharynx should be inspected for signs of posterior bleeding. Subsequent measures to control anterior epistaxis include nose blowing followed by gently placing cotton pledgets soaked in vasoconstrictor and local anaesthetic such as Co-phenylcaine





Figure 22.6 Demonstration of Hippocratic method to arrest bleeding with child seated, head tilted slightly forward and mouth open to prevent airway obstruction and swallowing of blood.

(lignocaine hydrochloride 5% with phenylephrine hydrochloride 0.5%) or Oxymetazoline in the anterior nasal cavity. This is followed by further digital pressure for 5 minutes. In small children the lowest concentration of phenylephrine should be used (e.g. phenylephrine 0.25% diluted with an equal volume of sterile saline to 0.125%).

If bleeding continues the next step is usually chemical cautery with silver nitrate if a bleeding point can be seen anteriorly and the child can tolerate the procedure. Using a stick, 75% silver nitrate is applied to the bleeding point for up to 5 seconds (Figure 22.7) until a grey-white eschar develops (Figure 22.8a,b). Excess chemical should be gently mopped away with a cotton bud, topical antiseptic applied to the site and a barrier lubricant such as soft white paraffin applied to the external skin to protect it. The topical antiseptic preparation is continued twice daily for up to 2 weeks. Local chemical cautery is sufficient to control most epistaxis in children.

The placement of an anterior nasal pack under direct vision may be required if the bleeding continues despite local cautery, in the presence of diffuse mucosal bleeding or in a child with a coagulopathy pending treatment directed at rectifying the bleeding problem. Absorbable packs such as gelatin sponge, alginate or oxidized cellulose are favoured in children over non-absorbable packs, having the obvious advantage of not requiring subsequent removal, which in itself may cause further trauma to the anterior nasal septum (Figure 22.9). If an anterior pack is placed, the child should be admitted to the ENT or children's ward for observation.

Examination under anaesthesia may be required if bleeding continues, or in a young child unable to tolerate



Figure 22.7 Stick with 75% silver nitrate used for chemical cautery.



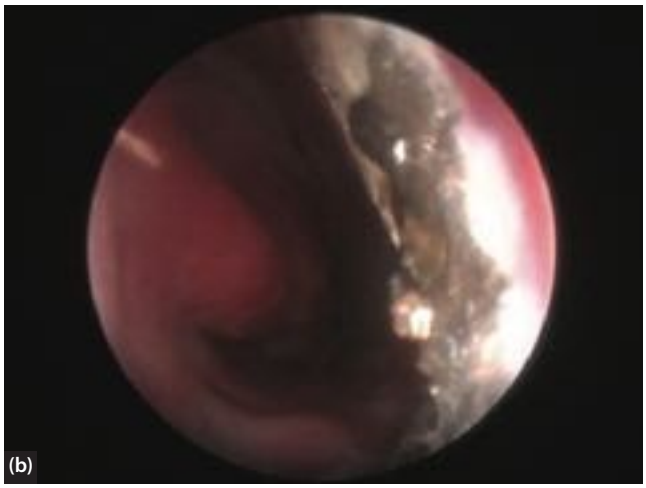


Figure 22.8 (a) Bleeding vessel on anterior septum before silver nitrate cautery and **(b)** the grey/white eschar that appears post-cautery.



Figure 22.9 Gelatin sponge pack (left) and Alginate packing material (right).

chemical cautery or placement of an anterior pack under local anaesthesia. Chemical cautery or electrocautery can be undertaken with or without placement of an anterior pack.

Posterior bleeding in children is much less common but often more severe and should be suspected if the bleeding is profuse and bilateral, there has been no response to pressure and a bleeding site cannot be identified anteriorly. Rarely, placement of a posterior nasal pack or balloon inflated under general anaesthesia is warranted. Thorough examination of the nasal cavity and nasopharynx can be performed simultaneously. The child should be cared for post-operatively on the critical care floor until the post-nasal pack or balloon is removed, again usually under general anaesthesia.

The child with persistent anterior or posterior epistaxis refractory to these measures in the absence of a correctable bleeding disorder may require consideration of either arterial ligation or radiological selective arterial embolization. These are rarely necessary in children.

Management of recurrent episodes of bleeding

In children referred to the otolaryngologist for outpatient assessment and treatment of recurrent epistaxis a detailed history and examination should seek to determine if there is an underlying cause. It should also be established what treatment, if any, has already been provided in the primary care setting.

If the child is not at high risk of having a serious underlying cause for their recurrent epistaxis, treatment options should be discussed and include:

- mucosal hydration with saline drops or spray
- emollients, e.g. petroleum jelly
- topical antiseptic cream
- chemical cautery
- chemical cautery combined with antiseptic cream
- bipolar electrocautery.

The optimal management of recurrent epistaxis in children remains controversial as the available studies are limited by small numbers and short-term follow-up.[18] Petroleum jelly application to the nose is often recommended but it has no benefit over simple observation.[16] Topical antiseptic cream was found to significantly increase the resolution of recurrent epistaxis at 8 weeks when compared to no treatment.[15] Long-term benefit of topical antiseptic, however, has not been established.[19] It is not known if chemical cautery is better than no treatment but, if a child has been referred to a paediatric otolaryngology clinic and has already had treatment with an antiseptic cream, most would consider it reasonable to offer chemical cautery if a prominent vessel is visible as it is of low morbidity. Antiseptic cream would appear to be as effective as silver nitrate cautery in reducing the number of nosebleeds in children with recurrent epistaxis.[20, 21] It is therefore not unreasonable for antiseptic cream to be considered the first-line treatment for recurrent epistaxis in children in primary care. Treatment with chemical cautery and antiseptic cream may be more effective than antiseptic cream alone at 4 weeks after completing treatment in children with visible anterior septal vessels.[22]

It is recommended to use 75% rather than 95% silver nitrate for chemical cautery in children as it appears to be more effective, has fewer side effects and is less painful.[23] Simultaneous bilateral cautery is not recommended owing to the possible increased risk of septal perforation.[24]

Bipolar electrocautery may be superior to chemical cautery under general anaesthesia in children who will not tolerate outpatient chemical cautery. It has been shown to afford a longer epistaxis-free period and a lower incidence of recurrence within 2 years of treatment. After 2 years however, the outcomes of the two treatments are no different.[25]

Less commonly performed interventions in children include laser treatment, submucosal resection or limited septoplasty in the presence of septal deviation or a prominent septal spur and endoscopic diathermy but these are usually only applicable on an individual case basis and are not supported by a strong evidence base.

The management of HHT in children requires special mention as it may require unique approaches to treatment. Chemical cautery should be avoided and, when packing is necessary, absorbable packing is preferred. Treatment with topical fibrin glue or matrix sealant (e.g. Floseal), the anti-fibrinolytic agent, tranexamic acid, KTP laser, cold ablation and the anti-neoplastic agent Bevacizumab (Avastin) have been employed in some centres with some success though there is very little in the published literature with respect to their use, safety and efficacy in children. Septal dermoplasty remains a viable surgical option but has the disadvantage of a donor split skin graft site and associated discomfort for the child.

Prevention of further bleeds

After treatment for either acute or recurrent epistaxis, parents/caregivers should be educated in the correct first-aid management in the event of recurrence. Children's fingernails should be kept trimmed and clean. Management of suspected or proven allergic rhinitis is

essential to help prevent recurrence. Parents should be instructed how to apply their child's nasal steroid spray correctly, with advice to hold the bottle in the opposite hand (right hand for left nostril and vice versa) to ensure the spray is directed to the lateral nasal wall and away from the septum.

BEST CLINICAL PRACTICE

- ✓ In acute epistaxis the child's airway, breathing and circulation should be assessed and, if compromised, urgent transfer arranged to the emergency department.
- ✓ Adolescent boys with unexplained recurrent epistaxis require urgent referral to otolaryngology as JNA is possible, although rare.
- ✓ In children younger than 2 years of age consider referral to a paediatrician with child protection expertise as epistaxis is unusual in this age group.
- ✓ Laboratory investigations are not usually required unless an underlying cause for recurrent epistaxis is suspected.
- ✓ Chemical cautery with 75% silver nitrate in the hands of an appropriately trained clinician is a well-tolerated procedure with little morbidity and should be offered when there is a visible blood vessel.
- ✓ Antiseptic cream containing peanut oil must not be prescribed for children with known or suspected peanut allergy.

FUTURE RESEARCH

- ➤ It is unlikely that the role of silver nitrate cautery will ever be validated by randomized controlled trials as this treatment is operator-dependent.
- ➤ There is a lack of study data assessing the effect of recurrent epistaxis on the quality of life of the child and parent or the effect of intervention on quality of life indices.
- ➤ High-quality studies, with longer follow-up, are needed to ascertain which, if any, of the current treatments for recurrent epistaxis in children are optimal in its long-term prevention.
- ➤ As most epistaxis in children is managed in the primary care setting, large population studies on the natural history of epistaxis and the effect of intervention will need to be primary-care centred.

KEY POINTS

- Epistaxis in children is extremely common and usually innocuous.
- The most common cause of epistaxis in the paediatric population is digital trauma.
- Most episodes of acute epistaxis in children respond to simple compression and do not require hospital referral.
- Routine laboratory blood testing is not indicated for most children with self-limiting epistaxis.
- Spontaneous resolution of benign simple recurrent epistaxis in children is to be expected.

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CHAPTER 23

NEONATAL NASAL OBSTRUCTION

Michelle Wyatt

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keys nasal obstruction and neonatal and focusing on a variety of keywords appropriate to the individual topics. These include all the subheadings listed below (e.g. choanal atresia, piriform aperture stenosis). The Cochrane Database of Systematic Reviews and the National Electronic Library for Health for ENT were also consulted.

INTRODUCTION

The aetiology of neonatal nasal obstruction is diverse. Neonates are generally obligate nasal breathers for the first few months of life, and therefore they can present as acute respiratory emergencies, classically with cyclical cyanosis, relieved by crying. The extent of their problems will alter related to the neonate's ability to breathe orally which is dependent on their maturity and neurological development. Thus, an oral airway is often sufficient to relieve the respiratory distress until definitive treatment can be undertaken.

Neonates with nasal obstruction may also present with stertor and feeding problems. Failure to thrive particularly raises level of concern. Examination is essential.

BOX 23.1 Congenital causes of nasal obstruction in neonates

Anatomical/ skeletal anomalies	Congenital nasal cysts	Nasal masses
Choanal atresia	Dermoid cysts	Glial heterotopia
Pyriform aperture stenosis	Nasolacrimal duct cysts	Meningo- or encephalocoele
Midnasal stenosis	Thornwald's cyst	Haemangioma
Nasal agenesis	Nasoalveolar cysts	Teratoma
Craniosynostosis syndromes	Dentigerous cysts	Hamartoma
'Cleft palate' nose	Mucous cysts	Chordoma

BOX 23.2 Acquired causes of nasal obstruction in neonates

Structural	Inflammatory
Osseocartilaginous nasal deformity	Neonatal rhinitis

Flexible nasendoscopy is particularly useful and imaging via computed tomography (CT) and magnetic resonance imaging (MRI) is of great value in delineating both nasal and post-nasal lesions.[1, 2]

Boxes 23.1 and 23.2 list the variety of causes of neonatal nasal obstruction. This chapter aims to review those conditions not covered elsewhere in this book.

CONGENITAL DISORDERS

Skeletal anomalies

CHOANAL ATRESIA

This is a rare condition (incidence 1 in 7000 live births) in which there is complete obstruction of the posterior choanae on one or both sides (Figure 23.1). The blockage is thought to be either bony or membranous in origin, but in reality a mixed picture is usually seen (70% of cases), with the remainder being purely bony. It is believed to be secondary to persistence of the nasobuccal membrane.



Figure 23.1 Bilateral choanal atresia as viewed from the nasopharynx with a 120-degree endoscope.

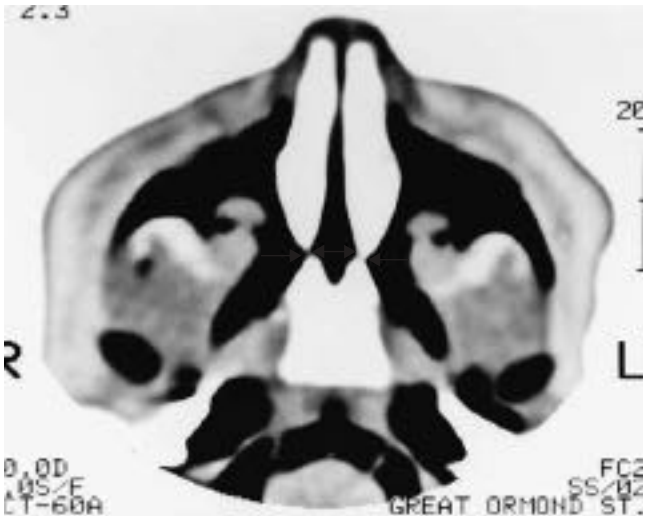


Figure 23.2 CT scan (axial view) to illustrate the expansion of the posterior vomer and medial maxillary walls of the nasopharynx in choanal atresia (arrows).

Bilateral choanal atresia in neonates presents as acute respiratory distress as neonates are obligate nasal breathers. Classically the neonate will have cyclical cyanosis relieved by crying, and placement of an appropriate-sized oral airway resolves the distress. Unilateral choanal atresia may present later in life, and can be picked up in neonates when there is an inability to pass a nasogastric tube through one nasal passageway.

Neonates with choanal atresia will have difficulty with feeding. The uvula and epiglottis usually form a respiratory channel from the nose to the larynx with two lateral pathways from the mouth to the oesophagus to allow for the safe passage of food. In neonates with bilateral choanal atresia this respiratory channel is lost and therefore cyanosis can develop during feeds.[1] McGovern nipples have been shown to be of benefit for children who develop feeding difficulties.

Misting upon placement of a metal spatula below the neonate's external nasal aperture excludes a diagnosis of choanal atresia, and this test can easily be performed in the clinic setting. If suspected, the diagnosis should be confirmed with flexible nasendoscopy, and CT scanning should then be performed to determine the extent and nature of the choanal atresia (with suction clearance of the nose and application of 0.5% ephedrine drops 30 minutes prior to scanning) (**Figure 23.2**). In neonates, often a simple oral airway is well tolerated, in which case endotracheal intubation can be avoided.

Choanal atresia can occur in isolation, but it can also be one feature of a number of associated congenital anomalies in the CHARGE (coloboma, **h**eart defects, **a**tresia choanae, **r**etardation of growth, **g**enital anomalies, **e**ar abnormalities) syndrome, due to mutations in the *CHD7* gene on chromosome 8. These abnormalities must be excluded in a child with choanal atresia and therefore the minimum investigations in addition to the nasal CT scan are cardiac echo, renal ultrasound scan, and an ophthalmology and audiology review.

The literature describes numerous techniques for the repair of choanal atresia, but there is little in the way of direct comparisons and outcomes are difficult to define objectively. Most studies report on the surgeons' assessment of the size of the nasal airway, and whether the family feel that the symptoms have resolved. The number of surgeries required and time taken to reach a satisfactory outcome are used to make comparisons. A recent Cochrane review concludes that there is no definitive evidence to demonstrate the potential advantages or disadvantages of any surgical technique for patients with choanal atresia.[3]

The two most common techniques for choanal atresia repair are the transnasal and transpalatal approaches, but the sublabial, transantral and transseptal approaches have also been described.[4] Transpalatal and transnasal surgery have been shown to have similar outcomes.[5] The transpalatal technique is not as common now, but it can be useful in those neonates with significant craniofacial anomalies where the dimensions of the nose and postnasal space are limited.

There are two methods described for the endoscopic transnasal approach. One involves using the zero degree endoscope transnasally, with serial dilatations using urethral sounds or using powered instruments such as microdrills. In cases where the nasal cavity is too small to accommodate both instruments a posterior septal window is created and expanded, thus allowing the endoscope through one nostril and the powered instrument through the other nostril, creating a 'neo-unichoana'.[6, 7]

The second transnasal approach involves a 120-degree endoscope being placed in the mouth and positioned in the nasopharynx behind the soft palate to give a view of the postnasal space. Instruments and the drill can then be introduced through the nose. This technique is described in three papers from Great Ormond Street Hospital in London and represents the largest reported experience at 161 patients using the endoscopic transnasal approach.[8–10]



Figure 23.3 Bilateral nasal stents with an endotracheal tube bridging piece.

There are reports in the literature of high success rates using the endoscopic endonasal approach with balloon dilatation for choanal atresia, although the numbers involved in these series are still quite small.[11]

The role of nasal stenting post choanal atresia repair is also debated. If used, bilateral nasal stents can be fashioned from two ivory Portex™ endotracheal tubes cut to length with the bevelled end of each sitting in the nasopharynx orientated towards the septum. The philtrum is protected by either a small length of size 12 suction catheter cut to act as a bridging piece or a further small piece of endotracheal tube (**Figure 23.3**). The stents are secured by a circumseptal '0' prolene suture and left *in situ* for up to 6 weeks. An alternative is to use a single tube as a stent, with a window cut in the middle to allow access for the securing suture. This avoids the need for a bridging piece (**Figure 23.4**). There is debate as to the need for stenting, and a systematic review with meta-analysis has shown that the success rates for bilateral choanal atresia repair are similar with and without nasal stents, and that the use of stents may be associated with more complications.[12]

There is evidence that regular suctioning to clear secretions and daily washing with sodium chloride solution results in successful outcomes.[13] Authors who do not support using stents stress the need for resection of the posterior aspect of the vomer and early (1 week post repair) repeat examination for removal of granulations and dilatation as required.[13]



Figure 23.4 Bilateral nasal stents without a bridging piece.

Given the limitations in the definition of outcome as described previously, success rates have been shown to be similar over the past 20 years with the three Great Ormond Street papers showing rates of 68–80% for bilateral and 82–93% for unilateral choanal atresia. A group of 78 children from the Philadelphia Children's Hospital were followed up for 35 months on average with similar results.[14]

Mitomycin C is thought to act to reduce granulation tissue and fibrosis by inhibiting fibroblasts and angiogenesis leading to its use during stent removal. However, several papers have found no benefit in terms of outcomes whether mitomycin C is used or not.[12, 15] Carter et al. suggest, however, that mitomycin does have beneficial effects.[16] The KTP laser has also been shown to be helpful in the treatment of granulation tissue which develops post-operatively.[5]

PIRIFORM APERTURE STENOSIS

This abnormality, first described in 1988, is a very rare condition leading to nasal obstruction in the neonate which arises due to bony overgrowth of the nasal process of the maxilla (**Figure 23.5**).[17] The piriform aperture is the narrowest part of the nasal airway and so even minimal reduction in diameter here can cause significant problems. Symptoms similar to bilateral choanal atresia occur and epiphora is also often seen secondary to bony involvement of the nasolacrimal ducts. Diagnosis is suggested by the inability to pass a narrow gauge nasogastric tube or 2.2 mm endoscope through the anterior nasal vestibule due to the bony obstruction. CT scan confirms the diagnosis with an aperture width of less than 11 mm measured on an axial CT at the level of the inferior meatus (in a term neonate). CT can also demonstrate a single central incisor, which exists in some affected individuals. This single central incisor is associated with an absent upper frenulum and arch-shaped lower lip. In this subgroup with a 'megaincisor' there is a suggested association with holoprosencepaly, a rare condition in which the developing forebrain fails to divide appropriately to form the cerebral hemispheres, diencephalon, and optic and olfactory bulbs. These patients should undergo further evaluation for central nervous system defects with an MRI and particularly the hypothalamic–pituitary–thyroid axis. There are variable reports on the incidence rates of this condition with piriform aperture stenosis, but a figure of around 50% is generally accepted.[18]

Conservative treatment with nasal steroid drops or decongestants (for up to 2 weeks) and saline irrigation is generally recommended as first-line treatment.[19] If there is severe obstruction, respiratory distress or failure to thrive, surgical treatment is warranted. It has also been found that an aperture of less than 5 mm on CT is almost always associated with the need for surgical intervention.[20]

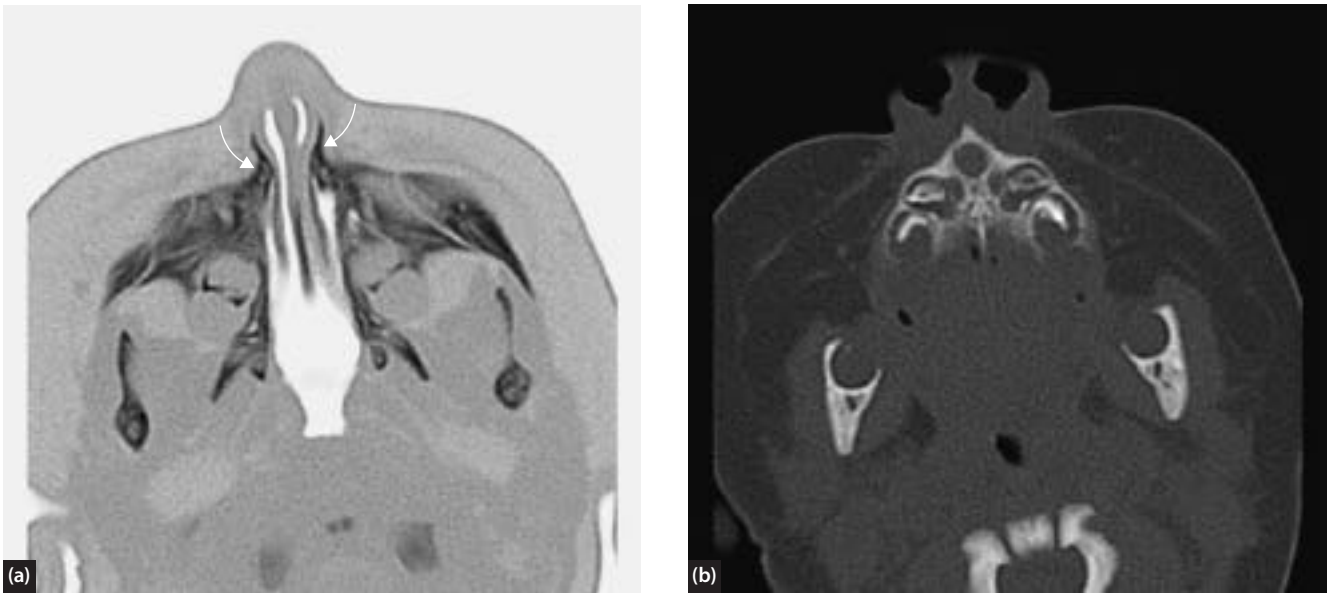


Figure 23.5 CT scan (axial view) of bilateral piriform aperture stenosis. Note the single central incisor.

Surgery involves either a transnasal approach with an alar-releasing incision or a sublabial approach with a gingival–buccal sulcus incision and elevation of the soft tissue and periosteum to expose the piriform aperture. The abnormal bone is drilled away using a diamond burr and the mucoperiosteal flap replaced. Post-operatively nasal stents can be used for up to 4 weeks, although more recent studies suggest that stenting is not necessary.[21] Complications include adhesions, septal perforations and septal ulceration, but the use of suctioning, nasal irrigation and treating gastro-oesophageal reflux minimizes this.[22]

MIDNASAL STENOSIS

Midnasal stenosis is a rare condition secondary to overgrowth of the nasal bones halfway along the nasal cavity. It usually occurs in association with syndromes characterized by midfacial hypoplasia, such as Apert syndrome, but cases in isolation are also reported.[23] Neonates will present in a similar fashion to those with piriform aperture stenosis or choanal atresia with apnoea, cyanosis and failure to thrive. Diagnosis can be confirmed with nasal endoscopy or CT scanning which will demonstrate isolated bony narrowing of the midpart of the nasal cavity or narrowing with stenosis of the rest of the nasal cavity (**Figure 23.6**). Treatment is usually conservative, allowing the child's midface to grow, such that by the age of 6 months the obstruction is relieved. For those children struggling with significant respiratory problems or failure to thrive, dilatations or stent placement can be considered.[1]

NASAL AGENESIS

Complete arhinia is very rare but can occur in isolation or as part of a syndrome. It originates at the fifth week *in utero* when the nasal placode fails to canalize to form the nasal passages. Presentation at birth with acute respiratory distress occurs. Management is initially with an oral airway and tube feeding. A tracheostomy may be required. Definitive surgical treatment usually involves a two-staged procedure aimed at reconstructing the nasal cavity as well as the external nose, and is usually delayed until facial development is almost complete.[24]



Figure 23.6 Midnasal stenosis associated with a patient with Apert syndrome.

Congenital nasal cysts

Congenital cysts, as listed in **Table 23.1**, can either obstruct the nose or cause discharge from an associated sinus tract.



Figure 23.7 Midline nasal sinus associated with an underlying dermoid cyst.

DERMOID CYST

Dermoid cysts (**Figure 23.7**) arise from the ectoderm and mesoderm and usually contain all the structures of normal skin. They are the most common midline nasal mass, and account for between 1% and 3% of all dermoids.

These cysts usually present as a slowly growing cystic midline mass over the nasal dorsum. An associated pit is often seen in any position from the nasal tip to the glabella, and hair may be present at its opening. Occasionally these dermoids can become infected and thus present as an abscess requiring drainage.

Between 4% and 45% of dermoid cysts have an intracranial component, thus pre-operative imaging with CT (for bony anatomy) and MRI (to delineate any connection to the central nervous system) is essential.[25]

Nasal dermoids are discussed in more detail in Chapter 41, Cysts and sinuses of the head and neck.

NASOLACRIMAL DUCT CYST (DACRYOCYSTOCOELE)

The nasolacrimal duct system should canalize *in utero* from a superior to inferior direction and is usually complete by the sixth foetal month through a process of reabsorption; however, not infrequently, at birth the lower end can remain closed. This barrier can be combined with a proximal valve-like obstruction at the junction of the common canaliculus and lacrimal sac, thus the tear fluid builds up resulting in a cyst. This is a common problem for neonates and it is reported that 5–30% of babies are born with nasolacrimal duct blockage.[26] These lesions can cause epiphora and nasal obstruction, sometimes leading to respiratory distress and feeding difficulties, and may present with a bluish cystic mass at the medial canthus. They are more commonly unilateral but can be bilateral,[27] and their incidence is slightly higher in female infants. CT imaging confirms the diagnosis and shows a dilated nasolacrimal duct, an intranasal cyst and cystic dilatation of the lacrimal sac.

Initial management is with nasal decongestants but, if surgical removal is required, endonasal marsupialization under endoscopic guidance is recommended.[27] Endonasal ablation with the carbon dioxide laser has also been reported previously.[26] Opthalmology input is helpful as intra-operative nasolacrimal probing and stenting may be necessary (see Chapter 25, Lacrimal disorders in children).

THORNWALDT CYST

The pharyngeal recess or bursa sits in the midline of the posterior wall of the nasopharynx. It ends next to the adenoids and is lined by the pharyngeal mucous membrane. Cystic transformation of this recess was first described by Thornwaldt in 1885 and so it bears his name. Inflammation of the lesion causes nasal obstruction, occipital pain, fullness in the ears and discharge. It rarely causes significant obstruction in neonates.

Endoscopic examination confirms the diagnosis. Imaging by CT and MRI demonstrates any adhesion to the cervical vertebrae. Incision and excision of the cyst have been described while total clearance requires a palatal approach.[28]

NASOALVEOLAR CYSTS

These are rare, non-odontogenic, soft-tissue lesions arising from the incisive canal during the development of the maxilla. They present lateral to the midline at the alar base and can cause asymmetrical alar flare. Excision is usually via a sub-labial approach, but the transnasal approach has been recently reported.[29]

DENTIGEROUS CYSTS

Dentigerous cysts present in the floor of the nose or maxillary sinus and have a dental origin. Endoscopic marsupialization or removal via the nose is usually satisfactory.

MUCOUS CYSTS

Mucous cysts have been described anywhere in the nose but appear to be more common in the floor. They may be congenital but are more usually seen as a complication of rhinoplasty. Endoscopic and open approaches are used depending on the position of the lesion.[30]

Nasal masses

ENCEPHALOCOELE, MENINGOCOELE, GLIOMA

A nasal encephalomeningocoele represents a herniation of meninges with or without associated brain through bony defects of the calvarium. A meningocoele consists of either



Figure 23.8 Broadened nasal dorsum in a child with a glioma.

meninges alone or with CSF and an encephalocoele contains nervous tissue. Their combined incidence is around 1 in 4000 live births and they have an equal male/female distribution. Encephalocoeles can be described as frontoethmoidal or basal.[31] Frontoethmoidal are usually associated with craniofacial deformity as they arise either at or anterior to the foramen caecum. The basal types present intranasally through defects in the skull base causing nasal obstruction and widening of the nasal bridge.

Nasal gliomas (**Figure 23.8**) are benign midline masses containing glial cells and fibrous and vascular tissue. They are similar to encephalocoeles but have become separated from the intracranial structures. Around 15% do, however, remain attached to the brain via a fibrous stalk. There is usually no associated abnormality of the brain. A better term for these lesions is 'glial heterotopia': glioma implies a neoplasm and these lesions are actually choristomas (aggregations of structurally normal tissue in an abnormal location). Presentation is usually early on as a firm, non-compressible, reddish swelling.

Differentiation between gliomas and encephalocoeles can be made in a number of ways. A probe will pass laterally but not medially to an intranasal encephalocoele while an intranasal glioma can arise from the lateral nasal wall. Furstenberg's test (compression of the internal jugular vein) usually causes an encephalocoele to enlarge but a glioma does not. Imaging is mandatory to confirm the nature of the lesion. MRI is the most effective modality due to its better resolution of soft tissue, and because the anterior skull base contains unossified cartilage which can be mistaken for bony dehiscence on CT, but CT has a role in image guidance. On MRI, an encephaocoele is seen as a mass in continuity with the brain with an associated skull base defect, while a glioma is discontinuous to the brain parenchyma and the tissue is dysplastic and gliotic, therefore more hyperintense on T2 compared to normal brain parenchyma.

Surgical excision is recommended for these masses, particularly if they are causing significant problems. As with dermoid cysts, masses in the lower part of the nose can be removed via the external rhinoplasty approach.[32] More recently, the endoscopic approach is advocated, and this has been shown to have successful outcomes with image guidance.[33, 34] The glial tissue can be removed with a zero-degree or 120-degree endoscope.

Encephalocoeles and meningocoeles that require surgery usually require a combined transnasal and neurosurgical approach. Ventriculoperitoneal shunting may be required pre-operatively. The intracranial portion can be excised via a bicoronal flap with a frontal craniotomy, but this can be associated with complications of epilepsy, anosmia, scarring and intracerebral haemorrhage. More recently, the endoscopic approach is advocated without the need for formal craniotomy.[35] The defect left by endoscopic excision can be closed with temporalis fascia graft, mucosa or a composite graft from the inferior turbinate, with Gelfoam® and packing (if small), or if a larger defect is present fascia lata and bone from the septum may be required. This prevents the risk of CSF leak potentially leading to meningitis. The role of prophylactic antibiotics is controversial.

NASAL HAEMANGIOMA

Vascular anomalies such as haemangiomas, arteriovenous malformations (AVMs) or vascular malformation (including lymphatic malformations) can present in the nose either externally or internally (**Figure 23.9**). Internal haemangiomas often arise from the inferior turbinate.

Classically, a haemangioma is either absent or flat at birth and then undergoes a period of rapid growth to present as a mass at around 6 weeks of age. Growth then continues for the first 6 months of life before gradual involution occurs, and the lesion generally disappears by around the age of 6 years. This natural history supports conservative management if possible. Ultrasound and MRI imaging are the recommended modes of imaging, particularly to exclude any intracranial connection, and treatment depends on the extent of involvement of the surrounding tissues.

Treatment for haemangiomas has been transformed with the use of oral propranolol and involvement of the appropriate paediatric medical team familiar with its use is recommended.[36, 37] In cases where there is encroachment on the orbit with a potential risk to vision, surgical excision has been used to good effect. The use of chemotherapy (such as methotrexate or vincristine) is reported but should be undertaken with caution due to the risks of side effects, and it has now largely been superseded by propranolol (see Chapter 42, Haemangiomas and vascular malformations).[38]

TERATOMA

A teratoma is a true neoplasm consisting of all three germ cell layers with cells varying in maturity. They occur in 1 in 4000 live births with less than 10% occurring in the



Figure 23.9 External nasal haemangioma in a 10-month-old girl.

head and neck. The cervical forms are the most common, followed by nasopharyngeal teratomas. They are associated with polyhydramnios, stillbirth and prematurity, and can result in significant airway compromise. They usually present as a firm mass.

Maternal serum alpha fetoprotein levels and beta HCG levels may be raised. Imaging is with CT and MRI. Teratomas will appear as heterogeneous masses on MRI, with fatty and bony components, and they may have a stalk, giving them mobility in different positions. Management is surgical, either endoscopic or open, depending on the size of the lesion.[39]

MISCELLANEOUS

Hamartomas, chordomas and craniopharyngiomas are extremely rare causes of nasal obstruction in the neonate.

ACQUIRED PATHOLOGIES

Osseocartilaginous septal deformity

The septum develops as an outgrowth from the merged medial nasal processes and nasofrontal process. At week 9, it fuses with the palate just posterior to the incisive foramen, and then fuses anteriorly and posteriorly.[40] A number of babies are born with a septal deviation either in isolation or in association with an abnormality of the bony pyramid. It is felt that the problem is due either to intrauterine positioning or to birth trauma. Closed reduction of the septal deformity with topical anaesthetic in each nostril in the first few days of life has been described and is thought to be successful if the deviation is severe.[41] However, most of the studies that advocate intervention have inadequate follow-up periods and there is little evidence for the adverse effects of conservative management.[42] Formal surgical repair is generally recommended later in childhood to avoid damage to the main growth centre of the nose; it is interesting, however, that the external rhinoplasty approach has been used for other pathology in very young children and no detrimental effects on nasal growth have been reported (see Vol 1, Chapter 103, Nasal septum and nasal valve).

Neonatal rhinitis

Swelling of the nasal mucosa in newborn infants can cause significant airway problems, particularly when feeding, as neonates are obligate nasal breathers. Idiopathic neonatal rhinitis is characterized by mucoid rhinorrhoea with nasal mucosal oedema in the afebrile newborn. This results in stertor, poor feeding and respiratory distress.[43] Structural abnormalities should be excluded. Treatment of neonatal rhinitis depends on the severity of symptoms. Nasal bulb suction with saline drops in the first instance is recommended. A short course of nasal steroid drops would be the next step. This should be closely monitored to avoid the potential side effects from systemic absorption.

It is important to consider chlamydia infection acquired in the birth canal. This usually results in conjunctivitis but involvement of the nose is seen in around 25% of affected individuals. Presentation is with obstruction, rhinorrhoea and a markedly erythematous nasal mucosa on examination. Swabs are diagnostic and the appropriate antibiotics should be given.

Rarely congenital syphilis (*Treponema pallidum*) can cause nasal symptoms in the neonate. Thin, clear secretions are seen between the second week and third month of life. This progresses to a mucopurulent discharge with significant obstruction and crusting of the nostrils. Antibiotic treatment is required both for symptomatic relief and to prevent chronic infection of the cartilage resulting in saddle deformity.

Fibrous dysplasia

This is an uncommon cause of nasal obstruction in older children and young adults. It is a benign fibro-osseous dysplasia and can present either as a solitary lesion (monostotic) or less commonly in multiple sites (polyostotic), typically in the craniofacial bones. Presentation is usually as pain with progressive facial deformity between the ages of 10 and 30.[44]

Nasal obstruction, with a mass on endoscopy or facial deformity due to growth of a lesion in the nose or sinus should raise suspicion. Imaging helps to confirm the diagnosis; normal healthy bone is replaced with a more radiolucent 'ground-glass' appearance. There can be endosteal scalloping of the inner cortex with a smooth non-reactive periosteal surface. Lesions have diffuse margins.

Management is expectant but surgical excision may be needed with the aim of preserving function and limiting disability. The mid-facial degloving approach has been shown to achieve good results with minimal cosmetic defect.

Medical treatment involves medication to increase bone density, for example biphosphonates.

A subgroup of polyostotic patients (around 3%) have associated endocrine abnormalities such as hyperthyroidism, adrenal disorders, diabetes, hyperpituitarism and hypercalcaemia with cafe-au-lait spots. This is termed McCune–Albright syndrome after the two physicians who first described it in 1937.

The condition usually becomes dormant by adulthood but there is a 1% risk of malignant transformation, mostly in the polyostotic form.

Neoplasms of the nasal bones

Juvenile ossifying fibroma (JOF) is a true neoplasm which is defined radiologically as a radiolucent, expansile, well-defined lesion with variable calcification. It can be unilocular or multilocular with cortical thinning and possible perforation. Pain is rare. There are two subtypes, trabecular and psammomatoid, which have different histopathological appearances.

Surgical excision is recommended and this may need to radical as recurrence rates are high (30–50%) probably due to the propensity of this disease to perforate cortical bone. Malignant change has not been reported.

Bony malignancies can rarely present as nasal obstruction or deformity; good-quality imaging will usually alert the clinician to the need for further investigations.

BEST CLINICAL PRACTICE

- ✓ Use of an oral airway in neonates with nasal obstruction can facilitate transfer for definitive treatment.
- ✓ Minimal additional investigations for a child with choanal atresia to look for CHARGE syndrome are echocardiography, renal ultrasound and ophthalmology/audiology review.
- ✓ Early surgical excision of dermoid cysts is recommended before infection or further expansion occurs.
- ✓ Nasal masses may not be as innocuous as they seem; always consider intracranial extension and imaging with CT (for bony anatomy) and MRI (to identify a CNS connection).
- ✓ Compression of the internal jugular vein (Furstenberg's test) usually causes an encephalocoele but not a glioma to enlarge.
- ✓ The treatment of nasal haemangiomas has been revolutionized by propranolol.
- ✓ Idiopathic neonatal rhinitis is underdiagnosed and improves with intranasal steroids.
- ✓ The endoscopic approach is rapidly becoming the procedure of choice for removal of neonatal nasal masses.

FUTURE RESEARCH

- ➤ Multicentre studies including long-term follow-up of patients who undergo surgery for choanal atresia.
- ➤ Studies looking at the success rates of the endoscopic approach for nasal encephalocoeles and gliomas are needed.
- ➤ Long-term follow-up of neonates who have had closed reduction of their septal deviation is unknown.
- ➤ Better evidence for the management of neonatal rhinitis is needed.

KEY POINTS

- Neonates are obligate nasal breathers; nasal obstruction can cause significant airway compromise.
- Affected neonates may develop stertor, mouth-breathing, feeding problems, sleep disturbance and rhinorrhoea.
- Immediate relief can be brought about by insertion of an oral airway.
- Choanal atresia may occur in isolation but is often one of a number of associated anomalies.
- A congenital nasal mass can consist of ectopic intracranial tissue.

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CHAPTER 24

PAEDIATRIC RHINOSINUSITIS AND ITS COMPLICATIONS

Daniel J. Tweedie

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: paediatric (pediatric) rhinosinusitis, sinusitis, complications, respiratory tract infections, immune deficiency, reflux, primary ciliary dyskinesia, cystic fibrosis, orbital cellulitis, endoscopic sinus surgery, adenoidectomy, and with particular reference to international consensus papers: the European Position Papers on Rhinosinusitis and Nasal Polyps (EPOS, 2007 and 2012).[1, 2] The American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) Consensus Statement on Pediatric Chronic Rhinosinusitis (2015)[3] and the International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR:RS, 2016).[4] These documents have made use of multinational consensus expert opinion and consider the latest available evidence.

OVERVIEW

Rhinosinusitis in children is extremely common, typically following viral upper respiratory tract infection, but other factors may be involved.

Paediatric rhinosinusitis (RS) and its complications describe a spectrum of disease, varying in aetiology, pathophysiology and duration, which influences clinical presentation and management. Apart from exposure to the common viral precipitants, known predisposing factors include allergy,[5–8] impaired cilial function,[9] immune deficiency, gastro-oesophageal reflux,[10] environmental pollution, malnutrition, and medical conditions such as diabetes mellitus and other metabolic conditions.[2] There are also specific congenital and acquired disorders in which rhinosinusitis is often a major component, for example cystic fibrosis and primary ciliary dyskinesia, and these warrant special consideration.

Rhinosinusitis is common in children[11–14] but frequently overlooked. It is significantly detrimental to quality of life[15] and costly in health economic terms. For example, the estimated annual cost of treatment of sinusitis in children under 12 years of age in the USA in 2012 was $1.8 billion.[16] While paediatric and adult rhinosinusitis are often considered together, these conditions are multifactorial, with predisposing factors and aetiology changing with age, and the childhood and adult forms differ in a number of ways. These have been summarized in the EPOS 2007 document[1] and are shown in **Table 24.1**.

ANATOMY

The paranasal sinuses are air-containing spaces which are positioned around the nasal cavities, communicating with these via natural ostia. They are lined by type II pseudostratified columnar ciliated epithelium (respiratory mucosal epithelium), with anatomical factors and cilial function optimized to facilitate mucus drainage and preserve a sterile environment.[17]

Sinus development is progressive throughout childhood. At birth, the maxillary sinuses measure 7 mm in depth, 3 mm in width and 7 mm in height.[1] The sphenoidal (sphenoid) sinuses and two or three ethmoidal (ethmoid) cells are found on each side at this stage, and the ethmoid labyrinth is complete by 4 years of age. The frontal sinuses,

TABLE 24.1 The differences between paediatric and adult chronic rhinosinusitis (reproduced with permission[2])

	Young children	Adults
Commensal microflora		
Coagulase-negative staphylococci	30%	35%
Staphylococcus aureus	20%	8%
Haemophilus influenzae	40%	0%
Moraxella catarrhalis	24%	0%
Streptococcus pneumoniae	50%	26%
Corynebacterium species	52%	23%
Streptococcus viridans	30%	4%
Immunity	Immature: defective response to polysaccharide antigens (IgG2, IgA)	Mature, except in a subset
History	Self-limited in time (improves after the age of 6–8 years)	No history of spontaneous improvement after certain age
Histology	Mainly neutrophilic disease, less basement membrane thickening and mucus gland hyperplasia, more mast cells	Mainly eosinophils
Endoscopy	Polyps are rare, except in CF	Polyps frequently present
CT-scan	Younger child more diffuse sinusitis, involving all sinus	Sphenoid and posterior sinus less often involved

not present at birth, develop from cranial extension of the ethmoid cells. Once the roof of these frontal cells reaches the level of the upper orbit, at around the age of 5 years, they are termed 'frontal sinuses'. These are demonstrable radiographically in 20–30% of children by 6 years[18] and more than 85% by 12 years of age. The maxillary sinuses expand in parallel, reaching the same level as the nasal floor by 7–8 years of age, and are 4–5 mm below this by adulthood. The sphenoid sinuses extend posteriorly over the first 7 years, and are radiologically distinct in 85% of cases by this stage, completing growth by 15 years, although some posterior extension can be seen into adulthood. Sinus expansion subsequently mirrors the dimensional changes of the midface during adolescence and towards adulthood. The maxillary and ethmoid sinuses reach full size by the age of 15 or 16, and the frontal sinuses by 19 years of age.[19]

DEFINITIONS

A number of consensus statements have sought to define rhinosinusitis in terms of symptoms and duration, but in practice the clinical diagnosis of rhinosinusitis in children can be challenging, and the diagnosis can be overlooked.

Rhinitis and sinusitis typically coexist in the same affected individual, given the close proximity of the nose and paranasal sinuses and their common mucosal lining. Guidelines and consensus documents including EPOS, ICAR:RS and statements from AAO-HNS now typically use the term **rhinosinusitis**, as opposed to sinusitis, reflecting the clinical and pathophysiological picture.[1–4, 20–22]

In a similar fashion as for adults, EPOS 2012 defines paediatric rhinosinusitis clinically as follows:[2]

'Inflammation of the nose and paranasal sinuses characterized by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):

- +/– facial pain/pressure
- +/– cough (as opposed to reduction or loss of smell in the adult definition).

and either:

- endoscopic signs of:
  - nasal polyps, *and/or*
  - mucopurulent discharge primarily from the middle meatus, *and/or*
  - oedema/mucosal obstruction primarily in the middle meatus

and/or:

- CT changes:
  - mucosal changes within the osteomeatal complex and/or sinuses'.

These diagnostic criteria are very similar to those endorsed in the AAO-HNS Pediatric RS consensus statement.[3]

SEVERITY OF DISEASE

According to EPOS,[2] as for adults, the severity of paediatric rhinosinusitis can be classed as mild, moderate and

severe according to a patient-reported visual analogue scale (VAS). However, although also applied to children, this system has only been validated in adults to date. Using a 10 cm scale, between 0 (not troublesome) and 10 (worst thinkable), the patient (or parent) is asked to mark the severity, when asked 'How troublesome are your (or your child's) symptoms of rhinosinusitis?' A score of 0–3 is classed as mild, >3–7 moderate and >7–10 is severe. A score of greater than 5 indicates symptoms which affect patient quality of life.

DURATION OF SYMPTOMS: ACUTE VERSUS CHRONIC RHINOSINUSITIS

Paediatric chronic rhinosinusitis will be considered later in the chapter, although clinical assessment, investigation and treatment options are similar in certain aspects.

Acute rhinosinusitis (ARS) in children is defined by EPOS[2] as:

'Sudden onset of two or more of the symptoms:

- nasal blockage/ obstruction/ congestion
- *or* coloured nasal discharge
- *or* cough (daytime and night-time)

for <12 weeks (with symptom-free intervals if the problem is recurrent).'

The symptom profile defined by ICAR:RS[4] is similar, but with ARS defined by a duration of less than 4 weeks. Both consensus documents stress the inclusion of questions regarding allergic symptoms (sneezing, watery rhinorrhoea, itching of the nose and eyes), to help differentiate allergic from viral and bacterial RS.

The EPOS system[2] favoured the omission of previously used terms such as 'subacute' and 'acute or chronic' RS.

In practice, the diagnosis of ARS in children is challenging[2] due to the overlap with other conditions, including viral upper respiratory tract infections (URTIs) and the subjectivity of parental reporting of symptoms. Young children often do not tolerate nasal endoscopy, and radiographic investigations are often avoided on account of radiation exposure, particularly in children with a short-lived, uncomplicated history.

PAEDIATRIC ACUTE RHINOSINUSITIS

Epidemiology and pathophysiology

It is now known from CT[23] and MRI[24] studies that, in the majority of children with symptoms of mucous nasal discharge, the sinuses are also involved (in decreasing order of frequency: maxillary and ethmoid (60%), sphenoid (35%) and frontal (18%), with resolution of the changes seen on imaging in parallel with clinical improvement of symptoms.[24] Viral URTIs occur extremely frequently in young children (six episodes per year,[25] more in day care), and it is generally agreed (despite low rates of virus recovery from sinus aspirates[26]) that these are the precipitant for most cases of paediatric rhinosinusitis.[27,28] In prospective longitudinal studies in young children, some 8% of viral URTI cases in patients 6–35 months of age were complicated by acute RS, equivalent to 0.5 episodes per patient year.[25] Epidemiological studies also suggest that:

- RS is commonest in younger children, and the prevalence decreases sharply after 6–8 years of age, probably reflecting immune system immaturity at an early age.[29,30]
- Seasonal variations in the prevalence of RS reflect rates of viral URTI, with an increase in occurrence in autumn and winter.[29]
- Young children looked after in day care with other children have markedly higher rates of RS than those managed at home.

The annual medical visit rate in the USA for acute RS is stable, at 11–14 per 1000 children.[31] The durations of episodes of viral and bacterial RS are broadly similar between children and adults.

The commonest bacteria isolated from maxillary sinus aspirates in children with acute bacterial rhinosinusitis (ABRS) are *Streptococcus pneumoniae*, untyped *Haemophilus influenza* and *Moraxella catarrhalis*, and less often *Staphylococcus aureus, Streptococcus pyogenes* and *Streptococcus viridans* and anaerobes, including *Peptostreptococcus* and *Fusobacterium*, particularly in longer-lived cases.[26,32–41] Interestingly, adoption of the 7-valent pneumococcal vaccine (PCV) in the United States from 2000 onwards has resulted in a decline in positive samples of *Streptococcus pneumonia*, but relatively higher proportions of aspirates with untyped *Haemophilus influenzae*.[42,43] *Staphylococcus aureus* is relatively commonly isolated from cases of sphenoid sinusitis[39] and rates of methicillin-resistant *S. aureus* (MRSA) are increasing in cases of ABRS.[44,45] Importantly, such infections are often polymicrobial (about one-third of cases), and this should be borne in mind with respect to antimicrobial treatment. Similarly, less common pathogens must be considered in particular circumstances. Anaerobes comprise some 8% of bacterial isolates, often oral pathogens seen in cases of odontogenic origin, and particularly prevalent in cases persisting for more than 1 month.[36,46] *Pseudomonas aeruginosa* is associated with nosocomial infection, particularly in the immunocompromised[47] (including HIV cases), patients with nasal catheters and other devices, and those with cystic fibrosis.[48] In these sorts of cases, fungal rhinosinusitis may also develop (see below).

While remaining the gold standard for diagnosis of ABRS (≥10 000 colony-forming units per mL), antral puncture and aspiration is seldom undertaken. One should also bear in mind that improper decontamination of the paranasal mucosa before aspiration may lead to misinterpretation of results.[26,49–51] As an alternative, cultures

from the middle meatus can be obtained, for example with endoscopic guidance.[52] The maxillary sinus aspirates correlate well with specimens taken from the middle meatus of the nasal cavity (83%) but poorly with those from the nasopharynx (45%).[53]

Clinical presentation of paediatric ARS: symptoms and signs

In the paediatric group, ARS typically presents with a combination of prolonged URTI, chronic cough, nasal discharge, plus fever >39 °C and facial pain in many cases. Most cases are viral in aetiology, but bacterial infection should be considered in cases with persistent and severe symptoms and those with deterioration after initially mild symptoms.

In terms of relative preponderance between acute and chronic RS, nasal, local and systemic clinical features differ,[30, 54, 55] as summarized in the EPOS 2007 document[1] and shown in Table 24.2.

Apart from these symptom differences between acute and chronic forms, the distinction in definition is made according to symptom duration, as above, recognizing the common scenario of a child with symptoms of chronic RS who also has infection-related acute exacerbations.

Classification of paediatric ARS by aetiology

As with the definitions and criteria discussed above, there is some variation between consensus documents regarding the aetiological classifications and diagnostic features differentiating the subtypes of acute paediatric RS.

For children, as for adults, EPOS,[1, 2] ICAR:RS[4] and the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS)[3] define **acute viral rhinosinusitis** (viral ARS, common cold), where nasal symptoms are present for less than 10 days. The most recent guidelines from the AAO-HNS included data on the duration of typical viral symptoms in support of the commonly accepted time frames used to differentiate acute viral RS from ABRS.

The EPOS 2012 statement[2] describes **acute post-viral rhinosinusitis** as an increase of symptoms after 5 days, or persistent symptoms after 10 days, but with symptom duration of less than 12 weeks. This is not recognized separately by the AAO-HNS guidelines.

Acute bacterial rhinosinusitis (ABRS) is diagnosed clinically, according to EPOS,[2] by the presence of at least three of:

- discoloured discharge (with unilateral predominance) and purulent secretion in the nasal cavity
- severe local pain (with unilateral predominance)
- 'double sickening' - deterioration after an initial milder phase of illness
- elevated erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP)
- fever (>38 °C).

The latter criterion is not considered diagnostically specific or sensitive for ABRS according to the AAO-HNS criteria.[3, 4]

For the clinician, the most common presentation of ABRS in children is a persistent and non-improving nasal discharge or cough (or both), which lasts for more than 10 days.[14] In children, the cough often worsens at night (in 80% of cases), with nasal symptoms (anterior/posterior discharge) in 76%, and associated fever for more than 3 days in 63%.[56] Halitosis is commonly seen in addition, but associated facial pain and swelling, headache and sore throats are unusual in children.

In terms of the variable clinical presentation, a number of consensus panels have identified the following three characteristic presenting features of ABRS which are diagnostically discriminating versus simple viral URTI.[57–60] Given the possible diagnostic difficulties already outlined, Wald identified three main clinical features which are suggestive of acute bacterial rhinosinusitis, over and above acute viral RS[61] which are supported by other studies:[9, 62, 63]

1. Persistent symptoms for more than 10 days, but less than 30 (although the EPOS documents define the duration of acute RS as up to 3 months).
2. Onset with severe symptoms (ill appearance, high fever >39 °C, purulent nasal discharge for at least consecutive 3–4 days at the onset of illness and other features including headache and facial pain).
3. Worsening after initial improvement (double sickening) is also strongly suggestive of ABRS.[58]

In non-allergic children, neutrophil proportions of ≥5% in nasal brushings have a 91% sensitivity and positive predictive value of 84% for maxillary sinusitis.[64]

TABLE 24.2 Presenting symptoms of rhinosinusitis in children (data reproduced with permission[2])

Symptom	Preponderance	Acute/chronic
Rhinorrhoea	71–80%	All forms
Cough	50–80%	All forms
Fever	50–60%	Acute
Pain	29–33%	Acute
Nasal obstruction	70–100%	Chronic
Mouth breathing	70–100%	Chronic
Ear complaints (recurrent purulent otitis media or OME)	40–68%	Chronic

Differential diagnoses

In children with nasal discharge, one should always exclude the possibility of a nasal foreign body or choanal stenosis or atresia. Dental disease may also give rise to sinonasal and facial symptoms. These cases most typically

present with unilateral findings, and often a suggestive history. These can usually be excluded with careful examination, including nasal endoscopy.

Hypertrophy and inflammation of the adenoids (adenoiditis) may also present with nasal obstruction and mucus. This tends to be more long-standing, with a suggestive parental history. Again, nasal endoscopy is useful to determine this.

Similarly, parental history may suggest allergic rhinitis as the basis for nasal symptoms.[65]

Clinical assessment of a child with acute rhinosinusitis

Considering the clinical features outlined above, the history and clinical examination should be focused towards confirming the diagnosis of ARS, distinguishing likely bacterial versus viral aetiology and excluding local and systemic complications.

HISTORY

The history should include enquiry about current symptoms, past history and risk factors (**Box 24.1**).

CLINICAL EXAMINATION

The clinical examination may be challenging in young children, but should ideally include:

- general observations, including temperature and neurological status
- complete ENT and head and neck examination (including the pharynx, oral cavity and teeth, orbits, ocular motility, vision, facial palpation and percussion over the paranasal sinuses, pupillary responses, cranial nerves)
- anterior rhinoscopy (oedema, inflammation, mucus/pus, foreign body) – this can by lifting up the tip of the nose and/or use of an otoscope[66, 67]
- nasal endoscopy (rigid or flexible), including middle meatal swabs for culture and sensitivity.

BOX 24.1 Clinical assessment – history

Current symptoms	Past history and risk factors
Onset	Similar episodes of sinusitis and RTI
Duration	Previous use of antibiotics
Precipitants (viral URTI, nasal foreign body)	Comorbidities
Improvement and deterioration in clinical picture ('double sickening')	Prior hospitalization and sinonasal surgery
Nasal/paranasal symptoms (congestion, mucopurulent discharge)	Allergy history
Facial/orbital pain or swelling	Day-care arrangements
Headaches and neurological sequelae	Exposure to cigarette smoke
Cough	Immunization history
Fever (severity and duration)	
Hyposmia	
Oral/dental/pharyngeal symptoms	

The nasal and pharyngeal mucosa is typically erythematous, with yellow/green nasal discharge of varying consistency. Studies have suggested the relative prevalence of associated features: post-nasal drip of mucus into the pharynx in 60%,[55] middle meatal pus in 50% and oedema of the inferior turbinates in 29%.[54] Adenotonsillar enlargement and modest, tender cervical lymphadenopathy is also sometimes seen.[66, 68]

Acute fungal rhinosinusitis in children

This is rare, and diagnosis and workup are already considered in Vol 1, Chapter 94. Allergic fungal rhinosinusitis is addressed later in this chapter.

Investigations in children with rhinosinusitis

The relevance and relative indications for investigations will depend upon the clinical presentation of rhinosinusitis, including the duration and severity of symptoms, complications and underlying comorbidities. For example, an acute, infective episode will direct a different investigative approach than a chronic, inflammatory case, where atypical organisms and/ or underlying inflammatory conditions or immunocompromise might be suspected.

Although microbiological and radiological investigations are certainly indicated in complicated cases, in most instances a clinical assessment of the child with acute RS is sufficient. In chronic RS, unusual organisms may be involved, and surgery may be warranted, prompting investigations to inform further management (see below).

MICROBIOLOGY

Cultures from nasal mucus are not needed in most cases of uncomplicated ARS. But there are some situations where this is needed. As mentioned above, antral aspiration, with measures to reduce contamination, remains the gold standard although it is impractical in everyday practice. This is reserved for particularly severe or resistant cases, or where surgical intervention is undertaken. An alternative method is to take a swab from the maxillary sinus[52] under endoscopic guidance. Nasal contamination is suggested by low bacterial quantities in the sample from a patient with significant symptoms, highly suggestive of acute bacterial RS, so isolates are considered positive when they contain more than 10 000 CFU/mL.[61]

Indications for culture are:[69]

- severe symptoms and toxic patient
- illness not improving after 48–72 hours of medical treatment
- immunocompromised patient
- suppurative complications (orbital, intracranial) or systemic sepsis.

IMAGING

The diagnosis of rhinosinusitis in children is typically clinical and usually does not require imaging. In any event, radiological investigations will not distinguish between viral and bacterial RS.[70]

Transillumination and ultrasound have been considered, but are limited in young children by thickness of soft tissues and the hard palate.[71] Plain sinus radiographs, once in common use, are now not indicated in the investigation of RS, as they correlate very poorly with CT findings. More than 50% of children with viral URTI will have abnormal maxillary sinus radiographs.[72] The radiation exposure is not justified in these circumstances.[23]

Imaging is occasionally indicated, for the same reasons as for microbiological culture above. Computerized tomography (CT) is the modality of choice, with intravenous contrast if intracranial complications are to be excluded. This is performed very quickly, usually without the need for sedation, and it is therefore favoured over MRI for these reasons.[73] But it is important to note that even asymptomatic children have a high incidence of abnormalities on CT,[72, 74] which by definition require no treatment. Additionally, in young adults, it has been found that 87% of those recovering from a viral URTI have maxillary sinus changes on CT.[27] Therefore any CT abnormalities in patients with RS must be correlated against clinical findings.

While CT has many advantages, MRI offers greater soft-tissue resolution[56] and does not involve any radiation exposure. The American College of Radiology has commented that CT and MRI are complementary modalities in the investigation of suspected orbital and intracranial complications of ABRS.[75] However, the bony resolution of CT is essential if surgery is considered, particularly given that the size of the developing sinuses in children often differs significantly on the two sides. This can be combined with image guidance systems at the time of surgical intervention. In addition, the practicalities and speed of CT and its widespread availability mean that it remains the most frequently used radiological modality in cases of RS, often as a sole imaging investigation.

Treatment of acute rhinosinusitis in children

The evidence based management of children with ARS has been presented very clearly in the EPOS 2012 document,[2] and is outlined in **Table 24.3**.

TABLE 24.3 Treatment evidence and recommendations for children with acute rhinosinusitis (reproduced with permission[2])

Therapy	Level	Grade of recommendation	Relevance
Antibiotic	Ia	A	Yes, in ABRS
Topical steroid	Ia	A	Yes, mainly in postviral ARS studies only done in children 12 years and older
Addition of topical steroid to antibiotic	Ia	A	Yes, in ABRS
Mucolytics (erdosteine)	1b (–)*	A(–)**	No
Saline irrigation	IV	D	Yes
Oral antihistamine	IV	D	No
Decongestants	IV	D	No

*1b (–): 1b study with negative outcome; **A(–): grade A recommendation **not** to use.

ANTIBIOTICS

Antibiotics are the mainstay of management of children with ARS. Meta-analysis of randomized controlled trials (RCTs), which included 17 studies (three of these in children), and 2915 adults and 376 children) showed an increase in resolution of symptoms. This effect was significant but modest,[76] and suggests that antibiotics may simply hasten slightly the resolution of uncomplicated cases of ARS, but that most cases will improve, irrespective of treatment.

The choice of antibiotics should ensure activity against the likely organisms, and include amoxicillin, amoxicillin-clavalunate and cephalosporins (the latter two covering beta-lactamase-producing organisms). Other options for patients with allergies to these agents include macrolides (azithromycin, clarithromycin) or trimethoprim/sulfamethoxazole. There is no formal recommendation for dose and duration of antibiotic use, which may be adjusted according to severity of symptoms and other factors.

INTRANASAL STEROIDS

There is evidence to support the use of intranasal steroids in conjunction with antibiotics in the management of children with ARS. In a specific paediatric trial, where 89 children received amoxicillin-clavalunate and either intranasal budesonide or placebo, significant improvements were seen by the end of the second week in those receiving intranasal steroids compared to placebo.[77] A number of other trials have considered adults and older children (12 years and above), demonstrating benefits in those receiving intranasal steroids during ARS, typically with antibiotics.[2, 77] However, while there is also evidence to

support the safety and efficacy of intranasal steroids for allergic rhinitis in younger children, data are so far lacking for ARS in this group, and the benefits are less certain. Therefore clinical judgement on an individual basis will determine whether intranasal steroids are offered in this context, most likely as an adjunct to antibiotics.

OTHER MEASURES

While saline douching may offer some benefit in children with ARS, there is no strong evidence to support the use of mucolytics and oral antihistamines in this context.[57]

Complications of paediatric acute rhinosinusitis

With the advent of antibiotics and improved standards and availability of medical care, the incidence and associated mortality from complications of paediatric ARS has declined. But these complications still occur and require prompt diagnosis and specialized management.

The overall rate of complications is 3–10 cases per million per year, equivalent to 1 per 12 000 ARS episodes.[2] Complications are more often seen in winter months,[78] and significantly more often in males than females. Importantly, studies from the Netherlands and the UK have shown that prescribing antibiotics in ARS does not prevent the occurrence of complications.[79, 80]

Complications occur as follows, although in some cases a combination may be seen:[81] orbital (60–75%), intracranial (15–20%), osseous (5–10%).

Rhinosinusitis is the presumed underlying cause in many cases of peri-orbital sepsis (10% of cases of preseptal cellulitis, 90% of cases of orbital cellulitis/subperiosteal abscess/orbital abscess)[82] and about 10% of intracranial suppuration.[83, 84]

Orbital complications are more often seen in small children, although intracranial complications can occur at all ages, particularly in the second and third decades of life.[79, 85]

ORBITAL COMPLICATIONS

Orbital complications can occur as a result of direct spread of infection across the lamina papyracea, or via a haematogenous route through small veins.[86] This is most likely from the ethmoid sinuses, and less often the maxillary, frontal and sphenoid sinuses in decreasing frequency.[79, 87] Such complications may occur with minimal pain or systemic upset.[88]

The Chandler classification is widely used to describe orbital complications of ARS[81] with respect to the orbital septum. This identifies five stages of orbital sepsis:

1. Inflammatory oedema (preseptal cellulitis)
2. Orbital cellulitis
3. Subperiosteal abscess
4. Orbital abscess
5. Cavernous sinus thrombosis.

It should be noted, however, that these are not necessarily seen clinically in a sequential manner. For example, intracranial complications including cavernous sinus thrombosis (see below) may occur without prior abscess formation. Additionally, the inclusion of preseptal cellulitis has also been questioned, which by definition is not an orbital infection, and is far less commonly seen as a result of ARS than true orbital complications. Other classification systems have therefore also been considered.[89, 90]

Preseptal cellulitis

Preseptal cellulitis describes inflammation of the eyelid and conjunctiva, anterior to the orbital septum). It may occur as a complication of upper respiratory tract infection, dacryocystitis or skin infection and less often sinusitis.[91–94] Presenting features include eyelid oedema and erythema, orbital pain, with or without fever and systemic upset. There is typically no proptosis or restriction of eye movements, but this can be challenging to assess in small children.

Preseptal cellulitis usually responds to an oral antibiotic but may spread beyond the orbital septum, with intraorbital complications. As such, it can usually be assessed clinically, but imaging is sometimes considered.

True orbital complications, while presented individually, can be considered together in terms of a more severe clinical presentation, and require far more aggressive investigation and management strategies.

Orbital cellulitis

Orbital cellulitis and subperiosteal abscess are seen more commonly than preseptal cellulitis as a result of ARS.[91, 93] Inflammation behind the orbital septum, within the tight confines of the orbit itself, will reduce the range of eye movements and produce pain on movement, diplopia, chemosis (conjunctival oedema) and proptosis. This requires a proactive management regime, including treatment with intravenous antibiotics and cross-sectional imaging to exclude orbital or intracranial abscess and other complications.

Subperiosteal and orbital abscess

A subperiosteal abscess forms between the periorbita (soft tissue orbital contents) and the sinuses, and is 'extraconal', lying outside the cone of ocular muscles. The clinical features of a subperiosteal abscess are similar to those of orbital cellulitis: oedema, erythema, chemosis and proptosis with painful, limited eye movements. Systemic upset and derangement of inflammatory markers may be more pronounced[95] but they cannot be relied upon to discriminate an abscess from cellulitis.

Orbital abscess is less commonly seen, with a frequency of between 8.3%[96] and 13% in studies of orbital complications in children.[97] This is 'intraconal', within the cone of the ocular muscles, and may result from diagnostic delay or immunosuppression.[98]

MANAGEMENT OF ORBITAL COMPLICATIONS

Orbital complications and their management are considered together, although in some cases these can coexist with intracranial and osseous complications, in many cases with similar investigation and treatment strategies. The child's vision is at risk, and there is also the possibility of life-threatening intracranial complications. The importance of a high index of suspicion, comprehensive history and clinical assessment cannot be overstated, as well as a considered, proactive approach to investigation, medical and surgical management. This mandates a multispeciality approach, with input from otolaryngology, paediatrics, ophthalmology, neurosurgery and microbiology personnel.

Clinical assessment

Considering the clinical features above, history and examination should include assessment of the eyes with respect to swelling, proptosis, movements, colour vision and acuity, plus assessment of the child's general condition, vital signs, level of consciousness and neurological status. This is undertaken with help from paediatric and ophthalmology colleagues. Twice-daily ophthalmology review of colour vision and acuity is recommended.[99] If there is failure to respond to medical management or otherwise any clinical suspicion, cross-sectional imaging is indicated.[99]

The first-line investigation is CT with contrast, including orbital detail, the paranasal sinuses and brain, with a view to assessing orbital and intracranial complications adequately. This is usually quick to perform and normally possible in an awake child. CT may allow distinction between cellulitis and orbital/subperiosteal abscess. In the case of subperiosteal abscess, findings include oedema of the medial rectus muscle, lateralization of the periorbita, and displacement of the globe downward and laterally. Orbital abscess is associated with obliteration of the detail of the extraocular muscle and the optic nerve by a confluent mass, sometimes with gas bubbles from anaerobic bacteria.

The predictive accuracy of a clinical diagnosis has been found to be 82% and the accuracy of CT 91%. MRI may be useful in cases of diagnostic uncertainty or when intracranial complications are suspected,[100, 101] but this usually requires sedation or general anaesthesia in young children, so this should not delay management.

Treatment

Initial medical treatment consists of high-dose intravenous antibiotics (according to local protocols), covering aerobic and anaerobic organisms, plus analgesia/antipyretics, intravenous fluids and adjuncts including intranasal steroids and saline douching. Antibiotics can be converted to an oral preparation when the patient has been afebrile for 48 hours.[102]

Where there is evidence of an abscess on CT and/or absence of clinical improvement after 24–48 hours of intravenous antibiotics, orbital exploration and drainage is indicated.[96] Current consensus from the EPOS 2012 document[2] suggests that preseptal and orbital cellulitis should be treated with antibiotics, while subperiosteal and intraorbital abscesses require surgical exploration.

In adults, drainage may be attempted endoscopically in expert hands, with adjuvant endoscopic sinus surgery (including ethmoidectomy)[95] and the consensus is to attempt to drain the abscess endoscopically by opening the lamina papyracea and draining the abscess after completing an endoscopic ethmoidectomy. However, in children with small noses and paranasal sinuses and marked nasal congestion, access and the quality of the endoscopic surgical field may be extremely unfavourable, such that external approaches (via a modified Lynch Howarth incision in the case of medial subperiosteal abscess or eyelid approaches for superior/lateral orbital abscess) are often used.

However, good outcomes can be seen with non-surgical management, with intravenous antibiotics in small children with subperiosteal abscess,[98, 100, 102] provided the following apply:

- There is clinical improvement within 24–48 hours.
- There is no decrease in colour vision or visual acuity.
- The abscess is subperiosteal and small (<0.5–1 mL volume) and medially located.
- There is no significant systemic involvement.
- The patient age is less than 2–4 years.

Sequelae of orbital complications

Where management has been prompt and appropriately directed, patients will usually recover very well with minimal long-term problems. However, in some cases vision may be permanently compromised or lost as a result of retinal artery occlusion and/or prolonged venous congestion, optic neuritis and corneal ulceration. There are also risks of diplopia and other long-term orbital complications resulting from the original infection and/or surgical drainage procedures. Sepsis may also spread intracranially.[103] Careful follow-up is therefore required to identify these issues.

INTRACRANIAL COMPLICATIONS

Intracranial complications include abscess formation (extradural, subdural or intracerebral), meningitis, cerebritis and dural venous thrombosis (including superior sagittal and cavernous sinus thrombosis).[83, 104, 105] These are most often associated with frontoethmoidal or sphenoidal ARS,[105] via direct extension or haematogenously via diploic veins.[106] Flora is often mixed aerobic/anaerobic, so the antibiotic cover should reflect this, if possible corroborated with culture of pus samples. Common pathogens in this context are *Streptococcus* and *Staphylococcus* species and anaerobes.[83]

A high index of suspicion is required, as the clinical presentation of intracranial sepsis is often non-specific, including high fever with severe, intractable headache, but

sometimes such symptoms are absent (masked), especially in immunocompromised patients and those who have had prolonged antibiotic therapy already.[101] However, in most cases, specific signs and symptoms are present, including nausea and vomiting, neck stiffness and altered mental state.[98, 103, 104, 106] Intracranial abscesses are often heralded by signs of increased intracranial pressure, meningeal irritation, and focal neurologic deficits, including cranial nerve palsies (III, VI and VII), or more generalized neurological deficit (altered consciousness, gait disturbance, confusion).[98, 107]

As with orbital complications, CT with contrast allows an accurate delineation of bone involvement. MRI is an excellent adjunct, especially where neurosurgical intervention is being considered. It is more sensitive than CT in discriminating intracranial complications,[108] with particular value in venous sinus thrombosis, or where there is soft-tissue involvement. The same considerations apply in terms of availability of MRI and likely requirement of general anaesthesia in young children.

Options for culture include swabs from the nose (with endoscopic guidance if practical), sampling of pus during formal sinus surgery or during neurosurgical drainage, plus blood cultures and lumbar puncture (after first excluding raised intracranial pressure).

As for intraorbital abscesses, drainage of intracranial abscesses is usually undertaken (neurosurgical burr hole drainage, craniotomy or image-guided aspiration), as needed. Combined drainage of the paranasal sinuses can be performed endoscopically or via an open approach.[108] In some cases, where abscesses are small and/or inaccessible, non-surgical management may be reasonable, only after expert neurosurgical consideration. High-dose long-term antibiotic therapy is often needed.[109, 110]

Cavernous sinus thrombosis

This potentially devastating complication is seen where veins around the paranasal sinuses are congested during ARS, and become phlebitic, with propagation centrally. This can lead to cavernous sinus thrombophlebitis causing sepsis and multiple cranial nerve involvement.[111] This accounts for around 9% of intracranial complications,[106] particularly after ethmoidal or sphenoidal sinusitis.[112] In adults, the mortality rate is 30%. No such data are available for the paediatric population, where the mortality rate for intracranial complications has been quoted at 10–20%.[113]

Clinical features include:[114]

- bilateral ptosis
- proptosis and chemosis
- ophthalmic nerve neuralgia
- retro-ocular headache, which can be severe
- complete ophthalmoplegia,
- papilloedema
- signs of meningeal irritation, associated with spiking fevers
- confusion and reduced level of consciousness.

Similar investigations will be required as for other forms of intracranial complications. MRI (in particular MR venography) is especially sensitive, with absence of flow in the thrombosed sinus. As an alternative, CT with contrast may show equivalent filling defects.

Treatment is undertaken in a specialist neurosurgical centre. Anticoagulants may be considered, as long as imaging has excluded intracerebral haemorrhage, in conjunction with intravenous antibiotics and/or steroids. Drainage procedures will include attention to the involved paranasal sinuses.

OSSEOUS COMPLICATIONS

ARS may lead to infection spreading to the surrounding bone, producing osteomyelitis and in some cases onward spread to the brain and central nervous system. The frontal sinuses are most often implicated, but ARS in any of the sinus groups may produce similar sequelae, particularly in infancy, where the maxillae can be affected.[114, 115]

Osteomyelitis produces avascular necrosis of bone and localized venous congestion. In the case of the frontal sinus, erosion of the anterior table in this way causes oedema of the overlying skin (Pott's puffy tumour). Spread via the posterior table can give rise to meningitis and other intracranial complications, with similar signs. The changes are well delineated by CT, with MRI as an adjunct if intracranial complications are suspected.

The incidence of these complications has been well documented in adults, but is less certain in children, although overall these are relatively rare events. Management, as with other complications, demands a circumspect, proactive approach, often requiring multimodality treatment under the care of a variety of specialities.

PAEDIATRIC CHRONIC RHINOSINUSITIS

Chronic rhinosinusitis (CRS) (with or without nasal polyps) in children is defined by EPOS[2] as:

'Inflammation of the nose and paranasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):

- +/– facial pain/pressure
- +/– cough
- persisting for >12 weeks.'

This duration is endorsed by the ICAR:RS[4] and AAO-HNS[3] consensus statements.

Clinical overview

Paediatric CRS has not been as extensively studied as in adults. The relative contribution of anatomical and other factors will differ between children and adults. Only a minority of cases present for treatment, and this is

typically medical, with surgery reserved for more resistant and severe cases.[2]

While the above definition is clear, confirming a diagnosis of CRS in children is often challenging or even impossible.[2] The precise history may be difficult to establish, particularly separating persistent symptoms lasting more than 12 weeks from frequently recurrent symptoms, interspersed with short periods of remission. Examination is not always straightforward, nasal endoscopy may not be tolerated and imaging is withheld in most cases. Even when CT scanning is undertaken, it should be noted that 18–45% of normal controls may have sinus-related changes.[116, 117] In one study, children without CRS were found to have a mean Lund-MacKay score of 2.8.[118] With this in mind, it has been proposed that a Lund-MacKay score greater than 5 in children indicates CRS,[119] but in reality most children with CRS will be managed on a clinical basis and will not undergo imaging.

There is also significant overlap with other very common childhood upper respiratory conditions, including recurrent viral URTI, allergic rhinitis and adenoiditis and/or adenoidal hypertrophy. In fact, the EPOS 2012 consensus group deemed it impossible to distinguish CRS from adenoid-related pathology in young children.[2]

Given these clinical and diagnostic uncertainties, it is important to establish which clinical features have the highest positive predictive value for CRS. Studies have suggested that the four most common features are:[120, 121]

- cough, particularly chronic cough
- rhinorrhoea
- nasal congestion
- post-nasal drip.

One study examined the correlation between chronic cough (>4 weeks) and CT sinus changes. In these patients, abnormalities on sinus CT were found in 66% of cases, with mild changes in 14%, moderate changes in 19% and severe changes in 33% of all cases.[122]

Pathophysiology of paediatric CRS

Some of the contributing factors in children with ARS will also apply in CRS, but it is worth considering separately the particular factors involved in CRS. This also applies to the differences in aetiology, pathology and management of CRS between children and adults.

Normal function of the nose and paranasal sinuses depends upon the health and integrity of the ciliated, columnar mucosal epithelium, and the overall anatomical pathways for mucus clearance, aeration and sinus drainage. The osteomeatal complex (OMC) is central to these considerations, which functionally represents the final common drainage pathway for the majority of the paranasal sinuses (frontal anterior/middle ethmoid cells and maxillary sinuses). The OMC comprises five structures:

- **maxillary ostium:** the main drainage channel of the maxillary sinus into the middle meatus
- **infundibulum:** a common channel draining the ostia of the maxillary and ethmoid sinuses to the hiatus semilunaris
- **bulla ethmoidalis:** a single air cell which projects inferomedially over the hiatus semilunaris
- **uncinate process:** a crescent-shaped process arising from the posteromedial aspect of the nasolacrimal duct, forming the anterior border of the hiatus semilunaris
- **hiatus semilunaris:** the final drainage passage, between the bulla ethmoidalis superiorly and free edge of the uncinate process.

The sphenoid and posterior ethmoid cells drain separately into the sphenoethmoidal recess.

The region of the OMC is subject to significant anatomical variation, often with little effect on sinonasal function. But mechanical obstruction of this area, as a result of congenital malformation, trauma, surgery and, more commonly, mucosal inflammation, may greatly impair its functional efficacy. This is considered to be the key event in most cases of chronic rhinosinusitis, although a diverse group of precipitating factors are involved. Obstruction of sinus drainage leads to retained secretions, reduced sinus aeration, mucosal hypoxia and dysfunction. Mucosal oedema and cilial impairment, with stimulation of further mucus production, lead to mucus stasis, further secretion retention and secondary infection.[56]

Contributing factors in paediatric CRS

With these considerations in mind, contributing factors for CRS in children can be subdivided into local/anatomical, inflammatory and infective, and systemic (**Box 24.2**).[56]

BOX 24.2 Contributing factors in paediatric CRS

Local factors	Inflammatory and infective factors	Systemic conditions
Sinus obstruction (anatomical, e.g. concha bullosa)	Viral URTI	Immune deficiency
Septal deviation	Bacterial infection	Cystic fibrosis
Nasal polyps	Allergy	Primary ciliary dyskinesia
Adenoidal inflammation	Gastro-oesophageal reflux disease (GORD)	
Trauma/iatrogenic	Tobacco smoke	
Foreign body		

The variation in contributing factors, and indeed the heterogeneity of individual anatomical variations and comorbidities, necessitates a circumspect approach in the investigation and management of such cases. Some particular issues warrant special consideration and are discussed below.

MICROBIAL FLORA

Microbial involvement in the pathogenesis of CRS has been increasingly considered, in addition to the cases of acute and chronic infection with the typical bacterial pathogens associated with ARS (above). It has traditionally been thought that the paranasal sinuses are sterile, but some studies have now suggested that this is not the case. In fact, reduced diversity of sinus microbial flora has been demonstrated in some cases with CRS, compared to healthy controls.[123] *Lactobacillus sakei* was shown in murine models of CRS to have a protective effect. In cases of CRS, it could therefore be possible that use of antibiotics may reduce the naturally protective effects of these organisms.

BACTERIAL INFECTION: EXOTOXINS AND BIOFILMS

On the other hand, infection by pathogenic organisms (as opposed to colonization by non-pathogenic flora) is a precipitant in some cases. The organisms involved are those which are typically implicated in acute bacterial RS (above). The mechanisms whereby these infections lead on to CRS are under review. Bacterial exotoxins may have an important role, with provocation of an excessive immune response by these mediators. For example, in patients with inflammatory nasal polyps, staphylococcal exotoxins have been found to affect T-cell function.[124] Biofilms (aggregates of bacteria within an external matrix of proteins, nucleic acids and polysaccharides) are also thought to be important, greatly decreasing the efficacy of antimicrobials. In fact, biofilms have been found in up to 80% of sinus biopsies from patients undergoing functional endoscopic sinus surgery (FESS),[125] and adenoid tissue, abundant in young children, may also harbour large volumes of biofilms, contributing to these processes.[126]

ADENOIDS

The role of the adenoids in the pathogenesis of paediatric RS, especially in chronic cases, is increasingly appreciated. It is also known that adenoidectomy reduces or eliminates symptoms in a high proportion of children with CRS. This is covered extensively in the EPOS 2012 document.[2] Several findings from a number of studies have highlighted this presumed aetiopathologic relationship.

- **Bacterial 'reservoir'.** In children with CRS, the bacteria cultured from middle meatal swabs and adenoidal core cultures are very similar, including *Streptococcus pneumoniae*, group A streptococci, *Haemophilus influenzae*, *Staphylococcus aureus* and coagulase-negative staphylococci.[127] The positive predictive value of adenoid core culture in predicting middle meatal culture results in one study was 91.5%, with a negative predictive value of 84.3%.[127]

  Interestingly, adenoid size alone has not been shown to correlate with the severity of disease on CT,[128] suggesting that the role of the adenoids as a reservoir for bacteria and associated inflammation ('adenoiditis') is more relevant than the size of the tissues (pure adenoidal hypertrophy).
- **Biofilms** are thought to have an important role within inflamed adenoid tissues in cases of adenoiditis and are also implicated in CRS in children, in the same patients. One study compared the biofilm volume on the surface of the adenoids excised in cases of adenoiditis/CRS versus those removed purely for obstructive symptoms. Although carried out in small numbers of cases, there was a major difference in the surface area of the adenoid tissue covered in biofilms between children with CRS symptoms, (88–99% of the surface area) and those with simple obstruction (0–6.5% of the surface area).[129]
- **Immunological effects** of the adenoid tissue have also been considered. In cases of CRS, adenoid tissue has lower IgA expression than in comparable tissue of children with simple adenoidal hypertrophy but no CRS symptoms.[130] Conversely, inflammatory markers (such as tissue remodelling cytokines, transforming growth factor β (TGF-β1), matrix metalloproteases MMP-2 and MMP-9) were found at higher levels in the adenoids of CRS patients than in controls.[131]

These studies, while small, correlate well with the near-identical clinical pictures of CRS and adenoiditis in children, and the relative benefit of adenoidectomy, independent of adenoid size, in the management of these patients. This is further addressed in 'Surgical management' below.

GASTRO-OESOPHAGEAL REFLUX DISEASE

Gastro-oesophageal reflux disease (GORD) is now recognized as a feature in a proportion of children with CRS. A large retrospective study comparing children with a diagnosis of GORD with non-reflux controls showed significantly higher rates of diagnosis of concomitant RS than in the non-reflux group (4.19% vs 1.35% respectively).[132] Effective antireflux therapy has been shown to reduce the need for sinus surgery in many of these cases.[133] But the presence of these conditions together, while suggestive, does not confirm a causal relationship. Further controlled trials will be required before antireflux medical treatment of children with CRS can be recommended routinely.

ALLERGY AND ALLERGIC RHINITIS

Children with CRS will often have an atopic history, including allergic rhinitis. But both conditions are common within the paediatric population and, again, their coexistence within the same individual does not demonstrate causality *per se*.

A number of studies have examined this relationship, albeit comprising relatively small numbers of children. Their findings are mixed, suggesting that the link between the two domains is not clear-cut. One examined the correlation between radioallergosorbent test (RAST) test and CT findings in patients (children and adults) with CRS symptoms which were resistant to treatment. Of 42 patients, 40% were atopic and 60% had negative RAST tests; the RAST-positive group also had more pronounced CT findings than the RAST-negative group.[134] But other studies have not shown significant correlations between atopic and non-atopic groups, either in terms of CT changes,[135, 136] or in the prevalence of atopy between children with and without a history of CRS.[137] The lack of consistent data has led the EPOS consensus group to suggest that there is probably no link between allergic rhinitis and CRS in children.[2]

ALLERGIC FUNGAL RHINOSINUSITIS

Allergic fungal rhinosinusitis (AFRS) results from hypersensitivity to fungi. It has a relatively high prevalence in adults with CRS who undergo surgery, and is estimated to occur in 5% to 10% of adults with chronic sinusitis who require surgery.[138] Children with allergic fungal rhinosinusitis may present with proptosis and polyposis.[139] Treatment includes sinus surgery to remove inflammatory tissue, polyps and fungus. Evidence is lacking for other treatments in children, although topical and systemic steroids and immunotherapy may be beneficial. The clinical diagnosis is easily overlooked, so a high index of suspicion is needed. Typical CT findings are unilateral sinus opacification with non-erosive expansion of the sinuses on CT.

ASTHMA

Some small studies examining the clinical course of children with asthma and CRS have shown marked improvements in asthma-related measures after medical and/or surgical treatment of CRS[120] (need for asthma medications, spirometry, wheezing and inflammatory markers in nasal lavage).[140] The improvements were seen to reverse once the CRS relapsed. These findings suggest that successful treatment of CRS in patients with asthma will help better control their chest symptoms, as is the case for allergic rhinitis. But while the links between asthma and allergic rhinitis are well documented, the relationship between asthma and CRS in children has not been demonstrated definitively by controlled trials.

IMMUNODEFICIENCY

A number of studies have evaluated the relationship between CRS in children and underlying immune deficiencies. These comprise series where cases of persistent CRS, which have been resistant to medical treatment, were investigated for a number of different immune parameters. Relatively small numbers of children were investigated in each series, with very variable results, including low IgA, Ig1 and/or Ig3 levels, poor pneumococcal antigen 7 responses in some cases (but normal vaccine responses in others).[141–143] Additionally, one study examined the clinical response of six children with refractory CRS who were treated with intravenous immunoglobulin for 1 year.[144] This showed a significant reduction in sinusitis episodes, total number of days of antibiotic usage and improved CT findings. These results suggest that various forms of immunodeficiency may have a role in a proportion of children with CRS, particularly in resistant cases. The EPOS 2012 consensus group therefore suggest evaluation of immune function in such cases, with quantification of Ig levels, and responses to various immunizations, including pneumococcal conjugate vaccine, tetanus and diphtheria.[2]

CYSTIC FIBROSIS

Cystic fibrosis (CF) is an autosomal recessive condition affecting 1 in 2500 live births in the UK, and is associated with high incidence of CRS and nasal polyposis in children. The mutated *CFTR* gene (cystic fibrosis transmembrane conductance regulator gene, long arm of chromosome 7–7q31.2) leads to abnormal cyclic AMP-mediated transmembrane chloride transport in epithelia and exocrine glands. This gives rise to multiorgan pathologies, including chronic pulmonary infections and bronchiectasis, pancreatic dysfunction and infertility. CRS is extremely common in these patients, and nasal polyposis is a feature in 7–50%.[145, 146]

Genetic testing and screening for suspected CF

More than 1000 mutations of the *CFTR* are known. The most commonly encountered mutation leads to a single amino acid deletion at position 508 in the *CFTR* protein (ΔF508). However, such is the number of possible mutations, and possible allelic combinations between individuals, that CF is not always straightforward to diagnose. It may be missed with screening, and can present variably (a disease spectrum), sometimes even into late childhood or adulthood.

Neonatal screening for the condition (as part of the Guthrie heel prick blood tests) has been offered universally in the UK since October 2007, having commenced earlier in some areas. This is also undertaken in a number of other countries. Blood levels of immunoreactive trypsinogen (IRT) are known to be high in cases of CF,[147] and this forms the basis of the CF component of the Guthrie test, undertaken universally within 5 days of life.

Babies with high IRT levels at or above the 99.5th centile are forwarded for genetic testing across four common loci (a four-panel DNA test, including ΔF508), with subsequent protocols designed to maximize accurate CF diagnosis as early as possible, while limiting parental anxiety associated with delays and false positives.

Babies with mutations in both *CFTR* genes have a presumptive diagnosis of CF and are reported as 'CF suspected', before referral to a paediatric service for evaluation (clinical assessment, sweat test and confirmatory mutation analysis).

Babies with one mutation detected will most often have a normal second allele, and are therefore

asymptomatic carriers. But a minority have an abnormal second allele which is not detected by the four-panel test. To identify such cases, a second IRT test is undertaken between day 21 and day 28, using a repeat dried blood spot specimen. Those with a high IRT on this second sample are reported 'CF suspected' and are referred as above, while those with IRT levels below a defined cut-off are considered probable carriers with a low risk of CF.

Those babies who have no detected mutation and a first IRT above the 99.5th centile but below the 99.9th centile are reported as 'CF not suspected'. Babies with an initial IRT at or above the 99.9th centile require a second IRT, as above, at 21–28 days; a second IRT below a given cut-off is reported as 'CF not suspected', but those with a high second IRT above the cut-off are considered 'CF suspected' and are referred on, with a presumptive diagnosis.

Sweat test

Owing to the great genetic heterogeneity of the condition, however, any genetic screening is accompanied by a sweat test, assaying the chloride levels in sweat induced by pilocarpine iontophoresis.[148] At the test site (usually the forearm), an electrode is positioned over gauze containing pilocarpine (a parasympathomimetic alkaloid) and an electrolyte solution. A second electrode is placed on untreated skin nearby, and a small electric current is applied, which draws sweat out of the skin. This is collected using preweighed filter paper over 30 minutes under controlled conditions to prevent contamination and evaporation.

Weighing and subsequent analysis of the sweat sample will determine the chloride level, and this is compared against age-appropriate levels (for children under or over 6 months of age). The sodium level should be commensurate with the chloride level. If not, then technical errors may be responsible; the reliability of the sweat test may be compromised by an insufficient sample, evaporation, contamination and other metabolic conditions, for example. A reliable positive test with high chloride levels on two separate days is diagnostic of CF.

Endoscopic sinus surgery in patients with cystic fibrosis

Surgical management of this group has been considered in the EPOS 2012 paper,[2] but studies are relatively small. The limited evidence from these studies suggests a significantly increased incidence of nasal polyps in children with CF, when compared with non-CF patients with CRS, and a high correlation between positive culture of *Pseudomonas* from sinonasal samples and underlying CF.[149] A further study demonstrated that, although certain measures, such as hospital admissions, were unaffected by ESS in this paediatric CF group, quality of life, nasal obstruction, discharge and other symptoms were significantly improved by ESS/polypectomy.[150] It would therefore appear reasonable to consider surgical management of children with CF who have sinonasal manifestations, bearing in mind the existing disease burden and the likelihood of symptom recurrence requiring multiple procedures throughout life. As such, the extent of surgery should be carefully considered on an individual basis, with the aim of maximizing benefits but limiting the risks of morbidity and complications.

PRIMARY CILIARY DYSKINESIA

Primary ciliary dyskinesia (PCD) is an autosomal recessive condition, involving dysfunction of cilia, present in 1 of 15 000 of the population.[151] The normal movement of mucus by mucociliary transport toward the natural ostia of the sinuses and nasopharynx is disrupted. Half of children with PCD also have situs inversus, bronchiectasis and CRS, collectively termed Kartagener syndrome. The diagnosis of PCD, like CF, should be suspected in children with atypical asthma, bronchiectasis, chronic wet cough or rhinosinusitis. Additionally, in PCD, children are prone to chronic and resistant otitis media, with persistent middle ear effusion. This tends to respond poorly to ventilation tubes, with persistent mucoid discharge.[9] Screening tests for PCD include nasal nitric oxide (NO) (with lower NO levels than controls) and the saccharin test, demonstrating slower mucociliary transit time from the anterior nares to the nasopharynx. Specific diagnosis involves examination of cilia (from mucosal brushings) by light and electron microscopy. In cases of PCD, this most often demonstrates lack of outer dynein arms, or a combined lack of both inner and outer dynein arms.[152] In contrast to CF cases, nasal polyposis is not typically encountered, despite significant sinonasal symptoms in many cases.[153]

Management of chronic rhinosinusitis in children

ASSESSMENT AND DIAGNOSTIC WORKUP

The clinical assessment of children with CRS is similar to that already described in cases of ARS. History, examination and further investigations should be targeted according to individual presentation, bearing in mind the possibility of underlying aetiologies, including adenoidal hypertrophy, and rarer conditions including CF, PCD, allergic fungal rhinosinusitis and immunodeficiency, for example. This heterogeneity of conditions demands a high index of suspicion when managing children with CRS, altering the threshold for referral for other specialist consultations and diagnostic tests, including cross-sectional imaging (CT and MRI) and culture of nasal samples. The sensitivity and specificity of sampling from the middle meatus (directly or under endoscopic visualization) for microbial culture has already been addressed.[52, 53]

Similarly, the rationale for CT and MRI, and their advantages and limitations have also been discussed.[119, 120] Plain radiographs do not correlate well with CT findings in CRS.[154] CT offers an excellent road map for surgical treatment, identifying anatomical variants and areas of bony erosion or distortion from disease.[155] Particular diagnoses in the context of CRS may be revealed by CT, for instance in the case of allergic fungal rhinosinusitis and CF. Characteristic features of AFS are expansile disease with attenuation of the skull base and orbital wall,

often with a 'starry sky' speckled pattern of high attenuation on soft tissue and bone windows, as a result of thick allergic mucin and calcification. This is corroborated by MRI, with low signal on T1 weighting in areas of mucin, with signal void on T2 weighting, plus a high signal rim of surrounding mucosal inflammation.[156]

In patients with CF, CT demonstrates panopacification of the sinuses and medial displacement of the lateral nasal wall, which may obstruct the nasal passages.[157]

MEDICAL THERAPY

In contrast to CRS in adults, young children with CRS typically can be managed conservatively, as symptoms tend to resolve spontaneously.[158] A moderate-sized prospective study following 169 patients over 6 months demonstrated that no children with persistent runny nose developed severe clinical symptoms or complications of CRS.[30] Data regarding specific medical treatment for CRS in children are very limited. The levels of evidence for each treatment are summarized in the EPOS 2012 document[2] and shown in **Table 24.4**.

While antibiotics have a modest overall benefit in the management of short-term RS symptoms, no such benefits have been demonstrated in the long term for children with CRS in one study.[159] No studies have demonstrated conclusive benefits of topical steroids in children with CRS, although a number of studies have demonstrated significant benefits in rhinitis, such that the EPOS consensus supports their use in paediatric CRS, albeit with little supporting evidence.[2] Nasal steroids in asthmatic patients with CRS may also reduce bronchial hyper-reactivity.[140] Saline douching with normal[160] or hypertonic saline[161] has some demonstrable efficacy in CRS, and may also improve parallel asthma symptoms,[162] but antral washouts are not recommended, with little evidence to support them. Treatment of active gastro-oesophageal reflux is also believed to improve CRS symptoms in patients affected by both conditions.[133, 163]

SURGICAL MANAGEMENT

Adenoidectomy

The role of the adenoids in the pathogenesis of paediatric rhinosinusitis remains uncertain, but adenoidectomy is known to improve symptoms in at least half of young children with CRS.[2] Whether the most important factor is the presence of the adenoids *per se*, their size or related bacterial colonization and inflammation (adenoiditis) is unclear, but there is likely to be a degree of heterogeneity in this context among young children with CRS. Nasal obstruction, snoring and hyponasal speech occur more often in children with adenoid hypertrophy while symptoms of rhinorrhoea, cough, headache, signs of mouth breathing, and abnormalities on anterior rhinoscopy occur as frequently in children with chronic rhinosinusitis as in children with adenoid hypertrophy.[164] In one study, antibiotic-resistant bacteria were found on culture of adenoid tissue in 56% of children undergoing adenoidectomy for hypertrophy plus otitis media with effusion and CRS, compared to 22% undergoing adenoidectomy purely for hypertrophy without those complications.[165] In another study, no significant correlation was found between the size of the adenoid and the presence of purulent secretions in the middle meatus on fibreoptic examination in 420 children aged 1–7 years. There was, however, a very significant correlation between the size of the adenoid and the complaints of mouth breathing and snoring.[166]

Endoscopic sinus surgery

Functional endoscopic sinus surgery (FESS) is a common intervention in adults with CRS, but its role in the management of paediatric CRS remains controversial. Certainly, conservative measures, initial medical management and adenoidectomy should be considered first, and where appropriate other underlying conditions should be excluded, before FESS is undertaken. Surgical management decisions will also be influenced by the presence of underlying pathology such as CF, PCD and AFS.

Importantly, washout procedures which were previously commonly undertaken (antral washouts, inferior meatal antrostomy and Caldwell Luc procedures) are ineffective and not recommended in this context.[1, 66, 67, 167, 168]

Absolute indications for FESS in children are the following:[69]

- complete nasal obstruction in cystic fibrosis due to massive polyposis or due to medialization of the lateral nasal wall
- orbital abscess
- intracranial complications

TABLE 24.4 Treatment evidence and recommendations for children with chronic rhinosinusitis (reproduced with permission[2])

Therapy	Level	Grade of recommendation	Relevance
Nasal saline irrigation	Ia	A	Yes
Therapy for gastro-oesophageal reflux	III	C	No
Topical corticosteroid	IV	D	Yes
Oral antibiotic long term	no data	D	Unclear
Oral antibiotic short term <4 weeks	Ib(–)[#]	A(–)*	No
Intravenous antibiotics	III(–)[##]	C(–)**	No

[#] Ib (–): Ib study with a negative outcome; *A(–): grade A recommendation **not** to use; [##]III(–): level III study with a negative outcome; **C(–): grade C recommendation **not** to use.

- antrochoanal polyp
- mucocoeles or mucopyocoeles
- fungal rhinosinusitis.

For other cases, where CRS symptoms persist despite optimal medical management, FESS may also be considered[1, 2] and can be limited to uncinectomy, partial ethmoidectomy and opening of the bulla and/or maxillary antrostomy.

In terms of demonstrable benefits, a small number of studies have shown improvements after FESS in children with CRS. A metanalysis of eight published articles (832 patients) showed positive outcome rates of 88–92%. The average combined follow-up was 3.7 years.[169] This concluded that FESS is a safe and effective treatment for CRS which is refractory to medical treatment. Other studies have produced similar results.[170–172] FESS is unlikely to be successful in very young children[173] and its efficacy is reduced if the child is exposed to tobacco smoke.[174] Disease duration prior to surgery does not affect outcome.[175] No obvious long-term differences in facial growth have been demonstrated in children with CRS undergoing FESS rather than those managed conservatively.[172]

Overall, therefore, FESS is likely to be beneficial in selected cases of paediatric CRS, but should be considered only after a period of medical management (and/or adenoidectomy) and exclusion of underlying pathologies. When undertaken, FESS should be limited in most circumstances, and typically avoided in very young children.

KEY POINTS

- Paediatric rhinosinusitis is extremely common.
- Evidenced based management has been presented in the literature, for example in the EPOS and ICARS documents.
- The characteristic features are rhinorrhea and nasal obstruction, often in conjunction with a cough and systemic upset in acute forms.
- Most cases of acute rhinosinusitis result from viral upper respiratory tract infections and some have an additional bacterial component, with a variety of common organisms implicated (typically gram positive).
- The majority of cases are self-limiting, some require treatment with antibiotics and very few result in complications.
- The possibility of orbital, intracranial and systemic sepsis should always be considered in children with rhinosinusitis, particularly in cases with pronounced symptoms and systemic derangement. This should prompt immediate investigation and specialist management.
- Chronic rhinosinusitis is also common. Many cases are exacerbated by adenoidal hypertrophy, and other anatomical factors are less commonly involved. Underlying inherited conditions such as cystic fibrosis and primary ciliary dyskinesia should also be considered in resistant cases.

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CHAPTER 25

LACRIMAL DISORDERS IN CHILDREN

Caroline J. MacEwen and Paul S. White

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SEARCH STRATEGY AND EVIDENCE BASE

PubMed MeSH searches were performed combining the terms lacrimal and disorders. Several thousand articles were identified, almost all too specific in context to guide this short overview chapter.

INTRODUCTION

The lacrimal system consists of a secretory portion and a drainage system. The secretory portion is made up of the lacrimal and accessory lacrimal glands which, together with the Meibomian glands and the goblet cells, secrete the components of the tear film. The accessory lacrimal glands produce basal tear secretion, and the lacrimal gland is largely responsible for reflex tearing in response to noxious or emotional stimuli. The drainage system consists of the lacrimal puncta, canaliculi, lacrimal sac and nasolacrimal duct (Figure 25.1). This active system pumps tears from the conjunctival sac into the inferior meatus of the nose. Clinical problems with the lacrimal system in children usually relate to the reduced drainage of tears. The underproduction of tears, causing dry eyes, is rare but more serious due to the potential for sight-threatening consequences.

ANATOMY

The lacrimal gland is an exocrine gland that sits in the anterior aspect of the supratemporal orbit. The ducts of the gland open onto the conjunctiva in the superior fornix. Embryologically the lacrimal gland develops from ectoderm that is supported by embryonic skull cap mesoderm. The lacrimal gland continues to grow up to the age of 4 years. Basal tearing is present in infants from birth, and reflex tearing begins at any time from birth to several months of age.[1] The lacrimal outflow system develops between the embryonic maxillary process and the lateral nasal process from a cord of surface ectoderm. By the end of the first trimester, this tissue begins to canalize and the nasolacrimal duct opens into the inferior meatus of the nose just before or after term birth. There may be a failure of this canalization process at any part of the system, but this is most frequent at the lower end.[2]

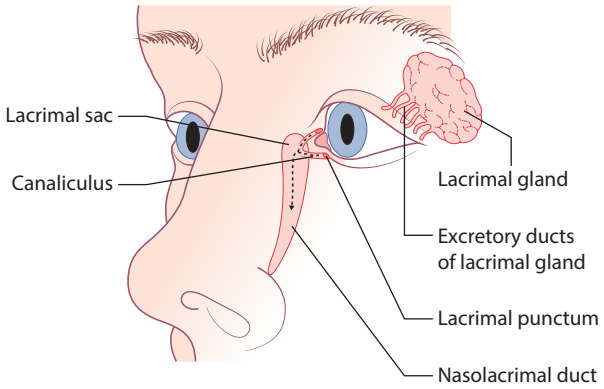


Figure 25.1 The lacrimal system, comprising the lacrimal gland, the lacrimal puncta, canaliculi, lacrimal sac and nasolacrimal duct.

Tears are actively pumped through the outflow system from the puncta and canaliculi and on into the lacrimal sac. This sits in the bony lacrimal fossa, separated from the middle meatus of the nose by the maxilla and lacrimal bone. The lacrimal sac extends superiorly under the medial canthal ligament as its fundus. The nasolacrimal duct exits from the lower end of the sac and passes in a downward, lateral and posterior direction. The duct is surrounded by bone in its upper part but becomes membranous inferiorly and opens into the medial wall of the inferior meatus of the nose through Hasner's valve. This can be located endoscopically in the inferior meatus approximately 1 cm posterior to the nasal spine.

DRY EYES IN CHILDREN

Children with dry eyes present with irritable, gritty eyes, which may be diffusely injected. On examination there is a reduced tear meniscus with punctate keratopathy, particularly affecting the interpalpebral zone. Staining occurs with fluorescein dye.

Congenital alacrima, or hyposecretion of tears, is rare. This may be due to absence of the lacrimal gland or to the lacrimal gland being ectopic. Alacrima may be associated with systemic conditions such as Allgrove syndrome (familial alacrima, achalasia of the cardia and glucocorticoid deficiency), anhydrotic ectodermal dysplasia and Riley–Day syndrome (familial dysautonomia),

Acquired tear insufficiency may be due to pathology of the lacrimal gland, causing failure of tear production, or to conjunctival damage, leading to ductule obliteration. The gland may be damaged by Epstein–Barr infection, as the result of HIV infection, or in patients following bone marrow transplantation (often associated with graft versus host disease). Sjögren's syndrome is rare in children; it can be a primary autoimmune event or secondary to rheumatoid arthritis or systemic lupus erythematosus (SLE). Children with Sjögren's syndrome often have lacrimal gland involvement, and they may have recurrent parotid gland swelling and salivary gland involvement. Sjögren's should be considered in any child with recurrent parotitis, keratoconjunctivitis sicca, and early tooth decay due to xerostomia.[3]

Isotretinoin treatment for acne can cause dry eyes in adolescence. This is usually reversible at cessation of the drug. Treatment of dry eyes involves copious use of artificial tears and temporary or permanent punctal occlusion in severe cases.

LACRIMAL TUMOURS AND GRANULOMAS

Lacrimal tumours are extremely rare in children. Orbital 'pseudotumour' (the preferred name is now idiopathic orbital inflammatory disease), causing painful swelling, is rare but may affect the lacrimal gland.[4] It is a non-infective inflammatory disease of unknown aetiology that occurs in the orbit and responds to steroids. Malignant epithelial tumours, including mixed-cell adenocystic and other carcinomas, have been recorded in childhood.[5] Lacrimal gland enlargement is also found in conditions such as sarcoidosis and leukaemia. Prolapse of the lacrimal gland, which is commonly bilateral, may present as a subconjunctival mass in the upper outer fornix. This may occur with craniofacial anomalies due to reduced orbital volume and increased orbital pressure.

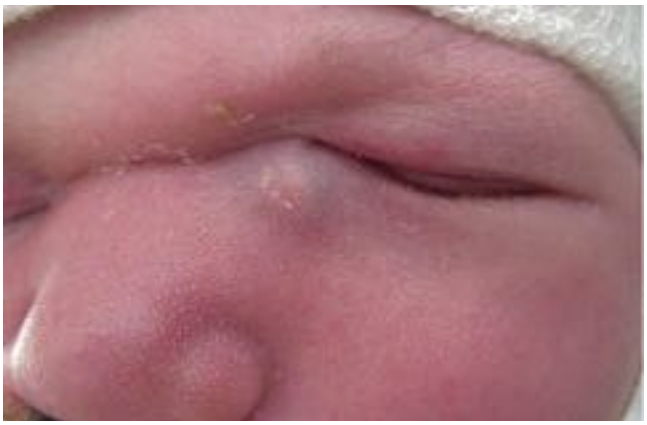


Figure 25.2 Congenital dacryocystocele. A bluish swelling is seen below the medial canthal tendon. It can present as nasal obstruction.

Dacrocystocele is a congenital swelling located at the medial canthus due to trapped fluid inside the lacrimal sac and nasolacrimal duct.[6] This usually presents as a tense, blue, non-pulsatile swelling below the medial canthus that is evident at birth (**Figure 25.2**). Congenital dacryocystocele must be differentiated from a meningoencephalocoele, a meningocoele, a midline nasal dermoid cyst or a capillary haemangioma. If there is any doubt, an MRI scan is helpful in identifying the dilated sac and nasolacrimal duct and in excluding other pathology. Routine imaging, however, is not necessary and the diagnosis is usually made clinically.

Treatment of a dacryocystocele involves observation during the first 2 weeks of life, during which time most will improve spontaneously. If it has not settled by this stage or if acute dacryocystitis or respiratory difficulties develop, then surgical treatment is required. A skin scar can be avoided by drainage of the dacryocystocele into the nose using an endoscopic approach.

CONGENITAL NASOLACRIMAL DUCT OBSTRUCTION

Congenital nasolacrimal duct obstruction (CNLDO) is clinically evident in up to 20% of infants, the vast majority of which become symptomatic with epiphora during the first month. The natural history is to spontaneously resolve with maturation (**Figure 25.3**).[7–9] Spontaneous resolution is rapid during the first year of life and continues, at a reduced rate, beyond this into childhood.[10, 11] CNLDO represents a delay in maturation of the lacrimal drainage system where it enters the nose, resulting in persistent membranous obstruction or stenosis (**Figure 25.4**)

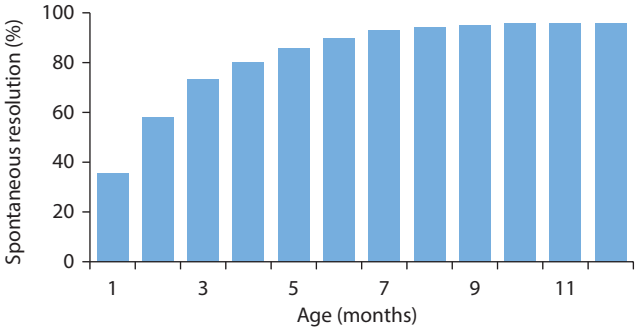


Figure 25.3 The rate of spontaneous resolution of nasolacrimal duct obstruction in 974 infants with congenital nasolacrimal duct obstruction as a function of age in months (adapted from MacEwen and Young[9]).

at the valve of Hasner. This should be differentiated from a dacryocystocoele.

Although usually an isolated abnormality, CNLDO may be more frequent in certain conditions, such as EEC syndrome (ectrodactyly, ectodermal dysplasia, clefting) branchio-oculo facial syndrome, craniometaphyseal or craniodiaphysial dysplasias, Down syndrome, lacrimo-auriculo-dento-digital (LADD) syndrome, and the CHARGE association.

On examination there is an increased tear meniscus and there may be stickiness or crusting on the lashes. A mucocoele may develop: the contents can be expressed into the conjunctival sac.

A fluorescein disappearance test (FDT) should be performed on children with epiphora as it provides objective evidence to support a diagnosis of lacrimal outflow obstruction.[12]

Treatment of congenital nasolacrimal duct obstruction

Congenital nasolacrimal duct obstruction has a very high rate of spontaneous resolution, so observation is recommended until the child is at least 1 year old. Under 1 year of age, probing is no better than observation and is generally not recommended. Between 12 and 24 months of age, the long-term results of probing and observation are the same but resolution is quicker with probing. Hence, most surgeons would recommend intervention some time after the first year of life.[10, 13–17]

Probing should be carried out in a stepwise fashion, identifying the patency or obstruction of each area between the puncta and the end of the nasolacrimal duct. The first stage of probing is a blind procedure and depends on awareness of resistance to the probe as it passes through the system. Thereafter the use of a 2.7 mm or 3.0 mm nasal endoscope will permit a direct view of the lower end of the nasolacrimal duct which assists in the diagnosis and management.[17, 18] The nose is first prepared with vasoconstrictor solution then a nasal endoscope is introduced into the inferior meatus after infracture of the inferior turbinate with a Freer elevator. This manoeuvre itself is often therapeutic as it opens up a narrow inferior meatus and may stretch a stenotic ostium.[19] Finally, fluorescein appearance is checked by syringing: stained fluid



Figure 25.4 Stenotic flow of fluorescene flush through the valve of Hasner within the inferior meatus of the right nasal cavity.

should be gently syringed into the system from above and observed through the nasendoscope.

The system should then be probed via the upper canaliculus using the smallest probe available (usually a Bowman's size 0000), which can be observed via the nasendoscope entering the inferior meatus through the valve of Hasner (see **Figure 25.4**). In cases of atresia the membrane can be incised endoscopically in the inferior meatus using a phaco knife. Unsuccessful probings can occur when the probe creates a false passage by missing the valve of Hasner, and either carries on in a submucosal plane to the floor of the nose or enters the meatus through a false and usually ineffective passage. Distal bony atesia of the duct is rare but will usually be rectified by conversion of the procedure to an endoscopic dacryocystorhinostomy (DCR).

PHYSIOLOGICAL (FUNCTIONAL) EPIPHORA

Functional epiphora is persistent watering despite a clear, patent, free-flowing syringing, observed endoscopically in the inferior meatus, with no resistance felt on probing. All other causes of lacrimation or epiphora must be eliminated. The FDT demonstrates delay. The cause of functional epiphora is probably physiological pump failure but such children may have an upper respiratory cause, such as large adenoids, and a careful history should be taken regarding nasal symptoms.

COMPLEX ABNORMALITIES OF THE OUTFLOW SYSTEM

Complex abnormalities of the canaliculi or the proximal nasolacrimal duct become a commoner cause of persistent epiphora in older children, as the simpler abnormalities settle spontaneously. These abnormalities may be very complex, especially in children with abnormal facial skeletons.[20]

A major advantage of endoscopic probing over 'blind' probing is that the common causes of failure can be

identified and treated at the first probing, improving the success rate of the procedure.[18] If endoscopic probing was not performed on the first occasion, this approach is useful in reprobings as it will identify the most frequent causes of failure and permit appropriate treatment.[18] Another option is intubation of the system with silicone tubes;[21] but intubation carries the risk of damage to the canaliculi, may be unnecessary (e.g. in functional cases), and is no more effective than endoscopic probing in repeat cases.[22] Children with upper nasolacrimal obstruction can be treated by endoscopic dacryocystorhinostomy (DCR) which offers the advantage of direct visualization of the common canaliculus at entry into the lateral wall of the lacrimal sac where distal occlusion of the common canaliculus may be amenable to a stenotomy.

Possible complications of intubation include cheesewiring through the canaliculi, dislocation superiorly or inferiorly, infection, and scarring of any part of the drainage system.[23] The optimum time to leave tubes in place is not known, and anywhere between 1 and 6 months is recommended.[23] Tubes should be removed under general anaesthetic via the nose to prevent aspiration of the tube. This system is then syringed with fluorescein under endoscopic control to confirm patency. Balloon catheter dilatation of the lacrimal system is a possible alternative to intubation in patients with failed probing.[24]

DACRYOCYSTORHINOSTOMY

Children rarely require a dacryocystorhinostomy (DCR), but may do so for persistent epiphora despite probing, for complex congenital abnormalities of the lacrimal outflow apparatus such as bony atresia, those involving the upper nasolacrimal duct, or for acquired disease usually caused by infection or trauma.[25] External and endoscopic routes are possible, and excellent success rates, comparable to those of adult DCRs, have been reported for both.[26, 27]

The availability of microdrill techniques has led to increased popularity of the endoscopic techniques which enable wide sac exposure and flap creation without a facial skin scar.

CONGENITAL FISTULAE OF THE LACRIMAL OUTFLOW SYSTEM

Fistulae of the lacrimal system are rare anomalies in which tracts open onto the skin directly from the puncta, canaliculi, lacrimal sac or nasolacrimal duct. They may appear as double puncta, or appear in the region of the medial canthus. They usually pass unnoticed as they are non-functioning and should be left untreated unless they allow flow of tears onto the face or result in epiphora (which is rare).

PUNCTAL AND CANALICULAR ABNORMALITIES

Failure of the proximal end of the lacrimal drainage system to canalize may result in punctal stenosis or atresia. This is often asymptomatic, especially if only one punctum is abnormal. Narrow puncta should be dilated with a 'Nettleship' lacrimal dilator. Membranous obstruction should be pierced with a needle and dilated. These cases do very well but are often associated with distal abnormalities and a syringing should always be performed.

Overall, abnormalities proximal to the sac result in surprisingly few symptoms. Agenesis should be suspected if the papilla is not readily obvious.[28] If only one punctum is missing, syringing via the other one detects the extent of the damage. Surgery to construct these areas is specialized. Retrograde probing from an external DCR incision may be attempted through the sac; otherwise, a Lester Jones canalicular tube is required. This type of surgery may be left until the child is in their teens when referral to a specialist should be made.

ACQUIRED CONDITIONS OF THE LACRIMAL DRAINAGE APPARATUS

Acute dacryocystitis may occur as a complication in non-patent nasolacrimal systems or as a primary event in a patent system. This is particularly common in infants with a dacryocystocoele.[29] Treatment comprises prompt intervention with intravenous antibiotics as retrobulbar abscesses may occur. Cultures should be taken of any pus or discharge that can be expressed through the punctum. Probing should not be performed as damage to the congested epithelium may cause false passage formation and lead to orbital cellulitis and fistula formation.[30] Skin incisions should not be made during the acute phase as an external fistula may occur. If a mass remains after resolution or a pyocoele has developed, evacuation can be performed through the skin with a needle through the lower pole of the sac or by urgent endonasal DCR if the pus is found to be inspissated or loculated.

Acquired nasolacrimal duct obstruction may be caused by facial trauma, diseases of the nose or paranasal sinuses – especially chronic allergic rhinitis – or persistent upper respiratory tract infections. These are more common in older children and adolescents.[31] Rarely, acquired obstruction may herald a more sinister cause such as fibrous dysplasia, cranial metaphysial or cranial diaphysial dysplasia, or tumour formation. Treatment should be aimed at the underlying cause.

The commonest causes of watery eyes in children are listed in **Box 25.1**.

BOX 25.1 Causes of watery eyes in children

Excess tear production (lacrimation)	Drainage failure (epiphora)
Allergic rhinitis	Congenital nasolacrimal duct obstruction
Upper respiratory tract infection	Skeletal and sinus abnormalities
Epiblepharon	Lid malposition
Subtarsal foreign body	Punctal malposition
Iritis	Punctal occlusion
Corneal abrasion/ulceration	Anomalous drainage system
Conjunctivitis	
Glaucoma	

FUTURE RESEARCH

- Knowledge of the aetiology and best treatment choices for proximal CNLDO are less well developed.
- While surgery is almost invariably successful for treating distal block, the management of proximal obstruction remains challenging.
- The increased application of endoscope and microendoscope technology in the future may offer better diagnostic and therapeutic options for resistant cases of CNLDO.

KEY POINTS

- Congenital nasolacrimal duct obstruction (CNLDO) is common, being present in up to 20% of neonates.
- The majority of cases of CNLDO resolve spontaneously in infancy.
- Epiphora persisting in the second year of life may benefit from intervention.
- Endoscopic-guided probing is the investigation of choice.
- Underproduction of tears causing dry eyes is rare but more serious due to the potential threat to vision.

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CHAPTER 26

THE ADENOID AND ADENOIDECTOMY

Peter J. Robb

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SEARCH STRATEGY

Data in this chapter may be updated by searches of The Cochrane Library, Medline, Google Scholar and PubMed using the keywords: adenoid, adenoidectomy and children. References from selected articles were reviewed after reading the abstract and included where relevant. The evidence in this chapter is mainly level 2/3/4, with some level 1 evidence.

INTRODUCTION

Santorini described the nasopharyngeal lymphoid aggregate or 'Luschka's tonsil' in 1724. Wilhelm Meyer coined the term 'adenoid' to apply to what he described as 'nasopharyngeal vegetations' in 1870. The adenoid forms part of Waldeyer's ring of lymphoid tissue at the portal of the upper respiratory tract. In early childhood this is the first site of immunological contact for inhaled antigens.

Historically, the adenoid has been associated with upper airway obstruction, as a focus of sepsis, and more recently with the persistence of otitis media with effusion.

DEVELOPMENT OF THE ADENOID

Lymphoid tissue can be identified at the 4- to 6-week gestational period, lying within the mucous membrane of the roof and posterior wall of the nasopharynx. The adenoid is clearly identifiable during the third month of gestation. Lymphoid tissue of the adenoid may extend to the fossa of Rosenmüller and to the Eustachian tube orifice as Gerlach's tonsil. The membrane is covered with stratified squamous epithelium. The adenoid receives a rich arterial supply from branches of the facial and maxillary arteries and the thyrocervical trunk. Venous drainage is to the internal jugular and facial veins. Lymphatic drainage is to the retropharyngeal lymph nodes and upper deep cervical nodes, particularly the posterior triangle of the neck. Nerve supply is from sensory branches of the glossopharyngeal and vagus nerves.[1]

The adenoid is visible using magnetic resonance imaging (MRI) from the age of 4 months in 18% of children.[2] At 5 months of age, the adenoid could be identified in all of 290 children studied. Growth continues rapidly during infancy and plateaus between 2 and 14 years of age. Regression of the adenoid occurs rapidly after 15 years of age in most children. The adenoid is at its relative largest in relation to the volume of the nasopharynx in the 7-year-old age group.[3] Clinical symptoms are more common in a younger age group, due to the relative small volume of the nasopharynx and the increased frequency of upper respiratory tract infections.

IMMUNE FUNCTION OF THE ADENOID

The function of the lymphoid tissue of Waldeyer's ring is to produce antibodies. The adenoid produces B-cells, giving rise to IgG and IgA plasma cells. Exposure to antigens via the mouth and nose is an important part of natural acquired immunity in early childhood. The adenoid appears to have an important role in the development of 'immunological memory' in younger children.[4] Removal of the adenoid in early childhood may be immunologically undesirable.[5] Evidence supports the concern that early adenoidectomy produces a detectable negative effect

on the development of serum IgG antibodies, resulting in impaired immunity to pneumococcus.[6]

In children aged 4–10 years, adenotonsillectomy does not appear to cause significant immune deficiency, although a slight decrease in IgG, IgA and IgM levels was found in the post-operative period 4–6 weeks after surgery.[7] The authors concluded that this represented a compensatory response of the developing immune system following a reduction of chronic antigen stimulation. Specific reduction in IgG may represent a reduction in antigenic stimulation. There appears to be no decrease in IgE after adenoidectomy.[8, 9]

The evidence that immune status is compromised by removal of the adenoid alone is inconclusive, as studies generally include children also having tonsillectomy.[10]

PATHOLOGICAL EFFECTS OF THE ADENOID

The adenoid may be implicated in upper respiratory tract disease due to partial or complete obstruction of the nasal choanae or as a result of sepsis. Pathological manifestations include rhinitis, rhinosinusitis, otitis media and otitis media with effusion. Adenoiditis, acute or chronic, is considered by some to be a related but distinct infective entity.[11]

Otitis media with effusion

The benefit of adenoidectomy in the management of otitis media with effusion (OME) has traditionally been ascribed to the relief of anatomical obstruction of the Eustachian tube.[12] While this may be a contributory factor, it is clear that adenoid size and physical obstruction alone cannot account for the benefit following adenoidectomy when the adenoid is small.[13] Adenoid size in children with and without OME is not significantly different. It is likely that recurrent acute or chronic inflammation of the adenoid and increased bacterial load, particularly of *Haemophilus influenzae*,[14, 15] results in squamous cell metaplasia, reticular epithelium extension, fibrosis of the interfollicular interconnective tissue and reduced mucociliary clearance in children with OME compared to those without OME.[16] These changes increase bacterial adherence, contributing to the development of a 'biofilm' infection resulting ultimately in middle ear effusion. (A biofilm infection may be defined as 'a structured community of bacterial cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface'.[17, 18]) Evidence from the MRC TARGET (Trial of Alternative Regimens in Glue Ear Treatment) study supports consideration of 'adjuvant' adenoidectomy in children over the age of 3 who are undergoing insertion of ventilation tubes (grommets)[19] (see Chapter 13, Otitis media with effusion).

RECURRENT ACUTE OTITIS MEDIA

A Cochrane intervention review concluded that adenoidectomy could not be recommended for the management of acute otitis media.[20] Randomized controlled trials of the management of recurrent acute otitis media have shown adenoidectomy was not effective in reducing episodes of infection in children younger than 2 years during the follow-up periods of 7–24 months after surgery.[21, 22] It is likely that a partial maturational selective IgA deficiency is a contributing factor in these 'otitis-prone' children.[23] Low-dose prophylactic antibiotic treatment is preferred to adenoidectomy in this group as a means of preventing recurrent acute otitis media and sequelae of infection until maturation of the immune system occurs naturally.[24]

Upper airway obstruction and sleep-disordered breathing

Sleep-disordered breathing in childhood is considered in detail in Chapter 27, Paediatric obstructive sleep apnoea. The prevalence of severe sleep disturbance in children due to upper airway obstruction is estimated to be approximately 1%, with a peak incidence between 3 and 6 years of age, and an equal sex incidence.[25, 26]

Airway obstruction due to adenoidal hypertrophy may produce depressed arterial PaO_2 and elevated $PaCO_2$ levels, which return to normal after adenoidectomy.[27] The respiratory improvement following adenotonsillectomy also results in a significant increase in serum insulin-like growth factor-1 (IGF-1),[28] accounting in part for the frequently observed growth spurt following surgery. Accumulating evidence suggest that habitual snoring, falling short of obstructive sleep apnoea may result in neurobehavioural morbidity, poor academic performance and hyperactive behaviour.[29, 30]

There is widespread recognition of sleep apnoea in childhood[31] and the acceptance of the benefits of adenotonsillar surgery in these children, with documented improvement in respiratory function following adenotonsillectomy.[32] In a prospective study of 40 children undergoing adenoidectomy, with or without tonsillectomy, for upper airway obstruction, the radiographic estimate of the adenoid size correlated highly with the improvement in polysomnographic scores following surgery. No significant correlation between tonsil size and grade of obstructive sleep apnoea was demonstrated.[33] Nevertheless, a Cochrane review of adenotonsillectomy for obstructive sleep apnoea found no randomized trials addressing the criteria required to nor the efficacy of surgery in managing obstructive sleep apnoea syndrome (OSAS) in children.[34]

Rhinosinusitis

In childhood, the adenoid is implicated in rhinosinusitis, acting as a reservoir for pathogenic bacteria.[35] In a retrospective study of 48 children with chronic sinusitis undergoing adenoidectomy or adenotonsillectomy, improvement was reported in the majority following surgery, and only three children subsequently required functional endoscopic sinus surgery.[36] A prospective study of children with recurrent rhinosinusitis showed that adenoidectomy was effective in abolishing infective episodes of infection, and that few children went on to require functional

endoscopic sinus surgery[37] (see Chapter 24, Rhinosinusitis and its complications).

Olfaction

Adenoidal hyperplasia may reduce olfactory sensitivity and, in particular, retronasal smell and taste, which improves following adenoidectomy.[38] It is, however, unlikely that physical obstruction of the airway alone impairs olfaction, and changes in the olfactory epithelium are a likely factor.[39] Where partial or total anosmia is reported, with no evidence of adenoidal hyperplasia, or failing to resolve after adenoidectomy, further detailed investigation is required to exclude congenital or hereditary causes for child's poor or absent sense of smell.[40]

Neoplasia

Unsuspected neoplasia of the adenoid (and tonsils) in childhood is rare. Non-Hodgkin lymphoma was reported in a series of six children.[41] Atypical lymphadenopathy, with persistent and asymmetric enlargement of the tonsils and adenoid, in the absence of infection are suspicious and should prompt early imaging and biopsy. Presentation is often assumed to be due to the more common infective and obstructive manifestations of adenotonsillar disease so diagnosis is frequently delayed. Consider lymphoma of the adenoid as part of a post-transplantation lymphoproliferative disorder when symptoms of nasal obstruction develop.[42]

ASSESSMENT AND MANAGEMENT

Clinical history

The history should form part of a full paediatric ENT history with special attention to symptoms of middle ear disease and nasal obstruction. Specific questions regarding sleep disturbance, eating and atopic symptoms are important. A family history of atopy may be relevant. A full history of medication, prescribed, over-the-counter and alternative or complementary, is important. In children in whom adenoidectomy is being considered, it is essential to positively exclude a history or family tendency of unusual bleeding or bruising, as a routine clotting screen may not confirm mild von Willebrand disease. In children with Down syndrome, consider potential atlantoaxial instability and cardiac abnormalities.

Clinical examination

Assessment of the external nose should be made prior to anterior rhinoscopy. In particular, look for a skin crease in the supratip region that may indicate frequent nose rubbing from symptoms of rhinitis. Simple anterior rhinoscopy in young children may be carried out using a halogen light otoscope with a large speculum. This is generally better tolerated than examination with a Thudichum speculum.

Assessment of the nasal airway may be made with a cold Lack tongue depressor or large laryngeal mirror. Posterior mirror rhinoscopy is not usually possible in children, but many will tolerate nasendoscopy,[43] using a flexible paediatric endoscope and topical intranasal local anaesthetic/vasoconstrictor spray, such as Co-phenylcaine. When examining children, topical cocaine must not be used.

In children, where adenoidectomy is the sole surgical procedure indicated, an assessment of the adenoid should be made prior to the decision to operate. Nasendoscopy is a highly accurate method to assess adenoidal status in an outpatient setting (**Figure 26.1**).

When endoscopy is not tolerated, assessment of adenoid size with lateral soft-tissue radiograph of the nasopharynx is helpful and correlates well with endoscopic assessment of adenoid size.[44, 45]

In children undergoing another surgical procedure, the adenoid size can be assessed per-operatively.[46] The adenoid can be classified, based on size and obstruction (**Table 26.1**).[47] Nasendoscopy of the nasopharynx to assess adenoid size at the time of surgery is probably the gold standard, while mirror examination underestimates choanal occlusion, and palpation is a poor measure of adenoid hypertrophy.[48]

Where the indication for adenoidectomy is OME rather than obstruction, the size of the adenoid is not relevant as

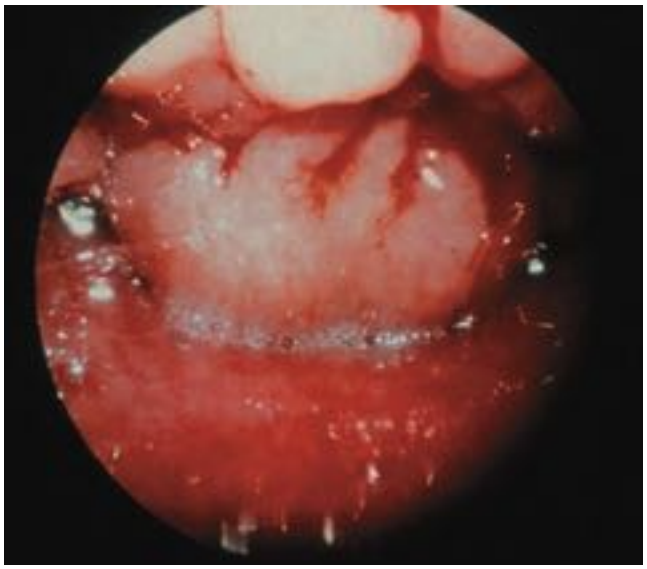


Figure 26.1 Endoscopic view of the adenoids.

TABLE 26.1 Clinical grading of adenoid size (reprinted from Clemens et al.,[47] with permission from Elsevier)

Grade	Description
Grade I	Adenoid tissue filling one-third of the vertical portion of the choanae
Grade II	Adenoid tissue filling from one-third to two-thirds of the choanae
Grade III	From two-thirds to nearly complete obstruction of the choanae
Grade IV	Complete choanal obstruction

an indication for removal (see Chapter 13, Otitis media with effusion).

While acoustic rhinomanometry is a useful research tool[49] and MRI provides extremely accurate volumetric estimation of the adenoid, these investigations are not applicable in clinical practice.

Pre-operative investigations

Routine pre-operative investigations are not indicated prior to adenoidectomy for children who are ASA grade 1 or 2.[50] Specific investigations for sickle-cell disease, thalassaemia, Down syndrome and congenital heart disease are indicated as appropriate. Management of type 2 diabetes mellitus should follow local paediatric guidelines for children with diabetes undergoing elective surgery.

MEDICAL TREATMENT FOR THE ADENOID

Traditionally, surgery and watchful waiting were the only options for symptomatic adenoid disease. There is now a reasonable amount of evidence that topical nasal steroid sprays can cause reduction in adenoid size with improvements in the presence of middle ear fluid, audiometric thresholds, nasal obstruction, rhinorrhoea, cough, snoring and sleep apnoea. This evidence comes from meta-analysis of a number of randomized controlled trials, although the trials themselves were judged to be of poor quality and further, better-quality studies are required.[51] Topical nasal steroids will probably find a role in clinical practice, although at present that role is unclear.

ADENOIDECTOMY

Adenoidectomy with or without tonsillectomy and/or insertion of ventilation tubes is one of the most frequently performed surgical procedures in children.

In the UK, blind curettage adenoidectomy continues to be the most used technique. Of these 79.2% use digital palpation and blind curettage, while only 8.1% use suction coagulation under direct vision.[52] It is surprising that curettage remains so popular, give the disadvantages of a blind procedure with unpredictable bleeding, poor access to choanal adenoid and risk of trauma to the Eustachian cushions. In contrast, suction diathermy affords direct vision with minimal blood loss[47] (mean 4 mL vs 50 mL), haemostasis and negligible risk of post-operative haemorrhage.[53] Suction diathermy is also effective in performing partial adenoidectomy, leaving a ridge of adenoidal tissue at the inferior part of the nasopharynx, reducing the risk of velopharyngeal insufficiency in those children where this is likely after removal of the adenoid.[54] Other direct vision techniques include Coblation® and microdebrider, which have the disadvantage of a high unit cost. KTP laser is associated with a high risk of nasopharyngeal stenosis.[55] This serious complication has not been reported in a small series using gold laser for adenoidectomy.[56] All single-use instrument techniques have the advantage of abolishing the potential risk of infection transmission.[57]

Of the direct-vision techniques, those with the largest clinical experience are the suction coagulator and the microdebrider. In a randomized controlled trial, the microdebrider was 20% faster than the curettage technique,[58, 59] but the suction coagulator is significantly cheaper than the microdebrider.[60] Coblation® is also suitable for adenoidectomy, with less blood loss and more complete adenoid removal,[61, 62] but cost limits it application to adenoidectomy as a sole procedure, while it is not a cost issue when tonsillectomy is performed using the same Coblation® wand.

A meta-analysis of suction coagulation adenoidectomy concluded that there was reduced intra-operative bleeding, reduced operative time, and a lower overall complication rate when compared to curette adenoidectomy.[63]

Where social and geographical factors allow,[64] and with appropriate surgical and anaesthetic techniques, pre-emptive fluid replacement, antiemetics and analgesia, the majority of children may be safely discharged home on the same day of surgery.[65, 66] Safe discharge home following adenoidectomy using the laryngeal mask airway within 20 minutes of surgery may be feasible but not preferable.[67]

COMPLICATIONS OF ADENOIDECTOMY

Bleeding

The reactionary haemorrhage rate, i.e. bleeding following adenoidectomy, within 6–20 hours of operation is reported as less than 0.7%.[68, 69] If bleeding is significant, early return to theatre and postnasal packing for haemostasis is the usual management. This study suggests that postnasal packing left *in situ* for 4 hours post-haemorrhage is as effective as packs left for 24 hours.[68] A small number of consultants in this questionnaire study (3/285) electively admitted children to an intensive care facility following postnasal packing and 4/285 routinely prescribed antibiotics. Increase in the use of direct-vision techniques and controlled haemostasis at the time of operation will make reactionary haemorrhage and the need for postnasal packing much less likely.

Secondary haemorrhage after adenoidectomy is rare. It may be due to bleeding from an aberrant ascending pharyngeal artery.[70] Unusual reactionary or secondary bleeding should raise the possibility of a clotting or coagulation defect. This requires specialist haematological investigation to confirm or exclude.

Dental trauma

Damage to the teeth during adenoidectomy may be accidental due to slippage of the gag or supports. Great care is needed, particularly if the secondary incisors have erupted: the teeth are large, but the mandible immature, and it is safer to use an adult gag, which will rest lateral to the incisors. It is customary to warn parents about damage

to teeth, but damage to the teeth will usually be considered indefensible. Where there are loose deciduous teeth, consent should be taken pre-operatively to remove these under anaesthetic to avoid the possibility of inhalation by the child during the operation or while recovering from anaesthesia.

Retained swab

If swabs are used, it is mandatory to confirm that the count is correct at the end of the operation before the gag is removed and the anaesthesia reversed. A swab may be retained either in the nasopharynx or in the laryngopharynx, hidden from the operator's view. While the early post-operative risk is of airway obstruction by a retained swab, late presentation months later with infection has also been reported.[71] Using direct-vision suction coagulation or Coblation® generally abolishes the need for swabs as haemostasis can be achieved during the procedure.

Nasopharyngeal blood clot

Blood may pool and clot in the nasopharynx during the procedure. The nasopharynx should be gently suctioned to clear any clot before removing the gag. Failure to do so may lead to the clot falling onto the larynx during recovery and causing potentially fatal acute airway obstruction ('coroner's clot'). Using a disposable rose-tipped sucker in the pharynx rather than a catheter via the nose reduces the risk of starting bleeding from the adenoid bed.

Infection

Infection in the nasopharynx following adenoidectomy is clinically uncommon, although many parents report foetor from their child in the week following surgery. Foetor is more common following suction adenoidectomy, and it is customary to prescribe a short course of antibiotics (e.g. azithromycin 10 mg/kg for 3 days post-operatively) to avoid this.[65] Rarely, retropharyngeal and mediastinal abscesses may occur as a result of trauma and secondary infection of the adenoid bed.[72] Post-operative chest infection in contemporary practice is uncommon.

Cervical spine

Non-traumatic atlantoaxial subluxation (Grisel syndrome) is rare, but it is recognized as a risk associated with adenoidectomy and tonsillectomy.[73] Early recognition is crucial in management, and post-operative torticollis should raise suspicion, leading to radiological investigation.[74] Overuse of diathermy must be avoided, either for removal of the adenoid or following curettage when used for haemostasis.[65] Minimum power settings for diathermy should always be used.[75]

Children with Down syndrome are at increased risk of atlantoaxial subluxation. Current evidence does not support routine pre-operative plain radiographs in asymptomatic children with Down syndrome. In any event, these are of limited value below the age of 3 years, at which age vertebral mineralization and epiphyseal development permit accurate radiographic visualization.[76] Special care of the child's neck during anaesthesia, surgery and recovery is essential.

Velopharyngeal dysfunction

Severe velopharyngeal incompetence is rare following adenoidectomy, estimated to occur in between 1:1500 and 1:10000 procedures. It may lead to significant problems with hypernasal speech and swallowing, severe enough to cause nasal regurgitation of fluids. It is mandatory to assess the palate and uvula for submucous cleft of the palate prior to surgery as adenoidectomy may unmask pre-existing palatal dysfunction.[77] Bifid uvula can be a marker of a submucous cleft, present in 59% of cases.[78] Using a direct-vision technique, it is possible to perform a partial adenoidectomy, clearing the choanal airway and superior nasopharynx, but leaving a rim of adenoid intact at the velopharyngeal junction, avoiding velopharyngeal insufficiency.[54]

Long-term velopharyngeal insufficiency is rare. Reconstructive surgery to correct hypernasal speech may be required if speech and swallowing are severely affected.[79]

Regrowth of the adenoid

A cross-sectional follow-up study of children after curettage adenoidectomy, 2–5 years after surgery concluded that 71% had no residual obstructing adenoid. However, the criterion for adenoid sufficient to cause nasal obstruction was tissue occupying more than 40% of the nasopharynx.[80] In a retrospective study of 3231 children, 1.6% required reoperation for recurrence of their symptoms following curettage adenoidectomy.[81] Direct-vision techniques are likely to minimize residual adenoid tissue and possible 'regrowth'.[63]

Death

Data separating the risk of death following adenoidectomy independent of tonsillectomy or general anaesthesia is limited. Expert reports from malpractice cases are the usual source of such data. Of 32 deaths related to bleeding following adenoidectomy and tonsillectomy, one followed direct vascular injury during adenoidectomy. In a review of malpractice cases from the United States, following tonsillectomy and adenoidectomy, during the period 1985–2006, 154 claims were identified.[82] Two deaths clearly followed infection secondary to aspiration of adenoid tissue. While not defined as adenoidectomy alone, four deaths were due to medication errors, route, dose or drug.[71] Following surgery in younger children with sleep-disordered breathing, special care should be exercised when prescribing opioid analgesics for both per-operative and discharge analgesia.[83] In those who are ultra-rapid metabolizers of codeine, toxic doses of morphine can develop, leading to fatal respiratory failure.

BEST CLINICAL PRACTICE

- ✓ It is no longer appropriate to combine adenoidectomy with tonsillectomy, unless there is a specific indication for adenoidectomy.
- ✓ Adjuvant adenoidectomy is effective as part of the surgical management of children over the age of 3 years with otitis media with effusion.
- ✓ Routine pre-operative investigations are not indicated prior to adenoidectomy for children who are ASA grade 1 or 2.
- ✓ Adenoidectomy under direct vision with single-use instrumentation – except the KTP laser – is more effective and safer than curettage.

FUTURE RESEARCH

For each of the following topics there is no evidence at level 1 currently available, and further studies are recommended.

- ➤ The role of topical nasal steroids in management of adenoid disease.
- ➤ Efficacy and morbidity of different techniques of adenoidectomy.
- ➤ Efficacy of adenoidectomy in the management of obstructive sleep apnoea in children.
- ➤ Efficacy of adenoidectomy in the management of chronic and recurrent acute sinusitis in children.
- ➤ The effects of adenoidectomy on the development of childhood immunity.
- ➤ The relationship between adenoidal hypertrophy and childhood rhinitis.
- ➤ The role of the adenoid in facilitating a biofilm infection in the upper respiratory tract.

KEY POINTS

- Adenoidal hyperplasia in childhood is common and self-limiting; mild symptoms of obstruction are not an indication for surgery.
- Significant obstructive symptoms, resulting in sleep-disordered breathing, short of obstructive sleep apnoea, may have signficant effects on daytime behaviour and cognitive function reversed by adenoidectomy.
- Adenoidectomy is effective as part of the surgical management of children with upper airway obstruction.
- Adenoidectomy may not be effective in the management of recurrent acute otitis media.

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CHAPTER 27

PAEDIATRIC OBSTRUCTIVE SLEEP APNOEA

Steven Powell

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the following keywords: sleep apnoea, tonsils, adenoids, sleep-disordered breathing, all child (0 to 18 years) in articles published in English. Abstracts were hand-searched and relevant articles were obtained and summarized.

HISTORY

Obstructive sleep apnoea in children existed for a long time without being widely recognized as a clinical syndrome. There were some exceptions to this. In 1889 Hill published an article in the *British Medical Journal* 'On some causes of backwardness and stupidity in children'.[1] There are a number of startling revelations in this work. Hill identified the neurobehavioural consequences of OSA:

> *'…children, the victims of nasal and pharyngeal obstructions, often suffer from headaches especially when engaged in study, and frequently evince marked inability to fix their attention on their lessons or work for any length of time…'.*[1]

Perhaps even more remarkably, he described the outcomes of treatment, recognizing that adenotonsillar surgery at the same time as treatment for glue ear resulted in neurobehavioural improvements over and above those expected for hearing improvement alone:

> *'I have been much struck by the fact that operations on children, undertaken for the relief of deafness associated with adenoidal growths, enlarged tonsils, and hypertrophic catarrhal conditions of the nose, have resulted in an immediate improvement in the mental acuteness of the patients as was altogether incommensurate with the often slight improvement in the sense of hearing.'*[1]

Many children who were being treated with adenotonsillectomies for various reasons from blocked noses to infections probably had unrecognized sleep apnoea. There had been some recognition of the cardiac complications of upper airway obstruction, but the first case series recognizing the syndrome of obstructive sleep apnoea was not published until 1976.[2] Guilleminault and colleagues described eight children with the night-time symptoms and the daytime consequences of obstructive sleep apnoea. It was the interest in this condition among the adult population that led to the recognition of the daytime symptoms in children. Six of the eight children underwent adenonsillectomy. Four of them had resolution of their symptoms, but two went on to have a tracheostomy.

Since then there has been growing interest in the condition and it has become the leading indication for adenotonsillectomy in young children.[3] The literature about the condition has expanded exponentially with over 2000 articles listed by Medline with relevance to paediatric sleep-disordered breathing in the last 3 years alone.

EPIDEMIOLOGY

Habitual snoring in children is quite common in the UK population, occurring in 12% of children.[4] Two large cross-sectional studies from the UK and Italy found the prevalence of obstructive sleep apnoea (OSA) to be 0.7–1.8%.[4, 5] In a German study looking at a community sample of children who went on to have polysomnography (PSG), the prevalence of primary snoring was found to be 6.1%.[6]

A large population-based cohort study with a wider remit had some questions geared towards mouth breathing, snoring and apnoeas. The Avon Longitudinal Study of Parents and Children (ALSPAC) studied 14 029 children. Nocturnal apnoeas always had a prevalence of 1–2% and were fairly steady throughout the first 6 years of the child's life. The prevalence of snoring always increased from 3–4% at the age of 1 year to a peak of 7–8% between the ages of 3 and 4. In terms of habitual snoring (which reflected snoring not being present all the time, but most), the prevalence rose from 10% at 1 year to 15% at 6 years. Habitual mouth breathing was present in up to 25% of children. Adenoidectomy reduced the risk of having sleep-disordered breathing by parental report in this study.[7]

NORMAL SLEEP

Paediatric sleep physiology is not completely understood, but what is clear is that a grasp of the basic elements is important to having a full understanding of the pathophysiology of sleep-disordered breathing.[8] Sleep is an essential human function and is part of the body's 'housekeeping' role, and good sleep is critical to normal daytime functioning. Sleep can be divided into phases of a cycle. There are phases of REM (rapid eye movement) sleep and nREM (non-rapid eye movement sleep). nREM sleep is divided into phases N1, N2 and N3. N3 is commonly described as 'slow wave' sleep. There is an orderly progression between the phases from N1 to N3 then REM sleep. The cycle in older children takes around 90 minutes. The proportion of time in slow wave sleep is higher at the beginning of the night and the proportion in REM sleep is higher at the end of the night. The proportion of time spent in REM sleep decreases from 50% as a newborn to 20% beyond the age of 4 years.[9] Premature babies and those up to 6 months of age can have central apnoeas, with cessation of breathing due to no respiratory effort, but it is rare for these to persist with any clinical significance beyond 6 months.[8]

Muscle relaxation occurs particularly during REM sleep, possibly as a protective mechanism to prevent sleep movements. The pharyngeal part of a child's upper airway is a tube with a soft collapsible wall held open only by active pharyngeal muscle tone. There can be relaxation of the pharyngeal constrictor muscles (hypotonia) and a narrowing of the airway at the pharyngeal level. A wide range of neural activity occurs during the sleep cycle which is critical to the consolidation and enhancement of memories within existing neural networks.[9]

DEFINITIONS

Obstructive sleep apnoea can be defined as 'a disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction that disrupts ventilation during sleep and normal sleep patterns'.[10] **Primary snoring** is defined as noisy breathing (snoring) without obstructive apnoea, frequent arousals from sleep, or gas exchange abnormalities.[10] **Sleep-disordered breathing** is a term which can be used to describe both snoring and OSA.

PATHOPHYSIOLOGY

Pathophysiology of airway obstruction

It becomes clear from the key points in physiology that there are phases within sleep when children will be particularly at risk of airway compromise. REM sleep, with its hypotonia of the pharyngeal muscles, can lead to airway narrowing particularly at this point.

There are well-defined groups in which sleep-disordered breathing may occur. There may be overlap between the groups, but they can be considered individually.

Children with no underlying medical diagnosis who have adenotonsillar hypertrophy form the largest group overall.[11] Here the physical obstruction of the nasal airway by the adenoids and the oropharyngeal airway by the tonsils results in increased airway resistance. The peak incidence of OSA in this group is between the ages of 3 and 6 years when the adenoids and tonsils undergo hypertrophy.[11] The situation is more complex than simple obstruction by adenoid and tonsil hypertrophy as not all children with large lymphoid tissue have OSA reflecting variation between individuals in pharyngeal muscle tone.[11]

The second group reflects the increasing prevalence of obesity in the paediatric population.[12] This may be in a slightly older age group. It may occur in combination with adenotonsillar hypertrophy. The obstructive element is primarily caused by oropharyngeal crowding due to excess adipose tissue, but the full extent of the pathophysiology surrounding obesity is considerably more complex.[12]

In a third group of children the cause of OSA is multifactorial. Children with congenital abnormalities such as achondroplasia or craniofacial abnormalities have narrow pharyngeal airways which will predispose them to obstruction. In Down syndrome there is a combination of abnormally narrow upper airway and reduced pharyngeal muscle tone. **Up to two-thirds of children with Down syndrome have some form of sleep-disordered breathing and regular screening for OSA is advised.**[13]

Neurobehavioural consequences

Neurobehavioural clinical outcomes result from the disturbance to sleep from a number of mechanisms.[8] In the worst cases where there are desaturations, hypoxia may

play a role, but sleep fragmentation from repeated arousals can interfere with the neural pathways which would otherwise occur. Even in children who have no OSA and primary snoring alone, there has been a link to the slow wave activity changes of the EEG, which may reflect impaired restorative sleep function.[14] OSA has a profound impact on sleep and arousal patterns during the preschool years, when children are in a critical period for neurodevelopment.[15]

Inflammatory basis

There is an underlying inflammatory basis to OSA and there appear to be several biomarkers which measure this activity.

Children often have elevated levels of highly sensitive C-reactive protein (CRP). This is produced by interleukin activity in the liver. Some children seem to have a predisposition to this and in one study abnormal DNA methylation was found in patients with OSA and high CRP, and the abnormal methylation was strongly linked to the apnoea–hypopnoea index (discussed in 'Investigations' below).[16] This epigenetic discovery may lead to the basis of future prognostic or therapeutic advances.

High levels of CRP may enhance inflammation, oxidative stress and procoagulant activity which may promote atherogenesis.[17] Inflammatory markers do not change when measured the night before and the morning after in children with OSA.[18]

In a group of obese patients with OSA, there was no significant decrease in CRP from baseline to 6 months post adenotonsillectomy. This may have been because of a direct link from the obesity to the inflammatory markers, but also a high proportion of children had residual OSA.[19]

Endothelin 1 has been found to be elevated in some patients with OSA and to decrease post-operatively following adenotonsillectomy. This is a potent vasoconstrictor and may be associated with cardiovascular risk.[20] Tumour necrosis factor (TNF) levels are higher in children with OSA, compared with controls.[21] Myeloid-related protein 8/14, which has an important role in the formation of atherosclerosis, has been found to have higher levels in children with OSA and the levels are in proportion to the severity of the OSA.[22]

Cardiovascular pathophysiology

There is evidence that baroreceptor sensitivity may be impaired in adolescents with sleep-disordered breathing so they do not mount appropriate blood pressure changes to variation in heart rate. In adults this is a risk factor for cardiovascular disease.[23] Blood pressure can be consistently raised in children with sleep-disordered breathing when compared to controls when monitored continuously overnight.[24]

Children with OSA have been shown to have an increased level of urinary catecholamines.[25] The full implication of this is unclear, but it does suggest some cardiovascular effects from OSA. In a large cohort asthma study, children with snoring (based on survey) did not have any abnormal cardiovascular parameters at the age of 8.[26]

Endothelial dysfunction and impaired cognitive abilities appear both to be worsened by worsening OSA, when measured by tests of hyperaemia and neurocognitive tests.[27]

CLINICAL FEATURES/ PRACTICE POINTS

Day- and night-time clinical features

A full sleep history should be taken from children presenting with any adenotonsillar problem and enquired about in patients referred with ear pathology too. The history has two key areas: night-time symptoms and daytime symptoms (**Box 27.1**).

BOX 27.1 Symptoms of OSA

Night-time symptoms	Daytime symptoms
Do they snore? Do they get a good night's sleep or are they restless? Do they wake through the night? Do they struggle with their breathing or stop breathing? This should be explored fully with a clear explanation of respiratory effort with obstruction and respiratory effort with snoring to try to clarify the history. Do they sleep in an unusual position (e.g. extended head)? Do they sweat excessively? Do they wet the bed?	Do they have any behaviour or concentration problems? Do they mouth breathe? Do they struggle with eating? Are they growing normally?

A full ear, nose and throat examination should be undertaken:

- Make a general examination, looking for any craniofacial abnormalities.
- Listen carefully for stertor while awake, or asleep.
- Watch for mouth breathing.
- Carry out an oral examination, to determine the size of the tonsils (**Figure 27.1**). These can be graded by:
  - the Brodsky score[28]
    - 0 - tonsils in fossa
    - 1 - tonsils occupying up to 25% of the airway
    - 2 - 26% to 50%
    - 3 - 51% to 75%
    - 4 - more than 75%
  - the Friedman score[29]
    - 0 - no tonsils
    - 1 - tonsil within pillars
    - 2 - tonsil beyond pillars
    - 3 - tonsil extending ¾ to midline
    - 4 - tonsils touching in midline.



Figure 27.1 Enlarged tonsils in a child about to undergo an adenotonsillectomy for OSA.

- Examine the nose to establish whether there is coexisting rhinitis and whether there is likely to be adenoid hypertrophy.
- Examine the ears for coexisting otitis media with effusion.
- Look for neck lymphadenopathy.

Parents now regularly have access to mobile recording devices and examination of videos on phones or devices can be very helpful in establishing the presence of snoring and obstruction.

A systematic review of the literature has concluded that history is unreliable at predicting OSA.[30] This review was slightly limited as nearly one half of the studies were retrospective, but the others included some well-designed cohort studies. A meta-analysis of the raw data showed history and examination to have poor positive predictive value for obstructive sleep apnoea.

A recent review of the literature and meta-analysis of clinical findings in 10 studies with a total of 1525 patients has looked at the sensitivity and specificity of some of the key clinical aspects of sleep-disordered breathing history.[31] Tonsil size and a history of snoring were the most sensitive clinical findings, but were poorly specific. Conversely, parent reports of apnoeas and daytime somnolence were highly specific but poorly sensitive. It is possible to understand that this is the case. Almost all children with significant OSA will have large tonsils and snore as a sign of their airway obstruction, but not all children with large tonsils will have OSA, and of those who snore, a proportion will be primary snorers. In terms of the apnoeas, if the parents report these, they have a high chance of being significant but, as in reference to sleep physiology, these apnoeas are more likely to occur during REM sleep,[8] which is more prevalent in the latter part of the night when the parents may be sleeping too and may not see these events.

A recent systematic review of tonsil size and the link to obstructive sleep apnoea has found conflicting evidence as to whether tonsil size is predictive.[32] The authors conclude that limitations in the standard sizing system for tonsils, which does not account for overall tonsil volume, may be one of the reasons for this.

OSA is worse during the winter and spring.[33] This may have implications for the time of year that the child is being assessed.

The overall result is that, even in expert hands, a clinical assessment may be inaccurate. Most being assessed will be snorers, so the inaccuracy will lie in differentiating between primary snoring and OSA.

Neurobehavioural symptoms

The neurobehavioural consequences of paediatric obstructive sleep apnoea are now well established in the literature, but new studies continue to clarify the potential deficits.

In a study of 136 children with OSA, ranging from primary snoring to varying degrees of OSA, behaviour and attention were affected in children with both primary snoring and OSA compared to controls, suggesting that primary snoring is not completely benign.[34] Cognitive abilities were also impaired across all groups with sleep-disordered breathing.[35] Memory tasks were impaired in children with all degrees of sleep-disordered breathing too. Interestingly, parents of children with only primary snoring tended to overemphasize their child's memory problems compared to the other groups, possibly as a reflection of behavioural problems.[36]

In a clinical comparison study of 44 snoring children versus 51 non-snoring children derived from a large population survey, polysomnography, neurobehavioural testing and quality of life scores were undertaken. The primary snorers who did not have OSA had significant impairment in language and naming function as well as behaviour.[37] A large cohort of over 1000 German children were studied and those who had primary snoring were found to have hyperactive and inattentive behaviours as well as specifically lower scores in mathematics, science and spelling.[6] All of these changes occur in the absence of hypoxia, and there has been a link to the slow wave activity of the EEG in these children, which may reflect impaired restorative sleep function.[14]

A short-term study of infants showed that those who habitually snored in the first few months of life had significantly decreased cognitive abilities compared to non-snorers at 6 months.[38] This gives rise to the possibility that there is an earlier range of snorers and obstructive patients who are at risk of these deficits. An Australian study demonstrated that both primary snoring children and those with OSA have worse behavioural findings in preschool years, but the cognition was the same as a group of controls. They postulate that this gives a window of opportunity in which treatment can be offered.[39]

A case control study examined the effect of poor sleep hygiene on a group of habitually snoring children versus non-snorers. The poor sleep hygiene did not seem to result in any problem behaviours in the non-snoring group, but in the snoring group there were strong correlations between poor sleep hygiene and behavioural problems.

These included impulsivity, hyperactivity and oppositional behaviours.[40]

Children with OSA have been shown to perform worse in pictorial-based memory tasks when compared to controls.[41]

A cohort of 249 children found that 2-3 years following the birth persistent snoring was associated with higher rates of problem behaviours.[42] Aggressive behaviour at school has been found to have an association with sleep-disordered breathing in a cross-sectional study.[43]

Cardiovascular presenting features

The inflammatory basis of paediatric obstructive sleep apnoea may cast light on the basis of cardiovascular dysfunction in paediatric OSA, which may be subtle and clinically unrecognized in many cases.

An Italian study of 49 children with PSG-proven OSA, compared to 21 matched controls found a higher CRP in the OSA group, and also increased left ventricular mass and early diastolic dysfunction. The dysfunction was worse and the inflammatory markers higher with increasing severity of OSA.[44] This confirms that early aspects of cardiac dysfunction may be higher than appreciated.

Cor pulmonale secondary to pulmonary hypertension is rare, but in a cohort of Taiwanese children, 5 out of 30 had cor pulmonale secondary to OSA. The OSA was more severe in this cohort than the children without cor pulmonale. All children showed improvement in their cardiac status following adenotonsillectomy.[45] This is an unusually high amount of cor pulmonale.

Enuresis

In a population-based study, over 6000 children had questionnaires completed and then polysomnography was undertaken on 597. Nocturnal enuresis was found to be associated with increasing severity of OSA in girls but not in boys.[46]

COMORBIDITY

As discussed above, there are a number of conditions in which OSA has a higher prevalence.

Obesity

Some studies have associated high body mass index (BMI) with OSA.[47] A large population cohort, examining the interaction of obesity, sleep-disordered breathing and cognition, found complex and interdependent relationships between these factors, with each of the factors seeming to have an adverse effect on the others.[48]

A group of 163 overweight children aged 10–16 years underwent polysomnography and neuropsychological testing. Children with worsening OSA were found to have worse concentration, behaviour and academic grades.[49]

Syndromes and associated neuromuscular conditions

Patients with Down syndrome have a high prevalence of OSA.[13] In a radiological study of Down syndrome patients using cervical-spine X-rays which were taken primarily to check on stability of the spine prior to surgery, the lingual tonsils were assessed. A significant increase in the size of the lingual tonsils in the Down syndrome patients compared with control groups was found.[50] Pharyngeal collapse can be found commonly at sleep nasendoscopy of Down syndrome patients.[51]

OSA seems to be particularly prevalent in patients with CHARGE syndrome.[52]

A strong association between craniofacial abnormalities and OSA has been confirmed by a large epidemiological study of over 1000 children.[53]

OSA was found on polysomnography in 95% of a cohort of patients with Treacher Collins syndrome, although the clinical examination was not predictive.[54] As with all cases, a clinical assessment in a subgroup of 13 patients with Treacher Collins syndrome was found not to be reliable for predicting OSA, and the authors suggest use of a polysomnogram in these patients due to the higher prevalence of OSA.[55] The prevalence in this group of children was 54% and the obstruction was multilevel.[56]

Patients with cleft palate may have a higher incidence of OSA, particularly when the palate is closed.[57] In one American study, the prevalence of polysomnographically proven OSA in the cleft palate clinic was 8.5%.[58]

There is a very high rate of polysomnography positive for OSA in patients with syndromic craniosynostosis (see Chapter 19, Craniofacial anomalies). Multiple interventions failed to completely resolve the OSA.[59]

The incidence of OSA in a cohort of 30 French children with achondroplasia was found to be 87%.[60]

Children with Prader-Willi syndrome are at particular risk for OSA and this may worsen with the institution of growth hormone. Adentonsillectomy may decrease but not completely resolve the obstructive sleep apnoea.[61]

The British Thoracic Society guideline identifies that there is a high incidence of sleep-disordered breathing in children with neuromuscular disease.[62]

Interaction of OSA with other conditions

In a group of 131 children with polysomnographically proven OSA, 37 had symptoms of reflux. After 24-hour pH monitoring, 21 were found to have acid reflux. These were treated with a 1–2-month course of proton pump inhibitors and the sleep study was repeated. The reflux group had mean reduction in apnoea–hypopnoea index from 13 to 8. Three children in the mild group had complete resolution of their OSA, while six children with severe OSA had no change in their apnoea–hypopnoea index.[63]

A case control study has demonstrated that children with sickle-cell disease have significantly more upper

aerodigestive tract lymphoid hyperplasia than controls (using MRI) and that the prevalence of OSA in this group of 36 sickle-cell patients (by polysomnography) was 19%.[64] A high incidence (8.3%) of OSA has been noted in patients in Thailand with beta thalassaemia.[65]

An observational study of 108 children with asthma in a children's respiratory clinic found that asthma was worse at 1 year in children who had symptoms of sleep-disordered breathing.[66] In a cohort of 92 poorly controlled asthmatics, 58 were found to have OSA on sleep study, and there were substantial improvements in the asthma following adenotonsillectomy.[67]

An assessment of a clinic population of 84 children with epilepsy found that 44% of severe epileptics and 31% of mild epileptics had symptoms of obstructive sleep apnoea.[68]

BOX 27.2 Indications for paediatric respiratory investigations[69]

- Diagnosis of OSA unclear or inconsistent
- Age <2 years
- Weight <15 kg
- Down syndrome
- Cerebral palsy
- Hypotonia or neuromuscular disorders
- Craniofacial anomalies
- Mucopolysaccharidosis
- Obesity (BMI >2.5 SDS (standard deviation scores) or >99th centile for age and gender)
- Significant comorbidity such as congenital heart disease, chronic lung disease
- Residual symptoms after adenotonsillectomy

INVESTIGATIONS

A UK working party consensus statement on the role of adenotonsillectomy in children with sleep-related breathing disorders said that performing adenotonsillectomy in a child with a history suggestive of OSA and enlarged tonsils, without further investigations, is reasonable and this could be undertaken in a non-specialist unit.[69] If the diagnosis of OSA is unclear or if the child is very young or at the extremes of the weight centiles, then further investigations are indicated. In patients with a suspected underlying syndrome or serious illness, investigations are essential before undertaking further management (Box 27.2).

Diagnostic investigations

OXIMETRY

Overnight pulse oximetry (Figure 27.2) can be useful if more detailed tests of sleep-disordered breathing are not available. It does not require an overnight hospital admission. This investigation provides two pieces of information: heart rate and oxygen saturation. It will detect apnoeas where the oxygen saturations drop, usually with an accompanying rise in heart rate. An oximetry scoring system has been defined by a group from Canada, which was associated with increasing severity of OSA in a prospective cohort study.[70] Oximetry has a high positive predictive value (97%) but, because not

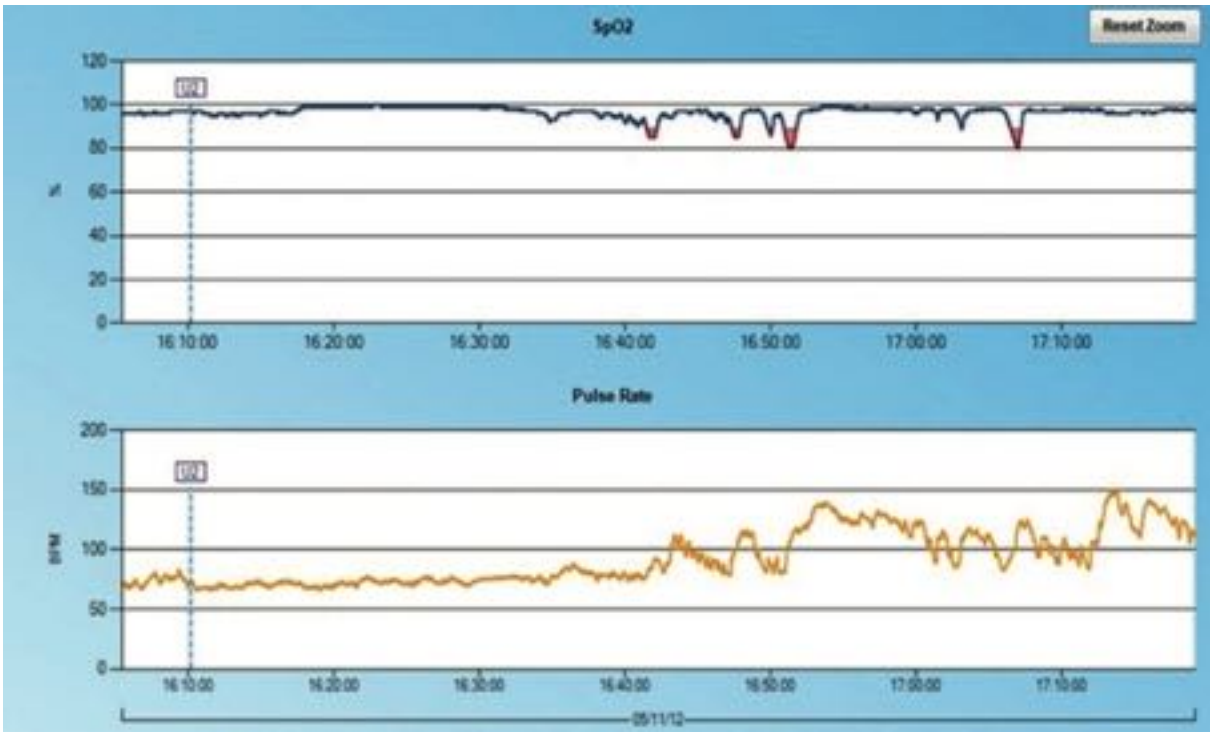


Figure 27.2 An oximetry trace showing periods of desaturation in red (SpO_2) with a rise in heart rate. With a positive history and examination, this has a high positive predictive value for OSA.

all apnoeas result in a drop in saturations, the negative predictive value is low (53%).[71]

POLYSOMNOGRAPHY

Polysomnography (PSG, a sleep study, **Figure 27.3**) is currently the gold standard of investigation. In this investigation, the child is monitored during sleep, usually in the hospital. This can be a variable quantity of measurements depending on local resources. The minimum features should be measurements of oxygen saturation, airflow, respiratory effort, electrocardiograph, video and sound.[13] This investigation can measure apnoeas (cessation in airflow) or hypopnoeas (reduction in airflow). These two are often combined as the apnoea–hypopnoea index (AHI) which is the total number of apnoeas and hypopnoeas per hour of sleep.

A study looking at visual scoring of arousals versus the interpretation of EEG found that the visual scoring of arousals was more appropriate than relying on the EEG alone.[72] A large case control study looked at the differences in sleep architecture on polysomnography for children of preschool versus school age and found some significant differences. Children of pre-school age were more likely to have central apnoeas, but less likely to awaken than older children with comparable levels of sleep-disordered breathing. This has implications for the interpretation of sleep studies for the different age groups.[73] Spruyt et al.[74] have demonstrated that children who have overnight polysomnography can be divided into six groups with clusters of severity based on polysomnographic criteria.

There is some questionnaire evidence that sleep patterns of children differ when in hospital having a sleep study, particularly in the under 3s group.[75] This indicates that caution needs to be applied to the interpretation of these tests and may be best assessed in the context of the parent's description of whether this was a typical night's sleep.

The way hypopnoeas are scored can make a large difference to the AHI. In a study looking at the American Academy of Sleep Medicine definition versus the Stanford definition (which requires no drop in oxygen saturation), the amount of OSA diagnosed varied from 19% to 99%.[76]

OTHER INVESTIGATIONS

- An ambulatory device (ApneaLink Plus, ResMed, Poway, Ca, USA) measuring nasal airflow, chest movement and oxygen saturation has compared favourably with polysomnography in the detection of obstructive sleep apnoea in a group of obese adolescent patients.[77]
- Actigraphy, using a wrist-worn sensor to detect sleep and wakefulness via motor activity, has been shown to be a good approximation to polysomnography in terms of sleep-wake pattern, but it gives no other information.[78,79]

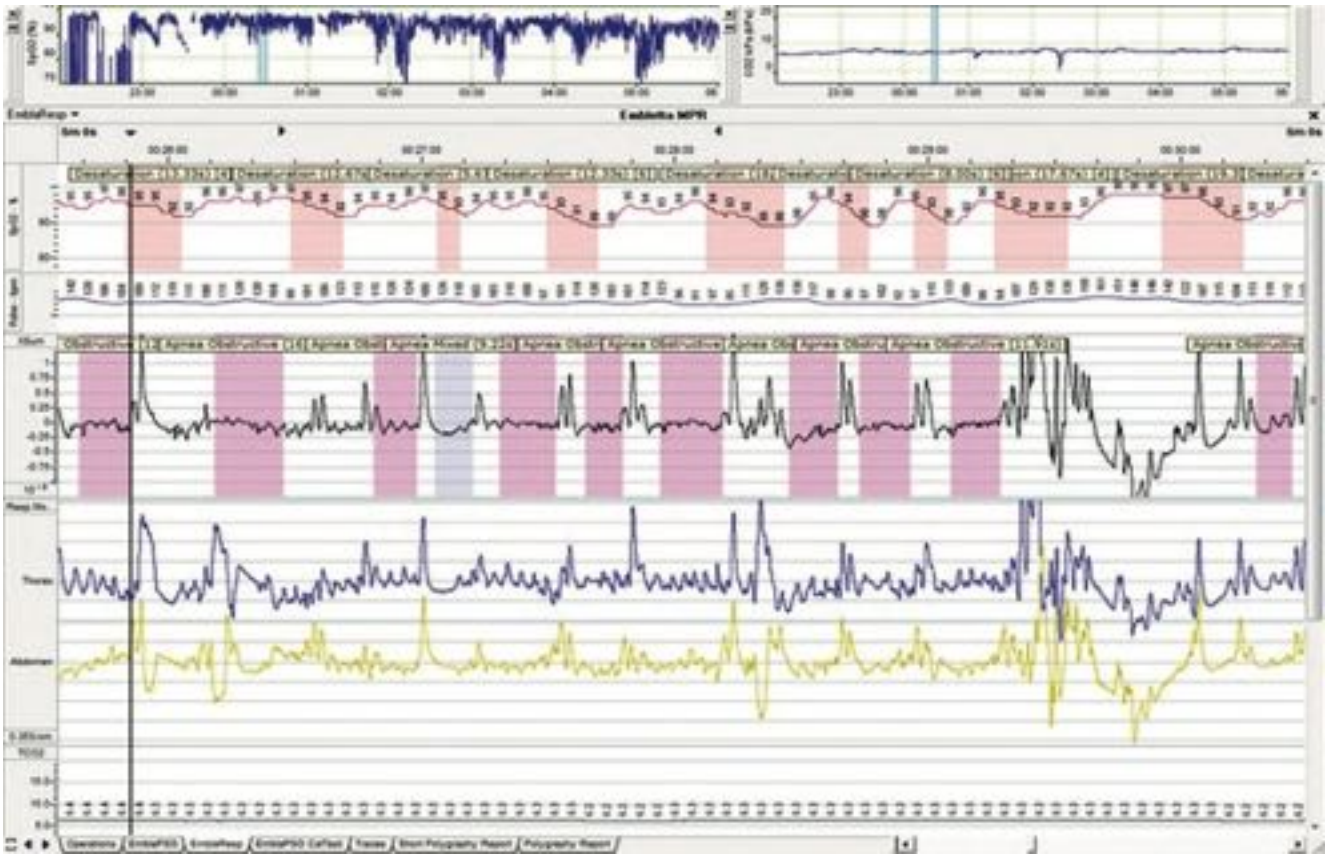


Figure 27.3 Part of a polysomnography study demonstrating desaturations (low SpO_2) and decreased airflow despite respiratory effort, confirming OSA.

- Cardiopulmonary coupling, using devices which measure the synchrony between pulse and respiration, has been proposed as a measure of sleep quality. In a study of OSA patients before and after adenotonsillectomy, the cardiopulmonary coupling appears to show improvement in sleep parameters for quality of sleep before the EEG.[80]
- Oesophageal pressure monitoring at the time of polysomnography to measure changes in intrathoracic pressure has been found to be more predictive for certain neurobehavioural variables.[81]
- Pulse transit time has shown some correlation with OSA at AHI above 3, but it is more limited at picking up milder OSA and differentiating between primary snoring.[82]
- Complementary investigations to measures of attention, such as the event-related potential, measured electrophysiologically, have shown some promise as measures.[83]
- Dynamic MRI is at an experimental stage, but has been used to demonstrate flow changes in paediatric patients with OSA.[84]
- Respiratory inductance plethysmography bands have shown promise in conjunction with oximetry as a pre-polysomnogram screening investigation.[85]
- Infrared monitoring of movements and chest/abdominal asynchrony during obstruction has also been proposed as a method of diagnosis.[86]

CARDIAC INVESTIGATIONS

If there are concerns about the severity of OSA, cardiac investigations in the form of ECG and echocardiography can be undertaken, but routine use of echocardiography has not been shown to be productive in the assessment of patients with OSA.[87]

TREATMENT

Diet and exercise

With the increasing proportion of obese patients, issues of body mass index and the underlying causes should be addressed.

A longitudinal study from Belgium looked at the impact of diet and exercise in a group of children with obesity and OSA. Of 114 obese patients, 41 had sleep apnoea. After weight reduction, 29 of the 41 patients had resolution of the OSA. Those who did not get resolution with weight loss were significantly more likely to have tonsil hypertrophy. Uric acid (a measure of oxidative stress) and CRP were significantly reduced by treatment.[88]

Medicines

A study in Brazil has looked at nasal douching and topical nasal steroids used in a sequential manner to treat adenoid hypertrophy. The study showed no change in the endoscopic appearance of the adenoids after douching alone, but a reduction after topical steroids for 40 days. The results of this are very restricted due to the lack of randomization and blinding.[89]

The Cochrane review has found in a short-term study that topical nasal steroid had a positive effect on the AHI of children with mild to moderate OSA.[90] There has been a well-produced double-blind randomized control trial of nasal steroids (6 weeks fluticasone) which has shown a reduction in the AHI.[91]

There is some evidence that treatment of reflux can help reduce the AHI in mild cases.[63]

Surgery

ADENOTONSILLECTOMY

Trials

The existing literature in this area demonstrates clearly the lack of level 1 evidence to inform treatment decisions. The 2015 Cochrane systematic review 'Tonsillectomy or adenotonsillectomy versus non-surgical management for obstructive sleep-disordered breathing in children' found only three trials meeting the criteria.[92]

The largest of these is the Childhood Adenotonsillectomy Trial (CHAT) from the USA, with 464 children randomized to early adenotonsillectomy or watchful waiting. The age inclusion criteria were 5–9 years and children who had polysomnographically proven OSA. The primary outcome measure was neuropsychological testing and there was no difference between the treatment and control arms, but secondary outcome measures of quality of life (paediatric sleep questionnaire, OSA-18, modified Epworth – all three of which are disease-specific – and pedsQL – measuring general quality of life) did show a significant difference. The control arm showed a spontaneous resolution rate of physiological sleep study measurements in 46% of the control arm versus 79% of the treatment arm. This was a negative trial for the primary outcome, and the high rate of resolution of symptoms in the control arm supports the clinical observations of spontaneous resolution beyond the age of 5 years due to reduction in the volume of adenotonsillar tissue.[93, 94]

In the second-largest study 80 patients with Down syndrome or muccopolysaccharidosis and polysomnographically proven OSA were randomized to adenotonsillectomy or CPAP. These comorbidities often result in more severe OSA and are therefore excluded from many larger studies.[95]

The final study was a small trial with just 29 patients with negative sleep studies and clinical symptoms randomized to adenotonsillectomy or watchful waiting and just 20 analyzed. This was judged to be a very poor quality study due to the dropout rate and the small initial sample size.[96]

There are several current trials comparing adenotonsillectomy versus watchful waiting in varying severities of sleep-disordered breathing from snoring to obstructive sleep apnoea. These include the Preschool Obstructive Sleep Apnoea Tonsillectomy Adenoidectomy (POSTA) trials from Australia, looking at younger age groups than the CHAT study.

A previous Cochrane review of treatment of obstructive apnoea by adenotonsillectomy only found one paper meeting the Cochrane criteria,[97] and this was primarily concerned with surgical technique.[98] Patients were randomized to either radiofrequency tonsil reduction and adenoidectomy or conventional adenotonsillectomy. There were no differences in the outcome measures.

An RCT looked at the addition of pharyngeal pillar closure to standard adenotonsillectomy. Patients with OSA were randomized to receive either a standard cold steel dissection adenotonsillectomy or the same procedure followed by apposition and closure of the pharyngeal pillars. Despite being adequately powered, there was a high dropout rate and a small length of follow-up. There was improvement in quality of life (QOL) scores and AHI for both techniques but no significant difference between them. In light of the limitations of the study these results should be treated with caution.[99]

Longitudinal studies

The main physiological outcome is the AHI from polysomnography as described above. There are a number of studies which demonstrate a reduction in the AHI and these have been summarized in a meta-analysis.[100] Included in this were paediatric patients with no underlying syndrome or diagnosis who underwent adenotonsillectomy with pre- and post-operative polysomnography. The meta-analysis pooled data on 355 children from 14 series. The data are limited by the fact that this is from case series and there are no control groups. An improvement of polysomnography to normal occurred in 83% and a reduction in the AHI of 14 events per hour was found.

More recently there has been a large multicentre retrospective analysis of outcomes of adenotonsillectomy at centres across North America. This analysis included 578 children and the AHI fell significantly from 18.2 pre-operatively to 4.1 post-operatively. However, only 27% of patients had a normal AHI of less than 1. Severe OSA pre-operatively and obesity were predictive of residual OSA post-operatively.[101]

A small study looked at outcomes of adenotonsillectomy in a group of patients with craniosynostosis and upper airway obstruction with moderate to severe OSA. Three out of five patients avoided a tracheostomy, and one of five patients had complete resolution of their symptoms.[102]

A study of 101 children with OSA, who underwent adenotonsillectomy, found that there was a significant reduction in central apnoeas, in those who experienced them, following the procedure.[103]

Adenotonsillectomy was an effective treatment for OSA in a cohort of cleft palate patients, with a reduction of mean AHI from 17.6 to 1.9.[57]

Use of a nasopharyngeal airway has been found to be a useful adjunct to surgery and seems to decrease reliance on PICU.[104]

Tonsillectomy technique

There is increasing evidence that intracapsular tonsil techniques may confer some advantages over conventional techniques. In a series of 500 patients who underwent Coblation® intracapsular tonsillectomy and adenoidectomy, the bleed rate was 0.4%. Requirements for analgesia were low and parental satisfaction and quality of life were high.[105] A study of quality of life by proxy at 3 months and 2 years found no difference between subtotal and full adenotonsillectomy.[106]

JAW DISTRACTION

Bilateral distraction osteoneogenesis has proven to be a reliable technique in producing an adequate pharyngeal airway in children with micrognathia and subsequent pharyngeal restriction secondary to tongue base collapse. In a report from Israel all 11 patients with tracheostomies were subsequently decannulated following jaw distraction with near normal oximetry.[107]

Rapid maxillary expansion has been proposed as an alternative technique in children with retrognathia. In a group of 15 children, 8 had a better respiratory distress index following treatment but 7 were either unchanged or worse.[108] For more detail, see Chapter 19, Craniofacial surgery.

TONGUE REDUCTION

In Beckwith–Wiedemann syndrome and other selected syndromes with macroglossia, tongue reduction may be indicated and results are usually good.[109]

Continuous positive airway pressure

Continuous positive airway pressure (CPAP) may be required in children where treatment is not possible, where treatment is awaited, or where treatment has failed. It is usually used in cases of moderate to severe OSA.

Adherence to CPAP can be poor, particularly in older children. In a sample of 51 patients the mean amount of time spent with CPAP on was just 3.3 hours per night. The authors developed a questionnaire to identify barriers to adherence.[110] A randomized controlled trial of different methods of administering CPAP showed no improvement in compliance with different delivery systems.[111] One American study linked socioeconomic factors rather than disease severity to poor compliance.[112]

CPAP is often reserved for treatment failures, complicated cases with comorbidities and in obesity. The first study to look at neurobehavioural outcomes in 52 patients on CPAP alone examined a heterogeneous group of patients. Assessments were performed at baseline and after 3 months of treatment. There were significant improvements in both disease-specific and general quality of life (QOL) scores. These improvements occurred with a mean use of just 3 hours per night.[113]

The only randomized controlled trial concerning positive airway pressure in paediatric OSA looked at the use of continuous or bilevel CPAP in children who were

unsuitable for adenotonsillectomy and found no difference between the methods.[114]

Nasopharyngeal airway

Nasopharyngeal airways can be used for the long-term management of patients with craniosynostosis and can result in significant improvements in quality of life (QOL) scores.[115]

Analgesia post-adenotonsillectomy for OSA

Paracetamol is considered part of the standard regimen for analgesia post-adenotonsillectomy. Non-steroidal anti-inflammatory medications are widely used in the UK, but there are concerns about a potential bleeding risk associated with their use. A recent Cochrane review with over 1000 children looking at post-operative bleeding in adenotonsillectomy with NSAIDs has shown no statistically significant increase in bleeding, but greater numbers would be needed to prove conclusively there was no increase.[116]

Opioid analgesics need to be managed very carefully. In 2012 the FDA in the US reported three deaths and one severe respiratory depression in children who had undergone tonsillectomy or adenotonsillectomy for obstructive sleep apnoea and had received codeine. It appeared that the children were 'ultra-rapid metabolizers' with a genetic variant which made the liver enzyme p4502D6 much more active. It is thought that this gene variant can exist in up to 7% of the standard population in the US, but up to 29% of those of Ethiopian origin. These children rapidly metabolize a standard dose of codeine, resulting in high serum levels of morphine.[117, 118]

The UK government has restricted the use of codeine in children, particularly those undergoing adenotonsillectomy. The relevant advice is shown in **Box 27.3**.[119]

A randomized double-blind study compared post-operative morphine with dexmedetomidine, a sedative medicine. The dexmedetomidine produced less respiratory compromise as measured by end tidal CO_2, but pain scores were higher.[120]

Location of post-operative care

While the majority of patients with OSA can be managed safely in a standard children's ward environment, careful consideration must be given to whether those at higher risk of respiratory compromise post-operatively need more specialized support (see below). In a prospective study looking at respiratory complications following adenotonsillectomy for OSAS the rate was found to be 10.4%. However, in children with no comorbidity, only 1.2% of these had a problem beyond 6 hours. This is suggested as a basis for day-case tonsillectomy in children without comorbidity. The rate of complications in those with comorbidity at 6 hours post-surgery was 21.6%.[121]

BOX 27.3 UK Government relevant advice on codeine use[119]

Codeine should only be used to relieve acute moderate pain in children older than 12 years and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen.

Codeine is contraindicated in all children (i.e. younger than 18 years) who undergo tonsillectomy or adenoidectomy (or both) for obstructive sleep apnoea.

Codeine is not recommended for use in children whose breathing might be compromised, including those with: neuromuscular disorders; severe cardiac or respiratory conditions; upper respiratory or lung infections; multiple trauma; or extensive surgical procedures. The symptoms of morphine toxicity may be increased in these settings.

In children aged 12–18 years, the maximum daily dose should not exceed 240 mg. This may be taken in divided doses, up to four times a day at intervals of no less than 6 hours. It should be used at the lowest effective dose for the shortest period. Duration of treatment should be limited to 3 days and, if no effective pain relief is achieved, treatment should be reviewed by a physician.

Information should be given to parents and caregivers on how to recognize the signs of morphine toxicity, and advice should be given to stop giving the child codeine and to seek medical attention immediately if their child is showing these signs or symptoms.

Symptoms of codeine toxicity include: reduced levels of consciousness; lack of appetite; somnolence; constipation; respiratory depression; 'pinpoint' pupils; nausea and vomiting.

Codeine is contraindicated in all patients of any age known to be CYP2D6 ultra-rapid metabolizers.

Post-operative complications

The main risk of adenotonsillectomy is post-operative haemorrhage, which has a rate of approximately 4%. A randomized allocation study of 50 children, allocated to either dissection adenotonsillectomy or Coblation® for obstructive sleep apnoea, found less time and less intra-operative blood loss with Coblation®. The failure to find a difference in secondary haemorrhage is not surprising given that this study is vastly underpowered to detect post-operative complications.[122]

A large case controlled trial undertaken in the US looked at over 9000 tonsillectomies, with an overall bleed rate of 2.4%. Using logistic regression, the bleed rate in tonsillectomies was found to be half the rate in those done for recurrent acute tonsillitis.[123]

Children who have OSA are at increased risk of peri-operative respiratory complications. They may be more sensitive to opiates and inhalational anaesthetic agents and are at risk of pulmonary oedema. In children who have been identified as high risk, surgery should be performed in a hospital with paediatric intensive care facilities.[124] In cases at high risk of airway compromise, a nasopharyngeal airway can help reduce the reliance on PICU.[125]

A retrospective review of 993 patients aged 3 years and under found a 9.9% complication rate, with airway obstruction, desaturations and bleeding being the three commonest complications.[126] Younger age (less than 2 years), nasal obstruction and cardiovascular

comorbidities were predictors of airway complications in this group.

Another retrospective review showed that young age, high apnoea–hypopnoea index and intra-operative laryngospasm were linked with complications.[127]

A systematic review has demonstrated that children with OSA put on a significant amount of weight post-operatively and this can predispose some to obesity.[128]

Treatment failure

Residual OSAS following adenotonsillectomy has been reported in 11.6% of children in one study following polysomnography.[129] It has been reported as high as 31% of children in some studies, with higher proportions in children with severe OSA, following surgery.[130] Hypertrophy of residual lymphoid tissue in Waldeyer's ring such as the lingual tonsillar tissue may be responsible for some failures.[131, 132]

Sleep nasendoscopy has been suggested as a method to assess the site of obstruction in airway failures. In a group of 13 children this was seen to be a combination of adenoid regrowth, inferior turbinate hypertrophy and tongue base collapse.[133] There may also be coexistent airway pathology. In a group of 43 patients with OSA secondary to laryngomalacia, 32 had already undergone adenotonsillectomy without resolution of symptoms. Sleep nasendoscopy was an effective way of diagnosing the condition and treatment with supraglottoplasty resulted in a statistically significant reduction in the AHI.[134]

Synchronous airway lesions were found in nearly two-thirds of patients in one series who were less than 3 years of age and undergoing adenotonsillectomy, but only a small number may require surgical intervention. Laryngomalacia and subglottic stenosis were the commonest pathologies.[135]

In a study looking at either supraglottoplasty or lingual tonsillectomy following adenotonsillectomy when there was residual OSA, there was improvement following these procedures, but less for lingual tonsillectomy in obese patients, and less improvement from supraglottoplasty in patients with other comorbidities.[136]

A retrospective analysis of 31 patients who had refractory obstructive sleep apnoea, who were subsequently treated with geniohyoid advancement, radiofrequency tongue base reduction and lingual tonsillectomy, resulted in a success rate of 61% judged by polysomnography.[137]

QUALITY-OF-LIFE OUTCOMES IN SLEEP-DISORDERED BREATHING

Measuring outcomes other than the physiological sleep outcomes is of increasing interest. Areas include neurocognitive outcomes and also quality of life by proxy. The first UK study to measure quality of life improvement was by Georgalas.[138] In a cohort of patients, adenotonsillectomy improved all domains of the Child Health Questionnaire. There has been further work on the use of disease-specific instruments in the UK.[139] In North America there is widespread use of disease-specific quality of life measures such as the OSA-18.[140] A review article found 11 publications measuring changes in behaviour, neurocognition and quality of life following adenotonsillectomy.[141] The authors probably overrate the quality of evidence as these studies are generally prospective single-sample observational studies, although 5 of the 11 do include a control group. Universal improvement in quality of life is reported in these studies. Behaviour and neurocognitive measures also show improvement. One year following adenotonsillar surgery in a group of preschool children, the OSA group showed fewer behavioural problems and a significant improvement in behaviour and quality of life.[142] Longer-term studies demonstrate that the quality of life improvement can be sustained over up to 4 years.[143, 144]

Quality of life studies generally fall into two categories: cross-sectional studies, which are looking at quality of life for a specific condition, and longitudinal studies, which look at the change in quality of life following an intervention.

Cross-sectional studies

Two of these studies were used to develop two of the main disease-specific quality of life tools: the OSA-18 and the Tonsil and Adenoid Health Status Instrument.[145, 146] The main differences between them are that the Tonsil and Adenoid Health Status Instrument was designed for any adenotonsillar disease, and children did not have polysomnographic investigation. The OSA-18 was designed specifically for sleep-disordered breathing and an abbreviated form of polysomnography was performed. The Tonsil and Adenoid Health Status Instrument has been used to derive the T14 instrument for UK practice. This instrument captures information in domains about the obstructive and infective symptoms which affect children, and the subsequent impact on quality of life through issues such as contact with medical services and time off school.

Three other studies looked at general quality of life measures in sleep-disordered breathing, and all found a negative impact of sleep-disordered breathing on quality of life.[147–149]

Two studies investigated obesity and sleep-disordered breathing using a general quality of life measure and found sleep-disordered breathing in obesity to impair quality of life.[150, 151]

Longitudinal studies

The OSA-18 had its development completed in one of these longitudinal trials.[140] It has been used to demonstrate large changes following adenotonsillectomy in the disease-specific quality of life for a general group of patients,[144, 152–159] and specific subgroups of severe OSA[160] and obesity.[161] The OSA-18 has also been used to demonstrate improvement in disease-specific quality of life in children with cerebral palsy[162] and attention deficit hyperactivity disorder (ADHD).[163]

One of the studies used a non-validated questionnaire so is difficult to compare to the others.[164]

The OSD-6 (obstructive sleep disorders 6) was developed in one of the studies[165] and subsequently used in longitudinal studies which show changes in all domains following adenotonsillectomy including improvements up to 3 years after intervention.[166, 167]

The Tonsil and Adenoid Health Status Instrument was used to evaluate the changes following adenotonsillectomy. This showed significant improvement across most scales in a longitudinal study.[168]

Most of the studies have the same limitations in that they feature usually consecutive or convenience samples of children and there is mostly one group. There is potential for bias in the inclusion criteria in a number of the studies. The intervention is made and there is a longitudinal design to the studies. While they all show improvement across the specified domains, there are no control groups in the studies who do not undergo the procedure, so it is not possible to state conclusively that the change is due to the intervention alone, or what magnitude of change there would be compared to a control group.

The only randomized controlled trial concerning quality of life was an evaluation of microdebrider tonsillotomy versus electrocautery to perform adenotonsillectomy. The microdebrider group were more likely to get back to normal activities and diet quicker than the electrocautery group.[169]

MANAGEMENT ALGORITHMS

For the purposes of discussion for this chapter, the term 'specialist children's hospital' refers in the UK to a hospital with specialist paediatric ENT surgeons, anaesthetists and intensive care facilities. The term 'non-specialist centre' refers in the UK to a unit without paediatric intensive care or specialist paediatric ENT or anaesthetic provision. Box 27.4 lists circumstances in which a child should be referred for treatment to a specialist children's hospital.

BOX 27.4 Children who should be referred for treatment in a specialist children's hospital[69, 124]

Age <2 years
Weight <15 kg
Failure to thrive (weight <5th centile for age)
Obesity (BMI >2.5 SDS or >99th centile for age and gender)
Severe cerebral palsy
Hypotonia or neuromuscular disorders (moderately severely or severely affected)
Significant craniofacial anomalies
Mucopolysaccharidosis and syndromes associated with difficult airway
Significant comorbidity (e.g. congenital heart disease, chronic lung disease. ASA 3 or above)
ECG or echocardiographic abnormalities
Severe OSA (described by polysomnographic indices including obstructive index >10, respiratory disturbance index (RDI) >40, and oxygen saturation nadir <80%)

Based on the evidence presented in this chapter the following management algorithm is suggested.

Non-specialist centre

A careful history and examination should be taken. Using the UK guidelines there are factors which can be derived from the history and factors which can be measured that would guide whether it is appropriate to treat in a non-specialist environment (without PICU support) (see Box 27.3).[69]

The factors derivable from the history are:

- age
- severe comorbidity which could influence the anaesthetic and post-operative course (heart/lung)
- comorbidity with impact on pathophysiology of OSA (cerebral palsy, hypotonia/neuromuscular conditions, craniofacial abnormalities, mucopolysaccharidoses or other airway syndromes).

Age 2 years or less would seem to be a sensible point at which a child should have an anaesthetic for adenotonsillectomy to treat obstructive sleep apnoea in a specialized children's hospital or a hospital with high-level children's facilities. The heart and lung factors make it more likely that a child could have intra- or post-operative difficulties therefore would be best managed in a centre with specialist paediatric anaesthetists and paediatric intensive care facilities. The comorbidity with an impact on pathophysiology are conditions which make it more likely that OSA will be more severe and more likely to have incomplete resolution following tonsillectomy and adenoidectomy alone. Removal of small amounts of tissue to try to make partial improvements in patients with OSA can also result in worsening of the condition if there is post-operative swelling.

Consideration should be given to referring these children to specialist children's hospitals prior to any investigations as it is likely that full polysomnography rather than pulse oximetry would be undertaken.

Factors which can be measured are:

- weight
- ECG – to look for cardiac complications
- oximetry – to exclude moderate to severe OSA.

In children over 2 years who have no comorbidity as listed earlier, it is sensible to undertake the above investigations. This is to ensure that children are not at the extremes of weight, do not have cardiac complications and do not have moderate to severe OSA. As discussed in 'Oximetry' above, the investigation has a high positive predictive value but a low negative predictive value.[71] Thus an oximetry trace showing clusters of desaturation is likely to represent moderate to severe OSA. A 'normal' oximetry trace may represent mild OSA/sleep-disordered breathing.

A child with minimal desaturations, none of the above comorbidity and not at the extremes of weight or age can

safely be managed in a non-specialist hospital environment. If the oximetry trace shows no desaturation in the presence of positive features of apnoea on history and large tonsils, the patient is likely to have obstructive sleep apnoea but may have primary snoring alone. Treatment with adenotonsillectomy in these circumstances will result in treatment for most patients with OSA, but may also result in treating primary snorers. There is increasing evidence that primary snoring is not a benign condition and may have neurobehavioural consequences, but there is no research or established role at this stage for adenotonsillectomy in the treatment of primary snoring.[34]

The other option in these circumstances is to refer the child to the local paediatric sleep team for a polysomnogram, which would give diagnostic clarity about the presence/absence of OSA.

Specialist children's hospital

A similar list of conditions exists in the UK guidelines for which children require investigations prior to treatment of OSA.[69]

In the specialist paediatric hospital setting the decision-making process will usually depend on establishing the need to investigate prior to intervention or proceed directly.

As with the non-specialist hospital assessment of the age, cardiorespiratory comorbidity and comorbidity causing or impacting on the severity of OSA can be derived from the clinical findings. Weight and ECG can be measured.

In many centres, in children with no significant comorbidity with clinical findings suggestive of OSA, the decision is taken to proceed directly to adenotonsillectomy. This should be an informed discussion with the parents explaining that, while there is a probability that a child with obstructive features in the history and large adenotonsillar tissue does have obstructive sleep apnoea, there is a chance that they may have primary snoring only.[31] Some parents and surgeons will prefer to investigate for improved diagnostic accuracy, and this can be in the form of oximetry or polysomnography.

If polysomnography is negative, the family can be reassured. If it shows evidence of OSA, treatment should be discussed. If it is mild, consideration could be given to intranasal steroids if the family are keen to avoid surgery.[91] If it is moderate or severe, consideration should be given to adenotonsillectomy.

If a child is at the extremes of weight, has serious cardiorespiratory comorbidity, craniofacial, muscle tone or syndromic problems, a polysomnogram should be performed prior to any intervention. This allows an improved diagnostic certainty in patients who are at higher risk for respiratory complications and also risk stratification. Surgery can be avoided in those who do not have OSA, while those who have moderate to severe OSA can have appropriate arrangements made for post-operative care. This will vary between centres from prolonged recovery, use of airway adjuncts to high dependency or intensive care beds. The intervention clearly needs to be tailored to the individual condition, and in those with syndromic or craniofacial problems it should be a multidisciplinary team decision.

CONCLUSION

Paediatric OSA is a common condition which will be seen by the majority of ENT surgeons. It is important to understand the pathophysiology, and to appreciate the limitations of history and examination in the diagnosis. Investigations need to be considered carefully in the context of their predictive values and a suggested algorithm for hospitals with and without paediatric anaesthesia and intensive care is suggested. Intervention in this condition can result in large and sustained quality of life, but a good awareness of the comorbidities which could result in complications or a poorer outcome is essential.

FUTURE RESEARCH

- Improved abbreviated diagnostic testing.
- Good randomized evidence to support decision-making.
- Increasing use of intracapsular tonsillectomy.
- Better understanding of the inflammatory basis of OSA.

KEY POINTS

- Paediatric obstructive sleep apnoea (OSA) is common, with an incidence of up to 2%.
- Clinical features in the history and examination can be unreliable in predicting OSA.
- Oximetry has a high positive predictive value but a low negative predictive value.
- There is good longitudinal evidence of physiological and quality of life improvement with adenotonsillectomy, but there has been only one completed large-scale randomized controlled trial.

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CHAPTER
28

STRIDOR

Kate Stephenson and David Albert

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SEARCH STRATEGY

The senior author has a personal bibliography of key papers on paediatric airway obstruction. This was supplemented with a Medline search using the following keywords: stridor, child, neonatal, paediatric, laryngomalacia, tracheomalacia, vocal cord palsy, vocal fold palsy, vascular ring, stenosis, laryngotracheobronchitis, croup, tracheitis and airway obstruction.

The rationale for most interventions in childhood stridor is based on the practices of experienced clinicians. Few treatments have been subjected to controlled trials. Hence, apart from steroid and nebulized adrenaline therapy in croup, recommendations in this chapter are Grade C and D.

INTRODUCTION

This chapter discusses the evaluation and management principles of a child with stridor. It then reviews the usefulness of special investigations. The clinician is directed to the appropriate chapter for detailed information on specific conditions. Care of the acutely stridulous child is also described.

The challenge of managing a stridulous child

A child labelled with a 'diagnosis' of stridor may have significant underlying pathology. Stridor is a symptom and not a diagnosis. History and general examination alone are insufficient for a firm conclusion to be drawn. Deciding which patients to investigate is sometimes difficult. Even after non-invasive investigations such as imaging there may remain a number of differential diagnoses. Awake flexible endoscopy is very useful but gives little or no information beyond the level of the glottis.

The definitive diagnostic technique of laryngotracheobronchoscopy (LTB) requires an experienced team of surgeon, anaesthetist and nursing staff. Both the equipment and expertise required are highly specialized and are not available in all institutions. Transfer of the child with stridor may be necessary and should be carefully managed.

A child with stridor typically induces significant anxiety in the carer and should be a clinical priority for the medical professional. In the acute situation the paediatric airway can deteriorate rapidly. In a specialized unit this is rarely a problem, with experienced anaesthetists to intubate and surgeons to perform the rare emergency tracheostomy. In a paediatric ward, emergency room or non-hospital setting, rapid deterioration can prove a real challenge.

Anatomical and physiological considerations

Neonates and young children develop upper airway obstruction and respiratory failure more readily than older children and adults. A significant contributor to this increased risk is the structure of the airway in the younger child. Mucosal swelling is more likely to result in a comparatively greater degree of obstruction of the smaller upper airway.

AIRWAY DYNAMICS

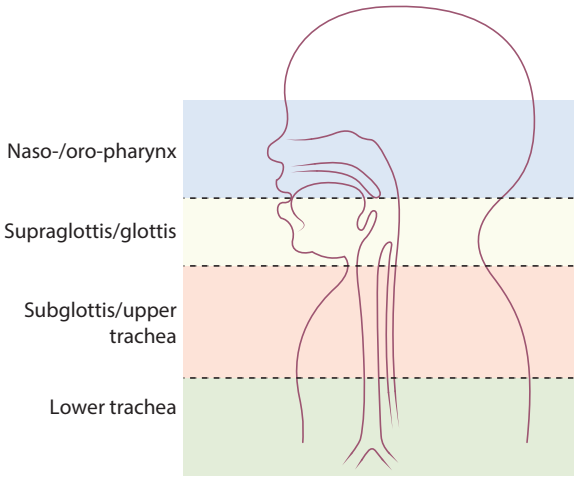
Poiseuille's law (the Hagen–Poiseuille equation) may be applied to the airway and dictates that the airway resistance is inversely proportional to the fourth power of its radius; a 50% reduction in the radius of the airway therefore results in a 16-fold increase in resistance to airflow. One millimetre of narrowing in a 4 mm diameter infantile airway thus results in a 75% change in airflow. As cross-sectional

area decreases, airflow velocity increases. The smaller the airway, the greater the impact of airway oedema and the more grave the concern.

The Bernoulli principle is also of fundamental importance in relation to the paediatric airway. Increased airflow velocity results in negative pressure on the walls of the airway leading to inward collapse. Previously smooth or 'laminar' airflow then becomes more turbulent. The 'Reynolds number' is a quantity described in fluid mechanics that defines the point at which the transition between laminar and turbulent flow occurs. Factors in the equation are the density, viscosity and velocity of the 'fluid', and the diameter of the 'pipe'. Increased turbulence is highly important, greatly increasing airway resistance. Increased airway collapse occurs with vibration of closely apposed tissues and the resultant noise of stridor.

Definitions and characteristics of stridor

Noise originating in the larynx or trachea is typically high-pitched and termed 'stridor'. It may have a musical quality. In contrast, the low-pitched snoring type of noise made by naso- and oropharyngeal obstruction (and rarely by the supraglottic larynx) has a rougher quality and is best described as 'stertor'. Obstruction of the small intrathoracic airways, such as in asthma, is termed 'wheezing'. A rigid differentiation between stridor and stertor cannot always be made and too rigid a distinction can lead to incorrect diagnosis (Figure 28.1).



	Airway noise	Voice/cry	Cough
Naso-/oro-pharynx	Stertor	Muffled	Typically absent
Supraglottis/glottis	Stridor-inspiratory	Hoarse (glottis)	Barking
Subglottis/upper trachea	Stridor-biphasic	Unchanged	Brassy
Lower trachea	Stridor-exspiratory	Unchanged	Wet sounding

Figure 28.1 Clinical presentation according to level of upper airway obstruction.

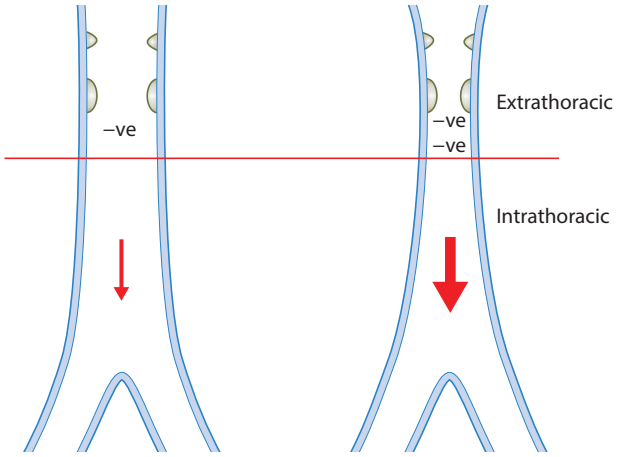


Figure 28.2 Increasing collapse on inspiration with extrathoracic obstruction.

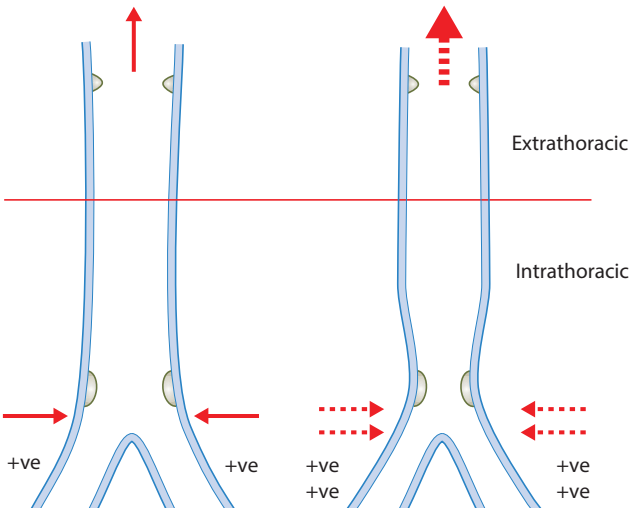


Figure 28.3 Increasing collapse on expiration with intrathoracic obstruction.

Typically, inspiratory stridor is due to an extrathoracic obstruction (Figure 28.2) from the larynx or high trachea. Bronchial or low tracheal obstruction produces an expiratory stridor. Biphasic stridor can occur with obstruction anywhere in the tracheobronchial tree. Even if expiratory stridor is absent, a prolonged expiratory phase may be present, indicating an intrathoracic obstruction (Figure 28.3).

EVALUATION OF THE CHILD WITH STRIDOR

The aim of the history, examination and special investigations is to determine not only the site and cause of the obstruction (the diagnosis) but also its effect on

the airway (the severity). It is important to consider the effect of airway obstruction on feeding, sleep, exercise and growth.

History

PERINATAL HISTORY

The obstetric and perinatal history is often relevant. This is particularly true if the child was born prematurely and required ventilation. Neonates admitted even for short periods to intensive care or a special care baby unit (SCBU) may have had endotracheal intubation but the parents may not volunteer this important information. Beware the term 'intubation', as this may be taken to mean the passage of a nasogastric tube or even suction of oronasal secretions. A history of a difficult delivery is also linked to vocal cord palsy.

Stridor that is present at birth, i.e. with the child's first breath, is unusual. This generally denotes a significant fixed congenital narrowing such as a laryngeal web, subglottic or tracheal stenosis or bilateral vocal cord palsy. Other dynamic conditions such as laryngomalacia typically become evident in the first few weeks of life. A gradual increase in severity of airway compromise implies progression of an obstruction which may be intrinsic (luminal), as in the case of a subglottic haemangioma, or extrinsic, as with a mediastinal mass.

TABLE 28.1 Symptoms associated with varying causes of airway obstruction

Symptoms	Typical diagnoses	
Prolonged expiratory phase	Tracheal and bronchial obstruction (e.g. tracheobronchomalacia, stenosis)	
Cough	TOF Vocal cord palsy Cleft larynx Foreign body Tracheomalacia Reflux	
Aspiration	TOF Vocal cord palsy Cleft larynx	
Hoarseness	Laryngeal lesion (e.g. vocal cord palsy, papilloma)	
Acute airway obstruction	Retropharyngeal abscess Tonsillitis Glandular fever Foreign body Epiglottitis Croup Bacterial tracheitis	
Dysphagia and feeding difficulties	Epiglottitis Tonsillitis Retropharyngeal abscess	NB Feeding affected with many causes of severe airway obstruction
Apnoeas	Tracheobronchomalacia	

PATTERN OF STRIDOR

Stridor is seldom constant. Any variation can help pinpoint the cause, though asking parents about the timing of stridor in the respiratory cycle is seldom profitable. Typically, laryngomalacia – as with other laryngotracheal causes of stridor – is better when the child is at rest or asleep but made worse by crying, feeding and excitement. Upper airway obstruction at the level of the pharynx is in contrast worse when the child is asleep and is associated with stertor. Airway obstruction greatest in a supine position can occur with a pedunculated laryngeal mass but more often is due to supralaryngeal obstruction such as micrognathia and resultant tongue base occlusion. Improvement in the airway with crying occurs in significant nasal obstruction such as bilateral choanal atresia.

ASSOCIATED FEATURES

Airway obstruction may be associated with a number of symptoms (Table 28.1) alongside stridor including apnoeas, cyanosis, 'dying spells', cough and hoarseness and increased work of breathing (dyspnoea, tachypnoea, recession, nasal flaring, head bobbing). Apnoeic episodes associated with cyanosis are typical of severe tracheobronchomalacia and are sometimes termed 'dying spells'. They may also be described as apparent life-threatening events (ALTEs) of which airway pathology is one of several causes. A newer potential label of 'brief resolved unexplained event' (BRUE) has also been proposed.[1] Parents will usually attempt resuscitation if these episodes are severe. It is often unclear how many of these attacks are otherwise self-limiting.

Tachypnoea and dyspnoea are not limited to upper airway obstruction but a clear description of exertional dyspnoea in an older child provides a useful functional assessment of severity. Cough is typical of tracheo-oesophageal fistula (TOF) and tracheomalacia and is rarely due to 'infantile asthma'. Hoarseness suggests a laryngeal lesion such as papillomatosis and also occurs in vocal cord palsy.

FEEDING HISTORY

Feeding is one of the most strenuous activities for a neonate and is closely connected with breathing. It is therefore vulnerable to compromise in upper airway pathology. A change in feeding or inability to feed is typically keenly noted by carers and is likely to be a key indicator of upper airway status.

An accurate picture of the feeding pattern must be obtained. Breastfed babies with airway obstruction will characteristically 'come up for air'; bottle-fed babies may require thickened feeds or a 'slow teat' (i.e. one with small holes). Aspiration suggests vocal cord palsy, tracheo-esophageal fistula, neuromuscular pathology or rarely a laryngeal cleft. Significant repeated aspiration may be associated with recurrent chest infections. Regurgitation ('posseting') is common in neonates and by itself may not represent significant gastro-oesophageal reflux. The end result of poor feeding may just be slow feeding which

troubles the carers more than the child or there may be failure to thrive with demonstrably poor weight gain. It is important not to assign failure to thrive to the common cause of laryngomalacia without first having considered and excluded other causes. Formal mapping of weight gain in a growth chart is useful in both the assessment of severity and planning of appropriate management. Figure 28.4 demonstrates an example of growth failure as might be seen in a case of significant prolonged upper airway obstruction.

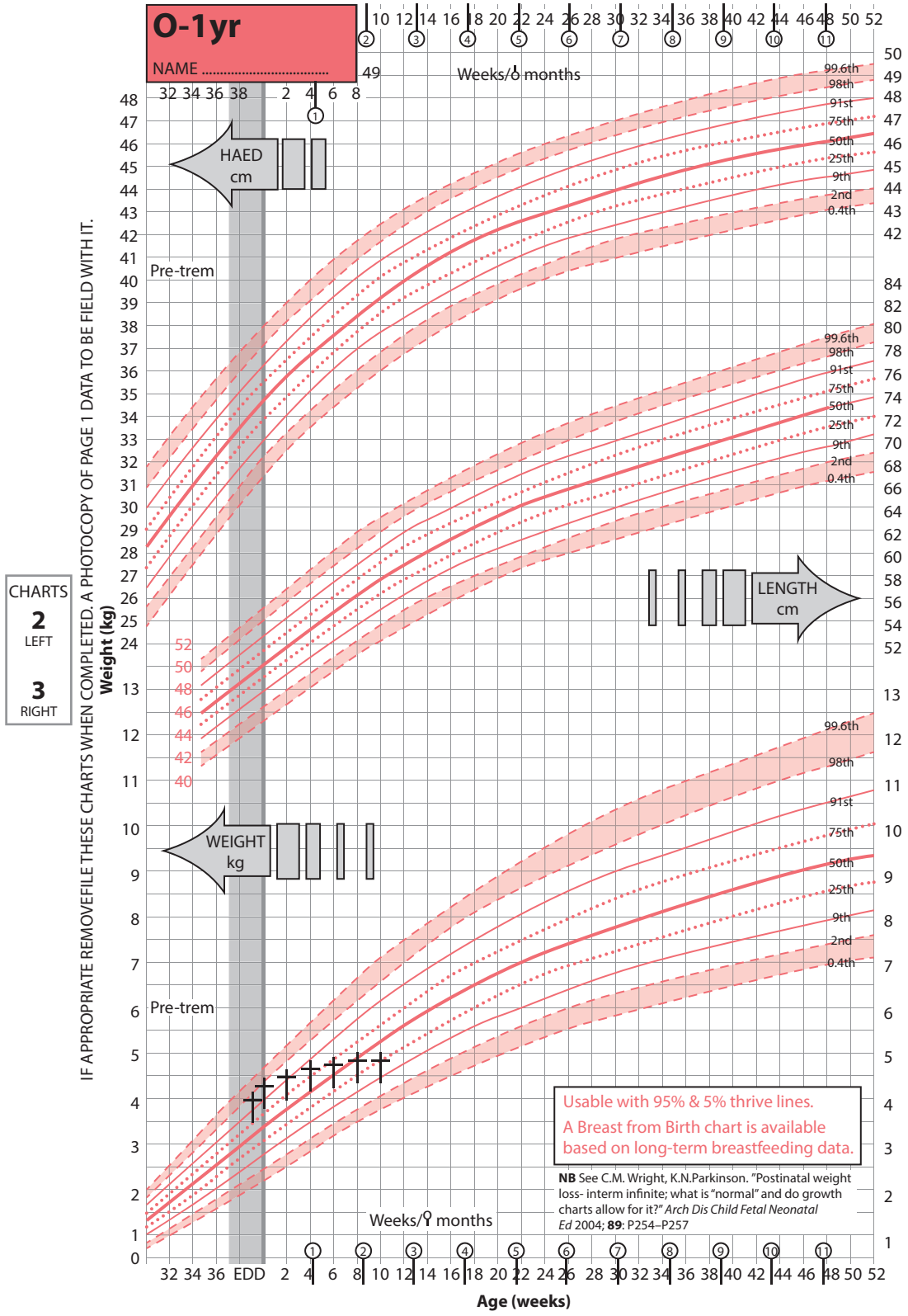


Figure 28.4 Growth chart demonstrating growth failure in the first 3 months of life. (Baseline data Child Growth Foundation.)

GENERAL MEDICAL CONDITIONS

Enquiry into the general past medical history may explain a vocal cord palsy occurring as a result of neurological disease or cardiothoracic surgery. It may also suggest vascular compression associated with congenital cardiac disease. The presence of any skin lesions is important; a cutaneous haemangioma may be associated with a subglottic haemangioma.

ACUTE OBSTRUCTION

In acute airway obstruction the history is taken in parallel with the examination and resuscitation. Take particular note of any possible foreign body aspiration or concurrent illness history. Rapid progression of airway obstruction typically occurs in acute infection and in foreign body inhalation.

Boxes 28.1, 28.2 and 28.3 give examples of congenital and acquired causes of upper airway obstruction and highlight the common pathologies.

Examination

OBSERVATION

Observing the child at rest before proceeding to formal examination provides not only an initial assessment of the degree of respiratory distress and the characteristics of any stridor but also gives time to gain the child's confidence. The characteristics of the stridor need to be observed as well as the effects of airway obstruction such as recession. An abnormal voice, wheeze or cough is a useful localizing sign. The site of the abnormal vibration can rarely be pinpointed with the aid of a stethoscope due to the variable transmission of sound through the thorax.

BOX 28.1 Examples of naso- and oropharyngeal causes of upper airway obstruction (bold = common causes)

Congenital	Acquired – neonates	Acquired – children
Choanal atresia	**Neonatal rhinitis**	**Allergic rhinitis**
Choanal stenosis		**Adenoiditis**
Mid-nasal stenosis		**Adenotonsillar hypertrophy**
Piriform aperture stenosis		**Foreign body**
Glioma		Non-allergic rhinitis
Encephalocoele		Retropharyngeal abscess
Meningocoele		Infectious mononucleosis
Dermoid/teratoma		Ludwig's angina
Craniofacial abnormalities		Thermal and caustic burns
Micrognathia – glossoptosis		
Lingual thyroid		
Lymphovascular malformation		

BOX 28.2 Examples of laryngeal causes of upper airway obstruction (bold = common causes)

Congenital	Acquired – neonates	Acquired – children
Laryngomalacia	**Intubation trauma**	**Intubation trauma**
Vocal cord palsy	Surgical trauma (e.g. laser)	**Croup**
Laryngeal stenosis	Laryngeal stenosis	**Recurrent respiratory papillomatosis**
Laryngeal cysts	Arytenoid fixation	Hereditary angioedema
Webs	Reflux laryngitis	Epidermolysis bullosa
Laryngeal atresia		**Foreign body**
Vallecular cyst		Dislocated arytenoid
Arytenoid fixation		**Epiglottitis**
Posterior laryngeal cleft		Trauma – fracture
		Caustic and thermal burns
		Haemangioma
		Lymphovascular malformation

BOX 28.3 Examples of tracheal causes of upper airway obstruction (bold = common causes)

Congenital	Acquired – neonates	Acquired – children
Tracheal stenosis	**Post- intubation/ instrumentation/ tracheal stenosis**	**Croup**
Tracheal atresia	Reflux tracheitis	Bacterial tracheitis
Trapped first tracheal ring		**Foreign body**
Complete rings		Localized malacia secondary to a tracheostomy or TOF repair
Micro (stovepipe) trachea		Thyroid masses
Haemangioma		Lymphovascular malformation
Primary tracheomalacia		Mediastinal tumours
Secondary tracheomalacia – vascular compression		

Auscultation is, however, useful to detect abnormal heart sounds and wheeze.

With rapidly advancing technology, it is increasingly commonplace for carers to have mobile devices with audiovisual recording capabilities. Useful information can sometimes be obtained from reviewing a parental recording of a symptomatic episode.

The pre-endoscopy assessment, though important, can be only a guide to the type and degree of pathology discovered at endoscopy. The combination of a thorough history, examination and limited investigation can in some

conditions (e.g. suspected mild laryngomalacia) provide sufficient diagnostic probability to give a working diagnosis and avoid progression to immediate endoscopy by default. The type of stridor may be characteristic of a particular pathology but is never diagnostic.[2] A second pathology alongside laryngomalacia may be present in up to 20% of cases though few will require treatment.[3] The diagnosis can only be confirmed by endoscopic evaluation. This does not mean that every child with stridor requires laryngotracheobronchoscopy. In most children seen in a secondary or tertiary referral centre, endoscopy will be required and in most conditions is the gold standard.

ASSOCIATED FEATURES

Subcostal, intercostal and suprasternal recession may occur separately or together and also be associated with 'see-saw' respiration. The severity of recession is a better indicator of the severity of airway compromise than the degree of stridor. Accessory muscles of respiration are not usually employed by the younger child, who depends predominantly on diaphragmatic movement. Nasal flaring and head bobbing are important and concerning signs, as is abnormal posturing; the child may adopt a position of neck extension and, in some instances, head rotation with airway obstruction as the position of greatest comfort.

The volume of stridor can paradoxically reduce as the obstruction increases due to the diminishing airflow. No comfort should be taken from the fact that a child still looks pink. Cyanosis is a very late event and suggests obstruction has been severe or prolonged.

If a supralaryngeal component is suspected, nasal patency should be assessed with a metal instrument or mirror, a wisp of cotton wool or using the bell end of a stethoscope. Make a conscious assessment of jaw and tongue size. Examine the ears, nose, throat and lastly neck with the usual caution that you must not use any instrumentation to examine the throat of child in whom pathology such as epiglottitis is suspected. Observing the child attempting to feed may be extremely valuable, particularly if there is a feeding or aspiration concern.

Investigations

Investigations need to be carefully selected on the basis of the history and examination. They may be categorized into pre- and postendoscopy investigations.

IMAGING

The value of radiological investigations was reviewed retrospectively by Tostevin et al.[4] Plain anteroposterior (AP) and lateral views of the neck, digitally enhanced to demonstrate the subglottis, oropharynx and nasopharynx, are rapid, inexpensive tests that do not require sedation or anaesthesia. The term 'Cincinatti view' describes a high-kilovolt filter AP film designed to highlight the soft tissues of the neck.

A chest radiograph may include the upper trachea and larynx in the smaller child, otherwise a separate AP neck film may be obtained. This can demonstrate the 'steeple sign' of croup and bulky lesions such as subglottic cysts, papillomata. Significant stenosis may also be delineated. A plain chest radiograph may show the ground-glass appearance of bronchopulmonary dysplasia or mediastinal shift resulting from a foreign body. If a foreign body is suspected in young children, diaphragmatic screening with videofluoroscopy is a more sensitive technique. In older children, inspiratory and expiratory films may demonstrate diaphragmatic immobility on the side of the obstruction. Foreign bodies that do not cause complete lower airway obstruction, those that are radiolucent and those located in the larynx represent particular diagnostic challenges.[5]

Airway fluoroscopy has been found to be highly specific in the diagnosis of both laryngotracheomalacia and fixed airway lesions, but its sensitivity is poor; it has not been proven to be a useful screening tool.[6] Airway fluoroscopy can be combined with a contrast swallow looking for vascular compression and aspiration. Contrast swallows are of limited diagnostic value in the investigation of paediatric stridor and may be best employed following endoscopy, particularly in cases in which a vascular ring or tracheo-oesophageal fistula is suspected.[7]

Bronchography may be performed using non-ionic contrast media. It requires expertise and is associated with risk, particularly in infants and those prone to apnoea. It is particularly useful for the lower airway, demonstrating tracheobronchial stenosis and malacia.[8] Opening pressures of the collapsed bronchi and lower trachea can be measured and used to determine the level of airway support needed.

Echocardiography can be used in cases of suspected vascular compression, demonstrating most but not all abnormal vasculature as well as coincidental or symptomatic congenital heart disease.[9] With experience, ultrasound of the vocal cords can be used to demonstrate vocal cord palsy with reasonable accuracy.[10] Laryngeal ultrasound may also demonstrate structural lesions such as cysts, polyps and papillomata; however, it is non-diagnostic.

Both computerized tomography (CT) and magnetic resonance imaging (MRI) can demonstrate the configuration of thoracic vasculature in cases of extrinsic tracheal compression and thus are particularly useful postendoscopy. CT and MRI may also aid in the evaluation of airway lesions although they are not usually sufficiently sensitive to fully characterize a lesion or stenotic segment. Helical or multidetector CT with multiplanar and 3D reconstruction offers increasingly better definition of fixed tracheal lesions, which are effectively 'virtual bronchoscopy'.[11, 12] Dynamic changes – primary and secondary tracheobronchomalacia – are not well evaluated by cross-sectional imaging. The degree, maturity and mucosal quality of a stenosis can be more accurately assessed at endoscopy.

Imaging may not be appropriate in situations of acute and severe upper airway obstruction. Should imaging be agreed to be of diagnostic and constructive use, it must be performed with close medical supervision so that the airway can be monitored and intervention provided in the event of deterioration.

RESPIRATORY FUNCTION TESTS

Lung function tests such as flow-volume-loops provide a graphical representation of inspiratory and expiratory flow. This can help to localize the site of obstruction; it may differentiate between intra- and extrathoracic obstruction and between fixed and variable pathologies. Other lung function tests such as peak flow testing may be best selected and reviewed with the advice of a pulmonologist. These tests require a degree of patient cooperation and are non-diagnostic. They may, however, assist in the assessment of severity, decision-making regarding management and monitoring of clinical progress.

Polysomnography or 'sleep studies' are also not often used in the assessment of the stridulous child. Airway obstruction that worsens during sleep is usually a feature of pharyngeal obstruction such as adenotonsillar obstruction or a craniofacial anomaly. Laryngomalacia and most laryngotracheal pathologies are rarely worse during sleep.

ASSESSMENT OF REFLUX

It is difficult to gauge whether reflux is secondary to airway obstruction with negative intrathoracic pressure drawing gastric contents into the oesophagus or if the reflux is a separate entity. Occasionally, reflux may be a primary causative factor with secondary reflux laryngitis.

Gastro-oesophageal reflux[13, 14] can be assessed with a radiopaque contrast study, milk scan (nuclear medicine), pH study or endoscopy. Contrast studies have low specificity and sensitivity and are dependent on positioning and radiological interpretation. The other investigations are more sensitive but are usually interpreted by gastroenterologists looking for reflux into the lower oesophagus. The laryngologist is interested in the pH in the upper oesophagus and pharynx, which can be measured using a second probe in the upper oesophagus. Episodes of reflux occur without an associated pH change. These events may be detected by impedance testing (multiple intraluminal impedance); this newer technique is, however, more expensive and less widely available.[15]

Reflux is considered in detail in Vol 3, Chapter 77, Reflux Disease.

Endoscopy

The two principal concerns in paediatric upper airway endoscopy are safety and diagnostic accuracy. To achieve these objectives requires not only a full range of specialized paediatric endoscopy equipment (**Box 28.4**) but, most significantly, a high level of experience in the endoscopist, anaesthetist and nursing staff. A systematic approach will provide a diagnosis in most cases.[16]

AWAKE FLEXIBLE ENDOSCOPY IN THE OFFICE/WARD

The introduction of ultra-thin endoscopes with good optics and a diameter of less than 2 mm has allowed even neonates to be evaluated without the need for a general anaesthetic.[17, 18] Peroral passage of an endoscope may be performed in the edentulous neonate using a finger between the gums to protect the instrument. This alternative approach is preferred by many to transnasal introduction in the young infant.[19]

Flexible laryngoscopy may be considered a diagnostic screening procedure. The view, particularly of the larynx, is often suboptimal. No invasive diagnostic or therapeutic procedure can be undertaken and, even if an abnormality is demonstrated (such as laryngomalacia), a second pathology can be missed. Awake flexible endoscopy is particularly useful to assess dynamic abnormalities such as vocal cord palsy. Flexible endoscopy under sedation in an endoscopy suite is widely practised by paediatricians and pulmonologists and is becoming more popular with otolaryngologists as an adjunct to rigid endoscopy.[20]

Awake flexible endoscopy is most feasible in the infant who may be swaddled (under 9–12 months) and in the older, cooperative child. Office-based flexible endoscopy of the lower airway to the level of the carina has also been described as feasible and safe in a paediatric population although this practice is not widespread.[21]

BOX 28.4 Suggested minimum equipment standards for paediatric airway endoscopy

- Adjustable laryngeal suspension system
- Operating microscope with 400f lens
- Selection of age-appropriate paediatric laryngoscopes of varying size and with a variety of viewing angles
- Dedicated laryngeal microsurgical instruments, e.g. microscissors, probes, cupped and straight forceps
- Selection of age-appropriate ventilating bronchoscopes with Hopkins rod telescopes to fit
- Suitable light source with fibre-optic cable
- Camera and monitor with image-capture facilities – video and still
- Colour printer
- Selection of forceps for the removal of foreign bodies
- Optical forceps with rigid telescope(s) of corresponding length
- Selection of fibre-optic bronchoscopes and a nasopharyngoscope
- Full range of paediatric tracheostomy tubes

LARYNGOTRACHEOBRONCHOSCOPY

Laryngotracheobronchoscopy (**Figure 28.5**) is the gold standard in the assessment of the stridulous child. It is a highly technical procedure. The whole team (surgeon, anaesthetist and nursing assistant) need to work closely together to perform the examination safely, and to optimize the assessment. The advent of video and high-quality image reproduction on a viewing monitor has been invaluable in training and teamworking. The anaesthetist and theatre team may also view the live image and may be able to anticipate interventions required.

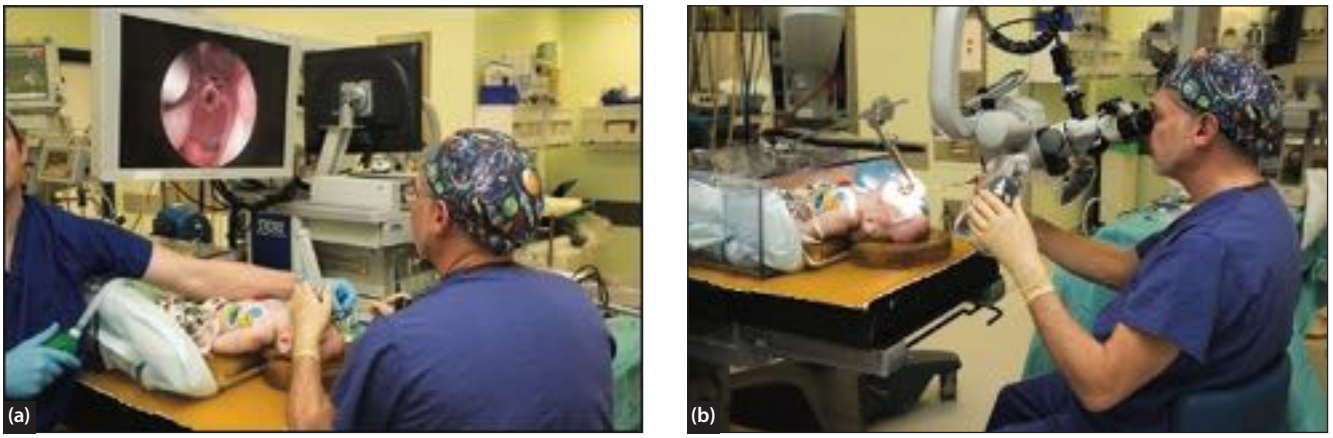


Figure 28.5 Laryngotracheobronchoscopy. (a) Handheld laryngoscope and Hopkins rod technique. **(b)** Supension laryngoscopy and microscope technique.

ANAESTHESIA FOR UPPER AIRWAY ENDOSCOPY

Major units around the world use a variety of techniques; it is probably more important that a theatre team work together effectively than that one particular technique is followed. High levels of cooperation and skill are required. Practice varies between centres as to whether intubation is used at the start of the procedure, however most units would now use spontaneous respiration rather than paralysis. Spontaneous respiration has much to recommend it as a technique: it maintains muscle tone, promotes gas exchange and is essential to detect dynamic conditions.

Induction

Some units will use a premedication such as atropine or glycopyrrhonium bromide to facilitate a dry surgical field and improve the efficacy of topical anaesthesia. Pre-operative steroids are a good safeguard if significant stenosis or likelihood of increased inflammation is suspected. Intravenous induction is preferable for older children; gas induction is best in infants, younger children, those with poor venous access and those with a precarious airway. Topical local anaesthetic spray (typically lignocaine) should be applied to the vocal cords when the anaesthetic level is sufficiently deep for this to be tolerated. This amount needs to be carefully measured as the preparations used in adults can easily result in overdosage.[22, 23]

Maintenance of anaesthesia

Two principal anaesthetic techniques are used for general anaesthesia with spontaneous respiration: maintenance with a volatile agent (e.g. sevofluorane) and total intravenous anaesthesia (TIVA) with an infusion such as propofol and remifentanil.[24]

A volatile agent and oxygen mix can maintain a level of anaesthesia that allows a thorough examination in a child who is breathing spontaneously. Sevoflurane is non-irritant to the airway and has the advantages of rapid onset and no pungency, allowing immediate delivery of high concentrations. This advantage of rapid induction may be offset by rapid termination of effect during periods of relative hypoventilation or airway obstruction. Now superseded by sevofluorane, halothane gas was also useful for this purpose. The anaesthetist needs to be able to control anaesthesia in response to surgical conditions and for this a video monitor visible to the anaesthetist is invaluable.

Airway tube technique

An endotracheal tube may be used as a nasopharyngeal airway or 'prong' to provide oxygen and volatile anaesthetic agent, if used. Should transnasal passage not be possible, an oropharyngeal tube may be used, placed at the angle of the mouth. A significant advantage of a non-intubation technique is that the endoscopist has a view of an airway that has not been altered by the passage of an endotracheal tube. Confusion relating to lesions caused by intubation for the procedure cannot occur and at any time airway control can be regained with intubation or the use of a bronchoscope.

An alternative technique is to intubate the child prior to withdrawal of the tube for endoscopy. This technique is not routinely used in our institutions. Intubation does facilitate rapid progress to the required level of anaesthesia. Nasotracheal intubation allows the endotracheal tube to be withdrawn into the nasopharynx once the child is breathing spontaneously. Careful positioning of the tube over the glottis by the endoscopist can also achieve good oxygen and volatile agent provision, when required.

Jet ventilation

This technique allows the child to be paralysed, preventing coughing and gagging. Gas exchange is maintained by short pulses of oxygen and anaesthetic gas. Subglottic jet ventilation may be provided in adults using a transglottic cannula but this is not only impractical but also risks barotrauma (pneumothorax and air trapping) in children. Supraglottic jet ventilation has been described although few centres use this technique.[25] Dynamic conditions such as malacia and cord palsy cannot be well identified.

Laryngeal mask airway

A laryngeal mask airway (LMA) is useful for fibre-optic tracheobronchoscopy, particularly if the patient is difficult to intubate because of mandibular hypoplasia.[26]

LARYNGOTRACHEOSCOPY TECHNIQUE

The following description assumes that the patient may have been intubated, suspension laryngoscopy is employed and that the larynx and/or trachea is to be examined with a rigid telescope or microscope.

A small sandbag or pad is usually required under the shoulders with sandbags laterally to support the head if required. A Mayo table supports the laryngostat (laryngeal support) clear of the chest.

It is important to prepare and check all equipment prior to the endoscopy so that the endoscopist is fully prepared for all eventualities. The range of Hopkins rod rigid endoscopes should include all lengths and diameters that could be needed. A 30° telescope may be able to better assess the supraglottic larynx without splinting. A microscope should be available, though is often not used unless surgical intervention is required when two hands are needed for manipulation. If a microscope is used, a 400 mm lens allows the use of standard laryngeal instruments but a 350 mm lens brings the patient closer, allowing easier laryngeal manipulation, which is particularly important in small neonates. For routine examination, the Hopkins rod and camera can be held in the left hand with a probe used in the right. The image quality available using a rigid endoscope is far superior to that of the microscope. Every unit should have a chart listing the appropriate sizes of bronchoscope for different ages. The age-appropriate bronchoscope should be checked and one at least a size smaller instantly available as well.

Laryngeal examination is usually begun by gently inserting the lubricated suspension laryngoscope, taking care to protect the teeth and lips and to keep the tongue central to provide a well-centred view. As in adults, it is important to check the overall appearance of the pharynx and supraglottis during introduction of the laryngoscope. The endotracheal tube, if present, is followed to the tip of the epiglottis. The epiglottis should be gently lifted forward making certain that it does not curl up in front of the laryngoscope preventing a complete view of the anterior commissure. An overall assessment of the larynx can be made with a tube *in situ*, providing a degree of stability that is particularly welcome in the child with a compromised airway.

Laryngeal examination with the endotracheal tube removed provides a superior view and, by using a probe to move the arytenoids independently, the mobility of the cricoarytenoid joints can be assessed. If an interarytenoid scar is present, the arytenoids will not move independently. A posterior laryngeal cleft is excluded by passing the probe between the arytenoids, comparing the lower limit of the interarytenoid groove with that of the posterior commissure. Finally, great care should be taken to pass through the vocal cords if a rigid endoscope is used to inspect the subglottis.

The time available for the examination will depend on the airway and respiratory reserve. In a child breathing spontaneously with a normal airway and normal lung function, anaesthesia can be maintained solely by the use of inhalational or intravenous agents and a nasopharyngeal airway. In some cases the time may be very limited and it is essential to be prepared to move ahead with bronchoscopy at any stage. If there is significant subglottic stenosis, an ultra-fine telescope passed through the laryngoscope will cause less trauma than a bronchoscope.

BRONCHOSCOPY TECHNIQUE

Traditionally, a ventilating bronchoscope (**Figure 28.6**) has been used which provides a means of actively ventilating the patient if required. With spontaneous ventilation, a smaller diameter rigid Hopkins rod telescope can be used with less trauma and reduced splinting of the airway.

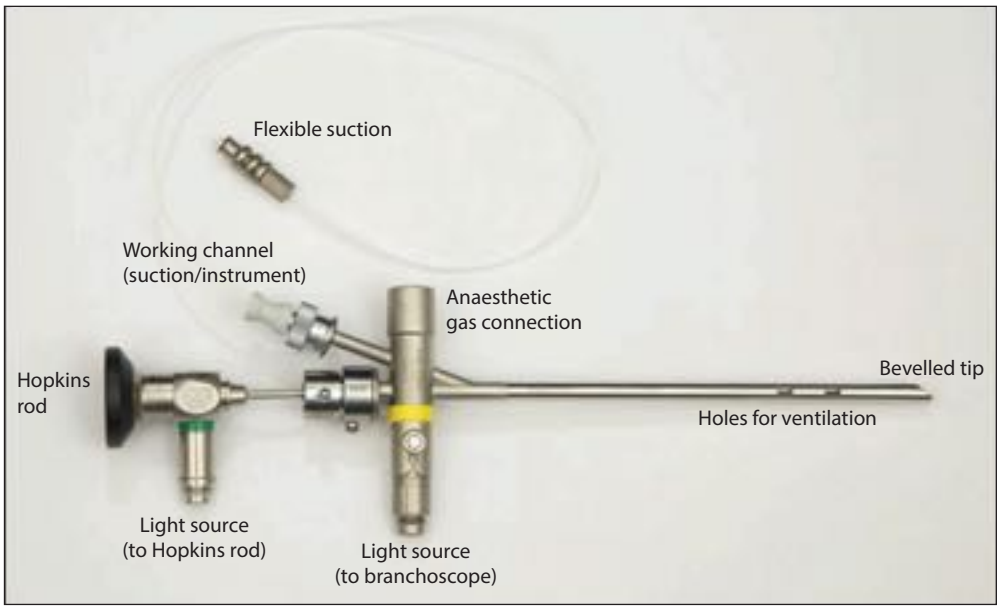


Figure 28.6 Ventilating bronchoscope and Hopkins rod.

An anaesthetic laryngoscope can be used in the vallecula to lift the larynx forward while passing either the tip of the Hopkins rod or the bevel of the bronchoscope through the vocal cords. If a bronchoscope is used, this can be performed under video control with a Hopkins rod coupled into the bronchoscope. Tracheomalacia should be observed with a small bronchoscope withdrawn from the area in question and without positive airways pressure to avoid splinting.

The subglottis, trachea, the carina and main bronchi are all systematically examined and videographs or digital images recorded. Photodocumentation of the endoscopic findings and printing of a compilation of images not only benefits the patient record but also is a useful visual tool for explaining findings to the family. A minimum of a 'four-shot view' of the supraglottis, glottis, subglottis and trachea, and lastly of the carina and main bronchi is suggested. Video recording of dynamic pathologies such as abnormal vocal cord movement, laryngomalacia and tracheobronchomalacia is also recommended.

It is vital that accurate records are kept. Use of a standardized data capture form facilitates this.[27] This provides an invaluable source of information for sequential clinical comparisons, medicolegal purposes and teaching. Use of a recognized staging system is important for research purposes, collaboration and publication of results.

DYNAMIC ASSESSMENT OF THE LARYNX ON RECOVERY FROM ANAESTHESIA

Typically, this can be achieved by withdrawal of the bronchoscope to just posterior to the tip of the epiglottis. This gives a good view of the vocal cords to exclude a cord palsy and of the arytenoids to exclude the common posterior form of laryngomalacia, though anterior collapse of the epiglottis may be masked. In this case, a 30° telescope can be used. The anaesthetist should describe the phase of respiration to enable the endoscopist to check for paradoxical vocal cord movements.

Techniques for dynamic assessment of the vocal cord movement are to insert a laryngeal mask with a fibreoptic bronchoscope passed through this to just above the laryngeal inlet or passage of the scope through a specially adapted face mask.[28] If a bilateral vocal cord palsy is suspected and structural abnormalities have been excluded with a full microlaryngoscopy and rigid bronchoscopy, it is sometimes necessary to reschedule the patient for a further examination in which a laryngeal mask and fibreoptic scope are used from the outset, reducing the influence of prolonged anaesthesia on the cord function.

MANAGEMENT OF ACUTE AIRWAY OBSTRUCTION

In the acute situation, assessment, history taking and resuscitation will often proceed in parallel. In the example of a child arriving in the emergency room with suspected croup, the physician will be assessing the child for the degree of airway obstruction by gauging the recession and dyspnoea at the same time as asking the parent/carer for the length of history and whether there is any possibility of foreign body inhalation. A nurse may be checking the oxygen saturation and setting up humidified oxygen. Another member of the team may have to call and alert the operating room that the child may need intubation as well as calling the anaesthetist and otolaryngologist. This situation clearly benefits from careful planning, with most units having a protocol for how to deal with the stridulous and airway-compromised child. The protocols vary considerably, with some units insisting on the presence of an otolaryngologist at intubation in case a tracheostomy is needed while others have managed for many years without.[29, 30]

In a child with a compromised but functional airway it is crucial that upsetting the child does not cause deterioration. Coughing, crying and distress may result and change obstruction from partial to complete. Significant consideration and skill are required in the management of such a patient. The child should be kept in a position of comfort with its carers in a calm environment and the applications of adjuncts such as pulse oximetry, oxygen and nebulized adrenaline carefully tailored. Interventions such as venepuncture, taking of radiographs and flexible nasendoscopy may jeopardize the critical airway.

Medical management

OXYGEN THERAPY

With an obstruction to airflow and normal alveolar function, raising the concentration of inspired oxygen will reduce the ventilatory requirement to maintain adequate oxygen saturation levels but will not aid carbon dioxide clearance. So long as the possibility of hypercarbia is appreciated, oxygen is a useful drug in the treatment of airway obstruction.

As previously emphasized, a face mask applied to the conscious child is likely to be upsetting and should be avoided. Use of nasal cannulae, wafting or 'head box' oxygen may be better options. Persistent hypoxia and cyanosis are very late signs in a child and are likely to precede rapid respiratory collapse.

HUMIDIFICATION

There is no objective evidence that raising the humidity of the inspired air is beneficial in upper airway obstruction and in croup.[31,32] Humidification has however been used for decades but few units still use humidity tents or 'croupettes' as these have the disadvantage of decreased visibility and may also frighten the child.

HELIUM-OXYGEN MIXTURES (HELIOX®)

Addition of helium to inspired gases is associated with a reduction in the turbulence of flow. Helium–oxygen mixtures are thus recognized to decrease airway resistance and have been used for several decades in the management of patients with upper airway obstruction.[33] Use of 70% helium/30% oxygen inhalation has been systematically

reviewed for use in treatment of croup in children; there is some evidence to suggest a short-term benefit in moderate to severe croup.[34]

PHARMACOTHERAPY

Intravenous and oral steroids such as dexamethasone have been shown to be beneficial in croup, with inhaled steroids having a similar effect.[35] Klassen summarizes: 'All children with croup symptoms who demonstrate increased work of breathing in the clinics or emergency departments should be treated with glucocorticoids.'[36] This treatment may be with nebulized budesonide (2 mg) or oral or intramuscular dexamethasone (the optimal dose needs to be defined; 0.15–0.6 mg/kg has been described). Oral glucocorticoids such as dexamethasone and prednisolone may be the best options due to ease of administration, widespread availability, and lower cost. Inhaled or nebulized budesonide can be used at home for children with recurrent croup.[35]

Nebulized adrenaline (400 µg/kg or 0.4 mL/kg of 1:1000 to a maximum of 5 mL) may result in a transient improvement within 10-30 minutes, lasting up to 2 hours. This should be considered in pathologies that have an inflammatory component, such as croup, with moderate or severe distress.[37] Again, a nebulizer should be applied only if it does not increase the distress of the patient.

Transfer of the child with stridor

Transfer of a seriously ill child with stridor to a centre of anaesthetic and surgical expertise may be necessary. The Advanced Paediatric Life Support (APLS) framework teaches that the right child should be taken at the right time, by the right people, to the right place, by the right form of transport, and receive the right care throughout.[38] This is often best achieved by a specialized children's retrieval team with advanced life-support capabilities.

It may be necessary and appropriate for the airway to be secured by intubation prior to transfer. Short-term placement of an LMA may be an alternative in cases where intubation is not possible.

The systematic approach requires preparation and planning for transfer. Frequent reassessment of the child by appropriately skilled staff is vital. Continuous monitoring should also be used where possible: oxygen saturations, pulse, arterial pH and gases, temperature, blood pressure, carbon dioxide monitoring (if intubated).

Surgical management

The increasing use of intubation as an alternative to tracheostomy in acute airway obstruction has been brought about by advances in anaesthesia and paediatric intensive management coupled with the appreciation that paediatric tracheostomy, even in the short term, can be associated with significant morbidity and potential mortality. Intubation may not be possible in all cases, despite anaesthetic skill, careful planning and monitoring. Severe subglottic stenosis, impacted foreign bodies and advanced epiglottitis are key examples; rarer conditions such as laryngeal atresia with ventilation being achieved via a tracheo-oesophageal fistula also necessitate a tracheostomy.

It is this uncertainty combined with the precipitate nature of paediatric airway obstruction that makes it mandatory in most hospitals for an ENT surgeon to be informed if a child with airway obstruction of unknown aetiology is to be intubated. Depending on the circumstances, it may be necessary to have an emergency tracheostomy set open with a tube of the correct size already selected.

Once the child has been slowly induced with a volatile anaesthetic agent it is possible to inspect the larynx and exclude epiglottitis. This may be all that is required; it may be possible to manage the child using a nasopharyngeal airway (prong) and/or continuous positive airway pressure (CPAP). If intubation is required, it is important to minimize any damage to mucosa that may already be inflamed; very gentle intubation with a small tube just large enough for adequate ventilation and suction of secretions is recommended. Even if an initial intubation is oral, which tends to be easier, the tube should be replaced with a nasal tube; this may be more secure and better tolerated. The sizing of the tube can be assessed by checking for a leak and the tracheobronchial secretions suctioned. If the secretions are very tenacious or there is still an element of airway obstruction, a ventilating bronchoscope should be passed to exclude bacterial tracheitis or a foreign body.[39,40] Significant tracheobronchomalacia is another reason for continuing airway difficulty after intubation and this will usually respond to CPAP.

EMERGENCY TRACHEOSTOMY

With experienced paediatric anaesthetists, this is now very unusual. Otolaryngologists are often asked to attend a potentially difficult intubation, but are rarely needed. A ventilating bronchoscope may be easier to pass than an endotracheal tube. An endotracheal tube mounted on a Hopkins rod telescope may also be particularly useful in a difficult intubation (**Figure 28.7**). If there is any potential for an emergency tracheostomy, the surgical set and appropriate tube need to be instantly available. It is important to stay strictly in the midline so the child needs to be carefully positioned without neck or head deviation. A finger either side of the larynx is helpful with a vertical incision through the skin and down to the trachea. If a paediatric tracheostomy tube is not available, a paediatric endotracheal tube can be used, ensuring it remains above the carina. Paediatric tracheostomy is described in detail in Chapter 35, Tracheostomy and home care.

'CHAOS' AND 'EXIT'

Advances in the availability and quality of antenatal imaging has led to significant advances in the recognition and treatment planning of children with congenital high airway obstruction syndrome (CHAOS). A significant risk of airway compromise at the time of delivery with associated morbidity and mortality at birth may be avoided by an



Figure 28.7 A Hopkins rod telescope with an endotracheal tube mounted and ready to introduce in a difficult intubation.

ex utero intrapartum treatment (EXIT).[41, 42] This highly specialized technique requires expert multidisciplinary input and is a broad topic with links and overlap with foetal surgery.

In brief, the underlying principle of the technique is to 'operate on placental support'; materno-placental and placento-foetal blood and gas exchange are maintained while the neonate's airway is secured. This is achieved by delivery of the foetal head and upper torso through a hysterotomy incision. Intubation, bronchoscopy, tracheostomy and excision of the obstructing lesion may be performed as permitted and indicated. Naturally, the EXIT technique requires an antenatal diagnosis of the pathology causing CHAOS and multidisciplinary care at a centre of expertise to coordinate this elective surgery.

Parental counselling and consideration of ethical aspects, particularly in the foetus with multiple congenital abnormalities, are of fundamental importance.

BEST CLINICAL PRACTICE

- ✓ In the acute situation, assessment, history taking and active resuscitation may proceed simultaneously.
- ✓ In suspected epiglottitis, instrumentation of the oral cavity and pharynx for clinical examination must be avoided.
- ✓ All children with croup who demonstrate increased work of breathing should be treated with glucocorticoids. Nebulized adrenaline may also be given. **[Grade A]**
- ✓ Wherever possible, endotracheal intubation is preferable to emergency tracheostomy.
- ✓ If a child with airway obstruction of unknown aetiology is to be intubated, an ENT surgeon should be informed. It may be necessary to have an emergency tracheostomy set open with a tube of the correct size already selected although this is very rarely needed.
- ✓ A difficult endotracheal intubation may be facilitated by the use of a small ventilating bronchoscope or by passing a Hopkins rod telescope on which a endotracheal tube has been mounted.

FUTURE RESEARCH

- ➤ The optimal glucocorticoid dose and agent for use in inflammatory upper airway obstruction conditions such as croup is yet to be determined.
- ➤ A growing trend towards specialization within otolaryngology will ensure that airway endoscopy in children is increasingly the remit of otolaryngologists with a special interest and training in this work.

KEY POINTS

- Stridor is the noise from a narrowed airway and is a symptom, not a diagnosis.
- The aim of the history, examination and special investigations is to determine not only the site and cause of the obstruction (the diagnosis) but also its effect on the airway (the severity).
- Hypoxaemia is a late feature of airway obstruction, particularly in children treated with oxygen.
- Improvement in stridor may paradoxically be due to worsening obstruction.
- Laryngomalacia is common but it is important not to assign failure to thrive to this without first having considered and excluded other causes.
- Rapid progression of airway obstruction typically occurs in acute infection and in foreign body inhalation.
- Laryngotracheobronchoscopy is the gold standard in the assessment of the stridulous child and is a highly skilled procedure involving a team approach between anaesthetist, endoscopist and operating room personnel. Adequate facilities are not available in all institutions.

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CHAPTER 29

ACUTE LARYNGEAL INFECTIONS

Lesley Cochrane

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SEARCH STRATEGY AND EVIDENCE BASE

Data in this chapter may be updated by a search of Medline using the following keywords: croup, acute laryngotracheitis, acute laryngotracheobronchitis, acute epiglottitis, diphtheria, bacterial tracheitis and child. The Controlled Trials Register of the Cochrane Library and the Cochrane Database of Systematic Reviews were also searched. The search was initially restricted to randomized controlled trials and meta-analyses and then widened, focusing on diagnosis, management and immunization.

INTRODUCTION

Laryngeal infection in childhood causes airway obstruction, of which the cardinal symptom is stridor. In the developed world, 'croup' – a clinical scenario characterized by a combination of stridor hoarseness and a typical barking cough – is the commonest (90%) cause of acute airway obstruction in children. Epiglottitis has been the next most common infective cause but is now seen much less frequently due to the widespread introduction of *Haemophilus influenzae* b (Hib) vaccine; bacterial laryngotracheobronchitis and diphtheria are less common. The differential diagnosis of acute acquired stridor includes 'spasmodic croup', retropharyngeal abscess, angioneurotic oedema, neoplasia, acute laryngeal trauma and foreign body aspiration.

In this chapter the various clinical syndromes of acute laryngeal infection are discussed and their distinctive features emphasized. For a number of these conditions several terms have evolved over the years; these are included in the headings for ease of reference but the first term, that most commonly used in the UK, is used in the text. The effects of immunization programmes on the changing patterns of disease are examined. The efficacy of medical treatment and the role of endotracheal intubation and/or tracheostomy for safe airway management in the different conditions are considered.

Good management depends on teamwork involving the primary care physician, the paediatrician, the paediatric otolaryngologist, the paediatric anaesthetist and the paediatric intensive care physician. Multidisciplinary evidence-based protocols should be established and followed to optimize outcomes.

CROUP (ACUTE LARYNGOTRACHEOBRONCHITIS, VIRAL LARYNGOTRACHEOBRONCHITIS)

Croup typically presents as a clinical syndrome of hoarseness and a distinctive barking cough progressing to inspiratory or biphasic stridor. There is usually a preceding history of upper respiratory tract symptoms, malaise and pyrexia. Children with croup do not typically drool or appear toxic, in contrast to children presenting with epiglottitis. The symptoms are thought to be due to mucosal oedema of the larynx and trachea following a viral illness. Croup is classically caused, but not limited to, infection with **parainfluenza virus type I**. Other causative

viruses include: **parainfluenza virus type II, respiratory syncytial virus (RSV) virus types A and B** and **rhinovirus.**[1] Due to improving methods of detection, an increasing variety of viruses are being implicated in the cause of croup including *Metapneumovirus, Coronavirus* and most recently *Bocavirus* in Korea with less predominance of parainfluenza type I.[2, 3] Croup usually affects children between 6 months and 3 years of age with a peak incidence in 2-year-olds.[1] Boys are more commonly affected than girls.[1, 4] There is a seasonal variation: in the USA and in Canada a minor peak in hospital admissions for croup has been noted in February and a peak in the autumn in odd numbered years, coinciding with biennial epidemics of human parainfluenza type I infection.[4, 5] In Australia, seasonal variation has also been observed.[6] Although croup is a self-limiting illness, it is a large burden on healthcare systems due to frequent visits to doctors and accident and emergency rooms. The annual incidence of croup in children younger than 6 years ranges from 1.5% to 6%.[1]

The diagnosis of croup is a clinical one and laboratory tests and radiological tests are generally not needed. In severe cases, however, if there is a diagnostic dilemma, a radiograph of the thoracic inlet will show characteristic narrowing of the subglottis on an anteroposterior view ('steeple' or 'pencil-tip' sign) (**Figure 29.1**).

There are inflammatory changes throughout the airway in croup but the critical symptom of stridor is due to oedema in the subglottis, the narrowest part of the paediatric airway. Just 1 mm of oedema in an 18-month-old child with a subglottic diameter of 6.5 mm will reduce the cross-sectional area by approximately 50%. Laminar airflow (proportional to the fourth power of the radius – 'Poiseuille's law') is thus greatly reduced. Some children are more at risk of severe symptoms than others; factors predisposing to severe symptoms include pre-existing subglottic or tracheal narrowing, chronic lung disease and airway reactivity, characterized by a history of inhalant or food allergies.[7]

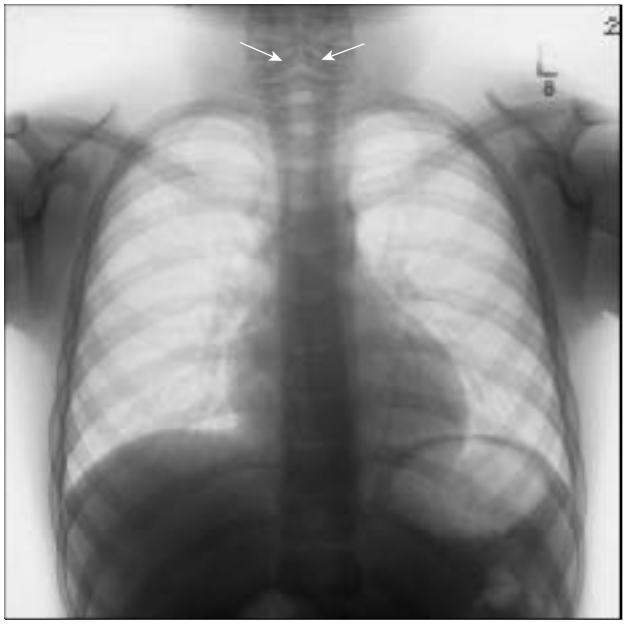


Figure 29.1 'Steeple' or 'pencil-tip' sign. Narrowing of the subglottic airway owing to mucosal oedema in croup (arrows). Image courtesy of Ben Hartley.

Croup is usually self-limiting; 50% of children improve within 24 hours of the onset of symptoms, and most recover within 4 days without treatment. Airway symptoms can become serious and life-threatening in rare cases. Mortality, however, is rare, with an estimated overall mortality of 1 in 30 000 cases in a large review.[8]

It is important to consider congenital or acquired mild subglottic stenosis in the differential diagnosis of infants presenting with 'recurrent croup'. In persistent cases endoscopy is mandatory.[9]

The management of croup consists of minimal disturbance while assessing the severity of the croup and guiding treatment accordingly. Croup severity can be classified using the Westley Croup Score (**Table 29.1**). The scoring system is based on five clinical features of croup (inspiratory stridor, retraction, air entry, cyanosis and level of consciousness). It has been clinically and radiologically validated, the total score correlating with the diameter of the tracheal lumen. A maximum score is 17, a score of 2–3 equates to mild croup, 4–7 to moderate croup and 8 or more to severe croup.[10] The scoring system is widely used in studies, although some authors report that it is less commonly used in daily clinical practice due to interobserver variance.

For mild croup, treatment can be supportive, with reassurance of both carers and child, and observation and monitoring of the child's symptoms, but without separating the child from its carer(s) as this will increase anxiety. Sedation is not advised because of the risk of respiratory depression, although chloral hydrate 30 mg/kg has been advocated if sedation seems necessary. Traditionally, it has been recommended that children with croup should be nursed in a humidified environment or mist tent; there is no evidence that this is of clinical benefit although it may be soothing.[11]

Corticosteroids

The mainstay of treatment for croup is corticosteroids. Corticosteroids have a systemic anti-inflammatory effect. There is a reduction in capillary endothelial permeability and therefore in mucosal oedema, and stabilization of lysosomal membranes, decreasing the inflammatory reaction. Topical corticosteroids theoretically have the added benefit of causing local alpha-mediated vasoconstriction. A number of studies have looked at clinical improvement after corticosteroid therapy. Clinical benefit can be measured by an improvement in croup score, reduced hospital admission rates, shorter length of stay, lower intubation rates or a reduced need for cointerventions such as the administration of epinephrine nebulizers.

In 2011, a Cochrane systematic review of the use of glucocorticoids in the treatment of croup analysed the results of 41 studies. The review concluded that, when compared to placebo, treatment with glucocorticoids resulted in a significant clinical improvement within

TABLE 29.1 Croup score based on Westley system (reprinted from Westley et al.,[10] with permission)

Score	0	1	2	3	4	5
Inspiratory stridor	None	Audible with a stethoscope	Audible without a stethoscope			
Retraction	None	Mild	Moderate	Severe		
Air entry	Normal	Decreased	Severely decreased			
Cyanosis	None				With agitation	At rest
Consciousness level	Normal					Altered

6 hours of treatment. The benefit of glucocorticoids is maintained at 12 hours post-treatment but no longer significant after 24 hours.[12] Children treated with glucocorticoids spent less time in the emergency department and were more quickly returned to care, concluding that glucocorticoid use should be not be confined to moderate or severe cases but should be extended to children with mild croup.[11, 12] The small numbers of patients in each study they analysed and the confounding variables made it difficult to make definitive recommendations regarding the superiority of any glucocorticoid, dose, or route of administration.[12] In the absence of further evidence, an oral dose of dexamethasone (0.6 mg/kg) is preferred because of its safety and efficacy. In a child who is vomiting, nebulized budesonide (2 mg) may be considered. Although also efficacious,[8] intramuscular dexamethasone (0.6 mg/kg) cannot be advocated as a first-line treatment given the potential for muscle necrosis with that route of administration. The use of glucocorticoids in primary care in the early management of croup symptoms has transformed the management of this disorder; affected children now rarely require active intervention to support the airway.

Nebulized epinephrine

Nebulized epinephrine (1 mL of 1 in 1000 epinephrine diluted in 3 mL of 0.9% saline) has an established role in the acute paediatric airway in reducing mucosal oedema by an alpha-agonist effect causing vasoconstriction and bronchodilation; a maximum effect is achieved within 30–60 minutes but there is no lasting benefit beyond 2 hours.

The administration of epinephrine does not alter the natural history of the disease but it may postpone or eliminate the need for an artificial airway, or give symptomatic relief until effective treatment can be given.[13] It can be administered at the same time as glucocorticoids.[10, 13] In a recent systematic review evidence did not favour racemic epinephrine versus L-epinephrine or epinephrine delivered by intermittent positive pressure breathing (IPPB) over simple nebulization.[13]

Heliox®

Heliox® is a mixture of helium and oxygen generally supplied with a helium:oxygen ratio of 70:30 or 79:21. Helium is less dense than air or oxygen and is more viscous. Owing to these properties, heliox® is more likely to produce laminar and more efficient flow in the presence of a partially obstructed airway than air or oxygen. Inhaled heliox® delivered through a high-flow system should reduce the work of breathing and result in larger tidal volumes and improved gas exchange. Helium has a high thermal conductivity and so care is needed with humidification in order to avoid hypothermia.[14]

Heliox® has long been used in the management of respiratory conditions and in airway obstruction including croup. There have, however, been few trials examining the benefit of heliox® in the management of children with croup. A recent Cochrane systematic review of the use of heliox® in croup concluded that there was some evidence to suggest a short-term benefit of heliox® in children with moderate to severe croup who have been administered dexamethasone.[15] However, adequately powered randomized controls trials comparing heliox® with standard treatments are required to further assess the role of heliox® in children with moderate to severe croup.

BACTERIAL LARYNGOTRACHEOBRONCHITIS (PSEUDOMEMBRANOUS CROUP, BACTERIAL TRACHEITIS, MEMBRANOUS LARYNGOTRACHEOBRONCHITIS, NEONATAL NECROTIZING TRACHEOBRONCHITIS)

Bacterial tracheitis is a rare but potentially life-threatening cause of upper airway obstruction in children. It is a severe form of laryngotracheobronchitis characterized by the presence of profuse mucopurulent secretions with sloughing of the respiratory epithelium. Secretions are often adherent, are not effectively cleared by coughing and may occlude the airway causing respiratory compromise.[16] Bacterial tracheitis must be differentiated from croup and other causes of infectious upper airway obstruction in order to initiate proper management.

Classically the child with bacterial tracheitis appears toxic with high fevers and worsening stridor that fails to respond to treatment with steroids and nebulized epinephrine. It typically affects children older (mean age 4–8 years) than the usual age group for croup.[17] Like croup, however, it is more common in boys than girls, and there is no single

factor, clinical, radiological or laboratory-based, which reliably distinguishes it from croup.[18] A high level of suspicion is therefore required for early diagnosis. Bacterial tracheitis is a much less common condition than croup.[17] However, there is increased susceptibility in children with Down syndrome or immunodeficiency.[18, 19]

Diagnosis can only be confirmed on airway endoscopy; there is a pseudomembrane in the subglottis and trachea and thick mucopus and debris extending into the bronchi (**Figure 29.2**). Direct laryngotracheobronchoscopy under general anaesthesia and removal of all tracheal secretions, with pulmonary toilet, is mandatory. It is then often necessary to secure the airway by endotracheal intubation for a period of days.[16, 17] The distal airway and the tube itself remain at continued risk of obstruction by secretions, and vigilant expert nursing care is essential. Repeated endoscopic procedures are almost invariably required.

Once the diagnosis is established, broad-spectrum parenteral antibiotics should be commenced immediately. They can later be adjusted in line with the results of microbiological studies. *Staphylococcus aureus* is the pathogen most commonly isolated from tracheal cultures although *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* have also been reported.[16–18] Viral cultures are also frequently positive, indicative that many cases of bacterial tracheitis represent a secondary bacterial infection that follows a viral respiratory tract infection. Most commonly influenza A is identified, although other viruses including the H1N1 strain of influenza A and metapneumovirus have also been isolated.[2, 16, 17, 20]

Complications of this dangerous condition include airway stenosis, acute respiratory distress syndrome, respiratory failure, toxic shock syndrome, anoxic encephalopathy and death.[17]

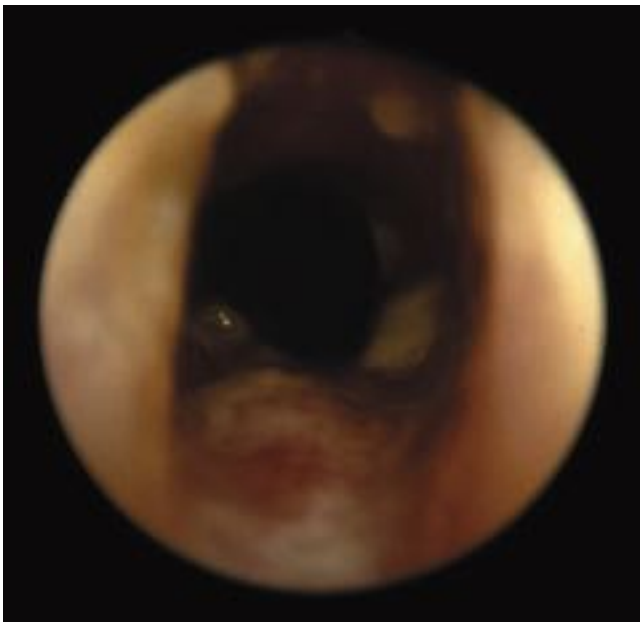


Figure 29.2 Tracheal pseudomembrane in bacterial laryngotracheobronchitis. Image courtesy of Ben Hartley.

Ventilated newborns with an unstable haemodynamic state are at risk of potentially fatal desloughing of the tracheobronchial mucosa. This may be characterized by repeated episodes of acute airway obstruction. Management involves repeated therapeutic tracheobronchoscopy to free the airways.[21]

Recent literature has raised awareness of a less severe clinical presentation which tends to elude diagnosis. There are several reported series of children presenting with a less severe form of bacterial tracheitis who have been effectively managed with antibiotics and endoscopic debridement without the need for endotracheal intubation. The term 'exudative tracheitis' has been proposed as an alternative nomenclature for those with a less severe form and are less systemically ill.[16]

DIPHTHERIA

Diphtheria is rare in countries which have a routine childhood immunization programme, but it continues to present a significant public health problem in the developing world. Diphtheria remains an important differential in the diagnosis of acute laryngeal infection in children, particularly in those who have travelled to endemic areas or have not been vaccinated. Every year there are several reported cases of diphtheria in the UK, primarily in patients who have recently travelled from endemic countries. In 2012, there was a case of fatal diphtheria in a non-immunized child in the UK.[22]

The causative organisms in pathogenic diphtheria are the toxogenic strains of *Corynebacterium diphtheria* and *Corynebacterium ulcerans*. The early clinical picture of upper respiratory tract symptoms is due to the effects of the organism itself. Delayed effects are due to the release of exotoxin.

Symptoms of diphtheria come on gradually and typically begin 2–5 days after exposure. Initial symptoms are of pharyngitis with sore throat and malaise. The child is feverish and on examination there is a typical appearance of the pharyngeal tonsils with necrosis and the development of a characteristic grey pseudomembrane over the surface. This consists of necrotic tissue, bacteria and a rich fibrinous exudate. Early removal causes bleeding but the pseudomembrane may separate more easily later in the course of the disease. There may be a bull-neck appearance due to cellulitis and regional lymphadenopathy.

Diphtheria infection may also involve the larynx. After initial symptoms of dysphagia and toxaemia, symptoms may progress to inspiratory stridor and a barking cough; the cough is frequently paroxysmal and exhausting. Death may follow owing to acute airway obstruction or as a result of the later effects of the exotoxin.[22]

The exotoxin can cause a toxic myocarditis in the second week of the disease and this may be fatal. Peripheral neuritis may also occur, palatal paralysis being the most common effect of peripheral neuropathy and presenting with nasal regurgitation of food and hypernasal speech.

Successful treatment depends on early diagnosis, and the timely administration of high-dose benzylpenicillin and antitoxin (10 000–100 000 units, depending on the severity of infection). Delaying the administration of the antitoxin is associated with increased mortality as the antitoxin does not neutralize toxin that is already bound to tissues. The decision, therefore, to administer antitoxin should be made based on clinical suspicion and should not await microbiological confirmation. Airway management consists of removal of the laryngeal membrane, administration of oxygen and humidification, and endotracheal intubation or tracheostomy if necessary. Systemic steroids may reduce the need for airway intervention.[23] Bed rest is recommended until the danger of myocarditis is past.

ACUTE EPIGLOTTITIS (SUPRAGLOTTITIS)

The classical presentation of acute epiglottitis is well described. It is of a toxic child with a short history of sore throat, inspiratory stridor, muffled voice and drooling due to odynophagia and dysphagia. Left untreated there is progressive respiratory distress. The child is febrile, tachypnoeic and classically will be sitting upright, with the neck extended to optimize the airway, and using the arms to provide support to the shoulder girdle to maximize the efficiency of the accessory muscles of respiration. It is commonest between the ages of 2 and 8 and there is an increased prevalence in winter.[24]

When acute epiglottitis is suspected, pharyngeal examination should not be attempted, as simple manipulation with a tongue depressor may precipitate acute airway obstruction, although the use of a fibreoptic or small rigid endoscope can assist the diagnosis in patients with an atypical presentation.[25] Direct examination of the airway should not be delayed, but should be undertaken in a controlled setting such as an operating room or paediatric intensive care unit by personnel skilled in airway intervention; endoscopic evaluation will confirm gross erythema and oedema of the supraglottic structures (**Figure 29.3**).

When the diagnosis is confirmed, the airway should be secured by endotracheal intubation. If this is unsuccessful, a rigid bronchoscope may be passed to allow tracheostomy. Endotracheal intubation is usually required for safe airway management.[26] Despite this, mortality remains as high as 3%.[27]

Investigations prior to securing the airway are contraindicated, but a soft-tissue lateral radiograph of the neck will typically show a thickened oedematous epiglottis – the 'thumb sign' (**Figure 29.4**). The causative organism can be identified from nasopharyngeal swabs, laryngeal swabs, sputum samples or blood cultures taken after intubation. Traditionally, acute epiglottitis has been a manifestation of invasive Hib infection. This can be confirmed as the cause in partially treated patients by Hib antigen detection in concentrated urine specimens. In the post-vaccination era, epiglottitis is more likely to be caused by 'vaccination breakthough' Hib infection or by another pathogen, including meningococci, group A streptococci, pneumococci, *Haemophilus parainfluenzae* and *Staphylococcus aureus*.[14] Immunocompromised individuals are at increased risk of epiglottitis. It may then be due to atypical organisms such as *Herpes simplex* type 1, *Varicella zoster*, *Parainfluenza* or *Candida albicans*.[14] Children with acute epiglottitis should be screened after



Figure 29.3 Acute epiglottitis. Endoscopic appearance. Reproduced by permission of Bruce Benjamin.



Figure 29.4 Acute epiglottitis. Radiological appearance of the oedematous epiglottis (arrowed).

recovery from the acute episode to ensure there is no underlying predisposing condition.

Treatment is with intravenous antibiotics; ampicillin resistance due to beta-lactamase production is now over 50% in *Haemophilus influenzae*, so empirical treatment with third-generation cephalosporins for 5–7 days is advised. Chloramphenicol and clindamycin are alternatives in the event of allergy to cephalosporins. Penicillin-sensitive streptococci are the usual cause of acute epiglottitis in children who have been immunized against Hib and they should be treated accordingly. Recovery is characterized by resolution of systemic symptoms and the supraglottic inflammation. The child can then be extubated and discharged from hospital. Since the introduction of Hib immunization, rifampicin prophylaxis has been recommended to eradicate the carrier state for the index case as well as household and school contacts.[28]

Despite the declining incidence of this disease and the changing bacteriology, there has been no change in its clinical presentation over time. It is critically important that reduced clinical experience is not accompanied by a sharp rise in mortality for affected children.

Haemophilus influenzae type b immunization

In addition to acute epiglottitis, other manifestations of invasive *Haemophilus influenzae* infection include meningitis, septic arthritis, septicaemia, pneumonia and osteomyelitis. Serious infections are usually caused by the capsulated forms, serotypes a to f. However, type b was responsible for more than 85% of invasive *Haemophilus influenzae* infection prior to immunization.[15] It has been estimated that, prior to the introduction of immunization, Hib meningitis accounted for 50% of Hib infections, epiglottitis being the next most common presentation.[28]

Routine infant immunization with conjugate Hib vaccine in the UK began in October 1992. Immunization is achieved by three primary doses followed by a late booster. The incidence of invasive Hib infections in children under 5 has fallen dramatically from an incidence of 35.5/100 000 for the year preceding vaccine implementation to 0.06/100 000 in 2012.[29] A reduction in the incidence of acute epiglottitis of approximately 90% has been documented in countries in which an immunization programme has been established. In the UK there was a resurgence of cases in 2003 with over 230 cases of Hib infection, causing a booster programme to be launched.[30] Vaccine failure does occur but in fewer than 10% of cases is there an identifiable clinical risk factor predisposing to infection. An increasing number of cases may be due to infection with an organism other than *Haemophilus* and continued vigilance among clinicians is required.[27] There is evidence that a longer duration of breastfeeding (more than 13 weeks) is associated with a significantly enhanced antibody response to Hib in children aged between 18 months and 6 years.[31]

In the Hib vaccine era, non-type b invasive *Haemophilus influenzae* disease has become more common than type b. It is likely to occur in younger children than is the norm for type b infection, but it is less likely to be meningitis or epiglottitis and more likely to be pneumonia or bacteraemia.[27, 32]

AIRWAY MANAGEMENT

For the child presenting with acute airway obstruction due to laryngeal infection, active intervention to secure the airway may be necessary if symptoms are severe. The options to provide an artificial airway include endotracheal intubation and tracheostomy. Prior to 1975 tracheostomy was the standard intervention, then endotracheal intubation was shown to be a safe alternative for acute epiglottitis and subsequently for croup. Endotracheal intubation is now considered preferable to tracheostomy if circumstances permit. However, the choice of intervention may be influenced by the availability of medical and nursing expertise and local hospital services. The intubated child will require specialized intensive care facilities for management whereas the child with a tracheostomy, while still requiring nursing expertise for optimal management, can be nursed on a normal paediatric ward.

A team approach to management is essential for optimal outcome. The paediatrician, paediatric anaesthetist, paediatric intensivist and paediatric otolaryngologist must collaborate to develop multidisciplinary evidence-based protocols which take into account the availability of local services. Immunization programmes and advances in medical management are changing patterns of disease and have resulted in a decline in the prevalence of acute airway obstruction due to acute epiglottitis, croup and diphtheria; clinicians with little experience of children with these conditions will depend on protocols for safe practice. If endotracheal intubation is to be undertaken, it should be performed in an operating room or paediatric intensive care unit with personnel and equipment available and ready to undertake tracheostomy if the airway cannot be secured.

Once an artificial airway is in place, humidified air should be administered to discourage the development of tenacious secretions. The tube should be aspirated regularly, using suction, to prevent tube obstruction. Nursing vigilance to prevent accidental displacement or self-extubation is essential. In ideal conditions, mortality rates can be as low as 1% for either intervention.[33]

Nasotracheal intubation

Endotracheal intubation for airway obstruction due to acute laryngeal infection is now widely practised with great expertise. When a prolonged period of intubation is anticipated, the nasotracheal rather than the orotracheal route is preferred; nasotracheal intubation is better tolerated so the child requires less sedation, the tube can be secured more reliably and nursing care is easier.

The tube is positioned with the patient anaesthetized and the child is then nursed under sedation, fed via a nasogastric tube. The cough and voice are absent during the period of intubation but after extubation there are normally no sequelae. Complications can occur, however, and include epistaxis at the time of intubation, the development of sinus sepsis during the period of intubation and hoarseness after extubation. The risk of acquired subglottic stenosis is small but is associated with younger age of the child, larger tube size, serial intubation and longer duration of intubation. It is more common in Down syndrome in which there may be an element of congenital subglottic stenosis as a predisposing factor. A tube one size smaller than that usually considered age-appropriate should be used.[34]

Extubation can be considered when the child is systemically well, with minimal tracheal secretions. The 'leak test' (air escape around the nasotracheal tube on application of positive pressure ventilation) is helpful but not an absolute prognostic indicator for successful extubation. In acute epiglottitis, visualization of the epiglottis with a flexible nasendoscope can be useful in monitoring resolution of inflammation. Likewise in laryngotracheobronchitis, whether viral or bacterial, the airway can be monitored using endoscopy until a reduction in tracheal inflammation shows that it is safe to extubate. Systemic steroids administered 6 hours prior to removal of the tube will minimize post-intubation oedema, and nebulized epinephrine can assist with airway patency after extubation.

For acute epiglottitis the period of intubation is usually less than 48 hours but for croup and bacterial laryngotracheobronchitis it may be up to a week.[17] If extubation fails after the acute laryngeal infection has resolved, and despite all the above measures being taken, this may be due to a pre-existing or developing subglottic stenosis. This, if acute and due to mucosal oedema and ulceration, may be successfully treated by a cricoid split (see Vol 3, Chapter 76, Laryngeal stenosis). If not, however, tracheostomy may become necessary and possibly later laryngotracheal reconstruction.

Tracheostomy

Tracheostomy is no longer considered the first choice to secure the airway in acute laryngeal infection. It may be chosen, however, if the availability of nursing expertise and intensive care facilities is limited such that nasotracheal intubation is contraindicated. It may also be necessary if there is severe acute subglottic narrowing precluding the passage of a nasotracheal tube of adequate size for ventilation, or if there has been significant intubation trauma. Equipment and personnel to perform an emergency tracheostomy should always be available in case attempted intubation fails.

Improvements in medical treatments in recent years have seen publications regarding tracheostomy in the management of acute laryngeal infections dwindle from case series to the occasional case report. The largest most recent published series of data on paediatric tracheostomy for croup is from the Red Cross War Memorial Children's Hospital in Cape Town. In that series, 75% of children were decannulated within 10 weeks of formation of the tracheostomy but 54% of children required one or more further procedures after tracheostomy to deal with granulation tissue, supraglottic collapse or subglottic stenosis prior to successful decannulation.[35] Clearly, nasotracheal intubation is preferable if it is possible and practical, depending on local circumstances.

BEST CLINICAL PRACTICE

- ✓ Pharyngeal examination is contraindicated if acute epiglottitis is suspected; it may precipitate acute airway obstruction.
- ✓ Children with croup, whether presenting with mild, moderate or severe symptoms, should be treated with oral dexamethasone at the time of diagnosis. [Grade A]
- ✓ Bacterial tracheitis should be considered in children presenting with croup who fail to respond to treatment with steroids and adrenaline.
- ✓ Nebulized epinephrine (1 mL of 1 in 1000 epinephrine diluted in 3 mL of 0.9% saline) has an established role in the acute paediatric airway. [Grade A]
- ✓ Subglottic stenosis should be remembered in the differential diagnosis of infants presenting with 'recurrent croup'. Consider endoscopy.
- ✓ Equipment and personnel to perform tracheostomy should be immediately available in case attempted intubation is unsuccessful.

FUTURE RESEARCH

- ➤ As Hib vaccination programmes are extended, the incidence of acute epiglottitis should fall even further.
- ➤ Further research is required to determine the optimum dose and route of corticosteroid administration in the treatment of croup.
- ➤ Further studies are required to assess the role of heliox® in the management of children with croup.

KEY POINTS

- The laryngeal airway in children is narrow, especially in the cricoid region. The mucosa is lax and a comparatively minor swelling may cause significant airway compromise.
- Immunization programmes and improvements in medical management have reduced the prevalence of acute laryngeal infection and its severity.
- Systemic steroids have transformed the primary care management of croup. Fewer cases now need hospital admission but vigilance is still required.
- Multidisciplinary evidence-based protocols influenced by the availability of local expertise and services should be formulated and followed to optimize outcomes.
- In acute laryngeal infections, nasotracheal intubation is preferable to tracheotomy if it is possible and practical, depending on local circumstances.

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CHAPTER 30

CONGENITAL DISORDERS OF THE LARYNX, TRACHEA AND BRONCHI

Chris Jephson

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the following keywords: congenital, anomalies, larynx, trachea and bronchi and focusing on diagnosis and treatment.

INTRODUCTION

The exact incidence of congenital abnormalities of the airway is uncertain, but a figure has been quoted for congenital laryngeal anomalies of between 1:10 000 and 1:50 000 births.[1] Some of these children will have more than one anomaly in the airway.[2]

LARYNX

The larynx is divided into three regions: supraglottis, glottis and subglottis. The supraglottic larynx comprises the epiglottis, aryepiglottic folds, false cords and ventricles. The glottis consists of the vocal cords (also referred to as vocal folds). In children, the subglottis extends from the under surface of the vocal cords to the inferior border of the cricoid cartilage.

Supraglottis

Laryngomalacia

Laryngomalacia is characterized by partial or complete collapse of the supraglottic structures on inspiration and is the most common congenital cause of stridor.[3] The pathophysiology is thought to be related to the characteristic anatomical abnormalities that are observed: the epiglottis is long and curled (omega-shaped); the aryepiglottic folds are short and tightly tethered to the epiglottis; there may also be redundant mucosa and submucosa of the aryepiglottic folds medially. The result is a tall, narrow supraglottis with a deep interarytenoid cleft where the epiglottis is soft and may curl and collapse and the mucosa may prolapse into the airway (Figure 30.1). It has been suggested that there may also be an element of neuromuscular immaturity and consequent incoordination of arytenoid movements.

The rather characteristic high-pitched, fluttering inspiratory stridor is usually present at, or shortly after, birth. It is very variable, typically being most noticeable when the infant is active or upset, and may disappear when the child is asleep. The severity of the stridor tends to increase as the child becomes more active during the first 9 months of life, and then gradually diminishes until by the age of 2 years it has generally disappeared. Very rarely, stridor may persist into late childhood.



Figure 30.1 Laryngomalacia.

The diagnosis can be confirmed in the outpatient setting by flexible fibre-optic laryngoscopy. Nasendoscopy is usually possible in children up to the age of 1 year. The child should be wrapped in a blanket and held firmly by a nurse or parent. The supraglottic collapse on inspiration, which is typical of laryngomalacia, is easily seen. In approximately 90% of reported cases the condition is mild, no intervention is needed and the parents can be reassured accordingly.[4] In these cases a period of observation should be undertaken with documented regular weights to demonstrate no failure to thrive. A 4-week course of antireflux medication can be prescribed for those children with regurgitation and gastro-oesophageal reflux disease (GORD).

In severe laryngomalacia, however, there is serious respiratory obstruction with substantial sternal and intercostal recession together with feeding difficulties which may be compounded by reflux enhanced by the high negative intrathoracic pressures generated, and consequent failure to thrive. Matters are made worse if there are other factors increasing the level of cardiorespiratory embarrassment, such as congenital cyanotic heart disease. In the most severe cases, cor pulmonale may ensue and in cases of severe sternal recession a permanent pectus excavatum may develop. Therefore, in children where the stridor is severe, if there is failure to thrive or there are any atypical features (e.g. history of previous intubation, cutaneous haemangioma) that may raise the suspicion of a second, coexisting airway pathology, a microlaryngoscopy and bronchoscopy (MLB) under general anaesthesia is indicated. Optimum conditions for diagnosis require the child to be breathing spontaneously under a very light level of anaesthesia, with the beak of the laryngoscope in the vallecula; the supraglottic collapse is not seen under deep anaesthesia and will be prevented if the tip of the laryngoscope is introduced into the laryngeal vestibule.

Children who show signs of failure to thrive should undergo an endoscopic aryepiglottoplasty (sometimes termed a supraglottoplasty).[5] In this procedure, the larynx is visualized using a laryngoscope in suspension, with its beak positioned in the vallecula. Using cup forceps and microscissors, each aryepiglottic fold is first divided to release it from the edge of the epiglottis, and any redundant mucosa and submucosal tissue are then excised from over the arytenoids, together, if necessary, with part or all of the cuneiform cartilages. In less severe cases it may only be necessary to incise the tight aryepiglottic fold.[6] The 'bridge' of mucosa between the arytenoids is carefully preserved to prevent interarytenoid scarring. Bleeding is minimal and is easily stopped by the application of neurosurgical patties dipped in topical adrenaline (1:10 000). Neither antibiotics nor steroids are routinely given, complications are very rare, and the stridor is usually improved immediately following the surgery. In cases where the stridor and feeding difficulties persist, an underlying hypotonic neurological disorder is likely.[7]

Saccular cysts and laryngocoeles

Laryngeal cysts are rare, can be congenital or acquired and may present with respiratory obstruction in infants and young children (**Figure 30.2a**). They are divided into laryngocoeles and saccular cysts. The ventricle is the fossa bounded by the false vocal fold and the vocal cord. The anterior portion of the ventricle leads superiorly to the saccule. A laryngocoele is an air-filled dilatation of the laryngeal ventricle which communicates with the laryngeal lumen. It is an uncommon lesion which usually occurs in middle age but may rarely be seen in infancy, when it can produce respiratory distress which typically becomes worse on crying due to increased distension of the laryngocoele with air. However, a laryngocoele may obstruct and fill with mucus or become infected (laryngopyocoele), thus becoming indistinguishable from a saccular cyst.

A saccular cyst also represents an abnormal dilatation or herniation of the saccule of the ventricle of the larynx; however, it differs from a laryngocoele in that there is no opening into the larynx and it is filled with mucus instead of air. It is considered to form as the result of a developmental failure to maintain patency of the orifice between the saccule and the ventricle, and may be of anterior or lateral type. The anterior saccular cyst extends medially

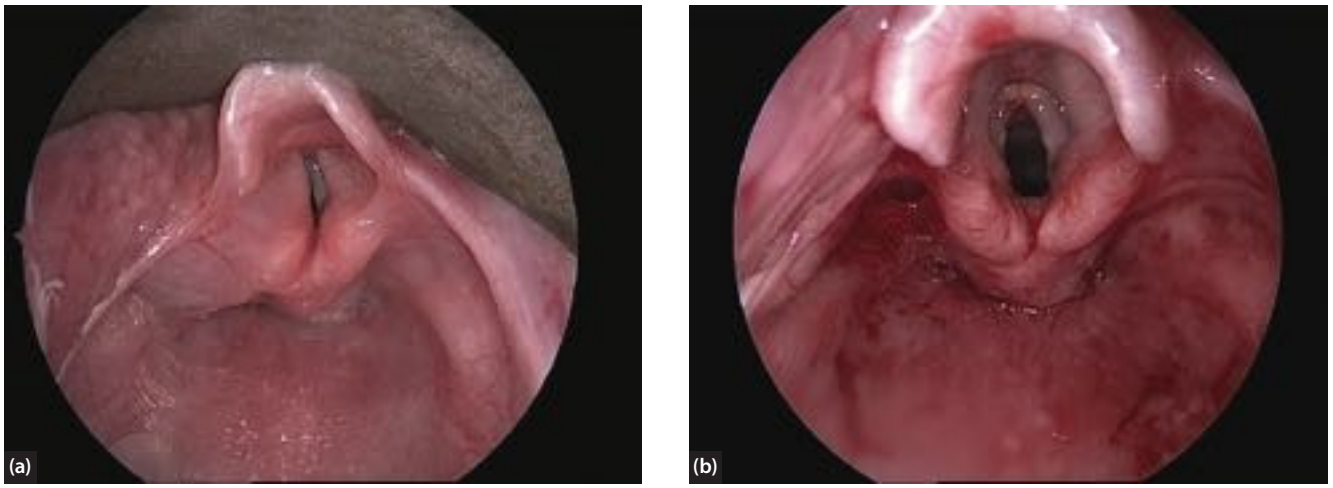


Figure 30.2 Left saccular cyst, showing **(a)** obstruction of the laryngeal inlet, and **(b)** post marsupialization.

and posteriorly from the saccule and so protrudes into the laryngeal airway between the true and false vocal cords. The lateral saccular cyst is most common in infants and expands posterosuperiorly into the false cord and aryepiglottic fold.[8]

Laryngeal cysts are classified as internal or type 1 if contained entirely within the laryngeal framework, and external or type 2 if it pierces the thyrohyoid membrane.[9] Diagnosis is confirmed by endoscopy, except in an external laryngocoele where no abnormality may be seen except on imaging. Saccular cysts are best treated at the initial endoscopy by wide endoscopic marsupialization (**Figure 30.2b**). If the cyst recurs, then the procedure of choice is a lateral cervical approach extending through the thyrohyoid membrane at the superior margin of the ala of the thyroid cartilage, with subperichondrial resection of a portion of the upper part of the ala. Through this 'window' the cyst can be completely excised, using short-term intubation to secure the airway post-operatively.

Vascular malformations

Vascular malformations include lymphatic malformations, venous malformations and arteriovenous malformations and are discussed in detail in other chapters. Vascular malformations are rare in the larynx, trachea and bronchi. Lymphatic malformations (also termed lymphagiomas or cystic hygromas) are cystic malformations that result from abnormal development of the lymphatic vessels. In the head and neck they may be macrocystic (usually infrahyoid), microcystic (usually suprahyoid) or a combination of the two. Occasionally, a microcystic lymphatic malformation may extend into the tongue base, valleculae and supraglottis, and airway obstruction may result. If the lymphatic malformation is very extensive, a tracheostomy may be required, but where supraglottic involvement is less severe it may be possible to debulk the lesion by endoscopic vaporization using a CO_2 laser or radiofrequency ablation.[10, 11]

Bifid epiglottis

Bifid epiglottis is a rare laryngeal anomaly in which the epiglottis fails to fuse in the midline and thus has a cleft extending down to its tubercle. It may be seen as a feature of Pallister–Hall syndrome, the cardinal elements of which are hypothalamic hamartoblastoma, hypopituitarism, imperforate anus and postaxial polydactyly. It usually presents with feeding difficulties due to aspiration and with stridor because of collapse and enfolding of the two halves of the epiglottis. Endoscopy establishes the diagnosis, and treatment options include amputation of the epiglottis and tracheostomy.

Glottis

Laryngeal webs

Failure of complete canalization of the larynx during embryogenesis may result in a glottic or, very rarely, a supraglottic web. The majority involve the anterior glottis, fusing



Figure 30.3 Anterior glottic web.

the vocal cords along a variable part of their length, and producing a correspondingly variable degree of respiratory obstruction and dysphonia (**Figure 30.3**). Characteristically there is inspiratory stridor and a rather weak, high-pitched, squeaky voice. The combination of a weak cry from birth and recurrent croup in infancy should always raise suspicion of a laryngeal web. Anterior laryngeal web can also be associated with 22q11 deletions, other chromosomal anomalies and cardiac abnormalities.[12] Occasionally, a congenital posterior, interarytenoid web occurs and may be associated with cricoarytenoid joint fixation.

Almost all anterior glottic webs are fairly thin posteriorly, close to their free border, but become progressively thicker anteriorly with increasing subglottic extension. Where the web is small and causing little in the way of symptoms it is usually best to treat conservatively. A longer isolated web with little or no subglottic involvement may be divided endoscopically along the margin of one vocal cord with a knife or CO_2 laser; if it is very thin, subsequent endoscopic dilatation may be sufficient to permit stable healing without the web reforming. However, most glottic webs are quite thick anteriorly and extend to varying degrees into the subglottis. A keel placed endoscopically following division can prevent recurrence. In the young child with a small larynx a covering tracheostomy is necessary for the 2 weeks that the keel is in place. In cases where the airway is very small and there is associated subglottic stenosis a laryngotracheal reconstruction (LTR) with anterior cartilage grafting is required. This can be carried out in the infant as a single-stage procedure with post-operative endotracheal intubation to stent the larynx for 5–7 days. However, in practice, most infants with a severe glottic web will have a tracheostomy performed in which case the LTR can be deferred to the age of about 1–2 years, when the larynx is larger and the vocal cord dissection can be undertaken more precisely.

Laryngeal atresia

Laryngeal atresia is incompatible with life unless there is an associated tracheo-oesophageal fistula (TOF) which

permits ventilation via a tube in the oesophagus, or unless an emergency tracheostomy is performed in the delivery room. However, there are now cases being recognized antenatally on ultrasound imaging and managed with an *ex utero* intrapartum treatment (EXIT) procedure, whereby a tracheostomy is undertaken following elective Caesarean section with the neonate still on placental circulation.[13]

Cri-du-chat syndrome

This syndrome is primarily characterized by a cat-like mewing cry in infancy, microcephaly, downward-slanting palpebral fissures, mental retardation and hypotonia. It is caused by chromosome 5p deletion. At endoscopy, observation during phonation reveals that the posterior part of the glottis remains open, giving it a diamond-shaped appearance.[14] There is no respiratory embarrassment and the cry becomes less abnormal as the child grows older.

Vocal cord paralysis

Vocal cord paralysis is the second most common congenital anomaly of the larynx after laryngomalacia. Up to 45% of patients may have other, coexisting airway pathology and so, although outpatient flexible fibre-optic laryngoscopy may indicate the diagnosis, a formal MLB under general anaesthesia is essential. Laryngeal ultrasound can be an accurate and reproducible method of assessing vocal cord movement, and it may be useful in monitoring a child with known vocal cord palsy and in the diagnosis of the very sick child who may be unfit for endoscopy under general anaesthesia.[15] Approximately half of cases are unilateral and half bilateral.

Unilateral vocal cord paralysis is usually not congenital, most cases being acquired as a result of surgical injury to the left recurrent laryngeal nerve, often following correction of a congenital cardiac anomaly. Patients present with mild stridor, dysphonia and sometimes aspiration. If the vocal cord lies in an intermediate position, surgical intervention is not usually necessary, and the voice can be expected to improve as time passes and either recovery occurs or the other vocal cord compensates. If the vocal cord lies in a more abducted position, the dysphonia may be more pronounced and aspiration more likely. Vocal cord medialization procedures such as thyroplasty and augmentation injection can improve the dysphonia and aspiration, but these may result in worsening of the stridor.

In contrast, bilateral vocal cord palsy is usually a congenital abductor paralysis. The vocal cords lie in the paramedian position with consequent inspiratory stridor, and a tracheostomy is necessary in approximately half of cases, most of which have other associated airway pathology. A classical cause of congenital bilateral vocal cord palsy is hydrocephalus with the Arnold-Chiari malformation. Once the diagnosis is made, prompt correction of the raised intracranial pressure with a shunt often improves vocal cord movement and a tracheostomy may thus be avoided. However, most cases of congenital bilateral vocal cord paralysis are idiopathic and the approach to management is greatly influenced by the fact that up to 58% will eventually recover, with 10% taking more than 5 years to do so and one reported case of recovery at the age of 11 years.[16] This strongly suggests that the problem is often one of delayed maturation in the vagal nuclei and argues convincingly in favour of a conservative management philosophy. Furthermore, where the airway is marginal, it may become adequate with laryngeal growth alone, and glottic enlargement surgery in order to avoid a tracheostomy or achieve decannulation may improve the airway at the expense of the voice.

The infant with an inadequate airway and failure to thrive will require a tracheostomy. If vocal cord movement does not develop and the airway does not become adequate as a result of laryngeal growth, then an endoscopic laser cordotomy or arytenoidectomy should be considered at the age of 11 or over, following a full discussion with the child and parents regarding the possible trade-off between airway and voice. If it is considered imperative to achieve decannulation earlier, perhaps because of poor social circumstances, an endoscopic laser cordotomy can be attempted as early as 2 years of age. If that fails, an external arytenoidectomy via a laryngofissure may be carried out at the age of 4–5 years with the prospect of an 84% decannulation rate;[17] however, there is a small risk of aspiration as well as loss of voice quality and the procedure is irreversible.

Subglottis

Congenital subglottic stenosis

Congenital subglottic stenosis is due to defective canalization of the cricoid cartilage and/or conus elasticus, resulting in either gross thickening of the anterior lamina of the abnormal cricoid (**Figure 30.4**)[18] or a small, elliptical, thickened cricoid with excessive submucosal soft tissue (**Figure 30.5**).[19] Alternatively, there may be anterior fusion of the vocal cords, forming a web with subglottic extension, as seen in 22q11 deletion syndromes. Subglottic stenosis is said to be the third most common congenital anomaly of the larynx, but its true incidence is hard to determine because many patients are intubated in the neonatal period and are then considered by definition to have an acquired stenosis. The reality in this situation may be a combined congenital plus acquired stenosis. Milder degrees of stenosis present as inspiratory or biphasic stridor as the child becomes older and more active, or as recurrent ‘croup’ owing to superimposed oedema from upper respiratory tract infections.

Diagnosis requires an MLB. The exact location of the stenosis with respect to the vocal cords, tracheostome and carina is measured and the number of normal tracheal rings above the tracheostome is counted. Passing endotracheal tubes and sizing the stricture measures the degree of stenosis. The Myer-Cotton grading system is widely used



Figure 30.4 Congenital subglottic stenosis, showing anterior cricoid thickening. Reused with kind permission from C.M. Bailey and Springer Science and Business Media.[18]



Figure 30.5 Congenital subglottic stenosis, showing elliptical, thickened cricoid with excessive submucosal soft tissue.

to classify paediatric laryngotracheal stenosis into four grades of severity:[20]

- **Grade I :** 0–50% obstruction
- **Grade II:** 51–70% obstruction
- **Grade III:** 71–99% obstruction
- **Grade IV:** 100% obstruction.

This helps to predict the outcome of surgical reconstruction.

If the airway is not severely compromised, surgery may not be required, especially as a congenital stenosis can be expected to enlarge with growth. Congenital cartilaginous stenosis represents a strict contraindication to dilatation or laser resection: any type of endoscopic treatment is liable to worsen the initial condition, and attempted dilatation is inevitably ineffective as the thickened ring of cricoid cartilage cannot be expanded.

If the airway is severely compromised, a tracheostomy is needed. This can sometimes be avoided in specialist centres where there are facilities for single-stage airway reconstruction in which an endotracheal tube is used as a stent, usually for a period of 5–7 days.

The surgical options have evolved from the classical castellated laryngotracheoplasty designed by Evans and Todd[21] in the early 1970s to achieve laryngeal framework expansion. This was superseded during the early 1980s by the LTR, devised primarily by Cotton.[22] The LTR involves augmentation of the laryngotracheal complex by anterior and/or posterior midline incision of the cricoid with insertion of costal cartilage grafts to expand the airway. This technique has now been supplemented by the partial cricotracheal resection (PCTR), which was introduced into the paediatric age group by Monnier et al.[23] in the early 1990s. This involves complete resection of the stenotic segment with end-to-end anastomosis of the tracheal stump to the thyroid cartilage.

Grade I subglottic stenosis usually requires no surgical intervention. Grade II stenosis can be reconstructed by means of an LTR with anterior cartilage grafting +/– posterior cricoid split. Mild grade III stenosis is likely to need an anterior graft with posterior cricoid split +/– posterior cartilage grafting. Severe grade III stenosis (a pinhole airway) requires both anterior and posterior grafts. Grade IV stenosis demands anterior and posterior grafts with prolonged stenting. For severe grade III and for grade IV stenosis, PCTR is an alternative technique with much to commend it. LTR remains the last surgical option after failed PCTR if it is impossible to resect a further segment of trachea.

In cases of congenital subglottic stenosis, the LTR may be combined with submucosal resection of cartilage to 'core out' the thickened anterior cricoid ring. A similar submucous resection technique can be used via a laryngofissure for thick anterior glottic webs with subglottic extension. In both situations stenting is essential.

The least severe grades (I and II) have a better outcome than the most severe grades (III and IV). For PCTR, however, the grading system is not a predictor of success or failure, because the stenotic segment is completely resected. Results from the most experienced centres[24, 25] show a success rate of over 90% for grades I and II subglottic stenosis following LTR and approximately 80–90% for grades III and IV subglottic stenosis. The latest results from the two centres with the largest experience in PCTR show a decannulation rate of 98% for primary surgery and 94% for salvage surgery after failed previous airway reconstruction.[26, 27]

For more detail on the management of laryngeal stenosis, see Chapter 31, Acquired laryngeal stenosis.

Subglottic haemangioma

Infantile subglottic haemangioma is a well-recognized cause of gradually worsening inspiratory or biphasic stridor presenting in the first few weeks of life, with 85% presenting within the first 6 months. Of patients with a cutaneous haemangioma 1–2% also have a subglottic lesion; 50% of patients with a subglottic haemangioma will have a coexisting cutaneous lesion. The natural history is typically a proliferative phase lasting 6–12 months followed by complete involution over 1–5 years.[28]

At endoscopy the typical appearance is of a compressible, pear-shaped red swelling in the subglottis on one side, left more commonly than right (**Figure 30.6**). Larger haemangiomas may be circumferential and, uncommonly, may extend down into the trachea or through its wall into the surrounding soft tissues of the neck or mediastinum. The appearance is so characteristic that biopsy is unnecessary; in rare cases where there is doubt, biopsy can be undertaken without fear of troublesome bleeding because the lesion is a benign endothelial cell tumour, not a vascular malformation. If extension outside the airway is suspected, magnetic resonance imaging (MRI) is indicated. Subglottic haemangioma is life-threatening because of its situation in the narrowest part of the airway and therefore requires rapid intervention.

Tracheostomy will maintain the airway until involution occurs. A review of the subject in 1984 by Sebastian and Kleinsasser[29] estimated that 50–70% of patients with airway haemangioma require a tracheostomy, and that children managed with tracheostomy alone could be decannulated at a mean age of 17 months. However, paediatric tracheostomy carries a mortality of 1–2% and a significant morbidity including delayed speech development.

Over the years, efforts have been made to develop alternative therapeutic strategies aimed at maintaining the airway without recourse to tracheostomy. Therapies used in the past include radiotherapy, CO_2 laser ablation, systemic steroids, intralesional steroid injection followed by intubation, and interferon alpha-2a. However, all of these are associated with unwanted side effects. Submucosal surgical excision of subglottic haemangioma was first described in 1949.[30] Surgery is carried out in a single stage and is stented with an endotracheal tube for 3–5 days. Surgical excision is unsuitable if the haemangioma is circumferential or extends onto the vocal cords.



Figure 30.6 Subglottic haemangioma.

The treatment of subglottic haemangiomas was revolutionized with the incidental finding that propranolol is an effective treatment for cutaneous haemangioma and subglottic haemangioma.[31,32] Prior to treatment commencing, a baseline pulse, blood pressure and blood glucose should be assessed together with an ECG and echocardiogram. Treatment is initiated at 1 mg/kg/day for 1 week, then advancing to 2–3 mg/kg/day as tolerated.[33] Propranolol has proven to be effective at reducing/resolving stridor in as little as 24 hours. Side effects of propranolol are rare but may include hypoglycaemia, hypotension and bradycardia. Treatment should be for a minimum 12 months to cover the natural period of proliferation, then weaning of the propranolol dose over 4 weeks. These patients should be closely monitored for recurrence.

Propranolol is now considered to be first-line treatment for subglottic haemangiomas. Steroid therapy can be used in the acute setting and in conjunction with propranolol for unresponsive lesions. Submucous resection remains a valid alternative for non-circumferential haemangiomas and those not involving the vocal cords.

Laryngeal and laryngotracheo-oesophageal cleft

Posterior laryngeal clefts result from failure of the posterior cricoid lamina to fuse, and in the more extensive laryngotracheo-oesophageal clefts there is also incomplete development of the tracheo-oesophageal septum. The classification devised by Benjamin and Inglis[34] has been widely adopted because it relates well to symptoms and treatment. A type I cleft extends down to the level of the vocal cords; a type II cleft extends below the vocal cords into the cricoid (**Figure 30.7**); a type III cleft extends down into the cervical trachea; and the, fortunately rare, type IV cleft extends into the thoracic trachea and may even reach the carina. Approximately 25% of patients with a laryngeal cleft will also have a TOF, but conversely the incidence of laryngeal cleft in patients with a TOF is low. Abnormalities of the tracheal ring structure in cleft patients may result in associated tracheomalacia, which can add to the difficulties of management.

The majority of laryngeal cleft patients have associated congenital abnormalities, of which TOF is the most common. These may include tracheobronchomalacia, congenital heart disease, dextrocardia and situs inversus. Often there is severe gastro-oesophageal reflux. Laryngeal clefts are characteristic of two syndromes: the Opitz-Frias syndrome (G syndrome) comprising hypertelorism, cleft lip and palate, laryngeal cleft and

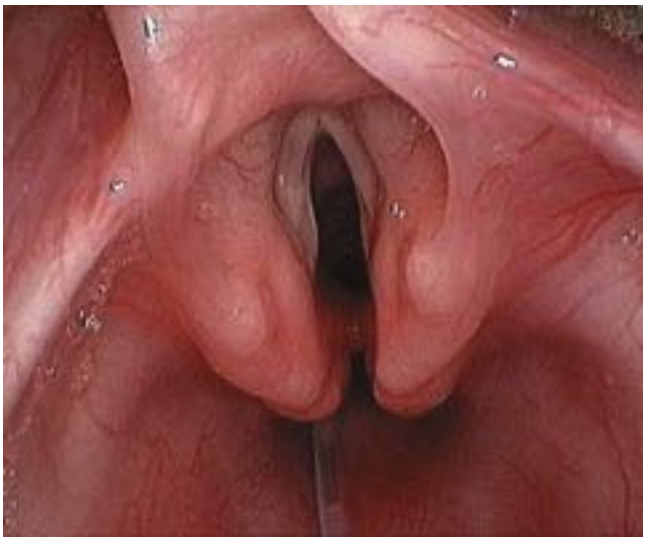


Figure 30.7 Larnygeal cleft (type II). Reused with kind permission from C.M. Bailey and Springer Science and Business Media.[18]

hypospadias; Pallister–Hall syndrome (described earlier in relation to bifid epiglottis), consisting of congenital hypothalamic hamartoblastoma, hypopituitarism, imperforate anus and postaxial polydactyly, and sometimes including a laryngeal cleft.

As might be expected, symptoms become more severe the longer the cleft. Type I clefts present with cyanotic attacks on feeding and recurrent chest infections. Stridor (similar to that of laryngomalacia) may be a feature, secondary to prolapse of the cleft edges into the airway. The differential diagnosis for infants presenting with these symptoms includes gastro-oesophageal reflux, neuromuscular incoordination of deglutition, vocal cord paralysis, raised intracranial pressure and TOF. Type II and III clefts produce dramatic aspiration with recurrent pneumonia, sometimes with stridor and an abnormal cry. Type IV clefts cause severe aspiration, cyanosis and incipient cardiorespiratory failure.

Investigation of the child with aspiration and stridor requires a careful MLB; no other diagnostic method can replace it.[35] Suspension microlaryngoscopy allows the use of two probes to part the arytenoids, and without this manoeuvre the diagnosis may be missed as redundant mucosa tends to prolapse into the defect and obscure it. A plain chest X-ray may show changes secondary to recurrent aspiration pneumonitis. A lateral neck X-ray may demonstrate vaguely increased laryngeal soft tissue and the nasogastric feeding tube may be seen protruding anteriorly into the airway. Videofluoroscopic contrast swallow studies may not differentiate laryngeal incompetence from neuromuscular incoordination, and a high index of suspicion is required.

The approach to treatment depends entirely upon the length of the cleft. A short type I cleft with no aspiration requires no treatment. Minimal aspiration may be managed by thickening the feeds. Significant aspiration requires endoscopic repair of the cleft in two layers, using a nasogastric feeding tube until the suture line has healed. A very short type II cleft may also be repaired endoscopically, albeit with difficulty, using a nasogastric tube. However, a long type II or a type III cleft needs to be approached anteriorly through an extended laryngofissure with a low tracheostomy to cover the procedure; a nasogastric tube will tend to erode through the suture line, and so a gastrostomy is required (usually combined with a Nissen fundoplication to control reflux reliably). These children take many months to learn to swallow after successful cleft repair and thus long-term gastrostomy feeding is necessary. Surgical repair of the cleft is undertaken in three layers in an effort to optimize healing: the two mucosal layers are reinforced by an interposition graft of tibial periosteum or temporalis facia.

The type IV cleft presents an altogether more difficult surgical challenge. Owing to the length of the cleft, a tracheostomy is unhelpful in stabilizing the airway, and the convexity of the tube would tend to erode through the party wall suture line; the repair must therefore be undertaken using a single-stage technique with endotracheal extubation taking place 7–10 days post-operatively. Short type IV clefts may be managed by an anterior approach through a cervical incision, if necessary pulling the trachea up into the neck to reach the lower end of the cleft. Longer clefts will require a lateral cervical approach in combination with a thoracotomy, or preferably an anterior cervicothoracic approach via a median sternotomy with repair on extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass. Post-operatively, tracheomalacia may prevent extubation and so a tracheostomy may be needed once the cleft has healed soundly.[36]

Mortality remains significant, being approximately 14% overall,[37] rising to 66% for type IV laryngotracheo-oesophageal clefts and up to 100% for full-length clefts ending at the carina.[38] A large proportion of the mortality is from causes unrelated to the cleft, and notable morbidity is produced by other associated congenital abnormalities and often by delay in reaching the correct diagnosis. Management should be in a major paediatric centre where a full multidisciplinary team is available with full neonatal and paediatric intensive care facilities.

TRACHEA AND BRONCHI

Advances in the field of airway regenerative medicine mean that tissue engineering is becoming a realistic potential therapy for congenital tracheal and bronchial malformations.[39] Initial research focused on engineering biocompatible and immunocompatible material to act as a scaffold to directly repair any defect, with the aim that the scaffold would become populated by the patient's own, normal-functioning cells – in particular, ciliated respiratory epithelium. Crucially in neonates and children, the scaffold needs to be able to grow with the child. Successful tracheal transplantation has occurred in paediatric patients using decellularized donated cadaveric trachea.[40, 41] The search for the perfect scaffold material, whether natural or synthetic, is ongoing.

Agenesis

Tracheal agenesis may be complete (full-length) or partial, but in either case there is no continuity between the larynx and the bronchi. Occasionally, short-term survival may be possible if there is a broncho-oesophageal fistula, which can permit some airflow into the lungs, but surgical efforts to use the oesophagus as a tracheal replacement have not been successful and long-term survival has not proved possible. The majority of cases are complicated by other severe congenital abnormalities.

Agenesis of one main bronchus and its associated lung is not as rare as tracheal agenesis and is compatible with survival, although such children often have coexisting congenital anomalies and are at risk from chest infections because of their much-reduced respiratory reserve. Bilateral bronchial and pulmonary agenesis is extremely rare and is, of course, fatal. Occasionally, localized atresia occurs in a peripheral bronchus, resulting in a distal mucocoele which may need to be resected if it is causing severe compression of the surrounding lung.

Stenosis

Occasionally, a membranous web may be encountered in the trachea with a normal underlying cartilaginous ring structure. Such cases usually fare well with endoscopic rupture and dilatation. Thicker congenital fibrous stenoses may be amenable to radial KTP laser incision and balloon dilatation, followed by application of mitomycin C to reduce the risk of restenosis[42] or tracheal resection with end-to-end anastomosis. A short stenosis may also be associated with one or two absent tracheal rings, although the most common finding in congenital tracheal stenosis (CTS) is a segment of complete tracheal cartilaginous rings with an airway lumen as narrow as 2 mm.[43]

CTS is usually described as being either short-segment or long-segment and according to whether it involves trachea alone, trachea and bronchus, or bronchus alone. A long-segment congenital tracheal stenosis (LSCTS) is one that is over 1 cm in neonates and 1.5 cm in infants or greater than 50% of the length in older children. Further classification depends on the associated anatomy of the respiratory tract: normal bifurcation, bronchial trifurcation, porcine bronchus or single lung.[44] Sixty per cent of patients with LSCTS will have associated malformations such as pulmonary artery sling, right-sided aortic arch, subglottic stenosis and tracheoesophageal fistula.

Children with congenital tracheal stenosis usually present with respiratory distress within the first year of life. Symptoms usually only appear when there is greater than 50% stenosis. Symptoms may become apparent in the neonatal period with biphasic stridor, respiratory distress, tracheal tug and episodes of cyanosis. However, presentation may be delayed until the infant is several months old when greater physical activity makes increasing demands upon the respiratory system. In addition, difficulty in breathing can develop rapidly as a result of a respiratory tract infection, with consequent oedema and increased secretions. In this situation the child may require endotracheal intubation, and it is then found that only a very small-sized tube can be passed. In the case of a long, tapering stenosis, which may narrow virtually to a pinhole, this is a dangerous situation. The tube tip tends to impact into the stenosis, granulations begin to develop and obstruct the already perilous airway, and endoscopic evaluation is then a procedure fraught with difficulty. In such cases the stenosis often seems surprisingly severe considering the child's mild symptoms prior to the precipitating illness.

Suspected LSCTS should be assessed and managed by a multidisciplinary team including cardiothoracics, ENT surgeons, upper GI surgeons, respiratory and cardiac paediatricians, interventional radiologists and allied healthcare professionals. Investigations should be targeted at identifying the extent of the abnormality.

Endoscopy remains the 'gold standard' investigation for a child with stridor. MLB demonstrates complete tracheal rings without the posterior bulge of trachealis (**Figure 30.8**). However, if LSCTS is found at MLB, great care must be taken not to traumatize the stenosis by attempting to pass an endoscope that is too large or the resultant oedema may convert an airway that is just adequate into one that is not. Frequently, the stenosis is too narrow to permit passage of the 4 mm rigid telescope or the smallest (size 2.5) bronchoscope, and it is necessary to use the unsheathed 1.9 mm telescope to survey the length of the narrow segment and assess the state of the distal trachea, carina and bronchi. Sometimes the airway is too narrow to admit even this extra-slim telescope, and then the surgeon must rely on contrast bronchography.

Bronchoscopy and bronchography (B&B) demonstrate the the size of the tracheal lumen and outline the trachea and bronchi distal to the stenosis, which may be too narrow to permit passage of a bronchoscope (**Figure 30.9**) and also provides a dynamic assessment of any malacic segments. Optical coherence tomography (OCT) can be combined with B&B to confirm the presence of complete rings if there is any doubt. Contrast CT and an echocardiogram are essential in view of the high incidence of associated anomalies of the heart and great vessels. CT is particularly helpful in assessing the vascular anatomy and its relationship to the trachea and 3D reconstructions allow better surgical planning.

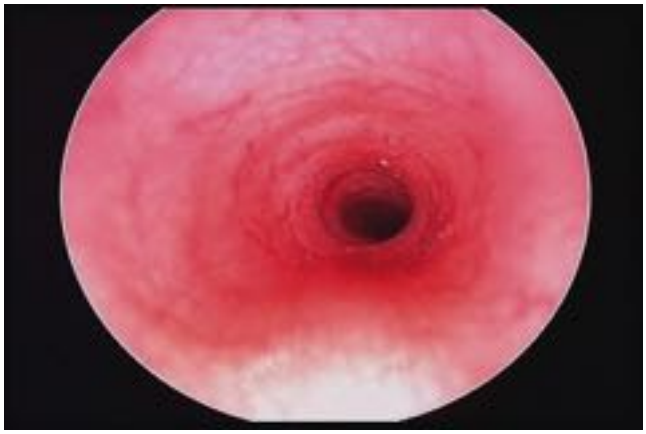


Figure 30.8 Complete tracheal rings.



Figure 30.9 Tracheal stenosis: bronchogram of a long-segment lower tracheal stenosis with associated stenosis of the main bronchi and with a 'pig' bronchus at its upper end.

Mild cases with minimal symptoms may require no intervention after the diagnostic endoscopy, as the trachea can grow and there may be only slight limitation of exercise tolerance. Very narrow, short segments can be excised with end-to-end anastomosis. In the past, several techniques have been employed to treat LSCTS. Augmentation tracheoplasty with costal cartilage grafting or a pericardial flap or free patch have been described. However, if the stenosis is severe with only a pinhole lumen, cartilage grafting cannot be expected to achieve an adequate airway, and a large suspended pericardial patch carries high risk of subsequent tracheomalacia. The overall mortality associated with costal cartilage or pericardial patch tracheoplasty is substantial, ranging up to nearly 50%.[45]

Successful endoscopic balloon dilatation of LSCTS has been reported. However, it is difficult to see why the airway does not quickly close down again to its original size, as the 'spring' in the cartilage is not broken by splitting it in just one place and fibrosis is bound to occur at the site of the split. For this reason, balloon dilatation is used as an adjunctive treatment modality for granulations and fibrous stenoses such as may develop post-operatively at the site of an anastomosis.

For LSCTS, the gold standard treatment of choice is slide tracheoplasty with the patient on cardiopulmonary bypass with concurrent repair of coexisting cardiovascular anomalies. The slide minimizes shortening of the trachea and hence reduces anastomotic tension. The oblique anastomosis also seems less liable to post-operative stenosis than an end-to-end anastomosis. The tracheoplasty is performed by dividing the stenosis at its midpoint, incising the proximal and distal narrowed segments vertically on opposite anterior and posterior surfaces and sliding these together. The stenotic segment is thus shortened by half, the circumference is doubled, and the luminal cross section quadrupled. Long resections may require a laryngeal drop and/or hilar release to avoid undue tension upon the suture line.

Survival rates for LSCTS following slide tracheoplasty over the last decade have risen to nearly 90%.[44] Poor prognostic indicators include pre-operative bronchomalacia and bronchial stenosis, although these groups still have survival rates of over 70%. Balloon dilatation is used to treat granulations and stenosis. Absorbable PDS stents offer an advantage over metallic stents and are used to treat malacia, particularly bronchomalacia.

Slide tracheoplasty has proven to be very successful in treating LSCTS. However, for those children who have failed surgery or in cases not amenable to slide tracheoplasty, few strategies are available. The advent of tissue engineering may hold the key for this group of patients.

Tracheomalacia and bronchomalacia

Tracheomalacia is a condition in which there is reduced stiffness of the tracheal wall, resulting in abnormal collapse of the trachea during expiration which, if severe, can produce symptoms of airway obstruction. Bronchomalacia is the equivalent condition affecting the bronchi. There is, however, no association between tracheobronchomalacia and laryngomalacia, although because the latter is a common condition it may sometimes coexist.

Pathologically, the striking finding is an increased muscle-to-cartilage ratio seen on the transverse section of the trachea; in other words, a widening of the trachealis relative to the cartilage rings, which become C-shaped instead of horseshoe-shaped. Normally, the ratio is 1:4 or 1:5, but in tracheomalacia it may be closer to 1:2. However, in children the trachea and bronchi are more compliant than in the adult and some degree of collapse may be observed during endoscopy in normal children. This is particularly obvious if the level of general and topical anaesthesia is too light and the child tends to cough and strain in consequence, often with anterior bulging of the trachealis. To be clinically significant, more than 50% obstruction is probably required, as visualized at the end of expiration in the well-anaesthetized child.

Tracheomalacia is traditionally classified as primary (idiopathic), due to an intrinsic abnormality in the wall of the airway, or secondary, due to another associated anomaly or to external compression. The primary form is less common and tends to affect a longer segment of the airway. Secondary tracheomalacia is usually more localized and may be associated with TOF or laryngeal cleft or with extrinsic compression by an anomaly of the great vessels or a mediastinal mass. A common but special form of localized secondary tracheomalacia is the suprastomal collapse which arises above most long-standing paediatric tracheostomies, produced by pressure from the convexity of the tracheostomy tube.

The stridor of tracheomalacia becomes apparent during the first few weeks of life and consists of a very variable high-pitched expiratory noise. This may be accompanied by a harsh, barking cough, especially in the localized form of the condition. Characteristically, the stridor becomes much worse when the child is active, feeding, upset, coughing or crying, and it may be associated with cyanotic attacks which are sometimes sufficiently severe to be termed 'dying spells'. The pathophysiology of these seems to be that, with vigorous respiration, airflow through the trachea increases and in accordance with Bernoulli's principle the pressure within the airway correspondingly falls. This encourages further collapse of the malacic segment and a vicious circle is established that can result in complete collapse of the trachea with respiratory obstruction. These episodes are probably self-limiting but, faced with total obstructive apnoea and cyanosis, parents and caregivers will usually attempt resuscitation rather than wait and see.

The stridor of tracheobronchomalacia is typically episodic, thus on examination the child may seem perfectly well. There may be a prolonged expiratory phase to respiration, possibly with faint expiratory stridor. However, crying or feeding can dramatically change the picture to one of an infant who is clearly obstructed and in respiratory distress.

Plain X-rays are not usually helpful. A barium swallow may identify a TOF and can also demonstrate the airway collapse on lateral screening. Echocardiography may be useful in defining any suspected anomaly of the heart and great vessels. CT angiogram is extremely useful for identifying the cause of extrinsic compression of the trachea by normal or abnormal vessels, including vascular rings. Contrast bronchography may be the most useful radiological investigation: it is a dynamic study that not only demonstrates the areas of collapse but enables the opening pressures to be measured, which is extremely helpful in setting continuous positive airway pressure (CPAP) levels for children with very severe tracheobronchomalacia who are intubated or have undergone tracheostomy. Even if tracheobronchomalacia has been demonstrated radiologically, it is nonetheless important to undertake a full MLB to examine the collapse directly and exclude other abnormalities such as a TOF or laryngeal cleft. Typically, anterior tracheal wall collapse will be observed, with flattened tracheal rings and a wide trachealis (**Figure 30.10**). In addition, the common vascular anomalies have sufficiently characteristic features to aid diagnosis (see below).

Mild tracheobronchomalacia (less than 75% collapse) requires no intervention, and the stridor can be expected to resolve spontaneously by around the age of 2 years. However, parents will require careful explanation and reassurance, as well as being taught cardiopulmonary resuscitation if their child is prone to 'dying spells'. Severe tracheobronchomalacia (more than 75% collapse) may require treatment, especially if associated with failure to thrive. If it is secondary to a vascular anomaly, this should be corrected. The severe localized tracheomalacia often associated with a TOF usually responds well to an aortopexy, whereby the aorta is sutured to the back of the sternum. If this fails, an extended tracheostomy tube will effectively support a midtracheal malacic segment, but this is not a satisfactory solution for lower-end tracheal or for bronchial collapse. For the infant in intensive care with severe primary tracheobronchomalacia who cannot be weaned off CPAP, it may be necessary to resort to a tracheostomy in order to apply long-term CPAP. Alternative surgical solutions for this most severe end of the disease spectrum have been sought by cardiothoracic surgeons: these include internal or external stenting of the trachea, segmental resection and cartilage grafting, but all present formidable difficulties and complications with very variable outcome, and the risks may exceed those of the condition itself.

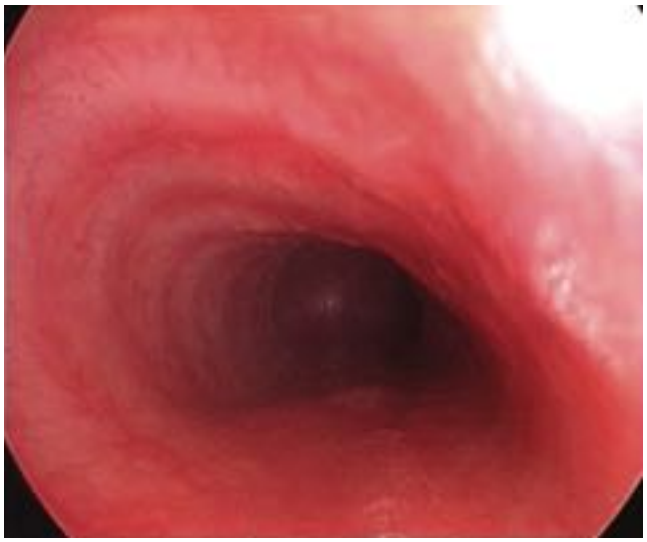


Figure 30.10 Tracheomalacia caused by external compression from an aberrant innominate artery.

Tracheo-oesophageal fistula

Tracheo-oesophageal fistula is a fairly common congenital malformation of the neonatal air and food passages, which usually occurs in association with oesophageal atresia. Eighty-seven per cent of cases have oesophageal atresia with a TOF communicating between the distal oesophagus and the mid- to lower trachea or a main bronchus. The remainder have oesophageal atresia without a TOF (6%); atresia with a proximal TOF (2%); atresia with a proximal and distal TOF (1%); or a TOF without atresia ('H-type fistula') (4%). Approximately 50% of infants with TOF have additional congenital malformations, and 10–20% have tracheomalacia (see Chapter 45, Oesophageal disorders in children).

Children who present to the paediatric otolaryngologist are invariably those with an H-type fistula. Since there is no oesophageal atresia, they are the least symptomatic of the group, with no swallowing difficulty, but small amounts of fluid pass through the fistula into the trachea and produce symptoms and signs of recurrent minor aspiration. The diagnosis is usually established by a barium



Figure 30.11 Tracheosophageal fistula seen at bronchoscopy.

swallow, but even thin contrast may not pass through a tiny fistula. In such cases MLB is required to identify the tracheal opening, which is typically characterized by a V-shaped mucosal fold around it in the posterior wall of the trachea (**Figure 30.11**). Treatment is by ligation and division of the fistula.

For further details on the management of TOF, see Chapter 101, Diseases of the oesophagus, swallowing disorders and caustic ingestion.

Vascular compression

It is estimated that 3% of the population have an anomaly of the great vessels, but only a few of these have symptomatic airway compression.[46] Such vascular anomalies are classified into vascular rings, which completely encircle the trachea and oesophagus, and vascular slings, which exert non-circumferential pressure.

VASCULAR RING

The commonest vascular ring is a double aortic arch. In this abnormality the ascending aorta divides into two arches, one of which passes to the right of the trachea and the other to the left, reuniting posterior to the oesophagus to form the descending aorta on the left. The left arch is usually smaller than the right, and the configuration of the main branches is variable, but the result is compression of both the trachea and the oesophagus, producing stridor, dyspnoea, dysphagia and a brassy cough.

A less common and less constricting ring is produced when there is a right-sided aortic arch and descending aorta associated with an aberrant left subclavian artery. In this situation the ring is completed by the ligamentum arteriosum which passes to the left of the trachea, connecting the descending aorta to the pulmonary trunk.

Patients with vascular rings tend to present earlier in life and with more severe airway symptoms than those with vascular slings. A barium swallow is diagnostic, showing a characteristic double impression upon the column of contrast, and an echocardiogram will confirm the anomaly. Surgical treatment, almost always necessary, is by dividing the lesser component of the ring, but there is invariably a localized area of tracheomalacia produced by the compression which may persist for months or even years.

VASCULAR SLING

The commonest vascular sling is an aberrant innominate artery. The artery arises further to the left and more posteriorly than usual, and crosses the anterior surface of the trachea obliquely just above the carina from the left inferiorly to the right superiorly.

Cases usually present during the first year of life with less severe airway obstruction than that caused by vascular rings. Typically, there is expiratory stridor, cough, recurrent chest infection and sometimes reflex apnoea. The bronchoscopic appearances are diagnostic, with a characteristic sloping, pulsatile compression of the trachea 1–2 cm above the carina which is most marked on its anterolateral aspect (see **Figure 30.10**). Upward pressure with the tip of the bronchoscope compresses the artery against the sternum and obliterates the right radial pulse. In severe cases, surgical relief of the obstruction is necessary: this can be achieved either by aortopexy, in which the vessel is suspended anteriorly from the sternum, or by reimplanting it further to the right on the aortic arch.

A 'pulmonary artery sling' is produced by an anomalous left pulmonary artery, which arises on the right and passes between the trachea and oesophagus, compressing both (**Figure 30.12**). This may be associated with lower-end tracheal stenosis which sometimes also involves the

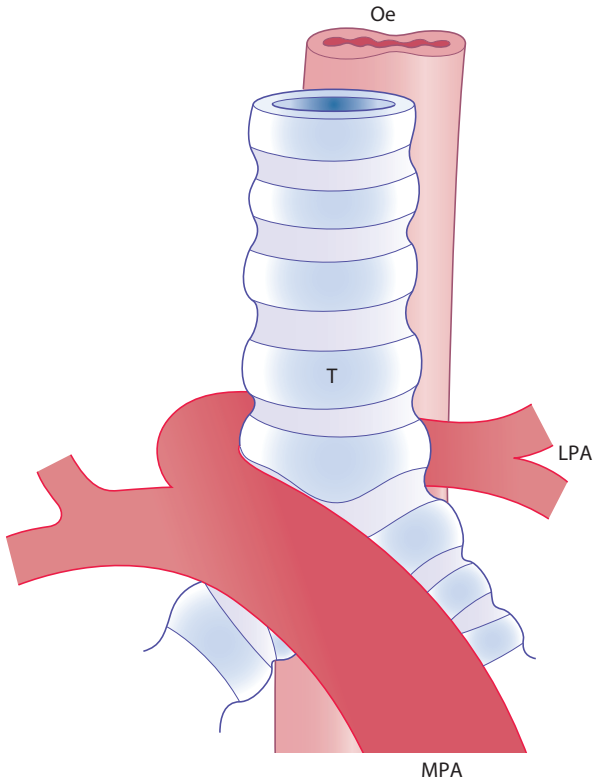


Figure 30.12 Diagram of a pulmonary artery sling. LPA, left pulmonary artery; MPA, main pulmonary artery; Oe, oesophagus; T, trachea. Redrawn with kind permission from C.M. Bailey and Springer Science and Business Media.[18]

carina and right main bronchus. Surgical reanastomosis may be needed to relieve the compression.

Enlargement of the pulmonary artery in association with a cardiac defect can also produce compression of the distal trachea and bifurcation. An aberrant right or, more rarely, left subclavian artery passing posterior to the oesophagus will compress the oesophagus alone, and so produces dysphagia but no stridor.

Anomalous bifurcations

The right upper lobe bronchus may take origin from the right lateral wall of the trachea above the carina, and is termed a tracheal bronchus or suis bronchus. This is the normal arrangement in a pig and so the anomaly in humans is often referred to as a porcine or 'pig' bronchus. It is usually an asymptomatic, incidental finding, but may sometimes be associated with tracheal stenosis. Minor alterations to the distal bronchial branching pattern are not unusual and, likewise, do not usually cause problems.

Congenital cysts and tumours

Tracheogenic and bronchogenic cysts are thought to originate from evaginations of the primitive tracheal bud and are sometimes termed reduplication anomalies. They may happen anywhere along the tracheobronchial tree: they are lined with respiratory epithelium, filled with mucus, and their walls may contain any elements of normal tracheobronchial wall. Bronchogenic cysts may communicate with the airway.

Some patients are symptom-free, but large cysts or those that become infected cause non-pulsatile compression of the airway and present with symptoms, signs and endoscopic appearances otherwise similar to those produced by vascular compression (see 'Vascular compression' above). CT or MRI will demonstrate the lesion clearly, and treatment is by thoracotomy and surgical excision.

Thymomas or teratomas may produce airway compression in the neck or mediastinum. CT or MRI is needed to define the size and situation of the mass prior to surgical excision.

BEST CLINICAL PRACTICE

- ✓ The diagnosis of mild laryngomalacia can be confirmed in the outpatient clinic by flexible fibre-optic laryngoscopy.
- ✓ Microlaryngoscopy and bronchoscopy under general anaesthesia are necessary if the stridor in laryngomalacia is severe, there is failure to thrive or any atypical features.
- ✓ Propranolol has become the first-choice treatment for subglottic haemangiomas, although surgical excision remains as a viable alternative for isolated, non-circumferential lesions.
- ✓ Slide tracheoplasty is the treatment of choice for long-segment congenital tracheal stenosis.
- ✓ Management of congenital disorders of the larynx, trachea and bronchi requires the multidisciplinary resources of a major children's centre.

FUTURE RESEARCH

- ➤ The rarity and often life-threatening nature of many congenital disorders of the larynx, trachea and bronchi means that evidence for their management tends to be confined to evidence levels 3 and 4. International collaboration between large centres is often the only way to generate sufficient patient numbers to generate evidence in this field.
- ➤ Advances in the field of airway regenerative medicine means that tissue engineering is becoming a realistic potential therapy for congenital tracheal and bronchial malformations.

KEY POINTS

- Laryngomalacia is the most common congenital disorder of the larynx, trachea and bronchi and is the most common cause of stridor, but be aware of the possibility of coexisting pathology.
- Congenital disorders of the airway may be asymptomatic but will tend to present in the first few weeks of life with stridor and/or feeding difficulties.
- Failure to thrive raises suspicion of a congenital airway disorder.
- Congenital disorders of the larynx, trachea and bronchi are often associated with underlying syndromes and other anomalies.

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CHAPTER 31

ACQUIRED LARYNGOTRACHEAL STENOSIS

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: paediatric, laryngeal, subglottic, glottic, posterior glottic, web, supraglottic, stenosis, laryngotracheoplasty, laryngotracheal reconstruction and cricotracheal resection. The focus is on evaluation, management and surgery.

INTRODUCTION

Over the past four decades, the presentation and management of paediatric laryngeal stenosis have changed significantly. Prior to 1965, this diagnosis indicated the presence of a congenital anterior glottic web or congenital subglottic stenosis (SGS). In many children, congenital SGS was expected to improve over time. Even in children requiring tracheotomy, decannulation could be achieved within a few years without requiring laryngeal reconstructive surgery. With advancements in neonatal critical care and the introduction of prolonged intubation, this clinical scenario became less common, and acquired SGS became and remains the most frequent cause of laryngeal stenosis. This condition is generally more severe than congenital SGS and typically does not improve over time. Modern paediatric laryngeal reconstruction was thus born of necessity to manage these otherwise healthy, but tracheotomy-dependent children.

Further improvements in neonatal care, particularly the use of nasopharyngeal continuous positive airway pressure (CPAP) and high-flow nasal cannulae, have led to a significant decline in the incidence of acquired SGS in children without other medical problems. These improvements have resulted in the salvage of premature and often medically fragile children whose laryngeal pathology is but one component of a myriad of health issues. The typical child who now presents with SGS is more likely to have problems associated with extreme prematurity or genetic or other birth defects. The management of these children is complex, ideally requiring an interdisciplinary team approach. In addition, their laryngeal pathology is more severe, with stenosis potentially involving not only the subglottis but also the supraglottis or glottis; while SGS is far more common, combined pathology is not uncommon.

Although the complexity and multifaceted needs of children with SGS have increased, so too have the management strategies used to treat these children. Endoscopic procedures, particularly balloon dilation, new open operative techniques (e.g. slide tracheoplasty), and new uses for medications (e.g. azithromycin and topical antibiotic and steroid combinations), have all made contributions to patient care.

Despite these advances, acquired laryngeal stenosis continues to cause significant morbidity and mortality, whether or not patients are tracheotomy-dependent. The primary aim of intervention is decannulation or preventing the need for tracheotomy. In selected patients, voice restoration or provision of a safer airway may be the primary consideration, with decannulation being a secondary goal.

Despite the large number of centres and surgeons that care for complex children with SGS, the needs of this patient population are often highly individualized. Similarly, the experience of managing surgeons and other healthcare providers may vary widely. As such, prospective randomized controlled trials of particular treatment strategies are lacking, and most recommendations are based on level 3 or 4 evidence.

PAEDIATRIC LARYNGEAL ANATOMY

Compared with the adult larynx, the infant larynx lies high in the neck, with the hyoid bone overriding its superior aspect. The narrowest point in the infant airway is the cricoid ring. Since this is the only fixed ring within the airway, it is the most vulnerable point for iatrogenic damage caused by intubation. In a term newborn, the diameter of the subglottis is between 4.5 and 5.5 mm. If the airway diameter in the term newborn is less than 4 mm, SGS is present. A useful guideline is that the outer diameter of a 3.0 mm endotracheal tube is 4.2 mm.

The superior margin of the supraglottis comprises the superior edge of the epiglottis, the aryepiglottic folds and the arytenoids, while the inferior margin is at the level of the true vocal folds. The glottis comprises the true vocal folds and the glottic chink. In the infant, the posterior 50% of the true vocal fold consists of the vocal process of the arytenoid. The subglottis lies between the undersurface of the vocal fold and the lower border of the cricoid cartilage. The subglottic mucosa is lined with respiratory epithelium. A transition to squamous epithelium occurs at the free edge of the true vocal fold.

EVALUATION

History

A child with laryngeal stenosis may present with stridor, extubation failure or tracheotomy dependency. In each of these clinical scenarios, a meticulous initial history forms the basis for further evaluation and investigation. It is important for clinicians to determine the overall health status of the child, exploring signs or symptoms and being aware of a past diagnosis of gastro-oesophageal reflux, aspiration, lung disease or cardiac disease.

In a child presenting with stridor, the duration of stridor must first be ascertained. If acute, stridor is a medical emergency. When it is more chronic, its mode of onset should be ascertained and the determination of whether it is stable or progressive should be made. In addition, the degree of compromise to the child's lifestyle should be assessed, particularly with regard to exercise intolerance and shortness of breath on exertion. Some children will also experience obstructive symptoms during sleep. These sleep problems are usually associated with supraglottic pathology although they may be indicative of a second non-laryngeal pathology such as adenotonsillar hypertrophy. The aetiology of the child's compromised airway should also be sought, in particular any prior history of intubation. If there has been such a history, relevant details such as the duration of intubation, the temporal relationship between intubation and the onset of airway symptoms, and whether an age-appropriate endotracheal tube was used should be determined.

In an intubated child, the reason for intubation should be assessed, as should any medical problems that could contribute to extubation failure. The relevant history should include the length of time the child was intubated, the size of the endotracheal tube, the number of attempts at extubation and whether extubation failure abruptly occurred following endotracheal tube removal or was due to gradual and progressive respiratory compromise necessitating reintubation.

In a child with tracheotomy dependency, the aetiology requiring initial placement of a tracheotomy should be ascertained and the duration of cannulation and size of the tracheotomy tube should be determined. Any history of airway reconstructive surgery is also extremely important. Another significant aspect of a thorough assessment is an evaluation of voice quality and the ability to tolerate a speaking valve.

Physical examination

Once a case history has been taken, the presence of stridor and retractions at rest should be assessed. The nature of the stridor — in particular whether it is purely inspiratory, expiratory or biphasic — should be noted. Nonetheless, retractions provide a better barometer of obstruction than stridor. Assessment of voice quality is particularly important in that it may provide an indication of the anatomic region of the pathology. Children with supraglottic stenosis usually present with a characteristic muffled or 'throaty' voice, while those with anterior glottic webbing tend to have a very hoarse voice. Those with posterior glottic stenosis and SGS usually have normal voice quality. In a child presenting with extubation failure, non-laryngeal causes such as nasal obstruction and glossoptosis are explored. In cases of tracheotomy dependency, the size of the tracheotomy tube, the child's ability to tolerate a speech valve and the possibility of tracheotomy tube plugging are pursued.

Imaging studies

Radiologic evaluation of the paediatric airway is most helpful in patients who are neither intubated nor tracheotomy-dependent. Imaging studies fall into two time-related categories: those that are performed prior to endoscopic evaluation and those that are best after endoscopic evaluation. Prior to endoscopy, soft-tissue airway films of the neck and chest should be performed in both lateral and anterior/posterior projections. These are useful in evaluating laryngeal stenosis and may also give timely warning of a possible tracheal stenosis. Anterior/posterior and lateral chest films indicate possible underlying lung pathology. A barium swallow study may not only provide information on the ability to swallow and the relative risk of aspiration but may also indicate the need to evaluate the airway for a posterior laryngeal cleft or a tracheo-oesophageal fistula. In addition, it may provide information on a child's propensity to gastro-oesophageal reflux, vascular compression of the airway and the presence of an oesophageal foreign body.

After endoscopic airway evaluation, more directed imaging studies are valuable. Spiral computed tomography (CT) scanning of the airway with contrast enhancement

provides a useful view of intrathoracic vasculature. If relevant, 3D reconstruction of CT axial images may be valuable in evaluating the intrathoracic airway. Although both magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) also provide excellent views of intrathoracic vascular anatomy, they require more time to perform and are more likely to require sedation or anaesthesia. In younger children, CT and MRI airway evaluation may complement endoscopic evaluation; however, they are not a substitute for it.

In children with upper airway compromise, sleep fluoroscopy or cine MRI may provide a valuable dynamic airway assessment.

Endoscopic airway evaluation

FLEXIBLE NASOPHARYNGOSCOPY

In a child who has not been evaluated previously, flexible nasopharyngoscopy with the child awake should be performed prior to rigid endoscopy. Although the nasal passages, nasopharynx, oropharynx, supraglottic and glottic airway should be assessed, and pathology such as choanal atresia, adenoid hypertrophy, tonsillar hypertrophy and laryngomalacia should be evaluated, the most important information to be sought relates to vocal cord movement. The ability of the vocal cords to normally abduct is critical information prior to any consideration of laryngeal reconstructive surgery, whether movement is compromised by unilateral or bilateral vocal cord paralysis, posterior glottis stenosis, or cricoarytenoid joint fixation. Although the risk of inducing laryngospasm is low, it is recommended that the nasopharyngoscope should not be advanced below the level of the glottis. Although the precise mechanism is unclear, even children with bilateral true vocal fold paralysis may have laryngospasm.

RIGID ENDOSCOPY

It must be emphasized that evaluation of the paediatric airway should not be considered a minor procedure, particularly when performed in a child with an unstable airway (see Chapter 28, Stridor). Extreme care must be taken not to exacerbate the child's condition. The surgical and anaesthetic team must work together closely and must have specific knowledge of the paediatric airway and of appropriate instrumentation. In a child with a compromised airway who does not have a tracheotomy tube, preoperative administration of dexamethasone, 0.5 mg/kg up to a maximum of 20 mg, is a prudent precaution.

Rigid endoscopy remains the 'gold standard' for paediatric airway evaluation, and this evaluation should begin with an assessment of the supralaryngeal airway. The possible presence of retrognathia and any associated glossoptosis or difficulty of laryngeal exposure should be initially assessed, as should tonsillar hypertrophy or evidence of pharyngeal scarring. The supraglottic larynx should be carefully assessed for scarring, laryngomalacia, short aryepiglottic folds and arytenoid prolapse. The glottis should be evaluated for scarring, anterior glottic webbing and posterior glottic stenosis, and care should be taken to exclude the presence of a posterior laryngeal cleft. If vocal motion is clearly seen, it can be assumed that neither true vocal cord is paralyzed. If, however, movement is not observed, nasopharyngoscopy with the patient awake should be performed. The subglottis should be evaluated, and any stenosis or scarring noted. If stenosis is present, its severity, length, position and physical characteristics should be noted. It may be characterized as soft or firm, as concentric or with lateral shelving, and with mucosa appearing either quiescent or actively inflamed.

If there is a sufficient lumen to allow passage of the endoscope, the trachea is next assessed. Hopkins rod endoscopes with an outer diameter as small as 1.9 mm are available, and can negotiate most grade III SGS. An assessment is made of the upper trachea, including the tracheotomy stoma site, looking for suprastomal collapse or the presence of a suprastomal granuloma. Assessment is also made of possible tracheomalacia and vascular compression of the airway. Although complete tracheal rings are rare, their possible presence should be evaluated cautiously, so as not to induce oedema within an already compromised segment of airway. The carina and mainstem bronchi are also evaluated.

If SGS has been identified, the area of stenosis should be graded according to the Myer–Cotton classification[1] (see **Table 31.1**). This is best carried out utilizing endotracheal tubes, with a small tube being placed initially. If this tube leaks at less than 20 cm of water pressure through the subglottis, the next larger size is placed. It should be noted that the Myer–Cotton grading system is not designed to address supraglottic, glottic or tracheal stenosis (**Figure 31.1**).

ANAESTHETIC TECHNIQUE DURING BRONCHOSCOPY

A collaborative relationship with the anaesthetist is essential in deciding upon the specific anaesthetic technique to be used when performing rigid endoscopy. Possible options include spontaneous ventilation, assisted ventilation, jet ventilation, total intravenous anaesthesia (TIVA) and apnoea with intermittent bag and mask ventilation. Spontaneous ventilation offers the best dynamic assessment of the airway and is thus recommended. Endoscopy may be performed with the laryngoscope introduced into the airway and suspended in position. This frees both the surgeon's hands for introduction of a telescope and instruments as required. Some surgeons prefer to expose the larynx with an anaesthetic laryngoscope blade held in one hand and use the other hand to introduce a telescope. Endoscopy may also be performed with a ventilating bronchoscope or a Hopkins rod telescope, keeping in mind that the technique itself is not as important as the information gained. We prefer to use the Hopkins rod telescope, exposing the larynx with a straight anaesthetic laryngoscope blade. The child spontaneously ventilates a mixture of sevoflurane and oxygen through an endotracheal tube placed in the oropharynx, and with additional intravenous anaesthesia provided by propofol bolus.

TABLE 31.1 The Myer–Cotton classification (redrawn from Myer et al.,[1] with permission)

Grade	From	To	Examples
I	 No obstruction	 50% obstruction	
II	 51% obstruction	 70% obstruction	
III	 71% obstruction	 99% obstruction	
IV	No detectable lumen		

FLEXIBLE BRONCHOSCOPY

In selected children, flexible bronchoscopy may complement rigid bronchoscopy and both may occasionally be required to evaluate a child's airway adequately. Also, in many instances, these techniques can be used interchangeably. In some cases, however, each technique offers clear advantages. Rigid bronchoscopy provides a superior assessment of the larynx, especially the posterior glottic area. Flexible bronchoscopy is often extremely valuable in assessing a larynx that is difficult to access with rigid instrumentation and may provide valuable information about airway dynamics, such as the degree of pharyngeal collapse, glossoptosis and the presence of laryngomalacia, tracheomalacia or bronchomalacia. Flexible bronchoscopy also permits evaluation beyond the eighth generation of bronchi in older children and allows specific lavage of bronchial subsegments, which may provide information about silent aspiration if lipid-laden macrophages are found.

Gastrointestinal evaluation

OESOPHAGOGASTRODUODENOSCOPY, OESOPHAGEAL BIOPSY AND PH PROBE

In selected cases, particularly in patients with complex underlying medical conditions or in those who have failed previous airway reconstruction, oesophagogastroduodenoscopy may be beneficial in the assessment of a child prior to airway reconstruction. It can provide information about oesophagitis, gastritis, and the status of the lower oesophageal sphincter, especially in regard to whether a previous fundoplication is still functional.

Pre-operative evaluation of gastro-oesophageal reflux with dual probe pH or impedance monitoring and/or oesophageal biopsy is advisable and should be mandatory in a child with an active larynx or recalcitrant airway stenosis following previous reconstruction.[2] Oesophageal biopsy will also provide information about oesophagitis,



Figure 31.1 Grade III acquired subglottic stenosis.

including the possibility of eosinophilic oesophagitis, and is currently the best method of diagnosing and monitoring this condition.

Placement of a pH or impedance probe may be done at the time of oesophagogastroduodenoscopy, at the time of bronchoscopic evaluation, or may be performed as an elective procedure unrelated to endoscopic evaluation. Patients should be off antireflux medication for at least 1 week prior to pH probe placement. A dual pH probe with the upper port lying in the postcricoid region is desirable. While normal paediatric values for the upper port do not exist, positive readings should be viewed with suspicion. The impedance probe not only measures acid but can also provide an indication of the volume of a reflux bolus and the height in the oesophagus to which it progresses. Impedance technology also allows evaluation of non-acid reflux. This enables a child to remain on antireflux medication prior to evaluation.[3]

Evaluation of aspiration

Paediatric airway reconstruction runs the inherent risk of turning a child with laryngeal stenosis into a chronic aspirator. Although this risk cannot always be accurately evaluated pre-operatively, in most cases a thorough evaluation provides ample warning signs. Recurrent pneumonia and an insidious drop in a child's baseline oxygen saturation are highly suggestive of chronic aspiration. A history of previous aspiration or current aspiration is extremely important. In a child who is tracheotomy-dependent, copious tracheotomy secretions or secretions stained by food material indicate chronic aspiration. This is more difficult to evaluate in a child who is entirely gastrostomy (G-tube) fed. A simple solution is to intermittently place a drop of green food dye on the child's tongue and evaluate whether green-stained secretions are subsequently suctioned from the tracheotomy tube. Alternatively, a radionucleotide spit study may be performed: a drop of radioactive material is placed on the tongue and its passage is monitored to either the stomach or lung fields. In a child suspected of aspirating, a bronchoalveolar lavage, which can identify lipid-laden macrophages, may be useful. This does not, however, provide useful information in a child who is wholly G-tube fed. Children with grade IV SGS, in whom aspiration is not possible prior to laryngotracheal reconstruction, present a particular challenge. In these children, pre-operative evaluation to assess the relative risk of aspiration is strongly advocated.

A barium swallow or video swallow study may provide information not only on the presence of aspiration, but also on what substances are most likely to be aspirated. Thin fluids are more likely to be aspirated than purees or solids.

A functional endoscopic evaluation of swallowing, whereby the larynx is visualized with a nasopharyngoscope while a child swallows food or drink, can provide valuable information about the relevant risk of aspiration and the mechanism of aspiration as well as the presence or absence of normal laryngeal sensation.

Having knowledge of the possibility of post-operative aspiration allows for appropriate pre-operative counselling and management to minimize this risk. Innately, there are three things that may be aspirated, namely food and drink presented by mouth, saliva and gastric reflux. The respective risk of each can be minimized by conversion to G-tube feeding, reducing saliva production through a 'drool' procedure, and performing a fundoplication. Most children and families presented with the choice of a gastrostomy tube or a tracheotomy tube will choose the former.

Sleep evaluation

A formal sleep evaluation may be a useful method to evaluate a child's respiratory efforts and oxygen needs, whether or not a tracheotomy is in place. The primary aim of laryngotracheal reconstruction is decannulation, and this operative procedure is rarely warranted if decannulation cannot be achieved. In children with tracheotomy dependency, it is important to evaluate whether surgical correction of laryngeal stenosis will permit decannulation. In children with significant lung disease, particularly bronchopulmonary dysplasia or in those who are dependent on a ventilator or CPAP, decannulation may be imprudent. Similarly, children with progressive neuromuscular disorders, diaphragmatic weakness or central hypoventilation syndrome may not be candidates for decannulation. If results of a sleep evaluation indicate pulmonary compromise that precludes decannulation, laryngeal reconstruction may be futile.

Voice evaluation

Voice evaluation in children with laryngeal stenosis, tracheotomy dependency or following laryngotracheal reconstruction is in its infancy and is poorly understood. It is clear, however, that laryngeal reconstruction frequently has a negative impact on the voice, particularly

in children requiring supraglottic or glottic surgery and in those in whom a laryngofissure is required to reconstruct the airway. What is unclear is which underlying pathologies and reconstructive procedures place the voice at greatest risk, and also the extent to which a voice disorder relates to the initial aetiology of the laryngotracheal stenosis.

Children have a tremendous drive to communicate, which often compensates for severe anatomic dysfunction. Some children will retain a surprisingly good-quality voice, even with a grade III SGS. However, children with a grade IV SGS are aphonic unless they have learned oesophageal speech techniques. In these children, laryngotracheal reconstruction may be extremely beneficial in terms of regaining voice, even if decannulation is not achieved.

CONSIDERATIONS PRIOR TO LARYNGEAL RECONSTRUCTION

Surgical intervention for laryngeal stenosis is not always warranted, and the decision as to whether or not to perform such surgery is generally predicated by the overall health status of the child rather than by the stenosis itself. In a child with a high risk for aspiration or with certain craniofacial anomalies, surgical reconstruction may be inappropriate in that the laryngeal stenosis may actually protect the lungs from aspiration. In some children, ongoing aspiration may lead to a consideration of laryngotracheal separation rather than laryngeal reconstruction. Similarly, in children with other significant medical conditions, such as those requiring CPAP, bilevel positive airway pressure (BiPAP) or ventilator support, reconstruction is unwise. While not universally accepted or rigorously proven, most experts in paediatric laryngotracheal reconstruction believe that gastro-oesophageal reflux disease is both a cofactor for the development of SGS and a negative influence on the outcome of operative reconstruction. Oxacillin or methicillin-resistant *Staphlococcus aureus* (MRSA) screening prior to open airway surgery is also recommended, as post-operative infection may greatly compromise the surgical repair. Although a child with a progressive neuromuscular disorder may be considered for laryngotracheal reconstruction to improve vocal function, this seldom enables long-term decannulation.

In some children, a period of observation prior to considering surgical intervention is the best course of action. This strategy is most appropriate in a child with an active or inflamed larynx that is not amenable to medical intervention. An active larynx is generally related to gastro-oesophageal reflux disease or eosinophilic oesophagitis and is, therefore, potentially amenable to such intervention. In children in whom the aetiology of an active larynx is unknown, laryngeal reconstruction is unwise until the laryngeal inflammation has improved. In some of these children, azithromycin given as an anti-inflammatory drug on a Monday, Wednesday, Friday dosing regimen may be effective in reducing inflammation in up to 50% of children with an idiopathic active larynx. In children who do not respond to azithromycin, spontaneous resolution often occurs within a 1- to 2-year period. A waiting period is also advisable in a child who has recalcitrant stenosis after a recent airway reconstruction, or in a child whose larynx is healing from laryngeal trauma. While only a guideline, a 6-month 'cooling off' period is often advisable in such children.

Although weight is a less important factor than the overall health status of a child and the child"s laryngeal disease, it is a frequently used criterion for postponement of airway reconstruction. While laryngotracheal reconstruction can be effectively performed in children less than 3 kg if other criteria permit, a 10 kg guideline is often used. Nevertheless, airway reconstruction in a larger child is technically much easier to perform.

The child with complex medical problems

Historically, children presenting for airway reconstruction were otherwise healthy children with a stenosed larynx. Increasingly, however, children presenting for airway reconstruction have multifaceted complex medical problems, most commonly related to either extreme prematurity or syndromic conditions (see Chapter 5, The child with special needs). In such children, an interdisciplinary team approach is advisable for adequate assessment both before and after planned reconstruction. The most important decision to be made is whether it is advisable to even attempt reconstruction. If so, consideration must be given to other interventions indicated prior to proceeding with laryngeal reconstruction. In a child with reflux disease, a fundoplication may be required. In a child with aspiration, a 'drool' procedure may be required. It is prudent to have most of these children undergo additional evaluation by paediatric subspecialists in pulmonology, gastroenterology, medical genetics and neurology. Pre-operative evaluation and optimization improve outcomes.

THERAPY

Medical therapy

When the larynx is stable and quiescent, there is no role for medical therapy. In the inflamed or active larynx, however, medical therapy plays an important role in alleviating laryngeal inflammation; in turn, this enhances the potential for a successful operative outcome. In children with SGS, medical therapy alone occasionally obviates the need for laryngeal reconstruction by providing sufficient improvement to permit decannulation.

Medical therapy for an inflamed larynx revolves around treatment of gastro-oesophageal reflux disease or eosinophilic oesophagitis. If reflux is diagnosed or even suspected, then a low threshold for treatment with H_2 antagonists or proton pump inhibitors is recommended. In children with recalcitrant acidic reflux or significant non-acid reflux, consideration should be given to performing fundoplication.

A recent observation has been the correlation between eosinophilic oesophagitis, laryngeal inflammation and a poor outcome following laryngotracheal reconstruction.[4] Eosinophilic oesophagitis has a characteristic appearance on oesophagogastroduodenoscopy, with oesophageal furrows often having microscopic white plaques noted. However, the definitive diagnosis is made on biopsy, with greater than 20 eosinophils per high-power field being noted. In children with eosinophilic oesophagitis, evaluation for underlying food allergies is indicated. In children in whom a food allergy is not proven, treatment with oral fluticasone is suggested. An initial dosing regimen of 440 µg, sprayed on the tongue twice a day and swallowed, is usually efficacious. Follow-up oesophagoscopy with further biopsies to confirm resolution of disease is suggested prior to undertaking laryngeal reconstruction, which is usually delayed for 6 months.

Tracheotomy

In a child with an unsafe or unstable airway in whom laryngotracheal reconstruction is not immediately advisable, temporary placement of a tracheotomy tube is advisable to secure an adequate airway until laryngeal reconstruction can be performed. Placement of a tracheotomy should be performed with a view to the subsequent laryngeal reconstruction that may be required. A high tracheotomy close to the cricoid increases the risk of exacerbation of stenosis, but it may make subsequent cricotracheal resection (CTR) simpler, as a shorter segment of airway can then be resected. Tracheotomy through the second to fourth tracheal rings is still recommended.

Although a tracheotomy provides a safer airway in a child with laryngotracheal stenosis, the airway is by no means completely safe. Tracheotomy-related deaths continue to occur in children who could otherwise anticipate good long-term quality of life, and the greater the degree of obstruction, the greater the risk. A tracheotomy is a marked compromise on both a child's and a family's quality of life and emotional health.

Endoscopic management of subglottic stenosis

A range of endoscopic and open procedures are currently used for the management of SGS, and these approaches are not always mutually exclusive. Endoscopic approaches are used both as the primary treatment modality and as an adjuvant treatment before or after open airway reconstruction. Children with grade I or II stenosis and no history of endoscopic failure have a higher likelihood of successful endoscopic management, whereas those with more severe SGS or multilevel stenoses are more likely to require open reconstruction.[5, 6]

Although dilation has a considerable history, balloon dilation has been widely adopted only over the last decade, and bougienage dilation, with associated mucosal trauma caused by the shear forces inevitable with this technique, has fallen from favour.

Balloon dilation of the airway using high-pressure non-compliant balloons has evolved considerably in recent years and is now considered an invaluable addition to the tools used to manage SGS,[7–11] reportedly reducing the need for open airway surgery by as much as 80%.[10] Balloons offer a number of advantages, as they exert a purely radial force over the circumference of the stenosis, thus minimizing the risk of airway rupture or mucosal trauma. Pressures of over 20 atmospheres may be applied by some balloons. By using a device that incorporates a pressure gauge, they also allow the surgeon to fine-tune the force applied to the stenosis. A third advantage is that balloon dilation catheters are long, narrow and flexible — all of which allow the surgeon to steer through a severe stenosis. Selection of balloon size is based on the expected size of the normal airway. For example, a 4 year-old should be intubated with a 5.0 mm endotracheal tube with an outer diameter of nearly 7 mm. The balloon size selected would be 7–8 mm for the larynx. For tracheal lesions, balloon selection is typically 1 mm greater than the size predicted for the larynx. Repeated dilation at 1- to 3-week intervals on up to four occasions is recommended. Adjunctive interventions such as steroid injection and scar division may provide additional benefit, especially in patients with established thicker stenosis. Scar division may be performed utilizing a sickle knife, microlaryngeal scissors or a laser. In selected patients, subglottic or tracheal scarring may be divided prior to balloon dilatation (**Figure 31.2**).

Appropriate patient selection for balloon dilatation is critical to a successful outcome. Children who are likely to respond well to this technique are those with thin or web-like and soft stenoses consisting of immature scar tissue. In contrast, patients with firm or mature scar tissue, cartilaginous airway narrowing, and structural problems of the airway exoskeleton (e.g. subglottic lateral shelves, missing cartilage) are less likely to respond.[11] Dilation is also less likely to yield positive outcomes in longer stenoses and in patients with additional airway lesions.[11]

The recommended technique for balloon dilation is having the patient not be forcefully breathing during the procedure; therefore, after an initial evaluation of the airway, the patient is pre-oxygenated and then either briefly paralyzed or given a bolus of propofol to minimize spontaneous respiration. The balloon is introduced with direct visualization with a Hopkins rod endoscope, and then inflated to the rated burst pressure. Care should be taken that the balloon does not displace (watermelon seeding). The balloon is kept inflated for 2 minutes or until the patient desaturates to 90%, and it is then deflated and removed.

The potential complications of balloon dilation are rare. Negative pressure pulmonary oedema may occur with forced respiratory attempts against a closed glottis. Airway rupture may occur if an over-large balloon is selected. Distal displacement of the balloon due to watermelon seeding may occur and, if the balloon catheter is pulled and stretched trying to prevent displacement, the balloon may not be able to be deflated and may need to be ruptured with a needle or knife to remove it from the airway. Although newer balloon designs are less prone to

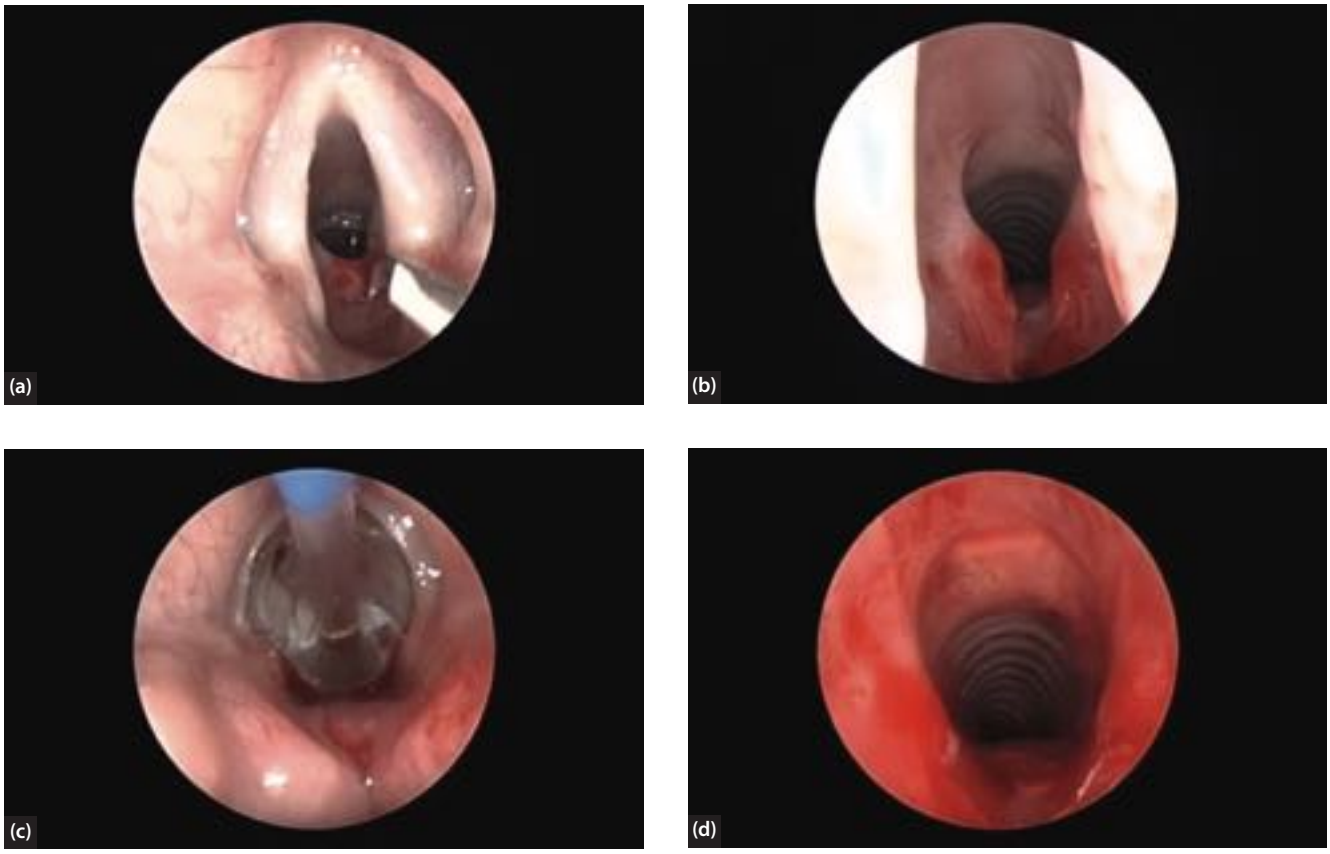


Figure 31.2 **(a)** Grade III acquired SGS immediately prior to endoscopic division with a sickle knife; **(b)** same stenosis after division in the midline posteriorly; **(c)** balloon dilatation in progress; **(d)** same child, immediately after balloon dilatation.

watermelon seeding, the main limitation of balloon dilation is that its success rate is lower than that seen with open airway reconstruction. If after four or five dilations the airway diameter has not significantly improved, then open surgery should be considered. Given that balloon dilation is relatively simple, fast and low-risk in children with mild to moderate degrees of SGS, it should be seriously considered prior to open airway reconstruction.

Laryngeal reconstruction

Laryngeal and upper tracheal reconstruction may be challenging and no single operation can adequately address all types of laryngeal stenosis. It is thus prudent to evaluate each child on an individual basis. In some patients, the most appropriate reconstruction technique may not become fully clear until the airway has been opened and the pathology directly inspected. The mainstay of laryngotracheal reconstruction is expansion cartilage grafting (**Figure 31.3**). In the subglottis, an alternative to this approach is resection and reanastomosis. Stenosis involving the supraglottis and anterior glottis is amenable to laryngoplasty without cartilage grafting. Whether congenital or acquired, tracheal stenosis may be best managed by a slide tracheoplasty (described later in this chapter).

In concept, laryngotracheal reconstruction may be managed either endoscopically or by expansion grafting, resection (tracheal or cricotracheal), or the slide tracheoplasty. Although the latter operation was conceived for the management of tracheal stenosis, it may extend into the larynx if appropriate.

GRAFTING MATERIALS

Costal cartilage is the most widely used grafting material, with excellent results noted on prolonged followup.[12, 13] It is readily available, robust, and easily shaped and carved. Moreover, it is possible to harvest more than one graft through the same incision. The usual donor site is the right fifth or sixth rib, with the incision being placed in the anticipated breast crease in girls for cosmetic reasons. The harvested graft should include the perichondrium on the lateral aspect of the graft, while leaving the inner perichondrial layer intact at the donor site to allow the potential for some cartilage regeneration. Once the graft is harvested, filling the wound with saline and performing a Valsalva manoeuvre will ensure that a breach of the pleura has not occurred. When the graft is carved to the desired shape, the perichondrium should face the lumen of the airway; lateral flanges will prevent prolapse of the graft into the airway.

When only a small graft is required, thyroid ala is a useful material. This is usually taken from the upper aspect of the thyroid cartilage on one side, at least 1 mm above the

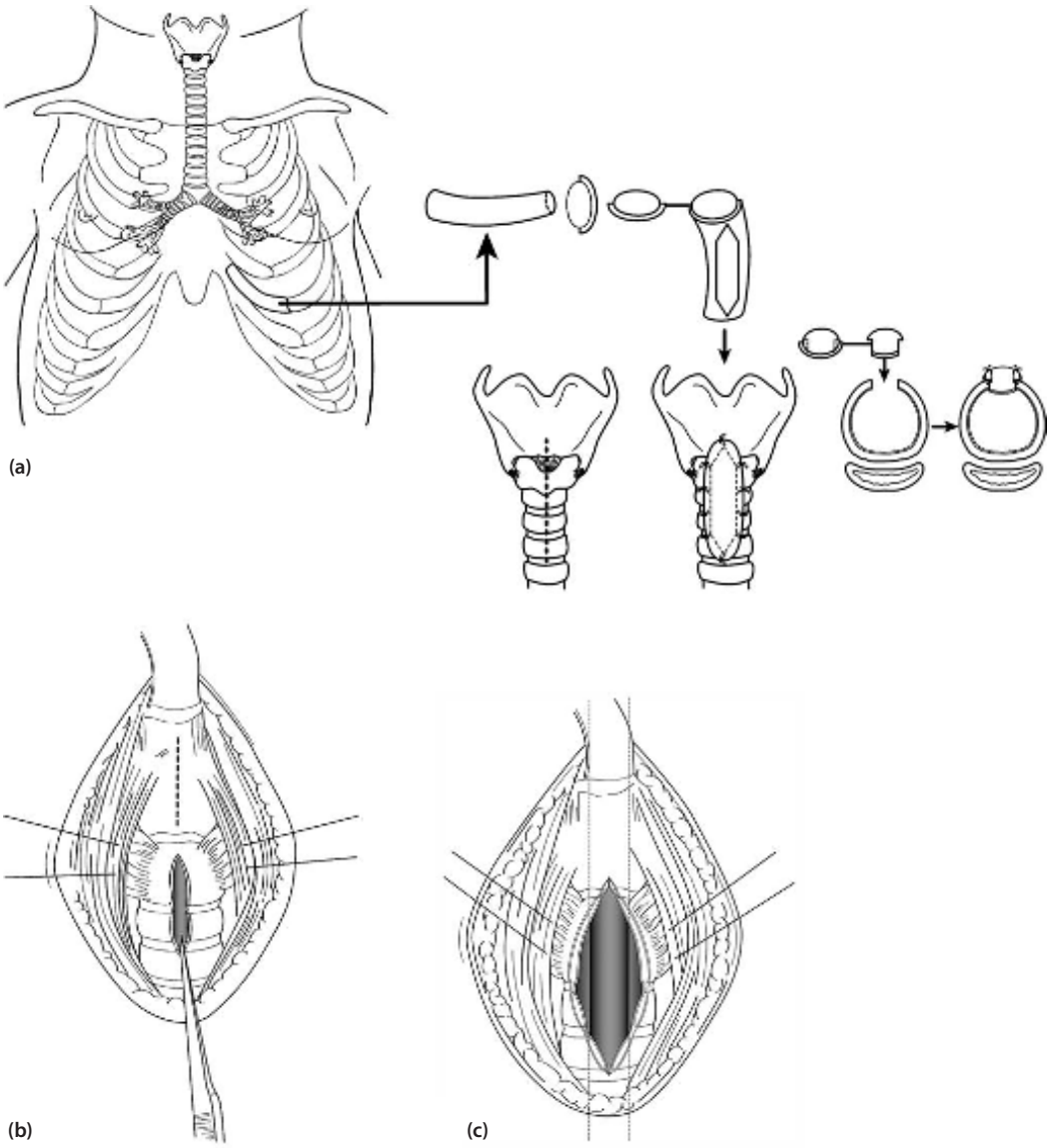


Figure 31.3 Expansion cartilage grafting.

level of the true vocal cord. Thyroid ala has the advantage of being quickly and easily harvested from within the surgical field. However, only a limited amount of grafting material is available and it is not amenable to being carved with flanges.

Auricular cartilage is also useful, in particular for the management of suprastomal collapse as part of a single-stage procedure. It is easily harvested and reasonably abundant. It makes an ideal cap or overlay graft, particularly over a stoma site, but it is comparatively weak and not appropriate for insertion between the cut edges of the cricoid. In both adults and older children, there is no cosmetic donor site deformity; however, in children younger than 1 year of age it is common to have some residual asymmetry of the ears.

Other grafting materials include buccal mucosa, septal cartilage, and a pedicled hyoid bone interposition graft. The results utilizing these grafting materials in children have been disappointing. Another described technique is the use of a clavicular periosteal graft, with its vascularity maintained by swinging the graft up on a pedicle of sternocleidomastoid muscle. This is a useful graft for older children in whom there is a significant deficit of tracheal cartilage, as after several months the graft will start to ossify, thereby providing support to the airway. In prepubescent children, the graft unfortunately seems less amenable to ossification, leaving the airway malacic.

STENTS

Not all laryngotracheal reconstruction techniques require stent placement. It may not be required in an anterior flanged graft for moderate SGS; however, it is advisable in virtually all other circumstances. Stenting maintains a lumen and prevents graft prolapse during post-operative healing, and it may remain in place for days to months. Longer-term stents are advisable when the laryngeal repair is unstable (e.g. when a posterior cricoid split has been performed in an older child without placement of a

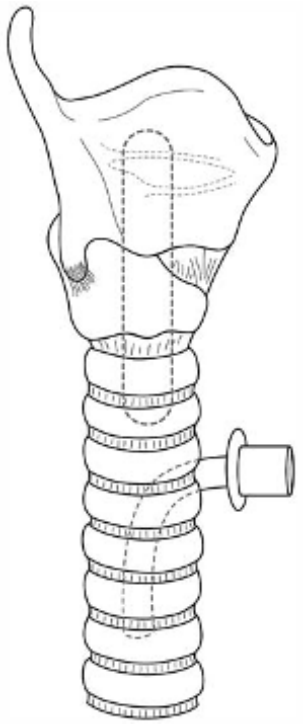


Figure 31.4 Rutter suprastomal stent.

cartilage graft) or in a recalcitrant larynx that has failed previous reconstruction. In patients in whom graft survival is threatened, such as diabetic patients and patients on continuous steroids, long-term stenting without cartilage grafts is advisable. The most commonly used stent is the silicone Rutter suprastomal stent (**Figure 31.4**), although Abouker, Monnier and Mehta stents are also available.

The Rutter stents are soft and deformable and do not interfere with placement of the tracheotomy tube. They tend to incite less granulation tissue at the distal end of the stent, and there is less dead space between the distal end of the stent and the tracheotomy tube in which scarring can occur. The proximal end of the stent is trimmed to the level of the false vocal cord and then plugged with a rounded cap that is less likely to induce epiglottic granulation tissue. Unlike the rigid Abouker Teflon stents, these soft silastic suprastomal stents may remain in place for longer than 6 weeks. There is a corresponding restriction of speech, as they permit only very limited air passage.

For longer-term stenting, tracheal T-tubes are recommended. Although T-tubes with an outer diameter of 5 mm are commercially available, because of the risk of crusting and obstruction, we do not routinely place T-tubes with an outer diameter of less than 8 mm. An 8 mm tube may be placed in a child as young as 4 years of age. Following laryngeal reconstruction, the upper end of a T-tube is generally passed through the vocal cords. Aspiration is therefore a significant risk and is expected for 2 weeks following stent placement. A supraglottic swallow technique is readily achieved by most children, minimizing the risk of aspiration. Unlike tracheotomy tubes, T-tubes cannot be easily changed. Meticulous T-tube care is thus essential.

SINGLE-STAGE RECONSTRUCTION

In children in whom a stenting period of less than 2 weeks is anticipated, an option to be considered is intubation, with the endotracheal tube acting as the stent.[14] Intubation for longer than 2 weeks, however, risks redevelopment of posterior glottic stenosis or SGS. For straightforward airway reconstruction, extubation may occur within a few days of the operation or, occasionally, even at the end of the reconstructive procedure. Although the optimal duration of intubation is not clearly defined, there has been a trend towards briefer periods of intubation following laryngotracheal reconstruction. Most children can be extubated within 2–7 days of a CTR or an anterior costal cartilage graft. Those with anterior/posterior cartilage grafts are usually intubated for 7–14 days. The older the child, the more forgiving the airway and the briefer the period of intubation required. For more complex airway surgery, a prolonged period of intubation is required.

A prerequisite for single-stage laryngotracheal reconstruction is an excellent intensive care unit (ICU) in which staff are familiar with the management of airway patients. It is undesirable for a child to have an unplanned self-extubation, and security of the nasotracheal tube is paramount. Therefore, in younger children, the use of arm restraints and sedation is usually required. Most children younger than age 3 require sedation, and children who have been previously intubated for long periods may require heavy sedation. Paralysis is undesirable, as in the event of accidental decannulation, the child is unable to maintain an airway and reintubation must be emergent. Since any child undergoing a single-stage procedure risks the need for reintubation, single-stage procedures should not be performed on children who are difficult to intubate. In the sedated child, commonly encountered problems include lung atelectasis, fluid overload from heavy sedation, pneumonia and narcotic withdrawal following extubation.

In children older than age 3 years with no major cognitive problems, sedation may not be required. Some of these intubated children may be able to ambulate, eat and visit the playroom. A fully awake child does not require ventilatory support and is less likely to have pulmonary complications from the intubation (**Figure 31.5**). The day prior to extubation, returning to the theatre to inspect the airway and downsize the tracheotomy tube is advisable (**Figure 31.6**). If the airway appears adequate to support extubation, a dose of dexamethasone, 0.5 mg/kg, is administered the night before extubation, and the patient is extubated while fully awake. Owing to the risk of laryngeal oedema, the patient should be closely observed on the ICU for the next 24 hours; oedema generally resolves within this period of time. In the event of airway distress following extubation, management options include the administration of racemic adrenaline, further steroids, helium/oxygen administration or even the use of CPAP or BiPAP. If the airway is still not adequate, the child may need to be reintubated. If so, a further trial of extubation should be performed a few days later. If this is again unsuccessful, a decision is



Figure 31.5 Single-stage laryngotracheal reconstruction. The child is intubated but awake in the intensive care unit.



Figure 31.6 One week after single-stage laryngotracheal reconstruction the anterior and posterior costal cartilage grafts are visible but already partly covered in mucosa.

required as to whether to proceed to a third trial of extubation or to proceed with tracheotomy. If a tracheotomy is required, the stoma should ideally be placed low in the neck, below the graft site. Glottic oedema and granulation from endotracheal tube irritation are often the cause of failure during a single-stage procedure, rather than the reconstructed site itself. In such cases, the tracheotomy tube may be removed once the oedema has settled, usually within a few weeks.

The ideal patient for consideration of a single-stage procedure is one in whom a reasonably simple procedure with a stable larynx is anticipated. This single-stage approach is preferable in children in whom a tracheotomy tube has induced suprastomal collapse. Poor candidates for single-stage reconstruction include children with poor pulmonary function, those who are difficult to intubate, those with recalcitrant airway disease who have failed previous reconstruction, and those with complex disease involving multiple levels of obstruction.

Supraglottic stenosis

Supraglottic stenosis is rare, difficult to treat, and is frequently associated with supraglottic collapse. While severe supraglottic stenosis may present with stridor, the primary complaint is more commonly obstructed breathing during sleep. Therefore, a sleep study may be extremely useful in the non-tracheotomized patient or in the patient in whom the tracheotomy can be capped, even if for a brief period. The underlying aetiology is often traumatic, due to severe direct airway trauma or airway burns, or is of iatrogenic origin. Supraglottic stenosis with associated collapse is a feature of the airway that has undergone numerous laryngeal reconstructions. Visualization of the supraglottic larynx in cases of supraglottic stenosis and collapse may be misleading. Rigid endoscopic evaluation with the larynx suspended by a laryngoscope may distort the appearance of the larynx, providing false reassurance about the supraglottic airway. Flexible endoscopic evaluation with the patient spontaneously ventilating allows for superior evaluation of the airway dynamics. Nevertheless, what is observed may be deceiving. A larynx that looks extremely compromised in an anaesthetized patient may function quite adequately in the unanaesthetized state.

In children with mild to moderate supraglottic stenosis and collapse, nocturnal CPAP may be very beneficial. The most common patterns of supraglottic compromise are arytenoid prolapse and epiglottic petiole prolapse. Arytenoid prolapse is a dynamic instability of the arytenoid, either unilateral or bilateral. It is characterized by its anterior displacement during inspiration, which may cause significant airway obstruction. This problem most commonly follows previous CTR or previous laryngotracheal reconstruction involving division of the posterior cricoid plate. In CTR, the pathogenesis of arytenoid prolapse may be attributed to division of the lateral cricoarytenoid muscle. In laryngotracheal resection, the pathogenesis of arytenoid prolapse may be attributed to either direct damage to the posterior cricoarytenoid ligament or lateral distraction of the posterior plate of the cricoid.

Arytenoid prolapse is usually managed endoscopically, using a laser to perform a partial arytenoidectomy. The preferred technique is to raise a mucosal flap and debulk the prolapsing cartilage of the arytenoid without damaging the mucosal 'diamond' of the laryngeal inlet. Injudicious use of the laser in the laryngeal inlet predisposes patients to scar formation, fibrosis and narrowing of the supraglottic airway. This, in turn, may induce superimposed supraglottic collapse due to the Bernoulli effect.

Epiglottic petiole prolapse

This presents as a compromised laryngeal inlet owing to the base of the epiglottis (the 'petiole', from the term used to describe the footstalk of a leaf, i.e. the part which connects the blade to the stem) obscuring the anterior true

vocal folds and foreshortening the anterior/posterior diameter of the laryngeal inlet. This problem is most commonly seen in children who have had repeated previous laryngofissure and is a consequence of damage to the thyroepiglottic ligament, where it inserts into the thyroid cartilage just above the anterior commissure. Epiglottic petiole prolapse is rare, and challenging to treat. Injudicious use of a laser in the endolarynx tends to exacerbate the problem, with further scarring narrowing the laryngeal inlet. Suspension of the epiglottic base to the hyoid bone provides some benefit, but is technically challenging and causes the patient significant pain on swallowing for several weeks post-operatively.

Our current management of this challenging problem is to perform a complete laryngofissure and reposition the epiglottic petiole back up to the inner surface of the thyroid ala. The laryngofissure is then closed over a T-tube or suprastomal stent and left in position as a translaryngeal stent for at least 2 months. These patients may have problems with aspiration for some weeks post-operatively.

Acquired anterior glottic webs

Anterior glottic webs are most commonly congenital in origin, and are usually associated with a subglottic extension of the web resulting in coexistent SGS (see Chapter 30, Congenital disorders of the larynx, trachea and bronchi). Acquired anterior glottic webs are less common and are post-traumatic in origin. There are two common aetiologies: anterior neck trauma, often associated with a fractured larynx; and iatrogenic damage, often associated with injudicious use of a laser at the anterior commissure while managing laryngeal papillomatosis. It is rare for prolonged intubation to induce anterior glottic stenosis unless there is also associated SGS.

The management of acquired anterior glottic stenosis differs significantly from the management of the congenital anterior glottic web. The latter has normal mucosa within the remaining glottic inlet, and during reconstruction there may be sufficient mobility of the mucosal layer to reconstruct the anterior commissure without requiring the use of a laryngeal keel. In contrast, acquired anterior glottic stenosis is, by definition, associated with fibrosis and scarring. As such, during reconstruction, following laryngofissure, the mucosa is fibrotic and not amenable to reconstruction of the anterior commissure. Therefore, reconstruction with placement of a laryngeal keel is mandatory while the raw surfaces on either side of the laryngofissure remucosalize.

The usual technique for repair of an acquired anterior glottic web is an open approach with complete laryngofissure, and it is recommended that this is performed with endoscopic guidance. With the laryngofissure complete, the demucosalized raw scar of the anterior vocal folds is noted and, in some cases, there may be enough mucosal mobility to place a pexing suture from the cut edge of the mucosa on either side towards the thyroid ala. Unlike repair of congenital anterior glottic webs, it is unusual to be able to pex the mucosal edge up to the anterior commissure — hence the need for a laryngeal keel. An appropriate size laryngeal keel, such as the Montgomery Keel,™ is then selected and trimmed. The vertical limb of the keel should not impinge into the posterior commissure. The vertical height of the keel should separate the raw surfaces of the laryngofissure. The upper limit of the keel should not be so high as to disrupt the insertion of the epiglottic petiole.

The keel is then sewn into place and the laryngofissure closed. This procedure is normally performed as a two-stage procedure, although a single-stage procedure may be performed with the patient intubated and with the endotracheal tube lying on one side of the vertical limb of the keel. In some children, there is an associated component of SGS, and a decision should be made as to whether the cricoid can be closed adequately over an age-appropriate endotracheal tube. If this is possible, the lower end of the keel should not extend beyond the cricothyroid membrane. If it is not possible, an anterior cartilage graft is placed in the anterior cricoid, distal to the keel.

The keel is removed through an open approach between 10 days and 4 weeks post-operatively. The resultant midline deficit in the thyroid ala is then closed with laterally placed mattress sutures, as the cartilage edges of the laryngofissure are friable and easily damaged if sutures pull out. For this reason, antibiotic coverage and antireflux measures are advised during the period that the keel is in place, and for an additional few days after keel removal.

Endoscopic placement of the laryngeal keel is increasingly a consideration. Even in younger children, it is possible to suspend the larynx on a laryngoscope and endoscopically divide the web with a sickle knife or a laser. The keel may be fashioned from a thin piece of silastic sheeting, with a central suture orientated in the anterior midline across the divided web, and with the silastic sheet placed like the leaves of a book over the divided mucosa. The suture may be placed as an ‘inside-out’ technique using a Lichtenberger needle driver or as an ‘outside-in’ technique using a Keith needle and hollow angiocath.

Posterior glottic stenosis

Posterior glottic stenosis is frequently misdiagnosed and often confused with bilateral true vocal cord paralysis. It may exist as an isolated entity or in combination with SGS. The most frequent aetiology of this condition is prolonged intubation, with the older child being at greater risk than the neonate. The posterior glottis is also susceptible to damage from thermal injury caused by inhalational or airway fires or to iatrogenic damage from use of the laser in the posterior commissure. Occasionally, posterior glottic stenosis may be a result of direct laryngeal trauma.

If not already tracheotomy-dependent, patients present with stridor and exertional dyspnoea. Normal vocal function is usually preserved and, in this regard, presenting symptomatology is similar to that seen in bilateral vocal cord paralysis or cricoarytenoid joint fixation.

Definitive diagnosis requires assessment with rigid bronchoscopy, which confirms the presence of posterior glottic scarring, as a rigid telescope provides excellent visualization of the posterior glottis. Posterior glottic stenosis can, however, be misdiagnosed on bronchoscopy if the telescope is passed directly through the vocal folds to evaluate the subglottis without proactive inspection of the posterior glottis. Bronchoscopic evaluation should also include assessment of the subglottis, which is frequently involved with scarring. An assessment of arytenoid mobility is required as cricoarytenoid joint fixation is an occasional co-pathology. Formal sizing of the airway utilizing endotracheal tubes may be misleading. Posterior glottic stenosis may limit the size of the endotracheal tube that may be inserted. In some cases, however, the vocal folds easily bow laterally to accommodate an age-appropriate endotracheal tube despite still being tethered posteriorly, compromising the airway. It should again be emphasized that the Myer–Cotton grading system is only applicable to SGS.

While flexible bronchoscopy provides a poor view of the posterior glottis and is an inadequate method of diagnosing posterior glottic stenosis, awake flexible nasopharyngoscopy may be extremely useful in determining if vocal fold function is intact. The usual finding is that the vocal folds are mobile but tethered and unable to abduct.

The differential diagnosis for posterior glottic stenosis commonly includes SGS (which frequently may also be present), an interarytenoid scar band, and cricoarytenoid joint fixation. In children referred for the management of posterior glottic stenosis, it is rare to find vocal cord paralysis. By contrast, children referred for the management of bilateral vocal cord paralysis may, in fact, have posterior glottic stenosis tethering the vocal cords and masquerading as vocal cord paralysis. Bilateral vocal cord paralysis and posterior glottic stenosis rarely coexist.

Placement of a posterior costal chondral graft is the mainstay of management and is a highly effective way of achieving an adequate glottic airway.[15, 16] This procedure is best performed through an anterior approach, traditionally through a complete laryngofissure. This approach allows excellent exposure of the posterior glottis and direct visualization of the posterior glottic scar band. The posterior glottis is then infiltrated with 1% Xylocaine with adrenaline. The needle is guided through the posterior plate of the cricoid in the midline until it can be felt to pop through into the space between the posterior cricoid and the oesophagus. A further small amount of Xylocaine and adrenaline may then be injected in two or three positions down the cricoid. This has the advantage of providing not only haemostasis in the postcricoid region but also an additional buffer zone between the posterior cricoid plate and the oesophagus. The posterior cricoid can then be split vertically for its entire length, ensuring that the incision is kept completely in the midline. It is important that the interarytenoid scar band is completely divided. The incision may be continued superiorly through the interarytenoid muscles (which are frequently fibrosed) up to the level of the interarytenoid mucosa itself. Care must be taken not to inadvertently form a posterior laryngeal cleft. Following the posterior split, the cricoid should be easily distracted laterally. A costal cartilage graft is then harvested and carved so that its height is approximately the height of the cricoid split and its depth allows the graft perichondrium to lie reasonably flush with the cut mucosa of the posterior cricoid. The graft may be sewn in place with 4.0 Monocryl™ sutures on a P2 needle. An alternative approach is to form a flanged graft that can be snapped into place and stabilized with a small amount of fibrin tissue glue. With the posterior graft in place, the laryngofissure is then closed over an age-approximate endotracheal tube. If the cricoid does not easily close anteriorly, a further segment of costal cartilage is used as an anterior cricoid graft. A posterior graft rarely needs to be more than 6 mm wide as the primary aim of surgery is to incise the scar tissue and hold the raw edges apart while healing takes place. A graft surpassing this width carries an increased risk of aspiration and a poor vocal outcome.

It is possible to perform this procedure without performing a complete laryngofissure. If the anterior airway incision is carried up to the true vocal cords but not through them, there is usually sufficient access to perform a safe posterior cricoid split and allow insertion of a flanged graft. Such a graft is required, as there is not adequate access to comfortably place sutures with this technique. This technique can even be used in small children.

Posterior cricoid grafting may be performed as a single- or two-stage procedure. Other variations of open reconstruction include scar excision alone, buccal mucosal grafting and a posterior cricoid split without graft placement. However, a posterior split without a graft normally requires a considerable period of stenting before full stability is achieved. A posterior cricoid split without graft placement is most effective in children younger than 9 months of age, and even then, in a single stage procedure, usually requires a 10-day period of intubation.

A posterior costal cartilage graft may be placed endoscopically,[17] and this approach has become increasingly popular over the last 10 years. Patient selection requires no anterior component of SGS, and a larynx that can be adequately exposed. The posterior cricoid may be split with a laser of a sickle knife, and balloon dilation may be used to distract the posterior split. Pockets are created behind the posterior plate of the cricoid to accommodate the posterior flanges of the graft. Significant force is required to place the graft, and balloon dilation may assist with graft placement. This technique may be used to expand the posterior cricoid in posterior glottis stenosis, SGS, or bilateral vocal cord paralysis.

Other endoscopic techniques may also be efficacious; however, they are generally not as reliable as the open approach. Although a laser posterior cordotomy with or without partial arytenoidectomy is effective, there is a significant chance of restenosis. In order to prevent restenosis, the use of mitomycin C is a consideration, as well as placement of a temporary transglottic stent. Other described techniques for the endoscopic management of

posterior glottic stenosis include mucosal advancement flaps, microtrap-door flaps, vocal cord lateralization, and botulinus toxin (Botox) injections.

Whether reconstruction is open or endoscopic, there is a restenosis rate of 10–20%. This rate is higher in children who have had thermal injury to the posterior glottic stenosis. If a child has failed an endoscopic procedure, then open reconstruction is appropriate. Conversely, if a child has failed an open procedure, endoscopic management may be appropriate. In a recalcitrant airway, it is possible to place a second posterior costal cartilage graft if required.

Posterior glottic stenosis

Interarytenoid adhesion is a distinct variant of posterior glottic stenosis, with presentation similar to this condition or to bilateral true vocal cord paralysis. An interarytenoid adhesion results from prolonged intubation, when tongues of granulation tissue lying anterior to the endotracheal tube in the region of the vocal process unite in the midline to form a fibrous scar band. While this usually progresses to form posterior glottic stenosis, mucosal sparing of the posterior commissure sometimes occurs, resulting in the formation of an interarytenoid scar band (**Figure 31.7**). Endoscopic evaluation confirms a small posterior commissure air passage and a larger anterior glottic airway passage. However, there may be a marked limitation to the size of endotracheal tube that can be used for intubation if there is not a tracheotomy tube already present. Endoscopic resolution of this problem is simple and effective. In most cases, microlaryngeal scissors are used to excise the scar band, with immediate resolution of symptoms. In some children, this problem may coexist with either or posterior glottic stenosis.

Subglottic reconstruction

REPAIR TECHNIQUES

Anterior cricoid split

In the neonate who has failed extubation, the anterior cricoid split procedure is an alternative to tracheotomy (**Figure 31.8**). The criteria for anterior cricoid split are specified below:[18]

- failed extubation on at least two occasions
- weight >1500 g
- extubation failure secondary to laryngeal pathology
- no assisted ventilation for 10 days before evaluation
- supplemental O_2 requirement <35%
- no congestive heart failure for 1 month prior to evaluation
- no acute upper or lower respiratory tract infection at the time of evaluation
- no antihypertensive medication for 10 days before evaluation.

The procedure involves an anterior incision of the trachea from the second tracheal ring, up through the cricoid and into the lower third of the thyroid cartilage, just

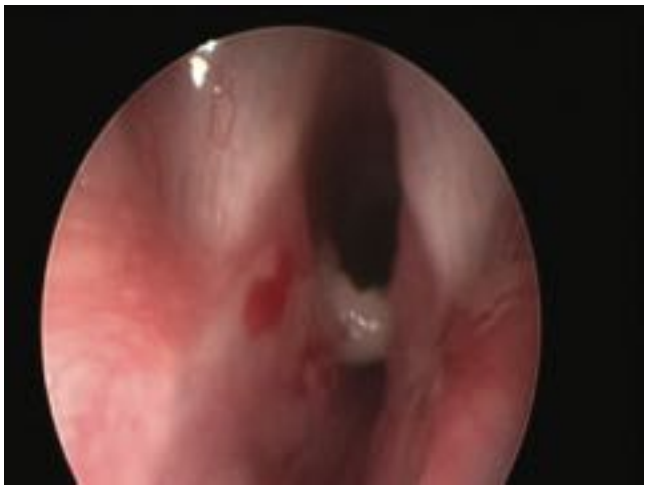


Figure 31.7 Interarytenoid scar band resulting from intubation trauma.

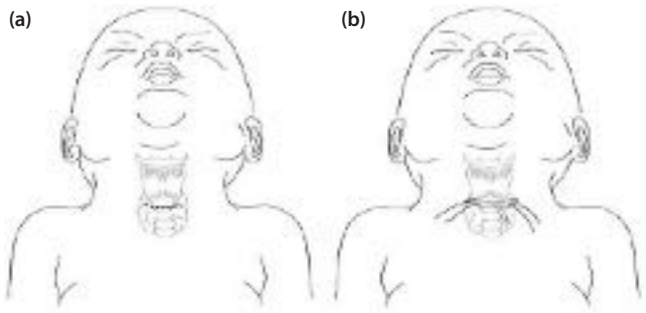


Figure 31.8 The anterior cricoid split procedure.

below the insertion of the anterior commissure. The child is then left intubated for 10 days, with the neck wound left at least partly open to minimize the risk of subcutaneous air build-up. A thyroid alar interposition graft is a modification that permits earlier extubation. It should be noted that while the success rates for this procedure were impressive in initial series, this rate has dropped over time, reflecting advances in neonatal care. Infants who failed extubation 30 years ago are no longer intubated due to the introduction of nasopharyngeal CPAP and high-flow nasal cannulae. Currently, infants requiring intubation and subsequently failing extubation are far more likely to be affected by extreme prematurity or to have other genetic or congenital comorbidities and, as a consequence, success rates for the anterior cricoid split are significantly lower.

Laryngotracheal reconstruction: anterior cartilage graft

Mild to moderate SGS is well managed with costal cartilage grafting to the anterior cricoid (see **Figure 31.3**).[19] The anterior airway is split from the tracheotomy site to the lower aspect of the thyroid cartilage. An age-appropriate sized endotracheal tube or suprastomal stent is then inserted, and a measurement is taken of the size of graft needed to comfortably close the deficit in the anterior airway. A costal cartilage graft is then harvested and carved

to allow a boat-shaped and perichondrium-lined insert to distract the anterior cricoid. An outer flange prevents graft prolapse into the airway. This technique is also useful for managing suprastomal collapse or narrowing of the upper trachea.

Laryngotracheal reconstruction: posterior cartilage graft

Costal cartilage grafting of the posterior cricoid for SGS may be performed in an identical fashion as for posterior glottic stenosis. If the anterior cricoid can then close comfortably over an appropriate sized endotracheal tube or stent, the additional anterior grafting is not required.

Laryngotracheal reconstruction: anterior and posterior cartilage grafts

If the anterior cricoid cannot comfortably close over an appropriately sized endotracheal tube or stent, then an additional anterior graft is required, as previously described. This is necessary for most grade III and all grade IV stenoses.

Cricotracheal resection

Cricotracheal resection (CTR) has an increasing role in the management of SGS. This procedure requires the removal of the subglottic scar tissue, with the anastomosis of healthy trachea to a healthy larynx. This is a technically more challenging operation than laryngotracheal reconstruction with cartilage grafts (**Figure 31.9**).

The success of CTR in infants and children has been documented in large series of patients in three separate centers.[20–22] The results reported are superior to those of the laryngotracheal reconstruction procedures for similar indications and stenosis grades. CTR with primary anastomosis is a safe and effective procedure for the treatment of severe SGS in infants and children. Diagnostic precision is essential, operative timing should be judged carefully, and operative technique must be precise. The reasons for the high success rate include the complete resection of the stenotic segment with restoration of a lumen using a normal tracheal ring, the preservation of normal laryngotracheal support structures without disruption of the cartilaginous framework, and full mucosal lining on both sides of the anastomosis, thus minimizing or preventing granulation tissue and restenosis.

The possible complications of the surgery, however, should not be underestimated. The first is injury to the recurrent laryngeal nerve. Typically, this nerve is not identified during the procedure as it lies posterior to the cricothyroid joint and the resection margin is anterior to the cricothyroid joint. The second complication is dehiscence of the anastomosis. This is most likely to happen if the operative site gets infected or if there is tension at the site of the anastomosis, or because of forceful reintubation if the endotracheal tube becomes dislodged. In the paediatric larynx, the technique of laryngeal release is not required in most cases of CTR. If mobilization of the trachea is difficult or tracheal resection is extensive (more than five tracheal rings), laryngeal release should be performed to minimize the risk of dehiscence. If granulation tissue is allowed to grow, there is also a risk of restenosis. For this reason, sutures through the cartilage should emerge submucosally at the edge of the anastomosis.

Experimental data in primates show that when CTR and primary tracheal anastomosis are performed with a good initial result, the thyroid cartilage and tracheal ring sutured together continue to grow normally. A further advantage of the CTR technique may be that voice quality should not deteriorate because the anterior commissure of the larynx is maintained in its initial position and there is no widening of the larynx posteriorly with an interposition graft. However, in older children, CTR may limit the ability to tilt the thyroid cartilage on the cricoid cartilage, in turn restricting cord tensioning and leading to a loss of vocal range.

Slide tracheoplasty

The slide tracheoplasty was originally conceived as an operation to expand a congenitally stenotic trachea due to complete tracheal rings[23] and is currently the operation of choice for the management of complete tracheal rings.[24] It is a versatile operation and may also be employed for patients with acquired laryngotracheal stenosis. Although originally described using an intrathoracic approach, a cervical approach allows access to the upper two-thirds of the trachea.[25] For patients with combined disease, if the associated SGS makes a graft to the anterior cricoid an option, then the lower trachea may be slid into the split anterior cricoid as an alternative to a costal cartilage graft.

The technique involves adequate exposure of the larynx and trachea, with the stenotic segment then being delineated by an assistant performing bronchoscopy (rigid or flexible) while the surgeon places a 30G needle into the airway. The proximal and distal aspects of the stenosis are marked on the anterior airway, and the length of the stenosis is measured. The trachea is then transected, typically with a bevelled transection commencing on the anterior trachea proximal to the midpoint of the stenosis, and extending over two rings distally, with the posterior transection point being at or just distal to the midpoint of the stenosis. The distal trachea is then split in the midline posteriorly to just beyond the stenosis, while the proximal trachea is split anteriorly to just beyond the stenosis – typically to thyroid cartilage. The most damaged and stenotic segment of trachea tends to lie at the midpoint of the stenosis, and this may be resected if desired. The trachea is then anastomosed with a double-armed PDS suture, typically a 4.0, with RB-1 needles in an older child or adult. A running suture technique is employed, with no attempt to keep the suture extraluminal but with care taken to tighten the running suture as the anastomosis is completed. A single proximal anterior knot completes the anastomosis. The airway is leak-tested and then sealed with fibrin glue, and the patient is typically extubated at the end of the procedure. While it is feasible to perform a slide tracheoplasty into the posterior cricoid, it is technically challenging, and the results are unpredictable. Because of this, it is not recommended.

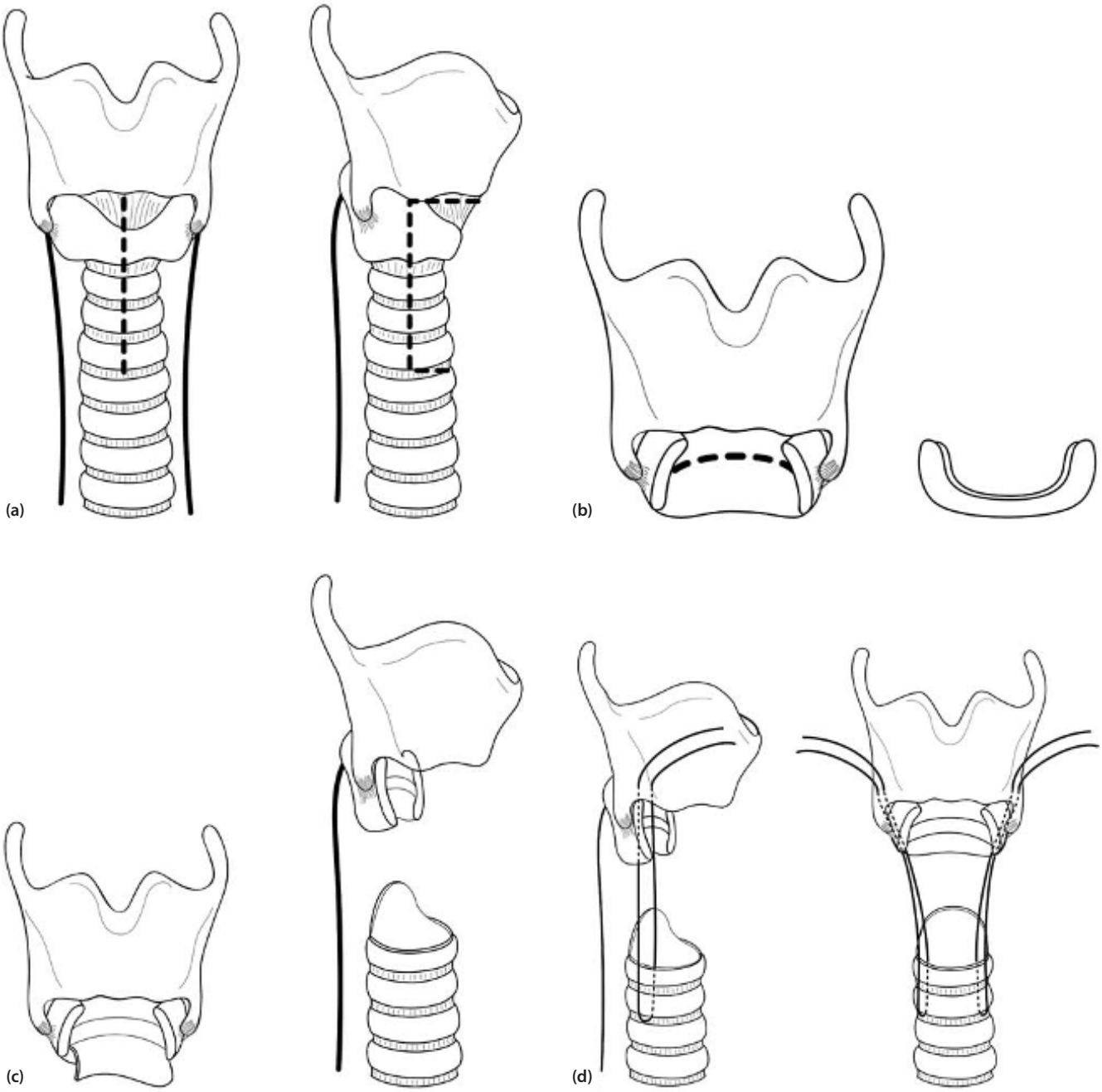


Figure 31.9 Cricotracheal resection.

(Continued)

CONTRAINDICATIONS

All contraindications to airway reconstruction are relative. Usually, airway reconstruction is not attempted unless decannulation is the goal. Gastro-oesophageal reflux disease and eosinophilic oesophagitis should be controlled pre-operatively, and pulmonary function optimized. Operating on a child requiring pulmonary pressure support to ventilate adequately is unwise. Single-stage reconstruction is inadvisable in a child who is difficult to intubate. In children with a history of sedation problems, past failure of airway reconstruction or multiple levels of airway pathology, single-stage reconstruction should be approached with caution. In children undergoing CTR, the risk of anastomotic dehiscence seems higher in the presence of Down syndrome, MRSA or a past history of distal tracheal surgery. The greatest disservice to a child is for airway reconstruction to cause or exacerbate ongoing aspiration.

COMPLICATIONS

Complications may be subdivided into intra-operative, early post-operative and late post-operative.[26] Intra-operative complications include bleeding, pneumothorax

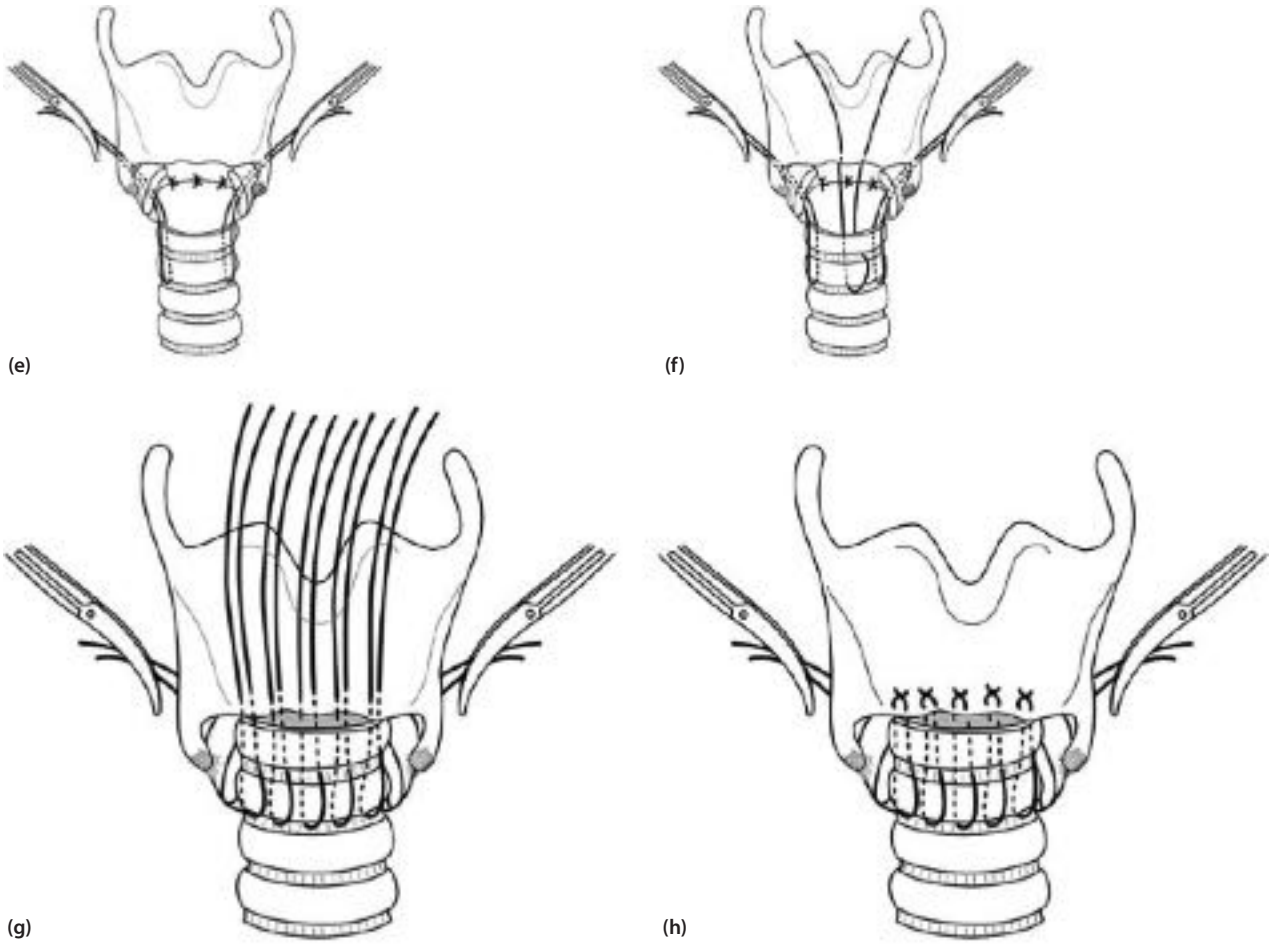


Figure 31.9 (Continued) Cricotracheal resection.

and loss of the airway with resultant hypoxia. Early post-operative complications include infection, air leakage from the operative site, dehiscence of an anastomosis and loss of a graft. The risk of air leakage and graft loss is highest when systemic steroid use is continued beyond two or three peri-extubation doses. With single-stage procedures there is a risk of accidental extubation and risks associated with paralysis or sedation. Extubation may be compromised because of glottic oedema and granulation caused by the endotracheal tube (Figure 31.10). The most significant long-term complication is failure of the reconstruction with restenosis of the subglottis, with an incidence between 10% and 20% in most series.

Revision airway surgery/ the recalcitrant airway

Failure of laryngotracheal reconstruction or CTR does not preclude further attempts at reconstruction but it may complicate further reconstructive efforts. In revision airway surgery, particular care should be taken to optimize the outcome by careful pre-operative evaluation of the patient and their airway. Failed expansion cartilage grafting may still be amenable to either further cartilage grafting or resection, while failed resection may still be amenable to further resection or cartilage grafting.



Figure 31.10 Large granulation arising on an anterior costal cartilage graft in the subglottis 3 days after extubation (10 days after surgery).

BEST CLINICAL PRACTICE

- ✓ In the neonate who has failed extubation, the anterior cricoid split procedure is an alternative to tracheotomy.
- ✓ Pre-operative evaluation of gastro-oesophageal reflux should be mandatory in a child with an active larynx or recalcitrant airway stenosis following previous reconstruction.
- ✓ Functional endoscopic evaluation of swallowing can provide valuable information about the risk and mechanism of aspiration as well as the presence or absence of normal laryngeal sensation.
- ✓ In a child who has not been evaluated previously, flexible nasopharyngoscopy with the child awake should be performed prior to rigid endoscopy.
- ✓ In children with significant lung disease, decannulation may be imprudent. Children with progressive neuromuscular disorders, diaphragmatic weakness or central hyperventilation syndrome may not be candidates for decannulation.
- ✓ In a child with a compromised airway who does not have a tracheotomy tube, pre-operative administration of dexamethasone, 0.5 mg/kg up to a maximum of 20 mg, is a prudent precaution.
- ✓ Spontaneous ventilation offers the best dynamic assessment of the airway and is thus recommended.
- ✓ In children in whom a stenting period of less than 2 weeks is anticipated, consider intubation, with the endotracheal tube acting as the stent (see 'Single-stage reconstruction').
- ✓ A prerequisite for single-stage laryngotracheal reconstruction is an excellent ICU in which staff are familiar with the management of airway patients.

FUTURE RESEARCH

- ➤ While laryngotracheal reconstruction and CTR have become accepted management techniques for SGS, supraglottic airway management remains poorly understood and managed.
- ➤ Pre-operative evaluation and optimization of patients prior to reconstructive airway surgery still requires refinement.
- ➤ Recent technological advances, such as impedance probe evaluation of gastro-oesophageal reflux, need critical evaluation.
- ➤ Balloon dilation of SGS is an area that would benefit from clinical and animal research to help formulate management guidelines.
- ➤ Paediatric voice research may be an area for future endeavour.
- ➤ An airway grading system that is not limited to just the subglottis needs to be developed.
- ➤ Tissue-engineering techniques may offer alternatives to current methods of airway reconstruction.

KEY POINTS

- The narrowest point in the infant airway is the cricoid ring. The only fixed ring within the airway, it is the most vulnerable point for iatrogenic damage caused by intubation.
- Acquired SGS secondary to prolonged endotracheal intubation remains the most frequent cause of laryngeal stenosis.
- Laryngeal stenosis continues to cause significant morbidity and mortality. The most common primary aim of intervention is decannulation or preventing the need for tracheotomy. In selected patients, voice restoration or provision of a safer airway is the primary consideration, with decannulation a secondary goal.
- Evaluation of the paediatric airway should not be considered a minor procedure, particularly when performed in a child with an unstable airway. Extreme care must be taken not to exacerbate the child's condition.
- Rigid endoscopy remains the gold standard for paediatric airway evaluation.
- SGS may be managed endoscopically in selected cases, with balloon dilation being the most effective tool.
- Laryngeal and upper tracheal reconstruction may be challenging; no single operation can address all types of laryngeal stenosis. It is prudent to evaluate each child on an individual basis.
- The most significant long-term complication of surgery for laryngeal stenosis is failure of the reconstruction with restenosis of the subglottis, with an incidence of 10–20% in most series.
- CTR has an increasing role in the management of subglottic stenosis. CTR is particularly effective as a salvage procedure following failed laryngotracheal reconstruction.
- The greatest disservice to a child is for airway reconstruction to cause or exacerbate ongoing aspiration.

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CHAPTER 32

JUVENILE-ONSET RECURRENT RESPIRATORY PAPILLOMATOSIS

Rania Mehanna and Michael Kuo

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed (NLM) search using the keywords: respiratory papillomatosis and laryngeal papillomatosis.

INTRODUCTION

Recurrent respiratory papillomatosis (RRP) is a potentially life-threatening disease characterized by the development of papillomata anywhere in the respiratory tract from the nasal vestibules to the terminal bronchi. Predominant sites are where there is a change of epithelium (e.g. from squamous to ciliated) and especially the tonsillar pillars, uvula, vocal folds and laryngeal commissure. There is a bimodal age distribution with a juvenile-onset peak occurring at 3–4 years of age and an adult-onset peak occurring at 20–30 years of age. A younger age at onset tends to reflect more aggressive disease. Boys and girls appear to be nearly equally affected in juvenile-onset RRP (JORRP). This contrasts with adult-onset RRP, which is a disease transmitted via sexual contact or via indirect contact with anogenital lesions, preferentially affecting men by a ratio of approximately 3:2. Although adult-onset respiratory papillomatosis and juvenile-onset respiratory papillomatosis share many features, this chapter addresses only JORRP.

AETIOLOGY

Juvenile respiratory papillomatosis was first described by Morrell Mackenzie in 1880. By 1923, Ullmann had demonstrated an infective aetiology by injecting homogenized papilloma from a child's larynx into his own forearm and inducing local growth of papillomas. Further direct evidence of the association between human papilloma virus (HPV) and RRP came from the identification of HPV DNA within laryngeal papillomas by Southern blot hybridization and the subsequent recognition in papillomas of HPV types 6 and 11.[1] Human papillomavirus is a naked, double-stranded, icosahedrally shaped virus with circular supercoiled double-stranded DNA genome surrounded by an outer capsid of protein that belongs to the papovavirus family. There are over 200 known subtypes of HPV – although many vary only slightly in their DNA sequence – but only types 6, 11 and rarely 16 are associated with RRP, with HPV 11 conferring a more aggressive course than HPV 6.[2] HPV types 6 and 11 are also associated with condyloma acuminata (genital warts). Types 16 and 18 have been implicated in carcinogenesis, particularly in the uterine cervix and in squamous cell carcinoma of the head and neck. HPV is thought to first enter traumatized epithelium and reside in the basal layer of the mucous membrane, where it replicates by a process known as episomal maintenance. This replication interferes with the normal process of cell maturation, causing epithelial proliferation and neovascularization. Conversely, the virus may lie dormant, causing subclinical infection, and can often be recovered from apparently normal tissue adjacent to papillomas. Viral protein, DNA synthesis and virion assembly only takes place in the granular and cornified layers of the terminally differentiated epithelium.

EPIDEMIOLOGY

Juvenile-onset RRP is an uncommon condition, with a prevalence of only 4 in 100 000 children. The oft-quoted triad of susceptibility factors for JORRP – young mother, vaginal delivery and low maternal socioeconomic status – is of limited predictive usefulness.[3] Latent or active HPV has been detected in cervical swabs from 10–25% of women of childbearing age. The associations between HPV, JORRP and a history of maternal genital warts are well established but what is uncertain is the influence, if any, these associations should have on obstetric management. HPV DNA has been found in one-third to one-half of aerodigestive tract swabs of children born to affected mothers. However, the majority of these children do not develop disease. Calculations suggest that only 1 in 400 infants delivered to women with genital warts subsequently develops JORRP. This relative risk is much lower than that for sexually transmitted diseases.

Although a history of maternal genital warts is not universal, a large retrospective study has shown that children born to mothers with genital warts carry a 231× relative risk of developing JORRP. A prolonged delivery time (exceeding 10 hours) conferred a twofold increased risk but delivery by Caesarean section did not appear to reduce that risk.[4] The clinical corollary of this is whether elective Caesarean section should be recommended for subsequent deliveries when one child has RRP. The overwhelming majority of children born to women with HPV do not develop RRP. In addition, many individuals with HPV in the tissues of the respiratory tract never develop papillomas. Additional host factors, such as immunological or genetic ones, determine the development of RRP in individuals with HPV. Other factors such as timing, length and volume of exposure to the HPV also play a role.[5] The evidence for protection from vertical transmission of HPV into the baby's upper respiratory tract by Caesarean section is conflicting and therefore the decision on method of delivery must be made on a case-by-case basis. Current evidence does not warrant Caesarean section as a prophylaxis against RRP.

Variation in the susceptibility of the host to viral infection may be associated with specific HLA polymorphisms, several of which have been reported. Two recent, large independent studies have shown an association between HLA-DRB1*0301 and severe disease.[6, 7] T-cell responses were shown to be the same by one group between HLA-DRB1*0301-positive patients and negative controls, leading to speculation that the clinical severity of disease is due not to a failure of T-cell proliferative response to HPV but a delay in that response due to a low frequency of HPV-specific T cells or modulation of the T-cell response by immunoregulatory networks.[7] Bonagura et al.[6] showed that HLA-DRB1*0301-positive patients exhibited reduced interferon-gamma expression. While the associations between JORRP and HLA-genotype are being increasingly well recognized, the underlying mechanism for evasion of the cellular immune response is far from clear.

CLINICAL PRESENTATION

Although respiratory papillomas can arise in any respiratory mucosa, their initial presentation is usually in the larynx. The diagnosis requires the surgeon to have an awareness of the condition as the presenting symptoms can be variable and mimic many common laryngeal and respiratory pathologies in children. In addition to hoarseness and stridor, children may present with a chronic cough, paroxysms of choking, recurrent respiratory infections or failure to thrive. These latter symptoms may lead to a misdiagnosis of asthma, laryngitis, bronchitis or croup and a delay of diagnosis of JORRP of up to 8 years.[1]

DIAGNOSIS

If at all possible, the clinical diagnosis should be established with awake fibre-optic nasolaryngoscopy (using an infant 2.2 mm or 2.7 mm endoscope) because the difficulties presented to the anaesthetist by unexpected laryngeal papillomas prolapsing into and obstructing the glottis cannot be overstated.[8–10] The preferred anaesthetic technique in our institutions is that of spontaneous respiration without endotracheal intubation. General anaesthesia is induced either by intravenous propofol or, more frequently, by inhalation of sevoflurane in oxygen. The larynx is topically anaesthetized with 2% lidocaine and anaesthesia maintained by sevoflurane in oxygen through a nasopharyngeal airway, of a size and length appropriate for the child's age. This allows excellent surgical access to the airway but carries the disadvantage that the lower airway is not directly protected from bleeding. Meticulous haemostasis is therefore required during the procedure using topical epinephrine (1:10 000 applied on neurosurgical patties). Regardless of the surgical technique, it is important for the child to recover from anaesthesia with humidified oxygen. Many units use pre-operative dexamethasone to reduce laryngeal oedema but some surgeons feel that anti-inflammatory agents are best avoided during active manipulation of papilloma tissue. Laryngopharyngeal exposure to gastric acid is increasingly being recognized as a cause of laryngeal pathology. This is particularly relevant during the immediate post-operative period where laryngeal mucosa has been breached.[11] Therefore it is our practice to give prophylaxis against gastro-oesophageal reflux with an H_2-antagonist or a proton pump inhibitor for 48 hours after all laryngeal surgery, including surgery for JORRP.

Macroscopically, papillomas can be pedunculated or sessile, spread over the mucosal surface of the larynx (**Figure 32.1**). They tend not to be friable and can be grasped using microlaryngeal instruments and excised for histological examination. Microscopically, the papillomas appear as exophytic projections of keratinized squamous epithelium overlying a fibrovascular core, with varying degrees of dyskeratosis, parakeratosis and dysplasia. Koilocytes (vacuolated cells with clear cytoplasmic inclusions) are often seen indicating viral infection.

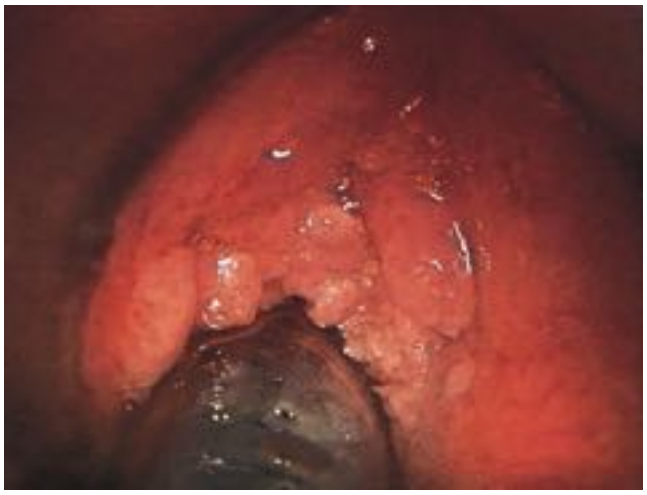


Figure 32.1 Recurrent respiratory papillomatosis in the larynx.

STAGING

Staging of disease is not universally undertaken even in units with a large caseload of RRP. The staging system proposed and modified by Derkay (Figure 32.2)[12, 13] is based on a combination of the anatomical distribution and extent of lesions and their clinical effects on voice and the child's airway. It is increasingly used by members of the American Society of Pediatric Otolaryngologists (ASPO). Widespread adoption of a universally agreed staging system would enable comparison of results between centres and facilitate multicentre trials, particularly of adjuvant treatments.

For each site, score as:
0 = none, 1 = surface lesion, 2 = raised lesion, 3 = bulky lesion

Larynx	
Epiglottis:	Lingual surface _____
	Laryngeal surface _____
Aryepiglottic folds:	Right _____ left _____
False vocal folds:	Right _____ left _____
True vocal folds:	Right _____ left _____
Arytenoids:	Right _____ left _____
Anterior commissure	_____
Posterior commissure	_____
Subglottis	_____
Trachea	
Upper one third	_____
Middle one third	_____
Lower one third	_____
Bronchi:	Right _____ left _____
Trachotomy stoma	_____
Other	
Nose	_____
Palate	_____
Pharynx	_____
Oesophagus	_____
Lungs	_____
Other	_____
Total score all sites	_____

Figure 32.2 Derkay staging for RRP.[12]

TREATMENT

The aim of surgical treatment is the removal of papillomas and restoration of a safe and patent airway while minimizing trauma to the mucosa and vocal cords. Risk of scarring and webbing can be reduced by the avoidance of two opposing raw surfaces, especially at the anterior commissure. In children requiring repeated extirpations of extensive papillomas, especially if they predominantly occur in the larynx, it may be ultimately impossible to achieve normal voice. Though the papillomas do not extend beyond the basement membrane, there is often inevitable inadvertent damage to surrounding tissues.[14] It is in these patients that the surgical technique, balance of the extent of lesion removal against interval timing, and application of adjuvant therapies must be combined and finely judged to ensure minimal dysphonia and airway stenosis, both of which can be extremely difficult to manage. No single treatment modality is better than another. The heterogeneity of the disease and its natural history is reflected in one series of 118 patients who underwent surgical management for their JORRP; the total number of operations per patient ranged from 2 to 402.[15]

Surgical treatment

POWERED MICRODEBRIDER

The use of the powered microdebrider is a relatively new development in the surgical removal of laryngeal papillomas, but one which has become the gold standard for papilloma removal in the larynx (Figure 32.3).[16] A non-serrated laryngeal blade is used with a setting of 300–700 rpm which allows the papillomas to be suctioned into the debrider with minimal cutting trauma to surrounding normal tissues. The laryngeal debrider blade allows gentle but comprehensive removal of papillomas with minimal contamination of the lower respiratory tract with blood or papillomas. There is no thermal trauma and, using direct endoscopic control, it is extremely precise with minimal mucosal damage. Small retrospective studies demonstrate that, compared with the CO_2 laser, patients undergoing laryngeal papilloma debridement have good disease clearance, require a shorter procedure and experience less post-operative pain. One retrospective study showed no incidence of delayed soft-tissue complications using the microdebrider.[17–20]

COLD STEEL SURGERY

Advocates of papilloma removal using microlaryngeal instruments claim that the use of a microflap technique minimizes trauma to the vocal fold while satisfying disease clearance. Thermal damage to neighbouring tissue is also avoided, as is the vapour plume. Cold steel surgery has

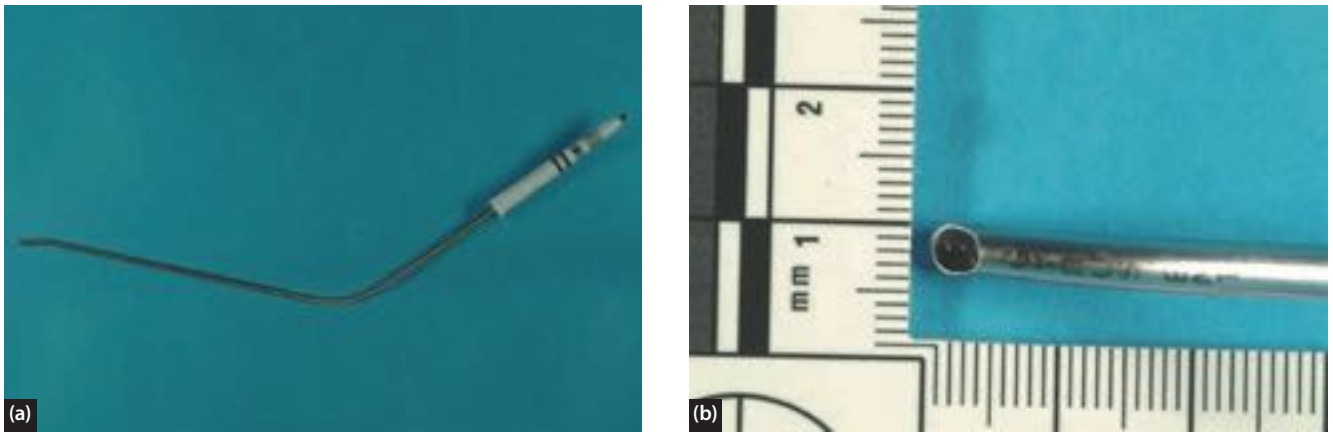


Figure 32.3 (a) Microdebrider; **(b)** close-up of blade.

the distinct disadvantage of having no direct haemostasis when dealing with a very vascular lesion. Nevertheless, such surgery is successful in the hands of the exponents of this technique.

CO_2, KTP, ND:YAG AND PULSED DYE-LASER

The carbon dioxide (CO_2) laser has been, for many years, the mainstay of surgical management of JORRP. It remains the treatment of choice for many surgeons because of its ability to ablate the papillomas with minimal bleeding and its ease of use with a microscope and micromanipulator. However, the frequency of late soft-tissue complications, such as vocal fold fibrosis, interarytenoid fibrosis and stenosis, glottic webbing and arytenoid fixation, has been reported to be 13–45%.[8, 21, 22] This increases with frequency of treatment and the number of laser ablations the child has received. Soft-tissue complications can be minimized by appropriate laser settings and careful assessment of depth of ablation. A Japanese group has suggested, based upon a single case, a two-stage procedure whereby the bulk of the papillomas are removed at the first operation, which is then followed by a repeat endoscopy and laser ablation 10 days later, by which time the coagulum and carbonized tissue have resolved, allowing a more precise laser clearance of residual papillomas.[23] It is also important to have an effective plume extractor. This serves to allow a clearer image of the larynx, but also removes the potentially infectious laser vapour plume which carries a significant viral load. The latter may be simple conjecture as there has only been one reported case of a surgeon developing laryngeal papillomas with a history of repeated laser treatment to a patient with anogenital condylomas, *in situ* hybridization showing HPV types 6 and 11 in both the patient's and his lesions.[24]

The KTP laser and the Nd:YAG laser are as effective as the CO_2 laser in papilloma ablation and haemostasis but, in addition, can be delivered through an optical fibre. Fibre-delivered laser systems play a role predominantly in the treatment of tracheal and bronchial papillomas. A new fibre-guidance system with a bendable distal tip developed for the Nd:YAG laser achieves a 50° range of directional manoeuvrability with minimal power loss.[25] In adult patients, the delivery of pulsed-dye laser through a flexible bronchoscope can render it an outpatient procedure.[26]

The advantages of the pulse-dyed laser are that it can be fibre-delivered and causes minimal vocal-fold fibrosis and consequently minimal voice damage. However, it also distinguishes itself from the other forms of laser treatment in its mode of action. Rather than direct vaporization of tissue, it has been proposed that the 585 nm pulsed-dye laser is a vascular laser which causes photoangiolysis of sublesional microcirculation, denaturation of epithelial basement membrane linking proteins, and cellular destruction.[26] Therefore, it is less effective against large exophytic lesions and can be used as an adjunct to surgery either before or after the laser application.[27] The application of the pulsed-dye laser in the paediatric population is still under evaluation, but the results in adults with recurrent respiratory papillomatosis are very encouraging.

Photodynamic therapy

Photodynamic therapy (PDT) relies upon the observation that rapidly proliferating tissue selectively takes up a number of photosensitizing agents when administered intravenously, and that these agents release tumouricidal oxygen derivatives when activated by laser light of the appropriate wavelength. A non-blinded randomized prospective trial using dihaematoporphyrinether (DHE) at two different doses in combination with 50 J of 630 nm argon laser light was compared with laser treatment alone. The patients remain photosensitive for 6–9 months and may experience skin erythema, blistering and ocular discomfort. Patients on the higher dose of DHE (4.25 mg/kg body weight) were reported to show a significantly larger decrease in papilloma growth rate but, despite that, only approximately half of the 48 patients receiving DHE showed a response, and no response was seen in patients previously treated with PDT.[28] A further randomized trial by the same group using meso-tetra (hydroxyphenyl) chlorin (mTHPC) as a photosensitizer showed reduction of severity of laryngeal papillomas in the mTHPC group, but this was not maintained and there was no effect on tracheal disease.[29] It should be noted that this trial recruited only 23 patients,

of whom only 15 completed the study. In both trials, there was a combination of juvenile-onset and adult-onset patients.

Coblation®

Coblation® is a minimally invasive low-heat technology that delivers a plasma layer to dissolute target tissue while maintaining the integrity of surrounding tissues. The wands (**Figure 32.4**) are designed to function at temperatures as low as 40–70 degrees Celsius (°C), thus minimizing rapid heating, charring or burning. In comparison, commonly used bipolar devices function at temperatures of approximately 400 °C. There are very limited data on the use of Coblation® for JORRP, with most of the literature being case reports or retrospective results on small number of patients.[30, 31] A recent cross-sectional study in the United Kingdom showed that Coblation® procedures accounted for 3% of interventional treatment conducted in the UK RRP population.[32]

Adjuvant therapy

Adjuvant medical therapies can be broadly divided into antiviral therapies and drugs with antiproliferative or immunomodulatory properties.[33–35] The decision to implement adjuvant therapy must depend on a careful consideration of the benefits against potential adverse effects of the therapy.[36] Adjuvant therapies which have been described in isolated case reports have been included for reference because, while their use in 'routine' cases may not be justified, one may wish to consider their use when other better-tested avenues are exhausted.

INTERFERON-α

Interferons are naturally produced by human leucocytes although, as a pharmaceutical, interferon is now produced via recombinant DNA technology. Interferon-α can claim to have antiviral, antiproliferative and immunomodulatory properties. Interferons exert an indirect antiviral action by interfering with normal host cell translation mechanisms and by inducing synthesis of intracellular enzymes that act to control viral growth. By depleting essential metabolites in papilloma cells, interferon-α increases the length of their multiplication cycle, thereby slowing target cell growth. Interferon-α also facilitates recognition of papilloma cells by circulating leucocytes by enhancing expression of cell surface antigens. It is administered systemically by subcutaneous injection at a dose of 2–5 MU/m^2 of body surface area.[37] It is the most well studied of the adjuvant therapies for JORRP. A large randomized trial of 123 patients showed significant reduction in papilloma growth rate within the interferon arm. However, this was only significant for the first 6 months and the difference was not statistically significant during the second 6 months.[37] In another randomized crossover trial of 66 children, there was significant reduction in disease bulk in the interferon arms of the trial.[38] This was extended to longer follow-up, at which data on 60 children were still available, showing complete remission in 22 children, partial remission in 25 patients and no response in 13.[39] The main problem preventing more widespread use of interferon-α is that there are many serious, idiosyncratic and unpredictable side effects including pancytopenia, hepatorenal failure and cardiac dysfunction. There is also a rebound phenomenon associated with withdrawal of the drug therapy. There is anecdotal evidence of the use of intralesional interferon in combination with laser debulking of JORRP, but this has not found widespread use.[40]



Figure 32.4 PROCISE laryngeal Coblation® wand (courtesy of Smith & Nephew).

BEVACIZUMAB

Bevacizumab (Avastin) is a recombinant monoclonal antibody that inhibits angiogenesis (VEGF-A). It is licensed for use in a wide range of metastatic cancers. Trials involving small numbers of patients with recurrent respiratory papillomatosis have shown promise both by systemic and intralesional administration. A series of five patients treated with systemic bevacizumab responded dramatically with 18 surgical interventions being required in the 12 months prior to treatment and only one in the 12 months following treatment.[41] Usually administered at a concentration of 2.5 mg/mL for three consecutive injections at 2–3 week intervals, it can be used in conjunction with cidofovir (see below) and/or the KTP laser. Early studies report an increased time interval between operations, and thus a reduced number of procedures per year. They also report improved voice quality of life when using the Paediatric Voice-related Quality of Life (PVRQOL) score.[42]

CIDOFOVIR

Cidofovir is an acyclic nucleoside phosphonate which is active against a broad spectrum of DNA viruses including cytomegalovirus, Epstein–Barr virus and HPV. Its mechanism of action is by inhibition of viral DNA polymerases essential for viral replication. The principal application of this drug has been in the treatment of cytomegalovirus (CMV) retinitis in human immunodeficiency virus (HIV)-infected patients by intravenous injection. This mode of administration and high doses is associated with neutropenia and nephrotoxicity. Intralesional injection

of cidofovir in JORRP is not associated with similar side effects. A canine model has shown that local irreversible soft-tissue damage could be avoided in twice weekly cidofovir injections if the dose is limited to below 40 mg/mL.[43, 44]

Based on their animal work, Chhetri and Shapiro[45] have proposed a schedule for treatment of JORRP based on intralesional injections of cidofovir at a concentration of 1 mg/mL. Injections were given at 2-weekly intervals for four treatments and then the interval between treatments extended by 1 week after each and every subsequent treatment. Concomitant laser surgery was reserved for bulky lesions. Five patients were treated with this schedule with a mean follow-up time of 66 weeks. The mean papilloma stage decreased from 9.2 at initial presentation to 3.4 within 2 weeks of the first injection, and continued to decrease for the remainder of the follow-up period. After 9 weeks of treatment, no patients required further laser surgery. The authors counsel caution that the potential long-term carcinogenic effects of cidofovir are unknown and a 'response' may be related to the natural history of the disease.[46]

In vitro studies have shown that the use of cidofovir raised the HPV E6 RNA levels by 8-fold in low-risk and 20-fold in high-risk E6 expressing HPV cervical cancer cells.[47] A cross-sectional study incorporating adult and paediatric laryngeal surgeons found that the incidence of upper aerodigestive tract cancers was not significantly increased in patients in whom cidofovir was deployed. Thus, the RRP Task Force recommended that intralesional cidofovir should be considered in patients with RRP that require surgery at less than 3-month intervals, with regular biopsies. Administration should remain below the established safe dose of 3 mg/kg. In all cases, informed consent must be obtained including off-label use and possible side effects.[48] A recent meta-analysis by Fusconi et al.[14] looked at all published data using cidofovir as an adjuvant treatment option for RRP since 1998. It looked not only at the concentration of cidofovir used and the response rate, but also at the incidence of dysplasia secondary to cidofovir injections. There still appears to be no consensus on the ideal dose, frequency of administration and duration of cidofovir treatment. Importantly, there was no evidence that cidofovir promotes evolution towards dysplasia even after cumulative doses.[14]

RIBAVIRIN

Ribavirin is a synthetic nucleoside which has activity against a broad spectrum of viruses, but which is principally used as an aerosol in the treatment of respiratory syncytial virus pneumonia and systemically in the treatment of hepatitis C. There have been reports of its use both as an aerosol and systemically.[49–51] However, these remain anecdotal reports and ribavirin is not widely used as an adjuvant treatment of JORRP.

ACYCLOVIR

The evidence on the efficacy of acyclovir is weak and conflicting.[52, 53] Although HPV is a DNA virus and acyclovir has a medium spectrum of antiviral activity, it does not directly inhibit HPV. Acyclovir is a nucleoside analogue, which inhibits thymidine kinase, which is present in herpes simplex viruses (HSV) but not HPV. Adult patients, but not paediatric patients, with RRP have been shown to have molecular evidence of coinfection with other viruses, particularly HSV, which may have a potentiating effect on HPV. It has been suggested that the mechanism of action of acyclovir is to eradicate HSV, thus removing this synergism. Side effects are rare and include nausea, vomiting, diarrhoea, fatigue and headache.

INDOLE-3-CARBINOL

Indole-3-carbinol is a substance derived from cruciferous vegetables (e.g. cabbage, broccoli, cauliflower, brussels sprouts), which has been shown to alter growth patterns of JORRP cell cultures *in vitro*. It affects oestrogen metabolism, shifting production to antiproliferative oestrogen. A prospective observational study with a mixed adult and paediatric population who received indole-3-carbinol as an adjunctive treatment to surgical removal showed partial or total responses in 21 of 33 patients. Within the paediatric subgroup, four out of nine showed partial or total response with no evident side effects.[54]

CIMETIDINE

Cimetidine – a histamine receptor type 2 (H2) antagonist – has been reported as a useful treatment for cutaneous warts. It has also been successfully used in treatment of an 11-year-old boy who had an 8-year history of diffuse conjunctival papillomas. The mechanism for this is attributed to immunomodulatory side effects of cimetidine at high doses. There is a single case report of very advanced JORRP with tracheobronchial-pulmonary involvement being treated successfully with adjuvant cimetidine at a dose of 40 mg/kg for 4 months with remarkable improvement.[55]

NATURAL HISTORY

The natural history of RRP is extremely variable. This makes it difficult for the surgeon to be able to reliably counsel the anxious parents on how their child's pathology will behave or at what age they might expect remission. Pathologically, severe disease is strongly associated with HPV-11 infection and thus patients should have viral typing as part of their initial pathology workup. Poor prognostic signs include onset of disease before the age of 3 years, and birth by Caesarean section. In the United States, Medicaid insurance – often seen as a proxy measure of low socioeconomic status – is also associated with severe disease.[56] However, there are no other studies showing correlation between socioeconomic status and disease severity. Most affected children require debulking of papillomas at 2–3-month intervals during periods of disease activity. Severe disease may necessitate weekly surgical intervention to prevent

airway obstruction from rapidly growing papillomas. The median number of debulking procedures required in a patient is reported to be 7–13.[57, 58] Not surprisingly, the repeated debulking of laryngeal papillomas results in chronic voice changes.

There is a tendency for remission in the early teenage years and this has been attributed to hormonal changes occurring with the onset of puberty. Interestingly, women with adult-onset RRP commonly experience severe exacerbations of their disease during the hormonal fluctuations of pregnancy. What is clear is that remission is not related to the clearance of HPV from the mucosa as viral DNA is detected in previously affected mucosa in patients in remission as well as in normal mucosa of patients with active disease.[59]

TRACHEOBRONCHIAL DISEASE

Extralaryngeal spread of JORRP beyond the larynx occurs in approximately one third of patients, with spread to the trachea in approximately one quarter of patients. Tracheal involvement may appear as cobble-stoning of the mucosa coupled with the presence of papillomas. Factors predisposing to tracheal spread include the presence of subglottic papillomas, presence of a tracheostomy and a long duration of disease.[60] More distal bronchopulmonary involvement is reported in 4–11% of children with long-standing disease and may result in obstructive pneumonias.[37] Patients may develop cavitary pulmonary lesions leading to fever, sepsis and pulmonary atelectasis. Radiographically, these lesions may appear as solid or cystic pulmonary masses (**Figure 32.5**).[61] A high index of suspicion must be maintained for malignant degeneration of bronchopulmonary lesions.



Figure 32.5 Chest radiograph showing extensive pulmonary involvement with papilloma.

TRACHEOSTOMY

The indications for tracheostomy in patients with JORRP continue to divide clinicians. The source of this debate is that tracheostomy essentially constitutes an iatrogenic squamociliary junction and may present an additional area of predilection for papillomas.[62] There is anecdotal evidence that tracheostomy may promote extensive tracheobronchial 'seeding' of disease. However, it is not universal that all patients with a tracheostomy develop either stomal papillomas or tracheobronchial disease. Tracheostomy is very much a last resort but in patients with severe disease it may be life-saving. It may also facilitate a longer interval between debulking procedures to restore some normality to the child's life.

MALIGNANT DISEASE

Malignant degeneration of papillomas is a rare but devastating sequel. It is universally fatal.[61] There is a higher incidence of invasive carcinoma ex-papilloma in children with a younger age of onset (2 vs 6 years old; $P = 0.009$) and those with tracheal involvement.[63] Irradiation of papillomas dramatically increases the risk of malignant transformation but as this is no longer used as a treatment modality, it is of only historical relevance. Most instances of malignant transformation have been reported in adult patients and have been associated with other risk factors including tobacco use and long-standing disease. Malignant transformation appears to be more likely with HPV 16, an unusual cause of JORRP, but HPV 6 and HPV 11 have been shown to oncogenically transform cell culture lines *in vitro*. In adults, malignant degeneration usually involves the larynx, unlike children where cancer usually develops in the bronchopulmonary tree.

Approximately 20 paediatric cases of malignant degeneration have been reported, all of which have been fatal. The currently proposed mechanism of malignant transformation involves oncoproteins E6 and E7. HPV types 6 and 11 produce transforming oncoproteins E6 and E7 that have been implicated in growth dysregulation through their ability to inactivate the tumour suppressor proteins p53 and the retinoblastoma tumour-suppressor gene product (pRb). The inactivation of the tumour suppressor genes results in a loss of control over proliferation and cell division and contributes to the development of the malignant phenotype. It is also becoming clear that the E6 and E7 proteins function to promote tumorigenesis through direct interactions with cell-cycle regulatory proteins.[64] Unfortunately, apart from closer clinical and radiological surveillance particularly in children with tracheal and/or pulmonary disease, there is little to aid the clinician in predicting the rare cases of malignant transformation.[65] There is no evidence of a papilloma–carcinoma sequence while *p53* overexpression is variable and not a marker of malignant transformation.[64] HPV expression may be lost in malignant transformation but this may not be a sufficiently robust clinicopathological predictor.

VOICE MORBIDITY

Although there are numerous papers on the various treatment on options for JORRP, there are limited data on the vocal outcomes of these patients. The majority of data are based on adult-onset RRP looking at voice both due to the papillomas themselves and the resultant morbidity of multiple surgical procedures. Well-recognized voice assessment scales include the GRBAS (grade, roughness, breathiness, asthenia and strain) scale, the Voice Handicap Index (VHI), Short-Form 36-Item Health Survey (SF-36).[66]

Objective assessment of voice by GRBAS scale and Visi Pitch II 3000 acoustic analysis has shown significant difference between JORRP patients in remission and normal controls, but a Voice-related Quality of Life Questionnaire (V-RQoL) showed that the dysphonia does not have any impact on quality of life.[67]

A high number of surgical procedures correlates with a poorer voice in acoustic analysis using the GRBAS. This was statistically significant for grade. Interestingly, Ilmarinen et al. showed no statistical significance in VHI score. When comparing post-op acoustic voice parameters, patients treated with the microdebrider appeared to have lower scores for jitter, shimmer and perceptual scores, thus indicating a better voice outcome with the microdebrider when compared to the CO_2 laser. Increased frequency of interventions using the CO_2 laser is associated with poorer voice quality.[66, 68]

VACCINATION/PREVENTION

There are currently two HPV vaccines, Cervarix® and Gardasil®. These vaccines contain no live virions and are thus incapable of causing an infection, but they are designed to induce an antibody response. Cervarix® is bivalent vaccine against HPV 16 and 18. Gardasil® is a quadrivalent vaccine against HPV 6, 11, 16 and 18 containing virus-like particles of the L1 protein of the four strains. The vaccination schedule comprises three intramuscular injections: the initial dose, 2 months later, and finally 6 months after the initial injection. More recently, Gardasil® has been enhanced to a nonavalent vaccine (HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58). Ideally, the vaccine should be given to young boys and girls, from the age of 9 years old, prior to them becoming sexually active, thus reducing the spread of HPV and its sequelae in the general population.

Australia was the first nation to introduce a nationwide government-funded vaccination programme in 2007, directed towards the eradication of cervical cancer. Vaccination resulted in a statistically significant decrease in the prevalence of HPV 6, 11, 16 and 18 in cervical samples in the post-vaccination period (2010–2011) as compared to the pre-vaccination period (2005–2007).[69] Much interest has been directed at evaluating the use of HPV vaccination in influencing the clinical course of RRP. Only one study explored this in an entirely juvenile-onset population. There was no change in the clinical or anatomical scores, the number of relapses or the intervals between surgeries before or after vaccination with Gardasil®.[70] Other studies involving juvenile-onset and adult-onset patients have shown more promising results. Albeit involving small numbers of patients, these studies have demonstrated both a clinical and an immunological response to quadrivalent HPV vaccine, suggesting vaccination may have both a preventive and a therapeutic role.[71, 72]

BEST CLINICAL PRACTICE

- ✓ Current evidence does not warrant Caesarean section as a prophylaxis against RRP.
- ✓ Ideally, the clinical diagnosis should be established with awake fibre-optic nasolaryngoscopy prior to general anaesthesia.
- ✓ Patients should have viral typing as part of their initial pathology workup.
- ✓ The powered microdebrider is the 'gold standard' for papilloma removal in the larynx.
- ✓ Spread to the tracheobronchial tree is associated with a greatly worsened prognosis.

FUTURE RESEARCH

- ➤ JORRP has a great impact on the child's life during active disease and constitutes a big surgical load for the surgeon. While the majority of patients enjoy spontaneous remission, a small number continue to develop distal disease which may be fatal. Improvement in surgical technologies have reduced operative time and improved operative morbidity.
- ➤ There is consistent level 3 evidence that cidofovir extends the treatment interval and promotes remission of disease. Consolidation of this evidence will require multicentre collaboration in order to standardize protocols and increase patient recruitment. Such a multicentre initiative has already been proposed to seek critical genes in the pathogenesis of RRP.[73]
- ➤ The future of the management of RRP lies in a better understanding of its pathogenesis.
- ➤ Trials for the HPV vaccine have yet to demonstrate any therapeutic efficacy for children with established RRP while immunological and clinical benefit has been shown in pilot studies in adults. Longitudinal studies will also be needed to explore the impact of HPV vaccination on the pathogenesis of RRP in a preventative role, as with cervical cancer.
- ➤ Despite extensive and sophisticated molecular immunology research, the precise relationship between the human papilloma virus, host immunity and the development of papillomas eludes us. The elucidation of this relationship holds the key to conquering this disease.

KEY POINTS

- Juvenile respiratory papillomatosis can affect any part of the respiratory tract.
- While it is uncommon, its management can constitute a major surgical burden to the otolaryngologist.
- The mainstay of treatment is by surgical debulking.
- The role of adjuvant therapy is uncertain but supported by level 3 evidence.
- In the majority of cases, the disease goes into spontaneous remission.
- Some children develop uncontrolled disease, which in rare cases may be fatal.

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CHAPTER 33

PAEDIATRIC VOICE DISORDERS

Ben Hartley and David M. Wynne

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: paediatric, voice and dysphonia.

INTRODUCTION

There have been tremendous advances in the understanding of voice disorders and their management in recent years. The subspecialty of phoniatrics has evolved principally in adults and this knowledge may now be applied to voice disorders in children. Disorders of voice – where the predominant symptom is hoarseness or 'dysphonia' – must be distinguished from disorders of speech, articulation and language. Speech and articulatory disorders are characterized by difficulty in producing speech sounds, often in the presence of normal laryngeal function. In language disorders, the child uses words and sentences inappropriately, again usually despite normal laryngeal function.

Voice disorders are largely a manifestation of laryngeal pathology. Six to 23 percent of 5–18 year olds have some form of voice 'problem'.[1, 2] In school aged children 6–9% of children have been reported to have a voice disorder.[3] Actual prevalence rates are thought to be higher as many children present directly to speech and language therapy rather than direct to paediatric otolaryngology.[4] In the UK it is estimated that the prevalence is around 6% when perceptual evaluation was undertaken by speech and language therapy and around 11% based on parental reporting.[5, 6]

The identification and subsequent management of paediatric voice disorders is important. Paediatric dysphonia may negatively impact on a child's education, emotional and psychosocial development.[7, 8]

In adults the European Laryngological Societies (ELS) recommend evaluation of five parameters of voice, namely perceptual evaluation, videostroboscopic evaluation, aerodynamic performance, acoustic analysis, impact.[9] In children there is still much debate on the 'minimum' level of evaluation, especially if laryngoscopy requires general anaesthesia.[5, 6]

The spectrum of voice disorders seen in a specialist paediatric voice clinic is very wide. Patients range from child performers who have a normal conversational voice but whose parents have been concerned about a loss of the upper range of their singing voice, to children with severe congenital or acquired laryngeal disease with no voice at all.[6]

With careful assessment, voice therapy and occasionally surgical intervention, most paediatric dysphonias can be corrected or improved.

GROWTH AND DEVELOPMENT OF THE LARYNX

The paediatric larynx is quite different from that of the adult (**Figure 33.1** and **Table 33.1**). The embryonic development of the larynx is described in detail in Vol 3, Chapter 58, Anatomy of the larynx and tracheobronchial tree. This section focuses on those aspects relevant to voice disorders and on normal growth and development after birth. Current knowledge stems largely from the detailed studies of Hirano et al.[10, 11]

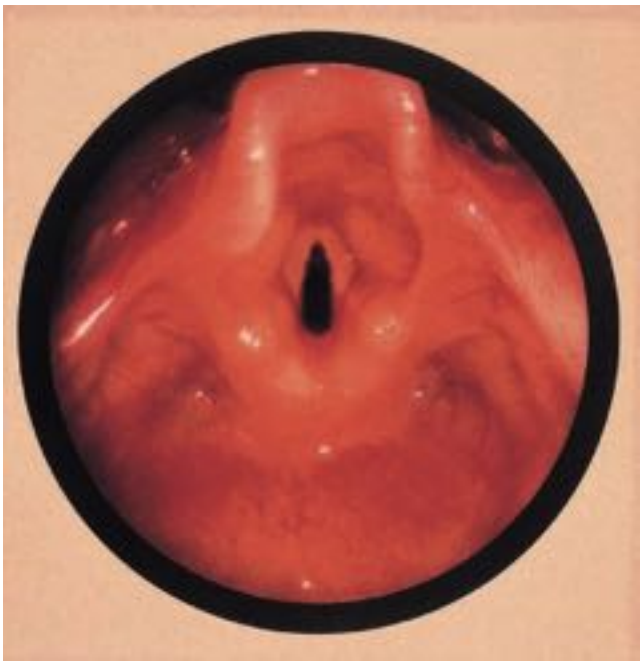


Figure 33.1 Normal larynx in a 6-month-old child.

TABLE 33.1 Differences between the larynx of an adult and child

Feature	Difference
Size	The paediatric larynx is relatively smaller
Position	The child's larynx is relatively higher
Shape	Curled epiglottis, shorter vocal folds
Mucosa	More reactive and prone to airway obstruction Croup is uncommon in adults
Laminar vocal fold structure	Immature in young children

Elongation of the vocal folds

Hirano found that up to the age of 10 years, the length of the vocal fold was very similar in both males and females (6–8 mm). At puberty there is a substantial increase in growth, much more marked in males with the membranous vocal fold increasing to 14.8–18 mm (more than double). In females the increase is to 8.5–12 mm – an increase in length of a third. The cartilaginous portion of the vocal fold also grows with age but less rapidly, with a relative increase in the ratio of the membranous to cartilaginous vocal fold from 1.5 in the newborn to 4.0 in the adult female and 5.5 in the adult male. Hirano devised the concept of the respiratory glottis posteriorly with a wider aperture and the phonatory glottis anteriorly. These concepts are useful in planning surgical procedures. For example, in bilateral vocal cord paralysis it is possible to increase the airway by performing an ablative procedure, such as a laser arytenoidectomy. If this procedure is kept to the posterior part of the larynx, the anterior membranous vocal fold can be preserved for phonation.

Changes in vocal fold laminar structure

Much has been written about the layered structure of the vocal folds and its importance both to the understanding of disease and the development of phonosurgical treatment.

The five layers of the vocal fold are the **epithelium, superficial layer** of lamina propria (Reinke's space), the **intermediate layer** and **deep layer** of the lamina propria and the **muscle layer**. The first two are referred to the as the 'cover' and move freely over the deeper layers which form the 'ligament' and 'body' of the vocal fold.

This laminar structure is not present at birth, but starts to differentiate over the first few months of life. It becomes more developed throughout childhood and the adult form is quite easily recognizable by puberty. One surgical implication of this is that microflaps are more difficult to raise in early childhood due to a less well-developed plane for dissection in the superficial lamina propria.

Changes in pitch

An important feature of the paediatric voice is its pitch. This drops throughout infancy and childhood in males and females, with a marked change at puberty, particularly in males. This change in pitch corresponds to the anterior growth of the thyroid cartilage in response to testosterone and coincides with the development externally of the thyroid prominence or Adam's apple. The fall in pitch is approximately proportional to the growth of the membranous vocal fold.

ASSESSMENT OF THE CHILD'S VOICE

Children with voice disorders may present to a general clinic or to a specialist voice clinic. An otolaryngologist and speech and language therapist should staff paediatric voice clinics. Videostroboscopic equipment and the expertise to use it should be available. The history and basic otolaryngological examination is the same in both settings. Whether laryngeal videostroboscopy and/or speech therapy assessment is required will depend on the clinical situation.

History and examination

Mild or moderate dysphonias that have been present for some time tend to be accepted as part of the child's personality and not a medical disorder. Often, an incidental remark years later leads to the parents seeking medical assessment to exclude an underlying disorder. Some children and families see no problem with their dysphonia. Alternatively, some children and families find a mild

dysphonia very troublesome, particularly if they are performers or have aspirations to perform.

Information should be sought from both the child and the parents. If the problem has been present from birth, a congenital lesion is likely. However, a history of endotracheal intubation around the time of birth or around the time of onset of symptoms may suggest laryngeal stenosis, cricoarytenoid joint fibrosis, intubation granuloma or cyst formation. Much more commonly, symptoms start with an upper respiratory tract infection that has been accompanied by laryngitis, a situation made worse by habitual patterns of voice misuse.

The severity of the disorder may range from a loss of singing voice to complete loss of conversational voice. The time course of the dysphonia is also important. For example, dysphonia is often persistent with discrete vocal fold lesions and rarely returns to normal, although it may fluctuate and fatigue during the day.

Enquire about symptoms suggestive of gastro-oesophageal reflux, as this may irritate the larynx and cause dysphonia. Post-nasal drip associated with allergic rhinitis will do the same, particularly if there is a habit of forceful or constant throat clearing. Cough is quite harsh on the vocal mechanism and constant coughing associated with respiratory disease may lead to hoarseness.

Restrictive respiratory disease may cause reduced infraglottic pressure and subsequent dysphonia. The use of corticosteroid inhalers can also cause dysphonia and this can be helped by modification of drug regime or possibly inhaler technique and the use of spacer devices.[12]

Hearing loss may make the child shout. This can be the underlying cause of a dysphonia secondary to vocal misuse. Voice misuse – shouting – is common in children and may lead to disorders of hyperfunction such as nodules. Other abusive behaviours, such as smoking and alcohol, may occasionally be relevant.

It is extremely important to enquire about exercise intolerance and stridor, symptoms and signs that may be caused by laryngeal stenosis. Swallowing problems or choking may be the first indication of laryngeal paralysis. A general otolaryngological examination, including assessment of the ears and hearing, should be performed. Important clues can be gained by carefully listening to the quality of the child's voice during history taking. Laryngoscopy should be undertaken in all cases.

Laryngoscopy

The objectives of laryngoscopy are twofold, first to identify any structural lesion, such as a vocal nodule or papilloma, and second to assess laryngeal mobility during phonation.

Older children may be cooperative enough for indirect laryngoscopy but examination of the paediatric larynx has traditionally been performed under general anaesthetic. Detailed structural information can be obtained but little information is gained with regard to mobility. It is usual to watch vocal mobility on awakening from general anaesthesia. This can provide information with regard to vocal paralysis, but it should be recognized that by today's standards this is a very crude method of assessment. Awake laryngeal and voice examination should be the standard of care in a compliant child.

Most focal lesions can be excluded by awake fibre-optic laryngoscopy. This can be performed on a child of almost any age. It is usually quite straightforward, performed transnasally with a 2.2 mm fibre-optic endoscope. The optics of the larger fibre-optic endoscopes are better and, if possible, a 4 mm endoscope should be used. These larger fibre-optic endscopes are commonly being replaced with newer 'chip in the tip' videoendoscopic systems. These give an excellent view of the larynx with high quality images.[5,6] From age 1 to age 5 years, compliance is limited and general anaesthesia and microlaryngoscopy may need to be considered. Some images are of sufficient quality to permit stroboscopy with examination of the mucosal wave.

Rigid laryngoscopy requires significant cooperation, which can only be obtained in children over 6 years of age. High-quality images of the larynx combined with stroboscopy give unparalleled information on vocal fold movement and structure. They also provide an important educational tool for parents and older children. Paralysis of a vocal cord is generally obvious but this technique gives insight to more subtle mobility disorders such as limited posterior glottic closure (glottic chink) and supraglottic constriction. This degree of information is useful and relevant to planning voice therapy.

ACOUSTIC ANALYSIS

With greater availability and use of computerized speech systems, acoustic data are increasingly being recorded. Unfortunately, in the paediatric population (unlike adults) there are no agreed protocols or standards to compare studies from different centres.[9] The most useful acoustic comparison in keeping with ELS guidelines would be measurements of perturbation.[13,14] There is ongoing research and much debate in how to advance this.

PERCEPTUAL EVALUATION

Perceptual evaluation is one of the most important and available measures of voice. The most common scales currently used are 'GRBAS' and 'CAPE-V'.[15,16] Both of these were developed for adult voice disorders and completion of the full data set may be difficult in children.

IMPACT/QUALITY OF LIFE

Although there are numerous questionnaires designed to assess the impact of a voice disorder, these were developed for adults. There have been a few developed for children based on their adult counterparts, including paediatric VOS,[17] paediatric V-RQOL,[18] paediatric VHI.[19] One of the issues with paediatric questionnaires is that the parent/carer is acting as a proxy for the child and their view may not match.[20] There is increasing evidence that children should be self-assessed and questionnaires are being designed for this purpose.[21]

SPECIFIC DISORDERS

Vocal nodules and functional voice disorders

Vocal nodules – now regarded as an organic manifestation of laryngeal hyperfunction – are the commonest cause of dysphonia in children (**Figure 33.2**).[22] The mainstay of treatment is voice therapy to correct the hyperfunction. While in adolescents this therapy is similar to that employed in adults, different strategies are necessary in younger children.

The traditional view, based on clinical experience, was that most vocal nodules in children could be expected to improve at puberty.[23] Puberty is a time of great change in the larynx, with tremendous growth of the membranous vocal fold in the male and, to a lesser extent, in the female. One can see how the dynamics of vocalization might change with potential improvement in the nodules. Mori,[24] however, reported that 12% of nodules did not improve at puberty. In the same study it was found that those treated with vocal hygiene alone (i.e. general advice regarding voice care) did not improve. Those given voice therapy under the supervision of a speech and language therapist did tend to improve and the degree of improvement was related to the number of therapy sessions. The essentials of voice therapy include reduction of vocal strain. Various techniques can be employed to reduce shouting, whispering, coughing and throat clearing and to encourage the use of a smooth easy voice. Periods of quiet play are recommended after noisy activity (e.g. football) to allow vocal fold recovery.

Surgery for nodules is rarely recommended in children. Concerns about the potential effects of scarring are very real. On occasion it can be justified when prolonged voice therapy has failed. Bouchayer and Cornut[25] reported cysts, polyps and sulci in children previously diagnosed as having nodules when examined at microlaryngoscopy. Some children with nodules have vocal cord cysts with a nodule on the contralateral cord and this might explain why some fail to respond to voice therapy. The use of videostroboscopic techniques in the voice clinic should help diagnose these conditions earlier. Cysts are treated by microsurgical excision.



Figure 33.2 Vocal cord nodules.

A wide range of functional voice disorders can be demonstrated in children without demonstrable nodules. These children may present with dysphonia, or even aphonia, secondary to underlying psychological factors. For these children, voice therapy may need to be combined with a psychological assessment. Aphonia in the presence of a normal laryngoscopy evaluation is suggestive of psychological disturbance. A normal cough or laugh adds support to this contention. Puberphonia, when the prepubertal voice persists into adolescence or adulthood, is another condition associated with psychological disturbance. Highly specialized voice therapy, possibly in conjunction with a psychologist, is important to help these children develop an adult voice.

Laryngeal papillomatosis

A detailed account of laryngeal papillomatosis is given elsewhere (Chapter 32, Juvenile-onset recurrent respiratory papillomatosis). From the voice perspective, there are a number of important considerations.

The emphasis of modern surgical techniques is to minimize damage to the underlying lamina propria and to restrict surgery to the papillomas. In this way, voice quality will be optimized in the long term. Glottic scarring and webbing are well-known complications of surgical intervention with the laser.[26] The use of a microdebrider and cold steel instruments has much to commend it. After all, surgery cannot cure papillomatosis. Medical treatments have been advocated including intralesional acyclovir with some reported success.[27] In theory, any medical adjunct that reduces the number of surgical procedures would be beneficial in terms of voice preservation, although voice outcomes following these therapies have yet to be reported. Cidofovir is showing some promise and its use is considered in Chapter 32, Juvenile-onset recurrent respiratory papillomatosis.

Intubation injuries and voice

Much has been written about acquired subglottic stenosis consequent on prolonged endotracheal intubation in premature infants. Surgical techniques have evolved to correct this abnormality and allow eventual decannulation.[28–31] Voice problems following this surgery have been documented and are not uncommon.[32]

Subglottic stenosis is just one example of laryngeal injury caused by intubation. More minor scarring may affect the voice but not the airway (**Figures 33.3** and **33.4**). Damage to the vocal fold or underlying lamina propria causes dysphonia. Cricoarytenoid joint fixation and posterior glottic scarring may also be caused by endotracheal intubation and reduce vocal fold mobility. It is easy to confuse these conditions with vocal cord paralysis.

Voice therapy can be successful in some children. Surgical treatment of voice problems caused by intubation trauma remains a significant challenge. There is



Figure 33.3 Intubation granulomas.



Figure 33.4 Vocal cord polyp following prolonged endotracheal intubation.

potential for the introduction of medialization techniques in this group of children, but there must be an adequate airway before this can be considered and this situation is uncommon.

Vocal cord paralysis

In general terms, children with bilateral vocal cord paralysis have a good voice or cry. It is the airway that gives concern. Spontaneous recovery of function takes place in some, but after 2–3 years of observation this is unlikely to happen.[33] A number of lateralization procedures can be performed to develop a wide posterior glottis for respiration while preserving the anterior glottis for phonation. Either laser arytenoidectomy[31, 34, 35] or endoscopic suture lateralization can achieve these goals.

In contrast to bilateral cord paresis, children with unilateral cord paralysis present with aspiration and a weak cry. The airway is relatively spared. Most improve with time due to compensation from the contralateral nonparalyzed vocal fold or to spontaneous recovery.

Medialization thyroplasty can be considered for those who do not improve and continue to have a significant voice problem. However, there is limited published information on this and it should be remembered that its efficacy to diminish aspiration has been limited.[36]

The concept of placing a silastic implant before puberty has raised concerns that this might interfere with the anticipated physiological growth spurt. It is the author's practice to consider medialization using a fat injection in dysphonic, prepubertal children and to restrict silastic thyroplasty techniques for dysphonic post-pubertal patients. There is also increasing use of newer laryngeal injectables such as calcium hydroxyapatite in children.

The concept of re-innervation is attractive. In a series of eight children with unilateral vocal cord paralysis, three underwent implantation with ansa cervicalis/strap muscle pedicles. This, together with post-operative voice therapy, gave 'good' results.[37] There has to be some scepticism about these procedures as re-innervation techniques are capable of restoring laryngeal tone but have had limited success in achieving voluntary movement. Nevertheless, children seem to be the ideal population on which to carry out these procedures as nerve grafting in general is more successful in this age group.

It is worth restating that it should never be assumed that an immobile vocal cord is paralyzed. Vocal cord immobility in previously intubated children may be due to joint fixation or posterior glottic scarring. The distinction between these diagnoses is extremely important, particularly when vocal cord immobility is bilateral. The management of paralysis is conservative with a tendency towards spontaneous recovery. Fixation and scarring do not improve and children may be subject to years of unnecessary waiting with a tracheotomy before a surgical lateralization procedure is contemplated.

Tracheotomy and voice

Children with tracheotomies will often have impaired voice; this may also result in a speech and communication delay. This is only partly due to the tracheotomy tube diverting air from the glottis. The main factor is usually the laryngeal lesion that required tracheotomy formation in the first place. Children with a healthy larynx can obtain good voice by occluding the tube on expiration (with a finger or speech valve) and projecting air around the tube and up through the glottis. To facilitate this, the tube needs to have sufficient space around it and may need to be 'downsized'. This is usually possible without restricting the airway. Speech valves are frequently used in the author's practice for children. As well as helping with speech they help with secretion management and swallowing.

BEST CLINICAL PRACTICE

- ✓ Laryngeal microflaps are more difficult to raise in early childhood due to a less well-developed plane for dissection in the superficial lamina propria. **[Grade A]**
- ✓ An immobile vocal cord is not always paralyzed. Consider joint fixation and posterior glottic scarring, especially if the child has been intubated.
- ✓ The term 'vocal abuse', often used to describe adult dysphonias, is best replaced by 'voice misuse' in the paediatric setting. Beware the sensitivity of recording the word 'abuse' in children's records.
- ✓ Advances in endoscopic equipment are such that awake laryngeal and voice examination should now be the standard of care in a compliant child.
- ✓ Due to the potential for permanent scarring, surgery for nodules is rarely recommended in children. It should be considered only as a last resort when prolonged and skilled voice therapy has failed.

FUTURE RESEARCH

- ➤ **Laryngeal transplantation for voice.** Perhaps the most challenging of paediatric voice conditions is the child with no voice due to complete laryngeal stenosis which is beyond surgical reconstruction. Such children are encountered after severe burns or caustic ingestion. They are tracheotomy-dependent and communicate with signing and non-oral devices. Laryngeal replacement using transplantation carries the best hope for these children and, although there has been one successful adult patient, this has yet to be repeated.
- ➤ **Re-innervation of the paralyzed larynx.** Phonosurgery can be helpful for the voice in laryngeal paralysis with medialization using injection or thyroplasty techniques. However, the biggest concern for children with laryngeal paralysis is not voice but aspiration. We do not have a universally accepted solution for aspiration due to laryngeal incompetence. Withdrawal of oral feeding and gastrostomy remains the mainstay. Fortunately, compensation frequently takes place for unilateral lesions but often not bilateral problems. Laryngeal re-innervation may hold the key but it is still in its infancy.
- ➤ **Repair of damaged vocal cords with synthetic 'SLP'.** Vocal cords damaged by intubation or surgery have lost the mucosal wave due to destruction of the important superficial layer of the lamina propria (SLP layer). Medialization of damaged vocal cords has had only limited success and attempts are being made to create a synthetic substitute for this important gel layer for potential replacement by injection into Reinke's space.

KEY POINTS

- Voice disorders in children are common; few require medical intervention.
- The impact of dysphonia in children should not be dismissed.
- A diagnosis can usually be made by careful history taking and examination to include laryngoscopy and ideally videostroboscopy.
- The child's perceptual reporting should be sought.
- Laryngeal muscle hyperfunction with or without nodules constitutes the commonest group of disorders.
- These disorders respond well to skilled voice therapy (speech and language therapy - 'SALT').

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CHAPTER 34

FOREIGN BODIES IN THE EAR, NOSE AND THROAT

Adam J. Donne and Katharine Davies

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SEARCH STRATEGY

Data in this chapter may be updated by PubMed searches using the keywords: foreign body and ear, nose, throat, inhalation and oesophagus. The searches returned the following numbers of articles: ear, nose, pharynx, larynx and trachea/bronchus. The majority of the articles identified were level 3 in the form of retrospective reviews.

Hospital episode statistics data were accessed via the public access website. The Susy Safe project statistics were accessed via a public access website.

INTRODUCTION

For the purposes of this chapter a 'foreign body' is an object or substance that is inappropriately situated in a particular anatomical location. Children commonly present with a foreign body in the ear, nose or throat. Young children tend to explore using their mouths and this puts them at risk of the foreign body entering the aero-digestive tract.[1] Impaired behavioural development due to a neurological diagnosis or attention deficit/hyperactivity disorder[2, 3] may increase the risk of foreign body insertion, ingestion/inhalation. In adults, poor dentition, alcohol consumption and old age may be important factors for eating-related airway obstruction.[4] Adults may also have neurological or psychological factors.[5]

Child abuse by neglect or direct non-accidental injury (NAI) may be relevant. However, adults also present with foreign bodies which may be due to a chance event or accident (e.g. pin inhalation or an insect in the ear) or may herald an underlying pathology (e.g. oesophageal malignancy and food bolus obstruction). Foreign bodies can be categorized by location and type. The location of the foreign body may be life-threatening as in the larynx, or benign, such as a bead in the ear. They can be subdivided into organic and inorganic. The nature of the foreign body may pose a direct threat to tissue (e.g. battery ingestion).

INCIDENCE

The largest active registry of non-food foreign body incidents is the Susy Safe project.[6] The number of foreign body incidents in the European Union in children aged 0–14 years is 50 000 per annum, and 1% are fatal. Around 10 000 are inorganic and 2000 involve toys.[6] Unfortunately, it has been reported that up to 22% have a repeat of the foreign body incident,[7] therefore education must be essential for the long-term management of this risk.[8]

It is difficult to determine the relative frequency of foreign bodies within the trachea, bronchus and oesophagus compared to ear and nose as little has been published to demonstrate the complete range of ear, nose and throat foreign bodies in any particular series. A literature review would indicate foreign body frequency is higher in ear and nose compared to throat.[9] An eastern European retrospective study (over 10 years with 849 patients) identified the following relative proportions: tracheobronchial 11%, pharyngo-oesophageal 17%, and ear, nose and post-nasal space 72%.[10] Using data from the Susy Safe project, it is possible to determine the following relative percentages for foreign bodies: ear 25.9%, nose 27.4%, pharynx and larynx 4.3%, trachea, bronchus and lungs 12.8%, and mouth, oesophagus and stomach 29.7%.[11] This Susy Safe publication used ICD9-CM codes and reported on a total

of 8593 incidents. As the categories differ from the eastern European study, it is not possible to make close comparisons. However, it is clear that ear and nose form around half of the incidents recorded. Both studies agree that incidents affecting the tracheobronchial region constitute around 11–12%. The Susy Safe project identified that foreign bodies were food in 26% of cases. The data specifically for food-related foreign bodies indicates a difference in proportions of anatomical site affected: ear 7%, nose 19%, pharynx and larynx 16%, trachea, bronchus and lungs 50%, and mouth, oesophagus and stomach 8%.[12] Clearly, there is a different profile, which might be explained by the fact that the Susy Safe project originally attempted to identify non-food foreign bodies with only later collection of food foreign bodies. A further compounding factor is that different countries and cultures eat different food types, which may be significant and skew the data.

Self-inserted foreign bodies may occur more frequently in children with attention deficit or hyperactivity disorder.[2] Children with neurological disorders have been shown to present later with foreign body in the aerodigestive tracts. Furthermore, these children remain in hospital for longer and may have a more complicated management.[13] For children who are otherwise healthy before foreign body inhalation, reviews suggest that the majority (96%) did not require supplementary oxygen support beyond 2 hours.[14] This implies that, even though foreign body inhalation is potentially life-threatening, for most patients the removal is without complication. If there is a pre-operative respiratory impairment, the risk of post-operative complication is higher.[15] Immediate post-operative chest radiographic features are predictive of pulmonary complications.[16] However, the mortality for foreign body inhalation is still high.

Hospital Episode Statistics (HES) data for Accident and Emergency admissions in England are available online from the Health and Social Care Information Centre (hscic) at NHS Digital.[17] These data indicate that for the years 2011–2012 and 2012–2013 the attendances for 'foreign bodies' as a group represented about 1% of attendances – and during 2012–2013 there were a total of over 18 million Accident and Emergency attendances. These data are crude as there is no indication of the anatomical location of the foreign body. However, it is clear that foreign bodies are an important problem.

The Susy Safe project was supported by the European Commission and resulted in the development of toy safety directives which aim to make small parts on toys safe for children 0–3 years but also control the use of heavy metals in toys. In general, boys tend to present with foreign body incidents more commonly than girls[18] and they are more frequently involved with more severe injuries.[19] However, when the foreign body is jewellery, 76% of those presenting are female.[20]

EAR FOREIGN BODIES

Right-handed children tend to insert foreign bodies into their right ear and left-handed children into their left ear.[21] However, bilateral foreign bodies have also been reported in ear (and nose).[22]

Inert foreign bodies may be identified as an incidental feature.[18] However, as there are significant consequences of delayed removal of certain items (e.g. button batteries) examination is appropriate with a positive history. The isthmus of the external auditory meatus is the narrowest section and foreign body impaction may occur at this point. Many aural foreign bodies will migrate out of the ear. Grommet extrusion is testimony to this fact. The urgency of removal of foreign bodies should be based upon the foreign body in question. Potentially corrosive foreign bodies should be removed without delay. However, inert foreign bodies are often found incidentally in the ear and nose as they are asymptomatic in 47% and 43% of cases respectively.[18]

Management of ear foreign bodies

A variety of techniques to remove aural foreign bodies exist and the technique adopted is determined by the foreign body characteristics (i.e. size, shape, consistency), position and cooperation of the patient. A smooth, hard foreign body (e.g. bead) is difficult to grasp and evidence suggests that non-graspable foreign bodies are better removed by otolaryngologists with fewer complications compared to emergency department staff removal.[23] Methods include microsuction, wax hook and irrigation.[24] The cooperation of the child is essential and up to 30% require a general anaesthetic to allow safe removal.[25] It has been reported that up to 47% sustain trauma such as laceration and tympanic membrane perforation. Approximately half have had previous attempts before seeing an otolaryngologist,[26] which suggests that aural foreign bodies should be dealt with by otolaryngologists as a matter of course.

Irrigation should be a safe technique as long as the tympanic membrane is intact. Studies indicate that the pressure exerted may be sufficient to cause tympanic membrane rupture, ossicular disruption and round window fistulae.[27] If the irrigation fails to expel a foreign body which is organic (e.g. dried pea), swelling may occur, which can result in further removal difficulty and pain due to pressure exerted against the canal wall skin.[25, 28] Adults more frequently present with insects in their ears (**Figure 34.1**). These cause irritation and distress and a consequent urgency to remove.[26]

NASAL FOREIGN BODIES

A nasal foreign body must be considered in any child with unilateral nasal discharge (especially with unilateral excoriation of nasal rim).[29, 30] The most common age of presentation is 2–4 years. A nasal foreign body usually requires a minimum of 4 days before discharge occurs[22] unless it is a button battery when discharge is immediate. Inert nasal foreign bodies may be present for a considerable number of years.[31, 32] With prolonged indwelling a foreign body granulation develops (**Figure 34.2**) and may result in rhinolith formation. Rhinoliths consist of salts of

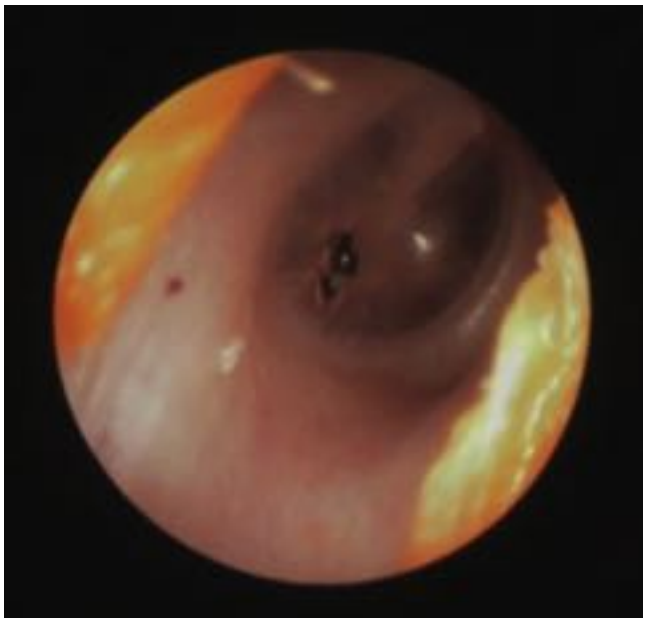


Figure 34.1 Otoscopic image of an insect in an ear.

calcium, magnesium phosphate and carbonate[33] and are radio-opaque.[34] A long-standing nasal foreign body may even result in hypoplasia of the inferior turbinate.[35]

Management of nasal foreign bodies

The usual technique for removal of a nasal foreign body is the placement of a hook or preferably a bent Jobson Horne probe over and behind a foreign body. The foreign body is then pulled forward.[36] If the foreign body moves posteriorly, there is a theoretical risk of inhalation.[37] Other techniques include the 'mother's kiss' whereby there is mouth-to-mouth gentle blowing into the mouth of the child with the unaffected nostril being held closed. This may allow the foreign body to be expelled in around 60% of cases.[38] Hollow foreign bodies may be resistant to this technique.[39] Balloon catheters (Fogarty) have also been used placed intranasally behind the foreign body then partially inflated and pulled out of the nose, bringing the foreign body ahead of it.[40] Occasionally, it may be difficult to remove a foreign body through the anterior nose and therefore pushing it into the pharynx of the anaesthetized patient is an option for removal.[41] An alternative may be to break the foreign body *in situ* and remove it in numerous pieces.[35]

There is a risk that nasal foreign bodies may be inhaled;[42] however, this is more probable if the gag reflex is impaired. A foreign body falling into the laryngopharynx would usually be swallowed or coughed up. In the past, many of us were taught that 'the sun should never rise or set on an inhaled or ingested foreign body' but it is almost certainly safe to leave nasal foreign bodies in neurologically normal children for operative removal during normal working hours if required.

INHALED FOREIGN BODIES

Most inhaled foreign bodies occur in the under 3 years age group.[11, 43, 44] They are more common in boys than girls.[45] In children younger than 3 years the foreign body is typically organic (food) whereas in children older than 5 years they are more often inorganic.[46] A large variety of foreign bodies have been published.[47, 48] The lack of molar teeth is thought to be significant due to the reduced ability to chew food adequately.[1, 49] Young children tend to put objects in their mouths which may additionally explain the high incidence of foreign body aspiration.[50] The mortality from foreign body inhalation is around 1% and the commonest cause of accidental death in children under 3 years of age. Foreign bodies in the tracheobronchial system seem to cause more complications that in other anatomical sites.[51]

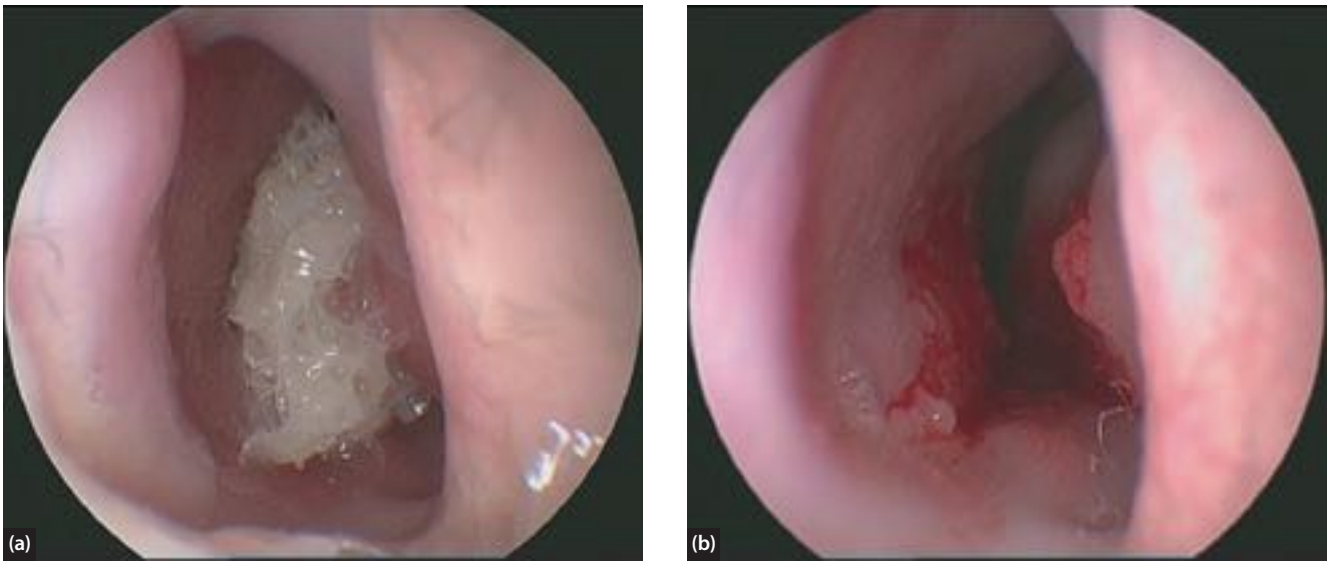


Figure 34.2 Endoscopic images of a fabric foreign body in a nose **(a)** and the immediate post-removal appearance of granulation at the point of contact with the foreign body **(b)**. This indicates chronic contact.

It has been shown that children are often able to clear their own airways, but this ability is less well developed in the younger the child. In one report 85% of inhaled objects were cleared before emergency medical services arrived at the scene. Food and coins have been identified as the main culprits.[52] In 1975 Heimlich published a report on a manoeuvre to expel laryngeal foreign bodies.[53] A report suggests that this manoeuvre may be responsible for reducing deaths in the under 15 years age group from foreign body inhalation.[54] There may be significant complications to the procedure but doing nothing commands a greater risk. Serious complications include oesophageal-gastric rupture,[55, 56] diaphragmatic hernia[57] and emphysema (in subcutaneous space[58] and mediastinum[59]).

Inhaled foreign body presentation may vary depending upon the exact site of obstruction with the airway. The history may present with a witnessed foreign body in the mouth or even no apparent foreign body presentation in a young child, and this can delay diagnosis. Symptoms and signs of foreign body inhalation include choking, coughing, hoarseness, shortness of breath, wheeze, increased work of breathing, cyanosis, asphyxiation and death. Foreign bodies arising anywhere within the large respiratory airway may result in stridor. Laryngeal foreign bodies may give rise to hoarseness which is unlikely with an object in the right main bronchus. The history is paramount as a parent/guardian is present in about half (49%) the incidents and the child was eating in 34% of cases.[1] Indeed, even if the child is symptom free, if no object is fully expelled by coughing after a choking episode, further evaluation is indicated. A low threshold is essential so that the asymptomatic foreign body[60] or occult foreign body is not missed.[61] Delayed presentation is not uncommon in children and may have been treated as asthma due to the low-grade cough and noisy breathing. In almost 40% of cases the diagnosis was delayed for more than 24 hours.[48] One report of flexible bronchoscopy for respiratory symptoms (where foreign bodies were coincidentally identified) indicated that symptoms (due to the foreign body) were present from 1–132 months. The longer the duration of foreign body placement, the increased probability of long-term complications. When present for less than 1 month, all patients recovered completely but, if present for more than 3 months, only 30% recovered. The remainder had chronic cough and wheeze or bronchiectasis.[62]

The location of the foreign body within the airway has been identified from meta-analysis to be in decreasing frequency for the following locations: bronchus (right more frequent than left side),[63] trachea, larynx and lung.[48]

Laryngeal foreign bodies are relatively infrequent (2–12%)[64, 65] compared to the rest of the tracheal and bronchial incidence. They present with either partial or complete airway lockage. The former may result in voice issues (hoarseness), stridor, dyspnoea, prolonged atypical croup or even odynophagia[66] and as such can result in misdiagnosis and delay in identifying the laryngeal foreign body.[67] The latter will result in hypoxia and/or laryngospasm and death by asphyxiation[64] and classically require the Heimlich manoeuvre. The shape of the foreign body within the larynx is either spheroid or flat.[68] However, sharp metallic items that may penetrate the vocal cord or wall of trachea such as safety pins present a surgical challenge.[69, 70, 71] Within the larynx foreign bodies can be very difficult to identify even with spiral CT scanning.[72] If there is a delay in diagnosis, there can be significant associated granulation tissue at the glottis level where the foreign body is in contact with the mucosal surface, similar to the bronchus.[73]

Radiographic findings on chest films will often be normal (11%–26%)[74, 75] unless there is a radio-opaque foreign body present.[48] Additional radiographic features include atelectasis, hyperinflation, mediastinal shift, pneumonia and pneumothorax. Classically there is hyperinflation of the lung on the side of the foreign body due to the 'ball-valve' effect. The intrathoracic pressure is decreased on inspiration such that air can enter the bronchus. On expiration the intrathoracic pressure reduces to compress the bronchus (somewhat) around the foreign body (**Figure 34.3**). The sensitivity and specificity of radiographs for airway foreign bodies have been calculated to be 73% and 45% respectively,[76] which implies that the radiological investigation is an aid but should not deter an airway endoscopy. Fluoroscopy improves foreign body detection but even this additional modality radiology does not identify a significant proportion.[75]

Computed tomography virtual bronchoscopy is highly sensitive at identifying a foreign body within the airway[77] but, if this requires a general anaesthetic, most would consider a rigid bronchoscopy as the patient's condition may change suddenly while anaesthetized. In asymptomatic patients CT bronchoscopy may therefore be a reasonable option but it cannot replace endoscopy.[78, 79]

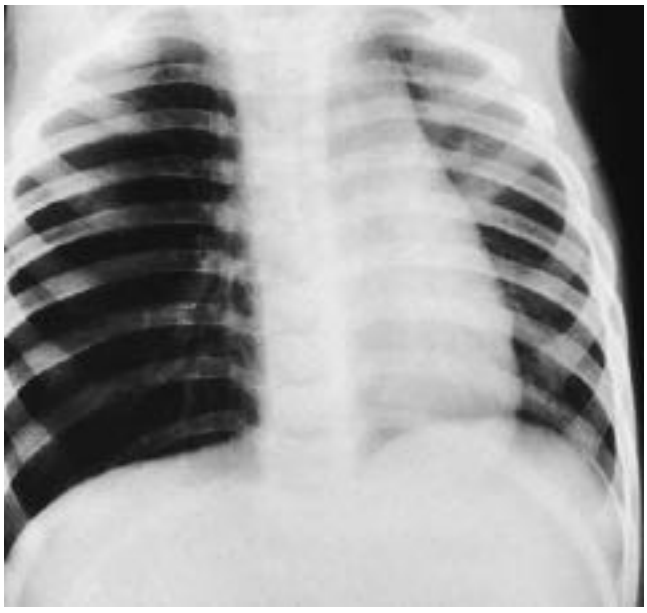


Figure 34.3 Chest X-ray showing hyperinflation of the right lung due to a foreign body in the right main stem bronchus.

Management of inhaled foreign bodies

Some surgeons advocate flexible bronchoscopy via a laryngeal mask or endotracheal tube to diagnose and remove foreign bodies.[80] Some have reported very high success rates,[63] and the benefit of flexible endoscopes is that they are flexible and able to approach the bronchus at a different angle. However, the flexible endoscope cannot ventilate the patient and presents a significant obstruction.[63] Flexible bronchoscopy may be possible in older children and adults without general anaesthesia but rigid bronchoscopy under the controlled conditions of a general anaesthetic is the mainstay for foreign body removal.[62] Use of the urological basket with flexible bronchoscopes has been reported in cases where rigid bronchoscopy has failed.[81, 63] There is genuine value in flexible endoscopy in the repertoire for foreign body removal.

A direct laryngotracheobronchoscopy or microlaryngotracheobronchoscopy (MLTB) should be performed to diagnose and remove the foreign body without undue delay. The level of urgency depends on the clinical condition of the patient and resources available. The endoscopy is best performed during daylight hours. If a child presents during an evening with a history of possible foreign body inhalation and is well, it is reasonable to delay endoscopy until the morning.[82] This remains somewhat controversial. The exceptions include unstable symptoms, type of foreign body (e.g. peanut, **Figure 34.4**), and broken seeds as these cause oil release and granulation formation,[83] beans (especially dried as these cause swelling and inflammation)[47] and batteries (see below).

MLTB for removal of foreign bodies is best performed for children using inhalation anaesthesia as this has been shown to be associated with fewer complications.[44]

MLTB to remove a foreign body is best performed in children without endotracheal intubation as there is a small risk that the foreign body may be lodged at the larynx or immediate subglottis and the endotracheal tube may push the object in such a way as to cause complete airway closure. It is therefore advisable that the rigid bronchoscope is ready for use. Furthermore, paralysis is not advised until the airway has been assessed and secured. Topical anaesthetic on the larynx prevents laryngospasm, which is undesirable during such cases.



Figure 34.4 A peanut in the bronchus.

Topical adrenaline is very useful to decongest the area immediately around the foreign body, especially if there is any granulation present, with the inherent risk of bleeding.[63] On successful removal of the foreign body an immediate second look is necessary to ensure other fragments are not retained. Steroid is typically administered to reduce effects of oedema due to airway instrumentation as steroids have been well described to reduce oedema of airway surgical intervention and prolonged intubation.[84] Most patients require post-operative observation until the following day.

There is a reported risk of up to 4% for life-threatening complications following endoscopic removal of foreign bodies. The risks include pneumothorax (unilateral and bilateral),[47] tracheal laceration, pneumonia, haemorrhage into the airway, and cardiac arrest due to hypoxia.[85] Even if foreign body removal is successful, delayed pneumothorax can occur post-operatively. The risk of hypoxia during foreign body removal by MLTB is higher if the child is less than 1 year of age,[86] with certain types of foreign body[47] and the longer the duration of procedure.[44, 86] The latter may indicate the increased difficulty of removing the foreign body from the airway. Further risk factors for hypoxia for the patient during endoscopic removal include pre-existing pneumonia[87] and foreign body fruit seeds.[87, 88] Extracorporeal membrane oxygenation (ECMO) may be a useful technique to maintain oxygenation where the patient is too unstable and when the tracheal foreign body removal is otherwise impossible without complete airway obstruction and significant risk of cardiac arrest.[89] The risk of death during endoscopy for foreign body removal is significant and reported at 0.42%[90] yet a more recent study using USA nationwide data over 3 years indicated a death rate of nearer 1.8%.[91]

A negative MLTB is not a failure as the threshold to suspect foreign body inhalation must be low. The negative rate has been reported to be as much as 60%.[91] However, since delayed diagnosis occurs in a significant proportion and may result in bronchiectasis, the index of suspicion should be low.

In some circumstances it may be impossible to remove a foreign body using endoscopy. An alternative strategy may include tracheal fissure (as tracheostomy incision) for tracheal foreign bodies or thoracotomy for bronchial sites.[47]

INGESTED FOREIGN BODIES

A variety of foreign bodies are ingested by children. Peak incidence is in children less than 4 years of age (up to 75%). The most common item ingested is probably the coin (up to 70% of cases) (**Figure 34.5**). Symptoms include drooling, pain, dysphagia and odynophagia. Small, blunt foreign bodies may pass through unhindered. Foreign bodies such as chicken and fish bones may stick in the tonsil, tongue base, cricopharyngeus and pharyngeal wall

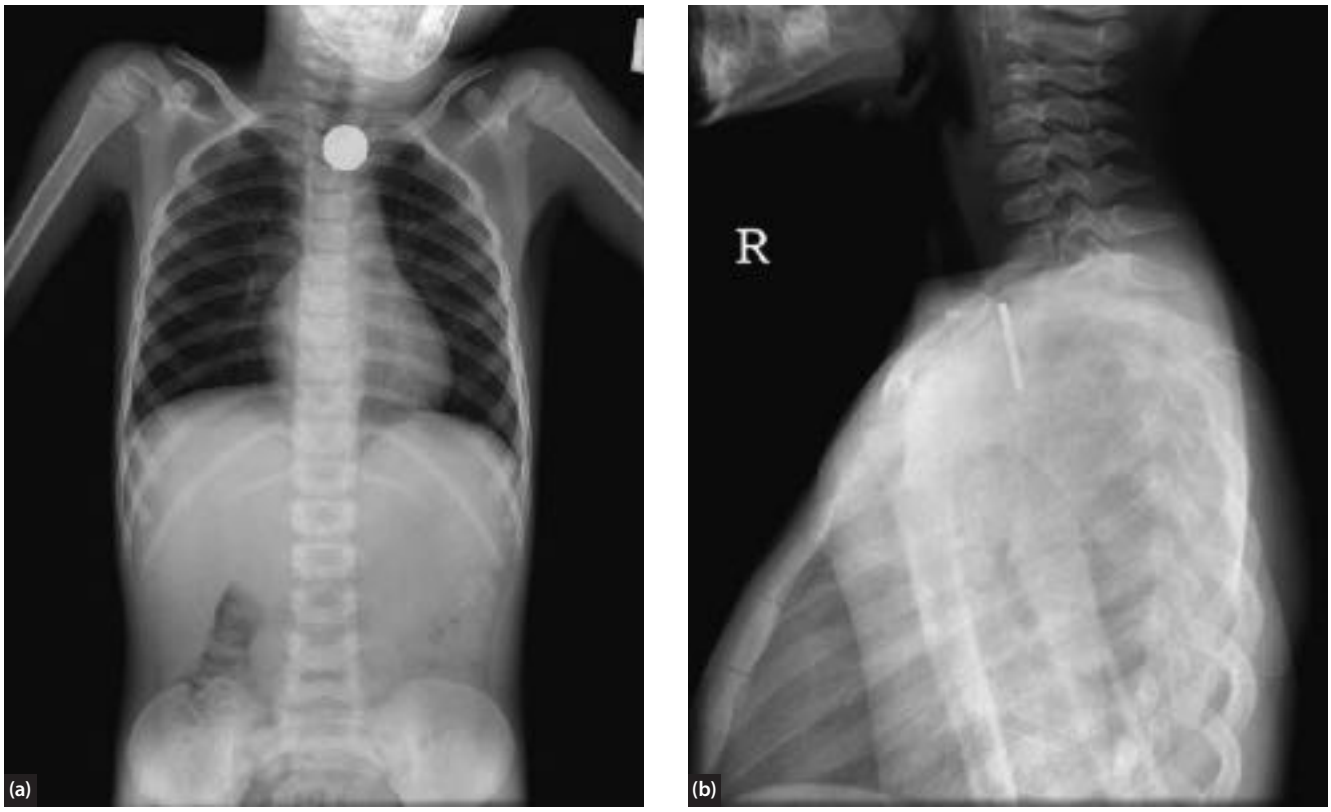


Figure 34.5 (a) Foreign body (coin) in the oesophagus. **(b)** The lateral view confirms the position.

in reducing order of occurrence.[92] Larger items typically stick at the cricopharyngeus or upper oesophagus above the aortic arch. Pathology within the oesophagus can present with foreign body impaction.[93]

Management of ingested foreign bodies

For food-related impaction, medical management is often trialled. Agents include hyoscine (buscopan) and diazepam. The evidence for the use of buscopan or diazepam in this situation is inconclusive. Small retrospective studies have indicated that effervescent fluids may confer some benefit.[94] Food bolus impaction is quite uncommon in children and should raise the possibility of eosinophilic oesophagitis. This condition is discussed in more detail in Chapter 44, Reflux and oesinophilic oesophagitis. When a food bolus is found in a child, the surgeon should take three biopsies from the lower oesophagus for histology and specifically request examination for eosinophils.

Flexible nasendscopy may either identify the foreign body in the pharynx or demonstrate saliva pooling in the pyriform fossae indicating a hold-up in the oesophagus. Metallic foreign bodies may be detected by metal detector or more usually radiography (see **Figure 34.5**). Contrast swallow is not an appropriate initial management as it obstructs endoscopy and may result in aspiration.[95]

Whereas foreign bodies such as small fish bones may absorb without removal, most will require surgical removal.[96] If not removed, some foreign bodies migrate into the soft tissue of the neck.[97] Controversy remains around the choice of flexible or rigid endoscopy (**Figure 34.6**). The latter has a significantly higher perforation rate compared to flexible type (0.2–1.2 versus 0.02–0.05),[98] yet both methods have similar success rates.[99] Early intervention confers benefit of reduced complications in particular for sharp foreign bodies such as bones and pins.[98, 100, 101] Complications include perforation, mediastinal infection/abscess, retropharyngeal abscess and oesophageal stenosis.[102] Delaying intervention beyond 24 hours may increase duration of therapeutic endoscopy.[103]

SPECIAL CONSIDERATIONS

Batteries and magnets

Special consideration needs to be given to batteries as foreign bodies. There has been a significant and increasing rise in battery foreign body incidents since one of the earliest reports of battery ingestion in the 1970s.[104] This was a camera mercury battery which was removed by gastrostomy. Between 1985 and 2009 there was a 6.7-fold increase.[105] The increase in incidence is thought to be due to the increased usage in small electronic devices, the size, shape and smoothness of the button battery and the extent of injury due to the battery power output.[106] There is a male preponderance (57%).[107]

Batteries cause harm in a variety of ways:

- soft tissue forming an electrical circuit between the terminals (sides) of the button battery, hydrolyzing tissue by forming hydroxide at the negative terminal[105, 108]

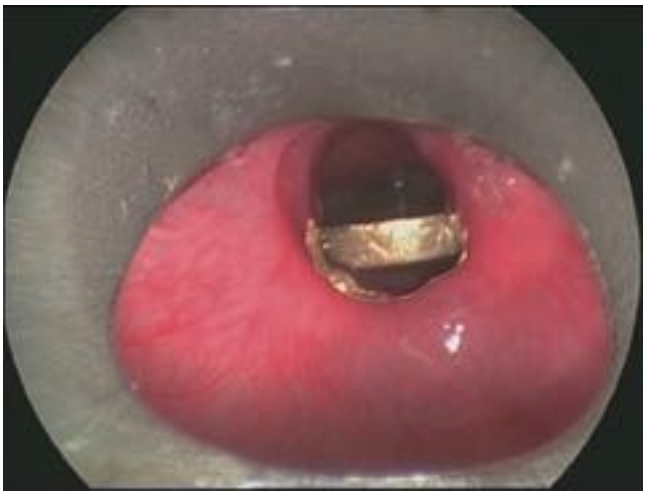


Figure 34.6 Image of a coin in the upper oesophagus on endoscopy.

- leakage of alkaline[109] from the battery when in a saline environment
- pressure necrosis[110] if compressed at a particular site
- release of toxic compounds[111] (e.g. mercury) to cause systemic toxicity.

The majority of batteries are the alkaline variety.[107]

The Susy Safe project has a button battery database component and a report on 348 cases has revealed the following anatomical sites affected. Most cases occurred in the mouth, oesophagus, stomach (188/348), nose (112/348) and ear (44/348).[106] There was only a single case of an inhaled battery. This report identified that 30% of children had dysphagia and perhaps surprisingly 26% had fever and cough.

The size of the battery seems to be important determinant for complications. The highest risk is a 20 mm battery in children under 4 years old.[105] A battery causes a rise in temperature and pH when ingested.[112] Burns occur within 2–2.5 hours. Fifty-four per cent of cases with a fatal outcome were misdiagnosed.[105] This indicates the importance of urgent X-ray investigation and removal. The X-ray feature of button batteries is a double contour.[107] The larger size of button battery is important as it may get stuck at sites of anatomical narrowing such as within the oesophagus at the arch of the aorta. If the battery is past the stomach, serial abdominal X-ray investigation may be appropriate. MLTB is also of value during pharyngo-oesophagoscopy and battery removal to rule out tracheo-oesophageal fistula or prodromal granulation within the airway.[113, 114, 115] Other complications of button batteries in the oesophagus include oesophageal perforation, haemorrhage,[116] vocal cord palsy,[117] ulceration/necrosis and death.[118] A report of a 2-year-old child with an 8-month history of a battery impacted in the oesophagus but still able to swallow has been reported. This case is of significance as the battery had become implanted into the oesophageal wall and surrounded by granulation so dense that the metallic nature of the foreign body was not identifiable intraoperatively. A decision was made to perform an external approach (right posteriolateral thoracotomy) the following day with success.[119]

Debate surrounds the post-operative management of the patient following pharyngo-oesophagoscopy and battery removal. An initial post-op chest X-ray may identify a pneumothorax (around 0.8%)[15] or pneumomediastinum.[112] Possible options include nasogastric tube, proton pump inhibitors, repeat endoscopy or contrast swallow a few days to a week later.[120] Steroids have not been shown to confer a clinical benefit following caustic ingestion, even though there is a theoretical expectation that fibrosis and stricture formation might be reduced.[121] The placement of a nasogastric (NG) tube serves to allow adequate nutrition and perhaps is a form of stenting. However, the blind placement in a corroded oesophagus may present increased risk.[122]

Nasal button battery foreign bodies have been shown to cause septal ulcerations, septal perforation, inferior turbinate ulceration and necrosis.[123] An external auditory canal button battery foreign body may cause skin ulceration, serosanginous discharge and tympanic membrane perforation.[123]

Magnets have been used to remove metallic nasal foreign bodies.[124] Magnets can be problematic as foreign bodies. The danger arises if either more than one magnet is inserted (e.g. nose or swallowed) or one magnet and another metallic object is inserted. The median number of magnet-associated foreign body incidents was two items. Again, there is a prevalence in boys (63%). Magnetic foreign bodies have a larger median volume compared to non-magnetic foreign bodies.[125] The fashion for magnetic earrings across the nasal alar region has inadvertently resulted in some cases of the magnets being misplaced and attracting across the nasal septum resulting in septal injury and even septal perforation due to pressure necrosis.[126, 127] When swallowed, the same mechanism is responsible for attraction across different regions of intestine, with resultant perforation and death.[125]

Caustic agent ingestion

Caustic ingestion is important in young children as these liquids typically have no flavour or odour. Strong alkalis cause injury by tissue liquefaction and necrosis. Furthermore, thrombosis of the supplying vessels results in reduced blood flow to hamper healing. A significant proportion in older teenagers and adults are due to a suicide attempt.[122] Detergents in the home are regulated by legislation. Since 2013 there has been a voluntary change by industry to prevent infant access to laundry tablets as these are alkaline. Liquitabs (liquid detergent parcels/tablets) are responsible for 1500 incidents each year in the UK.[128] The liquid within these tablets can also be inhaled and cause ocular injury and even death has been reported.[129] Caustic ingestion injury to the oesophagus can be graded 1–4 based on the

depth of injury. A review of caustic injury to children indicates that grade 1 is erythema and oedema, which can be managed conservatively. However, grade 4, which is perforation, has a poor prognosis.[122] Most strictures occur within 8 weeks of caustic ingestion and the subsequent dilatations may result in perforation. Furthermore, the risk of subsequent carcinoma is significantly higher (1000-fold). The carcinoma develops at the site of stricture.[130] For more detail on caustic ingestion, see Chapter 45, Oesophageal disorders.

KEY POINTS

- Foreign body-related incidents are common.
- Battery foreign bodies are increasing in frequency and can be fatal.
- Battery foreign bodies require removal without delay.
- A history of possible foreign body inhalation despite a comfortable patient should prompt bronchoscopy, even when chest examination and X-ray are normal. Neither examination nor plain chest films can exclude foreign body, and the risk of lung damage from an undiagnosed foreign body outweighs the small risk of complications of bronchoscopy in experienced hands.

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CHAPTER 35

PAEDIATRIC TRACHEOSTOMY

Michael Saunders

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords tracheostomy and child. The author has a personal bibliography of key papers on tracheostomy in children.

INTRODUCTION AND HISTORICAL PERSPECTIVE

Widely acknowledged as one of the oldest documented surgical procedures, detailed historical accounts of tracheostomy are many and vivid. Use of the procedure in children developed in the 19th century after Trousseau used the technique to relieve airway obstruction in diphtheria. Subsequently, the procedure was widely used in the treatment of poliomyelitis. With the introduction of extensive vaccination programmes these diseases have largely disappeared in the Western world.

Until the late 1970s many tracheostomies in children were performed to relieve airway obstruction in acute airway infections such as epiglottitis and acute laryngotracheobronchitis (ALTB, or croup).[1–3] As the standard of paediatric intensive care facilities improved and prolonged endotracheal intubation became a practical alternative to surgical tracheostomy, progressively fewer procedures were carried out for these indications. By the time haemophilus influenza b (Hib) vaccine was introduced in the 1990s, endotracheal intubation rather than tracheostomy had become the accepted mode of airway management for acute bacterial epiglottitis.[4]

In a series of 153 paediatric tracheostomies, Line et al.[2] report that prior to 1980 38% of tracheostomies were performed for acute airway infections whereas after 1980 this figure had dropped to 12%. Similar findings were reported by Friedberg and Morrison[5] when comparing a series of tracheostomies from 1981 to 1985 to a similar series from the same institution from 1976 to 1980. Crysdale et al.[6] also report an overall reduction by half in the incidence of tracheostomy in the same period, attributed to the change in management of epiglottitis. Corbett et al.[7] reviewed 116 cases over a 10-year period (1995–2004) and reported a further shift in indications, with no tracheostomies for acute airway infections alone and an increasing proportion required for congenital defects such as craniofacial anomalies and major upper gastrointestinal defects. Eighteen children (15.5%) required tracheostomy for acquired airway lesions including subglottic stenosis, vocal cord palsy and respiratory papillomatosis, while 14 tracheostomies (12.1%) were to facilitate management of airway malacia (laryngotracheal, bronchial or a combination). Tracheostomy was also required for long-term ventilation in patients with neuromuscular disorders (14; 12.1%) or ventilator dependency (31; 26.7%).

Tracheostomy in children is now an uncommon operation. Due to a shift in tertiary paediatric treatment to larger centres in the last decade and the lack of a reliable means of collecting data on a national basis, it is difficult to estimate the true incidence of paediatric tracheostomy. A survey of 2065 tracheostomies across the United States estimates a rate of 6.6 tracheostomies per 100 000 child years, with the highest incidence in the first year of life

but with a second peak in incidence in the late teens due to increased risk of serious injury and trauma.[8]

A more recent study of indications in 501 tracheostomies between 1984 and 2014 has found that the commonest indications for tracheostomy in children are now cardiopulmonary disease (34%), neurological impairment (32%) and airway obstruction (19%).[9]

As a consequence of the relative scarcity of the procedure, the medical literature relating to paediatric tracheostomy is generally related to level 3 and 4 evidence. There are no significant randomized controlled trials and the majority of publications tend to document the authors' own series of tracheostomies and their complications in larger children's hospitals. Reports of changing indications from such institutions may also be skewed by changes in medical practice in individual units.

INDICATIONS FOR PAEDIATRIC TRACHEOSTOMY

The general indications for tracheostomy are as follows:

- to relieve upper airway obstruction
- to prevent complications of prolonged intubation
- to reduce anatomical dead space
- to allow suction toilet of the trachea.

In practice, tracheostomies in children are nearly always performed to relieve upper airway obstruction or to allow or assist with mechanical ventilation.

Obstruction of the upper airway

The upper airway (from the lips and anterior nares to the carina) may become obstructed at one or more anatomical levels by a range of pathologies (Table 35.1). If the obstruction is significant and life-threatening and no other means of relieving the obstruction (e.g. nasopharyngeal airway or prong) is appropriate, then a tracheostomy must be considered.

Increasing availability and standard of paediatric intensive care facilities has allowed surgical procedures involving the airway to be undertaken without the need for a covering tracheostomy. Instead, the risk of post-operative airway obstruction is avoided by a period of intubation and ventilation (the 'single-stage' approach).

TABLE 35.1 Examples of obstruction of the upper airway potentially requiring tracheostomy

Anatomical site	Example
Oropharynx, tongue base	Macroglossia Treacher Collins/Goldenhar syndrome Cystic hygroma
Nose, nasopharynx	Choanal atresia
Supraglottis	Supraglottic cyst
Glottis	Vocal cord palsy Physical trauma
Subglottis	Subglottic stenosis, haemangioma
Trachea	Tracheomalacia High tracheal stenosis

The relative indications for tracheostomy continue to evolve: until the late 1990s, tracheostomy was considered the mainstay of management for obstructing subglottic haemangioma. Tracheostomy can be avoided using drug treatment[10] or surgical excision[11, 12] Similarly, the introduction of the cricoid split[13] and single-stage laryngotracheal reconstruction[14] has reduced the need for tracheostomy for extubation failure due to subglottic oedema or stenosis.

Prolonged intubation

The long-term complications of prolonged endotracheal intubation are well recognized: ulceration at the level of the glottis and, particularly in children, the subglottis, can lead to cicatrization and stenosis of the airway.[15] Being softer and more flexible than the adult and with correct selection of tube size and appropriate intensive care, the neonatal larynx is able to tolerate prolonged intubation for relatively longer than the adult.

There is no clear consensus as to the maximum safe duration of intubation. Premature babies may now be intubated for several weeks before permanent damage becomes a risk. Although practice varies in different units, tracheostomy should normally be considered in older children after 2–3 weeks of endotracheal intubation.

Long-term and home ventilation

An increasing number of children are now surviving previously lethal conditions, resulting in chronic respiratory failure because of the availability of long-term ventilation, either in a hospital setting or at home. In a 2011 survey of centres offering this service, out of 933 home-ventilated children in the UK, 206 had tracheostomies.[16] Indications for long-term ventilation include:

- congenital central hypoventilation syndrome
- spinal injury
- congenital myopathy
- airway malacia
- chronic lung disease.

Increasingly, these patients can be ventilated at home rather than in hospital although the cost in terms of manpower and equipment is high. The demands placed on the tracheostomy itself are higher and there is a higher risk of tracheostomy-related complications in home-ventilated children.

Tracheal toilet

In practice, very few children now require tracheostomy for toilet of the airway. Children with intractable aspiration may need regular suction but the presence of a tracheostomy can predispose to aspiration in itself and increase the risk of respiratory tract infection.

TECHNIQUES OF TRACHEOSTOMY SPECIFIC TO CHILDREN

Strictly speaking, a **tracheotomy** is the creation of a hole into the trachea. A **tracheostomy** is the fashioning of a permanent opening or stoma between the trachea and the skin. Although this difference has been largely semantic until recent years, it is now an important distinction as surgical technique in children's tracheostomies has evolved.

Positioning

Under general anaesthesia the infant is positioned supine on the operating table. Neck extension is achieved with a rolled towel or gel pillow under the shoulders. The neck can be fixed in extension and stabilized in the midline using adhesive tape such as Elastoplast® (Figure 35.1) or by using a horseshoe-shaped head rest. Theoretically, extension of the neck in infants increases the risk of injury to the great vessels in the root of the anterior neck; in practice, with careful dissection and identification of structures this is rarely a clinical problem. Overextension does, however, risk exposing a significant part of the intrathoracic trachea and can lead to an incision in the trachea which is too low.

Skin incision

In adult practice the conventional skin incision used is horizontal, situated halfway between the cricoid and sternal notch. Traditionally, a vertical incision has been avoided for fear of a poor cosmetic outcome after decannulation. However, after removal of a long-standing tracheostomy, the resulting scar is such that it is unlikely that the orientation of the original incision will make a significant difference. In the last two decades a vertical skin incision has become more popular with specialized paediatric otolaryngologists[17] and is now standard practice in most major children's units (Figure 35.2). A vertical incision has a number of advantages over the horizontal incision: it tends to keep dissection in the midline, reducing a tendency to stray away from the trachea in a difficult dissection, and allows easier placement of maturation sutures. The incision is placed halfway between the cricoid ring and the sternal notch. The skin incision does not need to be a great deal longer than will allow the insertion of the selected tube; surgical retraction of infant skin during surgery tends to lead to the skin defect appearing larger at the end of the procedure than the original incision.



Figure 35.1 Child positioned on the operating table for tracheostomy.

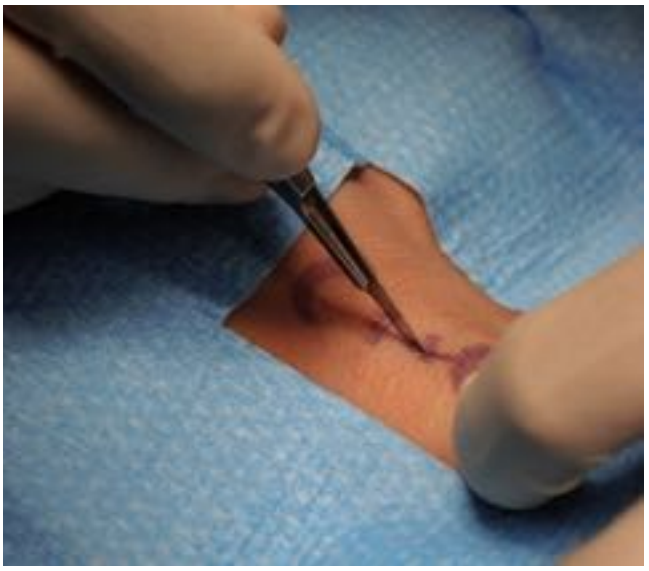


Figure 35.2 Skin incision in paediatric tracheostomy.

Removal of subcutaneous fat and maturation sutures

A disc of subcutaneous fat immediately surrounding the incision should be removed after completing the skin incision. This allows the skin edges to invert slightly so as to create a stoma lined with healthy squamous epithelium. This effect can be increased by suturing the edge of the skin incision to the edge of the tracheal incision (maturation sutures)[18] using absorbable sutures (the author's preference is 4/0 Vicryl Rapide). The resulting opening is more secure and tends to stay open even without the tube *in situ* and is therefore more akin to a surgically fashioned stoma (Figure 35.3) rather than the traditional approach which is essentially an incision in the neck and trachea only held open by the tracheostomy tube itself. Theoretically there is a lower risk of the tracheostomy tube being misdirected into the soft tissues at an emergency post-operative tube change (a false passage).

Stay sutures are placed in the wall of the trachea on either side of the vertical incision. These are generally a removable suture (e.g. 4/0 PROLENE) and are left *in situ* until the first tube change. In the event of accidental decannulation, upward and lateral traction on the sutures will open the tracheostomy to make tube reinsertion simpler. The sutures may be taped to the chest wall (Figure 35.4) to prevent accidental removal.



Figure 35.3 Maturation sutures and stay sutures in a paediatric tracheostomy prior to placement of the tracheostomy tube.



Figure 35.4 Stay sutures taped to the chest wall at the end of the procedure.

Dissection

Dissection using monopolar or bipolar diathermy is advisable in small children to minimize blood loss and should be restricted to the midline to avoid risk to other structures in the neck. Although in adults and larger children the thyroid isthmus is traditionally divided and transfixed to prevent haemorrhage, in infants it is usually adequate to divide the isthmus of the thyroid with bipolar diathermy.

Given the relatively small size of the infant neck and trachea, and secondly the relative proximity of the carotid sheath, it is advisable to palpate the trachea regularly throughout the dissection to ensure that the direction of dissection has not strayed from the midline.

Tracheal incision

A vertical incision is made in the midline, usually in tracheal rings 3–4. It is vital that the cricoid cartilage is identified before the incision is made so that the correct incision can be made. It has long been established that too high an incision in the trachea predisposes to subglottic stenosis.[19] A variety of other incisions has been advocated, including excision of an anterior tracheal window, a superiorly or inferiorly based tracheal flap which is raised and sutured to the skin or, recently, a cruciate incision in the trachea, the tracheal edges being closely apposed to the skin edges.[20] The theoretical advantage of most of these techniques is increased stability of the initial tracheostomy tract and therefore greater safety in the event of accidental decannulation. However, although there is no evidence available from randomized clinical trials, animal experiments[21] suggest that tracheal flaps may lead to an increased risk of long-term stenosis and the majority of authors currently favour a simple vertical incision.

Securing tracheostomy tubes

Until the tracheostome has epithelialized and matured, the risks associated with accidental decannulation are more significant. Initially, it is the author's practice to fix the tube into position in the neck using the inelastic linen tapes supplied with the tube. The tapes are tied in a secure knot, sufficiently tight to allow one finger to be inserted between the tapes and the neck skin (**Figure 35.5**). The tapes should be tightened with the neck flexed, rather than in the operative position with the neck extended. Suturing the flange of the tracheostomy tube to the skin should be avoided in children; infant skin is flexible and thin and does not provide a strong enough anchor point for fixing the tube.

After 7 days the first change is undertaken and the linen tapes may be changed for a Velcro® fastening (**Figure 35.6**) which allows for easier changing and is less traumatic to the skin of the neck. It is vital that, whatever fixing devices are used, they are applied correctly and at the right tension to prevent accidental decannulation.

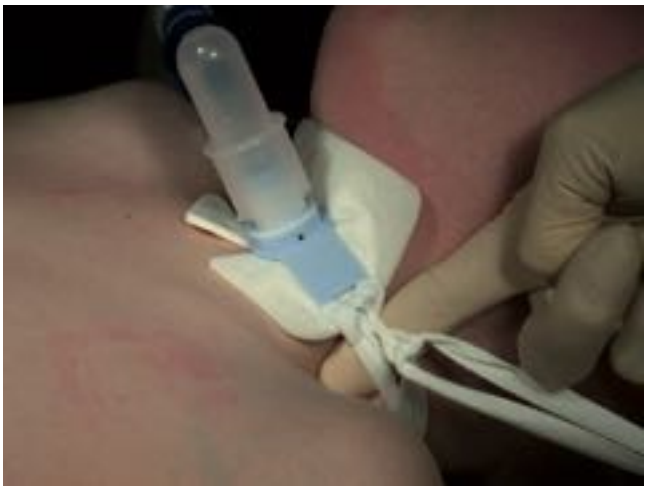


Figure 35.5 Adjusting the correct tension of securing tapes.



Figure 35.6 Velcro® tracheostomy fitting.

TRACHEOSTOMY CARE

Adequate tracheostomy care is critical in the first 2–3 post-operative days. It is during the formation of the tract of the stoma that the risk of tube displacement is at its highest as initially the tract can close very quickly, making reinsertion difficult. It is difficult to overstate the importance of tracheostomy nursing care in the post-operative period. With meticulous and skilled care, most of the complications of tracheostomy can be avoided. Inexperienced staff with no specific training are often reluctant to intervene. It is therefore essential that hospitals maintain a high standard of internal training in this regard, and many units have specific teams and regular training programmes for nursing staff.

Suction

Immediately after tracheostomy, the change from air that is warmed and humidified by the upper airway to dry, cold air leads to a rapid increase in airway secretions. This gradually reduces after a few weeks. Secretions dry on the inside of the tracheostomy tube and gradually reduce the effective lumen. Humidification of inspired air and regular suctioning will reduce this tendency. Suctioning is required as often as is necessary to keep the tube and airway clear. Overzealous suctioning may lead to mucosal trauma in the distal trachea if the catheter is inserted into the tracheal lumen itself[22] and eventually granulation may form at the tip of the tracheostomy tube, which in itself may lead to tube obstruction. It is suggested that the suction tube be inserted as far as the tip of the tracheostomy tube and withdrawn with a finger occluding the side port. The exact distance may be measured and marked on the suction tube.

The need for suctioning decreases in frequency over time, although with lower respiratory tract infections, secretions may become thicker and more profuse. On such occasions, irrigation of the tracheostomy tube with sterile saline to loosen secretions prior to suctioning is often advocated but there is little evidence to support this practice and it may increase contamination of the lower airway.[23]

Humidification

Initially, humidification should be given via nebulizers and a tracheostomy mask. After a week or so, secretions reduce and the level of humidification required is less. A few weeks after tracheostomy, more mobile devices can replace permanent humidification. Longer-term humidification may be achieved by using a Swedish nose or a tracheostomy bib (Figure 35.7). A heat and moisture exchanger (HME or 'Swedish nose') attachment (Figure 35.8) contains a filter which becomes saturated by the moisture in exhaled air; this in turn humidifies the inhaled air. The tracheal bib works in a similar way. Both devices have the advantage of acting as filters for inspired air.

Skin care

The tracheostomy wound itself becomes rapidly infected with skin commensals and is impossible to keep sterile. The wound heals by secondary intention and eventually the tract becomes lined with squamous epithelium and organized scar tissue. Securing the wound edge skin to the trachea with maturation sutures hastens the development of an epithelialized tract. At this stage the tracheostome is considered mature. Until this point there is usually a considerable discharge from the wound itself and, if the skincare in the first few days is not meticulous, skin and wound breakdown will occur. Usually a dry gauze or foam



Figure 35.7 Tracheostomy bib.



Figure 35.8 Heat and moisture exchanger (HME).

(e.g. Lyofoam®) dressing is inserted between the peritracheostomy skin and the flange of the tube. This is rapidly saturated and needs to be changed regularly. Of course the action of changing the dressing increases the risk of accidental decannulation and there is often reluctance on the part of nursing staff to do this. Adequate training in tracheostomy care is essential in a hospital where regular paediatric airway surgery takes place.

Large skin incisions are generally not required in elective paediatric tracheostomy. If not adequately closed, a large incision will lead to gaping and wound breakdown. It is futile to attempt closure in this instance because of the bacterial colonization of the wound and inevitable infection. Large tracheostomy wounds require careful dressing and packing similar to a healing ulcer, and a range of wound products are available. The wound will eventually close by secondary intention.

The tapes used to secure the tube in place can lead to ulceration of the neck skin if they are left too tight or for too long. Although the linen tapes supplied with tubes are secure, they are inelastic and have a tendency to cut into the skin. Again, meticulous nursing and skin care is vital. The problem can be reduced by tying the tapes inside a sleeve of Tubigrip™ or part of a large plastic (e.g. endotracheal) tube (Figure 35.9). When the tracheostomy matures, wider softer bands with Velcro® fittings may be used and are less traumatic to the neck skin.

Change of tracheostomy tube

The first change of tube is generally undertaken at around the seventh post-operative day. This allows some time for maturation of the stoma but is short enough to reduce the risk of tube obstruction from dried and thickened secretions. The first change should be undertaken by an otolaryngologist; in the relatively rare instance of difficulty reinserting the second tube, an emergency surgical procedure may be required.

If oral intubation is difficult or impossible (e.g. retrognathia, laryngeal stenosis), it is advisable to undertake the first change in the operating theatre in case further surgical intervention is needed. In children who can be easily intubated (including the majority of children tracheostomized for prolonged ventilation), it is more usual to undertake the first change on the intensive care unit, with an intubation trolley and senior ITU medical staff on hand should reinsertion be difficult and re-intubation be required.

If this procedure is uneventful, the nursing staff can carry out subsequent changes. If discharge home is anticipated, the parents must be taught the tube-changing technique in a secure environment.

There is no standard proscribed interval at which tubes should be changed; this varies between children and also in the same child given variation in season and in the health of the lower airway. The tube needs to be changed before dried secretions start to reduce the lumen of the tube. The old tube should be inspected after removal to determine the degree of contamination and this will influence the interval until the next change. If a tube visibly contains dried secretion on external inspection (Figure 35.10), has an audible whistle due to obstruction ('if you can hear a tube, you should change it') or if the suction catheter cannot be passed due to obstruction, then it should be changed. If the suction catheter does not pass freely after changing the tube, the advice of an otolaryngologist should be sought. (The manufacturers recommend that the commonly used Bivona® and Shiley® tubes are changed after a maximum of 28 days although most tubes are changed more frequently than this on clinical grounds.)

TRACHEOSTOMY TUBES

Diameter

Modern tracheostomy tubes are sized in relation to the diameter of the lumen in millimetres and the length of the tube from the skin flange to the tip of the tube. Some older silver tubes still use the French gauge system of sizing. The age-appropriate size for a tracheostomy tube can be derived from the guide shown in Figure 35.11. In general terms, smaller-sized tubes become obstructed more easily



Figure 35.9 Modified endotracheal tube used to protect the neck skin from tracheostomy tapes.



Figure 35.10 Tracheostomy tube partly obstructed with secretions.

			Preterm – 1 Month	1–6 Months	6–18 Months	18 Months – 3 Years	3–6 Years	6–9 Years	9–12 Years	12–14 Years
	Trachea (Transverse Diameter mm)		5	5.0–6.0	6.0–7.0	7.0–8.0	8.0–9.0	9.0–10	10–13	13
PLASTIC	Great Ormond Street	ID (mm)	3.0	3.5	4.0	4.5	5.0	5.5	6.0	7.0
		OD (mm)	4.5	5.0	6.0	6.7	7.5	8.0	8.7	10.7
	Shiley	Size	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5
		ID (mm)	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5
		OD (mm)	4.5	5.2	5.9	6.5	7.1	7.7	8.3	9.0
		Length (mm) Neonatal	30	32	34	36				
		Paediatric	39	40	41*	42*	44*	46*		
	* Cuffed Tube Available	Long Paediatric					50*	52*	54*	56*
	Portex (Blue Line)	ID (mm)	3.0	3.5	4.0	4.5	5.0	5.0	6.0	7.0
		OD (mm)	4.2	4.9	5.5	6.2	6.9	6.9	8.3	9.7
	Portex (555)	Size	2.5	3.0	3.5	4.0	4.5	5.0	5.5	
		ID (mm)	2.5	3.0	3.5	4.0	4.5	5.0	5.5	
		OD (mm)	4.5	5.2	5.8	6.5	7.1	7.7	8.3	
		Length Neonatal	30	32	34	36				
		Paediatric	30	36	40	44	48	50	52	
	Bivona	Size	2.5	3.0	3.5	4.0	4.5	5.0	5.5	
		ID (mm)	2.5	3.0	3.5	4.0	4.5	5.0	5.5	
		OD (mm)	4.0	4.7	5.3	6.0	6.7	7.3	8.0	
	All sizes available with Fome Cuff, Aire Cuff, & TTS Cuff	Length Neonatal	30	32	34	36				
		Paediatric	38	39	40	41	42	44	46	
	Bivona Hyperflex	ID (mm)	2.5	3.0	3.5	4.0	4.5	5.0	5.5	
		Usable Length (mm)	55	60	65	70	75	80	85	
	Bivona Flextend	ID (mm)	2.5	3.0	3.5	4.0	4.5	5.0	5.5	
		Shaft Length (mm)	38	39	40	41	42	44	46	
		Flextend Length (mm)	10	10	15	15	17.5	20	20	
SILVER	Alder Hey	FG		12–14	16	18	20	22	24	
	Negus	FG			16	18	20	22	24	26	28
	Chevalier Jackson	FG	14	16	18	20	22	24	26	28
	Sheffield	FG	12–14	16	18	20	22	24	26	
		ID (mm)	2.9–3.6	4.2	4.9	6.0	6.3	7.0	7.6	
	Cricoid (AP Diameter)	ID (mm)	3.6–4.8	4.8–5.8	5.8–6.5	6.5–7.4	7.4–8.2	8.2–9.0	9.0–10.7	10.7
	Bronchoscope (Storz)	Size	2.5	3.0	3.5	4.0	4.5	5.0	6.0	6.0
		ID (mm)	3.5	4.3	5.0	6.0	6.6	7.1	7.5	7.5
		OD (mm)	4.2	5.0	5.7	6.7	7.3	7.8	8.2	8.2
	Endotracheal Tube (Portex)	ID (mm)	2.5	3.0	3.5	4.0	4.5	5.0	6.0	7.0	8.0
		OD (mm)	3.4	4.2	4.8	5.4	6.2	6.8	8.2	9.6	10.8

Figure 35.11 Chart for sizing tracheostomy tubes. Reproduced from Tweedie et al.[25]

and may impair respiration if too small for the age of the child. A child with a long-standing tracheostomy should undergo regular age-appropriate 'upsizing'. However, tracheostomy tubes tend to almost completely fill the trachea in very young children, making normal speech difficult. In some cases – for example, if the airway above the tracheostome is not completely obstructed – a smaller-sized tube will allow air to flow up thought the glottis and aid in normal speech production. Too large a tube will predispose to suprastomal collapse and may increase the risk of granulations and stenosis.

Tube length

When inserted correctly, the end of the tracheostomy tube should sit comfortably proximal to the carina. Too long a tube will abut the carina and lead to ventilation problems, mucosal injury and potentially subsequent scarring. Too short a tube increases the risk of accidental decannulation. Ideally, the tube should be at least 2 cm, inside the stoma and 1–2 cm clear of the carina.[24] Tube tip position can be assessed on chest X-ray, at regular rigid bronchoscopy or by passing a flexible endoscope down the lumen of the tube to inspect the carina.

Material

The use of metal and very rigid plastic tracheostomy tubes in children has been largely superceded. Soft or siliconized PVC is now the most widely used material in paediatric tracheostomy tubes and materials may be hydrophobic to reduce the deposition of secretions. The relative flexibility of newer tubes reduces the risk of mucosal trauma during neck movements and the soft flange is less likely to lead to skin injury around the tracheostome. One advantage of metal tubes was that, as the stronger metal wall could be made thinner, it was possible to achieve a larger lumen for the same outside tube diameter and as a result an inner tube could be used. The thickness of the wall of standard tubes makes inner tubes impractical in all but the largest children's tracheostomy tubes.

Fenestration

Fenestrated tubes allow air to pass upwards through the glottis in expiration to improve phonation. These are less practical in smaller children as the fenestration tends to become a focus for granulation and mucosal trauma on suctioning. Adequate passage of air upwards into the larynx is usually achieved by selecting a smaller tube diameter and allowing air leakage around the tube on expiration.

Cuff

There are two specific indications for cuffed tubes in children: first, where there is a significant risk of aspiration (although a cuff will not completely protect against this) and, second, where there is a decrease in lung compliance with intercurrent infection in a ventilated child and ventilation pressures need to be raised temporarily. In this instance, the risk of tension pneumothorax is significantly increased. In the author's institution, children on the home-ventilation programme are admitted to hospital for observation if the ventilation pressures become high enough to require a cuffed tube.

The presence of a cuff increases the risk of mucosal ischaemia and subsequent tracheal stenosis, particularly if high cuff pressures are employed. Traditionally, cuffed tubes are rarely indicated in paediatric practice; until adolescence, a sufficient seal to allow positive pressure ventilation can normally be achieved with an uncuffed tube. In the last decade there has been an increase in the use of cuffed endotracheal and tracheostomy tubes in paediatric intensive care units. This may reflect the increasingly complex nature of children being treated in hospital but it is not currently clear if this will lead to an increase in the rate of subglottic and tracheal stenosis.

Types of tube

An increasingly wide variety of tracheotomy tubes is available for specific indications. An excellent review of available tubes is given by Tweedie et al.[25] The commonest standard tubes used in the UK at the time of writing are the Shiley® and Bivona® tubes. They are available in neonatal and paediatric lengths, and the Shiley® tube is also available in a paediatric long (PDL) size for older children.

The Bivona® Flextend™ tube is a silicone tracheostomy tube with a longer external component than a normal tracheostomy tube (**Figure 35.12**). This allows a greater degree of flexibility in children who are mechanically ventilated and is particularly useful in very small infants with a limited gap between the chin and chest (**Figure 35.13**). The main disadvantage of this tube is the increased length of tube, which increases the dead space and risk of obstruction by secretions.



Figure 35.12 Bivona® Flextend™ tube (with Rusch speaking valve).



Figure 35.13 Anatomical difficulty with limited space between the chin and the chest wall.

The Bivona® Hyperflex™ tube has an adjustable flange which allows change of the effective length of the tracheostomy tube (Figure 35.14). This is useful in children with particular anatomical constraints, for example where a low tracheal obstruction needs to be bypassed by the tube and a standard length tube cannot be used. The disadvantages of this sort of tube are that it is expensive and that the wall of the tube is thick, resulting in a relatively small tube lumen. Other custom-made tubes are available for children with specific anatomical difficulties. Tube manufacturers should be approached directly for advice.

Speaking valves

Speaking valves are one-way valves which allow inhalation though the tube but force air upwards through the glottis on exhalation, creating sufficient subglottic pressure to allow phonation. As well as allowing speech, by increasing tracheal pressure on exhalation, these may improve lung function and reduce aspiration.[26] In addition to these possible benefits, it is beneficial to a child to get used to the sensation of expiration through the normal airway, particularly pre-decannulation. Speaking valves should be used under supervision and not while the child is asleep, and they are best used with advice from speech therapy. Small infants will not always tolerate the valve and quickly learn to blow the valve off the tracheotomy by coughing hard. Many children learn to occlude the end of the tube on exhalation by flexing the neck and occluding the end of the tube with the neck skin to achieve the same result to help phonation. Rusch speaking valves (see Figure 35.12) are open apart from in significant expiration whereas the Passy-Muir® valve (Figure 35.15) is designed to be closed apart from in inspiration and encourages use of the normal airway for expiration even in quiet respiration. The Passy-Muir® valve may be modified in children who find it hard to tolerate by drilling small holes to allow some expired air to escape.[27]



Figure 35.14 Bivona® Hyperflex adjustable tube.



Figure 35.15 Passy-Muir speaking valve.

COMPLICATIONS OF TRACHEOSTOMY

General

Tracheostomy complications are more likely in children than in adults, and more common in children under 2 years of age,[1, 28] particularly preterm infants.[29] Overall complication rates are quoted between 25%[30] and 77%.[31] There is likely to be considerable variation in the documentation and reporting of minor complications – some authors do not consider granulation to be a reportable complication (Table 35.2).

The higher complication rate in smaller children is likely to reflect the relatively small diameter of the airway in small children and the ease with which the airway may be occluded (for example by secretions, granuloma or suprastomal collapse), but also the fact that younger children receiving tracheostomy may remain tracheostomized for a longer period.[31]

As with adult tracheostomies, emergency procedures are associated with a higher rate of complications[32] and longer duration of tracheotomy is associated with a higher risk of long-term complications.[33] Given the relative scarcity of

TABLE 35.2 Complications of tracheostomy

Time after tracheostomy	Complications
General	Tube obstruction Accidental decannulation General complications of surgery and anaesthesia Death
Early post-operative (up to 1 week)	Bleeding: post-operative, wound edge Pneumothorax Subcutaneous emphysema Infection Apnoea
Late post-operative (after 1 week)	Granulation Bleeding Suprastomal collapse Skin complications Aphonia, speech delay Psychological factors Adverse effects on family

paediatric tracheostomy and the limited number of large published series, it is difficult to accurately derive a risk for fatal complications of paediatric tracheostomy. Of larger studies reported since 1980, the mortality related to the tracheostomy tube itself ranges from 0% to 3.6% (Table 35.3).[30, 34] In nearly all cases, the cause of tracheostomy-related death is tube obstruction or accidental decannulation. Earlier reports quote higher mortality rates but paediatric otolaryngology practice has changed considerably in the last 30 years and older studies are unlikely to reflect current practice and safety. Mortality from non tracheostomy-related medical conditions, such as respiratory or cardiovascular disease, is consistently high (7–36%) in all series,[32, 35] reflecting the complex medical conditions of children requiring tracheostomy.

Accidental decannulation

If there is little or no natural airway above the tracheostomy or if a child is ventilator-dependent, accidental decannulation can be fatal. The risk is increased by insufficiently tight ties, too short a tracheostomy tube and excessive traction on the tube from ventilator tubing. In the first few days before the tract matures, it is likely to be harder to reintroduce the tube if decannulated. Wetmore et al.[1] report accidental decannulation in 29 of 420 (6.9%) children in the first week.

The risk of accidental decannulation may be reduced by meticulous tracheostomy nursing care, and surgical techniques (stay sutures, maturation sutures) may help reduce the morbidity by allowing easier and safer reinsertion of a displaced tube. In the event of accidental decannulation, the tube should be reintroduced in a controlled manner to prevent the creation of a false passage.

Tube obstruction

Immediately after tracheostomy the tube is most likely to become blocked with secretions. Regular suction is required. Humidification reduces the rate of secretion and helps to prevent the secretions drying in the lumen of the tube and narrowing the airway. In a mature tracheostomy, the tube is more likely to be obstructed by granulation as

TABLE 35.3 Large ($n > 100$) series of paediatric tracheostomies and complications

Study and publication year	Number of tracheostomies	Years of study	Overall complication rate (%)	Early complication (%)	Late complication (%)	Overall mortality (%)	Tracheostomy-related death (%)
Line et al. 1986[2]	153	1970–1985	38	12	26	22	3
Crysdale et al. 1988[6]	319	1976–1985	32	9	23	13.5	0.9
Carter and Benjamin 1983[30]	164	1972–1981	25	5 (est)	19 (est)	10.9	0
Carr et al. 2001[31]	142	1990–1999	77	14	63	15	0.7
Prescott and Vanlierde 1990[3]	293	1980–1985	32 (est)	–	–	10	2
Carron et al. 2000[34]	218	1988–1998	44	–	–	19	3.6
Midwinter et al. 2002[35]	143	1979–1999	46	–	–	7	2.8
Wetmore et al. 1982[1]	420	1971–1980	49	28.3	52.6	28	2
Ward et al. 1995[32]	103	1980–1990	45.6	30	15.6	36	2.9
Corbett et al. 2007[7]	116	1995–2004	45	11.2	44.8	19.6	1.8
Levi et al. 2016[36]	264	2001–2011	32.6	7.6	25.0	22.0	n/a
Mahadevan et al. 2007[37]	193	1987–2003	51	7.4	43.0	14.0	1.6
D'Souza et al. 2016[38]	302	2000–2014	19.9	13.9	3.4	n/a	0
Ozmen et al. 2009[39]	282	1968–2005	18.0	8.5	10.0	19.0	1
De Trey 2013[40]	119	1990–2009	23	–	–	23	0.84

(est) = figure estimated from text.

the tube tip, as a result of either use of suction catheters or direct trauma from the tube itself.

Pneumothorax, pneumomediastinum, surgical emphysema

In the infant the domes of the pleura extend well into the neck. Inadvertently straying from the midline during dissection increases the risk of post-operative pneumothorax. This should be detected immediately post-operatively on a routine chest X-ray. Small pneumothoraces can be treated conservatively while larger ones will require chest drainage.

If the tracheostomy wound is closed too tightly around the tube, or the dressings are too tightly applied to the neck skin, air may leak into the soft tissues of the neck (surgical emphysema) or track down into the mediastinum. In this instance the wound should be reopened to allow air to track back out through the tissues and a corrugated drain should be inserted. Pneumothorax is a rare complication in elective tracheostomy but commoner in emergency tracheostomy.[41, 42] Although it considered normal practice to perform a chest X-ray after all paediatric tracheostomies both to check tube position and to exclude pneumothorax, Genther and Thorne have suggested that the radiation risk from this may not be justified in an otherwise uncomplicated elective procedure.[43]

Bleeding

Bleeding in the first few days after tracheostomy usually arises as a result of failure to achieve complete haemostasis during surgery. Commonly, bleeding may persist from the wound edge, anterior jugular veins or their tributaries, or the edge of the thyroid isthmus. If direct pressure is not adequate to control haemorrhage, the wound may be carefully packed with haemostatic gauze (Surgicel or Kaltostat®). Re-exploration is rarely required.

Later, minor bleeding may arise from areas of granulation around the tube. This can normally be controlled with cautery and ongoing medical treatment such as application of steroid and antibiotic ointment.

Tracheo-innominate fistula

Tracheo-innominate artery fistula is a rare but lethal complication. There is no reliable estimate of the risk in children, which in adults has been estimated as 0.4%.[44]

In some children the innominate artery lies abnormally high in the neck (**Figure 35.16**). If this finding is made at the time of surgery, the decision to perform a tracheostomy should be reconsidered. If there is no safe alternative, it is acceptable to place the tracheal incision higher than one would normally advocate and accept the risk of subglottic stenosis. An abnormally low tracheostomy will also increase the risk. A fistula into the artery forms as a result of erosion of the arterial wall by direct pressure from the tube.



Figure 35.16 High innominate artery.

Although most bleeding coming from the tracheostomy tube itself is likely to represent granulation formation at the tube tip, in all cases the possibility of tracheal innominate artery fistula should be considered. The trachea should be examined by flexible bronchoscopy on the ward or by rigid endoscopy under anaesthesia. If the bleeding appears to arise from the anterior tracheal wall rather than tube-tip granulation, the wound must be re-explored immediately, ideally with the assistance of a cardiothoracic surgeon. It may be possible to tamponade the bleeding by using a cuffed tube temporarily and, if the laryngeal anatomy permits, endotracheal intubation should be established prior to exploration. The mortality from this complication remains very high.

Granulation

The presence of the tracheostomy tube as a foreign body and the persistent presence of bacterial flora in the tract act as an ongoing stimulus for the formation of granulation tissue. Granulation may form at the skin edge of the tract (peristomal granulation) and inside the trachea itself, both on the anterior wall of the trachea above the tube (suprastomal granulation) and also at the tube tip lower in the trachea. Excessive or overexuberant suctioning can lead to more granulation through mucosal trauma and the tube itself can cause mucosal injury. This was generally more common with more rigid tube designs, particularly the silver[45] and PVC designs.

Granulation tissue can pose a number of problems: on the surface, granulations tend to discharge and bleed and, when severe, they can lead to difficulty in changing the tube. More modern tubes made from less reactive silicone are more flexible and softer and are felt to reduce the problem both at the skin and inside the trachea.

Peristomal granulations can generally be controlled with topical steroid/antibiotic preparations. When more severe, they may be removed with bipolar diathermy. Caution needs to be exercised when using silver nitrate cautery as the silver nitrate solution can easily enter the

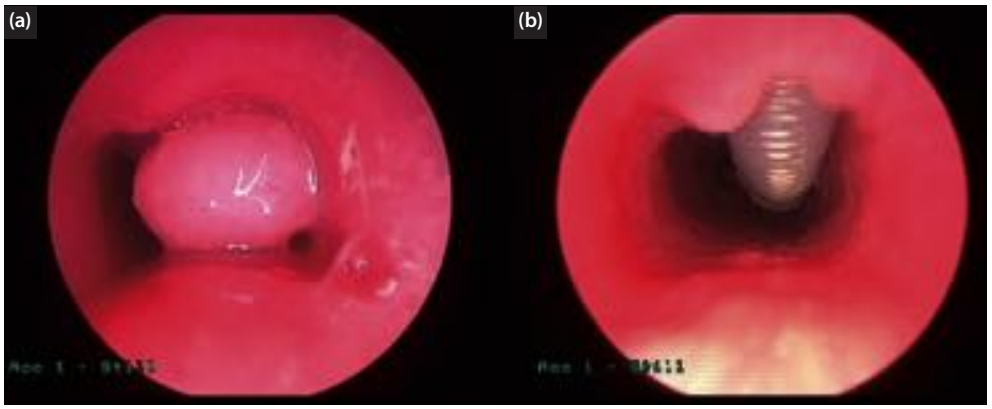


Figure 35.17 Obstructing suprastomal granuloma
(a) before removal, and
(b) 1 month after removal.

trachea itself, leading to irritation, coughing and mucosal injury. In the author's unit, this practice is avoided.

Suprastomal granulations are almost universal. In theory, if they are large, they will reduce the lumen of the supraglottic airway above the tube and increase the risks associated with accidental decannulation. Large suprastomal granulations can affect tube changing and make the use of a speaking valve impossible (**Figure 35.17**). Many authors advocate their removal at endoscopy on a regular basis,[46] however others feel that they are an inevitable consequence of tracheostomy; Rosenfeld and Stool[47] describe granulation in 80% of 265 tracheostomies at bronchoscopy and advise against interval endoscopy to remove granulation tissue. At microlaryngoscopy, immediately prior to planned decannulation, all granulation should be removed to maximize airway patency. After decannulation and stomal closure, granulation generally resolves spontaneously.

REMOVAL OF SUPRASTOMAL GRANULATION

If required, suprastomal granulations may be removed endoscopically using microlaryngeal instruments, a microdebrider using a Skimmer® or Tru-Cut® blade or by KTP or CO_2 laser. The KTP laser has the advantage of beam delivery using a flexible optic fibre in the relatively limited confines of the subglottis.

Large granulation may be removed using a small sphenoid punch or a sinus surgery backbiting forceps inserted into the tracheostome from externally, under endoscopic guidance at mircrolaryngoscopy. Alternatively, if the child can be intubated normally, the ET tube pushes the granulation externally out of the stoma where it can be excised by sharp dissection.[48]

Suprastomal collapse

Suprastomal collapse is distinct from suprastomal granulation although the two conditions often coexist. For reasons that are not completely understood, the anterior tracheal wall immediately superior to the stoma itself softens and prolapses into the lumen of the subglottic trachea (**Figure 35.18**). This can significantly reduce the available airway, which in turn increases the risks associated with accidental decannulation and also leads to decannulation failure.



Figure 35.18 Suprastomal collapse.

Minor collapse may be left, as it will tend to improve after decannulation. More significant collapse will require surgical treatment. The simplest of these involves excision and transfixion of the tracheostomy tract followed by endotracheal intubation for 2–3 days to support the trachea as the stoma heals.[49]

The author's preference in mild to moderate suprastomal collapse is to explore the neck, identify the area of suprastomal collapse and pass a suture through the cartilage and around the strap muscles to elevate the collapsed section. This is carried out with excision and transfixion of the tracheostome skin. Sharp and Hartley[50] describe ablation of the collapsed segment with KTP laser, and a number of authors have described supporting the collapsed segment with a cartilage graft in more severe collapse.[51] The specific procedure will depend on the degree of collapse and the surgeon's personal preference.

Speech development

A tracheostomy may adversely affect the development of speech in children. Clearly, normal phonation will be impaired for the duration of a tracheostomy as insufficient subglottic pressure is generated, and small infants tend not

to tolerate speaking valves well. A significant proportion of tracheostomized children have coexisting developmental abnormalities which can make it difficult to assess the relative effect of the tracheostomy. If decannulation occurs in the first 12–18 months, before the time at which normal speech patterns begin to develop, the long-term outcome is favourable,[52] whereas longer-term tracheostomy may lead to longer-term impairment of speech function.

Effects on caregivers and family

Caring for a child with a tracheostomy puts a significant strain on carers and families. The demands on the caregiver's time may be exhausting and the extra effort required may prevent carers engaging in employment. As a result, mental health status[53] and social-economic status[54] are adversely affected in caregivers of children with tracheostomy. The degree of community nursing support that families currently receive in the UK is very variable and dependent on local healthcare policy and provision.

TRACHEOSTOMY SAFETY INITIATIVES

The majority of life-threatening tracheostomy-specific complications (tube displacement and blockage) should be avoidable with correct tracheostomy care. Furthermore, if these complications are recognized quickly, they should be rapidly treatable. Children with tracheostomies are unusual and the medical and nursing skills required are not always immediately available. The UK National Tracheostomy Safety Project[55] is a multidisciplinary collaboration devised to improve the management of child and adult patients with tracheostomies. The recommendations of the project include the following:

1. An emergency minimum set of equipment should accompany a tracheostomy patient at all times, including spare tubes, suction catheters and dressings (Figure 35.19).



Figure 35.19 Box containing emergency equipment for a tracheostomy patient.

2. Bedhead documentation should be displayed at all times providing immediately visible information including tube size and length, and existing upper airway abnormalities (Figure 35.20).
3. Emergency treatment algorithms should be provided for attending resuscitation teams (Figure 35.21).

It is hoped that making this information and equipment visible to first responders and resuscitation teams will improve the safety of patients with tracheostomies and

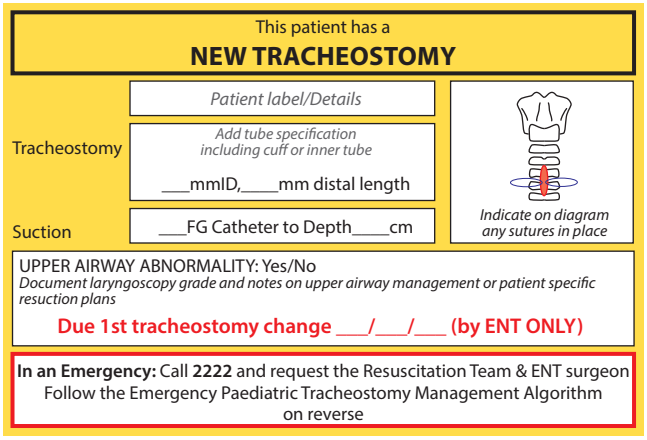


Figure 35.20 Bedhead documentation for a new tracheostomy.

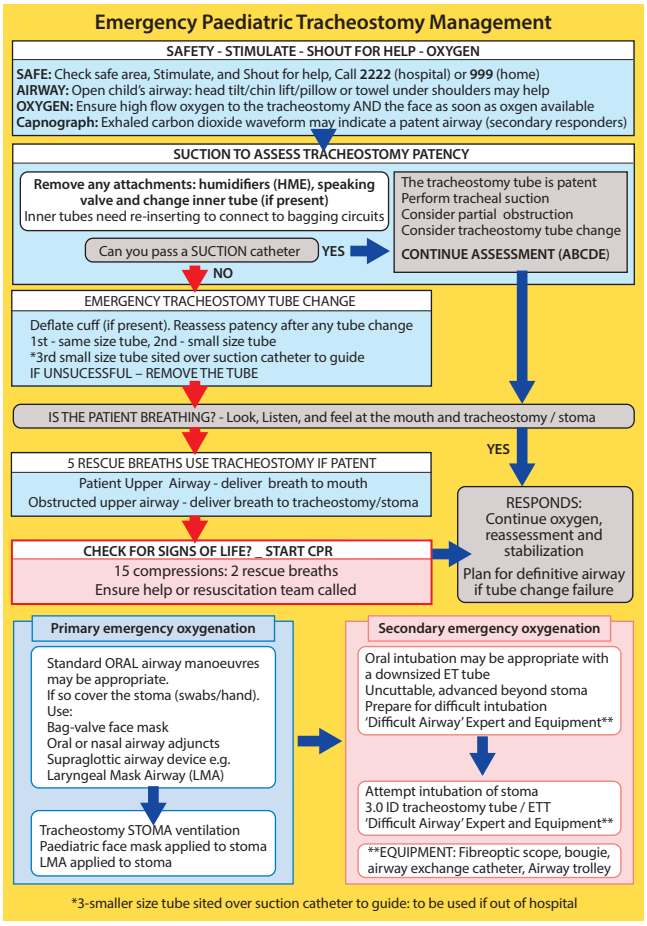


Figure 35.21 Emergency algorithm for resuscitation.

the outcome of complications. The Global Tracheostomy Collaborative formed in 2012 is a multidisciplinary and international organization which shares information and experience to disseminate best practices and improve outcomes.[56]

DISCHARGE AND HOME CARE

Discharge

Getting home with a tracheostomy is a complex and time-consuming process. Not all families will have sufficient support or resources at home to care for children with a tracheostomy. While in hospital, the caregivers must be educated to care for the day-to-day eventualities of tracheostomy, including tube changing, the recognition and initial treatment of complications and basic life-support training.[57] Generally, two responsible adults are required for tube change; home tracheostomy care is difficult but not impossible for single carers. Children who are included in home-ventilation programmes tend to be more carefully supervised and a national protocol for discharge requirements is well established.[58] Non-ventilated tracheostomized children tend to have less structured support. In some areas, specific local organizations exist for the community nursing care of children with complex illnesses; in other areas home care is shared between hospital and primary care district nurses who have little specific training.

With sufficient support and education of teachers and coworkers, tracheostomized children without other significant disabilities can now attend mainstream schooling in the UK, although certain activities must be avoided, particularly swimming, water-based sports and contact sports.

Physical requirements

Boxes 35.1 and 35.2[59] list the resources required for the child with a tracheostomy at home. In the author's experience, the ease with which equipment and accessories can be obtained by caregivers is extremely variable in the

BOX 35.1 Requirements for children at home with tracheostomy

Caregivers	Physical	Support
Generally two responsible adults	Home with adequate space, heating, electricity, telephone, access to transport	District nurse Community paediatrician Health visitor General practitioner Hospital-based support Specific community organizations where available

BOX 35.2 Equipment requirements for children at home with tracheostomy with and without home ventilation

Most of the items need to be duplicated in a portable set. A battery-powered suction machine is essential and, if the child is oxygen-dependent, portable cylinders. Reprinted with permission.[57]

Requirements for children without ventilation	Additional requirements for children on home ventilation
Appropriate-sized tracheostomy tubes and one a size smaller	Two ventilators/CPAP machines, one of which is portable plus batteries and chargers for use outside the home
Neck ties to hold tube in place	Disposable ventilator circuits
Scissors for emergency tube change to cut neck ties	Humidifier for ventilator circuit and water for inhalation to supply humidifier
Lubricant for inserting tube	Dry circuit for ventilation when outside the home
Sterile saline and syringes for saline suction if required	Heat and moisture exchanger for dry circuit
Tracheostomy dressing if required	Nebulizer
Gauze to clean stoma	CO_2 monitor
Appropriate-sized suction catheters	Rechargeable torch for use at night in the event of a power cut
Heat and moisture exchangers / Swedish noses	Uninterrupted power supply – battery which powers ventilator in the event of a power cut
Speaking valves	Suitable trolley in bedroom for equipment
Gloves – non-sterile for procedures and alcohol gel hand rub	Adequate power sockets in house, particularly child's bedroom
Plastic aprons and protective goggles	Trolley for children with a lot of equipment to transport equipment at nursery/school
Stethoscope	Larger than normal buggy when baby/toddler to transport child and equipment
Two suction machines, one of which must be portable. Most children keep a third machine at school as spare	
Saturation monitor and possibly portable saturation monitor for use outside the home	
Ambu bag	
Oxygen: concentrator if used on a daily basis, cylinders if used less frequently, portable cylinders	

community as financial constraints in the delivery of care lead to reluctance to supply regular consumables. Prior to discharge, it is essential to communicate with the child's general practitioner and other primary care workers and establish responsibility for provision of equipment.

DECANNULATION

Decision to decannulate

Decannulation may be considered when the original condition requiring tracheostomy has improved but, to make decannulation successful, the child must be able to maintain an adequate airway without the tracheostomy in place.

The majority of paediatric tracheostomies are short term, as the natural airway tends to improve with overall growth of the child or as a result of corrective surgery such as laryngotracheal reconstruction. The decision to decannulate is a complicated one which needs to be taken by a senior clinician after careful discussion with the parents and other relevant healthcare professionals.

In paediatric otolaryngology practice it is generally considered essential to undertake endoscopic assessment of the airway prior to definitive decannulation.[49] Suprastomal collapse and granulation lead to a considerable reduction in the lumen of the subglottic airway in children. Prescott[60] suggested that this was the most common cause of decannulation failure in children, finding significant granulation in 50 and significant suprastomal collapse in 52 of 300 tracheostomies. In addition, vocal cord mobility should be assessed at endoscopy. Granulation may be removed at the time of endoscopy using punch forceps or laser ablation. More significant suprastomal collapse requires KTP laser ablation or reconstructive surgery using cartilage grafting if the collapse is greater than 50%.[50] If the subglottic airway is deemed satisfactory at endoscopy, the child may then proceed to formal decannulation in the next few days.

One should also consider comorbidity, such as pulmonary, neurological disease, and the need for further surgery; if a child requires operations that may temporarily compromise the airway (e.g. mandibular advancement or cleft palate repair), decannulation should be deferred until these treatments are complete.

Decannulation technique

Removal of a tracheostomy leads to a significant change in the physiology of the upper airway. The dead space is doubled and airway resistance is trebled. With a long-standing tracheostomy, the child may have no memory of mouth and nose breathing and the new sensation may be distressing ('decannulation panic').

STAGED DECANNULATION

To effect these changes more gradually, decannulation protocols have been developed which involve tube 'downsizing' and reversible capping (**Table 35.4**).[61] To assess whether the child can breathe through the normal anatomical airway, the tube is capped off, either with a button, by taping or by inserting the obturator. However, the tracheostomy tube itself occupies a significant fraction of the tracheal lumen and, to try to reduce this effect, the tube size is reduced to a size 3.0 (or size 2.5 in children under 13 months[62]), either in stages or in one step. Leaving the small tube *in situ* allows a certain amount of respiration if required and also prevents the tract from closing down should decannulation fail.

TABLE 35.4 Great Ormond Street protocol for ward decannulation. Reprinted with permission[47]

Day	Procedure
1	Admission, downsize to 3.0 tube
2	Block for 12 hours from 8 a.m. If successful, continue overnight for a further 12 hours
3	Decannulate, occlude stoma with adhesive tape and dressing. Observe on the ward
4	Observe off the ward
5	Discharge

IMMEDIATE DECANNULATION

The tracheostomy tube may occupy as much as half of the lumen of the trachea in an infant. If a child can tolerate this degree of obstruction, the airway after decannulation is likely to be more than sufficient. However, some children will not be able to tolerate this degree of tracheal obstruction. In this instance, it may be considered appropriate to simply remove the whole tube and occlude the stoma with a dressing. However, it is vital that this be carried out in a controlled setting (i.e. intensive care) where facilities for intubation are available should decannulation fail and reinsertion of the tracheostomy not be possible. If the nature of the child's airway obstruction is such that oral intubation is not possible (e.g. some cases of Treacher Collins syndrome), then it is not safe to remove the tube in this manner, and decannulation should be delayed until the child is large enough to tolerate staged decannulation with capping off.

Persistent tracheocutaneous fistula

After decannulation, a fistula may persist between the trachea and skin. This may be small and only lead to problems with discharge of tracheal secretions. A larger fistula may continue to function as an alternative airway.

The incidence of tracheocutaneous fistula (TCF) is between 19% and 42% in various series. Certain factors lead to an increased risk: lower age at initial tracheostomy, duration of tracheostomy and, most importantly, persistent obstruction above the level of the stoma (e.g. inadequate reconstruction of subglottic stenosis). Although it is often felt likely that stomal maturation sutures lead to an increased risk of fistula formation, this has been disproven in larger recent series ($n > 100$).[36, 63]

There is no specific consensus as to how long a persistent TCF should be allowed to close before considering surgery. Most authors would allow 6–12 months before formal closure is attempted.

Closure of TCF

It is essential that the upper airway be reassessed prior to TCF closure to exclude persistent obstruction and tracheal granulation. Some children will still be using the fistula as an accessory airway if the original obstruction is not resolved. The persistence of squamous epithelium lining the tracheostome increases the likelihood of a persistent fistula. Surgically removing the skin lining the tract, or cauterizing the tract using diathermy, coblation or chemicals such as trichloroacetic acid may lead to scarring and satisfactory closure.[64] This has become known as **secondary closure** or closure by secondary intention.

More commonly, the tract of the stoma is dissected down to the level of the trachea and closed with transfixion sutures. This is referred to as **primary closure**. The strap muscles can then be reapposed to each other, which tends to fill in the cosmetic defect left after conventional decannulation. Lastly, the scarred skin surrounding the tracheostome can be excised in a fusiform incision with horizontal skin closure. This leads to a much improved cosmetic result. It is the author's practice to leave a drain in the wound for 24 hours in case of air leak from the closure, which might otherwise lead to surgical emphysema and pneumomediastinum.

Because of the increased risks associated with primary closure, some authors advocate secondary closure as the preferred technique[65] although a recent systematic review found no difference in outcome or complication between the two techniques.[66]

Revision of the tracheostomy scar

Revision of the tracheostomy scar (**Figure 35.22**) usually involves a fusiform horizontal incision to excise the scarred skin of the tracheostome with wide undermining of surrounding skin to assist in primary closure. The strap muscles should be identified and reapposed in the midline to eliminate the defect in the contour of the neck skin. Deep dermal/platysmal sutures are used to support the wound and then the skin edges are closed meticulously. Flexing the neck makes it easier to close a large skin defect.



Figure 35.22 Scar following long-term tracheostomy.

BEST CLINICAL PRACTICE

- ✓ Endotracheal intubation rather than tracheostomy is the accepted mode of management for acute obstructing airway infection in children.
- ✓ Premature babies may be safely intubated for several weeks. Tracheostomy should normally be considered in older children after 2–3 weeks of endotracheal intubation.
- ✓ Large skin incisions are generally not required in paediatric tracheostomy. A vertical skin incision is preferred to a horizontal one.
- ✓ Careful dissection using diathermy is advisable in small children to minimize blood loss.
- ✓ Palpate the trachea regularly throughout the dissection to ensure that you have not strayed from the midline.
- ✓ A simple vertical incision to open the trachea is associated with the lowest risk of long-term complications. Avoid removing any cartilaginous tissue in children.
- ✓ Stay sutures in the wall of the trachea on either side of the vertical incision facilitate reintroduction of the tube in the event of accidental decannulation before a mature track has developed.
- ✓ Maturation sutures securing the edge of the skin incision to the tracheal wall lead to a safer and more secure tracheostomy in the initial post-operative period.
- ✓ In children who are difficult to intubate (e.g. retrognathia, laryngeal stenosis), it is safer to do the first tube change in the operating theatre in case surgical intervention is needed.
- ✓ The small diameter of the child's airway makes suction and humidification especially important as secretions can quickly occlude the airway.
- ✓ Tube obstruction or accidental decannulation may be fatal.
- ✓ An 'inner tube' reduces the diameter of the lumen and is therefore not practical in small children.
- ✓ Fenestrated tubes are impractical in smaller children: the fenestration tends to become a focus for granulation and mucosal trauma on suctioning.
- ✓ Cuffed tubes are rarely needed in children.
- ✓ Speaking valves should be used under supervision and not while the child is asleep.
- ✓ The airway should be thoroughly assessed prior to decannulation.

FUTURE RESEARCH

- Paediatric tracheostomy is now largely undertaken in specialist paediatric units. It is difficult for otolaryngologists in training to get experience in the management of children with tracheostomies outside these centres. This trend is likely to increase.
- Research in paediatric airway disorders is focused on conditions which give rise to the need for tracheostomy, such as laryngotracheal stenosis and major congenital anomalies.
- There is a need to improve training resources and support in primary care and community settings to enable families to look after tracheostomized children at home. The work of national and international organizations is helping to improve tracheostomy care.

KEY POINTS

- Tracheostomies in children are performed in the main to relieve upper airway obstruction or to assist with mechanical ventilation.
- A reduction in the incidence and change in the treatment of infections affecting the airway has led to a gradual change in the indications for tracheostomy. Many are now undertaken to allow prolonged ventilation in children with complex medical problems.
- Tracheostomy in children is now an uncommon operation.
- Tracheostomy technique in children has changed in the last decade. Vertical skin incisions and maturations sutures are now considered standard practice.
- Tracheostomy complications are more likely in children than in adults. Preterm infants are at particular risk.
- Specific medical and nursing skills are essential in postoperative care.
- Suprastomal granulations are almost universal in children.
- Getting home with a tracheostomy is a complex and time-consuming process. Not all families will have sufficient support or resources at home to care for a child with a tracheostomy.

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CHAPTER 36

PERINATAL AIRWAY MANAGEMENT

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the term ex utero intrapartum. Reference lists were reviewed for further articles.

INTRODUCTION

Neonates with potentially fatal airway obstruction can have good outcomes if the abnormality is recognized prenatally and the pregnancy managed by a team with experience in interventional delivery. Prenatal and fetal imaging has improved, which allows for earlier and more detailed analysis of the abnormality and planning of the delivery. Advances in anaesthetic techniques and intervention at delivery improve outcomes and reduce morbidity and mortality in this group of patients.

This chapter summarizes developments in imaging, anaesthesia and delivery techniques for neonates with airway obstruction.

PRENATAL AND FETAL IMAGING

A potentially fatal airway obstruction in the fetus can be recognized at prenatal imaging, often initially identified at the routine 20-week ultrasound as part of the fetal anomaly screening programme.[1] Once a neck anomaly has been established, the remainder of the fetal survey is carefully conducted to detect the presence of any other abnormalities. Further information may be gathered via three-dimensional (3D) and four-dimensional (4D) ultrasound or magnetic resonance imaging (MRI), such as fetal swallowing, lung function and neck mass mapping, including the presence of calcifications.[2] Ultrasound modalities are more widely available than fetal MRI, which is currently offered in tertiary centres only. A detailed plan for delivery can then be made as well as preparation for postnatal management.[3]

A fetal neck mass may also present via a fetal growth scan requested due to suspected macrosomic (excessive birth weight) fetus and polyhydramnios (excess amniotic fluid in the amniotic sac) is discovered instead. A large neck lesion may compress the oesophagus and impede fetal swallowing, therefore leading to increased liquor volume, uterine irritability, and threatened preterm labour.

After diagnosis, the pregnancy is closely monitored with regular sonograms, in order to detect any development or worsening of fetal hydrops (accumulation of fetal fluid) – a sign of cardiac failure. Elective delivery with *ex utero* intrapartum treatment (EXIT) is planned if there are markers of hydrops or when the fetus is deemed mature.[4]

Ultrasound

Ultrasound is the mainstay of prenatal imaging as it is deemed safe for the fetus and the mother with prudent use. 3D scanning provides a reconstructed 3D volume

image of the fetus, whereas 4D ultrasound allows a 3D picture in real time showing fetal movements.

In addition to antenatal diagnosis of fetal neck anomalies, pre-operative ultrasound can be used to determine fetal position, mass location and placental site prior to an EXIT procedure.[2] In the case of a large cystic neck mass which may contribute to a difficult and traumatic delivery of the fetal head, ultrasound-guided percutaneous aspiration of the cystic mass can be performed prior to the EXIT procedure.

MRI

An adjunct tool to ultrasound is MRI (Figure 36.1). It has superior soft-tissue delineation and anatomical detail (i.e. assessment of tracheal distortion, compression and position). It has better differentiation between solid and cystic structures.[2] Furthermore, when using MRI, there is less adverse influence of raised body mass index, poor fetal positioning and oligohydramnios compared with ultrasound. As measurements can be made of fetal facial features and skeletal angles, syndromes and intracranial anomalies may be more easily identified on MRI.[5]

Static images of the whole fetus can be examined at MRI, therefore a more global view of the mass can be obtained and its spatial relationship to the airway more easily appreciated, in particular using the multiplanar function.[6] It has been suggested that ultrafast MRI without fetal sedation can provide a more comprehensive view regarding the size and position of the lesion.[7] In 50% of cases the MRI finding was different from the ultrasound diagnosis, however the MRI diagnosis was in agreement with final histology in 73% of cases.[8]

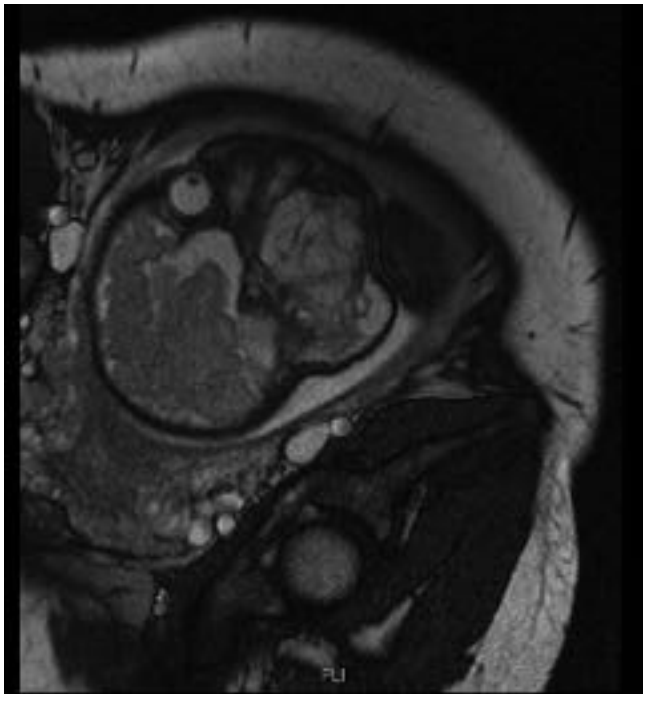


Figure 36.1 Fetal MRI. A large lymphatic malformation (*) is demonstrated.

EPIDEMIOLOGY

The most common fetal neck lesions causing airway obstruction are lymphatic malformations (formerly cystic hygroma) and teratoma. Other neck masses include haemangioma, branchial cleft cyst, cervical thymic cysts, fetal goitre, sarcoma, neuroblastoma, and kaposiform haemangioendotheliomas (Box 36.1).[9, 10]

BOX 36.1 Causes of congenital airway obstruction

External compression	Internal blockage	Developmental
Lymphatic malformation	Laryngeal web	Laryngeal atresia
Cervical teratoma	Laryngeal stenosis	Tracheal atresia
Brachial cleft cyst	Laryngeal cyst	Micrognathia
Cervical thymic cyst	Tracheal stenosis	
Thyroid goitre	Epignathus	
Ectopic thyroid	Choristoma	
Sarcoma	Glioma	
Neuroblastoma	Encephalocoele	
Dermoid cyst	Choristoma	
Granular cell tumour	Haemangiomata	
Vascular ring		

Cervical lymphatic malformations are typically located in the anterior and posterior triangles of the neck and appear sonographically as fluid-filled cysts with fine septae. Conversely, cervical teratomas are unilateral and asymmetrically located. They are characterized as complex masses with mainly solid components and well-defined edges, often with vascular spaces and calcifications.[11] Preterm labour from polyhydramnios due to local mass effect causing obstruction in the tracheo-oesophageal complex which leads to impaired fetal swallowing is more common in teratomas (up to 40%) than lymphatic malformations.[12] [Level 1 evidence]

Extrinsic compression of the fetal airway

LYMPHATIC MALFORMATION

The incidence of lymphatic malformation is 1 in 6000 to 1 in 16 000 live births. This congenital malformation of the lymphatic system is thought to be due to failure of the jugular lymph sacs to join the lymphatic system. As well as an association with chromosomal abnormalities in 60% of cases, in particular Turner syndrome and Down syndrome, they are also linked to underlying genetic conditions, such as Noonan syndrome and multiple pterygium syndrome.[2] Antenatal care therefore involves detection of other fetal structural anomalies, especially cardiac abnormalities, and the offer of prenatal karyotyping. There is a perinatal mortality rate of over 80% if fetal hydrops is detected. Postnatal intubation may be particularly difficult due to obstruction of the pharynx and larynx from very large lesions. Prognostic scores

such as de Serres staging or Cologne Disease Score have been used to predict long-term outcome.[13, 14]

CERVICAL TERATOMA

Teratomas contain tissue from all three germinal layers (ectoderm, mesoderm and endoderm). Cervical teratomas represent 3–5% of all teratomas and have an incidence of 1 in 35 000 to 1 in 20 000 live births.[15] Cervical teratomas cause airway obstruction via both compressive and distortive factors. A presumed prenatal diagnosis of teratoma is an indication for an interventional birth procedure. It is associated with lung hypoplasia and a higher mortality rate.[16]

Maternal serum alpha fetoprotein (AFP) levels may be very high as these tumours contain neural tissues as the predominant histological component. Only <5% undergo malignant transformation, which occurs in those who are diagnosed in later life. By undergoing EXIT procedure, the neonatal mortality rate is improved to 36% from 80% in those with untreated cervical teratomas.[16]

Intrinsic defects in the fetal airway

CONGENITAL HIGH AIRWAY OBSTRUCTION SYNDROME

There are several causes of congenital high airway obstruction syndrome (CHAOS); these include laryngeal web, laryngeal stenosis, laryngeal atresia, laryngeal cyst, tracheal stenosis and tracheal atresia. Antenatal imaging shows large echogenic lungs, dilated tracheobronchial trees and flattened or inverted hemidiaphragms. Fetal hydrops can develop from reduction in venous return due to compression of the lungs on mediastinal structures.[17] Extrinsic airway obstruction by vascular rings, such as right aortic arch with aberrant left subclavian artery or double aortic arch, can mimic CHAOS.

There is a low risk of future pregnancies being affected as most CHAOS occurs sporadically. However, laryngeal atresia is associated with other anomalies such as anophthalmia, hydrocephalus, syndactyly, absent radius, bronchotracheal fistula, oesophageal atresia, cardiac anomalies, Fraser syndrome, genitourinary anomalies, imperforate anus, uterine and vertebral anomalies.[4] Compared with laryngeal atresia, low thoracic tracheal obstruction or tracheal atresia has a much poorer prognosis for EXIT procedure.[18] It is difficult to diagnose laryngeal atresia on prenatal ultrasound in the presence of a tracheoesophageal fistula as the lung fluid can escape into the stomach or amniotic sac, rather than being trapped in the lungs.

Micrognathia

At the 20-week fetal anomaly ultrasound scan, fetal features of small chin, prominent upper lip or polyhydramnios may raise the suspicion of micrognathia. Fetal MRI can be used to further assess the severity of micrognathia by evaluating the relationship of the tongue to the airway (glossoptosis). Several congenital syndromes are associated with micrognathia, including Cornelia de Lange, Treacher Collins, Marshall syndrome, Stickler syndrome, the Robin sequence and 22q11 deletion.[3]

Oronasal masses

Fetal nasal masses amenable to prenatal ultrasound diagnosis include congenital midline nasal masses, such as dermoids, gliomas and encephalocoeles (extranasal or intranasal), and abnormal nasal anatomy seen in 22q11 deletion syndromes. In the case of fetal oral masses, congenital epulis (granular cell tumours), epignathi (teratoma of the oropharynx) and dermoid cysts of the floor of mouth or tongue base may be detected.[12, 19, 20]

INTERVENTIONAL DELIVERY

The concept of accessing the fetal airway in an elective, controlled and secure manner under placental support was first developed in 1990. The fetus underwent laryngoscopy and intubation prior to clamping the umbilical cord.[21] Previously, an ENT team would be on 'standby' to establish the airway in the neonate under time pressure.

There are currently a number of options for interventional delivery:

- operation on placental support (OOPS)
- *ex utero* intrapartum treatment (EXIT) procedure
- delivery then attempted airway intubation or tracheostomy.

Operation on placental support

Operation on placental support (OOPS) delivery is performed under maternal regional anaesthesia with the fetus completely delivered through a lower segment Caesarean section. The umbilical cord is unclamped and kept intact with the fetus on a Mayo table at the level of the placenta. In order to prolong the foetoplacental circulation, synthetic oxytocin administration to deliver the placenta is delayed. A window of 5–20 minutes for airway intervention has been documented before the umbilical cord goes into spasm.[22]

Ex utero intrapartum treatment (EXIT) procedure

The EXIT procedure has become the mainstay in the management of prenatally diagnosed fetal airway obstruction. Its initial indication was to manage fetuses with congenital diaphragmatic hernias who underwent *in utero* foetoscopic tracheal occlusion to increase lung growth.[23] An EXIT procedure to deliver a fetus with an airway-obstructing neck mass reduces the mortality rate from 10–57% to 8%.[24]

An EXIT procedure permits a longer interventional procedure as the neonate is only partially delivered. Via a lower segment Caesarean section the head and perhaps a shoulder are delivered to maintain uterine volume

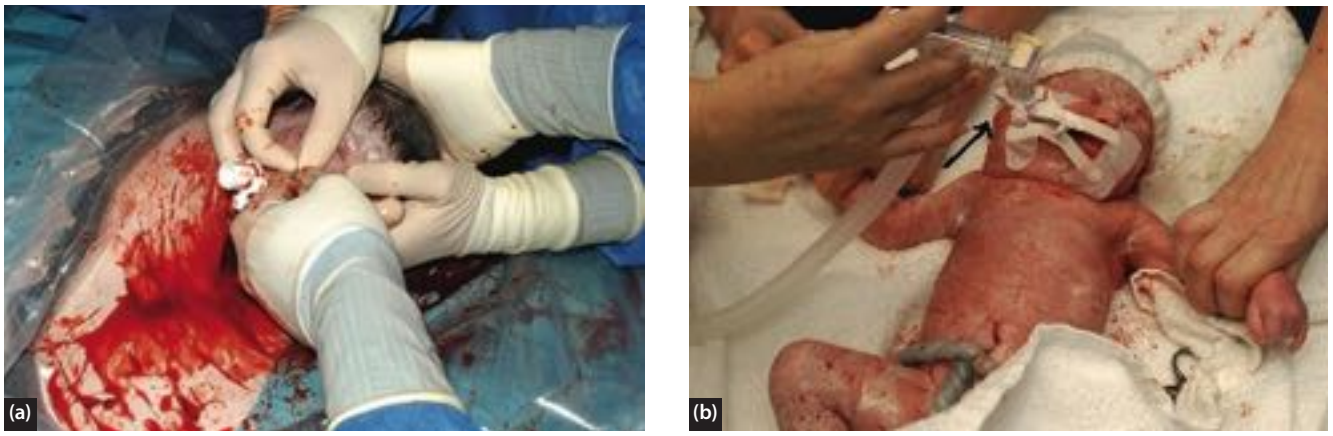


Figure 36.2 EXIT procedure. (a) Head of neonate delivered via lower segment Caesarean section and child intubated. The underlying abnormality was a large lymphatic malformation (fetal MRI of same child in Figure 36.1). **(b)** Intubated neonate with large lymphatic malformation (arrow) assessed by paediatricians.

which in turn avoids compression of the umbilical cord, and allows preservation of the uteroplacental circulation (**Figure 36.2**). A 2.5-hour timeframe is afforded on this circulation to perform airway interventions.[4] These include establishing an airway, direct laryngoscopy and bronchoscopy, performing a tracheostomy, surfactant administration, and resection of an obstructing mass. There is a greater chance of maternal haemorrhage due to uterine atony in an EXIT procedure compared with OOPS (**Table 36.1**).[25] Moreover, it may be difficult to perform fetal intubation and bronchoscopy with only the head delivered. Nevertheless, this procedure can be easily converted to an OOPS. Classically, an EXIT procedure is performed under maternal general anaesthesia[26] but it can also be performed under a spinal anaesthetic.[27]

Delivery then attempted airway intubation or tracheostomy

In certain circumstances, the risk of maternal haemorrhage is severe and a rapid, safe delivery of the baby and the placenta takes precedence. For example, in a mother with uterine fibroids and a fetus with other severe fetal anomalies,[10] a Caesarean section could be performed with the paediatric airway team in attendance to secure the neonatal airway by means of either rigid bronchoscopy and intubation or tracheostomy.

TABLE 36.1 Differences between EXIT and OOPS

	EXIT	OOPS
Anaesthetic	Traditionally uses inhalational general anaesthetic, hence greater risk of maternal haemorrhage Regional anaesthetic can be used	Regional anaesthetic or short general anaesthetic
After uterotomy	Partial delivery of fetal head and shoulders	Whole baby delivered onto Mayo table Umbilical cord left intact Placenta not delivered
Time for interventional procedures	20–50 minutes	5–20 minutes

PRE-OPERATIVE PLANNING

A multidisciplinary team (MDT) is involved in planning the procedure. The pre-EXIT rehearsal would consider the layout of the operating theatre and the location of the personnel and equipment. There should be a clear documentation of the prenatal counselling and consent, including a frank discussion of the options available and a realistic outlook for neonatal survival.[25]

Multidisciplinary team

Prenatal genetic counselling is invaluable in evaluating for underlying genetic syndromes based on the information available during pregnancy, such as fetal karyotype or other structural anomalies detected on antenatal imaging. The parents can then have an informed discussion on whether an interventional birth procedure is suitable for their baby in light of the probable prognosis. Neonates with an isolated airway obstruction (i.e. no other fetal abnormality) have a good prognosis and limited morbidity if delivered by a team with experience in interventional airway deliveries.[27] The prognosis is less good if multiple fetal abnormalities or lung hypoplasia is present.[27] Isolated cervical teratomas also have worse outcomes than compressible neck masses such as lymphatic malformations.

An MDT approach is essential for setting up an interventional airway delivery service (**Figure 36.3**). The team should include specialists from fetal medicine, otolaryngology, neonatology, paediatrics, paediatric anaesthesia and obstetric anaesthesia. Prior to meeting the parents the MDT meets to develop the birth plan. The following



Figure 36.3 Multidisciplinary team involvement in EXIT procedure. **(a)** Surgical team; **(b)** neonatal team.

factors need to be considered when contemplating an interventional delivery:

- **Maternal factors:** comorbidities, risk of maternal haemorrhage (i.e. coexisting uterine pathology such as uterine fibroids)
- **Fetal factors:** suspected pathology (i.e. isolated neck mass causing airway obstruction, other fetal abnormalities, lung hypoplasia), gestational age
- **Anaesthetic factors:** this will be determined by risk to maternal health and anticipated length of time required to intervene to secure the neonatal airway
- **Access factors:** presentation of the fetus (breech, head first), size of mass, accessibility for OOPS, EXIT or other intervention
- **Timing of intervention:** an elective lower segment Caesarean section is planned at a gestation guided by the volume of amniotic fluid and the gestational age of the fetus
- **Primary intubator:** the person whose prime responsibility is to intubate the neonate
- **Time allowed for intubation:** this will be determined by the interventional procedure performed, i.e. OOPS or EXIT.

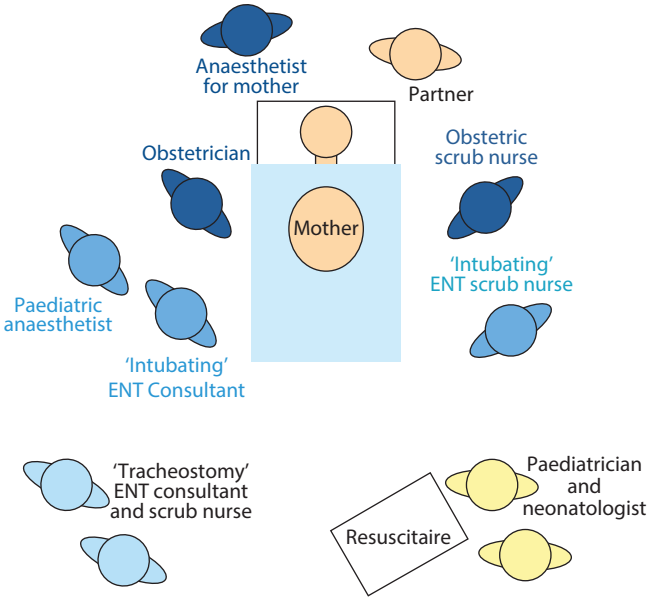


Figure 36.4 Example of theatre layout for an interventional delivery procedure (from Yaneza et al).[27]

A unit that undertakes interventional airway deliveries should be supported by an established framework, i.e. paediatric and neonatal intensive care, extracorporeal membrane oxygenation service, etc. A contingency plan is also developed at the MDT meeting should the mother present in spontaneous labour before her planned date of delivery with the availability and awareness of the on-call MDT able to conduct an emergency Caesarean section and EXIT or OOPS procedure. Extracorporeal life support to provide respiratory support may be considered in neonates with difficult access to airway but a good prognosis, such as a large vascular mass requiring resection followed by a tracheostomy.[25] Due to the number of team members involved, a large operating theatre is preferable (Figure 36.4).

Airway intervention

After the fetal head is delivered, the fetal medicine surgeon ensures maternal wellbeing and prevents placental separation, while the airway surgeon works simultaneously (Figure 36.5). The presence of two ENT consultants is recommended: an 'intubating' ENT consultant with rigid bronchoscopy skills (Figures 36.5b and c), and a 'tracheostomy' ENT consultant. In the event of a failed intubation, the other 'tracheostomy' ENT consultant and scrub nurse can perform a tracheostomy with fresh minds that are not adversely affected by the previous incident. Furthermore, having two ENT consultants allows for a consensus to be reached if a stressful or difficult situation is encountered. The primary intubator could also be a paediatric anaesthetist who specializes in ENT and thus is experienced at managing difficult airways.

Timing

In choosing the gestation for Caesarean section, the balance between early operation to avoid spontaneous labour and delayed delivery to improve fetal maturity

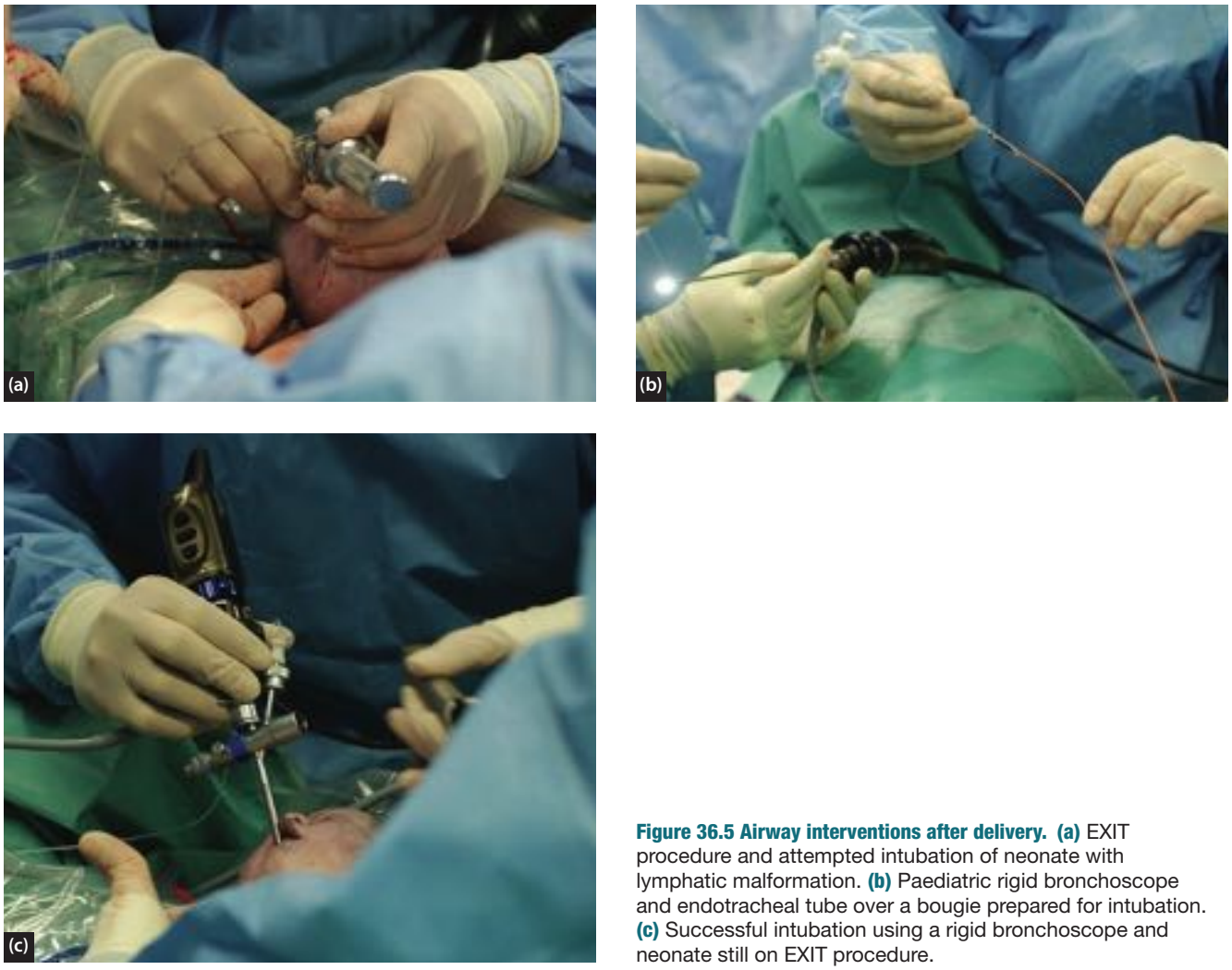


Figure 36.5 Airway interventions after delivery. **(a)** EXIT procedure and attempted intubation of neonate with lymphatic malformation. **(b)** Paediatric rigid bronchoscope and endotracheal tube over a bougie prepared for intubation. **(c)** Successful intubation using a rigid bronchoscope and neonate still on EXIT procedure.

is considered. In many cases, a Caesarean delivery is planned around 36–38 weeks' gestation, after corticosteroid administration to promote fetal lung maturation. However, the delivery may be expedited in the presence of polyhydramnios as the risk of preterm labour increases with the volume of amniotic fluid.[26]

Anaesthesia

A Caesarean section is usually performed using regional anaesthesia, i.e. spinal or epidural anaesthesia. An OOPS procedure can be performed on regional anaesthesia while an EXIT procedure is classically conducted under general anaesthesia to achieve uterine relaxation with a deep plane of anaesthesia. The mother is kept in a left lateral tilt position to avoid aortocaval compression from the gravid uterus, which reduces maternal cardiac output. EXIT procedures have been conducted under regional anaesthesia by the combined spinal epidural technique, with adequate uterine relaxation.[27–29] Agents such as glyceryltrinitrate can be used to induce further uterine relaxation if required.

Two anaesthetists should be present at an interventional airway delivery: an obstetric anaethetist for the mother, and a paediatric anaethetist for the neonate. Despite the intention to have two healthy patients by the end of the procedure, if any conflicts of interest arise intraoperatively, the mother's safety should override any fetal concerns.

During EXIT procedure, uterine relaxation is paramount as the uteroplacental circulation supplies oxygen and anaesthesia to the fetus. The preservation of maternal-fetal gaseous exchange at the placenta prevents fetal hypoxia and neonatal hypoxic-ischaemic encephalopathy. All volatile anaesthetics cross the placenta and fetal anaesthesia is related to uterine blood flow, drug solubility and distribution in the fetal blood circulation.[30] Narcotics or muscle relaxants can be administered to the fetus via intramuscular or intravenous routes to achieve additional anaesthesia.

Obstetric issues

At an elective Caesarean section, the average maternal blood loss is 500 mL,[31] whereas for an EXIT procedure it is 1500–1800 mL.[24] Haemorrhage can occur from the uterine incision, the placenta (premature placental separation) or from an atonic uterus once the baby is delivered.[7]

Bleeding from the uterotomy can be reduced with surgical haemostatic techniques including the placement of a uterine stapling device. Placental damage from the uterine incision should be prevented by mapping the placental edges on antenatal ultrasound and planning the uterine incision. However, a large neck mass may obscure the placenta at ultrasound. One should also exercise caution in the setting of polyhydramnios as the placenta can be compressed and give a false impression of its location on the antenatal scan. Furthermore, upon uterine incision, the sudden release of high volumes of amniotic fluid can lead to intrauterine pressure changes and early placental separation (i.e. placental abruption). Therefore, amnioreduction should be considered prior to EXIT procedure in such cases.

During EXIT procedure, delayed placenta separation is accomplished by uterine relaxation, maintenance of uterine volume and uterine and placental perfusion. Uterine relaxation can also cause uterine atony and further obstetric haemorrhage after full delivery of the neonate. In order to maintain maternal haemodynamic stability, the dose of inhalational anaesthetic agents is decreased and oxytocin administered just before umbilical cord ligation to deliver the baby. This is accomplished through good communication and close coordination between the fetal medicine surgeon and the obstetric anaesthetist.[32]

Immediate post-operative complications are more frequent in comparison to standard Caesarean sections. In a study of 34 EXIT procedures, there were longer operating times, higher estimated blood losses and more wound infections compared with 32 matched controlled Caesarean deliveries.[33] However, there was no statistical difference in the length of post-operative hospital stay and haematocrit levels.

In subsequent pregnancies, there is a higher chance of uterine scar dehiscence or uterine rupture because of possible unusual uterotomy sites. Instead of a lower uterine segment incision, other areas may have been used in order to avoid the placenta. Lazar et al. showed that mothers who delayed pregnancy for 2 years following an EXIT procedure were able to have an uncomplicated delivery of at least one more child.[24]

Fetal considerations

Fetal circulation is preserved via the maintenance of placental perfusion and prevention of respiration. In some centres, the fetus is given direct injections of narcotics and muscle relaxants to avoid respiration and establishment of neonatal circulation as well as to reduce fetal movements to aid airway management.[7, 21] Others have argued that the same effects are obtained by fetal airway obstruction and fetal anaesthesia via the transfer of maternal anaesthetic through uteroplacental circulation.

OUTCOMES

Experience in our centre has demonstrated that an interventional delivery decreases mortality from 50% (n = 2) to 14.2% (n = 1). All deaths were associated with other fetal abnormalities, i.e. where airway obstruction was not an isolated feature.[27] Of seven children delivered by an interventional team, two are tracheostomy-dependent. A case series of 12 children with giant neck masses after EXIT procedures demonstrated more cranial nerve palsies, feeding difficulties and speech delays in this group of children. However, the complications were thought to be linked to the underlying pathology rather than the mode of delivery. For example, the neck mass itself could have damaged and distorted local anatomy or the surgical resection of the mass could have led to iatrogenic injury.[24] In our case series none of the children have cranial nerve palsies or feeding difficulties.

A successful interventional airway delivery service is dependent on careful planning and infrastructures, local guidelines and protocols, as well as a continuous audit cycle of outcomes.

FETAL THERAPY

Intrauterine treatment may be considered in cases where there is a high risk of *in utero* demise or severe disability and a low risk to the mother.[34] Fetal hydrops may occur as a result of cardiac failure from a highly vascular neck mass, such as teratoma or kaposiform haemangioendothelioma, where intrauterine surgical resection has been offered.[35]

Complete obstruction of the larynx in laryngeal atresia causes lung fluid congestion, *in utero* pulmonary hyperplasia, pulmonary hypertension and fetal cardiac failure. Fetal therapy for laryngeal atresia and CHAOS has been reported using percutaneous fetoscopic tracheal decompression.[36, 37] Intrauterine sclerotherapy of large fetal macrocystic lymphatic malformations with a single injection of OK-432 (penicillin-killed *Streptococcus pyogenes*) has also been described.[38] Other sclerosant agents could be used as OK-432 is not available in the UK.

In certain circumstances, *in utero* treatment is contraindicated; these include lethal or severely disabling structural and/or genetic fetal anomalies or serious maternal comorbidities.

CONCLUSION

Congenital airway obstruction is potentially life-threatening and associated with high mortality rates.[17, 21, 39, 40] If there is a delay in establishing airway and ventilation in the neonate, the risks of hypoxia, acidosis and anoxic brain injury, which are associated with neonatal morbidity and mortality, increase. In contrast, for those with effective airway access at delivery, the long-term outcome is excellent in most cases.[27]

Ultimately, with advances in fetal interventions, such as *in utero* surgery, fetal transcutaneous transuterine bronchoscopy, intrauterine sclerotherapy, fetal airway assessment and fetoscopic tracheal decompression, we can expect improvements in prognosis for neonates with congenital airway obstruction.

BEST CLINICAL PRACTICE

- ✓ A unit that undertakes interventional airway deliveries should be supported by an established framework, i.e. PICU, NICU, ECMO.
- ✓ A multidisciplinary team including specialists from fetal medicine, otolaryngology, neonatology, paediatric anaesthesia and obstetric anaesthesia is essential.
- ✓ Decide on the timing of intervention, nominate a team member to undertake endotracheal intubation and consider the time allowed for intubation.

FUTURE RESEARCH

There are exciting future developments in novel therapeutic concepts in airway reconstruction. For example, in the field of fetal tissue engineering, an airway construct can be designed according to gestation using autologous fetal cells.[41–43] The proof of principle has been provided in a large animal model of perinatal airway repair.[44]

KEY POINTS

- Effective airway access at interventional delivery improves long-term prognosis.
- Better antenatal detection has greatly improved perinatal management of airway problems in the newborn.
- Careful planning of the delivery makes for better outcomes.

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CHAPTER 37

CERVICOFACIAL INFECTIONS

Nico Jonas and Ben Hartley

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SEARCH STRATEGY

Data in this chapter may be updated by Medline and Scopus searches using the keywords: infection and child, neck, cervical node and cervical adenopathy, and focusing on the diagnosis and treatment of specific conditions. The Cochrane Library was also consulted.

TERMINOLOGY

Abscess formation refers to an accumulation of pus in a confined space as a result of an inflammatory response to a bacterial or parasitic infection or foreign material. The deep cervical fascia is arranged so as to create compartments or spaces between the various structures in the neck. A collection of pus in one of these spaces is often termed a **deep neck space infection** (**DNSI**).

Cellulitis refers to inflammation of subcutaneous or connective tissue and is usually characterized by fever and pain as well as redness, swelling and warmness of the affected area.

Fasciitis refers to inflammation of the connective tissue (fascia) that surrounds and binds muscles, blood vessels and nerves together.

Necrotizing fasciitis is an aggressive tissue infection that spreads rapidly across fascial planes causing necrosis of tissue along the way.

INTRODUCTION

This chapter will deal with cervicofacial infections in children. Because these infections usually present as a neck mass, we will also aim to discuss the general approach to a child with a neck lump.

Cervicofacial infections in children usually present as a neck swelling. The majority of infections are related to lymph nodes. These are rarely indicative of serious pathology. Lymphadenopathy secondary to the common acute upper respiratory infections that are a feature of normal childhood – notably pharyngitis and tonsillitis – is the most common cervicofacial infection in childhood. Lymphadenopathy is usually self-limiting but may progress to cellulitis, suppuration and abscess formation. Infections may also involve the parotid, the submandibular or the thyroid glands.

Congenital lesions do not always declare themselves at birth; they may present in older children. The onset of the swelling may be precipitated by an acute inflammatory episode.

Chronic infections are less common but need to be considered if the swelling persists.

In a very a small number of children, a neck swelling will be due to a malignancy. These are most often lymphoproliferative or connective tissue tumours. Squamous carcinoma is extremely rare in children. A child with a neck mass requires an entirely different approach to that required in an adult.[1] Open biopsy is rarely needed. Nevertheless, it is important to maintain an index of suspicion for malignancy in all persistent neck swellings in children.

BOX 37.1 Inflammatory adenopathy in children: Infective

Viral	Bacterial	Fungal	Parasitic
Upper respiratory: rhinovirus, adenovirus, enterovirus Common childhood illnesses: measles, mumps, rubella, varicella Infectious mononucleosis Cytomegalovirus (CMV) HIV	Acute lymphadenitis: *Streptococcus*, *Staphylococcus*, less commonly Gram-negative organisms Suppurative lymphadenitis with deep or superficial neck abscess; usually pyogenic organisms (*Streptococcus* and *Staphylococcus*) Mycobacteria: tuberculosis or non-tuberculous mycobacteria (NTM) – sometimes termed 'atypical mycobacteria' Other granulomatous bacterial infections: cat scratch disease, actinomycosis, brucellosis, tularaemia, bubonic plague, syphilis	Histoplasmosis Uncommon fungal infections (immunocompromised host) *Candida* and *Aspergillus*	Toxoplasmosis Filariasis

CLASSIFICATION OF CERVICOFACIAL INFECTIONS

- **Infections related to lymph nodes:**
  - Acute infective lymphadenopathy
  - 'Complicated/progressive' infective adenopathy causing cellulitis, suppuration and abscess formation
  - Chronic infective lymphadenopathy
- **Infections related to congenital lesions or malformations:**
  - Thyroglossal duct cysts
  - Dermoid cysts
  - Branchial anomalies
  - Lymphatic malformations / cystic hygromas
- **Infections related to acquired anatomical malformations:**
  - Plunging ranula
- **Infections of glands:**
  - Salivary gland infections
  - Thyroid gland infections
- **Infections of dental origin:**
  - Dental abscess
  - Ludwig's angina
- **Infected vascular structures:**
  - Infective thrombophlebitis
  - Lemierre's syndrome

AETIOLOGY OF INFLAMMATORY NECK NODES IN CHILDREN

Lymphadenopathy is one of the most common clinical problems encountered in paediatrics.[2] The precise incidence of lymphadenopathy is not known, but estimates of palpable adenopathy in childhood vary from 38% to 45%.[1] There are approximately 300 lymph nodes in the neck and they have considerable capacity to undergo growth and change.[3] With their high concentration of lymphocytes and antigen-presenting cells, lymph nodes are ideal for receiving antigens that gain access through the skin or gastrointestinal tract. They are barely perceptible in neonates, but a progressive increase in antigen exposure will lead to an increase in lymph node size until later childhood. Lymph node atrophy will start during adolescence and continues through later life.

BOX 37.2 Inflammatory adenopathy in children: Non-infective

Kawasaki syndrome
Sarcoidosis
Sinus histiocytosis with massive lymphadenopathy
Kikuchi-Fujimoto disease
PFAPA syndrome (periodic fever, apthous stomatitis, pharyngitis, cervical adenitis)
Langerhan's cell histiocytosis

Inflammatory lymphadenopathy can be classified into infective conditions (Box 37.1) and non-infective conditions (Box 37.2). Non-inflammatory disorders will need to be considered in the differential diagnosis of a neck mass, especially if there are unusual features.

CLINICAL ASSESSMENT OF A PATIENT WITH A NECK MASS

History

- **Age of child:** Most acute lymphadenitis presents in children older than 6 months. Swellings occurring at or shortly after birth are more likely to be pathological and may be neoplastic.
- **Duration of swelling:** A short history (a few days) suggests acute inflammation. After 6 weeks a swelling is regarded as chronic and further investigation should be considered – even earlier if there are suspicious clinical features.
- **Size:** Very large swellings or swellings that progressively enlarge despite antimicrobial treatment should be investigated.
- **Associated symptoms:** A preceding upper respiratory infection is often a feature of inflammatory lymphadenitis. Fever, rhinorrhoea, sore throat and malaise are common. With chronic swellings, enquire about weight loss, night sweats, chronic cough and swellings elsewhere in the body.
- **Contacts:** Enquire about tuberculosis, other infections and exposure to cats, farm animals and ticks. Recent travel should also be noted.

- **Medical history:** Identify any known illnesses. Note recent immunizations against polio, typhoid or DTP (diptheria, tetanus and pertussis). Document regular medication including carbamazepine, phenytoin or isoniazid.
- **Family and social history:** Identify any familial disease or congenital anomalies and any relevant social factors.

Site of the swelling

The anatomical site of the swelling within the neck provides important information about the possible aetiology.

LATERAL NECK SWELLINGS

Lymph nodes are distributed throughout the neck but the most common site is along the superficial and deep cervical chains. These lie deep to the sternomastoid muscle in the upper neck and along its anterior border in the lower neck. Enlarged lymph nodes are the most common cause of lateral neck swellings. The principal differential includes anomalies such as congenital cysts, which may also become acutely inflamed. Vasoformative lesions, haemangiomas and vascular malformations including lymphatic abnormalities may present as a lateral neck swelling. Benign and malignant neoplasms arising from the neural or connective tissue elements and rarely secondary lymph node metastases may present as a lateral neck mass.

CENTRAL NECK SWELLINGS

The principal causes of a neck swelling in the central area of the neck around the midline are thyroglossal duct cysts, lymph nodes and dermoid cysts. Thyroglossal duct or dermoid cysts may become acutely inflamed. Children can also develop inflammatory and neoplastic thyroid disease. Lymphatic vascular malformations can occasionally involve this region.

PAROTID SWELLINGS

Acute viral parotitis (mumps) is common and is a self-limiting infection. Although vaccination for measles, mumps and rubella (MMR) is now reducing the frequency of mumps and to some degree the clinical awareness of this condition, outbreaks still occur sporadically in the developed world. It remains a significant problem in the developing world.

Bacterial parotitis can occur in children and may be recurrent. It is usually characterized by acute painful swelling followed by resolution on antibiotics. Massaging the parotid will produce infected saliva or pus at the parotid duct opening opposite the second upper molar.

Occasionally, chronic inflammatory swelling persists and must be distinguished from neoplasia. Rhabdomyosarcoma or other connective tissue tumours can present in this way. Vascular malformations and haemangiomas can also present as swellings in the parotid region. Magnetic resonance scanning can be very helpful with this differential diagnosis.

The parotid gland in adults is mainly made up of parenchymal glandular tissue. In children, intraparotid lymphoid tissue is more prominent, hence parotid swelling is often due to lymphadenopathy (e.g. non-tuberculos mycobacteria, NTM), especially in the toddler age group.

SUBMANDIBULAR SWELLINGS

Enlarged lymph nodes, floor-of-mouth infections, acute sialadenitis, plunging ranula and occasionally lymphatic or vascular malformations can all cause swelling in the submandibular region. A more detailed discussion of salivary swellings can be found in Chapter 39, Salivary glands.

POSTERIOR TRIANGLE SWELLINGS

Most commonly posterior triangle swellings are lymph nodes but branchial anomalies, vascular malformations and neoplasia enter into the differential diagnosis.

Nature of the swelling

Classical signs of acute inflammation such as redness, tenderness and heat may be present. Chronic swellings usually do not show these signs. If abscess formation has occurred, the clinical sign of fluctuance may be present and the mass may feel cystic. A classical tuberculous abscess lacks the clinical features of acute inflammation and is described as a 'cold abscess'.

HEAD AND NECK EXAMINATION

A careful examination for a source of primary infection should be made. This should include examination of the pharynx, nose and ears as well as looking for any cutaneous lesion, including the scalp.

General examination

Fever, tachycardia or a rash should be noted. A general examination should include a search for any associated lymphadenopathy and hepatosplenomegaly. The otolaryngologist may wish to enlist the help of a paediatrician.

Investigation

In many cases no investigation is required. Symptomatic treatment of presumed viral infection or antibiotic treatment of bacterial infection with careful clinical follow-up will result in resolution.

Laboratory and skin tests

If the child is systemically unwell, a full blood count may demonstrate neutrophilia consistent with bacterial infection. A blood count may also be a screening investigation for suspected haematological malignancy. C-Reactive Protein (CRP) is raised in bacterial infections and can be useful in monitoring response to treatment.

Consider a 'Monospot 'test for infectious mononucleosis. Serological tests for toxoplasmosis, bartonella (cat scratch disease), or cytomegalovirus (CMV) should be considered for persistent lymphadenopathy. Mantoux or Heaf tests for tuberculosis may be helpful, particularly in the non-immunized.

Imaging

There is a limited place for plain radiographs, but calcification in a lymph node is highly suggestive of tuberculosis. A chest X-ray may be helpful in tuberculosis, and a lateral neck view may demonstrate a retropharyngeal mass. Ultrasound examination of a neck mass may be undertaken without sedation or anaesthesia. Ultrasound will help determine if a lesion is cystic or solid. An experienced radiologist can comment on the internal architecture of lymph nodes and may raise suspicion of malignancy. Benign characteristics include size less than 1 cm, oval shape with short : long axis ratio less than 0.5 to 1, normal hilar vascularity and a low resistive index with high blood flow on Doppler technology.[4] If an abscess is identified, sonography will help with determining the anatomical relationships of the abscess and with surgical planning.

Computed tomographic (CT) scanning may require general anaesthesia in small children. Good anatomical detail is provided and it is helpful in surgical planning. Neither ultrasound nor CT is absolutely accurate in the diagnosis of an abscess and in the presence of strong clinical features surgical exploration should be considered.[5]

Magnetic resonance (MR) scanning rarely adds useful information in the case of acute inflammatory lesions but is very useful for vascular malformations, salivary gland and soft-tissue masses.

SPECIFIC CERVICOFACIAL INFECTIONS

Viral infections

VIRAL UPPER RESPIRATORY INFECTIONS

Adenovirus, rhinovirus or enterovirus (Coxsackie A and B) may cause reactive lymphadenopathy. This is generally self-limiting.

INFECTIOUS MONONUCLEOSIS

This is an acute infection caused by Epstein–Barr virus (EBV). It occurs mainly in adolescence and is spread by close contact. Fever, fatigue, malaise and an exudative tonsillitis are characteristic (**Figure 37.1**). Cervical lymphadenopathy may be massive. Other lymphoid tissue including liver and spleen may be enlarged. There is a characteristic picture on the blood film with the presence of atypical lymphocytes. Serological tests such as Monospot or Paul–Bunnel will usually confirm the diagnosis. Although the aetiology is viral, intravenous antibiotics may be needed to treat any coexistent bacterial infection. Ampicillin and amoxicillin are contraindicated as they can cause a skin rash when used in Epstein–Barr virus infection.

In cases where the acute tonsillitis is associated with airway obstruction, steroids may be considered. On occasion, endotracheal intubation may be required to protect the airway until the swelling subsides, or acute –'hot' – tonsillectomy to remove the obstructive tonsils.[6, 7] Cases with hepatosplenomagaly should be managed in cooperation with a paediatrician. Patients should be warned that splenomegaly will last at least 4 weeks but can take as long as 8 weeks to settle and should refrain from contact sports during this time.[8]

HIV

Infection is associated with repeated opportunistic infections. Most cases of paediatric HIV infection are acquired from the mother by vertical transmission. Acute infection may mimic infectious mononucleosis. Persistent generalized lymphadenopathy including the cervical nodes becomes a feature as the disease progresses. Weight loss and recurrent fevers occur. Following HIV infection it may be years or decades before full acquired immune deficiency syndrome (AIDS) develops. There is significant evidence of increased life expectancy with early antiretroviral treatment.[9]

Investigation and management should be in cooperation with a specialist in paediatric infectious diseases.

Bacterial infections

MICROBIOLOGY

Group A *beta haemolytic streptococcus* and *Staphylococcus aureus* are the most common causative organisms for suppuration in the neck. Other bacteria that may be implicated include anaerobes (19%); *Haemophilus influenzae*, *Moraxella catarrhalis*[10] and beta lactamase-positive organisms.



Figure 37.1 Exudative tonsillitis in infective mononucleosis.

ACUTE LYMPHADENOPATHY WITH SUPPURATION

Cervical abscesses

Bacterial infection within a cervical lymph node may progress to cause local cellulitis and abscess formation (**Figure 37.2**). Occasionally, a solid mass of inflammatory tissue forms due to coalescence of a group of lymph nodes and this is clinically referred to as a 'phlegmon'. The distinction between phlegmon and abscess is important, as abscesses usually require surgical drainage whereas phlegmons settle with intravenous antibiotics. The most important assessment is clinical. Abscesses are tender, usually reddened and exhibit the clinical sign of fluctuance, confirming their cystic nature. Imaging in the form of an ultrasound scan is helpful but not always required.

Many neck abscesses require surgical drainage. This may be performed by a neck incision, which is ideal for superficial lesions and the majority of deep cervical abscesses. A wide-bore needle aspiration may be adequate if the pus has coalesced and liquefied.

Dental abscess

An infected molar or premolar may cause extensive swelling extending into the face and neck and should be considered in the differential of a neck abscess (**Figure 37.3**).

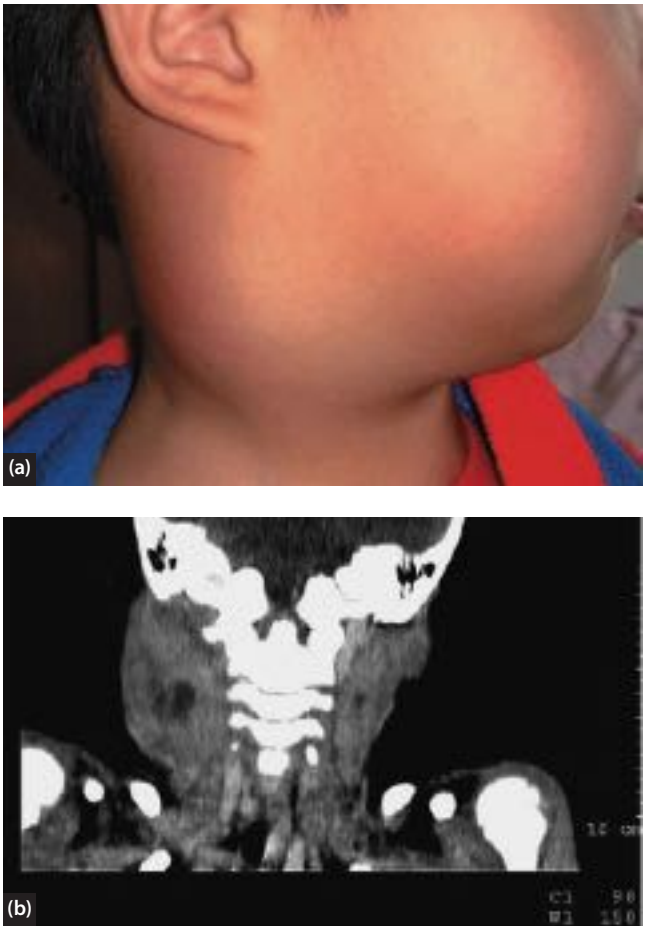


Figure 37.2 Cervical abscess. (a) Child with acute cervical abscess. **(b)** CT scan of the same child.

Deep neck space infections (DNSIs)

Deep neck spaces are described in relation to the hyoid bone. They can be suprahyoid, infrahyoid or comprise the entire length of the neck. A sound knowledge of the fascial layers and neck spaces is needed to correctly diagnose the affected space as well as plan the surgical approach. Deep neck space infection may lead to other severe and potentially life-threatening complications, such as mediastinitis, septic embolization, dural sinus thrombosis and intracranial abscess.

In paediatric patients, DNSIs are typically caused by the suppuration and perforation of parapharyngeal and retropharyngeal lymph nodes, which serve as a drainage pathway for adenoid and tonsillar infections in children aged 1–5 years. The retropharyngeal, parapharyngeal and peritonsillar spaces are therefore more frequently involved in children.[11]

Retropharyngeal abscess is now uncommon but should be recognized because of its potential to cause fatal airway obstruction.[12] The child is usually febrile, drooling and may adopt a characteristic posture with the neck flexed and the head extended. If suspected, the child must be admitted for intravenous antibiotics, rehydration and careful observation. Imaging is required to confirm the suspected clinical diagnosis, distinguish between drainable abscesses and cellulitis, define the precise extent of the disease, identify complications and also monitor infection progression. CT scanning with contrast is the modality of choice but may itself require anaesthesia (**Figure 37.4**).[13] In patients requiring a general anaesthetic the patient should be carefully intubated with the help of a skilled paediatric anaesthetist and arrangements should be made for surgical drainage if indicated as soon as the CT scan has been completed. Drainage can be via an intraoral or external approach.



Figure 37.3 Dental abscess.

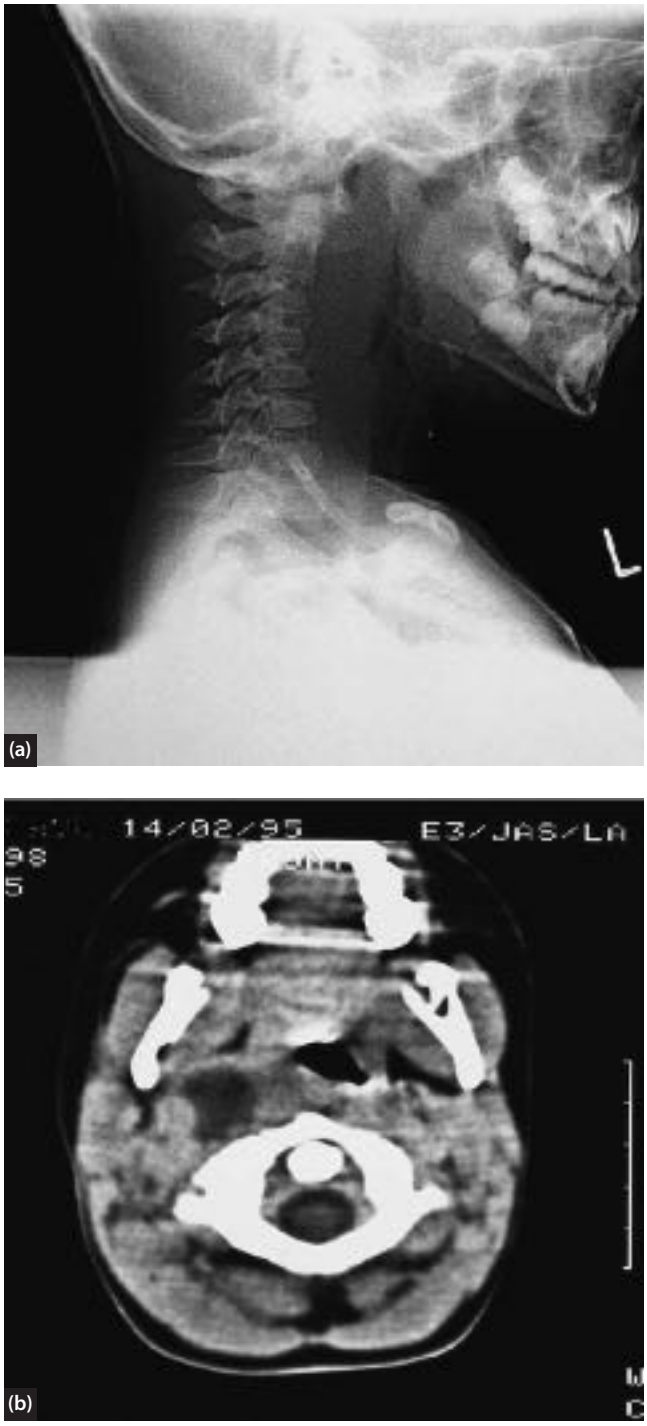


Figure 37.4 Retropharyngeal abscess. (a) Plain film showing large prevertebral shadow with compression of the airway; **(b)** CT scan of same child showing swelling filling the retropharyngeal space.

Ludwig's angina

This is a rapidly progressing cellulitis of the floor of mouth, involving the submandibular neck space. It is usually secondary to concomitant dental infections[14, 15] but has been described after frenuloplasty in an adolescent.[16] Causative organisms include *Streptococcus* species, Gram-negative rods and anaerobes. Patients usually present with swelling of the neck and submandibular space as well as firm induration of the floor of mouth, resulting in elevation and protrusion of the tongue, which can lead to airway obstruction.[17] Securing the airway is the mainstay of treatment, followed by intravenous antibiotics. Prompt initiation of antibiotics is usually sufficient and surgical intervention is reserved for persistent or progressive infections or when there is evidence of abscess formation.[18, 19] Surgical techniques for surgical decompression include intraoral and external approaches to ensure drainage of submaxillary and sublingual spaces.[20, 21]

Lemierre's syndrome

This is a septic thrombosis of the internal jugular vein. It is most often caused by the bacterium *Fusobacterium necrophorum*. It was common in the pre-antibiotic era, with a mortality rate exceeding 50%. Following an episode of upper respiratory sepsis the patient develops high spiking fevers with tenderness and fullness of one side of the neck. Pulmonary emboli may occur causing lung abscess formation (**Figure 37.5**). Incidence in the UK is rising, perhaps related to changing patterns of antibiotic use.[22]

Doppler ultrasound can detect flow rate and is useful in making the diagnosis. Unfortunately, it is suboptimal for detecting thrombosis deep to the mandible and clavicle.

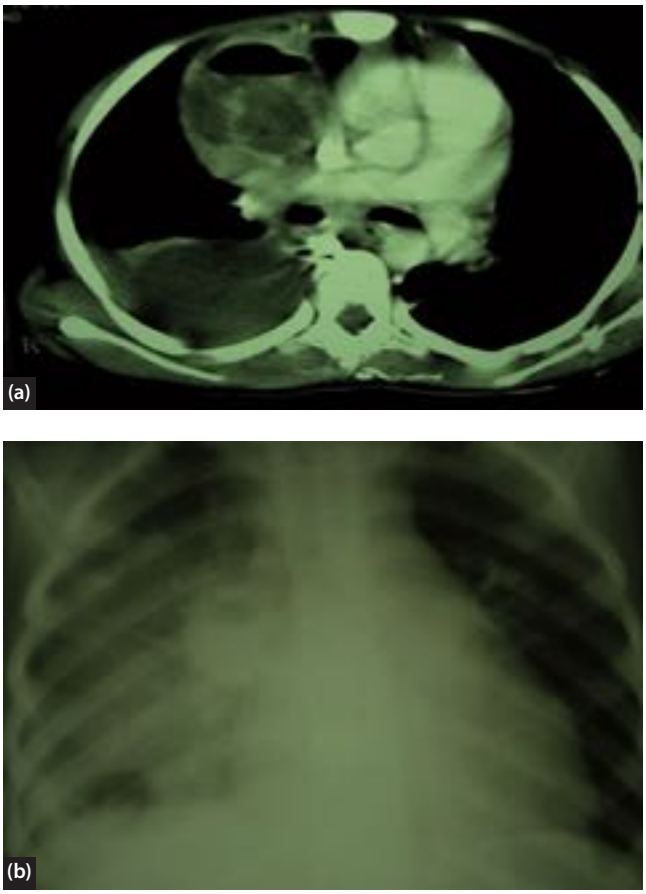


Figure 37.5 CT scan and chest X-ray demonstrating a lung abscess secondary to septic emboli from internal jugular vein thrombosis.

CT scan with intravenous contrast is considered by many to be the study of choice. Treatment with intravenous antibiotics and drainage of any abscess is usually curative. The role of anticoagulants is controversial and surgical treatment of the suppurating internal jugular vein is rarely required, although it has been used in cases of repeated septic emboli.

CAT SCRATCH DISEASE

This is a granulomatous condition characterized by lymphadenopathy with fever and malaise. The disease has been recognized for over 50 years but only recently has the causative organism been identified as the bacteria *Bartonella henselae*. It is spread by close contact with cats while kittens are more likely to carry the bacteria than adult cats. Fleas have been shown to serve as a vector for transmission among cats and viable *Bartonella henselae* has been isolated in the faeces of cat fleas. It has been postulated that transmission of *B. henselae* from cats to humans may be by inoculation with flea faeces containing *B. henselae* through a contaminated cat scratch wound or across a mucosal surface.[23–25]

Patients are mainly under 20 years of age and more than 90% have a history of feline contact.[26, 27] Serologic testing has a high sensitivity and specificity. Although there is no medical treatment, confirmation of the diagnosis by performing a blood test will reassure parents who often become concerned about possible malignancy. Lymphadenopathy may persist for months after other symptoms have disappeared.

TULARAEMIA

Tularaemia, named after Tulare County in California, is also known as rabbit fever or deer fly fever. It is caused by infection with the Gram-negative bacillus *Francisella tularensis*. It is transmitted to humans by rabbits, ticks or contaminated drinking water. Skin or mouth ulcers may be present with associated lymphadenopathy, fevers, malaise and headache. Diagnosis can be difficult but organisms can be isolated from blood cultures during periods of pyrexia. The diagnosis can also be confirmed by rising serological titres in the convalescent phase of the illness. The treatment of choice is streptomycin but tetracycline, aminoglycosides or chloramphenicol has also been used. Immunotherapy has shown promise in animals but is still not licensed in adult use.[28]

ACTINOMYCOSIS

Actinomycosis is caused by Gram-positive non-spore forming bacteria. The most common human pathogen is *Actinomyces israelii* but there are several other species which can rarely be pathogenic. Approximately 50% of cases are cervicofacial. Actinomyces are normal commensals in the oral cavity and infections arise from a breach of the mucosa (e.g. dental extraction). The most common presentation is a slow-growing painless mass near the mandible. Local lymph nodes may be involved and in a small number of cases metastasis of disease to liver or brain may occur. Untreated, the mass progresses to fibrosis and chronic suppuration with draining sinuses. A less common presentation is with an acute, warm, tender mass with fever. The presence of sulphur granules on pathological examination is suggestive but not diagnostic. If the diagnosis is suspected, special culture conditions increase the chance of culturing this organism. Most cases are treated by surgical excision followed by prolonged antibacterial therapy, usually penicillin for up to 6 months.

BRUCELLOSIS

Brucellosis is a zoonosis, i.e. an infection transmitted from animals to humans. It can be acquired through working with livestock or consumption of unpasteurized dairy products or infected meat products. It is caused by several species of the genus *Brucella,* which are small Gram-negative bacilli. There is lymphadenopathy involving the neck and other body regions associated with fever, malaise and migratory myalgia and arthralgia. Diagnosis is by serology and management is with tetracycline in adults and trimethoprim-sulphamethoxazole in children. Up to 10% of patients will present with relapse and treatment will have to be repeated.

SYPHILIS

This is a spirochaete infection caused by *Treponema pallidum*. Primary syphilis is associated with an ulcer (chancre) and local lymphadenopathy. Early presentation with a neck mass may occur in patients with HIV. It presents in the paediatric population as congenital syphilis and the majority of patients are asymptomatic at birth. If untreated, patients can present with late congenital syphilis. Head and neck manifestations include neurosyphillis, saddle nose deformity and Higoumenakis' sign, which is unilateral sternoclavicular joint enlargement caused by periosteitis in congenital syphilis.[29]

Serological diagnosis starts with venereal disease research laboratory (VDRL) and rapid plasma reagin (RPR) tests. Occasionally these tests can yield false-positive results and confirmation is required with treponemal-specific tests, *Treponema pallidum* haemagglutination assay (TPHA) or fluorescent treponemal antibody absorption (FTA-ABS) tests.[30, 31]

First-line treatment for uncomplicated infection consists of a single dose of intramuscular penicillin or oral azithromycin. Because of the poor penetration of penicillin into the central nervous system, treatment of neurosyphilis requires high-dose penicillin for a prolonged period (at least 10 days).[31, 32]

Mycobacterial infections

Two groups of mycobacterial infections involve the neck in children. The distinction is important and can be challenging. First there are infections caused by *Mycobacterium tuberculosis* (TB). Second are a group of infections caused by other mycobacteria. Commonly referred to as atypical

mycobacteria or environmental mycobacteria, these are most accurately termed non-tuberculous mycobacteria (NTM) or mycobacteria other than tuberculosis (MOTT). They include *Mycobacterium avium intracellulare*, *Mycobacterium scrofulaceum*, *Mycobacterium fortuitum* and *Mycobacterium haemophilum*.[33] They particularly affect children between the ages of 18 months and 3 years, presumably because younger children are less commonly exposed to the pathogens and because older children have developed immunity.

NTM is found throughout the environment and can be isolated from water, soil, dust animals and birds.[34–37] These organisms are low-grade pathogens in humans and cross infection is rare.

The typical presentation is of a painless, firm, enlarging mass in the neck. In NTM infection the overlying skin is frequently discoloured (**Figure 37.6**). In children with tuberculosis, weight loss, fever and anorexia may be present.

The differential diagnosis includes lymphoma. To exclude this, a tissue diagnosis is usually required. Biopsy specimens are sent for both histopathological examination and microbiology, including staining and culture specific to mycobacterium. The typical histopathological appearances of tuberculosis are of caseating granuloma formation. Acid- and alcohol-fast staining bacilli may be seen. However, it may not be possible histopathologically to distinguish tuberculous from NTM infection. Culture remains the cornerstone of diagnosis of opportunistic mycobacterium but may take several weeks. In this situation all patients should have a chest X-ray to identify features of tuberculosis. A tuberculous skin test is often helpful. A positive test in a non-immunized population (such as the US or children under 13 in most regions of the UK) is highly suggestive of tuberculous infection. Unfortunately, there is an incidence of positive testing with non-tuberculous infection and this test is not absolutely diagnostic for tuberculosis. In cases of doubt, antituberculous medication may be commenced pending the outcome of cultures. Genetic probing of the cultured organisms can also be used to try and make the distinction between tuberculous and NTM infection. Great promise is shown with the use of multiplex real-time PCR testing with targeting different housekeeping genes.[38]

The management of confirmed mycobacterium tuberculosis lymphadenopathy is medical treatment with a combination of antituberculous drugs. The management of NTM lymphadenopathy is controversial. Complete surgical excision of the involved nodes results in higher short-term cure rates compared to medical treatment.[39] Prolonged medical therapy is an alternative[40] but there is no evidence that it is any better than doing nothing and waiting for spontaneous resolution.[41] There is obviously a trade-off: with surgery there is a scar and possible injury to the facial nerve or its branches and, depending on the circumstance, this may or may not lead to a better cosmetic result than the scarring left after the disease has run its natural course; untreated NTM usually resolves in 3–6 months but a few cases can take a year or more.[42]

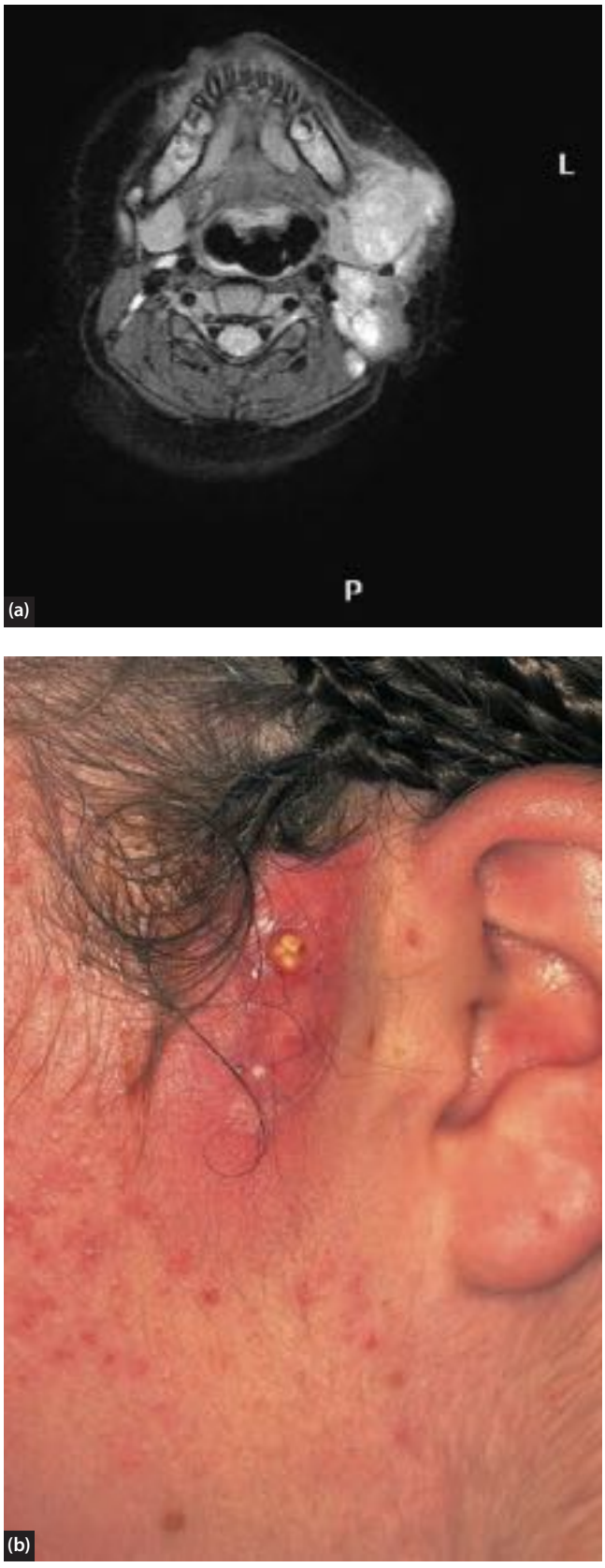


Figure 37.6 NTM. **(a)** MR scan showing large left neck mass; histology confirmed NTM. **(b)** Skin changes in NTM.

SINUS FORMATION AND DISCHARGE

If the nodes have been breached by the infection and there has been spread into the surrounding tissue, there is a risk of skin breakdown and formation of a sinus. These sinuses often persist for months with troublesome discharge. Once a sinus has formed, there is a stronger indication to perform surgery as the constant discharge is extremely disruptive to the life of an otherwise well child. Curettage has been advocated as a treatment for infection that has spread beyond the lymph nodes and is not amenable to complete excision. This may reduce the duration of the disease.

Primary medical treatment of non-tuberculous neck masses has been advocated using either macrolide antibiotics based on some *in vitro* experiments[43] or antituberculous therapy. This usually involves prolonged treatment as the organisms are notoriously resistant to antituberculous therapy. Whether such prolonged antibiotic therapy produces better results than doing nothing is currently unclear.[31]

Fungal infections

HISTOPLASMOSIS

Histoplasmosis is caused by the fungus *Histoplasma capsulatum*. It is associated with bird droppings and acquired via airborne spores. Infection in the central US is very common and typically asymptomatic. Pulmonary and systemic disease may occur in immunocompromised patients and is common in HIV/AIDS patients. Mucosal head and neck lesions may mimic squamous carcinoma and severe infections can cause lymphadenopathy.

The diagnosis is best established by urine antigen testing. Serum antigen tests can produce false-negative results in the first 4 weeks of the infection and blood cultures take 6 weeks to produce diagnostic growth.[44] Immunocompetent patients do not often require treatment as the infection usually resolves. Antifungals such as amphoterizine B and itraconazole are used to treat severe acute and chronic disseminated infections.

CANDIDA AND ASPERGILLUS

Mucosal candidiasis is a common problem in children but neck masses caused by these infections are extremely rare and limited to immunocompromised patients.

Parasitosis

TOXOPLASMOSIS

Infection with the parasite *Toxoplasma gondii* is usually through the ingestion of poorly cooked meat or of oocytes excreted in cat faeces. Cervical adenitis occurs in more than 90% of clinical cases.[45] Subclinical infection and positive serology may be found in asymptomatic individuals. It is estimated that up to a third of the world population carry *Toxoplasma* infection.[46]

Organisms can be detected by polymerase chain reaction in human blood samples.[47] The lymphadenopathy may persist for months and children may require a biopsy to rule out malignancy. Treatment is rarely required for cervical lymphadenopathy, which is self-limiting, but the infection responds to sulphonamides and pyrimethamine.

Non-infective inflammatory disorders

SARCOID

Sarcoidosis is a chronic multisystem disorder of unknown aetiology. It mainly occurs in the second decade of life and is rare in children. It causes generalized and pulmonary symptoms but may involve other parts of the body. Neck masses, parotid masses and facial nerve paresis, often bilateral, may result. Cervical nodes are typically bilateral and non-tender. The diagnosis is often suspected from the chest radiograph and can be confirmed by biopsy, which shows typical non-caseating granulomas. Angiotensin-converting enzyme blood levels are used in diagnosis and monitoring of sarcoidosis. Treatment is usually conservative although steroids, and in some cases more potent antineoplastic agents, can be used.

Conditions which simulate lymphoma

This heterogeneous group of benign lymphoproliferative disorders is characterized by prolonged unexplained cervical adenopathy which can give rise to concerns regarding lymphoma. Some authors refer to these conditions as 'pseudolymphomata'. They include Rosai–Dorfman disease, Castleman disease, Kawasaki syndrome and Kikuchi-Fujimoto disease.[48]

KAWASAKI SYNDROME

This is an acute multisystem vasculitis of unknown aetiology. It tends to affect children under 5 years of age and the clinical presentation is similar to many childhood infectious diseases. The diagnosis is clinical and children should have four of the five following criteria:

1. acute nonpurulent lymphadenopathy – usually unilateral
2. erythema, oedema and desquamation of the hands and feet
3. polymorphous exanthema
4. painless bilateral conjunctival infection
5. erythema and injection of the lips and oral cavity.

There may be a thrombocytosis and pericardial effusion. In the subacute stage, coronary artery aneurysms develop in 15–20% of cases. The goal of management is to reduce inflammatory responses with anti-inflammatory or gamma globulin therapy.[49] The vasculitis is self-limiting but unfortunately causes permanent cardiac damage in around 20% of untreated patients. All patients should have an initial echocardiogram and cardiac follow-up. A mortality of 1–2% is associated with this disease due to the cardiac sequelae.

SINUS HISTIOCYTOSIS (ROSAI–DORFMAN DISEASE)

Children present with massive cervical lymphadenopathy which is similar to infectious mononucleosis or lymphoma. This disease is thought to represent an abnormal histiocytic response to some precipitating cause, possibly a herpes virus or EBV.[50] Fever and skin nodules may be present. Treatment is expectant but biopsy is usually required to rule out malignancy. Histopathologic examination reveals dilated sinuses, many plasma cells and marked proliferation of histiocytes.

KIKUCHI-FUJIMOTO DISEASE

This is an idiopathic disorder, first described in Japan. It is characterized by lymph gland enlargement which may occur anywhere in the body but is typically cervical.

Fever chills and weight loss are common. Women and young adults are more commonly affected. The disease is self-limiting but biopsy is often performed to rule out malignancy. Histology shows a characteristic necrotizing lymphadenitis.

BEST CLINICAL PRACTICE

- ✓ A blood count is a useful screening investigation for haematological malignancy.
- ✓ Ultrasound will help determine if a lesion is cystic or solid. An experienced ultrasonographer can comment on the internal architecture of lymph nodes and may raise suspicion of malignancy.
- ✓ In NTM, once a sinus has formed there is a relative indication to perform surgery as discharge is extremely disruptive to the life of an otherwise well child.
- ✓ Needle core biopsies of suspicious lymph nodes under radiological guidance will usually be sufficient for histological diagnosis.
- ✓ Open biopsy may be the only way to exclude a lymphoma in the non-infective inflammatory lymphoproliferative disorders.

FUTURE RESEARCH

- ➤ The increasing survival of children with malignant disease, often with highly immunosuppressive chemotherapy, will produce therapeutic challenges in the management of infectious disease in the head and neck.
- ➤ Pooling of data on relatively uncommon conditions such as NTM may produce better treatment protocols.
- ➤ Imaging continues to be refined and, as spiral CT scanners permit higher-resolution images at lower radiation doses, imaging the architecture of cervical structures will improve.
- ➤ Aspiration biopsy cytology has proved disappointing in children and increasing specialization in pathology may expand the role of this technique.

KEY POINTS

- Lymphadenopathy is common in children and rarely requires investigation.
- Viral adenitis is the most common cause of neck swelling.
- Much anxiety can be caused by lesions that simulate lymphoma but careful clinical assessment supplemented by non-invasive investigations, and very rarely biopsy, will provide a diagnosis.
- Immunocompromised patients pose a particular challenge and liaison with a paediatrician is essential in this group of children.

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CHAPTER
38

DISEASES OF TONSILS, TONSILLECTOMY AND TONSILLOTOMY

Yogesh Bajaj and Ian Hore

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SEARCH STRATEGY

Data in this chapter may be updated by searches of the Cochrane Library, Medline, PubMed and Ovid databases using the keywords: tonsils, tonsillitis, pharyngitis, sore throat, children, paediatric and carrying out further subsearches for anatomy, microbiology, immunology, complications and therapy. These were complemented by hand searches of current English language texts and the following journals: *Journal of Laryngology and Otology*, *Clinical Otolaryngology*, *Laryngoscope*, *Archives of Otolaryngology*, *Annals of Otolaryngology*, *International Journal of Pediatric Otolaryngology*. The information available from the published results of the National Prospective Tonsillectomy Audit available on the Royal College of Surgeons of England website (www.rcseng.ac.uk) has also been taken into account. In addition, the UK Department of Health (www.dh.gov.uk) and the National Institute for Health and Care Excellence (NICE) (www.nice.org.uk) websites were consulted.

DISEASES OF TONSILS

STRUCTURE AND FUNCTION OF TONSILS

The palatine tonsils are paired structures consisting of lymphoid tissue. They are located in the tonsillar fossa between the anterior and posterior tonsillar pillars formed by palatoglossus and palatopharyngeus muscles respectively. Along with the adenoids, the lingual tonsils, the tubal tonsils and the diffuse aggregates of pharyngeal submucosal lymphoid tissue, they make up Waldeyer's ring.

Histologically the tonsils consist of aggregates of lymphocytes arranged in a follicular manner and embedded in a stroma of connective tissue. The epithelial lining is stratified squamous, which invaginates into the parenchyma forming crypts.

The organisms cultured from the tonsils are very variable, with recognized differences in surface and core samples.[1, 2] The most commonly identified organism from the surface of a diseased tonsil is the group A beta-haemolytic streptococcus (GABHS). This organism is also found on culture in nearly 40% of asymptomatic individuals.[3, 4] Other organisms found on the surface include *Haemophilus influenzae*, *Staphylococcus aureus*, alpha-haemolytic streptococci, *Branhamella* spp, *Mycoplasma*, *Chlamydia*, anaerobes and respiratory viruses.[5, 6] In recurrent tonsillitis the samples grew a range of pathogens but the predominant organisms were *Haemophilus influenzae* and *S. aureus* including methicillin-resistant *Staphylococcus aureus* (MRSA),[7] mixed flora being quite common. Beta-haemolytic streptococci were less common.

Function: Role of tonsils within the immune system

The tonsils are composed of lymphoid tissue with germinal centres located immediately submucosally. Both T- and B-lymphocytes are present though B-lymphocytes predominate. Tonsil serves both the cell-mediated and humoral immune function. The tonsils have no afferent lymphatics. The B-cells have the capability to synthesize specific antibodies. On exposure to antigen, immunoglobulin IgG and IgA plasma cells are produced. Contact with allergens in the upper respiratory tract therefore enhances

local immunity and also contributes to the development of systemic immunity.

There is no evidence to suggest that tonsillectomy results in impaired immunity, presumably as a result of the extensive 'back-up' in the immune system.[8] The role of bacteria and viruses in this process is also controversial. The evidence suggests that they may act synergistically, with the presence of certain latent viruses (particularly Epstein–Barr virus, adenoviruses and herpes simplex) sensitizing the pathogenic bacteria present incidentally on the tonsils of asymptomatic individuals.[9]

INFLAMMATORY DISORDERS OF THE TONSIL

Acute tonsillitis

Acute tonsil inflammation may be a localized episode, in association with an upper respiratory illness or as a part of generalized systemic infection such as infectious mononucleosis. The causative organism usually is GABHS, although a range of other organisms including viruses and anaerobes may be implicated.[3, 4]

Acute tonsillitis is diagnosed mainly on the basis of clinical assessment. There is a short history of sore throat with fever and pain on swallowing. Examination generally reveals erythema of the tonsils and posterior pharyngeal wall, with obvious exudates on the tonsils occasionally. This is usually associated with tender jugulodigastric lymph node enlargement. Both bacteria and viruses play a part in acute inflammation of the tonsils, either separately or together. Also, there is no evidence to suggest that viral tonsillitis is more or less severe than bacterial tonsillitis. In most of the cases both viral and bacterial tonsillitis tend to resolve quickly without treatment.[4] Corticosteroids (oral or intramuscular), in addition to antibiotics, expedite the resolution of pain.[10, 11]

The management of acute tonsillitis is mainly symptomatic, i.e. using analgesia and hydration until the symptoms subside. Antibiotics will shorten the illness and may reduce the risk of sequelae.[12] In those patients in whom the illness shows no sign of improvement within 48–72 hours, antibiotics should be started, benzyl-penicillin being the drug of choice. If there is clinical concern about the severity of disease at the beginning, antibiotics should be started soon.

Evidence suggests that corticosteroids provide symptomatic relief of pain in sore throat, in addition to antibiotic therapy, especially in severe cases.[13]

Complications of acute tonsillitis

Acute tonsillitis can lead to septicaemia and local abscess formations. The non-infective complications of streptococcal tonsillitis include rheumatic fever and glomerulonephritis.

PERITONSILLAR ABSCESS (QUINSY)

A peritonsillar abscess is a collection of pus lateral to the tonsil. The clinical symptoms include severe usually unilateral sore throat, odynophagia, trismus and lymphadenopathy. The treatment includes antibiotics, needle aspiration of pus or incision and drainage.[14] The antibiotics usually given are intravenous high-dose penicillin or a cephalosporin.[15] Indication for interval tonsillectomy should take into account any background history of tonsillitis or more than one episode of quinsy on the same side. Tonsillectomy during the acute attack is not a very popular treatment option,[16] as the release of pus into the oral cavity either spontaneously or therapeutically carries with it the risk of aspiration in severely ill patients. Using local anaesthetic before incision also increases this risk. The initial management of choice is aspiration of the abscess using a wide-bore needle along with intravenous antibiotics, usually high-dose penicillin or cephalosporin.

RETROPHARYNGEAL ABSCESS

This is a rare but serious complication of acute tonsillitis, seen mainly in infants and children less than 5 years of age. It presents as the infection tracks into the lymphoid tissue between the posterior pharyngeal wall and the prevertebral fascia. The child is usually systemically unwell and there may be evidence of airway compromise or an associated neck abscess. The diagnosis can be confirmed by CT scanning. Treatment is initially high-dose intravenous antibiotics.[17] If pus collection is suspected, urgent incision and drainage is done under a general anaesthetic by an experienced anaesthetist.[18] The drainage is usually done perorally but occasionally external drainage via neck may be appropriate. Very rarely, tracheostomy is necessary. Retropharyngeal abscess due to tuberculosis requires specific antibiotic treatment.

PARAPHARYNGEAL ABSCESS

Occassionaly, peritonsillar and retropharyngeal abscess may be complicated by spread of infection to the parapharyngeal space. Pus collection in this space presents with severe trismus and possibly airway compromise in a systemically unwell patient. The diagnosis is confirmed by ultrasound or CT scanning, which also helps in treatment planning. Treatment includes high-dose broad-spectrum intravenous antibiotics and drainage of the abscess. Deep neck space sepsis may be complicated by progression to life-threatening infections including mediastinitis or retroperitoneal sepsis. It is essential to be proactive in managing these conditions.[19]

LEMIERRE'S SYNDROME

Lemierre's syndrome is a rare but potentially fatal complication of oropharyngeal infection. It is characterized by septic thrombophlebitis of the internal jugular vein, at times associated with metastatic abscesses. The causative organism is usually fusiform bacillus. This condition should be suspected when there is severe neck pain and septicaemia in a patient with infection in the upper aerodigestive tract.[20] Treatment is with antibiotics for 6 weeks, usually penicillin with metronidazole or Co-amoxiclav.[21] If there is evidence of spreading thrombophlebitis,

anticoagulation may be considered. There is significant mortality associated with this condition.

IMMUNE COMPLEX DISORDERS

Acute tonsillitis caused by GABHS can occasionally lead to diseases related to immune complex formation, generated as a response to the infection. The two important diseases resulting from this phenomenon are acute rheumatic fever and acute gomerulonephritis.

TONSILLITIS AND PSORIASIS

There is possibly some association between GABHS tonsillitis and exacerbations of psoriasis, as a result of an immune phenomenon. Some dermatologists and otolaryngologists advocate tonsillectomy, but there is no good evidence to suggest that this relieves the condition.[22]

RECURRENT TONSILLITIS

Significant numbers of patients suffer from recurring episodes of acute tonsillitis. These episodes may gradually settle or may continue for several years. The infections need to be treated depending on the severity of the individual episode. There is no evidence of benefit of long-term antibiotics for this condition.

CHRONIC TONSILLITIS

Some patients get chronic throat discomfort associated with production of smelly white debris from tonsillar crypts. Occasionally, these debris may become inspissated, calcify and form a tonsillolith. There is no evidence to show a relationship to identifiable tonsillar pathology in these patients.

Infectious mononucleosis

Infectious mononucleosis commonly presents as acute tonsillitis. It is caused by Epstein–Barr virus (EBV) and is commonly seen in young adults. In addition to the throat symptoms, patients have significant systemic upset, splenomegaly and derangement of haematological and liver functions.[23] The diagnosis is helped with the Monospot test, which has sensitivity of less than 50% in children and 70–90% in adults. The diagnosis is confirmed by specific antibody titres. Although this is caused by a virus, in 30% patients secondary bacterial tonsil infection occurs. For those admitted to hospital, high-dose intravenous penicillin or cephalosporins is given. Ampicillin must be avoided if infectious mononucleosis is suspected as 90% patients can develop a significant rash as a result of transient immunostimulation. The incidence of rash with amoxycillin in these cases is 30%.[24]

In those patients with significant swelling of the tonsils leading to compromise of the airway and swallowing difficulty, a short course of corticosteroids is beneficial.[11] Steroids should be preferably given in combination with antibiotics. The use of antiviral medications (acyclovir) is debatable and should be considered only in severe cases.[25]

Other infective conditions

Syphilis and tuberculosis infections in the tonsils are potentially difficult to diagnose. The lesion in syphilis classically takes the form of a punched-out ulcer but the appearances are variable, as for tuberculosis. The differential diagnosis of a neoplasm should be borne in mind and the final diagnosis made by biopsy of the lesion.

NON-INFLAMMATORY DISEASES

Tonsillar asymmetry

Asymmetry of the tonsils is not an absolute indication for tonsillectomy, but in children, as adults, the clinicians need to be aware of the possibility of neoplasia (lymphoma). One study to measure actual size in cases of apparent asymmetry in children did not show any significant difference in size.[26] In general, the apparent size of the tonsils is not well correlated with disease within them. There is a wide variation in the degree to which the tonsils are buried within the tonsillar pillars, which can give a false impression of the actual size of the tonsil. In general, the tonsils tend to involute during late childhood, but this rate of involution is variable between individuals and can vary between the two tonsils, which can at times give an asymmetrical appearance.

Spontaneous tonsillar bleeding

Spontaneous bleeding can happen from inflamed tonsils occasionally. Bleeding can also be secondary to minor trauma. This usually will respond to topical cautery under local anaesthetic. If it persists, tonsillectomy is an option.

Neoplasia

Asymmetrical tonsils arouse suspicion of neoplasia especially if the surface of one of the tonsils is irregular or ulcerated. Difference in size is not always an indication for biopsy in children, but any unusual appearances need to be investigated. Lymphoma can occur within the tonsils in adults as well as children. In adults, squamous cell carcinoma is the most common malignancy encountered.

TONSILLECTOMY AND TONSILLOTOMY

TONSILLECTOMY

Paediatric tonsillectomy is one of the most commonly performed operations. In the 1950s in the UK 200 000 tonsillectomies were performed annually, which dropped down to 49 187 in 2008–2009 (www.hesonline.nhs.uk). Of the tonsillectomies carried out in 2008, 27 400 were in children. Among those 25% were for obstructive symptoms and the rest for infections. The proportion performed for obstruction rather than infection seems to be rising year-on-year. This may be due in part to more stringent criteria being applied to surgery for infections as a result of better

evidence from trials in addition to increasing awareness of obstructive sleep apnoea and its consequences in children.

Evidence base for tonsillectomy

Adenotonsillectomy is the treatment of choice for otherwise healthy children with obstructive sleep apnoea, with improvement in 90% cases, including improvement in their behaviour, growth and development.[27, 28] However, for recurrent infections there is a widespread perception that high-quality evidence of the efficacy of tonsillectomy is lacking. Certainly, the evidence for benefit of adenotonsillectomy for recurrent infections was sparse until quite recently.[29] A Cochrane review in 1998 concluded that there was no evidence from randomized controlled trials (RCT) to guide clinicians for setting up guidelines for tonsillectomy in children or adults.[30] However, trials have been carried out since then and the evidence base is a little clearer.

For a long time, the only trial of value was that done by Paradise[32] published in 1984. The Paradise group randomized children with sore throats into surgical and non-surgical groups and their inclusion criteria are widely known and still used: seven sore throat episodes in a year, five a year for the last 2 years or three a year for the last 3 years. Recruitment took many years as few families were willing to undergo randomization and a large parallel cohort of non-randomized children undergoing surgery was also studied. Efficacy was measured on the basis of reduction in the number and severity of throat infections. This trial showed that in severely affected children tonsillectomy was efficacious for 2 years and sometimes for a third.

The North of England and Scotland Study of Tonsillectomy and Adenotosillectomy in Children (NESSTAC) was a large multicentre randomized controlled trial which used broadly the same inclusion criteria as Paradise, and which also had a large parallel cohort of non-randomized children undergoing surgery.[32] This trial demonstrated significant improvements in episodes of sore throat, need for consultations, quality of life and health costs compared to medical management.

Two further trials (one by Paradise[33] and the other from the Netherlands[29]) looked at children with milder symptoms, who did not meet the original Paradise criteria. They both failed to show a significant advantage of surgery over watchful waiting, so it seems that the original Paradise criteria for tonsillectomy are a reasonable threshold for considering surgical intervention.

Studies looking at quality of life (QOL) before and after operation suggest that tonsil disease has a marked adverse effect on QOL and there is significant benefit from surgery.[34] The Scottish tonsillectomy audit was a large-scale audit to look at patient satisfaction after tonsillectomy in more than 5000 patients. This audit reported 97% satisfaction rate 1 year after tonsillectomy.[35]

Guidelines

Various guidelines are produced by the British Association of Otolaryngologists – Head and Neck Surgeons (see ENTUK, www.entuk.org). For tonsillectomy, the recommendations are in line with those of Scottish Intercollegiate Guidelines Network (SIGN, www.sign.ac.uk). The SIGN guidelines for tonsillectomy are based on the Paradise criteria outlined above and reflect the results of randomized controlled trials. According to these guidelines, patients for tonsillectomy for both adults and children should meet all the following criteria:

- sore throats are due to tonsillitis
- the episodes of sore throat are disabling and prevent normal functioning
- seven or more well-documented, clinically significant, adequately treated sore throats in the preceding year, *or*
- five or more such episodes in each of the preceding 2 years, *or*
- three or more such episodes in each of the preceding 3 years.

TONSILLECTOMY TECHNIQUE

The traditional methods of tonsillectomy are 'cold steel' techniques using metal instruments. Several other methods have been introduced with perceived advantages in terms of reduced bleeding, reduced pain, more rapid healing and ease of surgical technique. The National Prospective Tonsillectomy Audit (NPTA) was established in 2003 on behalf of the Royal College of Surgeons of England and ENTUK to look at the effect of surgical technique on complications of tonsillectomy. Data were collected on more than 50 000 patients and the results represent the nationwide practice and recommendations for the clinicians.[36] There are also good data available from the Swedish national tonsil registry which has prospective data on 37 530 patients undergoing tonsillectomy alone (17 319 patients) or adenotonsillectomy (20 211 patients).[37]

Cold steel tonsillectomy

The dissection technique is the most common method of cold steel tonsillectomy. In this technique, the tonsil is pulled medially and the mucosa overlying the tonsil capsule is incised. The dissection continues in the plane of loose areolar tissue between the tonsil tissue and the pharyngeal muscles using a dissector or gauze, and the tonsil is excised completely. The bleeding vessels are dealt with using diathermy or ligatures as required. Another technique is the guillotine technique, which involves using a specially designed guillotine to excise the tonsil.

In the NPTA, haemorrhage was defined as a bleed that prolonged the patient's stay in hospital, required blood transfusion or return to the operating theatre or for secondary haemorrhage readmission to hospital. The haemorrhage rates for various techniques are shown in Table 38.1. The Swedish registry gives similar results, with cold steel dissection and ties having a significantly lower bleed rate and less post-operative pain than any of the other techniques.

TABLE 38.1 Surgical techniques and primary and secondary post-operative haemorrhage

Surgical technique (n = 33 921)	Primary tonsillar haemorrhage rate (%)	Secondary tonsillar haemorrhage rate (%)
Cold steel and ties/packs	0.8	1.0
Cold steel and monopolar diathermy	0.5	2.4
Cold steel and bipolar diathermy	0.5	2.3
Monopolar diathermy forceps	1.1	5.5
Bipolar diathermy forceps	0.4	4.3
Bipolar diathermy scissors	0.6	4.6
Coblation®	1.0	3.6
Other	0.7	3.6

Source: Reprinted, with permission, from the National Prospective Tonsillectomy Audit, available from the Royal College of Surgeons of England website (www.rcseng.ac.uk), Table 4.6.

Diathermy tonsillectomy

Bipolar dissection tonsillectomy is an alternative method to traditional cold steel tonsillectomy. In a Cochrane review of dissection versus diathermy, it was demonstrated that diathermy reduced intra-operative bleeding but increased pain in the diathermy group with no difference in secondary haemorrhage rate.[38] In the NPTA, post-operative bleeding was more frequent with diathermy than with cold steel alone, and particularly worse with monopolar diathermy. Monopolar dissection is known to be associated with more post-operative pain than other techniques and has little to recommend it.

Recommendations from the NPTA are shown in Box 38.1.

Coblation® tonsillectomy

This technique uses a specially designed probe which both coagulates and cuts the tissues. In the NPTA, post-operative bleeding rates were unacceptably high. It has been suggested that post-operative pain is less than conventional dissection but some studies have cast doubt on this and shown that morbidity was less with cold steel dissection.[39] The National Institute for Health and Care Excellence (NICE) advises that electrosurgery (diathermy and Coblation®) can be used for tonsillectomy but that surgeons must be appropriately trained.

Ultrasonic dissection

Ultrasonic dissection uses an oscillating blade, which acts as both a cutting and a coagulating device. Some studies claim reduced pain with this technique but evidence of benefits is lacking.[40]

Laser tonsillectomy

Using a laser as a tool to dissect out the tonsils has been claimed to have advantages in terms of reduced bleeding and post-operative pain, but studies have failed to confirm this. There is evidence that the rate of secondary bleeding[39] and pain is greater with laser.[42]

BOX 38.1 Recommendations of the National Prospective Tonsillectomy Audit (2005)

- When a patient is counselled for surgery, the risk of tonsillectomy complications, and in particular post-operative haemorrhage, should be carefully explained to the patients/parents.
- This risk should be quantified, preferably using the surgeon's own (or department's) figures.
- National figures can be used, but this should be made clear to patients.
- Surgeons using monopolar diathermy should consider using an alternative technique. There are no advantages to using this instrument over other methods.
- All trainee surgeons should become competent in cold steel dissection and haemostasis using ties, before learning other techniques in tonsillectomy.
- Emphasis must be placed on teaching the correct use of, and the potential hazards of, diathermy and other 'hot' techniques. Checks should be made of the power settings before starting the operation.
- Inexperienced trainees must be supervised by a more senior surgeon until competency has been achieved. This recommendation is in agreement with the College's Standards on Good Surgical Practice issued in 2002.
- Irrespective of seniority and experience, surgeons who wish to start using new techniques, such as Coblation®, should undergo appropriate training.
- All ENT departments should have regular morbidity and mortality meetings to monitor adverse incidents affecting patient outcome. For tonsillectomy, data should be presented by the surgeon, indicating the technique used for dissection and haemostasis and power settings if applicable, type of instrument used, and any difficulties encountered.
- It is the responsibility of the surgeon, and if appropriate his or her trainer, to follow up any identified problems appropriately.

Source: Modified and reprinted, with permission, from the National Prospective Tonsillectomy Audit, available in full on the Royal College of Surgeons of England website (www.rcseng.ac.uk).

TONSILLOTOMY

Tonsillotomy involves removing a part of the tonsil lymphoid tissue, leaving the capsule intact. The technique is reminiscent of what was historically called guillotine tonsillectomy. Techniques include microdebrider, laser, or most recently radiofrequency ablation (Coblation®),[43] using the instrument from medial to lateral. The amount of tissue removed can be from just the lymphoid tissue up to the anterior tonsillar pillar, to leaving a cuff of tonsil tissue lining the tonsillar fossa, to taking the tissue all the way back to the capsule (sometimes called intracapsular tonsillectomy).

These techniques, particularly Coblation® tonsillotomy, have only recently started being trialled. Earlier studies have used the technique – when tonsils for example need

to be debulked in young children with obstructive sleep apnoea – but it was thought it might be desirable to leave some functioning lymphoid tissue.[44] Some studies have already shown that recovery-related outcomes (days until pain-free, secondary haemorrhage rate) for intracapsular tonsillotomy were better than for total tonsillectomy in children with obstructive symptoms.[45] In some parts of the world, such as Scandinavia, tonsillotomy has now become the most common operation performed for obstructive symptoms, more common than tonsillectomy.[43]

The fact that the muscle is disturbed less than in tonsillectomy may explain why post-operative pain can be reduced. If the technique is found to be of similar efficacy to tonsillectomy, with a similar or lower bleed rate, the technique could represent an important step forward in tonsil surgery, potentially being applicable to all tonsil surgery for children, except where the tonsils are needed for histology. With time it will become evident how much tonsil tissue to take to achieve the balance in terms of minimal complications and maximum benefit. This is an exciting area of research.

TONSILLECTOMY MORBIDITY

Pain

Significant morbidity is associated with tonsillectomy.[46] Post-tonsillectomy sore throat is normal for at least 1 week and on an average return to school or work can take 1–2 weeks.[35] Various articles have been written on the management of post-tonsillectomy pain (see 'Anaesthesia and analgesia' below).

Peri-operative complications

If the mouth is opened too widely during the tonsillectomy operation, the patient may experience temporomandibular joint dysfunction. Dissection beyond pharyngeal musculature can lead to injury to the glossopharyngeal nerve and rarely the carotid sheath. Non-traumatic atlantoaxial subluxation (Grisel syndrome) can occur secondary to any inflammatory process in the neck.

Bleeding

Bleeding after tonsillectomy can be primary (within 24 hours after the operation) or secondary (after 24 hours until 2 weeks). The NPTA reported that the readmission rate for bleeding was 4.57%, with 1.44% requiring return to theatre. The most likely explanation for secondary bleeding is infection with *Streptococcus* in the granulating tonsil bed. Treatment depends on the severity and potential cause of the bleed. Antibiotics are advised for secondary bleeding. Severe primary or secondary bleeds need to be controlled in theatre.

Infection

The first symptoms of post-tonsillectomy infection are fever and halitosis. Treatment should be administered according to the severity.

PERI-OPERATIVE MANAGEMENT

Post-tonsillectomy morbidity can be minimized by skilled anaesthesia, analgesia, and antiemetic and steroid treatments.

Anaesthesia and analgesia

In the UK, the technique used by anaesthetists is very variable. Total intravenous anaesthesia with propofol and remifentanil leads to fast wake-up, and propofol is a helpful antiemetic agent. Using inhalational agents for intubation obviates the need for muscle relaxants and speeds up the reversal process.

Adequate analgesia is important in the immediate post-operative period. Narcotics have a potent emetic effect and should be used with caution. Paracetamol is the drug of choice as it is safe and efficacious. Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to cause significantly less post-operative nausea and vomiting than narcotics. Also concerns that effect of these drugs on platelet adhesion might increase bleeding from the tonsil bed have been unfounded. Recent guidelines have suggested that codeine should not be used in children after tonsillectomy. Also aspirin should not be used in children because of the risk of Reye syndrome.[47] Studies have reported on injecting long- and short-acting local anaesthetic pre- or post-operatively into the tonsil beds. There is no current evidence to suggest any significant benefit from the use of these techniques.[48]

Steroid treatment

Use of pre-operative glucocorticoids has gained wide acceptance. A Cochrane review has shown that a single intravenous dose of dexamethasone was an effective and relatively safe treatment for reducing morbidity from paediatric tonsillectomy.[49] Some more recent studies have confirmed that a single dose of dexamethasone at induction reduces early incidence of nausea, vomiting and level of pain post-operatively.[50]

Post-op antibiotics

Using antibiotics prophylactically after tonsillectomy has been looked at in various studies.[51] A Cochrane review of these studies published in 2012 advocated against routine use of antibiotics after tonsillectomy.[52]

Day-case surgery

Tonsillectomy as a day-case procedure is gaining popularity. The main reasons for patients to stay in overnight are the risk of bleeding and associated morbidity from pain and vomiting. Day-case tonsillectomy in children has been demonstrated by numerous studies to be a safe alternative to surgery as an inpatient.[53, 54] Recently a study has demonstrated safety of adenotonsillectomy as a day-case procedure for children with mild obstructive sleep apnoea in a tertiary unit.[55]

BEST CLINICAL PRACTICE

- ✓ In acute tonsillitis clinical diagnosis alone should not be relied upon in distinguishing between a bacterial and a viral aetiology.
- ✓ Both throat swab culture and RAT are of questionable value in guiding prescription of antibiotics for sore throat.
- ✓ Widespread indiscriminate antibiotic prescription promotes the genesis of resistant organisms, allergy and anaphylaxis. There is no justification for routine use of antibiotics in children with sore throat. [Grade A]
- ✓ In those patients in whom the illness shows no sign of improvement within 48–72 hours or in whom there is clinical concern because of the severity of symptoms, antibiotic therapy is appropriate and the drug of choice remains benzylpenicillin. A 7-day course is usually adequate.
- ✓ A single dose of dexamethasone as adjuvant therapy reduces pain in acute pharyngotonsillitis.
- ✓ Aspiration using a wide-bore needle and syringe, together with antibiotic therapy, is now the management of choice for quinsy. As a significant proportion of peritonsillar abscesses grow anaerobes, metronidazole should be considered.
- ✓ Treatment of both parapharyngeal and retropharyngeal abscess is initially high-dose antibiotic therapy. When pus formation is suspected, incision and drainage under general anaesthesia, with the airway protected by intubation by a skilled and experienced anaesthetist is recommended.
- ✓ Ampicillin must be avoided in infectious mononucleosis as patients may suffer a severe rash in consequence.
- ✓ Systemic glucocorticoids are of value in infectious mononucleosis where there is extreme swelling of the tonsils with impending airway compromise.
- ✓ 'Cold steel' dissection tonsillectomy is widely available and associated with the lowest post-operative haemorrhage rates in the hands of most surgeons.
- ✓ Adequate analgesia is essential in the post-operative care of children following tonsillectomy.
- ✓ There is now a sufficient body of evidence supporting the use of peri-operative glucocorticoids to justify considering their use as routine. [Grade A]
- ✓ In secondary haemorrhage, surgery is rarely needed. Bleeding usually settles with antibiotic therapy alone.
- ✓ Continuing audit is essential; surgeons should familiarize themselves with the findings and recommendations of the NPTA.

FUTURE RESEARCH

- ➤ The role of the tonsil in the development of immunity needs to be more fully understood.
- ➤ Data to shed light on the natural history of recurrent tonsillitis and define any subgroups in which natural resolution of recurrent symptoms is likely to happen would be helpful.
- ➤ The precise place and value of antibiotic therapy is still not fully defined. Robust randomized controlled trials of antibiotic therapy versus placebo in sore throat/tonsillitis, both in the acute single episode situation and in recurrent tonsillitis, are required. The results should be applicable to everyday practice.
- ➤ High-quality randomized controlled trials of tonsillectomy versus standardized conservative management are essential to define the optimal management of recurrent tonsillitis. The trials need to consider outcomes other than reduction in number of episodes of tonsillitis.
- ➤ The morbidity of tonsillectomy remains significant. The optimal strategy for control of pain and emesis post-tonsillectomy still requires to be defined. The use of newer antiemetic agents and peri-operative glucocorticoids seems set to increase.
- ➤ The possibility that tonsillotomy, for instance by Coblation®, could be associated with better post-operative recovery than tonsillectomy is currently being investigated. With less tissue trauma, specifically to the muscle, recovery may be quicker. Given the great potential benefits, the key question that needs to be answered is how much of the tonsil to remove to keep the same effectiveness as tonsillectomy, and also if the bleed rate is truly less. If bleed rates are reduced, this could well represent a significant step forward in the continuing evolution of tonsil surgery.

KEY POINTS

- Acute tonsillitis is common and self-limiting.
- Complications are rare.
- Treatment is largely symptomatic with an emphasis on analgesia and rehydration.
- Antimicrobial therapy has a small but measurable effect on outcome.
- The tonsil rarely may be the site of presentation of lymphoma or malignant disease.
- Tonsillectomy is one of the most commonly performed surgical procedures in the developed world.
- The evidence base for current practice is poor.
- Tonsillectomy rates vary considerably in different populations. These variations are not accounted for by variations in disease prevalence.
- Improvements following surgery are particularly small in less severely affected children. The morbidity of surgery usually outweighs any potential benefit in this group.
- There is no evidence that the benefits of tonsillectomy for recurrent sore throat are prolonged beyond 2 years.

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CHAPTER 39

SALIVARY GLANDS

Neil Bateman and Rachael Lawrence

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the following keywords: saliva, salivary, parotid, submandibular, sialendoscopy, parotitis and sialadenitis, supplemented by articles from the author's own library.

INTRODUCTION

Diseases of the salivary glands are uncommon in children. Many are similar to those pathologies occurring in adults but some present mainly in children and form the focus of this chapter. The surgical management of these conditions requires knowledge of the anatomy and experience of surgical techniques in children.

CONGENITAL ABNORMALITIES

Salivary gland aplasia

Aplasia or agenesis of the salivary glands is very rare but well recognized.[1] Some or all of the glands may be affected; children present with the effects of xerostomia such as dental caries, fissuring of the lips and oral ulceration. The diagnosis can usually be made with imaging in the form of ultrasound or MRI, augmented with radioisotope scanning if necessary. Lacrimo-auriculo-dento-digital (LADD) syndrome is a rare genetic disorder characterized by abnormalities in the lacrimal apparatus, dentition and digits. Patients may have no salivary glands.

The management of xerostomia in these cases is supportive and symptomatic, with artificial saliva and meticulous dental care.

Congenital salivary cysts

These present more commonly in the parotid gland and most often as a mass within the gland which is confirmed as cystic with ultrasound imaging. Distinguishing between a congenital salivary cyst and a branchial anomaly (see Chapter 41, Cysts and sinuses of the head and neck) may be difficult but the treatment is similar in both conditions. Treatment options include aspiration, sclerotherapy and surgical excision.

Congenital ductal abnormalities

Duplicate or imperforate ducts are rare. They are diagnosed by sialography or MR sialography. They may cause problems associated but ductal obstruction and stasis of saliva. If they are symptomatic, duct 'marsupialization' is the preferred treatment.

Ectopic salivary tissue

Ectopic salivary tissue may be found in the neck, the mandible and cervical lymph nodes and can cause discharging sinuses in these areas. The distinction between these lesions and branchial cleft sinuses can be difficult and in many cases the primary pathology is a first branchial cleft anomaly. The treatment is the same for

both conditions: surgical excision with complete preservation of the facial nerve.

Cystic fibrosis

Like other exocrine mucus-secreting glands, salivary glands are affected by the autosomal recessive disease cystic fibrosis. Abnormal mucus produced by the glands obstructs their ducts and causes progressive damage to the related parenchyma. The parotid gland, which produces mainly serous secretion, is less affected than the submandibular gland.[2]

ACQUIRED DISEASES

Mucous extravasation cysts

These mucocoeles are relatively common and usually caused by trauma that tears the duct of a minor salivary gland allowing mucus to escape into the surrounding tissues. The commonest site is the lower lip but these cysts are sometimes found in buccal mucosa or in the floor of the mouth. They present as soft, dome-shaped, swellings with a bluish hue. They are rarely more than a centimetre in diameter. Mucous extravasation cysts inevitably require excision as they do not resolve spontaneously.[2]

Ranula

A ranula is a fluid-filled lesion arising from the floor of the mouth. It is an extravasation pseudocyst and can be classified into two types: the much commoner simple or intraoral ranula, and the 'plunging' cervical type. A simple ranula is localized to the floor of the mouth. In the plunging type, extravasation of mucus occurs beyond the confines of the floor of the mouth and the mucus collection is therefore in the infra-mylohyoid compartment of the neck, with or without a clinically apparent intraoral collection.

AETIOLOGY

They may be congenital but are more frequently acquired as a result of obstruction to one of the sublingual salivary glands or ducts. This obstruction may be spontaneous but is sometimes due to trauma to the sublingual gland duct, following procedures on the floor of the mouth.

PRESENTATION

A ranula presents clinically as a smooth swelling in the floor of the mouth with a bluish translucent appearance. If of sufficient size, elevation of the tongue may occur with subsequent interference with swallowing, speech, mastication or respiration.[3] A plunging ranula may appear as a swelling in the neck. It can be difficult clinically to differentiate a plunging ranula from a lymphatic malformation. However, histologically a ranula is contained by loose connective tissue whereas a lymphatic malformation has a simple epithelial lining.

INVESTIGATIONS

Imaging is unnecessary for confirming the clinical diagnosis of a simple intraoral ranula.[4] However, if there is a history of previous surgery, if the ranula has a cervical component or of if the diagnosis is uncertain clinically, then MRI is preferred.[5–7]

TREATMENT

Simple aspiration or drainage of a ranula results in a high recurrence rate. Marsupialization of a plunging ranula is inadequate with a recurrence rate of 80%.[8] Both intraoral and plunging ranulas should be excised together with the sublingual gland as excision of the gland results in a low rate of recurrence.[9, 10] A retrospective analysis of 65 patients with a diagnosis of ranula showed that treatments which included complete sublingual gland excision were associated with the lowest recurrence rate (3.6%) and that a statistically significant difference was observed in the recurrence rate between complete sublingual gland excision and ranula excision alone.[10] Laser excision is reported as an alternative treatment for intraoral ranula, with reported low rates of recurrence and surgical complications.[11]

A transoral surgical approach is common for masses that are located intraorally and an external transcervical approach for those presenting predominantly submentally or in the neck. Care must be taken to identify and preserve the lingual nerve, which lies in close proximity.

Injection of the sclerotherapeutic agent OK-432 has been reported as a primary, non-surgical method for treating ranulas, but experience with paediatric patients is currently limited.[12, 13]

Viral parotitis ('mumps')

Mumps is the commonest disease of the salivary glands in childhood. It is a viral infection of the parotid glands, caused by a paramyxovirus, spread via droplets or contact. The incubation period is 2–3 weeks. The characteristic clinical course is a prodromal illness of malaise and pyrexia followed by painful swelling of the parotid glands, typically bilaterally. Less commonly, other salivary glands may be involved. Asymptomatic infection can occur in 20% of infected individuals. The diagnosis is made clinically, although it can be confirmed serologically. There is no specific treatment for this usually self-limiting condition and symptomatic management is usually all that is required.

The disease has become less common in the UK following vaccination which is given as part of the MMR (mumps, measles, rubella) vaccine at 12 months with a preschool booster.

Post-pubertal males may develop a painful orchitis with an associated risk of subfertility. Other potentially serious complications are sensorineural hearing loss, encephalitis and pancreatitis.

Human immunodeficiency virus (HIV)

The salivary glands, most commonly the parotid, may be involved in HIV infection. Parotid enlargement,

which may be painful or painless, should raise suspicions. The British HIV Association recommends considering HIV testing in all children with chronic parotitis.[14] There may be associated xerostomia. Multicystic change in the parotid glands results from lymphepithelial lesions termed benign lymphoepithelial lesions (BLEL) or benign lymphoepithelial cysts (BLEC). These are thought to result from localized ductal ectasia and/or ductal obstruction from lymphoid tissue hyperplasia.

The clinical picture is similar to Sjögren's syndrome although patients with HIV salivary gland disease do not have anti-Ro or anti-La antibodies. Imaging may show cystic disease or lymphadenopathy.

The management of HIV salivary disease is largely symptomatic and supportive. There is some evidence that it is controlled with anti-retroviral treatment.[15] Otherwise, cyst aspiration and sclerotherapy, surgical excision and the supportive treatment of any patient with xerostomia are the mainstays of treatment. Localized radiotherapy has some role to play in adults but is likely to have limited application in children.

For more information about HIV, see Vol 1, Chapter 23.

Acute parotitis of infancy

Acute pyogenic infection of the parotid gland in infancy presents with a painful enlargement of the gland with erythema of the overlying skin. The child is typically unwell, pyrexial and reluctant to feed. The commonest organisms are *Staphylococcus aureus, Streptococcus pyogenes* and anaerobes.

Ultrasound is useful to distinguish inflammatory change from a collection of pus. Treatment consists of intravenous antibiotics, adequate hydration and drainage of any collection. Incision and drainage should be performed with caution because of the superficial position of the facial nerve in infants. Needle aspiration in many cases is a safer option (**Figure 39.1**).

Acute suppurative sialadenitis

Acute bacterial sialadenitis may also occur in older children and is associated with salivary stasis. Obstructive causes include salivary stones, which are considered below. Where there is no obstruction to salivary flow, children with comorbidities (cystic fibrosis, malignancy, HIV and cerebral palsy) are more commonly affected.[16] The typical causative organisms are *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae* and anaerobes. Children usually present with fever, pain, gland swelling and tenderness. Pus may be visible at the duct orifice of the affected gland. Treatment consists of broad-spectrum intravenous antibiotics, hydration and sialogogues.

Bacterial infection may lead to abscess formation which is diagnosed on imaging. Ultrasound is usually adequate to make the diagnosis. Drainage of any abscess is necessary but needs to take into account the superficial nature of the facial nerve in children.



Figure 39.1 Acute suppurative parotitis in a baby aged 3 weeks.

Juvenile recurrent parotitis

Juvenile recurrent parotitis (JRP) is characterized by acute intermittent painful swelling of one or both parotid glands often accompanied by overlying cutaneous erythema, malaise and pyrexia. The usual age of onset is between 3 and 6 years. The condition is most commonly unilateral although may occur bilaterally. The swelling often settles within 2–3 days but may last up to 2 weeks.

Acute attacks are treated symptomatically with analgesia and anti-inflammatory drugs. Antibiotics are often used empirically although their use is controversial in the absence of obvious clinical infection (such as purulent discharge from the duct).

The diagnosis is made clinically, often after more than one episode has occurred. Sialography may show appearances of sialectasis but is often difficult to perform in children and unnecessary to establish a diagnosis. Ultrasound, in the correct hands, should confirm the absence of any mass lesion in the glands. In the absence of a mass apparent clinically or on ultrasound, no further imaging is warranted.

Many authors report resolution of the condition spontaneously, usually around puberty, and this appears to be the case in the majority of patients.[18] For this reason, and to control the effects on life quality of recurrent attacks, recent efforts have focused on reducing the frequency of attacks. There has been considerable interest in the use

of therapeutic sialendoscopy in this area with a number of authors reporting long-term resolution with its use.[19, 20]

Sjögren's syndrome

Sjögren's syndrome is a multisystem autoimmune disorder. The salivary and lacrimal glands are characteristically affected. When Sjögren's syndrome occurs in children and adolescents, swelling of the glands predominates over xerostomia and ocular symptoms, and systemic manifestations are less common.[21, 22] When the diagnosis is suspected, rheumatoid factor, antinuclear antibodies, and anti-Ro and anti-La antibodies should be measured. The diagnostic criteria for adults have a lower sensitivity for diagnosing the condition in children and a multidisciplinary approach to both diagnosis and treatment is recommended.

GRANULOMATOUS CONDITIONS

These are disorders of the intraparotid nodes rather than of the gland parenchyma. The salivary glands are composed of parenchymal tissue (i.e. salivary gland acini and ducts) and a surrounding stroma. Some of the stroma is lymphoid tissue, and the proportion of lymphoid tissue is much higher in children than in adults. Some cases of 'sialomegaly' in children – particularly in the parotid – are caused by lymphoid rather than parenchymal pathology. Non-tuberculous mycobacterial infection (NTM) and less frequently cat-scratch disease (*Bartonella henselae* or *B. quintana*) may present in this way. Non-tuberculous mycobacterium results from infection with a variety of species of mycobacterium including *Mycobacterium avium-intercellulare, M. scrofulaceum, M. kansasii, M. haemophilum* and *M. fortuitum*. The presentation, investigation and management of these conditions are considered in Chapter 37, Cervicofacial infections.

Sarcoidosis

Sarcoidosis is rare in children. When the parotid gland is involved, this can take the form of gland swelling, often as part of Heerfordt syndrome (or uveoparotid fever). Facial palsy can also occur. Non-caseating granulomas may be identified in minor salivary glands on sublabial biopsy and this was used as a diagnostic test, but it is now rarely needed. Cervical tuberculosis (caseating granuloma) can present in the parotid lymph nodes. Treatment is medical (see Chapter 37, Cervicofacial infections).

Salivary gland stones

The presentation, investigation and management of salivary stones in children is similar to that in adults, but salivary stones are uncommon in children. They are more common in the submandibular than the parotid glands. Children are less likely to tolerate local anaesthesia and may require a general anaesthetic if surgery (e.g. sialendoscopy) is considered.[23, 24]

SALIVARY GLAND TUMOURS

Salivary gland tumours are extremely rare in children. They can be classified as:

1. vasoformative tumours (most commonly haemangioma)
2. neoplasms of salivary gland tissue origin
3. proliferative disorders of the perisalivary lymphoid tissue (lymphoma).

Vasoformative tumours

A retrospective review of 324 consecutive cases of paediatric salivary gland masses showed 192 to be haemangiomas (59.2%), 89 to be lymphangiomas (27.5%) and the remaining 43 (13.3%) to be other solid masses.[25]

In 1982 Mulliken and Glowacki[26] created a classification system of vascular anomalies, dividing them into tumours and malformations. This classification system was recently expanded at the 2014 International Society for the Study of Vascular Anomalies (ISSVA) workshop.[27] The distinction between neoplasm and vascular anomaly is highly important when considering the management of these lesions.

Haemangiomas are reported to account for almost 60% of salivary tumours in children. Eighty per cent occur in the parotid gland, with involvement of the submandibular region in 18% of cases, while 2% are associated with the minor salivary glands.[28] Although not truly salivary in origin, the management of vascular anomalies requires an extensive knowledge of salivary gland anatomy.

PRESENTATION

The diagnosis of a haemangioma is primarily based on history and clinical examination. Haemangiomas are typically not present at but grow rapidly after birth. They exhibit rapid growth initially. This period of growth slows and stops after 9–12 months and a subsequent process of involution then follows over the next 3–5 years. Lesions have varying degrees of compressibility according to the extent of their underlying fibro-fatty architecture.[29] Skin involvement makes the diagnosis obvious although the absence of skin lesions does not exclude the diagnosis as the tumour may be deeply placed and lie within the parotid gland. Where the growth pattern exhibited by the lesion is not consistent with the pattern typical of a haemangioma, consideration should be given to further investigation including histological examination.

INVESTIGATIONS

The diagnosis of a haemangioma is a usually clinical. However, if lesions are more complex, where there is diagnostic uncertainty or if surgical intervention is being considered, additional investigations may be

helpful in determining the extent of involvement. The use of ultrasound (colour-flow Doppler) is useful for diagnosing vascular malformations in addition to identifying cystic and semisolid masses in the major salivary glands. The use of CT and MRI may also help to delineate the extent and depth of surrounding tissue involvement.[29]

TREATMENT

Almost all haemangiomas will involute and surgery should be confined to management of bleeding or ulceration, or to cases where the diagnosis is in doubt.[30] Kasabach–Merritt syndrome, a consumptive coagulopathy, is another indication for active intervention.

If the haemangioma is of such a size or position as to be life-threatening, treatment may be required. Several treatment modalities have been described in the literature and include systemic and intralesional steroids and more recently propranolol. However, systemic steroid therapy is associated with side effects and rebound growth is often seen after cessation of therapy. Intralesional steroids have fewer side effects but are effective only in actively proliferating lesions.[31]

The incidental observation of a clear response of haemangiomata to beta-blockers was published in 2008.[32] This revolutionized the therapeutic approach for infantile haemangiomas. Propranolol has been shown to significantly reduce the size of parotid haemangiomas with minor side effects[33] and has become the first-line treatment of choice where active therapy is required. Sclerotherapy for expanding parotid lesions has been shown to be successful, and a recent study that combined sclerotherapy and propranolol for the treatment of 26 infantile parotid haemangiomas demonstrated this to be a safe and effective treatment method.[34] Where active treatment is necessary and no response to propranolol is observed, embolization and/or surgical excision may be necessary.

Pulsed-dye laser treatment may be used for residual superficial skin discolouration, however it does not penetrate deeply enough to treat a haemangioma within the parotid gland. Previously, systemic interferon was utilized for its anti-angiogenic properties, but significant side effects were reported so it is no longer recommended as a treatment in children with haemangiomas.[31]

Salivary gland neoplasms

Salivary gland neoplasms are uncommon in children comprising approximately 1% of all paediatric tumours and less than 10% of all paediatric head and neck tumours. Approximately 5% of salivary tumours occur in children. Over 95% are epithelial with a minor group being mesenchymal in origin. The most common benign neoplasm is a pleomorphic adenoma; the most frequent malignant epithelial salivary gland neoplasm is a mucoepidermoid carcinoma. Rhabdomyosarcoma is the most common malignant neoplasm of mesenchymal origin.[29]

PRESENTATION

The most common presentation for a tumour affecting the major salivary glands is a painless, slowly growing mass. Pain is rarely a dominant symptom, whether benign or malignant.[25] The parotid gland is the most commonly affected salivary gland and is involved in over 85% of all reported paediatric salivary gland tumours.[29, 35–37] Facial nerve palsy is rare but usually indicates malignancy. Evidence of cervical lymphatic metastasis is uncommon, reported in 3.5% of patients at presentation.[38] Although uncommon, tumours affecting the minor salivary glands do occur, with the majority located in the oral cavity.[29] They most commonly present as a lump or submucosal nodule that is frequently non-ulcerated and firm to palpation, with pink or flesh-coloured surfaces. Others are described as being fluctuant, with colour alterations ranging from a light blue hue to purple.[29, 39]

INVESTIGATIONS

All cases of salivary gland neoplasms in children should be treated as potentially malignant. As previously mentioned, the use of ultrasound is very useful for identifying cystic and semi-solid masses in the major salivary glands and is easy to perform, non-invasive and generally well tolerated by children.[29] However, limitations include an inability to establish the extent of a lesion (i.e. extension into the deep lobe of the parotid gland) and to accurately differentiate between benign and malignant tumours.

CT imaging is unhelpful in distinguishing benign and malignant disease. However, certain MRI features, such as T2 hypointensity, restricted diffusion, ill-defined borders, and focal necrosis, although not specific, should raise concerns about malignancy.[40]

Fine-needle aspiration cytology (FNAC), while well established and routine in adult practice, is controversial in children. Younger children often require general anaesthesia for this procedure and assessment of salivary gland histology is reported to be notoriously difficult. Occasionally, however, the use of a diagnostic fine-needle core biopsy may be considered under certain circumstances, such as in cases of suspected lymphoma where major and unnecessary surgery could be avoided.[29]

Benign salivary gland tumours

PATHOLOGY

Pleomorphic salivary adenomas (PSA) are the most commonly encountered benign tumours and account for approximately 30% of all paediatric salivary neoplasms. Presentation is commonly between the ages of 8 and 18 years and the majority occur within the parotid gland. However, they may also occur in the submandibular gland and minor salivary glands.[41]

TREATMENT

Although a benign tumour, there is a risk of recurrence up to 30 years following initial presentation, and a lifetime

risk of malignant degeneration of between 2% and 25%. Treatment of these benign tumours consists of complete surgical resection[41, 42] by either superficial or complete parotidectomy, dependent on the location of the tumour. Surgery must aim for a complete resection of the tumour with a surrounding cuff of normal salivary tissue and complete facial nerve preservation. Submandibular gland resection is indicated for tumours in the submandibular gland, with complete local resection for the minor salivary glands. Incomplete resection is the cause of recurrences. This is particularly problematic in children, since adjuvant radiotherapy cannot be used safely in children to salvage an unsatisfactory surgical procedure.

Malignant salivary gland tumours

PATHOLOGY

Malignancies of the salivary glands in children and adolescents are rare, with an estimated annual incidence of 0.08 per 100 000.[43] Most malignant salivary gland tumours present in the older child, at an average age of 13.5 years.[38] In comparison with adults, children with salivary neoplasms are more likely to have malignant disease.[29, 35–37]

The parotid gland is the most frequent site for malignant salivary tumours (82%), followed by the submandibular gland (7%), minor salivary glands (11%) and sublingual gland (less than 1%).[29, 38] Mucoepidermoid carcinomas are the malignant tumours most frequently described in childhood followed by acinic cell carcinomas and adenoid cystic carcinomas. These three cancers account for 80–90% of all malignant salivary gland tumours in children and adolescents. Adenocarcinomas, basal cell carcinomas and squamous cell carcinomas of the salivary glands are less common.[28]

TREATMENT

The rarity of salivary tumours in children is such that treatment should only be in specialist centres. Management will involve a multidisciplinary approach with input from a paediatric oncologist. These children and their families are best treated in a designated centre where the whole range of support services for children with cancer is available.

Clinical stage and histologic grade are the main prognostic factors. As with benign tumours, complete excision (superficial or total parotidectomy) with preservation of facial nerve is the treatment of choice. It is, however, vital to counsel the child and parents carefully prior to operation regarding the possible need for facial nerve sacrifice. The facial nerve is smaller and courses more superficially within the parotid in children than in adults. Neck dissection should be considered when there is clinical evidence of regional metastasis, high TNM stage, high histologic grade, and involvement of regional nodes.[44] Radiotherapy should only be used in selected cases because of the possibility of long-term adverse effects in paediatric patients. Long-term follow-up is essential to monitor for late recurrence. The overall survival is 70–90% at 5 years, and 26% develop a recurrence.[29]

BEST CLINICAL PRACTICE

- ✓ Excision of a ranula together with the cyst wall and the sublingual gland results in a low rate of recurrence.
- ✓ HIV testing should be considered in children with otherwise unexplained salivary gland swelling.
- ✓ Bacterial infections should be treated with intravenous antibiotics and hydration. Ultrasound imaging should be used to exclude an abscess.
- ✓ Care should be taken in draining parotid abscesses in children to avoid damage to the facial nerve.
- ✓ Almost all haemangiomas will involute and surgery is rarely needed.
- ✓ Malignancies of the salivary glands in children and adolescents are rare. A solitary salivary gland neoplasm in a child, however, is more likely to be malignant when compared with an adult.
- ✓ Salivary tumours should be managed by an appropriate multidisciplinary team and surgery should be undertaken by surgeons with appropriate training and experience in paediatric head and neck surgery.

FUTURE RESEARCH

- ➤ Clinical trials are needed in the management of Juvenile Recurrent Parotitis in order to determine whether there is any benefit from medical therapies or sialendoscopy.
- ➤ It would also be helpful to have better clinical studies on the utility of investigations such as imaging and fine needle aspiration cytology for diagnosis of salivary gland tumours in children.

KEY POINTS

- Salivary gland agenesis may present late in childhood with dental caries.
- A ranula is an extravasation pseudocyst and may present intra-orally or in the neck.
- Mumps is generally a self-limiting disease but with the potential for serious complications.
- HIV salivary gland disease may mimic Sjögren's syndrome clinically and is characterized by gland swelling and xerostomia.
- Bacterial sialenitis occurs as a result of salivary stasis.
- Juvenile recurrent parotitis is a self-limiting disease which generally resolves around puberty although there is current interest in the use of sialendoscopy.
- Parotid haemangiomas present with a rapid enlargement of one parotid gland shortly after birth. The diagnosis can usually be made with a combination of clinical history and imaging.
- Salivary tumours are rare in children. The proportion of malignant tumours is greater in children than adults.
- Pleomorphic salivary adenoma is the commonest salivary gland tumour in children.

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CHAPTER 40

TUMOURS OF THE HEAD AND NECK IN CHILDHOOD

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SEARCH STRATEGY

Systematic reviews were identified using the key words: childhood cancer, head and neck, thyroid cancer, rhabdomyosarcoma, nasopharyngeal carcinoma, neuroblastoma, lymphadenopathy, Hodgkin's lymphoma, non-Hodgkin's lymphoma, sarcoma, and palliative care; these subject headings were used to search the Cochrane database of systematic reviews. Individual articles were then identified using the same search terms in Ovid Medline. A hand-search of the ensuing bibliographies completed the search.

INTRODUCTION

This chapter will focus on the epidemiology of childhood cancers of the head and neck region and the general principles of assessing and managing malignancy in children. It will then discuss the more common histological types individually. The long-term sequelae of treatment in survivors, palliative care and future developments will be addressed.

EPIDEMIOLOGY

After trauma, cancer is the most common cause of death in childhood. Approximately one-third of childhood malignancies are leukaemias, 25% are brain and spinal tumours, 15% are embryonal (neuroblastoma, retinoblastoma, Wilms' tumour and hepatoblastoma) and 11% are lymphomas. The remainder are bone and soft-tissue sarcomas and miscellaneous tumours (see 'Miscellaneous tumours' below). Up to 12% of primary childhood malignancies originate in the head and neck area and so may present to the otolaryngologist. Lymphoma is the most common diagnosis in all series, followed by thyroid and neural tumours. Sarcomas and salivary gland tumours are less common; squamous cell carcinomas are rare.[1] The distribution of histological types varies greatly depending on the age and sex of the child, with neuroblastoma the most common in infants and thyroid carcinoma the most common malignancy in adolescent females. There is a bimodal age distribution of malignancy in children. The most common age group affected is 15–18-year olds, closely followed by those under 4 years of age.[1–3] Incidence of head and neck malignancies in children increased throughout the decades leading up to the 1990s in line with a general increase in cancer diagnoses in children, but has now stabilized. In parallel, the consistent use of effective multimodality treatments, including combination chemotherapy, surgery and radiotherapy, has resulted in a significant improvement in prognosis. A study from the UK observed 5-year survival rates of 42% for diagnoses made between 1968 and 1977[4] but modern treatment strategies have transformed the outlook for children with cancer. Survival rates well in excess of 80% are now commonplace in the developed world and services are improving wordwide.[5, 6] Early recognition is therefore increasingly important.[7, 8]

Some malignancies in childhood are inherited. The underlying aetiology of the non-inherited types remains unclear but certain chemotherapeutic agents, viruses (e.g. Epstein–Barr) and irradiation are known to play

a role. Other potential carcinogens are suspected but not proven (pollution, parental exposure to toxins, electromagnetic fields).[1, 9] There is some evidence that exposure to dietary carcinogens *in utero* may lead to malignancies in early childhood.[10]

PRESENTATION AND ASSESSMENT

The most common presentation of a malignancy in the head and neck region in childhood is the asymptomatic mass. Otalgia, rhinorrhoea, otorrhoea and nasal obstruction may be present in both benign and malignant disease. More worrying symptoms would include stridor, dysphagia and haemoptysis.[11] Reactive lymphadenopathy in children is extremely common and gives rise to frequent therapeutic dilemmas. See Chapter 37, Cervicofacial infections in children.) Studies have suggested that the best predictors of malignancy in cervical lymphadenopathy are the size of the node, the number of sites involved and the age of the patient. Other concerning features would be lymphadenopathy in the supraclavicular region, an associated abnormal chest X-ray or fixed lymph nodes.[12, 13]

Examination would involve a complete assessment of the head and neck region and systemic evaluation with particular regard to the presence of lymphadenopathy elsewhere and the presence or absence of abdominal masses. Flexible nasendoscopy is possible in many children (**Figure 40.1**). Imaging with the help of a paediatric radiologist can often obviate the need for biopsy. However, full assessment of a mass may require examination under anaesthetic with biopsy.



Figure 40.1 Flexible nasendoscopy under local anaesthetic in the clinic setting.

BIOPSY

Fine-needle aspirate (FNA), sometimes referred to as aspiration biopsy cytology (ABC), has a more limited role to play in the child than the adult. Young patients may simply not tolerate this method of biopsy. With particular regard to cervical lymphadenopathy, the most likely neoplastic diagnosis is lymphoma and at the present time it is recognized that excision biopsy is the best method of confirming and typing this histologically.[14, 15] FNA, often under ultrasound control, can be useful in the assessment of thyroid and salivary gland lesions and these tumours often present in older children who may tolerate such intervention.[16]

The biopsy specimen should be sent to the lab fresh to enable molecular in addition to histopathological studies to be undertaken.

IMAGING

Ultrasonography, CT and MR scanning can all have their part to play in further assessment. Imaging of the neck is more accurate than clinical examination in detecting lymphadenopathy. CT and MR scanning may require a general anaesthetic in a younger child and it is helpful to discuss the available imaging options with a paediatric radiologist prior to proceeding, to avoid unnecessary and additional anaesthetics. Positron emission tomography (PET) scanning is also becoming increasingly used in the assessment of neoplastic lesions in the head and neck in children, but is not always readily available.[11]

THE CHILD WITH CANCER

The history and subsequent investigations of a child presenting with a suspicious lesion of the head and neck region must be tailored to the age and maturity of the child. In most situations, when the child is old enough, he or she should be included in any discussion about investigations and treatment and should also be involved in consent for any procedures required.

The diagnosis of cancer in a child has a tremendous impact not only on the patient, but also on parents, siblings, other family members and friends. Immediate involvement of a specialist paediatric multidisciplinary oncology team is mandatory. An open and realistic approach should include an explanation of what to expect from the investigations and treatment, the side effects and some idea of prognosis. This is vital in maintaining trusting relationships with the child and his or her family, in reducing uncertainty, preventing inappropriate hope and allowing proportionate adjustment.

Parents may feel guilty that they waited too long before seeking medical advice. They may be concerned that they

have, in some way, caused their child's cancer. They can also feel guilty about making their child go through a series of invasive investigations and radical treatments. This can put an immense strain on the parents' relationship with each other and with other family members and friends, not least the child involved. Also, siblings of the affected child may resent the additional time and attention that their sick brother or sister receives. Support services are therefore vital in reassuring and supporting all the individuals concerned.

The amount of information that any child will require regarding their illness depends to some extent on the age and maturity of that individual. Most children aged 6 years or more (and some more mature younger children) need to know their illness has a name and what that name is. All children require an explanation of the procedures to be performed and reassurance that any intervention is not a 'punishment'. In children between the ages of 6 and 11, these procedures and side effects of treatment may provoke much more anxiety than the illness itself. For example, loss of hair or a limb seems much more real and distressing than the prospect of death. Alterations in physical appearance can cause great insecurity in a child or adolescent, resulting in isolation and poor self-esteem. Children aged around 11 and over will have fears surrounding the diagnosis and its prognostic implications in addition to the above. Children should be encouraged to talk about their feelings or, if they are too young, they can express themselves in drawings or play.[15]

ONCOLOGY SERVICES

The importance of centralization of paediatric cancer services is widely recognized.[7] This enables care to be provided by highly trained and specialist paediatric oncologists and allied staff, and facilitates the progress of research. There are now 20 centres within the United Kingdom Children's Cancer and Leukaemia Group – CCLG.[17] Working in conjunction with the medical staff are social workers, nurses, dieticians, psychologists and other healthcare professionals in order to provide comprehensive support for children and their families. The emphasis on centralization of paediatric oncology services, the sharing of data and the establishment of international working groups has resulted in the publication of a number of treatment protocols that are widely used in the management of children with cancer.[17]

The practicalities of investigating and treating children with cancer provide some particular challenges. Venous access for blood sampling and to administer chemotherapeutic agents can be difficult, and indwelling venous catheters are usually inserted at an early stage. Radiotherapy may require general anaesthesia in younger patients to ensure that the child remains still during irradiation. Other interventions (e.g. lumbar puncture and intrathecal injection) may also require general anaesthesia. Children tolerate the immediate side effects of chemotherapy and radiotherapy much better than adults but the long-term sequelae of such interventions can have a very significant effect on the health of childhood cancer survivors (see 'Long-term sequelae of treatment' below).

THE MORE COMMON CHILDHOOD CANCERS

Lymphoma

Lymphomas are malignant neoplasms of the lymphoreticular system. Most lymphomas of the head and neck region in the paediatric age group present with enlarged cervical lymph nodes.

Cervical lymphadenopathy in childhood is common and although the huge majority of cases will be due to reactive hyperplasia, it may be necessary to exclude malignancy. Lymph nodes in the neck larger than 2 cm are unusual in childhood and systemic symptoms such as weight loss, fever and organomegaly are usually indicators of serious pathology.[12] FNA has a limited role and excision biopsy will provide the diagnosis.[16, 18]

Hodgkin lymphoma

This is distinguished morphologically by the presence of Reed Sternberg cells which are large and multinucleated with abundant cytoplasm. It has the propensity to involve the lower cervical, supraclavicular and mediastinal lymph node groups. There were several classifications for lymphomas but the most widely recognized now is the 'World Health Organisation / Revised European American lymphoma' system (WHO/REAL).[19, 20]

Nodular Lymphocyte-predominant Hodgkin Lymphoma (nLPHD) is now recognized as a separate entity. Classic Hodgkin lymphoma (HL) is further subdivided into 4 types: (1) Nodular sclerosis classic HL, (2) Lymphocyte-rich classic HL, (3) Mixed cellularity classic HL, and (4) Lymphocyte-depleted classic HL. The commonest type in children and young adults (0–24 yrs) is nodular sclerosing classic HL. There is an association with previous infection with Epstein–Barr virus.[21]

Staging of disease is based on the Cotswolds modified Ann Arbor system (see **Table 40.1**)

Hodgkin lymphoma most commonly presents with lymphadenopathy in the neck and two-thirds of all children will have mediastinal lymphadenopathy at presentation. It rarely occurs under the age of 5 years and there is a male predominance. 'Constitutional' symptoms such as fever, night sweats and weight loss are present in 25–30% and this is associated with a more aggressive disease and a poorer prognosis.[11]

Following careful examination and biopsy confirmation, the diagnostic workup of a child with Hodgkin disease (following thorough examination and biopsy confirmation) would include a chest X-ray, routine blood tests (although abnormal results are usually nonspecific) and staging scans (CT chest and MRI abdomen). Recently, PET scanning has become a routine part of staging and of assessing effectiveness of treatment. There is no longer a place for staging laparotomies. Bone marrow biopsy and bone scan are

TABLE 40.1 Stages of Hodgkin lymphoma according to the Cotswolds revision of the Ann Arbor staging system

Stage I	Involvement of a single independent lymph node region or lymph node structure
Stage II	Involvement of 2 or more lymph node regions on the same side of the diaphragm
Stage III	Involvement of lymph node regions or lymph node structures on both sides of the diaphragm
Stage IV	Involvement of extranodal sites beyond 'E'-sites
Annotations	
A	No B symptoms
B	At least one of the following systemic symptoms • Inexplicable weight loss of more than 10% within the last 6 months • Unexplained persisting or recurrent temperature above 38 °C • Drenching night sweats
E	Involvement of a single extranodal site contiguous or proximal to known nodal site.

only indicated in children with more advanced disease.[22] (see Volume 1, Chapter 25, Hamato-oncology.)

Treatment depends on the age and physical maturity of the patient, the disease stage and bulk and the potential treatment sequelae. In the paediatric population, the trend is to treat in multimodality fashion so as to reduce the morbidity and mortality associated with high doses of chemotherapy or radiation therapy needed for single-modality treatment. Disease-free survival is over 90% in many series.[23] Those children with intermediate risk of disease (constitutional symptoms, bulky disease or spleen involvement) may require an increased number of cycles of chemotherapy and, in some cases, an increased dose or volume of radiation therapy. Modern chemotherapy treatment protocols with newer agents such as dacarbazine have reduced the risks of sequelae such as subfertility. Radiotherapy is far less frequently needed, also helping to reduce the risk of later complications. Haematopoetic stem cell transplantation can be indicated in some children who relapse following more conventional treatment but the risk of transplant-associated morbidity and mortality is not insignificant.[21]

Non-Hodgkin lymphoma

Approximately 60% of paediatric lymphomas are non-Hodgkin lymphomas (NHL). There is a male predominance. The low-grade, relatively indolent NHLs seen in adults are exceedingly rare in children. Paediatric NHLs tend to be aggressive with a propensity for widespread dissemination and half of these are small cell lymphomas (Burkitt and Burkitt-like). The classification of NHL is confusing and controversial but paediatric NHLs are usually divided into three main histological categories. These are lymphoblastic lymphoma (predominantly of T-cell origin), small non-cleaved cell lymphoma (Burkitt and non-Burkitt subtype of B-cell origin) and large cell lymphoma (B- or T-cell origin).[24] The Revised European American Lymphoma (REAL) classification is used in paediatric NHL and is a useful guide to management and prognosis of NHL.[19]

The relative frequency and incidence of NHL varies quite markedly from country to country. In equatorial Africa, Burkitt lymphoma accounts for approximately 50% of childhood cancers. In Europe and the US, approximately one-third are lymphoblastic lymphomas, one-third are Burkitt and Burkitt-like lymphoma and the rest are predominantly large cell lymphoma. In some parts of the world, an extremely high number of these tumours are positive for Epstein–Barr virus (EBV), e.g. parts of Africa. In contrast, the percentage of tumours positive for EBV in the US is much smaller. There is an increased incidence of NHL in association with immunosuppression and congenital and acquired immunodeficiency.[24]

Many childhood NHLs are rapidly growing neoplasms and a significant number of children will have widespread disease at the time of diagnosis, which may involve the bone marrow, central nervous system or both. Involvement of extranodal sites, especially Waldeyer's ring, can be a particular challenge in children. Apparent activity in Waldeyer's ring on imaging may not always represent disease, hence the need for caution during disease staging. Lymphadenopathy occurs in 50–80% of all patients and 45% have cervical lymphadenopathy at the time of presentation. Bone marrow involvement is not infrequent and the replacement of more than 25% of the bone marrow by 'blast' cells is usually assigned a diagnosis of leukaemia. Children with endemic Burkitt lymphoma frequently present with involvement of the jaw and this is particularly common in the younger age group.[24]

DIAGNOSIS AND STAGING

Because NHLs in children progress more rapidly, a speedy diagnosis is extremely important. A biopsy will provide tissue for histological confirmation and surgery then has little further role to play. Staging investigations will follow and will include relevant blood tests (full blood count, urea and electrolytes and liver function tests) lactic dehydrogenase (LDH) is a useful marker of disease – bone marrow biopsy and cerebrospinal fluid (CSF) examination. Staging laparotomy is not advocated in patients with NHL and ultrasonography, CT (chest) and MR (abdomen) scanning are used in assessing spread.[24] FDG-PET scanning is increasingly used. The Ann Arbor staging classification can be applied to NHL (see Volume 1, Chapter 25, Haemato-oncology) although a new staging system for

TABLE 40.2 The International Pediatric Non-Hodgkin Lymphoma Staging System

Stage I	Single tumour with exclusion of mediastinum and abdomen.
Stage II	Single extranodal tumour with regional node involvement, two or more nodal areas on the same side of the diaphragm, or primary gastrointestinal tract tumour with or without the involvement of associated mesenteric nodes, that is completely resectable.
Stage III	Two or more extranodal tumours above and/or below the diaphragm, two or more nodal areas above and below the diaphragm, intra-abdominal and retroperitoneal disease, including liver, spleen, kidney, and/or ovary localizations, regardless of degree of resection, with or without involvement of associated mesenteric nodes that is completely resectable, any paraspinal or epidural tumour, and a single bone lesion with concomitant involvement of extranodal and/or non-regional nodal sites.
Stage IV	Any of the stage I—III findings with initial involvement of the central nervous system, bone marrow, or both.

paediatric NHL has recently been proposed by an international expert panel (Table 40.2).[25]

TREATMENT

The treatment of choice in childhood NHL is multiagent chemotherapy. The rapid doubling time of high-grade NHL makes it particularly chemosensitive. Chemotherapeutic regimens vary depending on the histological classification of the disease. Newer agents such as rituximab (an antibody to the B-cell marker CD20) have a role in B-cell NHL, allowing lower doses of standard chemotherapy agents to be used and thereby reducing morbidity from treatment.[26] Radiation therapy has a limited role in NHL and is generally reserved for selected anatomical sites such as the cranium where a child has overt central nervous system disease. Some children with high-grade NHL may need intrathecally administered chemotherapy.[22, 24]

PROGNOSIS

Long-term event-free survival (EFS) is excellent in lymphoblastic lymphomas. It ranges from 80% to 90% in patients with limited disease and from 65% to 80% in patients with advanced disease. In Burkitt lymphoma, where chemotherapeutic regimes are more intense and shorter, the long-term EFS ranges from 90–100% in patients with limited disease to 75–85% in patients with extensive disease. Even in patients with extensive bone marrow disease, the EFS is improving. Large cell lymphomas are more of a challenge to treat because of their biological heterogeneity and long-term EFS ranges from 50% to 70%.[22, 24]

Patients who relapse after receiving dose-intensive multiagent chemotherapy have an extremely poor prognosis. These patients are treated with high-dose chemotherapy regimes with or without bone marrow transplantation or would be candidates for newer drugs in trials.

Rhabdomyosarcoma

Rhabdomyosarcomas account for up to 60% of all sarcomas in the paediatric population and 40% occur in the head and neck region. Nearly half of these tumours occur in children under the age of 5 years.[7] The prognosis for this tumour used to be extremely poor but over the last 30 years survival rates have increased dramatically, particularly with the introduction of multimodality therapy in which surgery, multiagent chemotherapy and radiotherapy have been combined.[27]

Histologically, rhabdomyosarcomas resemble normal fetal skeletal muscle before innervation. Two types are identified and these are embryonal (80%) and alveolar (20%). The alveolar type is found in older children and is often associated with nodal spread and typically a poor prognosis[28, 29] where such tumours also harbour a chromosomal translocation that fuses two transcription factor-encoding genes together including the *FOXO1* gene.[30]

PRESENTATION

Rhabdomyosarcomas of the head and neck occur most frequently in the orbit or parameningeal sites and these include the paranasal sinuses, nose, nasopharynx and middle ear. The most common presenting symptoms are pain and swelling. Paranasal rhabdomyosarcoma may present with a gradual onset of nasal obstruction and bloody nasal discharge. Tumours within the ear may present with symptoms of bloody discharge and persistent otalgia, despite treatment. A polypoid mass may be visible in the ear canal or nasal cavity.[29] The reported incidence of lymph node involvement varies between 3% and 36%.[28] Metastases occur by both haematogenous and lymphatic spread.

ASSESSMENT

Assessment should include a thorough examination of the upper respiratory tract and head and neck region including the cranial nerves. Flexible nasoendoscopy may be employed in the clinic. An MRI scan should be performed to evaluate the primary lesion and to rule out metastatic disease (Figure 40.2). A CT scan may be a useful complementary tool, particularly in the paranasal sinuses and skull base, to determine bony erosion and it is the best method to assess the chest. Bone marrow examination should also be performed. The Inter Group Rhabdomyosarcoma Study (IRS) recommends the clinical staging shown in Table 40.3. The majority of children are stage II at the time of assessment[31] as it is rarely possible to completely excise these tumours.

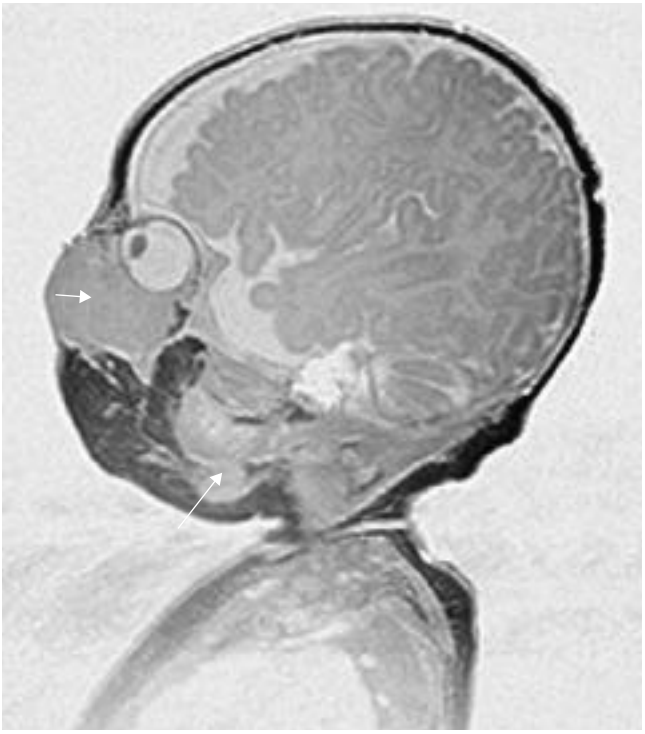


Figure 40.2 Paramedian T1-weighted MRI scan through the left orbit of a 3-month-old boy. There is a huge mass of rhabdomyosarcoma in the anterior orbit (short arrow) displacing the globe and submandibular lymphadenopathy (long arrow).

TABLE 40.3 Staging of rhabdomyosarcoma according to the IRS

Group I
Localized disease completely resected. No regional nodes
Confined to muscle or organ of origin
Contiguous infiltration outside muscle or organ of origin
Group II
Localized disease with microscopic residual disease, or regional disease (lymph nodes)
Group III
Incomplete resection or biopsy with gross residual disease
Group IV
Metastatic disease present at onset

TREATMENT AND PROGNOSIS

Since the establishment of the IRS Study Committee in 1972, protocols have been developed and are now widely adhered to. A multimodality approach has been adopted. In general, the role of surgery today is simply to evaluate the extent of the lesion and biopsy the tumour. Very occasionally, when the rhabdomyosarcoma is an easily accessible polypoid lesion, then wide surgical removal may be appropriate. A debulking procedure is rarely useful. Sophisticated skull base surgery can now be implemented in areas that were previously thought to be inaccessible, but is nearly always an adjunct to chemotherapy or radiotherapy.[29] Multiagent chemotherapy and radiotherapy are then implemented as appropriate.

Prior to 1960, approximately 10% of patients survived 5 years. Now the prognosis is excellent in patients with early tumours (over 80% survival). With more advanced tumours the prognosis is still relatively poor and in those with meningeal involvement the 5-year survival is less than 10%.[30] Although nodal mestastases at initial presentation are not synonymous with an unfavourable prognosis, development of nodes during follow-up does imply a poor outlook.[29, 31, 32]

Thyroid carcinoma

Thyroid carcinoma in the paediatric population is uncommon. In the US there are five new cases per million per year. It is much more common in adolescents than in younger children and is also much more common in females with a ratio of 4:1. Approximately 45% of these lesions in children will be differentiated papillary carcinomas with a further 45% of mixed papillary/follicular types with only 10% being follicular lesions.[33] Medullary thyroid carcinoma (MTC) is rare (only 10% of thyroid malignancies in children) and must be suspected in children with multiple endocrine neoplasia (MEN) types IIa and IIb (see 'Medullary thyroid carcinoma' below). Anaplastic and undifferentiated tumours are extremely rare in children and adolescents.

AETIOLOGY

A clear relationship has been established between the development of thyroid carcinoma and previous irradiation. In one study, as many as 17% of patients had previously received irradiation to the neck.[34]

PRESENTATION

Patients usually present with an asymptomatic solitary mass in the anterior or lateral neck. At presentation, there is often regional lymph node involvement (74%) and distant parenchymal metastases (25%).[32]

INVESTIGATIONS

Investigations will include an ultrasound scan, usually in conjunction with an ultrasound-guided FNA. Regional and distant metastases can be assessed with a chest X-ray and CT scan. Thyroid function tests and plasma thyroglobulin levels should be obtained and also plasma calcitonin where a diagnosis of medullary carcinoma is suspected.

TREATMENT

Controversy remains over the optimum treatment in differentiated thyroid carcinoma in children because the long-term mortality in these patients is low and serious operative and post-operative complications can occur following radical surgery. These include recurrent laryngeal nerve damage, hypocalcaemia and airway obstruction requiring tracheostomy.[32] It has become clear that these tumours in children are slow-growing and associated with prolonged survival rates, even in the presence of extensive disease. Some authors maintain that an aggressive approach is mandatory[35, 36] while others have adopted a more conservative approach with the use of lobectomy and subtotal thyroidectomy for small and isolated lesions.[33, 34, 37]

Ideally, treatment should include complete surgical excision if possible. Total or subtotal thyroidectomy should be performed if adjuvant radioiodine treatment is planned. Following surgery, a whole-body radioiodine scan is performed and ablative radioiodine treatment given if necessary. Plasma thyroglobulin can then be used as a tumour marker and suppressive levothyroxine should be given. Radiotherapy is rarely indicated in differentiated thyroid carcinoma in childhood.[11]

PROGNOSIS

A long-term study of 329 patients under the age of 21 confirmed only eight deaths over a long period of time and of these only two were disease related. The risk of progression of disease was more common in younger patients and those with residual cervical disease after definitive thyroidectomy. The majority of recurrences are in cervical lymph nodes or thyroid bed (54%), or lungs (16%).[37] The majority of relapses occur within the first 7 years but have been seen as long as 25 years after treatment.[33]

Medullary thyroid carcinoma

The detection of MTC in younger children is usually made following screening in 'high-risk' individuals who have a family history of MEN 2.[11] This is confirmed by elevated baseline levels of calcitonin or screening for the *RET* (rearranged during transfection) protooncogene on chromosome 10. If positive, the child should be considered for prophylactic total thyroidectomy.[11] See Volume 2, Chapter 63, Management of medullary cancer.

Nasopharyngeal carcinoma

In the US and Europe, nasopharyngeal carcinoma (NPC) is an uncommon tumour comprising only 1–2% of paediatric malignancies, but in other geographical locations, such as parts of Africa, 10–20% of childhood malignancies are due to NPC. There is a bimodal age distribution of this disease with an early peak of 10 to 20 years and a second peak between 40 and 60 years. NPC is one of few malignant tumours in childhood that emerges from the epithelium and there is an association with EBV. Males are twice as likely as females to develop NPC. Children with NPC almost invariably have the undifferentiated variant that is associated with higher rates of advanced locoregional disease and distant metastases.[38] Despite this, the 5-year disease-free survival is not significantly different to that of adults at 30–60%.[39]

PRESENTATION

Children may present with a cervical mass secondary to lymph node metastases. Other presenting symptoms and signs may include nasal congestion, epistaxis, otitis media with effusion, otalgia and cranial nerve palsy. As many as two-thirds of children with NPC have metastatic disease in the neck at presentation. Delay in the diagnosis occurs frequently because many of its symptoms mimic those of an upper respiratory tract infection.

ASSESSMENT

Nasopharyngeal examination and biopsy is required for tissue diagnosis. CT or MR scanning allows precise evaluation of the primary tumour and confirmation of the presence or absence of metastases, most particularly in the neck. The American Joint Committee in Cancer staging of NPC (see Volume 3, Chapter 8, Nasopharyngeal carcinoma) is used by most.

TREATMENT

Undifferentiated NPC is a radiosensitive tumour and as such is usually treated with external beam radiotherapy. Such therapy is limited to the primary tumour and its regional metastatic spread. Chemotherapy is required in patients with disseminated systemic disease. There is now evidence that combined chemotherapy and radiotherapy provides better disease-free survival as compared with radiotherapy alone and combined chemoradiotherapy – including consideration of Proton Beam Therapy is therefore becoming routine practice in the UK.[39, 40, 41] (see Volume 3, Chapter 8, Nasopharyngeal carcinoma).

Because of the tumour's close proximity to major structures, radiotherapy in this region is difficult to give and is associated with significant post-treatment morbidity. This includes mucositis, xerostomia, neck fibrosis and panhypopituitarism (see 'Long-term sequelae of treatment' below). Newer radiotherapy techniques, such as intensity-modulated radiation therapy (IMRT) and proton beam radiotherapy[39] may offer reduced morbidity following treatment as it becomes more readily available (**Figure 40.3**). As craniofacial surgical techniques improve, surgical resection is now becoming appropriate in certain situations, particularly in primary recurrence following treatment.

Neuroblastoma

Neuroblastoma is a common malignancy of early childhood and is the most common malignancy in infants younger than 1 year. These tumours arise from undifferentiated sympathetic nervous system precursor cells of neural crest origin. The adrenal gland is the most common site of origin and additional sites include the

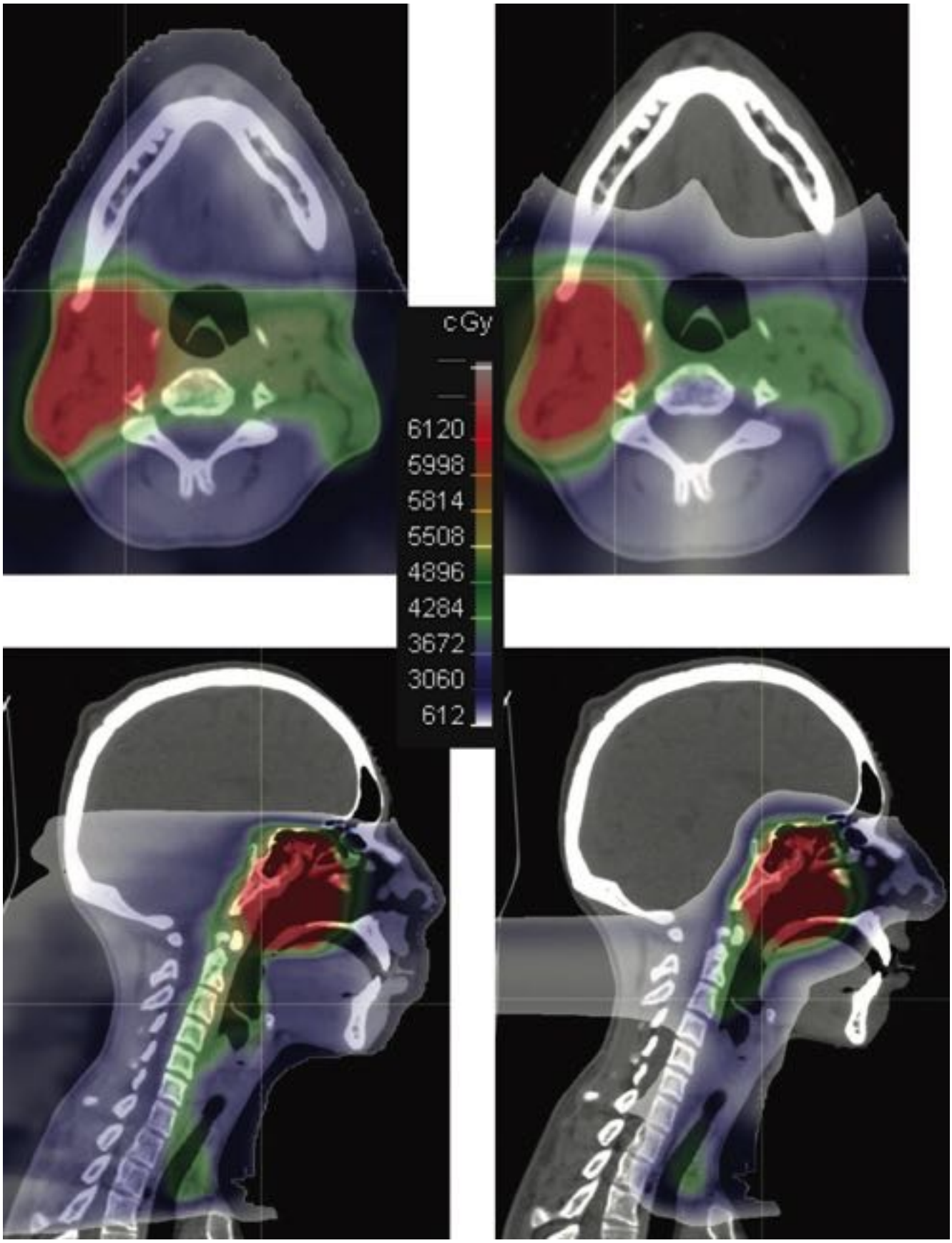


Figure 40.3 Sixteen year-old boy treated for nasopharyngeal carcinoma incuding a positive cervical lymph node. Panels on the left show planning scans using IMRT and on the right using Proton Beam Therapy. Note the reduced dose to the oral cavity and the brain using PBT. Image courtesy of Dr Danny Indelicato, Associate Professor, Department of Radiation Oncology, University of Florida.

sympathetic chain, posterior mediastinum and cervical regions. Neuroblastoma has a high propensity for lymphatic spread and regional lymph nodes are involved in up to 35% of cases. Metastases to the head and neck region are common, but primary neuroblastoma in the head and neck region is uncommon.[43]

PRESENTATION

Symptoms and signs will be dictated by the size and position of both the primary lesion and any metastases. Children with primary cervical neuroblastoma may present with a firm mass in the lateral neck, occasionally associated with a Horner syndrome (due to cervical sympathetic chain involvement). Classical ophthalmological manifestations include proptosis and periorbital ecchymosis (usually secondary to intraorbital metastatic deposits). Bilateral eye haematomas are a classical sign ('racoon' eyes). Chronic destruction of the ophthalmic sympathetic fibres in some children can lead to heterochromia of the irides. Involvement of the paranasal sinuses is also described.[43]

ASSESSMENT

A full assessment of the disease will include obtaining a histological diagnosis. Examination should include a visual assessment, intraoral inspection and a thorough neurological examination. MRI and CT scanning are usually employed to assess the primary and the extent of any metastatic spread (**Figure 40.4**). An iodine-123-metaiodobenzylguanidine (MIBG) scan is a useful method of assessing metastases. A bone marrow aspirate and trephine should be performed, with a bone scan reserved for those with a negative MIBG scan. Urinary catecholamine levels should be measured as they are raised in over 90% of cases.

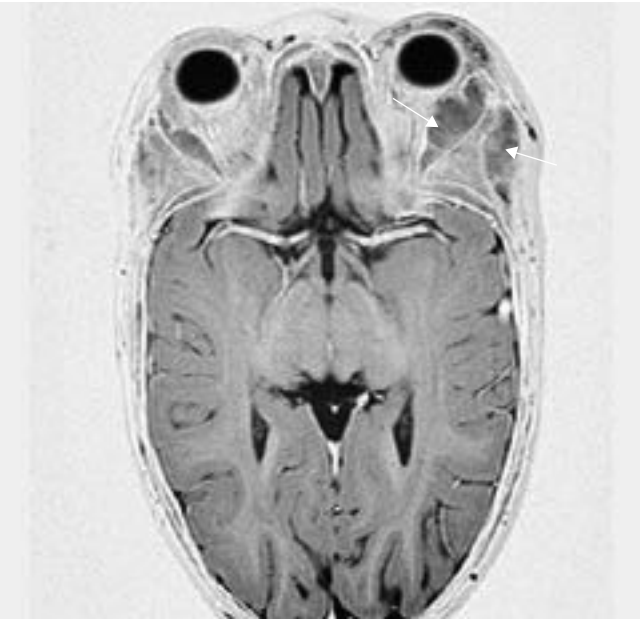


Figure 40.4 Metastatic neuroblastoma from an adrenal primary is extending out of both sides of the lateral orbital walls (more marked on left – arrows). Patient has incidental scaphocephaly.

TREATMENT

The choice of single modality or multimodality therapy depends on the individual patient. Localized cervical neuroblastoma may be treated by curative surgery. Multi-agent chemotherapy is usually indicated in patients if resection is incomplete, where there is amplification of the *MYCN* proto-oncogene or where there is evidence of metastases. The role of radiation therapy is becoming more clearly well-defined and many tumours are highly radiosensitive.[44, 45]

PROGNOSIS

In young patients with resectable disease, complete excision offers the best chance of cure and at least a 90% survival rate. Primary neuroblastoma of the head and neck has a better prognosis than that of other sites. Prognosis is poorer in children over the age of 1 year at presentation.[43]

MISCELLANEOUS TUMOURS

A large variety of tumours can rarely affect the head and neck region. The small numbers involved can make meaningful analysis of data difficult and it is not really feasible to address therapeutic questions in the context of randomized controlled trials. However, the UK CCLG have published guidelines for some of the rarer childhood cancers.[17]

Soft-tissue sarcomas

Sarcomas other than rhabdomyosarcoma can occur in the head and neck region of children. some features of these tumours are listed in **Table 40.4**. There is a bimodal age distribution with incidence peaking in the under-5s and in adolescents. Those in the younger age group tend to have lesions situated in the head and neck region while older children present with lesions in the extremities. In general, these tumours have a tendency to recur locally and to metastasize. The treatment is tailored to the individual case but in general involves chemotherapy often followed by surgery and radiotherapy (**Figure 40.5**). The prognosis remains relatively poor despite multimodality treatment.[29]

Squamous cell carcinoma

Squamous cell carcinoma (SCC) outside the nasopharynx is extremely rare in childhood. There is some evidence of an association between SCC and previous exposure to immunosuppressive medication, and also previous irradiation for laryngeal papillomatosis. Pre-existing xeroderma pigmentosum makes any patient extremely susceptible to the development of cutaneous SCC. The principles of management of SCC in the head and neck in children are the same as in adults.

Malignant teratoma (Germ cell tumour)

Malignant teratomas in the head and neck region are rare (most are benign) and usually present at birth, often as an airway emergency. Large tumours are usually diagnosed *in utero*, resulting in a multidisciplinary team being

TABLE 40.4 Some features of head and neck soft tissue sarcomas
Fibrosarcoma
Peripheral nerves
Slowly enlarging painless mass
Metastatic infrequent
Complete resection is treatment of choice
Good prognosis
Neurofibrosarcoma or Malignant Schwannoma
Neck, larynx, oropharynx (see Figure 40.5)
Foci of calcification typical
Peripheral nerves
Develops in 3–16% of children with Von Recklinghausen neurofibromatosis (NF1)
Arise from capillary pericytes
Skin lesions, lymphadenopathy
Can compress cervical spine
Multimodality treatment
50% five-year survival
Wide surgical excision
Cranial nerve deficits, local recurrence, lung metastases complicate treatment
Haemangiopericytoma
Nasal cavity and sinuses
Nasal mass, and epistaxis
Associated with HIV
Kaposi's Sarcoma
Ewing's Sarcoma

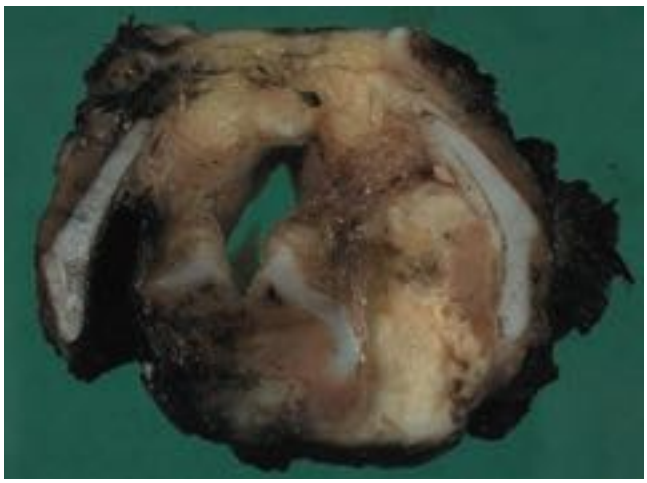


Figure 40.5 Cross-section of a laryngectomy specimen from a 12-year-old boy with residual synovial cell sarcoma despite chemoradiotherapy.

needed at delivery to secure a safe airway. Tracheostomy may be necessary. Assessment should include nasoendoscopy, alphafetoprotein (AFP) and beta human chorionic gonadotrophin (hCG) levels, and imaging. Metastases are rare. Treatment is surgical excision although salvage chemotherapy and radiotherapy may be required. The prognosis is good in the absence of metastases.

Chordoma

This is a rare slow-growing bony tumour which is locally aggressive and which arises from embryonic remnants of the notochord. The presentation depends on the site of origin which, in the head and neck region, is most commonly found in the nasopharynx and adjacent skull base. Patients present with headache and diplopia and compression of the lower cranial nerves can result in a number of neurological signs (see Volume 3, Chapter 8, Nasopharyngeal carcinoma). Biopsy is necessary for diagnosis and MR and CT scanning will delineate the tumour extent. Complete surgical excision is rarely possible because of the anatomical location and adjacent structures and so post-operative radiotherapy is usually employed. Proton beam therapy is increasingly employed in centres where it is available.

LONG-TERM SEQUELAE OF TREATMENT

The aim of cancer treatment in children is to maximize the chance of long-term survival and at the same time minimize the side effects, particularly in the longer term. With overall 5-year survival rates in children now over 80%, it is particularly important to examine the effects of the more recently employed multimodality treatments. The Childhood Cancer Survivor Study (CCSS) report that some 50.4% of survivors of childhood cancer have, by the age of 50 years, developed disabling or even fatal health conditions, as against 20% in a sibling control group.[46] Children tolerate the acute side effects of radiotherapy and chemotherapy reasonably well but other sequelae may not become apparent for several years.[47]

Second tumours may occur many years after treatment, particularly in a radiotherapy field.

Growth

Cranial radiotherapy can result in growth hormone deficiency and growth retardation and chemotherapy can also have significant effects on growth. Localized tumour treatments can also affect growth and function of specific organs or tumour sites. For example, radiotherapy to the maxilla in a child can result in asymmetrical growth of the midface.

Reproductive function

An important issue for survivors of childhood cancer is the impact of the disease and its treatment on reproduction and the implications for the health of any offspring. In males there is evidence for impaired spermatogenesis after treatment but it appears that any sperm produced carries as much healthy DNA as produced by the population in general. However, it is not always possible to predict fertility outcome in boys who receive treatment prior to puberty. Cryopreservation of sperm in young males (14–17 years) is effective but depends on the ability of the young patient to produce a specimen and, in the UK,

consent for storage requires him to be 'Gillick' competent (see Chapter 62, The paediatric consultation). Another technique is to harvest a 'wedge biopsy' of testicular tissue' for extraction of sperm. Radiotherapy to the hypothalamus or pituitary can result in precocious puberty in females and patients should therefore have their pubertal status checked regularly. There are now detailed CCLG guidelines on this topic.[17] Chemotherapy in general is less harmful to gonadal function in females but pelvic irradiation can affect ovarian function. Spontaneously conceived offspring of patients treated for cancer in childhood have no excess of congenital abnormalities or other diseases.[48]

Cardiac problems

Anthracyclines have a significant cardiotoxic effect and can cause cardiac failure in later life. Long-term echocardiogram surveillance is recommended for some follow-up regimes. Mediastinal radiotherapy can also result in impaired cardiac function (and an increased risk of breast carcinoma) and this should be monitored as appropriate.[49]

Thyroid disorders

Thyroid dysfunction can result from radiotherapy to the neck or to the hypothalmic/pituitary axis. Chemotherapy is a risk factor. Survivors require regular thyroid function evaluation. Radiotherapy to the neck is a recognized aetiological factor in the development of thyroid carcinoma in later years.

OTHER OTOLARYNGOLOGICAL MANIFESTATIONS OF TREATMENT

Radiotherapy to the head and neck region results in a large variety of long-term sequelae that can affect function and cosmesis. Damage to the major and minor salivary glands can cause xerostomia and subsequent tooth and gum disease. Post-radiotherapy scarring within the nasopharynx can result in middle ear effusions and subsequent deafness, and in the region of the midface can result in recurrent sinusitis, temporomandibular joint dysfunction and trismus. Certain chemotherapeutic agents – notably cisplatin – are known to cause deafness and tinnitus. Vincristine can cause bilateral vocal cord paralysis. Immunodeficiency with a propensity to develop opportunistic infections of the head and neck may complicate some chemotherapy regimens.[47]

Cognitive and psychological problems

Surgery and/or radiotherapy to the brain or adjacent structures can result in neurocognitive defects such as low IQ, learning difficulties and an increased risk of seizures. Survivors of childhood cancer are at an increased risk for a wide range of disabling psychological problems such as low mood, low self-esteem and anxiety.

Follow-up

It is important to follow up these children in the long term and to educate them and their parents about the possible late consequences of their treatment. It is also important to promote a healthy lifestyle and discourage cancer promoting behaviours such as smoking and excessive sun exposure.[48]

The dying child

The death of a child is one of the greatest tragedies that can befall a family. It is important to recognize that palliative care of the dying child should address not only the control of pain but the social, psychological and spiritual needs of children and their families. Planned terminal care for children has become increasingly community-based and therefore requires involvement of the primary healthcare team, including the patient's general practitioner at an early stage. An experienced and multi-skilled team is required with a named key worker and access to advice and support 24 hours a day. The child should participate in the planning and provision of this care as much as is realistically possible.[50]

Once the focus of treatment shifts from curative to palliative care, quality of life becomes of prime importance. Most children and their families will wish to maintain some semblance of normality while optimizing symptom control and minimizing medical intervention. For instance, many children will opt to remain at school for as long as they are able, mixing with friends and getting a break from the home environment. Others may benefit from a daily visit at home from a play specialist.[50, 51]

Regular respite should be offered to parents and it is important to explore the financial assistance, benefits and grants that families may be entitled to. Practical help with funeral arrangements should be given and it is important to continue to support the grieving family after their child's death and to withdraw support slowly and appropriately.[15, 50, 51]

NON-MALIGNANT CONDITIONS THAT RESEMBLE TUMOURS

Rosai–Dorfman disease

Rosai–Dorfman disease (sinus histiocytosis with massive lymphadenopathy) is an inflammatory condition of unknown aetiology. It typically causes massive bilateral cervical lymphadenopathy with fever and malaise in older children and young adults.[52] Histologically, it is characterized by histiocytes (an old-fashioned term for macrophages and dendritic cells) accumulating in large numbers in lymph nodes and occasionally other sites such as orbit, nose, oropharynx and salivary glands. In most cases it runs a benign course with spontaneous regression, but the disease can be quite prolonged. Excision biopsy of a lymph node is required to exclude lymphoma, and more extensive surgical debulking may be necessary for compressive symptoms.

Langerhans cell histiocytosis

Langerhans cell histiocytosis (LCH) can also present with lymphadenopathy, usually in the children under the age of 5 years. It is characterized by clonal proliferation of Langerhans cells and their accumulation in tissue. It is unclear whether this process is neoplastic or inflammatory

in nature. LCH is a spectrum of disease, ranging from unifocal (previously known as eosinophilic granuloma), which presents as a solitary bone lesion, to multifocal multisystem disease (previously known as Letterer–Siwe disease). The multifocal form can involve bone lesions (often in the mandible, causing jaw pain or loose teeth), skin eruptions (commonly on the scalp), pituitary gland lesions, chronic otitis media and bone marrow involvement. Fever, lethargy and weight loss may occur. LCH with cervical lymphadenopathy will usually be of the multifocal type. Diagnosis requires excision biopsy of an affected node for histological examination, together with radiology of the chest and any affected bones and MRI of the pituitary. Prognosis can be poor, especially under the age of 2 years, and aggressive treatment may be required with steroids and in severe cases cytotoxic chemotherapy. Mortality is approximately 10% overall, but 50% in multifocal disease in children under the age of 2 years.

Castleman disease

The main importance of Castleman disease is in the differential diagnosis of lymphoma. It presents as a mass of enlarged lymph nodes. The diagnosis is made on histology which shows a B-cell lymphoproliferative disorder, and some cases are thought to have a viral cause. Children most often have the unicentric form, with nodes confined to one area of the neck. Surgical excision is all that is needed. The multicentric condition is more common in adults and much more serious. It is sometimes associated with HIV infection and can run an aggressive course, requiring prolonged treatment with antivirals and monoclonal antibodies. For this reason, children with apparently unicentric disease should probably have imaging of the chest, abdomen and pelvis, and HIV testing.

Fibromatosis colli (sternomastoid tumour of infancy)

This condition is surprisingly common and important to recognize. It is often blamed on birth trauma but its aetiology is obscure and it is most likely an idiopathic fibrosing condition of the muscle. Fibromatosis colli is the preferred term as 'tumour' suggests neoplasia which is as frightening as it is inappropriate. It presents in newborns as torticollis and a palpable lump within the sternomastoid muscle. It is associated with developmental dysplasia of the hip so it is probably reasonable to get an ultrasound of the neck to confirm the diagnosis and the hips can be scanned at the same time. Treatment is simply physiotherapy to stretch of the muscle and encourage the baby to turn the head to the affected side. The tragedy of this condition is that, despite being common and simple to treat, it often goes untreated leaving the child to develop fibrosis and permanent contracture of the muscle. The torticollis becomes permanent and this can affect the development of the facial skeleton. The eyes and mouth develop on a cant so that even when the muscle is surgically released, the face remains abnormally aligned (**Figure 40.6**).



Figure 40.6 **(a)** Untreated fibromatosis colli on the right side presenting in childhood with contracure of the sternomastoid muscle. **(b)** After surgical release of both ends of the right sternomastoid muscle the resting position and range of movement of the neck are improved but note that the planes of the eyes and mouth are not parallel and the whole face has grown in an asymmetric fashion.

BEST CLINICAL PRACTICE

- ✓ The vast majority of enlarged cervical lymph nodes in children are harmless. Imaging should usually be considered before biopsy.
- ✓ FNA has a more limited role to play in the child than the adult.
- ✓ All children diagnosed with malignancy should be referred to a specialist centre.
- ✓ Children receiving chemotherapy should have central venous catheters placed for venous access and chemotherapy treatment.

FUTURE RESEARCH

- ➤ The long-term survival of children with cancer is improving, and a better appreciation of the long-term sequelae of treatment should result in an improved quality of life for children surviving cancer. We are likely to encounter more physical and psychological problems in adults related to cancer treatment in childhood.
- ➤ Basic science research should bring better understanding of the underlying aetiology of childhood cancer. This may help in introducing preventative measures such as vaccines and environmental interventions. Agreed protocols on the management of paediatric thyroid malignancy would be helpful. Centralization of services, the establishment of better databases and the implementation of multicentre trials will provide us with a better evidence base for the future management of childhood cancer.
- ➤ Better imaging techniques with wider access to sophisticated equipment will aid in more accurately assessing the initial disease and in detecting recurrence at an earlier stage. Greater knowledge of molecular genetics has resulted in new approaches to diagnosis and treatment. The advent of polymerase chain reaction (PCR) techniques has, for example, permitted the detection of cells bearing chromosomal translocations in the peripheral blood and bone marrow, thereby detecting minimal residual disease in lymphoma and even defining patients at high risk of relapse. Other novel strategies include the use of immunotherapy (immunotoxins or vaccines) to target specific cells or cell proteins. Radiotherapy techniques such as IMRT are allowing much greater flexibility in targeting tumours in awkward anatomical sites whilst avoiding some of the post-treatment complications. IMRT is an advanced mode of high precision radiotherapy where combinations of several intensity-modulated fields coming from different beam directions deliver a maximal dose to the tumour while minimizing the dose to surrounding tissues. Surgical advances, such as navigation systems with the use of endoscopes, mean that areas once inaccessible can now be approached surgically whilst maintaining good function and cosmesis. Proton beam therapy looks set to have a significant role in childhood malignancies.
- ➤ In conclusion, we have made major advances in the investigation and management of childhood malignancy in the last 30 years and a number of promising diagnostic and treatment developments promise much in the next 30.

KEY POINTS

- Head and neck tumours are uncommon in children. Early diagnosis is essential.
- Survival rates are improving.
- Multimodality treatment has improved the prognosis while reducing both early and long-term complications.
- Treatment should be provided by a specialized, centralized multidisciplinary paediatric oncology team.

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CHAPTER 41

CYSTS AND SINUSES OF THE HEAD AND NECK

Keith G. Trimble and Luke McCadden

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the following keywords: branchial arch, branchial cleft, branchial pouch, preauricular sinus, thyroglossal cyst, lingual thyroid, nasal dermoid and congenital midline cervical cord.

INTRODUCTION

A child with a congenital cyst or sinus in the head or neck is the quintessential paediatric ENT patient and can present a welcome diagnostic challenge in the humdrum of afternoon clinic. Although a preauricular sinus is common and easily diagnosed by the undergraduate student, it takes an experienced otolaryngologist to consider the infrequent first branchial cleft sinus diagnosis in a child with facial abscess repeatedly incised and drained elsewhere. For obvious reasons, an understanding of embryology of the branchial clefts is a prerequisite for the paediatric or adult otolaryngologist managing infected cysts or draining sinuses around the head and neck. Excluding reactive cervical lymphadenopathy as the most frequent cause of referral with neck lump and the common pilomatrixoma, which is slowly enlarging and fixed to the skin, thyroglossal duct cysts, branchial arch anomalies and dermoid cysts are seen in decreasing order of frequency.

This chapter discusses the best management of congenital cysts and sinuses of the neck, none of which is based on randomized controlled trials or meta-analyses, but rather single-surgeon, single-centre large case series or systematic review. Special mention should be made regarding modifications of Sistunk's procedure, which should be effecting lower recurrence rates following excision of thyroglossal duct cyst anomalies and endoscopic cautery of third pharyngeal pouch sinuses in older children to reduce complications of open surgery. Unusual entities such as the congenital midline cervical cleft and congenital sinus at the sternoclavicular joint (sinus sternoclavicularis) will also be discussed. Plunging ranulas, teratomas and vascular anomalies also present at birth but are discussed elsewhere in this book. Sternomastoid pseudotumours of infancy present as a painless unilateral mass low in the neck with decreased neck rotation and are easily managed with ultrasonography and physiotherapy; these are not discussed further in this chapter.

BRANCHIAL ANOMALIES

Branchial anomalies usually present as lateral neck masses with infection, cyst enlargement or an intermittently draining sinus. Treatment usually involves surgical excision with identification and preservation of nearby neurovascular structures. The embryology of the branchial apparatus is discussed in Volume 1, Chapter 53, Developmental anatomy of the thyroid and parathyroid glands. But it is worth noting the following brief points. The branchial arches are mesodermal structures that go on to form muscle, cartilage and bone. First and second branchial arch anomalies, therefore, will result in structural deformities of the face, as in Treacher Collins syndrome or hemifacial microsomia (see Chapter 19, Craniofacial anomalies). There are spaces between the arches on the

outside of the embryo, lined with ectoderm, called the branchial clefts. Branchial cleft anomalies, therefore, will result in a congenital sinus with an opening on a skin surface. This may be around the angle of the mandible or in the EAC (first branchial cleft sinus) or in the neck along the anterior border of sternomastoid (second branchial cleft sinus). There are also spaces between the arches on the inside of the embryo, as the arches bulge into the foregut. These are called the pharyngeal pouches and they are lined with endoderm. Pharyngeal pouch anomalies (third or fourth) will result in a sinus with an opening on a mucosal surface, typically in the left piriform fossa.

First branchial cleft sinuses

First branchial cleft sinuses are rare and account for less than 10% of branchial cleft anomalies.[1] The external opening in the neck varies in position but lies on a line between the tragus and the hyoid bone. The opening is often inconspicuous and appears as a skin-lined pit. The superior attachment of the sinus is variable: there may be an opening anterior to the tragus or the tract may form a true fistula running inferior to the floor of the EAC and opening at the osseocartilaginous junction in the external auditory meatus or rarely forming a frenulum-like band between the floor of the meatus and the umbo of the tympanic membrane (**Figures 41.1** and **41.2**).

Histology

The sinus (sometimes known as a collaural fistula) is usually a sizeable tract, often formed of cartilage, and lined with squamous epithelium. The original classification by Work and Work[2] divides them into two types according to the presence or absence of mesothelial elements within the wall.

- **Type I lesions** are of ectodermal origin and are present medial to the concha. They are usually superficial and simple in nature.
- **Type II lesions** are both ectodermal and mesodermal in origin and contain cartilage and hair follicles. The more inferior opening of the type II fistula is usually below the angle of the mandible and the tract is intimately related to the facial nerve trunk.

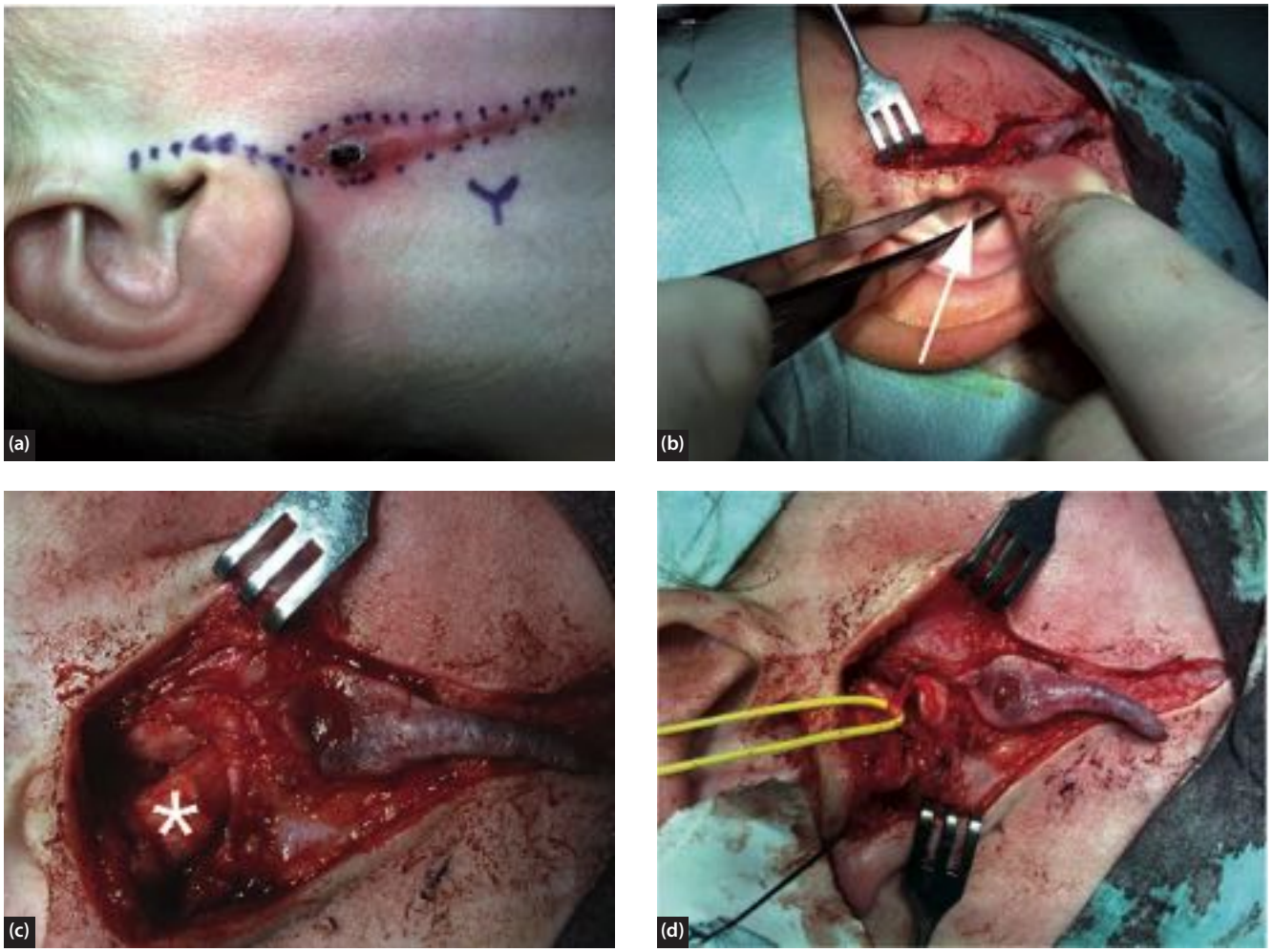


Figure 41.1 **(a)** Type 2 first branchial cleft anomaly with two previous incision procedures in another hospital. **(b)** Proximal fistula opening in floor of ear canal. **(c)** The fistula tract (*) passes over the angle of the mandible deep to the facial nerve trunk, intraparotid and terminates at the bony-cartilaginous junction of the external auditory meatus. **(d)** Yellow sloop over the main trunk facial nerve.



Figure 41.2 Type 1 first branchial cleft anomaly with ear canal duplication anomaly lateral to the facial nerve extending to the umbo of the tympanic membrane.

Presentation

The opening is present at birth and may become more obvious by the discharge of epithelial or sebaceous debris. The sinus may become acutely infected and may progress to abscess formation. Being lined with skin, these lesions do not discharge mucus.

Investigation

Cross-sectional imaging will usually show the tract, which is often substantial in calibre but will not clearly demonstrate its relationship to the facial nerve. MRI is preferable over CT in children to minimize exposure to ionizing radiation and provide excellent visualization of soft-tissue planes. However multislice helical CT may be preferred in some institutions because of cost, availability and speed of image acquisition which could obviate the need for sedation or anaesthesia. A radiopaque sinogram is not routinely indicated.

Treatment

Surgical excision of these lesions is usually advocated if at all symptomatic or if one or more episodes of infection have already occurred. Surgery is ill-advised during acute infection and a period of quiescence should be awaited followed by elective excision, which necessitates dissection of the tract in its entirety, assisted by intra-operative facial nerve monitoring.

A parotidectomy-type incision is modified to include the lower opening of the sinus. The sinus tract at this point can be followed for a small distance upwards; when its nature and direction are confirmed, the facial nerve trunk must be identified as it leaves the skull base and enters the parotid gland. The mandibular branch in particular should be followed so that it can be preserved while freeing the tract. Sharp dissection will often be required to free the nerve from the tract, particularly if multiple infections have ensued or previous attempts at incision and drainage have been made. In most instances the lesion will run deep to the branches of the facial nerve, which may be adherent if there has been recurrent infection, though the relationship is unpredictable. The superior part of the sinus tract also has an unpredictable relationship to the cartilages of the external auditory canal (EAC). It may terminate at the canal or may form a duplicated canal parallel and inferior to the EAC proper. The lesion does not extend medial to the cartilaginous canal but a strand may cross the lumen of the canal from the osseocartilaginous junction to be attached to the umbo.

Facial nerve exposure and protection is required in nearly every case of first branchial cleft sinus. If this is done, then risk to the facial nerve is minimized. The superficial position of the facial nerve in small children must be considered. The upper end of the lesion must be followed and excised to ensure that no squamous epithelium remains, and this may require opening of the EAC and use of the otological microscope and ear instruments.

Closure of the wound with suction drainage and, if necessary, light packing of the ear canal completes the operation.

Second branchial cleft sinuses

Second branchial cleft sinuses are the commonest of the branchial anomalies (up to 90%[1]) (**Figure 41.3**). The second branchial arch forms the epidermis of the upper neck and dorsal pinna. The mesoderm forms the facial muscles and the body of the hyoid, and the endodermal elements form the root of the tongue, the foramen caecum, the thyroid stalk and the tonsil. The second branchial cleft sits immediately caudal to these structures and it is persistence of this cleft that leads to the formation of the second branchial arch sinus.

Second branchial arch sinuses may be associated with branchio-oto-renal syndrome, especially if bilateral.

The second branchial cleft sinus presents as a congenital opening on the lower neck, anterior to the sternocleidomastoid muscle. The tract of the second branchial cleft sinus is directed proximally and medially to pass between the internal and external carotid arteries. The proximal end may communicate with the pharynx through the palatine tonsil to form a true fistula in some cases, although most lesions are not patent through their whole length. The sinus nearly always leaks clear or mucoid fluid from the distal external opening due to secretions from ectopic salivary tissue in the wall of the sinus itself rather than any leakage from the pharynx. In some cases the sinus may become infected and, on occasion, the infected tract may form an abscess in early infancy, requiring intravenous antibiotics or surgical drainage.

Second branchial cleft cysts are thought to be congenital in origin even though they rarely present in childhood and are much more common in young adults. They typically present as a spherical swelling inferior to the angle of the mandible, anterior to the sternocleidomastoid, although other unusual locations occur. It is helpful to



Figure 41.3 Second branchial cleft sinus tract dissection **(a)** peters out adjacent to the pharynx **(b)**. The white arrow indicates the lacrimal probe. **(c)** Post-operative image: note the asymptomatic preauricular sinus (white arrow) and the 1-week old post-operative scar (white arrowhead).

recall Bailey's classification of second branchial cleft cysts which provides a framework at the clinic for diagnosis and surgical planning of unusually placed cysts:

- **type I:** deep to platysma, anterior to sternocleidomastoid
- **type II:** abutting internal carotid artery and adherent to internal jugular vein (most common) (Figure 41.4)
- **type III:** extending between internal and external carotid arteries
- **type IV:** abutting pharyngeal wall and potentially extending superiorly to skull base.

Investigation

As a rule with second branchial cleft sinuses, the diagnosis is evident and no further investigation is required. Neck ultrasonography can characterize the size of tract or associated sharply demarcated cyst, and renal tracts can be imaged to exclude horseshoe or duplex kidney. However, a radiopaque sinogram is not routinely indicated. Cross-sectional imaging will usually show the close relations of a second branchial cyst and is particularly helpful for type III or IV presentations (Figure 41.5). MRI is preferable to CT in children to minimize exposure to ionizing radiation and provide excellent detail of soft-tissue planes.



Figure 41.4 Excision of a common type II second branchial cleft cyst deep to the sternocleidomastoid muscle and abutting great vessels.

Treatment

Because of the risk of infection, excision of second branchial cleft sinuses is advisable. Surgery can be performed at any age and aims to excise the tract completely when no infection is present. A fusiform skin incision is made



Figure 41.5 **(a)** Pre-operative appearance of a type IV second branchial cleft cyst/sinus, **(b)** with coronal and **(c)** axial T2-weighted imaging.

around the external opening and the tract can be followed upwards with microbipolar dissection and counter traction with lacrimal retractors. If the distance between the external opening and pharynx is too great to allow good access, a second stepladder incision is made superiorly in the neck to enable the cranial portion of the tract to be visualized and excised; however, this is rarely necessary in the young child. The tract will be seen to enter the pharyngeal muscle at the level of the palatine tonsil and can be ligated and excised at this level. Although ipsilateral tonsillectomy is unnecessary in the vast majority of cases, tonsillectomy should be considered in the larger type IV second branchial cleft cyst that abuts the pharynx (**Figure 41.5**). Care must be taken to avoid the hypoglossal nerve in the superior part of the dissection. Complete excision of the sinus should prevent recurrence. Surgery for second branchial cleft cysts should be planned when infection has resolved, taking care to avoid injuring the internal jugular vein and hypoglossal nerve superiorly.

Third and fourth pharyngeal pouch sinuses

Third and fourth pharyngeal pouch sinuses are rare abnormalities, accounting for 1–2% of branchial lesions, which can present as a sinus, cyst, thyroid gland abscess or even a fistula from pharynx to skin.[3] They almost always occur on the left side. They tend to present in early childhood with associated infections or in neonates with airway obstruction. The third and fourth branchial arches are related to the thyroid, parathyroid and thymus and

therefore tracts may course close to or through these structures: both originate at the pyriform sinus. The third arch is associated with the glossopharyngeal nerve whereas the fourth is related to the superior laryngeal branch of the vagus nerve. This can explain the theoretical course of third and fourth pharyngeal pouch anomalies, however case reports to demonstrate these are lacking. A proposed theory by James[4] is to consider these as branchial anomalies of the pyriform fossa. Development may arise from the incomplete closure of the thymopharyngeal duct of the third pouch, a similar concept of how cysts may form in the thyroglossal duct tract.

Presentation

These anomalies present most commonly with some form of infection, often recurrent thyroid abscess, which is treated with incision and drainage without recognition of the diagnosis and rendering recurrence inevitable.

Investigation

Various investigations have been proposed: barium swallow, radioiodine scan, ultrasonography and CT. However, MR imaging alone is suitable followed by rigid endoscopy under anaesthesia to identify an opening in the pyriform sinus.

Treatment

Although wide-field extirpation of the cyst, tract and ipsilateral thyroid lobe using a hybrid open and endoscopic approach to the pyriform sinus was the standard treatment, modern management utilizes endoscopic cautery of the pyriform fossa sinus alone as first-line treatment. Bailey described successful endoscopic diathermy of the pyriform fossa opening in two cases in 2004 which has become first-line treatment to obliterate the tract and avoid recurrent infection.[5] Garabedian recognized a higher recurrence rate in neonates in a series of 20 children and recommended resection via open approach rather than endoscopic approach in this younger age group.[6]

PREAURICULAR CYSTS AND SINUSES

Embryology

The external ear begins to develop at week 6 of gestation. Auricular hillocks, three from the first and three from the second branchial arch, surround the first branchial cleft below the level of the mandible. The hillocks will form the pinna and the first cleft will form the external canal. As they ascend, some mandibular hillocks contribute to the tragus, while the remainder form the bulk of the auricle. A blind-ended sinus results from incomplete fusion of the hillocks. The sinus is skin-lined and may result in recurrent discharge and infections. While a sinus found above the line of the tragus is usually an isolated preauricular sinus/cyst, a sinus found below the level of the tragus is more likely related to a first branchial cleft anomaly and checking the EAC for fistula is imperative.

One inherited (autosomal dominant with variable penetrance) disorder to be recognized is branchio-oto-renal syndrome which involves structural defects of the outer, middle and inner ear, branchial cleft anomalies and renal abnormalities. Bilateral preauricular sinuses and bilateral second branchial cleft sinuses may be present with hearing loss. Mutations in the *EYA1* gene on chromosome 8q13 are found in 40% of patients.[7] Hearing assessment and ultrasound of renal tracts are recommended management.

Presentation

Preauricular cysts and sinuses are common, with an incidence ranging from 0.9% in the Western European population to 10% in East Africa.[8] The majority of preauricular sinuses will remain asymptomatic and can be managed conservatively. However, frequent discharge or abscess formation following preauricular lymphadenitis should prompt early intervention.

Treatment

If the sinus or cyst is symptomatic, local excision is the treatment of choice (**Figure 41.6**). The sinus is explored under general anaesthetic with a lacrimal probe which usually shows deep extension towards the roof of the ear canal for 10 mm or more. The punctum is excised with a fusiform skin paddle and excised in continuity with the entire tract, which is usually adjacent to the underlying cartilage; excising a portion of this reduces the risk of recurrence. Some will use methylene blue to guide dissection but others avoid this in case of spillage into the field, which makes dissection more awkward. If there is skin breakdown secondary to lymphadenitis in the surrounding area, this can be left alone, as it will settle following successful removal of all epithelial tract related to the preauricular cyst and sinus.

THYROGLOSSAL DUCT CYST

Embryology

Thyroglossal duct cysts are the most common congenital abnormality in the head and neck region. The thyroid develops from the foramen caecum, which lies in the midline of the tongue at the junction of the anterior two-thirds and posterior one-third. In normal development, the thyroid descends through the tongue, passing caudally with an intimate relationship to the hyoid bone and finishing in the anterior neck overlying the trachea and laryngeal cartilage. In around one-third of cases the duct has been found posterior to the hyoid bone, which has important implications in surgical treatment. The duct may fail to

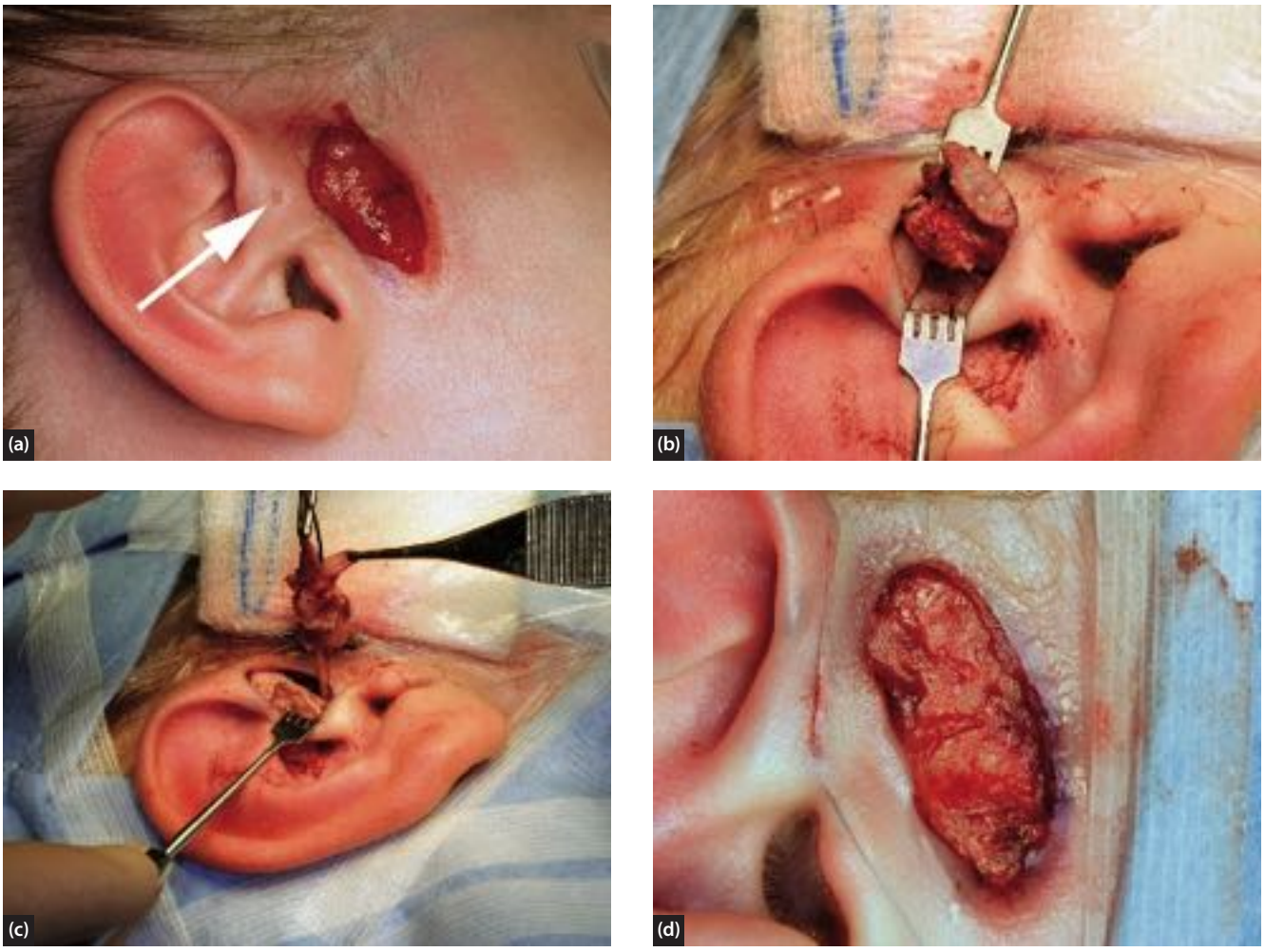


Figure 41.6 **(a)** Preauricular sinus right ear (white arrow) with lymphadenitis, skin breakdown and pre-parotid granulation tissue. **(b,c)** Excision of the sinus, cyst, sliver of cartilage and tract. **(d)** The area of skin breakdown heals by secondary intention following complete excision of the congenital epithelial tract.

involute during the weeks 8–10 of gestation and as a result an abnormal cyst may arise anywhere along the tract and may contain thyroid tissue.

Presentation

Despite being a congenital lesion, thyroglossal duct cysts often present later in childhood or early adulthood. The complaint is usually of a midline swelling in the neck although it can occur laterally, usually left-sided in around 10% of cases. The mass elevates on swallowing and tongue protrusion. It may present with a complication of infection or fistula formation to the skin if surgically drained.

Investigation

It is possible for the thyroglossal cyst to contain the only functioning thyroid tissue and therefore removal would result in hypothyroidism. Ultrasound is useful in confirming the diagnosis and the presence of a normal thyroid gland in the usual position. Cross-sectional imaging before revision surgery is advised to ascertain an intact hyoid bone or localize recurrent cyst.

Treatment

Treatment is nearly always surgical excision unless the cyst is very small and asymptomatic. If a fistula to the skin is present, this is excised with the underling cyst and tract. The definitive operation is that described by Sistrunk from the Mayo Clinic in 1920,[9] removing with the thyroglossal duct a portion of the hyoid bone, a portion of the raphe joining the mylohyoid muscles, a portion of each genioglossus muscle and the foramen caecum. If the surgery is performed as he described, recurrence rates can be kept below 5%; this was confirmed in a 2013 systematic review including 750 patients having primary surgery. Problems arise where there has been a deviation from Sistrunk's procedure resulting in an incomplete resection. Recurrence rates following incomplete excision rise to 27%.[10]



Figure 41.7 Extended Sistrunk procedure for thyroglossal duct fistula with skin paddle including fistula, soft tissue medial to straps, central hyoid (white arrow) and core of tissue towards foramen caecum. The white arrowhead indicates the laryngeal prominence/thyroid notch.

The operation has been developed further with an extended or modified Sistrunk procedure (Figure 41.7), which involves a wider block dissection incorporating the infrahyoid region to the thyroid isthmus initially used for recurrent disease but now applied to all patients to minimize complications.[11] Complications include haematoma, seroma, cyst recurrence, salivary fistula and hypoglossal nerve injury.

LINGUAL THYROID

Lingual thyroid is the result of failure of descent of the thyroid anlage from the foramen caecum of the tongue (Figure 41.8). It is a rare entity with prevalence of 1:100 000. Girls are more commonly affected.[12] In 70–80% of these cases, the lingual thyroid is the only thyroid tissue present. Up to one-third have hypothyroidism. Malignancy has been reported and seems to carry the same risk as thyroid in a normal cervical location.

Presentation

Depending on size, lingual thyroid can present with dysphagia, airway obstruction, haemorrhage or endocrine dysfunction. More often the patient is completely asymptomatic with suspicion only after other investigations, following routine ENT examination or detected on parental curiosity.

Investigations

Imaging will confirm lingual thyroid with either CT or MRI; sagittal views are particularly helpful. Unenhanced CT outlines the lingual thyroid well, given its hyperdensity compared with the surrounding tongue muscle, although MRI is preferred to avoid ionizing radiation. In addition to the lingual thyroid, imaging is used to identify if there is thyroid tissue in the normal cervical location. Ectopic thyroid has been reported in the oropharynx, larynx, infrahyoid neck, mediastinum, oesophagus and heart. Technetium (^{99m}Tc) thyroid scan will identify metabolically active thyroid tissue in the tongue base and no uptake in the neck. Thyroid function tests are usually normal but up to a third of patients demonstrate hypothyroidism; hyperthyroidism is rare.

Treatment

For small, asymptomatic lingual thyroids, suppression with TSH may be effective in checking growth. Reduction is often slow and dramatic results should not be expected. Paediatric endocrinology input is essential. Use of radioactive iodine for thyroid ablation is generally avoided in children. Surgical excision is occasionally required when significant obstructive symptoms are present or repeated or severe haemorrhage is an issue. Transoral resection is usually possible using nasotracheal intubation. For larger and deeper lesions, an external approach may be required. This may even necessitate planned tracheostomy for large masses where swelling and obstruction are inevitable. Lifelong monitoring of thyroid function is essential.



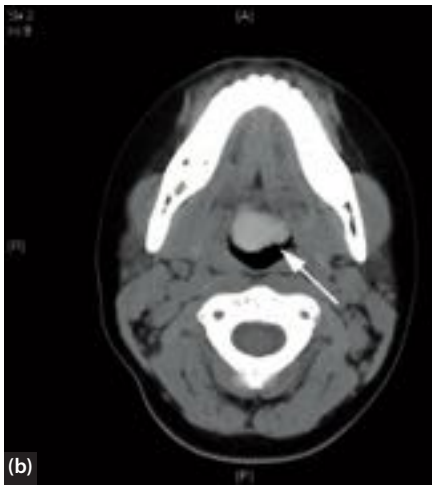


Figure 41.8 **(a)** Lingual thyroid arising from the foramen caecum on the tongue protrusion (black arrow). **(b)** Unenhanced axial CT imaging showing the lingual thyroid (white arrow).

NASAL DERMOID

Dermoid cysts contain ectodermal and mesodermal elements. They occur along the lines of embryonic closure. Nasal dermoids are a rare entity representing 3% of all dermoids and 12% of head and neck dermoids.[13] Incidence is estimated at 1:30000 births.[14]

There is debate over the origin of these cysts. One theory is that they originate from an embryological aberration resulting in inadequate closure of the fonticulus frontalis, allowing dermal tissue to extend between the nasal bones and cartilage. Dura can also extend through this area. The other theory involves the prenasal space, which is an area that runs in the midline between the developing nasal bone and underlying cartilage from the brain to the nasal tip. There is a suggestion that there is persistence of residual dura in this space which forms a contact with the skin and then it retracts to result in a sinus, in which a cyst develops.

A punctum may lie anywhere on the nasal dorsum and may discharge or even have hairs extruding, which is considered pathognomonic. The cyst will lie somewhere between the columella and the glabella (**Figure 41.9**). A tract may also extend superiorly and intracranially. Occasionally the tract connects with a median upper lip sinus.

Presentation

Clinical presentation may be simply a small punctum or isolated mass, often presenting at birth or soon after. Recurrent infection may be a problem and erosion through nasal bones, and periorbital and intracranial spread are unusual complications (**Figure 41.10**). Familial links have been reported.[15]

There are some reported associations with other congenital anomalies such as hydrocephalus, aural atresia and cardiac abnormalities.[16]

Differential diagnoses include glioma, encephalocoele and nasal polyposis.

Treatment

Complete excision is the treatment of choice. Early surgical excision is advocated to reduce bony distortion or atrophy and minimize infective complications. Bradley published results for surgery on nasal dermoids in children.[17] Lesions were classified into simple or complex, depending on involvement outside of skin and histologically described as true dermoid or epidermoid. Hartley et al. published a series of 103 cases and suggest a pragmatic staging system depending on deep extension of the lesion (**Figure 41.11**):[15]

- **superficial:** remain within the soft tissue and readily excised, also the most common
- **intraosseous:** extend to frontal and nasal bones, requiring drill out for excision
- **intracranial extradural:** breech the anterior cranial vault; can be accessed and excised through a frontonasal osteotomy and peeled from the dura
- **intracranial intradural:** most complex and may require bicoronal flap and frontal craniotomy; endoscopic transnasal approach may be possible.

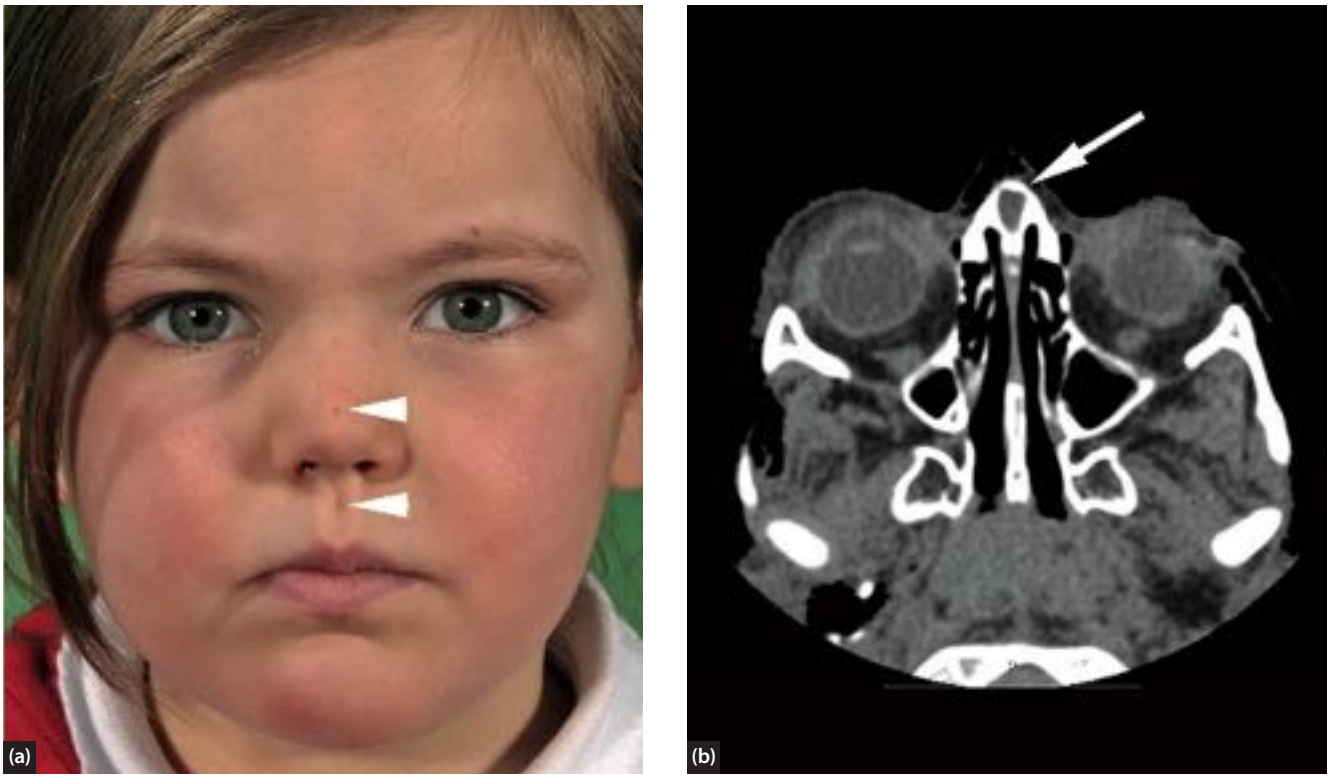


Figure 41.9 **(a)** Nasal dermoid sinus with associated philtrum sinus (white arrowheads). **(b)** Intraosseous extension nasal dermoid cyst deep to the nasal bones (white arrow).



Figure 41.10 **(a)** Complication of intraosseous nasal dermoid cyst/sinus/tract with acute abscess and erosion with loss of skin and left nasal bone. **(b)** Combined surgical approach via external rhinoplasty and direct bishop-mitre rotation flap to replace skin loss. **(c)** Post-operative nasal contour satisfactory with new bone growth.

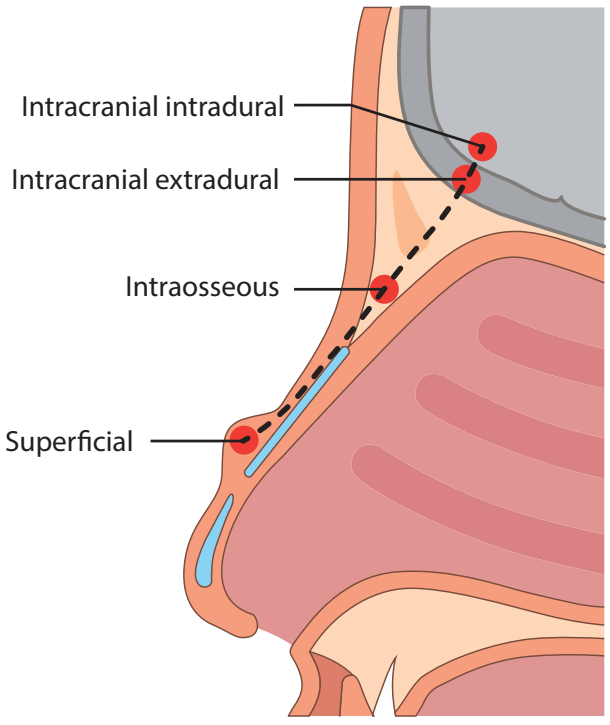


Figure 41.11 Hartley classification of nasal dermoids[15] (permission for reproduction granted from Elsevier publisher).

The position of the cyst or sinus does not predict the likelihood of intracranial extension. Extension has been reported in 4–45% of cases. Imaging is essential to exclude or confirm intracranial extension and planning surgical approach. Dual modality imaging with MR and CT is recommended for maximum understanding of bony and soft-tissue anatomy prior to surgical planning. Imaging is evaluated for size and location of the tract and signs of intracranial extension whether direct (intracranial high-signal cyst) or indirect (bifid crista galli, widened foramen caecum or cribriform plate defect).

Early surgical excision is recommended to prevent infections or further expansion, and consequent damage to surrounding tissue. In 1992 Koltai reported the external rhinoplasty approach for removal of complex nasal dermoids in children[18] and this has become the standard technique for superficial and intraosseous disease. The cosmetic results are good.[19] Identifying the superior limit and site of the dermoid will influence the surgical approach. Most will be adequately accessed via the external rhinoplasty approach or a direct midline incision as either allows access to the radix of the nose in a young child. Brow incisions and lateral rhinotomy are alternatives, and endoscopic techniques have been described more recently.[20, 21] If there is intraosseous extension, a median osteotomy of the nasal bones is required or in a young

child the otologic drill can be used to follow the disease superiorly. The post-operative appearance is very satisfactory and no bone reconstruction is required. A neurosurgical opinion is required for discussion around timing of surgery and to plan the single-stage craniofacial approach. In future, it may become possible to avoid an open craniotomy for some selected intracranial intradural lesions. Re et al. have described two paediatric cases of endoscopic endonasal removal of intracranial extradural dermoid cysts via hemitransfixion incision; however, resection of 1.5 cm superior septal cartilage is required for access to the nasal dorsum.[22] Long-term follow-up is required akin to management of cholesteatoma in the temporal bone; delayed interval MR imaging with diffusion restriction is advised to exclude recurrence.

CONGENITAL MIDLINE CERVICAL CORD AND CLEFT

Embryology

Congenital midline cervical cord/cleft (CMCC) is a rare congenital abnormality forming on the anterior neck which may extend to the mediastinum. It was first described by Bailey in 1924. Aetiology is unclear but it is felt to arise due to failed midline fusion of the second and third branchial arches.

Presentation

CMCC may present at birth with a cleft extending from the mentum to the sternum. There may be no external defect seen but a characteristic 'cord' seen or palpated below the skin when the neck is extended. If a cleft is present, serous discharge may be evident and the upper end will have a pseudonipple appearance.[23]

Imaging

CT or MRI allows characterization of the location and depth of the tract and differentiation from other midline congenital lesions.

Treatment

If there is no skin breakdown and the patient is asymptomatic, a conservative approach may be adopted. Surgery is indicated for cosmetic reasons and prevention of cervical contractures. Elective surgical excision is advocated using stepladder horizontal incisions or Z-plasty closure to avoid contracture (Figure 41.12).

SINUS STERNOCLAVICULARIS

Presentation

Sinus sternoclavicularis is usually present at birth with an asymptomatic sinus at or near the sternoclavicular joint, more often on the left side.

Imaging

Ultrasound allows characterization of the location and depth of the tract and confirmation of normal thyroid gland. Often no further imaging is required.

Treatment

If there is no skin breakdown and the patient is asymptomatic, a conservative approach may be adopted. Elective surgery is indicated for cosmetic reasons, usually involving excision of a blind-ending sinus which peters out adjacent to the sternoclavicular joint (Figure 41.13).

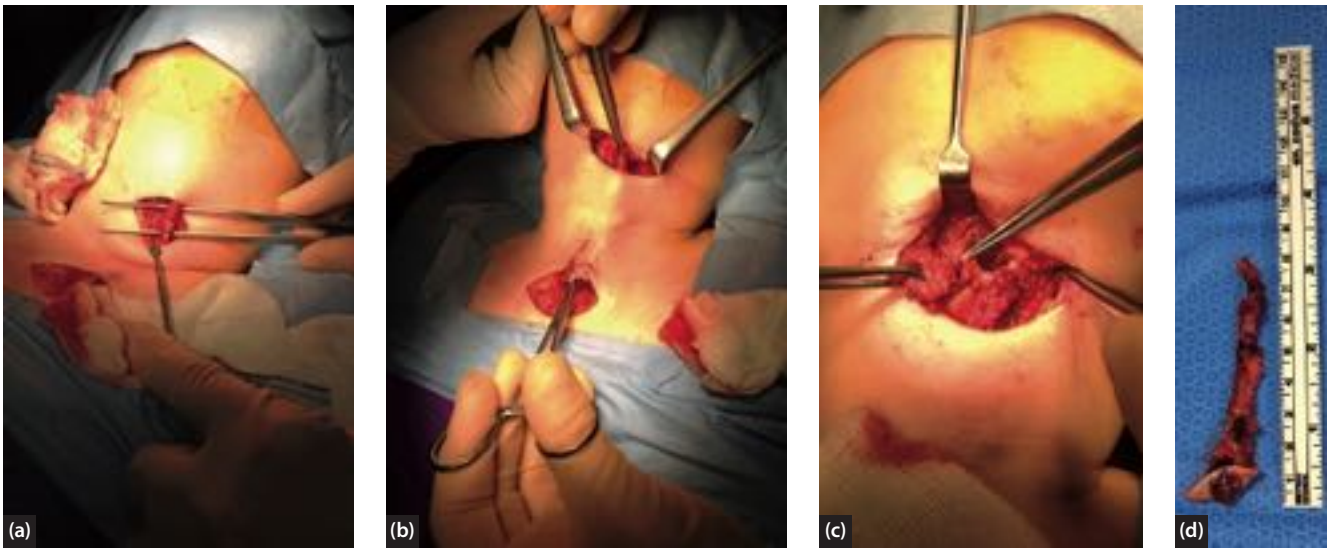


Figure 41.12 Unusual congenital midline cervical cord **(a)** with suprasternal sinus **(d)** removed using stepladder incision **(b)** attached to the thyroglossal tract **(c)**.

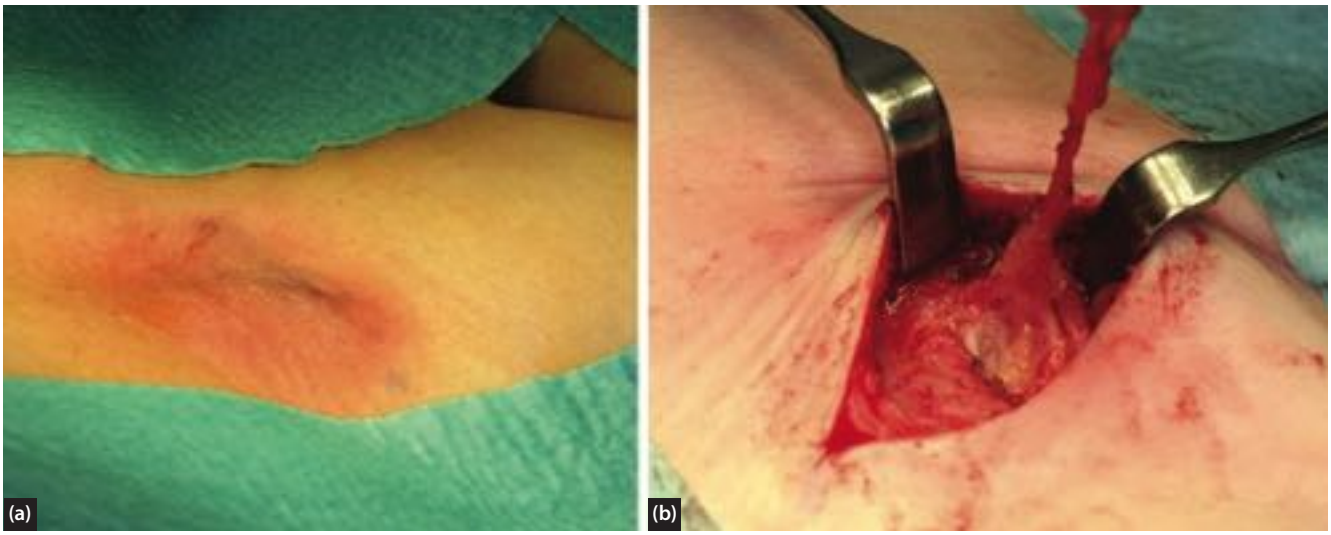


Figure 41.13 Excision of sinus sternoclavicularis.

KEY POINTS

- Congenital cervical anomalies can present as palpable cystic masses, infected masses, draining sinuses or fistulae.
- Thyroglossal duct cysts are most common, followed by branchial cleft anomalies and dermoid cysts.
- Branchio-oto-renal syndrome should be considered if bilateral preauricular pits and branchial sinuses present.
- Appropriate diagnosis and management of these lesions requires a complete understanding of their embryology and anatomy.
- Correct diagnosis, appropriate imaging, management of infection before planned surgery and complete surgical excision are essential to minimize recurrence.
- The extended Sistrunk's operation is the minimum procedure advised to reduce complication rate for thyroglossal cyst/ tract excision.

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CHAPTER 42

HAEMANGIOMAS AND VASCULAR MALFORMATIONS

Daniel J. Tweedie and Benjamin E.J. Hartley

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: vascular anomaly, vascular malformation, lymphatic malformation, venous malformation and haemangioma.

INTRODUCTION

Vascular anomalies include a number of conditions of distinct pathology, which may be classified as either vascular tumours or vascular malformations. Historically, these diverse lesions have been poorly understood. This is reflected in varied and often incorrectly applied terminology, difficulties in diagnosis and inconsistent approaches to management. This chapter considers the advances in our understanding of vascular anomalies, the subsequent evolution of nomenclature, classification and current management strategies. Such considerations are central to the optimum treatment of children and adults with these conditions and their sequelae.

HISTORICAL PERSPECTIVES

Vascular anomalies were first described histopathologically by Virchow. He separated them into angiomas and lymphangiomas, with later classifications of both groups into simplex, cavernosum and racemosum, according to histological appearance.[1] This system took no account of the varied biological behaviour of these lesions, nor their clinical characteristics. Subsequent attempts at classification were based on pathological and embryological properties, which again failed to correlate well with clinical behaviour. Poor understanding was further compounded by the use of a multiplicity of descriptive terms (such as port wine stain and strawberry naevus), often erroneously or ambiguously for several pathologically distinct entities.

Edgerton in 1976 proposed a three-category system according to whether the lesions remained unchanged without treatment, resolved spontaneously or alternatively progressed and/or caused growth in surrounding structures.[2] While recognizing a range of outcomes, this scheme failed to consider the underlying histological basis for the observed clinical manifestations.

Mulliken and Glowacki in 1982 were the first to produce a practical clinical classification for vascular anomalies according to histological appearance, histochemistry and clinical behaviour, separating them into haemangiomas and vascular malformations.[3] This classification has been supported by subsequent clinical, radiological and biochemical studies.

Widespread confusion surrounding terminology and appropriate management of vascular anomalies persists nonetheless. This chapter addresses the biological basis, clinical manifestations and natural history of these distinct diseases, the understanding of which is central to their proper management.

CORRECT NOMENCLATURE

The dichotomous biological system of Mulliken and Glowacki[3] originally considered vascular lesions in infants and children as haemangiomas (with proliferating and involutional phases) or malformations (capillary, venous, arterial, lymphatic and fistulae). This simple classification has since been modified somewhat by the International Society for the Study of Vascular Anomalies (ISSVA) in 1996, taking into account advances in histopathology, histochemistry and radiological imaging (**Box 42.1**).[4] **Vascular tumours** now represent a group of lesions which includes haemangioma subtypes in addition to other rarer tumours, and **vascular malformations** are now described according to whether they are **slow-flow**, **fast-flow** or **complex**. In parallel with these adjustments, the ISSVA has recommended that older terms such as 'angioma' and 'birthmark' should be discarded. The suffix -oma should be used only in the context of a proliferating tumour and should therefore not be applied to vascular malformations.

BOX 42.1 Updated ISSVA classification of vascular anomalies (1996)[4]

Vascular tumours	Vascular malformations
• Infantile haemangiomas • Congenital haemangiomas (RICH, NICH) • Tufted angioma (with or without Kasabach–Merritt syndrome) • Kaposiform haemangioendothelioma (with or without Kasabach–Merritt syndrome) • Spindle-cell haemangioendothelioma • Other rare haemangioendotheliomas • Dermatological acquired vascular tumours (pyogenic granuloma, targetoid, glomeruloid and microvenular haemangiomas)	*Slow-flow malformations* • Capillary malformation (CM) • Port wine stain • Telangiectasia • Angiokeratoma • Venous malformation (VM) • Common sporadic VM • Bean syndrome • Familial cutaneous and mucosal VM • Glomerulovenous malformation • Mafucci syndrome • Lymphatic malformation *Fast-flow malformations* • Arterial malformation (AM) • Arteriovenous fistula (AVF) • Arteriovenous malformation (AVM) *Complex combined vascular malformations* • CVM, CLM, LVM, CLVM, AVM-LM, CM-AVM

C, capillary; V, venous; L, lymphatic; AV, arteriovenous; M, malformation; RICH, rapidly involuting congenital haemangioma; NICH, non-involuting congenital haemangioma.

VASCULAR TUMOURS

Vascular tumours may or may not be present at birth, and grow by cellular (predominantly endothelial) hyperplasia. Haemangiomas are certainly the commonest type although a number of other vascular tumours are occasionally seen, most often acquired, sometimes in the presence of syndromes. Advances in histopathology have allowed further subdivision within these groups adding to the original haemangiomas grouping of Mulliken and Glowacki.

HAEMANGIOMAS

Presentation and natural history

Haemangiomas are the commonest tumours in white infants, present in up to 10–12%.[5] Two-thirds are found in the head and neck, with a female : male ratio of 3–5 : 1. This is in contrast to vascular malformations, which have no gender preponderance. Extremely premature infants (birth weight <1000 g) are at particular risk, with around 30% affected. They are less common in non-Caucasians. Most lesions are solitary, with multiple cutaneous lesions being associated with a higher risk of visceral involvement. Facial haemangiomas tend to be found in a segmental distribution, and particularly along lines of embryological fusion.

Haemangiomas have recently been subdivided according to presentation and behaviour as **congenital**, by definition present and obvious at birth, and **infantile**, the commoner variants, which usually proliferate from original pink macules during the first 2 months of life.[6] Congenital haemangiomas (CH) have been further categorized by rate of involution as **rapidly involuting** (RICH), **non-involuting** (NICH) or **non-progressive**.

Their precise appearance may vary significantly according to their depth (superficial, deep or visceral) and subsite, but location does not influence biological behaviour (**Figures 42.1** and **42.2a**). Cutaneous lesions may appear as a patch of erythema, a blanched area or telangiectasia with a peripheral pale halo, and they may be confused with other vascular anomalies such as venous malformations. The child may alternatively present primarily with visceral



Figure 42.1 Cutaneous frontal haemangioma, infantile type. This child presented at the age of 2 months with worsening stridor secondary to a subglottic haemangioma.

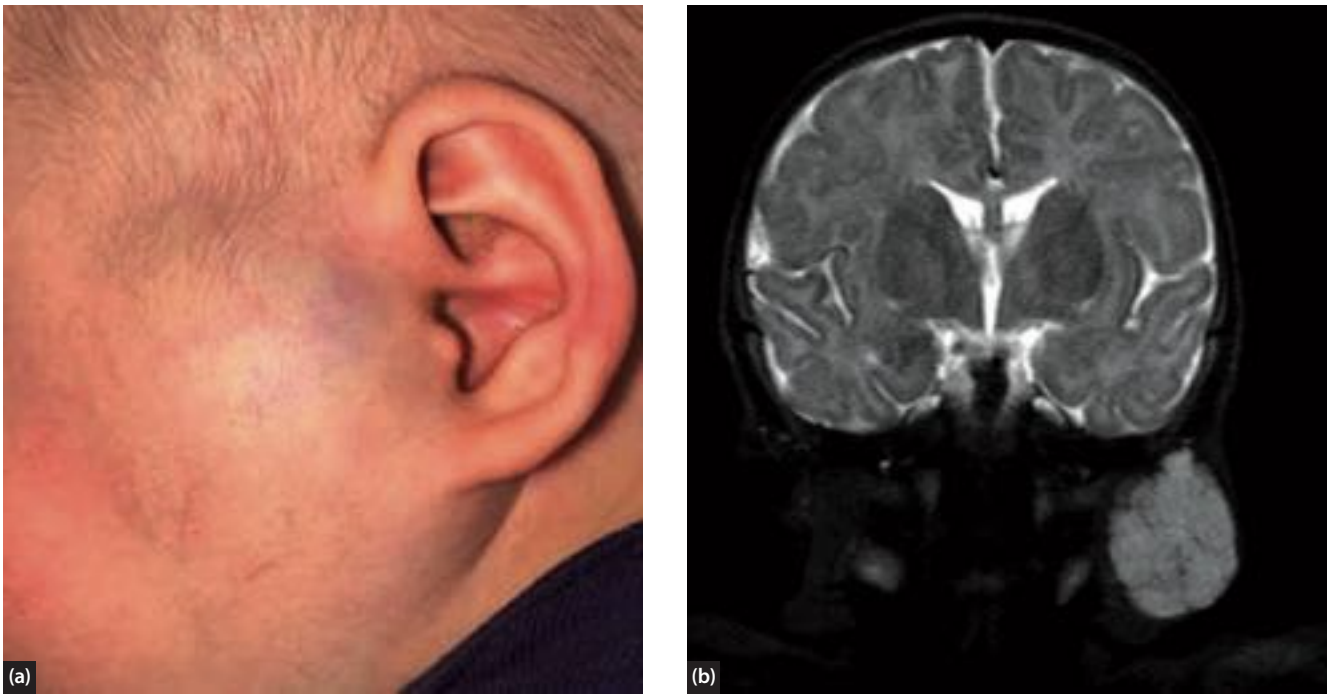


Figure 42.2 Parotid haemangioma. (a) Clinical appearance. Note the blue hue, hence the differential diagnosis of vascular malformation. **(b)** Coronal T2-weighted MRI of the same patient. The haemangioma is of moderately high-signal intensity, with small, scattered linear flow voids of associated vessels.

manifestations (such as stridor secondary to a subglottic haemagioma): only a small proportion of patients with cutaneous disease will also have visceral lesions, but around 50% of those with visceral haemangiomas will have no cutaneous manifestation. The overall picture, certainly for the infantile type, is one of proliferation and rapid tumour growth, resulting in a tense and minimally compressible mass which will tend to plateau in size by 4–8 months of life. This is reflected by progressive cutaneous and/or visceral effects which develop during early infancy. Alternatively, the progress of CH is more variable. Together with their presence at birth, this variability may also promote confusion with vascular malformations.

Involution of haemangiomas tends to begin at around 1 year of age, and continues for the next 5–7 years.[6, 7] An overlapping period of proliferation and involution may be seen.[5, 7] Some 50% of haemangiomas will have completely involuted by the age of 5 years and 70% by 7 years with some further involution seen in the remainder by age 12. The only factor associated with improved outcome is an early age of first involution. Importantly, patients and parents should be aware that permanent skin changes (loose skin, altered colouration, telangiectasia and scarring) may occur in over 50%, even after complete tumour involution.[7]

Most cases have no obvious genetic basis, although some may be inherited in an autosomal dominant fashion, with a possible locus on chromosome 5q.[8] Associations have also been noted. Large cervicofacial haemangiomas are seen in conjunction with other malformations in about 10% of cases (PHACES syndrome: **P**osterior cranial fossa malformation, including Dandy–Walker; **H**aemangiomas; **A**rterial anomalies, including absent carotid or vertebral vessels; **C**ardiac anomalies; **E**ye anomalies; **S**ternal anomalies, bifid or cleft).[9]

The majority of those affected are girls (90%), with a particular risk of thromboembolic stroke in childhood. Otherwise, there is thought to be an increased likelihood of laryngeal involvement in those with a facial haemangioma in a beard distribution,[10] and spinal, anorectal or urogenital abnormalities in patients with lumbosacral lesions.

Cellular basis

Histologically, haemangiomas comprise proliferating immature endothelial cells and disorganized vessels. Various theories for the development of haemangiomas have been proposed.[11] They are thought to arise as a result of abnormal angiogenesis, which leads to uncontrolled endothelial proliferation. This may be due to **intrinsic** endothelial cell anomalies (favoured by the chromosome 5q inheritance patterns), resulting in hyperplasia from a single abnormal cell, and/or as a result of an abnormal, **extrinsic** cellular environment. Implicated in either process is an interplay between a variety of angiogenetic markers, including fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF), and angioinhibitory substances, such as tissue metalloproteases. Glucose transporter-1 (GLUT-1) is a specific marker for infantile haemangiomas, with 97% of these lesions testing positive for this.[12, 13] GLUT-1 is otherwise only found in the placenta and endothelium of the blood–brain barrier. This may have implications for the diagnosis and management of infantile haemangiomas versus other lesions, which will not have the same cellular markers, and respond differently to treatments including propranolol. Apart from endothelial cells, other lineages are also involved, including mast cells, fibroblasts and macrophages. The up- and

down-regulation of these cells at various times is believed to account for the variability in proliferation and involution manifested clinically.

Diagnosis

The mode of diagnosis will depend typically upon the site and clinical presentation. Cutaneous lesions are most often diagnosed clinically, although they may be difficult to distinguish from the main differential diagnoses, namely macular stains, vascular malformations and other rarer vascular tumours.

Macular stains are common vascular cutaneous lesions, also known by a number of terms such as 'stork bite' or 'salmon patch'. These are flat, usually pink to red, and are typically seen on the face or neck. They are physiological and will tend to resolve, without the dramatic proliferation exhibited by haemangiomas. Vascular malformations are usually distinguished by being present at birth and growing proportionally with the child, although these differences may be subtle, particularly in congenital cases during infancy.

Investigations may be required in those difficult cutaneous cases or where visceral involvement and/or other associations are suspected. Diagnostic imaging, in the form of ultrasound, magnetic resonance imaging (MRI), computerized tomography (CT) with contrast or arteriography will usually distinguish haemangiomas very well. For deeper lesions, MRI is preferred, demonstrating a lobulated soft-tissue mass with flow voids (feeding and draining vessels). The mass is iso- or hypo-intense on T1 and hyper-intense on T2 weighting, respectively (**Figure 42.2b**). Alternatively, other modes of tailored investigation, such as diagnostic microlaryngobronchoscopy, may be appropriate for visceral lesions.

Complications

The sequelae and complications of haemangiomas will depend upon their anatomical subsite, size and depth. There may also be complications associated with related pathologies.

Permanent skin changes and cosmetic abnormalities are anticipated in a significant proportion of cases, particularly those with large superficial facial lesions and where involution has been slow or incomplete.[7] Excisional surgery and scar management (by means of Z-plasty and other releasing techniques) may be indicated. Ulceration affects fewer than 5% of cases. This is most commonly seen with perioral and perineal lesions, perhaps related to increased day-to-day skin trauma in these areas. The risks of associated infection are significant. Scrupulous wound care and antibiotic ointments may allow these areas to resolve, but excision or medical treatment may be required.

Obstruction of the visual axis by periorbital haemangiomas is occasionally seen, and demands a circumspect, multidisciplinary management approach. In the case of large periorbital lesions, vision may be obstructed as a result of the haemangioma protruding across the globe, or alternatively pressing on and distorting the cornea. In rarer instances, intraorbital lesions may compress the conal muscles, producing diplopia. The mammalian visual cortex is extremely sensitive to stimulus deprivation during the first year of life, such that permanent amblyopia may develop within as little as 1 week of such insults. Urgent referral to a paediatric ophthalmologist is therefore mandatory, stressing the importance of treatment without delay.

The ear canal may also become obstructed by parotid haemangiomas, occasionally resulting in conductive hearing loss, with the secondary risk of speech delay.[5] Active treatment should be considered in these circumstances, particularly for rare bilateral lesions, albeit on a non-emergency basis.

Airway obstruction by haemangiomas may occur at several possible levels, and it should be noted that in up to 50% of cases there may be no cutaneous manifestation to raise diagnostic suspicion. Nasal obstruction from cutaneous haemangiomas is often obvious, although endonasal disease may lead to insidious, progressive obstruction in infants, who are obligate nasal breathers. Subglottic haemangiomas (**Figure 42.3**) typically present with progressively worsening stridor from 2–3 months,

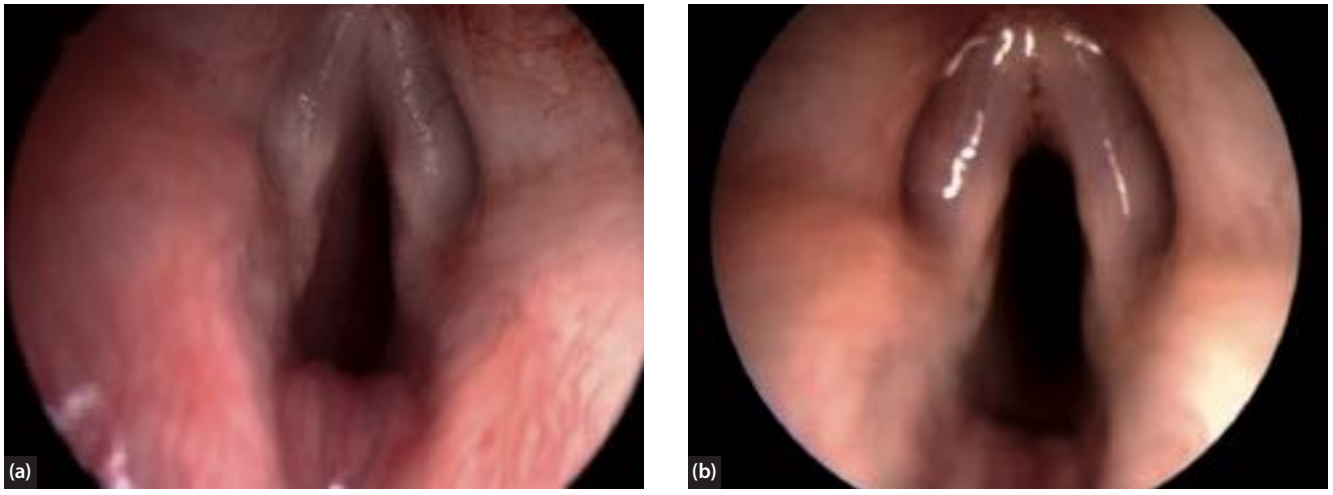


Figure 42.3 Subglottic haemangioma. (a) First presentation in a 3-month-old infant. **(b)** Same patient aged 6 months, after 3 months' treatment with propranolol.

with eventual airway obstruction, in the absence of other obvious precipitants or symptoms. Medical treatment with propranolol is now the mainstay of management of these cases, although tracheostomy and/or open excision via laryngofissure are occasionally still required.

Congestive cardiac failure is an unusual complication, seen most often in the context of either diffuse disease in the neonatal period or alternatively as a result of arteriovenous fistulation within large visceral haemangiomas, causing cardiac insufficiency.[10]

Management

Assuming a correct diagnosis is reached as early as possible, treatment of haemangiomas should be tailored according to the individual patient, taking into account the local and systemic effects of lesions and associated complications. For the majority of haemangiomas, particularly smaller ones, active monitoring and reassurance for the parents will usually suffice. But it is worth emphasizing that the onset and rate of involution are variable, and residual tumour, scarring and other skin changes may compromise the final cosmetic outcome. Lesions which are larger and affect function, or those resulting in significant complications, will usually require non-surgical treatment (typically propranolol) and/or surgical intervention. This is most appropriately delivered in a multidisciplinary setting, combining dermatologists, paediatricians and plastic, general paediatric and ENT surgeons as necessary. The merits of any intervention, medical and/or surgical, must be evaluated in each case, bearing in mind the long-term risks of waiting for natural resolution. Additionally, most medications are not licensed for these applications in young children, which should also be explicit from the outset.

Non-surgical treatment: Propranolol

Propranolol has revolutionized the management of children requiring active treatment for haemangiomas, largely replacing other medical treatments and, in many cases, surgery. Its efficacy was first described by Leauté-Labrèze and her team from Bordeaux, France, who noted a dramatic reduction in size of a nasal haemangioma in a child receiving propranolol for cardiomyopathy.[14] The mechanisms of action are not entirely clear. Vasoconstriction, a direct beta-blocker effect, will allow the haemangioma to become softer and paler, often within 24 hours of treatment, with decreased expression of FGF and VEGF and promotion of apoptosis perhaps accounting for accelerated resolution. Cyclic AMP (cAMP) and tyrosine kinase pathways are also now thought to mediate the actions of propranolol in promoting apoptosis.[15, 16]

Following successful use locally[17] at other paediatric centres, propranolol is the preferred option for children with subglottic haemangiomas and, with time and a better appreciation of the sequelae of propranolol use in children, this treatment can be considered for haemangiomas in other locations, particularly those impacting the vision, other functions, and large lesions in cosmetically sensitive areas. Patients are often managed jointly by ENT and dermatology departments, with additional input from other specialities as required. A full clinical assessment is made prior to treatment, and a number of blood tests are organized (to exclude anaemia, coagulopathy, diabetes, and renal, hepatic and thyroid abnormalities). Baseline pulse and blood pressure assessments, electrocardiography and echocardiography are also mandatory. Further radiological imaging and other investigations may be arranged in addition to the original diagnostic methods (including microlaryngobronchoscopy).

Although the precise regime varies between centres, a consensus statement in 2012 suggested a target dose of 1–3 mg/kg per day in three divided doses, after appropriate screening.[18] In our practice, propranolol is commenced at 1 mg/kg/day, in three divided oral doses. At this point, and at any time the dose is increased, pulse rate and blood pressure are checked every 30 minutes for the first 2 hours before allowing the child home. The dose is increased to 2 mg/kg/day after the first week of treatment, with further adjustments over the coming months to match the child's weight gain. Blood pressure is checked twice weekly for the first 2 weeks, and then weekly thereafter. Side effects are sought, typically minor (weakness, fatigue, altered sleep) or occasionally major (bronchospasm, hypotension, bradycardia and hypoglycaemia), although these are more often seen in neonates than in older children. Propranolol should not be used in asthmatics, or together with salbutamol and other selective beta-2 agonists.

Serial assessment (clinical and endoscopic, in the case of subglottic lesions) allows monitoring of initial response to propranolol. This is typically done at 6 weeks and then 3-monthly for the first year, covering the proliferative phase of disease. Weaning from propranolol in stages may then be possible, usually over about 4 weeks.

The response of infantile haemangiomas to propranolol occurs within a few days, during the proliferative period in 97% of cases.[19] Where minimal response is seen, one should consider differential diagnoses, and biopsy of the lesion, with staining for GLUT-1.

For smaller, superficial lesions, topical timolol has shown some benefits in the treatment of infantile haemangiomas.[20, 21]

Non-surgical treatment: Other

In some cases, the response to propanolol is less dramatic. In these circumstances, other medical treatments may be considered. These include corticosteroids, once the mainstay of medical management. Previous studies have confirmed resolution rates reaching 90% for haemangiomas treated with prednisolone 2–3 mg/kg/day, tapered down over several months.[22] But side effects are unfortunately frequently seen, including rebound lesion growth, Cushingoid facies, altered mood, gastritis and growth retardation. Oral steroids are therefore now seldom used for haemangiomas in our practice, given in conjunction with propranolol if the initial response to this has been limited, or if the lesions are large and complicated.

Injection therapy with corticosteroids and alpha-interferon has been used historically, with variable success reported, mainly for those patients with poor response to oral steroids. Similarly, systemic chemotherapy (with cyclophosphamide and vincristine) and radiotherapy have both been shown to arrest the proliferative phase of haemangiomas. However, these modalities may all produce serious local and systemic side effects and are not used routinely in our current practice. Other non-surgical treatments have included cryotherapy. While effective in some superficial lesions, it often results in unacceptable scarring, and has therefore fallen out of favour.

Compression therapy has been attempted, although formal data regarding its efficacy are lacking, and it is not usually a practical option for head and neck lesions, particularly in infants. Embolization is occasionally attempted for larger, highly vascular haemangiomas, particularly those associated with life-threatening complications. This is most often done to facilitate surgical excision, although there are reports of embolization alone leading to rapid regression.[23]

Surgical treatments

Excision, via a variety of methods, remains a reasonable option in some cases, particularly those with poor response to propranolol and other medical treatments. Alternatively, as a primary treatment, direct excision of cutaneous and subglottic disease, for example, will have the potential for complete cure from the outset, in contrast to medical therapy which requires a long period of treatment, regular follow-up and carries significant risks of its own. The relative benefits of surgery in this context should not be overlooked, and must form part of the initial multidisciplinary discussion of treatment options. It is also very reasonable in some cases to employ a dual modality approach, using propranolol to reduce proliferation, followed by excision as necessary.

Laser therapy, using a variety of types (carbon dioxide, pulsed dye, Nd-YAG, argon and KTP) has been used predominantly for cutaneous lesions. Partial laser-assisted excision of lesions around the eye, for instance, allows rapid clearance of the visual axis, in contrast to medical treatment, which may take longer to achieve the same effect. The laser energy may be delivered superficially or intralesionally, particularly for deeper haemangiomas. The authors caution against laser treatment for subglottic haemangiomas because of the risks of circumferential scarring and stenosis, and favour open excision via laryngofissure as a second-line treatment after propranolol.

OTHER VASCULAR TUMOURS OF CHILDREN

Kaposiform haemangioepitheliomas

Kaposiform haemangioepitheliomas are vascular tumours which behave far more aggressively than simple haemangiomas, from which they have only recently been definitively distinguished. They are often associated with thrombocytopaenia, known as Kasabach–Merritt syndrome (KMS). Consumptive thrombocytopaenia is believed to occur as a result of platelet trapping within extensive lesions. This may itself result in secondary coagulopathy, as clotting factors and fibrinogen are used up. Disseminated intravascular coagulation may then develop, with an overall mortality risk in KMS of 30–50%.[24] Importantly, in contrast to previous suggestions, KMS is not associated with simple haemangiomas.

Kaposiform haemangioepitheliomas can be distinguished clinically, histologically and radiologically from haemangiomas. Both may be seen congenitally, but haemangioepitheliomas tend to have equal gender incidence, and are more often seen outside the head and neck, sometimes in the retroperitoneum. Traditional therapeutic options have been similar to those for haemangiomas, although high-level evidence for these treatments in this context is lacking. In practice, given the high risk of KMS and other serious complications, multimodality treatment is often used, including corticosteroids, chemotherapy, embolization and/or excision, together with parallel treatment of coagulopathy. Propranolol has also been used with some success in a small number of cases, prescribed long-term after a brief initial course of chemotherapy.[25] It is important that heparins should not be used to manage the thrombocytopaenia of KMS, as they may lead to increased FGF release, itself associated with increased tumour proliferation.

Tufted angiomas

Tufted angiomas – also known as angioblastomas – are very similar to kaposiform haemangioepitheliomas. Indeed, these lesions may represent a spectrum of pathology rather than separate entities. KMS may complicate tufted angiomas in the same fashion, and treatment options are similar.

Pyogenic granulomas

Pyogenic granulomas are acquired vascular lesions which are very similar in appearance to haemangiomas but are typically seen in older children and young adults. In contrast to popular belief, they tend to arise suddenly and without a history of trauma. Treatment options include surgical excision, laser ablation and chemical or electrocautery.

Haemangiopericytomas and angiosarcomas

Congenital haemangiopericytomas are very rare tumours, found in the extremities of newborns. Biopsy and surgical excision may be required.

Angiosarcomas are uncommon malignancies in children. They typically arise in the liver and behave aggressively, metastasizing to the lungs. Prognosis is very poor.

VASCULAR MALFORMATIONS

Vascular malformations, in contrast to vascular tumours, have normal endothelial mitotic activity and are errors of morphogenesis.[4] They are present at birth, although some may not initially be obvious, and they grow with the child. They do not involute, but may vary in size with time according to inflation with fluid and/or blood and subsequent deflation. At a molecular level, the markers of proliferation (such as VEGF and FGF) and endothelial proteins (GLUT-1, merosin, Fcγ receptor II), seen frequently in association with vascular tumours, are not usually elevated in vascular malformations.

The clinical impact of these lesions is very variable, depending on location, size, subtype and shunts, ranging from mild cosmetic deformity to life-threatening airway obstruction or haemorrhage. Several varieties are described, according to their cellular components and flow characteristics (**Box 42.1**). These distinctions greatly influence appropriate management. Vascular malformations are associated with skeletal abnormalities in up to 35% of cases and other malformations and syndromes.

SLOW-FLOW VASCULAR MALFORMATIONS

Capillary malformations

Capillary malformations (CMs) occur in 0.1–0.3% of live births,[26] although they may be overlooked in the neonatal period as a result of generalized plethora and/or anaemia. Most involve the head and neck, particularly in the distribution of the trigeminal nerve (**Figure 42.4**). They consist of postcapillary venules within the papillary and superficial reticular layers of the dermis, hence the alternative term **venular malformations**. Initially presenting as flat, pink areas, they have a tendency to darken in colour with age (port wine stain) and to thicken, with a cobblestoned surface in two-thirds of affected adults. Some will develop associated pyogenic granulomas. This evolving appearance is believed to result from abnormal neural modulation of the sympathetic papillary plexus, with vessel thickening and dilatation in the absence of proliferation. Lesions may be graded I–IV (the Waner classification) according to the degree of vessel ectasia, thought to be related to the degree of sympathetic denervation.[27] This system correlates well with clinical severity and treatment outcomes.



Figure 42.4 Capillary malformation in the distribution of the maxillary division of the trigeminal nerve. Even in an infant, the skin in this affected area is slightly thickened and raised. Without treatment, this thickening is likely to progress with time.

Although most cases are isolated, some may be associated with syndromes and/or other vascular malformations. These include Sturge–Weber syndrome: CM in the distribution of the ophthalmic branch of the trigeminal nerve (CN V1), seizures of neonatal onset, cataracts, learning difficulties and ipsilateral leptomeningeal angioma. Importantly, patients with large facial CM in the distribution of V1 may have ocular involvement, including glaucoma, and/or central nervous system involvement without other features of Sturge–Weber syndrome. Klippel–Trénaunay syndrome (CM, varicose veins, central visceral varices, lower limb hemihypertrophy) is rarer, with complications including variceal haemorrhage and thromboembolic events. These features together with the addition of an arteriovenous malformation (AVM) comprise the Parkes Weber syndrome, presenting in childhood with an enlarged, warm extremity.

Rarer associated syndromes are also described, such as Cobb syndrome (CM overlying the spine, with associated spinal meningeal vascular malformations) and Wyburn-Mason syndrome (facial CM with associated unilateral AVM of the retina and intracranial optic pathway).

In keeping with other vascular malformations, CM may be associated with skeletal and limb abnormalities, even in the absence of other syndromic features.[28] This is particularly the case for lesions overlying the spine, especially if these are multiple and lumbar, for which MRI is indicated.

TREATMENT

In the first instance, careful clinical assessment should confirm the diagnosis, although further investigations (including imaging) may be necessary to exclude associated pathology. For example, suspected syndromic cases should undergo MRI (with gadolinium enhancement) to exclude cerebral and spinal lesions, although these may not always be evident in early life, such that serial scanning may be necessary. A supportive, multidisciplinary approach to treatment and follow-up is essential in these cases, often requiring parallel ophthalmological and neurological/neurosurgical input.

At a simple level, cosmetic cover-up creams may be beneficial. Tattooing with skin-coloured pigments has also been used, albeit not in routine practice. Neither of these approaches, however, will alter the lesions' natural history. Any specific treatment of CM must take into account a typically progressive deterioration in appearance, which may be accelerated by trauma and puberty,

and its associated psychosocial impact. Earlier intervention is therefore now considered in some centres, even before 1 year of life, although the relative benefits of such early therapy are likely to be more psychosocial than physical, and have not been unequivocally demonstrated.

Treatment options depend to some extent on vessel diameter. Pulsed dye laser is widely accepted as the treatment of choice for CM,[29] targeting the oxyhaemoglobin chromophore in abnormally dilated superficial vessels to allow selective thermolysis. Ultra-short laser pulses are used, particularly at wavelengths of 577 nm or 585 nm, limiting lateral thermal injury and related risks of scarring. Some lesions, particularly those which are thicker and more cobblestoned, may not respond well to pulsed dye laser, in which case other lasers (KTP, copper, argon) may be used, although scarring, hyper- and hypo-pigmentation are more likely.

Multiple treatments are typically needed, between two and six on average. Reviews of various studies suggest that the response will vary according to depth, colour and location of the lesion (best on the neck, then torso and face, worst on the hand and arm), as well as the extent of previous therapy and the age of the patient, although the optimum treatment age is not known. Recurrence of CM is common in these circumstances, up to 50% at 4–5 years, most probably representing persistence of vessels innervated by the abnormal papillary plexus. Interval treatments which touch up areas of residual vessel ectasia are therefore an alternative strategy. Depending on forthcoming clinical trials, future options might include laser speckle and photoacoustic imaging to allow more precise assessment of the local effect of laser treatment, or alternatively treatment with anti-angiogenic compounds such as imiquimod (used primarily, or just after laser therapy).[30, 31]

OTHER VARIANTS OF CAPILLARY MALFORMATIONS

Telangiectasias, visible dilated vessels in the skin or mucosal surfaces, are very common in the population, increasing in incidence with age. The great majority are **primary** or **essential**, with no obvious precipitant. In many cases, telangiectasias are found in a symmetrical malar distribution. Alternatively, **generalized essential telangiectasia** affects a smaller number, typically seen first on the distal lower limbs, then more proximally. The pathophysiology is unknown. Treatment options include active monitoring, cover-up creams, topical agents (including ketoconazole), systemic treatments (such as tetracyclines and acyclovir) and pulsed dye laser. **Secondary telangiectasias** are seen in systemic disorders such as hereditary haemorrhagic telangiectasia and chronic liver disease.

Angiokeratomas are vascular ectasias which involve the papillary dermis. Several variants are described, with elements of papillomatosis and hyperkeratosis in addition to vascular dilatation. Like other CMs, some have associations including Klippel–Trénaunay syndrome and Cobb syndrome. Importantly, some variants including **angiokeratoma circumscriptum** may be mistaken for melanoma; excision biopsy is indicated in these circumstances. Appropriate treatment depends on the subtype, with options including observation, laser therapy or excision.

Venous malformations

Venous malformations (VMs) are characterized by abnormal collections of veins, typically without a uniform smooth muscle layer, which have no demonstrable endothelial or pericyte mitotic activity and no increased expression of VEGF or FGF.[32–34] They are usually solitary and sporadic (**common sporadic**), but some patients have multiple lesions which may have an inherited basis, and a thorough family history should be sought. An autosomal dominant form results in a subtype termed **multiple glomangiomas**, and a number of other rare familial forms exist. These include Bean syndrome (blue rubber bleb naevus syndrome, BRBNS), characterized by multiple cutaneous VMs in association with visceral VM, particularly affecting the gastrointestinal tract and occasionally the airway (**Figure 42.5**). These carry a risk of life-threatening haemorrhage and often require endoscopic treatment. Patients with Turner syndrome may also have intestinal or lower limb VM. Recent work suggests that an abnormal gene on chromosome 9p coding for an endothelial receptor may be responsible for some familial disease.

All VMs are congenital, although again some are not initially apparent. Presentation is variable, depending upon size, depth and anatomical location. They most often involve the skin of the face, limbs and trunk, but they may also be found in viscera, including the aerodigestive tract, muscle and bones, particularly the mandible. Clinical manifestations therefore vary accordingly, but in general VMs increase in size as the child grows, do not regress, and may swell as a result of raised venous pressure (Valsalva manoeuvre, straining or crying, or when placing the patient with the affected area below the level of the heart, increasing venous drainage to the lesion). Thrombotic events and local infection, with resulting phleboliths, may alter their consistency with time, from soft and compressible to tender, lumpy lesions, especially as more blood flows in but cannot easily drain out. Pain from venous stasis and thrombosis is a strong diagnostic pointer to VM, rather than other vascular malformations. Associated bleeding may occur, in addition to low-grade consumptive coagulopathy.

TREATMENT

The diagnosis of VM is typically clinical, with biopsy undertaken only if there is any doubt. Imaging is usually warranted, both to determine the extent of lesions and to assess relations to large vessels and other hazardous structures. MRI is the most informative modality for deeper lesions, but CT and ultrasound are also helpful.

Many VMs are managed by reassurance and monitoring. Aspirin and compression may be used to limit thrombotic events.[35] Pain is one of the commoner indications for



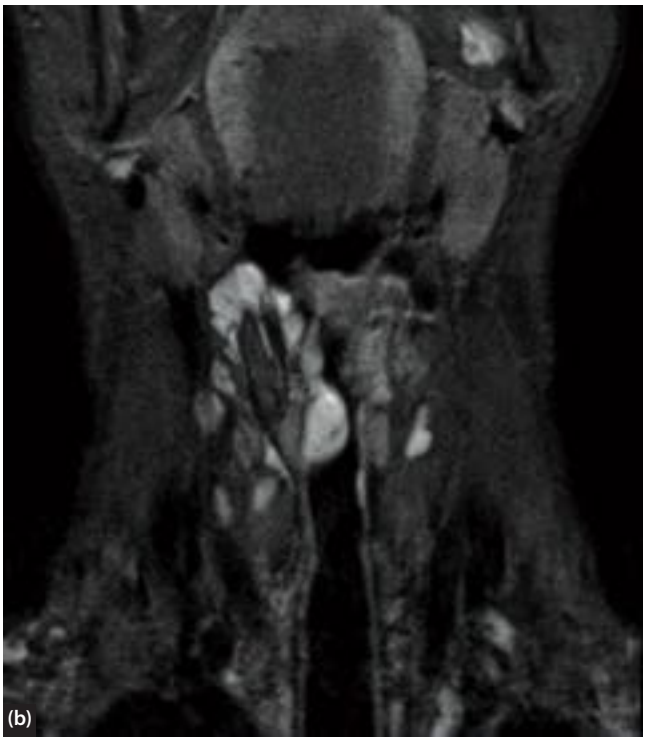


Figure 42.5 Venous malformation. **(a)** Large venous malformation of the upper trachea. This 15-year-old patient recently developed cutaneous venous malformations of the feet, suggesting the diagnosis of blue rubber bleb naevus syndrome. **(b)** Coronal T2-weighted MRI of the same patient, demonstrating numerous venous malformations of the upper aerodigestive tract.

active treatment, although this may also be considered for bleeding, cosmetic and functional reasons, depending on lesion location and size. Once again, a multidisciplinary approach should be adopted, as combinations of treatment, repeated visits and psychosocial support are often necessary.

Sclerotherapy is the primary non-surgical treatment for VM, performed by interventional radiologists under general anaesthesia. Typically, 3% sodium tetradecyl sulphate (STS), instilled as a foam under fluoroscopic guidance, is used. Alternatives at other centres include 95% ethanol and Ethibloc® (ethanol and cornflour), although the risks of tissue necrosis and neurological injury (e.g. the facial nerve branches) have been relatively high in our experience.[36] No controlled trials have assessed the relative efficacy of these agents. Single treatments, with post-injection compression and observation, may be suitable for smaller lesions, but repeated injections and compression are often required for larger VMs. With all forms of sclerotherapy, patients and parents should be aware of significant risks to local soft tissues and nerves, post-operative swelling, secondary infection and the additional risks of communication with deeper structures via fistulous channels, hence the need for prior assessment and imaging.

Superficial components of VM, or entirely superficial lesions, may be treated with laser. Nd:YAG is preferred, owing to the size of the vessels. This may be used in isolation, but it also offers the option of reducing vessel bulk in the skin, thereby facilitating surgical access to deeper components of extensive lesions.

Surgical excision is often extremely challenging. In addition to the friable, vascular nature of excised tissue, VMs often have large communications with major veins, particularly in the head and neck. Complete excision is required to eliminate the risks of recurrence, but the merits of this have to be balanced against major risks. As a result, surgery is often staged and/or combined with sclerotherapy and laser treatment, highlighting the importance of a long-term team approach to management.

Lymphatic malformations

Lymphatic malformations (LMs) are low-flow vascular malformations resulting from abnormal embryologic development of regions of the lymphatic system, although the precise mechanisms are uncertain. The overall result is a collection of varying-sized lymphatic spaces and channels, instead of the normal regular network of fine channels in the dermal papillae which travel to deeper lymphatics, with one-way valves to limit backflow. LMs are found in the head and neck in 75% of cases, from where they may extend into the thorax.

With an overall incidence of some 1:5000, LM accounts for 6% of all paediatric soft-tissue masses.[36, 37] Around half are diagnosed at birth and 90% by 2 years of age, although presentation is variable. This, together with eventual treatment options, depends on the extent of disease and its location, but also upon the size of cysts within it. **Macrocystic** refers to disease with a few large cysts (volume >2 cm^3) and **microcystic** to disease with smaller cysts, but in reality most lesions contain a mixture. Common presentations include cystic masses in the neck and face, but sublingual and tongue base disease may lead to macroglossia, progressive airway obstruction and mandibular distortion. As with other vascular malformations, LMs exhibit commensurate growth with the child. However, although they are usually initially soft and fluctuant, they tend to become firm and lumpy

with time, particularly after respiratory tract infections. Interestingly, these events may also lead to sclerosis within the lymphatics and eventual reduction in size, although the disease does not regress *per se*.

Several classification systems exist based on location. We prefer the dichotomous type 1 and type 2. Type 1 lesions are found below the level of the mylohyoid muscle, in the anterior and posterior triangles of the neck (Figure 42.6). They are more often predominantly macrocystic, and have a better prognosis. Type 2 lesions are found above the mylohyoid, involving the oral cavity, cheek and parotid regions (Figure 42.7). They are more microcystic, responding less well to treatment. In reality, a number of patients have cervicofacial disease of both types.

Alternatively, the De Serres staging proposal has been used.[38] LMs are staged I–IV:

- **Stage I:** unilateral infrahyoid
- **Stage II:** unilateral suprahyoid
- **Stage III:** unilateral suprahyoid and infrahyoid
- **Stage IV:** bilateral suprahyoid.

These stages correspond to the cyst size, functional deficits and treatment complexity associated with the distribution of disease. Low and lateral disease is generally macrocystic, relatively easily managed by surgery or sclerotherapy, with cosmetic but less significant functional deficits. High and medial disease is typically microcystic, involves the face and/or upper aerodigestive tract, and may require tracheostomy and long-term, multimodality treatment.

The diagnosis is usually obvious clinically, although single large cysts may be mistaken for other pathology in particular areas. These include the floor of mouth (ranula) and the lateral neck (branchial cyst, thymic cyst), for example. Imaging (particularly T2-weighted MRI) is useful in these circumstances, especially when treatment is considered, although the diagnosis may remain in doubt in some cases (see Figure 42.7). MRI will certainly help to differentiate macro- and microcystic disease, as well as demonstrating relations to surrounding structures, informing further management.

TREATMENT

As in the case of other vascular malformations, we manage LMs in a multidisciplinary setting. The most appropriate treatment options will be directed by age, the nature of the disease, related symptoms and the wishes of the parents and child. Some smaller, asymptomatic LMs may require no treatment at all, and are simply monitored, but the majority will require some form of therapy, because of relentless increase in size.

In terms of active treatment, our main options are sclerotherapy and surgery, used in isolation[37] or in combination.[36] In broad terms, surgical excision is the only means of achieving complete elimination of disease and cure, thereby offering a one-stop treatment option in selected cases (see Figure 42.6). In reality, the mixed cystic nature of many LMs and their complex anatomy means that they often require multimodality management, delivered in multiple stages. It should also be borne in mind that LM may cause significant bulk-related complications, such as airway obstruction, particularly in the neonatal period. Urgent interventions, such as tracheostomy and debulking surgery, may be required in advance of attempts at definitive treatment.

Sclerotherapy is performed by interventional radiologists under general anaesthesia, with fluoroscopic control. This form of treatment may be used at any time, including the neonatal period, as required. OK-432 (Picibanil, an inactive strain of group A *Streptococcus pyogenes*) was commonly

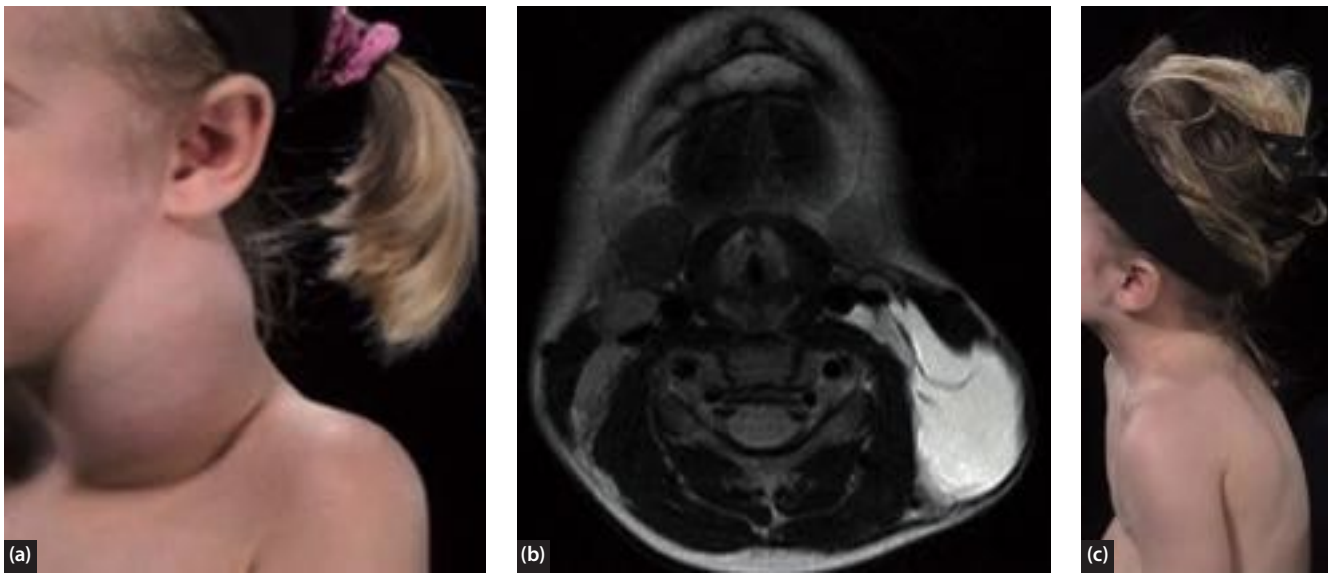


Figure 42.6 Lymphatic malformation: macrocystic, cervical disease (type 1). (a) Clinical appearance, aged 3 years. **(b)** Axial T2-weighted MRI of the same patient. The lesion consists of a few large fluid-filled cysts, of high-signal intensity, in the posterior triangle of the neck. **(c)** Appearance 3 months after uncomplicated surgical excision.



Figure 42.7 Mixed micro- and macrocystic lymphatic malformation of the tongue, floor of the mouth and upper neck (type 2 disease) in a 1-year-old infant (tracheostomized). (a) Gross enlargement of the tongue, protruding further as a result of disease in the floor of mouth. Note the microcystic disease on the dorsum, amenable to radiofrequency ablation (coblation). **(b)** Coronal T1-weighted MRI of the same patient, demonstrating mixed type 2 disease. **(c)** Immediate post-operative appearance following tongue reduction surgery (anterior wedge plus excision of a central core of tongue disease) and transoral floor of mouth clearance.

used until recently,[36] but has been discontinued owing to a lack of supply and withdrawal of USFDA approval for any indication. Our agent of choice is now 3% STS, injected as a foam. This is injected directly into larger cysts after aspiration of fluid, resulting in an inflammatory response with subsequent fibrosis and sclerosis. Multiple treatments are usually required, at intervals of a few weeks or months, since deeper parts of the malformations are difficult to access reliably. Such treatment is generally not beneficial for microcystic disease, as the penetration into adjacent areas is poor. Similar possible side effects may occur as for sclerotherapy to venous malformations. Parents and clinicians should be particularly aware of the likelihood of gross swelling of the injected areas after treatment, risking airway obstruction and worsening deformity.

Surgery may be performed with different objectives in mind. In some circumstances, particularly in the context of localized macrocystic disease of the neck, a single excision procedure may be straightforward and curative. Alternatively, debulking procedures, including in the neonatal period, will allow removal of an area of relatively accessible disease in order to preserve function. In our practice, the anterior cervical portion of large cervicofacial LMs may be cleared in this way within the first few days of life, with limited risk of neurovascular injury. This may obviate the need for tracheostomy, leaving the facial/parotid disease component to be addressed when the child is older and larger, such that the risks to the facial nerve and other structures are reduced. Transoral approaches may be necessary for disease of the tongue and sublingual regions, which is typically microcystic. Mucosal incisions through the floor of mouth, preserving the submandibular ducts and lingual nerves, allow safe access to sublingual disease. Tongue base and mucosal lesions have been treated with partial glossectomy (see **Figure 42.7**), laser or monopolar diathermy in the past, although we now favour Coblation® (radiofrequency ablation), which avoids lateral thermal injury and allows rapid recovery.[39]

For extensive, mixed disease, a combination of surgery for microcystic areas and sclerotherapy for larger cysts is usually undertaken. The relative merits of the different modalities at each stage of life will vary according to the patient and their disease. Apart from a comprehensive multidisciplinary approach, it is essential that parents are fully aware of the scope of each treatment, risks, prognosis and the long-term management entailed.

FAST-FLOW VASCULAR MALFORMATIONS

This group of lesions, like other vascular malformations, are congenital but may go unrecognized for several years, typically presenting in childhood or adolescence. They are distinguished by characteristics related to high blood flow, such as palpable thrills, audible bruits, warmth and redness.

Arteriovenous malformations

Although the ISSVA classification distinguishes a number of fast-flow malformations,[4] the majority have connections between arterial feeders and draining venous systems, centred on a nidus, and are therefore arteriovenous malformations (AVMs) rather than purely arterial lesions (Figure 42.8). Although far rarer in the head and neck than their slow-flow counterparts, AVMs are 20 times commoner within the cranial cavity. Growth is typically relentless but steady, with periods of acceleration in response to trauma, infection and hormonal changes of puberty. Many patients remain asymptomatic for some time, even into adulthood, but given their typical location, these lesions may rapidly produce significant sequelae and life-threatening complications including neural compression and high output cardiac failure. Schobinger in 1990 proposed a clinical staging classification for AVM, illustrating their natural history:[40]

- **Stage I:** Quiescence. Pink-bluish stain, warmth, AV shunt on Doppler
- **Stage II:** Expansion. As per stage I, with enlargement, pulsation, thrills/bruits and tense, tortuous veins
- **Stage III:** Destruction. As per stage II, with dystrophic skin changes, ulceration, necrosis, bleeding, pain
- **Stage IV:** Decompensation. As per stage III, plus cardiac failure.

MANAGEMENT

Owing to their location and possible complications, AVMs particularly demand a multidisciplinary approach to management at a specialist centre. Initial imaging is essential, typically involving ultrasound and colour Doppler to determine flow characteristics and fistulae, and MRI to evaluate extent. In contrast to the situation for slow-flow malformations, angiography is very useful to further delineate vascular anatomy, while also allowing access for embolization if required.

Asymptomatic AVM may be monitored, although the clinicians and family should be aware of the risks of accelerated growth, making the clinical picture and its management more hazardous.[41, 42] The development of symptoms, both local and distal, will often prompt active treatment although this may itself be extremely challenging. The only reliable cure is complete excision of the central nidus and network of vessels, although in the head and neck and especially intracranially this may prove impossible. Benefits of surgery must be assessed against major risks, including death in some cases. Pre-operative embolization may be undertaken 24–72 hours pre-operatively to reduce blood loss.

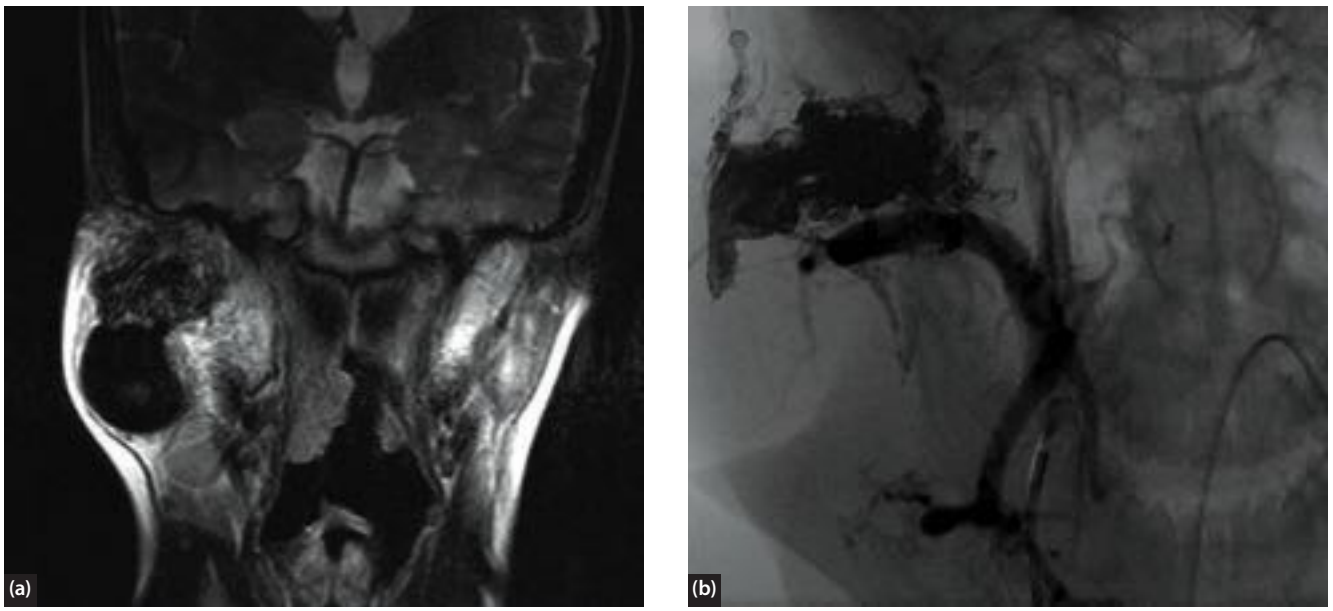


Figure 42.8 Large right arteriovenous malformation in a 15-year-old male. **(a)** Coronal T2-weighted MRI, demonstrating a large flow void (the nidus), and numerous interconnections with other vessels. **(b)** Angiographic appearance at the time of embolization. The nidus is clearly seen, along with multiple arteriovenous anastomoses with intra- and extracranial vessels.

Partial excision is ineffective, as new vascular channels will almost certainly develop. This is also true for embolization with curative intent. However, repeated trials of embolization may be used to palliate symptoms such as recurrent major epistaxis although this treatment carries risks including cerebrovascular thromboembolism and blindness. The relative merits of the various active therapies, as well as palliative options, must be communicated effectively with the patient and family.

COMPLEX COMBINED VASCULAR MALFORMATIONS

A number of complex malformations are possible, comprising various slow- and fast-flow subtypes and combinations of the two. Although the lesions themselves may differ in terms of presentation and behaviour, the principles of investigation and management are similar.

KEY POINTS

- Vascular anomalies, comprising vascular tumours and vascular malformations, are congenital lesions with complex underlying pathology, which account for a variety of presentations.
- Recent advances in histopathology and histochemistry, together with an evolving appreciation of their varied biological behaviour, have enabled precise classification of these lesions, replacing previous redundant and ambiguous nomenclature.
- A comprehensive understanding of these lesions is fundamental to accurate diagnosis and successful multidisciplinary management.

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CHAPTER 43

DROOLING AND ASPIRATION

Haytham Kubba and Katherine Ong

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SEARCH STRATEGY

Data in this chapter may be updated by an Ovid Medline search using the keywords: sialorrhoea (and its American spelling), drooling, saliva, hypersalivation and aspiration, supplemented by articles from the authors' own libraries.

DEFINITIONS

Sialorrhoea or **drooling** is the involuntary loss of saliva from the mouth. It is a normal feature of infancy but becomes rare in normal children as they develop oral motor control, sensory awareness and appreciation of social norms. Drooling beyond the age of 4 years is considered abnormal.

Anterior drooling, which is just another term for sialorrhoea, can be distinguished from **posterior drooling**, which is the spillage of saliva into the pharynx. Posterior drooling leads to an increased risk of aspiration. Aspiration of saliva typically presents with coughing and choking, often most obvious when the child is lying supine in bed, as well as recurrent pneumonias and concurrent evidence of aspiration of food and drink.

Drooling is distinct from **hypersalivation**, which is the excessive production of saliva. The majority of children who drool do not hypersalivate so the terms are not interchangeable.

CAUSES

Drooling may be a normal feature in young children up to the age of 4 years, and occasionally slightly older than this in children whose development is otherwise normal. Some children have a delay in achieving this particular motor milestone, perhaps due to a lack of awareness of social niceties but without any obvious physical deficit. The prognosis for these children is good and few require more than simple reminders and cues.[1]

Generally speaking, drooling is the result of a swallowing disorder, due to an impairment of the oral phase of the swallow. Inability to maintain lip closure, altered tone in the oral musculature, impaired oral sensation and difficulties controlling tongue movements all can lead to reduced frequency and efficiency of the swallow.[2–5]

Drooling accompanied by unclear speech (dysarthria) and difficulty chewing solid food may be labelled **oromotor dyspraxia**. The oromotor problems may be quite significant, with some children unable to manipulate food in the mouth with the tongue, resorting to pushing the food around their mouths with a finger. However, the problem is specific to the oral cavity and these children typically have no other developmental issues.

The majority of children who drool also present with other associated disorders affecting general development and muscle control, typically cerebral palsy. The drooling is primarily a motor issue. The drooling is not associated with any structural difference in the saliva glands[6] or in the amount of saliva produced.[2–4] Aspiration is a feature in those with bulbar palsy.

Some children (such as those with autistic spectrum disorders and intellectual disability) will drool because of a lack of awareness that saliva is pooling in the mouth or that the chin is wet, and that this is not socially acceptable. This is primarily a sensory issue.

In fact, most children who drool present with some combination of both a sensory issue and a motor impairment affecting their swallow.

PREVALENCE

Drooling is a common problem in children with neurodisability, although most do not receive any medical attention for this. Parents do not always know that effective treatments are available, or it may be that the family doctor, paediatrician or otolaryngologist does not know enough about the problem to make a recommendation. In 2005, we conducted a survey of 358 children in the 17 special schools for children with complex disability in the city of Glasgow. Twenty-six per cent suffered from sialorrhoea, most of moderate or severe degree, and this was most common in those with cerebral palsy. Only 21% had previously sought medical attention for the problem (J. Leonard and H. Kubba, unpublished data). Other studies have found prevalence figures of 40–58% specifically in children with cerebral palsy.[2, 7–9]

IMPACT ON THE CHILD AND FAMILY

Drooling might be seen as a trivial problem, especially for children with complex disabilities. Speaking to families, however, it becomes apparent that it has a surprisingly large impact on their day-to-day life. Children who are aware of their problem are very embarrassed and sialorrhoea is a very visible sign that they are 'different'. They may suffer discomfort from skin excoriation on the face or from having wet clothes. They are often avoided by their peers in school or nursery and they receive fewer physical displays of affection from their family members such as hugs and kisses. Families often restrict social activities such as visiting relatives or going out to eat. Frequent changes of clothes are a major time burden, and there is a significant cost associated with frequent washing and replacement of clothes. The impact of drooling is obvious and measurable[10–12] and treatment of the drooling, whether medical or surgical, can result in substantial improvements in quality of life for both child and family, and in the child's social interactions with their peers.[13–15]

THE MULTIDISCIPLINARY CLINIC

In most places, no coordinated care exists for saliva control problems and paediatricians see too few children with drooling to build up any useful experience.[16] A child with sialorrhoea can potentially seek help from a number of different specialists, each of whom might have only limited treatment options available. Treatment would depend on which specialist saw the child rather than which treatment would be best for the child. Thus, if the child sees a speech and language therapist, only exercises would be offered. If the child sees a paediatrician, only anticholinergic drugs would be offered. If the child sees a neurologist, only Botox injections would be offered, and if the child sees a surgeon, only surgery would be offered. There is a saying, 'When all you have is a hammer, everything looks like a nail.'

As a response to this problem, many children's services have set up multidisciplinary clinics for saliva control,[17, 18] mostly modelled on the service set up in the early 1970s at the Toronto Hospital for Sick Children.[19] Various specialists may be involved including developmental paediatricians, speech and language therapists, otolaryngologists, orthodontists and dentists. All benefit from having a variety of skills available so that all treatment modalities can be discussed and offered, including behavioural therapies, drugs, botulinum toxin injections, oral appliances, orthodontics and surgery, along with assessment of swallowing and dental health. Treatments are offered in a stepwise, progressive fashion starting with the least invasive options and tailoring the treatment to the specific circumstances of the child (**Figure 43.1**).[18–21]

HISTORY AND EXAMINATION

Look for evidence of aspiration

About a third of the children seen in the clinic aspirate as well as drool. This may be evident from a history of coughing and choking (often most evident at night) or frequent chest infections, or it may be evident on a clinical swallow assessment. If there is any doubt, a videofluoroscopic swallowing study (VFSS, also known as a modified barium swallow), or a fibre-optic endoscopic evaluation of swallow (FEES) should be performed (see below). The presence of aspiration makes a difference to almost all of the decision-making in the clinic. Children who do not aspirate can be safely observed, and there is plenty of time to see the effects of general growth and development on oral motor skills therapy: non-invasive treatments may be reasonable but surgery should not be performed until the child is at least 6 years old. If the child aspirates, however, intervention should not be delayed and the best chance of preserving lung function in the long term comes from aggressive management of the aspiration before 4 years of age.[22]

Assess general development

Most children with sialorrhoea will have general developmental delay often associated with a neurological disorder such as cerebral palsy. Cerebral palsy is a diagnosis that includes children with a very broad range of abilities and prognoses so it is good to ask a few questions about feeding, mobility, speech and communication.

For children with no known underlying neurological diagnosis, it is worth asking a few questions about speech, chewing, swallowing, social interaction and general developmental milestones. In young children there may be early signs of an autistic spectrum disorder or a specific oromotor dyspraxia that are only now becoming evident.

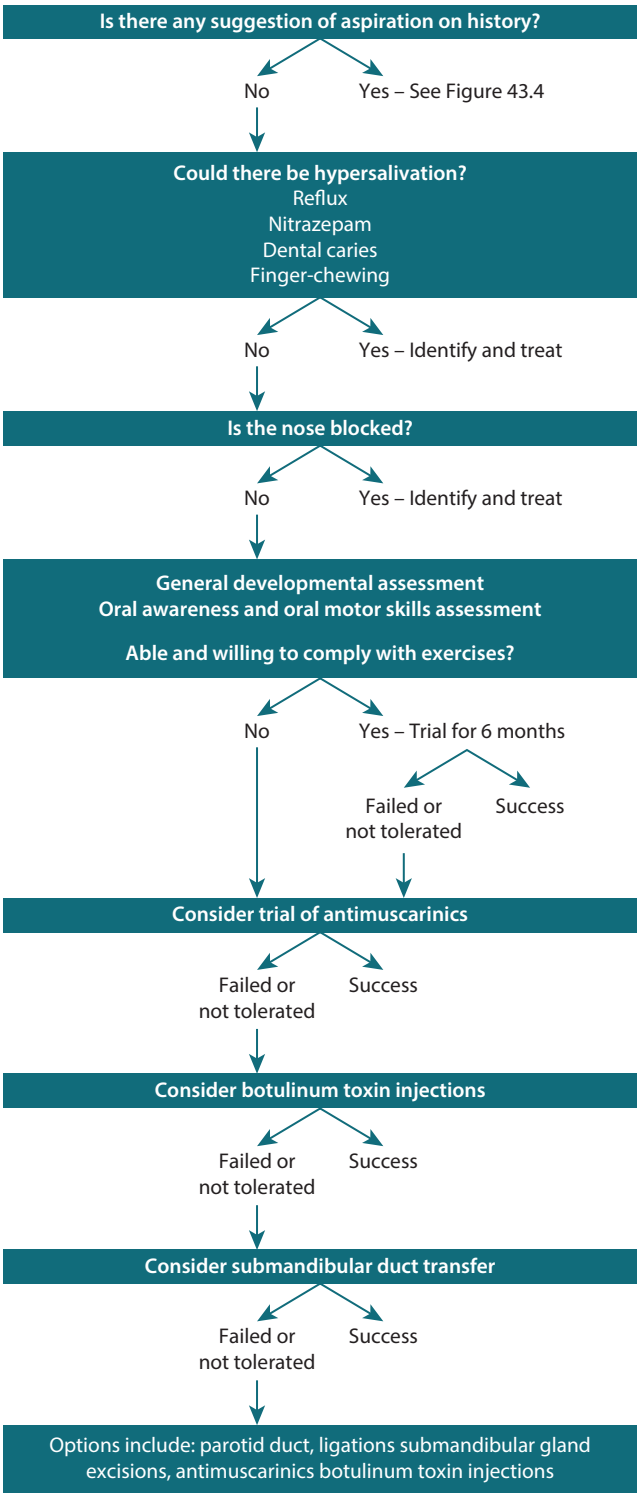


Figure 43.1 A suggested protocol for assessment and stepwise, progressive management of drooling in children.

Look for causes of hypersalivation

Most children with drooling produce a normal volume of saliva; the problem is in controlling it. There are some children, however, who genuinely produce too much saliva (true hypersalivation). This includes children with dyskinetic cerebral palsy, where hyperkinetic oral movements increase saliva production.[3] Other causes include habitual finger-chewing, dental decay, gastro-oesophageal reflux and drugs (particularly nitrazepam, often used for seizures). Where possible, these issues should be addressed before embarking on specific treatments for the sialorrhoea, otherwise success is unlikely. If the child requires nitrazepam for seizure control, there is not much we can do except to warn the family that interventions for saliva control are unlikely to control the problem completely, although they may still be worthwhile. If dental caries are found on examination, a referral for dental care should be the first step before any specific measures are undertaken for the saliva. With regard to reflux, there is a randomized controlled trial of cisapride and ranitidine therapy in children with drooling and proven reflux oesophagitis[23] that did not show any benefit for the drooling. Whether more modern drug treatments (specifically, proton pump inhibitors) would be beneficial is unknown, and there are anecdotal reports of reflux surgery (fundoplication) curing drooling that had been refractory to other measures.[18]

Look for causes of an open-mouth posture

The inability to form or maintain a lip seal is one of the most important factors producing a tendency to drool.[2, 5] Nasal obstruction will, of course, lead to a persistent open-mouth posture and this alone can lead to a significant drooling problem in young children. It should be straightforward to identify features of adenoid hypertrophy or perennial rhinitis on history and examination, and these should be treated on their own merits. In the Glasgow saliva control clinic series, 12% of children had adenoidectomy (with or without tonsillectomy) as the only treatment required for drooling.[18]

An open-mouth posture can also be caused by dental malocclusion, typically an anterior open bite, and the advice of an orthodontist can be very useful.

Many children seen in the clinic (particularly those with quadriplegic cerebral palsy who are in a wheelchair) have very poor posture due to inadequate support of the trunk and head (**Figure 43.2**). Poor trunk support leads to poor



Figure 43.2 Child with cerebral palsy showing poor posture due to poor trunk support in the wheelchair.

head control, which in turn leads to poor jaw control. No progress will be made with salivary continence until the trunk and neck are stable. The wheelchair may need to be modified or replaced. For children with a specific problem of drooling onto schoolbooks or a computer keyboard when they lean forward, use of a slant board is a very simple and effective way to lift and angle the book or computer to encourage a more upright head posture.

INVESTIGATIONS

In routine clinical practice, it is not common for clinicians to measure the severity of the drooling issue although there are certainly a few ways to do this. The simplest is to ask about frequency of bib changes or changes of clothing, but this is very subjective. The Teacher's drooling scale rates frequency of drooling on a scale of 1 to 5. The Drooling Severity and Frequency Scale (DSFS) takes this concept a little further by rating severity of drooling 1–5 and frequency 1–4 and then adding the two together.[24] The drooling quotient (DQ) measures the frequency of drooling in two standardized periods of 5 minutes (one at rest, one at play) with the child sitting up and at least 1 hour after meals. Every 15 seconds, the rater scores whether new saliva has appeared at the lips and the proportion of positive 15-second episodes is converted to a scale of 0–100.[25] This is obviously more time-consuming and difficult to measure than the simple rating scales mentioned above and it appears the DSFS correlates well enough with the DQ to be a good proxy in clinical practice.[26]

Symptom questionnaires and quality of life (QOL) scores have been developed in an attempt to capture the wider impact of the drooling on the child and family.[11, 12]

Various techniques exist to measure salivary flow including weighing cotton swabs that have been placed in the floor of mouth, or technetium scintigraphy, but salivary flow is rarely a useful measure in the context of the drooling child.

The most important area for investigation is in the context of aspiration. The presence or absence of aspiration has a big influence on decision-making and therefore it is crucial to complete a clinical assessment of the swallow (including neck auscultation) by an experienced speech and language therapist whenever aspiration is suspected, supplemented by either VFSS or FEES. VFSS involves X-ray screening while the child swallows various fluid or solid food textures mixed with barium. FEES uses transnasal flexible fibre-optic nasopharyngoscopy to achieve similar results, namely an assessment of the pharyngeal phase of swallow, in particular the presence of preswallow pooling, laryngeal penetration and/or aspiration, and post-swallow residue.

In most cases where aspiration is identified, a neurological cause will be evident. Where no neurological cause is known and an anatomical issue is suspected microlaryngobronchoscopy under general anaesthetic is mandatory to rule out laryngeal cleft or H-type tracheo-oesophageal fistula since it would be tragic to miss such treatable causes of aspiration and lung damage.

ROLE OF THE SPEECH AND LANGUAGE THERAPIST

It is very useful to have the opinion of an experienced speech and language therapist in clinic. They can assess oral motor skills appropriate for the child's age and development, and can judge likely ability and motivation to comply with behavioural therapy. They can also assess the safety of the swallow and risk of aspiration. Associated issues with speech and chewing can also be addressed.

Activities to increase oral awareness include water play to teach the concepts of 'wet' and 'dry' and the use of a mirror to provide visual feedback. Parents can incorporate exercises into play, such as blowing bubbles or toy trumpets. They can also encourage straw drinking, ensuring the straw is held in the lips only (not in the teeth) and progressively lengthening the straw over a period of weeks and using thicker drinks such as fruit smoothie or milkshake.

Issues with jaw strength and stability can be addressed through graduated strengthening exercises such as holding a chewy tube between the molar teeth against resistance as the therapist tries to gently pull the tube out of the mouth. Lip strength can be improved by holding a wooden tongue depressor between the lips for increasing lengths of time.

Behavioural modification may involve giving verbal cues to swallow or wipe, together with positive and negative reinforcement. So, for example, the child may enjoy reading a bedtime story and may be cued to swallow and/or wipe at the end of every page. Towelling sports wristbands can be very practical for wiping but also serve as a visual reminder of the need to wipe or swallow. Auditory cues to wipe and swallow, such as the timer on a microwave oven or the phone app 'Swallow Prompt' can also be used.

All these interventions rely on a degree of cooperation from the child and so are only of use in cognitively able children. With children who are able to comply, it is essential to have at least 6 months of speech and language therapy intervention before considering invasive treatment such as surgery.

There is no strong evidence base for any of these interventions, with clinical practice based on theory and experience rather than any controlled clinical studies.[27]

ROLE OF DENTAL AND ORTHODONTAL SERVICES

It can be very helpful to have the advice of a dentist. Dental caries can be a cause of salivary stimulation leading to hypersalivation. Restorations, extractions and advice on dental hygiene should precede any other interventions for drooling if this is the case.

Drooling does not itself predispose to dental caries[28] but all forms of saliva reduction treatment do, including drugs, botulinum toxin injections and surgery.[29, 30] Saliva has a protective effect for the teeth so families should be warned that treatment for drooling puts the child at greater risk for dental caries. Teeth should be brushed

twice a day with a fluoride toothpaste and there should be dental check-ups every 6 months, with preventative treatments such as fissure seals if appropriate.

Orthodontists can assess those children for whom malocclusion is a contributory factor to persistent open-mouth posture. In addition, there are some enthusiasts for the use of intraoral appliances, such as the ISMAR (Innsbruck Sensory Motor Activator and Regulator) to treat drooling. The device looks much like a dental retainer with an acrylic plate covering the hard palate, held in place with wires around the teeth. A projection is added to the posterior edge with a rotating bead which stimulates the soft palate and tongue to initiate a swallow. Only about a third of children with cerebral palsy will tolerate such a device but, in those who do, significant improvements are seen in eating and drooling.[31]

PHARMACOLOGICAL TREATMENTS

Antimuscarinic (less accurately known as anticholinergic) medication is by far the most common treatment used for drooling. These drugs stop acetylcholine from binding to receptors in nerve cells and therefore have wide-ranging effects on the central and peripheral nervous systems. In the context of saliva control, the effect of the drugs is to reduce the volume of salivary secretions. In doing so the saliva is also thickened and this can be unpleasant. Side effects are common and include dry eyes, dilated pupils with intolerance to bright light and impaired vision, constipation, urinary retention, worsening of seizure control, hallucinations and changes in sleep and behaviour. Anyone prescribing these drugs should be aware of their side-effect profile and should be able to discuss the recognition and management of side effects with the family. Some of these side effects are quite serious. As examples, impaired bladder emptying may lead to frequent urinary tract infections and any suspicion of this should be investigated with a post-micturition ultrasound of the bladder and measurement of residual volume. Constipation is common and sounds trivial but antimuscarinic treatment has been associated with toxic megacolon requiring defunctioning colostomy.[32] Optometry and sometimes ophthalmology advice may need to be sought for visual problems.[33]

Various drugs are in use and their names can be confusing. The most commonly used are hyoscine hydrobromide (also known as scopolamine hydrobromide but distinct from hyoscine butylbromide, which is not used for this indication), glycopyrronium bromide and trihexyphenidyl hydrochloride (also known as benzhexol hydrochloride). There are also anecdotal reports of atropine eye drops being used sublingually for drooling.[34]

A UK survey of paediatricians showed that hyoscine hydrobromide transdermal patches are the first-line treatment for most, with oral (or gastrostomy) glycopyrronium bromide second-line.[16] Hyoscine hydrobromide patches have the advantage of effectiveness and ease of use.[35] They can be applied to any area of thin, hairless skin and changed every 3 days. They are waterproof enough to survive showering. Their main drawback is their high incidence of significant side effects, up to 71% in one series.[36] Skin reactions to the adhesive are common and cessation of patch therapy is required. The other significant drawback is that it is awkward to adjust the dose for the age and size of the child. A full patch every 3 days is appropriate for most children of high school age but this would be too much for younger children, for whom half or even a quarter of a patch would be more appropriate. The patches can be cut with scissors but the dose release mechanism then becomes very unpredictable. Placing the patch over an occlusive dressing so that only half is in contact with the skin may lead to more controlled dosing but it is fiddly for parents to do this. Oral hyoscine hydrobromide seems anecdotally to be much less effective than the patch.

Trihexyphenidyl hydrochloride has the advantage of availability in syrup form, which makes for convenient dosing via the oral or gastrostomy route. The dose can be easily adjusted according to response up to a maximum of 2 mg/kg/day in two or three divided doses.

Glycopyrronium bromide is available as an oral solution and is very effective.[37] It has the distinct advantage of not crossing the blood–brain barrier unlike atropine, hyoscine and trihexyphenidyl. This should lead to significantly fewer central side effects although peripheral effects (on bladder, bowel, sweat glands and eyes) will still be seen and 20% of children will have to stop using the drug due to side effects.[38]

Our own experience in the Glasgow saliva control clinic has been that 45% of children discontinue transdermal hyoscine due to side effects, compared with 15% for trihexyphenidyl and 6% for glycopyrronium.[18] About half the adverse reactions to hyoscine patches were skin reactions to the adhesive: the remainder were visual problems, behaviour change and hyperactivity, constipation, urinary retention and sleep disturbance. Overall, only half the children who commenced antimuscarinics continued to use them as their definitive long-term therapy, the remainder moving on to more invasive options as outlined below.

BOTULINUM TOXIN INJECTIONS

Botulinum toxins are neurotoxic proteins produced by *Clostridium botulinum* bacteria. There are seven types of toxin but only A and B are used medically. The toxins produce their effect by blocking acteylcholine release from axons at the neuromuscular junction causing muscle paralysis. Their use in saliva control comes from their ability to block release of acetylcholine from parasympathetic secretomotor nerves in the salivary glands.

There is a variety of different brands of botulinum toxin available on the market and they are not interchangeable. Dosing is specific to each manufacturer and cannot easily be extrapolated from one brand to another as each has a protein of a slightly different molecular weight and with different diffusion and pharmacokinetic profiles. Botox is the brand of botulinum toxin A made by Allergan. It is now referred to by the generic name onabotulinumtoxin A. Dysport now has the generic name abobotulinumtoxin A. Myobloc and Neurobloc have the generic name

rimabotulinumtoxin B. Onabotulinumtoxin A (Botox) is the most common agent used for saliva gland injections as it has the largest molecular weight: although this gives it the slowest onset of action, it may also help limit its radius of diffusion and therefore should, in theory, reduce the incidence of side effects from spread of the drug. In reality, no convincing difference in effect has been seen between the various preparations.[39,40] Clinicians should familiarize themselves with the dosing, administration and side-effect profile of one formulation of toxin (in this context, probably onabotulinumtoxin A) and only use alternatives if the child has developed antibodies to the toxin as shown by reduced clinical effect over time. Switching to an alternative toxin type can restore effectiveness very well when this occurs.

No consensus exists on which glands should be injected or on how much toxin should be put into each gland. Many clinicians will inject an equal amount (25% of the total dose) into each of the submandibular and parotid glands,[41] others will inject mostly the submandibular glands (66% of total dose) with the remainder into the parotids[42] and others even inject either the submandibular or parotid glands exclusively. Since the majority of resting saliva secretion is from the submandibular glands it makes sense to direct the injections there to some degree.

There is a little more agreement about total dose. For most children the optimal dose is 80–100 units of onabotulinumtoxin A (Botox)[43] or around 4 units/kg bodyweight for those less than age 4 years, with larger doses causing more side effects but not any increase in effectiveness.[42] The same is true for rimabotulinumtoxin B (Myobloc): increasing the dose above 3000 units causes increasing side effects without any benefit in success rate.[44]

Success is somewhat subjective but a worthwhile response usually occurs in 50–80%[45,46] with most large series reporting success in around two-thirds of cases.[36,41,42,47] The toxin can take 2–6 weeks to take maximum effect. The effect of the toxin is often detectable clinically up to 6 months from injection to some extent but the median duration of a worthwhile response, when it occurs, is around 4 months.[41,42,45,46] Very occasionally, repeated injections cause gland atrophy with prolonged responses up to 18 months reported.[42]

Side effects from botulinum toxin injections are less common than with antimuscarinics.[36] The most common and worrying is dysphagia. This is most often a transient phenomenon, lasting just a few days and only apparent if specifically asked about. More severe dysphagia can last for weeks or months and require tube feeding. Reported rates are 7% for transient dysphagia with no intervention required and 3% for severe dysphagia requiring tube feeding.[42,48] Children undergoing botulinum toxin injections often have an abnormal swallow to start with but, if they are only just managing to feed orally, botulinum toxin has significant potential to tip them over into a situation where nasogastric feeding is required. Oral feeding may then be difficult to re-establish. Recent international guidelines urge caution in the use of botulinum toxin in children with swallow impairment.[20] The ideal candidate for botulinum toxin is the child who is already tube-fed, in which case any transient worsening of swallow is unlikely to have a major impact. For those who are orally fed, the decision to use botulinum toxin is one that should be approached with caution and a full discussion of the potential risks.

Botulinum toxin thickens the saliva[49] but this is uncommon as a clinical issue, seen in only 1.5% of one large series.[42] Spread to cervical muscles may cause torticollis, seen in 0.5% of a series of injections done without ultrasound,[42] or even total head instability requiring hospitalization, seen in 4% of another series done with ultrasound.[48]

In most centres, botulinum toxin injections are done under ultrasound guidance. There is no doubt that ultrasound allows more accurate placement of injections but, since the toxin is known to spread through fascial planes up to 4.5 cm from the injection site,[50,51] it is unclear how much difference this actually makes in practice. When injection is done by anatomical landmarks alone (**Figure 43.3**),[42] the success rate is no different to that in series where ultrasound guidance is used.[36,41,45–47] The use of ultrasound has been reported to produce impressively few side effects in one series[52] but, in general, most series report similar rates of complications regardless of whether ultrasound is used.[42,48]

There is a drawback to using ultrasound, namely the time required to do the procedure and the consequent need for general anaesthesia or sedation. If injections can be achieved quickly and effectively by anatomical landmarks alone, skin anaesthesia with local anaesthetic cream is usually all that is required and general anaesthesia can be avoided in 75% of cases.[42] Obviously, careful patient selection is required to achieve rates as high as this, but the very children who are ideal for botulinum toxin injection on the grounds of being tube-fed are also more likely to be tolerant of (and possibly less aware of) awake injection. This makes repeated, regular injections a viable long-term treatment option for this select group of children. For those children who would not be tolerant of awake injection, serious consideration must be given as to whether it is reasonable to give a general anaesthetic to a child three times a year for salivary botulinum toxin



Figure 43.3 Botulinum toxin injection into the left submandibular gland by palpation of landmarks, in this case under general anaesthesia.

injections on a long-term basis. Some clinicians do this but many would judge it inappropriate. There are those who perform botulinum toxin injections just once as a way to select candidates for a permanent surgical procedure, on the assumption that a response to botulinum toxin predicts a good response from surgery.[53] There is no evidence for this assumption and in fact many children with a poor response to botulinum toxin injection will go on to have surgery with good effect.[18]

In order to minimize complications, it is important to consider which botulinum toxin preparation to use (small molecules spread further) and to place the injections accurately. Also very important is the dilution of the toxin. More dilute preparations spread further[54] so the toxin should be made up with no more than 2 mL of saline in total.

There is a group of children, about a third of all those injected, who do not seem to respond to the toxin very well. Children who respond well to the first injection tend to respond well to subsequent ones, whereas those who do not respond well to the first injection tend not to respond well to subsequent injections, suggesting there are features intrinsic to the child which affect response.[42] The effectiveness of the botulinum toxin is not related to cerebral palsy subtype or clinical features[55, 56] and we do not yet understand why some children respond and others do not.

SURGERY

Anything from 22% to 47% of patients attending a multidisciplinary drooling service will end up undergoing surgery at some point in their treatment, usually once more conservative options have been exhausted.[17, 18] Surgery, of course, includes adenoidectomy for nasal obstruction and fundoplication for intractable reflux, but in this section we will consider specific salivary procedures only. Surgery has an advantage over botulinum toxin in that it is a one-off intervention with long-lasting results,[57] but obviously surgery comes with risks and discomforts and the need for a general anaesthetic.

The most important distinction to make is whether or not the child is at risk of aspiration. A swallowing assessment by a speech and language therapist is invaluable and, if there is any doubt, VFSS or FEES should be completed. For children who are not at risk of aspiration, the best long-term results come from bilateral submandibular duct transfer. The operation requires no external incision and is done entirely intraorally. The submandibular ducts are dissected free and tunnelled submucosally to the inferior border of the tonsil fossa where they are sutured in place behind the anterior pillar. The operation causes considerable pain and discomfort and it is not unusual for children to require 3–4 days in hospital for post-operative analgesia. Recovery usually takes 3 weeks. Families and children need to have a full and frank discussion of the likely post-operative pain before agreeing to surgery. This surgery should not usually be done in children who still have time to develop oral continence on their own, i.e. it would rarely be offered below the age of 6 years. Success from surgery is quite subjective to measure, but substantial or complete resolution of drooling can be expected in 80–88% of cases[18, 29, 58–61] and the results are well maintained when assessed 5–15 years later.[29, 58, 61–63] The main determinant of outcome is the severity of the child's underlying neurological disability[59, 60, 64] so the ideal candidates are those with reasonable swallow function, such as those with milder cerebral palsy (diplegic or hemiplegic) or oromotor dyspraxia.[65]

The most common complication of submandibular duct transfer surgery is ranula formation due to obstruction of drainage from the sublingual glands. This affects 4–20% of children after surgery.[59, 60, 61, 63] and on that basis many surgeons elect to excise the sublingual glands at the same time as the duct transfer. This prevents the ranulas but at the expense of longer operating times, greater blood loss, more pain and longer hospital stay.[66] Excision of the sublingual glands makes no difference to the control of drooling.[64, 66]

Another common complication from submandibular duct transfer is swelling of the submandibular gland, which may be transient or persistent. It occurs in 2–22% of cases[59, 60, 61] and the gland may need to be excised if the swelling is troublesome. Careful handling to prevent injury or twisting of the duct during surgery helps to reduce the incidence. Dry mouth is rare in most series but has been reported to occur in 10% by one author who also reported dental caries in 3% after surgery.[29] Aspiration pneumonia after surgery can be disastrous but should be rare if patient selection has been appropriate and aspiration excluded, although it certainly does still occur.[62, 63] Tongue swelling, lingual nerve injury and troublesome bleeding have also been reported.[62]

The morbidity from duct transfer has led to various alternative procedures being popularized. Four-duct ligation (parotid and submandibular ducts bilaterally) is very easy and very quick with little immediate post-operative morbidity.[67, 68] The initial results are similar to those of duct transfer (success 81%, ranula 10%, submandibular gland swelling 15%)[69] but the long-term results are poor, as the ducts tend to recanalize.[70, 71] Submandibular gland excision (with or without concomitant ligation of the parotid ducts) is effective for drooling[72, 73] and is a reasonable alternative to duct transfer. Surgeons have probably avoided it due to concerns about leaving two visible scars in the neck, but carers don't seem to mind the scars as much as we might think.[74] Tympanic neurectomy (transtympanic sectioning of Jacobson's nerve and the chorda tympani) has largely been abandoned due to poor results,[75, 76] as has cervical sympathectomy.[77] Parotid duct ligation has a role for salvage if initial submandibular duct transfer fails.[78]

CHRONIC ASPIRATION

Symptoms of aspiration should be actively sought in the history in all cases, particularly recurrent episodes of pneumonia or coughing and choking on secretions or drinks. A clinical swallowing assessment by an experienced speech and language therapist may be supplemented by VFSS or FEES to confirm the diagnosis. If no neurological cause

is obvious, a structural cause such as laryngeal cleft or H-type tracheo-oesophageal fistula should be actively excluded by means of microlaryngobronchoscopy under general anaesthesia (Figure 43.4).

Mild cases of aspiration can be managed by the speech and language therapist with advice on head positioning during swallow, modifications to food and drinks and other simple strategies. More severe cases will require restriction or complete cessation of oral intake with tube-feeding, usually by means of gastrostomy. If aspiration of gastric refluxate is an issue, fundoplication will often be performed at the same time as gastrostomy insertion. The role of the otolaryngologist in this context is to advance the case for fundoplication with the upper GI team, emphasizing that reflux could be contributing to the drooling and aspiration.

If aspiration of oral feed and gastric refluxate have been dealt with already, or if saliva is the obvious cause of coughing and choking, then saliva reduction becomes important. The younger the child is when saliva reduction is commenced, the more effective it is likely to be in reducing the frequency of pneumonia and preserving lung function.[22]

Management should occur in a stepwise fashion, starting with behavioural strategies and/or antimuscarinic drugs as the least invasive option. Botulinum toxin injections have been shown to reduce the symptoms of aspiration and to reduce the number of episodes of pneumonia and hospital admissions.[79, 80] If surgery is required, duct transfer would be disastrous and the only safe and effective option is bilateral submandibular gland excision with parotid duct ligation. This has been demonstrated to be effective in reducing episodes of pneumonia and hospital admissions.[81]

A small number of children with intractable aspiration have failed all other treatment modalities. In this circumstance, a permanent procedure to separate the air and food tracts can be truly life changing, albeit at the cost of a rather drastic operation and the loss of the ability to make voice. Most children with aspiration of this severity are non-verbal anyway and voice is not an issue. Laryngotracheal separation involves transecting the cervical trachea and bringing out the lower end as a permanent end-stoma. The upper end of the trachea can be closed off as a blind pouch or anastomosed end-to-side to the oesophagus. The procedure produces good results and may allow the resumption of oral feeds.[82, 83]

Total laryngectomy is technically simpler and heals predictably with few complications in the well child but has the disadvantage of being irreversible. Whether this matters in reality is debatable.

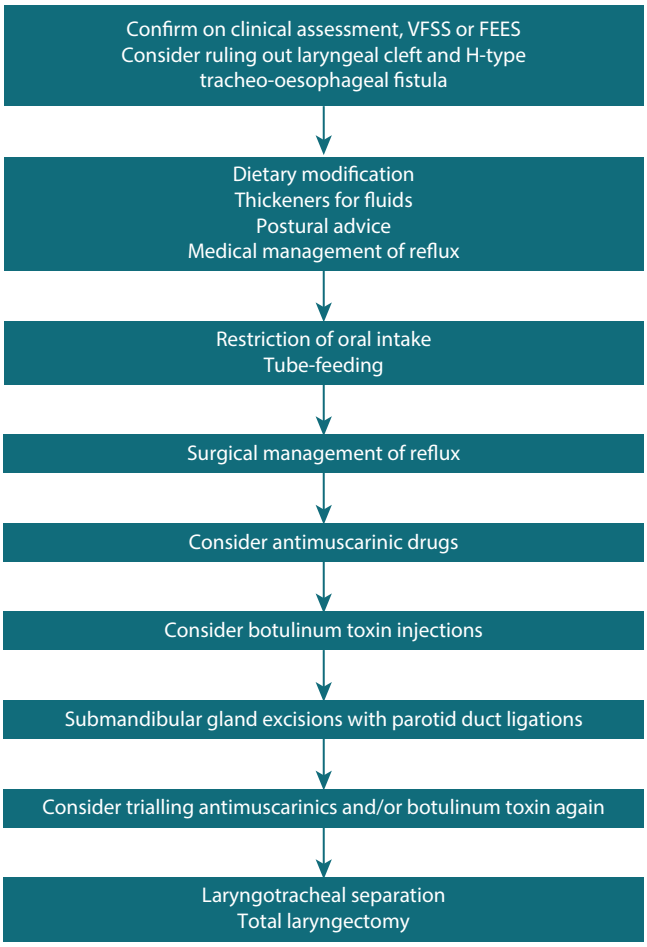


Figure 43.4 Progressive steps in the management of chronic aspiration.

BEST CLINICAL PRACTICE

- ✓ Assessment for aspiration is crucial in management and the advice of a speech and language therapist is invaluable.
- ✓ Causes of nasal obstruction and open-mouth posture should be sought and treated on their own merits.
- ✓ Drooling should be seen in the context of the child's overall development. If development is otherwise normal, the prognosis for the drooling is good.
- ✓ Speech and language therapy exercises require motivation and cooperation on the part of the child.
- ✓ Drugs, botulinum toxin and surgery all have drawbacks as well as potential benefits. The clinician should be able to discuss these with the family to help them make informed choices about treatment.

FUTURE RESEARCH

- ➤ None of the treatment options currently available is perfect and new therapies would be very welcome, particularly to reduce adverse effects.
- ➤ Reasonable evidence exists for the effectiveness and side-effect profile of each treatment modality in current use but studies are needed on treatment philosophies, pathways and decision-making.

KEY POINTS

- Drooling is common in children with neurodisability and it has a significant effect on quality of life.
- It is usually caused by poor swallowing.
- Oral exercises, antimuscarinic drugs, botulinum toxin injections and surgery each have a role in management.

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CHAPTER 44

REFLUX AND EOSINOPHILIC OESOPHAGITIS

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: laryngopharyngeal reflux, gastroesophageal reflux, eosininophilic esophagitis, pediatrics and otolaryngology.

INTRODUCTION

The appreciation of the role of reflux in the genesis and propagation of head and neck conditions in the child is a relatively new phenomenon. Over the last 35 years there have been a large number of papers published on the subject. Eosinophilic oesophagitis is an even more recent clinical entity. As gastro-oesophageal reflux disease and allergic disease increase in prevalence among the general population, it stands to reason that we would encounter both these entities more commonly in clinical practice. This and increased awareness have, indeed, led to this increase. Unfortunately, despite the recent large volume of literature, there remains significant confusion. There is as yet no clear robust causality demonstrated for any otolaryngological condition although there is plenty of evidence of association. There remains no 'gold standard' diagnostic test for extra-oesophageal reflux disease. Dual pH/impedance manometry seems the most helpful relatively objective test available, although normative data is lacking and agreed thresholds for pathology elude us.

That said, it is important to remember that we are relatively early in the understanding of the condition although huge strides have already been made. The evidence for the association of reflux in a large variety of conditions of the head and neck is compelling. There is also very encouraging clinical data that antireflux therapy is helpful, particularly in reflux-mediated airway disease.

This chapter attempts to pull together the current evidence in what is a rapidly evolving field. The challenges are explained and hopefully a working understanding of the field as it stands is presented.

TERMINOLOGY

Gastro-oesophageal reflux occurs when stomach contents travel in a retrograde direction above the level of the lower oesophageal sphincter. The 'refluxate' will usually contain hydrochloric acid and pepsin and may include bile and pancreatic enzymes. This may occur to some extent physiologically in which case it is known as gastro-oesophageal reflux (GOR). At the point at which the patient develops symptoms, signs or histological changes, the term gastro-oesophageal reflux disease (GORD) is used. This refluxate may travel the length of the oesophagus and emerge from the upper oesophageal sphincter and result in disease within the realm of the otolaryngologist, particularly at the level of the larynx. The term in widespread use for this phenomenon is laryngopharyngeal reflux (LPR). However, there is now a greater appreciation that this may impact not just the laryngopharynx but also areas such as the lingual tonsil, pharyngeal tonsils, sinuses,

Eustachian tubes and trachea. Hence a more appropriate term is extra-oesophageal reflux (EOR). The term extra-oesophageal reflux disease (EORD) may be used when this reflux causes symptoms and pathology. For reasons that will be explained, patients may have EORD in the absence of GORD.

Note: As there are regional variations to the spelling of oesophagus/esophagus, GER, GERD, EER and EE (eosinophilic esophagitis) are synonymous with GOR, GORD, EOR and EO (eosinophilic oesophagitis).

PHYSIOLOGY AND MECHANISM OF INJURY

It has been known for many years that the pharynx and particularly the glottis and subglottis are sensitive to the injurious effects of reflux. In a classic study from the 1960s, intermittent application of gastric acid on canine vocal cords produced granulomas which were histologically similar to that of subglottic stenosis.[1]

In another famous study Little[2] created a standard mucosal lesion in canine subglottic larynges, which were then exposed to gastric contents, over 3–4 weeks. This resulted in a nine-fold increase in subglottic stenosis when compared to saline controls. This occurred despite the fact that the exposure to gastric contents was only for 1 minute every other day.

This would suggest that, especially in the presence of mucosal trauma, even minimal reflux exposure might result in significant pathology. Mucosal trauma to the subglottis might occur after endotracheal intubation.

Both the pepsin[3] and the acid probably cause the deleterious effects to the mucosa although bile acids may also play a role. As pepsin works optimally in a low pH environment, acid suppression has been a mainstay of therapy. While pepsin is generally thought to be inactive at high pH levels, there is some evidence that it may be active up to pH 6.5 and may alter the stress protein response which protects epithelium from damage.[4] Cellular damage in cultured hypopharyngeal cells is seen after pepsin exposure at a pH of 7.4.[5]

Low pH causes a reduction in ciliary motility,[6] which may increase the exposure time and potentiate the inflammatory effects of reflux. This may promote cough or throat clearing which may increase the inflammation. Acidification of the lower oesophagus and micro-aspiration may lead to bronchospasm and pulmonary disease.[7]

In addition to direct mucosal effects, there are also chemoreflexic effects on cord mobility. Acid applied to the glottis of piglets causes fatal apnoeas.[8] This chemoreflexive apnoea seems to be vagally mediated. Stimulation of the lower oesophagus produces laryngeal adduction and laryngospasm in puppies.[9] There has been an awareness of reflux-induced awake apnoea for 30 years.[10]

There are therefore many local effects and chemoreflexic effects of EOR. The presence of GORD makes EORD more likely but, of course, not inevitable. However, due to the differences in the sensitivity of the substrate, EORD can and often does occur in the absence of GORD. These differences have led to confusion, especially when using parameters for GORD in the assessment of EORD.

HISTORY AND EXAMINATION

As with all conditions, a full history provides key clues to nature of the disease. If an infant has the typical symptoms of reflux such as emesis, regurgitation, burping, feed refusal and back arching, then the connection is generally easily made. Sandifer syndrome occurs in children with GORD and causes irritability, and regurgitation after feeds with episodes of arching, crying and torticollis. Older children may complain of heartburn, abdominal pain, hoarseness, throat clearing or chronic cough. It is important to recognize that the child with reflux may have none of these symptoms. The key is to have a high index of suspicion that the child's symptoms are related to reflux.

Signs of increased work of breathing such as a history of tracheal tug, subcostal or intercostal recession should be inquired about if not detected in the examination.

A sleep history should be taken. Apnoeic and cyanotic spells are always significant. Apparent life-threatening events (ATLEs) should also be noted.

Chronic cough, especially if it is nocturnal, may be related to reflux. An abnormal voice or cry may be a manifestation of reflux laryngitis.

The frequency and severity of emesis should be noted. A temporal relationship of airway symptoms to meals where present is suggestive of reflux (and/or aspiration). Wet-sounding respirations, cough or 'wet burps' are often present. Irritability and increased noisy breathing after feeds may be seen. The duration of feeds is an important marker of the severity of airway compromise. Infants with airway issues tend to take a long time to take a feed and feeds taking over 30-40 minutes are considered significant.

A history of recurrent pneumonias or croups with multiple hospitalizations or antibiotic courses is very relevant. Signs of neurological impairment could potentiate the effects of reflux. This is because pharyngeal hypotonia and uncoordinated swallowing will lead to pooling of secretions in the hypopharynx. This will increase the exposure time of the larynx to refluxate and increase the risk of aspiration.

The infant should be examined with regard to the airway. Stridor or stertor may not be present at rest but may become apparent if the infant becomes agitated during the examination. Tachypnoea should be noted and in infants may be associated with head bobbing. Signs of increased work of breathing, which includes sternal and subcostal recession, may be seen. A pectus excavatum should be noted. There may be a 'wet sound' heard from the throat. Examination should include examination of the oral cavity to assess tonsil size.

BOX 44.1 Possible symptoms of extra-oesophageal reflux in children[4]

Airway symptoms	Feeding problems	General ear, nose and throat symptoms
Cough	Dysphagia	Nasal obstruction/congestion
Throat clearing	Odynophagia	Nasal pain
Recurrent croup	Gagging	Snoring
Wheezing	Choking	Snorting
Cyanotic spells	Globus sensation	Postnasal drip
Noisy breathing – stertor/stridor	Failure to thrive	Drooling
Hiccups		Oral sores
Recurrent pneumonia		Halitosis
Hoarseness		Taste/tongue problems
Tracheostomy problems, e.g. stomal granulations		Otalgia
Gurgly respirations		
Apnoea		
Sleep-disordered breathing		

The child's height and weight should be noted and plotted on a centile chart to assess failure to thrive, which may serve as an indication to intervene.

The examination in the neonate and potentially in the older child is usually completed with an awake flexible fibre-optic nasopharyngoscopy. This will provide information about the nasopharynx and the larynx. It is the investigation of choice to assess cord mobility and is excellent at visualizing laryngomalacia. In order to assess the area below the glottis, a microlaryngotracheobronchoscopy (MLTB) is performed in a spontaneously breathing infant under general anaesthesia. This allows better optical examination as well as offering the opportunity to perform endoscopic interventions.

Possible symptoms of EOR in children are listed in Box 44.1.

INVESTIGATIONS

Within the realm of gastroenterology clear guidelines exist for what constitutes GORD[11] and what reflux index (RI) scores (see below) are pathological. It is clear that certain levels of reflux exposure to the oesophagus are physiological and not associated with pathology. In view of differences described earlier between the oesophagus and the pharynx and airway, it seems likely that lower levels of reflux exposure may cause disease in the pharynx than would cause disease in the oesophagus. Early authors suggested than any reflux exposure in the pharynx was abnormal[3, 12] although there is increasing awareness that this is likely not the case. In neonates, it is clearly recognized that a certain degree of reflux is both physiological and common. That said, normative data are still not available for this. A threshold figure for pathological EOR does not exist as yet. In view of the variety of substrate tissue and the spectrum of disease, it is possible that a threshold figure for reflux exposure in any of the tests will never be achievable. What is clear is that the threshold figures for GORD do not apply to EOR although a diagnosis of GORD makes EOR more likely.

There is no one 'gold standard' test for EOR. Each of the tests described provides supporting information towards or against a diagnosis of EOR. A diagnosis of GORD will, however, make EOR more likely and treatment should be considered. Likewise, a reduction in the RI below threshold for GORD will not necessarily mean successful treatment of the EOR.

Contrast swallow

A contrast swallow has the advantage of demonstrating anatomical abnormalities such as a tracheo-oesophageal fistula, a hiatus hernia and achalasia. It may detect aspiration especially when used as part of a videofluoroscopic examination of swallow. It is a brief study and so is not a good investigation to detect reflux events. It is not routinely done in reflux unless an underlying anatomic abnormality is suspected.

pH monitoring

Ambulatory 24-hour pH monitoring has been the mainstay of diagnosing GORD in children. This is usually done passing the probe nasally, attempting to site the electrode 5 cm above the gastro-oesophageal junction. The position of the electrode can be determined directly if passed as part of an upper GI endoscopy or can be ascertained via a chest X-ray and repositioned. A wireless capsule can also be used, which has the advantage that it cannot be pulled out by the child. The probe remains in place for 24 hours and patient position, meals and symptoms are documented. pH monitoring provides excellent information regarding lower oesophageal acid exposure but does not provide evidence of non-acid reflux or about extra-oesophageal reflux. Dual probe pH monitoring attempts to provide more information about pH at the upper oesophagus and pharynx and has been widely used in the literature. Achieving a consistent position for the upper electrode has been difficult and drying has led to inaccuracy in pH reading.

A pH drop below 4 is considered significant and the reflux index (RI) refers to the percentage of the entire time of the study that the reading is below this. Within the realms of GORD a reflux index of less than or equal to 4% is considered normal or physiological. As explained, this may not apply to extra-oesophageal reflux but a high RI makes it more likely.

Multichannel oesophageal intraluminal impedance testing

For multichannel oesophageal intraluminal impedance testing a probe is passed like a pH probe which has several sensors along its length and measures changes in electrical resistance when a liquid, semi-solid or gas bolus passes between the electrodes. A combined impedance and pH probe can detect and distinguish acid and non-acid reflux as well as aerosolized, liquid or mixed reflux. Interpretation of the 24-hour study is time-consuming and subject to interobserver variability. Normative data are still lacking. Despite these limitations, pH/impedance monitoring is currently the most valuable investigation in refractory EOR.

As with pH monitoring, the symptom correlation remains difficult. This may be because symptoms such as hoarseness are not paroxysmal and airway symptoms caused by EOR may not occur within any 24-hour period.

Gastric emptying scintigraphy

This investigation may be useful to detect GORD and aspiration, but it is particularly helpful for delayed gastric emptying. It is not an investigation that is routinely done in the investigation of reflux.

Biopsy

Oesophageal biopsy is the mainstay of making a histopathological diagnosis of oesophagitis and eosinophilic oesophagitis. It may also be helpful in inflammatory bowel disease, coeliac disease and Barrett's oesophagus. Multiple biopsies are usually taken, as oesophagitis may be patchy. Absence of histological changes does not rule out GORD. Biopsies of the postcricoid and pharynx have been used to detect inflammation but clinical application is limited.

ENDOSCOPIC FINDINGS

When examining the laryngopharynx and trachea, various appearances have come to be associated with reflux. Many challenges exist, especially as the changes may represent inflammation and not specifically indicate reflux. Another issue is that the findings may exist on a spectrum and may be open to the interpretation of the operator, leading to some degree of interobserver variability. The value and specificity of the findings is therefore contested although there seems to be an evolving consensus that some findings are suggestive of reflux. Care must be taken in the interpretation of these findings in isolation without clinical correlation.

Posterior laryngitis was described by Delahunty[13] in 1972 as a sign of reflux laryngitis in adults (**Figures 44.1** and **44.2**). As the posterior larynx is in close proximity to the oesophageal inlet, it seems likely that this would be the most vulnerable extra-oesophageal site to reflux exposure (**Figures 44.3** and **44.4**). This relates to postglottic oedema and arytenoid oedema with loss of the normal arytenoid contour. It is suggested that severe arytenoid oedema, postglottic oedema and enlargement of the lingual tonsil may be pathognomic for GORD (**Figures 44.2**, **44.3** and **44.5**).[14]

The laryngeal 'pseudosulcus' refers to the appearance of a fold parallel to the free edge of the vocal cord. This may involve just the posterior cord or extend the length of the cord. It is thought to be a manifestation of infraglottic oedema (**Figure 44.6**). This finding appears to have a high sensitivity for reflux[15, 16] although its specificity is lower.

Other findings that have been described include generalized erythema, ventricle effacement and cord nodules.



Figure 44.1 Larynx showing generalized erythema and ventricular effacement – a so-called 'active larynx'.



Figure 44.2 Laryngeal view of severe posterior inflammation.

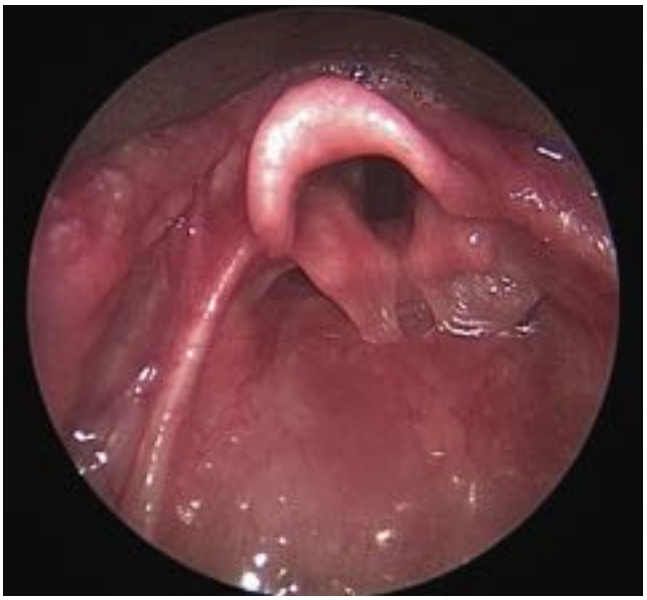


Figure 44.3 Larynx showing arytenoid inflammation and redundancy.



Figure 44.4 Laryngeal view showing an acute reflux episode bathing the posterior glottis.



Figure 44.5 View of the valleculae demonstrating lingual tonsil enlargement.

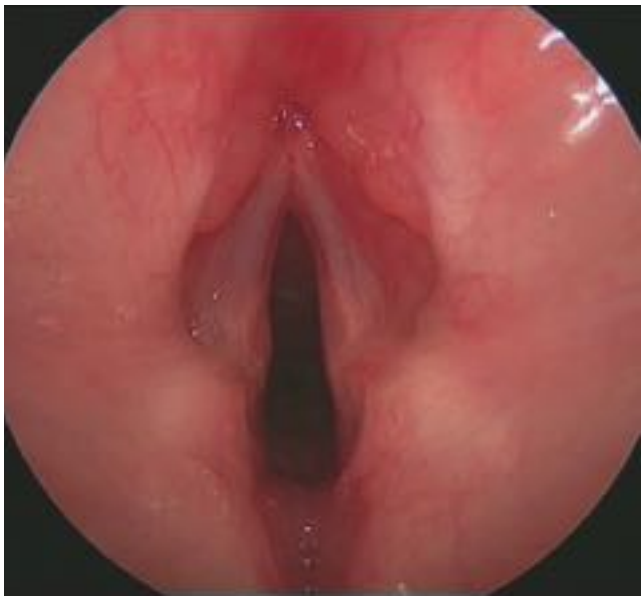


Figure 44.6 Vocal cords demonstrating vocal cord 'pseudosulcus'.



Figure 44.7 Tracheal view showing 'cobblestoning'.



Figure 44.8 Laryngeal view demonstrating posterior pharyngeal wall 'cobblestoning'.

Findings seen in the pharynx and trachea include general oedema, erythema, indistinct tracheal rings and mucosal 'cobblestoning' (Figures 44.7 and 44.8). Blunting of the carina with loss of the normal sharp contour is also suggested to be significantly associated with reflux.[14]

The utility of these findings remains contentious. In addition to the issues raised earlier, all the mucosal changes have been demonstrated in the absence of reflux.[17] The findings appear to represent inflammation and reflux is a common source of non-acute inflammation. The findings should therefore alert the clinician to the possibility of reflux and direct the history and investigation. The clinician must be mindful that, in isolation, these findings have limitations.

THE PAEDIATRIC AIRWAY

It appears that EOR will impact the airway in different ways. Many of the typical endoscopic signs of mucosal change are seen in the airway although these are manifestations of inflammation, which may be the result of exposure to reflux or other irritant or inflammatory process. These may result in coughing or throat clearing, which may create more irritation and irritability. Coughing or increased work of breathing may worsen reflux, which may further exacerbate the problem. Aspiration of refluxate may cause or exacerbate pulmonary disease, the manifestations of which may promote multilevel airway pathology such as tracheobronchomalacia. This confluence of digestive, pulmonary and laryngotracheal involvement may have reflux as a unifying factor. This may be as cause or effect or both. It is the amalgamation and evolution of these effects that have rendered scientific study so difficult. In many ways, breaking down the airway manifestations into specific diagnosis may be unrealistic as reflux has been implicated in hoarseness,[18] laryngomalacia, subglottic stenosis, croup, ALTEs and chronic cough.[19] These conditions may of course coexist in the same patient and impact each other. The more general term of 'reflux-induced airway disease' may be helpful in thinking about these conditions more broadly.

Laryngomalacia

Laryngomalacia is the commonest cause of neonatal stridor. Children typically present within the first few days of life with high-pitched inspiratory stridor. The mainstay of assessment is awake flexible fibre-optic nasopharyngoscopy. The fibre-optic features may reveal foreshortened aryepiglottic folds with the classical 'omega'-shaped epiglottis. The other common finding is redundancy of the arytenoid mucosa, which prolapses forwards causing the obstruction (**Figure 44.9**). The appearances echo the findings of posterior laryngitis seen in reflux. This area is in close proximity to the oesophageal inlet and potentially most at risk from EOR.

Reflux appears to be found in the majority of patients with laryngomalacia[20–23] although it is not entirely clear whether it is causative. The increased work of breathing will result in increases in negative intrathoracic pressure, which will promote reflux. At this point the conditions may become self-perpetuating.



Figure 44.9 Laryngomalacia with arytenoid redundancy with prolapse into the glottis on inspiration.

Children with reflux tend to have more severe laryngomalacia, which is more likely to require surgical intervention.[21] Surgical treatment of laryngomalacia tends to reduce the severity of reflux if present pre-operatively.[24]

In view of the high incidence of reflux in infants with laryngomalacia, this diagnosis should always be sought and excluded in these cases. Infants with laryngomalacia who have coughing, choking, regurgitation and feeding difficulties may be considered candidates for empiric acid reflux suppression,[20] especially in the presence of emesis. A certain number of infants will clinically improve and acid suppression should be weaned based on symptom resolution. However, if responses to empirical therapy are poor, or the infant requires prolonged acid suppression, then the reflux status of these infants should be investigated in the usual manner.

It may be prudent to use antireflux therapy in all patients who have aryepiglottoplasty and supraglottoplasty surgery in the immediate post-operative period. This is to mitigate the risk of reflux on the raw surfaces created by the surgery.

Subglottic stenosis

Subglottic stenosis (SGS) and its treatment continues to be a challenge to the paediatric airway surgeon. In children the stenosis may be congenital or acquired. Acquired SGS generally occurs after some kind of trauma to the subglottis, the most common being endotracheal intubation.[25] Acquired SGS became recognized in the 1960s with the introduction of long-term intubation for the management of neonates needing ventilatory support.[26]

Animal models demonstrate that gastric acid in the presence of mucosal trauma such as might occur during endotracheal intubation may lead to stenosis.[2] Children with SGS seem to have high rates of GOR.[27, 28] In adults the clinical entity of idiopathic SGS, a condition of young adult women, is recognized, and there is intriguing

evidence that reflux plays a role.[29] While the role of reflux in the genesis of SGS remains somewhat unclear, it seems to be a significant cofactor.

GORD has been seen in over 80% of children undergoing laryngotracheal reconstruction (LTR).[30] The appearance of the so-called 'active larynx' (see **Figure 44.1**) has been recognized as a concern for the clinician contemplating performing an LTR. A cause for this finding of which reflux would be commonest should be sought and treated prior to reconstruction. The exposed mucosal surfaces and prolonged endotracheal intubation could serve as an environment in which reflux exposure could affect wound healing. This could lead to failure.[31] Reflux therapy has been seen to improve outcomes of endoscopic treatments for SGS and possibly reduce the number of children requiring surgery.[27]

Reflux certainly seems to occur in SGS and may well sometimes be causative and/or a cofactor in its genesis. Every attempt should be made to identify it. While it has been suggested that all LTR patients should have blanket empirical therapy, others have questioned its utility.[32] There is an evolving consensus that, where reflux is present and especially in the context of the 'active larynx', aggressive treatment is advisable. In view of the complexity and morbidity of surgery, the potential for the presence of reflux should be actively sought. The threshold for antireflux measures may be commensurately lower in this group of patients.

Apparent life-threatening events

An apparent life-threatening event (ALTE) is an episode of apnoea, choking or gagging that to the caregiver appears to be a near-death episode. Over half may be associated with reflux[33] although the significance of this is uncertain.

The mechanism may be multifactorial with both central and local factors at play. When the ALTE occurs suddenly in a well child, vocal cord closure may be occurring. A mechanism for reflux mediation through direct contact,[8] vagally mediated via the oesophagus,[9] or indeed via aspiration-associated reflux events[34] have been suggested. There is also evidence that short non-pathological central apnoea is associated with reflux[35] and it may be that this is a protective phenomenon. While causation has not been proven, where reflux is present, it may well be a cofactor. Fundoplication in children with ALTEs and reflux may be universally effective in eradicating the events when the fundoplication succeeds in stopping the reflux.[36]

Recurrent croup

Croup (acute laryngotracheobronchitis) is usually a viral illness characterized by a prodrome of an upper respiratory tract illness followed by hoarseness, a barking cough and various degrees of inspiratory and expiratory stridor. The illness is usually self-limiting and responds to supportive therapy although it can occasionally result in significant airway compromise. Croup is unusual before 6 months of age and in older children. As croup is usually self-limiting, a child requiring admission, particularly if requiring high-dependency or intensive care, should be viewed as atypical. Recurrent croup (i.e. more than two cases in a year) is also atypical and in all these clinical scenarios an underlying cause should be sought. There is some evidence that reflux may be present in this clinical scenario.[37–39] The exact mechanism is unclear but may relate to high rates of SGS in this group as well as other airway lesions. Convincing causative data are lacking at this time.

Recurrent respiratory papillomatosis

There is limited evidence that reflux may play a role in recurrent respiratory papillomatosis (RRP) control. Where present, it may affect the rate of recurrence and in some cases reflux control may hasten resolution.[40] There is also evidence that reflux control may reduce anterior commisure web formation.[41] The numbers of cases in the literature are too small to draw definitive conclusions but certainly in cases of RRP where there is demonstrable and symptomatic reflux antireflux therapy would seem to be sensible in view of the creation of raw epithelial surfaces that often accompany surgery.

NASOPHARYNX AND OROPHARYNX

Rhinosinsitis

The role of EOR in rhinosinusitis is extremely contentious. Nasopharyngeal reflux exposure obviously occurs during emesis. There is some limited evidence that reflux may adversely affect choanal atresia repair.[42] A significant proportion of children with nasal symptoms appear to have histologically proven GORD.[43, 44] Increased exposure times to low pH have been seen in children with chronic nasal disease.[45] In children with sinus disease and GORD there is some evidence that antireflux therapy may reduce the need for sinus surgery.[46]

In adults with refractory sinus diseases, increased nasopharyngeal altered pH and increased rates of gastro-oesophageal reflux have also been demonstrated.[47, 48] Early results demonstrating pepsin in nasal lavage seem encouraging and may represent a possible means of detecting reflux involvement in sinus disease.[47]

While definitive causative data are lacking, there is emerging evidence to suggest that reflux may have an impact in some cases of sinus disease. There is insufficient evidence to recommend routine screening of asymptomatic children with sinus disease. However, it seems sensible to take a reflux history in these patients and, if suggestive, investigate and treat, particularly if the sinus disease is proving refractory to conventional treatment.

Otitis media

As mentioned above, EOR appears to impact the nasopharynx and sinuses. In 2002, pepsin/pepsinogen was

detected in middle-ear effusions at much higher concentrations than were present in serum.[49, 50] The source of this could only be gastric and raised the possibility that reflux might play a role in otitis media with effusion (OME).

Low pH reduces ciliary motility in respiratory epithelium.[6] In animal experiments acid and pepsin instilled into the nasopharynx increased the opening and closing pressures of the Eustachian tube (ET) as well as the mucociliary clearance times.[51] These impact the ability of the ET to equalize middle ear pressure during swallowing and, in addition to impaired ciliary motility, may explain reflux-induced ET dysfunction. Potentially, this may represent a model for the role of reflux in acute otitis media (AOM), recurrent acute otitis media (RAOM) and OME.

Assessing the role of GOR/EOR in otitis media (OM) is challenging as both have a high incidence, particularly in younger children. Multiple studies have suggested that the prevalence of GORD in children with OM is higher than overall prevalence.[52] The prevalence of GORD in OME ranges from 17.6% to 64% and in RAOM from 61.5% to 64.3%.[52] Small studies have suggested that, where GORD is present, antireflux therapy may reduce the incidence of RAOM.[53]

Unfortunately, despite initial excitement about the reflux–otitis link, no cause-and-effect relationship has been demonstrated satisfactorily. While it remains an area of research interest, there is insufficient existing evidence to support antireflux therapy in OM.[52]

Adenotonsillar hypertrophy

The effect of reflux within the nasopharynx may also impact on the adenoidal pad as well as the ET and sinuses. Children under the age of 2 years undergoing adenoidectomy alone appear to have much higher rates of GORD than their counterparts having grommets alone.[54] Children under 18 months having adenoidectomy also have higher rates of GORD and synchronous airway lesions.[55] Whether this is cause or effect remains to be demonstrated. There is anecdotal evidence that treatment of GORD has resulted in reduction of adenotonsillar size and resolution of obstructive sleep apnoea (OSA).[56]

When assessing children who remain symptomatic post-adenotonsillectomy for OSA, reflux should be considered.[57] Children with a history of GOR appear also to have a higher rate of post-operative complications after adenotonsillectomy.[58]

More recently there has been interest in the presence of *Helicobacter pylori* (HP) in adenotonsillar tissue. Infection with the agent has been shown to be a significant factor in peptic ulcer disease.[59] The evidence seems contradictory, with some studies showing PCR detection of HP in the removed adenoid in impedance-demonstrated EOR.[60] Other studies have not found adenoidal HP despite a strong history of EOR.[61]

Some studies, particularly those using the rapid urease test, failed to demonstrate significant HP involvement in tonsil tissue.[62, 63] Using PCR techniques, HP detection in tonsils has led to the hypothesis that the tonsil is an extragastric reservoir for the organism.[64, 65] It is further postulated that HP may play a role in tonsillitis. While the findings are interesting, their true significance is unclear. This area may prove clinically relevant but as yet remains within the realm of research interest.

MANAGEMENT

The diagnosis of EORD disease is made on an individual basis based on history, clinical findings, pathology and investigations and sometimes on response to therapy. It is often helpful to enlist the aid of a paediatric gastroenterologist.

Other diagnoses for the symptoms should be considered, especially cows' milk protein intolerance. Elimination should be tried. This may involve maternal dietary modification if the child is breastfed.

Limited literature exists to determine the efficacy of therapy for EOR. Most of the literature deals with response of GORD to therapy and we may extrapolate the results to EOR although it is by no means clear that it is appropriate. Certainly, when GORD is established, therapy is indicated and there is a large body of evidence supporting pharmacological therapy. Where there is EOR but no GORD, the evidence for the efficacy of therapy is less clear.

Simple lifestyle changes are often tried in the first instance. Neonates are fed upright with feeds 'little and often'. Feed thickening may help with emesis. For adolescents smoking cessation, alcohol avoidance and weight loss if obese are recommended. Cessation of habitual throat clearing and vocal hygiene advice may be of benefit.

In patients with a strong clinical picture, an empirical antireflux therapy trial is not unreasonable. This is done on the basis that investigations such as pH/impedance are unpleasant for children and antireflux therapy is relatively benign. That said, it should be borne in mind that therapy is not always tolerated and that there are risks.

Pharmacological agents include barrier agents, prokinetic therapy, histamine-2 receptor antagonists and proton pump inhibitors (PPIs).

Barrier agents tend to contain either an alginate or sucralfate. These treatments act to create a barrier between the mucosa and the gastric content. They are generally well tolerated although constipation and diarrhoea may be seen. There may be a risk of aluminium toxicity with prolonged sucralfate use.

Prokinetic agents attempt to reduce reflux by hastening gastric emptying, however there is currently insufficient evidence to support the routine use of these drugs in view of the significant risks.[11]

Histamine-2 receptor antagonist therapy is a well-established therapy usually used twice daily. It has been shown to increase gastric pH for 9–10 hours in infants.[66]

The main issue with use is tachyphylaxis, which is a drawback to long-term use.

Proton pump inhibitor therapy is probably the most widely used therapy for EOR and is more effective at treating oesophagitis and GORD symptoms than H2 receptor antagonists.[11] In contrast to H2 receptor antagonists, the effect of PPIs does not diminish with time. The main risks of therapy of both groups of drugs are an increased rate of community-acquired pneumonia and gastroenteritis. While empiric trials of therapy are useful, treatment should be maintained on as low a dose as possible. If there is failure to show a rapid response to therapy, more detailed investigations should be sought, such as impedance/pH studies.

Consideration to surgical intervention is limited to patients refractory to maximal medical and lifestyle modifications. Certainly in this group it is important to have as much supporting evidence of reflux as possible and to have ruled out a non-reflux diagnosis prior to consideration of surgery. The chief mainstay of surgical intervention is fundoplication, with laparascopic techniques now largely replacing open techniques.

EOSINOPHILIC OESOPHAGITIS

Eosinophilic oesophagitis (EO) is a relatively new clinical entity. It was first described in the literature in the 1990s and over the past 20 years has become an increasingly diagnosed condition in gastroenterology. It first entered the otolaryngology literature in 2002 with a description of a child with the condition who had failed multiple laryngotracheal reconstructive procedures despite effective antireflux therapy.[67] The association between SGS and EO has been seen in other studies[68] with possibly as many as 10% of EO patients being affected.[69]

The condition itself is an inflammatory oesophagitis related to eosinophilia that appears to be immune-mediated. In adults it is known to be a cause of dysphagia and lower oesophageal food impaction and hence the need for biopsy of the oesophagus in this clinical scenario. Children more commonly manifest choking, gagging, nausea, vomiting, diarrhoea and food refusal. GORD-type symptoms including heartburn and regurgitation are common and EO may commonly be mistaken for this. Reflux may coexist with the condition, which may further confuse the picture. A poor or limited response to antireflux therapy should alert the clinician to this potential diagnosis.

Within the realm of otolaryngology a wide variety of airway symptoms have been described particularly cough, stridor, croup and dyspnoea.

The diagnosis is based on a finding of more than 15 eosinophils per high-power field on oesophageal biopsy.[70] The oesophageal appearances are typically of mucosal oedema, erythema and furrowing. The mucosa may also appear normal in almost a third of cases.[70] Multiple biopsies should be taken from different oesophageal sites. There does not appear to be any value in pharyngeal biopsy of affected individuals.[71]

There is a strong male preponderance. The majority of patients have evidence of atopy, particularly allergic rhinitis, asthma and atopic eczema. There may be evidence of food allergy and a strong family history of atopy.

Once the diagnosis is suspected, it is helpful to enlist the aid of a gastroenterologist. A pH/impedance study is helpful, as are multilevel oesophageal biopsies. The current treatment consists of swallowing topical corticosteroids. If food allergy is identified, food elimination or ultimately an elemental diet may be beneficial.

CONCLUSIONS

The true role of reflux in the genesis and propagation of disease within the head and neck remains hugely challenging and controversial. There is good causative evidence for its role in GORD and consensus exists for both its diagnosis and treatment. Unfortunately, no such evidence or consensus exists for EOR. The variety of substrate tissue and function located in such a small area, as well as the interaction of disease processes in each of these with each other, makes the picture even more confusing. Symptoms such as cough or voluntary mechanisms such as throat clearing may increase inflammation, irritability and indeed reflux itself that may in turn exacerbate the problem. This complexity and variability may render robust data and consensus some way off, especially within the realm of reflux-mediated airway disease.

Ultimately, the diagnosis of EORD is a clinicopathological one. Each patient must be viewed as an individual. The diagnosis is made, taking into account the available information from the history, examination, investigations and possibly response to trials of therapy. This will usually be a collaborative effort between gastroenterologist, otolaryngologist, pulmonologist and paediatric surgeon.

Both EO and EORD require a high index of suspicion. Care must be taken to assemble as much information to support or refute the diagnosis as possible. If therapy is instituted, this should be regularly reviewed and the patient weaned off as soon as practical. Parents and clinicians should be aware of the potential complications of therapy. If the initial response to therapy is poor, a re-evaluation should be undertaken.

EORD remains a hugely challenging and controversial area in paediatric otolaryngology. It is clear that reflux plays some role in either the genesis or propagation of a variety of conditions in some children. It is helpful for all clinicians to have an awareness of the condition as well as the limitations of the evidence. It seems likely that our knowledge and understanding will continue to advance exponentially.

FUTURE RESEARCH

- To establish normative values for extra oesophageal reflux using impedance testing.
- To establish a casual link for EOR and airways disease, sinus disease, ear disease and adenotonsillar disease.
- To determine if H Pylori plays a significant role in paediatric reflux mediated otolaryngological disease.

KEY POINTS

- Extra-oesophageal reflux is implicated in the genesis and propagation of various paediatric airway disorders. There is possibly an association with Eustachian tube disorders, rhinosinusitis and adenotonsillar hypertrophy but the evidence is weaker.
- Extra-oesophageal reflux is a clinicopathological diagnosis based on history, examination, investigations, endoscopic findings, exclusion of alternate diagnoses and response to therapeutic trials.
- There is no one definitive investigation that proves or excludes extra-oesophageal reflux disease.
- Extra-oesophageal reflux disease can occur in the absence of gastro-oesophageal reflux disease although it is more likely if oesophageal reflux disease is present.
- Eosinophilic oesophagitis is an immune-mediated inflammatory oesophagitis. It is more common in atopic individuals and there is a male preponderance. There are airway manifestations. It is diagnosed by histological appearance of oesophageal biopsy. It is treated by swallowing topical corticosteroids and by food allergen avoidance.

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CHAPTER 45

OESOPHAGEAL DISORDERS IN CHILDREN

Graham Haddock

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: congenital anomalies of the oesophagus, acquired disorders of the oesophagus, achalasia, caustic oesophageal injury, other oesophageal injury, neonates, infants and children.

CONGENITAL ABNORMALITIES OF THE OESOPHAGUS

Introduction

Congenital abnormalities of the oesophagus are fairly common in paediatric surgical practice. Many of these arise during fetal foregut development when the oesophagus separates from the trachea, and many present early in the neonatal period, require prompt complex surgery and can have long-term sequelae. Some of the rare oesophageal abnormalities present later in life with symptoms which are often difficult to understand.

Oesophageal atresia with or without tracheo-oesophageal fistula

Oesophageal atresia (OA) with or without an associated tracheo-oesophageal fistula (TOF) (OA +/- TOF) is one of the most common conditions which present to neonatal surgeons. It is thought to affect between 1 in 2000 and 1 in 5000 live births.

The embryonic origin of OA and TOF is thought to be similar to that seen in laryngotracheal clefts. If the separation of the developing oesophagus and the trachea by the lateral mesodermal ridges fails, the result is an isolated TOF. The embryologic origin of the more complex OA + TOF is less clear.[1, 2]

There are a number of variants of OA + TOF. The commonest form, which accounts for approximately 85% of cases, comprises a blind-ending proximal oesophageal pouch with a fistula from the trachea or bronchus to the distal oesophagus. Isolated or long-gap OA accounts for approximately 10% of cases in most published series. Isolated TOF without OA (known as an H- or N-type TOF), OA with a TOF to both distal oesophagus and proximal oesophageal pouch, and OA with a TOF to the upper oesophageal pouch are much less commonly seen variations of this anomaly (Figure 45.1).

Antenatal maternal polyhydramnios, which can affect approximately half of pregnancies with the various forms of OA, may give a clue to the presence of this abnormality.

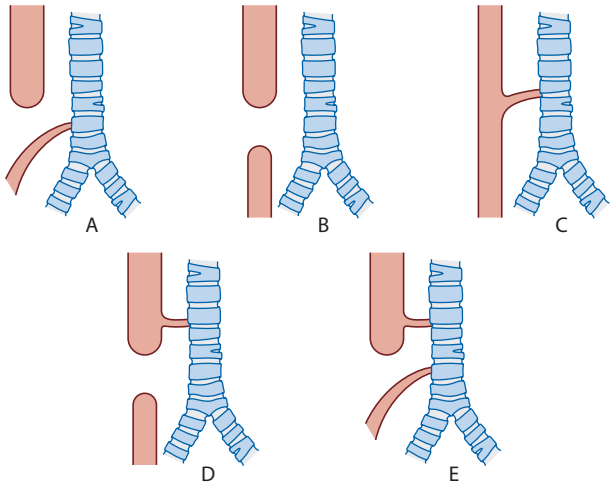


Figure 45.1 Types and incidences of oesophageal atresia with or without a tracheo-oesophageal fistula. Type A (OA with distal TOF): 85%; Type B (isolated OA): 8%; Type C (isolated H or N type TOF): 4%; Type D (OA with proximal TOF): 2%; Type E (OA with proximal and distal TOF): <1%.

A failure to identify the fetal stomach on antenatal ultrasound after 20 weeks' gestation may prompt a diagnosis of isolated OA, although this finding is not completely reliable. Either of these antenatal features should prompt the passage of an orogastric tube immediately after delivery of the newborn.

The newborn affected by any of the common variants of OA (but obviously not the baby with an isolated TOF) will present clinically with frothing at the mouth, choking episodes, cyanosis and respiratory distress. Attempts at feeding will clearly precipitate such symptoms and may cause aspiration and severe respiratory distress. Infants with an isolated TOF may present later in life with recurrent chest infections, symptoms of chronic respiratory disease and bronchospasm. Many will have been thoroughly investigated for cystic fibrosis. Some of these will present in the ENT clinic, hence otolaryngologists need to be aware of the clinical features so they can arrange appropriate investigations, including tracheobronchoscopy when indicated.

Many babies with OA will have associated anomalies. These might include vertebral anomalies, extra or missing ribs, anorectal malformations, cardiac abnormalities, renal or radial anomalies and limb deformities. These are often grouped together and are known as the VACTERL association. The aetiology of these associations is not clear.

The inability to pass an oro- or nasogastric (NG) tube in the newborn is virtually diagnostic. The tube should be a relatively large bore (at least 10 Fr) to avoid missing the diagnosis (**Figures 45.2a-b**). Thinner tubes may be seen to be curled up in the upper oesophageal pouch on a chest X-ray, which also confirms the diagnosis (**Figure 45.3**). Contrast studies or other imaging modalities are not required. The presence of gas in the abdomen on a plain abdominal or chest X-ray will indicate that the baby with OA has an associated TOF. Associated vertebral and rib anomalies can be detected on abdominal and chest X-rays (**Figure 45.2b**).

A comprehensive physical examination of the baby should be supplemented by a number of imaging modalities. An ultrasound scan of the kidneys is required to exclude associated renal anomalies. A cardiological assessment including echocardiography is essential pre-operatively to identify any life-threatening cardiac lesion and to locate the position of the aortic arch,[3] which can be on the right side in 2% of cases. A right-sided aortic arch may make the surgery even more challenging than usual.

In the older child suspected of having an isolated TOF, a pull-back ('tube') oesophagogram with the patient prone or in the left lateral position may make the diagnosis clear (**Figure 45.4**). Contrast may be introduced via an NG



Figure 45.2 Lateral (a) and AP **(b)** chest and abdominal X-rays of a newborn with OA and TOF. A large-bore tube has been placed under tension in the upper pouch. The stomach and intestine contain air which indicates the presence of a TOF. Vertebral anomalies can be seen in the mid thoracic spine.

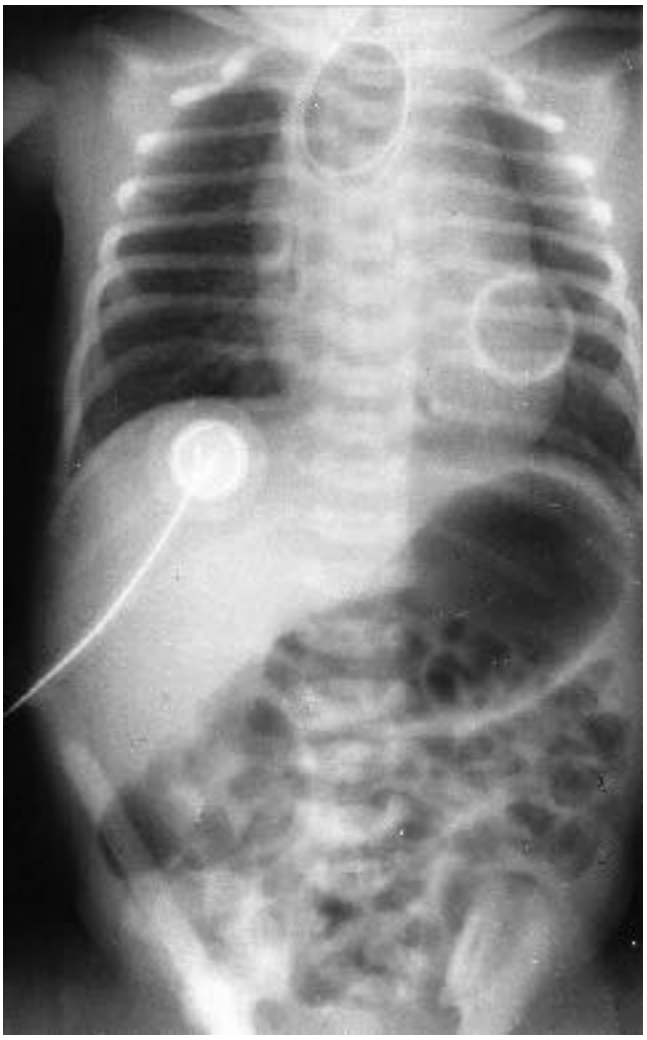


Figure 45.3 Thin nasogastric tube curled up in the upper oesophageal pouch in a newborn with OA and TOF.



Figure 45.4 H or N-type fistula study demonstrating an isolated fistula between the oesophagus and the trachea.

tube. A tracheobronchoscopy may be needed to identify an isolated TOF and occasionally the fistula is concealed in a mucosal fold, making diagnosis difficult.

Early patient management should focus on maintaining a patent airway and preventing the aspiration of saliva and upper pouch secretions. The baby should be nursed prone with a sump suction (Replogle) tube in the upper pouch set on continuous aspiration. This tube should be injected regularly with air to prevent blockage. Endotracheal intubation and ventilation should be avoided if possible. Positive pressure ventilation in the presence of a TOF may result in large amounts of gas passing into the stomach and intestine. This trapped gas may have no easy route of escape, especially if the baby has an associated intestinal abnormality, like an atresia or anorectal malformation. Abdominal distension due to gaseous distention may impair ventilation and result in hypoxia, hypercapnia and acid-base upset. Gastrointestinal perforation in such cases can have a devastating outcome.[4]

Management of OA and TOF is ligation of the fistula and end-to-end anastomosis of the oesophagus. Prior to surgery, most paediatric surgeons will request that a bronchoscopy be performed to identify any upper pouch fistula and confirm the exact position of the TOF. This may allow the anaesthetist to position the endotracheal tube past the fistula to limit the passage of ventilated gas into the stomach.

Repair can be achieved through an open extrapleural thoracotomy[5, 6] or by using a minimal access thoracoscopic approach.[7–9] The site of the fistula is identified and dissected from surrounding structures. The fistula is divided and sutured closed as flush as possible with the trachea. A large-bore tube passed into the upper oesophageal pouch by the anaesthetists will help identify the pouch. Careful dissection will ensure that the trachea is not damaged during upper-pouch mobilization. A single-layer all-coats anastomosis of the ends of the oesophagus over a transanastomotic feeding tube is probably the most common form of primary surgical repair.

In cases where the gap between the ends of the oesophagus is too far apart for primary repair, there are a number of options for treatment. Ligation of the TOF with creation of a feeding gastrostomy may be the preferred approach initially. This would be followed by a delayed primary repair at a later stage. This approach would require long-term use of a sump suction tube in the upper oesophageal pouch to prevent aspiration of secretions and may require a period of long-term inpatient care. The creation of an open oesophagostomy (or spit fistula) may avoid the need for inpatient care and allow the infant to sham feed but

almost always precludes delayed primary repair at a later date as the length of the upper oesophagus is lost.

The Foker technique of lengthening of the oesophagus by applying traction using two lengths of thread attached to each end of the oesophagus has been reported to achieve delayed primary anastomosis in a shorter timeframe.[10, 11]

In cases of isolated or long-gap OA without a TOF, delayed primary repair remains the preferred approach for treatment.[12] If this is not possible, replacement of the distal oesophagus with a colonic, jejunal or gastric interposition may be required.[13–18] Occasionally, oesophageal lengthening procedures may have a role to play in achieving a safe primary or secondary oesophageal anastomosis.[19]

Complications of surgery to repair OA include anastomotic breakdown and leak, anastomotic stricture, refistulation and gastro-esophageal reflux. If the fistula is not sutured flush with the trachea, a blind-ending pouch can be left behind. Occasionally, this causes problems with intermittent airway obstruction. Most children without other associated congenital anomalies grow and develop normally. Associated very low birth weight and the presence of associated major cardiac defects have been shown to be good markers of poorer outcome in OA.[6, 20]

Congenital oesophageal stenosis

Congenital stenosis of the oesophagus is thought to represent the mild end of the spectrum of conditions caused by problems during the separation of the fetal trachea from the foregut tube during development. The majority of these anomalies affect the middle and distal oesophagus. Three types are described: those containing remnants of cartilage,[21] those with fibromuscular thickening and those with membranous webbing.[22] Stenoses in other parts of the oesophagus have other causes including peptic strictures at the lower end secondary to acid reflux.

Minor degrees of oesophageal stenosis may be completely asymptomatic. Failure to thrive and regurgitation of feeds may be seen when the narrowing is more severe. Sometimes the symptoms do not become apparent until the infant starts to eat solid foodstuffs.

Investigations include an upper gastrointestinal contrast swallow, which will reveal the area of narrowing, and upper gastrointestinal endoscopy. Oesophageal biopsy, particularly if deep, may reveal cartilage.

Dilatation of congenital oesophageal strictures rarely succeeds, especially if there is cartilage in the stenosis. Surgical resection of the area of narrowing and the cartilaginous tissue is usually required in severe cases. Reports of successful minimally invasive surgery for these abnormalities have been published.[21]

Oesophageal webs and rings

In addition to the more commonly encountered OA, a rare, membranous, mucosal atresia of the oesophagus has been reported which is indistinguishable from OA if the membrane is complete.[23] Some cases have been associated with a TOF. A mucosal membrane occludes the oesophageal lumen. In cases where the membrane is perforate, symptoms may be minimal or absent.

The diagnosis of an oesophageal web causing complete obstruction by failure to pass an oro- or nasogastric tube necessitates surgical intervention. The perforate or crescentic membrane usually presents later in life and can be identified on a contrast swallow examination or at upper gastrointestinal endoscopy.[24]

Resection of the membrane at thoracotomy is usually the only possible treatment for the complete membrane. In incomplete membranes, dilatation[24] or endoscopic incision of the membrane by cautery or laser with or without balloon dilatation should be considered.[25] Associated gastro-oesophageal reflux may require vigorous treatment, including possibly surgery, to prevent further stricture formation.

Oesophageal duplication and bronchogenic cysts

Oesophageal duplications appear as tubular or cystic structures in the posterior mediastinum (**Figures 45.5** and **45.6**). They are similar in many respects to other gastrointestinal duplications: they are all lined by gastrointestinal epithelium, have a well-developed smooth muscle wall, and are attached to the normal gastrointestinal tract at some point through their length.

Duplication cysts of the oesophagus, while rare, are the most common of the foregut duplication cysts. Their embryology is not clear. Associated vertebral anomalies might support the 'split notocord' theory of development.[26] This theory suggests that abnormal adhesion between

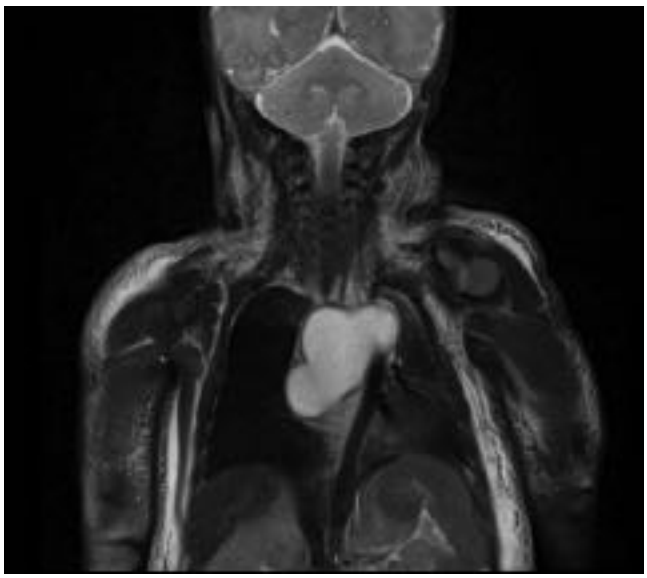


Figure 45.5 Coronal section of a T2-weighted MRI scan on a neonate with an antenatally diagnosed thoracic duplication cyst. The oesophagus and heart have been pushed to the left. The cyst was resected thoracoscopically. Histopathological examination confirmed the classical features of a foregut duplication cyst. It was lined by specialized gastric mucosa and otherwise comprised submucosa and well-formed muscularis propria.

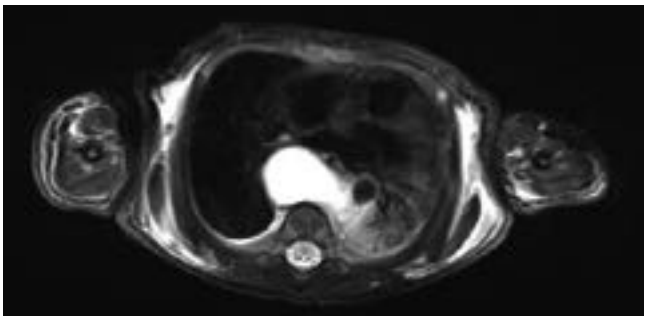


Figure 45.6 Transverse section of a T2-weighted MRI scan of the patient in Figure 45.5. Again the oesophagus can be seen pushed to the left.

ectoderm and endoderm prevents ventral notochordal fusion. Herniation of the yolk sac develops between the halves of the split notochord, resulting in foregut duplication and an associated vertebral anomaly. Alternatively, in those cases without associated vertebral anomalies it has been suggested that some oesophageal duplications occur due to incomplete recanalization after its solid phase of development.[27]

Bronchogenic cysts occur due to abnormalities in the budding process seen during the development of the tracheobronchial tree. Most of these mainly benign lesions are found within the lung parenchyma, but approximately 30% present as mediastinal masses. Occasionally, they are found in the oesophageal wall although they more usually compress the oesophagus from the outside. They are difficult to distinguish from oesophageal duplication cysts and may have a common embryological origin.[28, 29]

Oesophageal duplication cysts present most commonly in the neonatal period with respiratory distress caused by the cyst compressing the lungs and airways, but antenatal diagnosis of a thoracic cyst is becoming more common. Dysphagia can occur in older children. Smaller cysts may be asymptomatic and be detected on a routine chest X-ray. Erosion of the wall of the cyst by acid secreted by the gastric mucosa that can line these lesions can cause serious bleeding.

The diagnosis is usually suspected from the appearance seen on a chest X-ray. A contrast swallow may reveal a communication with the cyst or an indentation of the oesophagus. Chest CT or MRI are the most useful investigative tools (**Figures 45.5** and **45.6**).[30]

Excision of the duplication is the most appropriate treatment option. Excision may not be possible if the oesophagus and the cyst share a common wall. Excision of the bulk of the cyst with removal of the oesophageal mucosa may be an option in such circumstances. Open surgery is gradually being replaced by minimal access approaches to resection of these lesions.[31, 32] Percutaneous drainage under ultrasound guidance prior to definitive surgery may be helpful in newborns where the cyst is causing severe respiratory distress.[33]

Bronchogenic cysts should also be excised. This is usually fairly easy if the cyst is not part of the oesophageal wall but much more difficult if the cyst is within the oesophageal wall.

Oesophageal diverticula

True congenital oesophageal diverticula, which contain all layers of the wall of the oesophagus, are uncommon.[34] False or pulsion diverticula, which are herniations of the oesophageal mucosa between defects in the oesophageal muscular wall, are more common.

The symptoms caused by an oesophageal diverticulum depend on the size and position of the abnormality. Dysphagia can occur as a consequence of compression of the oesophagus from the diverticulum and is the most common presentation. Bad breath from debris retained in the diverticulum may also be obvious.

The diagnosis is usually made on contrast radiology or by endoscopic examination. Treatment requires resection of the diverticulum and repair of the resultant defect in the oesophageal wall and may require thoracotomy or thoracoscopy for lesions in the mid oesophagus.

Oesophageal bronchus

Oesophageal bronchus, where a bronchus takes its origin from the oesophagus, is the most common congenital bronchopulmonary foregut malformation and may be associated with OA and TOF.[35] It can present in different ways including with respiratory symptoms and signs with recurrent sepsis or from the consequence of the consolidated or collapsed lung. It may be found incidentally during investigation for other conditions.

A chest X-ray may reveal an opacity in the lung fields and a contrast or radioisotope study of the gastrointestinal tract for reflux may show contrast or tracer in the lung. An upper gastrointestinal (GI) endoscopy may reveal the fistula, usually in the middle or lower thirds of the oesophagus, and bronchoscopy will demonstrate the absence of a major bronchus. Angiography should be undertaken to demonstrate that the lung associated with the bronchus has an appropriate blood supply. A recent study has reported prenatal MRI findings in a patient with a fetus with an oesophageal bronchus.[36]

Resection of the bronchus and associated lung tissue is usually the treatment of choice. Anastomosis of the bronchus to the trachea may be possible in some cases.[37]

Congenital short oesophagus

Congenital short oesophagus is a rare anomaly that was first described clearly in 1958.[38] Since then, there has been considerable debate as to whether it is a true entity in itself; it has sometimes been described as a congenital hiatus hernia.

In this anomaly the oesophagus is short with an intrathoracic stomach and a hiatus hernia. Affected babies present with failure to thrive in the first few months of life.

Treatment options are very limited and may be technically extremely challenging.[39] A surgical procedure to treat gastro-oesophageal reflux may be possible.

ACQUIRED DISORDERS OF THE OESOPHAGUS

Achalasia of the cardia

Achalasia of the cardia is an uncommon motility disorder of the distal oesophagus in children which causes a functional obstruction at the level of the lower oesophageal sphincter. It tends to affect teenagers. In children it presents with vomiting, difficulty swallowing, respiratory symptoms, weight loss and occasionally chest pain. It can also cause night-time regurgitation. The swallowing difficulty usually starts with solid foodstuffs but can progress on to liquids. Bad breath may also be a feature.

The aetiology of this condition is poorly understood. An upper GI contrast study will reveal the classical appearance of a dilated, baggy oesophagus with a beaked appearance at the lower end (Figure 45.7). An upper GI endoscopy will reveal a baggy, dilated oesophagus which may contain food debris. This investigation may be important to exclude other even more uncommon conditions and allows an assessment of the presence or absence of inflammation. Affected patients have a high resting lower oesophageal sphincter pressure, failure to relax the lower oesophageal sphincter and poor oesophageal peristalsis on manometry studies.



Figure 45.7 Upper GI contrast study in patient with achalasia of the cardia demonstrating massive dilatation of the oesophagus.

Given our poor understanding of this condition, there is no general consensus of how best to treat it. Drugs (including anticholinergics, calcium channel blockers and nitrates) have little to offer in affected children due to the high incidence of side effects and lack of sustained benefit. Pneumatic balloon dilatation under imaging control may have a place. Repeated dilatations are usually required and complications, including oesophageal rupture, are not uncommon. More recently, botulinum toxin (botox) has been successfully used in several centres.

The surgical management usually involves a myotomy of the lower oesophagus, which is extended onto the stomach, protected by an antireflux procedure performed at the same time. The commonest combination is a Heller cardiomyotomy and a partial fundoplication. This can be achieved laparoscopically.[40] More recently, peroral endoscopic myotomy has been described with comparable results to laparoscopic cardiomyotomy.[41, 42]

Oesophageal injury

Injuries to the oesophagus in children are usually due to the ingestion of noxious substances or foreign bodies. Iatrogenic injuries from instrumentation of the oesophagus during endoscopy or surgery are less common. Prompt identification of the problem is essential if perforation or fistulation to an adjacent structure is to be avoided.

SWALLOWED FOREIGN BODIES

Ingested foreign bodies are not uncommon in children. The nature of the swallowed item varies with the age of the child. Coins, batteries and parts of, or whole, small toys are common in infants and younger children. In older children inadequately chewed foodstuffs are more common, especially in the presence of an underlying oesophageal abnormality including a previously repaired OA or a peptic oesophageal stricture. Children with learning or behavioural difficulties are particularly prone to swallowing foreign bodies.[43]

In the majority of cases the history of ingestion will be known and prompt attendance at an emergency department by anxious parents likely. In some cases, where the history is not known, an inability to swallow food or liquids, drooling, respiratory difficulty, wheeziness, hoarseness or chest discomfort may be the presenting symptom.[44]

Initial assessment should include an evaluation of the airway. A chest and abdominal radiograph will reveal radioopaque foreign bodies. Where the swallowed item is a coin (Figure 45.8), a metal detector can be used to determine whether the coin is lodged in the chest or has passed into the stomach. Foreign bodies which pass into the stomach do not usually require treatment. One exception to this rule is in situations where mini magnetic toys or button batteries have been swallowed. In such cases fistulization between loops of small intestine and subsequent perforation can occur due to the magnets adhering across bowel loops,[43] and leakage of the contents of a battery can cause heavy metal poisoning. Button batteries are now extremely

powerful and can cause rapid and severe ulceration, with a risk of catastrophic erosion of the mediastinal great vessels. NHS England has published an important Patient Safety Alert, *Risk of death and serious harm from delays in recognising and treating ingestion of button batteries*, highlighting the seriousness of swallowing these batteries.[45] See also Chapter 34, Foreign bodies in the ear, nose and throat.

Of greater concern are those items which lodge in the oesophagus. They can get stuck at the level of the thoracic inlet, the cricopharyngeus muscle, the mid-oesophagus behind the heart at the level of the aortic arch and the oesophagogastric junction. Items which get stuck in the proximal oesophagus can obstruct the airway. Items which get stuck more distally are more at risk of causing perforation and mediastinitis. Damage to the oesophagus is caused by direct contact in the case of coins and contact, the release of electrical current and leakage of their contents in the case of batteries. Foreign bodies which are impacted in the oesophagus for some time can cause oesophageal perforation,[46] fistulization into adjacent structures including the great vessels and the trachea, with sometime catastrophic consequences.[46, 47]

Rigid or flexible oesophagoscopy under general anaesthetic and endotracheal intubation to protect the airway is usually the preferred treatment option where the foreign body is impacted in the oesophagus. Different types of graspers and basket devices for use with endoscopes have been developed specifically to remove coins. This is usually fairly straightforward, especially when the coin has a raised rim. Batteries are more difficult to remove due to their smooth edges. A catheter with a balloon on the end is sometimes successful when other techniques have failed.[44] Open safety pins are a particular challenge. These are best pushed into the stomach if the open end is proximal. Once in the stomach, the hinge end of the pin can be grasped and the pin removed, using an oesophageal overtube if one is available.

CAUSTIC INJURY

Ingestion of caustic substances by infants and toddlers is becoming increasingly common. Alkali, or less commonly acid, household cleaning or other agents contained in lemonade bottles stored under the sink are frequently implicated. Newer formulations of clothes and dishwashing liquid in tablet and 'liquitab' form are also implicated (**Figure 45.9**).[48] Impulsive behaviour and attention deficit hyperactivity disorder have been shown to be risk factors for such ingestion.[49]

A child who has swallowed a caustic substance usually presents immediately with symptoms of crying, spitting, coughing and stridor. Potential airway compromise is a serious concern in all such cases. Later symptoms include chest pain, dysphagia and vomiting. Signs of burn injury may be seen on the lips and in the mouth, although the absence of such signs does not exclude ingestion. Fever and tachycardia may also be obvious.

As in swallowed foreign bodies, the first concern in such cases should be the integrity of the airway. Oedema of the larynx caused by the caustic substance might occlude the airway. Prompt endotracheal intubation may be required.

The injuries caused by the ingestion of such substances can be severe. Mucosal slough and necrosis are common. Deeper injury and liquefaction of all layers of the oesophagus can also be seen even after brief exposure to a caustic substance. Attempts to wash the caustic substance away by drinking water may result in an exothermic chemical reaction which may only serve to worsen the injury. Other attempts to neutralize the ingested caustic substance may fail if the pH of the ingested substance is not known, and again may result in an unwanted exothermic chemical reaction.

Children suspected of ingesting caustic agents should be admitted for evaluation. A chest X-ray may be useful. Early intubation may be needed if the airway is at risk. All affected



Figure 45.8 Coin impacted in the upper oesophagus in a toddler. The airway is at risk in this patient and prompt removal of the coin is required.



Figure 45.9 'Liquitabs' are increasingly implicated in caustic injuries.

children should be fasted and intravenous fluids administered. Early endoscopy is usually indicated in all cases to assess the extent and severity of the injury. The markers of superficial injury include mucosal erythema, oedema and mild mucosal damage. Deeper injuries will result in haemorrhage, exudates, mucosal sloughing, pseudomembrane formation and the development of granulation tissue. The deepest injuries will exhibit luminal narrowing or obliteration, severe oedema, eschar formation. Perforation and mediastinitis is possible in severe cases.

Blind passage of an NG tube is contraindicated in these patients. Placement of such a tube during the endoscopy is indicated to facilitate enteral nutrition and to maintain the integrity of the oesophageal lumen. The end of a blind-ending NG tube should be cut off to allow passage of a guidewire in the future. This may be helpful if the NG tube needs to be replaced or if a stricture develops (**Figure 45.10**) and might benefit from balloon dilatation under imaging control (**Figure 45.11**).[50]

The use of antibiotics and steroids to limit the effects of the injury and prevent stricture formation is controversial. Conflicting studies have shown both benefit and none. Serial balloon dilatations are the preferred treatment of a fibrous structure. Clearly, there is a risk of oesophageal perforation during this procedure. Placement of oesophageal stents is less well established. Oesophageal resection and replacement with a colonic or gastric tube may be required in long and the most resistant strictures.

In general terms, acid ingestion is less damaging to the oesophagus than alkali ingestion. Acid causes more damage to the stomach and the pylorus.

DRUG-INDUCED INJURY

Drug-induced oesophageal injury is very rare in children, and is most commonly seen in patients with an underlying structural abnormality. It usually only occurs where tablet or capsular formulations of the medication are used. The tablet or capsule gets stuck above a stricture and the release of its active agent causes oesophageal injury. Implicated drugs include non-steroidal analgesics, aspirin, slow-release potassium and the cycline family of antibiotics.

Symptoms of retrosternal chest pain and dysphagia may be reported. Endoscopic assessment is usually indicated.



Figure 45.10 Upper GI contrast study in patient with a long oesophageal structure caused by the ingestion of a caustic substance.



Figure 45.11 Balloon dilatation of a short stricture in the mid-oesophagus. The stricture can be identified where the balloon narrows.

Stricture formation is rare and, when it occurs, should be treated on its merits. The offending medication should be discontinued.

RADIATION-INDUCED INJURY

Radiation-induced injury of the oesophagus in children is extremely rare but can occur when radiotherapy for thoracic tumours is necessary. It is more common when chemotherapy is administered alongside the radiotherapy. Symptoms include dysphagia and chest pain. Endoscopy may reveal mucosal oedema and aphthous ulceration. Treatment is largely symptomatic.

Mallory Weiss tear

The classical Mallory Weiss tear of the lower oesophagus after a severe bout of vomiting is not common in children. However, the more frequent use of upper gastrointestinal endoscopy in paediatric practice has resulted in its more frequent recognition as an entity in children. The vomiting causes a mucosal tear to develop at the oeosphagogastric junction which bleeds.

The presenting features are usually a protracted period of vomiting followed by a haematemesis. Bleeding is usually self-limiting and acid suppression therapy using either proton pump inhibitors or H2 receptor blockers is usually indicated to encourage healing of the tear. In severe cases, often in the presence of an underlying coagulopathy, use of oesophageal balloon tamponade or pharmacological agents may be required to stop bleeding.

Oesophageal perforation and rupture

In neonates and children, the most common cause of oesophageal perforation or injury is nasogastric intubation, upper gastrointestinal endoscopy or other instrumentation. Swallowed foreign bodies may also be implicated.[51] In some cases where the history is unclear, non-accidental injury may need to be considered.

The risk of mediastinitis should be considered in all such cases and appropriate intravenous antibiotic and antifungal therapy initiated. The child should be fasted and parenteral nutrition may be necessary. Contrast or cross-sectional imaging studies may be helpful in determining the extent of the injury.

In the majority of cases, the oesophagus will heal without direct intervention, although clearly foreign bodies should be removed.

BEST CLINICAL PRACTICE

- ✓ The inability to pass a naso- or oro-gastric tube in the newborn is virtually diagnostic of oesophageal atresia.
- ✓ In oesophageal atresia, otolaryngologists need to be aware of the clinical features so they can arrange appropriate investigations, including tracheobronchoscopy, in most cases,
- ✓ Cross-sectional imaging (CT or MRI) is the most useful investigation for cysts associated with the oesophagus,
- ✓ Ingested coins or similar items lodged in the upper oesophagus can cause airway obstruction – urgent removal is indicated,
- ✓ Ingested button batteries which lodge in the oesophagus should be removed as a matter of some urgency to prevent oesophageal injury,
- ✓ The ingestion of caustic substances can cause laryngeal and airway oedema, inflammation and obstruction,
- ✓ Attempts to wash or neutralize an ingested caustic substance can result in an undesirable exothermic reaction and injury.

FUTURE RESEARCH

- ➤ The development of thoracoscopic surgical techniques and instruments is likely to result in more of the congenital anomalies of the oesophagus being managed thoracoscopically.
- ➤ Basic science and genetic research into the causes and the embryology of congenital anomalies of the oesophagus continues to improve our understanding of these complex conditions.

KEY POINTS

- Antenatal maternal polyhydramnios, which can affect approximately half of pregnancies with the various forms of OA, may give a clue to the presence of this abnormality.
- The newborn affected by any of the common variants of OA (but obviously not the baby with an isolated TOF) will present clinically with frothing at the mouth, choking episodes, cyanosis and respiratory distress. Clearly, attempts at feeding will precipitate such symptoms and may cause aspiration and severe respiratory distress.
- True congenital oesophageal diverticula, which contain all layers of the wall of the oesophagus, are uncommon. False or pulsion diverticula, which are herniations of the oesophageal mucosa between defects in the oesophageal muscular wall, are more common.
- Button batteries are now extremely powerful and can cause rapid and severe ulceration, with a risk of catastrophic erosion of the mediastinal great vessels.
- In general terms, acid ingestion is less damaging to the oesophagus than alkali ingestion. Acid causes more damage to the stomach and the pylorus.

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The Ear

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CHAPTER 46

ANATOMY AND EMBRYOLOGY OF THE EXTERNAL AND MIDDLE EAR

Peter Valentine and Tony Wright

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: external ear, middle ear, ossicles, facial nerve, Eustachian tube AND anatomy OR embryology OR development.

INTRODUCTION

The ear functions as an early warning system by detecting and locating potentially threatening environmental sounds. It is crucial for survival by accurately and rapidly detecting head movement so that the eyes can stay fixed on prey or predator. The ear plays a major part in the balance system, giving important information about sudden changes in the environment, both external and self, to avoid falls and injury. In addition, in many animals, and especially in humans, the ears form a major part of a communication system.

A three-dimensional appreciation of the complex temporal bone anatomy is crucial for the understanding of both the pathophysiology and surgery of the ear. Traditionally, the microscope has been used as the main tool to examine and operate on the temporal bone. In more recent years, endoscopic techniques have enhanced the visualization and magnification of vistas previously unseen.

Both convention and convenience have separated the ear into its three parts – external, middle and internal – for descriptive purposes. The structure of the internal ear is described in detail in Chapter 47, Anatomy of the cochlea and vestibular system: relating ultrastructure to function. This chapter deals with the external ear and the adult middle ear cleft including the mastoid air cell system and Eustachian tube. Finally, the embryology of the ear and subsequent development of the temporal bone, external ear and mastoid process are outlined.

THE EXTERNAL EAR

The auricle

The auricle (or pinna) projects at a variable angle from the side of the head and has some function in collecting sound. The lateral surface of the auricle has characteristic prominences and depressions (**Figure 46.1**), which are different in every individual, even identical twins. This unique pattern is comparable to fingerprints and can allow the identification of persons on the physiognomy of their auricles.[1] The curved rim is the helix, which often has a small prominence (Darwin's tubercle) at its posterosuperior aspect. Anterior to and parallel with the helix is another prominence, the antihelix. Superiorly, this divides into two crura, between which is the triangular fossa; the scaphoid fossa lies above the superior of the two crura. In front of the antihelix, and partly encircled by it, is the concha. This is divided into two portions by the descending limb of the anterior superior portion of the helix, known as the crus of the helix, which rests just above the external auditory meatus. The smaller superior portion is the cymba conchae and is the direct lateral relation to the suprameatal triangle of the temporal bone. The larger inferior portion is known as the cavum conchae. Below the crus of the helix and overlapping the external auditory meatus is the tragus, which is a small blunt triangular prominence pointing posteriorly. Opposite the tragus, at the inferior limit of the antihelix, is the antitragus. The intertragic notch separates the tragus from the antitragus. The lobule

lies below the antitragus and is soft, being composed of fibrous and adipose tissue. The medial (cranial) surface of the auricle has elevations corresponding to the depressions on the lateral surface, and possesses corresponding names, for example the eminentia conchae.

The body of the auricle is formed from elastic fibrocartilage and is a continuous plate except for a narrow gap between the tragus and the anterior crus of the helix, where it is replaced by a dense fibrous tissue band. This gap is the site for an endaural incision which, properly performed, should not damage cartilage or its perichondrium and which by splitting the soft-tissue ring surrounding the bony ear canal allows wide exposure of the deeper parts.

The cartilage extends about 8 mm down the ear canal to form its lateral third. The cartilage of the auricle is covered with perichondrium from which it derives its supply of nutrients, as cartilage itself is avascular. Stripping the perichondrium from the cartilage, as occurs following injuries that cause haematoma, can lead to cartilage necrosis with crumpled up 'boxer's ears'. The skin of the pinna is thin and closely attached to the perichondrium on the lateral surface. On the medial (cranial) surface, there is a definite subdermal adipose layer that allows dissection during pinnaplasty surgery. The skin of the auricle is covered with fine hairs and, most noticeably in the concha and the scaphoid fossa, there are sebaceous glands opening into the root canals of these hairs. On the tragus and intertragic notch coarse, thick hairs may develop in the middle-aged and older male.

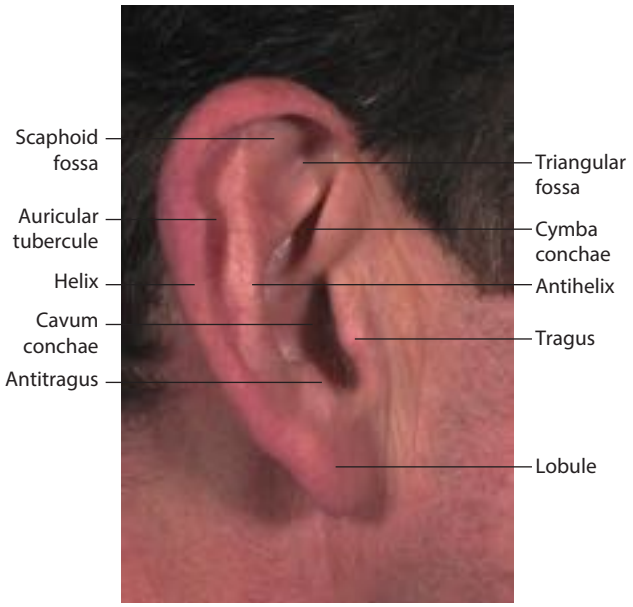


Figure 46.1 Right auricle.

The cartilage of the auricle is connected to the temporal bone by two extrinsic ligaments. The anterior ligament runs from the tragus and from a cartilaginous spine on the anterior rim of the crus of the helix to the root of the zygomatic arch. A separate posterior ligament runs from the medial surface of the concha to the lateral surface of the mastoid prominence. Intrinsic ligaments connect various parts of the cartilaginous auricle; that between helix and tragus has already been described and another runs from the antihelix to the posteroinferior portion of the helix. Extrinsic and intrinsic muscles are attached to the perichondrium of the cartilage. Temporal and posterior auricular branches of the facial nerve supply the extrinsic muscles and, while being functionally unimportant, they do give rise to the postauricular myogenic response following appropriate auditory stimulation.[2] There are three extrinsic muscles: auricularis anterior, superior and posterior, the last being supplied by the posterior auricular branch of the facial nerve. All three radiate out from the auricle to insert into the epicranial aponeurosis. The intrinsic muscles – six in number – are small, inconsistent and without useful function.

Arterial branches of the external carotid supply the auricle. The posterior auricular appears to be the dominant artery and supplies the medial surface (except the lobule), the concha, the middle and lower portions of the helix and the lower part of the antihelix. The anterior auricular branches of the superficial temporal supply the upper portions of the helix, antihelix, triangular fossa, tragus and lobule.[3] The superior auricular artery has a constant course and connects the superior temporal artery and the posterior auricular artery network. This branch can provide a reliable vascular pedicle for retroauricular flaps.[4] A small auricular branch from the occipital artery may assist the posterior auricular in supplying the medial surface.

Both cranial branchial nerves and somatic cervical nerves supply the auricle. Their distribution is heterogeneous and the overlap may be extensive; however, the greater auricular nerve prevails on the lateral and medial surfaces.[5] The essential features are described in Table 46.1.

The lymphatic drainage from the posterior surface is to the lymph nodes at the mastoid tip, from the tragus and from the upper part of the anterior surface to the preauricular nodes, and from the rest of the auricle to the upper deep cervical nodes.

TABLE 46.1 Sensory innervation of the auricle

Nerve	Derivation	Region supplied
Greater auricular	Cervical plexus C2, 3	Medial surface and posterior portion of lateral surface
Lesser occipital	Cervical plexus C2, 3	Superior portion of medial surface
Auricular	Vagus X	Concha and antihelix Some supply medial surface (eminetia concha)
Auriculotemporal	Vc mandibular	Tragus, crus of helix and adjacent helix
Facial VII		Probably supplies small region in the root of concha

The external auditory canal

The external auditory canal extends from the concha of the auricle to the tympanic membrane and is approximately 2.4 cm long. The supporting framework of the canal wall is cartilage in the lateral one-third and bone in the medial two-thirds. The diameter of the canal varies greatly between individuals and between different races. In adults, the cartilaginous portion runs inwards, slightly downwards and forwards. The canal is straightened, therefore, by gently moving the auricle upwards and backwards to counteract the direction of the cartilaginous portion. In the neonate, there is virtually no bony external meatus as the tympanic bone is not yet developed, and the tympanic membrane is more horizontally placed so that the auricle must be gently drawn downwards and backwards for the best view of the tympanic membrane.

In the adult, the lateral cartilaginous portion is about 8 mm long and is continuous with the auricular cartilage. The medial border of the meatal cartilage is attached to the rim of the bony canal by fibrous bands. There are two horizontal fissures, described by Santorini, that lie anteroinferiorly in the cartilaginous portion that possibly increase flexibility but allow passage of infection or tumour into the parotid gland. The bony canal wall, about 1.6 mm long, is narrower than the cartilaginous portion and itself becomes smaller closer to the tympanic membrane. The medial end of the bony canal is marked by a groove, the tympanic sulcus, which is absent superiorly. Although the tympanic bone makes up the greater part of the canal, and also carries the sulcus, the squamous bone forms the roof. Therefore, there are two suture lines in the canal wall with the tympanosquamous anteriorly and the tympanomastoid posteriorly. These suture lines may be more or less developed; they project into the canal with overlying closely adherent skin, which can make raising an intact tympanomeatal flap a challenge. The tympanomastoid suture is a complex suture line between the anterior wall of the mastoid process, a portion of the squamous bone and the tympanic bone.

Apart from these intrusions into the canal, there are two constrictions: one at the junction of the cartilaginous and bony portions and the other, the isthmus, 5 mm from the tympanic membrane where a prominence of the anterior canal wall reduces the diameter. Deep to the isthmus, the anteroinferior portion of the canal dips forwards forming a wedge-shaped anterior recess between the tympanic membrane and the canal. This recess can be a difficult spot for access either in the clinic or at surgery.

The external canal is lined with keratinizing stratified squamous epithelium, which lacks the rete pegs and skin appendages in the thin skin of the bony canal. Body skin normally grows directly from the basal layers towards the surface where it is shed into the surroundings. Excess proliferation in the scalp trapped by the hair is dandruff. If this pattern of growth were to occur in the external ear canal, the canal would soon become filled with desquamated skin. Instead of maturation taking place directly towards the surface, there is outward, oblique growth of the epidermis of the canal skin[6] and pars flaccida so that the surface layers effectively migrate towards the external opening of the canal. The normal rate of migration is about 0.1 mm/day,[7] although this range is hugely variable and in some conditions there is complete failure of migration with a consequent build-up of shed keratin in the ear canal. It has been postulated that patients who are prone to cerumen impaction may lack a 'keratinocyte attachment destroying substance' (KADS) based on the observation they have much longer sheets of desquamated keratin which are in continuity with the stratum corneum, when compared to patients with no issue.[8, 9]

The skin of the pars tensa has a different derivation from that of the deep canal and cell divisions occur randomly within the layer of basal cells. The effect of this, in a circular sheet with the handle of the malleus forming a central boundary extending halfway down the membrane, is to create outward mass migration of the skin of the pars tensa. Ink dots applied to the surface have an outward pattern of movement. However, if a hole is made in the tympanic membrane and a graft laid underneath the membrane (an underlay graft), migration of the skin from the outer edge of the perforation is directed centrally to cover the graft. This occurs because the boundary conditions have altered and fortunately provides the basis for the healing of grafts and for the re-epithelialization of mastoid cavities. Even a small piece of pars tensa skin has this ability and so is a precious material and needs to be preserved during ear surgery if a bare area needs covering. However, the property of canal skin to migrate can also bring problems with the formation of cholesteatoma if the skin becomes displaced into the middle ear cleft.

At the outer limits of the ear canal are some short hairs that project towards the opening of the canal. There are fine vellus hairs and larger terminal hairs called tragi (Greek: 'goat'), which tend to be more prominent in males in whom they are a second sexual characteristic. These hairs are oriented with their tips laterally and increase in number and length from the bony-cartilaginous junction laterally, so helping to prevent the entrance of foreign bodies. In the skin of the cartilaginous canal are clusters of ceruminous and sebaceous glands. The ceruminous glands are modified apocrine sweat glands that open into the root canal of the hair follicles and produce a watery, white secretion that slowly darkens, turning semi-solid and sticky as it dries. Since these glands are apocrine sweat glands, they respond to many stimuli such as adrenergic drugs, fever and emotion which, along with direct mechanical stimulation, can all produce an increase or altered secretion.

The sebaceous glands produce an oily material (sebum) from the breakdown of their fat-containing cells which is usually excreted into the root canals of the hair follicles. The mixture of desquamated cells, cerumen and sebum forms wax. Human earwax is a Mendelian trait consisting of wet and dry forms. Dry wax, lacking cerumen, is yellowish or grey and brittle, while wet wax is brownish and sticky. The wet phenotype is dominant over the dry type, and is frequently seen in populations of European and African origins. East Asians show the dry phenotype and there are intermediate frequencies among the Native American and Inuit of Asian ancestry. A single-nucleotide polymorphism in the *ABCC11* gene is responsible for the determination of earwax type, with the *AA* genotype corresponding to dry wax and *GA* and *GG* to wet wax.[10] There is dispute with regard to the specific antibacterial activity of cerumen in

in vitro studies.[11,12] However, the areas of skin that take part in cerumen production have all the components of an active local immune system and probably protect the canal by an antibody-mediated local immune response.[13]

Wax is not usually found in the deep ear canal and a lump of 'wax' overlying the upper portion of the tympanic membrane (pars flaccida or attic region) is rarely true wax, but is nearly always associated with an underlying cholesteatoma as it is, in fact, dried-up, oxidized keratin. The sense of the old adage 'beware the attic wax' is still just as true today as it was in the past.

The arterial supply of the external meatus is derived from branches of the external carotid. The auricular branches of the superficial temporal artery supply the roof and anterior portion of the canal. The deep auricular branch of the first part of the maxillary artery arises in the parotid gland behind the temporomandibular joint, pierces the cartilage or bone of the external meatus and supplies the anterior meatal wall skin and the epithelium of the outer surface of the tympanic membrane. Finally, auricular branches of the posterior auricular artery pierce the cartilage of the auricle and supply the posterior portions of the canal. The veins drain into the external jugular vein, the maxillary veins and the pterygoid plexus. The lymphatic drainage follows that of the auricle.

The external auditory canal receives its sensory innervation from the trigeminal, facial, glossopharyngeal and vagus nerves. Frequently, patients can cough when undergoing microsuction of the canal which is caused by stimulation of the vagus nerve via Arnold's nerve, its auricular branch.

The relationships of the external canal are depicted in Figure 46.2 and a coronal section through the external canal and middle ear are shown in Figure 46.3.

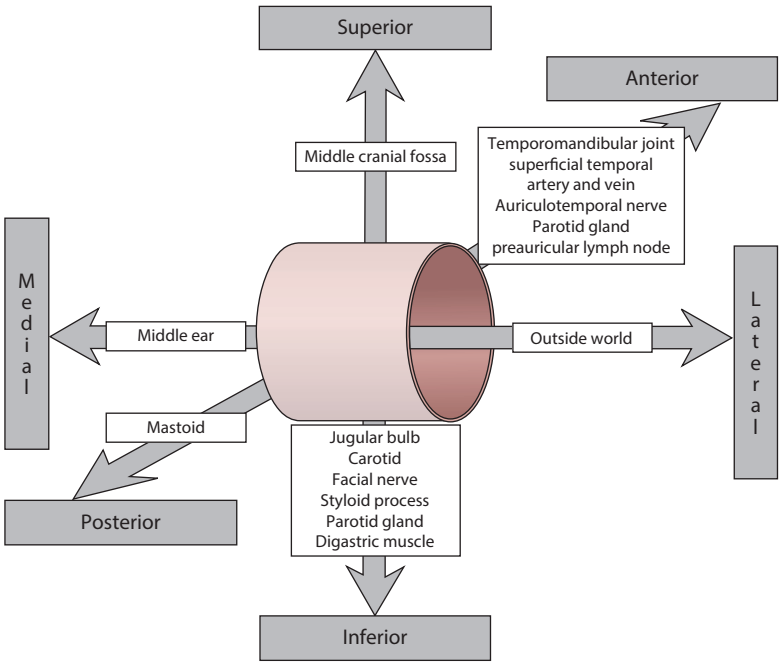
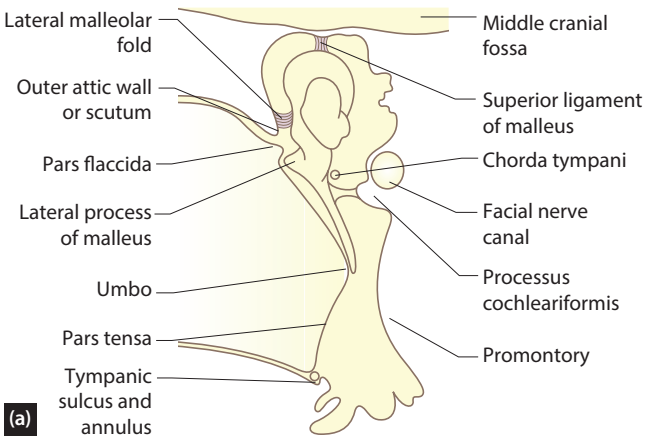


Figure 46.2 Relationships of the right external auditory canal.



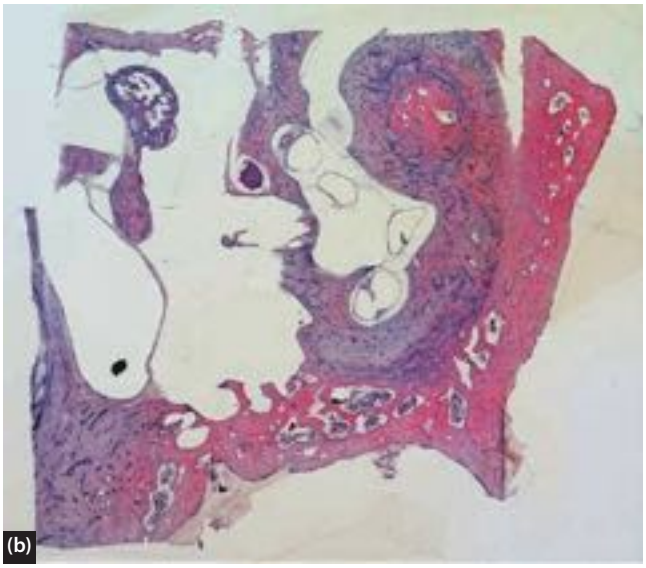


Figure 46.3 (a) Diagram of a coronal section through the external canal and middle ear at the level of the malleus handle. **(b)** Photomicrograph of a more posterior coronal section, including the malleus and the stapes.

THE MIDDLE EAR CLEFT

The middle ear cleft consists of the tympanic cavity, the Eustachian tube and the mastoid air cell system. The tympanic cavity is an irregular, air-filled space within the temporal bone between the tympanic membrane laterally and the osseous labyrinth medially. It contains the auditory ossicles and the tendons that attach them to the middle ear muscles. Other structures, including the tympanic segment of the facial nerve, run along its walls to pass through the cavity.

The tympanic membrane

The tympanic membrane lies at the medial end of the external auditory meatus and forms the majority of the lateral wall of the tympanic cavity. It is slightly oval in shape, being broader above than below, forming an angle of about 55° with the floor of the meatus. Its longest diameter from posterosuperior to anteroinferior is 9–10 mm, while perpendicular to this the shortest diameter is 8–9 mm. Most of the circumference is thickened to form a fibrocartilaginous ring, the tympanic annulus, which sits in a groove in the tympanic bone, the tympanic sulcus. The sulcus does not extend into the notch of Rivinus at the roof of the canal, which is formed by part of the squama of the temporal bone. From the superior limits of the sulcus, the annulus becomes a fibrous band which runs centrally as anterior and posterior malleolar folds to the lateral process of the malleus, the handle of which is clearly visible within the tympanic membrane. This leaves a small, triangular region of tympanic membrane above the malleolar folds within the notch of Rivinus, called the pars flaccida, which does not have a tympanic annulus at its margins. The pars tensa forms the rest of the tympanic membrane and is concave towards the ear canal but each segment is slightly convex between the lateral attachment of the annulus and the centre of the membrane where the tip of the malleus handle is attached at the umbo (Figure 46.4).



Figure 46.4 Endoscopic photograph of the right tympanic membrane.

Both the pars tensa and pars flaccida comprise three layers. There is an outer epithelial layer, the epidermis, which is continuous with the skin of the external meatus; a middle, mainly fibrous layer, the lamina propria; and an inner mucosal layer continuous with the lining of the tympanic cavity. The lamina propria of the pars tensa has radially oriented fibres in the outer layers and circular, parabolic and transverse fibres in the deeper layer. This arrangement probably accounts for the complex pattern of tympanic membrane displacement during sound stimulation. In the pars flaccida, the lamina propria is less marked and the orientation of the collagen fibres seems random.

The arterial supply of the tympanic membrane arises from branches supplying both the external auditory meatus and the middle ear. These two sources interconnect through extensive anastomoses within the connective tissue layer of the lamina propria. The epidermal vessels originate from the deep auricular branch of the maxillary artery coming from the external auditory meatus, whereas the mucosal vessels arise from the anterior tympanic branches of the maxillary artery, the stylomastoid branch of the posterior auricular artery and probably from the middle meningeal artery.

Branches of the auriculotemporal nerve (Vc), the auricular branch of the vagus and the tympanic branch of the glossopharyngeal nerve supply the tympanic membrane. These also run in the lamina propria and, while variations and overlap are considerable, both the vascular supply and innervation are relatively sparse in the middle part of the posterior half of the tympanic membrane.

The tympanic cavity

The tympanic cavity is traditionally divided into three compartments: the epitympanum (upper), the mesotympanum (middle) and hypotympanum (lower). The epitympanum, or attic, lies above the level of the malleolar folds and is separated from the mesotympanum and hypotympanum by a series of mucosal membranes and folds. The hypotympanum lies below the level of the inferior part of the tympanic sulcus and is continuous with the mesotympanum above. With the advent of endoscopic ear surgery, the mesotympanum may be considered as that part of the middle ear visible through the external canal with a microscope. The retrotympanum lies posterior to it and includes both the posteriomedial and posterior walls of the tympanic cavity, whereas the protympanum is anterior to the promontory and is contiguous with the tympanic portion of the Eustachian tube.

THE LATERAL WALL

The lateral wall of the tympanic cavity is formed by the bony lateral wall of the epitympanum superiorly, the tympanic membrane centrally and the bony lateral wall of the hypotympanum inferiorly. The lateral epitympanic wall is wedge-shaped in section and its sharp inferior portion is also called the outer attic wall or scutum (Latin: 'shield'). It is thin and easily eroded by cholesteatoma, leaving a telltale sign on a high-resolution coronal CT scan.

Three holes are present in the bone of the medial surface of the lateral wall of the tympanic cavity. The petrotympanic fissure is a slit about 2 mm long which opens anteriorly just above the attachment of the tympanic membrane. It receives the anterior malleolar ligament and transmits the anterior tympanic branch of the maxillary artery to the tympanic cavity. The chorda tympani, which carries taste sensation from the anterior two-thirds of the same side of the tongue and secretomotor fibres to the submandibular gland, enters the medial surface of the fissure through a separate anterior canaliculus (canal of Huguier) which is sometimes confluent with the fissure. It then runs posteriorly between the fibrous and mucosal layers of the tympanic membrane, across the upper part of the handle of the malleus and then continues within the membrane, but below the level of the posterior malleolar fold (**Figure 46.5**). The nerve reaches the posterior bony canal wall just medial to the tympanic sulcus, enters the posterior canaliculus and then runs obliquely downwards and medially through the posterior wall of the tympanic cavity until it reaches the facial nerve. The point of entry of the chorda tympani into the facial nerve bundle is quite variable. Usually this is at the level of the inferior third of the facial canal on its anterior wall, but on occasions the chorda can leave the skull base by a separate foramen before it joins the facial nerve.[14] During cortical mastoidectomy, the fibrous strands of the tympanomastoid suture line can often be confused with the chorda tympani although the angle of the white strands of the suture line is different from the angle of the chorda.

THE ROOF

The roof of the epitympanum is the tegmen tympani, a thin bony plate that separates the middle ear space from the middle cranial fossa. Both the petrous and squamous portions of the temporal bone form it; and the petrosquamous suture line, which does not close until adult life, can provide a route of access for infection into the extradural space in children. Veins from the tympanic cavity running to the superior petrosal sinus pass through this suture line. There is a bony crest, known as the cog, which projects from the tegmen tympani caudally to lie anterior to the head of the malleus and can be of variable size. This structure divides the larger posterior epitympanic space from the smaller anterior epitympanic space, where residual cholesteatoma may be left if not formally explored in canal wall-up surgery (**Figure 46.6**).

THE FLOOR

The floor of the tympanic cavity may consist of compact or pneumatized bone with spines and trabeculae. It separates the hypotympanum from the dome of the jugular bulb and its thickness can vary according to the height of the jugular fossa. Occasionally, the floor is deficient and the jugular bulb is then covered only by fibrous tissue and a mucous membrane. This should be kept in mind when raising the inferior portion of a tympanomeatal flap. At the junction of the floor and the medial wall of the cavity there is a small opening, the inferior tympanic canaliculus, that allows the entry of the tympanic branch of the glossopharyngeal nerve or Jacobson's nerve into the middle ear from its origin below the base of the skull. This also carries preganglionic parasympathetic fibres from the inferior salivary nucleus on their course to the otic ganglion.

THE ANTERIOR WALL

The anterior wall of the tympanic cavity is rather narrow as the medial and lateral walls converge. The lower third of the anterior wall consists of a plate of bone covering the carotid artery as it enters the skull and before it turns anteriorly. This plate, which can be wafer thin or up to 3 mm thick, is perforated by the superior and inferior caroticotympanic nerves carrying sympathetic fibres to the tympanic plexus and by tympanic branches of the internal carotid artery. In around 2% of cases, the bone



Figure 46.5 The tympanic membrane viewed from the middle ear. The corda tympani (CT) runs superior to the tensor tympani (TT) in its passage across the tympanic membrane, and lies medial to the anterior malleolar ligament in the anterior attic. The aditus to the mastoid antrum (A) lies posterosuperior to the short process of incus (I).

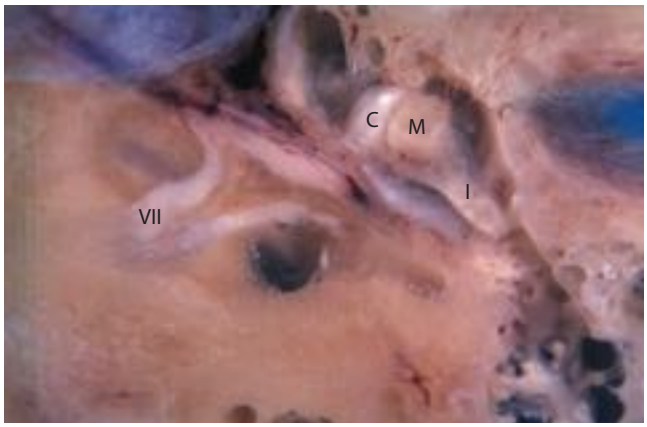


Figure 46.6 A specimen cut axially at the level of the labyrinthine and intratympanic segments of the facial nerve (VII), showing a small cholesteatoma (C) lying between the head of the malleus and anterior epitympanic space. The ossicular heads resemble a scoop of ice cream in a cone, which can be readily seen on a high-resolution axial CT scan. I, incus; M, malleus.

is dehiscent so that the artery is exposed in the protympanum.[15] The middle third of the anterior wall comprises the tympanic orifice of the Eustachian tube which can be irregular, rectangular or triangular in shape and average 5 × 4 mm in diameter.[16] Just above this is a canal containing the tensor tympani muscle that subsequently runs along the medial wall of the tympanic cavity enclosed in a thin bony sheath. The upper third is usually pneumatized and may house the supratubal recess, a small niche that can be separated from the anterior epitympanic space by the tensor fold.

THE MEDIAL WALL

The medial wall separates the tympanic cavity from the internal ear. The promontory is a rounded elevation occupying much of the central portion of the medial wall. It covers part of the basal coil of the cochlea and usually has small grooves on its surface containing the nerves which form the tympanic plexus. Sometimes the groove containing the tympanic branch of the glossopharyngeal nerve may be covered by bone, thereby forming a small canal (**Figure 46.7**). The promontory gently inclines forwards to merge with the anterior wall of the tympanic cavity in the protympanum but is more steeply sloped posteriorly.

Behind and above the promontory is the oval window. This is a nearly kidney-shaped opening that connects the tympanic cavity with the vestibule, but which in life is closed by the footplate of the stapes and its surrounding annular ligament. Its size naturally varies with the size of the footplate, but on average it is 3.25 mm long and 1.75 mm wide. The oval window lies at the bottom of a depression or niche that can be of varying width depending on the position of the facial nerve superiorly, and the prominence of the promontory inferiorly (**Figure 46.8**).

The round window niche lies below and a little behind the oval window niche from which it is separated by a posterior extension of the promontory forming a bony ridge called the subiculum. Another ridge of bone – the ponticulus – leaves the promontory above the subiculum and runs to the pyramid on the posterior wall of the cavity. Occasionally, this structure can resemble a bridge with a medial communication between the sinus tympani and posterior sinus, a space lying behind the posterior crus of the stapes. The round window niche is most commonly triangular in shape, with anterior, posterosuperior and posteroinferior walls. The latter two meet posteriorly and lead to the sinus tympani. The round window membrane is usually out of sight, obscured by the overhanging edge of the promontory forming the niche and mucosal folds within it. The membrane is roughly oval in shape, about 2.3 × 1.9 mm in dimension and lies in a plane at right angles to the plane of the stapes footplate. It tends to curve towards the scala tympani of the basal coil of the cochlea, so that it is concave when viewed from the middle ear, and it appears to be divided into an anterior and posterior portion by a transverse thickening. A further ridge of bone inferiorly running between the basal helix of the cochlea and the bone over the jugular bulb can used as a convenient landmark to separate the retrotympanum from the hypotympanum. Although first identified by Proctor,[17] this has been renamed by Marchioni et al.[18] as the finiculus (Latin: 'borderline').

The facial nerve canal (or Fallopian canal) runs above the promontory and oval window in an anteroposterior direction. It has a smooth, rounded lateral surface that often has microdehiscences and when the bone is thin or the nerve exposed by disease, there are two or three straight blood vessels clearly visible along this line of nerve. These are the only straight blood vessels in the middle ear and indicate quite clearly that the facial nerve is very close by. The facial nerve canal is marked anteriorly by the processus cochleariformis, a curved projection of bone, concave anteriorly, which houses the tendon of the tensor tympani muscle as it turns laterally to the handle of the malleus. Behind the oval window, the facial canal



Figure 46.7 The medial wall of the mesotympanum seen after removal of the tympanic membrane. The tympanic branch of the glossopharyngeal nerve (IX) can be seen crossing the promontory. Note the notch of Rivinus in the roof of the canal.

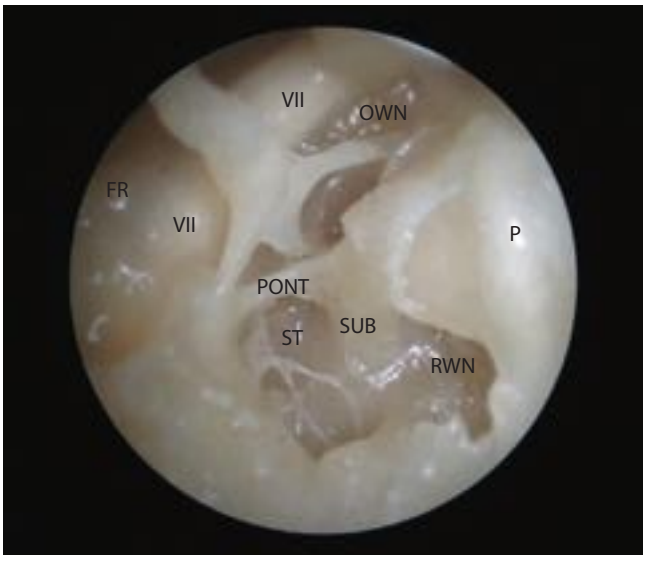


Figure 46.8 Endoscopic view of the retrotympanum showing the relationship between the oval window niche (OWN), round window niche (RWN), promontory (P), facial nerve (VII) and facial recess (FR). The sinus tympani (ST) lies medial to the facial nerve between the ponticulus (PONT) and subiculum (SUB).

starts to turn inferiorly as it begins its descent in the posterior wall of the tympanic cavity (Figure 46.9).

The region above the level of the facial nerve canal forms the medial wall of the epitympanum. The dome of the lateral semicircular canal is the major feature of the posterior portion of the epitympanum, lying posterior and extending a little lateral to the facial canal. During a cortical mastoidectomy, the triangular relationship of the lateral semicircular canal, the short process of the incus and the seventh nerve is often quite helpful. In well-aerated mastoid bones, the labyrinthine bone over the superior semicircular canal may be prominent, running at right angles to the lateral canal and joining it anteriorly at a swelling which houses the ampullae of the two canals. In front and a little below this, above the processus cochleariformis, may be a slight swelling corresponding to the geniculate ganglion, with the bony canal of the greater superficial petrosal nerve running for a short distance anteriorly.

THE POSTERIOR WALL

The posterior wall is wider above than below and has in its upper part a large irregular opening – the aditus ad antrum – that leads back from the posterior epitympanum into the mastoid antrum (Figure 46.10). Below the aditus is a small depression, the fossa incudis, which houses the short process of the incus and its suspensory ligament. Below the fossa incudis and medial to the opening of the chorda tympani nerve is the pyramid, a small hollow conical projection with its apex pointing anteriorly. This houses the stapedius muscle and tendon, which inserts into the posterior aspect of the head of stapes. The canal within the pyramid curves downwards and backwards to join the descending portion of the facial nerve canal.

The facial recess is a groove which lies between the pyramid and facial nerve and the annulus of the tympanic membrane (Figure 46.11). This is shallower lower down where the facial nerve canal forms only a slight prominence on the posterior wall. The facial recess is, therefore, bounded medially by the facial nerve and laterally by the tympanic annulus, with the chorda tympani nerve running obliquely through the wall between the two. The chorda always runs medial to the tympanic membrane, which means that the angle between the facial nerve and the chorda allows a posterior tympanotomy to be cut, thereby accessing the middle ear from the mastoid without disruption to the tympanic membrane (Figure 46.12). This angle can be small or large depending on the site of origin of the chorda from the facial nerve.

The sinus tympani is a posterior extension of the mesotympanum into the posterior wall and lies deep to the facial nerve, pyramid and stapedius muscle. It varies in size and, when extensive, is probably one of the most inaccessible sites in the middle ear when operating with the microscope. A surgical view can be enhanced using a 45° endoscope introduced from the opposite side of the ear being observed. The medial wall of the sinus tympani becomes continuous with the posterior portion of the medial wall of the tympanic cavity in the retrotympanum, and it is bounded superiorly by the ponticulus and inferiorly by the subiculum. Its importance is that cholesteatoma which has extended here from the mesotympanum is extremely difficult to eradicate. As the sinus can extend as far as 9 mm

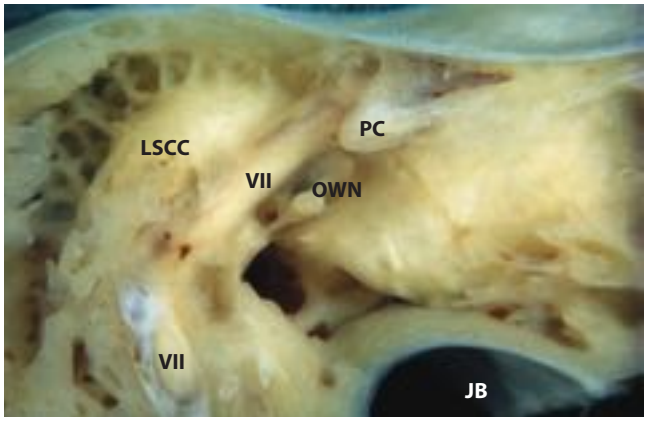


Figure 46.9 A specimen cut to show the medial wall of the tympanic cavity. The processus cochleariformis (PC) marks the anterior position of the intratympanic portion of the facial nerve, which passes between the lateral semicircular canal (LSCC) and oval window niche (OWN). Note the jugular bulb (JB) in the floor of the tympanic cavity.

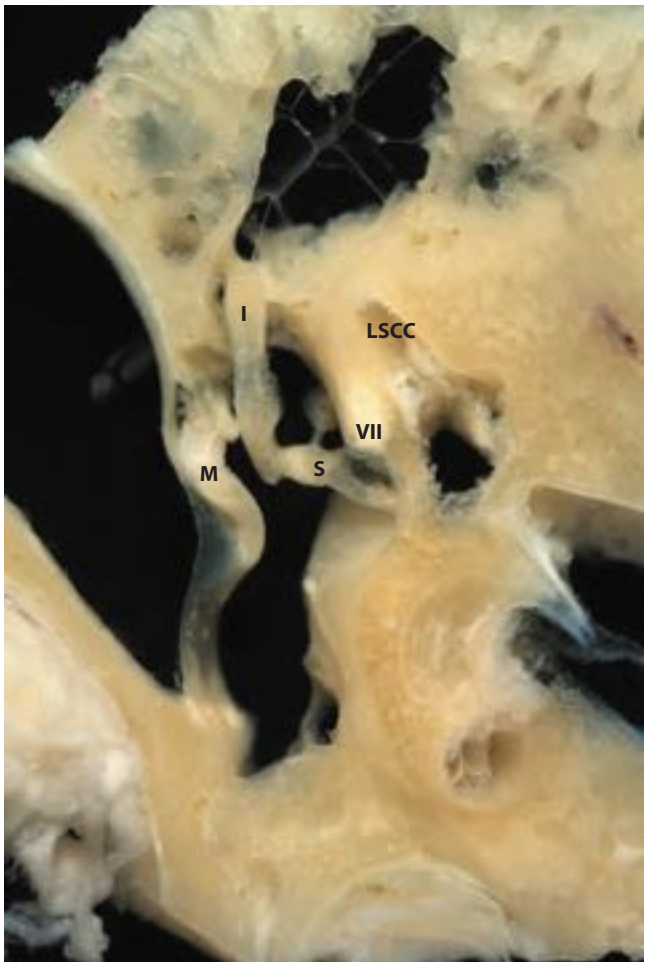
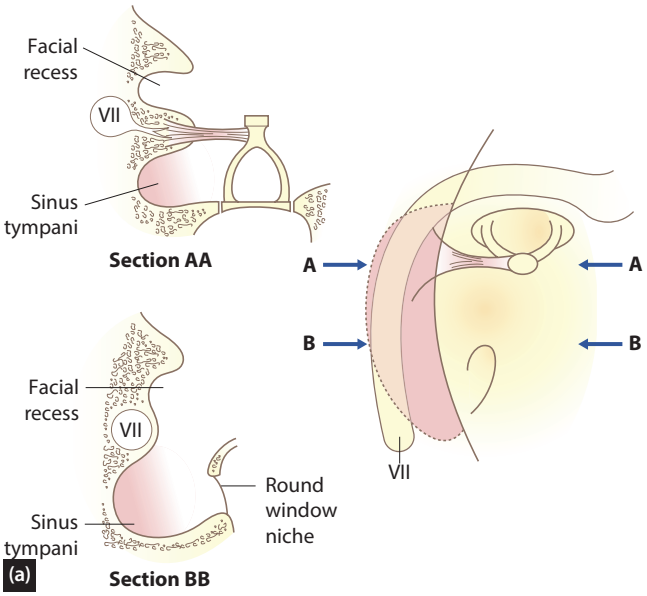


Figure 46.10 A specimen cut coronally at the level of the long process of incus. The aditus to the mastoid antrum lies posterosuperiorly to the incus (I). LSCC, lateral semicircular canal; M, malleus; S, stapes; VII, facial nerve.



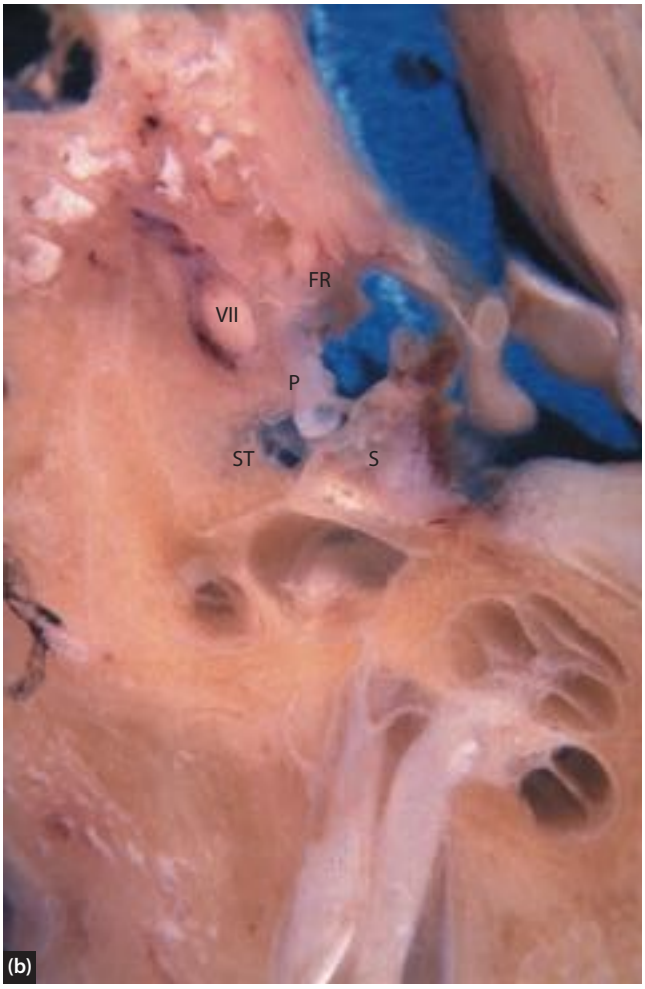


Figure 46.11 (a) The facial recess and sinus tympani at different levels in the middle ear. Section AA is at the level of the pyramid where the facial recess is relatively deep. In section BB, at the level of the round window, the facial recess is quite shallow. The extent of the sinus tympani, deep and posterior to the facial nerve is variable. **(b)** A specimen in section AA at the level of the pyramid (P). S, stapes; VII, facial nerve FR, facial recess; ST, sinus tympani.

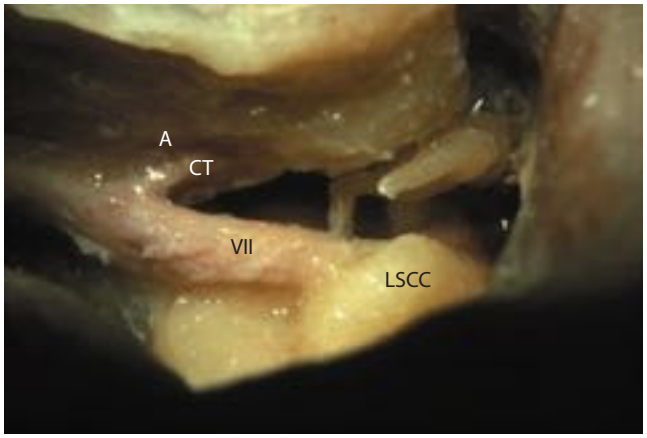


Figure 46.12 Posterior tympanotomy in a left ear, showing the relationship of the facial nerve (VII), corda tympani (CT), annulus (A) and lateral semicircular canal (LSCC). The promontory is readily accessible via this approach in cochlear implant surgery.

into the mastoid bone when measured from the tip of the pyramid,[19] a retrofacial dissection inferior to the posterior semicircular canal may be required should the disease be out of reach using a transcanal endoscopic approach.

The relationships of the middle ear space are shown diagrammatically in Figure 46.13.

The contents of the tympanic cavity

The tympanic cavity contains the ossicles, two muscles, the chorda tympani and the tympanic plexus. The ossicles are the malleus, incus and stapes that form a semi-rigid bony chain for conducting sound. They can be seen photographed with a scale in Figure 46.14. The malleus is the most lateral and is attached to the tympanic membrane, whereas the stapes is attached to the oval window.

THE MALLEUS

The malleus is the largest of the three ossicles, measuring up to 9 mm in length. It comprises a head, neck and handle or manubrium. The head lies in the epitympanum and is suspended by the superior ligament, which runs upwards to the tegmen tympani. The head of the malleus has a saddle-shaped facet on its posteromedial surface to articulate with the body of the incus by way of a synovial joint. Below the neck of the malleus, the bone broadens and gives rise to the lateral process, the anterior process and the handle. The lateral process is a prominent landmark on the tympanic membrane and receives the anterior and posterior malleolar folds from the tympanic annulus. The chorda tympani crosses the upper part of the malleus handle on its medial surface above the insertion of

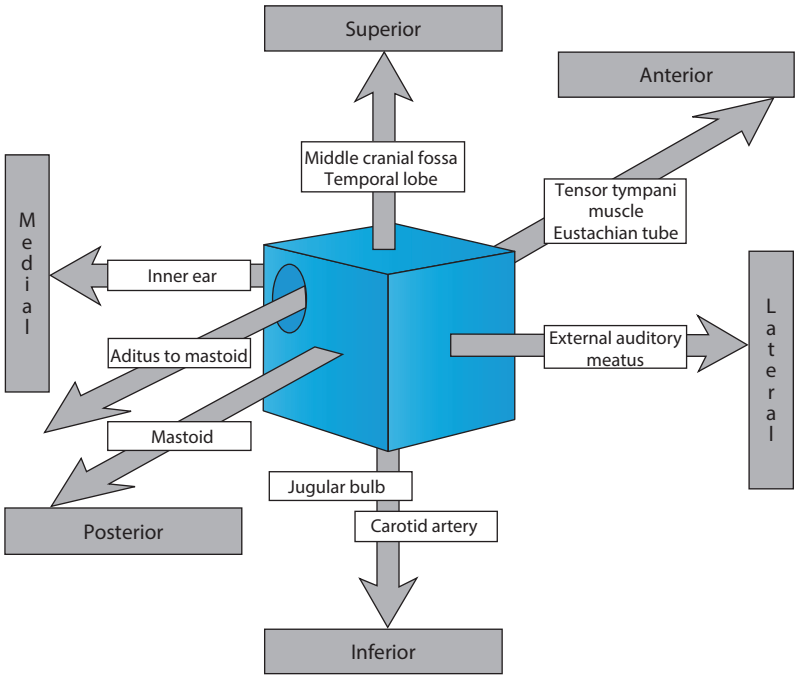


Figure 46.13 The relationships of the right middle ear.

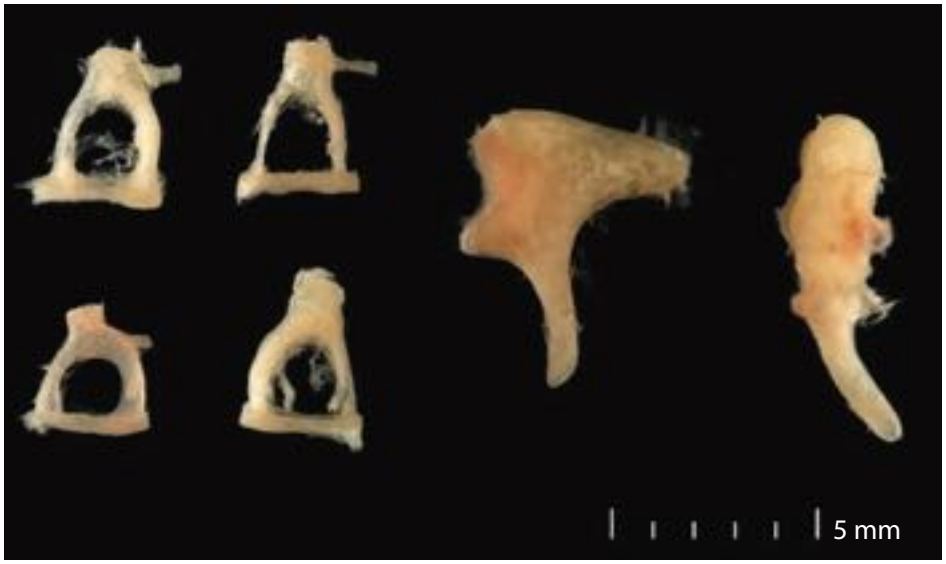


Figure 46.14 Stapes, incus and malleus with scale.

the tendon of tensor tympani, but below the neck of the malleus itself. The neck of the malleus connects the handle with the head and amputation of the head by cutting through the neck leaves both chorda tympani and tensor tympani intact. A slender anterior ligament arises from the anterior process to insert into the petrotympanic fissure. The handle runs downwards, medially and slightly backwards between the mucosal and fibrous layers of the tympanic membrane. While it is very closely attached to the membrane at its lower end, there is a fine web of mucosa separating the membrane from the handle in the upper portion before it becomes adherent again at the lateral process. This can be opened surgically to create a slit without perforating the membrane to allow a prosthesis to be crimped around the malleus handle in certain types of ossicular reconstruction. On the deep, medial surface of the handle, near its upper end, is a small projection into which the tendon of the tensor tympani muscle inserts.

THE INCUS

The incus articulates with the malleus and has a body and two processes. The body lies in the epitympanum and has a cartilage-covered facet corresponding to that on the malleus. The body of the incus is suspended by the superior incudal ligament that is attached to the tegmen tympani. The short process projects backwards from the body to lie in the fossa incudis to which it is attached by a short suspensory ligament. The long process descends into the mesotympanum behind and medial to the handle of the malleus, and at its tip is a small medially directed lenticular process. This has sometimes been called the fourth

ossicle because of its incomplete fusion with the tip of the long process, thereby giving the appearance of a separate bone or at least a sesamoid bone. The lenticular process articulates with the head of the stapes.

THE STAPES

The stapes is shaped like a stirrup and consists of a head, neck, the anterior and posterior crura and a footplate. The head points laterally and has a small cartilage-covered depression for a synovial articulation with the lenticular process of the incus. The stapedius tendon inserts into the posterior part of the neck and upper portion of the posterior crus. The two crura arise from the broader lower part of the neck and the anterior crus is thinner and less curved than the posterior one. Both are hollowed out on their concave surfaces, which gives an optimum combination of strength and lightness. The two crura join the footplate, which usually has a convex superior margin, an almost straight inferior margin and curved anterior and posterior ends. The average dimensions of the footplate are 3 mm long and 1.4 mm wide, and it lies in the oval window where it is attached to the bony margins by the annular ligament. The long axis of the footplate is almost horizontal, with the posterior end being slightly lower than the anterior. There is great variation in the shape of the two crura.

THE STAPEDIUS MUSCLE

The stapedius arises from the walls of the conical cavity within the pyramid and from the downward curved continuation of this canal in front of the descending portion of the facial nerve. A slender tendon emerges from the apex of the pyramid and inserts into the stapes. The muscle is supplied by a small branch of the facial nerve.

THE TENSOR TYMPANI MUSCLE

This is a long, slender muscle arising from the walls of the bony canal lying above the Eustachian tube. Parts of the muscle also arise from the cartilaginous portion of the Eustachian tube and the greater wing of the sphenoid. From its origins, the muscle passes backwards into the tympanic cavity where it lies on the medial wall, a little below the level of the facial nerve. The bony covering of the canal is often deficient in its tympanic segment where the muscle is replaced by a slender tendon. This enters the processus cochleariformis (see **Figure 46.9**) where it is held down by a transverse tendon as it turns through a right angle to pass laterally and insert into the medial aspect of the upper end of the malleus handle. The muscle is supplied from the mandibular nerve by way of a branch from the medial pterygoid nerve.

THE CHORDA TYMPANI NERVE

This branch of the facial nerve enters the tympanic cavity from the posterior canaliculus at the junction of the lateral and posterior walls. It runs across the medial surface of the tympanic membrane between the mucosal and fibrous layers and passes medial to the upper portion of the handle of the malleus (see **Figure 46.5**) above the tendon of tensor tympani to continue forwards and leave by way of the anterior canaliculus, which subsequently joins the petrotympanic fissure.

THE TYMPANIC PLEXUS

The tympanic plexus is formed by the tympanic branch of the glossopharyngeal nerve (Jacobson's nerve) and by caroticotympanic nerves, which arise from the sympathetic plexus around the internal carotid artery. The nerves form a plexus on the promontory and provide the branches to the mucous membrane lining the tympanic cavity, Eustachian tube and mastoid antrum and air cells. The plexus also provides branches to join the greater superficial petrosal nerve and the lesser superficial petrosal nerve that contains all the parasympathetic fibres of the glossopharyngeal nerve.

THE MUCOSA OF THE TYMPANIC CAVITY

The middle ear mucosa is essentially mucus-secreting respiratory mucosa bearing cilia on its surface.[20] The extent of the mucociliary epithelium varies in normal middle ears, being more widespread in the young. Three distinct mucociliary pathways can be identified – epitympanic, promontorial and hypotympanic, the latter being the largest. Each of these pathways coalesces at the tympanic orifice of the Eustachian tube.[21] The mucous membrane lines the bony walls of the tympanic cavity, and it extends to cover the ossicles and their supporting ligaments in much the same way as the peritoneum covers the viscera in the abdomen. The mucosal folds also cover the tendons of the two middle ear muscles and carry the blood supply to and from the contents of the tympanic cavity. These folds separate the middle ear space into compartments. As a result, the only route for ventilation of the epitympanic space from the mesotympanum is via two small openings between the various mucosal folds – the anterior and posterior isthmus tympani. Likewise, the Prussak space is found between the pars flaccida and the neck of the malleus, bounded by the lateral malleolar fold. This space can play an important role in the retention of keratin and subsequent development of cholesteatoma. The mucosal folds have been described in detail by Proctor[22] and are depicted in **Figure 46.15**.

THE BLOOD SUPPLY OF THE TYMPANIC CAVITY

Arteries supplying the walls and contents of the tympanic cavity arise from both the internal and external carotid system. The overlap between branches is extensive and there is great variability in the supply between individuals. **Table 46.2** outlines the general distribution of the arterial supply although the anterior tympanic and stylomastoid arteries are the biggest.

The Eustachian tube

The Eustachian tube is a dynamic channel that links the middle ear with the nasopharynx. In adults, it is about

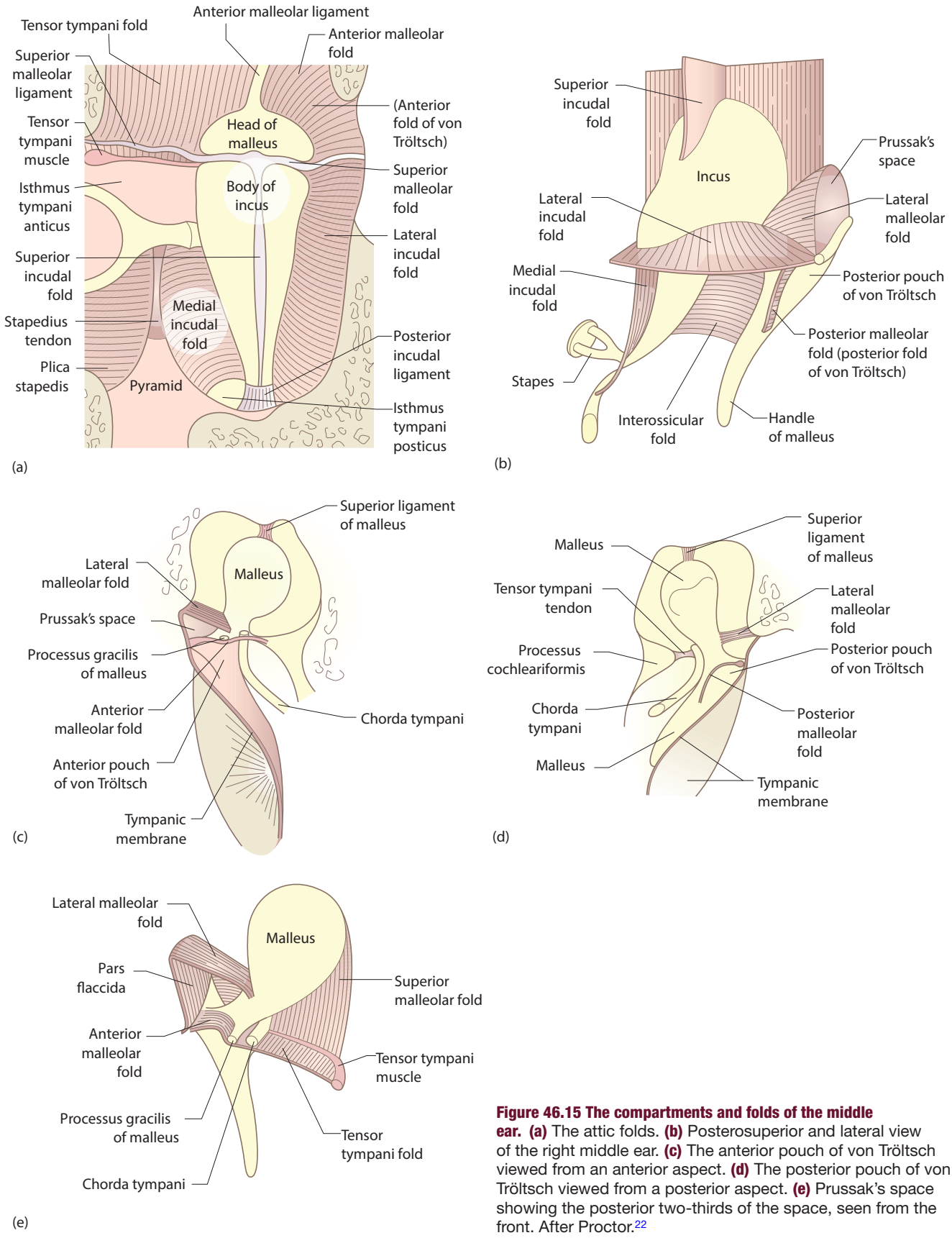


Figure 46.15 The compartments and folds of the middle ear. **(a)** The attic folds. **(b)** Posterosuperior and lateral view of the right middle ear. **(c)** The anterior pouch of von Tröltsch viewed from an anterior aspect. **(d)** The posterior pouch of von Tröltsch viewed from a posterior aspect. **(e)** Prussak's space showing the posterior two-thirds of the space, seen from the front. After Proctor.[22]

TABLE 46.2 Blood supply to the middle ear

Branch	Parent artery	Region supplied
Anterior tympanic	Maxillary artery	Tympanic membrane Malleus and incus Anterior part of tympanic cavity
Stylomastoid	Posterior auricular	Posterior part of tympanic cavity Stapedius muscle
Mastoid	Stylomastoid	Mastoid air cells
Petrosal	Middle meningeal	Roof of mastoid Roof of epitympanum
Superior tympanic	Middle meningeal	Malleus and incus Tensor tympani
Inferior tympanic	Ascending pharyngeal	Mesotympanum
Branch from artery	Artery of pterygoid canal	Meso- and hypotympanum
Tympanic arches	Internal carotid	Meso- and hypotympanum

36 mm in length, a size that is normally reached by the age of 7 years. It runs downwards from the middle ear at 45° and is turned forwards and medially. The tube can be considered to consist of two unequal cones, connected at their apices. The lateral third is bony and arises from the anterior wall of the tympanic cavity. This joins a medial cartilaginous part, which makes up two-thirds of the tubal length, just after its narrowest portion, called the isthmus (Figure 46.16). The tube is lined with respiratory mucosa containing goblet cells and mucous glands, having a carpet of ciliated epithelium on its floor. At its nasopharyngeal end, the mucosa is truly respiratory; however, in passing along the tube towards the middle ear, the number of goblet cells and glands decreases, and the ciliary carpet becomes less profuse.

The bony portion is about 12 mm long and is widest at its oval-shaped orifice in the anterior wall of the tympanic cavity. It runs through the squamous and petrous portions of the temporal bone, gradually tapering to the isthmus, where the diameter is only 0.5 mm or less. A thin plate of bone forms the roof, separating the tube from the tensor tympani muscle above. The carotid canal lies medially and can impinge on the bony Eustachian tube. In cross section, the tube is triangular or rectangular with the horizontal diameter being the greater (Figure 46.17).

The cartilaginous part of the tube is about 24 mm long and consists of a fibrocartilaginous skeleton to which are attached the peritubal muscles. At its upper border, the cartilage is bent over to resemble an inverted 'J', thereby forming a longer medial cartilaginous lamina and shorter lateral cartilaginous lamina. The cartilage is fixed to the base of the skull in a groove between the petrous part of the temporal bone and the greater wing of the sphenoid, which terminates near the root of the medial pterygoid plate. Thus, the back (posteromedial) wall is composed of cartilage and the front (anterolateral) wall comprises cartilage and fibrous tissue. The apex of the cartilage is attached to the isthmus of the bony portion, while the wider medial end protrudes into the nasopharynx, lying directly under the mucosa to form the torus tubarius. In the nasopharynx, the tube opens 1–1.25 cm behind

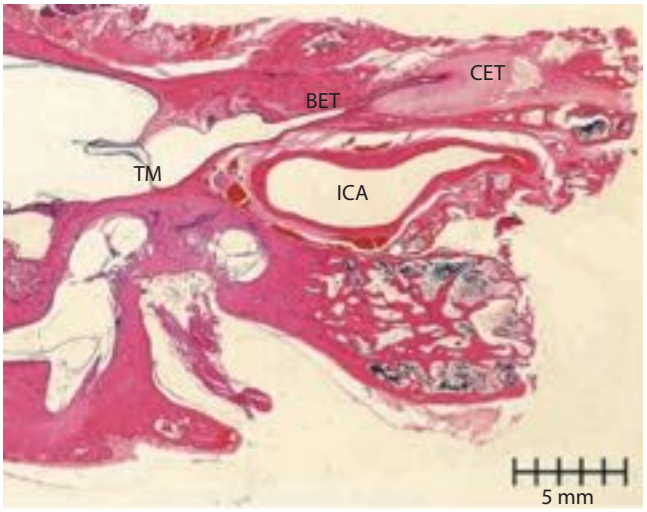


Figure 46.16 Photomicrograph of the left Eustachian tube in axial section, showing its bony (BET) and cartilaginous (CET) portions. The tympanic membrane (TM) is retracted towards the Eustachian orifice and note the adjacent position of the internal carotid artery (ICA).

and a little below the posterior end of the interior turbinate. The opening is almost triangular in shape and is surrounded above and behind by the torus. The salpingopharyngeal fold stretches from the lower part of the torus downwards to the wall of the pharynx. The levator palati, as it enters the soft palate, results in a small swelling immediately below the opening of the tube. Behind the torus is the pharyngeal recess or fossa of Rosenmüller. Lymphoid tissue is present around the tubal orifice and in the fossa of Rosenmüller and may be prominent in childhood.

MUSCLES ATTACHED TO THE EUSTACHIAN TUBE

The tensor palati muscle arises from the bony wall of the scaphoid and from along the whole length of the lateral cartilaginous lamina that forms the upper portion of the front wall of the cartilaginous tube. From these broad

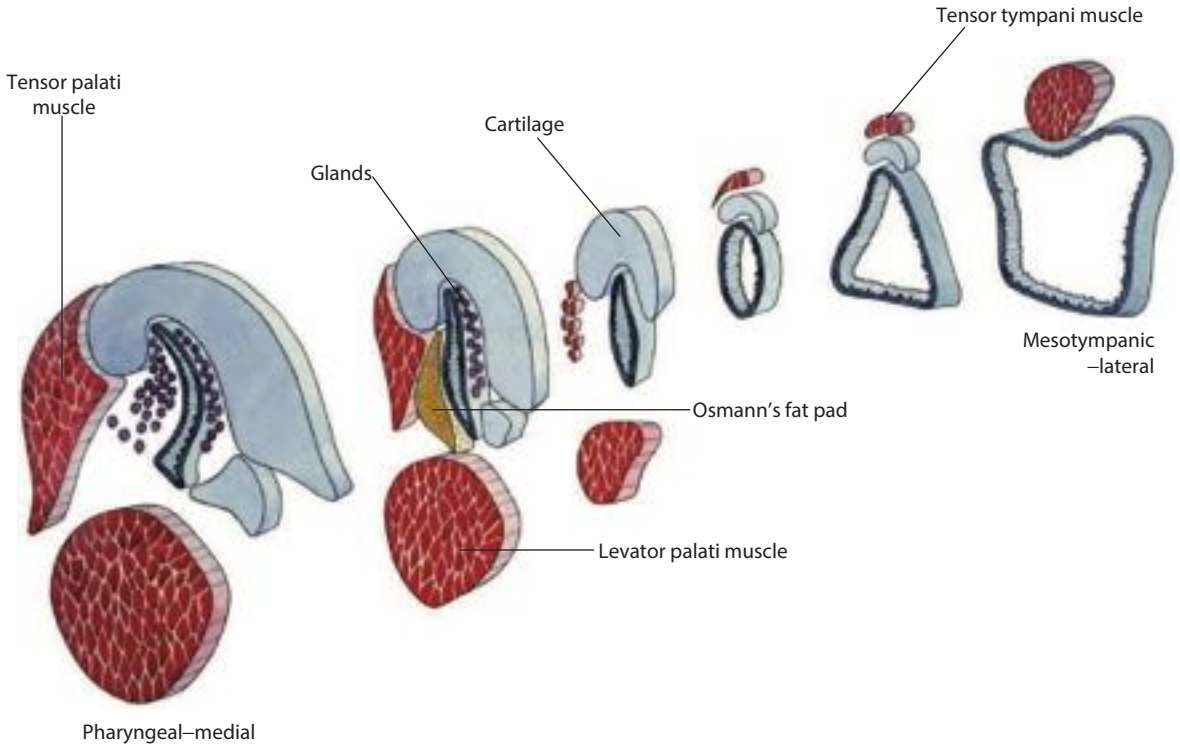


Figure 46.17 Schematic view of the right Eustachian tube. Redrawn from Sade and Ar.[23]

origins the muscle descends, converges to a short tendon that turns medially around the pterygoid hamulus and then spreads out within the soft palate to meet fibres from the other side in a midline raphe. The tensor palati separates the tube from the otic ganglion, the mandibular nerve and its branches, the chorda tympani nerve and the middle meningeal artery. It is supplied by the mandibular nerve.

The salpingopharyngeus is a slender muscle attached to the inferior part of the cartilage of the tube near its pharyngeal opening, and it descends to blend with the palatopharyngeus.

The levator palati contains a few fibres that arise from the lower surface of the cartilaginous tube and originates from the lower surface of the petrous bone, just in front of the opening for the entrance of the carotid, and from fascia forming the upper part of the carotid sheath. It first lies inferior to the tube, then crosses to the medial side and spreads out into the soft palate. Both the salpingopharyngeus and the levator palati are supplied from the pharyngeal plexus.

The ascending pharyngeal and middle meningeal arteries supply the Eustachian tube. The veins drain into the pharyngeal plexus and the lymphatics pass to the retropharyngeal nodes. The nerve supply arises from the pharyngeal branch of the sphenopalatine ganglion (Vb) for the ostium, the nervus spinosus (Vc) for the cartilaginous portion and the tympanic plexus (IX) for the bony part.

The mastoid air cell system

The mastoid antrum is an air-filled sinus within the petrous part of the temporal bone. It communicates with the middle ear by way of the aditus and has mastoid air cells arising from its walls. The antrum, but not the air cells, is well developed at birth and by adult life has a volume of about 2 mL. The roof of the mastoid antrum and mastoid air cell space form the floor of the middle cranial fossa, while the medial wall relates to the posterior semicircular canal. More deeply and inferiorly is the dura of the posterior cranial fossa and the endolymphatic sac. The latter emerges through the operculum on the posterior surface of the petrous bone and derives from the endolymphatic duct, which has passed through the vestibular aqueduct. Posterior to the endolymphatic system is the sigmoid sinus, which curves downwards only to turn sharply upwards to pass medial to the facial nerve and then becomes the dome of the jugular bulb in the middle ear space. The posterior belly of the digastric muscle forms a groove in the base of the mastoid bone. The corresponding ridge inside the mastoid lies lateral not only to the sigmoid sinus but also to the facial nerve and is a useful landmark for finding the nerve itself. The periosteum of the digastric groove on the undersurface of the mastoid bone continues anteriorly and part of it becomes the endosteum of the stylomastoid foramen and subsequently of the facial nerve canal.

The outer wall of the mastoid lies just below the skin and is easily palpable behind the pinna. Macewen's triangle is a direct lateral relation to the mastoid antrum and is formed by a posterior prolongation of the line of the zygomatic arch and a tangent to this that passes through the posterior border of the external auditory meatus. The relationships of the mastoid antrum are shown in Figure 46.18.

In most of the population, the mastoid air cell system is fairly extensive with air cells extending into the mastoid tip,

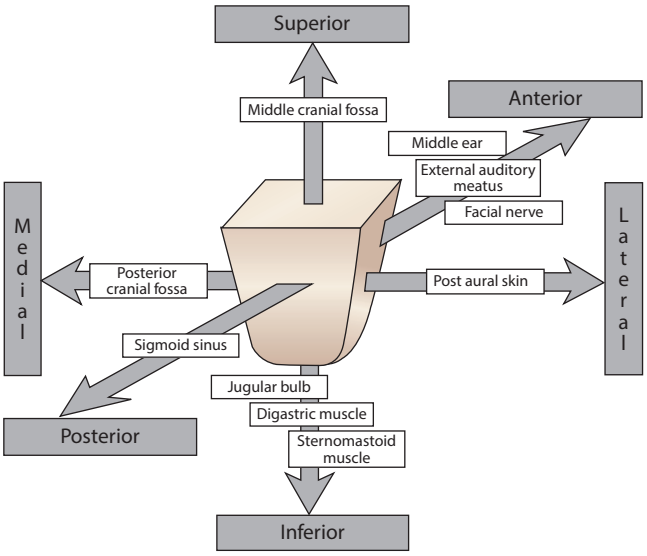


Figure 46.18 Relationships of the right mastoid antrum.

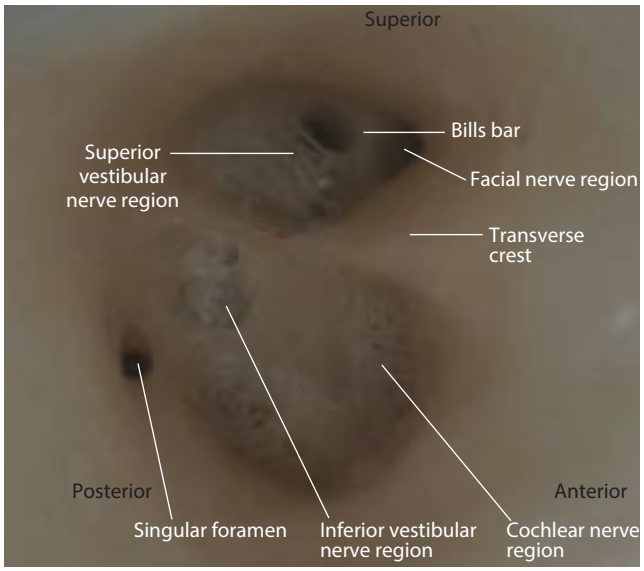


Figure 46.19 Endoscopic view of the apex of the left internal auditory meatus.

the retrofacial region, the sinodural angle and anteriorly into the petrous apex and arch of the zygoma. Alternatively, the mastoid antrum may be the only air-filled space in the mastoid process when the name acellular or sclerotic is applied. This condition occurs in perhaps 20% of adult temporal bones and is seen in individuals with chronic ear disease. In normal ears, the lining of the mastoid is a flattened, non-ciliated epithelium without goblet cells or mucus glands.

The petrous apex lies at the most medial aspect of the temporal bone and is shaped like a foreshortened pyramid, pointing anteriorly and medially. The posteromedial surface of the petrous apex is part of the posterior cranial fossa, while the superior aspect of the bone forms the floor of the middle cranial fossa. The internal carotid artery and the internal auditory meatus run through the bony petrous apex. At the apex of the petrous bone is the trigeminal nerve running into Meckel's cave with the abducent nerve passing close to its roof. Gradenigo's syndrome is the result of infection at the petrous apex and comprises a lateral rectus palsy, facial pain and discharging ear. Historically, the petrous apex has been the most difficult to access surgically but this has been advanced by the development of endoscopically assisted trans-sphenoidal techniques.

The internal auditory meatus

This is a short canal, nearly 1 cm in length and lined with dura, which passes into the petrous bone in a lateral direction from the cerebellopontine angle. It transmits the facial, cochlear and vestibular nerves and the internal auditory artery and vein. The meatus is closed at its outer lateral end, or fundus, by a plate of bone that is perforated for the passage of nerves and blood vessels to and from the cranial cavity.

The bony plate separating the fundus from the middle and internal ears has a transverse crest – the crista falciformis – on its inner medial surface, which separates a small upper region from a larger lower area (**Figure 46.19**). Above the crest and anteriorly is the opening of the facial canal carrying the facial nerve (VII). This is separated, by a small vertical ridge known as Bill's bar, from the posterior region that transmits the superior vestibular nerve through several small foramina to the superior and lateral semicircular canals, to the utricle and a part of the saccule. Below the transverse crest, the cochlear nerve lies anteriorly and leaves the meatus through the cochlear area, which comprises a spiral of small foramina and a central canal. The inferior vestibular nerve passes through one or two foramina behind the cochlear opening to supply the saccule. Just behind and below the inferior vestibular foramen is the foramen singulare, which contains the singular nerve. This runs obliquely through the petrous bone close to the round window to supply the sensory epithelium in the ampulla of the posterior semicircular canal.

DEVELOPMENT OF THE HUMAN EAR

The outer and middle ears

The 9 months from implantation of the fertilized and dividing egg – the blastocyst – to birth is divided into three periods, namely, pre-embryonic, embryonic and foetal. The pre-embryonic stage lasts 21 days, the embryonic stage 35 days and the foetal stage is the longest phase at 210 days.

During the embryonic phase there is rapid growth and differentiation of the ecto-, meso- and endoderm, so that by the end of this period all the major organ systems have been formed and the late embryo has an external shape that is obviously human. In the foetal period there are changes in the shape, size and orientation of the various structures, as well as rapid overall growth, but no new tissues develop.

During growth from the fertilized egg into the fully formed foetus, animals pass through phases that represent, to a certain degree at least, their evolutionary precursors.

The phrase 'ontogeny recapitulates phylogeny' has been used to express this reflection of earlier forms. In mammals, a phase is reached during early embryonic life when the mesenchyme surrounding the primitive foregut and pharynx differentiates into a maxillary and mandibular swelling on each side of the midline just above and below the buccopharyngeal membrane. This membrane then breaks down and a space, which will later become both nasal and buccal cavities, is formed. Further down the embryo and in the mesenchyme surrounding the pharynx, five or six parallel thickenings develop as bands that surround the pharynx. These are the branchial arches, which are numbered 1 to 5 from head to tail. They are formed anterior to the 40–43 paired somites that subsequently give rise to the trunk and limbs. On the external surface a groove develops between each branchial arch and this is matched by a cleft or pouch on the inner pharyngeal surface. In each branchial arch a bar of cartilage, a group of muscles, an associated artery and a cranial nerve, supplying these structures and their derivatives, all develop. The cranial nerve is called the post-trematic nerve. In addition, a nerve from the arch lower down supplies the inner endodermal surface of the arch above and is called the pretrematic nerve.

The first arch has the trigeminal nerve (V), the second arch the facial (VII) and the third arch the glossopharyngeal (IX). These are the post-trematic nerves. The pretrematic nerves are the chorda tympani (from VII) running to the first arch (V) and Jacobson's nerve (the tympanic branch of IX) running to the second arch (VII).

DERIVATIVES OF THE FIRST AND SECOND BRANCHIAL ARCHES

The innervation of the lower arches and indeed their derivation are much less clear (**Table 46.3**). In fish, the layers between the arches break down to form the gill clefts, but in mammals this does not occur although grooves on the external surface of the embryo do develop and for a very short time come into contact with the endoderm lining the pharynx. However, mesoderm rapidly intervenes and develops into the normal adult structures. Occasionally there is failure of this system when the various branchial arch defects can occur as sinuses (blind-ended tracts opening onto an epithelial surface) as a cleft or groove fails to regress, or less commonly as fistulae (a tract running from one epithelial surface to another) when the ecto-endodermal junction breaks down.

The first pharyngeal pouch on the inside expands due to the rapid growth of the surrounding mesenchyme and, after dragging in some of the second pouch endoderm, results in the formation of the Eustachian tube, middle ear and mastoid antrum. In creating these large spaces the neural structures are forced to take a convoluted path to stay within mesenchyme and yet remain bound to their original arch structures and the derivatives. The facial nerve is a good example as it turns posteriorly from the geniculate ganglion, then inferiorly and then anteriorly in order to leave the skull.

The endoderm of the slit-like sac that is the precursor of the middle ear lies against the ectoderm of the first pharyngeal groove by the fourth week. Mesenchyme grows in between these two layers to form the middle layer of the future tympanic membrane. The underlying sac expands and as it reaches the developing ossicles and labyrinth, the epithelium is draped over these structures and their associated muscles, tendons and ligaments, so that a complex series of mucosal folds is formed.

The future Eustachian tube lumen and middle ear spaces are formed by 8 months' gestation and the epitympanum and mastoid antrum are developed by birth. A few mastoid 'air cells' may be present at birth, albeit filled with amniotic fluid. However, development of the mastoid air cell system does not occur until after birth, with about 90% of air cell formation being completed by the age of 6 with the remaining 10% taking place up to the age of 18.

The ossicles develop from the outer ends of the first arch (Meckel's) and second arch (Reichert's) cartilages that lie above and below the first pharyngeal pouch. The process begins at 4 weeks and adult shape, size and ossification are present by 25 weeks. The muscles attached to the ossicles

TABLE 46.3 Derivatives of the first and second branchial arches

Cartilage	Post-trematic nerve	Pretrematic nerve	Artery
First arch derivatives			
Meckel's Malleus Incus 'Mandible' Anterior malleolar ligament Sphenomandibular ligament	Mandibular V	Chorda tympani VII	
Second arch derivatives			
Reichert's Stapes superstructure Styloid process Lesser cornu of hyoid Stylohyoid ligament	Facial VII	Tympanic branch IX	Stapedial

arise from the arches that give rise to that part of the ossicle to which the muscle attaches.

Thus the tensor tympani is attached to the upper part of the handle of the malleus, which is derived from the first arch and is, therefore, supplied by a branch of the Vth (mandibular) nerve. In a similar way the stapedius muscle is supplied by the VIIth (facial) nerve. The chorda tympani, which is the pretrematic nerve of the second arch that supplies endodermal structures of the first arch (i.e. taste to the anterior two-thirds of the tongue and submandibular gland secretomotor fibres) has to run through mesoderm since it cannot run through air. This mesoderm subsequently becomes the middle layer of the tympanic membrane and is the physical connection between the first and second arches.

The external ear canal develops from the first pharyngeal groove in a complex fashion. A complete description is beyond the scope of this chapter and may be sought from Michaels and Soucek.[24] It is sufficient to say that the meatus deepens by proliferation of its ectoderm and that an anteriorly placed bud of epithelial cells expands vertically to form the skin, which will cover the future tympanic membrane. This clump of cells then opens up as a slit to form the canal lumen and produce the pars tensa and deep external canal epithelium. These two types of skin both have migratory properties so that the ear canal becomes self-cleansing.

The external auricle or pinna develops from a series of small cartilaginous tubercles that surround the first pharyngeal groove. These enlarge and coalesce, although it seems that the majority of the auricle is derived from the second arch cartilages and that the tragus is the only contribution from the first arch. The rudimentary pinna has formed by 60 days although it apparently continues to grow throughout life.

Failure of formation of the first and second branchial arch structures gives rise to problems which range from failure of adequate skin migration with 'ear canal cholesteatoma' (which are very rare) through bat ears, accessory auricles and preauricular sinuses, to complete failure of formation of the external ear canal and middle ear. There are also the rare first arch fistulae (collaural fistulae), which comprise a tract between the external ear canal and the skin of the cheek, with the fistula path passing through the parotid gland and frequently between branches of the facial nerve.

The internal ear (labyrinth)

The internal ear initially develops independently of the middle and external ears, although the two become interconnected by the stapes superstructure, becoming attached to the stapes footplate, thereby giving continuity to the auditory pathway.

The development of the labyrinth can be thought of as the initial development of the generalized structure of the membranous labyrinth, followed by a period of encasement by the bony labyrinth and the production of a further series of spaces within this bony shell that in turn become the perilymphatic spaces of the complete structure. These different activities are happening at different times in different parts of the labyrinth so that damage or derangements at specific times give rise to many peculiar and varied abnormalities.

Within the first few days of embryonic life (i.e. at about day 22 or 23) ectodermal thickening forms on the side of the head end of the embryo close to that part of the developing neural tube and neural crest cells, which will later become the brain and brainstem and the cranial nerves, respectively. The ectodermal thickening is the otic placode, which deepens and then sinks below the surface as the sides close in to form an otic pit which eventually loses connection with the surface and forms the otocyst (Figure 46.20).

Associated with the otocyst is the cluster of neural crest cells that later become the separate facial (geniculate), auditory (spiral) and vestibular (Scarpa's) ganglion cell bodies. The otocyst then undergoes a series of spectacular changes, which result in the full-sized outline of the adult membranous labyrinth by 25 weeks' gestation.

The semicircular canals start to develop at around 35 days as three flattened pouches that grow out at right angles from each other from the utricle. At the centre of each semicircular ridge, the opposing epithelial surfaces meet, fuse and then coalesce to be replaced by mesoderm. The superior canal is the first to be fully formed by 6 weeks.

As these developments are taking place, the cochlea starts to be formed. The saccule, which has separated from the utricle, starts to put out a single pouch-like process that grows and then begins to coil from base to apex to reach its full 2.5 coils by 25 weeks.

Within the membranous labyrinth the sensory cells of the three cristae, two maculae and the organ of Corti are beginning to develop from areas of ectodermal specialization. This is encouraged either by the ingrowth of nerve endings from the cochleovestibular ganglion, which was originally outside the otocyst, or by the development of the sensory cells encourages neural ingrowth (Figure 46.21).

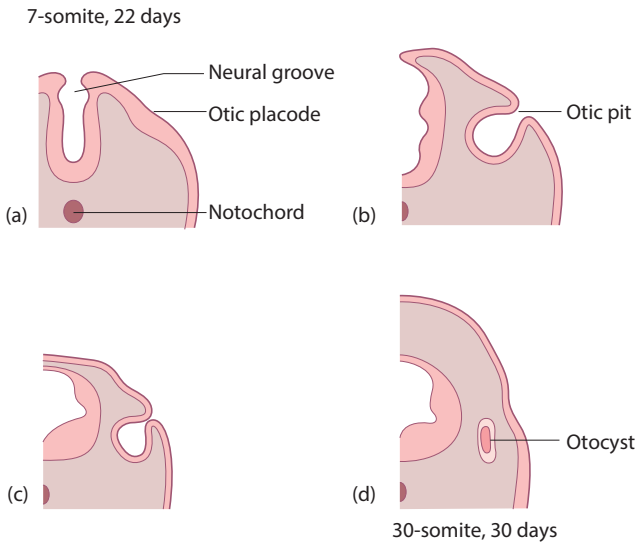


Figure 46.20 Development of an otocyst.

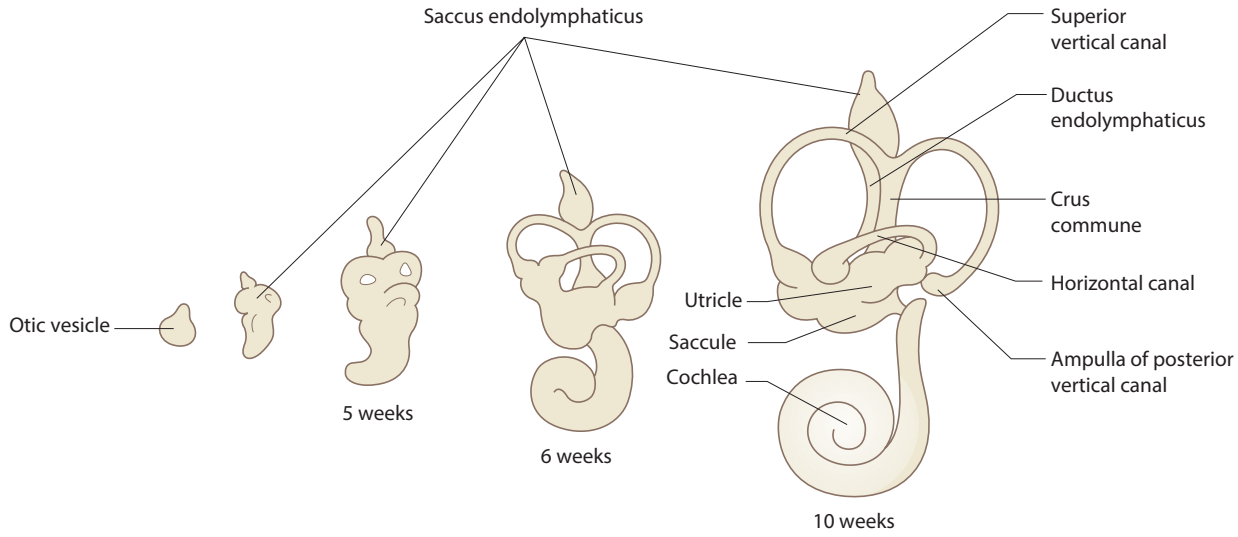


Figure 46.21 Development of the membranous labyrinth.

TABLE 46.4 Development of communication channels passing through labyrinth

	Channel
Internal auditory meatus	Persisting channel in cartilage model around VII and VIII nerves
Subarcuate fossa	Persisting vascular channel
Vestibular aqueduct	Fifth and sixth ossification centres fuse around the endolymphatic duct
Cochlear aqueduct	Resorption of precartilage
Fossula ante fenestram	Resorption of precartilage
Fossula post fenestram (inconstant)	Resorption of cartilage
Oval window	Otic capsule becomes footplate of stapes and annular ligament
Round window	Persisting cartilage becomes round window niche and membrane

The organ of Corti starts developing as a single block of heaped up ectodermal cells at about 11 weeks. Within this mass develop inner and outer hair cells and then specialized supporting cells. The tunnel of Corti appears between inner and outer pillar cells as clusters of stereocilia and a single kinocilium are developing on each hair cell. The cochlear kinocilium regresses, leaving the adult configuration of stereocilia, and the spaces between the outer hair cells open up as the supporting cells (the Deiters cells) change shape. Differentiation progresses from base to apex so that at any one time various stages of development can be seen in appropriately prepared material.

Epithelium close to the sensory regions develops into the specialized cell groups that maintain the ionic and electrical stability of the endolymph. These regions are the stria vascularis of the cochlear duct and the 'dark cell' regions of the vestibular sensory epithelium.

The bony labyrinth

The mesenchyme enclosing the otocyst becomes chondrified to form the otic capsule. As the membranous labyrinth expands, the otic capsule remodels and in places undergoes dedifferentiation to form fluid-filled spaces that eventually become the perilymphatic spaces. This dedifferentiation does not occur where nerves enter the sensory cell regions. Elsewhere, the perilymphatic spaces become continuous and a communication with the cerebrospinal fluid is formed by the development of the cochlear aqueduct, which runs to the posterior cranial fossa from the scala tympani in the base of the cochlea.

Ossification of the cartilaginous otic capsule begins in or around week 16 from a variable number of centres that finally fuse without leaving telltale suture lines. This dense bony mass is the petrous bone. Interestingly, this is frequently the last part of a whale to decompose and is sometimes the only remains of those eaten by sharks.

There are certain channels that remain within the otic capsule with one of the most important being the oval window where part of the otic capsule becomes the stapes footplate and the annular ligament, thereby allowing sound from the middle ear to enter the labyrinthine fluids (Table 46.4).

The temporal bone

Four separate elements eventually fuse to form the temporal bone, which is one of the most complex and interesting parts of the bony anatomy of the body. These four parts are the petromastoid complex, the squamous portion, the tympanic bone and the styloid process.

The petromastoid is derived from petrous bone described above and the continuing growth of its outer layers which form the roof of the middle ear, the lateral wall of the Eustachian tube, the floor of the middle ear, the canal of the facial nerve and the petrous apex.

The squamous bone develops in mesenchyme and starts to ossify from a single centre close to the roof of the zygoma as early as 8 weeks. The posteroinferior portion grows down behind the tympanic ring to form the lateral wall of the foetal mastoid antrum.

The tympanic bone also forms in mesenchyme, but from several centres around the external meatus. These form the major part of a ring with a groove on the inner aspect that becomes the sulcus for the tympanic membrane. Even by late foetal life the bony ear canal is unformed and only after birth do anterior and posterior protuberances grow to form the floor of the canal. These crescentic swellings eventually fuse laterally leaving a gap in the middle of the floor. This is the foramen of Huschke, which is usually closed by adolescence. The tympanic bone fuses with the mastoid process of the petromastoid and with parts of the squamous and petrous bones as the tympanomastoid, tympanosquamous and petrotympanic sutures. The petrotympanic suture has a canal for the chorda tympani nerve.

The styloid develops from two centres at the cranial end of the second arch (Reichert's) cartilage. The part close to the base of the skull starts to ossify before birth, but the styloid process itself does not start to ossify until after, and fusion of the two parts may not occur until after puberty.

Much of the growth of temporal bone occurs after birth with enlargement of the whole structure and major growth of the mastoid process so that the stylomastoid foramen, which was initially close to the surface, becomes buried by the development of the mastoid tip. At the same time there is generalized downwards rotation of the petrous bone so that the tympanic membrane moves from being almost horizontal in the neonate to an angle of about 55° with the horizontal in the adult. With these changes, the floor of the middle cranial fossa flattens and the relations of the geniculate ganglion, the semicircular canals and the internal auditory meatus change so that middle cranial fossa surgery in the baby is anatomically a different experience from that in the adolescent.

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CHAPTER 47

ANATOMY OF THE COCHLEA AND VESTIBULAR SYSTEM: RELATING ULTRASTRUCTURE TO FUNCTION

Jonathan Gale and Andrew Forge

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: structure, anatomy, cell biology; inner ear, endolymph, perilymph; cochlea, vestibular hair cell, supporting cell, organ of Corti, inner hair cell, outer hair cell, spiral ganglion, stria vascularis, spiral ligament, basilar membrane, tectorial membrane, Reissner's membrane , utricle/utricular, saccule/saccular, crista, macula/maculae, type1 hair cell, type 2 hair cell and dark cells.

INTRODUCTION

The inner ear (**Figure 47.1a,b**) collects, packages and delivers sensory information relating to hearing via the cochlea, and balance via the vestibular system. It is responsible for mechanoelectrical transduction, the conversion (transduction) of movements – initiated by sound waves in the cochlea or by changes in the position of the head in space in the vestibular system – into electrical signals that can then be passed to the brain along the auditory or vestibular nerves. It is formed of a series of bony channels that enclose interconnected fluid-filled tubes (the membranous labyrinth), the inner walls of which are lined by epithelial tissues (**Figures 47.1a,c** and **47.2**). In humans and higher primates, the bony channels are in the temporal bone (**Figure 47.1c**), the hardest bone in the body, which is fused with the skull. In other mammals, the inner ear is contained within a bony auditory bulla which is not fused with the skull but fills a recess in it and which can be isolated relatively easily.

The bony channels are filled with perilymph, which surrounds the membranous canals (**Figure 47.1a**). Perilymph is essentially a typical extracellular fluid, similar, but not identical, to cerebrospinal fluid (CSF) or serum; it has a high sodium ion (Na^+) and low potassium ion (K^+) concentration.[1] The perilymphatic compartment connects with the arachnoid space of the brain via the cochlear aqueduct so there is potential continuity between cochlear perilymph and CSF, although the exact compositions of the two fluids are different from each other and also from serum, indicating that perilymph is produced or at least significantly modified locally in the inner ear and is not derived directly from CSF (or serum).

The fluid inside the lumen of the membranous canals is **endolymph** (**Figure 47.1a**). This has an unusual composition for an extracellular fluid. It is high in K^+ (~140 mM) and low in Na^+ (~1 mM). In the cochlea, endolymph also has a high positive electrical potential of around +80 mV, the endocochlear potential (EP), but although the compartments are interconnected a similar electrical potential is not observed in the vestibular system. The boundary between perilymph and endolymph lies at the level of the junctions between the epithelial cells that surround the endolymphatic spaces. These junctions form a permeability barrier, the maintenance of which is essential for the function of the inner ear.

Three types of epithelium surround the endolymphatic compartment: sensory epithelia, ion-transporting epithelia, and relatively unspecialized non-sensory epithelia (**Figure 47.2a,b**). The vestibular system of mammals contains five sensory epithelial patches or sheets: the **maculae** of the **utricle** and **saccule**, and the three **cristae**, one

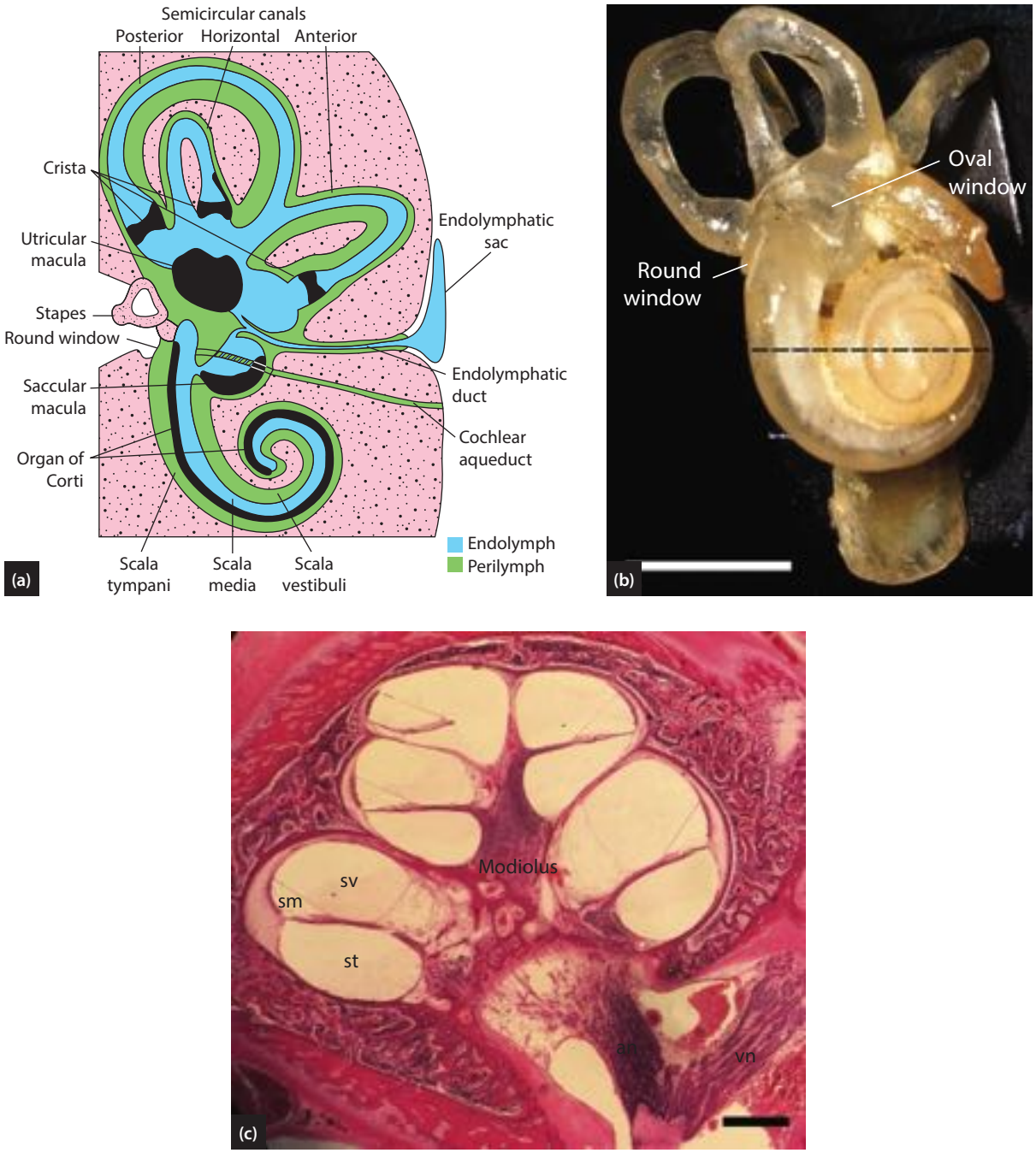


Figure 47.1 **(a)** Diagrammatic representation of the human inner ear showing the different compartments. **(b)** Human inner ear. Plastic injection moulding of the membranous labyrinth, with the temporal bone removed. Scale bar: 5 mm. Dashed line defines plane of section shown in panel (c). **(c)** Section through human temporal bone at approximately the mid-modiolar level of the cochlea. sm = scala media, st = scala media; sv = scala vestibuli; an = auditory nerve; vn = vestibular nerve. Scale bar: 1.5 mm.

in each of the **semicircular canals** (SCCs) (Figures 47.1a, 47.2a, 47.3). The sensory epithelium of the cochlea is the **organ of Corti**, named after the Italian anatomist Alfonso Corti. It comprises a relatively narrow strip of cells running along an acellular basement membrane and coiled in a spiral (Figures 47.2b and 47.4a,b,c). All of the sensory epithelia are composed of two main cell types: sensory hair cells and non-sensory supporting cells (Figures 47.3d and 47.4b,c). Each hair cell is surrounded and separated from its neighbours by supporting cells so that hair cells do not come into direct contact with each other. Viewed from above, each sensory epithelium appears as a more or less regular mosaic of cells at the apical (luminal [endolymphatic]) surface of the epithelium, sometimes referred to as the **reticular lamina**, with each hair cell surrounded by and thus in contact with several supporting cells, and each supporting cell contacting several other supporting cells (Figures 47.3e,f and 47.4d,e,f). The bodies of the supporting cells also intervene between the basal ends of the hair cells and the acellular basement membrane underlying the

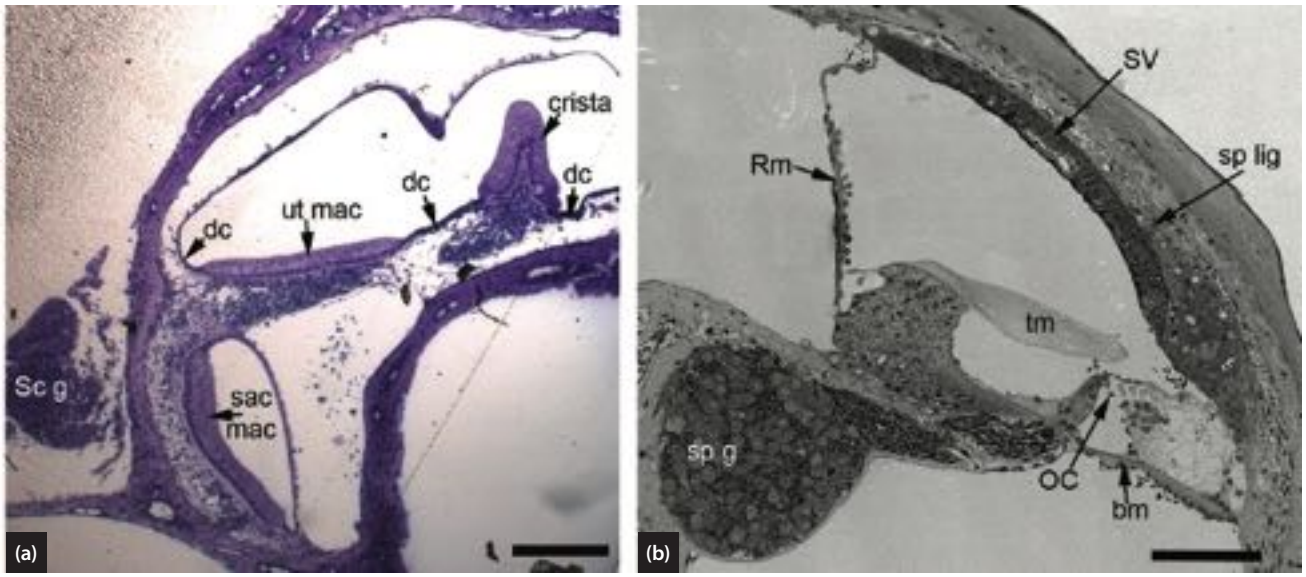


Figure 47.2 **(a)** Cross section through the vestibular labyrinth showing the relationship of the vestibular organs. ut mac = utricular macula; sac mac = saccular macula; crista = crista ampullaris; dc = dark cells; Sc g = Scarpa's ganglion. Scale bar: 100 µm. **(b)** Cross section of a single turn of the cochlea. OC = organ of Corti, tm = tectorial membrane; bm = basilar membrane; sp g = spiral ganglion; SV = stria vascularis; sp lig =spiral ligament; Rm = Reissner's membrane. Scale bar: 100 µm.

epithelium (which is known as the 'basilar' membrane in the organ of Corti) so that only the supporting cells and not hair cells are in contact with the basement membrane (Figures 47.3d and 47.4b,c). The sensory epithelia thus have the appearance of a pseudostratified epithelium. Each sensory epithelium is also covered by a specific acellular extracellular matrix structure: the **otoconial membrane** in macular organs (Figure 47.3g,h); a **cupula** overlying each the crista (Figure 47.3j); and the **tectorial membrane** in the cochlea (Figures 47.4b,g). The hair cells derive their name from the organized bundle of rigid projections at their apical surface (Figures 47.3f and 47.4d,e). Mechanical deflection of the hair bundle caused by either sound waves or changes in head position results in the opening and closing of cation-permeable **m**echanoelectrical **t**ransduction (**MET**) channels that modulate the flow of K^+ ions from endolymph into the hair cells, altering the hair cell's resting electrical potential and so its excitability. Thus, the hair cells are the mechanotransducers that convert auditory or vestibular-evoked mechanical stimuli into electrical signals.

The ion-transporting epithelia, the dark cell regions of the vestibular system and the stria vascularis of the cochlea (Figure 47.2a,b) are involved in active (energy-consuming) ion transport that is necessary to maintain the unusual endolymph composition and positive charge. The comparatively less specialized epithelia, including Reissner's membrane in the cochlea and those which constitute the 'roof' and linings of the saccule, utricle and ampullae of the semicircular canals (Figure 47.2a,b) and the membranous semicircular canals themselves, form important permeability barriers separating the perilymph from endolymph. If these membranes rupture or break down, the permeability barriers are disrupted, leading to fluid mixing and physiological dysfunction. It is thought such an event may occur to Reissner's membrane in Ménière's syndrome.

GENERAL CHARACTERISTICS OF HAIR CELLS

The hair bundle and cuticular plate

The hair bundle is composed of rows of **stereocilia** that increase in height in one particular direction across the apical surface of the hair cell, and a single kinocilium located behind the row of longest stereocilia (Figures 47.5a and 47.6a), but which is absent from the hair bundles of mature hair cells in the cochlea (Figure 47.5b). Stereocilia are really giant microvilli, plasma membrane-bound projections from the apical surface of the hair cell that enclose a packed array of filaments of the cytoskeletal protein, actin[2–4] (Figure 47.5d–f). The kinocilium is composed of microtubules similar in form to motile cilia but they are not motile.[5] In cochlear hair cells, the kinocilium is present only during development, reducing down as the cochlea matures to remain only as the basal body in the apical cytoplasm at one side of the stereociliary bundle (Figure 47.5c).[6] The position of the kinocilium (or the basal body) and the longest row of stereocilia define the polarity of the asymmetric hair bundle (Figures 47.3f, 47.4d,e and 47.5a,b). Deflection of the stereocilia towards the longest ones opens MET channels, K^+ enters and the hair cell becomes depolarized. Deflection in the opposite direction closes the transducer channels and the hair cell becomes hyperpolarized. The transducer channels are located at the tips of the stereocilia of the shorter rows but not in the longest stereocilia.[7]

The parallel actin filaments in the stereocilia (Figure 47.5e,f) are closely packed and are cross-linked by a number of different proteins such as espin, fimbrin, fascin and plastin 1, the last being the second most abundant protein in stereocilia after actin.[2, 8–13] The high

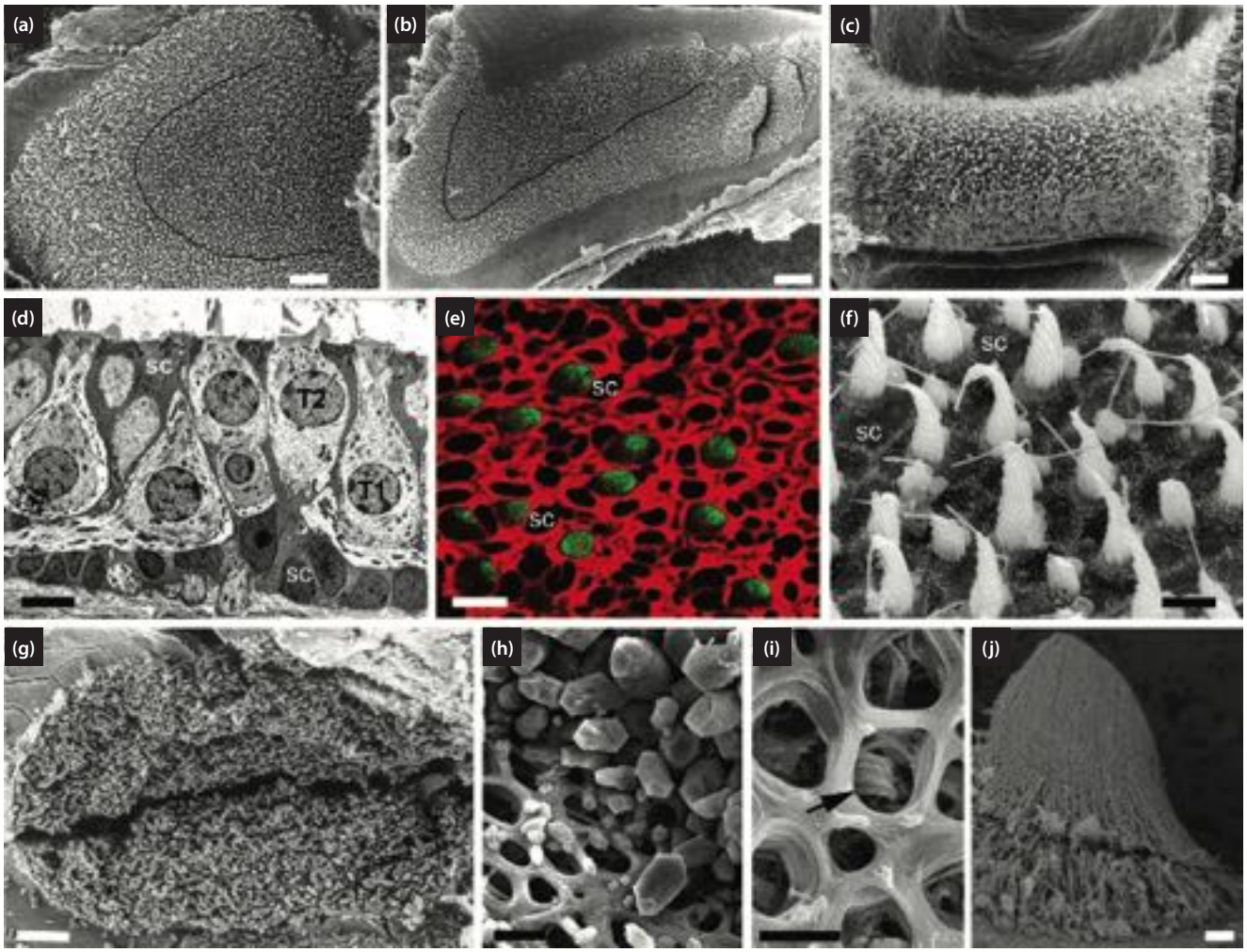


Figure 47.3 Vestibular sensory epithelia. (a) Utricular macula. Scanning electron microscopy of the entire intact utricular macula viewed from above after removal of otoconial membrane. Curved line indicates approximate location of line of hair bundle polarity reversal in the striolar region. Scale bar: 100 µm. **(b)** Saccular macula. As above for the utricular macula. Scale bar: 100 µm. **(c)** Crista ampullaris. Scanning electron microscopy of the upper surface of the crista 'saddle'. Scale bar: 100 µm. **(d)** Transmission electron microscopy of a thin section from a vestibular sensory epithelium (utricular macula of guinea pig). T1 = Type 1 hair cell; T2 = Type 2 hair cell; sc = supporting cell. Note that nuclei of each cell type are at different levels in this pseudostratified epithelium. Scale bar: 5 µm. **(e)** Human utricular macula labelled for filamentous actin (f-actin) with fluorescent-phalloidin (red) and an antibody to calretinin (green, labelling hair cells). Apical surface view to show reticular lamina. Phalloidin labels f-actin in the unusually wide junctional complexes around each cell. Each hair cell (green) is separated from its neighbours by intervening supporting cells (sc). Scale bar: 10 µm. **(f)** Apical surface of utricular macula. Hair cells are easily identified by the hair bundles that project out of the surface of the epithelium. Each hair cell is separated from its neighbour by intervening supporting cell (sc). Scale bar: 5 µm. **(g)** Scanning electron microscopy of the surface of the utricular macula with the otoconia still in situ covering the surface. Scale bar: 100 µm. **(h)** Higher magnification view of the utricular macular surface showing the perforated sheet of extracellular matrix component of the otoconial membrane beneath crystal-like otoconia. Scale bar: 5 µm. **(i)** Hair bundle (arrowed) projecting up into the otoconial matrix. Note that the hair bundle is aligned with a perforation in extracellular matrix component of otoconial membrane (utricle). Scale bar: 5 µm. **(j)** Cupula overlying a crista ampullaris. Scale bar: 10 µm.

density of actin filaments and the extensive cross-linking between them imposes rigidity on the shaft of the stereocilium, which tapers significantly at its proximal end (Figure 47.5a,g) where it is embedded into the **cuticular plate** (Figure 47.5a,c,d), a rigid platform formed of a meshwork of actin filaments and other proteins in the apical cytoplasm of the hair cell (Figure 47.5a,c,d).[14–17] As a result, when pushed at its tip, the stereocilium pivots at the taper like a stiff rod. The fundamental nature of this stereociliary rigidity for all hair cells is evidenced by the hearing impairment and vestibular disorders that result from mutations in genes that encode for such actin-cross-linker proteins. Mice with such mutations are often recognized by erratic and/or circling behaviours, for example the 'jerker' mouse strain, which has a mutation in the gene for the cross-linking protein espin, and in which stereocilia are thinner than normal.[10–13] Loss of plastin 1 results in progressive hearing loss and balance dysfunction and progressive thinning of stereocilia.[9, 12] Actin filaments descend from the stereocilium into the cuticular plate as a rootlet, which is cross-linked into the actin meshwork (Figure 47.5h).[15] The rootlet is formed of densely packed

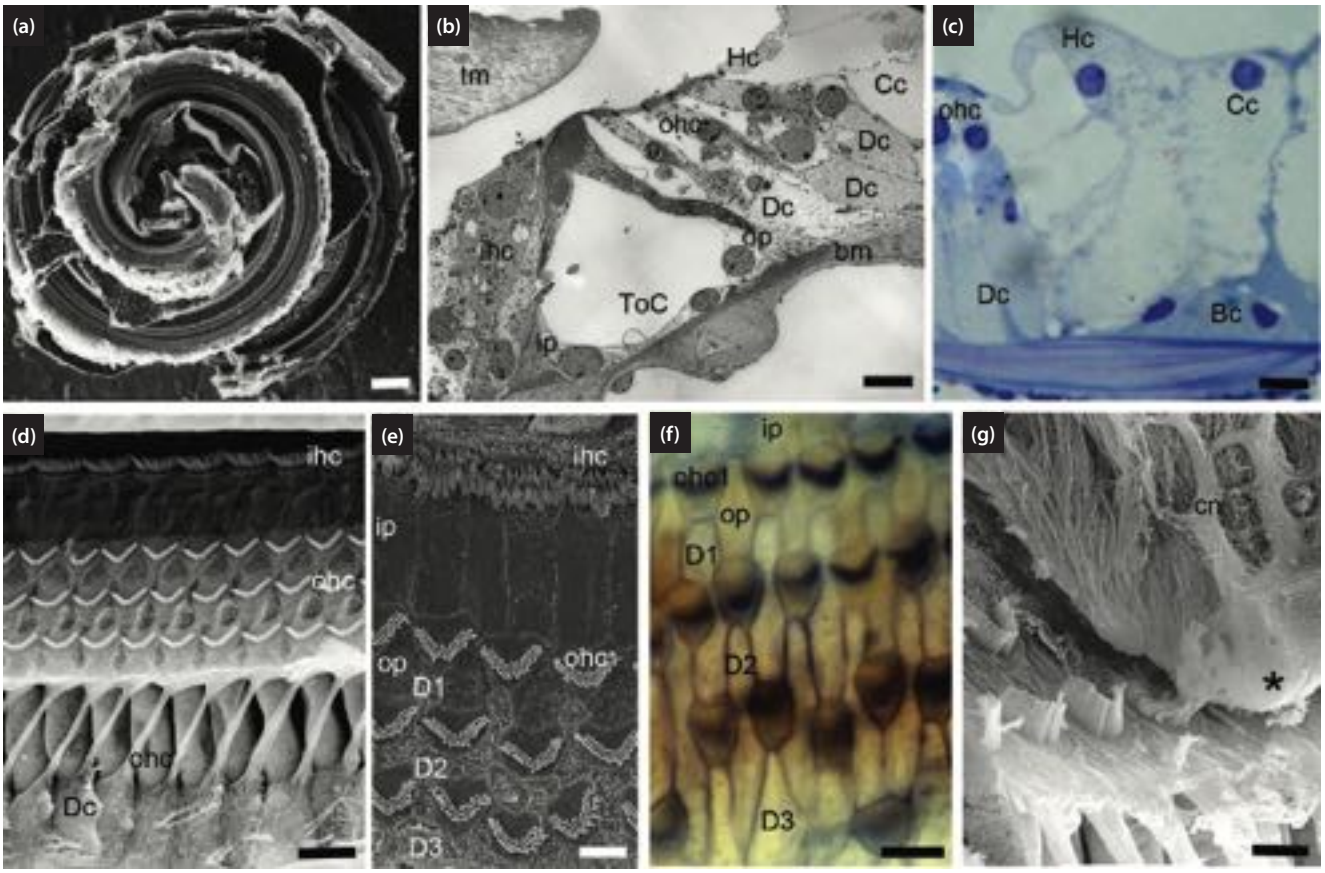


Figure 47.4 **(a)** Whole cochlear modiolus. Scanning electron microscopy showing the organ of Corti spiralling down from the apex for two and a half turns. Scale bar: 100 µm. **(b)** Cross section of the organ of Corti. Transmission EM of a thin section of the organ of Corti. The tectorial membrane (tm) retracts away from the surface of the organ of Corti during processing (see panel (g)). The tunnel of Corti (ToC) is created by the arch formed by the phalangeal processes of the inner and outer pillar cells. Scale bar: 10 µm. **(c)** Supporting cells to the outer, lateral side of the organ of Corti. Scale bar: 10 µm. **(d)** Surface and underside of the organ of Corti (gerbil): scanning electron microscopy of the apical surface with outermost (lateral) supporting cells removed to expose the outermost (third) row of Deiters' cells (Dc) and the outer third row of outer hair cells (ohc). The body of the Deiters' cell surrounds the base of the ohc and its phalangeal process ascends at an angle to the apical surface where the head expands. The hair bundles of the inner hair cells (ihc) in a single row. Scale bar: 10 µm. **(e)** Luminal surface of organ of Corti (mouse). Hair cell/supporting cell mosaic formed when the apical surfaces/heads of various supporting cells that join with and intercalate between individual hair cells. The head of the inner pillar cell (ip) and outer pillar cell (op) are indicated. Scale bar: 5 µm. **(f)** Human organ of Corti: reticular lamina at apical surface across the outer hair cell region (ohc1 = first row outer hair cell). Heads of various supporting cells surrounding each hair cell are indicated. Scale bar: 10 µm. **(g)** Tectorial membrane in situ over the organ of Corti. Radial filaments comprise the body of the tectorial membrane which has a greater density at the outer tip (*). The upper surface is covered by the densely packed fibres forming the covernet (cn). Scale bar: 5 µm. For all panels: Ihc or ihc = inner hair cell; ohc = outer hair cell; ip = inner pillar cell; op = outer pillar cell' Dc = Deiters' cell; HC or Hc = Hensen cell; Cc = Claudius cell; bm = basilar membrane; tm = tectorial membrane; Bc = Boettcher cells; D1, D2, D3 = heads of the three rows of Deiters' cells.

actin filaments (Figure 47.5e). The actin bundling protein TRIOBP plays a key role in the formation and maintenance of the rootlet.[18] In addition to actin, the cuticular plate contains spectrin,[19] another actin cross-linking protein that has elastic, deformation-resisting properties, and tropomyosin,[16, 17] a protein that binds around actin and stiffens it. Around its lateral margin, the cuticular plate is linked to the lateral plasma membrane at the level of the intercellular junction[15, 16] with which, on the supporting cell side, actin and other cytoskeletal proteins are also associated (Figures 47.6b,c,d and 47.7e,h). This may provide a means of support for the cuticular plate so that the stereocilia themselves are supported on a rigid platform, enhancing their ability to respond to small displacement forces.

Various members of the myosin family of motor proteins (types 1c, 6, 7a and 15 – all unconventional, non-muscle isotypes) are also localized in the cuticular plate region and the stereocilia. In addition, immunolabelling for myosins 6 and 7a shows these two proteins to be highly expressed throughout the hair cell cytoplasm, providing a distinguishing marker label for hair cells from their earliest differentiation during development and into adulthood (Figure 47.6e). Mice with mutations in the genes for myosins 6, 7a or 15 all show deafness and balance disorders and abnormalities in their stereociliary bundles.[20] In the mouse mutant where myosin 6 is defective (Snell's waltzer), stereocilia are fused and greatly lengthened.[21] Interestingly, a similar anomaly is seen in the human organ of Corti and

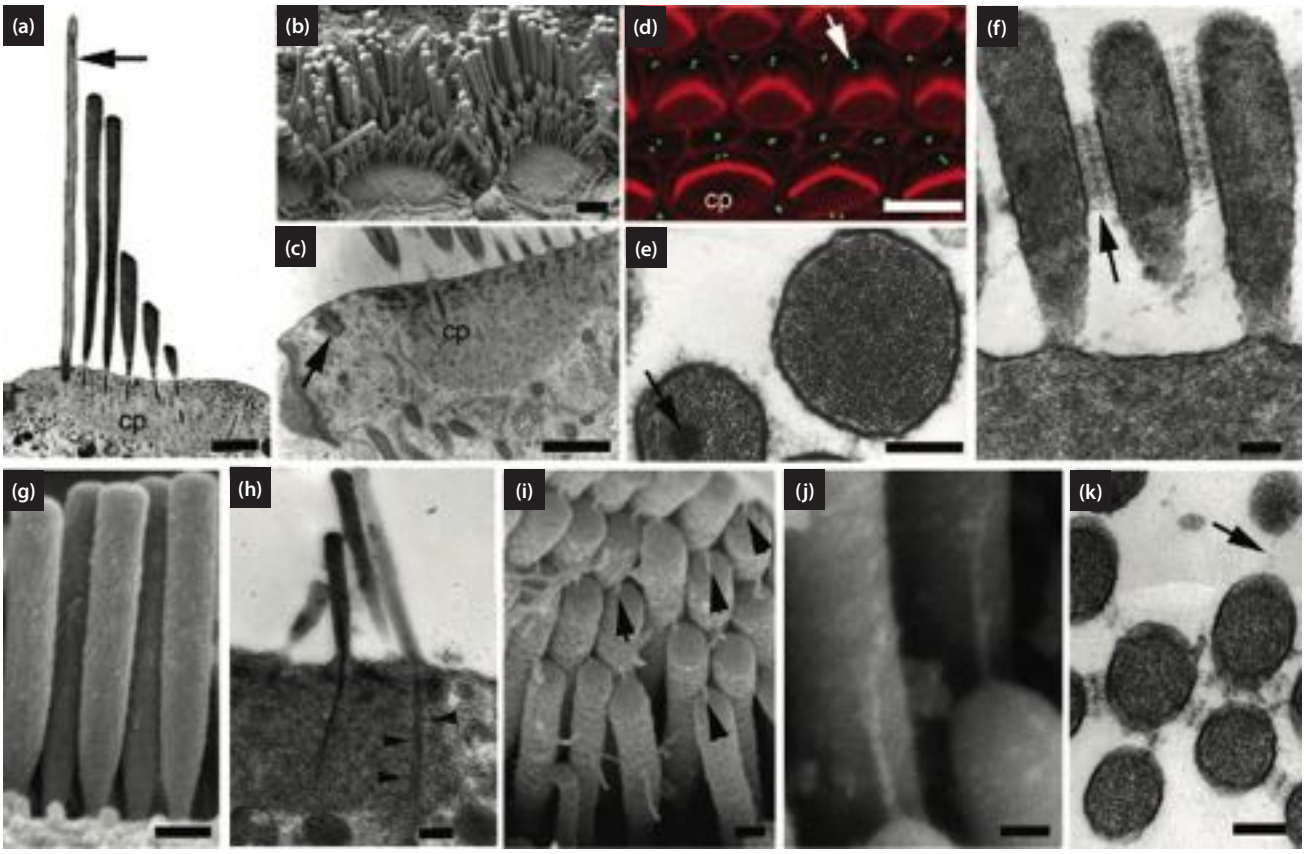


Figure 47.5 The hair bundle. **(a)** Hair bundle from utricular macula (TEM) shows stereotypical features. Rows of stereocilia of increasing height with a longer kinocilium (arrowed) behind the longest stereocilium. The stereocilia embed into the cuticular plate (cp) at their bases. Scale bar: 1 µm. **(b)** Hair bundle of outer hair cell in the human cochlea. Stereocilia in rows of increasing height, but no kinocilium. In humans, there are typically more stereocilia in the hair bundle than in most other mammals. Scale bar: 1 µm. (Preparation courtesy of Prof. Tony Wright, UCL Ear Institute.) **(c)** Apical end of inner hair cell in mature organ of Corti. The kinocilium has retracted to leave the basal body (arrow) to the side of the bundle with the tallest stereocilia in a region of cytoplasm outside of the cuticular plate (cp). **(d)** Labelling for f-actin with fluorescently tagged phalloidin (red) shows the stereocilia and the cuticular plate (cp) are composed of f-actin. Labelling for a protein that is present in basal bodies (Alms1; green) shows basal bodies located behind the stereocilia in a region free of the actin-labelled cuticular plate (arrow). Scale bar: 5 µm. (Figure courtesy of Dr Dan Jagger, UCL Ear Institute.) **(e)** Stereocilia in cross section showing closely packed filaments of actin. Filaments in rootlet are more densely packed (arrow). Scale bar: 100 nm. **(f)** Parallel closely packed filaments of actin in stereocilia. Lateral cross-links between the shafts of adjacent stereocilia in the same row appear to interdigitate at the midpoint of the space between them (arrow). Scale bar: 100 nm. **(g)** Individual stereocilia taper at their proximal end where they embed into the cuticular plate. Scale bar: 500 nm. **(h)** Stereociliary rootlets are cross-linked (arrowheads) before they descend into the filamentous meshwork that constitutes the cuticular plate. Scale bar: 250 nm. **(i)** Tip links (some arrowed) from the top of a short stereocilium to the shaft of the adjacent longer one in the direction of line of polarity in saccular macula of newt. Scale bar: 100 nm. (Figure courtesy of Dr Ruth Taylor, UCL Ear Institute.) **(j)** Higher-power view of tip links between stereocilia on outer hair cells showing branching at their ends. Scale bar: 50 nm. **(k)** Lateral cross-links between neighbouring stereocilia in the same row and adjacent rows. Arrow indicates apparent tip link. Scale bar: 100 nm.

vestibular system from elderly people and may be related to age-related hearing loss and balance dysfunction.[22, 23] It has been suggested that myosin 6 may be involved in holding the apical plasma membrane of the hair cell onto the cuticular plate in the regions between the stereociliary bases so that individual stereocilia can be maintained and, when it is defective, that membrane region becomes detached. In mice where myosin 15 is mutated (shaker-2) stereocilia are greatly reduced in height.[24, 25] Myosin 15 is thought to form a complex with other proteins including whirlin and Esp8 that regulates the height of stereocilia.[26–29] Mutations in the myosin 7a gene are responsible for Usher syndrome type 1B.[30] The mutant mouse strain carrying this mutation (shaker-1) shows hair bundles in which groups of stereocilia are separated from each other at the hair cell apex and the kinocilium is misplaced, suggesting an effect on maintenance of orientation and inter-stereociliary stabilization.[25] Myosin 7a may have a role in the various cross-links that are present between stereocilia (see below).

The stereocilia in an individual hair bundle are connected by a variety of fibrillar extracellular cross-links (**Figure 47.5**).[31] The most critical of these is the 'tip link' which runs from the top of one stereocilium to the shaft of an adjacent longer one along the line of morphological polarity and thus generating the line of functional

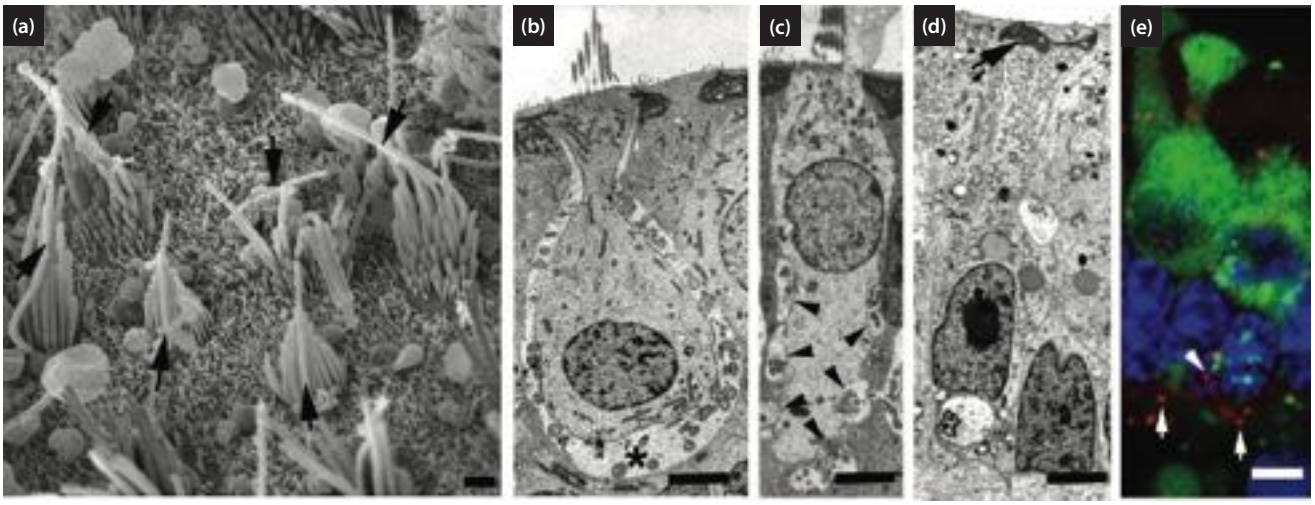


Figure 47.6 Hair cells and supporting cells in vestibular sensory epithelia. **(a)** Hair bundles across the line of polarity reversal in the striolar region of utricular macula. Kinocilia (arrowed) behind row of longest stereocilia. The polarity of the bundles changes by 180° (indicated by the direction of arrows) in the striolar region. Scale bar: 1 µm. **(b)** Type 1 hair cell. The flask-shaped cell body is entirely enclosed within the calyx terminal of a single afferent nerve (asterisk). Scale bar: 2 µm. **(c)** Type 2 hair cell. The cylindrical cell is contacted by several afferent nerve bouton terminals (arrow heads). Scale bar: 2 µm. **(d)** Supporting cell, with cell body basally resting on the basement membrane has a thinner process through the mid-region of the epithelium and a wide, dense cytoskeletal complex (arrow) at the apical head region at the level of the junctions with adjacent supporting cells. Scale bar: 2 µm. **(e)** Human utricular macula. Hair cells labelled for myosin VIIa (green). Punctate labelling for connexin 30 (red) reveals numerous large gap junction plaques (arrows) between the cell bodies of adjacent supporting cells. Nuclei labelled blue (DAPI). Scale bar: 5 µm. (Figure courtesy of Dr Ruth Taylor, UCL Ear Institute.)

polarity (**Figure 47.5i,j**).[32, 33] The tip link is thought to be the gating element that controls the opening of the MET channel.[34–37] As the bundle moves in the excitatory direction, tension on the tip link opens the channel; when the bundle moves in the opposite direction, tension is relieved and the channel closes. The tip link is composed of two coiled filamentous proteins that are adherent end-to-end: cadherin 23 (cdh23) and protocadherin 15 (pcdh15).[38–40] Unsurprisingly, mutations in the genes that encode for either of these proteins cause both hearing impairment and vestibular disorders: mutations in the cdh23 gene result in Usher syndrome type 1D in humans and are responsible for the 'waltzer' mouse strain; mutations in the gene encoding pcdh15 are associated with Usher syndrome type 1F and the 'Ames waltzer' mouse (the names of the mouse strains indicate the movement abnormalities resulting from defects in the vestibular system). At its upper end, around the point of its insertion into the membrane of the shaft of the longer stereocilium, the tip link is associated with a complex of proteins that may regulate tip-link tension thereby controlling transduction channel opening, as well as 'adaptation', the closure of the channel that occurs with sustained excitatory deflection of the stereocilia, of particular relevance in vestibular hair cells. Proteins involved in maintaining tip-link tension include myosin 7a, Sans and harmonin,[41] and again defects in these are associated with hearing impairment and vestibular dysfunction: Usher type 1B in humans and the shaker 1 mouse strain in the case of myosin 7a; Usher type 1C from defects in harmonin; and Usher type 1G from mutations in *Sans*.[38] In addition, myosin 1c localizes to the region near the upper insertion point of the tip link and is thought to be involved in adaptation.[42]

In addition to the tip link, there are 'lateral links' that connect the shaft of one stereocilium to all its neighbours. There are thought to be at least three different types of lateral link between stereocilia.[31] Ankle links, which are present in the hair cells of mammalian vestibular organs and the auditory and vestibular hair cells of non-mammalian vertebrates but not in those of the organ of Corti, connect stereocilia at their proximal ends. Shaft connectors are present along the mid-region of the stereociliary shaft (**Figure 47.5f,k**). Top-connectors link stereocilia just below the level of the tip links. The different types of lateral link were initially identified through the use/generation of antibodies that specifically label each subpopulation separately.[31] This indicates significant differences in protein composition between the links. Mice with defects in the genes for these different stereociliary cross-linking proteins also have hearing impairment and balance dysfunction. Lateral links may have a role in holding the bundle together, thereby stabilizing it and aiding the mechanical coupling of deflections of the stereocilia, such that the stereocilia in a hair bundle all move as a single unit. In agreement with this, mice with mutations in genes that encode lateral link proteins exhibit splaying of the stereocilia and thus loss of efficient MET, indicating the critical role for lateral cross-links in maintaining hair bundle cohesion.[31]

The basolateral plasma membrane

The basolateral membrane of a hair cell is characterized by the presence of a variety of ion channels essential for shaping the response of the cells to mechanical excitation.[43] Outwardly rectifying K^+ channels open when the hair cell is depolarized by the MET current that is generated

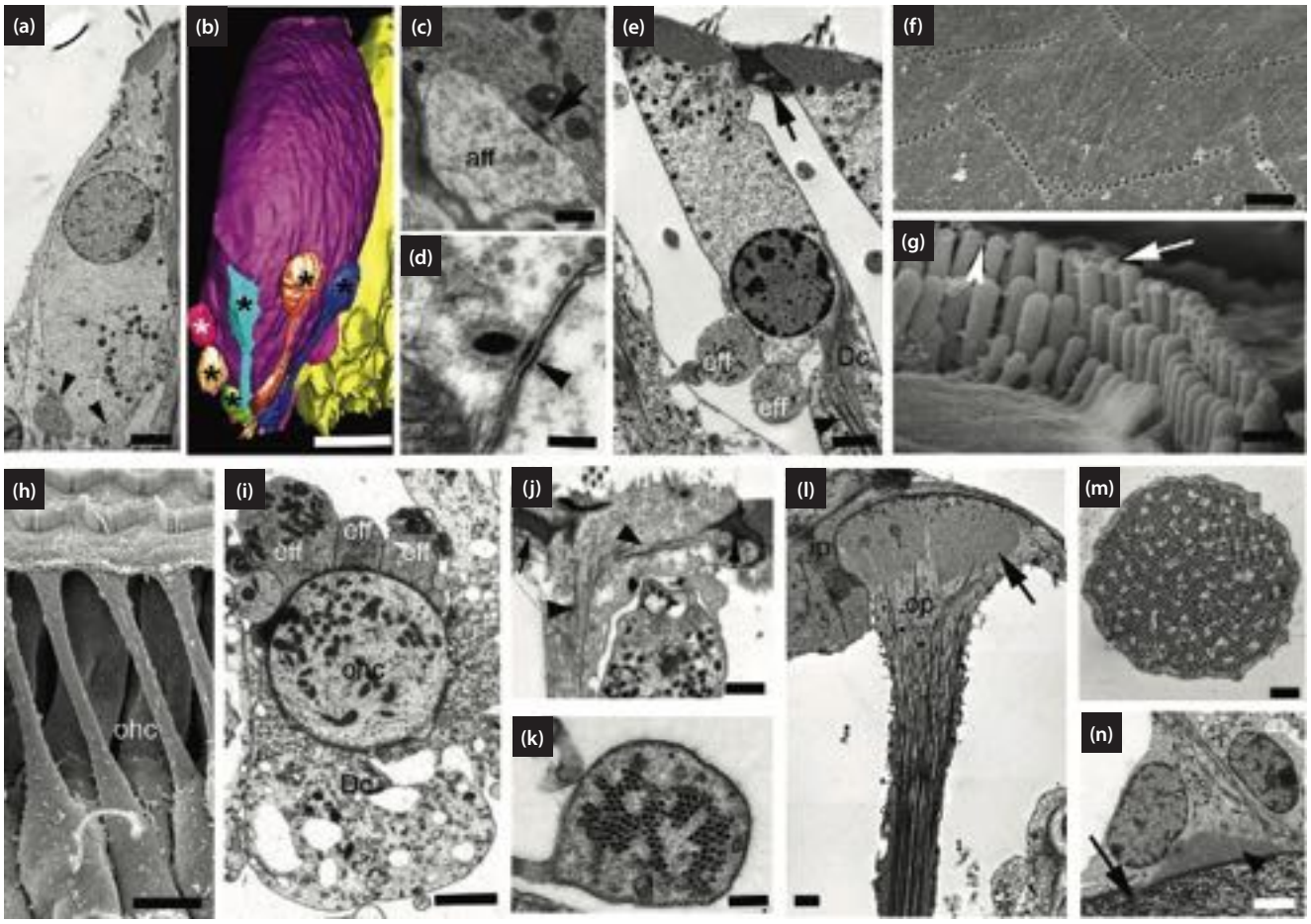


Figure 47.7 Ultrastructure of hair cells and supporting cells in the organ of Corti. **(a)** Inner hair cell. Flask-shaped cell closely surrounded by supporting cells. Terminals of afferent synapse at the base of the cell (arrowheads). Scale bar: 2 µm. **(b)** 3D reconstruction from serial sections of an inner hair cell and its innervation. Several different afferent terminals (coloured and indicated by asterisks) contact around the basolateral surface of the inner hair cell (purple). Scale bar: 5 µm. (Figure courtesy of Dr Anwen Bullen, UCL Ear Institute.) **(c)** Afferent nerve terminal and synapse. A TEM section through the postsynaptic terminal and the presynaptic ribbon in the inner hair cell side (arrowed). The circular ribbon opposes the postsynaptic density of the membrane of the afferent nerve terminal (aff). Scale bar: 1 µm. **(d)** Ribbon synapse. Higher power view showing the ribbon surrounded by neurotransmitter vesicles. Arrowhead indicates postsynaptic density of the membrane of the afferent terminal. Scale bar: 100 nm. **(e)** Outer hair cell. Efferent nerve terminals (eff) around the basal pole of the outer hair cell. The lateral surfaces of the outer hair cell bodies are surrounded by extracellular space (the space of Nuel). There is contact with a Deiters' cell (Dc) around the basal pole and with the head of a Deiters' cell at the apical surface (arrow). The head of the Deiters' cell contains a wide, deep cytoskeletal assembly at the level of the intercellular junctions and the hair cells' cuticular plates. Arrowhead indicates a microtubule bundle in the body of a Deiters' cell below the outer hair cell. Scale bar: 2 µm. **(f)** Underside of tectorial membrane showing indentations of the insertions of the tips of the longest stereocilia of each outer hair cell stereociliary bundle. Scale bar: 1 µm. **(g)** Outer hair cell stereociliary bundle. The tips of the longest stereocilia are crowned with fibrillary material (arrows) that attaches each stereocilium into its indentation in the underside of the tectorial membrane, probably composed of stereocilin. Scale bar: 0.5 µm. **(h)** Deiters' cell: consists of a main cell body region that at its upper end encloses the base of an outer hair cell (ohc); a phalangeal process that ascends at an angle to the apical surface; and an expanded head region at the apical end that contacts an outer hair cell, two cells away along the row from that which the cell body encloses. Scale bar: 5 µm. **(i)** Horizontal/oblique section through the Deiters' cell (Dc) body where it encloses the base of outer hair cell (ohc) in a cup-like fashion, open on the side towards the modiolus. Efferent nerve terminals (eff) contact the basal pole of the outer hair cell at the opening. Scale bar: 2 µm. **(j)** Deiters' cell head. Wide, deep cytoskeletal assemblies (arrow) attached at intercellular junctions with outer hair cells. Microtubule bundle (arrowheads) run across the head parallel to the apical surface and down phalangeal process. Scale bar: 2 µm. **(k)** Deiters' cell phalangeal process in horizontal cross section. The process encloses bundles of microtubules. Scale bar: 200 nm. **(l)** Outer pillar cell (op). The phalangeal process is filled with parallel microtubules. The expanded apical head region forms a buttress beneath the widening head of the inner pillar cell. The junction between the outer and inner pillar cells is supported by a dense, wide cytoskeletal assembly in the outer pillar cell (arrow) into which the microtubule bundles terminate. Scale bar: 2 µm. **(m)** Outer pillar cell phalangeal process in horizontal cross section. The process is filled with many closely packed microtubules in seemingly regular arrays. Scale bar: 1 µm. **(n)** Inner pillar cell, base. The cell body rests on a thin bony lip (arrow) extending out from the modiolus. Microtubules bundles descend from the phalangeal process to the very base of the cell and are associated with a dense triangular-shaped cytoskeletal assembly (arrowhead) that anchors the cell to the underlying bone. Scale bar: 2 µm. *(Continued)*

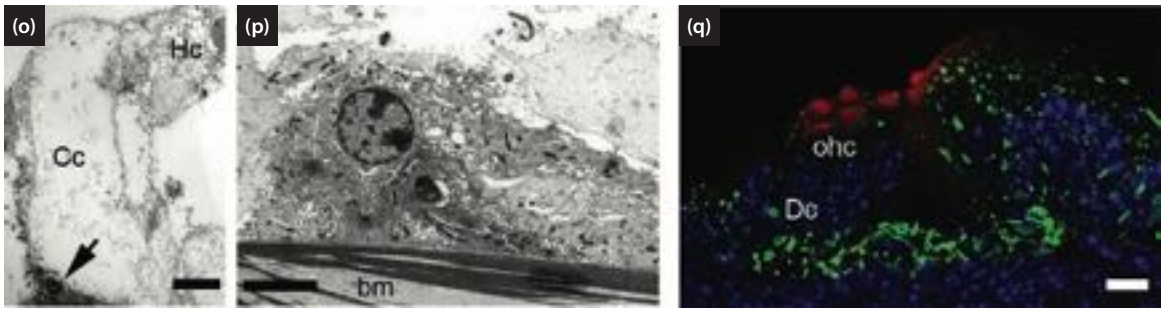


Figure 47.7 (Continued) Ultrastructure of hair cells and supporting cells in the organ of Corti. **(o)** Hensen's (Hc) and Claudius (Cc) cells. Hensen's cell covers the outermost extracellular space of the organ of Corti and does not reach the basilar membrane. Claudius cells are unusually devoid of organelles. They cover the Boettcher cells (arrow). Scale bar: 10 µm. **(p)** Boettcher cells sit on the basilar membrane (bm). They have a dense cytoplasm and numerous interdigitating infoldings. Scale bar: 5 µm. **(q)** The organ of Corti contains many gap junction complexes. Immunohistochemical labelling for connexin 26 (green) reveals gap junction plaques. F-actin is labelled using fluorescent phalloidin (red) and cell nuclei using DAPI (blue). There are numerous large gap junctions between adjacent supporting cells across the entire organ of Corti. Scale bar: 10 µm.

by hair bundle deflection. The resulting outward flow of K^+ through these channels repolarizes the hair cell membrane. The same depolarization also leads to the opening of voltage-gated Ca^{2+} channels and thus an influx of Ca^{2+} that triggers the fusion of intracellular vesicles with the plasma membrane and release of neurotransmitter at the synapses on to the primary afferent nerve endings. In this way, stereociliary deflection opens MET channels, causing depolarization in the hair cells, release of neurotransmitter onto afferent nerve fibres and thus activation of action potentials in neurons, i.e. neural discharge. In addition, hair cells in some rodent species also possess inwardly rectifying K^+ channels that are opened by cell hyperpolarization to restore hair cell resting potentials. Ion channels with these general properties can have different physiological characteristics in terms of their voltage dependence, the speed with which they respond (fast or delayed) and the size of the current that flows through them.[44] Although the general features of a hair cell are well conserved across many species, different types of hair cell are recognized depending on their location (auditory or vestibular), innervation pattern (afferent or efferent) and species of origin. The different types and numbers of ion channels expressed are characteristic features of particular types of hair cell.[44] In addition to the expression of different ion channels, hair cells in the organ of Corti show other specializations of their basolateral plasma membrane that are associated with particular unique functions that these cells perform (see 'Outer Hair Cells' below).

GENERAL CHARACTERISTICS OF SUPPORTING CELLS

The supporting cells provide mechanical support to the epithelium and thus to the hair cells. Their cell bodies contact each other and rest on the basement membrane that underlies the sensory epithelium (Figures 47.3d and 47.4b,c). Rod-like **phalangeal processes** extend from the cell body, interdigitating between the hair cells, to the luminal surface where they expand to fill the spaces between hair cells (Figures 47.3d,e,f and 47.4d,e,f). Supporting cells possess a fairly extensive cytoskeletal system that is particularly well developed in the cells of the organ of Corti. These phalanges contain bundles of microtubules, which can act like scaffolding poles/suspension struts to provide structural support (described in more detail later). At the apical, luminal poles, there are cytoskeletal assemblies that contain actin arranged in filamentous bundles running parallel to the luminal surface of the cell, anchoring to an adherens-like region within the intercellular junction that joins it to the adjacent hair cell (Figure 47.3e). Actin bands that run circumferentially around the neck or cortex of an epithelial cell are present in all epithelial cells and are thought to provide structural support at the points of adhesion between adjacent cells. These cortical actin bands are unusually wide in sensory epithelia of the inner ear (Figure 47.3e), indicating the importance of rigidity at the apical surface of these tissues.[45]

Supporting cells are functionally coupled to each other by substantial numbers of large **gap junctions** (Figures 47.6e and 47.7o).[22, 46–48] Gap junctions are sites of direct cytoplasmic communication between adjacent cells where clusters of pore-forming channel proteins in the membrane of one cell are in direct register with clusters of pore-forming channel proteins in the membrane of its neighbour. When these clusters of proteins dock together, they can form continuous aqueous pores that connect the cytoplasm of the adjacent cells. The protein subunits that form gap junction channels are members of the **connexin** protein family. At least 20 different types, or isoforms, of connexin have been identified. Six connexins form a **hemi-channel** or **connexon**, and the connexons of two adjacent cells align symmetrically to form the communication pathway between the cells. Gap junction channels are clustered in the plane of the membrane to form 'plaques' that can contain up to several thousand connexons. The channels allow the passage of small metabolites (up to 1.2 kDa in size), ions and second messengers, coupling the cells both electrically and chemically. Numerous gap junctions are present at points of contact between adjacent supporting cell bodies and between the head regions of adjacent cells, but there are

no gap junctions associated with hair cells.[22, 47] The large size and number of gap junction plaques between all supporting cells mean that the supporting cell population can be regarded as a functional syncytium, from which hair cells are functionally isolated.[22, 47] In all vertebrate classes from fish to mammals, gap junction plaques in inner ear sensory tissues are typically enormous, among the largest in the whole body, covering several square micrometres (μm^2) in area and containing several thousand channels.[46] One suspected role for supporting cells is thought to be the removal of excess K^+ ions from the intercellular spaces of the sensory epithelium during hair cell repolarization events.[48] Such a mechanism could thereby maintain the low K^+ environment around the body of the hair cell necessary for transduction and sensitivity to stimulation. It has been proposed that the gap junctions provide a means to ferry the K^+ away, preventing local accumulation. Gap junctions in the organ of Corti and in mammalian vestibular sensory epithelia contain two connexin isoforms, Cx26 and Cx30.[46, 48] Mutations in the genes for these connexins have been identified as causes of hereditary sensorineural hearing loss.[49] Those mutations in the gene encoding for Cx26 (*GJB2*) are the most common cause of non-syndromic hereditary deafness. There is increasing evidence that gap junctions with particular connexin composition, in particular Cx26, are important during development of the organ of Corti.[48] However, connexin mutations appear to have much less effect on the vestibular system.

THE VESTIBULAR SYSTEM

The vestibular system can be generally divided into two parts: the **saccule** is anatomically a separate chamber from the **utricle** and the three **semicircular canals** which arise from and terminate in the utricle and run in orthogonal planes – horizontal (lateral), posterior and superior (anterior) (**Figures 47.1a** and **47.2a**). Not only is there anatomical separation; the utricle and semicircular canals are evolutionarily and developmentally separate from the saccule. In the evolutionarily most primitive extant vertebrates (e.g. hag fish), the inner ear is composed of only two semicircular canals that are continuous with a single utricle-like chamber with a macula.[50, 51] During ontogenetic development, the utricle and semicircular canals arise on one side of the embryonic otic vesicle, opposite to that of the saccule which develops close to the site at which the cochlea is defined.[52] There is thus an anatomical and developmental relationship between the saccule and the cochlea, and in fish and some amphibia, the saccule does have an auditory function.[53, 54] This biological relationship may be an underlying factor in the sound-induced vertigo and dizziness characteristic of Tullio syndrome.

Sensory epithelia

The maculae of the utricle and saccule are flat sheets of epithelium that are oriented at right angles to each other (**Figure 47.2a**), the utricle in the anterior–posterior plane, the saccule in the superior–inferior. The utricular macula is approximately U-shaped and the saccular macula, in mammals, is almost S-shaped (**Figure 47.3a,b**). The **cristae ampullares** of the semicircular canals are saddle-shaped epithelial mounds (**Figure 47.3c**) contained within swellings, the ampullae, which open to the utricle at one end. The cell bodies of the nerves that innervate the sensory cells of the vestibular system are collected together in **Scarpa's** or vestibular **ganglion**, which is just external to the medial wall of the inner ear (**Figure 47.2a**).

OTOCONIAL MEMBRANES AND CUPULA

The utricular and saccular maculae are each overlaid by an 'otoconial membrane' which consists of a large number of otoconia (Greek: 'ear dust') (**Figure 47.3g**), crystalline particles composed of calcium carbonate surrounding a proteinaceous core that sit on a honeycomb-like perforated sheet of non-collagenous fibrillar extracellular matrix (**Figure 47.3h,i**). This matrix is composed of proteins unique to the inner ear including otogelin, α- and β-tectorins and ceacam 16 (carcinoembryonic antigen-related cell adhesion molecule 16).[55, 56] In fish, rather than numerous small particles, there is a single, large calcium carbonate particle, the otolith (Greek: 'ear stone'), hence the term 'otolithic organs' is sometimes used (incorrectly) to describe the saccule and utricle of mammals. Hair bundles of the utricular and saccular hair cells appear to align with the perforations in the sheet of extracellular matrix with the longest stereocilia, possibly in contact with the edge of the hole (**Figure 47.3i**). The utricular and saccular maculae detect translational motion of the head in the horizontal and vertical planes. With a linear motion, because of its mass, movement of the otoconial membrane lags in relation to the movement of the epithelium itself, which follows the head movement without any inertia. As a result, the stereocilia are deflected and hair cells stimulated. With a head tilt, the force of gravity acts on the otoconial membrane to produce a relative displacement between the membrane and the tilting surface of the epithelium that deflects the stereocilia. In the semicircular canals, the extracellular structure overlying a crista, known as the **cupula**, is a dense fibrous mass with no otoconia that extends to the roof of the ampulla (**Figure 47.3j**). The principal proteinaceous component is otogelin; neither tectorins nor collagen are are present in the cupula.[55] The longest stereocilia of hair cells of the cristae appear to contact the underside of the cupula. The cristae detect rotational acceleration of the head. When the head rotates, movement of endolymph through the semicircular canals lags behind that of the crista epithelium because of the fluid's inertia. The consequent differential movement displaces the cupula, leading to deflection of the stereocilia.

HAIR BUNDLES AND THEIR ORIENTATIONS

Hair bundles of vestibular hair cells have a stereotypical morphology consisting of stereocilia arranged asymmetrically in a staircase pattern of increasing height in one particular plane, that of activation or sensitivity, and a single kinocilium located behind the tallest stereocilia (**Figures 47.3f**, **47.5a** and **47.6a**). At least four different

arrangements of the stereocilia have been described for the hair bundles on macular hair cells.[57] Although these differences suggest divergent physical and biophysical properties of hair bundles, the functional significance has not been clarified.

In the cristae the orientation of the hair bundles, i.e. the alignment of the staircase pattern which defines morphological and functional polarity, is the same for all the hair cells in an individual crista. In the cristae of the horizontal and superior canals the shortest stereocilia of all hair cells are on the side of the bundle towards the utricle, while in the cristae of the posterior canal the bundles are oriented the opposite way, with the longest stereocilia (and kinocilium) on the side facing the utricle. Because of the uniform orientation of hair bundles across the cristae, a rotation in a particular direction will produce excitatory deflections of all stereociliary bundles of the cristae in one ear and inhibitory deflections of the hair bundles of the cristae in the same semicircular canal in the opposite ear, the integration of signals thereby providing information on the direction of rotation.

In the saccule and utricle there are opposing orientations of the hair bundles across the maculae: all the hair bundles located on one side of a region running across the epithelial sheet are oriented the same way with respect to the periphery, and at 180° to those on the other side of that region (**Figure 47.6a**). In the utricular macula, the shortest stereocilia face the centre (the bundles are oriented 'front-to-front' across the line of polarity reversal) so that excitation of the hair cells occurs with deflections of the stereocilia towards the periphery of the macula, whereas hair bundle orientations in the saccular macula are the reverse of those in the utricle: the longest stereocilia, and excitatory hair bundle deflection, are towards the centre. The line of hair bundle polarity reversal in a macula is located in the middle of the 'striola', a delineated strip, approximately 50–100 µm wide within the body of the macula and shaped to follow its contour.[58] The opposing orientations of the hair bundles, coupled with the asymmetric shape of the maculae and orientation of the saccular and utricular maculae in orthogonal planes, means that as head position changes differing patterns of hair cell excitation are elicited, providing fine-grained information on translational motion.

HAIR CELL TYPES

The basic cellular composition of all vestibular sensory epithelia is essentially the same (**Figure 47.3d**). There are two types of hair cell and these are both surrounded by non-sensory supporting cells. Type 1 hair cells are flask-shaped with a single large afferent nerve ending, a calyx, enclosing the entire basolateral surface of the cell (**Figures 47.3b** and **47.6b**). The endings of efferent nerves (i.e. those that carry signals from the brain to the sensory epithelium) contact the afferent calyx but not the hair cell itself. Type 2 hair cells are cylindrical with several small bouton-like afferent endings that form synapses towards the basal end of the cell (**Figure 47.6c**). In type 2 hair cells the efferent endings contact the hair cell directly. The nuclei of type 2 hair cells are generally located higher (closer to the luminal surface) in the cell than those of type 1s (**Figures 47.3d** and **47.6b,c**) and since the nuclei of the surrounding supporting cells are located beneath the hair cells, cross sections of vestibular sensory epithelia can appear to have three layers of cells (**Figure 47.3d**). There are other morphological features that distinguish the two hair cell types: for example, the stereocilia of type 1 cells are thicker (i.e. they contain more actin filaments) than those of type 2 hair cells. The physiological properties of the two hair cell types, as defined by ion channel expression in the basolateral membrane, are also different.[59] The calcyeal nerve terminals around type 1 hair cells express high levels of a calcium-binding protein, calretinin, which is not expressed in the afferent endings that synapse with type 2 hair cells.[58, 60] Accordingly, immunolabelling for calretinin provides a means for distinguishing and exploring the number and distribution of type 1 hair cells.[61] Use of this and other assays of hair cell morphology combined with dye tracing of the nerves,[62] has shown that the two hair cell types are differentially distributed across the organs. Type 1 cells predominate across the striolar region of the maculae and at the crest of the cristae. Type 2 hair cells are mainly confined to the extrastriolar regions of the maculae and the skirts of the cristae.[58, 60, 62] It is worth noting that the hair cells with a type 1-like innervation pattern are not present in fish or amphibians, rather they appear in vertebrates with necks which initially evolved as terrestrial animals. Thus, type 1 hair cells are likely to be providing information such as detecting rapid and/or smaller incremental head movements that are independent of whole body movements, and necessary for life on land.

PATTERNS OF INNERVATION

The patterns of afferent innervation of the different types of hair cells, often revealed following injection of a tracer dye into a single neurone,[62] are quite complex. An individual afferent neuron usually branches to innervate more than one hair cell. The neurons that innervate hair cells in the striolar region of the maculae and the crest of the crista form calcyeal nerve endings with only a single type 1 hair cell. In the peripheral regions of those organs a few individual afferent nerves form only bouton endings with several type 2s, but the majority of the afferent nerves are 'dimorphic', innervating both type 1 (≥1) and type 2 (typically >1) hair cells.[58, 60, 62] As a result, individual 'dimorphic' afferent fibres carry signals to the brain that result from the integration of convergent inputs from a number of different hair cells. Neurons innervating the striolar regions of the macula and the crest of the cristae do not cross into the extrastriolar regions of maculae or the skirts of the cristae, nor do they cross from one side of the striolar to the other so that the innervations in different regions of the sensory epithelia are anatomically separate. Moreover, there is some evidence from rats that, while afferent neurons from one side of the utricle project to the vestibular nuclei in the brain, those from the opposite side project to the cerebellum.[63] This indicates that there is significant integration and processing of information derived from vestibular sensory periphery that is carried up to higher centres in the brain.

SUPPORTING CELLS

The supporting cells of the vestibular sensory epithelia (Figure 47.6d,e) conform to the general pattern outlined above. They are relatively much less specialized than their counterparts in the organ of Corti and are little different from supporting cells in the sensory epithelia of the inner ear in all other vertebrates. Given that they form the reticular lamina (Figure 47.3e), they play critical roles in the barrier function of the epithelium and are also thought be important in phagocytosing and removing dead or dying hair cells.[64–66]

Ion-transporting epithelia of the vestibular system

The ion-transporting epithelium of the vestibular system is the region of 'dark' cells, so named because in histological sections the cells stain much more intensely (i.e. darker) than any others (Figure 47.8a). Dark cell epithelia are confined to the utricle and semicircular canals; there are no dark cells in the saccule (Figure 47.2a). In the utricle the dark cell epithelium forms a band all around the periphery of the macula separated from the sensory epithelium by transitional cells, a strip of relatively unspecialized cuboidal epithelial cells of as yet undefined function. A band of dark cell epithelium is also located all along the bottom of the skirts of each crista, again separated from the sensory region by a strip of transitional cells. The dark cell is a specialized cuboidal epithelial cell, in which the basolateral membrane is extensively infolded to create a large surface area. These infoldings house numerous large mitochondria likely to be critical for the function of these cells (Figure 47.8a).

Dark cells are crucial to maintaining the ionic concentration of endolymph. Lying underneath the dark cell epithelium is the mesenchyme of the connective tissue, the intercellular spaces of which are part of the perilymphatic compartment (Figure 47.8a). Unusually, there is no basement membrane or permeability barrier between the dark cell epithelium and the connective tissue, so the basolateral surfaces of the dark cells are exposed directly to perilymph. During the ongoing process of MET K^+ is shunted from the endolymphatic to the perilymphatic compartment. The basolateral membranes of the dark cells contain high levels of the Na^+/K^+-ATPase pump,[67] which use ATP to 'pump' two K^+ ions into and at the same time three Na^+ ions out of the cell against their respective ion concentration gradients. The presence of numerous large mitochondria within the basolateral infoldings is likely a specialization necessary for provision of the local energy supply required for this energetically expensive active ion transport. In addition, the dark cells' basolateral membranes contain an Na^+–K^+–Cl^- cotransporter NKCC1 (or SLC12A2).[68] This membrane protein uses energy derived from the Na^+ concentration gradient to cotransport the other two ions into the cell. Entry of Na^+ stimulates activity of Na^+/K^+-ATPase to return Na^+ equilibrium, thereby further enhancing K^+ uptake into the cell. The apical surfaces of the dark cells which face endolymph contain ion channels selective for K^+.[69] K^+ entering the dark cell at the basal side exits through the K^+ channels at the apex, into endolymph.

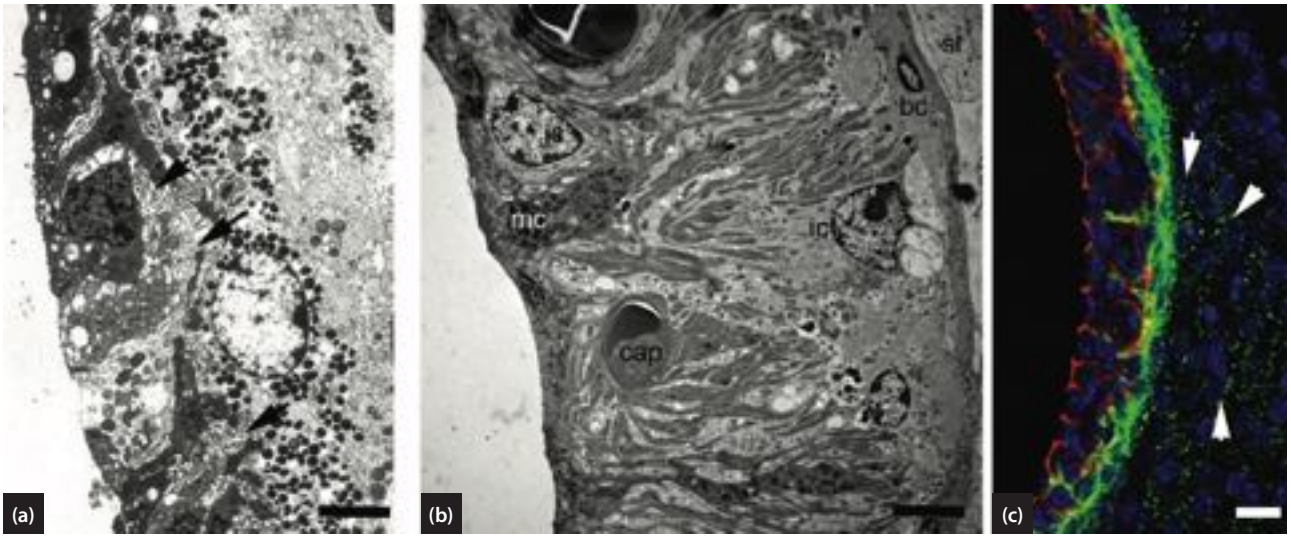


Figure 47.8 Ion-transporting epithelia. (a) Vestibular dark cell layer. The dark cells have numerous basal infoldings (arrows). A layer of pigmented cells containing melanin granules underlies the dark cells with mesenchyme beneath. Scale bar: 5 µm. **(b)** Stria vascularis. mc = marginal cells; ic = intermediate cells; bc = basal cells; cap = capillary; sl = spiral ligament underlying the stria vascularis. Marginal cells line the endolymphatic space and have numerous basal infloldings that extend down to the level of the basal cells. Intermediate cells, which contain melanin pigment granules, are entirely enclosed within the body of the stria. Elongated basal cells in one to two layers separate the stria from the underlying spiral ligament. Capillaries enclosed within the body of the stria are contacted by marginal cell processes and by intermediate cells. Scale bar: 5 µm. **(c)** Stria vascularis. Basal cell layer delineated by intense labelling for connexin 26 (green), indicating numerous gap junction plaques associated with basal cells. Gap junctions are between adjacent basal cells, between basal cells and intermediate cells and basal cells and fibrocytes in the spiral ligament. There are also numerous gap junctions between adjacent fibrocytes in the spiral ligament, indicated by green labelling for Cx26 in puncta (arrows) in tissue below the stria. Scale bar: 20 µm. (Figure courtesy of Dr John Kelly.)

In this way, K^+ ions are transported into endolymph and ion homeostasis in the vestibular system is maintained.

THE COCHLEA

Gross anatomy

The **cochlea** is formed of three parallel canals (or **scalae**, Latin: 'ladders'), coiled in a spiral around a central 'stalk', the **modiolus** (Figure 47.1c). The axons of the central projections of the auditory nerves that innervate the sensory epithelia, and the vessels of the cochlear blood supply, the cochlear artery and cochlear vein, run through the length of the modiolus. There are 2.5 turns in the human cochlea. The number of turns varies between different mammalian species but at present this is not known to have any specific functional significance. The central canal, the **scala media**, is lined by epithelia (part of the membranous labyrinth) and is filled with endolymph. In cross sections of the cochlea, the scala media is bounded by three 'walls' and appears approximately triangular in shape (Figures 47.1c and 47.2b). The sensory epithelium, the **organ of Corti,** running along the **basilar membrane**, forms the 'floor' of the triangle. The primary ion-transporting epithelium, the **stria vascularis**, runs along the lateral side and **Reissner's membrane** forms the 'roof' of the scala media (Figure 47.2b). Above Reissner's membrane is the **scala vestibuli**, and underneath the basilar membrane is the **scala tympani**. These two scalae are filled with perilymph. Reissner's membrane acts as the barrier between endolymph and perilymph in the scala vestibuli. Perilymph from both the scala vestibuli and scala tympani is freely permeable into the intercellular spaces of the spiral ligament that underlies the stria vascularis but, unlike the vestibular system, there is a barrier to direct diffusion of ions from the spiral ligament into the ion-transporting epithelium (see below).

The height and width of all the three scalae decrease systematically from base to apex of the spiral (Figure 47.1c). At the basal end, the scala tympani terminates at the **round window** (Figure 47.1a,b), a flexible membrane formed of two epithelial sheets sandwiching connective tissue, containing collagen and blood vessels.[70, 71] The apical surface of the outer epithelium is exposed to air in the middle ear; that of the inner epithelium is bathed in perilymph. The scala vestibuli at its basal end is continuous with the vestibule and the perilymphatic compartment of the vestibular system. The **oval window**, opening over the vestibule, is covered by a membrane and is filled with the footplate of the stapes. The gap between the border of the stapes footplate and the edge of the oval window is sealed with a ligament. At the apical end of the cochlea, the scala media is closed by epithelial tissue, arising partly by extension of Reissner's membrane, leaving a small opening, the helicotrema, through which the scala vestibuli and scala tympani are connected. Sound-induced movements of the tympanic membrane drive piston-like 'in–out' movements of the stapes footplate displacing incompressible perilymph along the scala vestibuli, through the **helicotrema** and down the scala tympani leading to 'out–in' movements of the round window. As fluid is displaced, the pressure difference across the scala media between the scala vestibuli and scala tympani, produces vibrational movement of the basilar membrane, described by Von Békésy. This 'travelling wave' stimulates the sensory cells housed in the organ of Corti that sits on the vibrating basilar membrane.

Organ of Corti

The mature organ of Corti is a ridge of cells resting on the basilar membrane and overlain by the tectorial membrane (Figure 47.4b,c). The length of the coiled basilar membrane and attendant organ of Corti varies with species; in humans it is about 35 mm long (range, 28–40 mm),[72] ~12 mm in mice, ~20 mm in guinea pigs and ~40 mm in whales. The widths of the basilar membrane and the organ of Corti increase systematically from the base to the apex of the cochlea. The thickness of the basilar membrane and the height (and mass) of the organ of Corti also both increase systematically from base to apex.[73] The consequent changes in the inherent mechanical properties of the basilar membrane, combined with changes in the mass on the membrane, result in sounds of different frequencies producing maximum vibrations at different locations along the cochlea; high frequencies are detected at the basal end and low frequencies at the apex. This frequency-place, or '**tonotopic**' relationship is preserved along the neural pathways in the brain: nerves that innervate the hair cells at the high-frequency, basal end of the cochlea project to a specific place in the cochlear nucleus, and those that innervate hair cells in the apical low-frequency region project to a different but specific place in the cochlear nucleus, i.e. there is a tonotopic map projected onto the cochlear nucleus and this tonotopicity is carried on up the auditory pathway.

There are two hair cell types in the organ of Corti, the **inner** and **outer hair cells** (IHCs and OHCs) (Figure 47.4b,d,e). In most mammals these are regularly arranged into a single row of IHCs on the medial or inner side of the spiral and three, sometimes four, rows of OHCs (Figure 47.4b,d,e) on the lateral or outer side. The human organ of Corti, however, appears less well ordered than the cochleae of lower mammals, with regions containing two ranks of IHC and areas where the rows of OHCs are less clearly definable, less evenly spaced and with occasional discontinuities (Figure 47.4f).[74] Within the body of the organ of Corti are large extracellular spaces (Figure 47.4b,c): the **spaces of Nuel** around the OHCs, and the **tunnel of Corti** between the OHC region. Both of these spaces are created during late stages of developmental maturation of the organ of Corti as a result of morphological specializations of the supporting cells, during which the phalangeal processes between the cell body region and expanded head at the apical (lumenal) end become reduced in width. The spaces are filled with perilymph as the basilar membrane is not a permeability barrier. The actual border and permeability barrier between the perilymph of the scala tympani and endolymph in the scala media is created by the intercellular junctions at the lumenal side of the organ of Corti and lies at the level of the reticular lamina. Mutations in the proteins that

comprise the tight (occluding) junctions in the organ of Corti, result in hearing impairment,[75–77] emphasizing the essential nature of the junctions and the barrier that they form.

BASILAR MEMBRANE

The basilar membrane (BM) is a sheet formed predominantly of extracellular matrix (**Figure 47.4b,c** and **47.7n**). It is composed of filaments within a ground substance, with a discontinuous layer of thin, elongated tympanic border cells on the underside facing the perilymph of the scala tympani.[17] The fibrils of the BM run predominantly radially, and are composed of collagen, mostly collagen type IV α1–α5 chains (COL4A1–COL4A5).[78] In addition, fibronectin[79] and laminin type 11,[80] adhesive-type molecules common to extracellular matrices, are localized to the BM and presumably compose the ground substance in which the collagen fibrils reside. The composition of the BM does not appear to be unique in comparison with basement membranes elsewhere in the body, except for a novel extracellular matrix protein (named 'usherin')[38, 81] that has been identified through the genetic mutation which is associated with Usher syndrome type 2A, in which there is high-frequency hearing loss. Mutations in the genes for the proteins composing the BM might be expected to affect the mechanics of the organ of Corti in response to sound and thereby cause hearing impairment. X-linked Alport syndrome has been attributed to mutations in the *COL4A5* gene. It has been suggested that it is the loss of this protein from the BM that results in the high frequency hearing loss associated with this condition.[82]

TECTORIAL MEMBRANE

The tectorial membrane (TM) is the structured sheet of extracellular matrix material that overlies the organ of Corti (**Figures 47.1b** and **47.4b,g**). At its inner edge it is attached to the interdental cells of the spiral limbus, a bony prominence to the inside of the organ of Corti (**Figure 47.1b**). It appears not to be attached to the surface of the organ of Corti at its outer edge. The longest stereocilia of each OHC are embedded in the underside of the TM (further described below). The TM is not merely a fibrous mass but it is quite highly structured, with a defined shape (**Figure 47.1b**). Its thickness decreases and its radial length increases systematically from base to apex. Over the top surface densely packed fibres are arranged in a network, the 'covernet' (**Figure 47.4g**), that is not unlike the perforated sheet of the otoconial membrane. The outermost tip is also distinguished by a higher density of fibre packing (**Figure 47.4b,g**). On the underside – facing the apical surface of the organ of Corti – there is a thickened ridge known as Hensen's stripe located just lateral to the position of the IHC stereocilia which is thought to contribute to the fluid-coupled deflection of the IHC stereocilia.

The body of the TM is formed of fibre bundles running approximately radially, embedded within a matrix composed of striated sheets formed of fine cross-linked fibrils.[83] The fibre bundles are formed of collagen types II, V and IX,[84, 85] different types to those found in the BM. Associated with the collagen bundles are the glycoproteins otogelin,[86] and α- and β-tectorin[87, 88] and ceacam 16.[89, 90] Otogelin, α- tectorin and β-tectorin are unique and essential to the inner ear, since mutations in the genes that encode for them are associated with non-syndromic hearing loss in humans.[86, 91, 92] Expression of mRNA for otogelin and the tectorins is detected only during development of the cochlea;[93, 94] they are not expressed in the organ of Corti of adults. The cessation of mRNA production indicates that there is no turnover of these key proteins, suggesting that the TM is a lifelong structure produced only during cochlear development. The implication is that damage to the TM (e.g. by disease or noise trauma) would not be repaired and would result in permanent hearing loss.

INNER HAIR CELLS

Rather than being positioned on the flexible BM, the IHCs reside above a thin and inflexible bony extension from the bone that surrounds the modiolus (**Figure 47.2b**). They are roughly flask-shaped (**Figure 47.7a**) and the shape of their hair bundles approximates to a straight line or a shallow 'U'-shape so they appear to form an almost continuous 'fence' along the medial or inner aspect of the organ of Corti (**Figure 47.3d,e**). Unlike the tips of OHC hair bundles, the IHC hair bundles do not appear to contact the TM directly. IHCs are innervated exclusively by **afferent nerve fibres** and 90–95% of all the afferent fibres from the cochlea to the brain arise from IHCs,[95, 96] making them the principal receptor cells that send auditory information to the brain. **Efferent nerve fibres** that terminate in the IHC region arise from the ipsilateral lateral superior olive in the mid-brain. Rather than contacting the IHCs, the efferent fibres contact the afferent fibres that terminate on the IHCs. These **lateral olivocochlear efferent nerve fibres** constitute approximately 20% of the efferent innervation to the organ of Corti.

Each IHC forms synapses with several (up to around 20) different afferent nerve endings that surround its basolateral membrane[97] (**Figure 47.7a,b**) but crucially a single auditory nerve fibre (ANF) innervates only a single IHC. The synapses between an IHC and its innervating afferent nerve endings are specialized **'ribbon' synapses** (**Figure 47.7c,d**). On the pre-synaptic, IHC side of the synapse adjacent to the membrane there is an elongate or rounded structure, the ribbon, surrounded by tethered **secretory vesicles** containing the **neurotransmitter** (glutamate), which release the glutamate into the synaptic gap or cleft when the hair cell is stimulated. The neurotransmitter binds to receptors on the post-synaptic membrane to initiate action potentials in the synapsing ANF. The 'ribbon' specialization provides for a constant pool of neurotransmitter at the site of neurotransmission to allow rapid and sustained release of glutamate and so rapid and sustained firing of the ANFs necessary for audition. Physiological recordings combined with dye tracing of individual ANFs have uncovered different response characteristics within the group of afferent fibres that innervate an individual IHC.[95, 98–101] At least two subpopulations have been identified: afferent fibres with low spontaneous firing rates

(i.e. the numbers of action potentials fired per second in quiet conditions) and high thresholds (i.e. requiring a relatively high sound intensity input to elicit a change in that firing rate); and fibres with high spontaneous rate and low thresholds. This diversity in the firing characteristics of the nerves innervating a single IHC provides a means to enhance the dynamic range of a single IHC that allows it to accurately encode a wide range of sound intensities. There is now increasing evidence that the subpopulations of afferent fibres that innervate an individual IHC are differentially sensitive to the effects of noise and ageing and the loss of a subpopulation of the afferent terminals under these conditions results in what has become known as 'hidden hearing loss'.[101, 102] In this situation, since the IHCs still have some neural connections, the auditory thresholds measured by standard audiological pure tone tests appear normal, but there are deficits in more subtle but critical aspects of audition, for example the ability to discriminate sounds (such as speech) in noise.

OUTER HAIR CELLS

OHCs are located across the most flexible part of the BM (**Figure 47.4b**). They are cylindrical cells with a basally positioned nucleus (**Figures 47.4b** and **47.7e**). Their hair bundles form a characteristic 'W'-shape (**Figure 47.4d,e**) and contact the underside of the overlying TM in which impressions of the longest OHC stereocilia can be seen (**Figure 47.7f**). A fibrous protein, stereocilin, appears to link the tips of the longest stereocilia to the insertion into the TM (**Figure 47.7g**).[103] Mutations in the gene for stereocilin are associated with hearing impairment.[104] Coupling between the longest stereocilia and the TM provides the mechanism by which OHCs are stimulated. The up-and-down movements of the travelling wave that is generated along the BM in response to the sound-induced fluid displacements along the scala vestibuli and scala tympani translate into radial (medial to lateral) movements at the apical surface of the organ of Corti. The TM mass remains static, so there is a relative shearing motion between the reticular lamina (the apical surface of the organ of Corti) and the TM. Since the longest stereocilia of OHCs are embedded in the underside of the TM, this differential movement results in the deflection of the hair bundle along the line of functional polarity resulting in opening and closing the MET channels. Deflection of OHC stereocilia generates a change in membrane potential in the cell, a receptor potential. In the case of the OHCs this generates a motile response (as described below).

OHCs increase in length systematically from the base of the cochlear spiral to the apex.[73, 105] In addition, the longest stereocilia on OHCs also increase in height systematically along the base-to-apex length of the cochlea, in humans increasing from around 2.5 µm in the basal coil to around 7.0 µm at the apex.[106] These systematic, or tonotopic, changes mean that the length of the cell body and height of the stereocilia for a particular OHC are precisely defined for its particular position on the BM. OHCs, in contrast to IHCs, are directly innervated at their basal ends, by several large bouton-like efferent endings (**Figure 47.7e**). About 80% of the efferent cochlear innervation terminates on OHCs.[95, 96] These **medial olivocochlear efferent nerves** that synapse with the OHCs arise primarily from the medial portion of the contralateral superior olive. Afferent nerve fibres that synapse with OHCs, which constitute only 5–10% of the total cochlear afferent innervation,[95, 96] branch considerably within the organ of Corti so that an individual neurone synapses with many OHCs in all three rows. The afferent innervation pattern suggests that OHCs may signal more global, large displacements of the BM, i.e. at high sound pressures, and recent research supports this.[107] The extensive efferent innervation, on the other hand, strongly indicates that OHCs have a modulatory role in the cochlea.

In experiments in which OHC function is disrupted or OHCs are destroyed, in the continued presence of functioning IHCs, there are hearing threshold shifts of 40–60 dB and a loss of fine-tuning of ANF responses (i.e. the sharpness of tuning, whereby an individual nerve fibre is especially sensitive to a specific or **characteristic frequency**).[108] Thus OHCs are critical for the exquisite frequency discrimination of which the cochlea is normally capable. These and other data have suggested the OHCs are the cellular basis of the 'cochlear amplifier'.[109, 110] A particularly unusual feature of OHCs is that they exhibit a unique form of motility. Isolated OHCs maintained in short-term culture undergo fast reversible axial length changes at up to auditory frequencies (at least 20 kHz) when stimulated electrically. It is thought that, *in vivo*, changes in OHC-membrane potential deriving from the normal MET mechanism drive the length changes.[43, 109, 110] Thus motion of the BM induces these motile responses, which are thought to feedback into the BM motion, thereby removing local damping and enhancing the movements. The end result of this cochlear amplification process is to fine-tune and amplify the signal before it reaches the IHCs, which as described do not sit on the flexible BM. Interestingly, as predicted by Thomas Gold in 1948[111, 112] and shown by David Kemp in 1978,[113] the excess energy released by this active process generates sound waves that are emitted from the ear as an **otoacoustic emission** (OAE).[114, 115] These OAEs can be recorded from probe microphones fitted in the external ear canal and they form the basis of the now routine audiological screening test for hearing impairment that can be performed in newborns or adults, and that provides an objective measure of the 'health' of the OHCs.[116–118] The fast motile responses of the OHCs, and the concomitant OAEs, are driven by a motor protein called **prestin,**[119] which is unique to OHCs and which is densely packed all down the lateral plasma membrane of the cell.[120, 121] Mutation or functional absence of the gene encoding prestin causes hearing impairment due to loss of cochlear amplification.[122]

The activity of OHCs upon stimulation is thought to generate a radial flow of endolymph across the surface of the organ of Corti which deflects IHC stereocilia and stimulates IHC responses. In essence, at lower sound pressure levels (below about 60 dB) OHC activity 'drives' IHC responses, but at higher sound pressure levels the larger movements of the organ of Corti produce fluid flow sufficient to deflect IHC stereocilia, and stimulation of the cell, directly.[109]

SUPPORTING CELLS

Several different morphologically recognizable types of supporting cell are present in the mature organ of Corti (Figure 47.3b,c). The **Deiters' cells** that intercalate between OHCs have cell bodies that contact with each other at their basal end and rest on the BM (Figures 47.4b,d,e and 47.7h). Each one forms a cup-shaped enclosure around the very base of an OHC and its nerve endings (Figure 47.7h, i). Deiters' cells extend a thin phalangeal process up through the space of Nuel (Figure 47.7h) so that the entire lateral membrane of each OHC is free from contact with another cell (Figures 47.4b and 47.7e). Contact between the OHC and its surrounding supporting cells is only at the apical junctional complex (Figure 47.7e,j) and at the basal cup around the base of hair cell (Figures 47.4b and 47.7e,h,i). The OHCs and IHCs are separated in the radial plane by the **outer and inner pillar cells** (Figure 47.4b) 'phalangeal cells' that are similar in general morphology to the Deiters' cells, the phalangeal processes of which form the **tunnel of Corti**, the outer pillar cell buttressing against the underside of the head of the inner pillar cell (Figures 47.4b and 47.7l).[123] Unlike OHCs, IHCs are closely surrounded by columnar supporting cells, the inner border cells to the medial side and the phalangeal cells to the lateral side, between the body of the IHC and the inner side of the inner pillar cell (Figures 47.4b,c and 47.7a). Lateral to the outermost (third) row of Deiters' cells are **Hensen's cells** (Figure 47.4b,c and 47.7o) which, in some species contain large lipid droplets that are thought, among other things, to provide additional mass. Additional epithelial cell types including the relatively unspecialized and uncharacterized **Claudius cells** that form the outer skirt of the organ of Corti ridge (Figure 47.4b,c and 47.7o), and lateral to these are the cuboidal epithelial cells of the outer sulcus that extend to the tissues on the lateral wall of the cochlea. In the basal cochlear coils, sitting on the basilar membrane and covered by the Claudius cells are a group of **Boettcher cells** (Figure 47.4c and 47.7p) that have a densely staining cytoplasm and multiple infoldings at their cell–cell interfaces. In most species these cells are absent from the apical coils. The function of these cells is still ill-defined but their morphology suggests some role in maintaining the physiological environment in the cochlea. There is also a suggestion they have a role in the maintenance of the BM.[124]

The Deiters' and pillar cells are thought to provide mechanical support to the organ of Corti that is essential for normal sound-evoked movements of the BM that lead to stimulation of the hair cells. They contain large numbers of microtubules in parallel arrays running from the base to apex of the cell (Figure 47.7k–n).[85, 123, 125] These arrays are some of the largest microtubule bundles in the entire body.[123] The microtubules are packed closely in regular arrays, filling almost the entire phalangeal process (Figure 47.7l,m); they would act like scaffolding poles or suspension struts to provide rigidity. The inner pillar cell lies on the thin bony lip, which extends from the bone covering the modiolus providing a rigid support (Figures 47.4b and 47.7n). The stiffness of the inner pillar cell, anchored on the rigid support provided by the bone and extending to the apical surface, will minimize movement of the reticular lamina on the medial, IHC side of the tunnel of Corti in response to sound-induced basilar motion thereby optimizing sensitivity to deflection of the IHC stereocilia by the fluid motion. In contrast, the rigidity of the outer pillar, anchored to the flexible region of the BM (Figure 47.4b), together with the rigid phalangeal processes of the Deiters' cells, could enable it to act as a stiff rod maximizing transfer of BM motion to movement of the reticular lamina; translation of that movement into the relative shear motion with the TM results in deflection of OHC stereocilia. In this way, pillar cells are crucial elements in the biomechanics that result in detection of sound. Any loss of supporting cell rigidity would, therefore, upset the mechanics by which stereociliary deflection is normally achieved, resulting in loss of hearing acuity. The microtubules of these supporting cells are composed of a form of tubulin that is resistant to depolymerization, which would indicate that the microtubules are long-lived structures,[125] but it has been suggested that changes in the tubulin isoforms may occur with ageing,[126] thereby impacting rigidity and function.

In addition, these cells are thought to play a crucial role in cochlear homeostasis. They take up K^+ from the extracellular spaces around the hair cells[127–129] and ferry it out of the sensory epithelium by an intracellular route through the intercellular coupling provided by the large gap junctions (Figure 47.7q).[48] Removal of K^+ from the spaces around the hair cell bodies is crucial, not only to prevent accumulation of K^+ that would disrupt ionic gradients and thus normal transduction, but also because high extracellular K^+ is toxic to the cells and OHCs are especially sensitive. Consistent with this model, mutations in the genes that encode the K^+-transporting proteins present in the membranes of the Deiters' cells, KCC4 and Kir4.1 (KCNJ10), cause hearing impairment and death of hair cells.[127, 130]

INNERVATION

The afferent ANFs that innervate the inner and outer hair cells arise from two distinct neuronal populations.[95, 96] The majority (90–95%) are myelinated **type 1 neurons** that innervate IHCs. The remaining 5–10% are unmyelinated, thin **type 2 neurons** that innervate OHCs. The cell bodies of both these types of neurons are collected together in the **spiral ganglion** (hence the designation 'spiral ganglion neurones' that is sometimes used) which is enclosed in Rosenthal's canal and located within the bony lip of the modiolar wall just medial and below the organ of Corti itself (Figure 47.2b). The central axonal projections of these bipolar neurons collect together in the modiolus (Figure 47.1c), the number of axons and the width of the nerve (and the modiolus itself) systematically increasing from apex down to the base of the cochlea as the centrally projecting axons from the cell bodies of neurones at successive locations are incorporated. The large bundle of neurons exits the inner ear via the internal auditory meatus as the VIIIth cranial nerve. The peripheral neurites from the cell bodies access the sensory epithelium through a series of holes, the **habenula perforata**, through the thin bone that separates the organ of Corti

from the ganglion and over which the IHCs are located (Figure 47.2b). The type 1 neurons lose their myelination as they reach the habenula, and so are unmyelinated in the organ of Corti as they project directly to the base of the IHCs. The peripheral neurites of the type 2 cells, after crossing through the habenula, turn to run between the bodies of the inner pillar across the floor of the tunnel of Corti, then between the bodies of the outer pillar cells into the region of OHCs. Here they branch, each one sending projections between the Deiters cell bodies to an average of nine (though sometimes many more) OHCs, their terminals mostly synapsing at the very base of the cell.

The innervating efferent neurons have their cell bodies in the mid-brain regions from which they project. The peripheral axons of these neurons also enter the organ of Corti through the habenula perforata. Those projecting from the contralateral medial superior olive in the brain that innervate the OHCs contribute about 80% of the total efferent innervation of the organ of Corti.[95, 96] They pass between the phalangeal processes of adjacent inner pillar cells, cross the tunnel of Corti at a level about the middle of its height, and then pass between phalangeal processes of the outer pillar cells into the OHC region where each individual nerve branches, sending projections to OHCs in each of the three rows. Axons of the efferent nerves arising from the ipsilateral medial superior olive, after passing through the habenula perforata, project directly to the region of the IHCs, branch and form terminals that synapse with the terminals of the type 1 afferent neurons beneath the IHCs.

Ion-transporting epithelia

The **stria vascularis** (SV) is a strip of tissue 150–300 µm wide (depending on location and species) lining the lateral wall of the scala media and running along its entire length (Figures 47.1a and 47.2b). It is responsible for the production and maintenance of both the high endolymphatic K^+ concentration and the EP.[1] The SV encloses a complex capillary network and is composed of three cell types (Figure 47.8b):

- **marginal cells** that line the endolymphatic compartment
- **intermediate cells** in a discontinuous layer enclosed entirely within the body of the epithelium
- **basal cells** that separate the SV from the underlying spiral ligament.

The SV is reputed to have the highest rate of oxidative metabolism (i.e. where oxygen is used to generate energy from carbohydrates) in the entire body, most likely due to the huge energy demand resulting from the mass of active ion transport that takes place in this tissue. The EP provides a source of energy or 'battery' to drive the cochlear amplifier.[131] As would be expected, any loss of EP therefore results in significant hearing impairment.

MARGINAL CELLS

The marginal cells of the SV are primarily involved with the transport of K^+ and are essentially the same as the dark cells of the vestibular system. Their basolateral membranes are extensively infolded, enclosing numerous large mitochondria and they contain high levels of Na^+/K^+-ATPase, both α- and β-isoforms[67, 132] and the $Na^+/K^+/Cl^-$-cotransporter NKCC1 (SLC12A2).[68] NKCC1 is the therapeutic target of action for loop diuretics in the kidney and loop diuretics have rapid, acute ototoxic side effects through an action on the cotransporter in the strial marginal cells[133, 134] inhibiting ion transport, which results in accumulation of ions in the extracellular spaces of the stria and a consequent oedema. The apical membranes of the marginal cells (like the dark cells) contain a K^+ channel which is formed of two subunits, the KCNE1 regulatory protein and the KCNQ1 channel proteins[130, 135] that provide the pathway through which K^+ is secreted into endolymph.[69] Mutations in the *KCNE1* gene disrupt endolymph production, leading to collapse of Reissner's membrane and deafness. In the vestibular system they cause collapse of the epithelia of the roof of the utricle, saccule and ampullae and shaker/waltzer-type behaviours in mice, indicating dysfunction of the vestibular sensory organs.[130, 135] During development, high levels of K^+ are found in cochlear endolymph, and strial marginal cells show high Na^+/K^+ ATPase activity, before an EP can be recorded.[136, 137] These, and other physiological data,[1] indicate that strial marginal cells, like dark cells, are primarily concerned with active transport to maintain the endolymphatic K^+ concentration, but the generation of EP is a separate phenomenon. The absence of any other cell type from the ion-transporting tissue of the vestibular system suggests that the strial intermediate and basal cells play a role in EP generation. During cochlear development the onset and rise in EP coincide with the incorporation of intermediate cells and blood vessels into the body of the stria and the formation of the limiting basal cell layer.[138]

INTERMEDIATE CELLS

The intermediate cells are a type of melanocyte – melanin pigment-containing cells – that arise during development from cells that migrate from the neural crest. They are entirely enclosed within the corpus of the stria, interdigitating with the other two cell types (Figure 47.8b). They contain a variety of enzymes that enable energy production from alternative substrates such as lipids as well as enzymes that detoxify oxidative wastes.[139] In addition, melanin can act as a free radical scavenger. These cellular properties suggest that one role for intermediate cells is to protect the stria under conditions of stress and perhaps also to provide alternative energy sources to maintain activity during periods of reduced blood supply. A population of intermediate cells also sends thin processes to contact the capillaries and express a number of proteins that are found in macrophages, further indicating the role of these cells in protecting the stria from damage. These cells have been termed perivascular macrophage-type melanocytes.[140]

The crucial role of intermediate cells, however, is in the generation and maintenance of EP. In the *viable dominant spotting* mouse mutant, there is a neural crest defect resulting in a highly reduced number or absence of intermediate

cells and no EP is generated,[141] but other than the absence of intermediate cells, the stria appears normal and the marginal cells possess ATPase activity.[132] In wild-type mice, measurement of EP from electrodes inserted into the lateral wall of the cochlea, which pass first through the spiral ligament and then into SV, has shown that under normal conditions a high positive potential is present within the body of SV, i.e. before the electrode actually penetrates into the endolymphatic space, locating the site of EP generation at the intercellular spaces of SV.[142] The intermediate cells are characterized by very high levels of the K^+ transporter protein Kir4.1 in their plasma membranes facing the intercellular spaces and the basolateral infoldings of the marginal cells.[143] Thus EP is considered to be generated by rapid and extensive passage of K^+ via Kir4.1 across the intermediate cell membrane into the intercellular space, followed by immediate uptake of K^+ by marginal cells such that a high positive potential is generated in that space. The basal cell layer provides an insulating seal that prevents dissipation of the potential into the perilymph in the intercellular spaces of the spiral ligament.

BASAL CELLS

The basal cells are flattened and elongated, forming between one and three layers delimiting the basal aspect of SV (**Figure 47.8b**). They arise during development from the mesenchymal cells that also form the spiral ligament. Basal cells closely appose each other and there is extensive sealing of the intercellular spaces between them by tight junctions.[137, 144] This creates an impermeable barrier between the perilymph in the underlying spiral ligament and the body of SV. During development, the initial formation of these tight junctions and the increase in their complexity coincides with onset of EP,[137] suggesting that these junctions are necessary to provide the electrical insulation required for the potential difference to be generated and maintained within the body of SV. Mutations in the gene for the protein claudin 11, which is present in the basal cell tight junctions, cause the loss of EP and so hearing impairment.[145]

Large numbers of gap junctions are also associated with basal cells (**Figure 47.8c**).[46, 144] They are present between adjacent basal cells, between basal and intermediate cells and between basal cells and fibrocytes in the spiral ligament.[46, 144] Thus, basal cells appear to be the central element in a functionally coupled unit or **syncytium**, connected together by intercellular gap junctions, consisting of basal cells, intermediate cells and spiral ligament fibrocytes. Marginal cells are excluded from this syncytium; they do not form gap junctions either with each other or with either basal or intermediate cells[46, 144] and are thus separated, functionally, from each other and from the basal cell/intermediate cell/ligament fibrocyte syncytium.

The gap junction-mediated intercellular communication between basal cells and ligament fibrocytes can provide a pathway for access of ions into SV cells from the ligament that bypasses the tight junctional sealing.[48] Fibrocytes of the spiral ligament possess Na^+/K^+-ATPase activity[67] and thus probably function to take up K^+ from the perilymph in the intercellular spaces of the ligament. The gap junctions between fibrocytes would, therefore, provide an intracellular route for K^+ to those fibrocytes beneath the SV, which are coupled to strial basal cells and which in turn are coupled by gap junctions to the intermediate cells. This gap junctional system, therefore, provides a route for recycling K^+ from endolymph, through hair cells to perilymph in the spaces in the organ of Corti and into supporting cells; out to the intercellular spaces of the spiral ligament and into fibrocytes; then into strial basal cells; into intermediate cells out to the intrastrial spaces and back to endolymph via the marginal cells.[48] The intercellular communication provided by gap junctions may, therefore, be vitally important for the maintenance of EP. During development, the onset and subsequent rise in EP corresponds not only with the formation of the permeability barriers that isolate the SV from the surrounding tissues but also with the initial formation and subsequent increase in size and number of gap junctions associated with basal cells.[137] The gap junctions in the cochlear lateral wall – the SV and spiral ligament – in rodents are all composed of both Cx26 and Cx30,[46, 146] but only functional disruption of Cx30 is associated with loss of EP.[147]

CAPILLARIES

The functional isolation of the SV from the surrounding tissues created by the permeability barriers at the level of the basal cells means there is little or no access of oxygen and nutrients required for the active processes necessary for EP maintenance. These are supplied by the network of intrastrial capillaries that run predominantly longitudinally along the SV (i.e. in an apicobasal direction along the cochlea, so that they are cross-sectioned in sections cut parallel to the modiolus in **Figure 47.8b**) with short interconnecting branches running across the strial thickness. The capillaries are often closely surrounded by extended processes from marginal cells. While allowing passage of oxygen and essential nutrients, the walls of the capillaries form a 'blood labyrinth barrier'[140] that controls exchange between the intrastrial spaces and the blood supply. The capillaries are supplied from branches of the cochlear artery that run from the modiolus through the connective tissue over the roof of the scala vestibuli and further branch into the spiral ligament and SV where the network of capillaries forms. They drain through capillaries that run in the connective tissue beneath the scala tympani to the cochlear vein in the modiolus. The strial capillaries are unfenestrated and the junctions between the endothelial cells that surround the lumen are connected by tight (occluding) junctions that establish a tight seal between the vessel lumen and the intrastrial space.[140] This tight sealing of the capillary lumen from the body of the stria in addition to the tight junctions between marginal cells and the extensive tight junctional sealing between basal cells are crucial to the functional isolation of stria from the surrounding tissues that prevents dissipation of EP as it is generated.

The endothelial cells are surrounded by a basement membrane. Pericytes discontinuously cover the basement membrane extending long, thin processes along the capillary wall. Where these cells are present the basement

membrane thickens to cover them. It has been suggested that macrophage-like melanocytes (the intermediate cell subpopulation), pericytes, BM and endocytes act as a complex to monitor and regulate exchange between the intrastrial spaces and the vessel lumen and maintain the blood-labyrinth barrier.[140] There is increasing evidence that ageing, noise and some genetic mutations may cause disruption of the barrier, leading to dysfunction of the stria, loss of EP and hearing impairment, but further work in this area is needed.

Reissner's membrane

Reissner's membrane is a thin epithelial sheet formed of two cell layers (**Figure 47.2b**).[148–150] A continuous layer of epithelial cells lines the scala media side and, since their apical surfaces face endolymph, they have tight junctions sealing the spaces between adjacent cells. The basal side of the epithelium, in the scala vestibuli, is covered with mesenchymal cells that are bathed in perilymph. The primary role of Reissner's membrane, to maintain the electrical and chemical separation of endolymph and perilymph, is achieved at the level of the tight junctions between the epithelial cells. There is also some evidence that the epithelial cells may have a phagocytic function taking up and then breaking down cell debris released into the endolymphatic compartment. Reissner's membrane also appears to have some elasticity as it can accommodate by swelling outwards into the scala vestibuli quite large increases in endolymph volume – endolymphatic hydrops – such as occurs with ion imbalance that results in water influx into the scala media, before it ruptures (as in Ménière's syndrome).[151, 152] How this is achieved, and whether Reissner's membrane has additional roles, remains to be determined.

FUTURE RESEARCH

- Molecular characterization of the transduction channel and its accessory components.
- Proteostasis (turnover, breakdown and re-synthesis) of hair cell proteins in particular stereociliary components.
- Effects of ageing and stress on tissues, cells and accessory structures other than hair cells, e.g. supporting cells and their microtubule bundles, the tectorial membrane, cells of stria vascularis.
- Detailed structural analysis and determination of the functional and permeability properties of Reissner's membrane and its potential role in clearing debris when cochlear tissues are damaged.
- Understanding of the roles of various glial and glial-like cells in the cochlea.
- The structure and permeability properties of the round-window membrane in relation to delivery of therapeutics to the inner ear fluids.

KEY POINTS

- The cochlea and the vestibular system contain sensory epithelia and ion-transporting epithelia.
- The sensory epithelium of the cochlea is the organ of Corti, a strip of cells coiled in a spiral.
- There are five sensory epithelia in the vestibular system: the utricular macula, saccular macular and 3 cristae, one in each of the three semi-circular canals.
- Sensory epithelia consist of sensory cells – 'hair' cells – and supporting cells, each hair cell separated from its neighbour by intervening supporting cells.
- Hair cells derive their name from the organised bundle of hair-like projections from their apical surface.
- The hair bundle is formed of stereocilia organised in rows of increasing height across the apical surface of the hair cell defining both a morphological and functional polarity.
- In vestibular hair cells, a single true cilium – the kinocilium – is positioned behind the row of longest stereocilia.
- In mature cochlear hair cells there is no kinoclium; the kinoclium is present during cochlear hair cell-development but retracts as the hair cell matures to leave only the basal body.
- There are crosslinks of various types between stereocilia in an individual hair bundle.
- Lateral cross-links produce a cohesive unit of stereocilia in the hair bundle.
- Tip-links are found between the tip of a shorter stereocilium and the adjacent longer stereocilium in the line of functional polarity; these gate the transduction channel at the tip of the shorter stereocilium.
- Each sensory epithelium is overlaid by an acellular extracellular matrix, that provides direct input for the deflection of the stereocilia that stimulates the hair cell.
- There are two types of hair cell in the organ of Corti: inner hair cells and outer hair cells.
- Inner hair cells are the primary receptor cells innervated by 95% of the cochlear afferent nerves that take information to the brain.
- Outer hair cells respond actively to basilar membrane motion to amplify the micromechanics and thus the signal reaching the inner hair cell.
- The cochlea is 'tonotopically' organised; different frequencies are detected at systematically different places along the basilar membrane: high frequencies at the basal end and low frequencies at the apical end.
- There are systematic changes in the basilar membrane and organ of Corti dimensions in line with the systematic tonotopic variation.
- There are two types of hair cell in vestibular sensory epithelia: type 1 hair cells and type 2 hair cells.
- Type 1 hair cells are innervated by a single afferent 'calyceal' nerve ending that enclose the entire baso-lateral surface of the hair cell.
- Type 2 hair cells that are innervated by several afferent nerve bouton endings.
- The stria vascularis is the ion-transporting epithelium of the cochlea.

- The stria vascularis is formed of three cell types and is highly vascularized; it is physiologically and electrically isolated from the rest of the cochlea.
- The stria vascularis generates and maintains the high positive electrical potential of cochlear endolymph – the endocochlear potential – as well as the high potassium ion composition characteristic of endolymphatic fluid.
- The ion-transporting epithelium of the vestibular system is the dark-cell region at the base of each crista and around the utricular macula; there is no dark cell region in the saccule.
- The dark-cell region is a single layer of ion-transporting epithelial cells responsible for maintaining potassium levels in vestibular endolymph, but it is not electrically isolated from the rest of the inner ear tissue, and there is no equivalent of endocochlear potential in the vestibular system.

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CHAPTER 48

PHYSIOLOGY OF HEARING

Soumit Dasgupta and Michael Maslin

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SEARCH STRATEGY

The data may be updated by a PubMed search using the keywords for 'Fundamentals of sound': soundwaves, measuring sound, decibel scales and acoustic impedance. For 'Applied physiology of Hearing', use the following keywords: pinna, external auditory canal, ossicles, tympanic membrane, cochlea, outer hair cells, inner hair cells, auditory nerve and cochlear efferents.

INTRODUCTION

This chapter consists of two parts. The first (Fundamentals of Sound) will discuss properties of sound and important concepts related to hearing; the second part (Applied Physiology of Hearing) will discuss the applied physiology of the peripheral ear correlated to normal functioning of the ear from the hearing point of view and the aftermath of an affliction by a disease.

FUNDAMENTALS OF SOUND

Michael Maslin

A SOUND WAVE

For something to be a source of sound it must vibrate. Sound is vibratory energy that is transmitted from the source through surrounding media in the form of pressure waves. Sound waves cannot therefore travel through a vacuum; a physical medium is required to convey the vibratory energy. In the context of otolaryngology, the most relevant physical medium is air since most sounds reach the ear by the vibrations of air molecules. Vibratory energy that arrives at, and is detected by, the ear gives rise to hearing. Hence, some understanding of the physical properties of sound is required in order to understand the way in which sound is detected by the ear.

As a starting point one might consider a scenario whereby no force is applied to a region of air. In such a scenario, the air molecules are said to be at ambient (or atmospheric) pressure. When an object in the region vibrates, a force is applied to those air molecules that are in contact with the object, causing their displacement. For example, take the loudspeaker shown in Figure 48.1. As the diaphragm of the loudspeaker moves to the right of its centre position, the air molecules at the surface of the diaphragm are displaced to the right. This movement causes the air molecules to be pushed closer to adjacent air molecules that are further over to the right. Relative to the ambient pressure, a localized pressure increase is produced and this pressure increase is known as compression. Next, when the diaphragm of the loudspeaker moves back through its centre position and over to the left, those air molecules that were displaced to the right are now drawn to the left. When the displaced molecules reach their centre (equilibrium) position, the pressure will momentarily be equal to ambient pressure, but as the molecules move further to the left they are drawn increasingly further apart from their adjacent air molecules. The pressure will now drop below the ambient pressure and this decrease in pressure is called rarefaction. As each molecule vibrates

backwards and forwards around its equilibrium position, alternating regions of compression and rarefaction arise. If these pressure variations can be detected by the ear, they can be described as sound. (It is worth noting that the variations in density of the air molecules shown in Figure 48.1 have been exaggerated for the purposes of illustration. In reality, pressure fluctuations associated with sound are only a small fraction of the overall atmospheric pressure.) Since air is a continuous and elastic medium, the pressure variations will propagate away from the source such that sound generated by the source can be detected in regions of air that are remote. This is known as acoustic radiation.

The air molecules move about their equilibrium position, so there is no permanent displacement of the air. Rather, it is the vibratory pattern (i.e. mechanical disturbance) that is transmitted. Since the air molecules move in the same axis as the sound wave, it is known as a longitudinal wave.

There are two key properties of a sound wave:

- the frequency of the sound wave, which is linked to the perception of pitch
- the intensity of the sound wave, which is linked to the perception of loudness.

Frequency, velocity, period and wavelength of sound

As the air molecules vibrate about the equilibrium, their velocity is greatest as they pass through the equilibrium position and is momentarily zero when at the extreme displacement (where direction of movement reverses). The movement of air molecules from equilibrium to maximum displacement in one direction, back through equilibrium to the maximum displacement in the opposite direction, and back to equilibrium, is one complete cycle of vibration. Frequency (f) is the number of cycles per second (usually expressed in Hertz (Hz) (named in honour of the German physicist Heinrich Rudolf Hertz). The simplest type of sound wave is a sinusoidal (or sine) wave, where the cycles of vibration occur at a single frequency. A concept related to frequency is the period (T), the time required for a vibration to complete one cycle. The higher the frequency, the less time it takes a vibration to complete one cycle. Hence, frequency and period have an inverse relationship which can be expressed as follows:

$$T = 1/f \text{ or } f = 1/T$$

Please note that while the velocity of the displacement of the air molecules relates to the frequency of the sound, there is also the velocity of the sound wave to consider, as it progresses away from the source (i.e. the speed of sound, c). This is not an absolute value. Sound travels more quickly in warm air than in cooler air. Therefore as temperature drops with altitude or in colder climates the speed of sound becomes lower. The velocity of sound waves radiating from a source at sea level is about 344 metres per second (ms^{-1}). Furthermore, at least in air, the velocity is the same irrespective of the frequency of vibrations. The velocity of a sound wave and the frequency of that wave are related by wavelength (λ), which is the distance between corresponding points of displacement in successive cycles (see Figure 48.1). We therefore have four quantities that are related to one another: the frequency, the period, the velocity and the length of a sound wave. The relationship between these quantities is described in the following equations:

$$\text{Wavelength} = \text{velocity} \times \text{period}$$

$$\text{Velocity} = \text{frequency} \times \text{wavelength}$$

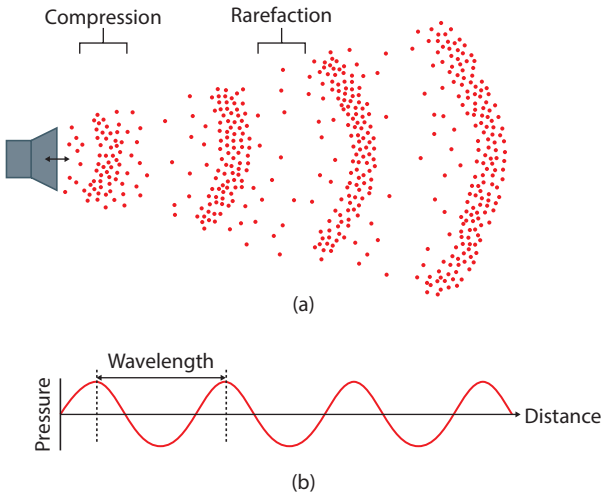


Figure 48.1 **(a)** A schematic of a sound wave propagating away from source via alternating regions of compression and rarefaction of (air) molecules. **(b)** The (air) pressure variations plotted as a function of distance. This example shows pressure varying at a single frequency, to produce a sinusoidal waveform. The distance between two consecutive points on the waveform is the wavelength.

Pressure, impedance, particle velocity and intensity of sound

As we have discussed, as a sound wave radiates from a source, the air pressure fluctuates in cycles of compression and rarefaction as air molecules are displaced about their equilibrium. Let us consider a 'plane progressive' sound wave, i.e. a sound wave with an advancing wavefront that is treated essentially as a flat surface, as it moves unperturbed through a sound field. (In reality a progressive wavefront is almost spherical as it expands from a point source, but at the point of measurement, which might be some distance away, the wavefront will appear flat. Furthermore, there are often objects in a sound field that produce reflections, all of which means that peak pressure and velocity do not necessarily coincide in reality.) The pressure variations about the ambient pressure that occur are directly proportional to the velocity of the particles as they vibrate. That is, the greater the peak particle velocity, the greater the peak pressure of the sound wave. Pressure and particle velocity are therefore said to be in

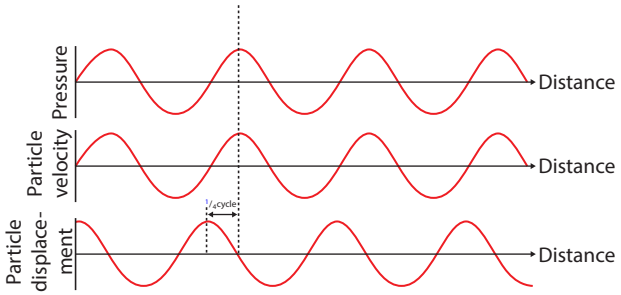


Figure 48.2 The relationship between pressure, velocity and particle displacement. **(a)** Pressure variations plotted as a function of distance. **(b)** Particle velocity plotted as a function of distance. Note that (air) pressure and (air molecule) particle velocity vary in phase with one another. **(c)** Particle displacement plotted as a function of distance, showing a 90° phase lag in relation to particle velocity and pressure variation.

phase, as illustrated by the upper and middle traces shown in Figure 48.2. However, while peak particle velocity and peak pressure are in phase, the displacement of the air molecules shows a one-quarter cycle, or 90-degree, phase lag, illustrated in the lower trace in Figure 48.2.

Phase relates to the temporal relationship between two (or more) oscillatory components that are present simultaneously. In this case, pressure, particle velocity and displacement. One cycle is defined as 360 degrees. If the two components vary together over the cycle, there is no timing difference between then, and they are said to be in phase. However, the second component can lead or lag the first according to its starting point relative to the first, i.e. there is a timing difference. The actual timing difference for a given phase lead or phase lag will depend on the frequencies of the two components, with higher frequencies producing shorter timing differences.

As air molecules become compressed, we also have to consider acoustic impedance, or more specifically characteristic impedance ($\rho_o c$) when referring to a plane progressive wave. The concept of impedance may be illustrated by drawing analogy to electrical circuits, where impedance behaves rather like the resistance to electricity in a circuit. It acts to dissipate energy and so if the sound wave is to radiate out from the source then it must overcome the acoustic impedance of the medium. Impedance depends on the stiffness and density of the medium (in this case air), and so the acoustic impedance at a particular frequency will contribute to defining how much sound pressure is generated by a sound wave. The greater the impedance of air molecules at a given displacement velocity, the lower the sound pressure level. Peak pressure can be related to peak velocity and characteristic impedance (which is independent of frequency), according to the equation:

$$\text{Peak pressure} = \text{characteristic impedance} \times \text{peak velocity}$$

Impedance varies greatly according to the media, especially between gases and liquids. Liquids, being much denser than gases, have a higher acoustic impedance. Therefore, they will convey sounds with much lower intensities for a given pressure variation than if that pressure variation were to occur in a gas.

To continue the analogy drawn with circuits of electrical current, where sound pressure is analogous to voltage (volts) and acoustic impedance is analogous to resistance (ohms), particle velocity is analogous to current (amps), but there is a further component still to consider: power.

The energy of sound and how this is transferred (dissipated) is referred to as the intensity of sound and, in electrical circuitry, this is analogous to power (measured in watts). The more energy that is supplied by the source, the greater the intensity of the sound. Since pressure variation is the means by which sound energy is transmitted, and pressure is force per unit area, then intensity is the power transmitted by the wave through a unit area (watt/metre^2). For a sinusoid, the relationship between intensity, pressure and particle velocity and impedance is expressed using these equations:

$$\text{Intensity} = \frac{\text{Peak pressure}^2}{2 \times \text{impedance}}$$

$$\text{Intensity} = \frac{\text{Peak velocity}^2 \times \text{impedance}}{2}$$

At this point the importance of root mean square (RMS) values becomes apparent. The equations that are shown above relate to the **peak** pressure and **peak** velocity, yet pressure and velocity are continually varying throughout the cycle of vibration hence the intensity of sound will vary throughout the cycle. A solution is therefore to consider the average intensity (kinetic energy) across a complete cycle of vibration. Simple averaging will not suffice, since the mean values will be zero (see Figure 48.3).

One solution is to consider the distance between the most positive peak and the most negative points in the cycle. Alternatively, the square root of the average squared value for pressure (known as RMS pressure and expressed in Pascals or Nm^{-2}) and velocity (known as RMS velocity or ms^{-1}) are perhaps the most common way to overcome this challenge. The equation can now be read as:

$$\text{Average intensity} = \frac{\text{RMS pressure}^2}{2 \times \text{impedance}}$$

$$\text{Average intensity} = \text{RMS velocity}^2 \times \text{impedance}$$

It is also important to note that sound waves spread in all directions, and as the wavefront moves away from the source it spreads over a larger area. Sound intensity

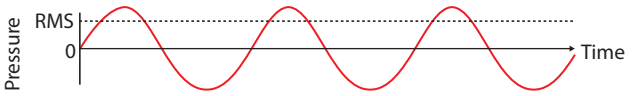


Figure 48.3 A sinusoidal wave. When measuring sound, the time-varying pressure variations would average to zero, which is not representative of the peak pressure. Root mean square (RMS) can be used instead, where RMS pressure = $\frac{1}{\sqrt{2}}$ = ≈ 0.7 of the peak pressure.

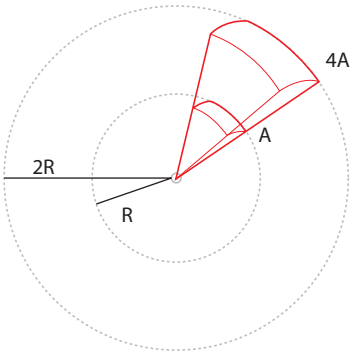


Figure 48.4 Schematic of a point source of sound. Sound waves would spread equally in all directions to produce a spherical wavefront. Due to the expanding area of the wavefront with distance from the source, the energy of the wavefront will progressively attenuate with distance. Sound is attenuated by distance from the source and the amount by which this occurs is given by the inverse square law; intensity falls as the inverse square of the distance. Other factors that influence attenuation with distance in real-world scenarios include, for example, reflections from, and interactions with, obstructions in the sound field, interactions with other sound waves, heat dissipation and net flow of air (wind).

decreases with distance from the source. The total area increases with the square of the distance, so intensity falls as the inverse square of the distance. This relationship is known as the inverse square law, as depicted in Figure 48.4 for a point source of sound in a free field, i.e. with no objects reflecting or blocking the path of the sound.

PERCEPTUAL CORRELATES OF FREQUENCY AND INTENSITY

The two key properties of a sine wave, frequency and intensity, each have a perceptual correlate. The subjective correlate of frequency is pitch and of intensity, loudness.

The bandwidth of human hearing (at least for a young person with normal hearing) is typically from around 0.02–20 kHz. Vibrations of around 20 times per second correspond to a low pitch whereas vibrations of 20 000 times per second correspond to a much higher pitch. Each time the frequency of a sine wave is doubled, the pitch increases by an octave, so human hearing spans around 10 octaves. A sound which has one frequency is known as a 'pure tone' although, in reality, typical sounds are made up from many frequencies and are therefore complex sounds.

As intensity increases above the threshold of hearing, a sound becomes louder. For a 1 kHz sine wave, a young and normal-hearing human listener can detect pressure fluctuations in the air from as little as 0.00002 Pa (the quietest sounds) and increases in pressure become progressively louder to the listener up to as much as 200 Pa (where the threshold of pain is approached). Hence the relationship between the softest audible pressure variation and the maximum tolerable one (known as the dynamic range) is around one million times.

It is important to note that perceived loudness is in fact dependent on both frequency and intensity. The ear is less sensitive to very low frequencies and very high frequencies, and maximally sensitive to frequencies around the 2–4 kHz range. Typically, pure-tone audiometry, as performed in the test battery for diagnosing hearing loss, covers the frequency range 0.25–8 kHz (five octaves) that is most clinically relevant since this corresponds to the frequency range where normal speech occurs. The intensity of pure tones used in pure-tone audiometry is normalized according to the different sensitivities of the ear as a function of frequency in order to plot a pure-tone audiogram. More on this will be described below.

THE INFLUENCE OF A SOUND'S DURATION

In addition to frequency and intensity, a third dimension of sound is its duration. The duration of a sound interacts with frequency and intensity to influence pitch and loudness sensations. For example, a sound must exceed a certain minimum duration before its pitch characteristics become apparent. Below this point, about 200 ms, and the sound will have a click-like sensation regardless of its duration. Similarly, loudness increases as a function of intensity over time, a phenomenon known as temporal integration. Below durations of about 200 ms the sound intensity will need to increase progressively in order to maintain the same sensation of loudness. Therefore, audibility reduces as sounds become briefer below 200 ms (although the perception of duration does not). Paradoxically, despite this reduction in audibility with sound duration, sounds with extremely short duration can become more audible again, at least when close to threshold. We can think of pure-tone sounds used in hearing tests as being comprised of three segments: an onset period when the intensity increases (also known as the rise time), an offset period where the intensity reduces again (also known as the fall time) and between these two extremes there may be a steady period where the sound intensity is maintained. Imagine the steady-state period getting shorter, so that the volume of the pure tone is reducing as the overall duration drops below 200 ms. Eventually, there would be no steady-state period, and so the intensity of the sound would ramp up and immediately down again. Now the only way to make the sound shorter is to reduce the duration of the onset and offset periods themselves. As the onset and offset periods get shorter, the frequency spectrum of the sound becomes progressively broader (the so-called 'spectral splatter'); sound duration and bandwidth are inversely proportional. It is these additional frequencies that may be heard, causing the paradoxical increase in audibility for very short duration signals. Clinically, this is especially relevant in audiological applications where short duration signals are required, such as auditory evoked potential testing. Here, the need for brief stimuli such as a transient click, producing a more synchronous discharge of neural energy (and greater signal strength), must be weighed against the need for frequency-specific analysis of hearing sensitivity (i.e. minimizing spectral splatter) in order to diagnose hearing loss accurately where hearing at some

frequencies is different from others. However, it is also relevant with regards to understanding the way in which normal everyday sounds such as speech, not just audiological test sounds, are heard.

MEASUREMENT OF SOUND

The three dimensions of sound that we have encountered so far (frequency, intensity and duration) can each be described according to principles that have parallels with the way in which sound is detected and processed by the ear (the mechanisms of which will be described in detail later in the chapter). The amplitude of a sound (either in terms of the intensity or resulting pressure fluctuations) can be described by the decibel scale, and the frequency composition of a sound can be shown by spectral analysis of the signal. The influence upon both of these quantities by the duration of the signal will also be described.

The decibel scale

As described, when the energy of a sound wave increases, the pressure fluctuations become greater. A common way to describe the average variation of these quantities is by referring to an increase in the amplitude of the sound.

Given the dynamic range of hearing described above, if sound was routinely described in Pascals (using the most common and practical way to measure sound by observing the electrical output of a pressure-sensitive device or transducer), calculations for the amplitude of sound would soon become cumbersome and unmanageable. To overcome this, a compressed scale which produces a more manageable range of values for describing amplitude is used: the decibel scale. The basic unit of measurement is the bel, named in honour of Alexander Graham Bell, inventor of the telephone. Even this is somewhat large for convenience and so the decibel (dB), one-tenth of a bel, is typically used. Compression of a large-scale dynamic range (either intensity or pressure) to the decibel scale is achieved by finding the logarithm (to the base 10). Importantly, the decibel is not an absolute unit of measurement. It is a ratio. This means that the bel is the logarithm of intensity of sound divided by some agreed reference intensity. Zero dB therefore simply indicates that the measured sound is the same as the reference; it doesn't mean silence. A negative dB value means that the measured sound is less than the reference, and a positive dB value means that the measured sound is greater than the reference. Multiplying the bel by 10 produces the decibel such that a sound's intensity in dB can be calculated using the following equation:

$$\text{dB} = 10\,\text{Log}_{10}\frac{\text{Intensity}_{\text{measured}}}{\text{Intensity}_{\text{reference}}}$$

Sound pressure as measured in Pascals can also be expressed in decibels. This is the logarithm to the base 10 of a measured pressure relative to some agreed reference pressure, multiplied by 20 (to reflect the fact that intensity is related to the square of the pressure). A value very close to the threshold of human hearing for a 1 kHz pure tone at sea level (0.00002 Pa) commonly serves as such a reference pressure, and in this case the scale is referred to as decibel sound pressure level (dB SPL) according to the following equation:

$$\text{dB SPL} = 20\,\text{Log}_{10}\frac{\text{Pressure}_{\text{measured}}}{\text{Pressure}_{\text{reference}}}$$

The dB SPL scale is convenient because 0 db SPL is close to the threshold of hearing. The threshold of pain, near the top of the dynamic range of hearing, is 140 dB SPL, i.e. when the pressure in Pascals is multiplied by 10, 20 dB is added to the dB level.

Note that, in addition to convenience of calculation, a second advantage of using a logarithmic scale is that the response of the ear is also logarithmic. This means that loudness is not spaced linearly across the dynamic range, so linear increments in the amplitude of sound do not produce even increments of loudness (e.g. 100 Pa is almost as loud as 200 Pa). However, logarithmic increments in amplitude do produce even increments of loudness; a 1 dB change in amplitude (approximately the minimum detectable change) gives almost the same relative change in loudness across the whole dynamic range.

An important consideration when discussing the relationship between the amplitude and loudness of sound is that the ear is not equally sensitive to sounds of different frequencies, as mentioned earlier. Further complications are that the difference in sensitivity to sounds across frequencies is more pronounced closer to threshold, and less at high SPLs well above threshold. Loudness is also strongly affected by the duration of sounds. That is, sounds of short duration (below approximately 200 ms) will sound less loud than a sound of longer duration with the same sound pressure level. (For further information on the interaction between acoustics and perception, please refer to Moore.[1]) Consequently, this means that, while 0 dB SPL is (close to) the threshold of hearing for a 1 kHz pure tone, the same is not the case for pure tones of other frequencies. Bear in mind also that 'threshold', the quietest sound one can hear, is variable and depends on the way it is defined, the method of measurement and psychological factors such as attention and motivation.

Figure 48.5 shows the threshold, in dB SPL, for a range of pure tones of different frequencies as measured under

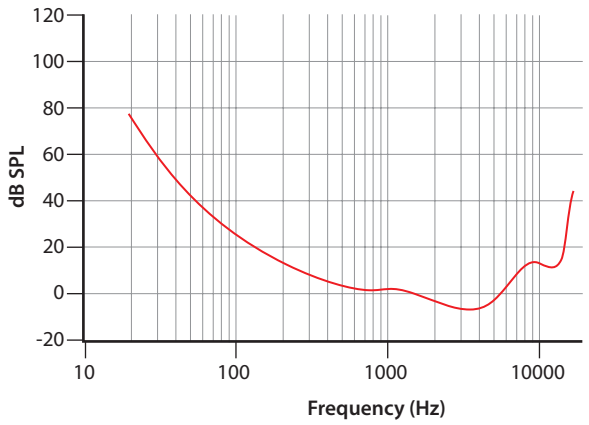


Figure 48.5 Reference threshold of hearing, in dB SPL, based on a group of ontological normal, young adults in binaural listening conditions (ISO 389-7[2]).

binaural free-field listening conditions (ISO 389-7).[2] Hearing sensitivity declines at very low and very high frequencies, and it is not the same even within the central frequencies that comprise the audiometric range. For clinical purposes these differences in hearing sensitivity according to sound frequency present some complications when describing the extent of hearing loss; the same degree of hearing loss across different frequencies produces a different threshold in dB SPL. For example, an individual whose hearing threshold was 40 dB worse than the average threshold at 1 kHz would have a hearing threshold slightly higher than 40 dB SPL. However, if the same individual had a 40 dB reduction in hearing sensitivity at 4 kHz, their hearing threshold would be around 35 dB SPL.

To bypass this complication, audiology uses different reference sound pressures. Perhaps the most important among these is for pure tones in which the reference is the threshold of hearing for normal listeners; this is the decibel hearing level (dB HL). The reference sound pressures for pure tones therefore change in a frequency-specific way to allow a convenient comparison of an individual's hearing thresholds compared to normal, i.e. the amount of hearing loss. The resulting audiogram (see **Figure 48.6**) shows normal hearing (0 dB HL) towards the top of the chart whereas increasing amounts of hearing loss are plotted downwards. For an interesting historical account of the why the audiogram is upside down, the reader is referred to Jerger.[3]

There are other decibel scales used in audiology such as Sensation Level (dB SL), which uses the individual's own threshold of hearing as the reference. For example, a 1 kHz sound presented at 50 dB HL to a patient with a threshold of 10 dB HL would be 40 dB SL. However, to a patient with a threshold of 20 dB HL the same sound would be 30 dB SL. Presentation at the same sensation level may therefore produce different intensities of sound according to alternative scales such as dB HL. Another scale that is in common use is decibel normal Hearing Level (dB nHL). In the strictest sense dB nHL denotes a reference for a sound that is either the mean or the median threshold of hearing for ontologically normal young adults, the same concept as dB HL for pure tones. However, in practice dB nHL usually refers to the level of short-duration sounds as used in auditory evoked potentials. Other important decibel scales in audiology are the peak Sound Pressure Level (pSPL) and peak-to-peak equivalent Sound Pressure Level (ppeSPL). Both of these scales have audiological applications in the measurement of short-duration sounds. Peak sound pressure level is the greatest sound pressure (be it condensation or rarefaction) over the duration of a signal. Peak-to-peak equivalent sound pressure level is the sound pressure level of a long-duration signal (such as a 1 kHz pure tone) that produces the same peak-to-peak sound pressure as a short-duration sound typically used in measuring auditory evoked potentials. The need for these alternative scales arises because, in a similar way in which there is a minimum duration of perception, the ability to measure sound acoustically with a microphone has a lower limit of duration. This limit arises because the measuring device (e.g. a sound level meter) is usually incapable of responding quickly enough to produce an accurate and stable reading of the sound pressure level.

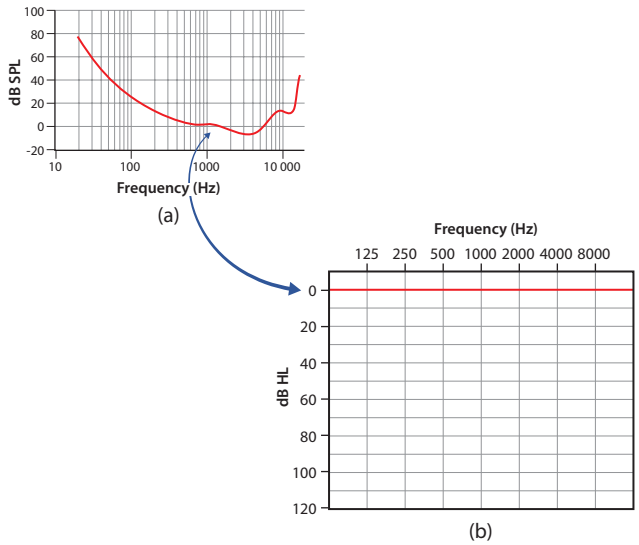


Figure 48.6 Schematic showing the relationship between dB SPL and dB HL. Note that the actual reference equivalent sound pressure levels (RETSPLs) used for audiometric zero in the calibration of audiometers and other diagnostic equipment are specific to transducer type in a specific coupler.

Spectral analysis of sound

So far we have considered sounds in the time domain, where the summed pressure variances as a function of time (or distance) are drawn. It is possible to represent sound in the frequency domain, where the spectral (or frequency) content of the sound is considered irrespective of the temporal relationship between different frequency components. As mentioned earlier, most everyday sounds are complex sounds so, by breaking down such a sound into its individual frequency components one might more easily describe the behaviour of a system in operation (such as the ear in sound detection) and infer the behaviour of that system to more complex sounds. Another reason for considering sounds in the frequency domain is that the ear itself acts as a spectral analyzer. As will be described in more detail later, a filtering action arises within the cochlea that allows sounds of different frequencies to be separated and then transduced into neural energy at different places within the cochlea, known as tonotopicity. Therefore, an understanding of the spectral content of a complex sound can give insight into the way in which that sound will produce activity within the auditory system.

The primary means of decomposition of a complex sound into its constituent frequency components is called Fourier analysis (for a continuous signal), or Fourier transform for any signal (devised by the French mathematician Fourier in the 1820s). A useful starting point is to consider a pure tone, since the spectral content of such a signal will consist of just a single frequency component, as illustrated in **Figure 48.7** for a 0.1 kHz pure tone. **Figure 48.7a** shows the temporal pattern of amplitude fluctuations for the signal (i.e. it is in the time domain); **Figure 48.7b** shows the spectral content of the signal (i.e. it is in the

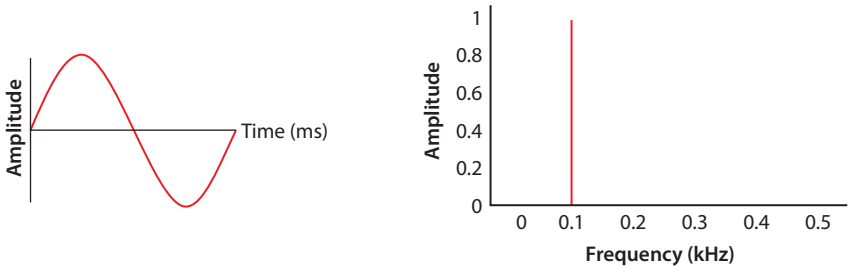


Figure 48.7 A 0.1 kHz sinusoid shown in the time domain (a) and in the frequency domain **(b)**.

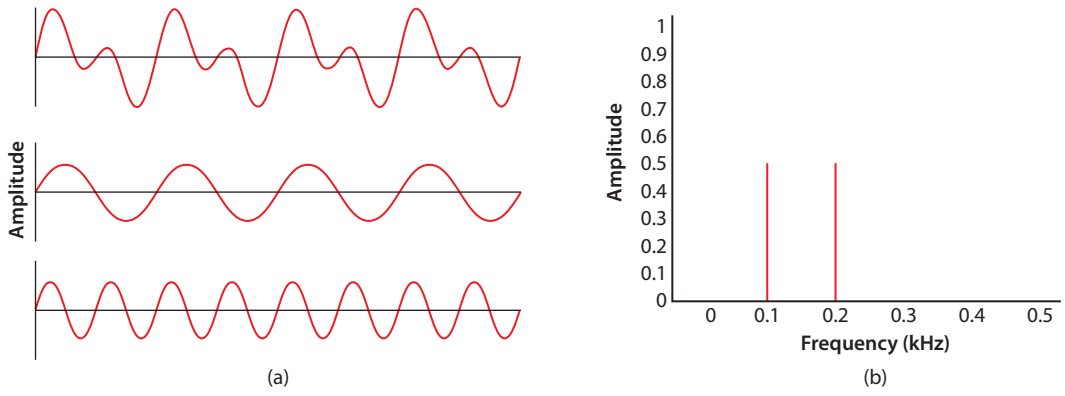


Figure 48.8 (a) The upper row depicts a complex tone in the time domain, comprising 0.1 kHz and 0.2 kHz sinusoids depicted in the middle and lower rows, respectively. The two components are in phase. **(b)** The components of the complex tone are displayed in the frequency domain where the frequencies and amplitudes of the two components are apparent.

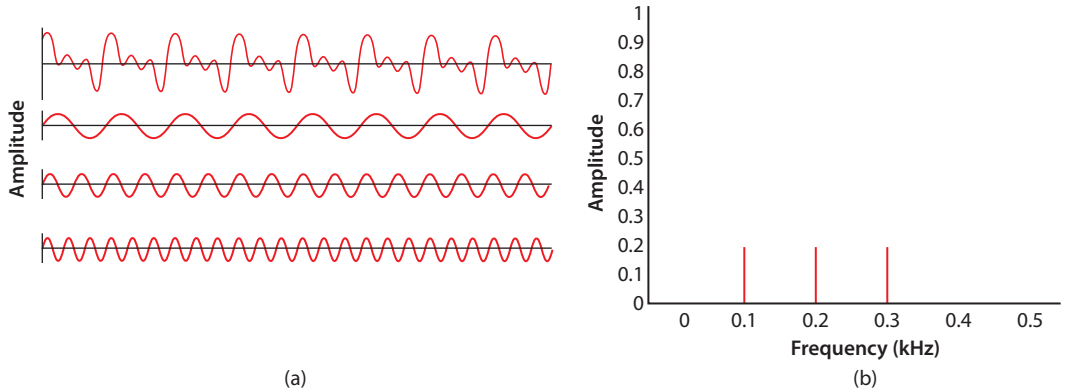


Figure 48.9 (a) The upper row depicts a complex tone in the time domain, comprising three components at 0.1 kHz, 0.2 kHz and 0.3 kHz (second, third and fourth rows, respectively). **(b)** The components of complex tone, displayed in the frequency domain.

frequency domain). Three-dimensional displays may be used to show both amplitude and timing of the different frequency components of a complex sound simultaneously.

A complex tone can be similarly decomposed to produce line spectra at the various different components. For example, the upper trace in Figure 48.8a illustrates a complex tone in the time domain, made up from two components, 0.1 kHz and 0.2 kHz, that are of the same amplitude and both starting from a zero degree phase angle. There are four cycles of the 0.1 kHz component (middle trace), and in the same period eight cycles of the 0.2 kHz component arise (lower trace). Figure 48.8b provides the line spectra corresponding to the complex tone formed by these two components.

In a further example shown in Figure 48.9, a complex sound comprising three pure tones is displayed in the left column (a) (upper trace) with constituent pure tones of 0.1 kHz, 0.2 kHz and 0.3 kHz all at zero degrees phase and of equal amplitude (second, third and fourth traces respectively). The corresponding line spectra are displayed in Figure 48.9b.

The above examples show the effect of adding sinusoids that are in phase. Since sinusoids are periodical sounds, their summation will produce a repeating pattern, the frequency of which (repetition frequency) is known as the fundamental frequency (F_0). In the above examples, 0.1 kHz is the highest common factor between each of the constituent components (i.e. the highest integer that

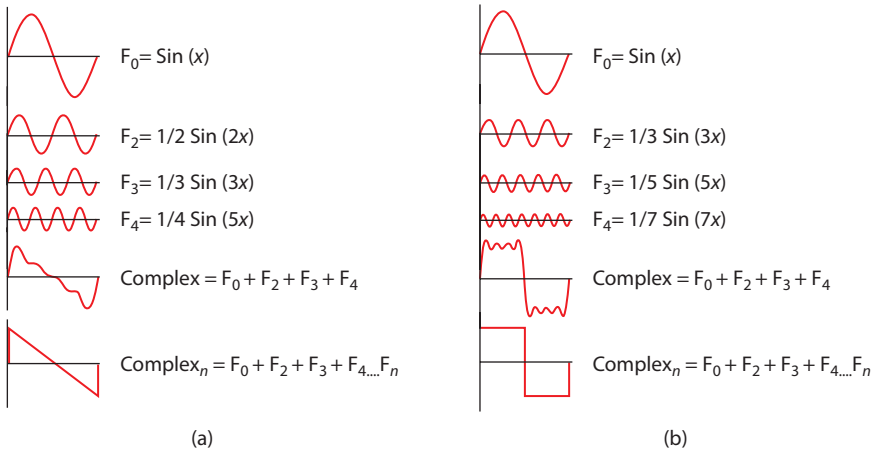


Figure 48.10 **(a)** The upper row shows a sinusoid, beneath which are odd- and even-numbered harmonics which, when added indefinitely, will form a sawtooth wave. **(b)** The same sinusoid with only odd-numbered harmonics added will form a square wave.

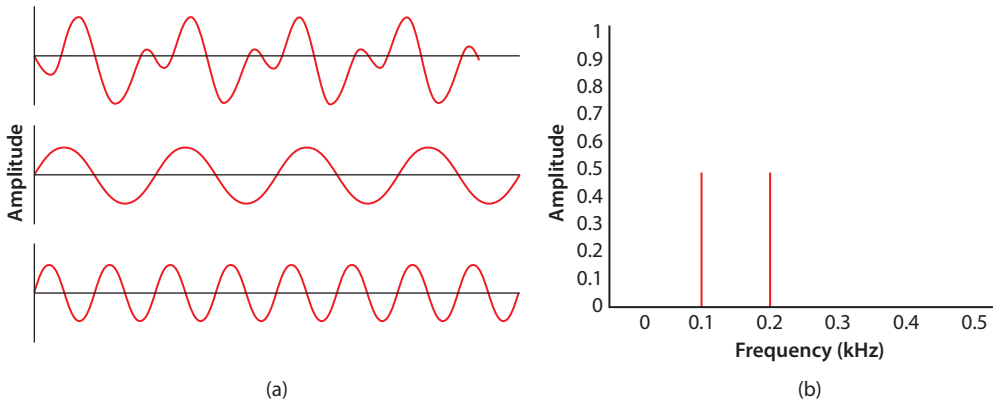


Figure 48.11 **(a)** The upper row depicts a complex tone in the time domain, comprising 0.1 kHz and 0.2 kHz sinusoids depicted in the middle and lower rows, respectively. The 0.2 kHz component has a 90° phase lead over the 0.1 kHz tone. **(b)** The two components are shown in the frequency domain, which does not display the timing relationship between components.

all components will divide into). The period (and therefore the repetition frequency) of the complex periodical sound is equal to the highest common factor. The higher-frequency components, which are exact integer multiples of the fundamental frequency, are known as harmonics.

Continuing the pattern illustrated in Figure 48.9 indefinitely would produce a 'sawtooth' pattern: sine waves with odd and even multiples of the fundamental. However, there are other combinations. For example, a square wave contains only the fundamental and an indefinite number of odd-numbered (or odd-order) harmonics. Sawtooth and square waves are shown in Figure 48.10 a and b respectively.

So far, all of the complex sounds have comprised components of different frequencies, but all with the same phase. Figure 48.11 shows the effect of complex sound that results from combining two pure tones as before, 0.1 kHz and 0.2 kHz of the same amplitude, but this time with a different phase. The 0.2 kHz component has a 90-degree phase lead over the 0.1 kHz component. The result is a different pattern of interaction, resulting in a different complex wave pattern (a) from that shown in Figure 48.8, although both examples have the same fundamental frequency. Note the line spectra (b) are unchanged because the temporal relationship between frequency components is not reflected in the frequency domain. The ear itself is relatively insensitive to phase. What the ear detects are the amplitude and frequency characteristics of the components that made up the complex signal. (The auditory system does respond to phase characteristics of sound, such as phase differences between sounds presented binaurally, and this is achieved by interaural comparisons within the central auditory system. For further information, see the review by Moore.[4])

For a complex sound to be periodic, the sinusoidal components must have a harmonic relationship; each component is an integer multiple of the fundamental. An aperiodic sound is the opposite of this as it does not repeat over time. It is therefore impossible to predict what such a waveform will look like from one moment to the next. While sounds that are (at least nearly) periodic are common in some forums, such as the sounds produced by pitched musical instruments, the majority of sounds in nature are aperiodic and therefore cannot convey pitch. Aperiodic sounds include wind noise, traffic noise and percussive instruments. Spoken speech contains both periodic and aperiodic sounds. The spoken vowel sounds are typically periodic, while consonant sounds are aperiodic.

Since there is no fundamental or harmonic structure, the spectra of aperiodic sounds cannot be a series

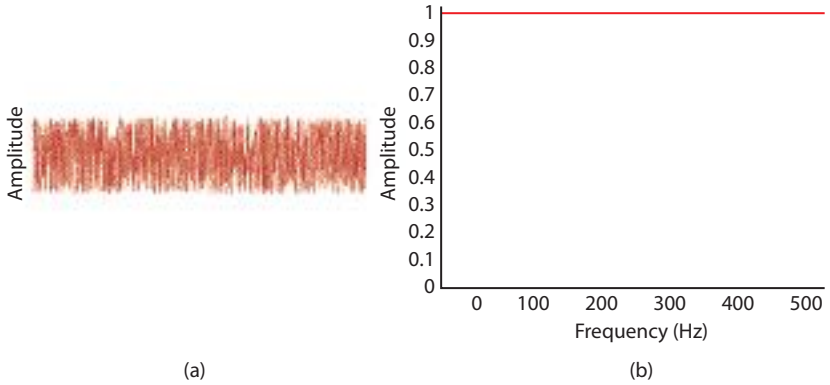


Figure 48.12 A sample of white noise, an aperiodic sound with equal energy at different frequencies, in (a) both the time domain and **(b)** the frequency domain. The relevant frequency range for white noise is 0.02–20 kHz, i.e. the range of human hearing.

of vertical lines. They are a continuous line, with differences in height corresponding to the differences in amplitude across the frequency range of the sound. Perhaps the simplest example is white noise, which is an aperiodic waveform with equal energy in every frequency band (1 Hz wide), as shown in Figure 48.12.

The name 'white noise' is analogous to white light, which has energy in all light wavelengths. Following this convention, different 'colours of noise' typically refer to noise whose energy levels across the spectrum reflect the colour of light with a similar spectrum, such as pink noise (where power density decreases with frequency) and blue noise (where power density increases with frequency).

TRANSMISSION OF SOUND BETWEEN DIFFERENT MEDIA

Earlier we briefly discussed the speed of sound through the medium of air, i.e. the rate at which sound propagates through the air. The speed of the propagation and the extent to which a sound may propagate at all are determined by physical properties of the medium such as the stiffness and density. Air is low density, and low stiffness. This means that vibratory energy from the source is passed from one molecule to the next relatively easily but relatively slowly. As the density of the medium increases, so does the speed of sound. For example, the speed of sound in water is around 1500 metres per second. The speed of sound is calculated using the following equation:

$$c = \sqrt{\frac{\text{Stiffness}\,(K)}{\text{Density}\,(\rho)}}$$

However, as density increases so does the stiffness of the medium. For example, air is far more elastic, and compressible, than fluid. This means that, when an object vibrates in air, the sound waves can propagate relatively 'easily', i.e. small pressures are required to produce a given velocity of movement of the air molecules. However, as the density of the medium and therefore the stiffness increase, such as with a fluid, then the same pressure will produce a smaller velocity of movement. This is the effect of acoustic impedance. The closer the impedances of two media (such as air and fluid), the more acoustical energy will be transmitted between them. The relationship between acoustic impedance (Z) of any substance, sound pressure and velocity of vibration is provided in the following equation:

$$z = \frac{\text{Sound pressure}\,(P)}{\text{Velocity of vibration}\,(\nu)}$$

The effect of different acoustic impedances of media such as air and fluid is relevant because, while sound typically reaches the ear via propagation through air, the physiologically vulnerable structures of the ear within the cochlear are filled with (and bathed in) fluid. Therefore, if the sound waves of a given pressure were to arrive directly at the cochlea from the remote source, the resulting velocity of vibration within the fluid-filled cochlea would fall due to the increased acoustic impedance; most of the energy would instead be reflected back into the air. That this does not happen is a result of the outer and middle ears, which act as an impedance matcher, so that a large proportion of acoustic energy is transmitted into the cochlea. The way in which this happens will be outlined below.

KEY POINTS

- Sound is variations in the pressure of the air (or other medium).
- Key dimensions of a sound wave are its frequency, intensity and duration.
- Each of these three dimensions of a sound can be detected and processed by the cochlea.
- The outer and middle ears match the acoustic impedance of the air in the external environment and the fluid of the cochlea, allowing efficient transmission of sound.

APPLIED PHYSIOLOGY OF HEARING

Soumit Dasgupta

This section looks at the applied physiology of how sounds or acoustic stimuli behave in the ear as well as what happens to the detection of these stimuli in diseases of the ear.

The peripheral ear consists of the pinna, the external auditory meatus and canal, the middle ear with the

tympanic membrane, the ossicles, the middle ear ligaments and the mucosal folds, the ossicles, malleus, incus and stapes, the Eustachian tube opening, the oval and the round windows, and the inner ear with the cochlea and the early part of the auditory nerve. Each component is crucial for normal functioning (i.e. audition) and it follows that any mechanism or process interfering with normal functioning will lead to a decrease in the perception of the auditory signal, generating a hearing loss.

THE PINNA

The pinna is vestigial in man, with non-functional auricular muscles. In lower groups of mammals, especially predators, these muscles are well developed and can move the pinna to localize and concentrate acoustic energy to the external auditory meatus, hence participating in spatial resolution of sound as well as focusing the energy to a relatively smaller area to be incident on the tympanic membrane.

The pinna and the external auditory meatus and the canal develop from similar morphological structures *in utero*. Therefore a dysmorphic pinna might reflect a dysmorphic external auditory canal and middle ear. Simple preauricular tags can indicate an underlying problem further down in the auditory pathway. Indeed, simple pinna deformities may be associated with an inner ear disorder.[5] It has been shown that in Down syndrome 3.5 pinna defects are observed, on average, in each ear as compared to 2.5 defects in the non-Down population; all of these are associated with conductive hearing loss in the former.[6] A pinna deformity is therefore clinically significant and demands an audiovestibular workup and, if necessary, monitoring. Since a pinna deformity may be a part of certain craniofacial syndromes, a genetic workup may be essential.

In terms of acoustic function, although the pinna is vestigial, when coupled with the external auditory meatus and canal, the unit acts to provide frequency specific resonance of sound incident on the ear to make up for the impedance encountered at the air–fluid interface between the cochlea and the middle ear. The applied importance of this is considered below.

The role of the pinna in localization of sound cannot be underestimated.[7] It has been postulated that the unique position of the pinna on the head and its relative size to the craniofacial skeleton transform the incoming sound signal with delay paths dependent on the wavelengths of the acoustic waveform to provide localization clues for the listener to an incoming signal. The head shadow, i.e. the intervening head and the pinna on either side, is an important factor for auditory localization, with interaural time and interaural intensity differences generated by the same acoustic signal impinging on the pinna with different temporal and intensity values at each side.[8]

There are numerous anatomical ridges and convolutions in the pinna. Sound waves from either the horizontal or the vertical direction are reflected from these ridges and enter the ear canal with the original non-reflected incident sound (see below). Then, via the fixed external auditory canal, they are transferred to the eardrum, further modifying the transfer function. The different changes of transfer function from the pinna to the external auditory canal when delivered to the cochlea through the middle ear are encoded accordingly to be finally perceived by the cognitive cortex as directionality of sound or a spatial representation of sound.[9] A pathology in the pinna may therefore interfere with this localization and directionality process.

It is logical to consider the pinna as a funnel to collect sound. As mentioned earlier, however, it can also be a reflector of sound and works best above 1 kHz. Some of the reflected waves enter the canal and may interfere with the original waves if they are out of phase, noted particularly between 7 kHz and 10 kHz where they produce a pinna notch.[10] The frequencies at which the reflected and incident waves boost each other are 2–3 kHz, roughly at frequencies which possess wavelengths of four times the length of the pinna.

The postauricular myogenic response (PAMR) is a measurable compound action potential generated in response to an electrical or acoustic stimulus.[11] The reflex magnitude is a large one and the afferent substrate is the cochlea rather than the vestibular system with the efferent pathway being the facial nerve.[12] The reflex is a bipolar compound action potential with typical latency of 12.5–15 ms and can be elicited by either tone-burst or click stimuli. The reflex is obtained at 20 dB SL and can be detected in 80% of the population.[11] The PAMR has been reported to be inconsistent and variable, with significant test–retest variations. It is also difficult to measure with standard auditory brain stem response (ABR) settings and therefore does not find much clinical use. However, there is evidence that, when measured, it can still be clinically useful to screen for hearing loss, especially in difficult-to-test children,[13] in facial nerve function monitoring for intracranial facial nerve palsies[8] and in auditory neuropathy (AN now called auditory neuropathy spectrum disorder where there is an abnormality in sound conduction and propagation from the inner hair cell synaptic junction all the way up to the brain stem and includes the auditory nerve) where it can be abolished.[14] Given the observation that the acoustic reflex is useful to test for AN in the clinical setting, PAMR can augment suspicion before an ABR for confirmation due to its potential ease of use.

The pinna is an important landmark for taking an impression of the ear, an important step in hearing aid fittings. The antihelix and the concha are anchors for hearing aid retention,[15] and a dysmorphic pinna lacking important landmarks may preclude standard behind-the-ear hearing aid fitting.

The pinna is made of fibrocartilage except at the region of the lobule and an area just above the tragus. These anatomical features provide areas for potential surgical accessibility. The lobule can be used as a fat graft and the supratragal notch can be used in endaural incisions, thereby not injuring the tight cartilage mucoperichondrium of the external auditory canal (see next section).

THE EXTERNAL AUDITORY CANAL

The external auditory canal (EAC) commences at the conchal opening called the external auditory meatus (EAM), includes the ear canal itself and ends at the tympanic membrane lateral surface, which separates it from the middle ear. It is made up of an outer cartilaginous part

and an inner bony part with two constrictions, one at the junction of the distinct anatomical parts and one 5 mm before the tympanic membrane in the bony part. Thus, it can be considered as a tube which is open at one end. The typical length is 25–26 mm in the adult human.

The EAC has acoustic and non-acoustic functions and pathologies of the ear canal will therefore interfere with both of these functions.

Acoustic physiology of the EAC

The most important physiological function of the EAM and the EAC is to 'transfer' the acoustic signal from a sound field to a much smaller area, i.e. the tympanic membrane. The EAC transfer function is a mathematical representation of the output of the external ear in dB SPL plotted against an input of sound in db SPL at different frequencies. The resultant acoustic energy delivery to the tympanic membrane is thus a modified and amplified signal which undergoes resonance amplification and provides directional/localization cues.

The ear canal can be considered as a resonating tube following the quarter-wave principle for resonance; i.e. at a frequency with a wavelength four times the length of the canal, the canal and the pinna together will resonate and vibrate with the incoming signal to augment or magnify the incident acoustic signal given by the equation:

$$f = c/4l.$$

where f is the frequency, c is the speed of sound and I is the length of the canal.[16] The resonant frequency which amplifies the incident sound by 10–20 dB is generally 2.7 kHz with a range of 2–7 kHz.[17] Signals below 1 kHz are generally resonated by the head and the torso whereas frequencies above 3 kHz are augmented by the pinna.

It follows, therefore, that the length of the ear canal plays a significant role in modifying the incident sound signal before its delivery to the tympanic membrane. This amplification is essential to overcome the air–fluid impedance at the oval window.

The EAC and the pinna acting as a unit are also involved in providing monoaural and binaural cues for localization of sound (see 'The pinna' above). The EAC pressure gain and transfer factor changes with directionality of the incident signal especially above its resonant frequency and can be as much as 30 dB in both the horizontal and vertical planes.[18]

The EAC canal is subject to variation in size and may grow from the neonate until the age of 7–9 years.[17] The transfer function may change during this period, with important amplification issues in fitting hearing aids, and must be calibrated accordingly by referring to the normal range. The resonant frequency remains more or less constant from the age of 2 years.[19] However, the resonance amplitude changes at old age.[16] Since prescribed hearing aid function is significantly dependent on external ear canal function, this change of resonance must be taken into account to prevent inappropriate amplification.

In some frequencies the EAC generates a standing wave phenomenon. A standing wave is defined as being created when two sounds of the same frequency travel in opposite directions in the canal (e.g. when the same sound is reflected by the tympanic membrane) and cancel each other out. For sounds of high frequencies, a standing wave may be produced which may interfere with circum or supra aural head phones measured hearing threshold at 8 kHz, which might generate a spurious hearing deficit.[20] Another reason why a spurious threshold may be obtained is because in adults supra aural headphones may collapse the soft cartilaginous part of the external auditory canal. This consideration also becomes important when performing real-ear measurements.

In disorders of the EAC ranging from dysplasia to occlusive pathologies (e.g. wax or tumour), the effect on the external canal resonance gain is real and tangible and some conductive hearing loss (a hearing loss which is caused by any factor interfering with the conduction of sound in the external auditory apparatus i.e., the meatus, canal and pinna and the middle ear) is expected. This hearing loss is usually concentrated around the area of maximum resonance, i.e. at about 2.7 kHz. In cases of occlusive hearing aid moulds, this loss must be incorporated in the prescription.

Morphology of the EAC

The EAC is characterized by its skin and by the production of wax, each of which serves its own functions.

The skin is tightly adherent to the underlying perichondrium without any subcutaneous tissue. It is thicker in the cartilaginous part than in the bony part.[15] Minor trauma to the skin may directly involve the perichondrium, potentially leading to serious infection. A skin breach may damage the mucoperichondrium too, therefore due care must be taken not to damage the skin. Surgical incisions utilize the cartilage-free supratragal notch and the superior wall of the canal which spare the cartilage. Earrings are recommended to be worn in the lobule which is devoid of cartilage.

The migration of dead skin is towards the meatus, i.e. lateral. A blind pocket in the ear canal will trap this skin and prevent its migration, leading to infection and finally to a cholesteatoma if it affects the posterosuperior region of the canal.

The skin of the canal is supplied profusely by nerves. Irritation of the canal may provoke a cough reflex or even a vasovagal spell by stimulating the vagus nerve, which serves the canal by way of the nerve of Arnold. Paraesthesia or anaesthesia of the posterior meatus wall may be a feature of a vestibular schwannoma, which is supplied by the nerve of Arnold.

The canal skin is lined in the outer third by two different types of secretory glands: the sebaceous glands and the modified apocrine ceruminous glands. Sebum and cerumen from the glands mixed with dead skin, dust and shed hair form wax. Therefore wax is a product of secretions from both sebaceous and apocrine glands. It turns brown on oxidation in air. There are two types of wax, dry and wet, which are genetically determined. The functions of ear wax are to lubricate and clean the canal, to act as a vehicle for carrying migrating dead skin from the canal skin in the lateral direction and a protective function due to its bactericidal effects against some bacteria and the antimicrobial effects of the lysozyme, immunoglobulin A (IgA) and fatty acids which it contains.[21]

The ear canal is sometimes called the 'greenhouse of the human body', being warm, dark, humid and moist.[21] It is a perfect culture medium for microbes, especially fungi. The wax provides some protection by trapping these microbes, by virtue of its antimicrobial properties and by providing an acidic milieu. Sodium bicarbonate drops to soften wax in the canal disturb the acidic pH and may lead to infection. It is therefore best to use a neutral agent for this purpose (e.g. olive oil).

Impacted wax generates morbidity. Complete occlusion of the ear canal leads to a hearing loss of 40 dB in addition to possible tinnitus and cough.[21] There is usually a high-frequency shift on lesser occlusions starting from 2 kHz, probably due to the compromise of the resonant gain of the ear canal. Wax may irritate Arnold's nerve to cause a vagal-induced cough reflex, especially during microsuction. Superadded infection may lead to social isolation and even a frank otitis externa.

THE MIDDLE EAR

The middle ear in the human acts as an efficient passive and linear transformer to conduct acoustic energy from the tympanic membrane to the stapes footplate at the oval window and to the cochlea. The middle ear apparatus consists of the tympanic membrane, the ossicular chain of the malleus–incus–stapes complex along with the middle ear muscles. Its fundamental function is to provide critical modifications to the sound energy by providing mechanical advantages to overcome the impedance encountered by the acoustic signal when it is conducted from an air-filled medium (the middle ear cavity) to a fluid-filled medium (the perilymphatic and the endolymphatic fluid in the cochlea). Essentially, therefore, acoustic energy is transferred from a low-impedance, high-velocity medium to a high-impedance, low-velocity medium through this ossicular coupling (**Figure 48.13**). The impedance difference is mainly matched by the ratio of the surface area of the tympanic membrane to the stapes footplate and by the lever action of the ossicles and the membrane. The Eustachian tube links the nasal cavity to the middle ear. This tube supplies air to the middle ear for the air particles to vibrate and also equalize pressure across the tympanic membrane between the EAC and the middle ear.

Middle ear function is assessed by impedance audiometry which measures compliance and pressure of the system by tympanometry, which, in addition, also measures volume of the external auditory canal and the stapedial reflex tests. Tympanometry is essentially a measure of admittance (i.e. the reciprocal of impedance) of the middle ear system. The EAC volume can indirectly verify a tympanic membrane perforation or a patent grommet where the canal volume is higher than the average range of the normal and the stapedial reflex tests provide information about the auditory nerve pathways (see 'The middle ear muscles' below). Middle ear function tests are discussed further in Chapter 51, Psychoacoustic audiometry.

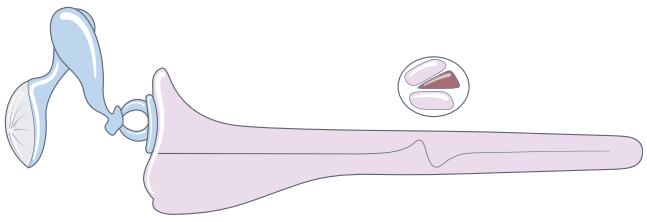


Figure 48.13 Ossicular coupling.

The middle ear space

The middle ear is a closed cavity consisting of the medial surface of the tympanic membrane, the ossicles, the oval window, the Eustachian tube and the middle ear muscles and the ligaments with mucosal folds. The greatest transfer function of the middle ear is at the resonant frequency between 1 and 3 kHz and is determined by the mass and the stiffness of the system. In other words, the middle ear may be considered to be a system with a band pass filtering action.[22] The stiffness or elasticity of the middle ear is determined by the tympanic membrane, the ossicular ligaments and the middle ear cavity compression of the air column while the mass is governed by the ossicles. The stiffness factor limits passage of low-frequency sounds while the opposite is true for the mass factor.

The tympanic membrane

Like the EAC, the middle ear mechanism delivers acoustic energy from a relatively large area of the tympanic membrane to the much smaller area of the stapes footplate. The ratio is about 18:1.[23] This disproportionality contributes to overcoming the acoustic impedance mismatch at the air-fluid interface between the middle and the inner ear. The process begins at the lateral or outer surface of the tympanic membrane which, strictly speaking, is a part of the EAC. The canal side of the membrane exhibits a uniphasic response with little pressure variation and is relatively uniform[24] while the middle ear side is multiphasic with significant pressure variations. This can be explained by the consistency and the structure of the membrane which is non-uniform and provides a multiple integrated multilever mechanical advantage.[25] There is also a destructive interference due to reflection of the sound waves by the membrane, which is important to create a pressure difference across the membrane.

The incident sound from the EAC hits the membrane and sets up a travelling wave, which is mainly collected at the rim of the membrane. This is then conducted to the umbo and coupled to the manubrium of the malleus.[26] At lower frequencies, the membrane transfers all its energy by uniform movement to the malleus; at higher frequencies, the movement is more complex and part of the vibration is shunted by the middle ear.

The reflectance of the membrane is high at the lower frequencies below 1 kHz while it is lowest between 1 kHz and 4 kHz, which means that between these frequencies maximum energy is delivered to the cochlea and the middle ear is most efficient.[27] This range of frequencies happens to be where the middle ear apparatus resonates to the incident stimulus and amplifies the signal to overcome the impedance at the stapes oval window interface.

At higher frequencies up to 15 kHz, the reflectance rises to near total again, which suggests that the middle ear limits sound wave propagation at higher frequencies.[28]

In disorders of the tympanic membrane (e.g. tympanic atelectasis or perforations) the multiple lever action is compromised, leading to a hearing loss, and a myringoplasty cannot restore this feature of the membrane in all cases. A unique case is tympanosclerosis where hearing is preserved in spite of a loss of action of the membrane, presumably because the preferential distribution of the acoustic energy to the oval window from the middle ear is intact due to preservation of some structural integrity.[29] Therefore, structural integrity is crucial for the middle ear transformer mechanism. Note that, when the rim of the membrane is intact (i.e. central perforations), hearing is better preserved than when the margins are affected as energy transfer from the canal to the membrane is via the rim of the membrane.

In perforations, the volume velocity of the sound waves (the volume of vibrating air particles conducting the sound per unit time) is not preferentially distributed to the stapes–oval window interface as normal displacement of the membrane is precluded, but a part of it is absorbed or shunted by the middle ear cavity. Sound transmission may still occur but in a perverted and unnatural way. The main reason for a hearing loss is the reduction in pressure across the tympanic membrane due to this shunt and preclusion of the multilever action.[27] The degree of the loss is proportional to the size of the perforation and inversely proportional to the frequency, i.e. the greatest loss is at lower frequency. This is because reflectance of the membrane, which is an important factor for the pressure difference across the membrane, is lost or diminished at lower frequencies, which does not aid compliance and transfer of energy to the oval window.[30]

The Eustachian tube

The Eustachian tube opens to supply air into the middle ear cavity and is controlled by the muscles in the tube, which are under tonic control and follow the nasal cycle. The tubal opening is best demonstrated at 6–8 kHz, i.e. high-frequency sounds. An evolutionary hypothesis can be proposed to account for this. Since high-frequency sounds are the most important consonant-containing sounds, the middle ear must act in the most efficient way to conduct these sounds, which should be close to its resonant frequency and unaffected by the damping effect of reduced air supply. In other words, maximum air entry from the tube needs to occur at high frequencies to facilitate sound conduction. In Eustachian tube dysfunction where the middle ear cavity is deprived of air, as in early stages of otitis media with effusion (OME), the stiffness of the system is augmented, which leads to a low-frequency hearing loss. With further progression, fluid collection in the middle ear cavity increases the mass of the system, which generates a high-frequency hearing loss.[22] This model may be useful to prognosticate one of the commonest causes of hearing loss in children, i.e. glue ear. It is important to bear in mind that, unlike perforations, which do not affect eventual transmission of sound, OME physically disrupts transmission.

The middle ear cavity

The reflections of the acoustic signal from the walls of the middle ear cavity may contribute to pressure differences across the tympanic membrane[31] and may provide an additional drive to the membrane function.

The transfer function of the middle ear is linear. If stapes velocity which is proportional to acoustic frequency is considered the output of the middle ear mechanism, then it has been shown that there is a peak function at 3 kHz and the shape is that of a shallow band pass cut off.[32] The stapes velocity drives the cochlear fluid movement. Once again, note that the transfer function is most efficient around the resonant frequency range of the middle ear. The cochlear impedance itself makes the middle ear highly damped, which is essentially the impedance the middle ear needs to overcome in order to preserve acoustic stimulus characteristics.

The middle ear mucosal folds

The mucosal folds in the middle ear, which thicken in some instances to form ligaments, divide the middle ear cavity into a superior epitympanum and an inferior mesotympanum and hypotympanum. The ligaments in this epitympanum diaphragm are formed by malleal folds, with the lateral malleoincudal fold posteriorly and the tensor fold anteriorly.[33] The connection between the two is the tympanic isthmus, which is the only conduit for a ventilation stream in the epitympanum from the Eustachian tube, unlike the mesotympanum, which is flooded by air at all times. Congenital defects in the folds, or folds affected by inflammatory processes (e.g. mucosal disease or cholesteatoma), can block the narrow isthmus, leading to loss of air from the epitympanum and provoking further inflammation.[34, 35]

The middle ear muscles

There are two middle ear muscles with function in man: the tensor tympani and the stapedius. They both participate in a reflex contraction, thought in part to protect the delicate sensory epithelium of the cochlea by attenuating high amplitude sounds. Of these, the tensor tympani is less efficient and active than the stapedius, which is the dominant muscle driving the reflex. The muscles are also important for eliciting a prevocalization reflex, i.e. a reflex when someone is about to speak.[36] Given the bony continuity of the human skeleton, vocalization leads to cochlear stimulation via the bony EAC, the ossicles and the skull bones. The middle ear muscles modulate this acoustic signal so that the ear is protected from one's own voice. In the evolutionary sequence, if we consider bats, the acoustic reflexes completely disarticulate the ossicular chain when the bat emits a high-frequency and otherwise very loud echolocating pulse.

The tensor tympani supplied by the Vth nerve has very low electrical activity in response to sound. It attaches to the malleus manubrium and pulls the malleus anteriorly. However, it is active in the following situations: tactile stimulation of the EAC and face, pneumatic pressure on the eyelids, sudden forced opening of closed eyelids or forced closing of the eyelids, swallowing, head movements, anticipation of loud sounds and a startle.[37] It is

interesting that these movements all entail some movement of the bony skull which can stimulate the cochlea. Disorders of the tensor tympani may generate the 'tensor tympani syndrome', which manifests as an audible thump in the ear; the condition is rare.[37]

The stapedius muscle supplied by the VIIth nerve is the dominant muscle in the middle ear and attaches to the stapes neck. Its contraction pulls the annular ligament in the footplate. The stapedius responds primarily to high-intensity low-frequency sounds – about 0.8 kHz[38] –which tend to overpower the high frequencies to preserve high-frequency consonant-containing speech sounds (see below). The middle ear system at lower frequencies therefore generates the maximum impedance to incident sounds. Stapedius contraction is responsible for the stapedial reflex which moves the stapes about 50 microns, increases the stiffness of the ossicular chain and can attenuate the sound transmission to the inner ear by as much as 30 dB.[39]

At the 80–90 dB SL intensity range, the reflex is elicited. However, the stapedius tendon takes about 100–200 ms to contract fully, which implies that it will be unable to protect the cochlea from intense short-impulse noise such as a gunshot, although a noise primer just before the gunshot may address this latent period and may be otoprotective.[37] Although the role of the reflex is controversial, it is thought to serve three important functions:

- Protection of the cochlea to high-intensity sounds to preserve a dynamic range of the auditory system.
- Reduction of output of the middle ear from high-intensity low frequency sounds – these high-intensity low-frequency sounds may mask the high-frequency speech consonant sounds at the base of the cochlea due to the forward propagating cochlear wave (see 'Cochlear travelling wave' below), thereby aiding speech recognition.
- Modulation of self-monitoring of voice and preserving high-definition, high-frequency ambient sounds when one is speaking or by self-generated noise.

The neuronal circuitry of the reflex crosses over to the other side and therefore the reflex can be elicited by both ipsilateral and contralateral stimuli delivered to one ear. As a result, there are several possible response patterns that reflect conductive, sensory and neural hearing losses. The author [SD] believes that the most important utility of measuring the stapedial reflex is to screen for auditory neuropathy spectrum disorder (ANSD) in case of hearing/listening problems with preserved otoacoustic emissions[41] and in cases of spurious hearing losses, for example third windows (see 'The middle ear windows' below) where, in the presence of a significant air–bone gap in pure-tone audiometry (the difference between air conduction and bone conduction thresholds), the reflex may be preserved (the reflex is usually unobtainable in middle ear disease). The reflex may be abolished in brainstem lesions although the response cannot be used to diagnose such a lesion. The reflex itself may be audible, generating an objective tinnitus in the ear which is due to a stapedial tendon myoclonus.

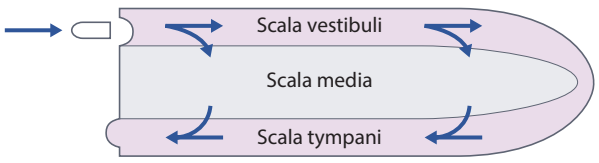


Figure 48.14 The oval window–round window pressure difference for the cochlear travelling wave.

The middle ear windows

The middle ear is characterized by two natural windows or real connections between the middle and the inner ear. The oval window articulates with the stapes footplate while the round window is covered by the secondary tympanic membrane.

The pressure difference between the oval and the round windows is fundamental for the cochlear travelling wave (see below) which drives cochlear function (**Figure 48.14**).[42] Cochlear fluid is not compressible and therefore, to allow a cochlear travelling wave while protecting the sensory epithelia from excessive movement, a mechanism must be present to dissipate part of the mechanical vibration-induced pressure through a channel in the opposite phase. The oval window is the site of the preferential distribution of sound energy although, at higher frequencies, this preference is occasionally shunted by the middle ear cavity.

Disorders of the oval window or in the vicinity (e.g. stapedial or cochlear otosclerosis), congenital absence of the oval window or X-linked gusher syndromes will lead to a loss of this preferential distribution and have a significant effect on auditory sensitivity.

In addition to providing the integrity of the cochlear travelling wave, the round window also participates in absorption and secretion of the perilymph by virtue of a semipermeable membrane.[43] This has opened up possibilities for intratympanic drug delivery through the round window to achieve effective intralabyrinthine concentrations. The round window approach is also used as an alternative to a standard cochleostomy approach for insertion of cochlear implants to minimize operative trauma and subsequent intracochlear fibrosis.[44]

In addition to the two natural windows, virtual third windows may exist for some absorption of the sound from the middle ear thereby affecting the preferential stapes-oval window sound distribution. This includes the vestibular aqueduct and the bony skull itself as well as the ossicular inertia, all of which may shunt away some of the energy, with variable cochlear effect. A pathological third window which can be a real one (perilymph fistula, X-linked gusher i.e., real connection between the inner and middle ear) or a virtual one (dilated vestibular aqueduct or semicircular canal dehiscence i.e. no direct communication between the inner and middle ear) also absorbs or shunts part of this preferential distribution. The cochlea might in part be directly stimulated by the vibrations in the third window itself. Measured air-conduction thresholds therefore decrease and bone-conduction (BC) thresholds increase, generating a spurious conductive hearing loss or 'false' or air–bone gap.[45] The improved BC can also be explained by the fact that the third window generates a pressure drop across the two natural windows. However, it must be noted that third window pathology may directly damage

the cochlear or the vestibular sensory epithelia. As a result, it is very difficult to accurately estimate auditory sensitivity in patients with the disorder and consequently prescriptive fitting of digital amplification which is based on pure-tone thresholds may not give a favourable outcome.

Bone conduction

Apart from being stimulated by the stapes–oval window interface acoustic energy transfer and the round window effect, the cochlea can be directly stimulated by the bony skull composed of canal, ossicles and bony cochlea within which the whole inner ear apparatus is enclosed. Airborne and internally generated sound produces vibrations in the hard bony skull which in turn can lead to endolymphatic movement of the cochlear basilar membrane (BM), bypassing the middle ear and the external ear mechanisms. In addition, there is a non-osseous pathway for stimulation by the acoustic energy which is conducted through the brain and the cerebrospinal fluid (CSF) and transmitted to the cochlea by its fluid channels.[46]

The cochlea is directly stimulated by factors including the sound pressure level in the bony canal vibrating the skull, the ossicular inertia, the cochlear fluids and the cochlear space vibrations.[47] Thus, there are three methods of bone stimulation:[48]

- vibration-induced compression and distortion of the cochlear space consisting of the intralabyrinthine bony skeleton which causes distortion of the BM due to the flexibility of the vestibular aqueduct
- vibration-induced inertia of the ossicles transferring to the bony labyrinth
- particle vibrations leading to vibrations of the EAC, the tympanic bony sulcus and directly transmitted to the cochlea.

The middle ear has a resonant frequency around 1–3 kHz considering both air and bone conduction. If this resonance is reduced or damped by a mechanical problem in the ossicular chain (e.g. adhesion, fixation or sclerosis), the ossicular component of bone conduction as outlined above is jeopardized and generates a drop in the pure-tone thresholds as measured by BC of about 5–10 dB. This classically appears at 2 kHz as Carhart's notch in the BC thresholds in stapedial fixation; however, in any pathology involving the ossicles, a Carhart's effect may be present between 1 kHz and 4 kHz with dips in BC thresholds. Occlusion of the EAC to a significant degree may improve bone-conduction thresholds as the vibrations from the bone travel through the skull and on re-entering the external ear are contained within the canal to directly stimulate the inner ear by the osseotympanic route and do not escape to the outside.

The ossicles

The three ossicles (the malleus, the incus and the stapes) are connected together by synovial joints for transmitting the acoustic stimulus from the tympanic membrane. The geometric length of the malleus is approximately 2.1 times that of the incus and thus the lever action multiplies by 2.1 times; with velocity decreased by a factor of 2.1, the net mechanical advantage or impedance ratio is therefore 4.4. Further, the lever action changes with frequency with its most efficient at 2 kHz.[49]

The malleus and the incus rotate around an anterior–posterior axis of the malleus–incus complex that passes through the centre of gravity of the ossicles.[50] At low frequencies there is relatively less motion between the malleus and the incus; however, at higher frequencies the motion becomes more complex, allowing some slippage between the two to conduct higher-frequency sounds more efficiently.[27] The stapes shows a similar pattern of movement, i.e. simple piston-like movements at low frequencies and more complex spatial movements in higher frequencies along the long and short axes of the footplate.[51]

In ossicular discontinuity, whether congenital or acquired, the ossicular coupling-led preferential distribution of sound to the oval window is lost and the cochlear partition pressure between the round and the oval windows, which drives the cochlear travelling wave, is compromised.[52] The total expected conductive loss is about 60 dB, but much less if there is incomplete discontinuity or when there is a pathological bridge between the ossicles (e.g. a cholesteatoma). In ossicular fixation, such as in chronic adhesive otitis media involving ossicular joints or their ligaments, especially the anterior malleolar ligament, continuity is present but mobility is restricted and leads to a high impedance in the system. This is offset to a certain extent by inbuilt redundancy mechanisms in the middle ear. Thus, the hearing loss which is generated is less than that obtained with ossicular disruption. Otosclerosis is one type of ossicular fixation where the output substrate of the EAC and the middle ear concentrated on the stapes footplate affect forward propagation to the cochlea, thereby generating a significant conductive hearing loss proportional to the mobility of the stapes affected by the disease.

Tympanoplasty and ossicular chain reconstruction surgery attempts to re-establish the broken ossicular bridge either using soft tissue or by synthetic or autologous grafts.

Middle ear impedance match

The two primary mechanisms to match loss of acoustic energy at the stapes–oval window interface due to change of acoustic transmission from an air to a fluid medium, i.e. the surface area ratio of the tympanic membrane to the stapes footplate and the lever actions of the tympanic membrane and the ossicular levers, are responsible for a pressure gain in the middle ear conducted sound. Ossicular coupling, which is mainly contributory to the pressure gain, is frequency-dependent;[53] between 0.25 and 0.5 kHz it is 20 dB, reaching to 26.6 dB at 1 kHz and then decreasing by about 8.6 dB per octave until near zero above 7 kHz. The cochlear impedance is less at higher frequencies than at lower frequencies.

The effectiveness of impedance matching varies according to sound frequency. At 2 kHz, when the external canal and the middle ear transfer the acoustic energy most efficiently, the average sound pressure loss at the cochlea is 39.5 dB, which is partially compensated for by an external canal gain of 9 dB and a middle ear gain of 26.6 dB for a total gain of

35.6 dB factoring in some loss due to frequency-dependent middle ear function. In humans, at 2.7 kHz (i.e. the resonance of the canal) the sound pressure loss is approximately 35 dB, which is very closely matched by the external and the middle ear transfer function.[54] Note the difference in the impedance match at 2 kHz and at the resonant frequency of 2.7 kHz; the latter is a closer match than the former.

THE COCHLEA

The stapes–oval window interface delivers the mechanical and kinetic energy of the incident acoustic signal to the cochlea. The cochlea is a 2.5-turn coil in humans resembling a snail in the anterior compartment of the bony inner ear labyrinth. Sound introduced to the cochlea undergoes two major processes: a biological and active compression/amplification by the outer hair cells (OHCs) and an electrochemical transduction by the inner hair cells (IHCs), both contained in the scala media of the cochlea. The resulting neural output is a coded and gated signal conveyed by the auditory nerve via the spiral ganglion cells to the brainstem, which preserves frequency information, the amplitude and the phase of the sound by cochlear tonotopicity (frequency specificity), auditory nerve firing rate, phase locking and synchrony.

The cochlea is characterized by amplification to make hearing more sensitive, tuning to make it sharply frequency-selective and compressive non-linearity so that relatively large stimuli are translated to proportionally lesser systematically encoded mechanical functions to maintain integrity.[56] Cochlear mechanisms for the above actions are therefore responsible for the essential functions of the cochlea that include frequency analysis, loudness discrimination, temporal resolution, and the spectral analysis of the incoming signal. This is a highly complex process and interference with any of the component processes will lead to a hearing disorder.

Cochlear OHC function is measured by otoacoustic emissions that include transient emissions in response to a broadband click and distortion product emissions in response to frequency-specific pure tones. It can also be measured by electrocochleography and cochlear microphonics, the latter being incorporated in the software for auditory brainstem response (ABR) testing (see Chapter 9, Hearing tests in children).

Cochlear travelling wave

The mechanical displacement of the stapes–oval window junction is conducted along the cochlea, impinging on the base first and then travelling all the way up to the apex (**Figure 48.15**). In its wake, it causes mechanical movement of the BM which divides the cochlea into two compartments: the scala vestibuli above and the scala tympani below with a small connection between the compartments at the helicotrema in the apex. In addition, there is a third component called the scala media between the scala vestibuli and the scala tympani separated from the scala vestibuli by the Reissner's membrane and the scala tympani by the basement membrane. There are therefore three different travelling waves generated: the wave as a result of the pressure difference of the two compartments, the wave as a result of the mechanical displacement of the BM, and the acoustic energy wave which displaces the cochlear fluids.[56] The displacement wave is by far the most important wave for cochlear function.

The travelling wave propagates aided by the gradual diminution of the thickness and stiffness of the basement membrane from base to apex. As it propagates, it is acted upon by numerous critical oscillators, the characteristic frequency of which is specific to a particular region of the BM. These oscillators move the BM in addition to the travelling wave by expending active energy and are coupled with OHCs in the organ of Corti. The mechanical travelling wave propagates from the base to the apex, so there is a biological need to maintain signal strength at a relatively stable state due to gradual changes in thickness and stiffness of the BM along its length. The oscillators become active when they compress or modify this signal and passive when they allow the signal to pass. There is a critical point at which these may cancel each other out called the Hopf bifurcation.[57] In order to prevent this, the oscillators must possess an autoregulation process or a self-tuning property which, as can be seen later, generates a very important attribute of the cochlea in the form of a cochlear tuning curve.

Given that the critical oscillation function and the compressive function of the OHC (see below) are responsible for tuning the BM in response to an acoustic signal, which is variable along the length of the BM and is spatially represented, it can be inferred that the acoustic output, which is the end result of the BM function, is a non-linear output. In pure tones with frequencies well below the characteristic frequency (see below 'Cochlear tuning curve'), the function is linear and passive. In disease processes, the non-linearity may become linear and can be measured in the growth function of distortion-product otoacoustic emissions. Pathologies such as ototoxicity and possibly age-induced hearing loss will interfere with the non-linear function of the cochlea.

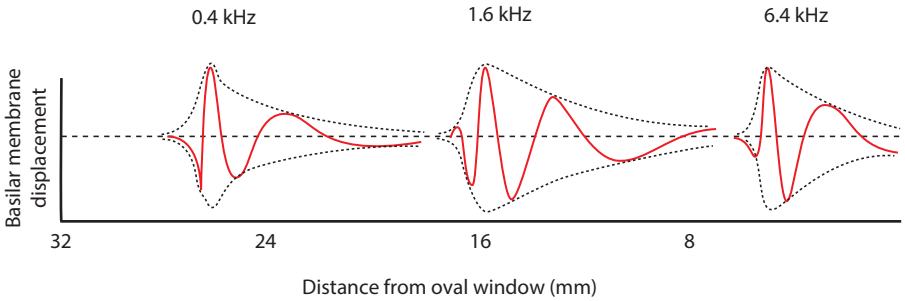


Figure 48.15 The cochlear travelling wave.

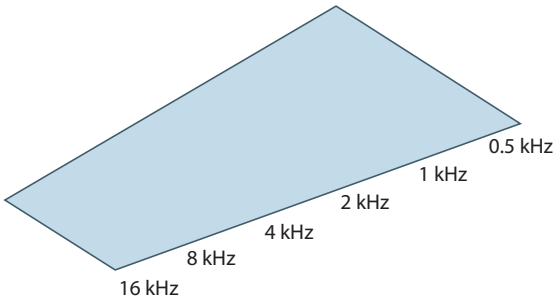


Figure 48.16 Tonotopic representation of the cochlear BM.

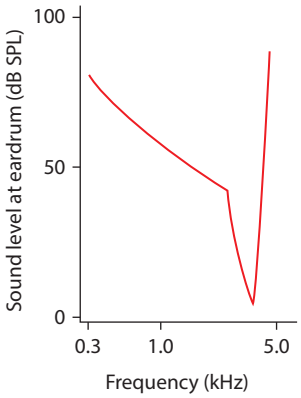


Figure 48.17 The cochlear tuning curve.

Cochlear tuning curve

The cochlear travelling wave in response to an acoustic stimulus reaches a maximum displacement somewhere along the BM following which it starts to dissipate. High-frequency sounds produce peak displacement towards the base of the cochlea whereas the peak moves progressively towards the apex as sound frequency decreases. There is therefore a clear relationship between frequency and displacement in the BM. The frequency at which the maximum displacement occurs is also called the characteristic frequency[58] at a specific place in the BM making it highly frequency-specific or tonotopic (Figure 48.16).

A cochlear tuning curve is the response of the cochlear BM to changing intensities to achieve a maximum amplitude response and is plotted as a function of intensity with frequency (Figure 48.17). A psychophysical tuning curve is the plotting of the amplitude of a narrow band masker required to mask a fixed pure tone as a function of the masker signal.[59]

The human ear has a dynamic range up to 120 dB which inherently dictates that signals of very high intensity must undergo modification at the cochlear level without damaging the cochlea and need to be compressed. The cochlea does this via the OHCs and their non-linear function, and depends on the frequency specificity or the tonotopicity of the BM.

Compression is achieved by the OHCs to generate the tuning curve. For example, a 50 dB SPL tone will result in a 10 dB SPL equivalent change in BM displacement, which inherently implies that the dynamic range is maintained with relatively lesser displacements of the BM.[58] This compression is essential for maintaining the integrity of the BM and increasing its stability in the presence of high-intensity stimuli. For lower-intensity signals, the OHCs amplify the BM response by mechanical elongation/compression of their cell bodies which sharpen the tuning curve; again, this is variable across the response, preserving non-linearity.

Another property of the cochlea is its filtering action. This is indirectly dependent on the tonotopicity. In simplified terms, the characteristic frequency is where other neighbouring frequencies are filtered so as not to interfere with the frequency selectivity i.e., the characteristic frequency is best resolved at a given point in the BM in preference to other frequencies. In other words, these neighbouring frequencies undergo some sort of a filtering action. It has been proposed that this filtering also explains the attribute of perceptual streaming.[59] This is essentially a central auditory function contributed by the ability of the cochlea to discern a rapid sequence of sounds coming from a single or a multiple source (i.e. whether the single sound is an overlap of multiple sounds or whether multiple sounds can be perceived on their own). When the sounds are close together in frequency, fusion may occur and the perception will be of a single sound as the filtering action becomes less in neighbouring frequencies. However, factors other than this overlapping of exciting frequencies may interfere.[59]

The dynamic range is significantly lost and reduced in cochlear pathologies. The tuning curve loses its sharpness and frequency selectivity is compromised along with perceptual streaming. Different pathologies may affect the shape of the tuning curve in different ways: for example, some genetic losses involve the lower-frequency sensitivity while ototoxicity affects the high-frequency sensitivity. Cochlear hearing loss therefore may show some characteristic features, including loss of frequency selectivity leading to difficulties to understand speech and appreciate music, loudness recruitment due to reduced dynamic range and a compromise of perceptual streaming which manifests itself as an inability to perceive or segregate multiple sounds at a given time. (see 'Pathophysiology of cochlear hearing loss' later in the section). These pathologies lead to a perceived hearing loss.

Cochlear fluid

The cochlea contains perilymph in the scala vestibuli and scala tympani. This is an ultrafiltrate of blood plasma and the CSF, rich in sodium and low in potassium and calcium. The scala media or the cochlear partition consists of the endolymph which is actively pumped by the stria vascularis in the scala media. This, in contrast, is rich in potassium, low in sodium and has negligible calcium. The stereocilia of the hair cells are bathed in the endolymph while the hair cell bodies are bathed in perilymph. There is another compartment called the intrastrial space which is the space between the extracellular matrix of the stria vascularis.

The cochlea is supplied by the spiral modiolar artery, which is a branch from the vestibulocochlear artery (VCA) from the anteroinferior cerebellar artery. The VCA is an end artery. The microcirculation of the cochlea, especially the stria vascularis, has certain characteristic features.

The capillary network is arranged in a parallel fashion in the lateral wall of the cochlea; there is an abundance of pericytes and fibrocytes in the network, and the cochlear blood flow is autoregulated by multiple factors which are exquisitely sensitive to changes in the internal environment.[60] These factors include local metabolites such as lactate, nitrous oxide and potassium, the pericytes and the fibrocytes, and the blood vessel smooth muscle cells. Cochlear microcirculation ensures the integrity of the cochlear fluids and there exists a blood–labyrinth barrier which is responsible for ultrafiltration and abundantly supplied with enzymes and protein subunits, for example the Na^+ - K^+ ATP subunit so important for ionic transport. The objective is to deliver energy and provide processes for ionic transport for the cochlear internal milieu. Cochlear microvasculature is affected in a number of disease processes with secondary involvement of cochlear fluid hydrodynamics which in turn lead to impaired cochlear functions. These include noise-induced hearing loss, endolymphatic hydrops and possibly age-induced hearing loss. In addition, the artery is an end artery, which implies that a blockade or obstruction to it (e.g. an embolus) if it persists beyond a certain period of time (about 15–30 minutes[61]) will lead to irreversible damage (ischaemia) to the organ it supplies, which is the cochleovestibular apparatus.[61]

The highly intricate cochlear microvasculature ensures nutrition in the cochlear compartment and also provides the internal environment for cochlear function. The main driving ion for cochlear function as furnished by different cochlear processes is potassium. The way it is recycled is called a potassium cycle, responsible for the endocochlear potential. This potential is the resting potential kept at a constant level in the scala media. From the teleological point of view, potassium is the chosen cation as the other cellular ion, sodium, entails far more cumbersome active transport systems between different media which would crowd up the BM, precluding highly sensitive hair cell function. Potassium, on the other hand, simply utilizes a concentration gradient.[62] However, the role of Na^+ for maintaining the endolymphatic potential cannot be ignored as the Na^+Cl^- ATP cotransporter in the marginal cells and in the fibrocytes of the spiral ligament ensures further potassium efflux and influx by coupling with the potassium.[63] The endocochlear potential results in a dynamic flux of ion transport in the cochlear endolymphatic space in the scala media. The stria vascularis has four cell types:[64] the marginal cells related to the medial scala media, responsible for maintaining a low potassium composition in the intrastrial space by continuous active uptake of the ion from the endolymphatic space; the intermediate cells, which have the marginal cells medially and the basal cells, laterally, are connected to the basal cells by gap junctions regulated by the connexin family genes and where the endocochlear potential is generated; and the basal cells, with the intermediate cells in their medial end and laterally connected to the spiral ligament in the lateral wall of the cochlea by gap junctions as well. potassium from the blood is actively taken up by the fibrocytes of the spiral ligament and pumped to the basal, cells which in turn deliver the ion to the interstitial cells. These cells present the ion to the intrastrial space from where they are taken up by the marginal cells. The scala media receives its ions from the marginal cells. All the active processes are regulated by various enzymatically driven potassium channels and Na–K ATP systems; the end result is maintenance of a high potassium ionic composition in the scala media which is vital for hair cell function by virtue of the endocochlear potential. Some potassium finds its way back by basolateral potassium channels in the perilymph.[65] The whole process is shown schematically in **Figure 48.18**.

Hyperacoustic stimulation depresses the potassium cycle for protecting the cochlea and actually leads to a drop in the endolymphatic potential[66] and stimulation of the P2X by the ATP pathway, which inhibits OHC motility (see below), while beta adrenergic stimulation as a part of sympathetic stimulation swings the cycle to the opposite side.[64]

Genetic mutations in the connexin family or the potassium transport family interfere with maintaining endocochlear potential and therefore sensory epithelia function. Examples include connexin 26/30 hearing loss, the commonest genetic autosomal non-syndromic prelingual genetic hearing loss, and Jervall–Lange–Nielsen syndrome with long QT interval where the *KCNQ1* ionic transport gene in the stria vascularis and cardiac conductive system is deficient.

Cochlear sensory epithelia and supporting cells

The mammalian cochlea is characterized by the presence of two distinct subtypes of sensory epithelia which differ in orientation, morphology and function. The OHCs number about 12 000 in humans; are arranged in three rows;

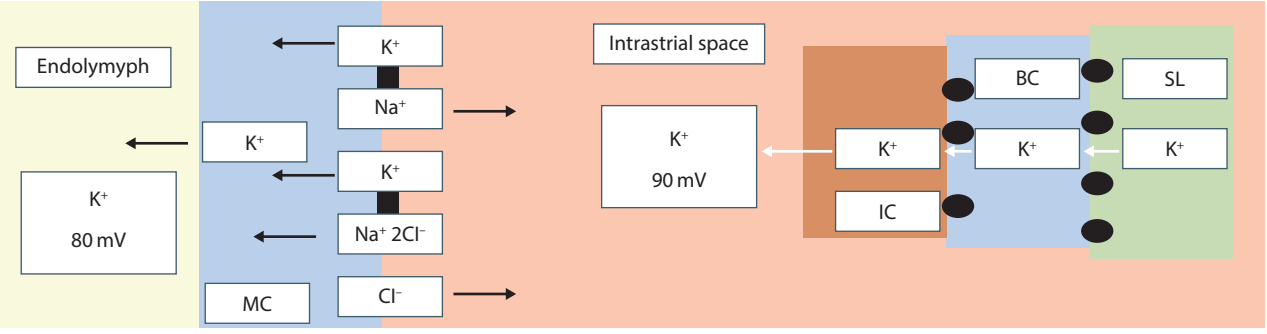


Figure 48.18 Endolymphatic fluid dynamics for generating the endocochlear potential. SL, spiral ligament; BC, basal cells; IC, interstitial cells; MC, marginal cells.

participate in electromotility leading to cochlear tuning, amplification, compression and frequency selectivity; and are innervated by type 2 spiral ganglion afferents and cochlear efferents from the medial olivocochlear bundle. IHCs are arranged in one row; number about 3500 in humans; participate in cochlear transduction of the incoming acoustic signal; largely generate the cochlear afferents to the spiral ganglion type 1 cells from where the auditory nerve commences and also receive efferents from the lateral olivocochlear bundle. Both these cells form the sensory epithelium in the organ of Corti with their apical or stereocilia side bathed in the endolymph of the scala media and their bases bathed in the perilymph of the scala tympani.

Undulations or mechanical vibrations from the BM lead to a shearing force in the tectorial membrane which in turn moves the stereocilia of the hair cells in the endolymph. Following this initial mechanical displacement, the behaviour of the OHCs and the IHCs differ and will be considered separately.

As will become apparent below, cochlear hair cell integrity depends on enzymatically driven functions to maintain structural stability. Thus mutations in the protein-encoding genes are likely to cause a sensory hearing loss.

THE OUTER HAIR CELLS

The OHCs are cylindrical with bundles of stereocilia composed of actin filaments which project at their apical ends in the scala media. BM-led tectorial membrane displacements in response to acoustic stimuli result in movement of these stereocilia in a plane parallel to their plane of orientation: depolarization when the movement is towards the tallest stereocilia and hyperpolarization/repolarization when the movement is towards the smallest stereocilia. Displacement opens up the cation-selective ionic gates responsible for transduction and generation of an action potential. A displacement of just 0.3 nm can displace the stereociliary bundle.

An action potential thus generated happens within 10 ms, which is a graded action potential (AP) mediated through the tip links between adjacent stereocilia which regulate ionic flow in this case potassium from the potassium-rich endolymph. The OHC itself is more negative than the endolymph, which facilitates movement of potassium without any energy expenditure, and it appears that, given the overall metabolic rate of the OHC with its specialized energy-expending function in modulating the acoustic signal, is nature's way of conserving energy. Potassium entry through the transduction channels then generates voltage-gated calcium channels and results in the influx of Ca^{2+} ions in the cells which participate in synaptic transmission and 10% of the depolarizing voltage.[67] The entry of potassium constitutes the depolarization stage. Repolarization occurs in two distinct processes: by the efflux of cell-rich potassium to the potassium-poor perilymph across the concentration gradient through the cation-selective ionic channels in the basolateral portion of the OHC, and by the influx of the Ca^{2+} mentioned above. There is a fine balance between the two and, if this balance is lost (i.e. if there are fundamental problems with either the potassium or the Ca^{2+} delivery or gated controls), then the cochlea OHC loses its tuning curve and therefore part of its function.[68]

The action potential is transmitted to the type 2 spiral ganglion cells, which are essentially non-myelinated and smaller than their IHC counterparts and not as developed. They show reciprocal synapses with their OHC counterpart, i.e. the type 2 cells feed back to the OHC providing a pathway for a closed loop neuronal circuit for bidirectional signalling and reverse transduction.[69] It should be noted that the action potential in the OHCs does not carry auditory information to the auditory nerve. Its job is to provide a motor for altering OHC physical dimensions for further displacement of the BM. The force contributed by this motor is sufficient to drive the acoustic signal through the entire length of the cochlea as an additional travelling wave as well as providing enhanced modulation at a local, site-specific area of the BM[70] (see also 'Cochlear travelling wave'). It also leads to movements of the tectorial membrane itself to open up further ionic gates and augment the AP and amplification process. Note that some type 2 cells are carried through the auditory nerve (only 5%) to synapse at the cochlear nucleus.

The OHC exhibits the special feature of electromotility, which is a highly sensitive attribute as cochlear motility translates frequency specificity and amplification and is responsible for fine-tuning of the acoustic signal. In response to acoustic stimulation of the BM, this motility is driven by two forces: a voltage-dependent mechanotransduction (MET – see last paragraph) that moves the hair bundle with an active movement[68] and a somatic non-linear capacitance prestin-mediated motility[71] which modulates the stiffness of the stereocilia and makes them alter their sizes. Prestin is a crucial component, abundantly located in the lateral membrane of the OHC, which belongs to the SLC26A family and participates in selective anion transport and binder, in this case chloride and carbonate. The action of prestin is voltage-dependent and results in either contraction or elongation of the OHC necessary for augmenting the acoustic signal incident on the BM. Cochlear electromotility is sensitive to frequencies and intensities of the signal.

The OHC in addition receives efferents from the medial olivocochlear bundle in the brainstem which synapse with the spiral ganglion type 2 nerves, offering a regulation of the reverse transduction process.

THE INNER HAIR CELLS

The IHCs are the true sensory end organs for hearing and are responsible for generating the action potential which then is conducted to the type 1 spiral ganglion cells to be delivered to the auditory nerve. The spiral ganglion type 1 nerve endings are myelinated and synapses here are well developed with ribbons and glutamate activity, unlike the OHC synapses.[72] The IHCs are non-actively motile and receive the output from the OHCs through the modified movement of the BM at a given region of the BM.

The IHCs are depolarized as a result of BM movements causing deflection of the stereocilia. The depolarization is mediated by cations potassium and Ca^{2+}, the latter being crucial for synaptic action through chemical neurotransmitters

especially glutamate.[73] The IHC synapses do not exhibit any reciprocal arrangement, unlike the OHC. Ca^{2+} release is mediated by voltage-dependent depolarization mediated by potassium of the IHC apical membrane, i.e. the stereociliary deflections.

Since it delivers the eventual output of cochlear function, the IHC needs to contain all the information amassed so far in the form of coding to the cochlear nerve. There are two types of coding, namely frequency coding and intensity coding.[74] The IHCs phase-lock with the stimulation frequency under 5 kHz while, above this frequency, the frequency-specific depolarization/repolarization is too fast for the IHCs to phase-lock. Intensity coding is by way of an increasing number/rate of action potentials proportional to stimulus intensity (see also 'The auditory nerve').

THE COCHLEAR SUPPORTING CELLS

Increasing evidence is emerging as to the important function served by the cochlear supporting cells (i.e. Hansen cells, Deiters cells, pillar cells, interphalangeal cells and border cells). In addition to providing a scaffold for anchoring the hair cells, these cells also participate in cochlear function and stability.

The supporting cells contribute to the development, differentiation, patterning and synaptogenesis of the hair cell sensory epithelia. From a common precursor, cellular differentiation and their mosaicism dictate variable cell line maturity and feed into each other by the process of autoregulation: if this enzyme-driven process is disrupted, then supporting cell populations might be converted to hair cells and vice versa.[75] Another important function of the supporting cells is that they contribute to the planar cell polarity (PCP) of the hair cells, which essentially is the stable plane of orientation of the basal and apical ends of the hair cells which expose them to the right environment for mechanotransduction. In fact, the supporting cells are abundant, with a PCP regulator which has been shown to regulate the orientation of the stereocilia.[76]

In the mature cochlea, the supporting cells provide the anchor and the platform for tight adherence of the sensory epithelia to the BM at the basal surface and form the reticular lamina at the apical surface where it separates the endolymph from the perilymph and helps maintain the endocochlear potential. They provide proteins for maintaining the extracellular matrix of the BM and thus maintain rigidity and stability of the hair cell population. They further contribute importantly to the homeostatic process by serving four functions:

- By virtue of being endowed with Na^+ gates, they take up Na^+ from the endolymph, ensuring a low concentration of the ion in the scala media.
- They assist in the potassium cycle, especially in the basolateral part of the BM.
- They influence glutamate activity at the hair cell synaptic regions.
- By virtue of their gap junctions (which are regulated by connexin 26), they are involved in the passage of ions and compounds either across the concentration gradient or actively by the ATP mechanism. This ATP-mediated energy-expending process also leads to Ca^{2+} coupling in the hair cells;[75] Deiters cells have an internal Ca^{2+} store which can be readily available in cases of need.[77]

Supporting cells may play a role in the eventual repair and regeneration of the hair cells in response to damage, as they are shown to do particularly in birds.[78] At the moment, mammalian hair cells show no evidence of regeneration although there might be low-level repair in vestibular hair cells.[79]

Curiously, there is nerve innervation of the supporting cells which implies that these cells can generate an action potential. These nerve endings do not synapse with the cochlear efferents or contribute to the formation of the cochlear nerve; they are considered to be a part of the internal neural circuitry which characterizes OHC afferents and participates in OHC non-linear fine-tuning of the acoustic signal through BM activity.[80]

Mutations in genes encoding for supporting cell proteins will lead to cochlear sensory loss. For example, in addition to maintaining gap junctions in the stria vascularis, connexin 26 is also expressed in the supporting cells and a mutation will lead to the loss of structure, stability and integrity of the hair cells through the supporting cell mechanism. *DFNB29*, a cause of autosomal recessive hearing loss, is characterized by a mutation in the gene containing claudin, which is a structural protein of the reticular lamina responsible for tight junctions. A loss of this tightness leads to increased potassium permeability from the scala media to the hair cells, resulting in a drop of the endocochlear potential and loss of function.[81]

Pathophysiology of cochlear hearing loss

Loss of cochlear function for any reason will result in a drop in auditory sensitivity; a drop in complex sound appreciation and analysis due to the loss of frequency selectivity; loss of fine-tuning of the acoustic signal with narrowing of the dynamic range of hearing due the loss of non-linearity, amplification and compressive properties; loss of perceptual streaming due to the loss of frequency selectivity; and loss of temporal pattern of sounds due to the loss of spatial discrimination and the ability of the cochlea to distinguish between closely following frequencies and intensities.

- **Structural abnormality:** A cochlear dysplasia of any kind leads to ill-formed or absent cochlear components. This can follow a congenital maldevelopment, trauma or a space-occupying lesion and will lead to a cochlear hearing loss.
- **Abnormal metabolic activity:** Since ionic transport dictates cochlear function, it follows that a metabolic abnormality (systemic or otherwise) that interferes with cochlear ionic transport as a result of either a genetic syndrome or an acquired condition (e.g. problems with glucose metabolism or thyroid metabolism) will lead to changes in the endolymphatic potential and affect cochlear function.

- **Vascular changes:** Cochlear vascular afflictions (either systemic or local) will lead to a compromise in stria vascularis function; a diminution in cochlear nutrition and hypoxia; sluggish vascular flow or complete obstruction of the cochlear arterial blood flow. Examples include pressure effects due to any cause, noise trauma and ototoxicity, transient ischaemic attacks (TIAs) and hyperviscosity for any reason. Endolymphatic hydrops, i.e. an expansion of the endolymphatic space for any reason including a lack of integrity of the stria vascularis (e.g. Ménière's disease or endolymphatic fluid disturbances such as third window syndromes) will lead to a compromise in function of the stria vascularis.
- **Overloading the BM:** A crowded or loaded BM due to local or systemic causes (e.g. a metabolic syndrome such as diabetes, hyperlipidemias, iron overload, inflammation or autoimmune conditions) will prevent OHC motility and IHC loss of transduction.
- **Infection and inflammation:** An inflammatory involvement in the cochlea leads to the disruption of the biochemical pathway of cochlear function (see below) and the accumulation of toxic lipid-derived substrates which hamper cochlear function.
- **Genetic mutations:** As indicated earlier, a genetic mutation in the genes encoding for numerous proteins involved in cochlear function, from ionic transport to structural proteins, will lead to a cochlear hearing loss. The different genes expressed in the cochlea are given in a seminal publication by Nishio et al.[82] The Hereditary Hearing Loss home page lists genetic hearing losses with phenotypes and genotypes and is updated continually.[83]
- **Biochemical pathway abnormalities:** In response to noise trauma, ototoxicity and due to cumulative wear and tear action in presbycusis, a biochemical cascade for cochlear hair cell integrity loses its balance leading to apoptosis and subsequent cell death. This cascade suggests that, theoretically at least, pharmacological intervention aimed at various steps in the cascade can reverse the process. Figure 48.19 illustrates this.

Otoprotective endogenous compounds play an important role in preserving the delicate cochlear structures and influence the biochemical cascade, although in a rather heterogeneous way. These include heat shock factors (HSFs) and heat shock proteins (HSPs), both abundantly expressed in the cochlea, which can modify the apoptosis response;[84]

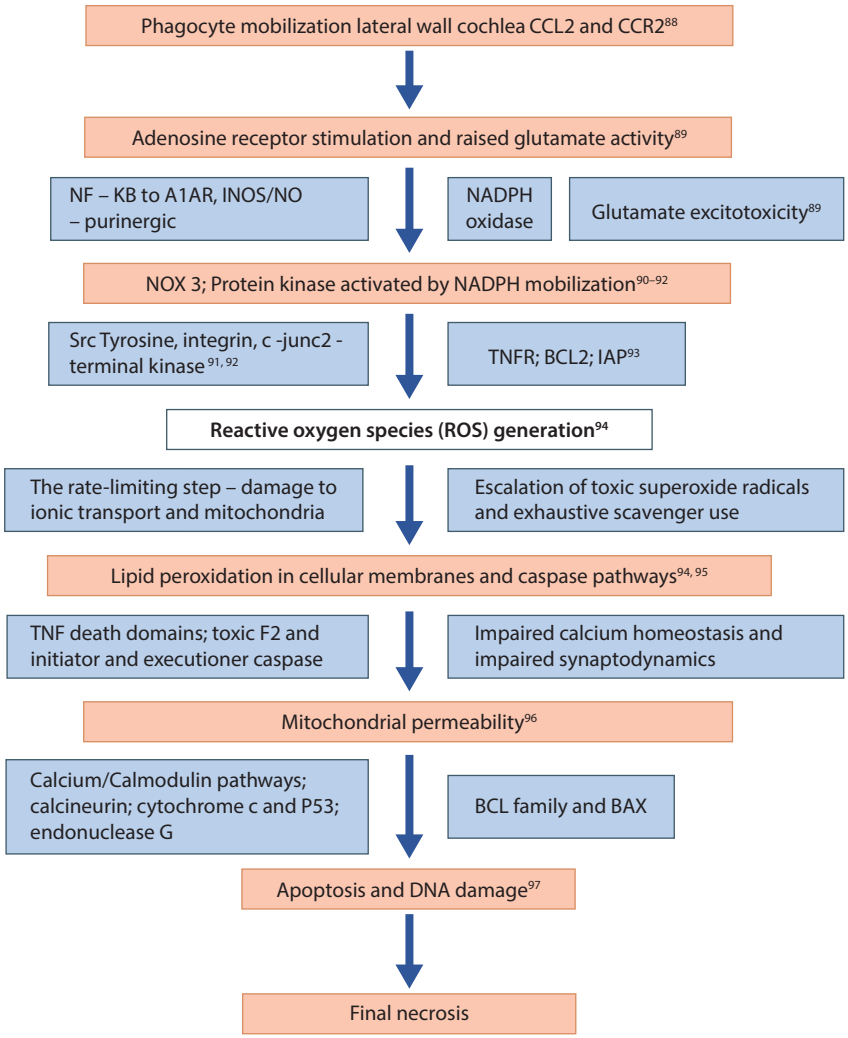


Figure 48.19 Biochemical pathway/enzymatic cascade for hair cell damage.

downregulation of some growth factors;[85] neurotrophin, mainly glial cell-derived neurotrophic factor (GDNF) regulation,[86] to modify the end result of apoptosis for recovery of function and the coenzymes Q9 and Q10.[87]

THE AUDITORY NERVE AND COCHLEAR EFFERENTS

The auditory nerve

The auditory or cochlear nerve, cranial nerve VIII, originates from the joining of the spiral ganglion cells in the cochlea where their cell bodies lie. There are two types of nerve fibres originating from the spiral ganglion cells: type 1, which have large diameters, innervate the IHCs constituting 95% of the nerve fibre population and are myelinated, and type 2 fibres, which are smaller diameter, innervate the OHCs and are unmyelinated. The nerve traverses the internal auditory canal and joins with the vestibular nerve forming the vestibulocochlear nerve. One type 1 fibre innervates one IHC but one IHC may synapse with several nerve fibres. The cochlear nerve fibres terminate at the cochlear nuclear complex located in the medulla of the brainstem.

The synaptic architecture of the hair cells and the spiral ganglions is discussed in detail in 'The cochlea' above. The cochlear nucleus synapses with the cochlear nerve and is represented tonotopically, which implies that frequency encoding by the cochlea is carried up to the central nervous system to be further analyzed.

The action potential of the cochlear nerve in response to acoustic stimulation entails a release of bundle synaptic receptors proportional to the stimulus, which results in spike potentials which are short-lived and attain their peaks quickly. The rates of the spikes vary depending on the intensity and the frequency of the incident sound. Each fibre fires most at a given frequency (called the characteristic frequency) like the spatially represented characteristic frequency in the cochlear BM which facilitates transfer of the tonotopicity to the nerve from the cochlea. For example, fibres from the base of the cochlea will lead to increased firing of the fibres with a high characteristic frequency.

The discharges of the fibres to low-frequency sounds occur at particular times, in other words, there is a phase-locking mechanism which occurs up to 5 kHz.[98] Phase-locking is important to convey temporal information of the incoming signal.[99] A two-tone suppression model is also present in auditory nerve function which dictates that a second stimulus close to the characteristic frequency of the first one will suppress the first, facilitating the representation of complex and multiple stimuli in the nerve which is a non-linear function.[100]

Intensity coding also occurs in the nerve fibres. Nerve fibres possess spontaneous firing activity without sound stimulation. Fibres with high spontaneous firing rates have a low threshold for intensity while fibres with intermediate and low spontaneous firing rates have a high threshold.[101] Stimulus intensity thus influences the firing rate of the nerve fibre: the higher the stimulus intensity, the higher the firing rate, with a saturation point where it plateaus off,[102] which is important for adaptation as explained below. Thus, the fibre codes for intensity as well.

The auditory nerve is the beginning of central processing of the acoustic stimulus delivered from the periphery. This is in the form of auditory nerve adaptation which entails a spike frequency adaptation where the spike in response to a stimulus quickly adapts and reaches a plateau that is more pronounced in high-frequency fibres than the lower ones.[103] Adaptation, which is found in neurons elsewhere, is crucial in the auditory context as it provides vital cues to the brain regarding timing of the signal. Adaptation gets progressively complex and sophisticated in the brainstem and the cortex.

The auditory nerve can be affected by a variety of disease processes which include pressure effects by space-occupying lesions such as a VS; the demyelination processes such as in multiple sclerosis; granulomatous lesions; head trauma; viral illnesses; congenital dysplasias and autoimmune disorders. Essentially, the tuning curve and the phase-locking properties are affected and lead to a failure in encoding time, frequency and intensity information. This is a classical neural deafness. ABRs are a robust way of measuring auditory nerve function and may be used for prognosticating a demyelinating lesion.[104]

The condition auditory neuropathy spectrum disorder (ANSD) deserves special mention. This is defined as a disorder with abnormal auditory brainstem morphology but preserved cochlear OHC function (although measured cochlear OHC function may disappear with time). Structurally, the nerve is unremarkable, especially on imaging, and most likely the damage is at the molecular level precipitated by a few known risk factors such as hypoxia, hyperbilirubinemia and prematurity. Neuropathies such as Charcot–Marie–Tooth and Mohr–Tranebjaerg syndromes or mitochondrial syndromes can cause ASND.[105] Metabolic conditions such as diabetes have a theoretical risk of causing it, especially those which are complicated.[106]

ANSD can be inherited as an autosomal recessive disease, now called *DFNB9* due to the mutation in the gene otoferlin, and presents with profound behavioural neural hearing loss.[107] A second autosomal recessive gene pejvakin has been identified as well which causes ANSD named as *DFNB59*.[108] This may respond to cochlear implants. Previously thought to be a condition involving only the auditory nerves after it has been formed, i.e. beyond the spiral ganglion level, it is now thought to extend to the IHC spiral ganglion synaptic junction and may include the IHC itself. It gets picked up by the newborn hearing screening programme but can affect adults also. The auditory sensitivity as measured by a pure-tone audiogram may be normal but the patient has significant processing problems or the sensitivity might be significantly decreased (e.g. up to severe hearing loss on the PTA). Aiding these patients is difficult as augmenting amplification at the cochlear level may not lead to any benefit in the nerve dysfunction, although it may improve some phase-locking; in addition, providing excessive amplification to a normal cochlea may

be damaging to the cochlea itself. The effect of implantation is also variable; however, theoretically, patients whose condition is limited to the inner ear (the IHCs or the IHC–spiral ganglion synaptic junction) have a better outcome than patients with the problem once the nerve is already formed.

Cochlear efferents

The cochlear efferent system consists of projections from both the lateral olive and the medial olivary complex which synapse mostly with type 1 spiral ganglion cells and type 2 spiral ganglion cells respectively and thus connect to both the IHCs and the OHCs.[109] The efferent fibres are carried by the inferior vestibular nerve and meet at the anastomosis of Oort through the saccular branch of the nerve to join up with the cochlear nerve.[110]

The ratio of efferent to afferent fibres in the OHC is 1:2 whereas those in the IHCs is 1:7,[111] suggesting that the biological amplifiers are the main substrates of efferent function which in turn inherently implies that the signal modulation is primarily a function of the OHC. The medial system innervates both ears while the lateral system supplies only the ipsilateral cochlea. Both project to the different parts of the ventral cochlear nucleus.

The cochlear efferents serve an important function by virtue of their modulation of inhibitory and excitatory neurotransmitter release in the cochlear processes thereby offering cochlear protection from loud noise. The activation of the efferent system modifies frequency-specific gain at the tonotopic BM by acting on the voltage-dependent OHC motility and attempts to linearize the signal with a damping effect.[109] Other functions include fine perception of the acoustic signal for localization, improving the signal-to-noise ratio and supporting adaptation and frequency selectivity. Their function may be compromised in acoustic trauma, ototoxicity, tinnitus and ANSD.[109] The medial olivocochlear bundle function can be measured by contralateral suppression of otoacoustic emissions.

KEY POINTS

- The pinna and EAC participate in localization of sound and, acting as a unit, contribute to add resonance to the incident sound which in turn aids in matching impedance encountered when sound travels from an air-filled medium in the middle ear to a fluid-filled medium in the cochlea.
- The middle ear by its mechanical processes contributes to match the impedance as described above.
- The cochlea receives the oncoming acoustic signal from the middle ear and a cochlear travelling wave is generated which traverses the BM of the cochlea stimulating cochlear OHC function which acts non-linearly as a biological amplifier/compressor and modifies the incident signal.
- The BM of the cochlea is highly frequency specific.
- The IHCs in the cochlea transduce the mechanical or kinetic energy of the OHC influenced cochlear travelling wave to an electric action potential and synapse at the spiral ganglion to form the auditory or cochlear nerve.
- The cochlea participates in frequency resolution, intensity discrimination and temporal ordering of incident sound.
- The auditory nerve phase locks and synchronizes with the IHCs and processing of sounds commence.
- The cochlear efferents originate from the brain to synapse with the cochlear hair cells regulating their function and help in localization and improving signal-noise ratio.

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CHAPTER 49

PHYSIOLOGY OF EQUILIBRIUM

Floris L. Wuyts, Leen K. Maes and An Boudewyns

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SEARCH STRATEGY

Data in this chapter may be updated a PubMed search using the keywords: vestibular system, vestibulo-ocular reflex (VOR), central pathways of VOR, hair cells and mechanoelectrical transduction.

ROLE OF THE VESTIBULAR SYSTEM

Introduction

Many physiological systems and functions have to be interpreted in view of survival of the species. The main function of the mammalian vestibular system is to generate information to the central nervous system with a fourfold purpose:

1. to ensure gaze stabilization
2. to enable balanced locomotion and body position
3. to provide general orientation of the body with respect to gravity
4. to readjust autonomic functions after body reorientation.

To achieve this, several input systems provide information to the brain, such as visual, vestibular and proprioceptive systems (**Figure 49.1**), but also other clues such as hearing are used, although these are of lesser importance.

Central processing of all this information in the brain leads to distinct outcomes:

- the vestibulo-ocular reflex (VOR) to ensure gaze stabilization
- the vestibulospinal (VSR) and vestibulocollic reflexes (VCR) to ensure maintenance of upright position of body and trunk and head stabilization in space
- orientation and, in higher species, navigation and the perception of self-position with respect to the surroundings and gravity mediated by the vestibular cortex
- autonomic function adjustments after alterations of body orientation.

This list of outcomes is certainly not restricted to these four tasks, since, for example, the vestibular system has recently been shown to influence the circadian rhythm,[1] and there are also connections with cognitive function.[2] Circadian influence is most likely due to direct projection of the vestibular nuclei to the Suprachiasmatic Nucleus (SCN). Hormonal connections are to be studied.

Although visual, vestibular and proprioceptive inputs are constantly processed by the brain, this information is heavily weighted by other factors, such as learning, memory, drugs, ageing, as well as environmental conditions. Additionally, the weight of the different inputs is constantly adjusted depending on the circumstances. It is obvious, for example, that when walking in darkness, balance cannot rely so heavily on vision and so reliance on the somatosensory and vestibular senses is increased. For optimal functioning in daily life, all systems are needed and there is little redundancy in the systems.

Motion decomposition and orientation in the head

Every motion in space can be broken down into three rotational degrees of freedom (yaw, pitch and roll) and three translational degrees of freedom (left–right, up–down, fore–aft). No event in one degree of freedom can

be described by the others, hence every movement is uniquely and appropriately described by a combination of all six degrees of freedom. The anatomical design of the motion sensors in the peripheral vestibular system in the inner ear reflects these six degrees of freedom. The semicircular canals (SCCs) measure predominantly rotations whereas the maculae of the utricle and saccule detect mainly translations.

The orientation of the vestibular system in the head is depicted in Figure 49.2. In a first approximation, one can model the left and right canals as parallel systems, i.e. the right anterior (RA) canal is parallel with the left posterior (LP) canal and both lie in a plane denoted as the RALP plane. Together with the right posterior (RP) canal the left anterior (LA) constitutes the LARP plane. Both horizontal canals are also parallel with each other in the lateral plane. The horizontal canal makes an angle of approximately 30° up with the horizontal axis of the upright head. The angles of the vertical canal are approximately 45° with the sagittal plane of the head. When studied in more detail, however, there exists a great variability of orientation within and between subjects.[3] In addition, the canals themselves are often quite curved, as seen in Figure 49.3.

Movement detection

Basic laws of physics are responsible for the detection of movement or orientation by the vestibular system. The first law of Newton states that 'objects in motion will stay in motion until acted upon by a force'. This force can change either the object's direction or speed. The second law states that a force (F) acting on an object equals mass (m) times acceleration (a) ($F = m \times a$). During daily life, body and head are continuously moving (even during each heartbeat, the head and body are shaking a little), and these movements are always related to forces, i.e. accelerations. These movements are sensed in the vestibular organ by a rigid coupling of sensory epithelium to the bony structure. Thus, a fluid-filled system is attached to the skull and the inertial forces drive the fluid. Motion of the fluid lags behind any motion of the head and this relative displacement is the trigger for movement detection. To limit the movement of the hair cells triggered by the accelerations that drive the head movements, the canal system is designed such that the deflection of the hair cells is proportional to the head velocity.

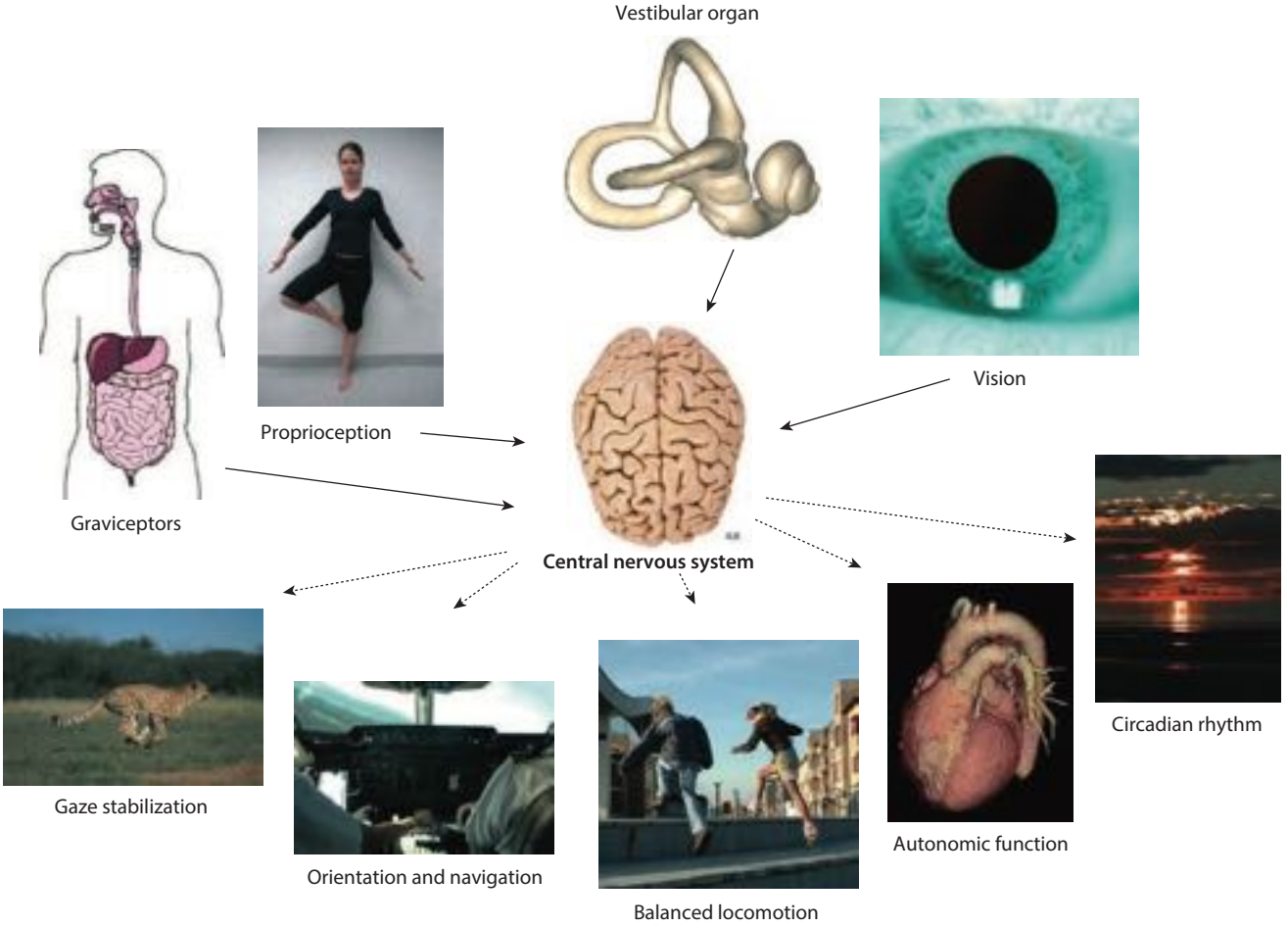


Figure 49.1 Basic input and output scheme of the vestibular system. Main inputs constitute vision, proprioception and information from graviceptors in the body and from the labyrinths. Outputs are gaze stabilization (needed for hunting and food tracking), balanced locomotion, perception of orientation in the surrounding world and autonomic function regulation after altered body position.

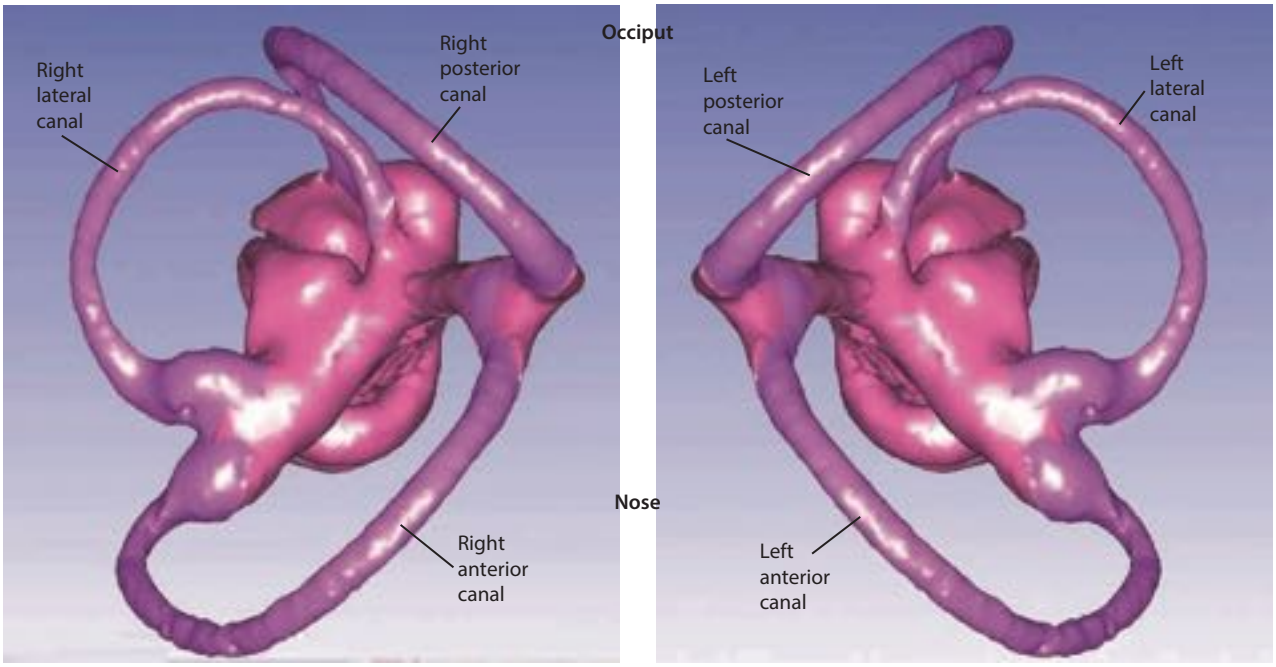


Figure 49.2 Top view of labyrinths as oriented in the human head. The labyrinths are of a gerbil.

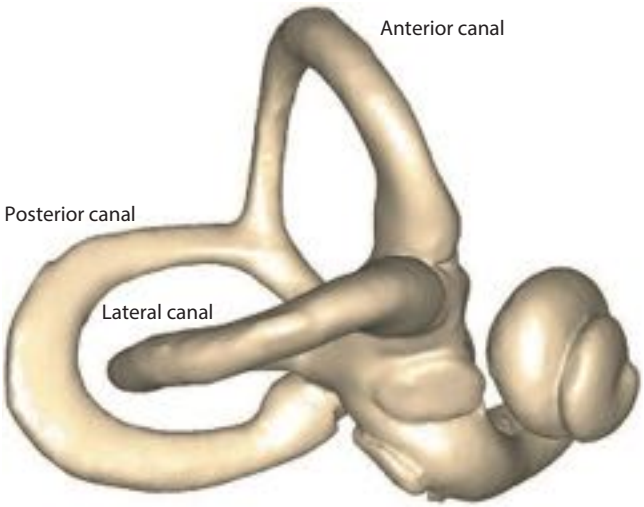


Figure 49.3 Side view of a right human labyrinth (labyrinth filled with resin and bone cut away). The nose is on the right side. The lateral canal makes, in general, an angle of 30° with the horizontal axis of the head.

OTOLITH ORGANS

On Earth, the gravitational force acts on us permanently, hence gravitational acceleration needs to be detected continuously. This is the role of the otolith organs. They additionally detect all linear accelerations. The otolith organs are designed such that they detect the accelerations and send encoded signals to the brain that processes this information. The otolith organs saccule and utricle are relatively orthogonally oriented to each other, with the utricle relatively horizontal and the saccule predominantly vertical (tangential in the head). Consequently, motion in the horizontal plane triggers predominantly the utricle, and vertical movements trigger mainly the saccule. Both organs are, however, quite curved so that any movement is in fact detected by both organs.

Thus, both the saccule and the utricle sense linear accelerations caused by translational movements of the head as well as static tilts of the head. This is enabled by an otolithic membrane, a gelatinous membrane stacked with otoconia (calcium carbonate crystals) characterized by a density about three times higher than that of the surrounding endolymph. Hair cells are embedded at the base of the gelatinous membrane, so that any movement of the membrane results in a deflection of the hair cells, which in turn codes for a signal to the brain. The working of the hair cell is explained under 'Vestibular sensory cells' below.

Einstein's equivalence principle states that no single physical device can distinguish gravity from linear acceleration. This poses a difficulty for the central nervous system, since the otoliths cannot differentiate between linear acceleration and tilt since only the deflection at the base of the hair cells is encoded and sent to the brain. This is illustrated in Figure 49.4. During natural movements (active or passive), the otolith organs sense the sum of all accelerations acting on the head and interpret these signals to initiate postural and eye reflexes mediated by the vestibular nuclei, diverting the appropriate signals either to limb, trunk and neck muscles via the vestibulospinal tract or to eye muscles via the VOR. The interplay of several senses at the same time (visual, vestibular and proprioceptive) enables the central nervous system to cope with the ambiguity of linear accelerations, enabling humans to distinguish tilt from linear translation under normal conditions. In darkness, however, when the system is relying on vestibular cues, Angelaki et al.[4] have shown evidence that an internal model of head orientation exists. This model is presumably constructed in the vestibulocerebellum

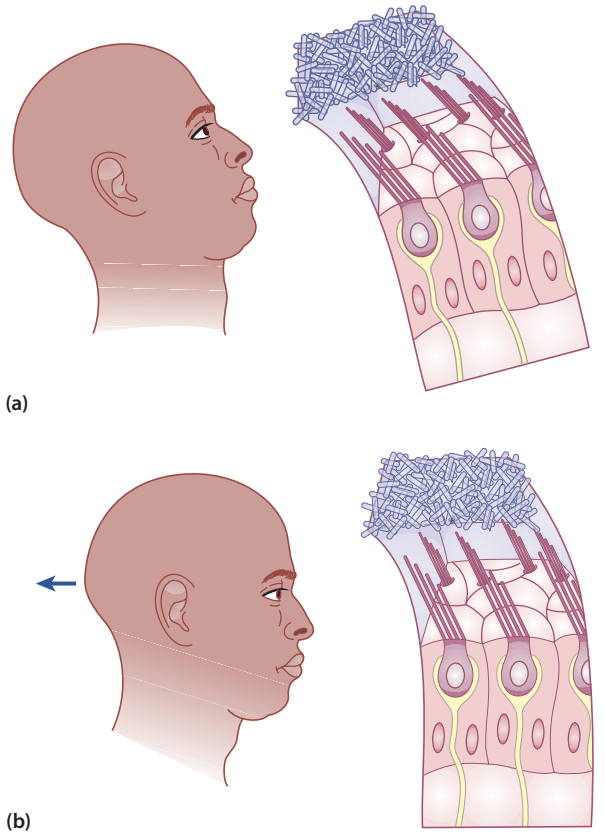


Figure 49.4 Deflection of the otoconial mass causes hair cell depolarization. This deflection is identical when the head is tilted backward **(a)** or when accelerating forward **(b)**.

(floculus and nodulus) and the vestibular nuclei, and it resolves the ambiguous gravitoinertial cues that are measured by the graviceptors, as well as with input from the SCCs. Both sets of information are used to help interpret ambiguous gravitoinertial cues. This implies that the signals from the otoliths and from the canals are not treated separately in the brain, and are continuously combined to optimize the VOR, as can be deduced from the fact that almost all partitions of the vestibular end organs overlap in most of the vestibular nuclei and project to several parts of the vestibulocerebellum.

SEMICIRCULAR CANALS

The moving endolymph in the SCCs is the key trigger for movement detection of the head. Natural movements of mammals consist dominantly of transient rotations, such as during back and forth movements of the head (e.g. nodding), or during walking and running. The SCC system is evolutionarily adapted for these movements. Whereas head accelerations trigger the sensory epithelium, the signal that is transmitted to the brain is proportional with the head velocity. Head accelerations can raise up to several thousands of degrees per second square, while head velocity is limited to several hundreds of degrees per second. Sustained velocity is no longer detected nor perceived after approximately 30 seconds.

Passive forms of motion, such as aeroplanes, merry-go-rounds, cars, rollercoasters or even spaceships, however, generate more intricate movements, and can readily introduce motion sickness since the vestibular apparatus is not adapted to this kind of motion.

The configuration of the SCC allows the movement of the endolymph only in the direction along the cylindrical canalicular cavity. When such a canal is rotated about an axis, three forces act upon the endolymph and cupula in the canal:

- the inertial force, proportional to the mass of the endolymph and cupula
- the elastic restoring force of the cupula that positions the cupula back to the centre position after stimulation
- the viscous forces that act upon the fluid when sliding past the internal wall of the tube. This viscous force is dependent on the speed of relative movement of the endolymph with respect to the wall.

The behaviour of the SCC, referred to as the pendulum model, is governed by the fact that any stimulus (head angular acceleration) provokes a number of reactions within the canal. These include movement of the fluid, determined by its inertial mass, together with its viscous drag along the wall and the restoring force pulling the cupula back to its resting position.

The cupular deflection can be described as a function of the applied stimulus to the head, purely based on physical laws, even without any interference of the central nervous system. The cupular deflection is ultimately the signal that is fed to the brain, because this deflection triggers hair cell depolarization or hyperpolarization. Therefore, it is important to know the specific behaviour of this endolymph–cupular system upon stimulation. Engineers typically approach this kind of system as a transfer function where a given input leads to a specific output. Gain and phase are two quantities that describe very appropriately the behaviour of such a system. Gain expresses the amount of output per input, and phase describes the time difference between output and input.

Given the very small size of the canal ($r \approx 0.15$ mm,[5] the inertial forces that act on the endolymph become very small with respect to the viscous forces that act upon the fluid. Although it is a quite watery substance, endolymph acts as a thick, viscous oil in the small dimensions of the canal. So, rather than being left behind due to its inertia, this fluid is dragged along the walls of the canal, and the relative displacement of the fluid with respect to the wall is of the order of a few microns for very fast head movements. Consequently, the viscous flow 'velocity' of the endolymph becomes proportional to the head's angular 'acceleration'. However, if this holds true for a system, then the flow displacement also becomes proportional to head velocity (after mathematically integrating for time). This is a very important finding, which implies that the message that is sent to the brain, initiated by a deflected cupula which is directly related to the fluid movement, is coding for the head angular velocity (and not its angular acceleration).

The time constant T1, determined by the viscosity and the mass of inertia of the endolymph yields approximately 0.003 s. This means that, when a sudden angular velocity is applied to the head, the cupula reaches 67%, i.e. $(1-e^{-1})$, of its ultimate deflection after just 3 ms. Translated to actual movements, this means that the cupula is deflected almost instantaneously upon movement of the head, signalling the amount of deflection to the brain, which is proportional to the head angular velocity. The design of the SCC enables it to function as an integrator, i.e. inertial force-driven acceleration is reduced to velocity. In normal conditions the head angular accelerations can be very high (in the range of 4–5000 degrees/s^2)[6] so that the time integrator from acceleration to speed limits the deflection of the cupula and presumably prevents it from large excursions that may damage the sensory epithelium.

Many dynamic systems are frequency dependent and yield functionally different kinds of information according to the frequency content of the input stimulus. The frequency region is determined by cut-off frequencies, denoted often by 1/T1 and 1/T2, with T1 and T2 being time constants of the system. Between these frequencies, 0.1–5 Hz, the canal–cupula system is characterized by an appropriate response in amplitude and phase. A gain equal to 1 implies that the output (cupular deflection) matches closely the input (head angular velocity). A phase close to zero indicates an instantaneous reaction. A bode plot (**Figure 49.5**) illustrates this behaviour.

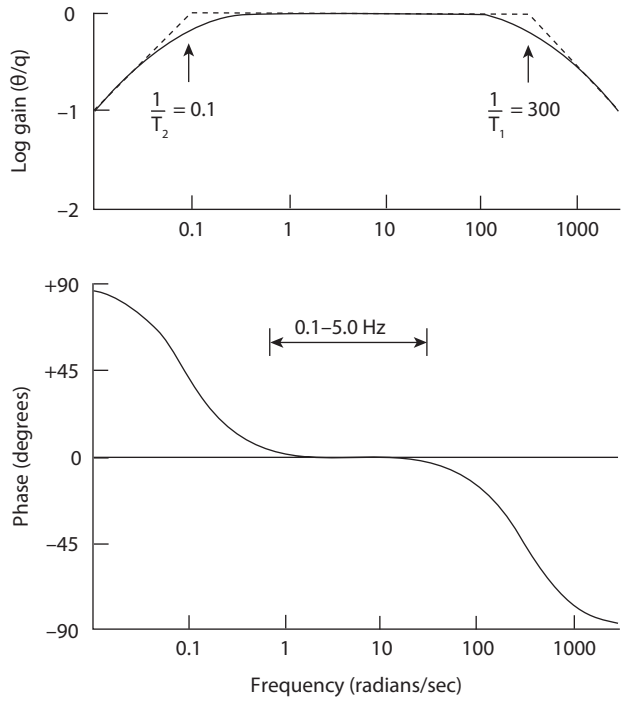


Figure 49.5 Bode plot representing the response of the SCC sinusoidal rotations. The optimal response consists of immediate and appropriate deflection of the cupula what is transmitted to the brain. This optimal situation is characterized by a gain of 1 (log gain = 0) and a phase of zero degrees. Between 0.1 Hz and 5 Hz, this optimal behaviour of the endolymph-filled SCC is achieved in humans, enabling gaze stabilization for these frequencies.

Below or above the frequencies 1/T2 and 1/T1, the gain is reduced and the phase lag is increased. For humans the typical frequencies of natural head movements during walking and running for yaw, pitch and roll are approximately between 0.5 Hz and 5 Hz.[7] Recent work by MacDougall and Moore[8] proves that the 'human resonant frequency for locomotion' is 2.00 Hz ± 0.03 Hz (mean ± s.e.) for vertical head movement, regardless of the activity (e.g. walking, riding a bike uphill, cleaning).

Velocity storage

The above description modelling the deflection angle of the cupula largely explains the behaviour of the vestibular system during laboratory testing, achieved with rotatory chairs. Typical stimulation patterns exist of sinusoidal rotations, usually around 0.05–0.1 Hz, although with more sophisticated equipment higher rotations up to 1 Hz can be achieved. Characteristic for sinusoidal rotations is that the angular velocity and acceleration are varied with sine and cosine functions, respectively. Also used are velocity step tests where a sudden acceleration rotates the subject at a constant velocity and then, after a plateau of constant speed, the chair is suddenly stopped (a ramp test). A variation of this is the test where the speed is gradually increased by applying a constant yet slow acceleration (e.g. 5 degrees/s^2) for 40 seconds to reach a speed of 200 degrees/s, followed by a plateau during which the nystagmus fades away, and then suddenly the chair is stopped.

The SCC system is not designed for sustained rotations, and even rotating at relatively high but constant speeds (> 200 degrees/s) is not sensed by the SCC after approximately 30 seconds. Only the acceleration or deceleration phase is detected. During constant speed rotations, elastic forces pull the cupula again into its centre position. However, after sudden cessation of the rotation (e.g. with a deceleration of 400 degrees/s^2), the endolymph continues to move within the SCC and a nystagmus in the opposite direction becomes evident for another 20–30 seconds. The subject has the impression of being spun around in the opposite direction. After a longer time the nystagmus fades away and may reappear again in the initial direction (post-rotatory nystagmus). Based on mathematical principles and physiological measurements, the time constant during which the cupula repositions itself is determined as approximately 5–7 seconds, which implies that the cupula is almost entirely restored to its central position after 12 seconds. This gradual decrease in cupular deviation results in a decrease in firing rate of the vestibular neurons to the brain, suggesting erroneously a progressively lower head velocity. The fact that the nystagmus outlasts this mechanical phenomenon is due to the so-called 'velocity storage mechanism' (VSM)[9] which is a neurophysiological process, taking place mainly in the nucleus prepositus hypoglossus and the adjacent medial vestibular nucleus. The VSM serves to maintain the VOR at low frequencies (below about 0.02 Hz). The VSM uses principally the peripheral labyrinthine signal and by a process of integration, in the mathematical sense, increases the frequency

response of the VOR, by prolonging the time constant (originally 7 seconds) of the decay of the vestibular nystagmus to approximately 20 seconds. This circuitry is therefore a mechanism that stores neural activity related to head and eye velocity and discharges it over its own time course.

In conditions where visual information of the surrounding rotating world is present during sustained rotations, the optokinetic reflex comes into play and, although slower in response, this takes over the fading performance of the vestibular system. The transition between both reflexes is facilitated by the VSM. Indeed, the VSM not only regulates the dynamics of the VOR but also accounts for optokinetic (after) nystagmus (OKN), i.e. the reflexive eye movements that are induced by a moving background (e.g. while looking outside the window of a moving train). The VSM coordinates these two oculomotor responses that are related to self-motion. Whereas the VOR shows high-frequency behaviour, the OKN reflects low-frequency characteristics. Matching of their time constants in the brain assures smooth transition from the quick-onset vestibular response into the slow-onset optokinetic response. Together, the VOR initially and the OKN subsequently, matched and fine-tuned by the VSM, ensure gaze stabilization.

Interestingly, the time constant of velocity storage is influenced by static inputs from the otoliths. It can be reduced considerably when the head is suddenly tilted (tilt dumping) just after the velocity step, and it is shorter during off-vertical axis rotations.[10–11]

Vestibulo-ocular reflex

The peripheral sensors transmit motion to the brain through frequency encoding. Similar to FM radios, the brain continually receives 'frequency-modulated' signals. A normal resting discharge rate of approximately 90 spikes per second (recorded in the squirrel monkey vestibular nerve)[12] is modulated such that increase of this rate corresponds with an excitation and decrease with inhibition.

The left and right SCCs are oriented in the head such that any movement always induces an antagonistic response in both canals. For example, consider horizontal head movements occurring in the yaw plane. During rightward head rotation, the endolymph in the lateral SCCs on both sides lags behind, bending the cupula of the right SCC towards the vestibulum (ampullo- or utriculopetal) whereas simultaneously the cupula of the left SCC is deflected away from the vestibulum (ampullo- or utriculofugal). A key difference is the polarization of the hair cells. Indeed, since the implantation of the hair cells is opposite for both right and left canals as a mirror image, the deflection on the 'leading' right side induces a movement of the stereocilia towards the kinocilium, whereas on the opposite 'following' ear the movement of the stereocilia is away from the kinocilium. Consequently, the activity of right lateral SCC primary afferent neurons increases, while at the same time the activity of left lateral SCC primary neurons decreases with respect to the normal resting discharge rate. This is called the push–pull principle of the VOR.

The right medial vestibular nucleus in the brainstem receives an increased input from the right lateral SCC primary neurons (no crossing), which excites the activity of type 1 position vestibular pause (PVP) secondary vestibular neurons. These excitatory neurons drive the leftward compensatory eye movements of the VOR, to ensure gaze stabilization. However, commissural disinhibition from the left lateral SCC primary neurons also contributes to the excitation of the PVP neurons. Therefore, both the excitation of the right SCC and the disinhibition of the left SCC are needed for an optimal VOR. In first approximation, the VOR process is a three-arc neuron reflex (first-order vestibular neurons, second-order vestibular neurons and oculomotor plant neurons) as depicted in **Figure 49.6**.

The simplified principle of VOR generation (yaw-plane rotation and horizontal SCC) is as follows:

1. During head rest, hair cells in both SCCs have a resting discharge rate of 90 spikes per second.
2. Head rotation is to the right.
3. Endolymph fluid lags behind, i.e. moves relative to the left within each SCC due to inertia.
4. The cupula bends to the left in each canal.
5. In the (leading) right SCC the stereocilia bend towards the kinocilium.
6. In the (following) left SCC the stereocilia bend away from the kinocilium.
7. The discharge rate increases in the leading right ear (e.g. from 90 to 300 spikes per second).
8. The discharge rate decreases in the following left ear (e.g. from 90 to 20 spikes per second).
9. The vestibular nuclei interpret the difference in discharge rates between left and right SCCs as movement to the right, and therefore trigger the oculomotor nuclei to drive the eyes to the left to maintain gaze stabilization.

Similar to the horizontal canal, a push–pull principle also governs the vertical canal excitatory and inhibitory functions. For example, the left anterior canal is excited while the right posterior canal is inhibited for the same movement. Also, the vertical canals are direction-sensitive, but at this stage ampullopetal movement results in a decreased firing rate. Thus, the ampullar deflection in the vertical canals, corresponding to excitation, is in the opposite direction to the horizontal SCC. For the horizontal canal, excitation is elicited upon ampullopetal endolymph movement (towards the vestibulum–utricle) whereas for both the vertical posterior and anterior SCC ampullopetal flow is inhibitory.

The horizontal canal is involved in pitch movements to only a small extent. The inclination of the vertical canals is more than 90° to the horizontal so that horizontal movements are always detected also by the vertical canals. However, given the antagonistic response of the anterior and posterior SCC on each side, horizontal head movements produce primarily horizontal eye movements.

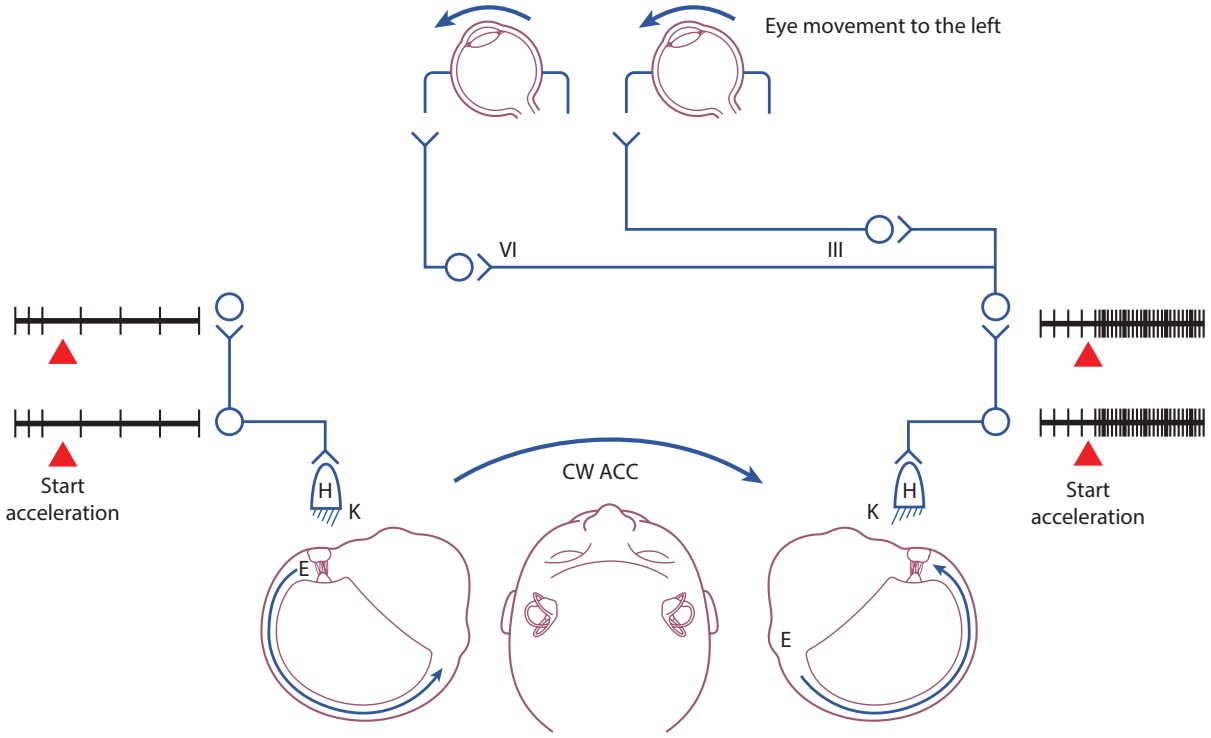


Figure 49.6 Three-arc neuron representation of the VOR. Upon head rotation to the right (CW ACC, clockwise acceleration), the hair cells on the 'leading ear' side are excited and increase their discharge rate, whereas the hair cells on the following ear are inhibited, thereby decreasing the discharge rate. The vestibular nuclei encode the increased discharge rate and redirect the excitation to the ipsilateral ocumolotor nuclei to contract the medial rectus of the right eye, while the contralateral abducens nucleus is triggered generating a contraction of the contralateral lateral rectus. Consequently, the eyes are driven to the left to compensate for the head movement to the right. This is the essence of the VOR. However, only the excitatory pathway is represented here; the actual VOR is much more complex. (E, endolymph; H, hair cell; K, kinocilium; III, oculomotor nucleus; VI, abducens nucleus)

The SCCs and the otolith organs provide the inputs for the VOR. Horizontal VOR compensates for both horizontal rotation and horizontal translation. The former is due to the canal system where the latter due to the utricular system. It is therefore more convenient to use the angular VOR (aVOR) and linear VOR (lVOR). A third type of VOR, the ocular counter-rolling, is provided by the otoliths as a response to, for example, tilting of the head with respect to gravity or a stimulus that results in a shift of the gravito-inertial acceleration (the sum of an acceleration in any direction and gravity).

There are three types of rotationally induced eye movements: horizontal, vertical and torsional. Each of the six pairs of eye muscles must be controlled to produce the desired response. The vertical SCCs and the saccule are responsible for controlling vertical eye movements, whereas the horizontal canals and the utricle control horizontal eye movements. Torsional eye movements are controlled by the vertical SCCs and the utricle.

Stimulation of a single canal results in eye movements that lie in the plane of the canals. To understand the generation of the different eye movements, it is necessary to analyze the stimulation of individual canals and their effect on the eye muscles. Table 49.1 gives an overview of the active and passive eye muscles for each stimulated canal.

TABLE 49.1 Schematic canal stimulation and concomitant eye muscle contraction and relaxation

Canal stimulation	Contracted eye muscle	Relaxed eye muscle
Lateral SCC	Ipsimedial rectus	Ipsilateral rectus
	Contralateral rectus	Contramedial rectus
Anterior SCC	Ipsisuperior rectus	Ipsi-inferior rectus
	Contrainferior oblique	Contrasuperior oblique
Posterior SCC	Ipsisuperior oblique	Ipsi-inferior oblique
	Contrainferior rectus	Contrasuperior rectus

Figures 49.7 to 49.11 represent the effects of single or multiple canal stimulation on the eye muscles and consequently which type of compensatory eye movement is generated.

Figure 49.7 and Figure 49.8 illustrate the stimulation of the anterior and posterior canals. Every stimulation in whichever direction always evokes the push–pull principle. When the head is tilted sidewards (Figure 49.9), a torsional nystagmus is generated, as both posterior and anterior canals are stimulated. When the head is pitched forward (Figure 49.10), both left and right anterior canals are

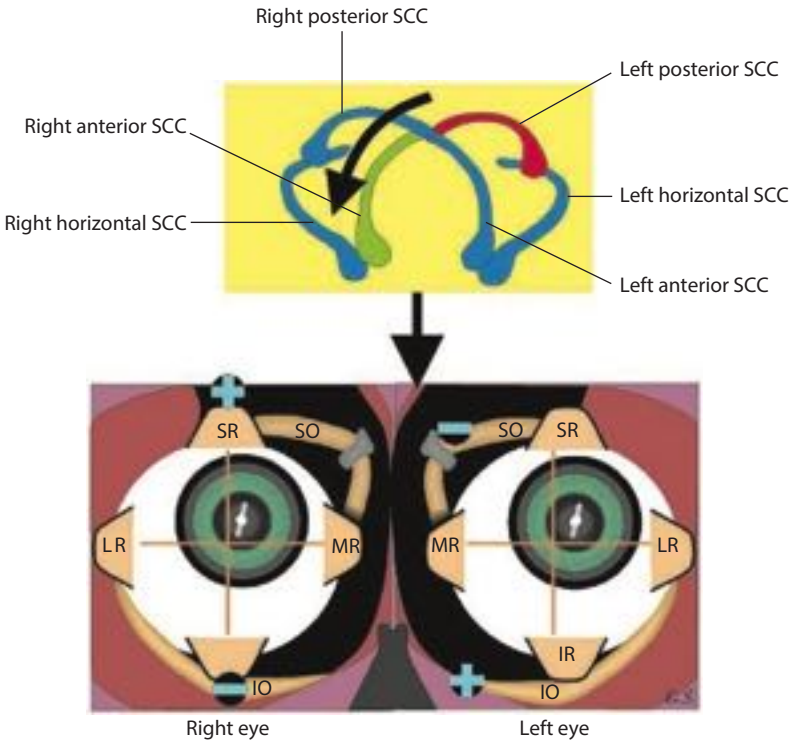


Figure 49.7 Stimulation of the right anterior SCC while the left posterior canal is inhibited occurs during a head movement in the right anterior—left posterior (RALP) SCC plane, i.e. turn the head 45° to the right and move the head downward in that plane. This generates a counterclockwise movement of the eyes (seen from the examiner's view), together with an elevation. The right superior rectus (SR) muscle and the left inferior oblique (IO) muscle are contracted. The right inferior rectus (IR) muscle and the left superior (SO) muscle are inhibited. +, excitation; -, inhibition; LR, lateral rectus muscle; MR, medial rectus muscle. The black arrows show the direction of movement of the head.

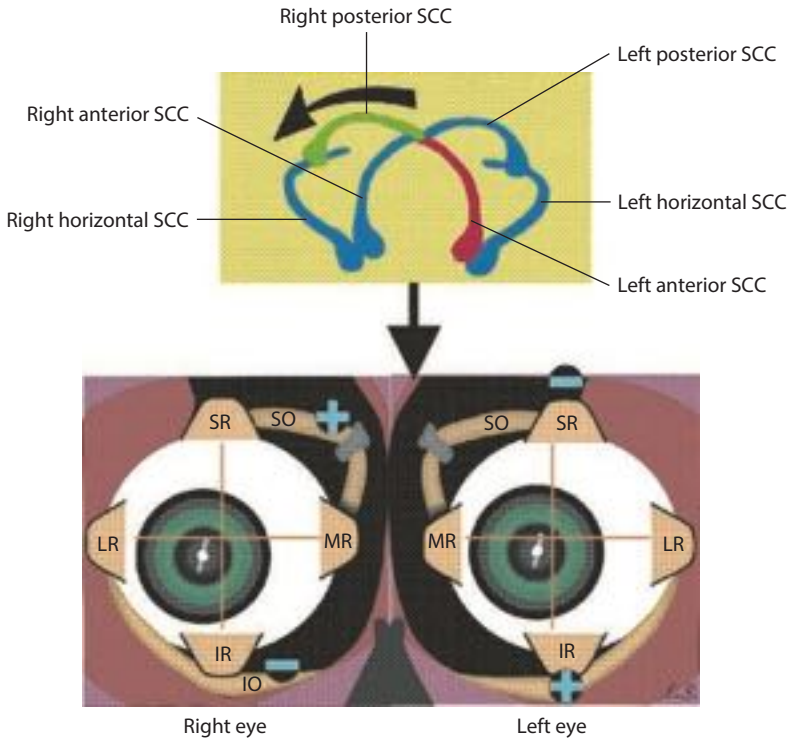


Figure 49.8 Stimulation of the right posterior SCC while the left anterior canal is inhibited occurs during a head movement in the left anterior–right posterior (LARP) SCC plane, i.e. turn the head 45° to the left and move the head upward in that plane. This generates a counterclockwise movement of the eyes (seen from the examiner's view), together with a depression of the eye. The right superior oblique (SO) muscle and left inferior rectus (IR) muscle are contracting, while the right inferior oblique (IO) muscle and the left superior rectus (SR) muscle are relaxing. +, excitation; -, inhibition; LR, lateral rectus muscle; MR, medial rectus muscle. The black arrows show the direction of movement of the head.

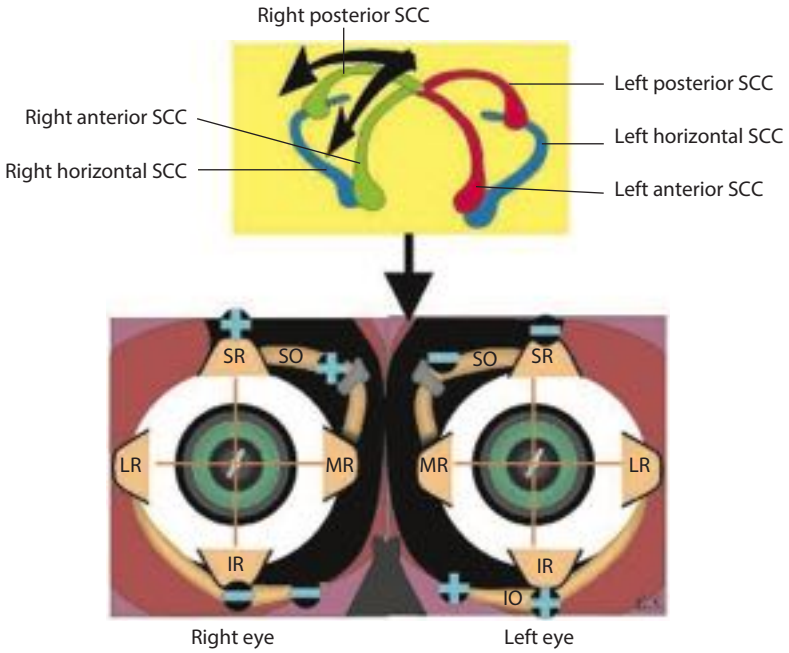


Figure 49.9 Stimulation of the right posterior and right anterior SCCs while the left anterior and left posterior canals are inhibited occurs during a rightward sideways tilting of the head towards the shoulder. This generates a counterclockwise movement of the eyes (seen from the examiner's view). The right superior rectus (SR) muscle and superior oblique (SO) muscle, as well as the left inferior oblique (IO) muscle and inferior rectus (SR) muscle, are contracting while the right inferior rectus (IR) muscle and inferior oblique (IO) muscle and the left superior rectus (SR) muscle and superior oblique (SO) muscle are relaxing. The elevation and depression cancel out and a pure counterclockwise torsional nystagmus is generated. This suggests why during a unilateral lesion, such as a vestibular neuritis that affects the whole peripheral vestibular system, there is never a vertical nystagmus, but only a torsional and a horizontal (not depicted here). Spontaneous vertical nystagmus is therefore almost always due to a central neurological pathology. The black arrows show the direction of movement of the head. LR, lateral rectus muscle; MR, medial rectus muscle.

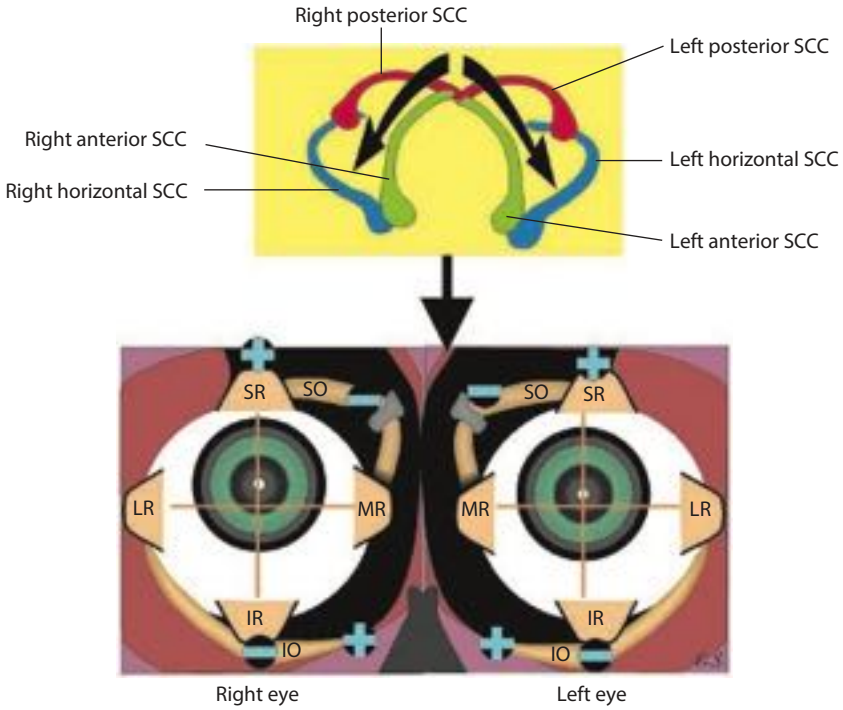


Figure 49.10 Stimulation of the right anterior and left anterior SCCs while the right posterior and left posterior canals are inhibited occurs during a forward bending of the head. This generates an elevation of the eyes or a downbeat nystagmus, depending on the amplitude and speed of bending the head. The right superior rectus (SR) muscle and inferior oblique (IO) muscle, as well as the left inferior oblique (IO) muscle and superior rectus (SR) muscle, are contracting while the right inferior rectus (IR) muscle and superior oblique (SO) muscle and the left superior oblique (SO) muscle and inferior rectus (IR) muscle are relaxing. Given the activity of these muscles, any torsional components are cancelled out. The black arrows show the direction of movement of the head. LR, lateral rectus muscle; MR, medial rectus muscle.

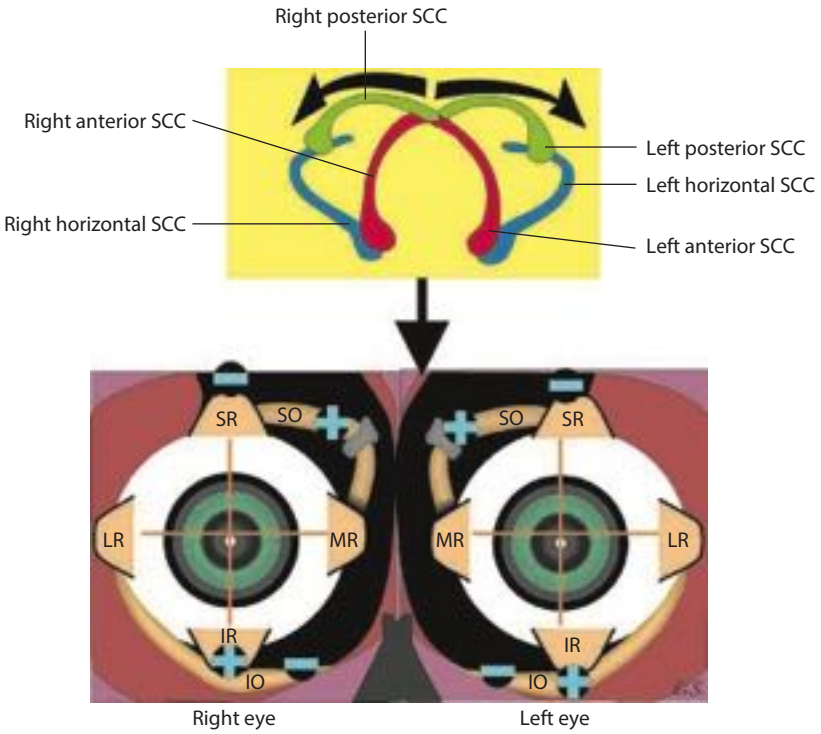


Figure 49.11 Stimulation of the right posterior and left posterior SCCs while the right anterior and left anterior canals are inhibited occurs during a backward bending of the head. This generates a depression of the eyes or an upbeat nystagmus, depending on the amplitude and speed of bending the head backwards. The right inferior rectus (IR) muscle and superior oblique (SO) muscle, as well as the left superior oblique (SO) muscle and inferior rectus (IR) muscle, are contracting while the right superior rectus (SR) muscle and inferior oblique (IO) muscle and the left superior rectus (SR) muscle and inferior oblique (IO) muscle are relaxing. Given the activity of these muscles, any torsional components are cancelled out and a pure vertical nystagmus remains. The black arrows show the direction of movement of the head. LR, lateral rectus muscle; MR, medial rectus muscle.

stimulated, whereas both posterior canals are inhibited. This produces an upward eye movement. Each anterior canal also produces an ocular counter-rolling movement, but as both are in different directions, the counter-rolling is cancelled out. The same applies when the head is tilted backwards (Figure 49.11), but now both posterior canals are stimulated producing a downward compensatory eye movement.

For the horizontal canal stimulation, a more detailed neurological pathway is explained later in this chapter.

Nystagmus

The eye response to a head rotation consists of a combination of a slow phase or drift until the eye reaches the edge of the outer canthus, and a fast phase to reset the eye in its initial position. This pattern repeats itself as long as the head rotation lasts. This saw-tooth pattern is called nystagmus (Figure 49.12). The direction of the nystagmus is defined by the fast reset phase, since that is easiest identified by the clinician. The slow phase, however, represents the actual vestibular output and is quantified. An upward excursion, by convention on electronystagmography or video-nystagmography, represents eye deviation to the right. If the slope of the sawtooth is upward to the right, i.e. a positive slope, this corresponds to a slow drift of the eye to the right, followed by a quick leftward reset saccade, as represented by a steep downward trace. This is defined as a left nystagmus. It is quantified by measurement of the slope of the upward trace, which indicates the speed of the eye movement (degrees/s).



Figure 49.12 Typical pattern of nystagmus to the left. This trace represents the eye movement amplitude in degrees (vertical) as a function of time in seconds (horizontal). Upward deflection denotes rightward eye movement. The trace indicates a series of slow eye deviations to the right (upward) followed by fast beat to the left (downward). This typical behaviour of slow movement followed by a fast reset movement is called nystagmus. Although the slow phase is the vestibular partition of the movement, by convention the nystagmus is called after the direction of the fast beat, since clinically this is more easily discernible. The slope of the slow component represents the velocity that characterizes the VOR.

NYSTAGMUS INDUCED BY ACUTE UNILATERAL DEAFFERENTIATION

The push–pull principle is very convenient to explain the origin of the nystagmus observed during acute peripheral lesions. In the case of an acute unilateral vestibular

deafferentiation (uVD) on, for example, the right side, all three right canals and the otoliths cease spontaneous activity (from 90 spikes per second to zero), while the spontaneous activity of the left SCC remains at 90 spikes per second. Although the head is not moving, the brain perceives an apparent imbalance (R: 0 spikes/second versus L: 90 spikes/second) similar to, for example, when the left system is triggered during head movements towards the left. This tonic imbalance drives the vestibular and, consecutively, the ocular motor nuclei to move the eyes towards the right, as would be appropriate for a head movement towards the healthy side (left).

The brain erroneously interprets the abruptly decreased or absent firing rate of the ipsilateral-affected peripheral system as a relative increase of the contralateral system, resulting in a nystagmus that beats away from the acute lesion.

Additionally, the combination of muscle contraction and relaxation generates not only a pure horizontal nystagmus but also a torsional nystagmus. Indeed, when all the canals are lesioned on the right side, this is interpreted by the brain as a sudden excitation of the contralateral vestibular system, which generates a contraction of the left eye medial rectus, superior rectus and superior oblique muscles. Eye movements may be considered as additive and so, although both superior muscles are on the upper surface of the eye, they have an opposite effect on the eye movement, cancelling any vertical movement. Consider the right eye, activation of the superior rectus results in an elevation, adduction and intorsion, whereas the superior oblique generates a depression, abduction and again an intorsion. When all muscles contract simultaneously, as is the case upon stimulation of all three canals on the same side, the elevation and depression cancel out, as does the abduction and adduction. The torsional movement remains, as well as a horizontal nystagmus due to the contraction of the medial rectus of the left eye (and the lateral rectus of the right eye).

For a left uVD, the torsional nystagmus is counterclockwise (CCW) (from the examiner's perspective) in combination with a horizontal nystagmus beating to the right, whereas a clockwise (CW) and leftward nystagmus is seen for a right-sided uVD. A torsional and horizontal nystagmus is the clinical sign indicating an acute whole labyrinthine deficiency. Conversely, a pure vertical nystagmus is very unlikely to be produced by an acute labyrinthine lesion, and the clinician should in that case firstly consider a central neurological lesion rather than a peripheral vestibular lesion. The sudden onset of this nystagmus is associated with vertigo and disorientation, since the absence of real movement constitutes a conflict between vision, proprioception and the vestibular system.

Vestibulocollic and vestibulospinal reflexes

When they are walking, pigeons move their heads backwards and forwards. This head movement is actually a head nystagmus, meant for gaze stabilization and controlled in an exactly similar manner to the VOR in higher species. In rabbits, however, both eye and head nystagmus are equally present, whereas in the primate eye nystagmus predominates.

The extraocular muscles are the effector organs for the VOR, while the extensor muscles of neck, trunk, arms and limbs are those for the vestibulocollic (VCR) and vestibulospinal reflex (VSR). Similar to the VOR, the same push–pull mechanisms are used for controlling the balance between extensor and flexor muscles.

It is obvious that any change in movement, detected by the vestibular organ, is compensated by a series of contractions and relaxations of several muscles. Since the freedom of motion of the body is much larger than that of the eye, a multitude of muscles are involved in the reaction chain to maintain upright position and stability.

These reflexes are mediated through projections of the vestibular nuclei on to the medial and lateral vestibulospinal tract. These pathways project to the lower limb and neck muscles to maintain an upright position and balanced locomotion. The driving input here is mainly gravity detected by the otolith system. However, proprioceptive and visual information is also necessary to provide the correct body position, given the fact that gravity is only detected in the head, regardless of the position of the trunk and lower body.

Cervico-ocular reflex

In some cases, when the head is fixed but the body is rotated, nystagmus may be observed. This reflex is based on the stimulation of neck receptors, rather than vestibular receptors. However, in humans, this reflex is very unreliable and unpredictable. Only in subjects with, for example, congenital peripheral vestibular loss does this alternative strategy for gaze stabilization become more robust. According to a review by Brandt,[13] the clinical significance of lesions involving the cervico-ocular reflex (COR) are debatable. The fact that voluntary eye movements interfere with the reflex eye movements makes objective measurements very questionable.

Vestibulosympathetic reflex

Moving from a supine to a standing position generates a substantial orthostatic stress on the body, inducing a pooling of blood of approximately 800 mL in the lower limbs and the abdomen. Maintenance of the supply of blood to the brain and other vital organs (orthostatic tolerance) requires the activation of sympathetic outflow in response to such changes in posture, generating increases in heart rate and vascular tone that maintain blood pressure and prevent pooling of blood in the lower body. The otoliths have recently been shown to participate in mediating a vestibulosympathetic reflex that could help maintain orthostatic tolerance when upright.[14–16] The baroreflex is a negative feedback response that buffers short-term changes in blood pressure, with a latency (1.4 s) that, among other factors, depends on the response to pooling of fluid in the legs. The vestibulosympathetic reflex

has a shorter latency (0.4 s) that could provide earlier feed forward excitation to maintain orthostatic tolerance.[14] In addition, recent studies have described an otolith-sympathetic reflex that acts to increase vasoconstriction during nose-up linear acceleration,[14, 16] which may be a short latency mechanism to sustain blood pressure upon standing.

Besides this reflexive sensorimotor control of gaze and balance at the level of the brainstem and cerebellum, the vestibular system is also responsible for the perception of self-motion and sensorimotor control of voluntary movements and balance which are regulated at the cortical/subcortical level. Another important function of the vestibular system is the processing of higher cognitive vestibular functions such as spatial memory, orientation and navigation, where the hippocampus and parahippocampus play an important role.[17]

Vestibular cortex

The insular cortex is a part of the cerebral cortex folded deep within the lateral sulcus and is believed to have a main role in the processing of vestibular signals.[48, 49] Moreover, a predominant role of the right hemisphere in the cortical processing of vestibular afferents has also been proven in the meta-analysis by zu Eulenburg et al.[47] More specifically, zu Eulenburg et al. suggest that operculum parietale 2, a histological defined part of the human parietal operculum in the right hemisphere, is the core region of the human vestibular cortex and possibly processes only vestibular information instead of multisensory input. Recently, changes in the vestibular cortex have been shown in an astronaut returning from space.[50] Space is a unique lab to investigate the effect of unusual physiological stimuli on the human body such as weightlessness. These preliminary findings corroborate the concept of neuroplasticity and may guide further research to find possible causes in the brain of vestibular disorders such as visual vestibular mismatch among others. Until recently, many vestibular dysfunctions were traditionally attributed to peripheral vestibular lesions, but the brain will become more and more important in vestibular physiology.

CENTRAL PROJECTIONS OF THE PERIPHERAL VESTIBULAR SYSTEM

Any movement is detected by several parts of both left and right vestibular organs, and the results converge in the vestibular nuclei after being passed through the ganglion of Scarpa. The different canals and otolith maculae project to different portions of the vestibular nuclei from where they trigger other brain centres so as to maintain gaze stabilization, as well as body stabilization.

Projections to the central nuclei

The vestibular nerve consists of a superior and inferior branch. Afferents coming from the horizontal and anterior canals, as well as from the utricular macula and anterosuperior region of the saccular macula, form the superior vestibular nerve, whereas the inferior vestibular branch contains fibres coming from the posterior canal and the saccular macula. The relative position of these vestibular afferents changes as the vestibular nerve approaches the brain. Fibres coming from the three SCCs are situated at the anterior side of the vestibular nerve, whereas saccular and utricular branches come together at the ventroposterior margin of the vestibular nerve.[18] This knowledge is important for interpreting clinical vestibular tests, i.e. caloric and rotary tests evaluate the horizontal SCCs and thus the superior branch of the vestibular nerve, while the collic vestibular-evoked myogenic potential (cVEMP) test evaluates the saccule and thus the inferior branch.

These vestibular primary afferents mainly project to the vestibular nuclear complex in the pontomedullary region of the brainstem and the cerebellum, with the highest projections to the nodulus and uvula. In the brainstem four classical vestibular nuclei (VN) have been identified: the superior (SVN), lateral (LVN), medial (MVN) and descending vestibular nuclei (DVN). In addition, several small cell groups lie at the periphery of this vestibular complex and also receive vestibular primary afferents. These include, among others, the y-group, the interstitial nucleus of the vestibular nerve (INT8), the parasolitary nucleus (Psol), and the nucleus intercalates.[18–19] Canal and otolith afferents enter the vestibular nuclear complex at the level of the LVN and rostral DVN, and thereafter divide into ascending and descending pathways. The ascending branch mainly projects to the SVN and further on to the cerebellum, whereas the descending branch of all primary vestibular afferents innervates the central region of the vestibular nuclear complex.[18]

Topography within the vestibular complex exists, but it does not conform to the cytoarchitecturally defined boundaries.[19] Several studies have tried to unravel the existence of a topographical map of the single end organ partitions, which confirmed large inconsistencies dependent on the type of test animals and the type of examination technique used.[18, 20–26] This confusion about the topography is not surprising since VN are not simple relay nuclei passing along sensory information to other parts of the brain, but include a mix of complex intrinsic and projection neurons which are responsible for spatial transformation and sensory integration of the incoming head movement signals.[26] In general, it can be concluded that most peripheral systems project to the larger part of all the VN. In early reports[22, 24] common patterns in the central projection of vestibular afferent fibres have been demonstrated, with projections from the canals being prominent in the rostral part of the VN (horizontal and anterior SCC project laterally and posterior SCC medially) whereas otolith fibres terminate more caudally. More recent reports seem to agree more or less on the following findings: the SCCs project to all four VN, with the most heavy projection to the MVN and SVN. Saccular afferents project strongly to the DVN, the INT8, and the y-group, and weakly to the other VN, whereas the utricle mainly projects to the lateral and dorsal portions

of the MVN, the ventral and lateral portions of the SVN and the rostral portion of the DVN.[18, 23, 26]

Besides input from the primary vestibular afferents, non-vestibular systems such as the optokinetic system, the neck-proprioceptive system and the cerebellar Purkinje cells also project to the vestibular nuclear complex,[19] affecting the processing of vestibular signals.

Within the vestibular brainstem nuclei there are commissural projections, which centrally reinforce the differential detection of vestibular signals by commissural inhibition. For signals coming from the SCC, these commissural projections allow push–pull reactions in the VOR, by interconnecting vestibular neurons with bilateral coplanar SCC-related signals. A similar organization exists for the utricular commissural connections, based on spatially aligned bilateral utricular epithelial sectors.[27] This commissural inhibition results in a central amplification which is essential for the detection of small angular and linear head accelerations, and for the prolongation of the dominant time constant of the VOR which is regulated by the VSM.[23, 27–28] In the saccular system this commissural inhibition is present to a lesser extent; however, cross-striolar inhibition enhances here the sensitivity to linear acceleration.[28] This amplification mechanism is based on the fact that neurons in the VN are typically excited monosynaptically by unilateral afferents from the striola of the saccule, whereas they are inhibited disynaptically by afferents from the other side.[28]

From the vestibular nuclear complex, second-order vestibular neurons project to different pathways. These neurons contribute to the control of balance by influencing the discharge of motor and pre-motor neurons. For the **vestibulo-ocular pathways**, the central and dorsal regions of the SVN, the MVN and ventral part of the LVN, as well as the dorsal division of the y-group project heavily to the oculomotor nuclei by means of the medial longitudinal fascicle (MLF) and the ascending tract of Deiters (ATD).[23, 26] The most important **vestibulo-spinal pathways** are the lateral vestibulospinal tract (LVST) and medial vestibulospinal tract (MVST), as well as the lateral and medial reticulospinal tracts (LRST and MRST). Vestibulospinal pathways originate from a wide area in the vestibular nuclear complex including MVN, LVN and DVN.[18] **Vestibulocerebellar pathways** contain neurons coming from all parts of the vestibular nuclear complex, and mainly project to the cerebellar flocculus, paraflocculus, nodulus and uvula.[23] Next, there are also projections found to the nucleus prepositus hypoglossus (NPH), nucleus tractus solitarius, parabrachial nucleus, medullary autonomic centres, the thalamus and even further cortical into the parietoinsular vestibular cortex (PIVC).[18, 23, 29] Most of these projections are beyond the scope of this chapter, but it should be kept in mind that mainly the vestibulocerebellum plays a dominant role in the fine-tuning of the vestibular functions, by adapting and readjusting central vestibular processing if necessary.

A detailed neurological pathway of the horizontal canal stimulation will be explained below.

Two types of neurons have been traced in the MVN, triggered by the lateral SCC input, namely type 1 and type 2 neurons. Their resting discharge rates are approximately 80–90 spikes per seconds. This relatively low resting discharge rate implies that, under specific high accelerations, the discharge rate is blocked to 0 spikes/s. Increased rates, however, can exceed 300 spikes/s. This intrinsic asymmetry is responsible for a limited VOR at higher frequencies when lesions occur. Some type 1 neurons are excitatory (the PVP neurons) and some are inhibitory. Primary vestibular afferents synapse with inhibitory as well as excitatory type 1 neurons (**Figure 49.13**).

Excitatory pathways

Upon head rotation to one side (**Figure 49.14**), denoted as the ipsilateral side, the ampulla of the ipsilateral horizontal canal is stimulated followed by an immediate increase in firing rate of the neurons, proportional to the velocity of the head turn. These signals project mainly on to the ipsilateral MVN, but other parts of the VN are also involved. From there, axons decussate onto the contralateral abducens nucleus which innervates the lateral rectus of the contralateral eye through the VIth nucleus. Additionally, the interneurons of the contralateral abducens nucleus project through the longitudinal medial fasciculus to the ipsilateral medial rectus subnucleus in the oculomotor nucleus (III) that activates the medial rectus muscle of the ipsilateral eye.

There is also an accessory pathway that originates from projections of the ipsilateral horizontal canal ampulla on to the ipsilateral magnocellular part of the MVN (formerly denoted as the ventral lateral vestibular nucleus).[26, 30] From there, increased activity is transmitted via the ATD onto the medial rectus subnucleus of the ipsilateral oculomotor nucleus, activating the medial rectus muscle of the ipsilateral eye. This drives both eyes to rotate towards the side opposite to the direction of the head to stabilize the image on the retina.

It is important to realize that this is not a strict parallel circuit. Although the ipsilateral medial rectus and the contralateral lateral rectus muscles contract simultaneously, the signals coming from the VN neurons are not sent through collateral axons but through different pathways. This separation permits distinct regulation of muscle contraction to combine vergence movements with the VOR, while fixating targets at different distances. Additionally, studies have shown that there is a difference in physiological signals that are conveyed by the abducens internuclear (eye velocity and eye position) and ATD (head velocity) pathways, which suggests that there is a separate control of visuomotor and vestibular functions.[31]

Inhibitory pathways

In addition to the contraction of the appropriate eye muscles (ipsilaterally the medial rectus and contralaterally the lateral rectus), a relaxation of the antagonist eye muscles has to be initiated in the context of the push–pull principle (**Figure 49.15**). This is generated by inhibitory type 1 neurons in the ipsilateral MVN.

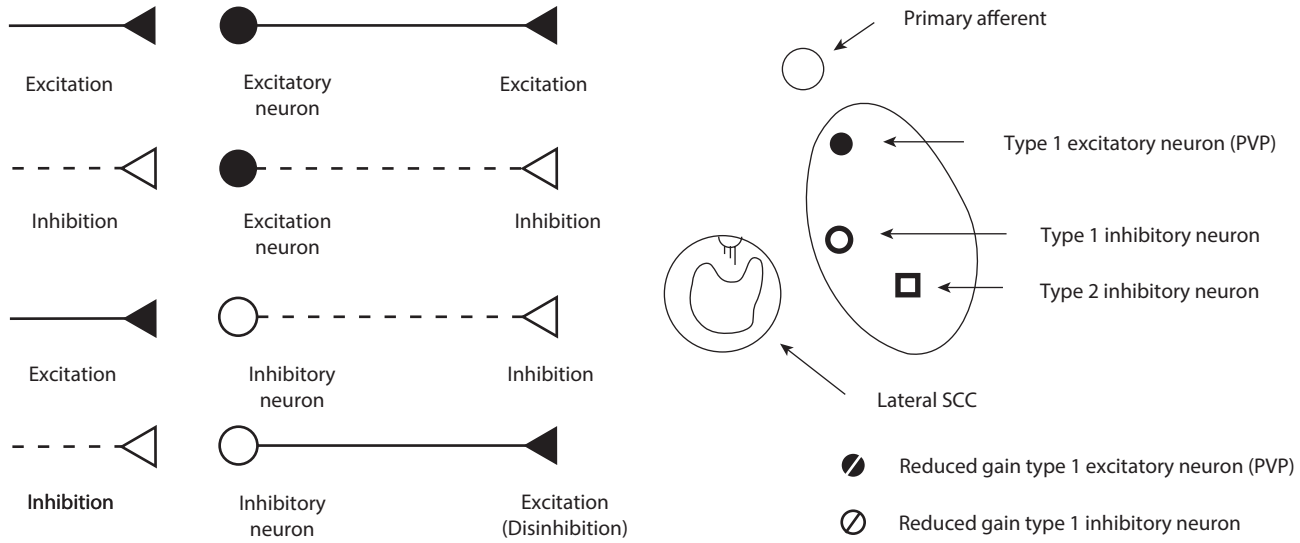
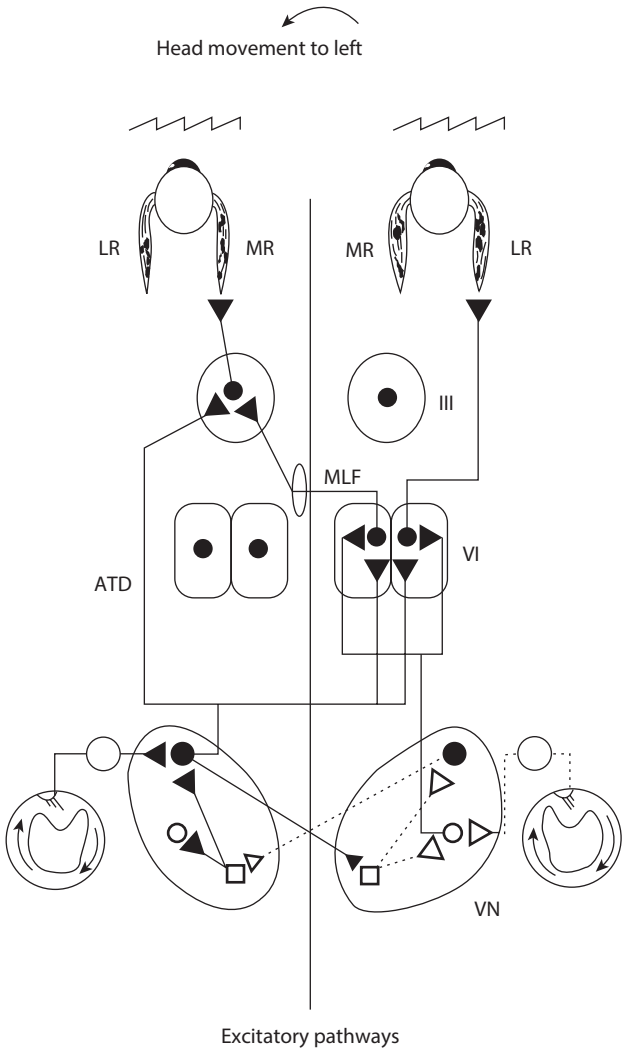


Figure 49.13 Code for excitation and inhibition of vestibular nuclei and oculomotor plants in the brain. Closed symbols represent excitation (full of neurotransmitters). Dashed lines denote inhibitory signal transfer. Solid lines denote excitatory signal transfer. Excitation of an inhibitory neuron will result in further inhibition. Inhibition of an inhibitory neuron results in excitation. This figure provides the key for Figures 49.16, 49.17, 49.18 and 49.19.



These inhibitory type 1 neurons project onto the ipsilateral abducens neurons and interneurons and, by inhibition, relax the lateral rectus on the ipsilateral eye through the VIth nerve. Likewise, the medial rectus of the contralateral eye is relaxed by inhibition of the contralateral oculomotor neurons where the signals come from the ipsilateral superior vestibular neurons and pass through the MLF.

To enhance this mechanism even further, at the same time the contralateral ampulla is deflected such that the firing rate of the primary afferents is decreased. This inhibits the contralateral MVN, resulting in an opposite effect for the antagonist eye muscles, again optimizing the gaze stabilization during movement.

To summarize, the generation of the VOR is mediated through a combination of signals coming from both labyrinths. During rotation to the ipsilateral side, the ipsilateral horizontal SCC with ampullopetal endolymph movement will transmit an increased firing rate to the central VN, whereas the contralateral SCC will transmit a decreased firing rate to the contralateral VN due to the ampullofugal endolymph movement.

Figure 49.14 During head rotation to the left, a VOR is generated to stabilize the eyes, with the concomitant nystagmus to the left. Stimulation of the horizontal SCCs initiates an excitatory pathway through the ganglion of Scarpa on to the vestibular nuclei. Given the projections of the canals and otolith organs to almost all parts of the vestibular nuclei (VN), we did not subdivide the nuclei into superior, inferior, medial and lateral VN. ATD, ascending tract of Deiters; LR, lateral rectus; MLF, medial longitudinal fascicle; MR, medial rectus; III, oculomotor nucleus; VI, abducens nucleus. See Figure 49.13 for key.

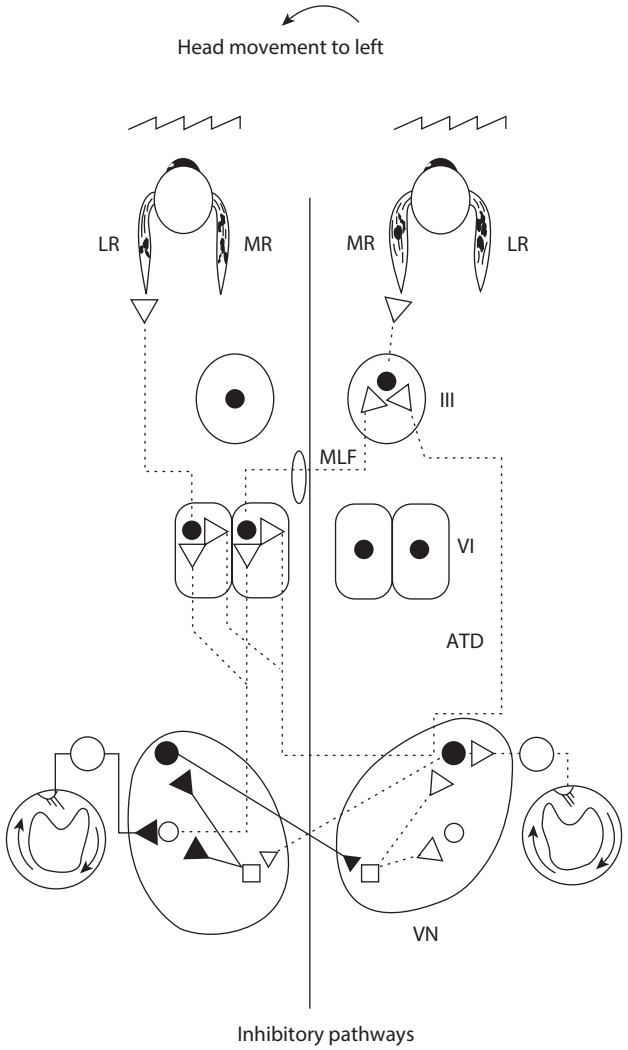


Figure 49.15 During head rotation to the left, a VOR is generated to stabilize the eyes, with the concomitant nystagmus to the left. Stimulation of the horizontal SCCs also initiates an inhibitory pathway. ATD, ascending tract of Deiters; LR, lateral rectus; MLF, medial longitudinal fascicle; MR, medial rectus; III, oculomotor nucleus; VI, abducens nucleus. See Figure 49.13 for key.

Commissural pathways

In the VN, there are also type 2 secondary vestibular neurons, which behave in an exactly opposite manner to type 1 neurons. Activating the inhibitory type 2 neurons silences the neighbouring type 1 neurons. Whereas type 1 neurons increase their discharge rate upon ipsilateral head acceleration, inhibitory type 2 neurons decrease their firing rate. For movement towards the contralateral side, ipsilateral type 1 neurons decrease their firing rate and ipsilateral type 2 neurons increase it.

The VOR-generating mechanism is enhanced in a positive feedback loop by commissural pathways where the excited type 1 neurons in the ipsilateral MVN excite the type 2 neurons on the contralateral side that in turn silence the contralateral type 1 neurons.

Excitation of the ipsilateral type 1 neurons is increased as the silenced type 1 neurons on the contralateral MVN inhibit the ipsilateral type 2 neurons, so that their inhibitory effect is reduced on the ipsilateral type 1 neurons. Therefore, type 1 cells receive direct input from the ipsilateral SCC, as well as indirect input from the contralateral SCC.

The commissural pathway is indicated at the bottom of Figures 49.14 and 49.15. This feedback loop proves to be crucial in the case of unilateral lesions.

Acute peripheral vestibular lesion and central vestibular compensation

As a model for a peripheral lesion, the acute uVD is commonly chosen. After uVD, specific changes occur immediately at the level of type 1 and type 2 neurons in the MVN on the ipsilesioned site. Given the absence of peripheral activity by the SCC afferent neurons, the firing rate of the type 1 neurons decreases.

Due to the decreased inhibitory effect of the ipsilateral type 1 neurons, the contralateral type 2 neurons are less stimulated so their inhibitory effect on the contralateral healthy type 1 neurons is decreased, and thus the healthy type 1 neurons increase their firing rate. This increased type 1 activity on the healthy side in turn activates the inhibitory type 2 neurons on the lesioned side, so that they additionally inhibit the neighbouring type 1 neurons on the lesioned side.

This imbalance generates the typical clinical signs of acute labyrinthine lesions, such as spontaneous nystagmus, i.e. a nystagmus that is present even under static conditions. The direction of the slow phase of the nystagmus is towards the lesioned side, i.e. the fast phase of the nystagmus beats towards the healthy side. The generated nystagmus reflects the situation as if the subject rotates towards the intact side. Indeed, both the absence of the ipsilesioned tonic input from the affected labyrinth and the increased contralesioned activity in the MVN mimic a rotation towards the intact side. This is illustrated in the scheme with acute uVD (Figure 49.16), where a nystagmus is generated by pathways that are very similar to the generation of VOR response upon rotation to the contralateral side. The difference is that no input from the contralateral SCC is present and still a nystagmus is generated. Also the gain of the ipsilesioned type 1 neurons is largely decreased and this will remain that way for a long time.

Stance and gait disturbances, as well as vertigo, are clearly observed in most patients. The postural disturbance often includes head and trunk flexion towards the damaged labyrinth with the head tilted so that the ipsilesioned ear is directed down. The appearance is of the healthy side being pushed towards the damaged side, which lacks the power to counteract the push.

These disturbances also occur under static, immobile conditions. The dynamic alterations yield a dysfunctional VOR, so that gaze stabilization during, for example, locomotion is hampered. Whereas the static symptoms improve within a week, the dynamic disturbances can last much longer, from weeks to years. The static symptoms decrease

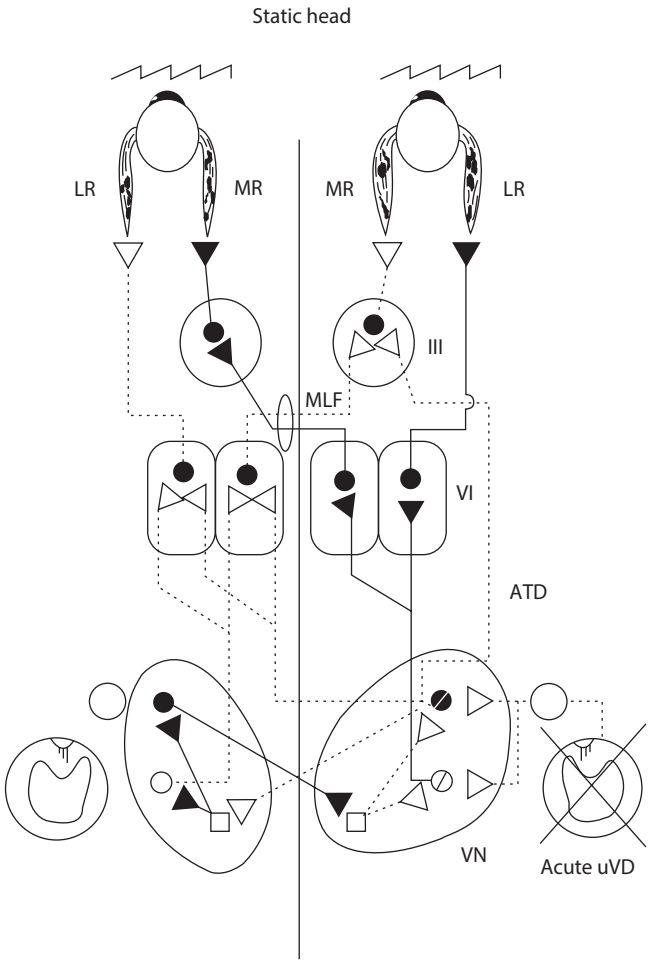


Figure 49.16 Acute stage of a right lesion of the peripheral vestibular system. Only the horizontal pathway is depicted, although a torsional nystagmus can also be observed. No vertical eye movement is seen, since the effect of inhibition of both anterior and posterior canals cancels the vertical eye movements out. Now all excitatory pathways are secondary induced through the commissural pathways and the inhibition of the type 2 inhibitory neurons, generating an excitation. ATD, ascending tract of Deiters; LR, lateral rectus; MLF, medial longitudinal fascicle; MR, medial rectus; III, oculomotor nucleus; VI, abducens nucleus. See Figure 49.13 for key.

over time, as a restoration of the resting discharge rate is affected at the level of the vestibular nuclei. This results in the disappearance of the spontaneous nystagmus: a process called 'vestibular compensation'. In humans, the gain of the VOR is permanently limited to a variable degree, depending on the acceleration of the head movements.

Many VN neurons show convergent input from both canal and otolith systems. The spontaneous activity of otolith afferents arriving in the VN is important for the generation of the oculomotor compensatory responses to SCC stimulation. The consequence of this is that an otolith loss affects not only the lVOR but also the aVOR during angular acceleration. The otoliths are therefore fundamental for the optimal operation of the entire vestibular system.

The imbalance in resting discharge rate between the lesioned vestibular neurons and the healthy vestibular neurons after uVD is the key factor that generates the acute clinical signs of nystagmus and unsteadiness. The short-term restoration of the imbalance of resting activity at the level of the VN results in a recovery of the static clinical symptoms, and the acute spontaneous nystagmus disappears within a week.

Very soon after uVD (within 52 hours), type 1 neurons in the MVN generate a spontaneous firing rate to balance the situation, although this firing rate is not influenced by afferent input from the lesioned side during rotation towards the lesioned side. It is, however, modulated through the ipsilesioned type 2 neurons that receive their input from the intact side type 1 neurons. Therefore, the ipsilesioned type 1 neurons are inhibited when the type 1 neurons on the healthy side are excited during rotation towards the healthy side, and are disinhibited when the contralateral type 1 neurons are inhibited during rotation towards the lesioned side. The responses of the ipsilesioned type 1 neurons are only half of their initial responsiveness, but qualitatively they act in a similar manner as before the lesion. This recovery takes place over a period of weeks to months and parallels the clinical recovery of the patient. The type 1 neurons on the intact side regain a firing rate equal to that before the acute lesion. The sensitivity (gain) decrease of the ipsilesioned neurons explains why the overall VOR gain after a lesion is lower than before the lesion. Even given the commissural network that largely enhances the efficiency of the generation of the appropriate VOR, an optimal VOR is never obtained. At slow accelerations, a relatively normal situation can be obtained, since the VN also receive input from extravestibular systems such as vision and proprioception, and they are not saturated. At higher accelerations, however, even in the physiological range, the intrinsic saturation of the inhibitory neurons (i.e. not being able to inhibit more than to 0 spikes per second), increases the deficiency of the VOR.

Figure 49.17 represents the pathway upon rotation towards a lesioned side. As indicated from the diagram, the only input is the inhibition sensed at the contralateral side. Due to the commissural pathways, a very similar reflex arc is established, generating an appropriate VOR under normal conditions. Nonetheless, the time taken to evoke the appropriate eye movement may be increased, which is demonstrated as an increase in phase during laboratory testing. The clinician may be surprised by the fact that the nystagmus appears symmetrical, i.e. movements to the left and right induce a similar gain (eye velocity/head velocity), but when the phase is too high (>18 degrees), the reaction comes too late, with suboptimal gaze stabilization as a consequence. For the patient, this translates into global unease and unsteadiness, and general fatigue and psychotropic drugs will worsen this.

A clinical bedside test to detect severe unilateral loss of SCC function is the head impulse or head-thrust test, first described by Halmagyi and Curthoys in 1988.[32] The head-thrust test is based on the fact that inhibition of primary and secondary vestibular neurons cannot produce fewer than 0 spikes per second. Excitation can drive the discharge rate from 90 to 300 or more spikes per second. So when the healthy side is excited for a high acceleration

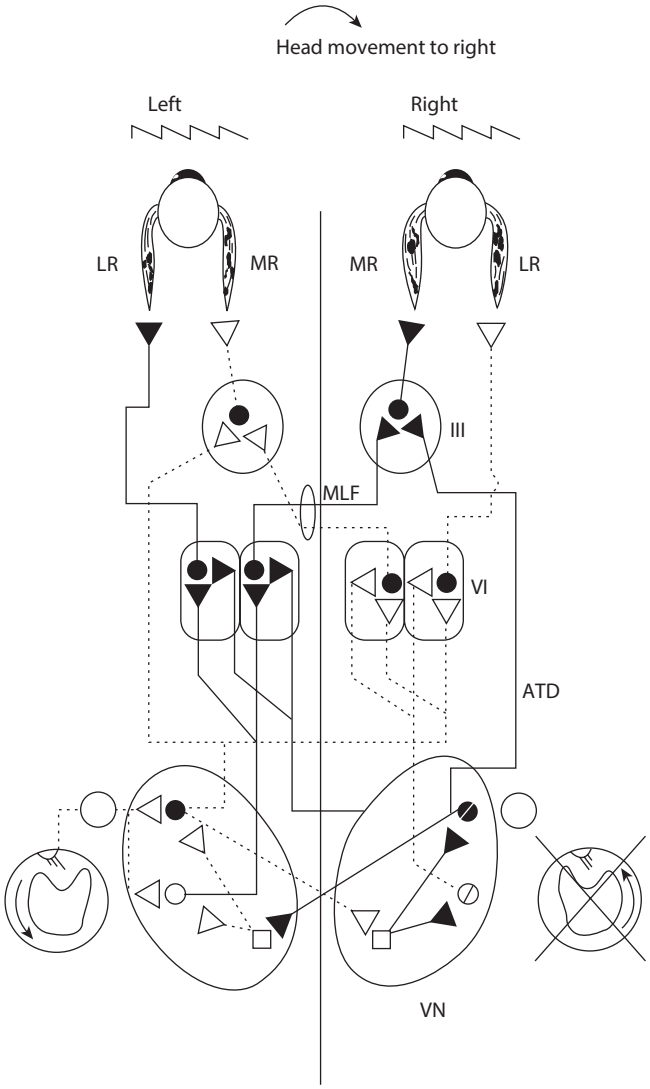


Figure 49.17 Under slow movement, rotating the head towards a stable lesioned side generates conditions for an appropriate nystagmus for gaze stabilization. ATD, ascending tract of Deiters; LR, lateral rectus; MLF, medial longitudinal fascicle; MR, medial rectus; III, oculomotor nucleus; VI, abducens nucleus. See Figure 49.13 for key.

head movement, the healthy side will generate the larger part of the VOR since the disinhibition of the ipsilateral type 1 neurons by the contralateral SCC contributes relatively little to the VOR. When the subjects head is turned to the lesioned side, the VOR is deficient and the eyes move together with the head, so that they no longer fixate. The patient therefore has to make one or more refixation saccades just after the thrust. When the head impulse is imposed in the direction of the healthy side, the VOR is able to maintain the target on the fovea and no refixation saccade is needed. The head-thrust test is positive for the side that causes the refixation saccades upon thrust (**Figure 49.18**). Not only can the lateral SCC be examined, which is in a sense a clinical approximation of the caloric test, but also the other SCC can be investigated. The patient's head has then to be moved in the RALP or LARP planes.

Gaze holding

Not only is it necessary to drive the eyes in the opposite direction to the head movement, but when the head has stopped turning, the eyes should remain in position. This is a complex task as elastic-restoring forces drive the eyes back to their primary position (straight ahead). This gaze-holding system is generated by the neural integrator, which is located in the NPH and the MVN for horizontal eye movements, and in the interstitial nucleus of Cajal (INC) for vertical movements. It is a circuit that integrates the velocity signal over the time the eye movement has occurred and this is mathematically equivalent to a position. In this way, the nuclei that command the eye muscles have input about the position that the eyes have to maintain and receive input mainly from the MVN.

Horizontal or vertical retinal image motion of a target should be held below 5° in order to maintain visual acuity. Torsional movements along the line of sight are much better tolerated. Additionally, it is desirable for optimal vision that the image of the object is directed within 0.5° on the centre of the fovea. This explains the need for an intricate image stabilization system with high gains for horizontal and vertical movement, but much lower gains for torsional movements.

To ensure gaze stabilization during normal movements of head and body, two mechanisms have evolved, namely the VORs and the visually mediated reflexes (optokinetic and smooth pursuit). The first is based on the detection by the labyrinth of the head movements, whereas the latter depends on the ability of the brain to determine the speed of image drift on the retina. Both reflexes work synergistically to maintain gaze stabilization during head movements. The eye movements generated by the VOR have, however, a much smaller latency (<16 ms),[33] whereas the visually mediated reflexes have latencies greater than 70 ms.[34]

During typical head perturbations that occur while walking (1–2 Hz),[8] the main stabilization task is performed by the vestibular system, which explains why patients with a bilateral labyrinthine deficit cannot read street signs when walking. In specific circumstances one system is overridden by the other.

- Watching a tennis match, for example, sitting alongside the court, the head moves from left to right as do the eyes to follow the tennis ball. In this case, the smooth pursuit system is mainly responsible for the image tracking.
- During sustained movements, such as on a merry-go-round, the vestibular system is assisted by the optokinetic system. This is because the vestibular receptors cannot cope with prolonged movements, and the VOR is degraded over time, therefore the optokinetic system takes over to ensure visual stability.

There are also, however, specific systems designed to shift gaze so that new objects of interest can be placed on the fovea. The main functional classes are summarized in **Table 49.2**.[35]

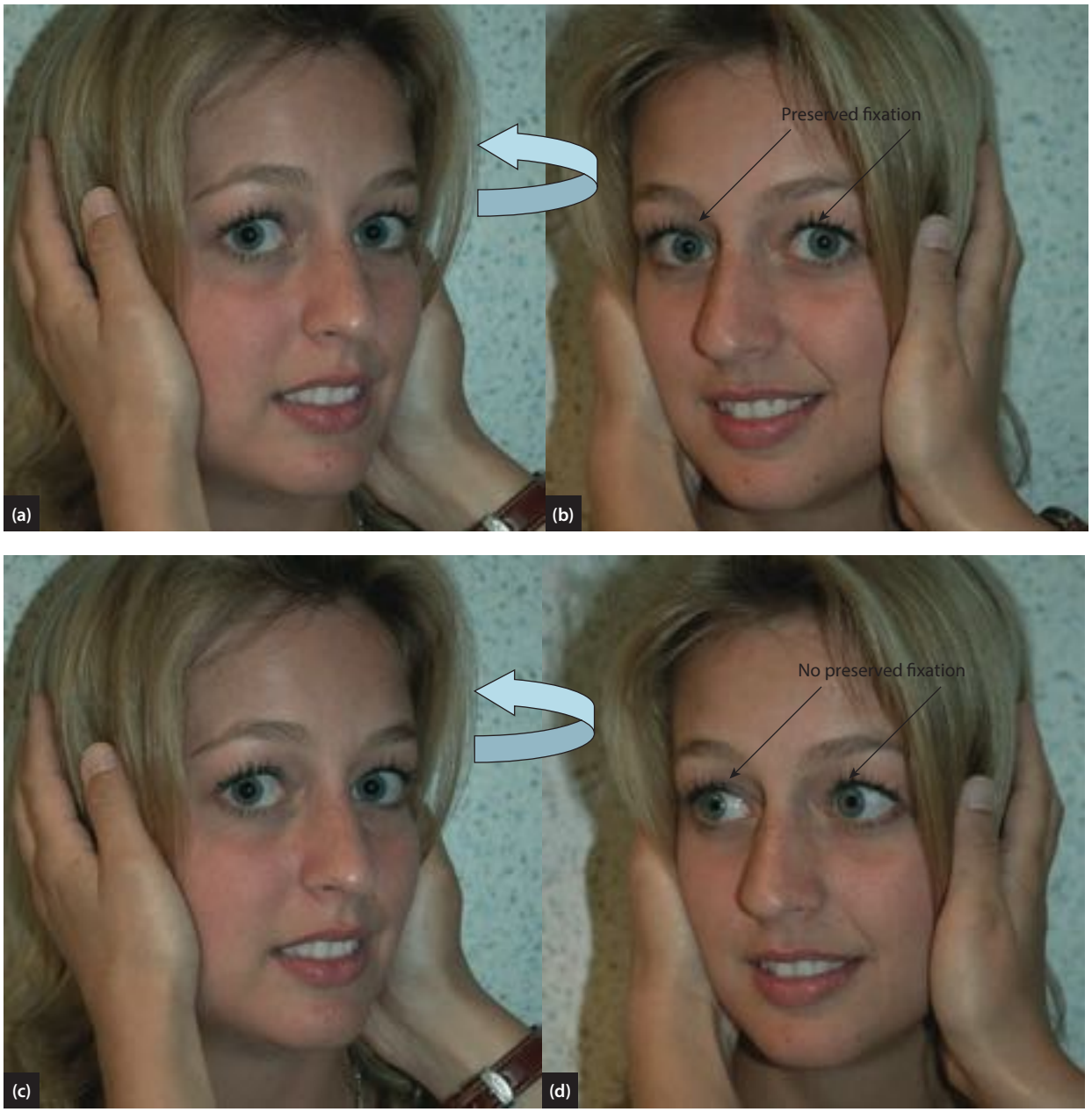


Figure 49.18 Head impulse test for horizontal canals. Hold the subject's head slightly turned to one side ((a) and (c)), and ask them to maintain fixation on a target behind you. Then, turn the head briskly to the opposite side. If the gaze is still focused on the target (as in **(b)**), then the SCC on the side towards which the head was turned (in this picture to the right) is functioning properly, generating compensatory eye movements upon excitation. However, when the eyes rotate together with the head and are no longer focused on the target, the SCC on the side towards which the head was turned is not functioning properly **(d)**. The off-target eye movement is quickly followed by a refixation saccade, so that the target is in sight again. Since this happens quickly, careful observation and handling by the investigator is required to notice abnormalities. When posterior and anterior canals need to be investigated, brisk head movements need to be made in the right anterior–left posterior (RALP) and left anterior–right posterior (LARP) planes while observing the gaze stabilization.

VESTIBULAR SENSORY CELLS

Each response of the peripheral vestibular system starts at the level of the sensory epithelium located in the SCCs and the otolith system. This section describes the functional anatomy of the peripheral vestibular system and its physiological properties related to the processing of vestibular stimuli.

The vestibular sensory epithelium is formed mainly of hair cells, which are very similar to those located in the cochlea. Two types of hair cells (I and II) can be distinguished. Type I hair cells are amphora-shaped, have a spherical nucleus and are surrounded by a chalice-like afferent nerve ending. Efferent nerve buds impinge on the afferent nerve chalice. Type II hair cells are more cylindrical, contain a cylindrical nucleus and have bud-shaped

TABLE 49.2 Functional classes of human eye movements

Class of eye movement	Main function
Vestibular	Gaze stabilization, i.e. holds images of the surrounding world steady on the retina during transient head movements (0.5–5 Hz) (see **Box 49.1**)
Visual fixation	Holds the image of a stationary object on the fovea
Optokinetic	Holds the image of the surrounding world steady on the retina during sustained head movement
Smooth pursuit	Holds the image of a small slow-moving target on the fovea
Nystagmus quick phase	Resets the eyes during sustained head movement and directs gaze towards the oncoming visual scene
Saccades	Bring images of objects of interest onto the fovea
Vergence	Moves the eyes in opposite directions to place targets simultaneously on both foveas

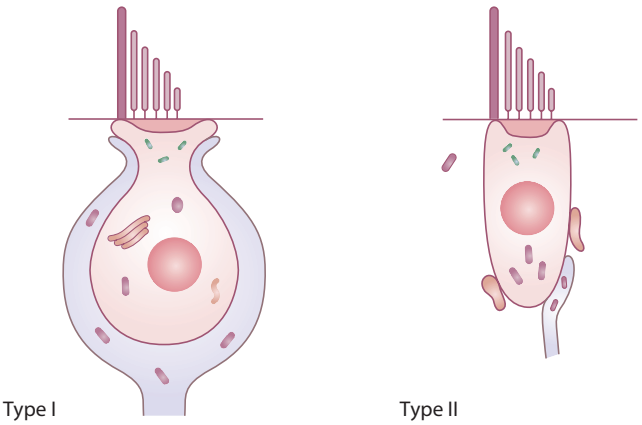


Figure 49.19 **(a)** Type I and **(b)** type II hair cells of the vestibular system.

afferent and efferent nerve endings located at the distal end of the cell. The apex of the hair cells is bathed in endolymph and is surrounded by non-sensory, supporting cells and dark cells (**Figure 49.19**).

The cell's hair bundle serves as the receptor for mechanical stimuli and is located at the apical end of the cell. Each bundle consists of 20–300 stereocilia and a single kinocilium. Hair bundle length varies: from 40–120 µm in vestibular hair cells to 0.5–30 µm in auditory hair cells.[36]

The sterocilia are rigid tubes of plasma membrane with a cytoskeleton of actin filaments, cross-linked by fibrin. They are arranged in a hexagonal pattern and vary in length across the surface of the cell, with the shortest stereocilia at one end and the tallest at the other end of the apical membrane, adjacent to the kinocilium. Consequently, the hair bundle looks like a staircase. The ion channels involved in mechanoelectrical transduction are located in

BOX 49.1 Gaze stabilization and the VOR

Shake your index finger at arm's length left and right, with increasing speed. As soon as you shake it at a frequency above 1 Hz, the eyes are not capable of following the movement and you see a blurred image of your finger. Next, shake your head while you fixate your finger, held stable at arm's length. You'll notice that the image remains sharp even at higher accelerations of your head. Up to frequencies of 5–6 Hz of head movements, many people are able to maintain a clear image of the target. This is the effect of a properly working VOR.

the stereocilia and each stereocilium possesses only one or a few transduction channels.[37]

Stereocilia are connected to each other by tip links, fibrillary strands running obliquely from the distal end of one stereocilium to the side of the longest adjacent stereocilium. The tip links are connected to the molecular gate of the transduction channels and the tension in the tip links controls the opening or closing of the transduction channels. The hair cell bundle is stiffer along its axis of mirror symmetry.[38] This increased stiffness is accounted for by the tip links. The upper end of each tip link is anchored to the stereocilium at a particular structure, known as the 'insertional plate' or 'insertional plaque', an oval disc that joins the plasmalemma of the stereocilium to its actin core (**Figure 49.20**).

The kinocilium is located at the tall edge of the bundle. The kinocilium is a true cilium consisting of an axoneme (nine paired microtubules and sometimes an additional central pair of microtubules). The role of the kinocilium is the transmission of stimulus forces to the stereocilia, but this appears not to be essential for mechanotransduction.

Hair cells are organized differently depending on their location in the SCCs or the otolith organs. Hair cells in the SCCs are located at the crista ampullaris, an elevated sensory area within the ampulla of the SCC. The tips of the cilia are embedded in a gelatinous cupula attached to the membranous labyrinth and functioning like a diaphragm (**Figure 49.21**). Hair cells in the SCCs are sensitive to changes in angular velocity and the output of the sensory cells is proportional to the angular displacement of the cupula, not to its velocity of motion.[39] Displacement amplitude of the cupula due to endolymph flow was found not to exceed 1 µm or 35° in the natural situation.[40] Larger displacement of the cupula is restrained by cupular attachments to supporting cells. As the hair cells located at the crista are all oriented in the same direction, they are all excited or inhibited by endolymph flow in the same direction. Hair cells in the horizontal SCC are excited by flow of endolymph towards the utricle (utriculopetal), whereas hair cells in the vertical SCCs are excited by endolymph flow in the opposite direction (utriculofugal). This organization is the basis of Ewald's first law which states that head and eye movements always take place in the plane of the canal being stimulated and in the direction of endolymph flow.[41]

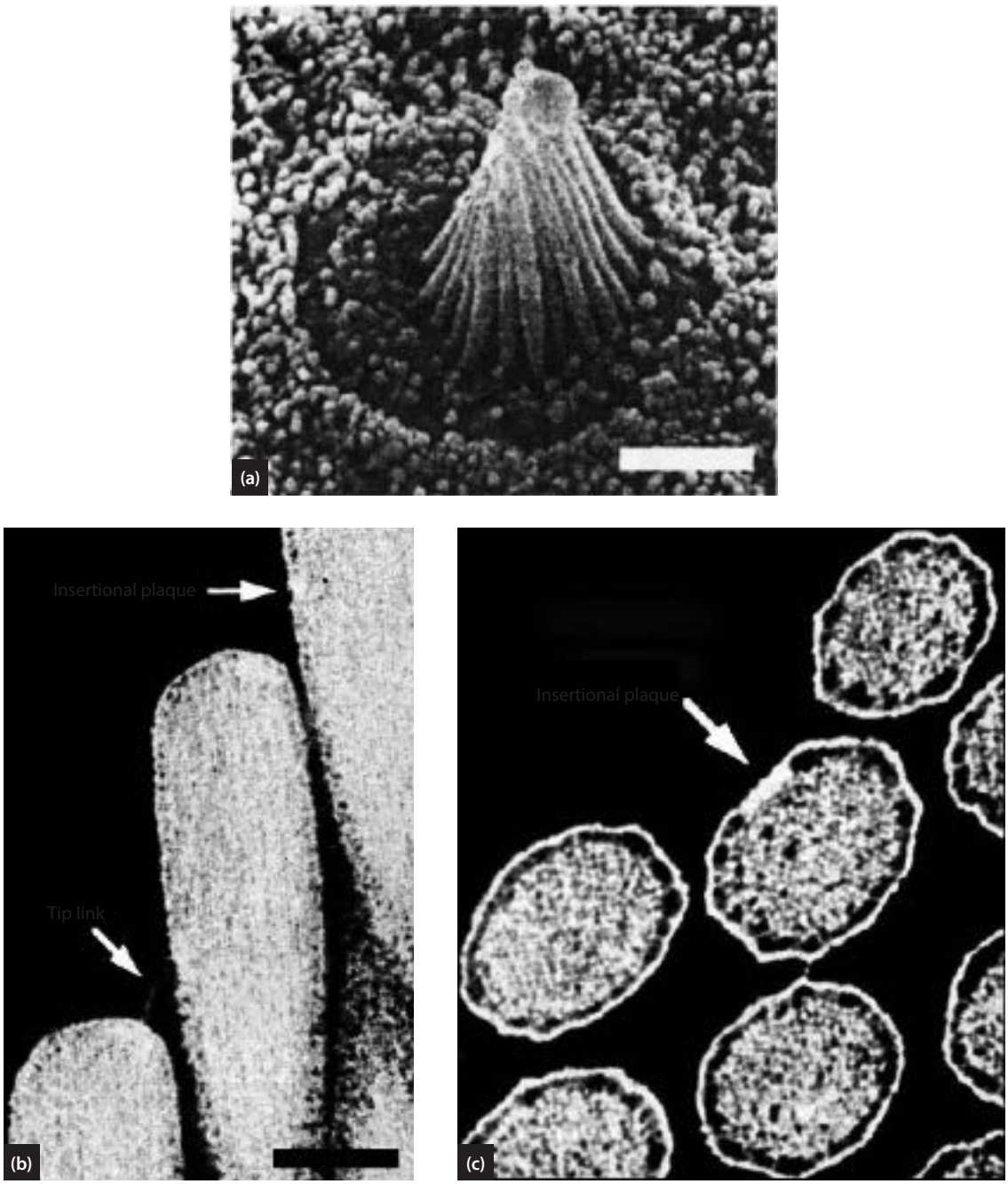


Figure 49.20 The hair cell's transduction apparatus. (a) The hair bundle comprises about 20–300 stereocilia and a single kinocilium surmounted by a bulbous swelling. The stereocilia monotonically increase in length across the mirror-symmetrical bundle. The bar in this scanning electron micrograph of a bullfrog's saccular hair cell represents 2 µm. **(b)** A tip link, a fibre about 160 nm in length and 3 nm in diameter connects the end of each stereocilium to the side of the longest adjacent process. A link often appears to comprise two or more strands, and it may splay into a pair of filaments near its upper termination at the osmiophilic insertional plate. A tip link's lower end is secured to the density capping a stereocilium. Each link is thought to be attached to the molecular gate of one or a few ion channels. **(c)** A section across several stereocilia reveals in one the insertional plaque at which a tip link's upper insertion occurs. The plaque, which interconnects the plasmalemma and the outermost tier of microfilaments in the stereociliary core, is about 50 nm high, 70 nm across and 20 nm thick. Transmission electron micrograph **(b)** is from a bullfrog; **(c)** is from a leopard frog. Scale bar: 200 nm in both. (Reprinted from Hudspeth and Gillespie.[45] Copyright 1994 with permission from Elsevier.)

In the utricle and saccule, hair cells are located in a structure known as the 'macula'. The utricular macula lies on the floor of the utricle and the saccular macula is usually in a vertical plane, on the posterior wall of the saccule. The hair cells of the utricle and saccule are embedded in a gelatinous layer impregnated with crystals of $CaCO_3$ called otoliths or otoconia. A filamentous network, the so-called subcupular meshwork, connects the lower surface of the otoconial membrane to the supporting cells of the sensory epithelium (Figure 49.22).

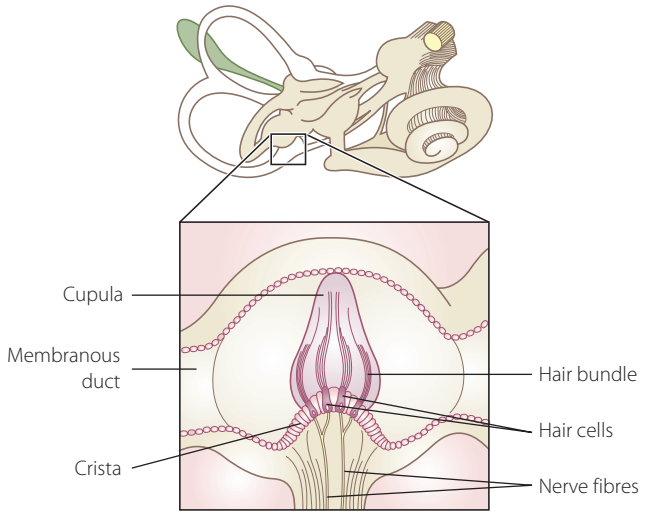


Figure 49.21 Organization of hair cells in the SCC. Hair cells are located at the crista ampullaris. The tips of the hair cells are embedded in the cupula.

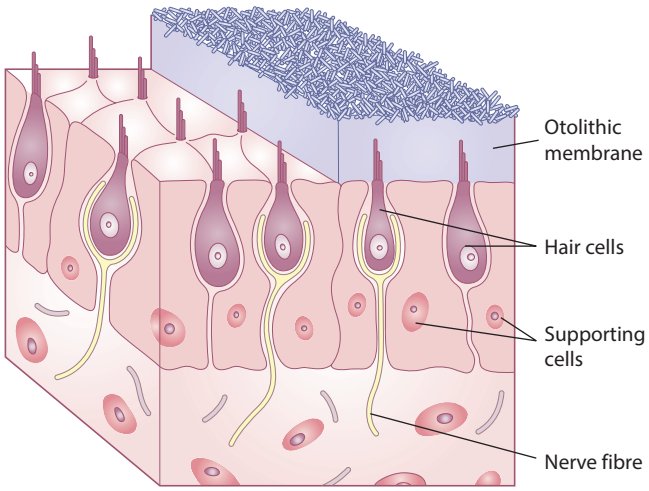


Figure 49.22 Hair cells of the otolith organs are located at the macula. The tips of these hair cells are embedded in the otolithic membrane (a gelatinous mass covered with calcium carbonate crystals, the so-called otoliths or otoconia).

Utricular hair cells are oriented in the shape of a fan with a medial group of cells pointing in an anterior–lateral–posterior direction and a lateral group of cells pointing in the opposite direction. Saccular hair cells can be divided into two parts with opposing orientation (a ventral group and a dorsal group), separated from each other by a virtual central line (the striola). Responses originating from hair cells located at opposite sides of the striola are coordinated in the central vestibular system, thus generating a common excitatory or inhibitory input. The otolith organs are sensitive to linear acceleration or changes in gravitational forces.

The endolymph surrounding the apical pole of the hair cells is characterized by a positive endolymphatic potential which plays an essential role in the transduction process. It was found that the endolymphatic potential in the vestibular part of the labyrinth (the endovestibular potential) is much lower (1–10 mV) in comparison to the endolymphatic potential in the cochlea (the endocochlear potential with values of 80 mV).[42] A more detailed analysis has shown that the ampullar and utricular endolymphatic potentials are respectively generated within the ampulla and utricle and independent of the endocochlear potential. By contrast, the endolymphatic potential of the saccule (with values of 4 mV) depends upon the integrity of the first turn of the cochlea. It is assumed that the presence of an utriculoendolymphatic valve between the saccule and the cochlear duct on one side and the ampullae and utricle on the other side might account for these differences in endolymphatic potential.[42]

Mechanotransduction

Hair cell function can be described in terms of a biological strain gauge; mechanical stimulation opens ion channels (transduction channels) in the cell membrane.[37] Displacement of the stereocilia towards the kinocilium stretches the tip links, which increases the ion permeability of the channel, resulting in an influx of cations (mainly K^+ and Ca^{2+}), thus depolarizing the hair cell. Displacement of the stereocilia away from the kinocilium shortens the tip links. This results in closure of the transduction channels and hyperpolarization of the cell. In a steady state condition, 10–20% of the transduction channels are open. Hair bundle displacement in the positive direction opens transduction channels. Channel opening decreases the stiffness of the hair bundle, which in turn promotes further movement in a positive direction, thus resulting in a positive feedback mechanism. This mechanism is known as 'gating compliance', an intrinsic property of direct mechanoelectrical transduction that enhances hair cell sensitivity.[43] The hair bundle's compliance is similar to other biological systems characterized by a non-linear stress/strain behaviour, i.e. stiffness increases when more tension is exerted on the system.

Adaptation

The extreme sensitivity of hair cells calls for a mechanism to prevent saturation of the mechanotransductor response from large and sustained stimuli (longer than 25 ms). Since mechanotransduction is a direct and fast process without intervening second messenger molecules, a unique mechanism has been developed, known as 'adaptation'. During adaptation, the transducer's sensitivity is maintained but the position at which the hair bundle displays maximal sensitivity changes from the resting position towards that at which the bundle is displaced with sustained stimulation. The stimulus/response relationship of the hair cells shifts in the direction of the applied stimulus and causes a return of the channel open probability to its resting value.[44] In this respect, adaptation in hair cells is completely different from the desensitization process encountered in other cell types. If a second stimulus is imposed during the adaptation process, the cell responds again.[45] In the primary vestibular afferents, adaptation manifests itself as a decay in spike rate during sustained head movement.

During sustained angular head velocity, deflection of the cupula decays so slowly that it does not affect afferent responses in the physiological range of human head movements (0.1–5 Hz). There is no adaptation of otolith movement during linear acceleration.[46]

Adaptation in vestibular hair cells may have at least four different purposes:[43]

- It avoids saturation of hair cell responsiveness by large or sustained stimuli.
- It allows a cell to detect small stimuli in the presence of an enormous background input.
- It places the hair cell bundle in a sensitive region of its operating domain.
- It contributes to high-pass filtering because hair cells with very fast adaptation responses are insensitive to low-frequency stimuli. Cells in the same receptor organ may have different adaptation responses, accounting for differences in frequency responsiveness.

Frequency selectivity

The length of the hair bundle varies from cell to cell in the same receptor organ. Hair cells responding to low-frequency acoustic vibration and acceleration stimuli bear relatively long bundles whereas receptors for the highest-frequency stimuli have the shortest bundles. Shatz et al. suggested that hair bundle length might be related to frequency selectivity and that longer hair bundles, such as those encountered in the vestibular hair cells, contribute to the low-frequency selectivity in the vestibular organs.[36]

FUTURE RESEARCH

- ➤ The development and implementation of vestibular implants, similar to cochlear implants in the past decades.
- ➤ Study of the vestibular cortex and regions of interest relevant for the vestibular system by application of advanced MRI scan methods such as e.g. diffusion tensor imaging (DTI), resting state functional MRI (rsfMRI) and voxel and surface based morphometry (VBM and SBM).
- ➤ The efferent vestibular system and its regulatory characteristics.
- ➤ Study of functional dizziness and its physiological correlates.

KEY POINTS

- The vestibular system ensures gaze stabilization, postural control, balanced locomotion and autonomic function readjustment.
- The geometry of the SCCs is such that head velocity is measured and used for the generation of VOR.
- The optimal efficiency of the SCC is obtained for frequencies of 0.1–5 Hz.
- The typical head frequencies for human behaviour peak around 2 Hz.
- The VOR is essentially a three-arc neuronal reflex, but the central pathways of the VOR generation use multiple inputs from both ipsilateral and contralateral vestibular afferents, through commissural fibres.
- The push–pull principle states that, upon head rotation to one side, the discharge rate in the hair cells in the leading ear increases while it decreases in the following ear. This imbalance generates the appropriate nystagmus for gaze stabilization upon rotation.
- After an acute unilateral vestibular lesion, a spontaneous nystagmus is generated due to the imbalance in discharge rate of the peripheral organs, similar to that induced during head rotation to one side.
- An acute spontaneous vertical nystagmus is more commonly due to a central nervous system disorder than to a peripheral vestibular disorder.
- Conflict between sensory inputs often leads to motion sickness.
- The head-thrust test is a bedside test that investigates directly the efficiency of the VOR.

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CHAPTER 50

PERCEPTION OF SOUNDS AT THE AUDITORY CORTEX

Frank E. Musiek and Jane A. Baran

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SEARCH STRATEGY

The data in this chapter maybe updated by a search using the keywords: auditory cortex, auditory pathways, tonotopic maps, cortical mapping, and auditory field maps.

INTRODUCTION

In discussing the auditory cortex (AC) and what it does, one must realize there is probably much more about this structure that is unknown than known. That said, to adequately cover what is known about the AC would require books and not just a single chapter. So in an attempt to provide some meaningful information about the AC we will follow a course that provides glimpses of what this central auditory nervous system (CANS) structure is and does.

The first part of the chapter will discuss the anatomy of the AC, touching on some of the basic principles and findings. Questions to be addressed include: What is the extent of the AC and how do we define it? How is it connected to other parts of the auditory system and brain? Are the ACs in each hemisphere highly similar or different?

The second major area of discussion in the chapter addresses some of the functions of the AC. How does the AC represent the various parameters of sound? How does it respond to sound and how do we measure these responses? The physiology of the AC provides us with much of the meaning that we garner from both simple and complex stimuli – do we know how this happens?

The final section of the chapter will relate information on what happens when the AC is compromised in some way. Some classic animal ablation studies are reviewed and cryoloop cooling will be introduced. Also discussed will be lesion studies in humans. This particular discussion will be clinically oriented. The studies that look at humans with damage to the AC can provide us with some very practical and highly relevant views of what the AC can or cannot do in regard to hearing and related processes.

Many of the questions that have just been posed cannot be answered fully, but hopefully they will provide the reader with some direction and guidance regarding the organization and contents of this chapter. Throughout the chapter, we will stress basic elements of understanding and build upon them as much as the scope of this chapter will allow.

The orientation of the chapter will be one that necessarily utilizes some of the traditional literature for establishing a foundation of knowledge. However, whenever possible we will touch upon some of the newer studies that are garnering attention. Certainly, there has been an explosion of knowledge about the brain recently and, along with this, there have been many advances in our understanding of the structure and function of the AC. We hope that this mixture of information provides a worthwhile learning experience for the reader.

GROSS ANATOMY OF THE AUDITORY CORTEX

It is difficult to fully define the extent of the human AC, mainly because there is considerable variability among the findings in many of the studies on the anatomy of the AC. These variances are reflected in imaging studies, electrophysiological reports and investigations of human cadaver brains.[1,2] Also it is difficult to discern what constitutes primary versus secondary or associative AC.[1] Given these kinds of limitation, this chapter will provide our best deductions regarding the anatomical definition of the AC in humans.

Defining the auditory cortex

Two approaches to defining the AC will be rendered here: one will be what we term the 'traditional approach' and the other the 'core–belt approach'. In the traditional view the primary AC is generally considered to be limited to Heschl's gyrus, which is positioned on the superior temporal plane of the superior temporal gyrus (**Figures 50.1** and **50.2**). This gyrus runs in an anterior–lateral to posterior–medial direction. Heschl's anterior segment is located in the posterior third of the superior temporal gyrus. It is bordered anteriorly by the planum polare and posteriorly by the planum temporale. The medial border is formed by the insular sulcus and the insula. There often are one or two gyri in this auditory structure, but three or more have been reported, although this is quite rare. Depending on the stimulus, recording technique and other variables, additional areas in the vicinity of Heschl's gyrus can be found to respond rather vigorously to sound, making one consider anatomical areas such as the planum temporale, the supramarginal gyrus, the inferior central gyri, the frontal lobule, and the posterior part of the planum polare as part of the AC, and if not a part of the AC itself, at least a 'highly responsive auditory area' in the vicinity of the AC. This roughly defined region is strikingly similar to the auditory areas defined in the classic paper by Celesia based upon recordings from humans[3] – though Celesia[3] and others[2] confine the AC to the planum polare, Heschl's gyrus and the planum temporale. Although there are differing views as to the extent of what may be considered the AC and the auditorily responsive area(s) around it, most would agree that the anatomical region just defined would provide some insight into the general location and extent of the AC in humans.

The core–belt approach to defining the AC has gained popularity recently (**Figure 50.3**). This increased interest is based primarily on non-human primate studies and the subsequent extrapolations of the results of these studies to humans.[2] In non-human primates the AC has a central or 'core' designation, which receives inputs from the medial geniculate body (MGB), mostly from the ventral division of this CANS structure. The core, if adapted from the non-human primate to the human, is estimated to take up about one-half or more of Heschl's gyrus.[2] The 'core' constitutes the primary auditory reception area and is immediately surrounded by a 'belt' region, which then is surrounded by a 'parabelt' area. The concept that is promulgated here is that, at this level, neural activity originates at the core and then spreads to the belt and parabelt

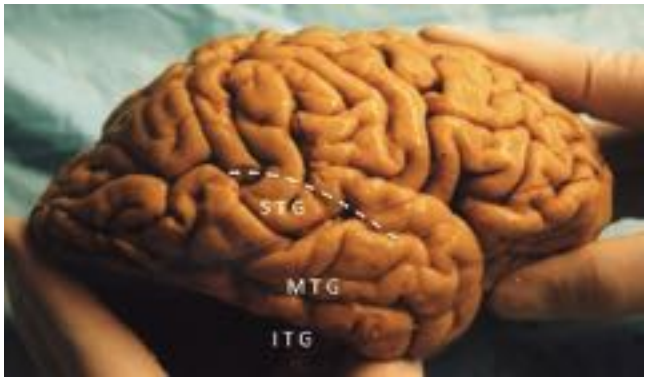


Figure 50.1 Right lateral view of the human brain with focus on the temporal lobe. The white arc signifies the course of the Sylvian fissure. The superior (STG), middle (MTG) and inferior (ITG) temporal gyri are indicated.



Figure 50.2 View looking down on the left superior temporal plane. The orientation of the numeration is from posterior to anterior. Key: 1 = planum temporale, 2 = Heschl's gyrus, 3 = planum polare, 4 = insula.

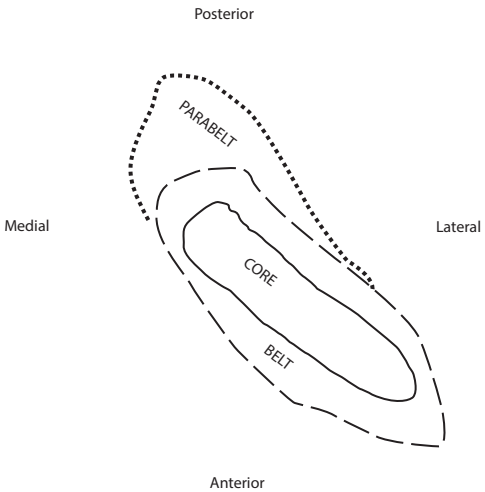


Figure 50.3 Sketch depicting the authors' interpretation of the core–belt anatomy of the auditory cortex. The drawing is aligned at a similar angle as seen in Figure 50.2 with Heschl's gyrus on the superior temporal plane. The core covers most of Heschl's gyrus with the belt and parabelt extending to parts of the planum polare and planum temporale.

regions as part of processing and neural connectivity of the CANS. Beyond the parabelt region there is neural communication with other parts of the brain in a rather non-modular fashion.[4, 5]

The core–belt arrangement makes sense in many ways and certainly there is good evidence that it exists in the non-human primate. However, the existence of a similar anatomical arrangement in humans remains an unsettled argument. Some evidence does exist from imaging data in humans, but it is not convincing to the present authors' interpretation. Moreover, even if there is a core–belt arrangement in humans, a question remains as to what form it may take; i.e. is it highly similar to that which is seen in the non-human primate, or does it vary considerably from the non-human primate model?

Projections to the auditory cortex

Heschl's gyrus receives projections from other cortical areas of the brain, but the present discussion will focus on the inputs that ascend from the thalamus. Neurons arising from the MGB project to the AC via the internal capsule. Specifically, the ventral division of the MGB is the main input to the AC. The dorsal division of this CANS structure also sends fibres to the AC, though not to the extent of the ventral division.[1] In referring to the core–belt model, the core receives input from the ventral MGB and the belt areas receive inputs from the other areas of the MGB.[6]

Projections from the auditory cortex

There are intrahemispheric, interhemispheric and efferent output projections (either direct or indirect) from the AC. Heschl's gyrus has immediate connections within this structure and then connections outside the structure. The key intrahemispheric connection is input to the arcuate fasciculus, which has fibres that connect to the insula and the frontal lobe (Broca's area).[4] The core–belt model has proposed connections from the core to the belt and parabelt regions in the superior temporal gyrus, which is similar to the Heschl's gyrus connections mentioned above.[1, 2, 6] Efferent connections originate in the AC regions and project to the inferior colliculus and MGB forming a loop that feeds back to the AC. The interhemispheric connections leave the AC and likely course around the lateral ventricles and across the midline via callosal fibres. These connections are mostly to similar loci in each hemisphere (i.e. homolateral connections), but some callosal fibres connect to different neural substrate in the opposite hemisphere (i.e. heterolateral connections).[7] Of course, the AC has connections to other parts of the brain as well, making its neural network more of a non-modular than a modular one.[5]

Asymmetries of the auditory cortex

The classic study of Geschwind and Levitsky[8] alerted us to the concept of anatomical differences between the left and right sides of the planum temporale (see **Figure 50.2**). This study and many subsequent studies have shown that in normal brains the left planum temporale is significantly larger than its right-sided counterpart. There is also anatomical evidence that is definitely slanted towards the Sylvian fissure being longer and more horizontal on the left than the right side of the brain.[2, 9] In regard to Heschl's gyrus there is also evidence supporting a left-sided size advantage, but this is not without some exceptions that point to both left and right Heschl's being similar in size.[1, 2, 10, 11] The existence of asymmetries for the core–belt orientation is, at least for the present authors, difficult to glean from the literature and requires more investigation before a definitive determination of the existence of any asymmetries (or lack thereof) can be rendered. This lack of information regarding asymmetries in the core–belt areas is due in part to the lack of understanding of the borders of the core–belt designation as it applies to humans.

It is important when discussing asymmetries of the AC that variations in the contour of the Sylvian fissure be considered. Rubens'[12] classic article brought attention to the concept that approximately the last third of the Sylvian fissure can course horizontally, or it can ascend or descend. Most Sylvian fissures run essentially a horizontal course, but in many instances this fissure ascends – often termed an ascending ramus (**Figure 50.4**). An ascending ramus has been shown to alter the morphology of a number of auditory structures, including Heschl's gyrus, the planum temporale, the angular gyrus and the supramarginal gyrus.[13] This altered morphology obviously has an influence on anatomical interpretations of imaging, lesion and evoked potential studies, rendering interpretations of the structures on the posterior third of the superior temporal gyrus and adjacent regions complex and controversial. Structural asymmetries may well exist if one hemisphere has an ascending ramus and the other does not. However, the impact of brains that have ascending rami compared to brains that do not is not fully understood at this time, but it is anticipated that with more investigation the effects will likely be found to be considerable.

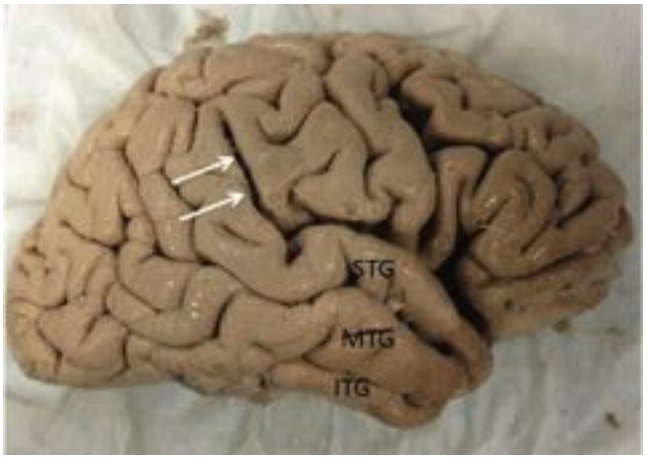


Figure 50.4 Right lateral view of a human brain with the arrows pointing to an obvious ascending ramus. Key: STG = superior temporal gyrus, MTG = middle temporal gyrus, ITG = inferior temporal gyrus.

Vascular anatomy relevant to the auditory cortex

A familiarity with the vascular anatomy of the AC is essential to understanding both its function and dysfunction (Figure 50.5). The key vessel for the AC is the middle cerebral artery (MCA). As shown by Waddington and Ring[14] and related by Musiek and Baran,[1] the MCA is derived from the internal carotid artery deep within the cerebrum. The MCA essentially runs along the Sylvian fissure before sending branches to the frontal, temporal and parietal regions of the brain. The length and morphology of the MCA proper varies greatly before it changes into branches and the MCA can no longer be discerned. Key auditory branches originating from the MCA include two or three temporal branches that infuse the temporal lobe (anterior to posterior) as well as the angular gyrus, and provide the vascular supply for the posterior temporal lobe, the supramarginal gyrus and the angular gyrus. These major arteries then give rise to smaller branches and even arterioles that penetrate the auditory regions.

AUDITORY CORTEX PHYSIOLOGY

The discussion of the physiology or function of the AC will initially focus on the manner in which this structure codes intensity, frequency and temporal information. Much of the available information in this area is a result of animal recordings where the intensity, frequency and/or temporal characteristics of an acoustic stimulus are varied and the effects are measured intracranially. Human physiological data, on the other hand, are generally obtained using functional imaging, evoked potentials, and psychoacoustic paradigms using non-invasive procedures, and although these non-invasive procedures do provide some insights to the physiology of the AC, they do not offer the spatiotemporal resolution that intracranial recordings afford.

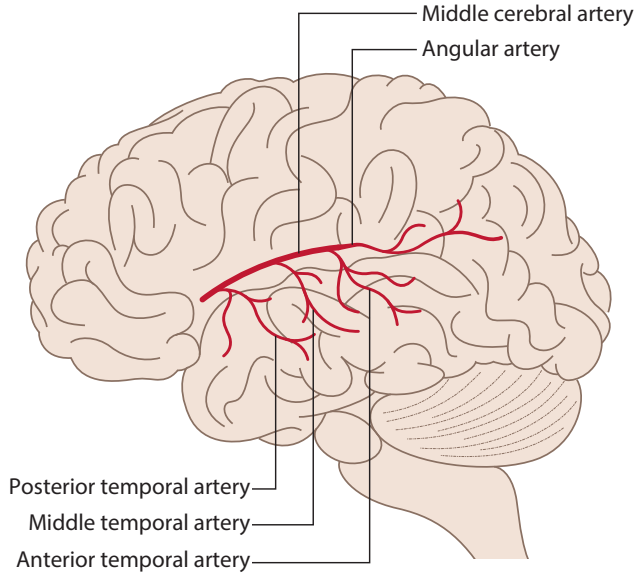


Figure 50.5 Sketch of the key arteries for the auditory cortex and immediate areas around it.

Intensity representation at the auditory cortex

Intensity in the AC is coded in three major ways. One is that as the intensity of the stimulus is increased neurons increase their firing rates.[15] Though this concept is often true, there are some exceptions that are indeed interesting and insightful. It is true that many AC fibres do increase their firing rates in a monotonic fashion, but some neurons will show a different firing pattern, i.e. they will 'roll over'. These neurons increase their firing rates with increases in stimulus intensity up to a certain level and then they actually decrease their firing rates as stimulus intensity increases further, yielding what are called non-monotonic intensity functions. The range of intensities for which there is continuous increase in a neuron's firing rate and the level at which the neuron 'rolls over' varies greatly across neurons.

A second way in which intensity is coded is related to the number of fibres that respond to a stimulus.[16] Generally, as the stimulus intensity increases, more neurons will respond, resulting in a larger neural response area. This increase in the number of neurons firing has been documented in imaging, fMRI and evoked potential studies in humans.[16] In general, as intensity increases, the response area for functional imaging responses becomes larger. Also, with increases in intensity, auditory evoked potentials (AEPs) will become larger in amplitude, likely reflecting changes not only in the number of neurons firing but also their firing rates.[16, 17]

The third way that the AC codes intensity is a complex interaction between excitatory and inhibitory neurons in the cerebrum. For example, a neuron could be non-linear in its amplitude representation and could be inhibited or enhanced in its response to a sound stimulus by activity in other neurons in and around its cortical field.[1, 18]

Changes in the latency of the neural response can also be noted if responses from the AC are recorded for a stimulus that systematically increases in intensity. In such cases, the latency of the neural response will often decrease. Though some of this shortened latency can be attributed to the travelling wave time in the cochlea, this cochlear phenomenon cannot account for all of the decrease in latency. Therefore, it appears that the neurons that respond to higher intensities may be favoured in some way to allow faster neural conduction times. This can be demonstrated by the decrease in late cortical potentials generated from the AC.[16, 17]

As has been discussed above, the AC employs a number of different neuronal mechanisms to process and code intensity information. It is likely that these mechanisms interact in various ways to provide the neural response that forms the foundation for the perception of loudness as well as changes in loudness.

Frequency representation at the auditory cortex

The representation of frequency at the AC depends on whether one is ascribing to the traditional or core–belt view. Early animal studies seemed to indicate that low

frequencies were located rostrolaterally and high frequencies were found in a caudomedial location in the AC. This, at least for present purposes, is referred to as the classic view. This view gained momentum with the functional imaging study performed by Lauter et al.[19] for which results in humans were found to be similar to those in earlier studies conducted in other animals. More recent functional imaging work with humans supported the Lauter et al. findings.[20, 21] However, it has become clear that there was variability surrounding these studies:[21] these studies in general would use only a few frequencies to map the tonotopic representation of the AC and this limitation could have lead to an overinterpretation, if not a complete misinterpretation, of the tonotopic contour in the human AC. For example, the classic investigation by Lauter et al.[19] used only two acoustic stimuli (500 Hz and 4000 Hz). The 500 Hz stimulus resulted in AC activity that was lateral and caudal to that evoked by the 4000 Hz tone. Therefore, these responses, though likely accurate for the specific frequencies studied, may or may not paint a valid picture of the complete tonotopic organization of the human AC as only two frequencies were tested. Certainly, a number of assumptions must be made in studies like those of Lauter et al. to allow an accurate interpretation of frequency contour of the human AC. It seems clear that the frequency arrangement described earlier is what is seen in non-human primates, as more comprehensive mappings of frequency representations in non-human primate studies have been completed. However, this does not mean that this same tonotopic arrangement occurs in humans and caution is recommended before applying non-human primate findings to humans. Moerel et al.[2] tried to reconcile the varying views on the tonotopic arrangement within the human AC. These investigators relate that perhaps the tonotopic arrangement may stretch from the planum polare to the planum temporale with a more general high–low–high representation. This varies from the more concentrated (less area) that has been postulated. This frequency representation has the core area segmented into three regions, each having its own frequency display. The anterior and the posterior segments have a low to high frequency representation coursing medially and maybe slightly posteriorly. The middle segment has essentially the opposite representation.[22]

It seems that perhaps many issues emerge in understanding what the tonotopic arrangement really is in humans, but two will be offered here. One is the adoption of the non-human primate tonotopic findings for human models. The other is the lack of specificity of the frequency representation in the human, and even (to a lesser degree) the non-human primate. These issues, among others, make the clear identification and definition of frequency maps within the human AC an unresolved issue.

Coding of temporal information at the auditory cortex

Frequency-modulated (FM) and amplitude-modulated (AM) signals are often used to gain insight to temporal processing capabilities, and in this case the AC. A basic concept of interest and import is that many neurons in the AC respond to changes in an acoustic signal over time, and a good example of this is the response of cortical neurons to AM and FM signals. Perhaps one of the most insightful concepts in regard to how the AC responds to acoustic signal modulations is that some neurons will only respond to modulated signals and not to steady-state signals.[23] It has long been suggested that modulated tones create more activity in the cortex than steady-state tones. A glimpse of this kind of AC activity was related by Whitfield and Evans[24] over 50 years ago. Notable is research showing that FM modulation depth discrimination thresholds are strikingly better than those derived with static tones.[25] Extending this concept, this could be one reason why complex acoustic stimuli such as FM and AM signals are more appropriate than traditional pure-tone stimuli for evaluating dysfunction of the AC clinically.

Modulation rates of AM and FM signals are an important consideration when reviewing the topic of temporal processing within the AC. Although there is variability in findings as well as in opinions, it appears that lower modulation rates seem to favour activity from the AC as opposed to higher modulation rates, which align better with brainstem and auditory nerve activity. It has been suggested that AM rates of less than 50 Hz are optimal for involving the AC, whereas rates above 50 Hz better suit brainstem neurons and the AC becomes less involved.[26] However, it must be understood that there is considerable overlap of cortical and subcortical neurons in regard to their responses to both high and low modulation rates but that, as modulation rates decrease, the neurons that respond best to the stimuli ascend in their location from the low brainstem to the AC.[23]

Another factor related to AC temporal processing of AM and FM signals is phase locking, which of course is related to overall responses to various modulation rates as just discussed. For AC neurons, phase locking is best for lower rates (again below 50 Hz), but in unsedated animals some phase locking for frequencies of over 100 Hz has been shown.[23, 27]

As recently reviewed,[28] the sweep of FM signals (low to high to low) appears to have a laterality factor in regard to AC activity. For slow sweeps, the right AC seems to respond better than the left, while just the opposite is true for fast sweeps. More fundamentally, however, is the key concept that there are neurons in each AC that are specifically sensitive not only to FM signals but to the direction of the sweep of these signals.[28] These kinds of functions would likely be related to the manner in which the AC processes speech stimuli as speech is represented by rapid changes in its underlying acoustic representation(s).

Gap detection procedures also have been used to measure temporal acuity of the AC as well as other areas of the auditory pathway. As in other regions of the CANS, neurons within the AC synchronize to the offset and onset of the lead and trailing segments within the stimuli. In addition, there is suppression of activity during the silent interval – although some spontaneous activity remains.[29] Accuracy for gap detection perception requires that the neuron array, whether in the cortex or elsewhere, follows the acoustic pattern in the stimulus (**Figure 50.6**).

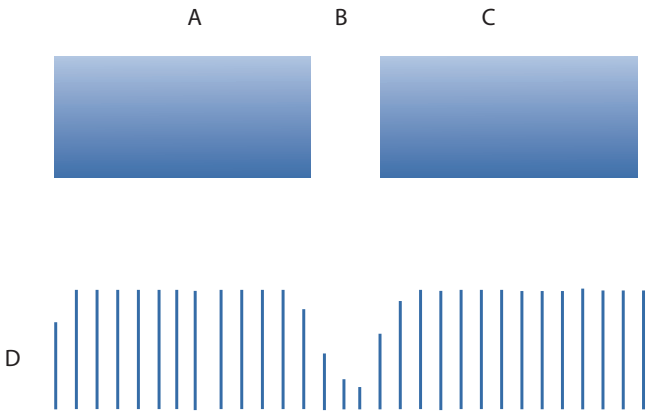


Figure 50.6 Depiction of a gap-in-noise stimulus array. Key: A = lead white noise, B = gap, C = trailing white noise, and D = predicted neural response (firing rate).

That is, when the lead element is 'on', cortical neurons are firing, and when the stimulus stops, the neurons must synchronously shut down quickly (i.e. reduce their activity to their spontaneous firing rate) and then synchronously initiate increased firing rates again when the stimulus (trail element) returns. The available research appears to indicate that the termination of the gap physiologically is of more import than the onset of the gap.[30]

Localization

The AC plays an important role in spatial hearing, which has been shown to underlie two major auditory functions: the ability to identify the location or the source of a sound, and auditory scene analysis or the ability to separate sounds based on their locations.[31–33] Research findings in both other animals[34] and humans[35] have demonstrated that the accurate localization of a sound source is affected if the AC is compromised. In humans, sound localization in the horizontal plan is largely dependent on the neural processing of interaural time differences (ITDs) and interaural intensity level differences (ILDs). Research findings have demonstrated that the perceived location of low-frequency sounds is largely mediated by processing of ITDs, while perception of high-frequency sounds is more heavily weighted on the processing of ILDs.[36,37] The time and intensity differences in these binaural cues are represented by excitatory and inhibitory responses in the cells of the AC.[38] Within the AC, there are two main types of cells, including excitation–excitation (EE) cells and excitation–inhibition (EI) cells. EE cell responses are excitatory to stimulation at each ear, whereas EI cells usually present an excitatory response at the contralateral ear and an inhibitory response at the ipsilateral ear.[38] The identification of the elevation of a sound source is based primarily on monaural spectral cues, although some weak binaural cues may be available due to small head asymmetries that often exist in individual listeners.[33]

Non-human primate studies have suggested the existence of a number of distinct subregions within the AC that are responsible for processing distinct sound properties. For example, a number of investigations have revealed that the tonotopic organization representing frequency that is first seen in the cochlea is maintained in some topographic fashion up to and including the belt regions of the AC.[33] However, investigations of the AC in humans have not yielded consistent findings and, as a result, the existence of similar topographic fields and/or representations in the human AC has not been established.[1,33]

Although the existence of clear frequencies maps within the human AC have not been established, results of fMRI testing in humans have provided evidence for two broad processing areas in humans, an anterior 'what' and a posterior 'where' area.[33] The posterior auditory 'where' pathway in humans is involved in the processing of spatial information and encompasses two non-primary AC areas, the planum temporale and the posterior superior temporal gyrus. These posterior non-primary AC areas have been shown to be strongly activated by horizontal sound direction changes, distance changes and sound movement. However, they are also activated by a wide variety of other stimulus features (e.g. frequency and phonetic stimuli), which suggests that the processing of acoustic information in these areas is not limited to purely spatial information (see 'Complex sounds (speech)' below).[33,39]

Research studies in humans have shown that unilateral lesions interfered with the localization of sound in the contralateral hemisphere of space, suggesting that each cortex preferentially processes acoustic signals on the contralateral side.[40] However, there appear to be some differences between the right and left ACs in their responses to sounds. For example, Spierer et al. found that lesions in the right hemisphere typically affected the localization of sound sources originating from both the ipsilateral and contralateral hemifields, whereas left hemisphere lesions were limited to contralateral sound sources.[40,41] They also found that the deficits noted among their subjects tended to be more severe following right hemisphere compromise than left hemisphere damage, and that greater deficits were noted for the processing of ITD than ILD cues. Based upon their findings, these researchers have proposed that the right hemisphere plays a dominant (but not an exclusive) role in the processing of spatial location, and it has an integrative role in representing sound localization.[41]

The processing of acoustic cues for moving sound sources is different from the processing of acoustic cues for stationary sources,[15] with the available evidence implicating the presence of separate processing mechanisms for stationary and moving sounds. The existence of direction-specific motion sensitive neurons in the non-primary areas of the AC (planum temporale and the posterior superior temporal gyrus) has been suggested in a number of studies.[33,42,43] However, it is not clear if the neural responses to moving acoustic targets are the result of activation of unique 'motion'-sensitive neurons, or whether the perception of auditory movement is based upon the sampling of discrete locations in space as the target moves.[33]

Complex sounds (speech)

In humans, research has documented that a variety of speech sounds activate areas immediately anterior to

Heschl's gyrus in both hemispheres,[44] while others have shown that speech stimuli (syllables and words) activate cortical areas both immediately anterior and posterior to Heschl's gyrus in the left hemisphere.[45] These findings (i.e. that speech stimuli activate areas both anterior and posterior to Heschl's gyrus) are consistent with more recent theories that posit a 'where' area in the non-primary AC as has been discussed above, as well as a 'what' area, which incorporates the anterolateral Heschl's gyrus, the anterior superior temporal gyrus and the posterior planum polare.[39] Recent auditory evoked response findings have suggested that these two processing mechanisms occur in parallel with activation of the 'where' processing pathway, occurring slightly ahead of the activation of the 'what' processing mechanism, which may enable the brain to employ top-down spatial information to assist with the processing of speech sound identity cues.[39]

Dichotic listening studies have shed some light on how the AC processes dichotic stimuli. In 1999, Hugdahl et al. in a positron emission tomography study using dichotic CVs as stimuli found activation in the mid to posterior segment of the superior temporal gyrus, with the most noticeable activation levels occurring around Heschl's gyrus in both hemispheres.[46] However, when the activation patterns of the two hemispheres were compared, the extent of the activation in the left hemisphere was greater than that noted for the right hemisphere, a pattern that is consistent with behavioural findings for dichotic speech materials. In addition, the activation area in the AC appeared to extend beyond the 'core' and possibly even the 'belt' areas. Finally, results from fMRI and magnetoencephalography (MEG) studies have shown that directing attention to one ear or the other during dichotic listening to speech stimuli influences the amount of activation in the primary AC, with increased activity noted in the hemisphere contralateral to the attended ear.[47, 48]

Auditory evoked potentials

AEPs reveal stimulus-related responses that can be measured both near and far field. These responses can tell us, at least to some degree, about the functional integrity of the AC. Of course, the AEPs that are most relevant to AC function are those for which the generator sites are in the AC.

Perhaps the earliest of AEPs that are generated by the AC is the middle latency response (MLR) (**Figure 50.7**).[49]

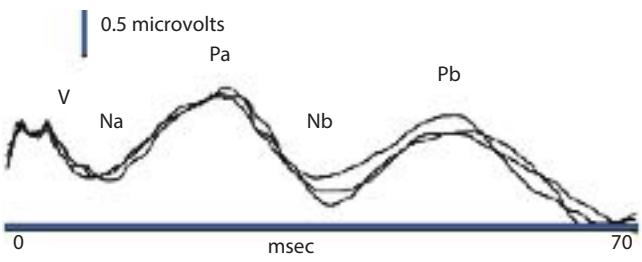


Figure 50.7 Sketch of a normal middle latency response (MLR). V = wave V of the auditory brainstem response (ABR) and Na, Pa, Nb, Pb are the wave components of the MLR.

The MLR is considered a thalamocortical potential, meaning that it is likely generated by the thalamocortical pathway. However, the main wave component of the MLR is the Pa wave, which most would agree is generated by the AC. The Pa wave has a latency of approximately 30 msec in adults for stimuli such as tone bursts and clicks presented at moderately intense levels. It appears to be generated by the medial aspect of Heschl's gyrus.[50]

The N1 and P2 potentials are often considered late and/or cortical AEPs. The N1 and P2 waves occur at about 100 and 200 msec after the onset of the stimulus in adults. The origin of N1 is Heschl's gyrus and possibly the planum temporale.[51] The P2 response also is generated by or in the area of Heschl's gyrus.[51, 52] The N1 appears to demonstrate laterality differences, with earlier latencies and greater amplitudes typically noted for the responses arising from the contralateral hemisphere, and with the right hemisphere showing greater lateralized activity (i.e. greater amplitude) than the left.[53] The P2 component may have laterality differences as well, but this has been debatable for a long time. Hine and Debener[53] relate that, if laterality differences exist for the P2, they are not as great as those noted for the N1. Even as far back as 1977 reports indicated that there was little agreement on laterality differences for AEPs.[54] Lesion effects on AEPs will be discussed in the next section of this chapter, which will provide additional information on AC function.

THE DISORDERED AUDITORY CORTEX

There is a long and respected history of learning about the function of the AC by measuring the effects of damage to it. This approach to learning about the AC can take a variety of forms. In this chapter we will focus on various ablation studies, and a new technique called cryoloop cooling as well as clinically based studies of various disorders of the human AC.

Ablation studies

Ablating the AC in mammals in most cases is related to some depression in performance on auditory tasks. Though cortical damage is generally not associated with changes in tonal thresholds, this may not be entirely true. One of the key investigations was performed on monkeys with bilateral AC ablations.[55] Immediately after these ablations the animals, at least in some cases, were unable to respond to simple stimuli but over a period of time ranging from months to years their detection thresholds improved in some cases to essentially normal levels.

Sound localization is dependent on good AC function. The early work by Neff in the late 1940s indicated that with cortical ablations animals could discriminate left-from right-sided sounds but could not locate these sounds in space with any degree of accuracy.[56] Later work showed that, if one AC was damaged, deficits of localization were often noted in the opposite auditory field.[57] Like most structures along the auditory pathway, damage to the AC compromises consistent and accurate sound localization.

Diamond and Neff[58] performed a series of bilateral AC ablations on cats. They initially measured the animals' intensity and frequency discrimination abilities before surgery and then reassessed these abilities post-surgery. The cats were able to relearn discriminations to near their pre-surgical performance levels. However, when the cats were tested on the discrimination of tone patterns, they did not regain pre-ablation performance levels. Since Diamond and Neff's studies in the late 1950s and early 1960s their findings on intensity and frequency discrimination have been both supported and disputed.[1] It has been shown that, after AC ablation, intensity discrimination suffers, especially for detecting decreases in intensity. Also, after AC ablations, non-human primates cannot distinguish a tone at given frequency from one that is changing in frequency.[55] This finding was consistent with animal research that demonstrated that, after AC ablations, gerbils were not able to accurately discriminate FM tones, while discrimination of steady-state tones was largely unaffected.[59] The findings of impaired pattern perception following AC ablation have been well accepted. In fact, these findings on auditory pattern discrimination influenced the development of two popular clinical tests of central auditory function (frequency pattern sequences and auditory duration patterns).

Cryoloop cooling

A relatively new technique termed cryoloop cooling presents some advantages over ablation procedures and other techniques that create permanent lesions.[60] Lesion effect studies often provide valuable clinical information in regard to disordered auditory systems. Cryoloop cooling involves passing cooled methanol through specially designed tubing directly into the brain. This tubing can be inserted for short-term study or implanted for long-term investigation of the physiology of the AC or other areas of the brain. The cooling has been shown to deactivate areas of the brain in a rather discrete manner, rendering the underlying neural circuitry inactive. However, the cooled area of the brain can then be allowed to warm and resume normal function. This capability provides the investigator with a research design that permits a measure of normal function, impaired function and then a return to normal function. It also allows the animal to retain a healthy system. Recent work with the cryoloop cooling procedure has shed light on a number of functions and dysfunctions of the auditory system, including the underlying mechanisms for localization[61] and effects of impairment in one auditory field on an adjacent field,[62] as well other processes.

Clinical studies

Clinical and clinically relevant studies have provided a significant amount of information on AC function and dysfunction in the human. One of the key findings reported in the mid 1950s was that simple high redundancy stimuli such as pure tones were not highly sensitive to AC damage, but more complex stimuli such as altered (distorted) speech materials were.[63] Low redundancy speech stimuli such as filtered speech, compressed speech, speech stimuli presented in noise and especially dichotic speech often revealed deficits for the ear contralateral to the damaged AC.[64] In addition, deficits in auditory pattern perception have been noted in individuals who suffered damage to the AC, though interestingly many of these patients with unilateral damage revealed deficits in both ears.[65]

Though not as commonly used clinically, studies employing AEPs on patients with AC lesions have often shown deficits. Principally, middle and late potentials (MLR, N1, P2 and P3) have been shown to be compromised in patients with AC pathology.[49] In humans, lesions of the AC can result in extended latencies and reduced amplitudes of cortically generated AEPs. However, in general it appears that changes in amplitudes of AEPs may be a more sensitive index for detecting dysfunction than changes in latency. Key in utilizing AEPs in AC lesion studies are multichannel recordings. Electrodes placed over the auditory areas and midline will allow comparisons of responses between the two hemispheres. Also, each ear can be, and should be, tested independently to allow ear comparisons. These types of comparisons can reveal differences which, if present, can document CANS dysfunction.

KEY POINTS

- The precise anatomical extent of the auditory cortex (AC) is uncertain.
- The auditory cortex codes intensity, frequency and temporal information from acoustic stimuli.
- The key vessel for the AC is the middle cerebral artery (MCA).
- The AC plays an important role in the ability to identify the location or the source of a sound.
- Auditory evoked potentials (AEPs) are clinically useful and can tell us about the functional integrity of the AC.

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CHAPTER 51

PSYCHOACOUSTIC AUDIOMETRY

Josephine E. Marriage and Marina Salorio-Corbetto

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: pure-tone audiometry, audiogram, hearing loss, hearing thresholds, degree of hearing loss, type of hearing loss, speech audiometry.

INTRODUCTION

What the mind perceives as sound is not directly equivalent to the physical stimulus that reaches the ear. Psychoacoustics is the science that studies the transformation of the physical signal of sound into a mental percept. In other words, Psychoacoustics studies auditory perception. Psychoacoustic audiometry requires that a person is able to cooperate by giving a suitable response to the auditory stimuli being presented. In general, the methods described in this chapter will relate to adults and children older than approximately 5 years of age. Younger children require adjustments to the test protocol and to the type of response required, depending on age and abilities. These will not be covered here.

Psychoacoustic methods are valuable in clinical practice as their outcomes can give a first indication of the site of a lesion in the auditory system (i.e. external or middle ear, cochlea, or higher levels of the auditory system). Also, these methods provide a basic measure of the impact of ear pathology on communication.

AUDITORY DEVELOPMENT AND DECLINE OVER A LIFETIME

The auditory system in humans is permanently scanning and interpreting sound signals in the environment, moment by moment. The anatomical structures of the ears begin to develop around day 22 of gestation.[1] By weeks 25–30 of gestation, the outer, middle and inner ears are structurally developed, and the auditory system has experience of speech and other physiological sounds.[2] The fetus is capable of auditory learning while still *in utero*, as has been shown in fetuses as young as 33 weeks' gestational age.[3] There is evidence of auditory plasticity elicited by maternal voice and heartbeat before the full period of gestation is completed.[4] Near term, the fetus learns to recognize its mother's voice or a particular melody and is able to discriminate between these sounds after birth.[5]

Input from the peripheral auditory system shapes and drives the development of the central auditory system from the first years of life. Auditory deprivation arising from unidentified hearing loss can result in delays in linguistic,[6] social[7] and cognitive[7] development. The human auditory system continues to develop the capacity to receive, interpret, and respond to complex sound stimuli such as language and music over the first decade of life and well into the teenage years.[8] In later years, the auditory system starts to decline. 'Presbyacusis' (derived from the Greek words *presbys,* meaning 'elder', and *akusis,* meaning 'hearing') describes age-related changes to the auditory system. Four predominant pathological types of presbyacusis have been described: sensory, strial, neural and cochlear-conductive.[9] An individual may have more

than one type of presbyacusis, with age-related changes affecting both the peripheral and central auditory systems. Typically, changes to the periphery are seen in elevated pure-tone thresholds[10] and absent or reduced otoacoustic emissions (OAEs),[11] with decreased speech recognition scores, while changes to the central auditory pathways are demonstrated by even poorer speech recognition scores[12] and low scores on gap-detection tests,[13] which may indicate abnormal temporal processing. In other words, as the threshold for detecting a sound deteriorates with age, it may be paralleled by the reduced ability to discriminate and categorize complex sounds. In other cases, the hearing thresholds may be normal or near-normal, but suprathreshold abilities, such as the ability to use the information about the rapid time changes in sound (temporal fine structure), and some top-down cognitive processes involved in speech processing may deteriorate, which is reflected by poor speech intelligibility in noise.[14]

USEFUL DEFINITIONS

Sound level: Sound levels are measured in decibels (dB). Decibels are used to express the magnitude of a sound relative to a reference. The number of decibels is 10 times the logarithm of the ratio of two intensities, or 20 times the logarithm of the ratio of two amplitudes or pressures. The reference commonly used for sound in the air is 20 µPa, as this is close to the average absolute threshold for 1000 Hz (see Chapter 48, Physiology of hearing). This is defined as 0 dB SPL (sound pressure level). Decibels are a convenient unit, as the human dynamic range of hearing is very wide. The ratio between the intensity of the softest detectable sound and that of the loudest tolerable sound one can hear is vast, being in the order of 1 000 000 000 000:1, which corresponds to 120 dB.[15]

Frequency: The frequency of a sound is the number of times the wave is repeated within 1 second.[15] Each repetition is known as a cycle, and one cycle per second corresponds to 1 Hertz (Hz), which is the standard unit used to specify frequency (see Chapter 48, Physiology of hearing).

Absolute threshold: The level at which a person reliably just detects a signal in the absence of any other sounds is referred to as the **absolute threshold** for that sound. If the sound level were to be increased even slightly, the person would always hear the sound; if the sound level were to be decreased, the sound would be generally inaudible. The absolute threshold is the 'lowest sound pressure level or vibratory force level at which, under specified conditions, a person gives a predetermined percentage of correct detection responses on repeated trials'.[16] In audiology, the absolute threshold is also referred to as the **hearing threshold**. Measuring the absolute threshold for pure tones at different frequencies is standard practice in clinical settings. This is known as 'pure-tone audiometry' (PTA), and it aims to quantify the degree of hearing loss.

Minimal audibility curve: The human ear does not have equal sensitivity for pure tones across frequencies. For example, a pure-tone signal of 100 Hz is just detectable to the normal-hearing person when delivered to the ear via headphones at a level of about 35 dB SPL. However, a 4500 Hz pure-tone signal at a level of about 12 dB SPL will be just audible to a normal-hearing person. Figure 51.1 shows the minimal audibility curve for normal-hearing listeners. The dashed line shows thresholds measured monaurally, usually delivering the sound by headphones. The sound pressure levels at thresholds were measured with a probe microphone placed closed to the eardrum. A threshold measured in these conditions is called the minimum audible pressure (MAP). The solid line shows thresholds measured bilaterally, by delivering the sound through a loudspeaker in an anechoic chamber. The sound pressure levels are thresholds measured in the sound field, at the point where the centre of the head of the listener was placed, after the listener has left the room. A threshold measured in such conditions is called the minimum audible field (MAF). MAP thresholds are about 2 dB higher than MAF thresholds, since the latter are binaural and the former monaural. The MAP and MAF curves also differ in shape, particularly at around 3000–4000 Hz and around 8–9 kHz.[15] This is due to the effect of the head, the pinna, and the ear canal when thresholds are measured in the sound field. Remember that the conditions of measurement for these curves are different. The maximal sensitivity is around 2000–5000 Hz as this is the range where the least sound pressure is required to just detect a sound at threshold. Between 500 Hz and

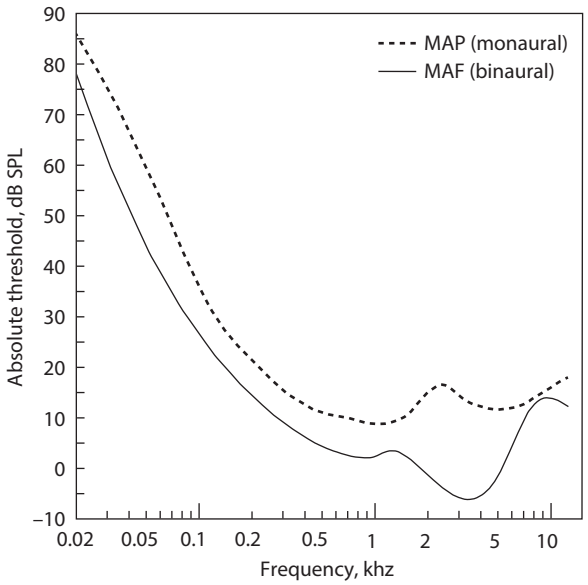


Figure 51.1 The solid line shows the MAF estimates for binaural listening as published in the standard ISO 389-7:1996. The dashed line shows the MAP estimates for monaural listening. Figure courtesy of Brian C.J. Moore. Published in *An introduction to the psychology of hearing*, 6th ed. Emerald Group, 2012.[15]

5000 Hz the variation in sensitivity is less than 10 dB and this is the frequency range that encompasses most speech sounds. Outside this range, hearing becomes increasingly less sensitive. This is partly due to the characteristics of the transmission of vibrations by the middle ear to the cochlea.[17] It is generally agreed that the range of human hearing for typically hearing young adults falls between 20 Hz and 20 000 Hz.

Upper level limit of hearing: The upper limit of hearing before pain and possible damage to the auditory system is in the region of 120–130 dB SPL; the upper limit of comfort for most people is well below this, however, in the region of 100 dB SPL.

PSYCHOACOUSTIC CORRELATES OF SOUND PRESSURE LEVEL AND FREQUENCY

Loudness and sound pressure level: It is generally understood that the higher the level of a sound is, the louder it will sound. In other words, loudness is the subjective psychoacoustic correlate of sound pressure level, although there are additional factors that can influence loudness. Loudness is the term used for the attribute of sensation by which a listener can order sounds on a scale going from quiet to loud,[15] whereas the measured level of a sound is based on the physical properties of the signal. The relationship between loudness and sound level is not straightforward. Two sounds of different frequencies can have different sound pressure levels but lead to the same loudness level. For example, a 40 dB SPL 1000 Hz pure tone may be judged to have the same loudness as a 250 Hz pure tone presented at 50 dB SPL. The unit used to quantify loudness levels is the **phon**. The phon is referenced to a particular level of a 1000 Hz pure tone against which the loudness of all other tones is matched. The 250 Hz tone would therefore have a loudness level of 40 phon. Figure 51.2 shows the equal loudness contours and the lower dashed curve represents the hearing threshold. The shape of the loudness contours changes with increasing level, with contours becoming flatter at high input levels.

The healthy auditory system is able to operate in a very wide range of sound levels, as described above. There are several mechanisms that may be involved in supporting the wide dynamic range of human hearing: the compressive behaviour of the basilar membrane, changes in the firing rate of the auditory nerve, the spread of excitation on the basilar membrane, and the information provided by phase-locking of the responses of the auditory nerve.[15] Although describing these mechanisms and discussing their contribution is beyond the scope of this chapter, they are mentioned here because one of the most common manifestations of cochlear damage in ENT clinics is **loudness recruitment**. Loudness recruitment occurs when the dynamic range of hearing is narrower than normal.

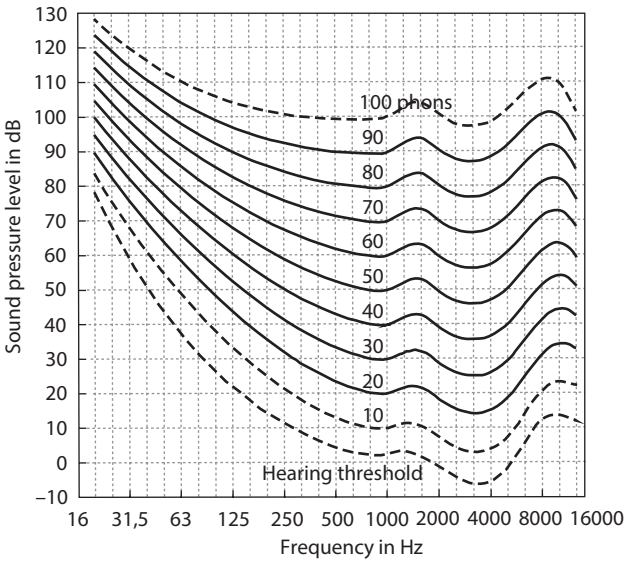


Figure 51.2 Graph showing the equal loudness contours and the lower dashed curve representing the hearing threshold. Figure courtesy of Brian C.J. Moore. Published in *An introduction to the psychology of hearing*, 6th ed. Emerald Group, 2012.[15]

In other words, the range between the sound level that is just detectable and the maximum comfortable level is less than for normal-hearing people.

Pitch and frequency: Pitch is an 'attribute of the auditory sensation in terms of which sounds may be ordered on a scale extending from low to high'.[18] Periodic sounds have pitches, as pitch is related to the repetition rate of the sound. For pure tones, the repetition rate of a sound is given by its frequency. Thus, pitch and frequency are closely related for pure tones. As stated above, frequencies are objectively measured using units of Hertz (Hz). Pitch cannot be measured directly because it is a subjective quality. Pitch is coded in the auditory system using both a place code (given by the distribution of activity across the auditory neurons) and a temporal code (given by the temporal patterns of firing within and across neurons). The relative importance of these codes for a given sound may depend on its frequency range and other characteristics.[15]

The thresholds for sounds of different frequencies are measured in PTA. The frequencies of the tones presented to the patient during audiometric testing are measured at octave intervals, i.e. their frequencies increase by a factor of 2 from tone to tone: 250, 500, 1000, 2000, 4000 and 8000 Hz. Sometimes semi-octave frequencies are tested too, as will be explained later. It should be noticed that pitch perception, as many other suprathreshold abilities, is not explored during PTA. The detection of a sound does not imply the perception of all the qualities of that sound. For example, two patients with identical pure-tone audiograms may have completely different outcomes for speech perception. Similarly, it is not uncommon to find patients who have rather good hearing thresholds but relatively

poor sound discrimination or even speech perception. From a clinical point of view, it is important not to dismiss any functional problems described by the patient solely based on a normal or near-normal audiogram.

PURE-TONE AUDIOMETRY

The purpose of PTA is to determine the hearing thresholds for pure tones, which are sinusoidal signals with a single defined frequency, amplitude and phase (see Chapter 48, Physiology of hearing). While pure tones are rare in nature, they are easily characterized, which makes them suitable for quantitative tests of hearing sensitivity. Pure tones can be considered as the basic components for all periodic sounds generated by the human larynx and many tones from musical instruments, thus having validity for hearing assessment in addition to convenience of use.

There are international and national standards that specify the characteristics and calibration of the equipment used to carry out PTA (e.g. IEC 60645-1:2017[19] and BS EN 60645-1:2017[20]), as well as the characteristics of the test room and the procedure followed for identifying thresholds (ISO 8253-1:2010[21]). These specify the types of signal used, the way in which they are presented and their duration, the type of response expected from the patient, and the presentation mode (air conduction (AC) or bone conduction (BC), as will be explained later). It is crucial to follow these conventions in order to obtain valid, comparable results across sessions and clinicians. Local professional societies usually publish their own guidelines for the procedures, which in turn are in line with the current standards (e.g. American Speech–Language–Hearing Association,[22] British Society of Audiology[23]).

Equipment for pure-tone audiometry

The principal equipment for deriving the clinical audiogram is the audiometer. There are four different levels of complexity of functions and options, classified as: screening, clinical, diagnostic, and more recently, via computer-integrated software applications.[19, 20] **Figure 51.3** shows a clinical audiometer. All types of audiometer generate pure tones at specified levels for standard test frequencies. In addition, there are narrow and broad bands of noise for use in clinical testing, as discussed later. The option of being able to present pure tones as modulated warble tones or pulses can help listeners detect signals in the presence of tinnitus. Warble tones are also crucial for getting around standing-wave artefacts particular to a given booth in the sound field. Some audiometers include options for higher-frequency hearing assessment up to 16 000–20 000 Hz, used, for example, for monitoring the effect of ototoxic drugs on high-frequency hearing thresholds.[24]

The calibration of test equipment is required at least annually and perhaps twice-yearly in some situations. Calibration may drift over time so that the gradual change in signal output is not apparent without systematic daily checks and measurement routines as specified in ISO 8253-1:2010.[21] Changes in the transducer type – for example, between headphone sets, or from headphones to insert earphones – require different calibration settings to be stored within the audiometer. The audiometer, transducers and response buttons (used by the patient to indicate that they hear the stimuli) need to be clean, functioning consistently, and used with the correct calibrated equipment.



Figure 51.3 A clinical audiometer.

Transducers: air-conduction and bone-conduction measurements

When performing PTA, the tester fits the transducers to the patient, and the patient is instructed not to move or hold the transducers. The examiner should check for any discomfort caused by the transducers.

The use of AC and BC transducers seeks to separate the conductive (outer and middle ear) and sensory (cochlear) components of hearing loss. Signals presented from headphones or insert earphones are transmitted by AC. In BC testing, a bone vibrator is positioned on the mastoid behind the pinna, or sometimes on the forehead, with a known force so that mechanical vibrations are coupled to the skull bone to stimulate the cochlea through bone transmission. The sensitivity for detecting these mechanical vibrations depends largely on the inner ear function, with reduced influence of the outer and middle ears. Thus, comparison of results obtained by AC and BC often allows the separation of conductive and sensorineural components of hearing loss. There are, however, caveats in this simple model which have useful diagnostic indications, as described later in this chapter.

AIR-CONDUCTION TRANSDUCERS

The most common headphone type is the Telephonics TDH-39, 49 or 50 headphone, which is a **supra-aural** headphone. These rest on the surface of the pinna, without enclosing the pinna in their cups. Supra-aural headphones can fail to achieve good coupling with the ear. Thus, air

leaks can occur, and the hearing thresholds below 500 Hz may be overestimated as a consequence.[25]

An alternative type is the **circum-aural** headphone, which encloses the pinna in its cups. These are designed to give a close fit to the outer ear to prevent leakage of the test signal or ambient noise from the test environment, and reduce the amount of physiological noise in the ear.[25] Examples include Sennheiser HDA-200 headphones, which have noise-excluding muffs and can be used for high-frequency audiometry (i.e. 8000–20 000 Hz). However, circum-aural headphones, as well as supra-aural headphones, are less reliable at high frequencies due to wave effects in the cavity defined by the headphone and the ear canal, which in turn depend on the positioning of the headphone.[25]

A third type of AC transducers are **insert earphones** (e.g. Etymotic Research EAR-Tone 3A). These consist of two probes (right and left) covered by a disposable foam tip that is placed in the ear canals for testing. Insert earphones give improved attenuation of ambient noise relative to supra-aural headphones, along with reduced likelihood of infection transmission as inserts are single use,[26] and the positioning of the insert reduces the likelihood of the ear canal becoming collapsed in soft or elderly ears.[26] They also reduce the amount of physiological noise in the ear and the occurrence of air leaks even further than circum-aural headphones, and reduce the wave effects associated with the other types.[25] In addition, they are more convenient when testing patients with profound loss at the low frequencies, for whom responses are given to vibrotactile stimulation. Insert earphones reduce vibrotactile stimulation when delivering high-level low-frequency tones.[27] They also have a higher 'interaural attenuation' compared to supra- and circum-aural headphones.[25, 26]

Interaural attenuation (or transcranial transmission loss) is the attenuation of sound delivered by a transducer to one ear as it reaches the opposite ear. While supra-aural headphones typically have 40 dB interaural attenuation, Etymotic Research ER3 or ER5 insert earphones inserted deeply have at least 75 dB interaural attenuation at frequencies below 1000 Hz, and about 50 dB interaural attenuation at frequencies above 1000 Hz.[28] This is relevant when testing the AC hearing thresholds of persons with asymmetric hearing or with bilateral conductive hearing loss, and it will be addressed later in this chapter. However, insert earphones are not recommended when there is excessive earwax in the ear canal, or when obstructions and abnormalities affect the ear canal or in the event of ear infection.[23]

The correct position for supra- or circum-aural headphones is to have the sound opening of the headphone aligned with the ear canal entrance. For insert earphones, the correct position is to have the outer end of the foam tip flush with the ear canal entrance. It is important to use an appropriate-size tip for the earphones. **Figure 51.4** shows the correct placement of supra- and circum-aural transducers. **Figure 51.5** shows correct insert positioning.

Calibration standards are different for supra-aural headphones (ISO 389-1:2017[16]), insert earphones ISO 389-2:1994[29]) and circum-aural earphones (ISO 389-8 2004[30]).

BONE-CONDUCTION TRANSDUCERS

The most commonly used BC transducer for clinical audiometry is the Radioear B-71. The transducer is held at one end of a rigid vertical headband. The opposite end has no transducer attached and serves only as support. When placed correctly, the headband holds the BC transducer against the skull with a given static force. The BC transducer is placed first on the mastoid prominence of the worse-hearing ear.[23] The transducer must be placed so that it is as close as possible to the pinna, without touching it and avoiding the hair (see **Figure 51.6**).

The Radioear B-71 is prone to distortion below 500 Hz[31] and limited above 6000 Hz.[32] Thus, testing is generally done for frequencies between 500 Hz and 4000 Hz. For 3000 Hz and 4000 Hz, especially when testing at relatively high-level, the Radioear B-71 produces airborne sounds. In order to prevent the patient from responding to these, an earplug can be used in the test ear when testing the BC threshold in this ear. It is important to record the use of an earplug during testing on the audiogram form as this causes an occlusion effect. Airborne sounds are reduced when placing the BC transducer on the forehead. However, corrections should be made to the calibration in this case.[23] Recently, it was proposed to adjust the reference equivalent force threshold level (REFTL), especially for 4000 Hz, to reduce observed false air–bone gaps at this frequency.[33] Calibration for BC transducers is specified in the standard ISO 389-3:2016.[34]

Environment for clinical testing

The acceptable level of ambient noise in the test environment is specified by standard ISO 8253-1:2010.[21] It is generally accepted that the ambient noise should not exceed 35 dB(A). Additionally, the examiner should be aware that transient noise (i.e. coughing, furniture noise following movement, etc.) can also affect the test results.

It is crucial that the examiner can see the face of the patient at all times. This helps to detect situations when the patient is confused, or has lost their focus on the task, or feels that the test sounds are unpleasant. It is equally important that the patient is not able to see or hear the examiner manipulating the audiometer controls. Usually, the patient sits in a soundproof booth during the test, and the examiner controls the audiometer from outside the booth (**Figure 51.7**). Soundproof booths used for clinical testing have silent fans, light and a double-glass window or a closed-circuit TV system through which the examiner can see the patient and the patient can see the face of the examiner. The examiner and the patient should be able to talk to one another when needed, thus an intercom system is available in most clinical audiometers.

Audiometric procedure for clinical assessment

BEFORE THE TEST

The following is based mainly on the recommendations of the British Society of Audiology.[23] The examiner relies



Figure 51.4 Correct position of the supra-aural headphones **(a,b)** and circum-aural headphones **(c,d)**.

on the patient's responses for the accuracy of the test and therefore establishes at the beginning of the test that the patient understands what they are expected to do and that they feel comfortable in the test environment. Several factors about the patient, including age, hearing deficit, language skills and communication problems (whether or not related to their hearing problem), should be taken into account. Important communication difficulties must be recorded as they are likely to affect the outcomes of the test. If the test is carried out in a soundproof booth, claustrophobia will constrain testing for some patients. In this case, the environment should be modified (e.g. by





Figure 51.5 Insert earphones. (a) Correct position of earphones. **(b)** View of the inside of the ear canal in an ear model. This illustrates the depth of the transducer into the ear canal when the foam is placed flush with the entrance of the ear canal, as shown in (a).

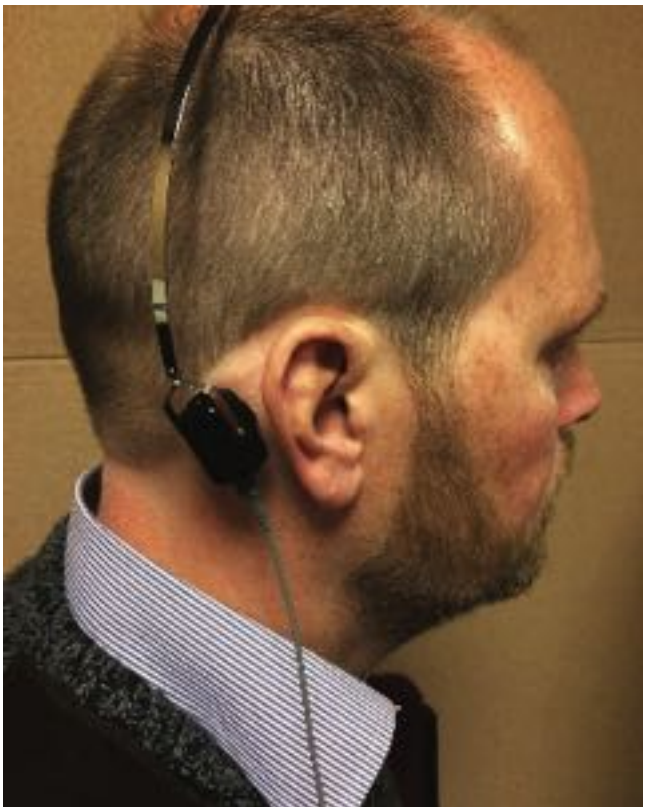


Figure 51.6 Correct placement of the bone-conduction transducer. Note that the transducer is not touching the hair or pinna.

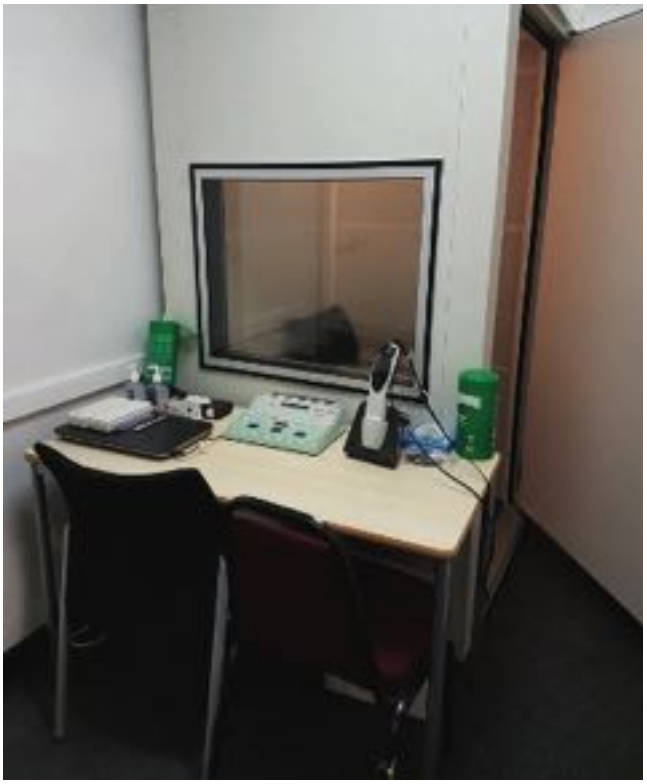


Figure 51.7 A typical clinical audiometric booth. The examiner sits outside and the patient inside the audiometric booth. The booth has a window that allows the examiner to see the patient. Photograph courtesy of Joanna Lemanska.

not closing the door of the booth) to avoid subjecting the patient to undue anxiety, and any modifications to the test procedure should be noted in the outcome form or audiogram.

Typically, the patients are asked about two situations that can interfere with the detection of the test tones:

- **Exposure to loud sounds in the last 24 hours:** In this case, it may be necessary to retest the patient as loud sounds could temporarily shift the hearing threshold.
- **Tinnitus:** In this case, the patient must be asked to ignore their tinnitus as much as possible. The clinician may decide to use warble tone signals to make it easier for the patient to distinguish between their tinnitus and the test stimuli. Frequencies where there was variation in thresholds and any modification in the protocol to measure the thresholds should be recorded.

Patients are also asked whether they have better hearing in one ear, as in this case testing should start in that ear.

It is essential that the PTA is preceded by otoscopic examination, and that the findings are noted on the audiogram. Hearing thresholds will be affected by the presence of occluding earwax so, if occluding earwax is detected, the patient should have earwax removal first. If it is determined that the ear canals are likely to collapse during the test, this should be noted in the audiogram, and insert earphones should be used if possible.

Before carrying out the test, instructions are given to the patient about what they are expected to do during the test. While the wording can be varied, the essential points of the instructions should be kept constant in order to be able to compare test results across sessions and/or examiners. The British Society of Audiology proposes the following instructions to the patient:

> *'I am going to test your hearing by measuring the quietest sounds that you can hear. As soon as you hear the sound (tone), press the button. Keep it pressed for as long as you hear the sound (tone), no matter which ear you hear it in. Release the button as soon as you no longer hear the sound (tone). Whatever the sound and no matter how faint the sound, press the button as soon as you think you hear it, and release it as soon as you think it stops.'*[23]

A printed version of these instructions may be useful. The patients should be asked whether they understood the instructions, and should be told to sit quietly during the test, and that they may interrupt the test in the event of discomfort.

The patient responds by pressing a button or perhaps raising a finger, in the way indicated in the instructions. Every time the button is pressed a light indicator is lit on the audiometer panel, so that the examiner knows that the patient has responded.

MEASURING THE HEARING THRESHOLDS

As discussed above, the procedure for PTA is specified by the relevant standards.[21] For AC audiometry, the test is started in the better ear, and the threshold for each of the pure tones is measured before moving to the next pure-tone test frequency. Traditionally, the order of the pure tones presented to the patient is: 1000 Hz, 2000 Hz, 4000 Hz, 8000 Hz, 500 Hz and 250 Hz. Inter-octave frequencies can be tested if there is a difference of 20 dB hearing loss or more between contiguous frequencies. The threshold at 1000 Hz is then retested for the ear tested first only. If the test–retest difference is within 5 dB, the best hearing threshold is noted. If the test–retest difference is greater than 5 dB, it is necessary to check that the patient understands the procedure, the transducers are still in place, and the response button works properly, together with other possible sources of variation. After testing the first ear, testing is carried out in the other ear. Retesting of the hearing threshold at 1000 Hz is not required for the second ear if there was no significant test–retest difference for the first ear.

Testing is preceded by a familiarization trial. Details of the step-by-step procedures for familiarization and testing are shown in **Figures 51.8** and **51.9**. Each test signal is introduced at an easily audible level, and then systematically attenuated, or reduced in volume, in 10 dB steps until the signal is inaudible. When the patient does not respond, the signal is increased in steps of 5 dB until the signal becomes audible and the patient responds. This can be described as a 'bracketing technique' and it is also called the '10 dB down, 5 dB-up technique'.

The bracketing technique used to determine the hearing threshold is schematized in **Figure 51.9**. This technique is used until two corresponding ascending thresholds have been derived, with the listener responding for the full duration of the signal. The duration of the signal is varied between 1 and 3 seconds. At very short durations, there is a trade-off between time and intensity, with the hearing threshold being higher for shorter sounds. This occurs for sounds shorter than about 200 msec. It is therefore convention that signal durations shorter than 500 msec are not used during the measurement of the audiogram. Duration is usually varied between 1 and 3 seconds.[23] The onset and offset of the pure-tone signal is the most salient feature for detection when listening close to threshold. For accurate assessment of hearing thresholds, the listener is required to respond by pressing the button, or perhaps raising a finger, for the full duration of the perceived signal rather than just at the onset. Effective audiometry requires unpredictable silent gaps (lasting 1–5 seconds) between signal presentations, as rhythmic presentation leads the patient to respond at regular times, even if they did not hear the signal. It is generally accepted that the threshold of hearing is defined as the stimulus level giving rise to 50% or more correct detection responses, or a minimum of two out of two, three or four ascending presentations.[23]

Testing is carried out by AC first and then, if necessary, by BC. Test frequencies for BC are those in the range 500–4000 Hz, with no retest at 1000 Hz required. The mechanism for transmission of sound through BC conduction is more complex than for AC. However, comparison of results for AC and BC generally provides evidence for

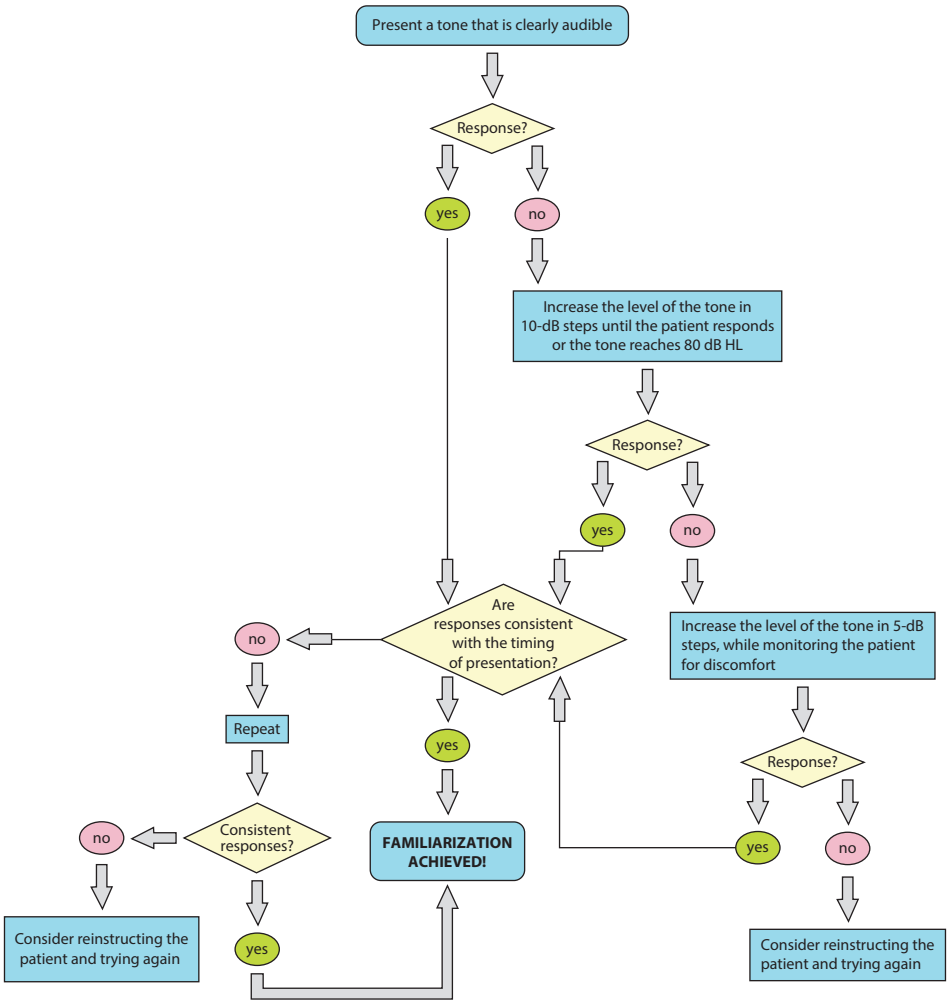


Figure 51.8 Procedure to achieve the familiarization of the patient with the task.

conductive and sensorineural components of hearing loss, although BC thresholds can be increased in the absence of sensorineural loss

The AC pure-tone audiogram is the basic test used to express the degree of hearing loss. BC thresholds provide important information for differentiating between conductive and sensorineural disorders. An equal extent of hearing loss for AC and BC generally indicates a sensorineural lesion whereas a larger loss by AC than BC, referred to as an air–bone gap (ABG), often indicates a conductive lesion. The ABG at a single frequency needs to be at least 15 dB in order to be considered clinically significant, particularly at 4000 Hz where there is a recognized artefact in the BC threshold norms.[33] As mentioned above, it should be noted that BC thresholds can occasionally be increased due to pathology affecting the middle ear and not the cochlea. An example is the hearing loss due to otitis media with effusion. Although in most cases BC thresholds are normal, these can be slightly elevated, especially at lower frequencies. According to Huizing[35] this can occur because: a) The round window is being pressed by a fluid; b) the stiffness of the middle ear is increased by the negative air pressure; c) the resistance of the mass of the middle ear may be increased by the presence of fluid and

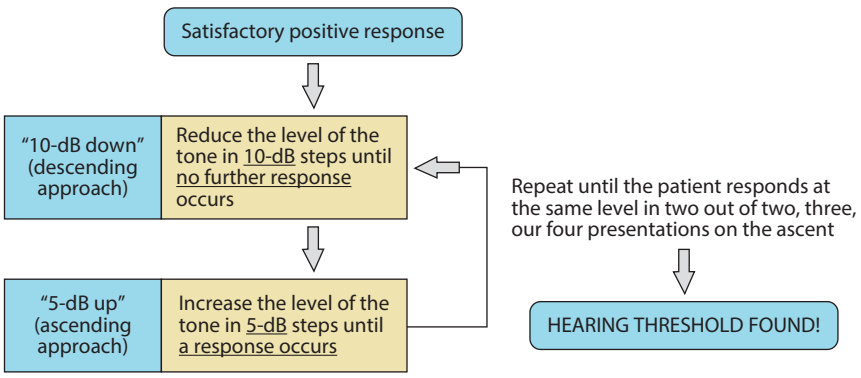


Figure 51.9 Method to measure threshold.

the swelling of the mucosa (which can improve or worsen BC thresholds depending on its point of action on the ossicular chain). Another example is the 'Carhart notch' (originally thought to be present more often at 2000 Hz),[36] described as an increased BC threshold that improves after surgical treatment in cases of otosclerosis.[37]

MASKING

In order to accurately measure hearing in each ear, signals are presented directly to the right and left ears. In the case of poorer hearing in one ear, when a signal is delivered to that ear at a sufficiently high level, it may be perceived in the contralateral ear. This is known as **transcranial transmission** or **cross-hearing**, and it is related to the concept of interaural attenuation introduced in 'Air-conduction transducers' above. If the hearing threshold of the non-test ear is equal to or lower than the level of the stimulus minus the interaural attenuation, then the stimulus may be detected by the non-test ear. Using conservative estimates of interaural attenuation, it is recommended to present a continuous masking noise (or masker) to the non-test ear to prevent cross-hearing of the test tone whenever there is an interaural difference of 40 dB or more when using supra- or circum-aural headphones, or 55 dB or more when using insert earphones.[23] As BC signals are transmitted to both cochleae, regardless of the side on which the transducer is placed, it is necessary to deliver masking noise to the non-test ear to prevent the test signal being detected in that ear. Calibration for the narrow-band noise signals used for clinical masking are specified in the standard ISO 389-4:1994.[39] Masking noises used in clinical masking are calibrated in dB 'effective masking level' (dB EML). Presenting the masking noise at a given EML will raise the threshold for a pure tone of the same frequency as the geometric centre frequency of the noise to that level.[23] For example, if the threshold for a pure tone of a given frequency were taken when presenting (to the same ear) a noise centred at the same frequency and whose level was 50 dB EML, the masked threshold would shift from 0 to 50 dB HL.[23, 28]

A procedure for plateau-seeking for clinical masking is specified in ISO 8253-1:2010.[21] The masking noise is presented continuously to the non-test ear and is introduced first at a level where it is just audible. It is increased in steps of 10 dB and the threshold for the pure tone signal is re-evaluated. When the masking noise level can be increased by three 10 dB steps without changing the detection level of the test tone, this constitutes the masking plateau (See **Figure 51.10**). This is interpreted as the true hearing threshold of the poorer test ear. This method is known as the 'plateau-seeking' method.

There are constraints in the use of clinical masking: sometimes the masking plateau cannot be reached because the level of the masking noise is so high that it reaches the test ear by cross-hearing and it shifts the measured hearing thresholds. This is called 'cross masking', and is likely to occur when testing listeners with a large bilateral conductive hearing loss. Use of an insert earphone reduces the likelihood of cross masking in addition to the necessity for clinical masking. Additionally, special masking techniques may be required in these cases.

Although the plateau-seeking method is the standard procedure for clinical masking, clinicians sometimes use abbreviated procedures in which an initial masking noise level is used, and subsequent increments of this level, if necessary, are adaptively varied depending on the threshold shift in the presence of the masking noise (e.g. see Yacullo).[28] Such procedures have the advantage of using lower masking noise levels in most cases, and the disadvantage of not producing a masking noise level–threshold function. Masking noise level–threshold functions (usually called 'masking functions') can be useful to detect cases of central masking (a usually 5 dB threshold shift that occurs when the tone is presented together with a contralateral masking noise and may be related to central processes)[28] or cases of cross-masking. The clinician should use their judgement to determine which type of procedure is most suitable in each case.

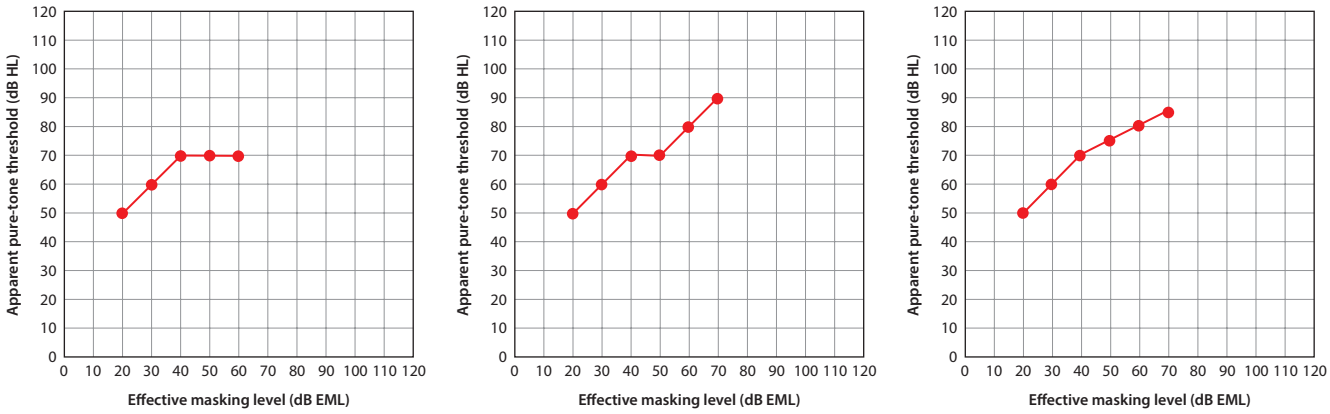


Figure 51.10 Examples of masking functions. The left panel shows a typical shape of the curve when a plateau is reached and the masked threshold is found. In this example, the threshold is 70 dB HL, as this is the level where the plateau is found. The central panel shows an example of cross-masking. Here the plateau is short, consisting only of two points. This is followed by a second 1 dB per dB slope. The right panel shows an example of central masking, where the slope of the function is less than 1 dB per dB. In this example a 5-dB increase of the hearing threshold follows a 10-dB increase in the masking noise, so the slope is 0.5 dB per dB.

TABLE 51.1 Rules or indicators for the use of clinical masking

'Rule'	Situation	What to do
1	The not-masked AC thresholds differ by 40 dB or more when using supra- or circum-aural headphones, or by 55 dB when using insert earphones.	Retest the AC threshold of the worse ear masking the contralateral ear.
2	The not-masked BC threshold of one ear is better than the AC threshold of either ear by 10 dB or more.	Retest the BC threshold of the ear with the worse AC threshold masking the contralateral ear. Use clinical judgement. Is it critical to diagnosis to apply this rule (e.g. when there are only small BC thresholds)? If the masked BC threshold has changed little (i.e. up to 10 dB), it may be necessary to retest the BC threshold of the ear with better AC thresholds masking the contralateral ear.
3	Rule 1 was not applicable, but the BC threshold of one ear (ear A) is 40 dB (for supra- or circum-aural headphones) or 55 dB (for insertion earphones) better than the not-masked AC threshold for the other ear (ear B).	Retest the AC threshold of ear B masking ear A.

Although interaural attenuation varies across individuals, there are some rules or 'indicators' for the use of clinical masking during audiometric testing. These rules are based on typical values of interaural attenuation. Table 51.1 summarizes the rules for the use of clinical masking as recommended by the British Society of Audiology,[23] for AC and BC testing. In clinical practice, there are often cases where it is difficult to obtain accurate masked thresholds.

It is fundamentally important for ENT doctors to have reliably masked audiometric information for discussion and decision-making of surgical options.

DURATION OF TESTING

The total time for testing should be managed with care to avoid fatigue and its subsequent impact on test results. It is recommended that the subject should have a short break if the test exceeds 20 minutes.[23]

INTERPRETING RESULTS

Test–retest difference

The test–retest difference in hearing levels measured on two different occasions is accepted as +/–5 dB without necessarily indicating a real change in hearing levels. If assessing average change in threshold across two or three frequencies, a difference of 10 dB is more likely to be significant.[38] The test–retest accuracy for absolute thresholds derived with BC transducers is poorer than that for AC transducers.[38]

Variability in responses

Variability in hearing thresholds can be influenced by multiple factors including:

- **subject variables**, including physiological noise or tinnitus, attention state, fatigue and motivation, and precise wording of instructions to the subject
- **method of assessment**, including the duration and variation in the intervals between signal presentations, subject positioning in test booth, ambient noise levels in the test environment, method of response (e.g. pressing a button or lifting a hand)
- **type and placement of signal transducer**, including removal of earrings and glasses when needed; relatively small changes in placement over the earphone in relation to the ear canal can affect the sound pressure at the eardrum
- **calibration of test equipment**, monitoring and maintenance of all parts including transducers, plugs and connectors.

Screening audiometry

There are procedures for screening audiometry, for example the one described in ISO 8253-1:2010.[21] The outcomes are either a 'pass' or a 'fail' rather than defined audiometric thresholds. Industrial or occupational hearing screening is often provided using automated audiometry and is not within the remit of this chapter.

The pure-tone audiogram

The results of PTA are plotted on the pure-tone audiogram, which is a graphic representation used to characterize hearing detection thresholds in each ear for clinical assessment.

The pure-tone audiogram is a graph where the *x*-axis shows the frequency of sounds in Hertz and the *y*-axis shows the sound level expressed in decibels hearing level (dBHL), where 0 dBHL represents the average threshold for otologically normal young individuals at each frequency. Thresholds in the minimal audibility curve (see Figure 51.1) are expressed in dB SPL (decibel sound pressure level). As mentioned above, the minimum sound pressure level required for the hearing threshold of a sound varies with frequency. Therefore, if the mean normal-hearing thresholds were plotted in dB SPL, a curve would be obtained. In contrast, in a pure-tone audiogram, the average normal-hearing thresholds across frequency lie on a straight line, as they are expressed in dBHL. Another difference between the graph in Figure 51.1 and

a pure-tone audiogram is that the levels in the *y*-axis are ascending from bottom to top in the former, but they are descending from bottom to top in the latter. Levels are shown in the pure-tone audiogram from –10 to 120 dB HL. Negative numbers mean that the measured thresholds are better than the average.

The *x*-axis, which is logarithmic, represents frequency in the range 125–8000 Hz, thereby covering the frequencies important for understanding speech and the frequencies of many environmental sounds. For example, 250 Hz is close in frequency to middle C on the piano keyboard.

Assessment is performed at each frequency across octave spaces, typically at 250, 500, 1000, 2000, 4000 and 8000 Hz. Inter-octave frequencies (e.g. 750, 1500, 3000 and 6000 Hz) may be included in steeply sloping hearing loss configurations or when the desired frequency resolution is greater (e.g. for the fitting of hearing aids). It is recommended to use forms with an aspect ratio of 20 dB : 1 octave to facilitate the visual reading of the audiometric curve. It is important to register the date of the test, the name of the examiner, the audiometer and transducers used and the date of the last calibration.

Figure 51.11 shows an audiogram chart. Note that the test results for each ear and transducer have different symbols. Outcomes for the right ear are usually plotted in red, and those for the left ear are usually plotted in blue. AC symbols are open circles for the right ear and crosses for the left ear. The thresholds are joined by continuous straight lines. In the UK, BC thresholds are either an open triangle for unmasked thresholds or a square bracket for masked thresholds (see below). BC thresholds are usually joined by broken straight lines. Conventions may vary slightly between countries. It is important to use conventional symbols in order to facilitate the interpretation of test results across institutions.

Figure 51.12 shows a simplified representation of the levels and frequencies of the sounds of speech and of environmental sources on the audiogram. Graphs of this type are used for counselling purposes, and the area where the speech sounds are represented is colloquially known as 'the speech banana'. Although the perception of these sounds should not be thought of as an 'all-or-nothing' event, merely reliant on the audibility at a given frequency/level, it is useful to see where conversational and environmental sounds fall on the audiogram plot. It should be noted that the audiogram is mainly focused on the range of frequencies that are important to understand speech.

Interpreting the pure-tone audiogram

QUANTIFYING THE EFFECT OF HEARING LOSS

Traditionally, hearing loss is characterized by its degree: mild, moderate, severe and profound. These degrees are defined as ranges where the average hearing threshold falls. An example of these categories is the classifications of the British Society of Audiology (2011),[23] which is based on the average of the hearing thresholds for 250, 500, 1000, 2000 and 4000 Hz, and describes four categories:

- Mild: 21–40 dB
- Moderate: 41–70 dB
- Severe: 71–95 dB
- Profound: 96 dB and above.

Classifications based on the average hearing loss originated from the need to have an easy way of describing cases among professionals or from professional to patient.[40] However, they do not describe the implications of hearing loss accurately for several reasons. First, hearing loss often affects hearing thresholds unevenly across frequencies. Examples are shown in **Figure 51.13**. The hearing losses shown for 'Example 1' and 'Example 2' have the same pure-tone average (60 dB HL) but the audiogram configuration (i.e. the shape of the audiogram, given by the difference in hearing thresholds across frequency) differs considerably across the two. The functional consequences of each hearing loss will vary significantly. These examples, most common in clinical practice, illustrate how inadequate the classification of hearing loss by degree based on hearing thresholds is.

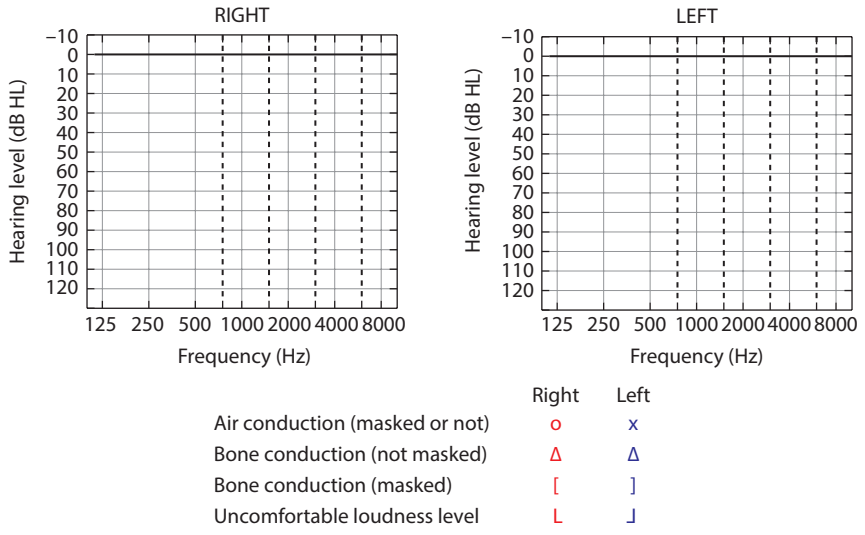


Figure 51.11 Audiogram chart and symbols used in clinical audiometry.

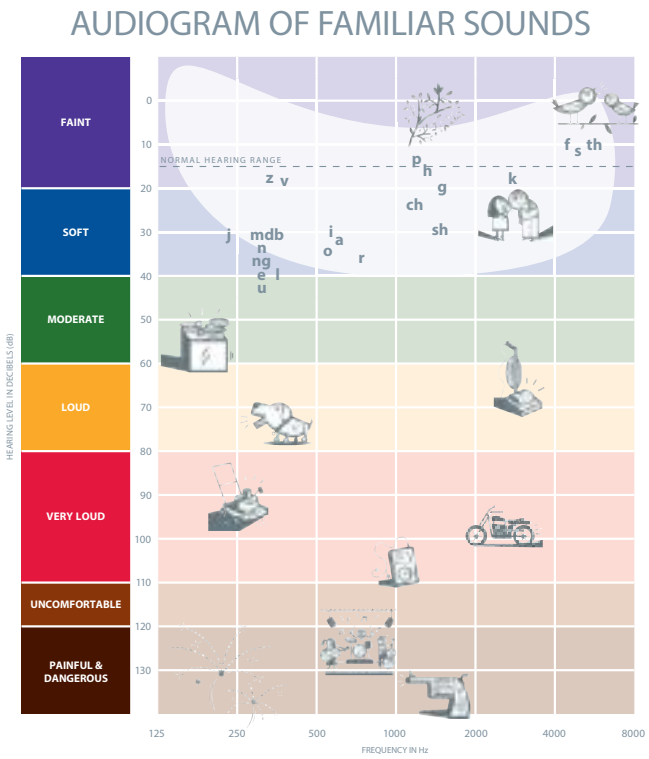


Figure 51.12 Audiogram of familiar sounds by the American Academy of Audiology. Reproduced with the permission of the American Academy of Audiology in the format "Republish in a book" via Copyright Clearance Centre.

It is also worth mentioning that even individuals with the same degree and configuration of hearing loss may have very different outcomes in real-life communication. The impact of hearing loss cannot be appreciated based purely on the audiogram, as characterization of the degree of hearing loss based purely on the hearing threshold does not account for suprathreshold deficits, such as in the mechanisms for frequency selectivity, temporal resolution and integration, etc. Thus, the degree of hearing loss defined by the hearing threshold does not adequately reflect the impact of hearing loss on auditory perception, communication and quality of life. In addition, other factors that can have an influence on the functional implications of hearing loss, such as the existence of other sensory deficits, use of hearing aids, lip-reading abilities, cognitive abilities and family support, among others, are not considered.

FUNCTIONAL IMPACT OF HEARING LOSS ON SPEECH COMMUNICATION

In terms of the functional effect of hearing loss categories, it can be seen that what is categorized as mild hearing loss may reduce half of the audible information in conversational-level speech, or even more for quiet speech or when at a distance. Thus, 'mild' is a misnomer in this context: the communicational impact of mild hearing loss is not mild but significant. For example, a person of school or university age will have trouble following teachers or lecturers, and persons of working age may struggle at company meetings. A moderate loss may make distant speech inaudible and degrade the quieter parts of conversational speech even at close range. A severe hearing loss makes speech inaudible even at close range, though the person may be able to hear some of her own vocalizations. A profound hearing loss prevents a listener from hearing his/her own speech or that of others at all without hearing-aid or cochlear implant use.

TYPES OF HEARING LOSS

As already mentioned, hearing loss can be broadly divided into four types: conductive, sensorineural, mixed or auditory neuropathy (see Figure 51.14).

Conductive and mixed hearing loss

A hearing loss is classified as 'conductive' when there is a difference of more than 10 dB between AC and BC thresholds at any frequency, which, as mentioned in 'Measuring the hearing thresholds' above, is considered a significant ABG. BC thresholds are generally at normal-hearing levels (equal or better than 20 dB HL) in cases of conductive hearing loss. If the BC thresholds are raised above 20 dB HL and there is a significant ABG, this is referred to as a 'mixed' hearing loss. Conductive hearing loss occurs due to the disruption of the transmission mechanisms of

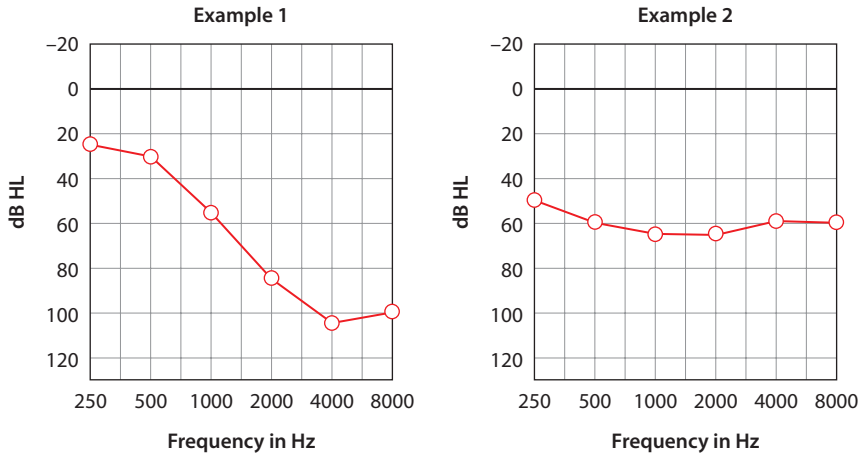


Figure 51.13 The hearing losses shown in the two right-ear examples have the same pure-tone average up to 4000 Hz (60 dB HL). However, the audiogram configuration (i.e. the shape of the audiogram, given by the hearing loss across frequency) is very different for the two ears. The functional consequences of each hearing loss will vary considerably.

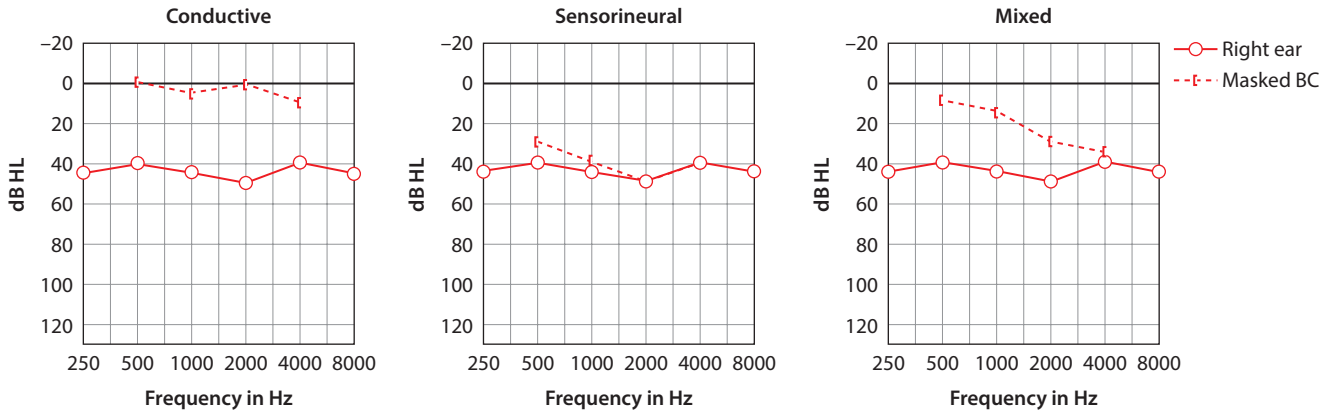


Figure 51.14 Types of hearing loss. **(a)** A conductive hearing loss, where the BC thresholds are normal, the AC thresholds are increased and there is significant ABG. **(b)** A sensorineural loss, where both BC and AC thresholds are increased and there is no significant ABG. **(c)** A mixed hearing loss, where the AC thresholds are increased, at least some of the BC thresholds are increased too and there is significant ABG.

the external and/or middle ear. For example, abnormalities of the tympanic membrane or the ossicles, or presence of fluid in the middle ear, lead to conductive hearing loss. Conductive hearing loss causes reduction in hearing sensitivity that may vary across frequency, but most aspects of sound perception remain generally unaffected as long as the signal is fully audible. This means that conductive hearing loss can be well compensated for by hearing-aid amplification. The maximum possible extent of conductive hearing loss is traditionally deemed to be 60 dB HL. However, all sounds are attenuated (reduced) equally by the extent of the hearing loss, regardless of their input level, so overall auditory deprivation from conductive hearing loss may be greater than for an equivalent level of sensorineural hearing loss with loudness recruitment.

The fluctuating nature of conductive hearing loss means that children with this type of hearing loss may have inconsistent perception of sound patterns and consequently reduced opportunities for recognizing familiar patterns of sound.[41] With the relatively high incidence of middle ear pathology in children, conductive hearing loss is very common and can also overlie cochlear-based sensorineural hearing loss, giving rise to a 'mixed loss'. Medical and surgical treatments are available for many cases of conductive hearing loss, sometimes with the possibility of hearing restoration. When there is a permanent conductive or mixed hearing loss, hearing aids stimulating via AC or BC and BC hearing implants are treatment options.

Sensorineural hearing loss and auditory neuropathy

Sensorineural hearing loss (SNHL) refers to impairment in the cochlea and/or the immediate (primary) nerve connections. The extent of SNHL can range from minimal to total and is usually permanent. The inclusion of 'neural' in 'sensorineural' only refers to the nerve connections from the inner hair cells to the auditory nerve (CN VIII). This is therefore different from auditory neuropathy spectrum disorder (ANSD) in which neural firing may be diminished or out of synchrony across nerve fibres, causing fluctuations and distortion in speech information.

SNHL is shown on the audiogram by both AC and BC thresholds being within 10 dB of each other. Recall that there is an artefact in the standards for BC thresholds at 4000 Hz which means that a discrepancy of 15 dB between AC and BC thresholds is often seen but does not indicate a conductive hearing loss.[33] Be aware that in moderate-to-profound hearing loss some low-frequency BC signals may be felt as vibration, giving the impression of an apparent mixed hearing loss at the low frequencies. The thresholds at which individuals can feel the bone conductor vibration can be as low as 25 dB at 250 Hz, 55 dB at 500 Hz and 70 dB at 1000 Hz.[23]

Options for medical or surgical interventions are very limited in cochlear-based mild or moderate impairment. Most cases of SNHL are treated with hearing aids or hearing implants.

Example audiograms for the different types of hearing loss are illustrated in **Figure 51.14**.

WHAT THE AUDIOGRAM DOES NOT SHOW

Sources of distortion in cochlear hearing loss

Although the measurement of hearing thresholds is the most commonly used method of characterizing hearing status in clinical settings, there are many changes in sound perception that can occur and are not apparent on the audiogram.

These other features of impaired auditory perception may combine to cause reduced clarity of hearing for complex sounds, particularly in understanding speech in noisy listening environments. The interested reader is referred to Moore[42] for a comprehensive analysis of the perceptual effects of cochlear hearing loss. Below is a brief description of the perceptual deficits most commonly associated with cochlear hearing loss.

Loudness recruitment: As stated above, this refers to the reduced dynamic range of hearing between the hearing threshold and the upper limit of loudness tolerance for the listener. A feature of cochlear hearing loss is that loudness grows faster with increasing sound level than for normal hearing. Therefore the dynamic range over which a person

with hearing loss can hear becomes narrower compared to that of a person with normal hearing. In other words, if a person had a hearing threshold of 60 dB HL and a loudness discomfort level of 90 dB HL, their dynamic range of hearing would be 30 dB. This would be about one-third of the dynamic range of someone with normal hearing (when measured in dB) and creates difficulties in providing amplification to make more low-level sounds audible while preventing amplified sounds from being uncomfortably loud. The 'active mechanism' of the outer hair cells (OHCs) on the basilar membrane is believed to be involved in the normally wide dynamic range of hearing. By virtue of this mechanism, the response of the basilar membrane increases in a compressive manner with increasing input level for a wide range of sounds levels between moderate and perhaps very high levels. This means that, for example, a 10 dB increase in sound level leads to only a 2.5 dB increase in the response of the basilar membrane.[43] Damage to the active mechanism in hearing loss cases leads to a reduction or loss of cochlear compression and thus to a narrower dynamic range. Loudness recruitment is addressed by the use of amplitude compression in current hearing-aid design.[42]

Loss of frequency selectivity: Frequency selectivity is the ability of the hearing system to separate out the individual frequency components of a complex sound.[15] Damage to the OHCs in the cochlea leads to a reduction in the sharpness of the basilar membrane response to a narrow-band sound. When the active mechanism of the OHCs becomes damaged, perhaps through noise exposure and/or ageing, the ability to separate the frequency components of complex sounds is degraded. The loss of frequency selectivity makes hearing-impaired people more susceptible to masking.[42] This leads to problems in understanding speech, particularly in a background noise, even when the noise does not have the same spectrum as the speech.[43] The perception of timbre, which allows the listener to distinguish between sounds of the same loudness and pitch (e.g. the same note played by two different musical instruments), is also affected when frequency selectivity is impaired. A reduced ability to perceive differences in timbre can lead to poorer vowel discrimination.[42]

Loss of ability to use temporal fine structure (TFS) information: A complex sound reaching the ear is separated in the cochlea into a series of narrow-band signals. These signals can be characterized by their envelope (the slow changes in the amplitude of sound over time) and their TFS (the rapid changes in the amplitude of sounds, with rate close to the centre frequency of the band). Deficits in TFS perception may result from loss of auditory neurons or loss of synapses between inner hair cells (IHCs) and neurons. These aspects are represented in the timing of neural spikes. TFS information is relevant for pitch perception. Deficits in pitch perception can lead to problems in the identification of the prosodic aspects of speech (i.e. to distinguish a question from a statement), the identification of a speaker, and the discrimination of speech sounds.[42] In addition, impaired TFS perception may reduce the ability for listening in the dips of a fluctuating masker, for example, when listening to a talker in the presence of a competing background talker, and to 'hear out' a target speaker in the presence of a competing talker based on differences in fundamental frequency (the fundamental tone produced by the vibration of the vocal folds).[42, 44] Deficits in the processing of TFS information may also lead to reduced sound localization abilities.[44]

Loss of temporal resolution: Temporal resolution refers to the ability to detect changes in auditory stimuli over time, particularly in their envelope.[15] Temporal resolution may be compromised in cochlear hearing loss due to the partial or complete loss of the compressive mechanism of the basilar membrane. When cochlear compression is reduced or lost, sounds that have fluctuations in their envelope may seem to have even greater fluctuations. This may make it difficult to detect gaps in those sounds.[42] This is relevant to speech perception as one feature of consonants such as /p/, /b/ and /t/ is the presence or absence of a gap between the burst of the consonant and the start of voicing of the following vowel, and this feature is one of the cues for the discrimination of these consonants. Another consequence of a loss of temporal resolution is an increased threshold for detecting a sound preceded by another more intense sound. In speech perception, this can make low-level consonants preceded by more intense vowels more difficult to hear.[42]

Cochlear dead regions: A dead region in the cochlea is a place on the basilar membrane where the IHCs or synapses are not functional or function very poorly.[45] When a signal excites only a region with such IHC damage, such signal would theoretically be inaudible. However, if the sound level is increased, the area of excitation along the basilar membrane spreads to a non-dead region, and the signal may become audible. If a person has a dead region at 4000 Hz, they may hear sounds with a frequency of 4000 Hz using IHCs placed at a neighbouring point along the basilar membrane, tuned to a different frequency. This is known as 'off-frequency listening'.[45] The pure-tone audiogram might show a detection threshold for 4000 Hz, but this would not reflect encoding of the signal by the correct part of the cochlear hearing mechanism. The recognition of speech cues falling well within extensive dead regions is limited.[46–48]

In summary, SNHL is associated with changes in the individual experience of loudness perception, frequency selectivity, pitch perception and speech recognition, especially when listening in noise. It is therefore important to recognize that people with similar pure-tone audiograms may have very different experiences of hearing in everyday life and they may receive very different help from hearing-aid amplification.

Human speech is a great deal more complex than the simple pure-tone signals that are used to define the lowest level of detection across frequencies on the audiogram. The distortions that occur with SNHL are not assessed by the pure-tone audiogram, and are often not acknowledged by professionals working in hearing loss.

Improved hearing for speech is, however, the primary motivation of the patient looking for ENT intervention for hearing impairment.

SPEECH AUDIOMETRY

In the past speech audiometry was an important component of the diagnostic test battery for distinguishing peripheral from central causes of hearing loss, particularly acoustic neuroma. This role has been superseded by imaging techniques.

Speech audiometry is now mainly used for assessing rehabilitation outcomes from both hearing aids and cochlear implants. There are also specialist test applications developed for auditory processing disorders which may have central auditory components.

Speech intelligibility

SPEECH INTELLIGIBILITY INDEX

The speech spectrum for conversational speech can be represented on the audiogram as a shaded area covering the frequencies range 125–8000 Hz and the level range from 20 to 60 dB, as previously shown in **Figure 51.12.** Some of the acoustic information to detect consonants has levels lower than 20 dB, requiring hearing levels below 20 dB in order to hear all the speech sounds. A way of predicting the impact of hearing loss on speech intelligibility is to consider the proportion of speech information that is audible to the patient given their hearing deficit on the audiogram. The Speech Intelligibility Index (SII)[49] is calculated as the product of a band–importance function (the contribution of a frequency band to the intelligibility of speech) and a band–audibility function summed across all the frequency bands. Additionally, the SII takes into account the known sources of distortion in cochlear hearing loss and the impact of these on speech understanding for the listener. However, predictions of the SII for listeners with hearing loss are not always accurate, particularly when hearing loss is greater than 55 dB.[50] It is important to understand that no method of amplification can offset the sources of cochlear distortion or provide 'normal hearing'; it can only improve the audibility of sounds. Additionally, there is usually a period of relearning the new sound patterns of speech through amplification, derived from a consistent period of hearing-aid use over several weeks or longer.[51]

HEARING LOSS AND SPEECH INTELLIGIBILITY

Normal-hearing listeners use multiple cues to understand speech. For sustained vowels, the main cues are the formant patterns (the frequencies of the resonances of the vocal tract, added to the fundamental tone produced by the larynx).[52] For vowels in conversational speech, duration and temporal pattern of the direction of the change of the formant frequencies into and out of the syllable nucleus are more relevant.[52] For consonants, there are several possible cues that can be used for identification. These vary across consonant groups. Because of the redundant nature of speech, there is usually more than one cue available at a given time. In general, features such as the gross spectral shape of a sound and the relationship with the spectral shape of the next sound, the rate of spectral or amplitude change, the presence or absence of periodicity, the presence or absence of a silent gap, the delay in the start of voicing after this silent gap, the formant transitions and envelope cues (given by the relative slow changes in amplitude over time) have all been shown to provide important information.[15] Detecting these features requires the auditory system to perform temporal and spectral analyses of the speech signal. These analyses are disrupted by the perceptual deficits associated with SNHL, and this has an impact on the ability to understand speech in quiet and in noise. The interested reader is referred to Revoile[53] for a review of the use of cues for speech intelligibility by persons with hearing loss. It is extremely common in the clinic to find patients with SNHL who have trouble understanding speech, particularly in situations where the talker they want to hear is not the only speaker, and there are other talkers in the background. This is known as the 'cocktail party problem',[54] and it is an issue to some extent even with the use of hearing aids or hearing implants.

Speech testing in clinical audiometry

Hearing loss impacts greatly on speech understanding in everyday situations in ways that cannot be represented simply by the ability to detect pure tones. This role is fulfilled by the use of speech testing both in identifying the cause of hearing loss and, more importantly, in the potential for improved ease of speech understanding through surgery or applied technology. Speech audiometry methods are specified in the standard ISO 8253-3:2012.[55] They are an important component of hearing assessment which cannot be represented by simpler psychoacoustic testing or assessing the hearing-aid output levels to estimate the audibility of amplified speech. In addition, an important diagnostic and often underutilized role of speech testing is in identifying non-organic or feigned hearing loss, either in isolation or as an overlay to a true physiological hearing deficit.

Historically, speech testing used single words presented at different levels in a defined procedure called 'speech audiometry' to derive an individual's performance-intensity (PI) function. Different features of the PI function were used to infer diagnostic indications. Features such as the optimal discrimination score (ODS) and the corresponding half peak measure were used to characterize and differentiate potential central causes from peripheral hearing loss.[12, 56]

There are a number of terms still used when testing with speech material from these earlier roles. **Speech discrimination** implies an ability to hear a difference between a set of alternative response options. **Speech intelligibility** and **speech recognition** are used interchangeably now,

rather than in the defined circumstances of their original use (as a measure of fidelity of a transmission system, and as defined by the PI function in speech audiometry, respectively).

HEADPHONE OR SOUND-FIELD TESTING

As part of the diagnostic process of hearing assessment, speech material may be presented to each ear through the use of headphones or insert earphones. When the test material is used to assess benefit for speech understanding from use of hearing devices, speech is presented in the sound field, thereby being processed by the hearing aid or hearing implant before being delivered to the patient's ears. As with any ear-specific testing, clinical masking may need to be delivered to the non-test ear to prevent cross-hearing in the non-test ear. When measuring the threshold for speech, contralateral masking is used when the speech presentation level in dB HL exceeds BC thresholds in the better-hearing ear by 40 dB or more at two frequencies. The noise masker used for speech audiometry is a 'speech-shaped noise'. This means that it is the result of having filtered white noise to match the long-term average speech spectrum.

CALIBRATION OF SPEECH TEST MATERIAL

Recorded speech materials should be used for testing, as this increases control of the testing conditions and quality of the stimuli. The recorded speech materials include calibration signals. When testing in the sound field (presenting the stimuli via a loudspeaker), the calibration signal is usually a narrow band of noise or a frequency-modulated tone at 1000 Hz, as defined in ISO 8253-3:2012.[55] The level of this calibration signal is equal to the level of the speech signal derived with a specified frequency- and time-weighting and is expressed as the equivalent sound pressure level, L_{eq} with A-weighting. The silent pauses between words or test items are discarded in the measurement of the equivalent sound pressure level. When speech testing is in the sound field, the calibration method is typically performed using a sound level meter and defined in dB A. Presentation levels need to be checked in the calibration position (corresponding to the position of the listener's head) – on a regular basis.

When speech testing is performed with headphones, the speech signals are usually calibrated by playing the calibration sound (usually a 1000-Hz pure tone) and adjusting the audiometer and so that the VU-meter displays the desired value, usually 0. In computer-based audiometers instructions for calibration vary depending on the options of each device. The presentation level of speech through headphones is typically expressed in dB HL.

EQUIPMENT FOR SPEECH TESTING

The level of presentation of speech is typically controlled through a two-channelled clinical audiometer or computer-based audiometer software. In sound-field audiometry the loudspeaker is typically placed at a distance of 1 m from the listener and at the same height as the head. Competing noise may be presented either from the same loudspeaker or from a pair of loudspeakers located on either side, at a recommended azimuth (i.e. angle relative to the head of the listener) of +/– 45 degrees, 90 degrees or 180 degrees depending on the functional testing required. Multi-speaker configurations can also be used.

SPEECH MATERIAL

The simplest and most commonly used speech material in clinical audiology is lists of monosyllable, real words made up of three speech sounds, or 'phonemes', usually a consonant, a vowel and a consonant, for example 'hat'. Most languages have enough monosyllabic, familiar vocabulary items to develop lists of words in which each list has a similar number of types of phonemes in approximately the same proportion as these speech sounds occur within the given language. Some languages have a small number of monosyllabic words available and use two- or three-syllable words (e.g. Spanish, Finnish, and Arabic).

PRESENTATION METHOD

The typical way that speech tests are delivered is through prerecorded material played from a computer or CD and passed through the audiometer so that the level of presentation can be controlled. As with PTA, the method of presentation, calibration and the acoustic characteristics of the test room need to be specified and consistent for valid and comparable results.

The acoustic characteristics of a test room fulfilling a quasi-free sound field considered adequate for clinical speech testing is specified in ISO 8253-3:2012[55] but the requirements of ambient noise levels are less restrictive than for PTA since the speech signal is presented at suprathreshold levels.

OPEN-SET AND CLOSED-SET TESTING

Responses are typically made by the patient repeating the word they identified. This is referred to as 'open-set testing' as there is no constraint on the options that the patient has in the response that they make. The tester records their response or the number of speech sounds they correctly identified from the target word. For example, response 'cat' for test item 'hat' gives a score of two out of three, although there are many variations on scoring methods for different languages. For open-set speech material to be valid the test material must be novel to the listener. Repeated use of the same material, whether made up of single words or sentence material, in open-set testing makes results invalid due to learning effects. There are therefore practical constraints from the number of speech tests available for patients requiring ongoing speech recognition assessment, such as those with hearing aids, cochlear or brainstem implants.

An alternative method of presenting closed-set speech material gives the listener a selection of items from which to choose a response. This may be from a list of options on a computer screen, a written list of words or a constrained

range of options, for example by repeating spoken numbers between 1 and 100. The benefit of closed-set testing is that one can analyze the individual speech sound confusions that were made between the target word and the response and therefore derive confusion matrices, which can be crucial when adjusting hearing-aid features or fine-tuning cochlear-implant maps for instance. Scoring of responses in closed-set testing does not require clear articulation by the patient, and results can be scored by the computer in many cases.

There are many different types of material that can be used to assess speech detection, discrimination and recognition. In order to assess the functional benefit of a particular hearing aid for an individual, open-set sentences presented in quiet and in different types of noise may be required. For assessing the discrimination potential of a cochlear-implant recipient, one may use closed-set nonsense syllables (such as /aka/, /ubu/, and /isi/) to evaluate consonant discrimination while keeping the vowel context consistent. For assessing whether the frequency-lowering feature in a hearing aid is helpful (a feature intended to increase the access to high-frequency information for people with high-frequency hearing loss), one could use a single word final-s test in closed-set testing; for example, a plural detection test, where the pictures of a 'brick' and a selection of 'bricks' are presented as alternative response options, are used to indicate whether detection of the sound /s/ is improved with the frequency-lowering feature activated.[57, 58]

RESPONSE MEASURES

The speech reception threshold (SRT) is defined as the lowest speech presentation level at which the individual is able to correctly identify 50% of the items.[59] For a given individual, the outcome depends on the type of speech material that is used. In general, the more familiar and meaningful the information that is audible to the listener, the lower the minimum presentation level that is required for them to identify the test item. Thus, meaningful sentences will be correctly identified at lower presentation levels than single words. Familiar single words will be identified at lower levels than nonsense syllables. Cognitive resources are employed when performing intelligibility tasks,[60] especially when not all of the speech cues have been audible or there are competing speakers in the background. In other words, listeners use cognitive resources such as memory and attention to focus on the target speaker and fill in the gaps of missing information. In practice this tends to conspire against patients with high cognitive ability fulfilling criteria for cochlear implantation on the basis of their sentence recognition score, as they are very efficient in working out the spoken message in spite of their poor auditory abilities. However, the increased demand for cognitive resources often leads to fatigue and therefore has an impact on quality of life.

Different types of speech material are shown in Table 51.2. For each of the types of speech material used there is a different level of linguistic and acoustic redundancy and the opportunity for the cognitive and linguistic function of the listener to influence scores, independent of hearing status. Any single test material is a compromise between validity in terms of representing real-life listening experience (e.g. sentences in noise) and repeatability of results in defining audibility (e.g. by using nonsense words in quiet).

The difference in two scores that infers a significant change in the two test conditions is related to the number of test items in the list. The PI function can be quite steep. For example, for normal-hearing listeners, an increase in presentation level from 20 dB to 25 dB may lead to a 20% increase in the score for word recognition.[12] The more the steepness of the slope of the function increases, the more predictable speech material is. Thus, the level at which speech is presented and the consistency in calibrating this level in test sessions is critical in deriving useful comparative information across test sessions and conditions.

SPEECH-IN-NOISE TESTING

Measures of speech recognition in competing noise give a better representation of cochlear distortion and the potential benefit from hearing aids than speech in quiet, which aims to characterize performance in optimal listening environments. Speech-in-noise testing is generally carried out using sentences presented in a specific type of noise, by scoring the number of keywords correct. In adaptive scoring algorithms the signal-to-noise ratio (SNR) is varied (by changing the level of the speech or the noise) depending on how many of the keywords are correctly identified. Typically, tests are performed to find the SRT in noise. This is the SNR required to identify 50% of the test items correctly. An outcome of 5 dB SNR

TABLE 51.2 Different types of speech material commonly used in clinical practice

Speech material	Detection	Discrimination	Recognition	Speech in noise	Clinical uses
Phoneme	Ling six-sound test (/m/ /a/ /u/ /i/ /s/ /sh/)[61]	Repetition of Ling sound	Identification of item containing the Ling sound, e.g. snake for /s/		Setting sensitivity, e.g. hearing-aid gain, cochlear-implant map
Word	Plurals test[57]	AB words lists[62]	McCormick toy test[63]	Adaptive McCormick toy test[64]	Evaluation of frequency-lowering hearing aids, indication or assessment of assistive technology
Sentence		ASL[65] BKB[66]	GASP[67]	HINT[68]	Assessment of hearing aids, cochlear implants and remote mics

means that the speech needs to be presented at 5 dB above the level of the noise for the individual to identify 50% of words correctly. Similarly, an SRT equal to −5 dB SNR, means that the noise level was 5 dB above the speech level and still the words were recognizable 50% of the times. In a clinical setting, the speech-in-noise measure gives an indication of distortion in the hearing mechanism, regardless of hearing level on the audiogram. Aside from the auditory factors involved, the value of the SRT depends on the characteristics of the background noise[69] (e.g. steady noise, competing talker, multi-talker babble), reverberation,[56, 70] as well as linguistic[71] and cognitive factors.[60]

It can be seen from this short section on clinical testing with speech materials that this is an area of rapid development, largely driven by changes in hearing-aid technology and hearing implants and the new testing that is necessary for evaluating individual hearing potential.

OBJECTIVE TESTS OF AUDITORY FUNCTION

Decades ago special tests with pure tones, usually termed 'suprathreshold audiometry', were used to distinguish cochlear and retrocochlear hearing loss. The most popular tests were the Short Increment Sensitivity Index (SISI) test[72] and the tone decay test (TDT).[73] The SISI test is based on the detection of an intensity increment superimposed upon a pure tone. Traditionally, the outcomes of the SISI test have been considered indicative of cochlear pathology if the person was able to detect a critical number of 1 dB increments in a continuous pure tone presented at 20 dB above the threshold. The TDT is based on the phenomenon of adaptation. The TDT outcomes have been interpreted as suggestive of retrocochlear pathology if the person is unable to perceive a pure tone presented at 10 dB above the threshold over 60 seconds, requiring several 5 dB increments of the sound level to maintain perception over this interval. However, some persons with cochlear hearing loss present pathological adaptation and therefore score positive in the TDT probably due to dysfunction of the IHCs/neurons.[74] In addition, some individuals with retrocochlear pathology such as acoustic neuroma score positive in the SISI test and/or negative in the TDT.[75] The consistency of outcomes of the special tests varies within groups classified by audiogram shape (e.g. flat loss, high-frequency hearing loss, low-frequency hearing loss) and with tumour size (smaller tumours leading to greater inconsistencies).[75]

Nowadays, image studies and objective tests have replaced these special tests in the differential diagnosis of cochlear and retrocochlear hearing loss. The most popular objective audiology tests used for topographic diagnosis are briefly introduced below.

Measuring middle ear function

A test-battery approach is used to assess middle ear function and hearing threshold levels. Tympanometry is used to assess middle ear function and the mobility of the eardrum. This test confirms the presence of middle ear effusion when tympanometry shows a flat compliance trace. Additional testing through the use of tympanometry includes measurement of the acoustic stapedial reflex, elicited by brief pure tones or noise bursts. The lowest intensity of sound that triggers the reflex is the acoustic reflex threshold (ART), and this can give an objective measure of loudness recruitment in addition to the subjective uncomfortable loudness level, which can be subjectively measured following the PTA.[76] An absent or abnormal stapedial reflex with normal middle ear pressure is characteristic in cases of otosclerosis.[77] The stapedial reflex threshold and decay have been used in the assessment of cases of acoustic neuroma.[75] However, it emerged in the last decades that its sensitivity is relatively low compared to PTA asymmetry and, most importantly, because of the high levels required in these cases, it poses a hazard on residual hearing.[78] The stapedial reflex can be electrically evoked in users of cochlear implants in order to obtain information about their dynamic ranges.[79] These tests are covered in Chapter 48, Physiology of hearing.

Otoacoustic emissions

Otoacoustic emissions (OAEs) are low-level sounds that are recordable in the external auditory meatus and reflect the active mechanism of the OHCs in the cochlea.[80] These are absent if there is damage to the OHCs. OAEs are an important part of the evolving test battery, particularly when screening for hearing loss in early life. It is advised that the measurement of OAEs is combined with tympanometry, especially in screening cases where the OAEs are absent. The reason for this is that middle ear problems can interfere with the recording of OAEs. Thus, clinicians may misinterpret the absence of OAEs as indicative of sensorineural loss if they are unaware of the existence of middle ear pathology.[81] These tests are covered in Chapter 48, Physiology of hearing.

Electrophysiological tests including ABR

Auditory brainstem response (ABR) testing measures the nervous system activity around the primary auditory pathway which can be affected by tumours of the eighth nerve and neural demyelination. The normal result is a waveform with multiple peaks (known as waves I, II, III, IV and V) that are generated by neurons at different levels of the auditory system from the distal portion of the eighth nerve to the midbrain. The ABR is a test of neural synchrony but is also used to estimate hearing sensitivity, particularly in predicting hearing thresholds in infants.[82, 83] Aside from the analysis of the morphology of the response, the observation of response parameters such as the wave I–V interpeak latency and the interaural latency difference of wave V and others are useful in the functional assessment of the auditory nerve.[84, 85] Electrophysiological tests can be electrically evoked in users of cochlear implants.[86] These tests are discussed in Chapter 48, Physiology of hearing.

FUTURE RESEARCH

- Methods that involve machine learning have been developed to automate audiometric testing and decrease its duration. This approach tends to minimize the number of trials used while achieving outcomes that are close to conventional PTA and some additional information, as testing is not limited to the standard frequency intervals. For example, in the implementation developed by Schlittenlacher et al.,[87] the frequency and level of each signal after the initial stimulus are selected based on the responses to all previous trials in order to maximally decrease the uncertainty of the outcome.
- Systems have been developed lately that perform audiometry with a computer and a special headset composed of insert earphones enclosed by circum-aural cups. These systems monitor background noise and do not require a soundproof booth.[88] This has potential for use in caring for persons unable to attend a clinic, or in surveillance audiology, where workers exposed to noise are screened for hearing loss.
- Internet-based systems have been developed to perform PTA remotely. This is known as 'teleaudiometry'.[89] Some of these systems allow for the storage of results in a 'cloud' format, making them available to the user from any device. They also have potential for the analysis of the large datasets collected.
- Smartphone and tablet apps have emerged recently to perform PTA with domestic headphones. However, the reliability of these systems is usually low.[90]
- Psychoacoustic tests have been developed that test for the dysfunction of the IHCs by detecting and characterizing 'dead regions' in the cochlea.[91, 92] Other tests assess the ability to use temporal fine structure information.[93, 94] Although these tests have been available for some time, most of them are not implemented in clinical equipment. They can be carried out easily with a computer and good-quality sound card and headphones, but it is expected that clinical use will increase once they are integrated in the test batteries included in audiometers.
- Speech audiometry is being complemented with objective measurements of listening effort such as pupillometry[95–97] or EEG[95, 98] in order to increase the sensitivity of the test battery when comparing different hearing devices or evaluating technology features (i.e. algorithms for noise reduction). It is expected that new clinical tools will be developed based on these findings.
- Speech recognition systems are being developed in order to replicate the speech recognition issues associated with ageing. Such systems could assist audiologists, reducing the time needed to optimize hearing-aid selection and fitting.[99]

KEY POINTS

- PTA is often the first functional test of hearing performed in the clinic. It provides basic information about the type and degree of hearing loss.
- However, performance in PTA relies on sound detection and therefore the PTA outcomes do not quantify or characterize other deficits that have a significant impact on communication.
- PTA and speech audiometry must be carried out following standardized procedures, equipment and environment, and the outcomes must be recorded in forms following conventions to facilitate the circulation of clinical information among health professionals.
- Speech audiometry is essential in the assessment of the impact of hearing loss on communication, particularly when assessing candidacy for or the outcome of hearing aids, hearing implants or assistive listening devices. The test battery in speech audiometry is rapidly evolving to adjust to the technological changes of hearing aids and hearing implants, and new measures are emerging that assess listening effort in order to achieve greater sensitivity.

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CHAPTER
52

EVOKED MEASUREMENT OF AUDITORY SENSITIVITY

Jeffrey Weihing and Nicholas Leahy

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: auditory evoked potentials, auditory brainstem response, middle latency response and auditory late response.

INTRODUCTION

Excitation of auditory neurons by an acoustic stimulus presented at the ear results in electrical activity that can be recorded at the scalp using electrodes. Though small in amplitude, this electrical response can be isolated from the background electroencephalogram (EEG) by averaging the auditory electrical activity across many successive presentations of an acoustic stimulus. This averaged auditory electrical response, or auditory evoked potential (AEP), can be used to infer the relative health of various peripheral and central auditory regions. For instance, a reduction in amplitude of the evoked potential or prolongation of its latency may indicate an inability of the auditory neurons to respond efficiently to the stimulus, or it may reflect a reduced ability of the cochlea to respond to the sound and stimulate the auditory neurons. In either case, the AEP would reflect auditory pathology.

There are several obligatory AEPs that are used by audiologists in the diagnosis of hearing disorders. These potentials include the auditory brainstem response (ABR), middle latency response (MLR), and auditory late response (ALR). Historically, much of the clinical interest in AEPs has focused on the ABR. Initially used as a diagnostic measure in the detection of acoustic neuromas, applications of the ABR have expanded to include assessment of cochlear hearing sensitivity (i.e. threshold ABR). Part of the utility of the threshold ABR is a result of this AEP being relatively unaffected by sleep or sedation. Thus, patients who are difficult to test or who are too young to have their thresholds assessed by behavioural audiometry can often have their hearing thresholds quantified using the threshold ABR.

Neural generators for the remaining obligatory AEPs, the MLR and ALR, are situated superior to the ABR generators. Like the ABR, these measures have also been used to identify neurologic dysfunction and/or to establish hearing threshold. Since the MLR and ALR both include cortical contributions, they provide a more comprehensive view of the ability of the central auditory nervous system (CANS) to respond to sound. They are limited, however, by the requirement that the patient remain awake during the procedure. In addition to the diagnosis of neurologic dysfunction and establishing threshold, some of these later AEPs have also been used in the assessment of central auditory processing disorder (CAPD). CAPD occurs as a result of CANS dysfunction and is thought to interfere with the processing of speech when in complex listening situations.

The present chapter will provide a discussion of these three AEPs as they relate to clinical audiology. Given the broad application of the ABR in current audiology practice, the majority of this discussion will centre on this AEP and how it can be used to establish threshold and diagnose neurological issues. However, some consideration will also be given towards the end of the chapter to the MLR and ALR. These latter potentials complement the ABR in many clinical situations and can be used to test some aspects of auditory function that are not assessed by the ABR alone.

EVOKED POTENTIAL BASICS

There are several principles that apply to all of the AEPs discussed in this chapter that we will consider here briefly. AEPs are a reflection of synchronous activity in auditory neural generators resulting from the presentation of an auditory stimulus. Activity in these generators creates an electrical field that has a positive and a negative pole. To measure this activity at the scalp, at least three electrodes must be placed: an inverting, non-inverting and ground electrode. **Figure 52.1** shows electrodes placed on the scalp for acquisition of different AEPs following the 10–20 system.[1] For the ABR, the non-inverting electrode is placed at Fz and the inverting electrode is placed at either A1 (for left-ear stimulation) or A2 (for right-ear stimulation). The ground electrode is also placed on the forehead some distance below Fz. For the MLR and ALR, the location sites for the inverting and ground electrodes are similar to the ABR. However, for the non-inverting electrode, these potentials may utilize Cz or a combination of C3 and C4 instead of Fz.

There are many sources of noise that can interfere with the acquisition of AEPs. These sources may be acoustic, electric or biological in nature. In order to partly reduce the negative influence of these noise sources, AEPs are acquired through a process called physiological averaging. In averaging, the auditory system's electrical responses to many presentations of a stimulus are averaged together. Averaging will tend to enhance the AEP while reducing the effect of noise.[2] This occurs in part because noise is mostly random in its occurrence while AEPs occur at a predictable latency post-stimulus onset.[2] A common exception to this rule is 60 Hz electrical line noise, which can cause sinusoidal-type interference with the evoked potential. This line noise can sometimes be reduced by using special filters, changing stimulus rates or instituting improved grounding precautions.

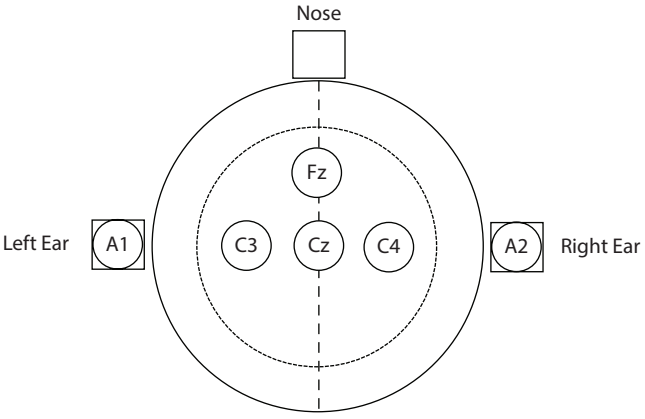


Figure 52.1 Electrode locations following the 10–20 system. The image is a superior view of the top of the scalp. A1 and A2 are located on the earlobes or mastoids. Fz is located on the high forehead and Cz is located at the centre of the scalp. C3 and C4 are located to the left and right of Cz, respectively. A ground electrode (not pictured here) is placed some distance below Fz on the forehead.

AEPs are commonly evoked with a click stimulus, which is a 100 microsecond (msec) rarefaction or condensation square wave pulse. The very rapid acoustic wave front of a click yields an abrupt stimulus onset. As the ABR is a stimulus-onset response, the abrupt onset provided by a click will frequently evoke well-formed ABRs. Spectral energy of the click measured acoustically at the ear canal is broadband but tends to be greatest in the 2000–4000 Hz range.[3] AEPs can be evoked to other stimuli, including tone bursts. Tone bursts are sinusoidal and, relative to a click, can be longer in duration with a more gradual onset and offset. The longest duration tone bursts can be used for the MLR and ALR, while the ABR makes use of shorter duration tone bursts. The spectrum of tone bursts varies by the duration of the stimulus, with longer stimulus durations showing less splatter of spectral energy into bands around the centre frequency.[4]

Stimulus intensity level for AEPs is expressed as dB normal hearing level, or dB nHL. This dB unit uses the average behavioural hearing threshold for normal hearing individuals as its reference. As an example: if calibrating a click stimulus, one would obtain an average behavioural threshold to the click in a sample of normal hearing individuals. This threshold would correspond to 0 dB nHL. Subsequently, any given dB nHL presentation level used in the clinic would reflect how much higher or lower the presentation level was relative to the average behavioural hearing threshold for normal-hearing individuals. If an 80 dB nHL presentation level was used, this would indicate that the level was 80 dB above the average normal behavioural threshold to the stimulus. Sometimes AEP equipment is not calibrated in dB nHL for all stimuli. In such cases, the clinic should make sure to establish their own behavioural calibration so a correction factor can be applied to the presentation level on the equipment display.

DIAGNOSTIC AUDITORY BRAINSTEM RESPONSE

Overview

The ABR is a response to stimulus onset and arises from the auditory nerve and low brainstem. It was first reported by Jewett and Williston,[5] who identified a complex occurring under 10 msec post-onset of an auditory stimulus that was comprised primarily of five potentials. These potentials, or waves, are labelled consecutively from I to V, with the earliest wave occurring near 1.5 msec and the latest around 5.5 msec in the normal auditory system. The waves were subsequently correlated with various neural generators of the peripheral and central auditory system.[6–8] Wave I reflects a neural response which originates from the distal end of the auditory nerve, wave II from the proximal end of this nerve, wave III from the cochlear nucleus, wave IV from superior olivary complex and lateral lemniscus, and wave V from the lateral lemniscus and possibly the inferior colliculus. Frequently, waves IV and V will present as a complex, with wave IV at the peak and wave V as a smaller shoulder to this peak occurring

later in latency. A negativity follows wave V that in many cases is the SN10 wave. The SN10 is a low-frequency negative potential that is most readily apparent when using low frequency stimuli.[9, 10] The negativity following wave V for other stimuli most likely receives some contribution from this potential. The SN10 is thought to arise from the inferior colliculus.[9] **Figure 52.2** shows an ABR with the major peaks identified.

The ABR initially emerged as a tool for diagnosis of retrocochlear pathology, such as acoustic neuromas.[11] More recently, it has found application as an estimate of hearing sensitivity for difficult-to-test patients. The current section discusses uses of the ABR as a diagnostic tool to detect lesions of the auditory nerve and central auditory system. The section that immediately follows this discussion of diagnostic ABRs considers applying the ABR to obtaining electrophysiological thresholds.

Description of diagnostic protocol

Many stimulus and recording parameters can be used in acquisition of the ABR. Subtle changes in these parameters can affect the quality of the electrophysiological response. Presented below is a description of recommended parameter values. The ABR is evoked separately from the left and right ears using these settings.

- **Stimulus:** A 100 msec click stimulus is most commonly used for assessment of retrocochlear function using the ABR. Tone-burst stimuli are sometimes used because they can be less influenced by peripheral hearing loss effects.[12] A tone-burst waveform envelope of 2-cycle onset, 0-cycle plateau, and 2-cycle offset is used. Stimuli are administered through insert earphones for diagnostic ABR testing.
- **Presentation level:** The presentation level of the ABR stimulus varies between 80 dB nHL and 100 dB nHL. If there are not concerns that hearing loss will affect the ABR indices, then 80 dB nHL is an appropriate level to use.

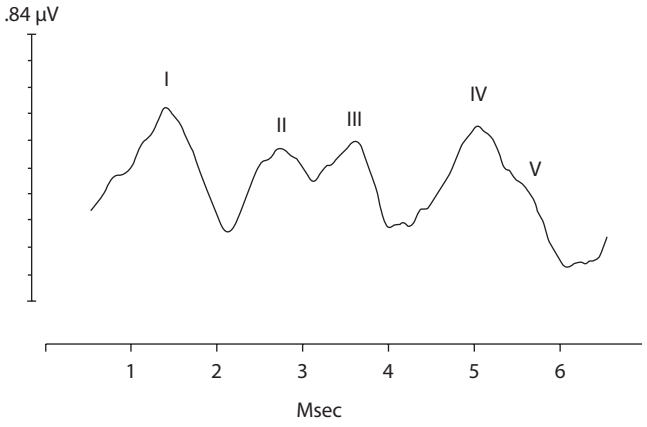


Figure 52.2 ABR with the first five peaks identified.

- **Polarity:** A rarefaction click stimulus will yield slightly earlier latencies than a condensation click.[13] As most normative values utilize a rarefaction click, it is recommended that this polarity by applied in diagnostic ABR protocols. If a tone-burst stimulus is being used, then alternating polarity should be applied.
- **Time window:** The recording time window refers to the duration over which the auditory system's response is recorded following presentation of a stimulus. A recording time window of 10–15 msec is recommended to ensure full view of the ABR response.
- **Filters:** The electrical activity recorded from the scalp is generally filtered out both above and below the frequency range of the ABR response. In adults, ABR electrical energy at the scalp is primarily in the 100–3000 Hz range, and therefore the filter is designed to pass energy in this range only. An exception to this is when the ABR is evoked to 500 Hz tone bursts, which requires the use of a lower high-pass filter setting around 30 Hz. Additionally, in infants the morphology of the ABR can sometimes be improved by using a lower high-pass setting.[14] If electrical artefact is encountered and cannot be resolved by other means, a notch filter option is available in most AEP units. This filter will reduce the amplitude of energy around 60 Hz. This filter should be used only sparingly as it can sometimes negatively affect the ABR morphology.
- **Stimulus rate:** Neurons contributing to the ABR have relatively short refractory periods and, for this reason, the response is acquired at a relatively high stimulus rate of 20–30 clicks per second. A non-integer rate, such as 17.7 clicks per second, should be used to avoid the time locking of periodic noise sources. For fast-rate ABRs, the stimulus rate is increased to 77.7 clicks per second.
- **Number of trials:** As mentioned previously, averaging the ABR across many trials will enhance the AEP and reduce noise. At least 2000–3000 trials per recording are recommended. Another viable option is to acquire a response until a predetermined signal-to-noise ratio has been reached, at which point testing can be stopped.[15] This method can help to reduce test time.
- **Replications:** Clinical analysis of ABRs requires some comment on whether the response was replicable. A replicable response is one that appears morphologically similar across two waveforms. After completing 2000–3000 trials, the ABR is acquired a second time to ensure reliability of the response. If there is concern regarding the consistency of the response, a third waveform may sometimes be acquired.

Diagnostic ABR analysis

The presence of retrocochlear lesions, including unilateral acoustic neuromas, can affect characteristics of the ABR waves, such as latency and amplitude. For instance, the neuroma can prolong the time it takes click energy to reach a particular neural generator, thus delaying the latency of the wave that arises from that generator. Likewise, a neuroma can negatively affect the synchrony of neural firing

and reduce the number of neurons being recruited for the response. In this scenario, amplitude of the wave may also be reduced. Measures of the ABR waves are discussed below and normative values are provided in Table 52.1.

Latency in the context of ABR measurement is defined either as the absolute latency of the wave, which indicates the time it takes for the wave to occur post-stimulus onset, or as the interwave latency difference, which indicates the time it takes for the neural energy to be conducted from one neural generator to the next. Interwave latency differences are calculated as the difference between the absolute latencies of two ABR peaks. This measurement is identified by the waves used in the calculation. Typical interwave latency differences are the I–III, III–V and I–V intervals.

Both absolute and interwave latency measurements can be abnormally delayed by lesions that directly involve the ABR neural generators. Absolute latencies can also be delayed by lesions occurring earlier in the auditory pathway. For instance, an acoustic neuroma can delay the latency of wave V even though the lesion is occurring in the vicinity of where wave II is generated. In addition, interwave latencies can be prolonged by lesions occurring between the two neural generators contributing to the latency measurement. A lesion between the neural generators of waves III and V will increase the latency of the III–V interval even though the generators responsible for III and V may not be directly compromised by the lesion.

Both absolute and interwave intervals have been shown to be sensitive and specific to the diagnosis of retrocochlear dysfunction, particularly in the application of acoustic neuroma detection. Musiek et al.[16] showed that all three interwave intervals had 100% specificity for this type of lesion. They varied, however, in their sensitivity, with the I–III interval showing the largest sensitivity value of approximately 90%, followed by the I–V interval with around 75% sensitivity, and then the III–V interval with the lowest sensitivity of 45%. If one considers just the I–III and III–V intervals, then 100% of the patients with acoustic neuromas in the study failed at least one of these measures and high specificity was still maintained.

TABLE 52.1 Normal limits for diagnostic ABR indices

Index	Normative value (msec)
Absolute latency of wave V	<6.2
Interwave latency I–III	<2.5
Interwave latency III–V	<2.4
Interwave latency I–V	<4.4
Inter-ear latency difference	<0.5
Fast rate shift	<1.0

Source: Values reflect adult cut-offs for ideal test efficiency based on clinical decision analysis and are obtained from Dartmouth Hitchock Medical Center normative data (Musiek). Protocol was click stimulus, monaural presentation of stimuli, presentation level 80 dB nHL, presentation rate of 17.7 clicks per second for slow rate and 77.7 clicks per second for fast rate, a 10 msec time window with 2000 accepted trials, and an online filter of 100–3000 Hz with recordings made from Fz.

Two additional latency measures that can be calculated are the inter-ear latency difference (ILD) and the fast-rate latency shift (e.g. fast-rate ABR). The ILD reflects the difference between the left ear wave V latency and the right ear wave V latency. As acoustic neuromas commonly present unilaterally, the affected side will often show an extended latency relative to the unaffected side. This leads to a larger ILD value for patients with the disorder. Sensitivity and specificity for ILD are 90% or greater.[17]

The fast-rate latency shift quantifies the degree to which the latency of wave V will shift when the click stimulus is presented at higher repetition rates. Presentation of the stimulus at these higher rates can lead to longer latency and smaller amplitude ABR waves even in the normal auditory system. This is a consequence of the stimulus rate more closely approximating the refractory period of the neurons that contribute to the ABR. In the disordered auditory system, increasing the repetition rate can lead to even longer extensions in wave latency and/or the absence of waves.[18] Normal limits on this measure are calculated as follows:[19]

[Normal wave V latency at standard repetition rates] + [0.1 msec for every 10 clicks/second increase in repetition rate] + 0.2

Therefore, if the normal latency is 6.1 msec and the repetition rate is increased from 20 clicks/second to 70 clicks/second, we would expect the new normal limit to be 6.1 + [0.1 × 5] + 0.2, or 6.8 msec. If the latency of wave V is beyond this value when the stimulus rate is 70 clicks/second, it would be considered an abnormal shift in latency.

Amplitude characteristics of the ABR are also sometimes examined to determine the presence of retrocochlear pathology. Amplitude is measured as the wave V to wave I (V/I) ratio. The amplitude of both peaks is measured from wave peak to the nearest negativity that follows the wave. The ratio is computed by dividing the wave V amplitude by the amplitude of wave I, and values less than 1.00 indicate that wave V amplitude is below that of wave I. While the specificity of this measure is relatively high (92%), the sensitivity is low enough to limit the diagnostic utility of this measure (44%).[20] As a result, amplitude is not used as commonly as latency measurements in the diagnosis of retrocochlear pathology.

Related to wave amplitude is the concept of examining wave presence or absence as an indicator of acoustic neuroma. This index does not appear always to be a reliable indicator. For instance, the percentage of patients with known acoustic neuromas who lack a wave I, III or V is 41%, 85% and 33% respectively.[21] Therefore, while the absence of a wave might be cause for follow-up testing, a high number of patients with neuromas will demonstrate the ABR waves.

Middle ear/cochlear hearing loss and test interpretation

Middle ear or cochlear hearing loss can negatively affect the latency and amplitude of the ABR peaks and can

sometimes complicate interpretation of the diagnostic ABR results. These hearing losses can prolong the latency and reduce the amplitudes of ABR waves. In such situations it is not always clear if these abnormal results are obtained because of the middle ear/cochlear hearing loss or because of a retrocochlear lesion.

There are several ways in which hearing loss can be addressed in the diagnosis of acoustic neuromas using ABR. First, if the degree of hearing loss is symmetrical, then the ILD can be used.[17] This is because the wave V latency shift being caused by the decrease in hearing sensitivity should be relatively equal in each ear. Second, interwave intervals can be used instead of absolute latencies to determine dysfunction as hearing loss would be expected to shift all waves relatively equally.[16] This approach can sometimes be limited if one or more waves cannot be visualized due to the severity of the hearing loss, particularly in the case of cochlear hearing loss. Finally, the Selters–Brackmann method yields an adjustment to the expected normal maximum latency of wave V based on the degree of sensorineural hearing loss at 4000 Hz. The new normal limit based on this method is computed as:

[Normal wave V latency] + [0.1 msec for every 10 dB of hearing loss above 50 dB HL at 4000 Hz].

Thus, if someone had a 70 dB HL loss at 4000 Hz, we would expect the new normal limit to be 6.1 + [0.1 × 2], or 6.3 msec. This modification yields reasonably good test efficiency.[22]

Diagnostic accuracy of ABR vs MRI

There has been much consideration in recent years over the diagnostic utility of the ABR when compared to magnetic resonance imaging (MRI). This arises from the observation that MRI has improved detection of acoustic neuromas when compared to ABR.[23] While this has led to the implication that all patients suspected of acoustic neuromas should be referred for MRI,[24] others have advocated for the continued use of the ABR in testing for the disorder. The value of the ABR in this capacity arises from both its very high diagnostic efficiency (e.g. sensitivity and specificity) and its reduced cost relative to MRI.[25, 26] Mangham[27] has suggested determining referral for ABR versus MRI based on the degree of average interaural hearing asymmetry at the octave frequencies of 1000–8000 Hz. If the average asymmetry is 20 dB HL or greater, patients should be referred for MRI, while average asymmetries less than 20 dB HL would warrant referral for an ABR. Using this approach they report about 2% less sensitivity than if all patients had received a diagnosis based on MRI. The cost saving was approximately US$25 000 per tumour diagnosed.

An alternative approach to acquiring ABRs has been proposed which improves the sensitivity of the test to small acoustic neuromas. The stacked derived-band ABR (or stacked ABR) utilizes the presentation of ipsilateral noise during the ABR procedure to derive responses from specific tonotopic regions of the auditory nerve.[28] This approach is based on the observation that standard click ABRs may miss dysfunction in certain frequency regions of the auditory nerve due to the spectral properties of the unmasked click stimulus. By introducing ipsilateral masking noise with different low-pass cut-offs, these various frequency regions can be assessed more directly. This approach has been shown to detect small tumours that are missed by conventional ABR.[28]

It has also been suggested that sensitivity of the ABR to small acoustic neuromas may be improved by comparing patients' ABR click threshold to their behavioural click threshold.[29] The trend witnessed in cases of acoustic neuroma is that ABR threshold tends to be poorer than behavioural threshold. Results in the study showed that patients with acoustic neuromas show approximately a 40 dB mean difference between these thresholds in the affected ear, while unaffected ears tend to yield a much smaller mean difference of 15 dB. Applying an abnormal criteria of >30 dB difference between the thresholds yielded excellent sensitivity and specificity.[29]

THRESHOLD AUDITORY BRAINSTEM RESPONSE

Overview

The ABR is commonly used in the electrophysiological assessment of hearing thresholds. ABR testing can be utilized to estimate hearing sensitivity in many cases where reliable behavioural audiometric results cannot be obtained. The test is commonly used in paediatric populations who are too young for reliable visual reinforcement audiometry or who otherwise would not condition to audiometric tasks. Acquisition of the ABR in this context allows for an estimate of hearing sensitivity that would not otherwise be obtainable.

It should be noted that the morphology of the ABR at threshold levels is different from the suprathreshold response. As the level of the stimulus is decreased, the latency of the ABR waves increases while the amplitudes decrease.[30] This occurs because fewer neurons are recruited at less intense stimulus levels and neuron firing occurs less synchronously. Earlier ABR waves (e.g. wave I) are more affected by these changes in intensity than later waves (e.g. wave V). For this reason it is not uncommon for the ABR to show only a wave V and SN10 at threshold. It is based on detection of these two peaks that ABR threshold estimates are generally made.

Description of threshold protocol

The equipment parameter settings for the threshold ABR are nearly identical to those used for the diagnostic ABR described above. As the lower stimulus levels used in the threshold ABR will increase the latency of the ABR peaks, a slightly longer time window is used, between 15 msec and 25 msec. In addition, unlike diagnostic ABRs, there tends to be a greater variety of stimuli used when completing a threshold ABR protocol. The click provides a good estimation of hearing at 2000–4000 Hz in many

clinical groups[31, 32] and tends to yield a robust ABR waveform. Since the click only assesses this 2000–4000 Hz range, it is recommended that tone bursts also be used in the assessment of hearing threshold via ABR.[31, 33] To this end, low (e.g. 500 Hz) and mid-frequency (e.g. 1000 Hz) stimuli are added to the protocol to provide a more complete evaluation of the patient's hearing. In cases where hearing thresholds demonstrate a sloping configuration for the 500 Hz, 1000 Hz and click threshold, acquisition of responses to 4000 Hz can sometimes provide a better estimate of the severity of a high-frequency loss.[31]

A typical threshold ABR evaluation will begin with assessment of the click ABR at suprathreshold levels (e.g. 70 dB nHL). There are several reasons why the acquisition of the suprathreshold response is advantageous to the clinician. First, except in cases of substantial hearing loss, this provides a well-formed template response to which subsequent click ABR responses can be compared. Second, this suprathreshold ABR should be evoked to condensation and rarefaction clicks to also test for auditory neuropathy (see below). Finally, though the patient was referred for a threshold ABR evaluation, there may be reasons to investigate the integrity of the auditory nerve and/or brainstem in a diagnostic manner, such as in cases of Chiari malformation or neurofibromatosis type 2. Acquiring a suprathreshold response will allow for this evaluation of retrocochlear pathology.

Once the suprathreshold ABR has been established, threshold can be determined for each of the frequencies being evaluated in the ABR protocol. Threshold may be defined as the lowest level at which wave V and SN10 are present. Alternatively, some clinics will only test down to a minimal hearing level (e.g. 15 dB nHL), as a detectable threshold at this level establishes that hearing is normal.

There are several ways in which threshold can be assessed. A modified Hughson–Westlake procedure[34] can be used in a fashion similar to what is done in pure-tone behavioural audiometry. However, it is sometimes more convenient and less time-consuming to test for a response at a minimal normal hearing level first. If a replicable response is not obtained, the presentation level can be increased in 5–10 dB steps until wave V is reliably evoked.

ABR testing must be undertaken when the patient is completely relaxed or asleep in order to minimize recording artefact generated by muscle movement. For newborn infants, ABR testing can be completed without sedation. Sleep deprivation, along with feeding just prior to the appointment, can increase the likelihood of a sufficient period of relaxation or sleep during the test. However, time to complete testing is often limited and testing may be interrupted or terminated early when the patient awakes. Multiple follow-up appointments may sometimes be necessary to obtain complete results in newborns.

An ABR utilizing sedation is often necessary for difficult-to-test patients. ABR can be performed under sedation or anaesthesia without degradation in response morphology. While sedation is generally used as a last resort, it can be valuable in providing the uninterrupted time necessary to perform a thorough audiological examination.

Correlation between AEP and behavioural threshold

The goal of performing the threshold ABR is ultimately to comment on the patient's hearing sensitivity. While the correlation between ABR threshold and behavioural hearing sensitivity is less than perfect, there tends to be a strong relationship between the two measures. ABR thresholds to clicks show a high degree of correspondence with some behavioural thresholds. The strongest correlation is seen between the ABR click threshold and the pure-tone average of 2000 Hz and 4000 Hz, with 89% shared variance.[31] The mean difference between the click ABR threshold and this pure-tone average threshold is approximately 1 dB, with the largest differences being in the vicinity of 35 dB.[31] Other studies have confirmed this high correlation between click ABR thresholds and the pure-tone average of 2000 Hz and 4000 Hz, with 81% shared variance, a mean ABR–behavioural threshold difference of 4 dB and a modal difference of 0 dB.[32]

ABR thresholds to tone bursts also show a relatively high level of association with their respective behavioural thresholds. The 500 Hz and 1000 Hz ABR thresholds share between 86% and 89% of their variance with behavioural measures.[31] The mean difference between the 1000 Hz ABR threshold and the corresponding behavioural threshold is approximately 1 dB, with the largest differences being in the vicinity of 30 dB.[31] In this regard, prediction of threshold at these frequencies using the ABR is as accurate as using the click threshold to predict the average of 2000 Hz and 4000 Hz.

Contralateral masking, conductive hearing loss and asymmetrical hearing

Certain clinical situations may require the use of a contralateral masking stimulus to eliminate the contribution of the non-test ear from the ABR. Testing the poorer ear of a unilaterally deaf subject has been shown to evoke a response from the contralateral ear that can be successfully eliminated with sufficient masking.[35] The presence of contralateral masking does not appear to influence the ipsilateral waveform.[35, 36] For air-conduction testing, the interaural attenuation for using ER-3A earphones and a click stimulus is approximately 70 dB.[37] Since click presentation levels will generally not much exceed 90–100 dB nHL, using a contralateral masking level of 50 dB nHL will eliminate most crossover. A white noise masker is typically provided with commercial ABR units.

Special consideration must be given to administration and interpretation of the threshold ABR in cases of conductive hearing loss and asymmetrical hearing. In cases where unilateral conductive hearing loss is suspected, the degree of hearing loss being contributed by the conductive component can sometimes be determined by obtaining bone-conduction ABR thresholds. Bone-conduction stimuli are elicited in an approach similar to that taken when obtaining behavioural thresholds, with placing a bone vibrator onto the mastoid. The contralateral non-test

ear will require masking during bone-conduction threshold assessment of the test ear.

There are several potential limitations to bone-conduction testing with ABR. First, responses evoked using this type of transducer tends to be more susceptible to stimulus artefact and this can decrease the ABR morphology and detectability. Alternating polarity stimuli must therefore be utilized to minimize the effect. Second, as artefact is sometimes high even at mid-intensity levels, the maximum intensity level at which ABRs can be reliably elicited by bone conduction (i.e. the equipment limits) is often lower than that obtained by air conduction. Finally, the spectrum of the stimulus is different when conducted through earphones as compared to the bone oscillator.[38] While this would imply that it is difficult to equate air- and bone-conduction thresholds, it has been noted that, at least in normal hearing individuals, air- and bone-conducted ABR threshold testing yields similar ABR results despite these spectral differences.[39]

Another approach to determining whether a conductive hearing loss is contributing to an ABR threshold shift is to use a latency–intensity function.[40] The latency of wave V is inversely related to stimulus intensity. Plotting wave V latency as a function of stimulus intensity generates a predictable curve in normal hearing subjects, with wave V latency increasing as stimulus intensity decreases. Conductive hearing impairment causes a latency shift in the curve that is relatively equal at all intensities and which yields no change to the slope of the curve.[41] Conversely, sensorineural hearing loss can cause a greater deviation from normal latency for stimuli closer to threshold and this can contribute to an increase in the slope of the latency–intensity curve.[41] In this way, the latency–intensity function can sometimes be used to discriminate conductive from sensorineural hearing loss.

As with behavioural audiometry, the presence of bilateral conductive hearing loss can pose a masking dilemma for the clinician. Assessment of cochlear hearing using the bone oscillator requires contralateral masking in order to prevent the contralateral cochlea from responding. However, when the masking level in the contralateral ear is raised to an intensity level that exceeds the degree of conductive impairment on that side, the masking signal can cross over to the cochlea in the test ear. This can elevate the bone-conduction threshold in the test ear, with subsequent increases in contralateral masking level further elevating this threshold. This phenomenon creates a situation in which bone conduction thresholds cannot be assessed by standard methods.

Jerger and Tillman's[42] sensorineural acuity level (SAL) technique has been advocated as an approach to measuring ABR bone-conduction thresholds in these cases of bilateral conductive hearing loss.[43] The rationale behind this method is to apply masking via a bone oscillator placed on the forehead and then quantify the degree of air-conduction threshold shift as a function of the masker level. In sensorineural hearing loss, the bone-conducted masker is less effective at shifting air-conduction thresholds since some or all of the masker energy will be below cochlear threshold. In cases of conductive loss, the masking noise is more effective at shifting air-conduction thresholds because the cochlea is unaffected by the conductive pathology. Therefore, the degree of air-conduction threshold shift that presents when a bone-conducted masking signal is introduced can assist in discriminating conductive from sensorineural hearing losses.

Central maturation

Morphology of the ABR changes with age from the perinatal period through the first years of life. The ABR response to high-intensity stimuli emerges at 28–32 weeks conceptual age.[44, 45] A repeatable three-peaked response is present by 35 weeks conceptual age. The ABR gradually becomes better defined with a full five-peaked response emerging in the first months of life. The ABR is similar in morphology to an adult response by 1–3 years of age.[45]

Maturation effects are also seen in ABR latency measures. All components of the ABR show a rapid reduction in latency during the first weeks of life, with wave I of the ABR reaching adult latency by 8–10 weeks postpartum.[40, 45] Waves III and V continue a gradual decrease in latency over the next several years, reaching adult latency by 2–3 years of age.[40, 45]

Perhaps of greater relevance to the clinician interpreting threshold ABRs is the effect of central maturation on threshold detectability. Studies have shown that, in some cases, ABR thresholds are initially elevated in newborns and show a gradual reduction over the first 6 months of life.[46–49] The degree of threshold elevation from suspected immaturity ranges from a few dB to as much as 25 dB. Often the greatest elevation in threshold occurs for higher-frequency stimuli such as 4000 Hz, whereas lower-frequency stimuli such as 500 Hz are more similar to adult levels at birth.[46, 48] ABR thresholds are also more variable in infants and this variability decreases with age.[46, 47]

Due to this trend of elevated thresholds and greater threshold variability in infants, the possibility of over-treatment may present itself when mild–moderate hearing loss is identified with the ABR at a young age. A conservative approach that includes close audiological monitoring through infancy may be warranted in cases where central immaturity is suspected. Follow-up electrophysiological testing or behavioural audiometry can be used to confirm the presence of hearing loss.

Auditory neuropathy

Auditory neuropathy is a condition that is characterized by normal cochlear responses on otoacoustic emissions and/or cochlear microphonic testing, but absent or abnormal suprathreshold ABRs.[50] Hearing loss can occur with the disorder and the site of dysfunction is localized to auditory structures beyond the outer hair cells through the auditory nerve.[51] There is a variety of risk factors associated with the disorder, including hypoxia, prematurity and hyperbilirubinaemia. There may also be genetic causes of the disorder.[51]

The patient is evaluated for the disorder as part of the threshold ABR protocol to eliminate neuropathy as a cause

of their listening difficulties. The disorder is assessed by comparing the presence/absence of the cochlear microphonic to the morphology of the ABR. The cochlear microphonic is an electrical potential that mimics the acoustic properties of the stimulus. It starts at near zero latency and, in some cases of neuropathy, it can also contribute to peaks later in the recording time window. If the cochlear microphonic is present but the ABR is otherwise compromised, auditory neuropathy would be suspected.

To evaluate the AEP for the presence of a cochlear microphonic, the ABR is evoked to a rarefaction and condensation click at suprathreshold levels. The cochlear microphonic will appear as peaks in the ABR waveform that invert in amplitude when the polarity of the stimulus is switched from rarefaction to condensation. Observation of the inversion in these peaks is typically consistent with detection of the cochlear microphonic.

One pitfall to be wary of when evoking the cochlear microphonic is not to misinterpret stimulus artefact as the microphonic response. Stimulus artefact arises from the transducer and is not a physiological potential. This artefact, when present, will show similar morphology to the cochlear microphonic and will sometimes overlap this AEP in time. Artefact will also invert its amplitude with changes in stimulus polarity. At stimulus levels of 80 dB nHL or greater there is an increased risk of stimulus artefact being present in the waveform.[52]

Alternatives to the conventional threshold ABR protocol

AUDITORY STEADY-STATE RESPONSE

The auditory steady-state response (ASSR) is sometimes used to predict hearing thresholds in difficult-to-test populations. Unlike the ABR, the procedure uses a continuous tonal stimulus instead of frequent repetition of a transient stimulus (e.g. click or tone burst). A carrier frequency is presented which is amplitude-modulated at a given modulation rate and depth. If the sound is detected by the cochlea and stimulates the auditory system, the neural generators underlying the ASSR will respond at a rate equal to the modulation rate of the stimulus. When neural firing is detected at this rate, the response is said to be 'phase-locked'.[53] A phase-locked response indicates that the auditory system has responded to the carrier frequency and this information can be used to establish threshold.

A potential advantage of this approach is that multiple frequencies can be assessed simultaneously as long as their carrier frequencies utilize different modulation rates.[53] Another benefit is related to the analysis of the ASSR. While ABR analysis involves the subjective interpretation by a clinician to identify response peaks, the ASSR can be analyzed using statistical methods that are applied and interpreted automatically.[53] This removes some of the subjectivity inherent to the process of obtaining an electrophysiological threshold.

The accuracy of the ASSR in predicting behavioural thresholds is similar to that of the tone-burst threshold ABR.[53, 54] There is some evidence that ASSR may be less likely to underestimate hearing loss in patients with steeply sloping audiometric configurations than is the ABR.[54] The ASSR may also be negatively affected by state of arousal[55, 56] and this could potentially limit its clinical application. This is particularly problematic for difficult-to-test populations where the ABR may be acquired while the patient is asleep or sedated.

ABR CHIRP STIMULUS

The chirp stimulus was developed to achieve greater neural synchrony by compensating for the travel time of the cochlear wave.[57] When a traditional click stimulus is presented, higher-frequency regions of the basilar membrane near the base of the cochlea are stimulated before the lower-frequency regions nearer the apex. This time delay causes different portions of the basilar membrane to respond in succession rather than synchronously. Conversely, chirps are acoustically designed to compensate for the tonotopic arrangement of the cochlea. This is accomplished by using a tone that increases in frequency throughout its duration, so that low-frequency cycles occur earlier than high-frequency cycles. Therefore, low-frequency energy enters the cochlea first and, by the time it reaches the apex, the higher-frequency energy is stimulating the base of the cochlea. The chirp creates a situation in which all regions of the basilar membrane are likely to be stimulated simultaneously. A potential benefit of the higher neural synchrony provided by chirp stimuli includes a larger response that is more easily detectable at lower intensity levels.[58]

MIDDLE LATENCY RESPONSE

Overview

The middle latency response (MLR) was first reported by Geisler and colleagues.[59] It is an AEP that is both larger in amplitude and later in latency than the ABR. It has multiple neural generators in the thalamocortical system, which includes the medial geniculate body, thalamocortical connections, auditory cortex and reticular formation.[60] The MLR comprises four separate potentials, a negativity occurring in the latency range of 12–21 msec (Na), a positivity that occurs between 21 msec and 40 msec (Pa), a negativity that follows Pa (Nb), and a second positivity that follows Nb in the latency range of 50 msec (Pb). MLR indices include the latency of the potentials, as well as the peak-to-peak amplitude (i.e. Na–Pa or Nb–Pb voltage difference). The Na and Pa amplitudes are the only two measured with any regularity in the clinic. This is a result of Pb being more difficult to evoke.[61] **Figure 52.3** shows an MLR with the Na–Pa peaks recorded and identified.

Historically, the MLR was pursued as a measure of hearing sensitivity. Relative to the ABR, this AEP provided an advantage in this regard since its larger amplitude made it more detectable near threshold.[62, 63] This application was limited, however, by the discovery that

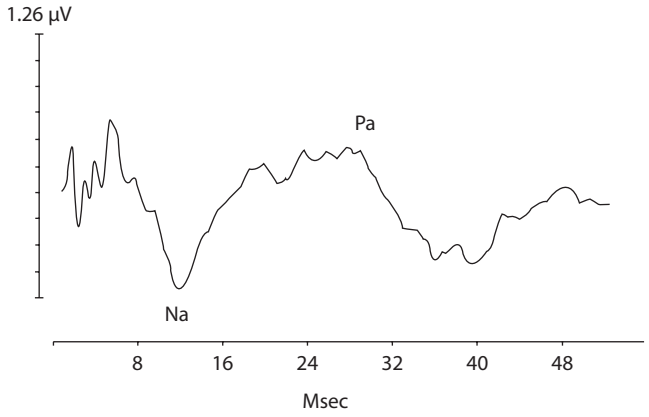


Figure 52.3 MLR with Na–Pa identified. The waves present at less than 8 msec are the ABR.

characteristics of the MLR morphology were negatively affected by degree of wakefulness.[64] Acquiring the MLR during sleep can lead to a reduction in peak amplitude or a complete absence of the complex. This posed a limitation for the use of this potential in the objective assessment of hearing sensitivity as the testing is frequently performed when the patient is asleep or sedated.

Presently, there are two primary applications of the MLR in the clinic: detection of neurological dysfunction of the CANS and diagnosis of CAPD. In regards to the former, patients with lesions that include the generator sites of the MLR will often show abnormalities on this measure. Lesions in the vicinity of the primary auditory cortex can give rise to changes in the morphology of Pa, frequently when measured over the affected hemisphere.[65, 66] Conversely, damage to the midbrain appears to affect the characteristics of the Na peak.[67] MLR abnormalities appear to be more common overall with brainstem lesions than with cortical lesions and this may be because large brainstem lesions are more likely to denervate thalamic projection nuclei.[68]

Applications of the MLR have also been reported in the diagnosis of CAPDs. CAPD refers to dysfunction of the CANS that contributes to significant listening difficulties, particularly when in the presence of background noise.[69] In addition to neurological dysfunction, it has been attributed to ageing-related changes to the CANS in older adults[70, 71] and CANS immaturity in younger populations.[72–74] There exists some controversy related to diagnosing the disorder by using tests that require patients to make a behavioural response (e.g. repeat back what they hear or press a button). For instance, it has been speculated that these types of tests may be susceptible to cognitive issues.[75] In this regard, using the MLR to evaluate for CAPD may be advantageous because no patient response is required and cognitive demands may be reduced as a result.

Description of MLR protocol

The MLR is evoked in a manner similar to the ABR, but there are several key differences. Figure 52.1 shows the electrode montage for recording this potential. Note that the response can be assessed using Cz as the non-inverting site (one-channel recording), or a combination of C3 and C4 can be used as the non-inverting electrodes (two-channel recording). The MLR settings are further characterized below, and differences from the ABR protocol are highlighted.

- **Stimulus:** A click stimulus is used to evoke the MLR for clinical purposes. Tone bursts can also be used and, due to the longer time window and slower stimulus presentation rate, a larger number of cycles can be included in these stimuli when compared to the ABR. Use of low- and mid-frequency tone bursts in this manner may be advantageous when evoking the MLR from patients with high-frequency hearing loss.
- **Presentation level:** The presentation level used for evoking the MLR is 70 dB nHL. This can be increased if there are concerns about sufficient audibility, although postauricular muscle artefact (PMA, see below) may be more likely to be evoked at these higher levels.
- **Polarity:** Rarefaction or condensation clicks may be used to evoke the MLR. If tone bursts are used, the polarity should alternate.
- **Time window:** Stimulation of the neural generators responsible for the MLR occurs only after the ABR neural generators have responded. For this reason, the latencies of the MLR peaks are later than the ABR peaks and a longer time window is needed. If only Na and Pa are being assessed, then a 50 msec time window is usually sufficient. For Nb and Pb, the time window should be extended to 75 msec.
- **Filters:** The frequency range of the MLR is lower than the ABR, extending down to 30 Hz.[76] For this reason a bandpass filter from 30–1500 Hz is used during acquisition of the MLR. Post-acquisition, an offline filter with a bandwidth of 30–300 Hz can be applied to assist in smoothing the MLR peaks. A 60 Hz notch filter should not be applied when acquiring the MLR as a filtering at this frequency could reduce a large proportion of MLR energy.
- **Stimulus rate:** Neurons contributing to the MLR have longer refractory periods than those that contribute to the ABR. For this reason, a slower stimulus rate of 9.7 clicks per second is used to evoke the MLR.
- **Number of trials:** Relative to the ABR, a fewer number of trials need to be averaged together to measure the MLR. Approximately 800–1000 trials are collected in the MLR average.
- **Replications:** As with the ABR, the MLR average is acquired at least twice to confirm response reliability.

MLR analysis

Although the latency and peak-to-peak Na–Pa amplitude of the MLR can be analyzed to determine dysfunction, these measures tend to have high between-subject variability in normal listeners.[77, 78] If normal variability on a

clinical measure is too high, it becomes difficult to establish practical normative values. One way in which MLR between-subject variability can be reduced is to compare MLR amplitude between ears (left vs right) or electrodes (C3 vs C4). Therefore, instead of examining the amplitude at either ear or either electrode individually, the difference between the two ears or two electrodes is calculated and this difference is used to determine normalcy. Sources of individual variation that are common to both ears or electrodes will be subtracted out of the index by computing this difference, and this will decrease between-subject variability on the MLR.[71, 79] In addition, amplitude measures of the MLR tend to be more sensitive to dysfunction than latency measures,[80] so differences in amplitude are used instead of latency.

Between-ear and between-electrode amplitude differences are referred to as ear effects and electrode effects, respectively.[80] They are computed as the absolute value of the difference between the two amplitude measures, or |Left ear Na–Pa amplitude - Right ear amplitude| for ear effects and |C3 amplitude - C4 amplitude| for electrode effects.[79, 80] For patients with neurological lesions, normalizing the difference by dividing by the smallest amplitude can improve the sensitivity of the index.[80] Normative values for ear and electrode effects are included in Table 52.2.

One pitfall to be aware of when interpreting the MLR is to not misinterpret PAM artefact as the MLR. PAM artefact is a myogenic response that can be evoked by the MLR stimulus.[81] The latency of PAM artefact is approximately 10–15 msec and, given its much larger amplitude relative to the MLR, the presence of this myogenic activity makes the MLR difficult to measure accurately. It has been suggested that the presence of PAM artefact is related to the direction of gaze and neck tension.[82] If the artefact is encountered, it can sometimes be reduced by having patients stare directly straight ahead at a picture on the sound booth wall and/or reclining them in a chair so as to relax the neck.

TABLE 52.2 Normal limits for MLR indices

Index	Normative value (μV)
7–8 years (AD)	Ear effect: <0.49 Electrode effect: <0.15
9–10 years (AD)	Ear effect: <0.43 Electrode effect: <0.17
11–12 years (AD)	Ear effect: <0.27 Electrode effect: <0.19
13–14 years (AD)	Ear effect: <0.24 Electrode effect: <0.20
15–16 years (AD)	Ear effect: <0.35 Electrode effect: <0.22
Adult (N)	Ear effect and electrode effect: <20% to 50%

Source: Values reflect upper limit of 95% confidence interval in normal hearing participant and are obtained from Musiek et al.[79] and Weihing et al.[78] Protocol was as follows: click stimulus, monaural presentation of stimuli, presentation level 60–70 dB nHL, presentation rate of 9.8 clicks per second, a 72 msec time window with 1000 accepted trials, and an online/offline filter of 20–1500/20–200 Hz with recordings made from the C3 and C4 electrodes.

Key: AD = Absolute difference: |Amplitude 1 – Amplitude 2|

N = Normalized: (|Amplitude 1 – Amplitude 2| / Smaller amplitude) × 100

AUDITORY LATE RESPONSE

Overview

The auditory late response (ALR), or long latency response, is an AEP that is primarily cortical in origin and was first reported by Pauline Davis.[83] The neural generator system contributing to the ALR is broad but receives important contributions from the Sylvian fissure and the superior aspect of the temporal lobe including Heschl's gyrus.[84–86] A total of six or more neural generators may contribute to the response.[86] The peaks most commonly measured in the ALR are the N1 and P2. The N1 is a negativity that can be observed between 60 and 170 msec, while the P2 is a positivity that is seen between 115 and 290 msec. Amplitude of the ALR waves is larger than the ABR or MLR wave amplitudes. Figure 52.4 shows an ALR with the N1–P2 peaks recorded and identified.

The ALR can be used clinically to diagnose lesions of the CANS. Patients with lesions of the temporal lobe have been shown to demonstrate prolonged ALR latencies, reduced amplitudes and/or absent potentials.[87] The ALR can also be used in the assessment of hearing sensitivity and in auditory rehabilitation applications.[88–92] Stimuli of relatively long duration can be used to evoke the response due to the very slow stimulus repetition rate and long time window of the ALR (see below). This allows for an increased number of cycles in pure-tone stimuli, which may yield better frequency specificity of

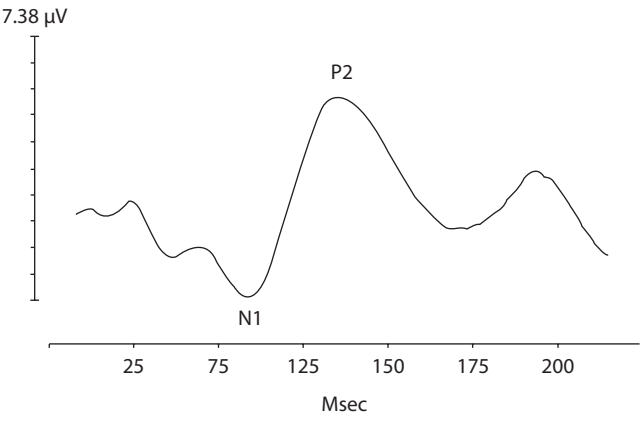


Figure 52.4 ALR with N1–P2 identified.

the evoked response in adults.[88] The ability to use longer stimuli also allows for the inclusion of more complex sounds, such as speech, in the ALR paradigm.[89] The ALR has also been used in rehabilitation contexts for demonstrating that amplification makes sounds audible in infants[90] and to show outcomes from auditory training.[91, 92]

Similar to the MLR, the ALR morphology is affected by sleeping and this can limit its utility as a threshold measure in difficult to test populations.[92, 93] In addition, the amplitude and latency characteristics of the response are affected by whether the auditory stimulus is attended to or not.[94] This may be the result of ALR arising from generator sources that respond to multiple modalities and/or that are responsible for mediating attention.[85, 95, 96]

Description of ALR protocol

Due to the many novel applications for which the ALR is used it is not possible to discuss all configurations the clinician may encounter when attempting to measure this response. However, we present below a minimal protocol that can be used to evoke an N1–P2 to address basic clinical questions. Note that, while the ALR protocol shares similarities with the ABR and MLR protocols, differences exist because of the later latency of the ALR peaks and the longer refractory periods of the cortical neurons. Recording sites include some combination of Cz, C3 and C4, as the N1 and P2 amplitudes are sufficiently large in these regions.[97] The ALR settings are further characterized below, and differences from other AEP protocols are highlighted.

- **Stimulus:** Although a click stimulus can be used to evoke the ALR, the much longer time window and slower stimulus rate allows for long duration tones and complex stimuli to be used in the task. For example, consonant–vowel syllables are frequently used to assess the response of the CANS to speech stimuli.[87, 98]
- **Presentation level:** A presentation of level of 70–80 dB nHL is sufficient for evoking the ALR if there are no concerns about audibility.
- **Polarity:** Rarefaction or condensation clicks may be used to evoke the ALR. If tone bursts or complex stimuli are used, the polarity should alternate.
- **Time window:** The latencies of the ALR peaks are later than the ABR and MLR peaks. For this reason, a much longer time window of 300–400 msec is utilized to acquire the N1–P2.
- **Filters:** The frequency range of the ALR is considerably lower than the ABR and MLR, from 1–30 Hz.[99] A bandpass filter in this range is applied online.
- **Stimulus rate:** ALRs are evoked using a slow rate of 1.1 stimuli/second due to the longer refractory periods of cortical neurons. Given the slow rate of presentation, there is sometimes concern that eye blinks will become time-locked with the AEP unit. To prevent this, an electrode should be placed at the outer canthus to reject trials on which eye blinks occur.
- **Number of trials:** Relative to the ABR and MLR, fewer trials need to be averaged together to measure the ALR. Approximately 100–200 trials are collected in the ALR average.
- **Replications:** As with the other AEPs, the ALR average is acquired at least twice to confirm response reliability.

TABLE 52.3 Normal limits for ALR indices

Index	N1	P2
Amplitude (μV) (male)	<-2.28	>2.99
Amplitude (μV) (female)	<-2.73	>3.83
Latency (msec) (male)	<109.24	<170.53
Latency (msec) (female)	<102.23	<163.35

Source: Values reflect upper or lower limit of 95% confidence interval in young adult normal hearing participants and are calculated based on data from Swink and Stuart.[100] Protocol was as follows: ~750 Hz tone burst with a 10.5–49–10.5 envelope and a duration of 70 msec, binaural presentation of stimuli, presentation level 75 dB peak SPL, presentation rate of 1.1 tones per second, a 500 msec time window with 150 accepted trials, and an online filter of 1–30 Hz with recordings made from the Cz electrode. Amplitude was measured from pre-stimulus baseline.

ALR analysis

ALR indices include the latency of the potentials, as well as a single peak-to-peak amplitude (i.e. N1–P2 voltage difference). Alternatively, N1 and P2 amplitudes are sometimes measured relative to the baseline voltage of the response. In these cases a separate amplitude measure is obtained for the two peaks (see Table 52.3 for example normative values). In neurological cases, ear and electrode effects are not calculated even though the ALR recorded over the affected hemisphere is more likely to show dysfunction.[87]

SUMMARY

The present chapter described basic approaches to acquiring AEPs in clinical populations. Perhaps the most relevant of these AEPs is the ABR, which can be used diagnostically to assess retrocochlear function or as a threshold measure in difficult-to-test populations. The resistance of the ABR to sleep effects and its high reliability make it a valuable tool in this regard. In addition to the ABR, protocols and characteristics of the MLR and ALR were also considered. These potentials assess regions more superior in the CANS and their acquisition provides a more comprehensive description of hearing health in this regard. The MLR has been used in the diagnosis of CAPD, while the ALR has a found a broad range of applications that include assessment of neurological function, validation of hearing aid fittings and quantifying neural benefits from auditory training.

KEY POINTS

- AEP can be used to infer the relative health of various peripheral and central auditory regions.
- Patients who are difficult to test or who are too young to have their thresholds assessed by behavioural audiometry can often have their hearing thresholds quantified using the threshold ABR.
- AEPs are commonly evoked with a click stimulus.
- ABR is a response to stimulus onset and arises from the auditory nerve and low brainstem.
- Auditory neuropathy is a condition that is characterized by normal cochlear responses on otoacoustic emissions and/or cochlear microphonic testing, but absent or abnormal suprathreshold ABRs.

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CHAPTER 53

PREVENTION OF HEARING LOSS

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SEARCH STRATEGY

Data in this chapter may be updated by Medline and PubMed searches using the keywords: hearing loss, deafness, epidemiology, prevention, infection, vaccination, cytomegalovirus, measles, mumps, meningitis, ototoxicity, barotrauma and noise trauma. Epidemiological data from the World Health Organization have been used. Material from previous editions of this textbook on the same chapter has also been used.

EPIDEMIOLOGY

Hearing loss is a very common worldwide problem affecting all age groups and leading to marked disability and handicap. The World Health Organization (WHO) lists hearing loss in the 20 leading causes of burden of disease and as a most common cause of disability globally.[1]

In 2012, the WHO estimated that there are 360 million people worldwide with a disabling hearing loss, which is 5.3% of the world's population.[2] Of these, 91% are adults and 9% children. The prevalence of disabling hearing loss is greatest in South Asia, Asia Pacific and Sub-Saharan Africa both for children and for adults over the age of 65. The prevalence of hearing loss increases with age: in children it is 1.7%, 7% in individuals over the age of 15, and in adults over the age of 65 it is almost one in three. However, a noteworthy point is that half of all cases of hearing loss can be avoided through primary prevention.[3]

In the UK the incidence of children born with a permanent hearing impairment is about 1 in 1000, but this figure nearly doubles in early childhood.[4] In 2011 there were approximately 10 million people in the UK with some form of hearing loss.[5]

DISABLING HEARING LOSS AND ITS PREVENTION

Disabling hearing loss refers to hearing loss greater than 40 dB in the better ear in adults (15 years or older) and greater than 30 dB in the better-hearing ear in children (0–14 years).[3] The majority of people with a disabling hearing loss live in the developing countries.

For any disease or disability, there are three levels of prevention:[6]

- **Primary prevention:** This is prevention of pathology by reduction in the causative factors leading to that pathology.
- **Secondary prevention:** This is prevention or limitation of disability and handicap in those individuals with an impairment. This can be by screening for affected individuals prior to clinical presentation and, when possible, providing treatment to prevent progression of pathology and impairment.
- **Tertiary prevention:** This is prevention or limitation of handicap by early management of the disability.

The three levels of prevention of hearing loss are further subclassified in **Box 53.1**.

PRIMARY PREVENTION OF HEARING LOSS

The effects of primary prevention have markedly altered the profile of the aetiology of hearing loss in the developed countries. The incidence of hearing loss due to chronic suppurative otitis media has fallen dramatically. However, this still remains a leading cause in the developing countries.

BOX 53.1 Subclassification of the three levels of prevention of hearing loss[6]

1. Primary preventable causes of hearing loss
   - Genetic
     - Genetic counselling
   - Infective (congenital or acquired)
     - Immunization
     - Early treatment
     - Avoidance and education
   - Traumatic (noise, physical trauma and barotrauma)
     - Avoidance
     - Early treatment
   - Ototoxic medications
     - Avoidance
     - Monitoring
     - Treatment
   - Prevention of deafness by improving lifestyle to prevent other diseases
2. Secondary prevention
   - Screening
   - Treatment
3. Tertiary prevention
   - Early rehabilitation of hearing loss

Prevention of disease in the developing countries still lags far behind and ongoing efforts to promote uptake of preventive measures is essential. The WHO has developed a programme for the prevention of deafness and hearing impairment (PDH) and has produced guidelines on the prevention of hearing impairment from ototoxic drugs, chronic otitis media and noise-induced hearing loss.[7]

Genetic hearing loss

Around 60% of prelingual deafness is genetic. Of this, about 70% is non-syndromic. Between 75% and 80% of non-syndromic hearing impairment is autosomal recessive, 10–15% is autosomal dominant, and the rest are X-linked, mitochondrial or chromosomal.[8] The most common cause of genetic deafness is mutations in the gap junction beta 2 gene (*GJB2*), located on chromosome 13q and encoding the protein connexin 26.[9, 10] One particular mutation, 35 delG, is the commonest[11, 12] and has been reported to account for more than 80% of the *GJB2* mutation in the Caucasian population.[13]

PREVENTION OF GENETIC HEARING LOSS

Genetic counselling

Identifying the genetic profile of the hearing loss is the first step before any genetic counselling can be given to the individual and the family members. The genetic counsellor can inform a family about the risks of any child being born with a hearing impairment. This is especially applicable when they already have a child with hearing loss. The parents can then make an informed choice whether to have more children. Prenatal counselling would also enable early intervention and provision of support for a child with deafness, thus minimizing the impact of the hearing loss.

Role of consanguinity

With almost three-quarters of genetic hearing loss being autosomal recessive, the role of consanguinity assumes very important proportions. The prevalence of parental consanguinity has been found to be significantly higher in hearing-impaired children than in those with normal hearing. A decline in the prevalence of hearing impairment has been found with restriction of consanguineous marriages.[14] Improved education of the community about the risks involved with consanguinity should help to some extent to prevent deafness.

Infective causes of hearing loss

The role of primary prevention is quite significant and effective in the field of prevention of infective causes of hearing loss. This is true for both congenital and acquired infective causes. In the developing world, the focus on preventing hearing loss due to chronic suppurative otitis media remains as important as ever.

Where possible, the aim should be to prevent hearing loss due to infective causes. This can be through vaccinations, or, the adoption of measures which will prevent the development of chronic suppurative otitis media. If this is not possible, infection should be treated early to minimize the impact of hearing loss.

PREVENTION OF INFECTIVE CAUSES OF HEARING LOSS

Although infective causes of hearing loss may be congenital or acquired, the methods of prevention are the same for both. These include immunization, early treatment, and education and avoidance.

Rubella (or German measles) is a generally mild viral infection occurring mostly in children and young adults. Rubella infection during pregnancy can cause congenital rubella syndrome (CRS) with the classical triad of symptoms of sensorineural hearing loss (SNHL), ophthalmic abnormalities and congenital cardiac defects. There is no effective treatment for rubella, but the disease can be prevented by vaccination. Vaccines have been developed since 1969 and the immunization programmes have nearly eradicated CRS from most developed countries. However, the disease can still be a problem in developing countries. In 2014, the WHO estimated that there were 110 000 babies born worldwide with CRS.[15]

Hearing loss is a known complication following measles. The hearing loss can be sensorineural or conductive or mixed.[6] Prior to widespread vaccination for measles, it was reported to account for 5–10 % of cases of profound SNHL in the US.[16] Atrophy of the stria vascularis and loss of the organ of Corti after measles infection have been proposed to be the cause of SNHL.[17] Encephalitis is a rare complication of measles that can lead to profound SNHL. Measles is also associated with a high incidence of otitis media, which can also lead to hearing loss.[18] In addition, measles virus has been implicated in the aetiopathogenesis of otosclerosis.[19] Immunization against measles

may therefore play a role in reducing the incidence of otosclerosis.

Mumps is a systemic viral illness typically causing symptoms of fever, malaise, myalgia, headache and swelling of one or both parotid glands. Complications of mumps may include SNHL, orchitis, meningitis, encephalitis and pancreatitis. The incidence of SNHL after mumps has been estimated to be 0.5–5 per 100 000, but it has been reported to be as high as 1 in 1000 in Japan where mumps vaccination is optional.[20] The hearing loss is mostly unilateral but can also be bilateral. With the introduction of the Mumps, Measles and Rubella (MMR) vaccination, the incidence of mumps, and thereby hearing loss due to mumps, has reduced significantly.[21]

Effective immunization against mumps, measles, rubella and meningitis has led to a reduction in the incidence of hearing loss due to these conditions. The MMR vaccine was first licensed by the US government in 1971. In the UK it has been available for children between the ages of 1 and 2 years since 1988.[22] After the introduction of the MMR vaccine, the spread of measles was effectively halted in the mid 1990s. However, following adverse publicity, linking it with autism and Crohn's disease, there was a reduction in the uptake of the vaccination. Vaccine uptake levels in UK fell to 80% in 2003 and 2004 from levels of 92% in 1995.[23] This led to an increase in the incidence of these diseases, with 1370 cases of measles reported in England and Wales in 2008.[24] From November 2012 to July 2013, Wales experienced the largest outbreak of measles, with 1202 cases notified.[24] There has been a similar increase in mumps cases. The suggested association between MMR and autism has been proven to be baseless:[25] Public Health England investigated possible links between the MMR vaccine and autism and Crohn's and determined there was no evidence for this.

Meningitis remains the most common cause of acquired severe to profound SNHL in childhood.[26] Likewise, deafness is the most common long-term neurological sequela of the disease.[27] The hearing loss after meningitis can be unstable, with the deterioration occurring many years after the disease.[28] Another important consideration following meningitis is the development of labyrinthitis ossificans in which there is new bone formation within the lumen of the otic capsule. Ossification of the labyrinth can develop within a few days of meningitis.[29] This can make cochlear implantation difficult.[30] Early diagnosis of deafness after meningitis is therefore important. Of the various organisms causing bacterial meningitis, *Streptococcus pneumoniae* is associated with more profound hearing loss.[31] Various vaccinations against meningitis are available. These include the pneumococcal vaccine for *Streptococcus pneumoniae*, meningitis C vaccine for the serogroup C of *Neisseria meningitidis* and vaccination against *Haemophilus influenzae* type B. Quadrivalent vaccines effective against serogroups A, C, W-135 and Y of *Neisseria meningitidis* are also available. By protecting against mumps, measles and rubella, the MMR vaccine also protects against meningitis, which can arise as a complication of these diseases. Vaccination against serogroup B of *Neisseria meningitidis* has also become available, although it is still not available widely. Pneumococcal vaccines also have a role in the prevention of hearing loss arising due to otitis media: use of the 13-valent pneumococcal vaccine has been shown to reduce the incidence of pneumococcal otitis media in childhood.[32]

The use of adjuvant corticosteroid therapy in acute bacterial meningitis due to *Haemophilus influenzae* has been shown to reduce the incidence and severity of SNHL.[33] Its role in preventing hearing loss resulting from meningitis caused by other organisms is less well defined.

Cytomegalovirus (CMV) is the most common cause of congenital infections in humans.[34] Congenital CMV (cCMV) is being increasingly recognized as a leading cause of non-hereditary congenital SNHL,[35, 36] and it has been estimated to be the cause of congenital SNHL in 20–30% of cases.[37] The hearing loss associated with cCMV may be detectable at birth or can be of delayed onset.[38] It could be the only symptom in an otherwise asymptomatic baby. The hearing loss can be progressive. Fowler et al. reported a progression of hearing loss in 50% and fluctuation in around 23% of children with SNHL due to cCMV infection.[39] CMV is a ubiquitous infection and in adults causes mild flu-like symptoms. However, when a pregnant woman acquires the disease for the first time or develops a primary CMV infection, the risk of vertical transmission to the foetus is estimated to be around 30–40%.[40] Only about 13% of children with cCMV exhibit obvious symptoms at birth.[41] These may include permanent neurological sequelae including sensorineural deafness, blindness, seizures and learning disability. Treatment of cCMV with antiviral medications started within 1 month of life,[42] with 6-week therapy of intravenous ganciclovir[43] or 6-month therapy with oral valganciclovir,[44] has been shown to improve the audiological outcome. Recent evidence seems to suggest 6 months of oral valganciclovir produces better outcomes in the long term.[45]

Health education forms an important part of primary prevention for many diseases. Awareness about cCMV infection among the general public is still quite low. Providing health education materials to pregnant women has been shown to increase their knowledge about the infection and may reduce its incidence.[46] CMV is transmitted in body fluids including saliva and urine. It is a very common infection in toddlers and preschool children and exposure to saliva and urine of small children is the commonest cause of CMV spread to pregnant women. Simple hygiene measures adopted by pregnant women, such as avoiding kissing young children on the mouth or cheek, careful hand washing after contact with any bodily fluids and not sharing cutlery or drinks and food, can help to reduce the risks of pregnant women getting CMV.[47]

Toxoplasmosis is an infection caused by the parasitic protozoan *Toxoplasma gondii*. Cats are important vectors in the transmission of the infection. They can become infected by eating infected rodents, birds or other small animals. They then pass the parasite in their faeces. Handling cat litter can spread the infection. It can also be contracted by eating uncooked meat. *Toxoplasma* infection

during pregnancy is often asymptomatic or may present as mild flu-like symptoms. Congenitally infected infants are mostly asymptomatic at birth, but long-term studies have shown that up to 85% may develop sequelae including sensorineural deafness, chorioretinitis, developmental delay and microcephaly.[48] The incidence of *Toxoplasma*-associated hearing loss has been estimated to be in the range of 0–26%.[49] Careful hygiene during pregnancy, avoiding handling cat litter and eating only well-cooked meat can prevent toxoplasmosis during pregnancy. In children with congenital toxoplasmosis who received antiparasitic therapy initiated within 2.5 months of age, the prevalence of SNHL was 0%. The prevalence was 28% in children who did not receive any treatment.[49] However, there is no randomized controlled trial evaluating the benefits of treatment. The optimum duration of treatment is not clear and there are concerns about the adverse effects of treatment in the newborn period. In the UK, routine screening for *Toxoplasma* during pregnancy is not carried out as there is no clear evidence that prenatal treatment reduces maternal to foetal transmission of the infection.

Exposure to tobacco smoke is a known cause of increased ear infections in children, and parental education regarding the effects of passive smoking is vital to reduce the incidence of ear infections in children.[50] Inadequate treatment of acute otitis media, delay in seeking medical treatment, poor housing conditions, poor hygiene and nutrition, unhygienic ear cleaning and swimming in infected ponds and pools are some of the factors leading to chronic suppurative otitis media (CSOM) in developing countries.[51] Public education about the impact of the disease, and improvement in hygiene, nutrition and housing conditions will reduce the global burden of deafness due to CSOM.

Traumatic causes of hearing loss

Traumatic causes of hearing loss include acoustic trauma, noise-induced hearing loss (NIHL), direct physical trauma and barotrauma.

PREVENTION OF TRAUMATIC CAUSES OF HEARING LOSS

Noise

It has been estimated that worldwide about 16% of disabling hearing loss in adults is occupational noise-induced.[52] The risk of developing NIHL is proportional to the duration of noise exposure. Although most developed countries have legislation in place to prevent NIHL, it still remains one of the commonest health problems and one of the most common occupational diseases. Non-occupational noise exposure, such as that resulting from leisure activities, including music, power tools and motor sports, and also daily exposure to noise due to environmental conditions, can lead to NIHL. The formation of free radicals reactive oxygen species (ROS) and reactive nitrogen species (RNS) seems to be the molecular basis for NIHL and ototoxicity. Excessive noise exposure leads to the formation of these free radicals; they trigger cell death pathways through necrosis and apoptosis, resulting in loss of hair cells and neurons, which results in the hearing loss.[53] Apart from using adequate protection to prevent exposure to noise, the role of several antioxidants and therapeutic agents has been studied in the prevention of NIHL in mainly animal models but also in some human studies. These include glutathione,[54] *N*-acetylcysteine,[53] transforming growth factor (TGF)-β1 inhibitor,[55] alpha lipoic acid[56] and hydrogen sulphide[57] among other agents. The topic of NIHL is covered more extensively in Chapter 57 Noise-induced hearing loss and related conditions.

Acoustic shock is another phenomenon which can cause SNHL. This happens when there is exposure to a short-duration, high-frequency and high-intensity sound through a telephone headset. Use of telecommunications with an acoustic limiter reduces the risk of hearing loss associated with acoustic shock.[58]

Physical trauma

Hearing loss can be due to physical trauma to the ear such as temporal bone injuries. The trauma may also be self-inflicted or iatrogenic. A recent study found that, in adults, cotton swabs, first-aid products, hearing aids and other ear-specific accessories were common aural foreign bodies.[59] Public education about the risks of ear cleaning with buds or other materials has to be ongoing.

Iatrogenic trauma includes inexpert attempts at syringing or removal of foreign bodies. In some developing countries 'ear cleaning' services are offered by street vendors which may cause serious damage to the ear. Increasing public awareness about the risks associated with these actions is vital. Iatrogenic trauma can also be caused during ear surgery. Ensuring adequate and appropriate training is given to surgical trainees is necessary to reduce this. Radiotherapy to the head and neck for tumours can cause conductive hearing loss due to middle ear effusion or sensorineural deafness due to cochlear damage. This can be prevented by careful modulation of radiation fields to limit exposure of the cochlea.[60]

Barotrauma

Barotrauma results when there is failure to equalize the pressure between an air-containing space and the surrounding environment. Barotrauma to the ear is most commonly caused by pressure changes encountered in flying and scuba diving. It can result in damage to the middle or the inner ear. Middle ear barotraumas results when there is failure of equalization of pressure between the middle ear and the atmospheric air pressure. This occurs when the Eustachian tube function is compromised.

Inner ear barotrauma is encountered in divers when they force a Valsalva manoeuvre to try to equalize the middle ear pressure and the resultant increase in pressure causes inner ear damage by either the **implosive** or the **explosive** route. In the implosive route, if the forced Valsalva opens the Eustachian tube, there is a significant increase in the middle ear pressure which can cause either

rupture of the round window membrane or disruption of the stapes footplate. If the Eustachian tube remains closed, the increase in intracranial pressure can be transmitted along a patent cochlear duct or the internal auditory meatus, causing disruption of the round window or the stapes footplate. With either route, perilymphatic leak or intracochlear membrane damage may result in SNHL. Decompression sickness in divers occurs when dissolved gas, usually nitrogen, comes out of solution on ascent and forms bubbles in soft tissues and blood vessels, causing various symptoms including sensorineural deafness.

Preventive measures for barotrauma as a result of air travel would include avoidance of flying during or immediately after an upper respiratory tract infection. Frequent swallowing, for example by sucking sweets or sipping drinks during ascent and descent, helps equalization of pressure in the Eustachian tube. Similarly for divers, avoidance of diving during an upper respiratory tract infection is important. Proper training in equalizing pressure plays a major role in preventing barotrauma. Manoeuvres to equalize pressure include the Valsalva (blowing against closed nose and mouth) and Toynbee (holding the nose and swallowing simultaneously). Decompression sickness can be prevented by strictly following existing guidelines on decompression times relating to time and depth of dive.

Ototoxic medications

A wide variety of drugs may have ototoxic effects. Ototoxic medications include aminoglycosides, antimalarials (e.g. quinine), aspirin, anticancer drugs (e.g. cisplatin), diuretics (e.g. ethacrynate and furosemide) and industrial solvents (e.g. toluene). As in the case of NIHL, ototoxic medications may lead to the formation of free radicals which trigger cell death pathways through necrosis and apoptosis, resulting in hearing loss. Ototoxic hearing loss may be prevented by minimizing and controlling the exposure to these medications. There does not seem to be a safe dose with relation to vestibulotoxic effects.

There is a known genetic predisposition to ototoxicity. Individuals with the mitochondrial mutation *A1555G* develop a hearing loss with aminoglycoside exposure which often progresses after the use of aminoglycoside at therapeutic doses has ceased.[61] However, the prevalence of deafness in individuals with the *A1555G* mutation is likely to be high even in the absence of aminoglycoside exposure.[62] Screening individuals due to receive aminoglycoside treatment may lead to prevention of hearing loss from this cause.[63] Similar to NIHL, antioxidants may have a role in preventing ototoxic hearing loss. Aspirin has been shown to attenuate the ototoxic effects of gentamicin.[64] Ototoxicity is discussed in greater detail in Chapter 59 Ototoxicity.

Perinatal factors

The role of preventable perinatal factors in developing SNHL has reduced in the developed countries with better obstetric care, but it can still be a major concern in developing countries. Reduction in morbidity due to hazardous levels of hyperbilirubinaemia has been achieved in developing countries through a variety of preventive measures including better antenatal care, monitoring of serum bilirubin in infants, exchange transfusion, phototherapy and anti-D immunization. Use of other antibiotics and careful monitoring of aminoglycoside levels can prevent incidence of ototoxicity in the perinatal period. Paradoxically, in developed countries, improved neonatal care now enables several very preterm infants to survive and as a result of their extreme prematurity they may have long-term neurodevelopmental sequelae including SNHL. The major preventable perinatal factors which can cause SNHL include hypoxia, hyperbilirubinaemia and aminoglycoside toxicity. Although birth asphyxia is associated with SNHL,[65] it is thought that it is a combination of risk factors which leads to SNHL.[66] Severe neonatal hyperbilirubinaemia is associated with a higher incidence of SNHL.[67] Hyperbilirubinaemia may also be associated with auditory neuropathy spectrum disorders.[68]

Prevention of deafness by improving lifestyle to prevent other diseases

Smoking, obesity and poor gylcaemic control are well-known risk factors for cardiovascular diseases which in turn may increase the risk of hearing impairment.[69] Ongoing public education, especially in developing countries, about the risks of smoking and benefits of healthier diet with regular exercise would help in the prevention of hearing loss by reducing the risk of cardiovascular diseases. Hypertension is also associated with hearing loss. Optimizing blood pressure control should also, therefore, reduce the risk of hearing loss.[70]

SECONDARY PREVENTION OF HEARING LOSS

Screening

Increasing evidence that early identification of deafness and early intervention will result in significantly better outcome for language development[71, 72] led to the development of the Newborn Hearing Screening programme. The World Health Organization[73] recommended that the policy of universal neonatal hearing screening should be adopted in all countries with available rehabilitation services and that this should be extended to other countries and communities as rehabilitation services are established. This has been implemented in several developed countries in the world. Implementing it can be quite a challenge in developing countries due to factors including non-availability of expensive screening equipment and trained personnel to do the screening. In many developing countries, the majority of births may take place away from maternity hospitals so, typically, screening will not be performed by skilled staff and screening equipment will not be available in such settings.[74] In countries which

have adopted universal newborn hearing screening, the age of identification of hearing loss has reduced dramatically. In England, the median age at identification of permanent hearing impairment has come down from 18 months before the implementation of the screening to 10 weeks, with 90% of cases being identified before 6 months of age.[75] In many developing countries, family suspicion remains the main mode of diagnosing childhood hearing impairment.

Hearing loss undiagnosed at birth or during the first few years of life adversely affects speech and language development, academic progress and social and emotional development. In countries without universal newborn hearing screening programmes, a significant number of children with permanent childhood hearing impairment (PCHI) are not diagnosed until well into childhood. Milder hearing loss or unilateral hearing loss may not be identified until 6 years of age. Identification and rehabilitation of PCHI during the first few months of life will result in a significantly better outcome for speech and language development, school performance and social and emotional development.[73]

School screening is an effective method of identification of children with hearing loss. Even in countries with universal newborn hearing screening, school screening identifies those children who may have developed a hearing loss later in life, have a progressive hearing loss or have missed hearing screening at birth.

Regular hearing screening of those at risk of developing NIHL is mandatory in several industries. Early identification and cessation of the noise exposure will prevent the hearing loss from progressing.

Treatment

Early identification of hearing loss and its cause can enable commencement of appropriate treatment in several situations. For instance, in the case of NIHL and ototoxicity, once the hearing loss is diagnosed, cessation of exposure to the noxious agent will usually prevent the hearing loss from progressing. Several agents have also been shown to be effective in improving NIHL and hearing loss due to ototoxicity (see above). Early diagnosis of cCMV as a cause of hearing loss in the neonatal period and treatment with antiviral medication has been shown to prevent the progression of the associated hearing loss.

Hearing loss due to middle ear disease can be very effectively prevented by early identification of the disease and appropriate management. This is all the more important in developing countries where CSOM is still a leading cause of hearing disability.

TERTIARY PREVENTION OF HEARING LOSS

Tertiary prevention involves early rehabilitation of hearing loss. Provision of appropriate amplification is the first step, but ongoing support is equally important. In the case of children, educational support specially tailored for the hearing-impaired child is essential. The use of assistive listening devices, such as hearing loop systems, FM systems and personal amplifiers, are invaluable tools in the management of an individual with hearing loss. The provision of appropriate amplification is an ongoing challenge in the developing world. The WHO has made several efforts at improving the availability of high-quality hearing devices in low- and middle-income countries, where in many cases charitable institutions play a major role in providing hearing aids.[76] The financial aspects of cochlear implantation may be a significant limiting factor in its availability in the developing world. To overcome this, some developing countries produce their own indigenous cochlear implants.[77] However, continuing support for cochlear-implanted children, which is so vital for its success, may not be available. Efforts to improve education and support for the family of a hearing-impaired child or older person across the world must continue.

CONCLUSION

Hearing loss is a leading disability worldwide but there are several preventable causes of hearing loss. Health education and improving awareness about the role of preventive medicine should be an ongoing endeavour by health professionals worldwide to reduce the impact of disabling hearing loss. Although major advances have taken place over the years in preventing deafness, there is still much more work to be done. This chapter gives a broad overview of the various preventable causes of hearing loss. For more exhaustive knowledge the reader is directed to the references listed.

FUTURE RESEARCH

- More clinical trials in humans need to be carried out to establish firmly the role of various therapeutic agents in the prevention of NIHL and ototoxicity.
- Gene therapy has been shown to have a role in preserving inner hair cells exposed to ototoxic agents in animals. Gene transfer and stem cell therapy for the cochlea may become a possible way of treating SNHL, but much more research has to be carried out in this area before it can have any clinical benefits.

KEY POINTS

- The World Health Organization (WHO) lists hearing loss as one of the 20 leading causes of burden of disease and as a most common cause of disability globally.
- Around half of all cases of hearing loss can be avoided through primary prevention.
- The incidence of hearing loss due to chronic suppurative otitis media (CSOM) has fallen dramatically in developed countries but still remains a leading cause in developing countries.
- CMV is the most common cause of congenital infections in humans, and congenital CMV (cCMV) is a leading cause of non-hereditary congenital sensorineural hearing loss (SNHL), which can be progressive.
- Treatment of cCMV started within the first month of life can prevent progression of hearing loss.
- About 16% of disabling hearing loss in adults is occupational noise-induced.
- Formation of the free radicals reactive oxygen species (ROS) and reactive nitrogen species (RNS) seem to be the molecular basis for noise-induced hearing loss (NIHL) and ototoxicity.
- Several antioxidants and other therapeutic agents may have a role in the prevention of NIHL and ototoxicity.
- In babies early identification of deafness and early intervention will result in significantly better outcome for language development.

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CHAPTER

54

HEARING AIDS

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SEARCH STRATEGY

The developments and research described in this chapter are in part based on a PubMed search using the keywords 'hearing aid'. To a small degree, they are also based on technical reports provided by manufacturers and on otherwise unpublished measurements and calculations by the author.

INTRODUCTION

Hearing aids partially overcome the deficits associated with a hearing loss. For a sensorineural hearing loss, there are several deficits to be overcome. Some sounds are inaudible. Other sounds can be detected because part of their spectra is audible, but may not be correctly identified because other parts of their spectra (typically the high-frequency parts) remain inaudible. The range of levels between the weakest sound that can be heard and the most intense sound that can be tolerated is less for a person with sensorineural hearing loss than for a normal-hearing person.

To compensate for this, hearing aids have to amplify weak sounds more than they amplify intense sounds. In addition, sensorineural impairment diminishes the ability of a person to detect and analyze energy at one frequency in the presence of energy at other frequencies.

Similarly, a hearing-impaired person has decreased ability to hear a signal that rapidly follows, or is rapidly followed by, a different signal. Hearing-impaired people are also less able to separate sounds on the basis of the direction from which they arrive. This decreased resolution (frequency, temporal and spatial) means that noise, or even other parts of the speech spectrum, will mask speech more than would be the case for a normal-hearing person.

The physiological origins of sensorineural hearing loss include loss of inner hair cell and outer hair cell function, reduced electrical potential within the cochlea and changes to the mechanical properties of the cochlea. The resulting auditory deficits mean that a person with a sensorineural hearing impairment needs a signal-to-noise ratio (SNR) greater than normal in order to communicate effectively, even when sounds have been amplified by a hearing aid. In contrast, a conductive impairment simply attenuates sound as it passes through the middle ear, so the amplification provided by hearing aids comes close to restoring hearing to normal.

To understand how hearing aids work, the physical characteristics of signals must be understood. These characteristics include the rate at which sound fluctuates (frequency), the time taken for a repetitive fluctuation to repeat (period), the distance over which its waveform repeats (wavelength), the way sound bends around obstacles (diffraction), the strength of a sound wave (pressure and sound pressure level), the break-up of a complex

sound into pure-tone components at different frequencies (spectrum), or into several frequency bands (octave, one-third octave or critical bands), and the degree to which a body of air vibrates when it is exposed to vibrating sound pressure (velocity and impedance).

The amplifiers inside hearing aids can be classified as linear or non-linear. For sounds of a given frequency, linear amplifiers amplify by the same amount regardless of the level of the signal or what other sounds are simultaneously present. By contrast, the amplification provided by a non-linear amplifier varies with the amplitude of the signal input to the amplifier. The degree of amplification can be represented as a graph of gain versus frequency (gain–frequency response), or as a graph of output level versus input level (I–O curve). The highest level produced by a hearing aid is known as the saturation sound pressure level (SSPL). The SSPL is usually estimated by measuring the output sound pressure level (OSPL) for a 90 dB SPL input (OSPL90).

The sound output by a hearing aid can be measured in the ear canal of an individual patient, or in a small coupler or ear simulator that has a volume similar to that of a real ear.

Hearing aids are described according to where they are worn. In order of decreasing size these categories are: body, spectacle, behind-the-ear (BTE), in-the-ear (ITE), in-the-canal (ITC) and completely-in-canal (CIC). For behind-the-ear hearing aids, further categorization is needed to distinguish between styles where the hearing aid receiver (the output transducer) is within the hearing aid case (receiver-in-the-aid, RITA) or within the ear canal (receiver-in-the-ear, RITE).

Decreasing size has been a constant trend during the history of the hearing aid. This history can be divided into six eras: acoustic, carbon, vacuum, transistor, digital and wireless. The last of these eras, which we are just entering, promises to hold advances at least as significant as in the eras that preceded it.

HEARING AID COMPONENTS

Hearing aids are best understood as a collection of functional building blocks. The manner in which a signal passes through these blocks in any particular hearing aid is indicated in a block diagram. The first block encountered by an acoustic signal is a microphone, which converts sound to electricity. Modern miniature electret microphones provide a very high sound quality, with only very minor imperfections associated with internal noise and sensitivity to vibration. Directional microphones, which have two entry ports, are more sensitive to frontal sound than to sound arriving from other directions. These enable hearing aids to improve the SNR by several decibels (depending on acoustic conditions) relative to omnidirectional microphones, and hence they can improve the intelligibility of speech in noise. Dual-microphone hearing aids can be switched automatically or by the user to be either directional, or omnidirectional, as required in different listening situations.

The small signals produced by microphones are made more powerful by the hearing aid amplifier. All amplifiers will distort the signal, by peak clipping it, if they attempt to amplify the signal to too high a level. Excessive distortion decreases the quality and intelligibility of sounds. To avoid distortion, and to decrease the dynamic range of sound, compression amplifiers are used in most hearing aids. These amplifiers decrease their gain as the level of the signal put into them increases, in much the same way that a person will turn down a volume control when the level becomes too high.

Amplifiers can represent sound in an analogue or a digital manner. The signals within analogue amplifiers have waveforms that mimic the acoustic waveforms they represent. Digital systems represent signals as a string of numbers. Performing arithmetic on the string of numbers alters the size and nature of the signals these numbers represent. Fully digital circuits may be constructed so that they process sounds in ways specific to each device, or may be able to perform any arithmetic operation, in which case the type of processing they do depends on the software that is loaded into them.

Filtering a signal is a common way in which hearing aids alter sound. Filters can be used to change the relative amplitude of the low-, mid- and high-frequency components in a signal. When the filters are made with variable, controllable characteristics, they function as tone controls operated by the user or the clinician. Filters can also be used to break the signal into different frequency ranges, so that different types of amplification can be used in each range, as required by the hearing loss of the hearing-impaired person.

Receivers are miniature headphones that use electromagnetism to convert the amplified, modified electrical signals back into sound. Their frequency response is characterized by multiple peaks and troughs, which are partly caused by resonances within the receivers, and partly caused by acoustic resonances within the tubing that connects a receiver to the ear canal. Inserting an acoustic resistor, called a damper, inside the receiver or tubing will smooth these peaks and troughs. A damper absorbs energy at the frequencies corresponding to the peaks, and this improves sound quality and listening comfort.

There are several other ways to put signals into hearing aids. A telecoil senses magnetic signals and converts them to a voltage. A radio receiver senses electromagnetic waves and converts them to a voltage. A direct audio input connector enables an electrical audio signal to be plugged straight into the hearing aid.

Users operate hearing aids via electromechanical switches on the case of the hearing aid or via a remote control. The hearing aid performs all its functions by taking electrical power from a battery. These batteries come in a range of physical sizes and capacities, depending on the power needed by each hearing aid and the space available.

HEARING AID SYSTEMS

Components can be combined into hearing aids in an extremely customized manner, such that individual components are selected for each patient and are located in

the position that best suits each ear. At the other extreme are modular aids, including some ITC hearing aids, and all BTE hearing aids, which are prefabricated in a totally standard manner. Many hearing aids fall somewhere between these extremes.

Increasingly, the hearing aids on each side of the head communicate with each other by wireless transmission so that their amplification characteristics (directionality, noise reduction processing, compression characteristics and input source) can remain coordinated as the environment changes or as the user varies a control. In some cases, the complete audio signal is transferred from one side of the head to the other, which enables a telephone signal to be heard in both ears and will enable superdirectional microphones to be developed.

Hearing aid amplification characteristics are programmed from a computer, via a suitable wired or wireless interface, to suit the hearing capabilities of each user. Often, more than one program is put into the hearing aid so that different amplification characteristics can be selected, automatically by the hearing aid or manually by the user, in different listening conditions.

The most effective way to make speech more intelligible is to put the microphone near the lips of the person talking. This markedly decreases noise and reverberation but requires a means of transmitting the signal from the microphone to the hearing aid wearer some distance away. Methods to do this currently include:

- magnetic induction from a loop of wire to a small telecoil inside the hearing aid
- radio transmission of a frequency-modulated or digitally modulated electromagnetic wave
- infrared transmission of an amplitude-modulated electromagnetic wave
- acoustic transmission of an amplified sound wave.

Each of these systems has strengths and weaknesses compared to the others. The first three offer a very large potential increase in SNR, and hence intelligibility. It can, however, be a challenge to adjust the hearing aid and wireless system together so that both the wireless system and the hearing aid individually provide maximum benefit to the wearer without the wireless input and microphone input signals interfering with each other. Increasingly, wireless receivers are being built into hearing aids, considerably improving cosmetic appearance and convenience. A major application of these systems is to make teachers more easily understood in classrooms, but they can be used by children and adults in other situations as well.

Wireless reception is also enabling hearing aids to conveniently accept electrical signals from a range of audio devices, including televisions, MP3 players, computers and mobile phones. In many cases, this connection requires an intermediary wireless relay device, as the current consumption of the ubiquitous Bluetooth receivers and transmitters precludes them from being directly built into hearing aids. While there have been problems with mobile phones causing interference in hearing aids, this problem is decreasing due to improvements in hearing aid design and changes in the mobile phone transmission system. Use of a mobile phone via hearing aids is now often trouble-free. There is the potential for hearing aids to become the audio portal to the world, and possibly not just for hearing-impaired people.

Assistive listening devices enable hearing aid wearers to receive sounds other than just by the amplification provided in a self-contained hearing aid. Assistive listening devices include the transmitter/receiver pairs already described for remotely sensing and sending speech or music, and devices that alter sound at its source (such as a telephone amplifier). Other types of assistive listening devices enable the aid wearer to detect alerting sounds (e.g. the doorbell, a telephone ring, a smoke alarm). Some do this by transmitting the sounds wirelessly to the hearing aids; others convert sound to other sensory modalities (such as flashing lights or vibrating shakers).

The long-established distribution and fitting system for hearing aids is being somewhat challenged by over-the-counter hearing aids, and their more modern cousin, hearing aids sold over the internet, and even by disposable hearing aids.

ELECTROACOUSTIC PERFORMANCE AND MEASUREMENT

The performance of hearing aids is most conveniently measured when the hearing aid is connected to a coupler. A coupler is a small cavity that connects the hearing aid sound outlet to a measurement microphone. Unfortunately, the standard 2 cc coupler is larger than the average adult ear canal with a hearing aid in place, so the hearing aid generates lower SPL in this coupler than in the average ear. This difference is called the real-ear-to-coupler difference (RECD), a quantity that is worth measuring in infants because they have ear canals considerably different from the average adult. A more complex measurement device, which better simulates the acoustic properties of the average adult ear canal, is called an ear simulator.

Test boxes provide a convenient way to get sound into the hearing aid in a controlled manner. These sounds can be pure tones that sweep in frequency, or can be complex, broadband sounds that, like speech, contain many frequencies simultaneously. Broadband sounds are necessary to perform meaningful measurements on many non-linear hearing aids. Increasingly, it is necessary for the test sound to approximate the spectral and temporal properties of speech so that the various signal processing algorithms in the hearing aid alter the gain in a manner representative of actual use. The measurements most commonly performed using test sounds are curves of gain or output versus frequency at different input levels, and curves of output versus input at different frequencies. The curve of output versus frequency when measured with a 90 dB SPL pure tone input level is usually taken to represent the highest levels that a hearing aid can create. Some other test box measurements that are less commonly performed are measures of distortion, internal noise and response to

magnetic fields. These measurements are used to check that the hearing aid is operating in accordance with its specifications.

Test box measurements are but a means to an end. That end is the performance of the hearing aid in an individual patient's ear. This performance can be directly measured using a soft, thin probe-tube inserted in the ear canal. Real-ear performance can be expressed as real-ear aided response (REAR; the level of sound in the patient's ear canal), real-ear aided gain (REAG; the level of sound in the ear canal minus the input level of sound near the patient) or as real-ear insertion gain (REIG; the level of sound in the ear canal when aided minus the level in the same place when no hearing aid is worn). Each of these measures requires the probe to be carefully located, but the requirements for probe placement are a little less critical for REIG than for REAG or REAR.

Both types of real-ear gain are different from coupler gain, partly because of the RECD already mentioned, and partly because the input to the hearing aid microphone is affected by sound diffraction patterns around the head and ear. The changes in SPL caused by diffraction are referred to as microphone location effects. Insertion gain is further different from coupler gain because resonance effects in the unaided ear form a baseline for the insertion gain measurement. This baseline, referred to as the real-ear unaided gain, provides the link between the REAG and the REIG.

Many factors can lead to incorrect measurement of real-ear gain. These include incorrect positioning of the probe, squashing of the probe, blockage of the probe by cerumen, background noise and hearing aid saturation. Fortunately, there are some simple checks one can do to verify measurement accuracy.

Feedback oscillation is a major problem in hearing aids. It happens when the amplification from the microphone to the receiver is greater than the attenuation of sound leaking from the output back to the input. Clinicians must be able to diagnose the source of excess leakage. Other problems that often have simple solutions include no sound output, weak output, distorted output and excessive noise.

HEARING AID EARMOULDS, EARSHELLS AND COUPLING SYSTEMS

An earmould or earshell is moulded to fit an individual's ear and retains the hearing aid in the ear. Premoulded canal fittings, available in a range of standard sizes and shapes, are an alternative way to connect the hearing aid to the ear canal. Whether custom-moulded or preformed, the ear fitting retains the sound bore, which is a sound path from the receiver to the ear canal. In many cases the fitting provides a second sound path, referred to as a vent, between the air outside the head and inside the ear canal. Where no vent exists, as in high-gain hearing aids, the fitting is said to be occluding. Where the cross section of the ear canal remains largely unfilled for its entire length, the hearing aid is said to be an open fitting, or an open-canal fitting. The three functions of an ear fitting are thus physical retention, transmission of amplified sound to the ear canal, and control of the direct sound path between the ear canal and the air outside the head.

There is a wide variety of physical styles of both earmoulds and earshells. These styles vary in the extent of the concha and canal that they fill. These variations affect the appearance, acoustic performance, comfort and security of retention of the hearing aid.

One unwanted consequence of a hearing aid can be an occlusion effect, in which the aid wearer's own voice is excessively amplified by bone-conducted sound. For many hearing aid fittings, vent selection is a careful juggle between choosing a vent that is big enough to avoid an unacceptable occlusion effect, but not so big that it causes feedback oscillations or limits the ability to achieve sufficient low-frequency gain and maximum output. For patients with mild or moderate hearing loss, the choice will often be an extremely open fitting comprising a BTE connected to thin tubing, or a wire connection for an ITE style, terminating in a preformed, flexible, perforated, dome-shaped canal fitting.

For any ear fitting with a vent or other direct path to the outside air, the speech range of frequencies can be subdivided into the vent-transmitted frequency range, the amplified frequency range and the mixed frequency range that is intermediate to these. Hearing aids perform very differently in each of these ranges.

The shape of the sound bore that connects the receiver to the ear canal affects the high-frequency gain and output of hearing aids. Sound bores that widen as they progress inwards (horns) increase the high-frequency output. Conversely, those that narrow (constrictions), whether by design or as a consequence of poor construction technique, decrease the high-frequency output. Horns have to exceed a certain length if they are to be effective within the frequency range of the hearing aid.

Dampers are used within the sound bore to smooth peaks in the gain–frequency response. Careful choice of the placement and resistance of the damper can also control the mid-frequency slope of the response.

The key to a well-fitting earmould is an accurate ear impression. This requires an appropriate material (medium viscosity silicone is good for most purposes), a canal block positioned sufficiently deeply in the canal and smooth injection of the impression material.

Tighter earmoulds or shells that reduce leakage of sound from the ear canal can be achieved by a variety of techniques. These techniques include taking an impression with the patient's jaw open, patting down the impression material before it sets, using viscous impression material and building up the impression in the patient's ear.

Earmoulds are made from a variety of materials. The most important difference between materials is hardness. Soft materials provide a better seal to the ear, but they deteriorate more rapidly, can be more difficult to insert and are more difficult to modify and repair. Earmoulds and earshells are routinely constructed by computer-aided

manufacture in which lasers guide the 'printing' of plastic based on a scanned image of the ear impression.

COMPRESSION SYSTEMS IN HEARING AIDS

The major role of compression is to decrease the range of sound levels in the environment to better match the dynamic range of a hearing-impaired person. The compressor that achieves this reduction may be most active at low, mid or high sound levels. More commonly, it will vary its gain across a wide range of sound levels, in which case it is known as a wide dynamic range compressor. Compressors can be designed to react to a change in input levels within a few thousandths of a second, or their response can be made so gradual that they take many tens of seconds to react fully. These different compression speeds are best suited to different types of people.

The degree to which a compressor finally reacts as input level changes is best depicted on an input–output diagram or on an input–gain diagram. The compression threshold, which is the input level above which the compressor causes the gain to vary, is clearly visible on such diagrams. The compression ratio, which describes the variation in output level that corresponds to any variation in input level, is related to the slope of the lines on these diagrams.

Simple compression systems can be classified as input-controlled, which means that the compressor is controlled by a signal prior to the hearing aid's volume control, or as output-controlled, which means that the compressor is controlled by a signal subsequent to the volume control. This classification is irrelevant for hearing aids with no volume control and inadequate for hearing aids with multiple, sequential compressors.

Compression systems have been used in hearing aids to achieve the following more specific aims, each of which requires different compression parameters. Output-controlled compression limiting can prevent the hearing aid ever causing loudness discomfort or the signal being peak clipped. Fast-acting compression with a low compression threshold can be used to increase the audibility of the softer syllables of speech, whereas slow-acting compression will leave the relative intensities unchanged but will alter the overall level of a speech signal. Compression applied with a medium compression threshold will make hearing aids more comfortable to wear in noisy places, without any of the advantages or disadvantages that occur when lower level sounds are compressed. Multichannel compression can be used to enable a hearing-impaired person to perceive sounds with the same loudness that would be perceived by a normal-hearing person listening to the same sounds. Alternatively, it can be used to maximize intelligibility, while making the overall loudness of sounds (rather than the loudness at each frequency) normal. Compression can be used to decrease the disturbing effects of background noise by reducing gain most in those frequency regions where the SNR is poorest. Gain reduction of this type increases listening comfort and with some unusual noises may also increase intelligibility. Finally, compression can be applied by using the combination of compression parameters that patients are believed to prefer, irrespective of whether there is a theoretical rationale guiding the application. Although these rationales are different, they have various aspects in common. Furthermore, many of them can be combined within a single hearing aid.

Despite the complexity, the benefits of compression can be summarized simply, but accurately, as follows. Compression can make low-level speech more intelligible, by increasing gain and hence audibility. Compression can make high-level sounds more comfortable and less distorted. In mid-level environments, compression offers little advantage relative to a well-fitted linear aid. Once the input level varies from this, of course, the advantages of compression become evident. Its major disadvantages are a greater likelihood of feedback oscillation and excessive amplification of unwanted lower level background noises.

DIRECTIONAL MICROPHONES AND ARRAYS

Other than the use of a remote microphone located near the source, directional microphones (which work by sensing sound at two or more locations in space) are the most effective way to improve intelligibility in noisy environments.

Directivity is most commonly achieved in hearing aids with first-order subtractive directional microphones, in which the output of one omnidirectional microphone is delayed and subtracted from the output of the other. This internal delay, relative to the physical spacing between the two microphone sound ports, largely determines the polar sensitivity pattern of these microphones. The head itself also affects the polar pattern.

These subtractive directional microphones inherently cause a low-frequency cut in the frequency response, for which the hearing aid signal processing often compensates by a low-boost characteristic, but which also causes greater internal noise in the hearing aid. Split-band directivity, which combines a directional response for the high frequencies with an omnidirectional response for the low frequencies, avoids this problem but, of course, provides no noise reduction for the low frequencies. Irrespective of the frequency range over which the microphone is directional, the complete hearing aid fitting will have directivity only over the frequency range for which the gain of the amplified sound path exceeds that of the vent sound path. In open fittings, this will likely be only half the speech frequency range. Whether achieved by split-band processing or by the acoustics of an open fitting, the resulting pattern of high-frequency directivity and low-frequency omnidirectional processing simulates the directivity pattern of normal hearing.

Additive directional arrays create directivity by adding together the output of two or more omnidirectional microphones. They do not create additional internal noise. To be effective, however, the microphones have to be separated by distances larger than a quarter of the

sound's wavelength. They are therefore less suitable for hearing aids, but are suitable for accessories such as handheld microphones.

These simple fixed subtractive and additive arrays have a fixed pattern of sensitivity versus direction of the incoming sound. Adaptive arrays, by contrast, have directional patterns that vary depending on the location, relative to the aid wearer, of background noises. Adaptive arrays automatically alter the way they combine the signals picked up by two or more microphones so as to have minimum sensitivity for sounds coming from the direction of dominant nearby noise sources. The multiple microphones that provide the input signals can be mounted on one side of the head or on both sides of the head.

The most sophisticated directional microphone arrays apply complex, frequency-dependent, adaptive weights to the outputs of each omnidirectional microphone before combining them. Like all directional microphone arrays, complex adaptive arrays work most effectively in situations where there is a low level of reverberant sound.

Directional microphones are effective when either the target speech or the dominant (rearward) noise source(s) are closer to the aid wearer than the room's critical distance (at which the reverberant and direct sound fields have equal intensity). In the special case of a close frontal talker and many distant noise sources, the improvement in SNR will approximate the directivity index of the hearing aid averaged across frequency.

The disadvantages of directional microphones include insensitivity to wanted sounds from the sides or rear, increased internal noise if used in quiet places, reduced localization accuracy if the two hearing aids act in an uncoordinated manner, and increased sensitivity to wind noise. These disadvantages can be minimized by intelligent switching (automatically or manually) between directional and omnidirectional modes, on the basis of noise levels and apparent SNR at the output of the omni and directional microphones.

All hearing aid wearers are candidates for directional microphones because all hearing aid wearers need a better SNR than people with normal hearing. Adaptive directional arrays that combine (via a wireless link or a cable) the outputs of microphones on both sides of the head produce a superdirectional response that should enable people with mild hearing loss to hear better than people with normal hearing in many social situations.

ADVANCED SIGNAL PROCESSING SCHEMES

Adaptive noise-reduction schemes, such as Wiener Filtering and Spectral Subtraction, progressively decrease the gain within each frequency region as the SNR deteriorates. Although they generally improve sound comfort and the overall SNR, these schemes do not change the SNR in any narrow frequency band. Consequently, they do not generally improve intelligibility. Other types of noise reduction include wind noise reduction, achieved by a low-frequency cut, and transient or impulsive noise reduction, achieved by limiting the rate at which the waveform changes.

Feedback oscillation can be made less likely by several electronic means. One simple technique is to decrease the gain only for those frequencies and input levels at which oscillation is likely. A second technique is to modify the phase response of the hearing aid so that the phase shift needed for oscillation does not occur at any frequency for which there is enough gain to cause feedback oscillation. A third technique involves adding a controlled internal negative feedback path that continuously adapts to maintain the gain and phase response needed to cancel the accidental leakage around the earmould or shell. A final technique involves making the output frequency different from the input frequency. Often, a combination of these techniques is used.

High-frequency components of speech can be made more audible by lowering their frequency. This can be achieved by transposition: moving sections of the spectrum to lower frequencies and superimposing them on the spectrum already in the lower frequency range. Alternatively, frequency compression is used to compress a wide frequency range into a narrower (and lower) one. While both frequency transposition and frequency compression can guarantee audibility of high-frequency sounds, they do not necessarily guarantee better intelligibility, as the speech components shifted down in frequency may interfere with perception of the speech components that were originally dominant in this lower frequency range. The range of possible frequency-lowering methods, frequency transformation maps and gain characteristics is large. Finding the best combination is made more difficult by the time it takes people to adapt to a highly altered spectrum and by our present uncertainty over how best to evaluate success.

There are various theoretically appealing methods for enhancing features of speech that have been tried in research experiments. These include exaggerating the peaks and troughs in the spectrum of a speech sound, increasing the amount of amplification whenever a consonant occurs, increasing the amplitude at the onset of sounds, lengthening and shortening the duration of particular sounds, simplifying speech down to a few rapidly changing pure tones, and resynthesizing clean speech based on the output of an automated speech recognizer. On the evidence available so far, however, none of these techniques will produce a worthwhile increase in intelligibility compared to conventional amplification, so there is as yet little motivation to include the processing within commercial hearing aids.

Various other signal processing algorithms have already been implemented in commercial hearing aids, or could readily be implemented. Reverberant energy that does not overlap other speech sounds can be removed, giving a crisper sound quality. Hearing aids can automatically categorize the listening environment they are in, and select amplification characteristics that have been preprogrammed into the hearing aid for each type of environment. Their data-logging systems can record how often each environment is encountered, and how the user

adjusts the hearing aids in each environment. Trainable hearing aids can learn from the adjustments the aid wearer makes, and infer how the aid wearer likes the hearing aid to be adjusted as the acoustics of the listening situation vary. Fine-tuning is therefore carried out by the hearing aid and the client together, rather than by the clinician. Active occlusion reduction processing enables a hearing aid to sound like an open-canal hearing aid, despite the ear canal being completely blocked. In addition to cancelling the occlusion-induced sound, active occlusion reduction cancels the vent-transmitted sound, enabling directional microphones to work over the entire frequency range, increasing their efficacy.

ASSESSING CANDIDACY FOR HEARING AIDS

Although the decision to try hearing aids is ultimately made by the patient, many patients will be in doubt as to whether they should acquire hearing aids and so will look to the clinician for a recommendation. This recommendation must take into account many factors other than pure-tone thresholds.

Initial motivation to obtain hearing aids has been shown to be a key determinant of whether patients continue to use them. This motivation reflects the balance of all the advantages a patient expects hearing aids will provide offset by all the expected disadvantages, irrespective of whether all these positive and negative expectations are realistic. The advantages expected by the patient are affected by the degree of disability they feel they have. Disability includes how much difficulty the person has hearing in various situations, referred to as activity limitation, and the extent to which a person is unable to participate in activities because of the hearing loss, referred to as participation restriction. The advantages and disadvantages expected by the patient are affected by what the patient has been told about hearing aids by others. Disadvantages potentially include the impact on a patient's self-image of wearing hearing aids. The clinician must attempt to discover a patient's expectations and modify those that are unrealistically low or unrealistically high. Although hearing aids help in quiet and in noise, they help much more in quiet, so hearing aids are more likely to be valued and used if the patient needs help hearing in quiet places.

When a clinician encounters a hearing-impaired patient who does not want hearing aids, the clinician should find out whether this is because the patient is not aware of the loss and/or the difficulty that he has compared to others, or because the patient, although acknowledging the loss, does not wish to wear hearing aids. If the latter is true, the patient's reasons should also be discovered.

Difficulty managing a hearing aid can greatly affect use, so the clinician must consider likely manipulation difficulties when determining candidacy and aid type. People with tinnitus often find that hearing aid use diminishes their problems, so tinnitus positively affects candidacy. The presence of central processing disorders and extreme old age can both affect candidacy, but not in a manner sufficiently predictable to affect the clinician's recommendation. People who are not worried that hearing aids will stigmatize them are more likely to acquire them, and people who more readily accept the presence of noise while listening to speech are more likely to use them. Several personality characteristics also make hearing aid acquisition, use and/or benefit more likely.

People with a severe to profound hearing loss are likely to receive more benefit from cochlear implants than from hearing aids. The most useful indicator of which device will be better for them is the speech score they receive for well-fitted hearing aids after some years of becoming accustomed to them. For infants, this is not possible so the decision to implant has to be based primarily on aided or unaided hearing thresholds (as well as requiring no medical or psychological contraindications). Cochlear implants and hearing aids generally provide complementary cues, whether they are worn in the same ear, or in opposite ears.

Vibrotactile or electrotactile aids are a worthwhile alternative for those with too much hearing loss to receive useful auditory stimulation from hearing aids but who do not wish to receive a cochlear implant, or for whom a cochlear implant is not suitable on medical or psychological grounds. Training in integrating the tactile information with visual information is essential.

Hearing aids should not be withheld just because speech scores obtained under headphones fall below some arbitrarily determined criterion. There are, however, several audiological/medical indications that should cause hearing aid fitting to be delayed until the cause of the problems has been resolved.

A clinician therefore has to consider a large number of factors that may affect candidacy for hearing aids, none of which has such a strong effect that the remaining factors can be ignored.

PRESCRIBING HEARING AID AMPLIFICATION

Amplification can be prescribed using a formula that links some characteristics of a person to the target amplification characteristics. Prescription formulae most commonly used are based on hearing thresholds, but some are based on suprathreshold loudness judgements.

Popular procedures for linear hearing aids include prescription of gain and output (POGO), National Acoustic Laboratories (NAL) and desired sensation level (DSL). For all of these, gain can be prescribed based on hearing thresholds alone. These formulae all contain variations of the half-gain rule (in which gain equals half of hearing loss, in dB), but the variations are so different that the resulting prescriptions differ greatly, especially for people with a sloping hearing loss.

For non-linear hearing aids, all available prescription procedures include some aspect of normalizing the loudness of suprathreshold sounds. Procedures such as loudness growth in octave bands (LGOB), International Hearing Aid Fitting Forum (IHAFF), DSL[i/o] curvilinear, the Cambridge method for loudness restoration (CAMREST)

and FIG6 aim to normalize loudness at all frequencies, at least for sounds with levels above the compression threshold of the hearing aid. Other procedures vary from loudness normalization in some way. ScalAdapt decreases the loudness of low-frequency sounds; CAM2 and NAL-NL2 normalize only the overall loudness. CAM2 aims to equalize the contributions that different frequency regions make to loudness, whereas NAL-NL2 aims for the sensation levels across frequency that will maximize calculated speech intelligibility. As each of the formulae has been revised, their prescriptions have become more similar to each other, but marked differences still occur.

There are some issues related to prescription that are not yet resolved, although there is considerable information available about each issue. How much do patients' preferences and performance with hearing aids change following weeks, months or years of experience with amplified sound? How loud (a perception, not a physical quantity) do patients like sound to be? Should tests of dead regions in the cochlea routinely be conducted? How severe does hearing loss need to be before it is considered unaidable? As signal level decreases, down to how low a level should gain keep increasing? How accurately must prescription targets be met? What is the best combination of fast and slow compression?

Maximum output (OSPL90) has to be prescribed so that loudness discomfort is prevented, but so that enough loudness can be obtained without the hearing aid becoming excessively saturated. In many procedures, the target OSPL90 is assumed to just equal the loudness discomfort level (LDL), in others it is predicted from threshold, in which case it may fall above or below an individual patient's LDL as measured in the clinic. For patients with mild to severe hearing loss, an acceptable sound quality is more likely if compression limiting controls maximum output than if peak clipping controls maximum output. Many patients with a profound loss, however, will benefit from the additional SPL that is achievable with a peak clipper.

People with conductive and mixed hearing loss require greater gain and OSPL90 than people with sensorineural loss of the same degree. For a variety of reasons, the gain needed to compensate for a conductive loss seems to be less than the amount of attenuation that the conductive loss causes in the middle ear. Consequently, the same is true of OSPL90.

Multimemory hearing aids can have a different prescription for each memory. These alternatives can be prescribed as variations from the baseline response prescribed for the first memory. The variations are designed to optimize specific listening criteria or for listening to different types of signals, such as music. People who wear their hearing aids in many environments, have more than 55 dB high-frequency hearing loss and require more than 0 dB low-frequency gain are most likely to benefit from multiple memories.

Neither gain nor OSPL90 should be any higher than is necessary for a patient. Otherwise, a hearing aid may increase hearing loss because of the resulting high-level exposure to sound. The risk of temporary or permanent noise-induced loss is greatest for patients with a profound loss and can be minimized by using non-linear amplification.

SELECTING, ADJUSTING AND VERIFYING HEARING AIDS

The first decision to be made when a clinician and patient select a hearing aid is whether a CIC, ITC, ITE, BTE–RITE, BTE–RITA (with standard tubing and earmould, or thin tube and earmould or instant-fit dome), spectacle, body, or a subvariety of any of these would be most suitable. For each style there are advantages relating to ease of insertion, ease of control manipulation, visibility, amount of gain, sensitivity to wind noise, directivity, reliability, telephone compatibility, ease of cleaning, avoidance of occlusion and feedback, ability to assess and fit in the same appointment, and cost. The weight given to each factor will vary greatly from patient to patient.

The need for specific features, such as a volume control, a telecoil and switch, a direct audio input and a directional microphone, must be determined on an individual basis. These needs will also influence the style of hearing aid selected. BTEs have more advantages than the other styles for a majority of patients.

Next, signal-processing options appropriate to the needs of the patient must be selected. Compression limiting is a more appropriate form of limiting than peak clipping if it can provide a high enough maximum output. In addition to compression limiting, a low compression ratio, active over a wide range of input levels, is appropriate for most patients. This low-ratio compression will provide advantages whether it is single- or multichannel, and whether it is fast- or slow-acting. Multichannel compression will provide greater speech intelligibility and/or comfort for patients with moderately or steeply sloping hearing loss, and the multichannel structure facilitates other features such as adaptive noise suppression and feedback suppression. The comfort advantages of adaptive noise reduction are greatest for patients who wear their hearing aids in a range of environments and who also require amplification across a wide range of frequencies. These same considerations apply to multimemory hearing aids, the only difference being that the patient, rather than the hearing aid, chooses the response variations. Feedback cancellation is most beneficial for patients with a severe or profound hearing loss, patients with a severe loss in the high frequencies but near-normal hearing in the low frequencies, any patients fitted with open canal devices, and any patient who wishes to use the telephone without using telecoil input. This combination makes it useful for nearly every client. Frequency lowering is advantageous for some patients though it is not yet possible to predict which patients will benefit. Trainability enables patients to take responsibility for fine-tuning their hearing aids.

Hearing aid fitting software provides a first approximation to the prescribed gain–frequency response target. The software must appropriately allow for the

acoustic configuration of the earmould shell or dome fitting. The approximation can be made even more accurate by incorporating the individual patient's RECD in the prescription. This increased accuracy in the precalculation is probably only worthwhile for hearing aids intended for infants, where measurement of the final real-ear gain is difficult.

Any signal-processing scheme that requires adjustment for each patient must also be supported by an appropriate prescription method. Measurement of real-ear gain is necessary unless the hearing aid has been adjusted in the coupler using the individual's (or at least an age-appropriate) RECD.

Because it is not possible to prescribe OSPL90 with complete precision, the suitability of maximum output should be subjectively evaluated before the patient leaves the clinic. A variety of intense sounds should be presented to the patient to ensure that the hearing aid does not make sounds uncomfortably loud. Maximum output must, however, be great enough for the patient to experience intense sounds as being loud. This can be assessed by presenting speech signals at a high level and asking the patient to report their loudness.

PROBLEM SOLVING AND FINE-TUNING

Many hearing aid fittings need to be fine-tuned, either electronically or physically, after the patient has had a week or two to try the hearing aids. When a patient has trouble managing hearing aids (inserting, removing, using the controls, changing the battery), reinstructing the patient may solve the problem. If not, the hearing aid should be physically modified or, if necessary, a different style chosen. Physical modification will also be necessary when a patient is suffering discomfort from the earmould, shell or case, or when the hearing aid works its way out of the ear.

Feedback oscillation has several potential solutions: reducing gain at selected frequencies; reducing the vent size; making a tighter earmould or shell; or changing the hearing aid to one that has more effective feedback cancelling and management algorithms.

Complaints about the patient's own-voice quality are particularly common. The most common cause is physical blocking of the ear canal, so the best cure is to add a vent, or increase the size of an existing vent, including using an open-fitting. Where feedback oscillation precludes that, the earmould or shell can be remade with the canal stalk extended down to the bony canal, preferably using a soft material. Own-voice problems are sometimes caused, and cured, by electronic variation of the gain–frequency response for high-level sounds.

Complaints about the tonal quality of amplified sounds are fixed by changing the balance of low-, mid- and high-frequency gain. The hard part is knowing when to ask the patient to persevere with a gain–frequency response in the expectation that it will eventually become the preferred response and confer maximum benefit to the patient.

When a patient complains about the clarity or loudness of speech, or the loudness of background noise, he/she must be questioned particularly carefully so that the acoustic characteristics of the sounds causing the problems can be identified. The clinician's first aim is to identify whether it is the gain for low or high frequencies, and the gain for low, mid or high levels, that should be adjusted. Only then can the appropriate hearing aid controls be adjusted.

In those cases where it is not clear which control should be adjusted, or by how much it should be adjusted, a systematic fine-tuning can be performed using one of two general methods. The first of these is paired comparisons, in which the patient is asked to choose between two amplification characteristics presented in quick succession. Multiple characteristics can be compared by arranging them in pairs. Paired comparisons can be used to adaptively fine-tune a hearing aid control if the settings compared in each trial are based on the patient's preference in the preceding trial.

The second general method for fine-tuning relies on the patient making an absolute rating of sound quality. The best amplification characteristic (out of those compared) is simply the characteristic that is given the highest rating by the patient. The absolute rating method can also be used to adaptively alter a chosen hearing aid control. This is achieved by deciding on a target rating (e.g. just right) and adjusting a control in the direction indicated by the patient's rating (e.g. too shrill or too dull).

The paired comparisons and absolute rating methods are best carried out while the patient listens to continuous discourse speech material, or other sounds they are complaining about. Depending on the complaint being investigated, this can be supplemented with recordings of commonly encountered background noises. The paired comparisons method is more sensitive when the differences between the conditions are small. Fine-tuning is usually carried out only for patients dissatisfied with the prescribed response, but it can be used for all patients if desired.

PATIENT EDUCATION AND COUNSELLING FOR HEARING AID WEARERS

People with a hearing impairment benefit from patient education and may benefit from communication training and counselling. These activities may be aimed at giving patients information about their hearing loss, developing skills needed to operate and care for their new hearing aids, improving listening skills, or changing patients' beliefs, feelings and behaviour relating to their hearing and communication. Providing appropriate education and counselling increases the likelihood that hearing aids will be fully used and that residual communication difficulties will be minimized.

It is difficult to help patients understand the variety of hearing aid styles and performance features that may be suitable for them. The benefits and cost implications of

each (including ongoing service costs, warranty and trial periods) have to be presented in a suitably simple manner.

Once they start using their hearing aids, first-time hearing aid users experience a new world of amplified sound and may benefit from guidance about how to gradually increase their range of listening experiences. The aim is to provide them with the best experiences first and to avoid having them become overwhelmed by sound. Patients need to know that their brains may take some time to adapt to hearing parts of speech and other sounds around them that they have not heard for some time.

A major part of educating the new hearing aid user has nothing to do with hearing aids! A wide range of hearing tactics and strategies can help the hearing-impaired person understand more in difficult listening situations. The first group of hearing strategies requires the listener to look carefully at the talker and the surroundings. The second group requires the listener to alter the communication pattern in some way. The final group requires the listener to manipulate the environment to remove or minimize sources of difficulty. Patients will benefit if family members and/or other frequent conversation partners participate in education sessions on these topics.

Patients will more easily appreciate and learn this material if it can be taught in a patient-centred, individual problem-solving method, rather than as a set of rules disconnected from their everyday lives. Communication training comprises training in the use of these hearing strategies, plus practice in listening to speech (synthetic training) or to the basic sounds from which speech is built (analytic training), especially in difficult listening conditions. Increasingly, communication training is being provided in packages that patients can use on their computer or DVD at home. Patients should be advised about protecting their remaining hearing and be made aware of where they can obtain support (from peer groups or other professionals) beyond that which the clinician can provide.

Hearing aids do not provide an adequate solution to all hearing problems, so patients must be made aware of other assistive listening devices that may help them. Clinicians should be aware that different people learn in different ways. Consequently, the same material should be taught in different ways to different patients, and clinicians should develop the flexibility needed to accomplish this.

Clinicians must be flexible regarding how and when they present information and carry out other procedures. It is, nonetheless, useful to have in mind a standard programme from which variations can be made as required.

ASSESSING THE OUTCOMES OF HEARING REHABILITATION

Clients and clinicians both benefit when the outcomes of the rehabilitation process (i.e. changes in the patients' lives) are measured in some way. Systematic measurement of outcomes can help clinicians learn which of their practices, procedures and devices are achieving the intended aims. Some measures can also help determine how the rehabilitation programme for individual patients should be structured and when it should be ended.

Outcome assessment can be based on an objective speech recognition test (the results of which depend hugely on the measurement conditions) or on a subjective self-report and/or the report of a significant other person. Speech test scores show the increase in the ability to understand speech in specific situations, whereas self-report measures more generally reflect the patient's views about the impact of rehabilitation.

Many self-report measures have subscales so that outcomes can be separately assessed for different listening environments. Outcome measures can assess the domains of benefit, defined as a reduction in disability (comprising activity limitation and participation restriction), device usage, listening effort, quality of life or the satisfaction that the patient feels.

Self-report measures that assess benefit can be grouped into various classes. First, patients can be asked to make a direct assessment of the benefit of rehabilitation. Alternatively, patients' views of their disability can be assessed both before and after the rehabilitation programme. The change in score provides a measure of the effects of rehabilitation. Measures obtained both before and after rehabilitation provide a more complete view of disability status and change. These difference measures probably assess change less accurately than those that directly assess benefit because they involve subtracting two scores.

The second way in which self-report measures differ from each other is the extent to which the items are the same for all patients or are determined individually for each patient. Results can more easily be compared across patients if a standard set of items is used for all patients. When the items are individually selected for each patient, however, the questionnaires become shorter and can more easily be incorporated within interviews with the patient. They are also more relevant to each patient.

There are thus four types of self-report measures: standard questionnaires that directly assess benefit (e.g. Hearing Aid Performance Inventory (HAPI); standard questionnaires that compare disability before and after rehabilitation (e.g. Hearing Handicap Inventory for the Elderly (HHIE); Abbreviated Profile of Hearing Aid Benefit (APHAB)); individualized questionnaires that directly assess benefit (e.g. Client Oriented Scale of Improvement (COSI)); and individualized questionnaires that compare disability before and after rehabilitation (e.g. Goal Attainment Scaling (GAS)).

Self-report measures also commonly assess hearing aid usage (which can now also be measured objectively with data logging) and are the only viable way to assess satisfaction. Some measures contain questions that address only one domain (benefit, use or satisfaction) whereas others address more than one domain. One comprehensive questionnaire, the Glasgow Hearing Aid Benefit Profile (GHABP), addresses all three dimensions, contains standard and individualized measures, and assesses benefit both directly and by comparing disability before and after rehabilitation. A very simple and widely used

questionnaire that assesses several domains with a single question each is the International Outcomes Inventory for Hearing Aids (IOI-HA).

Some questionnaires are designed to assess problems experienced with the hearing aid, although freedom from problems with the hearing aid is more properly viewed as a means to an end rather than a life-changing outcome.

While outcomes can be assessed any time after hearing aid fitting, the extent of benefit does not appear to stabilize until about 6 weeks after fitting. Hearing loss is associated with a decrease in many aspects of quality of life (such as increased depression) and use of hearing aids is associated with general improvements in health and quality of life. Causal relationships between these quantities are difficult to establish, however. Generic measures of health outcome are not efficient means by which a clinician can assess the outcomes of rehabilitation.

BINAURAL AND BILATERAL CONSIDERATIONS IN HEARING AID FITTING

Sensing sounds in two ears (binaural hearing) makes it possible for a person to locate the source of sounds and increases speech intelligibility in noisy situations. Wearing two hearing aids (a bilateral fitting) instead of one hearing aid (a unilateral fitting) increases the range of sound levels for which binaural hearing is possible. Bilateral fitting is thus more important when hearing loss is severe than when it is mild or moderate.

Accurate horizontal localization is possible because sounds reaching the two ears differ in level and in arrival time, and hence in phase. These cues are also present, but altered, when people wear hearing aids. Most hearing-impaired people, once they become used to the effect of their hearing aids on these cues, can localize sounds accurately to the left and right in the horizontal plane. Vertical localization and front–back localization, which are based on very high-frequency cues created by the pinna, are extremely adversely affected by hearing loss and are not significantly improved by hearing aids.

When speech and noise arrive from different directions, head diffraction causes the SNR to be greater at one ear than at the other. Further, the auditory system can combine the different mixtures of speech and noise arriving at each ear to effectively remove some of the noise. This ability is known as binaural squelch. Even presenting identical sounds to the two ears provides a small improvement in speech intelligibility over listening with one ear, a phenomenon known as binaural redundancy.

Wearing a second hearing aid will improve speech intelligibility in noise whenever it causes speech to become audible in the previously unaided ear. Achieving audibility of speech in both ears is a prerequisite to attending to the ear with the better SNR, and to benefiting from binaural squelch and binaural redundancy. Bilateral fitting of hearing aids has several other advantages. These include improved sound quality, suppression of tinnitus in both ears and greater convenience if one hearing aid breaks down or when one battery dies. A bilateral fitting may help prevent a problem sometimes associated with unilateral fittings: a unilateral fitting can lead to decreased speech processing ability in the unaided ear if this ear is deprived of auditory stimulation for too long, a phenomenon referred to as late-onset auditory deprivation.

The advantages of bilateral fittings also apply to patients with asymmetrical hearing thresholds. If such patients must receive a unilateral fitting, it may be generally advisable to fit the ear with thresholds closest to about 60 dB HL.

Bilateral fittings also have disadvantages: they cost more, are more susceptible to wind noise and are more difficult for some elderly people to manage. Also, some people regard two hearing aids as an indication of severe hearing loss and do not wish to be perceived in this way. For some people, binaural interference causes speech identification ability to be better when unilaterally aided than when bilaterally aided. The causes of this interference may lie in differences between the two cochleae, differences between the two hemispheres of the cortex or distortions in transfer of information from one hemisphere of the cortex to the other.

Because of the variability associated with speech intelligibility testing, conditions have to be chosen carefully to reliably demonstrate bilateral advantage or detect binaural interference on an individual patient. To best demonstrate bilateral advantage, loudspeaker positions for speech and noise should be chosen to maximize the effects of head diffraction and binaural squelch. To best detect binaural interference, speech and noise should emanate from a single, frontal loudspeaker, so that the effects of head diffraction and binaural squelch are minimized. In either case, speech tests with steep performance–intensity functions should be used. A method for predicting whether individual patients will benefit more from a unilateral or bilateral fitting is urgently needed.

SPECIAL HEARING AID ISSUES FOR CHILDREN

When a child is born with a hearing loss, early provision of hearing aids is essential if he or she is to learn to speak and listen with the greatest possible proficiency. Hearing aids should be provided by 6 months of age. If cochlear implants are a better option, these should be implanted by 12 months of age. Children with bilateral loss should receive bilateral hearing aids. There is some uncertainty over optimal treatment for children with unilateral loss, mild loss or auditory neuropathy.

For the hearing aids to be optimally adjusted, frequency-specific hearing thresholds must be determined separately for each ear. No matter what type of transducer is used, the small size of a baby's ear complicates the interpretation of hearing threshold. This difficulty is overcome either by expressing threshold in decibels sound pressure level (dB SPL) in the ear canal, or by expressing it as equivalent adult hearing threshold in decibels hearing level (dB HL).

BTE hearing aids are most likely to be provided, in conjunction with soft earmoulds, until the child is at least 8 years old (and possibly much older). The hearing aid should contain features that will enable the child to receive the best possible signal. This is likely to include an audio input socket and/or telecoil and/or internal wireless receiver, so that there is some means to receive wireless transmission. Ideally, the wireless device should be able to automatically attenuate the local microphone whenever the person wearing the transmitter talks.

To communicate effectively, normal-hearing children learning language need a better SNR than do adults. They also understand speech less well than adults at very low sensation levels. These observations may lie behind the empirical finding that hearing-impaired children prefer more gain than adults with the same hearing loss. Compared to adults, they almost certainly do not need any more real-ear gain for high-level sounds, they probably prefer more gain for medium level sounds, and they almost certainly need more gain for low-level sounds.

There is an even greater need for wide dynamic range compression in hearing aids for children too young to manipulate the volume control than there is for adults. Similarly, infants have an even greater need than adults for directional microphones and adaptive noise-reduction systems. These algorithms also have potential disadvantages but they should be provided if the clinician has confidence in the automated manner in which the hearing aid selects them.

To achieve a certain real-ear gain, young children need less coupler gain than do adults, because children have smaller ear canals. An efficient way to allow for small ear canals is to measure RECD before prescribing the hearing aid, and to calculate the coupler gain that will result in the target REAG. A faster but less accurate way is to use age-appropriate values of RECD.

The maximum output that has been prescribed should be evaluated by observing the child when intense sounds are made and, for those over approximately 6 years of age, by assessing the loudness of these sounds.

Hearing aid fittings can be evaluated by speech testing (for those over 3 years of age), paired-comparison preference testing (for those over 6 years of age), and subjective reporting by the child, the parents or the teachers, whether informally or using systematic methods such as Parents' Evaluation of Aural/Oral Performance of Children (PEACH) and Meaningful Auditory Integration Scale (MAIS). The audibility of speech can be estimated by calculating the articulation index (also known as the speech intelligibility index (SII)) or assessed by measuring the presence, latency and perhaps morphology of the cortical responses elicited by speech sounds. The availability of speech to the child can be indirectly assessed by measuring the child's language development.

Effective amplification for young children is not possible without the support and understanding of parents. The audiologist must therefore inform and support the parents in a variety of ways. One way to provide ongoing habilitation is to base the service activities around goals determined jointly by the audiologist and the parents (and by the child when old enough). Information provided to parents includes safety aspects of amplification and hearing loss. Hazards include battery, earmould or hearing aid ingestion, excessive exposure to noise, physical impact and failure to detect warning signals if amplification is not functioning correctly.

CROS, BONE-CONDUCTION AND IMPLANTED HEARING AIDS

In the CROS (contralateral routing of signals) family of hearing aids, hearing aid components on opposite sides of the head are wirelessly linked. Basic CROS aids are most suitable for people with unilateral loss. CROS aids consists of a microphone on the side of the head with a deaf ear, combined with an amplifier, receiver and open earmould or shell on the side with a normal-hearing ear. Adding a microphone to the side of the better ear converts it to a BICROS hearing aid, which is suitable for patients with loss in both ears. A transcranial CROS has all the components in one ear, but sends a signal across the head by bone conduction. CROS hearing aids must be carefully fitted to ensure the aid wearer receives, in a single cochlea, an appropriate balance of sounds reaching the two sides of the head.

Bone-conduction hearing aids output a mechanical vibration instead of an airborne sound wave. They are most suited to people who, for medical or anatomical reasons, cannot wear a hearing aid that occludes the ear in any way, or for those who have a large conductive loss in either ear. For patients with normal external and middle ears, bone-conduction hearing aids cannot stimulate the cochlea as effectively as do air-conduction hearing aids because of the relative inefficiency of the bone conduction pathway. For patients with maximal conductive hearing losses, whether or not there is also a sensorineural loss, bone-conduction hearing aids can stimulate the cochlea as strongly as air-conduction hearing aids. Prescriptions for air-conduction hearing aids can be converted into bone-conduction prescriptions by using available standards for the thresholds of hearing for air- and bone-conducted sound. Bone-conduction output is specified in terms of output force level instead of OSPL and in terms of acoustomechanical sensitivity instead of gain.

Disadvantages of non-implanted bone-conduction hearing aids include their wearing comfort and the limited sensation level they can provide. A commonly used form of bone-conduction hearing aid is the bone-anchored hearing aid, in which the vibrations are transmitted to the skull via an embedded titanium screw, thereby increasing stimulation of the cochlea by about 15 dB compared to a bone conductor applied to the skin. Bone-anchored hearing aids have been used successfully for patients with unilateral or bilateral conductive or mixed loss. They are also routinely being fitted to people with unilateral sensorineural loss, referred

to as single-sided sensorineural deafness. The output levels they can achieve make them suitable for people with cochlear loss up to about 45 dB HL for head-worn devices and up to about 60 dB HL for body-worn devices. Bone-anchored hearing aids can provide greater cochlear stimulation than air conduction hearing aids for patients with air-bone gaps greater than about 30 dB.

A variety of other middle-ear implants have been researched, and several have been approved for routine use. Middle-ear implants may have only the output transducers surgically implanted or may be combined with implanted microphones and batteries to form completely implanted hearing aids. Four types of output transducers have been used: magnets enclosed by a coil that rely on the inertial mass of the magnet, magnets mounted on the middle ear chain driven by a remote coil, and piezoelectric or electromagnetic stimulators anchored to the mastoid bone and vibrating the middle ear chain. Three types of microphones have been used: external microphones, microphones implanted under the skin on the scalp or in the ear canal, and transducers that are driven by the vibration of the middle ear chain.

Several implanted hearing aids are now commercially available. For some clients, particularly those with mixed hearing loss, middle ear implants may have advantages related to freedom from occlusion, amplification gain and bandwidth, stimulation level and invisibility of the device. Fully implanted devices have additional advantages arising from there being no external parts. Candidacy criteria are still developing.

FUTURE RESEARCH

- Research is needed to better understand the barriers preventing many people with hearing loss from seeking rehabilitation through acquiring and wearing hearing aids. Equally important, psychological research is needed to find effective ways to overcome those barriers and so reduce the time that hearing loss adversely affects quality of life. Related to this, knowledge is needed on the minimal degree of hearing loss at which hearing aids become effective, and how this minimal aidable loss is also determined by the cognitive, psychological, psychoacoustic and lifestyle characteristics of each patient.
- At the other end of the hearing loss spectrum, prediction tools that take account of individual characteristics are needed to indicate which patients are likely to function better were they to receive one or more cochlear implants, rather than continue to wear hearing aids. Fully implantable hearing aids require a method of implanting microphones that enables them to achieve the same sensitivity and low internal noise levels that hearing aids mounted outside the head currently achieve.

KEY POINTS

- Hearing aids have become sophisticated devices, the amplification characteristics of which are adjustable to optimize listening over a wide range of hearing loss configurations and degrees.
- Digital signal processing has largely solved the previous major problem of feedback oscillation (whistling) even when the hearing aid is fitted to the ear with an acoustically open connection. Such open fittings leave the patient's own voice sounding more natural.
- Although nothing can reverse the reduced precision of signal analysis that inevitably accompanies sensorineural loss, hearing aids can restore audibility, and in many listening situations can improve the signal-to-noise ratio of the signal delivered to the ear, so that good speech understanding occurs despite the reduced analysis ability of the damaged auditory system.
- Wireless technology is increasingly being built into hearing aids, and in situations where a remote microphone can be positioned near the talker or source, speech understanding in noise can be superior to that enjoyed by someone with normal hearing.
- Compared to the number of people with significant hearing loss, hearing aids are an under-utilized solution. This applies even in developed countries, but much more so in the developing world.

ACKNOWLEDGEMENT

The material in this chapter is a slightly edited version of synopses of each of the chapters in the chapter author's book *Hearing aids*.[1] The reader is referred to that book, which is comprehensively referenced and elaborates on all the information covered in this chapter.

REFERENCE

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CHAPTER

55

BEYOND HEARING AIDS: AN OVERVIEW OF ADULT AUDIOLOGICAL REHABILITATION

Lucy Handscomb

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: aural rehabilitation, hearing therapy, hearing assistance technology and language service professionals.

INTRODUCTION

Hearing aids are often seen as the mainstay of adult audiological rehabilitation, and their benefits are undeniable. However, they are far from being a panacea. While some patients attend hearing services seeking hearing aids and are satisfied with the help they provide, others have needs which cannot be met by amplification alone. This chapter gives an overview of approaches to aural rehabilitation other than hearing aid fitting and provides guidelines about when they may be needed.

NON-TECHNOLOGICAL REHABILITATION

Hearing therapy

Hearing therapists provide one-to-one support to people with hearing loss and related problems (particularly tinnitus). The term aural rehabilitation specialist may also be used, and in some countries this kind of service is provided by clinical psychologists. Hearing therapy involves counselling and supporting patients as they adjust to living with hearing loss. For many people, the experience of losing hearing goes far beyond the frustration of mishearing speech, although this in itself is a significant problem. Hearing loss can necessitate changes in lifestyle, both at work and at leisure. It can change the way one interacts with others, making conversation effortful and tiring, and profoundly alter one's sense of identity.[1] An in-depth interview study found that people felt their hearing loss held them back in life, made them feel 'left out' and caused considerable emotional distress.[2] Personal relationships are also negatively affected, with couples in particular feeling that hearing loss places a strain on their interactions.[3, 4] People who are having difficulty adjusting to life with hearing loss may well benefit from an opportunity to discuss their feelings and explore ways of coping, whether or not they are also fitted with hearing aids (or cochlear implants). A group in particular need of urgent referral to rehabilitation services are those who develop sudden hearing loss, who often report feelings of utter bewilderment and confusion. In a medical emergency, it is easy for emotional needs to be neglected, but timely emotional support is just as important as prompt medical treatment.

Specialist rehabilitative support can also be beneficial to people who feel ambivalent about using hearing aids. There are many reasons why people feel unsure about using amplification including perceived stigma and lack of confidence.[5, 6] An opportunity to spend time discussing one's ambivalence in a supportive environment is likely to be more cost-effective than fitting hearing aids that are likely to remain unused.

A hearing therapy appointment is likely to consist of counselling and joint goal-setting, using a collaborative approach between patient and therapist. Hearing assistance technology may also be demonstrated (see 'Types

of technology' below). Most patients are seen for several appointments over a period of weeks or months as they develop and practise new coping strategies.

Access to specialist aural rehabilitation services is usually via ENT and may require a referral form or letter.

Aural rehab groups and lip reading classes

Some audiology clinics offer rehabilitation through an aural rehab group. As well as being cost-effective for clinics, groups have the advantage of bringing people with hearing loss together to share experiences and ideas and to support each other. Many encourage the participation of partners too. There are many different group formats, but typically participants meet weekly for five or six sessions of around 2 hours each. Groups usually follow a problem-solving format, with a facilitator encouraging participants to generate ideas themselves about how to manage difficult communication situations and then to role-play them with each other. A review of research into aural rehab groups found fairly consistent evidence that they are effective in reducing the amount of restriction people feel in relation to their hearing loss (as measured on self-report scales) and in improving use of communication strategies.[7] The author also points out that participants' comments after attending a group are overwhelmingly positive; people enjoy group sessions and perceive them to be very worthwhile.

Outside the healthcare system a number of groups and classes exist for people with hearing loss. Perhaps the most popular are lip-reading classes, often held in community centres and adult education colleges. These are usually run by trained lip-reading teachers and involve a mixture of lip-reading exercises and communication tips. Although effects of class attendance on lip-reading ability are equivocal, qualitative research indicates that people value their classes very highly.[8] Hard-of-hearing groups or clubs are also available in some areas which offer peer support and an opportunity to take part in social activities without being restricted by hearing problems.

The UK charity Hearing Link offers week-long residential rehabilitation courses for adults with acquired profound hearing loss and their families. Such courses are hugely beneficial to families struggling to adjust to the far-reaching changes that profound deafness brings. Referral from a medical professional – such as an ENT doctor – is normally required in order to secure funding to attend a course.

Auditory training

Auditory training attempts to improve speech discrimination in people with hearing loss by presenting a variety of listening tasks involving phonemes, words and sentences. Exercises such as listening in background noise or attending to sound in one ear and not the other might be included. Traditionally, auditory training was conducted one-to-one in clinics, but now a number of computer-based auditory training programs are available, enabling users to practise regularly at home with minimal intervention from clinicians. A systematic review of 13 computerized auditory training studies found firm evidence that performance on auditory training tasks improves significantly with practice.[9] Some (but not all) studies also showed generalization of learning to untrained tasks, which of course has more real-world benefit. The authors of the review conclude that better-quality evidence is needed, but computerized auditory training is already an increasingly popular option for motivated individuals who are willing to put in the practice time required.

The voluntary sector

A great deal of support for people with hearing loss and related problems (such as tinnitus and balance disorders) is provided by charities and voluntary organizations. Charities are very often an invaluable source of information; many produce fact sheets about a range of hearing-related topics and some have telephone and email helplines available. Regular magazines for members can help people with hearing loss feel better informed and connected to others with similar problems. There are also several forums available via the internet and social media through which people can share information and offer support. These are perhaps particularly helpful to younger people with hearing loss, who may otherwise feel rather isolated.

TECHNOLOGY OTHER THAN HEARING AIDS AND COCHLEAR IMPLANTS

The need for additional technology

While both hearing aids and cochlear implants are capable of providing great benefit, there are situations in which many users find them inadequate. In spite of recent advances in digital signal processing, interference from background noise is still a primary cause of dissatisfaction among hearing aid users and, in some cases, a reason for giving up with hearing aids altogether.[10, 11] Distance can also cause difficulties; many hearing aid users complain that, while they hear well in their own living room, they struggle to understand a speaker in a large church or hall. The two problems of intrusive background noise and distance are combined when, for example, fellow students cough and shuffle in a lecture theatre. Telephone use can also be problematic, particularly as many people experience interference when a mobile phone is placed close to their hearing aid. People with more severe hearing loss may find television unclear, even when using hearing aids, and disputes over TV volume have been found to be among the most frequent sources of irritation when one half of a couple has hearing loss.[12] Moreover, there are situations in which most people take their hearing aids or speech processors off (particularly while bathing or in bed) but still need to be aware of signals such as smoke alarms or alarm clocks. Additional technology goes some

way towards solving all of these difficulties but, as will be discussed, its use is not widespread.

Types of technology

Additional technology can broadly be divided into two categories: assistive listening devices (ALDs), which are designed to improve audibility, and alerting devices, which use visual or tactile signals as a substitute for sound. Collectively they are sometimes known as hearing assistance technology (HAT).

Connectivity

There are three ways in which hearing aids or speech processors can be linked with audio equipment and ALDs.

- **Telecoil:** A telecoil is a small receiver fitted as standard in most behind-the-ear (BTE) and many in-the-ear (ITE) hearing aids. When active, it picks up signals from an electromagnetic field created by an induction loop, which itself can be linked to a range of amplifiers and audio devices. The telecoil can be switched on and off by the hearing aid user, but it first needs to be activated by the person fitting the hearing aid. Switching the telecoil on normally disables the hearing aid microphone, thus reducing background noise substantially. A neckloop can be plugged directly into a standard headphone socket, essentially allowing hearing aids to function as headphones.
- **Direct audio input:** Some BTE hearing aids can have a small electric cable plugged into them either directly or via an adapter which clips onto the bottom of the hearing aid; this is sometimes known as a 'shoe' or 'boot.' The other end of the cable can be plugged into a standard headphone socket, enabling the user to receive the sound directly into the hearing aid without interference from surrounding noise.
- **Bluetooth:** In recent years a number of Bluetooth-compatible hearing aids have become available. Most of these require an intermediary device called a streamer (worn round the neck) to enable the hearing aid to pick up signals from paired Bluetooth-enabled devices such as smart phones and tablets. At the time of writing, some hearing aids which use Bluetooth technology without the need for a streamer are also available.

All of the options above enable users to connect their hearing aids directly to a range of standard audio devices and also to specialized ALDs.

Personal listening equipment

A number of devices exist which are designed to improve sound quality, increase amplification and reduce interference from background noise when listening to live speech, television, radio or music. All of the devices described below allow people direct control of the volume of sound going through their hearing aids, meaning that companions without hearing aids can listen alongside them comfortably.

FM SYSTEMS

These consist of a receiver connected to the user's hearing aids by means of direct audio input or a neckloop, and a transmitter (with an in-built microphone) which can be placed close to any sound source or clipped onto a speaker's clothing. The transmitter converts sound into a radio signal which is then picked up by the receiver. When linked to the FM system, hearing aids will only pick up signals from the receiver and not extraneous noise. FM systems are particularly valuable in classrooms and lecture theatres, where the speaker tends to be at a distance from the listener and may be moving about, and they are often used by hearing-impaired children in school. The sound quality is excellent.

LOOP SYSTEMS

A less expensive option than an FM system for those purchasing equipment privately is a portable loop system. At their most basic, these consist of a neckloop, an amplifier 'box' with volume control and a hardwired microphone which can be placed close to any sound source. Wireless microphones are also available. Portable loops tend to perform less well at a distance than FM systems but are useful in domestic environments and when travelling. Listening to a driver or travelling companion in a car or bus via the amplifier and neckloop cuts out interference from engine and road noise.

A convenient option for TV listening is a room loop. An amplifier is connected to the television (usually by means of a SCART lead) and a loop wire emerging from it is fixed to the skirting board around the room. Once installed, the user only needs to switch the amplifier on and activate the telecoil in the hearing aids in order to be able to listen through the loop from anywhere in the room.

INFRARED SYSTEMS

Sound can be converted to an infrared signal which is then transmitted wirelessly to a receiver worn by the hearing aid user with a neckloop attached. This is another neat and convenient option for TV watching, but it has the disadvantage that the signal can easily be interrupted if the user moves around.

STREAMERS

As well as giving access to Bluetooth, streamers can be used with compatible hearing aids as portable amplifiers with wireless microphones or plugged into personal music players. An additional adapter is needed in order for a streamer to be used as a TV listener.

Using personal listening equipment without hearing aids

Many personal amplifiers and FM systems can be used with headphones as an alternative to neckloops or direct

audio input. These make them accessible to non-hearing aid users and to people who need or prefer to be without their hearing aids temporarily, perhaps due to an ear infection.

An inexpensive personal amplifier with headphones can be particularly helpful as a communication device in hospital. Many hearing-impaired patients on a ward will not have their hearing aids in, either because they were left behind during an emergency admission or because they are uncomfortable to wear in bed. This sometimes results in confidential and sensitive information being spoken at high volume by hospital staff and being clearly audible to all those around. Speaking to the patient via a simple amplifier with headphones slipped over the ears can make all the difference to confidentiality and dignity.

ALDs in public places

Commercial loop systems have been installed in many public buildings such as theatres, cinemas, meeting halls and places of worship. Loops can also be found at reception desks, ticket counters, banks, post offices and in taxis. Where a public loop system has been installed, the user only needs to switch their hearing aid to telecoil to be able to benefit from clearer sound. The presence of a loop system is normally indicated by an ear symbol with the letter T (for telecoil).

Some theatres use infrared listeners instead of a loop system and will loan receivers to hearing-impaired customers at the box office.

Telephones

LANDLINES

Many conventional telephones available from mainstream suppliers have a small inductive coupler fitted into the receiver, which enables the hearing aid user to listen via the telecoil and thereby reduce ambient noise. If this does not provide adequate volume, a range of portable amplifiers is available, which either strap onto the receiver or can be connected to a corded phone between the handset and the base.

A wide range of telephones, both corded and cordless, is available with amplifiers built in, some of which are very powerful. Many have tone control as well, which can improve clarity. A selection of additional features are also available, such as large buttons for people with visual impairment, extra receivers to allow another person to assist with the conversation and adapted handsets which can be held against the mastoid bone to allow hearing via bone conduction.

Adapters can be bought to enable landlines to be heard via a streamer.

MOBILE PHONES

For many years the majority of hearing aid users found it impossible to use a mobile phone with a hearing aid, due to an unacceptably high level of interference. While interference continues to be an issue, more recently manufacturers have taken the needs of their hearing-impaired customers into account and a universal rating scheme has been introduced (although its use is not compulsory). Mobile phones can be given a rating of 1 (poor) to 4 (excellent) depending on how well they perform with hearing aids set to microphone (M) or telecoil (T). The very best mobile phone for hearing aid users would be rated M4/T4.

Even better clarity can still be obtained by the use of a mobile phone-compatible neckloop or a Bluetooth streamer (discussed above). These enable the phone to be held right away from the hearing aid and have the added advantage of making the ringtone audible in the hearing aid itself.

Some older people may be put off by additional gadgetry but want to use a mobile phone for security. A range of basic mobile phones is available with amplified speech and large buttons but with a minimum of extra features.

TEXTPHONES

People with severe or profound hearing loss can communicate using a textphone – sometimes known as a Minicom – which can send and receive typed messages over a phone line. Two people with textphones can communicate directly with each other or a textphone user can communicate with a conventional phone user via an operator. This system predates the internet and has been a lifeline to many, but its use is now in decline owing to the multiple methods of mainstream text communication available via computers and smart phones.

Alerting devices

STAND-ALONE EQUIPMENT

There are many quite simple and inexpensive devices which can be used to alert people with hearing loss to telephone ringers, door bells, alarm clocks, smoke alarms and baby monitors. Most use a loud sound accompanied by a flashing light. Some devices can be supplied with a vibrating pad which can be placed under the pillow to wake the user at night.

PAGERS

A practical option for many people is a pager, which can be linked to several devices at once. Normally, a small unit clipped onto clothing or worn on the wrist will vibrate when any device it is linked to makes a sound, and a small light indicates which device has been activated. Larger vibrating units can be supplied for night-time.

WIRED-INSYSTEMS

It is possible for an electrician to connect doorbells and telephones to the house lights so that they flash on and off in response to sound. However, this is a less popular option now that pagers are widespread.

HEARING DOGS

People with severe or profound hearing loss can apply to have a hearing dog. Such dogs are specially trained to alert their owners and lead them to the source of the sound when the doorbell, phone or other device is activated. They are also taught a 'danger' signal in response to a smoke alarm. Like other assistance dogs, hearing dogs wear a special coat and can accompany their owners in public places. Many deaf people feel more confident with a hearing dog by their side.

Research into HAT use and benefit

There is a paucity of research into the use of HAT and its benefits. However, when ALD users have been asked about their impressions, responses have been largely positive. An internet survey of 356 ALD users reported that the majority rated their ability to understand speech as 'better' or 'much better' when using a personal listening device as compared to when using their hearing aids or cochlear implants alone.[13] Ratings were particularly high for listening through an ALD when part of an audience. A qualitative interview study conducted by the charity Action on Hearing Loss also cites several very positive comments about the clarity of listening via a loop system.[14] FM systems have been subject to more rigorous investigation than other technology and a consistent finding is that their performance is superior to hearing aids alone when listening to speech in noise.[15–17] A smaller-scale study also showed use of a more basic listening device with headphones to result in fewer communication breakdowns in informal discussion.[18]

Despite these benefits, it appears that the use of any type HAT is not very widespread. A large survey of almost 3000 Australian adults aged 49 and over found that 11% owned hearing aids but only a quarter of these had used any kind of ALD over the past year.[19] The most commonly used type of ALD was a telephone amplifier, while only a tiny proportion had used a personal listening device. A survey of around 500 adults over 65 in the US found that only 5% of those with hearing loss used any kind of ALD, as compared to 26% who used hearing aids (notably, of those who did use ALD, all but two reported high levels of satisfaction).[20] In the UK, the aforementioned study conducted by Action on Hearing Loss found that only a few interviewees had ever used HAT of any kind. This study gives lack of awareness as a principle reason for non-use of HAT; most people simply did not know that technology other than hearing aids was available. A similar theme emerged from an earlier qualitative study in Canada.[21] Other potential barriers to HAT use which were identified by this study were concerns over adapting to new technology and lack of confidence. Previous research has found that ALDs may be rejected because of the extra effort required to set them up.[15] For personal listening systems particularly, a further possible barrier is that people may feel awkward about asking others to speak through a microphone on their behalf.

Chisolm et al. noted that, in previous trials of FM systems, most participants have not continued to use their devices afterwards despite clear benefits to hearing.[17] These authors tried a different approach, offering intensive support with FM systems over five visits which included discussion and role-play of difficult listening situations in addition to instructions for use. They found that 30 out of 36 of their participants were continuing to use their FM system a year later. Further research in this area is needed, but it seems that successful use of ALDs could potentially be increased by seeing them as an integral part of aural rehabilitation rather than an 'add-on'.

LANGUAGE SERVICE PROFESSIONALS

In certain situations where communication is difficult, a person with severe or profound hearing loss may find that even additional equipment is inadequate. In such cases, communication support is available from specially trained people known as a language service professional (LSP). LSPs are most often used to enable participation in meetings, conferences and training courses. They can also provide support in court rooms and at medical appointments. Different types of LSP are listed below.

- **Sign language interpreter:** Interpreters translate what is being said into sign language in real time and also 'voice over' what a deaf person is signing. Interpreting usually happens live but is sometimes provided by video link. Hands-on interpreters are available to deaf–blind people and 'relay' interpreting is possible for deaf people who use sign language from another country.
- **Lip speaker:** Lip speakers repeat exactly what a speaker is saying but without voice. They use clear lip patterns and always face the front to enable people to lip-read.
- **Speech-to-text:** A speech-to-text operator either types an instant summary of what is being said or converts speech to text verbatim using a special keyboard, with text appearing on a screen. Increasingly, this service is being provided over the internet, making it more widely available.
- **Notetaker:** A notetaker's role is to support a deaf student by taking lecture notes on their behalf, thus enabling them to look up and lip-read the lecturer.

OBTAINING HAT AND ACCESSING LSP

Unlike hearing aids, HAT is not provided by the UK National Health Service. Devices can often be purchased from private hearing aid dispensers or directly from the companies which supply them by mail order or online. However, some equipment and services are available free of charge to the user.

Domestic equipment

In the UK, equipment for home use by both adults and children can usually be supplied by the local social services. A referral can be made by the audiology department or an individual can refer themselves (or their child). Normally, an assessment of needs will be arranged before equipment is supplied. The range of equipment provided by social services is generally quite limited, but a major advantage is that help with set-up is available and faulty devices can be replaced.

The UK fire service offers domestic fire safety assessments on request. It is able to provide smoke alarms with flashing lights and vibrating pads free of charge to individuals with hearing loss.

Equipment for work

It is an employer's responsibility to supply additional equipment or support necessary for an employee with hearing loss to perform his role. This might be an amplified telephone, a loop system for meetings or a speech-to-text operator for a training course. In the UK, help with funding can be applied for through the government's Access to Work scheme.

Equipment for education

In the UK, FM systems for school children with hearing loss are provided by the Local Education Authority. In higher and further education, students with hearing loss can apply for a Disabled Students Allowance. A certain amount of money is allocated per year, depending on the level of disability, and the student is able to spend this on either equipment, communication support or a combination of both.

CONCLUSION

The consequences of hearing loss are far-reaching. Many people with hearing loss could benefit from a range of rehabilitation services, either as an alternative or as a supplement to hearing aids or cochlear implants. While it is not the responsibility of ENT doctors to provide such services, it is important to be aware of what is available in the local area and to be able to make appropriate referrals and recommendations.

KEY POINTS

- Hearing therapists provide one-to-one support to people with hearing loss and related problems (particularly tinnitus).
- In a medical emergency, it is easy for emotional needs to be neglected, but timely emotional support is just as important as prompt medical treatment.
- Auditory training attempts to improve speech discrimination in people with hearing loss by presenting a variety of listening tasks involving phonemes, words and sentences.
- A telecoil is a small receiver fitted as standard in most BTE and many ITE hearing aids. When active, it picks up signals from an electromagnetic field created by an induction loop, which itself can be linked to a range of amplifiers and audio devices.
- In recent years a number of Bluetooth-compatible hearing aids have become available.
- FM systems are particularly valuable in classrooms and lecture theatres, where the speaker tends to be at a distance from the listener and may be moving about, and they are often used by hearing-impaired children at school.
- There are many quite simple and inexpensive devices which can be used to alert people with hearing loss to telephone ringers, door bells, alarm clocks, smoke alarms and baby monitors.

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CHAPTER 56

AGE-RELATED SENSORINEURAL HEARING IMPAIRMENT

Linnea Cheung, David M. Baguley and Andrew McCombe

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SEARCH STRATEGY

Data in this chapter may be updated by Medline searches using the keywords: age-related hearing loss, presbyacusis and presbycusis. The search strategy included the keywords diagnosis and management for sourcing the relevant subsections. Some references have been hand-sourced from the authors' personal collections on this subject.

DEFINITION, BACKGROUND AND PATHOPHYSIOLOGY

DEFINITION

Age-related hearing loss may be defined as a progressive bilateral sensorineural hearing loss of mid to late adult onset, where underlying causes have been excluded. Strictly speaking, age-related hearing loss is a diagnosis which excludes hearing loss caused by primary factors including loud noise exposure, intrinsic otological disease (e.g. otosclerosis, chronic otitis media and Ménière's disease), head injury, ototoxic drug therapies and underlying medical conditions (e.g. atherosclerosis, diabetes, hypertension, Paget's disease of bone, myxoedema). 'Age-related hearing loss' is used interchangeably with 'age-associated hearing loss' and these are now terms in widespread use, replacing 'presbyacusis' (presbycusis in US spelling). Presbyacusis was originally derived from 'presbyacusia', used to describe a loss of high-frequency hearing acuity in the elderly observed when tested with tuned whistles designed by Sir Francis Galton for testing hearing.[1, 2] Age-related hearing loss is associated, in the majority of cases, with an audiogram that reveals greatest hearing loss at higher frequencies. Indeed, the definition of age-related hearing loss is also somewhat arbitrary; there is no agreed age above which an individual suffers from age-related hearing loss and below which one does not.

BACKGROUND

It would appear that auditory acuity is at its best in the late teenage years and into one's early twenties.[3] From then on there is a progressive decline,[4] which is greater for men[5] and for manual workers.[6]

It has generally been believed that at the extremes of life, there is relatively little progression of hearing loss, with most deterioration taking place in between. However, as the number of people surviving to extreme old age increases, there are emergent indications that the rate of progression of hearing loss in the 10th decade increases.[7]

Whilst the rate of deterioration tends to increase with age, the timing of onset is variable, with the greatest variability in the middle years (40–60 years). It appears that once a certain amount of hearing loss has occurred (approximately 75–80 dB HL), further progression is very slow,[8] particularly in the higher frequencies.[9] The variability of onset in the middle years can be explained by the concept of accelerated ageing.[10] In all likelihood this represents some form of hereditary/genetic degenerative process[11, 12] or some alternative process causing a sensorineural hearing loss. Table 56.1 summarizes the causes of sensorineural hearing loss.

TABLE 56.1 Causes of sensorineural hearing loss, shown in order of prevalence and with approximate values where available

Cause	Prevalence (%)
Age	Ultimately 100?
Noise	<5
Idiopathic	5–30
Ear infections	
Ménière's disease	
Head injury	> 0.004
Ototoxicity	
Non-syndromic genetic	0.7 (probably greater)
Syndromic genetic	0.3
Systemic illness (e.g. meningitis, renal failure, diabetes)	
Others (e.g. autoimmune, otosclerosis, acoustic neuroma)	

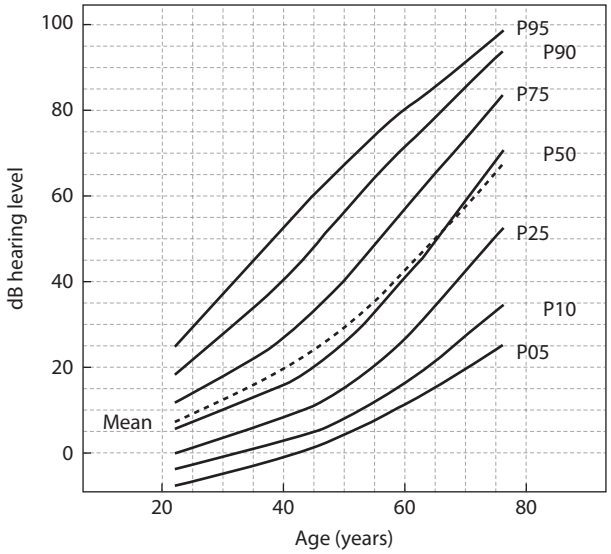


Figure 56.1 Hearing threshold and population percentiles for better ear at 8 kHz. Redrawn from Davis[14] with permission from Whurr Publishers, London.

TABLE 56.2 Prevalence of hearing impairment with age

Age group (years)	Prevalence (%)
18–30	2
31–40	5
41–50	10
51–60	17
61–71	30
71–80	53

Average threshold >30 dB HL; all causes; both ear average. Reproduced with permission from Davis A. *Hearing in adults*. London: Whurr Publishers; 1995.[14]

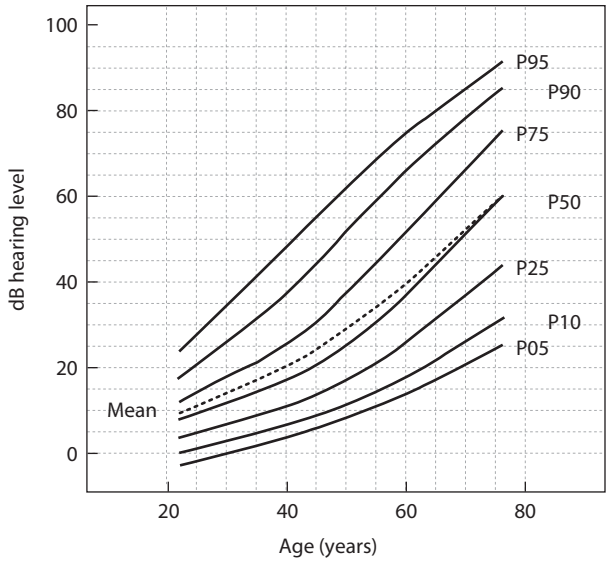


Figure 56.2 Hearing threshold and population percentiles for 4, 6 and 8 kHz average (better ear). Redrawn from Davis[13] with permission from Whurr Publishers, London.

It is probable that all these processes affect the cochlea in remarkably similar fashion but with a unique temporal course both in terms of onset and progression.[13] Almost invariably, databases displaying age-related, average hearing thresholds for either screened or unscreened populations show a marked increase in the rate of progression of the hearing loss once into the sixth decade. This is demonstrated in Table 56.2 and Figures 56.1 and 56.2.

It is, therefore, reasonable (although somewhat arbitrary) to attribute high-tone hearing loss in an individual over the age of 50 to age-related changes (in the absence of any alternative explanation). Under the age of 50 an alternative diagnosis should be considered. In the absence of any other clear diagnosis (e.g. noise, family history, ototoxic medication, systemic illness), it is reasonable to describe the loss as 'a non-syndromic, genetic, degenerative hearing loss'. With genetic mapping continuing apace, mutations and/or genetic explanations are becoming increasingly documented.[12, 13]

In addition, the problems and consequences of age-related hearing loss are compounded in the elderly as a result of additional degenerative processes in the central nervous system. This can result in a relative loss in neuronal plasticity, a loss of cognitive abilities and other sensory modalities, in particular, sight. The diagnosis of age-related hearing loss is, therefore, made on clinical grounds on the basis of a recognizable constellation of features.

Relatively recent research[15–17] tells us that age-related hearing loss impacts on psychological well-being as well as physical ability. Decreasing hearing acuity correlates with an increased incidence of falls,[18] depression[19] and dementia[20] in the elderly.[21] The feelings of imprisonment and anxiety that result from social isolation lead to reduced higher cognitive functioning which can in turn increase the economic and societal burden of age-related hearing loss.[22] It is therefore ever more important as the life expectancy of our population increases to make the diagnosis and offer treatment early.

PATHOPHYSIOLOGY

External and middle ear

Involvement of the middle ear in age-related hearing loss was suggested by Toynbee.[23] Several age-related changes occur in both the outer and middle ear (Table 56.3),[24] however these do not significantly contribute to resultant hearing loss.[25]

Inner ear

Schuknecht et al. hypothetically divided the age-related changes in the cochlea associated with hearing loss into six distinct types based on their histopathological studies.[26–28] Although this classification is deduced from a relatively small sample (n = 21), other authors[24, 29–31] have correlated clinical results with pathological findings leading to the consensus that this represents useful distinctions in the pathological substrate of age-related hearing loss.

Table 56.4 summarizes the different types and their pathological defining features known to date. The neural type of histopathology was believed to be the most common,[24] though a longitudinal study[31] has indicated that metabolic, and mixed sensory-metabolic phenotypes increase with increasing age.

TABLE 56.3 Summary of age-related changes in the outer and middle ear

Outer ear	Middle ear
Increased cerumen production	Stiffening, thinning, loss of vascularity of tympanic membrane
Reduced epithelial migration	Arthritic changes and ossification in ossicles and ossicular joints
Increased hair growth	Degeneration of middle ear muscles
Potential collapse of ear canal	Calcification of cartilaginous support of Eustachian tube
Enlargement of pinna	

TABLE 56.4 Histological subtypes of age-related hearing loss and the known defining features to date

Type	Defining features
Sensory	Loss of hair cells and sustentacular cells[32] at the basal end of the organ of Corti (Figures 56.3 and 56.4)
Neural	Degeneration of cochlear nerve neurons Cochlear ganglion cell loss
Vascular or metabolic	Atrophy of the cochlear stria vascularis Loss of strial tissue in the cochlea[33] primarily in the apical and middle turns of the cochlea[24]
Mechanical or cochlear conductive	Stiffened cochlear basilar membrane An increase in the number of fibrillar layers of the basilar membrane[6]
Intermediate	Submicroscopic changes of the cochlear duct[28] Possible changes in intracellular organelles involved in cell metabolism, decrease in synapse numbers and changes in endolymph composition[24, 25]
Mixed	A combination of the other five subtypes

The various histological types have been correlated with audiogram patterns in post-mortem studies:[26] sensory and neural histopathological types are associated with the common high-frequency loss pattern, with associated poor auditory discrimination abilities. In contrast, the strial type has been associated with a 'flat' audiogram and good discrimination abilities also seen in age-related hearing loss. It is not possible, however, to determine the site of pathology from audiometric data alone.[24] Given that the Schuknecht classifications are essentially hypothetical, it is not yet known whether these different histopathology patterns reflect the existence of a number of different underlying mechanisms for age-related hearing loss. Whilst cochlear hair cell loss has been the main focus of research into the pathophysiology of ARHL, the auditory neuroscience community have become interested in a precursive state wherein degeneration of cochlear synapses precedes hair cell loss and threshold elevation.[34] Whilst there is presently more evidence for this in animal models than humans, it does raise the possibility of novel potential therapies.[35]

Central nervous system

Age-related degenerative change in the central nervous system was suggested as a contributory factor in age-related hearing loss by Hinchcliffe.[36] Such change in the auditory system is relatively subtle[25] and highly variable;[24] a significant consequence is reduced plasticity, which in part accounts for the marked acclimatization period required for the elderly to obtain maximum benefit from hearing rehabilitation by amplification.[37, 38]

Central auditory processing abilities decline with age, and decrements in tests of temporal fine structure and word recognition and discrimination have been reported.[39, 40] Over recent years, there has been a strong association demonstrated between age-related hearing loss and cognitive impairment including dementia and depression.[21, 41] Although a causal relationship has not been proven, it is suggested that behavioural mechanisms such as the social isolation resulting from the chronic hearing loss results in reduced activation of the central auditory pathways leading to decreased cognitive performance.[19]

Animal models of age-related hearing loss, specifically inbred mice, have shed some light on mechanisms and pathological changes with age[33] and, in particular, upon metabolic mechanisms of age-related hearing loss. These include recent research into the possible roles of mitochondrial DNA mutations and reactive oxygen species.[42] It is hoped that such studies will lead to the development of targeted therapies applicable to humans although this prospect still remains distant.

GENETICS

The genetics of congenital, childhood and early-adult onset forms of deafness have been intensively studied and many of the responsible genes have been identified. However, the genetics of age-related deafness in humans are much more poorly defined and no associated genes or loci have been identified. The available data do, however, implicate genetic

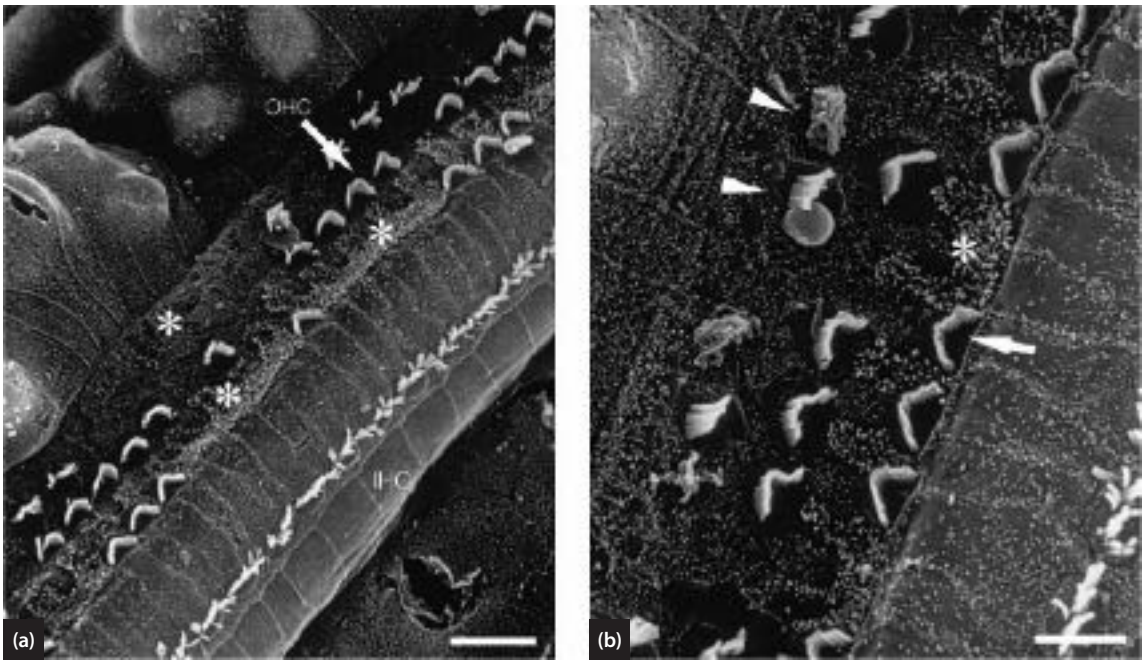


Figure 56.3 Scanning electron micrographs showing typical examples of the aged mammalian organ of Corti from a guinea pig. (a) The outer hair cell (OHC) rows show substantial patches where hair cells are probably missing (*) and in the process of degenerating, although the inner hair cells (IHC) are relatively undamaged. Scale bar: 20 µm. **(b)** Detail of the OHC region showing different levels of damage to the hair bundles of OHCs (arrowheads) including complete loss (*). The underlying hair cell is probably missing. Scale bar: 10 µm. Courtesy of Dr D.N. Furness, Mackay Institute of Communication and Neuroscience, Keele University.

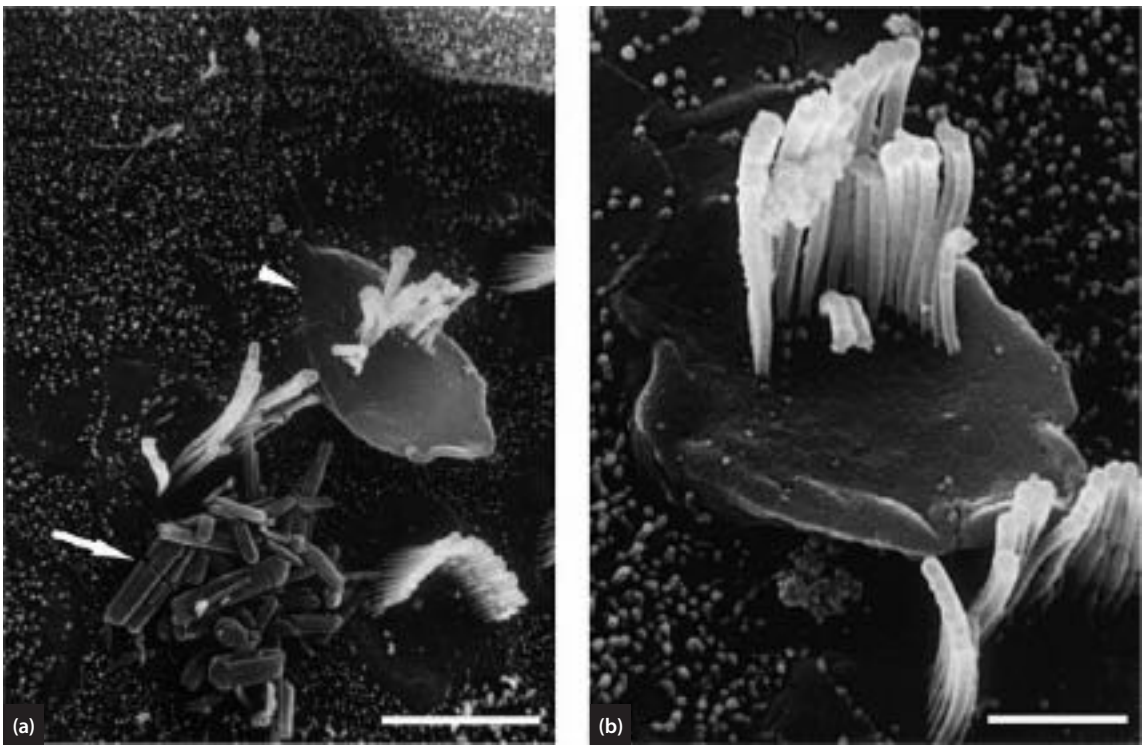


Figure 56.4 Scanning electron micrographs showing details of outer hair cell damage in an aged guinea pig. (a) Degenerating outer hair cells display different types of damage including, here, extrusion of the apical surface (arrowhead) and debris, probably from adegenerating cell (arrow). Scale bar: 10 µm. **(b)** Detail of the extrusion of an outer hair cell apex. The hair bundle itself is relatively intact. Scale bar: 2 µm. Courtesy of Dr D.N. Furness, MacKay Institute of Communication and Neuroscience, Keele University.

factors in causing age-related hearing loss. Standard methods for determining the genetic component of a condition involve twin studies, examining concordance rates in monozygotic versus dizygotic twins, and family-based case-control studies. Two studies assessing the contribution of genetic factors to age-related audiology thresholds and hearing loss are available. A Swedish twin study examined audiometric hearing thresholds in 557 male twin pairs aged 36–80 years, identified from the Swedish Twin Registry. Similarity in audiogram thresholds was consistently greater for monozygotic versus dizygotic twins in all age ranges, but particularly so in the youngest group. These findings were interpreted as showing that genetic and environmental factors are important sources of variation in hearing at all ages, with genetic factors being particularly important for younger men.[43]

A family-based case-control study examined members of the US Framingham Heart Study and Framingham Offspring Study cohorts. It compared aggregation of audiometric hearing threshold in spouse pairs versus sibling or parent–child pairs. It also examined the aggregation of hearing level in pairs where one member had age-related deafness, with either a sensory or a strial audiogram pattern. Significant aggregation of hearing thresholds was found in parent–child and sibling pairs, but not in spouse pairs. Parent–child and sibling aggregations in hearing threshold were also found when pairs including a member with a sensory or strial deafness phenotype were analyzed separately. Heritability (the proportion of population variance attributable to genetic variation) was estimated for the sensory age-related deafness phenotype at 35–55% and for the strial phenotype at 25–42%. All of the aggregations were stronger in women than in men.[44] A genome-wide linkage screen, carried out on the Framingham study population, failed to map any age-related hearing loss gene conclusively, perhaps because the test population lacked the power to do so.[45]

Genetic studies of mice have made an important contribution to the field of deafness and conclusively indicate that genetic factors can be important in age-related hearing loss.[12, 46] Many different inbred mouse strains show accelerated age-related hearing loss and in at least ten of these the gene involved is *ahl*, which maps to mouse chromosome 10.[47, 48] This gene is inherited in a recessive pattern. This same gene is also implicated in susceptibility to noise-induced hearing loss and to aminoglycoside-induced hearing loss.[49, 50] A mitochondrial genome variant that interacts with and modifies this locus has been identified.[51] A more recent study indicates that the *ahl* gene is the mouse orthologue of cadherin 23, a human deafness gene associated with non-syndromic hearing loss and Usher syndrome.[52] At least two other mouse age-related hearing loss loci, designated ahl2 and ahl3, exist,[53] with alh2 mapped to mouse chromosome 5.[54] Finally, it has been suggested that mitochondrial genome mutations or variations, either inherited or acquired with age, may contribute to age-related hearing loss in humans.[42, 55] The available evidence indicates that genetic factors are important in age-related hearing loss and in the determination of age-related hearing thresholds. The strength of the genetic effect in and the mode(s) of inheritance of the age-related deafness clinical phenotype are not yet clear, and much work is needed to identify the genes involved.

RISK FACTORS

Risk factors implicated in primary age related hearing loss (i.e. where underlying causes have been excluded) are not clear. Epidemiological studies have suggested two main categories of modifiable factors that may contribute to the development of age-related hearing loss: environmental factors (noise exposure,[56–58] cigarette smoking and alcohol use[59]) and health comorbidities (hypertension,[60] blood hyperviscosity[61] and cardiovascular and cerebrovascular disease[42]). Studies have failed to illustrate consistent associations of these factors with the development of age-related hearing loss in contrast to those considered non-modifiable factors such as increasing age, male gender and possible genetic predisposition. It is likely that these and other factors have complex interactions with each other and age-related hearing loss, but more work is needed to determine the associations between these factors.

DIAGNOSIS AND MANAGEMENT

HISTORY

Typically, the patient will describe a slow and insidious hearing problem. Often, the first symptom is difficulty in hearing conversation, particularly in the presence of background or competing sound. Normally, the description involves a lack of clarity rather than a loss of volume. The symptoms have often been present for many years and are frequently more of a problem to the rest of the family. Sometimes, tinnitus may be the presenting feature. These symptoms are, of course, no different from any other sensorineural hearing loss. As the hearing loss progresses, so the nature of the complaint may change. Patients may complain of a more obvious hearing problem and frequently having to ask others to repeat themselves. The television is often louder than is comfortable for other members of the household. These problems can all lead to significant domestic distress.

As the hearing loss worsens, a complaint of deafness becomes more apparent and recruitment may be described.[62] Recruitment is the abnormal growth in the perception of loudness by an individual with a hearing loss[63] and is exemplified by the line: ‘Speak up! No, don’t shout, I’m not deaf!’

Tinnitus is a frequent accompanying symptom (30–50%) and not uncommonly may be the most troublesome.[64] There is a strong and well-demonstrated correlation between worsening hearing thresholds and the presence of tinnitus.[65] The prevalence of troublesome tinnitus rises from 5% in the under-thirties to 16% in the over-sixties.[66]

Even if not particularly severe, the hearing loss may lead to social isolation, and depression may ensue.[19] This should be specifically asked for, especially in the elderly who often have less opportunity for social contact.[67] A positive family history of hearing loss in old age may often be encountered.

The frequency of falls increases with worsening hearing thresholds in old age.[16, 18] This can compound problems with social isolation and reduced overall mobility, and should be addressed with involvement of relevant allied

healthcare professionals and specialists as required. Given this relationship, recurrent falls in an individual may prompt earlier screening and enquiry into hearing loss.[22]

When making the diagnosis, it is important to be aware of other significant causes of sensorineural hearing loss.[68] Significant head injury, meningitis, serious systemic illness, often involving previous aminoglycoside treatment, and a strong family history of early hearing loss (indicating a non-syndromic hereditary/genetic degenerative hearing loss) should all be enquired for.

EXAMINATION

The patient will be older, normally at least in their fifties, to display some of the early symptoms. Typically, otological examination will be normal. However, evidence of either active or quiescent otitis media does not preclude the diagnosis. Age-related hearing loss occurs in all individuals to varying degrees and so appropriate allowance for coexistent pathologies will need to be made.

Investigations

Unfortunately, there is no specific test for age-related hearing loss. The first and often only investigation required is a pure-tone audiogram. Various audiometric patterns have been described and classified but the relevance of these is still debatable. Some argue that they indicate damage to different parts of the cochlea or auditory nerve. Most commonly, though, the audiogram shows a hearing loss which tends to be worse at the higher frequencies. Often in the early stages of the condition, the only finding will be a mild high-frequency hearing loss. As the condition advances there tends to be progressive loss of the middle (1 and 2 kHz) and even low (250 and 500 Hz) frequencies.[9]

If sufficient asymmetry exists, a magnetic resonance scan may be required to exclude an acoustic neuroma. No definite evidence exists on this issue but a difference of more than 10 dB averaged over the frequencies 0.5, 1, 2 and 4 kHz or 20 dB or more at any single frequency would be reasonably pragmatic indications. Scanning in the presence of unilateral tinnitus has been suggested. The presence of any associated middle-ear pathology will require further investigation on its own merits, as the diagnosis of age-related hearing loss in this group of individuals is only possible once all other reasonable causes of hearing asymmetry are excluded.

DIAGNOSIS

In an individual over the age of 60, with normal examination findings and a symmetrical (often predominantly high-tone) hearing loss, a diagnosis of age-related hearing loss is fairly secure. Diagnostic difficulties may arise if the patient is younger than expected or the condition seems to be progressing more quickly than expected. Here, there is often an overlap with the increasingly recognized and described, heterogeneous group of genetically determined, progressive, degenerative hearing losses. More often in this group there will be a family history of early age-related hearing loss. Whether this actually matters in terms of management of these patients remains a moot point.

MANAGEMENT

The management and rehabilitation of age-associated hearing loss (AAHL) can be directed to three broad areas: psychological and practical (both non-specific) and sensory (specific).

Non-specific management

Unfortunately, there is no way to return hearing thresholds to their pre-elevation levels of acuity. It is beneficial to give advice regarding the optimization of an individual's acoustic environment. This involves the reduction of background noise (as far as possible), face-to-face conversation to maximize exposure to non-verbal communication cues and an explanation of the problem, to allow the legitimization of their hearing loss.

Involvement of allied health professionals and general practitioners can offer psychological counselling and support in cases of severe hearing loss, especially in the presence of other comorbidities. This will help the patient to acknowledge their problem, which is often one of the first steps on the road to rehabilitation.

Practical measures for individuals with a more severe hearing loss include wireless headphones for use with their television, volume-controllable telephones and louder doorbells, often with an alternative alerting system such as a flashing light or vibrating pager system. Hearing dogs can take on such a role as well as providing a valuable source of companionship in the elderly. Lip-reading classes can be extremely valuable. As the hearing loss becomes more severe, a hearing aid or cochlear implant can take on an increasingly beneficial role.

Specific management

Systematic review has demonstrated that hearing aids are of benefit, even in cases of mild or moderate hearing loss,[69] and the benefits include improved health-related quality of life as well as listening abilities.

Binaural hearing has been shown[70, 71] to produce an approximate additional 10 dB signal to noise ratio advantage. Not surprisingly, then, a recent National Institute for Health and Clinical Excellence (NICE) report has suggested that there is significant benefit to patients in being fitted with binaural hearing aids.[72] The evidence suggests that digital aids are a substantial improvement upon the now obsolete analogue devices,[73] and there is very good evidence of the importance of follow-up and rehabilitative support after fitting to ensure maximum benefit and hearing aid use. Furthermore, success with hearing aid use in older adults has been shown to be greater in those where use is supported by their family members and in those with a positive attitude towards the technology.[74] Tinnitus should also be managed as part of the overall care package. Modern neurophysiological methods, such as tinnitus retraining therapy, utilize a combination of cognitive, directive counselling and sound therapy, including

hearing aids and/or white-noise generators, and success rates are reported in the region of 60–70%.[75] Anecdotal[76] evidence suggests open-fit hearing aids are particularly effective in this situation, and the reduction in the occlusion effect encourages usage and compliance for all indications.

The presence of comorbidities that affect cognition (dementia, for example), can significantly impact on an individual's ability and readiness to adapt to the use of hearing aids.[22, 77] In these situations, cooperation is required from caregivers and family members to support ear and hearing aid hygiene and assist with insertion of hearing aids. Early recognition of the need and thus early administration of hearing aids is likely to improve the time which is required for the individual to recognize speech and grasp the benefits of hearing aid technology.[77] This may reduce development of the psychosocial comorbidities that can occur with hearing loss.[22] And finally, whether cause or effect, there is a lower prevalence of depression and dementia symptoms in hearing aid users when compared with a similar elderly group of non-aided persons[78] with researchers increasingly undertaking trials of hearing treatment and support to reduce cognitive decline.[79]

BEST CLINICAL PRACTICE

- ✓ Make a thorough assessment of the patient to establish the level of hearing loss and consequent disability.
- ✓ Early recognition of hearing loss in the elderly may help to prevent the development of several psychosocial comorbidities.
- ✓ Treatment should include binaural digital hearing aids and appropriate audiological rehabilitative support, which may comprise assistive devices and lip-reading classes as well as advice and guidance regarding hearing aid usage.

FUTURE RESEARCH

- ➤ It is naive to believe that one can stave off the effects of ageing forever. However, progress in unravelling the genetics of ageing, and age-related hearing loss in particular, means that with advances in gene therapy we may be able to delay its arrival.
- ➤ Introduction of genes that programme for hair cell longevity or at least avoid early hair cell death, may be possible.[80]
- ➤ An increased understanding of cochlear physiology and molecular biology means that drug therapy may be able to slow the progress of symptoms. An example might be drugs or chemicals that could stimulate a genetic cascade for hair cell regeneration.
- ➤ Finally, where the hearing loss is unavoidable, continuing advances in electronics will hopefully allow better performance from hearing aids. In particular, the perennial thorn of signal detection in background noise might be ameliorated, perhaps by 'smart' programming.

KEY POINTS

- Age-related hearing loss is almost invariably inevitable.
- It occurs from the sixth decade onwards.
- It is usually symmetrical.
- The effects extend far beyond simple hearing loss.

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CHAPTER 57

NOISE-INDUCED HEARING LOSS AND RELATED CONDITIONS

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: noise-induced hearing loss, diagnosis and management including prevention. Unfortunately, this produced a high yield but of relatively poor quality or narrow focus, thus most of the references have been hand-sourced from our personal collections on this subject. Also used are the references from the course 'Medicolegal aspects of noise-induced hearing loss' now run at the University of Southampton, and other references found during the course of our ongoing clinical and medicolegal practices.

DEFINITION

The term noise-induced hearing loss (NIHL) refers to a reduction in auditory acuity as a consequence of excessive noise exposure. This situation may be temporary and is described as temporary threshold shift (TTS) (although a strict definition regarding duration is not available), or permanent and described as permanent threshold shift (PTS). PTS may occur following repeated noise exposures, or following a single episode; the term 'acoustic trauma' has been used to describe the situation where a single exposure to an intense sound leads to an immediate hearing loss.[1, 2] The use of these terms does not carry any implication about the nature of the noise exposure (occupational or leisure) or about the noise itself (intensity, frequency, duration).

This chapter will also cover the other common adverse consequences of excessive noise exposure, which include tinnitus, hyperacusis (see also Chapter 61, Tinnitus and hyperacusis) and the relatively new condition of 'acoustic shock'.

AETIOLOGY

By its very definition NIHL is caused by exposure to noise. The sources of such noise are common and various, recreational or occupational. Many examples can be given, but of particular concern in younger people is the use of personal music devices, and regular attendances at clubs and concerts. Gunfire exposure, motor-racing and power tools for DIY are all potential culprits for an older age group.[3]

However, worldwide, occupational noise exposure represents one of the most prevalent, potentially preventable, sources of health impairment. Recent reports suggest that, outside Europe and North America, up to 25% of adult males of working age have evidence of occupational NIHL. This seems to be a particular problem in those countries moving from agriculture to a stronger manufacturing base for their developing economies.[4]

Like all biological insults, the effects on any individual from exposure to excessive noise levels are extremely variable and relatively unpredictable, especially at moderate exposure levels.[5] However, there is no doubt that, with increasing exposure to excessive noise levels, noise damage becomes inevitable. It is generally agreed that, for the human ear, sound levels below 80 dB(A) are unlikely to cause hearing damage, no matter how long one is exposed to them. Sounds of 130 dB(A) or greater will cause hearing damage after even short time periods in almost all exposed individuals. Between these two extremes the 'safe' period of exposure decreases as the sound level increases. In this

regard, noise can be thought of as a toxin, which exhibits its toxic effects in proportion to the total 'dose'. To try to quantify this relationship, the concept of the 'noise imission level' (NIL) was developed by Burns and Robinson.[6]

It is given by the equation:

$$NIL = Lepd + 10\log_{10}T$$

where Lepd is the daily noise exposure in dB(A) and T is the time of exposure in years.

So, as an example, a 20-year career with exposure to 85 dB(A) would produce an NIL of 85 + 13 = 98.

They also described the 'equal energy principle'. In essence, this states that if exposure to 85 dB(A) is safe for an 8-hour working day, then a doubling of sound intensity to 88 dB(A) effectively doubles the 'dose', and so is safe for only half that time, i.e. 4 hours. This principle may well hold for continuous noise exposure but is less certain for the more common situation of intermittent exposure.

PATHOPHYSIOLOGY

Although the tympanic membrane and ossicles may be damaged or disrupted in very high-impulse noise, such as an explosion, it is generally the cochlea that is the predominant site for the pathological manifestations of noise damage.

Pathological change associated with NIHL is the source of considerable scientific enquiry and some controversy, and hypotheses regarding mechanisms abound.[7] To this end, there has been great sacrifice by a variety of animals, in particular the cat, guinea pig and chinchilla! The majority of studies consider cochlear function, particularly metabolic and structural changes.[8] Recovery from TTS is thought to imply a role for metabolic mechanisms, and the persistence of PTS, for structural change mechanisms; there is also some experimental evidence in this regard.[9]

Metabolic mechanisms

Acoustic overstimulation could potentially lead to the excessive release of neurotransmitters associated with the transduction function of the cochlea. The possibility that excessive glutamate release may contribute to NIHL has been proposed, based in part upon experimental evidence that the administration of glutamate receptor antagonists may reduce TTS.[10, 11]

There is substantial experimental evidence from animal studies for change in cochlear blood flow associated with acoustic stimulation.[8, 12] Specifically, there are indications that stimulation with sound of moderate intensity increases cochlear blood flow, and with sound of high intensity decreases cochlear blood flow (this being a potential mechanism for cochlear dysfunction associated with noise exposure).[8] The mechanisms of these phenomena are unclear but may reflect metabolic demand. It should also be noted that there is some evidence that NIHL and cochlear hypoxia precede changes in cochlear blood flow.[13]

Other metabolic cochlear mechanisms that are the focus of experimental investigation include outer hair cell (OHC) plasma membrane fluidity, the role of glucocorticoid receptors and oxidative stress.[14–17] Such mechanisms are not mutually exclusive, and there is a consensus that NIHL is a multifactorial and complex situation.

Structural mechanisms

Changes to the micromechanical structures within the cochlea have been reported as possible mechanisms of NIHL. The suggestion has been made that depolymerization of actin filaments in stereocilia may be a substrate of TTS. Additionally, changes to non-sensory elements of the cochlea, such as swelling of the stria vascularis, afferent nerve endings and supporting cells, have been noted.[18]

Apoptosis and necrosis

There is evidence that both apoptosis (programmed cell death) and necrosis play a role in NIHL[9, 19, 20] and OHC are particularly vulnerable in this regard.[21] The progression of OHC death well after the cessation of noise has implicated apoptotic mechanisms.[22] Apoptotic changes in chinchilla OHC (specifically nuclear condensation and cell body shrinkage) have been detected 5 minutes after exposure to impulse noise, whereas necrotic change (nuclear swelling) appeared 30 minutes following exposure.[20] A present focus for research is the role of caspases (a family of cysteine-dependent aspartate-specific proteases) in cochlear hair cell apoptosis.[23]

The evidence above regarding metabolic and structural change in the organ of Corti following noise exposure is indicative of necrotic mechanisms being involved. It has been demonstrated, however, that the relationship between NIHL and hair cell dysfunction is complex. Specifically, it appears that in the rat, high-frequency hair cells die rapidly after noise injury, but that low-frequency hair cells may survive but without auditory function. This finding may account for the common observation that the relationship between hearing thresholds and hair cell damage is not direct.[24]

Synaptopathy

The adverse effects of excessive noise are not limited to the cochlear hair cells. There is a growing body of evidence that the synaptic connections between the inner hair cells (IHCs) and spiral ganglion cells may be especially vulnerable to noise insults (and indeed to ageing), and that this may occur even when the hair cells themselves remain intact.[21, 25] This latter scenario has been given the name 'hidden hearing loss', as audiometric thresholds would be unchanged, but those affected demonstrate difficulties with hearing in background noise.

Predisposing factors

A potential genetic basis for susceptibility to NIHL has been considered but, while this is well established in

animals, in humans it remains elusive.[26] Experimental evidence gleaned from studies with mice has implicated the *Ahl* gene[27, 28] and there are several strains of knockout mice (both homo- and heterozygous) that are more susceptible to NIHL than their littermates that are wild-type.[26]

A clinical interaction between NIHL and age-related hearing loss has been reported and supported by further data.[29–31] The suggestion is that, as individuals with NIHL age, the effect of ageing upon thresholds affected by NIHL is slowed but for adjacent frequencies is accelerated. Mechanisms underlying this observation are presently unclear. The observation that populations in minimally industrialized areas of the world (specifically the Sudanese desert) experience not only no NIHL but also no age-related deterioration of hearing is of interest, but this needs corroborating, and with some urgency while such populations exist.[21, 32]

Other factors demonstrated to have an association with susceptibility to NIHL in humans include smoking and certain disease states such as diabetes and cardiovascular disease.[33–36] Hood et al. noted a greater extent of TTS in individuals with blue eye colour, and an association with PTS has also been demonstrated.[37–39]

A further suggestion has been that recreational drug use causes greater risk of NIHL and tinnitus although it should be recognized that intoxicated individuals may take more risks with intense sound.[40] The combination of exposure to ototoxic agents and noise has been shown to be synergistic in animal models and the potential existence of a common pathway for cochlear ototoxicity and NIHL has been suggested.[41–43] A similar situation has been proposed in humans with regard to industrial solvents, and this warrants investigation.[44, 45] Henderson et al. noted that the individual variability in human susceptibility to NIHL was so great that the situation is complex, and much further research, both animal and human, is needed to substantiate fully the effect of other factors on it.[43]

DIAGNOSIS

Unfortunately, there is no specific test available to make the diagnosis of NIHL. Furthermore, there are two different settings in which a clinician may be required to make such a diagnosis: in the clinical setting and in a medicolegal context. Although the degree of accuracy required is quite different, it is surprising how often the course through the former (which often comes first) can influence the course in the latter. It is therefore most important that as accurate a diagnostic process as possible is pursued in the clinical setting in order to avoid later inconsistencies and reversals in the medicolegal process. At the very least, an acknowledgement of the areas of uncertainty is required.[46]

Of some help, though, in the latter setting is the requirement to make the diagnosis 'on the balance of probabilities' – or simply more likely than not!

There are additional problems with which the clinician must grapple when diagnosing NIHL. There is the enormous biological variability and individual susceptibility to the effects of noise, as well as the insidious nature of the progress of NIHL. In practical terms, this means that, often, by the time an individual presents with symptoms, the noise exposure will have ceased and, in all likelihood, there will be a contribution from the ubiquitous age-related degenerative process.[47, 48]

Historically, the diagnosis of NIHL has been fairly straightforward. Typically, an individual would present with a hearing loss, confirmed by audiometry, and a career of exposure to, relatively undisputed, excessive noise. The diagnostic process would include separating the effects of ageing from the effects of noise. This process would be accomplished by reference to one or more of the many standardized reference tables detailing hearing thresholds with age for typical screened and unscreened populations (e.g. the NPL tables, among others).[49–52] Removal of an 'average' value for age-related hearing loss leaves an assumed NIHL.

The choice of appropriate control group here is obviously important. Comparison of the subject with a highly screened control group, and their better hearing thresholds, may suggest a significant hearing loss due to noise, while a less highly screened control group (with poorer thresholds) may suggest near-normal hearing for an individual of that age.

Much has changed in recent years: heavy manufacturing industry has almost completely disappeared from the UK, and machinery performance and design have improved, as have hearing protection programmes. This has all led to a workforce that enjoys far less in the way of very high levels of excessive noise exposure. Consequently, there have been far fewer claims based on just a hearing loss; more often now claims will also focus on the often-associated symptoms of tinnitus and hyperacusis.

Furthermore, new industries and processes have arisen such as call centres and covert surveillance. These have brought novel and unique problems and patterns of exposure, culminating in a new condition: 'acoustic shock'.[53–55]

Finally, there have been the problems, alluded to earlier, of recreational noise exposure in a younger population, and an increasing recognition of early degenerative hearing processes and other adventitious hearing losses.[56] This latter point has led to a renewal of the debate regarding the most appropriate control group for comparison.[57] The screening of the control group effectively removes all other otological pathology, such as ear disease, head injuries, positive family history of hearing loss, alternative noise exposure and so on. The net result is a group with better hearing thresholds than a so-called 'typical population' group where far less screening has taken place. This distinction is exemplified by databases A and B for the corresponding groups in ISO 1999.[46, 51]

For practical purposes it is probably best to start from a diagnostic assumption that, in a possible case of NIHL, the individual will have a hearing loss composed of three parts: an age-related component, a noise-induced component and, finally, a third, idiopathic degenerative component. The clinician's task is to separate and calculate the relative contribution (if any) from the three sources.

In the end the diagnosis is based on a combination of the clinical picture that emerges from the patient or claimant and the audiometric findings and, in a large part, is influenced by the experience of the examining clinician.

History

The patient or claimant is far more likely to be male than female, usually in middle age, but sometimes older. They may be younger, especially if the complaint is more about tinnitus (with or without hyperacusis) than deafness. Women more frequently present with acoustic shock.

Inevitably, there will be a history of hearing difficulties. Typically, in the early stages, especially as the OHC are first affected by noise damage, a history of hearing difficulties in the presence of background noise is encountered. Normally, the description involves a lack of clarity rather than a loss of volume. Difficulty with the television being louder than is comfortable for the rest of the family is frequently reported. Telephone conversations may become more difficult. The symptoms will often have been slowly progressing for many years.

Tinnitus is a common accompanying symptom of NIHL and often occurs early in the course of the condition. In fact, post-exposure tinnitus is a useful symptom when making the diagnosis, especially if reported unsolicited. The main effects of tinnitus tend to be on sleep, mood and concentration. Impact in these areas should be detailed and any medical attendance for it noted. This will help in grading its severity.[58]

Hyperacusis is found in 40% of tinnitus sufferers and is becoming an increasingly volunteered accompanying symptom in NIHL. Its presence should be recorded. The instrument to determine severity that is in most common use worldwide is the Hyperacusis Questionnaire, though some issues with the factor structure have been identified.[59, 60]

As the hearing loss progresses, so the nature of the complaint may change. Patients may complain of a more obvious hearing problem and frequently having to ask others to repeat themselves. With further progression, a clear complaint of hearing loss occurs.

NIHL is found far more often in men and produces particular difficulties in social functioning. There is often a history of social withdrawal although this will rarely be volunteered. There is often increasing reliance on the spouse for social and family interaction and this can lead to marital stress. There may be embarrassment, loss of confidence, anxiety and frank depression.[61]

It is important to be aware of other significant causes of sensorineural hearing loss when making the diagnosis. Significant head injury, meningitis, serious systemic illness, often involving previous aminoglycoside treatment, and a strong family history of early hearing loss (indicating a non-syndromic hereditary/genetic degenerative hearing loss) should all be enquired for.

It is axiomatic that, for a diagnosis of NIHL to be made, there must be a history of noise exposure. In the clinical setting it is important to establish that there has been sufficient noise exposure to cause NIHL. In the medicolegal setting it is essential to be thorough about this. It is important to detail all the potential sources of noise exposure and assess typical noise levels and duration of exposure.[62] If one is not familiar with the suspect machinery or device, get the claimant to describe and explain it. A useful yardstick of background noise levels is the ability to hold some type of conversation in its environment (Table 57.1).

For gunfire noise exposure, the type of weapons used and number of rounds fired are important questions; heavy artillery is particularly damaging. Provision and type of hearing protection should be known, although this by no means guarantees protection.[63] Post-exposure tinnitus is a useful surrogate for the presence of a TTS.[64]

If the total noise exposure has come from a variety of sources, it is important to document the contribution from each carefully and thoroughly (including recreational exposure).

The problem of acoustic shock is very different and is thought to be more of an acute stress reaction. It is found typically in call-centre workers who are under some pressure to process high volumes of calls in a defined time period. The sound comes through their headsets and may be the result of a technical malfunction, or a malicious act by the individual on the other end of the phone line. The sound is unexpected and is perceived as both loud and unpleasant by the affected individual, although when measured it may be less than classically damaging sound levels of 85 dB(A) or above. Objective hearing loss is rarely a feature but multiple symptoms and high levels of psychological distress are often described. Common symptoms are summarized in Table 57.2. Theories exist that the problem represents a combination of an excessive 'startle' response, and/or a form of post-traumatic stress disorder.[54] In addition, there is a view that myoclonic activity of the tensor tympani muscle is involved.[50] The degree of psychological distress is often enough to

TABLE 57.1 Typical background noise levels based on communication ability

	Distance from speaker to listener		
Voice level	**4ft**	**2ft**	**At ear**
Loud voice	93 dB(A)		
Shout	99 dB(A)	105 dB(A)	
Impossible to hear			Over 110 dB(A)

TABLE 57.2 Common otological symptoms of acoustic shock (derived from Westcott[55])

Symptom	Occurrence (%)
Hyperacusis	84
Otalgia	81
Tinnitus	50
Imbalance	48
Hearing loss	18

force the individual to leave the job where the exposure occurred.

Examination

Typically, otological examination will be normal. However, evidence of either active or quiescent otitis media does not preclude the diagnosis. Age-related hearing loss happens in all individuals in varying degrees and so appropriate allowance for this and any other coexistent pathologies will need to be made.

Investigations

The cornerstone of investigation is a pure-tone audiogram, with both air and bone conduction to identify any conductive hearing loss. The usual clinical frequencies should be tested as well as 3 kHz and 6 kHz. The classical audiometric pattern is of a high-tone hearing loss with a notched appearance centred on 4 kHz or 6 kHz, with some recovery at 8 kHz. However, the classic notch is often absent or not obvious, particularly in the presence of significant age-associated hearing loss or other causes of hearing loss. Furthermore, the presence of a significant notch at 4 kHz on its own is not evidence of NIHL. There are numerous case reports and population surveys of 4 kHz notches in individuals with no history of noise exposure.[65–67]

Significant audiometric loss at frequencies below 2 kHz is extremely uncommon in NIHL. If present, it should raise suspicion of some other pathological process affecting the cochlea.

Some authors have suggested an analytical approach to the shape of the audiogram as an aid to predicting the likelihood of NIHL.[48, 68] This analysis merely helps to increase the confidence in making a diagnosis of NIHL. Lutman et al. have more recently produced a follow-up paper to their original guidelines which attempts to provide quantification of the noise-induced component of any high-tone hearing loss.[69]

Since 2007, and the judgement in a group action by textile workers in Nottinghamshire,[70] there has been a much greater reliance on the Coles, Lutman and Buffin (CLB) guidelines;[48] in fact, many solicitors will not proceed with a claimant's case if their audiogram does not meet the relevant criteria. This is helpful and does provide a degree of certainty and clarity, but a lack of conformity does not exclude the diagnosis. Nor does it help in cases where non-hearing loss symptoms dominate.

Tympanometry is helpful to confirm normal middle ear functioning. A conductive hearing loss is not due to noise exposure and can even provide some protection to the cochlea by virtue of the sound attenuation.

In those individuals in whom a significant non-organic component (feigned thresholds) is suspected, cortically evoked response audiometry, or otoacoustic emissions (OAE), may be required to provide a more objective measure of hearing thresholds.

In cases with significant asymmetry, a magnetic resonance imaging (MRI) scan may be required to exclude an acoustic neuroma. Significant asymmetry is unusual in NIHL but can be found in certain military personnel due to the 'shadow effect' from the head with shoulder-borne weapons. More than 10 dB at the same frequency is uncommon and will indicate the need for MRI scanning.[71]

Tinnitus pitch and intensity matching are often performed. Although they may help to describe the tinnitus, there is little evidence that they have a role in the assessment of tinnitus severity.[72]

Loudness discomfort levels are a useful measure of the presence of hyperacusis. They can also be used to monitor the effects of treatment.

There is some evidence of changes in OAEs and decreased, contralateral, OAE suppression with early noise damage, although these findings are still a long way from regular and reliable clinical application.[73–75] They may yet help in the diagnosis of noise-induced tinnitus without measurable hearing loss.[76]

At the present time there is no practical means of determining the extent of synaptopathy in an individual exposed to noise and research in this regard is underway internationally.[21]

Diagnosis and report writing

Diagnosis is simple in an individual with a clear and prolonged history of unprotected exposure to excessive noise, no evidence of any other otological pathology and an audiogram showing good preservation of mid and low frequencies but a significant high-tone hearing loss with classical notching at 4–6 kHz.

However, in practice, such a case is relatively rare. Most commonly, one is faced with an older patient who has developed symptoms as a result of the combined effects of ageing and NIHL. There will be a history of excessive noise but in many cases this will not be overwhelmingly impressive or, alternatively, hearing protection may have been provided. The audiogram will show a sensorineural hearing loss, often with loss of the middle frequencies too. In this situation it is necessary to tease out the effects of ageing, balance the remaining hearing loss against the described noise exposure and try to make a judgement based on one's experience of NIHL as to whether all of this remaining loss can be attributed to the noise. If not, a third idiopathic, degenerative process has to be invoked to explain the discrepancy.[48, 55, 69]

Help for this task comes from both the 'Black Book' and the NPL tables. The NPL tables are particularly useful as they describe average noise imission levels (NILs) for various hearing losses. Where there is a significant discrepancy between the required NIL for a hearing loss and the noise exposure supposedly responsible, the presence of an additional degenerative process becomes more likely.[77] The 'Black Book' provides disability values for various hearing losses and for typical age-related changes.[62]

A medical report requires all of these points to be addressed. A value should be attached to the noise-induced portion, and any other components, of the total hearing loss. In addition, the writer should make some effort to

calculate the relative contribution to the NIHL from each noise source, if there is more than one.

Tinnitus, if present, should be graded for severity and, again, the various contributions to its aetiology should be apportioned. Guidance for severity grading has been published.[60] By and large, the courts tend to accept the premise that the cause of any tinnitus (and hyperacusis) is the same as the cause of any coexisting hearing loss, and in the same relative proportions if there are multiple contributions, such as age and noise, among others. Tinnitus following noise exposure without apparent hearing loss is a little more controversial.[78] Obviously, this does not apply if the onset of tinnitus followed closely from a specific incident, such as an episode of acute acoustic trauma, a head injury or following a known ototoxic medication. In these cases the specific incident in question is more likely, on the balance of probabilities, to have been the cause.

The report should also include a section on prognosis in respect to both hearing loss and tinnitus. In particular, comment should be made regarding the need (either current or predicted) for any hearing aids or rehabilitative treatment, and, if possible, some indication of their costs.

With the relatively recent changes in the civil justice system leading to the production of the Civil Procedure Rules in 1999, it is important that an expert does not comment outside his field of expertise and, where there is a range of opinion on a point or subject, it is acknowledged and commented upon.[79]

MANAGEMENT, INCLUDING MEDICOLEGAL

Prevention

From a clinical perspective, once a diagnosis is made, further noise exposure should be reduced as far as possible. This may be by avoiding the excessive noise altogether or, if this is not possible, by the use of ear protection in the form of earplugs or earmuffs. Changes to working practices might also be suggested. In the occupational setting, legislation exists to enforce this.

Employers have a statutory duty under the Health and Safety Act 1974 to minimize risks to employees, including risks from excessive noise exposure.[80] The 1989 Noise at Work Regulations described two action levels for daily, personal noise exposure: a first action level at 85 dB(A) and a second at 90 dB(A). In addition, there was a peak action level of 140 dB.[81, 82] These were replaced in 2006 by the European Control of Noise at Work Regulations 2005, where each action level is 5 dB lower, respectively.[83, 84]

In summary, at the first action level, an employer should conduct a noise survey, embark on a programme of employee education and provide appropriate hearing protection. The use of this hearing protection is at the discretion of the employee until the second or peak action level is reached, when it becomes compulsory. The employer is required to identify those areas where hearing protection use is required. Regular hearing tests should be offered to employees where and when a potential risk is recognized.

The main thrust of the regulations, though, is to reduce noise exposure 'as far as reasonably practicable' by reduction of noise at source (or time of exposure), with hearing protection very much the last solution. This reduction may be by means of engineering (quieter machines) or acoustic (sound-isolating) solutions.

PERSONAL HEARING PROTECTION

There is evidence that the use of hearing protection reduces the risk of NIHL from noise in both recreational and occupational contexts.[83, 84] As regards hearing protection, the choice is between earplugs, earmuffs and active noise reduction. The choice will often depend on the performance of the protector and the environment in which it will be used. Earplugs may be personally moulded or 'off the shelf', and are made from silicone rubber, acrylics or closed cell foam. They are relatively cheap and particularly useful when other protective devices (e.g. helmets or goggles) must also be worn. The best earplug can perform as well as the best earmuff in terms of sound attenuation but they are harder to fit correctly.[85] It is well established that the real-world performance of ear protectors is significantly poorer than the laboratory scores, largely as a result of inadequate or incorrect fitting. Therefore, earmuffs are generally a more reliable form of ear protector. In a real-world setting, earplugs can be assumed to give approximately 10–15 dB of sound attenuation and earmuffs at least 15 dB.[86]

Active noise reduction is an electronic method of sound attenuation. It uses electronics to provide sound, inside a set of earmuffs that is 180 degrees out of phase with the ambient sound. This effectively cancels out the background noise. This is a very effective form of sound attenuation, particularly for lower frequencies (around 1000 Hz), but the electronics required are expensive. Its most frequent use is in military and aircraft settings where additional communication devices are required and it can be incorporated into the headset.[87]

Unfortunately, given the known variation in susceptibility to noise damage, adherence to all the regulations does not guarantee protection for all employees.

Non-specific management

Unfortunately, there is no way to replace the hearing that has been lost. In those individuals with a mild high-tone hearing loss, hearing aids may provide benefit, but this can be meagre.[88] The best that can be done in this situation is to give advice regarding the optimization of their acoustic environment. This involves the reduction of background noise (as far as possible), face-to-face conversation to maximize exposure to non-verbal communication cues and an explanation of the problem, to allow the legitimization of their hearing loss.

In more severe hearing loss, directed rehabilitation programmes including psychological counselling, can help the patient to understand and acknowledge their problem. This acceptance is one of the first and, most crucial, steps on the road to successful rehabilitation. Inclusion of, and support for, the individual's partner should also be provided as part of such a programme.[89]

Practical measures for individuals with a more severe hearing loss include infrared headphones for use with television, volume-controllable telephones and louder doorbells, often with an alternative alerting system such as a flashing light or vibrating pager system. Lip-reading classes can be extremely valuable.

Specific management

As the hearing loss becomes more severe, a hearing aid takes on an increasingly beneficial role. There is solid evidence of a significant benefit to the patient in being fitted with binaural digital hearing aids.[88] There is also good evidence of the importance of follow-up and rehabilitative support after fitting to ensure maximum benefit and hearing aid use.[90]

Tinnitus should be managed as part of the overall care package. Modern neurophysiological methods (such as tinnitus retraining therapy) utilize a combination of cognitive, directive counselling and sound therapy (including hearing aids and/or white-noise generators) and report useful success rates in the region of 60–70% in terms of improvement in the perception of tinnitus and its severity.[91] Hyperacusis responds well to similar treatment methods.

Acoustic shock really requires psychological treatment as much as anything else. Many sufferers are unable to continue that occupation. Tinnitus is a frequent symptom and standard tinnitus treatment strategies do seem helpful for this and a number of the other auditory symptoms.

Pursuing a claim

In the clinical setting, once a diagnosis of NIHL is made, the patient may well ask advice about pursuing a claim for damages. There are two options.

If the individual has worked for 10 years or more in one of the prescribed occupations, they may be entitled to statutory DSS compensation, available since 1974.[92] The hearing loss is calculated on the basis of the average hearing levels at 1 kHz, 2 kHz and 3 kHz.

$$[(4 \times \text{better ear} + 1 \times \text{worst ear}), \text{ divided by } 5]$$

The entry point is 50 dB HL, which equates to a 20% disability. The disability payments are relatively modest. For illustration, in 2016 a 20% disability attracted a payment of £33.60 per week and complete deafness (100% disability) £168. There are many who think this entry point is too high; it equates to an approximate 38% disability in the 'Black Book'.[62] A similar scheme has operated for the military pension scheme since 1987.

The second and more common option is to pursue a civil claim, where the burden of proof is on the claimant. For such a case to succeed, the claimant must demonstrate 'on the balance of probabilities' (i.e. more likely than not) that:

- there has been exposure to excessive noise levels
- the hearing loss has been a consequence of that exposure
- there was a foreseeable risk of injury from the exposure
- the case was brought in time (3 years from the time of awareness).

The claimant must retain a solicitor to coordinate the case. Such a solicitor can normally be found through the employee's union or work federation, or through the Citizens Advice Bureau.

FUTURE RESEARCH

- While the dangers of hearing loss associated with noise exposure have been known for many years, there remains much to discover about pathological mechanisms of NIHL, genetic susceptibility and the influence of other factors. Animal studies will be of assistance in building the knowledge base, as will human population studies.
- Sound conditioning protects against the adverse effects of future sound exposure.[93] Understanding the physiological and biochemical explanation for this may allow drug therapy to protect against or possibly reverse the effects of excessive noise exposure. Current areas of interest include the intratympanic administration of corticosteroids, and the use of antioxidant medication.[26]
- Explanation and understanding of these phenomena may also be helped by further research based on our knowledge that certain individuals naturally have 'tough' ears when it comes to noise exposure.
- Advances in our understanding of hair cell regeneration may allow treatment to encourage this to take place in the noise-damaged cochlea.

KEY POINTS

- In noise-induced hearing loss (NIHL) cases there are usually three components to the hearing loss: age, noise and an idiopathic component.
- The diagnosis is clinical and requires sufficient noise exposure and the presence of a hearing loss greater than expected from age alone.
- Tinnitus and hyperacusis are frequent accompanying symptoms and nowadays often present without any evidence of a hearing loss or only a modest hearing loss.
- Treatment is essentially preventative and involves personal hearing protection (earplugs or earmuffs) or reduction of noise levels at source.
- This is a diagnosis that frequently enters the legal arena.

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CHAPTER

58

AUTOSOMAL DOMINANT NON-SYNDROMIC SENSORINEURAL HEARING LOSS

Polona Le Quesne Stabej and Maria Bitner-Glindzicz

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SEARCH STRATEGY

The data in this chapter may be updated by a search on NCBI PubMed, OMIM and the Hereditary Hearing Loss website at http://hereditaryhearingloss.org[1] using the keywords: autosomal dominant non-syndromic sensorineural hearing loss, next generation sequencing, hearing loss gene panel and DFNA.

INTRODUCTION

Hearing loss which is the result of damage to the hair cells within the inner ear, the vestibulocochlear nerve or central processing centres of the brain is called sensorineural hearing loss (SNHL). When SNHL occurs without any additional manifestations in at least one other body system, it is called 'non-syndromic' SNHL. This accounts for approximately 70% of all genetic SNHL cases, the other 30% being part of a syndrome in which clinical features form a recognizable association. According to mode of inheritance, non-syndromic SNHL can be autosomal dominant (AD) (15% of non-syndromic SNHL cases), recessive (80%), X-linked or mitochondrial.[2] Deafness is a highly heterogeneous disorder with genes encoding a plethora of different proteins involved in numerous pathways.

CLINICAL FEATURES OF AD NON-SYNDROMIC SNHL

Clinical evaluation of a patient with hearing loss includes involvement of a multidisciplinary team with audiologist, otolaryngologist, clinical geneticist and other specialists where appropriate. When environmental and syndromic causes of hearing loss have been excluded as far as possible, the hearing loss can be considered to be non-syndromic, until proven otherwise. If family history is available, a non-syndromic AD form of SNHL is recognized by the observation that several generations are affected; in a singleton case, probably due to *de novo* mutation, or reduced penetrance, the inheritance pattern is often not apparent.[2] To date, loci for more than 60 genes have been mapped (which means that the detailed chromosomal position has been localized), but only just over half of these genes have been identified.[1] Unlike the situation in which *GJB2* accounts for a significant proportion of cases recessive hearing loss, there is no single major gene accounting for a large proportion of dominantly inherited cases. Therefore genetic heterogeneity, relative clinical homogeneity (see 'History of AD non-syndromic SNHL gene discovery') and the fact that AD non-syndromic SNHL accounts for a minority of all genetic hearing losses means that genetic testing to achieve a molecular diagnosis has proved challenging and expensive until recently.

Clinically, AD SNHL is usually postlingual and progressive in contrast to non-syndromic autosomal recessive SNHL which is usually prelingual and more or less stable.[2, 3] There are some notable exceptions: mutations in some genes may cause prelingual or early childhood-onset hearing impairment such as those in *TECTA* (DFNA8/12) (**Figure 58.1**) and the recently described *CD164,* which may give rise to prelingual moderate to severe hearing loss with a distinctive mid-frequency 'U-shaped' pattern; *SIX1* (DFNA23), which may also cause prelingual high-frequency hearing loss associated with unilateral or bilateral ear pits; and *CRYM*, which may cause a downsloping, progressive hearing loss. Genes which cause onset of hearing loss in the first decade

include *WFS1* (DFNA6/14/38) (Figure 58.2), which can cause low-frequency progressive hearing loss (<2 kHz), *MYO6* (DFNA22), *HOMER2*, *OSBPL2* (DFNA67) (Figure 58.3), which causes a steeply sloping ('ski-slope') mild to profound progressive hearing loss, and *TMC1* (DFNA36), which can cause a high-frequency rapidly progressive hearing loss. However, even within a single family, age of onset of hearing loss, progression and even audiometric configuration can vary between individuals, making distinction between genetic causes difficult.

So, although some non-syndromic AD SNHL loci are associated with particular audiometric patterns or clinical presentations, such as mutations in *COCH*, also giving rise to prominent vestibular symptoms, a sufficiently distinctive, unique audiogram or clinical picture to confidently enable clinical diagnosis is unusual. This has spurred the development of 'AudioGene', an online automated tool which automatically analyzes audiometric data to predict the likely underlying genetic causes of hearing loss. It has been shown to have some success in predicting the gene/locus responsible for deafness based on audiogram,[4] particularly for *KCNQ4* mutations which cause a pattern of mainly high-frequency hearing loss and which has been found to be a relatively common form of dominantly inherited hearing loss.[5,6] Audioprofiles for many other loci have now been compiled and are available for use to try to predict the gene or locus involved based purely on audiometric pattern and progression. The currently known AD genes for SNHL are outlined in Table 58.1, together with age of onset and audiometric description.

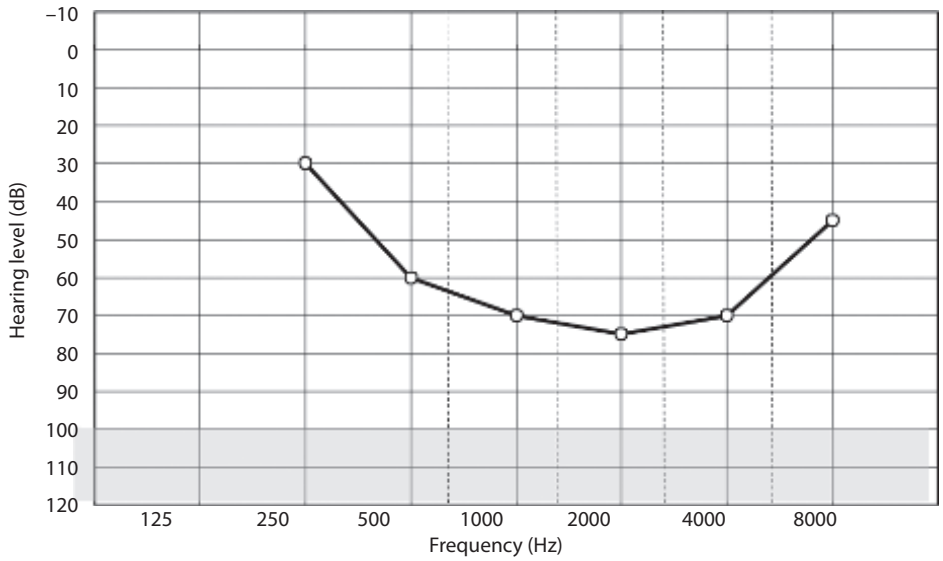


Figure 58.1 'U-shaped' or 'cookie-bite' audiogram typical of hearing loss caused by *TECTA* mutations.

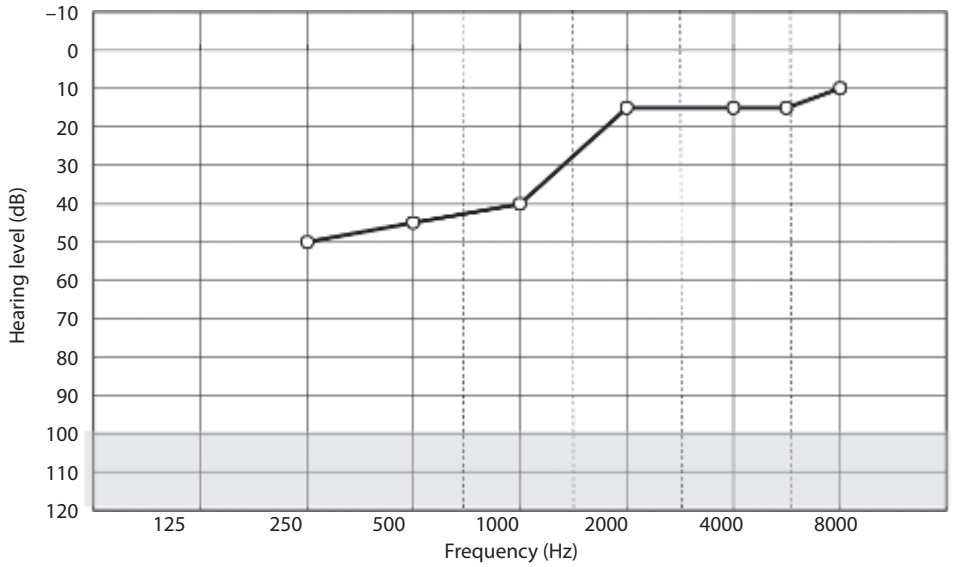


Figure 58.2 Low-frequency hearing loss seen with *WFS1* mutations.

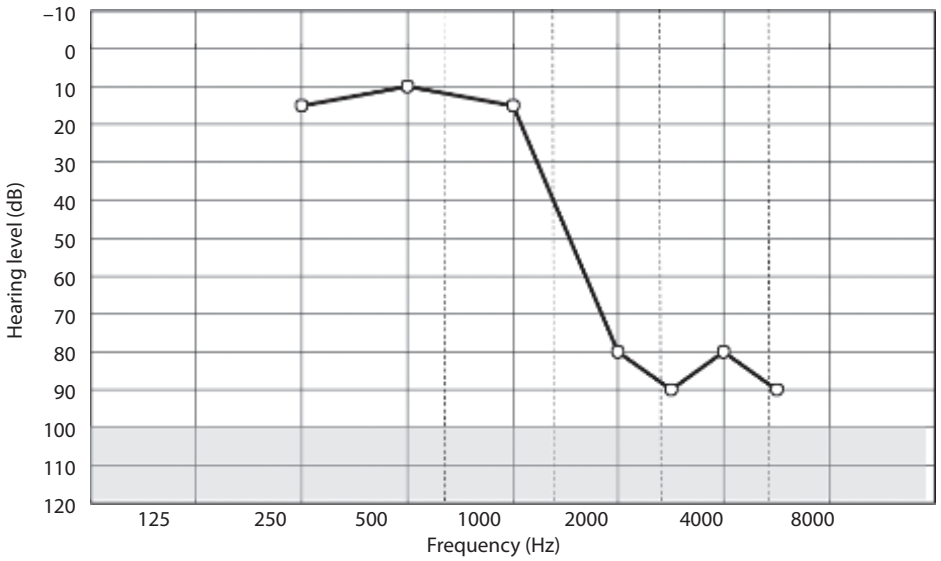


Figure 58.3 Steeply sloping, 'ski-slope' high-frequency hearing loss seen with OSBPL2 mutations.

HISTORY OF AD NON-SYNDROMIC SNHL GENE DISCOVERY

Non-syndromic AD SNHL can be identified by a multigenerational family history and is genetically heterogeneous with no single gene accounting for a high proportion of cases; there are currently 37 genes and 67 loci with yet unidentified genes listed on the Hereditary Hearing Loss website (see **Table 58.1**)[1] This extreme genetic heterogeneity makes genetic diagnosis of AD SNHL very difficult.

Box 58.1 defines the most important terms related to research in this area.

In 1992 the first AD SNHL locus (DFNA1) was mapped to chromosome 5q31 using linkage analysis in large multigenerational Costa Rican kindred. Five years later, in 1997, using laborious positional cloning as the human DNA sequence was not yet available, a splice mutation leading to a 4bp insertion in the mRNA and frameshift causing a truncating variant in *DIAPH1* gene was identified as the cause of AD SNHL in this family.[7, 8] Recently it has been shown that this leads to a constitutive activation of the encoded protein DIA1 by loss of autoinhibition.[9] In the same year, it was shown that an in-frame 9-bp deletion in *MYO7A* and a truncating mutation in *GJB2* were responsible for deafness in two families previously linked to DFNA11 and DFNA3A loci, respectively. Both genes were cloned after linkage analysis pointed to the two genes which were already known to cause autosomal recessive deafness.[10–12] Linkage analysis followed by positional cloning and sequencing of candidate genes further led to identification of *GJB3*, *DFNA5*, *COCH*, *POU4F3*, *TECTA*, *KCNQ4*, *TECTA*, *COL11A2* (see **Table 58.1** for full list).[13–19] Gene identification processes preceding the release of the human genome draft sequence in 2001[20] heavily relied on linkage analysis of large multigenerational families, bacterial artificial chromosome (BAC)-mediated cloning as well as singling out of candidate genes based on previous knowledge of gene function, mouse models or expression studies. In cases where no family members other than the proband were available, making linkage analysis impossible, a candidate gene approach was pursued (see **Box 58.1**). Examples of gene identification using the candidate gene approach are *GJB6*, *CRYM* and *MYH14* genes, which were selected as candidate genes based on expression in the cochlea and vestibule, and data from existing mouse models coupled with the knowledge that genes from the same family have been previously shown to cause deafness. However, due to extreme heterogeneity of SNHL, sequencing of candidate genes in large groups of patients had a low yield, identifying deafness-causing variants in only 1/198 deaf families for *GJB6*, in 2/192 families for *CRYM* and in 4/300 families for *MYH14*.[21–23] While the release of the human genome draft sequence in 2001 made targeted sequencing of candidate genes more straightforward, this approach is heavily biased as it relies on *a priori* knowledge of gene function and is therefore unlikely to reveal a novel deafness-causing gene or a novel pathway.

Since completion of the human genome (accomplished by Sanger sequencing), a demand for faster and cheaper methods led to the development of high-throughput sequencing called next generation sequencing (NGS) or massive parallel sequencing (MPS). On NGS platforms, millions of DNA fragments are sequenced simultaneously, enabling sequencing of the entire genome in a day.[24] This led to the development of the whole exome and genome sequencing techniques which have been successfully implemented in gene identification studies (see **Box 58.1**).[25] Exome sequencing is a robust, unbiased approach in which all protein-coding parts of the genome are amplified, sequenced and analyzed. Loci previously linked to AD deafness in families, containing hundreds of genes, could now be rapidly sequenced. Additionally, small families in whom linkage analysis was not feasible, could now be screened using whole exome sequencing (WES). The technique transformed genetic analysis and was soon applied in AD SNHL studies. Zheng et al. used a combination of linkage analysis and WES (with the analysis

TABLE 58.1 Autosomal dominant genes causing non-syndromic hearing loss (adapted from Hereditary Hearing Loss)[1]

Locus	Gene	Gene function	Onset (years)	Pattern of hearing loss	Reference(s)
DFNA1	*DIAPH*	Profilin ligand and target of Rho that regulates polymerization of actin, the major component of the cytoskeleton of hair cells of the inner ear	Postlingual (10)*	Low-frequency, rapidly progressive	8
DFNA2A	*KCNQ4*	Potassium channel; regulation of electrical signalling and the ionic composition of biological fluids	Postlingual (10–30)	Higher frequencies more affected, progressive	18
DFNA2B	*GJB3***	Gap junction protein, connexin 31; building blocks of GAP junctions; mediate diffusion of ions and metabolites between the cytoplasm of adjacent cells	Postlingual (20–40)	Higher frequencies more affected, progressive (one family described)	14
DFNA3A	*GJB2***	Gap junction protein, connexin 26; building blocks of GAP junctions; mediate diffusion of ions and metabolites between the cytoplasm of adjacent cells	Postlingual (6–20)	Higher frequencies more affected, or flat	12
DFNA3B	*GJB6**	Gap junction protein, connexin 30; building blocks of GAP junctions ; mediate diffusion of ions and metabolites between the cytoplasm of adjacent cells	Prelingual (age not mentioned)	High-frequency, progressive (one family described)	21
DFNA4	*MYH14***	Non-muscle myosin heavy chain IIC; ATP-dependent molecular motor which interacts with cytoskeletal actin	Postlingual (1st or 2nd decade)	Higher frequencies more affected, or flat	23
DFNA4B	*CEACAM16*	Carcinoembryonic antigen-related cell adhesion molecule 16 (CEACAM16) is an adhesion protein	Postlingual (early adolescence)	Higher frequencies more affected, or flat	26
DFNA5	*DFNA5*	*DFNA5* (*ICERE-1*); function unknown; it might be involved in apoptosis	Postlingual (5–50)*	Higher frequencies more affected, progressive	13
DFNA6/ 14/38	*WFS1*	Wolframin; transmembrane protein	Prelingual (5–15)	Low-frequency, gradually progressive	37, 38
DFNA8/12	*TECTA*	Alpha tectorin; structural component of tectorial membrane	Prelingual	Mid-frequency or high-frequency	17
DFNA9	*COCH*	Cochlin; extracellular matrix protein	Postlingual (16–52)	Higher frequencies more affected, gradually progressive	15
DFNA10	*EYA4*	Eye absent 4; transcriptional activator that interacts with members of other protein families to regulate early developmental event	Postlingual (20–60)	Flat, gradually progressive	39, 40
DFNA11	*MYO7A*	Myosin 7A; motor molecules that move along actin filaments	Postlingual* (before12)	Higher frequencies more affected, or flat, gradually progressive	10
DFNA13	*COL11A2*	Collagen, type XI, alpha-2; its association with type II collagen, which is known to be present in the tectorial membrane, led us to hypothesize that type XI collagen is essential for appropriate spacing of type II collagen within this structure	Postlingual (20–40)	Mid-frequency or flat, slowly progressive	19
DFNA15	*POU4F3*	Transcription facctor	Postlingual (18–30)	Higher frequencies more affected, progressive	16

(*Continued*)

TABLE 58.1 (*Continued*) Autosomal dominant genes causing non-syndromic hearing loss (adapted from Hereditary Hearing Loss)[1]

Locus	Gene	Gene function	Onset (years)	Pattern of hearing loss	Reference(s)
DFNA17	*MYH9*	Myosin heavy chain 9; non-muscle-myosin heavy-chain gene; localizes in the organ of Corti, the subcentral region of the spiral ligament, and the Reissner's membrane; contributes to cytoarchitecture	Postlingual (10)	Higher frequencies more affected, progressive	41
DFNA20/26	*ACTG1*	γ-actin gene; predominant actin isoform in the auditory hair cell; protein of the cytoskeleton	Postlingual* (7–30)	High-frequency, gently sloping, progressive	42, 43
DFNA22	*MYO6*	Myosin 6; unconventional motor molecule	Postlingual* (8–10)	Higher frequencies more affected, or flat, progressive	44
DFNA23	*SIX1***	Members of the SIX gene family encode proteins that are characterized by a divergent DNA-binding homeodomain and an upstream SIX domain, which may be involved both in determining DNA-binding specificity and in mediating protein–protein interactions	Prelingual (1–20)	High-frequency, sloping (one family)	45
DFNA25	*SLC17A8*	Vesicular glutamate transporter-3 (VGLUT3); VGLUT3 is essential for auditory coding at the IHC synapse	Postlingual (20 and older)	High-frequency, sloping, progressive	46
DFNA28	*GRHL2*	Grainyhead-like transcription factor	Postlingual (7 and older)	Flat, gently downsloping	47
DFNA36	*TMC1*	Transmembrane cochlear-expressed protein 1	Postlingual* (5–10)	High-frequency, rapidly progressive	48
DFNA39	*DSPP***	Dentin sialophosphoprotein	Postlingual (20–30)	High-frequency, progressive	49
DFNA41	*P2RX2*	Encodes the P2X2 receptor; in the inner ear, P2X2 receptors are thought to regulate sound transduction and auditory neurotransmission	Postlingual* (2nd decade)	Gently downsloping or flat, progressive	27
DFNA44	*CCDC50*	Encodes Ymer, an effector of epidermal growth factor (EGF)-mediated cell signalling that is ubiquitously expressed in different organs and has been suggested to inhibit downregulation of the EGF receptor	Postlingual (6–10)	Low- and mid-frequency, progressive (one family)	50
DFNA50	*MIRN96*	MicroRNAs (miRNAs) bind to complementary sites in their target mRNAs to mediate post-transcriptional repression, with the specificity of target recognition being crucially dependent on the miRNA seed region	Postlingual (12 onwards)	Flat, progressive	33
DFNA51	*TJP2 FAM189A2*	Tight junction protein; it is suggested that TJP2- and GSK-3β-mediate increase susceptibility to apoptosis of cells of the inner ear	Postlingual (4th decade)	High-frequency, progressive	31
DFNA56	*TNC*	Tenascin C; a member of the extracellular matrix (ECM); it is present in the basilar membrane (BM) and the osseous spiral lamina of the cochlea; it plays an important role in cochlear development	Postlingual (8–30	Low-frequency, ascending, progressive	28

(*Continued*)

TABLE 58.1 (*Continued*) Autosomal dominant genes causing non-syndromic hearing loss (adapted from Hereditary Hearing Loss)[1]

Locus	Gene	Gene function	Onset (years)	Pattern of hearing loss	Reference(s)
DFNA64	*SMAC/DIABLO*	Mitochondrial proapoptotic protein that is released from mitochondria during apoptosis and counters the inhibitory activities of inhibitor of apoptosis proteins	Postlingual (12–30)	Flat, progressive	51
DFNA65	*TBC1D24*	TBC1 domain family, member 24; GTPase-activating protein expressed in the cochlea;	Postlingual (3rd decade)	Gently downsloping, progressive	29, 52
DFNA66	*CD164*	Transmembrane sialomucin involved in cell migration and adhesion	Prelingual and postlingual (0–20)	Flat or mid-frequency, stable or progressive	53
DFNA67	*OSBPL2*	Oxysterol binding protein-like 2; possibly plays a role for the maintenance of hair cells' cytoskeleton	Postlingual* (10–30; possibly as early as 2)	Mild to profound, steeply sloping	30, 54
	HOMER2	Possibly has a role in cytoplasmic Ca^{2+} control	Postlingual* (*1st decade)	High-frequency, progressive	56
	CRYM	Mu-crystallin (CRYM; also known as 'NADP-regulated thyroid hormone-binding protein')	Prelingual (19 months)	Downsloping, progressive	22
DFNA70	*MCM2*	Nuclear protein important in cell cycle (onset of DNA replication and cell division)	Postlingual (earliest 13 years)	Mild to profound, slowly progressive, involving high frequencies or all frequencies	55
AUNA1	*DIAPH3*	Diaphanous-related formin 3; these proteins remodel the cytoskeleton by nucleating and elongating non-branched actin filaments, and they can also bind and stabilize microtubules	Postlingual (average 18.6)	Auditory neuropathy, moderate to profound, high-frequency, progressive (one family)	57
	KITLG	KIT receptor ligand	Prelingual	Unilateral or asymmetrical, Mild to profound	56
	DMXL2	Alpha subunit of rabconnectin protein complex that concentrates on synaptic vesicles	Postlingual (onset 2nd decade)	Mild to moderate, slowly progressive to severe to profound by 6th decade	22

*Onset can be in first decade; ** may also cause syndromic features in some families; reported in only one family.

BOX 58.1 Glossary of terms

Hereditary Hearing Loss website:[1] an important resource providing up-to-date information on mapped genes and loci associated with deafness as well as expression patterns of deafness genes
Linkage analysis: testing of DNA sequence variants that are near or within a gene of interest to track within a family the inheritance of a disease-causing mutation in a given gene; a prerequisite for linkage analysis is availability of a clinically well-characterized multigenerational family
Bacterial artificial chromosome (BAC): an engineered DNA molecule used to clone DNA sequences in bacterial cells (for example *Escherichia coli*)
Candidate gene approach: genetic analysis focused on the selection of genes that have previously been related to the disease in some way; it requires *a priori* knowledge of the gene's function, expression profile or pathway
Single nucleotide variant (SNV): a variation occurring in the genome when a single nucleotide in the genome is altered
Copy number variation (CNV): when the number of copies of a particular gene varies from one individual to the next
Whole exome sequencing (WES): a technique for sequencing all the protein-coding genes in the genome (known as the exome)
Whole genome sequencing (WGS): a technique that determines the complete genome sequence of an organism
Genetic heterogeneity: a term describing a single phenotype being caused by multiple genes and/or different variants in the same gene

focusing on the linked DFNA4 interval) to successfully identify a novel deafness gene *CEACAM16*.[26] Using similar approaches multiple novel genes followed: *P2RX2*, *TNC*, *TBC1D24*, *OSPBL2*.[27–30] However, in an Israeli family in whom AD deafness was linked to chromosome 9p13.3–q21.13, sequencing of all 121 genes in the linked region did not identify any potentially pathogenic variants because sequencing at that time was not able to detect quantitative variants such as duplications and heterozygous deletions. Using array comparative genomic

hybridization (a technique that can detect duplications and deletions in the genome), the cause of AD SNHL was found to be an inverted duplication spanning the *TJP* gene locus,[31] although new NGS technologies now offer sensitive tools for detection of genomic variants such as copy number variations (CNVs).[32]

Adding to the complexity of the molecular basis of SNHL is the discovery of a mutation in miR-96, a gene encoding micro RNA (miRNA) that binds to complementary sites in target mRNAs and mediates post-transcriptional repression.[33] It is therefore possible that other miRNAs may have a role in hearing and hearing loss. See **Table 58.1** for all non-syndromic AD SNHL genes.

Despite tremendous progress in sequencing techniques as well as exome sequencing becoming more and more cost-effective, the sequence produced by NGS is still imperfect. Certain regions are not well covered, particularly the 5′ regions of genes, or poorly assembled due to repetitive regions, and similarities in sequences of genes from the same family may be difficult to analyze. Therefore, although the process of sequencing the whole exome or genome is relatively fast, the downstream analysis requires a lot of time and expertise from bioinformaticians, genome analysts, molecular biologists and clinicians. While techniques will gradually improve and we will be able to produce an accurate sequence of the whole genome, the main challenge in the future will be interpretation of the variants, from single nucleotide variants (SNVs), insertions/deletion to CNVs. The whole exome sequence of one individual on average identifies between 70 000 and 90 000 SNVs; of them just over 21 000 SNVs are detected in coding regions.[34] The present and future challenge is how to reliably single out the disease-causing variant, which is especially difficult for novel genes with unclear functions. Current diagnostic yield with whole exome sequence technology is only ~25–30%; however, this is still higher than the diagnostic yield of other genomic assays such as karyotyping (<5%) and array comparative genomic hybridization (~15–20%). Currently, variants that cause Mendelian phenotypes have been identified in ~2937 human genes of the approximately 19 000 protein-coding genes predicted to exist in the human genome.[35] In the coming years, a huge number of additional variations in the genome will be produced by NGS and integration of this data will lead to better understanding of individual gene functions and identification of pathways leading to disease, which will result in improved diagnostic yield.

FUNCTIONS OF GENES INVOLVED IN NON-SYNDROMIC SNHL

Non-syndromic AD SNHL genes encode a variety of proteins essential for inner-ear function. Broadly, the non-syndromic AD deafness-coding genes with known function can be divided into four categories (adapted from Hilgert).[36]

1. Hair bundle morphogenesis (genes important for the development, structure and function of stereocilia in the hair cells):
   - proteins of the cytoskeleton: *ACTG1*
   - motor proteins: *MYO6*, *MYO7A*, *MYH9*.
2. Ion homeostasis (genes important in the recycling and transport of ions within the fluid-filled cochlea, often requiring energy):
   - connexins: *GJB2*, *GJB3*, *GJB6*
   - ion channels: *KCNQ4*, *SLC26A4*, *WFS1*.
3. Transcription factors (genes encoding proteins which are important for controlling expression of other genes, particularly during development): *EYA4*, *GRHL2*, *POU4F3*.
4. Extracellular matrix proteins (specialized structural molecules): *TECTA*, *COCH*, *COL11A2*.

CONCLUSIONS

Variants in 38 genes are currently known to cause non-syndromic AD SNHL; 21 loci are still awaiting gene identification together with numerous novel genes yet to be discovered. New sequencing technologies capable of sequencing the whole genome in a cost-effective manner are now, albeit still imperfect, in full flow and will lead to molecular diagnosis in many non-syndromic AD SNHL affected families. Due to high genetic heterogeneity, non-syndromic AD SNHL causing variants are individually rare or private, but collectively they play an important role in the pathogenesis of hearing loss.

Molecular genetic diagnosis is of critical importance for management of deafness, since it enables early and accurate clinical diagnosis, better prediction of the course of disease, early intervention essential for language and cognitive development, genetic counselling, as well as potential development of molecular treatments. As the whole genome sequence analysis is gradually making its way from research towards the diagnostic domain, clinicians must be aware of the genetic component of deafness and of the genetic tests and techniques available for molecular diagnosis.

BEST CLINICAL PRACTICE

- ✓ Always take a thorough history and ask about factors which may suggest a syndrome. History should include a 3 generation family history (or more if there is more significant information).
- ✓ Examine the patient to exclude obvious syndrome diagnoses (skin, pigmentation, facial appearance, general appearance).
- ✓ Request information (audiometry details) on other affected family members to look for similarity, or audiometric patterns in younger family members before progression.
- ✓ Investigate with visual acuity and dilated fundoscopy.
- ✓ Biochemical, immune and genetic testing where indicated by history/family history.

FUTURE RESEARCH

- Although the use of constantly evolving hearing loss panels has improved the molecular diagnosis of highly heterogeneous AD non-syndromic SNHL, the diagnostic yield is still limited as many SNHL genes are yet to be discovered.
- The identification of novel hearing loss causing genes has increased exponentially in the past few years; we are now faced with the challenge of accurate and consistent interpretation of novel variants and verification of these using functional studies.
- There is a need for clear guidelines and levels of evidence on inclusion of novel genes in hearing loss gene panels.
- Adequate guidelines and procedures should be set for genetic testing of children with hearing loss identified through newborn hearing screening to enable timely and sensitive clinical and molecular diagnosis.
- Affordable and timely molecular diagnosis will be important to ensure that novel genetic treatments can be offered to appropriate patients; novel therapies for dominant and recessive forms of hearing loss have proven successful in mice, and clinical trials in humans requires identification of suitable participants.[60–63]
- Finally, the rapidly changing landscape of SNHL genetic testing requires appropriate levels of genomic focused educational programs for genetic counsellors and clinicians who are the key to translation of the latest research findings into clinics.

KEY POINTS

- AD SNHL is characterized by marked genetic heterogeneity with most variants being private (e.g. disease-causing in a single family).
- It is usually, but not exclusively, postlingual and progressive.
- Linkage analysis coupled with whole genome/exome sequence analysis is a powerful tool enabling identification of novel pathogenic variants and discovery of novel genes and pathways in AD SNHL.
- Molecular diagnosis enables us to predict the progress of deafness and has important implications for early diagnosis, management of deafness and accurate genetic counselling for families.

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CHAPTER 59

OTOTOXICITY

Andrew Forge

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: ototoxicity, inner ear, hearing impairment, hearing loss, deafness, cochlea, aminoglycoside (and individual aminoglycoside), *cis*-platinum, salicylate, quinine, (loop) diuretics (or individual diuretics) and organic/industrial solvents (or individual solvents).

INTRODUCTION

The term ototoxicity is used to refer to the process by which a number of therapeutically useful drugs, certain environmental agents such as industrial solvents, and bacterial toxins cause damage to the peripheral end-organs of hearing and balance. This definition excludes agents which cause hearing impairment or balance dysfunction through primary action on the respective neural pathways and centres.

MODES OF ENTRY OF OTOTOXIC AGENTS TO THE INNER EAR

The complete enclosure of the inner ear structures within the temporal bone means that they are not exposed directly to potentially damaging environmental agents. Access to the perilymphatic compartment of the inner ear via the cochlear aqueduct from the cerebrospinal fluid (CSF) is possible and this may be a route of entry for bacterial toxins, such as those associated with meningitis. However, the cochlear aqueduct is not patent in many individuals and tends to close as an individual ages.[1] Access to perilymph is also possible from the middle ear cavity via the membrane covering the round window at the base of the cochlea and that filling the oval window over the vestibule. The permeability properties that determine what will and will not cross these membranes into the inner ear are not known. After entry into the perilymphatic compartment of the inner ear from the middle ear an agent would have access to the basal end of the cochlea and to the vestibular system. Subsequent drug distribution is somewhat complicated, influenced by a relatively slow diffusion rate away from the site of entry and localized clearance rates (e.g. along the cochlear aqueduct).[2–5] Nevertheless, if entry to perilymph is gained, because the basilar membrane is freely permeable, then there is direct access to the lateral membranes of the hair cells, to their synaptic regions and to the nerve fibres.

Potentially, bacterial toxins associated with middle ear infections as well as ototoxic drugs may enter the inner ear across the round window. There is evidence that some children who have had otitis media with effusion (OME) may develop extended high-frequency hearing loss, i.e. with a normal audiogram down to about 8 kHz but with significant threshold shifts at higher frequencies.[6, 7] This has been linked to what has become known as 'listening difficulties' that may underlie behavioural problems.[8] Temporal bones from patients who have had OME show loss of both inner and outer hair cells in the most basal regions of the cochlea[9, 10] and it is thought that this is caused by bacterial endotoxins released in the middle ear effusion crossing the round window membrane to access the basal coils of the cochlea. Ototoxic drugs may also reach the perilymph from the middle ear. In particular, the entry of aminoglycoside antibiotics applied to the middle ear cavity across the round and oval window membranes into the perilymphatic spaces of the inner ear is used as a clinical procedure to ablate hair cells in the vestibular system in cases of severe balance dysfunction

such as that resulting from unilateral Ménière's disease.[11] This approach is also a potential means for introducing therapeutics.[12]

Predominantly, however, ototoxic agents reach the inner ear through the blood supply but there are restrictions on the entry of agents to the fluids of the inner ear. Perilymph is not simply an ultrafiltrate of blood plasma, nor does it derive from CSF. The composition of perilymph is different both from CSF and from blood plasma and the composition of perilymph in scala vestibuli differs from that in scala tympani.[13] This indicates that perilymph is produced and circulated locally and that there is a so-called 'blood–perilymph barrier'. Glucose entry, for example, requires facilitated diffusion through glucose transporters.[13, 14] This may limit access of potentially damaging agents to the perilymphatic compartment. However, relatively little is known about the characteristics of this blood–perilymph barrier and how substances can cross it. Entry to endolymph in the internal compartment of the inner ear is even more restricted and endolymph composition is tightly controlled.[13] The principal boundaries between endolymph and perilymph, formed by selectively permeable membranes and tight junctions between adjacent cells, in the cochlea appear to be Reissner's membrane, at the level of the basal cells in the stria vascularis, and the network formed by the apical surfaces of the hair cells and adjacent supporting cells in the organ of Corti at the reticular lamina. In the vestibular system they are at the level of the tight junctions between hair and supporting cells in the sensory patches and between the epithelial cells that surround the endolymphatic, luminal spaces including the dark cells of the utricle and semicircular canals, the roofs of the utricle and saccule and the semicircular canals themselves. If an agent were to penetrate these boundaries, it would have access to the hair-bearing (apical) ends of the hair cells.

EFFECTS AND ACTIONS OF OTOTOXIC DRUGS

A diverse range of therapeutically useful drugs and some environmental agents have been reported to be ototoxic (Table 59.1). For some of these chemicals the evidence for ototoxicity is limited (see below); sometimes it derives from individual case reports, where other confounding factors may have contributed to the observed effect, and there are no confirmatory experimental studies in animals. The occurrence and extent of ototoxicity is to some extent dependent upon the dosing regime (or exposure conditions) but are compounded by the status of the patient receiving the drug and multiple drug regimes. Stress produced by infection may increase sensitivity as may malnourishment; the effects of aminoglycosides are more pronounced in nutritionally deprived animals.[15, 16] Drug interactions can also result in much greater damage than would be expected from single drug regimes. A number of ototoxic agents, including aminoglycosides, polypeptide antibiotics and anti-neoplastics, are also nephrotoxic so that possible damage to the kidney may result in reduced drug clearance and higher serum levels potentially increasing the risk to the inner ear. In addition, certain genetic factors may predispose to ototoxin-related damage (see below).[17] Individuals under similar conditions and with similar drug-dosing regimes differ in their sensitivity to ototoxic side effects. For these reasons it is not always possible to predict a likely effect following administration of a potentially ototoxic drug.

In Table 59.1 ototoxic drugs have been classified based on their therapeutic use, but perhaps a more useful classification derives from the sites and modes of action, which also provides a basis for illustrating the selective action of these different agents upon the inner ear. On this basis, ototoxins can be divided into three broad groups. The

TABLE 59.1 Compounds known to be or implicated in ototoxicity

Classification	Compounds
Aminoglycoside antibiotics	Amikacin, dibekacin, dihydrostreptomycin, framycetin, gentamicin, kanamycin, neomycin, netilmicin, ribostamycin, sisomicin, streptomycin, tobramycin
Macrolide antibiotics	Erythromycin, azithromycin, clarithromycin
Other antibiotics	Ampicillin, capreomycin, chloramphenicol, colistin (polymyxin E), minocycline, polymyxin B, rifampicin, vancomycin, viomycin
Antitumour agents	**Cisplatin (*cis*-platinum)** carboplatin Antinomycin, bleomycin, nitrogen mustards (e.g. mustine), misonidazole
Anti-inflammatory agents	**Salicylate** (aspirin) Fenoprofen, ibuprofen, indomethacin, naproxen, phenylbutazone,
Antimalarials	**Quinine**, **chloroquine**
Loop diuretics	Bumetanide, ethacrynic acid, frusemide (furosemide), piretanide
Iron chelators	Desferrioxamine
Beta-blockers	Practolol, propranolol
Contraceptives	Medroxyprogesterone
Industrial chemicals	**Trimethyltin**, **toluene**, **trichloroethylene**, **styrene**, **xylene**

first, exemplified by the 'loop' diuretics and erythromycin, have acute effects in the stria vascularis resulting in temporary hearing loss (temporary 'threshold shift' (TTS)). Agents in the second group, which includes salicylate and quinine, predominantly produce temporary impairment of hair cell function (TTS), often accompanied by tinnitus. These symptoms are completely relieved upon withdrawal of the drug. The third, and most significant, group of ototoxic agents cause death of the hair cells and permanent hearing loss (permanent threshold shifts (PTS)) and vestibular dysfunction. Aminoglycoside antibiotics and cisplatin (*cis*-platinum), as well as organic solvents, fall into this category. In mammals, the functional deficits resulting from the hair cell losses caused by these agents are permanent because, unlike the sensory epithelia in the inner ear in birds and other non-mammalian vertebrates,[18–21] the organ of Corti does not spontaneously regenerate hair cells to replace those lost, although the mammalian vestibular organs possess some capacity to regenerate hair cells.[22–27]

Agents affecting the ion-transporting epithelia

Those agents whose primary site of action is on the ion-transporting epithelia, the stria vascularis (SV) in the cochlea and the vestibular dark cells, adversely affect endolymph composition and, in the case of the SV, the endocochlear potential (EP). Such agents, including the loop diuretics, generally cause acute, completely reversible affects after a single drug administration,[28] although some cases of permanent deafness have been attributed to diuretic.[29] The SV has one the highest rates of oxidative metabolism in the body,[13] with oxygen delivered from the intraepithelial blood supply so agents that induce anoxia or ischaemia will affect strial activity. Aminoglycoside antibiotics and cisplatin[30, 31] may induce permanent strial pathologies although this does not necessarily correlate with effects on EP.

All **loop diuretics**, that is those diuretics whose principal site of action is in the ascending limb of the loop of Henle, including **ethacrynic (etacrynic) acid**, **furosemide (frusemide)**, **bumetanide** and **piretanide**, produce a transient hearing loss across most of the frequency range. This usually occurs following intravenous administration of large doses. The effects are rapid in onset, within minutes or hours, and persist for some hours but are usually completely resolved within a day if the drug is discontinued. Repeated diuretic administration does not appear to cause permanent damage to the inner ear. However, a single dose of diuretic when administered closely with a single dose of an ototoxin such as aminoglycoside or cisplatin which has the potential to cause hair cell loss only after chronic repeated treatment, results in rapid devastatingly extensive hearing loss and hair cell death (see below).

Histological studies of the temporal bones from patients who have died while on diuretic treatment[32, 33] have shown extensive oedema and swelling of the SV. Experimental studies in animals have confirmed the SV as the principle site of action and that diuretics produce a rapid, reversible decline in EP, falling from the usual +80 mV to negative values as low as around -40 mV, the K^+ diffusion potential.[34, 35] The rate of decline and the level of suppression are dependent upon the dose of drug administered.[28] The EP then recovers over a period of a few hours but takes several hours to return to normal levels after a single administration. In parallel with the decline in EP an extensive oedema occurs; the extracellular spaces become grossly enlarged (**Figure 59.1**) and strial thickness can almost double. This oedema is also reversible, resolving within about 2–4 hours, prior to complete recovery of EP.[35] The decline in EP correlates with threshold shifts in sound-evoked responses[36] and depression of otoacoustic emissions, a finding that provides evidence that EP is the power that drives the active mechanical responses of the organ of Corti in response to sound.[37] This illustrates the importance of EP maintenance to the cochlear

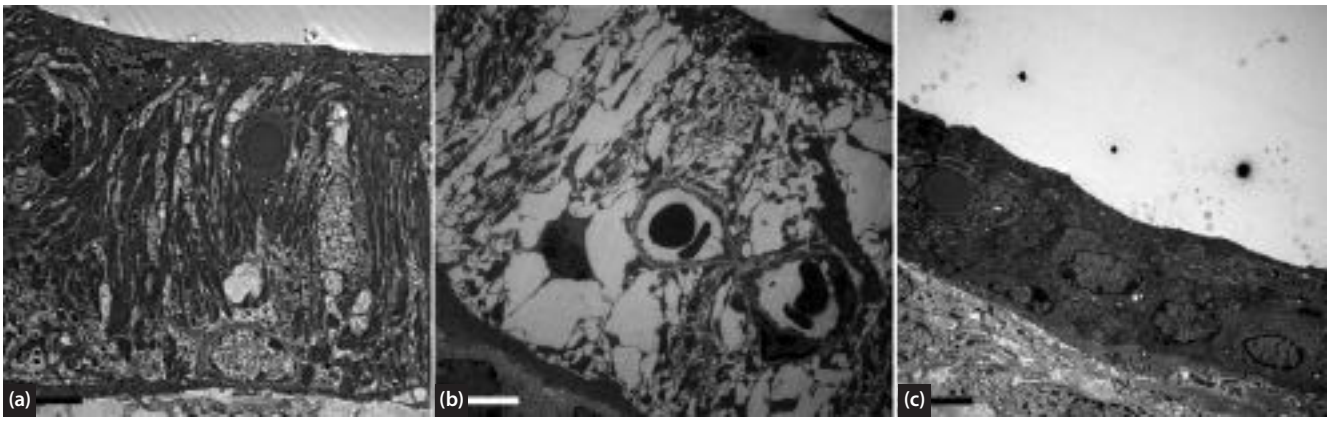


Figure 59.1 Effects of ototoxins on the stria vascularis (SV). Panels (a), (b) and (c) are all at the same magnification. (a) Cross section of the normal SV. **(b)** Effects of diuretic on the SV. There is significant oedema – enlarged extracellular spaces that are confined within the body of the tissue – and an increase in depth. The relative positioning of all the cellular elements of which the SV is composed is unaltered. **(c)** Atrophy of SV 12 weeks following chronic aminoglycoside treatment of the animal. The depth of the SV is significantly reduced. Scale bars on all panels: 5 µm.

amplification mechanism and why damage to the SV will cause hearing impairment.

The rapid onset of their effects suggests that diuretics gain direct access to their site of action through entry from the strial vasculature into the extracellular spaces of the SV and thus to the plasma membranes of all strial cell types including the basolateral membranes of the marginal cells. The development of oedema suggests that diuretics inhibit the ion-transporting processes: ions accumulating in the extracellular spaces would be confined by the tight junction sealing between basal cells, those between marginal cells and those between capillary endothelial cells, resulting in osmotic uptake of fluid. In the kidney, diuretics act on a Na/K/Cl cotransporter. The same cotransporter, NKCC1, localizes to the basolateral membrane both of vestibular dark cells and of marginal cell of the SV[38] and has been shown to be a target of the diuretics in the SV and vestibular dark cells.[39, 40] It is currently thought, therefore, that the diuretics reversibly inhibit the action of the electroneutral NKCC1 cotransporter, in the basolateral membranes of strial marginal cells and vestibular dark cells leading to inhibition of ion transport. In the cochlea, the generation of EP is thereby inhibited and along its entire length such that the consequent hearing impairment resulting from reduction of cochlear amplification is across almost the entire frequency range. (There is no equivalent of EP in the vestibular system so the effects are less pronounced.)

Na^+/K^+-ATPase is also present at high concentration on the basolateral membrane of marginal cells.[41, 42] Inhibition of this might have a similar effect as inhibition of the cotransporter. **Potassium cyanide**, along with its other actions in the body, causes TTS with a symptomatology similar to that of loop diuretics, thought to result from inhibition of marginal cell Na^+/K^+-ATPase.[43] **Macrolide antibiotics** such as **erythromycin** also produce effects similar to those of diuretics: generally transient threshold shifts[44] of the order of about 50 dB maximum across all frequencies[45] following high-dose intravenous administration; rapid, dose-dependent decline in EP in experimental animals;[46] an action on the basolateral side of the marginal cells affecting ion transport by these cells shown in isolated tissues maintained *in vitro*;[47] and, consistent with inhibition of ion transport in the SV, sections of temporal bone from patients who have died during a course of erythromycin therapy have shown extensive oedema of the SV.[45] However, the precise site of action of the macrolides in the SV has not yet been identified.

Agents causing reversible effects on hair cells

Salicylates and **quinine** cause TTSs across most of the detectable frequency range, and tinnitus. Dizziness is reported as a symptom of the use of either of these drugs, but there have been no experimental studies of their possible effects on the vestibular system. The ototoxic effects of these agents are generally reversible when treatment ceases; salicylates are rarely associated with permanent hearing loss.[48] Although it has been reported that excessive doses of quinine or chloroquine may result in permanent deafness,[49] quinine-induced ototoxicity is also usually completely reversible both in healthy volunteers and in patients with malaria.[50]

Salicylates produce threshold shifts across all frequencies simultaneously, indicating effects along the entire cochlear spiral. The shifts are usually no more than 40–60 dB and almost equal across the frequency range or somewhat greater at higher frequencies. These symptoms are completely reversible within 1–3 days following withdrawal of the drug and usually develop only at the high dosage levels used in treating rheumatoid arthritis, 2–5 g/day.[48] Salicylate enters perilymph rapidly after systemic administration, peak levels in perilymph being reached 1–2 hours after injection. The concentration in perilymph is linearly related to the serum concentration,[51, 52] and deterioration of auditory and neural thresholds is linearly related to perilymph salicylate concentration. Thus, the degree of threshold shift is quantitatively related to salicylate plasma concentration. These findings indicate that salicylate penetrates the blood–perilymph barrier readily.

Experimental studies in animals have shown that salicylate causes threshold shifts only at low stimulus intensities; responses to stimuli above about 60 dB appear to be unaffected. The tuning of responses of individual nerves to their characteristic frequency also is lost.[53, 54] In addition, otoacoustic emissions, are reversibly suppressed in humans[55, 56] and animals.[53, 54] These findings suggest effects of salicylate on OHCs and inhibition of the activity that produces signal amplification in the cochlea. EP is unaffected following salicylate administration[54, 57] and effects of salicylates on cochlear vasculature and thereby activity of the SV in generating EP are not considered to be a significant factor in their ototoxicity. Rather, OHCs appear to be the primary target of salicylate following its entry into the perilymph and access to a site of action on the basolateral membrane. Salicylates inhibit electrically driven motile responses of isolated OHCs.[58, 59] It is these responses that *in vivo* are thought to underlie the cochlear amplification mechanism.[60, 61] Investigation of basilar membrane mechanical responses to sound stimulation during salicylate perfusion *in vivo*[62] have confirmed direct effects on OHCs that adversely influence their active responses and thus, auditory sensitivity. The fast motile responses of OHC are driven by the 'motor' protein prestin, which is unique to OHC and is packed into its basolateral plasma membrane.[63] There is evidence that reversible interactions with anions produce conformational changes in prestin that result in the reversible electrically driven changes in OHC length.[64] Salicylate, an anion, appears able to interact with prestin and block this electromotility.[64]

Likewise, **quinine**, at therapeutic doses of 200–300 mg per day, can cause threshold shifts at all frequencies, effects which are usually entirely reversible, disappearing upon withdrawal of the drug.[50] As with salicylate, quinine enters perilymph rapidly,[65] reaching perilymph

concentrations directly related to serum concentrations and direct perfusion of quinine into the perilymphatic space revealed threshold shifts in a number of sound-evoked responses the magnitude of which are related to perilymphatic concentration of the drug between 10 µM and 100 µM.[66] However, unlike salicylate, quinine affects cochlear responses across all stimulus intensities, not just the lower ones, indicating a site(s) of action different from salicylate and not confined to the cochlear amplifier. It has been reported that at the lowest concentrations at which effects can be detected, around 0.05 mM, quinine does not affect OHC responses, such as OAEs, but produces a reversible elevation in threshold for the compound action potential (CAP), which derives from stimulation of inner hair cells (IHCs), without affecting neural tuning.[67, 68] Tuning derives from the activity of OHCs that produces amplification. This suggests that the initial site of action of quinine may be on the IHC, synaptic transmission at the base of IHCs, or/and upon the spiral ganglion neurons themselves, with OHCs affected only at higher concentrations. An effect of quinine at the hair cell synapse could also explain vertigo as the ready entry of the drug into perilymph would enable it to gain access to the basolateral membranes of vestibular hair cells. It has been found that quinine and its derivatives such as chloroquinine block nicotinic acetylcholine receptors (nAChR) composed of α9α10 subunits,[69] which are the predominant acetylcholine receptor subunit composition of hair cells in both chicks and mammals.[70, 71] Acetylcholine is the predominant efferent neurotransmitter in the cochlea. Efferent fibres synapse with the afferent neurones of IHC just below the hair cell body and modulate the responses of those afferents to stimulation, and they synapse directly with OHC whose activity is regulated by the efferent system. Thus, the effects of quinine may result from its action at these efferent synapses.

The ototoxic effects of salicylate and quinine thus derive from an ability to cross the blood–perilymph barrier freely, illustrated by the rapid onset of responses, so they may become distributed throughout perilymph along the entire cochlea, indicated by effects across the entire frequency range, and consequently gaining access to the basolateral membranes of hair cells and to the neurons and their synapses with the hair cells. Since the particular activities of OHC in producing signal amplification are associated with specializations along the basolateral wall, these will become vulnerable, as with salicylate. The characteristics of the symptomatology of the hearing impairment produced by salicylate and quinine thus provide an immediate insight into the likely routes of entry and potential sites of action of the ototoxins.

Agents that cause permanent hearing loss and balance disorders

The third group of agents are those whose administration causes permanent hearing impairment and/or balance dysfunction as a result of death of the hair cells. The ototoxicity of most of these agents usually develops only after repeated systemic administration; a single systemic application does not generally affect hearing or balance.

AMINOGLYCOSIDE ANTIBIOTICS

The aminoglycoside antibiotics constitute the clinically most important group of ototoxic agents. They are toxic to hair cells in all inner ear sensory patches in all vertebrate classes as well as neuromasts of the lateral line systems of fish and aquatic amphibia. Indeed, the nematocyst cells in marine and aquatic invertebrates, which are mechanotransducing cells thought to be evolutionarily related to vertebrate hair cells, are also affected by aminoglycoside.[72] Although all aminoglycosides are potentially both cochleotoxic and vestibulotoxic, the different aminoglycosides exhibit differences in their toxic potential and organ preference. Assessment of the degree and time course of functional impairment following cochlear perfusion with different aminoglycosides[73] and analysis of the extent of damage to cultured explants of the murine organ of Corti directly exposed to different aminoglycosides[74] have established similar rank orders of cochleotoxic potency for different aminoglycosides. These have indicated that neomycin is the most toxic, gentamicin, kanamycin and tobramycin less so, and amikacin and netilmicin least toxic, but such differential toxicity may not apply in a clinical setting. Streptomycin and gentamicin are considered more vestibulotoxic than cochleotoxic to humans, whereas amikacin and neomycin are primarily cochleotoxic in the human inner ear. The reasons for such preferences are not known, but it is not related to any site-specific uptake mechanism or drug levels in the tissues.[75] There are also species differences in susceptibility to the different aminoglycosides of which dihydrostreptomycin provides the most striking example.[76, 77] In early clinical use dihydrostreptomycin proved to be markedly toxic to the human cochlea. However, in the macaque monkey treated with large doses of dihydrostreptomycin for a prolonged period, there was only a very modest shift in auditory threshold at the highest frequency tested, and less than 10% of the hair cells were absent at the basal end of the cochlea.[77] In contrast, the patas monkey was affected in a manner similar to humans and appeared to be the only laboratory animal whose cochlea was sensitive to the toxic action of dihydrostreptomycin.

The effects of aminoglycosides usually become manifest only after days or weeks of parenteral treatment. Single systemic administrations are not normally damaging to the inner ear, but topical application of a single dose of the drug to the middle ear cavity can almost immediately initiate the progressive damage observed after chronic systemic treatment.[24, 78] The severity of the effects increases progressively with time, continuing after drug administration has been stopped; insidiously, in some cases, hearing impairment may not even begin until after treatment has ceased. The initial effect in the cochlea is a hearing loss confined to the high frequencies,[79] indicating hair cell damage in the most basal region of the cochlea. The hearing loss then continues progressively to include

successively lower frequencies, indicating a spread of the damage to hair cells apicalwards along the organ of Corti spiral and involving frequencies in the human speech range and thus ultimately to cause a permanent communication disability. A bilateral loss of 20 dB at two or more adjacent test frequencies is accepted as a hearing impairment.[80] However, most clinical audiometry usually covers the frequency range only from about 8 kHz downwards, whereas in the average person the high-frequency limit is about 16–18 kHz, so that the initial ototoxic effects of the drug will be missed unless high-frequency audiometry is used. Vestibular damage from systemic aminoglycoside administration results in severe unsteadiness that becomes worse in the dark. Perception of unreal movement, usually elicited by head motion, can also occur. Objective clinical assessment is, however, difficult and limited.[80]

Location and nature of lesions

Aminoglycoside-induced hair cell death occurs in a distinct pattern. In the organ of Corti, in line with the pattern of hearing loss, hair cells in the basal (high-frequency) coil are affected first, damage spreading progressively apicalwards with time and with increasing dosage. Outer hair cells are more sensitive than inner hair cells (**Figure 59.2**). IHCs do not usually appear to die until all the OHCs in their immediate vicinity and may persist for months after there has been complete loss of all OHCs.[81] The delay before IHCs are affected may suggest that their loss is a secondary event that occurs as a consequence of OHC loss and unrelated to the initial ototoxic events.[81]

There is also significant progressive loss of spiral ganglion neurons, the afferent nerves that innervate hair cells. This appears to progress following death of IHCs[76, 82] and has been ascribed to a loss of the neurotrophic factors NT-3 and BDNF derived from the IHCs that are necessary for neuronal survival[83, 84] together with loss of continuing stimulation normally provided by IHC activity. Perfusion of neurotrophic factors into the cochlea following aminoglycoside administration has been shown to ameliorate loss of the auditory neurons.[85] This has been suggested as a means to preserve cochlear innervation to enhance the efficacy of cochlear implants.[86, 87] However, recent work on the effects of noise and ageing has indicated that loss of a subpopulation of afferent terminals from IHCs may precede any overt hair cell loss.[88] This may be the basis of some more subtle forms of hearing impairment, such as difficulties in detecting speech in noise, when auditory thresholds as recorded by routine testing procedures are unaffected. The loss of the terminals is thought to occur by excess release of the neurotransmitter glutamate from the IHCs at synapses with afferent terminals causing excitotoxic damage to the nerve. However, it is not yet known if this occurs with aminoglycoside-induced injury.

In the vestibular system aminoglycoside-induced hair cell loss is seen initially in the central regions of the epithelia, i.e. at the crests of the saddle-shaped cristae and across the 'striola' along the middle of utricular and saccular maculae. HC loss then spreads progressively towards the peripheries.[89] There is also differential susceptibility among the vestibular organs; in an individual subject, cristae show greater HC loss than the utricle which in turn

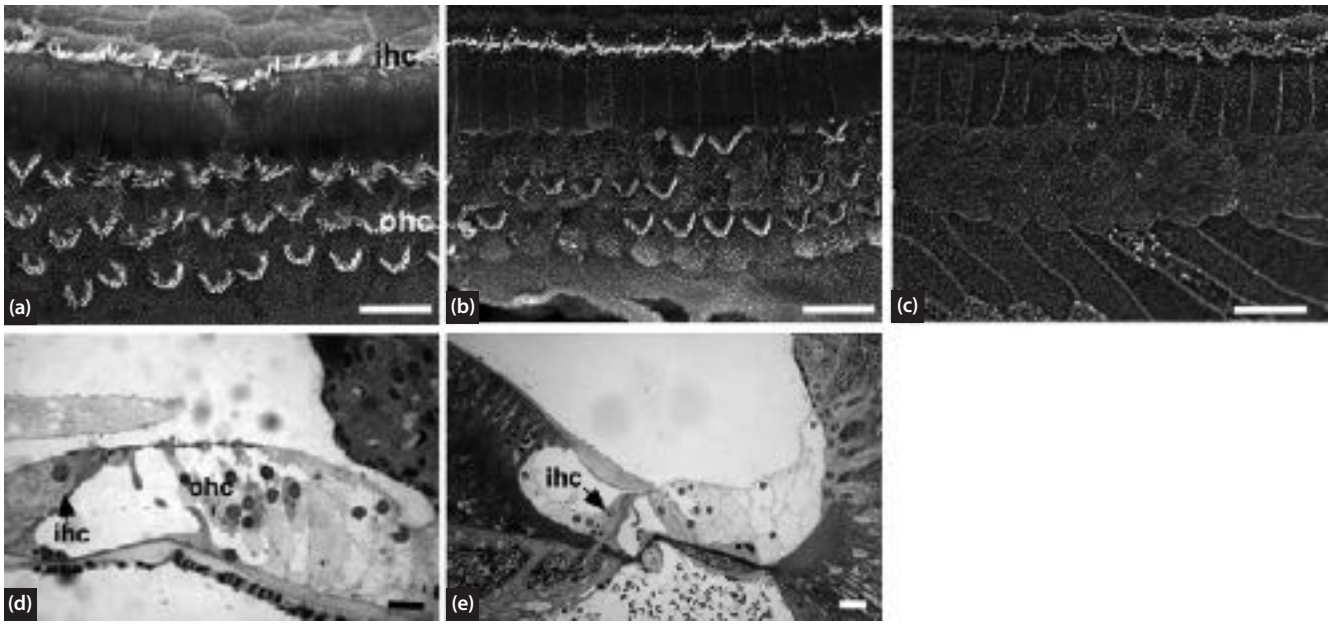


Figure 59.2 Effects of aminoglycoside in the organ of Corti. **(a,b,c)** Scanning electron microscopy of the apical surface of mouse organ of Corti in the apical coil: **(a)**, middle coil **(b)** and basal coil **(c)** after aminoglycoside treatment of animals. In the apical coil all inner hair cells (ihc) and almost all outer hair cells (ohc) are present. In the middle coil there is significant loss of ohc. In the basal coil, 6 weeks after the end of the treatment, all ohc are lost but almost all ihc are still present. **(d,e)** Sections of the organ of Corti of a mouse following chronic aminoglycoside treatment: **(d)** apical coil – all ohc as well as ihc are present; **(e)** basal coil – there are no ohc but ihc are present. Scale bars in all images: 10 µm.

shows more extensive damage than the saccule.[82] This differential susceptibility conforms to a differential uptake of aminoglycoside between the two hair cell types; immunohistochemistry has shown preferential uptake of gentamicin into the type 1 hair cells.[90] The type 1 hair cells predominate on those regions where damage is initiated and are thought to be more susceptible to aminoglycoside-induced damage than the type 2 vestibular hair cells.

The death of each hair cell is accompanied by expansion of the supporting cells around them to close the lesion and effect tissue repair (**Figure 59.2**).[27, 91–94] Supporting cells are not usually affected by aminoglycosides (or other ototoxins). Following the initial lesion closure by expansion of the supporting cells, reorganization of the sensory epithelium may continue for some time after hair cell loss and ultimately the crest of cells that normally constitutes the organ of Corti can become replaced by an apparently simple cuboidal-like epithelium across the basilar membrane.[95] In the organ of Corti lost hair cells are not replaced, but there is some evidence for regeneration of hair cells in the mammalian utricle,[23–26] including that of humans.[27] The extent to which this occurs is limited and only a proportion of the lost hair cells may be replaced by new ones.[24, 27] In birds and other non-mammalian vertebrates regeneration of hair cells is extensive and can lead to complete recovery of damaged sensory epithelia.[18, 21, 96] The replacement hair cells derive from the supporting cell population through initiation of cell division among the supporting cells and/or through direct non-mitotic transdifferentiation, or 'phenotypic conversion' of supporting cells into hair cells.[21, 22, 26, 97] Enhancing the phenotypic conversion mechanism is the basis of some attempts to develop therapies to induce hair cell regeneration in the mammalian inner ear.

Pharmacokinetics and mechanisms of toxicity

There is a linear relationship between serum concentration of aminoglycoside and the perilymph concentration,[2, 98] but aminoglycosides enter perilymph relatively slowly, the peak concentration after extravascular injection to guinea pigs occurring much later in perilymph (about 4 hours) than in serum (about 15–30 minutes). However, clearance from perilymph is delayed and the drug persists in the inner ear for some time. The half-life of aminoglycoside in the inner ear has been estimated as more than 30 days.[99] The peak level reached in perilymph after multiple dosing has been reported to be approximately 50–250 μM,[2, 99–101] but following systemic administration appears in greater amounts in the scala tympani of the apical turn than in the basal coil.[2] Aminoglycosides also enter endolymph, but only after a prolonged period following entry into perilymph. While this has been interpreted to suggest that aminoglycosides enter endolymph from perilymph,[99] some other evidence has suggested that they are taken up quite rapidly into marginal cells of the SV directly from the strial vasculature.[102] Once inside marginal cells there is the potential to enter endolymph directly. Whether there is a similar route into endolymph in the vestibular system, perhaps via dark cells, has not been tested. Nevertheless, persistence in perilymph and delayed entry to endolymph may account for the delayed effects of aminoglycosides. The delayed responses and the progressive effects may result from slowly increasing endolymphatic concentrations of the drug to critical levels that can cause damage. Several pieces of evidence from a range of experimental models suggest that aminoglycosides affect hair cells through access from their endolymphatic (apical) surface.

The susceptibility of all hair cell types in all vertebrate classes emphasizes that hair cells are specific targets of the aminoglycosides, and studies using radioactively or fluorescently labelled aminoglycosides administered to animals have shown that the drug is indeed taken up specifically into hair cells in the mammalian cochlea.[103, 104] The common feature of all hair cells is the transduction apparatus at their apical poles and it is apparent from a range of experimental studies in a variety of animal models that one of the major routes of entry for aminoglycosides into hair cells is through the mechanotransduction channels at the tips of the stereocilia.[105–107] In fact, aminoglycosides are one of the few known blockers of the hair cell transduction channel. Mutations in genes that encode proteins known to be involved in regulating opening of the transduction channels, such as myosin 7a, prevent entry of aminoglycosides into the hair cells and the hair cells are protected from lethal injury.[108] This demonstrates that entry of aminoglycoside into the hair cell is necessary to cause the cell death. Blocking entry would prevent aminoglycoside-induced hair cell death and one current line of research is to determine modifications of the aminoglycoside molecule that retain antimicrobial activity but are unable to enter the transduction channel.[109] Entry via the transduction channels could provide one explanation for the base-to-apex gradient in hair cell death along the cochlea: the probability of the open state of the transduction channels in OHCs in the basal coil is 50%, but the open state probabilities decrease towards the cochlear apex.[110] However, other/additional factors may also underlie the differential sensitivity to aminoglycosides of hair cells along the cochlear spiral.

Although entry into the cell is necessary for aminoglycosides to trigger hair cell death, it is not sufficient. Following systemic administration, gentamicin can remain inside hair cells for as long as 11 months without injury ensuing.[111] This implies that the cell death occurs only after some critical concentration of the drug has been reached inside the cell. Aminoglycosides cause death of hair cells by inducing apoptosis,[81, 91, 92, 112, 113] a programmed cell death pathway in which particular enzymes called caspases play the crucial roles. Gentamicin-induced hair cell death can be prevented by pan-caspase inhibitors.[112, 114, 115] A number of different cellular stress-activated biochemical pathways that lead to apoptosis have been identified as being triggered following aminoglycoside treatment[116–119] and offer potential therapeutic targets of intervention for preventing aminoglycoside-induced hair cell death.[120, 121]

One significant initiator of programmed cell death leading to apoptosis is generation of reactive free radicals.[122, 123]

Every cell in the body produces reactive oxygen species (ROS) as part of normal metabolism through enzymatic reactions and the oxidative respiratory mechanisms in mitochondria. Naturally produced ROS are normally removed as substrates or act as messengers in other biochemical reactions or they are neutralized by inherent cellular scavengers such as glutathione or specific enzymatic neutralizing systems such as superoxide dismutases. However, adverse conditions lead to overproduction and/or insufficient scavenging of ROS. The resultant oxidative stress upsets homeostatic redox balance, leading to damage to cellular components, proteins and lipids in particular, through oxidation/reduction reactions and can trigger cell death pathways.

There is evidence that hair cells may be vulnerable to oxidative stress. In strips of organ of Corti isolated from the cochlea and maintained in short-term culture, even without exposure to aminoglycosides, OHCs from the basal coil die much more quickly than those in apical coils. The survival of basal coil OHCs can, however, be enhanced by addition to the maintenance medium of free radical scavengers, including n-acetyl cysteine, salicylate and glutathione.[124] This indicates that in the cochlea, basal coil hair cells are more susceptible to oxidative damage than those at the apex. Effects of aminoglycosides that lead to the release of free radicals to levels in excess of cellular mechanisms to detoxify them has been considered one potential route through which aminoglycoside-induced hair cell death is triggered and a number of mechanisms of how this might occur have been proposed.[75, 120, 121] Following the discovery that mutations in mitochondrial genes that encode for mitochondrial rRNAs are associated with enhanced susceptibility to aminoglycoside-induced hearing loss (see below), a number of studies now suggest that aminoglycosides may damage mitochondria leading to production of ROS to lethal levels and release of pro-apoptotic factors from the mitochondria.[120, 121] Mitochondria are derived during evolution from bacteria and they contain their own distinct set of genes, separate from the genes encoded by the cell's nuclear DNA. These genes encode some of the mitochondrial proteins and the ribosomal- (r-)RNAs necessary for their translation. Bacterial r-RNAs are the target for aminoglycosides as antibiotics. Damage to mitochondria releases not only ROS but also a number of factors normally resident within mitochondria that regulate the cascade of reactions leading to apoptosis.

Suppressing the generation or enhancing the scavenging of ROS have therefore been proposed as potential therapeutic interventions for protecting hair cells from the lethal damage caused by aminoglycosides.[120, 125] However, the direct evidence that aminoglycosides trigger generation of ROS in hair cells *in situ* in the mature organ of Corti is limited. Nevertheless, in an experimental study the aminoglycoside apramycin, which has potent antibacterial activity and is used in veterinary medicine, was found to cause less hearing impairment and hair cell loss *in vivo* than other aminoglycosides and in explant cultures of the organ of Corti from neonatal mice generation of ROS was reduced in comparison with gentamicin.[126] The studies with apramycin are part of a further current line of investigation: to design aminoglycoside molecules with antimicrobial activity but which do not activate cell death pathways inside hair cells.

Effects of aminoglycosides on the stria vascularis

Although hair cells are the primary site of aminoglycoside action, the drugs are taken up quite rapidly into marginal cells in the SV.[127] A decrease in the volume of the SV (strial atrophy) has been observed in human temporal bones obtained within 2 weeks of aminoglycoside treatment.[128] In experimental studies in animals immediately following the end of a course of aminoglycoside treatment alterations to the stria can be seen at the same time as the earliest effects in the organ of Corti are apparent.[129] The subsequent decrease in the thickness of the stria is due to effects almost exclusively on marginal cells.[30] Some cells are lost by a process which shows morphological attributes of apoptosis, but the majority of marginal cells remain but with much reduced volume. Such alteration might be expected to affect EP and the ionic profile of endolymph, but EP appears to be maintained at close to normal levels for up to 4 weeks after the end of aminoglycoside treatment but is reduced by more than half 12 weeks after treatment when there is significant decrease in strial thickness (see **Figure 59.1**).[130] Interestingly, the changes to the stria and coincident relatively small decreases in EP that occur with aminoglycosides are similar to those seen with ageing in a gerbil model.[131] Here there is significant thinning of the stria but EP is little affected until the stria is less than one-third its normal volume when there is a catastrophic loss of EP. These results might suggest that there is significant redundancy in the stria; EP and organ of Corti activity can be maintained even when there has been considerable strial injury. Thus, it maybe that the stria can sustain injury for some time without a noticeable effect on auditory function, but in this 'compromised' state it might be less able to resist further insults. Consequently, a sudden loss of auditory function might ensue in conditions which would otherwise not be expected to cause hearing loss.

Confounding factors and genetics

The degree of vestibular or auditory impairment with aminoglycosides may depend upon the drug itself, the unit or total dose, the route and period of administration and the patient's age or pathological state; for example, the risk is substantially increased by impaired renal function.[132] The situation is further complicated in that the aminoglycosides, to varying degrees, are nephrotoxic. Genetic factors also play a role.[17] A predisposition to aminoglycoside ototoxicity is conferred by mutations in the gene that encodes 12s ribosomal RNA of mitochondria. The 'A1555G' missense mutation (an adenosine to guanosine substitution at base position 1555),[133, 134] a thymidine to cytosine mutation at 1095,[135] cytosine to thymidine missense at 1494,[136] and a cytosine insertion at position 961, all appear to confer particular sensitivity to aminoglycoside. In some

cases profound hearing loss may occur after only a single parenteral injection rather than the usual situation where hearing loss occurs only after several repeated administrations. The presence of these mutations in the mitochondrial chromosome has been identified through maternal inheritance patterns. The prevalence of A1555G mutation has been estimated as 0.19% in children in the UK[17] but is greater in Chinese, Arab-Israeli, Japanese and North American families[137, 138] and may be as high as 1% in these populations. A carrier rate of 17% of those developing aminoglycoside-induced hearing loss been estimated. However, the mutations appear to affect only the cochlea's sensitivity to aminoglycoside; there is no enhanced effect on the vestibular system, and no other organ of the system is affected. The reasons why only cochlear hair cells are affected or how the mutation enhances susceptibility are currently not known.

Aminoglycosides may also present a problem for those with tuberculosis and for cystic fibrosis patients. These antibiotics were first developed for use against tuberculosis and are still part of combination drug therapy against it. However, it has been estimated that as many as 80% of patients receiving aminoglycosides chronically to treat tuberculosis develop ototoxic side effects. There is also a significant incidence of hearing loss in cystic fibrosis patients who receive continuous treatment with aminoglycosides to combat pneumonia.[139–141] A further consideration is that aminoglycoside antibiotics can cross the placenta. Thus there is a potential to cause deafness in the foetus. Studies of development in animals have suggested a 'critical period' in development, when sensitivity to the ototoxic agent is greatest at around the time of the onset of auditory function during development. The existence and timing of a critical period in humans has not been identified but, based on anatomical findings comparing development of the human inner ear with that of experimental animals, it has been estimated that a critical period for the human cochlea maybe present in about weeks 18–20 of gestation. An ototoxic action of aminoglycosides during intrauterine life of human embryos has been reported.[141]

Interactions

Noise and aminoglycosides. Both epidemiological studies of the incidence of hearing loss in man and experimental studies in animals have indicated that noise exposure in conjunction with aminoglycoside may cause more extensive damage than with either agent alone.[143] Indeed, exposures under conditions in which neither noise nor the aminoglycoside alone would be expected to cause damage can result in marked auditory impairment and hair cell loss when the two agents are presented together. Animals reared in a sound-attenuated room do not take up gentamicin as extensively as animals raised in the environment of a normal animal facility.[144] This could result from increased uptake through the transduction channel; in the presence of sound stimulation, more transduction channels will be in the open state more frequently thereby enabling increased entry of the aminoglycoside than would be the case in a quiet environment. With increased sound exposure this effect will be enhanced. Thus, with exposure to noise, aminoglycoside uptake to a 'critical' level necessary to cause hair cell death would be reached more quickly. High sound pressure levels also lead to the generation of a variety of free radical species,[145, 146] which would exacerbate the effects of aminoglycoside-induced cellular stress.

Loop diuretics and aminoglycosides. Clinical experience and animal studies have also shown that coadministration of a single dose of loop diuretic with a single systemic administration of aminoglycoside, neither of which alone would cause hair cell loss, produces significant cochlear damage.[147] All aminoglycoside antibiotics have been found to interact with loop diuretics.[147] Administration of an intravenous dose of ethacrynic acid, frusemide or bumetanide shortly before a single, non-ototoxic dose of kanamycin rapidly produces depression of cochlear function which is permanent and associated with extensive hair cell destruction.[148, 149] A similar protocol applied to mice, subcutaneous injection of kanamycin followed after about 40–60 minutes with a single intraperitoneal injection of bumetanide causes almost complete loss of almost all OHCs within 48 hours of injections.[81] The SV is also affected, becoming progressively thinner through loss of marginal cells. The effects of the interaction are generally confined to the cochlea; no significant loss of hair cells is apparent in the vestibular system which appears to remain unaffected even at prolonged periods of time after all OHC have been lost from the organ of Corti.[81, 150]

The loop diuretics markedly increase the penetration of aminoglycosides into endolymph[151] and enhance uptake of gentamicin into cochlear hair cells.[81, 127] The potentiation of cochleotoxicity following systemic adminstration of both agents therefore likely arises because the diuretic enhances uptake of the aminoglycoside from the systemic circulation into endolymph. It is perhaps noteworthy that the interaction is only manifest when the time between administration of the two agents is relatively short, the diuretic administered no more than 1 hour before or 2 hours after the aminoglycoside[147] and that the vestibular system is not affected following the combined administration of single doses of these drugs. The timescale covers the time over which the EP is significantly reduced. The reduction in EP to negative values from the normally high positive potential may encourage entry of the cationic aminoglycoside into endolymph. Since there is no equivalent of EP in the vestibular system and diuretic does not cause a reduction of the positive diffusion potential of the vestibular endolymph, such enhancement of aminoglycoside uptake into vestibular hair cells would not occur.

CISPLATIN

Sites of action and nature of effects

Cisplatin (*cis*-dichlorodiammine platinum II [*cis*-DDP] or *cis*-platinum) is used to treat various tumours of soft tissue. Like the aminoglycosides, it is nephrotoxic as well as ototoxic.[120, 152–154] It has been estimated that the current clinical protocols for its use result in at least 60% of patients

suffering some degree of hearing impairment. Hearing loss often progresses after completion of drug therapy, which may in part be related to prolonged retention of platinum in the body; significantly higher levels of platinum than normal were detected in ex-patients at least 6 years, and in some reports longer, after the completion of *cis*-DPP therapy.[154, 155] Cisplatin induces a progressive loss of hair cells, the extent of which correlates with the dose of drug administered.[156] This occurs following repeated injections of relatively low drug doses (1 mg/kg daily) administered by intramuscular, intraperitoneal or subcutaneous routes, and after a single intravenous high dose (10–12 mg/kg).[31, 157, 158] The pattern of hair cell damage in the cochlea also resembles that of the aminoglycosides; hair cells in the basal coil of the cochlea are preferentially affected with damage spreading progressively apicalwards.[157, 158] As with aminoglycosides, the IHCs appear to be relatively resistant to damage following cisplatin administration.[159, 160] These histopathological findings correlate with assessment of auditory function in both animals and patients which shows an initial high-frequency hearing loss measured by auditory brainstem response (ABR), and suppression of otoacoustic emissions indicating an effect on OHCs.[161, 162] However, auditory neural threshold is increased to a greater extent than OAE, suggesting cisplatin may have direct effects upon the spiral ganglion cells themselves.[163] Since IHCs appear to be intact, these discrepancies suggest an effect at the level of the auditory nerve. Detachment of the myelin sheaths from type 1 spiral ganglion cells (those that innervate IHCs) has been observed and appears to progressively increase in extent in parallel with loss of OHCs. This suggests that the injuries at the two sites are separate phenomena.

Effects in the SV are also apparent. Cisplatin causes a decline in EP within 1 day of single intravenous high dose and it may become completely lost, though with lower repeated doses the effects take longer and appear less severe.[31, 164] Ultimately, strial atrophy develops several days or weeks after the end of the chronic treatment, which appears to be due primarily to apoptotic death of the marginal cells.[165, 166] That this was apparent in all turns of the cochlea when hair cell death was confined to the basal turns, as well as the fact that differing dosing regimes may influence which tissue is most affected,[167] suggests that effects in the stria and in the organ of Corti are independent of each other.

Cisplatin, therefore, appears to have effects at multiple sites in the cochlea: outer hair cells, spiral ganglion neurons, and the SV and perhaps also fibrocytes of the spiral ligament.[168] Furthermore, although not reported as extensively, cisplatin also causes vestibular dysfunction and loss of hair cells from vestibular sensory organs in patients.[169, 170] Experimental studies in a number of different animal models have confirmed HC loss from the vestibular organs in a manner similar to that resulting from aminoglycosides.[171, 172]

Mechanisms of action

Platinum can be detected in hair cells, spiral ganglion neurons and at particularly high levels in SV following repeated systemic administration of cisplatin.[173] Transport proteins megalin (LRP2), the organic cation transporter OCT2 (also known as SLC22A2) and the copper uptake transporter Ctr1 (SLC31A1) are thought to play roles in cellular entry of cisplatin. Ctr1 has been localized to hair cells, the SV and spiral ganglion cells in mice.[120, 153] Variations in the gene encoding megalin and that of Ctr1[174] have been associated with the severity of cisplatin ototoxicity, but the small size of the populations assessed requires caution in interpreting these results.[17] The uptake of the drug to strial marginal cells would assist potential entry into endolymph and this may be a crucial factor for access to hair cells.[153, 154, 159] A rapid deterioration in the auditory nerve response threshold is produced when cisplatin is present in the scala media at concentrations of about 5 mM, but no effect is apparent with perilymphatic perfusion at drug concentrations of less than 3 mM.[175] This suggests that one possible site of the drug action is at the apical end of the hair cells. Cisplatin has been shown to be able to block transduction currents in isolated hair cells from chicken,[176] and functional mechanotransduction channels have been shown to be required for uptake of fluorescently labelled cisplatin into hair cells in neuromasts of zebra-fish lateral line (a model system for screening for ototoxic drugs).[177] Thus, it is possible that, like aminoglycosides, cisplatin gains entry to endolymph from the SV, and an affinity for the hair cell transduction channel may underlie its specific action upon hair cells, but there is no conclusive evidence for this.

Once inside a cell cisplatin leads to cross-linking of nuclear DNA, which in proliferating cells, such as those of tumours, inhibits DNA synthesis, induces cell cycle arrest, suppresses transcription and ultimately leads to apoptosis. The majority of cells in the inner ear into which cisplatin enters are, however, non-proliferative. Nevertheless, damage to DNA is likely to occur which will activate DNA repair mechanisms. Polymorphisms in genes for two DNA repair enzymes, ERCC2 and XPC, have been associated as risk factors for cisplatin-induced hearing loss,[120, 152, 153] but the mechanisms underlying such risk are not clear. Cisplatin also binds to several other molecules, perhaps most significantly to sulphhydryl-containing molecules such as metallothineins and glutathione that scavenge free radicals and thereby it negatively affects redox balance. The binding to glutathione upsets the turnover and cisplatin ototoxicity correlates with a decrease in cochlear glutathione and significant decrease in the activity of glutathione peroxidise and glutathione reductase in cochlear tissues.[178] In addition, variants in the glutathione-5-transferase gene show a significant association with cisplatin ototoxicity.[17] Hearing loss in children receiving cisplatin has also been associated with genetic variants in two genes that encode enzymes in the methionine pathway that is involved in maintaining glutathione levels, thiopurine-5-methyltransferase (TPMT) and catechol-O-methyltransferase (COMT).[17, 179] Interference with antioxidant systems in the cochlea would lead to accumulation of free radicals and the consequent death of the hair cells though cisplatin may additionally cause generation of excess ROS,[120] possibly though effects in mitochondria.[153] However, there is evidence that agents

such as d-methionine and 4-methylbenzoic acid, which enable maintenance of glutathione levels or preserve the activity of associated enzyme systems, may be effective in preventing the ototoxic effects of cisplatin *in vivo* and clinical trials have been initiated.[152, 167, 180]

Interactions

Noise and cisplatin. There is some evidence, primarily from experimental studies in animals, that noise exposures above about 70 dB concurrent with cisplatin administration can induce hearing impairments and hair cell loss much greater than those expected from either the noise exposure conditions or cisplatin dosing regime alone.[181] In addition, cisplatin treatment appears to increase susceptibility to noise-induced hearing impairment and hair cell loss at prolonged periods after the end of cisplatin treatment.[182] Increased susceptibility to hearing loss in patients who have received cisplatin even some years prior to noise exposure has also been reported.[183] This may be a reflection of the long persistence of platinum in the body and might suggest prolonged suppression of antioxidant mechanisms. It argues for cautioning patients who have received cisplatin and perhaps long-term audiological follow-up.

Diuretics and cisplatin. Like aminoglycosides, a single dose of a loop diuretic administered shortly before or shortly after a single administration of cisplatin leads to extensive and quite rapid hearing loss and death of outer hair cells.[159, 184, 185] The underlying reason for this is likely to be similar to that with aminoglycoside–diuretic combination, the decline in EP enhancing uptake of the cisplatin into endolymph.

ORGANIC SOLVENTS

Exposure to high concentrations of organic solvents induce acute, reversible narcosis and neurotoxicity, but the possibility of ototoxic damage was initially recognized from the unusually high number of workers in the chemical industry who showed a hearing loss, and from case reports of hearing deficits in solvent abusers.[186] The effects of solvents may be exacerbated by concurrent exposure to high noise levels, or the converse, i.e. noise-induced hearing loss becoming more pronounced with concomitant exposure to certain solvents presenting a significant occupational hazard.[187, 188] Vestibular dysfunction may also follow from exposure to organic solvents but this may result from specific effects on vestibulo-oculomotor pathways in the vestibulocerebellum rather than from effects in the inner ear.[188] This would be classified as neurotoxicity rather than ototoxicity for the definitions used in this chapter.

A number of different aromatic solvents have been implicated in ototoxicity,[186] and in a comparative study conducted in rats of 21 different solvents 8 were identified as ototoxic: toluene, p-xylene, ethylbenzene, n-propylbenzene, styrene, ά-methylstyrene, *trans*-β-methylstyrene and allylbenzene.[189] Trichlroethylene has also been reported to be ototoxic.[190, 191] The features of the ototoxicity caused by all these agent are similar and are exemplified by the effects of toluene following exposure by inhalation in rats.[192] ABR and behavioural audiometry revealed auditory deficits after repeated exposures to high doses for periods of 2–16 weeks. Similar results were subsequently obtained after subcutaneous administration. Concomitant with the permanent hearing loss that results, OHCs are lost.[192, 193] Suppression of otoacoutic emissions by toluene confirms the OHCs as a site of injury *in vivo*.[194] However, unlike the ototoxins discussed above, the characteristic features of damage caused by toluene are:

- It is the mid-frequency ranges of hearing that are affected rather than the high frequencies,[190, 194] which coincides with HC loss in the middle and apical turns of the organ of Corti.[193–195]
- There is a distinct spread of damage from the third (outermost) row of OHCs inwards to involve subsequently the second and maybe the first row of OHCs. Additionally, the supporting cells, especially the third (outermost) row of Deiters cells, are affected.[193]

These features are characteristic effects of all the solvents implicated in ototoxicity.[189–191, 196, 197] The cell bodies of the afferent neurones may also be a target of trichloroethylene.[191] However, there are species differences in ototoxic susceptibility to solvents. While rats have proved to be sensitive, organic solvents do not cause damage in the inner ears of guinea pigs[198, 199] or chinchillas.[200] This obviously raises questions about the use of particular species of animals as models for the likely conditions in humans. However, it has been argued that the way solvents are distributed and metabolized in rats is similar to the human and thus that these animals are an appropriate model.[196]

Since organic solvents are minimally water-soluble their distribution in the inner ear is unlikely to be determined by entry into the fluid spaces. It is their distribution in the tissue that is significant. The pattern of damage across the organ of Corti, from outside to in, has suggested that the solvents reach the inner ear from the vasculature of the SV or the spiral prominence region just below it and then pass through the tissues to the organ of Corti.[196, 201] The cuboidal cells of the outer sulcus and the epithelial cells that connect the epithelia of the lateral wall to the organ of Corti along the basilar membrane may be a major transport route.[201] Upon reaching the organ of Corti, the supporting cells of the organ of Corti, the Hensen's cells that form the outer ridge of the sensory epithelium and the Deiters' cells that surround the hair cells, may then become injured. Deiters' cells, in particular those in the outermost row, have been reported to be the most vulnerable cells in the organ of Corti following styrene administration.[197, 202] The supporting cells are involved in the reuptake of K^+ from around the hair cells, and damage to these cells may therefore result in excessive K^+ levels around the OHC that would lead to their death. The effects of the solvents may be upon the membranes of the supporting cells and of the hair cells themselves. Loss of membrane integrity and cell swelling, perhaps as a consequence of membrane damage,

have been described as early events in the progression of damage in the organ of Corti. Whether the cell death is principally apoptotic[202] or necrotic[196] is contentious, but it has been reported that the death of Deiters' cells, unlike that of hair cells, is not prevented by antioxidants, suggesting that different mechanisms of cell death operate in the two cell types.[197]

Why damage is initiated in the middle frequency region of the cochlea is not clear. It may be of significance that the SV in the middle and apical cochlear turns is affected by trimethyltin,[203] perhaps indicating some characteristic of the vascular pathways and blood flow that may influence solvent distribution.

OTHER OTOTOXIC AGENTS

Good evidence for the ototoxicity of many of the other drugs listed in **Table 59.1** is relatively sparse. Vancomycin has been reported to cause transient hearing loss and/or tinnitus but many of these clinical reports derive from cases in which it has been used in combination with other potentially ototoxic drugs. The few experimental studies which have been performed suggest no loss of hair cells or permanent hearing impairment from systemic administration of polypeptide antibiotics even at very high doses.[204] Viomycin has been reported to be predominantly vestibulotoxic following chronic treatment regimes,[205, 206] and animal studies have confirmed that, after repeated systemic injections of relatively high doses, viomycin causes hair cell death in the vestibular sensory organs in a pattern similar to that seen with aminoglycosides.[207] Chloramphenicol has been shown to cause irreversible hearing loss following infusion into the middle ear cavity in animals,[208] presumably gaining access to the perilymph following uptake across the round window membrane, but clinical reports of hearing loss following use of chloramphenicol are rare. Polymyxin B when perfused through the perilymphatic spaces caused an almost immediate decline in cochlear microphonic (CM) potential followed shortly after by a decline in EP, suggesting separate effects on both the organ of Corti and the SV.[209] However, the rarity of clinical reports in which an ototoxic effect can be attributed directly to polymyxin B suggests the use of this antibiotic does not present a significant risk to the inner ear. Desferrioxamine (deferoxamine mesylate (DFO)) binds iron and is used in patients with β-thalassaemia to remove excess iron from the serum. In cultured explants of inner ear sensory epithelia DFO attenuates aminoglycoside-induced hair cell loss.[112] However, repeated high-dose systemic administration of DFO to patients has been reported to cause high-frequency hearing loss in about 20–40% of those receiving long-term therapy.[210–212] On the other hand, other clinical studies failed to identify a direct ototoxic effect of DFO[213, 214] and experimental studies with a mammalian model (chinchilla) could find no effects on cochlear physiology following long-term systemic treatment.[215] The reasons for these apparent discrepancies have not been resolved. Differences between experimental models may derive from the differences in susceptibility between species, known to be the case for aminoglycosides (above), and differing treatment regimes and/or patient groups may account for differences in clinical reports.[211, 216]

The reports of ototoxicity following the use of other agents listed in **Table 59.1** are often anecdotal and there are no rigorous, well-controlled clinical studies or experimental studies in animal models to confirm and define the ototoxic effects.

FUTURE RESEARCH

- Identification of the cellular stress mechanisms that lead to hair-cell death.
- Therapeutic interventions to inhibit stress-activated pathways or cell-death pathways.

KEY POINTS

- Ototoxic agents may affect hair cells directly; or ion-transporting epithelia and cochlear homeostasis; or both.
- Agents that affect stria vascularis (e.g. loop diuretics) cause temporary hearing impairment across all frequencies through inhibition of endocochlear potential.
- Agents such as salicylate and quinine that gain rapid access to perilymph, cause reversible hearing loss across all frequencies.
- Aminoglycoside antibiotics and *cis*-platinum cause permanent hearing loss that spreads progressively from high to low frequencies following chronic treatment regimes.
- Aminoglycosides and *cis*-platinum also cause vestibular dysfunction.
- Aminoglycosides and *cis*-platinum cause hair-cell death resulting in permanent hearing loss (and balance dysfunction).
- Hair-cell death follows entry of drug into endolymph and then into hair cells across the luminal surface of the cell probably via the transduction channels.
- One factor underlying hair-cell death may be production of excess free-radicals to toxic levels following aminoglycoside or *cis*-platinum challenges.
- Aminoglycosides and *cis*-platinum may cause atrophy of the stria vascularis. *Cis*-platinum may also have direct damaging effects on spiral ganglion neurones.
- Organic solvents (e.g. toluene, xylene, styrene) also cause hair-cell death and permanent hearing loss.
- Pattern of hair cell and hearing loss with organic solvents different from aminoglycosides and *cis*-platinum: lower middle cochlear turn and mid-range frequencies first affected, damage spreading progressively to lower and higher frequencies (apically and basally respectively along the cochlea).
- Various interactions – aminoglycosides with loop diuretics or with noise; *cis*-platinum with loop diuretic or noise; organic solvents with noise – produced greater damage and functional impairment than either agent alone.

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CHAPTER 60

IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS

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SEARCH STRATEGY

The data in this chapter are based on searches in Medline, Embase and CENTRAL for randomized controlled trials in idiopathic sudden sensorineural hearing loss (ISSNHL). The Cochrane ENT Disorders Group's specialist register of controlled trials was also searched for additional references to randomized controlled trials in ISSNHL. Keywords used were sensorineural hearing loss (SNHL), sudden sensorineural hearing loss (SSNHL), idiopathic sudden hearing loss (ISHL), idiopathic sudden sensorineural hearing loss (ISSNHL), randomized controlled trials, controlled clinical trial and random allocation.

INTRODUCTION

Sudden sensorineural hearing loss (SSNHL) is an otological emergency for which a definitive aetiology and treatment remains controversial, but prompt recognition and management have been shown to improve hearing outcomes and quality of life. The estimated annual incidence is 5–30 per 100 000 persons[1–4] and 99% of cases are unilateral.[5]

The definition is a hearing loss of 30 dB or more, over at least three contiguous audiometric frequencies, that develops over 72 hours or less.[1,2,6] There is a long list of possible causes, but the vast majority of cases are idiopathic. The aetiology is identified in less than 5–10% of cases. Factors including autoimmunity, vascular insult and viral infection have been postulated in the pathogenesis. The low incidence and high spontaneous recovery rate of between 32% and 65%[2,7,8] have made the validation of empirical treatments difficult. In the literature there are large numbers of case series regarding treatments but a relative lack of large randomized controlled trials assessing interventions, as a result of which there has been a wide variation in management of SSNHL to date. The recent development of evidence based clinical practice guidelines for SSNHL[6] should begin to address the heterogeneity in clinical practice. Steroid treatment (either systemic or via transtympanic injection) or hyperbaric oxygen treatments are advocated, but many other treatment regimes have been explored.

SSNHL often affects healthy individuals and is a frightening symptom that prompts the individual to seek urgent medical attention. There is a wide age distribution with an average of 50–60 years and no sex preference.[9] Early recognition and prompt management of SSNHL may improve hearing recovery and the quality of life of the individual.

DEFINITION

SSNHL was described in the literature by De Kleyn in 1944.[10] The following definition is currently accepted in the literature and in clinical practice:

- Sudden hearing loss is defined as the rapid onset, occurring over a 72-hour period, of a subjective sensation of hearing impairment on one or both ears.
- The audiometric criteria of a 30 dB sensorineural loss in at least three consecutive frequencies can be difficult to show clinically as premorbid audiometry is rarely available. Therefore the hearing loss is defined in relation to the contralateral side.
- Idiopathic sudden sensorineural hearing loss is defined as SSNHL with no identifiable cause in spite of thorough investigation.

Clinicians must decide the degree of certainty they are comfortable with when making a decision that the hearing loss is 'new'. There are four levels of 'certainty' about the 'newness' of the hearing loss in the affected ear:

1. Very certain: patient had previous audiometric evaluation.
2. Certain: patient had no prior otologic history and feels his or her premorbid hearing was normal bilaterally.
3. Fairly certain: patient had a long-standing hearing problem and reports that the current episode of SSNHL is subjectively poorer.
4. Uncertain: the clinician feels there was some pre-existing hearing loss, but the hearing loss was never documented.[11]

It is important to differentiate between SSNHL and other causes of SNHL so that early diagnosis and management can be instigated. The possible identifiable causes of SNHL can be divided into the following categories: infectious, traumatic, neoplastic, autoimmune, toxic, circulatory, neurologic and metabolic (**Box 60.1**). The most pressing of these are acoustic neuroma, stroke and malignancy.[12] Despite the long list of possible causes the vast majority of cases are idiopathic.

CAUSES OF IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS

Several factors have been postulated as central to the aetiology of idiopathic sudden sensorineural hearing loss (ISSNHL). Possible causes include labyrinthine viral infection, vascular insult, intracochlear membrane rupture and autoimmune inner-ear disease.

Viral

Viruses, particularly the herpes family, can cause SNHL in acute infection and it is possible that reactivation of the latent virus could cause SSNHL.[13–15] However, the serological evidence for a viral aetiology in SSNHL is conflicting. Wilson et al. found patients with SSNHL to have a statistically significant increase in seroconversion for cytomegalovirus (CMV), influenza B, mumps, rubella or varicella zoster, and 63% of 122 patients had evidence of seroconversion.[16] In contrast, Xenellis et al. showed seroconversion in only 27% of 262 patients with SSNHL for Epstein–Barr virus (EBV), herpes simplex virus (HSV) I and II or CMV.[17] In a smaller study of 48 patients Gross et al. reported positive serology for EBV in 6% and enterovirus in 2%.[18] Mentel et al. studied 55 patients with SSNHL for serconversion to enterovirus, HSV and varicella zoster virus (VZV). They found seroconversion rates of 40% to enterovirus but no evidence of HSV or VZV seroconversion.[19] More recently a large Taiwanese population-based study investigated the frequency and risk for SSNHL following a recent herpes zoster attack in the general population. The results showed that SSNHL is a rare event in the 2 months following an attack of herpes zoster, and the risk of developing SSNHL is not increased among people who have had a recent herpes zoster infection compared with a matching population.[20]

BOX 60.1 Possible causes of sensorineural hearing loss

Infectious	Traumatic	Neoplastic	Autoimmune
Meningococcal meningitis Encephalitis Herpes virus (simplex, zoster, varicella, cytomegalovirus) Mumps Measles Human immunodeficiency virus Lyme disease Rubella Syphilis Toxoplasmosis	Barotrauma Perilymph fistula Intense noise exposure Inner ear decompression sickness Temporal bone fracture Ear surgery (stapedectomy)	Cerebellopontine angle tumours, e.g. acoustic neuroma meningioma Leukaemia Myeloma	Wegener's granulomatosis Rheumatoid arthritis Sjögren's syndrome Polyarteritis nodosa Relapsing polychondritis Lupus erythematosus Ulcerative colitis Cogan's syndrome Antiphospholipid syndrome Sarcoid Autoimmune inner-ear disease (AIED)
Toxic	**Circulatory**	**Neurologic**	**Metabolic**
Aminoglycoside antibiotics Loop diuretics NSAIDs Salicylates Platinum-based chemotherapeutic agents General anaesthesia	Vascular disease/alteration of microcirculation Vascular disease associated with mitochondriopathy Vertebrobasilar insufficiency Red blood cell deformability Sickle-cell disease Cardiopulmonary bypass	Multiple sclerosis Focal pontine ischemia Migraine	Hyperlipidaemia Thyrotoxicosis Diabetes

Examination of temporal bones reveals histopathological evidence which is consistent with viral infection in patients with SSNHL.[21,22] There was shown to be greater loss of neurons in the apical spiral ganglion compared to the basal region without corresponding loss of hair cells and dendrites. This suggests a viral cause since other conditions such as hypoxia, acoustic trauma, presbyacusis and hereditary conditions would result in changes at the basal region. Animal studies experimentally inducing a vascular cause of hearing loss have resulted in cochlear fibrosis and inner ear ossification, which has not been seen in the temporal bone studies of SSNHL patients.[23] Animal experiments have demonstrated viral penetration of the inner ear,[24] and the isolation of virus and viral antigens in perilymph of affected patients provides further evidence for the viral aetiology.

Many similarities have been drawn between SSNHL and Bell's palsy, both neurological conditions with a sudden onset and their symptoms that can be improved with steroid treatment. However, in Bell's palsy a viral aetiology has been demonstrated following the identification of virus in the endoneural fluid of the facial nerve in effected patients.[25] Although a viral aetiology has been hypothesized in SSNHL, the epidemiological, serological and histopathological evidence is inconclusive.

Vascular

The cochlea is supplied by an end artery, and hence is susceptible to damage by vascular occlusion, making a vascular cause for ISSNHL a popular theory. Many treatments to date have been recommended because they are thought to improve cochlear blood flow. Changes in blood viscosity could lead to cochlear ischaemia and hearing loss. However, patients with ISSNHL are no more likely than the general population to have a hyperviscosity disorder.

Ballesteros et al. evaluated 99 patients with SSNHL for thrombophilic genetic polymorphisms and coagulation studies associated with vascular disorders but did not find a significant difference between patients and controls.[26] However, Capaccio et al. investigated 100 patients with SSNHL for five prothrombotic genetic polymorphisms and found a statistically significant association between the incidence of these polymorphisms in the patient group when compared to the control population.[27] In another study by Capaccio ten patients with SSNHL and previously documented cardiovascular disease were found to have a significantly higher number of thrombophilic allelic mutations when compared to the previous 100 SSNHL patients with no history of cardiovascular disease. Einer et al. reviewed a number of haemostatic parameters in 32 SSNHL patients compared to controls.[28] They concluded that, although isolated aberrations in the haemostatic pathway were observed, these were not of decisive importance for the pathogenesis of sudden deafness.

Isolated case series have reported that patients with sickle-cell anaemia and Waldenstrom macroglobulinaemia have a higher risk of SSNHL, but this is usually reversible with treatment.[29,30] Strokes involving the anterior inferior cerebellar artery are associated with auditory and vestibular symptoms, but also cerebellar symptoms. The risk of stroke is also said to be higher in the SSNHL population.[31] In addition, SSNHL following cardiopulmonary bypass has also been reported.[32] Many of these are small studies, however, and there is a lack of experimental, histological and clinical evidence to support this theory.

Intracochlear membrane rupture

Rupture of the intracochlear membrane was proposed as a cause of sudden hearing loss but the evidence is only coincidental and studies looking at temporal bones of patients with SSNHL found no evidence of Reissner or basilar membrane rupture.[21]

Autoimmune

Historically the inner ear has been regarded as an immunoprivileged site, separated by the blood labyrinthine barrier. However, we now know that immunoglobulins (predominantly IgG) are found in the perilymph at a fraction of their serum concentrations.[33] The endolymphatic sac is thought to be the likely site for immune processing due to the presence of lymphocytes in the perisaccular tissues.[34]

SNHL has been reported in many systemic autoimmune disorders such as Wegener's granulomatosis,[35] rheumatoid arthritis,[36] polyarteritis nodosum,[37] Sjögren's syndrome,[38] Cogan's syndrome,[39] systemic lupus erythematosus,[40] ulcerative colitis[41] and relapsing polychondritis.[42] This provides some evidence that autoimmunity can damage the inner ear although it does not address organ-specific disease and an audiological investigation of patients suffering well-characterized systemic lupus erythematosus (SLE) found no significantly worse hearing than age, sex and socioeconomically matched controls.[43]

In 1979 McCabe described autoimmune inner-ear disease (AIED) a rapidly progressive bilateral SNHL that responded to steroid therapy. The cause is thought to be antibodies or immune cells that damage the inner ear and there are several theories as to how these may arise.[44]

Yoo et al. reported that rodents injected with type II collagen developed new-onset SNHL and pathologic cochlear changes that appear to be immune-mediated.[45,46] However, a more recent study found the incidence of anti type II collagen antibodies to be very low and disputed it as a cause of AIED.[47]

Harris and Sharp used bovine inner-ear extract as antigen in Western blot assays and detected antibody to a 68 kDa antigen in 35% of patients with progressive SNHL.[48] This is now known to represent the ubiquitous rather than inner ear-specific highly inducible heat shock protein 70 (hsp70).[49] Although hsp70 antibodies are elevated in autoimmune SNHL, they are not thought to be the underlying cause of hearing loss.[50] The frequency of antibodies against hsp70 is not different in patients and controls and therefore it is not useful in the diagnosis of AIED.[51] The presence of antibodies to hsp70 found

in AIED patients has been correlated to responsiveness to steroid treatment.[52] The sensitivity and specificity of anti-hsp70 for the diagnosis of AIED was 42% and 90% respectively, and their positive predictive value 91%.[53] Further research is required to understand the aetiology of AIED fully and to develop diagnostic tests.[54]

Damage to the inner ear results in the release of cytokines, which trigger immune reactions. TNF-alpha, IL-1A, NFkB and IkBa have all been found in the cochlea.[55]

Activation of cochlear nuclear factor kappa B (NFKB) has been proposed as a mechanism of SSNHL as it would account for clinical and histological observations, but there is no direct evidence.[23]

The inner ear may share common antigens with potentially harmful substances and T-cells and antibodies may damage the inner ear when trying to fight these antigens. COCH5B2 has been proposed as a target antigen.[56]

The basic problem with any autoimmune theory for ISSNHL is that one would expect an immune condition to affect both ears and ISSNHL is usually unilateral.

Ménière's disease

The first presentation of Ménière's disease may be as SSNHL and therefore it is important to consider in the differential diagnosis. The classic triad of Ménière's is episodic vertigo, tinnitus and deafness. The aetiology is unknown and theories include autoimmune activation and labyrinthine ischaemia. Patients develop endolymphatic hydrops, which results in the classical symptoms. The audiogram classically shows a low-frequency hearing loss.

While there have been a number of proposed aetiological theories, it is possible that they are not mutually exclusive; for example, a viral insult can cause direct neural injury, direct vascular structure injury or direct injury to erythrocytes, leading to secondary microvascular insufficiency. Viruses can also lead to inflammation resulting in vascular insufficiency. Autoimmune disease can lead to vasculitis through antiendothelial cell antibodies.

CLINICAL ASSESSMENT

History

The aim in evaluating any patient with SSNHL is to identify any treatable causes.

It is important to cover the following key points in the history:

- The onset of the hearing loss. Patients with SSNHL often first notice their hearing loss on awakening in the morning and a better prognosis is associated with a short history.
- Sudden onset of blockage or fullness warrants prompt investigation. SSNHL often presents as a full or blocked ear. As this is a common and non-specific symptom it can be underestimated by both patients and clinicians, thus leading to a delay in evaluation and treatment.
- The premorbid hearing level. SSNHL can be either a new loss or an incremental deterioration in an ear with a pre-existing loss. Conditions such as Ménière's disease can cause sudden fluctuations in hearing.
- A poorer prognosis is associated with increasingly profound hearing loss.
- Is the loss unilateral or bilateral? Unilateral loss is commoner but autoimmune disease and ototoxicity are more likely to be bilateral.
- Associated symptoms such as tinnitus, vertigo, dizziness and aural fullness should be asked about and may point to a diagnosis of endolympatic hydrops. Vertigo is present in 30–40% of cases of SSNHL[57, 58] and is a poor prognostic indicator.
- SSNHL is frequently associated with tinnitus, which can cause significant anxiety and depression for patients. It is therefore important to recognize the psychological response to the sudden loss of hearing.
- Any history of trauma, straining, diving, flying and intense noise exposure should be noted. Patients should be questioned about previous or concurrent viral infections.
- A past medical history of other diseases associated with sudden hearing loss should be explored as SSNHL can rarely be the first presentation of a systemic disease.
- Any history of previous ear surgery should be noted.
- A full drug history should be elicited to rule out ototoxicity.

Examination

A complete examination of the head and neck should be carried out on all patients with SSNHL. Otoscopy should be performed to exclude middle ear effusions, infections, cholesteatoma and wax impaction. Tuning fork tests should be performed to distinguish a conductive hearing loss (CHL) from a SNHL.[59, 60] A fistula test may help identify a perilymph fistula. A thorough neurological examination of cranial nerves and cerebellar signs is essential.

Investigations

Audiometry must be performed and may give an indication of prognosis, as a downward sloping audiogram is associated with a poorer outcome.

An MRI scan with gadolinium enhancement should be performed to exclude an acoustic neuroma but is also useful in evaluating multiple sclerosis and cerebrovascular accidents. Around 10–20% of patients with acoustic neuromas will report a sudden decrease in their hearing at some point in their history.[61] However, the incidence of vestibular schwannoma in patients who present with SNHL is considerably lower but still noteworthy. Several studies have demonstrated a relatively high prevalence of cerebellopontine angle tumours in SNHL patients ranging from 2.7% to 10.2% of patients who are evaluated with MRI.[12, 62–66] When an MRI is contraindicated (i.e. pacemakers, other metallic implants, claustrophobia), a fine-cut CT of the temporal bones with contrast may be used.

Other investigations to rule out identifiable causes should be focused by the history. Bloods including FBC, ESR, urea and electrolytes, lipid profile, glucose, thyroid function tests, clotting screen, VDRL, serology for Lyme disease and autoantibodies (antinuclear antibodies, anti-cardiolipin antibodies, lupus anticoagulant, antineutrophil cytoplasmic antibodies) may be requested if clinically indicated. The American Academy of Otolaryngology – Head and Neck Surgery guideline makes a strong recommendation against routine laboratory testing.[6]

PROGNOSIS

Four factors have been shown to affect recovery from ISSNHL:[67]

- time since onset – the earlier the presentation the better the prognosis
- age – there is a worse prognosis in the over 60s
- vertigo – a poor prognostic indicator
- audiogram – patients with profound hearing loss and a downward-sloping audiogram have a poorer prognosis.

It is important to reassure patients that around 50% of cases have spontaneous recovery with no treatment. Due to the lack of evidence for any single treatment the risks and benefits of each treatment should be discussed with the patient to enable them to reach an informed decision about their care. Patients should be followed up to monitor for delayed symptoms, and audiograms should be repeated. Evidence shows that improvement rate in the first 2 weeks may predict long-term outcome.[68, 69]

Long-term follow-up is recommended as some patients will have an underlying cause identified that is not evident at initial presentation.[62] Also patients with limited or no hearing recovery or persistent tinnitus will require ongoing support from the audiological and psychological services.[70]

Unilateral SNHL has a significant impact on patients' quality of life.[71] So too does SSNHL and perhaps more so, especially if dizziness and significant tinnitus are suddenly present.[72–74]

TREATMENT

The high spontaneous recovery rate for ISSNHL and its low incidence make validation of empirical treatment difficult. Many treatment regimens have been proposed (Table 60.1).

TABLE 60.1 Proposed treatment regimes for ISSNHL

Treatment	Examples
Anti-inflammatory/ immunosuppression	Steroids[2, 75] Prostacyclin[76]
Antiviral agents	Acyclovir[77, 78] Valcyclovir[79]
Vasodilators 5% carbon dioxide with 95% oxygen (Carbogen)[75,80]	Papaverine[80] Pentoxifylline[81–83]
Volume expanders/haemodilutors	Hydroxyethyl starch[82, 84] Dextran[80, 82, 85]
Calcium antagonists	Nifedipine[86]
Other agents and procedures	Iron[87] Vitamins[86, 88] Procaine[85] Hyperbaric oxygen[89, 90] Gingko biloba[81] Zinc[91] Co-enzyme Q10[92]

Steroids

SYSTEMIC STEROIDS

Steroid therapy is widely used as the standard treatment for SSNHL, although systematic reviews and meta-analyses have revealed no evidence of benefit of steroids over placebo.[7, 93–95] The evidence for steroids comes from Wilson et al. who found that steroids had a significant effect on the recovery of hearing in patients with hearing loss of 40–90 dB.[2] Moskowitz et al. confirmed Wilson's findings in 1984.[96] However, the methodology of these studies has been criticized.[93] Cinamon et al. compared treatment with prednisolone, placebo, carbogen and room air inhalations and found no significant differences between the four groups.[75] Nosrati-Zarenoe et al. performed a prospective randomized, triple-blind, placebo-controlled trial comparing oral steroids to placebo in 103 patients. Prednisolone or placebo was given at 60 mg/day for 3 days then 10 mg less each day until day 8. The results showed no significant difference in hearing improvement.[97]

A more recent meta-analysis of various medical treatments, including corticosteroids, showed a slight but not statistically significant improvement with medical therapy compared to placebo.[98]

Risk vs benefit of oral corticosteroid therapy

In view of the limited evidence to support steroid therapy in the treatment of ISSNHL, clinicians must weigh up the risks and benefits of the treatment for an individual patient. Although the evidence for corticosteroids is limited, it is one of the few treatments with demonstrated efficacy.[2, 77, 96, 99–104] In view of the significant devastating impact of a severe to profound SSNHL on an often otherwise healthy patient, the treatment should be considered.

Spontaneous improvement in hearing is most likely to occur during the first 2 weeks;[8] late recovery has been reported but is rare. Early corticosteroid treatment within the first 2 weeks is associated with the greatest hearing recovery, with minimal benefit after 4–6 weeks.[57, 103, 105–107]

Dose

The best treatment outcomes are associated with a single dose of oral prednisolone of 1 mg/kg/day, up to a maximum of 60 mg daily, for 10–14 days.[6] This is based on

the maximum adrenal output of hydrocortisone (cortisol), which is 200–300 mg/day during stress. Prednisolone is 4 times, methylprednisolone is 5 times, and dexamethasone is 25 times more powerful than hydrocortisone. A dose of 60 mg prednisolone is equivalent to 48 mg methylprednisolone and 10 mg dexamethasone.

Complications of systemic steroid treatment

Systemic corticosteroids have a wide range of potential side effects as they affect many organ systems. They can suppress the hypothalamic–pituitary–adrenal function causing Cushing's syndrome.[108] Possible side effects of corticosteroid use are given in **Box 60.2**.

In view of the associated side effects and limited evidence for efficacy, systemic corticosteroids may not be an appropriate treatment for patients with increased risk of complications. For example, these will include those with insulin-dependent or poorly controlled diabetes, labile hypertension, tuberculosis, peptic ulcer disease and prior psychiatric reactions to corticosteroids.[109] The severe side effects are typically associated with long-term high-dose usage and adverse events are rare with the short 10- to 14-day course of steroids recommended for SSNHL.

Super high-dose steroid therapy has shown greater hearing recovery than standard dose treatment but further research is required.[110] Caution should be taken when prescribing very high-dose steroids to reduce the risk of serious complications.

INTRATYMPANIC CORTICOSTEROIDS

Intratympanic (IT) steroid therapy is gaining popularity as a treatment for SSNHL, particularly in refractory cases or those in which systemic steroids may be hazardous, but again evidence is lacking.[100, 111–113] There have been many small studies, often with very small numbers, but many are retrospective, without controls, and the steroid dosage, delivery method and frequency of injection have varied considerably, making it difficult to assess and compare outcomes. The main advantage of IT treatment is the reduction in systemic corticosteroid side effects. IT steroids very rarely cause changes in serum glucose levels in patients with diabetes.[114] They may also be given to patients with cataracts, myasthenia gravis and glaucoma.[115]

BOX 60.2 Possible side effects of corticosteroid use

Possible side effects with short-term use	Severe but rare side effects
Gastritis	Pancreatitis
Increased blood sugar	Bleeding
Increased hunger	Cataracts
Behaviour changes, insomnia, irritability	Myopathy
Weight gain, salt and water retention	Avascular necrosis of humeral and femoral heads
High blood pressure	Diabetes
	Osteoporosis
	Opportunistic infections[108]

IT injection is associated with higher inner ear steroid levels[116, 117] so many authors have explored its use in the treatment of SSNHL. An early prospective study using IT steroids in patients with profound ISSNHL found only 3 of 25 patients had hearing improvement.[118] However, another study combining a high-dose prednisolone taper with IT steroids resulted in partial or complete hearing recovery in 14 out of 16 patients.[119] Three separate randomized controlled trials comparing IT + oral steroids with oral steroids alone found that the addition of IT steroids did not show a significant benefit when compared to corticosteroids alone, although there was a trend towards greater improvement with the combination therapy.[120–122] Filipo et al. investigated IT steroids as the sole initial treatment in SSNHL and showed improvement in 31 out of 34 patients.[123] The same author went on to compare IT steroid with IT saline in a randomized controlled trial and found a significant improvement in hearing in the steroid group compared to the control.[124] Dispenza et al. compared IT with oral steroids and found no significant difference between the two groups.[125] Lim et al. compared the efficacy of three different steroid treatments: IT, IT + oral steroids, and oral steroids alone. Their results showed similar hearing recovery rates in all three groups.[126] The efficacy of simultaneous versus subsequent IT steroid with oral steroids has also been studied. The results showed that the administration of simultaneous IT steroid with oral steroid did not confer additional hearing gain or earlier recovery rate over those that had subsequent treatment with IT steroid.[127] A systematic review concluded that IT steroids can be a valuable solution for patients with ISSNHL who either cannot tolerate systemic steroid therapy or are refractory to it.[114, 128, 129]

Choice of steroid and dose

The most frequently administered IT steroids are dexamethasone and solumedrol (methyl prednisolone sodium succinate). The research shows a wide variation in the concentration given. Most studies quote doses of 10–24 mg/mL dexamethasone and 30–40 mg/mL solumedrol. Higher concentrations may have better outcomes.

Use of facilitator

Improved transport across the round window membrane has been demonstrated in laboratory studies with the addition of facilitator agents such as histamine and hyaluronic acid.[130, 131]

Frequency and injection technique

Studies vary widely in the frequency of IT steroid injection, from self-administration several times a day by the patient across a grommet, to clinician administered on consecutive days, to weekly. A variety of methods of administration have been reported, via a spinal needle on a syringe, through a grommet or myringotomy, via a MicroWick or microcatheter,[132] hydrogel applications, and nanoparticles. Transtympanic needle or grommets are the most frequently used.[133] IT steroids have been used as

the primary treatment, in combination with other therapies and as salvage treatment.

Complications of IT steroids

Even though IT steroids are widely used in clinical practice they are associated with an inconsistent clinical response.[134] This is due to the wide variability in diffusion across the round window membrane leading to unpredictable intracochlear bioavailability. This variability is further exacerbated by any inflammation or scar tissue in the round window niche.[135, 136] Adverse effects with IT steroids are infrequent but include pain, transient dizziness, infection, persistent tympanic membrane perforation, possible vasovagal episode during injection, and the need for repeat visits. The main risk appears to be a persistent tympanic membrane perforation at the injection site.

The largest randomized controlled trial comparing oral versus IT steroid therapy for ISSNHL was conducted at 16 centres and recruited 250 patients.[137] All patients were recruited within 14 days of onset of their SSNHL and followed up for 6 months. The first group, of 121 patients, received 60 mg/day of oral prednisone for 14 days with a 5-day taper; the other 129 patients received four doses over 14 days of 40 mg/mL of methylprednisolone injected into the middle ear. The results showed that, for initial therapy of SSNHL, promptly administered and equivalently dosed oral and IT steroid appeared to be equally effective, with hearing improvement seen in more than 75% of treated patients. Since the results for the two groups were equivalent, decisions on the choice of treatment for an individual should be based upon the risk of potential side effects and cost. Side effects were reported by 88% of the oral group, such as elevated blood sugar, increased thirst, and sleep or appetite changes, and 90% of the IT group, such as transient pain at the injection site and brief caloric vertigo. These were the anticipated manageable side effects, most of which were resolved within 1–2 weeks.

HYPERBARIC OXYGEN

Impairment of vascular supply and the resulting cochlear ischaemia is one of the proposed aetiologies for SSNHL. Hyperbaric oxygen therapy (HBOT) delivers 100% oxygen to a patient at a pressure greater than 1 atmosphere. This results in an increase in tissue oxygenation as well as potentiating the response to infection and ischaemia.[138]

HBOT has been used in the treatment of SSNHL since the 1960s.[90] Since then, numerous studies have investigated the use of HBOT in SSNHL, although very few have been prospective randomized controlled trials. The most recent Cochrane review included seven identified randomized controlled trials, published between 1985 and 2004.[139–145] The criterion used for determining significant benefit was a 50% improvement in hearing. Although the chance of a 50% improvement was not significantly increased following HBOT, the chance of a 25% increase was and the number needed to treat (NNT) to achieve one extra good outcome was five. For people with early presentation of ISSNHL, the application of HBOT significantly improved hearing loss, but the clinical significance of the level of improvement is not debatable. The data also suggested that improvement may be related to the severity of the hearing loss on presentation. However, further evidence is required from future randomized controlled trials.

A more recent prospective randomized control of HBOT for SSNHL[146] compared HBOT + oral steroid with oral steroid alone. Success was defined as hearing regained completely (>50 dB improvement) or moderately (10–50 dB improvement). The results showed no significant difference between the two groups and therefore did not support the addition of HBOT to oral steroids. HBOT has also been used in combination with IT steroids.[147] When HBOT + IT steroid was compared to HBOT + i.v. steroid, the overall success rate was higher in the IT steroid group but the result was not statistically significant.

Complications of HBOT

Complications are rare but include damage to ears, sinuses and lungs from pressure changes; temporary worsening of short-sightedness; claustrophobia; and oxygen poisoning. No significant adverse events were reported in the studies reviewed. In a large study (782 patients) looking at HBOT for a variety of indications, the most frequent complication was difficultly equalizing pressure in the middle ear, which occurred in 17% of patients.[148] Rates of Eustachian tube dysfunction of up to 45% have been reported in other studies of HBOT for a variety of indications.[149] Although the reported rates of Eustachian tube dysfunction are lower in patients undergoing HBOT for SSNHL, this may be a result of concurrent steroid treatment.[150] Another common complication of HBOT is claustrophobia while undergoing treatment.[148, 150]

Disadvantages of HBOT

HBOT is an expensive and time-consuming intervention that is not readily available. Therapy typically involves multiple sessions of 1–2 hours over days to weeks. Typical treatments have consisted of between five and ten sessions.

The evidence supports possible benefit of HBOT as an adjuvant treatment in cases of acute SSNHL when used within 3 months of the onset of the hearing loss, with potentially more benefit noted in cases of severe to profound loss.[6]

OTHER THERAPIES

Michel and Matthias compared intravenous prostacylin therapy with saline and found no significant difference between the groups.[76]

Acyclovir has been used for the treatment of SSNHL both alone and in conjunction with steroids but neither shows any significant improvement in hearing. Valcyclovir, although better bioavailability has also been used in conjunction with steroids but again offers no improvement above controls.[77–79]

Agents thought to increase cochlear blood flow, papaverine, pentoxifylline, hydroxyethyl starch, dextran, nifedipine and ginkgo biloba show no difference between active treatment and controls.[80–86]

Kronenberg et al. compared intravenous procaine, dextran and placebo and found no significant differences in outcomes.[85]

SALVAGE TREATMENT

For patients who are refractory to systemic steroid therapy, salvage therapy has become popular. Both IT steroid and HBOT have been investigated as salvage treatments.

There is now a large body of research investigating the use of IT steroid therapy in this setting, including numerous case series, a number of randomized controlled trials and a meta-analysis.[100, 112, 113, 116–118, 132, 151–155] The methodology in many of these studies has been criticized, however the majority do show improved hearing outcomes after IT steroid therapy with reported improvement rates ranging from 8% to 100%.[100, 122, 128, 129, 156–160]

The meta-analysis identified 184 studies of which five met the inclusion criteria and were analyzed.[112, 155, 161–163] There was a statistically significant greater improvement in hearing on pure-tone audiometry in patients who received salvage IT steroids than in those who did not.[154]

Side effects of IT steroids for salvage therapy were reported by four of the five studies. Minor side effects included transient dizziness, ear pain, and tinnitus. Of the 203 patients in these studies, three developed tympanic membrane perforation. Of the three, one healed spontaneously, one was treated successfully with a paper patch, and one required a myringoplasty (in this patient a round window catheter was used). No infective complications occurred.

The main limitation of this meta-analysis is the small number of trials involved. Although all the studies included were randomized controlled trials, only one was blinded and placebo-controlled. The subgroup analysis found that dexamethasone rather than methylprednisolone, administered via injections rather than a round window catheter, tended to demonstrate better outcomes. However, in view of the limitations of the analysis, further work is required to demonstrate this conclusively. While this meta-analysis showed a statistically significant improvement in hearing, the degree of clinical significance is questionable, as the improvement in audiological thresholds may not confer an improvement in usable hearing to the patient.

HBOT has also been successfully used in the treatment of refractory SSNHL.[152, 164–166] Recent studies have compared HBOT with IT steroids and with combined treatment of IT steroids + HBOT. Yang et al. found that IT steroid, HBOT and combination therapy all offered some benefit in hearing improvement but the largest gain in word recognition score (WRS) and recovery in hearing, especially in the lower frequencies, was seen with combination therapy.[153] However, the numbers in these studies was small.

OUTCOMES ASSESSMENT

In order to assess and compare outcomes there need to be standardized outcome measures. Unfortunately, for a long time there were no widely accepted standards, however 2006 guidelines from AAOHNS proposed recommendations for outcomes assessment.[167]

All patients diagnosed with ISSNHL need follow-up audiological assessment; this may reveal other aetiologies, as ISSNHL could be the first presentation of another condition. Also it will identify which patients have ongoing hearing loss and those who may benefit from hearing rehabilitation. Audiological assessment is important in determining the benefit of any given treatment and to identify those who may be suitable for salvage therapy.

Yeo et al. evaluated the long-term results for a 3 month retrospective series of 156 patients diagnosed with ISSNHL.[168] Of 121 patients who recovered over the 3 months of follow-up, 45.5% showed a delayed recovery after the end of 10-day course of therapy. Of these 55 patients, 78.2% recovered within 1 month, 5.5% recovered within 1–2 months, 12.7% recovered in 2–3 months, and 3.6% recovered later than 3 months after discharge. Only one patient showed any recovery beyond 6 months. In view of these results 6 months has been given as a reasonable follow-up period.

In patients with permanent hearing loss early discussion regarding rehabilitation options can reduce patient anxiety. Ideally, these discussions should take place when a hearing loss is first identified, as temporary aiding during treatment may be beneficial.

In order to assess the benefit of treatments for ISSNHL the audiological assessment should compare the pure-tone audiometry (PTA), speech recognition threshold (SRT) and/or WRS at each appointment following diagnosis. The evidence from this comes from a meta-analysis that reviewed 20 studies investigating a variety of treatments for ISSNHL. Although the treatments were diverse, the majority of studies used PTA, and/or WRS to monitor the effectiveness of treatment leading to recovery of hearing.[7]

Definition of recovery and improvement

In one of the early studies on SSNHL Wilson et al.[2] defined recovery as follows:

- **Complete:** if the follow-up PTA (dB HL) or SRT (dB HL) improved to within 10 dB of pre-sudden hearing loss hearing levels.
- **Partial:** if the follow-up PTA (dB HL) or SRT (dB HL) improved to within 50% of pre-sudden hearing loss hearing levels.
- **No recovery:** if the follow-up PTA (dB HL) or SRT (dB HL) was less than 50% of recovery of pre-sudden hearing loss hearing levels.

American Academy recommendations for outcomes assessment

The American Academy of Otolaryngology–Head and Neck Surgery (AAOHNS) makes the following recommendations for outcomes assessment:[6]

1. Unless a previous asymmetry of hearing was known or suspected, the unaffected ear should be used as the standard against which recovery should be compared;

2. a complete recovery requires return to within 10 dB HL of the unaffected ear and recovery of WRSs to within 5% to 10% of the unaffected ear;
3. partial recovery should be defined in two ways based on whether or not the degree of initial hearing loss after the event of SSNHL rendered the ear non-serviceable (based on the AAO-HNSF definition); and
4. anything less than a 10 dB HL improvement should be classified as no recovery.

Associated symptoms of tinnitus, sensation of fullness, vertigo, or nausea following treatment should also be recorded.

The problems with these strategies are that:

- although improvement in pure-tone threshold may be statistically significant, it may not be clinically significant
- there is often no pre-existing audiology.

Smyth and Patterson developed the 'Belfast Rule of Thumb' based on analysis of the relationship between the patient's perceived subjective benefit and post-operative audiometric changes. Although designed to look at hearing outcomes following surgery, it can equally be applied to determine the benefit to patients following treatment for ISSNHL. In order for the hearing gain to be appreciated by the patient, the hearing in the affected ear must be brought to 30 dB or better or to within 15 dB of the contralateral ear.[169]

CONCLUSION

The aetiology and treatment of SSNHL remains controversial. Current research supports several possible aetiologies and, although a variety of treatment options have been investigated, there is no clearly optimum management. Early steroid treatment, either systemic or intratympanic, is advocated, and HBOT may be useful within the first 3 months. There is, however, still a need for high-quality evidence and further research to determine the optimal management.

BEST CLINICAL PRACTICE

- ✓ Patients presenting with SSNHL should be investigated thoroughly.
- ✓ When it has been determined that a patient has probable or certain ISSNHL, the diagnostic uncertainty and management options should be discussed with the patient.
- ✓ The physician should use their expertise in evaluating the risks and benefits of any specific treatment in the light of the patient's individual medical status.

FUTURE RESEARCH

- ➤ The variability in diffusion across the round window membrane has led to a number of studies looking at:
  - ➤ the dose-dependent sensitivity of different hair cell types
  - ➤ pharmaceutical and surgical approaches to alter the permeability of the round window membrane
  - ➤ delayed drug release formulations to provide precise delivery of therapeutic agents into the inner ear.[170]
- ➤ The recent development of delayed-release gels placed on the round window membrane has the potential for continuous drug release[171] although they are still affected by the variable permeability of the membrane.[172] Microperforations in the round window membrane have been shown to be an effective means of increasing diffusion across the round window membrane.[173]
- ➤ The American Academy guidelines have highlighted the following areas in which further research is required:
  1. Investigation of the effectiveness of corticosteroid treatment vs a placebo.
  2. Further investigation of the benefit of HBOT. Current evidence looks promising; however, this is an expensive therapy and is not universally available. Standardised treatment protocols are needed.
  3. Develop standardised outcome criteria to aid the comparison of clinical studies.
  4. Further study the use of IT steroids as salvage therapy, particularly the optimal drugs, dosage, concentrations, and administration schedules for IT therapy.
  5. Develop criteria to determine at what level of hearing recovery IT steroids would be offered as salvage.
  6. Determine the percentage of patients who gain serviceable hearing as a result of treatment.
  7. Investigate the use of "combined therapy" (i.e. oral and IT steroids) in patients with ISSNHL.
  8. Develop long-term follow-up protocols for patients with ISSNHL.
  9. Evaluate therapies using standardised definitions and treatment protocols across studies.

KEY POINTS

- SSNHL is defined as a hearing loss of 30 dB or more, over at least three contiguous audiometric frequencies, that develops over 72 hours or less.
- The aetiology and treatment of SSNHL remain controversial, but prompt recognition and management have been shown to improve hearing outcomes and quality of life.
- Many alternative treatment strategies have been proposed.
- Steroid treatment (either systemic or via transtympanic injection) or hyperbaric oxygen treatments are advocated.

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CHAPTER 61

TINNITUS AND HYPERACUSIS

Don McFerran and John Phillips

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SEARCH STRATEGY

Data in this chapter may be updated by searches of Medline, EMBASE, the Cochrane Library and Clinical Evidence *BMJ* using the keywords tinnitus and hyperacusis, focusing on pathophysiology, diagnosis and treatment. The data are supplemented by hand searches of specialized books and proceedings from relevant meetings where tinnitus was the main subject. The evidence in this chapter covers all evidence levels.

INTRODUCTION

It is unusual to read any authoritative text or publication about tinnitus without the obligatory introductory paragraph that educates the reader of the etymology of the word 'tinnitus', usually quoting its classical derivation and citing Dennis McFadden's description of the term.[1] It is true that the word tinnitus originates from the Latin word *tinnire* (to ring) and McFadden's description of tinnitus as 'the conscious expression of a sound that originates in an involuntary manner in the head of its owner, or may appear to him to do so' is appropriate. However, there is a lot more to these standard definitions than are worthy of further explanation. In the 1950s, Heller and Bergman studied the descriptions of 180 subjects (80 with reportedly normal hearing and 100 with hearing impairment) who were interviewed regarding sounds that they perceived when introduced into a soundproof booth. Despite many subjects describing a 'ring', this was only one of 39 descriptions reported.[2] In reality, the sound perceived by the patient does not have to be ringing, does not have to be a continuous sound, and in some cases can even represent complex sounds such as musical tunes. As an interesting footnote to one of the most commonly cited tinnitus publications, McFadden was the chairman of a working group set up in the US by the Committee on Hearing, Bioacoustics, and Biomechanics (CHABA) and in his preface to the group's report wrote: 'A number of my friends have noted that tinnitus is an unlikely topic for me to be reviewing and critiquing, and I am the first to agree. I do not consider myself to be an expert on tinnitus: I have never done research on the topic, nor have I ever seen a tinnitus patient.'

Tinnitus has been one of the bugbears of humanity for as long as medical records have been kept: ancient Babylonian clay tablets from more than 600 years BC contain multiple references to tinnitus together with instructions on how to treat the condition using incantations and charms.[3] **Hyperacusis** has a much shorter written history: one of the earliest mentions of the word was in 1881 in a book entitled *Imperfect hearing and the hygiene of the ear*, written by Laurence Turnbull, an American physician.[4] Although often considered as independent entities, there is no denying that an association exists between both of these symptoms, although this does not rule out a link with a common disorder, rather than one being the cause of the other.

Tinnitus and hyperacusis are both fascinating symptoms which, contrary to popular belief, are becoming much better understood with respect to their underlying causes and associations, and their ability to be successfully treated. As we observe advances in our understanding as the result of animal studies, the use of sophisticated imaging techniques, and developments in pharmacology

and psychology, more and more patients are benefiting. In this chapter we will provide an evidence-based overview of tinnitus and hyperacusis, from both a clinical and a research perspective. The psychological aspects of tinnitus will be discussed in Chapter 70, Understanding tinnitus: A psychological perspective, so only a brief summary of this management modality will be provided.

TINNITUS

DEFINITIONS AND CLASSIFICATION

The definition produced by McFadden and described above is still useful, though it would include the hallucinations of mental illness and exclude tinnitus that is perceived outside the body. Other attempts at a definition have included the sensation of hearing a sound in the absence of an external stimulus or a sound sensation in the absence of an external or internal acoustical source or electric stimulation.[5] While perhaps an improvement on the McFadden definition, these would still include auditory hallucinations of mental illness as a form of tinnitus and the latter definition would exclude some types of pulsatile tinnitus where there is an intracorporeal sound source. A completely unambiguous definition has yet to be published.

Many classifications systems have been historically used to define tinnitus, based either on the proposed underlying cause or on the associated symptoms.[6] For consistency we have divided tinnitus into pulsatile and non-pulsatile. Pulsatile tinnitus is considered to be either synchronous or non-synchronous, depending on whether the sound is in synchrony with the patient's arterial pulse. Throughout this chapter non-pulsatile, synchronous pulsatile and non-synchronous pulsatile tinnitus will be considered separately.

Tinnitus can also be divided into subjective or objective forms: in the former, only the patient is aware of the sound sensation: in the latter, the sound can be perceived by others, either unaided, using a stethoscope or a microphone and amplifier. The majority of people with tinnitus report subjective non-pulsatile tinnitus with no specific associated pathological process other than age-associated hearing loss: this is often referred to as subjective idiopathic tinnitus. As described above, the sound perceived in this type of tinnitus can take virtually any form. Mostly, the sounds reported are simple sounds: whistling, humming, ringing or tones. More complex sounds are sometimes described including voices or music. When such complex sounds are present, they are generally indistinct and do not carry specific meaning, unlike the auditory hallucinations of mental illness.

NON-PULSATILE TINNITUS

Epidemiology

The largest investigation into the epidemiology of tinnitus was carried out as part of a UK, Medical Research Council, Institute of Hearing, study of hearing (n = 48 313).[7] This study discovered that the prevalence of persistent spontaneous tinnitus in the adult population was 10.1%, defining persistent spontaneous tinnitus as tinnitus that arose spontaneously, not as a response to sound stimulus, and lasted for periods of 5 minutes or more at a time. Of those surveyed, 5% described their tinnitus as moderately or severely annoying and 0.5% reported that it had a severe effect on their ability to lead a normal life. Studies in other countries have produced broadly similar figures: prevalence figures in Italy have been reported as 14.5% of the population,[8] in the US as 14.9%[9] and in Sweden as 15.8%.[10] Until recently most tinnitus epidemiology studies were limited to Western populations but a few studies have emerged from other countries in the last few years. An overall figure of 5.2% was reported from Egypt, rising to 17.7% in patients over 60 years of age.[11] In Japan, 18.6% of people aged over 65 described tinnitus[12] and in a similarly aged population sample in Nigeria the figure was 14.1%.[13]

Very few incidence or longitudinal studies have been carried out. One of the few published longitudinal studies was undertaken in a community in Beaver Dam, Wisconsin, US. As part of this study, participants aged between 48 and 92 years who did not have tinnitus at baseline were studied over a 10-year period. At the 5-year time-point, the cumulative incidence of new cases of tinnitus was 5.7%;[14] at 10 years the figure was 12.7%.[15] The prevalence of tinnitus in the population at baseline was 8.2% and it is noteworthy that these people tended to show improvement rather than worsening of their tinnitus during the study.

The prevalence of tinnitus seems similar in men and women though there are some differences in the way that the sexes perceive the symptom: women are more likely than men to perceive their tinnitus as a complex sound.[16,17] Presence of a hearing loss increases the likelihood of an individual experiencing tinnitus and, in particular, a high-frequency hearing deficit is a good predictor of tinnitus. Previous noise exposure is also a good predictor: Davis found a prevalence of tinnitus of 7.5% in adults who gave a history of little or no noise exposure but 20.7% in those with high exposure.[18]

Tinnitus is perceived in both ears or in the middle of the head by approximately half of sufferers. A few people perceive it as an external sensation. The remainder have unilateral tinnitus, with left-sided tinnitus slightly more common than right-sided. The reason for this left-sided preponderance is unknown and cannot be explained by asymmetrical hearing loss.[19] The location of tinnitus is not necessarily a fixed entity: it is not unusual for someone to report that they initially thought the sound percept was an external sound due to a faulty electrical item in their home. It was only when the sound sensation was audible in a different location with no electrical appliances present that they realized they had tinnitus and the perception then became internal. Similarly, a number of people who present with unilateral tinnitus subsequently report that the symptom has become bilateral.

Several studies have demonstrated that the prevalence of tinnitus increases with age.[20, 21] This is likely to represent the known association of tinnitus with hearing loss although, interestingly, the tinnitus prevalence does not rise as steeply as that of hearing loss and some studies have shown tinnitus prevalence reaching a plateau around the age of 70 and, in some cases, even diminishing thereafter.[7] There is some evidence that older people are more annoyed by their tinnitus than younger people.[7] It is popularly assumed that tinnitus is a condition of adulthood. Tinnitus does, however, present in children, with prevalence figures not dissimilar to those in adults. This is discussed in more detail later in this chapter. Although tinnitus experience is common in childhood, relatively few seem to find the experience troublesome. Furthermore, it is unusual to see an adult with tinnitus who reports that they have had the problem since childhood, suggesting that children must, by and large, habituate to the symptom.

Various risk factors for the development of tinnitus have been suggested. These include socioeconomic class, smoking, alcohol consumption and other health issues such as previous head injuries, cardiovascular disease and hypertension.[7] Specific otological conditions including Ménière's disease, otosclerosis and vestibular schwannoma are associated with an increased risk of tinnitus: such cases are sometimes referred to as cases of 'syndromic tinnitus'. Numerous drugs have been cited as possible triggers for the development of tinnitus. In most cases the risk is low and the association has not been examined with any great degree of scientific rigor – it is probable that in many cases the link is either idiosyncratic or coincidental. A few drugs do have a more definite link with tinnitus and these include salicylates, quinine, aminoglycoside antibiotics, and some antineoplastic agents, particularly the platinum-based drugs. It has been suggested in a recent study that tinnitus development may have a small genetic predisposition.[22] There have been suggestions that certain personality types such as type D personality are associated with the development of tinnitus.[23] Most studies, however, have suggested that tinnitus patients have a normal gamut of personality types.[24]

Although many patients report that they feel that tinnitus is affected by dietary factors, there has been very little research in this area. A recent publication described a cross-sectional study of 171 722 adults aged 40–69 years who had agreed to participate in the UK Biobank scheme.[25] The authors subdivided tinnitus into persistent, transient and bothersome subtypes and investigated the association of the subtypes with reported consumption of common food groups. An increased report of persistent tinnitus was associated with fruit, vegetable and bread consumption and dairy avoidance. Reduced reporting of persistent tinnitus was associated with consumption of fish and caffeinated coffee and avoidance of eggs. Transient tinnitus reports increased with dairy avoidance and decreased with caffeinated coffee and brown bread consumption. Bothersome tinnitus reports decreased with consumption of wholemeal, wholegrain bread. Although the authors of this study controlled for as many other factors as possible, they highlighted several potential shortcomings in their study and stressed that these results only show evidence of an association between certain foods and tinnitus; they do not imply a causal link.

Two other studies have investigated the relationship between caffeine and tinnitus. The first of these studied the effect of caffeine abstinence on tinnitus and concluded that caffeine has no effect on tinnitus severity.[26] The second study followed 65 085 women aged 30–44 years at baseline over an 18-year period.[27] During the course of the study 5289 participants developed tinnitus; higher caffeine consumption was associated with lower risk of developing tinnitus.

In addition to risk factors, tinnitus has several comorbidities. Depression and anxiety are not infrequently seen with tinnitus and in many instances it is impossible to determine whether these neuroses have precipitated the emergence of tinnitus or vice versa.[28] Temporomandibular joint dysfunction has also been reported as a comorbidity.[29] The tinnitus community is split as to whether this is a causal association or simple coincidence. Disorders of sound tolerance are commonly seen in association with tinnitus: 40% of people with tinnitus report some degree of hyperacusis[30] and, when this association is reversed, 86% of people reporting hyperacusis also report tinnitus.[31] Disorders of sound tolerance are discussed in more detail later in this chapter.

Pathophysiology

The most prevalent presentation of tinnitus in the general population is that of a subjective non-pulsatile sound. Although, in this form, the link between high-frequency hearing loss and tinnitus might be taken as evidence for a cochlear origin for tinnitus, most modern research underscores the importance of central auditory pathways in both the development and maintenance of distressing tinnitus.[32–34] Traditionally, it was considered that tinnitus can exist in the presence of a perfectly functioning auditory periphery but recently the definition of normal hearing has been disputed as many cochlear hair cells may be damaged before an apparent hearing loss is demonstrated using conventional pure-tone audiometry; furthermore, there is evidence that patients with tinnitus may demonstrate hearing loss at frequencies much higher than conventionally tested using standard methods.[35]

Conversely, tinnitus can exist even if the auditory periphery has been completely destroyed or after the neural connections between ear and brain have been severed, as can be seen following some forms of vestibular schwannoma surgery.[36] In addition, damage to the auditory system does not automatically induce tinnitus: although noise-induced hearing loss increases the likelihood of someone reporting tinnitus, the majority of people with cochlear damage secondary to noise exposure do not have significant tinnitus. These observations have been drawn together in a concept that makes a distinction between the location, within either the peripheral or central auditory system, at which an initial tinnitus signal is generated and the subsequent central auditory mechanism by which this signal is misconstrued as a sound with the potential to become

a clinical problem. The point at which the initial signal generation occurs has been dubbed the **ignition site** and the ensuing central mechanisms have been entitled **promotion**.[37] Pathological events which create an ignition site do not inevitably generate tinnitus – the central promotion must also be present. This theory has clinical relevance in that, if tinnitus distress is maintained by central auditory pathways, it may be futile trying to correct peripheral auditory pathology.

While the exact mechanism behind tinnitus ignition is not fully understood, it is now considered that any pathology that can potentially damage the auditory pathways has the potential to result in tinnitus. The following text outlines some of the pathophysiological mechanisms that have been suggested as giving rise to tinnitus, but this list is far from exhaustive and many other hypotheses have been proposed. Likewise, these theories are not mutually exclusive.

PERIPHERAL MECHANISMS

Discordant damage of cochlear hair cells

Outer hair cells have been shown to be more susceptible than inner hair cells to damage by certain agents including noise and aminoglycoside antibiotics. It has been suggested that, in areas where outer hair cells have been damaged but inner hair cells remain, the tectorial membrane is no longer supported by the outer hair cells and can sag onto the inner hair cells, causing them to depolarize.[38]

Calcium channel dysfunction

Calcium is fundamental to several functions of cochlear hair cells and some drugs that are known to cause tinnitus, including salicylates and quinine, affect intracellular calcium levels. Noise also affects the concentration of intracellular calcium. It has therefore been suggested that calcium flux may be implicated in tinnitus generation.[38]

Glutamate receptors

Glutamate is the main excitatory neurotransmitter in the auditory system and several subgroups of glutamate receptor exist. AMPA receptors are the main receptors found on the auditory nerve fibres under the inner hair cells and are responsible for the fast transmission of information from the cochlea to the brain.[39] However, glutamate in large quantities is toxic to nerve fibres. This effect, which can be observed following significant noise exposure, is mediated by AMPA.[40] Another subgroup of glutamate receptors, NMDA receptors are also present in auditory nerve fibres though their function is still a matter of some speculation. It has been observed that pharmacological blockade of NMDA receptors can be protective against both salicylate-induced[41] and noise-induced tinnitus in animal models.[42] Although the evidence that glutamate receptors are directly implicated in the causation of tinnitus is at best circumstantial, they do offer a potential site for therapeutic intervention and this continues to be an active research area.

CENTRAL MECHANISMS

Increased spontaneous firing

There is always a certain degree of electrical activity in the auditory system even when there is no sound input to the ear. Damage to the ear results in reduced activity in the auditory nerve which in turn downregulates inhibitory processes in higher auditory centres, thereby potentially generating increased spontaneous activity in the auditory cortex that could be perceived as tinnitus.[43]

Increased central neural synchrony

Spontaneous neural activity in the auditory cortex is normally random and, when this activity becomes synchronized, this is the signal that a sound is present. If the peripheral auditory system is damaged, spontaneous cortical activity tends to become more synchronized and there is speculation that this can give rise to tinnitus.[44]

Reorganization of the cortical auditory map

The auditory system is tonotopically organized from cochlea to cortex: structures within the auditory system that deal with adjacent sound frequencies are situated beside each other. When the peripheral auditory system is damaged, one change seen in the auditory cortex is that neurons that received inputs from parts of the cochlea that have been damaged tune in to the nearest adjacent frequency input that is still active. This results in over-representation of frequencies adjacent to areas of damage and increased neural activity at those frequencies.[45] It has been suggested that this produces tinnitus.

TINNITUS MODELS

Rather than becoming fixated on the neurobiology of tinnitus, many clinicians prefer to view the functional basis for the symptom. Many psychological and neurophysiological models for tinnitus exist, some of which form the basis for contemporary tinnitus therapies. In 1984 Hallam et al. suggested that tinnitus was caused by 'some neurophysiological disturbance in the auditory system at any point between periphery and cortex'.[46] They went on to suggest that normally the central auditory system should habituate to this activity. However, in certain situations such as high autonomic arousal this process does not happen and the tinnitus activity can become intrusive. Treatment modalities that arose from this concept included the use of relaxation therapy to reduce autonomic activity and cognitive behavioural therapy to help change the emotional significance of the tinnitus.[47] Psychological models of tinnitus and psychological management strategies are discussed in greater detail in Chapter 70, Understanding tinnitus: A psychological perspective. In 1990 Jastreboff published what has become known as the 'neurophysiological model' of tinnitus, drawing together all the available knowledge at the time and suggesting that, in addition to events within the classical auditory system, tinnitus involved altered activity within the limbic system, reticular system and autonomic nervous system.[38] This model was then

used to produce a clinical application that became known as 'tinnitus retraining therapy' (TRT).[48, 49]

TINNITUS MODULATION

Over the last two decades it has become apparent that tinnitus can be influenced by stimuli from outside the auditory system: many patients with tinnitus can modulate their symptom by touching their face,[50, 51] clenching their teeth[52] or changing their gaze.[53] Although this was initially dismissed as a rare curio, it has become apparent that this phenomenon is quite common, highlighting the importance of links between the auditory system and other somatosensory pathways. Furthermore, this interesting phenomenon is currently being employed to form the basis of a novel form of tinnitus therapy.[54]

Investigation

BASIC AUDIOMETRY

Specific forms of tinnitus, such as tinnitus in the presence of Ménière's disease, may require specialist investigations. However, it is well accepted that all patients with tinnitus, in addition to having a thorough history and examination performed, require, as a bare minimum, a pure-tune audiogram. Many people with tinnitus complain that their ear or ears feel blocked and tympanometry is therefore often valuable.

TINNITUS-SPECIFIC AUDIOLOGICAL MEASUREMENTS

A number of specific tinnitus tests are available, but their reliability is variable, even when assessed using contemporary research methods.[55] Tests include the assessment of loudness discomfort levels, tinnitus pitch matching, tinnitus loudness matching and minimal masking levels.

IMAGING

Patients with unilateral tinnitus, an asymmetrical sensorineural hearing loss or associated neurological symptoms or signs require imaging to exclude the presence of a retrocochlear pathology such as a vestibular schwannoma. The modality of choice is MRI and there are now sufficient MRI options that even the claustrophobic, obese and those unable to lie flat should be able to undergo MRI scanning. The presence of non-compatible medical devices such as pacemakers or the presence of metal foreign bodies may still preclude MRI, in which case CT may be utilized.

TINNITUS QUESTIONNAIRES

Tinnitus questionnaires are an essential tool for research[56] and also have a role in the assessment of patients during routine clinical practice: their use has been recommended in the UK by the Department of Health's good practice guide.[57] There are a plethora of questionnaires available and there is no clear winner. Examples include the Tinnitus Handicap Questionnaire,[58] the Tinnitus Handicap Inventory (THI),[59] The Mini Tinnitus Questionnaire[60] and the Tinnitus Functional Index.[61] A survey of audiology departments in 2012 showed that the THI was the most popular tinnitus questionnaire used in the UK.[62] However, this study was conducted prior to the release of the Tinnitus Functional Index, which is claimed to have several advantages over its older competitors.

OTHER QUESTIONNAIRES

Because of the comorbidity of psychological conditions such as anxiety and depression with tinnitus, it is often helpful to use a mental health questionnaire such as the Hospital Anxiety Depression Scale (HADS).[63] Similarly, sleep disturbance is commonly reported in patients with tinnitus and it may be advantageous to use a sleep assessment tool such as the Insomnia Severity Index.[64]

VISUAL ANALOGUE SCALES

Visual analogue scores are considered useful, particularly in the research setting, when assessing specific components or consequences of tinnitus. Scores are usually formulated by putting a mark on a straight line, the ends of which represent the extremes of the parameter being assessed.

Mainstream treatments

To date a whole host of medicinal, device and psychological treatments for tinnitus have been proposed. The evidence base to support these treatments is poor at best, mainly due to a paucity of well-designed randomized controlled trials (RCTs). The scientific community has often been criticized for relying too heavily on the gold standard double-blinded RCT, but for conditions such as tinnitus, where many treatments may work via a placebo effect,[65] and there being a general natural improvement in symptoms with time, it is difficult to consider any other method of scientific evaluation as fit for purpose.

EXPLANATION AND REASSURANCE

An explanation of the condition and reassurance is a key initial step in the management of any patient with tinnitus. Often, the process of education and information giving is not the only treatment provided but, when provided in a formal setting, a number of RCTs are supportive of this modality.[66–68] A common report of patients seen in specialist tinnitus clinics is that clinicians who they have previously consulted have offered a very pessimistic view of tinnitus outcome. Reports such as 'the doctor told me that I would have it forever and nothing can be done' are all too common. This negative counselling is damaging for patients with tinnitus and should always be avoided.[69]

HEARING AIDS

As there is an association between tinnitus and hearing loss, it would make sense that providing hearing amplification would in part ameliorate a patient's symptoms. The literature lends some support for this[70, 71] but a recent

robust appraisal of the literature concluded that there was limited support from well-designed trials.[72] Hearing amplification may amplify external sounds and mask tinnitus, but indirect effects, such as improving communication, may reduce stress and anxiety that may be exacerbating the patient's symptoms.

Hearing aids first featured as a method of tinnitus management in the 1940s.[73] Currently, when supplemented with education and advice, hearing amplification is considered to be the primary intervention for a patient with tinnitus and aid-able hearing.[62] A large best practice consensus document has recently been published that recommends the provision of hearing aids in tinnitus patients even if they would normally be regarded as marginal hearing aid candidates.[74] A Delphi review of the use of hearing aids in the management of tinnitus, however, showed that, although there is some consensus among professionals, there is also still considerable disagreement.[75] Despite this lack of consistent good quality evidence, many clinicians encourage patients who have a hearing loss in addition to their tinnitus to try appropriate hearing aids even if they feel that amplification is not yet required for the hearing loss.

SOUND THERAPIES

Sound therapy can be used as part of TRT or as a standalone treatment. It is possible to use sound to completely or partly suppress, or mask, tinnitus in 95% of tinnitus patients in a clinic setting using specialist equipment, with 92% experiencing complete masking.[76] Translating this into practical treatment is less successful. Also, it has been suggested that complete masking is counterproductive as it may prevent habituation to the tinnitus signal. Proponents of TRT suggest that sound therapy is important but not used as masking. Instead, it is advocated that sound should be used at very low levels at a point where the added sound is just below the perceived level of the tinnitus.[77] Sound therapy at this so-called mixing or blending point is supposed to facilitate the habituation process, although there is conflicting evidence to the efficacy of this approach.[78, 79] There are three methods of providing wearable sound therapy: patients may wear hearing aids that produce masking by amplifying ambient sound (as discussed above), small ear level devices that generate wide-band sound (known as tinnitus maskers, sound generators, white noise generators or wide-band sound generators) or combination devices that blend the functions of the first two types of device. Whether such devices deliver masking or sound therapy at a mixing point simply reflects the output level that is set on the device. An alternative to donning a wearable device is to use an appliance that produces sound in the patient's immediate environment. This is referred to as environmental sound enrichment and can be delivered by devices such as electric fans, wind chimes, water features, prerecorded compact discs and electronic environmental sound generators. Sound from the latter two devices can be fed to a loudspeaker fitted into or under a pillow, allowing the patient to hear the sound while preparing for sleep without impinging on his/her partner. There are numerous programmes for computers and apps for smartphones that can be used to produce environmental sound enrichment.[80]

NOVEL SOUND THERAPIES

Several devices deliver forms of sound therapy that claim to specifically target tinnitus rather than simply offering masking or distraction.[81] Some purport to do this using sound on its own whereas others deliver sound stimulation while simultaneously stimulating other sensory systems.

Neuromonics®

Neuromonics® is a device that uses music modified to compensate for any hearing loss that the patient may have. The music has a large dynamic range with peaks and troughs with the intention that tinnitus is audible in the troughs. The sound therapy is accompanied by education and counselling and it is claimed that gradual exposure to the tinnitus during the troughs aids habituation. Several studies have been undertaken, mostly by the team that developed the device [82] and scientific rigour has been questioned.[83] An RCT compared Neuromonics® against ear-level sound generators and concluded that they had a similar effect on tinnitus.[84]

Serenade®

Work undertaken on a patient with profound hearing loss and tinnitus who had undergone cochlear implantation showed that certain stimulation paradigms were effective in ameliorating the tinnitus.[85] Extrapolating from this work, an acoustic stimulation regime was developed using temporally patterned sound altered to account both for any hearing loss and the pitch of the patient's tinnitus. This sound therapy is delivered via a device called Serenade® and the sounds have been dubbed S Tones.[86] There is now some evidence that S Tones may have a modest benefit compared to wide-band sound.[87]

Noise cancellation

Noise cancellation has been investigated as a possible tinnitus therapy. One device, Phase-Out, matches a therapeutic tone to the patient's tinnitus tone and then phase shifts the therapeutic tone by 6 degrees every 30 seconds. The suggestion made by the developer is that the therapeutic sound cancels the tinnitus for one-third of the total time.[88] Although some supportive research was published,[89] more scientifically robust research showed no benefit.[90]

Acoustic CR neuromodulation

One of the theories regarding the pathophysiology of tinnitus is that it is due to increased neural synchrony in the central auditory system (see above). It was suggested that a specific form of sound stimulation could be used to disrupt this pathological synchrony: four tones are delivered via headphones, two above and two below the dominant frequency of the patient's tinnitus. The technology is known

as Acoustic CR (Co-ordinated Reset) Neuromodulation and initial research looked promising.[91, 92] An RCT was planned.[93] This research was undertaken but the results were not published owing to deviations from the trial protocol. Following a freedom-of-information request by a UK tinnitus charity, a limited disclosure of the results was published online.[94] This stated that the end-of-study report did not report a significant difference in the primary outcome measure (global Tinnitus Handicap Questionnaire scores) between the treatment group and the placebo group.

Sound therapy with vagal nerve stimulation

Another theory regarding the pathophysiology of tinnitus is that of cortical map reorganization (see 'Central mechanisms' above) in which damage to the ear causes plastic changes within the central auditory system. Animal studies have suggested that direct electrical stimulation of the nucleus basalis in the forebrain in conjunction with stimulation of the sensory organ could reverse such changes. Clearly, this is too invasive to become a mainstream treatment but animal experiments have shown that stimulation of the vagus nerve paired with sound stimulation could potentially achieve the same effect.[95] Small-scale studies to stimulate the vagus nerve both by electrodes implanted against the nerve in the left side of the neck[96] and by the transcutaneous route[97] have been undertaken. As yet, however, there is insufficient evidence to reach meaningful conclusions and further work is required.

Mute button

Another therapy that utilizes crossover between the auditory system and other somatosensory pathways is Mute Button. This pairs acoustic stimulation with electrical stimulation of trigeminal nerve fibres in the anterior tongue. To date this treatment modality is only available in the Republic of Ireland and scientific evidence is limited to conference proceedings.

ULTRASOUND

Ultrasound has also been used to treat tinnitus: high-frequency sound is applied by a bone-conduction transducer. The rationale of this approach is that the ultrasound should stimulate the cochlea without interfering with the patient's hearing for sounds occurring in the normal auditory spectrum. An initial study reported optimistic results but this was not repeated.[98]

COMBINATION TREATMENT MODALITIES

Following publication of his neurophysiological model in 1990,[38] Jastreboff went on to generate a clinical management strategy that combined directive counselling and sound therapy to counteract the pathological positive feedback process and promote habituation to the tinnitus.[48] This process was subsequently titled tinnitus retraining therapy (TRT)[49] and the technique has been extensively discussed in a book which outlines a rigorous protocol.[99] However, the neurophysiological model, from which it is derived, can be interpreted differently and many tinnitus practitioners apply the clinical extrapolates of the model in a less rigorous fashion. A Cochrane systematic review has considered the evidence for the administration of TRT.[100] The initial findings were that, based on a single, low-quality RCT, TRT is much more effective as a treatment for patients with tinnitus than tinnitus masking.[101]

COGNITIVE BEHAVIOURAL THERAPY

The use of psychological techniques such as cognitive behavioural therapy (CBT) in the UK is hugely hampered by a lack of psychologists with appropriate tinnitus training. A Swedish group has investigated delivering CBT via the internet and initial results suggest that this may be a useful approach.[102] A Cochrane systematic review has considered the evidence for the administration of CBT and it was concluded that CBT resulted in no significant difference in tinnitus loudness, but CBT did result in a significant improvement in both depression scores and in quality of life scores.[103] A recent systematic review concluded that both CBT and TRT were effective treatments for tinnitus and neither was demonstrably superior.[104]

OTHER PSYCHOLOGICAL TREATMENTS

More modern psychological treatment modalities have recently been explored for efficacy in the management of tinnitus: these include mindfulness meditation[105] and acceptance and commitment therapy (ACT).[106] Initial reports appear optimistic. Psychological treatments are discussed in more detail in Chapter 70, Understanding tinnitus: A psychological perspective.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Many forms of complementary medicine are promoted as being beneficial for tinnitus patients. A list of some of the more commonly used modalities is shown in **Box 61.1**. Many of these therapies involve much contact between the

BOX 61.1 Some of the complementary medicine therapies and exercise regimes that have been used in the management of tinnitus

Acupuncture	Hypnotherapy
Alexander technique	Massage
Aromatherapy	Meditation
Black cohosh	Osteopathy
Chiropractic	Reflexology
Craniosacral therapy	Reiki
Herbal medicine	St John's wort
Ginkgo biloba	Shiatsu
Homeopathy	Tai Chi
Ear candles	Yoga

therapist and patient and promote a sense of relaxation. It might therefore be expected that these therapies could help tinnitus patients, at least in a non-specific way.

Relaxation techniques have been studied as a specific therapy to treat tinnitus and three RCTs have been performed to assess their effectiveness.[107–109] These studies supported the efficacy of relaxation therapy for tinnitus intrusiveness but there was mixed evidence for its efficacy for depressive symptoms, and there was no evidence for an effect on anxiety.

In 2000 Park et al. systematically reviewed the efficacy of acupuncture as a treatment for tinnitus.[110] This review identified only six randomized trials: two unblinded trials and four blinded trials. The two unblinded trials demonstrated a positive effect of acupuncture treatment for tinnitus, whereas the four patient-blinded, sham-controlled studies demonstrated no significant difference between treatment with acupuncture and placebo.

There have been some claims that chiropractic manipulation benefits tinnitus patients, but there have been no scientific studies to substantiate any positive effect in comparison to placebo.

A note of caution must be sounded regarding the use of ear candles in the management of tinnitus. Not only has no benefit been demonstrated but in a few instances damage to the ear has resulted as a consequence of their use.[111]

Several exercise regimes such as Tai Chi and yoga have been promoted as helping patients with tinnitus. In these cases, no claim is made that the exercises treat the tinnitus directly but rather that the techniques promote relaxation and combat stress.

Ginkgo biloba has attracted more interest for the treatment of tinnitus than any other complementary therapy. The efficacy of ginkgo has had mixed support. A number of large double-blinded, placebo-controlled trials have been undertaken reaching different conclusions. In 2001 Drew and Davies failed to demonstrate a significant effect in treating tinnitus using ginkgo doses of 150 mg.[112] A double-blinded, placebo-controlled trial and meta-analysis of randomized trials recently concluded that ginkgo did not benefit patients with tinnitus.[113] Despite these reports it must be noted that the success of other studies has been based on much higher doses of up to a daily total of 480 mg of ginkgo extract.[114] Further supporting the role of ginkgo is a controlled study demonstrating a statistically significant reduction in tinnitus using an animal model.[115] Systematic appraisal of the role of ginkgo has been performed by way of a Cochrane review, which found no reliable evidence supporting its use as many of the studies performed have been flawed in one way or another.[116]

ELECTROMAGNETIC STIMULATION

Direct electrical stimulation of the ear has been shown to suppress tinnitus but delivering this stimulation is invasive and risks damage to the inner ear.[117] Partly because of this tantalizing glimpse of a tinnitus suppressant, other ways of delivering electrical and magnetic energy to the cochlea or central auditory system have been investigated. High-powered rare earth magnets have been placed in the ear canal but an RCT failed to show any benefit despite initial positive reports.[118] Electromagnetism has also been investigated: initial trials gave mixed results,[119] but the use of refined methods of delivery have promoted further interest in this area. Electromagnetism has been used in conjunction with functional imaging such as PET scanning or fMRI: pathologically active areas of brain are identified and electromagnetic therapy is then directed to this area.[120, 121] Repetitive transcranial magnetic stimulation (rTMS) can be delivered at a variety of different frequencies and in some circumstances employing complex wave administration.[122] A recent Cochrane systematic review has considered the evidence for the administration of rTMS and concluded that there is very limited support for the use of low-frequency rTMS for the treatment of patients with tinnitus.[123] When considering the impact of tinnitus on patients' quality of life, there was support from a single study with a low risk of bias based on a single outcome measure at a single point in time.

SYSTEMIC DRUG TREATMENTS

Although drug therapy should be relatively easy to investigate, much of the published information is of poor quality. The use of inert placebos, inadequate outcome measures and high drop-out rates are common in drug trials. Moreover, most trials have failed to make a distinction between helping concomitant psychological illness and direct effect on tinnitus. Tinnitus drug trials are often carried out on small groups of patients and consequently lack the power to detect small effects.

Psychoactive drugs have been used in the management of tinnitus, partly because tinnitus patients score highly for symptoms of psychological distress[28] and partly because many of the receptors that psychoactive drugs act upon are also found within central auditory pathways. While there is a role for such drugs in the treatment of any psychological or psychiatric disease that accompanies tinnitus, the situation with respect to the tinnitus itself is less clear. There are four reasonably well-constructed RCTs which investigated the use of tricyclic antidepressant drugs.[124–127] These all reported slight improvement in tinnitus but these conclusions may be attributable to methodological flaws, so no major conclusions can be drawn. A well-constructed trial of a selective serotonin reuptake inhibitor, paroxetine, showed no advantage over placebo for the majority of criteria investigated.[128] Benzodiazepines have been widely used in the management of tinnitus and some work has suggested that this group of drugs may have a direct effect on tinnitus.[129] Unfortunately, this research can be criticized for using an inert placebo and, in any case, the propensity for benzodiazepines to induce dependence restricts their usage.

Antiepileptic[130, 131] and antispasmodic[132] drugs have both been investigated for potential activity against tinnitus but the results have been disappointing. Likewise the use of vasodilators[133] and diuretics[134] has proved unhelpful. Betahistine is frequently administered to patients with idiopathic tinnitus: there is no scientific rationale for this action. In 2006 a group in China reported an improvement

in tinnitus loudness when subjects received betahistine as compared with subjects that received a control drug.[135] However, only a small number of subjects were studied and there have been no further studies published since to corroborate the original study authors' findings.

Local anaesthetic agents have offered one glimmer of hope for a possible pharmacological solution to tinnitus. Following a serendipitous discovery when procaine caused temporary abatement of tinnitus in a patient undergoing nasal surgery,[136] several trials have confirmed that intravenous injections of some ester and amide local anaesthetic agents cause short-term reduction of tinnitus. A double-blind, placebo-controlled, crossover trial investigated 16 patients who had post-operative tinnitus following translabyrinthine resection of a vestibular schwannoma.[137] Bolus intravenous injection of lidocaine produced significant short-term tinnitus suppression despite the fact that the auditory nerve had been divided during the surgical procedure. Although the trial can be criticized for using an inert placebo, the observations suggest that, at least within this group, the antitinnitus effect of the local anaesthetic agent was central rather than peripheral. Previous attempts to find a less hazardous and orally active agent that has the same beneficial effects as these local anaesthetics have failed.[138]

Two small-scale trials have shown that the hormone melatonin helps patients who have sleep disorders associated with tinnitus.[139, 140] As many patients with tinnitus do have sleep disorders,[141] this merits further investigation.

Tinnitus, like idiopathic sudden sensorineural hearing loss, has been thought to arise from a lack of oxygen secondary to vascular insufficiency. For this reason interest has been shown in the application of hyperbaric oxygen therapy to increase the supply of oxygen to the ear and brain to reduce the severity of hearing loss and tinnitus. A critical assessment of the role of hyperbaric oxygen therapy has been performed by way of a Cochrane review and no clear value could be demonstrated.[142]

As glutamate is the main excitatory neurotransmitter in the auditory system, there has been considerable interest in studying a variety of antagonist drugs, including memantine,[143] flutirpine[144] and neremexane[145] but no demonstrable benefits have been shown.

There have been sporadic reports of the successful use of drugs to treat specific subtypes of tinnitus. For example, it has been suggested that the antiepileptic drug carbamazepine can be effective in treating a variant of tinnitus that presents with an intermittent staccato quality, described as sounding like a typewriter or popping corn.[146] However, this report is from a small uncontrolled case series and better scientific evidence in the form of an RCT would be required before such therapy could be recommended.

REGIONAL DRUG TREATMENTS

Botulinum toxin has been shown to be beneficial through non-paralytic effects for conditions such as neuropathic pain and migraine. With respect to migraine, botulinum toxin is thought not only to block acetylcholine but also to inhibit the release of other neurotransmitters and neuropeptides involved in the autonomic pathway. Botulinum toxin A has been trialled in a small study of 26 tinnitus patients with the drug injected into soft tissues around the ear.[147] Benefit was demonstrated in the treatment arm as compared to the control arm but, due to the small number of patients recruited, no statistical significance was demonstrated.

INTRATYMPANIC DRUG TREATMENTS

The idea that drugs could have a therapeutic effect following instillation into the middle ear cavity has a long pedigree: work in the 19th century investigated the application of volatile vapours into the middle ear using Eustachian tube catheters.[148] Direct injection through the tympanic membrane was first utilized as a potential treatment for otosclerosis.[149] After initial enthusiasm this route of drug administration underwent a period when it was rarely used, but following the successful experience of using transtympanic administration of aminoglycosides in the treatment of Ménière's disease, the use of intratympanic therapies is once again being investigated for patients with subjective idiopathic tinnitus. It has been theorized that transtympanic administration allows direct labyrinthine drug absorption which may offer improved labyrinthine metabolism and hence reduction of tinnitus in those patients who have tinnitus in association with cochlear pathology. This mode of administration may appear to fly in the face of most modern theories of tinnitus pathophysiology, which suggest that the long-term problems of tinnitus occur in the central rather than peripheral auditory system. Events within the ear such as sudden sensorineural hearing loss, acute noise trauma or acute otitis media can trigger tinnitus and it has been suggested that there is a small therapeutic time window between the pathological event in the ear in these cases and the development of permanent changes in the central auditory system that produce troublesome tinnitus. It is therefore hypothesized that, in patients with sudden onset of tinnitus, there might be a short period when intratympanic treatments could be efficacious. Furthermore, it has been observed that some treatments that improve hearing, such as stapedectomy in otosclerosis, generally help any associated tinnitus. Extrapolating from this, intratympanic therapies that could potentially improve hearing could therefore also potentially be beneficial with any associated tinnitus.

Various agents, including steroids,[150] local anaesthetic agents,[151] anticholinergic drugs,[152] glutamate antagonists[153] and antioxidant compounds[153] have been delivered into the middle ear, either by single transtympanic injections, through perforations and grommets, or via an implanted micropump.[154] Most of the trials in this area are small observational studies. The solitary placebo-controlled trial in this field demonstrated no advantage of intratympanic dexamethasone over placebo.[155]

Although there has been no demonstrable benefit from using systemic glutamate antagonists in the management of tinnitus, interest in this class of drugs continues.

Some glutamate antagonists are too toxic to consider for regular systemic usage and consequently there has been interest in the intratympanic administration of these drugs. Recently there have been some encouraging results from preliminary studies investigating the use of esketamine, the S(+) enantiomer of ketamine, for acute 'inner-ear' tinnitus.[156] This compound acts as a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) subgroup of glutamate receptors. At the time of writing, larger-scale multinational trials are being conducted to decide whether the acute administration of this drug will prove to be a viable treatment in the future. Similarly, clinical trials are shortly expected to start for a sustained-release formulation of another NMDA antagonist, gacyclidine.

DIETARY SUPPLEMENTS

A large number of vitamins, minerals and other dietary supplements have been given to tinnitus patients in an effort to alleviate the condition. Some of the agents used are listed in **Table 61.1** although this is far from an exhaustive list.

There is some evidence that some of these compounds listed in **Table 61.1**, particularly the B vitamins, can help to defend the cochlea against noise trauma.[157] Indeed, some of the compounds on the list are being investigated for effectiveness in protecting people who are exposed to noise from developing tinnitus (see 'Prevention' below). However, there is no convincing evidence that they have any effect against established idiopathic tinnitus. The human cochlea has the body's greatest concentration of zinc. Some studies have demonstrated a significant decrease in zinc levels in some patients suffering from tinnitus and rectifying this deficiency has been shown to decrease tinnitus significantly.[158] Paaske et al., however, demonstrated little correlation between hypozincaemia and tinnitus[159] and no significant improvement in tinnitus with zinc supplementation. A randomized double-blind, placebo-controlled trial of the use of zinc in a population of tinnitus patients aged 60 or over showed no benefit with regards to their tinnitus.[160]

TABLE 61.1 Some of the dietary supplements that have been used in the management of tinnitus

Name of supplement	Class of supplement
Arginine	Amino acid
Beta carotene	Vitamin precursor
Calcium	Mineral
Club moss	Herbal
Coffee (unroasted)	Herbal
Cornus	Fruit
Folic acid	Vitamin
Foxglove	Herbal
Garlic	Herbal
Hydergine	Herbal
Ipriflavone	Bioflavonoid
Ligustrum	Herbal
Magnesium	Mineral
Manganese	Mineral
Melatonin	Hormone
Mullein	Herbal
N-acetylcysteine (NAC)	Antioxidant
Omega-3	Fish oil
Peruvian bark	Herbal
Plumbago	Herbal
Potassium	Mineral
Pulsatilla	Herbal
Salicyclic acid	Herbal
Selenium	Mineral
Sulphite of quinine	Herbal
Vegetable charcoal	Herbal
Vinpocetine and vincamine	Herbal
Vitamin A	Vitamin
Vitamin B1 (Thiamine)	Vitamin
Vitamin B3 (Niacin)	Vitamin
Vitmain B6 (Pyridoxine)	Vitamin
Vitamin B12	Vitamin
Vitamin C	Vitamin
Vitamin E	Vitamin
Wobezym	Enzyme formula
Zinc	Mineral

LASERS

Lasers have been used successfully in the management of some forms of chronic pain but the exact mechanism for this benefit remains contentious. Low-power lasers have been used in the treatment of tinnitus, applied either transmeatally or to the mastoid process. Although some workers have reported good results from such treatment,[161, 162] two well-constructed trials found no benefit above that derived from placebo.[163, 164]

SURGERY

Surgery has a definite role in the management of tinnitus associated with certain conditions such as otosclerosis when stapedectomy is reported as improving or eradicating tinnitus in 80–88.3% of cases.[165, 166] When tinnitus is associated with profound hearing loss, tinnitus suppression has been demonstrated as a secondary benefit of cochlear implantation. Improvement of tinnitus occurs in up to 86% of implanted patients and, interestingly, in up to 67% the benefit applies to the contralateral ear as well as the implanted ear.[167] There is no good evidence to support cochlear implantation for the sole purpose of tinnitus suppression and it would be ethically difficult to propose cochlear implantation for someone with significant residual hearing. The use of cochlear implantation with regard to the management of tinnitus in conjunction with single-sided deafness is discussed in 'Single sided deafness' below.

Destructive surgical procedures including VIIIth nerve neurectomy or selective cochlear neurectomy have been tried but there is no trial using good scientific methodologies such as validated outcome measures. Surgical treatments of Ménière's disease are generally aimed at control of vertigo and few trials have explored the effect on tinnitus. A Cochrane review of surgical treatments for Ménière's disease identified two studies that had commented on tinnitus outcome, both employing endolymphatic sac decompression. In both studies endolymphatic sac decompression showed no advantage over the control treatment with regard to tinnitus.[168]

PREVENTION

Cochlear damage caused by exposure to agents including noise, ototoxic agents and cytotoxic drugs is recognized as a trigger for tinnitus. Clearly, the best way to avoid damage from these agents is to avoid exposure to them: this is not always possible or practical. At a cellular level, the inner ear damage is generally mediated by a process of apoptosis[169] and this cascade has the potential to be therapeutically blocked. Driven in part by a need to protect military personnel from noise during combat,[170] several studies are researching the use of antioxidants including D-methionine (D-met),[171] ebselen[172] or a combination of beta carotene, vitamin C, vitamin E and magnesium (ACE Mg).[173] Stem-cell and gene therapies are also being investigated.[169]

PULSATILE TINNITUS

Pulsatile tinnitus is a form of tinnitus whereby the perception of sound is not that of a continuous form. The perceived sound takes on the form of a pulsation, clicking or fluttering. Pulsatile tinnitus is worthy of consideration as a specific subtype of tinnitus because the management of pulsatile tinnitus is different from that of the typical tonal tinnitus that patients report. Pulsatile tinnitus is classified as either synchronous or non-synchronous, depending on whether the tinnitus takes on the characteristics of a pulsation in synchrony with the patient's heart.

Synchronous pulsatile tinnitus

PATHOPHYSIOLOGY

Synchronous pulsatile tinnitus may present as the direct result of abnormal vascular anatomy in the vicinity of the peripheral auditory system. Systemic aberrations of the circulation, such as a hyperdynamic circulation, have also been implicated in the development of synchronous pulsatile tinnitus. Processes that result in altered arousal, altered selective attention, hearing loss, or altered cochlear blood flow or trauma may result in increased central auditory gain.[48] It has been proposed that, once this process has ceased, the increased gain will cause the subject to become more aware of their own physiological vascular pulsations. Table 61.2 summarizes the different pathological causes of synchronous pulsatile tinnitus.

TABLE 61.2 Pathological causes of pulsatile tinnitus

Type of pathology		Specific pathology
Vascular	Arterial	Atherosclerotic carotid artery disease[174] Arteriovenous fistula[175] Arteriovenous malformation[176] Intracranial aneurysm[175] Fibromuscular dysplasia of the carotid artery[177] Dissection of the carotid artery[178] Vascular anomalies of the ear[179] Vascular compression of the VIIIth nerve[180]
	Venous	Jugular bulb abnormalities[181] Dural venous sinus stenosis[182] Abnormal condylar or mastoid emissary veins[183] Idiopathic tinnitus, venous hum, essential tinnitus[184, 185]
Microvascular		Glomus tumour[186] Paget's disease[187] Cholesterol granuloma of middle ear[188] Meningioma of middle ear[189] Cavernous haemangioma[190] Histiocytosis X[191]
Circulatory		Increased cardiac output (anaemia, thyrotoxicosis, pregnancy)[192] Aortic murmurs[188]
Perceptual		Conductive hearing loss[193] Cochlear trauma[193]
Other		Benign intracranial hypertension[194–197] Superior semicircular canal dehiscence syndrome[198]

Whereas, traditionally, pulsatile tinnitus has been considered to be always a consequence of a primary vascular abnormality, over the last decade there has been a greater consideration of other primary causes. Intracranial hypertension is particularly gaining increased attention as a cause of pulsatile tinnitus.[196, 197] Idiopathic intracranial hypertension, or pseudotumor cerebri, is one cause of intracranial hypertension; this condition tends to occur more often in young, overweight women. Superior semicircular canal dehiscence syndrome is more usually featured in the medical literature as a cause of dizziness, however the emergence of this condition as a presentation of pulsatile tinnitus is beginning to gain acceptance.[198]

INVESTIGATION

Simple blood tests are considered helpful to exclude anaemia and thyrotoxicosis. In the absence of an obvious cause, synchronous pulsatile tinnitus requires imaging. Over the years there has been much debate regarding the ideal imaging modality. If otoscopy reveals a retrotympanic mass, a contrast-enhanced computed tomography (CT) of the temporal bone, brain and scalp is indicated.[199] If atherosclerotic carotid artery disease is suspected, duplex carotid ultrasonography can be helpful. Otherwise, the

advantages and disadvantages of magnetic resonance angiography (MRA) over contrast-enhanced CT has not been satisfactorily resolved. The gold standard mode of imaging the vascular system of the temporal bone, brain and scalp is via formal angiographic imaging, but this is not without risk, so this is often reserved for severe, recalcitrant cases where less invasive techniques have not revealed an obvious pathology. If idiopathic intracranial hypertension is suspected, an ophthalmological assessment, lumbar puncture, measurement of intracranial pressure and diagnostic reduction of intracranial pressure by draining off some cerebrospinal fluid may be required.

TREATMENT

Supportive

When no obvious cause is identified, providing reassurance that there is no untoward pathology present is often an important aspect of treatment. These patients may benefit from CBT or TRT to address the coexisting emotional effects of their tinnitus. Anecdotally, sound therapies can be used as for subjective idiopathic tinnitus though there is no evidence base to support this management.

Surgery

Surgery can play an important role in the management of pulsatile tinnitus,[195] depending on the causative pathology. Treatments may include decompressive and destructive procedures. Modern imaging techniques, and in particular MRI, have shown that vascular loops are commonly in close proximity to the cochlear nerves of patients with tinnitus. It has been suggested that laterally placed loops generate pulsatile tinnitus whereas vessels adjacent to the medial half of the nerve generate non-pulsatile tinnitus.[200] However, the prevalence of such loops in people who do not have tinnitus is unknown. Microvascular decompression of vascular loops in tinnitus patients has been used with very variable results, ranging from 40% improvement[201] to 77%.[202] The highly invasive nature of this surgery precludes its use in all but the most exceptional cases.

Non-synchronous pulsatile tinnitus

Tinnitus may manifest itself as a train of rhythmical clicks or a buzzing or fluttering noise or sensation that is not synchronous with the pulse. These sounds are often related to myoclonic activity resulting in repetitive contractions of the middle ear muscles, but other muscles within the head and neck region can be affected. Currently there is no evidence to suggest that the middle ear is part of a systematic myoclonic disorder. Within the middle ear, contraction of the tensor tympani and/or stapedius muscle are often proposed to be the cause of either a clicking or buzzing noise respectively; however, whether the associated tinnitus is the direct result of muscle contraction noise, vibration of the tympanic membrane or movement of the ossicular chain remains unknown.[203] The palatal muscles can also develop myoclonic contraction and this can produce sound that is audible to others. The clicking sound of palatal myoclonus is usually irregular with a frequency of one to two clicks per second. Involuntary palatal movements may be seen, either simply by inspecting the palate transorally or by visualizing the upper surface transnasally using a fibreoptic endoscope. Palatal myoclonus exists in two forms: symptomatic palatal myoclonus, which may be associated with lesions of the brainstem; and essential palatal myoclonus, which is usually idiopathic. It is generally essential palatal myoclonus that is associated with pulsatile tinnitus.

INVESTIGATION

The role of specialist testing for the assessment of middle ear or palatal myoclonus is unclear. While middle ear myoclonus can be diagnosed based on history and impedance changes on long-time-based tympanometry, an accurate differentiation between myoclonus of the tensor tympani and the stapedius muscle is not possible.[203] It is, however, important to differentiate a middle ear myoclonus from a palatal myoclonus. Palatal myoclonus usually produces an objective rhythmic sound that is associated with an involuntary movement of the soft palate and/or suprahyoid muscles. As palatal myoclonus has been associated with lesions in the central nervous system, MRI is recommended to exclude a pathology with the triangle of Guillain–Mollaret.[204]

TREATMENT

In cases of middle ear myoclonus, despite evidence to support the division of the middle ear tendons, a period of conservative treatment is recommended in the first instance. Pharmacological solutions that have been explored have included the use of benzodiazepines,[205] orphenadrine,[206, 207] carbamazepine,[208] piracetam[206] and botulinum toxin.[209]

Other reported supportive treatments include relaxation therapy,[210] psychotherapy,[211] tinnitus masking[212] and biofeedback,[212] although outcomes have been variable. In persistent cases, the surgical division of the middle ear tendons has been reported to be a definitive procedure: it is recommended that in these cases both tendons are divided as it is not possible to reliably identify the muscle which is responsible for the symptoms.

ALLIED CONDITIONS

Musical hallucination

As discussed earlier in this chapter, the sound perception of tinnitus can take virtually any form. A small number of patients report that they can hear music when none is present, usually describing short excerpts of music that they were familiar with in their youth. Although many feel that the music sensation is within their own head, some perceive it as an external sound. This may lead them to falsely accuse neighbours of playing the music, either unthinkingly or maliciously. The condition is more common in women, the elderly and those with significant

hearing impairment.[213] The association with hearing loss has led to the hypothesis that musical hallucination is caused by deafferentiation, in which reduced input to the central auditory system causes increased gain within the associative auditory cortex.[214] This results in the brain misinterpreting background neuronal activity as music. The difference between this and the 'earworm' or tune stuck in the head that we all get from time to time is that people with musical hallucination are convinced that the sound is real. It is important to ensure that the patient is not describing the auditory hallucinations of mental illness; if there is any doubt, a psychiatric opinion should be sought. Musical hallucination can rarely be associated with epilepsy so a neurological opinion is prudent. There is no substantial evidence base for the management of musical hallucination but addressing any associated hearing loss is anecdotally helpful.

Acoustic shock

Over the last quarter of a century a cluster of symptoms has been observed among call-centre operatives who are exposed to sudden unexpected sounds through their headsets or telephone handsets. This has become known as acoustic shock syndrome, acoustic shock injury or simply acoustic shock.[215–217] The symptoms of acoustic shock can be divided into immediate and delayed. Pain is the most common immediate symptom, with 81% of those affected describing otalgia, 11% describing neck or jaw pain and 7% describing facial pain. Tinnitus occurs in approximately half of these patients, and balance disorders are also common. Hearing loss is reported less frequently and, when it does occur, it is usually temporary. Delayed symptoms include hypervigilance, anxiety, sleep disorders, hyperacusis and a feeling of aural fullness. Examination is normally unremarkable and audiometry usually shows normal symmetrical hearing or an age appropriate sensorineural hearing loss. If there is any additional audiometric loss it is often of an atypical pattern and does not have the typical characteristics of noise induced hearing loss.

The sounds that cause acoustic shock have been analyzed and do not need to be excessively loud to trigger the symptoms. One study identified sounds with intensity in the range 56–100 dB whereas another reported sounds in the range 82–120 dB.[215, 218] One common feature of the causative sounds was that they had short rise times. It is not clear whether exposure to similar sounds when not wearing headsets can generate acoustic shock. Certainly there are anecdotal reports of other abrupt sounds generating similar symptom complexes. Sounds that are generated close to the ear seem more likely to cause these symptoms than distant sounds. The pathophysiology of acoustic shock remains obscure. Cochlear and central auditory system mechanisms have been suggested but the most popular current hypothesis is that acoustic shock represents tonic contraction of the middle ear muscles – tonic tensor tympani syndrome.[216, 219, 220] The management of acoustic shock is also uncertain. Many people with acoustic shock feel that they are being disbelieved or accused of malingering: supplying a diagnosis and offering general reassurance can be helpful in this respect. If the patient has persistent tinnitus and hyperacusis, these symptoms can be treated using the standard audiological or psychological techniques that are discussed elsewhere in this chapter. The question of whether someone who has experienced a significant acoustic shock can remain in call-centre employment is complex and as yet there is no consensus regarding the best course of action.

Low-frequency noise complaint

Low-frequency noise complaint is an unusual condition in which people report distress caused by the perception of intrusive low-frequency sound.[221, 222] This can result in major disruption of normal activities and is often associated with sleep disturbance. People with low-frequency noise complaint report sounds such as humming, rumbling or machinery noise. They generally feel that the sound is a real external sound, contrasting with standard tinnitus in which the person feels that the sound is within their own ears or head. Consequently, it is common for environmental health officers to be called in to investigate, but low-frequency sound levels are usually at or below hearing threshold. The UK and US press have been interested in this condition, christening the phenomenon 'The Hum' and referring to sufferers as 'Hummers'. There is no strong evidence base regarding either the pathophysiology or the management of this condition. In some cases there may be a real external sound source: dealing with this is the duty of environmental health teams. If there is no external source, which is the usual situation, techniques used for spontaneous idiopathic tinnitus can be utilized, including psychological treatments such as CBT[223] or audiological treatments using counselling and sound therapy.[224] Many people with low-frequency noise complaint are reluctant to embrace such therapeutic approaches because they remain convinced that their symptoms are generated by an external sound and do not represent a form of tinnitus.

Exploding head syndrome

Exploding head syndrome is a parasomnia phenomenon characterized by the perception of a sudden loud noise in the head or ears that occurs during a transition of sleep stages. Because there is an auditory hallucination some patients may be referred to tinnitus clinics though referral to sleep clinics or neurologists also occurs. Exploding head syndrome is generally hypnagogic, occurring at the interface from wakefulness to sleep, but can be hypnopompic, presenting at the onset of wakefulness. The range of sounds reported is large and includes sounds such as explosions, banging, roaring, voices yelling, a bell ringing or the thunder crack accompanying lightning. The auditory hallucination is accompanied by visual sensations in approximately 10% of cases, with sufferers describing experiences such as a brief vivid flash of light.[225] Other sensory experiences may be reported including a feeling of heat or an electrical sensation.[226, 227] The phenomenon is generally painless and has no serious medical sequelae

though understandably it may generate feelings of shock and fear. Tachycardia and palpitations have been reported after an episode. Historically exploding head syndrome has been said to be a rare,[228] to be more common in women than men[229] and to be more common in those over 50.[225] However, a study of 211 undergraduate students suggested that the condition may be more common than previously thought, may occur in younger people and may have no gender imbalance.[230] The natural history of the condition seems unpredictable from evidence derived from the available case reports, with some people reporting a single episode whereas others experience multiple events per night; the problem can be persistent over many years or can spontaneously remit.

Clinically, it is important to exclude other conditions such as nocturnal epilepsy or subarachnoid haemorrhage. If the patient describes significant pain, an alternative diagnosis should be sought. Once the diagnosis has been established, education and reassurance are reported to help. Various pharmacological agents have been assessed including tricyclic antidepressants,[226] anticonvulsants[231] and calcium-channel blockers.[232] However, drug studies have been small-scale and uncontrolled and further research is clearly required.

SPECIAL POPULATIONS

Tinnitus in children and adolescents

Tinnitus is not as rare in children as was once thought. In children with normal hearing, the prevalence of tinnitus can vary from 12% to 36%.[233] Tinnitus in children, like adults, is more common if there is hearing loss.[234–238] Tinnitus has been demonstrated to commonly occur in children with otitis media.[239, 240] Tinnitus in children, as compared to adults, presents itself in a different manner and, while many of the basic principles of tinnitus management still stand, a different approach is required when dealing with children. In 2015, the British Society of Audiology (BSA) published practice guidance on the management of tinnitus in children. Developed through the Paediatric Audiology Interest Group (PAIG) of the BSA by national specialists in paediatric tinnitus, the project was supported by the British Tinnitus Association and the guidance is available from the BSA website.[241]

Military personnel

The association between tinnitus and noise exposure is well known and military personnel experience both chronic noise exposure and sudden extreme noise exposure. Military personnel in the UK are legally protected during training, but in a combat situation the use of hearing protection may not be viable and noise exposure may be particular high. Indeed, noise levels can become so high that, even when wearing hearing protection, military personnel may be exposed to levels of sound that exceed safe limits.[170] In addition, service personnel may be exposed to ototoxic chemicals during their military service.[242] It is therefore perhaps not surprising that tinnitus is now reportedly the number one disability among US veterans.[243] Post-traumatic stress is high among service personnel and seems particularly high among those with concomitant tinnitus: a study of military veterans showed that 34% of those who attended a tinnitus clinic also fulfilled the diagnostic criteria for post-traumatic stress disorder.[244] Traumatic brain injury is also more common among military veterans and this may affect the central auditory system.[245] Management of tinnitus in this population is therefore often complex and may require a multidisciplinary approach.

Single-sided deafness

Acquired unilateral profound hearing loss is a relatively common clinical problem. A study in 2006 estimated that the incidence may be up to 8000 new adult cases per annum in the UK.[246] In a study of 21 patients with single-sided deafness, two-thirds reported tinnitus and in 29% the tinnitus was severe.[247] Various therapeutic interventions have been explored in these patients, including the use of contralateral routing of signal (CROS) hearing aids, bone-anchored hearing aids, bone-conduction hearing implants and cochlear implants. There is little evidence to support the effect of the first three of these options but there are several studies that have investigated cochlear implantation and a systematic review has suggested that tinnitus is generally lessened, at least during the period when the implant is activated.[248]

DISORDERS OF SOUND TOLERANCE

DEFINITIONS AND CLASSIFICATION

Hyperacusis is a word that is used to denote a specific disorder of loudness perception but is also frequently used as a blanket term to describe all forms of decreased sound tolerance. Originally, disorders of sound tolerance were divided into hyperacusis, defined as a dislike of loud sounds, and phonophobia, defined as a fear of particular sounds and loudness recruitment, which is a specific experience that is associated with cochlear hearing loss and specifically with dysfunction of the outer hair cells of the organ of Corti.[249]

Jastreboff and Jastreboff[250, 251] recognized that many of their patients reported dislike of particular sounds but their emotional response did not constitute fear. They therefore employed the services of a Cambridge University classicist, Guy Lee, who devised a new word, misophonia, which they defined as a strong dislike of specific sounds. This new classification has not garnered universal support and a recent publication from an international working group has proposed an alternative set of definitions for decreased sound tolerance comprising loudness hyperacusis, annoyance hyperacusis, fear hyperacusis and pain hyperacusis.[252] With this definition, loudness hyperacusis and pain hyperacusis approximate to the previous definition of hyperacusis, annoyance hyperacusis to misophonia

and fear hyperacusis to phonophobia. To further complicate the terminology of disorders of sound tolerance, the neurological community describes phonophobia as part of the symptom complex experienced during migraine attacks. Such patients generally report a general dislike of sounds which would probably equate better to the audiological definition of hyperacusis, rather than phonophobia. Clearly, this field is ready for rationalization and reorganization.

In the following section hyperacusis is discussed as a specific symptom, and misophonia and phonophobia will be considered later.

HYPERACUSIS

Definitions

Definitive descriptions depict hyperacusis as an 'unusual tolerance to ordinary environmental sounds'[253] and as 'consistently exaggerated or inappropriate responses to sounds that are neither threatening nor uncomfortably loud to a typical person'.[254] In simple terms, hyperacusis is dislike of sounds above a certain intensity.

Epidemiology

There is a paucity of data to define the prevalence of hyperacusis. The available population surveys have suggested a prevalence of between 8% and 15%.[255, 256] The relation between tinnitus and hyperacusis has long been recognized and it has been suggested that hyperacusis may be a precursor state for tinnitus. Approximately 40% of patients who present with tinnitus also complain of hyperacusis.[30, 257] Of those whose primary complaint is hyperacusis, up to 86% report tinnitus.[31]

Pathophysiology

Hyperacusis and tinnitus often present together, and often in combination with hearing loss. This had led to speculation regarding a common underlying aetiology.[258, 259] Nelson and Chen have suggested that increased perception of sound intensity in the auditory cortex (hyperacusis) together with the perception of phantom sounds (tinnitus) results from a common trigger (hearing loss). A number of conditions have specifically been associated with hyperacusis.[258, 259] Some of these conditions, such as Bell's palsy and Ramsay Hunt syndrome, are associated with facial nerve dysfunction. However, since it is likely that in these cases the mechanism is due to an increased perception of sound intensity, secondary to an inefficient or absent stapedial reflex, some have considered that the resulting 'sound sensitivity' cannot truly be defined as hyperacusis.[260] Williams syndrome is a disorder characterized by deficits in conceptual reasoning, problem solving, motor control, arithmetical ability and special cognition[261] and hyperacusis has been reported to feature in 90% of individuals with this syndrome.[254] As Williams syndrome is associated with an underlying dysfunction of 5-hydroxytryptamine (5-HT), some have considered that the effects of 5-HT in other conditions, including migraine, depression and post-traumatic stress disorder, may lead to the increased auditory gain that may be responsible for hyperacusis.[262] Many other mechanisms have been suggested to underpin the neurophysiology of sound perception, with Jastreboff and Hazell proposing the central auditory system as playing the key role in setting auditory gain and perpetuating the perception of increased loudness.[48]

Investigation

Hyperacusis questionnaires are available but their sensitivity to treatment responses limit their usefulness as an assessment tool.[263, 264] Some clinicians recommend the measurement of loudness discomfort levels (LDLs) to confirm the diagnosis and quantify the problem whereas others suggest that the test is unreliable, risks alienating the patient and making the problem worse and has limited value with regard to planning. Certainly, if LDL testing is proposed in a patient with hyperacusis, they should be thoroughly counselled beforehand and offered an opportunity to decline the investigation. Stapedial reflex testing should be avoided in patients with hyperacusis because the procedure involves a loud test tone that many hyperacusis patients find unpleasant or painful.

Treatment

The usual response to an increased perception of loudness is for the patient to use a variety of types of ear protection in the form of ear plugs or ear defenders. This will often have the opposite to the desired effect by further increasing central auditory gain and exacerbating the patient's distress: there is evidence that sound deprivation worsens sound tolerance whereas enhancement of the acoustic background improves tolerance.[265] Although TRT was introduced primarily for the treatment of tinnitus, with minor modifications, TRT has been advocated for hyperacusis, with several studies demonstrating improvements in loudness tolerance.[266, 267] Psychological treatments have been used in the management of hyperacusis and there is evidence to suggest that CBT is efficacious.[268] Although there are anecdotal reports that other psychological modalities such as mindfulness meditation and ACT are being used in the treatment of hyperacusis, there is as yet no supportive literature.

MISOPHONIA

Definitions

As discussed under 'Definitions and classification' above, the term misophonia was created in 2001 to define a group of patients who dislike particular sounds irrespective of the level of the sound.[250, 251] The neologism literally means strong dislike or hatred of sound. Within the

classification system, phonophobia was retained as a subsection of misophonia when fear is the dominant evoked emotion.

In the late 1990s North American audiologist Marsha Johnson[269] recognized a group of patients who demonstrated negative emotions to a range of specific sounds generated by other humans, often repetitive sounds and often produced by oral or pharyngeal action. Causative sounds included those of lip smacking, throat clearing, chewing or breathing. Typical emotions included anger, disgust or anxiety and patients often demonstrated avoidance behaviour. This was termed selective sound sensitivity syndrome. Other terms including soft sound sensitivity syndrome or 4S have also been used.

The word misophonia has not been universally accepted by otologists and audiologists but patient support groups and mental health professionals have adopted it much more readily and it has gradually become synonymous with selective sound sensitivity syndrome. There have been multiple reports of patients with misophonia associated with psychiatric conditions including obsessive–compulsive disorder,[270–272] eating disorders[272, 273] and Tourette syndrome,[274] which has led some clinicians to suggest that misophonia should be reclassified as a specific psychiatric condition.[272] The authors who developed the new word, misophonia, have opposed this proposed reclassification, stating that mental health issues are rare in their series of patients with misophonia. They go on to suggest that the other authors must be reporting patients with psychiatric conditions who have coincidental comorbid misophonia.[275] It seems likely that further debate in this field will ensue.

Epidemiology

Demographic details of misophonia are slowly emerging. Case reports and small series of patients have been reported from Europe,[272, 273, 276] North America,[277] South America[271] and Australia.[274] To date there is no gender difference but, because the number of subjects is small, this observation may be premature. The onset of the problem is generally peripubertal with the largest study (n = 157) demonstrating a mean age of onset of 12 years.[278] There is a dearth of information regarding the prevalence and incidence. Jastreboff and Jastreboff used figures regarding the prevalence of tinnitus and the comorbidity of tinnitus and misophonia to extrapolate a population prevalence figure of 3.2%.[275] However, a study performed in a group of psychology undergraduate students has suggested that the prevalence might be much higher: 23.4% of participants reported that they were sometimes sensitive to specific sounds and 19.9% felt that this has had an impact on their lives.[279]

Clinical features

Sounds that trigger misophonia are generally sounds produced by other humans and in many cases the sound is produced by a specific person, often another family member.[270–272] The most common causative sounds are orally generated including eating, breathing, whistling, gum chewing and lip smacking. Other repetitive sounds, such as fingernail clipping or clicking the top of a pen, may trigger the symptom.[272] Environmental sounds such as wind, rain or waves do not generally trigger misophonia. Sounds produced by the person with misophonia generally do not elicit a misophonia response even if the sound is very similar to their normal triggers. Anger, disgust or irritation are the most frequently described emotions,[278] followed by anxiety or panic. Most people with misophonia will display avoidance behaviour, trying to stay away from the trigger sound or sounds. A few will confront the person producing the sound but actual aggression seems uncommon.[274, 277] A few patients are reported to have developed tics as a response to their trigger sound and a few have developed coping strategies such as mimicking the causative sound.

Investigation

There is a general lack of data regarding the audiological status of patients with misophonia. One study investigated 20 patients with misophonia and 14 controls, using a form of evoked-response audiometry.[280] The results of this study suggested that patients with misophonia could have an underlying central auditory processing problem. A recent study compared six patients with misophonia and five controls when exposed to a range of sounds which included sounds such as birdsong, that are generally regarded as pleasant, and other sounds, such as fingernails on a blackboard, that are usually perceived as unpleasant.[270] Skin conductance measurements were obtained: both groups found similar stimuli to be unpleasant but the reaction demonstrated by the people with misophonia was greater than the reaction in the control group.

Various questionnaire tools for assessing misophonia have or are being developed. These include the Amsterdam Misophonia Scale,[272] the Misophonia Questionnaire,[279] the Misophonia Assessment Questionnaire,[281] the Misophonia Coping Response Survey[281] and the Misophonia Trigger Survey.[281] These tools have yet to enter widespread usage.

Pathophysiology

Various suggestions regarding the pathophysiology of misophonia have been made. These include abnormal activation of the limbic and autonomic nervous systems,[282] psychological conditioning to repetitive events,[272] a generalized hyper-reactivity condition, a defect in serotonin and dopamine utilization in the limbic system and basal ganglia, or a variant of synaesthesia.[270, 283] There is no robust scientific evidence behind any of these hypotheses and the mechanism must still be regarded as unclear. Moller has pointed out that, as the problem is linked to specific sounds, it is likely that the anatomical location of the problem is downstream from initial sound processing areas and may be situated in the inferior part of the temporal lobe where the nature of sounds or ‘what’ information is processed.[284]

Treatment

The management of misophonia is still a matter of conjecture.[285] Multidisciplinary team management has been suggested[286, 287] and, as both otological and mental health assessment may be required, this approach seems logical. Structural brain pathology has not been reported with misophonia so there is a low requirement to undertake brain imaging. Anecdotally, reassurance and education directed to both the patient and family may be helpful. The presence of an associated specific psychological problem may dictate a specific mental health pathway. CBT has been reported as effective in a single case.[269] Sound therapy can be used to desensitize patients: Jastreboff and Jastreboff suggest a treatment strategy based on TRT using a combination of counselling and sound therapy.[275] Allowing the affected person to wear headphones when in the presence of their misophonia trigger has also been suggested.[286] There is no pharmacological treatment yet identified, though drugs may have a role in the management of associated conditions such as anxiety.

BEST CLINICAL PRACTICE

- ✓ All patients with tinnitus should undergo a basic audiological assessment. Further investigation should be undertaken in the following groups: those with pulsatile tinnitus; unilateral tinnitus; tinnitus in association with asymmetric hearing loss; tinnitus in association with significant vertigo; tinnitus in association with neurological symptoms and/or signs.
- ✓ Comorbidities are common, particularly anxiety, depression and disorders of sound tolerance (hyperacusis). Insomnia is also common in tinnitus patients. These factors should be considered during the history-taking process.
- ✓ Although there is currently no drug treatment for subjective idiopathic tinnitus, drugs may have a role in the management of comorbid conditions such as anxiety and depression.
- ✓ Patients are often given negative counselling, being told that nothing can be done for tinnitus. While a cure for tinnitus remains elusive, there are many helpful management strategies, particularly sound based therapies, counselling and psychological therapies. Surveys have shown that many patients with tinnitus are investigated in secondary care but are never offered any therapeutic intervention. Negativity should be avoided, and patients should be referred onward to audiology, hearing therapy or mental health services as appropriate.
- ✓ When tinnitus is associated with hearing loss it is usually helpful to try and correct this loss, surgically if appropriate, or via the use of hearing aids.

FUTURE RESEARCH

Despite major advances in our understanding of tinnitus, many major questions remain unanswered. In particular, we do not fully understand the fundamental mechanisms behind the development of tinnitus in many groups of patients. There is no reliable method to consistently measure tinnitus, and a universally effective drug treatment does not currently exist. However, as we gain more understanding about this intriguing condition, basic research has introduced many different routes to allow the investigation of the pathophysiology, diagnosis and treatment of many of the different presentations of this condition. Furthermore, tinnitus and its allied conditions have become a focus of attention within many different disciplines outside the traditional domains of ENT and audiology. A number of major research organizations are currently investing significant amounts of money to research this condition. The goal for many is to identify a 'cure', but during this journey tinnitus research has benefited our understanding of how the auditory system and the brain perceive and process sound in ways that we might never have considered.

KEY POINTS

- Tinnitus is common: prevalence in the UK population is estimated at approximately 1 in 10. For about 1 in 200, tinnitus has a severe effect on the activities of daily living.
- Epidemiological studies suggest that most people with tinnitus go through a process of habituation and the impact of the symptom gradually lessens with time.
- Tinnitus is more common in people with a hearing loss but the degree of hearing impairment correlates poorly with tinnitus severity. About 1 in 10 people presenting with tinnitus have a normal audiogram. Tinnitus can exist after division of the auditory nerve.
- Modern models suggest that tinnitus is due to increased awareness of spontaneous electrical activity in the auditory system. Although changes in the auditory periphery can trigger tinnitus, the processes that cause the symptom to perpetuate and become distressing occur in the central auditory pathways and in associated brain regions, particularly the limbic system.
- Tinnitus is rarely a harbinger of serious pathology, but careful clinical assessment is recommended.
- A blocked sensation in the ears is common among tinnitus patients though generally there is no evidence of Eustachian tube dysfunction.
- Interventions that improve hearing are often helpful and various audiological and psychological management strategies for tinnitus have been developed.
- Disorders of sound tolerance are common but terminology is confused, pathophysiology is unclear and many questions remain regarding management.

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CHAPTER 62

EVALUATION OF BALANCE

Adolfo M. Bronstein

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: vestibular, eye movements, balance, clinical tests, dizziness and vertigo.

SYMPTOMS IN BALANCE DISORDERS

Patients with disorders of balance are common, not only in otolaryngology clinics but also in neurology, general practice, internal medicine and geriatrics. It can be estimated that dizziness, vertigo and unsteadiness accounts for one-fifth of referrals to ENT and neurology clinics. This is not surprising since approximately one-quarter of people experience dizziness at some time in their life and in 80% of cases this is severe enough to see a doctor.[1] The rise in ageing population worldwide is likely to increase these percentages since dizziness occurs in almost 50% of people over the age of 75 years.[2]

There have been many developments in the field of balance and vestibular testing but, as in other branches of medicine, nothing replaces a good clinical history. The techniques used and ranges of normality adopted by different vestibular laboratories can be very disparate and so 'positive', 'objective' vestibular findings must be taken strictly within the appropriate clinical context. Reciprocally, some clinical histories are so typical that the absence of corroborative findings on a single visit to the clinic should not make the clinician rule out a diagnosis: for example, a patient with brief vertigo on turning over in bed, so typical of benign paroxysmal positional vertigo (BPPV), but negative positional testing on his first visit.

The symptoms that patients with balance or vestibular disorders may report are vertigo, dizziness, nausea, motion intolerance, unsteadiness and oscillopsia. Associated anxiety and depression are also extremely common. It is of vital importance, in all balance symptoms, to identify triggers provoking the symptoms, such as position, movements or visual or acoustic triggers. It is equally important to determine if the symptom is acute, episodic or chronic, and whether it occurs alone or in association with other symptoms (e.g. audiological, visual or neurological).

Vertigo and dizziness

Vertigo, when defined as an illusion of either oneself or the environment rotating, is a reliable symptom. It indicates involvement of the angular motion sensing system, i.e. the semicircular canals and their central projections. However, such involvement can occur from the labyrinth up to the vestibular cortex so that the site of the lesion will have to be presumed by additional symptoms (**Table 62.1**). Of particular value are hearing loss or tinnitus, usually indicating labyrinthine or VIII nerve involvement, and brainstem symptoms such as frank diplopia, facial numbness/weakness and dysarthria. Acute vertigo is terrifying and disabling and its duration can be a good guide to diagnosis. In BPPV it is usually less than a minute; in migraine-associated vertigo (= vestibular migraine) it can be from minutes to many hours; in Ménière's disease a few hours; and in acute vestibular neuritis and consolidated brainstem stroke a few days.

Illusions that one is moving linearly, such as falling vertically downwards or linear vertigo, can arise from disorders of the otolith system but it is extremely difficult to confirm selective otolith lesions and thus the clinical value of linear vertigo as a symptom is less well established.[3, 4] There is no evidence to classify postural symptoms, such

TABLE 62.1 Additional symptoms helpful in the topographical diagnosis of balance disorders

Site of lesion	Symptom	Comment
Peripheral (labyrinth or VIII nerve)	Tinnitus	
	Hearing loss	
Special cases		
Labyrinthine	Ear fullness	Ménière's disease
CP angle	V, VI, VII cranial nerves	Extracanalicular growth
VII + VIII neuritis	Ext auditory canal vesicles + VII	Ramsay Hunt syndrome
Brainstem	Diplopia (III, IV, VI or skew deviation)	
	Facial numbness (V)	
	Difficulty swallowing, choking (IX, X)	
	Slurred speech (XII, cerebellum)	
	Uni-bilateral numbness, weakness, ataxia (long tracts, cerebellum)	
	Unilateral deafness (+ ataxia)	AICA infarct
Cerebral hemisphere	Unilateral weakness, numbness	
	Hemianopia (parieto-occipital lobe)	MCA/PCA
	Blindness (both occipital lobes)	Both PCAs
	Loss of consciousness	
	Syncope, cardiac arhythmia	Common
	Epilepsy	Rare (in vertigo)

AICA, anterior inferior cerebellar artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.

as lateropulsion or retropulsion, as specifically otolith-related. Despite traditional emphasis on defining symptoms precisely, patients may find it difficult to describe clearly and experienced clinicians know that dedicated efforts to distinguish vertigo from dizziness in individual patients does not always pay off. Dizziness and giddiness are common terms employed by vestibular patients to describe their problems. There is no good definition for these terms. One should encourage the patient to describe what they mean by dizziness and/or to compare it to situations that they may have experienced. Body language is also important as many patients wave a hand round and round when describing their dizziness, implying actual rotational vertigo. When the dizziness is non-rotational, it is less certain that the problem lies in the vestibular system. Descriptions such as rocking or swimming sensations, light-headedness, walking on cotton wool, feeling detached, can also be vestibular. However, one often needs independent evidence to reach this conclusion. Such evidence may be difficult to find on vestibular testing, such as a significant caloric canal paresis, or a preceding history of rotational vertigo. There are numerous non-primarily vestibular causes of dizziness and light-headedness, including anaemias, drug toxicity and psychological dizziness to name just a few (Table 62.2).

TABLE 62.2 Some non-vestibular causes of dizziness

Type	Possible causes
Endocrine	Hypoglycaemia Adrenal failure Pheochromocytoma
Cardiovascular	Vasovagal syncope Orthostatic hypotension Embolic disease Cardiac dysrhythmias
Haematological	Hyperviscosity syndromes Anaemias
Psychological	Anxiety Phobias Panic attacks

Some patients indicate clearly that they have no 'head' sensations. They are unsteady, off balance or clumsy on their feet, 'not dizzy in the head'. They feel fine if seated or lying down. In such cases it is useful to ask if relatives or friends have made any comments about the patient's balance. If there is an objective, visible balance problem, this is more likely to be a neurological gait disorder, with patients just perceiving their own objective dysequilibrium. If these patients trip over or are pushed over in a crowd, they can stumble or fall. The lesion may lie anywhere in the somatosensory motor chain (peripheral nerves, spinal cord, cerebellum or cerebrum) and the clinician should enquire about symptoms represented at these various levels in the neuraxis, such as weakness, numbness, incoordination, tremor, sphincters, memory and other cortical functions. Enquiries as to the presence of falls as a result of poor postural balance should be actively made, particularly in the elderly patient. If present, prevention of further falls becomes an urgent matter. Fall-related complications in the elderly are a major killer and public health problem.[2]

Motion intolerance

Anyone who has ever been motion sick will understand that patients with vestibular disorders dislike movement. In the acute phase of Ménière's disease or vestibular neuritis the picture is dramatic. The patient is bedridden and terrified of even going to the toilet; any movement brings more vertigo, nausea and vomiting. Symptoms gradually settle over time. A patient with vestibular neuritis may have strong rotational vertigo and nausea for 3 days, followed by dizziness for 3 weeks and by light-headedness for 3 months. In these latter stages, however, patients tend to avoid head movements or looking at moving visual scenes. Unfortunately, in some patients, light-headedness, dizziness and motion intolerance can last for many months or years, for reasons that are not completely understood.

A complex interrelation between lack of effective vestibular compensation, idiosyncratic perceptual style, migraine and anxiety may be at play.[5]

Oscillopsia

The intolerance to visual motion mentioned in the previous paragraph is sometimes called visual vertigo, visually induced dizziness, space and motion discomfort, visuovestibular mismatch or simply 'the supermarket syndrome'.[6] This should not be confused with oscillopsia, which is the movement or oscillation of the visual surroundings.[7] Oscillopsia is described by patients as jumpy, jerky, bobbing, wobbly or sometimes just blurred vision. In the balance disorder patients, always consider the possibility that a patient's complaint of blurred vision or difficulty in focusing might be oscillopsia.

The critical question to ask a patient with oscillopsia is 'when': when does it happen?[7, 8] Is the oscillopsia present during movement, or only triggered or present in certain head positions, or unrelated to movements (Table 62.3)? Oscillopsia during head movements (e.g. while walking, driving, shaking the head) is due to a defective vestibulo-ocular reflex (VOR), typically bilateral vestibular lesions as encountered after meningitis, gentamicin ototoxicity or idiopathic. Oscillopsia present in certain head positions (e.g. lying but not seated or vice versa) is likely to reflect a positional nystagmus, usually of a central CNS origin. Oscillopsia unrelated to head movement can be continuous, in which case the patient is likely to have an acquired CNS nystagmus (e.g. acquired pendular nystagmus, downbeat nystagmus (DBN), torsional nystagmus) or just be paroxysmal, i.e. in attacks. Paroxysmal oscillopsia can be spontaneous, as in paroxysmal nystagmus and ocular oscillations of central origin, vestibular paroxysmia or, more commonly, voluntary nystagmus. Some patients with idiopathic bilateral loss of vestibular function present with paroxysmal oscillopsia.[9] Triggered paroxysmal oscillopsia is rare; the most common being the Tullio phenomenon,[10, 11] as in the superior canal dehiscence syndrome,[12] where patients report jumpy vision and lateropulsion in response to loud sounds or Valsalva manoeuvres.

TABLE 62.3 Causes of oscillopsia

When?	Syndrome	Examples
During head movements	Absent VOR	Ototoxicity, idiopathic, post-meningitic
Triggered by head movements	Positional nystagmus	Positional DBN
Unrelated to head movements		
Continuous	CNS nystagmus	DBN, pendular nystagmus
Paroxysmal	Paroxysmal eye oscillation	Voluntary nystagmus Progressive vestibular failure, vestibular paroxysmia

DBN, downbeat nystagmus.
Modified from Bronstein.[7]

Vertigo presentations

The first thing to ascertain is whether the patient's problem is a single vertigo episode (acute vertigo), recurrent (or episodic) vertigo or chronic dizziness. Once this is established the key to diagnosis lies in identifying triggering factors and associated symptoms. Tables 62.4, 62.5 and 62.6 summarize this topic.

SINGLE ACUTE EPISODE OF VERTIGO

An acute single spontaneous episode of rotational or 'true' vertigo can be encountered in acute vestibular neuritis (or neuronitis), which has no hearing symptoms, a vascular or inflammatory disorder of the labyrinth (labyrinthitis), usually with hearing loss, and a brainstem stroke, usually with other CNS symptoms. In all

TABLE 62.4 Vertigo presentations: single vertigo episode

Hearing	Possible cause
Hearing spared	Vestibular neuritis (or neuronitis or viral labyrinthitis or neurolabyrinthitis)
	Head injury
Hearing involved	Head injury
	Labyrinthine fistula
	Viral infection (mumps, Ramsay Hunt)
	Vascular disorder (labyrinthine stroke)

Modified from Bronstein and Lempert.[8]

TABLE 62.5 Vertigo presentations: episodic or recurrent vertigo: accompanying features

Accompanying feature	Possible cause
Positional	BPPV (on lying or turning in bed) Orthostatic hypotension (on standing)
Paroxysmal	Vestibular paroxysms
Migraine	Vestibular and basilar migraine
Hearing disorder	Ménière's syndrome or hydrops
Ataxia	Episodic ataxias
Brainstem symptoms	Transient ischaemic attacks (TIA)
Autonomic-anxiety-avoidance	Panic attacks
Faintness	Heart disease, vasovagal syncope
No accompanying features	Benign recurrent vertigo (BRV)*

* Benign recurrent vertigo,[13] recurrent peripheral vestibular disorder or vestibular Ménière's disease are names given to describe patients with recurrent peripheral vertigo which does not fall into any other category such as Ménière's disease or migraine.
Modified from Bronstein and Lempert.[8]

TABLE 62.6 Vertigo presentations: symptom triggers in patients with episodic vertigo

Trigger	Possible cause
Lying down, turning over in bed	BPPV
Standing up	Orthostatic hypotension
Neck movements	Any vestibular disorder
Pressure changes	Fistulas
Loud sounds	Tullio phenomenon
Alcohol, exercise	Episodic ataxias

Modified from Bronstein and Lempert.[8]

these conditions the vertigo is usually severe and prolonged, inevitably leading to autonomic symptoms, such as nausea, vomiting, pallor, sweating and malaise. It must be borne in mind that any vertigo is more tolerable when the head is kept still. Only provocation, not exacerbation, of vertigo by movements or positions of the head should be labelled as positional vertigo. The clinician should actively ask for additional hearing or CNS symptoms, such as slurred speech, facial or limb numbness or weakness, diplopia and swallowing problems. Intense vertigo can be so overwhelming that some patients may not volunteer other symptoms (Table 62.4). In recent years the distinction between peripheral and central acute vertigo has become a hot topic because of new available therapies for stroke, mainly thrombolysis. Given that the window of treatment opportunity is only a few hours, various 'red flags' have been described (see Box 62.1).

The presence of recent or concurrent general illnesses should be sought. In vestibular neuritis, patients can report a recent upper respiratory tract infection. Mumps can affect both the cochlear and vestibular labyrinth. Patients with herpes zoster oticus or Ramsay Hunt syndrome can have a peripheral facial palsy and show herpetic vesicles in the outer ear canal. The presence of risk factors such as smoking, hypertension, obesity or diabetes can suggest a vascular aetiology.

RECURRENT OR EPISODIC VERTIGO

The presence of triggers becomes critically important for diagnosis in the patient with recurrent vertigo or dizziness. Certain triggering by head movements, such as looking up, lying down or turning over in bed, are highly suggestive of BPPV. Incorrectly, clinicians often jump to the conclusion that dizziness related to neck movements (inevitably associated with head movements!) indicates cervical or vertebrobasilar vertigo before excluding a much more likely vestibular disorder.[15] Triggering by loud sounds or Valsalva manoeuvres suggests the Tullio phenomenon, often due to superior canal dehiscence or labyrinthine fistula. In some patients with migraine-associated vertigo, food or sleep deprivation or certain foods (chocolate, cheese, red wine) may be triggers. Orthostatic hypotension induces light-headedness, dizziness and even true rotational vertigo,[16] on standing up suddenly or after being standing up for a long time, particularly in the heat or motionless. Exercise, alcohol or stress can trigger an attack in patients with episodic ataxias or channelopathies, which usually includes vertigo (see Tables 62.5 and 62.6).[17]

BOX 62.1 'Red flags' for acute brain imaging in acute vertigo

Modified from Seemungal and Bronstein[14]

- Acute unilateral deafness
- Acute (occipital) headache
- Any central symptoms or signs
- A negative (normal) head-impulse test

Associated symptoms, such as aural fullness, tinnitus and hearing loss, may suggest Ménière's syndrome. Associated brainstem symptoms can indicate vertebrobasilar transient ischaemic attacks (TIA) whereas palpitations, breathlessness or loss of consciousness would suggest a cardiac arrhythmia. Patients with panic attacks can also report dizziness, palpitations, fear of dying and breathlessness but the social triggers and the ensuing avoidance behaviour are highly suggestive of this diagnosis – the three 'As', autonomic, anxiety and avoidance. Patients with presyncopal dizziness can report sensations of feeling hot or cold, clammy and sweaty, greying out of vision and bilateral tinnitus. The presence of frank ataxia may indicate paroxysmal ataxia (e.g. episodic ataxia type 1 or 2, spinocerebellar degeneration type 6 or other channelopathies). The presence of migrainous symptoms, such as visual aura, throbbing headaches, nausea, photophonophobia, must be enquired;[18] migrainous vertigo can precede, overlap, follow or occur independently of a migraine headache.

CHRONIC DIZZINESS

The majority of patients with a single acute vertigo attack recover fully and the majority of patients with recurrent vertigo are free of symptoms between attacks, but not all. Since vertigo and dizziness are so prevalent in the community, this small proportion of patients with long-term dizziness makes up enough absolute numbers to fill up specialized clinics.

There is no simple explanation as to why some patients do not fully recover from a single attack or episodic vertigo. The actual vestibular loss is unlikely to be the reason since patients with vestibular schwannomas rarely suffer from any troublesome dizziness. Hence, a slow rate of progression as opposed to an acute onset may play a part. Failure of the compensatory mechanisms is also often invoked and this may be due to a variety of factors. This evidence cannot be fully reviewed here but aggravating or limiting factors include:

- fluctuating vestibular lesion, as in hydrops, which poses a challenge to the central compensatory processes
- an idiosynchratic trend in some subjects to rely excessively on visual cues, or 'visual dependence', which perpetuates intolerance to visual motion (visual vertigo or supermarket syndrome)

BOX 62.2 Factors interfering with vestibular compensation

Fluctuating vestibular disorder
Additional disorder:
- CNS
- Peripheral nerve
- Cervical spine
- Visual

Lack of mobility
Drugs
Visual dependence ('visual vertigo')
Psychosocial

CNS, central nervous system.

- psychological factors, including pre-existing or reactive anxiety, depression or phobias
- excessive bedrest and lack of physical activity, sometimes prescribed by doctors unaware of the importance of motion exposure as a promoter of vestibular compensation
- excessive use of psychotropic and antivertiginous medication
- concomitant visual or neurological disorders (**Box 62.2**).

In the elderly, there are usually many of these factors operating simultaneously.

Finally, the otologist should bear in mind the possibility that the sense of unsteadiness reported by the patient may be due to a general medical disorder or to neurological or psychogenic gait disorders (**Box 62.3**). The latter, particularly in the form of an overcautious gait, can be triggered in the elderly by a fall or an episode of vertigo, so full investigation is warranted. Pain during locomotion (e.g. hip arthritis) will also aggravate any gait disorder.

BOX 62.3 Chronic dizziness – mental checklist

Is it oscillopsia rather than dizziness?...See Table 62.3
Is it a gait disorder?.....See Tables 62.10 and 62.11
Is it a general medical disorder?.....See Table 62.2

EXAMINATION OF THE PATIENT WITH A BALANCE DISORDER

One of the disappointing aspects of balance disorders is that both the ENT and neurological examination are often entirely negative, except perhaps in the acute phase. This should not bias clinicians into thinking that it is not worth thoroughly examining the patient; much money, time and suffering can be spared by carrying out a Hallpike manoeuvre instead of organizing a head scan in a patient with BPPV!

A standard neuro-otological assessment should include auroscopy, eye movement, positional manoeuvres and posture and gait examination. Auroscopy is covered in Chapter 73, Clinical examination of the ears and hearing.

Eye movements

CLINICAL EXAMINATION OF EYE MOVEMENTS

The vestibular system provides a powerful input to the oculomotor system so eye movements must be examined in detail. In a patient suspected to have a peripheral vestibular disorder (labyrinth and VIII nerve) one can consider that the examination has two broad aims.

1. One is to search for direct ocular signs indicative of a peripheral vestibular disorder, typically nystagmus, BPPV or a positive head thrust test (see under 'Head-impulse test' below).
2. The other is to exclude CNS lesions by making sure that non-vestibularly mediated eye movements are normal.

The oculomotor examination should include:

- search for spontaneous and gaze-evoked nystagmus
- convergence
- smooth pursuit
- saccades
- vestibulo-ocular reflexes
- positional manoeuvres.

General updated reviews of eye movement assessment are available.[19, 20]

If the patient reports diplopia, or if at any point during the examination the two eyes appear disconjugate, a formal examination of the individual cranial nerves III, IV and VI is mandatory. This usually requires a separate eye cover test in the six cardinal positions of gaze to identify the weak individual muscle or group of muscles (right – horizontal, up and down; left – horizontal, up and down). Before embarking on a complex examination with which the ENT surgeon may not feel completely at ease, it is useful to confirm with the patient whether he was aware of the presence of an old squint, weak/lazy eye or congenital nystagmus. If there is an infantile squint, the ocular examination is more difficult to interpret.

SPONTANEOUS NYSTAGMUS

The search for spontaneous nystagmus begins in the primary, straight-ahead position of the eyes. In the presence of nystagmus, ascertain the waveform – essentially sawtooth or jerk nystagmus (in which case you should identify the direction of beat) or pendular nystagmus, which has no fast-phase or beating direction (**Figure 62.1**). Since spontaneous nystagmus often enhances by convergence, it is convenient to examine convergence at the same time, by slowly moving an object in and out along the visual axis. Absence of convergence occurs in midbrain lesions but one must remember that reduced/absent convergence is extremely common in normal people above the age of 60 years of age.

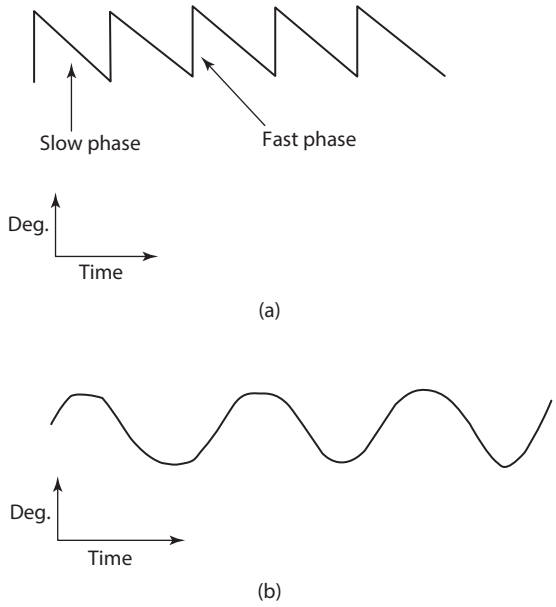


Figure 62.1 (a) Nystagmus waveforms, jerk or saw-tooth; and **(b)** pendular nystagmus. The former can be peripheral or central but the latter is only of central origin but usually non-acute.

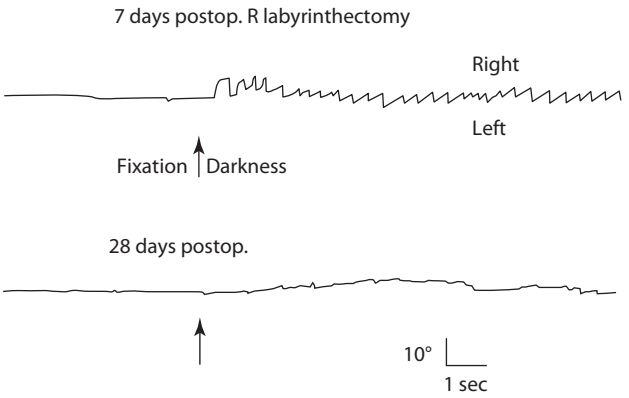


Figure 62.2 Acute and compensated peripheral vestibular nystagmus. Note that at 1 week after labyrinthectomy the nystagmus in the light was negligible but increased notably in the dark. At 1 month follow-up vestibular compensation had effectively reduced the nystagmus in the dark. Also note the rectilinear slow phase velocity of the nystagmus, in agreement with its peripheral origin.

While in primary gaze, one should undertake a cover test, particularly in patients with difficult-to-interpret eye signs. The cover test is usually part of the examination to assess diplopia and ocular alignment, but what we suggest here is a simplified version of the test, looking for the presence of latent nystagmus. Latent nystagmus is a common congenital oculomotor disorder.[3, 4] Typically, these patients have no nystagmus during binocular viewing but, on covering one eye, the uncovered eye beats horizontally away from the covered eye (both eyes beat but one can only see the uncovered one). It can be observed on covering one or the two (one at a time) eyes. The value of discovering latent nystagmus, which is essentially asymptomatic, lies in the fact that this condition is often associated with congenital squints, nystagmus, square wave jerks, abnormal pursuit or optokinetic nystagmus. Thus, finding latent nystagmus in a patient with an abnormal, 'central-looking' oculomotor examination strongly suggests that the findings are congenital rather than relevant to a recent complain of vertigo or loss of balance.

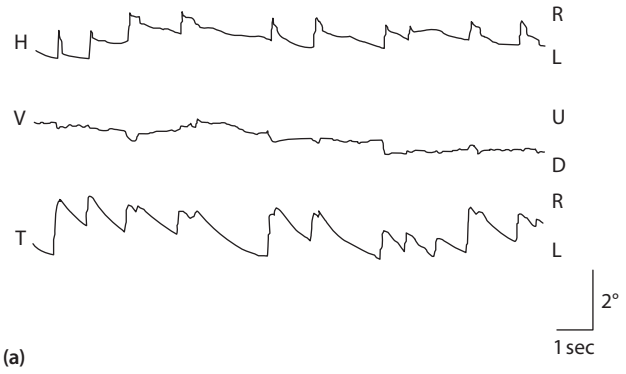
When examining nystagmus as well as other eye movements, patients have to be clearly instructed to look at a predetermined object and the eyes should be well illuminated. The presence of spontaneous nystagmus in primary gaze immediately raises the question of whether it is caused by a central or peripheral lesion. If the patient is in the middle of an acute vertigo attack, with severe unsteadiness and nausea, it can be peripheral or central, but if the patient comes as a routine ambulatory patient and does not look acutely ill, the nystagmus is more likely to be of central origin. In practice, a nystagmus of peripheral vestibular origin, observable by the naked eye in primary gaze, can only come from an acute, massive vestibular imbalance, as in vestibular neuritis, Ménière's attack, recent labyrinthine surgery or trauma (Figure 62.2). The nystagmus is essentially horizontal, with a minor torsional (rotatory) component. The fast phase beats contralesionally but can beat ipsilesionally in the acute irritative phase of a Ménière's attack.

Can a nystagmus like this result from a central lesion? Yes, in particular lesions in the VIII nerve root entry zone, vestibular nuclei or cerebellum but, almost invariably, there are additional brainstem symptoms and signs. Any other nystagmus is almost certainly of central origin. These differ from a peripheral vestibular nystagmus in waveform (e.g. pendular, a quasi-sinusoidal oscillation of the eye without distinction between slow and fast phases – Figure 62.1),[21] or beat plane (e.g. vertical up or downbeat or torsional nystagmus – Figure 62.3).[22] A large, horizontal nystagmus in a patient with no significant vestibular or neurological symptoms should always raise the possibility of congenital nystagmus.[23]

GAZE-EVOKED NYSTAGMUS

Soon after the acute stage of a peripheral vestibular lesion, the nystagmus is not visible in primary gaze but only on deviation of gaze to the opposite side of the lesion, i.e. in the direction of the fast phase. A useful classification for the severity of the nystagmus, based on this observation, has stood the test of time. First-degree nystagmus is a nystagmus only visible on gaze deviation in the direction of the fast phase, second-degree when present in primary gaze, and third-degree when it is also visible when the eyes are deviated in the opposite direction to that of the fast phase. A second- or third-degree nystagmus will enhance on gaze deviation in the direction of the fast phase (Alexander's law; Figure 62.4). However, the severity scale and Alexander's law apply mostly to peripheral vestibular nystagmus. For instance, DBN in primary gaze, which is always of central origin, often does not enhance on looking down but on looking sideways.

Nystagmus on gaze deviation can also indicate a central lesion. This is what is frequently called 'gaze paretic'



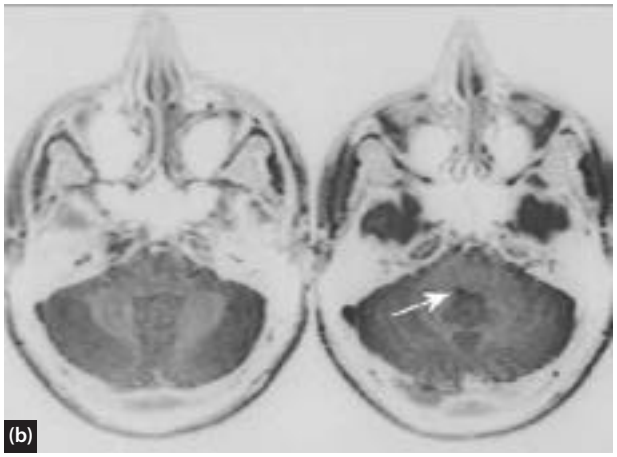


Figure 62.3 (a) Three-dimensional scleral search coiled oculography in a patient with a small demyelinating left-sided brainstem lesion, as shown on MRI **(b)** (arrow). The presence of a clinically observable torsional component in the spontaneous right beating nystagmus indicated that the lesion was central rather than peripheral. H, V and T are horizontal, vertical and torsional eye recordings. Left side of the brain is on the left side of the scan.

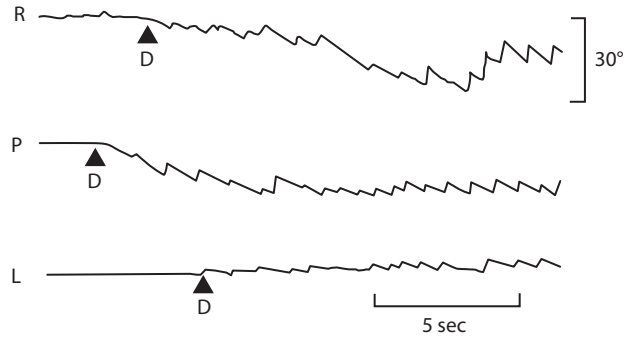


Figure 62.4 The effect of fixation and gaze deviation (L, left; P, primary; and R, right positions) on peripheral vestibular nystagmus. Horizontal EOG recordings begin in the light and continue in the dark (D). Note the increase of the nystagmus with gaze deviation in the direction of the fast phase (Alexander's law). Reproduced by kind permission of P. Rudge.

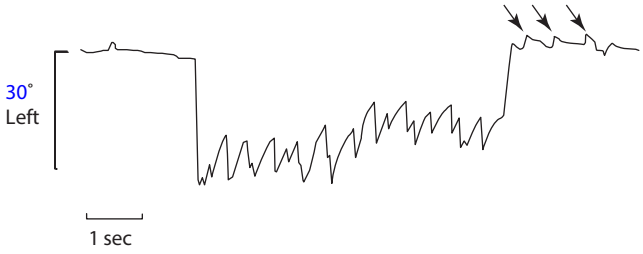


Figure 62.5 Left-beating gaze paretic and rebound nystagmus (arrows) in a cerebellar lesion. Note the exponentially decreasing slow phase velocity (slope) of the nystagmus. Reproduced by kind permission of P. Rudge.

nystagmus, not to be confused with the broader term 'gaze-evoked' nystagmus. A subacute peripheral vestibular lesion can have a gaze-evoked nystagmus, i.e. a second-degree nystagmus as discussed above. Instead, the term gaze paretic implies that the patient has difficulty in holding gaze in an eccentric position in the orbit. The eyes drift in centripetally with a slow phase which progressively decreases in velocity, until a new saccade refixates the eccentric target (Figure 62.5). This nystagmus, usually of larger amplitude than vestibular nystagmus, is due to damage to the gaze-holding mechanisms mediated by ipsilateral brainstem and cerebellar structures. An example of vestibular and gaze paretic nystagmus present in the same patient is Brun's nystagmus due to a large extracanalicular vestibular schwannoma. The vestibular nystagmus beats, as expected in any destructive vestibular lesion, in the opposite direction of the tumour. The coarser nystagmus, evoked by looking in the same direction of the tumour, is gaze paretic, due to cerebellar–brainstem compression (Figure 62.6). Gaze paretic nystagmus can be present in all directions of gaze in the same patient, typically in symmetrical processes such as cerebellar degenerations.

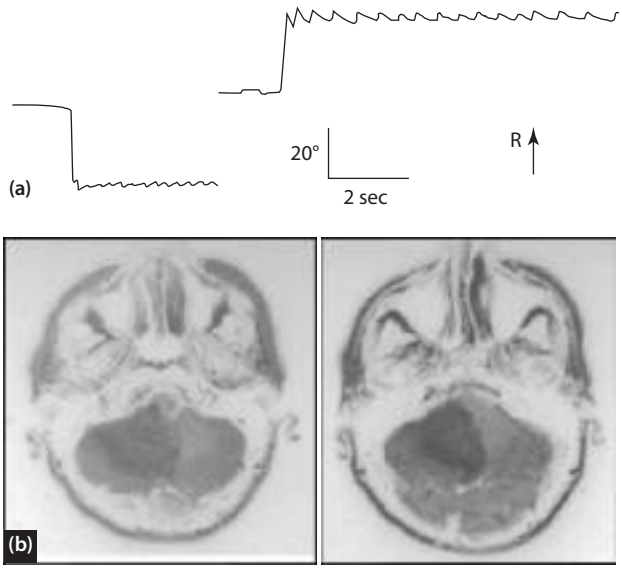


Figure 62.6 Brun's nystagmus due to a right-sided pontine glioma; **(a)** vestibular nystagmus on left gaze; **(b)** a larger gaze paretic nystagmus. Typically, large vestibular schwannomas compressing the brainstem produce this nystagmus combination.

SMOOTH PURSUIT EYE MOVEMENTS

When tracking an object with our eyes, we use a combination of fast (saccades) and slow-phase eye movements. Strictly speaking, only the latter should be considered smooth pursuit. When the target moves slowly (<10–15 degrees per second) the eye is capable of following it almost exclusively with smooth pursuit movements. The pursuit system is velocity limited so that, when targets move at velocities of 40–50 degrees per second or faster, the proportion of tracking carried out by saccades increases progressively. Clinically speaking, pursuit looks abnormal, or 'broken up', when the observer detects too much saccadic tracking; this gives a cogwheel, jerky appearance to the pursuit movements (**Figure 62.7**). The message for the clinician is: move the target slowly, otherwise everybody shows 'broken pursuit'.

Investigation of pursuit eye movements is a vital component of the neuro-otological examination. There may be occasional exceptions but, in principle, the presence of normal pursuit rules out a central vestibular disorder and, vice versa, a patient with balance symptoms and unequivocally broken pursuit movements almost certainly has a neurological rather than a labyrinthine disorder. In order for the clinician to reach these conclusions confidently, the examination has to be technically correct.

- Since pursuit movements are visually guided, rule number one is that the patient should be able to see the target correctly. Any object can be a target, not only the examiner's finger or pen. In patients who are too young, too old or with attentional problems, a substantial, solid target such as a key, a toy, a mobile phone or a credit card can increase performance. Make sure that in elderly subjects, with presbiopia and age-related convergence insufficiency, the object is presented at a comfortable viewing distance. Sometimes, the examination must be conducted with the patient wearing his/her own glasses.
- Rule number two is that the target has to be moved at a slow speed, taking 4–5 seconds to travel from right to left and vice versa (i.e. approximately 0.1 Hz). One cycle is usually not enough since many patients do not understand the task and tend to jump their eyes ahead of the target; the patient should be encouraged to 'glue your eyes to the target'. Pursuit should be investigated in the horizontal and vertical planes.

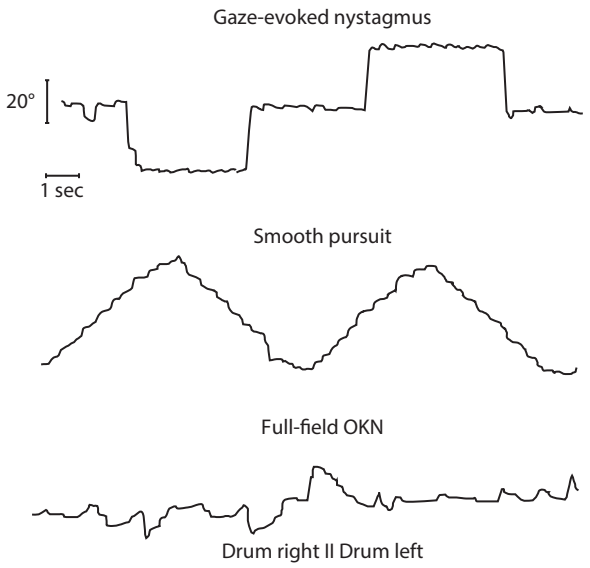


Figure 62.7 Cerebellar degeneration producing gaze-evoked nystagmus, broken ('cogwheel') pursuit and almost complete absence of optokinetic nystagmus.

It is easy to identify asymmetric pursuit, with excessive 'catch-up' saccades in one direction only. When pursuit is broken, say, to the right, the lesion is likely to be in the ipsilateral (right) cerebellum or parietal lobe. Brainstem lesions can have more complex effects (e.g. if they involve the vestibular nuclei which can generate nystagmus) but often are ispilateral too.[20, 24] Small asymmetries in the horizontal plane, if consistent, are significant. Asymmetries in the vertical plane are less useful since they occur in many normal subjects.

Global or pandirectional abnormalities of pursuit are somewhat more difficult to interpret. The reason lies in the fact that pursuit pathways are long, complex and multisynaptic, including visual pathways, parietal and frontal cortex, vestibular nuclei and cerebellar flocculus. This makes them vulnerable to trivial sources of mild diffuse CNS dysfunction, including ageing, psychotropic drugs and alcohol. The influence of age on pursuit is considerable, so one must be careful in diagnosing bilaterally abnormal pursuit in an elderly patient. During examination of pursuit or searching for spontaneous nystagmus, one may discover a limitation, or paresis, of gaze; this will be discussed under 'Saccadic eye movements' below.

SACCADIC EYE MOVEMENTS

Saccades are fast movements of the eyes (200–500 degrees per second) which allow us to shift gaze from one object of interest to another. Unlike smooth pursuit movements, that do require a visible moving target, saccades can be generated at will or command without a specifically defined target. These refixations occur incessantly so that gross saccadic defects are often detected while interrogating the patient. It should be said at the outset that just saying that a patient has abnormal saccades is not sufficient to make a topographic diagnosis; there are three independent properties of saccades to be clinically assessed: velocity (normal, slow or absent saccades, i.e. a gaze palsy), accuracy (normo-, hypo- or hypermetric) and binocular conjugacy (conjugate or dysconjugate, e.g. as in internuclear ophthalmoplegia).

With practice, all three aspects of saccadic function can be assessed in the clinic. Initially, however, it may be useful for the clinician in training to cross-validate subtle clinical findings with ocular movement recordings. One can gain some insight of saccadic velocity by simply asking the patient to look right, left, up and down. If one wishes to assess accuracy at the same time, however, a visible target should be provided, usually the examiner's

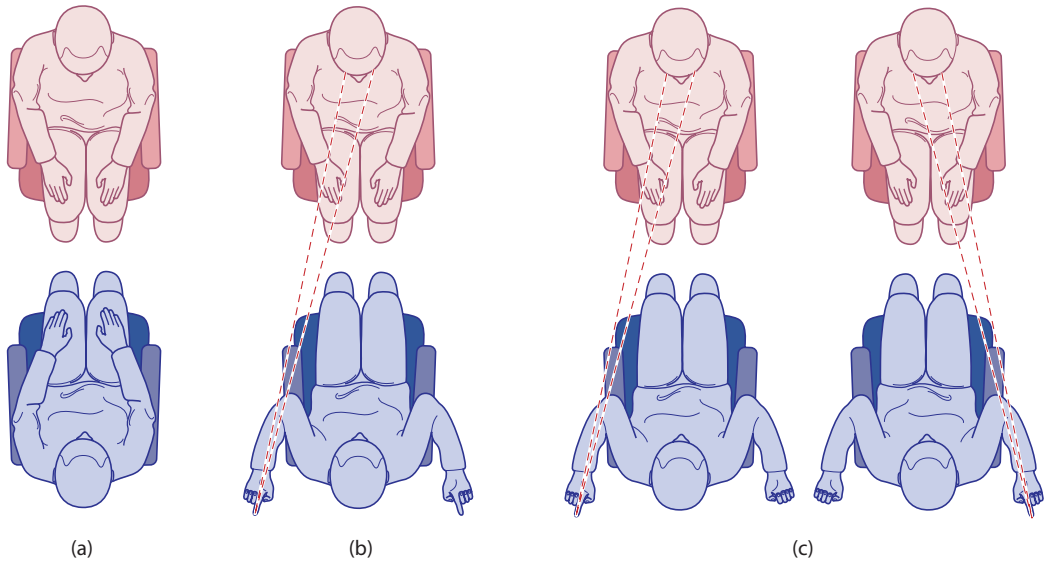


Figure 62.8 Different techniques for eliciting saccades during clinical examination: **(a)** on command; **(b)** self-paced; **(c)** visually elicited (to flicking fingers). During routine neuro-otological examination it does not matter which of these procedures, or combinations of procedures, is used. However, patients with cortical or basal ganglia disorder can show selective deficits with some but not other techniques. Redrawn with permission from Stell and Bronstein.[25]

finger placed 20–30 degrees to the right–left of primary gaze, for horizontal saccades, or up–down for vertical saccadic assessment. The patient can be instructed to look at the target when, for instance, the right or left finger flicks or when the hand opens up (Figure 62.8). It is customary, however, to reinforce the visual stimulus with a simultaneous verbal command such as 'right', 'left' (making sure to be directionally congruent with the patient's point of view) or 'pen', 'finger'. Subtypes of saccades (e.g. self-paced saccades, anti-saccades) can be elicited with more complex instructions and these can be selectively abnormal in frontobasal ganglia disorders, but these will not be reviewed here.[25, 26]

Saccadic velocity

A purely slowed-down saccade takes longer to travel from one target to another, but the movement is a unity, not fragmented. Saccadic slowing is the intermediate stage between normal velocity saccades and an absence of saccades (complete gaze palsy or paralysis). Neurodegenerative disorders involving the saccadic system reduce velocity from say 500 degrees per second to 100 degrees per second (taking up to 3–4 seconds longer than normal) before the patient becomes completely unable to transfer gaze at will or command (Figures 62.9 and 62.10).

Saccadic accuracy

Saccadic amplitude is normally slightly smaller than target amplitude; for example, for targets 30 degrees apart, the eye initial saccade is 27 degrees. In such cases the subject makes additional, smaller corrective saccades towards the target. Whereas one or two small corrective saccades can occur in normal subjects (usually bilateral in such cases), the presence of three or more corrective saccades is considered saccadic hypometria. Severely hypometric saccades look fragmented, often called 'multiple-step' saccades.

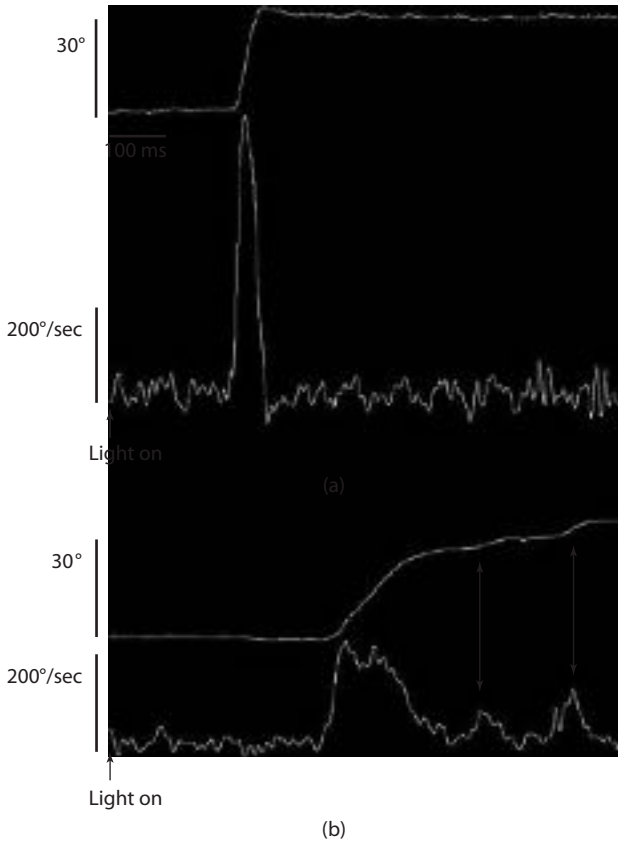


Figure 62.9 Examples of a normal saccade **(a)** and **(b)** a slow and hypometric saccade in a patient with a demyelinating brainstem lesion. Both the position (deg) and velocity (deg/second) traces are shown. The arrows point at two small corrective saccades.

In contrast, if the initial saccade is too large and travels past the target, the patient makes corrective saccades in the opposite direction of the initial saccade. This is saccadic hypermetria, a reliable cerebellar sign (anterior lobe)

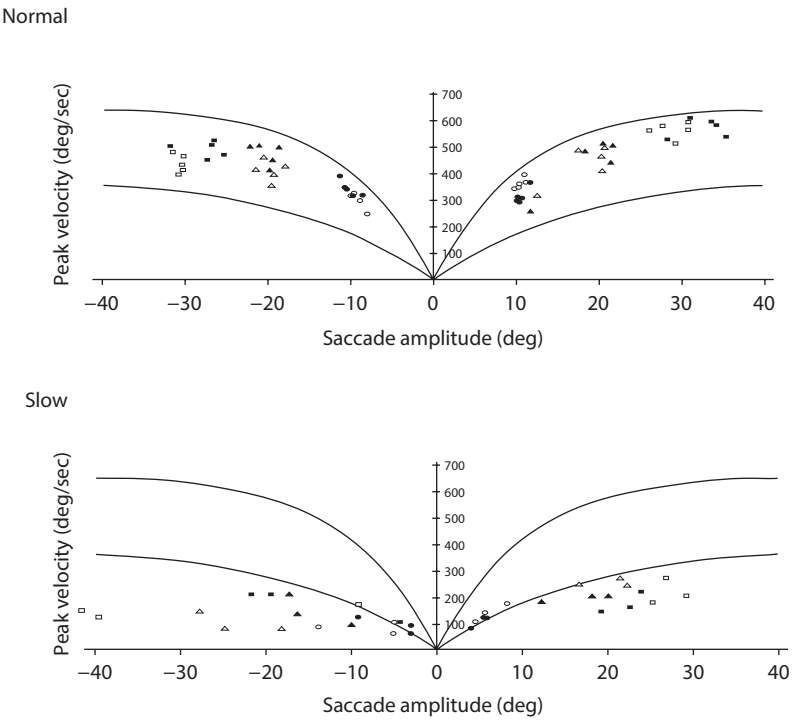


Figure 62.10 'Main sequence', obtained by plotting amplitude versus velocity of saccades in the normal and brainstem-lesioned subjects shown in Figure 62.9. The continuous 'butterfly' lines indicate the range of normality.

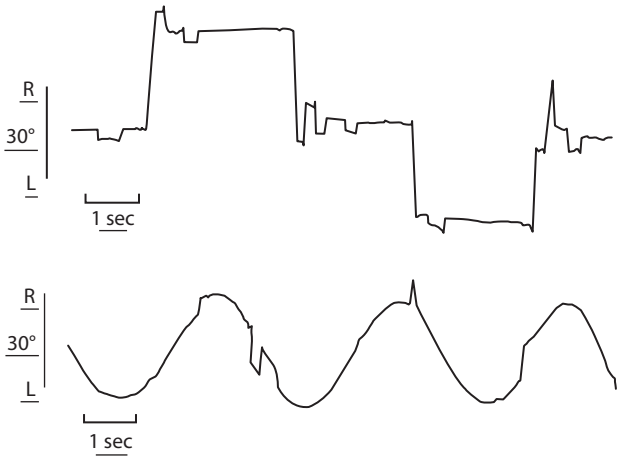


Figure 62.11 Eye movements in a patient with predominantly dorsal vermis cerebellar disease. Note the hypermetric saccades in spite of relatively normal smooth pursuit movements.

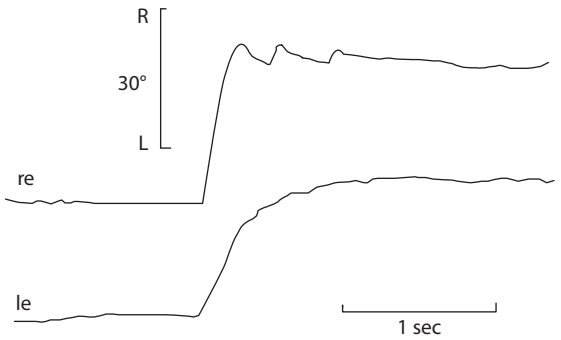


Figure 62.12 Separate eye EOG recording in a patient with a left internuclear ophthalmoplegia. Note the slower movement of the left eye to the right (adduction) and the right-beating nystagmus in the right (abducting) eye.

(Figure 62.11). The corrective saccade itself can be hypermetric so that the eye progressively homes in onto the target. The appearance and meaning is similar to abnormal past pointing during a 'finger–nose' test in an ataxic patient. By contrast, saccadic hypometria is much less specific and can be due to lesions in the cortex, basal ganglia, brainstem, cerebellum and oculomotor nucleus, nerve, muscle or metabolic (see Figure 62.9).

Saccadic conjugacy

When examining saccadic conjugacy (i.e. the two eyes should travel at the same speed), one should first make sure that there is no individual III, IV or VI nerve palsy (i.e. nuclear or infranuclear deficit). A common source of saccadic disconjugacy in the horizontal plane is, however, not nuclear but internuclear. This is the internuclear ophthalmoplegia (INO) in which the abducting eye saccades are fast and large whereas saccades in the adducting eye are slow and small. INOs are due to lesions of the medial longitudinal fasciculus (MLF) which connect abducens interneurons of the VI nucleus with medial rectus motoneurons in the contralateral III nucleus. Abducens interneurons cross the midline immediately to form the ascending MLF on the other side of the brainstem. Thus, a right INO means that right-eye adduction during gaze to the left is slow, hypometric or incomplete due to a right MLF lesion. Since innervation to the eyes is yoked, the attempt of the CNS to overcome the limitation in adduction makes saccades in the abducting eye to be larger (hypermetric). This sequence of overshoots in the abducting eye leads to the characteristic monocular, 'ataxic nystagmus' in INO (Figure 62.12).

Other essential 'supranuclear' clinical neuroanatomy concepts on saccades now follow.[24]

- The more important cortical areas for the generation of saccades are the frontal eye fields. At cortical level, saccadic control is contralateral, so that a left cortical lesion causes abnormal hypometric saccades towards the right.
- From these frontal (and also parietal) areas, pathways originate that reach the contralateral reticular formation of the brainstem, directly and indirectly.
- There are three important reticular saccadic areas.
  - A small central region in the pontomedullary junction (nucleus raphe interpositus (RIP)) which is the gateway for all saccadic movements; small lesions in this area can produce absence or slowness of saccades and quick phases of nystagmus in all directions.
  - The paramedian pontine reticular formation (PPRF) which generates the high frequency neuronal burst required to accelerate the eyes; this area is responsible for ipsilateral horizontal saccadic velocity so that a right side pontine lesion produces absence or slowness of saccades towards the right.
  - The midbrain reticular formation, in particular the rostral interstitial nucleus of the medial longitudinal fasciculus (RIMLF) responsible for the generation of vertical saccades. Lesions in this area can cause selective up, down or complete vertical saccadic gaze palsy or slowing, according to location and extension.
- Another area of importance for the accuracy (not velocity) of saccades is the anterior lobe of the cerebellum; lesions here can produce hyper- or sometimes hypometric saccades. Saccadic hypermetria strongly indicates cerebellar dysfunction but, in contrast, hypometria is not specific.

OPTOKINETIC NYSTAGMUS

The optokinetic nystagmus (OKN) system in man is not a truly separate oculomotor system but it will be briefly described here due to its historical and clinical value in neuro-otology. When a repetitive visual pattern moves in front of our eyes, such as a large curtain or traffic, our eyes follow one object with a smooth slow-phase movement. From time to time the eyes are reset in the orbit by a fast or quick component. This sequence of slow ipsidirectional and fast contradirectional eye movements constitute a visually or optokinetically elicited nystagmus. Its function is to complement the normal vestibular nystagmus during prolonged or slow head rotations. In animals, particularly those with poorly developed foveas, it is a peripheral retinal reflex. However, in man, particularly when OKN is elicited with a small handheld drum, the main contribution to the slow phase movement comes from the foveally driven smooth pursuit system. For these reasons, it is said that if smooth pursuit and saccades have been properly examined, what one can learn from observation of OKN is very little. Nevertheless, the alternating and repetitive nature of the nystagmus makes it sometimes easier to visualize some abnormalities; for example, a small asymmetry of pursuit may be easier to appreciate as an asymmetry of OKN.

OKN is usually investigated with a small hand-held striped drum (**Figure 62.13**). As in smooth pursuit assessment, the patient should be able to see the drum clearly; distance may have to be adjusted to age (presbiopia) and refractive defect of the patient. Subjects should be instructed to glance at the surface of the drum. If this fails to elicit nystagmus, one can try to ask the patient to follow or count the stripes as they pass by. The natural trend in the inexperienced examiner is to rotate the drum too fast, sometimes even letting the drum spin freely in front of a mesmerized patient. One or even half a stripe per second (for stripes of approximately 2–3 cm width) is what is required – if in doubt move it slower! If there is no drum available, OKN can be assessed with an open magazine or newspaper moved slowly in one direction and then the other. If what you want is to see nystagmus, the patient should be strictly instructed to look straight ahead; otherwise patients just follow a single word or image with smooth pursuit movements.



Figure 62.13 OKN elicited with **(a)** a small drum or **(b)** a newspaper. Rotation of the drum or movement of the large target object should be slow. The patient is usually instructed to look straight ahead, rather than follow the stripes or print.

The essential clinical neuroanatomy of OKN is that of pursuit, for the slow phase, and saccades, for the quick phase, but the clinician must be aware of the following practical points.

- The direction of OKN is defined by that of the fast phase. A directional preponderance of OKN to the right (elicited by drum rotation to the left) thus means that right-beating OKN is more active, better formed than left-beating OKN. Be aware that this usually means that slow-phase, smooth pursuit to the right is at fault.
- OKN assessment can be more useful than that of its pursuit-saccades constituents in cortical or subcortical lesions, due to the fact that a cerebral hemisphere is responsible for generating fast phases (saccades) contralaterally but slow phases ipsilaterally. Thus, a directional preponderance to the right of OKN observed in a right cortical lesion is due both to poor leftwards saccades and rightwards smooth pursuit. This functional coupling of slow and fast, oppositely directed eye movements is preserved in many brainstem areas so that, typically, a right brainstem lesion induces a left directional preponderance of OKN (e.g. by affecting the ipsilateral vestibular nuclei and ipsilateral PPRF saccade generators) (**Figure 62.14**). A right cerebellar lesion, with its massive loss of ipsilateral smooth-pursuit movements, usually generates a right directional preponderance of OKN.

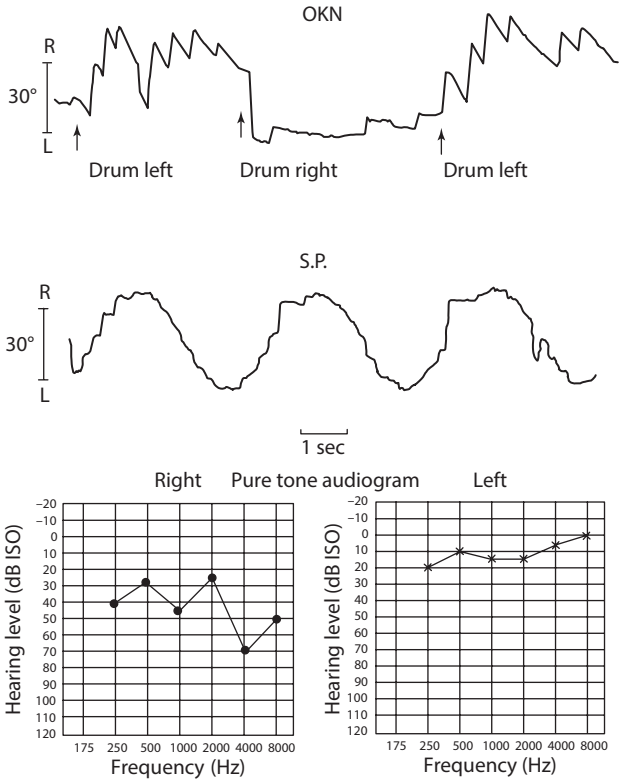


Figure 62.14 OKN asymmetry in a patient with an infiltrating brainstem tumour in the area of the right cerebellopontine angle.

- In disorders with selective or preferential saccadic problems (e.g. gaze palsies as in progressive supranuclear palsy) all one sees during OKN stimulation is the slow phase pursuit. Quick components of nystagmus are slow and scarce. This leads to the 'deviation of the eyes in the direction of the slow component of nystagmus' as described by Dix et al.[26] On reversing drum rotation direction, the eyes passively follow the drum, which is a useful sign in progressive supranuclear palsy.
- Peripheral (labyrinth and VIII nerve) lesions, unless acute and massive with clinically visible spontaneous nystagmus, leave OKN unaffected. A slight directional preponderance, concordant with the peripheral vestibular nystagmus, is all that can be observed in a peripheral disorder.

VESTIBULAR OCULAR REFLEXES

The vestibulo-ocular reflex serves a very specific function: to stabilize gaze in space during head movements. The VOR is what allows us to see clearly when we walk, run or turn our heads. It does so by generating slow-phase eye movements of equal velocity, but opposite in direction, to head movement. This is achieved by a three-neuron, short latency, reflex: a Scarpa ganglion neuron, a vestibular nucleus neuron and an oculomotor nuclear neuron (III, IV or VI).

For many years, clinicians relied almost exclusively on laboratory examination of the VOR, namely caloric or rotational tests. In the last 20–30 years, thanks to our increased understanding of the physiological basis of the vestibulo-ocular system and our improved skills in observing eye movements, we can now assess the VOR in the clinic room. Unilateral and bilateral loss of vestibular function can, in many cases, be identified clinically, but will be easier the more severe and the more acute the lesion is. In contrast, a unilateral, partial, long-standing, peripheral vestibular disorder cannot be detected clinically and a caloric test is required.

The clinical manoeuvres available rely on either:

- a slow doll's head manoeuvre, assessed by (i) direct observation of the eyes, (ii) measurements of visual acuity or (iii) ophthalmoscopy, or
- a fast version of the doll's head, the 'head-impulse' or 'head thrust' test (**Figure 62.15**).

THE DOLL'S HEAD (DOLL'S EYE) MANOEUVRE

This manoeuvre requires the patient sitting in front of the examiner, close enough to be able to observe the patient's eyes carefully. The patient is instructed to continuously fixate a feature of the examiner face (nose or bridge of nose), or an object across the room. The examiner then oscillates the patient's head from side to side, at a frequency of approximately 1 Hz. In the absence of VOR, the patient's eye movements will not be smooth but will be interrupted by 'catch-up' saccades towards the fixation target. This occurs because, at frequencies of 0.5–1 Hz, a head oscillation of ±30 degrees will generate peak head velocities of between 94 and 188 degrees per second, i.e. too high for the pursuit or cervico-ocular

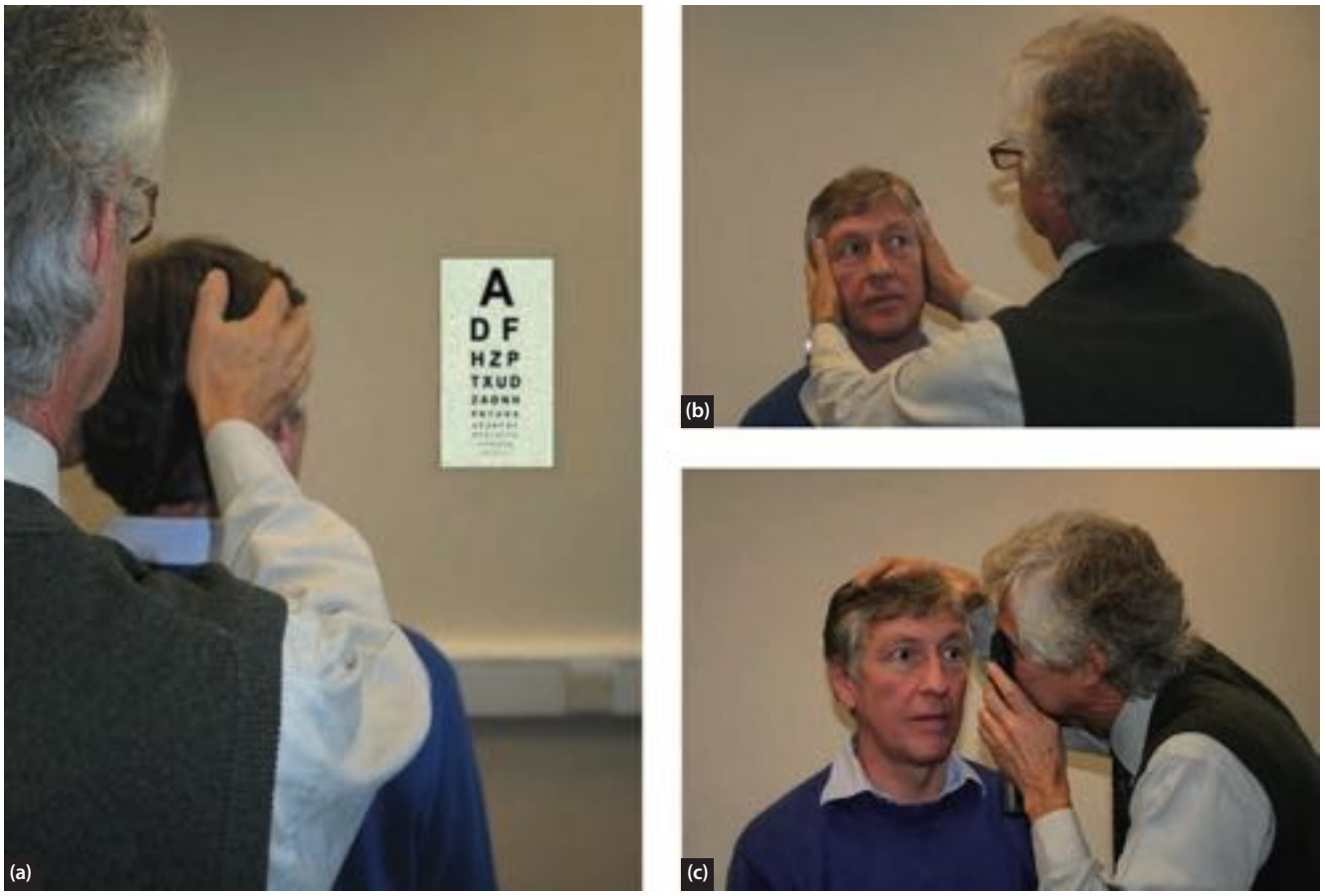


Figure 62.15 Techniques for assessing the VOR in the clinic. The general principle is that the examiner moves the patient's head, with two hands **(a)** and **(b)** or with one hand as in **(c)**. **(a)** Dynamic visual acuity. Two measurements of visual acuity are taken, one with the head stationary and one with the head oscillating at approximately 1 Hz. Reductions in visual acuity of two or more lines indicate bilateral abnormality of the VOR. **(b)** The examiner observes the patient's eye movements during either slow (doll's head) or fast, sudden head turns (head-impulse test). The presence of catch-up saccades towards a target (usually the examiner's nose) during a head turn indicates severe failure of the horizontal semicircular canal in the direction of the head turn. **(c)** The head is turned during ophthalmoscopy while the viewing eye maintains fixation on a distant object. If the optic disc remains absolutely steady, the VOR is functioning well. If the disc appears jerky during head (nose) turns in one direction, the ipsilateral horizontal semicircular canal is likely to be significantly impaired.

reflex to compensate.[27] As slow-phase eye movements are unable to keep up with the target, catch-up saccades are put in – and these can be easily observed if you are close enough. In patients with bilateral, complete or severe (>90%) loss of vestibular function (e.g. gentamicin ototoxicity, meningitis or idiopathic[9]), the manoeuvre is positive.

DYNAMIC VISUAL ACUITY

A similar movement of the head can be used to investigate the VOR while reading a visual acuity chart. A baseline, binocular visual acuity measurement is noted, for the sake of argument 6/6. Standing behind the patient, the examiner oscillates the patient's head at approximately 1 Hz while a new visual acuity measurement is taken. A normal subject's visual acuity does not change with respect to the baseline reading or it can deteriorate by one line, say, down to 6/9. A loss of two lines in visual acuity must be treated as suspicious and when three lines or more are lost, the results are frankly abnormal, i.e. indicative that the patient's VOR is grossly reduced. False positives may occur if the patient has a spontaneous nystagmus (e.g. a downbeating nystagmus) which is exacerbated by head movement and/or lateral gaze. However, this nystagmus should have been observed during conventional examination of the eye movements. False negatives occur if the patient himself oscillates the head, since they often 'cleverly' stop the head movement and get a snap of the visual acuity chart. In controlled conditions, a correlation between the degree of caloric response loss and dynamic visual acuity decrement was found.[28]

Although examination of the patient's eye during the doll's head manoeuvre can in some cases detect a unilateral vestibular lesion, this is detected more efficiently with the head-impulse test (see below). The reading or dynamic visual acuity test, as used clinically, cannot be applied to unilateral lesions.

OPHTHALMOSCOPY

A procedure first proposed by Zee[29] promotes the use of ophthalmoscopy for the assessment of vestibular disorders.

As the ophthalmoscope is a powerful magnifying glass, nystagmus of small amplitude can also be detected easily. However, as funduscopy is not routinely carried out by otolaryngologists, the reader is referred to the original reference and a recent brief review.[30, 31]

HEAD-IMPULSE TEST (OR HEAD THRUST TEST)

The value of VOR examination as described in the preceding sections is limited by the fact that they are all carried out with relatively low head velocities. The VOR is only really irreplaceable at high velocities and accelerations of the head. Pursuit, optokinetic or cervical mechanisms cannot fully take over from the VOR during brisk head movements. For this reason, Halmagyi and Curthoys have popularized the examination of the doll's head manoeuvre with discrete, sudden, brisk and unpredictable head turns, so that the VOR deficit is more apparent.[32, 33] In essence, the patient is seated with the examiner at close range so that the eyes can be observed carefully. The patient is instructed to fixate a target, preferably across the room (e.g. the video-camera lens if you wish to document the findings) or on the examiner's face. The head is turned in discrete steps of ±10–15 degrees, briskly, by the examiner thus producing head velocities of several hundred degrees per second. A fast right head (nose) turn will make a patient with right-sided vestibular loss introduce one or more catch-up saccades towards the target, i.e. towards the left. These catch-up saccades can be easily identified by a trained observer. The test is clearly useful for identifying acute unilateral peripheral vestibular deficits, for instance in patients with vestibular neuritis (neuronitis, labyrinthitis). In patients with chronic, compensated, incomplete unilateral lesions the test is often negative or inconclusive. A study comparing caloric testing versus the head-impulse test shows that the overall sensitivity of the head-impulse test is 34%.[34] This means that, when taking into account all patients with canal paresis, the sensitivity is low. However, specificity is high (100%) and all patients with a canal paresis ≥87% had a positive head-impulse test.[34] In the acute scenario the head-impulse test is extremely useful as it helps to confirm that an acute vestibular syndrome is of likely peripheral origin (abnormal result in vestibular neuritis). Although many small brainstem or cerebellar strokes show a normal head-impulse test, vascular lesions involving the labyrinthine artery (a branch of the anterior inferior cerebellar artery (AICA)) will also infarct the labyrinth hence producing vertigo, unilateral deafness and an abnormal head-impulse test when tuning the head towards the lesion. Combining the head-impulse test with other central oculomotor abnormalities indicative of a central lesion (skew eye deviation, bidirectional nystagmus) is, in experienced hands, more sensitive than diffusion-weighted image (DWI) MRI for the diagnosis of acute vertebra–basilar stroke (the HINTS for stroke protocol – head impulse, nystagmus characteristics, test for skew).[35, 36] Although HINTS is a nice protocol backed up by good research, clinicians should not forget many other hints or red flags suggestive of stroke (see **Box 62.2** above).

With practice it is possible to investigate clinically all six semicircular canals by moving the head obliquely in the planes of the vertical canals (LARP plane: left anterior–right posterior and RALP plane: right anterior–left posterior) (**Figure 62.16**).[37]

To feel fully confident with the head-impulse test one should be conversant with the oculomotor clinical examination and, like any other clinical manoeuvre, be shown how to do it – at least once. In some patients with spontaneous nystagmus or square-wave jerks the head-impulse test maybe inconclusive (i.e. it may be difficult to know whether you have seen the little saccade you are looking for, or just another square wave jerk). As with all other clinical procedures for VOR examination, the head-impulse test does not replace caloric testing. Quantitative versions of the test (video head-impulse test or VHIT) are now on the market and are useful (see vestibular testing below) but, despite pressure from the commercial manufacturers, they have not replaced the caloric test and perhaps they never will.

VESTIBULO-OCULAR REFLEX SUPPRESSION

When a subject rotates the head in the environment, his eyes adopt a pattern of alternating slow and fast phases, a physiological vestibular nystagmus (VOR). In a normally lit room this is aided by OKN. A property of the human brain, and other higher mammals, is the ability to suppress the VOR. This is executed by the vestibulo-ocular reflex suppression (VORS) system, closely related or identical to pursuit mechanisms and pathways. Abnormalities in VORS are thus indicative of central dysfunction, as discussed already for smooth pursuit.

Clinical examination of VORS is easy, both clinically and during oculography (**Figure 62.17**). The general principle is to oscillate the patient while he/she fixates a head-fixed target. Any obvious breakthrough nystagmus indicates poor suppression. In the clinic, this can be achieved by asking the patient to clasp the hands together in front of him and put the thumbs up as a target (**Figure 62.17b**); the patient can then oscillate side to side *en bloc*, by himself if standing up, or the examiner can oscillate the patient's swivel chair if sitting down. Alternatively, the patient can bite on a tongue depressor or ruler with his teeth, and fixate on the other end of the ruler or on an object attached to it while moving the head side to side (**Figure 62.17a**). As with pursuit, the oscillation should be slow, say 2–5 seconds from right to left, and vice versa (0.10–0.25 Hz) and one should have a good view of the patient's eyes.

Patients with peripheral vestibular lesions have normal VORS, or even 'super-normal' VORS as they are trained at suppressing their own spontaneous vestibular nystagmus. In central lesions, the abnormality of pursuit and VORS usually goes hand in hand, i.e. a patient with a right cerebellar lesion will show abnormal rightwards pursuit and abnormal VORS, with visible nystagmus breaking through, when oscillating the head towards the right.



Figure 62.16 Head movements required during the head-impulse test to investigate the horizontal canals (top, a–c) and the vertical canals (bottom, d–f). In the position shown in the figure the compensatory eye movement required during the head movement is horizontal (top) or vertical (bottom). Reproduced with permission from Bronstein and Lempert[8] and Bronstein et al.[37]



Figure 62.17 Clinical assessment of VOR suppression. The principle of the examination is that the patient fixates a head-fixed target during either **(b)** whole-body oscillation (his own thumbs) or **(a)** head oscillation (ruler or tongue depressor with an object on top, in the example shown the ear piece of an auriscope taped to the tongue depressor).

POSITIONAL MANOEUVRES

One of the most common causes of vertigo is BPPV, accounting for one-quarter of all patients with dizziness and vertigo. Positional manoeuvres are a vital component of the examination in the balance-disordered patient, particularly in light of the efficient treatments available for BPPV.

Positional manoeuvres must be conducted in all patients with vertigo or dizziness, particularly if provoked by head–neck movements or positions. Typical symptoms are vertigo on looking up, bending over, lying down and turning over in bed. If a patient is dizzy on standing up from the sitting position, the likelihood of the symptoms being primarily vestibular in origin is less. The latter challenges vascular orthostatic mechanisms but there is no reorientation of the head with respect to gravity.

The purpose of conducting a positional manoeuvre is to attempt to elicit vertigo, but vertigo is unpleasant. The patient should be made aware that despite modern technology this is the only way to make a diagnosis of a perfectly treatable condition such as BPPV. During the positional manoeuvre, and regardless of whether there is vertigo or not, the examiner should carefully observe the patient's eyes. In order to fulfil this purpose the following practical measures can be taken.

- Patients should be warned beforehand that, even if they feel vertiginous, they should look straight ahead at one point on the examiner's face (i.e. the nose or bridge of the nose). If the eyes are not in primary gaze or wandering around, the observation of the nystagmus is more difficult.
- At least one eye of the patient can be easily helped to stay wide open by one of the free hands of the examiner, as shown in Figure 62.18.
- Keep the patient in the head-down position for a few seconds. Some patients with BPPV show extremely long latencies, occasionally up to 20–30 seconds. If the suspicion of BPPV is strong, one should wait this long. In most cases, 10–15 seconds is sufficient, indeed most cases of BPPV have latencies of less than 5 seconds.



Figure 62.18 Positional manoeuvres. Examination technique for a right-sided, posterior canal BPPV. **(a,b)** The Hallpike manoeuvre, in which the head (face) is turned approximately 45° to the right. This is done so that the rotation, down to the head-hanging position, takes place in the plane of the right posterior canal. Note how the examiner's right hand can contribute to open the patient's eye widely. **(c,d)** 'Variant' Hallpike manoeuvre, starting from a sitting position. Note that the head reaches a similar final position, despite not actually being off the couch; this manoeuvre is useful if the couch is placed in between walls or cupboards.

There are no excuses for not doing a positional manoeuvre. However, two of the most commonly excuses heard are 'The couch in my room is placed awkwardly to do a Hallpike, I just cannot get the patient's head to hang off the couch' and 'We have not got Frenzel glasses in our clinic.' Wrong! A positional manoeuvre can be done with a couch in any position and Frenzel glasses are definitely not required for any positional nystagmus. **Figure 62.18a** and **b** show the conventional Hallpike manoeuvre with the head in the classical hanging position and a recommended alternative to the procedure when, for instance, the couch is placed between walls or cupboards (**Figure 62.18c** and **d**). Examination of these pictures shows that the final head position achieved is very similar. As to the use of Frenzel glasses, it must be remembered that all the classical descriptions of BPPV by Dix and Hallpike were carried out without Frenzel glasses. Presumably, the rationale for using Frenzel glasses is that, when the patient is able to fixate, the nystagmus can be potentially suppressed. However, the vast majority of patients either have or do not have BPPV. If they have BPPV, the nystagmus is extremely strong and so the patient is unable to suppress it with visual fixation. Furthermore, a critical component in the most common form of BPPV, posterior canal BPPV, is torsional (rotatory) nystagmus. The ability to suppress torsional nystagmus by visual fixation is less than nystagmus in other planes.[38] It is theoretically possible that Frenzel glasses could help in a patient with a mild form of BPPV. In practice, there seems to be no increase in diagnostic efficacy but controlled studies are lacking.

What can we expect to see during a Hallpike or variant Hallpike manoeuvre? The most common form of positional nystagmus is BPPV of the posterior canal. During a left-ear-down head hanging position one triggers a left posterior canal BPPV, with the main component of the nystagmus being torsional (or rotatory) beating clockwise from the observer point of view. This means that the upper pole of the patient's eye beats towards the patient's left shoulder. Technically speaking, it is left-beating torsional nystagmus, as expected from activation of the left posterior canal. A secondary upbeating component of nystagmus is often observed which is synchronous with the torsional beat. The nystagmus is often accompanied by intense vertigo and by the patient's attempt to close the eyes or to sit up – which the doctor will have hopefully instructed him/her in advance to resist. The characteristics of posterior canal BPPV are the presence of latency, as mentioned above, adaptation and fatigability. Adaptation refers to the decline and eventual disappearance of the nystagmus within a minute or so, usually less. Fatigability refers to the fact that on repeated positioning, the nystagmus and the vertigo are less with time. The patient can be reassured that usually the intensity of the symptoms will be less as we repeat the manoeuvre. Currently, one rarely repeats the manoeuvre to assess fatigability as it is advisable to proceed straight to repositioning treatment (see Chapter 64, Benign paroxysmal positional vertigo).

The positional manoeuvre should be conducted on both sides, particularly if no nystagmus is observed on the first side. On confirmation of the diagnosis, most specialists proceed to treatment with Epley or Semont manoeuvres. Partly because of fears that a new Hallpike after an Epley or Semont manoeuvre could undo the benefits of the treatment, many doctors do not do the Hallpike manoeuvre on the other side if BPPV has been diagnosed and treated on one side. If all symptoms resolve in the first session, that is end of story. If symptoms persist, the Hallpike manoeuvre will have to be carried out on a separate session on both sides. If the patient knows that a particular ear down provokes the vertigo, it is sensible to do the healthy side down first to increase patient confidence and so be able to examine both sides in the same session.

Several other types of nystagmus can be observed during the Hallpike manoeuvre, which are not posterior canal BPPV. In principle, a purely vertical nystagmus, be it up- or downbeating nystagmus, should be considered of central origin. Our review of 50 consecutive cases of positionally induced downbeating nystagmus we found that three-quarters of patients had independent evidence of neurological disease.[39] In the remaining quarter of patients the most likely diagnosis was anterior canal BPPV. Ideally, in anterior canal BPPV, one should see a torsional component added to the positional downbeating nystagmus. Of interest, the right/left specificity to trigger anterior canal BPPV seems less than for posterior canal BPPV.

A purely horizontal nystagmus can also be observed during a Hallpike manoeuvre. In a patient with a recent history of peripheral type positional vertigo, the diagnosis is almost certainly horizontal canal BPPV. As in posterior canal BPPV, it is usually due to canalolithiasis (free-floating particles in the lumen of the canal) and occasionally to cupulolithiasis (particles become adhesive to the cupula).[40] Horizontal canal BPPV produces intense nystagmus and vertigo and this happens when the head is turned both to the side of the lesion and to the opposite direction. The nystagmus usually beats in the direction of the face turn. The intensity of the nystagmus is stronger in the direction of the abnormal side, i.e. stronger right-beating nystagmus with the right ear down suggests right horizontal canal BPPV. Horizontal canal BPPV is a much more self-limiting condition than other canal BPPV and can disappear spontaneously in a few days.

When a patient gives a positive typical history of BPPV and no nystagmus can be elicited in the Hallpike or similar manoeuvres for posterior canal BPPV, other manoeuvres should be investigated. For horizontal canal BPPV the optimal plane of rotation should be in the plane of the canal. This can be achieved with the head end of the couch raised 20–30 degrees above the horizontal, followed by a full head turn about the longitudinal axis of the body in each direction. It can be estimated that the Hallpike (i.e. posterior canal) manoeuvre may not identify 20% of horizontal canal BPPVs. In other words, one in five patients with horizontal canal BPPV will require the specific horizontal canal manoeuvre for diagnosis.

For anterior canal BPPV, the left head-hanging Hallpike position should provoke a right anterior canal BPPV and vice versa. This is due to the coplanar orientation of the left posterior canal with the right anterior canal and

vice versa. However, a crucial factor in provoking anterior canal BPPV seems to be placing the head as low down as possible and this may be best achieved by taking the patient in one movement from the sitting upright position to the straight back, head hanging position.[39]

In summary, many positional manoeuvres exist and BPPV can come from any of the three semicircular canals. Bilateral cases, often post-traumatic, also exist. At least the Hallpike manoeuvre, or variant, for posterior canal BPPV must be carried out in all patients with head–neck movement or position triggered vertigo. If negative, the horizontal and straight back manoeuvre should be applied but the hit rate may be low. A typical nystagmus for posterior canal BPPV, with normal CNS examination, needs no imaging procedures. Successive failures to treatment should prompt imaging. Even in the absence of nystagmus, more than 80% of patients with a typical history improve with particle repositioning manoeuvres for posterior canal BPPV.[41] Observation of any other positional nystagmus, particularly if it lasts for longer than a month, should undergo detailed MRI investigation of the posterior fossa. Further details about examination and treatment of positional vertigo can be found in Chapter 64, Benign paroxysmal positional vertigo.

Laboratory assessment of eye movements

Not all patients with a suspected vestibular disorder, peripheral or central, require eye movement recordings (oculography); only a minority do. Not even patients requiring a caloric test may need eye movement recordings (see 'Caloric tests' below). In a research, academic or tertiary referral environment, vestibular and eye movement tests are conducted for a variety of reasons and not necessarily diagnosis. These are perfectly valid reasons such as research, training of medical and paramedical personnel and patient reassurance.

From the strictly clinical point of view, oculography is required firstly for formal vestibular testing, as this is usually conducted in the dark (Table 62.7). Otherwise, visual input may suppress spontaneous vestibular nystagmus and override abnormalities in rotational responses. Oculography is also required to elucidate the nystagmus waveform in some patients with spontaneous nystagmus, particularly when there is doubt if the nystagmus is acquired or congenital. Oculography is required when clinical examination of eye movements leaves doubts on the presence of a potentially significant abnormality such as INO or slow saccades.

The clinician must bear in mind, however, that routine oculographic examination, as carried out in most vestibular laboratories, will fail to answer these questions unless they are specifically formulated. This is no different to other special medical investigations.

Vestibular conditions that can be diagnosed clinically or with other laboratory investigations (audiograms, head scans) do not necessitate ocular recordings. Examples are BPPV, Ménière's disease and vestibular schwannomas. Formal vestibular testing in such cases is variably indicated according to the presence of complications, poor response to treatment, presurgical evaluation, evaluation of the 'healthy' labyrinth, or need for objective measurements on follow-up.

TABLE 62.7 Indications for oculography: eye movement recordings to investigate imbalance

Clinical problem	Recording/action
Assessment of eye movements in the dark	Is there vestibular nystagmus?
	Vestibular function (e.g. rotational test)
Nystagmus waveform	Vestibular versus gaze paretic?
	Acquired versus congenital?
Confirmation of subtle abnormalities of diagnostic value (e.g. abnormal pursuit, subclinical? INO?)	
Quantification	Research and follow-up

OCULOGRAPHY TECHNIQUES

There are many techniques available and they all offer advantages and disadvantages. The two techniques usually available in ENT or audiology departments are electro-oculography (EOG) and video-oculography (VOG). These two techniques are relatively easy to set up, inexpensive, non-invasive and have a range of signal linearity of approximately ±20–30 degrees, capable of coping with the large eye movements encountered during vestibular tests in the dark. The main disadvantages are poor spatial (EOG) and temporal (VOG) resolution, but in the clinical vestibular setting these two techniques are the ones to be recommended (note that EOG and electronystagmography (ENG), are synonymous). An increasingly popular use of VOG is as part of the video head-impulse test (VHIT).

Infrared oculography and the scleral search coil technique may be found in specialized departments with an interest in eye movement disorders. Infrared oculography has a small range of linearity which is not suitable for the large movements observed during vestibular testing. The search coil system has the single but major disadvantage of being a semi-invasive procedure as it requires wearing a copper wire coil embedded in a plastic contact lens.

EOG or ENG

In this technique, surface electrodes, usually disposable, are glued around the orbit. Pairs of electrodes record the difference in potential between the cornea and the retina and, since the corneal region is positive and the retina negative, the eye becomes a dipole. Two electrodes placed at each side of the orbit, right–left for horizontal movements or above–below the orbit for vertical movements, will detect movement of this dipole. The usual configuration of electrodes for conventional vestibular testing is two electrodes, one at each external canthus ('bitemporal recording'). This gives a better signal-to-noise ratio because the recording taken is of an ideal 'cyclopean' eye. If the patient has clearly disconjugate eye movements or if the question is whether this patient has got an INO, then simultaneous separate

eye horizontal recordings are needed. Vertical eye recordings are taken only occasionally in the vestibular scenario; there are not many instances when they are required, and they are often dogged by blink artefacts. If the question is whether the patient has a vertical nystagmus, ophthalmoscopy, Frenzel glasses or video techniques are often more reliable. Major disadvantages are that EOG cannot record torsional eye movements and that many other biological potentials can be picked up with periocular electrodes as artefacts, such as electroencephalography or electromyography. The presence of drifts in the recording and low voltage potential in some ocular diseases indicates that EOG, although popular, is far from ideal.

VOG

Small video cameras can be mounted on goggles to obtain good quality images of the eye. Infrared cameras work in darkness and these images can be used to directly observe the presence of nystagmus in the absence of visual fixation (videonystagmoscopy). If the images are further processed, on- or offline, so that traces or measurements are obtained, the technique is called VOG. The main limitation of this technique as compared to EOG/ENG is temporal resolution. This depends on the sampling video rate, usually 50 Hz, i.e. a video image taken every 20 ms; the velocity of a saccade, which only lasts 50–100 ms, may not be reliably measured. Other types of eye movements, all much slower than saccades, can be confidently recorded but eyelid artefacts and occasional difficulties with the eye-tracking software are also troublesome. Most commercial VOG systems are two-dimensional (2D) (horizontal and vertical) but the more sophisticated are 3D and this offers the unique advantage of being able to non-invasively record torsional eye movements.

Routine EOG or VOG

Oculography can be carried out very selectively, for instance to see if a patient has normal or abnormal rotational responses, but often a battery of investigations are grouped in a 'routine' ENG or VOG. There are many variations to this routine but it essentially involves a search for spontaneous and gaze-evoked nystagmus, visually guided eye movements (pursuit, optokinetic and, if requested, separate eye saccadic velocities) and a vestibular test, namely caloric or rotational stimulation. Mostly, the analysis of the eye movement trace is carried out automatically or semi-automatically by computer; automatic artefact rejection is often suboptimal. The analysis is often collated by a technician who then produces a report to the physician or surgeon. There are therefore a number of possible weak links in the chain which can potentially mislead the clinician. I have seen many untenable diagnoses of 'central vestibular disorder' on the basis of artefactual ENG or poor-quality interpretation.

Since it makes no difference whether an abnormality is detected by direct clinical observation or by oculography, the various possible findings and their interpretation have already been discussed above. Herewith we will concentrate on any added value or new aspects of the examination that can be provided only by oculography.

SPONTANEOUS AND GAZE-EVOKED NYSTAGMUS

A spontaneous nystagmus present in primary gaze or evoked by eccentric gaze can have many different meanings. Features helpful to the differential diagnosis are the effect of visual fixation and waveform characteristics, to be discussed below. The plane (horizontal, vertical, torsional) of the nystagmus is also a critical feature but it is best decided on clinical grounds, unless high-performance 3D oculography is used. With the head upright, horizontal or horizontotorsional nystagmus can be peripheral or central but any other direction, namely torsional (unless in the Hallpike position) or vertical, in principle indicates CNS disorder. The reader is referred to specialized references for neurological nystagmus.[21, 22, 42]

Visual suppression

Nystagmus of peripheral vestibular origin is suppressed, sometimes completely abolished, by visual fixation. Thus, peripheral vestibular nystagmus increases in size and slow phase velocity in the absence of visual fixation, that is, in the dark or with Frenzel glasses (**Figure 62.4**). In contrast, central lesions usually damage pathways involved in the suppression of nystagmus (VOR suppression) and so the nystagmus enhances little, not at all or even diminishes in the dark. Thus the effect of darkness on nystagmus is an extremely useful aid to the differential between labyrinthine and neurological nystagmus (**Table 62.8**). This can also be carried out by direct inspection of the eyes behind Frenzel glasses or with modern commercial video cameras which have a standard inbuilt infrared lens ('handycams'). The search for nystagmus must be done in the primary position of the eyes and on gaze deviation right and left by 20 or 30 degrees. There are no hard rules but a nystagmus which is less than 2–3 degrees per second on gaze deviation in the dark is not significant. Significant nystagmus is not only induced by vestibular or CNS lesions but also by neuropharmacological agents and alcohol.

Nystagmus waveform

There are two basic types of waveforms. Saw-tooth or jerk nystagmus, intercalating a fast and a slow phase (see the examples in **Figures 62.2**, **62.3**, **62.4** and **62.5**), and pendular nystagmus, a quasi-sinusoidal waveform with no distinct fast phases (**Figure 62.19**). Jerk nystagmus can be peripheral or central; pendular nystagmus is always central, but not always ominous as it may be congenital or secondary to severe visual loss.

Due to the ability of the normal CNS to suppress nystagmus, the rule of thumb is any large amplitude nystagmus recorded in the light, particularly if it does not enhance in the dark, is of central origin. The exception could be an acutely ill vestibular patient (vestibular neuritis, attack of Ménière's disease). It is not appropriate to review the many types of neurological nystagmus in a general chapter

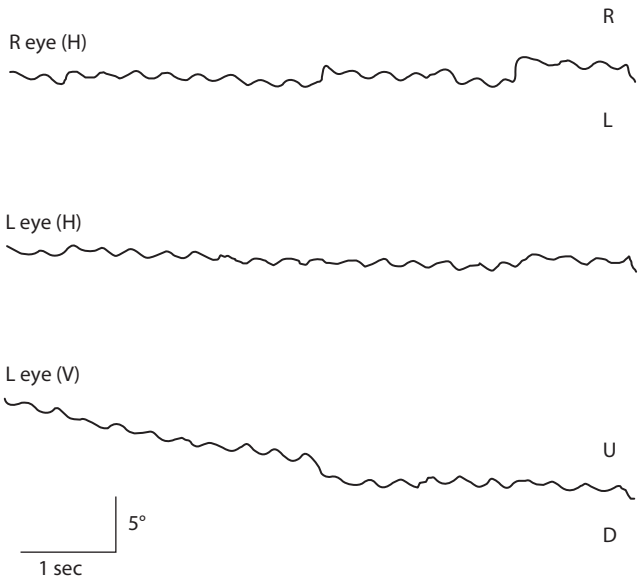


Figure 62.19 Pendular nystagmus in a patient with multiple sclerosis. The presence of simultaneous horizontal and vertical components, in this case in the left eye, produces complex movement trajectories (elliptical, 'banana'-shaped, circular). With kind permission from M. Gresty.

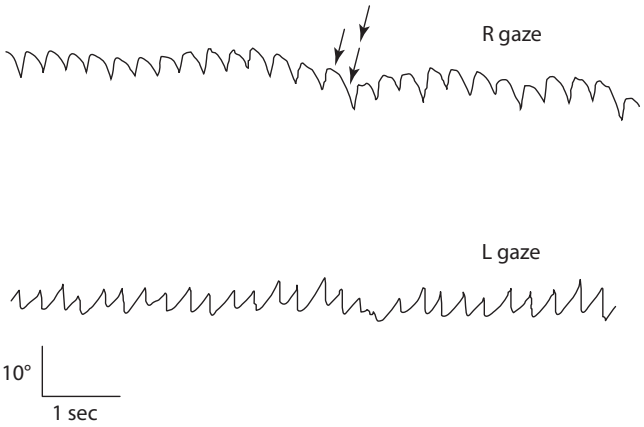


Figure 62.20 Exponentially increasing slow phase velocity in a patient with congenital nystagmus (CN).

TABLE 62.8 Differential diagnosis between central and peripheral nystagmus

Characteristic	Peripheral	Central
Plane	Hor or Hor > Tors	Any
Amplitude	Acute ++	++/+++
	Chronic +/–	++/+++
Fixation removal*	Appears/enhances	Variable (can diminish)
Waveform†	Rectilinear (jerky)	Exponential (jerky)
		Pendular

* By oculography, Frenzel glasses or fundoscopy in the dark.
† By oculography.
Hor, horizontal; Tors, torsional.

on the assessment of balance but it is worth mentioning some useful steps for the differential, peripheral versus central and acquired versus congenital nystagmus.

As mentioned under 'Clinical examination of eye movements' above, jerk nystagmus can be of peripheral or central origin. A jerk nystagmus of peripheral vestibular origin has a typically linear slow phase (Figure 62.4). Linear means that the velocity of the slow phase is constant and it is so because the magnitude of the velocity at rest is a direct measure of the vestibular tonus asymmetry. CNS lesions can also create a vestibular imbalance but they usually involve in addition central integrating mechanisms. This makes the slow phase of nystagmus to be non-linear, particularly during eccentric gaze, typically with an exponentially decreasing slow phase in velocity (Figure 62.5). A jerk nystagmus with a slow-phase velocity exponentially increasing (Figure 62.20), however, strongly suggests the diagnosis of congenital nystagmus, although some exceptions have been reported.[43] The diagnosis of pendular nystagmus is usually easy by simple clinical inspection and confirmed with recordings but establishing whether it is acquired or congenital is not possible on simple oculographic criteria. Patients with acquired pendular nystagmus usually have clinically severe vascular or demyelinating brainstem disease whereas patients with congenital pendular nystagmus have congenital or infantile visual loss and defects.

By way of summary (Table 62.8), a typical peripheral vestibular nystagmus is small in the light but increases amplitude in the dark and shows linear slow-phase velocity in the horizontal (or horizontotorsional) plane. It normally follows Alexander's law of increasing in magnitude when looking in the direction of the fast phase. Additional findings can be a caloric canal paresis (see under 'Caloric tests' below) or a positive head-impulse test contralateral to the beat direction of the fast phase, as in vestibular neuritis. Also, there should be no oculographic evidence of CNS lesion, namely visually guided eye movements should be normal.

VISUALLY GUIDED EYE MOVEMENTS

The clinical significance of abnormalities of pursuit, OKN, saccades and VOR suppression is the same whether documented clinically or by oculography. Recording very slow saccades or broken pursuits that have been definitely observed by the naked eye will not add anything to the diagnosis. Recording of mild abnormalities for confirmation of a questionable clinical abnormality is reasonable and, in addition, may provide a baseline for future comparisons on follow-up.

Saccades

Technical variations are unlimited but nowadays most oculography systems are computer-controlled. The target for saccades (or pursuit) can be projected, generated by rows of light emitting diodes (LED) or directly viewed on a computer screen. Unless specified, recordings are usually only conducted in the horizontal plane. For saccades, the target jumps to different locations and the latency (reaction time), velocity and accuracy of the saccade

is measured. Saccadic latency is a less important parameter for balance assessment. Since there is a fairly fixed relationship between the amplitude and the peak velocity of saccades (called the 'main sequence'), the results are often presented as an amplitude-velocity plot, with or without an exponential curve fitted (see **Figures 62.9** and **62.10**). The significance of slow and inaccurate saccades has been discussed above under 'Clinical examination of eye movements'.

Smooth pursuit

For smooth pursuit, the target slowly oscillates with a triangular or sinusoidal trajectory. Usually a range of frequencies and/or velocities are explored. Results are often expressed as 'gain', the ratio between peak velocity of the eye and peak target velocity. At low frequencies and velocities, say 0.10 Hz, peak target velocity 10 degrees per second, normal gain is close to unity. As frequency/velocity increases, gain values drop. In neurological patients, gain at a single frequency are lower than control, and the drop out occurs early. As discussed under 'Clinical examination of eye movements' above, abnormalities can be uni- or bilateral. The possibility that poor pursuit performance is just due to simple attentional factors is higher during laboratory than during clinical assessment, when the clinician can encourage and observe the patient directly. During all oculography procedures audiologists and technicians need to be trained to keep an eye on the patient's alertness, to recognize artefacts due to drowsiness and to urge patients to stay awake and cooperative.

Optokinetic nystagmus, particularly as elicited in the clinic with a small drum, is just a combination of pursuit and saccades. Large vestibular laboratories add a full-field encircling drum, covered in vertical black and white stripes, for OKN investigation, which is a more powerful stimulus. Whereas a peripheral vestibular asymmetry can occasionally bias small drum OKN, full-field OKN is never affected by a peripheral disorder (**Figure 62.21**).[44] As with all other visually driven eye movements, abnormalities are indicative of central disorder and can be uni- or bilateral (see under 'Clinical examination of eye movements' above). Although one often refers to asymmetries of OKN as directional preponderance (DP) of nystagmus, what matters is on which side the slow-phase velocity is subnormal. Thus, a left DP of OKN is due to the fact that the leftwards slow phase is subnormal; as a consistency check, the vast majority of patients should also have abnormal pursuit and VOR suppression during leftwards motion.

VESTIBULO-OCULAR REFLEX

In practice, there are three ways of assessing the VOR: clinically as discussed above, with caloric irrigation or with rotational stimuli. Electrical (galvanic) stimulation of the VOR has historical and experimental value. This will not be discussed here except to say that galvanic stimulation excites the VIII nerve afferents directly and this was occasionally used to distinguish if a caloric unresponsive ear was due to an VIII nerve lesion (absent galvanic response) or a labyrinthine lesion (present galvanic response).[45]

CALORIC TESTS

The principle of the caloric test is that changes in temperature in the external auditory canal influence the level of activity of the vestibular labyrinth. The caloric test is still the main test available to any clinician to assess individual-ear vestibular function whereas rotational tests stimulate both labyrinths simultaneously.

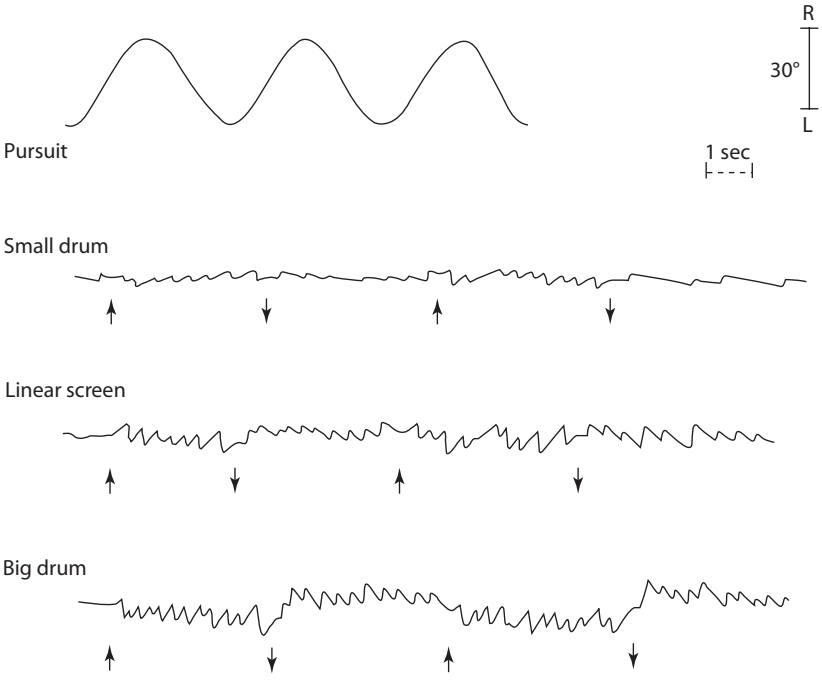


Figure 62.21 Pursuit and OKN in a patient with a right-sided acute peripheral vestibular lesion. Pursuit and big drum OKN are normal but minor directional preponderances (DPs) with the small drum can be observed in the acute phase (in this case to the left). Arrows represent drum or screen motion direction reversal. Reproduced with permission from Mossman et al.[44]

The disadvantages are that some patients cannot tolerate the caloric test (because of local discomfort or induced vertigo) and that disease or anatomical variability in the middle and external ear can preclude irrigation or interfere with the results.

To some extent, the mechanism of the caloric response is still debated. In order to obtain a satisfactory nystagmic response, the subject has to lie down with the head raised 30 degrees above horizontal. This places the horizontal semicircular canal in an approximately vertical position; the more lateral position of this canal leaves it more accessible to external temperature changes. The mechanism commonly invoked as responsible for the caloric nystagmic response is that the thermal change induces convection currents in the horizontal canal (when placed vertically) and thus cupular deflection. This hypothesis is strongly supported by the fact that, if the position of the subject during a caloric test is inverted (supine to prone), then the direction of the nystagmus reverses.[46] This is expected because the direction of the convection current will be reversed (note, convection currents occur in a gravitational field). However, the finding that a caloric response can be partly obtained in minimal gravity conditions, such as in the Space Lab mission, indicates that a direct thermal effect on the end organ is also present.[47]

Irrigation of the external auditory canal can be carried out with water or air. In the conventional procedure, two temperatures are used, one above and one below body temperature. Water irrigation at 30 °C and 44 °C (37 ± 7 °C) is the standard technique. In the original description by Fitzgerald and Hallpike,[48] the procedure follows the order left cold, right cold, left warm, right warm, for standardization purposes, with each irrigation lasting 40 seconds,[49] but this order is not essential. Temperature in the temporal bone has to be minimally stable before the next irrigation, so at least 5 minutes since the end of the previous irrigation has to be allowed for. Air irrigation offers the main advantage that it can be used in patients with eardrum perforations, but responses appear to be less consistent than with water. Technical modifications have improved this,[49] but insufficient patient data are available. If the surgeon needs to know whether there is any vestibular function at all in a perforated ear, then the answer is an air caloric test. For routine balance function assessment, water irrigation is preferred.

In the conventional testing position described above, cold irrigation induces horizontal nystagmus beating in the opposite direction of irrigation, and ipsilaterally during warm irrigation (cold-opposite-warm-same (COWS)). In this way, left cold and right warm irrigation induce right-beating nystagmus, and vice versa. Recording of the nystagmic response is usually carried out with EOG or VOG, often as part of a 'routine' computerized assessment. Measurements are taken of the velocity of the slow-phase component of the nystagmus and these are often displayed as a function of time. However, the original description by Fitzgerald and Hallpike is based on direct clinical measurement of the duration of the response and this technique is perfectly acceptable.

There are five main abnormalities of the caloric response.

1. Bilateral absence of caloric nystagmus, as in aminoglycoside ototoxicity or postmeningitis (see **Table 62.9**).
2. Unilateral canal paresis, a reduced/absent response from one ear, as in unilateral vestibular schwannoma or vestibular neuritis.[48, 50] Canal pareses can also be caused by a brainstem lesion in the VIII nerve root entry zone or vestibular nuclei but usually there will be other CNS symptoms or signs.[51]
3. DP, essentially an asymmetry in the VOR.[52] A right DP indicates that right-beating nystagmus is stronger, i.e. longer duration or faster slow-phase velocity according to the technique used, than left-beating nystagmus. A typical example is a patient with a, say, left vestibular neuritis. Initially the picture will be dominated by the complete left canal paresis and the spontaneous right-beating nystagmus. With time, all there may be left over is a right DP. Even if the caloric canal paresis does not recover at all, irrigation of the healthy right ear can show longer/stronger responses during warm irrigation (rightwards nystagmus) than cold irrigation (leftwards responses). Unfortunately, the finding of a DP in isolation is not specific and can be due to lesions ranging from the labyrinth to the cortex.[53, 54] One of the many possible visual representations used for canal paresis and DP is shown in **Figure 62.22**.
4. Abnormal VOR suppression. During caloric testing, VOR suppression is investigated in two possible ways.
   - With the conventional Fitzgerald and Hallpike technique the duration of the patient's nystagmus is directly timed in the presence of optic fixation. Once the nystagmic response has finished in the light the patient's eyes should be examined with either Frenzel glasses or an infrared viewer. In normal subjects or patients with peripheral vestibular disorders the caloric nystagmus then re-emerges. The duration of this nystagmus in the absence of optic fixation should be measured and the value compared to that obtained in the light.[56] Typically, a caloric nystagmic response in the light will last 80–160 seconds and this would be extended by 20–60 seconds without fixation. Values of less than 20 seconds may indicate loss of VOR suppression but this should be corroborated with clinical

TABLE 62.9 Causes of bilateral caloric hypofunction

Cause	Percentage (%)
Neurological (cerebellar degenerations, postmeningitis, neuropathies)	25
Ototoxic (usually gentamicin)	25
Miscellaneous (e.g. autoimmune, Ménière's, head trauma)	25
Idiopathic	25

Modified and simplified from Rinne et al.[9]

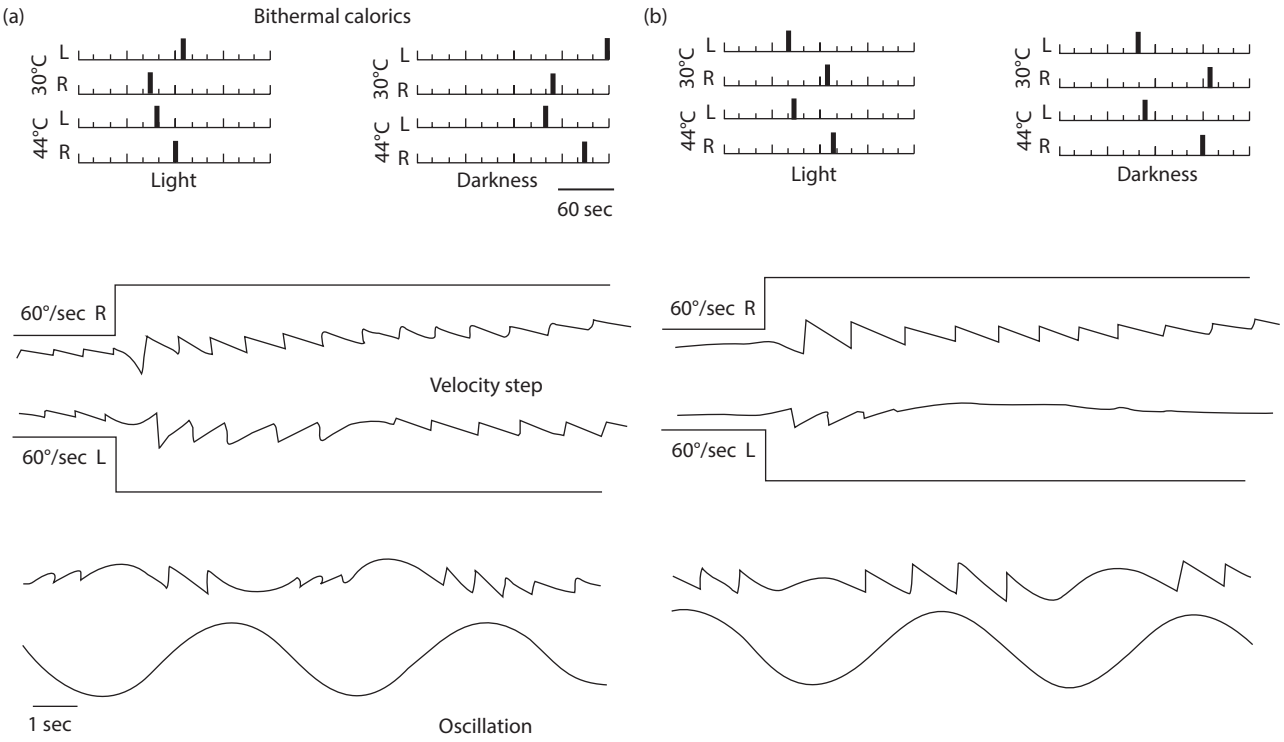


Figure 62.22 Caloric and rotational nystagmic patterns. (a) Right DP; **(b)** left canal paresis. Idealized recordings. Redrawn with permission from Bronstein et al.[55]

or rotational assessment of VOR suppression. It should be noted that subjects regularly exposed to intense vestibular stimulation may show little or no visible nystagmic response in the light but the response will be of normal magnitude without visual fixation. This can be observed in ballet dancers, acrobats, jet-fighter pilots and some patients with peripheral vestibular disorders with repetitive vertigo attacks.[57]

- VOR suppression is more often assessed by providing a fixation light for a period of 10–20 seconds in the middle of the caloric response. This requires ocular recordings and the results are expressed as the absolute or relative amount of reduction in slow phase velocity brought about by fixation. Results will depend, to some extent, at which point in time the fixation target is presented, but usually a reduction of approximately 50% is expected. With any technique, lack of VOR suppression indicates the presence of a central disorder of eye movement control, usually correlated with pursuit disorder, often of cerebellar/brainstem origin.[58]

5. Perverted nystagmus. This is the name given to the phenomenon whereby, instead of the expected caloric-induced horizontal nystagmus, one observes nystagmus in other planes, for example DBN (note, a minor torsional component added to the main horizontal nystagmus can be accepted as normal). If the caloric test is carried out pretty 'blindly', for instance with EOG in the dark, perverted nystagmus may be missed. However, perverted nystagmus rarely occurs in isolation, as it indicates posterior fossa disease, and other cerebellar or brainstem ocular signs should be seen.

ROTATIONAL TESTS

Most rotating chairs are motorized and computer-controlled so that velocity and rotational waveform can be delivered accurately. The patient's head should be comfortably immobilized, otherwise his own head movements interfere with the test and unwanted side effects, such as nausea, may develop. There are many velocity profiles used but here we will describe two of the more commonly used, velocity steps and sinusoidal oscillation (Figure 62.22). The more recently developed video head-impulse test will be described after the traditional rotational examination.

Velocity step or 'impulsive' rotational test

The stimulus consists of a sudden increase in chair velocity, say from 0 to 60 or 90 degrees per second. The time taken to reach this velocity, i.e. acceleration time, is of the order of 1–3 seconds.[48] Testing is conducted either in total darkness or with light-tight goggles. This elicits per-rotational nystagmus which slowly decays and eventually stops (if it does not stop the subject inadvertently may not be in total darkness). Full chair velocity is maintained for 60–90 seconds, or until any rotationally induced nystagmus disappears. At this point the chair is suddenly stopped and a similar nystagmic response, in the opposite direction, occurs (post-rotational nystagmus). The whole sequence

is then repeated in the opposite direction. Clockwise or rightwards rotation induces right-beating nystagmus (following the principle that the function of the VOR is to generate a slow-phase velocity in the opposite direction of head rotation); the stopping response is in this case a left-beating nystagmus.

As mentioned above, the nystagmus is of maximal intensity immediately after acceleration ('starting') or deceleration ('stopping') and then gradually (exponentially) decays. One can obtain time measurements of the response, such as duration of the nystagmus or time constant of decay of the slow phase velocity. In addition, the peak velocity of the slow phase component should be measured, which can be expressed as 'gain', the ratio between eye velocity and chair velocity. As with caloric testing, one assesses the overall level of activity and right–left response symmetry (DP) but normal values depend on stimulus parameters and laboratories.

I should like to mention that it is possible to obtain a semi-quantitative velocity-step assessment with an office swivel chair, to deliver rotation, and Frenzel glasses, to remove fixation. In this case, nystagmus duration is directly timed during the 'stopping response'. Stimulus velocity can be reasonably controlled by the examiner walking the chair round at a constant rate; for example, four steps per cycle (revolution) will deliver approximately 90 degrees per second and this should be maintained for 40–60 seconds and then suddenly stopped. Beware that you will be as dizzy as your patient, so plan your actions carefully!

Notice that, during rotation with the head in the normal upright position, or slightly tilted forwards to keep the lateral semicircular canals in the horizontal plane, the nystagmus will be almost exclusively horizontal. If the head were to be tilted backwards as much as possible, (e.g. the patient's face pointing up), the vertical semicircular canals (anterior and posterior) will now be placed in the plane of rotation. On stopping the chair the nystagmus observed is mostly torsional and so, timing its duration, assesses the function of the vertical canals *en bloc* (right and left, superior and inferior canals). Placing the head obliquely down to the left stimulates the left anterior–right posterior (LARP plane) semicircular canals; rotating with the head obliquely down to the right stimulates the right anterior–left posterior (RALP plane) canals. In order to fully assess vertical canal function accurately, however, one requires sophisticated 3D oculography and precision positioning of the head in a 3D rotating device.[59] The 3D VHIT can assess high acceleration function of all six canals with relatively simple and inexpensive technology (see below). However, it is not clear how much vertical canal testing adds to the day-to-day diagnosis and management of vestibular patients.

In summary, the 'impulsive' rotational test has been successful in practice since Barany's days. It has the advantage that it can be administered in a relatively short period of time, it is reproducible and is less affected by the patient's mental status than sinusoidal testing.

Sinusoidal rotation

In this test the velocity of the chair is sinusoidally modulated (**Figure 62.22**, bottom). Usually, a range of frequencies are used from approximately 0.05 Hz to 1 Hz, while the peak velocity of the stimulus is kept constant. This arrangement has the effect that acceleration increases progressively. A problem with this test is that a gentle oscillation in the dark is soporific and too predictable. Patients can be drowsy, giving responses difficult to interpret, or produce responses which are influenced by prediction and therefore look more normal than they really are. In order to avoid these complications, stimuli combining sinusoids of various frequencies in a random or pseudo-random fashion have been developed; these are effective but complicated software is required.

The results are usually expressed as gain (slow-phase eye velocity/chair velocity) and phase (the difference in degrees between maxima and minima of the chair and eye velocity waveforms), both plotted as a function of stimulus frequency. As in other vestibular tests, one examines the overall strength of the vestibular response, in this case as gain, and degree of asymmetry both as gain and phase. Unfortunately, variability is large from subject to subject and within the same subject due to concentration and mental set, both in health and disease.

The gain of the VOR in the light is, as mentioned earlier, close to unity. The test is normally conducted in the dark where normal gains at middle frequencies are between 0.4 and 0.8 but these values are only indicative; normal data should be collected under strict conditions, including mental tasks (e.g. mental arithmetic or imaginary targets). Indicative values of asymmetry should be larger than 20–30%, the lower gain and larger phase error occurring during the hemicycle with rotation towards the side of the vestibular lesion.

Although frequently used in research, in the clinic the sinusoidal test has problems with result variability and the time required for appropriate testing. An advantage is that it is an easy and reliable way of assessing VOR suppression by comparing gain values in the dark and those obtained during rotation with a chair-fixed target.

Interpretation of rotational results

Regardless of the technique, there are three main abnormalities of rotational responses.

1. Bilateral reduction or absence of response, as in bilateral vestibular failure, for instance due to ototoxicity, postmeningitis and idiopathic.[9]
2. Asymmetry, or DP, which if considerable (say >30%) is a valuable indicator of vestibular system disorder but, unfortunately, not a good localizing sign per se. However, an isolated DP is often the only 'objective' finding in a balance disorder patient. In the absence of any central vestibular or oculomotor disorder, it is supporting evidence in favour of a peripheral vestibular disorder but specificity and sensitivity data are lacking.

3. Loss of VOR suppression, investigated by providing a chair-fixed target during part of the rotation, indicative of central disorder (see 'Vestibulo-ocular reflex suppression' above).

VIDEO HEAD-IMPULSE TEST

In the last few years, computerized, video-based versions of the head-impulse test have appeared in the market. The physiological principle has been explained above but a head motion sensor and a VOG system records the head and eye velocity response. This makes detection of the corrective 'catch-up' saccades described above (see 'Vestibulo-ocular reflex' and 'Head-impulse test' above) easier, more objective and quantitative; the gain of the vestibulo-ocular response (peak eye velocity/peak head velocity) is also measured (**Figure 62.23**). At the same time, like with any automated analysis system, the possibility of recording and wrongly measuring undesirable artefacts such as blinks also increases. Therefore, the clinician should carefully compare his/her own findings during the clinical head-impulse test (HIT) with the results of the VHIT. As with other vestibular tests, the VHIT can detect uni- and bilateral loss of vestibular function (both by a low gain and by the presence of catch-up saccades). In contrast to conventional rotational tests, the side of the hypofunction can be reliably detected with VHIT but the level of agreement with the 'gold standard' caloric test is not great, particularly in chronic, compensated lesions. In many cases, particularly if there is clinical –VHIT discrepancy, a caloric test is warranted. Discrepancies will not always be due to technical problems though. The VHIT tests the VOR at high frequencies/accelerations of the head (a head impulse lasts 0.5 seconds = 2 Hz) whereas a caloric response lasting 2 minutes can be converted thus: 1/120 seconds = 0.008 Hz! Hence selective or preferential

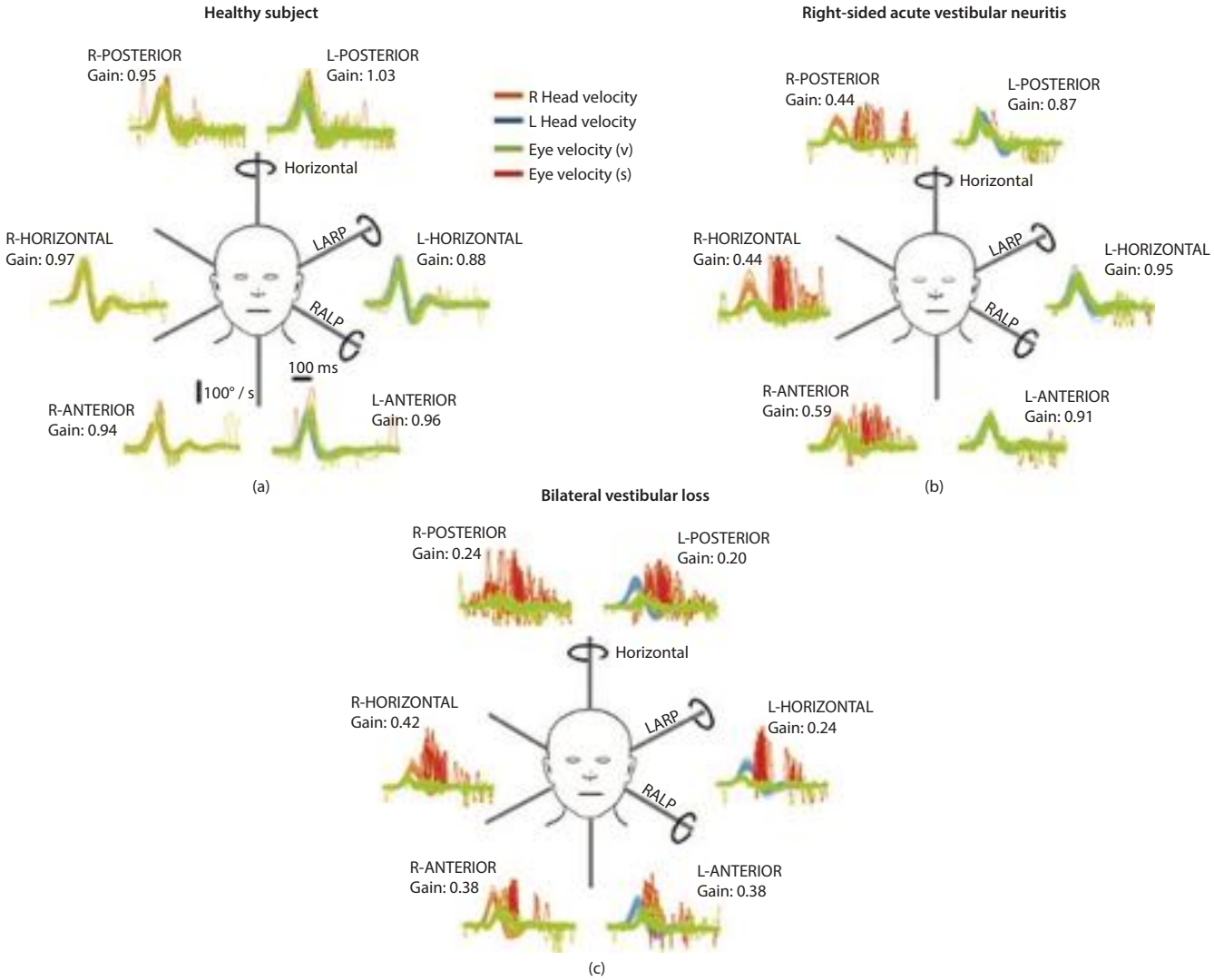


Figure 62.23 **(a)** A normal healthy subject, with gain values close to unity for all six canals and no 'catch-up' saccades. **(b)** A patient with neuritis of the right superior and inferior vestibular nerve showing reduced gain (close to 0.5) and many catch-up saccades (spiky traces). **(c)** Results in a patient with bilateral vestibular failure, showing low gains (0.2–0.4) in all six canals. Reproduced from Bronstein et al.,[37] with permission.

involvement of the high- or low-frequency VOR would produce selective abnormality in one but not the other test.

Several factors have contributed to the success of the VHIT, despite the fact that both the clinical HIT[60] and the VHIT are relatively new tool in diagnosis.[61] In contrast to rotating devices, VHIT systems are relatively cheap and take much less space than rotating chairs. Testing time is also shorter than a routine EOG/VOG rotational or caloric assessment and, usually, better tolerated by the patient even if all six canals are being assessed. Finally, the timing is also right. Acute vertigo has become 'fashionable' again given the need to separate acute vertigo due to vestibular neuritis from posterior fossa stroke, which requires thrombolytic treatment within 3–4 hours of vertigo onset. As mentioned already, in this scenario the clinical or video HIT can be critical in separating a unilateral peripheral vestibular deficit (likely vestibular neuritis – no thrombolysis needed) from brainstem–cerebellar ischemic stroke (thrombolysis often provided). Despite this success, most users and scientists using VHIT devices with no conflict of interest do not believe that this new development has replaced or will replace caloric testing in the near future.

Examination of postural balance

The investigation of postural balance is influenced by the clinician's own background. More research using posturography comes from ENT or audiology departments than from neurology ones,[30, 31] which could mean that ORL specialists see more dizzy patients than other specialists. It could also mean that neurologists tend to rely on their own clinical assessment of posture and gait, which is understandable since almost all neurological diseases impair gait and posture. Regardless of the clinician's background, the value of direct clinical observation of gait and posture in patients with unsteadiness cannot be overemphasized. I will first summarize the clinical examination of posture and gait and then address the contribution of posturography.

CLINICAL EXAMINATION OF BALANCE, POSTURE AND GAIT

Gait unsteadiness is associated with a wide range of disorders.[55] If it has never been associated with vertigo, dizziness, oscillopsia or hearing disorder, it is unlikely to be due to vestibular disease.[62] It is important to realize, however, that patients with mild gait disorders often describe their problem as dizziness and therefore do turn up in ENT and neuro-otology clinics.

It is usually possible to establish a topographical diagnosis (site of lesion) in a gait disorder on the basis of clinical observation of gait and a neurological examination (Tables 62.10 and 62.11).[63–65]

It is beyond the scope of this chapter to describe the many diseases with gait disorder. However, the aspects required when examining a patient with gait unsteadiness listed in Table 62.11 will be reviewed.

TABLE 62.10 Topographical classification of gait abnormalities

Level of abnormality	Topographical classification
Lower levels	Peripheral lesions: mono/polyneuropathies, root lesions and myopathies Vestibular and visual lesions
Medium levels	Spinal and brainstem lesions
Higher levels	Cerebellar syndromes
	Subcortical disorders (basal ganglia and internal capsule): Parkinson's disease, orthostatic tremor, choreas and corticospinal tract lesions
Highest levels	Frontal lesions of the cerebral cortex, white matter in the semioval centre and periventricular area (vascular, degenerative diseases, demyelinating, tumours and hydrocephalus) Cautious gait and psychogenic gait disorders

Modified from Dominguez and Bronstein,[63] Nutt et al.,[64] Marsden and Thompson.[65]

TABLE 62.11 Examination of posture and gait

Aspect	Examination
Posture	Head and neck Trunk Stance and Romberg test Postural reflexes
Walking	Step initiation Stepping pattern Associated trunk and arm movements Eyes closed walking
Neurological and relevant skeletal examination	

Modified from Dominguez and Bronstein.[63]

Posture

Observation of head and trunk posture can provide immediate useful information. There are abnormal tilts or rotations in dystonia, flexed posture in Parkinson's disease, hyperextension in progressive supranuclear palsy (PSP) and titubation in cerebellar disease. In lesions of the vestibular nuclei, as in the lateral medullary (Wallenberg) syndrome, there can be an ipsilesional ear-down head tilt, together with a skew eye deviation (ipsilesional lower eye) and ipsilesional body pulsion.

Observation of stance will reveal a broadening of the base of support in diffuse vascular disease, frontal lesions, cerebellar lesions, sensory ataxia, acute or bilateral vestibular lesions and patients with a cautious gait. Lateropulsion can be seen in acute unilateral peripheral vestibular lesions and in lateralized brainstem–cerebellar lesions. Midline brainstem–cerebellar lesions can show retropulsion. Minor degrees of unsteadiness can be brought about by asking the patient to put the feet together or in the heel-to-toe position. A 'bouncy' stance, with head-trunk oscillations about 2–3 Hz, may be observed in ataxic or ataxic–spastic disorders, typically in

multiple sclerosis. A shaky 'tremulous' stance, with higher-frequency oscillations, can be seen in some patients with Parkinson's disease and orthostatic tremor.

The Romberg test, originally described for patients with tabes dorsalis, is positive in patients with dorsal column or severe afferent polyneuropathy. A positive Romberg means that the patient shows a tendency to actually fall, unlike normal subjects and almost all patients with balance problems who show a small to moderate increase in body sway on eye closure. Only in the acute phase of a peripheral vestibular disorder will the Romberg test be positive, usually with an ipsilesional fall. In a patient with either cerebellar degeneration or polyneuropathy, a high level of unsteadiness on eye closure may indicate the presence of additional bilateral vestibular failure.[9] This syndrome has been named CANVAS (cerebellar atrophy, neuropathy, vestibular arreflexia syndrome).[66] Patients with anterior lobe cerebellar degeneration may show the characteristic trunk oscillation or titubation only on eye closure; when mild, this may just be visible as a tremor of the ankle extensors ('dancing tendons'). On a practical note, anyone who can stand on either foot unaided, with eyes closed, is unlikely to have any objective and organic postural balance problem.

Postural reflexes are an important part of the balance examination, particularly when the patient's dizziness cannot be explained in vestibular terms. They are examined by gently pushing and pulling the upper trunk. This can be carried out by standing behind the patient so he/she cannot anticipate the precise timing and direction of the push (forwards or backwards) to the shoulders. In akinetic syndromes, these responses may be completely absent – such as in Parkinson's disease, PSP and small vessel white matter disease with or without parkinsonism – patients falling rigidly like a log. A few shuffling steps backwards (retropulsion) or forwards can be seen in the early stages. In cerebellar syndromes, particularly anterior lobe disease, the trunk pushes may unmask a trunk titubation, observable as a 'trunk rebound' in response to the push. In the elderly, with fear of falling or a cautious gait, trunk pushes trigger a startle, panic-like response. Vestibular patients may be unsteady but the overall pattern of the response is preserved.

Walking

Step initiation can be impaired in frontal lesions, including the gait ignition failure syndrome[64, 65] and as part of the akinesia in the Parkinsonian syndromes. Initiation of gait is hesitant, the feet appearing to be stuck to the ground ('magnetic feet'; 'slipping clutch' phenomenon).

The steady-state stepping pattern may be less disturbed in patients with difficulty in step initiation, once they are off. In akinetic-rigid, Parkinsonian syndromes steps are often shallow, short and slow but with preserved rhythm. In contrast, cerebellar patients show irregular rhythm, variable length, oscillations and a wide base, giving a lurching, 'drunken' appearance to their walking. Patients with severe loss of sensory information from the lower limbs (sensory ataxia) lift the feet high and place them on the ground under intense visual control; in dorsal column lesions the heels strike the ground first (tabetic gait), in cases with ankle extensor weakness (foot drop) the toes make contact first (steppage). In spasticity, the knee-extensor and ankle-flexor hypertonus leads to the characteristic slow gait with circumduction movements of the leg during the swing phase.

The normal associated movements of the arms while walking are lost in Parkinson's disease. Unilateral loss of arm swing can be a useful early sign in Parkinson's disease and hemiparesis. The arms of patients with a cautious gait reach out as if expecting to fall and step with apparently unnecessary care, giving the appearance of 'walking on ice'. Although a cautious gait can be part of a psychogenic gait disorder, it can be triggered by a vestibular, vascular or falling episode. Sometimes this is the only finding in elderly patients.

Walking with eyes closed in a straight line can reveal a previously unsuspected degree of unsteadiness or a cautious gait in patients with bilateral loss of vestibular function. In somatosensory ataxia this task is often impossible. In unilateral vestibular lesions, particularly in the acute stage, patients veer in the same direction as the lesion. A paradoxical improvement while walking fast has been reported in acute vestibular lesions.[67] In the Unterberger test, instead of walking along, the patient is asked to walk on the spot with the eyes closed. In unilateral vestibular lesions the patient turns towards the hypoactive side. It is helpful to ask the patient to keep the arms and index fingers pointing forwards towards the examiner's index fingers; this allows a more precise assessment of the degree and consistency of turning (**Figure 62.24**).



Figure 62.24 The 'stepping on the spot' or Unterberger test. Lining up of the examiner and patient's fingers is useful to document mild abnormalities when the patient steps with the eyes closed. Repetition of the test, for consistency, is essential.

Summary of the relevant neurological examination

We present a summary of the neurological examination relevant to balance and gait disorders, in the hope that it may guide the non-neurologist who suspects a neurological cause for unsteadiness or gait disorder. Weakness of the legs can be documented by asking the patient to push against the examiner's hands with different muscle groups or by asking the patient to stand/walk on tiptoes or heels, crouch and rise. Identification of weakness of the ankle extensors is paramount as these muscles are responsible for toe clearance during the swing phase of the gait cycle. Lower-limb weakness is a major contributor to the gait disorder in muscle, root and peripheral nerve disease, motorneurone and corticospinal tract disease; the tendon jerks will be exaggerated in pyramidal tract disease and depressed or absent in all the others; extensor cutaneous plantar responses (Babinski sign) can be found in pyramidal lesions.

Normal somatosensory function is needed for voluntary placing of the feet while walking, as well as for the proprioceptive reflexes controlling upright posture. At least pinprick, tuning fork and joint position sense must be examined in the lower limbs. If large fibres carrying proprioceptive input are involved, the ankle and sometimes patella jerks will be absent and the Romberg test will be positive.

Gait disorders due to neurological involvement at medium or high levels (see **Table 62.10**) will have associated clinical neurological features. In spinal cord compression or lesions there is often sphincter dysfunction and sensory disturbances in the limbs. At brainstem level, cranial nerve involvement including central vestibular and ocular–motor disorders; at cerebellar level, trunk titubation, intentional tremor, abnormal eye movements including nystagmus; at basal ganglia level, Parkinsonian features (including tremor, cogwheel rigidity, hypomimia, bradikinesia, loss of postural reflexes) dystonic limb or neck posturing and choreoathetosis.

It is important to keep in mind the unabated weight of the clinical neurological examination in the assessment of balance and gait disorders. Observation of gait, postural reflexes and the Romberg test followed, if appropriate, by a quick examination of lower limb power, coordination, reflexes and tuning fork are likely to help more than posturography. Normal CT and MRI scans are extremely valuable but do not exclude neurological disease (e.g. Parkinson's disease) and posturography findings usually lack topographical and aetiological specificity. Functional (psychogenic) disorders can only be diagnosed on the basis of an inconsistent or theatrical gait pattern, in a patient with essentially normal findings. Finally, particularly in the elderly, examination of the skeletal and cardiovascular examination or referral may hold the key to the cause of balance or dizzy symptoms. Cardiovascular syncope is a major cause for unexplained dizzy spells and falls in the elderly, regardless of whether the patient reports loss of consciousness or not.[68, 69]

Posturography

Strictly speaking, posturography is any means of recording postural activity, not only sway or force platforms which are indeed the most convenient way. In fact, 'sway' platforms do not actually measure body sway but foot torque (Nm), conveniently expressed as movement of the centre of foot pressure (cm). For standard clinical purposes, platform signals alone are acceptable but research questions often require additional recordings such as photoelectrical or electromagnetic recordings of head sway, accelerometry of head or trunk motion and EMG signals from the lower limbs. If the patient just stands quietly on the platform, with eyes open or closed, the procedure is called static posturography. When additional balance perturbations or stimuli are added (e.g. moving platform, visual stimuli, muscle vibration), it is called dynamic posturography.

Three general questions can be asked in this area.

1. Has posturography advanced the knowledge of how the postural systems work?
2. Has posturography taught us how posture is impaired in certain patient groups?
3. Does posturography help in the management of an individual patient complaining of a balance problem?

The answer to the first two questions is certainly yes, but opinions are divided as to the third.

Posturography has been useful in defining the contribution of the different sensory-motor components in postural control. The first attempts to generate a comprehensive system approach to postural control were led by Nashner and coworkers.[70–73] They suggested that postural balance is maintained on the basis of a limited repertoire of centrally generated muscle synergies. During slight perturbations to balance, the body behaves essentially as an inverted pendulum, pivoting around the ankle joints. Muscular responses are organized in a distal-to-proximal manner, with activation of distal muscles such as tibialis anterior and soleus occurring earlier than proximal ones; this is the 'ankle strategy'. Larger perturbations to balance, or lesser possibility of response such as when standing on a narrow beam, leads to movements around the hip joints and earlier activation of proximal muscles, such as abdominal, paraspinalis, quadriceps and hamstrings; this was called the 'hip strategy'.

The posturography system designed by Nashner consists of a support platform and a visual surround which can be moved angularly about an approximate inter-ankle axis. This setting allows for the ankle and visual information available to the subject to be, at least partly, neutralized by means of coupling the visual surround or the support surface to the AP sway movements of the subject. This set-up formed the basis of the commercial product 'Equitest', a computerized dynamic posturography (CDP) system, in particular, a testing protocol known as the sensory organization test. If patients with vestibular deficits are allowed to stand freely on this system, they show little

or no difficulty if the platform is stationary, with normal visual information (e.g. stable surrounds) or with eyes closed. When either or both the platform and visual surround are sway coupled, patients have poor balance performance.[74, 75] When presented in a historical context, the findings in vestibular patients seem trivial. Clinicians have known for decades that vestibular patients are usually normal in static conditions and that the way to unveil their unsteadiness is to examine them with eyes closed under conditions of reduced proprioceptive accuracy (e.g. on a mattress – reviewed in Martin).[76]

POSTUROGRAPHY IN PERIPHERAL VESTIBULAR DISORDERS

Clinical observation of patients with severe acute, unilateral vestibular disorders (e.g. vestibular neuritis) shows that they tend to fall towards the side of the lesion on eye closure – i.e. in the direction of the slow phase of nystagmus.[77] This can be documented by posturography but with little practical clinical benefit for the individual patient. In the compensated state, static posturography with eyes open or closed is usually normal. CDP shows increased sway, in conditions in which the support surface, the visual surroundings or both simultaneously are unstable (sway referenced). In some early series, 100% of patients have been reported abnormal when both visual surround and support surface are sway referenced,[75] in others this figure drops to around 50%.[78] In a small but carefully controlled series, ten patients with severe unilateral caloric reduction were abnormal when tested in the acute stage only under unstable support/visual surroundings.[79] Within 2 weeks, all patients regained total normality in all test conditions. The reasons for these discrepancies are not clear but the inability to confirm the earlier optimistic reports is one of the reasons underlying the current disaffection with the technique.

What clinicians want to know is what the added value of posturography is, in comparison with traditional testing of the vestibular system. A comparison between posturography and the caloric test showed that the caloric test correlates better with a history of vertigo and that CDP can show abnormalities in patients with normal caloric function.[80] This finding can be interpreted essentially in two ways: either posturography is capable of detecting abnormalities that caloric tests cannot (which it can – think of a spinal cord lesion or Parkinson's disease as a cause of unsteadiness) or posturography can give false positive results. There is no simple solution to this problem and, as outlined above, the clinician's beliefs, training background and interests will influence his decision.

A similar problem arises when comparing CDP with inexpensive alternatives. To a large extent, the sophistication of the commercially available CDP systems comes from the fact that the support surface and the visual surround can be moved. Clinical observation of a subject's balance while standing on rubber foam (which makes lower limb proprioceptive input inaccurate) and with either optically reversing goggles or a Chinese lamp (dome) on their head (which makes visual input unreliable) makes a reasonable, inexpensive approximation to CDP. This is sometimes called the 'clinical test of sensory integration and balance' or simply the 'foam and dome' test (**Figure 62.25**). A study compared CDP with its clinical counterpart and found an excellent correlation between the two sets of results.[81] This is good news to clinicians, particularly in rehabilitation, who may want to assess postural control thoroughly but are not prepared to make a large investment. Another comparison between results in moving-platform posturography and clinical analysis of posture with subjects standing on foam also reported significant correlation, with sensitivity and specificity of 90% and above.[82] Surprisingly, static posturography has been reported to have a good predictive value to help in identifying elderly subjects at risk of falls.[83]

Bilateral vestibular lesions are easily diagnosed clinically and with conventional laboratory tests – an audiogram is a much more helpful test by comparison. Posturography in these patients has limited value in diagnosis but studies have been of interest in defining the contribution of the vestibular system to postural control. Static posturography is normal in most patients with bilateral vestibular failure.[84, 85] It has been known for more than 70 years[76, 86, 87] that a sudden tilt, particularly if the patient is on a mattress and blindfolded, throws these patients off balance. This observation has been confirmed with dynamic posturography, including the fact that rotation of the base of support is more effective than translation in unmasking the postural deficit.[88, 89] Although patients tend to use more hip strategy,[89] latencies and muscle synergies are not essentially different from normal. EMG amplitudes in lower limb musculature are reduced by more than 50% during platform tilts and this may explain why they actually fall.[90–92] If the postural responses to movements of the support surface are indeed centrally patterned, these findings indicate that vestibular input is essential for adequate gain setting of early muscular components operating at 80–120 ms.[92] The alternative explanation that independent vestibulospinal or vestibuloreticulospinal pathways mediates the observed effects is equally possible and compatible with known latencies following direct vestibular activation.[93, 94] Answering this question is difficult with whole-body postural responses, as investigated by posturography. However, isolated motion stimuli to the head showed delayed neck responses[95] in bilateral vestibular patients, indicating that short latency vestibulocollic responses (about 25 ms) have a specific role in righting the head during sudden perturbations.[93]

POSTUROGRAPHY IN NEUROLOGICAL DISORDERS

As already emphasized, it would be naive to think that a posturography assessment could screen for a neurological deficit. Even if results were abnormal, the topographical and etiological specificity of the finding would be very low.

Patients with peripheral neuropathy have increased sway and this correlates with the loss of vibration sense in the lower limbs.[96–99]

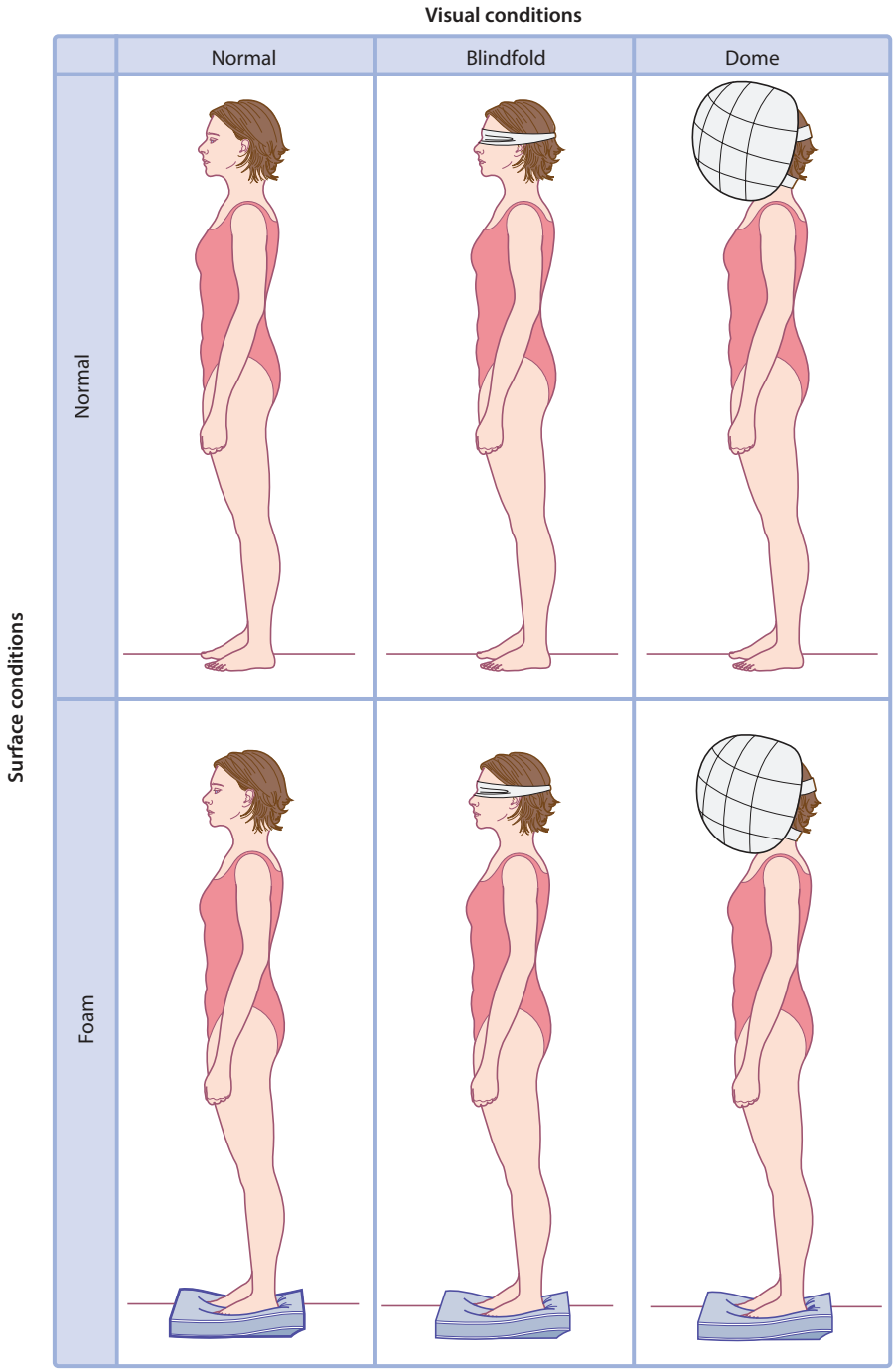


Figure 62.25 The 'foam and dome' test. The six testing conditions (visual 3 × support 2) correspond approximately to those of computerized dynamic posturography (CDP) as in the Equitest. Redrawn with permission from Pavlou et al. in Bronstein et al.[55]

The balance disorder in cerebellar disease is due to loss of muscle coordination,[100] central modulation of vestibular and somatosensory mechanisms,[101] neural adaptation to vestibular loss[102] and recalibration and learning processes.[103] On the basis of comparisons between lateral versus anteroposterior sway, eyes closed versus eyes open (EC/EO or Romberg quotient) and the frequencies of sway involved, four cerebellar sway patterns can be identified.[104] Perhaps the single most useful finding is the presence of a body tremor at approximately 3 Hz in patients with anterior lobe degeneration, either alcohol-induced or degenerative. In clinical practice, however, this tremor can be detected clinically and the value of posturography in its diagnosis has been questioned.[105]

The commonest basal ganglia disorder is Parkinson's disease and approximately one-third of patients report falls.[106] Falls, however, are not common in the early phases of conventional, idiopathic Parkinson's disease, in contrast to other 'parkinsonisms' such as PSP (Steele–Richardson–Olszewski syndrome).[107] Despite the

significant contribution made by posturography to the understanding of the postural disorder in Parkinson's disease,[108–112] there is very little room for the technique in the management of patients. Of possible diagnostic interest is the fact that in some patients the tremor is recorded by the platform,[108] in which case frequency analysis will show a peak of tremor activity at frequencies between 4 and 6 Hz, well beyond those of body sway (<1–2 Hz). Other conditions with unsteadiness and high-frequency peaks in posturography recordings include some cerebellar ataxias, with a 3 Hz tremor discussed before,[104, 113] and orthostatic tremor.[114, 115] Orthostatic tremor is a relatively rare disorder, usually misdiagnosed as a psychogenic balance problem, but platform recordings can easily identify the pathognomonic high-frequency tremor, typically at 16 Hz (**Figure 62.26**). During platform fore–aft motion postural reflexes are elicited and the stepping responses in parkinsonian patients are usually abnormal (hypometric and multiple stepped)[116] but, again, for the clinician the simple trunk pulls described above are equally useful.

PSYCHOPHYSIOLOGICAL UNSTEADINESS

Some patients report dizziness in surroundings with intense visual motion or repetitive visual patterns, such as driving, supermarkets, crowds, disco lights or ironing striped shirts. We use the term 'visual vertigo' or visually induced dizziness to describe these patients, when there is clinical and/or laboratory evidence of a vestibular lesion without clinically obvious psychiatric disorder.[117] Such patients are 'visually dependent', in that they rely excessively on visual cues for spatial orientation and postural control. Visual motion or optokinetic stimuli makes them selectively unsteady,[5] particularly if the vestibular disorder is central or if there is additional strabismus.[117] Posturographic and perceptual measures of visual dependence are correlated, albeit weakly, and this is important because identification of visual dependence helps in the selection of appropriate vestibular rehabilitation. This may also be identified with CDP, or its clinical version, the 'foam and dome' test, during testing conditions with sway-referenced visual surroundings. However, simple questionnaires[118] are equally useful to identify visually susceptible patients who are likely to benefit from additional optokinetic stimulation during vestibular rehabilitation.

PSYCHOLOGICAL UNSTEADINESS

The relationship between psychological disorders and balance is extremely complex. Anxiety can create dizziness and vice versa and there is no easy solution to this common 'chicken and egg' clinical dilemma.

Both vestibular[119] and anxiety patients[118] show increased sway in response to visual motion. Patients with panic and agoraphobia also show excessive sensitivity to platform or visual surround motion.[120] It has also been reported that posturography can identify inconsistent and incoherent responses in patients with non-organic dizziness.[121–123] An increase in sway frequencies of up to 8 Hz has also been reported in some patients with psychogenic unsteadiness.[124]

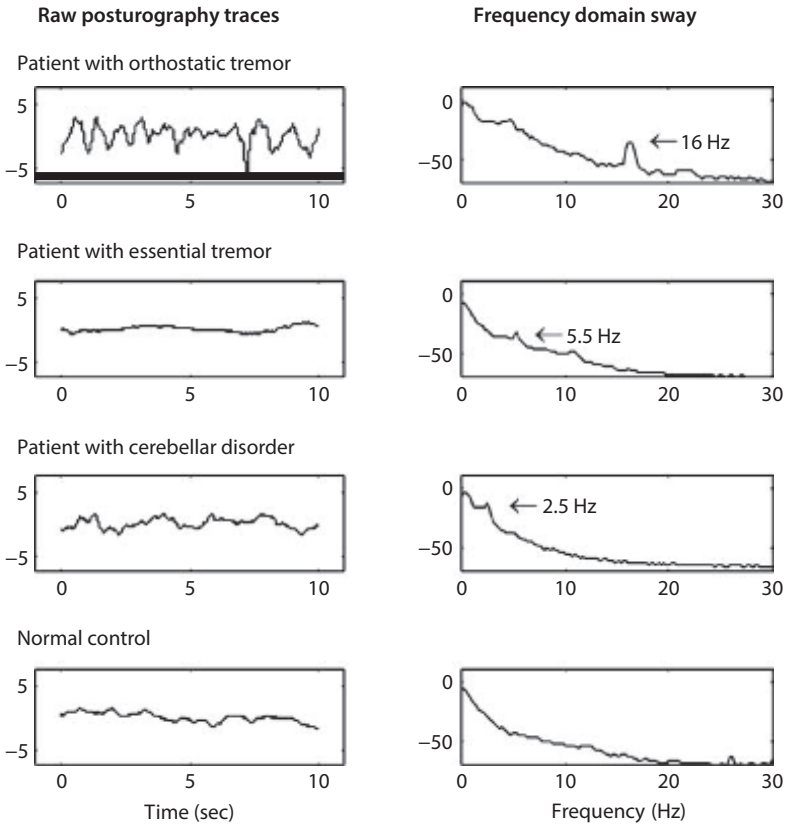


Figure 62.26 Fast Fourier analysis of posturography platform signals in patients with tremolous or 'shaky' stance. Reproduced with permission from Yarrow et al.,[115] with permission from Elsevier.

However, clinicians should rely on a constellation of negative findings (neurological, vestibular and imaging) and positive malingering or conversive (functional) features, as well as an appropriate psychological profile before making such a diagnosis.[125]

SUMMARY OF POSTUROGRAPHY

In summary, there is debate as to the clinical usefulness of posturography for the day-to-day management of patients.[126–129] A report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology remains a good and objective introduction to the topic for non-subspecialized clinicians.[130] The specialist panel concluded in 1993 that dynamic posturography had a promising role in the assessment of balance disorders patients. The ensuing discussion 25 years later testifies that such potential has not been fully developed. I am only able to make only one definite diagnosis with posturography, orthostatic tremor, but this is a rare condition. Similarly good specificity is also seen with the 3 Hz body postural tremor in certain cerebellar lesions, but the tremor is also observed clinically.[105]

The rationale behind clinical posturography is that it tests postural control as a whole, with the various sensory inputs interacting in physiological ways and mimicking potential real-life challenges to upright balance. This is its strength and its weakness at the same time, the latter because of its lack of topographic specificity. The findings of a meta-analysis of posturography indicates that its overall sensitivity and specificity is of the order of 50%.[131] As expected, the diagnostic power was enhanced if patients with CNS lesions were included in the studies surveyed, but this is of little consolation since there are much better ways of diagnosing CNS disease than posturography. It is often said that posturography can be useful for rehabilitation, and indeed posturography has been instrumental in proving the value of vestibular rehabilitation.[132, 133] However, the daily problem in neuro-otology is the patient who is not objectively unsteady, but still reports off-balance sensations and dizziness. Whether posturography has anything to add to simple questionnaire assessment of symptoms remains an open question.

OTOLITH AND PERCEPTUAL ASSESSMENT

Otolith and perceptual assessment tests will be discussed briefly because they are currently evolving and are rarely available as a routine test in clinical departments. We will briefly describe linear acceleration tests of otolith function but vestibulo-evoked myogenic potential (VEMPs, ocular and cervical) are thought to be of otolithic origin and so they will be mentioned in this section as well. Perceptual tests of vestibular function, with an emphasis on the procedure known as the subjective visual vertical (SVV), will follow.

Otolith testing

LINEAR ACCELERATION TESTS

The otoliths are selectively stimulated by linear acceleration, including gravity.[134] Due to their morphology and curved trajectory of the polarization vectors of the hair cells, both the utricular and saccular maculae are sensitive to multiple axes of linear acceleration. The predominantly horizontal orientation of the utricules, however, makes them mostly sensitive to accelerations in this plane (i.e. right–left, fore–aft) or tilt away from this plane. The predominantly (para) sagittal orientation of the sacculi makes them more sensitive to sagittal plane tilt (pitch tilt) and acceleration (e.g. fore–aft, rostrocaudal). One should remember that linear acceleration is also generated during rotatory motion (centrifugal and tangential acceleration) and this has been recently exploited in the field of otolith testing. Here, I will present the general principles of otolith testing and the reader interested in any individual technique should pursue the original references.

Otolith testing is technically challenging. The generation of pure linear acceleration of sufficient magnitude (>0.2 g) under controlled conditions requires motorized sleds running on precision tracks (**Figure 62.27c**). Although a linear acceleration version of the head-impulse test, the clinical head heave test can provide information on the utricular–ocular reflex,[135] but this has not been validated against quantitative techniques.

Centrifugal and tangential accelerations can be generated with rotating devices but these have to be powerful and sturdy to carry the weight of a human subject placed eccentrically from the rotational axis. Perhaps the simpler way to obtain tangential acceleration of the head and stimulate otolith–ocular reflexes is to make the subject lean forwards onto an eccentric chin- or headrest, while seated on a conventional rotating chair (head-eccentric rotation).[136, 137] Following this principle, one can also rotate a person around an earth-vertical axis passing through one of the labyrinths, thus creating a centred labyrinth and an eccentric labyrinth. Only the latter is subjected to tangential and centrifugal acceleration and this test is the only test capable of providing information on each individual utricle (eccentric centrifugation).[138, 139]

Another way of obtaining controlled stimulation of the otolith is to rotate the subject about an axis which is tilted (off-vertical axis rotation (OVAR)) or orthogonal ('barbeque-spit rotation') with respect to the gravitational vector; in these tests the stimulus is provided by the continuous reorientation of the head with respect to gravity.[140, 141] It is important to note that, whenever the linear acceleration is generated by rotation, the otolith response is assessed either by subtracting the component due to angular motion (e.g. subtracting head-eccentric response from head-centred response, in the head-eccentric test) or by waiting until the angular VOR has ceased (e.g. in OVAR or BBQ rotation). Finally, a simple way of stimulating the otoliths is head tilt with respect to gravity. This can be refined with



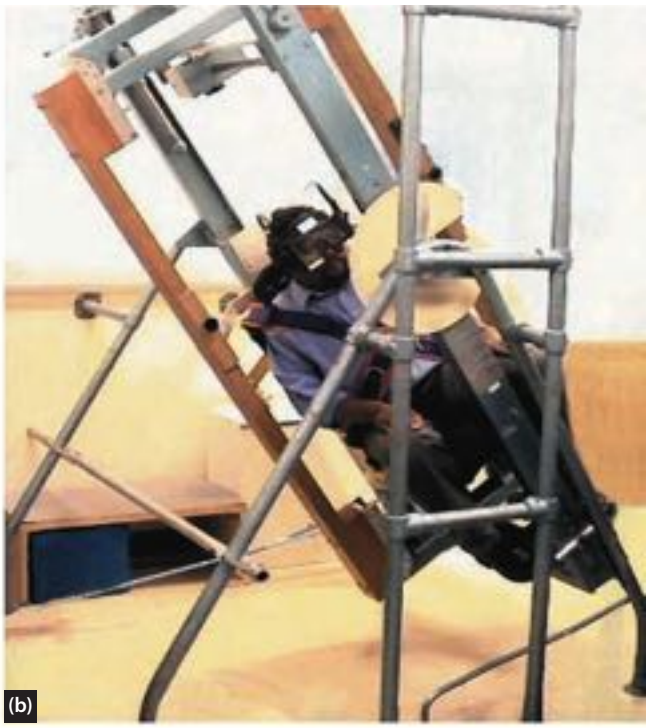




Figure 62.27 Otolith testing devices I. (a,b) Ocular counter-rolling measured by 3D VOG during body tilt. **(c)** Oculography (in this case conventional horizontal EOG) during lateral linear acceleration.

precision gimbals systems (**Figures 62.27a** and **b**).[142] A summary of the stimulation techniques for otolith assessment is presented in **Figures 62.27**, **62.28** and **62.29**.

What can be measured to assess otolith function? The more common measure is the slow-phase eye movement response, called linear or translational VOR or, more generally, otolith–ocular reflexes.[143] Recording of eye movements during otolith testing also poses technical problems. The forces involved usually generate more movement artefact than during conventional rotational or caloric procedures. In addition, the relatively small size of the otolith–ocular response, coupled with the fact that an important component of the otolith response is ocular torsion (not recorded by EOG or conventional VOG), often requires 3D oculography (VOG or search-coil technique).[138] Another response, which can be measured during linear acceleration, particularly in centrifugal tests,[144] is the SVV which largely follows ocular torsional position (see 'Subjective visual vertical' below).[145]

Difficulties in testing the otoliths are not only technical. The orientation of the hair cells is such that a single utricle (or sacculus) is capable of sensing linear accelerations in all directions. Thus, deficits due to unilateral otolith lesions are usually only acute and transient. For instance, the horizontal otolith–ocular reflex in response to interaural linear acceleration remains abnormally asymmetric for

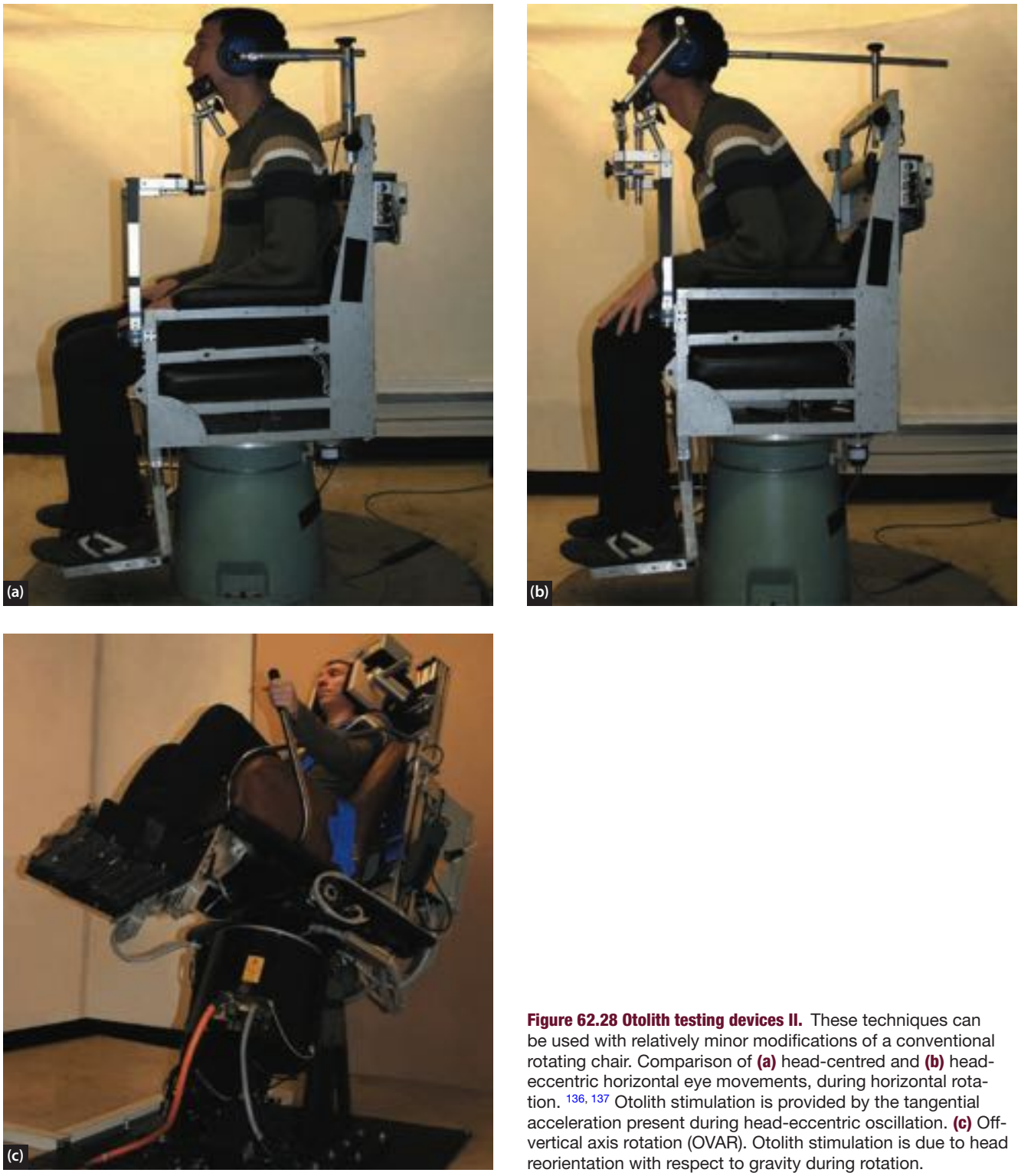


Figure 62.28 Otolith testing devices II. These techniques can be used with relatively minor modifications of a conventional rotating chair. Comparison of **(a)** head-centred and **(b)** head-eccentric horizontal eye movements, during horizontal rotation. [136, 137] Otolith stimulation is provided by the tangential acceleration present during head-eccentric oscillation. **(c)** Off-vertical axis rotation (OVAR). Otolith stimulation is due to head reorientation with respect to gravity during rotation.

only approximately 4 weeks after a unilateral vestibular nerve section.[143] Torsional and visual vertical deficits may be unmasked during eccentric centrifugation.[138, 144]

In summary, there are many tests of otolith function and most have been validated in patients with acute vestibular lesions (spontaneous or surgical). Such lesions are not selective and destroy not only the otoliths but large parts of the vestibular labyrinth. In such circumstances there is little clinical doubt that a patient has sustained unilateral vestibular damage and so documenting otolith involvement in such cases is just a research exercise. The challenge of devising a test of otolith function in a patient who lacks independent evidence of vestibular lesion still remains. Currently, there is no validated test to confirm that a patient has a selective otolith lesion. Claims that the SVV is a selective test of otolith function[3, 146] have not been scientifically

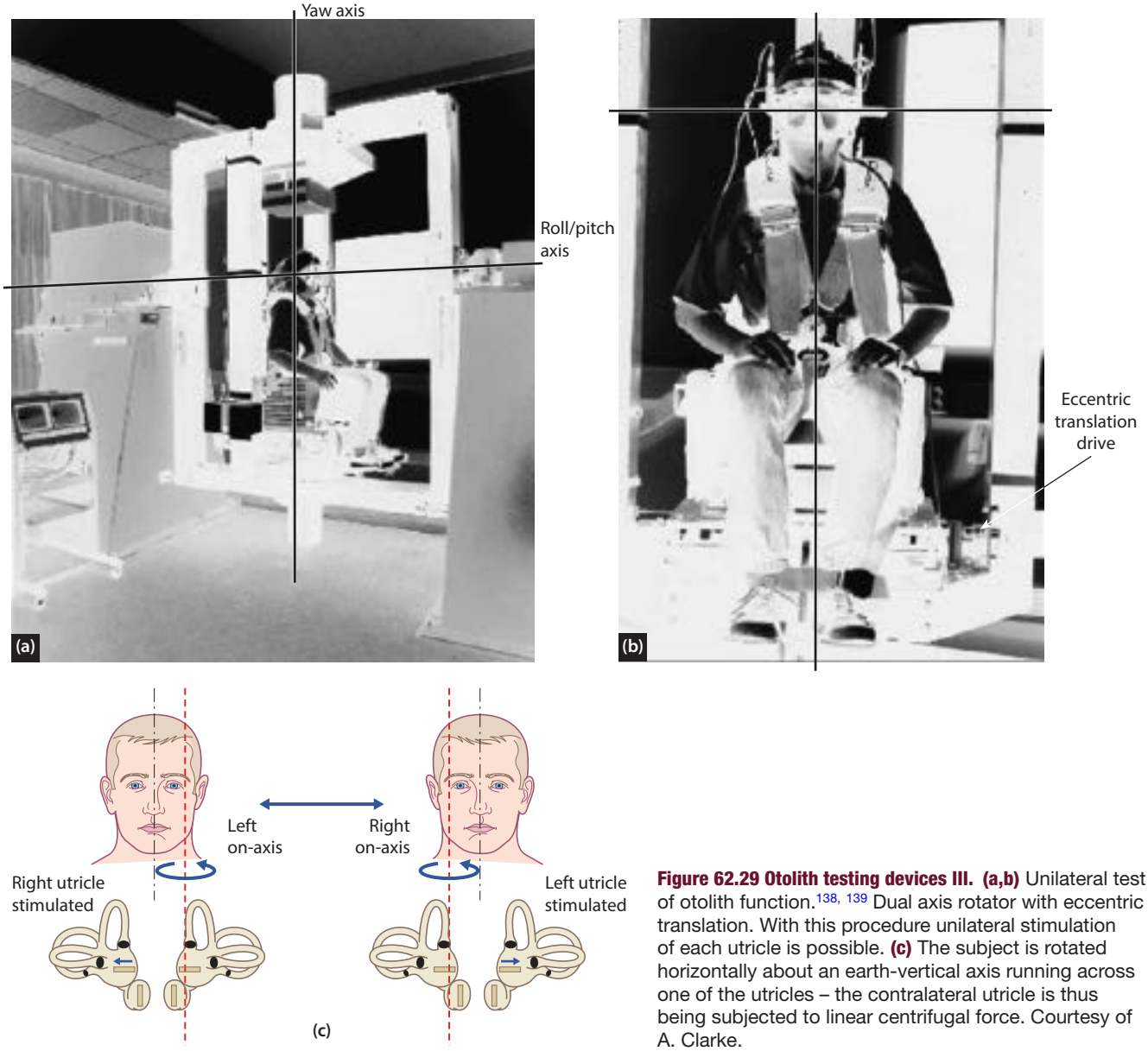


Figure 62.29 Otolith testing devices III. (a,b) Unilateral test of otolith function.[138, 139] Dual axis rotator with eccentric translation. With this procedure unilateral stimulation of each utricle is possible. **(c)** The subject is rotated horizontally about an earth-vertical axis running across one of the utricles – the contralateral utricle is thus being subjected to linear centrifugal force. Courtesy of A. Clarke.

validated. Furthermore, this view has been seriously challenged on the basis of clear experimental evidence showing that vertical semicircular canal input also induces tilt of the visual vertical.[147]

VESTIBULAR-EVOKED MYOGENIC POTENTIALS

Loud sounds can activate the vestibular labyrinth. If these sounds are brief in duration (clicks), the total amount of energy delivered to the ear is small and the procedure harmless. Using averaging techniques similar to those in brainstem auditory evoked potentials, an electromyographic (EMG) potential can be identified from neck muscles.[148, 149] The response is a sound-evoked vestibulocollic (or vestibulospinal) reflex and this is often called the cervical vestibular-evoked myogenic potential (cVEMP). The technique can be easily set up in any clinical neurophysiology or audiology department with access to calibrated sound generators, averaging equipment and surface recording electrodes and several devices are available commercially.

A useful feature of this procedure is that it can investigate each ear separately. The main response is an ipsilateral positive deflection at 13 ms (P13) and a negative deflection at approximately 23 ms (N23). Conductive deafness, by obstructing the clicks reaching the labyrinth, interfere or abolish the reponse, so auralscopy and a pure-tone audiogram are necessary if the response is absent. However, as expected from a genuine vestibular response, vestibular-sparing, sensorineural deafness does not interfere per se with the cEVMP. All available evidence indicates that the main inner ear structure activated by sound is the sacculus, so cEVMP can be considered an otolith test.[150]

Clinical applications of this test are developing. The main practical diagnostic use is for the diagnosis of the superior semicircular canal dehiscence syndrome, or more generally

the Tullio phenomenon.[149] These patients have lower threshold, higher amplitude potentials from the symptomatic ear only, even when the radiological abnormality is bilateral. (It is worth noting that, although useful, this test is not essential for diagnosis as, in most of these patients, one can usually see torsional nystagmus by naked eye or video-techniques in response to loud sounds or Valsalva manoeuvres.) The mechanism as to why a presumed saccular potential has abnormally high sensitivity in a superior semicircular canal syndrome is not exactly understood.

Clinical evidence suggests that the afferent fibres of this reflex travel in the inferior vestibular nerve. Patients with acute vestibular neuritis and absent caloric and cEVMP do not develop secondary BPPV.[151] This suggests that the absent cEVMP indicates loss of inferior vestibular nerve afferents which carry the macular fibres from the posterior semicircular canal; a deafferented posterior canal cannot produce symptoms of BPPV. Halmagyi et al. reported two patients with acute vertigo, normal lateral semicircular canal function but selective loss of posterior semicircular canal function as shown by absent cEVMP[53] suggestive of selective inferior nerve vestibular neuritis.

More recently, short-latency ocular EMG potentials recorded with periorbital surface electrodes in response to air-conducted sound and bone vibration have been elicited, which have been called ocular VEMPs (oVEMPs).[152] They are thought to represent a crossed excitatory utriculo-ocular response, hence a functional test of the superior vestibular nerve (as opposed to cVEMPs – inferior nerve). Ocular VEMPs can also be enhanced and show low thresholds in patients with superior canal dehiscence[153] but overall their clinical applicability has not yet gained wide support.[154]

Ideally, one would like to think that absent VEMPs would imply a selective, probably otolithic abnormality in a given patient with a vestibular-sounding history of dizziness but normal clinical and laboratory examination. Unfortunately, this does not seem to be the case and the meaning of an isolated VEMP abnormality is unclear, particularly in patients older than 40 years of age.[155] In patients with acoustic neuromas, however, an abnormal VEMP can occasionally be the only vestibular finding.[156]

PERCEPTUAL AND SUBJECTIVE VERTICAL TESTING

Perceptual tests of vestibular function were in use well before oculography came along with the advancement of electronics in the 1950s. Perceptual tests have underwent a revival in the last 20 years once the vestibular community realized that vestibulo-ocular test results often do not correlate well with patients' symptoms. The VOR is a simple reflex but a patient is a complex human being. It was therefore felt that assessment of how a patient perceives vestibular sensation may be more clinically relevant than oculography. Although the principle is sound, perceptual tests do not replace, but rather complement, eye movement tests, as oculography provides a more objective measure of vestibular function. In patients with long-standing blindness or eye movement disorders such as congenital nystagmus or chronic external ophthalmoplegia, perceptual tests are the only vestibular tests possible.

The simplest perceptual test is to ask the patient to compare subjectively the quality and intensity of the vestibular sensation for right and left stimuli. The stimuli can be the ones used in routine vestibular tests. Extremely useful information can be gained from simply asking a patient with a large congenital nystagmus or a complete ophthalmoplegia if they experience vertigo from caloric irrigation on both ears. The information can be improved by timing the duration of the vertigo or asking the patient to consider the subjectively better ear as 100%, and then estimate how much the other ear's vertigo is reduced. No formal normative data are available for this test but I personally give weight when a patient says that one ear is down 50% or more. (Note that most patients wrongly believe that the 'sick' ear is the one producing more, not less, vertigo!) In the appropriate clinical context this information can help in the diagnosis of a dizzy patient, specifically when they suffer from pre-existing visual or oculomotor disorders.

Even in patients undergoing conventional eye movement tests of vestibular function, enquiring about the quality of the sensation experienced during the caloric or rotational test can be extremely useful. One must not forget that a fundamental problem in the clinic is finding out if a patient's complaint of dizziness is of vestibular origin or not. In this scenario, a patient's equating the calorically elicited sensation to that of his own dizzy spells brings in considerable support for a diagnosis of vestibular disorder and, vice versa, when a patient says that his own dizziness does not resemble at all the caloric-induced vertigo.

Before the advent of EOG, the main quantitative vestibular perceptual test was cupulometry.[157] This test consists of measuring the duration of the postrotational sensation to a range of velocities, so that the sensitivity and time constant of decay of the sensation could be measured. The procedure could also be conducted with direct observation of the nystagmus with Frenzel glasses. In either case, the procedure took far too long to complete, was tiring for the subject and is no longer in use.

We have developed specific quantitative perceptual testing protocols, measuring either perceived displacement or velocity, to investigate vestibular function in patients with congenital nystagmus,[158] external ophthalmoplegia[159] or in selective semicircular canal lesions.[160] A useful aspect of these perceptual tests is that they can be conducted with the head placed in different positions, thus providing potentially useful information on vertical canal function.

SUBJECTIVE VISUAL VERTICAL

Intuitively, the perception of verticality must relate to the otoliths since these are linear acceleration/gravity sensors. However, one can easily conclude that one is lying sideways by the unambiguous asymmetry in pressure/contact cues between the two sides of the body, and/or by seeing that all buildings or trees appear to be tilted to our eyes. These examples illustrate that the perception of verticality is mediated not only by vestibular but also by proprioceptive and visual inputs.

In the clinical setting, the test of verticality more commonly used is the subjective visual vertical (SVV). The technique is easy, low cost, simple and reliable; examples include a system simply based on a bucket[161] and a laptop-based system with free download.[162] Essentially, a subject sits in front of an adjustable straight luminous line (**Figure 62.30**). The line may be viewed either in the dark or against a verticality cue-free background (e.g. all white or covered in dots). The subject's task is to set the line to what he/she thinks is real (gravitational) vertical. Normal subjects are quite accurate, all settings being within 1–2 degrees of real vertical.[163] The line can be either remotely controlled by the subject or an assistant adjusts the line according to the subject's instructions.

Initial excitement with this test was justified as vestibular lesions produce definite abnormalities of the SVV. Acute unilateral peripheral vestibular lesions produce tilt of the subject's SVV settings ipsilaterally.[141] Initially, in the acute stage, the tilt is of the order of 8–10 degrees but gradually disappears within a few months as compensation develops.[145]

Vestibular brainstem lesions cause larger and longer-lasting SVV tilts.[164, 165] Lesions involving the vestibular nuclei create ipsilateral SVV tilt (usually with an ocular-tilt reaction or skew eye deviation with the lower eye ipsilesional). Lesions in the upper brainstem induce contralateral SVV tilts and skew deviations with the upper eye ipsilesional, indicating a central vestibular pathway decussation at pontine level. Initially, these findings were thought to represent a global disruption of verticality perception due to an otholitic asymmetry. However, brainstem lesion patients with large tilts of the SVV usually show normal perception of verticality to other modalities, such as the haptic or tactile vertical or the perception of whole-body verticality (subjective postural vertical).[166, 167] Furthermore, 3D oculography has demonstrated an almost one-to-one correlation between torsional eye position measurements and SVV tilts.[145] Therefore, all evidence indicates that, for most, the tilt of the SVV is secondary to torsional VOR bias (i.e. ocular tilt), not a primary perceptual defect.

So long as the ocular torsional tilt (and usually associated skew) were due to an otolith–ocular pathway asymmetry, the SVV would still be useful as a simple test of otolith function. However, experimental studies have shown that sustained ocular torsion, skew deviation and SVV tilts can all be induced by pure stimulation of the vertical semicircular canals.[6, 147, 168] To summarize, SVV tilts of labyrinthine or brainstem origin can be taken to indicate an imbalance in the torsional ocular system. Claims of any specificity to otolith function (peripheral or central) are not tenable but a combined otolith–vertical canal effect is more likely.

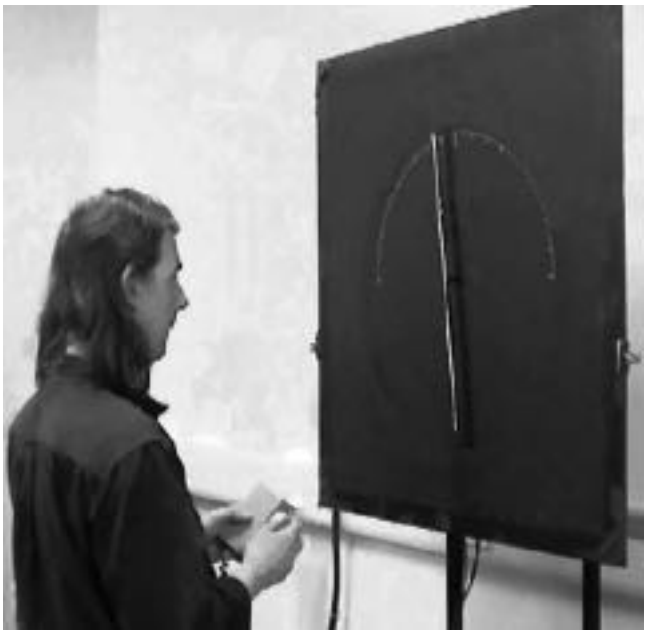


Figure 62.30 Measurement of the subjective visual vertical (SVV).

Hemisphere lesions can also induce tilts of the SVV but the magnitude is smaller; when the tilt is large, this is due to involvement of mesodiencephalic subcortical areas.[164, 165] The polarity is also variable. Interpretation of a cortical tilt is further confounded by the fact that proprioceptive input can also influence the SVV.[169] It is safer at this stage to consider any SVV tilt of cortical origin as due to disruption of central multisensory integration rather than to involvement of central vestibular pathways.[170] An extreme example of cortically induced tilt of all modalities of verticality perception (visual and postural) is seen in some stroke patients who develop the 'pusher syndrome'.[171] These patients 'push' themselves in the direction of their hemiparesis in order to align their body with the perceived tilted gravitational vector complicating the rehabilitation process. The subjective postural vertical can be measured with whole-body tilt devices of the type shown in **Figure 62.27a** and **b**[166] but this is only carried out for research purposes.

FUTURE RESEARCH

- Despite the fact that vertigo, dizziness and imbalance can comprise up to a fifth of all ENT and neurology patients, the problem is not taken seriously. This situation will get worse as population age increases, and further research in the area of dizziness in the elderly is required.
- Very few clinicians make the effort to cross the border between ENT and neurology, and more interdisciplinary centres are required.
- Few attempts are being made at classifying vestibular disorders on the basis of scientific evidence but the Bárány Society is currently attempting this.
- Further research is needed into laboratory diagnostic tools; studies comparing diagnostic efficiency are lacking. Pressures from equipment manufacturers on clinicians with little time for serious thoughts on the subject complicate matters further.
- More vertigo specialists in emergency departments are also needed to differentiate benign causes of vertigo from posterior circulation stroke, which often requires thrombolytic treatment acutely.
- Neuro-otologists should educate their peers, showing that understanding dizziness is not difficult and does not necessarily involve complex laboratory testing but good clinical skills.

KEY POINTS

- History taking remains the main approach for diagnosis of a patient with balance disorder.
- Rotational vertigo indicates semicircular canal system involvement, but the lesion can lie anywhere between the labyrinth and the cortex.
- Dizziness, giddiness and off-balance feelings can also indicate vestibular disease but care needs to be exercised as they may reflect a general medical condition, oscillopsia, gait disorder or psychological problems.
- Establish if there are additional aural or neurological symptoms and whether the vertigo/dizziness is acute, episodic or chronic.
- In patients with episodic vertigo always consider migraine.
- ENT and neurological examination is important but peripheral vestibular patients may only have signs in the acute phase of a disorder.
- Think 'stroke' in patients with acute vertigo. If the nystagmus is horizontal and unidirectional, there are no central symptoms/signs or deafness and the head-impulse test is positive, it is likely to be vestibular neuritis.
- So, you are interested in neuro-otology? If you are an ENT person, persuade a neurologist to work with you. If you are a neurologist persuade an ENT person. Both ENT and neurologists have to persuade an enthusiastic audiologist and/or physiotherapist to join the team.
- Cervical vertigo, if it exists, and vertebrobasilar insufficiency are grossly overdiagnosed. Always consider that dizziness on head–neck movements may be due to a vestibular disorder and do a Hallpike manoeuvre.
- Careful eye movement examination has two main aims: (i) detect any nystagmus, (ii) rule out CNS disease, since central vestibular disorders show additional abnormalities of pursuit, VOR suppression or saccades.
- Only a minority of patients require formal oculography for diagnosis.
- Caloric testing is cheap, efficient and examines one ear at a time. You do not need oculography to carry out caloric tests. The video head-impulse test (VHIT) is useful to detect canal paresis but it does not replace the caloric examination.
- Clinical assessment of posture and gait is a vital part of the examination. It is cheaper and better than posturography.
- There is no simple and clinically reliable way of testing the otolith system.
- Vestibular-evoked myogenic potentials (VEMPs) test otolith function but paradoxically they are most useful to detect superior canal dehiscence, a semicircular canal abnormality.

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CHAPTER 63

MÉNIÈRE'S DISEASE

Vincent W.F.M. Van Rompaey

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SEARCH STRATEGY

Data in this chapter may be updated by a search on Medline and the Cochrane Database of Systematic Reviews using the keywords Ménière's disease and endolymphatic hydrops.

INTRODUCTION

Ménière's disease is an idiopathic inner ear disorder characterized by recurrent spontaneous vertigo accompanied by fluctuating or progressive sensorineural hearing loss, tinnitus and aural fullness in the affected ear.[1] Of all audiovestibular symptoms, the vertigo episodes are experienced as the most incapacitating.[2]

The histopathological correlate is highly linked to endolymphatic hydrops, a finding which is not pathognomonic to Ménière's disease, but more likely a marker for overall disordered inner-ear homeostasis. Ménière's disease is, by definition, the idiopathic type of endolymphatic hydrops. A clear differentiation is made with the secondary type presenting a similar clustering of symptoms (which is called Ménière's syndrome) caused by, for example, syphilis, trauma, autoimmune disorders. Because Ménière's disease is an idiopathic condition lacking a gold standard for diagnosis, the search for an evidence base is difficult. Diagnostic criteria have been published but are based on expert opinion.

Ménière's disease affects the quality of life significantly and generally is treated with counselling on dietary restrictions, drug therapy and surgical interventions to prevent recurrence of vertigo. Hearing loss is treated by means of hearing aids, bone-conduction implants in cases of unilateral deafness and cochlear implantation in cases of bilateral profound hearing loss.

This review gives an overview of the current state of knowledge about Ménière's disease with a specific focus on management of vertigo, hearing loss and tinnitus.

EPIDEMIOLOGY

Incidence and prevalence

The exact incidence and prevalence of Ménière's disease are unknown and in fact difficult to demonstrate in any population because of inherent difficulties to diagnose this condition after exclusion of all other possible causes. First-line physicians tend to overdiagnose Ménière's disease in patients with chronic vertigo (with or without recurrent vertigo or any additional symptoms). In a secondary or tertiary referral balance clinic it is difficult to establish the exact catchment area. In a study on a Finnish population by Kotimäki et al.,[3] a prevalence of 43.2 per 100 000 persons and an incidence of 4.3 definite Ménière's disease per 100 000 persons per year was reported (1992–1996).

Age

The age of onset is more commonly reported in the second to sixth decade of life. Only 1–7% of Ménière's disease cases are seen in the paediatric population.[3] Surprisingly, 9% of all patients experience the start of Ménière's disease at the age of 65 or more, with a higher incidence of drop attacks.[4]

Sex

There is no difference in the female-to-male ratio.[3]

Sporadic and familial

While Ménière's disease is sporadic in the majority of cases, an estimated 5–15% of cases are familial.[5] Several candidate genes have been proposed for Ménière's disease, including *AQP2*, *KCNE1*, *KCNE3*, *HCFC1*, *COCH*, *ADD*, *HSPA1A*, *PTPTN22* and *IL1*. Many of them are linked to inner ear ion and water transportation. *AQP2* is one of the aquaporin water channel genes,[6] *KCNE1* and *KCNE3* are potassium channel genes[7] and *ADD1* is linked to a sodium–potassium pump activity regulator.[3] *COCH* is linked to cochlin protein production, which is part of the extracellular matrix of the inner ear.[8] *COCH* gene is also known as *DFNA9* and leads to progressive non-syndromic deafness and bilateral vestibular areflexia.[9] *HCFC1* is associated with the host cell factor C1 which has been involved in cell cycle control and transcriptional regulation during herpes simplex virus infection.[10] *HSPA1A* is related to single nucleotide polymorphisms of the heat-shock protein 70 gene,[11] *PTPN22* encodes a lymphoid protein phosphatase[12] and the interleukin-1 gene (*IL1*).[13] A higher prevalence of autoimmune diseases and longer spells of vertigo have been reported in patients affected by a familial form of Ménière's disease.[14, 15] The familial form is more prone to present bilaterally during a lifetime.[16]

PATHOPHYSIOLOGY

Endolymphatic hydrops

The cause of Ménière's disease is unknown. Hallpike and Cairns suggested the relationship with endolymphatic hydrops in 1938.[17] This finding was independently reported by Yamakawa in 1938.[18] However, this theory remains controversial although endolymphatic hydrops was observed in all temporal bones studied in deceased patients with Ménière's disease.[19] Foster and Breeze provide a critical review on temporal bone histopathology.[20] Clinical data supporting the theory of endolymphatic hydrops is based on electrocochleography and delayed magnetic resonance imaging after intratympanic or intravenous administration of gadolinium-based contrast agents. A large summating potential has been observed in 50–70% of patients with Ménière's disease, which can be reduced with administration of hyperosmotic substances.[8] Based on animal studies and clinical studies using cone-beam computed tomography, anatomical variations in the temporal bone could be identified that may predispose for blockage of the endolymphatic canal or foreign protein deposition in the perilymph, both of which have been observed to cause endolymphatic hydrops.[13, 21] Endolymphatic hydrops, however, is not pathognomonic to Ménière's disease. Endolymphatic hydrops was observed in a significant number of temporal bones from patients with hearing loss, without the classical symptoms of Ménière's disease.[22] Delayed MRI after intratympanic injection of gadolinium-based contrast agent in unilateral Ménière's disease reveals bilateral endolymphatic hydrops quite frequently.[23] Additionally, the use of diuretics does not unequivocally lead to an improvement of symptoms and/or hydrops. Membrane ruptures have been suggested to cause the acute episodes of vertigo. However, Merchant et al. observed clear histologic examples of membrane ruptures in patients without a history of vertigo, which contradicts this theory.[22] Based on a large human temporal bone study, Merchant et al. suggested that the endolymphatic hydrops observed in Ménière's disease might be a marker for disordered inner ear homeostasis in which a yet unknown factor produces both the clinical symptoms of Ménière's syndrome and endolymphatic hydrops.[22] Potential etiological or precipitating conditions include genetic variations, infection, vascular risk factors, diet, allergy, autonomic, endocrine and autoimmune factors.

Autoimmune factor

In approximately 1 in 3 patients with Ménière's disease there seems to be an autoimmune factor. Several theories were suggested, including cross-reactions between similar antigens, innocent bystander damage due to cytokine release, acquired intolerance to inner ear antigens (covert from the immunological system and exposed by trauma or infection), genetic factors (extended major histocompatibility complex haplotype).[24–26]

Viral factor

A viral etiology has been suggested as well, most often involving the herpes simplex virus. Viral structures have been observed by means of transmission electron microscopy in the vestibular ganglion cells of one Ménière's disease patient, which supports this theory albeit one case.[27] Vertigo control in 91% of Ménière's disease patients by means of acyclovir treatment also supports the potential viral etiology.[27]

Allergic factor

An association with allergy has been observed by Derebery. Vertigo control (Class A and B) was achieved in 47.9% (n = 137) accepting allergy treatment.[28] Potential mechanisms include the endolymphatic sac targeted by the allergic reaction, deposition of circulating immune complexes in the fenestrated blood vessels of the endolymphatic sac and stria vascularis and viral antigen-allergic interaction with T-cell homing to the endolymphatic sac.[29]

Vascular factor

It has been observed that endolymphatic hydrops impairs blood flow autoregulation.[30] The combination of endolymphatic hydrops and venous obstruction has shown to induce vertigo attacks similar to Ménière's disease in an animal model.[31]

DIAGNOSIS

Diagnostic criteria for Ménière's disease

The most recent guidelines for the diagnosis in patients with Ménière's disease were issued in 2015 by the Classification Committee of the Bárány Society, The Japan Society for Equilibrium Research, the European Academy of Otology and Neurotology (EAONO), the Equilibrium

TABLE 63.1 Diagnostic criteria for Ménière's disease (other causes excluded)

Diagnosis	Criteria
Definite Ménière's disease	≥ Two definitive spontaneous episodes of vertigo lasting 20 minutes to 12 hours + Audiometrically documented low- to medium-frequency sensorineural hearing loss in the affected ear on at least one occasion before, during or after one of the episodes of vertigo + Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear
Probable Ménière's disease	≥ Two episodes of vertigo or dizziness, each lasting 20 minutes to 24 hours + Fluctuating aural symptoms (hearing, tinnitus or fullness) in the reported ear

Committee of the American Academy of Otolaryngology–Head and Neck Surgery (AAO–HNS) and the Korean Balance Society.[32] According to these guidelines, the diagnosis of Ménière's disease in a vertigo patient is based on clinical symptoms and exclusion of identifiable other etiologies, rendering Ménière's disease idiopathic. They provide 2 degrees of certitude: definite and probable Ménière's disease. The definition of each of these categories can be found in Table 63.1. In the most recent 2015 guidelines, diagnostic criteria were suggested without providing minimal outcome criteria for use in daily practice in the absence of a gold standard test. Therefore, minimal outcome reporting is still based on the 1995 criteria issued by the AAO–HNS.[1]

A typical attack of Ménière's disease can be defined by the direction of the spontaneous nystagmus.[33] In the irritative phase the nystagmus will beat towards the affected ear in a horizontal or horizontal–torsional direction, a finding which usually lasts less than 1 hour. In the paretic phase, the nystagmus will beat away from the affected ear and last hours to days. In the recovery phase the nystagmus again beats towards the affected side because peripheral vestibular function recovers.

Particularly in the later stages of Ménière's disease, drop attacks (also known as Tumarkin crises) can develop. These may be related to acute otolythic dysfunction. The patient suddenly drops to the ground (without losing consciousness) without associated vertigo.

For the record, 'low-frequency sensorineural hearing loss' is defined as: increases in pure-tone thresholds for bone-conducted sound that are higher (i.e. worse) in the affected ear than the contralateral ear by at least 30 dBHL at each of two contiguous frequencies below 2 kHz. In cases of bilateral low-frequency sensorineural hearing loss, the absolute thresholds for bone-conducted sound must be 35 dBHL or higher at each of two contiguous frequencies below 2000 Hz. If multiple audiograms are available, demonstration of recovery of low-frequency sensorineural hearing loss at some point in time further supports the diagnosis of Ménière's disease. Bilateral synchronous sensorineural hearing loss (symmetric or asymmetric) can occur in some patients.

Figure 63.1 demonstrates the hallmark low-frequency sensorineural hearing loss and its recovery after low-sodium diet.

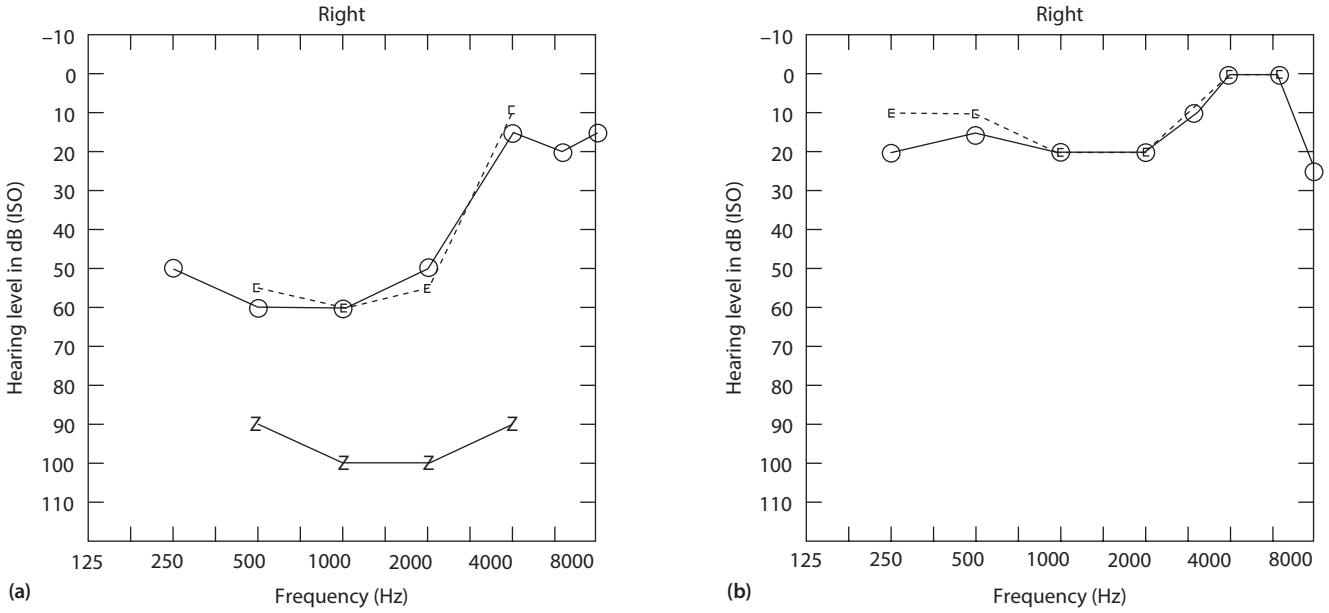


Figure 63.1 Audiogram in Ménière's disease. This patient, a 14-year-old female, began to have attacks of acute spontaneous vertigo with right-sided aural fullness and then tinnitus. **(a)** Audiogram on presentation shows a 60 dB low-frequency hearing loss with normal acoustic reflexes (Z), indicating a fully recruiting cochlear hearing loss. **(b)** Audiogram after 4 months of treatment with a rigorous low-sodium diet shows normal pure-tone thresholds.

The 2015 guidelines define Ménière's disease as an idiopathic syndrome of endolymphatic hydrops and therefore other causes have to be excluded. The following conditions are explicitly mentioned: transient ischemic attack, vestibular migraine, vestibular paroxysmia, recurrent unilateral vestibulopathy, vestibular schwannoma and endolymphatic sac tumour. The 1995 guidelines also mention trauma or surgery, infection (syphilis) and inflammatory disorders (Cogan's syndrome) as potential causes of endolymphatic hydrops and refer to the work of Schuknecht and Gulya for further causes.[34] The latter article additionally reveals the 'embryopathic symptomatic endolymphatic hydrops', related to inner ear malformations, and the 'acquired symptomatic endolymphatic hydrops' (also known as 'delayed hydrops'), related to trauma and inflammation caused by viruses, bacteria or spirochaetes. The case of a patient with bacterial meningitis and subsequent labyrinthitis was given to demonstrate the presence of 'delayed hydrops'. This report was published in the early 1980s and is limited by the contemporary state of the art where, for example, only polytomography was available as imaging tool. According to the 2015 guidelines the term 'delayed hydrops' should be avoided in favour of 'delayed Ménière's disease' in cases of sensorineural hearing loss antedating the vertigo spells.

To exclude these Ménière-like diseases any diagnostic technique available to the clinician should be used: for example, full clinical examination of the head and neck region (including vestibular examination), liminal and speech audiometry, tympanometry, multidetector computed tomography (CT scan) of the temporal bone (with or without intravenous injection of iodine-containing contrast), MRI of the posterior fossa (with intravenous injection of gadolinium), blood analysis (haematology, thyroid, biochemical and genetic testing). The posterior fossa MRI with intravenous administration of gadolinium is the most sensitive examination to exclude cerebellopontine angle and inner ear pathology (in the absence of any contraindications to MRI).

Since the diagnosis of Ménière's disease is based on a syndrome of idiopathic endolymphatic hydrops, it is good practice to challenge the diagnosis during follow-up of the patient. Simultaneously, these patients can report vertigo unrelated to their Ménière's disease, which needs careful examination and separate treatment. In the differential diagnosis of Ménière's disease, vestibular migraine, vestibular paroxysmia and chronic subjective dizziness have to be considered. These conditions can also coexist with Ménière's disease and need to be treated separately.[35] Unfortunately, since all of these conditions are idiopathic, their diagnosis relies on expert opinion-based criteria.[36] Diagnostic criteria for vestibular migraine,[37] vestibular paroxysmia[38] and chronic subjective dizziness[39] can be found respectively in **Tables 63.2**, **63.3** and **63.4** to enable direct comparison.

Diagnostic tools to detect endolymphatic hydrops

Evidence supplementary to the diagnostic criteria (which are in fact based only on history and audiometry) can be provided with electrocochleography (ECoG) or cochlear hydrops analysis masking procedure (CHAMP). More recently the use of delayed MRI after intratympanic injection of gadolinium has enabled the clinician to demonstrate endolymphatic hydrops *in vivo*.

ELECTROCOCHLEOGRAPHY

Electrocochleography records sound-evoked electrical activity near the cochlea by means of transtympanic or extratympanic measurement. This technique is not routinely available and was therefore not included as a minimal outcome criterion of the 1995 Committee guidelines. ECoG is assumed to measure endolymphatic hydrops by evaluating the amplitude ratio of the action potential (AP) and the summating potential (SP). The SP amplitude is increased by displacement of the basilar membrane towards the scala tympani. **Figure 63.2** demonstrates ECoG findings in the same patient as in **Figure 63.1**. Diagnostic SP/AP-ratio thresholds were suggested by Wuyts et al. by performing a meta-analysis of published results.[40] These thresholds differ between extratympanic and transtympanic electrodes and are presented in **Table 63.5**.

Diagnostic SP amplitude thresholds were also suggested when using tone-burst stimuli. These suggestions are not based on a meta-analysis because of insufficient data, but reflect the proposal of the Prosper Ménière Society's

TABLE 63.2 Diagnostic criteria for vestibular migraine

Diagnosis	Criteria
Vestibular migraine	A. At least five episodes with vestibular symptoms of moderate to severe intensity, lasting 5 minutes to 72 hours B. Current or previous history of migraine with or without aura according to the International Classification of Headache Disorders (ICHD) C. One or more migraine features symptoms with at least 50% of the vestibular episodes: (1) headache with at least two of the following characteristics: one-sided location, pulsating quality, moderate or severe pain intensity, aggravation by routine physical activity (2) photophobia and phonophobia (3) visual aura D. Not better accounted for by another vestibular or ICHD diagnosis
Probable vestibular migraine	A. At least five episodes with vestibular symptoms of moderate or severe intensity, lasting 5 minutes to 72 hours B. Only one of the criteria B and C for vestibular migraine is fulfilled (migraine history *or* migraine features during the episode) C. Not better accounted for by another vestibular or ICHD diagnosis

TABLE 63.3 Diagnostic criteria for vestibular paroxysmia

Diagnosis	Criteria
Definite vestibular paroxysmia	Patients suffered from a minimum of five vertigo attacks and fulfilled one criterion of each category (A)–(E): A. *Vertigo attacks:* Vertigo attacks (rotatory as well as to and fro vertigo) with short duration (seconds to minutes), which ceased spontaneously B. *Vertigo triggers:* Attacks occurred while in rest, were induced by a specific head and/or body position, or by a specific change of head and/or body position C. *Accompanying symptoms:* Attacks were accompanied by at least one of the following additional symptoms: unsteadiness of stance and/or gait, lateralized tinnitus, decreased hearing function or subjective sensory irritations, such as a feeling of pressure within or around one ear D. *Additional criteria:* The diagnostic procedures in addition to the anamnestic aspects revealed a neurovascular compression of the eighth cranial nerve on MRI scans including CISS sequences, a hyperventilation-induced nystagmus, a detectable progress of vestibular deficit over the course of disease, or patients responded positively to treatment E. *Exclusion:* Any other possible pathology or disease explaining the symptoms had to be excluded
Probable vestibular paroxysmia	Patients suffered from a minimum of five vertigo attacks and fulfilled criterion (A) and additionally at least three criteria out of the categories (B)–(E)

TABLE 63.4 Diagnostic criteria for chronic subjective dizziness

Diagnosis	Criteria
Chronic subjective dizziness	1. *Subjective unsteadiness or dizziness*: Persistent (≥3 months) sensations of unsteadiness or non-vertiginous dizziness that are present on most days. These symptoms may be described as: • rocking, swaying, or wobbling that is usually not apparent to others • a feeling that the floor is moving or wavy • light-headed, foggy or cloudy in the head • heavy-headed or full in the head • spinning 'inside the head' without a perception of movement of the visual surround • a feeling of dissociation from the environment
	2. *Hypersensitivity to motion*: Chronic (≥3 months) hypersensitivity to one's own motion, which is not direction-specific, and to the movement of objects in the environment
	3. *Visual dizziness (also known as visual vertigo)*: Exacerbation of symptoms in settings with complex visual stimuli, such as displays in grocery stores or shopping malls, or when performing precision visual tasks (e.g. reading or working on a computer).

International Standard.[41,42] SP amplitude is typically measured at 10 msec after stimulus start. Unfortunately, no studies were available on extratympanic ECoG through tone-burst stimuli.[40]

COCHLEAR HYDROPS ANALYSIS MASKING PROCEDURE (CHAMP)

The hypothesis of CHAMP is that endolymphatic hydrops causes changes in the response properties of the basilar membrane, i.e. travelling wave velocity is faster by basilar membrane stiffening in endolymphatic hydrops. These changes lead to impaired high-pass noise masking of auditory brainstem response (ABR) to clicks in stacked ABR. Unfortunately, different groups have reported conflicting results.[43–46] These results are potentially due to the different standards and diagnostic thresholds used. Therefore, the CHAMP cannot be used (yet) to prove or disprove the diagnosis of endolymphatic hydrops in Ménière's disease patients.

DELAYED MRI AFTER INTRATYMPANIC OR INTRAVENOUS INJECTION OF GADLINIUM

Since 'certain' Ménière's disease involves the histopathologic confirmation of endolymphatic hydrops, this level of certitude is only reached post-mortem and clinically irrelevant to the patient. Electrophysiological testing (such as ECoG or CHAMP) is based on measuring sound-evoked electrical responses and therefore quite circumstantial evidence for endolymphatic hydrops. The intratympanic injection of gadolinium-based contrast agent (hereafter called gadolinium) provides a potential *in vivo* biomarker to evaluate the perilymphatic and endolymphatic spaces separately. Gadolinium loads into the perilymphatic space without entering the endolymph in healthy inner ears.[47]

Normative values have been established in healthy volunteers.[48,49] Based on the study on normal individuals by Nakashima et al.,[49] the upper limit for enlargement of the endolymphatic space of the vestibule should be set at 33%. This new technique for visualizing endolymphatic hydrops demonstrated, surprisingly, that Ménière's disease is essentially a bilateral condition. Bilateral endolymphatic was observed in 79% of patients with unilateral definite Ménière's disease. Pyykkö et al. also argued that Ménière's disease rather is a continuum from monosymptomatic patients with endolymphatic hydrops to the full-blown patient profile of definite Ménière's disease.[23] This technique certainly is promising and might be helpful as a biomarker to confirm endolymphatic hydrops in cases

where clinical suspicion is present. Gadolinium can be administered intravenously 4 hours before MRI or intratympanically 24 hours before MRI. We remind the clinician that the intratympanic use of gadolinium is strictly off-label.

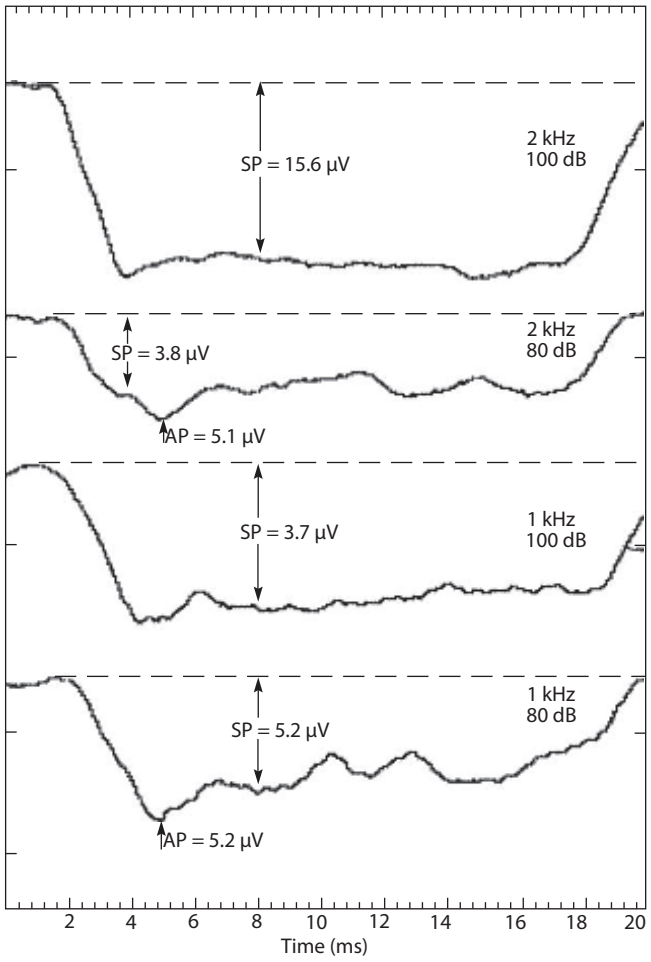


Figure 63.2 Electrocochleogram (ECoG) in Ménière's disease. Transtympanic ECoG of the patient whose audiogram is shown in Figure 63.1, showing large negative summating potentials (SP) in response to 16 ms, 1 kHz and 2 kHz tone-bursts at 80 and 100 dB nHL. The mean absolute negative SP levels in patients with definite Ménière's disease, who have subjective thresholds below 40 dB nHL, are as follows: 2 kHz, 100 dB 46 mV; 2 kHz, 80 dB 44 mV; 1 kHz, 100 dB 44 mV. These results show that tone burst ECoG responses are more likely to be abnormal in patients with Ménière's disease than are click-evoked responses.[75] Figure courtesy of W. Gibson, Sydney, Australia.

TABLE 63.5 Electrocochleography SP/AP ratio and SP thresholds

	Stimulus	Thresholds	
		Extratympanic	Transtympanic
SP/AP ratio	Click	>0.42	>0.35
SP	Tone-bursts	–	<–2 µV (<–3 µV at 1 kHz)

OUTCOME REPORTING

Vertigo

DEFINITION

The definitive spell of Ménière's disease is described as spontaneous rotational vertigo (i.e. the sensation of motion when no motion is occurring relative to Earth's gravity) lasting at least 20 minutes. The severity of vertigo is reported as prostrating or incapacitating by the patient. This spell might be followed by a period of disequilibrium, a sensation present for up to several days. The definitive spell is usually accompanied by nausea and/or vomiting. Consciousness is not lost during or after the spell. While examining the patient during the definitive spell, horizontal nystagmus (with or without torsional component) is always present.

FREQUENCY OF VERTIGO

The frequency of vertigo should be evaluated over a period of 6 months. The average number of definite spells per month lasting at least 20 minutes is used in the reporting index as shown in Table 63.6. Any treatment can only be evaluated 2 years after treatment started. At that follow-up visit, the frequency of vertigo over the last 6 months has to be reported. Class F is the category of Ménière's disease patients who require 'secondary treatment' due to disability from vertigo (e.g. vestibular nerve section).

SEVERITY OF VERTIGO

The AAO–HNS Committee released an update in the AAO–HNS Bulletin of April 2014. Its main consideration was that in the 1995 guidelines outcome reporting was based totally on frequency of vertigo, while information on the severity of vertigo spells would be more appropriate. Table 63.7 includes five categories ranging from 'no vertigo' to 'extreme attack'.

FUNCTIONAL LEVEL

It has been reported that Ménière's disease symptoms are highly intrusive in comparison to other conditions.

TABLE 63.6 Summary of reporting guidelines

Numerical value	Class
0	A (complete control of spells)
1–40	B
41–80	C
81–120	D
>120	E
Secondary treatment initiated due to disability from vertigo	F

Numerical value = $(X/Y) \times 100$, rounded to the nearest whole number, where X is the average number of definitive spells per month for the 6 months 18–24 months after therapy and Y is the average number of definitive spells per month for the 6 months before therapy.

TABLE 63.7 Severity of vertigo

Scale	Category	Definition
0	No vertigo	No vertigo
1	Mild attack	Brief episode of vertigo lasting less than 20 minutes and/or vague sense of disequilibrium lasting less than 2 hours
2	Moderate attack	Vertigo lasting 20–60 minutes and/or disequilibrium lasting greater than 2 hours with reduction in daily activities from 0% to 50%
3	Severe attack	Vertigo lasting more than 1 hour with or without accompanying nausea and vomiting, with or without lingering disequilibrium lasting greater than 2 hours with reduction in daily activities of 50–100%
4	Extreme attack	Vertigo lasting more than 1 hour with nausea and vomiting and persistent lingering severe disequilibrium requiring bedrest the entire day

Only fibromyalgia, human immunodeficiency virus (HIV) infection, anxiety disorders and chronic fatigue syndrome/myalgic encephalomyelitis are more intrusive, as reported by Arroll et al.[50] Functional level, commonly related to work or active recreational pursuits, is mainly related to the intrusiveness of the vertigo spells. The six categories are shown in **Box 63.1**.

DIZZINESS HANDICAP INVENTORY

The Dizziness Handicap Inventory (DHI) has gained widespread acceptance as a useful instrument to evaluate the handicap resulting from vertigo and achieves a responsiveness superior to other patient-reported outcome measures.[51] It has been used frequently as an outcome measure in clinical trials to document the effect of medical, surgical and rehabilitative interventions.[52]

MÉNIÈRE'S DISEASE OUTCOME QUESTIONNAIRE

In 2004, Kato et al. published an 18-item multiple-choice questionnaire for evaluating quality of life in patients with Ménière's disease before and after endolymphatic sac surgery: the Ménière's Disease Outcome Questionnaire (MDOQ). This questionnaire includes three domains: physical, emotional and social well-being. It was designed as a retrospective survey enabling patients to evaluate their symptoms after surgery and not requiring baseline analysis. This feature makes the MDOQ easy to use but it also reflects its main limitation: the retrospective and post-hoc evaluation.[53]

ELECTRONYSTAGMOGRAPHY

Electronystagmography cannot confirm the diagnosis itself, but reflects the residual horizontal semicircular canal response to caloric stimulation. In patients with Ménière's disease, these results can vary quite significantly. In case of treatments that aim for destruction of labyrinthine function (such as intratympanic injection of gentamicin or a vestibular nerve section), electronystagmography can measure residual function and evaluate the treatment's effectiveness to destroy vestibular function. However, the absence of caloric response does not invariably predict long-term vertigo control.[54]

Hearing loss

Hearing loss is essential in the diagnosis of certain, definite and probable Ménière's disease. If no hearing loss was documented, the patient can only be allocated

BOX 63.1 Functional level scale

Regarding my current state of overall function, not just during attacks (check the ONE that best applies):	
1. My dizziness has no effect on my activities at all.	
2. When I am dizzy I have to stop what I am doing for a while, but it soon passes and I can resume activities. I continue to work, drive, and engage in any activity I choose without restriction. I have not changed any plans or activities to accommodate my dizziness.	
3. When I am dizzy, I have to stop what I am doing for a while, but it does pass and I can resume activities. I continue to work, drive, and engage in most activities I choose, but I have had to change some plans and make some allowance for my dizziness.	
4. I am able to work, drive, travel, take care of a family, or engage in most essential activities, but I must exert a great deal of effort to do so. I must constantly make adjustments in my activities and budget my energies. I am barely making it.	
5. I am unable to work, drive, or take care of a family. I am unable to do most of the active things that I used to. Even essential activities must be limited. I am disabled.	
6. I have been disabled for 1 year or longer and/or I receive compensation (money) because of my dizziness or balance problem.	

TABLE 63.8 Staging of definite and certain Ménière's disease

Stage	Pure-tone average of 0.5–1–2–3 kHz (dB)
1	≤25
2	26–40
3	41–70
4	>70

to the possible Ménière's disease group (in the presence of other qualifying symptoms). The 1995 Committee guidelines combine the use of pure-tone audiometry and word recognition scores in order to evaluate hearing loss. However, they only use the pure-tone average of 0.5, 1, 2 and 3 kHz for staging of certain and definite Ménière's disease. The proposed staging system can be found in Table 63.8. This pure-tone average should be calculated on the worst audiogram during the 6 months before the start of treatment. The staging system cannot be used in probable and possible Ménière's disease according to the 1995 Committee guidelines. Once the patient is allocated, the stage cannot be changed. No suggestion was made to incorporate word recognition in staging, but a positive change of 15% in speech discrimination was considered clinically significant.

Tinnitus and aural fullness

According to the 1995 Committee guidelines, the evaluation of tinnitus and aural fullness is at the discretion of the clinician.

TINNITUS FUNCTIONAL INDEX

For evaluation of tinnitus severity, several self-reporting questionnaires have been developed and are currently in use. However, many questionnaires were not designed to maximize responsiveness (i.e. to measure positive or negative change after treatment). For this reason an expert panel based in the US and New Zealand developed the Tinnitus Functional Index (TFI).[55] In this study, a 13-point reduction was considered a clinically meaningful reduction of TFI scores.

VISUAL ANALOGUE SCALE

The visual analogue scale has been in use for reporting complaints that are difficult to quantify. Using the visual analogue scale, the patient has to indicate a value between 0 (no symptoms) and 10 (maximal intensity). The visual analogue scale can also be used for evaluation of average and maximal tinnitus loudness.[56]

MANAGEMENT

Based on the levels of recommendation produced by the Oxford Centre for Evidence-based Medicine we will discuss all different aspects in the management of Ménière's disease patients.

Diagnosis

The diagnosis of Ménière's disease can be suspected by acquiring a systematic otovestibular history (including family history and personal drug, trauma, surgery and disease history) while excluding all other potential causes of the Ménière's syndrome due to secondary endolymphatic hydrops, as required by the 2015 guidelines (recommendation grade D). Liminal and speech audiometry is essential to support the diagnosis of definite Ménière's disease. The clinician should be aware that there is considerable overlap in diagnostic criteria for vestibular migraine, vestibular paroxysmia and chronic subjective dizziness. It is uncommon but possible that more than one condition can be diagnosed and requires separate treatment.

There are no studies on how to exclude other potential causes of endolymphatic hydrops, which is left at the discretion of the clinician. A blood sample can be taken to evaluate thyroid and immunological status if thyroid disease or autoimmune diseases are suspected. Genetic analysis is not routine practice in every balance clinic. *COCH*-mutations can be screened in unaffected family members to provide information on individual prognosis. An MRI scan of the cerebellopontine angle can be performed after intravenous administration of gadolinium-based contrast agent to exclude inner ear malformations, neurovascular conflicts with the vestibulocochlear nerve, cerebellopontine angle and intralabyrinthine lesions (most often the vestibular schwannoma) or white matter lesions of inflammatory or vasculoischaemic origin. ECoG can demonstrate the electrophysiological substrate of endolymphatic hydrops. Delayed MRI after intravenous or intratympanic injection of gadolinium-based contrast agent can visualize endolymphatic hydrops and can provide an *in vivo* surrogate for the histopathologic confirmation of certain Ménière's disease.

Hygienic measures

DIETARY RESTRICTIONS

Dietary restrictions on sodium and caffeine are traditionally advised by clinicians to prevent the development of endolymphatic hydrops.[57] However, this hypothesis was only recently confirmed by means of a retrospective study.[58] Luxford et al. demonstrated that implementation of a low-sodium and caffeine-free diet had a statistically significant effect on functional level in Ménière's disease patients. Those patients who were compliant longer than 6 months had larger improvement in vertigo frequency and functional level. The latter group of patients also had a higher rate of class A/B vertigo outcome.

Recommendation Counselling may include a low-salt and caffeine-free diet.

Medication

DIURETICS

Diuretics, including hydrochlorothiazide, acetazolamide or a combination of hydrochlorothiazide and triamterene, are still the first-line medical therapy for Ménière's disease patients in many clinics. Their therapeutic mechanism is to reduce endolymphatic volume and pressure.[57] Osmotic diuretics, such as oral urea powder twice a week, are rarely used as a 'salvage oral therapy' to reduce endolymphatic hydrops. Thirwall and Kundu published a 2006 Cochrane analysis on the use of diuretics in patients with Ménière's disease. This analysis was assessed as up-to-date in 2009. Unfortunately, there was insufficient good evidence of the effect of diuretics on vertigo, hearing loss, tinnitus or aural fullness in clearly defined Ménière's disease.[59] Diuretics, however, can cause electrolyte disturbances and potentially interact with patient-specific drugs and conditions.

BETAHISTINE DIHYDROCHLORIDE

Betahistine dihydrochloride (hereafter called betahistine) is an oral preparation of a histamine precursor marketed in Europe as a specific treatment for patients with Ménière's disease. Betahistine is an analogue of histamine with weak agonist properties at histamine H1 receptors and more potent antagonistic effects at histamine H3 receptors.[60, 61] James and Burton published a 2001 Cochrane analysis on the use of betahistine in patients with Ménière's disease.[62] This analysis was assessed as up-to-date in 2010. Unfortunately, according to this analysis there was insufficient evidence to identify whether betahistine has any effect on vertigo control in patients with Ménière's disease. Six trials involving 162 patients were included. No trial met the highest quality standard set by the review because of inadequate diagnostic criteria or methods, and none assessed the effect of betahistine on vertigo adequately. Most trials reported some form of vertigo control. However, these results may have been caused by bias in the study design. Another, more recent, meta-analysis (performed by an employee of pharmaceutical company Abbott, commercializing Betaserc) demonstrated an overall beneficial effect of betahistine.[63] This study was not restricted to Ménière's disease and also includes 'vestibular vertigo', which might induce bias. Additionally, this meta-analysis introduces internal unpublished (Duphar) reports on placebo-controlled clinical studies with betahistine, which is a controversial issue (bypassing the challenge of peer review). High-dosage betahistine dihydrochloride (up to 480 mg or 30 tablets each day) has been reported in a case series to be effective in patients with Ménière's disease who do not respond sufficiently to lower dosages.[64]

Recommendation First-line medical treatment to prevent recurrence of vertigo may include betahistine dihydrochloride 16 mg thrice daily and/or diuretics. Betahistine has a limited side effect profile while diuretics can cause electrolyte disturbances, potentially interact with patient-specific drugs and conditions.

Transtympanic and intratympanic therapies

TRANSTYMPANIC LOW-PRESSURE THERAPY (MENIETT)

This therapy was established after reports of subjective improvement of acute vertigo attacks when pressure changes were induced in a pressure chamber.[65, 66] Based on these reports, the Meniett device was conceived, producing a repetitive 0.6-second pulse of low pressure (ranging from 0 to 20 cm H_2O) transmitted through a ventilation tube.[67] The treatment consists of three to four cycles of a 5-minute treatment sequence. A recent Cochrane review had to conclude that there is no evidence to demonstrate the effectiveness of positive low-pressure therapy.[68]

INTRATYMPANIC INJECTION OF CORTICOSTEROIDS

The suggested therapeutic mechanism of corticosteroids is inner ear homeostasis via transmembrane water transporters, the aquaporins.[69] Based on a 2011 Cochrane analysis by Phillips and Westerberg, one randomized placebo-controlled trial was identified comparing intratympanic injection of dexamethasone to saline solution.[70] This trial demonstrated a statistically significant improvement of vertigo frequency and severity measured 24 months after treatment start. Substantial vertigo control (Class A and B) was achieved in 11 patients (100%) of treatment group versus 4 patients (57%) in the control group.[71, 72] Therefore the authors of the Cochrane analysis concluded that limited evidence is available to support the effectiveness of intratympanic steroids in patients with Ménière's disease. An important aspect is that patients were only included if failing a combination of dietary restrictions and medical therapy with vasodilator and diuretics for 6 months.

INTRATYMPANIC INJECTION OF GENTAMICIN

Aminoglycosides are infamous for their vestibulotoxicity after intravenous use. There are several pathways that might cause this effect including excitotoxicity through N–methyl–D–aspartate (NMDA) receptor binding[72] and production of reactive oxygen species[74] which can be influenced by the antioxidant N-acetylcysteine.[74] Schuknecht first reported on intratympanic therapy with aminoglycosides as early as 1956.[75, 76] Based on a 2011 Cochrane analysis by Pullens et al., two randomized placebo-controlled trials were identified demonstrating the beneficial effect of intratympanic injection of gentamicin on vertigo control in Ménière's disease patients.[77] A meta-analysis was deemed impossible due to clinical heterogeneity. Huon et al.[78] did perform a meta-analysis which was published in 2012 confirming the beneficial effect of intratympanic gentamicin on vertigo control: 87.5% Class A and B. Sensorineural hearing loss was reported in 0–38.7% of cases. After the publication of these two articles another randomized controlled trial was published in 2012

comparing intratympanic gentamicin with dexamethasone.[79] Because different injection schedules were used, this trial could not be blinded. In the intratympanic gentamicin group substantial vertigo control (Class A and B) was achieved in 30 patients (93.5%) at 2-year follow-up. In the intratympanic dexamethasone group, substantial vertigo control was achieved in 17 patients (61%).[79]

Noteworthy is that intratympanic injection of gentamicin has demonstrated its effectiveness in patients with Ménière's disease experiencing drop attacks (Tumarkin crisis).[80]

Recommendation Salvage treatment in case of medical treatment failure may include repetitive intratympanic injections of dexamethasone (recommendation grade A), which enable substantial and long-term vertigo control in 80% of refractory cases without significant hearing loss. In refractory cases after intratympanic injection of dexamethasone, intratympanic injection of gentamicin (as-needed) can be offered (recommendation grade A). This treatment is based on the vestibulotoxic effect of gentamicin and aims to destroy vestibular hair cell function (therefore also called partial chemolabyrinthectomy). The typical Ménière's disease vertigo attacks are not detected and do not provoke nystagmus. Consequently, the patient does not experience vertigo any more but may develop some imbalance or visual vestibular mismatch.

Intratympanic injection of gentamicin may also be indicated in 'end-stage' patients who develop drop attacks/Tumarkin crises.

Sensorineural hearing loss is a potential complication of this treatment and should be considered in the evaluation of the individual patient.

Surgery

ENDOLYMPHATIC SAC SURGERY

Based on a 2010 Cochrane analysis by Pullens et al. (updated in 2013) only one surgical modality was studied in randomized controlled trials, i.e. endolymphatic sac surgery. Neither of the two studies reported any beneficial effect over grommet insertion or mastoidectomy,[80] therefore the authors concluded that there is insufficient evidence to support endolymphatic sac surgery in Ménière's disease. A more recent systematic review and meta-analysis of available clinical studies (although lacking a control population) supported the use of endolymphatic sac surgery in Ménière's disease patients refractory to medical treatment.[81] Different surgical approaches to the endolymphatic sac were compared including endolymphatic sac decompression and mastoid shunting. Sood et al. calculated a respective average of 79.3% and 76.4% vertigo control (Class A and B) at 12 months (short-term) and 81.6% and 75.7% at 24 months (long-term). Average hearing preservation rates (within 10 dB of pre-operative thresholds) were respectively 72.8% and 71.4% at 12 months and 71.6% and 69.3% at 24 months. These numbers, however, might reflect natural Ménière's disease progression since control groups are lacking.[82]

TENOTOMY OF THE TENSOR TYMPANI AND STPEDIAL MUSCLE TENDONS

Conflicting results have been reported on tenotomy of the tensor tympani and stapedial muscles' tendons.[52, 83–85] The suggested mechanism of action in Ménière's disease patients is that the tympanic membrane is pushed laterally by increased cochlear pressure against the ossicular chain. By sectioning the tensor tympani muscle this effect is (partially) alleviated.[86] Positive results were only reported in one centre that published several case series.[83–85] Randomization of patients undergoing intratympanic injection of gentamicin into one group who had simultaneous tenotomy and another group without tenotomy could not reveal any statistically significant differences.[52]

SELECTIVE VESTIBULAR NERVE SECTION

Surgical section of the vestibular nerve while preserving the facial and cochlear nerve can be used as an alternative to intratympanic injection of gentamicin to produce vestibular areflexia. Several case series were reported, but only three case-control studies were published reporting a similar outcome as intratympanic injection of gentamicin.[87–89] Hillman et al.[88] reported 90% substantial vertigo control (Class A and B) in the selective vestibular nerve section group, while 66% was observed in the intratympanic injection of gentamicin group, which favours the selective vestibular nerve section group on a statistically significant level. These results might have been provoked by the relatively low dosage of gentamicin (26.7 mg/mL) the authors used and the short irrigation time of 10 minutes in the supine position. Hearing preservation rates were 72% in the selective vestibular nerve section group and 52% in the intratympanic injection of gentamicin group. Statistically significant differences were reported favouring selective vestibular nerve section. However, pre-operative hearing was also better in the selective vestibular nerve section at a statistically significant level. Colletti et al.[89] reported substantial vertigo control (Class A and B) in 95.8% of selective vestibular nerve section cases and 75% of intratympanic injection of gentamicin cases. Schmerber et al.[90] observed recurrence of disabling vertigo in 7% of selective vestibular nerve section cases and 11.4% of intratympanic injection of gentamicin cases, while respective numbers of 74% and 85.7% hearing preservation were reported. The hearing preservation rate in intratympanic injection of gentamicin cases might have been biased by the specific inclusion of cases with pure-tone averages over 40 dB (only Class C and D hearing cases). All the studies mentioned above have significant limitations including their retrospective nature, selection bias, etc. A proper systematic review (and meta-analysis of raw data if possible) of selective vestibular nerve section is currently lacking. Randomized controlled trials using sham procedures are impossible due to ethical reasons in this type of surgical procedure and preclude the establishment of level 1 evidence. The conception of a delayed-start study design would enable randomization and increase the level of evidence.[91]

Recommendation Selective vestibular nerve section aims to abolish vestibular afferent signalling totally and is usually considered as an alternative to intratympanic injection of gentamicin in case of intact hearing or as salvage treatment after intratympanic injection of gentamicin.

There is insufficient evidence to support transtympanic low-pressure therapy (Meniett), endolymphatic sac surgery or tenotomy of the tensor tympani and stapedius muscles' tendons.

KEY POINTS

Diagnosis

- The diagnosis of Ménière's disease can be suspected by acquiring a systematic otovestibular history (including family history and personal drug, trauma, surgery and disease history).
- Potential causes of secondary endolymphatic hydrops need to be excluded.
- Liminal and speech audiometry is essential to support the diagnosis of definite Ménière's disease.
- There is considerable overlap in diagnostic criteria for vestibular migraine, vestibular paroxysmia and chronic subjective dizziness.
- An MRI scan of the cerebellopontine angle after intravenous administration of gadolinium-based contrast agent is the most sensitive imaging method to exclude inner ear malformations, neurovascular conflicts with the vestibulocochlear nerve, cerebellopontine angle and intralabyrinthine lesions (most often the vestibular schwannoma) or white matter lesions of inflammatory or vasculo-ischaemic origin.
- ECoG can demonstrate the electrophysiological substrate of endolymphatic hydrops.
- Delayed MRI after intravenous or intratympanic injection of gadolinium-based contrast agent can visualize endolymphatic hydrops and can provide an *in vivo* surrogate for the histopathologic confirmation of certain Ménière's disease.

Treatment

- Counselling includes a low-salt and caffeine-free diet.
- First-line medical treatment to prevent recurrence of vertigo may include betahistine dihydrochloride 16 mg thrice daily associated with diuretics.
- Salvage treatment in cases of medical treatment failure may include repetitive intratympanic injections of dexamethasone, which enable substantial and long-term vertigo control in 80% of refractory cases without significant hearing loss.
- In refractory or end-stage cases (Tumarkin crises), intratympanic injection of gentamicin (as needed) can be offered.
- Sensorineural hearing loss is a potential complication of this treatment and should be considered in the evaluation of the individual patient.
- Selective vestibular nerve section aims to abolish vestibular afferent signalling totally and is usually considered as an alternative to intratympanic injection of gentamicin in case of intact hearing or as salvage treatment after intratympanic injection of gentamicin.

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CHAPTER 64

BENIGN PAROXYSMAL POSITIONAL VERTIGO

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: benign paroxysmal positional vertigo, posterior canal, horizontal canal and anterior canal.

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is the commonest presenting cause of vertigo with an estimated lifetime prevalence of 2.4%.[1] In studies of both young adults and the elderly a prevalence of 9% has been described.[2, 3] It has a characteristic history and can easily be diagnosed on examination. Treatment can be performed in the clinic with a good outcome, making it the most rewarding vestibular condition to manage. BPPV may, however, be associated with a reduced quality of life, falls and depression, in which case the term 'benign' may be misleading, particularly when unrecognized and therefore untreated.[2]

The first clinical description of positional vertigo is attributed to Barany in 1921 and in 1952 Dix and Hallpike were the first to clearly describe the provoking maneuvers.[4, 5] Dix and Hallpike coined the term 'benign paroxysmal positional vertigo' in view of the associated benign (non-cancerous) origin and momentary (paroxysmal) bursts of intense vertigo upon head movements (positional).[5] Lanska and Remler provide a concise historical account of the work that has led to our understanding of this condition.[6]

PATHOPHYSIOLOGY

Otoconia are calcium carbonate crystals embedded in the macula of the utricle and saccule. They have a greater density than the surrounding endolymph thus making the macula sensitive to changes in linear acceleration and, importantly, gravity. The semicircular canals, on the other hand, are sensitive to changes in angular acceleration. In BPPV otoconia from the utricle are thought to collect in the semicircular canals, making them abnormally gravity-sensitive. The net result is that changes in head position with respect to gravity result in an abnormal displacement of the cupula and stimulation of the corresponding vestibular afferents. This results in the characteristically abnormal eye movements and vertigo.

There are two theories of how this might occur. **Cupulolithiasis** proposes that degenerative otoconia stick to the cupula making it gravity-sensitive. Post-mortem findings of such deposits in patients who had suffered from BPPV add weight to this theory.[7]

The more recent theory of **canalolithiasis** gained momentum after surgical observations of free-floating debris in the posterior semicircular canal during an occlusion procedure.[8–10] This theory suggests that degenerative

otoconial debris float freely in the endolymph of the semicircular canal. When exposed to gravity, the otoconia fall to the lowest part of the canal, causing a change in endolymph pressure with subsequent displacement of the cupula. The change in pressure is due to a hydrodynamic 'plunger effect' where the otoconial debris act like a piston creating endolymph flow which deforms the cupula. This theory explains the 'latency' (delay in onset) of the nystagmus that is related to the time taken for the otoconial debris to fall and the initial adherence to the membranous canal. In addition, it may also better explain the 'fatiguability' as with repeated movements the otoconial debris may be dispersed or may become trapped in some part of the canal.[8]

While the majority of BPPV cases seem to be more compatible with the theory of canalolithiasis, some cases with atypical features may be explained on the basis of cupulolithiasis. Canalolithiasis may be converted to cupulolithiasis when otoconial debris floating in the canal attach to the cupula.

SYMPTOMS AND NATURAL COURSE OF THE DISEASE

BPPV most commonly arises from the posterior semicircular canal (p-SCC). Much less frequently the horizontal semicircular canal (h-SCC) is involved while the anterior canal (a-SCC) is very rarely affected.[3, 11–15] Honrubia et al.[14] report the prevalence of p-BPPV, h-BPPV and a-BPPV in their clinic as being 93%, 5% and 2% respectively, although other authors report a higher prevalence of about 8–10% for h-BPPV.[3, 16] Using electronystagmography (ENG) to make the diagnosis, Jackson et al. report posterior canal BPPV in 66.9%, horizontal canal in 11.9% and 21.2% with anterior canal.[17] BPPV may also arise from pathology of more than one canal on one or both sides.[3, 15, 18, 19]

The propensity for the accumulation of particles in the posterior canal is postulated to be related to anatomical factors such as the size of the common crus of the posterior and superior semicircular canals, its position below the utricle when supine and its dependent position when both erect and supine. Particles can become trapped in the posterior canal; any debris that may have entered the superior canal is more likely to fall back into the utricle.[20]

In the upright position, the horizontal canal's opening into the utricle is undermost, thus facilitating particle migration out of the canal, while the posterior canal's opening is uppermost. Therefore, the horizontal canal can be easily cleared by natural head movements but the posterior canal is a trap for any particles that have entered it. Similarly, particles may leave the horizontal canal just by the action of the person rolling over in bed whereas particles in the posterior canal will only be shifted backwards and forwards. This may explain the infrequent presentation of h-BPPV.

During manoeuvres, p-BPPV can be converted to either a-BPPV or h-BPPV to p-BPPV and a-BPPV to p-BPPV.[13, 21, 22] Similarly, bilateral apogeotropic h-BPPV may spontaneously convert to bilateral geotropic and is attributed to debris located in the anterior part of the canal sticking to the cupula dislodging and shifting to the posterior part of the canal.[16] Plugging of the horizontal canal presenting with persistent spontaneous nystagmus, vertigo and oscillopsia has also been described.[23]

The hallmark of p-BPPV is vertigo lasting seconds with or without nausea and imbalance on lying down, sitting up from the lying position, or rolling in bed and when extending or flexing the neck. These symptoms can present in clusters with several attacks per day. In between attacks or shortly after successful treatment, patients are either symptom-free or experience a sensation of imbalance. This sensation of imbalance can be described as 'walking on pillows' and may be attributed to the underlying damage of the otolith organs.[24] However, some patients may report atypical symptoms, and it is worthwhile conducting the positional tests in all patients presenting with episodic vertigo.[25] In the majority of cases the BPPV symptoms will subside within a few weeks, but in up to 30% the symptoms may persist for months.[16, 24] Choi et al. report BPPV as recurrent in 12.5% of cases and persistent in 10%.[26]

AETIOLOGY

Hallpike described ear disease in 66 out of 100 BPPV patients, although in only 28 ears was it on the side with the BPPV.[5] No cause has been found in 34–86% of patients.[12, 26–28] These cases have been termed 'primary' or idiopathic BPPV. However, there may also be an association with other pathologies:

- BPPV occurred in 9.8–15.3% of cases following vestibular neuritis.[29–31]
- Otosclerosis may be associated with BPPV in up to 51% of patients and may also occur following stapedectomy.[12, 28, 32, 33]
- Studies have suggested that Ménière's disease may be found in up to 2% of cases but it has been reported to occur in up to 30% of cases.[12, 27, 28] It has been postulated that hydropically induced damage to the maculae or partial obstruction may be responsible.[34]
- Head trauma is one of the most common causes of BPPV in 14.5–18%[12, 28] and can involve more than one canal.[19, 35] The force of the injury may cause the release of otoconia into the endloymph. BPPV can also result following traumatic spinal cord injury in up to 14.5% of cases.[36]
- Patients with positional vertigo may have migrainous vertigo. Migrainous symptoms during the positional episodes, atypical features of positional nystagmus and frequent recurrence of symptoms may differentiate between BPPV and the central positional syndrome due to migraine.[37]
- Otosclerosis and osteopenia are found with greater frequency in females with BPPV, particularly older postmenopausal women.[38–40]

- BPPV also is associated with progressive cochlear or vestibular failure, vertebrobasilar ischaemia and other vestibular disorders.[12, 28]

The common feature of these conditions is that they may lead to dislodgement of otoconia from the utricle, which may invade one or several semicircular canals after days, weeks or months.

In idiopathic BPPV, which becomes more prevalent with advancing age, release of otoconia is probably related to degeneration of the otolith organs. Risk factors that may initiate an acute episode of BPPV include prolonged bedrest, bending forward with the head down, and general anaesthesia, because the supine, head-down and head-reclined position (e.g. during intubation) lower the opening of the posterior canal, thus promoting the penetration of particles.[1]

DIAGNOSIS OF BPPV

Diagnosis of BPPV is made on the basis of typical signs (nystagmus) and symptoms (vertigo and nausea) provoked by specific positional tests. Understanding the characteristic eye movements during these tests will help in making the diagnosis.[41] Our understanding of vestibular eye movements is based on fundamental principles described by Ewald:

- The direction of eye movement is in the plane of the canal or canals that are stimulated.
- In the horizontal canal, endolymph flow towards the ampulla (ampullopetal) results in an excitatory and stronger response than flow away from the ampulla (ampullofugal), which is inhibitory. The opposite holds true for the vertical canals.

For example, the posterior canal and anterior canal pairs are stimulated when performing the Dix–Hallpike test. The patient is seated along the couch, feet up, and the head is turned 45 degrees towards the side being tested, aligning the vertical canals with the sagittal plane. The head is brought down briskly over the end of the couch to lie 30 degrees below the horizontal while maintaining a position 45 degrees to the side being tested. Patients should be counselled prior to the test about dizziness but that they are to try and maintain their eyes open for examination.

The **L**eft **A**nterior and **R**ight **P**osterior canals (**LARP**) are stimulated during the right Dix–Hallpike and the **R**ight **A**nterior and **L**eft **P**osterior (**RALP**) in the left Dix–Hallpike. During the right Dix–Hallpike there is ampullofugal (excitatory) flow in the right posterior canal and ampullopetal (inhibitory) flow in the left anterior. Normally this balances out and there is no nystagmus. However, if there were particles in the posterior canal, the ampullofugal forces would be greater, resulting in a net excitatory effect and eye movement consistent with the plane of the canal. The slow-phase eye movements when excitatory would be towards the right ear or downwards and inwards via the ipsilateral superior oblique muscle and the contralateral inferior rectus muscle. The fast phase would be upwards and outwards or upbeating geotropic-torsional nystagmus. This is best seen by closely watching the scleral vessels. The nystagmus typically reverses when sitting up. A cupulolithiasis type BPPV can also rarely occur and is characterized by nystagmus that occurs without latency and does not fatigue.

The side-lying test is an alternative and has been shown to produce similar results to the Dix–Hallpike.[42] In contrast to the Dix–Hallpike, the head is turned 45 degrees away from the side being tested such that the vertical canals are in the frontal plane. The patient is quickly moved to a supine-lying position with the neck hyperextended 20 degrees. The typical torsional nystagmus is seen beating towards the lowermost ear.

Similarly, the anterior canal during a right Dix–Hallpike or side-lying tests will be inhibited, i.e. flow will be ampullopetal. If particles are present, they will cause an inhibitory effect which will predominate causing the opposite nystagmus to the posterior canal – beating downwards and intorsional in the ipsilateral eye. The straight head-hanging manoeuvre has also been shown to be useful to diagnose a-BPPV where the head is extended backwards to a head-hanging position of the end off the bed from seated to supine.[43]

Horizontal canal BPPV is assessed using the roll test. The head is flexed 30 degrees, bringing the horizontal canal into the axial plane, and is then briskly rolled to one side. The same is repeated to the opposite side. In the majority of cases the nystagmus will be horizontal and geotropic and towards the ear being tested. When turned to the opposite side, the nystagmus will reverse and beat towards the undermost ear again. When a canal is stimulated with an ampullopetal force, the nystagmic response is greater (Ewald's second law), therefore the ear containing the loose particles would generally present with the brisker nystagmus hence helping to make the diagnosis. An apogeotropic nystagmus is also described and is thought to be related to cupulolithiasis.[16] In this situation, when the head is turned to the affected side, the force is ampullofugal hence the nystagmus will beat away (apogeotropic) from the affected ear.

Frenzel glasses can be used to better observe the nystagmus or it can be recorded with electro- or video-oculography. As BPPV can sometimes coexist with other vestibular disorders and the history can sometimes be atypical, many would perform a Dix–Hallpike routinely as part of a vestibular assessment.

Differential diagnosis

Causes of vertigo that need to be distinguished from BPPV include otological and neurological among others.[44] Otolological disorders include Ménière's disease, vestibular neuritis, labyrinthitis, superior canal dehiscence syndrome and post-traumatic vertigo. Neurological disorders include vestibular migraine, vertebrobasilar insufficiency, demyelinating lesions and

CNS lesions. It is important to discriminate BPPV from positional vertigo arising from central pathology. Such pathology may exist in the pontomedullary brainstem or vestibulocerebellum, with lesions often found dorsolateral to the fourth ventricle or in the dorsal vermis.[24, 45] A central lesion should generally be suspected when features different from BPPV are present or when brainstem or cerebellar signs are found. Single characteristics of BPPV such as latency, duration and time course of nystagmus, and fatigability with repeated positioning can also occur in central positional vertigo. However, it is unlikely that a central lesion mimics the entire nystagmus pattern of BPPV. The most reliable criterion to distinguish BPPV from central positioning vertigo is the direction of nystagmus: when the affected canal is optimally stimulated in BPPV by specific head positioning in the canal plane, the nystagmus always beats in the plane which is expected from activation of that particular canal.[45, 46] Thus, in the Dix–Hallpike position, p-BPPV always provokes a combined torsional and vertical component, which is expected from the connections between the p-SCC and specific eye muscles. Likewise, h-BPPV evokes horizontal nystagmus of maximal intensity after specific positioning for the horizontal canal.

In contrast, central positional nystagmus is not attributable to the stimulated canal plane. Purely vertical or torsional nystagmus, verified by examination under Frenzel glasses, should always raise the suspicion of a central lesion as it cannot be explained by stimulation of a single semicircular canal. Central positional nystagmus often persists as long as the precipitating head position is maintained whereas BPPV produces transient nystagmus and vertigo, except for the horizontal cupulolithiasis variant. Moreover, central positional vertigo and nystagmus usually does not fatigue with repetitive positioning. Another feature distinguishing central positional vertigo from BPPV is its monophasic course that makes the diagnosis highly unlikely in a patient with a long-standing history of recurrences and remissions. Rarely, central pathology may mimic typical BPPV except for response to therapeutic positional manoeuvres.[16] In summary, imaging of the posterior fossa is required when:

- nystagmus is atypical for any of the BPPV syndromes
- brainstem or cerebellar signs are present
- positional vertigo does not resolve with repeated therapeutic manoeuvres.

In a patient with central positional vertigo and normal imaging, migrainous vertigo or drug effects (e.g. amiodarone) should be considered.[47, 48] When central positional nystagmus without vertigo occurs as an isolated finding, imaging is often negative and a specific diagnosis cannot be made.

Other causes of dizziness include anxiety disorders and postural hypotension.

TREATMENT OF P-BPPV

Repositioning manoeuvres

EPLEY'S REPOSITIONING MANOEUVRE

The canalith repositioning manoeuvre (CRM) (**Figure 64.1**) has been recommended following evidence-based reviews by the American Academy of Neurology and American Academy of Otolaryngology – Head and Neck Surgery Foundation.[44, 49] A recent Cochrane meta-analysis has found that the CRM on its own is effective in close to 80% of cases.[50]

Epley developed the canalith repositioning procedure (CRP) in 1992 based on the theory of 'canalolithiasis' in order to move the particles from the posterior canal into the utricle via the common crus.[51] It is well tolerated and non-invasive. Patients should be counselled about the procedure and the possibility of vertigo prior to commencement. The affected p-SCC is identified by the Dix–Hallpike manoeuvre and the latency and duration of nystagmus is noted in order to determine the timing of the procedure. The patient is seated longitudinally on the couch facing away from the examiner and brought down with the head turned by 45 degrees to the affected side and extended over the edge of the table, just as in the Dix–Hallpike manoeuvre, and can of course follow on from the Dix–Hallpike. The head is then turned 90 degrees to the opposite side, rotating the body 90 degrees so that the patient is lying on the side, while the head is maintained firmly in place is the next step. The head is then rotated a further 90 degrees so that the patient is looking obliquely downwards. The patient is then asked to swing their legs over the side of the couch in anticipation of the next step which involves the patient being brought to the sitting position with the head turned 45 degrees to the unaffected side. The CRP finishes with the patient in the sitting position and the head turned forward 20 degrees. Epley advocated repeating the manoeuvre until there is no nystagmus or no progress made in the last two cycles. He reported total resolution of symptoms in 90%, and resolution of BPPV but persistence of other symptoms in 10% of patients after the initial CRP treatment. There are several modifications of this manoeuvre involving longer maintenance at each position and gradual position changing with 30-second intervals.[52, 53] A recent Cochrane review suggested limited evidence to support postural restrictions post-treatment, but to remain upright and limit head movement for 24–48 hours appears to offer increased treatment benefit.[50]

A modified Epley's manoeuvre has also been used for self-treatment and its efficacy compared to the efficacy of the Brandt–Daroff exercises. The authors reported a 64% success rate after 1 week in the group of patients that were given the Epley's manoeuvre compared to 23% in those given the Brandt–Daroff exercises. Treatment failures in the Epley's group were attributed either to early discontinuation or to inaccurate performance of the manoeuvre.[54]

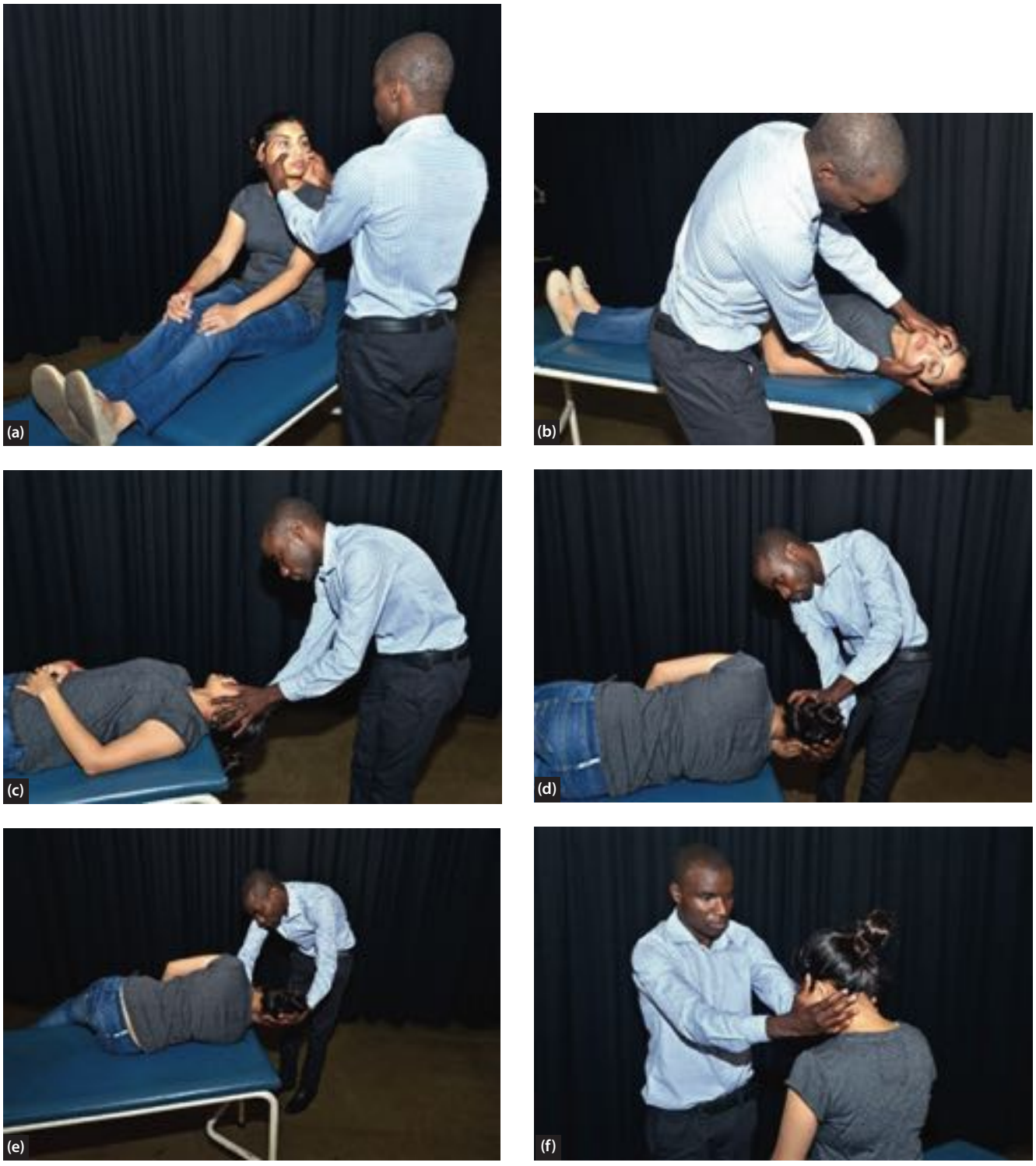


Figure 64.1 Epley's repositioning manoeuvre. Left posterior canal BPPV. The patient is sat on the table with the head turned 45° to left side (affected side) **(a)**, and **(b)** brought down rapidly with the head still turned 45° to the affected side and extended over the edge of the table. Note that the neck is well supported. **(c)** The head is then turned 90° to the opposite side (right). **(d)** This is followed by rotating the head and body 90° facing downwards (135° from the supine position). **(e)** The legs are then displaced over the side of the table in anticipation of a return to a seated position, and **(f)** the patient is brought to a sitting position with the head turned forward.

SEMONT'S LIBERATORY MANOEUVRE

Semont, Freyss and Vitte devised what is known as the Semont's liberatory manoeuvre (**Figure 64.2**) that involves laying the patient on the affected side from a seated position, with the face turned upwards 45 degrees away from the affected canal.[55] The patient is quickly swung through the sitting position without pausing to the opposite side with the face now facing downwards by 45 degrees. The head position relative to the shoulder remains unchanged during the manoeuvre and the position should be maintained for 5 minutes. The patient then slowly resumes the sitting position. The authors reported resolution of symptoms in 92% of patients treated once or several times with this manoeuvre.[58] While studies have shown an improvement when this procedure is performed, a superior benefit to CRP has not been conclusively demonstrated according to one review[44] and is possibly not as good as CRP according to another.[49] Some authors, however, maintain that the ease of use makes it a useful option.[56]

BRANDT–DAROFF POSITIONAL EXERCISES

In 1980, Brandt and Daroff proposed a mechanical self-treatment that is based on Schuknecht's hypothesis of cupulolithiasis.[57] This consists of a rapid sequence of lateral head/body tilts. Starting from the sitting position, the patient rapidly moves to the challenging position, i.e. lying on the affected side (nose 45 degrees up)

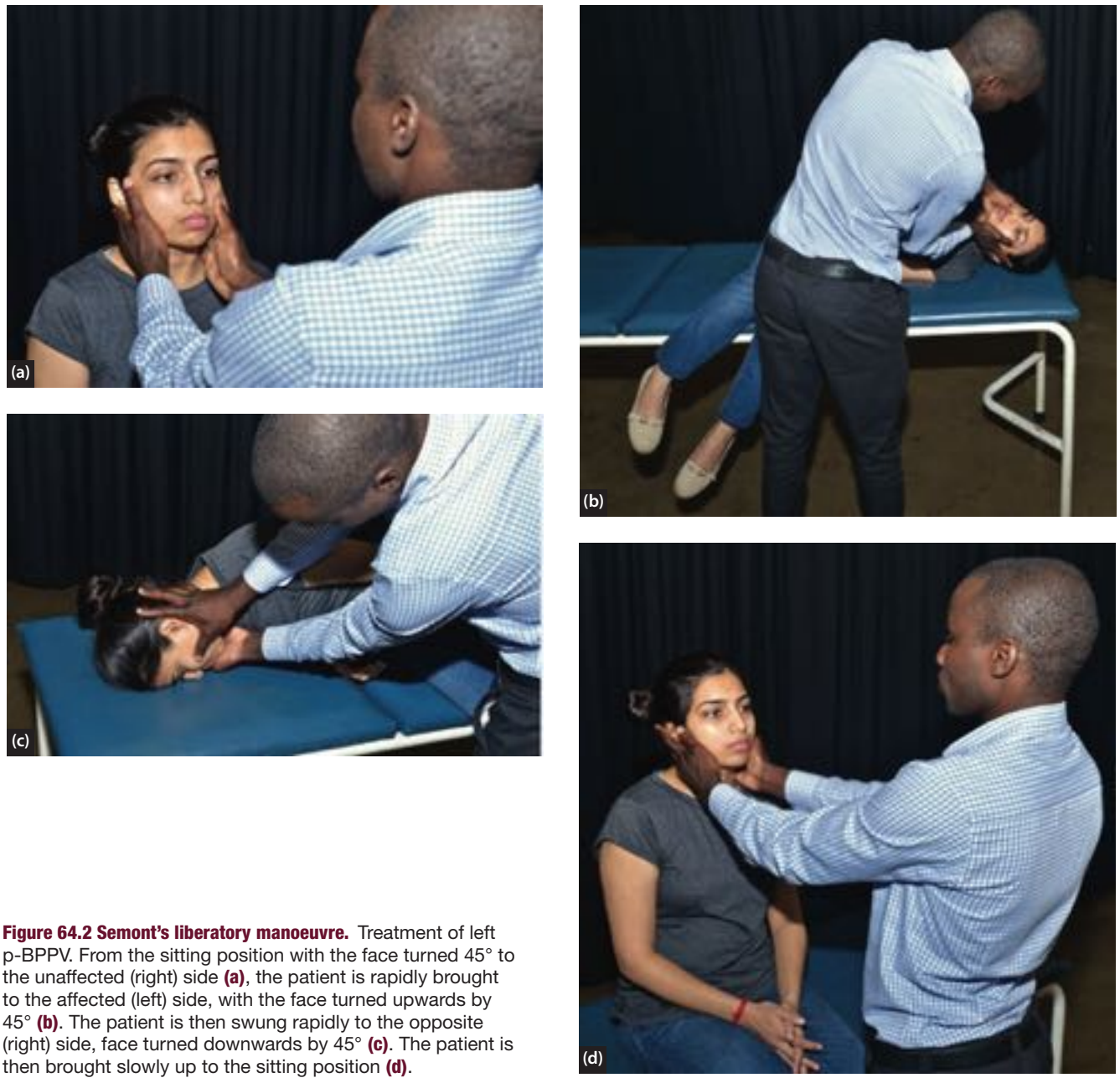


Figure 64.2 Semont's liberatory manoeuvre. Treatment of left p-BPPV. From the sitting position with the face turned 45° to the unaffected (right) side **(a)**, the patient is rapidly brought to the affected (left) side, with the face turned upwards by 45° **(b)**. The patient is then swung rapidly to the opposite (right) side, face turned downwards by 45° **(c)**. The patient is then brought slowly up to the sitting position **(d)**.

and remains in this position for at least 30 seconds or until the vertigo subsides. The patient then sits up for 30 seconds and thereafter assumes the opposite head lateral and nose-up position for 30 seconds before sitting up. This is repeated for 15 minutes three times daily. The authors reported that 66 out of 67 patients experienced complete relief from BPPV within 3–14 days, the exception being one patient who had a a perilymphatic fistula. Clinical experience has shown that response rates are usually lower and a controlled trial showed resolution of BPPV in only 23% after 1 week.[54] Thus, Brandt–Daroff involves dozens of self-induced vertigo attacks before BPPV may eventually disappear. For this reason, they are no longer a first-line treatment of BPPV. A review has shown that Brandt–Daroff exercises are not as effective as CRP.[49]

FACTORS THAT MAY INFLUENCE THE OUTCOME OF REPOSITIONING MANOEUVRES

Reports on whether the application of mastoid oscillation improves the efficacy of the particle-repositioning manoeuvre are contradictory, and in any case, the success rate of the CRP alone is quite high.[58, 59] Some clinicians give post-treatment instructions that include sleeping with two high pillows, wearing a collar and postural restriction for 48 hours after the repositioning manoeuvre. A≈recent Cochrane review has found a lack of evidence to suggest a benefit from mastoid oscillation although a significant but limited benefit may be obtained from postural restriction.[50]

The effect of the duration of symptoms before treatment on CRP success rate is controversial, as some authors report it to be a negative prognostic indicator while others report no correlation.[52, 60, 61] Patients with BPPV due to head trauma tend to improve less with treatment than idiopathic BPPV patients while patients with previous 'vestibular neuronitis' seem to have a better prognosis than patients with BPPV due to other aetiologies.[52, 62]

Studies have assessed the treatment of patients with positional vertigo but no detectable nystagmus on positional testing, i.e. 'subjective' BPPV. In these studies the side to treat was chosen on the basis of the symptoms reported on positional testing.[63–65] Tirelli et al.[63] found that treatment of 43 patients with positional vertigo without positional nystagmus by a modified Epley resulted in a 60% complete recovery rate and a 6% persistence of symptoms compared with a 90% complete recovery rate in 90 patients with typical BPPV. Haynes et al. reported symptomatic improvement with 86% in subjective BPPV after performance of an average of 1.1 Semont's manoeuvres and in 91% of patients with objective BPPV after 1.6 manoeuvres on average.[64] Neither of the studies included a control group with a sham manoeuvre. Weider[65] also reported on 48% of their cohort of 44 patients with symptoms of BPPV with no nystagmus on positional testing. Twelve patients had complete relief following an Epley manoeuvre but patients with long-standing symptoms were less likely to report a good result. It has been suggested that a subgroup of these patients may have otoconial debris in the short arm of the posterior canal.[66] However, other reasons could relate to the fatiguable nature of the nystagmus in BPPV, a mild form that may be suppressed by visual fixation or poor detection without the use of Frenzel glasses.[64]

The CRM has been recommended following evidence-based reviews by the American Academy of Neurology and American Academy of Otolaryngology – Head and Neck Surgery Foundation,[44, 49] and has been found to be effective on its own in nearly 80% of cases. The use of additional interventions such as post-treatment postural restrictions may further increase the treatment benefit but there is limited evidence to support this and only a small increase in treatment efficacy.[50] Hunt et al. did not find added benefit in using mastoid oscillation or additional steps with the Epley manoeuvre. There is no evidence to support the use of medication.[44, 49]

COMPLICATIONS AND ADVERSE REACTIONS

Several patients report gait instability following CRP, possibly due to the new position of the canaliths in the utricle.[67] Complications of CRP include conversion of p-BPPV to a-BPPV or h-BPPV in about 6% of treated patients.[13] In addition, the nystagmus may convert to a rapid form that persists and is unaffected by positional testing, possibly due to canalith jam, and these cases may be treated by the combination of the application of vibration with repositioning manoeuvres.[68]

Both Epley's and Semont's manoeuvres involve some neck strain and may be uncomfortable or impossible to perform in patients with severe cervical problems. The best solution in this situation is to do an Epley's manoeuvre on a couch where the upper half of the body can be lowered by 20–30 degrees, which obviates the need for head reclination. Brandt–Daroff exercises can be an alternative but are sometimes not pursued for long enough by immobile, elderly patients with neck pain.

Recurrence of BPPV increases with length of follow-up and eventually occurs in most patients. It is more likely in patients with secondary causes and should be treated with repeated positional manoeuvres.[26, 69]

Surgical treatment of BPPV

In a series of 5364 BBPV patients over a 20-year period, 53 patients failed to respond to repositioning manoeuvres and underwent p-SCC occlusion surgery.[70] While all were cured of their vertigo, nine patients suffered some degree of permanent hearing loss, ten developed objective balance dysfunction on caloric testing while five complained of subjective imbalance. Two patients later developed h-BPPV in the same ear and eight developed p-BPPV in the opposite ear, with two patients needing bilateral posterior canal occlusion. A number of case series describing the results of posterior canal occlusion can be found in the literature with similar results for control of the BPPV and many reporting the attendant risk of hearing loss and subjective dizziness.[71–77]

Gacek has advocated singular neurectomy via a transcanal approach for patients with chronic disabling vertigo for longer than a year and has reported on his and the results of others over three decades.[78–81] Surgery was performed on 242 patients, with 10 undergoing bilateral procedures. Complete relief (negative Dix–Hallpike) was achieved in 96.8% of cases with nine patients (3.7%) suffering sensorineural hearing loss.[81]

TREATMENT OF H-BPPV

Repositioning manoeuvres

'FORCED PROLONGED POSITION' ON THE HEALTHY SIDE

Vannucchi et al. advised patients with h-BPPV to lie down on the healthy side for 12 hours in order to facilitate gravitation of the debris into the vestibule by maintaining the affected h-SCC uppermost.[21] They reported total recovery within 3 days in 74.3% of cases out of 35 treated patients. They described occasional conversion of h-BPPV to homolateral p-BPPV, which was successfully treated with a Semont's manoeuvre. By contrast, the rate of recovery within 3 days in the group of patients who received no treatment (15 patients) and in those treated by head shaking (24 patients) was 26% and 16% respectively. Obesity and cervical spondylosis were factors that did not permit maintenance of the position for the time required.

270-DEGREE 'BARBECUE' MANOEUVRE

Lempert and Tiel-Wilck report the successful treatment of h-BPPV in two patients by an adaptation of Epley's manoeuvre.[82] This consists of turning the patient's head initially and then the body from the supine position in three 90-degree-step rotations (total 270 degrees) towards the unaffected ear. The body will eventually assume the prone position with the affected ear facing down, following which the patient will sit up. The rotation is performed within half a second and the head positions are maintained for 30–60 seconds.

Nuti et al. reported that, while both the 'barbecue' manoeuvre and the forced prolonged position are effective treatments for h-BPPV, the forced prolonged position may be successful in slightly more cases than the barbecue manoeuvre, which, however, achieves immediate results.[83]

360-DEGREE YAW ROTATION

Baloh et al. initially suggested a 180-degree rotation to the unaffected side with little success and then successfully treated two patients with h-BPPV with a 360-degree yaw rotation performed in 90-degree steps at 30-second intervals.[84] Casani et al. report an 89% success rate in 55 cases with geotropic h-BPPV treated by a combination of the 360-degree yaw rotation and forced prolonged position after one to three attempts.[16]

LIBERATORY MANOEUVRES

De la Meilleure et al. used this manoeuvre in six patients with h-BPPV. From the supine position, the head is lifted by 30 degrees, turned to the affected side and maintained in that position for 5 minutes.[15] The head is then turned quickly 180 degrees to the other side while maintaining 30-degree flexion and held there for 5 minutes. After the manoeuvre, the patient is asked to avoid head shaking and not to lie down for the next 48 hours. A 100% success rate has been reported, but patients may require treatment for bilateral h-SCC or for coexisting p-BPPV. Contraindications for this manoeuvre are cervical spondylosis, vertebrobasilar insufficiency or neck pain during the manoeuvre. The recommendation to perform an abrupt head rotation casts doubt on the safety of this procedure as vertebral artery dissection has been occasionally observed after chiropractic manipulations of a similar type.

Appiani et al. used the liberatory manoeuvre proposed by Asprella et al. for geotropic h-BPPV with a 78% cure rate after the first and 100% cure rate after the second attempt.[85] This manoeuvre begins with the patient seated on the side of the couch. A side-lying position is then quickly assumed on the unaffected side and maintained for 1 minute after the cessation of the nystagmus. The head is then quickly turned 45 degrees downwards and the position maintained for 2 minutes followed by a slow return to the sitting position. A similar manoeuvre, termed a 'modified Semont's', was used by Casani et al. for nine patients with apogeotropic h-BPPV with 55% success rate after two attempts.[16] The only difference between the Appiani manoeuvre and what Casani proposed is a rapid return to the seated position at the end.

A prospective randomized controlled trial for geotropic h-BPPV was conducted in 179 consecutive patients comparing the barbecue rotation, the Gufoni manoeuvre and a sham manoeuvre.[86] The Gufoni manoeuvre for geotropic nystagmus begins with the patient seated in an upright position and rapidly tilted to the unaffected side followed by a swift 45 degree downward turn of the head (nose down). A few minutes later the patient resumes a seated position. For apogeoptrpoic nystagmus the patient lies on the affected side followed by an upward turn of the head.

Outcomes included the resolution of vertigo and positional nystagmus assessed within 1 hour of two applications of each manoeuvre and the percentage resolution at 1-month follow-up. Both on the assessment day and at 1-month follow-up the barbecue rotation and Gufoni manoeuvre showed better responses than the sham manoeuvre, with no significant difference between the two procedures.

In another prospective randomized controlled trial of 157 consecutive patients with apogeotropic h-BPPV the Gufoni, head shaking and a sham manoeuvre were assessed.[87] Outcome measures included the resolution of vertigo and positional nystagmus assessed after a maximum of two applications on the same day, the following day and at 1-month follow-up. The therapeutic manoeuvres were better than the sham on the same day and at 1-month follow-up with no significant difference between the two. The Gufoni manoeuvre did, however, have a higher conversion rate to other types of nystagmus.

A prospective randomized controlled study of 63 patients with geotropic h-BPPV compared the Lempert (270 degree barbecue manoeuvre) manoeuvre with no treatment.[88]

Outcomes include patients' self-reported resolution of vertigo after the resolution of nystagmus and the time course in remission of positional vertigo. No significant difference was found in the time course of remission of positional vertigo between treated and untreated groups.

A prospective cohort was compared with retrospective data assessing prolonged forced position, head shaking and no treatment in patients with geotropic horizontal BPPV.[21] Forced prolonged position on the healthy side was significantly better than head shaking or no treatment at 3-day follow-up.

COMPLICATIONS AND ADVERSE REACTIONS

H-SCC canalolithiasis may convert to cupulolithiasis after a rotation manoeuvre, which, exceptionally, may in turn convert to horizontal canal-plugging by head shaking. The horizontal canal-plugging will be characterized by continuous unidirectional nystagmus that is not affected by positional testing. However, vigorous head shaking or gentle head percussion may unplug the canal.[23]

TREATMENT OF A-BPPV

A 96.7% efficacy has been reported for the modified Epley manoeuvre performed on 30 successive cases with a-BPPV.[89] The modified Epley starts using the Dix–Hallpike with the head turned 45 degrees away from the affected ear and brought to 30 degrees below the horizontal. It is kept in this position for 30 seconds then elevated while maintaining a supine position with the head at 45 degrees for 1 minute. A seated position is then assumed with the chin bent forwards at 30 degrees.

An alternative manoeuvre has been described involving moving from a seated to a head-hanging position with the head 30 degrees below the horizontal. After 30 seconds the head is brought to a chin-to-chest position for 30 seconds and then to a seated position for another 30 seconds. During the manoeuvre otoliths move towards the common crus and utricle. The authors described 84.6% success after a single manoeuvre, with complete resolution in all cases with repeated manoeuvres.[90]

BEST CLINICAL PRACTICE

- ✓ For posterior semicircular canal BPPV the canalith repositioning manoeuvre is safe and effective on its own in close to 80% of cases.
- ✓ Surgical options can be contemplated with long-standing BPPV where there has been no response to repeated appropriate repositioning manoeuvres.
- ✓ Imaging of the posterior fossa is required when:
  - ✓ nystagmus is atypical for any of the BPPV syndromes
  - ✓ brainstem or cerebellar signs are present
  - ✓ positional vertigo does not resolve with repeated therapeutic manoeuvres.

KEY POINTS

- BPPV is the commonest cause of peripheral vertigo.
- If unrecognized or poorly treated BPPV can lead to significant morbidity.
- BPPV results from particles floating in the semicircular canals (canalolithiasis) or attached to the cupula (cupulolithiasis).
- The posterior semicircular canal is most often affected.
- The vertigo typically lasts seconds and is positional.
- The majority of cases are idiopathic.
- The diagnosis is made using positional tests that produce nystagmus and vertigo.
- Repositioning manoeuvres displace the particles back into the vestibule and are successful in the majority of cases.

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CHAPTER 65

SUPERIOR SEMICIRCULAR CANAL DEHISCENCE

Harry R.F. Powell and Shakeel R. Saeed

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords superior semicircular canal dehiscence and superior semicircular canal dehiscence syndrome.

HISTORY

The association of vertigo or oscillopsia induced by pressure change or loud sounds, with dehiscence of the superior semicircular canal (SSC) was first described in 1998.[1] Using the scleral coil technique Lloyd Minor's team noted that eye movements evoked by sound or pressure stimuli aligned with the SSC.[2] Dehiscence of otic capsule bone overlying the SSC was identified on computerized tomography (CT). Superior semicircular canal dehiscence (SSCD) syndrome has subsequently become a recognized clinical condition that encompasses a wide variety of vestibular and auditory symptoms.

In 1949 Cawthorne[3] postulated that a 'third window' mechanism accounted for the positive Hennebert sign of labyrinthine fistula. Dehiscence of bone over the SSC and consequent connection with the middle cranial fossa provides a third mobile window into the inner ear in SSCD syndrome (SSCDS). Typical third window symptoms of SSCD occur either as a result of movement at the dehiscence from raised intracranial pressure, or at the oval or round windows from loud sounds or straining (e.g. a Valsalva manoeuvre against closed nostrils forcing air up the Eustachian tube and into the middle ear). Resultant alterations in inner ear fluid dynamics due to the third window cause increased firing of vestibular afferents and transient momentary vertigo.

As familiarity with SSCDS has increased there has been a massive increase in publications in the world literature, particularly in the last 5 years, as clinicians and scientists attempt to unravel the aetiopathogenesis and optimal diagnostic and management strategies for this relatively new condition.

PATHOPHYSIOLOGY

A constellation of symptoms can occur with SSCDS and the severity and spectrum of symptoms varies enormously. The mechanisms for all of them are not yet fully understood. However, the third window symptoms that underpin how the condition was discovered occur in two main ways. Marked inward movement of the stapes (raised middle ear pressure or loud sounds) leads to increased ampullofugal flow of endolymph away from the ampulla of the SSC (on the affected side), which is excitatory and causes tonic upward eye movement and ipsilateral intorsion (rotation of the upper pole of the eye towards the midline). Conversely, inward movement at the dehiscence causes ampullopetal flow towards the ampulla, which is inhibitory and causes tonic downward eye movement and ipsilateral extorsion.[2] The physiological basis for the variability of symptoms and signs between patients is not yet understood.[4] Suggested reasons are differences in the elasticity of the dura over the SSCD, differences in compliance of the round window

membrane, relative patency of the cochlear aqueduct and variance in the size of the dehiscence.[5]

EPIDEMIOLOGY AND AETIOLOGY

A 0.5–0.6% prevalence of SSCD has been observed in histological studies of cadaveric temporal bones.[6, 7] By comparison, reported prevalence from studies reviewing high-resolution temporal bone CT scans was 4–8%.[7–9] This discrepancy is explained by the effect of partial volume averaging in CT, which reduces with higher resolution finer slice collimation. Dehiscence alone is not sufficient to cause the syndrome, and many patients have dehiscence but are asymptomatic.

SSCDS could be congenital, acquired or a combination where a genetic predisposition followed by a secondary event triggers SSCDS. Predominant middle-aged onset and a statistically significant increase in prevalence with increasing age[10] make a pure congenital cause less likely. However, SSCDS has been reported in children[11] and affected siblings,[12] implicating genetic factors. Due to protrusion of the membranous labyrinth into the middle cranial fossa in fetuses, adhesion with the overlying dura has been postulated to prevent entire bone coverage of the SSC in some individuals.[13]

Ossification of the petrous bone over the labyrinth occurs from birth to the age of 3.[6] If the bone is insufficient, the resulting morphological abnormality may predispose certain individuals to SSCDS. Shearing force from a closed head injury, trauma to the temporal bone, slow erosion of thin bone, increased dural elasticity with time or sudden increase in intracranial pressure are all suggested secondary triggers.[14] A cadaveric study concluded that, when only an endosteal layer is present over the SSC, this is susceptible to a second event which could cause dehiscence and hence the SSCDS.[15] A progressive negative balance of labyrinthine osseous metabolism occurring with a congenital thin layer of bone over the SSC has also been suggested.[16] Absence of a single convincing theory suggests a combined or multifactorial aetiopathogenesis is responsible for SSCDS.

CLINICAL MANIFESTATIONS

Patients may present with a variety of signs and symptoms, either exclusive vestibular symptoms, less commonly exclusive auditory symptoms[12] or a combination. One study showed that, when the dehiscence is greater than or equal to 2.5 mm on CT, patients tend to experience combined auditory and vestibular symptoms.[17] Auditory symptoms include hearing difficulty/loss, autophony, pulsatile tinnitus and a description of hearing their eye movements or their footfall. The latter are from abnormal amplification of certain sounds in the body due to increased sensitivity to bone-conducted sound. The hearing loss is an apparent conductive loss with greater air–bone gap (ABG) in the low frequencies due to supranormal bone-conduction thresholds and suspected dissipation through the dehiscence of acoustic energy transmitted by air-conduction mechanisms.[18, 19] There is consensus from some studies that the dehiscence size correlates with the size of the ABG.[20, 21] The autophony of SSCDS usually involves hearing their own voice but not their breathing when compared with patients who have patulous Eustachian tube.[22] The Weber tuning fork test typically lateralizes to the affected side and patients may be able to hear a tuning fork placed on the lateral malleolus of the ankle.[23]

The Tullio phenomenon of vestibular symptoms occurring in response to loud sounds was first noted in patients with otosyphilis and described in 1929. Transient vertigo, imbalance and oscillopsia can all occur with loud sounds or intracranial or middle ear pressure changes in SSCDS and the physiological third window effect is responsible. Generalized imbalance may be a result of fluctuation in the vestibular system that the brain struggles to compensate for. Although a non-specific symptom, generalized imbalance has been shown to improve in patients undergoing surgical treatment for SSCDS.[19, 24]

INVESTIGATIONS

Cross-sectional imaging

High-resolution CT is the gold standard for identification of SSCD. The imaging data are reformatted in the coronal plane as standard (**Figure 65.1a**) but can also be reformatted in the plane of the SSC (Pöschl view) (**Figure 65.1b**) and/or the orthogonal plane (Stenvers view).[25, 26] Due to partial volume, averaging CT results in false-positives and overestimation of dehiscence size as shown in a study comparing CT and surgical findings.[27] To improve specificity and positive predictive value 0.5 mm collimated scans with Pöschl plane reformatting are advised.[28] More recently the senior author and colleagues have been utilizing cone beam CT to give higher-definition imaging and improve sensitivity and specificity.

Using magnetic resonance imaging as an adjunct or instead of CT has been suggested in an attempt to reduce ionizing radiation exposure. Fast imaging employing steady-state acquisition (FIESTA) MRI has been shown conclusively to exclude SSCD, with negative predictive values as high as 100%,[29] but MRI cannot consistently diagnose thin or dehiscent SSCs.[30]

Vestibular evoked myogenic potentials

Vestibular evoked myogenic potentials (VEMPs) are recorded in response to high-intensity narrow-band clicks or tone bursts. In ocular VEMP (oVEMP) testing surface electrodes beneath the eye pick up excitatory responses of the extraocular muscles. Sensitivity and specificity of oVEMPs are reported as greater than 90%[31] and their use has been suggested as a screening tool for SSCDS prior to high-resolution CT and consequent radiation exposure. Cervical VEMPs are short-latency relaxation potentials recorded by surface electrodes placed on the skin over the ipsilateral sternocleidomastoid muscle when it is



Figure 65.1 CT images of dehiscent right superior semicircular canal. **(a)** Coronal, **(b)** oblique coronal reformat in plane of SSC ('Pöschl view').

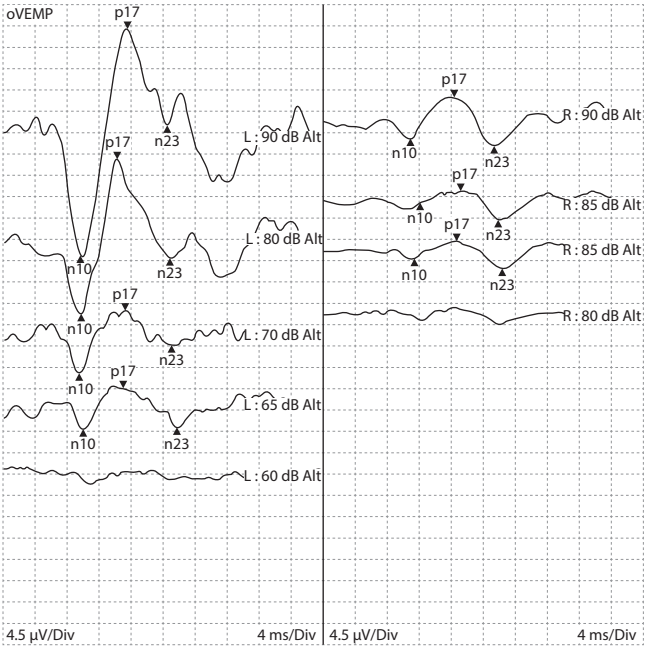


Figure 65.2 Cervical VEMP traces from a patient with left SSCDs. The lowest measurable response (initial inhibition followed by excitation) is at 85 dB on the normal right side. Responses on the left side are present down to 65 dB, which is lower than normal and suggestive of a third window.

tonically contracted (Figure 65.2). Cervical VEMP sensitivity and specificity for diagnosing SSCDS ranges from 80% to 100%.[31] VEMP responses are likely to be from the saccule (cervical) and utricle (ocular).[32–34] It is postulated that the saccule is more sensitive to sound stimuli than normal when there is a third window from SSCD.

Patients with SSCDS have VEMP responses present at lower than normal thresholds for the affected ear in both air conduction and bone conduction.[33] Some studies have also shown larger VEMP amplitudes.[23, 35]

Accurate diagnosis of SSCDS is reliant upon concordant clinical, radiological and electrophysiological findings.

MANAGEMENT

Patients with mild symptoms that are not intrusive or bothersome should be treated conservatively and given advice on avoidance of triggers or stimuli.[19, 36] Ventilation tube insertion has been beneficial for some patients with predominant pressure-related symptoms.[36] This reduces the influence of pressure change in the middle ear cleft but does not deal with the pathology directly.

Surgical management has evolved since 1998. Techniques that address the SSC itself include plugging, capping and resurfacing.[37] Initially, access was through a middle fossa craniotomy.[1] In 2009 the first transmastoid approach to the SSC was described.[38] Round window reinforcement has more recently been proposed in a multicentre series with six surgeons using a permeatal or endaural approach.[24]

If symptoms are disabling or detrimentally affecting a patient's day-to-day life and when those symptoms are predominantly attributable to a diagnosis of SSCDS, surgical management should be offered. The procedure, its risks and alternatives should be explained to enable patient-centred decision-making. In a single-centre series spanning 3.5 years 25/37 patients were offered surgical intervention.[19] The choice of technique or approach is obviously determined by the experience of the surgeon and team.

Middle fossa craniotomy has the advantage of direct visualization of the dehiscence. The disadvantages are the inherent risks of craniotomy and temporal lobe retraction and the necessity for longer inpatient hospital stay. Plugging, capping, resurfacing or combined plugging and resurfacing can all be achieved. The aim of capping and resurfacing is to cover but not occlude the SSC with the intention of inflicting less post-operative dysequilibrium or imbalance. These techniques are also thought to carry lower risk to the cochlea and consequent sensorineural hearing loss than plugging.[39] Bone, cartilage grafts, hydroxyapatite cement or fascia have all been used. A combination of temporalis fascia, bone pâté and/or bone wax have been used for plugging.[37]

An endoscopic middle cranial fossa (MCF) approach has been described.[40] It did enable shorter operative and recovery times but still carries the risks of craniotomy.

The transmastoid (TM) approach has become more common as otologists have become familiar with SSCDS. Kirtane et al.[38] adapted Lorne Parnes' technique for occlusion of the posterior semicircular canal described for benign paroxysmal positional vertigo (BPPV)[41] and applied it to the SSC as TM plugging. The disadvantage or main criticism from sceptics was a lack of direct visualization of the dehiscence. TM resurfacing[19, 39] has subsequently been reported using silicone elastomer sheeting (silastic) or a combination of bone pâté and fibrin sealant (Tisseel) to cover the dehiscence. TM resurfacing requires skeletonization of the labyrinth and exposure of the MCF dura lateral to the SSC. The dura can then be lifted off the MCF floor and the extent of the dehiscent SSC identified with the reflective surface of a round knife (**Figure 65.3**). The TM approach may be less feasible when there is significant 'overhang' of the dura lateral to the SSC or if there is extensive tegmen dehiscence requiring simultaneous reconstruction.[36] Another anatomical variant that poses a particular challenge to TM resurfacing is if the orientation of the dehiscence is such that the exposed canal, particularly the posterior limb, faces obliquely/medially.[19]

Round window (RW) techniques may in future obviate the need for craniotomy or mastoidectomy. Kartush hypothesized that patients previously thought to have perilymph fistula and successfully treated with round and/or oval window patching may actually have had SSCDS.[24] RW occlusion was reported using bone wax and fascia[42] but results were not replicable, heralding adaptation to RW reinforcement techniques utilizing temporalis fascia, tragal cartilage and perichondrium, fat, loose connective tissue, gelatin sponge and/or silastic.[24] Advantages include shorter anaesthetic/operative time and recovery, lower morbidity and none of the risks of intracranial surgery. The temporary nature of reinforcement does permit recurrence of symptoms if and when mobility of the RW recurs and thus the third window effect is re-established.[40] Proponents suggest RW reinforcement as an alternative option for patients with SSCDS in a better- or only-hearing ear, if a patient is not medically fit for general anaesthetic or longer general anaesthetic procedure and if/when the diagnosis is uncertain, to elucidate symptom improvement prior to more definitive surgery.[24]

OUTCOMES AND COMPLICATIONS

A 2015 systematic review and meta-analysis of 150 procedures from 20 studies reported an overall success rate of 94% for four methods of canal repair (plugging, capping, resurfacing or combined plugging and resurfacing), with no statistically significant differences observed between them.[43] The 10/150 procedures where there was no improvement in symptoms were considered failures; the successes include some patients with partial resolution of symptoms. The data analysis recognized a 100% success rate for combined resurfacing and plugging in 19 patients. The review found no significant difference in outcome when comparing the middle fossa approach with the TM approach.[43] Limitations to the meta-analysis include lower numbers of TM procedures and resurfacings compared with numbers of middle fossa approaches and pluggings. This may prove to be a consequence of time and experience as the TM technique shows promise, carries fewer risks and is gaining favour.[19, 44]

For 19 patients undergoing RW reinforcement techniques there was a statistically significant improvement in 8/9 symptoms of SSCDS (the exception being hearing loss).[24] RW reinforcement has distinct advantages but the potential temporary nature of the technique and the lack of intervention with the SSC itself necessitate ongoing/further evaluation in SSCDS. The Superior Semicircular Canal Dehiscence Patient Survey used in the RW study has already been used by other investigators evaluating benefit of interventions for SSCDS[19] but further study is required to assess its validity.

Combined major and minor complication rates have been reported as 12% (13/105) for MCF procedures and 16% (7/45) for TM SSCDS procedures.[43] The observed difference was not statistically significant. There were nine

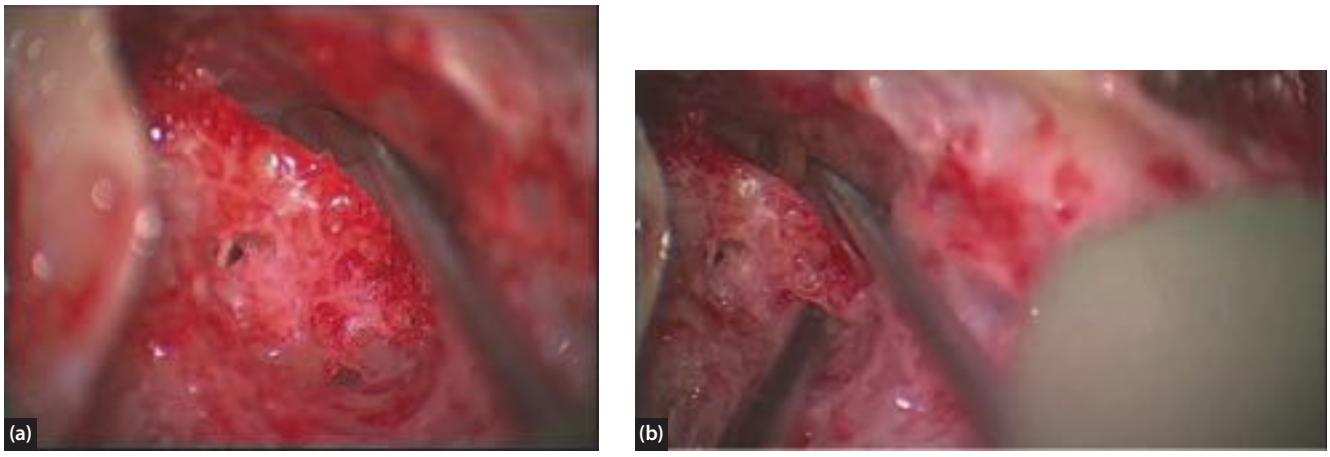


Figure 65.3 Intra-operative images from a left-sided resurfacing procedure. The position of the dehiscent lumen **(a)** and the dehiscent anterior limb **(b)** of the SSC are visualized in the reflective surface of the round knife.

major complications, six permanent total sensorineural hearing losses (four plugging; two resurfacing or capping) and three facial nerve injuries (respective approaches/techniques not reported). The 11 minor complications included transient sensorineural hearing loss, BPPV and transient post-operative dysequilibrium.

Exceptionally delicate surgical plugging technique to minimize the risk of rupture of the membranous labyrinth and consequent permanent sensorineural hearing loss cannot be emphasized enough. The risk of facial nerve injury is suspected to be higher in the MCF approach; however, significant experience of any chosen or preferred surgical technique is essential before attempting surgery for SSCDS.

CONCLUSION

As the experience of clinicians and surgeons treating SSCDS increases, so does the body of world literature to support or refute diagnostic and management strategies. Conservative management is advocated unless symptoms are bothersome. Current surgical interventions show high success and low complication rates. A focus on accurate diagnosis, patient-centred decision-making and a drive to improve the quality of patient care should enable ongoing publication of high-quality evidence. This should underpin future decision-making in all areas of SSCDS management as our experience and understanding of this relatively new condition evolves.

BEST CLINICAL PRACTICE

- ✓ The diagnosis of SSCDS requires a positive triad of history with typical clinical features, high-resolution CT and recording of VEMPs at lower than normal thresholds on the affected side(s).
- ✓ Patients whose SSCDS symptoms are affecting their quality of life should be considered for intervention in light of the severity of their symptoms.
- ✓ With sufficient neuro-otological experience of the surgical techniques, candid discussion of the options enables patient-centred decision-making. It is important to note, however, that in our experience, patients with multiple vestibular pathologies or atypical vestibular symptoms are the ones for whom SSCD surgery has not been curative (although they do report improvement in their SSCD symptoms).

FUTURE RESEARCH

- ➤ To elucidate the aetiopathogenesis of this condition and potentially thus enable development of preventative treatments.
- ➤ Investigate the physiological explanations for those symptoms not yet understood and investigate the causes for variable symptom severity.
- ➤ Robust evaluation of the RW reinforcement techniques.
- ➤ Further meta-analysis of surgical techniques.

KEY POINTS

- There are a huge variety of symptoms associated with SSCDS.
- Some of these are attributable to the third window, some are related to increased sensitivity to bone conducted sounds but for the remainder the pathophysiology is not yet understood.
- Third-window symptoms include transient vertigo, imbalance and/or oscillopsia in response to loud sounds or intracranial or middle ear pressure changes.
- SSC dehiscence alone is not sufficient to cause the syndrome; many patients have dehiscence but are asymptomatic.
- Patients with SSCDS have VEMP responses present at lower than normal thresholds for the affected ear in both bone conduction and air conduction.
- Patients with symptoms that are not intrusive or significantly bothersome should be managed conservatively and advice given regarding avoidance of triggers or stimuli.
- Transmastoid surgery enables shorter hospital stay and does not carry the risks of intracranial surgery when compared to the middle fossa approach.
- The round-window reinforcement technique shows promise; potential advantages are shorter surgical duration and less surgical morbidity with a suspected lower risk of sensorineural hearing loss. For some patients, the technique has only provided temporary relief and it does not deal directly with the SSC.

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CHAPTER 66

VESTIBULAR NEURITIS

Charlotte Agrup

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SEARCH STRATEGY

Data in this chapter may be updated by searches of Medline, EMBASE classic, EMBASE Ovid, CENTRAL (Cochrane Central Register of Controlled Trials), The Cochrane Ear, Nose and Throat Disorders Group Trials Register and additional sources for published and unpublished trials. Language was restricted to English.

INTRODUCTION

Sudden onset of sustained severe dizziness, nausea, sickness and postural imbalance is the characteristic presentation of vestibular neuritis. The patient will typically complain of vertigo (a subjective sensation of rotation/movement) and symptoms will worsen with change of position and head movements. The severely affected patient will not be able to walk unsupported but will prefer to lie down on their side, often lying on the affected ear. With milder cases the patient feels dizzy and imbalanced with some nausea but may not feel unwell enough to render seeking medical advice.

Even though vestibular neuritis is the preferred nomenclature, labyrinthitis is more commonly used among laymen and also medical professionals. However, if used strictly, labyrinthitis includes cochlear pathology (hearing loss/tinnitus) in addition to the vestibular symptoms. Other terms such as acute idiopathic peripheral vestibular dysfunction and vestibulopathy are occasionally also used.

In the adult population, around 40% of all dizziness is caused by a peripheral vestibular pathology (which includes the vestibular end organs of the inner ear and/or the vestibular nerve).[1] Of these peripheral pathologies, 3–23% have been reported to be due to vestibular neuritis.[1] There is only one publication on the prevalence of vestibular neuritis, which reports an occurrence rate of around 3.5 per 100 000.[2] This may well be an underestimate of the true incidence of the condition since no diagnosis is made in a substantial proportion of people who do not seek medical advice.[3] There is no difference in gender prevalence in vestibular neuritis and the typical age of presentation is around 40–50 years old. Although present in the paediatric population, it is much less common, with a suggested prevalence around 1.8% in children presenting with vertigo.[4]

The severe acute symptoms of vestibular neuritis normally last for between 3 and 7 days and are followed by gradual spontaneous resolution. The majority of cases will recover over a period of 6–12 weeks due to the effect of a number of different complex mechanisms collectively called central vestibular compensation.[5] A general rule appears to be that the more vestibular function that is lost during an acute episode of vestibular neuritis the more severe symptoms will be. However, different patients react very differently to symptoms.

PATHOAETIOLOGY

A selective inflammation of the vestibular nerve is the most favourable aetiology. Inflammation of a nerve may cause demyelination and associated loss of function, which can be irreversible. Temporal bone studies have shown evidence of chronic inflammatory changes of the vestibular nerve with diffuse perivascular lymphocytic infiltrates, consistent with post-infectious inflammatory changes.[6] These changes can be seen months to years after the initial acute episode. There is indirect evidence of inflammation of the vestibular nerve but not of inflammation of the

vestibular neurons and therefore vestibular neuritis is the preferred nomenclature, not vestibular neuronitis.

Vestibular neuritis may have a viral cause which is supported in some patients by the history of a preceding or coinciding cold/flu or epidemics of cases, at a workplace or among family members. However, this is not a prerequisite for the diagnosis. Reactivation of a latent virus has been suggested and the presence of herpes simplex virus type 1 (HSV-1) DNA in human vestibular ganglia and nuclei has been shown.[7, 8] Also colocalization of latent HSV-1 and CD8+ T-cells in vestibular ganglia further supports the hypothesis that HSV-1 reactivation is possible and may cause vestibular neuritis.[9, 10] Although HSV-1 is the most favourable viral agent, there is evidence that several other human viruses can cause isolated peripheral vestibular dysfunction, including rubella, cytomegalovirus, Epstein–Barr virus, adenovirus and certain strains of influenza types A and B.[11]

Using magnetic resonance imaging (MRI) an isolated enhancement of the vestibular nerve in connection with vestibular neuritis has been shown, supporting an inflammatory response.[12] Also, a decrease in vestibular nerve cross-sectional area and height in patients with unilateral vestibular neuritis has been shown using constructive interference in steady-state (CISS) parasagittal MRI.[13]

The evidence of viral infection being the aetiology remains indirect and circumstantial[14] and other aetiologies of acute vestibular loss are certainly possible, such as surgical unilateral vestibular deafferentation (i.e. vestibular neurectomy). Head trauma may cause acute vestibular loss and immunological causes have also been suggested.[15, 16] In the patient with vascular disease, particularly the elderly, a vascular aetiology seems likely but is very rarely proved.

CLINICAL PRESENTATION AND DIAGNOSIS

Vestibular neuritis presents with symptoms and clinical signs related to sudden, isolated unilateral vestibular loss. Symptoms typically consist of sudden onset of persistent vertigo (commonly a subjective sensation of rotation) with associated distressing autonomic symptoms such as nausea, vomiting, sweating and pallor. Severe symptoms would normally last for a few days before gradually starting to spontaneously resolve. There should be no associated cochlear symptoms (hearing loss and tinnitus), neurological symptoms or signs of brainstem lesion.

The vestibular nerve has two branches, the superior and inferior nerve. The superior nerve is more commonly affected with vestibular neuritis, which may be explained by its course through a longer and more narrow bony canal making it susceptible to swelling (associated with inflammation) causing entrapment.[17] Accordingly, only approximately 18% of vestibular neuritis affects the inferior nerve.[18, 19] The presentation of symptoms, clinical findings and results of vestibular testing will depend on which branch of the vestibular nerve (i.e. part of the vestibular system) is affected. Superior vestibular neuritis presents with a vestibular lesion that affects the anterior and horizontal semicircular canals and utricular function but spares the posterior semicircular canal function and most of the saccular function. In contrast, inferior vestibular neuritis affects the posterior semicircular canal function and the saccular function. Although vestibular neuritis is mostly unilateral, bilateral sequential involvement has been reported.[20]

Visual vertigo, dizziness provoked by visual environments with repetitive or moving visual patterns, is common with a peripheral vestibular dysfunction.[21] For this reason, this group of patients dislikes visually busy environments (such as traffic, crowds and supermarket aisles) which will induce dizziness/imbalance and a sensation of disorientation. Benign paroxysmal positional vertigo (BPPV) is a common sequel to vestibular neuritis and will develop in the affected ear in 10–15% of cases.[20] However, in a study of patients with inferior vestibular neuritis, none showed BPPV as a sequel. Anxiety disorders and panic episodes are very common in association with vertigo/imbalance. It is likely that, in some patients, vestibular dysfunction may play an important role in the aetiology of these disorders[22] and often anxiety and panic episodes may be the main presenting symptoms associated with the vestibular neuritis.

Diagnostic criteria for vestibular neuritis have been suggested by Coats (**Box 66.1**)[23] but there are no generally agreed specific criteria. History, clinical examination and vestibular tests are the basis for diagnosing vestibular neuritis and a clear, detailed history provides a big step towards a certain correct diagnosis.

The most characteristic clinical finding with sudden unilateral loss of vestibular function is the spontaneous peripheral vestibular nystagmus (**Box 66.2**). An acute loss of peripheral vestibular function results in a slow vestibular-induced drift of the eyes in the same direction as the lesion. This drift is interrupted by rapid saccadic eye movements in the opposite direction, towards the healthy ear. This combination of slow and fast eye movements constitutes the spontaneous peripheral vestibular nystagmus. The nystagmus is horizontal with a torsional component, its direction is defined by the fast phase and it is described as first-, second- and third-degree nystagmus. In acute severe cases, the nystagmus is initially present with optic fixation but, in milder cases and during recovery, there will be no visible nystagmus with optic fixation and it is not until the optic fixation have been removed that the nystagmus will be present. Of note is that, when only the

BOX 66.1 Modified diagnostic criteria for vestibular neuritis suggested by Coats[23]

Acute onset of non-recurrent vertigo often accompanied by nausea and vomiting
Absence of cochlear symptoms (hearing loss/tinnitus) or signs of central nervous involvement
Commonly unilateral partial or complete peripheral vestibular lesion
Complete subsidence of symptoms within 6 months

BOX 66.2 Characteristics of the spontaneous peripheral vestibular nystagmus

- Unidirectional
- Horizontal
- Conjugate
- Temporary
- Enhanced by removal of optic fixation
- Obeys Alexander's law

BOX 66.3 Characteristic clinical examination findings with acute vestibular neuritis

- Horizontal–torsional spontaneous nystagmus, beating away from the side of the lesion, more vigorous without optic fixation
- Headthrust test positive on the same side as the lesion
- Gait test and Unterberger test show deviation to the side of the lesion
- Romberg test shows marked increase of sway

inferior vestibular nerve is affected, spontaneous nystagmus is rare. It is also important to note that other types and directions of nystagmus (i.e. purely torsional, vertical or dysconjugate nystagmus) indicate a central pathology and should prompt further investigations.

Clinical examination

A detailed medical examination including neuro-otological examination, general neurological examination and examination of the cardiovascular system is essential and confirms diagnosis. The neuro-otological examination should include examination of the external ear and otoscopy, in addition to assessment of vestibulo-ocular and vestibulospinal function.

Examination of eye movements is a must and should include the cover test (looking for strabismus), the full range of eye movements and gaze testing (looking for nystagmus with central gaze, 30-degree left gaze and 30-degree right gaze, preferably with and without optic fixation). With the left and right gaze testing it is important that the angle does not exceed 30 degrees since a larger angle can induce physiological end-point nystagmus (beating in the same direction as the gaze). In the majority of patients the spontaneous nystagmus will subside within 48 hours and the nystagmus with optic fixation disappears within 1–2 weeks. However, with removal of the optic fixation (e.g. by using Frenzel glasses or videonystagmography (VNG) goggles) the spontaneous nystagmus may be observed for as long as 5–10 years.

The **headthrust test** is a simple bedside test of the horizontal vestibulo-ocular reflex and is positive for the side that causes the corrective saccades, indicating a vestibular dysfunction on the same side. A **Hallpike test** to exclude positional vertigo should always be performed, in the non-acute stage, since it is not unusual for BPPV to follow after the acute vestibular neuritis. Clinical tests assessing vestibulospinal function are non-specific and often insensitive. However, tests of stance and gait provide an indication of the extent of the patient's disability and interaction of vestibulospinal activities with other systems. A tendency to sway on the **Romberg test** may suggest peripheral vestibular pathology and a marked increase in sway has been demonstrated in elderly patients with a unilateral vestibular hypofunction.[24] Also with the **gait test** (5 m walk with the eyes open and then with eyes closed) a deviation towards the side of the peripheral vestibular lesion is commonly seen. The **Unterberger test** has been shown to have poor sensitivity and specificity.[25] However, with a peripheral vestibular dysfunction the patient may also deviate to the side of the lesion during this test.

Characteristic test findings are summarized in **Box 66.3**.

Diagnostic vestibular testing

The use of diagnostic vestibular testing confirms diagnosis. These testing facilities are only available at specialist centres and consist of the caloric test, videonystagmography/electronystagmography (VNG/ENG), cervical and ocular vestibular-evoked myogenic potential (c- and oVEMP), subjective visual vertical and horizontal and video head impulse test (VHIT). A detailed explanation of these different tests is beyond the scope of this chapter and they will therefore be discussed only briefly where they have particular relevance to vestibular neuritis.

The **caloric test** is the gold standard for diagnosing unilateral peripheral dysfunction, with a reduced or absent response on the affected side. In the study by Sekitani et al. 50% of patients with vestibular neuritis, investigated with the caloric test, were shown to have a partial canal paresis.[2] Of note is that, when only the inferior nerve is affected, the caloric test, which depends largely on the horizontal canal function, is normal. The **VNG/ENG recordings** of eye movements allow a more detailed evaluation compared to the clinical examination, in addition to providing a record of the eye movements. A number of the standard battery of eye movement recordings help to identify a unilateral vestibular dysfunction, for example the gaze testing with identification of the typical peripheral nystagmus, but also central neurological pathologies can be identified (typically cerebellar lesions).[26] The **rotatory chair** (used in combination with VNG or ENG) is the gold standard for diagnosis of bilateral vestibular loss. The standard test battery can also identify a peripheral vestibular asymmetry.[26]

The oVEMP and cVEMP can determine which branch is affected in an episode of vestibular neuritis (the superior or inferior vestibular nerve). Studies have shown that, when the superior nerve is affected, oVEMP is abnormal and cVEMP is normal (reduced or absent n10 amplitude at the eye contralateral to the lesion and large asymmetry ratio with oVEMPs as opposed to normal amplitude and asymmetry ratio with cVEMPs). Contrarily, when the inferior vestibular nerve is affected, the oVEMP is normal and the cVEMP is abnormal (increased asymmetry ratio and reduced or absent amplitude response).[27, 28]

Subjective visual vertical and horizontal are quick to perform and both show a deviation to the side of the lesion with vestibular neuritis.[29] The VHIT is a relatively new development and it has been suggested that video recording of the head impulse test improves the sensitivity of this test.[30] An abnormal VHIT has been shown to be associated with a vestibular loss of more than 62.5% identified with the caloric test. On the other hand, with a caloric deficit of less than 40%, the VHIT is normal.[31]

RECOVERY AND RESOLUTION

As mentioned above, the majority of patients with vestibular neuritis recover fully without intervention within 6–12 weeks. This process may be partly related to restoration of peripheral vestibular function[32] and partly to development of vestibular compensatory mechanisms which involve brainstem, cerebellar, cortical and spinal functions.[5, 33] The recovery does not follow a linear pattern but symptoms will often fluctuate. However, a ground rule is that reoccurring symptoms will not be as severe as symptoms appearing during the initial vestibular insult.

Vertigo is experienced when there is an asymmetric resting activity between the two vestibular nuclei (localized in the brainstem). Neural recordings in animals recovering from a unilateral peripheral vestibular lesion show that central compensation depends on an increased spontaneous neural activity in the ipsilesional vestibular nucleus and a decreased spontaneous neural activity in the contralesional nucleus, thereby rebalancing activity of the left and right vestibular nuclei.[34, 35] Some of resolution of symptoms can be related to recovery of peripheral vestibular function and 50–70% of patients have been shown to have a complete recovery of peripheral vestibular function assessed by using the caloric test.[36, 37] In line with this, around 20% of patients have been shown to remain symptomatic following surgical unilateral vestibular deafferentation, limiting peripheral vestibular recovery.[38] However, there is a lack of correlation between recovery of clinical symptoms and caloric recovery: where there has been no restoration of peripheral function some patients feel well recovered but up to 20% of patients experience continued symptoms despite normalization of caloric testing.[39] Hence, there are other factors than recovery of peripheral vestibular function that are significant for patient recovery.[40]

Patients who are able to compensate fully for the vestibular loss will mostly remain asymptomatic and unaware they are balancing using mainly one ear rather than two; they will feel subjectively 'back to normal'. In some patients, especially the elderly and those with additional central nervous system disorders, the compensation is often not as effective. This will lead to chronic peripheral vestibular dysfunction (with a persistent sensation of imbalance) or recurrent episodes of decompensation (with recurrent episodes of imbalance). Complaints about sensations of floating, rocking, lightheadedness, disorientation and/or depersonalization are frequent with decompensation.

The recurrence rate of vestibular neuritis is very low and may involve the other side. In a study by Huppert et al. only 1.9% of patients developed a second vestibular neuritis within 39 months after the first episode.[20] The patient would typically have only one episode of sudden-onset vertigo and any recurrent episodes that occur could be explained by episodes of temporary decompensation. However, with recurrent symptoms, other aetiologies must be considered, such as migrainous vertigo, BPPV and Ménière's disease.

MANAGEMENT AND TREATMENT

Symptomatic treatment with antiemetic medication during the acute stage is often required, and antihistamines, anticholinergic agents and antidopaminergic agents are the most commonly used drugs. Fluid replacement may be necessary in particularly severe cases. Most antiemetics are vestibular sedatives and will suppress the stimulus of sensory mismatch which is required for habituation and compensation. It is therefore important that they are only used during the acute stage since prolonged use has been shown to prevent development of vestibular compensation. Accordingly, regular vestibular sedatives are not indicated in patients with chronic dizziness and should preferably not be given for longer than 3 days, following which they should be used only as an emergency medication on an as-required basis.

Vestibular neuritis may cause adverse effects on quality of life, affecting activities such as driving, employment and loss of confidence in everyday living. An important part of management is to advise the patient clearly of the benign nature of the condition and to reassure patients their symptoms will settle. Also inform patients of the fluctuant nature of the recovery process and the common prevalence of decompensation. Advice on safety is important and may be required with regards to driving, workplace and increased risk of falls.

There is at present no clear consensus with regards to specific treatments for vestibular neuritis. Benefit of treatment with oral corticosteroids, in the acute stage of vestibular neuritis, has been suggested.[41] There are some published studies comparing the effectiveness of oral corticosteroids (methylprednisolone) with placebo,[42] but the studies are small and of low methodological quality. This Cochrane review[42] showed an overall significant effect of corticosteroids compared with placebo medication on complete caloric recovery at 1 month. On the other hand, there was no significant effect on complete caloric recovery at 12 months or on the extent of caloric recovery at either 1 month or 12 months. In addition, there was no significant difference between corticosteroids and placebo medication in the symptomatic recovery (using the Dizziness Handicap Inventory score) at 1, 3, 6 and 12 months. Accordingly, there is currently insufficient evidence to support treatment of patients with acute

vestibular neuritis with corticosteroids, particularly considering the risk of adverse side effects.

Despite the suggested possible viral aetiology of vestibular neuritis, no benefit of antiviral treatment in the acute stage has been shown.[41]

Vestibular rehabilitation is a safe and effective treatment for unilateral vestibular dysfunction and is required in some patients to enable recovery and development of effective compensation.[43] The central nervous system needs the stimulus of sensory mismatch for habituation and compensation and controlled studies have indicated that vestibular exercises can accelerate balance recovery and development of compensatory mechanisms.[33] Whether more frequent exercise leads to faster recovery is not known.

The vestibular rehabilitation should be started when the acute stage of nausea and vomiting has passed. It is thought that vestibular compensation develops more quickly and more effectively if the person is active as soon as possible.[44] Vestibular rehabilitation could partly consist of the Cawthorne–Cooksey exercises as well as gait retraining.[44] Although there is insufficient evidence to discriminate effectiveness between different forms of vestibular rehabilitation, more customized vestibular exercises are most probably of benefit with additional visual exercises to manage the visual vertigo.

Cognitive behavioural therapy may be required in the group of patients in which anxiety and panic disorders are the main presenting symptoms associated with the vestibular neuritis.

BEST CLINICAL PRACTICE

- A detailed medical history and examination including neuro-otological examination, general neurological examination and examination of the cardiovascular system is essential and confirms diagnosis.
- With recurrent episodes of vertigo other aetiologies must be considered such as vestibular migraine, benign paroxysmal positional vertigo and Ménière's disease.
- Sudden onset severe vertigo presenting with associated hearing loss, headache and/or neurological symptoms indicate other pathology than vestibular neuritis and require prompt further investigations.
- An important part of management is explanation and reassurance about the benign nature of the condition.
- The majority of patients with vestibular neuritis recover fully spontaneously within 6-12 weeks due to central vestibular compensation. However, in the elderly patient the compensation is often not as effective.
- Vestibular rehabilitation is a safe and effective treatment in patients who do not recover fully.
- Most symptomatic treatments (antiemetic medications) are vestibular sedatives and should only be used during the acute phase, preferably no longer than 3 days.

FUTURE RESEARCH

- ➤ Further research to clarify the pathogenesis of vestibular neuritis is essential for the development of effective specific treatment modalities.
- ➤ Development of specific diagnostic criteria for vestibular neuritis is imperative for research into evidence based specific treatments.
- ➤ Better understanding of development of vestibular compensatory mechanisms will enable improved guidelines for individualized and more effective rehabilitation of vestibular neuritis.

KEY POINTS

- Vestibular neuritis typically presents with one acute episode of sudden-onset vertigo and, if recurrent episodes occur, other aetiologies must be considered.
- The typical peripheral nystagmus is horizontal and increases when the optic fixation is removed.
- The presence of auditory or neurological symptoms indicates a different diagnosis.
- Symptomatic treatment during the acute stage may be required but should preferably not be given for longer than 3 days and is not indicated in patients with chronic dizziness.
- If the patient has atypical symptoms, consider referral to a balance specialist.

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CHAPTER 67

VESTIBULAR MIGRAINE

Louisa Murdin and Linda M. Luxon

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: vestibular migraine, migraine and migrainous vertigo.

CLASSIFICATION AND DEFINITIONS

Migraine is common. Almost everyone will either have experienced the condition personally or have friends, family or other acquaintances who are sufferers. The disorder has long been recognized from antiquity as a 'sick headache' or similar description. However, the understanding of the spectrum of migraine manifestations, pathophysiology and management options has increased rapidly over the last 20 years. The story of the concept of 'vestibular migraine' is a part of this fast expansion of understanding.

Migraine is defined by the International Headache Society International Classification of Headache Disorders (ICHD), most recently ICHD-3 beta (**Box 76.1**).[1] Of note, there is no objective diagnostic test and the diagnosis rests with the patient's subjective description of the symptoms, as well as the clinician's assessment that no other disorder better accounts for the clinical presentation. This can be supported to some extent by behavioural observation, especially in those unable to provide a history, such as young children.

The definition is intended to be workable for clinicians, and also to be of use to those executing clinical trials and other research into headache disorders. In addition to the features tabulated in **Box 76.1** there are many other characteristics of migraine that may be encountered in clinical practice. These include other sensory aversions such as osmophobia, motion sickness, sensitivity to alcohol in the form of hangover headaches, and family history. The latter, however, is of limited diagnostic utility given the frequency with which migraine occurs in the general population.

Migraine is primarily and most commonly an episodic disorder. In some cases symptoms it can become chronic. Even in those individuals whose phenotype has evolved to a chronic form, symptoms are usually fluctuating. Even in chronic migraine, careful history taking will elicit an initial period of episodic symptoms.

In about 30% of patients there is experience of aura (**Box 67.2**), comprising fully reversible focal neurological symptoms. These are characteristically followed by a migraine headache, although some individuals experience aura without headache.

Vertigo is mentioned three times in relation to migraine in this classification system. Firstly, it relates to benign paroxysmal vertigo of childhood, a condition of vertigo without headache that occurs in younger children and is thought to be a migraine precursor. Secondly, vertigo can be part of the aura of basilar-type migraine. The key feature of vertigo in basilar-type migraine is that the vertigo is thought to form part of a posterior circulation aura. To identify this with confidence it should conform to the timing definitions for an aura as laid out in **Box 67.3**. In addition, there should be other identifiable posterior circulation symptoms such as dysarthria, tinnitus, reduced hearing, diplopia, visual symptoms simultaneously in both temporal and nasal fields of both eyes, ataxia, decreased level of consciousness or simultaneously bilateral paraesthesias.

However, in neuro-otology and dizziness clinics, the majority of patients who describe dizziness and

BOX 67.1 Migraine headache as defined by ICHD-3 beta (2013)

A. At least five attacks
B. Headache 4–72 hours' duration
C. At least two of:
   - unilateral
   - pulsating
   - moderate/severe
   - aggravation by routine physical activity
D. During headache at least one of:
   - nausea and/or vomiting or
   - photo- and phonophobia
E. Not attributed to another disorder

BOX 67.2 Definition of aura

Fully reversible symptoms:
- sensory, visual, speech disturbance
- at least two of:
  - homonymous visual symptoms and/or unilateral sensory symptoms
  - at least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
  - each symptom lasts between ≥5 minutes and ≤60 minutes
- migraine headache begins during the aura or follows aura within 60 minutes

BOX 67.3 Migraine with brainstem aura (formerly basilar-type migraine)

A. At least two attacks fulfilling criteria B–D
B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor or retinal symptoms
C. At least two of the following brainstem symptoms:
   - dysarthria
   - vertigo
   - tinnitus
   - hypacusis
   - diplopia
   - ataxia
   - decreased level of consciousness
D. At least two of the following four characteristics:
   - at least one aura symptom spreads gradually over 5 minutes, and/or two or more symptoms occur in succession
   - each individual aura symptom lasts 5-60 minutes
   - at least one aura symptom is unilateral
   - the aura is accompanied, or followed within 60 minutes, by headache
E. Not attributed to another disorder

BOX 67.4 Vestibular migraine

A. At least five episodes with vestibular symptoms of moderate or severe intensity lasting 5 minutes to 72 hours
B. History of migraine according to IHS classification
C. Migraine feature with >50% of attacks:
   - headache with two of unilateral, throb, moderate–severe, aggravation by movement
   - photo- and phonophobia
   - visual aura
D. Not better accounted for by another disorder

vertigo in association with migraine headaches and other migrainous phenomena, do not meet strict criteria for aura.[2] This led to the proposal by Neuhauser in 2001 to define an entity they called **migrainous vertigo**. This definition was updated in 2012 in a joint statement by the International Headache Society and the Barany Society and termed **vestibular migraine** (VM) (**Box 76.4**, also in the Appendix section of ICHD-3 beta),[1] which is the third type of migrainous disorder mentioned in the classification system. The validity of the diagnosis has been supported by long-term follow-up studies in which its stability has been demonstrated over a period of up to 9 years.[4]

To be confident of the diagnosis of VM, note that criterion B in **Box 67.4** must be fulfilled, i.e. the patient must have a history of typical migraine, although this does not necessarily need to be highly active at the time of presentation. There is also a definition of **probable vestibular migraine**, in which criteria A and E are fulfilled but only one of B or C. **Definite vestibular migraine** was found to be a highly stable and valid diagnosis over 10 years or so in a longitudinal study, with probable VM unsurprisingly much less so.[5] Note also that migraine may be a risk factor for incomplete compensation from an acute vestibular episode, the pathophysiological basis for which is as yet incompletely understood.[6]

Other terms are encountered in the literature such as migraine-related dizziness, migrainous vestibulopathy and vertiginous migraine, but these have not found widespread international acceptance or standardized definitions.

EPIDEMIOLOGY

There has been only one large population-based epidemiological study of VM in the community.[7] In this study, which took place in Germany, the lifetime prevalence was estimated at 0.98%, two-thirds of participants with VM had consulted a doctor but only 20% of these were diagnosed correctly. Age-adjusted health-related quality of life scores (SF-8 Health Survey) were consistently lower in participants with VM compared to dizziness-free controls. As for migraine, there is female preponderance. It may be more common in women in mid-life, with 1 year prevalence of 5%.[8] This would make it one of the most common causes of episodic vertigo, more common than disease (population lifetime prevalence estimated at 0.12%[9] to 0.5%,[10] although less common than benign paroxysmal positional vertigo.

There are epidemiological associations between migraine and a number of vestibular disorders, including Ménière's disease,[11] benign paroxysmal positional vertigo,[12] episodic ataxia type II[13] and motion sickness.[14]

BOX 67.5 Six-fold relationship between migraine and vestibular symptoms

1. Benign paroxysmal vertigo of childhood (migraine precursor)
2. Migraine with brainstem aura (formerly basilar-type)
3. Vestibular migraine
4. Epidemiological and clinical associate of other vestibular disorders (e.g. Ménière's disease, benign paroxysmal positional vertigo, episodic ataxia type II, motion sickness)
5. Risk factor for slow compensation from acute vestibular event
6. Secondary vestibular migraine (underlying episodic vestibular disorder triggers migraine episodes)

BOX 67.6 Pitfalls in diagnosis

Many patients deny a history of migraine when first asked about headaches so, if VM is suspected, it is worth enquiring specifically about the experience of headache, including any that the patient describes as a 'normal' headache.

While it is increasingly recognized that vestibular symptoms can result from migrainous processes, it is also known that vestibular stimulation can act as a trigger for migraine headaches.[16] This means that some patients with vestibular symptoms and migraine have an underlying vestibular disorder that is triggering migraine headaches. To reduce headache frequency in these patients, the underlying vestibular disorder must be addressed.

While primary migraine is one of the commonest headache disorders, it should be recognized that there are many other causes of both primary and secondary headache. These should be delineated and managed appropriately.

Various mechanisms have been proposed for these associations including inner ear vasospasm,[15] overlapping pathophysiologies[11] and a secondary triggering effect of vestibular disorders on episodes of headache.[16] This latter mechanism distinguishes primary VM, in which vestibular symptoms are attributable to migrainous processes, from secondary VM, in which symptoms of migraine are triggered by a vestibular disorder that causes episodic vertigo (**Box 67.5**).

Migraine is also known to be associated with poor recovery from acute vestibular disorders, although the mechanism of this effect is not entirely clear.[17]

In summary, the current state of knowledge suggests that there are therefore six ways in which vestibular symptoms and migraine can coexist (see **Box 67.5**).

PATHOLOGY AND GENETICS

Theories about the pathology of VM derive from theories of pathogenesis of migraine. Migraine is considered a disorder of sensory modulation, involving both neural and vascular tissue.[18] Many theories of migraine pathogenesis centre on the 'trigeminovascular reflex', with aminergic brainstem nuclei activating trigeminal afferents responsible for the pain of migraine headache that is a central characteristic of the disorder.

Migraine is well recognized as a familial disorder and there are documented pedigrees of families with VM.[19] Rare forms of migraine where there are associated neuro-otological findings have a simple Mendelian inheritance with specified identified mutations (familial hemiplegic migraine Types 1–4 with mutations in *CACNA1A*, *ATP1A* and *SCN1A* and the episodic ataxias Types 1–7 with mutations in *KCNA1* and *CACNA1A*). These data suggest that migraine and its neurological manifestations are mostly likely ionopathies. However, a single genetic mutation for common forms of migraine, including VM, remains elusive, despite extensive work in this area. Genome-wide association studies have identified several candidate variations for common migraine, but the pathological significance of these is yet to be confirmed.[20–22]

Cortical spreading waves of depression of Leao are thought to be analogous to the aura symptoms of migraine.[23] Such a phenomenon affecting brainstem structures such as the vestibular nuclei has been proposed to account for some types of episodes of migraine-associated vertigo.[24] However, this theory does not account for all the clinically observed features of VM, including the time course of attacks that commonly last for several hours or days.

Another possible source for the vestibular symptoms of VM is ion channels within the inner ear. These are critical for neuronal excitation as calcium enters the neurons and potassium exits it into the endolymph. Serotonin, known to have an important role in the modulation of migraine headache, influences neurovascular homeostasis within the mouse inner ear.[25]

Yet another suggested theory is the possibility of vasospasm of the vestibular branches of internal auditory artery causing the ischaemia of the labyrinth and then resulting in cochleovestibular dysfunction experienced in migraine-associated vertigo.[26]

CLINICAL ASSESSMENT

Potential pitfalls in diagnosis to be aware of are given in **Box 67.6**.

History

The key feature of the history is the presence of episodic vestibular symptoms. In some patients with chronic symptoms the symptoms can be present constantly but are subject to fluctuation. Episodes can be of variable duration. Much discussion has taken place over whether very short-lived episodes (less than 5 minutes) can be classified as VM. There is no doubt that such episodes are frequently reported by individuals who otherwise have clear-cut VM, but on current criteria the diagnosis may not be made in those with exclusively short-lived episodes.



Figure 67.1 Everyday situations of work and leisure. (Images courtesy of artur34/arrbrey/Nathan Greenwood FreeDigitalPhotos.net.)

Headache need not necessarily be a prominent feature of the presentation, but it is useful for distinguishing VM from other causes of episodic vertigo.

Photo- and phonophobia are key diagnostic symptoms that should be specifically and carefully enquired about, since they are easily missed.[27] Sensitivity to self and visual motion are frequently associated, and can persist between acute episodes (the 'interictal period'). This can result in avoidance of everyday situations at work and at leisure, such as supermarkets, transportation systems and leisure activities (**Figure 67.1**).

Family history is often sought and can help in some settings but the statistical yield of such enquiry is low due to the high prevalence of migraine in the general population. A history of motion sickness may be of use since migraine and motion sickness are strongly linked.[14]

Other aspects of the history should be directed to symptoms that may be suggestive of an alternative diagnosis, such as the unilateral auditory symptoms of Ménière's disease. Similarly, consider in the history both other causes of primary headache (e.g. tension-type) and less common but potentially serious secondary causes of headache such as intracranial space-occupying lesion, meningitis, subarachnoid haemorrhage, temporal arteritis, primary angle-closure glaucoma, idiopathic intracranial hypertension and carbon monoxide poisoning.

Examination

The physical examination of patients with VM in the interictal period is usually normal. However, some patients report significant visual motion intolerance that can be detected during eye movement examination. One study of patients with VM in the acute setting found a range of eye movement abnormalities including positional nystagmus,, spontaneous nystagmus, mixed and central type patterns.[28] The presence of interictal eye movement abnormalities should alert the examiner to consider the possibility of either a different disorder altogether (e.g. episodic ataxia type 2) or an underlying neurological disorder causing migraine via secondary effects. **Figure 67.2** shows the MRI scan of a patient who presented with frequent headaches and episodic vertigo but was found to have a meningioma in the cerebellopontine angle that was thought to be contributory.

Neuro-otological investigations

Pure-tone audiometry is usually normal in VM, but it can also be helpful in differentiating VM from Ménière's disease in which low-frequency unilateral hearing loss may be detected. A directional preponderance may be

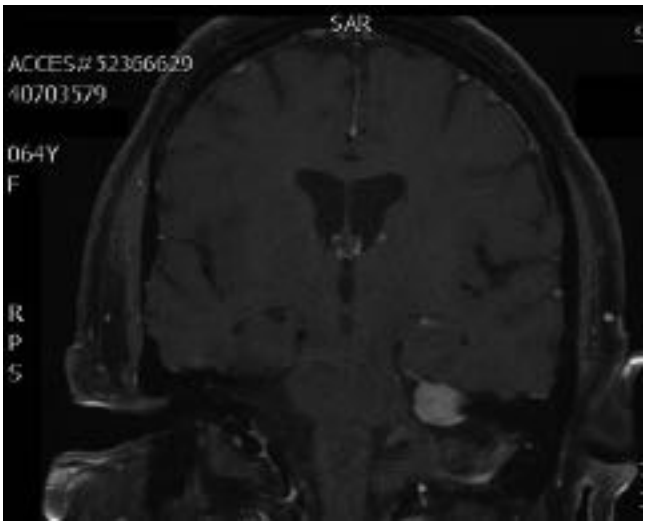


Figure 67.2 MRI scan of a patient who presented with frequent headaches and episodic vertigo but was found to have a meningioma in the cerebellopontine angle.

seen on rotation testing in around half of cases, abnormal posturography is present in around one-third and a canal paresis on caloric testing in around a quarter.[29] Vestibular-evoked myogenic potential (VEMP) abnormalities are likewise non-specific and variable.[30]

Other investigations

MRI scanning can be helpful in selected cases to look for secondary neurological disorders. In cases where the history is typical and examination findings normal, MRI scanning may not be required.

MANAGEMENT

The most important aspect of management after the correct diagnosis is a clear explanation to the patient about the nature of the condition. This is essential since the condition is frequently present over long periods and patients need to become expert in self-management of the disorder. Because migraine is usually thought of as primarily a headache disorder, careful discussion about how migraine may be responsible for vestibular symptoms is often required. The evidence base for management of VM is generally weak, and recommendations are generally made on the basis of what is known about management of other kinds of migraine.

Lifestyle

In some cases, trigger factors for migraine are clearly identifiable. These may be dietary, although there is no convincing evidence that large-scale exclusion diets are beneficial. Keeping regular sleep, exercise and meal times is advisable. In some cases patients can take action to avoid triggers, but this is not always possible (e.g. external stressors).

Drugs

ACUTE RELIEF

Migraine headache should be managed along standard lines with analgesics or migraine-specific relief medicines such as the 5HT1B/D agonists ('triptans'), taking care to avoid analgesic-overuse headache. Further up-to-date guidelines can be consulted.[31, 32] Acute symptoms of vertigo can be managed with vestibular sedatives such as prochlorperazine, cyclizine or cinnarizine. These drugs are not suitable for long-term administration. Nausea can also be relieved by vestibular suppressants; domperidone can also be used for this purpose.

PREVENTIVES

When symptoms of headache and vertigo together are sufficiently intrusive to justify the risk of adverse effects, migraine prophylactic agents can be considered. This judgement is made on an individual basis by each patient. These include propranolol, topiramate and many others. Medication can be selected according to comorbidities and individual preferences with regards to adverse effect profiles.[31, 32]

Physiotherapy

Vestibular rehabilitation can be used to manage symptoms of VM, especially head and visual motion intolerance, and associated underlying fixed vestibular deficits. Progress can be slower than in other conditions. Vestibular rehabilitation can also be associated with an increase in headache frequency, which may justify a decrease in the threshold for starting prophylactic agents.

Psychological

VM can be associated with secondary psychological effects that can be considered on neurochemical, neuroanatomical and neuropsychosocial levels. Patients with VM have higher rates of psychological symptoms than many other vestibular disorders.[33] The interaction of migraine, anxiety and vestibular symptoms is sufficiently common for the concept of migraine anxiety-related dizziness (MARD) to have been proposed.[34] Secondary psychological disorders such as anxiety and depression should be recognized and treated appropriately by medical and/or psychological means as indicated.

Other treatments

There is some evidence that acupuncture is of benefit when combined with other treatments.[35] Riboflavin, coenzyme Q10 and magnesium are all nutritional supplements with low-level evidence of efficacy in migraine.

Some of the pitfalls in effective management are given in **Box 67.7**.

BOX 67.7 Pitfalls in management

It is important to ensure patients have had adequate trials of medications before labelling them ineffective. Starting doses of drugs may not be adequate for therapeutic purposes. Patients should be supported to increase doses where appropriate.

Patients with VM can have a high rate of dropout from physiotherapy programmes due to increases in associated symptoms. The threshold for starting migraine prophylactics may need to be lowered in these patients.

Patients with unidentified and untreated secondary psychological disorders have a poorer prognosis. Consider such factors in individuals who are failing to make expected progress.

FUTURE RESEARCH

- Further work on the pathophysiology of VM is required to delineate ways in which it might be similar to or differ from other migraine subtypes.
- Genetic studies are likely to advance knowledge about pathophysiology through novel technologies such as exome sequencing.
- The evidence base for clinical trials is currently very weak, although some clinical trials have been registered and are proceeding at the time of writing.
- Due to the nature of the condition, including its episodic and unpredictable prognosis, multicentre trials are likely to be required to show adequate power.

KEY POINTS

- Vestibular migraine is a subtype of migraine in which vestibular symptoms predominate.
- Diagnosis is made predominantly on the history.
- Objective vestibular tests are usually normal although peripheral or central abnormalities can be seen in some cases.
- Management options include lifestyle modifications, medication, and physiotherapy, depending on symptom severity and frequency.

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CHAPTER 68

VESTIBULAR REHABILITATION

Marousa Pavlou

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Neurophysiological basis for vestibular rehabilitation 863
Vestibular rehabilitation interventions 864
Factors affecting outcome 868
Efficacy of vestibular rehabilitation 868
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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: vestibular rehabilitation, balance re-training, adaptation and novel techniques.

INTRODUCTION

Customized vestibular rehabilitation (VR) incorporating appropriate movements and sensory exposure is currently the standard of care for patients with peripheral vestibular disorders. Approximately 50–80% of individuals completing a customized programme achieve significant subjective symptom, dynamic visual acuity, gait and postural stability improvements.[1–5] A direct relationship has also been demonstrated between VR treatment outcome and improvements in psychological state[5, 6] and quality of life,[7–9] while specialized adjuncts to VR, such as exposure to visual motion stimuli, have been shown to significantly improve symptoms of visually induced dizziness,[5, 6, 10] which refers to symptoms of dizziness, disorientation and/or unsteadiness provoked or exacerbated in situations involving visual–vestibular conflict (e.g. walking down supermarket aisles) or intense visual motion (e.g. watching wide-screen movies).

However, despite a strong body of evidence supporting the use of VR for the management of peripheral vestibular disorders, referrals to VR remain low. A qualitative study evaluating clinicians' (neurologists, primary care, otolaryngologists) perspectives regarding the factors which influenced their management of people with vestibular disorders found that they were often unaware of the concept of VR and wanted to learn more to improve the healthcare delivery of their patients.[11] The main aim of this chapter is to provide an overview of VR including: (i) the physiologic basis, (ii) customized VR techniques including novel and supplementary techniques, (iii) factors that may affect outcome, and (iv) its efficacy for peripheral and central vestibular disorders.

NEUROPHYSIOLOGICAL BASIS FOR VESTIBULAR REHABILITATION

Habituation, adaptation, substitution and/or sensory reweighting comprise the neurophysiological basis for vestibular compensation and the improvements noted following a VR programme, with recent findings showing structural changes in grey matter volume in certain brain areas after people with vestibular neuritis have recovered functionally.[12]

Habituation is a decrease in the magnitude of the response to repetitive sensory stimuli.[13] Initial VR programmes such as the Cawthorne–Cooksey[14, 15] exercises are a type of habituation and involve repeating the provoking movement at regular intervals until symptoms are no longer experienced. However, although components of this exercises programme may still be used today, the evidence advocates customized VR programmes which focus on an individual's deficits and incorporate exercises based on multiple neurophysiological components.[2, 4, 16–18]

The vestibulo-ocular reflex (VOR) is responsible for our ability to maintain fixation on a target during head movement. The VOR functions to stabilize images on the retina during head movement by producing compensatory eye movements, simultaneously and at the same rate, in the direction opposite to head movement. Therefore the

'gain' of the VOR (eye velocity/head velocity) should be equal to 1.0. In people with a peripheral vestibular disorder, the VOR gain can be reduced, resulting in retinal image slip with visual blurring during head rotations.[19] Retinal image slip provides an error signal which generates VOR response changes that decrease (i.e. improve) the gaze error.[20–22] Adaptation exercises[23] (see 'Vestibular rehabilitation interventions' below) incorporating gaze fixation and head movements are prescribed to simulate retinal slip to promote VOR improvement with a reduction in blurring of the visual image during head movement. Recently it has been reported that, in addition to retinal slip, saccadic substitution and specifically compensatory saccades (the substitution of a saccade in the direction of the deficient VOR)[24] also contribute to improvements in VOR gain with a decrease in gaze instability.[25] The use of compensatory saccades appears to be related to the severity of vestibular hypofunction.[25]

Sensory reweighting is the central nervous system's ability to adapt its relative reliance on a specific sensory modality for orientation depending on environmental conditions, task demands and/or pathology.[6] Therefore, if a sensory input is reduced, absent or unreliable, other sensory inputs are centrally upregulated or weighted-up. For instance, in the dark or in the presence of unstable visual surroundings, when visuopostural responses are unavailable or unreliable respectively, the efficiency of vestibulo-proprioceptive responses increases whereas visuopostural responses are downregulated.[26] Similarly, a patient with uni- or bilateral vestibular failure will develop increased postural responses to visual motion stimulation.[27] It is thought that, by performing exercises in environments with altered sensory information, VR is able to affect a person's use of sensory information or sensory reweighting.[28]

Optokinetic stimulation can induce adaptation of specific vestibular parameters including VOR reflex gain in primates, healthy individuals and chronic peripheral vestibular patients.[16, 20, 29] Regarding patients' symptoms, post-rotational vestibular sensation duration also reduces in healthy subjects with exposure to repetitive, vestibular or optokinetic stimulation.[30] Short-term repeated exposure to visuovestibular exercises has been found to induce adaptive changes, decreasing (improving) the magnitude of visual dependency in healthy controls.[31] It is believed that improvements noted in visually induced dizziness following a programme of VR incorporating exposure to optokinetic stimulation is due to a decreased over-reliance on visual input for perceptual and postural responses. The underlying mechanism is likely to relate to motion-induced changes in neuronal excitability in visual motion cortical areas (V5/MT).[32, 33] PET and fMRI studies involving small or large-field optokinetic stimulation without additional vestibular stimulation note activation in cortical areas related to visual motion processing and eye movement control, and deactivation of parietoinsular vestibular cortices indicating a reciprocally inhibitory visual–vestibular interaction.[34–36] Similarly, when multisensory vestibular cortex areas are stimulated, bilateral deactivation is noted in visual and somatosensory cortex areas.[34, 37] It is suggested these interactions have a functional significance and indicate a sensory reweighting process, with greater weight given to the more reliable input thus suppressing the possible mismatch between contrasting sensory information.[36] Recurring exposure to conflicting visual input is also believed to promote reduced visual reliance and foster a more effective use of vestibulo-proprioceptive cues through sensory reweighting.[38] Overall, however, the mechanisms mediating sensory reweighting in postural control remain poorly understood.[39]

VESTIBULAR REHABILITATION INTERVENTIONS

Clinical assessment

A thorough assessment is required prior to the onset of VR. Vestibular function tests to assess for accuracy and normalcy[40] can be evaluated bedside by examination of spontaneous, gaze-evoked and positional nystagmus, dynamic visual acuity and headthrust tests.[41, 42] The recently developed Vestibular/Ocular Motor Screening test, which includes five domains (smooth pursuit, horizontal and vertical saccades, near point of convergence distance, horizontal VOR and visual motion sensitivity), is reported as a brief, sensitive vestibular/ocular screen for people with sport-related concussions that can be performed by physiotherapists.[43, 44]

The patient history will provide information regarding symptom severity, frequency, duration and triggers as well as falls history. Several validated questionnaires can aid in quantifying this information including the Vertigo Symptom Scale,[45] Dizziness Handicap Inventory,[46] Situational Characteristic Questionnaire[27, 47] and Activities-specific Balance Confidence Scale.[48, 49] A physiotherapist will also perform objective and subjective tests to identify functional deficits in people with a vestibular disorder, including the completion of questionnaires regarding perceived handicap due to their symptoms, objective static and dynamic balance tests (i.e. the modified Clinical Test of Sensory Integration and Balance (CTSIB),[50, 51] dynamic computerized posturography) and gait measures (i.e. gait speed, Functional Gait Assessment[52]).[40] Muscle strength, range of movement and sensation will be assessed and the eye, head and body movements or positions and challenging environments (e.g. visually 'busy' or unstable surroundings, irregular or compliant surfaces) which provoke symptoms will be identified in order to design an appropriate exercise programme.

Treatment goals are devised to address each person's individual subjective (i.e. dizziness, giddiness, nausea) and objective symptoms (postural and gait instability, falls). These goals often include:

- improve functional balance, gait and ability to perform daily activities
- decrease falls risk
- decrease symptom severity
- improve VOR function
- improve sensory integration and reweighting ability
- patient education.

VR should be based on the eye, head and postural exercises that provoke a patient's symptoms. Adaptation exercises (Figure 68.1)[23] incorporating gaze fixation and head movements and postural exercises are prescribed to promote recovery of VOR and vestibulo-spinal reflex function. Gaze fixation exercises are practised with varying target distances (i.e. 2 m, 1 m, 0.5 m) since VOR gain varies with target distance (closer targets require higher gains).[53] Fixation exercises are given to patients with oscillopsia and/or decreased VOR gain, most often seen in peripheral vestibular disorders.

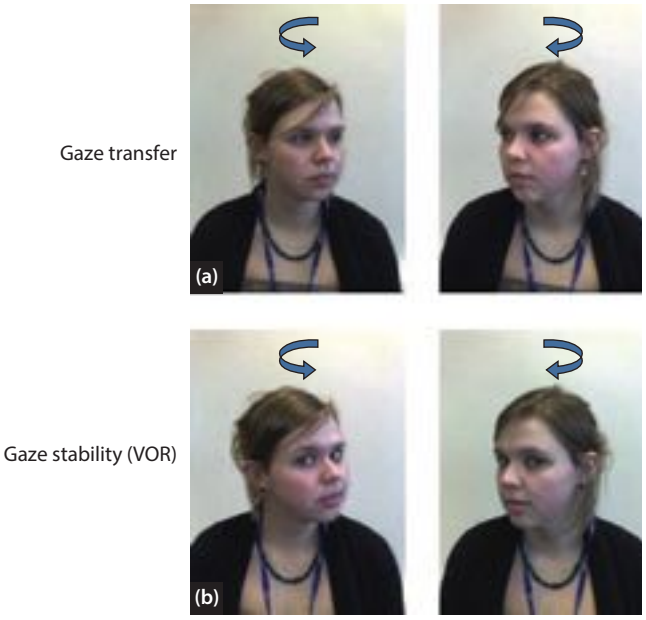


Figure 68.1 Gaze transfer and adaptation exercises[54] included within a vestibular rehabilitation programme. During 'gaze transfer' **(a)** the normal head and eye movement required for transferring gaze from one object to another is practised. The exercise can initially be practised without head movements with objects placed approximately 40 cm apart at eye level. During adaptation exercises **(b)** the vestibulo-ocular reflex (VOR) is being stimulated. This is responsible for maintaining a steady gaze on a fixated object with progressively faster head movements.

Saccades can support higher speed functional eye movements in people with bilateral vestibular hypofunction in whom the VOR gain is extremely reduced or absent.[40] Patients are asked to practise saccadic or gaze transfer exercises whereby they quickly shift their gaze between two horizontal or vertical targets. As the VR programme progresses, the complexity and difficulty of exercises should increase and therefore exercises will be practised in sitting, standing and walking on level ground or compliant surfaces (e.g. foam). Table 68.1 includes examples of commonly prescribed exercises, which can also be viewed online.[42]

Many people with a vestibular disorder will experience some level of balance and gait dysfunction. Exercises which focus on retraining postural alignment and movement strategies may need to be incorporated whereby patients learn to maintain an upright posture during progressively more difficult tasks including eyes closed and standing on compliant surfaces, with progressively reduced feedback about position.[55] The goal when retraining movement strategies is to develop those successful in moving the centre of gravity relative to a stationary base of support (ankle or hip strategy) and changing the base of support relative to the centre of gravity (stepping strategy). Retraining a coordinated ankle or hip strategy involves practising voluntary anterioposterior and lateral sway, without taking a step. Facilitating a hip strategy involves faster and larger displacements than an ankle strategy and may include activities such as tandem or single leg stance.

TABLE 68.1 Examples of commonly prescribed exercises in vestibular rehabilitation

Type of exercise	Examples
Head exercises (performed with eyes open and eyes closed)	Bend head backwards and forwards Turn head from side to side
Eye movement exercises	Head stationary follow movement of finger left and right/up and down Head movement to look back and forth between two vertical or horizontal targets
Visual fixation exercises	Perform head exercises while fixating stationary target Perform head exercises while fixating moving target
Positioning exercises (performed with eyes open and closed)	While seated, bend down to touch the floor While seated, turn to look over shoulder to left and then right Bend down with head turned first to one side and then the other Lying down, roll from one side to the other Sit up from lying supine and on each side
Postural exercises (performed with eyes open; eyes closed under supervision)	Practise static stance with feet as close together as possible Practise standing on one leg, and heel-to-toe Repeat head and fixation exercises while standing and then walking Practise walking in circles, pivot turns, up slopes, up stairs, around obstacles Stand and walk in environments with altered surface and/or visual conditions with and without head and fixation exercises Aerobic exercises, e.g. alternate touching the fingers to the toes, trunk bends and rotation

Retraining externally induced postural responses involves pushes or pulls of various amplitudes, speed and direction applied at the hips or shoulders, or the use of moving surfaces. Stepping can be practised by shifting the patient's weight to one side and then quickly bringing the centre of gravity back towards the unweighted leg, or in response to large anterioposterior or lateral perturbations. Multidirectional stepping, and stepping over a visual target or obstacle can also be practised.[55]

When the ability to select appropriate sensory input for postural stability is disrupted, exercises focus on asking patients to maintain balance in situations where the availability and accuracy of one or more sensory inputs is varied.[56] Sensory strategy retraining aims to help people with a vestibular disorder learn to effectively select appropriate sensory information for balance in various environments. Treatment focuses on maintaining balance during progressively more difficult static and dynamic balance and gait exercises while the availability and accuracy of sensory input are systematically varied. People who overrely on somatosensory cues for orientation (i.e. difficulty when walking on uneven surfaces, changing between different types of floor surface) practise tasks while sitting, standing or walking on surfaces with disrupted somatosensory cues such as compliant foam, moving platforms or tilt boards. For people with a visual dependency this involves exercises where visual input is incorrect, conflicting or absent, in order to learn to rely more on proprioceptive and available vestibular cues.[38] Guerraz et al.[27] suggested that rehabilitation programmes promoting desensitization and increased tolerance to visual stimuli through exposure to visual motion (i.e. optokinetic stimulation) would be specifically beneficial for patients with visual vertigo (VV). Advanced techniques in VR incorporate exposure to optokinetic stimuli[5] (**Figure 68.2**) or virtual reality[57] (**Figure 68.3**) environments. When the optokinetic stimulation has been incorporated into both the treatment session and the home programme, improvements have been noted in postural and gait stability, visually induced dizziness and psychological state, including depression and anxiety.[5] Easily accessible and economical computer games, YouTube videos or a DVD including visual stimulation recorded from the clinical equipment (i.e. optokinetic test in neuro-otology departments)[58] can also be used. Regardless of the type of optokinetic or virtual reality stimulus employed, exposure should be gradual and progressive.

People with a vestibular disorder may complain of poor concentration and memory impairment and a cognitive–vestibular function interaction has been highlighted in this population.[59] People with a vestibular disorder appear to have decreased attentional resources available when simultaneously performing a cognitive and posture or gait task (i.e. dual tasking) with priority given to maintaining the motor task to the detriment of performance on the cognitive task.[60, 61] Postural studies in standing, though, show varying results with regards to the effect of an additional cognitive task on postural sway, with some reporting that



Figure 68.3 Four aisles from a virtual reality supermarket,[57] showing a progression in visual complexity.

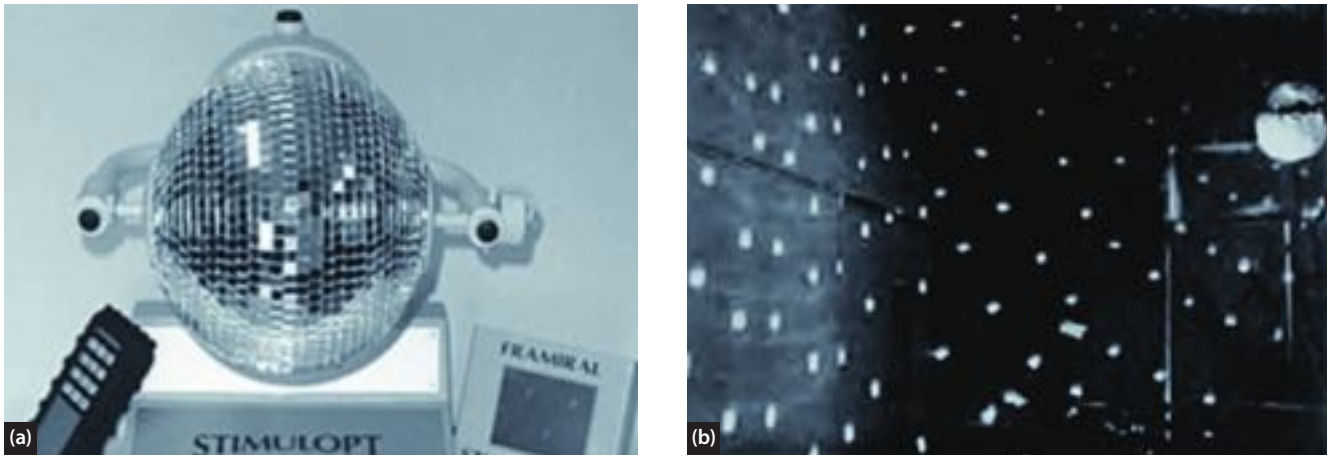


Figure 68.2 Apparatus used for full-field optokinetic stimulation-based intervention.[5] (a) A photo of the visual environment rotator apparatus (Stimulopt, Framiral, France). **(b)** Participants are asked to stare ahead while the apparatus rotates in different directions and at differing speeds. Participants practise exercises in sitting, standing and walking either towards and away from the stimulus or alongside it with or without vertical or horizontal head movements.

sway increases (i.e. worse),[62] decreases (i.e. improved)[63] or no change.[61] The disparate findings may be due to variations in task difficulty as well as the ability to isolate obvious sensory mismatches so they do not draw on attentional resources.[64] More recent studies investigating gait performance while performing a simultaneous cognitive task (dual-task) consistently show a significantly decreased gait speed[65, 66] and greater ataxia and deviation from a linear path[65] in this population when dual-tasking. Although no studies have specifically assessed the impact of incorporating dual task training within a VR programme, findings in older adults with increased falls risk show an increase in dual-task gait speed after training[67] and clinicians often include dual-task training into VR programmes when a functional deficit is noted in this area. Dual-task training involves practising progressive balance exercises (e.g. tandem standing or walking with or without upper limb activities) while simultaneously performing a secondary task such as counting backwards by 3s, recounting daily activities.[68] During training patients are asked either to constantly maintain attention on both tasks or to focus attention on one of them.[69]

Motor, sensory and cognitive strategy retraining should occur in parallel rather than sequentially. General characteristics of VR include specificity, repetition, progression, and patient education, for example explaining that initially symptoms may worsen, and improvement may be uneven. Patients should be aware that, even after symptoms have largely resolved, a temporary reoccurrence may occur during periods of stress, fatigue or illness. Patients should be advised to stop exercising and seek advice if they experience neck pain, loss of consciousness or vision, sensations of numbness, weakness or tingling in the face or limbs, or increased migraine frequency.

Novel and supplementary techniques

Various authors have discussed the potential benefit of virtual reality as a therapeutic protocol to improve postural and gait stability, VOR gain and subjective symptoms.[68–70] Two studies using a limited field-of-view head-mounted device noted improvements in VOR gain and symptoms in patients with a peripheral vestibular disorder.[69, 71] Two randomized controlled trials comparing customized VR versus virtual reality-based VR reported no significant pre–post treatment between-group differences in gait speed, functional gait performance, computerized dynamic posturography or subjective symptoms despite one study using a full-field immersive virtual environment consisting of a grocery store model[56] while in the other the low-cost Nintendo Wii Fit Plus® was employed (**Figure 68.4**).[72] The lack of difference in findings between the customized vestibular rehabilitation exercises versus virtual reality based rehabilitation in the two aforementioned studies[56, 72] may be due to the fact that both small- and large-field optokinetic stimulation shows similar reciprocally inhibitory visual–vestibular interactions, indicating that sensory reweighting occurs independently of visual field size and other factors including frequency,



Figure 68.4 A patient practising a balance exercise using the Nintendo Wii Fit Plus® system.[73]

velocity, texture, stimulus area and position within the visual field.[34–36, 73] Pavlou et al.[5] reported that this may explain why significant improvements were noted for both full and limited field-of-view optokinetic stimulation without significant between-group differences in their study. However, it should be noted that virtual reality systems may provide a more enjoyable rehabilitation method to re-train balance.[72]

Sessoms et al.,[74] however, reported that 12 sessions virtual reality exposure without additional VR provided greater benefit in gait speed and weight shift in people with traumatic brain injury (TBI) and vestibular dysfunction compared to virtual reality (6 sessions) plus VR (6 sessions). It is important to note that balance and vestibular exercises were practised during exposure to the virtual reality environment, thus providing multidimensional tasking. This provides a form of VR that is more demanding and may possibly be more appropriate than traditional techniques for people requiring more challenging tasks and who are required to operate at a higher level of performance in their profession (athletes, military servicemen).[75]

Current literature therefore suggests that virtual reality is beneficial and may offer a more enjoyable exercise method, particularly with regards to the Nintendo Wii® system.[73] Further work is needed, however, to identify the specific role of virtual reality within VR, particularly with regard to the patient groups for whom it is most suitable and to the optimal virtual reality format.

FACTORS AFFECTING OUTCOME

The relationship between psychological and dizziness symptoms is well documented as is the significant correlation between depression and anxiety in people with vestibular dysfunction.[82, 83] People who experience higher levels of somatic anxiety report greater handicap[84] and show a delay in recovery.[85] Every effort should be made to identify and act on these negative factors, referring the patient for counselling and/or adding psychopharmacological medication as appropriate. Studies combining VR with explicit cognitive behavioural therapy demonstrate improvements in patients' ability to cope, function, subjective symptoms and satisfaction with care.[86, 87] However, the clear additional effect of combining cognitive behaviour therapy with VR remains unknown.

People with peripheral or central vestibular disorders may experience visuomotor symptoms, such as oscillopsia or diplopia, which are capable of disrupting recovery and rehabilitation. Rehabilitation specialists should enquire directly about such symptoms. It has recently been reported that binocular vision abnormalities may affect the improvement of visually induced dizziness symptom improvement and these findings may have important implications for the management of subjects with refractory vestibular symptoms.[88] Clinicians need to be aware of the possible negative effect of this type of binocular abnormality on visually induced dizziness treatment outcome in order to manage their own and the patient's expectations from treatment.

Patients with vestibular migraine can adhere to and benefit from VR.[5, 89, 90] However, Bronstein and Pavlou[55] reported that, in their experience of treating patients with migraine-associated dizziness, an initial exercise programme including fewer exercises (i.e. three maximum) is better tolerated and adhered to. The exercises should be practised only once daily initially and gradually increased to twice daily. As symptoms and tolerance improve the number and total duration of daily exercises progressively increases. It is important for improvement to be noted with exercises such as those in **Table 68.1** before progressing to the inclusion of optokinetic stimuli.

Other factors that may impact on VR treatment outcome are listed in **Box 68.1**.

BOX 68.1 Factors that may delay vestibular compensation (adapted from Bronstein and Pavlou)[56]

- Fluctuating vestibular disorder (i.e. Ménière's disease)
- Migraine
- Additional disorder:
  - CNS
  - Peripheral nerve
  - Cervical spine
  - Visual (reduced visual acuity, modified optics (e.g. cataract operation), strabismus, diplopia)
- Age
- Lack of mobility (orthopaedic problem, forced bedrest, psychological/fear)
- Medication (antivertiginous drugs)
- Psychosocial
- Visually induced dizziness

EFFICACY OF VESTIBULAR REHABILITATION

VR, in the form of appropriate movements and sensory exposure, is currently the standard of care for patients with peripheral vestibular disorders regardless of age and symptom duration.[2, 4, 5, 91] Customized VR programmes provide greater benefit than generic ones (Cawthorne–Cooksey).[2, 4, 5, 91, 92] A recent Cochrane review and other systematic reviews have validated the safety and effectiveness of VR for the management of unilateral vestibular dysfunction.[93, 94]

People with bilateral vestibular hypofunction have an increased falls risk[95] and in one study a significant percentage of participants reported that they had to alter or change their professional activities and/or required the presence of another person due to the level of disability they experienced.[96] However, a number of studies have reported significant improvements in gaze, postural and gait stability, balance confidence, subjective symptoms and perceived handicap from dizziness in people with bilateral vestibular hypofunction,[1, 4, 97] with a systematic review stating that there is moderate strength evidence to support VR for improvements in gaze and postural stability but further work is need to identify its benefit for International Classification of Functioning, Disability and Health (ICF)–Participation outcome measures.[98]

In people with Ménierè's disease, management has been challenging due to recurring vertigo episodes. Long-term management may include dietary changes (low salt), medications (betahistine, steroids) and/or ablative therapy (e.g. intratympanic gentamicin administered to the affected ear).[99] Specifally for VR, significant improvements in postural stability, subjective symptoms and quality of life have been noted with customized VR physical exercises[2] or incorporating balance exercises with exposure to a virtual reality platform.[100] In the study by Garcia et al.,[100] participants in both the control and treatment groups had been given dietary recommendations and prescribed 48 mg/day of betahistine, however improvements were only noted in the treatment group.[100]

Some studies report similar responses for patients with peripheral, central and mixed pathology, but others claim poorer outcomes for the latter two groups. Differing results may be due to individual study variations regarding treatment duration (patients with central deficits are expected to require a longer duration for improvement), extent and location of central deficit (cerebellar dysfunction appears to reduce the effect of rehabilitation) and any additional cognitive or neuromuscular deficits.[101] Cerebellar and vascular disease, migraine and traumatic brain injuries (including concussion) are examples of central vestibular disorders associated with dizziness.

Current evidence suggests that VR can improve dizziness, gait and postural stability after mild traumatic brain injury (or concussion).[102, 103] In people with persistent neck pain, headaches and/or dizziness following a sports-related concussion, the time to return to sport is reduced following a programme of VR combined with cervical exercises.[104] McCulloch et al.[105] published clinical guidelines for rehabilitation providers regarding progressive return to activity after military mild traumatic brain injury and VR was recommended for those experiencing persistent dizziness and/or balance symptoms.

As stated above, people with vestibular migraine benefit significantly from a VR programme.[88, 106, 107] Patients with vestibular migraine or migraine history and a peripheral vestibular disorder can also tolerate and benefit from customized VR incorporating optokinetic exposure; surprisingly, migraineurs report significantly greater improvements for visually induced dizziness compared to non-migraineurs.[5] It has been suggested medication may help control visually induced dizziness symptoms in migraineurs, enabling them to better tolerate the exercises and thus leading to greater improvement.[89] However, Vitkovic et al.[107] reported that a 6-month VR programme without optokinetic exposure showed similar improvements in both participants with vestibular migraine and those with vestibular symptoms without migraine and, for the former, improvements were noted regardless of medication regime, although medication was not controlled for.

FUTURE RESEARCH

Further work is needed regarding:

- optimum interventions
- treatment duration
- long-term outcome
- the efficacy and potential benefit of novel techniques, i.e. virtual reality.

KEY POINTS

- VR is the mainstay of treatment for people with peripheral vestibular disorder.
- Evidence is emerging for its benefit in people with central vestibular disorders, particularly mild traumatic brain injury.
- VR should be informed by assessment and individually designed based on each person's impairments.

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CHAPTER 69

AUDITORY NEUROPATHY SPECTRUM DISORDER AND RETROCOCHLEAR DISORDERS IN ADULTS AND CHILDREN

Rosalyn A. Davies and Raj Nandi

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SEARCH STRATEGY

Data in this chapter may be updated by Medline and PubMed searches using the keywords 'auditory neuropathy', 'auditory neuropathy spectrum disorders', 'retrocochlear hearing loss' and 'auditory dyssynchrony'.

AUDITORY NEUROPATHY SPECTRUM DISORDER

Auditory neuropathy spectrum disorder (ANSD) is a specific form of hearing impairment when the patient can hear the sound of speech but has difficulties understanding the words. In infants, this problem understanding speech leads to difficulties developing speech. ANSD is caused by pathology in the inner hair cells of the cochlea or the auditory nerve and its synapses (i.e. 'neural' hearing loss). One of the major features of ANSD is that testing frequently shows pure-tone audiometric thresholds that are relatively well preserved but speech thresholds that are markedly impaired. It is in this context that the acoustic brainstem-evoked response (ABR) is performed and often found to be delayed or absent. Thus the concept of auditory dyssynchrony has arisen, i.e. the loudness of sound is relatively well perceived but the synchronization of acoustic signals is not adequate to evoke an ABR, or to elicit the stapedius reflex, or to suppress the contralateral otoacoustic emissions (OAEs). Because this synchronization requires the integrity of the VIIIth nerve, these causes of hearing loss were first described in the literature as 'auditory neuropathy' then 'auditory neuropathy/dyssynchrony', but since 2008 have been referred to as 'auditory neuropathy spectrum disorder' (ANSD).

The hearing difficulty in ANSD is typified by a characteristic pattern of abnormalities on audiological testing:

- normal to raised pure-tone auditory thresholds
- poor speech discrimination
- delayed, or absent, ABRs
- normal OAEs and cochlear microphonics.

There are many causes of ANSD and it is only with recent developments in assessing the function of cochlear receptor elements (inner and outer hair cells) that a finer definition of ANSD and a more accurate classification of aetiological factors have been possible.

Historical perspective

INCONSISTENT MEASURES OF HEARING

The term 'auditory neuropathy' arose as a way of grouping together those hearing disorders where observations of inconsistent measures of hearing are made, i.e. where hearing sensitivity is better than might be expected from the ABRs. The first publications presenting these paradoxical findings of absent ABR and behavioural audiometry[1–4] described children who responded behaviourally to moderate- or low-intensity sounds but had absent ABR.

PRESENCE OF OTOACOUSTIC EMISSIONS AND COCHLEAR MICROPHONICS

The first report of a further inconsistent test abnormality which helped to define both the concept and the diagnosis of neural synchrony disorder, came in 1991.[5] An 11-year-old boy was described with the characteristic findings of absent event-related potentials and acoustic reflexes with poor performance on temporally based psychoacoustic tests, but who had present click-evoked OAEs and cochlear microphonics. These latter two findings strongly pointed to normal preneural hearing. Further papers confirmed the presence of OAEs[6,7] in similar patients. One of these studies describes four infants in a special care baby unit who failed the ABR test but passed the click-evoked OAE screen. These infants were found in a series of 100 neonates admitted to the ITU. By following the infants, they observed that two out of the four showed normalization or reversal of the ABR abnormalities, but the other two retained their abnormal ABR. They concluded that, in instances where either no response or early waveforms only were obtained, ABR was insufficient as the sole evaluator of hearing sensitivity. They recommended concomitant use of behavioural audiometry with ABR and OAEs, and the importance of follow-up to guard against inappropriate diagnoses of cochlear hearing loss (see below).

SEQUENCE OF NAMES USED TO IDENTIFY THE DISORDER

'Auditory neuropathy' (AN) was first used as a clinical term by Starr and others in 1996[8] to describe patients whose hearing impairment was attributed to 'neuropathy of the auditory nerve'. Their hearing dysfunction was characterized by absent or disordered ABR in the presence of normal, even robust, preneural responses evidenced by the recording of normal OAEs or cochlear microphonics (CMs) in the same patients. The concept of 'auditory neuropathy/dyssynchrony' (first coined in 2001[9]) has challenged thinking about the physiology of hearing, and has provided a model for examining the role of neural synchrony of the VIIIth nerve and brainstem, and its impact on auditory perception. In 2008, after extensive review,[10] the term auditory neuropathy spectrum disorder was first adopted as a way of describing the heterogeneous and multifaceted nature of this disorder and the different ways ANSD affects patients, with symptoms ranging from very mild to very severe.

Further study has permitted the characterization of this group of disorders, and better assessment of these patients. These cases are now recognized as relatively common (5–12% of those previously considered to have severe to profound hearing loss in paediatric populations,[11,12] with an estimated 1 in 7000 of neonates, assessed by universal newborn hearing screening,[13] showed abnormal VIIIth nerve function) and probably represent a heterogeneous group where the common feature is disordered temporal processing (i.e. synchronization of sound). Progressive AN is reported in association with age-related degenerative changes, toxic effects of noise, mitochondrial, genetic and autoimmune disorders, etc.[14] The first large series[15] identified 49 cases from 543 patients who had either no ABR response or absent waves III and V. In seven patients, the audiometric data ranged from normal hearing to moderate impairment, i.e. 14% had better hearing sensitivity than might have been expected from their ABR, which was completely absent in these cases. Each of these seven patients also had abnormal acoustic reflex findings. Although the range of deficits as identified on medical, behavioural and electrophysiological testing was variable, there were many common features, including perinatal insults such as perinatal asphyxia, hyperbilirubinaemia or head injury. Tests of psycholinguistic abilities revealed significantly worse performance in auditory as compared to visual tasks, and speech discrimination testing revealed worse scores than would have been predicted from the patient's hearing thresholds in the majority.

Causes of auditory neuropathy

In classifying the causes of auditory neuropathy, Table 69.1 identifies those aetiologies that are genetic or acquired congenitally, and Table 69.2 identifies those that are acquired postnatally, including causes of retrocochlear hearing loss.[16] It should be remembered that some of the genetic causes only present with hearing impairment in adulthood, and so the tables do not differentiate 'paediatric' from 'adult' hearing disorders. The evidence for these aetiologies to be included in the tables is given by the references cited in the tables. The majority of the references are individual, or a series of, case reports with audiological, electrophysiological, imaging and in some papers histopathological evidence for a nerve VIII or brainstem cause of hearing impairment.

Starr[52] suggests an aetiological classification of AN that distinguishes between presynaptic and postsynaptic lesions. He suggests the following 'groupings' of AN:

- **Type I postsynaptic AN:** plus vestibular and peripheral neuropathies, e.g. Charcot–Marie–Tooth disease
- **Type I postsynaptic AN:** plus optic nerve disorders accompanying nuclear and mitochondrial mutations, e.g. Leber's optic atrophy, Wolfram syndrome (or 'DIDMOAD')
- **Type II presynaptic AN:** inner hair cell and neurotransmitter disorder, e.g. AN seen in otoferlin and *GJB6* mutations
- **AN unspecified:** affected sites unknown.

However, there is evidence to suggest that AN associated with specific gene mutations may change or progress to involve both pre- and postsynaptic locations. For example, patients with mutant *OPA1* gene show demyelination and axonal loss in advanced stages of disease and patients carrying the *DIAPH3* mutation show progressive deterioration of hearing thresholds from moderate to profound with gradual disappearance of OAEs.[53] Various types of genetic

TABLE 69.1 Genetic and congenital causes of auditory neuropathy

Genetic causes		
Non-syndromal	Non-syndromal recessive auditory neuropathy due to mutations in the otoferlin gene,[1, 17, 18] mutations in the pejvakin (*DFNB59*) gene[19] and in the connexin 26 gene[30] Non-syndromal autosomal dominant auditory neuropathy due to mutations in the *AUNA1* and *PCDH9* genes[20] Non-syndromal X-linked recessive auditory neuropathy due to the *AUNX1* gene[20]	
	Delayed maturation of auditory pathways[2]	
Syndromal	Degenerative conditions, with peripheral neuropathy	Hereditary sensory–motor neuropathy (HSMN), i.e. Charcot–Marie–Tooth[21]
		Friedreich's ataxia[22, 23]
		Roma (gypsy) families[24]
		Refsum disease[20]
	Degenerative conditions, without peripheral neuropathy	Usher syndrome[25]
		Mitochondrial myopathies: • MELAS[10] • chronic progressive external ophthalmoplegia[26, 27] • Mohr–Tranebjaerg syndrome 'deafness/dystonia peptide'[28]
Congenital causes		
Toxic/metabolic		Perinatal risk factors:[11, 29] • asphyxia • respiratory distress syndrome • low birthweight • cerebral palsy • hyperbilirubinaemia

TABLE 69.2 Acquired causes of auditory neuropathy and retrocochlear hearing loss

Acquired causes		
Infection	Viral	Herpes zoster/herpes simplex: • Ramsay Hunt[31, 32] • Bell's palsy[32]
		CMV[33]
		HIV/AIDS[34]
	Bacterial, fungal/ spirochaetal	Basal meningitis:[35, 36] • pneumococcal • meningococcal • haemophilus • tuberculosis • cryptococcosis • coccidiomycosis
		Syphilis
		Borrelia[37]
Immune-mediated	Post-infective	Guillain–Barré
	Vasculitic/ granulomatous	SLE, rheumatoid arthritis, sarcoid, Behçet's
Demyelination	Multiple sclerosis:[38, 39, 50–51] • VIIIth nerve • brainstem	

(Continued)

TABLE 69.2 ***(Continued)*** Acquired causes of auditory neuropathy and retrocochlear hearing loss

Acquired causes	
Neoplasia/ neoplasia-related	Vestibular schwannoma[40] Meningioma Cerebellopontine angle lesion
	Carcinomatosis[41]
	Radiotherapy
Metabolic/toxic	Uraemia[42]
	Paget's disease[43]
	Organic mercury[44]
	Cisplatin[45]
	Haemosiderosis[46]
Vascular	?Migraine[47]
	Posterior inferior cerebellar artery syndrome (PICA)
	Macrovascular:[48, 49] • posterior fossa aneurysms • AV malformations • vascular loops

mutations in AN result in different pathological changes in the auditory system as discussed by Manchaiah et al.[20] For example, the *AUNA1* gene is associated with changes in the distal auditory nerve, including dendrites and inner hair cells, the *OTOF* gene is associated with changes

mostly within the inner hair cells, the *AUNX1* gene results in demyelination and axonal loss of the auditory fibre, the pejvakin/*DFNB59* mutation is responsible for pathology in neural cell bodies in the auditory pathway from the spiral ganglion to the inferior colliculus causing degraded neural function, the *MPZ* mutation is associated with loss of auditory nerve fibres and ganglion cells and the *GJB2* mutation causes impairment of inner hair cells/synapses and/or auditory nerve terminals.[30]

Clinical presentation

Perhaps one of the more helpful ways of understanding the complaints of patients with AN is to consider the description given in an early account of patients with this disorder.[54] The case is of a young girl called 'Eve', who was identified at the age of 8 years because she had difficulty following her teacher's instructions at school and did not improve when placed in the front row of the class. She had measures of pure-tone hearing and ABR that were inconsistent with each other. Her evoked responses, both middle latency and cortical, were absent and tests of auditory processing were especially affected, but her hearing thresholds suggested better hearing than these would imply. Her comments prior to implantation were recorded as follows:

'seeking
so
desperately
to
underSTAND

The calls, the bangs, the thumps, the beats…

HEARING
FEELING

but never *TRULY* comprehending'

The common clinical features of patients with AN are that their hearing difficulties are worse with speech than with simple environmental sound, and using the telephone causes particular difficulty. Patients complain that they can identify the speech sounds and the language used, but they cannot understand the words. Their difficulties are always more marked in noisy environments when there are competing signals. The effect of an AN can be thought of as causing a 'time-smear' of sound. The severity of the hearing impairment may be variable (see **Figure 69.3**) and can range from transient, intermittent, to stable and deteriorating.

Pathophysiology

AN shows some features similar to other peripheral neuropathies. The latter have: (i) elevated thresholds for sensation; (ii) altered perception (paresthesia); (iii) rapid adaptation to stimuli; (iv) absent or hypoactive deep tendon reflexes. By comparison, patients with AN have varying degrees of elevation in pure-tone thresholds[55] (see (i) above); have altered perception of hearing (see (ii) above); exhibit absent acoustic middle ear reflexes (see (iii) above); have disordered or absent auditory nerve conduction (see (iv) above).

PHYSIOLOGY

In the physiology of audition, sound energy is transduced to electrical stimuli in the cochlea and transmitted via the auditory nerve. The inner hair cells in the organ of Corti (see **Figure 69.1**) are responsible for this transduction process as has been shown by Russell and Sellick[56] who first demonstrated the importance of the inner hair cells in this process. The afferent auditory nerve consists of 95% type I myelinated nerve fibres (with many type I nerve fibres innervating one inner hair cell), and 5% type II nerve fibres (each type II nerve fibre innervating many outer hair cells (OHCs)). The cell bodies of both these types of bipolar neurons lie in the spiral ganglion. The arrangement of type I neurons in relation to inner hair cells is conducive to synchronous neural impulses whereas the arrangement of type II neurons is not.[57] Thus these respective neural anatomical arrangements have implications in relation to the diagnosis of AN, where it is proposed that the afferent neural pathway is involved (**Figure 69.1**).

The auditory nerve is a myelinated cranial nerve, with the myelin in the distal portion of the nerve being derived from Schwann cells (which are responsible for myelination of peripheral nerves), while that more proximally is derived from the oligodendroglia (cells supplying myelin in the central nervous system). The change between the two different types of myelin occurs as the auditory nerve exits the internal auditory meatus at the porus acousticus. Neuropathies affecting the auditory nerve are considered to be due to either demyelination (see below) or axonal degeneration.

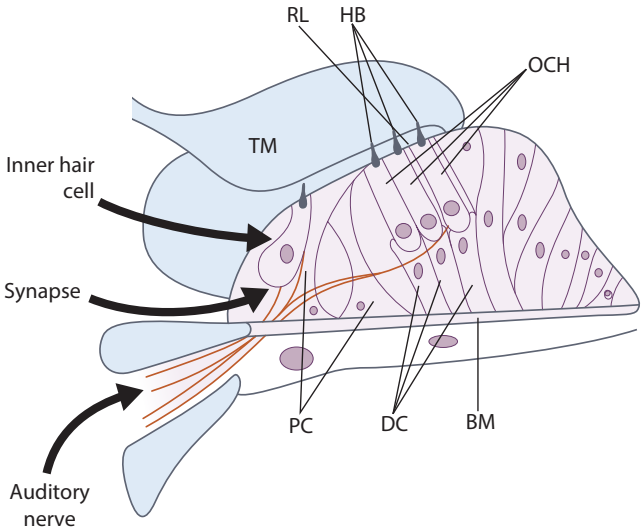


Figure 69.1 Diagram depicting proposed sites of lesion in auditory neuropathy. BM, basilar membrane; DC, Deiter's cells; HB, Habenula perforata; OHC – outer hair cell; PC, Pillar cells; RL, Reticular lamina; TM, tectorial membrane.

A combination of the two can also occur. The two functional consequences of these processes are a disruption of temporal synchrony of the auditory neural signals due to demyelination and a reduction of amplitude of neural signals because of axonal loss respectively. It is proposed that loss of neural synchrony (as can happen with demyelination) causes auditory nerve signals to be out of phase with the acoustic stimulus such that an averaged auditory brainstem response is not detected. Furthermore, dyssynchrony causes temporal tasks of audition to be disrupted (as tested by gap detection, localization and low-frequency pitch discrimination).[57, 58] Additionally, axonal loss results in reduced auditory neural input and therefore is also implicated in the absence of ABR recording, the loss of acoustic middle ear reflexes and disruption of temporal processes.

Demyelinating pathology results in the loss of the normal, rapid, 'saltatory' conduction of action potentials from one node of Ranvier to the next along the nerve fibre. This results initially in a conduction block where action potentials diminish to such an extent that the onward propagation of the neural impulse is halted. Over time the voltage-sensitive sodium channels (which are normally concentrated at the nodes of Ranvier) diffuse into the axon shorn of myelin, allowing for slow propagation of action potentials and hence slow neural impulses. Further, demyelination has been shown to cause increased sensitivity of nerve fibres to temperature increases, explaining cases of temperature-sensitive auditory neuropathy.[57] Finally, demyelination causes ephaptic transmission or 'cross-talk' between adjacent nerves that has the potential to interfere with synchronous auditory signals essential for understanding complex sounds such as speech.

Site(s) of lesion

It is now generally agreed that the term 'auditory neuropathy' encompasses heterogeneous conditions where the site of lesion may occur anywhere along the auditory pathways from the inner hair cells (IHCs) of the cochlea distally, through to the auditory brainstem pathways centrally (the afferent auditory pathway) (**Figure 69.1**). There is evidence accumulating to indicate at least three different sites of dysfunction:

- electromechanical transduction at the IHCs (including synaptic transmission)
- axons, cell bodies and myelin sheaths
- efferent influences through the olivocochlear feedback pathways.

ELECTROMECHANICAL TRANSDUCTION AT THE INNER HAIR CELLS

IHC disorders have been studied in animals[60] and have shown that anoxia and toxic agents (e.g. cisplatin) selectively impair IHC function, effectively removing the transduction process, including the release of neurotransmitters. Using the chinchilla animal model, scattered IHC loss (replicating the effects of sustained hypoxia) was induced, and OAEs, ABR thresholds and single unit tuning curves recorded at the inferior colliculus in the midbrain were measured. IHC damage correlated with ABR signal changes, but it was noted that individual inferior colliculus neurons had relatively normal thresholds across the frequencies, despite the loss of IHCs. This suggested that the number of active neural elements was reduced to the point that the remotely recorded compound action potential was reduced in amplitude. The single unit data was interpreted as implying that low threshold information was nonetheless reaching the central auditory system, and hence the dissociation of ABR and inferior colliculus neural thresholds. Extrapolating, it was suggested that patients with scattered IHC loss would have a reduced number of 'information channels', and therefore the speech information transferred to the brain would depend on the amount of redundancy in the system. However, studies of adult temporal bones have not shown isolated IHC loss.[61] [Level 1 evidence]

An excess of neurotransmitters, i.e. an infusion of synaptic agonists, has been shown to cause attenuation of auditory nerve activity.[57] A disorder affecting the synapse between the IHCs and the dendrites of the auditory nerve could account for many of the electrophysiological features of an auditory neuropathy. The disorder could be pre- or postsynaptic, affecting the release of neurotransmitters from the IHCs or their receptor sites on the dendritic cells. In neonates with an abnormal ABR release of neurotransmitters is deficient from ribbon synapses due to deficient ion vesicle turnover and acquired excitotoxic effects of noise damage on these synapses with subsequent neural degeneration.

The effect of stimulus rate on the ABR may be a useful tool in investigating synaptic dysfunction. In healthy controls, an increase in stimulus repetition rate results in an increase in the latency and decrease in the amplitude of wave I. Electrocochleography (ECoG) has also been used to identify presynaptic versus postsynaptic lesions in auditory neuropathy. Prolonged summating potential (SP) latencies indicated a presynaptic lesion whereas a normal latency SP often followed by a negative 'dendritic potential' (DP) was associated with a postsynaptic lesion. Electrically evoked auditory brainstem response (EABR) measured following cochlear implantation showed a normal EABR waveform in patients with prolonged SP on ECoG (presynaptic lesion) while EABR waveforms were either absent or of poor morphology in patients whose SP on ECoG had a normal latency with evidence of DP (postsynaptic lesion) (**Figure 69.2**).[62]

AXONS, CELL BODIES AND MYELIN SHEATHS

There are 30 000 auditory nerve fibres, most of which have diameters of approximately 3 µm. Type I nerve fibres, which innervate IHC, make up 95% of the afferent fibres, with 10–30 neurons innervating each IHC. Type II nerve fibres make up the remaining 5%, each one making contact with many outer hair cells (OHCs) (see above). These nerve fibres are myelinated bipolar neurons with their cell bodies in the spiral ganglion.

Distinguishing whether a neuropathy is principally demyelinating or axonal in type is primarily determined

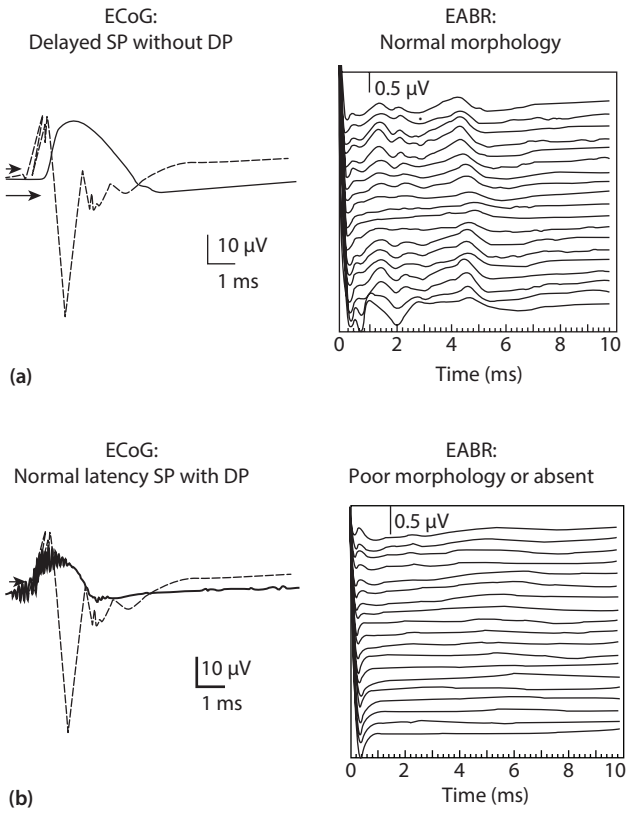


Figure 69.2 Precochlear implantation ECoG waveforms compared with postcochlear implantation EABR showing correlation between **(a)** delayed SP and normal EABR (presynaptic lesion) and **(b)** normal latency SP with DP and absent or poor morphology EABR (postsynaptic lesion). Redrawn with permission.[60]

histologically following biopsy, clearly not a procedure applicable to the auditory nerve. In the circumstances, electrodiagnostic studies (nerve conduction studies) can provide a functional categorization for the type of neuropathy. A patient with late-onset HSMN, beginning at age 40, and presenting with a hearing loss 10 years later, came to autopsy at the age of 77 years. Histopathological examination of both auditory and sural nerves showed a significant loss of nerve fibres more extensive in the sural nerve than in the auditory nerve. Photomicrographs of a section of the patient's auditory nerve and an age-matched control showed an extensive loss of large nerve fibres in the former. This woman's neuropathy was inherited in an autosomal dominant fashion, with genetic analysis of the affected members of the pedigree showing a duplication disorder on the *MPZ* gene of chromosome 1. The *MPZ* gene (myelin protein zero) was the first gene associated with auditory neuropathy in patients with Charcot–Marie–Tooth disease (CMT). The *MPZ* gene codes for a protein required for myelin formation and adhesion. Preserved cochlear hair cells were found on postmortem examination of a patient with CMT together with decreased spiral ganglion cells and degeneration of the residual axons. The proximal auditory nerve showed axonal loss and incomplete myelination at the entrance to the brainstem. [Level 1 evidence]

EFFERENT INFLUENCES THROUGH OLIVOCOCHLEAR FEEDBACK

Auditory efferent fibres travel from the olivocochlear bundle in the midbrain through the VIIIth nerve to the cochlea. Studies of the effects of the efferent pathway have demonstrated a reduction in the compound action potential (CAP) following electrical stimulation of the olivocochlear bundle in humans.[63–65] The contralateral pathway involves only crossed afferent fibres and is believed to mediate the suppression of OAEs in the presence of noise.[65] The ipsilateral pathway to the OHCs, however, involves crossing of both the efferent and afferent fibres. The suppression of OAEs in the presence of noise is known as the medial olivocochlear reflex, and has been studied in detail[65–67] showing the greatest suppressive effect in the 8–18 ms time period in the lower frequencies with low-intensity stimuli and with binaural noise (using a forward masking paradigm).

Two patients with AN, followed for some time, showed robust OAEs but, in both, contralateral noise failed to suppress their OAEs.[66] Three 'foil' subjects were chosen as controls: one with a similar audiogram to patient 1, one with a Bell's palsy and absent stapedius reflex thresholds (i.e. absent middle ear muscle reflexes), and one with bilateral temporal lobe disease. Testing of the 'foil' subjects showed that isolated normal hearing at 2 kHz, absent middle ear reflexes and conscious cortical awareness of sound did not contribute directly to the lack of efferent suppression.

Their suggestions to explain this included:

- deficiency of synchronous activation of type I afferent fibres (originating at the base of the IHCs), so they cannot activate efferent feedback
- restriction to only using type II afferent neurones (originating at or near the OHCs) to support normal zones of pure-tone sensitivity.

Discharge of primary neurons, synchronized by a primary deficit in the efferent system, has largely been discounted following studies on patients with unilateral auditory neuropathy,[67] where the function of the efferent system on the side with the profound hearing loss has been demonstrated to be functional (i.e. OAEs on this side can be partially suppressed by noise to the good ear). The efferent system requires input from the afferent system to be activated. The two patients above show the effects of disconnecting the afferent system from efferent stimulation and revealing this disconnection by leaving the patients with an absence of both static (middle-ear mediated) and dynamic (medial olivocochlear system mediated) efferent suppression.

Test battery

- Baseline audiometric tests
  - Pure-tone audiogram
  - Tympanogram
  - Stapedius reflex thresholds

- Electrophysiological tests
  - ABRs
  - ECoG
  - CMs
  - OAEs, both with and without contralateral suppression
  - Middle latency responses (MLRs)
  - P300
- Behavioural auditory tests
  - Speech recognition tests
  - Temporal pattern tests:
  - frequency pattern tests
  - temporal gap detection

Figure 69.3 shows a range of test results from a 7-year-old male patient with auditory neuropathy.

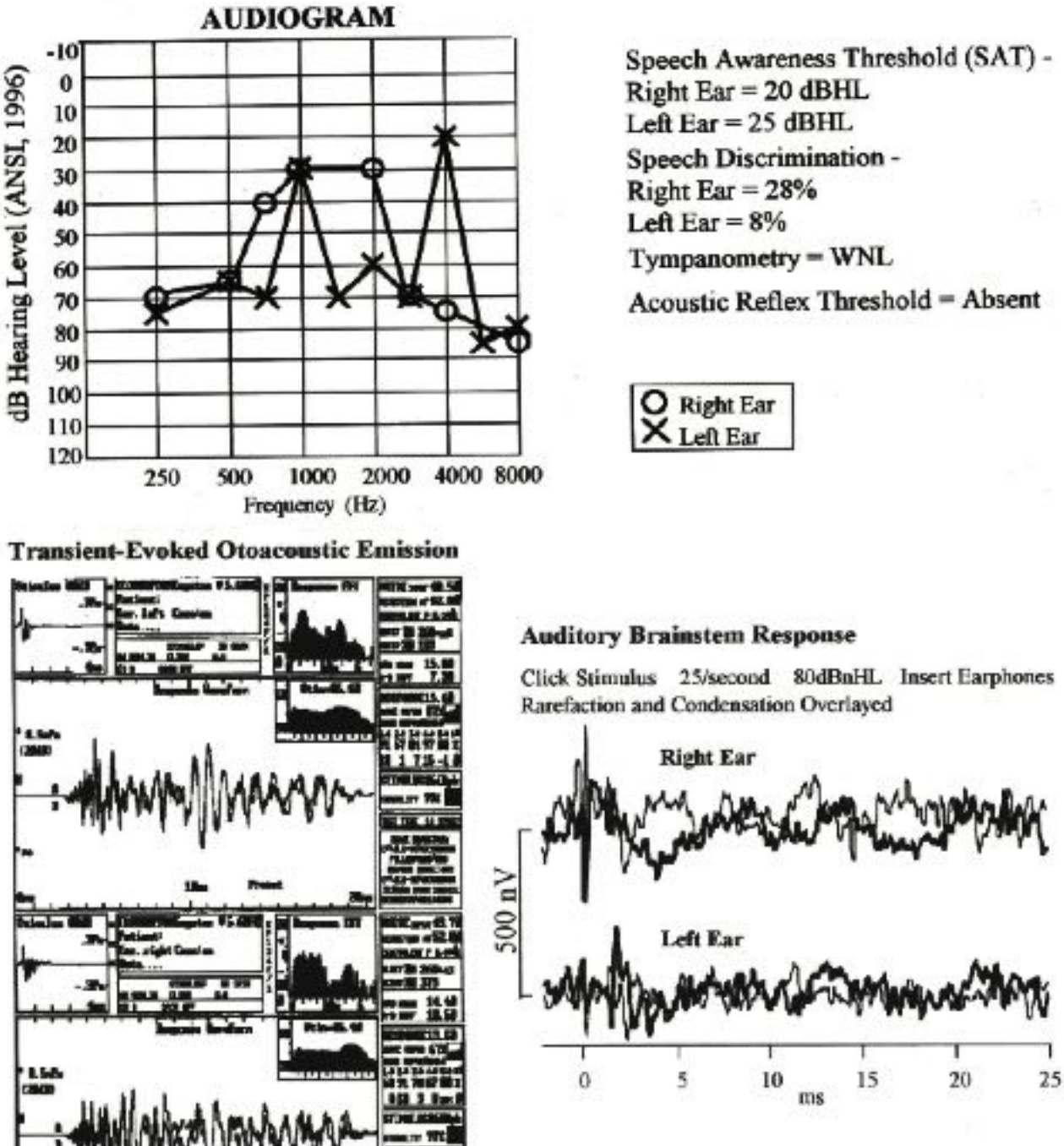


Figure 69.3 **(a)** Audiogram, **(b)** transient-evoked otoacoustic emissions and **(c)** auditory brainstem responses from a 7-year-old male patient with auditory neuropathy. Reproduced with permission.[55]

ACOUSTIC BRAINSTEM EVOKED RESPONSES

Acoustic brainstem evoked responses (ABRs) are detected by scalp electrodes and are a far-field reflection of electrical activity generated by the VIIIth nerve and brainstem auditory pathways in response to acoustic stimuli. Waves I and II are thought to come from generator sites in the distal and proximal sections of the VIIIth nerve, respectively, and III, IV and V from generator sites within the brainstem auditory pathways.[68] It has been proposed that the absent ABR of the patient with AN can be explained by the altered temporal synchrony of the auditory brainstem pathway, suggesting that, in these patients, auditory nerve and brainstem discharges are not precisely time-locked to the acoustic signal, so that short duration components (i.e. of 1 ms) are cancelled in the averaging process, rendering them indistinguishable from background electrical levels.

PURE-TONE AUDIOMETRY

Pure-tone audiometric thresholds show varying configurations of hearing thresholds (**Figure 69.4**) and variable degrees of hearing impairment (**Figure 69.5**).

Otoacoustic emissions (OAEs), first described in 1978,[64] are low-intensity sounds generated by the active movement of the OHCs of the cochlea. They are a marker of cochlear function and are left intact after section of the auditory nerve.[69] These acoustic echoes are evoked by stimulation with transients (clicks) at 80–86 dB sound pressure, and, typically, responses to 260 stimuli are captured over a time frame of the first 20 ms after stimulus application. These transient evoked otoacoustic emissions (TEOAEs) are present if the response amplitude, after subtraction of background noise, is 4 dB or more, and the waveform is reproducible in at least three octave bands. Measurement of distortion product otoacoustic emissions (DPOAEs) allows specific testing of a restricted region of OHCs, giving more frequency-specific information than TEOAEs. This is achieved by stimulation with two continuous tones of different frequencies (f1 and f2) that evoke DPOAEs that are largest at the 2f1–f2 frequency.

From the first papers describing TOAEs in these patients[8, 64] it was evident from the clearly recognizable waveforms that the hearing disorder was not due to significant dysfunction of the cochlear OHCs. On the occasions when these patients were monitored over a period of time, some started to lose their DPOAEs from small regions of the cochlea and this was attributed to a lack of trophic factors on the OHCs due to the auditory nerve disorder. Another study that describes the results of OAE testing in 17 children thought to have AN failed to show OAEs in either ear in more than half of their patients (8/17, with intersubject variation in behavioural hearing thresholds varying from 10 dB to 120 dB). However, in this latter report, how the authors felt confident to diagnose auditory neuropathy is questioned.

Contralateral suppression of OAEs can occur if noise (set at a level 5 dB louder than the click) presented to the contralateral ear fails to reduce the TEOAEs by 1 dB or more. This may occur if either the afferent pathway from the contralateral ear or the efferent pathway on the recorded side (via the olivocochlear bundle in the brainstem and carried with the inferior vestibular division of the VIIIth nerve) is dysfunctional.

Two studies have reported the lack of contralateral suppression of OAEs in patients with AN.[66, 70] The second of these describes the absence of contralateral suppression of OAEs in all eight of the patients tested from their series of ten. This is consistent with VIIIth nerve pathology occurring in either the contralateral afferent or the ipsilateral efferent pathway.

Cochlear microphonics (CMs) are an electrophysiological response generated in the cochlea to acoustic signals.[71] They represent the early components of the ABR and are small in size and susceptible to contamination by electroacoustic artefact. They can be better determined by reversing the click phase, at 5–25 ms, from condensation to rarefaction. They occur in the 0.7–1 ms window post-stimulus and show similar waveform characteristics to the stimulus itself[72] (the endocochlear potential of +80 mV is not measurable in humans). Transtympanic electrocochleograms indicate that the phase reversal to the click occurs at the level of the

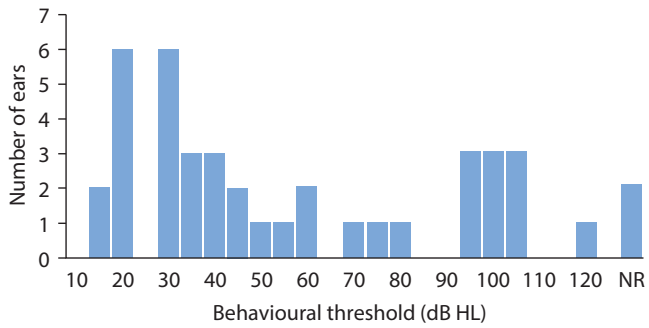


Figure 69.4 The distribution of behavioural thresholds (three-frequency average) for 38 years with auditory neuropathy. Reproduced with permission.[15]

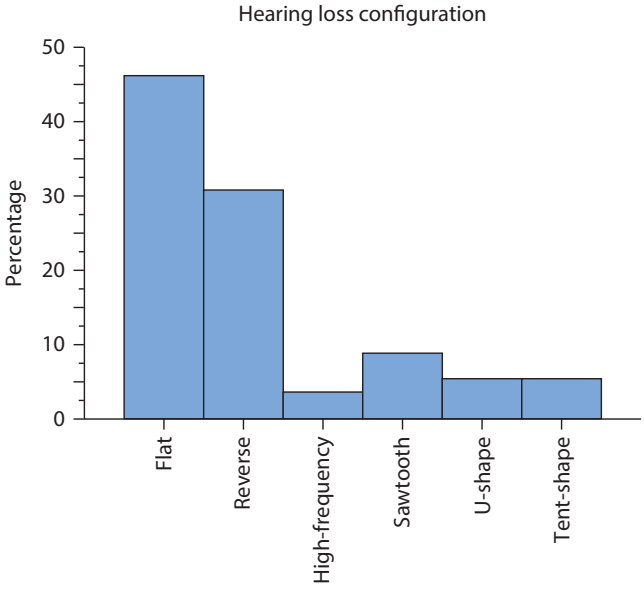


Figure 69.5 Hearing loss configuration (audiogram shape) distribution from a database of 59 patients with auditory neuropathy. Reproduced with permission.[95]

cochlea itself, and therefore the presence of CMs is indicative of a preneural response to sound.

Where investigation of the neural response is the primary aim, alternating polarity clicks are used in the recordings of the ABR because they cancel the cochlear potential and overwrite the CAP. This generates a 'microphonic-free' ABR leaving only the desired summating and action potentials, as evidence of a neural response. Thus, OAEs are preneural phenomena that reflect the integrity of the OHCs of the cochlea, whereas ABRs and the summating and CAP of the ECoG are tests of neural synchrony. The common stimulus to all these phenomena is the broad-spectrum 100 µs pulse.

The enhancement and detection of CMs was studied in five infants who had paradoxical results to hearing testing in a series of 60 deaf children.[73] By performing latency–intensity ABR studies using condensation and rarefaction clicks through insert earphones, intact preneural responses to sound with the characteristics described in **Table 69.3** were identified. It was suggested that, if diagnosticians do not have access to OAEs, patients with AN can be detected by comparison of ABR responses to condensation and rarefaction clicks at 100 µs (**Figure 69.6**).

Insert earphones are recommended[64] for recording ABRs to enable the separation of the stimulus artefact from cochlear potentials. The response of two opposite polarity clicks can be compared, with search for phase reversals and lack of shifts in latency with intensity changes. Adding the positive and negative polarity traces may uncover small residual neural events.

STEADY-STATE POTENTIALS

Sixty patients have been tested using steady-state potentials (SSEPs) to study the evoked potentials in the frequency domain rather than in the temporal domain, on the basis that the SSEP threshold might be more resistant to the effects of neural dyssynchrony. The study conclusion, however, was that SSEPs at a high rate had little or no predictive value for hearing thresholds in children with auditory neuropathy.

Tympanometry and stapedius reflex thresholds from 500 to 4000 Hz are also used in the test battery, as activation of the middle ear muscles (i.e. stapedius) by high-intensity sound is dependent on the integrity of the VIIIth nerve. The latter were absent in all ten patients in one study of auditory neuropathy,[8] irrespective of the pure tone threshold.

Speech recognition tests have been an essential item of the test battery for recognizing AN. Speech intelligibility is affected out of proportion to that expected if the pure-tone loss were entirely of cochlear origin. Speech intelligibility scores, tested at comfortable hearing level, are reduced disproportionately to the extent of the pure-tone impairment.[74] These scores are calculated from the average audiogram thresholds at 1, 2 and 4 kHz and, if the score falls below predicted values, the hearing impairment is likely to be retrocochlear in nature. Expected sentence recognition scores are calculated using the PTA to find the number of audible cues available to the patient and dividing by the total number of audible cues in the speech spectrum.

PSYCHOPHYSICAL

Further transmission of neural impulses via the auditory nerve to the brainstem is followed by auditory projections to higher centres where perceptual registration and cognitive elaboration takes place (see Chapter 48, Physiology of hearing). Psychophysical measures can also be used to assess patients with AN. They include the following tests which may be required to distinguish central auditory processing disorders from retrocochlear hearing disorders:

- monaural low redundancy speech tests, i.e. speech stimuli, presented to one ear
- dichotic/binaural interaction tests, i.e. stimuli presented to both ears, the task requiring the patient to attend to

TABLE 69.3 Comparison of the response characteristics of cochlear microphonics, compound action potentials and otoacoustic emissions (reproduced with permission)[73]

Response	Source	Measured by	Response to stimulus polarity inversion	Response to intensity decrease
Cochlear microphonic	Primarily from outer hair cells	Far-field or near-field electrical recordings using signal averaging and common-mode rejection	Inverts and follows the polarity of the stimulus; is not forward maskable and does not change in latency during simultaneous masking	No latency shift
Compound action potential (CAP)	Primary afferent neurons in primarily the basal turn of the cochlea	Far-field or near-field electrical recordings using signal averaging; comprises wave I of the ABR and the CAP of the ECoG	Does *not* invert, but shifts in latency by about one-half period of the stimulus; reductions in size and increase in latency occur during simultaneous masking in the same ear	Increase in latency at roughly 0.3 ms per 10 dB decrease in intensity
Otoacoustic emissions (OAEs)	Outer hair cells, with response size in humans probably mediated by the middle ear, transfer function	Sensitive microphones and amplifiers in response to clicks or tone pairs in the 2f1–f2 paradigm	Invert in polarity	No obvious change in latency with change in intensity

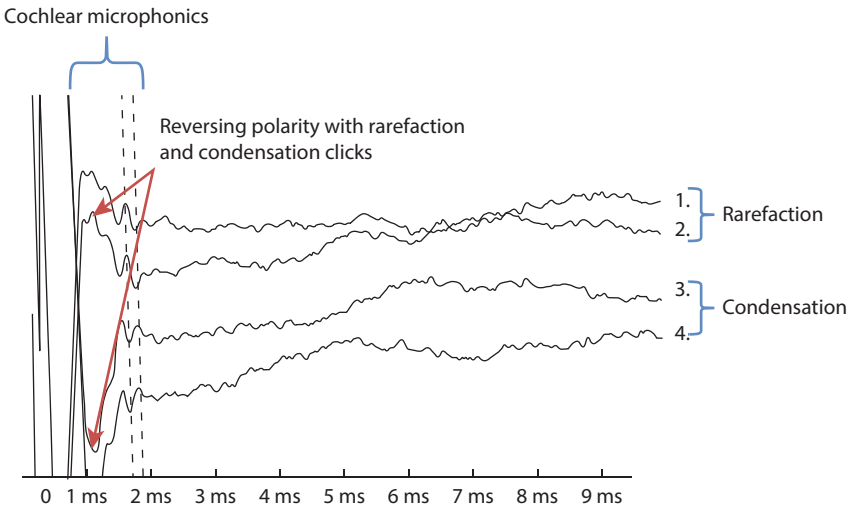


Figure 69.6 Acoustic brainstem evoked response to condensation (Con) versus rarefaction (Rar) polarity clicks. Note the complete biphasic inversion of elements even beyond 2 milliseconds. Reproduced with permission.[72]

one ear only, or both at the same time e.g. competing sentence tests
- temporal tests, i.e. sequencing tasks (e.g. the temporal gap detection test with a silent period embedded in a noise burst)
- modulation transfer function tests, i.e. fluctuations in levels of steady-state noise.

Further details are presented later in the chapter under 'Differential diagnosis'.

KEY POINTS

Criteria for diagnosis of auditory neuropathy

Evidence for preneural response to sound

- Normal otoacoustic emissions (OAEs)*
- Normal cochlear microphonic (CM)*

Evidence for abnormal neural synchrony

- Absent or severely abnormal acoustic brainstem auditory evoked responses**
- [Absent contralateral suppression of OAEs]
- [Absent middle ear reflexes]

plus

- Pure-tone thresholds ranging anywhere from normal to severely impaired

Diagnosis requires simultaneous presence of a pre-neural response to sound * *plus* abnormal neural synchrony **

PAEDIATRIC AUDITORY NEUROPATHY SPECTRUM DISORDER

Prevalence of disorder

A rigorous study[15] has been reported of 20 subjects fulfilling the criterion for AN, 12 of whom were identified from the Victorian Hearing Screening Programme for children considered at risk of hearing loss, and 8 of whom were identified by parental concern or failure to develop speech and language normally. An incidence of AN as 2.09% of those who failed ABR screening (n = 39), and 0.23% of those children at risk for hearing loss (n = 5199), i.e. 2/1000, was reported. A review of published literature which looked at prevalence of AN in the well-baby population and the false negative rate of OAE based on newborn hearing screening programmes showed that prevalence of AN in children in population hearing screening was between 0.006% (SD 0.006) and 0.03% (SD 0.02). The false negative rate, however, due to children with AN not detected through newborn hearing screening programmes using only OAEs is between 4% and 17%.[75]

Table 69.4 summarizes the results of the larger studies of paediatric populations assessed for AN.

From the studies in Table 69.4, it can be seen that the prevalence of AN in the population of children with permanent hearing loss is 5.1–15.38%, i.e. approximately 1 in 10. This compares with 1 in a 100 of those suspected of hearing loss (0.5–1.29%), or 2 in a 1000 of the 'at risk' population (0.23%).

Comorbidities such as developmental and learning delays, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), autism spectrum disorders, visual problems, blindness, cerebral palsy, motor disorders, apraxia, inner ear malformation, seizures and various syndromes are reported in up to 54% of children with AN. These can have an adverse influence on the child's speech and language development in addition to the underlying AN. In 2008 the Guidelines Development Conference on the Identification and Management of Infants with AN, meeting in Lake Como, Italy, considered the many aspects of AN, including comorbidities, and proposed the term 'auditory neuropathy spectrum disorder' in an attempt to encompass the heterogeneous nature of the condition.[10]

Causes of paediatric auditory neuropathy

PERINATAL RISK FACTORS

The first report of perinatal risk factors in babies who failed the ABR test but passed the click-evoked OAE

TABLE 69.4 Prevalence of disorder in neonates/children

Authors	Study population	Number with absent ABRs	Those fulfilling criteria for AN	% of study population with AN
Kraus et al. 1984[4]	543 with suspected hearing loss	49 with absent ABRs	7 with no worse than moderate hearing loss (14.3% of those with absent ABRs)	1.29% of those with suspected hearing loss
Davis and Hirsh 1979[1]	200 clinic population		1	0.5% of clinic population
Berlin et al. 1994[12]	60 children diagnosed as 'deaf'		5 with absent ABRs and present OAEs	12% of deaf children
Rance et al. 1999[15]	5199 with increased risk of hearing loss	37 with absent ABRs	12 subjects with absent ABRs and present CMs	0.23% of those at risk of hearing loss
Madden et al. 2002[11]	428 children with sensorineural hearing loss (SNHL)		22 with CMs/OAEs but absent ABRs	5.1% of children with permanent hearing loss
Foerst et al. 2006[76]	5190 children with hearing concerns and risk factors for hearing loss, of whom 3415 were tested with ABR and TEOAEs	379 with elevated or absent ABRs	32 with OAEs present but absent ABRs	0.94% of children at risk of hearing loss
Talaat et al. 2009[77]	112 children aged 6–32 months, with severe to profound hearing loss		15 with absent ABRs and OAEs present	13.4% of children with permanent hearing loss
Kirkim et al. 2008[78]	23 786 babies had universal newborn hearing screen; 2236 were referred for further tests	65 with absent or elevated ABRs	10 with absent or elevated ABRs and clear OAEs	15.38% of children with hearing loss, and 0.044% of babies undergoing universal newborn hearing screen

screen came in 1996. Four out of 100 fulfilled these criteria: one had periventricular leukomalacia, two were low birthweight and one was very low birthweight; three were diagnosed with having a respiratory distress syndrome; two received ampicillin and gentamicin; and three had hyperbilirubinaemia necessitating either exchange transfusion or phototherapy. Two out of these four normalized or reversed their ABR abnormality. Although these observations did not prove causality in any of the cases, the findings did imply that perinatal factors were likely to be involved, with some factors possibly causing temporary abnormalities only.

In an extensive report of neonates with AN[15] neonatal risk factors were documented and details of bilirubin levels recorded. Increased bilirubin (>350 µmol/L) was identified in 50% (Table 69.5).

Perinatal risk factors for AN were also analyzed in a retrospective study[11] of 22 patients with present OAEs and CMs but absent ABRs. These patients were identified from 428 children with permanent hearing loss in a paediatric otology clinic. Sixty-eight per cent of the children with AN had a complicated perinatal course, with hyperbilirubinaemia in 50%, prematurity in 45%, ototoxicity in 41%, neonatal ventilator dependency in 36% and/or cerebral palsy in 9%. In 36% a possible genetic link was identified, although this was apparently of a non-syndromic type as no other anomalies, particularly peripheral neuropathy, were identified. Following these children for an average of 32 months, 50% showed an improvement, not accounted for by normal development, within 1–15 months, and those with hyperbilirubinaemia

TABLE 69.5 Hearing loss risk factors in subjects with auditory neuropathy (reproduced with permission).[15] Figures in brackets represent the bilirubin level in micromoles/litre, except where otherwise indicated

Child	Risk factor	Other disabilities	Gestation
1	Jaundice (1010)		37
2	Jaundice (792)		36
3	Jaundice (467)		39
4	Jaundice (420)		40
5	Jaundice (380)		41
6	Jaundice (353)/hypoxia	Cerebral palsy	34
7	Hydrocephalus/hypoxia		33
8	LBW (900 g)/hypoxia		25
9	Parental concern	Cerebral palsy	40
10	Unilateral middle ear malformation	Unilateral facial palsy	39
11	Neonatal meningitis		39
12	Parental concern		41
13	Jaundice (540)		40
14	Jaundice (470)/hypoxia		32
15	Jaundice (420)		41
16	Jaundice (390)/hypoxia		31
17	None	Cerebral palsy	40
18	None		39
19	None		39
20	None		39

were more likely to improve than those without hyperbilirubinaemia ($p < 0.04$ at 2 kHz). Prematurity and perinatal anoxia were shown to predispose to bilirubin encephalopathy, with the risk for kernicterus and permanent sequelae being much higher at serum bilirubin levels thought to be safe for term babies.[6] 'Finer tools' such as ABR and other event-related potentials, have been recommended for use alongside biochemical measures to predict the risk of kernicterus and its sequelae. Children with hyperbilirubinaemia would thus appear to represent a unique subpopulation of patients with AN and require surveillance electrophysiologically as well as behaviourally.[79]

As children treated in neonatal intensive care units are found to have higher incidence of AN, the Joint Commission on Infant Hearing (JCIH, 2007) have recommended that infants treated in neonatal intensive care have their hearing tested using auditory brainstem response audiometry.[80]

KEY POINTS

Perinatal factors implicated in auditory neuropathy spectrum disorder

- Prematurity
- Perinatal anoxia/respiratory distress syndrome
- Low birthweight
- Hyperbilirubinaemia (>350 µmol/L)*
- Ototoxicity
- Cerebral palsy
- Neonatal ventilator dependency

* This level may be lower in preterm babies.

GENETIC

Non-syndromic recessive hearing loss is thought to account for approximately 40% of all cases of childhood hearing loss. Where that hearing loss has been demonstrated to have the characteristics of AN, genetic causes of the disorder have, until recently, only been associated with syndromic hearing loss, i.e. CMT[21] and Friedreich's ataxia.[22, 23] However, mutations in the otoferlin (*OTOF*) gene have been demonstrated to be associated with non-syndromic recessive auditory neuropathy (NSRAN).[17] The causative gene in four families was sought using a genome-wide linkage study and a critical region on chromosome 2p23 was identified that contained the *OTOF* locus. Out of eight alleles, four *OTOF* mutations were observed in the NSRAN families: a frameshift, a splice site and 2 missense mutations. These patients have been helped by cochlear implants but not by hearing aids. Thus, finding the genetic cause of this NSRAN has implications not only for aetiological diagnosis in newborn screening but also for prognosis and habilitation. Otoferlin is expressed in the IHCs in the region where afferent synaptic contacts are located.[17]

More recently, mutations in the pejvakin (*DFNB59*) gene, located on chromosome 2q31.1-q31.3 were identified in four families with AN. Pejvakin is a protein found in the cell bodies of neurons in the afferent auditory pathway and is thought to cause neural dysfunction.[19] Mutations to connexin 26 (*GJB2*) genes have also been implicated in auditory neuropathy. In a study reported in 2008, three children with hearing loss but preserved OAEs underwent transtympanic ECoG that showed normal CMs but abnormal neural responses.[30] [Level 1 evidence]

IMPACT ON NEONATAL HEARING SCREENING PROGRAMMES

Importantly, the association of a screening ABR fail and an OAE pass raises questions about whether OAE should be universally employed as the only initial screening tool for hearing loss infants in special care baby units.

Various protocols have been recommended for neonatal hearing screening.[6, 63, 73] One ABR intensity series protocol requires an estimate of threshold immediately if the infant fails an initial 60 dB nHL or 30 dB nHL test in either ear,[61] advising that records should be kept of threshold estimates and indicators of site of lesion (i.e. cochlear or neural). As ABR is also insufficient as the sole evaluator of hearing sensitivity, particularly if no response or early waveforms only are obtained, some[6, 63] recommend OAE testing at the same time as the ABR threshold series. Ideally, a system that can collect ABRs and OAEs simultaneously from the same sleeping infant is recommended. The importance of follow-up with the concomitant use of behavioural audiometry with ABR cannot be underestimated to guard against inappropriate diagnoses of cochlear hearing loss or reversible ABR abnormalities.[10, 63, 73]

KEY POINTS

Neonatal hearing screening programmes

- Checks of ABR and/or CMs should be considered in **high-risk newborns** who undergo OAE testing as their primary screening tool.
- Clinicians and audiologsts should include **auditory neuropathy spectrum disorder** in their differential diagnosis of SNHL in children.
- Patients with **hyperbilirubinaemia** should be seen as a distinct subset of those patients fulfilling the criteria for AN, particularly because they tend to show a distinct audiological improvement during the first year of life.

ADULT NEUROLOGICAL AUDITORY NEUROPATHY AND BRAINSTEM HEARING LOSS

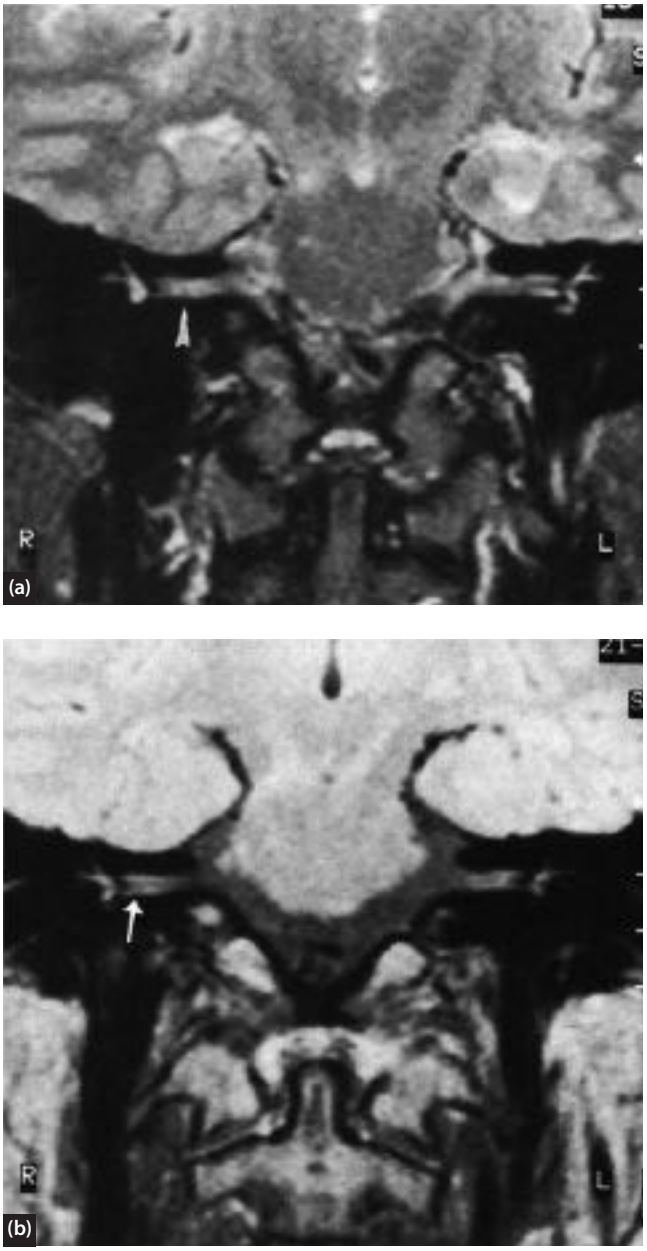
Neurological causes of AN and retrocochlear hearing loss include those with first-order cochlear neuronal degeneration (i.e. VIIIth nerve lesions) and those with pathology of the second-order cochlear neurons within the brainstem.

Multiple sclerosis

Multiple sclerosis (MS) is a disorder characterized by multiple areas of demyelination in the central nervous

system, and the clinical diagnosis rests upon the demonstration of two or more such lesions. Acoustic brainstem evoked response audiometry has been used for nearly 40 years in patients presenting with a single lesion suggestive of MS, to detect other sites of demyelination. In the first study in this area, wave V was the most consistently abnormal wave in patients with MS.[50] A correlation was demonstrated between this ABR abnormality and clinical evidence of a brainstem lesion due to MS in 79% of patients, but there was also an ABR abnormality in 51% of those patients without clinical signs of MS related to the brainstem. However, the presentation of MS with acute hearing loss is rare, and reported in only 1–3.5% of patients.[81, 82] Demyelinating lesions have been identified in the VIIIth nerve;[83, 84] in the nerve root entry zone/cochlear nucleus;[52, 85] and in the pons.[38] Conversely, an MRI study of 354 patients with sudden hearing loss, tinnitus and vertigo identified abnormalities in 12 (34.5%), only 2 of whom showed focal hyperintensities that were subsequently found to be the first evidence of MS.[86]

MRI and electrophysiological correlates have been reported as evidence for demyelination in the VIIIth nerve:[39] a small hyperintense lesion along the cochlear nerve which decreased in size and disappeared with steroid treatment (**Figure 69.7a, b**), and, in parallel, a return to normal of the ABR (**Figure 69.7c**). Wave I was initially undetectable, then delayed and finally normal, with invariably normal interpeak latencies throughout the time



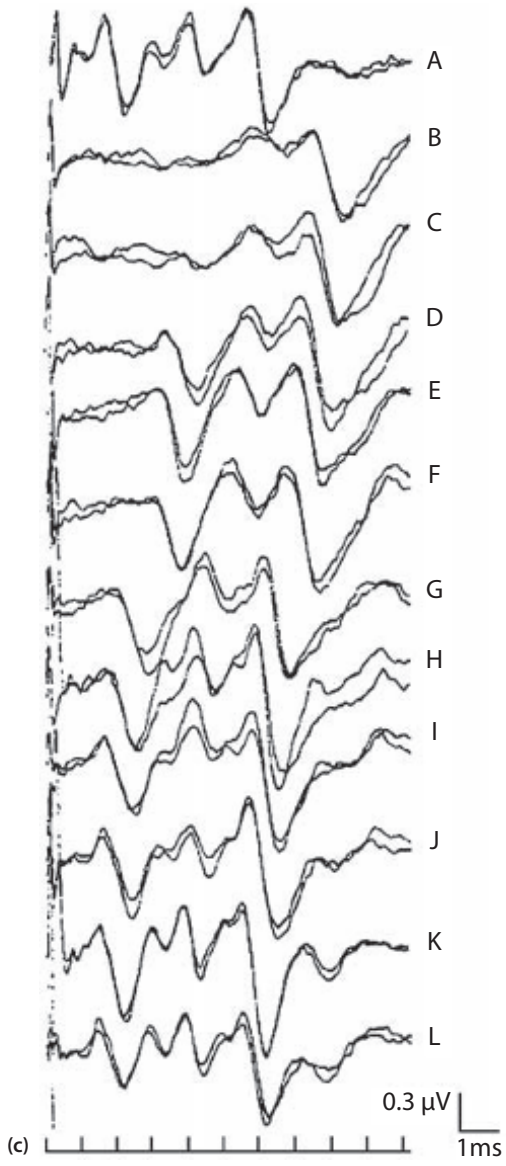


Figure 69.7 **(a)** Coronal T2-weighted MRI: mild enlargement of the right VIIIth nerve inside the internal auditory canal, and punctate area of hyperintense signal (arrow). **(b)** Coronal T2-weighted MRI: no lesion seen along the right VIIIth cranial nerve. **(c)** ABR recordings (rarefaction clicks, 65 dB SL intensity, 22.1 Hz frequency, Cz–A2 electrodes) before (A), and after (B–L), right sudden hearing loss. Reproduced with permission.[37]

frame of the recordings. The ABR abnormalities are likely to have been related to the sudden hearing loss because the ABR had been normal in previous testing, and then improved in parallel to the clinical recovery.

This was the most caudal site of a demyelinating lesion in MS reported to that date, and the authors felt that the lesion could still be accounted for as an abnormality of central myelin as the transition zone from glia to Schwann cells is quite distal in the VIIIth cranial nerve. Transtympanic ECoG[84] has also been used to demonstrate a disturbance of synchronization at the level of the first-order cochlear neurons in a patient known to have MS who developed sudden hearing loss. Investigation identified enhanced latency of the CP, a normal CM and SP, but absent ABRs, showing this hearing loss to have the characteristics of an AN. MRI has allowed the progression of demyelinating lesions of the ventral cochlear nucleus near the entry zone of the VIIIth nerve to be documented in MS patients with sudden hearing loss[52, 86] and also in MS patients with hearing loss who have pontine lesions.[39]

Extrinsic and intrinsic tumours of the cerebellopontine angle

There are a number of tumours of the cerebellopontine angle (CPA) which can present with retrocochlear hearing loss: cerebellar medulloblastoma, neurinoma, meningioma, cholesteatoma, ependymoma, jugular glomus tumour and metastasis. Imaging will generally identify these tumours and, in the case of metastases, CSF lumbar puncture for cytological examination, or serological search for antineuronal antibodies (anti-ro, anti-la, anti-RNP, anti-Jo-1, anti-SCL-70) will lead to the diagnosis. Cerebellar medulloblastomas are particularly common in childhood (25% of all intracranial neoplasia) where they tend to be midline, but in adulthood they tend to be located laterally and can present as CPA lesions. In a study comparing AN and neural deafness in acoustic neuromas, the following similarities in auditory tests were reported: presence of tone decay, normal distortion product OAEs and CMs and poor speech perception which was out of proportion to the pure-tone audiometry configuration. However, ABR abnormalities were different. In patients with acoustic neuromas only wave I of the ABR was seen with following waves absent, whereas in patients with AN ABR was absent or, when present, abnormal wave I was seen.[87]

Auditory neuropathy plus peripheral neuropathy

In a series of 70 cases of AN,[88] no aetiology was identifiable in 40% of affected individuals. The AN was typically bilateral and affected men and women equally. In general, ANs have been considered to be an infrequent associate of peripheral neuropathies but, where they do occur, other cranial neuropathies (i.e. optic, trigeminal and facial neuropathies) occur more frequently. However, a peripheral neuropathy was identified in 18/70 (26%) of the cases cited above following clinical assessment of deep tendon reflexes at the ankle, vibration sense at 128 Hz in the foot and investigations with nerve conduction studies plus sural/peroneal nerve biopsy. Hereditary sensory–motor neuropathy (HSMN) was found in 9 out of 70 of the patients, with 3 families providing all 9 of these cases. Several different genetic disorders may present with HSMN, and one Roma family from Slovenia[24] was shown to have a mutation on chromosome 8q24. In these patients, the peripheral neuropathy occurred first, and sural nerve biopsy demonstrated a mixed axonal and degenerative neuropathy, with hearing loss only developing later. These cases also had bilateral vestibular failure, presumably on the basis of VIIIth nerve involvement, and demonstrated a recessive mode of inheritance. [Level 1 evidence]

NERVE CONDUCTION STUDIES

This investigation allows the detection of a peripheral neuropathy and its characterization as a demyelinating or axonal type neuropathy. A demyelinated nerve fibre has a much reduced membrane resistance and increased capacitance to current draining through the axonal membrane and the action potential falls off much more rapidly than in a normal nerve fibre because of the reduced membrane resistance. The action potential cannot reach any excitable region of the axon with sufficient amplitude to regenerate itself. The result of this is a slowing of conduction velocity, and a widening of the whole nerve action potential as multiple axons become affected by the demyelinating process (**Figure 69.8**). Demyelinated axons also have an impaired capacity to transmit trains of impulses. Such high discharge rates would typically be seen in response to intense acoustic stimuli, contributing to the appreciation of loudness and mediating reflex activation of middle ear muscles and olivocochlear reflexes, explaining the absence of stapedius reflexes and loss of contralateral suppression of OAEs in patients with AN.

Two patients with AN who have a temperature-sensitive hearing loss have been reported. Demyelinated axons may also demonstrate 'cross-talk' (ephaptic transmission) between fibres, with one active fibre initiating impulses in an adjacent fibre, possibly accounting in the auditory system for distortion in the coding complex of speech. However, in an axonal neuropathy, there is no conduction delay and therefore relative preservation of velocity but reduced size of the nerve action potential due to the reduced number of functioning axons. This becomes more evident the greater the distance from the cell body, with the longest fibres most susceptible to pathology. This is likely to affect the low frequencies on the audiogram as the longest cochlear fibres extend to the apex of the cochlea.

The neuropathy associated with CMT type I is characteristically demyelinating, and that of CMT type 2 is axonal. The axonal neuropathy theoretically should not

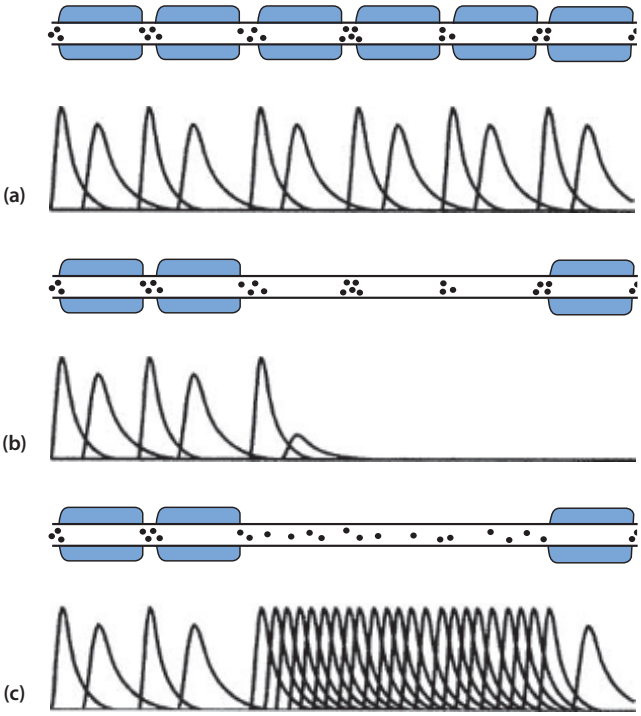


Figure 69.8 A diagrammatic representation of what happens when a nerve fibre becomes demyelinated. The blue regions are the myelin sheath. The dark dots are the voltage-sensitive sodium channels that are concentrated at the nodes of Ranvier. Three conditions are shown: **(a)** normal, **(b)** conduction block and **(c)** demyelination with slowing. The action potential is represented stroboscopically as it is conducted along the axon. The trace in (c) shows what happens when the sodium channels diffuse into the bare axon. The action potential can now regenerate itself, but this occurs over much shorter distances than when the axon was myelinated and the conduction velocity is therefore very slow. Redrawn with permission.[53]

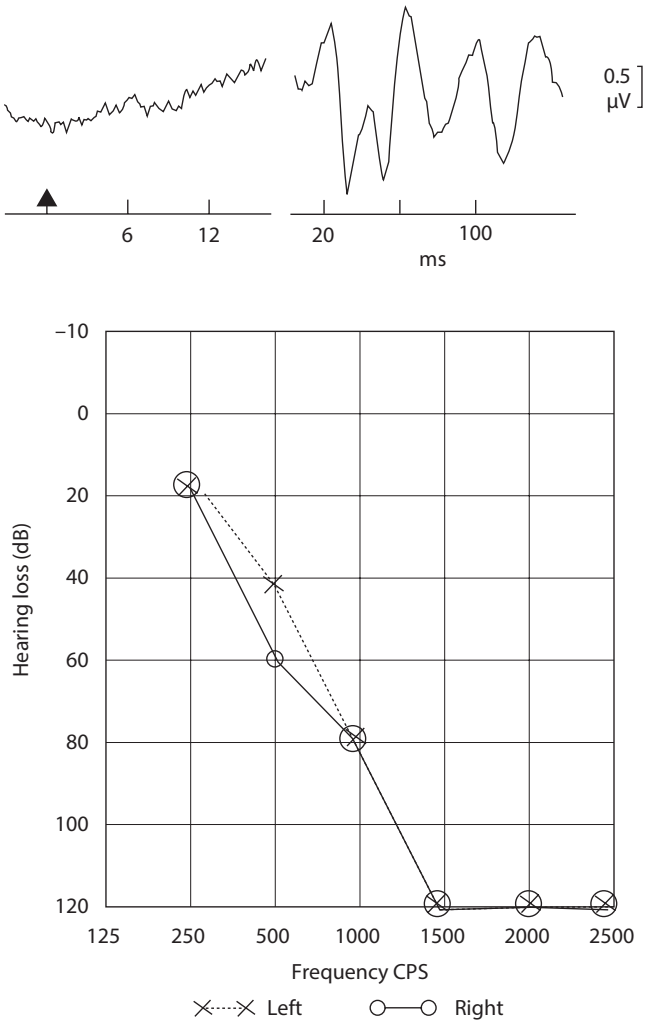


Figure 69.9 Pure-tone audiometry and acoustic evoked responses in a patient with congenital myotonia administered with high-dose quinine. Reproduced with permission of Dr Peter Rudge, The National Hospital for Neurology and Neurosurgery, London).

affect neural synchrony in the VIIIth nerve. However, as the axon and its myelin sheath are so closely related, one cannot exist without the other, and an axonal neuropathy is often accompanied by signs of secondary demyelination, which would then impact on neural synchrony, as above. Delmaghani et al. have described an autosomal recessive type of auditory neuropathy due to pejvakin, a protein within cell bodies of neurons of the afferent auditory pathway which causes neural dysfunction in the auditory nerve. *DFNB59* encodes pejvakin.[19]

DIFFERENTIAL DIAGNOSIS

Sharply sloping high-frequency hearing loss of cochlear origin

Quinine at a high dose is known to selectively destroy the OHCs of the cochlea. The pure-tone audiogram in Figure 69.9 shows a sharply sloping SNHL, induced by quinine in a patient with congenital myotonia. The acoustically evoked responses from the same ear are also shown, illustrating that in the time frame 0–12 ms, there are no reproducible waveforms (i.e. no ABR) whereas the MLRs are identifiable.

Distinction of auditory neuropathy from brainstem neuropathy

In a patient with normal preneural function but abnormal ABRs, only a full battery of tests as above can begin to distinguish a primary cochlear neuron lesion from a secondary cochlear neuron lesion. This would include other tests of neural synchrony such as stapedius reflex thresholds, in addition to ABRs, and, if the former are present, this might suggest a lesion higher in the brainstem than the pathways required to activate the facial nerve nucleus and cause contraction of the stapedius muscle bilaterally. Similarly, the type of ABR abnormality, specifically the pattern of abnormal or lost wave latencies, may give a relative clue as to site of lesion although, as in the case of MS, these patterns of abnormality have less localizing value than might be expected.

Central auditory processing disorders

With the advent of clinically available central auditory function tests, it has become possible to distinguish central auditory processing disorders (CAPDs) from other causes of deficits/delay in some children with language, reading and/or spelling difficulties. A 'bottom-up' approach to understanding these difficulties better now includes use of the behavioural central auditory tests.[89, 90]

- monaural low redundancy speech tests, i.e. speech stimuli, presented to one ear, that are:
  - degraded in frequency content
  - embedded in competing signals (multispeaker babble).
- dichotic/binaural interaction tests, i.e. stimuli presented to both ears, the task requiring the patient to attend to one ear only, or both at the same time:
  - dichotic digits
  - competing sentence tests.
- temporal tests, i.e. sequencing tasks:
  - frequency pattern test
  - temporal gap detection.

These are in addition to baseline audiometric tests and electrophysiological tests such as ABRs, MLRs, P300 and mismatch negativity. The characteristic abnormality of speech perception disproportionately poorer than the degree of hearing loss, plus abnormal ABRs in the presence of OAEs/CMs but absent stapedius reflex thresholds and absent contralateral suppression of OAEs, will distinguish patients with AN from those with CAPD.[91]

KEY POINTS

Differential diagnosis of auditory neural spectrum disorder

- Sharply sloping high-frequency hearing loss of cochlear origin.
- Distinction of auditory neuropathy from brainstem neuropathy.
- Central auditory processing disorders/language acquisition disorders.

AMPLIFICATION AND HABILITATION/ REHABILITATION STRATEGIES

Patients whose test results fulfil the criteria for AN represent a heterogeneous group. Not only is the site of lesion likely to vary, from the IHCs and synaptic connections within the cochlea to axonal degeneration and demyelination of the first- or second-order cochlear neurons, but also loudness sensitivity varies, as demonstrated by pure-tone audiometric thresholds. Degraded speech perception inconsistent with pure-tone sensitivity remains the common feature.

Early language intervention

For those children with auditory neural dyssynchrony, the onsets of plosive consonants and transitions, which make speech intelligible, would appear to be lost, preventing these children from categorizing or sequencing sounds. This makes early language intervention critical. A phoneme-based language therapy seems reasonable as it includes other tools for communication as well as audition. 'Cued speech' has been advanced as an adjunct to aural rehabilitation, as a way of 'eavesdropping' on family conversations, as it allows children to 'hear English phonemes and English grammar with their eyes'. It is a method whereby cues to vowel and consonant sounds that are difficult to perceive from lip-reading can be given by synchronous hand-shapes presented alongside either the mouth or pharynx of the speaker. These cues will give syntax and phonological structure to language and are more easily learned by parents. However, cued speech cannot aid in the phonological representation of language for children who are deaf or hard of hearing.

Total communication

Total communication uses spoken language and elements of sign language to link the different communication systems. Recognizing that each child with AN has a vast array of needs and that, for the individual, acquisition of language will also affect acquisition of culture, use of a system such as total communication to link aural–oral and manual communication systems would seem to have much to recommend it in a prelingual child.

Will hearing aids help?

Various studies have examined the benefits of hearing aids,[4, 15, 92] and shown variable results. In the earliest of these studies, three out of four patients fitted with hearing aids reportedly derived little benefit from amplification. In a later study, of 15/20 patients prescribed hearing aids, 8 were developmentally mature enough for speech perception threshold levels to be assessed, and 4 showed significantly increased aided threshold levels. Anecdotal reporting in the remaining 7 children suggests that 4 of these had benefited from hearing aids. The main concern regarding the use of hearing aids in patients with AN is that they can cause significant noise exposure and permanent threshold shift (up to as much as 20 dB HL) in children with SNHL.[93] It has been observed that TEOAEs may deteriorate in some children with AN after hearing aid use.[92, 93] Thus, the use of an algorithmic approach to hearing aid fitting and real-ear measures to verify parameters of the hearing aid needs to be calculated in much the same way as for the risk–benefit analysis for children with SNHL (**Table 69.6**).

Gap detection and modulation transfer function are abnormal in AN patients, and it has been hypothesized that these patients have 'a (time) smeared internal representation of a physical stimulus'.[55] A speech-processing type of hearing aid with a high-frequency emphasis to enhance high-frequency transient speech sounds (i.e. consonants) has been recommended. Also the use of directional microphones and personal FM systems to improve

TABLE 69.6 Breakdown of otoacoustic emission status by hearing aid status (reproduced with permission[54])

	OAE present		OAE absent		OAE once present now absent		All patients	
Hearing aid status		%		%		%		%
User	5	16	4	80	3	50	12	30
Past user	12	39	1	20	3	50	15	37
Never used	14	45	0	0	0	0	14	33
Total	31	100	5	100	6	100	42	100

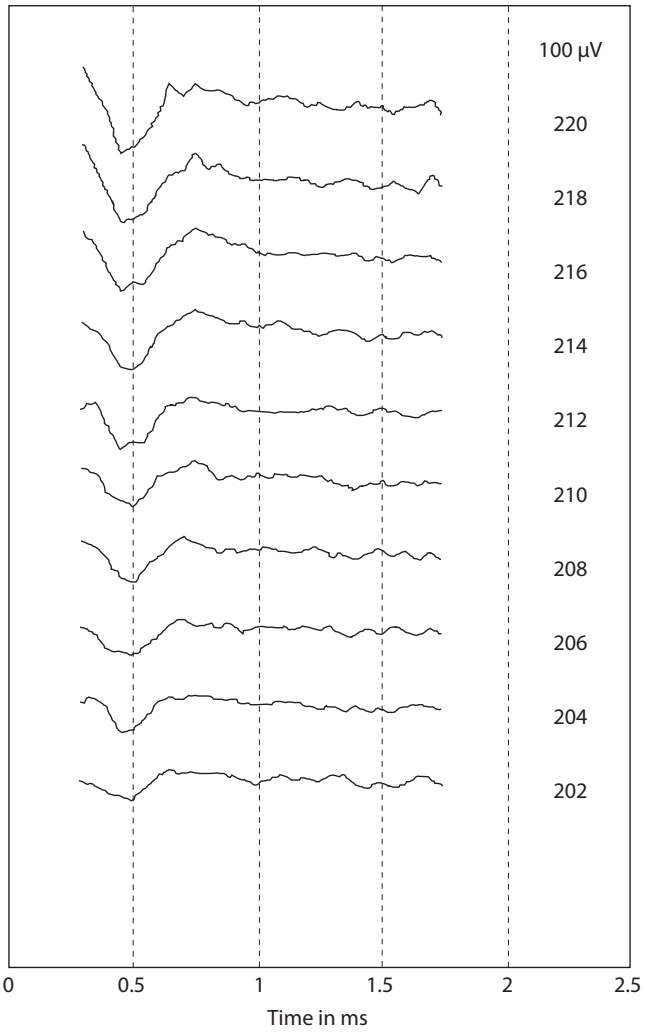
the signal-to-noise ratio in those patients with pronounced difficulties with speech in background noise has been proposed.[94]

Use of cochlear implants

The question arises as to whether cochlear amplification could be predicted to be of value and, if so, which patients would be likely to show a benefit. Theoretically, the patient with axonal degeneration/demyelination of the VIIIth nerve might not benefit from cochlear implantation (CI). However, electrical stimulation has been shown to produce synchronous ABRs in the presence of peripheral auditory nerve demyelination.[78] The potential benefits to these patients would be that CI provided consistent neural firing and the stimulus itself might promote neural survival and restore temporal activity. The disadvantages of CI would be not only the risk of surgery and anaesthesia, but also the chance that the electrode insertion might damage the cochlea itself and destroy residual hearing. Thus, proceeding to CI would need to be made with a thorough assessment and careful counselling of the child's family.

Studies published demonstrate the benefit of CI in children with AN. One child who wore aids from the age of 21 months for 2 years, and who was then fitted with a cochlear implant, was reported as receiving no benefit.[15] Six children with AN in whom CI was performed have also been reported.[95] Four of these children represented two sets of siblings, and all had undergone a trial period of powerful behind-the-ear-aid use. Five out of the six benefited significantly from implantation, as judged at the 1-year evaluation period using developmentally appropriate speech perception testing, with and without visual cues. Three of these children were considered to have adequate language and communication skills to attend mainstream school, having started their education in oral preschool for children with hearing loss. One child, however, showed no benefit from his CI. His understanding at 1 year post CI relied entirely on context, routines, gestures and lip-reading. There were no clear reasons why this particular child should have failed to benefit from CI.

Neural response telemetry (NRT) was used to assess neural synchrony and temporal coding post-CI (**Figure 69.10**). NRT uses a subtraction technique to remove the ECAP from the stimulus artefact using a forward masking paradigm.[95] The presence of the ECAP is interpreted as



NRT : Child C
Recording parameters:
Stimulating electrode 10
Recording electrode 12
Averages = 100

Probe:
Current level = variable
Pulse width = 25 µs/phase
Rate = 80 Hz

Masker:
Current level = fixed (220 units)
Pulse width = 25 µs/phase
Advance = 500 µs

Figure 69.10 Electrical compound action potential recording for 'Child C'. Reproduced with permission.[94]

indicating that electrical stimulation has restored some degree of synchrony and temporal encoding at the level of the cochlear nerve. These authors conclude that CI should be performed only after a trial of conventional amplification and that each decision to implant must be based on the individual circumstances. Children in the Sydney Cochlear Implant programme who had bilateral profound hearing loss were studied to examine the efficacy of CI. The study included 54 children and 15 of them were found to have cochlear nerve anomalies. Cochlear implant outcomes in terms of open-set speech discrimination were found to be poor in this group. Implant evoked electric auditory brainstem response (EABR) was uniformly poor in this cohort of children whereas children with normal cochlear nerves and AN had better open-set speech discrimination.[95]

In another study of 140 patients with a diagnosis of ANSD, over 40% were born pre-maturely and 38% had abnormal pre-operative MRI findings of the brain and inner ear. Thirty-seven per cent of these patients received cochlear implants, and 50% of those implanted demonstrated open-set speech perception abilities after implantation. None of those with cochlear nerve deficiency in the implanted ear achieved open-set speech perception abilities. Structural integrity of the cochlear nerve is therefore integral to achieving good outcomes following CI.[96]

BEST CLINICAL PRACTICE

- ✓ Suspect AN in patients whose pure-tone audiograms are normal or show a mild to moderate loss but who exhibit poor speech discrimination or delayed speech.
- ✓ Request electrophysiological tests of hearing including measurements of OAEs and ABR audiometry (preferably with measurement of CMs) to confirm diagnosis.

FUTURE RESEARCH

- ➤ Clear test protocols need to be developed for newborn hearing screening programmes to ensure that:
  - ➤ cases of AN are not missed (i.e. if only OAEs are performed)
  - ➤ those who have absent ABRs are not assumed to be profoundly deaf and amplified inappropriately (i.e. if OAEs are not performed).
- ➤ Test protocols for site-of-lesion diagnosis in patients with retrocochlear hearing disorders are needed, to distinguish:
  - ➤ first-order cochlear nerve lesions
  - ➤ second-order cochlear nerve lesions
  - ➤ central auditory processing disorders.
- ➤ Research is needed into the identification of predictors of stable AN vs progressive AN vs reversible AN vs maturational delay.
- ➤ Further work is needed in the following areas:
  - ➤ the relationship of pathophysiology to signs and symptoms
  - ➤ perceptual effects of AN
  - ➤ prospective case-controlled studies of hearing aid use versus CI
  - ➤ the identification of factors predicting the benefit from one type of hearing prosthesis over another
  - ➤ AN as a marker for neurodegenerative conditions.

KEY POINTS

- Auditory Neuropathy Spectrum Disorder (ANSD) is characterized by electrophysiological evidence of normal or near normal cochlear function (normal OAEs or cochlear microphonics) and abnormal auditory nerve signal transduction (abnormal ABR).
- Hearing may be normal or show mild to severe loss on pure tone audiometry.
- Speech discrimination is poor and language development may be delayed.
- Aetiologies are genetic or acquired.

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CHAPTER 70

UNDERSTANDING TINNITUS: A PSYCHOLOGICAL PERSPECTIVE

Laurence McKenna, Elizabeth Marks and David J. Scott

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: tinnitus, hyperacusis, psychology, cognitive and CBT.

INTRODUCTION

Affecting 10–15% of the population at any one time,[1] tinnitus is one of the most common persistent physical symptoms to affect humankind. Most individuals habituate to tinnitus with just 5% of the population reporting mild to moderate disturbance and 1–2% reporting severe and chronic disturbance attributed to tinnitus.[2, 3] The challenge for tinnitus researchers and practitioners is to understand why such variability exists and to develop effective interventions for those who suffer.

Medicine has traditionally focused upon the psychophysical characteristics of tinnitus. This 'linear' model fails to account for findings that acoustic characteristics of tinnitus are poorly related to its severity or treatment outcome,[4, 5] and that psychological treatments can lead to broad improvements in psychosocial measures, even when tinnitus loudness does not change.[6] More modern perspectives take into account the complex moderating and mediating factors in the experience of tinnitus; these are principally psychological and social in nature and interact with the underlying psycho-physiological changes.[7] To this end, a biopsychosocial model[8] provides a useful framework for understanding tinnitus.[9]

The biopsychosocial model of health and illness

The biopsychosocial model places health and illness within the context of the psychological and social influences affecting an individual, together with their biology. This approach offers a theoretical foundation for a multidisciplinary approach to tinnitus management. It explains how psychosocial factors influence the individual's behaviour in response to tinnitus (i.e. illness behaviour),[10] which in turn affects their health and well-being. This model implicitly indicates the influence of the doctor–patient relationships on treatment outcome. The clinician is thus responsible for minimizing unintentional iatrogenic harm and supporting patients' compliance with treatment recommendations. The focus of treatment is on a multidisciplinary approach that enables patients to manage tinnitus and its impact upon their life themselves, rather than being 'cured' of it.

Admittedly, few studies directly explore a biopsychosocial approach to tinnitus. However, there are convincing similarities between chronic pain and chronic tinnitus.[11, 12] In particular, both are linked to changes in the CNS after being triggered by peripheral changes, and both are associated with anxiety, depression, insomnia and reinforce each other within a vicious circle. A biopsychosocial approach to tinnitus would thus be a fruitful avenue for research.

PSYCHOSOCIAL FACTORS IN TINNITUS

Patients disturbed by tinnitus most commonly complain of emotional distress, insomnia and problems with sustained concentration and cognitive functioning. Over time, these difficulties have broader consequences, disrupting other aspects of daily life such as sleep.[13] There may also be

predisposing or precipitating psychosocial factors that make tinnitus-related distress a more probable outcome, such as personality traits, emotional state, psychiatric illness and cognitive style.

Personality factors

It is possible that stable personality characteristics can affect how an individual reacts to tinnitus and thus influence the degree of distress they experience. Studies have supported the idea that specific personality traits are associated with tinnitus severity, in particular, traits of perfectionism,[14] life satisfaction[15] and anxiety sensitivity[16, 17] have been found to relate to increased tinnitus severity. Optimism is negatively associated with tinnitus distress.[15] Erlandsson and Persson[18] found that 50% of a subgroup of more distressed tinnitus patients were diagnosed as suffering from a personality disorder.

Establishing a causal relationship between personality variables and tinnitus distress is challenging. These studies assume such traits were present through most of the person's life, and that anxious or depressed dispositions are not the product of tinnitus. Anxious traits identified in people soon after the onset of tinnitus have been found to predict greater tinnitus distress 6 months later.[19] These observations suggest that, when tinnitus arises in people who are already emotionally strained, it is more likely to lead to distress. Another study[20] examined the relationship between type D personality (a generally gloomy view of life and social inhibition), tinnitus distress and quality of life and found that the impact of type D personality on tinnitus severity was in part mediated by the presence of anxiety and depression. Additional evidence supports the idea that the relationship between personality variables and distress is not direct but is mediated by cognitive variables such as dysfunctional thoughts,[21] particularly catastrophization,[22] and tinnitus-specific illness perceptions.[23]

Cognitive variables related to tinnitus

The process of targeting illness perceptions begins right from the emergence of the illness and will be affected by the approach taken by healthcare professionals. In tinnitus, as in all illness, it is important for the whole care of a patient to be directed towards enhancing more helpful illness perceptions.

As well as general disposition, an individual's style of thinking about tinnitus is important in determining the nature of their experience of tinnitus. The psychological perspective suggests that distress arises because tinnitus is interpreted in a threatening way. The most common themes in the thinking of distressed tinnitus patients reflect despair, persecution, hopelessness, loss of enjoyment, a desire for peace and quiet, and beliefs that others do not understand.[24] Higher tinnitus distress is associated with more reported unhelpful thoughts about tinnitus.[24–26] Beliefs that tinnitus will lead to dreadful consequences (i.e. thoughts that overstate the impact of tinnitus, minimize the ability to cope and which involve rumination or excessive worry) appear to be particularly important. These kinds of catastrophic thoughts are associated with fear, which increases attention towards the tinnitus and reduces quality of life.[9] Catastrophic thinking has been observed to be associated with high subjective tinnitus loudness, poorer coping, depressive symptoms and with more frequent medical visits.[22] Catastrophization in the early stages of the tinnitus experience appears to have a pivotal role in determining the long-term distress, since patients quickly become caught in a vicious cycle of anxious and depressed thoughts about tinnitus, intensifying the intrusiveness, increasing distress and prompting frequent help-seeking behaviours, which in turn may maintain unhelpful illness beliefs.

The perception of an illness is known to influence coping behaviours and outcomes in chronic illness,[27–29] and, if interventions are to be helpful, they should address specific illness perceptions. Although research into illness perceptions in tinnitus is limited, one study reported on significant relationships between depression and anxiety and the perception of tinnitus in terms of the symptoms attributed to it and perceived consequences.[30] It has also been observed that an internal locus of control in tinnitus (i.e. the perception that you can control what happens to you rather than being affected solely by external factors) is associated with habituation, reduced psychological distress and reduced severity.[31–33]

With the perception of tinnitus determining its severity and related distress, psychological factors are clearly central to the tinnitus experience. This has direct implications for a clinician, as illness perceptions are influenced by historical, social and cultural context. Clinicians have a responsibility to remain aware of their contribution to this psychosocial context, as clinical contact will directly influence how a patient learns to perceive their tinnitus. Patients will benefit from a hopeful but realistic assessment of tinnitus, so it would be worth avoiding a purely biological focus on tinnitus, as this would suggest that there is 'nothing to be done'. Instead, offering a viewpoint that takes psychosocial factors into account will enable the patient to see potential areas of adaptability, leading to more helpful illness perceptions and thus possibly reducing distress.

Emotional consequences: Anxiety and depression in tinnitus

Patients with tinnitus report higher rates of psychiatric problems compared to the general population. In the late 1980s the use of formal psychiatric assessment tools demonstrated that 63% of a tinnitus sample could be classified as psychiatrically disturbed and that 78% had experienced one or more major depressive episodes in their lifetime, compared to 21% of a control group.[34] Since then other researchers have reported similar figures using both formal assessment[16, 26, 30, 35, 36–38] and self-report tools for measuring anxiety and depression.[39–42]

Psychological distress in tinnitus patients can clearly be a reaction to the tinnitus, but emotional disorders can also act as a trigger for tinnitus.[43] Goebel and Floetzinger[44]

found that, in 64% of tinnitus patients classified as suffering from a psychiatric disorder, the disorder preceded the onset of tinnitus. Clinical observations show that the more distressed the patient becomes the more problematic the tinnitus. Studies point to a link between problematic tinnitus and depression,[44, 45] with indications that the severity of tinnitus relates to the severity of the depression.[36] Stress is also thought to aggravate tinnitus, with evidence that a high workload and difficult shift-work patterns contribute to tinnitus distress.[46] An interaction between tinnitus distress and poor psychological state has been noted by others,[34] who found that depressed tinnitus patients reported more psychological and somatic complaints than those who were not depressed. Since the non-depressed group did not report more problems than the control group, the authors concluded that the problems reported by tinnitus patients were more closely related to the depression than to the tinnitus.

There is a risk of circularity of argument here, since anxiety symptoms often form part of tinnitus severity measures.[47] However, even when this is taken into account, tinnitus patients report greater than average cognitive anxiety (worry and negative self-talk) and somatic anxiety (rapid heart rate and shortness of breath), which continues after treatment.[30] There is also evidence that depressed and anxious patients report more tinnitus distress and severity,[14, 32, 48, 49] and that anxiety at onset predicts tinnitus distress 6 months later.[19] The interaction between tinnitus and psychological state is implicated by the relationship between post-traumatic stress disorder (PTSD) and tinnitus,[50] where it is likely that the symptoms of PTSD and tinnitus are mutually aggravating. The impression created by the literature is of a diathesis–stress interaction taking place in which the diathesis is the vulnerability to distress, and tinnitus level is the stress.[51]

Tinnitus and suicide

Of those individuals with tinnitus who do commit suicide, it seems that psychological and demographic factors play a more important role than tinnitus itself.[52–55] Jacobson and McCaslin[56] conclude 'it is not tinnitus per se that results in suicide but concomitant psychiatric conditions that amplify the effects of tinnitus on the individual patient'. Lewis et al.[53] found 40% of suicides occurred within a year of tinnitus onset and about 50% within 2 years. Psychological features known to increase the risk of suicide include hopelessness, helplessness, fear and anger. If patients are provided with messages about their tinnitus that evoke such psychological states, then their vulnerability to suicide is likely to increase.

Behavioural responses to tinnitus

Studies of the coping strategies used by tinnitus patients suggest that both avoidant coping strategies[34, 57, 58] and active coping styles[16] are associated with worse tinnitus. Hesser and Andersson[17] found that behavioural avoidance in an effort to reduce or stop tinnitus was a significant mediator in the relationship between anxiety sensitivity and tinnitus distress and tinnitus handicap. Kleinstäuber et al.[59] reported that tinnitus-related fear-avoidance behaviour is highly correlated with anxiety and depressive symptoms and plays an important role in predicting tinnitus handicap. Fear-avoidance behaviour serves to maintain catastrophic thinking. Thus, habituation may be enhanced by a middle-way that involves acceptance and engagement with *life* rather than employing strategies that involve either avoidance or attempts to *defeat* tinnitus.

Concentration/attention problems

Many tinnitus patients complain of difficulties in concentration or attention that they attribute to tinnitus. Research suggests a relationship between tinnitus and inefficiency in cognitive processing. Initial theories suggested that cognitive difficulties are a result of emotional distress,[26, 60] but such studies did not directly assess attention problems, and do not account for the fact that observed difficulties in cognitive functioning were not explained by differences in emotional state.[61–64] Other theories claim that attentional resources are depleted as the individual attends to the tinnitus, and related experiences.[65, 66] It has been argued that tinnitus acts as a competing stimulus that attracts attention away from other things.[67, 68]

Sleep

Sleep disturbance is one of the commonest tinnitus complaints with as many as 71% of tinnitus patients reporting problems sleeping.[69] It is particularly prevalent among children with tinnitus[70–71] and is the main reason why parents seek help for their child. An epidemiological study found poor sleep was reported by 14% of men and 28% of women in an older adult population with tinnitus.[72]

Sleep problems tend to be associated with more distressing tinnitus,[73-77] although direction of causality is unclear. Insomnia is not an inevitable consequence of tinnitus,[78] so tinnitus is probably not a specific sleep antagonist. A premorbid sleep disturbance may create an opportunity to focus upon tinnitus, thus emphasizing a lack of sleep.[79] It may be the anxiety associated with the tinnitus rather than the tinnitus per se that causes sleep problems, as seen in the cognitive behavioural model of tinnitus.[80, 81]

Family and relationships

The way a patient responds to tinnitus may act as a stressor within personal relationships. Emotional distress or avoidance of situations as a result of tinnitus can adversely affect relationships. It is important to consider how the social environment influences tinnitus. For example, the way in which people perceive the negative attitudes of others (e.g. people will treat me differently or get annoyed with me) is associated with severity and reduced quality of life.[82] Other people's responses to the patient can also have an impact by affecting their level of disability. As might be expected, punitive responses and poor marital cohesion tend to result in demoralization,

particularly in the context of depression.[83] Perhaps more surprisingly, solicitous responses by spouses can also have a detrimental effect, with enquiries about tinnitus increasing distress.[84] It is thought that both punitive and rewarding responses to tinnitus impede habituation.[83] Helpful responses to tinnitus should thus be supportive, acknowledging the distress, without encouraging further distress-related behaviour. This approach would seem to be relevant to all social contexts including the clinical one.

TREATMENTS FOR TINNITUS

Cognitive behavioural therapy

The main psychological therapy used in the management of tinnitus is cognitive behavioural therapy (CBT). CBT is an effective psychological treatment for a range of psychiatric disorders.[85, 86] It can bring benefits to individuals with long-term physical health conditions and somatoform disorders,[87, 89] insomnia[89] and tinnitus.[90]

CBT MODEL AND RATIONALE

CBT seeks to change *overly* negative thoughts and beliefs about tinnitus (and other issues causing distress), thus breaking unhelpful feedback cycles, reducing distress and improving habituation. Many of the negative thoughts that people hold about tinnitus are accurate: 'I have tinnitus,' 'I will never have silence.' However, they may also be troubled by thoughts that are inaccurate or unhelpful and which can increase tinnitus-related distress: 'Tinnitus will drive me mad' or 'This is affecting me so much I must be a weak person.' Thoughts tend to become more 'distorted' as stress levels increase and mood deteriorates. In CBT, the patient is helped to recognize the link between thoughts, mood and behaviour and to identify and challenged 'distorted' or unhelpful thoughts. The patient can then generate alternative, realistic and helpful thoughts.

Behaviour is also targeted because the actions taken by a person to reduce tinnitus tend to keep them focused upon tinnitus, reduces their quality of life and maintains their distress, by preventing the opportunity to test out and disprove negative (and often distorted) cognitions. Avoidance behaviours play a particularly important role in inhibiting habituation or even sensitizing a person to tinnitus or hyperacusis-related information. In therapy, unhelpful behaviours are identified and support for change is provided,[7] for example through exposure to noisy and quiet environments. Baguley and colleagues[1] outline a standard CBT package. CBT is time-limited (six to ten weekly sessions) and teaches skills that will enable the person to become their own 'therapist'. Homework assignments reinforce the skills learnt in therapy sessions. After therapy ends, a follow-up session can be offered to maintain progress. CBT for tinnitus can also be successfully delivered on a group basis.[91]

EVIDENCE BASE FOR COGNITIVE BEHAVIOURAL THERAPY

CBT is a well-validated treatment for tinnitus[90, 92] and a number of meta-analyses describe the beneficial effects of CBT on tinnitus-related distress. Andersson and Lyttkens[93] analyzed 24 studies (n = 700) of psychological therapy; this showed strong to moderate effect sizes on tinnitus annoyance post-treatment and at follow-up. CBT (Cohen's d = 1.1) was more effective than other psychological treatments (Cohen's d = 0.30) on ratings of annoyance in controlled studies. Smaller effect sizes were obtained for measures of negative affect and sleep problems. Effects upon tinnitus loudness were weaker and disappeared at follow-up. The largest meta-analysis to date[90] looked at 15 randomized controlled trials (n = 1091) and found CBT to have a significant positive impact on tinnitus-related distress (effect sizes ranging from 0.44 to 0.7) as well as a significant positive effect on mood. The benefits of CBT remained significant at follow-up.

Cochrane reviews of CBT for tinnitus[6, 94] have used tinnitus loudness as a primary outcome and tinnitus severity (a global measure of distress or quality of life) and depression as secondary outcomes. They found no effect of CBT upon tinnitus loudness but tinnitus-related distress improved with effect sizes ranging from 0.64 to 0.91. This review found a mild but significant impact on depression when compared with a waiting list control (effect size = 0.37). Since CBT is not designed to change tinnitus loudness, it is perhaps not the most appropriate primary outcome indicator, particularly as many CBT studies do not even measure it.

Self help and the internet

CBT equips patients with skills that ultimately should allow them to cope with difficulties on their own. As such, interest has grown in CBT-based self-help treatments that involve minimal therapist contact.[96] Bibliotherapy (self-help books or manuals) offers significant benefits, enhanced by minimal therapist support but attrition rates are higher[96, 97] and effect sizes smaller than in regular CBT.[6, 90, 93] Internet-based CBT delivers self-help via a computer programme, with therapist support provided over email. Outcomes are superior to self-help manuals in relieving tinnitus distress and depression,[98–100] with reports of benefits equal to those found in regular CBT,[100] although attrition rates can again be high.[101]

'Third wave' therapeutic approaches

'Third wave' approaches refer to CBT that has been developed and extended by increasing the emphasis upon accepting unwanted thoughts and feelings.[103] Suffering is regarded as a normal part of life, and attempts to resist or change suffering can potentially perpetuate distress. There are two overlapping strands: acceptance and commitment therapy (ACT) and mindfulness-based therapies such as mindfulness-based cognitive therapy (MBCT). ACT has been shown to reduce tinnitus distress,[103] with

effects equivalent to conventional CBT[104] and that surpass tinnitus retraining therapy.[105] ACT has been delivered effectively via the internet,[106] and a comparison of internet-delivered CBT and ACT found that acceptance mediated therapeutic change in both approaches. Mindfulness in the form of MBCT was originally developed as a treatment for recurrent depression[107] for which it is now a NICE recommended treatment.[108] More recently, MBCT has been developed for tinnitus and a randomized-controlled trial has found MBCT to be superior to applied relaxation in reducing tinnitus-related distress.[109] Further trials are under way.

HYPERACUSIS

Hyperacusis has been studied much less than tinnitus. Nonetheless, the evidence that does exist suggests that the two symptoms share many psychological characteristics and processes. As in tinnitus, patients with hyperacusis often report elevated levels of emotional and psychological distress, particularly anxiety.[110] Reports that 56% of patients with hyperacusis have at least one psychiatric disorder[111] is comparable to tinnitus patients. However, hyperacusis may exacerbate distress further, as tinnitus patients who report comorbid hyperacusis also report increased levels of psychiatric disorder compared to patients with only tinnitus.[44] The association between hyperacusis and emotional distress clearly points towards a need to improve our understanding of the psychological factors maintaining hyperacusis.

Behavioural responses in hyperacusis are characterized by avoidance and safety behaviours (avoiding noise and using ear protection).[110] Such behaviour is comparable to the fear-avoidance found in tinnitus and pain.[60] As in tinnitus, hyperacusis has important social implications. If patients react to noise with avoidance, their capacity to engage in normal daily activities and effective interpersonal functioning will be inhibited. However, here and in many other aspects of hyperacusis the research evidence is sparse, so the conclusions that can be drawn are limited.[110]

With such limited evidence, there is understandably little consensus about treatment strategies for hyperacusis. If we consider the presentation of hyperacusis in the clinic, two forms of intervention are indicated. The first is that of desensitization to sound.[111] This involves the use of white noise generators with sound levels gradually increased over time. There is, however, no evidence on the efficacy of this treatment. Weaknesses in extant studies of sound therapy for hyperacusis are present due to the reliance upon loudness discomfort levels (LDLs) as a subjective and unreliable measure and the paucity of peer reviewed studies.[110] To assess the value of LDLs as an outcome measure, well-controlled outcome studies are required.

The second main treatment approach involves talking therapies to reduce the distress that accompanies hyperacusis. Given the observation that anxiety is the predominant comorbid psychiatric presentation for patients with hyperacusis, CBT may be an effective treatment strategy.[112] A randomized-controlled trial of six sessions of CBT for hyperacusis, using psychoeducation, applied relaxation, exposure to sound and behavioural activation to reduce avoidance of noise, found improvement in LDLs and depression.[113] This is the first RCT into CBT for hyperacusis so further studies are needed before firm conclusions can be made.

SUMMARY

The experience of tinnitus involves the complex interaction of biological, psychological and social processes; this interplay is likely to be of relevance to hyperacusis as well. Psychological distress, particularly anxiety and depression, are common experiences among tinnitus and hyperacusis patients. Negative thoughts (particularly catastrophic thoughts), avoidant behaviour and emotional distress also act as provocations for tinnitus and hyperacusis-related problems. These processes are particularly important in determining the overall experience.

While a biological solution may still be the holy grail of tinnitus treatment, currently psychological treatments appear to offer the most effective remedy for patients. A psychological approach is unlikely to make tinnitus (or hyperacusis) disappear, but it can lead to a significant reduction in distress, and enable people to return to living a more 'normal' and meaningful life. The consultation with the clinician is a critical part of the experience of tinnitus (and probably hyperacusis) as it shapes the social context of tinnitus and can have a profound impact upon psychological processing. The clinical environment will shape the thoughts, behaviours and emotions of patients and their significant others, and therefore provides an important opportunity for therapeutic benefit, or a risk of iatrogenic harm. It is incumbent on the clinician to be aware of the multiple mechanisms at work in tinnitus and of the effective therapeutic strategies that can support them.

FUTURE RESEARCH

- More research is needed into a biopsychosocial approach to tinnitus.
- Mindfulness-based cognitive therapy has been shown to be superior to applied relaxation in reducing tinnitus-related distress. Further trials are needed.
- We need to improve our understanding of the psychological factors maintaining hyperacusis.
- Cognitive behavioural therapy for hyperacusis has shown improvement in loudness discomfort levels and depression. Further studies are needed before firm conclusions can be made.

KEY POINTS

- The experience of tinnitus is as much a psychological as a biological process.
- Cognitive factors, particularly catastrophic thinking, are leading determinants of tinnitus-related stress. The influence of personality type seems to be mediated by cognitive processes and emotional state.
- The clinical encounter can influence the patient's thinking for better but care is needed as an overly biological approach can contribute to negative thinking.
- Behavioural processes, particular avoidance and escape behaviours maintain and exacerbate distress.
- CBT and acceptance based psychological therapies can reduce tinnitus related distress.
- A number of psychological processes are common to both tinnitus and hyperacusis.

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CHAPTER 71

AUDITORY PROCESSING DISORDERS ACROSS THE AGE SPAN

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: auditory processing disorder, aging, children, cognition, language, diagnosis and management.

PREVALENCE AND DEFINITION

Approximately 5% of children and 1–10% of adults who present to audiology departments with complaints of significant listening difficulties in noise or in group conversations have normal pure-tone thresholds.[1, 2] In a proportion of these patients, their listening symptoms are attributed to functional deficits in sound processing within the extended central auditory nervous system.[3] This clinical presentation is categorized as auditory processing disorder (APD, category H93.25 in ICD-10).[4] This clinical presentation has attracted considerable debate that is summarized to some extent in several consensus statements from professional audiological organizations.[5–9] However, there is no international consensus on what constitutes APD as yet, nor is there explicit agreement on diagnostic criteria for this clinical entity.

AETIOLOGY ACROSS THE AGE SPAN

In children, as well as in adults, APD may be diagnosed in the background of neurological disease such as brain tumours, stroke, trauma, prematurity or low birthweight, epilepsy and brain infections or demyelinating conditions.[10] In some cases, APD may also be the first or even the only feature of neurological disease, both in children[11] and in adults[12] (see also **Figure 16.1** from Bamiou and Iliadou)[13], highlighting the need for clinicians to maintain a high clinical index of suspicion and to investigate for neurological causes. APD may also overlap with several developmental disorders such as language impairment (LI), dyslexia and attention-deficit and hyperactivity disorder (ADHD) and in such cases the clinician should carefully consider whether the clinical presentation is due to deficits in higher-order language or cognitive domains rather than to the deficits within the auditory modality.[14–17] Clinical comparisons of children with APD versus children with specific LI and/or dyslexia find broadly similar profiles in these children.[13, 15, 18] This has led to speculation that these language-based disorders may be different labels or parts of the spectrum of the same developmental disorder.[3, 15] Another subtype of APD is the 'spatial processing disorder' (SPD).[19] SPD is attributed to the presence of a prolonged history of chronic otitis media in childhood which gives rise to deficits in binaural auditory processing due to the prolonged or fluctuating auditory deprivation. SPD is thought to be present in 6% in a population with high incidence of chronic otitis media and in up to 15% in children referred for speech-in-noise difficulties.[19, 20] In adults, APD may be a feature of psychiatric presentations such as schizophrenia and some subtypes of dementia, or of central presbycusis, which is a multifactorial condition characterized by senescence-related and/or disease-related brain changes.[21–23]

THE DIAGNOSTIC APPROACH

The diagnostic process includes history taking, including patient/teacher/parent questionnaires, followed by targeted medical examination. Children and adults with APD have difficulties with speech in noise, auditory attention, localization of sound and other auditory difficulties.[24–26] The history should establish the patient's and/or carer's main concerns and related symptoms, and the symptom onset and progression. Children may experience difficulties in the classroom and psychosocial difficulties that may persist well into adulthood.[27, 28] Key symptoms and difficulties are summarized in **Box 71.1**. History should also include medical history (to ascertain risk factors/other impacting factors), as well as early developmental, educational and professional history of the individual, and family history for related disorders (hearing, auditory processing, other developmental, neurological disorders). This part of the evaluation will also include questionnaires, which are used to collect as much information as possible for the clinical presentation.[15, 25, 26, 29]

The initial information collected during the medical interview will guide the choice of appropriate audiological tests, which should include a thorough assessment of peripheral auditory function as well as tests of auditory processing, both speech and non-speech. The American Speech-Language-Hearing Association (ASHA) technical report proposes that, in addition to pure-tone audiometry and speech-in-quiet tests, a central auditory processing battery should include tests for auditory discrimination, temporal processing and patterning, dichotic speech, monaural low-redundancy speech, binaural interaction, and electroacoustic and electrophysiological measures (see **Table 71.1**).[5, 6] The rationale behind this proposal (which is still followed by most audiology clinics worldwide) is that one needs to check thoroughly cochlear and auditory nerve integrity and subsequently different domains of central auditory processing. However, with a few exceptions for tests developed in recent years, clinically available tests are affected by a range of higher-order factors.[30]

Assessments of other domains such as language and cognition are of paramount importance in order to provide a clearer understanding of the patient's communication profile and needs while other medical

BOX 71.1 Key symptoms and difficulties of auditory processing disorder

Difficulties understanding speech: In background noise, acoustically challenging/complex acoustic environments, when speech quality is degraded
Difficulties discriminating speech: Difficulties repeating or recalling similar-sounding words
Sound localization/streaming difficulties: Difficulties identifying the source of a sound; with separation of auditory foreground from auditory background
Auditory attention/memory difficulties: Difficulties recalling instructions; difficulties concentrating in noise
Hyperacusis: With or without a diagnosis of autism spectrum disorder
Need for multisensory cues: For example, seeking visual/facial cues to better understand
Disproportionate educational/cognitive/language difficulties:

- In the presence of normal audiometry and no other developmental disorders OR
- In the presence of normal audiometry and other diagnosed developmental disorders (specific LI attention deficit disorder; autism; dyslexia) and (i) DESPITE implementation of appropriate interventions or (ii) when other specialists or the educational environment seek further advice/assessment on management of the auditory aspect of this presentation

TABLE 71.1 An APD test battery[6]

AP domain	Test assesses	Test examples
Auditory discrimination	Ability to differentiate similar acoustic stimuli that differ in frequency, intensity and/or temporal parameters	Difference limens for frequency, intensity and duration; psychophysical tuning curves; phoneme discrimination
Auditory temporal processing	Ability to analyze acoustic events over time	Pattern tests; gap detection in noise; fusion discrimination, integration; forward and backward masking
Dichotic listening	Ability to separate (i.e. binaural separation) or integrate (i.e. binaural integration) disparate auditory stimuli presented to each ear simultaneously	Dichotic consonant–vowels, digits, words, sentences
Low-redundancy speech recognition (monaural)	Recognition of degraded speech stimuli presented to one ear at a time	Filtered, time-altered, intensity altered, speech-in-noise or speech-in-competition
Binaural interaction	Binaural processes dependent on intensity or time differences of acoustic stimuli	Masking level difference, localization, lateralization, fused-image tracking Listening in spatialized noise
Other tests		
Electroacoustic measures	Otoacoustic emissions, acoustic reflex thresholds and acoustic reflex decay	
Electrophysiological measures	Auditory brainstem response (consider middle latency response, cortical event-related potentials and other responses)	

investigations ought to be considered as required, and additional information gathered (e.g. school observation).[5, 6] It is also useful to establish how the individual and their family perceive and explain their communication-related difficulties, any previous related assessments conducted and any remedial action taken or strategies implemented.

The diagnostic decision-making will synthesize this information in order to interpret reported symptoms in the light of test/assessment results and other contextual factors. However, it must be noted that professionals in the audiology field use different diagnostic criteria for APD and a recent review by Wilson and Arnott revealed nine different diagnostic criteria with a diagnostic yield of 7.3% up to 96% for APD.[31]

CONFOUNDING FACTORS AFFECTING APD TEST PERFORMANCE ACROSS THE AGE SPAN

Throughout the age span different confounding factors might affect APD test performance and hence the aetiology and diagnosis of APD.

In children, the extent to which non-sensory factors, such as working memory and attention skills, might affect negatively the performance on APD tests is still under debate.[32, 33] This is because some non-auditory cortical areas, which are also involved in the neural processing of sound, such as inferior prefrontal cortex and the posterior temporoparietal areas, are still in development until the age of 10 years.[32] Thus, it is discussed whether the variability in the APD performance reflects the maturation aspects of cognitive skills rather than some specific auditory processing skill impairment. Additionally, some auditory processing tests include highly cognitively demanding tasks, especially those including verbal response, such as dichotic digit or frequency pattern test.[33] Thus, maturation aspects of cognitive skills (late or incomplete maturation) combined with highly cognitively demanding tasks might lead to confounding results and difficulties in interpretation. To minimize the cognitive influence, the use of intratest comparison measures, such as right ear advantage index and humming-label differential,[34] are taken into consideration. Additionally, the need for cross-modality testing is also discussed.[35, 36]

In middle-aged and elderly individuals, age-related hearing loss as well as age-related cognitive decline might also lead to difficulties in interpretation of APD performance.[37–41] Age-related cognitive decline is a well-known confounding factor for auditory processing performance, particularly because of the cognitive–sensory interaction that is observed with ageing.[42, 43] Research has also demonstrated that some tests are more susceptible to hearing loss effects, especially tests involving understanding speech. This is because the broadband nature of speech signals requires reasonable audibility over at least 4000 Hz for discrimination.[23, 44]

Given the increasing recognition of the influence of many confounding factors affecting auditory processing test performance, the appropriate selection of tests as well as their careful interpretation must be taken into consideration on APD diagnosis. Assessment of elderly subjects' cognitive skills, such as working memory, would be useful before interpreting their performance on auditory processing tests. In addition, both the degree and configuration of the hearing loss must also be taken into consideration, especially when considering results of auditory processing tests involving verbal stimuli. For children, further studies should focus on the development of clinical auditory processing tests with low cognitive demand to reduce the impact of non-sensory factors on APD performance.

MANAGEMENT STRATEGIES

The goal for APD rehabilitation is to improve the functional deficits of individuals with specific impairments that are impacting on their communication and overall well-being. In order to achieve maximum functional benefit, a multidisciplinary team approach should be employed.[45] Generally, a comprehensive management programme for APD should focus on the following three areas:[45, 46]

- to remediate the disorder by means of techniques that aim to harness the brain's ability for change (i.e. neuroplasticity) in order to enhance neuroauditory function (e.g. auditory training)
- to improve access to auditory information by changing the environment (e.g. signal enhancement strategies, including frequency modulation systems/remote microphone hearing aids and teacher/speaker based adaptations)
- to improve listening and learning skills by teaching children and adults various compensatory strategies to overcome their residual functional difficulties (e.g. metacognitive and metalinguistic training).

Auditory training

Auditory training (AT) aims to capitalize on the brain's ability for structural and functional reorganization in response to sensory input across the lifespan. This brain 'plasticity' may involve the activation of inactive neuronal connections and/or the formation of more efficient synaptic connections within the brain; such changes are often associated with behavioural changes.[47, 48] AT involves listening exercises that aim to improve auditory system function and to achieve successful auditory learning, i.e. a relatively permanent improvement of perception and behaviour.[49, 50] AT studies in normal adults indicate that learning is better when the listener works hard enough for attention to be taxed.[51] It is also important to train with a wide variety of materials and situations since studies indicate that learning may not generalize to untrained material.[52] AT can be categorized as formal or informal. Informal AT can be a school- or home-based programme

as well as therapy conducted by a speech and language therapist or audiologist in the clinic, and it involves predominantly language-based tasks that tap into multiple processes concurrently. Examples of informal AT are discriminating similar-sounding notes on a keyboard for training temporal patterning skills phoneme discrimination exercises for training auditory discrimination skills and listening to lyrics of songs for training speech-in-noise ability.[45, 48] Formal AT is typically conducted in a controlled setting, such as a clinic or a lab, by audiological professionals, or at home, by means of CDs/web-accessed services. Formal AT uses acoustically controlled training paradigms with the ability to specify and precisely alter the stimuli.[53] Formal AT employs a variety of auditory tasks including tonal and speech stimuli.

There are several commercially available computer-based AT programs in the English language, for both adults and children (see **Table 71.2** for some key examples). Post-training improvements are reported on a range of auditory and non-auditory measures for a broad range of paediatric populations with disorders that overlap APD, in APD populations as well as in adults.[49, 54–58] However, it remains unknown which program works best (compared to others) and what the optimum dosage and long-term benefits are.

Signal enhancement strategies

Signal enhancement strategies include environmental modifications, to reduce the synergistic deleterious effects of noise and reverberation of the acoustic environment on the target speech (or other acoustic) signal, and assistive listening devices such as remote microphone hearing aids (RMHAs). (For a list of environmental modifications that can be applied in school classrooms or elsewhere, please see BSA APD document, page 55[7] – discussion of these is beyond the scope of this chapter.) RMHAs are personal listening devices that bypass high-level classroom noise and transmit clearer speech to the child's ears. RMHA use may improve speech understanding by 53%.[59]

Studies of children with abnormal speech-in-noise performance due to abnormal auditory processing show improved speech reception even without FM (after 5 months FM use), improved observer-rated listening and behaviours as well as improvements in higher-order processing such as working memory after 12 weeks and spelling after 6 weeks.[27, 54, 60, 61] Importantly, some behavioural improvements in phonological processing have been shown to correlate with improved consistency of electrophysiological neural response to complex sounds (after 1 year of RMHA use), indicating that such interventions may have positive effects on brain plasticity.[62] There are a couple of studies in adults with auditory perceptual problems, in the presence of auditory neural pathology within a diagnosis of Friedreich's ataxia and another study in adults with multiple sclerosis.[63, 64] The study by Rance et al. on Friedreich's ataxia patients that included both children and adults reported a mean 18% improvement in communication and 20% improvement in speech-in-noise intelligibility with FM versus without FM in a hearing disability questionnaire that assessed listening in the patient's everyday situations after 6 weeks' use. Lewis et al. similarly reported good benefit in their adults with multiple sclerosis, indicating that this technology can be applicable for a wide range of APD presentations across the age spectrum.[64]

Compensatory strategies

Compensatory strategies are taught in order to help overcome dysfunction and maximize the use of auditory information.[45] These strategies may include, for example, 'active listening' where the individual is taught how to taking responsibility for their own listening, strategies that aim to enhance memory (e.g. auditory memory enhancement or auditory directives training) or attention (e.g. auditory vigilance strategies), and linguistic and metacognitive strategies.

TABLE 71.2 Computer-based AT programs for adults and children: key examples

AT for children	Description
FastForWord (Scientific Learning Corporation, USA)	This is an adaptive intervention program that employs acoustically modified non-speech and speech sounds (e.g. elongated tones, slower-rate speech sounds) and is designed to train temporal processing, speech perception and language comprehension skills.
Earobics (Houghton Mifflin Harcourt)	The activities aim to improve sound awareness, discrimination of sound in noise and quiet, sequencing sound, associating sound with letters, understanding of complex directions with and without background noise, and memory for sounds and words, and include items to strengthen reading, spelling and comprehension.
LisN & Learn (NAL, Australia)	This aims to improve listening in noise for children diagnosed with spatial processing disorder (SPD). It involves word identification from a target sentence that appears to emanate from 0° azimuth while background noise (looped children's stories) comes from either + or - 90° simultaneously.
Adult AT	
'Listening and Communication Enhancement' –LACE (Neuroton)	This is marketed as top-down intervention for speech-in-noise difficulties and includes degraded speech tasks, cognitive tasks and interactive communication strategies screens.
Brain Fitness Program for auditory processing (Posit Science)	This includes six adaptive exercises which aim to enhance the fidelity in auditory sensory input and language representations. It is specifically designed for older adults.

Curriculum modifications (such as preteaching new material, giving breaks to the student during the day) are also widely used. These are not formally validated in controlled studies, but there is good consensus that such strategies are of considerable benefit.[4]

AUDITORY TRAINING BENEFITS ON AUDITORY PROCESSING AND TOP-DOWN SKILLS: GENERALIZATION OF LEARNING

It is well established that AT improves auditory trained tasks. However, the extent to which auditory learning transfers to top-down skills such as language and reading skills remains unclear. This topic is important due to the co-occurrence of APD with other learning difficulties such as dyslexia, phonological disorder and ADHD. Some studies have demonstrated learning generalization following non-linguistic AT to measures of language, including reading, speech perception and phonological awareness.[65–67] Others reported on-task learning but no generalization to higher-level measures of language skills.[52, 68]

According to Mossbridge et al., generalization of learning can only occur if the neural circuits modified during training also influence the untrained task performance.[69] In general, during perceptual training such as AT training, several abilities are trained simultaneously (e.g. linguistic, cognitive and perceptual skills), thereby hindering investigation into how factors related to the training may affect the extent of generalization. Despite that, there is considerable evidence that the characteristics of the trained tasks might influence the transfer and specificity of learning.[51] The involvement of complex cognitive skills in AT for children, for instance, might act as a limiting process in the generalization of sensory learning due to the non-maturation of cognitive functions until adulthood.[32] Another important factor is the time course of training. Halliday et al.,[52] for instance, delivered AT for 6 hours and discussed if this length of time was sufficient to observe learning transfer, given that previous research reported successful transfer in training of more than 10 hours.[70, 71] Murphy et al. delivered non-linguistic AT for 9 hours and, as Halliday et al., found no generalization of learning.[68] Given the conflicting findings, further studies should investigate the extent to which different lengths of the same training affects learning followed training.

CONCLUSION

Despite the considerable research addressing APD aetiology and the development of several clinically available tests, APD diagnosis is not straightforward and it must be carried out taking into account all possible confounding factors affecting the test performance across the age span. A multidisciplinary approach aimed at the differential diagnosis between APD and other disorders with similar profiles is essential. Currently, several different management strategies are available to rehabilitate APD but well-designed studies are still needed to determine the extent of learning generalization and overall real-life benefits for the affected individual following the training as well as what is the best training method for the different populations with APD.

KEY POINTS

- Despite the lack of international consensus on diagnostic criteria and management of auditory processing disorder (APD), it is well-accepted that children and adults may experience significant listening difficulties in the presence of normal pure-tone audiograms, which might be categorized as APD.
- Different confounding factors such as memory, attention and hearing loss, may interfere on auditory processing test performance across the age span; as a consequence, an appropriate selection of tests as well as their careful interpretation must be taken into consideration on APD diagnosis.
- A multidisciplinary team approach should be employed for APD rehabilitation taking into account varied strategies such as auditory training, signal enhancement and compensatory strategies.

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CHAPTER 72

NEUROPSYCHIATRIC ASPECTS OF VESTIBULAR DISORDERS

Julius Bourke, Georgia Jackson and Gerald Libby

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SEARCH STRATEGY

Data in this chapter may be updated based on searches of relevant textbooks, PubMed and other online search tools using the keywords: chronic dizziness, unexplained dizziness, functional dizziness, psychogenic dizziness, phobic positional vertigo, space and motion discomfort, chronic subjective dizziness, alone and in combination with psychopathology, anxiety, stress, depressive disorder and psychiatric.

INTRODUCTION

Psychogenic, somatoform or functional dizziness refers to dizziness in the absence of objective organic pathology or an alternative diagnosis that is able to explain its presence. It is a common problem: 20% of primary care patients seek help for dizziness during their lifetime,[1–4] it is chronic in 30% of these[3] and 10% with chronic dizziness are functionally impaired.[2] Typically, patients are initially referred to cardiology, neurology and specialist vestibular clinics but in 30% of cases investigations and diagnosis are unable to account for the symptoms.[5]

'Psychogenic dizziness' is, however, a 'catch-all' diagnosis that is steeped in misunderstanding. Recent concepts of phobic positional vertigo, space and motion discomfort and chronic subjective dizziness have done much to clarify a syndrome of unexplained chronic dizziness. This has aided a disabled and sadly often disregarded patient group in terms of understanding and ultimately treatment. The common thread running through these three descriptive concepts is the presentation of dizziness with a predominance of anxiety and disordered affect that must be appropriately managed for an optimal outcome.[6]

Here we focus on the importance of neuropsychiatric contributions to these disorders and their treatment from a primarily psychopharmacological but also psychotherapeutic perspective.

NOMENCLATURE

Agoraphobia

In the 19th century, Karl Westphal described a disorder defined by debilitating dizziness, spatial disorientation and anxiety when exposed to open spaces: agoraphobia. Agoraphobia subsequently became a syndrome defined more by a phobic response to situational exposure and heightened anxiety with or without panic attacks, rather than by dizziness per se.

It was not until the 1950s that the concept of psychogenic dizziness as a clinical entity re-emerged. Since then, various approaches to reaching this diagnosis have been described.[7–9] The core premise to all of these proposed diagnostic strategies was the presence of dizziness without true vertigo, typically occurring in anxious individuals, replicated by hyperventilation and combined with the presence of psychiatric symptoms preceding the onset of dizziness. There are assumptions here that are problematic: that anxious individuals do not suffer from vestibular disorders and that individuals with vestibular disorders do not suffer from anxiety. This is obviously not so.

Phobic positional vertigo

In the mid-1980s, Brandt and Dieterich defined phobic positional vertigo (PPV): postural dizziness with a

subjective sense of disturbed posture and unsteadiness, which could be precipitated by complex and motion-rich environmental and situational stimuli. Similar to the concept of psychogenic dizziness, Brandt and Dieterich noted a prominence of anxiety-related symptoms, obsessive–compulsive personality traits and biological or vegetative symptoms, more typical of disorders of affect.[10] Precipitants for the disorder were noted as vestibular disorders and stress. They reported that PPV was the second most common cause of dizziness presenting to their practice and the most common in younger adults.[10]

Longitudinal studies have demonstrated that, as a diagnostic entity, PPV is a stable construct,[11] still being clinically identifiable in patients followed up 5–15 years later. As such, PPV demonstrates a chronicity with a fluctuating course of improvement and exacerbation of symptoms but without full remission.[11] Long-term follow-up also determined that the high incidence of major depressive and anxiety disorders in this cohort of patients was chiefly responsible for the significant disability and poor prognosis of the disorder.[10] The involvement of these neuropsychiatric disorders in disability and poor prognosis is something well recognized today in a variety of different clinical conditions. In PPV, this was so much the case that it has been debated as to whether PPV was in fact a vestibular or a psychiatric disorder. However, in spite of the strong link between anxiety, panic and major depressive disorder, PPV was argued to be a distinct pathology closely linked to these syndromes, rather than occurring as a direct sequela of them.[10, 11]

PPV was, therefore, a stable, reliable and inclusive diagnosis. However, in spite of its diagnostic stability, treatment studies of PPV were disappointing (involving a mixture of reassurance, behavioural desensitization through increasing exposure and serotonergic antidepressants). Longer-term studies have demonstrated some improvement in symptoms but rarely resolution, with almost half of all patients relapsing in the subsequent 12 months, once or repeatedly.[11]

Space and motion discomfort

Space and motion discomfort (SMD)[12] unified the previously described situationally specific syndromes characterized by anxiety and phobic symptoms combined with dizziness, such as street neurosis,[13] space phobia[14] and motorist vestibular disorientation syndrome.[15] SMD refers to the physical symptoms that arise when the sensory information necessary for normal spatial orientation is inadequate or conflicting. In SMD, visual and proprioceptive input is thought to compensate for defective vestibular sensory input, with consequent visual or proprioceptive dependence and heightened sensitivity to these inputs.

SMD describes discomfort that includes dizziness, imbalance or anxiety in situations characterized by certain spatial or motion characteristics. The avoidance of these symptoms leads to the avoidance of the situations likely to precipitate them and, ultimately, to increasingly phobic and disabling behaviour.

SMD therefore refers to situationally specific vestibular symptoms occurring with anxiety and ultimately resulting in phobic avoidance. A questionnaire measure for SMD has been successful in identifying vestibular dysfunction across five groups (panic disorder, agoraphobia with panic disorder, other anxiety disorders, major depressive disorder and healthy controls), with the highest frequency of vestibular dysfunction and SMD being in patients with agoraphobia with panic disorder.[16] In support of this, most studies, although not all, have found a high incidence of abnormalities on vestibular function tests in panic disorder, especially those with agoraphobia.[17] SMD is therefore common in anxiety disorders and its presence predicts vestibular dysfunction. Jacob et al. have subsequently suggested that the absence of panic disorder or acrophobia (a fear of heights) reduces the probability of peripheral vestibular dysfunction and that, where this dysfunction is present, it is likely to complicate the phenomenology of anxiety disorders.[18]

Psychiatric dizziness

Furman and Jacob[17] proposed the more narrow definition of 'psychiatric dizziness', namely dizziness occurring 'exclusively in combination with other symptoms as part of a recognized psychiatric symptom cluster and this symptom cluster is not itself related to vestibular dysfunction'. That is to say that dizziness occurring with panic attacks was 'psychiatric' but that dizziness occurring between panic attacks was not. The caveat made by the proponents here was that this diagnosis did not exclude the possibility of 'functional' or 'psychogenic' overlay, whereby non-psychiatric dizziness is exacerbated by the presence of psychopathology through 'amplification of somatic sensations'. They noted that this was most common in those disorders where hypochondriacal concerns were prominent (anxiety and panic disorders, major depressive disorder and somatoform disorders) as well as those with particular personality traits, citing those found by Brandt in his PPV sample (predominantly obsessive–compulsive).[10] Based upon their definition of 'psychiatric dizziness', Furman and Jacob[17] suggested that PPV was a reflection of vestibulopathy with 'psychogenic overlay' and that its aetiology in this regard was related to a predominance of particular personality trait clusters.

Chronic subjective dizziness

In the early 2000s, Staab and Ruckenstein[19–21] noted that what was previously described as psychogenic dizziness lacked diagnostic specificity as it was also present in migraine, mild traumatic brain injury and dysautonomias. Staab et al. further refined these concepts, removing emphasis from the presence of psychiatric phenomena and presenting the new diagnostic formulation of chronic subjective dizziness (CSD). Staab et al. concede that anxiety is responsible for most of the morbidity of somatoform dizziness but explain that it was not included as a core symptom in order to avoid the assumption that the syndrome is psychiatric alone.[5]

CSD consists of three central components, namely chronic subjective dizziness (of 3 months or more),

hypersensitivity to motion stimuli (including one's own movement) and difficulty or exacerbation of symptoms with complex visual tasks (e.g. reading, writing, using a computer). Three subtypes were described:[19]

- **Neurotological:** This group had a current or past history of transient illnesses (e.g. neuronitis, adverse drug reaction) or intermittent phenomena (e.g. migraine, Ménière's) that triggered secondary anxiety disorders that were predominantly phobic.
- **Psychogenic:** These patients exhibited primary anxiety disorders that resulted in dizziness, with panic disorder being the most frequent cause.
- **Interactive:** This group included those patients with a neurotological complaint that exacerbated a pre-existing anxiety disorder (most often generalized anxiety disorder).

Notwithstanding these subdivisions and the absence of anxiety as a core defining symptom, as a group, patients diagnosed with CSD are nearly all diagnosed with either psychiatric or neurological disorders.[20] Staab's group reported 59.7% of CSD patients demonstrating either primary or secondary anxiety. Others have suggested that this is higher, with one group reporting a clinic sample in which almost 80% were diagnosed with anxiety.[22]

CSD has been met with more consistent psychopharmacological treatment responses than PPV,[21] although psychotherapy has been less successful[23] and without long-term improvement beyond 6 months.[24, 25]

Persistent postural-perceptual dizziness

A further diagnostic category has been divined in a consensus document recently published: persistent postural-perceptual dizziness (PPPD),[26] which is expected to be added to the international classification of vestibular disorders (ICVD).

The diagnostic criteria include dizziness, unsteadiness, or non-spinning vertigo that are present pervasively over three months or more and which are exacerbated by upright posture, active or passive movement, and exposure to moving or complex visual stimuli.[26] This novel nomenclature represents a synthesis of the terms that have gone before over the past three decades. Within this context, PPPD allows for chronic vestibular symptoms that can be precipitated by other conditions that disrupt balance or cause vertiginous symptoms including dizziness. This takes into account peripheral or central vestibular disorders as well as other general medical and neuropsychiatric comorbidity, whilst emphasizing that it is not a psychiatric but a functional disorder, similar to the ideas underpinning CSD. Although yet to be fully pathophysiologically defined, it is thought to arise from an abnormality in function, including multi-sensory information processing, integration of spatial orientation and threat assessment. This brings pathophysiological concepts of functional vestibular disorders in line with the current neurophysiological understanding of other functional syndromes in which this has been demonstrated.[27] A problem similar to that found in the other functional syndromes also penetrates PPPD, namely the heterogeneity of pathoaetiology, presentation, response to treatment and so prognosis. Subtypes of PPPD are therefore proposed to exist. There is an argument that necessarily arises here – namely is there a single PPPD or a number of subtypes?[26] This too is a debate that has raged in the world of functional syndromes and which has been widely reported (for example the debate between Professors White and Wessely regarding 'lumping' and 'splitting'[28]).

The opinion of the authors of this chapter is that the assumption that subtypes exist, differing physiologically but giving rise to the same or similar phenotypes, matches clinical experience better than does the assumption that all similar presentations are the same. As noted above, this allies the concept of PPPD with other functional syndromes.[27] Such subtypes are yet to be explored fully and until defined are likely to impact upon studies of treatment strategies and responses to them. Any future research involving management strategies will need to take this into account as otherwise, results will need to be interpreted with caution in a similar manner to the interpretation of those studies performed to date, involving a variety of different historical diagnostic terms and criteria.

The importance of anxiety in chronic dizziness

The presence of personality traits that predispose to a state of anxiety (**Table 72.1**) along with varying degrees of clinically significant anxiety and avoidance behaviour have been consistent in the diagnostic formulations of unexplained chronic dizziness. Although the nomenclature has changed and with it the emphasis on these factors, they remain of fundamental importance.

Anxiety and major depressive disorders are common in patients with CSD but do not occur in all cases. The prevalence is, nevertheless, high: 60% of patients with CSD have clinically detectable and significant levels of anxiety, while 45% of patients with CSD have a major depressive disorder. This constitutes 75% of the CSD sample[10, 29] and is higher than in other vestibular disorders,[30–32] although these differences are not sufficient to differentiate between CSD and 'organic' vestibular disorders alone.

More recent studies using the CSD criteria have suggested that high trait anxiety (see **Table 72.1**) or a pre-existing anxiety disorder may predispose an individual to CSD and high state anxiety during an episode of vestibular dysfunction may act as a precipitant, while concurrent psychopathology contributes to disability in those with CSD.[33–36] However, this is perhaps an oversimplification since predisposition to high trait anxiety and anxiety disorders (personal history, personality traits and family history of anxiety disorders) also seems relevant as it is in these predisposed individuals that CSD is typically more chronic.[34] This would not come as a surprise to a liaison psychiatrist, seasoned in the diagnosis of functional somatic syndromes affecting other body systems, because this pattern of vulnerability is the same, so much

TABLE 72.1 Definitions

Trait anxiety	Refers to the general level of anxiety and stress that an individual characteristically experiences as a trait related to their personality. Trait anxiety is relatively stable. Higher levels of trait anxiety would typically be found in a characteristically anxious individual.
State anxiety	Refers to the emotional response experienced in the context of particular situations or events and so is a measure of anxiety that fluctuates with context. Threatening situations, including those experienced on a day-to-day basis, will result in raised levels of state anxiety. State anxiety is not a stable phenomenon and measures will vary depending on context.
Agoraphobia	A situationally specific anxiety disorder. Anxiety typically arises in public and crowded spaces, although it may be a lack of obvious exit or escape that precipitates the anxiety. Subgroups exist, determined by whether panic disorder is present or absent, although panic attacks are frequently present and some suggest that agoraphobia itself is a complication of these. ICD considers agoraphobia in terms of being with or without panic disorder, while DSM works in terms of panic disorder with or without agoraphobia.
Panic disorder	An anxiety disorder, the hallmark of which is panic attacks. These episodes are severe and associated with physical symptoms and disability. In ICD, the disorder is graded as moderate (one attack per week over 4 weeks) or severe (four per week over a 4-week period). DSM does not grade the disorder in the same way, referring instead to recurrent attacks and at least a month of persistent rumination over their recurrence and a behaviour change that accompanies this.
Conversion disorder	The presence of unfeigned neurological symptoms affecting voluntary motor or sensory function in the absence of an accompanying neurological diagnosis to explain them. The onset of symptoms is typically associated with a significant psychosocial stressor. In ICD, conversion disorders are referred to as dissociative disorders.
Malingering	The intentional production or feigning of physical or psychological symptoms or disabilities motivated by external stresses or incentives.
Factitious disorder	The consistent and repeated feigning of symptoms in the absence of a confirmed physical or mental disorder, disease or disability. The motivation for this behaviour is almost always obscure and presumably internal, and the condition is best interpreted as a disorder of illness behaviour and the sick role. Specifically, the unconscious desire appears to be to fill the sick role – to be a patient. Individuals with this pattern of behaviour usually show signs of a number of other marked abnormalities of personality and relationships.

so that a debate as to whether they are in fact representative of a single functional somatic syndrome has ensued.[37]

Ultimately the importance of recognizing and treating anxiety is not down to nomenclature and diagnostic criteria alone: the effect of anxiety on the disability suffered from a comorbid diagnosis[38] and its impact on suicide risk[39] are significant.

DIFFERENTIAL DIAGNOSIS

Although chronic dizziness frequently occurs in combination with clinically significant anxiety, there are additional considerations in the case of the patient who presents with chronic vestibular symptoms, negative investigation results and/or a significantly poorer response to treatment than expected.

The differential diagnosis in this instance should include conversion disorder[40] and, more rarely, malingering[41] and factitious disorder.[42] These are identifiable through a careful clinical history and by tracking the clinical course of the presentation and its response to treatment. The differences between these clinical syndromes are summarized in **Table 72.2**.

It is important to ensure that these differential diagnoses are taken into consideration on a secondary basis, i.e. other diagnostic and treatment avenues must be considered first. Care must be taken here and the diagnosis of conversion disorder should be made by a psychiatrist. The diagnoses of factitious disorder and malingering are potentially harmful to a patient's subsequent medical care and should be made with caution and, in the instance of factitious disorder, must include the early involvement of a psychiatrist.

NEUROANATOMICAL MODEL

The association between anxiety and mood disorders and chronic dizziness can also be found in and potentially explained by the overlap in neural correlates. Animal studies suggest that vestibular deafferentation is associated with increased anxiety-related behaviour,[43–45] while highly anxious strains of mice perform more poorly on tests of balance,[46, 47] with performance improving on administration of benzodiazepines[46] or SSRIs.[47]

In human models, the parabrachial nucleus is important in balance and dizziness with dense reciprocal connections with vestibular nuclei.[48] The parabrachial nucleus is also of importance in the experience of anxiety and related symptoms, including panic.[49–52] It has reciprocal connections with the amygdala, infralimbic cortex, hypothalamus and, via midline structures, the insula.[53–55] Functional neuroimaging studies involving caloric stimulation have also implicated the insula and hippocampus.[56, 57] Insula has been implicated in numerous interoceptive phenomena,[58] including pain,[59] as well as emotional processing.[60] Reciprocal connectivity between insula and amygdala, which is also vital in emotional, anxiety and stress responses,[49, 51, 52] forms a network of both functional and structural connectivity that is strongly associated with both state and trait anxiety.[61]

TABLE 72.2 Clinical differentiation between CSD, conversion disorder, factitious disorder and malingering

	CSD	Conversion disorder[40]	Factitious disorder[42]	Malingering[41]
History	>3 months subjective imbalance or dizziness Hypersensitivity to motion, including one's own or the environment's Exacerbation with complex and motion-rich stimuli	Subjective report of dizziness Difficulties with standing or moving Presence of other neurological complaints such as sensory loss, typically not fitting an anatomical pattern Onset of symptoms may coincide with a readily identifiable stressor Involves 'primary gain' (an unconscious internal motivator)	Subjective reports of dizziness May be accompanied by other varied symptoms History often inconsistent when taken on more than one occasion Falsified names and dates of birth may be used Recurrent presentations at multiple and often geographically diverse hospitals may be discovered May be a history of medical training or employment in an allied field Primary motivation is to be 'the patient'	Subjective reports of dizziness May be accompanied by other varied symptoms History often inconsistent when taken on more than one occasion Involves secondary gain (an external motivator that may or may not be unconscious, e.g. avoiding having to work)
Neurological examination	Normal	Symptoms are inconsistent with clinical signs and do not match anatomical pattern Symptoms may vary with distraction	Symptoms are inconsistent with clinical signs and do not match anatomical pattern Symptoms may vary with distraction	Symptoms are inconsistent with clinical signs and do not match anatomical pattern Symptoms may vary with distraction
Neurological and vestibular investigations	Non-diagnostic (normal or minor abnormalities that do not explain the clinical picture)	Normal May be minor incidental abnormalities that do not explain the clinical picture	Normal May be minor incidental abnormalities that do not explain the clinical picture	Normal May be minor incidental abnormalities that do not explain the clinical picture
Management	SSRIs SNRIs CBT VBRT	CBT Abreaction[96] Longer-term psychotherapy Hypnosis SSRIs or other antidepressants may be useful in treating an underlying depressive or anxiety disorder	Views on management strategies vary The more complex and chronic factitious disorder is often difficult to provide an intervention for Approaches include confrontation, non-confrontation and, in certain circumstances, compulsory detention through mental health legislation Underlying psychopathology must also be adequately treated	Confrontation is rarely successful and more indirect approaches that allow the patient to save face are more advisable The success of management approaches is inversely related to the rewards that are motivating the malingering

CSD, chronic subjective dizziness; SSRIs, selective serotonin reuptake inhibitors; SNRIs – serotonin–noradrenaline (norepinephrine) reuptake inhibitors; CBT – cognitive behavioural therapy; VBRT – vestibular balance rehabilitation therapy.

Connectivity between amygdala and hippocampus is well established and is also of known importance in stress-related responses, which in turn may serve to strengthen this network.[62] The effect of anxiety, mediated by the optimization of autonomic responses through cortisol release, is to switch the amygdala 'on' while switching 'off' the hippocampus. This serves to promote the learning of fear-related information (amygdala) and ensuring that resources are not wasted on more complex aspects of memory and learning (hippocampus). The strength of the 'learning' that occurs during heightened anxiety helps to explain why fear- and anxiety-related memories and associated behaviours are typically the hardest to extinguish. In turn, this might explain why the adequate recognition and management of anxiety is of vital consideration in the morbidity, chronicity and disability of chronic dizziness.

Functional connectivity between the vestibular nuclei and hippocampus is also of importance. Animal models have suggested that this connectivity is a potential link between vestibular lesions and the cognitive deficits seen in patients affected by them,[63, 64] with long-term non-spatial memory deficits arising in rats after bilateral (but not unilateral) vestibulectomy.[65] A small case control series has provided support for this in humans, with hippocampal down-regulation in patients with bilateral vestibular lesions as compared to healthy controls, suggesting that functional hippocampal deficits occur as a consequence of a chronic lack of vestibular input.[66] It has been proposed that anxiety disorders arising in the context of vestibular disorders occur as an indirect consequence of these cognitive deficits.[43] However, research in this area is contradictory[67] and, given that the dorsal raphe nucleus innervates limbic structures, including amygdala, in addition to vestibular nuclei,[48, 68] it is possible that affective aberrations directly influence vestibular networks, while the contribution of the vestibular system to autonomic control[69, 70] may explain how vestibular dysfunction gives rise to anxiety.[71] This interaction between networks, affective tone modulating vestibular function versus vestibular function affecting autonomic tone, has the potential to explain why vestibular complaints are common in psychiatric disorders and why psychopathology is common in vestibulopathy.

NEUROCHEMICAL MODEL

Studies examining the management of disorders such as CSD have predominantly focused on the use of medications that increase monoaminergic (serotonin, noradrenaline and dopamine) neurotransmission (see below). The monaoamines are considered central in the pathophysiology of anxiety and panic disorders.[49, 51, 72–74] Serotonin receptors are present in the vestibular ganglion,[75] with direct serotonergic innervation from the dorsal raphe nucleus (DRN – the largest serotonergic nucleus)[76] and collaterals projecting to amygdala.[68] Serotonergic activity in the vestibular nuclei has an effect on the responsivity of motion-sensitive neural pathways,[77] although the vestibular nuclei also receive non-serotonergic innervation from DRN, including gamma-aminobutyric acid (GABA) and neuropeptides. The locus coeruleus (the principal site for noradrenaline synthesis in the brain) innervates the vestibular nuclei and the cerebellum, in addition to connectivity with limbic areas such as orbitofrontal and anterior cingulate cortices, hippocampus and hypothalamus.[78, 79] These connections may be implicated in SMD and postural sway in patients with anxiety disorders.[18] It has been proposed that these monoaminergic inputs to the vestibular system mediate the effects of anxiety and the responsivity of these systems to novel stimuli.[80]

COGNITIVE BEHAVIOURAL MODEL

The cognitive behavioural models for PPV and CSD are similar and rely on an understanding of behavioural conditioning.[10, 21]

Vestibular symptoms result in strong physiological responses, often with anxiety. Anxiety, especially panic, results in strong physiological responses and physical manifestations that can include vestibular symptoms. These responses result in similar subjective experiences (e.g. lightheadedness, the room spinning, change in heart and respiratory rate). The two of these working in tandem result in a powerful conditioning response and anxiety in particular is a powerful reinforcer of behaviour. Hypervigilence for feared symptoms, particularly in given situations where they might be expected, means that this conditioning is able to sensitize responses to subsequent motion stimuli that may resemble or herald the onset of actual vestibular symptoms, which in turn further reinforces a sensitized response. Both anxiety and vestibular symptoms are unpleasant and the two major behavioural responses to these experiences are exaggerated rescue responses (reaching for something to stabilize the perceived motion) and avoidance. Avoidance is a powerful behavioural reinforcer and in this instance its effects are reciprocal – it reinforces itself. The feared consequences of symptoms that result in such strongly conditioning physiological responses, whether vestibular or anxiety in origin, also lead to the development of cognitive distortions such as catastrophization, lending greater weight to the worst perceived outcome.

It is the potent reinforcing effects of avoidance and associated cognitive distortions that are thought to lead to greater chronicity in such disorders and, as a consequence, greater disability, similar to the pattern seen in agoraphobia.

Cognitive behavioural therapy is aimed at psychoeducation to improve understanding of the origin of symptoms, the reattribution of the misinterpretation of anxiety-related symptoms in order to reduce catastrophization, the development of coping skills through the use of relaxation techniques, which in turn enables gradual exposure to both internal (such as through the use of hyperventilation to recreate symptoms) or external (exposure to environments associated with vestibular symptoms) phenomena. The approaches applied in vestibular rehabilitation are similar to those central to CBT but focus more on the behavioural elements, aiming for a reduction in pathological avoidance as a route to habituation to aversive stimuli.

TREATMENT STRATEGIES

Psychopharmacology

To date, no large-scale randomized controlled trials have been performed in cohorts of patients diagnosed with chronic dizziness with and without psychiatric morbidity. There is some variation in the diagnoses used to recruit to these trials on account of the timing in the historical changes in nomenclature detailed above. Uncontrolled trials indicate that selective serotonin reuptake inhibitors (SSRIs)[81–84] and serotonin–noradrenaline (norepinephrine) reuptake inhibitors (SNRIs)[85] may be of benefit for chronic dizziness in the presence of anxiety and major depressive disorders and that this benefit is independent of improvement in psychopathology.[86] However, in being from uncontrolled studies, these results should be interpreted with caution. Staab and Ruckenstein[86] examined the response of the three subtypes of CSD to SSRIs. They report that the otogenic and psychogenic subtypes demonstrated 'more complete' responses than did the interactive. This is likely to be a reflection of the fact that this subtype is likely to exhibit greater chronicity and treatment resistance requiring higher doses, longer treatment course, pharmacological augmentation perhaps in addition to subsequent psychological interventions.

There is sufficient evidence for the use of SSRIs in this group of patients, although further work is necessary; in particular, larger randomized and controlled trials and long-term follow-up studies are still lacking. Studies to date would advise starting at a lower dose than would be ordinarily used in the treatment of anxiety and affective disorders, with a gradual titration to the lower end of this treatment range. The major caveat here is that presence of anxiety symptoms typically requires higher doses than mood disorders do, and a longer course of treatment. A dosage limitation in this regard would provide a false ceiling and an unfair disadvantage to many patients. Another important factor to note is the potential for a dizziness to appear independently of the underlying diagnosis and as a consequence of the SSRIs. This may be in the form of a side effect but may also occur as part of the withdrawal phenomena associated with members of this family with longer half-lives (e.g. paroxetine and fluoxetine).

Psychotherapy

Psychotherapy, specifically cognitive behavioural therapy, has been examined in a number of trials looking at PPV or CSD.[24, 25, 87] In an uncontrolled trial in 41 patients, Edelman et al.[87] suggest that CBT is effective in improving scores of dizziness, avoidance behaviour and disability with high effect sizes after only three sessions but without effect on anxiety or mood-related symptoms. The response after so few sessions is surprising and may explain the lack of efficacy against psychopathology (between six and eight sessions are standard here) but this was conducted in relatively small cohorts of patients and was uncontrolled. The important question that is obviously begged by this potentially positive data after such a brief intervention is whether this clinical response is sustained. No details were provided on follow-up in this initial study but the same group reported that the effects were sustained at 6 months in a subsequent report.[25] This is promising, given that earlier groups suggest that at 12 months after an initial intervention no benefits are sustained.[24]

Vestibular balance rehabilitation therapy

Vestibular balance rehabilitation therapy (VBRT)[88] aims to facilitate the process of compensation and involves a habituation programme that ultimately encourages the 'avoidance of avoidance'. VBRT therefore also engages the behavioural component of the CBT model and is in this way similar in principle to graded exercise therapy in chronic pain syndromes such as fibromyalgia and chronic fatigue syndrome. VBRT is effective against hypersensitivity to motion, improves confidence with balance and reduces avoidance behaviour.[89] Early forays into the combination of VBRT and CBT have yielded mixed results from small randomized trials, with positive results in terms of disability but without effect on the core symptoms of vertigo, anxiety or depression.[90, 91] This is perhaps not surprising with respect to symptoms of vertigo, as exposure to the activity that provokes symptoms is core to the process of compensation (part of the goal of VBRT); the patient needs to experience the symptoms in order for these subsequently to diminish.[91]

AN APPROACH

The assessment and management of patients with complaints such as chronic dizziness is complicated by assumptions that are potentially made with ease. The first is that the discovery of psychopathology may lead to the assumption that this alone explains the presentation, preventing appropriate investigation being sought.[92] On the flip side of the coin, the discovery of 'organic' pathology may result in a lack of appropriate assessment and treatment of psychopathology,[93] with the ensuing negative effects on chronicity and disability. It is also a problem that those initially referred to 'organic' clinics are often reluctant to accept input from a psychiatrist,[94] as a consequence of both stigma and a fear that their disabling problem is being accounted for by 'just being in their head'.

The best practice in this regard is the early involvement of a psychiatrist. Ideally, this should be one who specializes in this area and is familiar with the practice of vestibular medicine. Even more optimal is the psychiatrist who is embedded in the outpatient department with vestibular specialists and is seen as being part of not just the same team but the same process. The advantage of this in terms of the patient's appraisal is that being seen by the psychiatrist is not in any way remote from being seen by the vestibular specialist. The advantage to the clinicians is that investigation can continue from both medical disciplines concurrently, contributing to a complete and ideally seamless clinical picture and subsequent management. We have

reported on the success of such practices from an inpatient perspective with another group of disorders that are met with very similar conflicts.[95]

CONCLUSIONS

Chronic dizziness is commonly associated with psychiatric morbidity, most frequently in the form of anxiety. The presence of anxiety adds to both chronicity and disability, irrespective of whether it is primary or secondary in nature. The early involvement of an appropriately experienced psychiatrist in the comanagement of this patient group for the detection and early management of such comorbidities is vital and need not delay ongoing vestibular investigations, which can be pursued in parallel.

BEST CLINICAL PRACTICE

Psychopathology should be an early consideration in the assessment of patients and, when present, should be actively treated as part of the overall diagnosis and management strategy. Optimally, this should be performed in conjunction with a psychiatrist working in tandem with vestibular specialists, rather than in a remote clinical environment.

FUTURE RESEARCH

- Rigorously designed randomized and placebo-controlled trials should form the mainstay of future research at this juncture, unified by the use of current nomenclature to define diagnostic groups.
- Such trials might explore the efficacy of the SSRIs, the SNRIs, CBT and VBRT independently, as comparisons and in combination with one another as well as in isolation.
- Further to this, the new concept of 'Persistent postural-perceptual dizziness' will require careful exploration for diagnostic reliability and stability and the identification of subgroups that may otherwise hamper the interpretation of results of studies into both pharmacological and non-pharmacological interventions.

KEY POINTS

- Psychopathology commonly coexists with chronic vestibular disorders.
- Typically this is in the form of disorders of anxiety and affect.
- Concurrent psychopathology is a source of chronicity, disability and suicide risk.

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CHAPTER 73

CLINICAL EXAMINATION OF THE EARS AND HEARING

George G. Browning and Peter-John Wormald

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search focusing on reviews using the keywords: examination and ear/otology/otoscopy, otoscopy, wax, cerumen, syringing and ear, tests/clinical and hearing, tuning fork, Rinne, Weber and Bing tests.

PINNA

The external ear or pinna is constructed of a cartilage skeleton covered by skin and soft tissue. The cartilage forms an outer helix and an inner antihelix. These structures surround the conchal bowl which is shielded anteriorly by the tragus (Figure 73.1). In humans the physiological purpose of the pinna is to collect high-frequency sounds which are thereby amplified in the external auditory canal. These normal features of the pinna are assessed as part of the initial examination of the external ear.

It is necessary to identify external surgical scars used for access, which are most commonly endaural (Figure 73.2) or post-auricular (Figure 73.3). These scars can be thin and may be difficult to see but, if present, alert the otoscopist to the potential for surgical abnormalities, especially in the attic, such as open mastoid cavities. Other scars to harvest graft material such as tragal cartilage and temporalis fascia are also worth identifying.



Figure 73.1 Anatomy of the ear (pinna).

EXAMINATION OF THE EXTERNAL AUDITORY CANAL

The external canal consists of a cartilaginous outer third and a bony inner two-thirds. It is angled and needs to be straightened before examination is attempted. This is done by gently pulling the pinna posterosuperiorly (Figure 73.4). This aligns the cartilaginous canal with the bony canal and should allow visualization of the

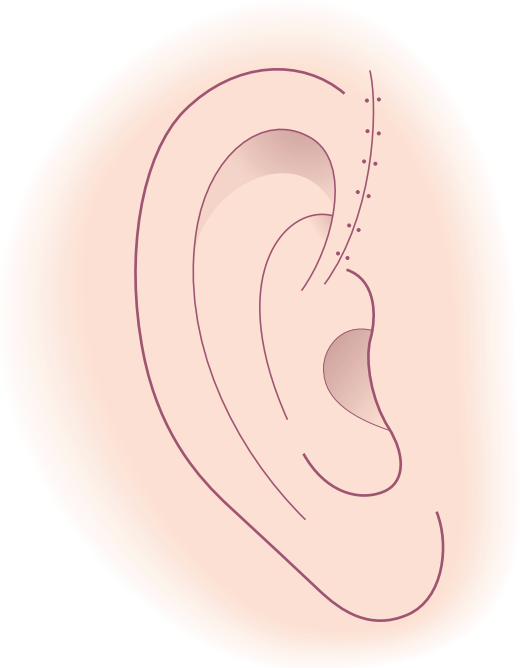


Figure 73.2 Endaural incision (right ear).

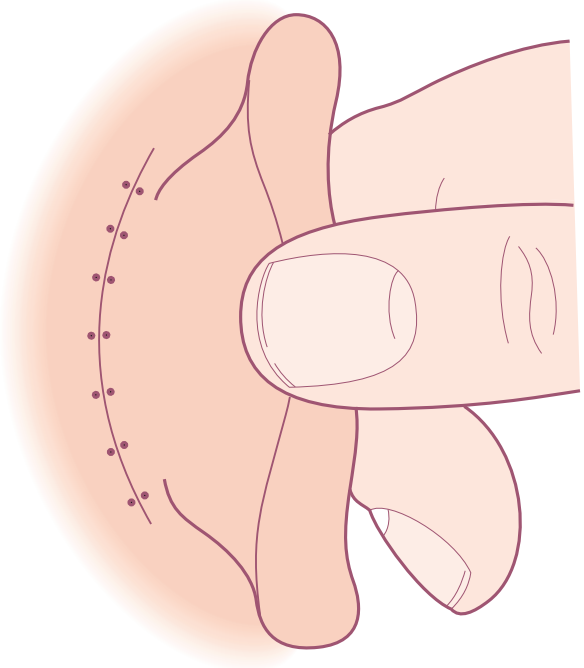


Figure 73.3 Post-auricular incision (right ear).

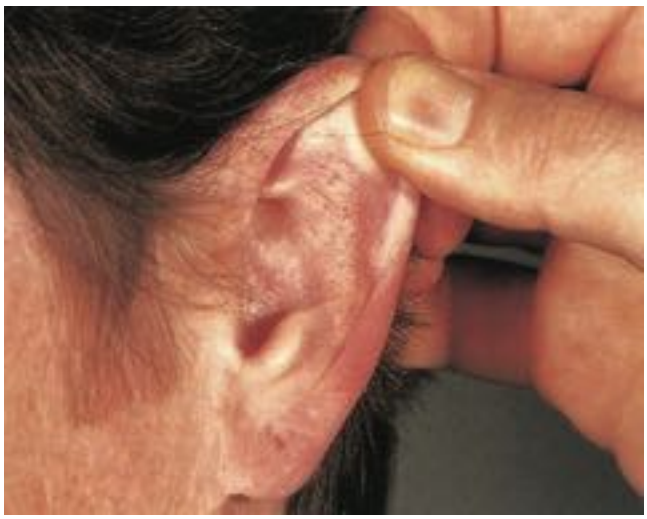


Figure 73.4 Positioning of ear for otoscopy.

entire canal and tympanic membrane. The temperomandibular joint creates an anterior bulge in the deep external canal that may obscure the anterior inferior tympanic membrane. A high proportion of adults and children will have visually occlusive wax plugs, where the tympanic membrane cannot be seen in its entirety. In clinical practice, visually obstructive wax is more common in those who wear a hearing aid. Patient indications for wax removal are the feeling that the ear is blocked, perhaps associated with impaired hearing. Clinical indications for removal are if the patient has otological symptoms that require the external auditory canal and tympanic membrane to be assessed, such as ear discharge, otalgia and hearing loss.

WAX PRODUCTION

Wax is produced by the hair-bearing skin of the external auditory canal. Wax is a combination of desquamated skin and cerumen formed by glands in the base of the hair follicles. Hairs are present in the outer third of the external canal. Most external canals are self-cleaning with the desquamated skin migrating up to the hair follicles where it is separated from the dermis and mixes with the cerumen to form wax. The wax migrates down the hair and migrates out of the ear canal (Figure 73.5). The most common finding is partial occlusion of the canal (Figure 73.6). In the majority of patients this will be an incidental, symptomless finding. In those with otological symptoms, wax



Figure 73.5 Wax on the tips of external canal hairs.



Figure 73.6 Wax totally obscuring view of right tympanic membrane. Associated hearing impairment is unlikely.

will need to be removed to enable the canal and tympanic membrane to be assessed. It is relatively uncommon for wax to cause a hearing impairment. It requires the wax to be impacted deep in the canal by the use of cotton buds or an ear mould for it to act like 'ear defenders' that are used to limit noise exposure.

Wax is amenable to removal by non-specialists by water syringing most commonly using a pressure-controlled irrigator. Specialists prefer to remove wax under direct vision with the aid of a headlight, microscope or endoscope, often via a speculum with ear wax hooks, Jobson Horne probes or suction irrigation.

WAX SOFTENING

In primary care settings various wax softening agents including olive oil, sodium bicarbonate and commercial agents such as Cerumol are frequently used to aid wax or ease of wax removal. Such substances are effective[1] but there is no evidence to support the use of one agent rather than another. Adverse effects are not common but can include skin irritation. In secondary care their previous use requires to be noted if there is inflammation of the skin of the ear canal.

EAR TOILET

In primary care ear toilet is mainly confined to clearance of wax. In secondary care, though removal of wax is the predominant reason, debris including pus, dried pus and blood will also require to be removed to aid assessment and management. Performing toilet under direct vision, especially if this is magnified with a microscope or endoscope, greatly aids the process of clearing out difficult areas including the attic and open mastoid cavities. Patients will tolerate extensive toilet better if they are in a relaxed position on a reclining chair or couch. They should be informed as to what to expect, especially the noise of suction or irrigation of water. The latter on occasions can cause a short episode of vertigo especially if the irrigation fluid is not at body temperature.

Syringing

Syringing to remove visually obstructing wax or wax considered potentially to be causing a mild hearing impairment is now most frequently performed by suitably trained, paramedical staff (**Figure 73.7**). As this is most often not performed under direct vision and the otoscopic diagnostic skills of the operator will be limited, there are usually firm contraindications to syringing. So ears with a discharge or previous ear surgery are not permitted. These contraindications do not apply to specialists in secondary care settings.

In the UK, various Health Boards have produced guidelines readily available online with titles such as *Ear irrigations: guidelines for Community Nursing*. That by Derby City Primary Care Trust can be recommended.[2]

Microscopic/endoscopic suction toilet

Ear toilet with magnification is popular among specialists as it allows the external canal and tympanic membrane to be magnified while wax, pus or debris is removed using a suction cannula or other instrument. The magnification afforded by the microscope or endoscope allows the ear to be cleaned with great precision and with minimal patient discomfort. Irrigation of troublesome areas with a small syringe filled with water often aids the process. Because such toilet is performed under direct vision, adverse effects including trauma to the ear canal or tympanic membrane/middle ear are uncommon. Haemorrhage, if it occurs, can be easily controlled.

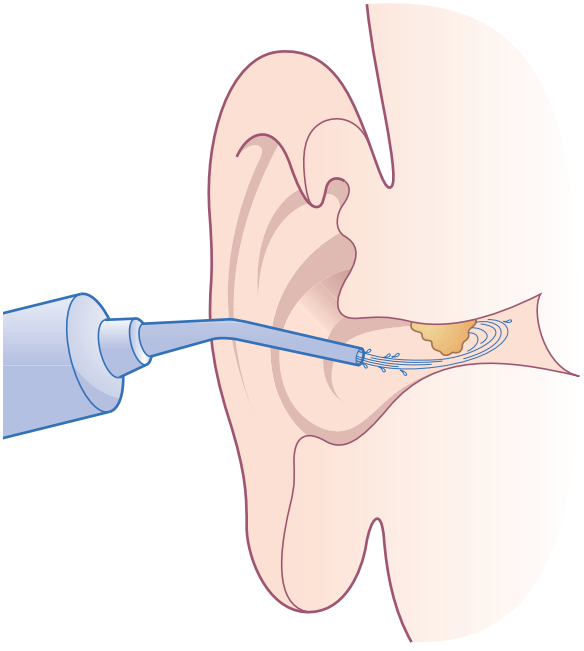


Figure 73.7 Wax syringing. The water bypasses the wax and is reflected by the tympanic membrane to expel the ear wax.

Mopping the ear canal

A mop can be used to remove discharge or debris from the ear canal for management purposes of otitis externa and active chronic otitis media, as well as allowing visualization of the underlying canal and tympanic membrane. Mopping can be performed without the aid of equipment such as suction which is the main alternative method. It can also be performed, after adequate instruction, by paramedical staff and patient carers.

A mop is made by winding a thinned-out piece of cotton wool around the end of an orange stick. Care should be taken to ensure that the stick extends only halfway into the cotton wool (Figure 73.8) and that the mop is about the same diameter as the stick. The protrusion of cotton wool beyond the end of the stick will ensure that, if the mop touches either the deep canal skin or the tympanic membrane, no damage will occur or pain be felt.

OTOSCOPY

With an otoscope

The first decision when performing otoscopy with an otoscope (auriscope) is to choose the most appropriate size of speculum (Figure 73.9). A narrow speculum limits the visible canal and/or tympanic membrane. The otoscope then has to be moved around and all the subsequent images mentally pieced together like pieces of a jigsaw until the overall picture is established (Figure 73.10). The larger the speculum, the less reconstruction will be needed by the examiner.

With an endoscope

Endoscopy with a short 4 mm diameter straight-view rigid scope has the advantage of not requiring a speculum. It is therefore perhaps more able to be angled to see the different areas including the attic and open mastoid cavities. If attached to a camera, both the patient and others can view the ear, allowing permanent photographic records to be kept electronically. Condensation of the lens is the main drawback. This can be mitigated to some extent by wiping the lens with an alcohol swab.



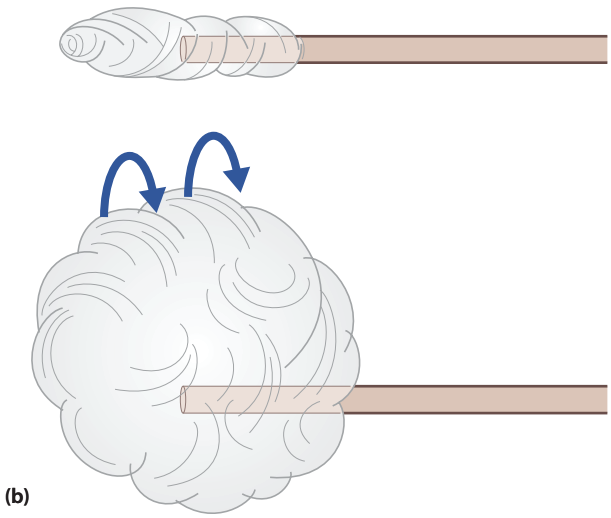


Figure 73.8 (a,b) Method of making a cotton bud.

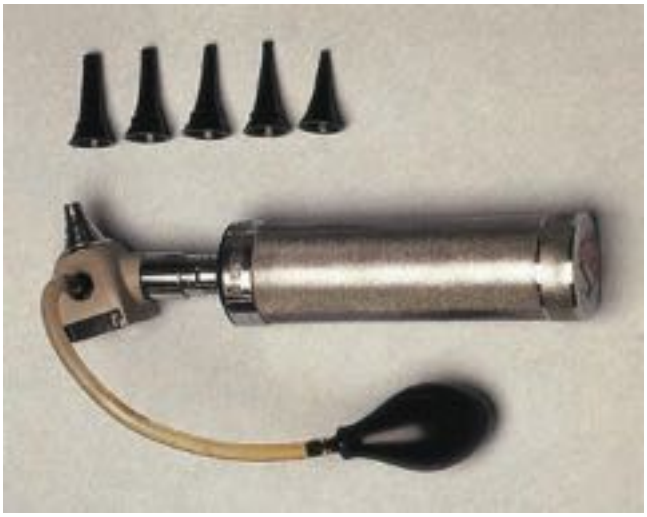


Figure 73.9 Closed pneumatic otoscope.

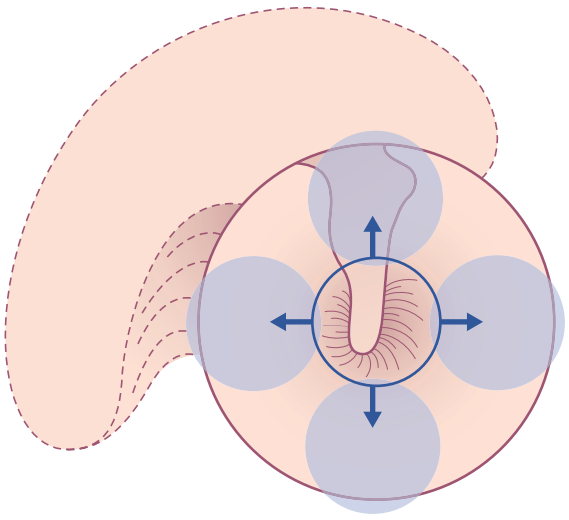


Figure 73.10 A wide view of the attic is obtained by multiple views via a speculum.



Figure 73.11 Normal skin in the left external auditory canal.



Figure 73.12 Normal left tympanic membrane. The anterior pars tensa is not entirely visible due to anterior canal bulge of the temporomandibular joint.

Normal external canal

The outer third of the normal external canal has hair-bearing skin which is relatively thick as it contains the ceruminous glands. At the junction of the cartilaginous and bony canal, the skin thins without glands and covers the underlying bony canal (Figure 73.11). This allows the bony prominence formed by the impression of the temperomandibular joint to be clearly seen anteriorly. This prominence allows photographs of tympanic membranes to be identified as either a left or a right ear as the prominence is always anterior (Figure 73.12). In some photographs taken through a Hopkins rod, the bony prominence may not be obvious.

Structured otoscopy

With the increased availability of texts on the pathology of the external canal and tympanic membrane,[3, 4] otoscopy is becoming easier for practitioners to learn. If a structured approach to otoscopy is taught, diagnostic skills improve and disease patterns are more easily recognized and appropriately dealt with.[5] The most recognizable feature in most ears is the handle of malleus and this should be the first structure sought (Figure 73.13). The umbo and lateral process should be identified and the adjacent tympanic membrane visualized (Figure 73.13). The tympanic membrane can be divided into the pars tensa and the pars flaccida (Figure 73.14). The examiner should then decide if the pars tensa is intact and, if this is the case, whether it is in its normal position. Clues as to its normal position should be sought in identifying the angle of the handle of the malleus. Foreshortening indicates retraction of the tympanic membrane medially as does lipping around the annulus creating a 'neoannulus' (Figure 73.15). Loss of the light reflex, while less important, may be caused by retraction, inflammation or scarring of the tympanic membrane (Figure 73.16). The tympanic membrane is normally a grey, slightly translucent colour. Hyaline degeneration of the fibrous layer sometimes associated with calcium deposition occurs as a consequence of previous episodes of middle-ear inflammation. This increases the whiteness of the tympanic membrane and can be a diffuse thickening

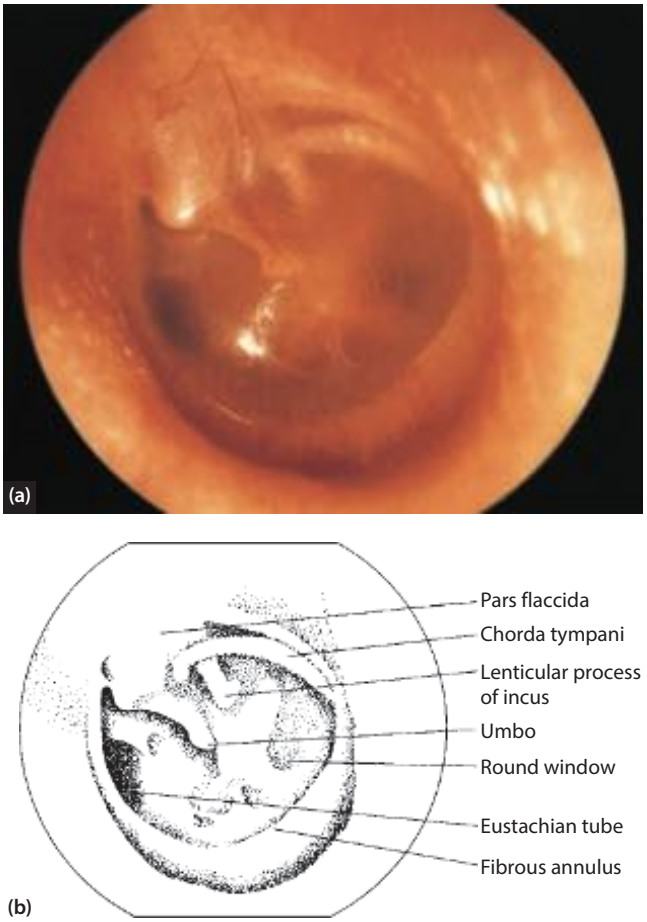


Figure 73.13 (a) Normal left tympanic membrane. **(b)** Important middle-ear anatomy structures often identified behind the tympanic membrane.

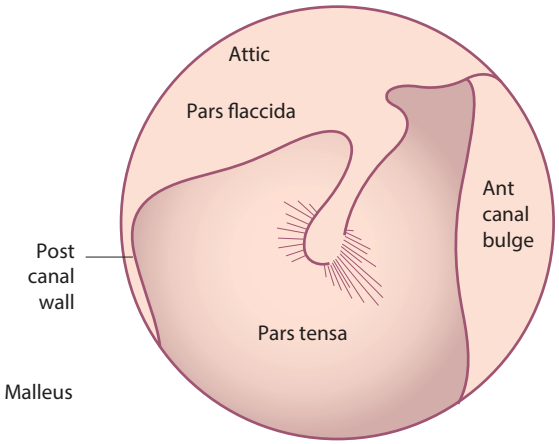


Figure 73.14 Diagram of the ear indicating the pars tensa and pars flaccida. Redrawn with permission from Browning, *Updated ENT.* 3rd ed. London: Hodder and Stoughton; 1994, p. 2.[6]

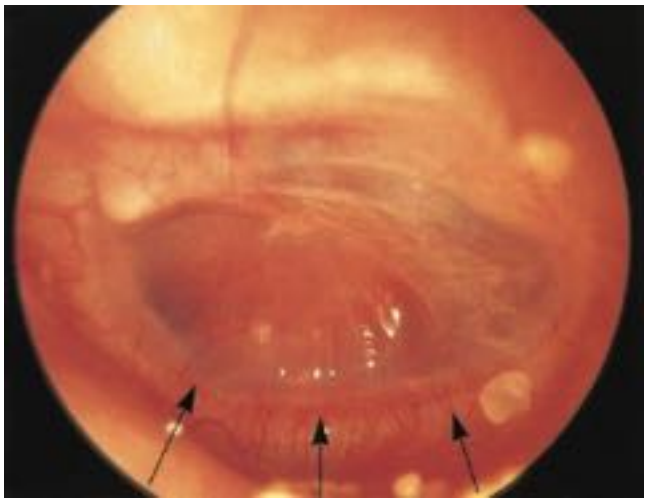


Figure 73.15 Severely retracted position of the malleus handle in otitis media with effusion (left ear). As retraction develops, a neoannular fold may form (arrows).



Figure 73.16 Tympanosclerotic plaques, extending from posterior to inferior. Remainder of the tympanic membrane scarred (right ear).



Figure 73.17 Chalk patch on the anterior pars tensa (right ear).

of the tympanic membrane or isolated tympanosclerotic plaques (Figure 73.17). Previous grommet insertion produces a rather characteristic crescent-shaped deposition of calcium in 32% (CI 30.6,32.8) of patients (Figure 73.18).[7] Tympanosclerosis may also fixate the middle ear ossicles with a resultant conductive impairment. If the tympanic membrane is perforated posteriorly, the ossicular chain may be visible. In Figure 73.19 the malleus handle, long process of the incus and stapes are all seen through a subtotal perforation in an ear with active, mucosal chronic otitis media.

Changes in the tympanic membrane and ossicles as a result of ageing

The tympanic membrane may lose its translucency and become less transparent with age. It had also been thought



Figure 73.18 Extruded ventilating tube with otoscopic recurrence of middle ear fluid. Left ear retracted and yellow.

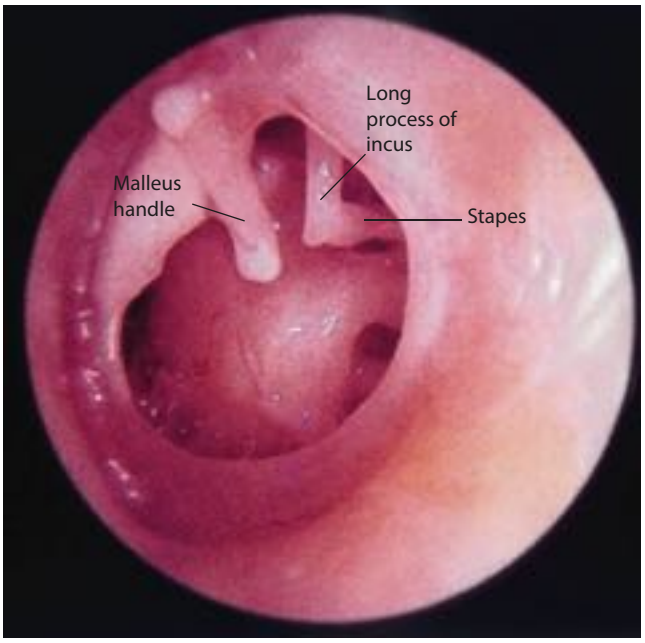


Figure 73.19 Perforated tympanic membrane with visible ossicular chain.

that the ossicular chain increased in stiffness with age. However, Holte[8] showed that there was no change in the middle ear resonance, admittance or tympanometry width with increasing age. The less translucent tympanic membranes seen with increasing age are likely to be as a consequence of episodes of middle ear inflation rather than directly related to ageing.

CLINICAL ASSESSMENT OF HEARING

It is useful before clinically assessing the hearing to have some idea of how impaired the patient is overall. If communication is difficult without hearing aids, this would suggest a bilateral severe or profound hearing impairment. If they find it difficult to hear conversation when out of sight of the speaker, they will have a bilateral mild to moderate impairment. The history from the patient and from any attending partner or friend as to what situations cause difficulty is also helpful. More often it is the attendant person who gives a truer record of the overall disability. One should be particularly wary if an individual is adamant that they have no hearing impairment.[9] Ascertaining whether the patient has a better hearing ear helps direct the clinical assessment, rather than being 'correct' in many instances.

Questionnaire assessment

Several questionnaires are available for ascertaining the degree, if any, of an individual's hearing impairment. These have been primarily designed as screening instruments[10] and are not sufficiently specific to determine the requirement for audiometry in secondary care. Individual questions from these questionnaires that ascertain the circumstances in which the patient finds hearing difficult can, of course, guide subsequent management.

Free-field speech testing

This is the main method of clinically assessing an individual's hearing[11] and is applicable to both adults and older children.[12] Its main value is in primary care when audiometric facilities are not available as a screening test for a hearing impairment. In secondary care its value is also as a screening test to determine whether an audiometric assessment is required. In addition, the test is such that it can assess the relative severity of a hearing impairment in each ear, which is sufficiently reliable to guide management. It can also be useful to demonstrate to the patient or parent of a child the presence/lack of a hearing loss.

GENERAL TECHNIQUE

The examiner explains to the patient that a combination of letters and numbers are going to be whispered or spoken and the patient's task is to try to repeat them. A number–letter combination is chosen as this has a reasonable mix of consonants that allows a relatively broad range of frequencies to be tested. For less experienced testers to have a list of these to read from allows a more consistent voice level to be produced. The examiner then positions themselves behind the patient so that the subject cannot lip-read and in a loud voice confirms that they understand the task by saying very recognizable numbers such as '99'. The next step depends on whether the patient is being screened to detect a hearing impairment or each ear is being screened separately for a hearing impairment.

SCREENING TECHNIQUE

When the tester is standing behind the subject at arm's length from their head and the subject cannot repeat more than 50% of the number–letter combinations spoken in a whispered voice, they will have a hearing impairment of at least 30 dB HL in both ears (Table 73.1).[13] The main variable to ensure control for is the level of the whispered voice. Some suggest that fully exhaling before whispering gives more consistent voice levels. It must also be remembered that testing has to be in a quiet environment.

If each ear requires to be tested, the non-test ear requires to be masked as sound attenuation across the skull from

TABLE 73.1 Sensitivity and specificity of a hearing impairment being detected by an individual's inability to hear a whispered voice at 60 cm (reproduced from Browning et al.[13] with permission)

PTA	Impairment (db HL)	Percentage	
		Sensitivity	Specificity
PTA over 0.5, 1 and 2 kHz	≤25	86	94
	≤30	95	90
	≤35	100	84
PTA over 0.5, 1 and 2, 4 kHz	≤25	91	96
	≤30	96	91
	≤35	98	86

one side to the other ear is in the region of 15 dB. Adequate masking is achieved most easily by the examiner closing the ear canal in the non-test ear by pressing the tragus over the canal with a finger. The tragus is then rubbed to produce a continuous masking noise that is in the region of 40 dBA. The examiner then positions themselves at full arm's length on the test-ear side of the patient which is approximately 60 cm from the test ear. The number–letter combinations are again whispered and the subject is asked to repeat them. If they cannot do this on more than 50% of occasions, the hearing level in that ear will be 30 dB HL or poorer.

While this test is not as accurate as pure-tone audiometry it will give the examiner a reasonable idea of the hearing, especially in the low frequencies (speech frequencies). The free-field speech test will in most cases (90–100 %) detect a hearing loss of greater than 30 dB with a false-positive rate of 13–30%.[13]

In primary care such voice testing can be sufficiently sensitive and specific to discriminate those requiring onward referral for audiometric testing.[12, 14]

DETERMINING THE DEGREE OF IMPAIRMENT IN EACH EAR

In secondary care the above 'by ear' screening method can be extended to determine the likely level of the impairment if the subject is not able to repeat what is said in a whispered voice. This requires the examiner to move their head in position from arm's length (60 cm) to 15 cm from the ear and repeat the test again in a whispered voice. If the subject can do this, that ear has a mild impairment (Table 73.2).[13] If they are unable to do it, the voice level is raised to a conversational level and the test repeated at arm's length. If the subject is able to do this, they will have a moderate hearing impairment and the conversational voice is then tested at 15 cm. If unable to repeat this, the subject has a severe impairment or poorer. If the test is to be taken any further, tragal rubbing will provide insufficient masking and a Barany box will be required.

The main variable between tests and testers is the reproducibility of the voice levels. Examiners should frequently compare their results with the audiogram to ensure that their conversational voice level and whisper levels are giving consistent results.

TABLE 73.2 Comparison of free-field voice thresholds and pure-tone average (PTA) over 0.5, 1, 2 and 4 kHz (after Swan and Browning)[14]

Voice level	Distance (cm)	Loudness (dBA)	PTA mean percentiles	
			5th	95th
Whisper	60	12	–	27
	15	34	20	47
Conversation	60	48	38	60
	15	56	48	67
Loud	60	76	67	87

Tuning fork tests

Tuning fork tests have a potential role in ears with a normal tympanic membrane to distinguish between a conductive and a sensorineural hearing impairment when accurate pure-tone audiometry, with both air and bone conduction, is not available. In these circumstances, if they suggest a conductive hearing impairment, then otosclerosis is the most likely diagnosis. Tuning fork tests have relatively little value if otoscopically the ear is abnormal with otitis media with effusion and acute or chronic otitis media where, by definition, there must be a conductive defect. What one requires to know in these ears is the magnitude of the conductive defect and pure-tone audiometry is the only method of doing this by measuring the air–bone gap.

The most commonly used forks are the 256 Hz and 512 Hz forks, as these give more reliable responses than the 1024 Hz fork.[14, 15] Tuning forks are activated by striking them lightly against the elbow. The sound generated should not be audible until the fork is brought close to the ear. Striking them against a solid object may produce harmonics that distort the pure-tone generated by the fork and result in an unreliable test. A correctly activated tuning fork held up to the ear generates about 70 dBA, while one activated by pushing the tines together and letting go can generate slightly higher levels (89–90 dBA).

In theory, masking should always be applied to the non-test ear, especially for bone conduction. However, such masking cannot be done by bone conduction as this would affect both ears. Consequently, it has to be done by air conduction and a Barany box is used because it generates sufficient noise. Other methods of masking (tragal rubbing and paper) produce an insufficient volume of noise to adequately mask the tuning fork.[13, 15]

RINNE TEST

The standard **loudness comparison method** of performing the Rinne test compares the relative loudness of air conduction against bone conduction. In ears with normal hearing or a pure sensorineural hearing impairment, the tuning fork will sound louder opposite the ear canal (air conduction) than when placed on the mastoid bone behind the ear (bone conduction). Therefore, with the tuning fork activated, the patient is asked to say which of the following sounds louder: the fork placed within 2 cm of the external auditory canal or placed firmly on the flat bone of the mastoid behind the pinna. To aid bone contact with the tuning fork base it is advisable to hold the patient's head with the other hand to prevent it from moving.

The alternative method of performing the Rinne test is the **threshold comparison method**. Here, the activated fork is held opposite the external canal until it is no longer heard. It is then placed on the mastoid bone. If the sound is heard again, then bone conduction is better than air conduction and there is a conductive impairment. This method of performing the Rinne is not as reliable as the relative loudness comparison method (Figure 73.20).[13, 16]

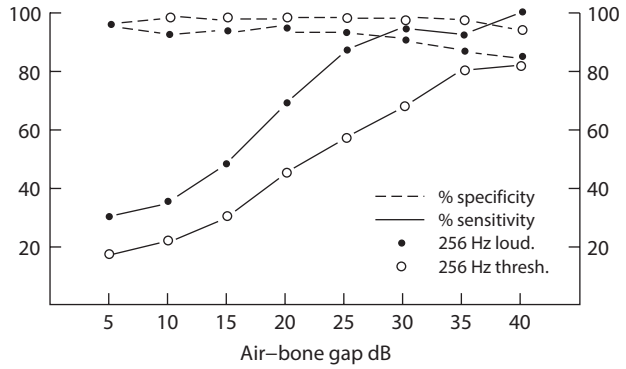


Figure 73.20 A comparison of the sensitivity and specificity of the 256 Hz fork using a loudness comparison method against the 512 Hz fork using a threshold method, in detecting air–bone gaps of various magnitudes. Redrawn with permission from Browning et al. Clinical role of informal tests of hearing. *J Laryngol Otol* 1989; **103**: 7–11.[13]

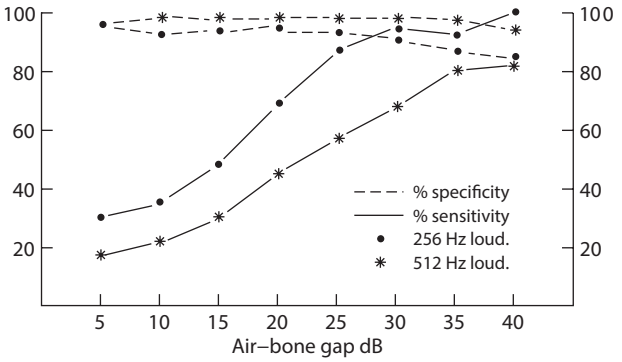


Figure 73.21 A comparison of the sensitivity and specificity of the 256 Hz against the same forks in detecting air–bone gaps of various magnitudes, but using the loudness comparison method. Redrawn with permission from Browning et al. Clinical role of informal tests of hearing. *J Laryngol Otol* 1989; **103**: 7–11.[13]

In practice, masking of the non-test ear only requires to be done when testing a poorer-hearing ear (determined by voice testing) and the bone conduction is louder than the air conduction. A false-positive Rinne could result in these circumstances by the bone conduction being heard by the better-hearing ear.

Although many clinicians use a 516 Hz tuning fork, the 256 Hz fork gives superior sensitivities and specificities (Figure 73.21). The 256 Hz Rinne tuning fork test will detect a conductive defect above 30 dB in 90% of patients (Table 73.3). Between 20 and 30 dB, the sensitivity will fall to 70% and between 10 and 20 dB it will be less than 50%.[13, 15–20] The specificity of the test is high above 30 dB conductive defect but falls as the air–bone gap narrows. The false-positive and false-negative rates again depend on the air–bone gap (Figure 73.20).[13] The false-positive rate in normal patients is 20%.[13, 15–20]

Table 73.4 shows the results with a 512 Hz fork in greater detail. Using the loudness comparison method, it shows there is a third type of response of no difference in loudness (ac = bc). This makes the test uninterpretable in up to 10% of patients with an air–bone gap of 11–40 dB at 512 Hz.

TABLE 73.3 Size of air–bone gap (dB) which would be correctly identified by Rinne test on various percentages of occasions

Fork	Study	Confidence limits		
		50%	75%	>90%
256 Hz	Crowley & Kaufmann (1966)[17]	25 dB		30 dB
	Gelfand (1977)[20]		40 dB	
	Browning et al. (1989)[13]	15 dB	20 dB	30 dB
512 Hz	Crowley & Kaufmann (1966)[17]	25 dB		30 dB
	Wilson & Woods (1975)[18]			40 dB
	Gelfand (1977)[20]		40 dB	
	Golabek & Stephens (1979)[19]	19 dB		
	Browning et al. (1989)[13]	20 dB	25 dB	40 dB

BING TEST

The Bing test is based on the principle that, if there is a conductive hearing loss, occlusion of the external auditory canal will not augment the sound of the tuning fork in the test ear. This is what would happen in those with normal hearing or a pure sensorineural hearing loss. The test is performed by placing the activated tuning fork on the mastoid bone and then occluding the external auditory canal with a finger. If the patient reports that this makes the bone-conduction sound louder, there is unlikely to be a conductive impairment. However, if it remains the same, then a conductive impairment is likely.

The sensitivity and specificity of this test are low as it frequently suggests a conductive hearing loss in patients with normal hearing.[18] The reliability of the Bing test correctly identifying an ear with a conductive deafness is only slightly better than chance (57–66%).[18] Today it is used less frequently than the Rinne to identify a conductive impairment in ears with a normal tympanic membrane as its sensitivity is less although its specificity is similar.[21]

WEBER TEST

The Weber tuning fork test is only applicable if a patient has unilateral or asymmetrical hearing. The test is based on a tuning fork placed centrally on the skull being heard

TABLE 73.4 Comparison of the Rinne test results with a 512 Hz tuning fork against the air–bone gap at 0.5 Hz using a loudness comparison (after Browning and Swan)[16]

Air–bone gap (dB)	Percentage ears		
	AC > BC	AC = BC	BC > AC
0–10	97	1	2
10–20	61	11	19
21–30	32	8	60
31–40	42	8	49
40+	10	0	90

AC – air conduction; BC – bone conduction.

louder in an ear with a conductive impairment or in an ear with better sensorineural thresholds. This distinction is only possible if the examiner has performed a clinical test of hearing previously and knows which ear is the better-hearing ear.

The test is performed by placing an activated tuning fork over the forehead, on the bridge of the nose or over the incisor teeth. The tuning fork can also be placed in the midline over the vertex of the skull. The patient is asked to identify in which ear the sound is heard or alternatively in which ear the sound is louder. If it is heard in the better-hearing ear, then the poorer ear has a sensorineural impairment. If it is heard in the poorer ear, then it has a conductive impairment.

Unfortunately, the Weber test has a low sensitivity and specificity and is marginally better than chance.[15, 19, 22] It is still in use but this test should not be relied upon, as the chance of accurately and reliably identifying conductive and sensorineural deafness is only 33%.[22]

OVERALL ROLE OF TUNING FORK TESTS

With the general availability of pure-tone audiometry, the distinction between a conductive and a sensorineural hearing impairment should generally be made on a comparison of the air- and bone-conduction thresholds, masked where appropriate. The air–bone gap will also give a measure of the magnitude of any conductive defect, which is essential when assessing the potential role of surgery to improve the hearing. Tuning fork tests should be held in reserve for otoscopically normal ears where satisfactory audiometry is not available to diagnose otosclerosis and should always be interpreted in the light of their generally low sensitivity and specificity.[23]

BEST CLINICAL PRACTICE

- ✓ Wax or pus that obstructs the view of the tympanic membrane is most easily removed by non-specialists by syringing.
- ✓ Wax softeners to aid syringing are of 'benefit' but there is no evidence to support a specific softener. [Grade A]
- ✓ Specialists will frequently use suction with microscopic vision to clear the canal.
- ✓ In otoscopy, the speculum should be as large as practicable.
- ✓ Free-field speech tests with a whispered voice at 60 cm from the ear can be used when audiometry is not available to detect those with a hearing impairment.
- ✓ Tuning fork tests are insufficiently reliable to make a distinction on their own between a conductive and a sensorineural hearing impairment. They are not recommended except when reliable audiometry is unavailable to test an ear that is otoscopically normal, mainly to diagnose otosclerosis. [Grade A]
- ✓ If the middle ear is otoscopically abnormal, there will be an element of a conductive hearing impairment to any hearing loss. In this situation tuning fork tests have minimal added value.

KEY POINTS

- Wax is a normal phenomenon.
- Wax only needs to be removed if it causes deafness or if the patient has symptoms related to the ear and the tympanic membrane cannot be visualized.
- The features of a normal tympanic membrane need to be recognized.
- Structured otoscopy provides a tool to evaluating normal from abnormal.
- Clinical assessment of hearing is useful in the primary care setting as a screening tool for hearing loss.
- The Rinne tuning fork test can distinguish between a conductive and sensineural hearing loss but the Weber tuning fork test has little clinical value.

ACKNOWLEDGEMENTS

Figures 73.2–73.4, 73.6–73.13, 73.15 and 73.16–73.18 are redrawn or reprinted from Wormald PJ and Browning GG, *Otoscopy: a structured approach*. London: Hodder Arnold; 1996.[3]

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CHAPTER 74

FURUNCULOSIS

Malcolm P. Hilton

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SEARCH STRATEGY

Data in this chapter may be updated by a search using the keywords: furuncle; ear, external and infection; otitis externa; ear, external and *Staphylococcus aureus*; alone and in combination.

DEFINITION

Furunculosis is a localized form of otitis externa resulting from infection of a single hair follicle. Hair follicles are only present in the lateral (cartilaginous) segment of the external auditory canal. Furunculosis is therefore confined to the lateral canal.

Bacterial invasion of a single hair follicle results initially in a well-circumscribed deep skin infection. As the infection progresses, a pustule forms and this progresses to local abscess formation, often with considerable associated cellulitis and oedema. Bacteria attach initially to the cells of the stratum corneum and proliferate around the ostium of the hair follicle. There is deeper invasion of the hair follicle between the inner and outer root sheath.[1]

DIAGNOSIS

Histology is the reference standard for diagnosis (**Figure 74.1**) but is never obtained in routine clinical practice. Symptoms do not usually discriminate furunculosis from severe diffuse otitis externa. The affected ear is extremely painful, feels blocked and exudes a scanty serosanguinous discharge. The pinna and tragus are tender on palpation. Otoscopic examination may be difficult if the external auditory canal is severely oedematous but usually establishes the diagnosis. Characteristically, the oedema and inflammation are restricted to the lateral segment of the canal, with relative sparing of the medial canal and an unaffected tympanic membrane. If the infection is advanced, the abscess may be seen to be pointing into the canal or have discharged already. If the oedema and secondary cellulitis spread to the post-auricular crease, the condition may be mistaken for acute mastoiditis as the pinna is protruded and swollen. Even very gentle movement of the pinna by the examiner causes pain and tenderness in furunculosis but it is typically painless in mastoiditis. Differentiation can be difficult and there are no good studies to examine the sensitivity and specificity of these clinical findings.[2]



Figure 74.1 Furuncle of the right external auditory canal. Localized rather than generalized oedema of otitis externa. Reproduced with permission from Wormald and Browning, *Otoscopy: a structured approach.* London: Hodder Arnold; 1996.[3]

Samples for bacteriological culture may guide therapy but do not contribute to the diagnosis of the disease.

AETIOLOGY AND EPIDEMIOLOGY

Staphylococcus aureus (*S. aureus*) is the most common organism causing furunculosis. Uncontrolled case series suggest that pathogenic strains of *S. aureus* responsible for furunculosis (at all body sites; not restricted to otological furunculosis) are of different phage types from *S. aureus* causing other skin infections such as impetigo and scalded skin syndrome.[4] The *S. aureus* frequently express genes for Panton–Valentine leucocidin (PVL).[5] *In vitro* evidence demonstrates that leucocidal toxins commonly isolated from pathogenic strains of *S. aureus* trigger lysis of phagocytic cells and may have an important role in cutaneous infection.[6] Sporadic cases of furunculosis happen when pathogenic organisms are introduced into the canal in the context of other local risk factors (e.g. heat, humidity, trauma, maceration).

Recurrent furunculosis presents as repeated episodes of infection at multiple sites. Colonization of the external nares and, less commonly, the perineum with the pathogenic strain of *S. aureus* is also a contributing factor in many cases of generalized recurrent furunculosis.[7, 8] Several conditions appear to be associated with recurrent furunculosis including hypogammaglobulinaemia, diabetes mellitus and dysphagocytosis.

OUTCOMES

If untreated, the infection usually progresses to a localized abscess, which then discharges into the external ear canal. Providing there is adequate drainage, the infection will resolve spontaneously. The infection can also spread towards the deeper tissues, where it may cause a diffuse soft-tissue infection spreading to the pinna, post-auricular skin and parotid gland.

Repeated infection can cause permanent scarring and fibrosis of the external canal with subsequent meatal stenosis. Ultimately, this may also predispose to chronic diffuse otitis externa.

MANAGEMENT OPTIONS

Furunculosis of the external canal is exquisitely painful and appropriate analgesics should be offered to all patients. No evidence exists that compares the efficacy of different analgesics. A recent systematic review of treatment for otitis externa specifically excluded furunculosis from consideration.[9]

Treatment choices include:

- oral or systemic antistaphylococcal antibiotics (penicillinase-resistant penicillin, macrolide, cephalosporin, clindamycin or quinolone)
- topical treatment (antibiotics, astringents, hygroscopic dehydrating agents)
- incision and drainage.

No evidence can be presented on the resolution rate for any individual treatment strategy or to compare the efficacy of different treatment strategies. Oral antibiotic treatment is recommended in the early stages of the disease. Severe spreading soft-tissue infection should be treated with intravenous antibiotic therapy. Abscess formation is an indication for formal drainage. After the abscess has discharged, surgically or spontaneously, topical treatment is preferable. Topical antibiotics active against staphylococcus are usually prescribed. Insertion of a wick into the ear canal facilitates treatment in the presence of severe canal oedema and narrowing. Alternative topical agents are available. Glycerol and ichthammol solution has a specific antistaphylococcal action[10, 11] and is hygroscopic, thus causing dehydration of the canal tissue. Aluminium acetate solution is an astringent as well as a hygroscopic agent.

For patients suffering generalized recurrent furunculosis who are carriers of pathogenic strains of *S. aureus*, each episode of furunculosis is treated on clinical merit but additional therapy should be considered. Options include:

- eradication therapy with nasal mupirocin
- eradication therapy with oral flucloxacillin or azithromycin for 14 days
- bacterial interference therapy: deliberately implanting a non-pathogenic strain of *S. aureus* (strain 502A is the most popular) to recolonize the nares and skin.

All treatments appear to show more rapid and effective resolution of colonization and subsequent infections compared with controls although there is a high spontaneous resolution rate of 75% over 2 years for untreated patients.[12, 13] It has been reported that correction of specific biochemical abnormalities (e.g. hypoferraemia, low serum zinc) may lead to a marked reduction in the frequency of infections.

BEST CLINICAL PRACTICE

- ✓ Furunculosis may be difficult to distinguish from simple but severe otitis externa.
- ✓ Optimum treatment combines specific antistaphylococcus antibiotics, either systemic, topical or in combination, along with topical treatment to reduce the oedema and swelling of the external auditory meatus.
- ✓ Strong analgesia is indicated.
- ✓ Incision and drainage is indicated when an abscess has formed.
- ✓ Eradication of nasal carriage of *S. aureus* should be considered in patients with recurrent furunculosis.

FUTURE RESEARCH

Comparative studies are needed of topical antibiotic/steroid drops (e.g. gentamicin with hydrocortisone) versus glycerol/ichthammol and/or aluminium acetate solution.

KEY POINTS

- Furunculosis is localized otitis externa.
- It is caused by staphylococcal infection of a single hair follicle.
- Oral antibiotics are the treatment of choice before abscess formation.
- Formal incision and drainage are recommended if an abscess forms.
- Severe associated soft-tissue infection or cellulitis is an indication for systemic antibiotic therapy.

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CHAPTER 75

MYRINGITIS

Samuel A.C. MacKeith

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: granular myringitis, chronic myringitis, myringitis granulosa, acute myringitis, bullous myringitis and myringitis bullosa haemorrhagica.

INTRODUCTION

Myringitis is, simply, inflammation of the tympanic membrane. It commonly occurs as part of either acute bullous myringitis or granular myringitis (which is usually described as a chronic disorder). These two terms represent two distinct clinical entities and are therefore considered separately in this chapter.

ACUTE BULLOUS MYRINGITIS

DEFINITION

Bullous myringitis (BM) is an acute inflammatory condition affecting the tympanic membrane (TM) characterized by the presence of bullae or vesicles on the surface of the TM. The bullae may be single or multiple, may affect a segment or the whole of the TM and may even spread on to the adjacent ear canal.[1–4]

PATHOLOGY

The bullae are believed to develop between the middle fibrous and outer squamous layer of the TM due to extravasation of serous fluid or blood, although this has never been confirmed histologically.[4, 5]

AETIOLOGY

The exact aetiology remains unclear. The long-held belief that BM was pathognomonic for mycoplasma pneumonia has been largely dispelled.[3, 6] Most of the evidence suggests the underlying pathogens to be similar to those seen in acute otitis media (AOM), namely bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, beta-haemolytic streptococci, *Moraxella catarralis* and respiratory viruses such as rhinovirus, enterovirus, respiratory syncytial virus, influenza A and parainfluenza virus.[2–5] Interestingly, *Streptococcus neumoniae* is consistently noted as the predominant bacterial pathogen

in BM. In most large case series published, BM is diagnosed with concurrent AOM in almost all (97%) cases.[1] This, in conjunction with the comparable aetiological pathogens, supports the theory that BM may simply represent a severe variant of AOM.[3] In contradiction with this theory is the fact that BM is known to occur (albeit less commonly) in isolation or with external ear canal disease where the pathogenesis may be different. What seems apparent is that the aetiology of BM (as with AOM) is a complex interaction of viral and bacterial pathogens in a susceptible host producing a severe acute inflammatory reaction affecting the TM.

EPIDEMIOLOGY

Although the true incidence is unknown, BM has been reported as occurring in 5.7% of children under 2 years of age in a 1-year follow-up period and in the same cohort to occur in 1 in every 20 episodes of AOM.[1] It is more common during the winter and, though it may occur at any age, it is most prevalent in the age group 2–8 years. This differs from AOM, which is more common in children under 2 years of age.[7, 8]

PRESENTATION

Diagnosis of this condition is clinical. Typically, patients present with sudden-onset severe otalgia, usually unilateral and often in association with an upper respiratory tract infection.[1, 2, 4] In most patients the pain is thought to last only 1–2 days[9] although discomfort may persist for longer, even after rupture of the bulla. A cohort of 2028 children under 2 years of age compared the symptoms of 86 diagnoses of BM (of which 97% had concomitant AOM) with the symptoms of AOM alone. They found symptoms to be more severe in BM, with higher rates of earache (58% vs 29%), fever (62% vs 41%) and excessive crying (80% vs 65%), again suggesting BM to be a severe variant of AOM.

Otoscopy reveals bullae on the TM (**Figures 75.1** and **75.2**). Rupture of the bulla may be associated with scanty serosanguinous otorrhoea, which is usually short-lived due to the absence of a TM perforation. In view of the high incidence of associated middle-ear effusion, conductive hearing loss is very common. However, mixed or sensorineural hearing loss is also well documented.

Sensorineural hearing loss

The prevalence of a sensorineural component to the hearing loss has been reported to occur in 15–66% of cases.[7, 8, 11–14] According to these series, complete recovery of hearing is seen in 57–100% of cases, regardless of treatment. Comparison of these studies is difficult due to significant heterogeneity regarding audiological criteria, follow-up and treatment. A further criticism is that none had pre-existing audiological data, meaning that sensorineural hearing loss (SNHL) which did not improve may in fact be long-standing. In addition, all these reports are in adults. We therefore do not know the patterns of hearing loss in the paediatric population in which this disease is predominant.

The pathogenesis of SNHL in BM is unknown but stapedial reflexes and auditory brainstem responses have implicated the cochlea as the site of the lesion.[8, 15]



Figure 75.1 A large single bulla arising from the posterior aspect of the left tympanic membrane.

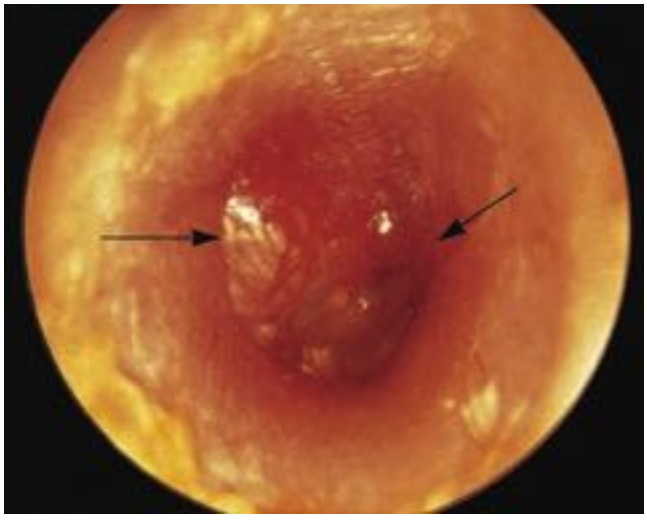


Figure 75.2 Multiple bullae on a tympanic membrane. Reproduced with permission from Wormald and Browning. *Otoscopy: a structured approach.* London: Hodder Arnold; 1996.[10]

Vertigo

Other than in the earliest reports, the presence of vertigo as part of BM has received little attention. However, in 2004 a prospective study showed 7 of 13 patients with BM (54%) reported vertigo at presentation.[13] Of the 13, 11 had abnormal electronystagmography, including 4 who did not complain of vertigo. In this cohort, a sensorineural component of hearing loss was seen in 82%. Again, the aetiology is unknown.

TREATMENT

There is no consensus, nor good evidence, to inform best practice in BM. In the majority of cases it is a self-limiting disease with spontaneous resolution of symptoms. The large case series in paediatric populations, demonstrating comparable aetiology with AOM and suggesting a possible common disease process, has supported the practice of management as for AOM.[2, 3, 9] Symptomatic treatments described include analgesia, warm compresses and incision of bullae. The third of these is of unproven benefit and may have a risk of secondary infection. The use of topical local anaesthetics has also been described.[16]

The frequent finding of inner ear involvement identified in adult case series is associated with more aggressive medical treatment, usually with broad-spectrum oral antibiotics.[4] In addition, the management of sudden-onset SNHL in association with BM has been treated by some authors with high-dose oral steroids as they would for isolated sudden-onset SNHL. Eliashar et al. treated all BM patients with an SNHL component with admission, oral steroids and carbogen, with complete recovery of hearing in 86%.[13] Drendel et al. reported 13 cases of BM with a SNHL component to their hearing loss, nine received steroids, of which five made a complete recovery and four only a partial recovery.[14] The four patients with a SNHL component who did not receive steroids all made a complete recovery.

Only one study has compared systemic antibiotics alone versus systemic antibiotics and steroids.[17] This did not demonstrate improved hearing outcomes with the addition of steroids. However, given the small sample size (23 patients), this may be subject to type 2 error. Therefore, currently there is insufficient evidence to determine the effectiveness of steroids as a treatment of SNHL in BM.

GRANULAR MYRINGITIS

DEFINITION

Granular myringitis (GM) can be defined as a chronic inflammatory disorder characterized by de-epithelialization of the outer (squamous) layer of the tympanic membrane (TM) and replacement with granulation tissue, all in the absence of middle ear disease.[18, 19]

PATHOLOGY

Histology has demonstrated oedematous granulation tissue with capillaries and diffuse infiltration of chronic inflammatory cells.[20]

AETIOLOGY

Aetiology is unknown but it has been suggested that non-specific injury to the lamina propria, such as trauma or infection, may impair epithelialization and promote granulation tissue formation.[20] This theory may be supported by the high incidence of myringitis following myringoplasty (5.5%) and the fact that in some series of GM nearly all patients had had prior otological surgery (93%).[18, 21]

The common finding of positive cultures from affected ears (*Pseudomonas aeruginosa*, *Staphylococcus aureus* (including MRSA), *Corynebacterium*, *Proteus mirabilis*, fungal species), in addition to the success of antimicrobial treatment, implicates the contribution of infection to the aetiology.[20, 22, 23]

PRESENTATION

Clinically this condition may be defined as persistent inflammation confined to the squamous layer of the TM for at least 12 weeks.[21]

Most patients present with persistent or recurrent painless otorrhoea, which may be malodorous.[18] In one study 70% of these patients had had symptoms for more than 1 year.[22] Other symptoms include intrameatal itch or fullness, mild conductive hearing loss and rarely otalgia. Some patients may be asymptomatic.

Following microsuction of otorrhoea, examination reveals granulation tissue/polyp replacing normal squamous epithelium on a sometimes thickened TM. Granulation can be localized to part of the TM (focal/segmental) or diffuse (**Figures 75.3** and **75.4**).[18, 19] The segmental type is more common, with the posterosuperior segment of the eardrum most frequently affected.[24] It may also involve the skin of the adjacent medial ear canal.

It is important to differentiate GM from other causes of chronic otorrhoea. Furthermore, most definitions of GM exclude patients with perforation or cholesteatoma.



Figure 75.3 Focal areas of granular inflammation affecting the anteroinferior and posteroinferior aspects of the left tympanic membrane with active inflammation and pus.

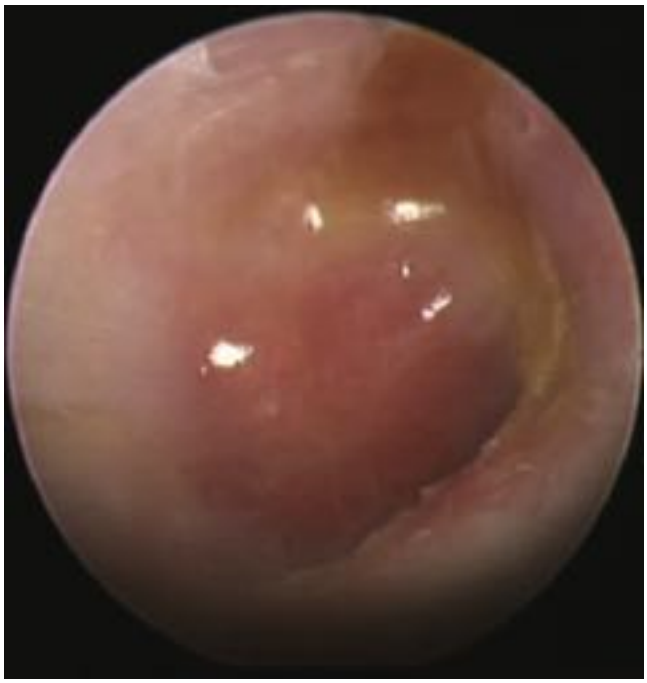


Figure 75.4 Diffuse granular myringitis affecting the entire right tympanic membrane.

INVESTIGATIONS

A swab should be taken for microscopy, culture and sensitivities to guide any antimicrobial treatment. Pure-tone audiometry and tympanometry may help to identify associated hearing loss or middle ear pathology. Occasionally, CT temporal bone may help exclude underlying middle ear/mastoid disease. Some published series include normal type A tympanogram and a normal CT as essential diagnostic criteria in GM.

Biopsy to exclude malignancy should be considered if there are concerning features such as significant otalgia or non-resolution despite treatment.

COMPLICATIONS

The natural history of this condition is difficult to determine as patients may be asymptomatic despite continued myringitis. However, we know that many patients have symptoms persisting for years.[18] This long-standing chronic inflammation of the TM and medial ear canal wall skin, in association with proliferating granulation tissue, can lead to fibrosis, scarring and stenosis of the medial ear canal with lateralization of the eardrum.[25] Although these sequelae may resolve any otorrhoea, there is likely to be a significant resultant conductive hearing loss.

MANAGEMENT

Most would agree that meticulous microscopic cleaning/debridement in combination with topical antibiotic or antiseptic agents forms the mainstay of initial management. Treatment is often more prolonged than for other types of otitis and recurrence is relatively common. A plethora of published treatment strategies exist. These can broadly be grouped into:

- topical antibiotic and antifungals, often with a steroid/anti-inflammatory agent
- topical antiseptic agents: acetic acid, aluminium acetate, phenol, hydrogen peroxide
- debulking of granulations with cold steel (curettage/cupped forceps), silver nitrate cautery or laser debridement/resurfacing
- surgical excision with grafting (onlay skin graft, temporalis fascia/perichondrium underlay technique).

A systematic review published in 2008 found 46 potentially relevant studies of which only two met the inclusion criteria.[19] The two non-randomized studies included in the review are summarized in Table 75.1.

This review concluded that, although there is insufficient evidence to support any particular management strategy, 'conventional topical antibiotic and steroid drops appear less efficacious that other treatment modalities'. In addition, dilute vinegar solution is an effective simple alternative to topical antibiotic drops.[23, 24]

Subsequent to this review, further published case series have shown good results with antiseptic topical preparations, CO_2 laser resurfacing as well as more aggressive surgical excision with overlay myringoplasty.[22, 26, 27] In addition, there has been a double-blind randomized controlled trial which compared topical 5-fluorouracil to placebo (petroleum jelly).[28] Unfortunately, as this is not a commonly used preparation and has not been compared

TABLE 75.1 Summary of the two studies included in the 2008 review of management options

Study	Design/Level of evidence	Sample size	Intervention group	Control group	Follow-up	Outcome
Jung et al. (2002)[23]	2b	30	Topical vinegar (acetic acid pH 2.43)	Topical ofloxacin	>6 months	Faster symptom resolution and reduced recurrence with topical vinegar
El-Seifi and Fouad (2000)[24]	2c	74	Surgical excision of granulation tissue with tragal cartilage underlay graft	Topical acetic acid with antibiotic/steroid drops	>6 months (average 6.25 years)	Reduced recurrence with surgery compared with topical treatment

with other more commonly used treatment modalities, it is of limited clinical utility.

In summary, there is a wide range of potential treatment modalities which have been found to be effective, but unfortunately all have reported problems with recalcitrant or recurrent cases. More recently, published studies are demonstrating the benefits of antiseptic agents in preference to antibiotic drops. Many clinicians may use more than one strategy, reserving more aggressive surgical management for recalcitrant cases as there may be a higher rate of subsequent perforation with these techniques.

FUTURE RESEARCH

- Further research is required to identify optimal treatment of BM especially when complicated by SNHL.
- Given the association of GM following otological surgery, research to identify operative risk factors for development may help reduce the incidence.
- Quality randomized controlled trials are required to compare the topical treatments most commonly used in GM.

KEY POINTS

- Bullous myringitis represents an acute severe inflammatory reaction affecting the TM.
- Aetiological pathogens in BM are similar to those in AOM.
- Inner ear involvement with SNHL (and vertigo) is not uncommon in BM and usually resolves spontaneously.
- As BM is usually a self-limiting disease, the mainstay of treatment is symptomatic. The optimal management of associated hearing loss, however, remains to be elucidated.
- Granular myringitis is a chronic condition usually presenting with otorrhoea.
- In GM, de-epithelialization of the outer layer of the TM and replacement with granulation tissue occurs in the absence of middle ear disease.
- Treatment of GM usually involves topical antimicrobial or antiseptics often for prolonged periods.
- More aggressive physical debulking or surgical excision and grafting is usually reserved for recalcitrant cases of GM.

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CHAPTER 76

KERATOSIS OBTURANS, PRIMARY AUDITORY CANAL CHOLESTEATOMA AND BENIGN NECROTIZING OTITIS EXTERNA

Tristram H.J. Lesser

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: keratitis obturans, wax keratosis, external auditory canal cholesteatoma, external auditory meatus cholesteatoma, external ear cholesteatoma, osteomyelitis of the ear, benign otitis externa, benign necrotizing otitis externa, osteonecrosis and ear canal necrosis, tympanic bone and epithelial migration of the ear. This was supplemented by obtaining all the references quoted in the papers. Sixty-six papers were considered after removing non-relevant papers and repeats. The only evidence found was in observational studies and from expert opinions.

DEFINITIONS

Keratosis obturans (KO) is a different clinical and pathological entity from primary auditory canal cholesteatoma (ACC) and benign necrotizing otitis externa (BNOE) (Table 76.1). There is a less clear distinction between ACC and BNOE. While ACC and BNOE are different diseases, they may have similar aetiologies and are not separated from each other by an identified abnormality. Whereas KO, is separated by having a specific deficit of the epithelial migration.[1,2]

The 1980s saw the definition of the difference between KO and ACC, and articles before then on KO contained some cases that were probably primary ACC and vice versa. More recent articles on necrotizing otitis externa (NOE) and ACC still contain cases that could be NOE or ACC in the same series and this may represent a clinical and pathological overlap.

Keratosis obturans is the accumulation of a large plug of desquamated keratin in the external auditory meatus.

Primary auditory canal cholesteatoma is the invasion of squamous epithelium into a localized area of bony erosion with or without bony necrosis.

Benign necrotizing otitis externa is the formation of an avascular bony sequestrum of the inferior tympanic bone with secondary inflammation of the overlying soft tissue and skin.

PATHOLOGY

In KO, a geometrically patterned keratin plug within the lumen of an expanded external auditory canal is seen (Figure 76.1). The keratin squames are shed from the complete circumference of the deep ear canal forming a lamina (onion skin) arrangement.

In primary ACC, the keratin is derived primarily from a sac that involves the bone of the ear canal with bony fragments within it and random keratin in the lumen of the ear canal. Keratin is found deep to the bone fragments.[3]

In BNOE the necrotic sequestrum of bone appears to involve the superficial cortical layer primarily.[4] Histology of the bone reveals dead lamellar bone with inflammatory

TABLE 76.1 Differential diagnosis of non-neoplastic conditions eroding the bony external auditory canal, with their clinical characteristics

	Keratosis obturans	Auditory canal cholesteatoma	Benign necrotizing otitis externa	'Malignant' necrotizing otitis externa
Aetiology	Abnormal epithelial migration	Abnormal bone leading to epithelial migration into bone	Avascular bone leading to inflammation of overlying skin	Immunocompromised Patient with necrotic bone in ear canal
Symptoms and findings	Severe otalgia Conductive hearing loss Lung or sinus disease Younger Occasionally bilateral	Otalgia mild No hearing loss Itchiness Older Usually unilateral Blocked feeling	Chronic painless infected otorrhoea Partial response to previous treatment Localized exposed bone in canal 3–10 mm diameter Dehiscent skin	Severe penetrating pain Cranial nerve palsy Diabetic/renal failure or otherwise immunosuppressed Raised inflammatory markers
Pathology	Keratin plug Tympanic membrane thickened Widened deep canal Hyperaemia of skin canal with granulations	Keratin in random pattern Tympanic membrane normal Localized osteitis/erosion of ear canal usually posterioinferior Sequestration of bone	Chronic inflammation with no associated keratin and no cholesteatoma deep to sequestrum Commensals on bacteriology	Chronic inflamation *Pseudomonas aeruginosa*
Treatment	Remove plug Treat granulations Occasionally biopsy	Surgically remove cholesteatoma graft with cartilage and fascia Biopsy	Conservative initially Surgical removal of sequestrum	Treat cause of immunosuppression High-dose antibiotics Long-term antibiotics Surgical debridement
Differential diagnosis	Wax impaction with infection Otitis externa Neoplasm	Necrotizing otitis externa Neoplasm	Auditory canal cholesteatoma Neoplasm Malignant otitis externa	Malignant neoplasm

Note: Modified from Shire JR, Donegan JO. Cholesteatoma of the external auditory canal and keratosis obturans. *Am J Otol* 1986; **7**: 361–4, by kind permission of Lippincott, Williams & Wilkins.[2]

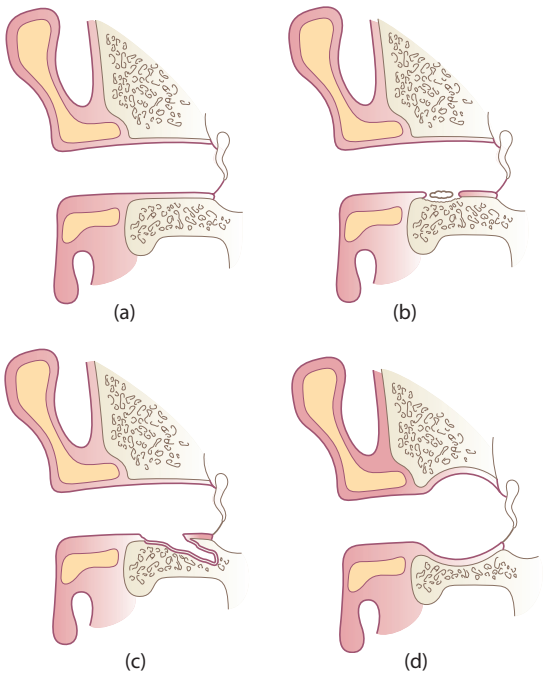


Figure 76.1 **(a)** Normal external auditory canal. Cartilage is shown in yellow, bone is stippled, and canal skin is shown as a line. **(b)** Benign necrotizing otitis externa. Note the deficient area of skin, and bony sequestrum. **(c)** Canal cholesteatoma. A sac of canal skin invades bone. **(d)** Keratosis obturans. The bony canal is 'ballooned' out.

cells filling the marrow spaces.[5] There are limited chronic inflammatory changes of the adjacent skin and subcutaneous tissue.

BACTERIOLOGY

In all three conditions skin flora and a wide range of bacteria may be cultured: *Proteus mirabilis*, *Staphylococcus epidermidis*, *Klebsiella pneumoniae* and betahaemolytic streptococci are found, but generally no *Pseudomonas* species. *Staphylococcus aureus* is the most frequent isolate.

AETIOLOGY

It is thought that KO is due to abnormal epithelial migration of the ear canal skin.[6] One case report found that the epithelium moved in an anterior direction across the whole drum. Another case that was not typical of KO but had a need for repeated aural cleaning had a grossly abnormal migratory pathway. The movement of the surface epithelium of the pars flaccida was reversed such that it migrated downwards to the pars tensa and then moved inferiorly across the whole drum.[7]

A condition called 'keratosis tympanicum' has been described with similar abnormal epithelial migration

associated with unilateral tinnitus.[8] It is not certain that these two diseases are related or that all cases presenting with KO are the same disease.

It has been suggested that there may be two types of KO. One is of an inflammatory nature which occurs secondary to an acute problem, such as a viral infection, causing inflammation of the ear canal which temporarily alters the epithelial migration. This is cured by removal. The second or the silent type is a disease that persists and is caused by abnormal separation of the keratin that continues even after the first removal and will need subsequent removals.[6]

The aetiology of external ACC is uncertain, but in some of the series primary ACC is post-traumatic or post-surgical (e.g. stapedectomy cases). It has been postulated that a piece of exposed bone of the primary auditory canal becomes infected and sequests, the epithelium migrates into this bony abnormality and the cholesteatoma is formed. Primary ACC is distinguished from cholesteatoma that arises secondary to a previous ear canal insult. Many authorities believe that idiopathic external ACC results from a reduced migratory capacity of the canal epithelium, which leads to 'keratinization *in situ*'.[9–15] This view has been challenged, however, by a study which showed no difference in the rate of epithelial migration between normal ears and those affected by external ACC.[16]

In some cases the occurrence of external ACC has been linked to branchial arch anomalies, which result in the retention of epithelial masses and lead to cholesteatoma formation in the floor of the external auditory canal.[17]

The cause of the necrotic bone in BNOE is unknown.[18] Theories relating to vascular insufficiency began with Goufas in 1954.[19] It is often stated that the tympanic bone is particularly susceptible to osteonecrosis because of its 'relatively poor blood supply'. The microangiopathy of diabetes has been advanced but there is only a little evidence that BNOE is more common in diabetics, as opposed to the 'malignant' form. Small arterial emboli have been suggested. Repeated local trauma, for example ear bud abuse, picking of the ear or the use of hearing aids, is a popular theory.[20] Bharadwaj et al. suggested association with respiratory tract inflammatory conditions is difficult to support. Bottari proposed 'neurotrophic disturbances'.[18, 21]

The overlap between ACC and BNOE if it exists is uncertain and has yet to be defined fully.[22]

The aetiology of BNOE may have some similarity with 'malignant' NOE.[23] As the tympanic plate appears to have a relatively poor blood supply, the additional microangiopathy in diabetes, as mentioned above, may predispose it to avascular necrosis and the formation of bony sequestra. The high sugar content of the bone may encourage *Pseudomonas* to grow. A similar pathogenesis is found in radionecrosis of the tympanic bone with a slowly progressive obliterative endarteritis.[24] Although diabetics may have a slightly higher incidence of BNOE as well as 'malignant' NOE, the pathogenesis of the avascular necrosis of the tympanic bone is not clear.[25]

CLINICAL SYMPTOMS

The clinical symptoms are different in KO and ACC/BNOE.

KO occurs more commonly in younger patients. It classically presents with acute severe otalgia and a conductive hearing impairment. Infrequently, the disease is bilateral. There may be an associated bronchiectasis or sinusitis.[26, 27] Many of the patients in the historical papers had a condition called 'wax keratosis', which is thought to be becoming less common as the associated lung disease and sinusitis are now better controlled. These are historical papers that may not agree with the current clinical presentation of KO.

ACC and BNOE have a similar set of clinical findings. The most common presentation is chronic otorrhoea with dull pain or itching. It is not associated with hearing impairment. Bilateral cases account for around 1 in 6–12 cases.[28, 29] A review of published case series concluded that the most common presenting symptoms of idiopathic external ACC are unilateral otorrhoea with mild to moderate otalgia.[12] A minority of patients complained of unilateral hearing loss, or were asymptomatic with the cholesteatoma being discovered on routine otoscopy performed for a separate indication.

INVESTIGATION

The primary investigation of these patients is microscopic examination of the ear either in the clinic or under general anaesthetic. In KO, the ear canal can become grossly widened or ballooned such that the tympanic membrane is left standing out in relief in a widened ear canal (**Figure 76.2**). In ACC the cholesteatoma is able to be suctioned (**Figure 76.3**) and has fragments of bone within it, and there may be some granulation tissue which needs biopsy. In BNOE the covering on the floor of the ear canal is deficient with granulations around the edges of the epithelial defect, yellow necrotic bone in the bare area with small necrotic fragments (**Figure 76.4**).[30]

Computed tomography of the temporal bones has become accepted as the gold standard for staging and preoperative planning in external auditory canal destructive disease.[32] This method allows accurate evaluation of the extent of local bone erosion and involvement of adjacent structures. Should surgery be contemplated for BNOE, a CT scan may be indicated in order to identify the extent of bone necrosis.

If gross infection is present, a pus swab may be taken. If *Pseudomonas* is cultured, the diagnosis should be queried in favour of 'malignant' NOE. If prominent inflammatory or granulation tissue coexists, chronic 'granulomatous' conditions including syphilis and tuberculosis should be excluded.

Audiometry should be normal or show a mild conductive hearing impairment in ACC and BNOE but will show a marked conductive hearing loss in KO.

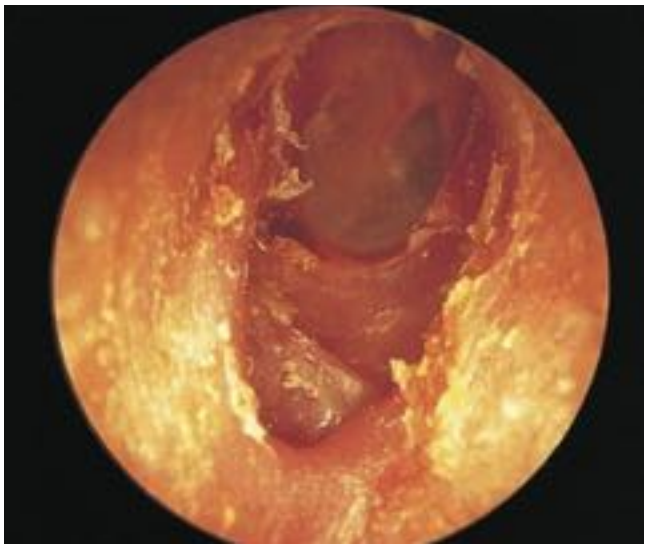


Figure 76.2 Keratisis obturans. The keratoma has been removed from the right ear with KO and shows expansion of the bony canal just lateral to the tympanic membrane. Reprinted with permission from Wormald and Browning. *Otoscopy: a structured approach.* London: Hodder Arnold; 1996.[31]



Figure 76.3 Cholesteatoma of the auditory canal after suction.



Figure 76.4 Typical appearance of benign necrotizing otitis externa. An area of denuded necrotic bone is visible in the floor of the bony external auditory canal.

BIOPSY

Histological examination of any granulation tissue is required to exclude malignancy, as the differential diagnosis will include carcinoma of the ear canal, 'malignant' NOE and benign neoplasm that has secondary infection in the external auditory canal.

EPIDEMIOLOGY

The frequency of primary ACC has been estimated as one in 1000 new otological cases and for every case of primary ACC there are four or five cases of KO.[33] BNOE is probably the most common of the three diseases.

NATURAL HISTORY AND COMPLICATIONS

Little is known of the natural history of these diseases. Sporadic reports demonstrate that normal ear canals can suddenly develop these conditions; for instance, KO can occur in either previously normal ears or in ears that have had plugs of keratin needing removal beforehand. KO can cause extensive bony erosion, including automastoidectomy.[7] There are no reports of intracranial complications from this disease. In ACC erosion through the anterior wall of the canal may affect the temporomandibular joint and rarely, in advanced cases, extension into the posterior fossa has been reported with resulting intracranial abscess.[34]

EXTERNAL AUDITORY CANAL CHOLESTEATOMA STAGING

There are two staging systems for ACC but none for the other two diseases.

Nairn et al. external ACC staging is based on the proposal that there is a preclinical disease. Stages I and II will not usually present as the disease of ACC.[15]

Nairn et al. staging:[15]

I	Epithelial hyperplasia
IIa/b	Periostitis hyperplasia with erythema (a), or denuded but not eroded bone (b)
III	Canal wall erosion and bony sequestrum
IV	Invasion into adjacent structures

Subclasses of disease stage IV include: mastoid (M), skull base and sigmoid sinus (S). temporomandibular joint (J), and facial nerve canal (F).

Seung-Ho Shin et al. clinical and radiological staging:[32]

I	Limited to the external auditory canal
II	Invades the tympanic membrane as well as ear canal
III	Creates a defect of the EAC and involves the cortex of mastoid bone
VI	Involves areas beyond the temporal bone (**Figure 76.5**)

This classification also includes treatment suggestions, as follows:

I	with local care or canaloplasty
II	with canaloplasty + tympanoplasty
III	with the above and mastoidectomy and canal wall reconstruction
IV	with removal of cholesteatoma using various techniques.

MANAGEMENT OPTIONS

The pain and deafness associated with KO mean that it is necessary to remove it, often under general anaesthetic. Canaloplasty has been suggested for recurrent KO with good results.[29] For ACC, conservative treatment is used where the extent of the cholesteatoma erosion can be seen (**Figure 76.6**). When this is not possible, patients are treated with excision of necrotic bone and cholesteatoma via the mastoid and repair of the defect using temporalis fascia.[35] The only other treatment suggested is a canal wall-up procedure with repair of the defect, but no long-term follow-up is available of such patients.

In BNOE conservative management consists of removing the bony sequestrum once it separates spontaneously,



Figure 76.6 Healing cholesteatoma of the ear canal after conservative treatment.

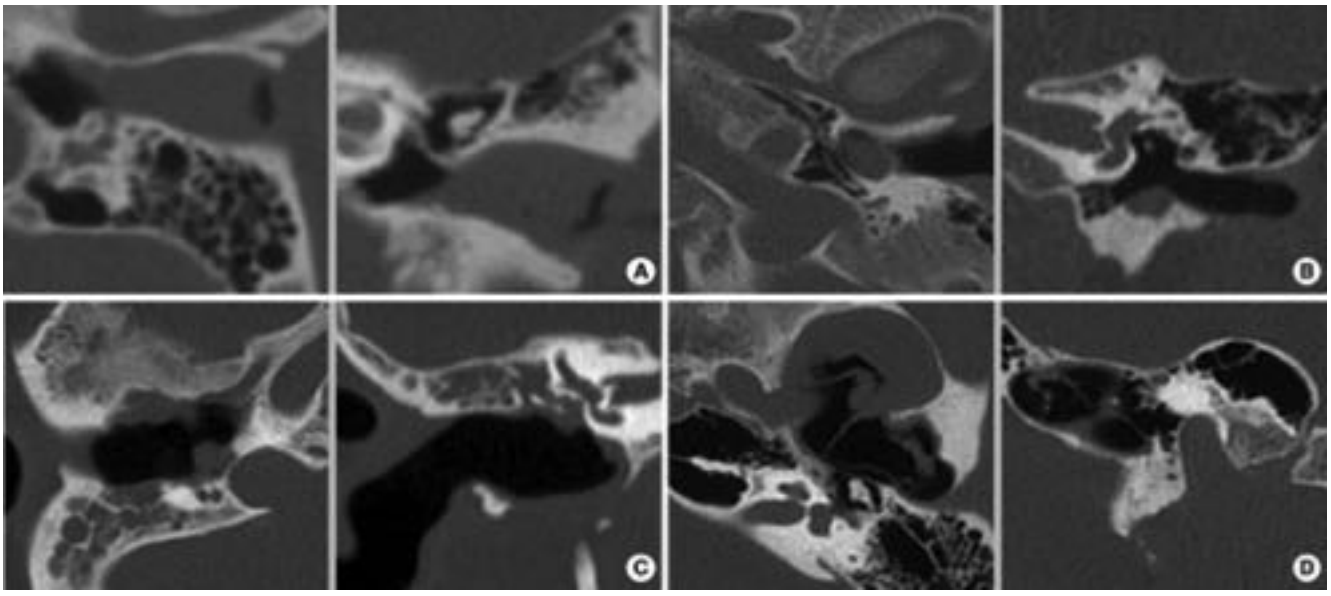


Figure 76.5 Radiology of the stages of ACC: A = I; B = II; C = III; D = VI. Reproduced from Shin et al. Classification of external auditory canal cholesteatoma by computed tomography. *Clin Otorhinolaryngol* 2010: **3**: 24–6.[32]

with local toilet and local treatment to control any infection. An oral antibiotic may be used.[22] Speculation based on a series of eight patients is that younger patients (less than 60 years) are more likely to respond to conservative management. Separation of the sequestrum, followed by epithelial growth to cover the bony defect, as encouraged by conservative management, is the most likely outcome.[21]

A more aggressive surgical approach has been advocated, with early surgical removal of the sequestrum down to healthy bone.[5, 25] Adjunctive hyperbaric oxygen may be considered when there is progression despite intensive local and systemic treatment and when there is necrosis beyond the tympanic plate.[4]

Treatments for these conditions are reported to be effective.

BEST CLINICAL PRACTICE

- ✓ Microscopic examination should be carried out in the clinic or under general anaesthetic.
- ✓ CT scan should be used for primary ACC.
- ✓ Biopsy should be undertaken to exclude carcinoma.
- ✓ Removal of the plug of keratin should be carried out in KO.
- ✓ Surgical removal and repair should be performed in primary ACC.
- ✓ Conservative treatment of BNOE is usually adequate providing 'malignant' otitis externa has been ruled out.
- ✓ Osteoradionecrosis, chronic inflammatory conditions and benign tumours should be excluded.
- ✓ These conditions may all resolve spontaneously or with local toilet and care.

FUTURE RESEARCH

- ➤ The true incidence of these diseases is not known.
- ➤ The clinical courses are not well defined.
- ➤ Further work needs to be undertaken to determine the aetiologies of these diseases and any relationship to abnormal epithelial migration and vascular insufficiency.
- ➤ The relationship between ACC and BNOE is uncertain.
- ➤ The relationship and possible shared aetiology between BNOE and malignant NOE is likewise uncertain.
- ➤ The rarity of the conditions makes level 1 or 2 evidence for treatment difficult to obtain.

KEY POINTS

- Primary ACC, KO and BNOE are different diseases.
- KO occurs in younger patients, presents with pain, may be associated with sinusitis or bronchitis, may be associated with disordered epithelial migration, either temporary or permanent, and is treated with removal of the keratin plug.
- Primary ACC is more common in the elderly, may be traumatic, presents with otorrhoea and itching and minimal hearing loss, and is treated with permeatal or mastoid surgery to remove the disease.
- BNOE is probably more common and has similar clinical presentation to ACC but may need less radical treatment.

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CHAPTER 77

ACQUIRED ATRESIA OF THE EXTERNAL EAR

Jonathan P. Harcourt

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Aetiology 950
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Natural history and complications 950
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Outcomes 952
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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: external ear, external ear canal, acquired and atresia.

DEFINITION

Atresia is defined as the absence of or closure of a passage of the body. This covers both congenital and acquired lesions. Tos[1] defines acquired atresia of the external ear as 'intraluminal sequelae of either intraluminal or extraluminal processes of varying aetiology, resulting in a blind sac in the external acoustic meatus'.

Atresias may be solid or membranous.

- **Solid atresia** consists of a continuous block of fibrous or fibrous and bony material which is continuous with the structure of the tympanic membrane and is of variable extent. The face of the solid atresia may be blunt or tapering, producing a funnel-shaped medial aspect to the lumen of the ear canal (Figures 77.1 and 77.2).
- **Membranous atresia** is typified by fibrous tissue that has a covering of ear canal skin on both sides, thus separating the ear canal into a medial and lateral segment (Figure 77.3). The medial part inevitably collects keratin from desquamation of the skin; this may become an erosive process and thus be defined as an external canal cholesteatoma.

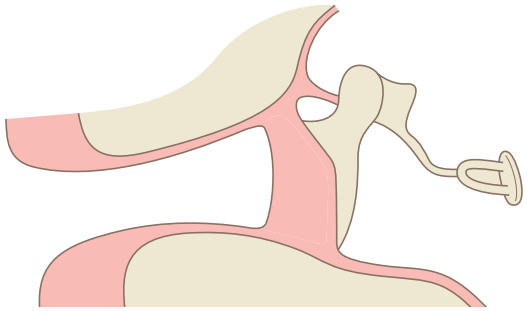


Figure 77.1 Solid atresia, obliterating the medial aspect of the bony external ear canal.

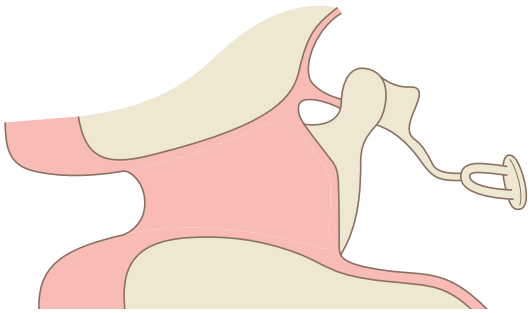


Figure 77.2 Extensive funnel-shaped solid atresia.

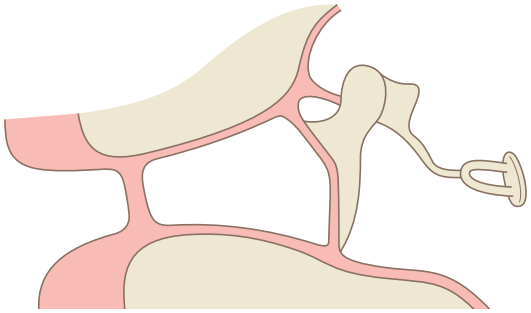


Figure 77.3 Membranous atresia in lateral external ear canal.

DIAGNOSIS

The clinical diagnosis of acquired atresia is supported by the use of CT scanning which gives a very detailed image of the bony and soft-tissue structure of the external ear. Figures 77.4 and 77.5 show examples of medial and mid-canal atresias. It particularly helps in the differentiation of solid and membranous atresia. This is an important distinction as there may be a substantial divergence of management between these two entities. Solid atresia is a safe form of ear disease, whose surgical treatment is very challenging. Membranous atresia will inevitably produce associated cholesteatoma and therefore erosion of local structure. Surgical outcome is superior to solid atresia.

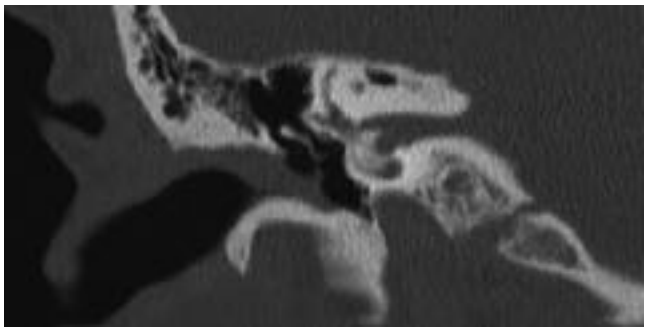


Figure 77.4 Coronal CT of right external ear canal showing medial atresia.

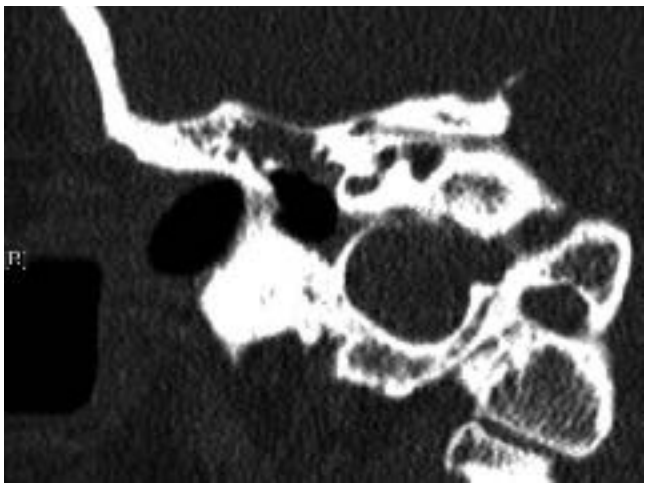


Figure 77.5 Coronal CT scan of right external ear canal showing lateral predominantly membranous atresia. The patient had undergone previous surgery for chronic otitis media.

AETIOLOGY

Acquired atresia may be caused by the following processes:[2]

- **Inflammation**, which may be as a result of :
  - otitis externa
  - psoriasis, eczema and other dermatological conditions
  - active chronic otitis media
- **Trauma**, by various mechanisms:
  - open injury, especially gunshot wounds
  - closed fracture of the tympanic plate, particularly associated with frontal facial injuries when the mandibular condyle is forced backwards through the anterior wall of the external ear canal
- **Burns**, which may be thermal, chemical, electrical or post-irradiation in nature
- **Surgery**. Any operation involving a meatal approach (tympanoplasty, etc.) has a remote risk of solid atresia but particularly with on-lay techniques. Meatal surgery (removal of an osteoma) may also precipitate membranous atresia in the lateral canal.

Pathogenesis

The pathogenesis of solid and membranous types differs.

SOLID ATRESIA

In cases associated with otitis externa or media the key development is of granular medial otitis externa with granulations of the tympanic membrane that persist for many months in spite of treatment. The granulations become fibrotic and the eardrum becomes thickened as the medial meatal mass is re-epithelialized. This process can be repeated again and again. If it is associated with active chronic otitis media, the granulations appear around the tympanic membrane perforations and eventually lead to closure of the defect before the process extends laterally as described above.

MEMBRANOUS ATRESIA

This originates in the lateral meatus as a web formation[2] which is precipitated by a circular irritation from inflammation, trauma or burns and ulceration of the skin around the entire circumference of the external ear canal. The web-like stenosis forms after fibrosis and re-epithelialization as with solid atresias. Repeated attacks or one massive injury such as a tympanic plate fracture leads to a complete atresia.

EPIDEMIOLOGY

Becker and Tos[3] estimated an annual incidence of 0.5 per 100 000 based on clinical presentation of cases over 26 years in a centralized otology practice in Denmark. The vast majority of cases were solid fibrous atresias and only a few were membranous, making the incidence of typical membranous atresias 20 times smaller than that of the solid form.

NATURAL HISTORY AND COMPLICATIONS

Once solid atresia has formed, though there may be further episodes of medial granulating otitis externa, fibrosis and re-epithelialization, overall there is a change from a 'wet' to a 'dry' phase. In the latter situation the principle

complaint is of conductive hearing loss and this is generally a stable situation. Membranous atresia is associated with medial cholesteatoma, which can potentially produce local erosion and complications. This is usually of a broad slow erosive nature, similar to keratosis obturans.

MANAGEMENT OPTIONS

Medical

During the wet phase, the medial granulations can be removed by aspiration and cauterization with silver nitrate or trichloroacetic acid and the ear packed with ribbon gauze or a wick. This local treatment may turn the ear dry and prevent further progression of the atresia.[4]

The conductive hearing loss (if bilateral) may be managed by an air-conduction hearing aid though the presence of a mould in the external ear canal can aggravate the process and lead to the ear becoming or persisting in an active state. A bone-anchored hearing aid is an alternative when a conventional air conduction device is not tolerated.

Surgical

FIBROUS ATRESIA

The principle of surgery for fibrous atresia is to remove the fibrous tissue by elevating it from the ear canal bone, the fibrous annulus and lamina propria of the tympanic membrane (Figure 77.6a). In most cases access is adequate via a speculum inserted into the external ear canal, though an endaural or retroauricular approach may be utilized. A circumferential incision is made lateral to the blunt face of the atretic plate and a plane of dissection developed between the bone of the ear canal and the canal skin, followed by the atretic plate and finally lateral to the fibrous annulus and lamina propria of the tympanic membrane (Figure 77.6b). The epithelial defect is repaired by a fine split-skin graft (SSG) which may be laid in single or multiple pieces (Figure 77.6c). A silastic disc or tube may be inserted to stabilize the epithelial surface and finally the ear canal is packed with ribbon gauze soaked in antiseptic. The ear canal requires regular suction toilet and may need repacking to prevent medial granulation and early recurrence of the atresia. This is also prevented by careful removal of all fibrous tissue with exposure of the entire circumference of the fibrous annulus. This allows stable long-term results.[3]

MEMBRANOUS ATRESIA

Similar to fibrous atresia, membranous atresia can be approached trans-canal using an ear speculum. This is satisfactory for a small atretic plate (Figure 77.7a) but, if the fibrous lesion is very thick, a retroauricular approach may be superior, allowing preservation of the lateral and medial epithelial coverings to aid repair of the ear canal skin. In the trans-canal approach the fibrous plate is excised via a circumferential incision just lateral to its margin. The whole lesion is excised with sacrifice of the minimum

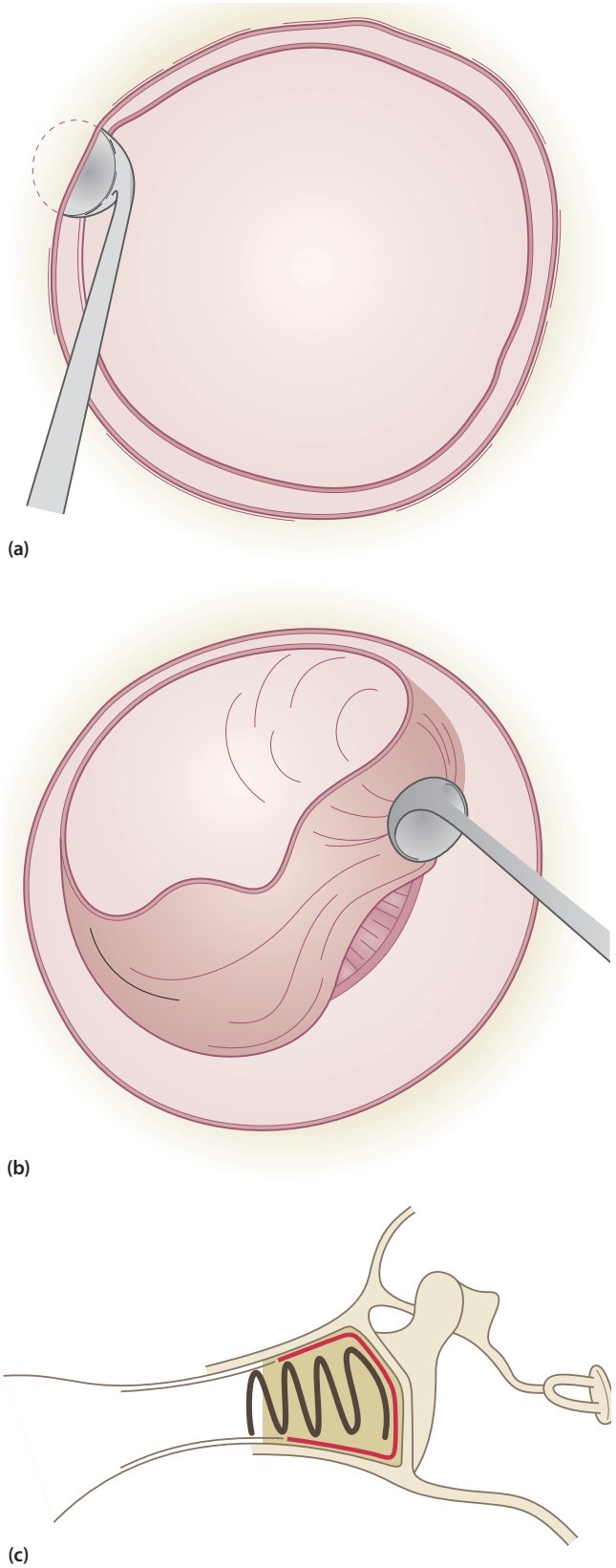


Figure 77.6 Surgery for solid atresia. **(a)** Circumferential canal incision lateral to fundus. **(b)** Dissection of the fibrous plate continues down to the lamina propria and the plate is excised. **(c)** Split-skin graft is applied to the bare medial bony canal wall and over the fibrous annulus and lamina propria and the canal is packed with ribbon gauze.

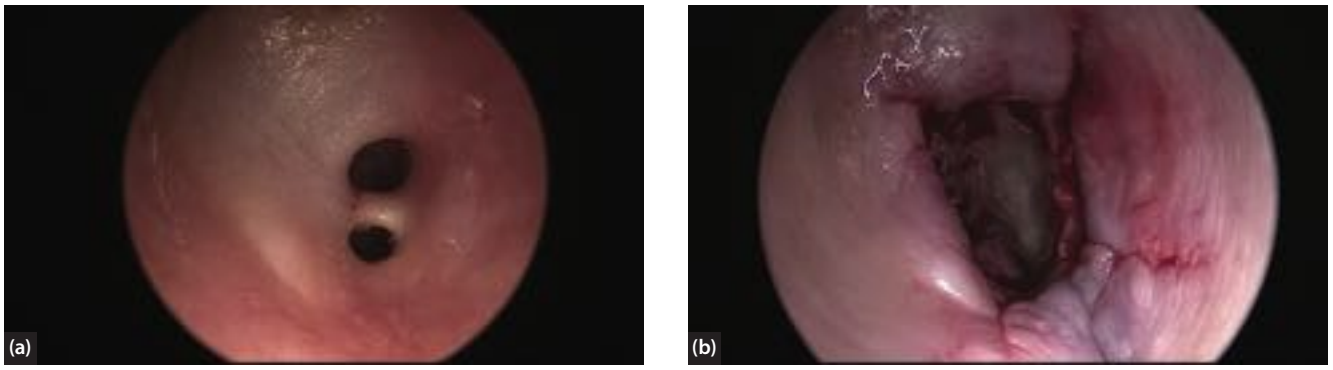


Figure 77.7 Surgery for membranous lateral atresia. (a) Predominantly membranous atresia with two small defects. **(b)** Lateral and medial flaps interleave to aid post-operative epithelialization.

of surrounding epithelium. Silastic sheets are overlaid, holding the lateral and medial skin edges against the bone of the ear canal. With thicker plates the retroauricular approach provides access to lift off the outer skin, remove the atretic plate and dissect it away from the medial skin covering. This aids the final reconstruction, providing skin flaps which can be turned to cover the bare canal bone at the site of the membranous atresia (**Figure 77.7b**).

Atresia surgery combined with tympanoplasty

As the underlying condition of atresia, particularly the solid form, is associated with middle-ear disease, such as chronic otitis media, it is not surprising that Becker and Tos[3] found that in 40% of their surgical cases there was an associated middle ear problem such as an ossicular discontinuity or tympanosclerosis. A tympanotomy may be combined with atresia surgery, especially in solid cases where the delicate fibrous layer of the tympanic membrane can be lifted to examine the ossicular chain and give access for reconstruction.

OUTCOMES

There are few published large series of long-term results in surgery for ear canal atresia. This is of particular relevance to this form of surgery because recurrence may be a late development, as the processes that drive the condition, such as otitis externa, may persist. The principal outcome measure is residual conductive hearing loss as the aim of surgery is to provide an open and stable ear canal with a relatively thin and mobile tympanic membrane.

Becker and Tos[3] published a series of 53 ear cases with follow-up of up to 27 years (average >10 years), Herdman and Wright[5] of 9 cases with about 5 years' follow-up and Magliulo[6] of 41 ears with 5 years' follow-up in the majority. The recurrence rates were 11%[3], 33%[5] and 36%.[6] The residual air–bone gap was less than 20 dB in 90%[3] in the Danish series but there was a recurrence of about a third of a clinically significant air–bone gap in the latter report.[6]

These results suggest that surgery can offer stable long-term results with good hearing in the majority but long-term recurrence is a significant risk.

BEST CLINICAL PRACTICE

- ✓ During the wet phase, the ear should be managed with regular suction toilet and local medical treatment to attempt to render the ear dry.
- ✓ Hearing loss may be managed with air-conduction or bone-anchored hearing aids.
- ✓ Atresia (particularly membranous) can be complicated by cholesteatoma and cases should undergo CT scanning.
- ✓ Surgery to relieve conductive hearing loss is possible and in expert hands may lead to stable long-term results.

KEY POINTS

- External ear canal atresia may be solid or membranous.
- It is caused by local irritation by inflammation or trauma.
- Assessment should include CT scanning of the temporal bone.
- It may be complicated by ear canal cholesteatoma.
- If in a wet phase, local treatment may render it dry.
- Auditory rehabilitation with air- or bone-conduction hearing aids should be considered.
- Ear canal surgery to relieve the conductive element and deal with any medial cholesteatoma is effective and stable in expert hands over the long term.

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CHAPTER 78

OTITIS EXTERNA AND OTOMYCOSIS

A. Simon Carney

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline (Ovid) search using the keywords: otitis externa, external otitis, external auditory canal and limiting the search to human, English language, full papers.

OTITIS EXTERNA

DEFINITION

Otitis externa is a generalized condition of the skin of the external auditory canal. It is characterized by oedema and erythema associated with itch, pain and discharge.

CLASSIFICATION

There is no universally accepted classification for otitis externa and it has been put into many subcategories in the past. In fact, most of these (e.g. eczematous otitis externa) are actually just predisposing factors (Table 78.1).

PATHOLOGY

The clinical course of diffuse otitis externa is extremely variable but has been divided into the following stages:[1]

Stage 1: Pre-inflammatory
Stage 2: Acute inflammatory (mild, moderate or severe)
Stage 3: Chronic inflammatory

TABLE 78.1 Predisposing factors for otitis externa

Type	Factor
Anatomical	Narrow external auditory meatus (EAM) (hereditary, iatrogenic, exostoses, trauma, etc.) Obstruction of normal meatus (kerratosis obturans, wax, foreign body, hearing aid, in-ear head phones, hirsute canal, etc.)
Dermatological	Eczema, sebhorrhoeic dermatitis, psoriasis
Allergic	Atopy, non-atopic allergy, exposure to topical medications
Physiological	Humid environment, immunocompromisation
Traumatic	Skin maceration (bathing or irrigation), ear probing, laceration, radiotherapy, ear candling
Microbiological	Active chronic otitis media, exposure to *P. aeruginosa* or fungi

In stage 1, the protective lipid/acid balance (normal pH 4–5) of the ear is lost and the stratum corneum becomes oedematous, blocking off the sebaceous and apocrine glands and producing aural fullness and itching.

With further oedema and scratching, there is disruption of the epithelial layer and invasion of resident or introduced organisms. This results in stage 2, with

a progressively thickening exudate, further oedema, obliteration of the lumen (mild: little or no obliteration; moderate: sub-total obliteration; severe: complete obliteration) and increasing pain. In the severe stages, auricular changes and cervical lymphadenopathy are often seen. After 6 months, by definition, chronic otitis externa occurs. Stage 3 is characterized by thickening of the external canal skin and this is covered in Chapter 77, Acquired atresia of the external ear.

DIAGNOSIS

Otitis externa is a clinical diagnosis based on the following symptoms and signs: pain, itch, oedema and erythema of the external auditory canal with purulent otorrhoea and debris in the meatus (**Figure 78.1**). An active chronic otitis media may be identifiable in some cases. There are no studies evaluating the accuracy of clinical diagnosis in otitis externa.[2]

EPIDEMIOLOGY

Otitis externa is estimated to have a prevalence of 0.4% per year, affecting approximately 10% of the population during their lifetime.[3]

AETIOLOGY

Any condition or situation that disturbs the lipid/acid balance of the ear will predispose an individual to otitis externa.[4] These conditions can be classified as in **Table 78.1**.

Water and moisture are thought to cause a change from a predominantly Gram-positive skin flora to a Gram-negative one. As the ear becomes inflamed, healthy cerumen (with its bactericidal properties) is rapidly removed from the ear and is no longer produced.

Secondary bacterial infection

Secondary bacterial infection is a major feature of the disease. The bacteriology of otitis externa has not changed significantly over the last few decades[5] and most patients will culture multiple organisms (**Table 78.2**). Case reports of methicillin-resistant *Staphylococcus aureus* (MRSA) in otitis externa do not appear to show it to be a management problem unless systemic involvement occurs[6] as most cases settle with topical treatment, whether the bacteria is sensitive to the topical antibiotic or not.[5] There is some evidence that the *Pseudomonas aeruginosa* strains in ear disease are different from those found elsewhere in the human body. These strains may have special adherence properties that allow the bacteria to enhance their pathogenicity.[4, 7]

Bathing

Current opinion would suggest that, although water is a well-established risk factor for the development of otitis externa, bacterial contamination is not required for the development of the condition[5] although bathing in freshwater lakes containing *Pseudomonas* contributed to a large outbreak of the condition in the Netherlands, whereas bathing in rivers, swimming pools or the sea were not shown to be risk factors.[9]

TABLE 78.2 The microbiology of otitis externa (from Agius et al.[8] and Anonymous[5])

Bacteria	Percentage
Pseudomonas spp.	50–65
Other Gram-negative organisms	25–35
Staphylococcus aureus	15–30
Streptococcus spp.	9–15

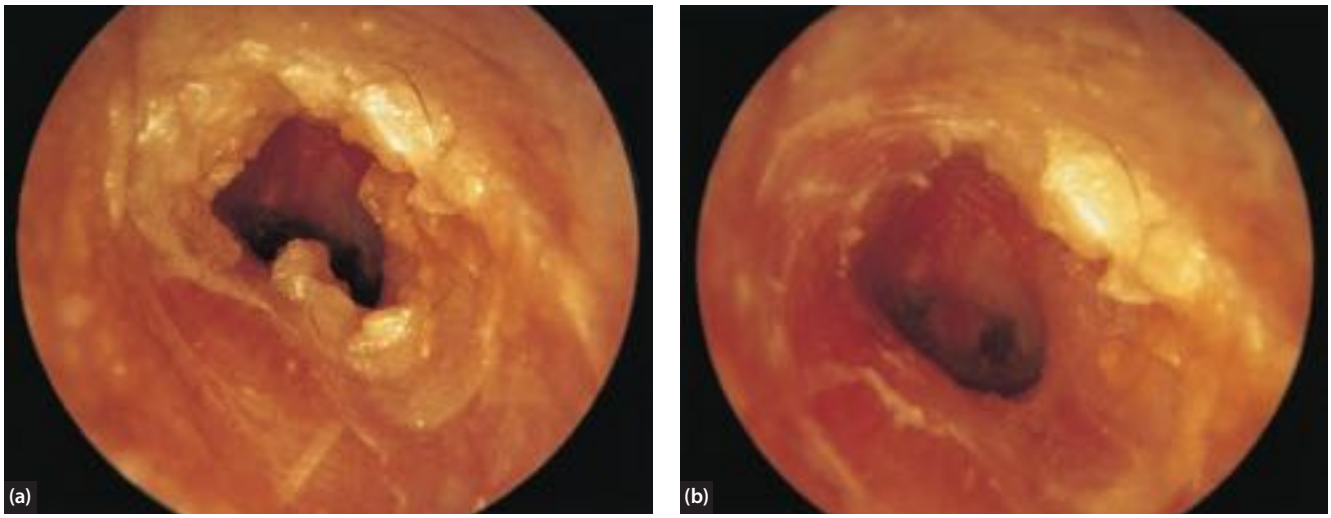


Figure 78.1 Acute otitis externa. (a) Debris inflammation in the left external auditory meatus. **(b)** After removal of the debris the swollen oedematous canal skin of the otitis externa can be seen.

Irritant/allergic reactions

Treatment of otitis externa is often with topical medications. Around 40–58% of patients have been shown to be sensitive to ingredients in topical agents on patch testing although clinical reactions may only develop in half that figure.[10, 11] There is increasing evidence that steroids may also sensitize the ear and steroid-only drops can still be a major exacerbating factor in some patients. This hypersensitivity can be through both atopic and non-atopic 'allergic' mechanisms and may or may not involve IgE.[12] In cases of resistant otitis externa, a patient should be investigated for topical hypersensitivity to possible therapeutic agents.

OUTCOMES AND COMPLICATIONS

If untreated, mild attacks of otitis externa often spontaneously resolve as the epithelial barrier becomes reestablished, the piloapocrine units produce normal secretions and the pH of the canal returns to normal. If the inflammation progresses faster than repair, increasing pain, otorrhoea and oedema of the canal occurs and the patient's condition will deteriorate. Due to the rich lymphatic drainage of the area, lymphadenopathy often occurs and soft-tissue infection can progress rapidly. This can lead to perichondritis, chondritis, cellulitis, parotitis and/or erysipelas. In the immunocompromised host, malignant otitis externa (periostitis/osteomyelitis of the skull base) can develop with significant associated morbidity and mortality.[3]

MANAGEMENT OPTIONS

The principles of treatment of otitis externa are as follows:

- thorough and regular aural toilet
- topical medication to the external auditory canal, with or without a wick
- analgesia
- treatment of regional and/or systemic complications with systemic antibiotics
- prevention of aetiological factors that could lead to exacerbation or recurrence.

Expert opinion is divided on the role of routine swabbing of the ear in otitis externa. Most otolaryngologists tend to reserve microbiological investigation for resistant or high-risk cases.[5]

Toilet remains the most effective single treatment for otitis externa. Although one primary care review claims irrigation of the ear canal is effective for the removal of debris,[2] expert opinion is generally against this and most specialists will perform aural toilet with or without microscopic assistance. There have been case reports of severe complications as a result of irrigation.[13] As microscopic toilet is not readily available to most general practitioners, patients are often treated with antibiotic/steroid medication in the form of drops or sprays without prior toilet. Aural medication commonly causes stinging or burning which may decrease compliance[14] and topical sensitivity is a common feature, especially in resistant or recurrent cases. There is no evidence for the efficacy of systemic antibiotic therapy for uncomplicated diffuse otitis externa.[15]

The use of a wick such as 1 cm ribbon gauze or a Pope otowick is often used to hold medication in the EAM. Glycerol and ichthammol (90% : 10%) used to be commonly used with an aural wick for moderate and severe cases of otitis externa, although it is now difficult to source. It has proven dehydrating and anti-inflammatory properties and antibacterial activity against *Streptoccocus* and *Staphylococcus* but poor activity against *Pseudomonas*.[16, 17] The dehydrating effect reduces canal oedema and also helps reduce pain but oral analgesia is usually necessary in moderate or severe cases. Non-steroidal anti-inflammatories, if not contraindicated, are excellent analgesics for otitis externa.

In patients who are prone to recurrent attacks, avoidance of water penetration into the ear is a major management issue. Cotton wool with petroleum jelly (e.g. Vaseline) will work well in the bath or shower and custom-made ear moulds can be made. Neoprene head bandages are a useful adjunct with the above for children in swimming pools. The use of alcohol ear drops or proprietary preparations (e.g. ear calm) after swimming will help remove any water that has penetrated into the canal. Blow-dryers (note: not on 'hot' setting) can also help remove moisture from the EAM.[5, 18]

Where dermatological conditions exist, multidisciplinary input is often required and tar preparations may be required. Any topical agent should be suspected as an exacerbating factor for eczema around the EAM.

In a small minority of patients who have recurrent attacks of otitis externa exacerbated by conventional hearing aids, insertion of a bone-anchored hearing aid can result in a spectacular and gratifying resolution of the condition.[19]

EFFECT OF MANAGEMENT ON OUTCOMES AND COMPARISON BETWEEN MANAGEMENTS

Randomized trials comparing interventions for the treatment of otitis externa are few in number. Scientific design of trials is difficult as the disease is heterogeneous in presentation, has a high rate of resolution with little or no intervention, endpoints are difficult to ascertain and often subjective and compliance with medication is known to be poor.[20]

A consensus panel convened by the American Academy of Otolaryngology – Head and Neck Surgery found no evidence for the use of systemic treatment in the absence of known risk factors or systemic signs and/or symptoms.[21] Although the choice of antibiotic used is controversial and toilet was not performed, in one randomized trial, addition of clotrimoxazole to Kenacomb ointment provided no benefit over the ointment alone.[22] The best available evidence shows little or no difference between the various topical agents, once thorough toilet has been performed,[2] although these studies are usually of low statistical power.

Likewise, toilet and topical hydrocortisone with an acidification agent (acetic acid) gives equivalent results to combination antibiotic/steroid preparations[23] and an acidification agent alone (aluminium acetate) produces similar outcomes to antibiotic (gentamicin) alone.[24] An early study compared steroid/aminoglycoside drops to placebo alone, showing a significant benefit with topical therapy at 10 days ($p < 0.001$).[25] Likewise, budesonide drops have been shown to produce better clinical outcomes than placebo.[26] Addition of any form of topical agent does seem to be better than toilet alone.[27] The sensitivity of the bacteria to the antibiotic in topical medication does not seem to influence outcomes. The fluoroquinolones ciprofloxacin and ofloxacin have been shown to be as effective as combination steroid–aminoglycoside drops[5, 28] and have the attraction of being non-ototoxic.[29] They are expensive but only need to be given twice daily, which has an advantage for compliance, especially in paediatric populations.[5] It is worth noting that many fluoroquinolone preparations still contain potentially ototoxic preservatives, although the question of ototoxicity is perhaps less relevant for otitis externa unless there is perforation of the tympanic membrane. The issue of topical ototoxicity is discussed at greater depth in Chapter 83, Chronic otitis media.

There is some evidence that spray-based medication systems provide better drug delivery to the meatus[30] although this remains controversial. In two studies from the same authors demonstrating improved outcomes from spray when compared to drops, one was non-blinded.[31, 32] It is also worth noting that the sprays used in these trials ('Otomize') also contained acetic acid, in contrast to the antibiotic/steroid drops.

TABLE 78.3 Randomized controlled trials in otitis externa

Treatment vs placebo	Trials	Result
Aural toilet	None	
Acetic acid	None	
Aluminium acetate	None	
Antibiotic, oral	None	
Antibiotic, topical	None	
Antibiotic and steroid, topical	Ref 25	80% vs 20% benefit
Antifungal, topical	None	
Ichthamol and glycerol	None	
Steroid, topical	Ref 26	Benefit
Tar	None	
Method of administration		
Drops vs spray	None	
Drops vs pack	None	
Drops vs wick	None	
Drops vs ointment	Ref 38	No difference
Wick vs gauze	Ref 36	No difference
Comparison of different treatments		
Multiple trials	The majority show no difference but are mostly underpowered.	

Self-administered powder was shown to cure otitis externa in 74% of patients when compared to drops (53%) in a randomized, non-blinded trial from Israel[33] and there may prove to be benefits from using sprays or powder, although more research is needed before firm conclusions can be drawn on this.

Compliance with medication has been shown to rise from 25% to over 90% if the medication is administered by a third party[20] and only 40% of self-medicating patients were able to get within 25% of the correct dose after 3 days of treatment.[34] Insertion of a Pope wick can cause trauma to the EAM[35] and there is only limited evidence of any enhanced efficacy for wicks over drops alone[5] although many experts find these useful in tight ear canals. In a randomized trial involving 94 patients, there was no difference in resolution rates when wicks were compared to medicated ribbon gauze.[36]

The results of randomized controlled trials comparing treatments for otitis externa are summarized in Table 78.3 and have now also been the subject of other systematic reviews.[37]

OTOMYCOSIS

Otomycosis (or fungal otitis externa) accounts for approximately 10% of all cases.[3] It is more common in hot, humid climates and is often secondary to prolonged treatment with topical antibiotics. Diabetes and other causes of immunocompromise also predispose to the condition. The diagnosis must be considered in patients with otitis externa who fail to respond to topical antibiotic/steroid drops.

Aspergillus accounts for 80–90% of cases with *Candida* being responsible for the remaining 10–20%.[3] Other fungi are rarely involved.

The commonest finding is a black, grey, green, yellow or white discharge with debris that is often said to resemble wet newspaper. Occasionally, debris is seen with visible fungal hyphae (Figure 78.2). Treatment is similar to that for diffuse



Figure 78.2 Otomycosis with *Aspergillis niger*.

otitis externa, namely toilet and removal of the debris but topical antifungal drops (e.g. clotrimazole or flumethasone with clioquinol) are usually used to expedite recovery.

In cases of resistant otomycosis, it is essential to exclude fungal infection elsewhere in the body. The 'foot and ear'[39] dermatophytid (i.d.) reaction can occur from a fungal infection in a remote location. Immunotherapy with dermatophyte (*Trichophyton*, *Oidiomycetes* and *Epidermophyton*: TOE) extracts and dust mite is the treatment of choice in this condition.[40]

Rarely, fungi can cause invasive otitis externa, especially in immunocompromised patients. Aggressive systemic antifungal therapy is required in these patients[41] who often have a high mortality from the condition.[42]

BEST CLINICAL PRACTICE

- ✓ Addition of any form of topical agent is better than toilet alone. [Grade A]
- ✓ Topical combination antibiotic/steroid drops or spray (with or without the addition of acetic acid) would be regarded as best practice for first-line treatment, given the current evidence. [Grade A]
- ✓ Regular toilet remains the most effective single treatment for otitis externa.
- ✓ Water avoidance is essential in the acute phase and to prevent recurrence. Consider hypersensitivity to topical medication in resistant cases.
- ✓ Think of otomycosis and treat with topical antifungal agents, especially if topical antibiotics have been previously used. Bone-anchored hearing aids can provide excellent results in chronic disease.

FUTURE RESEARCH

- ➤ More powerful prospective randomized controlled trials are necessary to compare different interventions for otitis externa.
- ➤ Accepted grading systems and outcome measures for interventions for otitis externa would greatly facilitate research in this area.

KEY POINTS

- Otitis externa occurs because the protective lipid/acid balance of the ear is lost.
- It affects up to 10% of the population in their lifetime.
- Up to 25% of patients may be clinically hypersensitive to topical medication.

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CHAPTER 79

PERICHONDRITIS OF THE EXTERNAL EAR

James W. Loock

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keyword perichondritis. This was augmented by references from these articles. No level 1 or 2 evidence was identified.

DEFINITION

The term correctly refers to infection or inflammation involving the perichondrium of the external ear: auricle and external auditory canal. However, it is commonly used to describe a continuum of conditions of the external ear, from erysipelas (infection of the overlying skin), through cellulitis (infection of the soft tissue) and true perichondritis to chondritis (infection involving the cartilage itself).

Classification and staging

See the definition above. A useful practical classification might be:

- erysipelas of the external ear
- cellulitis of the external ear
- perichondritis
- chondritis.

Prasad et al.[1] suggest a simple and logical staging of perichondritis/chondritis as:

Stage 1: early perichondritis without fluctuant abscess
Stage 2: perichondritis with fluctuant abscess
Stage 3: perichondritis with fluctuant abscess and cartilage destruction.

AETIOLOGY

The thin skin, minimal subcutaneous tissue and vulnerable anatomical position make conchal cartilage particularly susceptible to trauma with subsequent infection. Perichondritis usually happens secondary to trauma. Such trauma may include laceration of the auricle, surgery to the external ear, frostbite, burns, chemical injury, infection of a haematoma of the pinna, aspiration or incision of a haematoma and, in recent years, 'high' piercing of the (cartilaginous) portion of the auricle for the insertion of earrings.[2] Superficial infections of the skin (erysipelas) or subcutaneous tissue (cellulitis) of the external auditory meatus or pinna may spread deeply to involve the perichondium (perichondritis) or cartilage (chondritis).

In an analysis of 36 patients the organisms most commonly isolated were *Pseudomonas aeruginosa* (69%), polymicrobial (22%), *Streptococcus* spp. (22%) and *Staphylococcus aureus* (20%).[3] However, this may represent a selected subgroup of severe cases as in most (milder) cases no culture is taken. Other organisms cultured include Gram-negatives (*Proteus*, *Enterococcus* and *Escherichia coli*).

PATHOLOGY

Hyperplasia of the dermal layers, thickened subcutaneous tissue, intense infiltration with polymorphonuclear

leukocytes, thickening of the perichondium and destruction of the cartilage by phagocytes is described.[4]

DIAGNOSIS

The presentation is with a dull pain increasing in severity and the classical signs of inflammation involving the cartilaginous pinna (**Figure 79.1**). The lobule, which contains no cartilage, is spared. The severity of the pain and swelling of the pinna are indicators for true perichondritis as opposed to the more superficial conditions of erysipelas and cellulitis. The diagnosis is clinical and special investigations are not routinely required. A background history of underlying trauma to the external ear should be sought.

Differential diagnosis

Relapsing polychondritis may present with similar signs of inflammation, involving the pinna and fever, but it is differentiated on the basis of the systemic nature of the condition. This manifests in the involvement of cartilaginous structures at multiple sites, possibly ocular conditions (scleritis, iritis and keratitis) and, occasionally, vasculitis. See also Volume 1, Chapter 18, Connective tissue diseases: ENT complications.

Rare cases of extranodal non-Hodgkin lymphoma of the pinna, both with[5] and without[6] the presence of human immunodeficiency virus, have been reported to present similarly to perichondritis.

OUTCOMES

If untreated, a subperichondrial abscess may develop, leading to avascular necrosis of the underlying cartilage and marked deformity of the pinna. The infection may spread to the cartilage itself. Rare reported complications of perichondritis include fatal septicaemia secondary to streptococcal infection, subacute bacterial endocarditis and necrotizing fasciitis of the neck.



Figure 79.1 Perichondritis of the left ear. There is an associated subperichondrial abscess in this case.

MANAGEMENT OPTIONS

Prevention

Acute perichondritis should be prevented by careful placement of ear piercings away from the cartilaginous pinna. Surgery in and around the ear should avoid trauma to cartilage and tight head bandages. Haematomas of the auricle should be drained promptly and using careful aseptic techniques. The meticulous management of burn injuries to the ears should include the use of prophylactic antibiotics against Gram-negative bacteria and diligent local care including daily dressings and the removal of eschars and crusts.

First-line management

The mildest forms (cellulitis and Prasad stage 1) are adequately managed by the use of topical and oral antibiotics. Prompt treatment with a broad-spectrum antibiotic at a high dose, possibly intravenously, should be designed to cover common organisms and, in particular, *P. aeruginosa*.

The presence of subperichondrial abscess as evidenced by fluctuation requires drainage, but only when definite fluctuation is present, as premature invasive intervention may result in further spread of the infection. If pus is obtained, a pus swab should be sent for culture and sensitivity; however, pending the result, intravenous antibiotic treatment should not be delayed. Standard drainage would be by incision; Pattanaik[7] reports success with a procedure involving aspiration, syringing the cavity two or three times with streptomycin solution, and then refilling the cavity with a premixed solution of streptomycin, triamcinolone and hyaluronidase.

Resistant cases

Non-response to the above treatment, accompanied by persistent pain, suppuration and extensive signs of inflammation, necessitates further intervention.

Various authors advocate aggressive excision of necrosed cartilage including the overlying skin and subcutaneous tissue.[8, 9] However, it is difficult to decide how much cartilage to excise, and repeated debridement may be required. Furthermore, this procedure usually results in deformity, especially if the peripheral cartilagenous framework has to be removed. In severe cases, where the entire area is involved, these authors advocate total chondrectomy via an incision in the helical margin, the ear being split in bivalve fashion, the necrotic cartilage resected, and a layer of fine mesh gauze placed between the flaps and changed daily.

An alternative is a system of continuous drainage and irrigation with an antibiotic and steroid solution in order to preserve the structure and form of the auricle.[10–12] Fenestrated polyethylene tubes are placed in subperiosteal tunnels on either side of the cartilage, and aminoglycoside/cortisone solution used to irrigate these twice daily. The authors report good results and minimal deformity.

The principle of preservation of the perichondrium is supported by experimental work on rabbit ears (animal evidence), which showed that new cartilage formed when the subperichondrial space was preserved.[13] These results could however not be reproduced in monkey auricles (animal evidence).[14]

Other forms of management

The difficulty of delivering adequate antibiotic levels to devascularized cartilage, particularly in burn injuries, led to the investigation of iontophoresis (electromotive drug administration) as a means of effective local antibiotic delivery without systemic absorption. This technique creates an electric field to drive medication (antibiotics in this case) through the skin to deliver high-tissue concentration. This form of treatment is rarely used despite compelling animal and human clinical evidence. A number of authors have demonstrated experimentally the effectiveness of iontophoresis in delivering high levels of penicillin and gentamicin, respectively, to burn-injured rat and rabbit ears (animal evidence).[15–18]

In perichondritis resistant to antibiotic treatment alone, low-dose radiation has been successfully used, based on the lethal effect of such radiation, on three or four sessions of approximately 0.8 Gy of radiation over a period of 2 days.[19]

Ultraviolet radiation has been employed; however, the side effects can be significant and the efficacy of this form of treatment has subsequently been questioned.[20]

Effect on outcomes

All the above case series report resolution of the condition using the therapy they advocate. Aggressive surgery, while it may at times be necessary, may aggravate the ultimate deformity.

BEST CLINICAL PRACTICE

The available clinical literature constitutes Grade D recommendations. Consequently, recommendations must be guarded but the following would seem logical.

- ✓ Consider broad-spectrum (including antipseudomonas) antibiotic prophylaxis in severely traumatized or burnt pinnas.
- ✓ Make early use of local and systemic broad-spectrum, anti-pseudomonal antibiotic if perichondritis is suspected.
- ✓ Fluctuation indicative of pus collection requires drainage with or without irrigation and/or an indwelling drain.
- ✓ In resistant cases, add effective local antibiotic delivery by irrigation or iontophoresis.
- ✓ If further surgery is needed for excision of necrotic cartilage, preserve the perichondrium and a cartilage framework wherever possible.

FUTURE RESEARCH

- ➤ The relative rarity of this condition and the need to individualize management mitigate against level 1 and 2 evidence.
- ➤ Burns units are best placed to provide data.

KEY POINTS

- Trauma, including piercing, may contribute to perichondritis of the pinna.
- Pseudomonas is the commonest organism, but the infection may be polymicrobial.
- Cartilage necrosis and deformity may result.
- First-line management is in the form of (anti-pseudomonal) antibiotics.
- Severity, pus collection, and failure to respond may call for surgical or other forms of treatment.

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CHAPTER 80

EXOSTOSIS OF THE EXTERNAL AUDITORY CANAL

Philip J. Robinson and Sophie J. Hollis

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SEARCH STRATEGY

Data in this chapter may be updated by Medline and PubMed searches, both using the keywords ear and exostosis.

DEFINITION

An exostosis (Figure 80.1) of the external auditory canal (EAC) is a benign growth of periosteal bone, which forms a smooth, sessile, hemispherical swelling in the deep part of the meatus, adjacent to the tympanic membrane. Exostoses are usually multiple, occurring in a group of three, and are bilateral. They may arise from the anterior and posterior walls of the EAC. They are usually found as an incidental finding during the examination of an asymptomatic patient. Internal auditory canal (IAC) exostoses have been described, but these are rare clinical entities.[1]



Figure 80.1 Multiple exostosis of the right external auditory canal. One exostosis is anterior and two are posterior.

PATHOLOGY

Histopathological studies of exostoses are few, as a result of the lack of suitable specimens available from the drilling method of surgical excision. However, Graham[2] described exostoses as broad-based, dense and composed of lamellated bone, covered with periosteum and its overlying squamous epithelium with an internal structure formed by concentric, dense layers of subperiosteal bone with abundant osteocytes. A lack of fibrovascular channels and the features mentioned here were proposed as a histopathological method of differentiating exostoses from the other bony swelling seen in the ear canal, an osteoma. However, a later histopathological study[3] demonstrated a considerable overlap of histological features between the two clinical entities.

AETIOLOGY AND EPIDEMIOLOGY

The relationship between cold water exposure and exostoses is now widely accepted. Exostoses are common among water sports enthusiasts, with a prevalence as high as 73.5% in a surfing population.[4] The incidence rises with length of exposure to cold water, from 55.3% for individuals who had surfed for 10 years or less to 90.9% for individuals who had surfed for longer than 20 years.

In a study of two similar groups of Japanese divers, exostoses were significantly more common and more severe in the group working in the cold water area and again showed a significant increase in incidence as the diving career progressed.[5]

Laterality of exostoses is also thought to be related to the cooling effect of wind direction in those who surf. A Californian study proposed that surfers spent most of their time in the water facing west, waiting for waves, which corresponded with the right ear being exposed to more evaporative cooling. Accordingly, the study showed that severe exostoses were twice as likely to be found in the right ear.[6]

An anthropological study of over 1000 prehistoric crania from northern Chile demonstrated a significantly higher prevalence (30.7%) in the coastal area, compared with 2.3% in the valley area and 0% in the highland population, which may be a consequence of habitual fishing in the cold waters of the Pacific ocean.[7] Fowler and Osman,[8] working with guinea pigs, were able to demonstrate the formation of new bone on the inner surface of the tympanic bulla following irrigation of the external canal with cold water. Harrison[9] carried out similar experiments with guinea pigs and found histological evidence of new bone formation in the deep meatus.

The formation of exostoses may represent a rudimentary, evolutionary response to protect the middle ear against immersion in cold water. In the hooded seal (*Cystophora cristata*), there is a broad-based exostosis in the floor of the EAC, lateral to the tympanic membrane, which helps to obstruct the EAC. In addition to cavernous tissue in the middle ear, this feature allows the seal to dive to depths of greater than 1000 m, where it stays for close to 1 hour at pressures of 100 atm, without damage to the middle ear or tympanic membrane.[10]

DIAGNOSIS

The diagnosis of exostoses (**Figures 80.1** and **80.2**) is usually made clinically from the characteristic otoscopic appearances of multiple and usually bilateral sessile, hemispherical, bony swellings arising deep in the EAC, adjacent to the tympanic membrane. It is usually straightforward to differentiate them from an osteoma, which is generally a unilateral, solitary, discrete, pedunculated mass, arising from the lateral part of the bony EAC.[11]



Figure 80.2 Single anterior exostosis of the right external auditory canal.

Exostoses are generally an incidental finding and asymptomatic when small. However, when the exostoses enlarge to cause a stenosis of greater than 80% of the canal lumen, there may be a history of recurrent otitis externa, chronic infection, wax and debris accumulation and conductive hearing loss. As noted above, exostoses are common among water sports enthusiasts.

In the presence of a tight stenosis of the deep ear canal, a high-resolution computed tomography (CT) scan will help differentiate large exostoses from other causes of stenosis, such as chronic otitis externa. A scan will also demonstrate complications, such as a canal cholesteatoma, developing medial to the exostoses.[12]

OUTCOMES AND NATURAL HISTORY

The incidence of exostoses and their size increases with duration of exposure to cold water. In a population of surfers, 44.7% of those who had surfed for 10 years or less had normal ear canals and only 6% had severely obstructed ear canals. In comparison, in the group that had surfed for greater than 20 years, only 9.1% had normal ear canals and 16.2% were severely affected.[4]

There are no longitudinal studies of individuals with exostoses, but it seems unlikely that there would be any significant growth in the absence of continued water exposure.

In most cases, exostoses are an incidental finding and symptoms are rare, with mild to moderate stenosis only. However, with greater than 80% canal stenosis, debris may accumulate medial to the obstruction, leading to recurrent episodes of otitis externa, conductive hearing loss and occasionally a canal cholesteatoma.

MANAGEMENT OPTIONS

In the majority of cases, no treatment is required as the patient is asymptomatic. However, general advice about avoidance of cold water should be given, with a recommendation to use earplugs or a wetsuit hood for water sports.

Hearing loss due to debris collection, or otitis externa, can be managed medically, by meticulous aural toilet using a microscope and suction. Topical application of steroid, antibiotic, antifungal or combination ear drops, may be necessary to treat inflammation or infection.[13]

Surgery

Surgery to remove the exostoses and enlarge the meatus by a meatoplasty procedure is indicated for cases refractory to medical treatment, causing recurrent or persisting otitis externa, frequent cerumen obstruction causing hearing loss and cases where wider access is required for middle-ear surgery.

Surgery is carried out, via a postaural, endaural or permeatal approach, with very careful elevation and preservation of the skin overlying the exostoses. The bone of the exostoses is removed by high-speed drill, using both cutting and diamond burrs. Great care is necessary to avoid damaging the tympanic membrane and facial nerve.

COMPLICATIONS OF SURGERY

Sheehy[11] has recommended a postaural approach in all cases of diffuse exostoses of the EAC, because of the incidence of complications and recurrence of the lesions in patients operated on transmeatally. Of the transmeatal group 25% required revision procedures (6 of 24) compared to 0/55 in the postaural group.

In some series of cases, the permeatal approach seems to be favoured, particularly in the hands of an experienced surgeon,[14] although House and Wilkinson[15] conclude from a series of more than 400 ears that the postaural approach results in complications being kept to a minimum.

Complications of surgery can include infection, tympanic membrane perforation, facial palsy, hearing loss from damage to the ossicular chain or inner ear, exposure of the temporomandibular joint with chronic pain or subluxation and early or late soft-tissue stenosis of the ear canal.

BEST CLINICAL PRACTICE

- ✓ Most exostoses are asymptomatic and are incidental findings. These are best managed by advice to minimize exposure to cold water by using swim plugs or a wetsuit hood for water sports.
- ✓ Recurrent episodes of otitis externa or cerumen impaction may be associated with exostoses and should be managed medically in the first instance with microsuction and antibiotic ear drops.
- ✓ Cases of severe exostoses may require meticulous surgical removal via a postaural approach using a high-speed drill.

FUTURE RESEARCH

- ➤ There are currently inadequate histological data.
- ➤ Further studies are required to establish the true natural history of untreated exostoses.

KEY POINTS

- Exostoses are common in water sports enthusiasts.
- Exostoses are usually an incidental finding and require no treatment.
- There is evidence that prolonged exposure to cold water in the EAC leads to increasing size and incidence of exostoses.
- Exostoses causing greater than 80% stenosis may lead to recurrent episodes of otitis externa, hearing loss and, occasionally, canal cholesteatoma.
- Treatment is usually unnecessary in small exostoses, but advice to avoid further cold water exposure may be appropriate.
- Meticulous medical management will often control the symptoms but, in cases refractory to medical treatment, excision of the exostoses may sometimes be necessary.

ACKNOWLEDGEMENTS

Figures 80.1 and 80.2 are reprinted from Wormald and Browning, *Otoscopy: a structured approach*. London: Hodder Arnold, 1996.[16]

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CHAPTER 81

OSTEORADIONECROSIS OF THE TEMPORAL BONE

James W. Loock

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: osteonecrosis/osteoradionecrosis and temporal bone/petrous temporal bone/ear. Most of the evidence is level 3 or 4 and is based upon the more frequent mandibular form of the disease.

DEFINITION

Osteoradionecrosis of the temporal bone is defined as exposure and necrosis of a variable portion of previously irradiated petrous temporal bone which fails to heal over a period of 3 months.

INCIDENCE, AETIOLOGY AND PATHOGENESIS

Because of its density, bone absorbs a greater proportion of radiation than soft tissues. Osteoradionecrosis and chondroradionecrosis may occur in various sites in the head and neck following high-dose radiotherapy, despite the relative radioresistance of bone and cartilage.[1] Osteoradionecrosis of the mandible (see Volume 3, Chapter 19, Principles and practice of radiotherapy in head and neck cancer) occurs far more frequently than in the petrous temporal bone. Chondronecrosis of the larynx, and osteonecrosis of the maxilla and nasal bone, nasopharynx/skull base, zygoma, palate,[2] clavicle and hyoid[3] have all been described.

Osteoradionecrosis of the petrous temporal bone occurs as a result of high-dose radiotherapy administered to and around the petrous temporal bone for malignancies of the parotid gland, external auditory canal, middle ear, maxilla, nasopharynx[4] and pituitary.

The radiation causes inhibition of mitosis and the capacity for tissue repair, and a vasculitis leading to obliteration of blood vessels and avascular necrosis.[5, 6] Marx et al.[7, 8] characterized the tissue as hypoxic, hypocellular and hypovascular.

The compact, rather than cancellous, nature of the petrous temporal bone, and poor blood supply of the tympanic ring, may increase susceptibility.

Radiotherapeutic techniques which have been developed to reduce the risk of osteoradionecrosis include increased energy of the beam (megavoltage versus kilovoltage) which reduces the dose to bone, the use of multiple fields to contain dose distribution, intensity-modulated radiotherapy, and the use of heavy charged particles (Hadron therapy) where the dose-distribution avoids exit dose.

The occurrence of osteoradionecrosis may be increased in patients with microvascular disease (atherosclerotics and diabetics), and as a result of trauma after radiotherapy – classically dental extractions in the case of the mandible. High local doses of brachytherapy may give an increased incidence.

PATHOLOGY

The tissues affected include bone, overlying subcutaneous tissues and skin. Auricular cartilage is seldom affected due to the low superficial radiotherapy dose received in all but irradiation of skin tumours.

The histological changes in bone include death of osteocytes and osteoblasts resulting in empty lacunae,

preponderance of osteoclasts, demineralization, osteolysis, loss of marrow substance, reparative fibrosis and often secondary infection.[6, 9] Soft-tissue histological changes include epithelial hyperplasia, atrophy of dermal structures, dermal fibrosis and soft-tissue necrosis with replacement by fibrosis.[9]

Macroscopically, there is loss of skin and soft tissue exposing bone, bony sequestration and frequently the complication of secondary infection. Of the parts of the temporal bone, the tympanic ring appears particularly susceptible.[9]

The effects of radiation on the middle and inner ears and hearing are not discussed here. The reader is referred to the publications of Borsanyi et al.,[10] Anteunis et al.,[11] Gyorkey and Pollock[12] and Jereczek-Fossa et al.[13]

DIAGNOSIS, CLINICAL PICTURE, NATURAL HISTORY AND OUTCOMES

The time interval between radiotherapy and clinically evident osteoradionecrosis can vary considerably – from less than 12 months to 23 years.[14]

Ramsden et al.[14] usefully divided cases into localized and diffuse (extensive) forms. The localized form presents mild otalgia and otorrhoea, with small areas of exposed bone in the external auditory canal (**Figure 81.1**). It generally occurs when the petrous bone was in the periphery of the irradiated field. Computed tomography (CT) scanning should show not more than small areas of sequestration. This type can heal if managed conservatively, with resolution occurring typically over 1–4 years, after spontaneous separation of the sequestrum.

The diffuse or extensive form occurs generally when irradiation is directed at the petrous temporal bone, and has more severe symptoms of pain and otorrhoea (**Figure 81.2**). CT imaging may show widespread bony destruction. Erosion of the facial canal and extension to the inner ear can occur, as well as intracranial complications, brain abscesses, meningitis and death. Radical surgical debridement and repair is often necessary to prevent complications and effect healing.

There are no studies analyzing the reliability of CT scanning in indicating the extent of bony non-viability.



Figure 81.1 Radionecrosis of the right ear. In this ear, there is a bony defect of the posterior canal wall, a bone sequestrum having been extruded. Reprinted from Wormald and Browning, *Otoscopy: a structured approach.* London: Hodder Arnold; 1996.[15]



Figure 81.2 Osteoradionecrosis of the right petrous temporal bone. There was extensive bony destruction, multiple small sequestra, granulation tissue and superinfection.

MANAGEMENT OPTIONS

Prevention

The likelihood of osteoradionecrosis should be reduced by careful planning of the radiotherapy, by the scheduling of any surgical intervention prior to radiotherapy, and by waiting for full wound healing before irradiation. A relatively large case series has suggested that, when treatment for parotid neoplasms requires mastoidectomy, a situation in which the risk for radionecrosis is high, subtotal petrosectomy with mastoid obliteration and oversewing of the external ear canal should be performed *ab initio* as a better option than simple mastoiodectomy.[16]

Treatment

In an established case, the first step should be to exclude an underlying recurrence of malignancy. Thereafter, the severity of the problem guides management.

LOCALIZED NECROSIS

Cases, which just leave an area of exposed dead bone in the floor of the external auditory canal can successfully be managed conservatively, with toilet careful removal of

sequestra, local antibiotics and analgesics, although healing may take up to 4 years. Hill et al.,[17] and subsequently Metselaar et al.,[18] describe the use of a local rotational flap from postauricular skin to cover small exposed areas of bone in the external auditory canal.

DIFFUSE NECROSIS

Conservative management is inadequate for severe diffuse necrosis of the temporal bone. However, the poorly vascularized irradiated field is less than ideal for surgery. In Ramsden et al.[14] and Thornley et al. series,[19] radical surgical debridement alone required revision in half the cases.

For this reason, subsequent authors[20] recommend bringing in a vascularized soft-tissue flap at the time of debridement, as well as radical mastoidectomy or subtotal petrosectomy until healthy vascularized bone is reached. Careful placement of incisions is required in order to optimize blood supply.

The use of hyperbaric oxygen in radiation-injured tissue and osteoradionecrosis is controversial. There is a paucity of evidence in relation specifically to the petrous temporal bone but extrapolation from related literature suggests it might be helpful. In a randomized controlled trial, Marx reported four to five times reduced tissue-related complications in a series of 160 heavily irradiated head and neck patients receiving combined treatment with hyperbaric oxygen in support of debridement and surgical repair.[21] Two reviews have concluded that the available trials constitute a modest level of evidence but suggest an improved outcome with hyperbaric oxygen therapy for late radiation injury in tissues of the head and neck (*inter alia*).[22, 23]

BEST CLINICAL PRACTICE

- ✓ Radiotherapy should be carefully planned to avoid osteoradionecrosis.
- ✓ In making the diagnosis, underlying recurrent malignant disease should be excluded.
- ✓ Mild localized forms of osteoradionecrosis are best managed conservatively.
- ✓ Severe diffuse forms require aggressive surgical debridement to healthy tissue and covering with well-vascularized soft tissue.
- ✓ Hyperbaric oxygen is an adjunct worth considering in severe forms.

FUTURE RESEARCH

- ➤ The prevalence of temporal bone osteoradionecrosis is unknown but is likely to be falling because of improved radiotherapeutic techniques.
- ➤ The value of imaging in assessing the extent of osteoradionecrosis warrants study.
- ➤ The rarity of the condition makes evidence in support of management options difficult.

KEY POINTS

- Radiotherapy to and around the petrous temporal bone may cause osteoradionecrosis.
- This may occur months to years after the radiotherapy.
- Careful planning of surgery and radiotherapy can prevent this complication.
- Underlying malignancy should be excluded.
- Mild cases can be managed by local care.
- Extensive osteoradionecrosis may require radical debridement and vascularized flaps.

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CHAPTER 82

ACUTE OTITIS MEDIA AND OTITIS MEDIA WITH EFFUSION IN ADULTS

Anil Banerjee

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SEARCH STRATEGY

Data in this chapter may be updated by PubMed searches using the keywords mentioned here. The first search used the keywords acute otitis media and adults, limited to human. The second search used the keywords otitis media with effusion, adults, limited to humans. These were assessed for relevance and quality. Further articles were identified from citations and other publications.

Acute otitis media and otitis media with effusion are often temporally related due to pathology also seen in childhood. They are also encountered due to specific adult-related aetiologies.

ACUTE OTITIS MEDIA IN ADULTS

DEFINITION

'Acute otitis media' (AOM) translates as acute middle ear inflammation. It is generally seen in infective conditions with the causative organism being viral or bacterial. It is a relatively common childhood condition and is seen less often in adults.

PREVALENCE AND INCIDENCE

An international multicentre primary care setting study recorded the total number of patients seen with symptoms consistent with a diagnosis of AOM (n = 3224). Sixteen per cent of the total number was over the age of 15.[1] This condition is therefore not as uncommon in the adult population as was previously thought. It remains, however, predominantly a disease of childhood and more specifically infancy.

A separate study calculated the relative risk of getting AOM to be about 200 times higher during the first 2 years of life than as an adult.[2]

AETIOLOGY

Bacterial infection accounts for the majority of adult AOM cases presenting to ENT doctors (Table 82.1). The organisms found are similar to those in paediatric cases.

TABLE 82.1 Bacteriology of middle ear aspirates from adults with acute otitis media (reprinted from Celin et al.)[3]

Bacterium	Percentage*
Haemophilis influenzae	26
Streptococcus pneumoniae	21
Moraxella catarrhalis	3
Streptococcus aureus	3
Other bacterium	26
No growth	26

* This includes multiple growths (n = 36).

DIAGNOSIS

History

Unlike presentation in the paediatric population, the affected adult can usually describe symptoms in detail and seek treatment of his or her own volition. Despite this, some may still delay treatment until a fulminating middle ear infection results in perforation of the tympanic membrane. The pain experienced together with the resultant mucopurulent otorrhoea should be distinguished from bullous myringitis, which produces a similar history of hearing loss and increasing otalgia but ends in a bloody otorrhoea secondary to bursting of blood blisters on the tympanic membrane. The two conditions occasionally occur together.

In those cases of AOM presenting before perforation occurs, hearing loss, tinnitus and otalgia are the cardinal symptoms.

Secondary symptoms include balance disturbance, general malaise, pyrexia and headache.

Examination

Otoscopy may be challenging as the bulging red tympanic membrane may prove difficult to focus on until the examiner realizes the drum is more lateral than is usually the case and withdraws the otoscope slightly to allow the drum to appear in focus. If the tympanic membrane has already perforated, it will have reverted to its usual anatomical position and the perforation may be visible. Pus may be seen in the external auditory meatus and on the tympanic membrane. Microsuction is often required to allow adequate inspection of the perforated drum.

Confusion can arise between a normal tympanic membrane with a profusion of blood vessels radiating from the umbo and a case of AOM. The most reliable otoscopic indicator of AOM has been found to be tympanic membrane bulging.[4] The diagnosis should therefore be made on a combination of history and otoscopy. Pure-tone audiometry is usually only performed if the diagnosis of AOM has been missed, but it typically shows a significant conductive hearing loss in the affected ear.

MANAGEMENT

Most cases will resolve spontaneously and only analgesia is required.

Although antibiotics are often given for this condition, there is no evidence to suggest efficacy in the adult population. Extrapolation from a Cochrane Database review of antibiotics for AOM in childhood suggests that treatment may reduce pain and the incidence of tympanic membrane perforation but this remains untested by clinical research in an adult population.[5] Studies have been bedevilled by diagnostic uncertainty. Definitive diagnosis of otitis media involves tympanocentesis and this is almost never done so that many cases of otalgia are characterized as otitis media in both adults and children.

Approximately 10% have a perforation with otorrhoea at presentation.[1] Adults with AOM are at higher risk of intracranial complications than adults with chronic otitis media.[6] While all complications of AOM are rare, acute mastoiditis, labyrinthitis, sigmoid sinus involvement and intracranial abscesses have been described as the commonest. Facial palsy accounts for 30% of these complications.[7] Full recovery of the facial nerve is the expected outcome in most cases.[8] Unlike childhood disease, meningitis in adults is an uncommon complication.

OTITIS MEDIA WITH EFFUSION IN ADULTS

DEFINITION

Otitis media with effusion (OME) describes a collection of fluid in the middle ear often extending into the mastoid air cells. This may be secondary to a severe upper respiratory tract infection (URTI). It may also follow on from, or precede, AOM. Most episodes of OME in adults will resolve untreated, but in some cases they may persist for months or longer. In adult cases it is important to ensure that other pathology has not been missed. Patients will often describe hearing loss, crackling or popping of the ears, tinnitus and sometimes balance disturbance.

PREVALENCE AND INCIDENCE

For those with both a paediatric and adult ENT practice it is well known that adults make up a very small proportion of the overall number of OME patients seen. Robinson described a prevalence of 0.6% over the age of 15.[9]

AETIOLOGY

Infection

Most adults report a URTI preceding an episode of OME.[10] Sinus infections often occur in affected individuals.[11–13] As in childhood, OME can follow on from AOM or precede it.

Liederman et al. reported that, when cultures of effusions were matched with polymerase chain reaction (PCR) detection, the organisms found were the same as in childhood disease. PCR detected *Streptococcus pneumoniae* and *Haemophilus influenzae* in 15 of 19 samples. Other organisms found were *Moraxella catarrhalis* and adenovirus.[14] Fungi have been found in the middle ear fluid of 100% of individuals with OME (n = 12) when effusions were collected and stained. Whether they also exist in the middle ear cavities of normal individuals is unknown.[15]

HIV has been reported as predisposing to a high rate of middle ear problems. In a study of 155 HIV-positive adults 18% were identified as having chronic middle ear disease – most with effusion.[16]

Allergy

The evidence for allergy as a causative factor in OME is mainly reported in paediatric studies. In a large Norwegian study, the authors found surgery for otitis media to be more common in subjects who reported an allergy.[17] Pelikan reported 71 of a group of 87 adults having positive responses to nasal allergen challenges, and 119 of the 131 positive challenges resulted in Eustachian tube dysfunction leading to significant audiometric changes. He concluded that nasal allergy can lead to Eustachian tube dysfunction.[18]

Barotrauma

Barotrauma from air flights, typically during descent, is a common cause of OME in adults, particularly when travelling with a URTI. Spontaneous resolution within a few days of landing is the usual course of events but, if this fails to occur, medical evaluation is required. There are no reliable data on the incidence of glue ear in adults following air travel.

Hyperbaric oxygen treatment can also cause OME although in most cases this will resolve without the need for ventilation tube insertion.[19]

Eustachian tube obstruction

In the paediatric population adenoidal hypertrophy or inflammation is a common cause of poor Eustachian tube function. Although this is not the case in adults, a middle ear effusion can be due to an obstructing tumour of the Eustachian tube.

A skull base tumour such as a meningioma can obstruct the upper part of the Eustachian tube leading to a middle ear effusion.[20] Although still rare, a more common cause for Eustachian tube obstruction is a tumour of the nasopharynx occluding the lower end of the tube.

Radiotherapy of the skull base can lead to impaired Eustachian tube function and induce long-term OME, in one or both ears. A retrospective study of 81 patients with nasopharyngeal carcinoma found 52% of patients had an effusion at presentation and 26% developed an effusion after radiotherapy.[21]

Eustachian tube dysfunction may also be caused by reflux. In one study, 40% of effusions taken from adults were positive for *Helicobacter pylori* (HP) by PCR assay. Of these, seven grew HP when cultured and had a positive urease test.[22] Sone et al. found that in 24 adults with high pepsinogen levels in unilateral middle ear effusions a low-frequency audiometric bone-conduction threshold elevation was present in the affected ear when compared with the healthy ear and matched controls. This led them to postulate that this may be a diagnostic sign of high pepsinogen level effusions. Unfortunately, the authors did not have sufficient data after resolution of effusions to evaluate whether this was a temporary or permanent audiometric finding.[23]

Miscellaneous

Cerebrospinal fluid in the middle ear secondary to a skull-base defect may be mistaken for OME. Ventilation tube insertion can lead to persistent otorrhoea and a route for intracranial infection.

Prolonged endotracheal intubation is a risk factor for post-operative OME. The condition has also been described in approximately 20% of patients undergoing head and neck surgery.[24]

Rare conditions producing OME include amyloidosis[25] of the nasopharynx, Wegener's granulomatosis[26] (now called vaculitis), multiple myeloma,[27] cystic fibrosis,[28] polyarteritis nodosa[29] and immune deficiency syndrome. Nasal polyposis can also be associated with OME. A history of previous surgical treatment for nasal polyps or Samter's triad (a chronic condition of asthma, recurrent sinus disease with nasal polyps, and a sensitivity to aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs)) is associated with an increased risk of synchronous OME.[30]

PRESENTATION

The majority of adults seeking treatment do so because of hearing loss. The condition is bilateral in between 42% and 69% of those affected.[9, 10, 12] In a case-control study[12] symptoms in OME sufferers were:

- hearing loss: 97%
- aural fullness: 77%
- pulsatile or crackling tinnitus: 60%.

Balance disturbances are also sometimes reported.

Subjects frequently have predisposing factors which include smoking, childhood ear infections and nasal symptoms. A recent URTI, AOM and/or barotrauma is often a feature.

Unilateral OME in adults, unexplained by past history, should always be treated with suspicion.

EXAMINATION

Features on otoscopy described in childhood disease apply equally to adult disease. The tympanic membrane is usually retracted with an abnormal light reflex and the membrane may appear dull or a fluid level may be seen.

It is important to examine not only with otoscopy but also with flexible fibre-optic nasopharyngolaryngoscopy and/or a 0 degree Hopkins rigid nasendoscope. The nose and nasopharynx should be inspected. Evidence of rhinosinusitis will direct treatment. Postnasal space lesions will require imaging and biopsy while simultaneously dealing with the aural symptoms.

INVESTIGATIONS

Audiology

A pure-tone audiogram will show the level of impaired hearing function and typically reveal a conductive hearing loss. Experienced clinicians will usually make

the diagnosis of OME from tympanic membrane appearance and tympanometry is often not necessary. However, tympanometry does have a high correlation with MRI evidence of middle ear effusion[31] and may be used for diagnosis and monitoring of OME. Pre-operative tympanometry has also been shown to have a high correlation with myringotomy findings when gas displacement of fluid is controlled for.[32]

Myringotomy

The presence of fluid at surgery confirms the condition of OME but the absence of fluid does not necessarily refute it. Although the displacement of middle ear fluid by anaesthetic gases is thought to be minimal or absent, MRI scans have shown fluid in the mastoid air cells but not in the mesotympanum.[31] Immediate pre-operative tympanometry has been compared with tympanometry once a general anaesthetic was applied. In a group of 93 patients 30% of tympanograms were found to change under general anaesthetic. A type B pre-operative tympanogram was found to be predictive of a middle ear effusion in 92%.[33]

MANAGEMENT

There are four management options in adults: (i) non-medical treatment, (ii) medical treatment, (iii) hearing aids, and (iv) surgical treatment.

Non-medical treatment

Using a Toynbee manoeuvre or Valsalva technique can be beneficial. It is particularly useful in the perennial sniffer who needs to be educated against continuing this practice and encouraged instead to increase middle ear pressures. The Valsalva technique should be performed several times a day and the patient warned that the first time air enters the middle ear space may be uncomfortable and noisy. This tends to become less dramatic as the middle ear space is gradually aerated with continued application. In children, or in adults who fail to clear their effusions using the Toynbee or Valsalava techniques, mechanical devices such as the Otovent™ balloon and Ear Popper™ can be employed to achieve the same effect.

Medical management

Nasal decongestants such as xylometazoline are widely advocated for OME in adults but there is little evidence to indicate that they alter the natural course of the disease, which is to resolve without treatment in most cases.

Most research into antibiotic use for OME has been in the paediatric population. No large studies of adults were identified in the literature searches. Using a combination of both culture techniques and confocal laser scanning microscopy, a study of middle ear effusions in children found approximately 92% to contain live bacteria. A high proportion showed biofilm morphology. This strengthens the evidence for bacteria in the aetiology of OME in children but requires further investigation in the adult population.[34]

There has been no strong evidence to indicate that N-acetyl cysteine is a reliable form of therapy for OME in adults. Although in theory a mucolytic would appear to hold promise as an alternative form of treatment, laboratory studies show that the concentration of the drug reaching the mesotympanum together with the time it remains there would be critical in determining efficacy.[35] These variables remain difficult to control in a clinical setting.

Eosinophilic otitis media (EOM) has been defined as an intractable otitis media characterized by a highly viscous effusion containing eosinophils and high levels of immunoglobulin E. A pilot study found that long-term anti-IgE therapy produced significant benefits in patients. Larger clinical trials are awaited.[36]

Hearing aids

Hearing aids are highly effective for any conductive hearing loss depending upon the underlying sensorineural function, and should be offered as a form of treatment for hearing loss in adults with long-term OME.

Surgical treatment

Several studies have shown evidence for the short-term efficacy of ventilation tube insertion in adult OME. Unfortunately, once tubes extrude, the condition may return. Sade and Fuchs found that, in 50 adult ears treated with ventilation tube insertion, the majority reverted to the disease state within 3 months of tube extrusion.[37] Similar results have been reported in a more recent study.[38] The problems of infected ventilation tubes and chronic otorrhoea have led some authors to caution against the insertion of ventilation tubes (VTs) in patients treated for nasopharyngeal carcinoma.[21]

Different types of tube design and material are used depending upon the surgeon's intentions but all have a risk of long-term perforation. Recently, the subannular tube has been advocated as a method of reducing this risk.[39]

LASER MYRINGOTOMY

The use of a laser to produce fenestration of the tympanic membrane produces a short-term solution. A mean of 15–22 days for a functioning myringotomy has been reported.[40, 41]

MASTOID VENTS

Mastoid vents bypassing the need to perforate the tympanic membrane have been shown to have good long-term efficacy in chronic OME patients with significant atelectasis. In a multicentre trial of 23 subjects, 20 of the 23 vents were

still patent after 18 months and 18 of the 23 patients had improved hearing.[42]

LASER EUSTACHIAN TUBOPLASTY

Eustachian tuboplasty using a laser has been found to confer significant benefit on a small group of patients with OME when reviewed after a year. Practised as an outpatient technique under local anaesthetic, the authors reported it to be safe and well tolerated.[43]

BALLOON DILATATION OF THE EUSTACHIAN TUBES

Dilatation of the Eustachian tubes has been proposed as a treatment by some authors.[45] A recent meta analysis of studies to date which included 1155 patients in total concluded that the treatment offers short-term benefit in the majority of cases and medium to longer term benefit in a smaller number of patients.[45] There remains a need for large placebo controlled trials.

BEST CLINICAL PRACTICE

- ✓ Acute otitis media is diagnosed on symptom history and otoscopy. Pure-tone audiometry and tympanometry are not required.
- ✓ Otitis media with effusion in adults is uncommon. Treatment options, as described, should be discussed with the patient together with the attendant risks and benefits.

KEY POINTS

- Although relatively uncommon, AOM in adults is usually bacterial and is typically caused by the same organisms found in the paediatric form of the condition.
- Vascularity of the normal tympanic membrane should not be confused with the bulging red tympanic membrane seen in AOM.
- An unexplained middle ear effusion in an adult requires endoscopic visualization of the Eustachian tube entrance in order to exclude an obstructing lesion.
- Balloon dilatation of the Eustachian tubes may be an alternative treatment to ventilation tube insertion in adult OME.

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CHAPTER
83

CHRONIC OTITIS MEDIA

George G. Browning, Justin Weir, Gerard Kelly and Iain R.C. Swan

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SEARCH STRATEGY

A PubMed search was carried out using the search terms cholesteatoma, middle ear/ or mastoiditis/ or otitis media, suppurative/ or tympanic membrane perforation; randomized controlled trial; controlled clinical trial; randomized controlled trials/ random allocation/ double-blind method/ single-blind method. Comparative study/ exp evaluation studies/ follow-up studies/ prospective studies. Placebos/random. Limited to animal; limited to human; animal and human. An additional search for inactive squamous COM used the search terms: tympanic membrane and/or retraction.

DEFINITION

George G. Browning

The diagnosis of chronic otitis media (COM) implies a permanent abnormality of the pars tensa or flaccida, most likely a result of earlier acute otitis media, negative middle ear pressure or otitis media with effusion. COM equates with the classic term chronic 'suppurative' otitis media (CSOM) that is no longer advocated as COM is not necessarily a result of 'the gathering of pus'. However, the distinction remains between **active COM**, where there is inflammation and the production of pus, and **inactive COM**, where this is not the case though there is the potential for the ear to become active at some time. A third clinical entity is **healed COM** where there are permanent abnormalities of the pars tensa, but the ear does not have the propensity to become active because the pars tensa is intact and there are no significant retractions of the pars tensa or flaccida. 'Healed COM' can also be the end result of successful surgery. The differences are summarized in Table 83.1.

Our current ability to accurately assess an individual's ear, particularly with magnification, has made redundant the earlier, mainly anatomical, distinction between 'tubotympanic' and 'atticoantral' disease. The terms 'safe' and

'unsafe' are incorrect and misleading as complications can occur from any ear with active COM irrespective of its pathology.

PATHOLOGY

Justin Weir

INTRODUCTION

It is widely believed that COM often starts with episodes of acute otitis media (AOM) or otitis media with effusion (OME) in childhood. OME may lead to thinning of the tympanic membrane, hearing loss and delayed speech development, and it can impact on the child's educational development.[1] COM can be characterized histopathologically by middle ear pathology such as granulation tissue, cholesterol granulomas or cholesteatoma formation.[2]

Active COM is chronic inflammation of the middle ear and mastoid mucosa, with recurrent discharge (at least 2 weeks) through a chronic perforation of the tympanic membrane.[3] The World Health Organization (WHO) estimated that 65–330 million people worldwide are affected by CSOM, of whom 50% suffer from hearing impairment and approximately 28 000 deaths per annum are attributable to the complications of OM. Some of these figures have been confirmed by Monasta et al.[4] who recorded a CSOM incidence of 31 million cases globally. The highest incidence occurs in the first year of life (15.4 per thousand) and Oceania is the geographical area with the highest incidence (9.37 per thousand). They also found that OM-related hearing impairment has a prevalence of 30.8 per 10 000, and that 21 000 people died annually from complications of otitis media.

MOLECULAR PATHOLOGY

OM and COM are complex multifactorial diseases with no single genetic defect, which makes detection of those genes responsible for the disease process difficult to ascertain. Furthermore, it is likely that the multifactorial nature of this disease is in part due to innate immunity (toll-like receptors, cytokines, surfactant), adaptive immunity (immunoglobulins), non-specific immunity (epithelial barriers and mucin production), inflammatory regulation and craniofacial abnormalities. Towards the end of the last century several authors showed a genetic component to both AOM and OME.[5–7]

The exact molecular pathways by which persistent inflammation occurs are now beginning to be unravelled. OM is frequently caused by bacteria, which enter via the Eustachian tube, though sterile OM is not uncommon and the initiation of inflammation in this scenario is unclear. A number of murine models of OM have been developed[8] to resolve this conundrum and, in particular, two non-syndromic mouse models of COM have analyzed the heterozygous *Jeff*[9, 10] and *Junbo*[11] mutant mice.

Jeff carries a mutation in the F-box only protein 11 gene (*Fbxo11*) and *Junbo* a mutation on the zinc finger domain at the ecotropic virus integration site 1 (*Evi1*) gene. Both mutant models demonstrate hypoxia and hypoxia-inducible factor (HIF) mediated responses (more so in *Junbo* than *Jeff*).[12] HIF signalling is regulated at the transcriptional level by interactions with the master regulator of inflammation – nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) – and at the translational level by cytokines, which are glycoproteins produced by inflammatory cells and epithelial cells, such as interleukin-1 (IL-1β) and tumour necrosis factor alpha (TNF-α or TNFA) which induces the acute phase of the inflammatory response and releases other cytokines.[13, 14] Indeed, both IL-1β and TNF-α act synergistically and have similar functions in activating neutrophils, promoting fibroblast proliferation and stimulating prostaglandin and leukotrienes, all of which are important in the pathogenesis of OM.[15] NF-κB can be activated by a range of factors, other cytokines, including bacterial lipopolysaccharides, viral pathogens and growth factors.[16]

The downstream HIF signalling protein vascular endothelial growth factor (VEGF) has been shown to play a role in OME[17] and the link between HIF and VEGF was further investigated and confirmed by Cheeseman et al.[12] Essentially, hypoxia drives inflammation by activation of NF-κB, IL-1β and TNF-α and also increases angiogenesis,

TABLE 83.1 Classification of COM and synonyms used in this chapter

COM classification	Synonyms	Otoscopic findings
Healed COM	Tympanosclerosis; healed perforation	Thinning and/or local or generalized opacification of the pars tensa without perforation or retraction
Inactive (mucosal) COM	Perforation	Permanent perforation of the pars tensa but the middle ear mucosa is not inflamed
Inactive (squamous) COM	Retraction	Retraction of the pars flaccida or pars tensa (usually posterosuperior) which has the potential to become active with retained debris
Active (mucosal) COM		Permanent defect of the pars tensa with an inflamed middle ear mucosa which produces mucopus that may discharge
Active (squamous) COM	Cholesteatoma	Retraction of the pars flaccida or tensa that has retained squamous epithelial debris and is associated with inflammation and the production of pus, often from the adjacent mucosa

COM, chronic otitis media.

vascular permeability and recruitment of neutrophils through activation of VEGF. The introduction of tympanostomy tubes (grommets) alters the oxygen tension and this might be an important mechanism in the downregulation of HIF signalling.

The recruitment of inflammatory cells, whether neutrophils, mast cells, lymphocytes, plasma cells or monocytes/macrophages, is integral to the initiation and subsequent chronicity of OM.[15] Once inflammation is initiated, there is an accumulation of fluid and inflammatory cells in the middle ear cavity, causing conductive deafness and rarely secondary cochlear dysfunction through diffusion of cytokines through the round window.[18] Moreover, cytokines, such as TNF-α and IL-8, induce upregulation of mucin genes within the middle ear and the altered viscosity impairs mucociliary clearance.[15, 19] Both TNF-α and IL-8 can increase inducible nitric oxide synthase (iNOS) in the middle ear mucosa and nitric oxide stimulates mucin production.[20]

Fbxo11 and *Evi1* also interact with the transforming growth factor beta (TGF-β or TGFB) signalling pathway in mice[21] and in humans.[22] Tateossian et al.[23] identified a further link between TGF-β and COME in mutant TGF-β-induced factor homeobox 1 (*Tgif1*) mice, highlighting the importance of the TGF-β signalling pathway and its effects on the responses to hypoxia in the chronically inflamed middle ear. There is considerable crosstalk between TGF-β and HIF-1α pathways as both SMAD-3 (which is one of the many mediators of the TGF-β pathway) and HIF-1α are coactivators of VEGF expression.[24] Furthermore, TGF-β /SMAD signalling leads to downregulation of p38 by including MAPK phosphatase-1 and the subsequent suppression of the mucin protein MUC5AC,[25] resulting in the impaired mucociliary defence. Conversely, NTHi strongly induced upregulation of MUC5AC via activation of the Toll-like receptor 2-MyD88-dependent p38 pathway in a middle ear epithelial cell line.[25] In addition, *MUC5AC* rather than *MUC5B* or *MUC2* was shown to be associated with OME,[26] though this has been challenged by Preciado et al.[27] who showed that MUC5B is the predominant mucin in middle ear effusions from children with OME. However, Kerschner et al.[28] showed that the *MUC5AC* gene was upregulated by more than 150 times in OME samples compared with controls. Either way, the upregulation of mucins, whether by microbial pathogens, cytokines, growth factors, cigarette smoke[29] or gastric acid,[30] results in overproduction of mucin within the middle ear and the subsequent conductive deafness.

Toll-like receptors (TLR) are a group of pattern-recognition receptors that are involved in the innate immune system against microbial pathogens. In particular, Toll-like receptor 4 (*Tlr4*) responds to and recognizes the lipopolysaccharide (LPS) of Gram-negative bacteria such as nontypeable *Haemophilus influenzae* (NTHi), *Streptococcus pneumoniae* and *Klebseilla oxytoca*.[31] Thus, a lack of *Tlr4* results in a poor response to Gram-negative bacteria. The innate immune system is the first line of defence against invading pathogens and has been widely studied in OM.[32, 33] Several studies have shown that TNF-α is important in the regulation of inflammation in the middle ear. Downregulation of TNF-α results in the formation of mucosal polyps,[34] the lack of activation of TLRs and downstream proteins such as CC chemokine ligand 3 (CCL3) and the subsequent lack of recruitment of inflammatory cells.

The human homologues *FBXO11* and *TLR4* of the mouse genes *Fbxo11* and *Tlr4* have been investigated in genetic association studies of human OM. The Minnesota OME/rOM Family Study cohort looked at 142 families with 248 children diagnosed with recurrent or chronic OM.[35] They were genotyped using 13 single-nucleotide polymorphisms (SNPs) across the *FBXO11* gene[36] and a significant association with univariate but not multivariate analysis was found. However, in the larger Western Australian Family Study of Otitis Media, Rye et al.[22] found a significant association with two *FBXO11* polymorphisms on both univariate and multivariate analyses. Interestingly, *EVI1* was not associated with OM in three independent predominantly Caucasian cohorts,[22, 37] suggesting that this gene does not exert the same effect on OM susceptibility in humans as it does in mice.

In a Dutch population of 348 children aged less than 7 years with two or more episodes of AOM, Emonts et al.[38] found that there was a significant association at the *TLR4* D299G polymorphism with 'otitis-prone' (four or more episodes of AOM in the preceding year) when compared to 'non-otitis-prone' children (two to three episodes of AOM in the preceding year).

Genome-wide linkage studies have identified OM susceptibility loci at several regions of linkage on chromosomes 3p25, 10q22, 10q26, 17q12 and 19q13.[35, 39, 40] To date, the susceptibility genes underlying these linkage regions have not been mapped, though Casselbrant et al.[39] proposed a cluster of chemokine genes on 17q12 and several surfactant protein genes near 10q26, while Daly et al.[35] proposed *ADAM8* gene (a disintegrin and metalloproteinase domain), an allergy-associated gene, as a possible candidate for 10q22 linkage peak and Chen et al.[40] suggested potential candidate genes at 19q such as *ZNF71*, an endothelial zinc finger gene induced by TNF-α, and *ZNF304*, which activates lymphocytes.[41] Other candidate genes included members of the inflammasome protein complex which are key regulators of the innate immune response to harmful exogenous or endogenous stimuli.

In summary, the genetic studies, whether from mouse to human or vice versa, have highlighted the importance of regulating the pro-inflammatory and anti-inflammatory effects of pathogens. No doubt the next-generation sequencing methods such as exome sequencing and whole-genome sequencing will help to identify the candidate genes and clarify the molecular pathogenesis of this disease.[8]

EOSINOPHILIC OTITIS MEDIA

Eosinophilic otitis media is a relatively new subgroup of OM/COM which was first described in Japan.[42] It occurs mainly in patients with bronchial asthma who have T–helper type 2 dominant predisposition, and a patulous Eustachian tube which allows entry of

antigenic material into the middle ear resulting in an eosinophilic dominant inflammatory infiltrate.[43] IL-5 is one of the key cytokines in this entity as it has a direct chemotactic effect on eosinophil recruitment. In COM there can be either a simple perforation with a thick yellow viscous effusion or a proliferation of granulation tissue extending into the external ear canal which can often be intractable.

PATHOLOGY OF SUBTYPES OF CHRONIC OTITIS MEDIA

Inactive mucosal COM (dry perforation)

WHO includes inactive mucosal COM (dry perforation) under CSOM.

There is permanent perforation of the pars tensa but the middle ear and mastoid are not inflamed (Figure 83.1). The mucocutaneous junction is usually located at the margin of perforation which can extend up to the fibrous annulus.

Active mucosal COM (perforation with otorrhoea, CSOM)

There is chronic inflammation within the mucosa of the middle ear and mastoid with varying degrees of oedema, submucosal fibrosis, hypervascularity and an inflammatory infiltrate including lymphocytes, plasma cells and histiocytes (Figure 83.2). There is also an increase in the number of goblet cells and basal cell hyperplasia in the middle ear epithelium.[44] Granulation tissue can occur (Figure 83.3) and this is often clinically described as 'aural polyps' which have protruded through the perforated tympanic membrane. Some areas with active COM (both mucosal and cholesteatomatous subtypes) demonstrate focal areas of cholesterol granuloma formation, which microscopically consists of a giant cell reaction surrounding cholesterol clefts (Figure 83.4).

Chronic inflammation can affect the whole of the middle ear cleft including the mastoid antrum and some surgeons believe it is important when a perforation is repaired that the whole of the infected mucosa and granulation tissue from the mastoid and middle ear space is removed in order to control the disease. There is, however, no good evidence that this is necessary and many surgeons only close the perforation even in active disease (see role of adjuvant mastoidectomy in the discussion of management below).

Active mucosal COM is often associated with destruction of the ossicular chain.[45] The affected ossicles typically show areas of hyperaemia with proliferation of capillaries and prominent granulation tissue (Figure 83.5). The long process of the incus, stapes crura, body of incus and manubrium are involved in decreasing order of frequency. Bone resorption or destruction occurs by osteoclast activity. There are a number of bone-modelling molecules/proteins such as receptor activator NF-κB (RANK) and RANK ligand (RANKL) that are expressed in COM which can activate osteoclasts, whereas osteoprotegerin acts as an antagonist to RANKL.[46, 47] Kuczkowski et al.[45] also investigated the expression of TNF-α, IL-1α, IL-6 and IL-10 (an immunosuppressive regulator of acute inflammation) in COM with cholesteatoma formation and bone destruction and found a significant correlation with TNF-α, IL-1α and IL-6. IL-10 is a key anti-inflammatory cytokine and inhibits the production of TNF-α, IL-1, IL-6 and IL-8 as well as inhibiting macrophages and the production of oxygen radicals by neutrophils.[48]

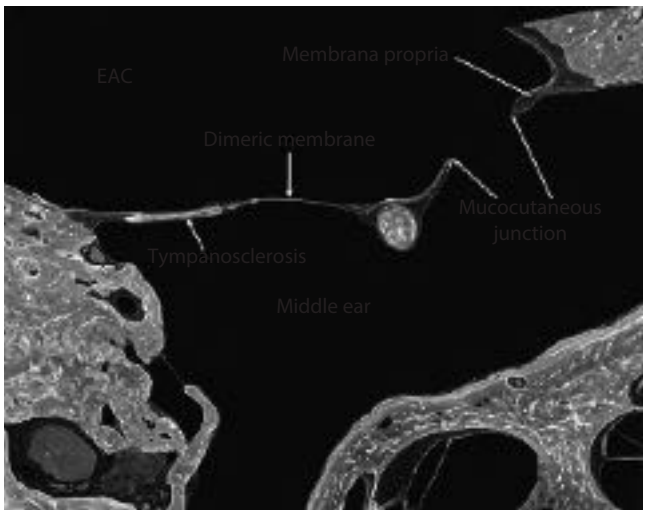


Figure 83.1 Axial temporal bone section from a 43-year-old man. There is a dry perforation of the anterior part of the pars tensa. The mucocutaneous junction is located at the margins of the perforation. The drum remnant anterior to the perforation shows fibrous thickening affecting its middle layer, the membrana propria. There is also a dimeric membrane and tympanosclerosis in the posterior part of the tympanic membrane. EAC, external auditory canal. (*Magnification ×13.*)

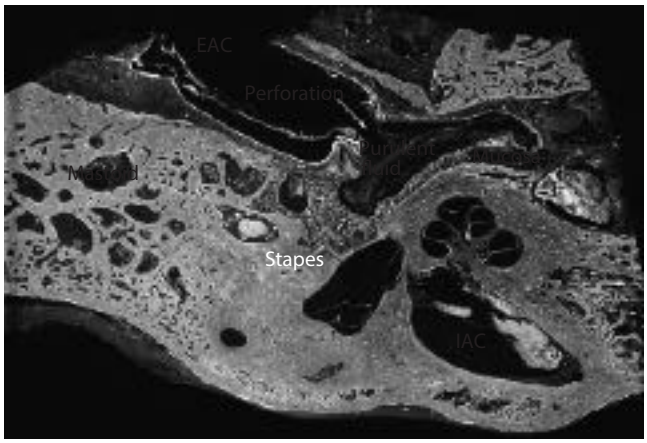


Figure 83.2 Axial temporal bone section from a 77-year-old woman with active mucosal COM. There is a perforation of the pars tensa anterior to the manubrium. The middle ear mucosa is markedly thickened with hypervascularity and active chronic inflammation. There is purulent fluid in the tympanic cavity that is draining through the perforation. The mastoid air cells also show chronic inflammation. EAC, external auditory canal. IAC, internal auditory canal. (*Magnification ×4.*)

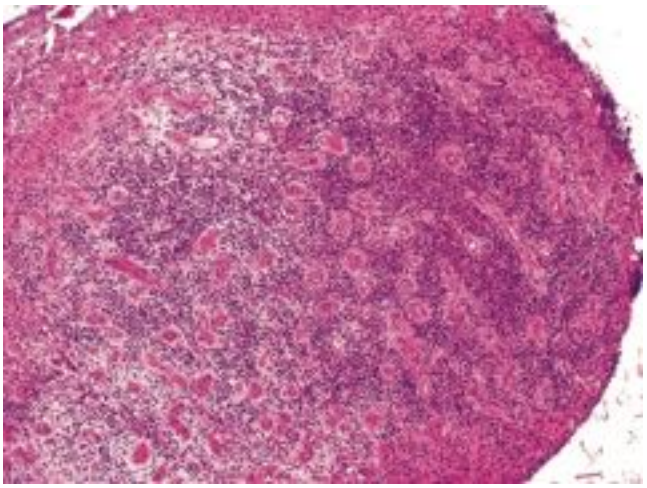


Figure 83.3 Granulation tissue consisting of numerous blood vessels and an inflammatory infiltrate of neutrophils, lymphocytes and plasma cells. (*Magnification ×100.*)

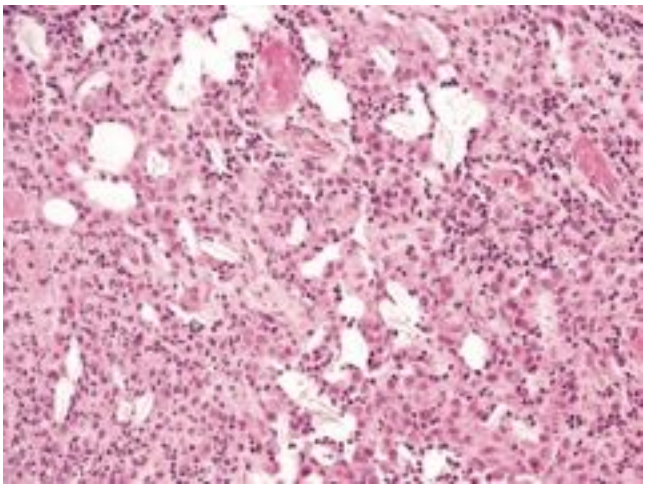


Figure 83.4 Cholesterol clefts (++) surrounding flakes of keratin. Around the cholesterol clefts are numerous macrophages as well as the smaller lymphocytes and neutrophils. (*Magnification ×200.*)

It most likely contributes to the elimination of middle ear inflammation and provides a negative feedback mechanism to the pro-inflammatory effects of TNF-α.

Bacteria also play a role in the bone destruction seen in COM and infected cholesteatoma. Nason et al.[49] showed that *Pseudomonas aeruginosa* LPS (the main antigenic component of the bacterial cell wall) stimulates RANKL-primed precursor osteoclasts into bone-resorbing osteoclasts by an autocrine/paracrine mechanism involving at least 11 cytokines including TNF-α, IL-1α, IL-1β, IL-9 and IL-10, granulocyte-colony stimulating factor (G-CSF), monocyte chemotactic protein-1 (MCP-1) and macrophage inflammatory protein (MIP-1α) among others.

Inactive squamous epithelial COM (retraction, atelectasis and epidermization)

Negative static middle ear pressure can result in retraction (atelectasis) of the tympanic membrane. A 'retraction pocket' consists of an invagination into the middle ear space of part of the tympanic membrane and this may be **fixed**, when it is adherent to the structures in the middle ear, or **free**, when it can move medially and laterally depending on the state of inflation of the middle ear. 'Epidermization' is a more advanced type of retraction and refers to replacement of the middle ear mucosa by keratinizing squamous epithelium without retention of keratin debris.[50]

Active squamous epithelial COM (acquired cholesteatoma)

Cholesteatoma is a benign keratinizing epithelial-lined cystic structure found in the middle ear and mastoid (**Figure 83.6**). It can cause destruction of the local structures – ossicular chain and otic capsule, thereby



Figure 83.5 High-power view of cross-section of manubrium from a 23-year-old woman with active mucosal COM, showing resorptive osteitis with replacement by granulation tissue. (*Magnification ×81.*)

leading to complications such as hearing loss, vestibular dysfunction, facial paralysis and intracranial disease or infection. The term 'cholesteatoma' was first coined by the German physiologist Johannes Muller in 1838.[51]

The annual incidence of cholesteatoma was found to be approximately 3 per 100 000 in children and 9.2 per 100 000 in an adult Caucasian population in Northern Europe.[52, 53] There is variability of prevalence across racial types, however, with Inuit Eskimos having a significantly lower rate, of 5 per 100 000.[54] Moreover, an Australian study of Aboriginal children and adults reported a low incidence of cholesteatoma (1–3%) compared to higher rates of COM (25–45%), suggesting that the anatomical location of the perforation may have a bearing on the development of a cholesteatoma.[55]

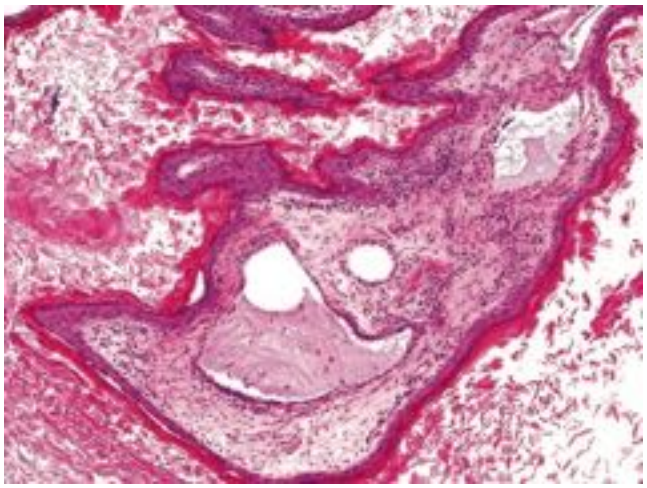


Figure 83.6 Cholesteatoma consisting of keratinizing squamous epithelium. In the submucosa there are a few dilated glands (+) containing mucus. (*Magnification ×100.*)

The pathogenesis of cholesteatoma is due either to the retraction of Shrapnell's membrane (pars flaccida) or the posterior superior quadrant of the pars tensa, or to retraction of the entire pars tensa[56, 57] – the so-called 'retraction pocket theory' first described by Bezold in 1890.[58] This was developed by Sudhoff and Tos[59] who proposed a combined retraction and proliferation model. Key to this theory is Eustachian tube dysfunction which leads to retraction of the pars flaccida into the epitympanum, and subsequent cholesteatoma formation.[60, 61]

A number of other theories relating to the pathogenesis of cholesteatoma, in addition to the retraction pocket theory, have been proposed:[56]

- **basal cell hyperplasia:** proliferation of papillary cones in the basal layer of the squamous epithelium of the pars tensa or flaccida
- **immigration:** based on the ingrowth of squamous epithelium through a pre-existing perforation
- **metaplasia:** of colonies of epithelial cells in the middle ear from cuboidal to keratinizing squamous epithelium.

Cholesteatoma can also be classified according to its topology. Thus, attic cholesteatoma is a mixture of retraction and papillary proliferation as proposed by Sudhoff and Tos,[59] whereas sinus cholesteatoma is a posterosuperior retraction or perforation of the pars tensa extending to the tympanic sinus, posterior tympanum and beyond. Tensa cholesteatoma is retraction and adhesion of the entire pars tensa and may involve the tympanic orifice of the Eustachian tube. On occasions it may result in an acquired epidermal remnant behind the intact tympanic membrane. The pathogenesis of such a remnant remains elusive, but it is thought to develop either from a resolved retraction of the pars tensa, where residual squamous epithelium remains in the middle ear cavity, or from an ingrowth of meatal squamous epithelium.[59, 60] Of note, those individuals who have a perforation of the tympanic membrane rarely have a cholesteatoma on the posterior superior quadrant of the pars tensa or in the pars flaccida.[1]

Recently, Yamamoto-Fukuda et al.[62] performed an elegant study using a hybrid gerbil model to demonstrate that the epithelial cells in cholesteatoma are derived from the tympanic membrane and not from the epithelial cells within the middle ear or epithelium from the external auditory canal. Indeed, the molecular pathology of cholesteatoma has been investigated by a number of authors. Using DNA chip analysis, 282 genes were found to be differentially expressed in comparison to the control samples[63] and Klenke et al.[64] identified 3558 new cholesteatoma-related transcripts. Of those, 811 were upregulated and 334 downregulated more than twofold. The genes involved are found in a number of different biological processes including signal transduction, cell growth, cell communication, metabolism, transport and the immune response. Hamajima et al.[65] determined the role of inhibitor of DNA-binding (Id1) in the proliferation of cholesteatoma keratinocytes. They found that Id1, a protein that leads to cell immortalization, induces up regulation of NF-κB/cyclin D1/keratin 10 in the keratinocytes. The authors concluded that Id1 contributed to the thickening of the middle ear mucosa, cell cycle progression and removal of cell cycle inhibition.

The role of keratinocyte proliferation has also been described in animal models of cholesteatoma[66] and in humans the proliferation rate of cholesteatoma in comparison to external auditory skin has been investigated and been shown to be 2.3 times higher.[67] More detailed studies on keratinocyte proliferation including the *p53* tumour suppressor gene, c-jun and c-myc protein were all found to be upregulated in cholesteatoma.[56, 68, 69] This is coupled with the increased apoptotic rate of cholesteatoma leading to the accumulation of keratinous debris.[70, 71]

Others, such as Huisman et al.[72] have explored the function of TGF-β in cholesteatoma from 12 patients. They ascertained that, while TGF-β is not upregulated in the keratinocytes, it is upregulated in the stroma. They concluded that cholesteatoma behaves as a chronic wound healing process. Further support for this argument has been provided by Lee et al.[73] who demonstrated an increased expression of some pattern recognition receptors (PRRs) mRNA including those encoding for TLRs, TLR-2, -3, -4, -6, -7 and -10, and nucleotide-binding oligomerization domain-containing protein 2 (NOD-2). PRRs, which recognize conserved microbial structures, activate the innate immune system and the activation of TLRs lead to the mobilization of cytokines, chemokines and interferons as well as proteases, defensins, collectins, lysozyme and lactoferrin.[74] Furthermore, downstream mediators of inflammation such as IL-1 and IL-8 were also upregulated. Indeed, TLRs can induce NF-κB as well as TNF-α.[75]

The interplay between the epithelium of cholesteatoma and the surrounding stroma is key to understanding its destructive effects. There are defects in the regulation of epidermal growth factor receptor (EGFR) system,[76]

as well as IL-1 and TGF-α[77] – all important factors in the inflammatory process. Furthermore, TGF-α has been shown to upregulate matrix metalloproteinase-9 (MMP-9),[78] which has been demonstrated to cause bone destruction.[79]

The inflammatory nature of cholesteatoma has gained credence and some authors believe that inflammation rather than retraction is the precursor event required for acquired cholesteatoma formation:[80] when a perforation has occurred, the normal epithelial migration on the external aspect of the tympanic membrane is altered, resulting in a proliferation of squamous epithelium through the perforation into the middle ear cavity. If infection intervenes, migration ceases and squamous hyperplasia with the resultant keratin formation commences, leading eventually to the formation of a cholesteatoma.[60] However, as noted, perforations per se are not often associated with cholesteatoma and it may well be that there are different pathological processes involved in the formation of cholesteatoma secondary to perforated tympanic membranes compared to cholesteatoma derived from an intact tympanic membrane.

In the rare instances of cholesteatoma occurring behind an intact tympanic membrane it has been shown that the cholesteatoma is derived from the tympanic membrane.[62] Whether it is due to a hyperproliferation of squamous epithelium which forms protrusions into the tympanic cavity and, with repeated bouts of chronic inflammation, these turn into cholesteatoma,[72, 81] or whether there is a proliferation of squamous cones or papillary ingrowths from the epidermal basal layer within the retraction pockets[57] remains to be determined.

Healed chronic otitis media

Jensen et al.[82] observed a 39% spontaneous healing rate among a long-term population-based cohort of Greenlanders. Of those healed ears, circular atrophy indicating a healed perforation was the commonest finding. The presence of circular atrophy can lead to a higher risk of reperforation from further episodes of AOM or barotraumas. De Beer et al.[83] followed up 358 subjects from a birth cohort with and without OM histories and/or ventilation tube insertion. They found that at 8 and 18 years of age the prevalence of abnormalities (tympanosclerosis, atrophy, atelectasis, pars tensa retraction pockets and pars flaccida retraction) fell from 92% to 46%. By 18 years of age, many of the tympanic membrane abnormalities had completely resolved, though the prevalence of tympanosclerosis remained high in those treated with tubes.

In OME the tympanic membrane can be damaged by matrix metalloproteinases within the effusion.[84] Tympanosclerosis develops in the lamina propria between the epidermis and mucosal epithelium. It consists of hyaline deposits of acellular material visible as white plaques and white nodular deposits. Pathologically, these hyaline deposits are composed of thickened collagen fibres I, II and III admixed with calcium phosphate deposits[50] and over time osseous metaplasia can occur. Tympanosclerosis surrounding the ossicles in the epitympanum and the stapes superstructure or footplate in the oval window causes varying degrees of immobility of the ossicular chain and it is a well-recognized adverse factor in tympanoplasty (**Figure 83.7**).

PATHOLOGY OF COMPLICATIONS OF CHRONIC OTITIS MEDIA

Routes of spread of infection

The prevalence rates for the extracranial and intracranial complications of COM have been reported as ranging between 0.69% and 5%.[85–87] The most common extracranial complication remains a mastoid abscess. In cases with both extra- and intracranial complications, cholesteatoma was frequently found in the middle ear and mastoid cavity. Facial nerve paralysis can complicate OM in the absence

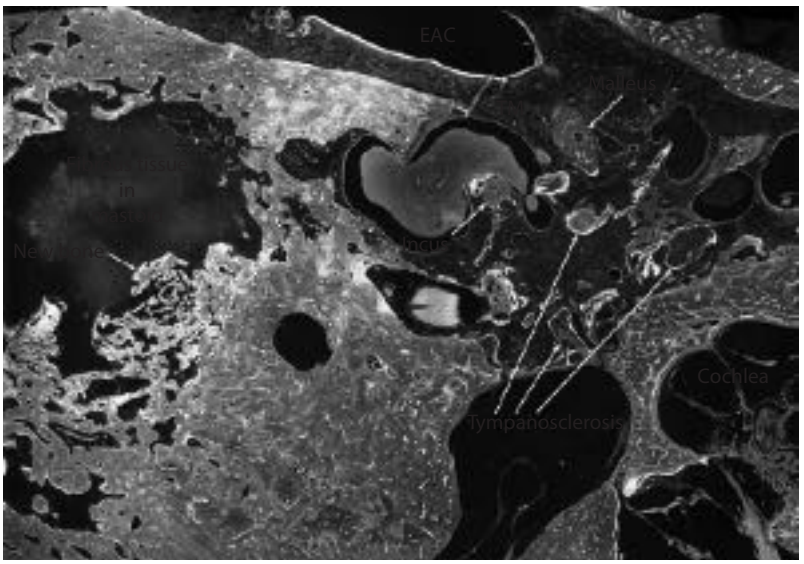


Figure 83.7 Axial temporal bone section from a 77-year-old man with healed COM. The tympanic membrane (TM) is markedly thickened due to proliferation of fibrous tissue. The middle ear and mastoid spaces have been overrun by fibrosis and cyst formation ('fibrocystic sclerosis'), as well as deposition of new bone ('fibro-osseous sclerosis'). There are extensive deposits of tympanosclerosis within the middle ear. It is very difficult to restore hearing by tympanoplasty surgery in such cases of end stage pathology. EAC, external auditory canal. (*Magnification ×9.*)

of cholesteatoma. Patients with COM and cholesteatoma were more likely to develop complications than those with just COM.[86] The most frequently isolated pathogen from ear swabs was *Proteus mirabilis* in 33.3% of cases.

Ibrahim et al.[88] analyzed the incidence of meningitis secondary to suppurative OM in adults. They found that acute and chronic suppurative OM accounted for 13% and 3% of cases of meningitis respectively and calculated that the incidence of otogenic meningitis was 0.42 per 100 000 per year.

Labyrinthine fistula

Labyrinthine fistula can be caused by active mucosal COM or cholesteatoma. The lateral semicircular canal is the most commonly affected site and the reported incidence of fistula formation is 4–13% of all cases.[89] Histologically, cholesteatoma matrix or granulation tissue becomes apposed to the endosteum of the inner ear or directly to the membranous labyrinth. In many fistulae reactive inner ear changes are absent thus a protective walling off phenomena appears to occur (**Figure 83.8**). The margins of some labyrinthine fistulae show evidence of new bone formation and this probably explains the clinical observation that many fistulae show spontaneous bony closure after removal of the offending cholesteatoma or granulation tissue.

Labyrinthitis

Labyrinthitis, whether serous or suppurative, can cause sensorineural hearing loss by affecting various cochlear structures including the hair cells, spiral ganglion cells and striae vascularis. Adams[90] demonstrated that the type I fibrocytes within the spiral ligament expressed NF-κB, which may alter the function of the ion channels within the spiral ligament, resulting in hearing impairment. Suppression of cochlear NF-κB activity by steroids before antibiotic treatment may suggest a role for steroid therapy in recovering from sensorineural hearing loss although there is no evidence for their efficacy in clinical practice.

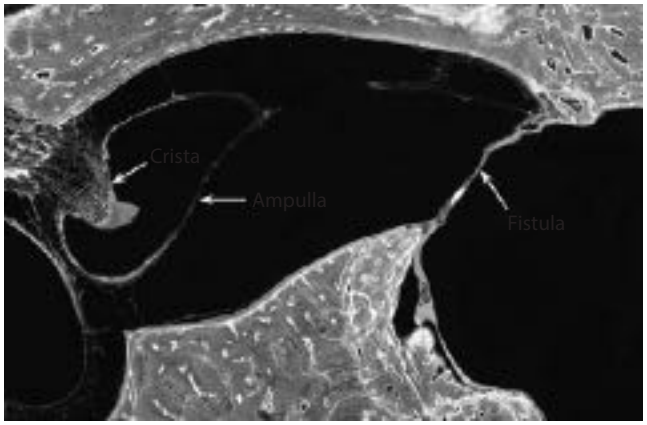


Figure 83.8 High-power view of temporal bone section from a 76-year-old woman with active mucosal COM that resulted in resorption of bone over the lateral semicircular canal with resulting fistula. Only the endosteum separates the perilymphatic space from the middle ear space. Note the absence of reactive inner ear change at or adjacent to the fistula site. (*Magnification ×34.*)

Facial nerve paralysis

The frequency of facial nerve paralysis ranges from 0.16% to 2.62%.[87, 91, 92] Granulation tissue and/or cholesteatoma may cause facial nerve paralysis with a dehiscent or eroded bony facial canal.[92] The nerve and surrounding vascular plexus can become inflamed and swollen and result in degeneration of the axonal fibres. Of note is the fact that the prognosis of the paralysis is worse in COM than in paralysis from trauma, Bell's palsy or AOM.[92]

Otogenic intracranial complications

Although death from intracranial complications of COM has decreased in the developed world,[93] it still remains problematic in developing countries,[94] where Dubey et al. reported a mortality rate of 31.2% in their series. Intracranial complications include meningitis, otitic hydrocephalus, lateral sinus thrombosis, cavernous sinus thrombosis and intracranial sepsis (e.g. extradural, epidural, subdural, perisigmoid sinus and cerebral abscess formation).[87, 91, 95] The routes of infection are via osteitis of the mastoid or temporo-occipital bone, resulting in thrombophlebitis of the venules with or without bone erosion, or by thrombosis of the sigmoid sinus by infected cholesteatoma.[94]

Hearing loss

COM can produce inflammatory changes at the round window and inflammation in the adjacent scala tympani.[96] This can rarely result in loss of both inner and outer hair cells in the basal turn as well as a reduction in the area of the stria vascularis leading to sensorineural hearing loss. The pathogenesis of the inner ear inflammation has been linked to the spiral ligament fibrocytes (see 'Labyrinthitis' above) which release chemokines in response to the middle ear pathogens, in particular monocyte chemoattractant protein-1 (MCP-1/CCL2).[97] Using the C3H/HeJ mouse model which lacks the gene for TLR4, MacArthur et al.[98] observed disruption of inner ear ion and water transport functions as well as alteration in tissue remodelling genes. As many of these channels and transporters are located on the lateral wall of the cochlea, both endolymph production and maintenance are at risk when COM occurs.

AETIOLOGY AND EPIDEMIOLOGY

Gerard Kelly

PREVALENCE OF CHRONIC OTITIS MEDIA

The prevalence of adult middle ear disease in the British population was obtained from the UK National Study

of Hearing,[99] a prospective clinical study of a randomly selected UK population (Table 83.2). An otoscopic diagnosis was made in over 2000 individuals. The overall prevalence of healed, inactive and active COM was 11.9%, 2.6% and 1.5% respectively. The prevalence of active and inactive COM was 4.1%, with 3.1% of individuals having unilateral and 1.0% bilateral disease.

The UK National Study of Hearing[99] also examined the relationship between COM and age, sex and socioeconomic group. There was no sex difference in the prevalence of COM.

Individuals in the age group 41–80 years were twice as likely to have COM as those in the age group 18–40 years. COM has a higher prevalence in lower socioeconomic groups, with manual workers having twice the prevalence of non-manual workers.

Unfortunately, in this study, it was not possible to separate patients with COM into those with mucosal and those with squamous disease. Surgical data is all that is available to give the relative frequencies of mucosal and squamous disease.

Alho et al.[100] reported the rates of surgery in the general population in 1992. The surgery rates were 13 per 100 000 for inactive COM, 7 per 100 000 for active mucosal disease and 4 per 100 000 for active squamous disease. These figures clearly underestimate the true incidence of this disease in the population as not all patients with COM will be seen by a physician or undergo surgery. A similar study[101] identified an incidence of chronic squamous otitis media to be 9.2 per 100 000, with a bilateral incidence of 4.4% within this subgroup. This study showed no socioeconomic difference in incidence; however, unlike the UK National Study of Hearing, these individuals were not randomly selected but presented with ear symptoms and therefore the sample may have been biased with patients in higher socioeconomic groups being more inclined to seek medical intervention.

AETIOLOGY OF CHRONIC OTITIS MEDIA IN GENERAL

Acute otitis media and otitis media with effusion

Both childhood AOM and OME can cause long-term changes of the tympanic membrane.[102] Histological degeneration of the tympanic membrane occurs in the outer and inner fibrous layers of the lamina propria and in the submucosal layer.[103] These changes may reduce the elastic properties of the tympanic membrane making it more susceptible to chronic perforation or retraction. Cases of adults acquiring COM are not uncommon but, again, this could be the result of adult episodes of AOM.

Why some individuals progress from AOM to COM is not clear but the risk factors for this occurring are likely to include some of those for AOM and OME. What is required is for one of the cohorts of children that have been studied for OM to be followed up into adulthood. Unfortunately, none has yet been reported. An alternative is to study a group of adults with COM and record risk factors in comparison to a group of adults that do not have COM. In this type of study a multifactorial analysis would be required. The only study in this category was the

TABLE 83.2 Population prevalence (%) of adult chronic otitis media.[99] The 95% confidence intervals are in parentheses

	Healed otitis media	Inactive chronic otitis media	Active chronic otitis media
Overall	11.9 (10.2, 13.6)	2.6 (1.8, 3.4)	1.5 (1.1, 1.9)
Age (years)			
18–40	10.1 (8.6, 14.4)	2.5 (1.0, 4.0)	0.9 (0.2, 1.6)
41–60	11.5 (9.3, 13.7)	2.1 (1.2, 3.0)	2.1 (1.3, 2.9)
61–80	16.2 (12.8, 19.6)	2.7 (1.6, 3.8)	2.1 (1.3, 2.9)
Sex			
Male	12.6 (9.8, 15.4)	2.8 (1.4, 4.2)	1.9 (1.1, 2.7)
Female	11.3 (9.3, 13.3)	2.4 (1.7, 3.1)	1.2 (0.8,1.6)
Occupation			
Manual	13.5 (11.0, 16.0)	3.3 (2.3, 4.3)	2.2 (1.5, 2.9)
Non-manual	10.1 (7.7, 12.5)	1.9 (0.8, 3.0)	0.8 (0.4, 1.2)

UK National Study of Hearing and the factors included in this were limited to those in Table 83.2. This leaves studies that report on single factors as the highest level of evidence available for these factors.

Genetics and race

The incidence of COM varies in different populations and, in the developed world, is highest in Eskimos, American Indians, New Zealand Maoris and Australian Aborigines.[104] It appears that the prevalence of COM, at least in populations predisposed to it, is declining. In one study of New Zealand Maori children,[105] the prevalence of COM decreased significantly from 9% in 1978 to 3% in the corresponding months of 1987 ($p < 0.02$).

It is difficult to answer the question of whether genetic factors influence COM because of confounding variables such as low socioeconomic grouping of some genetic groups with a high incidence of COM. It is known, however, that there is a high incidence of COM in American Indians, and this incidence varies considerably among different tribes of American Indians, a finding that is likely to have a genetic basis.[106] In a prospective population-based, 2-year cohort study on the incidence of both active and inactive COM in a high-risk Greenlandic population,[107] being of Inuit descent was identified as a risk for the condition, with a HR of 5.56.

In a review of COM in developing countries[108] high levels of COM were noted in some countries, but rates varied considerably. This is likely to be due to population characteristics and environmental factors rather than antibiotic usage.

Environment

As has already been stated, the prevalence of COM is greater in lower socioeconomic groups. The reason for this is multifactorial. In a cohort study, with results on 12 000 children[109] factors significant for ear discharge (although not necessarily COM) were general health scores, maternal smoking and day-care attendance. While sometimes quoted as a factor, the effect of breastfeeding was weak and did not show statistical significance. The decrease in prevalence of COM in New Zealand Maori children from 1978 to 1987 is thought to be due to improvement in both health care and housing conditions.[105] In Koch's prospective population-based 2-year cohort study[107] on the incidence of both active and inactive COM, identified risk factors included: attending childcare (hazard ratio (HR) = 3.18) and household smokers (HR = 4.56).

Eustachian tube dysfunction and upper respiratory tract infections

Eustachian tube dysfunction is more common in patients with COM than in individuals free from middle ear disease.[110] It is not known, however, if the Eustachian tube dysfunction is the initiating factor in COM or whether it is a result of COM. Koch et al.[107] also showed that upper respiratory tract infections (URTIs) increased the risk of COM, but whether URTI is an independent risk factor in COM was unclear and, whereas there are many studies which examine the relationship with AOM and URTIs, studies which examine this relationship with COM are scant.

Gastro-oesophageal reflux disease (GORD)

There has been interest in the role of GORD in ear disease but only anecdotal evidence exists that there may be a relationship between GORD and COM.[111] A systematic review concluded that there may be a higher prevalence of GORD in children with OME and recurrent AOM and that the presence of pepsin or pepsinogen in the middle ear could be related to physiologic reflux, although a cause and effect relationship was unclear.[112]

Craniofacial abnormalities

The incidence of COM in cleft palate patients followed up to 10 years of age is around 20%, with 2% of them having a cholesteatoma.[113] The tensor veli palatini muscle is hypoplastic in cleft palate children and may predispose to Eustachian tube dysfunction.[114]

Autoimmune disease

It is not known if autoimmune disease predisposes to COM. In one study, however,[115] COM was present in 29% of consecutive patients with ankylosing spondylitis.

Immune deficiency

AIDS is associated with higher levels of COM compared to the human immunodeficiency virus (HIV)-negative population. This had been suggested[116] and was the subject of previous debate, although it was known that AIDS could present as aural polyps due to *Pneumocystis carinii* infection.[117] Higher-level evidence has been presented[118] in a case control study of children in Sub-Saharan Africa (Angola) which found a rate of active COM of 26% in HIV-positive children versus less than 4% in the HIV-negative group (with similar findings of dry tympanic membrane perforation rate of 9% versus 1% and bilateral hearing loss of >25 dB of 13% versus 1% in the HIV-positive versus HIV-negative groups). Antiretroviral treatment is associated with a lower prevalence of COM in HIV-infected individuals.[119]

FACTORS INFLUENCING ACTIVITY OF CHRONIC OTITIS MEDIA

Infection

The mucopus removed from ears with active COM is rarely sterile.[120] Microbiology cultures frequently yield multiple organisms and these vary depending on climate, patient population and whether antibiotics have or have

not been used recently. Studies therefore report different isolates in differing proportions. In a prospective study of patients whose active ears were swabbed and cultured in the clinic,[121] 64% cultured only aerobes, 32% both aerobes and anaerobes, and 5% had no growth. In those with aerobes (Table 83.3) most ears had several isolates with a mean of 2.5 different aerobes. None of the patients in this study had been treated with oral or topical antibiotics for the previous 4 weeks.

There is debate about whether the presence of a cholesteatoma influences microbiological findings. Some studies have shown no difference in the microbiological cultures between squamous epithelial disease and mucosal disease[121] whereas other studies have suggested that *Pseudomonas* is less common in squamous epithelial disease.[122] It seems obvious and logical to assume that the activity of the ear in COM would be caused by pathogenic organisms. However, cultures from almost 50% of patients with inactive COM yield an identical flora to that found in active COM.[120] Furthermore, although anaerobes can be isolated from 32% of ears, their elimination by metronidazole does not cause the ear to become inactive.[123] *Pseudomonas aeruginosa* is infrequently found in the normal ear and rarely initiates acute infection. *Pseudomonas* is ubiquitous in our physical environment and has a predilection for moist areas. It is thought to infect tissues first by adherence to epithelial cells by means of pili or fimbriae.[124] In common with *Pseudomonas* infections in other sites of the body, normal tissues usually resist such attachment, unless there is cellular injury such as in chronic lung disease in cystic fibrosis. This phenomenon of 'opportunistic adherence' may represent an important step in the pathogenesis of middle ear infections as it does in respiratory infections. Thus it could be argued that the bacteria in COM are secondary invaders with the mucosal inflammation caused by other factors.

Biofilms

Bacteria preferentially exist in complex, surface-attached organizations known as biofilms which confer advantages over their planktonic counterparts and express markedly different phenotypes. Biofilm bacteria have greater antimicrobial resistance and host defences and can best be thought of as 'self-assembling multicellular communities'. These biofilms are important in chronic infections. Studies to examine the presence of biofilms in active COM have shown a 60% biofilm incidence as opposed to 10% in the control, uninfected group.[125] Biofilms are more abundant in squamous OM,[126] where 82% of cholesteatoma ears were found to have biofilms as opposed to 42% of the mucosal COM and 9% of the control, normal middle ear (cochlear implant) group.

TABLE 83.3 Aerobic bacteria isolated from patients with active COM who had had no antibiotic therapy in the previous 4 weeks; *n* = 83 (from Sweeney et al.)[120]

Bacteria	Number of isolates	% ears
Proteus spp.	79	95
Staphylococcus aureus	33	40
Pseudomonas spp.	25	30
Coagulase-negative staphylococci	24	30
'Coliform' bacilli	21	25
Other*	23	28
Total	**205**	

* Other includes *Corynebacterium* spp., *Escherichia coli*, *Streptococcus faecalis*, *Streptococcus pyogenes*.

Upper respiratory tract infections

Although many patients report activity of COM with a URTI, this has not been examined scientifically. URTIs produce transient Eustachian tube dysfunction in healthy individuals[127] and, as the respiratory mucosa of the Eustachian tube continues into the middle ear, this may become infected, resulting in activity of the mucosa either primarily or secondary to bacterial superinfection.

AETIOLOGY OF CHRONIC MUCOSAL OTITIS MEDIA

It is generally believed that mucosal COM arises from an episode of AOM where, after rupturing, the tympanic membrane fails to heal. Before immunization was practical, COM resulting from a single infection of measles was common, and it has been shown that acute measles may cause severe necrotizing otitis media.[128] A permanent perforation of the pars tensa can also result from the insertion of a ventilation tube in the tympanic membrane, which fails to heal. Long-stay ventilation tubes (T tubes) increase the risk of this occurring over simple grommets, with a perforation resulting in 2.2% of children treated with grommets compared with 16.6% treated with T tubes. The relative risk of long-term ventilation versus simple grommets was 3.5 (CI 2.6, 4.9).[129]

If COM is a sequela of AOM, the predisposing factors of AOM and COM should be the same. If there is a small but tangible risk of the tympanic membrane failing to heal after an episode of AOM, the number of attacks of AOM would increase the risk of COM developing, the risk of perforation being cumulative with each acute infection. There is evidence that the number of siblings, the type of day care, sex, duration of breastfeeding, maternal socioeconomic class and prematurity are all independent factors in the development of AOM in the first year of life (Table 83.4)[130] It would seem reasonable to assume that these factors are likely to be associated with the development of COM and there is evidence of association of some of these factors with COM (see above).

AETIOLOGY OF CHRONIC SQUAMOUS EPITHELIAL OTITIS MEDIA (CHOLESTEATOMA)

There is general acceptance of the theory that OME predisposes to chronic retraction of the pars tensa or flaccida and that this subsequently progresses to cholesteatoma.

TABLE 83.4 Variables associated with the parental report of acute otitis media during the first year of life, when the preceding variables have been taken into account, with the respective odds ratio[130]

Variable		Odds ratio	95% confidence interval
Number of siblings	≥3 vs 0	2.5	1.9, 3.4
	1–2 vs 0	2.0	1.3, 2.9
	≥3 vs 1–2	1.3	1.0, 1.7
Type of day care outside home vs at home		1.6	1.4, 1.9
Male vs female		1.3	1.2, 1.5
Duration of breastfeeding (months)	<3 vs ≥9	1.5	1.2, 1.8
	3–5 vs ≥9	1.4	1.3, 1.6
	6–8 vs ≥9	1.3	1.1, 1.5
Maternal socioeconomic status	Class 3 vs class I	1.8	1.3, 3.1
	Class 2 vs class 1	1.7	1.2, 2.3
	Class 3 vs class 2	1.1	1.0, 1.2
Prematurity yes vs no		1.4	1.1, 1.8

In a retrospective study of almost 46 000 Australian children who had a ventilation tube (VT) insertion operation,[131] 460 children developed cholesteatoma. The cumulative percentage of children who developed cholesteatoma within 15 years after one VT was 0.9%, after two VTs it was 2.1%, after three VTs it was 3.8%, and after four or more VTs it had risen to 5.2%. The rate of developing cholesteatoma increased 10% for each additional year in age before the first VT. For children who underwent two or more VTs, the rate of cholesteatoma increased 21% with each additional year between VTs. Adenoid removal was associated with a 27% reduction in the rate of developing cholesteatoma. This study concluded that 'children with persistent or refractory middle ear disease who required multiple VTIs were at increased risk of cholesteatoma'. First VTs inserted at an early age, subsequent VTs inserted without delay, and adenoid removal were associated with a reduced rate of cholesteatoma development.

VTs are not a panacea for cholesteatoma prevention but their use by aerating the middle ear may play a part in the reduction of cholesteatoma rates, perhaps by preventing retraction. Even if this is the case, why some cases of retraction progress and others do not is uncertain. Several other factors in cholesteatoma genesis have been postulated including the following.

Squamous metaplasia

There has been long-standing debate over the aetiology of chronic squamous epithelial OM. One theory suggests that cells from which a cholesteatoma arise originate from metaplasia of the middle ear mucosa. Another theory suggests that a cholesteatoma arises from the skin of the tympanic membrane. Although squamous metaplasia of respiratory epithelium occurs in the lower respiratory tract, it is unlikely to be a source of middle ear cholesteatoma. The best evidence suggests that cholesteatoma arises from skin cells of the tympanic membrane. All cells contain a cytoskeleton made from filaments comprised of protein subunits. The cytokeratins are a family of these proteins found in epithelial cells and middle ear cholesteatoma has a cytokeratin pattern typical of skin and closely resembling skin of the external auditory meatus.[132] Cholesteatoma sacs are found in close proximity to the tympanic membrane and are not encapsulated but are connected to the tympanic membrane by a neck of invaginated squamous epithelium, and the tympanic membrane appears to follow progressive changes from normal to retraction pockets and then to cholesteatoma.[133] This inference in the progression to cholesteatoma comes from histological studies of temporal bones. A large cohort study is needed to identify if there is a real progression from normal to retraction pockets and then to cholesteatoma. This would require subjecting thousands of children to otoscopic examinations for many years, and until this study is attempted the question of whether retraction pockets form cholesteatomas is unanswered.

Misplaced epithelium

If cholesteatomas are derived from the skin of the tympanic membrane, there are various ways in which this skin might become trapped in the middle ear and mastoid. Cholesteatomas may form from retraction pockets, from papillary ingrowth through the tympanic membrane, from ingrowth of squamous epithelium through a perforation or from implantation of squamous epithelium in the middle ear.

Cholesteatomas are most likely to arise from a retraction pocket in the pars flaccida or the posterosuperior part of the pars tensa and the initiating factor is probably dysfunction of the Eustachian tube resulting in negative middle ear pressure. Because of their greater blood supply compared with the rest of the tympanic membrane, the pars flaccida and the posterosuperior quadrant of the pars tensa are more affected by inflammatory cell infiltration in AOM and in OME.[134] This may leave the fibrous

layer in these areas thinner than the fibrous layer in the remainder of the tympanic membrane. Further evidence that cholesteatomas arise from retraction pockets comes from the fact that retraction pockets are frequently found after surgical removal of a cholesteatoma and grafting of the tympanic membrane. Retraction pockets and cholesteatoma can also be induced in some experimental animals by electrocautery to the Eustachian tube orifice.[135]

Ingrowth of skin through a tympanic membrane perforation has been suggested as a cause of cholesteatomas. These 'perforations', however, are more likely to be the misdiagnosed opening of a retraction pocket. It is assumed that the retraction continues to grow and the sac fills with the desquamated cells leading to the accumulation of keratin and cholesteatoma formation.

It is the case, however, that retraction pockets are common whereas cholesteatomas are uncommon. There are factors in the development of cholesteatoma other than just Eustachian tube dysfunction. Ruedi[136] suggested that papillary ingrowth of squamous epithelium through its own basement membrane in the pars flaccida could result in a cholesteatoma. Inflammation in the middle ear in addition to retraction pocket formation is likely to be an important factor and the retraction pocket formation and papillary ingrowth of squamous epithelium may coexist as a mechanism for the aetiology of cholesteatoma.[137]

In cholesteatoma, as in a normal wound, there is hyperproliferation and migration of the epithelium but, unlike the situation in a wound, this growth pattern persists.[138] It may be that the area of maximum growth is found in the neck of the cholesteatoma sac.[139]

Cholesteatomas may result from implantation of squamous epithelium into the middle ear. This could occur as a result of trauma to the tympanic membrane, either through injury or by surgery. Although likely to exist as a mechanism for their development, it could only account for a small proportion of cholesteatomas.

DIAGNOSIS AND ASSESSMENT

Iain R.C. Swan

INTRODUCTION

Examination of the ear with a microscope is the 'gold standard' for the diagnosis of COM although to reach an acceptable standard requires training, aided by operative experience exploring ears that have previously been otoscopically assessed. History taking and investigations are an aid to management rather than to diagnosis.

OTOSCOPY

Whenever there is a suggestion of COM, otoscopy is improved by using a microscope and appropriate aural speculum. This also greatly facilitates aural toilet, which is almost always required to fully visualize all areas. Such toilet can be any combination of suction, irrigation, mopping or instrumental removal (see Chapter 73, Clinical examination of the ears and hearing).

An otoscopic camera linked to a monitor gives a good overall view of anatomy and pathology that is particularly applicable if there is an open mastoid cavity. It is also helpful in viewing the anterior recess of the tympanic membrane, which is often blocked from view by the anterior canal bulge. A camera is extremely useful for teaching and to explain disease to the patient.

After any aural toilet, the clinician has to assess all areas of the external ear and the tympanic membrane to decide if there is pathology and if so what the pathology is (see **Table 83.1**). Before illustrating examples of various pathologies in different areas, some aspects that are generally applicable are discussed.

OPERATION SCARS

Prior to otoscopy, operation scars should be looked for. Endaural scars (see **Figure 73.2** in Chapter 73, Clinical examination of the ears and hearing) can be difficult to detect but suggest previous middle ear surgery which may have included canal wall-down mastoid surgery. Postauricular scars (see **Figure 73.3** in Chapter 73, Clinical examination of the ears and hearing) suggest previous surgery requiring access to the middle ear or mastoid singly or in combination.

SITE OF PATHOLOGY

Anatomically the pars tensa can be divided into four quadrants (**Figure 83.9**) but pathology, such as perforations, tends to be anterior, posterior or inferior (**Figure 83.10**). Hence, division into thirds rather than quarters is preferred. To record the proportion of the pars tensa involved by a specific condition, percentages are preferred to non-defined terms such as small, large and subtotal. By definition, all perforations of the pars tensa are 'central', indicative of 'tubotympanic disease'. The pars flaccida in the attic has to be cleared of any debris and assessed for pathology which may occur alone or along with pars tensa disease. By definition, all attic disease is 'atticoantral' and 'marginal'. The attribution of the term 'marginal' goes along with the absence of an annulus, which is not normally present in the attic/pars flaccida. If the term 'marginal' is applied to pars tensa pathology, its interpretation becomes confusing and should be avoided. The annulus is almost invariably present in pars tensa perforations unless it has been previously removed surgically.

OPEN MASTOID CAVITIES

These are usually created surgically but can occur spontaneously by the natural resolution of attic cholesteatoma, albeit the resultant cavity is usually small and confined to the atticoantral region (**Figure 83.11**). Open mastoid cavities can be difficult to detect if there is a narrow external auditory meatus or the cavity is not in continuity with the attic/antrum (**Figure 83.12**). If an ear has been operated on, and in particular if there is a postauricular scar, the

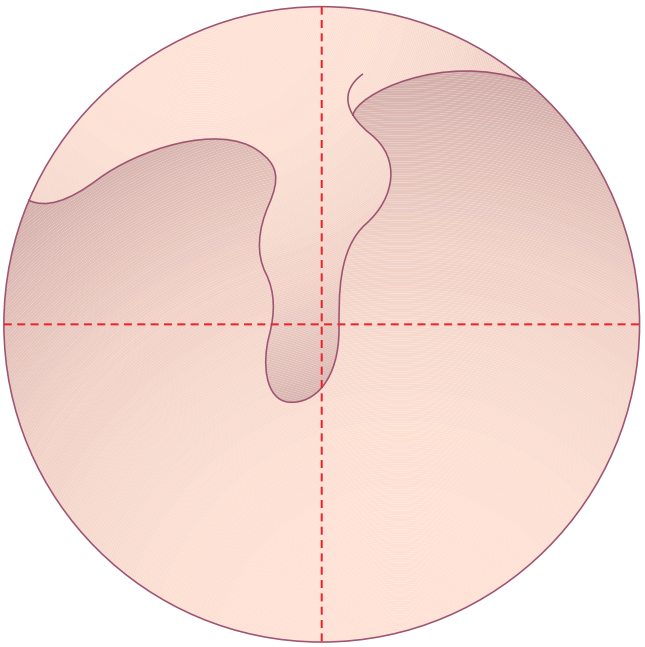


Figure 83.9 The four quadrants of the pars tensa (right ear).

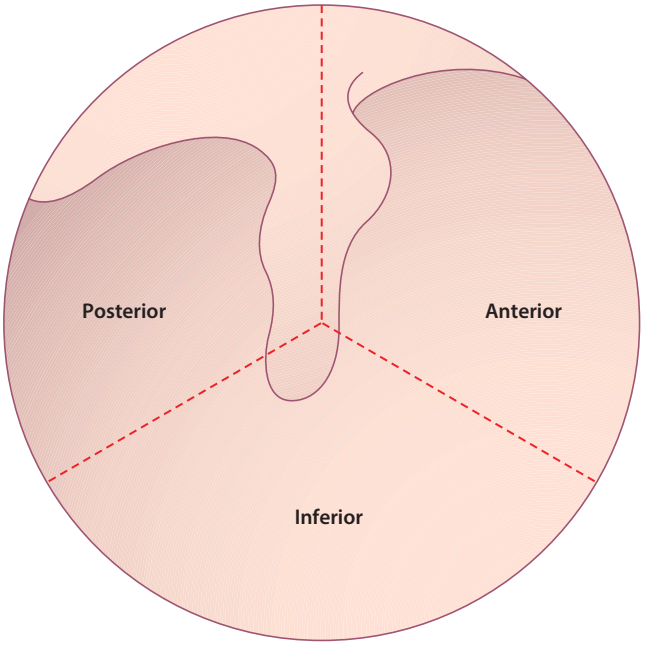


Figure 83.10 The three thirds of the pars tensa (right ear).

posterosuperior canal wall should always be closely examined. Sometimes, because of a narrow external auditory meatus or a high, residual posterior canal wall, an open cavity cannot be fully viewed.

ACTIVE OR INACTIVE?

A decision as to whether an ear is currently active, i.e. inflamed with the production of inflammatory products including pus, is primarily based on visualization of an inflamed mucosa and secretions. In squamous epithelial disease that is active with a cholesteatoma, there is almost invariably associated

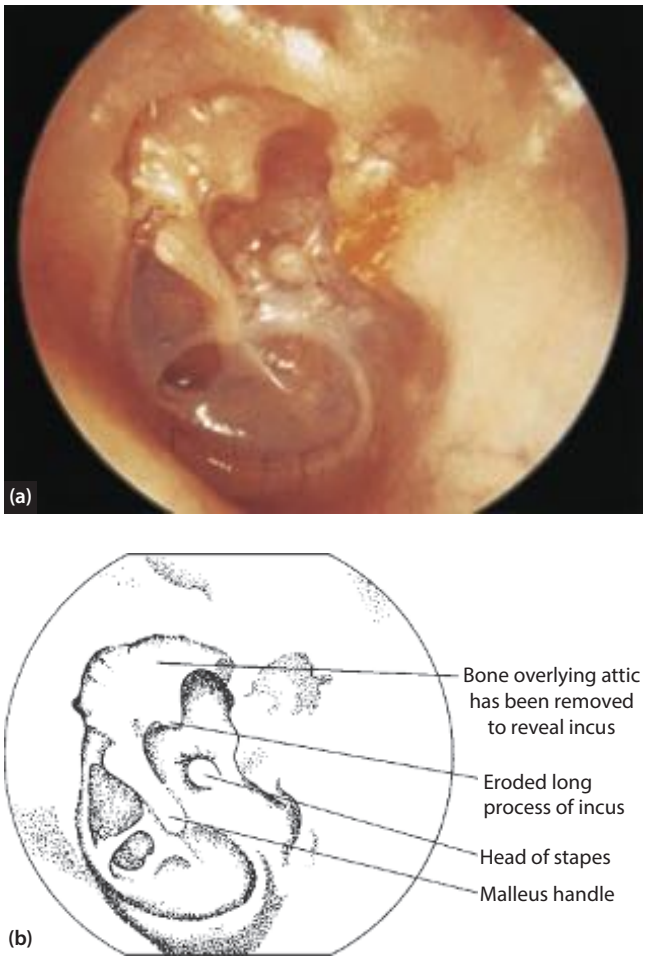


Figure 83.11 Left atticotomy. The attic has been exposed by drilling and is lined by a dry retraction pocket, part of which is out of vision. The malleus handle and body are present, as is the body of the incus. The long process of the incus has been eroded. The pars tensa is intact but retracted onto the head of the stapes.

mucosal disease that can be seen and produces the secretions, perhaps along with squamous epithelial debris. Secretions, and in particular mucopus, can dry and be mistaken for wax. Once removed, the underlying disease may still be active or have become inactive (Figures 83.13 and 83.14).

OTOSCOPIC DIAGNOSTIC CATEGORIES

In an ear with COM that has not previously been operated upon, it should be possible otoscopically to put the ear into one of four diagnostic categories (see Table 83.1).

Healed otitis media

This term is given to an ear where the pars tensa is intact but abnormal. Such a diagnosis can be, and often is, in association with other middle ear conditions such as OME. The most common abnormality of the pars tensa is chalk patches/tympanosclerotic plaques, there being no



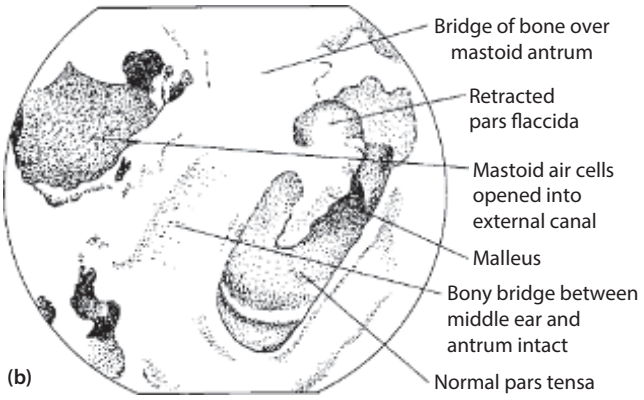


Figure 83.12 Right inactive modified (Heath) mastoidectomy. The pars tensa is normal. The pars flaccida is retracted but inactive. Posteriorly, the mastoid air cells have been surgically opened into the external canal by partial removal of the posterior canal wall. The bridge of bone over the incudal fossa and the mastoid antrum is normally removed in a modified radical mastoidectomy (and in an attico-antrostomy). It has not been removed in this case. There is no evidence of activity.

clear distinction between these two terms (Figure 73.17 in Chapter 73, Clinical examination of the ears and hearing; and Figure 83.15). The other abnormality covered by the definition of healed otitis media is thin replacement membranes, usually circular in outline and suggestive of an old perforation that has healed without the middle, fibrous tissue layer (Figure 83.16). When there is uncertainty as to whether such an area is a perforation or not (Figure 83.17), pneumatic otoscopy can be of value, or the patient can be asked to perform a Valsalva manoeuvre. Replacement membranes may be slightly retracted (Figure 83.18), when the additional diagnosis of OM with effusion should be considered. The distinction between these localized and more generalized, posterior marginal retractions is discussed below.

Inactive (mucosal) COM

This diagnosis implies a permanent perforation of the pars tensa and that the middle ear mucosa, as seen through the perforation, is inactive (Figures 83.19, 83.20 and 83.21).



Figure 83.13 Left active COM. Pars flaccida obscured by pus. The pars tensa is normal.



Figure 83.14 Same ear as Figure 83.13 after aural toilet. Active COM clearly visible affecting pars flaccida in the attic. The white debris is squamous epithelial debris, indicative of cholesteatoma.

Active (mucosal) COM

Activity is evident, usually with a generally inflamed middle ear mucosa, but sometimes with granulation tissue that is localized (Figure 83.22) and which can become polypoidal (Figure 83.23).

In both active and inactive COM, particularly when the defect involves the posterior third, the intactness or otherwise of the ossicular chain should be assessed and recorded (Figures 83.21, 83.24 and 83.25). Surgical classifications for these have been proposed but most prefer to record what the defects are, if any.

Inactive (squamous) retractions

These can occur in the pars tensa or the pars flaccida. Pars tensa retractions are primarily of the posterior tympanic membrane, the classification most used to document their



Figure 83.15 Tympanosclerotic plaques, one anterior, one posterior (right ear).

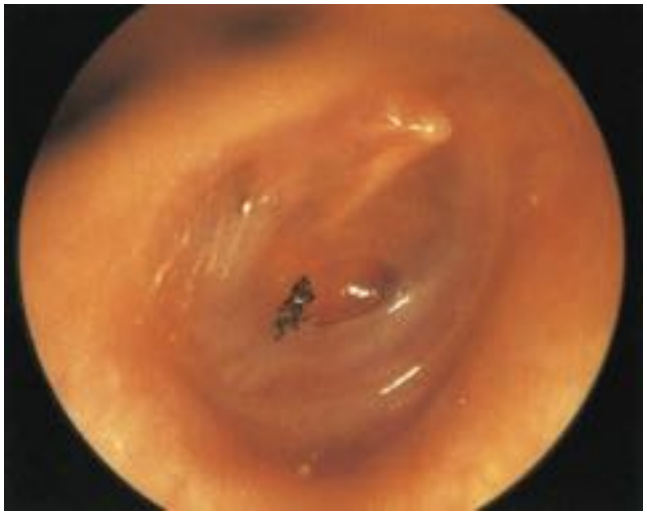


Figure 83.16 Healed otitis media (right). In this ear there is a thin replacement membrane over what is presumed to be an old inferior perforation.



Figure 83.19 Inactive left COM. There is anterior inferior pars tensa defect through which the middle ear mucosa can be seen to be normal, i.e. not inflamed.



Figure 83.17 Scarred pars tensa associated with left healed otitis media.



Figure 83.18 Localized retraction of pars tensa affecting central area (right ear).



Figure 83.20 Inactive (mucosal) chronic otitis media, right ear.



Figure 83.21 Not eroded long process of incus in inactive (mucosal) COM (right ear).



Figure 83.23 Left active mucosal COM. There is pus and debris on the canal wall. The tympanic membrane cannot be fully visualized but there appears to be an inferior defect. The main finding is a polyp protruding through the perforation and granulation tissue on the remaining tympanic membrane.



Figure 83.22 Left active mucosal COM. There is pus on the canal wall. The middle ear mucosa, seen through a 60% inferior pars tensa perforation, is minimally inflamed. The activity is mainly from granulation tissue on the edge of the perforation (arrowed).



Figure 83.24 Posteroinferior perforation in inactive (mucosal) COM (right ear).

degree being that of Sadé and Berco.[140] In essence, what requires to be recorded is what structures the pars tensa is retracted onto and whether the pars tensa is adherent to them. Most important is whether the retraction is totally in view or whether there are areas out of view that might not be self-cleansing and have the potential to become active with a cholesteatoma (Figures 83.26, 83.27, 83.28, and 83.29).

Pars flaccida retractions have been diagrammatically classified into four stages by Tos et al.[141] (Figure 83.30). In stage 1, the pars flaccida is dimpled and more retracted than normal but not adherent to the malleus (Figure 83.31). In stage 2, the retraction is adherent to the neck of the malleus and the full extent of the retraction can be seen (Figure 83.32). In stage 3, part of the retraction is out of view and there may be partial erosion of the bony attic wall (Figure 83.33). In stage 4, there is definite erosion of the attic wall with the full extent of the retraction being uncertain because it is out of view (Figure 83.34). Tos's classification is relatively simple to apply, the only difficulty being making a distinction between stages 3 and 4. Hence, these are often grouped together as stage 3/4.

Cholesteatoma (active squamous disease)

Cholesteatomas are the end stage of (squamous epithelial) retractions of the pars tensa (Figure 83.35) or flaccida (Figure 83.33) that are not self-cleansing, retain epithelial debris and often elicit a secondary, inflammatory mucosal reaction. In the majority of cases the extent of the cholesteatoma cannot be determined otoscopically because the retraction pocket containing the debris is not fully in view.



Figure 83.25 Active left mucosal COM. In this ear the stapes is seen through the perforation. The long process of the incus has been eroded.



Figure 83.26 Stage 1: pars tensa retracted. There is no middle ear fluid (left ear).



Figure 83.27 Stage 2: Pars tensa severely retracted. The tympanic membrane is in contact with the long process of incus (left ear).



Figure 83.28 Stage 3: Posterior retraction of tympanic membrane onto promontory. Ossicular chain intact. Small anterior chalk patch (right ear).



Figure 83.29 Stage 4: Adhesive otitis. the pars tensa is adherent to the promontory and draped around the long process of the incus and stapes (left ear).

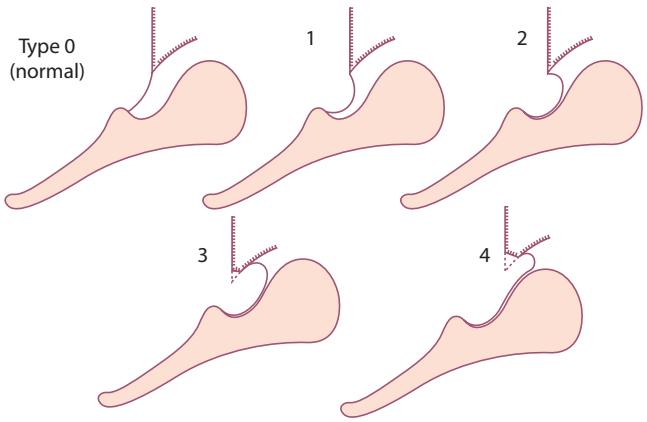


Figure 83.30 Staging of attic retraction. Redrawn with permission from Tos et al.[141] © 1987, American Medical Association. All rights reserved.

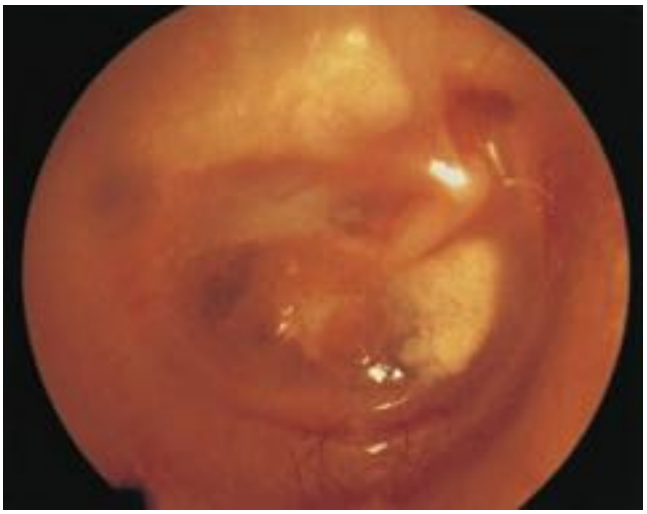


Figure 83.31 Stage 1 retraction of pars flaccida. Simple attic dimple. Coincident anterior tympanosclerotic patch of pars tensa (right ear).



Figure 83.32 Stage 2 retraction of pars flaccida. Retraction adherent to neck of malleus (right ear).



Figure 83.33 Stage 3 retraction of pars flaccida. Part of retraction out of view. Suggestion of middle ear fluid (right ear).



Figure 83.34 Stage 4 retraction of pars flaccida. Erosion of bony attic wall and part of retraction out of view. No activity (right ear).



Figure 83.35 Posterior atelectactic pars tensa with erosion of posterior canal wall, as well as long process of incus and stapes superstructure. Prominent granulations on posterior canal wall suggestive of progressive cholesteatoma (left ear).

HISTORY

As COM will be diagnosed in the majority of cases by otoscopy, history taking should focus on symptoms and previous management. This allows future management and potential outcomes to be discussed more appropriately. An exception to this attitude is when there is a history of peripheral type vertigo. If present, this merits more detailed assessment (see 'Labyrinthine complications' below).

The majority of adults (~80%) presenting with COM report a hearing impairment and approximately 70% an ear discharge (Table 83.5).[142] Even in those with currently active COM, only around 75% will report a current discharge and there is no difference in this report whether a cholesteatoma is present or not. There also is no apparent difference in the smell associated with cholesteatoma compared with active mucosal disease.[143]

TABLE 83.5 Symptoms of active COM, broken down into mucosal disease and cholesteatoma (squamous disease)

Symptom	Percentage	
	Active mucosal	Cholesteatoma
Hearing loss	74	83
Otorrhoea	69	56
Otalgia	37	39
Childhood ear disease	26	43

Reprinted from Sheahan et al.,[142] with permission.

Enquiry will be made as to any previous surgery and about recent topical aural medications and how effectively they were used.

AUDIOLOGY

Pure-tone audiometry, air and bone conduction with appropriate masking will provide numerical values to the degree of hearing impairment, the magnitude of the air–bone gap and whether there is an associated sensorineural impairment for each of the two ears. Such information is important to inform decisions regarding management.

ADDITIONAL INVESTIGATIONS

Additional investigations are only relevant if they modify, to a material extent, decisions that have been previously made based on otoscopy, history and pure-tone audiometry.

Vestibular assessment

Vestibular assessment will be performed on those with episodes of peripheral-type vertigo and some patients undergoing revision surgery. A fistula test, if positive with the production of acute vertigo accompanied by nystagmus, is suggestive of a semicircular canal fistula created by a cholesteatoma or previous mastoid surgery. A negative fistula test does not exclude such conditions. Caloric testing to determine whether there is residual vestibular function after previous surgery can be helpful in determining which surgical procedures are applicable.

Imaging

High-resolution computed tomography (CT) scanning in both the coronal and axial planes of the temporal bone is recommended in the pre-operative evaluation of cholesteatoma.[144] CT may help to assess the extent of disease in a partially aerated mastoid. However, cholesteatoma appears as a homogeneous mass with similar density to oedematous mucosa and to brain tissue. In the absence of aeration, the extent of disease is rarely visible, though it may be suggested by erosion of air cells. CT shows the pneumatization of the mastoid which may influence surgical approach and will demonstrate any anatomical variants. It may demonstrate erosion of the bony labyrinth, most commonly the lateral semicircular canal, the tegmen tympani, or of the facial canal, but cannot be relied upon to do so.[145]

Diffusion-weighted magnetic resonance imaging (DW-MRI) differentiates cholesteatoma and inflammatory tissue and brain. It has been shown to be reliable at detecting small residual or recurrent cholesteatoma after surgery, and at assessing the intracranial extension of cholesteatoma.[146] As DW-MRI becomes more widely used, it is likely to replace second-look operations in some patients after intact canal wall mastoid surgery.

Endoscopy

The endoscope is sometimes useful in the outpatient clinic. It may allow assessment of the extent of a retraction pocket in a patient who is not particularly fit for surgery. It may help to visualize the middle ear in patients with very narrow ear canals.

Bacteriology

Bacteriological and fungal cultures are of potential value only when the ear is active or if there are infective complications. If systemic antibiotic therapy is being contemplated, culture of any secretions with antibiotic sensitivity pattern of any growths being assessed can be of value in deciding which antibiotic to prescribe as most do not cover the full range of bacteria that can be isolated as potential pathogens from the ear. The same could be said for topical antibiotic therapy although, if gentamicin or ciprofloxacin is chosen, their spectrum is broad enough to cover most probabilities.

NATURAL HISTORY, MANAGEMENT AND OUTCOMES

Iain R.C. Swan

INACTIVE MUCOSAL CHRONIC OTITIS MEDIA

Natural history

Inactive mucosal COM (see **Figure 83.19**) is the condition of the middle ear where the structure and often the hearing are impaired by the presence of a permanent tympanic membrane defect, but in which there is no active infection or mucoid discharge. Such an ear may remain inactive, become active or even occasionally heal.

PROGRESSION TOWARDS HEALING

The progression towards healing is presumably impaired by the disease that resulted in COM in the first place. This is usually recurrent episodes of acute infection with

perforation of the tympanic membrane, which initially heals successfully within a few days, but after a variable number of attacks the tympanic membrane fails to heal. This is regarded as a result of failure of the blood supply to the perforation edges due to endarteritis, but there may be other factors related to repair mechanisms at cellular level. If for any reason the blood supply improves, this may tip the balance in favour of healing. There are no data on the probability of this occurring but observation and experience suggest that natural healing is a relatively rare event in adults though it appears to occur more often in children. Lehmann et al.[147] reported a significant reduction in the prevalence of tympanic membrane perforations in Aboriginal children due to improved hygiene after the opening of a community swimming pool. It is probable that closure will only occur following a period of disease inactivity and this is the goal of medical therapy in mucosal disease and indeed the goal of surgical treatment is to achieve a healed state.

PROGRESSION TOWARDS ACTIVITY

Progression towards activity is more common, theoretically provoked by factors such as a URTI or the ingress of water, particularly if contaminated by bacteria or irritants. The diverse flora occurring in active ears and the fact that the bacterial flora are similar in mucosal and squamous epithelial disease suggest that bacterial contamination is not the primary event in most cases.[121] It is the increased mucus production that provides the culture medium for opportunist organisms to flourish. The fact that the same organisms may be isolated from inactive as from active ears in 50% of cases would also support this contention.[120] Traditional concepts about the role of sinonasal disease in the precipitation of activity in COM are not supported by convincing evidence.

Presentation

Inactive COM presents with a hearing impairment or may be an incidental finding in older patients with a mixed hearing impairment. Some patients present because of discomfort in the ear during swimming when water gets into the middle ear. A careful history of discharge should be sought. If the only history of discharge is many years previously, this may not influence management. However, many patients have more recent episodes of discharge and this does influence management.

Examination

Pure-tone audiometry assesses the magnitude of the conductive hearing impairment due to the disease. The degree of air–bone gap depends on:[148]

- the size of the perforation in the tympanic membrane
- erosion of the ossicular chain, most commonly the long process of the incus and sometimes also the stapes superstructure
- significant granulation tissue around the ossicular chain which can reduce its mobility
- tympanosclerosis around the ossicular chain.

If surgery is contemplated, microscopic examination is important as this may give some information about the state of the ossicular chain.

Management

Management options are surgery, a hearing aid or no treatment. Hearing aids should always be considered in the management of hearing disability (see 'Hearing aids in chronic otitis media' below).

OBJECTIVES OF SURGERY

The aim of middle ear surgery for hearing is reduction in the patient's hearing disability, not just closure of the air–bone gap. Hearing disability is largely dependent on the hearing in the better-hearing ear, therefore the hearing thresholds in the non-operated ear need to be taken into account when considering the likely benefit to the patient from reconstructive surgery. If successful closure of the air–bone gap still leaves the patient with significantly poorer hearing in the operated ear, then benefit from successful surgery is dubious. The objectives of any surgery should be carefully considered. Dry perforations that are symptom-free do not usually require closure. If the only symptom is a hearing impairment, the chances of improving hearing with surgery should be considered carefully, not just the hearing in the operated ear but the overall hearing ability of the patient. In patients with a history of intermittent activity, surgery to close the perforation is probably indicated to minimize future activity. Those patients whose main symptom is discomfort when swimming should be encouraged to wear ear plugs. These are usually extremely effective at preventing discomfort and are a simpler and safer option than surgery.

MYRINGOPLASTY

Tympanoplasty refers to any operation involving reconstruction of the tympanic membrane and/or the ossicular chain. Myringoplasty is a tympanoplasty without ossicular reconstruction. Over the years many methods have been used for closing perforations. The most widely used and accepted method is underlay graft of temporalis fascia or sometimes perichondrium. Cartilage has become increasingly popular as a graft material, particularly when the tympanic membrane is retracted (see discussion of myringoplasty in 'Inactive squamous chronic otitis media' below). The basic procedure is to excise the rim of the perforation so that there is a raw surface from which new tissue will grow. The mucosa on the undersurface of the remaining tympanic membrane near to the perforation is removed or scraped with a sickle knife or similar instrument to provide a bed for the graft. This is then placed under the tympanic membrane remnant and acts as a scaffold for new growth of the squamous epithelial layer. The mucosa over the promontory should be carefully preserved to reduce the likelihood of post-operative adhesions between the graft and the promontory.

Outcomes: tympanic membrane take rate

The success rate in achieving an intact tympanic membrane in expert hands is often quoted as around 95%. However, when results of large numbers of operations in the hands of many surgeons are reported, the success rate is much lower (**Table 83.6**). Palva and Ramsay[149] looked at the outcome of 281 myringoplasties in their department. The closure rate in Palva's hands was 97%, while in the hands of other members of the department it was only 74%. Similarly, Vartiainen[150] reported that the successful tympanic membrane closure rate for trainees was 78% compared to 95% for the senior staff. Successful outcome seems to be significantly influenced by the expertise of the surgeon. Many reports of results are based on relatively short follow-up of 6–12 months. However, longer-term follow-up suggests that some ears which are initially intact develop recurrent perforation.[151]

The closure rate is reported to be higher in small perforations (74%) than large perforations (56%).[154] Numerous authors have reported that the failure rate in anterior perforations is higher. However, this failure rate can be greatly reduced by anchoring the anterior margin of the graft beneath the annulus.[156]

There is no evidence that prophylactic antibiotics influence closure rate or other outcomes. A Cochrane review found 11 randomized trials of prophylactic antibiotics in middle ear surgery. None of these trials reported significant difference in outcomes between the prophylactic antibiotic and control groups.

Revision surgery can be considered in those ears where the graft fails. The possible reasons for failure should be considered and, if necessary, the surgical method can be modified. Halik and Smyth[151] found that only 60% of tympanic membranes were intact after revision surgery, which is a much lower success rate than usually claimed for primary surgery.

Outcomes: hearing

Successful closure of the tympanic membrane usually gives only a small improvement in hearing (Table 83.7).

It is uncommon to get total closure of the air–bone gap in myringoplasty, as closure of a tympanic membrane perforation does not make the ear a normal ear. In those patients in whom the air–bone gap is 35 dB or more, there will be either erosion or fixation of the ossicular chain.[148] Here, surgery would require myringoplasty and ossiculoplasty (see below).

TABLE 83.6 Successful closure rate in myringoplasty

Reference	No. of cases	Closure rate (%)
Kotecha et al.[152]	1070	82
Wielinga et al.[153]	555	88
Lee et al.[154]	423	64
Black and Wormald[155]	211	78

Complications

The complication rate in myringoplasty is low in all series. Kotecha et al.[152] reported one facial nerve palsy in 1070 patients and one extradural abscess.

OSSICULOPLASTY

The most common pathology in the middle ear is erosion of the long process incus. This is reasonably straightforward to correct surgically. The preferred option is to place a prosthesis between the handle of malleus and the head of stapes. Various materials are used, most commonly autograft incus or head of malleus and alloplastic prostheses. When the stapes superstructure is also missing, the malleus handle has to be connected to the stapes footplate and autograft materials are rarely suitable. Occasionally there is also erosion of the malleus handle; here the prosthesis connects the tympanic membrane directly to the stapes superstructure or footplate. The choice of material is largely dependent on the situation in the operated ear and the surgeon's personal preferences. Homograft materials are not recommended because of the theoretical risk of transferring prion disease.

Outcomes

There are many reports in the literature of the outcome of ossiculoplasty. Iurato et al.[157] reviewed 20 published reports of the results of ossiculoplasty when the malleus and stapes superstructure were present. In expert hands, a post-operative air–bone gap of 0–10 dB is achieved in only 50% of patients while 80% have an air–bone gap of 0–20 dB. Iurato found no reported difference in hearing outcome between different types of prosthesis.

When there is erosion of the stapes superstructure as well, the success rates of surgery are generally lower. Mills[158] reported a mean hearing improvement after ossiculoplasty of 14 dB when the stapes arch was intact and 6 dB when it was eroded. Shinohara et al.[159] reported 68% 'success' rates at 1 year with partial ossicular replacement prostheses where only the incus needs to be replaced. This compares with 46% for total ossicular replacement prostheses where the incus and the stapes superstructure are absent, though 'success' was not defined.

Most authors report the results of surgery after 3–12 months. Those who look at long-term results report that success rates are lower: at 5-year follow-up, Shinohara's 'success' rates had fallen to 60% (from 68% at 1 year) and 34% (from 46%).[159]

Myringoplasty and ossiculoplasty can be carried out as a one- or two-stage operation. It is generally accepted that the success rate of ossiculoplasty is higher if the procedure is staged, but this is to be expected as only those ears that have a closed aerated middle ear are chosen for the second-stage procedure. Staging does require two separate operations, and most surgeons would carry out a one-stage procedure if it seemed feasible in that particular ear. It would seem much more efficient to attempt a one-stage procedure and revise it if it fails.

TABLE 83.7 Hearing after successful myringoplasty

Reference	No. of cases	Mean hearing improvement (dB)	Residual air–bone gap (dB)
Lee et al.[154]	261	8.1	–
Palva and Ramsay[149]	281	8.0	9.3

TYMPANOSCLEROSIS AND SURGERY

Tympanosclerosis is found in the middle ear in around 25% of ears at surgery. In some cases, the mobility of the ossicular chain is reduced by tympanosclerosis in the attic or in the oval window. If the ossicular chain is intact and only the incus and head of malleus are fixed, this can be corrected by removing the incus and head of malleus and reconstructing the ossicular chain between handle of malleus or tympanic membrane and stapes. Alternatively, the outer attic wall can be removed and the malleus and incus mobilized. This is often effective in the short term, but there is a tendency for refixation of the ossicles by fibrous tissue or bone.

When the stapes is involved, surgery involves mobilization of the stapes or stapedectomy. Results of stapes surgery in tympanosclerosis are not as good as in otosclerosis with a post-operative air–bone gap of 20 dB or less reported in only 72% (111 of 154 operations)[160] and 70% of cases (45 of 64 operations).[161] The complications of surgery, such as dead ear, are reported to be more common; Albu et al.[162] reported a 4% (1 of 25) and Gormley[163] a 5% (3 of 67) incidence of post-operative sensorineural loss.

THE EUSTACHIAN TUBE AND SURGERY

An aerated middle ear is necessary for middle ear function. Sometimes reconstructive middle ear surgery that appears technically successful at the time of surgery subsequently has a poor outcome because of non-aeration of the middle ear. A functioning Eustachian tube is necessary for an aerated middle ear. Assessment of Eustachian tube function pre-operatively is a poor predictor of the successful closure of the tympanic membrane.[164] If the contralateral ear is atelectatic, suggesting poor Eustachian tube function, it is unlikely that the Eustachian tube will function in the operated ear.

New methods of improving Eustachian tube function have been tried in recent years. In laser tuboplasty, soft tissue in the wall of the Eustachian cushion is ablated. Kujawski and Poe reported improved tubal function in 65% of patients,[165] but long-term outcomes are not yet known. In balloon Eustachian tuboplasty, a balloon catheter is inserted into the tubal ostium and inflated for 2 minutes. Sudhoff et al. reported that 87% of 351 patients were satisfied with the improvement in tubal function after 12 months;[166] long-term results are awaited. In actively inflamed ears, it is possible for Eustachian tube function to improve when the middle ear mucosa reverts to a more normal state after closure of the tympanic membrane. It may sometimes be worthwhile inserting a VT in the tympanic membrane, or in the graft, as a temporary method of improving aeration, hoping that the function of the Eustachian tube will improve.

KEY POINTS

- The degree of hearing impairment depends on the size of the perforation and the state of the ossicular chain.
- Myringoplasty closes perforations in 64–95% of cases, depending on the experience of the surgeon.
- As the hearing improvement from ossiculoplasty when the malleus and stapes are present is only 14 dB, hearing aids should always be considered in management.

ACTIVE MUCOSAL CHRONIC OTITIS MEDIA

Natural history

Active mucosal COM (see **Figure 83.25**) may remain active, become inactive or progress to complications. Continuing activity may be the result of infection with a particularly virulent or persistent organism, commonly *Pseudomonas*. Impaired immunity plays a role in some groups of patients such as diabetics but the increased incidence of active COM in deprived communities in the developed world (see 'Aetiology of chronic otitis media in general' above) suggests that nutritional and environmental factors including hygiene play a part in predisposing individuals to COM.[147]

PROGRESSION WITH CONTINUING ACTIVITY

Continuing activity of COM is likely to result in increasing damage to the ossicular chain and potentially to the inner ear. The former is common but the latter seems to be relatively rare. The precise incidence of ossicular damage in COM is unknown but if there is significant ossicular involvement a substantial deterioration in hearing results. The otorrhoea, particularly with multiple infecting organisms,[167] may be a factor relevant to more rapid deterioration. The inflammatory reaction in the middle ear associated with granulation tissue is agreed to be the most likely factor for ossicular damage occurring. The non-specific changes in bone associated with the inflammatory reaction include osteoclastic and osteoblastic activity which results in the resorption and remodelling of bone. Frequently, permanent damage to the most finely constructed parts of the chain occurs, mainly to the incus long process and the stapes superstructure where there is abundant osteoclastic activity but osteoblastic influences appear weak. The same process may play a part in the development of a sclerotic mastoid in COM where osteoblastic activity predominates.

HEARING IN ACTIVE MUCOSAL COM

One of the cardinal symptoms of COM is hearing loss and usually this is conductive in type although sensorineural loss may occur (see 'Sensorineural hearing loss' below). In the early stages of disease, conductive hearing impairment occurs in most cases but this is usually mild and often only causes significant handicap if disease is bilateral. As the disease process advances only slowly, the patient appears to adapt to the loss so that thresholds of 30–40 dB HL are common with little complaint from the patient. In mucosal disease, the size of the perforation in the pars tensa is relevant to the hearing loss but other important factors such as the presence of granulation tissue, mucus, adhesions and tympanosclerosis are also of importance in determining the hearing level. If the ossicular chain loses continuity, there may be a substantial increase in hearing impairment with thresholds increasing up to 50–60 dB HL in such cases. In bilateral disease this constitutes a significant handicap and hearing rehabilitation including reconstructive surgery may be a priority for the patient.

Presentation

The two main symptoms of active mucosal COM are otorrhoea and hearing impairment. The discharge varies in quantity and character. It may be continuous or intermittent, mucoid or purulent. In patients with intermittent otorrhoea, an increase in discharge may follow a URTI or entry of contaminated water into the middle ear, most commonly when swimming. However, many patients present with hearing difficulty as their only symptom. Though they have active mucosal COM, they are unaware of otorrhoea as the quantity is insufficient to appear at the external auditory meatus. The small amounts of discharge dry up at the medial end of the external auditory canal and form crusts. These crusts are sometimes mistaken for wax by inexperienced otoscopists. The hearing impairment is conductive, though older people may present primarily with age-related sensorineural hearing impairment but have an additional unilateral conductive component. On questioning, these patients will often report that they had otorrhoea when they were younger.

Examination

The hearing should be assessed by pure-tone audiometry. As potentially ototoxic agents are commonly used in the management of active mucosal COM, it is important to record the hearing before treatment. There is usually associated hearing impairment which is mainly conductive. Bacteriology is usually not necessary unless complications are suspected or initial antibiotic therapy fails to reduce the inflammation. *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the most commonly reported pathogens, most of the other organisms being Gram-negative coliforms (see 'Factors influencing activity of chronic otitis media' above).

Management

AURAL TOILET

The initial stage in management is thorough aural toilet. This is most effectively carried out with a microscope and suction which also allows accurate assessment of the extent of ear pathology. However, some clinicians use gentle syringing with saline or antiseptic agents. In the past, aural toilet was carried out with cotton wool on probes, but this is probably not as effective. It is, however, an effective way for the patient to clean his or her own ear between clinic visits prior to the insertion of topical medication.

TOPICAL MEDICATION

Numerous studies have been carried out over many years comparing various topical agents: antibiotics, steroids, antifungals and antiseptics. Topical antibiotics with steroids are significantly better than dry mopping alone,[168] dry mopping in combination with a topical saline solution[169] or topical aluminium acetate solution.[170] Topical antibiotics are more effective than oral.[171, 172] or intramuscular antibiotics.[173]

Gentamicin or neomycin, usually with hydrocortisone, has been the most popular topical agent for many years. More recent studies have compared topical quinolone antibiotics (ciprofloxacin or ofloxacin) with these more traditional agents. Miró et al.[174] compared topical ciprofloxacin with topical polymyxin B, neomycin and hydrocortisone suspension and found no significant difference in effectiveness (91% and 87%, respectively) in a study of 322 patients. Tong et al.[175] reported a significant difference in the effectiveness of topical ofloxacin (93%) compared with neomycin, polymyxin B and hydrocortisone (71%, $p = 0.04$) in a small study with 52 patients.

SUMMARY

Topical antibiotic therapy is the most effective means of treating active otorrhoea in COM. Topical aminoglycosides have been shown to be ototoxic in animals and can be ototoxic when administered parenterally in humans. There have been several anecdotal reports of possible ototoxicity from topical preparations in humans, though it is difficult to separate the effects of treatment from the effects of the disease. There is no conclusive evidence that topical aminoglycosides are ototoxic when used in treatment of COM.[32] The consensus view in the UK is that their use is acceptable but they should only be used in actively discharging ears and for a limited time.[176] The available evidence suggests that quinolones are at least as effective at reducing otorrhoea as aminoglycosides. As they do not appear to be ototoxic in animal experiments, quinolones may be preferable to aminoglycosides in active COM. An overview of the scientific literature on the management of active mucosal COM is provided by Cochrane reviews.[177, 178]

Though medical management is effective in reducing otorrhoea in most cases, it recurs in many patients. Recurrence of activity 4–6 weeks after completion of treatment was reported in 5%[174] and 43%[179] of patients.

SURGERY

In those cases that do not become inactive on medical management, surgery is required to heal the ear. Those cases that become inactive should have closure of the perforation (see 'Myringoplasty' above) to prevent recurrence of activity, together with ossiculoplasty if appropriate.

Myringoplasty

Though it is preferable to make active ears inactive before surgery, this is not always possible, and surgery should not be postponed because of this. Activity in the ear has been suggested as a cause of failure of tympanoplasty. However, Kotecha et al.[152] and Black and Wormald[155] found no influence of the condition of the ear at the time of surgery on the subsequent graft take rate. A Cochrane review found no evidence that the success rate of surgery is influenced by prophylactic antibiotic therapy.[180]

Role of adjuvant cortical mastoidectomy

Many authors suggest that a cortical mastoidectomy should be carried out at the same time as myringoplasty in active ears. Mishiro et al.[181] compared 104 ears treated by tympanoplasty alone with a previous group of 147 ears treated by tympanoplasty with mastoidectomy. There was no significant difference in tympanic membrane closure rates between groups (94% in tympanoplasty alone and 91% in tympanoplasty with mastoidectomy). Balyan et al.[182] reported 81 ears that were actively discharging at the time of surgery treated with tympanoplasty without mastoidectomy (53 ears) and tympanoplasty with mastoidectomy (28 ears). There was no significant difference in the graft success rates between these groups (91% and 86% respectively). Hall et al.[183] reviewed five studies comparing tympanoplasty with and without mastoidectomy and found no evidence that mastoidectomy increases the success rate of surgery in these ears.

AURAL POLYPS

In some cases, aural polyps are found protruding from the middle ear. In compliant patients, these can sometimes be removed or partially removed in the clinic with suction or perhaps small aural forceps using microscopic vision. It should be remembered that polyps can be attached to the stapes superstructure or to the facial nerve, and that damage to these structures can occur. Cauterization of polyps with silver nitrate on a stick may be helpful, though this should be done with care as damage to the facial nerve can occur. Both methods should be followed by topical treatment as outlined above.

In those with persistent otorrhoea and an aural polyp not managed in the outpatient clinic, the polyp should be removed. If this requires an anaesthetic, it would seem more efficient to perform the definitive surgery at the same time whenever possible, rather than simply removing the polyp and listing the patient for further surgery at a later date. Removal of polyps usually causes bleeding in the ear that interferes with surgical access, but this can be greatly reduced by the use of a laser in the removal of the polyp.

KEY POINTS

- In many patients with active mucosal COM, the only symptom is hearing impairment.
- Initial management is aural toilet and topical antibiotics with or without topical steroids.
- Quinolones are probably preferable to aminoglycosides because of the theoretical risk of ototoxicity, though there is no evidence that they are more effective.
- Definitive management is surgery, at least to close the perforation, but preferably to improve hearing as well.
- There is no evidence that prophylactic antibiotics influence the outcome of surgery.
- There is no evidence that the outcome of surgery is poorer in active ears.
- There is no evidence that concomitant mastoidectomy improves outcomes after tympanoplasty.

HEALED OTITIS MEDIA

Natural history

Healed otitis media (see **Figure 83.16**) may be the end result of episodes of AOM or OME. It may also be the end result of natural healing of ears with either mucosal or squamous COM. It is also the aim of surgery in most cases of COM irrespective of its type or activity.

PROGRESSION OF HEALED OTITIS MEDIA

The usual outcome in healed otitis media is a stable ear which does not accumulate debris and in which the hearing impairment does not increase. Such ears frequently have tympanosclerosis in the tympanic membrane that does not progress or result in any hearing impairment. In a few cases, tympanosclerosis affects the ossicular chain, particularly in the attic, and may result in a conductive impairment that is difficult to treat surgically. The incidence of and risk factors for tympanosclerosis have been studied by several authors. The incidence of tympanosclerosis in all cases of COM is estimated at 25%.[184] The incidence of attic tympanosclerosis fixing the ossicular chain is low and the factors which trigger this in otherwise currently healed ears is unknown. Tympanosclerosis of the pars tensa is reported to resolve in some cases, but this is not common.[185] It is generally thought that tympanosclerosis occurs less commonly in squamous epithelial disease and in active mucosal disease, but supporting evidence is lacking.

PROGRESSION TOWARDS ACTIVITY

Reperforation of the tympanic membrane may occur if there is a subsequent episode of AOM or minor trauma. The most likely causes for the latter are barotrauma and ear syringing but there is no evidence that defines the frequency of this occurring. Episodes of AOM are most likely to occur in children but may occur occasionally in adults, particularly if there is a predisposition to chronic ear disease. The tympanic membrane rarely heals normally. Although the

membrane may heal to a state of intactness, the supporting fibrous layer of the drum may be weakened or fail to regenerate, resulting in a thin scar at the site of the previous perforation or indeed the whole membrane may be thin and attenuated. If chronic Eustachian tube dysfunction persists, as it often will, the drum becomes retracted and may become draped over and adhere to the structures in the medial wall of the middle ear, a condition known as adhesive otitis media. This condition may be exacerbated or precipitated by inflammatory adhesions within the middle ear.

HEARING IN HEALED OTITIS MEDIA

The hearing in healed otitis media may be normal or there may be a mild conductive hearing impairment unless there is ossicular damage or fixation. There may also be an underlying sensorineural hearing impairment from any of the causes of this or specifically as a result of cochlear damage related to previous infection. Once the healed state has occurred, further increase in either conductive or sensorineural hearing impairment is unlikely but there is no evidence that looks at this issue specifically.

Presentation

Patients with healed otitis media may present with a hearing impairment. In elderly patients, it is commonly an incidental finding when they present with age-related hearing impairment. Some patients give a history of ear problems many years previously, often in childhood, but many do not recollect ever having had otorrhoea.

Examination

Diagnosis is made on otoscopy. As the only symptom is hearing impairment, the hearing thresholds in each ear must be assessed. Pure-tone audiometry determines the magnitude of the conductive hearing impairment. Many cases have a minimal air–bone gap, but in ears where there is fixation of the ossicular chain by tympanosclerosis or by adhesions in the middle ear, or erosion of the ossicular chain, most commonly of the long process of incus, the air–bone gap can be up to 60 dB.[148]

If there is a significant air–bone gap and surgery to improve the hearing is contemplated, careful microscopic examination of the ear should be carried out as this may give information about the extent of pathology, particularly tympanosclerosis, and the likelihood of reconstructive surgery being successful (see **Figure 83.7**).

Management

Management is only indicated in the presence of significant hearing disability and hearing aids should always be considered (see 'Hearing aids in chronic otitis media' below).

SURGERY

Many patients, particularly younger ones, prefer surgery, which will usually include ossiculoplasty. It should, however, be borne in mind that the success rates of surgery are limited. Successful surgery requires a well-aerated middle ear, but careful examination of the ear will usually give appropriate information about aeration. Significant adhesions in the middle ear limit the success of surgery as these frequently recur after surgery. Tympanosclerosis may also reduce the chances of successful surgery (see 'Inactive mucosal chronic otitis media' above).

KEY POINTS

- As hearing impairment is usually the sole symptom, hearing aids are often the optimal management option.

INACTIVE SQUAMOUS CHRONIC OTITIS MEDIA

Inactive squamous COM is defined as retraction of the pars tensa or pars flaccida with the potential to be active with retained debris (cholesteatoma). There may be associated damage to the ossicular chain and other middle ear structures. It is commonly referred to as 'tympanic retraction' or a 'retraction pocket'. Typical examples of inactive squamous COM in the pars tensa and pars flaccida can be seen in the section on 'Diagnosis and assessment' above (see **Figures 83.26–83.30**).

The majority of evidence is from personal case series that use a number of different classifications of retractions. Consequently, it is difficult to make meaningful comparisons between series. Furthermore, the retractions are frequently reported in case series in association with OME. The results of treatment for such retractions can be impossible to disentangle from the effects of treatment for the OME.

Examination

The ear should be carefully examined when a retraction is present and particular attention should be drawn to the following possible changes. Where possible, a clinical photograph should be obtained to enable comparisons to be made over time, because diagrams and staging systems, such as those developed by Sadé and Tos, have been shown to be unreliable.[186–188]

RETRACTION OF THE PARS FLACCIDA

Classify the retraction according to Tos. Can I see the fundus of the retraction pocket or not? Is this thought to be self-cleansing or not? Whether a retraction pocket is self-cleansing or not is a qualitative judgement based upon size and appearance. A small, clean retraction pocket in the pars flaccida or pars tensa is likely to be self-cleansing, but such judgements can only be confirmed over time by clinical review.

RETRACTION OF THE PARS TENSA

Is this retraction pocket thought to be self-cleansing or not? What is the relationship of the tympanic membrane to the incudostapedial joint? Is there partial or complete

erosion? What effect has this had upon hearing thresholds? Has the bony ear canal at the level of the tympanic membrane been eroded by long-standing retraction of the pars tensa and become wider? This can be evaluated because structures not normally visible, such as the stapedius tendon and facial nerve, becoming visible. Is the pars tensa adherent to the promontory or not? Whether or not the tympanic membrane is adherent to the promontory may be difficult to evaluate, but Charachon[189] and Gersdorff and Garin[190] argued that autoinflation may provide evidence of such adherence.

Tympanometry may be helpful. An unusually high peaked tympanogram, type A_d, is suggestive of tympanic membrane hypermobility or ossicular discontinuity and may provide further evidence of adherence of the tympanic membrane to the promontory or not. Sadé[191] reported a long-term series of 59 patients with 'hyperinflated' tympanic membranes, in which the middle ear pressure is elevated above atmospheric pressure resulting in ballooning out of the tympanic membrane, so-called hyperectasis. A type A tympanogram with a peak above atmospheric pressure would be indicative of hyperectasis. Sadé[191] noted that hyperectasis was preceded by atelectasis and that this hyperinflated state could persist for weeks, months or even years. If the pars tensa is adherent to the promontory, the perceived wisdom is that the retraction is likely to be long standing although this has not been formally tested in studies. A type B, or flat, tympanogram will suggest the presence of a middle ear effusion, in association with a retraction, and if accompanied by an associated hearing loss, may be a factor in deciding management.

OTHER FACTORS

The role of allergy and sinonasal infection is traditionally thought to be important and usually is included in the treatment of middle ear disease. The precise role of these other factors is not clear other than a general interference with Eustachian tube function. Any relationship between sinonasal factors and tympanic retraction has not been formally examined in clinical studies, but clinical examination of the nose would have a place if symptoms, such as obstruction or discharge, are present.

Natural history

The first assumption is that pars tensa and pars flaccida retractions are clinical consequences of the same predisposing factors. If so, then pars tensa and pars flaccida retraction should coexist. There is good case series evidence that pars tensa and pars flaccida retractions coexist. In a series of 250 adults and children with atelectatic tympanic membranes, Luntz et al.[192] found evidence of pars tensa retraction in 60% and pars flaccida retraction in 86%. Both sites of retraction were found in 49% and only one site in 53%. Another large case series (n = 327) also found a similar association between pars tensa and pars flaccida retraction; if pars tensa retraction was Sadé grade 1, then pars flaccida retraction was present in 43%, and if grade 2 then in 61%, respectively.[193] The lesson here is that, if pars tensa retraction exists, a careful examination should be made to see if pars flaccida retraction is present and vice versa.

PROGRESSION OF RETRACTION POCKETS

Once a retraction of either site is present, the key clinical question is whether such a retraction is likely to progress, remain static or resolve. They may reach such a size and configuration that they cease to become self-cleansing and accumulate inactive squamous debris. This debris may become infected and the clinical picture can then be characterized by repeated episodes of discharge, often with symptom-free intervals in between: intermittently active squamous COM. There is evidence that tympanic retraction can behave in this way, although reliably identifying those ears that will progress from those that will remain stable is not possible. Consequently, regular review is necessary. Retraction may lead to histological changes in the tympanic membrane with loss of elasticity and rigidity so that the tympanic membrane no longer 'drives' the ossicular chain or areas of the tympanic membrane may be eroded leaving a perforation. Tympanic retraction may also damage middle ear structures, for example erode the long process of incus.

There is evidence from follow-up of pars tensa retractions in children with OME that it is a dynamic condition with around 70% resolving spontaneously.[194] Studies of retraction of the tympanic membrane in children and adults over a longer period usually include surgical and medical treatment groups which makes it much more difficult to infer the natural history of this condition. Certainly the balance of evidence when a retraction is in association with otitis media in children is that VTs do little to affect the condition.[195, 196] Indeed, the insertion of a VT may significantly increase the chances of retractions and atrophy of the pars tensa.[197] Charachon,[198] in a study of adults and children (n = 95) of stage 1 and 2 (Charachon classification) tympanic retractions followed up over a period of 5 years, found that 16% deteriorated to stage 3 (follow-up 82%) and underwent surgery.

RETRACTION POCKETS AND CHOLESTEATOMA

That there is a relationship between tympanic retraction and significant pathology, such as cholesteatoma, is suggested by several temporal bone studies[199–202] and experimental animal work.[203, 204] Longitudinal population studies indicate that there is a significant association between cholesteatoma and pars flaccida retraction in adults and pars flaccida and pars tensa retraction in children.[205, 206]

Certain clinical groups have a greater chance of middle ear pathology leading to significant changes to the tympanic membrane. Children with a cleft palate have an approximately 20% chance of developing retraction in the pars tensa[207, 208] and those with Turner syndrome have approximately a 50% chance of tympanic pathology.[209] There is, somewhat surprisingly, no evidence that those with cystic fibrosis are more likely to develop tympanic or middle ear changes compared with the general population.[210]

No studies were found that specifically examined the natural history of tympanic retraction and erosion of the ossicular chain, particularly in relation to any change in hearing.

Management

The general assumption is that the complications described above have a reasonable chance of occurring despite the lack of research evidence that this actually happens. A wide variety of treatments have been proposed, but none has been submitted to a randomized controlled trial. Consequently, there is only case series evidence of the efficacy of various treatments.

MANAGEMENT OF NASAL DISEASE

There is evidence that a poorly functioning Eustachian tube plays a role in the pathogenesis of tympanic retraction, so it is common practice to look for and treat any sinonasal disease such as infection or allergy. This practice seems reasonable but no case series could be identified of such management of retraction pockets. Small case series examined the usefulness of tubal insufflation in the management of tympanic retraction. One series (n = 13) politzerized atelectatic middle ears with either carbon dioxide, oxygen, air or nitrogen.[211] The tympanic retraction did disappear, only to slowly reappear at a speed corresponding to the diffusion coefficient of the gases used. No long-term benefit was seen.

AURAL TOILET

Sadé[212] maintains that small retraction pockets can be managed by regular suction cleaning and many experienced otologists would agree with this view. However, no case series has reported its efficacy.

SURGICAL TREATMENTS

Surgical treatments have been undertaken to prevent complications such as discharge, progression of tympanic retraction and restoration of hearing. They are conveniently divided into:

- management of the tympanic membrane
- ventilating the middle ear.

MANAGEMENT OF THE TYMPANIC MEMBRANE

Surgical management of the tympanic membrane is essentially an anatomical approach designed to restore the normal anatomical appearance. The thin retracted tympanic membrane, lacking its normal elastin and collagen component, is unable to withstand any negative middle ear pressures and can become more retracted over time. This has led to a wide variety of surgical approaches.

Excision, no graft

Some have argued that the retracted tympanic membrane is abnormal, should be excised and a new 'normal' eardrum will naturally grow in its place. Sharp and Robinson[213] found that after one excision there was no recurrence in 65% of cases with a mean follow-up of 14 months, but 8% (5 of 66) of ears had persisting perforations. Others have combined excision with insertion of a VT in the remaining tympanic membrane.[214–216] All were small personal case series of less than 40 ears. The incidence of recurrence of the tympanic retraction and persisting perforation were of the same order. The evidence is not of good quality so it is difficult to make a case for inserting a VT at the same time as excising the retraction pocket.

Excision, myringoplasty

A number of larger case series combine excision of the tympanic retraction with a conventional myringoplasty using a variety of graft materials: temporalis fascia,[217–221] dura[222] and reinforcement with cartilage.[205, 223–230] These studies have variable follow-up periods and frequently include both children and adults and other treatments such as insertion of a VT, reconstruction of the ossicular chain or mastoid exploration. These case series suggest that recurrent retraction may be more reliably prevented with cartilage than with temporalis fascia grafts alone. However, there is no good evidence that myringoplasty has any benefit over a watch-and-wait policy in the management of retraction pockets.[231]

Excision, myringoplasty with cortical mastoidectomy

The role of mastoid surgery, undertaken at the same time as the tympanoplasty, seems to suggest that no further benefit is gained.[232–234] However, there may occasionally be a place for removal of small quantities of osteitic bone in the posterosuperior quadrant of the pars tensa to 'marsupialize' a tympanic retraction that is beginning to become no longer self-cleaning.[235]

VENTILATION TUBES

At first sight, to many clinicians, the use of VTs for tympanic retraction would seem obvious. Assuming that the basic pathophysiology is Eustachian tube dysfunction, if air could once again gain access to the middle ear, normal pressures would be restored and the tympanic retraction stabilized or reversed. Evidence that VTs play a temporary role was demonstrated by Sadé et al.[236] They closed a long-term VT used in the management of retraction and showed that retraction returned within 1–2 hours in 89% (33 of 37 cases). Despite this, the evidence seems to suggest that long-term benefit from VT insertion in established retraction is not so straightforward.

Much of the evidence to support or refute the use of VTs has been gained from studies that have been principally concerned with the treatment of OME. Such studies suggest that the use of VTs[195, 237, 238] had no long-term effect on the tympanic membrane. Indeed, the use of VTs in OME seems to increase the prevalence of pars tensa atelectasis and attic retraction. A meta-analysis of both randomized controlled trials and case series of OME showed that long-term VTs increased the risk of perforation

by 3.5 (95% CI, 1.5–7.1) and cholesteatoma by 2.6 (95% CI, 1.5–4.4).[197] The apparent lack of success of VTs in the management of tympanic retraction may be because histological changes have taken place in the tympanic membrane rendering the situation irreversible.

In ears with very poor aeration, Yung[239] has devised a method of inserting a permanent titanium vent into the mastoid antrum at the time of tympanoplasty. This allows aeration of the middle ear and has been successful in a significant proportion of patients. The technique requires surgical expertise and regular long-term follow-up to unblock the vent. It is not yet commercially available.

HEARING LEVELS AND RETRACTION

No studies have tried to associate hearing levels and degree of retraction. Such an association is unlikely to exist with pars flaccida retractions. Significant retractions of the pars tensa are likely to interfere with sound conduction, but erosion of the ossicular chain, usually the incus, will have a greater effect. In addition, no studies were found on the use of hearing aids in tympanic retraction, but this management makes sense, is by definition safe, and is likely to be how many patients are managed.

RECOMMENDATIONS FOR MANAGEMENT FOR AN INACTIVE RETRACTION

In an adult patient

If the patient is an adult (over the age of 12), the Eustachian tube function is likely to be normal and the retraction has a substantial chance of being stable. If there is no significant hearing loss and the retraction pocket is self-cleansing, then follow-up on an occasional basis would be appropriate until it seems clear that it is not progressing. If the retraction pocket is not self-cleansing, then it may be managed with regular microscopic suction clearance.

If there is a conductive hearing impairment, this may be due to loss of effectiveness of the atelectatic tympanic membrane or an ossicular problem. The decision to manage this surgically will depend upon the wishes of the patient, the hearing in the other ear and the expertise of the surgeon. The eardrum may be reconstructed with a graft with a cartilaginous component to help prevent recurrence of retraction. An ossiculoplasty would also be performed where relevant.

In a child under 12 years

In a child under 12 years there is a greater likelihood that a retraction will be unstable and it is important that such children are kept under review. If the hearing is normal, or near normal, then intervention is probably not necessary. If there is modest retraction and a hearing loss due to the presence of a middle ear effusion, then the usual guidelines for managing OME should be followed. There is no evidence that ears with OME and a retraction should be managed any differently as spontaneous resolution is common.[194]

If the retraction is progressing, with, for example, clinical evidence that the incudostapedial joint is beginning to be eroded, or the fundus is beginning to disappear out of view, then most otologists would recommend surgery. The situation is an exercise in damage limitation because the feeling is that, left untreated, this particular retraction will progress to incudostapedial joint erosion or a cholesteatoma. There is an argument for simply excising the abnormal atelectatic tympanic segment and hoping that a more normal tympanic membrane will grow back. The child and their guardians need to be advised that there is a good chance of leaving a tympanic perforation, but that this may be preferable to ossicular erosion or a cholesteatoma. There is little evidence that inserting a VT at the same time influences the outcome. Many otologists would argue that it is possible to go further and consider a tympanoplasty with thin cartilage or pallisades to reinforce the tympanic membrane and prevent a recurrence. There is an increasing body of evidence that this can be accomplished with good hearing and with an eardrum that can remain stable for a good period of time.

There is no evidence that concomitant exploration of the mastoid improves the outcome and this should, by and large, not be considered unless the possibility of unexpected cholesteatoma needs to be ruled out.

KEY POINTS

- Self-cleaning retraction pockets are usually stable in adults but they should be followed carefully in children.
- There is no evidence that surgical management of self-cleaning retraction pockets influences the natural history.

ACTIVE SQUAMOUS CHRONIC OTITIS MEDIA (CHOLESTEATOMA)

Natural history

Active squamous epithelial disease (**Figure 83.36**) is a retraction pocket filled with keratinous debris which may remain active or become inactive. In the former case the disease may or may not anatomically extend. The factors upon which this depends are not clear, but the issue of whether the degree of sclerosis of the mastoid is relevant is controversial. In well-pneumatized temporal bones, such as in children, the disease is frequently extensive, expanding down the well-formed air cell tracts. Squamous epithelial disease is more commonly found in poorly pneumatized sclerotic bones, but whether the sclerosis is relevant to the aetiology of the disease or is caused by it has also not been fully resolved. The evidence suggests that the most important factor in the development of mastoid sclerosis is poor Eustachian tube function. In a prospective study of cleft palate children in whom one ear only was managed with a VT, the mastoid air cell system was noted to be larger on the ventilated side in 86% (19/22) of ventilated ears.[240] Poor Eustachian tube function and reduced middle ear cleft volume has been shown to be characteristic of ears with cholesteatoma.[241]

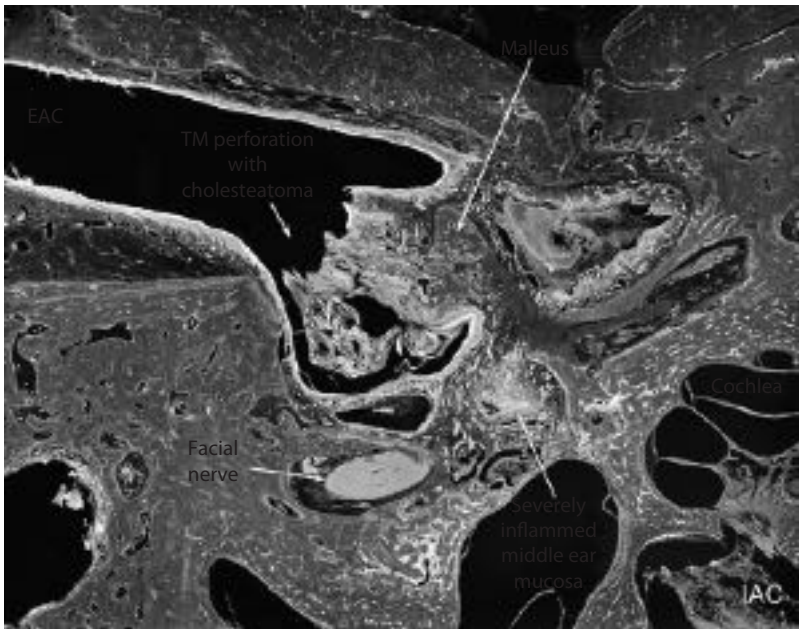


Figure 83.36 Axial temporal bone section from an 18-year-old woman with active squamous epithelial COM (cholesteatoma). There is a posterior perforation of the pars tensa extending to the annulus with ingrowth of squamous epithelium into the middle ear forming a cholesteatoma. Note the retained keratin within the cholesteatoma sac. There is granulation tissue within the middle ear that surrounds the cholesteatoma sac. EAC, external auditory canal. IAC, internal auditory canal. (*Magnification ×8.*)

PROGRESSION TOWARDS HEALING

There are no figures available which define the proportion of cases of active squamous epithelial disease which heal but cases are occasionally encountered where the patient has a well-formed 'atticotomy' or 'mastoidectomy' cavity but denies ever having surgery. In these cases presumably the disease process has selectively resulted in bone erosion of the outer attic wall and in some cases the whole posterior meatal wall. The epithelial migration pattern is restored from medial to lateral and the ear develops a 'normal' albeit widened external meatus or 'automastoidectomy' cavity.

In a proportion of cases, also undefined in the literature, there is a change from an active keratin producing retraction pocket to one that no longer produces or accumulates squamous epithelium but reverts to a clean, non-progressive retraction. This is only likely to occur if the retraction pocket is small and in the situation of established cholesteatoma, by definition active squamous epithelial COM, spontaneous reversion to inactivity must be rare but its frequency has not been documented.

PROGRESSION OF ACTIVE DISEASE

The natural history of cholesteatoma is for anatomical progression of disease over a variable timescale with inevitable involvement of the ossicular chain and possible involvement of the labyrinth by erosion of the lateral semicircular canal. The serious and potentially life-threatening sequelae of intracranial and intratemporal complications are discussed below (see 'Intracranial complications'). The timescale for this is extremely variable and it is likely that many patients live with active squamous epithelial disease with minimal disability or inconvenience. Bacteriology is non-specific with a wide range of organisms frequently cultured. Madana et al. found *Pseudomonas* in 32%, *Proteus* in 20% and *Staphylococcus aureus* in 19% in children with cholesteatoma.[242] As with mucosal disease, these organisms are likely to be opportunistic rather than primarily pathogenic (see 'Factors influencing activity of chronic otitis media' above). As the disease process advances, erosion of bone takes place as the lesion enlarges, by the mechanisms of osteoclastic and osteoblastic remodelling discussed in 'Active mucosal chronic otitis media' above. Although bone erosion in cholesteatoma takes place in the absence of acute inflammation and granulation tissue formation in some cases, the norm would be for the disease process to be associated with chronic granulation tissue formation with osteitis in the adjacent bone.

HEARING IN ACTIVE SQUAMOUS COM

It is well recognized that hearing is often preserved until a very late stage in ears containing cholesteatoma in spite of the ossicular chain being disrupted. Severe erosion of the incus with absence of the long process is common in established cholesteatoma and frequently the disease engulfs the whole incus and the malleus head. The stapes superstructure is also often involved and may be eroded. Fortuitously for the patient, hearing preservation occurs because the cholesteatoma sac bridges the gap between the functioning part of the ossicular chain and the inner ear. The unfortunate consequence is that removal of the disease surgically may reduce the hearing by increasing the air–bone gap. Involvement of the incus in cases of cholesteatoma is almost universal but precise figures are not available. Fortunately, in many cases it is possible to reconstruct the middle ear in such a way that hearing loss is minimized.

Presentation

Classically, active squamous COM presents with foul-smelling otorrhoea and hearing impairment. However, many patients complain only of hearing impairment and

are unaware of any discharge from their ear as the quantities of pus are small and these dry up and form crusts. Sometimes, the inexperienced otoscopist can miss the disease as the pars tensa appears normal, but a small crust obscures the attic (see **Figure 83.11**). The crust can be mistaken for wax, though wax only occurs in that site if the patient pushes it there with a cotton bud.

Examination

Microscopic examination is usually required to allow thorough cleaning of the discharge and to confirm the diagnosis. In very inflamed ears, a cholesteatoma may not be visible at first presentation. Sometimes there is an aural polyp obscuring the attic or posterior pars tensa; such a case should be assumed to be a cholesteatoma until proven otherwise. Removal of crusts can be uncomfortable and, particularly in children, may require an anaesthetic. When debris is removed from a retraction pocket in the attic or posterior pars tensa, the extent of the retraction pocket may not be visible with a microscope. Examination with a rigid endoscope may be helpful if knowledge of the extent is important for management decisions.

IMAGING

Many clinicians favour radiology before undertaking surgery for cholesteatoma. CT has been the standard method of imaging for many years. It provides very good resolution of anatomical landmarks. Its disadvantage is poor differentiation of cholesteatoma from other soft tissues, such as granulation tissue, cholesterol granuloma[243] or brain tissue. Bone erosion of the scutum and the incus and malleus though rarely the stapes can be demonstrated. CT can often demonstrate erosion of the inner ear with fistula formation or dehiscence of the facial nerve, but a negative CT does not rule out a fistula. Fistulae are reported to occur in 10–15% of cases of cholesteatoma but the sensitivity of CT at identifying fistulae is not reliable (**Table 83.8**). Dehiscence of the facial nerve is identified surgically in up to 19% of cases of cholesteatoma,[244] most commonly in the horizontal portion.[244] Fuse et al. reported that facial nerve dehiscence was detected on CT in only 66% of 29 cases.[245] Yu et al. found that the condition of the facial canal on CT corresponded with surgical findings in only 67 of 76 ears (88%).[246] The surgeon should not rely on CT but should assume that there is a fistula and that the facial nerve is dehiscent in all cases to minimize the complications of surgery.

Conventional MRI shows cholesteatoma as a soft-tissue mass but does not differentiate this from other soft tissues. It does not provide enough bony detail to be useful on its own. More recently, non-echoplanar DW-MRI has been shown to be very reliable at detecting cholesteatoma and differentiating it from other soft tissues.[250] It has been shown to be of value in detecting residual cholesteatoma and reducing the necessity for second-look surgery.[251]

If intact canal wall surgery is to be considered, knowledge of the anatomy, in particular the pneumatization of the mastoid, is important. If the mastoid is acellular, intact canal wall surgery is more difficult. If canal wall-down surgery is planned, some experienced surgeons do not consider radiology necessary, unless intracranial complications of disease are suspected. There is no evidence that pre-operative CT influences the surgical management of cholesteatoma in canal wall-down surgery.[252, 253]

TABLE 83.8 Surgically proven fistulas identified on CT

Reference	No. of cases	Fistulae identified on CT (%)
Herzog et al.[247]	8	38
Vanclooster et al.[248]	48	90
Kvestad et al.[249]	20	55

Management

The aims of management of active squamous COM are to relieve the patient's symptoms and to minimize the risks of complications of the disease. However, complications are rare (see 'Complications of surgery' below). Surgical removal is the only effective treatment for cholesteatoma, but surgery has potential complications too. Are the risks of the treatment greater than the risks of the disease? The likelihood of complications of the disease varies with the life expectancy of the patient, while the risks of surgery vary inversely with the skill of the surgeon. When surgical treatment is considered appropriate, topical treatment for granulations and associated mucosal disease while awaiting surgery may lessen the otorrhoea and therefore be socially beneficial (see 'Active mucosal chronic otitis media' above). Some patients, particularly the elderly, may be unfit for surgery and the risks of the disease may be minimal. In these cases, careful aural toilet with removal of squamous debris from the retraction pocket and topical treatment at regular intervals may keep the symptoms at a level acceptable to the patient. Hearing aids should always be considered when there is hearing disability (see 'Hearing aids in chronic otitis media' below).

The aims of surgery for active squamous COM are:

- eradication of disease
- an epithelialized, self-cleaning ear
- hearing maintenance or improvement.

The principle aim of surgery for cholesteatoma is to completely remove disease and minimize the risk of recurrence, but, in addition, the ear should be returned to as near normal as possible. The ear should be self-cleaning and should not require regular aural toilet, and the hearing should be restored, although this is not always possible. The idea that the aim of surgery is simply to remove disease in order to create a safe ear is obsolete. Many patients present because of hearing impairment and will not be satisfied with management that provides no apparent benefit.

There are many different surgical techniques for managing active squamous COM, which can largely be categorized as open cavity (canal wall-down) and closed cavity (canal wall-up) mastoidectomy. Over the last 30 years

there has been much discussion among otologists about the comparative benefits of these techniques, and there is no more agreement now than there was 30 years ago.

CANAL WALL-DOWN MASTOIDECTOMY

The traditional method for removal of cholesteatoma was modified radical mastoidectomy using the posterior to anterior approach. The mastoid was opened behind the external auditory canal, the cholesteatoma identified and followed forwards through the aditus into the attic with removal of the posterior bony wall of the canal. This usually resulted in a large cavity, much larger than is required to control the disease. Large cavities can be problematic: many continue to discharge and, even if well epithelialized, they often do not self-clean so regular clinic attendance is required for removal of squamous debris and wax from the cavity.

Small cavity mastoidectomy, or atticoantrostomy, the anterior to posterior approach, has become more popular. The cholesteatoma is identified in the epitympanum or posterior mesotympanum and followed backwards. Sadé[254] gave a very clear description of the surgical method. Smyth and Brooker[255] showed that this technique resulted in a much smaller cavity with a mean volume of 1.4 cm^3 compared with 2.4 cm^3 after modified radical mastoidectomy, and that there was no difference in the number of ears that continued to discharge between the two techniques. In addition, when the cholesteatoma is small, surgery can be limited to atticotomy and the defect in the attic wall can be closed with tragal or conchal cartilage with its perichondrium attached.

Wormald and Nilssen[256] evaluated the mastoid cavities in 101 patients attending an outpatient clinic between 6 months and 20 years after mastoidectomy. The cavity was actively discharging in 52% and dry in 48% of patients. They found the following significant differences in the active cavities:

- high facial ridge
- sump in cavity below floor of external auditory canal
- perforation in tympanic membrane
- small external auditory meatus.

The problems of mastoid cavities can be reduced by good surgical technique and by partial obliteration of cavities, either with cartilage or prosthetic materials. The cavity must be rounded and smoothly contoured with no overhanging ridges and no facial ridge in order to allow migration of epithelium. The tympanic membrane should be repaired to close all communication between the mastoid cavity and the mesotympanum and Eustachian orifice. The meatus should be an adequate size relative to the size of the cavity, so a meatoplasty is almost always required. The conchal cartilage removed from the meatus should be used to reduce the size of the cavity.

Canal wall-down surgery has lower rates of recurrence of cholesteatoma (5–15%) and recurrences are usually easily identified in the outpatient clinic, so second-look operations are rarely necessary. Residual cholesteatoma should be a rarity in competent hands. A significant proportion of patients (20–25%) continue to have otorrhoea, either intermittent or continuous, after mastoid surgery.[257–259] Experienced otologists of repute have much higher success rates at creating dry ears. Smyth and Brooker[255] reported that only 5% of ears were moist 5 years after surgery. This is probably an indication that attention to detail in these operations results in much better outcomes for the patients.

CANAL WALL-UP MASTOIDECTOMY

Canal wall-up mastoidectomy (combined approach tympanoplasty) has the advantage of leaving an intact external auditory canal and no mastoid cavity. However, the incidence of recurrent and residual cholesteatoma is high (20–50%), therefore second-look operations after 12–18 months are necessary in most cases, and some cases require further procedures subsequently. Second look can often be avoided nowadays by the use of DW-MRI.

The advantage of canal wall-up mastoidectomy is the preservation of a (relatively) normal external auditory canal and the absence of a mastoid cavity. It has been claimed that post-operative hearing thresholds are better, but there is no evidence for this as all reports are case series and outcomes depend on selection of patients. Many authors claim that their hearing outcomes after canal wall-down mastoidectomy are comparable.

A minority of surgeons, most of whom are experienced otologists, favour this procedure. It is technically more difficult and requires significantly longer operating time. In addition, at least one further operation may be required. Patients must be made aware of this. More recently, some surgeons have recommended canal wall-up surgery with obliteration; these ears are followed up with diffusion-weighted MRI to exclude residual cholesteatoma.[251]

CANAL WALL-UP VERSUS CANAL WALL-DOWN MASTOIDECTOMY

Reconstruction of the middle ear can be achieved with either technique and there is no evidence that the long-term hearing results differ between procedures. It has been claimed at times that post-operative hearing results are better following canal wall-up mastoidectomy. These claims are usually based on an author's comparison of cases that have undergone one of these procedures. It must be remembered that the procedure is not randomized but is the one thought most appropriate for the patient. Some authors have pointed out that, though the post-operative hearing thresholds are worse after canal wall-down mastoidectomy, the pre-operative hearing thresholds are also worse.[260] Karmarkar et al.[261] found no significant difference in post-operative hearing results between 176 cases of canal wall-down mastoidectomy and 257 cases of canal wall-up procedures. Toner and Smyth[262] reported better hearing outcomes 1 year after surgery for canal wall-up compared with canal wall-down mastoidectomy. However, at long-term follow-up (mean of 9 years), there was no significant difference between groups. Many

surgeons, by doing canal wall-down surgery but partially obliterating the cavity, achieve an outcome that is similar to canal wall-up surgery.

PARS TENSA CHOLESTEATOMA

Cholesteatoma arising from the pars tensa may be confined to the middle ear, most commonly growing into the facial recess and sometimes spreading anteriorly beneath the pars tensa and malleus handle. This can be removed by opening the facial recess, which is more easily accessible than inexperienced surgeons sometimes think. When the cholesteatoma grows anteriorly, care must be taken not to leave some under the tympanic membrane remnant. Complete clearance from the oval window, especially when there is an intact stapes superstructure, can be difficult. If there is doubt over clearance of disease, the tympanic membrane can be closed and the ear reopened after 12–18 months.

OSSICULOPLASTY IN ACTIVE SQUAMOUS COM

The incus is probably the most commonly used prosthesis for ossicular reconstruction. The possibility of an allograft incus from an ear with cholesteatoma containing squamous cells has been explored. Rupa et al.[263] examined histologically 60 mallei and 53 incudes from ears with cholesteatoma and found no evidence of squamous epithelial cells, while Dornhoffer et al.[264] examined 11 incudes removed at the time of surgery in ears with cholesteatoma and found evidence of squamous epithelial cells in seven incudes (64%). There is thus the theoretical risk that the use of such an incus could cause a recurrent cholesteatoma. The possibility that these cells could regenerate without a blood supply seems remote. No case of recurrent cholesteatoma arising from an allograft incus has been reported in many extensive surgical series.

COMPLICATIONS OF SURGERY

Complications of mastoid surgery are not uncommon. In an audit of results in the UK, facial palsy occurred in 1% and dead ear in 2% of 365 canal wall-down mastoidectomies.[258] Wormald and Nilssen[265] reported the outcome of mastoid surgery in 1024 patients. The incidence of intra-operative facial nerve palsy was 2% and of total loss of hearing was 2%. The incidence of facial palsy is widely accepted to be rare in the hands of expert surgeons. However, total loss of hearing also occurs in the hands of experts, usually in ears where there is a fistula into the inner ear.

PROBLEM MASTOID CAVITIES

Mastoid cavities that continue to discharge can usually be corrected surgically. Regular aural toilet over many years with frequent antibiotics is ineffective and is poor medical practice in the modern world. Most commonly the problem arises because of poor surgical technique at the initial mastoidectomy: the meatus may be too small, a high facial ridge may have been created, there is a sump in the mastoid tip or the tympanic membrane has not been closed. If the cavity is well epithelialized but debris collects, correction of the cause of poor drainage – narrow meatus, high facial ridge – may result in significant improvement. For cavities with more extensive disease, revision surgery requires meticulous surgical technique. Jackson et al.[266] give a careful description of the principles of management of problem cavities. In their series of 541 ears, 89% were clean, healed and dry after revision surgery.

However, many surgeons nowadays prefer to obliterate, at least partially, large cavities that are not epithelialized. Revising these cavities and making them even larger rarely succeeds in creating a dry ear. Skin does not readily grow on bare bone and the naturally moist environment in the ear encourages the growth of respiratory mucosa. The cavity can be made smaller by obliteration which can be achieved by filling the cavity with bone pâté [267]or hydroxyapatite granules.[268] Both of these materials must be covered by a vascularized fascioperiosteal flap. Alternatively, the posterior canal wall can be reconstructed with a hydroxyapatite prosthesis.[269] The different methods of mastoid obliteration have not been directly compared. In numerous case series using these and other techniques, the proportion of patients who have dry ears following obliteration is reported as 80–95%.[270] Irving et al.[271] reported better symptom scores in patients who had mastoid obliteration than in patients who had revision mastoidectomy. Meticulous surgical technique is considered necessary to avoid leaving squamous epithelium in the obliterated cavity, though cases of this have not been reported.

KEY POINTS

- Cholesteatoma continues to enlarge in most patients, but the rate of progression on average is very slow.
- The preferred management in patients who are otherwise fit is surgery.
- The aims of surgery are to remove disease, to create a trouble-free ear and to improve the hearing.
- At least 1% of patients get a facial palsy and 2% a dead ear after mastoid surgery in the UK. The incidence is very much lower when the surgery is performed by experienced surgeons.

HEARING AIDS IN CHRONIC OTITIS MEDIA

Healed COM

Hearing aids are straightforward and effective forms of management. When listening in low- and medium-level environments, a person with a conductive hearing impairment will have poorer speech recognition ability than someone with a sensorineural impairment of the same degree. The person with the conductive hearing impairment will, however, derive more speech recognition benefit from hearing aids than the person with the

sensorineural hearing impairment.[272] There is no evidence to compare successful surgery with provision of hearing aids in this patient group. For many patients, hearing aids are the more acceptable form of management. Their success rate in lessening disability is much greater than that of surgery and the complication rate is much smaller. In patients with hearing disability and bilateral healed COM, a hearing aid is appropriate even if surgery is planned for the poorer-hearing ear. Unless surgery is very successful, they will still have a hearing disability afterwards.

Inactive COM

Many people believe that closure of the perforation in inactive COM is necessary prior to fitting a hearing aid, though there is no evidence to confirm this. It is accepted that some patients with inactive COM who are fitted with a hearing aid then develop active COM and otorrhoea. However, the likelihood of this happening is not known. Adults who have a history of intermittent otorrhoea are probably likely to develop further otorrhoea when using a hearing aid. However, the chances of otorrhoea in a patient with a totally inactive ear and no recent history of otorrhoea are probably small, though there is no evidence to confirm this. A sensible management plan in such a patient would be to try a hearing aid. If the ear becomes active, the tympanic membrane should be repaired. If the ear remains inactive, then the patient has avoided an unnecessary operation.

The only presenting symptom in patients with inactive squamous disease is hearing impairment. If they have a hearing disability, a hearing aid is often the most effective management.

Active COM

Hearing aids are effective in patients with hearing disability, as in inactive mucosal COM. However, closure of the external auditory canal with a hearing aid usually exacerbates the otorrhoea, so the otorrhoea should be managed first and the preferred option is usually surgical repair of the tympanic membrane. In some patients, for example patients who are medically unfit for surgery and patients with only one hearing ear, surgery is better avoided. Such patients can often be managed by regular aural toilet and occasional topical treatment.

All otologists have some problem discharging mastoid cavities that are resistant to all attempts at treatment. Occasionally, such a patient has bilateral problem cavities or has a profound hearing loss in the opposite ear. If such a patient requires hearing amplification, conventional air conduction hearing aids cause problems: they exacerbate the activity and the otorrhoea interferes with the function of the hearing aid. These patients can often be effectively managed with a bone-anchored hearing aid (BAHA) (see Chapter 93, Bone-conduction hearing aids) that does not interfere with the disease.[273] Such management often has the additional benefit of reducing the amount of discharge from the cavity.

KEY POINTS

- In many patients with COM, the main symptom is hearing disability and this should be managed at an early stage.
- Conventional hearing aids are effective management of patients with hearing disability and inactive COM.
- Bone-anchored hearing aids can be very effective management of patients with hearing disability and active COM which does not respond to treatment.

COMPLICATIONS OF ACTIVE CHRONIC OTITIS MEDIA

Classification of complications

The complications of active COM may be classified as intratemporal (cochlea, labyrinth and facial nerve), sometimes expressed as extracranial, and intracranial. Extracranial complications are postauricular abscess, facial palsy, petrous apicitis and Bezold abscess (neck abscess as a result of direct extension from suppuration in the mastoid tip). Intracranial complications are meningitis, brain abscess, extradural abscess subdural abscess, lateral venous sinus thrombosis and otitic hydrocephalus.

RELATIVE INCIDENCE OF COMPLICATIONS

In a large series of 268 patients with complications of COM, the incidence of extracranial complications was 32%, intracranial complications was 56% and combined intracranial and extracranial was 12% (Table 83.9).

RISK OF COMPLICATIONS

Traditionally, ears with squamous epithelial disease have been regarded as being more at risk of serious complications as opposed to those with mucosal disease. In fact, the evidence confirms that there is a significant risk with both types of disease. Singh and Maharaj[274] report an incidence of 41% squamous epithelial versus 59% mucosal disease in their group of extracranial complications and 59% squamous versus 41% mucosal disease in the intracranial group. In the combined group, 58% had squamous epithelial disease and 42% had mucosal disease.

Otorrhoea as an obvious symptom may or may not be present and there is no evidence that ears with COM are more or less likely to suffer complications if they are

TABLE 83.9 Relative incidence of complications in active mucosal and squamous COM

Extracranial	%	Intracranial	%
Postauricular abscess	75	Brain abscess	51
Facial palsy	6	Subdural abscess	20
Bezold abscess	2	Extradural abscess	10
Petrous apicitis	0.2	Lateral sinus thrombosis	20
Meningitis	12		

Reproduced from Singh and Maharaj,[274] with permission.

actively discharging. However, the development of pain may indicate that an acute infection has supervened and that there may be a build-up of pus under pressure in the middle ear or mastoid. Although there is no direct evidence that such ears have a higher incidence of complications, the clinician should bear this possibility in mind. As discussed above, the incidence of brain abscess arising from mucosal disease is significant and indeed otogenic abscess may occur from ears previously treated by mastoidectomy.[275] The annual risk of developing an otogenic brain abscess has been estimated at 1 in 10 000, making the lifetime risk of a 30-year-old patient with chronic ear disease of the order of 1 in 200.[276]

MORTALITY FROM COMPLICATIONS

The intracranial complications of COM are serious, with a mortality of 8% in the series of Singh and Maharaj.[274] Of the 15 deaths, 7 were in ears with squamous epithelial disease and 8 in ears with mucosal disease. There was 1 death from meningitis, the others being from brain abscess (12) and subdural abscess (2). There were no deaths from extracranial complications.

Extracranial complications

SENSORINEURAL HEARING LOSS

It has been suggested that toxins in COM can damage the cochlea. However, comparison of the two ears in patients with unilateral COM and no history of any factors predisposing to hearing loss have shown no difference in bone-conduction thresholds between the diseased ears and the contralateral normal ear (Dumich and Harner,[277] 200 patients; Noordzij et al,[278] 69 patients). Browning and Gatehouse[279] found no difference in bone-conduction thresholds between 395 ears with COM and 920 control ears after correcting for the Carhart effect. It has been suggested that the risk of sensorineural hearing loss may increase with age.[280] One recent study found a strong association between COM and sensorineural loss, but the authors comment that their data showed extreme variability, which implied that there may by a group of patients particularly vulnerable to sensorineural loss.[281] On the evidence available it seems reasonable to conclude that sensorineural hearing loss may occur as a result of COM, but that this is a rare occurrence and does not affect the great majority of patients. Sensorineural hearing loss may result from the treatment of active COM with potentially ototoxic eardrops, but most practising otolaryngologists regard this as rare, probably at least as rare as sensorineural hearing loss due to the disease.

SUDDEN SENSORINEURAL HEARING LOSS

Sudden sensorineural loss may also occur, but the incidence and precise reasons for this have not been defined nor has the precise relationship to the COM as distinct from other causes.

LABYRINTHINE COMPLICATIONS

Acute bacterial labyrinthitis or cochleolabyrinthitis is a serious complication that often results in a dead ear. Fortunately, in the context of such a common disorder as COM, it is a relatively rare event to lose all the hearing from mucosal disease and the main risk to the inner ear may be from surgery. Similarly, balance disturbance is a serious complication due to labyrinthine involvement by the infective process and may be the first sign of the development of a labyrinthine fistula, almost invariably into the lateral semicircular canal. Chronic low-grade imbalance, with or without detectable nystagmus, implies the development of a labyrinthine fistula. This entity can occasionally result in sudden acute vertigo although this is rare. Erosion of the bone overlying the lateral canal arises in both mucosal and squamous epithelial disease, particularly if there is extensive granulation tissue formation. The frequency of fistulae at surgery is usually reported as 10–15%. The mechanism is likely to be the inflammatory reaction provoking osteitis in the labyrinthine bone which is then subject to the forces of osteoclastic and osteoblastic activity with the osteoclastic element predominating. When the inflammatory process is eliminated by surgery, bone regeneration may occur over such a fistula.

FACIAL NERVE COMPLICATIONS

The incidence of facial palsy is small in the context of the commonness of the disease and it is usually associated with dehiscence of the fallopian canal. Erosion of the bony fallopian canal can occur in active mucosal COM but probably more commonly in squamous epithelial disease where it has been reported in up to 19% of cases,[244] particularly in the presence of granulations, and granulation tissue may form on the nerve sheath itself. Removal of this granulation tissue, which may be exuberant enough to form a polyp, is extremely hazardous to the nerve and should only be carried out under direct vision.

MANAGEMENT OF EXTRACRANIAL COMPLICATIONS

Labyrinthine complications

Acute labyrinthitis should usually be managed medically with bed rest, intravenous antibiotics and labyrinthine sedatives such as prochlorperazine. The patient should be observed carefully for early signs of meningitis. When the general condition has improved, usually after several days, the middle ear and mastoid should be formally explored and appropriate surgery carried out.

Patients with active squamous COM and a suspected labyrinthine fistula should have early surgical management to prevent deterioration of inner ear function. Most surgeons recommend a canal wall-down mastoidectomy. The cholesteatoma matrix should be left undisturbed over the semicircular canals until all other disease is removed and all other aspects of the procedure such as meatoplasty are completed. The matrix should then be carefully lifted and the fistula identified. It is

then peeled off the membranous labyrinth and the fistula is immediately sealed with fascia and bone dust. The fascial graft for the tympanic membrane provides a further layer of closure. Though the risks of loss of cochlear function are higher in large fistulas, Herzog et al.[247] reported no loss of cochlear function in 17 fistulas not exceeding 2 mm.

Facial nerve complications

In the presence of a facial nerve palsy, active COM should be managed urgently and almost always surgically. Appropriate intravenous antibiotics should be commenced on admission. Squamous COM should be managed by the appropriate surgical approach and the cholesteatoma matrix should be carefully dissected off the fallopian canal and facial nerve. Active mucosal COM should be managed by cortical mastoidectomy and exploration of the middle ear with careful removal of granulation tissue from the fallopian canal. Some surgeons believe that the canal should be widely decompressed and the nerve sheath opened, but others think that removal of disease is adequate and that opening of the nerve sheath increases the risk of surgical trauma to the facial nerve. Complete recovery of facial function can be expected in most cases after careful surgical management within a few days of onset. Delay in management results in poorer outcomes.[282]

Intracranial complications

ROUTES OF INFECTION OF THE CRANIAL CAVITY

There are several routes by which sepsis may spread to the cranial cavity from an infected ear and, indeed, considering the proximity of the dura and sigmoid sinus to the infective process, in many cases, it is surprising that intracranial complications are not more common. These routes are most commonly by direct erosion of osteitic bone by the inflammatory process or via infected thrombophlebitis of the emissary veins traversing the bone and also the dura. Infection may also reach the cranial cavity via fractures and surgical defects. Normal anatomical points of weakness, such as the oval and round windows and the internal auditory meatus and cochlear aqueduct, are other possible routes for infection entering the cranial cavity.

OTOGENIC INTRACRANIAL SEPSIS

The main intracranial septic complications are meningitis and intracranial abscess. The latter may be subdivided into extradural abscess, subdural abscess and intracerebral or cerebellar abscess. Thrombophlebitis of the sigmoid sinus and otitic hydrocephalus are the other main complications.

MENINGITIS

Meningitis usually presents as an acute illness with severe headache, neck stiffness and in the later stages drowsiness and coma in a systemically ill patient. Early diagnosis is essential to minimize the risk of death and serious sequelae such as sensorineural hearing loss. The suspicion of meningitis should be raised in any otherwise fit individual with a severe acute pyrexial illness with headache who has a history of a discharging ear, particularly if there is neck stiffness. The diagnosis is confirmed by lumbar puncture, and culture of cerebrospinal fluid will identify the organism.

INTRACRANIAL ABSCESS

In intracranial abscess the presentation is often much more insidious, with low-grade headache, occasionally more severe, mild pyrexia and in the later stages drowsiness, lethargy and weakness. Subdural abscess tends to present more acutely and may be accompanied by fits and focal neurological signs depending upon site, whereas abscess within brain tissue has a notoriously insidious onset with symptoms developing over several days, and neurological signs, dependent upon site, relatively infrequent. Classically, there is an early period of more acute symptoms due to a localized encephalitis with associated brain oedema. The predominant symptoms are headache and vomiting with fever and general malaise. These symptoms then settle as the abscess develops and the more insidious symptoms supervene. The most common sites for otitic intracranial abscess are temporal lobe and cerebellum, as would be expected from their proximity to the temporal bone. The frequency of and mortality from brain abscess have declined markedly in recent years, with mortality of 6–14% quoted in one series.[283] The diagnosis is made by CT scanning, which should be undertaken early if any of the above symptoms develop in a patient with COM.

LATERAL VENOUS SINUS THROMBOSIS

Lateral venous sinus thrombophlebitis is a rare but extremely serious complication of COM requiring urgent recognition and treatment. Infection spreads to the venous sinus directly from the mastoid or via any of the venous channels draining the middle ear and mastoid. Prior to the development of infected thrombus within the lumen of the sinus, there may be abscess formation in the close vicinity of the vein. Initially, mural thrombus forms in the sinus which gradually propagates and organizes. Septic embolization frequently occurs which may result in metastatic abscess formation and occlusion of the sinus may result in raised intracranial pressure. The clinical features will frequently be modified by antibiotic therapy but pyrexia, otalgia and mastoid and neck tenderness in a systemically ill patient are suggestive. Drowsiness and lethargy supervene as the illness progresses and the disease is frequently complicated by other intracranial septic complications such as meningitis or brain abscess. Papilloedema is frequently present and highly suggestive of the diagnosis. The investigation usually undertaken first is CT scanning but MRI may add further information, particularly about venous flow in the sinus.

OTITIC HYDROCEPHALUS

Otitic hydrocephalus (benign intracranial hypertension) is the rarest of the intracranial complications of ear disease and may occur after an episode of AOM, as well as complicating COM. The aetiology remains obscure but the consensus view is that it results from lateral sinus thrombosis, presumably with concomitant obstruction of other intracranial venous channels.[284] Symptoms are the same as those mentioned above, which may raise the suspicion of any intracranial complication, and the presence of papilloedema is suggestive. Early CT scanning is necessary to make the diagnosis and rule out more serious intracranial septic complications.

MANAGEMENT OF INTRACRANIAL COMPLICATIONS

General principles

The basic principles of management of intracranial sepsis resulting from COM are:

- antibiotics
- full neurological observations
- neurosurgical advice
- management of the ear.

Broad-spectrum intravenous antibiotics in effective dosage should be started. A bacteriology swab of the ear should be taken but choice of antibiotic agent should not await the results of culture and sensitivity, especially as ear swabs do not necessarily correlate with abscess swabs. Choice of antibiotic depends on the location of the patient, as the likely organisms vary in different parts of the world. In addition, the range of drugs available and the likely resistance of organisms change with time.

Full assessment of the neurological condition of the patient should be recorded and regularly monitored. The neurosurgeon will usually decide on the management of the patient, but this decision may be influenced by the neurological condition and its progress.

Meningitis

Treatment is antibiotic therapy and observation. Management of the ear should be deferred for a few days until the patient's condition improves. However, if the patient's condition does not improve after 48 hours, or if it deteriorates, then immediate exploration of the ear is indicated.

Intracranial abscess

Abscesses usually require drainage. Otogenic extradural abscesses usually lie adjacent to the temporal bone. The most appropriate surgical approach to the abscess is through the mastoid, therefore the ear disease should be managed at the same time.

Subdural and intracerebral abscesses were traditionally managed by the neurosurgeon, by aspiration through a burrhole, which may require to be repeated, or by craniotomy and excision of the abscess. More recently, these abscesses have been managed by transmastoid drainage of the abscess with mastoidectomy, either canal wall-up or wall-down depending on the pathology in the ear.[285, 286]

Lateral venous sinus thrombosis

Most clinicians advocate early surgical management of the ear. It used to be thought that the lateral sinus should also be opened. After clearing disease from the mastoid, the bone covering the lateral sinus is removed, the sinus opened and the infected clot removed. However, more recent case series have recommended mastoidectomy and antibiotics without opening the sinus.[287, 288]

Otitic hydrocephalus

Otitic hydrocephalus may result from raised intracranial pressure associated with lateral venous sinus thrombosis.

Management is reduction of the raised intracranial pressure by steroids, diuretics and hyperosmolar dehydrating agents. Treatment may need to be continued for many weeks. Occasionally a ventriculoperitoneal shunt may be required.

BEST CLINICAL PRACTICE

- ✓ Complications should be considered in any patient with COM who is generally unwell and in particular with symptoms such as pyrexia and headache.
- ✓ Early and effective management of complications is important. Expert, non-otolaryngological advice may be required.

FUTURE RESEARCH

- ➤ Advances in sequencing technologies and mass spectrometry for gene expression and proteomics.
- ➤ Use of bioinformatics to anlayze gene networks.
- ➤ Development of mouse models for CSOM and cholesteatoma.
- ➤ Development of bacteriophages, small interfering RNA (siRNA) in treatment of COM.
- ➤ Novel methodologies for middle ear drug delivery.

KEY POINTS

- Chronic otitis media (COM) implies a permanent abnormality of the pars tensa or flaccid.
- Active mucosal COM is often associated with destruction of the ossicular chain.
- Cholesteatoma is a benign keratinizing epithelial-lined cystic structure found in the middle ear and mastoid.
- Epithelial cells in cholesteatoma are derived from the tympanic membrane.
- In the rare instances of cholesteatoma occurring behind an intact tympanic membrane it has been shown that the cholesteatoma is derived from the tympanic membrane.
- The prevalence of COM is greater in lower socioeconomic groups.
- COM in cleft palate patients followed up to 10 years of age is around 20%, with 2% of them having a cholesteatoma.
- Studies to examine the presence of biofilms in active COM have shown a 60% biofilm incidence as opposed to 10% in the control, uninfected group.
- OME predisposes to chronic retraction of the pars tensa or flaccida and this subsequently progresses to cholesteatoma.
- Tympanosclerosis is found in the middle ear in around 25% of ears at surgery.

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Figures 83.9–83.29 and 83.31–83.35 are reprinted from Wormald PJ and Browning GG. *Otoscopy: a structured approach*. London: Hodder Arnold; 1996.[289]

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CHAPTER 84

MYRINGOPLASTY

Charlie Huins and Jeremy Lavy

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline and Embase search using the keywords: myringoplasty, tympanoplasty, tympanic membrane, perforation, chronic otitis media and focusing on surgery and management.

INTRODUCTION

Myringoplasty can be defined as the surgical repair of the tympanic membrane.[1] In the majority of cases the damage is likely to be a persisting perforation of the drum but there are also situations where a thin or retracted drum may need to be reinforced. This chapter will focus on the perforated eardrum but some of the techniques described are also applicable to reinforcement myringoplasty. Wullstein in 1956[2] classified tympanoplasty, with myringoplasty being classified as a Type I tympanoplasty.

HISTORY

Descriptions of artificial animal-based plugs being used to cover perforated tympanic membranes date back to the 1640s.[3] Such plugs probably served the purpose of keeping the ear dry and therefore reducing the risk of infection, but it is unlikely that there would have been any positive effect on the hearing acuity of the ear. For the first accounts of more sophisticated treatment one has to wait until the 1850s when Yearsley described an artificial eardrum consisting of moistened cotton wool.[3] This was inserted into the perforation and plugged it, often affording a noticeable improvement in hearing. Toynbee describes an artificial eardrum comprising a gutta percha disc and a silver wire. Around this time William Wilde and Roosa were advocating the use of cautery to the remnant tympanic membrane to encourage healing. Silver nitrate and trichloracetic acid were commonly used agents. Joynt (1919) combined cautery with the use of a paper patch overlying the perforation; Blake first described the paper patch on its own in 1887. In 1878 Berthold described his technique of using a full-thickness skin graft, describing this alongside 'freshening' or excision of the perforation edges to 'render these parts into a wound'; he is also credited with being the first to use the term 'myringoplasty'. Ely described a similar technique but his work was not published until a year later in 1879.

Although these techniques were being described in the medical literature, they were not consistently successful and it was not until the 1950s with Wullstein's split skin graft and Zollner's pedicled skin graft that higher rates of successful repair were being reported, albeit only up to 71% in ideal cases.[4] The other crucial development that was occurring around this time was that of the operating microscope. The availability of illumination and magnification afforded by the operating microscope transformed this area of surgery probably more than any other.

The use of skin grafts was associated with a relatively high rate of reperforation, inflammation and cholesteatoma formation.[5] Attention passed to other graft materials, with Zollner describing fascia lata (1956), Heerman temporalis fascia (1958) and Shea vein grafts (1960). Since then the list of potential graft materials has expanded to include perichondrium, cartilage, periosteum, fat, subcutaneous tissue, amniotic membrane, dermal matrix, fibroblasts, animal pericardium and sclera!

AETIOLOGY

Infection

The commonest cause of an acute perforation is following an episode of acute otitis media. Spontaneous healing of such perforations is the norm, with 70–80% healing within 30 days,[6, 7] with pre-existing tympanosclerosis, malleus injury, infection and large perforations negatively influencing spontaneous closure rates.[8] Loss of contact inhibition of the squamous epithelial cells is postulated to be the driver for repair of acute injuries to the membrane. When a perforation becomes chronic, the margin of the perforation can be seen to be stable with the squamous epithelial cells coming into contact with the epithelial cells of the mucosal layer, creating a barrier against further vascular proliferation.[9]

Trauma

A direct blow to the ear can result in rupture of the tympanic membrane. This can be an isolated injury or, in cases of more severe trauma, can be associated with fractures of the temporal bone and damage to other structures in the middle ear. Barotrauma related to air pressure changes with air travel or water pressure and diving can similarly cause rupture, as can direct trauma such as with a cotton bud.

Iatrogenic

Iatrogenic trauma from middle ear surgery or following the extrusion of a ventilating tube (VT) should be evident from the history. The risk of a chronic perforation following short-term VT is 2.2%, with long-term VTs increasing the risk to 16.6%.[10]

PRESENTATION

Perforations may be completely asymptomatic and can be found incidentally. The majority of patients, however, will present to the ENT surgeon as a result of their symptoms, the commonest being discharge and hearing loss.

Discharge

A mucoid discharge from the ear, be it simple mucus or mucopurulent, should always alert the clinician to the likelihood of a tympanic membrane defect. There are no mucous glands in normal ear canal skin whereas they are in abundance within the middle ear mucosa. Discharge, in most cases, is associated with infection. This can be from ingress of potentially infective organisms from the outside into the middle ear through a pre-existing perforation or from mucosal reaction to a systemic infection (e.g. an upper respiratory tract infection), with the rapid build-up of mucopus resulting in an acute perforation.

Common pathogens include *Pseudomonas*, *Staphylococcus aureus* and *Moraxella*.[11] A swab for microscopy, culture and sensitivity is not routinely sent, being reserved for cases of recurrent infections not responding to 'standard' topical antibacterial medications, in immunocompromised individuals or where suspicion of unusual bacteria is present.

Management of mucopurulent discharge from the ear would follow guidelines set by NICE,[12] with first line being thorough microsuction to reduce the bacterial load followed by regular application of topical antibiotic preparation to the external ear canal. It is acceptable to use short courses of a topical antibiotic with or without corticosteroid, but careful consideration must be given to potential risk of aminoglycoside-induced ototoxicity in patients with a suspected or confirmed perforation.[13] In such circumstances many ENT surgeons would use quinolone-based drops as they are not ototoxic.[14] An ENT-UK position paper stated that a short course of topical aminoglycoside-based drops in the presence of a perforation was acceptable since pus in the middle ear associated with otitis media carries a higher risk of ototoxicity than the drops themselves. This course must be short and stopped as soon as the infection has cleared.[15] An oral antibiotic may also be given in severe or unresponsive infections. An ear wick may be used for severe infections, but the duration of use of each wick should be kept to a minimum.

Hearing loss

Hearing loss can vary depending on the size and location of the perforation. More severe hearing loss should alert the clinician to the possibility of coexistent ossicular involvement/discontinuity. Very small perforations may not cause any hearing loss, but larger defects can cause moderate conductive hearing loss (CHL) due to loss of surface area available to absorb sound energy.[16]

Perforations tend to affect the lower frequencies, having less of an impact as frequency increases.[16]

The site of the perforation has not been seen to correlate with the magnitude of hearing loss, except for those affecting the posterosuperior quadrant.[16] Complete ossicular discontinuity can result in a maximal CHL of around 60 dB.

INDICATIONS FOR MYRINGOPLASTY

The three principal indications for myringoplasty are recurrent otorrhoea, hearing loss due to a chronic perforation, and the desire to swim without having to waterproof the ear.[17]

Infection

The presence of a perforation exposes the middle ear to the risk of recurrent infection from external sources. This can have a significant effect on the quality of life, together with a risk of progression of the middle ear pathology.[18]

Hearing loss

The repeated insult of infections is not only unpleasant for the patient but can affect hearing through both the presence of mucopus and the potential destruction of the ossicular chain. The distal aspect of the long process of the incus is the most vulnerable part of the chain, due to its tenuous blood supply. Erosions at this point can lead to loss of continuity with the stapes and hence a CHL.

Small perforations under 25% may not lead to any significant hearing deficit. Perforations greater than 25% have been shown to cause a greater CHL as size increases.[16] Post-operative audiometric gain has been shown to correlate well with increasing size of the repaired perforation,[19] with those >50% demonstrating a greater pre-operative loss and greater post-operative gain.[20] Exposure of the ossicular chain appears to be more of a factor for hearing loss than loss of the round window baffle effect; perforations in the posterosuperior quadrant have a larger CHL than other sites. Perforation-induced hearing losses appear greatest at lower frequencies with less influence on higher frequencies.[16]

Social

In the presence of a perforation, the general advice is to protect the ear from water to prevent pain and infection, though there does not appear to be any high quality evidence to support this. To enable swimming without the need to protect the ear from water, particularly in children, is a relative indication for myringoplasty.

CONTRAINDICATIONS TO MYRINGOPLASTY

Cholesteatoma

The presence of cholesteatoma is an absolute contraindication to myringoplasty alone. All squamous epithelium must be excised from the middle ear prior to closure of the tympanic membrane defect to prevent further progression of the cholesteatoma and its subsequent well-recognized complications.

Contralateral hearing

Relative contraindications include a contralateral dead ear. Hearing loss from myringoplasty is rare at 1.5%, potentially from infection or manipulation of the drumhead and ossicular chain during surgery.[21]

Bilateral perforations

Should bilateral perforations be present, most would advocate operating on one ear at a time. While the incidence of severe hearing loss from myringoplasty is rare,[21] unilateral surgery avoids any risks to the contralateral ear, leaving this side available for hearing and communication, certainly while the post-operative packing is present (in the other). However, other studies have suggested that bilateral myringoplasty is safe, reduces costs and increases patient satisfaction, with post-operative packing causing only a modest CHL that is readily acceptable to patients.[22]

Eustachian tube dysfunction

Severe Eustachian tube dysfunction can be extremely challenging to treat. Attempting to elevate a Sade grade IV retraction from the ossicular chain can increase the risk of hearing loss. There is also an increased chance of an iatrogenic cholesteatoma should any epithelial cells be left *in situ*.[23] Reconstructing the tympanic membrane using cartilage can provide more resilience against the negative middle ear[22] but, despite this, recurrence of the retraction can occur.[18]

As when considering all surgery, the general medical fitness of the patient must be taken into account. Multiple factors adversely affect wound healing and can potentially influence the surgical result and should therefore be optimized prior to surgery. Chronic general medical conditions, such as diabetes and cardiovascular disease, lead to poor oxygenation of tissues, with infection and stress disrupting neuroendocrine immune equilibrium. Medications, obesity, smoking and alcohol consumption and poor nutrition should be optimized prior to surgery.[24] The insult of a general anaesthetic must also be taken into account for patients with multiple medical comorbidities. Myringoplasty can frequently be performed under local anaesthetic and particular consideration for this should be made in this patient group. Day-case surgery for tympanoplasty is increasingly the norm without compromising patient care and safety.[25]

FACTORS INFLUENCING TREATMENT OPTIONS

Various tympanoplasty prognostic scoring systems have been proposed, including SPITE (surgical, prosthetic, infection, tissues and Eustachian tube) and MERI (Middle Ear Risk Index), to try to stratify possibilities of success.[26] Other factors to consider prior to surgical intervention include patient age, presence of infection, status of the other ear, reperforation rates, the influence of the mastoid and smoking.

Timing and age

There is a debate as to whether age plays a part in success rates following myringoplasty. Some would advocate avoiding such surgery in younger children, awaiting Eustachian tube (ET) maturity prior to contemplating perforation repair. Morphological changes in the ET that accompany improvement in function are most marked after the age of 7 years,[27] with many managing these patients conservatively until after this age, assuming these patients were relatively asymptomatic. Others, however, suggest that age does not play a part in surgical outcomes

and will offer surgery to children younger than 7 years old. The state of the contralateral ear is an important guide as to overall function of the ET. Problematic perforations, such as those with recurrent infections or marked hearing loss causing developmental delay, may warrant earlier operative intervention.

Adenoidectomy

Evidence regarding the contribution of adenoidectomy to myringoplasty success is conflicting,[17] with the majority of reviews suggesting that prior adenoidectomy confers no benefit in success rates of myringoplasty.[28–31]

Infection

The literature has differing opinions regarding the influence of infection present at the time of surgery on outcomes. Up to 20% of perforated ears (both wet and dry) have been shown to grow pathogens on culture[32] and infection is one of the most common causes of failure in myringoplasty.[33] Some studies demonstrate that the presence of infection at time of surgery negatively influences outcomes, with higher rates of failed perforation closure, retraction pocket formation and myringitis.[18] The majority of studies, however, have shown that the presence of infection does not negatively influence surgical outcomes and therefore most surgeons would not be deterred from proceeding in the presence of active infection.[34, 35]

Other ear

A normal contralateral ear is a positive predictor of success of tympanoplasty as this suggests favourable overall Eustachian tube function.[26]

Conversely, abnormalities in the opposite ear should be checked to exclude the possibility of bilateral hearing loss or even the presence of cholesteatoma. With the presence of abnormalities in the other ear, success of graft uptake has been found to be poorer.[26, 36]

The presence of a bilateral perforation may influence the choice of graft material. Though there is little evidence to support any one particular graft material producing more favourable results over another,[17, 25] the use of cartilage is becoming more popular, particularly in this group, subtotal perforations and revision surgery, due to its perceived superior resilience over temporalis fascia alone and therefore potential higher closure success rates.

Reperforation rates

The literature quotes success rates of 60–99% in adults and 35–94% in children.[37] Most studies have short follow-up periods yet reperforation can occur several years after the initial surgery. There are relatively few long-term studies, with some suggesting that success rates fall over time from around 85% at 1 year to 78% at 10 years.[36] Reperforation rates in children under 15 years have been quoted at 18%, over double the rate of that in adults.[18]

Most failures occur in the early post-operative period, mainly due to graft failure from infection with graft necrosis or failure of the anterior aspect of the graft – the most tenuous area due to this region's apparent hypovascularity compared to the rest of the tympanic membrane.[5, 18, 38] Following initial failures, there are no clear guidelines as to whether surgical revision is indicated and, if so, how long one should wait before reoperating, though 3 months would seem a reasonable time to allow for the postsurgical changes to resolve.

Mastoid

The influence of the mastoid air cell system on chronic otitis media (COM) is still subject to debate. Poor pneumatization of the mastoid, together with Eustachian tube dysfunction, often predispose to chronic suppurative otitis media.[7] It is thought by some that mastoidectomy can improve outcomes in non-cholesteatomatous COM surgery by creating a reservoir of aerated bone to buffer pressure changes in the middle ear and by eradicating residual mucosal disease hidden in the mastoid air cells.[33, 39] While a recent study comparing myringoplasty alone with the same in combination with mastoidectomy did not show any statistically superior advantage with the latter, that group obtained better hearing results and required fewer subsequent ear procedures.[40] Other studies have demonstrated the presence of residual mastoid disease on CT scans of the temporal bones in patients whose graft had failed,[33] with mastoidectomy being advised in cases of COM not responding to pre-op intensive medical treatment[41] or in revision cases.[39] Although mastoidectomy has been claimed to be a safe procedure that neither significantly increases operative time nor results in further complications,[17] others argue that mastoidectomy does not improve surgical outcomes and exposes the patient to increased surgical risks.[42, 43] A recent literature review did not show any benefit of performing mastoidectomy with tympanoplasty for uncomplicated perforations.[44] More complicated otological disease, such as active mucosal COM or repeat perforations, show worse outcomes and may benefit from concurrent mastoidectomy, but there is insufficient evidence to recommend this.[45]

Social

The influence of smoking on surgical outcome is not clear. Some studies suggest no statistically significant effect on graft take rate[19] whereas others have noted the local, regional and systemic negative effects of smoking on the middle ear and Eustachian tube.[26, 46] Locally, nicotine causes cutaneous vasoconstriction, and increases thrombosis risk with carbon monoxide reducing the oxygen carrying capacity of blood. Regionally, chemical irritation leads to increased mucous viscosity and reduced mucociliary clearance with Eustachian tube obstruction. The systemic negative effects of smoking are well documented in the literature, particularly on the respiratory system.

INVESTIGATIONS

Ear swab

The value of microbiological culture of all discharging ears has not been shown to be statistically beneficial over empirically treated ears.[47]

Audiometry

All patients with a perforation or perceived hearing loss should undergo audiometric testing at the time of their clinic visit. This allows for quantification of the degree of hearing loss and can assist the surgeon in predicting what may be found in the middle ear at the time of surgery. Certainly, audiometry pre- and post-operatively allows for analysis of surgical outcome, both for surgeons to audit their results (and perhaps change their practice) and to demonstrate to the patient a successful outcome. The hearing in the contralateral ear is an important factor in guiding decision making in myringoplasty.

Imaging

Most myringoplasties do not require pre-operative imaging. In those in whom the history is unusual, or examination findings suggest further pathology, a fine-cut CT of the temporal bone can reveal unexpected opacification or unusual bone erosion, together with providing some insight into the state of the ossicular chain.

In cases with sensorineural asymmetry, a difference of greater than 20 dB at two adjacent frequencies is an indication for screening for the rare possibility of a concurrent vestibular schwannoma. T1-weighted MRI with gadolinium of the internal acoustic meatus is the gold standard investigation of choice.[48]

GRAFT MATERIALS

Since the full-thickness skin graft, first used by Berthed in 1878, many graft materials have been tried.[17] From autologous, to allogenous and heterogeneous, a wide spectrum of alternatives is available and there is no one ideal material.[17, 25]

The least invasive and perhaps simplest is the paper onlay technique, using a thin cigarette paper or similar placed onto the tympanic membrane as an outpatient procedure. This has been used with reasonable success to assist closure of small perforations, occasionally requiring repeat applications for a successful outcome. It is least successful for large perforations.[26]

Of the autologous materials, temporals fascia is the most frequently utilized for all perforations given its availability, the abundance of tissue and ease of use. Success rates of 77–99% in adults and 35–94% in children are quoted,[37] depending on experience and technique,[38] though multiple other factors may be influential. Easily harvested via a postauricular or endaural approach, a separate scalp incision, hidden in the hairline, may also be used during a permeatal approach. Treating the fascial graft prior to use with formaldehyde[18] does not appear to enhance successful closure rates, while the topical application of adhesive following graft placement is claimed to do so, although the median follow-up was relatively short at 4 months.[49]

Perichondrium from either the tragus or concha provides an alternative material, with the former being easily accessed either via a small and cosmetically acceptable retrotragal incision or by extending an existing end aural incision (if used as the approach). Several surgeons prefer tragal perichondrium due to its ease of harvest, particularly for the permeatal approach, and its long-term reliability.[50]

Cartilage, either from the tragus or concha, is gaining popularity as a more reliable material. A composite graft from the tragus provides a very practical material with a good thickness and curvature for use in tympanoplasty, together with a very low metabolic rate.[50] Keeping the cartilage attached to the perichondrium helps placement and aids graft stabilization and is now considered one of the best materials for use in larger perforations (greater than 50%),[17] adhesive otitis media and revision surgery for recurrent perforations, with quoted closure rates of up to 100%.[50]

Fashioning a cartilage 'butterfly' is a technique that has been proposed for smaller perforations less than 6 mm, with the cartilage disc being circumferentially incised by 1 mm. This groove is engaged into the perforation rim, thereby stabilizing the graft. Mild myringitis was encountered in 11%, resolving within 3 months, with a quoted closure success rate of 94%.[51]

There is some debate as to whether the hearing gain obtained with cartilage is inferior to that of fascia or other more flexible material. Short-term post-operative hearing with cartilage is not as good as that with temporalis fascia or perichondrium, but results at 1 year were the same,[50] with long-term hearing outcomes of cartilage and fascia being equivalent.[52, 53] This is presumed to be due to the partial resorption of cartilage over time[50] which causes it to lose its rigidity.[54]

Other autologous materials have been used, either locally accessible such as periosteum, subcutaneous tissue, ear canal or other skin graft and fat, the latter usually being harvested from the lobule or post auricular region[55] though umbilical fat has also been used.[56] Fascia lata and vein[57] provide a more distant autograft. Autograft and xenograft have been combined using fat and a hyaluronic acid ester (Epidisc) with quoted overall closure rates being 92.7%.[55, 58]

Experimental investigations of allogeneic materials include extracellular matrix in the form of urinary bladder matrix (in 14 animals with a closure in 13 out of 14 ears at the end of the experiment at 12 weeks)[59] and stem cells.[60] Results were encouraging though numbers were very small in both studies.

Alloderm, processed from human allograft skin and rendered immunologically inert, can provide an alternative when temporalis fascia is not available, with a success rate of 87.5%, equivalent to that of temporalis fascia.[61]

Several xenogenous materials have been investigated. Equine and bovine pericardium were found to be inferior

to temporalis fascia.[38] Basic fibroblast growth factor (FGF) has been studied since exogenous bovine FGF stimulates the proliferation of fibroblasts and vascular cells, induces endothelial cell migration, releases matrix-degrading proteases and forms tubular structures resembling blood capillaries.[62, 63] FGF has been used either in combination with atelocollagen, a type 1 collagen material derived from calf dermis, with closure achieved in 92% of 87 patients,[64] or to large (greater than 50%) traumatic perforations applied either via a Gelfoam patch over the perforation, or as drops alone with very encouraging results of 97% and 100% closure respectively within 10 days, compared to 55% in the control group within 41 days.[65]

TECHNIQUES

Two main techniques have been described for placement of graft materials, namely overlay and underlay. Overlay derives its name from the graft being placed lateral to the fibrous layer of the drumhead and hence over the fibrous annulus, the epithelial layer having been elevated alone and then replaced onto the graft. The underlay technique involves placement of the graft medial to the entire tympanic membrane, with elevation of a flap of ear canal skin together with the drumhead being most commonly used for access, stabilizing the graft under the fibrous annulus. A prospective randomized controlled study of both techniques did not show any difference in temporalis fascia graft uptake rates between the two techniques.[23] The authors concluded the underlay technique to be superior due to its technical ease, shorter post-operative healing time, fewer complications and better hearing gain.

There is debate as to correct placement of an underlay graft, particularly with a medialized handle of malleus. Usually the graft should pass under the malleus though, with a subtotal or central perforation with an exposed umbo, some advise a small hole in the centre of the graft through which the umbo can pass to try to prevent the 1.4% risk of graft lateralization.[18]

Access can be achieved permeatally or utilizing a cartilage-avoiding incision – endaural or postaural – depending on the location of the perforation and size of the ear canal. Since the development of the binocular microscope in the 1950s, this has become the standard for all middle and inner ear surgery. Recently, endoscopic techniques have been gaining popularity with the advantages of minimal access surgery and avoidance of visible scars.

COMPLICATIONS

Risks of reperforation have been discussed earlier in this chapter.

Retraction of the drumhead following grafting can occur in up to 10%,[18] with some suggesting the use of cartilage to try to prevent this.[50, 52, 53, 66]

Elevation of the anteroinferior aspect of the tympanic membrane runs the risk of anterior blunting, a risk with both overlay and underlay techniques.[23] Various techniques or packing methods have been proposed to try to prevent this as it can impact on hearing outcomes.

The incidence of iatrogenic cholesteatoma, particularly with the overlay technique which runs a higher risk of leaving some squamous epithelium medial to the graft, can be as high as 4.4%.[67, 68]

Myringitis can occur, influenced by the presence of infection[18] or choice of material,[51] though most cases resolve within 3 months with short-term topical medication and observation.

BEST CLINICAL PRACTICE

- ✓ Most surgeons wait until the patient is at least the age of 7 years before considering myringoplasty.
- ✓ The presence of infection at the time of surgery does not negatively impact success rates.
- ✓ Adenoidectomy confers no benefit on success rates for myringoplasty.
- ✓ There is insufficient evidence to support concurrent mastoidectomy during tympanoplasty.
- ✓ Temporalis fascia is the most frequently used autologous material, with the use of cartilage increasing in popularity for larger perforations (greater than 50%).
- ✓ Cartilage tympanoplasty has equivalent long-term hearing outcomes to temporalis fascia or perichondrium.
- ✓ Underlay and overlay techniques have similar outcomes.

FUTURE RESEARCH

- ➤ The quality and quantity of randomized controlled trials are limited.
- ➤ Further research should involve levels 1 and 2 evidence with regard to:
  - ➢ the role of mastoidectomy with tympanoplasty in chronic otitis media
  - ➢ ideal minimal age for surgery
  - ➢ the role of tissue engineering and growth factors should be a productive area for future research.

KEY POINTS

- Around 70–80% of acute perforations heal spontaneously within 30 days.
- The risk of chronic perforations following short-term ventilation tubes is 2.2% rising to 16.6% with long-term tubes.
- Aminoglycoside antibiotics are ototoxic but quinolone-based are not; a short course of topical aminoglycoside-based drops in the presence of a perforation is acceptable but, if used, this should be stopped as soon as the infection has cleared.
- Three indications for myringoplasty are recurrent infections, hearing loss and social impact such as pain on swimming.
- Success rates for myringoplasty are 60–99% in adults and 35–94% in children.
- Post-operative retraction of the drumhead can occur in up to 10%.
- The risk of iatrogenic cholesteatoma is 4.4%.

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CHAPTER 85

OSSICULOPLASTY

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: ossiculoplasty, ossicular chain, reconstruction, prosthesis, middle ear, hearing, with additional searching of secondary sources.

INTRODUCTION

This chapter covers the principles and practicalities of surgery to correct ossicular chain abnormalities with the aim of improving hearing. The surgical priorities when treating chronic middle ear disease are first to make the ear safe, then to make it dry, and finally to make it work. The last of the three is often the most difficult – and of great concern to the patient – which is why ossiculoplasty can be both challenging and rewarding.

AETIOLOGY/PATHOLOGY

Conductive hearing loss due to ossicular chain abnormalities may be either congenital or acquired, and is due to either ossicular chain discontinuity or fixation.

Congenital

Deformities of the ear occur in approximately 1 in 15 000 births with isolated middle ear abnormalities or 'minor' malformations being less common than 'major' malformations which may also involve the tympanic membrane and external ear.[1, 2] Favourable results following surgical reconstruction of major malformations are dependent on the severity of the abnormality. The status of the ossicles, presence of the round window, pneumatization of the middle ear space, and course of the facial nerve are key determinants.[3] Prognostic grading systems such as the Jahrsdoerfer score can be used to predict the likelihood of achieving good hearing outcomes.[4]

A diverse range of isolated middle ear deformities has been described, the most common being fixation of the stapes footplate which may occur in isolation (which is often bilateral) or in association with stapes superstructure or other ossicular abnormalities.[5] Epitympanic fixation of the ossicular heads and ossicular discontinuity are described less frequently.[6] The most challenging cases involve aplasia of the oval or round window; however, fortunately these are rare. Surgery for congenital ossicular chain abnormalities should only be attempted by experienced otologists after careful consideration of alternatives which include air- or bone-conduction hearing aids.

Acquired

The majority of ossicular chain defects arise as a consequence of chronic otitis media with or without cholesteatoma. Ossicular chain erosion is much more common in the presence of cholesteatoma (**Table 85.1**). The most common acquired abnormality is erosion of the long process of the incus, which may be confined to the incudostapedial joint (ISJ) or extend a variable distance superiorly. The stapes superstructure may be partially or completely eroded, whereas the malleus handle is the most frequently preserved. Shortening or absence of the malleus handle is generally associated with subtotal perforations.

Ossicular disruption secondary to trauma may occur following direct injury to the tympanic membrane,

TABLE 85.1 Ossicular chain defects in 1211 consecutive chronic middle ear cases

Defect	% Incidence with cholesteatoma *n* = 692	% Incidence without cholesteatoma *n* = 519
Ossicular chain intact	27	71
Incus alone eroded	26	18
Incus and stapes eroded, malleus intact	24	7
Incus, stapes and malleus eroded	11	2
Incus and malleus eroded, stapes intact	8	2
Stapes alone eroded	2	0.4

TABLE 85.3 Modifications to classification system by Kartush[9]

Group	Ossicular status
O	Intact ossicular chain
E	Ossicular head fixation
F	Stapes fixation

TABLE 85.5 Middle Ear Risk Index 2001[13]

Otologic factor	Maximum score
Otorrhoea	3
Perforation	1
Cholesteatoma	2
Ossicular status	4
Middle ear granulation	2
Previous surgery	2
Smoking	2

barotrauma or temporal bone fracture. These defects are further described in Chapter 91, Ear trauma. Idiopathic cases of resorption of the long process of the incus in the absence of active suppurative ear disease have been described in the literature but are rare.[7]

CLASSIFICATION OF DEFECTS

The value of a classification system is to enable a systematic description of pre-operative ossicular status to facilitate meaningful analysis of surgical outcomes. Given the multitude of surgical approaches for correcting ossicular chain abnormalities, it is essential when evaluating results that the pathologies are comparable. While each patient will present a subtly unique anatomical situation, defects can be broadly characterized by the presence or absence of different components of the ossicular chain.

The most widely used classification system is the Austin–Kartush system which applies to situations without an intact incus. First proposed by Austin in 1971,[8] four distinct

TABLE 85.2 Austin classification of ossicular chain defects with absent incus[10, 11]

Group	Ossicular status	Abbreviation	Prevalence (%)
A	Malleus handle and stapes superstructure present	M+ S+	60
B	Malleus handle present, stapes superstructure absent	M+ S–	23
C	Malleus handle absent, stapes superstructure present	M– S+	8
D	Malleus handle and stapes superstructure absent	M– S–	8

TABLE 85.4 Belluci classification of otorrhoea[12]

Otorrhoea	Risk value
Dry ear	0
Occasionally wet	1
Persistently wet	2
Persistently wet + cleft palate	3

anatomical situations are described (Table 85.2). This was modified by Kartush in 1994,[9] with the addition of three further categories to include a normal ossicular chain, and cases of fixation (Table 85.3). Situations not covered by the Austin–Kartush classification are rare and include isolated malleus handle fracture and fracture of the stapes superstructure. The classification also makes no specific allowance for partial incus erosion where incus remnant preservation is attempted.

PROGNOSTIC FACTORS

The ideal scenario in which to perform ossiculoplasty is in a stable well-ventilated middle ear, with an intact tympanic membrane, in the absence of ongoing middle ear infection or cholesteatoma. Absence of any of the above factors increases the risk of failure, as do patient factors such as smoking status.[13]

The Middle Ear Risk Index (MERI) was devised by Kartush in 1994 and generates a numeric value which corresponds to severity of disease, and the likelihood of a successful outcome following surgery.[9] This can be used to guide case selection and counselling of patients pre-operatively but is perhaps most useful for research purposes. It is an amalgamation of the Austin–Kartush classification of ossicular defects, the Belluci classification of otorrhoea (Table 85.4),[12] and takes into consideration the presence of tympanic membrane perforation, middle ear granulation, and cholesteatoma. The MERI was originally scored 0–12, and was later modified in 2001 to include smoking and increase the weighting for granulation and cholesteatoma thus giving a score of 0–16 (Table 85.5).[13] Alternative risk stratification or scoring

systems include the Ossiculoplasty Outcome Parameter Staging (OOPS) index,[14] or SPITE factors (surgical, prosthetic, infection, tissue, Eustachian).[15]

KEY POINTS

- Use of a classification system such as the Austin–Kartush allows a meaningful analysis of results and comparison of results between surgeons.
- Ossiculoplasty results are significantly affected by the status of the middle ear.

MATERIALS FOR RECONSTRUCTION

The ideal material for ossicular reconstruction should be biologically stable (resistant to resorption and non-reactive), of the correct mass and stiffness, be easy to handle, and ideally low cost. There are many options for reconstruction which can be broadly divided into autografts, homografts and alloplastic materials.

Autograft

Autografts are tissues that are harvested from the same patient on which they are to be used, and can include ossicles, cortical bone and cartilage. Their primary advantage is excellent biocompatibility with low risk of extrusion. When available, an autograft offers a low-cost solution compared to ossicular prostheses.

Incus interposition is an example of a well described and popular technique in situations with an intact malleus handle and stapes superstructure.[16, 17] Cartilage tends to be less stable due to displacement or resorption and is less commonly used.[18, 19]

Limitations to the use of autologous ossicles are that the incus is not uniformly present in diseased ears, while technical skill and time are required to sculpt the incus to the required shape. There is a risk of implanting residual disease if the ossicle has been enveloped in cholesteatoma, therefore careful assessment of its integrity is required. Some surgeons recommend autoclaving ossicles prior to reimplantation to reduce the risk residual disease[20] but this is not widely practised.

Homograft

Homograft material is derived from human donor tissue. A wide choice of pre-prepared graft material is available with options including cortical bone, cartilage, ossicles, and *en bloc* ossicular chain with tympanic membrane attached.[21, 22]

Benefits over autografts include a shortening of the operative time as pre-prepared prostheses can be inserted directly or with minimal modification. Homografts offer reconstructive options that may be absent or eroded in diseased ears, and do not carry the risk of residual cholesteatoma provided they are harvested correctly.

The major barrier to the use of homograft materials is the potential risk of disease transmission from donor to recipient, with viral infections and the transmissible spongiform encephalopathy Creutzfeldt–Jakob disease (CJD) of particular concern.

The majority of cases of iatrogenic CJD transmission have occurred following neurosurgical procedures using infected dural grafts.[23] Two cases of CJD transmission have occurred following ear surgery, one as a result of cadaveric dura mater, and another due to the use of pericardium. There are no reported cases of CJD transmission from the use of homograft tympanic membranes or ossicles while they have been used in thousands of procedures.[24, 25]

A combination of serological donor screening, and appropriate methods for ossicle preparation can reduce the risk of disease transmission to a very low level. However, ongoing concerns about potential infectivity combined with significant infrastructure required to maintain an ossicle bank, and the improvement in artificial materials mean that homografts have fallen out of favour in many countries.

Alloplastic materials

The use of alloplastic materials for ossiculoplasty was first described in 1952 by Wullstein who used a 'palavit' (vinyl–acrylic resin) columella prosthesis to connect a mobile stapes footplate with the tympanic membrane.[26]

Since that time, a wide range of materials have been used in the search for a prosthesis that retains its structural integrity yet can be easily shaped or modified. Of equal importance is that the prosthesis does not induce unwanted inflammatory reactions in middle ear tissues yet bio-integrates in such a way that it is not extruded.
Materials that have been used include:

- solid plastics: polytetrafluoroethylene, polyethylene
- solid metals: stainless steel, gold, titanium
- porous sponge-like plastics: Proplast®, Plasti-Pore®
- ceramics: aluminium oxide, hydroxyapatite.

Solid plastics and stainless steel were some of the earliest materials used but were largely abandoned due problems with absorption at bony interfaces and extrusion.[27] Plasti-Pore® became one of the most widely used artificial materials following its introduction in 1976, but it has high extrusion rates when placed in contact with the tympanic membrane therefore cartilage interposition is required.[28] Histopathological studies have also shown porous plastics can elicit a foreign body giant cell reaction with evidence of implant degradation.[19]

Hydroxyapatite is a calcium-based bio-ceramic with a mineral composition similar to bone and continues to be a popular and proven material with low extrusion rates.[29] Some prostheses are compound designs to take advantage of the different properties of the materials, for example a hydroxyapatite head that can be placed directly against the tympanic membrane with a composite shaft that can be easily trimmed to length.[30]

Titanium implants were introduced in the early 1990s,[31] and have excellent mechanical properties due to high rigidity allowing low-weight prosthesis designs.

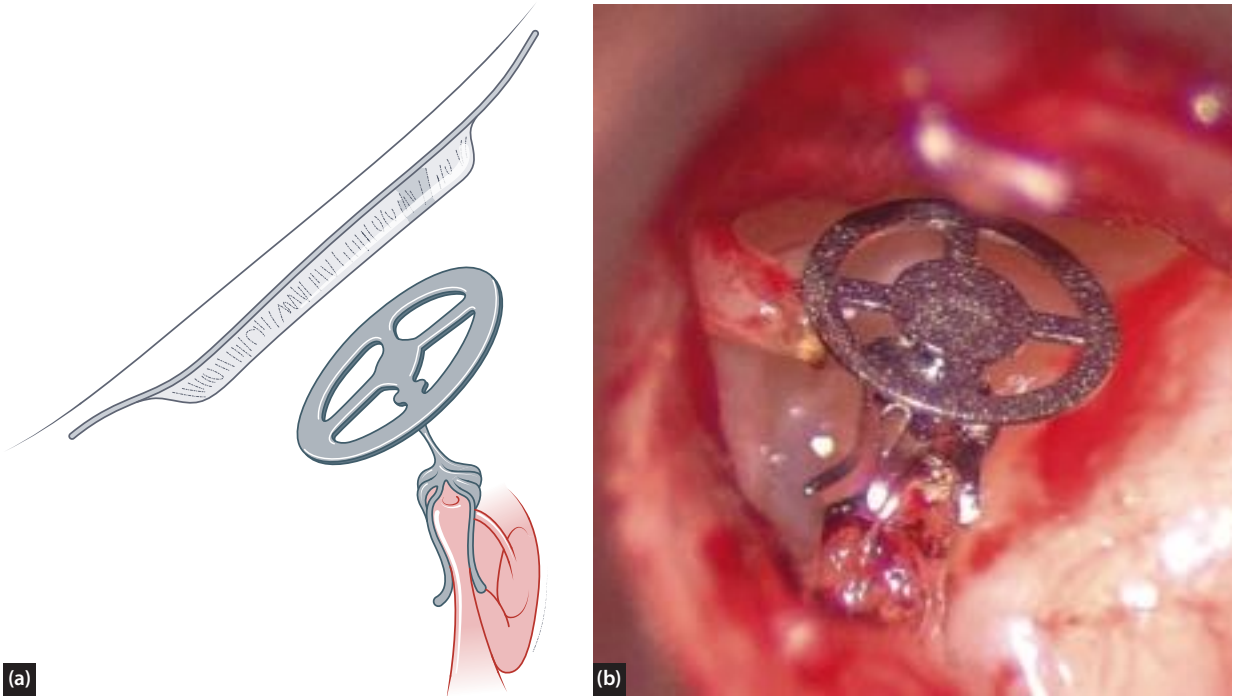


Figure 85.1 PORP on intact stapes. (a) Partial ossicular replacement prosthesis *in situ* on intact stapes superstructure. The cartilage and perichondrium graft lies between the prosthesis and the tympanic membrane. **(b)** Partial clip prosthesis sitting on stapes inferior to eroded incus long process which remains in place.

Complex designs are possible with open head configurations to improve visualization during placement, and delicate 'claw' attachments to fasten securely to the stapes head (Figure 85.1a). Titanium is biocompatible with low extrusion rates of less than 5%.[27] While most surgeons interpose cartilage between a titanium prosthesis and the tympanic membrane, Pringle has questioned whether this is necessary.[32]

KEY POINTS

- Autograft incus continues to be a widely used material for ossicular reconstruction.
- Ideal prostheses should not induce reaction in the middle ear.

BOX 85.1 Terminology

PORP = partial ossicular replacement prosthesis. Generally used to mean a prosthesis that is designed for situations with an intact stapes superstructure.
TORP = total ossicular replacement prosthesis. For use in situations where there is no stapes superstructure and the prosthesis restores a connection with the stapes footplate.

Ossicular reconstructions are referred to as **columellae** when the sound transmission is restored with an ossicle to tympanic membrane connection, and **assemblies** where there is an ossicle-to-ossicle connection.

SURGICAL OPTIONS TO CORRECT SPECIFIC DEFECTS

Due to the wide variation in surgical practice and increasingly large range of prostheses available it is not possible to give an exhaustive account of all surgical options for each reconstruction. What follows are illustrative examples of proven surgical strategies.

Box 85.1 introduces ossicular reconstruction/replacement terminology.

Eroded long process of the incus

This is the most common ossicular chain defect encountered in patients with chronic middle ear disease of all aetiologies.[33] Early attempts to restore hearing in cases of ISJ separation included stapediopexy where the tympanic membrane is brought into direct contact with the stapes head.[34] This approach has the obvious disadvantage of losing the amplification and dampening functions of the ossicular chain. Preservation of the natural anatomy is preferable and can be achieved by the following methods.

BRIDGING WITH AUTOLOGOUS TISSUE

Where there is a small distance of separation between the stapes head and incus long process remnant, interposition bridging may be attempted.[34] Materials that are most frequently used for this purpose include autologous cortical bone – harvested from the mastoid or external auditory canal – or cartilage.[35] Reconstruction of longer defects may be unstable and can lead to unpredictable results.[16] Bridging material may be partially resorbed, displaced, or form bony ankylosis with the canal wall.

PROSTHESIS

The first dedicated ISJ replacement prosthesis was reported in 1993 and consisted of a basic cuboidal hydroxylapatite design with a circular aperture for the stapes head and a groove to accommodate the long process remnant.[36] A variety of other prostheses have been developed over time, differing in both material and design. The interface with the stapes head may be a simple cup although more recent adoption of titanium and improved manufacturing techniques allow more complex designs such as self-securing clips.[37] The prosthesis may accommodate the incus long process remnant with a groove, wire coil or circumferential crimping attachments.

BONE CEMENT/BONE PATE

The use of bone cement to reconstruct the long process of the incus is a more recent development and has been shown to give good hearing results at least in the short term. Studies show 80% of patients achieve air–bone gap closure to within 20 dB at 1 year.[38, 39] Care must be taken when applying bone cement to avoid spillage onto the stapes footplate or unintended fixation to the posterior canal wall.

An alternative to cement is the use of bone pate which can be collected by drilling healthy mastoid cortex. This option works best where there is still a partial connection between the long process of the incus and the stapes head (Figure 85.2). Some surgeons mix the bone dust with blood and/or fibrin glue to aid adhesion.

Eroded incus with malleus and stapes present (Austin–Kartush type A)

In cases where the incus is partially or completely eroded and anatomical reconstruction of the ossicular chain is not

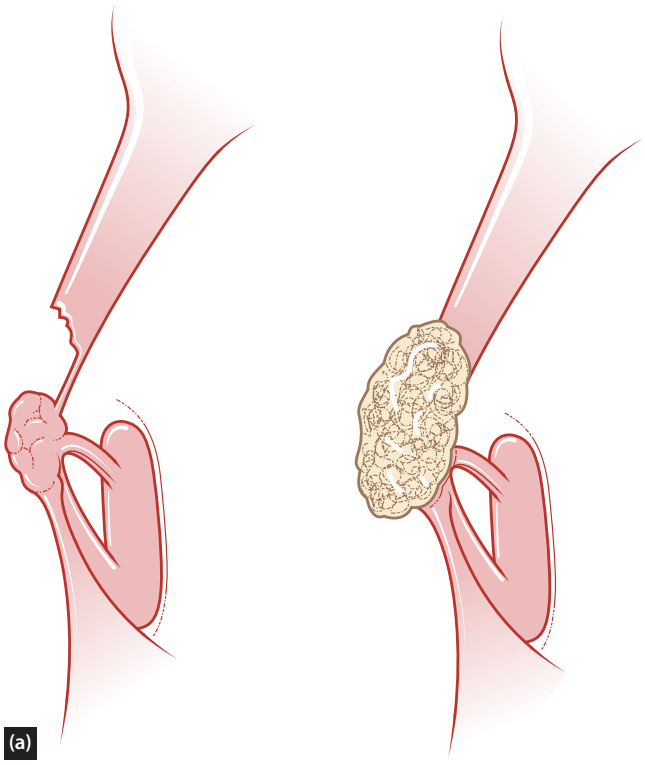






Figure 85.2 Incudostapedial joint reconstruction. (a) Erosion of the long process of the incus with a tenuous fibrous attachment (left) can be reconstructed with cement or bone pate (right). **(b)** Eroded incus. **(c)** Incus reconstructed with bone cement.

possible, there are several alternative options for restoring hearing when the malleus handle and stapes superstructure remain intact.

AUTOLOGOUS OSSICLE INTERPOSITION

Repositioning the incus as a method for restoring the function of the ossicular chain was first described in 1957 by Hall and Rytzner,[40] since which time it has been shown to be a stable option for reconstruction.[41]

When the body and short process of the incus are intact, it may be used for reconstruction provided the surgeon is confident it harbours no residual disease. Ossicle forceps and a microdrill are used to sculpt the ossicle into the desired shape with a variety of configurations possible.

The classical method involves placing the body of the incus on the stapes head with the short process directed towards the malleus handle and medial to it.[16] Modifications of the technique include creating a groove in the short process so that it rests against the malleus handle, or alternatively lateral to the malleus handle.[39] The malleus head may be used where the incus is not available (**Figure 85.3**), although usually it is brought into direct contact with the tympanic membrane, in contrast to the incus assembly which aims to rest against the malleus handle. Cartilage and sculpted cortical bone can be used although these are more prone to resorption or ankylosis.[18]

The use of homograft ossicles or cortical bone has also been described[22, 42] and continues to be used in some countries, with up to 90% of patients achieving <20 dB air–bone gap in one series of cases receiving sculpted homograft incus interposition.[43]

PARTIAL OSSICULAR REPLACEMENT PROSTHESIS

Selecting an appropriate ossicular replacement prosthesis requires careful consideration of the anatomical configuration of the middle ear and ossicles. The two main options for prosthesis placement are stapes to malleus or stapes to tympanic membrane.

Stapes to malleus

Advantages of this configuration are preservation of the catenary lever mechanism of the tympanic membrane.[44] Placing the prosthesis medial to the handle of the malleus may also reduce the rate of extrusion as compared to prostheses in direct contact with the tympanic membrane.[45]

A significant drawback is that in most situations the malleus–stapes offset means the vector of force is never perfectly in the line of the stapes, thereby resulting in inefficient energy transfer (**Figure 85.4**). When the malleus–stapes offset is of sufficient magnitude for the interposition prosthesis to have an angle greater than 45 degrees relative to the vertical axis of stapes movement, significant tilting movements occur at the footplate with resultant marked loss of sound transmission.[46]

This can be improved by malleus relocation, which involves separating the malleus handle from the tympanic membrane, division of the tensor tympani at its insertion, and stretching or avulsing the anterior suspensory ligament by pulling posteriorly on the neck of the malleus. The superior ligament is left in place to support the malleus. The malleus handle is placed more posteriorly towards a position overlying the stapes head (**Figures 85.5** and **85.6**).[47]

Stapes to tympanic membrane

This approach can be used in cases where the malleus handle orientation is unfavourable due to anterior angulation or medial displacement. The disadvantage of this method is that the catenary lever mechanism is lost, and the prosthesis may be unstable as it does not have any fixed lateral attachment other than the relatively compliant tympanic

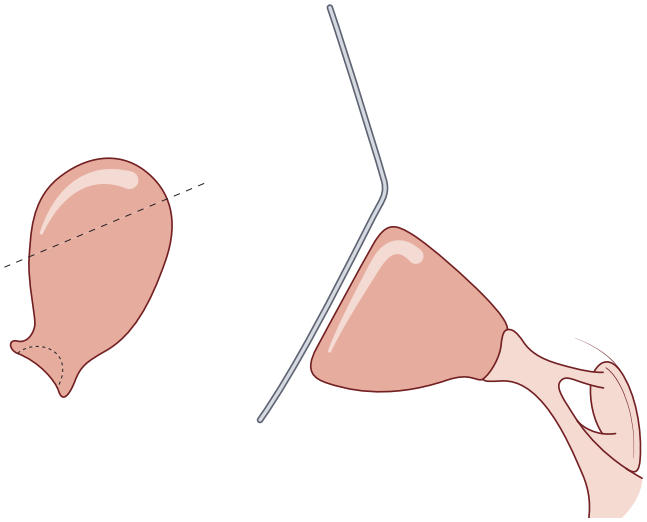


Figure 85.3 Malleus head reconstruction with intact stapes. The malleus head can be used in a stapes-to-drum configuration to reconstruct Austin–Kartush type A or C defects. The left-hand image indicates the reshaping required prior to use.

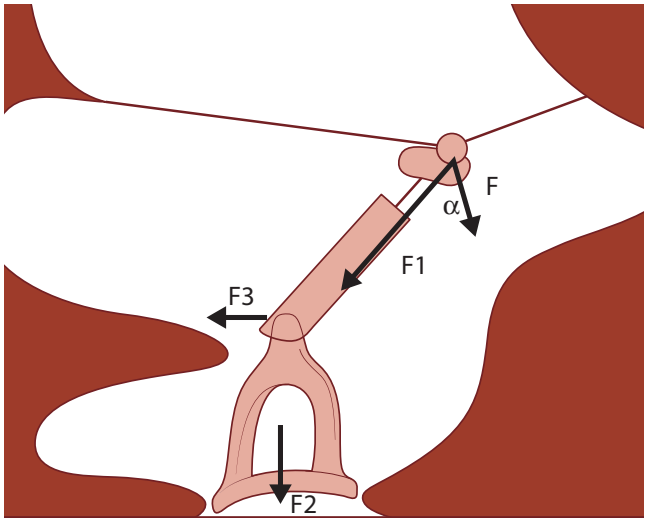


Figure 85.4 If the malleus is very anterior and medial, angle α increases. As angle α gets larger the desirable force through the footplate F2 decreases and the undesirable tilting force F3 increases (Courtesy of Robert Vincent).

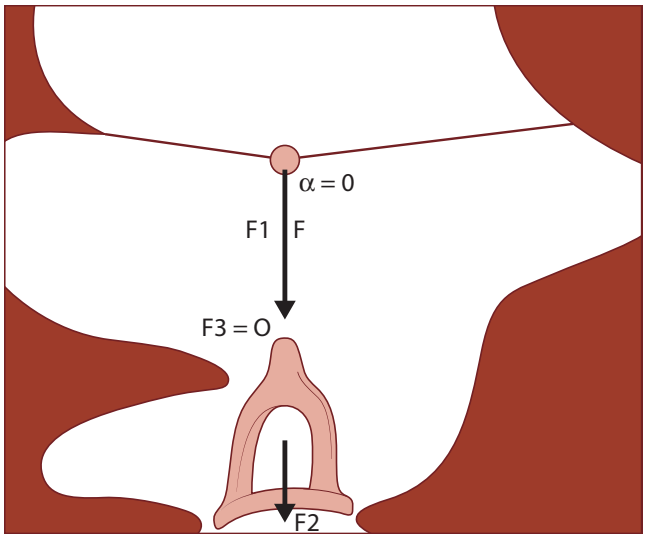


Figure 85.5 When the malleus is repositioned over the stapes, the undesirable tilting force F3 is reduced (Courtesy of Robert Vincent).

membrane. Some prostheses require interposition of a thin cartilage strip between the tympanic membrane and the head of the prosthesis to reduce the risk of extrusion although not all surgeons feel this is necessary.[27, 32]

Most prosthesis designs are in the shape of a drawing pin with a strut which attaches to the stapes head, and a perpendicular flat disc which may be centred on the strut or eccentrically placed. Some newer designs have an open head which allows the surgeon to visualize the stapes during insertion thereby facilitating this manoeuvre.

Interestingly, some surgeons advocate using TORPs in the presence of an intact stapes. The prosthesis shaft is placed between the stapes superstructure and the facial nerve directly onto the stapes footplate. This aims to improve prosthesis stability and energy transfer.[48]

Malleus present, stapes absent (Austin–Kartush type B)

When the stapes superstructure is absent, mechanical coupling between the stapes footplate and the tympanic membrane or malleus handle must be achieved. This type of reconstruction is inherently less stable due to the distance that must be bridged and the absence of a fixed attachment point on the stapes footplate. Several studies using multivariate analysis have identified presence of the stapes superstructure as being a key determinant of success following ossiculoplasty, with poorer hearing outcomes to be expected when it is absent.[49–51]

HOMOGRAFT OSSICLE

Autologous incus is rarely available as a reconstructive option in this situation as absence of the stapes superstructure will almost invariably be accompanied by a degree of long-process erosion. Homograft incus has been used extensively for this purpose with most reports describing the long process resting on the footplate and a sculpted notch at the opposite end to accommodate the malleus handle.[22, 42, 52] Results for this technique are highly variable.

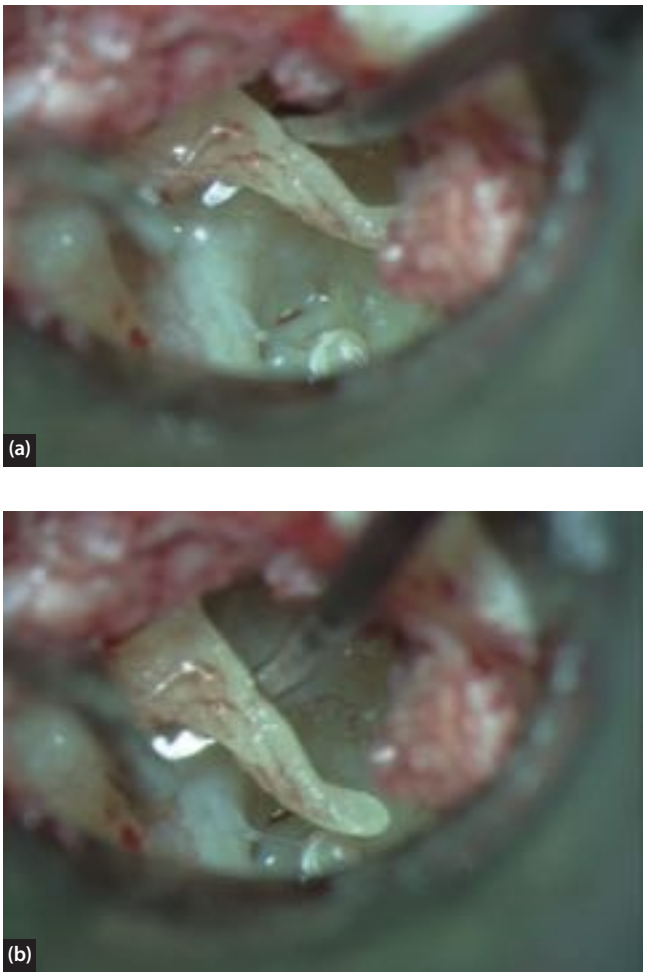


Figure 85.6 (a) A heavy hook is placed anterior to the neck of the malleus, which has been separated from the tympanic membrane and divided from the tensor tympani. It is then pulled posteriorly and the anterior malleolar ligament gives way to allow the malleus to be placed more posteriorly. (Robert Vincent.) **(b)** The repositioned malleus now lies directly over the stapes. (Robert Vincent.)

TOTAL OSSICULAR REPLACEMENT PROSTHESIS

TORPs bear structural similarity to PORPs with the range of head designs often shared, however the strut is longer to reach the stapes footplate, and the medial end of the prosthesis is often flattened to rest on the footplate rather than cupped. As with PORPs, some designs of TORP are shaped specifically to accommodate the malleus handle with a notch or groove, whereas others have a flat disc leaving both footplate-to-malleus and footplate-to-tympanic membrane options open.

One of the challenges of this type of reconstruction is the tendency for prosthesis displacement. TORPs can be placed directly on the stapes footplate, although stability may be improved with a cartilage 'shoe' or a

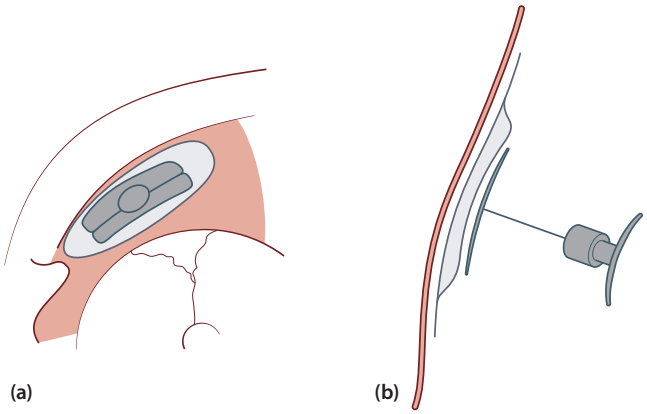


Figure 85.7 TORP with footplate shoe. (a) The footplate prosthesis in position on the oval window beneath the facial nerve. **(b)** A typical configuration with a cartilage and perichondrium graft between the prosthesis and tympanic membrane.

specially designed footplate prosthesis.[53, 54] The footplate shoe acts as an anchoring point for the medial end of the prosthesis, thereby reducing displacement while also helping to direct the vector of force through the centre of the footplate improving sound transmission (Figure 85.7).[55]

Malleus absent, stapes present (Austin–Kartush type C)

Several retrospective analyses have shown absence of the malleus handle to be a major independent prognostic factor resulting in poorer hearing outcomes following reconstruction.[56, 57] This is partly due to the loss of the amplification produced by the tympanic membrane–malleus handle complex, and loss of a solid point of fixation for any reconstructed assembly.

The simplest surgical option is to proceed with a stapes-to-tympanic membrane reconstruction as described above for type A defects. An alternative approach is to recreate the malleus handle, either with autologous material or with a prosthesis. Homograft tympanic membrane with attached malleus handles have also been used widely.[58]

NEOMALLEUS

Creation of a neomalleus strut can be achieved with incus, cortical bone or cartilage. Black showed superior hearing outcomes with a neomalleus assembly technique as compared to collumella only approach.[59] He described a neomalleus strut being placed medial to the tympanic membrane graft with the preferred source being a strip of cartilage from the root of the helix.

MALLEUS REPLACEMENT PROSTHESIS

The design and use of a malleus replacement prosthesis is a recent development described by Vincent et al. Patients receiving the malleus replacement prosthesis showed improved hearing results as compared to using a footplate to tympanic membrane TORP (12.5 dB air–bone gap and 23.3 dB respectively) and reduced prosthesis displacement.[60]

Malleus and stapes absent (Austin–Kartush type D)

This is the most challenging ossicular defect and is likely to lead to the poorest outcomes. It may be managed with a combination of the above techniques and will require reconstruction with autologous tissue, ossicle interposition or TORP. The reconstruction may be footplate-to-tympanic membrane, or alternatively a neo–malleus or malleus replacement prosthesis may be used to improve stability.

OPERATIVE CONSIDERATIONS

Length of prosthesis

Several studies have investigated the effect of the tension of the ossicular reconstruction on sound transmission at the oval window. Lower-tension reconstructions with a short prosthesis resulted in better sound transmission than higher-tension reconstructions with a long prosthesis.[46, 61] The beneficial effect of a more loosely fitting prosthesis on hearing must be balanced against the potential increased risk of displacement.

Staged reconstructions

As the majority of ossicular chain defects arise as a consequence of chronic suppurative otitis media, tympanic membrane retraction or cholesteatoma, the primary goal of the initial operation is generally to achieve a safe, dry ear. The decision whether to attempt ossicular chain reconstruction at the first operation or whether to perform a staged reconstruction at a later date depends on several factors.

The most important issues to consider are the risk of recurrent or residual disease. Eustachian tube function is a key determinant of outcome following tympanoplasty surgery,[62, 63] and the associated tympanic membrane retraction causes specific problems in ossiculoplasty due to increased risk of prosthesis displacement or extrusion. Similarly, where there is judged to be a significant risk of residual cholesteatoma, performing primary ossiculoplasty can complicate potential revision surgery if the recurrence involves the reconstructed ossicular chain.

In ears at higher risk of retraction or residual disease it may be prudent to delay reconstruction until a disease-free, aerated middle ear space has been achieved. However, it is often possible to offer primary reconstruction, particularly as improved imaging techniques with diffusion-weighted magnetic resonance imaging allow the option for radiological cholesteatoma surveillance without necessitating second-look surgery.[64, 65]

AUDIT AND RESEARCH

One of the challenges facing ossiculoplasty surgeons is being able to predict what outcome is likely to be achieved with a particular type of reconstruction or prosthesis. While published series may give an indication of the range of outcomes that can be expected, it is essential that surgeons are aware of their own results when consenting patients for surgery. Individual data collection and self-audit may be facilitated by specialized software or internet-based data entry.[66, 67]

There is a paucity of randomized controlled trials for evaluating ossiculoplasty methods or prostheses. Most results published in the literature are case series from a single surgeon or institution, with comparisons often occurring at the time of transitioning between an established method and a newer approach. Comparing results between studies may be confounded by several uncontrolled variables such as population differences, case complexity (although previously mentioned risk scoring systems may help adjust for this) and, perhaps most importantly, surgical technique.

It is important to be aware of variation in the way results are reported as there is no universally accepted measure of a 'successful outcome'.[68] The main considerations following ossiculoplasty are hearing results, and complication rates which may be prosthesis-related (extrusion, displacement, inflammatory reaction) or general (graft failure, taste disturbance, etc.). Most studies report short observation periods of 1 year; however, it has been established that audiometric results frequently deteriorate over time, and complications may present after many years.[56, 69]

KEY POINTS

- While prosthesis design and surgical technique undoubtedly affect results, the status of the middle ear is probably the most significant factor in outcome.
- Surgical results from ossiculoplasty tend to deteriorate over time.

BEST CLINICAL PRACTICE

✓ As ossiculoplasty results are variable, surgeons should endeavour to record their own results to enable accurate consent of their patients.

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CHAPTER
86

EUSTACHIAN TUBE DYSFUNCTION

Holger H. Sudhoff

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: Eustachian tube, Eustachian tube dysfunction, imaging, chronic otitis media focusing on diagnosis, surgery and management.

INTRODUCTION

The Eustachian tube (ET) is part of a system including the nose, palate, rhino-pharynx and middle ear spaces.[1] This comprises the tympanic cavity, which includes the bony ET and the mastoid air cell system (**Figure 86.1**). The tympanic cavity and mastoid cells are interconnected and allow for gas exchange and pressure equalization. The ET is a complex organ consisting of a dynamic, mucosal lined canal, cartilage, surrounding soft tissue, peri-tubal muscles, superior bony support and the sphenoid sulcus. Clinical experience as well as numerous patient studies and animal models prove that the ET plays an important role in various middle ear pathologies.[2–4] Despite improvements in the understanding of ET function, significant uncertainties remain due to its complex anatomy, multiple functions as well as the impact of intrinsic and external factors.[5,6] Intermittent transitory tubal dilation is probably the major mechanism for equalizing middle ear cleft and ambient atmospheric pressure.[7] Barometric and chemical receptors within the middle ear cleft are assumed to provide autonomic nervous system feedback that impacts on the frequency of involuntary tubal opening.[8,9] Our understanding of the anatomy and physiology of the ET still continues to evolve. Recently, McDonald et al. demonstrated that the ET might have a sequential peristaltic-like mechanism.[10]

Currently, there are various medical and surgical interventions available for chronic obstructive ET dysfunction

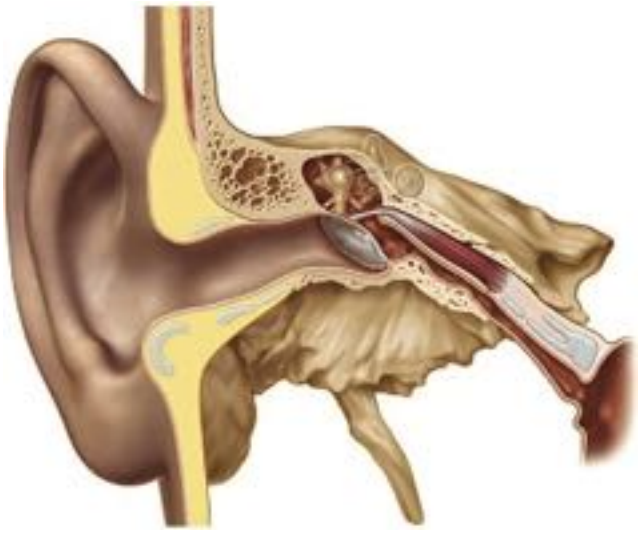


Figure 86.1 Temporal bone drawing of the cartilaginous and bony portion of the ET and middle ear spaces.

including balloon Eustachian tuboplasty (BET) and laser or microdebrider tuboplasty.[11–17] However, the small sample sizes in the reviewed literature represent a significant limitation when assessing their efficacy. The majority of available studies are underpowered and unable to detect a significant effect.[18] Long-term results with these procedures still have to be established.

DEFINITION

The term Eustachian tube dysfunction (ETD) describes impairment of ET function and leads to a variety of symptoms and physical findings. The condition does not necessarily lead to detectable middle ear pathologies. Dysfunction of the ET can be either acute or chronic. Acute ETD can occur during nasal congestion due to a common cold or allergic rhinitis, for example, and is generally transient. ETD lasting longer than 3 months consecutively is considered chronic. Chronic ETD can be due to obstruction or to a patulous (branching) Eustachian tube (PET). ETD is nevertheless a poorly defined condition.[18]

AETIOLOGY

Allergic disposition with accompanying mucosal hyperplasia and nasopharyngeal acid reflux may play an important role in ETD. ETD can lead to clinical symptoms such as aural fullness, impaired pressure equilibration, altered middle ear aeration, hearing loss and autophony (the unusually loud hearing of a person's own voice).

ETD is estimated to be present in about 1% of the general population.[19] Because the most common cause of obstructive dysfunction is mucosal inflammation within the cartilaginous ET, patients should be questioned about inflammatory processes such as allergic rhinitis, chronic rhinosinusitis, laryngopharyngeal reflux (LPR) and smoke exposure.[20, 21] ETD has been found to be associated with a higher number of nasopharyngeal reflux events and higher reflux finding score in adult patients.[22] Paediatric ETD may be caused by adenoidal hypertrophy and mucosal swelling due to acute or chronic upper respiratory tract infections. Cleft palate, granulomatous diseases, cystic fibrosis, Samter's triad and Kartagener syndrome are predisposing factors. ETD may be a contributing factor to vertigo.[23, 24] It is important to distinguish ETD from other causes of aural fullness such as temporomandibular joint (TMJ) disorders, superior semicircular canal dehiscence syndrome, Ménière's disease and increased intracranial pressure employing a tailored assessment. Almost 40% of all children up to the age of 10 years develop temporary ETD.[25, 26] Studies accessing paediatric and adult patient cohorts demonstrate that ETD is detectable in up to 70% of patients undergoing middle ear surgery.[27] Good ET function is believed to be important for the successful outcome of middle ear surgery.[28, 29] Patients with a PET usually present with positional autophony and hearing both voice and breathing sounds or aural fullness.[26] The precise distinction between the obstructive and 'patulous' ET is essential for appropriate medical or surgical treatment but is often challenging. Patients with PETs may benefit from augmentation or reconstructive procedures.[30, 31]

ASSESSMENT

A large variety of methods have been employed to assess ET function,[31–39] with more than 40 described in the literature.[31] None is able to give detailed insight into all aspects of ET physiology and pathology. Clinical tests such as otoscopy, endosocopy, Politzer test, Valsalva (exhaling into a closed airway by pinching the nose and closing the mouth) and Toynbee manoeuvre (pinching the nose and swallowing) may give initial guidance. Manometric testings (tympanometry, reflex decay tympanometry, nine-step inflation deflation test, modified inflation deflation test, forced response test and tubomanometry (TMM)) have some value.[31–39]

TMM was described by Estève in 2001[36, 37] and is a tool to measure the opening of the ET tube and the transportation of gas into the middle ear by registering pressure changes (**Figure 86.2**). A stimulus of a controlled gas bolus is applied to the nasopharynx during swallowing and recorded by a pressure sensor in the occluded external ear canal. If ET opening is registered, the time of opening in relation to pressure application can be measured (opening latency index or index R). An R value of <1 indicates early opening of the ET, which is considered optimal.[36]

TMM R values have been used together with clinical symptoms to generate an ET score, a semi-objective rating system used for quantification and inter-individual as well as prospective comparison of ET function (**Table 86.1**).[12] The ET score can range from 0 (= complete obstruction) to 10 (= normal tubal function). The clinical symptoms 'clicking sound when swallowing' and 'positive Valsalva manoeuvre' are rated with 0 points for 'never', 1 point for 'sometimes' and 2 points for 'always'. TMM results at 30, 40 and 50 mbar are incorporated in the ET score as well. An immediate opening of the ET ($R \leq 1$) is weighted with 2 points, a delayed opening ($R > 1$) with point and no opening (negative or not measurable R) with 0 points. The ET score gives a quantitative assessment of ET function and allows inter-individual as well as prospective comparison.

The pressure chamber is a useful device for assessing ET function under varying pressure conditions, regardless of whether the eardrum is intact or perforated.[31] However, pressure chambers are complex, expensive and not widely available.

For the technique of sonotubometry, sound is applied via a probe in the nose. Sound is then measured in the external auditory canal and fluctuations during swallowing are recorded.[31]

There are numerous other approaches to assess ET function such as phototubometry, scintigraphy, ultrasound, application of dye and taste-bearing substances, electromyography, flowmetry, and (opto)tensometry.[31] At present, none of these methods has produced data of clinical significance.[18, 33]

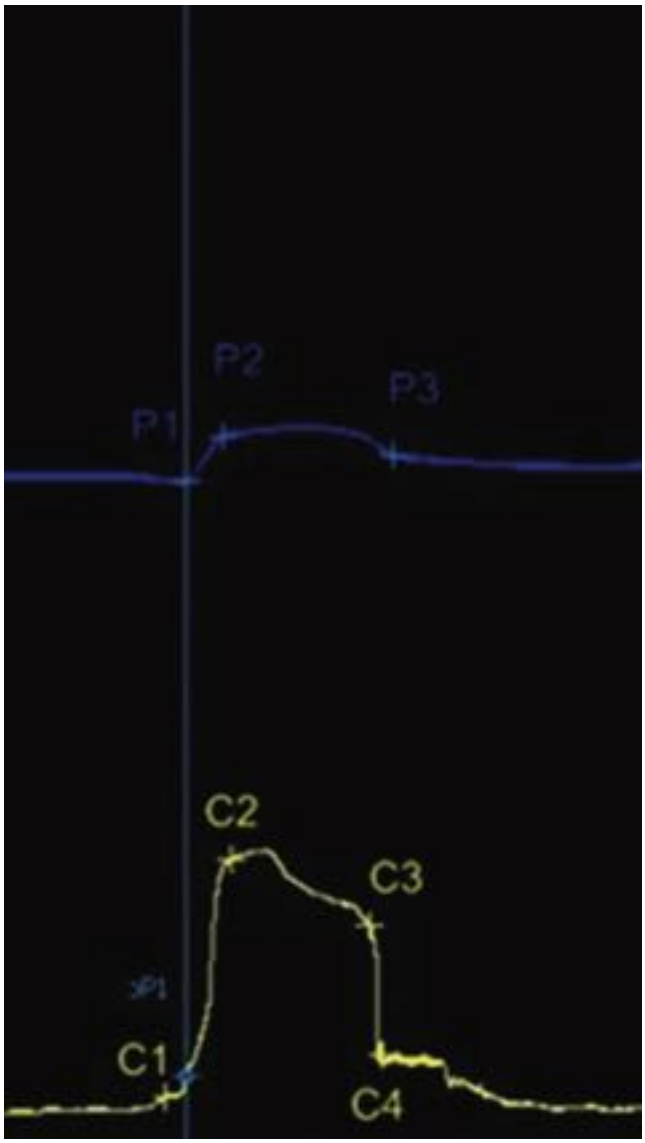


Figure 86.2 ET measurement. The yellow line represents the pressure in the nasopharynx, the blue line the pressure in the external ear canal.

Imaging with computed tomography (CT), cone beam tomography and magnetic resonance (MR) has long been used to examine anatomic and functional deficiencies as well as to rule out pathology in the nasopharynx or superior canal dehiscence syndrome (SCDS)[4, 20] (see Chapter 65, Superior semicircular canal dehiscence).

TABLE 86.1 The Eustachian tube score

Symptom/finding	2 points	1 point	0 points
Clicking sound when swallowing	Always	Sometimes	Never
Positive Valsalva manoeuvre	Always	Sometimes	Never
TMM 30 mbar	R<1	R≥1	No R
TMM 40 mbar	R<1	R≥1	No R
TMM 50 mbar	R<1	R≥1	No R

A seven-item ETD questionnaire (ETDQ-7) was recently developed to assess patient symptoms (**Table 86.2**).[38, 39]

The lack of high-quality studies means multiple gaps remain in the evidence base for assessment of ETD.[18, 40]

PATULOUS EUSTACHIAN TUBE

A patulous Eustachian tube (PET) (tuba aperta, hyperpatent ET) may lead to an enormous reduction in quality of life. Symptoms of PET include autophony, breath synchronous tinnitus, pressure sensation in the ear, and hearing loss. In combination with so-called 'sniffing', it may rarely lead to the development of cholesteatoma.[41] Due to the diffuse symptoms, the correct diagnosis of this disease and especially the distinction from obstructive ETD can be challenging. The movement of the tympanic membrane in synchrony with respirations is not always present but is diagnostic when seen. PET disorders may occur in two types: the PET type, in which the lumen remains anatomically open, even at rest. The other type, the semi-patulous Eustachian tube, is a less severe form. In the latter the tube lumen is anatomically closed at rest but, due to low tubal resistance to airflow, it may open during exercise. It may then become patent due to a decrease in peritubal extracellular fluid volume attributable to disease, exercise, weight loss (leading to reduction of Ostmann's fat pad which lies inferomedial to the ET) or concurrent medical treatment for another condition.

TABLE 86.2 The ETDQ-7 questionnaire – a tool for the evaluation of chronic obstructive Eustachian tube dysfunction[37]

Over the past 1 month, how much has each of the following been a problem for you?	No problem		Moderate problem			Severe problem	
1. Pressure in the ears?	1	2	3	4	5	6	7
2. Pain in the ears?	1	2	3	4	5	6	7
3. A feeling that your ears are clogged or 'under water'?	1	2	3	4	5	6	7
4. Ear symptoms when you have a cold or sinusitis?	1	2	3	4	5	6	7
5. Crackling or popping sounds in the ears?	1	2	3	4	5	6	7
6. Ringing in the ears?	1	2	3	4	5	6	7
7. A feeling that your hearing is muffled?	1	2	3	4	5	6	7

The incidence of PET has been reported with 0.3% of the general population.[42] Münker diagnosed this condition in 6.6% of 100 women with normal ears.[43] Pulec reported on 41 cases identified at the Mayo Clinic in 19 years in 1964.[44] Clinicians' awareness of patients with PET generally results in a higher recognition of this disorder. Only 10–20% of the patients seek medical help for their complaints.[44]

A PET can be best diagnosed through a well-structured examination including patient history, physical examination with thorough observation of movements of the tympanic membrane, and tympanometry with reflex decay. Tympanometry with reflex decay is helpful in the diagnosis but it requires an intact tympanic membrane and it should be evaluated in comparison with the contra lateral side. TMM does not require an intact tympanic membrane and is a valuable tool in diagnosing ET disorders. TMM allows a definite distinction of patulous and obstructive ET dysfunction.[36, 37] TMM regularly reveals an immediate opening with $R < 1$.

When the diagnosis of patulous ET is made, thorough counselling of the patient is important. It is important for the patient to acknowledge that the disease is annoying but harmless. All treatment options have to be outlined to the patient and conservative treatment should be regarded as the first choice. If conservative measures do not lead to an improvement of the symptoms, there are several surgical or interventional treatment options.

Oestrogen nasal drops or oral administration of saturated solution of potassium iodide has been used to induce swelling of the ET opening. Nasal medication containing diluted hydrochloric acid, chlorobutanol and benzyl alcohol has been demonstrated to be effective in some patients. This has been reported to be well tolerated with little or no adverse effects.[41, 44]

Myringotomy and grommet insertions have demonstrated ability to reduce symptoms but are not definitive therapy.[45] In a retrospective analysis of 46 patients (60 ears) with patulous ET, grommets significantly reduced the symptoms in 53% of the ears.[46] An additional option for symptomatic treatment is the augmentation of the tympanic membrane with cartilage especially in severely atrophic eardrums. The effect of augmentation can be tested by placing a small piece of paper on the tympanic membrane prior to surgery.

There are different surgical strategies such as the PET reconstruction with, for example, cartilage, the Kobayashi plug or the injection of Vox® implants into the torus tubarius.[28–30] In patients with ETD that is refractory to medical management, newer surgical techniques may provide symptomatic relief with a reasonable duration.[29, 30] Continued basic science research into the cause of dysfunction, the mechanisms of benefit from intervention and long-term clinical outcomes are necessary.

MEDICAL MANAGEMENT

Medical management of ETD should be directed at the underlying cause. There is currently low evidence of any efficient medical therapies for ETD.[18] Pharmacological interventions include application of nasal steroids, antihistamines, inhaled and systemic decongestants.[47–49]

A randomized, double-blind, placebo-controlled trial studied the effect of a decongestant agent (xylometazoline chloride 0.1%) and placebo (saline 0.9%) applied directly to the pharyngeal opening of the ET. The study concluded that a topical decongestant improves ET function but only at unphysiologically high pressures.[48] Another trial investigated the efficiency of intranasal aqueous triamcinolone acetonide in treating the tympanometric signs and symptoms of ETD.[47] Their findings did not support the use of intranasal steroid sprays to treat the manifestations of ETD.[47]

POLITZERIZATION/OTOVENT™/ EAR POPPER®

No statistical difference in equalization of the middle ear pressure was found between Valsalva manoeuvres, Toynbee manoeuvres and Ear Popper®. The Ear Popper® is an automated device that is applied to the nose and delivers a regulated flow of air into the nasal cavity in healthy adults under physiological conditions.[50, 51] The automated device's ease of administration and its ability to control airflow suggest that it has the potential to be an effective home treatment that can be administered by the parents or guardians of children suffering from otitis media with effusion.[52, 53] Autoinflation using the Otovent™ system was found to be an effective short-term treatment for children with OME when used regularly under supervision.[52] However, available data are too limited to draw any definite conclusion.

LASER TUBOPLASTY

Kujawski, Poe and Caffier reported on their results of laser Eustachian tuboplasty. It seems to be a feasible, safe and in suitable cases effective treatment of chronic obstructive ETD. Using a KTP-laser, inflamed or hyperplasic tissue and sometimes also cartilage is resected from the pharyngeal orifice of the ET. This technique is reported to be successful in almost 70% after 1 year.[13–15]

BALLOON DILATION EUSTACHIAN TUBOPLASTY

Balloon dilation Eustachian tuboplasty (BET) is a minimally invasive interventional method to treat chronic obstructive ETD. It is usually performed with the patient under general anaesthesia.[54] A balloon catheter is introduced into the ET via the nose, under transnasal endoscopic vision.[11, 12] Once the balloon is correctly positioned in the cartilaginous portion of the ET, it is filled with saline up to a pressure of 10 bars. The pressure is maintained for 2 minutes (**Figure 86.3**). BET can be performed as a unilateral or bilateral procedure in adult patients and children



Figure 86.3 Instruments for balloon dilatation Eustachian tuboplasty (Spiggle & Theis Medizintechnik, Overath, Germany).



Figure 86.4 Novel insertion tool with three angled extensions: 30°, 45° and 70°, colour-coded according to Hopkins endoscopes.

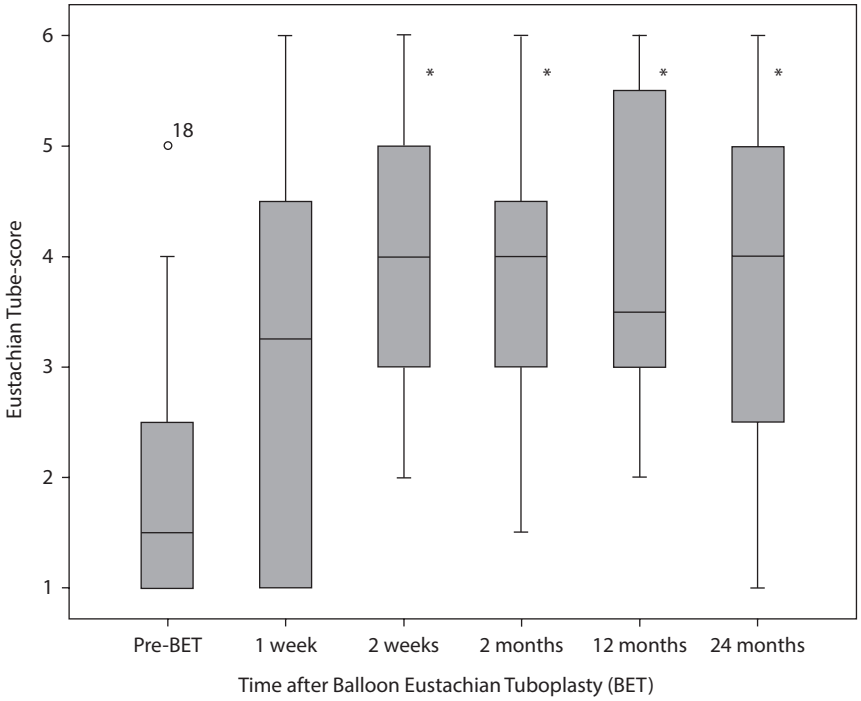


Figure 86.5 Eustachian tube score (see Table 86.1) at the 2 months follow-up. Patients with 24 months follow-up data available were included ($n = 22$). (Asterisks indicate $p \leq 0.001$ in Wilcoxon's test.)

from the age of 7 years. For younger children, additional data are required and currently under investigation.[55] BET is indicated for symptomatic patients with an ET score of ≤5 and the presence of at least one of the following clinical symptoms of obstructive ETD:[56]

- uncomfortable sensation of pressure in the ears especially with changes of atmospheric pressure (e.g. on an aeroplane)
- inability to perform Valsalva manoeuvre
- chronic otitis media with effusion
- middle ear atelectasis
- recurrent middle ear diseases (e.g. perforation, cholesteatoma)
- failed tympanoplasty (e.g. protruding middle ear prosthesis).

In a series of more than 400 patients suffering from obstructive ETD, approximately 80% reported a subjective benefit from BET, and had a significant improvement of their ET score without serious side effects.[56] Significant scarring in the nasopharynx, for example following radiotherapy for nasopharyngeal tumours or after injury of the torus tubarius during adenoidectomy, can be technically challenging. Cleft palate patients do not seem to benefit from BET since the underlying pathology in these cases is a muscular dysfunction rather than obstruction of the ET.[56] Poe et al. described a quite similar method of BET with a modified catheter in 2011 and 2014.[16, 57] They performed the dilatation with a modified sinuplasty balloon with 12 atm for 1 minute and later 2 minutes. Post-operatively all treated patients were able to perform the Valsalva manoeuvre.[16] BET does not seem to require

imaging in normal cases.[58, 59] The results of the present data seem to reveal BET as a safe and effective method.

DISCUSSION

ETD is often regarded as a 'black box' in which the function of the system remains unclear.[18] It has become increasingly clear that there are a variety of underlying reasons leading to ETD. Their identification and treatment is crucial for clinical improvement. Over many years, a variety of different treatment options for chronic obstructive ET dysfunction have been proposed. They range from nasal decongestives and steroids to golden tube conductor wires, grommet insertion and tympanoplasty. Convincing evidence of long-lasting benefit is absent. More recent publications focus on balloon catheter dilation of the ET, microdebriders and laser tuboplasty and these appear more promising.[11–17]

BET as a minimally invasive treatment for obstructive ETD was presented in 2008.[11] A balloon catheter with a newly designed endoscope to widen the cartilaginous portion of the ET was introduced. The available results for the treatment of obstruction of the ET are promising. There are uncertainties about the use of the procedure in children due to the obvious anatomical differences. Additional studies are necessary to identify patients who are most suitable candidates for this procedure and defining cut-off levels for the procedure. Patient selection is the most crucial point and requires more clinical data.[56]

The results of the present data seem to prove BET as a safe and effective method. BET may have potential to improve the long-term results of tympanomastoid surgery through the enhancement of middle ear ventilation.[60–62]

CONCLUSIONS

ETD is still a poorly defined condition. Due to the limited and poor-quality evidence, it is difficult to draw definite conclusions on the effectiveness of any therapy. Consensus on diagnostic criteria for ETD is required to define inclusion criteria of future trials. There is, however, emerging work with encouraging, but preliminary, results that suggest evidence for safety in the surgical management of ETD. As with many newly introduced techniques, the current data remain limited to non-controlled case-series, with heterogeneous data collection methods and lacking substantial long-term outcomes. Nevertheless, short-term data provide favourable results. Recent treatment options including BET and patulous ET surgery may be offered as a treatment option to selected patients.

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BEST CLINICAL PRACTICE

- ✓ Clinical assessment will vary what investigations are available. Ideally assessment should include otomicroscopy, tympanomatry, Rinne's and Weber's tuning fork tests and pure tone audiometry and nasopharyngoscopy (to visualize the orifice of the Eustachian tube). There is no single test to diagnose Eustachian tube dysfuntion. Therefore at this stage we have to rely on the clinical observations (symptoms and signs) detailed above.
- ✓ A number of tests for Eustachian tube function have been described, including tubomanometry, sonotubometry, nine-step inflation-deflation test and pressure chamber tests. At the current time, these tests can be useful research tools.

FUTURE RESEARCH

- ➤ Our understanding of ET anatomy and physiology still remains incomplete, including the epidemiology of Eustachian tube dysfunction, development and validation of patient-reported symptom scores and subjective and objective pressure tests, the development of a core set of outcome measures and further randomized controlled trials of treatments for Eustachian tube dysfunction.
- ➤ There is a strong requirement for consensus on the definition of ETD and for the development of precise diagnostic and treatment criteria.
- ➤ All current studies suggest that balloon dilation of the Eustachian tube is beneficial to patients with Eustachian tube dysfunction. Additionally, placebo controlled trials are still needed.

KEY POINTS

- Sound conduction requires a stable air compartment within the middle ear spaces maintained by a functioning ET.
- ETD plays a significant role in various middle ear pathologies.
- There are a number of methods of assessing ET function, but none provides detailed insights into all aspects of ET physiology and pathology.
- Management of any underlying allergies or reflux is necessary for long-term success in patients with obstructive dysfunction.
- Patients with problems with pressure equilibration or chronic otitis media may be potential candidates for balloon dilation of the cartilaginous portion of the Eustachian tube (BET).

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CHAPTER 87

OTOENDOSCOPY

David A. Bowdler, Annabelle C.K. Leong and David D. Pothier

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: ear, endoscope, otoendoscopy, endoscopy, microscope, surgery and otology.

INTRODUCTION

In otology, the operating microscope revolutionized ear surgery by improving the accuracy and safety of operative procedures. Indeed, the use of the microscope with microinstruments led to otology being one of the first fields of minimally invasive surgery. The advantages of the operating microscope are obvious: it delivers a stable image in the familiar head-on view with the ability to vary magnification while freeing both of the surgeon's hands to operate. However, its straight-line view is also the microscope's main limitation as it is unable to navigate around anatomical corners to provide a wide and variable direction of view, unlike the endoscope. Modern advances in endoscope design have provided a new tool for the examination of anatomical structures in the middle ear and more challenging applications extend to neuro-otological operations such as the removal of acoustic neuromas. A spectrum of approaches currently exists between totally microscopic ear surgery and totally endoscopic ear surgery, with an increasing number of otologists using the endoscope to some extent during an otologic procedure. This chapter deliberately concentrates on the otoendoscope, often to the exclusion of the microscope, as traditional or conventional methods are covered elsewhere. The authors vary in their views from mixed usage to a totally endoscopic approach but all believe that the otoendoscope is an essential piece of equipment for the best practice of otology. Each individual must decide his or her own position with respect to the degree of usage of the otoendoscope.

HISTORY OF OTOENDOSCOPY

Although the fibre-optic endoscope was invented in 1954 by Hopkins,[1] otoendoscopy only began with the use of the fibre-optic hypodermic microscope by Long in 1965.[2] Subsequent forays by Mer[3] in 1967 involved practical issues with manoeuvring the great mass of the microscope to attempt safe passage into the middle ear space. Around the same time, Proctor, Donaldson and Wigand were all undertaking detailed studies of the middle ear spaces and their significance, especially the sinus tympani, epitympanic sinus and protympanum, which were the anatomical blind spots for the operating microscope.[4–6]

From the early 1980s onwards, otoendoscopy was increasingly used to inspect and diagnose middle ear disease, particularly residual disease after canal wall up mastoidectomy procedures.[7–11] Second-look operations in patients who had previously undergone intact canal wall mastoidectomy with tympanoplasty operations were performed with the aid of otoendoscopes to exclude residual epitympanic or mastoid cholesteatoma.[9–11] Thomassin strongly influenced the field of endoscopic middle ear surgery by emphasizing the use of endoscopes to search for and remove disease in the anterior epitympanic recess, tubal orifice and sinus tympani with special microinstruments and observed a distinct reduction

of residual cholesteatomas as a result. He also advocated the otovideoendoscopic technique, which involved coupling of the endoscope to a camera and performing the operation while looking at the video image.[12]

In addition, Eustachian tube endoscopy with small fibre-optic endoscopes had begun in 1976 and was developing alongside middle ear endoscopy, with many studies initially using a nasopharyngeal approach to investigate the relationship of Eustachian tube pathology with chronic otitis media and cholesteatoma.[13, 14]

OTOENDOSCOPY VERSUS THE MICROSCOPE

Debate continues unabated as to whether the role of the otoendoscope remains that of an adjunct to the microscope or if it truly has come into its own as an alternative. On the one hand, otomicroscopy with magnification and a sharp image is advantageous whenever it is possible to get the entire area of surgery into the field of view. On the other hand, the advantages of the otoendoscope are clear in terms of its manoeuvrability, proximity of image, wide field of vision and angle of view (Figure 87.1). Its direction of view is also variable and is influenced by the angulation of endoscope employed, usually 0, 30, 45 or 70 degrees (Figures 87.1 and 87.2). It represents a more advanced form of minimally invasive surgery than the microscope alone and is hence associated with reduced surgical morbidity.

Proponents of entirely transcanal endoscopic ear surgery argue that, although there is a spectrum of use of the endoscope as described previously, the reduced morbidity afforded by the endoscope arises from the fact that no postauricular or endaural incision is required to gain appropriate access to the middle ear space. Moreover, there is a reduced requirement to violate healthy tissue purely to access a relatively limited area of disease. When the endoscope is used as an adjunct to microscopic surgery,

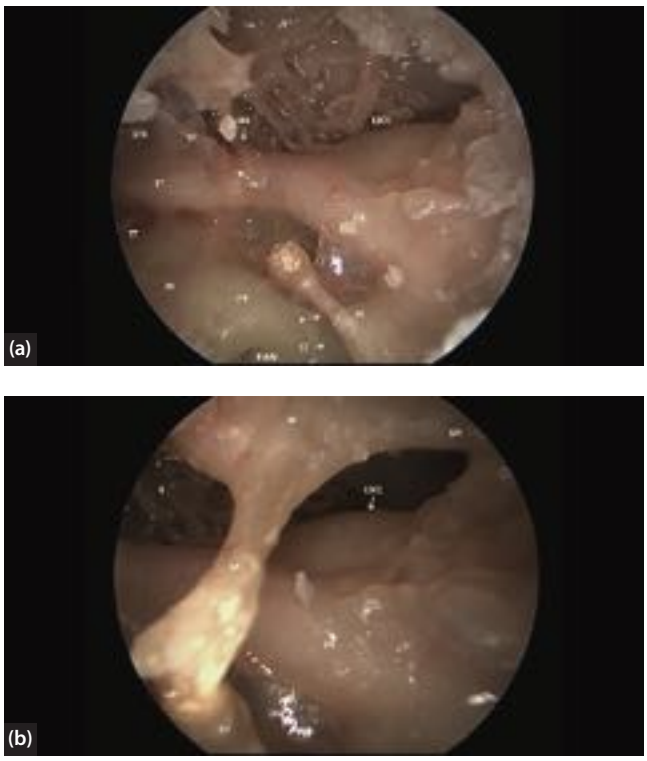


Figure 87.1 **(a)** Anatomy of the middle ear as viewed with a 0° endoscope. **(b)** Anatomy of the tympanic isthmus region as viewed with 0° endoscope. T – tympanic isthmus; E – epitympanum; LSCC – lateral semicircular canal; FN – facial nerve; PE – pyramidal eminence; P – ponticulus; ST – sinus tympani; RWN – round window niche; SH – stapes head; PR – promontory; JN – Jacobsen's nerve; ET – Eustachian tube; TT – tensor tympani; STR – supratubal recess; TF – tensor fold; GG – geniculate ganglion; PC – Processus cochleariformis; OW – oval window area; LPI – long process of incus; LtPI – lenticular process of incus; BI – body of incus; SPI – short process of incus.

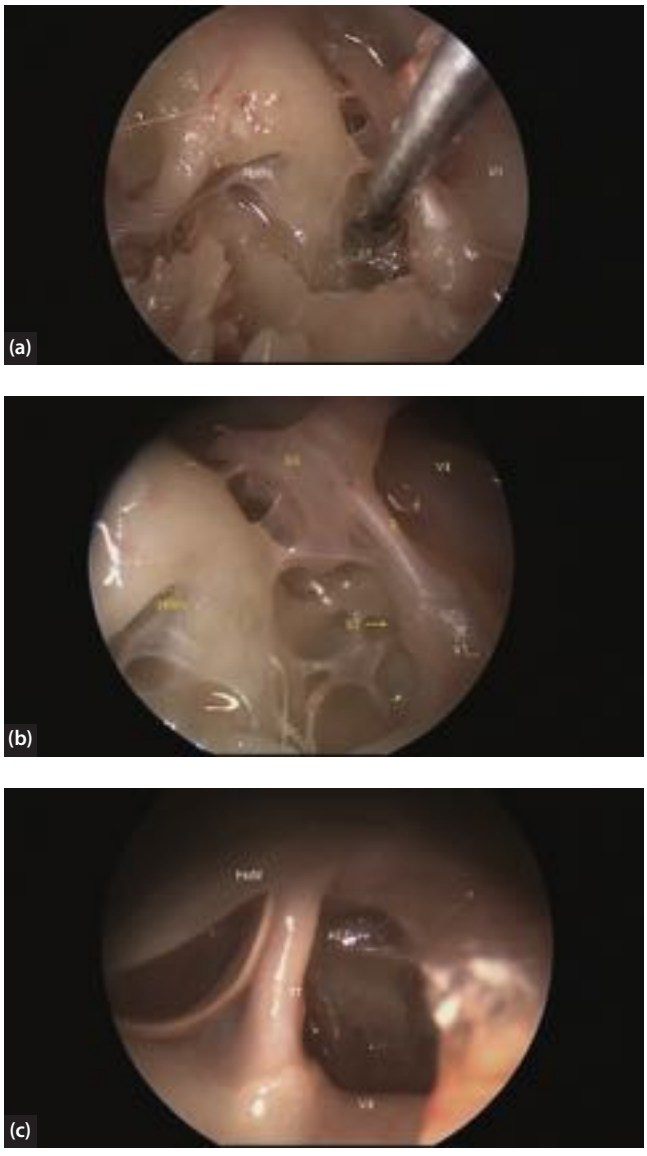


Figure 87.2 **(a)** 30° endoscopic view of the sinus tympani. **(b)** 45° endoscopic view of the sinus tympani. **(c)** 70° endoscopic view of the anterior epitympanum and tensor tympani. JN – Jacobsen's nerve; RWN – round window niche; ST – stapedius tendon; S – stapes; VII – facial nerve; SS – stapes superstructure; HoM – handle of malleus; AET – anterior epitympanum; TT – tensor tympani.

although there are clear clinical gains in terms of access, these advantages of reduced morbidity are largely lost.

It is acknowledged that the operating microscope does not allow good surgical control of the hidden areas in the middle ear such as the sinus tympani, the anterior epitympanum, the protympanic recess and the facial sinus recess. Bowdler and Walsh compared the accessibility of different middle ear subsites in canal wall-up and canal wall-down temporal bone dissections, using the 0 degree 4.0 mm diameter and 70 degree 2.7 mm diameter Storz® rigid otoendoscopes and operating microscope.[15] In canal wall-up dissections, the sinus tympani, facial recess, protympanum, attic and posterior tympanotomy could be seen with the 0 degree otoscope and good views of the sinus tympani and Eustachian tube were obtained with the 70 degree otoscope. In comparison, the microscope failed to give a view of the sinus tympani either through the posterior tympanotomy or via the ear canal (**Figure 87.3**). In canal wall-down dissections, the otoendoscopes were able to offer a good view of all sites but once again, the microscope provided poor views of the sinus tympani. Karhuketo reported similar advantages with 1.7 mm diameter 0, 30 and 90 degree endoscopes over the microscope.[16] In fact, the view offered by the endoscope so differs from that of the microscope that Marchioni published a detailed anatomical report of the sinus tympani using the transcanal endoscopic approach, classifying the sinus tympani into various types based on morphology and depth (**Figure 87.4**).[17] A new term 'finiculus' was also devised to describe the ridge of bone that marks the border between the retrotympanum and hypotympanum.[17]

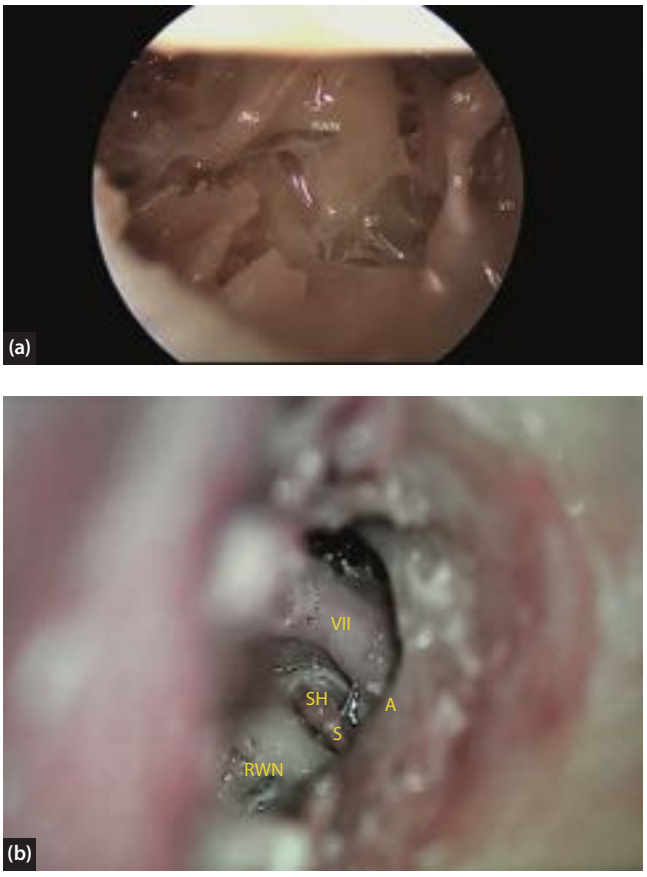


Figure 87.3 **(a)** View of the sinus tympani obtained with 0° endoscope. **(b)** View obtained with the microscope with optimal positioning through the ear canal. S – stapes; ST – stapedius tendon; SH – stapes head; JN – Jacobsen's nerve; RWN – round window niche; VII – facial nerve; A – bony annulus.

Another example of this difference in access between the two techniques is the facial recess. If approached through transcanal endoscopy, it ceases to be a recess and becomes merely a small depression on the posterior wall of the mesotympanum that can be reached within minutes of the start of the operation. In contrast, microscopic technique requires a cortical mastoidectomy and subsequent identification of the facial nerve, providing a limited keyhole access in the space between the chorda tympani and the facial nerve.

The use of the otoendoscope is, however, accompanied by several disadvantages. For example, using the otoendoscope leaves only one hand free to operate. Another perceived disadvantage is the lack of true three-dimensional (binocular) vision during the operation, but with sufficient experience, this appears to have limited impact. The more common limitation for otoendoscopy tends to be peri-operative haemorrhage that leads to fogging and smearing of the endoscope tip, hence it has to be cleaned often. Frequent irrigation can be helpful in clearing the field of blood but may often be inadequate in clearing the sinus tympani and epitympanum.[18] New instruments are in development which address the limitations of standard instruments when used with an endoscopic approach (**Figure 87.5**). Less frequently, due to the inherent rigidity of the instrument, otoendoscopy may be limited by the extreme curvature of the external auditory canal (EAC). Anatomical structures such as the mallear body and lateral semicircular canal may also be difficult to see.[19] Thomassin found that 2.7 mm diameter endoscopes had an advantage over their 1.7 mm cousins in this respect.[12] Current transcanal endoscopic ear surgery relies on 3 mm or 4 mm endoscopes for most applications. Furthermore, smaller diameter endoscopes are extremely fragile; the shorter its working length, the less the bending torque achievable with the same force, but the 1.7 mm endoscopes are unable to tolerate any bending.[20]

Safety issues

Safety issues surrounding endoscopy have focused on the risk of thermal injury to the middle ear. An *in vivo* canine study found that the temperature rise at the lateral semicircular canal increased in relation to endoscope diameter and the Hopkins rods (3.0 mm and 1.9 mm diameter) produced the same or greater heating effect as a warm 44 °C water caloric test.[21] More worrying findings were the discovery of a 5 mm burn on the medial wall of the middle ear when using a 3 mm Hopkins rod and charring effects on the edge of the myringotomy. MacKeith et al. measured the temperature reached by the tip of the endoscope and found that, although temperatures at the tip of the endoscope were sufficient to cause thermal injury, measurements taken 5 mm from the tip were far lower

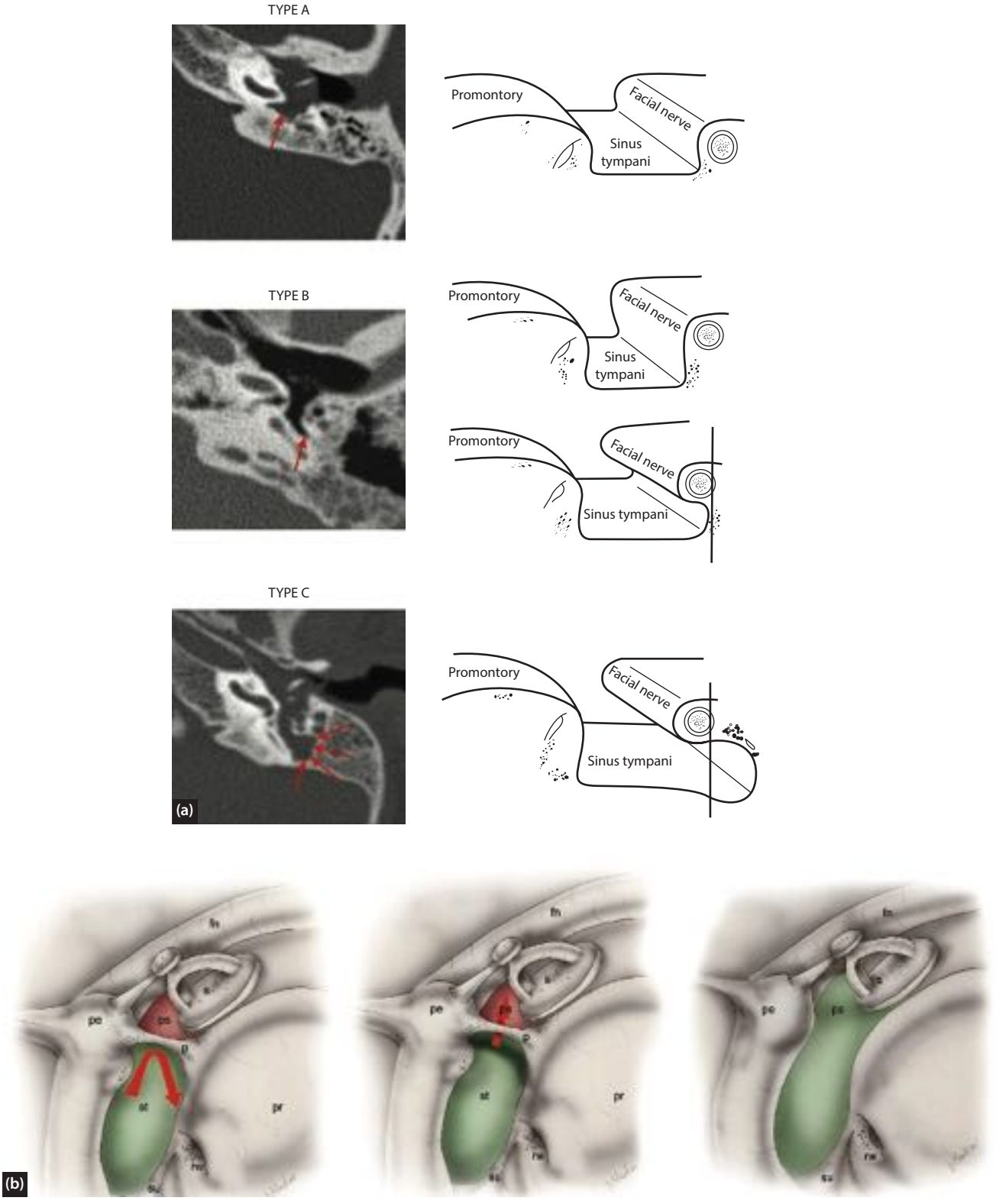


Figure 87.4 (a) Anatomical classification of the sinus tympani based on morphology and depth on axial CT scan. Type A – limited sinus tympani; Type B – deep sinus tympani with medial extension with respect to the facial nerve; Type C – deep sinus tympani with posterior extension with respect to the facial nerve. **(b)** The sinus tympani lies medial to the pyramidal eminence, stapedius muscle and facial nerve and it lies lateral to the posterior semicircular canal and vestibule. The superior limit of this space is represented by the ponticulus, while the inferior anatomical limit is represented by a prominent ridge extending from the styloid eminence to the posterior rim of cochlear window niche: the subiculum. Different morphologies of the ponticulus are shown here. fn – facial nerve; pr – promontory; rw – round window; st – sinus tympani; p – ponticulus; ps – posterior sinus; s – stapes; pe – pyramidal eminence; su – subiculum. Images reproduced with kind permission of Dr Daniele Marchioni.

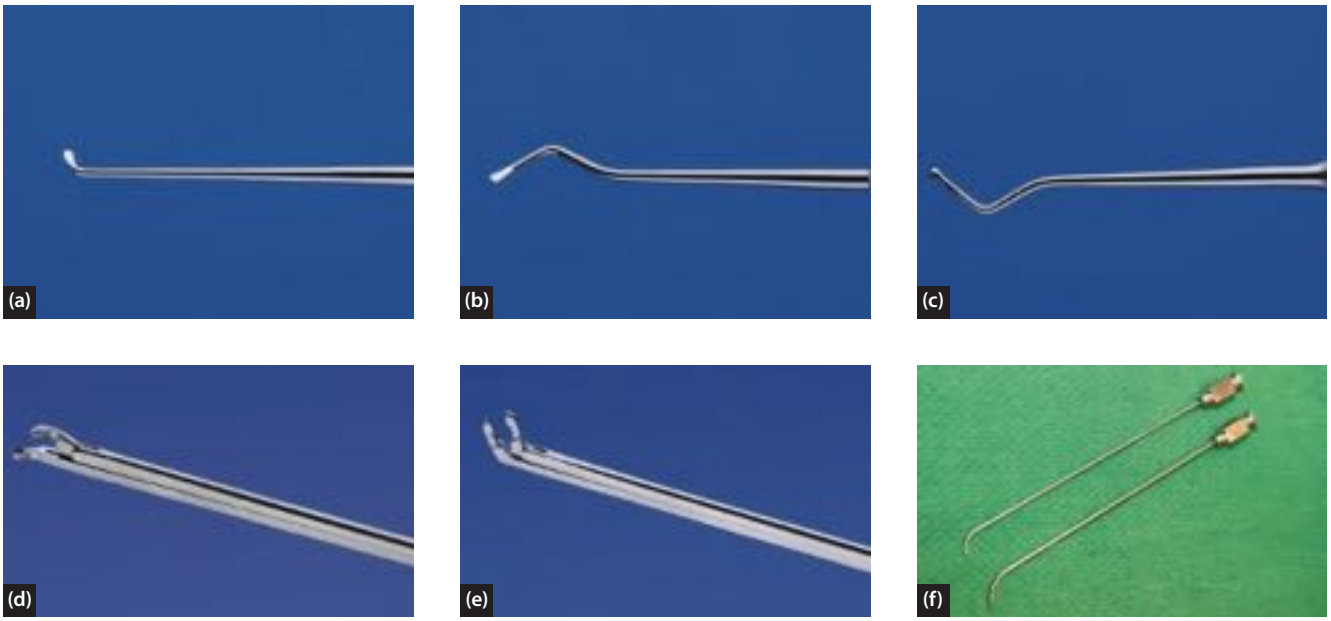


Figure 87.5 Different types of instrument used in endoscopic ear surgery. (a) Single curved dissector, **(b,c)** double curved dissector, **(d)** left-angled forceps, **(e)** up-angled forceps, and **(f)** curved suction cannulae.

and cooling took place rapidly when the endoscope was removed.[22] In addition, the learning curve in otoendoscopy means that it will take some time for the surgeon who is accustomed to an entirely microscopic technique to adapt accordingly. Lack of endoscopic experience or indelicate tissue handling may lead to unsafe advancement during otoendoscopic exploration and possible forceful dislocation or fracture of ossicles.[19]

GENERAL REQUIREMENTS

Pre-operative imaging with high-resolution computed tomography (CT) is recommended before any middle ear procedure where the endoscopic and microscopic approach is planned, but for many surgeons this is equally true of any procedure for middle ear cleft disease. Standard axial, sagittal and coronal views are not as helpful in the true endoscopic setting as they are in the microscopic setting. The best series of views to use are reconstructed along the plane of the external auditory meatus to allow the surgeon to anticipate what he/she will duly encounter endoscopically (Figure 87.6).

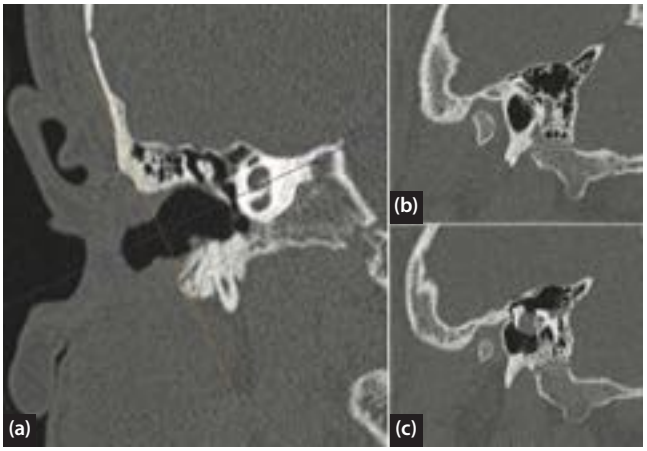


Figure 87.6 Reconstruction of CT scan images along plane of external auditory meatus, best used for pre-operative planning in endoscopic ear surgery.

Endoscope specifications

There are two schools of thought when it comes to selecting which type and size of endoscope to use for ear surgery. Many otologists will use both operating microscope and endoscopes symbiotically, performing part of their surgery with 2.7 mm diameter 0, 30 and 45 degree endoscopes and rarely, using the 70 degree endoscope as well as the 1.9 mm endoscopes, especially to pass through the posterior tympanotomy. Others may undertake the majority of their surgery using a 14–18 cm long 4 mm diameter 0 degree Hopkins rod and endoscope, the very same endoscope used for sinus surgery (Figure 87.7). The latter practice has been termed endoscopic ear surgery (EES) to denote its distinction from the former and is steadily gaining popularity among some otologists.[17, 23, 24] The advantages of using a longer and wider endoscope include a wider field of view, as well as the fact that the surgeon's hands are farther away from the ear canal and hence less likely to interfere with one another intra-operatively.

Digital camera specifications

Although using a high-quality Hopkins rod is essential in otoendoscopy, the digital camera attached to the endoscope also needs to be of high specification. One of the most important considerations is that it should be a camera whose imaging system uses three charge-coupled devices (CCDs), where each one takes a separate measurement of the primary

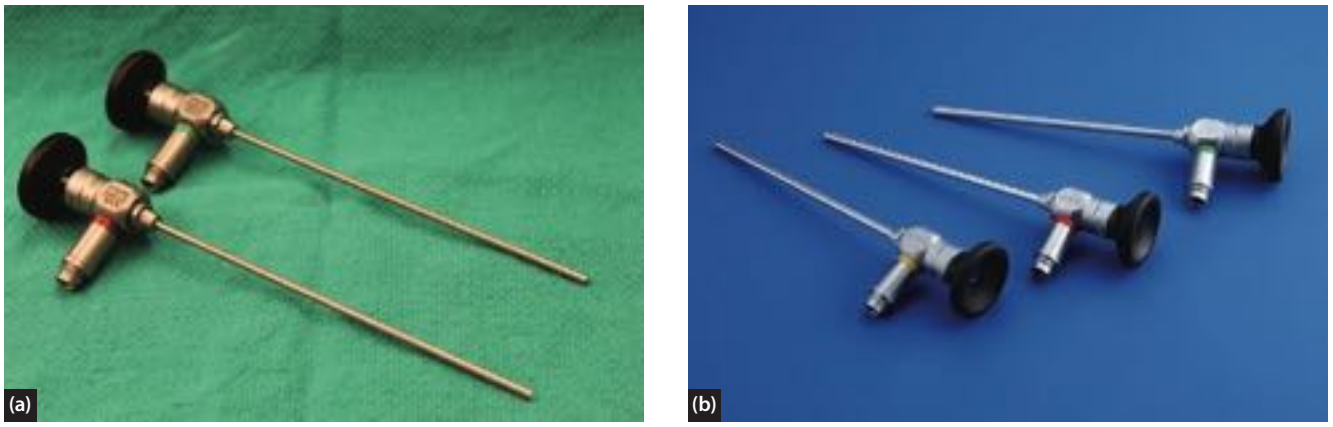


Figure 87.7 (a) Straight and angulated endoscopes (length 14 cm, 4 mm diameter) used in endoscopic ear surgery. **(b)** Straight and angulated endoscopes (length 11 cm, 2.7 mm diameter) more suitable for diagnostic purposes in ear surgery.

colours, red, green or blue light for each pixel, rather than a single CCD camera which can only detect one-third of the colour information for each pixel.[25] Three CCD cameras generally provide superior image quality through enhanced resolution and lower image noise. Single CCD cameras are prone to 'red-out' when they are used in a very small area with a lot of bleeding.[25] Even though there is not much bleeding during EES, the field tends to become reddened, causing complete saturation of the camera. The entire field assumes an orange hue that makes the identification of anatomical structures extremely challenging.

DIAGNOSTIC INDICATIONS

Extent of retraction pockets and cholesteatoma

The diagnostic potential of the endoscope lies most commonly in the evaluation of retraction pockets and cholesteatoma, particularly in blind spots such as the sinus tympani, attic, protympanum and hypotympanum.[7–10] Endoscopy can be performed in the clinic setting as part of the otological examination to assess the extent of middle ear disease and assist in planning the surgical approach. Serial photodocumentation of retraction pockets over a follow-up period may help the otologist to decide whether to adopt a conservative management approach or embark upon surgical intervention.[26]

Ossicular continuity through perforation

Evaluation of ossicular chain continuity may be undertaken endoscopically through an existing tympanic membrane perforation, as demonstrated by Nomura.[27] This procedure may be performed in the outpatient setting with the application of local anaesthesia if required.

Otoendoscopy through myringotomy

Middle ear endoscopy may also be carried out through a myringotomy for many indications such as unexplained conductive hearing loss,[20] perilymphatic fistulas[28] or occult cholesteatoma.[29] Fabinyi and Klug reported on the pathological findings in the middle ear of 60 patients using the transtympanic endoscopic approach, concluding that this method could be used to rule out ossicular anomalies and check for displaced stapes prostheses.[30] Ogawa made the diagnosis of idiopathic perilymphatic fistulas with a 45 degree 1.2 mm diameter Olympus® endoscope through a myringotomy and went on to close the fistulas with fascia and fibrin glue after elevating a tympanotomy flap.[31]

Laser-assisted tympanostomy assisted by otoendoscopy was first performed by Silverstein to examine the relationship between healing of secretory middle ear disease and the tympanic membrane.[32] He went on to use endoscopy to evaluate round window patency as the presence of adhesions might affect the instillation of intratympanic medication in cases of Ménière's disease and sudden sensorineural hearing loss, noting that 17% of patients had partial round window obstruction while 12% had total obstruction.[33] More recently, Kakehata used a similar technique in the outpatient setting to insert the endoscope through a 2 mm laser-assisted myringotomy for assessment of the ossicular chain and stapedial fixation in otosclerosis.[34] The location of the perforation was made between the oval and round windows with a single pulse of 10 watts from the Otoscan™ carbon dioxide laser. Diagnosis of stapes fixation with this technique involved direct endoscopic observation of the stapedial reflex, which was achieved by evaluating the mobility of the stapes in response to contralateral sound stimulation.[34]

THERAPEUTIC USES

Tympanoplasty/ossiculoplasty

The least complicated therapeutic application of endoscopy in ear surgery is probably that of tympanoplasty. Endoscopic type I tympanoplasty (myringoplasty) was first described in 1992 with a graft take rate of 92% and air–bone gap closure to less than 10 dB in 83% of cases.[35] Subsequent studies of endoscopic transcanal myringoplasties followed, with similar success rates as microscope-assisted cases.[36, 37] Tarabichi described his endoscopic technique in a series

of 165 patients and felt that its greatest potential was in tympanoplasty and cholesteatoma surgery.[38] Endoscopic transtympanic tympanoplasty and ossiculoplasty with columella reconstruction or interposition with tragal cartilage was later described in another study, albeit small, with acceptable post-operative hearing results.[24]

Retraction pocket surgery

The use of endoscopy in the surgery of retraction pockets imparts the ability to 'see round corners' to ensure that no epithelium has inadvertently been left in the middle ear cleft after the retraction pocket has been dissected free. It enables the surgeon to retrace the sac, starting from the mesotympanum and continuing through its twists and turns around the ossicles and ligaments. This improved access also facilitates preservation of the ossicles while ensuring the complete removal of the matrix, rather than piecemeal and through different access portals.[23] Tarabichi described an endoscopic transcanal tympanotomy with extended atticotomy and tragal cartilage reconstruction technique in 168 patients with retraction pockets/cholesteatoma and reported a recurrence rate of 7%.[39] He concluded that, while this approach allows the use of the ear canal as the direct and natural access point to cholesteatoma within the mesotympanum, attic, facial recess, sinus tympani, hypotympanum and Eustachian tube, it does not improve access to mastoid disease. Endoscopic access through a mastoid antrostomy may still be required to evaluate an extensive retraction pocket from a posterior perspective.[40]

Mastoid surgery

Numerous techniques have been proposed to facilitate removal of cholesteatoma from the sinus tympani, such as the use of intratympanic mirrors or the retrofacial approach to the sinus tympani, but these methods have not been widely accepted.[41, 42] The last 20 years have seen a myriad of reports on the use of rigid endoscopes to inspect and clear disease in the middle ear.[8, 11, 40, 43] The most detailed studies originated from Thomassin et al.,[10] where the most of the operation was performed with the microscope and the endoscope was employed only in certain situations: at the end of primary canal wall-up mastoidectomy procedures to verify the degree of eradication, when the cholesteatoma had reached the posterior region of the tympanic cavity, the epitympanic recess, or when there was extension to the level of the orifice of the Eustachian tube. Thomassin used a camera coupled to the endoscope whenever it was possible to perform true endoscopic surgery.

Otoendoscopy can also be helpful in canal wall-down mastoid procedures. Yung studied 92 such cases, consisting of small cavity mastoidectomies, canal wall reconstruction and primary obliteration following open cavity mastoidectomies, with 2.7 mm and 4.0 mm diameter (30 and 70 degree) rigid endoscopes.[43] He found that more than one-third of cases had disease extending into the sinus tympani, which was made visible and accessible with the use of side-viewing endoscopes.[43] He did not use the otovideoendoscopic technique recommended by Thomassin et al.[10] as the attachment of the video camera to the endoscope increased the weight of the endoscope and made it more difficult to be manoeuvred. Yung concluded that routine use of endoscopes to control the sinus tympani gives the otologist more confidence at the end of the operation that eradication of the disease is complete as it provides direct vision and also allows better documentation of operative findings.

Minimally invasive second-look combined approach tympanoplasty

Second-look surgery to check for residual and recurrent cholesteatoma is common practice after canal wall-up mastoidectomy operations, as the rate is reported to be higher than with canal wall-down procedures, varying from 10% to 43%.[44–46] One major reason for this is poor access, particularly to the sinus tympani and anterior epitympanum with the operating microscope, leading to increased residual disease. Thomassin et al. showed that the rate of residual disease detected at second-look surgery could be reduced from 47% to 5% with the routine use of otoendoscopy at primary surgery.[10] More recently, Ayache et al. reported the use of otovideoendoscopy to identify and excise residual disease overlooked by otomicroscopy in canal wall-up procedures.[47] Otoendoscopy revealed rates of 44% residual disease in the epitympanum and 34% in the retrotympanum with conversion to canal wall-down procedure avoided in many cases. Their study also suggested that the need for a second-look look combined approach tympanoplasty (CAT) procedure after endoscopic removal at primary surgery would be influenced by the quality of excision achieved with endoscopy.

With the aid of endoscopes, the morbidity of second-look procedures can be reduced by using a minimally invasive approach. A 1 cm stab incision is made anteriorly to the original postauricular incision in the sulcus that allows insertion of a 2.7 mm endoscope into the mastoid cavity to search for residual disease (**Figure 87.8**). Any residual pearls of disease may then be removed without resorting to wider exposure. The posterior tympanotomy may also be reopened through this approach to allow insertion of the endoscope, although a 1.7 mm endoscope is usually required. The accuracy of detecting residual cholesteatoma with this endoscopic technique was verified by performing conventional second-look mastoidectomy procedures with the microscope on the same patients; the results after both techniques were similar.[48] Moreover, the operating time with this approach is shorter than reopening the original incision.[18] McKennan reported that patients find it more comfortable and also reduces the time taken off work.[9] Factors that may require reopening of the original postauricular incision, however, include excessive bleeding, extensive recurrence, reossification over the mastoidectomy site, scar tissue in the mastoid or middle ear cleft, dehiscent facial nerve and lateral semicircular canal fistula. More experienced surgeons would not deem any but the first two factors to be absolute contradictions.

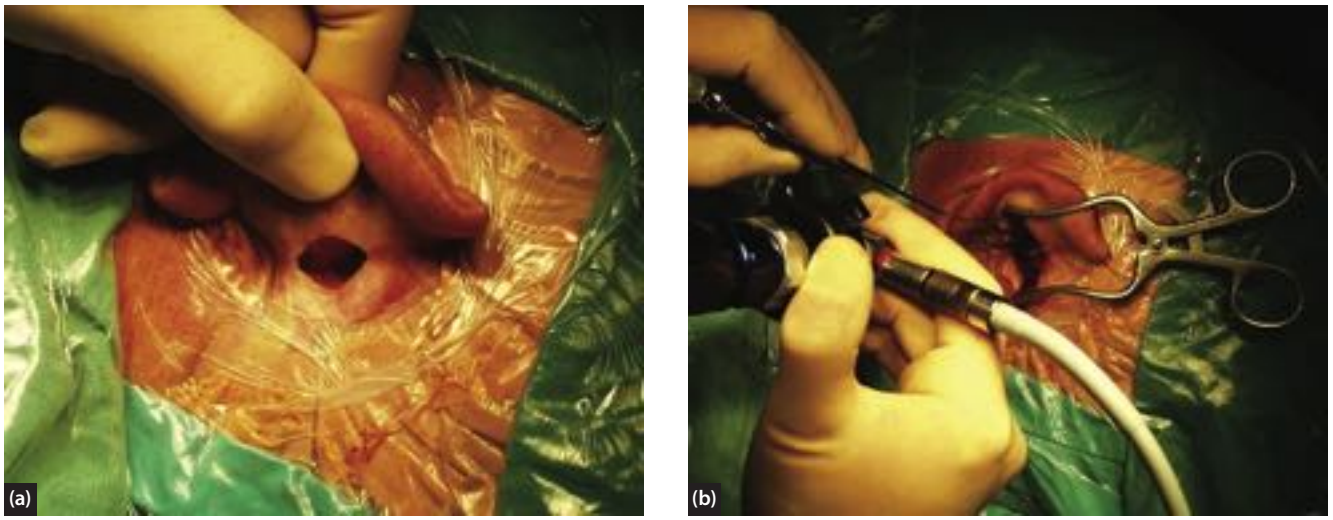


Figure 87.8 **(a)** Performing a minimally invasive stab incision at second-look combined approach tympanoplasty (CAT) surgery. **(b)** Insertion of a 0° (and subsequently a 30°) rigid endoscope into the stab incision to assess for residual disease.

Newer applications

NEUROTOLOGIC SURGERY

Endoscopy of the cerebellopontine angle is not new, but Magnan first described its use in patients with vestibular schwannoma, trigeminal neuralgia hemifacial spasm and incapacitating vertigo.[49] He inserted 1.7mm and 4.0mm 0 degree and 30 degree angled Hopkins rods through a small retrosigmoid craniotomy to access the cerebellopontine angle endoscopically to help identify the relationship between nervous and vascular structures. Endoscopic assistance also helped to prevent cerebrospinal fluid leak after vestibular schwannoma surgery by helping to find patent air cells so that these could be sealed with bone wax and fat grafts.[18]

The role of the endoscopic surgery in the inner ear and internal auditory canal (IAC) is limited and usually used as an adjunct to the microscopic approach. The endoscopic approaches of the inner ear and petrous bone may be summarized as combined transmastoid approaches (translabyrinthine suprameatal, transotic, infralabyrinthine approaches); combined retrosigmoid approach; and exclusive endoscopic transcanal approach.[50, 51] With the combined transmastoid approach, after the microscopic step in the translabyrinthine and transotic approaches, the introduction of the endoscope into the mastoid cavity gives a good view of the geniculate ganglion, medial and anterior portion of the intralabyrinthine facial nerve and removal of residual disease without manipulation of the nerve. With the combined retrosigmoid approach, the aim is to obtain good control of the intrameatal portion of the nerve endoscopically, removing the residual acoustic neuroma within the inner canal, and it is similar to the use of endoscopy in the retrosigmoid neurosurgical approach.

The third approach is the exclusive endoscopic transcanal approach which is still in its infancy.[51] This approach allows endoscopic access to the inner ear from the EAC, preserving facial nerve function and avoiding the need for mastoidectomy or external incisions. After removal of the tympanic membrane and ossicular chain, access to the medial wall of the vestibule is possible. This wall lies adjacent to the fundus of the IAC, representing a portal to access the inner ear and IAC. Endoscopic removal of the bone between the geniculate ganglion and the medial wall of the vestibule will give direct access to the intralabyrinthine path of the facial nerve all the way to the IAC. The use of high-speed drills as part of the endoscopic approach provides a number of challenges, namely the accumulation of bone dust and the need for constant irrigation. Although an otologic drill can be used, for this surgery, it is usual to make use of piezoelectric cutting instruments to remove bone without injury to soft tissues and minimize the production of bone debris. Removing the medial wall of the vestibule will allow direct access to the intrameatal portion of the facial nerve, obtaining entire control of the first segment of the facial nerve.

Although there are currently few indications for the entirely transcanal approach to the inner ear, the technique has been used successfully to remove cochlear schwannomas and small intracanalicular acoustic neuromas. The necessity to approach the lesion through the labyrinth and/or the cochlea makes the technique suitable only in situations where the preservation of hearing is not planned. While far less invasive than a traditional translabyrinthine approach, an endoscopic excision of a lesion of the inner ear or IAC has few indications as the technology currently stands. The risk of bleeding following the removal of the tumour in the IAC makes the endoscopic approach a risky proposition, as there is no way to control haemorrhage under these circumstances owing to the limited access to the IAC at its medial end.

ENDOSCOPIC STAPEDOTOMY

Endoscopic stapedotomy is another novel application of EES. Poe performed stapedioplasties (stapedotomies without prosthesis insertion) in 11 patients by making argon ion laser cuts under endoscopic assistance in the anterior crus and footplate, so as to mobilize the posterior segment

of the stapes while the anterior portion remained fixed.[52] He reported that these patients' hearing improved with air–bone gap closure to a mean of 8.3 dB. More recently Nogueira published a series of 15 patients who had undergone fully endoscopic stapedotomy using a transcanal approach.[53] He used 4.0 mm 0 degree and 30 degree endoscopes, the former to elevate a tympanomeatal flap and the latter to inspect the middle ear and for subsequent stapes work. The advantages associated with the use of endoscopy during stapes surgery include achieving excellent exposure of the oval window niche without removal of healthy bone from the EAC, avoiding any manipulation of the chorda tympani and obtaining a good view of the anterior crus of the stapes to allow its removal without blind manoeuvres.[53]

ENDOSCOPIC COCHLEAR IMPLANTATION

Currently, the use of an endoscopic approach in cochlear implantation is controversial. No case series have yet been published regarding this application of otoendoscopy, but there have been a number of individual cases presented at conferences on EES. The surgical technique involves the routing of the electrode through the epitympanum after a 'well' has been created for the receiver. A small cortical mastoidectomy is fashioned to allow access to the middle ear via the epitympanum after which the ear canal skin is raised from the bony portion of the EAC without the requirement for transection. Once the middle ear has been reached, the implant is guided into the cochleostomy under endoscopic guidance. Another technique involves the passing of the electrode down the ear canal within a bony groove into the middle ear after which the groove is filled with bone wax or other material.

Supporters of these techniques claim that the electrode can thus be placed in a minimally invasive fashion without risk to the facial nerve that is inherent in a technique that requires access through a posterior tympanotomy. The elevation of the tympanic membrane and the skin of the posterior canal wall, however, may lead to an additional route for infection of the mesotympanum and there have been a number of cases of extrusion of the electrode from its groove in the posterior EAC wall through the skin of the EAC, all requiring explantation.

FUTURE DIRECTIONS AND INNOVATIONS

3D otoendoscopy

The disadvantage of the two-dimensional view that comes with an endoscopic approach has been of little hindrance to the development of EES. This mirrors the development of endoscopic sinus surgery in this regard. The development of 3D endoscopy is an area that shows promise; the limited dimensions of the EAC make the use of twin endoscopes very challenging and the 3D view that is achieved by the Da Vinci® robot system cannot be achieved in the ear canal with current technology. To overcome this limitation, 3D CCD chips have been developed to allow a 3D image to be generated with a chip with a diameter of 3.3 mm. This may pave the way for the routine use of 3D camera systems for this purpose.

SUMMARY

Fibre-optic technology, endoscopic expertise, microinstrumentation and laser equipment have all greatly improved over the past few years. It is likely that otoendoscopic surgical techniques will prove increasingly important in otologic surgery. Most of the anatomical spaces in the middle ear that are considered challenging to access with the microscopic technique can easily be approached with endoscope-assisted surgery. The inclusion of the endoscope in microscopic procedures on middle and inner ear pathology, as well as in neuro-otological procedures, could potentially help the surgeon to achieve improved results with regard to the preservation of important structures, limitation of injury to healthy bone for access and allowing a minimally invasive approach in certain situations. At present, opinion continues to be divided as to whether the role of endoscopy in otology should be that of an all-encompassing technique or more as a useful adjunct to the microscope. Regardless, exciting developments in technology and expertise mean that otoendoscopy is likely to remain a key tool of technique in the otologist's armamentarium into the future.

KEY POINTS

- The microscope has traditionally been the workhorse of ear surgery but modern advances in endoscope design and endoscopic surgical techniques have ushered in a new era for the rigid endoscope as a key tool in otology.
- New anatomical terms to describe detailed middle ear anatomy have been devised to accommodate the different view obtained endoscopically.
- There are currently two schools of thought when it comes to selecting size and type of endoscope for ear surgery, divided between shorter 2.7 mm diameter endoscopes, and longer 3 or 4 mm diameter rigid endoscopes. The latter practice has been termed Endoscopic Ear Surgery (EES).
- A wide range of diagnostic indications exist for endoscopic ear surgery, most commonly the assessment of the extent of retraction pockets and cholesteatoma.
- Multiple therapeutic applications exist for the endoscope in middle ear surgery, ranging from endoscopic tympanoplasty and retraction pocket surgery, to minimally invasive second look canal wall up mastoid surgery.
- Newer applications include endoscopic stapedotomy, endoscopic cochlear implantation and total transcanal approaches to the inner ear.
- The role of endoscopy in otology continues to grow in importance but debate remains as to whether the endoscope in ear surgery should be exclusively used with the omission of the microscope or if the endoscope will endure instead as a useful adjunct to the microscope.

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CHAPTER 88

TUBERCULOSIS OF THE TEMPORAL BONE

Ameet Kishore

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: tuberculosis, otitis media and temporal bone.

DEFINITION

Tuberculosis is a chronic granulomatous infection caused by *Mycobacterium tuberculosis*. Other mycobacteria such as *Mycobacterium bovis*, *Mycobacterium avium* and *Mycobacterium fortuitum* can also cause infection referred to as 'atypical tuberculosis' or non-tuberculous mycobacterium (NTM) (see also Chapter 37, Cervicofacial infections). While tuberculosis (TB) is predominantly pulmonary, 12–15% of reported cases of TB involve extrapulmonary sites.[1] Rarely the temporal bone may be involved with TB – tuberculous otitis media or tuberculous otomastoiditis.

PREVALENCE

The WHO estimates there are 8 million cases of TB reported annually.[2] The majority of these occur in Asia (55%) and Africa (31%). TB of the temporal bone, however, is extremely uncommon and constitutes less than 1% of all cases of chronic otitis media.[3, 4]

Tuberculous otitis media is even rarer in developed countries and its incidence in the UK is said to be only 0.04% of cases of chronic otitis media.[5, 6] The advent of BCG vaccination and the use of effective antituberculosis therapy have led to a significant reduction in incidence of TB particularly in developed countries.[2] In a previous review of the literature, of the 320 cases of tuberculous otitis media reported in the medical literature between 1986 and 1990, 83% were from Africa.[7]

In developing countries, where TB is still endemic, tuberculous otitis media remains an important differential diagnosis of chronic otorrhoea that is unresponsive to conventional treatment. In a study from Africa, of over 11 000 patients with TB identified over a 6-year period, 43 (0.37%) were diagnosed as having tuberculous otitis media.[4]

PATHOGENESIS

Tuberculous otitis media occurs frequently in ears with pre-existing chronic middle ear infection where the organisms enter the middle ear through an existing tympanic membrane perforation.[8, 9] There are two other potential routes through which the tubercle bacilli may reach the middle ear: either through the Eustachian tube or by haematogenous spread from another focus.[10, 11] Pulmonary tuberculosis may predispose to the development of tuberculous otitis media by providing a source for haematogenous spread to the temporal bone.[12] Tuberculous otitis media in children has been reported to be secondary in up to 50% of cases.[8]

Tuberculous otitis media may present in different pathological phases. In the acute phase there is congestion

followed by thickening of the tympanic membrane and the appearance of tubercles and perforations. The chronic form is slow and painless with perforations and pale pink granulation tissue. The necrotic or caseous form destroys the bone with sequestrum formation.[13]

DIAGNOSIS

The clinician needs to have a high index of suspicion of tuberculous otitis media in patients living in highly endemic areas who present with otorrhoea not responsive to conventional treatment. Up to 50% of patients with tuberculous otitis media may give a history of exposure to TB.[14–16] The initial symptoms and signs are frequently non-specific and similar to those of chronic otitis media. The patients may have symptoms and signs of pulmonary tuberculosis such as cough, night sweats and fever, and should have a thorough clinical examination and a chest X-ray.[17] The prevalence of active or inactive pulmonary tuberculosis in patients with tuberculous otitis media can range from 14% to 93%. However, a number of patients may not present with findings suggesting pulmonary tuberculosis if the disease is inactive.[8, 12]

CLINICAL PRESENTATION

The classical description of tuberculous otitis media is painless otorrhoea, multiple perforations, pale granulations, early severe hearing loss and bone necrosis.[4, 18–20] Otoscopic examination reveals a tympanic membrane perforation through which the middle ear mucosa may appear pale or denuded.[13–15] The bone of the middle ear cleft may be denuded of mucosa in up to 30% of patients.[12]

Multiple tympanic membrane perforations were once considered a hallmark of the disease, but this is seldom reported and is thought to be rare.[21, 22] Small perforations may coalesce to form a single, large perforation.[19, 20] Ng has suggested a triad of signs for tuberculous otitis media: regional lymphadenopathy in the absence of typical systemic features of TB refractory otitis unresponsive to conventional antimicrobial agents, and the presence of complications such as facial nerve palsy or sensorineural hearing loss relatively early in the course of the disease.[23] The hearing loss is usually conductive due to tympanic membrane perforation, although it is not uncommon to have a mixed hearing loss which is disproportionate to the disease due to the occurrence of labyrinthitis. Hearing loss out of proportion to otoscopic findings, the absence of otalgia and the presence of complications such as a facial nerve paresis should alert the clinician to the possibility of tuberculous otitis media.[3, 16, 24] Facial palsy is reported in 10–20% of patients and occurs early in the disease process.[11, 16, 25] It has been suggested that the presence of a facial palsy in the absence of a cholesteatoma should alert the clinician towards the possible diagnosis of tuberculous otitis media.

BACTERIOLOGY

While a positive culture for the acid-fast bacillus *Mycobacterium tuberculosis* confirms the presence of tuberculous otitis media, ear discharge provides a poor yield for positive cultures. This is believed to be due to the low bacterial count in the ear discharge.[11, 26] A positive swab for culture and sensitivity is diagnostic in less than 20% of cases of tuberculous otitis media.[8, 27] Polymerase chain reaction (PCR) has been used to detect mycobacterium tuberculosis in pus or tissue specimens to confirm the diagnosis.[28]

HISTOPATHOLOGY

Histopathological examination of a biopsy specimen is the most definitive way of confirming the diagnosis of tuberculous otitis media.[4, 28] This necessitates a biopsy of granulation tissue, middle ear polyps from the external canal or tissue removed at mastoidectomy. The microscopic finding of granulomata with caseous necrosis, epithelioid cells and Langerhans giant cells is a strong indicator of TB. The false-negative rate of histopathological diagnosis has been suggested to be 10%.[4] In one series of patients, however, the diagnostic yield from histology of middle ear biopsy and aural polypectomy was only 30% and 35% respectively.[15]

IMAGING

Plain skull X-rays are non-specific. They may demonstrate haziness or erosion within the mastoid air cells that are similar to the findings in any other form of chronic otitis media.[29] **A CT of the temporal bone is the radiological investigation of choice** and will usually demonstrate the presence of soft tissue in the middle ear cleft with a relatively well-preserved mastoid air cell system. There is typically minimal sclerosis of the mastoid, mucosal thickening of the bony external auditory canal, or soft-tissue extension within the external auditory canal without erosion of the scutum.[11, 21, 30] With advanced disease, CT may demonstrate diffuse destruction of the temporal bone in contrast to selective destruction of the scutum seen in active squamous chronic otitis media.[20] A CT is important when assessing the degree of involvement of the temporal bone and the likelihood of any complications such as facial nerve involvement, erosion of the semicircular canals or labyrinthine ossification.

DIAGNOSTIC CHALLENGES

TB of the temporal bone is seldom considered as the initial diagnosis in a patient with a discharging ear owing to its rarity. This, however, explains the frequent delay in diagnosis.[18] This is particularly true in developed nations. In developing countries in Africa and Asia, the index of suspicion should be higher. Many patients have no previous history of TB infection and have a normal chest X-ray.[3]

The absence of disease-specific clinical findings and the very high false-negative rate of bacteriological culture makes it difficult to confirm the diagnosis of tuberculous otitis media early in the disease process.[11] **The widespread use of neomycin- and gentamicin-containing ear drops can mask the clinical features of tuberculous otitis media as these drugs have a weak antituberculous effect.**[15, 26, 31]

As early treatment can prevent complications such as irreversible hearing loss and facial nerve palsy, the clinician needs to have a high index of suspicion.[11]

The differential diagnosis of tuberculous otitis media includes other chronic conditions affecting the temporal bone such as Wegener's granulomatosis, histiocytosis X, chronic otitis media, cholesteatoma, histoplasmosis, blastomycosis, syphilis and lymphoma.

COMPLICATIONS

Complications of tuberculous otitis media are commoner and tend to be more severe in children. Facial nerve paralysis has been reported in 16% of adults and 35% of children with tuberculous otitis media.[4] Profound hearing loss can occur following spread of infection into the cochlea.[5, 19, 20, 32] Granulation tissue invading the Fallopian canal and compressing the facial nerve results in a facial nerve palsy in 10–20% of patients.[11, 24, 25, 33, 34] Other complications reported are postaural fistula, temporomandibular joint involvement,[34] intracranial complications such as meningitis, tuberculomata,[35] otitic hydrocephalus[36] and multiple cranial nerve palsies.[4, 31]

MANAGEMENT

The two components of treatment are antituberculous therapy and surgery. Medical management with antituberculous therapy is the mainstay of treatment once the diagnosis has been confirmed.[4, 5, 11, 12, 18, 26, 28] Antitubercular treatment using the current standard medication of isoniazide, ethambutol, pyrazinamide and rifampicin may be required for a minimum period of 6 months. Treatment over a longer period may be required in cases of disseminated TB and meningitis.[37] Patients may only require medical treatment.[38, 39]

Surgery may be required to obtain tissue for histology, drain a subperiosteal abscess or remove a bony sequestrum.[4, 18] The incidence of sequestrum formation may be as high as 30%.[27] Surgery may be indicated in the presence of facial nerve palsy for the purposes of a facial nerve decompression if medical management fails to demonstrate clinical improvement in facial nerve function.[4, 18]

Resolution of the otorrhoea with medical management alone can begin to be seen after 2–3 weeks of treatment and the disappearance of granulation tissue can be observed in 1–5 months.[12, 17] Some authors have suggested that combined modality treatment of surgery and antituberculous therapy is likely to be more effective and result in quicker healing with better outcomes.[11, 16, 20, 24] The role of surgery for facial nerve palsy in tuberculous otitis media is contentious as similar results are reported with medical management alone.[4, 14] In the case of bilateral tuberculous otitis media resulting in bilateral profound hearing loss, cochlear implantation is an option for hearing restoration. However, the labyrinthine ossification that follows tuberculous otitis media can make surgery difficult.[40]

KEY POINTS

- Tuberculous otitis media is a rare condition and constitutes 0.3–0.9% of all patients with chronic otitis media.
- Most cases have been reported from countries where TB is endemic such as in Africa and Asia.
- There are no specific clinical features as symptoms and signs are similar to chronic active otitis media.
- The confirmation of diagnosis is difficult as bacteriology is insensitive. Histopathology is often required to confirm the diagnosis.
- Complications such as profound hearing loss and facial nerve paralysis can occur early in the disease process.
- The mainstay of management is medical using antituberculous treatment for 6 months or longer.
- Surgery in the form of mastoidectomy with or without a facial nerve decompression is reserved for patients who do not respond to medical treatment, for removal of sequestrum, drainage of a subperiosteal abscess or facial nerve decompression.
- The clinician should have a high index of suspicion in patients with persistent otorrhoea that is resistent to standard medical treatment or where complications occur disproportionately early in the disease.

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CHAPTER

89

OTOSCLEROSIS

Christopher P. Aldren, Thanos Bibas, Arnold J.N. Bittermann, George G. Browning, Wilko Grolman, Peter A. Rea, Rinze A. Tange and Inge Wegner

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SEARCH STRATEGY

Definition and pathology

Data in this section may be updated by a Medline search using the search string ("Temporal Bone/pathology"[Mesh]) AND "Otosclerosis/pathology"[Mesh].

Aetiology

Data in this section are may be updated by a search in PubMed, Embase, CINAHL and the Cochrane Library using synonyms for 'otosclerosis' and 'aetiology' in title and abstract.

Incidence

Data in this section may be updated by a Pre-Medline and Medline search using the keywords otosclerosis and incidence, and otosclerosis and prevalence.

Diagnosis

Data in this section may be updated by a Medline search using the keywords otosclerosis and diagnosis.

Natural history
Data in this section may be updated by a Medline search using the keywords otosclerosis; audiometry, pure-tone; hearing loss, otosclerosis and natural history.

Management options: fluoride
Data in this section may be updated by a Medline search using the keywords otosclerosis and sodium fluoride.

Management options: hearing aids
Data in this section may be updated by a Medline search using the keywords otosclerosis or stapes surgery, and hearing aid.

Management options: surgery
Data in this section may be updated by a Medline search using the keywords otosclerosis or stapes surgery, and 5015 references were identified. Each key topic was cross-referenced independently (e.g. antibiotic prophylaxis, steroids, etc.).

DEFINITION AND PATHOLOGY

Thanos Bibas

DEFINITIONS

Otosclerosis is a localized hereditary disorder of bone metabolism of otic capsule enchondral bone that is characterized by disordered resorption and deposition of bone.[1–2] It is thought to result from increased and pathologic bone remodelling and the basic lesion consists of areas of bone resorption by osteoclasts and new bone formation by osteoblasts, accompanied by vascular proliferation and tissue stroma.

Clinical otosclerosis refers to lesions that affect the stapes, stapediovestibular joint or round window membrane and thus cause conductive hearing loss. In cases of mixed hearing loss it is assumed that there are lesions affecting the cochlear endosteum as well. **Cochlear otosclerosis** refers to lesions involving the cochlear endosteum without affecting the stapes or the stapediovestibular joint, thus causing pure sensorineural hearing loss, with no conductive element. It is considered very rare, but prevalence is difficult to judge as some authors include cases with mixed hearing loss. **Histologic otosclerosis** refers to histopathological lesions that do not affect the stapes, stapediovestibular joint or cochlear endosteum, and thus remain asymptomatic during life.[2] Although the prevalence of histologic otosclerosis has been estimated as high as 8.3%, an unselected series of temporal bones has found a prevalence of 2.5%.[3]

HISTOPATHOLOGY

Bone remodelling in the otic capsule and animal models

The otic capsule is unique compared to the rest of the bony skeleton in that it exhibits limited remodelling. There is a gradient of decreased remodelling rate from the periphery of the otic capsule towards the membranous labyrinth. It has been hypothesized that otic capsule remodelling is related to the ratio of two cytokines, osteoprotegerin (OPG) and RANKL (receptor activator nuclear-kb ligand).[4] OPG is a potent inhibitor of osteoclast maturation and functions in competition with RANKL (an activator) for the osteoclast RANK receptor. OPG is highly expressed within the spiral ligament and perilymph and may easily diffuse into the lacunocanalicular network of bony otic capsule through intercellular gaps of the inner ear lining. Impedance of the patency of this signalling pathway may lead to increased bone remodelling and development of the abnormal otosclerotic pattern.[5] Although there are no good animal models for otosclerosis, OPG knockout mice demonstrate progressive loss of hearing, stapes fixation and abnormal focal bone remodelling with many histological similarities to human otosclerosis.[4] However, active remodelling in these mice occurs throughout the entire skeleton and diffusely within the otic capsule. It also involves the incus and malleus, which is rare in otosclerosis, and the effects are reversed by administration of bisphosphonates.[6]

Light and electron microscopy findings

The earliest indication of otosclerotic process is resorption of enchondral bone around blood vessels, with consequent enlargement of perivascular spaces followed by deposition of immature (woven) bone. Through continuous remodelling, more mature bone (lamellar bone) is deposited, mediated by osteoblasts. Active otosclerotic foci are characterized by increased vascularity and increased bone turnover, while inactive (sclerotic) foci consist of dense mineralized bone. Both types may coexist in the same focus.[2] The connective tissue stroma in otosclerotic foci consists of fibroblasts and osteocytes, while there is complete absence of acute inflammatory cells. Electron microscopy studies usually describe osteoclasts in the centres but not in the periphery of otosclerotic foci, thus possibly indicating a lesser role in bone resorption in the advancing front.[7]

Origin, sites of involvement and distribution of lesions

The most common site of involvement is the cochlear wall anterior to the oval window. This is followed by the round window niche and the cochlear apex.[8] Less frequent sites include foci posterior to the oval window, the walls of the internal auditory canal, around the cochlear duct and the semicircular canals, the entire footplate (**Figures 89.1** and **89.2**), and involvement of the middle ear ossicles.[9] Invasion of labyrinthine spaces and the vestibular aqueduct are rare, while invasion of the internal auditory canal or the facial nerve canal have not been reported.

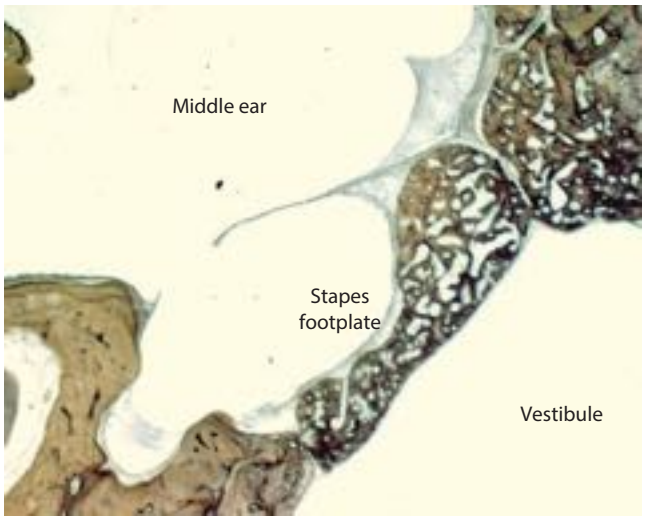


Figure 89.1 Left temporal bone of a 27-year-old female patient with a history of bilateral otosclerosis and Hodgkin disease. The entire stapes footplate is replaced by otosclerotic bone and is fixed both anteriorly and posteriorly. (UCL Ear Institute Temporal Bone collection, specimen F23.)

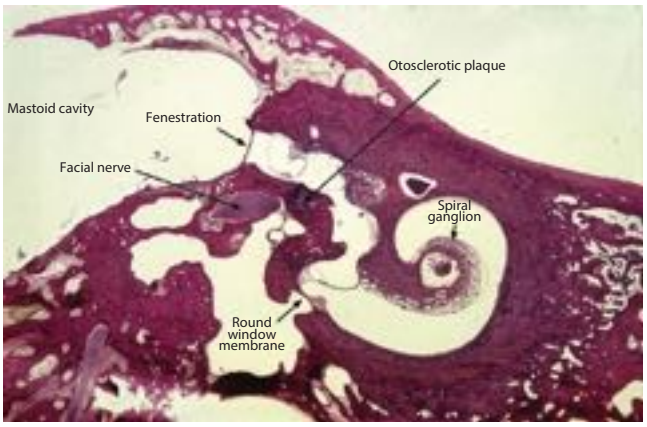


Figure 89.2 Right temporal bone of a 49-year-old female patient with bilateral otosclerosis and bilateral surgical fenestration of the lateral semicircular canals. This specimen is unique as it is sectioned in the vertical plane to demonstrate the fenestration, as well as the oval and round windows in a single section. There is a surgically created window of the LSSC measuring 1.3 mm in the vertical diameter, which is bridged by a thin layer of squamous epithelium. The ampulla appears normal. There is a large otosclerotic plaque causing thickening of the footplate of the stapes. Otosclerotic bone at the superior and inferior margins of the oval window overlaps and partially obliterates the oval window. Round window niche and membrane and spiral ganglion in the basal turn appear normal. (UCL Ear Institute Temporal Bone collection, specimen F267R.)

Michaels and Soucek studied in detail the development of the otic capsule in relation to the origin of the otosclerotic plaques.[10] In all but 2 of the 65 temporal bones studied, a single plaque of otosclerosis occupied much of the otic capsule posterior to the cochlea. Each of the posterior plaques had a well-defined edge at the periosteum lining the otic capsule, extending from the level of the posterior edge of the processus cochleariformis to a level of approximately one-third of the distance along the tensor tympani muscle from the processus. It is the progression of this that will eventually involve the stapes footplate, leading to fixation and conductive hearing loss. In addition, in 42 of these temporal bones there is also a plaque of otosclerosis in the anterior cochlear part of the otic capsule, showing a wide area of contact with the periosteal surface bordering the canal for the internal carotid artery. In both types of plaques, the pattern of change suggests that they commence at the periosteum and, as the immature advancing front of the plaque grows outwards, the tissue that is left behind matures with time, so that the most mature bone in the plaque is near the periosteum.

Very rarely, large cavities may form within otosclerotic foci, a condition termed cavitating otosclerosis.[11] These cavities may act as a 'third window' in cases where the cavitation is in contact with the endosteum of the scala tympani, and may be implicated in persistence of the air–bone gap following a successful stapedectomy. Cavitating foci may also communicate with the CSF space in the internal auditory canal, and may result in gushers during cochlear implantation. There is also an increased risk of the implant electrode being misplaced through a cavitating lesion to the pericochlear cavity.[11]

Conductive hearing loss

Conductive hearing loss is usually related to pathology (narrowing or ankylosis) of the annular ligament, especially the posterior part. A recent study showed that the size of the air–bone gap appeared to be determined by the extent and degree of this pathologic change, and that bony ankylosis was associated with an air–bone gap greater than 30 dB. However, the degree and extent of bony footplate ankylosis could not be reliably predicted by the size of the air–bone gap. Since a lack of bony ankylosis increases the risk of a floating footplate during stapes surgery, one should be aware of this complication even in cases with large air–bone gaps.

Other factors that may contribute to conductive pathology in cases of otosclerosis include complete obstruction of the round window niche (this is frequently associated with a persistent air–bone gap following stapes surgery, and if recognized pre-operatively may be a contraindication to surgery), cavitating otosclerosis (due to a 'third window' effect) and malleus fixation (see 'Surgical pathology' below).

Sensorineural hearing loss

Although the effect of otosclerosis on cochlear function has been controversial in the literature, most temporal bone studies show that, in cases with otosclerosis and sensorineural hearing loss, the hair cells, stria vascularis and spiral ganglion cells either are unaffected or their loss is insufficient to account for the recorded hearing thresholds.[2] Some studies have shown that, when sensorineural hearing loss occurs, it is often in cases with otosclerotic involvement of the endosteum, where it tends to induce hyalinization and atrophy of the spiral ligament.[12] In contrast, in a study of five temporal bones with pure cochlear otosclerosis, one case had normal hearing, while in the rest,

the reduction in the population of cochlear elements was not related to the extent and location of endosteal involvement.[13] However, a temporal bone study by Doherty and Linthicum using objective estimates of stria vascularis width and quantification and localization of spiral ligament hyalinization within the cochlea demonstrated a direct relationship between stria vascularis atrophy and sensory hearing loss that correlated well with the amount of spiral ligament hyalinization.[14] It is worth mentioning that, although temporal bone pathology studies have demonstrated that pure cochlear otosclerosis does occur, its incidence appears to be quite low and that otosclerosis as a cause of idiopathic sensorineural hearing impairment in individuals without clinical evidence for otosclerosis in the form of stapedial fixation is rare.[2]

Vestibular symptoms

Vestibular symptoms may be experienced by 10–30% of patients with otosclerosis but its pathophysiology is obscure in most cases. In a comprehensive temporal bone study by Saim and Nadol, the incidence of vestibular symptoms was correlated with the degree of sensorineural hearing impairment.[15] These cases also demonstrated degeneration of Scarpa's ganglion, which was independent of the severity of otosclerotic involvement of the vestibular end organs. Conversely, almost half of temporal bones in the same study demonstrated involvement of the superior vestibular canal or cribrose area, regardless of vestibular symptoms.

Vestibular symptoms may also be caused by comorbid pathology, such as Ménière's disease. Otosclerotic foci may rarely involve the vestibular aqueduct, but it may also occur without any prominent associated pathology. Yoon et al. looked at 128 temporal bones with otosclerosis, and direct involvement of the vestibular aqueduct was observed in four temporal bones from two patients.[16] In all four, the vestibular aqueduct was filled with active otosclerotic foci. The lumen of the endolymphatic duct and sac was narrowed as a result of fibrosis, and endolymphatic hydrops was observed, which was more severe in the pars inferior than the pars superior. Collapse of the ductus reuniens and dilated saccule was seen in three temporal bones. Issa et al. studied the position of the saccular and Reissner's membranes in relation to the stapes footplate in eight temporal bones from patients with otosclerosis and Ménière's disease. It was found that the saccular and Reissner's membranes did not contact the stapes footplate in cases where pre-operative bone-conduction levels were 35 dB or better at 500 Hz and there was no high-frequency loss. Stapedectomy was reported successful and it was therefore concluded that surgery does not increase the risk of sensorineural hearing loss when these criteria are met.[17]

SURGICAL PATHOLOGY

Stapes surgery

In a histologic human temporal bone study, Pauw et al. measured the distances between the medial surface of the stapes footplate and the utricle and the saccule in normal and otosclerotic bones.[18] No statistical difference was found between the two groups and they concluded that the safest place for a stapedotomy is in the central and inferior-central thirds of the footplate. However, a 0.4 mm stapedotomy piston can be introduced relatively safely to a depth of 0.5 mm in the vestibule over the entire surface of the stapes footplate. Although stapes experiments in animal studies have showed an association between saccular rupture and hair cell loss in the basal and middle turns, it is not clear whether these are associated with the rupture itself, or by shock waves in the perilymphatic spaces following aggressive manipulation of the footplate. However, collapse of the saccular wall by a contact injury from the piston can lead to endolymphatic hydrops postoperatively, presumably by interfering with the longitudinal flow of endolymph.[19]

Although closure of the air–bone gap to within 10 dB is observed in the majority of primary stapedectomies, a residual or recurrent conductive hearing loss may occur. In a comprehensive human temporal bone study by Nadol, it was found that the most common histopathological findings related to conductive hearing loss after stapedectomy included resorptive osteitis of the incus at the site of prosthesis attachment, obliteration of the round window by otosclerosis, and a malpositioned prosthesis at the oval window.[20] Round window obliteration resulted in the largest air–bone gap, but in most of the temporal bones there were more than one finding that could account for this.

Although malleus fixation may be a cause of residual conductive hearing loss, its isolated incidence in temporal bone studies is 1–8%.[21, 22] In an otopathological study of 1108 bones, fixation of the malleus was observed in only 1% of the cases, was usually unilateral and involved the lateral epitympanic wall rather than the anterior mallear ligament.[22] However, temporal bone studies have shown that the incidence of malleus fixation seems to have a higher incidence in patients with otosclerosis. In a temporal bone study by Nandapalan et al. it was apparent that otosclerotic bones have a significantly higher incidence of hyalinization of the anterior malleal ligament (AML), which seems to be related to the duration rather than the severity of otosclerosis.[23] In another study by Oktay et al., although no relationship between hyalinization of the AML and otosclerosis was found, otosclerosis seemed to be a predisposing factor for bony fixation of the head of the malleus to the lateral epitympanic wall.[21] It is therefore prudent to evaluate mobility of the malleus in all stapes surgery.

Cochlear implantation

Cochlear implantation in otosclerotic patients may be complicated by round window obstruction and/or facial nerve stimulation. The round window may be partially or completely obstructed by otosclerotic foci. In rare instances, there is formation of new bone in the scala tympani of the basal turn of the cochlea.[24] Intraoperatively this can potentially cause difficulties at

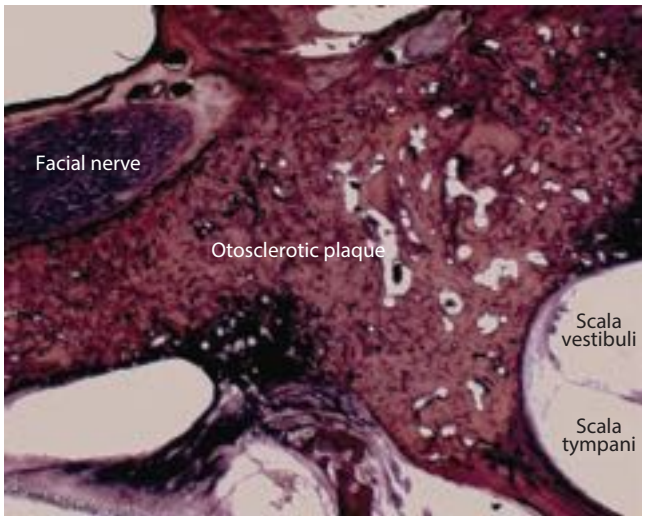


Figure 89.3 Left temporal bone of an 86-year-old male patient with otosclerosis. A large otosclerotic plaque is extending from the cochlea endosteum to the medial aspect of the facial canal in the horizontal segment. (UCL Ear Institute Temporal Bone collection, specimen F41.)

inserting the electrode arrays, necessitating a cochlear drill-out. The incidence of unintentional facial nerve stimulation is significantly higher in patients with otosclerosis than in the general population, especially when a straight electrode is used.[25] Full-thickness involvement of the otic capsule between the cochlea endosteum in the basal turn and different parts of the facial canal may explain the incidence of facial nerve stimulation in these cases, possibly due to altered spread of the current (**Figure 89.3**). It is therefore suggested that a perimodiolar electrode should be preferred, especially in cases in which the pre-operative CT scan suggests that the otic capsule is involved between the facial nerve canal and the upper basal turn of cochlea.

Facial nerve dehiscence

The histopathological incidence of facial nerve dehiscence in otosclerosis was studied by Nomiya et al. in 84 cases compared to 102 age-matched controls.[26] No significant difference was found between temporal bones with and without otosclerosis. Interestingly, the otosclerotic focus did not invade the inside of the canal and did not show any deformity of the canal or injury of the nerve, thus explaining the lack of facial nerve palsy in otosclerosis. It is also suggested by the authors that otosclerotic lesions have the potential to close dehiscences of the facial canal in the oval window area.

AETIOLOGY

Arnold J.N. Bittermann, Inge Wegner and Wilko Grolman

In this chapter we are looking for evidence to support the aetiology of otosclerosis. Aetiology has been a topic of discussion for decades now, but in modern medicine the evidence base has rightfully gained much importance.

GENETIC PREDISPOSITION

OTSC1 (chromosome 15q25-26), *OTSC2* (chromosome 7q34-36), *OTSC3* (chromosome 6p21.3-22.3), *OTSC4* (chromosome 16q21-23.2), *OTSC5* (chromosome 3q22-24) and *OTSC7* (chromosome 6q13-16.1) are monogenetic otosclerosis loci.[27] A recent study has shown mutations and altered expression of the *SERPINF1* gene in patients with familial otosclerosis. This gene encodes PEDF (pigment epithelium-derived factor) which is a known regulator of bone density and is the first disease-associated gene to be identified in otosclerosis.[28]

Monogenic otosclerosis is relatively rare and in most patients otosclerosis occurs without a clear familial background or with only a few affected family members, suggesting the involvement of both genetic and environmental factors.[29] Genes associated with this complex form of otosclerosis include *COL1A1*, *TGFB1* and *RELN*.

A systematic literature search reveals different association and family studies of a genetic cause of otosclerosis. However, the number of studies with low risk of bias is limited. Risk of bias concerns the methodological strengths and limitations of a study. The fewer the methodological limitations, the lower the risk of bias. High-quality studies show that otosclerosis in Japanese patients is not linked to the *NOG* gene[30] and that a polymorphism in the Sp1 binding site located on the *COL1A1* gene is associated with otosclerosis[31] as well as *OTSC1*.[32] Studies with a moderate risk of bias show a statistically significant association of otosclerosis with the *ACE* gene,[33] the *AGT* gene,[33] *OTSC2*,[34] the *RELN* gene,[35, 36] the *TGFB1* gene[36] and 11q13.1.[36] Family-based studies of moderate quality show a statistically significant association of otosclerosis with *OTSC2*,[37] *OTSC5*,[38] *OTSC8*[27] and *OTSC10*.[39] It is important to note that results from studies with moderate to high risk of bias may report spurious associations due to their bias and low statistical power. Interestingly, sex-specific association of *COL1A1* to otosclerosis could be found in one study.[40] The same goes for the *RELN* gene.[36] One single-nucleotide polymorphism (SNP) in the *COL1A1* region was associated with female gender (odds ratio 1.395) and one SNP in the same region with male gender (odds ratio 0.865).[40] One SNP in the *RELN* gene was identified that was associated with male gender (odds ratio 1.392). These findings suggest that both the *COL1A1* and *RELN* gene association with otosclerosis might be influenced by gender, which we should expect since the dominance of presentation is in women.

KEY POINTS

- Despite the extensive availability of studies on the genetic aetiology of otosclerosis it is not possible to assign one or more responsible genes that play a key role in the pathophysiological pathway that leads to otosclerosis.

VIRAL INFECTION

The possibility that a persistent viral infection of the otic capsule may cause otosclerosis was first proposed based on the histological similarity between otosclerosis and Paget's disease, along with mounting evidence of a viral aetiology of Paget's disease.[41, 42]

Otosclerotic foci show all the characteristics of chronic inflammation.[43] An initial active and lytic phase of bone resorption, with proliferation of blood vessels, osteoclasts and mononuclear cells, is followed by the formation of new bone. Support for this hypothesis comes from immunohistochemical evidence of measles virus proteins and antigenicity in active otosclerotic lesions.[44, 45] More recently, two studies have shown an increased expression of specific measles virus receptor CD46 isoforms in otosclerotic footplates.[46, 47] Furthermore, lower levels of anti-measles virus IgG were found in serum from otosclerosis patients with virus-positive footplates compared to healthy controls without otosclerosis and otosclerosis patients with virus-negative otosclerotic footplates.[48–50] In this context, Karosi et al. have shown that combining the assessment of anti-measles virus IgG serum level and the presence of conductive hearing loss results in high diagnostic specificity of 90% and high sensitivity of 96% during the pre-operative evaluation of patients suspected of otosclerosis.[50] Elevated levels of anti-measles virus IgG have been detected in perilymph.[48, 51] Others have found measles virus RNA in archival and fresh frozen footplate specimens with otosclerosis.[52–55] However, failure to do so has also been reported.[56–58] The complete measles virus RNA sequence has never been reported, nor has the isolation of measles virus from otosclerotic samples been successful. It may be argued that the reason is that measles virus titres in otosclerotic samples are too low to be detected. This in turn raises the question whether such a low level of virus could ever cause disease.

Decreasing numbers of stapes surgery and a shift towards older patients following the introduction of vaccination programmes in the US and Europe have been reported by various surgeons.[59–61] Epidemiological surveys of hospitalized otosclerosis patients showed a significant decrease in otosclerosis among the vaccinated population.[62] Interestingly, the decrease in the vaccinated female group was minor in comparison with the male group, which may indicate gender-specific differences in susceptibility or reactivity to measles virus. However, the measles virus hypothesis does not explain why otosclerosis is extremely rare among Africans,[63] despite the fact that the measles virus does occur frequently in African children.

KEY POINTS

- Inconsistencies between current research studies mean that the role played by the measles virus in otosclerosis remains uncertain.

AUTOIMMUNE DISEASE

It has been suggested that otosclerosis represents a form of autoimmune disease with humoral autoimmunity to type II collagen or a closely related antigen that is abundantly present in the regions of predilection. The available evidence is somewhat conflicting. Elevated circulating antibodies against type II collagen[64–66] and type IX collagen[66] in the blood of patients with otosclerosis have been reported. Others, however, have not found a difference in the circulating autoantibody levels between otosclerosic patients and healthy controls.[67–69] A subgroup of patients with disease duration of between 3 and 5 years did show increased autoantibody concentrations in one of these studies.[68] Animals immunized with type II collagen have been found to produce lytic bone lesions in the otic capsule that strongly resemble otosclerosis.[70–72] In similar animal models such otogenic lesions have not been identified.[73, 74]

Criticism of this hypothesis is based on the ubiquitous presence of type II collagen in other sites and the concurrent production of joint lesions in type II collagen-immunized animals, which is not a feature of otosclerosis. Also, patients with relapsing polychondritis have extremely high titres of circulating antibodies against type II collagen, with involvement of multiple organ-sites, but without evidence of otosclerosis.[75]

CYTOKINES

As mentioned above under 'Genetic predisposition', several genes encoding for cytokines have been associated with otosclerosis. These cytokines are transforming growth factor β1 (TGF-β1) and bone morphogenetic protein (BMP).

Bone morphogenetic protein, an inflammatory cytokine that is part of the TGF-β superfamily, may be involved in pathological bone remodelling in otosclerosis. BMPs play a pivotal role in bone formation as well as the healing cascade of bone.[76, 77] Various isoforms, such as BMP2, BMP4, BMP5 and BMP7 have been detected in fresh frozen footplates with active otosclerotic foci.[78–80] Significant expression of BMP receptors 1B and 2 has been shown, whereas BMP receptor 1A was always absent within otosclerotic foci.[78]

HORMONAL FACTORS

Since angiotensin II stimulates the secretion of TNF-α, the renin–angiotensin-aldosterone system (RAAS) may play a role in the regulation of bone remodelling. This theory was first presented by Imauchi et al. in 2008.[33] There is conflicting evidence regarding the association between genes encoding RAAS and otosclerosis.[33, 81] To date, active expression of members of the RAAS family has not been confirmed in otosclerotic stapes footplates.[82]

INCIDENCE

George G. Browning, Arnold J.N. Bittermann, Inge Wegner and Wilko Grolman

GENERAL

It is important to distinguish histological otosclerosis from clinical otosclerosis. In case of histological otosclerosis, otosclerotic foci could be present within the temporal bone without clinical symptoms such as hearing loss and vertigo.

Literature reporting the incidence of otosclerosis is limited. Prospective studies, exclusively designed to identify the incidence of histological and clinical otosclerosis, are rare. Recent studies, describing otosclerosis incidence, mostly present the epidemiology of a variety of otologic disorders including otosclerosis as a subpopulation.[83] This could result in biased results and conclusions. The publication of Declau et al. is the best available evidence reporting the incidence of histological otosclerosis.[84] The incidence of clinical otosclerosis is best described in the publication from the British National Study of Hearing.[85]

HISTOLOGICAL OTOSCLEROSIS

The 'gold standard' for the reporting of the incidence of histological otosclerosis would be a prospective study of the histology of bilateral temporal bones removed consecutively from a population. Such a study has been reported from the University of Antwerp, Belgium, where harvesting of the ossicular chain is routine, as everyone is classified as a donor candidate unless otherwise indicated.[84] The study was of 118 consecutive pairs of temporal bones from white individuals whose mean age was 63 years. The bones were processed and the gross sections visually screened to identify possible bones with otosclerosis. These bones, along with any others that had a suggestion of otosclerosis on microradiography, proceeded to conventional histology. Four of the 118 individuals were found to have histological otosclerosis, an incidence of 3.4%. Two of the patients had bilateral otosclerosis. In none of the four bones where the stapes was still present was it fixed. The limited size of this study did not allow for gender and age to be investigated. This incidence is considerably lower than that of approximately 8% reported from larger temporal bone collections.[86–88] The reason for this is almost certainly a bias to process bones likely to have ear pathology. In these collections, the proportion of males to females is about equal. Age makes no difference to the incidence of histological otosclerosis over the age of 10 years.[86] The percentage of bones with histological otosclerosis that have ankylosis of the stapediovestibular joint is only approximately 12%. Taking these two figures together, it makes the likelihood of clinical otosclerosis in the white population to be approximately 1%. Insufficient data have been reported from temporal bone collections to calculate the effect of gender and age on the incidence of clinical otosclerosis.

One collection had 576 bones from black individuals and only 5 (0.9%) had histological otosclerosis.[86] Ohtani et al evaluated a total of 1011 temporal bones from an unselected series of temporal bones from 507 Japanese persons without signs of otosclerosis. Histologic otosclerosis was found in 15 out of the 1011 ears (1.48%).[88]

CLINICAL OTOSCLEROSIS

Despite the existence of histological otosclerosis, in daily practice, only otosclerosis resulting in complaints such as hearing loss will be clinically relevant. Many prospective studies have reported the incidence of audiometrically assessed hearing impairments in a sample of the population. Unfortunately, few have included otoscopy and bone-conduction thresholds, which are essential to identify patients with clinical otosclerosis. However, the British National Study of Hearing included these measures. They defined presumptive clinical otosclerosis as an ear where the tympanic membrane was normal, the tympanogram was peaked with normal pressure range and associated with an air–bone gap of 15 dB or greater over 0.5, 1 and 2 kHz.[85] In adults, the overall prevalence of otosclerosis was 2% (confidence interval 1.5 to 2.7) with an equal distribution between men and women (Table 89.1). It was only when the air–bone gap was 30 dB or greater that women were (×3) more likely to have otosclerosis than men. The incidence increased with age, those aged 41–60 years were twice and those aged 60–80 years were four times as likely to have clinical otosclerosis.

The proportion of patients that had had surgery was less than 10% and this explains the relatively low population prevalence of otosclerosis reported from clinical series. These are considerably influenced by the proportion of patients with an impairment that seek advice, the referral pattern and the attitude of the specialist to surgery and hearing aids. Studies that report audiometric outpatient data are likely to be less biased. In one such study

TABLE 89.1 Population prevalence per 100 of the presumptive diagnosis of otosclerosis (reprinted from Browning and Gatehouse,[85] with permission)

	Otosclerosis (%)	95% CI
Overall	**2.1**	**1.5, 2.7**
Age (years)		
18–40	1.6	0.6, 2.6
41–60	2.2	1.3, 3.1
61–80	3.0	1.7, 4.3
Sex		
Women	2.0	1.3, 2.7
Men	2.2	1.2, 3.2
Occupational group		
Non-manual	1.5	0.8, 2.2
Manual	2.7	1.9, 3.5

from Copenhagen, the prevalence over a 5-year period of clinical otosclerosis was 2% of patients seen with a hearing impairment.[89, 90] When the proportion of individuals that have bilateral as opposed to unilateral otosclerosis is examined, both clinical and temporal bone case series are likely to be biased towards reporting a higher proportion having bilateral disease. From these, approximately 75% of patients have bilateral disease. Unfortunately, the UK National Study of Hearing[85] did not report its results in this format. In 2012, Hannula et al. presented an epidemiological study on the prevalence of ear diseases in Finland. A total of 850 native Finnish subjects with an age between 54–66 years old were randomly selected. Within this group, the prevalence of otosclerosis was 1.3%.[83] Declau et al. also included an extrapolated estimation of clinical otosclerosis, based on their temporal bone findings and indicated that clinical otosclerosis has a prevalence of 0.3–0.4% among the white ethnic population.[84]

The incidence of clinical otosclerosis in non-Caucasians must be considered unknown because of their dependence on surgical series. These report that surgery for otosclerosis is uncommon in Mongoloid races and is extremely rare in Negroid races.

DIAGNOSIS

George G. Browning and Christopher P. Aldren

OTOSCOPY

Otosclerosis is the presumptive aetiology of a conductive hearing impairment in the presence of a normal, mobile tympanic membrane. The 'gold' reference standard of diagnosis is made at surgery, when it should be possible to exclude the considerably rarer causes of such an impairment, such as congenital ossicular chain abnormalities and other diagnosis (5% and 3% of cases respectively).[91] Ossicular chain discontinuity subsequent to head trauma will give a similar presentation but can be diagnosed by the temporal relation of the hearing loss to the trauma in the history. A 'flamingo flush' or Schwartz sign, a red blush of the tympanic membrane over the promontory, is said to be due to the vascularity of an active otosclerotic focus but is rarely seen.

Otosclerosis can also occur when the tympanic membrane is abnormal, such as in chronic otitis media. This is because otosclerosis will occur in the same percentage of patients with such a condition as it does in the general population (approximately 2%).[85] Thus, in patients with chronic otitis media, around 2% of them will have otosclerosis as an additive component to their conductive hearing impairment. This additive component only becomes apparent when stapes fixation is identified at surgery for pathology other than otosclerosis.

SURGICAL DIAGNOSIS

On raising a tympanomeatal flap, the middle ear will appear anatomically normal. The bone around the oval window may be whiter than normal but no clear junction between otosclerotic and non-otosclerotic bone will be apparent, as in histological sections (Figure 89.4). The mobility of the stapes and other ossicles will be assessed. Minor degrees of fixation are difficult to assess as long as the ossicular chain remains intact, which is the case until the incudo stapedial joint is divided. After surgical removal of part of the bony attic wall to visualize the stapes footplate, it will usually be seen to be thicker than normal. Occasionally, the oval window will be filled with obliterative otosclerosis. If the footplate is found not to be fixed, alternative causes of the conductive hearing loss such as fixation of the malleus should be sought.

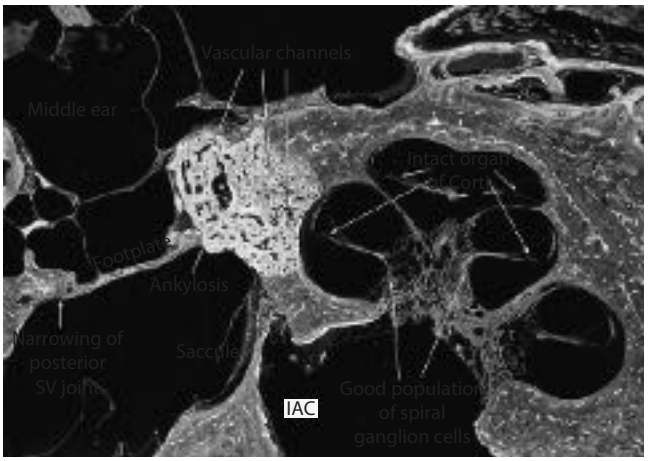


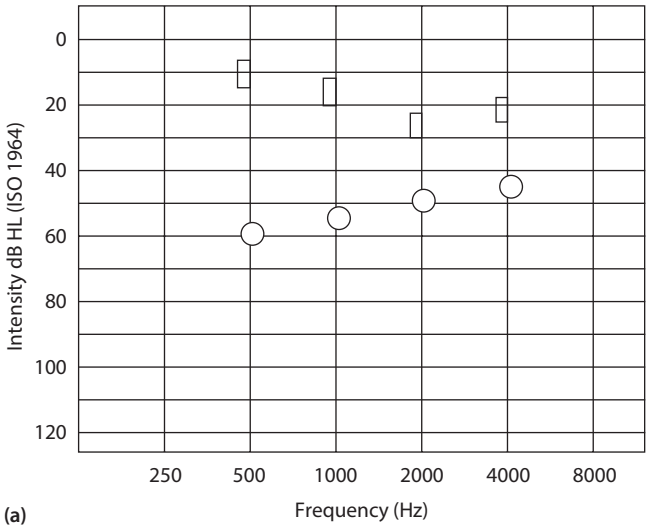
Figure 89.4 Temporal bone section in the axial plane from an 85-year-old man with clinical otosclerosis. There is a single focus of otosclerosis anterior to the oval window, which contains many vascular channels. The focus has caused ankylosis of the anterior portion of the stapes footplate and has also pushed the footplate posteriorly, resulting in narrowing of the posterior stapediovestibular (SV) joint. The otosclerotic focus has also reached the endosteum of the basal turn of the cochlea. Note that the sensory and neural elements of the cochlea are intact, including the organ of Corti, stria vascularis and spiral ganglion cells. IAC, internal auditory canal. (**Magnification ×13.**)

HISTOLOGICAL DIAGNOSIS

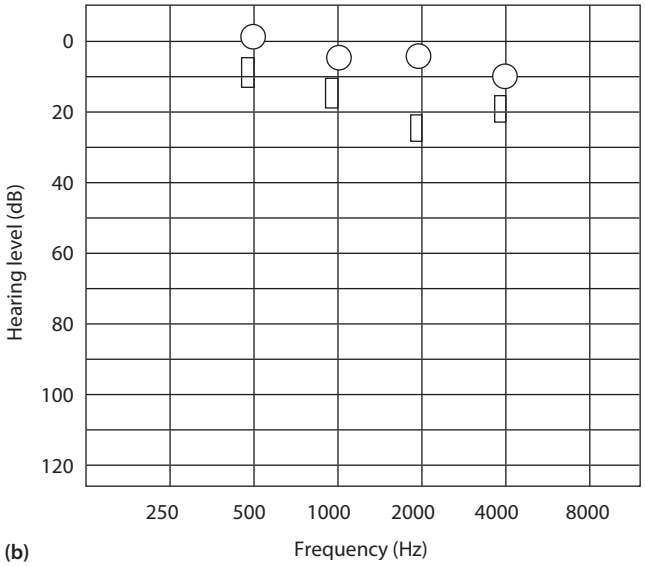
Histological confirmation of otosclerosis is more readily obtained if a total stapedectomy is performed. However, now that stapedotomy is the favoured surgical procedure, the stapes superstructure is the only material available. As fracturing of the crura to remove it occurs in non-otosclerotic bone, histology of this specimen is usually valueless.

PURE-TONE AUDIOMETRY

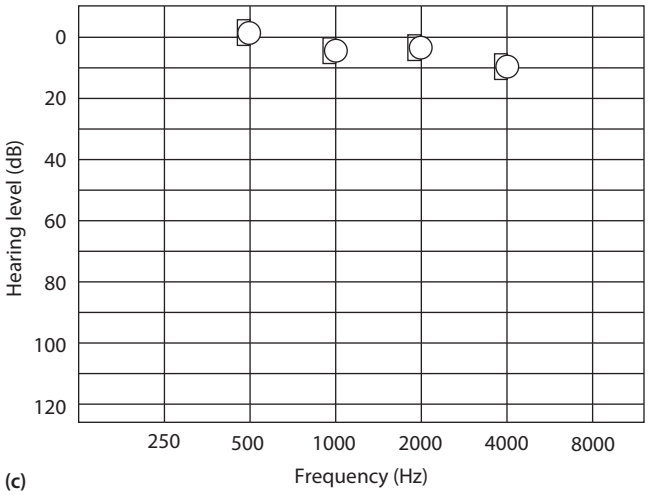
Pure-tone audiometry with appropriate masking will be required to confirm, by the presence of an air–bone gap, any clinical suggestion of a conductive hearing impairment. In those with normal bone-conduction thresholds, the air–bone gap will usually have the classical pattern of being greater at the low frequencies (Figure 89.5) with a Carhart notch.



(a)



(b)



(c)

Figure 89.5 **(a)** Pre-operative audiogram showing classical appearance of a conductive impairment in clinical otosclerosis. The air–bone gap in the right ear is greater at the lower frequencies and a Carhart notch is present at 2 kHz. **(b)** Audiogram of the same patient following successful stapes surgery using the pre-operative bone-conduction thresholds. The air–bone gap has been overclosed. **(c)** Audiogram of the same patient using the post-operative bone-conduction thresholds. The air–bone gap has been closed and the bone-conduction thresholds are better than the pre-operative ones, with elimination of the notch at 2 kHz.

Air–bone gap

The magnitude of the middle ear conductive impairment can only be measured by magnitude of the air–bone gap; the difference between the average air-conduction thresholds and the average bone-conduction thresholds. Traditionally, a three-frequency average over 0.5, 1 and 2 kHz has been recommended, primarily as the air–bone gap is greatest at these frequencies. Others use a four frequency average over 0.5, 1, 2 and 4 kHz, as the air-conduction average of these more accurately reflects the monaural hearing disability. The technical criticism of using this four-frequency average is that the bone-conduction thresholds at 4 kHz are less reproducible than at the lower frequencies. The American Academy of Otolaryngology and Head and Neck Surgery[92] recommends that a four-frequency average over 0.5, 1, 2 and 3 kHz be taken. In practical terms it probably does not matter what air-conduction four-frequency averages are taken as they are usually within 2–3 dB.[93, 94]

What the magnitude of the air–bone gap has to be to diagnose a conductive impairment is usually taken as 10 dB irrespective of what frequencies are averaged. This is because any lesser gap might be due to test/retest error of the audiometric assessment. What the magnitude of the air–bone gap has to be to justify consideration of surgery as a management option has historically been taken as 20 dB. However, many recent series include patients with smaller air–bone gaps down to 10 dB. The assertion is that, if an air–bone gap of between 10 and 20 dB can be closed to the pre-operative bone-conduction, the patient will materially benefit. Before patients with such a small air–bone gap are operated upon, it is essential for a surgeon to audit his results to ascertain how often this occurs in otosclerotic individuals with larger air–bone gaps.

Carhart notch

The Carhart notch is closely related to the Carhart effect. This effect was initially described following successful stapes surgery where overclosure of the air–bone gap occurred when the post-operative air–bone gap was calculated using the pre-operative bone-conduction

thresholds. However, on testing the post-operative bone-conduction thresholds, these had improved, particularly at 2 kHz, where the Carhart notch had been eliminated (Figure 89.5). The magnitude of this effect has been variously calculated (Table 89.2) but averages an improvement over 0.5, 1 and 2 kHz of at least 12 dB.

The reason this occurs is that, when the skull is vibrated by bone-conduction sound, the sound is detected by the cochlea via three routes. In Figure 89.6 route A is by direct vibration within the skull, route B is by vibration of the ossicular chain, which is suspended within the skull, and route C is by vibrations emanating into the external auditory canal as sound and being heard by the normal air-conduction route. In a conductive hearing impairment the latter two routes are deficient but are regained by successful reconstruction surgery. Hence the bone-conduction thresholds improve following surgery. The reason that there is a Carhart notch at 2 kHz before the surgery is that the Carhart effect is greatest around that frequency.

Coincidentally, though the notch was initially described in otosclerosis, it occurs in all ears that have a conductive impairment irrespective of the aetiology. Although in non-otosclerotic ears there is the potential for the Carhart effect to occur following surgery, this seldom happens because the surgery is usually less effective at correcting the conductive hearing impairment than it is for otosclerosis.

Many otosclerotic patients will have a mixed hearing impairment, the potential aetiologies of the sensorineural component being discussed below. In mixed impairments the Carhart notch tends to disappear (Figure 89.7). With increasing sensorineural hearing impairments it becomes increasingly difficult to mask the bone-conduction thresholds (Figure 89.8) and in severe, profound and total hearing impairments (Figure 89.9) to decide whether there is a conductive

TABLE 89.2 The magnitude of the Carhart effect (dB) from various authors (reprinted from Browning,[99] with permission)

Study	kHz			
	0.5	1	2	4
Carhart (1950)[95]	5	10	15	5
Gunderson (1973)[96]	12	12	12	9
Ginsberg et al. (1978)[97]	15	17	18	17
Gatehouse and Browning (1982)[98]	5	8	12	5

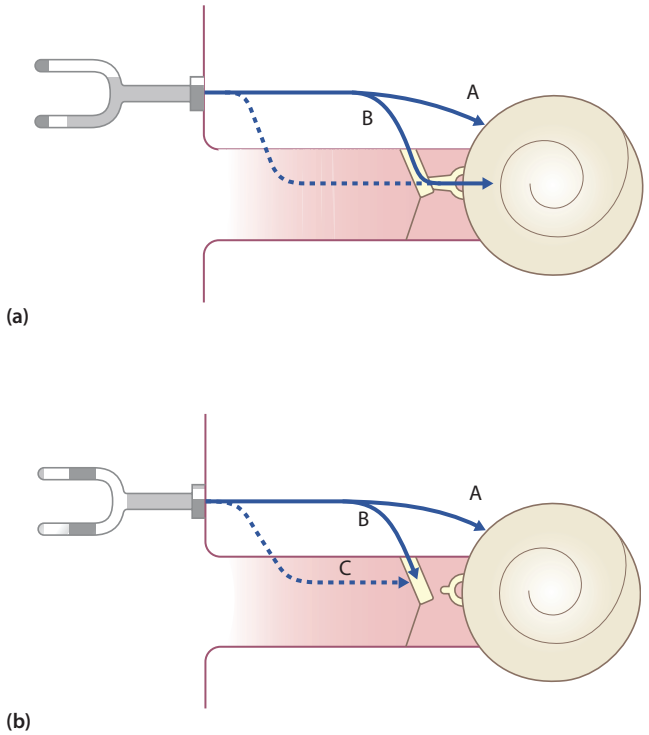


Figure 89.6 (a) The three normal routes of bone-conduction of sound vibrations to the inner ear: route A: via the skull bone; route B: via the ossicular chain; and route C: via the external auditory canal. In a normal ear, when the skull is vibrated by bone-conduction, it not only vibrates the cochlea via route A, but it also vibrates the tympanic membrane and ossicular chain (route B) and the air in the external auditory canal (route C). **(b)** In the presence of a conductive defect, the osseous route A is the only route for sound vibrations to reach the inner ear. When there is a middle-ear conductive defect, routes B and C are materially diminished in magnitude. Redrawn from Hannula et al.[83] with permission.

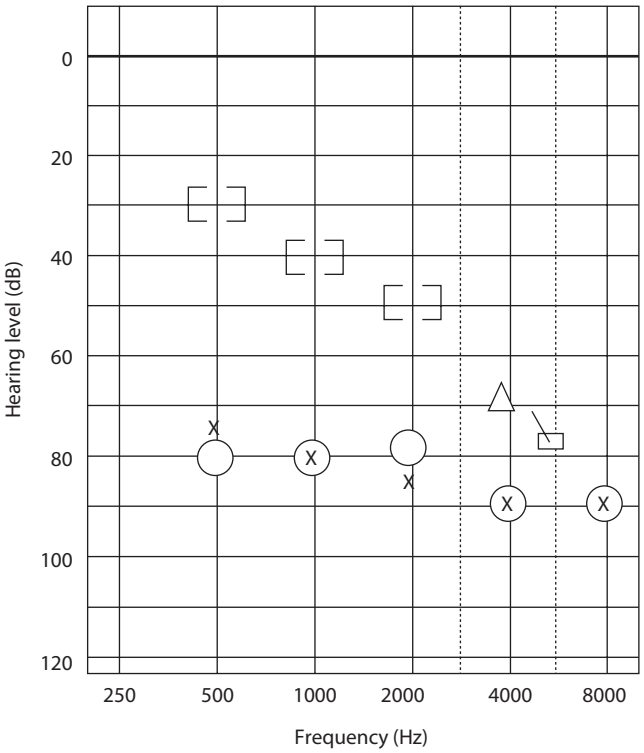


Figure 89.7 Audiogram showing a mixed hearing impairment, the conductive component being presumed due to clinical otosclerosis because the tympanic membrane is normal on otoscopy. The Carhart notch is hidden by the associated sensorineural hearing impairment. Redrawn from Browning,[99] with permission.

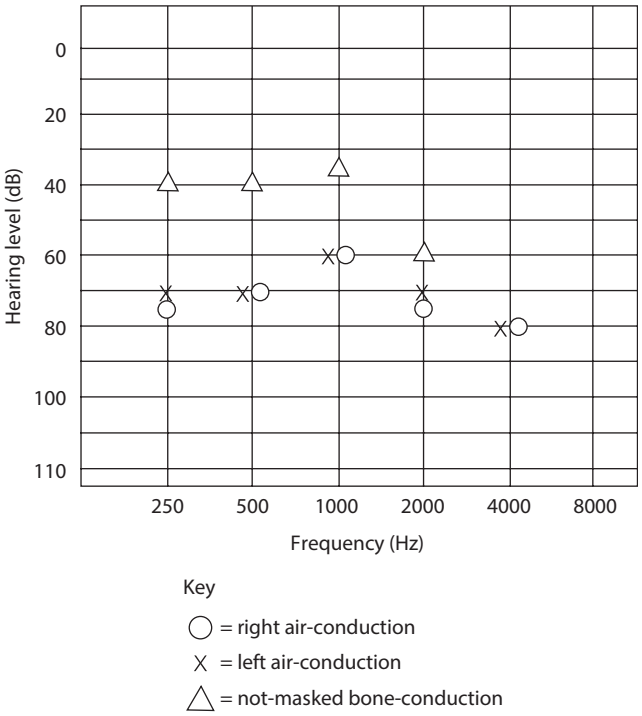


Figure 89.8 Audiogram of a patient with a bilateral severe impairment where it is not possible to mask the bone-conduction thresholds. One or both ears may have a conductive component to the impairment. Redrawn from Browning,[99] with permission.

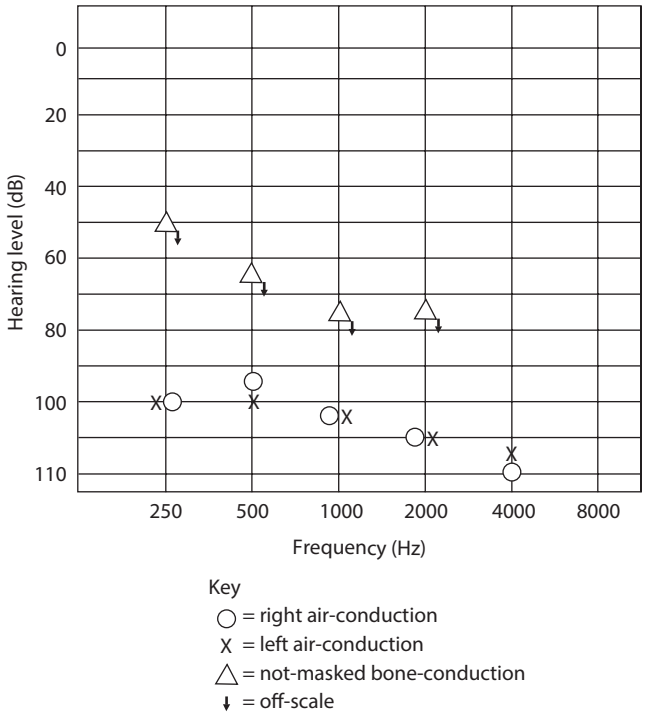


Figure 89.9 Audiogram of a patient with a bilateral profound impairment where bone-conduction thresholds are not recordable but there could be a 30 dB conductive impairment in one or both ears due to otosclerosis. Redrawn from Browning,[99] with permission.

component or not.[100] In these circumstances, various factors in the history or investigations can increase the certainty with which clinicians can come to a diagnosis of otosclerosis.

Given that the Carhart notch can be seen in any case of ossicular chain fixation it is perhaps not surprising that a recent literature review showed little to support the predictive value of the Carhart notch in the diagnosis of otosclerosis.[101]

HISTORY

The classic history is of a progressive hearing loss in early adulthood. In those with a severe or profound impairment, an earlier audiogram showing a mixed impairment or a history of a previous operation to improve the hearing as an adult will be suggestive of otosclerosis. A family history of hearing problems, unless it is clearly identified as being an otosclerotic history, covers too many potential aetiologies to be of value. A history of deterioration of the hearing during pregnancy is often cited to occur and indeed 50% of those with bilateral and 25% of those with unilateral otosclerosis will report such a change.[102] However, no data are available on how many individuals with hearing impairments due to other causes report such deterioration. The audiometric evidence for deterioration is retrospective and uncontrolled for time.[103] Certain features of a patient's history may suggest a diagnosis other than otosclerosis. These are early age of onset, no history of progression, associated discharge or trauma, associated vertigo.

TYMPANOMETRY

As might be expected, the compliance in ears with subsequently surgically confirmed otosclerosis is less than normal but the range is such that in an individual ear it does not add to the diagnosis.[104] The same comments also apply to multifrequency/multicomponent tympanometry.[105] If there is any doubt about there being otitis media with effusion as an alternative diagnosis, tympanometry is obviously then of value.

RADIOLOGY

High-resolution CT (HRCT) scanning is able to detect abnormal bone densities within the otic capsule. HRCT shows active otosclerosis as hypodense or lucent areas within the otic capsule, typically anterior to the oval window (**Figure 89.10**). The stapes footplate may be seen to be thickened. Other typical findings are narrowing of the oval and round window niches and a classic double ring sign around the cochlea. During the inactive sclerotic phase of disease, bone densities increase towards normal and CT diagnosis may be more difficult. Quesnel et al. compared HRCT with histology in cadaveric temporal bones from patients with known otosclerosis. Two blinded

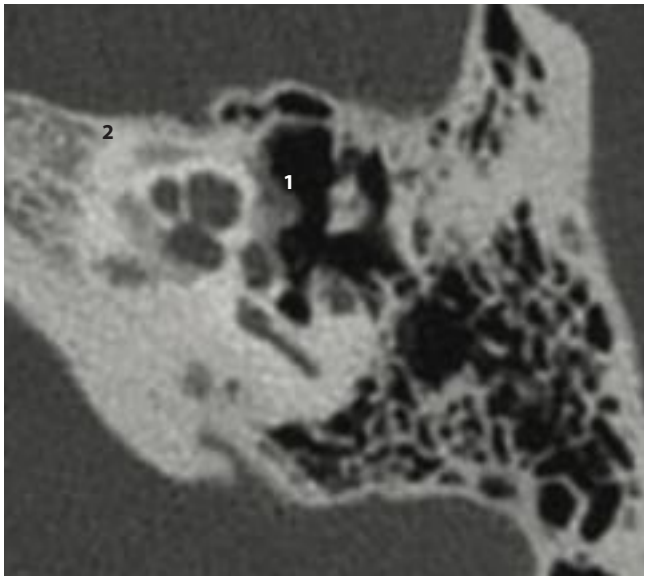


Figure 89.10 Axial CT scan of the left middle ear through the stapes footplate showing lucency anterior to the stapes footplate (1) and around the cochlear (2).

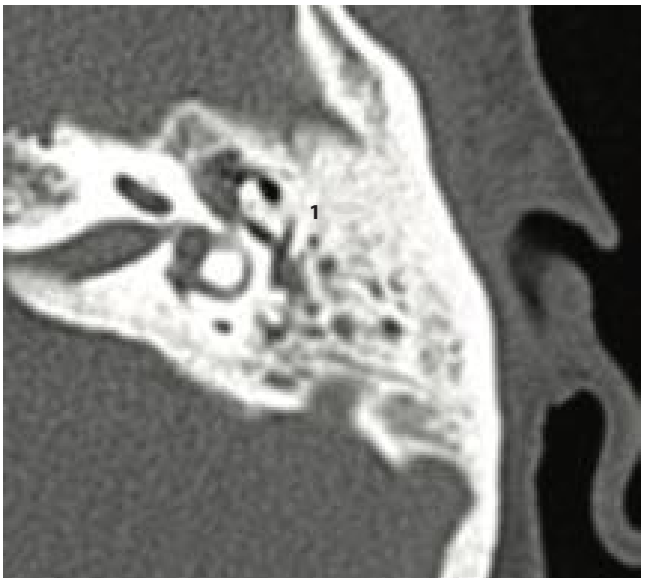


Figure 89.11 Axial CT scan of the left temporal bone showing the incus fused to the lateral wall of the attic (1).

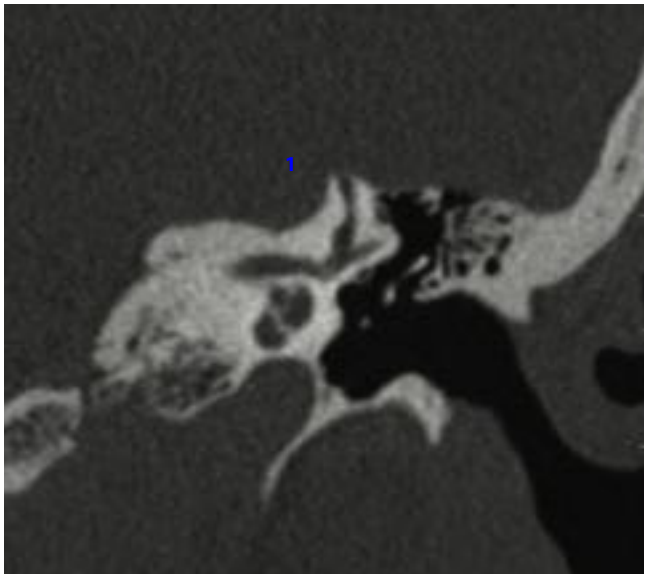


Figure 89.12 Coronal CT scan of the left temporal bone showing superior semicircular canal dehiscence (1).

neuroradiologists correctly identified 8 of 10 otosclerotic temporal bones from a group including 36 control non otosclerotic bones. There were three false positives where an area of lucency anterior to the oval window was due to soft tissue and not otosclerosis. This gives a sensitivity of 80% and specificity of 91.6% against the gold standard of histological diagnosis.[106] Various studies have compared CT and surgical findings with typical sensitivity of 70–80%. More recent studies with better CT scanning techniques using smaller pixel sizes have shown sensitivity for fenestral otosclerosis of over 90%.[107] With these improved sensitivities the case for routine CT scanning is growing, although many surgeons would not use CT scanning for classic cases of otosclerosis given the accuracy of the clinical assessment. CT does, however, have the ability to detect other pathologies such as malleus head fixation, incus fixation (**Figure 89.11**), superior semicircular dehiscence (**Figure 89.12**) and widened vestibular aqueduct as well as the extent of disease and anatomical variants. HRCT is therefore recommended if the diagnosis is in doubt, for example with early-age onset or associated vertigo. It is also of value if cochlear implantation is being contemplated. Pre-operative CT scanning is now obligatory in France prior to stapes surgery.

Cone beam CT scanning has the ability to resolve very thin slices down to 0.3 mm but with lower radiation doses than HRCT. Sensitivities appear similar to HRCT.[108, 109]

MRI scanning is useful if cochlear implantation is contemplated.

AUDIOLOGICAL ELIGIBILITY FOR SURGERY

Because clinical otosclerosis is a presumptive diagnosis in patients with a conductive hearing impairment and no evidence of other middle ear pathology, it is important that one is certain that there is indeed a conductive hearing impairment before deciding that an individual patient might benefit from surgery.

In the majority of patients, the pure-tone audiogram will be the audiological deciding factor provided this can be relied upon, particularly in the appropriate masking of bone-conduction thresholds. Traditionally, it was felt that there had to be at least an air–bone gap of 20 dB or more to benefit from surgery and the majority of stapes surgeons still use this cut-off. However, experience would suggest that an improvement in the hearing of less than 20 dB is appreciated by patients, particularly if they have a bilateral hearing impairment. Hence, experienced stapes surgeons may operate on ears with an air–bone gap of

10–20 dB, knowing that in a high proportion of them the air–bone gap will be closed.

More recently, some surgeons have been operating on patients with an air–bone gap of l0 dB or less. The concept here is that in reality there is the potential for a greater improvement in the air-conduction thresholds than 10 dB because of the Carhart effect.[110] The problem with this approach is that air–bone gaps of 10 dB or less may be artefacts of the audiometric test method. Hence, these authors suggest that there should be other evidence of a conductive hearing impairment, such as multiple audiograms, an absent acoustic reflex or appropriate tuning fork test results.

DIAGNOSIS OF COCHLEAR OTOSCLEROSIS

Two distinct situations exist when the diagnosis of cochlear otosclerosis may be made. The first is where there is a mixed impairment and the conductive component is due to clinical otosclerosis. The second is where there is a pure sensorineural impairment and aetiology is being sought.

In association with clinical otosclerosis

There is no reason why otosclerosis should protect against the majority of recognized aetiologies for a sensorineural impairment with the possible exception of noise trauma. It is therefore possible to compare individuals' bone-conduction thresholds with age-, sex- and socioeconomic-controlled population values. However, before doing this, they have to be corrected for their artificial depression due to the Carhart effect. The majority of papers do not do this. In addition, surgery can cause a sensorineural hearing impairment so the judgement can only be made on unoperated ears. When this is carried out, the data are again conflicting. Browning and Gatehouse found, on average, individuals with otosclerosis have no poorer thresholds than expected in the population.[111] However, both Topsakal et al. and Redfors and Moller also showed significantly greater sensorineural loss in non-operated otosclerotic ears than in age-matched controls.[112, 113] In post-operative studies examining progressive sensory hearing loss over time the data are again conflicting, with one 20-to-30-year-longitudinal study[114] showing the bone-conduction thresholds in patients after fenestration surgery for otosclerosis deteriorating with time at the same rate as the general population (1 dB every 2 years) but another with follow-up at 30 years showing significantly greater loss.[113, 115] Whatever the cause, there are undoubtedly a number of otosclerotic patients with a mixed hearing impairment, where the sensorineural impairment is considerably greater than expected from population data. Indeed, in cochlear implantation programmes, such patients make up approximately 1% of the population (see 'Cochlear implantation' below).

In the absence of a conductive impairment

To date, from the hundreds of temporal bones reported with histological otosclerosis, only three patients have been reported with a sensorineural impairment and no clinical otosclerosis in one or both ears. In these patients, the otosclerotic focus surrounds the cochlea without involvement of the oval window.[116, 117] On the other hand, there are many case reports of cochlear otosclerosis being diagnosed radiologically in individuals with a bilaterally normal middle ear and a pure sensorineural impairment. Evaluation of CT scans to identify differing areas of density is subjective and methods that calculate the density of various anatomical areas are superior. If this is carried out, the range of normal values overlaps that of patients with suspected pure cochlear otosclerosis.[118]

KEY POINTS

- Otosclerosis is the presumptive aetiology of a conductive hearing impairment in the presence of a normal, mobile tympanic membrane.
- Tympanometry does not generally aid the diagnosis of clinical otosclerosis.
- The case for pre-operative CT scanning is growing as scanning becomes more accurate.

NATURAL HISTORY

George G. Browning

CONDUCTIVE HEARING IMPAIRMENT

Ideally, to study the natural history of otosclerosis, one would like to follow up a cohort of young adults with serial audiometry over many years. This would enable the clinician to answer the following three questions that would be of clinical interest in the management of patients:

- How likely is unilateral otosclerosis to become bilateral with time?
- What is the average rate of progression of the magnitude of the air–bone gap in the better and poorer ears?
- Are there some individuals in whom the air–bone gap deteriorates and others in whom it does not?

Unfortunately, no study of this type has been identified. The main body of data available as an alternative way of trying to address these questions are surgical series that have been followed up for some years and report the non-operated otosclerotic ear as well as the operated ear. It is unfortunate that the operated ear, which in many instances will start as the poorer hearing ear, cannot be used to describe the natural history because the operation itself can have an effect on both the air- and bone-conduction thresholds. Reporting the natural history in the non-operated ear is likely to underestimate the magnitude of change in the air- and bone-conduction thresholds because in many instances it will be the better, and hence less affected, ear.

For an average of 9.5 years, Vartiainen et al.[119] followed up a series of patients that they had operated on one ear for

otosclerosis. In 122 of them, the other ear had clinical otosclerosis and their interest in reporting these ears was to see whether fluoridation of the water supply made any difference to the progression of the disease (see 'Fluoridation of drinking water' below). The 91 patients that had low levels of water fluoridation are those that are of particular interest because they are the larger group. Taking threshold averages over 0.5, 1 and 2 kHz, there was a yearly deterioration in the air-conduction thresholds of 2.1 dB, in the bone-conduction of 1.2 dB and the air–bone gap of 0.9 dB. Hence, one could postulate that the air–bone gap in an otosclerotic ear would deteriorate by around 10 dB every 10 years. The deterioration in the bone-conduction thresholds is just slightly greater than that which might be expected due to ageing and could be partly related to the Carhart effect.[120]

KEY POINTS

- From the limited data available in patients with unoperated otosclerosis, the air–bone gap and the bone-conduction thresholds both deteriorate by around 1 dB per year. Hence, the air-conduction thresholds will deteriorate by around 2 dB per year.

MANAGEMENT OPTIONS: FLUORIDE

George G. Browning and Christopher P. Aldren

FLUORIDATION OF DRINKING WATER

Sodium fluoride is a known inhibitor of osteoclast activity and so a stabilizer of bone turnover. It also leads to increased calcium deposition in otospongiotic foci and decreased bone remodelling.[121] This property makes it a potential treatment for otosclerosis and its use was first reported in 1964.[122] The release of cytokines from bony remodelling adjacent to the cochlear spiral ligament may be responsible for the sensorineural hearing loss sometimes seen in otosclerosis. Sodium fluoride has the potential to reduce this.

Flouridation of the drinking water to 1 mg/L in the town of Kuopio, Finland, between 1959 and 1992 allowed Vartiainen to compare patients exposed to fluoridated drinking water for an average of 21 years with those in the surrounding areas who had a natural low level 0.1 mg/L of fluoride in the drinking water with no added flouride. They found no difference in the prevalence of clinical otosclerosis over a 25-year period.[123] They also followed the change in hearing over an average of 9 years in the operated ears of patients who had had surgery for otosclerosis from the two populations. They found no significant difference in deterioration of bone-conduction or air-conduction over time in the operated ears. In the same patient population they were able to assess hearing loss in the non-operated ears. At presentation the hearing in the non-operated ear in the patients from the fluoridated water area was significantly better. Looking at those patients with >10 dB AB gap in the non-operated ear for an average of 9 years they noted a non-significant reduction in progression of the hearing loss in those in the area with fluoridated water.[120]

In another study comparing patients from areas of low and high water fluoride levels, those from the low area had a ×4 incidence of clinical otosclerosis.[124] However, their exposure was for all of their lives averaging 21 years and the level of the fluoride in the water was nearly twice as high at 1.9 mg/L as the low-fluoride areas. Targets levels for optimum flouride for dental health in the UK are 1 mg/L. It must be concluded that fluoridation of tap water to 1 mg/L has no impact on the prevalence of clinical otosclerosis but may slow the rate of deterioration of hearing in non-operated ears.

ORAL FLUORIDES

Flouridation of tap water gives a daily intake of 0.53 mg. However, oral fluoride supplements allow much higher doses to be given.

A number of case controlled series comparing patients with and without sodium fluoride supplementation are suggestive of benefit.[125, 126] In a double-blind Danish randomized controlled trial 43 untreated otosclerosis patients were given 40 mg sodium fluoride daily together with 500 mg of calcium gluconate and 400 units of vitamin D. The control group of 52 otosclerosis patients had the calcium gluconate and vitamin D but not the sodium fluoride. All patients had between 12 and 24 months of treatment. In the control group 13 of 52 saw their average air-conduction reduce by over 10 dB during the study which was significantly greater than 3/43 in the treatment group.[127] Unfortunately, no data were reported on the bone-conduction thresholds. It would appear that high-dose oral fluoride may decrease the rate of hearing loss in otosclerosis patients. There are no studies looking specifically at the optimum time period of treatment, however typically 2 years is recommended.

Data on side effects from the use of long-term high-dose sodium flouride come from the literature on osteoporosis treatment. Synovitis, gastrointestinal disturbance with pain and vomiting, painful plantar fasciitis and anaemia are commonly seen.[128]

The highest strength of sodium fluoride tablet available in the UK is 2.2 mg. This means that, to emulate the Danish study above, 20 tablets would need to be taken each day. This combined with the risk of side effects, the limited data on efficacy and the excellent results from stapedotomy mean that few UK surgeons currently use sodium fluoride. However, it may be considered in otosclerosis patients with progressive sensory hearing loss.

BIPHOSPHONATES

Biphosphonates are frequently used in the treatment of osteoporosis and Paget's disease. They are known to reduce bone remodelling and as such like sodium fluoride

may offer benefit in patients with otosclerosis. Early studies showed little benefit however a recent study using new third generation biphosponates showed a reduction in rate of progressive sensory hearing loss in patients with cochlear otosclerosis.[129] These drugs require further investigation but may reduce the deterioration of sensorineural hearing loss over time.

MANAGEMENT OPTIONS: HEARING AIDS

Peter A. Rea and Christopher P. Aldren

CONVENTIONAL HEARING AIDS

The importance of conventional hearing aids is not reflected in the number of publications on the subject: they make up less than 2% of the literature on otosclerosis.

Conventional hearing aids offer one of the four options in otosclerosis management, the others being no treatment, surgery and rarely bone-anchored hearing aids.

As a primary treatment, hearing aids are a particularly effective method of managing conductive hearing impairments. Hearing thresholds obtainable compare favourably with surgical outcomes. The choice of surgery or hearing aids in pure conductive hearing impairment depends on other factors: attitude to risk, aesthetic and comfort considerations, hearing-specific functional status and quality of life. Surgical risk is discussed under 'Management options: surgery' below. The perceived aesthetic disadvantages of hearing aids are particularly important in otosclerosis because of the relatively young population being treated. However, modern hearing aids can be very discreet and patients are often pleasantly surprised if they try them. Surprisingly little is published on hearing-specific health status and quality of life outcomes in the treatment of conductive hearing impairments. The limited literature available suggests that hearing-specific health status may be significantly improved by hearing aids. In contrast, quality of life measures are typically at population averages pre-treatment and, perhaps surprisingly, do not improve further.[130] Randomized trials comparing hearing aids to surgery are not available.

As the patient ages, the conductive impairment may become mixed with sensorineural impairment secondary to both age-related and cochlear otosclerosis. In this situation, recruitment may become a problem. Eventually, the level of hearing impairment may exceed the power of hearing aids alone. Suitable comparisons between hearing aids for mixed conductive and sensorineural impairments and surgical outcomes are not available.

FAR-ADVANCED OTOSCLEROSIS

Far-advanced otosclerosis (FAO) was first described by House and Sheehy in 1961 as a patient with otosclerosis with average air-conduction of over 85 dB and bone-conduction unmeasurable due to limits of audiometric equipment.[131] These patients are beyond the help of conventional air-conduction aids alone and can be managed in one of three ways: stapedectomy and subsequent conventional hearing aids, cochlear implantation or the new direct acoustic cochlear stimulation (DACS) device. A careful history to distinguish FAO from a pure sensorineural hearing impairment is essential. Clues include the timescale of the hearing impairment, family history, previous audiograms showing an air–bone gap, normal speech and CT evidence of cochlear otosclerosis.

A patient with FAO may, for example, have a sensorineural impairment of 65 dB HL with an air–bone gap of an additional 60 dB. This may show a complete hearing impairment on an audiogram. Stapedectomy, however, may raise the air-conduction threshold to 65 dB HL. This could be satisfactorily aided. Case series report successful hearing aid use post-stapedectomy in 46–82% of these patients.[132] While cochlear implantation gives the best overall results in these patients, it is much more expensive and so in many cases stapedotomy with conventional hearing aid offers a good first-line treatment, with cochlear implantation reserved for failures.[133] Following a review of the literature, Merkus et al. produced an algorithm to aid decision-making. Patients with pre-op speech discrimination <30%, more severe changes on CT scanning and small air–bone gaps do worse with stapedotomy and should be considered for primary cochlear implantation.[134]

During post-stapedectomy rehabilitation with hearing aids it is likely to be the sensorineural rather than conductive hearing loss that is being aided. Functional recovery, as demonstrated by word recognition scores, may continue for months or years post-surgery. It has been proposed that this reflects acclimatization or recovery from auditory deprivation.[135] Thus, both improved auditory thresholds and recovery from auditory deprivation may be noted with dual therapy.

As a 'rescue' treatment many years after surgery for otosclerosis, hearing aids are likely to be needed frequently. Truly long-term figures are notoriously difficult to obtain. From their series of large fenestra stapedectomy, Smyth and Hassard[136] estimated a requirement for a hearing aid on average 13 years after surgery and at 21 years after small fenestra surgery. Shea's figures[137] showed the need for a hearing aid at 30 years post-surgery in 30% of patients in whom initial stapedectomy had been successful. In a study following up stapedectomy patients at 30 years after surgery Redfors and Moller found that 66% of ears had moderate to profound hearing loss worthy of aiding. They also noted that the progression of sensorineural hearing loss was greater in operated compared with than the non-operated ears.[113]

It has been argued that all patients considering surgical treatment of otosclerosis should undergo a reasonable trial of hearing aid use to allow a fully informed consent to be obtained,[138] though this view is far from universally held. Informed consent requires available options to be discussed in a manner a patient will understand, so a trial of an aid may be the best method of addressing this. It is certainly a luxury to be able to offer a 'risk-free trial' of one of the options.

BONE-ANCHORED HEARING AIDS

Bone-anchored hearing aids (BAHA) have been proposed as an alternative method of managing otosclerosis in a limited number of situations. Selection criteria are similar to those typically used in BAHA programmes for other conditions. A specific benefit is that they do not produce the risk of a dead ear that may result from stapedectomy. An only hearing ear with otosclerosis combined with difficulty using a conventional aid, or a post-fenestration cavity, would be typical scenarios. Outcome data are limited. Objective testing of free-field thresholds and speech discrimination scores appears similar to conventional aids. Subjective outcomes including comfort and sound quality have been reported in a small series of patients with otosclerosis to be better with a BAHA than with a conventional aid.[139]

DIRECT ACOUSTIC COCHLEAR STIMULATION

The direct acoustic cochlear stimulation (DACS) device is of use in patients with mixed hearing loss where a successful stapedotomy alone would not allow the patient to manage without a hearing aid. The device consists of an active middle ear implant attached to a stapes prosthesis. First described by Hausler et al. in 2008,[140] the DACS allows direct acoustic stimulation of the perilymph via the stapes prosthesis. Subsequently developed by the Cochlear company, the Codacs™ has recently been reported to give good hearing in 14 patients. Indications were a minimum average bone-conduction of over 30 dB and with an additional air–bone gap of over 30 dB. Average pre-op unaided hearing and conventional hearing aided thresholds were 86 dB and 52 dB respectively. Post-operative aided Codacs™ thresholds were 37 dB.[141]

COCHLEAR IMPLANTATION

Patients with FAO or failed stapedotomy may be candidates for cochlear implantation and these patients make up approximately 10% of adult cochlear implant programmes. Their audiological results are comparable to those of non-otosclerotic patients receiving cochlear implants. Rea showed speech discrimination scores (using binaural CID sentences) improved from 12% (range 0–52%) pre-operatively to 88% (range 22–100%) post-operatively,[142] results which are mirrored in other series.

However, there may be problems in electrode placement due to otosclerotic ossification of the round window or basal turn of the cochlear which may necessitate extra drilling. Ossification of the apical region of the cochlear can lead to incomplete electrode placement. Non-auditory stimulation from the cochlear implant is also reported to be commoner in otosclerosis patients. Most commonly this is facial twitching but also can be otalgia and dizziness. This is thought to be due to demineralization of the otic capsule.[143] These pitfalls are summarized in Table 89.3.

TABLE 89.3 Pitfalls of cochlear implantation in otosclerosis

Source	Pitfalls
Resulting from previous otosclerosis surgery	Incus subluxation Severe middle ear adhesions Tympanic membrane vulnerable at site of bony curettage Ossification of scala tympani from post-stapedectomy labyrinthitis
Resulting from disease process	Obliteration of round window by spongiotic bone Incomplete electrode placement 'Looping' of electrode through soft spongiotic bone in cochlea Facial nerve stimulation by electrodes within cochlea

BEST CLINICAL PRACTICE

✓ For best clinical practice in relation to hearing aids, see Chapter 54, Hearing aids, and Chapter 93, Bone-conduction hearing aids.

FUTURE RESEARCH

➤ No randomized trials can be found comparing outcomes using hearing aids versus stapedectomy.
➤ Evidence for the role of bone-anchored hearing aids remains limited.

KEY POINTS

- Conventional hearing aids are effective in the management of hearing loss in otosclerosis.
- Their role is likely to increase with technological advance.
- A trial should at least be discussed prior to contemplating surgery.
- They may be used in addition to stapedotomy in FAO.

MANAGEMENT OPTIONS: SURGERY

Peter A. Rea and Rinze A. Tange

HISTORICAL PERSPECTIVE

Three distinct phases can be identified in the development of surgery for otosclerosis: mobilization and extraction of the stapes, in late 19th-century Europe; fenestration of the horizontal semicircular canal in the first half of the 20th century; and mobilization of the stapes revisited, along with stapedectomy and stapedotomy with prostheses in the latter half of the 20th century.[144, 145]

In 1876 Kessel described his work on the columella of pigeons, and the stapes of dogs and humans. He removed the footplate 'allowing a new membrane to form'. He, and

other early otological adventurers, also removed the malleus, incus and tympanic membrane to 'free up' the footplate. Miot and Boucheron from Paris reported cases in the 1880s in which the stapes was rocked to mobilize it after removal of part of the tympanic membrane. They noted the technique to be most successful in early ankylosis. Their efforts were limited by poor surgical equipment, poor illumination, lack of magnification, lack of antibiotics and consequent risk of deaths from meningitis, lack of adequate or standardized audiometry and lack of understanding of the functioning of the ossicles as shown by the 'ossiculectomy' technique described. While these surgeons were perhaps ahead of their time, not surprisingly due to the limited success and risks of serious complications stapes surgery fell into disrepute and in 1900 Siebenmann, Politzer and Botey stated 'mobilization of the stapes in otosclerosis is not only useless, but often harmful'. This was to remain the consensus view for the next 50 years.

Fenestration of the horizontal semicircular canal can be traced back to 1897, and was developed by Sourdille (1930) through his multistage operations. It was Julius Lempert in 1938 who described a single-stage endaural technique that became the mainstay of otosclerosis surgery for two decades. There was a 65% chance of the fenestration remaining patent and a 2% risk of serious complication. On long-term follow-up over half the patients had hearing better than prior to surgery.

Modern stapes surgery re-emerged in 1952 when Rosen had a patient whose hearing was restored following 'palpation' of the stapes. Stapes mobilization became accepted as the treatment of choice for those with only partial ankylosis, though re-ankylosis tended to develop a few years later. Fenestration was reserved for footplates that could not be mobilized. John Shea rediscovered the stapedectomy procedure and reconstructed the sound transmission system with a prosthesis. The first prosthesis inserted in 1956 was a replica of a normal human stapes. A huge backlog of untreated otosclerotic ears was operated on in the following decades, during which time the technique evolved. In the first decade of stapedectomy, the fenestration procedure fell from favour. In the next 10 years, the use of prostheses and a living oval window seal gained popularity, and in the subsequent decade the debate over small versus large fenestra surgery emerged. More recently, technological advances and research contributions have refined our approach, but the caseload is diminishing.

CONTRAINDICATIONS TO SURGERY: CONTROVERSIES IN OTOSCLEROSIS SURGERY

The smaller number of operative cases, coupled with increasing numbers of otolaryngology trainees with some exposure to this potentially demanding surgery, raises the question, 'who should be performing stapes surgery?' Opinions vary widely. The evidence suggests that there is a significant association between experience and both technical ability and surgical outcomes for stapes surgery.[146] While rules are not established, it seems sensible that only a limited number of surgeons need training in this operation, and only a limited number need to perform it. A requirement for individuals to audit their results is emphasized in the literature.

Returning to the patient, the indications for surgery have been discussed under 'Diagnosis' above. Controversies, or 'when not to operate' above, will be reviewed here. Caution should be exercised when interpreting the survey figures quoted for current practice: they do not necessarily equate to best practice.

Age

Large series of stapes surgery report cases between 6 and 92 years of age. Surgery in children represents only a very small proportion of operations. This reflects both the common use of hearing aids to manage otosclerosis in children and the rarity of cases in this age group. We reviewed the five largest paediatric series covering 200 cases, and found post-operative air-conduction was within 10 dB of pre-operative bone-conduction in 89%. One series followed their children for a mean 11.6 years post-operatively. None redeveloped a conductive impairment, and sensorineural thresholds deteriorated at a mean 0.7 dB (range 0–2.3 dB) per year.[147] Special precautions are required when contemplating surgery on children with a conductive hearing impairment, however, in particular the risk of congenital middle and inner abnormalities. In the presence of a mixed hearing impairment, CT imaging of the temporal bone is advised to rule out inner ear abnormalities that may be associated with a cerebrospinal fluid gusher, in particular X-linked progressive mixed hearing impairment. The incidence of obliterative otosclerosis, at 26–41%, is also reported to be much higher in children than adults having stapes surgery. The results of surgery at the other end of the age spectrum, aged 70–92 years, are reported to be similar to those in a younger adult population.[148] In summary, caution is required when considering surgery in children, while no upper age limit needs to be applied in adults on technical grounds alone.

Occupation and leisure activities

Occupation and leisure activities that may predispose to barotrauma are important. Historically, military pilots were grounded after surgery, but they may now fly military jets in several countries post-stapedectomy. Commercial air travel, snorkelling, scuba diving, strenuous activities and parachuting have also been cautioned. Clinical evidence of the feasibility of such activity was suggested by a study from The House Ear Clinic. Questioning 208 patients who had snorkelled, scuba dived or parachuted following stapes surgery, no immediate relationship to otological difficulties was identified.[149] No consensus exists between surgeons regarding advice to patients. In the UK, 18% of otolaryngologists give no flying restrictions, while 82% suggest avoidance for between 1 and 24 weeks.[150] In a survey of members of the American

Otological Society, 12% gave no restrictions on flying post-stapes surgery, 20% recommended a 2-day restriction and 60% suggested 2 weeks or more. Similarly, with scuba diving, 35% recommended restrictions for between 1 and 6 months, while more than 50% recommended permanent abstinence.[151] The suggested time delay is said to allow the connective tissue seal time to mature. A post-operative test has now been proposed: applying tympanometric pressure of 400 mm H_2O to the ear while recording nystagmus matches the maximal possible displacement of the prosthesis. If pathological eye movements are not evoked, and the appearances of the tympanic membrane are normal, it is suggested diving or parachuting can be safely performed.[152]

Ménière's disease and general vestibular symptoms

Ménière's disease is often stated as a contraindication because of the proximity of the distended saccule to the footplate. A small clinical and temporal bone study suggested that the saccule did not contact the footplate in patients with bone-conduction levels of 35 dB HL or better at 500 Hz and with no high frequency impairment, concluding surgery could be performed within these constraints.[17] Caution is, however, clearly required. More general vestibular symptoms do not appear to be a contraindication to surgery. This is supported by a large temporal bone study that found a strong association between loss of Scarpa's ganglion cells and vestibular symptoms in patients with otosclerosis, suggesting neuronal degeneration and not hydrops to be the cause.[15] Clinical studies have shown no difference in hearing outcomes between patients with or without pre-operative vertigo.

Unilateral otosclerosis

Whether to operate on unilateral otosclerosis is contentious. It is worth remembering that unilateral conductive hearing impairment is less likely to be caused by otosclerosis than bilateral impairment. A survey in the UK revealed 81% of consultants may operate for unilateral otosclerosis.[139] However, a patient's disability is mainly determined by the hearing threshold in the better hearing ear. So, to be of maximum benefit, surgery will have to provide symmetrical hearing in this group: in effect closing the post-operative air–bone gap to within 10 dB. The initial bone-conduction will also have to be near normal, or be able to be normalized after surgical correction of the Carhart effect. Most papers quote this degree of closure being achieved initially in 80–95% of procedures but, as will also be shown under 'Hearing outcomes' below, longer-term results may not be as good. Patients may still, however, have some benefit in certain circumstances even when symmetrical hearing is not achievable.

Second-side surgery

Second-side surgery is equally controversial. Seventy-five percent of UK consultants surveyed would perform bilateral stapes surgery.[150] The perceived risk is of delayed bilateral cochlear impairment. Total cochlear impairment may occur many years after a stapes procedure, but the risk is low, at around 1%. The potential benefits are twofold. A second-side operation gives both a greater chance of obtaining one normally functioning ear, and also of gaining binaural hearing. This has been demonstrated by de Bruijn et al. and is clearly illustrated in **Figure 89.13**.[153] The incremental benefits to the individual appear significant,

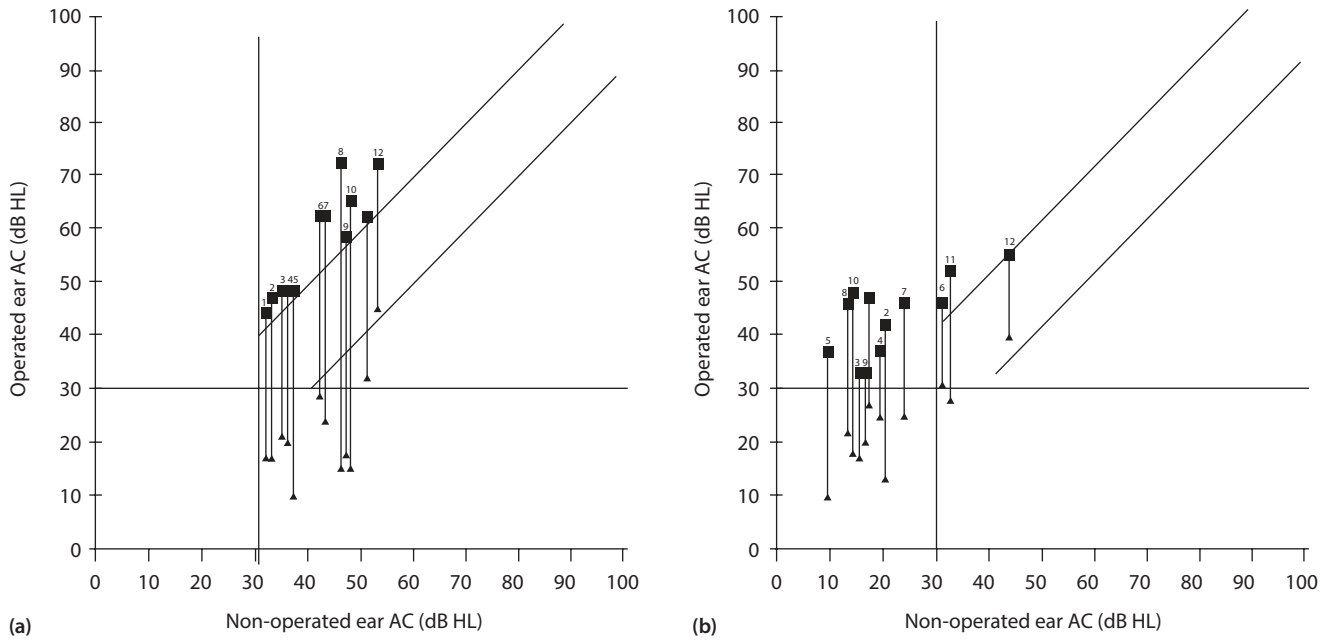


Figure 89.13 Pre- (■) and post-operative (▲) air-conduction (AC) thresholds. Each patient is indicated by an Arabic numeral. **(a)** Results from stapedotomy on the first side. **(b)** Results after stapedotomy on the second side. Reproduced from Vartiainen et al.,[119] with kind permission of S. Karger AG, Basel.

but are less with second-side surgery than with first.[154] Using the American Medical Association (AMA) criteria it was found that the 'Binaural Hearing Impairment Score' fell from 26% to 10% after surgery to one side, and from 11% to 7% after second-side surgery. The 'Impairment of the Whole Person Scores' fell from 9% to 4% and 4% to 2%, respectively.

Air–bone gap

Twenty dB is traditionally taken as the minimum air–bone gap before considering surgery. Some expert stapes surgeons will operate on patients with air–bone gaps of as little as 10 dB in the belief that overclosure will allow a relatively greater improvement in air-conducting thresholds. One series of 136 stapes procedures on patients with air–bone gaps of 10 dB or less equalled or overclosed the pre-operative bone-conducting threshold in 90% of cases, producing a mean air-conduction improvement of 17 dB. It is worth noting that a further 18 patients in this series did not have stapes surgery performed at all at the exploratory tympanotomy, suggesting that diagnosing otosclerosis may be more difficult in this group.[110]

Other factors

A number of other factors are frequently cited. General health and safety of anaesthesia may be significant. Active infection in the outer or middle ear and pregnancy are absolute contraindications to surgery. Whether surgery should be deferred until no further childbirth is planned is debatable. Lippy et al. looked at the hearing results before and after surgery for otosclerosis in women with and without children and found those with children were slightly better. No correlation between the number of children or breastfeeding with hearing loss was seen.[155] Eustachian tube dysfunction is cited as a potential contraindication though quantifying this is not clearly described. Active otosclerosis as indicated by the 'Schwartze sign' is quoted as a contraindication, though much of the evidence is anecdotal. Diabetes has been considered a relative contraindication, though this is not supported by a literature review.

SURGICAL TECHNIQUES

Medical prophylaxis

The ear is prepared with an aqueous antiseptic solution. There is no evidence to support the use of steroids or antibiotics peri-operatively. Indeed, the use of prednisolone has been reported to increase post-operative vertigo.[156]

Anaesthesia

Stapes surgery may be performed under either local or general anaesthesia. A surgeon's personal experience strongly influences the decision. In the UK, over 90% of procedures are performed under general anaesthesia but local anaesthesia is much more popular in Europe. There is no evidence to support superior hearing results or differences in post-operative vertigo with either anaesthetic technique.[157]

General anaesthesia has the advantages of flexibility if complications or difficulties are encountered, and of a motionless operative field. Hypotensive anaesthesia is useful to reduce bleeding.

Local anaesthesia is also generally well tolerated. Short-acting intravenous analgesia and sedation may be given at the beginning of surgery, while infiltration of local anaesthetic (1% lidocaine) and dilute adrenaline (1 : 30 000–1 : 100 000) is performed. Initial infiltration of the posterior wall of the external auditory meatus via the postaural sulcus is followed by slow direct infiltration of the canal skin just lateral to the bony and cartilaginous junction. A pretragal injection may also be made to reduce discomfort if a retractor is used. Some surgeons recommend sedation throughout the procedure; others prefer the patient fully awake to prevent movement on sudden arousal. Local anaesthesia allows the patient to report dysequilibrium, which may be useful in revision surgery where adhesions can extend into the vestibule. Confirmation of hearing restoration after prosthesis placement is also possible as the surgeon talks to the patient. Difficulty may result if complications are encountered during surgery, in particular those that may induce vertigo. Transient facial palsies may result from the infiltration. Patients may complain of the noise, dizziness, anxiety, backache, claustrophobia and discomfort.

Exposure

The surgery can usually be performed through a purely permeatal approach although some surgeons use an endaural incision. When using a permeatal approach a speculum holder is very useful to stabilize the speculum and give a stable platform to allow the surgeon to stabilize his or her hands. A tympanomeatal flap is elevated from 7 o'clock to 12 o'clock (in the right ear), hinging forwards just posterior to the handle of the malleus. The chorda tympani nerve is gently freed from any mucosal folds. The posterosuperior bony annulus is reduced with curettes, drill or hammer and gouge, further releasing the chorda tympani if required. A heavy hook can be useful to remove the bony covering of the chorda tympani and liberate the nerve. Enough bone should be removed from the annulus to expose the stapes, oval window, facial nerve and the base of the pyramid.

Establishing the diagnosis

Anatomical anomalies which may compromise surgery, such as a persistent stapedial artery or overhanging facial nerve, should be identified, as should alternative causes of the hearing impairment such as tympanosclerosis. The stapes superstructure should be gently palpated to check for fixation of the footplate. The diagnosis is often clearer after disarticulation of the incudostapedial joint. The footplate and round window should be examined for evidence of otosclerosis, in particular very extensive disease.

If there is complete obliteration of the footplate, a drill-out of the footplate will be required and inexperienced surgeons may choose not to proceed. Total round window obliteration is rare, occurring in less than 1% of operative cases, not easily corrected, and associated with poor outcome. The malleus should be palpated to test for fixation of the malleus head, anterior ligament and malleoincudal joint. Again, this assessment is more easily performed after disarticulation of the incudostapedial joint.

Restoring the sound transmission mechanism

The historical review described many ways in which sound transmission may be restored across the stapes footplate. While variations on all these themes are still practised, stapedotomy is now used most widely. The surgical methods will be outlined first. A more detailed outcomes review of specific technical aspects is made under 'Hearing outcomes' below.

Stapedectomy and partial stapedectomy

The steps in a stapedotomy are shown in Figure 89.14. First, the incudostapedial joint is divided using a joint knife. This should be inserted from the posterior aspect of the joint and moved anteriorly as the stapedius tendon will reduce movement of the stapes superstructure. The mobility of all ossicles is then reassessed to make sure the stapes is indeed fixed and that a fixed malleus is not missed. The stapedius tendon is now divided with a laser, scissors or microhook. The stapes superstructure may now be removed by fracturing the crura down, away from the facial nerve, but it is better to first divide the posterior crus with a laser or crurotomy scissors to reduce the risk of mobilizing the footplate. If possible, the anterior crus should also be divided prior to removing the stapes. This may be hidden from view but can be accessed by feel using a handheld laser. The laser should be angled away from the facial nerve. The distance between the footplate and the incus should now be measured. It is most common to measure from the undersurface of the incus to

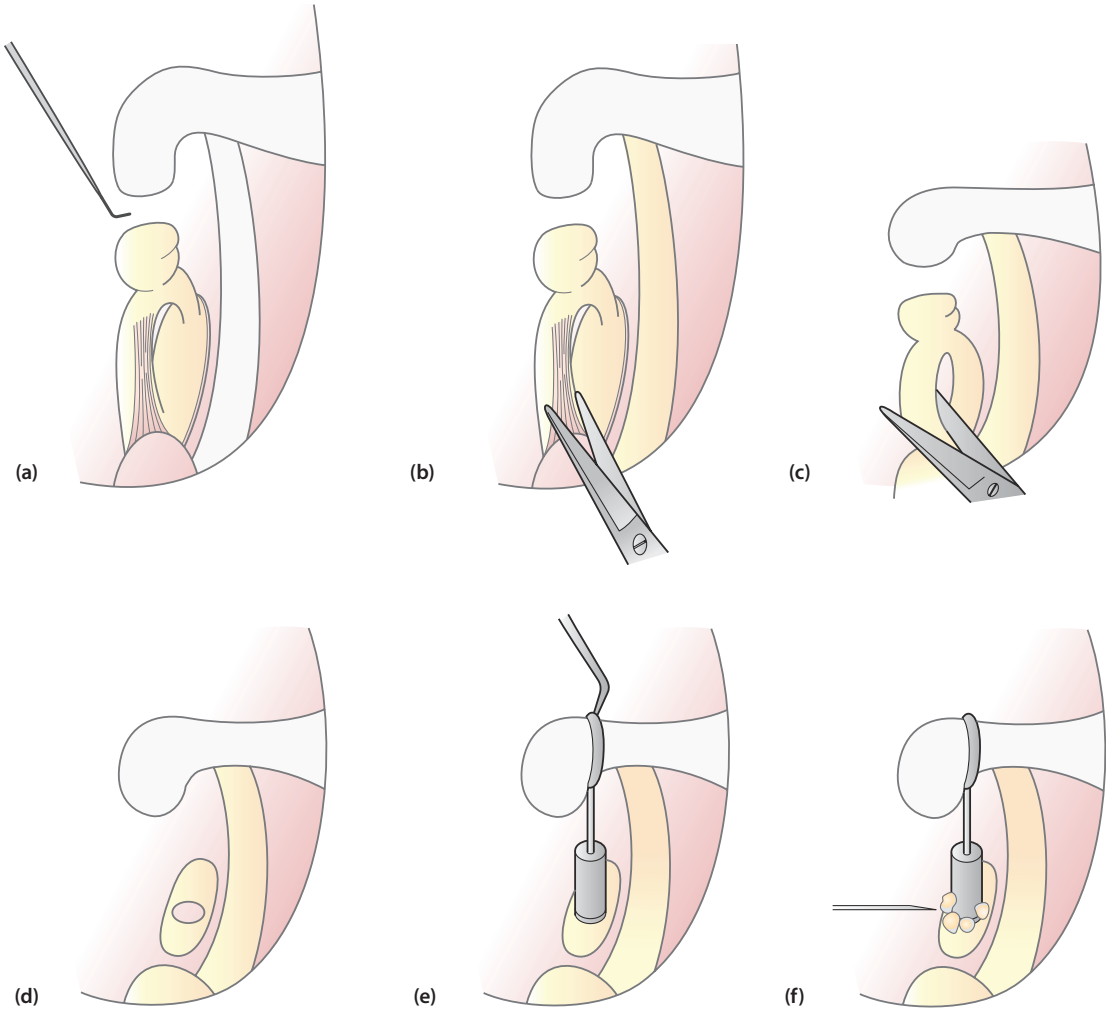


Figure 89.14 Steps in stapedotomy. **(a)** Following disarticulation of the incudostapedial joint, a fixed footplate is confirmed. **(b)** Division of the stapedius tendon. **(c)** Division of the posterior crus of the stapes using crurotomy scissors or a laser followed by down fracture of the crura. **(d)** Stapedotomy drilled in posterior third of the footplate. **(e)** Following insertion of the prosthesis, final adjustments are made and crimping carried out if required. **(f)** Packing around the footplate with fat or connective tissue.

the footplate. If the footplate is thickened, the measurement should be made again after the footplate is thinned just before the stapedotomy is performed. Manufacturers do differ in their labelling of prostheses, though the length is usually from the bottom of the loop. The functional length of the piston is from the upper surface of the lower half of the loop to the tip of the shaft. It therefore is the sum of the shaft length and the thickness of the loop material. For wire pistons the thickness of the loop material is negligible; for the Teflon loop piston this is 0.5 mm and has to be taken into consideration when cutting the shaft. The prosthesis selected should be 0.25 mm longer than the distance from the undersurface of the incus to the surface of the perilymph to allow sufficient penetration. This will usually result in a 4.25 mm, 4.5 mm or occasionally 4.75 mm prosthesis being selected.

The stapedotomy should be made at the junction of the middle and inferior thirds of the central portion of the footplate where the distance between the underside of the footplate and membranous labyrinth is greatest.[18] It may be made with a laser, electrical microdrill or handheld perforator. The perforation should be slightly wider than the prosthesis. If a 0.4 mm prosthesis is being used, it is usual to fashion a perforation of approximately 0.5–0.6 mm. The tighter the fit, the less the need for a connective tissue seal. However, if too tight, the hearing will be reduced as movement of the prosthesis will be impaired. In thick footplates the perforation should be of sufficient size to prevent the prosthesis touching the side of the hole, especially if it cannot be suspended absolutely perpendicular to the footplate. An interposition graft is placed over the footplate perforation at this point if used. If a Teflon loop is chosen, it must first be opened out on the shaft of a middle ear needle and then positioned on the incus with the help of crocodile forceps or an otological suction tube, where it will close around the long process of the incus. The shaft is simultaneously positioned in the footplate perforation. Wire loops will need crimping, or closing with laser or diathermy in the case of certain alloys. The piston is then assessed for adequate tightness at the incus and length at the footplate. Blood, fat or a connective tissue seal is usually then placed around the footplate perforation in an attempt to seal it, if a vein graft has not been placed over the stapedotomy first (this is discussed further below under 'Hearing outcomes'). The tympanomeatal flap is then replaced and the external ear canal packed.

Stapedectomy has fallen in popularity as stapedotomy has risen, though it was still the technique of choice for 19% of UK otolaryngologists in 2002.[150] The approach to the footplate is the same as for stapedotomy (**Figure 89.15**). A control hole is made in the footplate. The whole footplate or more typically the posterior third is removed with picks. The defect is covered with a connective tissue graft, most commonly vein from the forearm, and the prosthesis placed on the graft and suspended from the long process of the incus.

Footplate mobilization

In the 1950s, Rosen developed the stapes mobilization technique, but refixation occurred in months. In 1956, Fowler developed the anterior crurotomy technique with similar results. A recent variation is the laser stapedotomy minus prosthesis (STAMP) procedure. All these techniques depend on a lack of ankylosis at the posterior stapediovestibular joint. The laser procedure described by Silverstein et al. uses a handheld laser probe to vaporize the anterior crus of the stapes and perform a linear stapedotomy across the anterior third of the footplate. The stapes mobilizes if otosclerosis is confined to the anterior third of the footplate. It is claimed to be possible to achieve this in one-third of operative cases.[158, 159]

Revision surgery

Revision surgery is more technically challenging than primary stapes surgery. The clinical indications for revision operations are summarized in **Table 89.4**, while the discussion that follows will outline the possible findings at revision surgery. Three themes emerge from reviewing the literature. First, local anaesthetic is more frequently, though not exclusively, described as being advantageous. This is because the presence of adhesions between the prosthesis or footplate graft and the membranous labyrinth may induce vertiginous symptoms on manipulation of the prosthesis during revision surgery under local anaesthetic. This may prevent the surgeon further traumatizing the membranous

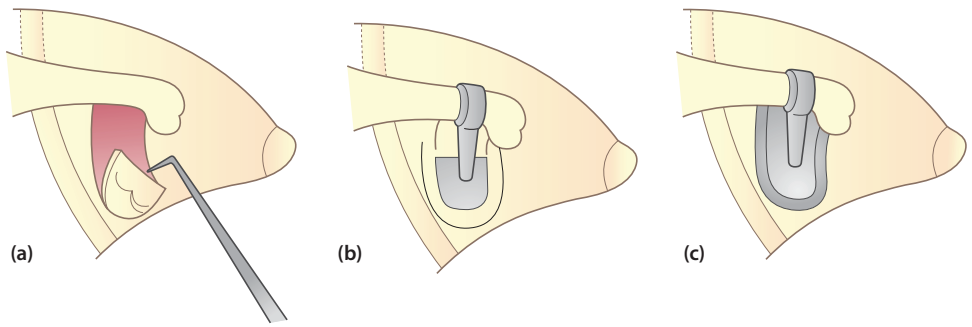


Figure 89.15 Steps in stapedectomy. **(a)** After division with picks, the posterior footplate fragment is removed. **(b)** If the anterior fragment remains fixed, the partial oval window defect is covered with vein or fascia and the prosthesis positioned. **(c)** If the anterior footplate has become unstable, it is removed and a larger graft used to cover the oval window.

TABLE 89.4 Pre-operative indications for revision stapes surgery in 522 cases (reproduced from Lippy et al.[160] with permission)

Indication	Cases (%)
Conductive hearing loss	92.5
Dizziness	2.5
Sensorineural hearing loss/perilymph fistula	1.9
Far-advanced otosclerosis	1.7
Distortion or vibration	1.1
Previous fenestration	0.2

labyrinth and so prevent a dead ear. Second, a much wider variety of surgical techniques may need to be employed to deal with the related ossicular pathology. Third, many centres recommend the use of lasers for revision surgery. Advocates state that vaporizing middle-ear adhesions with a laser allows more accurate assessment of the underlying pathology, aids removal of a non-functioning prosthesis, and allows a new fenestration to be fashioned without manipulating the footplate. These variables will be analyzed under 'Hearing outcomes' below.

PERI-OPERATIVE HAZARDS

Surgical approach

The external auditory canal may be excessively narrowed by pathology such as exostoses. While on occasions it may be necessary to correct these in a separate operation, it is frequently possible to do both operations at once.

Tympanic membrane perforation is reported to occur during approximately 2% of stapes operations. The procedure need not be abandoned as the perforations are usually small tears which can easily be repaired with an underlay myringoplasty. A spare piece of vein from a vein graft makes an ideal repair material but tragal perichondrium can also be used. Long-term results are unchanged.[161]

Anatomical

The chorda tympani nerve needs to be gently displaced from the operative field. This may require extended bony curettage. The facial nerve is dehiscent above the oval window in approximately 10% of ears. It may rarely herniate down over the oval window. In the former case, caution is needed. In the latter, surgery may need to be abandoned although a bucket handle prosthesis which sits under the lenticular process often allows a better angle with the shaft of the prosthesis coming from further inferiorly than a standard prosthesis. Care should be taken at revision surgery where a dehiscent nerve may be embedded in fibrous tissue and vulnerable as this is cleared. The facial nerve canal may also overhang the footplate limiting surgical access. Again, a bucket handle prosthesis can be useful in this situation.

Major vascular anomalies are rare. An aberrant internal carotid artery needs no further elaboration. A persistent stapedial artery may run from the facial canal between the stapedial crura. This may obstruct safe access and cause troublesome bleeding. There are reports of safely dividing smaller vessels and proceeding with surgery. Anatomical accounts of the stapedial artery giving segmental supply to the facial nerve and even brainstem are noteworthy for the brave contemplating dividing larger vessels.

Access to a narrow oval window niche can be improved in selected cases by drilling on the promontory with a microdrill, without evidence of significant sensorineural impairment in published series.

Other diagnoses

Congenital abnormality, fracture or post-inflammatory fixation or erosion of the ossicles must be identified. Their management is beyond the scope of this chapter.

The management of tympanosclerotic fixation of the stapes footplate remains controversial and to some is a contraindication to surgery. It has been historically considered to have a high rate of post-operative sensorineural hearing impairment, the highest reported being 26%, though this assumption stems from only a small proportion of the published series. We reviewed 14 case series totalling 382 stapedectomies and stapedotomies. Dead ears are reported in 2.6%. Surgery may need to be staged as tympanic membrane perforation frequently coexists. Surgical techniques are also varied because of the frequent associated fixation of the other ossicles. Consequently, a total ossicular replacement prostheses is often required. Hearing outcomes are inevitably not as good as with surgery for otosclerosis. Vincent et al.[162] clearly reported series showed closure of the post-operative air–bone gap to 10 dB in 39% and 10–20 dB in a further 31%. Only 22% achieved normal bilateral hearing on the Glasgow Benefit Plot.

Osteogenesis imperfecta has also traditionally been associated with poorer stapedectomy outcomes than for otosclerosis. This in part reflects the progressive mixed nature of the hearing impairment that has been shown to worsen late outcomes.[163] There are also higher risks of a floating footplate and unusual ossicular or tympanic ring fractures. Authors of the larger case series conclude surgery is a reasonable alternative to hearing aids, particularly when hearing aid use alone does not provide adequate amplification.[164]

Ossicular problems

Ossicular problems may arise as a complication of surgery or be identified in combination with footplate fixation. The incus may be displaced during curettage of the bony annulus or instrumentation of the oval window. If it can be maintained in its anatomical position, an incus to footplate prosthesis can still be employed, otherwise a malleostapedotomy will be required. Congenital or inflammatory fixation of the incus may be encountered. Incus–malleus fixation has been reported in 1% of stapedectomies.

Malleus head fixation is typically reported in primary otosclerosis surgery at a rate of 1%, though Causse quoted 10.6%.[165] This may reflect how carefully it is sought. It has become an area of particular interest following the work of Fisch who reports partial or total malleus fixation in 46% of his revision stapedectomies. This is seven times the rate of most other authors. He employs an epitympanotomy to examine the anterior malleolar ligament, as well as the incudomalleolar joint, both sites of potential fixation. A malleostapedotomy is recommended in most cases.[166] Biomechanical evidence emphasizes the importance of a particularly firm attachment of the wire loop to the malleus handle to prevent tilting movements of the angulated prosthesis.[152]

Stapes footplate

Peri-operative difficulties with the stapes footplate increase the risk of sensorineural hearing damage. Minimal stapes fixation or a previous mobilization procedure predispose to a floating footplate. This occurs in less than 1% of procedures. A preliminary burr hole in the footplate prior to fracture of the crura may reduce the risk of a floater. If it does occur, it may be possible to drill an inferior marginal burr hole to aid extraction of footplate fragments. Others advise placing a tissue graft and prosthesis on the footplate. If in doubt, it may be safest to place a large tissue graft over the footplate and not revisit for at least 6 months to allow refixation.

In 3–11% of cases the footplate may be solid or obliterated. Otosclerotic foci within the footplate itself may produce a thick 'rice grain' footplate. This situation is also associated with an increased risk of a floating footplate. The oval window may become extensively involved with new bone in obliterative otosclerosis. Wide saucerization of the footplate has been associated with high rates of sensorineural hearing damage. A stapedotomy technique is recommended, but the perforation should be wide enough to prevent lateral contact of the prosthesis onto surrounding bone, which would cause attenuation of sound transmission.[165] If the footplate reobliterates, revision surgery has been associated with very high rates of sensorineural hearing damage.

A cerebrospinal fluid 'gusher' is rarely encountered. Causse and Causse [165] quoted 0.03% in his series. It presents as a rapid flow of fluid on entering the vestibule. It is most commonly seen in congenital mixed hearing impairment. There are reports of it originating from either an abnormally wide cochlear aqueduct or an internal auditory canal defect. No individual has large experience of this condition. The patient should immediately be positioned head up. It is then most commonly managed by a tissue graft over the oval window with a prosthesis to anchor it. The use of a lumber drain has been advocated by a minority. There were occasions when the flow could only be stemmed by ablation of the cochlear aqueduct or packing the internal auditory canal.

The operative field should be dry enough to prevent blood entering the oval window. The aspiration of blood or perilymph from the oval window is significantly associated with high-frequency sensorineural hearing damage.

POST-OPERATIVE COMPLICATIONS

Conductive hearing impairment

Post-operative conductive hearing impairment may present immediately after surgery, suggesting the sound transmitting mechanism was never successfully restored, or months or years later. Statistical analysis of published data is difficult in part because the exact nature of the previous surgery is often in doubt, as it is difficult at revision surgery to assess the entire footplate, which is often encased in fibrous tissue. This is important as the literature does not clearly distinguish the differing risks of each complication between stapedectomy and stapedotomy techniques, despite the use of lasers in revision surgery having improved assessment of the footplate. However, we have reviewed 19 major series published between 1980 and 2003, adequately describing 2670 revision stapedectomies and stapedotomies. Three causes of failure were particularly frequently reported. Prosthesis displacement out of the footplate was identified in 953 cases (36%, range 18–82%), and incus erosion in 549 (21%, range 5–32%). Bony regrowth over the fenestration was less consistently quoted but where stated it was found in 1–24% of each series.

Displacement of the prosthesis out of the oval window fenestration has a number of possible causes. A short prosthesis may be displaced from the vestibule simply by Valsalva or sneezing. A short piston may result not only from incorrectly measuring the distance from long process to footplate, but also from the distortion of the loop around the long process of the incus that may result from the variable diameter of the long process, different loop properties and different crimping techniques.[167] Contracture of the connective tissue seal over the fenestration appears capable of pushing the prosthesis out of the vestibule. There is anecdotal evidence to suggest that the thicker the oval window sealant, the greater the lateralization of the prosthesis. This would imply that a vein graft, being very thin, would be most suitable, followed by perichondrium, fat and fascia. In theory, better still is a tight laser stapedotomy. This may require no seal and so may reduce the risk of lateralization.[168] Traction from adhesions between the prosthesis and adjacent structures appears capable of displacing a prosthesis, so minimizing surgical trauma around the oval window is recommended. Anecdotal evidence also suggests that middle ear adhesions, lateralization of the oval window neomembrane and prosthesis migration are more severe following stapedectomy than stapedotomy. Finally, an intact footplate that was never fenestrated is frequently reported. No conclusions can be drawn from the literature as to whether any specific prostheses are particularly prone to these complications.

Necrosis of the long process of the incus causes loosening of the attachment of the prosthesis and a conductive

hearing impairment. The hearing impairment may fluctuate. Although often attributed to a reduction in blood supply secondary to cutting the stapedial tendon, and pressure on the long process from the prosthetic loop, some authors have claimed two other observations make this unlikely. The marrow of the incus may be able to provide adequate blood supply, and the frequent findings of a circumferential bony defect filled with granulation tissue are said to be more typical of a foreign body reaction.[165] It is common for both long process erosion and displacement from the vestibule to coexist. Necrosis should be distinguished from loose attachment of the prosthesis to the long process of the incus through faulty crimping, a complication that may be easily corrected.

Bony regrowth is more common in cases that initially demonstrated obliterative otosclerosis. It is reported both within a year of primary surgery and many years later.

Fibrous adhesions fixing either the ossicles or prosthesis are reported in 8–24% of revision operations. Such fixation develops independently of the incus or malleus fixation discussed previously, though both should be sought at revision surgery.

Footplate refixation may be encountered following mobilization procedures, though these are performed rarely now.

Sensorineural hearing damage

This may occur peri-operatively or present many years after surgery. Quoted results are subject to publication bias and an absence of randomized trials. Caution is also required as the largest series reflect the results of established experts. The majority of recent publications on stapedotomy quote no dead ears or cases of severe sensorineural damage in their series. One of the largest series of stapedotomies identified 13/1911 (0.7%) cases of sensorineural damage, combining early and late failures.[169] Rates for stapedectomy are generally higher and range from 0 to 11%, though are not necessarily directly comparable. However, one of the largest series reported no immediate cases of permanent sensorineural impairments in over 4000 procedures.[170] Revision surgery is usually associated with higher rates of sensorineural hearing damage. Reviewing 20 papers analyzing 2585 revision procedures, we identified 113 cases of severe sensorineural hearing impairment, a rate of 4.4%. Sensorineural impairment was identified in 0–20% of each series, while a dead ear rate of 0–14% was quoted. Length of follow-up was variable. This is significant as approximately half the episodes of acute sensorineural hearing impairment in both primary and revision cases were delayed, often by very many years.

Early mild sensorineural hearing loss is common. Sperling et al. noted 62% of patients had some sensorineural threshold shift in at a least one frequency when measured at day 5 post-operatively. This reduced to 32% at 6 months.[171]

Causes of peri-operative sensorineural damage are most often attributed to surgical trauma, in particular, extensive drilling associated with obliterative otosclerosis (particularly revisions), floating footplates and perilymph aspiration. Congenital footplate fixation and cerebrospinal fluid (CSF) gushers make up a second group. Delayed sensorineural damage is often unexplained. Causes include barotrauma from air travel and blast injury, reparative granuloma, perilymph fistula and suppurative labyrinthitis. An association with influenza has been quoted.

These late conductive and sensorineural failures, which could total several per cent of procedures, may influence the decision to proceed to surgery. In addition to the slow progressive cochlear impairment, they are discussed under 'Natural history' above.

Facial nerve injury

Immediate temporary facial nerve palsy may occur immediately post-operatively as a result of local anaesthetic infiltration. Delayed temporary facial palsy is well described between days 4 and 10 post-operatively. Rates of 0.1–0.5% are quoted. The cause is unknown but in some cases it may result from facial nerve swelling, resulting from the nerve being heated by a drill or laser. Full recovery is always reported over days or weeks. The role of steroids is not clear.

Permanent injury is very rare in stapes surgery (0.07% in the largest series). It is reported in association with aberrant nerves crossing the footplate, with laser or burr injury in the presence of a dehiscent canal and while clearing fibrous tissue from the footplate during revision surgery.

Vertigo

Transient dysequilibrium or vertigo post-operatively is not uncommon and can be managed with vestibular sedatives. Vertiginous symptoms combined with sensorineural hearing impairment and tinnitus occurring in the first week post-operatively most commonly result from a 'serous labyrinthitis' from which a rapid recovery can be expected. No treatments have been shown to improve outcomes.

Should dysequilibrium persist or arise later, a cause should be sought. Benign positional paroxysmal vertigo was reported in 4/63 post-stapedectomy patients in one study, all successfully treated with the Epley manoeuvre.[172] Vertigo is reported in 20–35% of patients with reparative granuloma and one-third of patients with a perilymphatic fistula. Both conditions are discussed below. An overlong prosthesis may cause vertigo and may be diagnosed by a positive fistula test on pneumatic otoscopy. Other causes described include a depressed footplate, bony fragments compressing the saccule, suppurative labyrinthitis, endolymphatic hydrops and vestibular schwannoma. Careful neuro-otological examination is required. Diagnosis of the labyrinthine cause is reported to be possible in many cases using HRCT scanning.

Perilymphatic fistula

A primary perilymphatic fistula is, by definition, present at the end of stapedectomy, a secondary fistula develops

months or years later. The largest series quote oval window fistula rates of 0.25–2.5% following stapedectomy. Rates appear significantly lower following stapedotomy. Fistulae are reportedly identified at 1.5–12% of revision operations. In many ways, symptoms are similar to those of endolymphatic hydrops: a persistent or fluctuating hearing impairment in 71–87% of cases, which may be sensorineural, mixed or conductive in nature; vertigo in approximately one-third of patients and dysequilibrium in a further third; tinnitus in 28–45%; and sometimes a sense of fullness in the ear. Some patients with a fistula have presented with meningitis. A positive fistula test may be present in two-thirds of cases. The greatest risk factor for a fistula is repeatedly reported as having been the use of gelatin sponge to seal a stapedectomy, a technique now largely abandoned. Treatment should be prompt. At re-exploration, if the prosthesis is displaced, the defect should be grafted and anchored with a new prosthesis. If the prosthesis still enters the vestibule, there may be adhesions with the membranous labyrinth and it may be safest to pack the footplate with fat without disturbing the vestibule.

Reparative granuloma

This is a well-recognized cause of early post-stapedectomy hearing impairment. The term granuloma is a misnomer. It refers to granulation tissue formation around a stapes prosthesis and the oval window which may extend into the vestibule. Early stapedectomy series quoted rates of 1.3–5%. A more recent postal survey of American otologists suggested an incidence of 0.1% post-stapedectomy and 0.07% post-stapedotomy,[173] though this is likely to be an underestimate. They are associated with the type of graft material used, most commonly Gelfoam or fat, and rarely with perichondrium, fascia or vein. Reparative granuloma usually presents 1–2 weeks post-stapedectomy, though a recent paper had one severely destructive case occurring 2 years after surgery.[174] It should be suspected when the commoner symptoms of 'serous labyrinthitis' fail to settle. They present with deterioration in hearing after an initial post-operative improvement in 70–100% of cases. The hearing impairment is progressive or sudden and sensorineural or mixed. It is associated with vertigo in 20–35% of cases and sometimes tinnitus.[161] There may also be otalgia.[174] Examination shows a dull red tympanic membrane, particularly in the posterior–superior quadrant. Management is controversial. Most papers advise early surgical intervention within 2 weeks of stapedectomy. It is uncertain whether the granulation tissue and prosthesis or granulation tissue alone should be removed. Outcomes are split evenly between hearing improvement, stabilization and profound impairment.

Many surgeons would now advocate a more conservative policy of steroids and antibiotics initially and some would consider delayed surgery if no improvement occurred. CT and MRI can be useful in assessing the extent of the granuloma which can rarely be very large and destructive.[174] Evidence-based conclusions cannot be drawn.

Discomfort to loud noise

This symptom has been reported in 35–41% of patients following stapes surgery and, although it frequently settles, it can persist on long-term follow-up.[175] It may, of course, reflect solely the improved hearing in the operated ear as normal hearing subjects will experience noise intolerance at certain volumes and loudness discomfort levels seem little changed. The role of stapedius tendon reconstruction is discussed under 'Hearing outcomes' below.

Alteration in taste

Damage to the chorda tympani nerve is reported in up to 30% of procedures, while in revision series the nerve has been quoted as being found intact in as few as 20% of cases. Sectioning or stretching the nerve may result in a metallic taste, impairment of taste, dry mouth and soreness of the tongue, typically for 3–4 months following surgery, though on occasion much longer. Cutting the nerve appears to lead to greater and longer-lasting symptoms than preserving it.[176] Bilateral damage will produce severe symptoms. For similar levels of damage, altered taste is noted more commonly after otosclerosis surgery comparted with cholesteatoma surgery as it is thought the chorda may often have pre-existing damage in cases with cholesteatoma.[177]

Cholesteatoma

Cholesteatoma has been reported in the oval window secondary to skin elements implanted during harvesting of a fat graft.

Meningitis

Meningitis and death have been reported, particularly in the older literature, following stapedectomy with fistula formation. Some authors have advocated exploratory tympanotomy in any patient with meningitis who has a stapes prosthesis to exclude a fistula.

HEARING OUTCOMES

Background

Reviewing outcomes data for middle ear surgery is not straightforward and is discussed under 'Conductive hearing impairment' above. The techniques used for stapes surgery have evolved gradually over four decades, with multiple variables to contend with including fenestration size and technique, graft material, prosthesis diameter and design, stapedius tendon repair, pathological severity and surgical expertise. Published series often combine several techniques. Reporting methods have also evolved making direct comparisons difficult. Randomized trials are notable for their scarcity. Furthermore, several series have quoted converting approximately 20% of stapedotomies into stapedectomies because of technical difficulties. This may introduce further bias as the results of stapedectomy

are made to appear worse as they reflect more difficult cases. Meta-analyses either are not possible or have not been attempted.

When comparing technical factors such as the type of prosthesis or biomaterial, closure of the air–bone gap is often a satisfactory measure. Cochlear damage may be broadly assessed by comparing pre- and post-operative bone-conduction or speech discrimination. The hearing gain experienced by the patient in one ear is best assessed by the air-conduction thresholds. However, from a patient's perspective, two other outcomes matter. First, the reduction in their auditory disability. This depends very much on the hearing in the better ear, information that historically was rarely presented. Second, 'average' outcomes become meaningless. It is the relative likelihood and implication of good, bad or very bad results that are important, which explains the role of presenting data in audiometric 'bins' of 10 dB, or graphically, to highlight extreme outliers.

Comparison of different techniques

STAPEDECTOMY VERSUS STAPEDOTOMY

As the debate between small or large fenestra techniques evolved, there were many series published from excellent centres quoting closure of the air–bone gap to less than 10 dB in over 90% of cases using either stapedectomy or stapedotomy techniques, though typically pre-operative bone thresholds have been used.[178–180] When comparing their stapedectomy series to their subsequent stapedotomy series, it is apparent that more than the size of the fenestra had changed. Often the piston and grafting technique altered making direct comparison difficult. However, a trend began to emerge that suggested stapedotomy was less traumatic to the membranous labyrinth, resulted in fewer complications and offered potentially better hearing gain in frequencies of 4 kHz and above. The benefits that have been claimed are shown in **Table 89.5**.

In 1978, Smyth and Hassard[181] offered a more direct comparison that supported the developing consensus. Reviewing results of 750 stapedectomies and stapedotomies, the immediate hearing outcomes were similar in the two groups except for sensorineural impairments of greater than 20 dB, which occurred in 1.5% of stapedectomies but no stapedotomies. Most impairments could be related to surgical trauma while trying to remove the footplate. The rate of fistulae was also higher in the stapedectomy group (2.0% versus 0.6%).

TABLE 89.5 Suggested benefits of small versus large fenestra techniques

Technique	Suggested benefits
Stapedectomy	Better low-frequency hearing gain May be only method technically possible
Stapedotomy	Better high-frequency hearing gain Lower incidence of: • perilymphatic fistula • sensorineural hearing impairment • lateralization of graft • post-operative vertigo • revision surgery More stable hearing gain Less 'labyrinthine trauma'

In reviewing the literature, we identified only one randomized controlled trial comparing stapedectomy (59 cases) and stapedotomy (32 cases).[182] This supported the consensus that higher-frequency hearing outcomes tend to be better with stapedotomy. In keeping with many studies, the need for revision was greater in the stapedectomy than stapedotomy group (7% versus 3%).

Direct comparison between the case series that make up the rest of the literature is difficult. The majority of publications show a similar degree of early closure of the air–bone gap in lower frequencies with both large and small fenestra techniques. Short-term closure to within 10 dB (most papers using pre-operative bone-conduction) occurred in 54% to over 95% of cases, with the majority of the published series quoting 80–95%. However, there is a clear majority that report better high frequency (4–8 kHz) outcomes for stapedotomy over stapedectomy. This has been shown to be associated with better speech discrimination in a small number of publications. The clinical significance of this has been questioned. A minority of papers report better low-frequency gain for stapedectomy, but this is not always maintained on longer-term follow-up.

Long-term hearing outcomes are addressed in several papers. The largest cohort has been followed by Shea.[137] He reviewed more than 4100 primary stapedectomies in his series of 14 449. Although the details of follow-up are unclear, the size of the series makes the findings influential. Both total and partial stapedectomies were performed with a variety of grafts. Averaging hearing at 0.5, 1 and 2 kHz, and identifying those with an air–bone gap of 10 dB or less and no loss in speech discrimination of greater than 10%, he quoted success in 95% at 1 year post-operatively, 90% at 6–10 years, and 63% at greater than 30 years. Most importantly, he believed that sufficient sensorineural impairment would be present in 30% of patients by 20 years post-operatively and that a hearing aid would be required.

A long-term follow-up in Finland comparing stapedectomy and stapedotomy obtained an impressive 63% follow-up at an average 20 years post-operatively.[175] Mean hearing results were not statistically different between the groups on short- or long-term follow-up. Air- and bone-conduction thresholds fell at a similar rate of 0.9 dB per year in both groups, which matches other publications that have previously quoted 0.6–1.2 dB per year. These numbers imply there is little worsening of the conducting mechanism on longer-term follow-up in the 'average' patient, but does not address individual failures. At an average 20 years after surgery, 37% of the group were occasional or regular hearing aid users, results very similar to those of Shea.[137]

STAPEDOTOMY TECHNIQUES

Stapedotomy techniques have been compared in a number of studies. No differences in outcomes were identified in

a prospective study between the use of a microdrill and handheld microperforator.[183] KTP, CO_2, erbium:YAG and argon lasers have all been frequently used in stapes surgery since initial results were published in 1980. There are potential risks to the membranous labyrinth with their use including photothermal, photochemical and photoacoustic damage. There are reports of temporary threshold changes using the CO_2, KTP and erbium:YAG lasers. The authors of a study using the erbium:YAG discontinued its use on the basis of their findings. The use of lasers versus the microdrill was reviewed in 550 cases at The House Ear Clinic in Los Angeles and similar results were reported,[184] the same finding to a review of the use of picks, drills and lasers in Marquet's series of 1681 procedures.[169] Despite this report, there is evidence to suggest that laser stapedotomy may have a lower complication rate than traditional methods. Rauch and Bartley[185] published a comparison between argon laser fenestration and traditional techniques and demonstrated a fivefold greater rate of footplate fracture using conventional fenestration methods. CO_2 and argon lasers have been compared and no outcome differences found. A recent systematic review was inconclusive on which was the optimum laser to use for stapes surgery.[186]

CONNECTIVE TISSUE SEALS

The use of connective tissue seals to cover the fenestration is another area of controversy. They will increase the surface area to transmit energy (this needs to be remembered when considering piston diameter outcomes which are discussed under 'Prosthesis types' below), may prevent perilymph leakage and restore the stiffness of the annular ligament in theory. It has already been mentioned that vein appears to be the most suitable material for stapedectomy. For stapedotomy it is not easy to compare series because of multiple variables, in particular the size of the stapedotomy is often not reported. Certainly, Causse[187] has reported excellent results using vein. Many otologists prefer not to interpose a graft but fashion a tight-fitting stapedotomy and seal the fenestration with blood or fat placed around the prosthesis.

ENDOSCOPIC STAPEDOTOMY

With the current interest in endoscopic ear surgery it is not surprising there are an increasing number of studies looking at endoscopic stapes surgery. These studies have demonstrated that endoscopic stapes surgery is safe and has similar audiologic outcomes to microscopic stapes procedures. Advantages compared to peraural stapes surgery would appear to be few but possibly a reduced amount of resection of the bony annulus is required.[188, 189]

PROSTHESIS TYPES

Prostheses vary in their design, material (Teflon, steel, gold, platinum, titanium and alloys), weight, diameter and anchorage to the long process of the incus. There are many good publications comparing piston diameter. Theoretical constructs would favour larger piston diameters, particularly in frequencies below 1.5 kHz. (If this argument sounds familiar, remember that a larger fenestration will effectively increase the sound-transmitting area of the end of the piston, and the largest fenestration is a stapedectomy.) This has to be balanced against the perceived risk of increased labyrinthine trauma and the technical limitations of larger fenestrations.[165] A minority of studies show no difference in hearing outcomes between different piston sizes, a majority appear to show benefit for larger pistons, particularly for frequencies up to 2 kHz. Teig and Lindeman[190] attempted to avoid the many confounding variables and demonstrated a 0.6 mm piston produced mean hearing results 4–10 dB better than a 0.4 mm piston, while a 0.8 mm piston was better than the 0.6 mm piston by 5–7 dB. While temporal bone studies have also suggested superiority of larger pistons,[191] a recent systematic review showed no evidence to support the superiority of large pistons over smaller diameter pistons.[192]

There are some published data to suggest that heavier pistons (steel – 12.5 mg, or gold – 10 mg) may produce better results in the lower frequencies, while lighter pistons (Teflon – 3 mg) may be better in higher frequencies,[165] a trend well illustrated by de Bruijn et al.[193] At present, there is insufficient evidence to confirm these differences are of clinical significance.

The material used is important only in that it must attach firmly to the incus and not incite a foreign body reaction. There are a number of individual case series of different products but most studies fail to show significant differences in hearing results between the prostheses as the majority are small and lack statistical power.

There has been a growth in use of self-crimping pistons made of thermally triggered alloys, of which a number of varieties are available. The piston is placed as normal but then heated with diathermy or a laser which causes it to self-crimp. Early results suggest these prostheses may be easier to use as satisfactory crimping is often felt to be one of the most difficult parts of the operation.[194] It is also felt that these pistons perhaps give more consistent results. Although long-term hearing results are not yet available, mid-term results appear stable.[195]

PRESERVATION OF THE STAPEDIUS TENDON

This is proposed as a method of preserving the blood supply to the long process of the incus, of reducing discomfort at high sound pressure levels and of improving speech intelligibility. Evidence regarding the benefits to blood supply is limited and it is likely much may be obtained from the marrow in any case. Causse et al. series[196] of 3457 tendon reconstructions was published in 1997 and claimed to show improved speech intelligibility in noise and reduced intolerance of loud noise, but the analytical methods used make it difficult to draw conclusions. A large questionnaire study by another group failed to show any difference in outcomes. Of note is that the surgeons at the Causse clinic no longer reconstruct the stapedius tendon due lack of perceived benefit to the patients.

Revision surgery

Revision surgery is associated with a greater risk of sensorineural hearing impairment, as described above, and with poorer hearing outcomes than primary stapes surgery. It is particularly difficult comparing case series because of the variables involved. However, we have reviewed 24 series and found closure of the air–bone gap (using old reporting guidelines) to within 10 dB was achieved in 54% (mean value unweighted for series size, range 17–81%).

While there are many claims that revision surgery is safer under local anaesthetic, it is difficult to establish this from the literature.

The use of a laser is often advocated for revision surgery to allow adhesions to be cleared from the oval window, to free an ankylosed prosthesis from the incus, to sculpture the incus or to control bleeding. Most papers comparing revision surgery with and without a laser do not report any differences in hearing outcome. However, in Lippy et al. series of 483 revisions,[160] it was noted that in the period the laser was not available, closure to within 10 dB was achieved in 70% of cases and when it could be used, if required, this increased to 80%.

Malleostapedotomy is usually reserved for cases of severe incus erosion.

The more revisions an ear has undergone, the less likely a good result can be expected. Lippy et al.,[160] for example, quote closure to 10 dB in 76% of first revisions, 66% of second, 57% of third and 38% of fourth revisions.

TINNITUS OUTCOME

Tinnitus is common in those undergoing stapes surgery, being reported in 56–79% of cases pre-operatively. Surgery is a successful method of alleviating this symptom. The results of seven series involving 696 patients with tinnitus were looked at. Post-operatively, 44% (mean unweighted for series size, range 27–64%) of patients had no tinnitus, 34% (16–56%) had less tinnitus than pre-operatively, 16% (8–27%) had equal symptoms and 5% (1–11%) had more tinnitus.[197] Looking at those who had no tinnitus pre-operatively, symptoms are reported to occur in 0–16% post-operatively, with most papers quoting no new cases.

Several authors have reported that the prognosis for low-pitched tinnitus is particularly good after surgery, while the prognosis for high-pitched tinnitus is poor. This has not been corroborated by all studies.

COCHLEAR IMPLANTATION

Cochlear implantation is a potential management option for those patients with FAO in whom other modes of sound amplification have failed. Otosclerosis accounts for approximately 10% of implants in adult programmes. Most patients being considered will have had surgery for otosclerosis previously, either stapes procedures or fenestration. If not, stapedectomy in combination with conventional aiding should be seriously considered prior to proceeding to implantation.

This population has its own unique surgical challenges, due to both previous surgery and the disease process. These have been summarized in **Table 89.3**.

In a large series presented by one of the authors,[142] speech discrimination scores (using binaural CID sentences) improved from 12% (range 0–52%) pre-operatively to 88% (range 22–100%) post-operatively, results which have been mirrored in other series.

BEST CLINICAL PRACTICE

- ✓ A trial of a hearing aid should be discussed before proceeding to stapes surgery.
- ✓ Stapes surgery should be performed only by those who undertake it regularly.
- ✓ Appropriate outcome data should be audited by individual surgeons.

FUTURE RESEARCH

The surgical correction of hearing impairment caused by otosclerosis has a long and interesting history. It is currently one of the most successful operations we have to improve hearing. Large gaps remain in our knowledge, however.

- ➤ More accurate and standardized outcomes data will allow comparisons between techniques and refinement of the indications for surgery.
- ➤ Further exploration of patient-orientated outcomes, both for hearing aids and surgery, will help the debate over treatment of unilateral disease and bilateral surgery.
- ➤ Randomized trials rather than case series are desirable and possible for stapes surgery and hearing aid use, but they may require multicentre studies. These are required to assess variations in technical aspects of surgery, such as prosthesis design, dimensions and graft material. These will eventually allow meta-analysis of results and clearer guidelines, something still not currently possible on evidence-based criteria.

KEY POINTS

- Stapes surgery is an effective treatment for both the hearing loss and tinnitus of otosclerosis.
- Debate continues over indications for stapes surgery, in particular its role in unilateral disease and in second-side surgery.
- Revision surgery carries higher operative risks than primary surgery.
- Stapedotomy seems to be associated with fewer complications than stapedectomy.

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CHAPTER 90

OTOLOGICAL EFFECTS OF PAGET'S DISEASE

Ian D. Bottrill

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search and a search of the Cochrane and Bandolier libraries using the keywords: osteitis deformans, Paget's disease of bone, temporal bone, deafness, hearing loss, tinnitus, vertigo, imbalance, dizziness and focusing on pathogenesis, aetiology, diagnosis and management.

DEFINITION

Sir James Paget gave the first account of the disease which bears his name in 1877.[1] The disease was initially termed 'osteitis deformans'. Paget's disease of bone (PDB) is a progressive, focal disorder of bone remodelling and is the second most frequent metabolic bone disorder. There is an increase in osteoclastic activity producing bone reabsorption, with reactive stimulation of osteoblasts producing increased bone deposition, resulting in bone that is architecturally unsound. This leads to bone pain, deformity and fragility. Affected individuals typically have enlargement of the skull with involvement of the pelvis, tibia or femur. It is interesting to note that skeletons from archeological sites in Western Europe are the only ones to show evidence of Paget's disease.[2] This chapter will focus on the impact of Paget's disease on the temporal bone. [Level 1 evidence]

EPIDEMIOLOGY

PDB is the second most common bone disease in the world. It has a 3:2 male predominance. The disease is more common in Britain, North America, Australia and New Zealand. It is rare in Scandinavia, Asia and in non-white races.[3] The UK prevalence in the over 55 year age group is 0.3%; incidence rates for clinically diagnosed PDB rise steeply with age.[4] The same study found that, over the 10-year study period, the incidence of PDB disease declined significantly with time.

AETIOLOGY

The exact cause of PDB is unknown. The current opinion and evidence support an interplay between genetic and environmental factors, possibly viral infection of the bone cells, as the cause. The first gene found to be affected in PDB is the *SQSTM1* gene; currently more than 25 mutations have been identified in this gene. This gene encodes p62, a protein that is involved in regulating osteoclast function. Those patients who carry the abnormal gene are more likely to develop more advanced disease than PDB patients who do not express this abnormal gene. Other candidate genes have also been isolated in recent years.[5]

Polyclonal antibodies reveal paramyxovirus antigens in pagetic osteoclasts compatible with measles and respiratory syncytial virus infections. Studies with monoclonal antibodies implicate measles, simian virus and human parainfluenza virus. Electron microscopic studies have shown that the nuclei in pagetic osteoclasts have a fingerprint pattern, which supports a viral infection as a possible aetiological agent.[6] However, not all studies have found paramyxovirus particles or RNA in pagetic bone. In addition, there have been no convincing viral particles isolated from the cells of pagetic osteosarcoma, and it has not been possible to pass the disease to uninfected cells in culture.

PATHOPHYSIOLOGY

Bone changes

The basic abnormality is increased bone turnover in the involved bones. PDB can exist in monostotic and polyostotic form, with 10–30% of patients having monostotic disease. Any bone can be involved, with the most frequently affected bone, in decreasing order, being the pelvis, femur, skull, tibia, vertebrae, clavicle and humerus.

The changes in bone occurring in PDB can be divided into three phases: osteolytic, mixed and osteoclastic.[7] In the temporal bone a fourth phase has been described: a lamellar remodelled phase, in which the osteoblastic pagetic bone may undergo a process of remodelling into quite normal-appearing lamellar bone with distinct Haversian canal systems. This process is particularly seen in relation to the internal auditory canal, producing bossing of pagetic bone. In the temporal bone the endochondral bone is more resistant to resorption.[8, 9]

Different histological phases may coexist within a single temporal bone specimen.[7] Within the temporal bone, histological studies have shown that PDB involves the periosteal bone first. With increasingly aggressive disease, the process may extend into the enchondral layer and may finally invade the endosteal layer. [Level 1 evidence]

Symptoms and signs

In the early stages, the disease may be asymptomatic. Symptoms gradually progress, frequently starting with pain, stiffness and fatigability. The bone pain of PDB is typically constant, deep and boring. The cause of the pain is likely to be related to the increased periosteal blood flow exerting intraosseous pressure and stimulating bone pain fibres.

HEARING LOSS IN PAGET'S DISEASE

Sir James Paget, in his original publication, recognized hearing loss as a complication. The prevalence of hearing loss in PDB is quoted has varying between 13% and 40%. Van Staa et al.,[4] in their large epidemiological study, found that patients with PDB had a greater risk of hearing loss compared to age and sex matched controls (relative risk 1.6; 95% confidence intervals 1.3–1.9). This study was based on questionnaire data and did not include audiometric testing. A study by Young et al.[10] compared audiometric data in a group of patients with PDB selected at random from a tertiary hospital database and compared this with age- and sex-matched controls. They found the PDB group had significantly elevated auditory thresholds when compared to the control group: 41/75 PDB had a pure-tone average threshold of >40 dB compared to 8/76 controls. The hearing loss is typically of a high-frequency sensorineural nature.

It has also been noted that PDB may be associated with a low-frequency air–bone gap. Baraka[11] attempted to determine the rate of progression of hearing loss in patients with PDB. He reported that, on average, patients with PDB experience a greater reduction in hearing over time compared with age-matched controls. The pagetic ears deteriorated by approximately 2 dB per annum compared to 0.5 dB per annum in controls. His conclusions are limited by the very small sample size (4 patients with a minimum of 4 years of regular testing out of an initial study population of over 100 patients with proven PDB). Tinnitus is also slightly more common in Paget's than in controls, with a relative rate of 1.5 (95% confidence intervals 1.1–2.2).

The majority of pathological studies published relate to isolated case reports. Khetarpal and Schuknecht[7] have reviewed reported cases and tabulated the proposed mechanisms of sensorineural and conductive hearing losses, demonstrating the wide variation in suggested aetiology for the two types of deafness. Of the 26 temporal bones in 16 individuals, the only consistent feature they demonstrated was age-related histological changes. Pagetic lesions were present in the periosteal layer in all 26 temporal bones. In 22, they demonstrated extension to the enchondral layer and the endosteal layer was involved in 14. They found no evidence of ossicular fixation to account for the air–bone gap that was documented in seven individuals. The essence of their study was that 'both the conductive and sensorineural components of the hearing loss in Paget's disease are caused by changes in bone density, mass and form that dampen the finely tuned motion mechanics of the middle and inner ears'.[12] However, Dimitriadis et al.,[13] in their temporal bone study of eight subjects showed stapes fixation in two bones and a fractured stapes footplate in one specimen. The conductive component does not improve surgically even if otosclerosis coexists.

Historically, the hearing loss has been attributed to narrowing of the internal auditory canal[14] with compression of the vestibulocochlear nerve. Latterly this association has been brought into question. Monsell et al.[15] also looked for evidence of nerve compression as a cause of the sensorineural deafness. In a study of 64 ears with radiographically confirmed PDB of the skull, they demonstrated no relationship between the mid canal diameter and minimum diameter of the internal auditory canal and the hearing thresholds. In addition, auditory brainstem responses were normal in 56 out of the 64 ears, indicating that a retrocochlear lesion is unlikely to be the source of the hearing loss. However, this study did not look at tests for cochlea hearing loss (e.g. recruitment) to support their hypothesis. In a separate study Monsell et al.[16] also demonstrated a strong and statistically significant relationship between the bone mineral density of cochlea capsule versus both the high-frequency pure-tone air-conduction thresholds and the air–bone gap in subjects with Paget's disease of the skull. This latter study supports the conclusions from Khetarpal and Schuknecht's earlier histological study. In Dimitriadis et al. study they found occlusion of the inferior cochlear vein in 78% of cases leading to secondary changes in the stria vascularis and postulated fluid homeostasis abnormalities.

VESTIBULAR DISTURBANCE IN PAGET'S DISEASE

The literature regarding vestibular disturbance in PDB is not as extensively reported as studies on hearing loss.

The incidence is generally reported to be in the region of 20–30% of individuals with PDB suffering from vestibular dysfunction, but this is not compared to age-matched controls.[9] However, van Staa et al.[4] compared the frequency of reported dizziness/giddiness in 2456 patients with PDB compared to 7395 age- and sex-matched controls. They found rates of 5.0% and 3.7% respectively, producing a crude relative rate of 1.3 (95% confidence interval 1.2–1.5).

In Khetarpal and Schuknecht's study, vertigo was recorded in 4 of the 16 subjects investigated. The symptoms have the characteristic of motion-provoked imbalance. Histological analysis of these patients with imbalance did not reveal any changes such as loss of hair cells in the maculae or cristae. Even with histological evidence of pathology of the vestibular system, not all patients with changes had a history of imbalance. They found that losses of vestibular nerve fibres, greater than normal for age, occurred in nine ears of six subjects, three of whom had a history of vertigo.

DIAGNOSIS

PDB is often found incidentally on X-ray or laboratory tests performed for other reasons. It can be diagnosed through radiology, radionuclide bone scanning, and biochemical tests of bone resorption or formation. Plain X-ray findings in the early stages of the disease may be confined to osteolytic lesions in the involved bones. As the disease progresses, further radiographic changes occur, including increased bone density, abnormal architecture, cortical thickening, bowing and overgrowth. Microfractures may be seen in long bones. Laboratory testing should include renal function and liver function tests, calcium, albumin, alkaline phosphatase and 25-hydroxyvitamin D.

Computed tomography may show the involvement of the temporal bone (**Figures 90.1** and **90.2**) and in extreme cases may show complete obliteration of the otic capsule. When PDB affects the temporal bone, it typically spreads from the petrous apex laterally, producing a washed-out appearance of the involved bone caused by extensive demineralization. The process frequently affects the internal auditory canal first, progressing to involvement of the otic capsule. In advanced disease, the deposition of irregularly mineralized bone occurs, resulting in thickening of the petrosa and narrowing of the internal auditory canal. Nuclear medicine scans using technetium-labelled phosphonates show increased nuclide localization to the pagetic sites and can be a useful screen for disease extent.

Abnormal laboratory investigations include an elevated serum alkaline phosphatase (or bone-specific alkaline phosphatase). This enzyme is a marker of new bone formation and not resorption. The degree of osteoclastic activity can be assessed by measuring urinary hydroxyproline/creatinine (a measure of collagen breakdown) as well as measurements of urinary and serum deoxypyridinoline, N-telopeptide and C-telopeptide. Serum calcium and phosphorus levels usually are normal, but serum calcium may increase during bedrest.[16] [Level 1 evidence]



Figure 90.1 CT Paget's axial.

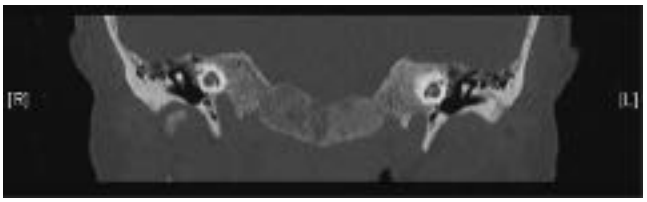


Figure 90.2 CT Paget's coronal.

MANAGEMENT OPTIONS

From the clinical descriptions and research findings it would appear that early PDB is not associated with significant otological complications. With advanced disease, otological complications do occur but with only modestly increased rates compared to the normal population. It is unlikely that the otolaryngologist is likely to pick up a new, early case. The patient will usually be under the care of the rheumatologists and combined management will be required. The dilemma is what to do with the known case who may present in the otolaryngology clinics.

Four main methods of treatment exist for PDB: physiotherapy, antiresorptive therapy, analgesics and surgery. Drug therapy is the mainstay of treatment for the non-otological aspects of the disease but may have beneficial effects on the otological aspects of the disease as well.

The current criteria for treating Paget's disease vary, ranging from those who treat only advanced disease to those who intervene early, to try to prevent the development of any complications, with no conclusive evidence to support either strategy. Crisp[17] lists his indications for the treatment of PDB (**Box 90.1**). He quotes skull disease as an indication for treatment but does not expressly mention audiovestibular symptoms.

Drug therapy is based on antiresorptive therapy. The mainstays of drug treatment are the biphosphonates.

BOX 90.1 Indications for treatment (reproduced from Crisp,[17] by permission of Oxford University Press)

1. Pain arising from the site of known PDB
2. Early, potentially deforming disease
3. Osteolytic lesions, especially in weight-bearing bones
4. Skull disease
5. Complications:
   a. progressive neurological syndrome
   b. fissure fractures (avoid etidronate)
   c. immobilization hypercalcaemia
   d. high-output cardiac failure
6. Disease in patients aged under 55 years
7. Serum alkaline phosphatase and/or urine hydroxyproline concentration more than twice the normal upper limit
8. Patients likely to undergo joint replacement at involved sides within 6 months, primarily to reduce blood loss due to hypervascularity present in active pagetic bone

These drugs act to reduce bone turnover and normalize the raised biochemical markers. Early biphosphonate use required daily treatment for 6 months, but as newer drugs have been introduced current recommendation is for a single 5 mg intravenous dose of zolendronic acid. Reid et al.[18] double-blind randomized trial showed a single infusion of zoledronate produced greater level of biochemical disease control when compared to daily treatment of risedronate for 2 months. In an open follow-up, of up to 6.5 years, the relapse rate with risedronate was 20% compared to 0.7% with zolendronic acid. [Grade A evidence]

Reid et al.[19] did, however, report a single case of potential otic toxicity related to pamidronate infusions. Their patient received five infusions of the drug and immediately after the second to fifth infusions the patient reported problems with tinnitus, vertigo and hearing loss. With the exception of the tinnitus, his symptoms resolved completely. No other report of potential otic toxicity exists in the literature with regard to biphosphonate treatment.

The results of middle-ear reconstruction in PDB are generally poor due to the lack of a consistent pathology to explain the conductive hearing loss. Modern hearing aids offer a useful modality in the management of both the conductive and sensorineural loss. There are other surgical modalities mentioned in the literature, including the use of a bone-anchored hearing aid in one subject.[20] Because of the vascularity of the bone, the procedure was performed in two stages, to allow the fixture to osseointegrate. There are also case reports of the use of cochlear implantation with reasonable results.[21]

OUTCOMES

There is no direct evidence that aggressive treatment of PDB is associated with the prevention of progression or a reduction in risk of future complications.[17] However, indirect evidence, as shown below, suggests that this may be the case. The evidence for this includes:

- the failure to treat PDB has been associated with further destruction of bone and progression of bony deformities
- successful treatment of PDB has been associated with restoration of normal patterns of bone deposition.

Lando et al.[22] reported the use of calcitonin and etidronate in two patients with polyostotic PDB with rapidly progressing sensorineural hearing loss demonstrating stabilization of hearing in one patient and improvement in the other. Other studies (references 13–18 in their paper) confirm these findings with calcitonin alone.

Complications of clinical conditions

The most devastating complication of PDB is the development of osteosarcoma. This occurs in less than 0.1% of patients with PDB but at a significantly higher rate than in non-affected individuals. It tends to occur more frequently in the polyostotic variant of the disease. In van Staa et al. study[4] the incidence rate was found to be 0.1 per 100 person-years.

Skull expansion may lead to disfigurement, typically frontal bossing. Extensive involvement of the skull base, producing softening of the bone, may lead to platybasia – the descent of the cranium on the cervical spine – which may lead to vertebrobasilar compromise. Skull involvement may also lead to headaches and other cranial nerve involvement.

Pain, osteoarthritis, deformity and fractures are commonly associated with PDB. Other rarer complications include high-output cardiac failure, when more than one-third of the skeleton is affected, hypercalcaemia and hyperuricaemia.

Although remission after treatment is related to the degree of biochemical control, and very strong histological evidence that effective suppression promotes more normal bone remodelling, evidence is lacking that intensive treatment inhibits the development of long-term complications.[17]

KEY POINTS

- Paget's disease commonly affects the skull.
- It is a condition of abnormal osteoclast activity.
- Otological sequelae occur more commonly than in age- and sex-matched controls.
- The weight of evidence supports direct involvement of the otic capsule as the cause of the otological symptoms.
- Treatment with biphosphonates can suppress osteoclastic activity although the long-term benefits on the otological complications remain unproven.

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CHAPTER 91

EAR TRAUMA

Stephen C. Toynton

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SEARCH STRATEGY

All searches were performed using Medline Plus, Embase using Ovid, PubMed, Google Scholar, and the Cochrane database. Original or definitive references have been given priority over more recent ones that do not add significantly to the knowledge base.

Auricular haematoma and associated injuries

Ear surgery, ear external, external ear, pinna, auricle, auricular, helix and concha were all searched against, individually: trauma, haematoma, pseudocyst, cyst, chondritis and chondromalacia. Specific terms also searched were: auricular haematoma, otohaematoma, haematoma auris, wrestler's ear, asylum ear, cauliflower ear, hyperchondroplasia auris traumatica, auricular pseudocyst, benign idiopathic cystic chondromalacia, endochondral pseudocyst.

External ear canal trauma

Ear surgery, ear external, external ear canal, external auditary canal and external auditary meatus were all searched against, individually: trauma, injuries, wounds, lacerations and fractures. Specific terms also searched were: meatal step fracture and canal cholesteatoma.

Traumatic tympanic membrane perforations

Tympanic membrane and ear drum were searched against, individually: trauma, perforation, acute injury. Specific terms/phrases also searched were: traumatic perforations of the tympanic membrane, blast injury, primary blast injury, caustic ear injury, caustic trauma, batteries, CSF otorrhoea and cerebral spinal fluid.

Ossicular trauma

Ossicles, ossicular chain, malleus, incus and stapes were searched against, individually: trauma, fracture, dislocation, conductive hearing loss, hearing loss, head injury and temporal bone fracture.

Temporal bone trauma

Temporal bone, fracture, injury, head injury, trauma, craniocerebral trauma, epidemiology, CSF leak, vertigo, imbalance, otorrhoea, perilymph, fistula, deafness, hearing loss and evaluation using the keywords ossicle, ossicle and dislocation, middle and (ear and adhesions), middle and (ear and trauma), traumatic and tympanic and (membrane and perforation).

Whiplash injuries

The same terms as were used for temporal bone trauma were searched, but adding: whiplash injuries, whiplash-related disorder, therapy, vertigo, hearing loss, physical therapy techniques, neck and rehabilitation.

Otitic barotrauma and otitic decompression illness

There are a number of different clinical conditions that are included under the umbrella term of ‘otitic barotrauma’. Each has been searched separately with the primary search terms: diving, scuba, SCUBA, diving medicine, hyperbaric medicine, decompression illness, flight, aviation and aviation medicine in all the subgroups.

External ear barotrauma (external ear squeeze, reversed ear, reverse ear squeeze)

Ear external, external ear canal, ear canal, external auditary canal and external auditary meatus were searched against the primary search terms. Specific terms: external ear barotrauma, external ear squeeze, reversed ear, reverse ear, reverse ear squeeze. Neither original research papers nor specific reviews were found.

Middle ear barotrauma (barotitis media, middle ear squeeze)

Middle ear barotrauma, barotitis media, middle ear squeeze, middle ear trauma, haemotympanum and perforation were searched against the primary search terms. This delivered several hundred results, almost all of which are review articles, adding little to the overall knowledge. Additional specific terms: prevention of middle ear barotrauma, otalgia, decongestants, pseudoephedrine, xylometazoline, oxymetazoline. This identified four randomized controlled trials.

Caloric vertigo

Caloric vertigo was searched against the primary search terms. Searches failed to reveal any reports or research specifically targeting this.

Inner ear barotrauma (compression inner ear barotrauma)

Inner ear and inner ear barotrauma were searched against the primary search terms. Specific terms: perilymphatic fistula, round and oval window fistula(e/s), fluorosceine and cochlin-tonoprotein. Numerous citations were found, including review articles, but no randomized controlled trials.

High-pressure nervous (neurological) syndrome (isobaric gas counterdiffusion)

High-pressure nervous syndrome, high-pressure neurological syndrome, isobaric gas counterdiffusion were searched against the primary search terms. Despite numerous references, very few were relevant to otology.

Alternobaric vertigo

Alternobaric vertigo, asymmetric pressure, pressure difference and differential middle ear pressure were searched against the primary search terms.

Barotraumatic facial palsy (facial baropareisis, alternobaric facial palsy)

Barotraumatic facial palsy, facial baropareisis, alternobaric facial palsy, were searched against the primary search terms. Additional searched terms included facial palsy, facial paresis, neuropraxia, nerve injury. Sporadic case reports were identified and several animal studies.

Decompression illness

For detailed accounts of the physiology and practice of decompression illnesses extensive general texts are available relating to both diving and aviation medicine. Highly recommended are: 'The physiology and medicine of diving' in *Bove and Davis' Diving medicine*[1] and *Fundamentals of aerospace medicine*.[2] Diving texts usually refer to the effect of altitude in aviation when relevant. Searches including the above terms failed to locate any randomized controlled trials. Level 1 evidence was available in both pathology and physiology studies.

Cerebral air gas embolism

Searched against primary terms also with additional search terms including: intracranial embolism, air embolism, CAGE and accidents.

AURICULAR HAEMATOMA AND ASSOCIATED INJURIES

The following are covered in this section:

- auricular haematoma (otohaematoma, haematoma auris, wrestler's ear)
- cauliflower ear (hyperchondroplasia auris traumatica)
- auricular pseudocyst (benign idiopathic cystic chondromalacia, endochondral pseudocysts).

AURICULAR HAEMATOMA

Definition

An auricular haematoma is a collection of blood occurring in the subperichondrial layer or an intracartilagenous space of the pinna.

Aetiology and natural history

The most frequent modern associations are wrestling, boxing and rugby union.[3–5] There is a very important link with non-accidental injury in children.[6, 7] Spontaneous haematomas are extremely unusual although possibly occur in patients with hypertension or with severe coagulopathies.[8, 9] Folding the helix into the concha may lead to auricular haematoma formation.[10] In the veterinary literature auricular haematoma was thought to have an autoimmune aetiology. This theory has now been discarded in favour of trauma.[11]

Auricular haematomas usually occur on the anterior (lateral) surface of the pinna. Here the skin is firmly attached to the perichondrium. The shearing of the perichondrium and an attached thin underlying cartilage layer creates a potential space, the plane of cleavage being within the cartilage itself, that is filled with blood following the rupture of small vessels[4, 12–14] (**Figure 91.1**). Any haematoma within the posterior soft tissues is readily absorbed with minimal effect on the cartilage.

Early evacuation results in good resolution with minimal cosmetic deficit. If the auricular haematoma is not removed, there is an invasion of chondroblasts into the organizing haematoma, forming granulation tissue which results in new cartilage formation.[15] As the perichondrium is the source of new cartilage growth, this occurs on the anterior surface, from the side of the separated perichondrium. Breeches in the perichondrium result in the cartilage buckling over the haematoma and causing the typical irregularities associated with a 'cauliflower ear' (see 'Caulifower ear' below).[15] Trauma to the thinned skin overlying the helix may result in infection, pain, cosmetic deformity and meatal stenosis. In the most chronic cases ossification or 'petrification' may occur between the cartilage layers resulting in a bone hard area.[16, 17]

Reports of auricular haematoma occurring in Morquio-Brailsford disease (osteochondrodystrophia deformans, mucopolysaccheridosis type IV) and Rosai–Dorfman disease (sinus histiocytosis with massive lymphadenopathy (SHML)) do not describe a convincing association.[18, 19]

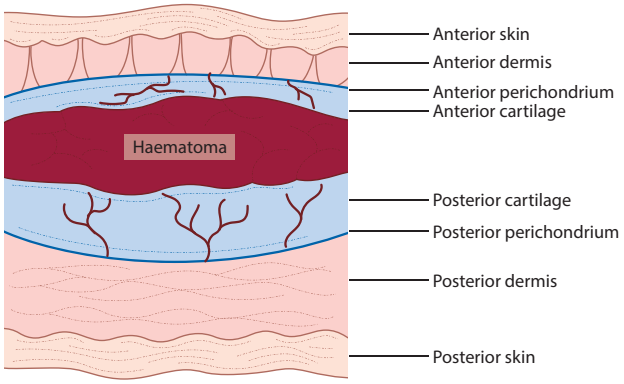


Figure 91.1 Splitting of cartilage layer by haematoma. (Modified with permission from Bull and Lancer.[12])



Figure 91.2 Recurrent auricular haematoma, previously incised and aspirated.

CAULIFLOWER EAR

Cauliflower ear is hyperplastic proliferation of the external ear cartilage following repeated episodes of trauma (typically auricular haematoma) or perichondritis from infection or other causes of inflammation. Improvement of this deformity is difficult. Specialist texts on plastic surgery to the pinna should be consulted.

AURICULAR PSEUDOCYST (BENIGN IDIOPATHIC CYSTIC CHONDROMALACIA)

Definition

An auricular pseudocyst is an intracartilaginous cystic collection, devoid of any epithelial lining, containing viscous, straw-coloured, sterile fluid, similar to an auricular haematoma in its anatomical location and its treatment. It is more often seen by dermatologists due to its association with local irritation and dermatoses.

Aetiology and natural history

Intrachondral pseudocysts are swellings of straw-coloured, slightly gelatinous fluid, high in glycosaminoglycans, occurring in cartilage spaces with no epithelial lining.[20] There is a low risk of progression to a cauliflower ear, unless acute trauma or infection intervene. They are usually located in the triangular fossa.

The pathoaetiology is thought to be a chondromalacia probably caused by repeated minor trauma, although often there is no such history. They usually occur in adult men between 30 and 40 years of age.[21] There appears to be an increased incidence in motorcycle helmet wearers but not due to a single episode of trauma.[22]

CLINICAL FEATURES OF AURICULAR HAEMATOMA AND PSEUDOCYST

Auricular haematomas present as a painful acute swelling, usually of the anterior surface of the conchal bowl, antihelix or helix. After several days the tenderness decreases leaving a non-tender, slightly fluctuant, bluish-coloured lump. Rarely, infection may intervene, particularly if associated with local cuts or abrasions. A specific history of trauma is almost always present. If this is not forthcoming, then assault and non-accidental injury must be strongly suspected. The condition is so unusual in children and so strongly associated with local trauma that, almost regardless of the alleged history, a Child Protection Team should be asked to investigate.

Auricular pseudocysts are painless and symptom-free, usually with no history of preceding trauma. Local areas of skin irritation are a frequent association.

MANAGEMENT OF AURICULAR HAEMATOMA

There are no formal comparative studies.[23] All recommendations are based on level 4 evidence.

Treatment regimens are based on the requirement to:

- evacuate the haematoma
- remove granulation tissue
- compress or obliterate the dead space to prevent reaccumulation.

Evacuation of haematoma and granulation tissue removal

ASPIRATION

Aspiration is performed under sterile conditions from the anterior surface in the area of maximum fluctuation. It may be attempted for up to 48 hours post trauma. There is, however, an apparent high recurrence rate. If aspiration has been delayed, appears incomplete or there is a recurrence, or if granulation tissue has formed, formal incision and curettage will be required.[4] A closed liposuction method has been described,[24] but the anterior and posterior approaches are both frequently used.

Anterior approach

The incisions are made along the inferior border of the helix along the scapha, in the antihelical fold, or along the conchal fold, as necessary.[3, 25] The skin and elevated periosteum and any associated anterior cartilage layer are incised along the same line. The flap is elevated, the underlying haematoma evacuated and the granulation tissue curetted off the underlying cartilage, including any damaged or necrotic cartilage. Care must be taken not to perforate the posterior skin. The flap is then returned and the incisions carefully closed (**Figure 91.3**).[4, 26] Measures to prevent reaccumulation are required.

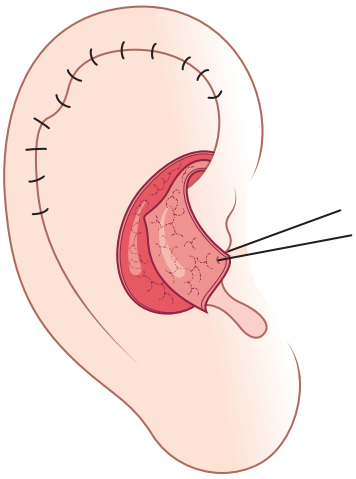


Figure 91.3 Anterior approach. (Modified with permission from Giffin.)[3]

Posterior approach

This approach is preferred in patients who wish to continue to play sport straight away and in those who already have a degree of cauliflower ear following repeated trauma. It may provide better cosmesis. An incision is made opposite the haematoma, on the posterior aspect, down to the surface of the cartilage. A 5 mm window of cartilage is removed, releasing the haematoma, taking care not to perforate the anterior skin.[27] Any granulation tissue on the anterior cartilage surface is easily curetted via this window, which may be enlarged if necessary. The incision does not require closure. Measures to prevent reaccumulation are mandatory (**Figure 91.4**).

Non-surgical methods and compression or obliteration of the dead space

Alternative methods include the injection of sclerosants, such as OK-432, steroids, streptomycin with hyaluronidase, triamcinolone or even fibrin glue, although two or three treatments per ear are often required.[28–33]

Recollection must be prevented but simple bandages and bolsters do not work well. Sutureless compression techniques include the use of moulded silicone, thermoplastic splints, swimmer's nose clip.[34–37] Suction drainage via a posterior incision or an indwelling 18-gauge catheter with a pressure dressing is an alternative.[12, 37–39] Despite their effectiveness, these drains may be accidentally removed and interfere with continuing sport. Compression suture methods with absorbable, or non-absorbable, through-and-through mattress sutures are most commonly used over bolsters and are probably the most effective (**Figure 91.5**).[40] The bolster material enables the application of even pressure to both sides. Bolsterless techniques using sutures alone, or with silicone moulds, plastic tubing or buttons on both sides are alternatives.[40–45] The author prefers using dental rolls as their sponginess enables better definition of the contours and helps to prevent overtightening of sutures. The patient may return to contact sports although a head guard to provide extra protection is advised.

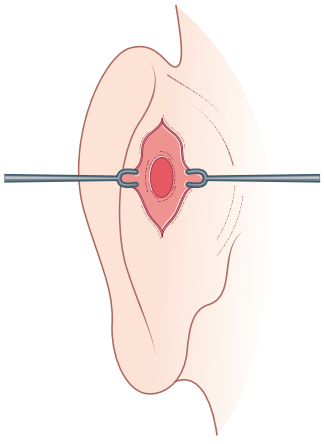


Figure 91.4 Posterior approach with cartilage window.[27]



Figure 91.5 Through-and-through sutures over bolsters (dental rolls or soft tubing).

TREATMENT OF AURICULAR PSEUDOCYST

The treatment principles are the same as above but, as there is no granulation tissue, curettage is unnecessary. Recurrence approaches 100% for simple aspiration without compression.[46, 47] A popular technique is deroofing by removal of a disc of anterior skin and the underlying perichondrium. The exposed cartilage is allowed to granulate with a bolster compressing the surrounding areas.[48] A simple method of achieving this is with a skin biopsy punch.[49] The anterior and posterior drainage techniques described above are equally applicable to auricular pseudocysts. The success of bolsterless techniques is widely described,[42, 43] and superior to sutureless compression.[50]

PREVENTION OF AURICULAR HAEMATOMA AND PSEUDOCYST

The use of headgear in wrestlers approximately halves the rate of haematomas from 52% to 26%; 10.6% of those regularly using headgear, and 26.6% of those who do not, develop them.[51]

The use of tape around the head covering both ears and/or the application of lubricants are frequent preventative measures used by rugby union players, although these measures are relatively ineffective. Wearing headgear gives a relative risk of about 0.59, demonstrating reasonably effective protection.[52]

KEY POINTS

Auricular haematoma and associated injuries

- Early haematoma evacuation is recommended.
- Curettage of granulation tissue is important if drainage is delayed.
- Whichever surgical approach is used, compression sutures are recommended.

EXTERNAL EAR CANAL TRAUMA

MILD TRAUMA

Minor bruising, lacerations or small subcutaneous haematomas are often caused by the use of cotton buds or sharp implements in an attempt to remove wax or to alleviate irritation. External ear barotrauma may cause similar injuries. Such injuries are usually inconsequential. No specific treatment is usually required; however, if there are any signs of infection, then an appropriate topical antibiotic drop should be prescribed. In those who cannot keep their ears dry for the following 14 days, prophylactic acetic acid ear drops may be used.[53, 54]

MODERATE AND SEVERE TRAUMA

Moderate or severe trauma may present with bleeding from the external meatus. A history of trauma should always be sought, especially if the patient is found unconscious. Soft-tissue lacerations may result in canal stenosis (see Chapter 77, Acquired atresia of the external ear).

Association with mandibular fractures

Ear canal bleeding with pain is a frequent presentation of temporal bone fractures and also of those of the tympanic plate associated with mandibular trauma and condyle fractures. The association of trismus with bleeding and pain is highly suggestive of such injuries.[55, 56] Mandibular trauma, particularly posterior dislocation of the condyle, may result in damage to the cartilaginous parts of the external auditory canal with laceration and bleeding and, more rarely, fracture of the tympanic plate. This may occur without an associated condylar fracture. Although the initial impression may be of an external ear canal fracture, one of the mandible must be excluded.[57] Three-dimensional CT imaging is useful in fully assessing tympanic plate fractures.[58] Extreme bleeding may indicate an associated jugular bulb tear with blood coming from either a tympanic membrane perforation or a fracture line through the temporal bone. Death may result.[59]

There are no appreciable differences in presentation, or of the features of the fractures, between adults and children.[60] The management of mandibular fractures is beyond the scope of this publication.[61]

FRACTURES OF THE EXTERNAL AUDITARY MEATUS

Temporal bone fractures, with resulting tegmen defects, may be seen as a longitudinal step defect extending medially and including the annulus. They are usually associated with a haemotympanum. A tympanic membrane perforation with ossicular disruption may coexist. Severe displaced fractures may result in herniation of brain and meninges (meningoencephalocele) into the external canal.[62, 63]

Management

As most cerebrospinal fluid (CSF) leaks close spontaneously, initial conservative management is indicated. Rarely, when they do not, surgical intervention is required, usually via a middle fossa approach. If there is a superior meatal roof defect associated with the presence of granulation or polypoid soft tissue, MRI is recommended to exclude prolapsed intracranial contents. A mastoid approach may be considered for access to the ossicles or facial nerve, in which situation the opportunity should be taken to smooth off any meatal step deformities and to reinforce or fill any wide fracture lines to prevent the potential formation of canal cholesteatoma.

Canal cholesteatoma

Trapped non-migratory keratin may result from the growth of an inclusion dermoid caused by superficial trauma or irregularities within the walls of the external canal interfering with skin migration. Trapped keratin acquires the features of tympanic cholesteatoma with local bone destruction and may erode adjacent structures.

Unlike non-traumatic cases, which are often self-limiting (see Chapter 76, Keratosis obturans, primary auditory canal cholesteatoma and benign necrotizing otitis externa), surgical intervention is usually necessary. The cholesteatoma should be removed and the canal bone smoothed, enlarging the defect as necessary to create a flat profile. An associated soft-tissue meatoplasty may also be required to aid self-cleansing. Bone pâté and thinned cartilage sheets may be used to fill bone defects, particularly if the fracture, or drilling, has resulted in a posterior canal wall defect into mastoid air cells. Such repairs should be covered with temporalis fascia or perichondrium.

KEY POINTS

External ear canal trauma

- Minor abrasions usually require no treatment.
- Blood from the external meatus requires that both temporal bone and mandibular fractures are excluded.
- If a fracture is suspected, any meatal soft tissue should be left alone pending imaging to exclude herniation of brain/meninges.

FOREIGN BODY TRAUMA

Foreign body trauma is covered elsewhere in this volume (see Chapter 34, Foreign bodies in the ear, nose and throat).

TRAUMATIC TYMPANIC MEMBRANE PERFORATIONS

Tympanic membrane perforations may occur as the result of a pressure wave in the external ear canal, or by direct penetration. About 50% are attributable to slap injuries or direct blows. Self-inflicted penetrating injuries account for about 25%, with 25% being due to causes that include diving and aviation barotrauma, foreign bodies such as button batteries, other caustic substances, insects, welding debris and blast injury. Associated tinnitus and vertigo have been reported in 30.8% and 8.1%, respectively, but only in 2.0% and 0% during follow-up.[64]

TYMPANIC MEMBRANE PERFORATION AS A MARKER OF PRIMARY BLAST INJURY

Primary blast injury (PBI) is defined as: 'A combination of tympanic membrane perforation, pneumothorax, pulmonary contusion, non-penetrating facial sinus injury and bowel perforation'. The presence of tympanic membrane perforation has been considered a significant predictor of PBI. A study of US soldiers demonstrated, unexpectedly, that only 16% of all blast exposure patients had perforations, 50% of these being bilateral. Only 7% of blast injuries had PBI and only half of these had tympanic membrane perforations. Therefore, the presence of a perforation would appear to be a poor predictor of PBI.[65]

TYMPANIC MEMBRANE PERFORATION AS A MARKER OF CONCUSSIVE HEAD INJURY

The presence of a perforated tympanic membrane, from head trauma, is a strong predictor for concussive head injury. The relative risk appears to be about 2.76.[66]

CAUSTIC PERFORATION

The most common cause of caustic membrane perforation is button batteries in children. There were an estimated 3748 battery-related emergency department visits among children in the USA between 1990 and 2000.[67] This may be a presentation of non-accidental injury.[68] Electrical shorting between the battery terminals from mucosal contact, and possibly cerumen, causes battery leakage. The battery may become corroded at the crimp area, resulting in a permanent short, considerably speeding up the leakage and consequent trauma. Severe burns may result. Ear drops act as an electrolyte, rapidly enhancing the process, and therefore must not be used.[70] Local inflammation and erosion may extend into surrounding structures and cause deafness, facial palsy, meatal stenosis and even death.[68, 71] As these complications may occur quickly, removal of the button battery, thorough irrigation of the meatus with sterile water and any necessary debridement, should be performed urgently.

Damage from button batteries can occur quickly and they should be removed as a matter of urgency. The reader is referred to the section entitled 'Batteries and magnets' in Chapter 34, Foreign bodies in the ear, nose and throat.

CLINICAL ASPECTS

A careful history of the trauma modality is required, with attention given to concomitant injuries such as those associated with penetrating injury, temporal bone fractures, blast injury and lightening strike. Examination should include the pinna and canal, with microscopy as necessary. Microsuction may be required to observe the tympanic membrane in detail.

Injuries range from mild injection of the vessels over the malleus handle, to actual perforation. These changes may be classified in the same way as those resulting from barotrauma (see **Table 91.8** below). CSF otorrhoea requires exclusion.

Any foreign body should be removed. If a general anaesthetic is necessary, the opportunity should be taken to apply cigarette paper or absorbable gelatin sponge to any perforation. Infections should be treated with aural toilet and topical quinolone antibiotic drops. In the outpatient situation, if the patient is tolerant, clearance of blood, wax and keratin debris by microsuction is appropriate. Application of a paper patch or absorbable sponge is straightforward with the aim of speeding up spontaneous healing. In the intolerant patient, when no foreign body is present, no active treatment is appropriate.

A 3-month interval should pass before considering a formal repair as early surgery may have worse outcomes than conservative treatment or paper patches.[72] A reasonable exception to this policy might be when a quick, strong repair is desirable, such as in elite water sport athletes or commercial divers.

PROGNOSIS

Spontaneous resolution rates are high, typically 80–94%. Poorer outcomes are observed with increasing age and perforation size[73, 74] and are significantly lower in blast injury.[75] The worst follow welding injuries.[64]

Large studies have shown that the mean time for spontaneous healing is about 1 month, and a majority will have healed within 3 months. A slower speed of healing occurs if there is a middle ear infection. The site of the perforation is, however, insignificant. Penetrating injuries, and a

history of ear syringing post trauma, are the only risk factors important in predicting non-healing.[76, 77]

Office treatments, such as paper or gelfoam patches, are unlikely to increase the likelihood of healing but increase the speed of healing by up to 17 days (28.2±3.6 days in the spontaneous healing group 11.1±2.1 days, $p = 0.0017$ for sponge patching).[78] The biocompatibility, and lack of tissue toxicity, of cigarette papers has been validated.[79] There appears to be no extra advantage in formally repairing in the acute stage (12.5±1.9 days),[80] with no advantage in painstakingly aligning the perforation edges.[81, 82] Small underpowered studies of new interventions, such as the application of epidermal growth factor or hyaluronic acid, may enhance the rapidity of healing but not the chance of healing.[83, 84] Nanofibrillar patches, similar in structure to spiders' webs, have also given promising results.[85]

KEY POINTS

Traumatic tympanic membrane perforations

- Caustic substances, particularly batteries, should be removed straight away.
- No liquid, including drops, should be administered if a battery is present.
- Primary blast injury is a clinical condition whose definition includes tympanic membrane perforation, but this is a poor predictor for the condition.
- Tympanic membrane perforation is a good predictor for concussive head injury.
- Application of a cigarette paper patch or gelfoam increases speed of healing but not the likelihood.
- Surgical repair is only indicated after 3 months as over 80% of perforations heal spontaneously.

OSSICULAR TRAUMA

Most ossicular injuries are dislocations that are identifiable radiologically.[86] Any of the joints may be affected but dislocation of the incus is the most frequent (**Figure 91.6**; **Table 91.1**).[87–90] This may simply be disruption of the incudostapedial joint with minimal incus displacement, although with more severe trauma there may be complete separation.[91] Dislocation out into the ear canal may be associated with a tegmen fracture.[92]

Fractures of the ossicles are much less frequent,[86] being mostly of the incus long process.[93] Studies of cadavers following severe head injuries have noted a variety of damage that includes disconnection of the malleoincudal or incudostapedial joints and fractures of the malleus or stapes.[94] The malleus handle may be fractured, particularly in cases of middle ear barotrauma.[95, 96] Complete malleus dislocation has also been described.[88] Isolated fracture dislocation of the stapes footplate is very rare[97] and almost always the result of penetrating injuries, with associated pneumolabyrinth and perilymphatic fistula.[98] Trauma to the stapes may result in fracture of the arch,[88, 91, 93] or dislocation of the whole stapes.[99] In some cases, a combination of these lesions may be found and there may also be fractures of the bony external auditory meatus or fixation of the incus and/or malleus.[93, 100] Ossicular disruption following trauma may occur without perforation of the tympanic membrane.[101]

TRAUMA MODALITIES

Skull trauma from blows to the temporal, parietal or occipital region (with or without fracture of the temporal bone)

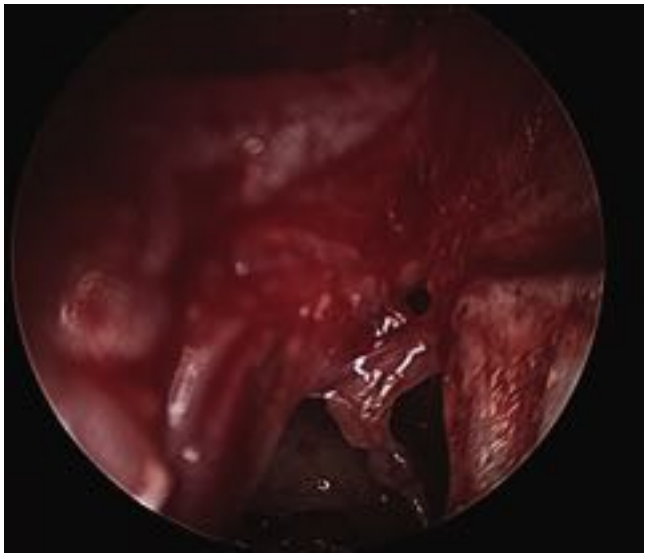


Figure 91.6 Dislocated incus; showing adjacent canal fracture.

TABLE 91.1 Frequent sites of injury

Author(s)	Year	Ears	Incus dislocation	Stapes fracture	Malleus fracture	Stapes luxation	Incus fracture	Ossicular fixation	EAM fracture
Hough[91]	1969	31	26	9	3	0	0	8	20
Rohrt[89]	1973	8	1	2	0	2	3	1	0
Spector et al.[93]	1973	28	10	7	1	0	8	5	0
Mills and Starriit.[120]	2002	12	12	2	0	0	0	2	1
Yetiser et al.[90]	2008	40	13	5	0	6	7	2	-
Total		119	62	25	4	8	18	18	21

Modified from Robert Mills, Scott Brown's *Otorhinolaryngology, Head and Neck Surgery,* 7th ed. Volume 3, Table 237g.1, p. 3493.

is the main cause; other modes of injury are rare.[102] About 60% occur without a concomitant temporal bone fracture.[101] Hearing loss occurs in about 22.5% of temporal bone fractures.[103] Around 16–30% of these have a conductive component, of which some will be due to transient causes such as a haemotympanum.[103, 104] Direct penetrating trauma is less common[105, 106] and may be iatrogenic as a result of intratympanic injections, particularly if there has been previous middle ear surgery or stapedectomy.[107] Other causes include middle ear barotrauma, surgical trauma and lightening strike.[108] Several large studies identify similar aetiologies. Drill-induced trauma to the incus during tympanomastoid surgery usually causes incudostapedial joint dislocation and a corresponding conductive hearing loss. Permanent sensorineural hearing loss is also highly likely in this situation but prophylactic disarticulation of the incus does not protect against it in a standardized guinea pig model.[109] Simple manipulation of the ossicles during surgery should, however, not result in a sensorineural deficit.[110] Digital pressure applied to the external auditary meatus may result in a sudden pressure change resulting in an isolated malleus fracture.[96] A comprehensive forensic post-mortem study looking at head injury victims using multislice CT methods suggests that the type of energy imparted is more important than simply the amount.[111] Damage to the ossicular chain may also occur secondary to osteoradionecrosis.[112] Congenital incus dislocation has also been described.[113]

DIAGNOSIS

A conductive component to the hearing loss following trauma of any sort should alert the surgeon to the possibility of ossicular injury. It may be difficult to diagnose ossicular disruptions that occur without perforation of the tympanic membrane, or once it has healed. Once acute sequelae, such as a haemotympanum, have resolved, further evaluation is necessary. Patients may present at variable times after the traumatic event, sometimes many years later.

INVESTIGATIONS

An initial audiometric assessment should be performed as soon as is practical after the injury. The initial conductive loss is often due to a haemotympanum or tympanic membrane perforation. A concomitant sensorineural loss may partially resolve (cochlear concussion). Rarely, however, audiometry may be normal,[114] or become so following healing despite a lack of reduction of the dislocation or fracture.[115] Any haemotympanum should be allowed to clear and time given for natural healing processes to take place before repeating the audiometric assessment, as excellent spontaneous hearing resolution may take place.[115] A varying degree of conductive impairment may therefore be present, often accompanied by a high-frequency impairment due to cochlear trauma. A tympanogram may show unusually high compliance, with a high peaked type A_D tympanogram, although this may occur in normal ears.

High-resolution CT is the imaging of choice for investigating ossicular trauma. Both axial and coronal images are needed for the evaluation of fractures and dislocations of all three ossicles. Reformated images are useful.[86] Three-dimensional CT imaging gives better information about the spacial orientation of the ossicles,[101] but virtual endoscopy enables even more of the ossicular chain to be seen, particularly the stapes crura.[116] This technique has given excellent predictive results of 100% in a small series of 17 patients.[117]

MANAGEMENT

Conservative management

Since surprisingly good hearing recovery may take place with fibrous healing when the incudostapedial joint is disrupted, even if the incus is entirely displaced,[115] a 3-month period is recommended prior to surgical exploration. Those patients who do not wish to undergo surgery should be offered aiding. Results from ossiculoplasty are inversely related to the degree of ossicular disruption. Coexisting sensorineural losses with major ossicular disruption may make surgical intervention unjustifiable, particularly if there is normal hearing in the contralateral ear. Detailed CT scanning is therefore recommended to aid this decision. Before undertaking surgery for a unilateral conductive deficit, consideration should be given to the likelihood of an adequate surgical result providing true benefit.[118] An exception may be when the air conduction thresholds in a mixed loss are sufficiently high that aiding would give poor results. In such cases, provided speech discrimination is adequately preserved, ossiculoplasty with the intention to aid post-operatively is a justifiable approach ('surgery for aiding').

Surgery

After elevating the tympanic membrane, identification of the nature and exact location of the ossicular injury is essential. After major trauma there is usually little doubt, although minor dislocations and fractures may be difficult to locate with confidence. A methodical process should be used whereby the malleus, incus and stapes head are palpated in turn while carefully watching the stapes footplate under high power. The impression of a lag, or failed transmission of movement, is indicative of the site of injury. Adhesions may be present around the specific site of injury. Watching the stapes superstructure rather than the footplate may result in missing subtle crural fractures. Delay in operating makes little difference to the long-term results.[119]

Since 1957 many surgical techniques have been described.[88] The displaced incus may be replaced by any standard ossiculoplasty method (see Chapter 85, Ossiculoplasty). Fixing it in its anatomical position via a posterior attic approach, combined with a tympanotomy, may be very successful.[120] Good results have been

described for the repair of simple incudostapedial subluxation with cartilage tip interposition, cement[121] or cyanoacrylate glue.[122, 123] Disappointing results using incus tip techniques may occur due to an unrecognized subluxation of the malleoincudal joint. Such cases may be identified at revision surgery where consideration should be given to an incus replacement technique. Cartilage repair of an isolated malleus fracture is straightforward and should give good results.[124] In cases of isolated stapes crural fractures, a strut or piston may be placed between the incus and footpate.[88, 93] A laser stapedotomy technique, however, gives more stability and is also useful for cases of stapes luxation.

RESULTS

There are no published randomized controlled trials (RCTs) addressing any aspect of ossicular chain trauma surgery. Numerous publications give the results of small series of specific interventions, or larger ones giving their overall results. The larger series available are presented in Table 91.2. These all include cases with a range of middle ear pathology and treatments, resulting in small numbers and therefore making conclusions difficult. Physiological repositioning of the incus has been described in several small series as giving the most impressive results,[91, 93, 120] the transmastoid posterior attic approach achieving the best.[120] Conventional ossiculoplasty techniques should give better results when performed for trauma than chronic suppurative otitis media in that there is usually no associated middle ear pathology and Eustachian function is normal. Soft-tissue adhesions within the middle ear and attic may compromise the outcome of treatment.[120] Cases with a greater degree of damage to the middle ear structures represent a greater reconstructive challenge than those with isolated incus dislocation.

TABLE 91.2 Hearing results (case series only)

Author(s)	Year	Ears	Technique(s)	Air–bone gap<10dB post-operatively (%)
Hough[91]	1969	31	Bone chip	100
			Per-meatal repositioning	80
			Ossiculoplasty	88
			Other	29
			Overall	78
Spector et al.[93]	1973	28	Per-meatal repositioining	
			Ossiculoplasty	
			Other	
			Overall	66
Mills and Starriit[120]	2002	12	Posterior attic approach repositioning	71
			Ossiculoplasty	25
			Overall	54

KEY POINTS

Ossicular trauma

- A variety of fracture/dislocation combinations is possible.
- The tympanic membrane may be intact.
- A conductive hearing impairment that persists following head trauma is most likely to be due to incus dislocation (62%).
- High-definition 3D CT scanning, or CT virtual endoscopy, is helpful in establishing the diagnosis.
- The cause may only be definitively determined by exploratory tympanotomy.
- The results of reconstructive surgery are generally better than those obtained in chronic suppurative otitis media, as the middle ear space is healthy.

TEMPORAL BONE TRAUMA

EPIDEMIOLOGY/AETIOLOGY

The overall incidence of temporal bone injuries is not determinable, and that reported for fractures varies widely. One estimate is that 8.5/100 people have either lost consciousness or suffered temporary confusion as a result of a head injury.[125] Blunt trauma to the temporal bone is much more frequent than penetrating injury. Skull base fractures occur in 3–30% of head injury attendances to Emergency Departments, 9–40% of these having temporal bone fractures.[126–128] About 7.9% are bilateral.[129] Men in their late twenties and early thirties predominate (male : female 2.8–4 : 1).[127, 129–131] Temporal bone trauma without fracture has similar aetiologies. Road traffic accidents probably account for about 50%, other frequent causes being falls (16–40%), assaults (10-37%) and, in the US, gunshot wounds (3–30%).[132–134] The profile may be different where medicolegal proceedings are taking place, when as many as 45% of cases may be due to work related injury.[131]

About 15% occur in children (males : females 2 : 1), the peak incidence being at approximately 5 years of age. Falls from a height predominate as the cause (40%) in children, with road traffic accidents accounting for only 34%.[60]

INNER EAR TRAUMA WITHOUT TEMPORAL BONE FRACTURE

Inner ear concussion (labyrinthine concussion, cochlear concussion, inner ear concussive syndrome) and mild traumatic brain injury

'Concussion' describes a temporary unconsciousness or confusion, with other symptoms, caused by a blow to the head. The term is often used synonymously with mild traumatic brain injury. This has been defined as: 'A traumatically induced physiological disruption of brain function

characterized by brief loss of consciousness (30 minutes or less), any alteration in mental state at the time of accident, anterograde or retrograde amnesia, negative neuroimaging [CT], Glasgow Coma Scale [GCS] score of 13–15 and post traumatic amnesia of not more than 24 hours'.[135, 136] The terms 'mild' and 'minor' are often used interchangeably although minor head injury is sometimes used to indicate extremely mild injuries in patients with an initial GCS of 15.

Head injuries account for about 1.4 million Emergency Department attendances per annum in the UK, approximately 90% of all traumatic brain injury being classified as mild. About 80% are discharged directly from the Emergency Department.[137] Although CT scans may be normal, MRI scanning has demonstrated a high incidence of parenchymal injury even when the GCS was as high as 14.[136, 138]

HEARING LOSS

About 52% of patients suffering from mild traumatic brain injury experience a subjective short-term transient hearing loss for several hours to 2 days immediately after the trauma.[139] Despite this, several studies have found no evidence of permanent hearing loss, as measured by pure-tone audiometry.[149, 150] More detailed audiometric evaluation has, however, suggested abnormal amplitude differences of transiently evoked otoacoustic emissions and absent stapedial reflexes in 12/31 patients.[139] Despite the implication that almost all concussive symptoms and signs recover, any associated hearing losses may very rarely be permanent even in those whose other symptoms have resolved.[131, 141] Histological analysis has demonstrated microfractures involving the otic capsule when imaging has been negative, suggesting an explanation for this.[141] No accounts of hearing loss, without dizziness, could be found.

A study of 100 consecutive head injury patients found 44% of those with mild traumatic brain injury to have auditory symptoms; this figure increased to 75% in the moderate/severe brain injury group. In both groups, about 75% of patients were found to have measurable vestibular abnormalities. Those few patients having a conductive loss all had a sensorineural component. Auditory abnormalities were shown to increase with the severity of the head injury whereas vestibular abnormalities were no more frequent in those with more severe injuries.[131]

TINNITUS AND HYPERACUSIS

Fifty-three percent of all patients suffering from traumatic brain injury develop tinnitus, particularly following trauma directly to the ear. Hyperacusis occurs to some degree in 87%. These symptoms may be due to direct cochlear injury, trauma to the auditory nerve and to brain parenchyma. Tinnitus and hyperacusis may be present in as many as 21% of those injuries where there is no measured hearing loss.[131, 142]

DIZZINESS AND VERTIGO

Dizziness may be described within four categories: vertigo, pre-syncopal light-headedness, multisensory dizziness, and psychophysiologic dizziness. Of these, only the symptom of vertigo may be clearly linked to the vestibular system.[143] This affects about 24% of patients with mild traumatic brain injury.[134] Possible specific sites of injury include the vestibular nuclei, the labyrinth or the upper cervical spine.[144, 145] Symptoms almost always resolve within 10 days.[146]

MANAGEMENT

A careful history, with particular reference to witnesses, is important in determining the modality and severity of any head injury. The initial assessment and investigations are in the domain of the emergency physician and, as necessary, the neurology and neurosurgical teams. The evaluation should, however, include a full neuro-otological examination. A policy of no active treatment for an isolated sensorineural hearing loss is appropriate. In patients with vertigo, undefined dizziness and tinnitus, CT of the temporal bones is indicated. Bed rest, head elevation and avoidance of straining are advised. A diagnosis of perilymphatic fistula should be considered (see below). Other causes of sensorineural loss, which may be coincident, may require exclusion with MRI.

No studies have specifically addressed the use of steroids although, given the likely aetiological factors of shear, microfractures and the assumed consequent inflammation, their use in cases of mild traumatic brain injury and cochlear concussion might seem persuasive. Large RCTs have not, however, found any benefit for the overall outcome with steroid treatment in any level of traumatic brain injury.[147]

Audiovestibular symptoms with or without hearing loss are a major component of traumatic brain injuries. A full range of supportive and rehabilitative measures should be provided, including hearing aids, vestibular rehabilitation, tinnitus and hearing therapy as well as general psychosocial rehablitation.[148] The evidence for psychogenic causes for audiovestibular symptoms is weak.[131]

PROGNOSIS

During the first week following their injury most patients report a range of symptoms that include headaches, dizziness, fatigue, memory deficits, anxiety and depression.[149] Up to 40% of patients have persistent residual symptoms one year later.[150, 151] Those with three or more symptoms beyond 3 months are defined as having postconcussive syndrome.[152] There is some evidence to suggest that there is the rare occurrence of a progressive hearing loss. This may be immunologically mediated via the HSP 70 antigen.[153]

Perilymphatic fistula

Rupture of the round or oval windows may occur with or without a temporal bone fracture. The management is as for other causes of perilymphatic fistulae (see 'Inner ear barotrauma' below).

Benign paroxysmal positional vertigo

Benign paroxysmal positional vertigo (BPPV) is the most common cause of vertigo post trauma, affecting 61% of the

patients who consult for persistent symptoms.[131] In a large retrospective study, 67% required multiple repositioning manoeuvres in the post-traumatic group compared to only 14% in the idiopathic.[154] It has been hypothesized that this worse prognosis may be due to an increased incidence of bilateral involvement and the occurrence of additional labyrinthine injuries, such as microscopic haemorrhages or tissue shearing[154, 155] (see also Chapter 64, Benign paroxysmal positional vertigo).

Delayed endolymphatic hydrops (post-traumatic Ménière's syndrome, secondary Ménière's disease)

Symptom combinations indistinguishable from Ménière's disease, either in the same or the contralateral ear, may develop some years after the initial onset of a sensorineural hearing loss following trauma of almost any sort, including acoustic trauma, head injury with and without fracture, infectious sequelae of measles, mumps and syphilis, and acoustic trauma.[156–158] Symptoms may also develop following surgical trauma, particularly stapes (and historically fenestration) surgery.[159] The prevalence is uncertain but it would appear to be uncommon. One study of patients with endolymphatic hydrops found a history of trauma in 5/31 patients (16%) including in contralateral ears.[157] The management of this condition should be as for idiopathic Ménières disease (see Chapter 63, Ménière's disease).

KEY POINTS

Mild traumatic brain injury

- Around 90% of traumatic brain injury is classified as mild.
- About 52% with mild traumatic brain injury have subjective hearing loss.
- Persistent measurable hearing loss is very rare.
- Tinnitus and hyperacusis may occur without hearing loss.
- Around 24% have dizziness or vertigo that has usually resolved within 10 days.
- Benign paroxysmal positional vertigo (BPPV) is the most common vestibular condition but it may be more resistant to repositioning manoeuvres than the idiopathic type.
- Perilymphatic fistula is a rare consequence.
- Clinical features of endolymphatic hydrops may occur in both the affected or contralateral ear many years later.

EAR TRAUMA WITH TEMPORAL BONE FRACTURE

Classification

The most commonly used system classifies temporal bone fractures according to their orientation relative to the axis of the petrous ridge: longitudinal or transverse.[160, 161] Most series describe 80–90% of fractures as longitudinal and 10–20% as transverse.[133] Although a convenient system, it has not been proven to correlate well with clinical signs or outcomes. Fractures have been found to be randomly placed or comminuted, and they are often not adequately described by the traditional classification.[162] True longitudinal fractures are uncommon so alternative classifications attempt to include oblique and complex fracture orientations.[91, 163]

An alternative system considering fractures as otic capsule violating or sparing is becoming more widely adopted.[60, 126, 132] This system emphasizes the structures involved rather than simply describe the fracture orientation.[127] Otic capsule fractures are associated with an increased incidence of serious sequelae.[126] Facial nerve paralysis, CSF leak and profound hearing loss were twice, four times and seven times, respectively, more likely in otic capsule violated cases. Some caution is, however, required as others have found no statistical difference using this differentiation.[127, 129] An attractive approach is simply to differentiate between petrous and non-petrous fractures. In one study CSF leak was only 1.1 times more common in transverse than in longitudinal fractures but was 9.8 times more common in petrous than in non-petrous fractures. Facial nerve injury is also more strongly correlated with fractures through the petrous temporal bone than with other fracture types. Sensorineural hearing loss did not correlate with the transverse fracture classification but was significantly more prevalent in petrous fractures.[164]

No convincing new classification system has evolved that repeatedly achieves reliable reproducibility to justify standard adoption. Therefore, a more descriptive strategy is suggested where the clinician combines the classifications by describing the fracture both in terms of its predominant orientation and whether it involves the petrous bone, otic capsule and brain parenchyma.

Temporal bone fractures in children

In children there is a relative increase in transverse fractures with 59% being longitudinal and 41% transverse.[60] This may be due to the different stress and resistance lines in the paediatric skull as a result of non-fused sutures and different bone density.

Clinical features of temporal bone fractures

HEARING LOSS

Any pattern of loss – immediate, delayed, transient, permanent or progressive – may be seen in cases of temporal bone fracture.[133] A conductive hearing loss of greater than 20 dBHL is likely to occur in two-thirds of patients tested within 72 hours of injury, with 17% persisting 6 weeks afterwards.[165] The management of conductive injuries is discussed above (see 'Ossicular trauma'). Although a persistent hearing loss is rare in cases of mild head injury, a sensorineural loss is often found in patients who have sustained a temporal bone fracture. The affected frequencies are usually at 4 kHz and higher.[131, 140] The degree of hearing loss is proportional to the degree of head injury.[130]

Complete loss of hearing in the affected ear is reported in about 17% of patients with a fracture.[165] Tinnitus and hyperacusis are frequent symptoms, and their management should be supportive.[131]

SYMPATHETIC HEARING LOSS

A delayed and progressive loss, without vestibular symptoms, may occur many months or years following the injury. It is thought to occur in 1–11% of ears following temporal bone fracture and to be immunologically mediated.[166] Similar occurrences have been identified after revision stapes surgery,[167] and vestibular schwannoma surgery.[168] Exposure of antigens from traumatized cochleovestibular membranes is thought to lead to immune sensitization and hence an attack on the contralateral ear. The same mechanism has been hypothesized as the cause of delayed progressive hearing losses occurring in the injured ear.[169] Animal studies have supported this mechanism.[170, 171]

VERTIGO

Similar rates of post-traumatic dizziness occur following severe temporal bone trauma and after minor head injuries. It occurs in at least three-quarters of cases.[131] Where the petrous bone/otic capsule are spared then a mechanism of vestibular concussion is thought to occur and resolution should be relatively fast, taking a matter of days.[146] This is unlike the destructive process with fractures through the otic capsule where resolution as a result of central adaptation may take up to 12 months.[133]

Clinical examination

A complete neuro-otological examination should be performed including a conscious state assessment (Glasgow Coma Scale), and examination of the cranium looking for evidence of penetrating injury, lacerations and mastoid bruising (Battle's sign) indicative of a skull base fracture. The absence of external injuries, particularly soon after the injury, does not preclude an underlying fracture. Cranial nerve examination is mandatory, with particular reference to facial nerve function. Examination of the neck, and the rest of the body, should be performed in conjunction with emergency physicians as appropriate. Tuning fork tests may be useful until formal audiometry is practical. Clinical tests of balance, gait and cerebellar function should be performed as soon as the patient's general state permits.

Otoscopic examination may reveal cerumen, blood, oedema, a canal step fracture, CSF, haemotympanum and tympanic membrane perforation. A good view may be difficult to obtain. Syringing and irrigation methods of cleaning are contraindicated due to the risk of ascending infection via open fractures and tympanic membrane perforations. Microsuction is rarely useful in the early stages of management; imaging usually gives sufficient information for the necessary decision-making. It is, however, indicated if infection is observed in the meatus. CT images should be available enabling any risk to be evaluated. Any soft tissue encountered should be left alone. Packing the meatus should be performed only in cases of uncontrolled haemorrhage. If this is required, a pack without a radio-opaque marker should be used to prevent interference with subsequent imaging.

Investigations

IMAGING

High-definition CT scanning is the investigation of choice. Better CT technology will increase the diagnostic rates of both temporal bone trauma with fracture[172] and mild traumatic brain injury, where a negative CT scan forms part of the diagnostic criteria.[135] It is the recommended initial investigation for the evaluation of all head injuries in patients with a Glasgow Coma Scale score of 14 or less.[173] If available, a high-definition temporal bone scan should be obtained straight away as part of the brain scan evaluation, particularly if temporal bone trauma is suspected; if not, then scan as soon as is practicable. Where hearing loss or vertigo is evident, but with no fracture demonstrated on CT, T1-weighted MRI may demonstrate a hyperintense signal in the labyrinth indicative of haemorrhage,[174] and may also identify temporal lobe contusion.[175] In the recovery phase labyrinthine enhancement may also be seen on MRI suggestive of an inflammatory process.[172] Targeted imaging may be necessary to examine specific injured structures, such as gadolinium-enhanced MRI of the facial nerve, or angiography for vascular injury. Despite CT findings, patient management is primarily guided by symptoms and clinical signs.[176]

HEARING ASSESSMENT

Clinical speech and whisper tests and tuning fork tests give useful initial hearing information long before the patient is sufficiently well to undergo formal audiometry. Early baseline audiometry is useful so that subsequent progress or deterioration may be monitored. In cases of bilateral temporal bone fracture, urgent hearing assessment is indicated and an audiometer should be taken to the bedside if necessary. Formal audiometry 6 weeks following temporal bone injury usually allows sufficient time for a haemotympanum to resolve, enabling assessment of residual conductive and sensorineural deficits.

Tympanometry will assist in determining the role of middle ear fluid in any conductive impairment. Rarely, evoked response audiometry may be useful in unconscious patients or children.

VESTIBULAR ASSESSMENT

Following head injury of any type, dizziness is a predominant, but often non-specific, symptom.[143] The presence of nystagmus may provide evidence of vestibular involvement although the observed movements may be complex if there is cerebellar trauma (see Chapters 49, Physiology of equilibrium and Chapter 62, Evaluation of balance). The typical finding of a horizontal nystagmus may be observed

with the fast phase directed away from the side with the failed labyrinth. Gait testing, augmented by other clinical tests such as Romberg and Unterberger tests, is useful, particularly in documenting resolution.

Caloric testing and other electro- or videonystagmographic tests seldom influence management, but they may be important during recovery to document the extent of any deficit and to objectively document progress or deterioration, particularly in the context of ongoing medicolegal proceedings.[177]

Treatment

ACUTE GENERAL

The general management of head trauma is outside the clinical domain of the otolaryngologist. A team approach is, however, indicated.

ACUTE SPECIFIC

Steroids

Despite widespread use for otological indications, such as sudden acute idiopathic sensorineural hearing loss, there are no convincing data suggesting benefit from the use of systemic steroids.[178] The use of intratympanic steroids has attracted much recent interest and may achieve better results (see Chapter 60, Idiopathic sudden sensorineural hearing loss). These techniques are unlikely to be applicable in the acute phase following temporal bone fracture for both practical reasons and the presence of a haemotympanum. Large randomized controlled studies have demonstrated no benefits with the use of steroids in overall outcome when used in the acute setting, even finding a very significant increase in mortality in more serious cases of traumatic brain injury.[147, 173] In view of this there is no justification for their routine use.

Antibiotics

Meningitis complicates about 2% of skull base fractures.[179] The routine use of prophylactic antibiotics confers no benefit with respect to: frequency of meningitis (even in patients with a CSF leak), all-cause mortality, meningitis-related mortality, or the need for surgical correction in patients with CSF leakage.[180]

MEDIUM AND LONG TERM

The management of any conductive loss is discussed above. Persistent mild to moderate hearing losses may be fitted with conventional air-conduction aids. Unilateral profound losses may benefit from a CROS or bone-anchored hearing aid with the aim of counteracting the head-shadow effect, convincingly improving hearing in noise performance.[181] Improvements in directional discrimination have, however, proved disappointing,[182, 183] although even in the elderly 65% satisfaction was evident.[184] Cochlear implantation in such cases may soon be shown to provide the best results, although availability and funding issues may prevent it.[185] If disabling tinnitus persists, implantation may be the treatment of choice.[186] MRI, as well as promontory stimulation testing, are necessary to check the integrity of the VIIIth nerve components if no hearing is elicited. CT scans should also be examined to check the integrity of the cochlea for implantation.

Regular monitoring of patients with progressive losses is important as an obliterative labyrinthine process may compromise successful implantation in the future. If there is a significant delay between the time of the injury and that of implant surgery, repeat imaging is essential preoperatively to rule out labyrinthitis ossificans or other structural abnormalities that may prevent successful electrode insertion.[187]

In patients with bilateral otic capsule fractures, and profound bilateral deafness, bilateral implantation is indicated as soon as the patient is sufficiently well to undergo confirmatory hearing tests and to tolerate general anaesthesia.[188, 189] If returning function in one or both ears is suspected, the worse ear should be implanted and the other carefully monitored. This ear may then be implanted if subsequent deterioration is observed. Implantation provides good rehabilitation results although persistent facial nerve stimulation secondary to electrical leakage through fracture lines occasionally causes difficulties.[190]

The management of tinnitus and vestibular symptoms should be managed as for temporal bone trauma without fracture (see above).

KEY POINTS

Temporal bone fracture

- Descriptions of fractures as longitudinal or transverse have a poor correlation with actual fracture orientation or clinical features.
- Fractures in children are more likely to be transverse.
- All patterns of hearing loss are possible.
- The absence of external injuries does not preclude an underlying skull base fracture.
- Ear syringing is contraindicated as it risks ascending infection.
- High-definition CT is the investigation of choice.
- MRI is indicated if neurological or vascular injury is suspected.
- Use of steroids may increase mortality.
- There is no evidence of any benefit conferred by the routine use of antibiotics.
- In cases of complete hearing loss, cochlear implantation should be performed as soon as possible before intracochlear fibrosis or calcification preclude effective electrode placement.

Complications of temporal bone fracture

FACIAL PALSY

Facial nerve palsy complicates about 7% of temporal bone fractures, dependimg on the type of trauma and fracture pattern.[191] Penetrating trauma has a higher incidence of about 52%.[192] Facial nerve injuries occur in 10–25% of longitudinal fractures, in 38–50% of transverse,[133] and are more common with otic capsule violating fractures.[191] Sixty-six percent of fractures are located at the geniculate

ganglion, 20% at the second genu, 8% in the tympanic segment and 6% in the mastoid portion. Six percent of geniculate ganglion lesions exhibited a second site of trauma in the mastoid portion.[193]

Clinical issues

It is important to ascertain whether the onset of the facial palsy was immediate or delayed and if partial or complete. These details are often unclear due to other potentially life-threatening issues (e.g. a palsy may not be noticed in ventilated patients). The implication of an immediate palsy is that the nerve has been directly traumatized, impinged or perhaps transacted. Delayed onset, even if only by a few minutes, and any residual function, imply neural continuity. Those cases where time of onset cannot be ascertained are best considered as immediate onset.[191]

Investigation

An excellent prognosis for recovery exists in cases of partial or delayed facial nerve palsy. Elecrophysiological testing is only necessary in cases of immediate complete palsy or in those cases of complete paralysis, with an uncertain history, that were thought to have been of delayed onset but have failed to improve. The timing of electrophysiological investigations remains controversial (see Chapter 112, The facial nerve and its non-neoplastic disorders). Most protocols are derived from studies performed on patients with idiopathic, Bell's palsy. Electroneuronography performed at about 10 days post injury is advocated but in patients with severe trauma this is usually not practical.[193] If it shows no response, electromyography is indicated. There is an established standard whereby good recovery of facial function is expected if the decline in the compound action potential on electroneuronography does not reach 90%. Although this seems to have evolved into a treatment threshold, 67% of patients who reach this level of degeneration also have excellent outcomes. A comparative study between idiopathic and traumatic facial palsies only demonstrated the importance of the 90% threshold in the idiopathic group.[194]

High-definition CT should have been performed in all patients as part of the head injury assessment. In cases of complete facial palsy contrast MRI may identify the main location of injury. This may be particularly useful if there is a comminuted or double fracture, or if no fracture is seen to be in the vicinity of the nerve on CT.[195]

Treatment

There is no evidence that any intervention for incomplete palsies gives superior results to no treatment. All of these patients are expected to make a complete, or almost complete, recovery (House–Brackmann I or II).[126, 191]

Steroids Systemic steroid treatment is usual for both delayed and immediate cases of facial palsy despite there being no controlled studies specifically examining their use in this setting. As they improve the degree of recovery and reduce synkinesis in Bell's palsy, without evidence of harm,[196] until there is evidence to the contrary, their use may be justified although the degree of coexisting traumatic brain injury takes priority. This often precludes the use of steroids as their use increases mortality.[147] There is no comparative study examining the optimum dose nor duration of treatment. An appropriate dosing regimen is 1 mg per kg per day of prednisolone, or equivalent, for 1–3 weeks, with a taper for longer courses.[133]

Surgical decompression The role and timing of surgery remains controversial. There are no RCTs to assist decision-making and no direct comparisons of treatment versus no treatment. Studies have not convincingly made the case for surgery. Complete nerve transection that cannot spontaneously recover accounts for about 14% of cases[193] and complete, immediate palsies, treated conservatively, may expect a 50% chance of complete or near-complete recovery without surgery.[191] A standard has evolved whereby immediate palsies showing the requisite 90% degeneration on electroneuronography within 2 weeks of injury are considered for surgery. Further research is clearly required. Despite these uncertainties, early identification and repair of a transacted nerve, and decompression of a clearly impinged nerve, are appropriate. This will only be achieved if immediate, complete palsies are comprehensively investigated, differentiating them from other cases that are more likely to recover spontaneously.

KEY POINTS

Post-traumatic facial nerve palsy

- Facial palsy complicates 7% of temporal bone fractures.
- Only complete, immediate onset, palsies require electrophysiological testing.
- A finding of 90% degeneration on electroneuronography at 14 days is a commonly used standard for consideration for surgical intervention although 67% with this result have good resolution without intervention.
- With no treatment 50% of complete immediate-onset palsies achieve good recovery.
- About 100% with incomplete palsies achieve House–Brackmann I or II grade recovery.
- Steroids may be effective but must only be used only if there is no significant associated brain injury.

OTHER NERVE PALSIES

Additional cranial nerve injuries occur in 7.8% of cases of temporal bone fractures. These consisted of VIth nerve injury when the petrous apex was fractured, also lower cranial nerve palsies as a result of jugular foramen haematoma.[193]

CEREBROSPINAL FLUID LEAK

Clinical features

Estimates of the frequency of CSF leaks following temporal bone fracture vary widely between 11% and 33%.[191, 197] Most (81%) resolve spontaneously within 5 days and 95% within 14 days,[191] although it is likely that many go unnoticed.

The risk of meningitis in temporal bone fracture is about 2%,[179] which probably increases to 7% with a CSF leak.[191] Concurrent ear infection increases this risk to as much as 20%.[191] Low-pressure headache and increasing risk of meningitis occur if leaks persist. Larger defects are probably less likely to heal spontaneously.

Management

Although not validated, bed rest with head elevation and avoidance of straining and lifting is advocated. If the leak has not stopped within 10 days, insertion of a lumbar drain is a sensible intervention. Prophylactic antibiotics are unhelpful in the absence of an ear infection.[180]

The requirement for surgical closure is unusual. Location of a persistent leak is not necessarily straightforward, particularly with comminuted fractures. The presence of a defect on a CT scan is not necessarily the site of the leak. Peri-operative fluorescein cysternography is sometimes useful for identifying the site.[198] For larger defects there is a risk of herniation of meninges and brain into underlying spaces. An MRI scan is also recommended to establish this pre-operatively. It is probable that some cases of meningoencephalic herniation go unrecognized but, due to the risk of infection, repair is recommended.[199]

The surgical approach and method used varies according to authors' preferences; however, large defects and revision cases are best closed by a middle fossa, extradural approach, sometimes with a combined mastoid approach. Smaller defects in more accessible areas of the tegmen and posterior fossa may be successfully closed via a transmastoid approach, with or without disarticulation of the ossicular chain. Numerous different materials, including autologous cartilage, temporalis fascia, fascia lata, and porcine- and bovine-derived artificial dura have been used. No superior results have been described with any particular material. If no hearing remains in the ipsilateral ear, consideration should be given to repair with a blind sac closure.[199] Rarely this may require the addition of a subtotal petrosectomy in those cases that violate the otic capsule.[200]

KEY POINTS

Post-traumatic CSF leaks

- CSF leaks complicate 11–33% of temporal bone fractures.
- Around 95% resolve spontaneously within 14 days.
- Large tegmen defects and persistent CSF leaks should be surgically closed to prevent meningitis.

RECURRENT LATE MENINGITIS AND MENINGOCOELE/ENCEPHALOCOELE

Despite spontaneous healing, recurrent CSF leaks and meningitis may occur, even many years after the primary injury. The diagnosis is often made when CSF is found in the middle ear when ventilation tubes are being inserted for an assumed middle ear effusion, or when a defect is noted on a CT scan performed prior to a lumbar puncture for meningitis.[133] MRI is indicated if there is a large defect, or if any suspicion of herniation of intracranial contents is seen on CT. Defects should be repaired and reinforced.

VASCULAR INJURY

Fractures of the bony canals of the internal carotid artery and sigmoid venous sinuses are relatively common but publications are sparse and mainly confined to the neurosurgery and neuroradiology literature. Those patients with worse injuries and a lower GCS are more likely to have a fracture involving the carotid canal.[201] Only 4% of skull base fractures result in vascular injury despite about a quarter of fractures entering the carotid canal. Sixty-two percent occur at the junction between its lacerum and cavernous portions (the spheno-occipital suture), and about 18% of these sustain a vascular injury. Fractures through the petrous segment are less common but carry a higher, 25%, risk of vascular injury.[201] Internal carotid artery dissection with carotid–cavernous fistula is a rare consequence.[193] Intimal damage resulting in aseptic sigmoid sinus thrombosis is rare (1 in 82 temporal bone fractures).[163]

A high index of suspicion is required in those patients with more severe skull base fractures, particularly if there is evidence of otic capsule fracture or cranial nerve palsies. The jugular and carotid canals should be routinely, and carefully, examined on the CT scan with a low threshold for requesting angiography. Examples are shown in **Figure 91.7**.

WHIPLASH INJURY

DEFINITION

This is indirect injury to the neck caused by an acceleration–deceleration incident resulting in a flexion–extension injury of the cervical spine. There is no direct trauma. Whiplash injury (or whiplash-associated disorder (WAD)) is the resulting functional impairment.[202] The term whiplash implies an amplification of relatively small forces into larger ones.

CLASSIFICATION

In 1995 the Quebec Task Force (QTF) produced a landmark consensus publication that provided a useful classification of these injuries into five grades, dependent on clinical symptoms and signs (**Table 91.3**).[202] Symptoms and signs should occur within 72 hours to be considered attributable to the whiplash trauma.[203, 204]

EPIDEMIOLOGY

The incidence varies greatly between 70 and 300 per 100 000 population.[202, 204] There are estimated to be more than one million new patients per year in the US. In the UK 250 000 patients per annum cost an estimated £3 billion[205, 206] with legal submissions occurring at a rate of about 150 per day. They increased by 268% in the year following the introduction of the compulsory use of seat belts.[205]

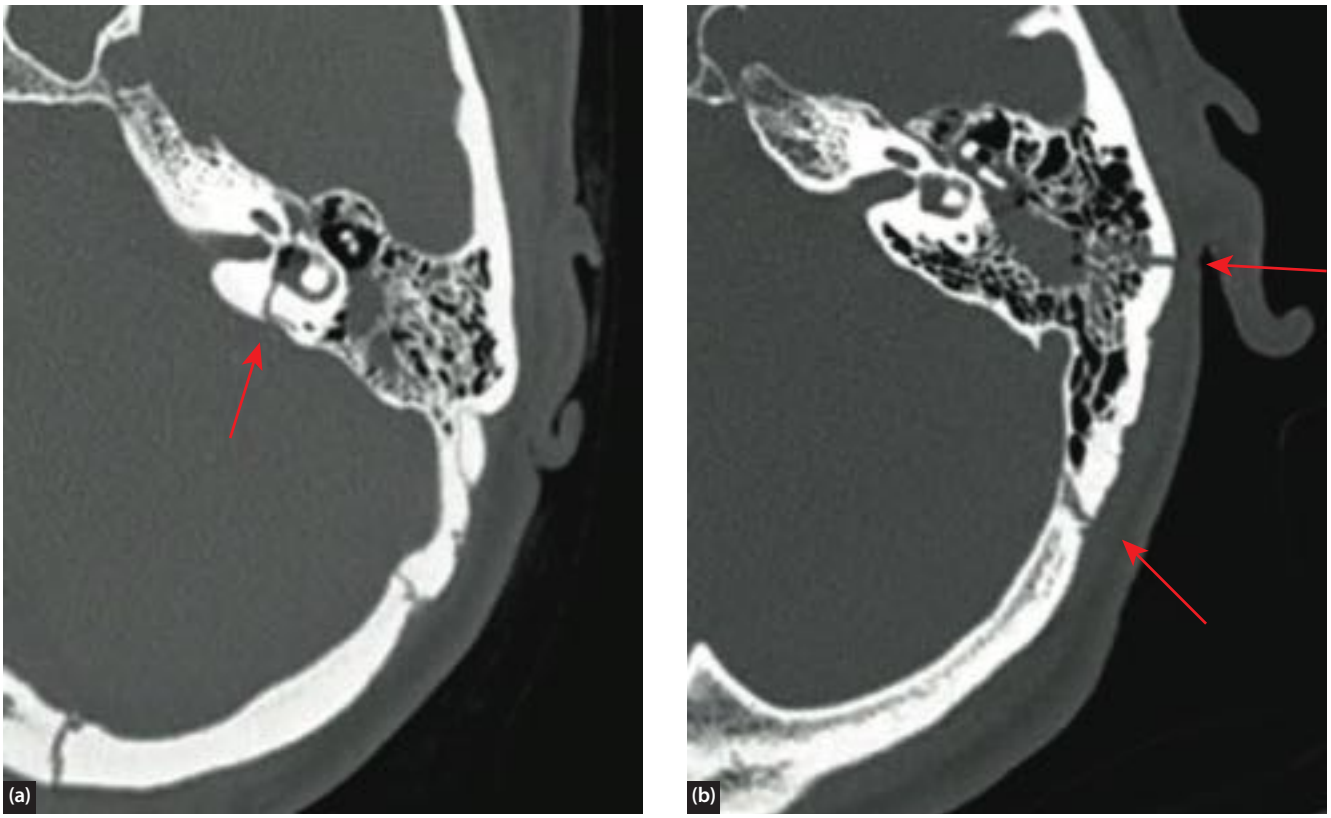


Figure 91.7 High-definition CT scans demonstrating (a) otic capsule-sparing and **(b)** otic capsule-violating fractures.

TABLE 91.3 Whiplash-associated disorder grading system after the Quebec Task Force conference

Grade	Symptoms and signs
0	Nil symptoms
I	Complaint of pain on motion, but no pain on physical examination
II	Complaint of pain on motion, with pain on physical examination
III	As grade II, but with neurological symptoms
IV	Fracture or dislocation

Adapted with permission from Spitzer et al.[202]

AETIOLOGY

Simulated accidents have shown that a 5 mph (8 km/h) rear-end car collision results in a positive acceleration of 8.3 G and 4.7 G of the head and chest, respectively. Below 3 mph (4.8 km/h) the difference between the displacement of the head and that of the chest is small or absent, causing no real whiplash movement of the head on the neck.[207, 208]

Despite what are clearly surprisingly large forces, the causes of many of the resulting symptoms remain unclear but incude soft-tissue neck trauma, skeletal spine damage and vascular or direct trauma to the spinal cord/brain stem or vestibular nuclei. Transient ischaemia or haemorrhage in the labyrinth as a result of transient compression of the vertebral artery, direct labyrinthine concussion, the noise of the collision causing acoustic trauma and psychological triggering of a pre-existing hearing disorder are also hypothesized.[177, 202]

CLINICAL FEATURES

General

Symptoms usually begin within 72 hours of the incident, the most common being neck pain and stiffness, with or without definite clinical signs such as tenderness or a decreased range of motion (grades I and II). Symptoms are shown in Table 91.4[204] and are similar to those reported in patients following head injury (see above).

Otological

In a study of 197 731 cases of whiplash 15–20% developed late whiplash syndrome with persistent complaints including headache, vertigo, instability, nausea, tinnitus and hearing loss.[209]

HEARING LOSS

Subjective hearing loss occurs in approximately 13%.[210, 211] Measurable hearing loss by pure-tone audiometry, in patients with grade I and II whiplash injury is at most rare and has not been confirmed by various studies.[212, 213] Some patients complain of hearing difficulties,

TABLE 91.4 Mild whiplash (grade I and II): most frequent symptoms experienced in the first week following injury

Symptom	Approximate prevalence (%)
Neck pain	94
Neck stiffness	96
Interscapular pain	35
Headache	44
Numbness/paraesthesia	22
Vertigo	15
Eye symptoms	12
Hearing symptoms	13
Sleeping problems	35
Memory problems	15
Signs of stress	30

Adapted with permission from Jansen et al.[204]

usually of poor speech discrimination, despite having a normal audiogram. A controlled 'speech in noise' study has shown demonstrable abnormalities in 30% of whiplash patients as compared to 5% of matched controls.[213] No study could be found associating the degree of whiplash injury to pure-tone audiometry findings or to audiological symptom scores. However, given the deceleration nature of the injury, it is reasonable to suppose that severe cases of whiplash (grade III and IV) may induce intralabyrinthine trauma similar to that found in head injury (see above). Therefore, any patient sustaining a whiplash injury who complains of hearing loss, tinnitus or vertigo should undergo a full neuro-otological assessment.

TINNITUS

Despite appearing in the list of acute symptoms, tinnitus does not appear to occur as a persisting symptom attributable to minor (grade I and II) whiplash.[212,213] More severe whiplash injury has many of the features of minor head injury, although no specific associations between audiological symptoms and whiplash-related disorders have been confidently identified.[204]

VESTIBULAR SYMPTOMS

The most common vestibular problem after whiplash injury is BPPV and it is usually a feature of more severe injury (grade III). Its management is as for the idiopathic condition (see Chapter 64, Benign paroxysmal positional vertigo).[214] As in BPPV following head injury, the condition may be more refractory to repositioning techniques requiring more treatments.[215]

Only 3.65% of those with low-grade (I and II) whiplash injury undergoing medicolegal assessment for otological and vestibular symptoms complained of non-specific dizziness symptoms in the acute phase following their original injury. Caution should therefore be exercised before attributing such symptoms to whiplash injury.[212]

TABLE 91.5 Guidelines for imaging in whiplash injury

Grade	Imaging
I	No X-ray examination **Exceptions:** Over age 65 years, concurrent skeletal disease (e.g. rheumatoid arthritis). History of neck surgery. Unsafe to examine
II	Plain X-ray or CT **Exceptions:** CT mandatory if any spinal nerve root or cord symptoms
III	CT Additional investigation with MRI often indicated

Adapted from Jansen et al.[204] and National Institute for Health and Care Excellence[218]

The nature and causes of the imbalance that often occurs in the late whiplash syndrome remains unclear. A study using electronystagmography only found abnormalities if there was a concomitant minor head injury. Posturography was, however, similarly positive in both groups, making a labyrinthine cause unlikely.[216] Comparative studies have found some evidence of vestibulopathy by VNG testing: 19% in whiplash (11% peripheral, 5% central, 3% indeterminable) compared to 60% in minor head injury.[217]

INVESTIGATIONS

Imaging

Indications depend on the clinical grade of whiplash injury (Table 91.5).[218]

Other tests

Audiometry should be performed as soon as possible in any patient complaining of hearing loss. Other tests are seldom necessary in the acute phase. Every attempt should be made not to overinvestigate as this may be linked to a poor outcome.[218] Neurophysiological tests should be reserved for use in those patients who do not make a full recovery.

TREATMENT

A Cochrane review was unable to support or refute the effectiveness of conservative treatments in grade I and II whiplash injury.[219] There is only limited evidence for mobilization strategies over immobilization collars.[218,220] In the acute phase of whiplash injury simple analgesics are recommended.[218] High-dose intravenous steroids given in the first 8 hours after injury decrease neck pain at 1 week but there was no difference in outcome at 6 months.[221,222] There is no strong evidence to support the use of any patient advice strategies.[223]

Hearing losses and tinnitus should be treated on their own merits. Dizziness, vertigo and imbalance have been shown to be effectively improved by vestibular exercises, even if differentiation between these vestibular symptoms

in various studies is unclear.[204, 224] The performance of vestibular rehabilitation exercises in patients with neck pain and limitation of neck movements is safe. Their symptoms and signs are correlated with their self-perceived dizziness handicap score.[225] Stress disorders, anxiety, sleeplessness and depression should be addressed to ensure optimum overall outcomes.[204]

PROGNOSIS

Mild (grade I and II) whiplash injury spontaneously recovers in 97–100% within 1 year.[202, 226, 227] Overall (grades I– IV) most patients recover within 8 weeks[202] but 14–50% develop WADs.[228, 229] It is possible that up to 50% of all patients have minor residual symptoms that may persist for as much as 2 years.[230] Degenerative changes seen on initial MRI scans all progress over 10 years but in over 50% of patients symptoms improve. There is no correlation between the progression of the degenerative findings and patient symptoms.[206]

Audiovestibular symptoms are uncommon initially (3.6–13%) and are expected to completely disappear within 5 months. Dizziness is, however, such a frequent complaint of more severe cases that the prognosis of this should be considered to be that of the overall condition.[212]

Systematic reviews strongly suggest that high initial pain intensity is the strongest indicator of a poor prognosis.[204, 218, 231] Other indicators are: the severity of the initial trauma, double collisions (rear-end followed by front-end collision), serious car damage, previous mental ill-health and a high grade of WAD.[206] Worse outcomes have been refuted in older patients, women, high acute psychological response, angular deformity of the neck, rear-end collision and compensation.[204, 231] The interactions between physical injury and an individual's pre-existing medical and mental condition significantly affect their illness behaviour. The worse the perception of the initial injury, the worse their neck pain at 1 month.[232] Despite most fully recovering within 2 months, not recovering by this time holds a worse prognosis. Likewise, if not resolved by 6 months, long-term difficulties are likely.

Controversy exists regarding the effects of seeking compensation, or malingering, on patient outcome. Studies from Lithuania and Greece, where there is no cultural expectation of compensation or of chronic disability, have excellent outcomes within 12 months. The very few patients with residual symptoms had them prior to their injury.[218, 226, 227] There is very little evidence to suggest that seeking compensation in itself is linked to the severity of patients' symptoms.[233] The resolution of legal cases, or the receipt of compensation, does not appear to improve outcomes.[234, 235] Ongoing research is investigating why countries such as Britain have such high numbers of claims.[236]

More high-quality research is required into the neuro-otological symptoms and outcomes following whiplash injury.

KEY POINTS

Whiplash injury

- Whiplash injury is extremely unlikely at speeds under 3 mph (4.8 km/h).
- There are persistent symptoms in approximately 20% of cases.
- Subjective hearing loss is seen in 13%.
- Objective hearing loss is rare and very rare, or absent, in grade I–II whiplash injury.
- Tinnitus is not a feature of grade I–II whiplash injury.
- Dizziness/vertigo is a rare complaint in grade I–II whiplash injury but common in more severe cases.
- Benign paroxysmal positional vertigo is the most common vestibular complaint.
- Around 97–100% of all symptoms in grade I–II whiplash injury recover within 1 year.
- Encouraging activity rather than rest and immobilization is recommended in patients with grade I–II whiplash injury.
- If vertigo or dysequilibrium is a symptom, vestibular rehabilitation should be provided. [Grade A]

OTITIC BAROTRAUMA AND OTITIC DECOMPRESSION ILLNESS

INTRODUCTION TO OTITIC BAROTRAUMA

'Barotrauma' is defined as an injury produced by mechanical forces caused by a change of pressure in a gas-filled space.[237] Otitic barotrauma, therefore, encompasses those pathological conditions of the ear induced by pressure changes. Severe cases occur from sudden large pressure changes, such as slap injuries typically sustained during an assault, when water skiing, high board diving and blast injury. Mild occurrences are common in airline passengers, scuba divers and in single-breath free diving.[237, 238]

The physics and pathophysiology behind most of the clinical entities are established. An exception is the exact role of 'bubbles' in the pathoaetiology of decompression illnesses. There is some temporal bone evidence for the various conditions described, but some of the pathophysiological explanations relating to the described inner ear conditions are incomplete. Most of the respiratory physiology, particularly relating to compression and decompression, and the fate of gases in the body, was established in the early 20th century by John Haldane.[239]

Pressure/volume relationships

The clinical conditions resulting from barotrauma are most easily described by considering the physiological events that occur during subaqua diving with scuba apparatus. Similar events occur during flight but, because of the lower pressures involved, the resulting barotraumatic injuries are usually less pronounced. Boyle's law describes the inverse relationship between the pressure of a gas and the volume it occupies (**Table 91.6**). Its importance is demonstrated by the relative bubble volume decrease observed

TABLE 91.6 Gas laws

Law	Detail	
Boyle's law	The volume (V) a gas occupies is inversely proportional to its pressure (P) at a constant temperature (T).	($V = k/P$, where k is a constant)
Dalton's law	The total pressure of a gas mixture always equals the sum of the partial pressures each gas would exert if it alone occupied the available volume.	($P_T = pP_1 + pP_2 + pP_3$ ..... pPn)
Charles's law	At a constant pressure the volume of a gas dissolved in a liquid is proportional to the temperature.	($PV = RT$, where R is a universal gas constant)
Henry's law	The amount of gas that will dissolve in a fluid, at a given temperature, is proportional to the partial pressure of that gas.	

TABLE 91.7 The effect of depth (seawater) on gas volume

Depth (m)	Atmospheres pressure	Pressure (kPa)	Volume (%)	Bubble (%) diameter
0	1	101	100	100
10	2	202	50	79.3
20	3	303	33	69.3
30	4	404	25	63.3
40	5	505	20	58.5
50	6	606	17	55

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with increased pressure (Table 91.7). The pressure increase with depth is a linear relationship of approximately 1 kPa for every 10 cm, while descent in air from 5500 m to sea level represents a pressure increase of only 0.5 atmospheres (50.5 kPa) (Figure 91.8). When diving, the largest percentage change in gas volume occurs during the first 10 m of descent (Table 91.7) (the first 1000 m of altitude for aviators), the ambient pressure doubling to 2 atmospheres and the corresponding gas volume being halved. This explains not only why a diver's impression of middle ear pressure change is maximal during the first 10 m, but also why the risk of developing otitic barotrauma is greatest in shallow dives or in low-flying, non-pressurized aircraft.

AMBIENT PRESSURE

The concept of ambient pressure is central to the understanding of the mechanisms involved. The external pressure is uniformly distributed over an object. In a system that has no air spaces within it, this pressure is transmitted equally throughout the structure. This is of particular relevance to the vasculature. If a large vein (e.g. the internal

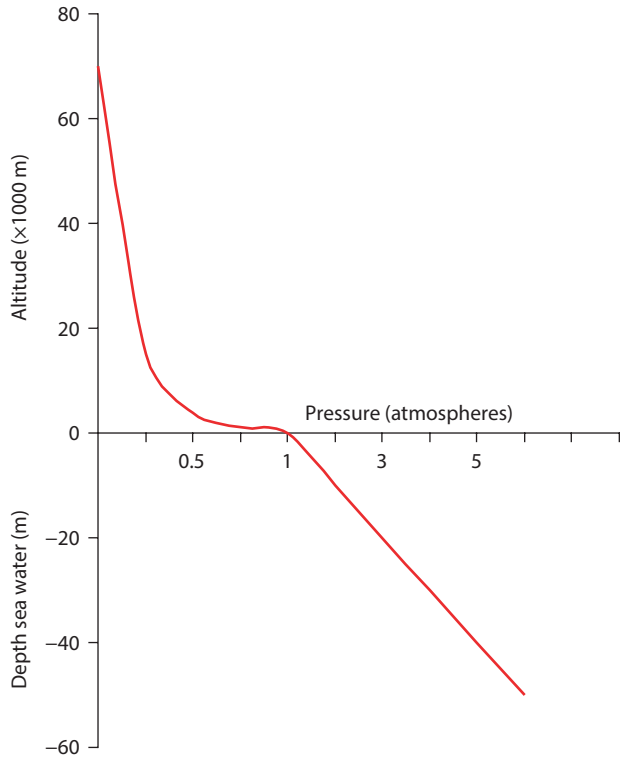


Figure 91.8 Altitude and depth versus pressure.

jugular) has pressure applied from the outside, provided that the whole body is submerged, it will transmit that pressure onwards. Head-out immersion causes a significant squeezing of blood volume from the lower limbs into the chest and into the head causing an increasing cardiac output and raised intracranial pressure with headaches.[238, 240] In the diver, or aviator, the pressure is equally applied to all body structures, there is no differential pressure across any membranes or systems so function is essentially unchanged. The exception, however, is when there is an air-filled cavity within the body. As the middle ear is a bony cavity, no distension or expansion is able to take place. The vasculature within the wall of the middle ear is, however, in continuity with that of the rest of the body, and therefore the intraluminal vascular pressures reflect the ambient pressure. If there is a relatively negative middle ear pressure due to a failure to equalize via the Eustachian tube, then there will be an increasing difference between the intraluminal vascular pressure and the middle ear pressure. If a sufficient gradient exists, then oedema and even rupture of those vessels within the mucosal lining will occur.

PHYSIOLOGICAL CONSEQUENCES OF COMPRESSION (DESCENT)

Figure 91.9 illustrates a diving model whereby the external auditory meatus is separated from the middle ear by the tympanic membrane, with the Eustachian tube connecting the middle ear cavity with the nasopharynx. During breathing, the nasopharynx is filled with inspired air from a compressed air cylinder via a regulator. This air pressure is equilibrated, by the regulator in the mouthpiece, to be equal to the ambient external pressure, provided the diver continues to breathe normally. As the diver descends, the ambient pressure increases. The middle ear pressure becomes increasingly negative compared to the ambient pressure unless equalization via the Eustachian tube takes place. This occurs by the voluntary action of the tensor and levator palati muscles opening the usually closed tube.[241] If the Eustachian tube cannot be opened effectively, the equalization of the pressure within the middle ear space with that of the external ambient pressure cannot occur. The relatively negative pressure within the middle ear will increase with further descent, resulting in a pressure differential across the tympanic membrane, which is therefore pushed inwards by the external ambient water pressure. This stretching is perceived as a sensation of external pressure and discomfort, which stimulates further attempts at equalization. If this does not prove possible, then the diver should return towards the surface to decrease the pressure gradient, thereby improving the ability to equalize. If this is not done and descent continues, then middle and inner ear barotrauma may occur.

The perception of the requirement to equalize occurs at a maximum of 86 cm (2.6 ft) reflecting a pressure change of only 8.7 kPa (60 mmHg). At this pressure, if no equalizing manoeuvre is performed, then mucosal congestion and oedema will occur. This is because the ambient pressure is reflected in the vasculature of the middle ear. This increases the transmural pressures, thus increasing transudation. Continued descent results in 'Eustachian locking', which occurs at a pressure difference of about 13 kPa (90 mmHg), an equivalent depth of approximately 1.3 m (3.9 ft).[242, 243] At this pressure, the power of the levator palati muscles is insufficient to voluntarily overcome the external closing pressures. Should this situation occur, middle ear barotrauma will follow. If the pressure gradient across the tympanic membrane is large, and occurs before the middle ear fills with an effusion or blood, then the tympanic membrane may rupture. If this occurs in one ear only, then a sudden influx of cold water into the middle ear may result in unequal thermal stimulation inducing a rigorous caloric vertigo.

The pathoaetiology of inner ear barotrauma is illustrated in Figure 91.9. The perilymphatic space is separated from the middle ear by the oval and the round window membranes. Alterations in intracranial and corresponding CSF pressures may be transmitted to the inner ear fluid compartments via the cochlear and vestibular aqueducts. If the diver or aviator fails to equalize his middle ears, then the pressure within the external ear canal will cause the tympanic membrane to be pushed inwards with a resultant inward force on the stapes footplate via the ossicles. This causes a corresponding bulging of the round window membrane into the middle ear space. The pressure gradient is also increased by the ambient pressure of the spinal fluid transmitted through the aqueducts to the inner ear fluids, this pressure being relatively positive compared to the middle ear pressure. Sufficient pressure by these mechanisms alone may be generated to cause round window membrane rupture; however, a forced Valsalva manoeuvre would certainly increase the intracranial, and therefore CSF, pressures by up to three times

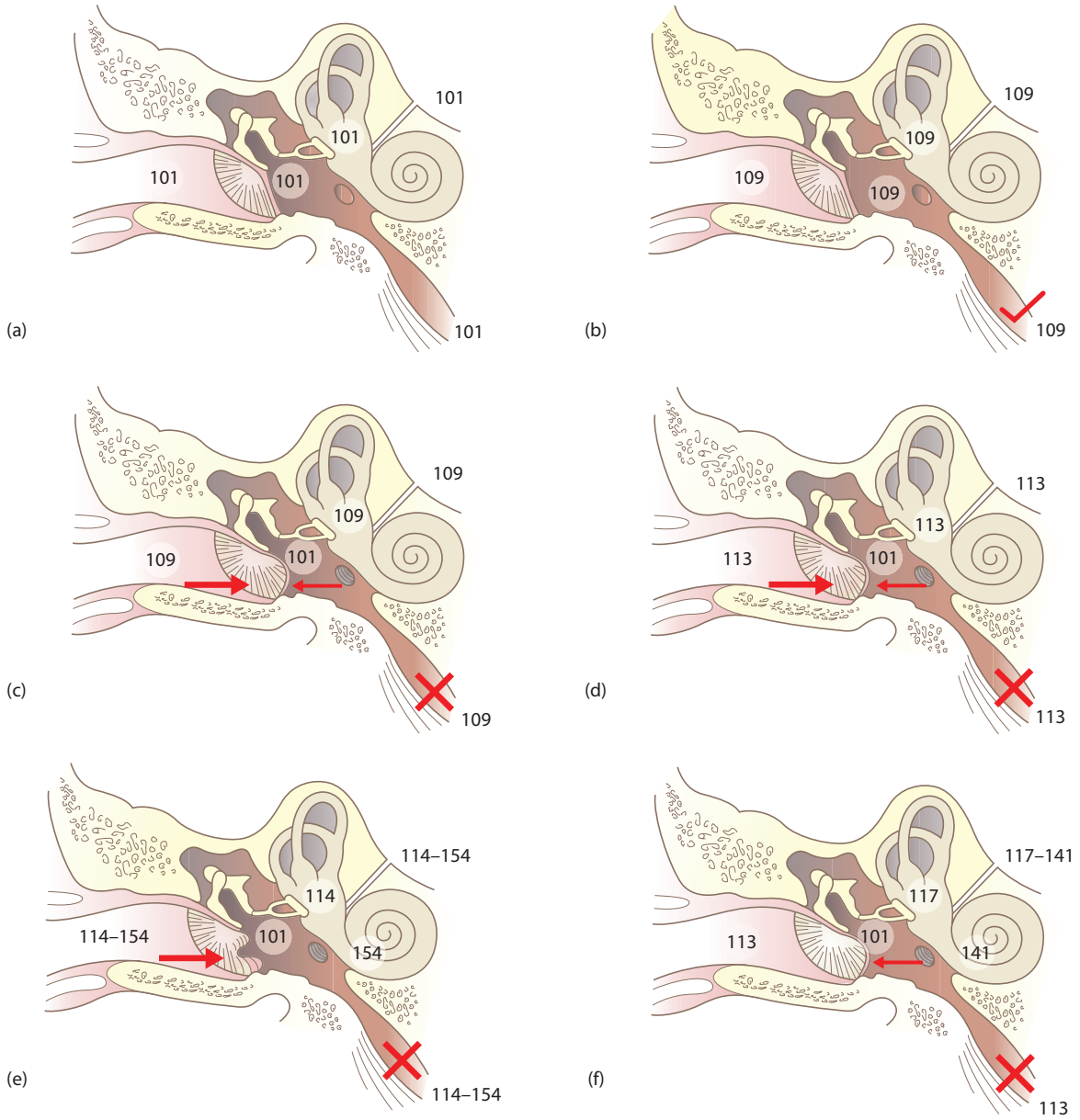


Figure 91.9 Otitic barotrauma on descent: theoretical pressure changes (kPa) and potential pathology. **(a)** Equal pressures on surface (sea level). Actual inner ear perilymph pressure is really slightly higher than ambient pressure. **(b)** Normal equalization with descent. **(c)** Depth 0.86m and pressure difference of 8 kPa, bulging tympanic membrane and round window into the middle ear. **(d–f)** Blocked and locked Eustachian tube. **(d)** 1.29 m with 12 kPa pressure difference. **(e)** Tympanic membrane ruptures at variable pressures. **(f)** Forced Valsalva increases CSF and perilymph pressure resulting in round window rupture. Adapted with permission from Farmer JC, Thomas WG. Ear and sinus problems in diving. In: Strauss R (ed.). *Diving medicine.* New York: Grune and Stratton; 1976.

that of normal. Studies in cats have demonstrated that the round window will rupture at pressure gradients of between 16 and 40 kPa (120–300 mmHg).[244] A perilymphatic fistula may therefore be expected to occur at the oval or round windows due to these implosive, or explosive, forces.[245] It is possible that these events are more likely to occur in patients with a congenital weakness of the annular ligament, or in those who have had stapes surgery, chronic middle ear disease, or perhaps have congenitally large cochlear or vestibular aqueducts.

PHYSIOLOGICAL CONSEQUENCES OF DECOMPRESSION (ASCENT)

If normal equalization of the middle ear pressures has occurred during descent, then the middle ear pressure is equal to that of the surrounding ambient pressure. During subsequent normal ascent, as the middle ear pressure exceeds that of the ambient pressure, passive ventilation of air through the Eustachian tube into the pharynx occurs.[246] When flying, this is normally every 13.25 m (43.5 ft) of ascent, regardless of the speed

of decompression.[247] If both Eustachian tubes are functioning correctly, the only conditions experienced on ascent are decompression illnesses.

During a diver's descent (or, for the aviator, during the previous flight), mild middle ear barotrauma may occur due to suboptimal Eustachian tube function, resulting in mucosal oedema and possibly haemorrhage. As a result, the usual passive ventilation, which should occur during subsequent ascent, can no longer take place. To continue ascending in these circumstances would result in a relatively positive middle ear pressure (**Figure 91.9**) compared to the ambient pressure, causing an outward bulging of the tympanic membrane. By similar mechanisms to those described during descent, the reverse effect on the oval and round windows may be seen. The tympanic membrane is pushed outwards and a traction force is applied to the oval window via the ossicles. This is accompanied by an inward force on the round window membrane. The pressure gradient is increased further as the perilymphatic pressure, reflecting the ambient pressure, has decreased with ascent. It is possible, therefore, for perilymphatic fistulae to occur during this phase of a dive. A sudden outflow of air down the Eustachian tube is sometimes described, immediately followed by the symptoms and signs of a perilymphatic fistula.

Clinical features

The manifestations of otitic barotrauma may be conveniently divided into the following three categories, which are discussed below:[248]

- compression injuries
- injuries at high pressure
- decompression injuries.

COMPRESSION (DESCENT) INJURIES

External ear barotrauma (external ear squeeze, reversed ear, reverse ear squeeze)

This occurs when a pocket of air is trapped within the external auditory meatus by cerumen, earplugs, foreign bodies or exostoses, although it is usually due to the wearing of a tight-fitting diving hood. The insertion of occlusive earplugs during aircraft descent is an uncommon cause.

If Eustachian tube function is normal, then, with increasing compression, the pressure of the trapped meatal air becomes negative compared to that of the middle ear and the external ambient pressure. As a result, the pressure gradient across the tympanic membrane results in it being displaced outwards. If with sufficient force, perforation may occur.

The main symptom is of pain, increasing with depth. The ear canal skin and tympanic membrane become injected and petechial haemorrhages, and bleeding, may be observed. The immediate remedial action is to decompress by ascending. If relevant, the diving hood should be adjusted or modified and the meatus cleaned, preferably by microsuction. The ear should be kept dry and diving avoided until the skin appears normal and the causative factor is addressed. Occlusive earplugs should be avoided when diving to more than 1.5 m and when flying.

KEY POINTS

External ear barotrauma

- External ear barotrauma involves a trapped air pocket in the external meatus.
- Pain increases in proportion to compression.
- There are tympanic membrane features as for middle ear barotraumas.
- **Prevention:** avoid occlusive earplugs and headgear.
- **Treatment:**
  - clear external meatus of blood/wax debris
  - use antibiotic drops for secondary infection
  - surgically repair any perforation if spontaneous healing fails
  - consider exostectomy.
- **Advice:** complete resolution should be observed and the causative factor corrected prior to further flying/diving.

Middle ear barotrauma (barotitis media, middle ear squeeze)

Middle ear barotrauma is the most frequent pressure-induced ear condition and may occur wherever there is Eustachian tube dysfunction resulting in a transtympanic pressure gradient.[249] Commercial flights, scuba and free diving, rollercoaster rides[250] and hyperbaric therapy are common causes. Transient evidence of middle ear barotrauma has been demonstrated in 5% of adults and 25% of young children after flying.[251]

CLINICAL FEATURES

Predicting who might be at risk during flight is difficult. Tympanometry is unhelpful as it is usually normal. Many people who have no problems with their ears when flying cannot voluntarily equalize their middle ear pressures. The sensation of equalization when performing the Valsalva manoeuvre has a poor (0%) predictive value for potential barotrauma. The Toynbee test has a positive predictive value of 25%. A nine-step inflation/deflation tympanometric Eustachian tube test has a much better chance of accurate prediction (25% positive predictive value, 75% negative predictive value).[252] Reliable (100%) predictive results have been obtained by combining the nine-step test with the Toynbee test.[253] Studies have correlated poor mastoid pneumatization with an increased chance of developing middle ear barotraumas. When estimating mastoid area by the simplified rectangular method, no patients with a mastoid area greater than 34.7 cm^3 sustain barotrauma, whereas those less than 13.6 cm^2 suffer from it.[254, 255]

For diving, the inability to 'equalize' by performing the Valsalva manoeuvre is a useful guide. Those unable to equalize both ears have a 91% chance of developing middle ear barotrauma compared with only 37% of controls.[256] Sonotuberometry and tubotympanometry have been suggested in an uncontrolled study, as methods that may accurately predict those who will develop middle ear barotrauma.[257] The speed of descent appears to be an important factor. The faster the compression, the less opportunity exists for equalization, especially if the person is distracted, working or asleep, particularly during the aircraft's descent.[258]

Initial symptoms are the sensation of a blocked ear and a strong desire to equalize. Progressive otalgia results with increased compression and there is an inability to equalize. An initial minimal conductive loss is due to the decreased compliance that results from the transtympanic pressure differential. The development of a middle ear effusion will follow quickly if the middle ear vacuum effect is maintained. This has been confirmed experimentally by introducing carbon dioxide into unilateral ears in monkeys, which results in the development of rapid negative middle ear pressures ('underpressure'). Subsequent MRI scans showed that the contrast leaked into the middle ears readily in those with induced negative pressure, but not into the control ears.[259] Mucosal oedema predictably occurs, even in those with normal Eustachian function, after repeated or long duration dives.[260] The increasing pressure differential may result in a perforation of the tympanic membrane and this is characterized by sudden severe pain. If diving, a sudden ingress of water into the middle ear may result in caloric vertigo (see 'Caloric vertigo' below). Severe middle ear barotrauma may also result in ossicular damage. Larger conductive losses may be observed with damage to the stapes footplate,[261] incus dislocation[262] and even a fractured malleus handle.[95, 263]

Examination of the tympanic membrane will reveal changes varying from a normal appearance (with mild symptoms), to free haemorrhage with a tympanic membrane perforation. These changes have been classified (**Table 91.8**)[264] and are a modification of Teed's four-grade classification.[265] Pure-tone audiometry and tympanometry are minimum investigations, a conductive hearing loss with decreased compliance and a negative middle ear pressure being expected. These tests should be used to monitor resolution in more severe cases. A treatment regimen has been suggested on the basis of a three-level clinical classification of severity.[242]

- Type 1: When there are symptoms of middle ear barotrauma, but no (or minimal) signs, no specific treatment is required.
- Type 2: When significant signs are present, but no perforation, conservative treatment is indicated with either oral or topical nasal decongestants.
- Type 3: Where there is middle ear barotrauma with perforation, an initial observation period is recommended with cleaning of the affected ear if necessary.

A myringoplasty is indicated in those cases that fail to heal spontaneously. Patients should be advised to await complete resolution of their symptoms before they return to diving or flying. Although Farmer's recommendations are of Grade C, and not specifically evidence-based, they are the result of a wide clinical experience, and are logical and consistent with established practice. As perforations secondary to middle ear barotrauma are usually found in otherwise healthy ears, the surgical results should be better than in cases following otitis media.

TABLE 91.8 Tympanic membrane appearance in middle ear barotrauma

Grade	Symptoms and signs
0	Symptoms, no signs
1	Redness and retraction
2	Intratympanic membrane haemorrhage
3	Gross tympanic membrane haemorrhage
4	Haemotympanum
5	Perforation

PREVENTION OF MIDDLE EAR BAROTRAUMA

Medical

High-quality RCTs have shown a strong effect for oral pseudoephedrine in the prevention of barotrauma when flying but not for topical xylometazoline.[266, 267] Similar results have been found in scuba divers.[268] No significant difference was found in the occurrence of otalgia between two groups of children under 6 years taking oral pseudoephedrine or placebo.[269] The use of oral psudoephedrine is recommended before flying, in those with mild Eustachian symptoms. This advice should not, however, be extended to scuba divers with acute Eustachian dysfunction due to the larger risk of middle ear barotrauma and the greater potential consequences of it.

Slowing down the rate of change of pressure is beneficial. The use of occlusive earplugs when diving or flying is contraindicated due to the risk of external ear barotraumas; pressure-equalizing earplugs are currently sold at many airports, but their benefit remains unproven. Small studies have suggested no benefit,[270] or possibly even an increase in the incidence of barotrauma.[271] A recent small double-blind, controlled pressure chamber study does, however, suggest that a 7-minute delay in the time taken to equalize the external ear canal pressure may be achieved, and that despite no measurable improvement in Eustachian tube function, symptoms are significantly improved. Slower rates of compression when delivering hyperbaric treatments may decrease the frequency.[272]

The use of nasal balloon inflation (auto-Politzerization) using Otovent™ (Abigo, Sweden) may be helpful in improving the ability to equalize by those who have difficulties performing equalization manoeuvres.[251]

Surgical

Performing myringotomies (often as a simple local anaesthetic procedure), and the insertion of ventilation tubes, may be appropriate for preventing otalgia and middle ear barotrauma in those wishing to fly. This procedure is clearly contraindicated for diving.

Eustachian tube balloon dilatation (balloon Eustachian tuboplasty) is gaining popularity and may become the treatment of choice, particularly for those who suffer from equalization difficulties flying.[273]

EUSTACHIAN TUBE DYSFUNCTION AND NASAL SEPTAL DEVIATION

The role of the nasal airway and nasopharynx in Eustachian tube function is complex and has been the subject of much research. There is, however, little knowledge regarding the effect of nasal surgery on the ability to equalize middle ear pressure. Only one controlled study has been attempted where posterior septal surgery considerably increased the ability to equalize to 10 m as compared to controls.[273] The author's experience is in marine biology students or commercial divers, who stand to lose their careers or licences because of inability to equalize their middle ear pressures. Despite some success, caution is advised, especially in those with minimal septal anomalies. More validation is required regarding the efficacy of this procedure.

DIVING AND FLYING AFTER MIDDLE EAR SURGERY

There are no specific data that precisely identify a 'safe' post-operative period after which it is safe to fly. Following reconstructive surgery most surgeons advise a restriction of any activity which might result in a sudden change in the middle ear pressure, for several weeks. Tympanic membrane grafts and ear canal healing should be complete before water sports are resumed, and flying should not be permitted until any aural packs are removed and healing verified. Slap injuries following stapes and total ossicular replacement surgery may be prevented by the use of earplugs. Evidence of adequate Eustachian function should be obtained prior to resuming diving or flying. Scuba diving after stapes surgery remains controversial and there are no good studies addressing this. Some patients insist on continuing with the sport and report no difficulties.[274] Animal experiments have shown no significant increase in inner ear barotrauma after stapedectomy when compared to control ears.[275] Safe diving should be possible in those post-tympanoplasty patients whose Eustachian function appears adequate.[249] If, however, it is poor, given the mechanisms of fistula formation, it is likely that particularly those who have undergone stapes surgery are at an increased risk of a perilymphatic fistula and even prosthesis displacement. As there are potentially fatal consequences of a perilymphatic fistula when diving, pursuing this after stapes surgery is considered by many to constitute an unnecessary risk. If patients are insistent, strict advice regarding Eustachian function and a post-operative wait of 6 months is recommended.

KEY POINTS

Middle ear barotrauma

- Middle ear barotrauma is very common during flight and scuba diving.
- The perceived ability to 'equalize' is a useful predictor for diving, but not for flying.
- Speed of compression is an important risk factor.
- Conductive hearing loss is usual.
- Oral pseudoephedrine and Otovent™ balloon may be effective preventative measures.
- Surgical repair of the tympanic membrane and even ossicles may be necessary.
- Nasal septal (vomeroethmoidal) surgery may improve the ability to 'equalize' middle ear pressures.
- Consider Eustachian tube balloon dilatation.
- **Prevention:**
  - oral decongestants [Grade A]
  - Otovent™ balloon
  - consider Eustachian tube balloon dilatation
  - no flying or diving with upper respiratory infections
  - identify those at risk
  - asymmetric equalizers
  - inability to voluntarily equalize at sea level (divers)
  - nasal obstruction.
  - treat nasal conditions
  - consider septal surgery
  - myringotomies/ventilation tubes for flying.
- **Diagnosis:**
  - obtain specific history: pain on descent
  - otoscopic appearance (Table 91.8)
  - audiometry: conductive loss.
- **Treatment:**
  - conservative/symptomatic initially
  - elective repair of the tympanic membrane and/or ossicles
- **Advice to patients:**
  - complete resolution is expected in mild cases
  - scuba adiving is contraindicated if problems persist
  - oral decongestants are helpful before flying/diving. [Grade A]

CALORIC VERTIGO

Asymmetrical contact of cold water with both tympanic membranes, or cold water ingress into one middle ear via a perforation, may result in a caloric effect. Causes include wax, exostoses, otitis externa, tight diving hoods, leaking earplugs or a foreign body in the external meatus. It is usually short-lived and mild. Cold water ingress through a tympanic membrane perforation may give severe symptoms. The colder the water, the more pronounced is the effect. On surfacing, the caloric stimulus is removed and the vertigo is self-correcting.

A history of Eustachian tube dysfunction may be present and examination may reveal a perforation or impacted ear wax. No residual audiological nor neurological signs or symptoms should be present after surfacing.[264]

KEY POINTS

Caloric vertigo

- Caloric vertigo involves the asymmetric exposure of each ear to cold stimulus.
- It is short-lived and self-correcting.
- It is very common in mild forms.
- There are no residual audiological or neurological symptoms or signs.

Inner ear barotrauma (compression inner ear barotrauma)

The pathophysiological mechanisms have been described above (see 'Physiological consequences of compression'). Histopathological studies have demonstrated three different pathological entities in the inner ear resulting from compression barotrauma:

- inner ear haemorrhage
- labyrinthine membrane tears
- perilymphatic fistula.

Various clinical matches have been proposed to explain the corresponding distinct patterns of presentation seen in temporal bone specimens.[276]

INNER EAR HAEMORRHAGE

This gives transient, or minimal, vestibular symptoms and mild to moderate sensorineural hearing loss. A good recovery is expected.

LABYRINTHINE TEARS

Tears of the labyrinthine membrane may produce similar symptoms, but any loss is permanent, often at 1–2 kHz. Patients may present with symptoms closely resembling those of an acute Ménière's disease attack, with vertigo and tinnitus, complete with the characteristic low-frequency hearing loss. Temporal bone studies have demonstrated Reissner's membrane rupture.[277] Similar occurrences have also been shown in airline passengers, either with or without labyrinthine window rupture.[278] Temporal bones from divers who died under such circumstances showed bleeding into the middle ear and mastoid. Inner ear damage consisted of haemorrhage around Reissner's and the round window membranes, as well as rupture of the utricle and saccule.[279] Implosive forces to the inner ear due to middle ear overpressure (occurring on ascent with a locked Eustachian tube) may cause more severe inner ear trauma than the more commonly occurring barotrauma on compression (descent).[280]

PERILYMPHATIC FISTULA

The diagnosis and management of perilymphatic fistula generates considerable debate. The condition was first recognized in aviators, although it has became of great interest in diving medicine.[281, 282] Detailed descriptions of labyrinthine window ruptures and inner ear trauma associated with inadequate middle ear pressure equalization were published in the early 1970s.[283, 284] Perilymphatic fistula is a well-recognized consequence of head injury, surgery, congenital anomalies, cholesteatoma and neoplasia. Spontaneous fistulae possibly occur, without any recognized aetiological factors, although controversy surrounds both their existence and management.[285–287] As many as 0.5% of divers have suffered from a perilymphatic fistula.[288]

Clinical features

The exact timing of the onset of symptoms relative to the injury is the single most helpful piece of clinical information. The dive profile is important for scuba divers and this will also assist in deciding if the dive was one from which a decompression illness could reasonably result (see below). The time of onset of these symptoms is usually definite in aviators but may only be recognized on surfacing in divers. A typical history is of difficulty equalizing the middle ear pressure during descent, particularly during an upper respiratory infection, resulting in a rigorous Valsalva manoeuvre being attempted. There is a sudden onset of vertigo, an accompanying hearing loss (sensorineural or mixed) and often tinnitus.[289] Muffled hearing and occasional, but persistent, dysequilibrium may be the only symptoms. Any acute symptoms often resolve rapidly after several days, although mild dysequilibrium (which may change to transient vertigo on straining), mild persistent nausea and motion intolerance, often with a subtle sense of 'not coping', are the most common symptoms of a chronic perilymphatic fistula. Fluctuating hearing is typical.

A perilymphatic fistula should be suspected in an otherwise healthy ear (or in one with evidence of middle ear barotrauma) if there is a sensorineural hearing loss of rapid onset, constant or intermittent dysequilibrium, positional nystagmus, Tullio phenomenon, a positive fistula sign and tinnitus. The main differential diagnosis is of inner ear decompression illness (**Table 91.9**). It is an important distinction as recompression in error may cause further middle and inner ear barotrauma. Conversely, not recompressing a patient with a decompression illness may result in permanent cochleovestibular damage, further progression of the decompression illness and even death.

Clinical signs

Examination of the tympanic membrane may reveal signs of middle ear barotrauma (see **Table 91.8**) but, unless it is an acute presentation, the appearance is often normal. A full neurological examination, including of the cranial nerves, should be performed. Nystagmus may be present, usually towards the contralateral side, but this may disappear over a few days as symptoms of vertigo often give way to the more typical dysequilibrium. The Romberg test is normal in more mild cases and, if it is possible to perform the Unterberger step test, this often yields a positive result. The 'side-step' test, a modification of the Singleton 'side-step turning test'[290] has been described, and has promising results.[291] With the eyes closed, the patient takes two consecutive broad steps sideways, and then stops with both feet together. A subsequent sway or overshoot in the same direction as the steps were taken is regarded as a positive result, the affected ear being on the side towards the direction of movement. Dix–Hallpike tests for positional vertigo are often positive but often do not give the typical results for BPPV. The nystagmus may be difficult to identify, is not usually rotatory and is often not towards the downward ear. The latency may be short or absent with little sign of any fatigability.[292]

TABLE 91.9 Differential diagnosis of inner ear barotrauma and labyrinthine decompression illness

	Middle ear barotrauma	Inner ear barotrauma	Inner ear decompression illness
Phase of dive/flight symptoms first noticed	Usually descent, possible on ascent (reverse squeeze)	Usually descent; may occur on ascent, or just after surfacing (<10 min)	Only during or after ascent; usually after surfacing; more likely near surface
Difficulty equalizing middle ear pressure	Yes	Yes	Not usual
Associated middle ear barotrauma	N/A	Usual	Not usual
Associated non-otological symptoms	None	None	Usually other symptoms of decompression illness
Vertigo	None	Usual	Usual – dysequilibrium may predominate
Sensorineural hearing loss	None	Frequent	Frequent – may be difficult to ascertain
Effect of recompression on symptoms	Worsened	Worsened	Improvement
Hearing loss	Conductive loss	Mixed loss – common (85%)	SN loss (38–66%)*

*Nachum et al.[345]

Investigations

The larger the fistula, the more likely are the clinical signs, and any special investigations, to be positive. Baseline pure-tone audiometry should be performed as soon as possible. Fistula tests are unreliable. An improvement in pure-tone thresholds when lying for 30 minutes compared to sitting (Frazer test), and external auditory meatus pressure change fistula tests using a Siegel's speculum, are only positive in 25–40% of surgically proven fistulae.[293, 294] Improved results (being positive in 90% of proven cases) have been obtained when using accurate pressure stimulation with tympanometry in conjunction with electronystagmographic recordings. The results, however, include fistulae from other causes, such as temporal bone trauma, post-surgical and congenital.[294] Unfortunately, it is the more subtle presentations, with smaller or intermittant fistulae, that cause the diagnostic uncertainty. In an attempt to address this, extensive studies utilizing transtympanic electrocochleography with tone-burst stimuli to confirm the presence or absence of surgical, post-traumatic and spontaneous fistulae have been performed.[295] Despite reasonable validation during stapes surgery, this method of investigation has not gained popularity. High-definition MRI and CT scans may prove useful. Their use may assist making the diagnosis, but the predictive value is unknown and probably low overall. The results of radiological investigations therefore should be considered only in the context of other clinical findings. Features which may be seen include intralabyrinthine air,[296, 297] fluid in an otherwise non-diseased mastoid or middle ear, and fluid in the round window niche on T2-weighted MRI.[298] Confirmatory tests at the time of surgery are considered below.

Treatment

Treatment options are based on hearing and balance restoration and preservation. Opinions vary between a conservative, expectant strategy and surgery. The results of hearing conservation and salvage are poor. This is probably because of frequent diagnostic delays that contribute to the permanence of any sensorineural hearing loss. For this reason, immediate surgery in all suspected cases has been advocated by some.[299] This approach clearly does not allow any time for spontaneous closure to take place. Many prefer an initial conservative approach, including bed rest for a minimum of 5 days. Exploration is then reserved for (i) those with progressive hearing deterioration observed on daily, or more frequent, audiometry, (ii) failure of the vestibular symptoms to improve after 5 days, (iii) failure of complete resolution after 1 month.[292] In reality there is a range of severity of the presenting symptoms and signs so, in the absence of definitive trial results, a pragmatic approach is suggested. This should be dictated by the observations that surgery seldom improves a hearing loss, although it may stabilize it, and that dysequilibrium is well treated, but the timimg of surgery for this indication is relatively unimportant. The initial management should therefore be dictated by the severity of the hearing loss. The following treatment strategies assume that a typical presentation of hearing loss with imbalance has occurred.

Moderate to severe hearing loss The overall picture is inevitably influenced by the time taken for the patient to present to the otologist. Emergency exploration is of relevance in more severe acute cases with both a significant sensorineural hearing loss and vertigo (30–40 dB HL or worse). Given the overall poor prognosis for hearing, there is no advantage in delaying and immediate exploration is therefore recommended.

Minimal hearing loss (high-frequency only, or mean 20 dB HL loss) Many patients with inner ear barotrauma do not have an obvious history and findings consistent with a perilymphatic fistula. For those with more mild sensorineural hearing losses and vestibular symptoms, an initial conservative approach is reasonable. Bed rest is

advised, with elevation of the bed head to 30–40 degrees. Raising the intracranial pressure by coughing, straining, vomiting or performing the Valsalva manoeuvre should be avoided. This is also recommended as the initial management of all cases where there is any suspicion of a perilymphatic fistula, while deciding on further action. Steroids are often prescribed, despite the lack of evidence for their use, particularly when a presumed diagnosis of an intralabyrinthine haemorrhage or tear is supposed. An initial conservative approach has become more favourable as surgical exploration appears to treat vestibular symptoms more effectively than it does improve the sensorineural hearing loss.[300] This may be because some of those reported may not have had fistulae, but intralabyrinthine pathology only. Patients should have daily audiometry performed and this should be repeated immediately if there is any subjective deterioration. If confirmed objectively, surgical exploration should be performed without delay.

Mild to moderate hearing loss (20–40 dB HL) If presentation is less than 24 hours following the event, and vestibular symptoms and signs predominate, then immediate exploration is appropriate. After 24 hours, the need for exploration should be judged predominantly on serial daily, or more frequent, audiometric findings. An ear with evidence of deteriorating hearing should always be explored, without waiting until the next day to validate the deterioration. If the hearing has spontaneously improved, it is reasonable to wait for 5 days before exploration for persistent vestibular symptoms; if there is no hearing loss, a conservative strategy may be followed for up to 4 weeks. Once stable good hearing has been verified, this may be at home provided that rest and the above-mentioned precautions are observed. Some surgeons do not perform surgery before 2 weeks have passed as spontaneous resolution is often encountered. The earlier the presentation with hearing loss, the worse the hearing loss, and the worse the vestibular component, the stronger is the indication for urgent surgery.

Despite a trend towards a conservative approach, several other issues should be considered. An exploratory tympanotomy should present very few surgical risks if performed by a specialist otologist in an otherwise medically fit patient.[301] There is little evidence to support either the conservative or aggressive surgical strategy but deterioration is necessarily a retrospective finding. The overall morbidity, inconvenience and cost of 2 weeks or more of bed rest are often ignored. Overall, a low threshold for exploration is recommended.

Future studies

The identification of idiopathic perilymphatic fistula remains controversial.[287] However, it is unlikely that any further significant progress will occur until a reliable marker of perilymph (possibly cochlin-tonoprotein) is identified and studies on those patients with sudden hearing loss and vestibular symptoms, without a suggestive fistula history, are performed.

Acute sensorineural hearing loss without vestibular symptoms

A sudden hearing loss may occur in the absence of any vestibular symptoms. An isolated intracochlear decompression illness is the main differential diagnosis, so the appropriate history, including middle ear symptoms associated with inner ear barotraumas, must be sought. An intracochlear haemorrhage is the probable aetiology and this may be apparent on MRI. Despite a lack of convincing evidence, oral or intratympanic steroids should be considered for patients with moderate and severe losses (see Chapter 60, Idiopathic sudden sensorineural hearing loss). An immediate tympanotomy would be difficult to justify unless serial audiometry suggests fluctuating hearing without overall spontaneous improvement. In those cases where there is a dead ear, alternative pathologies require exclusion (see Chapter 60, Idiopathic sudden sensorineural hearing loss).

Care should be taken that all patients are followed up, as cases of perilymphatic fistula presenting with chronic dysequilibrium are encountered many months or even years after the event.

Surgery for perilymphatic fistula

Numerous series and case reports have been published covering a broad spectrum of aetiologies, usually post-trauma or congenital fistulae in children.[300, 301] A standard tympanotomy is performed but care must be taken to avoid mucosal damage. Identification of the site of the fistula is notoriously difficult. It may be useful to place the patient in a head-down position and increase the ventilatory pressure. Unfortunately, this also encourages bleeding, which may further increase the degree of uncertainty.

Intra-operative identification using intrathecal fluoroscein is not reliable for locating perilymphatic fistulae as the timing of the injection relative to the surgery, the slow and unpredictable diffusion rate of the marker into the perilymph and the differing patencies of the cochlear aqueduct make it unreliable.[302] Intravenous fluoroscein is not useful as it appears as a transudate in the middle ear and is not taken up readily into the perilymph.[303] Mixing it with the local anaesthetic infiltration may be useful as perilymph, not being stained, will appear to displace any fluorescein containing fluid.[304]

Careful inspection of the round and oval windows, around the middle ear and the Eustachian tube orifice for a source of the leak is performed. An endoscopic technique may have the advantage of keeping the dissection to a minimum hence decreasing the amount of blood and exudate in the middle ear at the time of surgery.[305] Despite these advantages, when used alone, the method may not be adequate to exclude a perilymphatic fistula,[306] and the adequacy and interpretation of the view is more important than the method used. The round window membrane itself is usually hidden within the bony niche and it is easy to mistake mucosal folds for the true round window membrane. If this occurs, or if endoscopic methods are unfamiliar or unavailable, then curetting away the bony overhang should enable a better view. If a drill is used, it may be useful to mix fluorescein into the irrigation fluid.

Care is required not to traumatize the membrane. Any fistula found should be covered with a tissue plug and supported by absorbable middle ear packing material. If no definite fistula is observed, it is sensible to place a tissue graft in the round window and over the footplate. Fat has the advantage of filling in depressions whereas vein is useful due to the 'sticky' nature of its adventitial surface. The author usually uses both.

It is probably unwise to perform ossicular surgery at the same procedure. Given the possibility of a cochlear concussion type of injury, the inner ear may be susceptible to even minor degrees of further trauma. Repair of the tympanic membrane should, however, be performed at the time. If a delayed exploration for persisting dysequilibrium with a stable sensorineural loss is performed, appropriate ossicular surgery might be considered, provided the necessary audiological criteria are satisfied.

Confirmatory intra-operative tests

The collection of fluid for analysis as a confirmatory test for the presence of perilymph may provide retrospective evidence for a perilymphatic fistula. Beta 2-transferrin is 100% specific but its low sensitivity of 29% makes this test not worthwhile.[307, 308] Cochlin-tonoprotein is a 16 kDa protein that has been identified in human perilymph.[309] It is not present in other body fluids[310] and has been found in 92% of perilymph samples, as compared to 0% of CSF, from the same patients.[311] There is a claimed specificity of about 98%.[311] There may therefore be a confirmatory diagnostic test available in the future.

Results

The data available are difficult to interpret as some patients without surgically identified fistulae improve as a result of, or despite, their surgery. Spontaneous improvement is often seen in more mild cases, even if no surgery is performed. Despite these restrictions, surgical intervention appears to relieve vestibular symptoms (87%) and to improve the hearing in about 40% of sudden hearing loss cases.[299] Other reports suggest that hearing stabilization, rather than necessarily improvement, is achieved in most cases.[301]

KEY POINTS

Inner ear barotrauma

- There are three types of inner ear barotrauma: inner ear haemorrhage, labyrinthine tears and perilymphatic fistulae.
- The history of pressure/time profile of the incident is important.
- The most suggestive symptom is dysequilibrium with manoeuvres which increase intracranial pressure.
- Other symptoms include sensorineural hearing loss (may fluctuate), chronic dysequilibrium, mild nausea, unaccustomed motion sickness, vertigo, tinnitus, positional vertigo and Tullio phenomenon.
- Clinical fistula signs are only useful if positive.
- Otoscopy is sometimes normal.
- The decision for surgical exploration is based on the severity of the presenting hearing loss and failure of the vestibular symptoms to resolve.
- Surgical results are good for vestibular symptoms and relatively poor for hearing improvement.
- **Prevention:**
  - as for middle ear barotrauma (above)
  - avoid over-rigorous attempts to equalize middle ear pressure
  - identify those at risk:
    - as for middle ear barotrauma (above)
    - previous perilymphatic fistula.
- **Diagnosis:**
  - must distinguish from decompression illness (**Table 91.9**)
  - obtain the exact nature and timing of symptoms
  - establish the time/pressure profile
  - conduct a full neurological examination, including postural balance tests
  - pay attention to the direction and nature of nystagmus, with/without the removal of optic fixation
  - maintain monitoring with daily audiometry
  - conduct a tympanometric held pressure fistula test with electronystagmography
  - consider tone-burst electrocochleography.
- **Treatment:**
  - always consider the need for early surgery – continue to review
  - use steroids for moderate and severe hearing losses
  - carry out immediate surgical exploration if there is short presentation and moderate/severe hearing loss
  - surgical exploration for:
    - progressive hearing loss
    - persistent disequilibrium
    - close obvious fistulae, if unclear then cover both windows with fat/vein adventitia.
- **Advice to patient:**
  - complete resolution is expected in mild cases
  - scuba diving is contraindicated if problems are persistent
  - take decongestants before flying/diving
  - beware of lifting/straining/flying for 6 weeks post-operatively.

INJURIES AT HIGH PRESSURE

High-pressure nervous (neurological) syndrome (isobaric gas counterdiffusion)

High-pressure nervous syndrome may occur when divers are exposed to extremely high pressures. The characteristic symptoms are of tiredness, general dizziness and tremors (both postural and intentional, of the hands and even of the whole body) that may progress, with increasing pressure, to ataxia and myoclonus. Unlike nitrogen narcosis, psychomotor impairment exceeds intellectual impairment. The depth at which the condition occurs depends on the compression rate. Symptoms may occur at high pressure, but characteristically soon after changing the inspired gas mixture to one that includes a second inert gas. The sudden onset of vertigo and nausea with nystagmus has been reported as part of this syndrome.[312] Permanent vestibular damage has been described, but there is no hearing loss.[313, 314]

KEY POINTS

High-pressure nervous syndrome

- High-pressure nervous syndrome occurs with extreme pressure exposure.
- It usually occurs on changing inspired gas mixtures.
- It is characterized by tiredness, general dizziness and tremor.
- It may progress to include vertigo, ataxia and myoclonus.
- Psychomotor impairment exceeds intellectual impairment.
- Permanent vestibular damage may result, with no hearing loss.

DECOMPRESSION (ASCENT) INJURIES

Alternobaric vertigo

This is a condition of asymmetrical middle ear overpressure stimulation occurring in divers,[315, 316] air passengers and crew.[317] It usually occurs in those who describe unilateral equalization problems. On ascent, failure of equalization due to minor middle ear congestion and oedema, or unilateral Eustachian tube dysfunction, may lead to a relatively higher pressure in one middle ear. Of 2053 Swedish divers, 22% described symptoms consistent with alternobaric vertigo at some time during their diving careers.[318] The condition occurs on ascent or within 2 minutes of surfacing. Episodes are not usually severe, with a maximum duration of about 10 minutes. Divers may also describe a tumbling sensation, or a tilting of their surroundings, rather than simple rotation. Experimental evidence supports these clinical observations, with true vestibular nystagmus demonstrated when middle ear overpressure was present in only one ear during controlled decompression in a pressure chamber.[319, 320] Animal studies have also demonstrated an increase in vestibular neuronal impulses as a response to middle ear overpressure.[321] It is, however, not exclusively a condition of ascent. Twenty-seven percent of cases occurred during descent.[315]

KEY POINTS

Alternobaric vertigo

- Alternobaric vertigo is caused by asymmetric middle ear overpressure.
- It is common in divers and aircrew.
- It often has a preceding history of unilateral difficulties 'equalizing'.
- It usually occurs with decompression (27% with compression) or within 2 minutes of surfacing. It is rare for signs to persist for more than 10 minutes.
- There are no permanent sequelae.

Barotraumatic facial palsy (facial baropareisis, alternobaric facial palsy)

A transient facial nerve palsy may occur as a result of high middle ear pressure during ascent. It has been described in both aviators and divers.[322, 323] A correct diagnosis is important to avoid potentially hazardous, and unnecessary, recompression treatment. It is probably due to a pressure-induced neuropraxia in an individual with a congenital dehiscence of the facial nerve in its intramastoid portion (0.5–57% of all temporal bones).[324] Animal studies have demonstrated that blood flow in the vasa nervora of the facial nerve decreases if increased middle ear pressure is transmitted through a dehiscence of the facial canal.[325] A neuropraxia has also been induced by applying increasing pressures to an exposed part of the facial nerve in cats.[326] In a non-dehiscent facial canal, pressure may be transmitted through the fenestra of the chorda tympani.[327] The blood flow, and the palsy, rapidly return to normal when the middle ear pressure is relieved. The condition may be associated with alternobaric vertigo. It is important to rule out other causes of facial palsy (see Chapter 112, The facial nerve and its non-neoplastic disorders). Clinical evaluation should include complete general neurological and neuro-otological examinations, the main differential diagnosis being a decompression illness. A facial palsy due to this would be very unlikely to occur in isolation without any other neurological symptoms or signs. Patients are likely to have associated symptoms and signs of otitic barotrauma (see Table 91.8). The onset is typically rapid and the condition resolves after a few minutes. This would be very unlikely to be the case if a decompression illness were the cause.

If there is a bulging tympanic membrane, then a myringotomy should be performed, although a persisting palsy should be investigated and treated as for a decompression illness. Recompression treatment may worsen symptoms when Eustachian tube dysfunction is still present, but it is clearly not indicated when a diagnosis of isolated barotraumatic facial palsy has been made. If a decompression illness is also suspected, or if uncertainty as to the true diagnosis persists, a myringotomy should be performed and a grommet inserted prior to proceeding with recompression treatment. A full recovery is expected.

KEY POINTS

Barotraumatic facial palsy

- Barotraumatic facial palsy is caused by middle ear overpressure during ascent.
- It involves neuropraxia secondary to compression of the vasa nervora.
- No other neurological symptoms or signs are present.
- It is often associated with mild middle ear barotraumas.
- Rapid spontaneous resolution is expected.
- Myringotomy should be performed if there is persistence, when a bulging tympanic membrane is identified.

NON-BAROTRAUMA-ASSOCIATED INNER EAR PROBLEMS IN DIVERS

Frequent high pressure exposure itself has been refuted as a cause of sensorineural deafness.[328, 329] Animal studies have suggested inner ear damage,[330, 331] but with adequate controls no histological inner ear damage was then

found even after the application of extra high ambient pressures.[332] The predominant cause of increased hearing thresholds in commercial divers is noise induced with no evidence for hearing loss or vestibular impairment associated with diving itself.[333, 334] There is a similar lack of convincing evidence in sports divers.[335]

DECOMPRESSION ILLNESS AND HYPERBARIC MEDICINE

Pathophysiology

VENTILATORY EFFECTS

The exchange of oxygen and carbon dioxide between the alveoli and blood occurs down concentration gradients. Assuming normal ventilation, as oxygen is utilized by respiration, there is a continuous transfer of oxygen into the blood from the alveoli, with carbon dioxide transfer in the opposite direction. Pulmonary transfer of inert gases depends on the solubility of that gas in blood. At low ventilation rates, highly soluble gases exchange slowly as they remain more easily equilibrated with their blood concentrations across the alveolar membranes. Gases, such as nitrogen and helium, have low solubility in blood (i.e. tend to remain in gas phase rather than solution), resulting in their rapid exchange almost whatever the ventilation rate. Thus equilibration of their alveolar–arterial gas tensions readily occurs.

Henry's law states that the amount of gas dissolved in a tissue is proportional to the pressure on that tissue. During descent (compression), the increased ambient pressure results in a greater amount of nitrogen dissolved in both the arterial and venous blood. During ascent (decompression), as the ambient pressure falls, a gas phase will form within the tissue unless the gas is metabolized or removed at a sufficiently fast rate. Nitrogen and other inert gases, which cannot be metabolized, are only transferred via a concentration gradient from the tissues back into the blood stream. Nitrogen has a low partition coefficient (water/oil, 0.19) as it is more soluble in lipids than in water. Consequently, its transfer from the tissues to the vasculature is slow. Once in the blood it is transported to the lungs where the gas tensions in the pulmonary capillaries are equilibrated with the partial pressures of gases in the alveoli before exhalation. If subsequent decompression is too rapid, nitrogen bubbles will form.

BUBBLES

A bubble in the body is only absorbed when its nitrogen partial pressure exceeds the nitrogen tension in the surrounding blood/tissue.[239] If a short dive takes place, there will be little time for nitrogen to dissolve and diffuse into tissues, and therefore a rapid ascent is possible. When decompressing after a longer dive, carbon dioxide will come out of solution very quickly due to its high solubility. Provided adequate ventilation continues, it traverses the alveolar membranes and is expired so quickly that bubbles do not have time to form. Due to nitrogen's low partition coefficient, interstitial nitrogen microbubbles will form and subsequently enlarge, unless the rate of transfer through the endothelium into the vasculature exceeds the rate of their formation. Likewise, primary intravascular bubbles will form if the rate of nitrogen forming a gaseous phase is faster than the lungs' ability to remove the excess dissolved nitrogen. Doppler ultrasound has shown that bubbles are present in the venous systems of many divers during decompression, without consequence.[336] These bubbles pass through the venous system until they are trapped and filtered by the pulmonary vascular bed, where diffusion into the alveoli occurs. Pathological effects may be seen if there is: saturation of the pulmonary filter (resulting in arteriovenous shunts), a patent foramen ovale of the heart or rupture of alveoli (or a pre-existing lung bulla) causing pulmonary barotrauma.

Exercise significantly affects tissue uptake of nitrogen during compression[337] and speeds expulsion on decompression.[338] Obesity (nitrogen being more soluble in lipids than in water) and increased age may increase the tendency to develop decompression illness, although this is disputed.[339]

KEY POINTS

Hyperbaric pathophysiology

- Increased ambient pressure (compression) increases the amount of dissolved gases in blood and tissues.
- Decompression results in a gas phase, unless metabolism or removal are at a sufficient rate.
- Nitrogen transfer from tissues to blood is slow (low partition coefficient).
- Short dives give insufficient time for nitrogen to dissolve and diffuse into tissues.
- Exercise during compression increases the amounts of dissolved nitrogen.
- Vascular bubbles forming on decompression cause vascular occlusion and direct endothelial damage.

Hyperbaric oxygen treatment (therapy)

Bubbles in the blood are a common occurrence in decompression situations. They are inconsequential, unless their number or size is sufficient to cause symptoms. The two central concepts of hyperbaric medicine are the ability to (i) dissolve gas nuclei by rapid compression and (ii) increase the amount of gas in solution.

The Undersea and Hyperbaric Medical Society indications for hyperbaric oxygen treatment are shown in **Box 91.1**. A systematic review has found that convincing results have only been achieved in treating decompression illness and gas embolism.[340] This is supported by established physiology, results from animal experiments and extensive clinical experience spanning over 100 years. Using the Grading of Evidence, Assessment, Development and Evaluation (GRADE) system for reviewing evidence, the evidence level has been elevated from C to A for these indications.[341] There is a convincing physiological case for its use in carbon monoxide poisoning. In conditions such as clostridial myonecrosis, synergistic gangrenes, crush syndromes and osteomyelitis, results are difficult to assess as its role is predominantly adjuvant and, therefore, controlled studies are very difficult to perform. Anecdotal and series reports describe good results in many cases.

BOX 91.1 Approved indications for hyperbaric oxygen therapy

Air or gas embolism
Carbon monoxide poisoning
Clostridial myositis and myonecrosis (gas gangrene)
Crush injury, compartment syndrome and other acute traumatic ischaemias
Decompression illnesses
Arterial insufficiencies: central retinal artery occlusion
Enhancement of healing in selected wound problems
Severe anaemia
Intracranial abscess
Necrotizing soft-tissue infections
Osteomyelitis (refractory)
Delayed radiation injury (soft tissue and bony necrosis)
Skin grafts and flaps (compromised)
Thermal burns
Idiopathic sudden sensorineural hearing loss
(Source: Undersea Medical Society 2014, www.uhms.org. Reproduced with permission.)

Hyperbaric oxygen treatment is indicated in all cases of suspected decompression illness because failure to treat is associated with permanent functional damage, and death.

Pathological effects of bubbles on the inner ear

Obstruction of small vessels may cause damage to susceptible organs, including the inner ear. Animal experiments following forced decompression showed evidence of irritation of the semicircular canal endostea with osteoblastic and fibroblastic differentiation, finally leading to fibro-osseus labyrinthitis,[342] and also to cause both bubbles and haemorrhages in the labyrinthine fluid spaces.[343] In humans vascular obstruction, haemorrhage and exudates in the inner ear fluid spaces and bubbles within endostial bone immediately around the semicircular canals. Microfractures into the pericanal spaces and new bone growth have been described.[344]

KEY POINTS

Hyperbaric treatment

- Hyperbaric treatment increases the amount of gas in solution.
- It dissolves gas nuclei by rapid compression.
- It is highly effective for cases of decompression illness and gas embolism.
- It has an adjuvant role in gangrenes, crush syndromes and osteomyelitis.
- Failure to give hyperbaric oxygen treatment rapidly in decompression illness is associated with permanent functional damage.

INNER EAR DECOMPRESSION ILLNESS

Decompression illnesses have been classified into two types:

- Type I: Musculoskeletal pain predominates, although cutaneous features (itching, urticarial rash, burning sensation) and systemic symptoms of malaise, anorexia and fatigue are also included.
- Type II: Cardiorespiratory and/or central nervous system involvement.

As many as 70% of all divers with this condition have followed their decompression tables correctly, many reports occurring after shallow sport dives.[345] The diagnosis may be very difficult to distinguish from inner ear barotrauma, especially as both often coexist with middle ear barotrauma. A careful history of the dive profile, the timing of the onset of symptoms, and their exact nature, is essential. The verification of the dive history is usually straightforward as many divers now carry electronic dive computers that provide at least a depth/time printout. The onset of decompression illness symptoms is usually only a few minutes (but may be as long as up to 36 hours) after surfacing. A history of symptoms starting when returning from a diving holiday by air is not uncommon as flying after diving may exacerbate, or even cause, decompression illness.[346] There is an increase in the tendency for more nitrogen to come out of solution due to the lower partial pressures of the inspired air and the decreased ambient pressure at altitude.

Organs with high metabolic rates and unit blood flow, such as the stria vascularis, are more susceptible.[347, 348] Isolated vestibular or hearing symptoms are rare. A history of other symptoms attributable to a decompression illness should be sought. Localized pain (91.8%), numbness or paraesthesia (21.2 %), muscular weakness (20.6%) and skin rash (14.9%) are the most frequently described. Non-specific dizziness or vertigo was the fifth most common (8.5%) with auditory disturbance occurring in only 0.3%.[349]

The time of onset is an important factor when attempting to differentiate decompression illness from other conditions. In cases of central nervous system (type II) decompression illness, 50% of patients report the onset of their symptoms within 10 minutes of surfacing and 90% within 3 hours.[350] Type I decompression illness has a longer delay, but 90% become symptomatic within 6 hours of surfacing. Most patients presenting to the otolaryngologist following a dive or a sudden decompression aviation incident, who do not only have middle ear barotrauma, will complain of dizziness or vertigo. Very few of these, however, will have either inner ear barotrauma or inner ear decompression illness (**Table 91.10**). True vertigo is unusual,[351] as is a sensorineural hearing loss (**Table 91.11**). The low numbers of inner ear barotrauma and perilymphatic fistula patients emphasizes the relative rarity of these conditions, and also the difficulties establishing a diagnosis when frequent complex symptoms and signs coexist, with the presentation often being delayed.

Clinical signs

Otoscopy, fistula tests and a full neurological examination, Romberg, Unterberger, head-thrust and Dix–Hallpike positional tests should all be performed if possible. Nystagmus may be present and the use of Frenzel glasses

TABLE 91.10 Coexisting symptoms in 97 consecutive divers presenting to a tertiary centre with 'dizziness'

Symptom	Number of patients
Paraesthesia	26
Joint pain	25
Pain in limbs	18
Weakness in limbs	11
Hearing loss	9
Back pain	5
Abdominal pain	4
Skin rash	4
Unconsciousness	4
Blurred vision	3
Convulsions	1

Source: Primary database - Diving Diseases Research Centre, Plymouth, UK.

TABLE 91.11 Final diagnoses in 97 divers presenting with 'dizziness' to a tertiary centre

Diagnosis	Number of patients
Anxiety	1
CAGE	6
Near-drowning	2
Decompression illness, unspecified	3
Decompression illness, neurological	47
Decompression illness, joint	7
Decompression illness, skin	3
Decompression illness, musculoskeletal	3
Decompression illness, spinal	7
Decompression illness, pulmonary barotrauma	1
Decompression illness, pain	10
Decompression illness, inner ear/vestibular	4
Gas embolism	1
Hypocapnia	1
Muscle pain	3
Trauma right knee	1
No abnormality found	2

More than one diagnosis may apply. Source: Diving Diseases Research Centre, Plymouth, UK, (Bryson P./Toynton S. unpublished data).

to remove optic fixation typically enhances the nystagmus occurring with peripheral vestibular lesions. The clinical assessment should concentrate on differentiating not only between inner ear barotrauma and inner ear decompression illness, but also between a localized peripheral vestibular and a brainstem decompression illnesses. The distinction between central and peripheral causes of vertigo is discussed elsewhere (see Chapter 62, Evaluation of balance). Clinical features, which may aid in the differential diagnosis, are shown in Table 91.9.

Investigations

Investigations for general dizziness and hearing loss should be performed as appropriate, and as soon as the clinical situation allows (see Chapters 49, Physiology of equilibrium and Chapter 62, Evaluation of balance). Otological evaluation is often only practical after substantial hyperbaric and supportive treatment. An audiogram may be possible, but caloric and electronystagmographic testing is not well tolerated in the acute stage. Intracranial gas bubbles may form within any of the tissue or fluid spaces, including within the endolymph and perilymph. Probably more commonly however are embolic phenomena caused by large quantities of bubbles that have not been filtered by the pulmonary bed. Patients with evidence of an inner ear or other intracranial decompression illness should therefore undergo echocardiography to exclude a patent foramen ovale, which may occur in 48-80% of cases.[351–353]

Treatment

Recompression treatment should be instigated straight away. If there has been any suggestion of middle ear barotrauma, difficulty with middle ear pressure equalization, doubt as to the exact diagnosis, or a possibility of an overlooked perilymphatic fistula, then performing myringotomies (and preferably the insertion of grommets) beforehand is essential. The clinical features in a small series of 29 cases of inner ear decompression illness were as follows: pure vestibular involvement in 10 (34%), localized cochlear insult in 4 (14%), combined cochleovestibular event in 15 (52%). Two-thirds had a hearing loss at presentation. Consistent with most publications, they described a great difference in decompression illness resolution if treated with hyperbaric oxygen treatment within 6 hours (53% complete resolution of symptoms) as compared to those treated after this time (only 1 of 9 patients' symptoms resolved). Overall, only 6 of the 19 patients (32%) with cochlear damage made a full recovery.[345]

KEY POINTS

Inner ear decompression illness

- Many scuba divers have followed decompression tables correctly.
- Inner ear decompression illness may occur after shallow 'sports' dives, in common with other decompression illness.
- The differential diagnosis between inner ear decompression illness and inner ear barotrauma may be difficult (Table 91.9).
- Inner ear decompression illness may be precipitated by flying soon after diving.
- Isolated vestibular/cochlear decompression illness is rare; concurrent decompression illness symptoms/signs should be expected.
- All cases must be screened for a patent foramen ovale;
- Recompression within 6 hours is mandatory for all cases.
- **Prevention:**
  - avoid sudden decompression
  - ensure sufficient decompression times when diving
  - identify those at risk

  - those working/exercising under compression conditions
  - previous decompression illness
  - repeated dives
  - flying after diving.
- **Diagnosis:**
  - must distinguish from inner ear barotrauma (Table 91.9)
  - obtain exact nature and timing of symptoms
  - establish time/pressure profile
  - comprehensive neurological examination, including postural balance tests
  - echocardiography to exclude patent foramen ovale.
- **Treatment:**
  - urgent fluid resuscitation
  - early recompression hyperbaric oxygen therapy, within 6 hours
  - recompress if in doubt
  - myringotomy/grommets if impaired consciousness or equalization difficulties.

MIDDLE AND INNER EAR BAROTRAUMA SECONDARY TO HYPERBARIC OXYGEN TREATMENT

Middle ear barotrauma is the most common complication of hyperbaric oxygen therapy occurring in about 8% of patients undergoing repeated treatment dives.[354, 355] The incidence of vestibular symptoms with hearing loss is about 1.5% of dives or in 3% of those treated.[355] This is far more likely to occur in those in whom the indications included osteoradionecrosis of the head and neck region.[356] An inability to voluntarily autoinflate the middle ears prior to treatment increases the risk of developing middle ear barotrauma.[357] Unconscious patients or those with artificial airways while anaesthetized have a 94% chance of barotrauma, therefore routine insertion of ventilation tubes in such patients is indicated.[358] Other risks include the elderly, females, a history of cardiovascular disease and head and neck cancer, particularly following radiotherapy.[359]

KEY POINTS

Middle and inner ear barotrauma secondary to hyperbaric oxygen treatment

- Barotrauma is a common sequela of hyperbaric therapy.
- Risk is increased with:
  - increasing frequency of treatments
  - unconscious patients
  - osteoradionecrosis of temporal bone
  - inability to voluntarily equalize middle ear pressures
  - cardiovascular disease.
- There should be a low threshold for prophylactic myringotomies/ventilation tubes.

CEREBRAL AIR GAS EMBOLISM

Cerebral air gas embolism (CAGE) is the most serious and dramatic event for both scuba divers and aviators. It may occur during any depth of dive, even in swimming pools. It is usually seen in inexperienced divers who breath-hold when surfacing in an emergency. Ascent of only 1 m, without exhalation, is sufficient to produce microalveolar tears. Massive air gas embolism therefore occurs in the brain and the rest of the body. Involvement of the coronary arteries and brain are the predominant causes of the high rate of sudden death. Symptoms and signs are typically of very sudden onset and occur on ascent or very soon after surfacing. These include chest pain, severe dyspnoea, subcutaneous crepitus, dysphagia, dysphonia, general or focal seizures, confusion, hemiplegia, focal weakness, visual field defects and blindness. Blood-stained frothy sputum is a common feature.

Vertigo is commonly described and may be the presenting symptom in about 25% of cases. This usually occurs without either sensorineural hearing loss or tinnitus. Usually other neurological signs develop rapidly. The main differential diagnosis being of inner ear decompression illness, but the history, speed of onset, severity, associated signs and symptoms (such as surgical emphysema in the neck and on X-ray) usually prevent diagnostic difficulties. Emergency treatment is to place the patient in the Trendelenberg (head-down) position breathing oxygen. Following this, recompression takes priority over all other treatment and assessment options.[360]

FUTURE RESEARCH

➤ This chapter has provided an in-depth review of the otological conditions associated with barotrauma and hyperbaric conditions. While the underlying physics and physiology are well researched and understood, the clinical conditions, their diagnosis, treatment and prognosis are not.

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CHAPTER
92

OTALGIA

Philip D. Yates

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: earache, otalgia, referred otalgia, geniculate neuralgia, carotidynia, glossopharyngeal neuralgia, temporomandibular joint and earache and/or otalgia, and by the Cochrane Database of Systematic Reviews.

INTRODUCTION

Otalgia can arise from pathology within the ear (primary otalgia) or as a result of disease processes elsewhere (secondary or referred otalgia). While in children otalgia is much more frequently otogenic, in adults referred otalgia is the more common cause.[1]

Anatomy

The sensory supply of the ear is highly complex and not fully determined. It is this complexity that can lead to diagnostic difficulty in a patient presenting with otalgia, particularly when it is the only symptom. There are four cranial nerves and two cervical nerves that contribute to the sensory supply of the ear. The greater auricular nerve and, to a lesser extent, lesser occipital nerve supply sensation to the whole of the cranial surface of the pinna and to the lateral surface below the meatus (C2 and C3) (**Figures 92.1** and **91.2**). The auriculotemporal nerve, a branch of the mandibular division of the trigeminal nerve, supplies the lateral surface of the tympanic membrane, the external acoustic meatus and the lateral skin of the pinna above the level of the external meatus. The auricular branch of the vagus (Arnold's nerve) supplies the posteroinferior quadrant of the tympanic membrane, posteroinferior meatal skin and an area of the concha. The extent of facial nerve innervation of the ear roughly corresponds with that of the vagus, but its contribution is sparse.

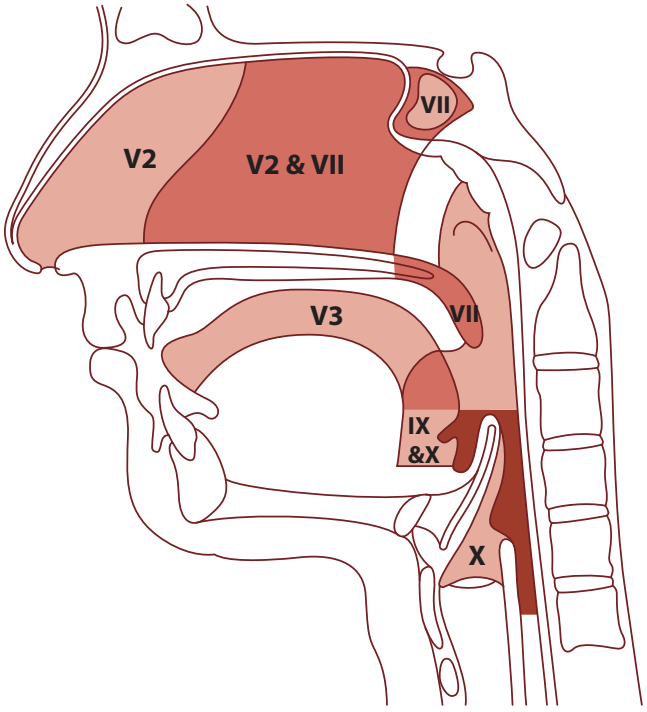


Figure 92.1 Otalgia arising from head and neck sources. Essentially any pathology residing within the sensory net of cranial nerves V, VII, IX and X and upper cervical nerves C2 and C3 can potentially cause pain referred to the ear. Adapted from Scarbrough et al. *Am J Clin Oncol* 2003; **26**(5): e157–62.[8]

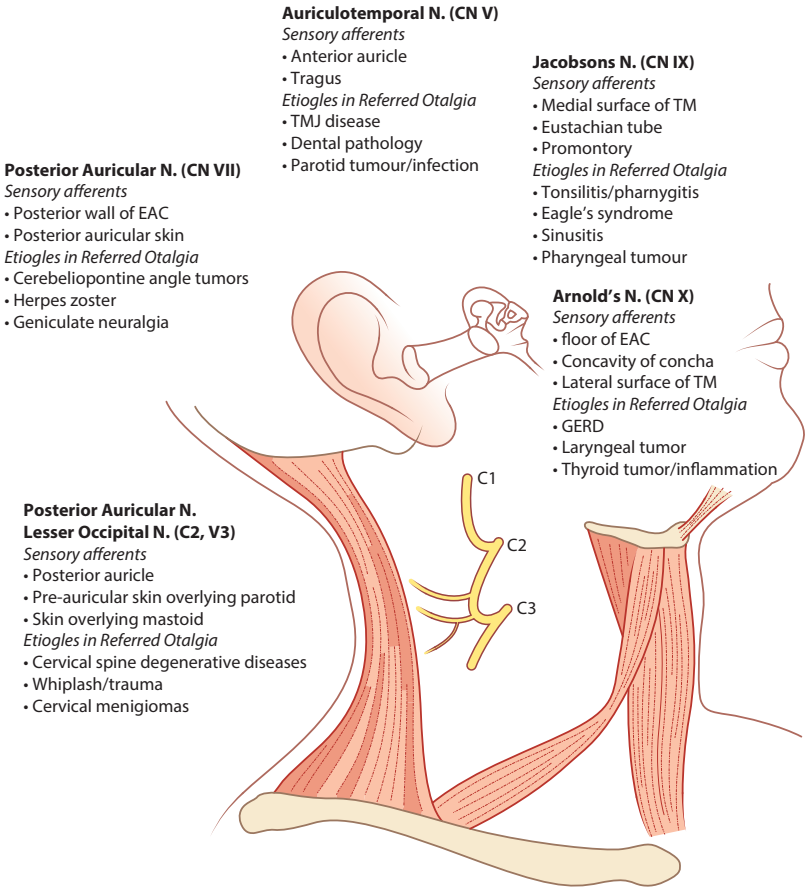


Figure 92.2 Complex sensory innervation of the ear and periauricular structures and various aetiological causes in referred otalgia. Adapted from Jaber et al. *Otolaryngol Head Neck Surg* 2008; **138**(4): 480.[22]

The middle ear is supplied by the tympanic branch of the glossopharyngeal nerve (Jacobson's nerve).[2, 3]

Referred pain is a commonly encountered clinical phenomenon, although its mechanism is not fully understood. **The trigeminal nerve is probably the most common pathway of origin of referred pain to the ear.** The mandibular division of the trigeminal nerve carries sensation from the anterior two-thirds of the tongue, floor of the mouth, palate, lower teeth, major salivary glands, temporomandibular joint (TMJ) and mandible. Referred pain arising from structures in these areas tends to be perceived in the ear canal. Although the facial nerve is mainly motor, it has sensory divisions including the nervus intermedius of Wrisberg and the greater superficial petrosal nerve, which conveys sensation from the posterior nasal cavity and sphenoid sinus. The glossopharyngeal nerve receives sensory input from the posterior third of the tongue, palatine tonsils, nasopharynx, hypopharynx and parapharyngeal and retropharyngeal spaces. Pain referred from these structures tends to be perceived as a deep intense otalgia. The vagus nerve supplies the valleculae, supraglottis, thyroid gland and more distant sites within the thorax including the tracheobronchial tree and oesophagus. The upper cervical nerves (C2 and C3) innervate the muscles and facet joints of the cervical spine.[4, 5]

The fact that sensory innervation of the ear is so diverse means that the potential origin of referred otalgia is widely distributed through the head and neck, and even beyond.

PRIMARY OTALGIA

External and middle ear diseases can lead to otalgia, and most otolaryngologists and primary care physicians are trained to recognize an abnormality in these areas. Conditions of the ear resulting in localized pain are discussed elsewhere in this book and further discussion will not be duplicated in this chapter. Table 92.1 summarizes the causes of primary otalgia.

REFERRED OTALGIA

In a patient presenting with otalgia with no identifiable primary cause, an origin for the referred pain must be sought. In some cases, for example a patient with acute follicular tonsillitis associated with earache, the diagnosis is obvious and therefore requires no further discussion here. However, in many cases referred otalgia can represent a diagnostic challenge and it is the aim of this chapter to highlight the possible causes.

TABLE 92.1 Causes of primary otalgia

Site	Possible cause(s)
Pinna	Chondrodermatitis nodularis helicis Chronic relapsing perichondritis Trauma/haematoma Cellulitis Herpes zoster oticus Malignancy
External canal	Otitis externa: • acute • chronic • benign necrotizing • 'malignant' Furuncle Bullous myringitis Keratosis obturans/canal cholesteatoma Trauma Herpes zoster oticus Malignancy
Middle ear	Otitis media +/- complications Malignancy
Inner ear	Noise discomfort

MALIGNANCY

Although malignancy is not the commonest cause of referred otalgia, its importance as a potential cause warrants this differential being high on the assessing clinician's list. Malignant tumours of the upper aerodigestive tract can present with various symptoms depending on their site of origin. It is important to remember that referred otalgia may be part of a symptom complex, or perhaps more importantly, can be the sole presenting symptom. A full examination of the oral cavity and flexible nasendoscopy to examine the pharynx and larynx are therefore an essential part of the assessment of a patient with otalgia in the absence of local pathology within the ear. The presence of otalgia, dysphagia, nodal metastasis and weight loss have all been shown to be independent predictors of duration of survival of patients with head and neck cancer.[6]

The majority of oropharyngeal carcinomas arise within the lateral wall, commonly involving the tonsil or the tongue base. Unlike carcinomas of the oral cavity, oropharyngeal tumours may not be visible until they are at an advanced stage and therefore imaging may be required to identify a primary in this area. Lymph node metastases are common at presentation. Like other aerodigestive tract malignancies, the most significant aetiological factor is smoking and to a lesser extent alcohol, but with a significant synergistic effect. However, HPV infection has had a dramatic effect on oropharyngeal malignancy rates and has been responsible for a significant increase in incidence over the last decade or more. This increase has been seen in younger patients (40–60 years) and non-smokers.[7]

Otalgia and odynophagia are often presenting symptoms of hypopharyngeal malignancy. On occasions, a supraglottic malignancy may lead to otalgia before involving the glottis and presenting with hoarseness, which is the cardinal symptom of laryngeal malignancy. The nasopharynx is not usually a subsite referring pain to the ear, but otalgia has been reported as being the presenting symptom in up to 14% of patients with nasopharyngeal carcinoma.[8]

Neoplasms arising in the infratemporal fossa can cause referred otalgia via the trigeminal nerve, Arnold's nerve or Jacobson's nerve. In a retrospective review of 18 cases presenting over a period of 8 years, all cases had otalgia with normal otological findings and a minority had subtle cranial nerve signs such as reduced corneal reflex. Adenoid cystic carcinoma was the most common pathological diagnosis, followed by adenocarcinoma, squamous cell carcinoma and osteogenic sarcoma.[9] If more common causes of otalgia cannot be identified by physical examination and appropriate investigation, an MRI scan with gadolinium enhancement should be considered to diagnose this rare finding.

While still rare, temporal bone metastases are seen more frequently due to the increasing incidence of cancer and to increase in life expectancy.[10] Haematogenous spread is the commonest route of spread and the commonest sites for the primary tumour are breast, lung, kidney, stomach and prostate. Although temporal bone metastases are often asymptomatic, they may present with otalgia, hearing loss (conductive, sensorineural or mixed), facial nerve paralysis and balance disturbance. The triad of symptoms of otalgia, periauricular swelling and facial nerve weakness should raise the suspicion of temporal bone malignancy. CT scanning will usually be diagnostic. Treatment is almost always palliative.[11]

DENTAL

Dental disorders are the most common cause of referred otalgia and were traditionally thought to account for up to 5.75% of all cases seen in an ENT clinic, but recent work by Fenton et al. suggests they may be considerably less frequent.[12–14] Dental otalgia may arise from the teeth, periodontal tissues or the TMJ.

Teeth/periodontal tissues

Dental pain arising from the teeth and periodontal tissues poses a diagnostic problem to a trained dentist, so it is understandable that referred otalgia from dental pathology may present more of a challenge when presenting to an ENT clinician. The commonest cause of inflammation of the dental pulp (pulpitis) is dental caries. The pain of pulpitis is often poorly localized as the sensory innervation is mainly via non-myelinated type C pain fibres. Chronic pulpitis may fluctuate over a period of weeks or months and, with poor localization of pain and lack of physical signs, is difficult to recognize. Pain associated with acute apical periodontitis and acute apical abscess tends to be severe, throbbing and localized to the affected tooth but, if the inflammation is mild and chronic, localization

may be poor. Partially erupted or impacted wisdom teeth can lead to inflammation of the surrounding soft tissue (pericoronitis). Chronic pericoronitis can present as poorly localized facial/jaw pain with referred otalgia.[15]

Temporomandibular joint dysfunction syndrome

The cardinal features of TMJ dysfunction are diffuse pain felt in or around the joint, crepitus and trismus. Pain is the most common and prevalent symptom. The true prevalence of TMJ dysfunction is not certain but it is estimated that between 20% and 40% of the population suffer from symptoms at some time.[15] Pain from the TMJ, or from related tissues, is common but there is often no definable organic disease. Sufferers of referred otalgia from TMJ dysfunction are more likely to be female, with statistically significant elevated levels of physical comorbidity and psychological stress.[16] Otalgia has been reported to be a symptom of TMJ dysfunction in 64% of patients.[17] Bruxism is a major aetiological factor and has been reported to be present in more than 50% of cases.[18] Patients who have a tendency to bruxism at night often awake with pain that settles during the day. Those who clench or grind their teeth through the day, perhaps secondary to stress, are prone to symptoms in the evening.[15]

The most reliable diagnostic clinical finding in TMJ dysfunction is tenderness of the masticatory muscles. In a large study of patients with TMJ dysfunction, muscle tenderness was seen in the majority of patients, with tenderness of the lateral pterygoid reported in 85%. Tenderness of the joint itself was reported in 67% of patients and 38% had crepitus on auscultation.[18] Intraoral palpation of the lateral and medial pterygoids frequently reveals tenderness, and this finding is more commonly seen in patients with referred otalgia.[19] Patients who have bruxism will often have flattening of the occlusal surfaces of the molar teeth, worn incisors and linear scarring of the buccal mucosa and lateral border of the tongue. Patients should also be assessed for malocclusion as this may cause stress on the TMJ, predisposing to TMJ dysfunction. Radiology rarely contributes to the diagnosis but MRI can demonstrate joint effusion or internal derangement of the joint.[5]

The mainstay of treatment for TMJ dysfunction is rest, a soft diet and simple analgesia, particularly nonsteroidal anti-inflammatory drugs. Application of local heat can be of benefit. Benzodiazepines or low-dose tricyclic antidepressants can help symptoms for more refractory symptoms, but there is risk of dependence. A small proportion of patients may require further investigation and treatment by maxillofacial surgeons, using occlusal splints in the first instance. TMJ surgery is generally considered only as a last resort.

Costen's syndrome[20] includes a variety of ear symptoms thought to originate from the TMJ. The original description was a constellation of symptoms including otalgia, tinnitus, impaired hearing, dizziness and aural congestion. Active treatment of TMJ dysfunction has been shown to relieve otological symptoms.[21] However, Bush et al.[22] found no association of TMJ dysfunction with tinnitus or dizziness, concluding that these symptoms may be more related to psychological distress.

CERVICAL

With the increasing age of the general population, cervical spine degenerative disease (CSDD) must be considered as an increasingly common cause of referred otalgia. Pain referred from the cervical spine is usually persistent retroauricular or infra-auricular and is frequently related to neck movement. In a retrospective study, Jaber et al.[23] found that 42% of referred otalgia was secondary to cervical disorders and the majority of these (37/51) were secondary to CSDD. The condition was also found to be much more common in females (4:1, female:male). This makes referred pain from the upper cervical plexus (greater and lesser auricular nerve) second only to pain referred from the region of the trigeminal nerve.

If cervical otalgia is suspected, clinical examination combined with imaging of the cervical spine is indicated. Imaging studies of the cervical spine have a high false-positive and false-negative rate. MRI of the cervical spine has been shown to be abnormal in nearly 20% of asymptomatic patients,[24] and therefore results should only be interpreted alongside the clinical findings.

First-line treatment of CSDD should be conservative with treatments such as analgesia and physiotherapy.[23]

NEURALGIA

Otalgia can present as one of the features of various cranial neuralgias. Trigeminal neuralgia and post-herpetic neuralgia are the commonest forms of craniofacial neuralgia, both of which have a similar incidence.[25] Trigeminal neuralgia has an incidence ranging from 4–5/100 000 per year up to 20/100 000 per year after the age of 60, and is more common in females than males.[25] It is defined as a sudden, usually unilateral, brief stabbing recurrent pain in the distribution of one or more of the branches of the fifth cranial nerve. Because of this classic mode of presentation and the fact that otalgia is only infrequently reported as a symptom of trigeminal neuralgia, it is not discussed further here. Herpes zoster oticus is often associated with severe acute otalgia, which can persist in the form of a post-herpetic neuralgia. Although the origin of the pain at presentation may initially not be obvious, the diagnosis becomes clear once the typical herpetic vesicles erupt.

Primary neuralgias should be considered as a diagnosis of exclusion and in most cases an MRI scan of the affected cranial nerve is indicated.

Glossopharyngeal neuralgia

The International Headache Society defines glossopharyngeal neuralgia as a severe transient stabbing pain experienced in the ear, base of tongue, tonsillar fossa, or beneath the angle of the jaw.[26] It is much less common than trigeminal neuralgia, the incidence being between 0.2 and 0.7 per 100 000 per year.[27, 28] Glossopharyngeal

neuralgia has been described as two clinical types based on the distribution of the pain: a tympanic type which mainly affects the ear, and an oropharyngeal type which affects the throat.[29] The onset of pain is commonly provoked by swallowing and on occasion by coughing, yawning or talking. A trigger zone may be present within the preauricular or postauricular area, the neck or external auditory canal. Symptoms are paroxysmal and last for seconds to minutes and remission periods occur. Because it is rare, glossopharyngeal neuralgia is often misdiagnosed.[30]

Glossopharyngeal neuralgia usually occurs without any evident lesion affecting the glossopharyngeal nerve. However, most authors implicate vascular compression of the nerve at the root entry zone as the main cause of 'idiopathic' glossopharyngeal neuralgia.[31] From MRI findings and observations during posterior fossa surgery, the posterior inferior cerebellar artery is the most frequent vessel responsible for compressing the glossopharyngeal nerve.[32] Secondary causes of glossopharyngeal neuralgia include stylohyoid syndrome, cerebellopontine angle tumours, parapharyngeal space lesions, pharyngeal malignancy, posterior fossa arteriovenous malformations and multiple sclerosis.[29, 33]

Patients with neuralgia do not respond to conventional analgesic drugs. Since the mechanism of pain begins in demyelinated fibres which become hyper excitable and generate high-frequency discharge, the ideal drugs are those which are able to limit the discharge frequency. Currently, the first-line medical treatment of neuralgia is with carbamazepine.[31] Although about two-thirds of patients who take carbamazepine for neuropathic pain can expect to achieve good pain relief in the short term, two-thirds can expect to experience at least one adverse event.[34] Surgery for glossopharyngeal neuralgia most commonly involves microvascular decompression.[35] This procedure has demonstrated complete pain relief in 64–75% of patients and substantial improvement in a further 16–25%.[36, 37] Nerve section can also be performed, either through a posterior fossa approach, through the neck or with a transtonsillar approach.

Stylohyoid (Eagle's) syndrome

The stylohyoid syndrome results in neuralgia secondary to an elongated styloid process or mineralization of the stylohyoid ligament. The condition was first reported by Eagle[38] in 1937 and subsequently came to bear his name. The normal styloid process is approximately 2.5 cm long and is generally accepted to be elongated if its length exceeds 4 cm. An elongated styloid process is said to be present in 4% of the population, but it has been reported that only 4% of these people present with symptoms.[39] Although Eagle originally described the syndrome as arising following tonsillectomy, later studies have concluded that tonsillectomy is not always an aetiological factor.[40, 41] Symptoms are postulated to occur as a result of compression of the hypoglossal nerve, impingement of the carotid vessels or inflammatory changes at the insertion of the stylohyoid ligament.[41] In fact, the existence of this syndrome is controversial and the Headache Classification of the International Headache Society dismissed it as 'not sufficiently demonstrated'.[26] The symptoms are classically a dull pharyngeal pain, often located within the tonsillar fossa, with radiation to the ipsilateral ear, odynophagia and a foreign body sensation. Although there may not be any specific findings on examination, the styloid process may be palpable in the tonsillar fossa and this can aggravate symptoms. Local injection of local anaesthetic can temporarily relieve symptoms. Radiological diagnosis of an elongated styloid process can be made either by orthopantomography or CT scan. Conservative management with steroids and local anaesthetic along with carbamazepine have been suggested but surgical reduction of the styloid process is considered the preferred treatment.[41, 42] Excision can be performed either transorally through the tonsillar fossa or via an external transcervical approach.

Geniculate neuralgia

Geniculate neuralgia, also known as intermediate nerve neuralgia or tic douloureux of the nervus intermedius, is a rare disorder characterized by brief paroxysms of neuralgic pain felt deeply in the ear. The intermediate nerve (of Wrisberg) is a root of the facial nerve containing sensory and parasympathetic fibres. It is considered to be responsible for the sense of taste in the anterior two-thirds of the tongue, floor of the mouth, palate and sensory information from the skin of the external auditory canal as well as the mucous membranes of the nasopharynx and nose. Its cell bodies are located within the geniculate ganglion. The cutaneous field of the nervus intermedius has been described as the zone of Ramsay Hunt (or zoster zone) and consists of the tympanic membrane, auditory meatus, tragus, concha and the groove between the pinna and scalp.[43] Although the aetiology is often not clear, symptoms have been ascribed to vascular loops[44, 45] and previous herpes zoster infection.

The literature on this condition stresses surgical management, concentrated on the nervus intermedius and geniculate ganglion, and vascular decompression.[44–47] Histological examination of the geniculate ganglion has concluded that geniculate ganglionectomy alone is inadequate, and that nervus intermedius section is also required.[47] Pulec[46, 48] has reported a 30-year experience excision of the nervus intermedius and geniculate ganglion via a middle fossa approach in 64 patients. All patients bar one (who had Lyme disease) had excellent results with respect to relief of ear pain. Other case series describe a combination of microvascular decompression of various cranial nerves combined with section of the nervus intermedius.[44, 47]

MISCELLANEOUS

inflammatory conditions affecting the pharynx and parapharyngeal spaces, larynx, major salivary glands cervical lymph nodes and the thyroid can all cause referred otalgia. Cardiac pain can also present as otalgia via vagal pathways.

Vestibular schwannoma (VS)

Although the commonest presenting symptoms of a vestibular schwannoma are progressive unilateral hearing, tinnitus and disequilibrium, otalgia can be a presenting feature. Studies reporting the incidence of otalgia in this condition suggest it is present 4–5% of the time,[49, 50] although in one study a further 25% complained of mastoid ache on direct questioning.[50] It is hypothesized that otalgia/mastoid ache is due to either compression of the nervus intermedius or dural stretching. The cranial dura mater is innervated by the upper three spinal nerves (C1–C3) and by the three divisions of the trigeminal nerve. As a result of this, pain arising in the dura can be referred to the ear. Indeed, a case of a non-traumatic subdural heamatoma presenting with otalgia as the sole feature has been reported.[51]

Cholesterol granuloma

As discussed above, malignancy within the petrous temporal bone can present with otalgia. Equally, benign processes in this area can cause otalgia. Cholesterol granulomas are expansile lesions of the temporal bone and can present with various symptoms including otalgia, pressure, hearing loss, vertigo and tinnitus.[52]

Nasal/sinus disease

The vidian nerve and greater superficial petrosal nerve supply the posterior ethmoids, sphenoids and nasal mucosa. Inflammation of the posterior ethmoids or sphenoid sinus can therefore cause referred otalgia although this is not a common pathway.[4]

Laryngopharyngeal reflux

As with many medically unexplained symptoms of the aerodigestive tract, laryngopharyngeal reflux (LPR) has been implicated as a cause of otalgia in both children and adults.[53, 54] It is hypothesized that the upper airway mucosa is more sensitive to tissue damage from acid exposure than oesophageal epithelium, therefore otalgia can occur in the absence of other symptoms more typical of gastro-oesophageal reflux.[55]

BEST CLINICAL PRACTICE

- ✓ Otalgia in the absence of discharge, hearing loss or otoscopic abnormality while the patient is symptomatic should raise suspicion of secondary otalgia.
- ✓ Expert dental examination may reveal the primary source of the pain to be the teeth/periodontal tissues or TMJ.
- ✓ Careful examination of the upper aerodigestive tract should be part of the routine clinical examination of a patient with unexplained otalgia.
- ✓ Further investigation/imaging should be guided by clinical suspicion.
- ✓ If a neuralgia is suspected, the opinion of a neurologist should be sought to guide medical management.

KEY POINTS

- Isolated unilateral otalgia may be an indicator of an otherwise asymptomatic malignancy in the aerodigestive tract.
- Dental and cervical disorders are relatively common causes of referred otalgia.
- Numerous neuralgias have been implicated as causes of referred otalgia, but all are rare.

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CHAPTER 93

BONE-CONDUCTION HEARING DEVICES

James Ramsden and Chris H. Raine

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SEARCH STRATEGY

Data in this chapter may be updated by a search on Medline, Embase, Cochrane, TRIP and NICE Evidence Search for systematic reviews, meta-analyses, randomized controlled trials, prospective non-randomized clinical studies and health economics studies looking at the following devices: Sophono, Bonebridge, Baha systems and Ponto.

INTRODUCTION

Hearing impairment varies in severity and can affect patients of all ages. Hearing loss in infancy and during childhood can significantly impact on communication, language development and education. For adults it can lead to reduced quality of life, depression, social isolation and impact on employment.

Hearing loss may be unilateral or bilateral. In most situations, acoustic hearing devices (ACHDs) will provide benefit (see Chapter 54, Hearing aids). Patients who for various reasons are unable to use ACHDs now have access to a wide variety of audiological implants; each has different indications, benefits and drawbacks. Broadly speaking, bone-conduction hearing aids (BCHAs) can be helpful for purely conductive hearing loss, for mixed or mild to moderate sensorineural hearing loss (SNHL), and for single-sided deafness (SSD).

Related devices include middle ear implants (MEIs) (see Chapter 95, Middle ear implants), cochlear implants (CIs) (see Chapter 94, Cochlear implants) and auditory brainstem implants (see Chapter 96, Auditory brainstem implants). This chapter focuses on bone-conduction hearing devices (BCHDs) that aid conductive, mixed or mild to moderate SNHL and SSD.

HISTORY

The principles of hearing by conducting sound through bone have been known about for centuries. Following the development of the carbon microphone, transcutaneous 'oscillators' emerged in the early 1920s. It was in 1977 that Anders Tjellström first implanted patients with percutaneous bone-anchored hearing aids, ushering in the modern era of bone-conduction hearing.[1] This followed Per-Ingvar Brånemark's well-known work with titanium implant osseointegration.[2] Tjellström's implants allowed direct sound transmission to bone, avoiding the attenuation of the soft tissue over the mastoid. Nobel Pharma commenced initial production, with the Entific company subsequently created to take things forward. For additional background information, Mudry and Tjellström's paper is recommended.[3]

PHYSIOLOGY

Bone-conduction hearing devices (BCHDs) deliver sound energy to both inner ears.[4] The overall principle is to establish pressure differences between the scala tympani and the scala vestibuli such that there is movement of the

basilar membrane and hence neural stimulation. There are multiple complex sound pathways[5] (Figure 93.1):

- **Outer ear:** In addition to normal air conduction, bone-conduction (BC) sound vibrations enter the external auditory canal (EAC) via soft tissue and bone vibrations which are transmitted to the tympanic membrane (TM). The sound energy to the TM can change notably if the EAC is occluded.[6, 7]
- **Middle ear:** With a normal ossicular chain connected between the TM and stapes footplate, the ossicles have been shown to vibrate in phase with low frequencies but become decoupled at higher frequencies.[8]
- **Inner ear:** Sound and vibration transmission relies on fluid pressure changes and inertia/fluid inertia. Sound is therefore acting both by direct inertial forces through bone but also from the outer and middle ear.

Transcranial transmission is recognized to be quite efficient and hence the contralateral ear requires masking when BC audiometry is performed. Transcranial transmissions are close to 0 dB for frequencies up to 700 Hz and decrease with higher frequencies.[9]

This has clinical implications because BC sensitivity is fairly similar between percutaneous and transcutaneous modes of transmission for frequencies below 1 kHz.[10] There would be an expected 5–15 dB improvement in efficiency with percutaneous systems when a BC transducer is directly attached to the skull at higher frequencies. Transmission increases through the skin in line with the area of skin transducer interface.[11]

In cases of bilateral stimulation a low transcranial transmission is better for binaural cues; for single-sided deafness a high transcranial transmission is better. Looking into the benefit of bilateral implants, an improvement in terms of hearing thresholds, sound localization and speech perception has been reported.[12] Binaural fitting is preferred for bilateral conductive loss when the BC thresholds do not vary by more than 20 dB in the higher frequencies of 3 kHz and 4 kHz. In cases of unilateral hearing loss the contralateral ear should have a BC average of ≤20 dB HL to reduce the head shadow effect.[13]

CLASSIFICATION

BCHDs should be considered in context with other implantable devices such as middle ear, cochlear and brainstem implants. All these have a role in helping with hearing rehabilitation when acoustic aids are unable to give benefit.

BCHDs are broadly categorized as either **percutaneous**, i.e. where the device is in direct contact with the skull, or **transcutaneous,** where the skin and soft tissue are interposed. Percutaneous systems are well established, with a titanium abutment passing through the skin to allow a hearing aid to pass the sound directly into the bone. The transmission across the skin is 'passive' as there is no active component apart from the external hearing aid.

Transcutaneous systems are those with intact skin. These can pass the sound passively across the skin, or can be active with an internal vibrating actuator or amplification device (Table 93.1).

CLINICAL INDICATIONS

BCHDs are generally used for the rehabilitation of hearing loss only when conventional acoustic aids cannot be fitted, or have been trialled and have failed to improve the hearing.

Common current indications include the following:

- **Conductive and mixed losses**
  - congenital causes such as atresia or microtia (see Chapter 12)
  - acquired causes such as chronic otitis media or ossicular pathology (see Chapter 83)
  - chronic discharging ear (such as chronic suppurative otitis media (CSOM) or recurrent otitis externa) (see Chapter 78 and Chapter 83)
  - inability to wear a hearing aid following radical mastoid surgery
  - unilateral mixed hearing loss.
- **Single-sided deafness – sensorineural or conductive**
  - trauma resulting in hearing loss.

TABLE 93.1 Surgical classification of BCHDs

Type of device	Skin relationship
Percutaneous	Passive
Transcutaneous	Passive (skin drive)
	Active (direct drive)

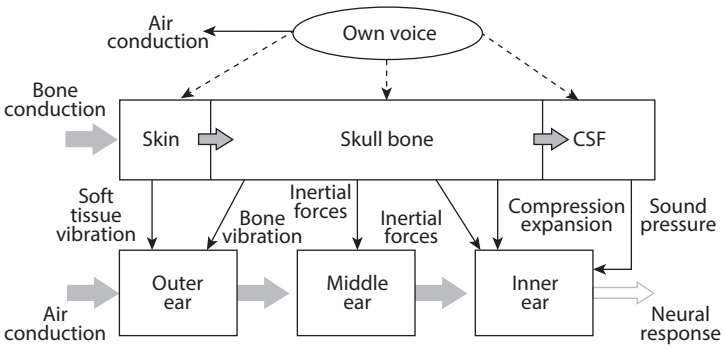


Figure 93.1 A model of the pathways involving sound conduction (reproduced courtesy of Stefan Stenfelt Karger publications).[9]

- unsuitable ear canal for a conventional hearing aid, e.g.
  - in a radical mastoid cavity
  - an extremely narrow ear canal
  - 'blind sac' ear canal closure
  - lateral temporal bone resection
  - extensive cranial base surgery.

ASSSESSMENT

The assessment of patients must be within a multidisciplinary team (MDT) framework, to ensure that the most appropriate system is used, as alternative devices such as MEIs and CIs complement the whole process.[14]

The devices are in continuous development. New systems will emerge in the future so it is recommended to follow the manufacturer's fitting criteria, but not to implant at the upper end of such fitting criteria, as a small additional drop in hearing will mean that the device is no longer suitable.

In 2016 NHS England published commissioning guidelines.[15] Funding would be considered for the following:

1a Patients with unilateral or bilateral conductive or mixed hearing loss within the manufacturer's fitting criteria
AND
Stable BC thresholds (≤15 dB deterioration in >2 frequencies in a 2-year period)
OR

1b Unilateral sensorineural hearing impairment (including SSD) where the better ear has BC hearing thresholds within the manufacturer's fitting criteria including SSD
AND

2 The patient has trialled an ACHA or wireless CROS/BiCROS hearing aid for a minimum of 4 weeks, or is anatomically or physiologically unable to undertake a trial of an ACHA
AND

3 Has trialled a BCHD on a softband or headband for a minimum of 14 days and shown benefit in speech tests.[10]

Systems are available to trial processors in a passive transcutaneous format. These are supplied as headbands and elasticated softbands and the recently introduced Sound Arc (manufactured by Cochlear) and the adhesive skin attachment ADHEAR (manufactured by MED-EL) prior to any surgical intervention (**Figure 93.2**).



Figure 93.2 Sound Arc.

For the child with congenital meatal atresia/microtia, consider carefully the management of the pinna, be it with prosthetics or reconstruction so that surgical approaches used for BCHDs do not compromise future reconstruction. Surgical correction of meatal atresia is now rarely performed in the UK (see also Chapter 16, Microtia and external ear abnormalities).

BCHDs will not be commissioned for:

- patients with a bone disease that is unable to support an implant
- patients who have a sensitivity or allergy to the materials used
- patients with physical, emotional or psychological disorders that, despite suitable treatment and support, would interfere with surgery or the ability to allow suitable rehabilitation such that significant benefit would be unlikely.

SURGICAL OPTIONS

Percutaneous (bone-anchored) devices

Two devices are currently available in the UK – the Baha® (Cochlear™ Bone Anchored Solutions) and the Ponto bone-anchored hearing system (Oticon Medical). The Cochlear Baha system was initially commercially available from 1984 (manufactured by Entific), and the Oticon from 2009.

Both are semi implantable, with a titanium osseointegrated fixation into the skull and a skin-penetrating abutment to facilitate attachment for the sound processor aid. This abutment allows for direct and effective transmission of sound vibrations to the skull and hence to the inner ear (**Figure 93.3**).



Figure 93.3 The Cochlear BAHA system (courtesy of Cochlear Limited).



Figure 93.4 Cochlear connect based on the BA400 abutment and BI300 implant (courtesy of Cochlear Limited).

In 2010 Cochlear introduced changes to the osseointegrated titanium fixture which included a wider base (4.5 mm versus 3.75 mm) for increased stability, smaller treads at the implant neck to improve load distribution and a tioblast™ coating for faster osseointegration to the BI300 system. In 2012 it further modified the abutment with a hydroxyapatite coating (BA400) (Figure 93.4).

Oticon Medical's system similarly comprises an implant and options of various lengths of percutaneous abutments to cater for various skin thicknesses which enable tissue preservation surgery. The dermatome to take split skin is no longer used.

Audiological criteria

The results of presurgical assessment with a transcutaneous processor give a good indication of outcome as skin attenuation can account for 10–15 dB. The power of processors has increased, with BC levels of about 65 dB over 1, 2 and 3 kHz using the most powerful processor currently available.



Figure 93.5 Oticon abutment inserted using minimal extended incision.

Surgical considerations

The Food and Drug Administration have set a minimum age for paediatric use at 5 years. However, the minimum age for implantation is debated and there is no fixed worldwide guideline. In 2005 an international consensus was issued regarding BCHAs, which recommended that surgery not be undertaken prior to age 2–3 years. This was to allow the skull to reach a minimum thickness and conditions to be suitable to fit the fixture and allow osseointegration.[16]

Though successful implantation has been reported in patients as young as 14 months, the complication rate is inversely proportional to the age at implantation.[17] It is important to stimulate hearing as early as possible, and therefore in children too young for implantation the use of a BCHA via a softband, which holds the hearing aid to the skin of the scalp via a metal or elastic headband, is advocated from about the age of 3 months.

In the past, bone-anchored hearing aid (BAHA) surgery on children was staged, but the newer tissue-preserving single-stage implants mean this is not always necessary. A simple linear incision eliminates the need for a skin flap (Figure 93.5).

However, in children a longer time to osseointegrate is recommended to compensate for the thinner bone, although this is subject to further evaluation at present.[18]

The implantation is usually performed under local anaesthetic and is well tolerated, although anxious patients and children may require sedation or general anaesthetic.

MRI compatibility

With the external processor removed, the remaining titanium implant and abutment are non-magnetic and pose no issue with MRI compatibility. A small area of artefact will, however, be caused adjacent to the implant.

Outcomes

The main post-operative difficulties from transcutaneous BAHAs relate to the protrusion of the abutment through the skin. There are cosmetic issues, although these vary in importance in different cultures. A practical and quite

TABLE 93.2 Classification of cutaneous complications of transcutaneous abutments in BAHAs (after Holgers et al.)[19]

Severity	Complication(s)
Grade 0	No skin reaction
Grade 1	Redness with slight swelling
Grade 2	Redness, moistness and moderate swelling
Grade 3	Redness, moistness and moderate swelling with tissue granulation
Grade 4	Profound signs of infection, resulting in removal of the implant

frequent (up to 10% of patients) difficulty with percutaneous BAHAs is that the skin requires daily hygienic care and there can be skin overgrowth around the abutment, skin infection and low-grade inflammation. This requires medical attention and can occasionally lead to loss of the fixture/abutment.

The most useful classification of cutaneous complications of transcutaneous abutments in BAHAs was suggested by Holgers et al. (**Table 93.2**).[19] This scale, which ranges from 0 to 4, with 0 being reaction-free skin around the implant and 4 being overt infection requiring implant removal, is usually used to report skin complications.

These complications seem to affect children more than adults. There is a higher rate of fixture loss (up to 14% over 15 years) in the paediatric population.[20] A much higher rate of fixture loss occurs with the shorter 3 mm fixture, so a 4 mm fixture should always be used where practical.

Challenges in a paediatric setting include accommodating for growth and increases in soft-tissue thickness, especially during puberty. The abutment is available in various lengths and may be changed to adapt to the child's growing needs.

Passive transcutaneous devices

Two passive systems are available for use with adults and children: the Sophono™ (Medtronic, Boulder, CO) and the Cochlear™ Baha® Attract (Cochlear™ Bone Anchored Solutions). Both depend on the fixation of an internal magnet to the skull, which is passive. An external hearing aid with oscillator can then be attached to an external magnetic pad, made soft with padding, to allow the firm attachment of the device to the skin. This then transmits the sound in a similar way to a softband, although there is additional transmission of sound through the firm connection of the internal magnet to the bone. One of the benefits of such systems is a reduction in the risk of inflammation, injury and the psychological problems that are associated with percutaneous devices.[21]



Figure 93.6 The Sophono plate *in situ*.

SOPHONO™

Professor Siegert initially published his results of the 'Otomag' system, a partially implantable bone-conduction device, in 2011.[22] The Sophono Alpha 2 MPO™ system comprises a surgically implanted internal plate containing twin hermetically sealed magnets (**Figure 93.6**) and the external digital sound processor is coupled to a base plate housing twin magnets corresponding to the internal ones. The processor transmits vibrations through the skin into the bone and then to the cochlea. The device is intended for people with conductive hearing loss, SSD and mixed hearing loss.

Audiological criteria

As processors have developed, so has candidacy. BC hearing thresholds should be ≤45 dB or in the case of SSD, ≤20 dB in the contralateral ('good') hearing ear. However, care should be taken to stay well within these limits as there is high-frequency attenuation in all passive transcutaneous devices which limits amplification significantly.

Surgical considerations

Magnets are implanted into shallow 2 mm bone beds in a one-stage procedure. They are secured with five titanium screws (**Figure 93.6**). The skin above the magnets should be reduced to a thickness of 4–5 mm, which reduces the attenuation to less than 10 dB compared to direct bone stimulation. Programming typically commences 4–6 weeks after surgery.

MRI compatibility

The Sophono™ is MRI conditional up to 3 Tesla.[23] It is reported that the magnets create a 5 cm shadow/artefact.

BAHA® ATTRACT SYSTEM

A new transcutaneous system, the Baha® Attract, uses a magnet to secure the BAHA. While a major advantage in a paediatric setting is eliminating the soft-tissue complications of a BAHA, disadvantages include artefact on subsequent MRI scans and possible dampening of the high-frequency signal through the skin.

Audiological criteria

These are essentially the same as the Sophono, and caution should be exercised if there is significant SNHL at the high frequencies.

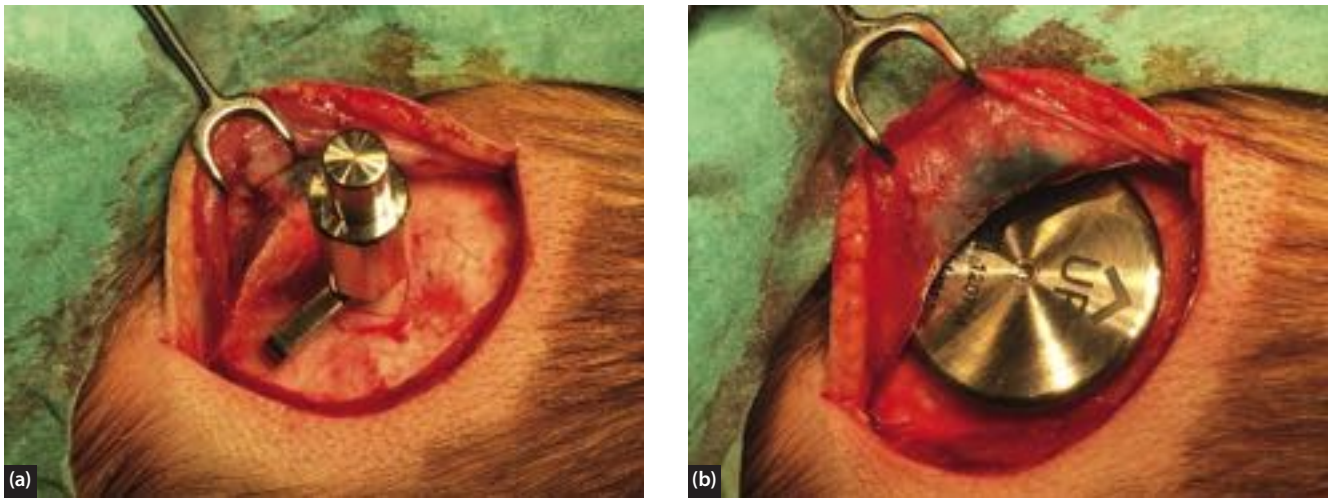


Figure 93.7 The BAHA® Attract. (a) A rotating sizer is used to make sure the bony bed is flat with no secondary points of contact with the magnet. **(b)** The BAHA Attract magnet *in situ*.

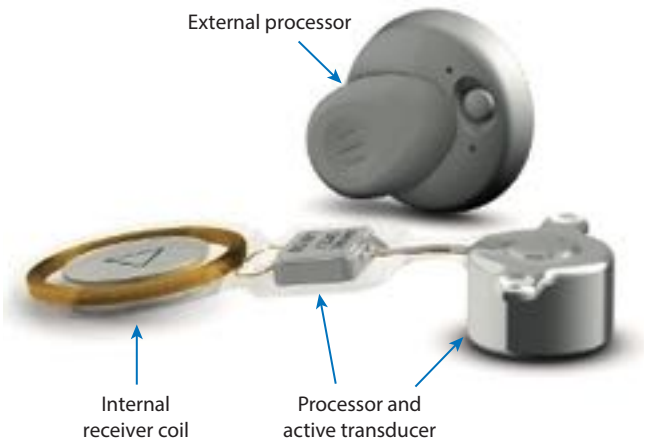


Figure 93.8 The Bonebridge components.

Surgical considerations

The system is based on the established osseointegrated BI300 implant secured to the skull behind the pinna and a BIM400 implant magnet that are implanted beneath the skin. Surgery is usually performed under local anaesthetic as a one-stage procedure. Surgically the magnet has to be correctly aligned and must not be in contact with the bone. A special bone bed indicator is used to ensure compliance (**Figure 93.7**). Prior to closure the optimal skin thickness is 3–6 mm. If the skin is too thick, the processor may be less efficient or fall off.

MRI compatibility

Non-clinical testing has demonstrated that the BIM400 implant magnet, in combination with the BI300 implant, is MRI conditional in a static field of 1.5 Tesla. An image artefact is approximately 11.5 cm.[24]

Active transcutaneous devices

There is currently one commercially available active transcutaneous system. This is the Bonebridge, an active semi-implantable internal device produced by MED-EL (Vibrant MED-EL Hearing Technology GmbH). Other devices are in clinical trials.

Introduced in September 2012 following on from the principles of the successful development of the Vibrant Soundbridge middle ear implant (see Chapter 95, Middle ear implants), the Bonebridge consists of an external audio processor and an internal BC implant (**Figure 93.8**). The internal component has a receiver coil, a magnet, a demodulator and a bone-conduction floating mass transducer (BC-FMT) secured to the bone by two titanium screws. The power to drive the FMT is transmitted transcutaneously via an inductive link to the internal coil, processed by the demodulator and then relayed to the BC-FMT, which then transduces the signals into mechanical energy. Osseointegration of the titanium screws is not thought to be crucial.

Audiological criteria

The Bonebridge is designed for patients with conductive and mixed hearing losses as well as SSD. The BC level should be better than 45 dB between 500 Hz and 4 kHz and 20 dB or better in the contralateral ear for SSD. There should be stable thresholds and no evidence of auditory neuropathy, retrocochlear or central hearing impairment.[25, 26]

Surgical considerations

The principle of surgery is the placement of the BC-FMT either within the mastoid or in the retrosigmoid position. The BC-FMT should not be placed in an unhealthy mastoid. Surgery is typically performed under general anaesthesia but local anaesthesia is a practical option.[27] Because of the size of the device, surgery is reserved until there has been sufficient skull growth to accommodate it.

It is recommended that radiological planning using 3D reconstruction be performed prior to surgical intervention (**Figure 93.9**).

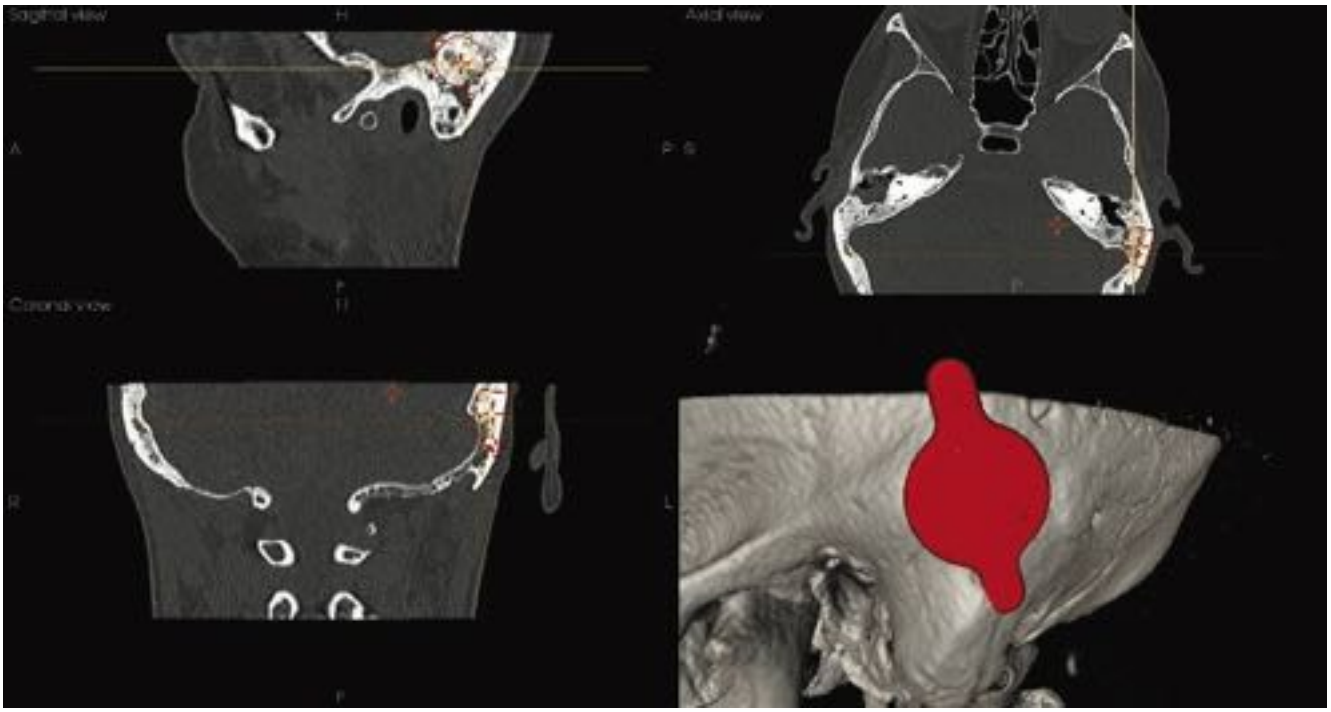


Figure 93.9 3D planning using radiological images.



Figure 93.10 The Bonebridge *in situ* with 'lifts'.

Compression of the sigmoid sinus and/or dura may be necessary but 'lifts' of up to 4 mm can be used and are often required. The device is held in place by titanium screws (Figure 93.10). The system was found to be safe and effective.[28]

MRI compatibility

The device has a non-removable magnet. Following testing, the manufacturers report the device is conditional to 1.5 Tesla. As with the presence of a magnet, image artefacts will occur.

CONCLUSION

New devices continue to be introduced and current technology continues to evolve. With time, new indications continue to arise in the treatment of paediatric deafness. Despite the rapidity of introduction of new technology, it is important that the introduction and application of this into patient care be conducted in a rigorous evidence manner. In achieving this, it is essential that good collaboration continues between the clinicians and industry and, most importantly, that regular and thorough feedback from patients and caregivers about the influence on these on their quality of life is sought.

BEST CLINICAL PRACTICE

- ✓ A multidisciplinary team should oversee all children considered for BCHDs.
- ✓ Implanting children with percutaneous devices at too young an age risks an increase in complications. Children should be aged at least 2 years to permit sufficient growth in the skull. The FDA has set a minimum age of 5 years.
- ✓ Careful planning is especially important for children with microtia so that later reconstruction or cosmesis is not compromised.
- ✓ A simple linear incision with no elaborate skin flaps is usually sufficient for BAHA surgery.
- ✓ Some devices and device components cause difficulty with MRI scanning. Devices may also cause issues with airport security systems. Make sure clinicians, patients and parents are aware by consulting individual manufacturer's guidelines.

KEY POINTS

- A range of devices to transmit sound energy to the inner ear via the bones of the skull (BCHDs) is now available.
- BCHDs are used for the rehabilitation of hearing loss when conventional acoustic aids cannot be fitted or have been trialled and have failed to improve the hearing.
- Indications for use are increasing.
- Very good results are now reported in children with single-sided deafness.

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CHAPTER 94

COCHLEAR IMPLANTS

Andrew Marshall and Stephen Broomfield

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: cochlear implants, cochlear implantation AND hearing implants, surgery, candidacy, criteria, standards, adults, paediatric, children, elderly, quality of life, outcomes, complications and future.

INTRODUCTION

Cochlear implants have transformed the management of severe to profound hearing loss, particularly in both the very young and the elderly. Cochlear implant surgery and the subsequent rehabilitation are normally straightforward for implant centres within the UK and across the developed world. The technology has had greatest impact in transforming the education of children born with a profound hearing loss who are implanted early. The majority of these children attend mainstream education, using spoken language to communicate.

At the other end of the age spectrum, it is recognized that there is significant unmet need in the treatment of severe to profound hearing loss in the adult population, particularly the elderly.[1] The impact of this unmet need can have a significant effect on the individual's health and impose a financial burden on society as a result.[2]

BASIC PRINCIPLES

Cochlear implantation (CI) is considered in patients with severe to profound hearing loss who are failing to gain sufficient benefit from appropriate and well-fitting hearing aids. Audiological and other criteria for implantation are different for adults and children and are discussed further below. The external part of the cochlear implant detects the sound signal and converts it to an electrical signal which is transmitted to the internal processor. The way in which the signal is passed into the electrode array depends on the speech processing strategy utilized by that device. Each implant manufacturer has developed strategies that they believe have advantages over the others.

All cochlear implants make use of the tonotopic arrangement of the auditory system, whereby high-pitched sounds are transmitted through spiral ganglion cells corresponding to the basal turn of the cochlea, and low-pitched sounds by those at the apex of the cochlea. In normal young adults, there are approximately 35 000 auditory nerve fibres; it is estimated that at least 10 000 are required for speech recognition using a cochlear implant.[3] The success of an implant depends upon the transmission of the signal to the auditory cortex via the auditory pathways from the ear, followed by appropriate central processing to ensure understanding of the signal. Consideration of these central functions therefore forms part of the assessment of the cochlear implant candidate.

Performance with a cochlear implant is optimized postoperatively through a process of programming known as 'mapping', combined with intensive rehabilitation. The cochlear implant team is therefore multidisciplinary and includes teachers of the deaf, speech and language therapists, psychologists, audiologists, audiological scientists, radiologists and surgeons. Widely accepted standards exist for the assessment and management of patients being considered for CI.[4–6]

CANDIDACY

In the earliest years of cochlear implants, the technology was considered to be experimental and was offered only to the most profoundly deaf adults. In modern practice, the reliability and outcomes of CI have improved and criteria for candidacy have evolved to include both adults and children with some residual hearing as well as congenitally deaf infants. Criteria differ according to the healthcare systems and funding arrangements of individual countries. In England and Wales, the National Institute for Health and Care Excellence (NICE) have stipulated the following criteria for CI, based on clinical and cost-effectiveness assessments:[7]

- A cochlear implant should be considered for any person with a severe to profound hearing loss who does not gain adequate benefit from acoustic hearing aids.
- Severe to profound deafness is defined as the ability to hear only sounds louder than 90 dB HL at 2 kHz and 4 kHz without hearing aids.
- Hearing aids should be used for at least 3 months unless inappropriate or contraindicated.
- Adequate benefit with hearing aids is defined as:
  - For adults, a score of 50% or greater on Bamford–Kowal–Bench sentence testing at a sound level of 70 dB SPL.
  - For children, speech, language and listening skills appropriate to age, developmental stage and cognitive ability.
- Assessment should be by a multidisciplinary team and the tests used should be adapted to take into account the candidate's disabilities as well as their language and communication ability.
- Simultaneous bilateral CI is recommended for children and for adults who are blind or who have other disabilities that increase their reliance on auditory stimuli as a primary sensory mechanism for spatial awareness.

The audiological assessment of potential cochlear implant recipients usually also includes an auditory brainstem response (ABR) test. This aids in: validating the accuracy of the behavioural responses; detecting a central problem or absent cochlear nerve; and (in older patients) ruling out non-organic hearing loss.

Special cases

In many cases, a candidate clearly meets the above criteria and, following a full assessment (described in 'Assessment' below), decision-making is straightforward. Often, however, there are additional factors that must be taken into account. These factors are likely to lead to a further evolution of cochlear implant candidacy criteria in future.

Adults

RESIDUAL HEARING

Traditionally, any residual hearing in an ear receiving a cochlear implant would be lost. With current surgical techniques (described in 'Surgical technique' below), it is possible to preserve hearing in some cases. This allows for combining a hearing aid with a cochlear implant in the same ear, known as electric–acoustic stimulation (EAS). Typically, this applies to the patient with a 'ski-slope' hearing loss, i.e. some hearing in low frequencies, dropping abruptly to a severe to profound loss in the higher frequencies such that the criteria for CI are still met. Specially designed electrode arrays are available for this situation, for example the 'Hybrid' electrode (Cochlear Ltd) that is shorter than other electrodes, entering only the basal turn of the cochlea and therefore covering just the higher frequencies. Many surgeons prefer, however, to use a medium or standard-length atraumatic electrode with which residual hearing can often still be preserved; but should hearing be lost, the full range of frequencies is covered by the electrode, ensuring optimal performance.

THE ELDERLY

With the rising average age of the population of developed countries, cochlear implant candidates increasingly present in their seventies and eighties. There is good evidence that this group perform well with cochlear implants, with similar speech perception and improvement in quality of life when compared to younger recipients.[8, 9] Recently, a link between hearing impairment and cognitive decline in older adults has been shown,[10] and CI may have a role to play in improving social interaction and preventing cognitive decline in profoundly deaf elderly patients.[11]

FAR-ADVANCED OTOSCLEROSIS

The term 'far-advanced otosclerosis (FAO)', first used by House and Sheehy in 1961, is applied to the patient with otosclerosis and a profound hearing loss. Such patients may undergo stapedectomy in an attempt to restore their ability to wear hearing aids. However, results from CI are also good, with some series finding patients with FAO to be among the best performers, possibly due to the fact that the otosclerosis process generally spares the sensory elements of the cochlea.[12] Studies suggest that the outcomes of CI in FAO are equivalent to those in other aetiologies of deafness, with an improved quality of life.[13, 14] Patients with FAO are more prone to non-auditory stimulation (e.g. facial nerve stimulation), though in most cases this can be easily resolved by switching off the electrodes that are responsible, albeit with some potential reduction in performance.[13, 15, 16]

NEUROFIBROMATOSIS TYPE 2

Hearing loss in patients with neurofibromatosis type 2 (NF2) may be secondary to bilateral vestibular schwannomas or their treatment. Using modern surgical techniques, it is sometimes possible to excise tumours with preservation of the cochlear nerve. This allows for consideration of CI rather than auditory brainstem implantation, with more reliable outcomes. Intra-operative testing using electrically evoked auditory brainstem responses or cochlear nerve action potentials may be used to determine whether

a cochlear implant is appropriate. In England, the four specialist NF2 centres have agreed a protocol for the management of hearing loss in this challenging group.[17]

SINGLE-SIDED DEAFNESS

Following CI in a group of patients with single-sided deafness (SSD) who underwent surgery as a primary treatment for troublesome tinnitus, it was discovered that not only did the tinnitus improve but, in addition, the patients experienced significant audiological benefit.[18] It became apparent that previous concerns regarding the brain's ability to integrate electrical and acoustic signals from the two ears were unfounded. For patients with SSD, CI provides particular improvement in speech recognition in noise.[19] Criteria in the UK do not yet allow for CI for SSD, as cost-effectiveness is yet to be established.

PATIENTS OUTSIDE CURRENT CRITERIA

Whatever audiological criteria are applied, all cochlear implant centres frequently encounter patients who are struggling to hear using standard hearing aids but whose speech recognition scores are outside those criteria. Despite this, such patients often benefit significantly from CI.[20] Similar findings have been reported in children.[21] This highlights the need continually to review selection criteria and to reassess the measures used for assessment.

Children

ADDITIONAL DISABILITIES

In the early days of CI, children with significant additional disabilities (including cognitive impairment, developmental delay, visual impairment and communication disorders) were considered unsuitable candidates. As candidacy criteria have expanded, such children have been increasingly assessed for CI. In addition, with infants receiving CI before the age of 12 months, a number of children are diagnosed with additional disabilities (e.g. autistic spectrum disorder) only after their cochlear implant. Traditional assessment tools and post-operative speech perception measures may be unsuitable for children with additional disabilities, many of whom will never develop oral communication; decision-making and post-operative rehabilitation therefore often rely upon the experience of the cochlear implant multidisciplinary team.[22] Careful counselling of parents is crucial to decision-making and to ensure realistic expectations of outcome.

AUDITORY NEUROPATHY SPECTRUM DISORDER

Auditory neuropathy spectrum disorder (ANSD) is characterized by absent auditory brainstem responses with normal otoacoustic emissions. The prevalence of ANSD may be as high as 10% in children with permanent hearing loss.[23] There is a range of functional hearing impairment in ANSD, and in cases with severe to profound hearing loss CI can be an effective means of rehabilitation.[24] However, as the hearing in ANSD may improve over time, a period of observation is recommended before proceeding to surgery. This explains why the majority of children with congenital sensorineural hearing loss (SNHL) are observed until at least the age of 6 months, when behavioural hearing assessments are possible and the decision to proceed to surgery can be made with increased confidence. Longer periods of observation may be appropriate in some cases, though timely intervention is crucial to ensure optimal cochlear implant outcomes.[25]

ANATOMICAL ABNORMALITIES

Congenital profound SNHL is associated with inner ear anatomical abnormalities in approximately 20% of cases.[26] The cochlear nerve itself may be absent or hypoplastic; such cases require careful clinical and electrophysiological assessment to determine whether cochlear or auditory brainstem implantation is appropriate.[27] In some cases such abnormalities are isolated findings, but they may be associated with other anatomical variations (e.g. facial nerve position) or particular syndromes (e.g. CHARGE syndrome). Pre-operative assessment and surgical planning must be undertaken with additional care to ensure appropriate management of these complicated cases.[28]

ASSESSMENT

Medical

When considering cochlear implantation, patients who are found to meet the audiological criteria must undergo additional medical, otological, imaging and psychological assessments. Modern surgical and anaesthetic techniques mean that CI surgery is straightforward in uncomplicated cases. The pre-operative assessment of the patient considering CI focuses on ensuring fitness for general anaesthesia. This particularly applies to the very young and very elderly. CI is possible under local anaesthesia in adult patients who may not be fit for surgery otherwise.[29]

Otological

CI is contraindicated in patients with active middle ear infection or cholesteatoma, as infection around an implant may be associated with an increased risk of meningitis.[30] In addition, chronic infection is extremely difficult to eradicate and may necessitate device removal or lead to the device extruding. In such cases, any infection or disease in the middle ear or mastoid must be fully eradicated prior to implantation, with surgical treatment being required in many cases. Perforations of the tympanic membrane should be closed to provide a barrier against infection. In patients who have had canal wall-down mastoid surgery previously, or who require it to treat their disease in preparation for implantation, the usual recommendation would be to obliterate the middle ear and mastoid cavity and close the ear canal with a blind sac procedure. This must be done with meticulous surgical technique to

reduce the risk of development of cholesteatoma, which may remain asymptomatic for many years.[31] In cases that require surgical treatment for middle ear or mastoid disease, CI can be performed simultaneously or as a staged second operation, usually 3–6 months later.[32,33] The management of otitis media with effusion (glue ear) in children requiring CI, or who develop it following implantation, remains controversial. However, significant complications related to ventilation tube insertion either prior to, or following, CI are rare.[34]

Imaging

Cross-sectional imaging is a key part of pre-operative planning prior to CI. Identification of cochlear or cochlear nerve aplasia, which would make implantation impossible, is particularly important in prelingually deafened infants. Magnetic resonance imaging (MRI) is therefore the preferred initial imaging modality in this group.[35] Other abnormalities, including inner ear anomalies, cochlear lumen obliteration (e.g. following meningitis or in cochlear otosclerosis), middle ear pathology and anatomical variations (e.g. low-lying dura or anterior position of the sigmoid sinus) should also be identified pre-operatively. Computerized tomography (CT) scanning may improve the identification of such anomalies, and is routine practice in some centres. It is the authors' practice to use CT scanning selectively in infants, to avoid exposure of the developing brain and orbits to ionizing radiation. In adult patients, previously undiagnosed coexisting pathologies (e.g. acoustic neuroma) may be identified using MRI scanning, which is again the modality of choice.[36]

Psychological

The clinical psychologist is an important member of the cochlear implant team. Every patient and parent considering CI must be carefully counselled, to ensure that they are prepared for the surgery and post-operative rehabilitation, to ensure realistic expectation of outcome, and to discuss potential concerns regarding the process. While in some cases this work can be done by the other members of the multidisciplinary team, the psychologist is best placed to explore the complex social, family, cultural and peer-related issues that are not uncommon in this population.[37] Some groups, including adolescents, patients with a long duration of deafness and patients with a history of psychiatric problems, may have a particular need for psychological input prior to CI.

DEVICES

There are four manufacturers providing cochlear implants for use in the UK (Advanced Bionics, Cochlear, MED-EL and Oticon Medical (previously Neurelec)). A full discussion of the differences between the available devices is outside the scope of this chapter. Outcomes are generally similar with all devices (see 'Outcomes' below), and all have similar reliability according to internationally agreed reporting guidelines.[38] All of the devices share a similar basic design:

- the external part: the microphone, sound processor and transmitter coil
- the internal receiver–stimulator package
- the intracochlear electrode.

These components are summarized below.

The external part: the microphone, sound processor and transmitter coil

This part of the cochlear implant detects the acoustic signal and converts it to an electrical signal with both temporal and spatial components. The encoded signal is transmitted to the internal device using radiofrequency via the external coil. New developments in the external components include: the position of the microphone (including devices that are a single magnetic unit, with no behind-the-ear processor); improved functionality drawing on advances in hearing aid technology (for example the Advanced Bionics Naida system that allows direct communication between the cochlear implant and a hearing aid in the contra-lateral ear to provide bimodal hearing); wireless connectivity to external devices; improved waterproof capability.

The internal receiver–stimulator package

This contains the internal magnet, telemetry coil and hermetically sealed electronics system. There is also a ground electrode for current return, either incorporated within the package or as a separate electrode placed under the temporalis muscle. Once received, the decoded signal is sent to the electrodes within the cochlea according to the processing strategy being used. New developments in the receiver–stimulator package include new processing strategies and smaller size. In addition, the latest generation of cochlear implant devices are all compatible with MRI scanning to 1.5 Tesla without magnet removal. Special precautions may be required to reduce potential complications.[39] Stronger MRI fields may necessitate magnet removal, though new designs such as MED-EL's rotating magnet that self-aligns when in the MRI field allows MRI scans up to 3 Tesla with the magnet *in situ*.

The intracochlear electrode

The electrode that is placed into the cochlea is in fact a group of individual wires, each ending at a contact point along the silicone casing. The number of individual wires varies depending on the manufacturer and type of electrode. Electrodes have become generally smaller in an attempt to reduce the trauma of insertion and allow for hearing preservation as well as the potential use of future technologies that might require preservation of cochlear function. Modern electrodes can be inserted via the round window or through small cochleostomies with a diameter of 0.5–0.8 mm.

The optimal resting position of the electrode within the scala tympani is debated; various manufacturers advocate lateral wall, mid-scala or modiolar-hugging designs. There is also much debate as to the optimal length of electrode; longer electrodes may allow for stimulation of the full length of the spiral ganglion cells but are also more likely to cause trauma to the apical basilar membrane. New imaging techniques to calculate the cochlear duct length may allow for an electrode of optimal length to be selected for individual patients.[40] Some electrode designs are available for specific situations: examples include the short electrode for EAS (see above), the compressed array or split/double electrode for cochlear ossification, and the electrode with a stopper incorporated into the silicone casing for plugging the cochleosotomy in case of a perilymph gusher.

OUTCOMES

Advances in technology in recent years, in particular the improvement in speech-processing strategies, have led to improved speech perception with CI. In infants, speech perception is of paramount importance for the development of spoken language. Other outcomes in children and adults, such as effect on educational achievement, social interaction, employment and quality of life, are also important. Key evidence regarding outcomes can be summarized as follows.

Outcomes in children

- Earlier age at CI is associated with better language development. This is now well accepted and has been shown in many studies. Many children implanted before 18 months of age show a similar rate of language development as normal hearing peers. Those implanted after 3 years of age may struggle to catch up, and it is recognized that a proportion of children will remain language-delayed when compared to normal hearing peers.[41,42] It is important to note, however, that children with cochlear implants consistently show a higher level of language attainment than profoundly deaf children using hearing aids.
- The importance of early age at implantation is due to the fact that there is a 'sensitive period' of around 2–3 years during which development of the central auditory system shows greatest neural plasticity.[43] The introduction of universal newborn hearing screening has allowed for the early identification of children with profound hearing loss.
- The preferred age of implantation of profoundly deaf infants in the UK is currently considered to be around 12 months. There is emerging evidence that even earlier implantation (between 6 and 12 months) may be optimal, and this has been shown to be safe in experienced centres.[44]
- Cognitive impairment is an important factor in outcome following CI. Children with additional disabilities that include cognitive impairment may never acquire spoken language. Nonetheless, CI may still be an important method of improving quality of life in this group.[22]
- Other factors associated with improved language outcomes in children include the fitting of up-to-date processors, greater residual hearing prior to implantation, better interaction between parent and child, and higher socioeconomic status.[45]

Outcomes in adults

- Duration of severe or profound deafness (and not age at implantation) is the most important factor in predicting speech perception outcomes in adult patients. As with neural plasticity in infants, this is due to a deterioration in the spiral ganglion cell population and the central auditory pathways with a long period of auditory deprivation (e.g. 20–30 years).[46]
- Duration of deafness is often a key consideration in deciding which ear to implant. A common scenario is the patient presenting with one ear that has been unaided for more than 20 years and a small amount of residual hearing on the other side; such a patient is advised to undergo implantation in the better ear, putting the residual hearing at risk to ensure optimal outcome with the cochlear implant (compare this to the more usual situation where the preference is to implant the worse-hearing ear to optimze hearing aid use on the contra-lateral side).

Special considerations

When considering outcomes, some situations warrant special attention.

BINAURAL HEARING

Patients with binaural hearing, bilateral cochlear implants or bimodal hearing (a cochlear implant in one ear and a hearing aid in the other) have improved outcomes when compared to those using a unilateral implant. Advantages include sound localization, spatial acuity and improved speech understanding in challenging listening environments, such as in the presence of background noise (see Wanna et al.[47] for a review of this topic). Some of these advantages improve over time, often years, following implantation. Quality of life is improved in bilateral cochlear implant recipients compared to unilateral recipients, though in sequentially implanted cases the relative increase is higher following the first implant.[48] Due to the advantages offered, there is increasing interest in CI in SSD (see 'Candidacy' above).

For similar reasons, cochlear implant manufacturers are increasingly working closely with hearing aid companies to improve the compatibility of the two devices and thereby provide optimal binaural hearing when only one cochlear implant is inserted.

MUSIC PERCEPTION

Despite recent advances in cochlear implant technology, music perception in implant recipients remains generally poor.[49] Recently developed music test batteries have shown limited ability among postlingually deafened

adults in melody, pitch and timbre identification, albeit with some notable exceptional cases. Rhythmic identification remains normal in implant users when compared to the normal population. Some prelingually deafened infants are able to enjoy music, and there is much current interest in the use of musical training in postimplantation rehabilitation.

SURGICAL TECHNIQUE

The majority of cochlear implant surgeries undertaken in the UK are via the transmastoid approach, accessing the cochlea via the facial recess. Other surgical techniques have been described including the suprameatal[50–52] or the transcanal approaches (with or without use of an endoscope).[53–55] The transmastoid approach will be discussed here.

Most surgeons use a postaural incision, sufficient in length to allow the implant to be introduced. The surgeon should avoid placing the incision line directly over the receiver–stimulator package to minimize post-operative wound complications.

The soft tissue is dissected down to the periosteum, which is incised to create an anteriorly or posteriorly based flap. A cortical mastoidectomy is then performed. A subperiosteal pocket is created to house the receiver–stimulator. Some surgeons may drill a well in the bone to secure the implant and/or tie the implant down to secure it in position. However, with the evolution of thinner implants without a 'footprint', more surgeons are choosing simply to create a subperiosteal pocket. Often, a gutter is drilled for the electrode as it passes into the mastoid cavity.

A posterior tympanotomy is created to give access to the round window niche, taking care to preserve the chorda tympani. Depending on the surgeon's preference and the access achieved, the entry into the cochlea may be via a cochleostomy, via the round window membrane (once the niche has been drilled away), or by opening the round window in an anterior and inferior direction. Optimal placement of the electrode is within the scala tympani.

Once inserted, a soft-tissue seal is placed around the electrode as it enters the cochlea, to prevent the leak of perilymph. The residual electrode wire is coiled within the mastoid cavity, and the wound is closed in layers.

Hearing preservation

Increasingly surgeons are adopting less traumatic approaches to entering, and introducing the electrode, into the cochlea. This has come about due to the development of less traumatic electrodes, a recognition that atraumatic insertion leads to the electrode remaining within the scala tympani with better outcomes,[56] an understanding that paediatric recipients are likely to undergo multiple implant surgeries in the same ear over the course of their lifetime, and the need to preserve residual low-frequency hearing in individuals who are going to use combined electro-acoustic stimulation (EAS).

Hearing preservation surgery is undertaken in individuals with good or aidable low-frequency hearing as described earlier. The surgeon may opt for a shortened or full-length electrode. Electrode insertion can be via a separate cochleostomy, or via the round window membrane.[57–59] Most surgeons advocate a slow electrode insertion, to minimize intra-cochlear pressure change, when attempting to preserve hearing. Various steroid regimes are employed, including a systemic dose on induction of anaesthesia (e.g. dexamethasone), steroid solutions placed into the middle ear or soaked onto spongistan placed directly onto the round window membrane (e.g. triamcinolone), and varying regimes of post-operative steroid administration. All of these options are an attempt to protect cochlear function thus preserving residual hearing to facilitate EAS.

Challenging cases

Although the majority of cochlear implant surgeries are straightforward, there are some scenarios that can prove more challenging. These include cochlear ossification, perilymph gushers and abnormally formed cochleas.

Cochlear ossification is most frequently encountered if the patient has had meningitis. The degree of ossification can range from a small amount of immature bone in the proximal end of the basal turn to complete ossification and obliteration of the cochlea. It may be possible to predict the degree of ossification with pre-operative imaging and in this circumstance performing both MRI and CT scanning can be helpful. However, sometimes the surgeon may come upon ossification without prior notification from imaging, in particular if there has been a delay between imaging and surgery or if there is early scarring or bone formation in the proximal basal turn.

In early ossification, it is usually possible to drill through the immature bone and identify the cochlear duct in the more distal basal turn. If this is not the case and the cochlear duct cannot be identified, the surgeon may opt to insert the electrode into the drilled-out channel (partial insertion), or to consider a dual-array electrode, drilling a further channel anterior to the oval window to access the middle turn of the cochlea. In the significantly ossified cochlea the results can be difficult to predict.[60] In completely ossified cochleas, it may be necessary to consider an auditory brainstem implant (ABI) in place of CI.

A cerebrospinal fluid (CSF) gusher may occur in an abnormal inner ear, most commonly in patients with abnormal cochleas such as in X-linked deafness. Lesser degrees of perilymph leakage are most commonly seen in large vestibular aqueduct syndrome (LVAS) (**Figures 94.1** and **94.2**). In a true gusher, when the cochlea is entered, there is a rapid and significant filling of the mastoid cavity with CSF. The head of the patient should be raised and, when the flow of CSF slows, the electrode should be inserted in the usual manner. Following insertion, care should be taken to pack muscle or soft tissue tightly around the insertion of the electrode into the cochlea to stop any further leak. If a leak persists, despite all of the above, then a lumbar drain should be considered in the immediate post-operative period to reduce the pressure of the CSF and allow the leak to settle.

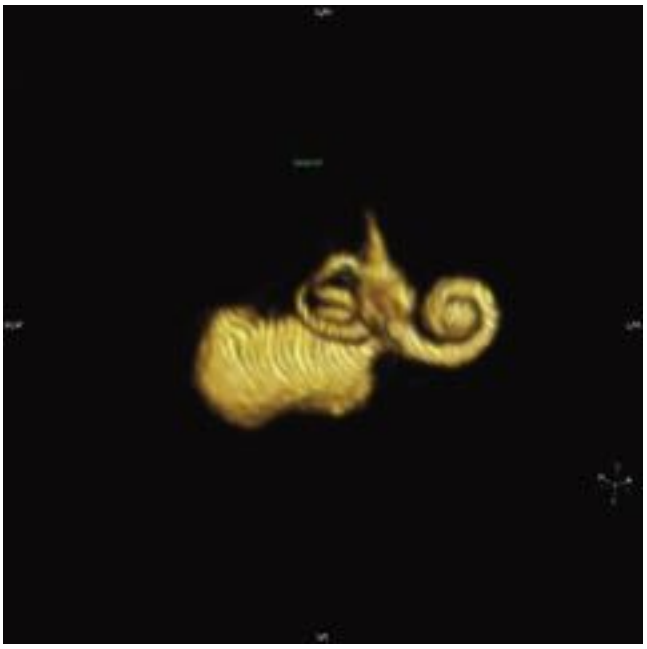


Figure 94.1 3-D reconstruction of the inner ear showing large vestibular aqueduct.

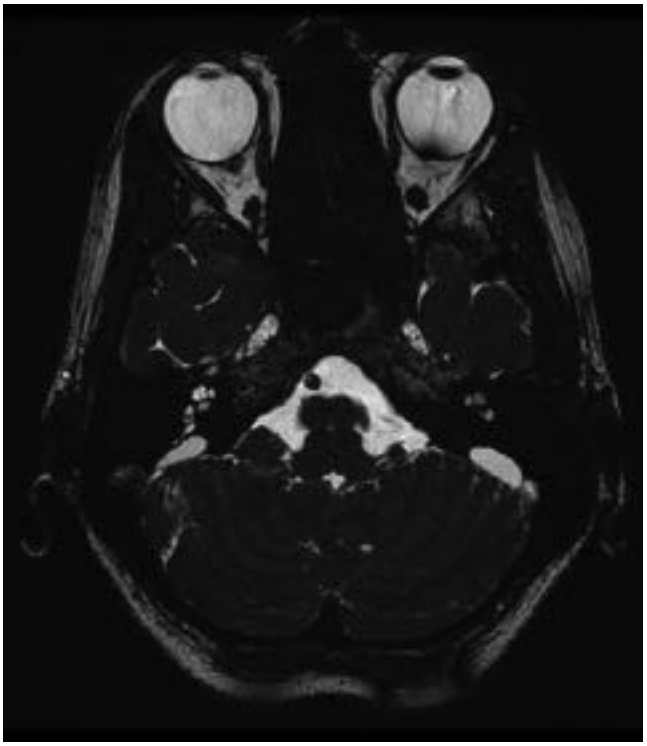


Figure 94.2 Axial T2-weighted MRI scan showing bilaterally enlarged vestibular aqueducts.

Due to the high quality of pre-operative imaging, it is possible to understand the anatomy of each cochlea to be implanted and the challenges they present. The surgeon may choose to use a shortened electrode in a malformed cochlea, or may request a custom electrode from one of the manufacturers in special cases such as a common cavity.

COMPLICATIONS

Complications in cochlear implant surgery can be classified by severity and timing:

- A major complication is one occurring during or after surgery that requires a major surgical intervention or results in a permanent disability (e.g. facial weakness).
- A minor complication is one that can be managed by medical measures or a minor surgical procedure (e.g. wound aspiration).

There are many published series quoting overall major and minor complication rates. Bhatia et al. looked at rates in 300 consecutive paediatric implants. They found major complications to occur in 2.3% of cases and minor complications in 16% of cases.[61] A recent prospective audit of 1397 paediatric bilateral cochlear implants in the UK reported a major surgical complication rate of 0.9%, with a minor complication rate of 6.5%, excluding device failure.[62]

Vertigo

Vertigo after CI is not uncommon.Most series report subjective and/or objective symptoms of dizziness or vertigo, usually transient, in approximately 30% of adult implant recipients.[63–65] In their series of 146 implanted adults, Enticott et al. noted that one-third of patients had vestibular disturbance and patients over the age of 70 were more prone to permanent injury.[65]

In a retrospective case review by Steenerson et al. almost three-quarters of adults with implants experienced vestibular symptoms, relieved by vestibular therapy. Of the 47 patients they studied, 74% experienced post-operative vertigo or imbalance; 19 of these 35 patients had experienced some imbalance sensations pre-operatively.[66] Forty-eight per cent demonstrated benign paroxysmal positional vertigo (BPPV) with positive Dix–Hallpike responses, arising from the implanted ear.

Limb et al. noted that BPPV occurs more frequently after CI than in the general population, and that routine BPPV treatment is effective in this group.[67]

With the advent of routine bilateral implantation, there is the potential risk of causing bilateral vestibular hypofunction. In patients with a pre-operative balance problem, vestibular assessment may be a useful adjunct enabling the team to select which ear to implant if unilateral implantation is proposed (i.e. opting for implanting the ear with poorer vestibular function).

The reported incidence of dizziness is less in the paediatric population.[68]

Device failure

With successive generations of implants, each manufacturer has pushed the agenda of device reliability. This is significant, as a large proportion of implant recipients are infants who will require an implant for the duration of their lifetime. Increasingly, a significant proportion of an implant programme's workload is replacing failed devices in their existing patients.

Device failure after CI surgery is one of the more common problems, although it should not be considered as a surgical complication, the cause rarely being surgical mismanagement. Trauma is linked to failure despite the device being built to withstand significant impact. Similarly, the device may fail suddenly or insidiously over time, sometimes referred to as 'soft' failures.

An implant is classed as failed if 50% of the electrodes are non-functioning. In a series of more than 900 implants from 1985 to 2003, Lassig et al. noted a device failure rate of 3.7%.[69] Battmer et al. looked at the European experience of 12 856 implants and found a similar device failure rate of 3.8%.[70]

Experience has shown that reimplantation is safe and effective (e.g. Woolford et al.).[71] Other studies, however, have shown variable post-reimplantation performance (e.g. Henson et al.)[72] and have also noted that patients need careful counselling regarding the possibility of differences in sound quality and speech recognition performance with the replacement device.

The facial nerve

Immediate post-operative facial palsy is due to damage to the nerve from direct trauma or by thermal injury. Facial nerve monitoring is commonly used and may help reduce problems. Gibbin et al. reviewed 1524 patients.[73] Four had an immediate partial facial nerve palsy, two of whom made a complete recovery. One immediate complete palsy occurred and partially recovered, leaving a permanent disability rate of 0.2%.

In the UK paediatric bilateral audit there were two (0.2%) temporary, partial facial nerve palsies in the post-operative period and no permanent facial palsies.[62]

Facial nerve stimulation has been reported to occur in between 7%[74] and 25%.[12] It occurs more frequently in patients with otosclerosis, particularly with the use of non-modiolar hugging electrodes in severe disease.[13] Facial nerve stimulation can be controlled by device reprogramming in nearly all cases.

Rare complications

MAGNET DISPLACEMENT

Many of the cochlear implant designs feature removable magnets. This facilitates temporary magnet removal, when an MRI is required of an implant recipient's brain, to minimize artefact on the scan. If an implant recipient experiences a degree of trauma over the implant, it is possible for the magnet to become displaced from its silicone pocket. The external component may then not connect to the internal device, as the coils are not aligned, or the displaced magnet may be palpable through the skin in an abnormal position. An X-ray confirms the diagnosis (**Figure 94.3**). A revision procedure is required to remove the displaced magnet and replace it within the implant or if the electrode is not fully functional following removal (this can be determined using intra-operative telemetry testing).

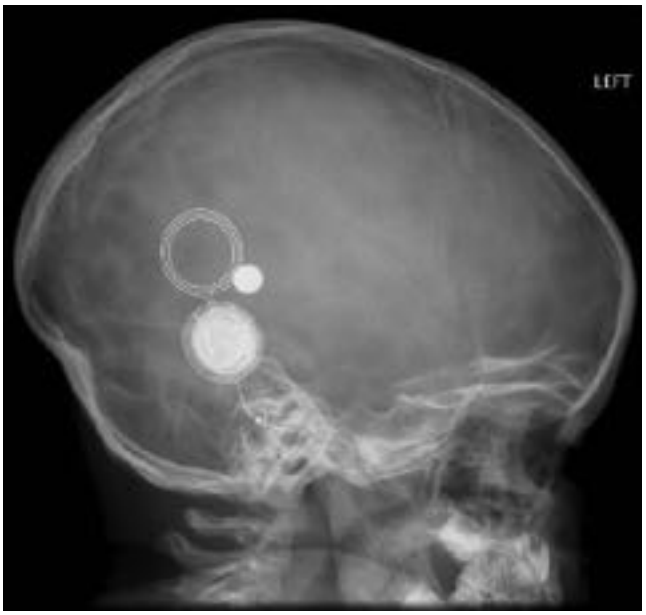


Figure 94.3 Plain lateral skull X-ray showing magnet displaced outside of the receiver-stimulator package.

TIP FOLD-OVER

Depending on the electrode design and insertion technique used, it is possible for the electrode tip to fold over upon itself. This may only involve a few electrodes, or a more significant portion of the array (**Figure 94.4**). This may not be recognized at the time of surgery, and is usually detected on post-operative imaging. The surgeon may choose to leave the implant if there is a minor degree of fold-over, or they may choose to revise the procedure. At revision, it may be possible to salvage the existing electrode by removing and reinserting (on-table imaging for confirmation of correct positioning is recommended), but the team should be prepared to use a second device if this is not possible or if the electrode is not fully functional following removal (this can be determined using intra-operative telemetry testing).

LOOKING TO THE FUTURE

Despite recent advances in CI, there is clearly still a great deal of work to be done to maximize the potential benefit to patients receiving this life-changing intervention. Some areas for potential developments include the following.

Unmet need

Despite the fact that many healthcare systems in the developed world already offer CI to appropriate patients, there are a large number of eligible patients, particularly adults, who are missing out on the potential benefits of this technology. For example, a recent study in the UK found that while 74% of eligible children between the ages of 0 and 3 years received an implant (increasing to 94% by age 17 years), only 5% of eligible adults underwent surgery.[1] This perhaps reflects a lack of awareness of the criteria for and benefits of CI in the wider medical and audiological

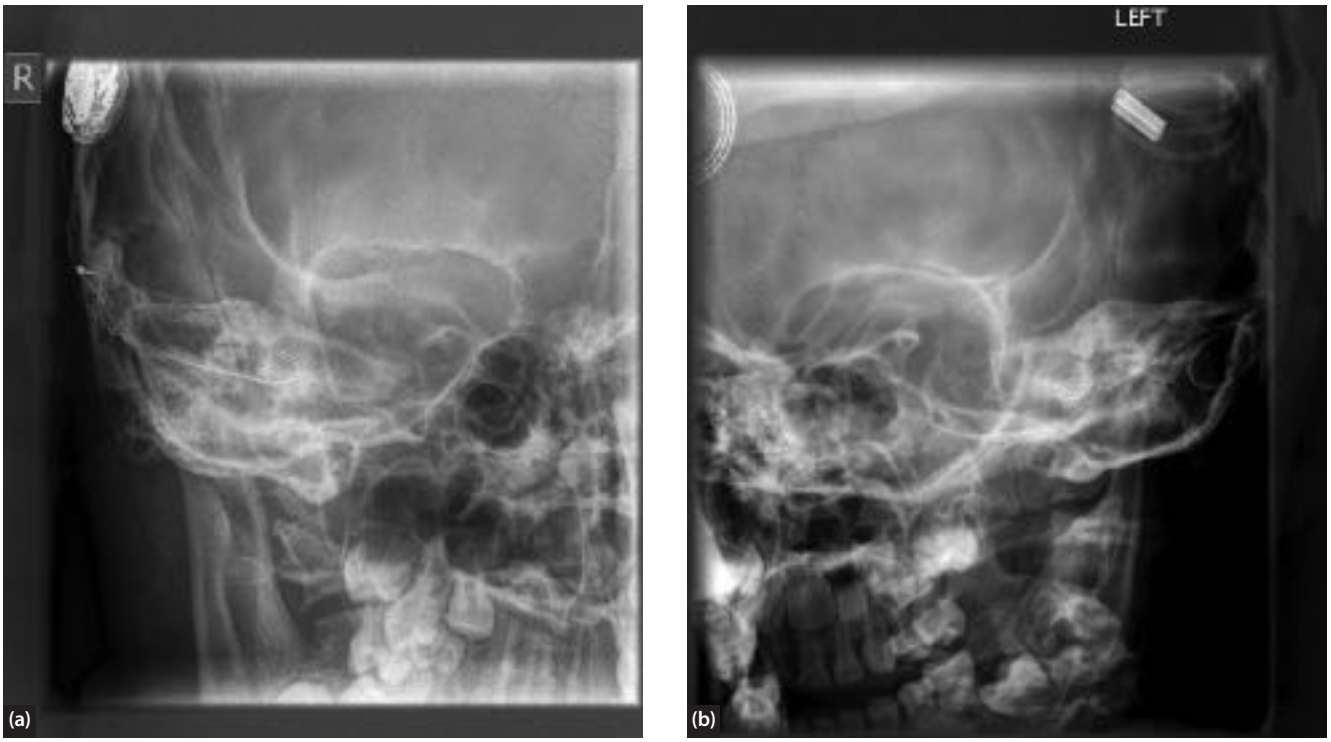


Figure 94.4 Plain skull X-rays showing **(a)** tip rollover of the distal electrode (note also incomplete electrode) and **(b)** more significant fold-over of the electrode.

communities as well as the general public. The unmet need in developed countries also highlights the huge burden of undertreated (or untreated) profound deafness in the developing world. While CI has been performed in many developing nations in isolated cases on a humanitarian basis,[75] wider implementation of CI is likely to require a change in the political and financial structures surrounding health care in such countries. Interestingly, uptake of CI in large numbers in emerging economies such as India and China has led to new avenues for research (e.g. the performance of cochlear implants in patients using tonal languages) and cochlear implant manufacturing, with global implications.

New technology applied to current devices

With the increasing uptake of CI, the cumulative number of adults being looked after by an individual centre rises rapidly, placing a significant burden on the professionals within that team. To reduce this demand, and to better serve patients who may be geographically remote from their cochlear implant centre, new methods of programming individual implants remotely have been explored. The majority use web-based connections between the implant audiologist and the patient. In future, software may allow the computer-literate patient to alter his or her own map without any external input.

Developing technologies

While the current design of the cochlear implant is continually being improved and updated, and new processing strategies developed, there are other potential developments that could change the nature of cochlear implants altogether.

- **The totally implantable cochlear implant (TICI).** Early prototypes of completely implanted cochlear implants have shown that such a device can be safe and effective.[76] Challenges remain in designing a microphone that can detect external signals without picking up unwanted noises related to movement, breathing, etc.
- **Drug-eluting electrodes.** These could be used to introduce anti-inflammatory or neurotrophic agents directly into the inner ear to prevent postimplantation neural degeneration, to prevent progression of deafness, or to improve the interface between the electrode and the neural elements.[77]
- **New insertion techniques.** As CI evolves, the need for atraumatic insertion is becoming increasingly important. This is reflected in the design of new implant electrodes. There has also been much interest in the use of robots to ensure a smooth and atraumatic electrode insertion (Zhang et al.)[78] and for minimally invasive and atraumatic drilling of the temporal bone and cochlea (Assadi et al.).[79] Such an instrument could potentially allow CI in remote settings using telesurgery.
- **New methods of neural stimulation.** At present, cochlear implants transmit an electrical signal through multiple electrodes and are therefore prone to current spread, meaning that the neural stimulation is not as specific as required for optimal performance. This has led to research into different ways to stimulate the auditory pathway (e.g. using optical stimulation).[80] To date, these techniques have not been applied in clinical

practice, but they may be important for future devices, particularly when used in combination with biological nanotechnology.

Inner ear treatment

Perhaps the ultimate measure in the management of profound sensory hearing loss will be treatment of the underlying aetiology and restoration of natural hearing. Such treatments would potentially have huge implications for patients with presbyacusis, the leading cause of deafness worldwide. Current research is examining the role of stem-cell and gene therapy in treating deafness (e.g. Kanzaki);[81] cochlear implants in the future may be as much about delivering such therapies to the inner ear to restore natural hearing as providing artificial stimulation.

KEY POINTS

- Cochlear implants have transformed the management of severe to profound hearing loss.
- Criteria to identify potential cochlear implant candidates differ between countries. In England and Wales, the NICE guidelines state that a patient must have severe to profound hearing loss (audiogram worse than 90dBHL at 2 and 4KHz) as well as failure to benefit from hearing aids (in adults, worse than 50% score on BKB sentence test at 70dB SPL; in children, failure to gain speech and language skills appropriate to age and development).
- Newborn hearing screening programmes allow early identification of children with severe to profound deafness. Implantation at or before 12 months of age gives optimal outcomes.
- Criteria are constantly evolving and cochlear implants may be appropriate for some patients with residual hearing, single-sided deafness, complex needs or anatomical abnormalities.
- Surgery is usually via a cortical mastoidectomy and posterior tympanotomy. Modern techniques allow for preservation of hearing in some patients. Serious complications are rare.
- One of the greatest challenges in cochlear implantation is to overcome the unmet need in both developed and developing countries.
- In addition to the continually improving electrode design, processing strategies and surgical techniques, future advances in cochlear implantation may include a totally implantable device, improved neural stimulation, routine use of drug-eluting electrodes and inner ear treatment with gene or stem-cell therapies.

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CHAPTER 95

MIDDLE EAR IMPLANTS

Maarten J.F. de Wolf and Richard M. Irving

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the phrases 'middle ear implants', 'implantable hearing devices', 'middle ear implantable hearing devices' and 'vibratory ossicular prostheses', searched as keywords and also by combining the sets 'hearing aids' (all references) with 'middle ear' (all references).

INTRODUCTION

The primary impetus for active middle ear implant (AMEI) development is the desire to overcome many of conventional hearing aid shortcomings such as distortion, feedback, occlusion effect, discomfort and ear canal irritation. Next to that, AMEIs offer the potential for improved sound clarity, because most AMEIs bypass the external auditory canal (EAC) and do not use a speaker for signal amplification. A common characteristic of all implantable hearing aids is that the transducer is coupled to the ossicular chain or directly to the inner ear fluid. These implantable devices were initially designed for the treatment of sensorineural hearing loss (SNHL) in patients with healthy middle ears. Indications have expanded to patients with mixed hearing loss and middle ear malformations.[1] With the application of prostheses and coupling elements, the systems now cover all types of middle ear reconstructions for patients with moderate to severe mixed hearing loss.[2,3] This chapter addresses the application as well as the results of AMEIs for these indications.

HISTORY AND DEVICE DEVELOPMENT

Wilska[4] is credited with being the first to use electromagnetic induction to stimulate the middle ear, in the 1930s. Iron particles were placed on the tympanic membrane of a human subject and stimulated by an electromagnetic coil placed in the ear canal. Since then, and particularly over the past 30 years, much work has been done looking at different sites and methods of attachment of microphone, amplifier and transducer.

The majority of devices have utilized a postauricular microphone with resultant loss of the pinna effect. Overcoming this by placing the microphone in the EAC has been tried, but to date this has not been successful, largely due to problems with feedback.

Devices have predominantly used either a coil and magnet (electromagnetic) or a piezoelectric mode of transmission. The piezoelectric transducer works on the principle that, when a voltage is applied to a particular ceramic (piezoceramic or piezoelectric crystal), it causes a proportional deformation and hence displacement of that ceramic. This voltage-dependent displacement can then be coupled to the ossicles to drive them (used in the TICA and Envoy systems, see 'Devices no longer available' and 'Current devices' below). In the case of the electromagnetic transducer, the electrical signal is used to produce an electromagnetic field by means of a transduction coil. This then drives a magnet that can be attached to the ossicles in a variety of ways to transfer the vibrations.

The coupling mechanism of the device is the method by which the transducer is connected to one of the middle ear ossicles or cochlear windows. Most of the different devices are connected to one of the middle ear ossicles with or without need for disruption of the ossicular chain. The possibility of hydroacoustic transmission, via a

water-filled tube, either to the ossicles or directly to the round window membrane has been investigated.[5]

A major problem with these devices has been to produce a device that is small enough to fit within the confines of the middle ear and yet powerful enough to produce the required gain. Over recent years technological advances have resulted in a number of devices that have fulfilled these basic requirements. The translation from theory to a viable surgical and financial product has, however, proved extremely difficult and many projects have ultimately ended in failure.

CURRENT DEVICES

Vibrant Soundbridge (MED-EL, Innsbruck, Austria)

The Vibrant Soundbridge (VSB) developed by Symphonix and currently by MED-EL is an active semi-implantable hearing device. It consists of an internal, surgically implanted part – the vibrating ossicular prosthesis (VORP) – and an external audio processor. The VORP consists of a receiving coil, conductor link and transducer. The transducer employs a small electromagnetic coil and enclosed magnet to produce vibrations in this floating mass transducer (FMT), which can be coupled to the ossicles or round window. The VSB obtained the European certification mark for implantation in 1998 (Symphonix Devices Inc., 2000) and has also received Food and Drug Administration (FDA) approval.[6] In addition, the VSB received the European Union CE Marking for treatment of conductive and mixed hearing loss in adults (2008) and children (2009).[7]

Direct acoustic cochlear implant (DACI) (Cochlear Ltd, Sydney, Australia)

Initially called the direct acoustic cochlear stimulator (DACS, Phonak Acoustic Implants, Phonak AG, Stäfa, Switzerland) and later the Codacs™ Investigational Device, this device consists of an implantable electromagnetic transducer, which transfers acoustic energy directly to the inner ear via a conventional stapes prosthesis. An audio processor is worn externally behind the implanted ear. The stapes has to be removed in total. In order to restore the natural sound transmission of the ossicular chain, a second stapes prosthesis is placed in parallel to the first one into the oval window and attached to the patient's own incus.[3] This implant is indicated for profound mixed hearing loss. The device is CE approved but to date there has been no FDA approval.

Otologics semi-implantable middle ear transducer (MET) and fully implantable Carina (Otologics, Boulder, Colorado, USA, later Cochlear (Sydney, Australia)

This device is currently fully implantable, although the initial trials were done with a semi-implantable version, which has CE approval.[8] The technology was purchased by Cochlear (Sydney, Australia) in September 2012. The semi-implantable MET uses an external unit called the button external audio processor, containing a microphone, battery, signal processor and transmitter. The transducer drives an electromagnetic probe coupled to the body of the incus. The tip of the probe is made of aluminium oxide, which forms a fibrous connection with the incus body. The ossicular chain is left intact.

The fully implantable Carina uses the same electromagnetic transduction system, but consists of a subcutaneous microphone, battery and an electronic receiver connected to a transducer. The latter is used in patients with mixed hearing loss with a variety of implantation sites and aetiologies, including the round window and footplate.[9, 10] The device is CE marked for this purpose in Europe and South America.

Fully implantable Envoy Esteem Device

This device comprises a piezoelectric sensor placed on the incus body, acting as an internal microphone, and a driver cemented to the stapes head. Implantation of the device requires disarticulation of the ossicular chain with removal of the lenticular process of the sensor interface linked to the body of the incus, and the driver is cemented to the stapes head.[11] This device is indicated for patients with SNHL. CE marking was accomplished in 2006, and the FDA granted approval in 2010.[12]

EMERGING TECHNOLOGIES

Maxum Hearing Implant (Ototronix, LLC, Texas, USA)

The SOUNDTEC Direct Drive Hearing System (DDHS), initially designed by SOUNDTEC Direct, is another semi-implantable device containing an electromagnetic transducer. The implanted part consists of a magnet attached to the incudostapedial joint via a titanium alloy wire ring. Placement requires a transmeatal approach. The electromagnetic coil forms part of the external portion of the device and is placed deep in the ear canal.[13] The SOUNDTEC DDHS has had FDA approval,[6] but the results have been mixed.[14] The device was removed from the market in 2004 because of device-related adverse events. In 2009 Ototronix purchased the SOUNDTEC technology, and the device was rereleased as the Maxum Hearing Implant after incorporating several notable upgrades, including a self-crimping Nitinol wire that obviates incudostapedial joint separation. To date there are no clinical studies concerning this new upgraded system.

Semi-implantable middle ear electromagnetic hearing device

For this semi-implantable middle ear electromagnetic hearing device (SIMEHD), the magnet is cemented to the incus body and a titanium frame fixed to the temporal

bone supports an implanted electromagnetic coil. The gap between magnet and coil can be adjusted on the frame. Both magnet and coil are encased in titanium.[15] The SIMEHD has been implanted in cats and a human study has been proposed.[15]

Piezoelectric round window implant with infrared optical signal

This AMEI comprises a micro transducer, placed on the round window. It can receive power and signal transmission through an infrared optical transmitter located in an external unit. This also contains a microphone, sound processor and battery and is placed in the ear canal.[16] Notably, this AMEI can be implanted endaurally without mastoidectomy. The system has not yet been tested *in vivo*.

EarLens tympanic contact transducer

This device consists of a magnet placed in a silicone lens that sticks to the tympanic membrane by oil-induced surface tension. A small induction coil is placed in the ear canal.[17]

DEVICES NO LONGER AVAILABLE

Semicircular canal piezoelectric vibrator

This device stimulates inner ear fluids directly by means of a lateral canal fenestration, bypassing the middle ear. Welling and Barnes[18] used a piezoelectric biomorph material that could activate the auditory system via vibromechanical stimulation and thus showed the feasibility of this approach.

University of Bordeaux implantable piezoelectric transducer

The device consists of a piezoelectric biomorphic material with a short rod and platinum ball placed against the round window. However, since its initial publication in 1995,[19] no reports have been published regarding application of this technology to living individuals.

Rion partially implantable hearing aid

The Rion partially implantable hearing aid (PIHA) uses a piezoelectric transducer connected to the head of the stapes or footplate by a hydroxyapatite coupling. The transducer is held in place by a fixing plate screwed to the temporal bone.[20] This device has been implanted in patients in Japan under Japanese approval but is no longer in production.

Totally implantable cochlear amplifier

Developed by Implex, the totally implantable cochlear amplifier (TICA) was the first fully implantable middle ear device. Comprising an ear canal subcutaneous microphone and piezoelectric transducer, the device was revolutionary but problems with feedback necessitated disarticulation of the chain. The device is no longer in production.[21, 22] The technology was purchased by Cochlear to be implemented in cochlear implants.

PATIENT SELECTION

Candidates

Ideal candidates for middle ear implants are patients with high-frequency sensorineural or mixed hearing loss, in which amplification with conventional hearing aids – with or without stapedotomy – or bone-conduction implant (BCI) has failed. In most cases failure is caused by acoustic feedback, occlusion effect, insufficient high-frequency amplification or wearing discomfort. Although the VSB and the MET/Carina is cleared for use in patients under the age of 18,[7, 23] the majority of these devices have been placed in adults. Candidates should not have any skin conditions that may prevent attachment of any external component of the device and should be medically fit for surgery and the anaesthesia required. In addition, candidates should have been appropriately counselled by a surgeon and be judged to have realistic expectations. Further selection is made based upon audiological and otological conditions.

Audiological

Current devices are most suitable for mild to severe SNHL. In case of conductive or mixed hearing loss, the main objective of AMEI placement is to overcome the residual sensorineural component. Preferably, hearing loss should ideally be stable, while accepting very slowly progressive losses. The Codacs system is specifically designed for patients with a profound mixed hearing loss such as in advanced otosclerosis.[3] Aided thresholds for the candidates' present hearing aid should be taken into consideration. Tympanometry and acoustic reflexes may be required to assess middle ear function and speech audiometry to assess retrocochlear loss. The worse-hearing ear is usually selected for implantation.

Otological

In general, there should be an absence of retrocochlear or central involvement in the hearing loss. Middle ear inflammation must be controlled prior to implantation. In case the external processor is worn in the EAC, the ear canal must be assessed before surgery in order for it to be suitable. Beleites et al[1] suggested a classification of the different types of applications of AMEIs for specific pathological middle ear situations.

A Type A vibroplasty involves the coupling of an AMEI on an intact ossicular chain in patients with a mild to moderate SNHL (the classic indication). Different attachment points to the ossicular chain (e.g. umbo, incus or stapes) are used. The stapes head and footplate are the most favourable attachment points.[24] AMEIs that can be considered for this situation are the VSB, MHI and Carina.

Type B vibroplasty consists of aided hearing by means of an AMEI – mostly the VSB – coupled to a remnant of the ossicular chain, which is in most cases the stapes or its footplate. Although still experimental, solutions with the Carina and Esteem using additional couplers or passive prostheses are being researched.[25–29]

Type C vibroplasty involves the coupling of the actuator on one of the middle ear window membranes. The VSB is the only implantable actuator to suit this application on the round window. In recent years round window coupling has become an increasingly common alternative for the 'classic' coupling of the VSB on the long process of the incus.[1]

Type D vibroplasty is described as the direct coupling of an AMEI to the inner ear fluid. For this approach, the oval window is mostly used. The DACI system was designed for this application, but the VSB combined with a conventional stapes piston can also be used.

SURGICAL CONSIDERATIONS

For the AMEIs on the market today (VSB, MET/Carina, DACI and Envoy) the surgical approach is similar to that of a cochlear implant. It compromises retroauricular transmastoidal access to the middle ear via the facial recess (VSB) atticus (Carina) or a slightly different approach is needed to gain access to the round window niche (Codacs). Sometimes a combined approach is needed to gain sufficient access to the middle ear in case of a joined placement with a passive implant. An implant bed is drilled in the cortical temporal bone to accommodate the internal receiver and conductor link. For most implants (Carina, Esteem and Codacs) the transducer is fixed to the cortical bone in the mastoid cavity by means of cement or screws. Although the mastoid has more space available than the tympanic cavity, allowing stronger transducers, this procedure requires meticulous placement and is slightly more difficult than placement of other AMEI systems with separated coil and magnets (MHI and EarLens), which only require an transmeatal tympanotomy. The performance of the latter, however, depends heavily on the distance between the coil and magnets.

For VSB placement the posterior tympanotomy should be large enough to pass a 3 mm diamond burr in order to ensure sufficient space to site the FMT. For a classical placement its attachment clip is folded and crimped around the long process of the incus, although with the introduction of a short process clip this approach without a posterior tympanotomy is proving more popular and technically more straightforward. Also, placement of the FMT on the stapes head, footplate or round window can be performed.

The main advantages of these procedures are that they utilize an approach already familiar to otologists and do not require disruption of the ossicular chain, in case of an intact ossicular chain. However, bone work is required close to the facial nerve and there is also concern about crimping the clip to the long or short process of the incus. If the clip is crimped too tightly, there is a potential for necrosis of the long process of the incus; if it is too loose, the implant may fail. Placement of the FMT, other than the classical way, can be challenging. A consensus statement was published in 2014 to address this issue.[30]

For placement of the Codacs system a special 'retromeatal approach' is used to assess the facial recess at the level of the oval window. The device is electronically and mechanically tested during surgery.

For an MET/Carina device, the bone work is away from the facial nerve but perhaps less familiar to the otologist. An atticotomy is performed to expose the incus body and malleus head. A laser is used to make a hole in the body of the incus. The transducer is then inserted into the mounting system secured to the skull and the probe tip is aligned with the laser-made hole in the incus. Fine-positioning of the probe tip is made by screw adjustment.[8] For the Carina, a separate microphone connected to the implanted sound processor is placed in a postauricular subcutaneous pocket. For the Esteem system a large facial recess opening is needed so that resection of chorda tympani is often inevitable. Intraoperative testing by means of laser Doppler vibrometry is needed to assess the mobility of the incus and stapes. Hypomobility will require aborting the surgical procedure at this point. Meticulous cleaning of the stapes head and incus is needed for adequate placement of the sensor and driver.

RESULTS

Surgical results

In general, complications regarding AMEI implantation are poorly reported and may be subject to reporting bias.[31–33] Worldwide, the VSB has been implanted in the largest group of patients. Initial audiological and surgical results for this device came from a European multicentre trial including 47 patients.[34, 35] They showed no major complications in terms of permanent facial weakness or profound sensorineural loss. One delayed onset of temporary, partial facial weakness occurring 10 days post surgery was reported.[35] Clinical experience with this device has been described in a number of studies.[26, 34–41] Complications mainly consisted of damage to the chorda tympani[34, 42] and dislocation of the FMT, particularly in type C vibroplasty.[38, 41, 43] A consensus statement published in 2014 proposed a specific surgical technique to address the variable results due to the dislocation issue.[30] Also extrusion of the (sometimes) accompanied passive prosthesis has been reported.[26] Another frequently reported symptom following VSB implant surgery is aural fullness.

Initial studies on the Codacs system showed that most common post-surgical complaints were tinnitus, deterioration of bone conduction and vertigo. No major device-related adverse effects were noted.[3, 33, 44–46]

The most common event reported for the Carina device was device malfunction or failure, mostly related to charging. This occurred in 17.6% of patients in a pooled population of 68 patients. Device malfunction led to four explantations and three revision surgeries. Partial device extrusion occurred in four patients and resulted in two explantations.[10, 47–53]

After placement of the Esteem device, 8% of the patients in a pooled group of 87 patients reported facial weaknesses,

while 30% of the patients reported taste disturbance, mostly caused by a chorda tympani lesion, which was temporarily experienced in approximately 50% of the cases. Also, 13% of the patients underwent explantation or revision surgery because of insufficient benefit or device malfunction.[11,12,54–56]

Pooled data from a systematic review by Klein et al.[57] showed that, overall and in experienced hands, AMEIs are considered a safe alternative to amplification options such as conventional hearing aids (CHAs) or osseointegrated BCIs for patients with mixed hearing loss. Taking into account the challenging pathology of COM, advanced otosclerosis and congenital malformations,[33] Tysome et al.[31] concluded that AMEIs were safe to implant for SNHL, based on his systematic review.

With regard to long-term results, most studies show no initial decline of bone-conduction threshold after implantation. However, one study reported a mean threshold elevation of 8 dB in post-operative hearing thresholds in a series of 20 patients 2 years post implantation.[42] This might suggest overstimulation-induced cochlear trauma.

Patient-reported outcome measures

The Abbreviated Profile of Hearing Aid Benefit (APHAB) self-assessment questionnaire[58] was mostly used to evaluate patient satisfaction for all AMEIs. In general, patients experience a significant improvement of benefit for all current AMEIs in terms of ease of communication, reverberation and listening in background noise compared to the unaided situation. Regarding comparison with previous conventional hearing amplification, far less information is available. APHAB results suggest that patients experienced more benefit from the VSB over conventional amplification.[35,59,60] Kraus et al.[12] reported clinically significant greater benefit with the Esteem compared with CHAs in all subcategories. Jenkins et al.[10] found the Carina to be superior in all subcategories. However, the data are not statistically significant. The most convincing significant increase of benefit was seen for the Codacs system compared to the use of a conventional hearing aid and the unaided situation.[3,44,46] Overall, the reported benefits included improved quality of sound, elimination of occlusive effect, and an improved ability to lead an active lifestyle when compared with CHA use. With regard to subjective hearing improvements, patients generally prefer the sound quality of an AMEI to that of a CHA. Direct ossicular stimulation maximizes the ability to hear high-fidelity, naturally produced sound. Additionally, the proximity of the implant transducer to the cochlea reduces distortion.[32]

Audiology results

AMEIS IN SENSORINEURAL HEARING LOSS (TYPE A VIBROPLASTY)

Since open-fit hearing aids and AMEIs both service patients with high-frequency hearing loss, it seems logical to compare the benefit of these devices. However, since these patients are by definition dissatisfied with conventional aids, such a comparison is difficult, due to a patient bias.[61] AMEIs currently used in type A vibroplasty are the VSB on the long proces of the incus, Esteem and Carina. Functional gain between pre-operative non-aided and aided versus post-operative implanted conditions has been tested, both in quiet and noisy environments. Studies showed statistically significant post-operative AMEI-assisted hearing improvement in varying levels (ranging from 16 dB to 48 dB) compared to pre-operative unaided condition.[9–12,35,48,56,60–70] Compared to the best aided pre-operative condition, a positive – but not significant – functional gain was demonstrated in most studies. Some studies report a (clinically) statistically significant improvement with the VSB device[35] and Carina device[9,10,48,66] compared to optimally fitted conventional hearing aids, respectively. In general the functional gain was quite similar among the devices.[9–12,35,48,56,60–65,67–70]

In a quiet environment, these comparisons showed a statistically significant improvement in most studies.[11,12,48,71] However, word recognition scores declined in one study.[72] Finally, when comparing AMEI performance (VSB) to the best aided condition in a noisy environment, clinically statistically significant improvements were demonstrated too.[73] This suggests that AMEIs have a functional gain at least as good as, if not better than, conventional hearing aids. However, reports are contradicting and sparse.

AMEIS IN MIXED HEARING LOSS (TYPE B, C AND D VIBROPLASTY)

For the heterogeneous group of pathologies causing mixed hearing loss (otosclerosis, tympanosclerosis, cholesteatoma), different strategies for hearing rehabilitation have been proposed. AMEIs most commonly used for mixed hearing loss are VSB, MET/Carina and Codacs. In general, the status of the middle ear affects the performance of the AMEI. Reduced load impedance due to a partially missing ossicular chain is usually an advantage that improves performance.

Mostly, a VSB coupled on the round window (type C vibroplasty) is used to service mixed hearing loss. The results of the VSB with its actuator coupled to one of the cochlear windows shows statistical significant difference in terms of speech perception in quiet and in noise compared to conventional hearing aids.[38,39,74,75]

However, audiological results in round window placement (type C vibroplasty) of the VSB vary due to effectiveness of the coupling.[1,74,76,77] Recent publications report that adequate coupling might account for as much as 20 dB of the hearing benefit.[78,79] A type C vibroplasty with the MET/Carina has shown to provide an improvement of functional gain over the unaided situation, but there was no comparison with conventional hearing aids.[50,51,80] An interesting situation is the presence of a fixed stapes footplate.[23] Some authors perform a round window vibroplasty, others a clipping of the VSB on the fixed stapes. The results remain variable and some even with limited benefit.[78] Although it has been suggested that, with a VSB or Carina device placed on the round window, SNHL due to oval window fixation can be serviced, there was no comparison with conventional aiding.[51,81] Research has shown that the round window application of the VSB can be used in chronically diseased middle

ears, after subtotal petrousectomy with obliteration of the middle ear cavity, and in atretic ears.[82, 83]

As an alternative to round window placement, the VSB can be coupled to the stapes head by means of a partial ossicular replacement prosthesis (PORP) or on the footplate by means of a total ossicular replacement prosthesis (TORP) (type B vibroplasty). Although there is a risk of extrusion, the audiological results are promising and are comparable with placement on the ossicular chain or round window.[27–29, 84] Another solution to stapes fixation could be a type D vibroplasty, although opening the inner ear is not always possible. The DACI system or a VSB or Carina system in combination with a conventional stapes can be used. Significant improvement in terms of functional gain, speech perception in noise and word recognition scores was seen in favour of the Codacs compared to conventional hearing aids in several studies.[3, 44–46] Both the Carina and VSB–stapedotomy combination showed favourable results, but these were not compared to conventional hearing aids.[53, 85–87]

Recently, Zwartenkot et al.[88] compared the maximum output of both the Codacs and the VSB, mostly used in a vibroplasty type B, to bone-conduction devices and found that only with the Codacs is a patient capable of using his full dynamic hearing range. Nonetheless, only patients with advanced otosclerosis were included and long-term data are not yet available.

BEST CLINICAL PRACTICE

- ✓ Implantation of these devices using the classical indications of moderate to severe SNHL is now well established, although it should only be carried out in centres with considerable experience in implantation otology and after a proper trial with optimal fitted conventional aiding such as hearing aids or bone-conduction devices.
- ✓ The evaluation of middle ear implants for patients with mixed or conductive losses including otosclerosis should be undertaken only within the context of a clinical trial.

FUTURE RESEARCH

- ➤ The fundamental for the development of implantable hearing aids is based on the desire to provide an alternative hearing solution than conventional hearing aids for patients with moderate to severe hearing loss. Benefits for the patients would in theory include hearing improvement, as well as an increased potential for an active lifestyle.
- ➤ AMEIs have gained substantial improvements over the years in terms of sound quality and patient comfort. However, most theoretical advantages of an AMEI are still unaccomplished, as most studies do not reveal a statistically significant improvement compared to optimally fitted conventional hearing aids. Overall, the benefits of AMEI do not yet convincingly outweigh the drawbacks of this technique in all patients, especially since some patients experience unstable progressive hearing loss, which could exceed the output capabilities of their implanted device.
- ➤ The use of visible external components in semi-implantable devices still restricts patients from certain activities, while in the canal components may still result in an occlusion effect and canal irritation. Likewise, placement of one of the fully implantable devices requires ossicular resection, which could leave a patient with a more pronounced conductive hearing loss. There are also concerns of long-term device reliability and the need for revision surgery or battery replacement in totally implantable systems.
- ➤ Although use of AMEIs is expanding to patients with mixed hearing losses, the population benefiting is limited. On the one hand, the indications exclude patients with mild to moderate hearing loss. On the other hand, indications for cochlear implantation are steadily extended. Therefore, AMEI companies may suffer signicant financial obstacles. To be successful, their devices will need to be priced in such a way as to be competitive to other devices, especially the non-implantable alternatives and the more traditional bone-conduction devices.
- ➤ The level of evidence and the quality of the included studies were judged to be moderate to low. More comprehensive data comparing device performance with conventional hearing aids or alternatives for speech in noise is needed. More long-term follow-up data are also needed.

KEY POINTS

- Middle ear implants are classically indicated for patients with mild to severe SNHL as an alternative to a conventional amplification aid.
- The indications have expanded to moderate and severe mixed hearing loss by means of the round window membrane stimulation of direct inner ear fluid coupling.
- A middle ear implant service requires close collaboration between an experienced audiologist and otologist. To date these services have developed on the back of pre-existing cochlear implantation programmes. This trend is likely to continue.
- The current devices have established in being safe in terms of extrusion and maintaining residual hearing.
- Overall device performance is comparable to, and some are slightly better than, conventional hearing aids.
- Patients describe a higher satisfaction with AMEIs in terms of sound quality.
- More comprehensive data comparing device performance with conventional hearing aids or alternatives for speech in noise are needed.

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CHAPTER 96

AUDITORY BRAINSTEM IMPLANTATION

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SEARCH STRATEGY

Data in this chapter may be updated by a search using the keywords: 'auditory brainstem implantation in NF2' and 'auditory brainstem implantation in neurofibromatosis type 2'. The chapter is written without detailed explanation about neurofibromatosis type 2 or cochlear implantation, which are covered in separate chapters.

INTRODUCTION

The auditory brainstem implant (ABI) is indicated in severe to profound hearing loss when congenital or acquired abnormalities of the cochlea or auditory nerve (or sometimes both) preclude cochlear implantation (CI). The congenital group (invariably infants and children) includes those with dyplastic or aplastic cochleas and/or auditory nerves while the acquired group predominantly comprises neurofibromatosis type 2 (usually adults) and occasionally acquired cochlear diseases such as otosclerosis or post-meningitic cochlear ossification.

HISTORY

A single-channel ABI was first used to successfully stimulate the cochlear nucleus in 1979.[1] Prior attempts to elicit auditory sensations by stimulating the inferior colliculus had failed.[2] The House Institute developed their implant for patients with neurofibromatosis type 2 (NF2) who had no remaining hearing having undergone surgery for bilateral vestibular schwannoma (VS).[1, 3] Two ball electrodes were implanted near the surface of the cochlear nucleus.

The first multichannel device was implanted in 1991 and subsequently modified.[4, 5] Cochlear® Limited (Sydney, Australia) produced the device which had 21 electrode contacts and was based on their Nucleus™ cochlear implant (CI). In the UK, the use of the ABI was first introduced by Richard Ramsden in Manchester as part of a European multicentre clinical trial, paving the way for the utility of ABI in NF2 in the UK.[6] In 1997 the first MED-EL (Innsbruck, Austria) ABI was carried out. The device was based on their Combi 40+ CI. It has a paddle array of 12 electrode contacts on a 5.5 mm × 3.0 mmm soft silicone matrix and works with an external audio processor in the same manner as a CI. At the time of writing both the Cochlear® and MED-EL ABI are commercially available devices.

The aim of ABI is to rehabilitate patients with no hearing as a result of absence or damage to the auditory nerves and thereby no cochlea to brainstem connections.

ABI IN ACQUIRED HEARING LOSS – NF2 AND NON-NF2 DISORDERS

ABIs were initially designed for patients with NF2.[1, 3] Bilateral VSs are the pathological hallmark of NF2, occurring in 90–95% of patients.[7] NF2 patients may also have multiple central and peripheral nerve system tumours including meningiomas and gliomas. Less commonly, juvenile cataracts and skin lesions are a feature.

Hearing loss occurs as a result of tumour growth causing auditory nerve compression or cochlear damage from ischaemia, infarction or tumour involvement. The rate or extent of hearing loss does not correlate with tumour size or tumour growth.[8] Patients report hearing loss to be the most disabling symptom of the disease.[9] Auditory rehabilitation is therefore one of the key considerations in NF2 management and decision-making. Gold-standard care is delivered by MDTs.

AUDIOLOGICAL ASSESSMENT

The English consensus protocol for auditory rehabilitation in NF2[10] recommends annual audiological assessment as part of the regular review process for NF2. This involves pure-tone audiometry (PTA) and speech discrimination testing with the Arthur Boothroyd (AB) word test as well as hearing aid review to maintain optimum performance. If speech discrimination scores (SDS) fall below 50%, Bamford–Kowal–Bench (BKB) sentence testing is recommended. This should trigger assessment for auditory implantation if scores are below 50% in best-aided conditions at the optimum sound intensity (identified by the SDS), in accordance with the National Institute for Health and Care Excellence (NICE) guidelines.[11]

Auditory implant assessment involves free-field speech discrimination testing with and without lip-reading with hearing aids and potentially environmental noise discrimination tests as well. Sudden deterioration or noticeable progressive hearing loss requires interim review and reassessment.

The decision to operate/offer an auditory implant is complex and is underpinned by MDT decisions about patient tumour management.[7, 12] This involves consideration of patient factors, tumour factors (including size and growth rate), the contralateral ear/tumour and facial nerve function CI may be possible and assessment of auditory nerve function is therefore important to try to predict whether a functional auditory pathway still exists from the cochlea. Promontory electrical stimulation in an apparent dead ear involves electrical stimulation through a transtympanic needle placed on the promontory to attempt to elicit an auditory percept in a conscious patient. Auditory perception suggests a functioning cochlear nerve (CN) but does not predict outcome with a CI.[13] Transtympanic electrical auditory brainstem response (TTEABR) testing is useful in assessing the CN: it has been shown to correlate well with CI-evoked EABR and aids decision-making in patients with CN aplasia/hypoplasia.[14, 15] It may also aid decision-making pre-operatively in NF2 patients.

INTRA-OPERATIVE MONITORING

Intra-operative monitoring of the auditory nerve to aid hearing preservation has been used with varying degrees of success. Proponents use a combination of direct cochlear nerve action potential (CNAP) monitoring and fast auditory brainstem responses (ABR).[16] The ABR is elicited by a 104 dB sound pressure level click stimulus from an ear mould placed inside the ear canal pre-operatively. A combination of analogue and digital filters with specific software enables an interpretable trace and the surgeon is alerted if there is a change in latency of wave V of >0.5 milliseconds. To monitor the CNAP, a multistrand silver wire attached to a cotton pledget is placed proximal to the tumour adjacent to the CN. This acts as the positive electrode, and together with surface negative and ground electrodes enables monitoring of the CNAP. Any change in morphology of the wave is reported to the surgeon. CNAP is difficult to use in the middle fossa approach, as the brainstem proximal to the tumour is relatively inaccessible.

In a study of intra-operative monitoring in 75 patients with serviceable hearing undergoing VS surgery, it did not improve the rate of serviceable hearing preservation.[16] Absent or diminished fast-ABR or CNAP at the end of the procedure correlated with poor post-operative hearing in almost all cases. Sensitivity was poor; over 50% of those with a response after tumour resection did not have serviceable hearing preserved. Problems with these monitoring techniques include persistent presentation of a suprathreshold stimulus; difficulties with placement and maintenance of position of the positive electrode for CNAP; response to surgical manipulations; and interference or artefact from electrocautery.

The presence of post-tumour resection ABR, CNAP, EABR or CI-evoked EABR provides some prognostic information and is an indicator of residual auditory nerve transmission of electrical stimulation. In this situation CI may be worthwhile. In contrast, if these are negative and/or the auditory nerve has definitely been sacrificed, then ABI is the auditory rehabilitation choice.

MULTIDISCIPLINARY DECISION-MAKING

The English consensus of the options and numerous permutations for decision-making with regards to auditory rehabilitation in NF2 are shown in **Table 96.1**.[10] Surgery is usually only offered once hearing has deteriorated below 50% on BKB sentence testing. ABI may be indicated when planning VS excision where CN preservation is not likely to be possible or previous contralateral excision has taken place and there is no remaining hearing or a poorly performing/failed CI/ABI.

CN preservation surgery may be attempted for growing tumours up to 3 cm intracranial tumour diameter (ICTD), but the likelihood of success diminishes progressively over 1 cm ICTD. Hearing preservation is rarely possible for tumours >1.5 cm ICTD. For patients with no serviceable hearing and when intra-operative/post-resection evoked potentials are present, CI is the aim but there is still the possibility of a non-functioning CI.

TABLE 96.1 Indications for cochlear implantation and auditory brainstem implantation in neurofibromatosis type 2

	Cochlear implantation	Auditory brainstem implantation
VS excision planned	CN preservation thought possible	VS in contralateral ear and • CN preservation not thought possible **OR** • CN preserved but intra-operative ECAP and EBAR poor
		Contralateral VS excised and • no contralateral hearing **OR** • contralateral CI/ABI providing poor hearing rehabilitation
Bilateral profound hearing loss and no VS excision planned	Bilateral small to medium-sized stable tumours Stable unilateral tumour where previous contralateral VS excised and CN lost Hearing preserved at previous VS surgery	

CN, cochlear nerve; EABR, electrically evoked brainstem response; VS, vestibular schwannoma.

Counselling of patients requires comprehensive explanation and may take multiple sessions. As well as an introduction to the implants and an explanation of the risks of surgery and alternatives as part of formal consent, there are a number of key areas that must be emphasized:

- Pictorial explanation of the site/positioning of the implants is advised.
- The possibility of the implant being a 'sleeper' device while serviceable hearing is present in the contralateral ear is important to address in specific cases.
- The range of possible outcomes and the difficulties with predicting prognosis/benefit should be explained.
- Managing patient expectations is crucial.[10]
- It is important to stress the immense workload and commitment required by the patient and team for rehabilitation.

Introducing the patient to one who has previously been through surgery and the process of auditory habilitation with a CI/ABI is beneficial.

SURGICAL CONSIDERATIONS

There are a number of surgical approaches. The middle fossa, retrosigmoid and retrosigmoid–retrolabyrinthine approaches are options when aiming for hearing preservation in small tumours, the middle fossa approach being favoured when there is more tumour in the fundus of the internal auditory canal. However, hearing preservation is not often attempted in NF2 patients in England since common practice is to wait until the hearing has deteriorated. Translabyrinthine and retrosigmoid approaches are the two commonest approaches for larger tumours. A modified translabyrinthine approach has been described to enhance access for large tumours.[17] The extent of tumour resection has been classified as total (complete excision), near-total (<1% of tumour volume remaining), subtotal (1–5% of tumour remaining) and partial (>5% of tumour remaining).[7]

The aim of surgery in NF2 is total tumour removal with preservation of the facial nerve and CN. Surgical approach should be chosen based on experience and selecting the one most likely to enable optimal access to achieve the above. For unknown reasons, VSs in NF2 are 'more aggressive' than sporadic VS, which makes preservation of the cochlear and facial nerves more surgically challenging.[7] The tumour biology in NF2 is thought to be different and it is postulated that NF2 schwannomas may encapsulate the fibres of the CN rather than the stretching and spreading that is associated with sporadic VS.[18] Preservation of function is vital[19] hence more commonly nowadays, when there is severe adherence to critical structures (particularly in sporadic VS surgery), a small cuff of tumour may be left to avoid major complications.[12] However, this has implications of future growth, ongoing long-term surveillance and possible further treatment requirements that are not taken lightly, especially in NF2.

Total tumour excision is achievable in 78–92% of patients.[7, 12, 20] The cohorts undergoing surgery vary between centres; some units only offer surgery for patients when tumour growth is observed, others advocate early surgical intervention, as they believe this affords better functional outcomes. As expected, the centres with lower total tumour excision rates generally have better functional outcomes. The English consensus is for hearing deterioration or tumour growth to trigger reassessment, MDT discussion and consideration of the options with the patient and family.[10]

Auditory implantation usually takes place after tumour resection at the same operation. If a retrosigmoid approach has been used, a cortical mastoidectomy and posterior tympanotomy to enable EABR testing and potential subsequent CI are necessary. There are important considerations for all VS surgery that have specific implications for outcomes of auditory rehabilitation.[21]

Meticulous surgical technique is essential to minimize brainstem trauma from direct physical damage or collateral effects of electrocautery. A secondary effect of electrocautery is neural damage from repeated stimulation and excitotoxicity. There is therefore an argument for early division of the vestibulocochlear nerve at the brainstem. This decision may be made early with a large tumour, or cases where it is deemed unlikely to be able to preserve the CN. ABI would then be performed. To prevent migration of the receiver–stimulator, a well or anterior lip is usually drilled on the skull to recess the CI or ABI that is placed in a tight periosteal pocket. A channel for the array can also be drilled from the well to the edge of the craniotomy/mastoidectomy.

Particular challenges for ABI in NF2 include distortion of the brainstem anatomy making placement more difficult than in non-tumour cases. Subsequent remodelling/moulding of the brainstem to fill the tumour void may lead to movement or displacement of the array.

Intra-operative implant evoked ABR testing is a critical step in ABI surgery to optimize paddle position. Usually the four corners of the array are activated in succession, followed by other electrodes as necessary. Based on the presence or absence of ABR, the merits of adjustment of the paddle are discussed with the surgeons. Subsequent repositioning with further testing occurs until placement is optimal. Simultaneous facial and glossopharyngeal nerve monitoring take place to pick up any non-auditory stimulation and anaesthetic vigilance and close attention to the electrocardiogram is also warranted. The silicone mesh on the ABI paddle can be trimmed prior to placement. The advantage of the mesh is that it aids adherence to the brainstem, although, conversely, this may be a disadvantage when repositioning. Maintenance of the optimum position is crucial but challenging. If the implant is placed deep in the lateral recess, the brainstem itself may hug the implant and help keep the paddle stable, but this depends on the amount of distortion left by the tumour and the optimum position dictated by the EABR. Fibrin and dural sealants can be used to help prevent displacement as retraction is relaxed and closure takes place. Anchoring the array in the cavity or at the craniotomy edge should also be considered.

POST-OPERATIVE CARE

Post-operative care and recovery is similar to that for non-implantation VS surgery. Antibiotic prophylaxis for intracranial surgery is in keeping with antimicrobial guidelines, which vary from one unit to another. Meningitis risk should be explained as part of the consent, and pre-operative vaccinations 2 weeks or more before surgery are advised as per CI.

Device activation for CI patients follows the same procedures as for non-NF2 CI recipients. However, ABI activation is done with the patient nil by mouth in a setting (usually either an anaesthetic room or recovery) where there is cardiac monitoring and an anaesthetist present. This is due to the possibility of non-auditory stimulation and, in particular, the risk of vagal stimulation causing bradycardia, tachyarrhythmia or the need for a secure airway. Programming of the ABI involves stimulating each electrode in turn and then in groups across the array. Threshold and comfort levels are varied. Auditory perception with feedback on loudness and pitch enables programming, with the aim of access to a good range of frequencies while avoiding non-auditory stimulation. Numerous appointments over the first year enable adjustment of current levels according to progress and changes in perception. Speech and language therapists and habilitation specialists play a crucial role in helping the patient to learn to recognize sounds. Motivation, commitment and perseverance are important for the patients to be able to maximize their potential benefit from their implant. Assistive listening devices may also help to optimize performance in day-to-day situations.

TUMOUR SURVEILLANCE

Ongoing interval magnetic resonance imaging (MRI) is an important consideration in these patients who invariably require tumour surveillance, either of residual ipsilateral VS or contralateral VS. Previously with the Cochlear® device, temporary removal of the magnet reduced pain and discomfort during scanning and diminished the extent of the artefact/signal void from the implant body. There were, however, resultant problems with infection[22] and degradation of the magnet can occur with multiple removal and reinsertions over time.[10] The most recent MED-EL ABI implant is MRI conditional, enabling patients to be scanned in a 1.5 Tesla machine without the need for magnet removal so there is no pain/discomfort. This is due to an advance in magnet polarity technology where the magnet is self-aligning and rotates freely within its housing. Despite this innovation, artefact remains a problem, posing an issue for monitoring especially with ipsilateral residual VS, and hence magnet removal/replacement may still be necessary.

OUTCOMES

Outcomes of ABI are far more variable than outcomes of CI. CI placement in the scala tympani naturally guides the array around the cochlear turns close to the spiral ganglion neurons with presumed tonotopic organization. Comparatively uncertain positioning in the lateral recess of the fourth ventricle adjacent to the cochlear nucleus is then reliant on patient perception and feedback of auditory tones with pitch ranking for subsequent programming of the ABI. Patient factors, either NF2/tumour-related or from concurrent medical problems, may cause disabilities that interfere with programming and auditory habilitation. Intra-operative factors from mechanical or ischaemic damage to the cochlear nucleus or brainstem are also likely to influence outcomes.[21] Furthermore, habilitation and performance take longer with ABI and may not

plateau for several years[5] compared to several months for most CI users.

Initial hearing benefits with ABI ranged from sound awareness, identification of some environmental sounds and improved performance over lip-reading alone when communicating face-to-face.[6, 23–25] Better results were achieved with non-NF2 patients[26] and subsequently 'open-set' speech recognition (understanding without visual cues) has been reported in NF2.[27–31]

Collaborators from multiple centres have tried to identify reasons for better outcomes.[21] They looked at good performers, those with speech recognition scores >30%, totalling 26/84 patients in a series from June 1997 to September 2011 and found that short duration of deafness (<1 year) was associated with a mean increase in word recognition score of 20%. This suggests a possible degenerative process in the brainstem or higher auditory centres with time. Good results have, however, been reported with deafness durations of 15 years or more.[32] Two surgeons who operate with the patient in the semi-sitting position have achieved the best ABI outcomes. The effect of gravity on the cerebellum enables lower intracranial venous pressure, which in turn means less bleeding when compared to the supine position. This may, however, be a surgeon effect or in part due to less electrocautery use. The semi-sitting position does carry an increased risk of air embolism and tension pneumocephalus[33] and this approach is therefore only recommended for teams familiar with it. The maximum comfortable level (MCL) can be an indicator of distance/proximity to the cochlear nucleus[34] and a relationship between lower thresholds and better outcomes with higher stimulation rates was observed, the inference being (as one would expect) that proximity of the paddle to stimulable tissue is important. Increasing number of distinct pitch electrodes also had a positive correlation with performance such that number alone has less of an influence than the spectrum of pitch perceptions achieved with those in use. Good results where ABI provides more than an aid to lip-reading are definitely achievable in NF2, even in large tumours, but outcomes remain variable and difficult to predict.

ABI IN CONGENITAL HEARING LOSS

The experience described above of ABI in NF2 provided an impetus for exploration of the utility of this technology in non-NF2 patients in whom a CI could not be utilized. A small but important group is those infants and children with bilateral congenital profound hearing loss who are identified through newborn hearing screening programmes and referred for CI and found to have inner ear or CN abnormalities that preclude CI. These include children with absent cochleas or absent CNs or a combination thereof. While the precise incidence or prevalence of such abnormalities is unknown, it is a reasonable estimate that for every 100 children referred for CI one or two will have the abnormalities described and therefore not be suitable for a CI (Saeed, personal observation). For the parents or care-givers of such children this proves to be a substantial additional burden as they are often still coming to terms with the realization that their child has bilateral profound hearing loss and are then advised that the highly successful CI intervention is not appropriate. This challenging situation draws heavily on the skills acquired by experienced CI/skullbase teams in terms of assessment, surgery, habilitation and, critically, the management of the expectations of the family in terms of commitment to the habilitation process and outcomes of ABI in such children.

Nevertheless, based on the outcomes of ABI in a substantial number of non-NF2 adults, Colletti and his team extended the indications for ABI to include such children.[35, 36] This pioneering work served as catalyst for other centres across the world to utilize ABI in selected congenitally deaf children. In the UK the first three children were implanted by Richard Ramsden and his team in Manchester in 2005 and this was followed by teams in the USA, Turkey, Korea and, subsequently, London and Cambridge in the UK.[37–39] The emergent literature emphasized the importance of careful case selection as well as the surgical and habilitative challenges in such children but also the variable outcomes, ranging from no auditory benefit, environmental auditory perception through to development of vocabulary and the slow trajectory in achieving these outcomes when compared with children undergoing CI.

In an attempt to standardize the assessment and indications for ABI in children internationally, Sennaroğlu convened a meeting of key stakeholders in Istanbul which resulted in the first consensus statement, published in 2011.[15] This was followed up by a second such meeting and a second consensus statement in 2016.[40] Such a collaborative exercise involving 20 centres from 11 countries explored the clinical and radiological indications and timing of surgery, habilitation and evaluation of outcomes and emphasized the importance of appropriate teams managing such complex children. Key points include:

- The importance of a comprehensive MDT drawing on extensive CI and lateral skullbase experience and the management of the expectations of the family was emphasized.
- It was agreed that, in order to balance the potential auditory benefit based on neural plasticity against the metabolic stress of intracranial surgery and anaesthesia, the optimal age for ABI in congenitally deaf children is 18–24 months.
- The children with cochlear and or CN aplasia should be considered for ABI while those children with hypoplastic CN should be offered a CI in the first instance with a view to fast-tracking for ABI if the CI does not confer any benefit.
- It was also recognized that the majority of ABI recipients do derive auditory perception but not necessarily speech acquisition, in contrast to children with a CI.
- Finally, it was clear from the accrued global experience that those children with additional physical or cognitive disabilities fared less well than the non-sydromic otherwise healthy children.

In one of the largest series examined to date, Sennaroğlu and his team have reported the longer-term outcomes (<1 year) in 35 children undergoing ABI.[41] The majority of the recipients achieved grade 5 on the Categories of Auditory Performance (CAP) scale, implying understanding common phrases without lip-reading. The outcomes, however, as expected, were not as good as a comparable age group that had undergone CI, and those children with additional disabilities fared less well than those who had no additional physical or cognitive problems. Nevertheless, as has been observed by all who work in this field, in appropriately selected infants and children and appropriately counselled families, the ABI is a viable option for the family to consider as part of the habilitative process for their congenitally profoundly deaf child.

In summary, the assessment, surgery and management of a child undergoing ABI for congenital profound deafness, as well as the counselling of the child's family, is a complex process that is continuing to evolve as experience among centres undertaking this work continues to accrue. CI programmes that identify a child who is not suitable for a CI should refer the child to an ABI centre so that the family can have the benefit of appropriate multidisciplinary evaluation.

FUTURE RESEARCH

- ABI design to optimize the placement of the electrode array paddle with reference to the tonotopicity of the cochlear nuclei.
- Electrophysiological evaluation of the cochlear nerve post-NF2 surgery or the hypoplastic cochlear nerve.
- Auditory habilitation and rehabilitation of ABI recipients to improve outcomes.

KEY POINTS

- A vast number of factors affect decision-making and outcomes for this complex patient group. The multidisciplinary teams for neurofibromatosis and auditory implantation must work cohesively. In particular, the roles of the audiological scientists for pre-operative investigation, peri-operative monitoring/testing and post-operative programming are crucial to guide patient-centred decisions. Surgical and peri-operative management by experienced teams with fastidious attention to every detail are paramount.
- Outcomes continue to be varied; but, with centralization of services, technological advances, increasing experience and ongoing International collaboration, improvement will be seen in patient pathways, shared decision-making, quality of care and patient benefit.

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CHAPTER 97

IMAGING OF THE TEMPORAL BONE

Steve Colley

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search from using the following keywords: temporal bone, imaging, CT and MRI.

INTRODUCTION

The temporal bone is a complex anatomical area that is made up of five osseous components: the squamous, mastoid, petrous, tympanic and styloid portions of the temporal bone. Anatomically, the temporal bone may be separated into five distinct regions that demonstrate some specific types of pathology, and can dictate the optimum imaging method depending on the area of concern and the pathology suspected. These anatomical sub divisions of the temporal bone are: the external ear; the middle ear and mastoid; the inner ear; the internal auditory canal (IAC); and the facial nerve canal.

The imaging modalities used in common practice include computed tomography (CT), magnetic resonance imaging (MRI), nuclear medicine and, more recently, cone beam computed tomography (CBCT). The main imaging methods utilized in temporal bone imaging are CT and MRI, and a brief overview of scanning techniques, benefits and disadvantages is summarized as follows.

SCANNING TECHNIQUES

Computed tomography (CT)

Multidetector CT scanning allows extremely quick acquisition of imaging of the temporal bones. The data acquired is a volume, which can then be reconstructed in a variety of imaging planes depending upon the anatomical area being scrutinized. Typical temporal bone CT images are acquired at a thickness of 0.5–0.6 mm, and they provide excellent bony detail of the external auditory canal (EAC), middle ear and mastoid, ossicular chain, inner ear, and the facial nerve canal. CT also allows accurate identification of masses or opacification within the anatomical areas of the temporal bone, but suffers from its ability to differentiate between different types of opacity (e.g. fluid versus cholesteatoma).

CT utilizes ionizing radiation. The dose employed in CT of the temporal bones is more of an issue in imaging of children, adolescents and young adults – especially where repeat imaging is employed. CBCT offers a reduced radiation dose in comparison to MDCT, and is certainly an effective alternative in these settings.

Magnetic resonance imaging (MRI)

MRI utilizes strong magnetic fields (30 000 to 60 000 times greater than the earth's magnetic field) in order to produce images based upon the mobility of nuclei, especially protons within water molecules.

Advantages include excellent soft tissue contrast, and the ability to visualize and resolve the cranial nerves as they traverse CSF and the IAC. MRI can also differentiate between differing types of soft tissue opacification in the middle ear and mastoid, helping discriminate cholesteatoma from inflammatory or post-surgical changes.

Disadvantages of MRI include longer scanning times (up to 45–60 minutes), artefact from movement, surgical implants and metal, and safety issues secondary to the strong magnetic fields employed.

ANATOMICAL VARIANTS

Before considering the different types of pathology encountered in the temporal bone, there are a number of anatomical variants that are highly relevant for radiologists to assess and cover in reports, in order to avoid prolonged procedures and operative complications in a surgical field where access is often rather limited.

Tegmen tympani

A low-lying tegmen may hinder access to the middle ear via a mastoid approach, and pre-operative recognition is important in order to avoid breach during surgery.

Sigmoid sinus

The sigmoid sinus passes along the posterior margin of the mastoid, and varies greatly in the degree of anterior indentation in to the mastoid cavity. An anteriorly located sinus may have a very thin slip of cortical bone between it and the mastoid cavity, and sinus injury could result in significant bleeding complication during surgery.

Jugular fossa

Wide variation exists in the size and height of the jugular fossa and jugular bulb, both between patients and on either side in the same patient. A high riding jugular bulb may project into the hypotympanum, it may have a thin bone covering that may be damaged at surgery or be completely dehiscent of bone covering, or a small diverticulum may protrude from the jugular bulb towards or into the hypotympanum (Figure 97.1).

Carotid canal

Whilst there may be very minor variations in the internal carotid artery (ICA) canal course, these are generally insignificant. A true aberrant ICA is rare, but it is vitally important to identify on pre-operative imaging studies. Failure of the normal cervical carotid artery development leads to anastomosis between inferior tympanic artery and an enlarged caroticotympanic artery. An aberrant ICA is formed, which traverses the middle ear cavity.

Typically, an aberrant ICA passes through the infero medial middle ear cavity, adjacent to the cochlear promontory (Figure 97.2). In addition to a significant intra operative surgical complication risk, it may present as a pulsatile retro tympanic mass, or cause CHL via mass effect on the incudostapedial joint.

Facial nerve canal

The normal VIIth nerve canal arises from the anterior lateral IAC, passing to the geniculate ganglion (anterior genu). The geniculate segment then passes posteriorly along the middle wall of the middle ear, lying below the lateral semi-circular canal, above the oval window niche and stapes superstructure. At the posterior genu, the canal turns another 90 degrees, forming the descending or mastoid segment, which exits the temporal bone at the stylomastoid foramen. Variation in VIIth canal anatomy is important to highlight pre-operatively, to avoid inadvertent injury and to plan potentially difficult middle/inner ear access. More common variations include a nerve that protrudes inferiorly into the oval window niche, a dehiscent tympanic segment with no discernable bone covering, or a truly aberrant VIIth nerve course.

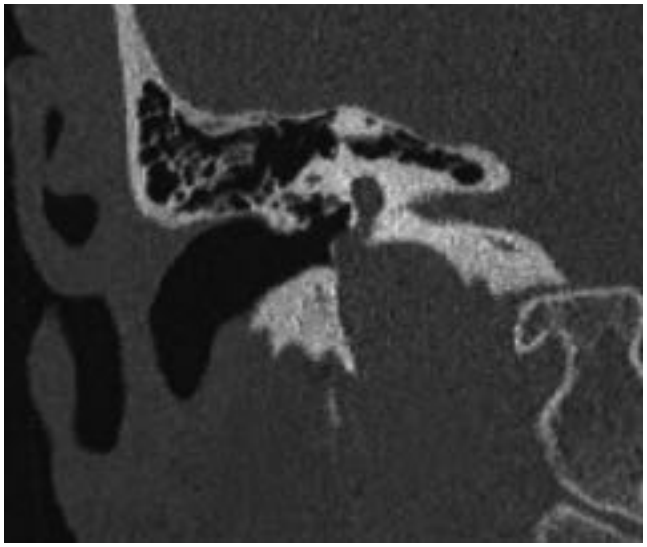


Figure 97.1 Coronal CT showing high riding right jugular bulb, protruding into hypotympanum.

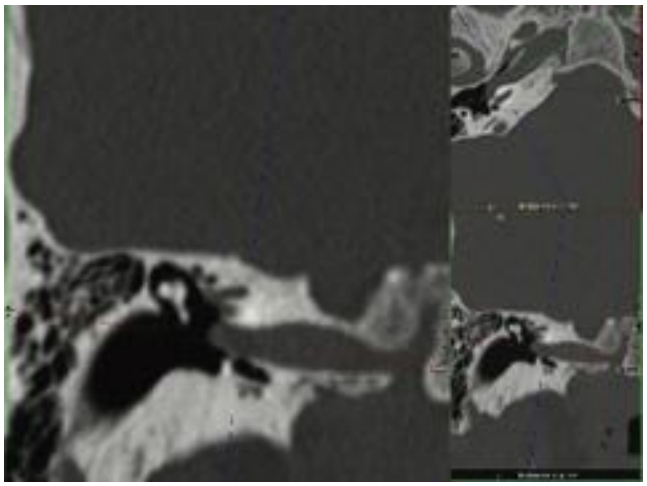


Figure 97.2 Coronal and axial CT with aberrant right ICA course, passing into middle ear cleft, just lateral to cochlear promontory.

IMAGING OF TEMPORAL BONE PATHOLOGY

Acute otitis media and mastoiditis

A mild degree of mastoiditis will generally been seen with acute otitis media. The more prevalent use of antibiotics in treatment of acute otitis media has reduced the number of significant cases of mastoiditis. The importance for radiologists is to identify the potentially serious coalescent mastoiditis, and any complications arising from mastoid infection.

Uncomplicated, or mild mastoiditis is seen as fluid within the mastoid air cells but, importantly, with preservation of the internal bony septations and peripheral bone margins. Destruction of the internal bony septations indicates the presence of acute coalescent mastoiditis, which requires prompt treatment to prevent complications such as soft tissue or intracranial extension and abscess formation.

When a more aggressive mastoiditis is present, the bony margins of the mastoid and surrounding soft tissue planes should be assessed. Infection can spread through the sutures to form a subperiosteal abscess, and extending into the upper neck, forming a Bezold abscess. Infection may spread posteriorly into the sigmoid sinus, or superiorly into the middle cranial fossa.

Chronic otitis media

Chronic otitis media (COM) is usually due to Eustachian tube dysfunction, and has a clinically different presentation to acute infection, being generally painless with chronic discharge with or without CHL often present. Negative middle ear pressure may cause tympanic membrane retractions, and subsequent acquired cholesteatoma formation. Imaging usually shows a middle ear and mastoid effusion, with increased sclerosis of the adjacent bony structures. Further complications from chronic otitis media include ossicular erosions (without cholesteatoma) due to chronic surrounding hyperaemia, and ossicular chain fixation. Fixation of the ossicles secondary to COM may be fibrous or calcific, the latter being termed tympanosclerosis. Calcifications with COM may affect the tympanic membrane, or surround and fix the ossicles in the epitympanum (Figure 97.4).

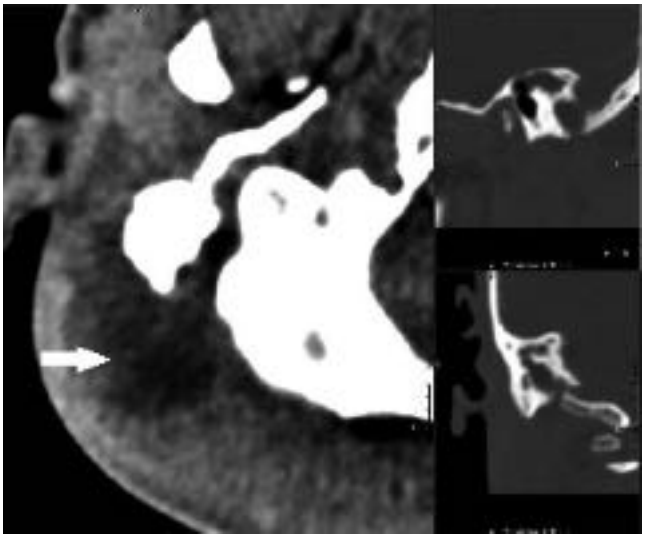


Figure 97.3 Axial, coronal and sagittal CT images showing right masoiditis, with loss of internal bony septation, and Bezold abscess below the mastoid tip (arrow).

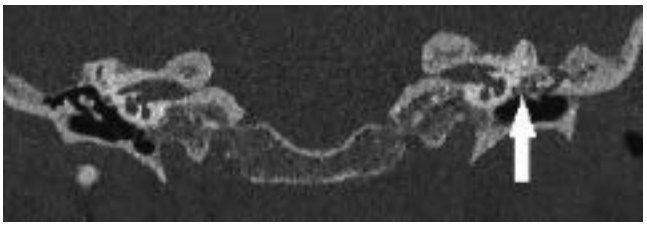


Figure 97.4 Coronal CT showing diffuse ossification (tympanosclerosis) in the medial left epitympanum (arrow) with adjacent chronic effusion. Note the normal right epitympanum.

Necrotising (malignant) otitis externa

Necrotising otitis externa (NOE) usually presents in elderly patients with ear discharge and severe otalgia, generally with an underlying history of diabetes or chronic immune suppression. *Pseudomonas aeruginosa* are the most common causative organisms.

Imaging has a role to play in diagnosing presence and extent of disease, identifying complications, and in the long-term management and follow-up of this complicated and often difficult to manage condition. CT is normally the first imaging technique, and MRI can provide complimentary information when there is evidence of bone involvement and osteomyelitis.

Early disease is seen as subtle soft tissue thickening in the EAC. Disease can progress and invade the submucosa and spread beyond the bony or cartlagenous confines of the EAC. Early changes suggesting an aggressive or progressive form of NOE are the identification of subtle cortical bone erosions (osteomyelitis). Comparison with the normal contralateral side is often of benefit here (Figure 97.5).

Infection can then spread along a few different, but predictable, pathways: the petrotympanic fissure allows infection to spread from the middle ear to the temporomandibular joint (TMJ) and the soft tissues below the skull base. Disease extension medially to the carotid canal is often seen and, again, comparison with the contralateral side can help pick up early osteomyelitis and bone erosions in this region. Inferiorly, disease can spread through the soft tissue spaces below the skull base, and assessment of these regions is important on imaging (Figure 97.6).

Invasion of the central skull base (central skull base osteomyelitis) may occur from direct extension along the

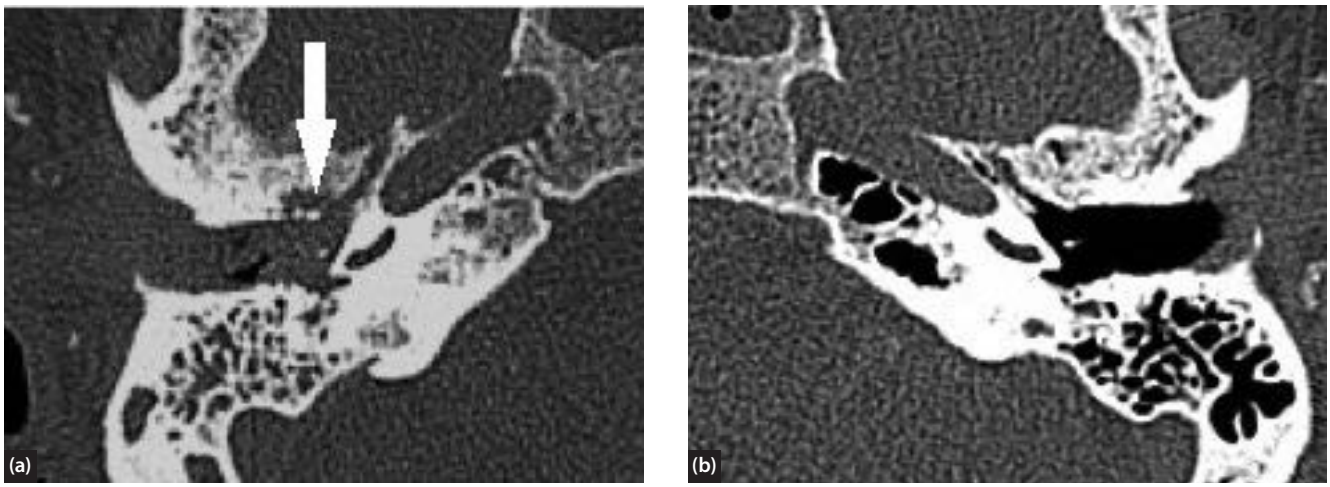


Figure 97.5 a and b Axial CT with thickened soft tissue in EAC, middle ear effusion and early subtle erosion of anterior epitympanum (arrow). Normal left middle ear for comparison.



Figure 97.6 Axial CT in patient with NOE, with diffuse infiltration of soft tissue beneath the skull base, and loss of normal fat planes. Normal fat planes depicted by left sided arrow.

petrous apex and across the petroclival fissure, or from subtemporal disease directly invading the lower clivus. MRI is better at detecting early central skull base disease, with bone marrow changes being apparent on standard T1 weighted images before frank cortical destruction occurs. Intracranial extension of disease, either direct from the mastoid and middle ear, or via neural foramina, is best identified on MRI (Figure 97.7).

Imaging may be used to follow up patients and dictate appropriate antibiotic treatment duration. There remains confusion as to the best imaging strategy in follow-up of NOE. It is clear that both CT and MRI abnormality can persist after adequate disease treatment, and notably abnormality can remain in the bone marrow on MRI with imaging improvement lagging behind clinical improvement. Various nuclear medicine studies have been utilized in follow-up of NOE, with ^{99m}Tc or Gallium 67 bone scans potentially helping in follow-up; however, Gallium scans are thought better for follow-up, as imaging tends to return more rapidly to normal after infection has settled.[1]

Cholesteatoma

Cholesteatomas are a collection of keratinizing squamous cells in the middle ear cleft, which are associated with resorption or erosion of adjacent bony structures. Lesions may be congenital (occurring anywhere in the temporal bone) or acquired (middle ear location), the latter being far more common (around 98% of cholesteatomas)[2] as a complication of chronic otitis media.

Initially, CT is the imaging method of choice in depicting middle ear opacification and bone erosions of the scutum and adjacent ossicular. A normal CT has extremely high NPV for absence of cholesteatoma. The limitation of CT is that it cannot differentiate mucosal or inflammatory middle ear disease from the soft tissue mass of a cholesteatoma, cholesterol granuloma, granulation tissue or malignancy.[2] CT is also the best modality for detecting bone erosions that are seen with high frequency in both pars flaccida and pars tensa cholesteatomas.

Acquired cholesteatomas arise from invaginations of the tympanic membrane, or grow into the middle ear via perforations. The former type, derived from an apparently intact membrane, are more common, and typically arise from the pars flaccida region. Keratin accumulates in the lateral epitympanic (Prussak) space, and causes scutum erosion, medial displacement of the ossicular chain, and ossicular erosion (Figure 97.8). Cholesteatoma growing into the middle ear via a perforation usually arises from the pars tensa. These 'secondary acquired' cholesteatomas are often located medial to the ossicular chain, and cause



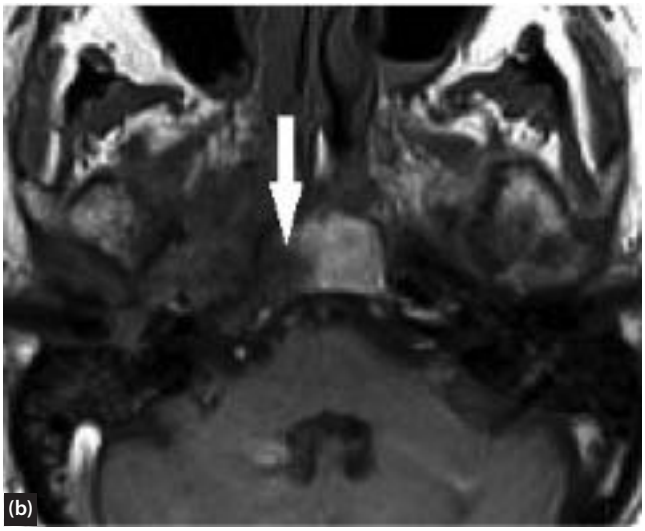


Figure 97.7 Axial CT (a) and T1 weighted MRI without fat suppression (b) in patient with right NOE. Normal bone cortex is preserved on CT, but T1 MRI shows early marrow infiltration and loss of normal fatty marrow signal (arrow) in keeping with early central skull base osteomyelitis.

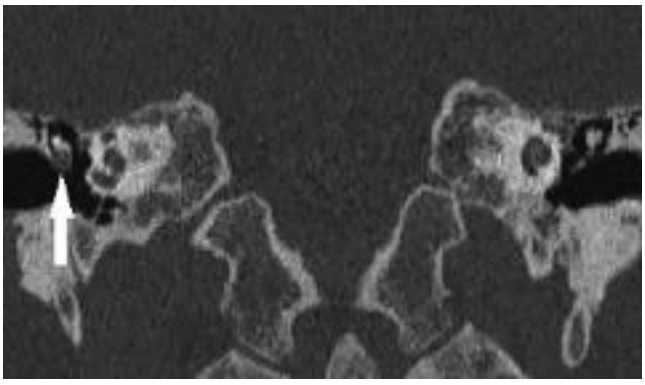


Figure 97.8 Coronal CT with 4 mm right lateral epitympanic pars flaccida cholesteatoma (arrow), with early ossicular erosion.



Figure 97.9 Coronal CT with left middle ear soft tissue opacification, with subtle lateral displacement and erosion of the ossicular chain compatible with pars tensa cholesteatoma.

early erosion of the long process of incus (LPI) and tend to more erosion of the inner ear structures (Figure 97.9).

Modern MRI techniques utilizing functional imaging sequences can assist in delineating extent of disease, but more importantly can now detect recurrence, replacing routine second-look surgery in many centres. Functional MRI utilizes diffusion weighted imaging (DWI), which characterizes tissues based upon the mobility of water molecules within them. Inflammatory disease will have good water mobility, whereas cholesteatoma, with tightly packed keratin and limited extracellular space, show reduced water diffusion. Early MRI techniques (echo-planar DWI – EPI) showed significant artefact at bone, soft tissue and air interfaces with both false positive and false negative results. Newer non-echo-planar (non-EPI) DWI does not suffer from such artefact, and allows imaging of sufficient resolution to detect cholesteatoma down to 2 or 3 mm diameter, without post-contrast sequences.[3] Positive scans typically show high signal on the b1000 sequence, with matched low signal on the Apparent Diffusion Coefficient Map (Figure 97.10).

A number of potential complications should be sought on imaging. Labyrinthine fistula due to lateral semicircular canal erosion (Figure 97.11) can result in vertigo, imbalance and sensorineural hearing loss. Less commonly, cochlear promontory erosion may occur. Importantly, the tegmen should be assessed for potential erosion or breach, as a meningocoele should be excluded in such cases pre-operatively.

Otosclerosis

Imaging is not always employed in the diagnosis of typical otosclerosis with CHL, but may be utilized in patients with sensorineural or mixed hearing loss, or an atypical history. CT is the imaging method of choice, as it depicts the early bone changes associated with otosclerosis in both fenestral and retrofenestral disease.

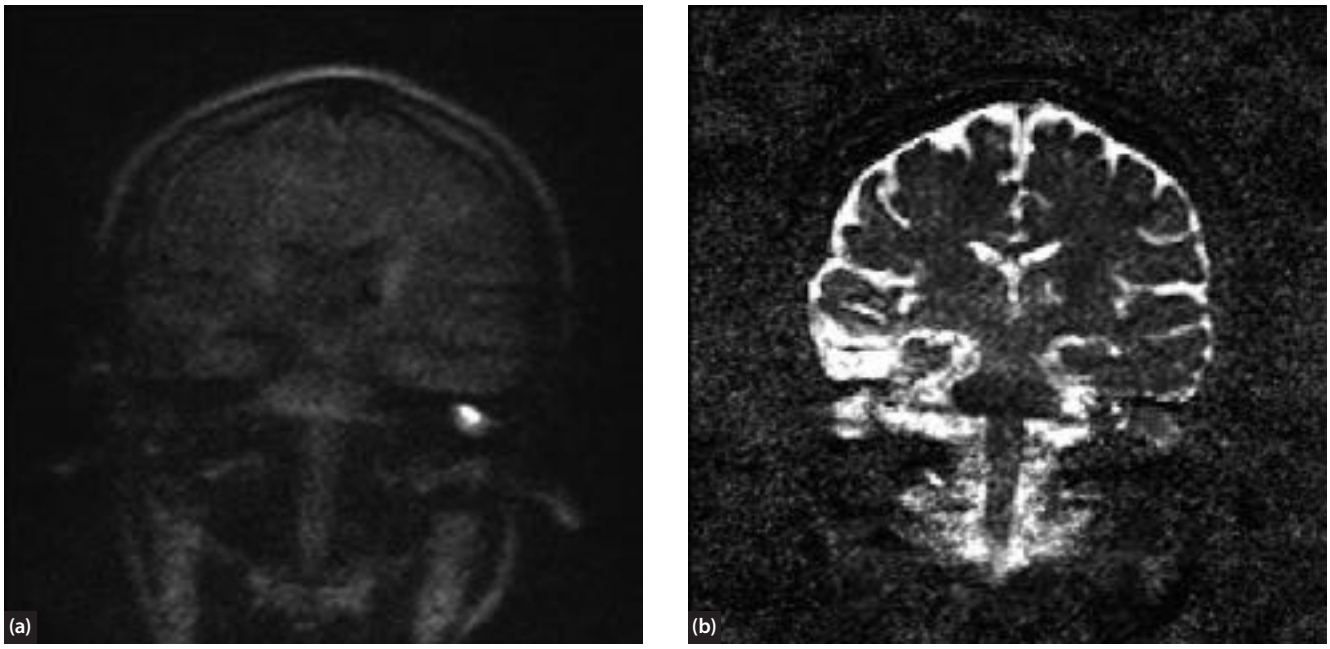


Figure 97.10 Coronal DWI MRI shows left sided high signal on the b1000 sequence (a) with matched low signal on the ADC map (b), compatible with left sided cholesteatoma.

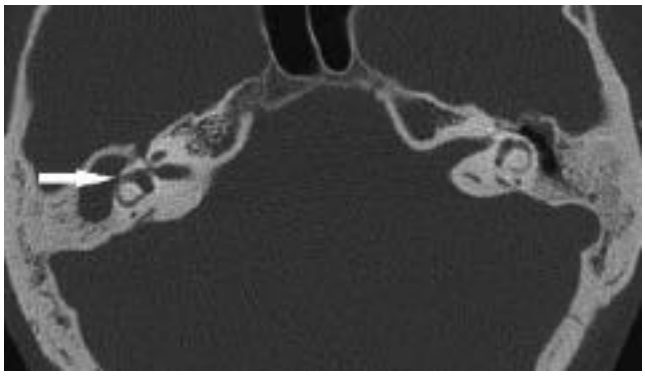


Figure 97.11 Axial CT shows right sided epitympanic cholesteatoma, with erosion of lateral semi-circular canal (arrow). Note normal bone covering of left lateral semicircular canal.

Thin section CT shows low-density (demineralized) plaques in early disease, which typically affects the fissula antefenestrum at the anterior border of the oval window. The otoscerotic plaque can extend to involve the stapes foot-plate, occlude the oval window and extend to the cochlear promontory and round window region. Disease is often bilateral (up to 85% of cases).[4]

Retrofenestral disease is the less common of the two types of otosclerosis – and often considered a continuation of fenestral disease. Low density is seen extending around the otic capsule, termed the fourth ring of Valvassori (Figure 97.12). Again, disease is usually bilateral.

CT for assessment of otosclerosis should also be used to evaluate alternative causes of conductive hearing loss (CHL). Anatomical temporal bone variants described at the beginning of the chapter should also be sought prior to considering surgical treatment – normally with stapedectomy and ossicular prosthesis in the setting of fenestral disease.

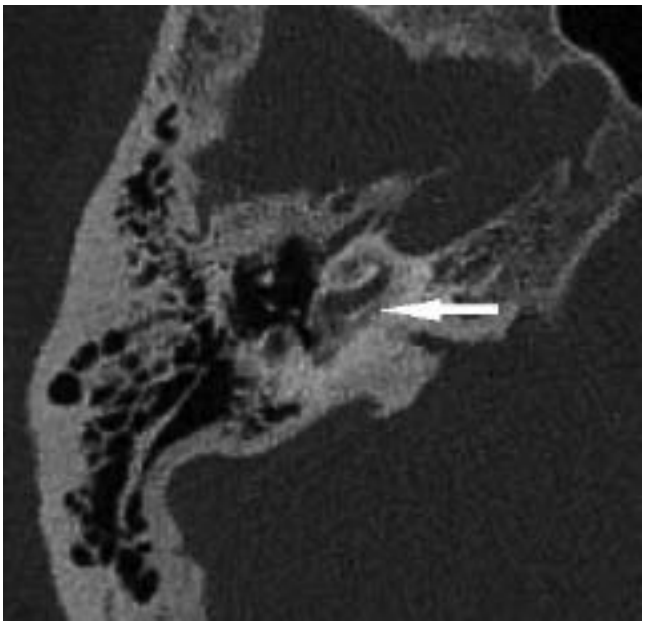


Figure 97.12 Axial CT at the level of the basal turn of cochlear shows low density surrounding the cochlea (arrow), indicating retrofenestral otosclerosis.

Superior semicircular canal dehiscence

Superior semicircular canal dehiscence (SSCD) has been increasingly recognized as a cause of a variety of vestibular and auditory symptoms. SSCD is thought to be due to a bony defect affecting the arcuate eminence of the superior canal, resulting in a mobile third window into the labyrinth. Absent bone over the SSC, however, is described in up to 13% of asymptomatic individuals.[5]

Thin section CT scans can demonstrate bone thinning and bone defects. Images should be reconstructed in

planes parallel (plane of Pöschl) and perpendicular (plane of Stenver) with respect to the superior canal to allow accurate demonstration of defects, the angle they subtend, and to help plan surgery if symptomatic.

Temporal bone trauma

Temporal bone fractures normally result from high-impact blunt trauma, such as road traffic accidents, falls from height or direct assault. High resolution CT is the imaging method of choice, and is normally undertaken as part of an initial trauma CT study. A dedicated temporal bone CT should be considered when there is suspicion of a temporal bone fracture but no obvious injury on initial trauma study. Traditional classification has described fractures as longitudinal or transverse, with respect to the long axis of the temporal bone (i.e. longitudinal fractures passing transversely through the temporal bone on an axial image, and transverse fractures running antero-posterior on axial images).[6]

Longitudinal fractures are by far the most common, accounting for up to 90% of temporal bone fractures. These fractures are more commonly associated with CHL, which may be due to tympanic membrane (TM) involvement, haemotympanum or ossicular chain disruption (fracture or dislocation, or both) and normally spare inner ear structures (**Figure 97.13**). Transverse fractures more commonly pass through the otic capsule and internal acoustic meatus (IAM), and are hence more commonly associated with sensorineural hearing loss, facial nerve paralysis and cerebrospinal fluid (CSF) leak.

Facial nerve paralysis is seen more commonly with transverse fractures (up to 50%) than longitudinal fractures (10–20%). Onset is usually more rapid with transverse fracture patterns due to nerve transaction in the labyrinthine segment, whereas longitudinal fractures may have delayed onset due to nerve contusion or compression from adjacent haematoma.

Further complications that should be considered are CSF leak, meningitis, meningocoele from tegmen involvement, and vascular injury to the carotid canal or jugular fossa. Delayed complications can include labyrinthine ossificans and post-traumatic cholesteatoma.[7]

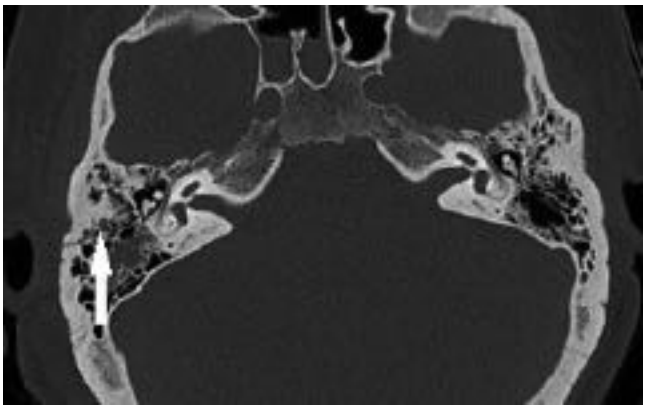


Figure 97.13 Axial CT showing right longitudinal temporal bone fracture (arrow), with incudostapedial joint disruption and widening. Note normal left incudostapedial joint.

TEMPORAL BONE TUMOURS

There are a number of benign and malignant tumours that may affect the temporal bone. Benign lesions include vestibular schwannoma, cholesterol granuloma, paragangliomas, facial nerve haemangioma, and osteomas. Malignant lesions include squamous cell carcinoma (SqCC) and other rarer EAC tumours, direct invasion (e.g. nasopharyngeal cancer or parotid malignancy) or perineural spread, or distant metastases.

Vestibular schwannoma

Vestibular schwannomas are the most common CPA and IAC tumour, accounting for 70–80% of lesions, with meningioma and metastases less common. MRI is preferred for detecting tumours and delineating extent. Thin section T2 weighted images (constructive interference in steady state, (CISS), Fast Imaging Employing Steady-state Acquisition (FIESTA)) (**Figures 97.14** and **97.15**) provide excellent CSF high signal and clear delineation of the cranial nerves traversing the IAC. Post-contrast thin section T1 weighted images can help pick up small or subtle lesions, and assist in follow-up.

Small lesions appear homogenous on T2 sequences, and show homogenous enhancement. Larger lesions may show heterogeneity on T2 and post contrast sequences due to areas of cystic change. Such cystic lesions often demonstrate more rapid growth patterns, but respond better to radiosurgical techniques than solid lesions.[8]

Lesions may be purely intra-cannalicular, extend through the IAC meatus to the cisternal compartment (producing a typical 'ice cream cone' appearance) or, less commonly, may be purely cisternal. Larger lesions may cause mass effect upon the brainstem and 4th ventricle. Occasionally, lesions may undergo acute internal

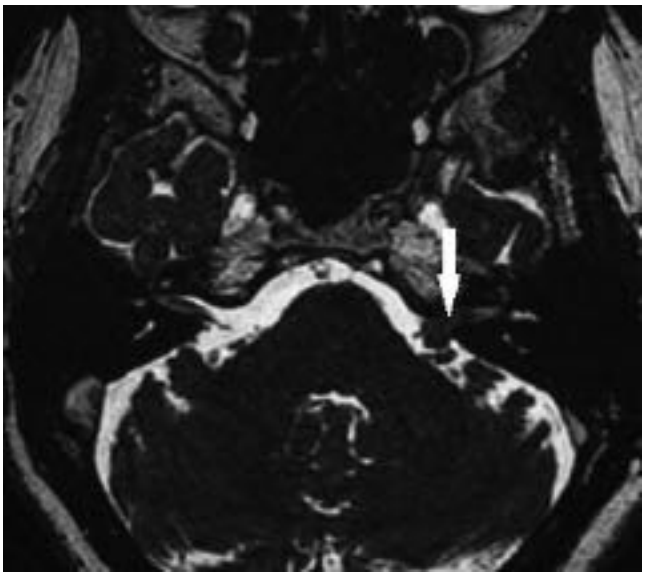


Figure 97.14 Axial CISS MRI showing left sided vestibular schwannoma (arrow), with intra cannalicular and cisternal component, but no brainstem compression.

haemorrhage with rapid expansion and development of cerebellar signs and vomiting.

Post-treatment scanning should assess volume reduction and, importantly, post-contrast T1 sequences may show nodular enhancement associated with tumour recurrence or regrowth.[9]

Cholesterol granuloma

Regardless of the aetiology of cholesterol granuloma, it is the repeated haemorrhage and accumulation of blood products that creates typical imaging appearances of high T1 and T2 signal intensity on MRI scan. There is no appreciable enhancement post-contrast, but T1 weighted scans pre-contrast should be performed in order to identify the characteristic high signal intensity. Diffusion weighted MRI does not show restriction. CT often shows a degree of smooth bone erosion.[2]

Paragangliomas

Temporal bone paragangliomas include glomus tympanicum, glomus jugulare and jugulotympanicum lesions, the latter being a combination of the former two.

Glomus tympanicum paragangliomas are the most common middle ear tumour.[10] On CT, tumours are seen as a nodular area of soft tissue located on the cochlear promontory. Lesions are often small but may extend to the TM and attic if larger, but do not normally cause erosion of the ossicular chain.

Glomus jugulare tumours are the most common lesions to arise in the jugular foramen, with schwannomas and meningiomas being less common. The glomus tumours arise from the jugular bulb, the Xth nerve ganglion, or from the Arnold or Jacobsen nerves.

CT of glomus jugulare shows a typical pattern of permeative bone destruction that involves the carotico-jugular spine early in the disease process. Large lesions may extend to the middle ear (jugulotympanicum tumours) or below the skull base. MRI scanning shows prominent post-contrast enhancement of lesions. Larger tumours may show a classical 'salt and pepper' appearance, which is a combination of flow voids from intratumoural vessels, and areas of microhaemorrhage.

Facial nerve haemangioma

These vascular lesions typically affect the geniculate ganglion, Fallopian canal and anterior aspect of the tympanic facial nerve canal. Low density change may surround an expanded geniculate ganglion on CT, progressing to permeative bone loss, and distinctive intralesional spicules of bone. Thin section MR imaging may show prominent enhancement of the tumour.



Figure 97.15 Axial CT shows a well demarcated soft tissue nodule behind the right TM, overlying the cochlear promontory – typical of a glomus tympanicum tumour.

Malignant tumours

Malignant lesions in the EAC are most commonly SqCC, with other histopathological types being numerous but much less common. CT and MRI imaging are complementary in assessment of such tumours. The aim of imaging is to assess the degree of aggressive tumour invasion into the various temporal bone anatomical sites, and involvement of critical neural and vascular structures, which would affect surgical planning (e.g. facial nerve or dural invasion). Where biopsy has proven a malignant lesion, appropriate staging should be obtained, which should include a CT of the neck and chest for SqCC, and sometimes systemic whole-body CT, or PET CT where metastasis is a diagnostic possibility.

KEY POINTS

- CT and MRI are the main imaging modalities used for temporal bone imaging.
- There are a number of important anatomical variants that should be sought by radiologists interpreting temporal bone imaging studies.
- Identification of anatomical variants can assist surgical planning and reduce potential complications.
- A variety of inflammatory, non-tumoral and tumour pathologies may affect the temporal bone.

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CHAPTER
98

ANATOMY OF THE SKULL BASE AND INFRATEMPORAL FOSSA

Charlie Huins

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SEARCH STRATEGY

Data may be updated by a search using the following keywords: anatomy, temporal bone, skull base, anterior and lateral.

OVERALL TOPOGRAPHY OF THE SKULL BASE

In this chapter, the surgical anatomy of the skull base with reference to otolaryngology will be covered. In depth detail of the ear and nose are covered in separate chapters; details regarding the surgery of all aspects of the skull base are dealt with in the relevant chapters.

Anatomically, the skull base can be considered from both superiorly – within the cranial cavity – and inferiorly, and both aspects will be described here. The boundaries of the skull base are:

- *anteriorly* - by the upper incisor teeth
- *posteriorly* - by the superior nuchal line of the occipital bone
- *laterally* - by the remaining upper teeth, the zygomatic arch & its posterior root, and the mastoid process.

The three main areas of the skull base will therefore be described:

1. anterior
2. posterior
3. lateral.

ANTERIOR SKULL BASE

The anterior skull base forms the floor of the anterior cranial fossa, and a 'roof' over the orbits and ethmoid air cell system (sinuses). It is formed by the frontal bone, the cribriform plate of the ethmoid, the lesser wings and the body of the sphenoid.

The orbital part of the frontal bone forms the roof of the orbital cavity from its superomedial articulation with the nasal bones (the conjoint of these three being the Nasion), to its fusion with the zygomatic bone superolaterally, the anterior aspect being the supraorbital rim; medially, to form the medial orbital wall, it articulates from front to back with the nasal bone, the frontal process of the maxilla, the lacrimal bone, and the paper-thin orbital plate of the ethmoid bone (lamina papyracea) to its posterior articulation with the lesser wing and anterior part of the body of the sphenoid.

The ethmoid bone consists of:

- the central perpendicular plate
- the cribriform plate
- the paired labyrinths.

The midline perpendicular plate forms the central superior aspect of the nasal septum, articulating anteroinferiorly with the quadrilateral cartilage and posteroinferiorly with the vomer. It extends superiorly as the crista galli; either side of the crista lie the cribriform plates, through which pass 20 or so olfactory nerve filaments on each side. The labyrinths, containing numerous air cells, lie medial to the orbit and form part of the lateral wall of the nose, being anterior to the body of the sphenoid. They occupy much of the upper part of the maxillary hiatus, a large defect in the medial aspect of the maxilla, itself closed by several

bones, and the medial aspect of these is surgically important in endoscopic sinus surgery. The superior and middle conchae ('turbinates') are part of the ethmoidal labyrinth, as is the bulla ethmoidalis anteriorly. The lamina papyracea, the paper-thin orbital plate of the ethmoid, separates the ethmoid sinuses from the orbital cavity, knowledge of which is important for endoscopic access to the medial aspect of the orbit, such as for (medial) periorbital abscess drainage, orbital decompression or access to infraorbital/intrazonal tumours.

Two important structures are in this region, providing the blood supply to part of the nasal cavity. The first, found 24 mm posterior to the anterior lacrimal crest on the frontal process of the maxilla, along the frontoethmoid suture on the medial wall of the orbit, is the anterior ethmoidal foramina, transmitting the anterior ethmoidal artery; 12 mm behind this is the posterior ethmoidal foramina and its corresponding artery; 6 mm behind that lies the optic nerve in its canal. The second, found at the top of the perpendicular plate of the palatine bone, posterior to the maxillary hiatus (and so the middle concha), is the sphenopalatine foramen. This transmits the corresponding neurovascular bundle, important in control of the main blood supply to the nasal cavity and also in treating juvenile nasopharyngeal angiofibroma. Of note is the fact that the sphenopalatine artery rarely presents as one arterial trunk, as it divides in two or more (up to 10 branches) just after exiting the sphenopalatine foramen.

The posterosuperior nasal cavity is formed by the sloping anterior aspect of the body of the sphenoid; on the anterior aspect of this, the sphenoethmoidal recess, lying above and behind the superior concha, contains the sphenoidal sinus ostium.

Posterior to the inferior concha, the Eustachian tube orifice marks the medial end of its cartilaginous portion, behind which is found the fossa of Rosenmüller. This lies just anterior to the anteromedial aspect of the foramen lacerum and hence the petrous apex (see below). A nasopharyngeal carcinoma involving this fossa of Rosenmüller may invade upwards through the foramen lacerum, sometimes producing a lateral rectus palsy by compressing the VIth cranial nerve as it crosses the apex of the petrous bone and enters the cavernous sinus.

The salpingopharyngeus muscle arises from the posterior aspect of the tubal orifice, running vertically downwards inside the pharynx to insert into the posterior border of the thyroid cartilage. Its contraction, stimulated via the pharyngeal branch of the vagus, opens the tube.

The pharyngobasilar fascia, a rigid membrane connecting the superior constrictors to the skull base, with two 'paratubal' muscles arising either side of it. Levator palati arises medially (within the pharynx) and tensor palati originates laterally (outside the pharynx). Collectively, they aid opening of the tube due to their attachment to its cartilaginous portion.

Endoscopic endonasal approaches to the central skull base gain access to the:

- frontal sinuses
- cribriform plate
- olfactory bulbs
- frontal lobe
- ethmoid roof
- sphenoid sinus
- pituitary gland
- suprasellar region
- cavernous sinuses
- mid-clival regions.

The latter are accessed trans-sphenoidally; the pair of sphenoid sinuses vary greatly in size, each side separated by a septum usually not in the midline. When small, the sinus lies in front of the pituitary fossa but, when large, may extend beneath the fossa posteriorly to the basiocciput. Tiny at birth, their main development is during puberty. Superior to the sinus lie the pituitary fossa and middle cranial fossa, laterally is found the cavernous sinus and internal carotid artery (ICA), and posteriorly the posterior cranial fossa and pons.

Traversing the superolateral wall of the sphenoid is the optic nerve in its canal on each side; laterally lie the internal carotid arteries and inferiorly the pterygoid canal with its nerve. Further detail of this region is covered in Volume 1, Chapter 87, Anatomy of the nose and paranasal sinuses.

POSTERIOR SKULL BASE

The posterior skull base forms the base of the posterior cranial fossa and is formed by the occipital bone. It houses the cerebellar hemispheres together with the pons and medulla oblongata, the latter of which extends through the foramen magnum, the largest foramen in the skull base and encased by the basilar part of the occipital bone (basiocciput). Either side of the anterior aspect of the foramen magnum are the convex occipital condyles which articulate, via hyaline cartilage, to the convex surface of the atlas, allowing a nodding motion and slight abduction only; rotation is achieved via the atlantoaxial joints. Behind each condyle is the shallow condylar fossa perforated by the condylar canal carrying an emissary vein from the sigmoid sinus to the suboccipital plexus. Above the occipital condyle is the hypoglossal canal carrying the XIIth cranial nerve, which emerges medial to the jugular foramen.

The foramen magnum is oval shaped with the fibrous dura mater attaching to its margins; below this, the latter projects down the spinal canal as the spinal dura mater (theca); above it sweeps up into the posterior cranial fossa. Passing through the foramen, within the dural sheath in the subarachnoid space, lie the lower medulla with the cervical roots of the spinal accessory nerves, the spinal arteries and veins and the vertebral arteries.

A number of ligaments arising from the axis attach to the anterior margin of the foramen magnum: the membrana tectorial, the vertical limb of the cruciform ligament, together with the apical and pair of alar ligaments of the odontoid peg. The anterior and posterior atlantooccipital membranes attach to their corresponding edges of the foramen magnum.

The basiocciput extends forward from the foramen magnum to fuse with the basisphenoid. Along its midline, one third of the way from the foramen magnum to the posterior edge of the nasal septum, lies the pharyngeal tubercle, marking the midline attachment of the pharyngobasilar fascia and the highest fibres of the superior constrictor. Anterior to the tubercle, the bone forms the roof of the nasopharynx. Posterior to it attach the uppermost prevertebral muscles, longus capitis in front of rectus capitis anterior. Separating the nasopharynx from the prevertebral region is the pharyngobasilar fascia, with the prevertebral fascia just behind it.

Posterior to the foramen magnum and hence the basiocciput, the squamous part of occipital bone continues up to fuse along the lambdoid suture with the parietal bones superiorly and mastoid regions of the temporal bones laterally. Externally, a midline crest, the external occipital crest, extends from the foramen magnum up to a projection of bone around 6cm below the lambda, the external occipital protuberance. This crest separates the two sides of the occipital area. Either side of the external occipital protuberance, a concentric ridge of bone extends around to the mastoid process - the superior nuchal line - providing the surface landmark for the attachment of the tentorium cerebelli the transverse sinus (**Figure 98.1**). Sternocleidomastoid attaches to the lateral half of this line, trapezius to the medial half.

The muscles of the back of the neck are attached below this line. Each half of the occipital area is further subdivided by another concentric line – the inferior nuchal line – thus dividing this area into four. The two areas adjacent to the foramen magnum receive the rectus muscles, acting to extend and rotate the head, generally innervated by C1. The two areas between the nuchal lines receive semispinalis medially and superior oblique muscles laterally, giving lateral flexion to the head and also innervated by C1.

Surgical approaches via the occipital bone and posterior skull base include the retrosigmoid and lesser used suboccipital approach to cerebellopontine angle tumours, together with access to:

- occipital bone
- sigmoid sinus
- posterior cranial fossa
- foramen magnum
- upper cervical spine.

LATERAL SKULL BASE

The lateral skull base covers the remaining base of the skull between the anterior and posterior regions described above. Most surgical approaches to this both this area and midline structures anterior to the foramen magnum are made from a lateral, antero- or anterolateral direction.

It is bordered anteriorly by the anterior border of the *sphenoid* body together with its greater wings, and the zygomatic arch; the posterior border is the occipital bone. Laterally it is made up of the squamous and petrous parts of the *temporal bone*. Various regions relate to the undersurface of the sphenoid and temporal bones, which will be expanded upon below.

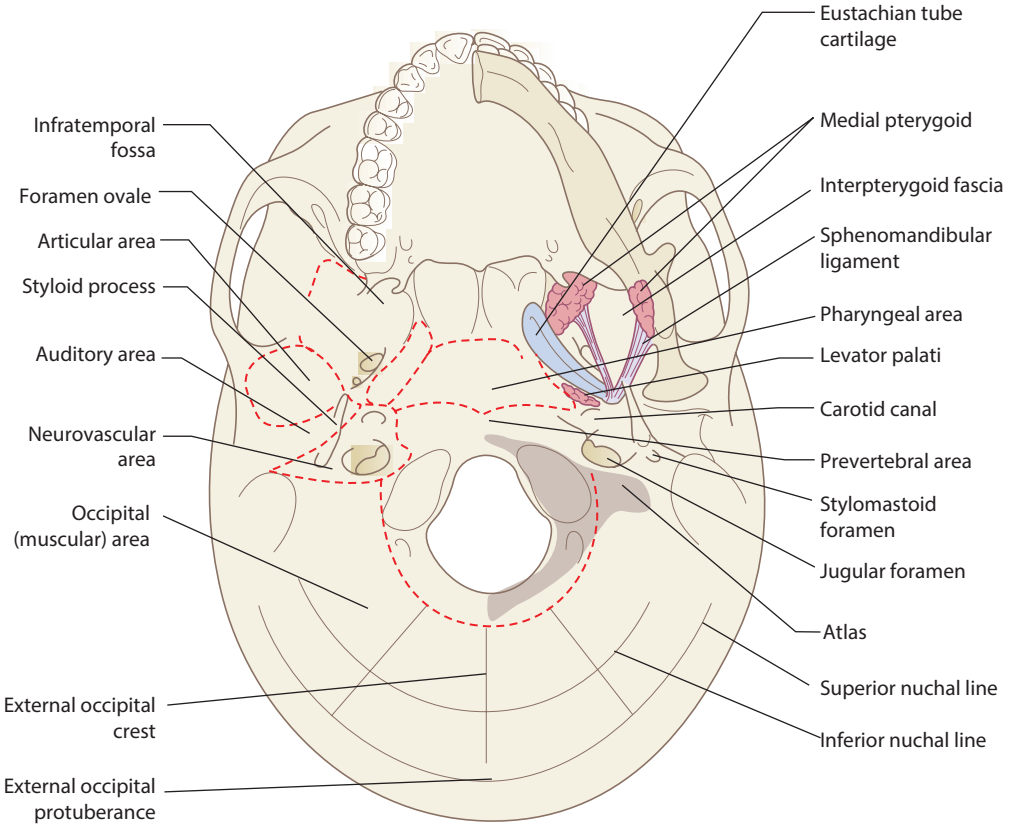


Figure 98.1 The skull base viewed from below. On the right half of the skull are indicated the regions of the central base.In the left half the mandible has been added in the occlusion, with the interpterygoid fascia and Eustachian tube in position. Redrawn from van Huijzen (1984), with permission of S. Karger.

Sphenoid bone

The anterior aspect of the lateral skull base is made up from the body, posterior border of the lesser wings, and the greater wings of the sphenoid superiorly, with the medial and lateral pterygoid plates inferiorly.

The central part of the sphenoid is the *body*, between the clinoid processes, its sloping inferior surface forming the roof of the postnasal space and containing the sphenoid sinus. Its superior surface is hollowed as the pituitary fossa, or sella turcica ('Turkish saddle'), itself roofed by a sheet of fibrous dura mater, the diaphragma sellae. This sheet is continuous laterally as the roof the cavernous sinus, this lying on and grooving each side of the sphenoid body.

Extending superolaterally from the body are the *lesser and greater wings* of the sphenoid, the former anterosuperior and the latter originating posteroinferior from the body, thereby encasing the obliquely slanting *superior orbital fissure*; the contents of this are the ophthalmic nerve and veins, together with the oculomotor, trochlear and abducent nerves.

Extending laterally, the greater wing articulates anteriorly with the frontal bone, laterally with the zygomatic bone and posteriorly with the petrous part of the temporal bone; it therefore forms part of the floor of the middle cranial fossa.

Medially, just in front of the petrous part of the temporal bone, the greater wing is perforated posteriorly by the small *foramen spinosum* (containing the middle meningeal vessels) and, anteromedial to this, by the much larger *foramen ovale* (transmitting the mandibular and lesser petrosal nerves). Occasionally, two smaller foramina also exist in proximity to the foramen ovale – the foramen of Vesalius medially and the innominate foramen posteriorly; anterior to the foramen ovale, the *foramen rotundum* extends forwards, transmitting the maxillary nerve to the pterygopalatine fossa.

Perforating through the base of the lesser wing is the *optic canal*, through which passes the optic nerve and ophthalmic artery.

Of note, the sharp posterior edge of the lesser wing of the sphenoid forms the posterior aspect of the anterior cranial fossa.

Dropping down, from the base of the greater wing of the sphenoid are the pterygoid plates. The *medial pterygoid plate* forms the posterior part of the lateral nasal cavity, articulating anteriorly with the vertical plate of the palatine bone. Inferiorly, it ends as the pterygoid hamulus, around which the tendon of tensor palati hooks. The cartilaginous Eustachian tube grooves the upper aspect of its posterior border, above which the border splits to pass posterolaterally to enclose the scaphoid fossa and give attachment to the tensor palati.

The *lateral pterygoid plate* extends backwards into the infratemporal fossa, giving attachments laterally to the lower head of the lateral pterygoid and medially to the deep head of the medial pterygoid; both involved in protruding the mandible and opening the mouth.

Temporal bone

The temporal bone consists of four parts, which each ossify independently and later fuse:

1. squamous
2. petromastoid
3. tympanic
4. styloid.

The *squamous* part is the largest, forming the convex lateral aspect of the temporal fossa. It articulates anteriorly with the greater wing of the sphenoid and posterosuperiorly with the parietal bone; where these three meet (together with the frontal bone) is an important landmark - the pterion, the weakest part of the skull under which passes the middle meningeal artery (MMA). A fracture here runs the risk of laceration of the MMA and thereby an extradural haematoma.

The *zygomatic* process of the temporal bone originates anteriorly, below which is the mandibular fossa housing the synovial temporomandibular joint. Behind this, the squamous part (together with part of the petrous bone) forms the anterior aspect of the external ear canal, the remainder formed by the curved c-shaped tympanic part of the temporal bone. Medially, the squamous part adjoins the petrous part which, together with the mastoid part (commonly collectively called the petromastoid), forms part of the medial bony external ear canal and thereon encases the middle and inner ear.

Anteriorly, the squamous part's inferior surface forms the posterolateral aspect of the infratemporal fossa, whilst on its lateral surface, the curved temporal line (suprameatal crest) delineates the lower aspect of the attachment of the temporalis fascia, limiting the origin of the temporalis muscle and, together with a small triangle of bone at the posterosuperior aspect of the external auditory meatus, the suprameatal (Macewen's) triangle, are important superficial landmarks for cortical mastoidectomy.

The petrous part is full adult size at birth. However, the *mastoid* process is absent, leaving the stylomastoid foramen near the lateral surface of the skull, covered only by thin fibres of sternocleidomastoid (SCM); the extracranial facial nerve is therefore very superficial and vulnerable in neonates. As the SCM grows, it draws down and thereby develops the mastoid tip, palpable in the second year of life, thereby protecting the emerging facial nerve on its medial surface. This mastoid process is filled to a varying degree by air cells, the *sigmoid sinus* deeply grooving its inner surface, itself receiving the superior petrosal sinus at its upper end, the latter draining part of the cavernous sinus. The deep surface of the mastoid is grooved by the digastric ridge for the origin of the posterior belly of the digastric muscle; just medial to this, the *facial nerve* exits the skull base through the stylomastoid foramen, the styloid process lying just anteromedial to this. Medial to the digastric notch, the occipital groove indents the mastoid bone along the temporo-occipital suture, in which lies the occipital artery.

Angled forwards and medially at 45 degrees, the anterior aspect, the apex, of the pyramidal shaped *petrous* part joins the clivus medially and greater wing of sphenoid anterolaterally; its tip forms the posterolateral boundary of the ragged-shaped foramen lacerum, the latter closed in life by dense fibrous tissue.

The superior surface of the petrous temporal bone contributes to part of the floor of the middle cranial fossa, a sharp ridge along its posterosuperior aspect, angled at 45 degrees, separating this from its near vertical posterior surface which borders the anterior aspect of the posterior cranial fossa. Several important landmarks can be found on this superior surface. Most laterally, just medial to its articulation with the squamous part of the temporal bone, the petrous part forms the roof of the epitympanum, the tegmen tympani. Running along the posterior aspect of the petrous ridge is found the groove for the superior petrosal sinus. Between the two, posteromedial to the tegmen tympani, a curved prominence - the arcuate eminence - is made by the underlying superior semicircular canal. Just anteromedial to this is found the hiatus and groove for the greater petrosal nerve, passing obliquely to the foramen lacerum; the groove for the lesser petrosal nerve lies just anterolateral to this en route to the foramen ovale. Towards the anteromedial aspect of the superior surface, the trigeminal impression houses the trigeminal ganglion.

The posterior aspect of the petrous bone is perforated by the internal auditory meatus (IAM), through which pass the VII and VIII cranial nerves, together with the superior and inferior vestibular nerves and the labyrinthine artery, an internal auditory branch of the basilar artery. Just behind the IAM, a small slit leads to the aquæductus vestibuli containing the endolymphatic duct.

Inferiorly, medial to the base of the styloid process, the petrous bone is hollowed to form the jugular fossa, itself the lateral aspect of the jugular foramen. Divided into three compartments by two transverse septa of fibrous dura, this transmits the jugular vein in the posterior compartment; the middle compartment is shared by the vagus nerve (X) and cranial root of the accessory (XI); the glossopharyngeal (IX) and inferior petrosal sinus occupy the anterior compartment.

Above this, the jugular bulb is the point at which the sigmoid sinus feeds into the upper end of the internal jugular vein. It usually lies inferior to the posterior part of the floor of the middle ear, divided from it by a thin bony covering that may be dehiscent, leaving only mucosa to separate it from the middle ear cavity. However, its position is extremely variable and it may intrude right up into the middle ear ('high jugular bulb').

The ICA enters the skull base through the carotid canal just anterior to the jugular foramen, separated from it by a wedge of bone; erosion of this 'keel' of bone is an early finding in patients with a glomus jugulare tumour. It traverses the petrous apex at an oblique direction, passing anteriorly, superiorly and medially. It gives off some small intrapetrous branches, including the caroticotympanic artery, which may enlarge as feeding vessels for a glomus tumour.

It emerges just lateral to the petrous apex to enter the cavernous sinus (see below). The carotid sheath in the neck will be discussed below in 'Inferior skull base'.

Superolateral to the emerging carotid artery at the apex, the bony Eustachian tube connects to its cartilaginous portion, itself lodged between the greater wing of sphenoid and the petrous apex (see **Figure 98.1**). It is in reverse proportions to the external auditory canal: the lateral third (around 1 cm long) is bony within the petrous bone, originating from the anterior mesotympanum (middle ear); the medial two-thirds is cartilagenous. This transition from bone to cartilage – the isthmus – marks the Eustachian tube's narrowest point. Angled forwards, inferiorly and medially at around 30 degrees and 45 degrees respectively, the cartilaginous portion grooves the posterior border of the medial pterygoid plate before opening into the nasopharynx, as described above.

Posteromedial to the traversing carotid artery, within the dense 'otic capsule' of the petrous temporal bone, are the inner ear structures, practically full adult size at birth.

Housed within an osseous labyrinth, the membranous labyrinth contains endolymph, running throughout the inner ear structures; surrounding this membrane labyrinth is perilymph, which does not communicate with the endolymph. The most anterior structure of the osseous labyrinth is the cochlea, behind which lies the vestibule followed by the semicircular canals, in that order; the parts of the membranous labyrinth, in the same order from front to back, are the cochlear duct, saccule and utricle (within the vestible, concerned with vertical and horizontal movement detection respectively) and semicircular ducts (concerned with kinetic balance). The conical-shaped cochlea lies at an oblique angle; its base at the fundus of the internal acoustic meatus and its apex directed across the long axis of the petrous bone, pointing anterolaterally towards the middle ear. It curls two and three-quarter turns around the central modiolus containing the spiral ganglion.

Detailed anatomy of the middle and inner ear can be found in the Chapters 46, Anatomy and embryology of the external and middle ear and 47, Anatomy of the cochlear and vestibular system: Relating ultrastructure to function. However, brief mention of the innervation will be made here. The tympanic branch of the IXth nerve (Jacobson's nerve) leaves the glossopharyngeal nerve at the petrous ganglion and passes through a canaliculus in the keel of petrous bone between the jugular and carotid foramina to supply the middle ear (tympanic plexus).

The auricular branch of the Xth nerve (Arnold's nerve) passes behind the internal jugular vein and enters the mastoid canaliculus on the lateral wall of the jugular foramen, from which it emerges by way of the tympanomastoid fissure to supply the skin of part of the external auditory meatus.

The *tympanic* part of the temporal bone lies lateral to the petrous bone, its lateral border ending at the cartilagenous part of the external auditory canal. The posterosuperior surface is concave, forming the anterior, floor and part of the posterior wall of the bony ear canal. Where each extent of the c-shaped bone attaches, a suture line forms along the ear canal – anteriorly the tympanosquamous

and posteriorly the tympanomastoid sutures; the skin is particularly adherent along these. The inferior aspect of the tympanomastoid suture line is an important operative landmark for identifying the facial nerve as it exits the stylomastoid foramen.

Medially, the tympanic part houses the tympanic sulcus, in which lies the fibrous annulus for attachment of the tympanic membrane.

Anteroinferiorly, the tympanic part makes up part of the posterior boundary of the mandibular fossa.

Arising from the inferior aspect of the fusion of the tympanic and petrous bones, the *styloid* part of the temporal bone projects downwards and forwards, giving attachment to several ligaments and muscles bearing its name.

Three muscles attach to the styloid process, each having a different nerve supply but all involved in swallowing:

- stylopharyngeus
- stylohyoid
- styloglossus.

The stylopharyngeus arises from the medial aspect of the base of the styloid process and slopes down across the lateral aspect of the ICA before passing between the superior and middle pharyngeal constrictors alongside the pharynx, inserting into the posterior border of the thyroid cartilage. It is both innervated and traversed by the glossopharyngeal (IX) nerve, the sensory part crossing over the muscle to reach the tongue; its action is elevation of the pharynx and larynx.

The stylohyoid arises from the posterolateral aspect of the base of the styloid process, passing anterolaterally to the posterior belly of digastric with which it shares its innervation from the facial nerve (VII). It inserts onto the greater cornu of the hyoid, its attachment here perforated by the intermediate tendon of digastric, to give retraction to the hyoid.

The styloglossus is the shortest of the three, arising from the anterolateral aspect of the styloid process, passing downward and forwards between the internal and external carotid arteries to insert into the side of the tongue, innervated by the hypoglossal (XII) nerve, retracting the tongue.

The external carotid artery is intimately related to these muscles above. Running deep to the stylohyoid (and hence the posterior belly of digastric, it lies superficial to the stylopharyngeus and the styloglossus en route to the parotid gland. Conversely, the retromandibular vein runs superficially to all elements of the styloid apparatus.

Facial nerve

The VIIth cranial nerve emerges from the brainstem, between the pons and olive. The nervus intermedius emerges between the pons and inferior cerebellar peduncle. Joining the main facial nerve in its cisternal segment, it traverses the cerebellopontine angle to enter the porus of the IAM, together with the VIIIth cranial nerve, as mentioned above. Lying anterosuperiorly in the IAM, it is above the cochlear nerve, the superior and inferior vestibular nerves being posteriorly located. At the lateral extent of the IAM, the facial nerve passes through its narrowest portion via the labyrinthine segment, between the cochlea and vestibule. It exits this segment to form the geniculate ganglion before turning backwards at its first genu. Here, it gives off the greater superficial petrosal nerve which runs in its groove along the floor of the middle cranial fossa between two layers of dura mater; intra-operative traction on this nerve can result in a facial palsy secondary to haemorrhage or oedema.

From the first genu, VII runs in its horizontal tympanic segment in the medial wall of the middle ear, passing above the promontory. It curves over the oval window niche before reaching the second genu, just inferior to the lateral semicircular canal, at which point it curves downwards into its vertical mastoid segment behind the external auditory canal. The nerve to Stapedius branches off here, reaching the muscle via a tiny canaliculus. Just before it exits the skull base, VII gives off the fibres of the nervus intermedius as the chords tympani, thereafter passing through the stylomastoid foramen as a purely motor nerve.

The extracranial facial nerve gives off the posterior auricular nerve (supplying the occipital belly of occipitofrontalis) and a muscular branch (supplying the posterior belly of the digastric and stylohyoid), before swinging forward to enter the parotid gland and dividing into its upper and lower branches. Further divisions in the parotid result in the five branches supplying motor innervation to the muscles of facial expression.

NOTABLE REGIONS OF THE SKULL BASE

Cavernous sinus

The *cavernous sinus* extends from the apex of the orbit back to the apex of the petrous temporal bone, its medial and inferior walls being deep grooves into the body and base of the greater wing of the sphenoid respectively. The medial, upper and lateral walls are made up of a fold of the inner layer of dura, medially continuous with the diaphragma sellae; posterolaterally, the wall is medial to the anterior parts of the trigeminal (*Meckel's*) cave, itself containing the trigeminal ganglion.

Containing cranial nerves III, IV and V (ophthalmic and maxillary branches) embedded within its lateral wall and, inferolaterally, VI, the sinus' main content is the ICA as it emerges from the petrous apex through the superior aspect of the irregular foramen lacerum and projects upwards, forwards and medially to the anterior clinoid process, a small posterior extension of the lesser wing. Here, just posterior to the optic canals, the ICA perforates the dura mater to enter the middle cranial fossa, immediately dividing into its terminal branches.

Each sinus also receives blood from the orbit and cerebral hemispheres, and each drains via the superior and

inferior petrosal sinuses to the sigmoid sinus and internal jugular vein respectively.

INFRATEMPORAL FOSSA

As the greater wing articulates with the squamous temporal bone, just in front of the articular eminence, it forms the medial roof of the *infratemporal fossa*, a space beneath the skull between the pharynx and the ramus of the mandible. Anteriorly, this infratemporal surface ends in the inferior orbital fissure behind the maxilla, transmitting the maxillary nerve. Laterally, the superior extent of the fossa is the space deep to the zygomatic arch, its lateral extent limited by the ramus of the mandible. The medial pterygoid muscle, together with the interpterygoid fascia, mark the medial border. The posterior boundary is the styloid process, with the carotid sheath behind. It has no anatomical floor, being continuous down into the neck.

The contents include the deep lobe of the parotid, the lateral and medial pterygoid muscles, the insertion of the temporalis muscle into the coronoid process, the maxillary artery and its branches, the mandibular nerve and otic ganglion, chorda tympani, the pterygoid venous plexus and maxillary veins.

Lateral pterygoid muscle

This muscle arises from two heads: the upper from the infratemporal surface of the greater wing of the sphenoid, the lower from the lateral surface of the lateral pterygoid plate. Passing backwards, these two heads converge forming a tendon that inserts into the front of the neck of the mandible. Supplied by the mandibular division of the Vth nerve, it acts to open the mouth by pulling the condyle forwards, down the articular eminence.

Medial pterygoid muscle

Also arising from two heads, the larger of these arises from the deep (medial) surface of the lateral pterygoid plate; a small slip joins from the tuberosity of the maxilla and the pyramidal process of the maxilla, initially passing over the inferior free edge of the lateral pterygoid. Angled laterally, posteriorly and inferiorly, it inserts into the angle of the mandible (Figure 98.2), acting to close the mouth and move the mandible towards the opposite side in chewing. It is innervated by the mandibular nerve.

Maxillary artery

A terminal branch of the external carotid artery, the maxillary artery enters the infratemporal fossa as the other terminal branch, the superficial temporal artery, passes laterally up behind the temporomandibular joint (see Figure 98.3.) Passing deep to the neck of the mandible, between this and the sphenomandibular ligament, it runs a variable course around the lateral pterygoid muscle medially towards the pterygomaxillary fissure and hence into the pterygopalatine fossa.

Traditionally, the artery is described in three parts in relation to the lateral pterygoid muscle. Proximal, on and distal to this; five branches come from each part.

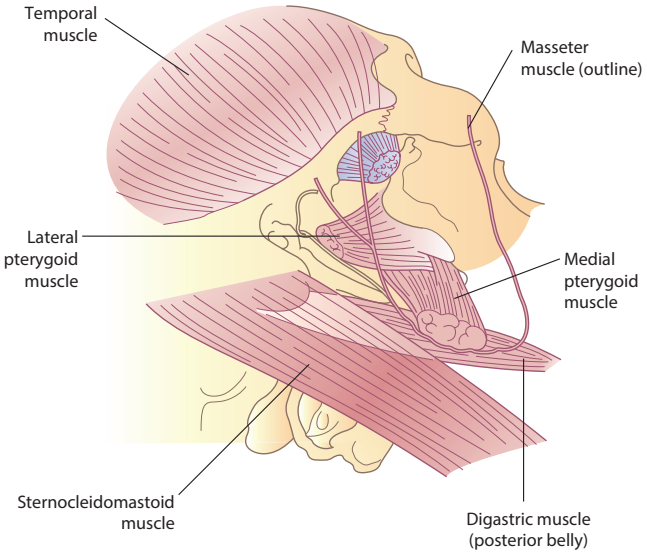


Figure 98.2 The superficial muscles of the central skull base. Redrawn from Goldenberg (1984), with permission.

The first part of the maxillary artery gives off the:

- inferior alveolar artery
- middle meningeal artery
- accessory meningeal artery
- deep auricular artery
- anterior tympanic artery.

The inferior alveolar artery passes down to join the inferior alveolar nerve and enter the mandibular foramen. The MMA passes straight up through the foramen spinosum, while the accessory meningeal artery passes through the foramen ovale. The deep auricular artery passes up to supply the external auditory canal and the anterior tympanic artery enters the petrotympanic fissure on its way to the middle ear.

The second part of the maxillary artery gives off five branches to the soft tissues:

- lateral and medial pterygoid muscles
- temporalis muscle
- lingual and long buccal nerves.

The third part of the artery divides in the pterygopalatine fossa, these five branches accompanying nerves including branches of the pterygopalatine ganglion, supplying the orbit, nose and palate. Of note, the *sphenopalatine artery* enters the nasal cavity through the sphenopalatine foramen to form the cavity's principal arterial supply. Endoscopic cautery or ligation of this artery is performed for persistent epistaxis; however, as mentioned previously, it rarely presents as one arterial trunk, as it divides in two or more (up to 10 branches) just after exiting the sphenopalatine foramen.

The pterygoid plexus and maxillary veins

The pterygoid plexus of veins lies within and on the lateral surface of the lateral pterygoid muscle, and receives tributaries corresponding to the branches of the maxillary artery.

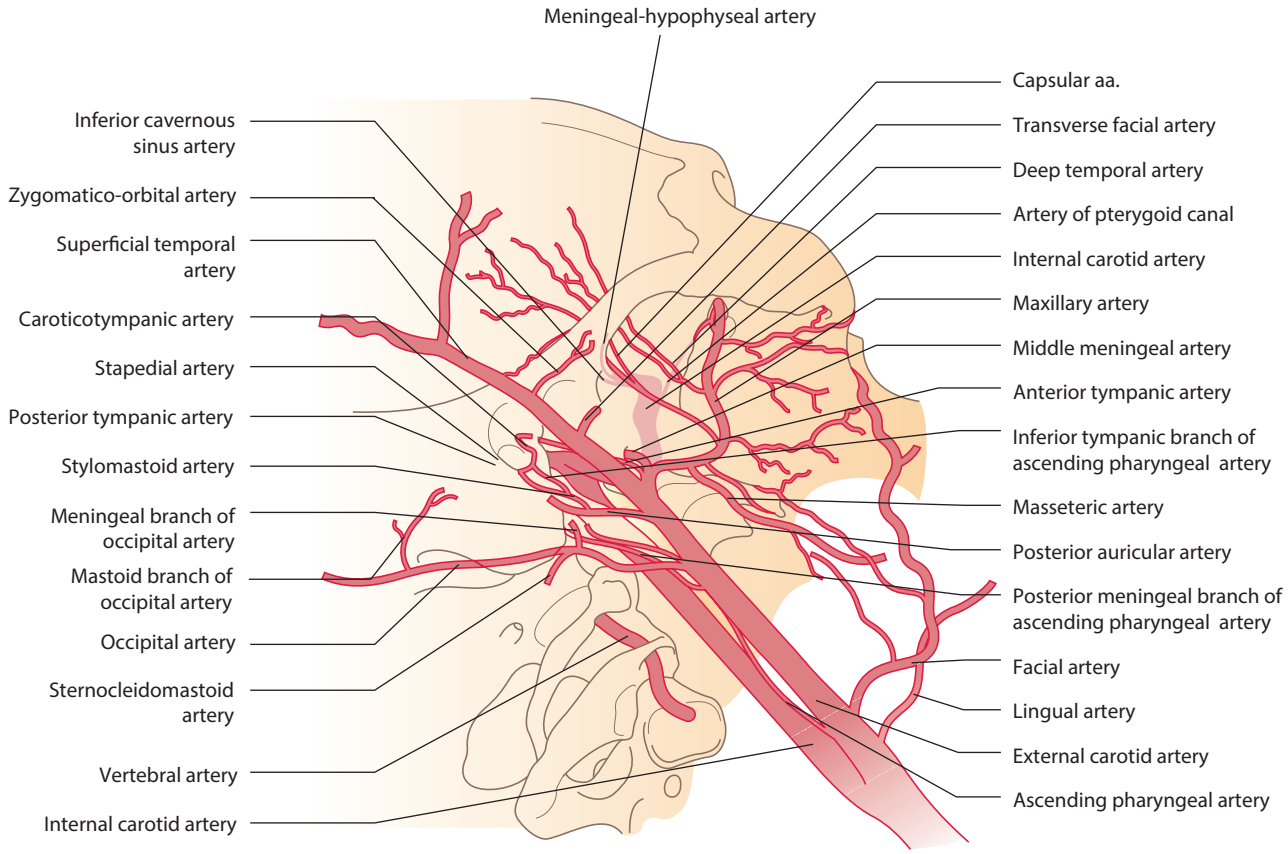


Figure 98.3 The arteries of the central skull base. Redrawn from Goldenberg (1984), with permission.

The plexus drains into two short, large maxillary veins which pass horizontally backwards deep to the neck of the mandible to join the superficial temporal vein and form the retromandibular vein (Figure 98.4).

The pterygoid plexus has three important communicating veins.

1. The inferior ophthalmic vein passes through the inferior orbital fissure to join the facial vein.
2. A connecting vein passes vertically down from the cavernous sinus via the foramen ovale or, when present, the foramen of Vesalius.
3. The deep facial vein runs forward beneath the zygoma to join the anterior facial vein.

These connections can allow infection from the face to spread by way of the pterygoid plexus to produce a cavernous sinus thrombosis.

The mandibular nerve

The mandibular nerve passes through the foramen ovale and, after a short course just deep to the upper head of the lateral pterygoid muscle, the main trunk divides into anterior and posterior divisions (Figure 98.5). Before it does so, the main trunk gives off the sensory nervus spinosus (which re-enters the middle fossa through the foramen spinosum) and the motor nerve to the medial pterygoid, which also supplies the tensor palati and tensor tympani.

The anterior division is motor except for the long buccal nerve. The latter passes between the heads of the lateral pterygoid to swing forwards and downwards on the deep surface of the temporalis muscle, and then pierces the buccinator to supply the mucous membrane of the cheek. The motor branches supply the temporalis, masseter (by a branch which emerges through the mandibular notch) and the lateral pterygoid.

The posterior division is sensory, except for the mylohyoid nerve. The auriculotemporal nerve springs from two roots, which pass either side of the MMA, and pass backwards between the sphenomandibular ligament and neck of the mandible. The inferior alveolar nerve swings downwards on the surface of the medial pterygoid muscle, passes between the sphenomandibular ligament and neck of the mandible, and gives off the mylohyoid nerve before entering the mandibular foramen. The lingual nerve is joined by the chorda tympani 2 cm below the base of the skull and passes downwards and forwards on the medial pterygoid, grooving the mandible before entering the mouth.

The otic ganglion lies close to the mandibular nerve just below the foramen ovale, between the nerve and the tensor palati muscle. It relays secretomotor fibres for the parotid gland, which it receives by way of the lesser superficial petrosal nerve and transmits to the auriculotemporal nerve. The lesser superficial petrosal nerve leaves the middle fossa through the foramen ovale, or sometimes through its own foramen, the foramen innominatum.

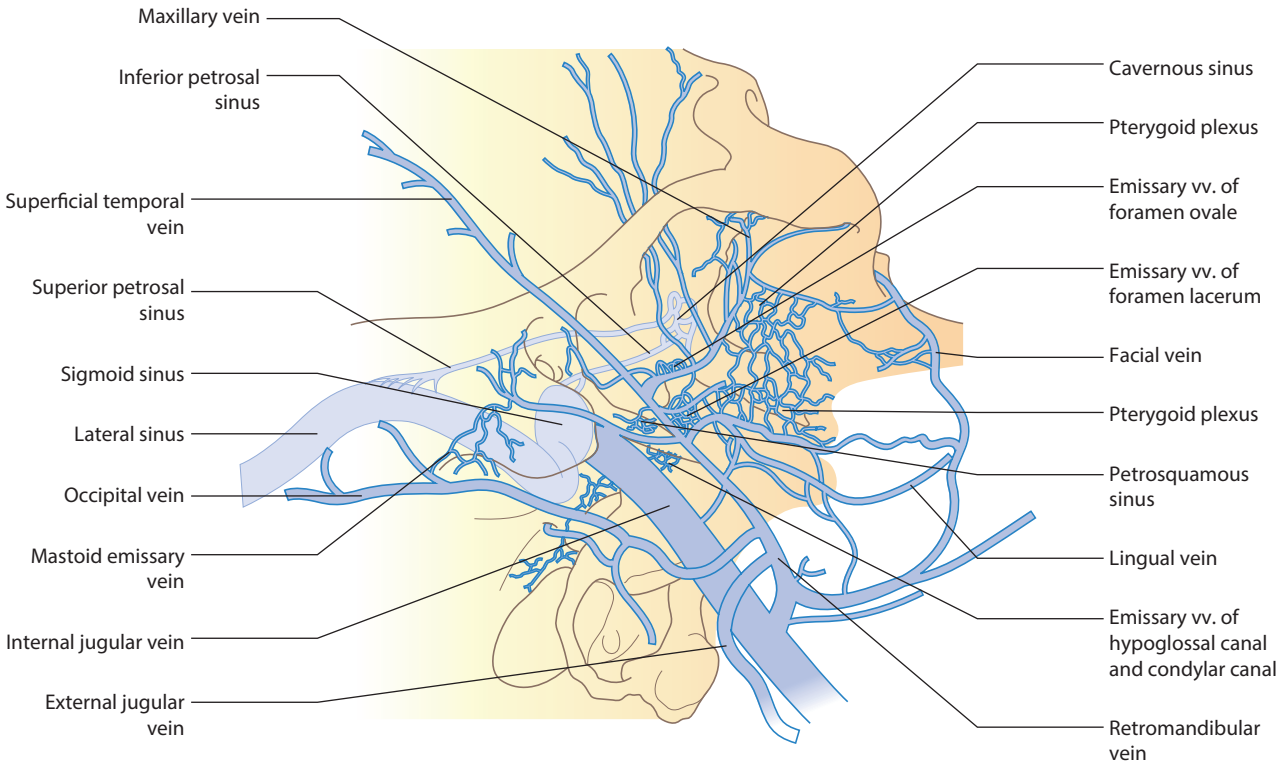


Figure 98.4 The veins of the central skull base. Redrawn from Goldenberg (1984), with permission.

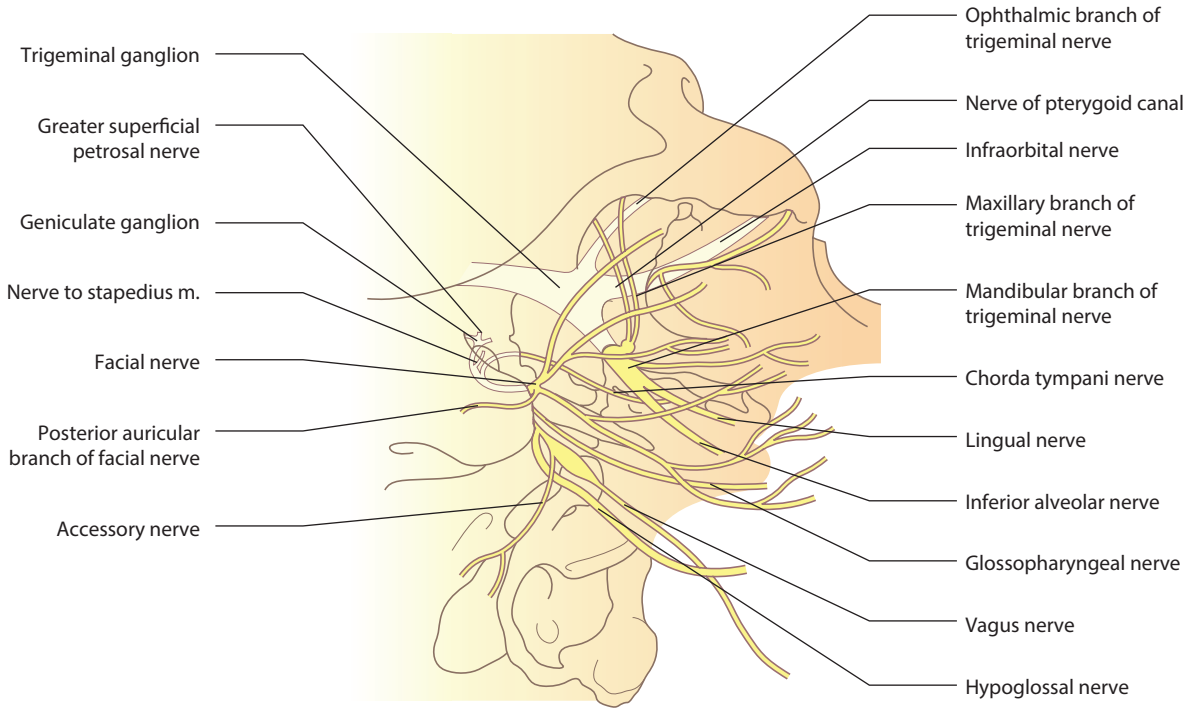


Figure 98.5 The nerves of the central skull base. Redrawn from Goldenberg (1984), with permission.

PTERYGOPALATINE FOSSA

A cone-shaped depression deep to the infratemporal fossa, posterior to the maxilla near the orbital apex, the small pterygopalatine fossa contains the terminal third of the maxillary artery, the maxillary nerve (V_2), the pterygopalatine ganglion just in front of the pterygoid canal (itself containing the Vivian nerve, a union of the greater and deep petrosal nerves, which then runs anteriorly to the sphenopalatine ganglion) and fat. Its roof is the body of the sphenoid and medially it abuts the

perpendicular plate of the palatine bone in the lateral nasal wall. It has several communications to other parts of the skull base, principally laterally via the pterygomaxillary fissure to the infratemporal fossa, medially via the sphenopalatine foramen to the nasal cavity and anteriorly via the inferior orbital fissure to the orbit; posteriorly, the pterygoid (Vidian) canal has been described, with the foramens rotundum and lacerum communicating to the middle cranial fossa.

MECKEL'S CAVE

As the trigeminal nerve leaves the pons in the posterior fossa, it runs forwards along the superior aspect of the petrous part of the temporal bone, grooving its surface. Passing under the superior petrosal sinus, an evagination of the tentorium cerebelli (inner layer of dura and the arachnoid) surrounds it to form the trigeminal cave of Meckel, lying in the trigeminal impression on the superior aspect of the petrous apex. Here lies the trigeminal ganglion, its posterior half therefore bathed in cerebrospinal fluid. The anterior half of the ganglion, together with the three divisions of the trigeminal nerve, lie in front of Meckel's cave, the dural and arachnoid layers having fused at the halfway point of the trigeminal ganglion. An extradural approach to the anterior half of the cave is therefore possible via the middle fossa.

The sphenomandibular ligament

The sphenomandibular ligament is a fibrous band joining the spine of the sphenoid to the lingula of the mandible. It is derived from the first branchial arch (Meckel's) cartilage. Anteriorly, it blends into the interpterygoid fascia, which separates the lateral and medial pterygoid muscles, stretching forward as a sheet to be attached to the posterior edge of the lateral pterygoid plate.

PAROTID SPACE

The space enclosed within the capsule of the parotid gland lies partly superficial to the mandible, and extends through the retromandibular space behind the infratemporal fossa to abut against the parapharyngeal space (Figures 98.6 and 98.7).

PARAPHARYNGEAL SPACE

The parapharyngeal space is described as having two compartments:

1. pre-styloid
2. retro- or post-styloid.

These compartments are separated anatomically by the styloid process of the temporal bone and its associated apparatus (see 'Temporal bone' above).

Pre-styloid compartment

This compartment contains the two palati muscles and two arteries, the ascending palatine and ascending pharyngeal (see Figures 98.8, 98.7 and 98.9 respectively).

The tensor palati muscle arises from the skull base between the pterygoid fossa and the spine of the sphenoid and is attached to the lateral side of the Eustachian tube. It tapers down to a tendon, which takes a right-angled

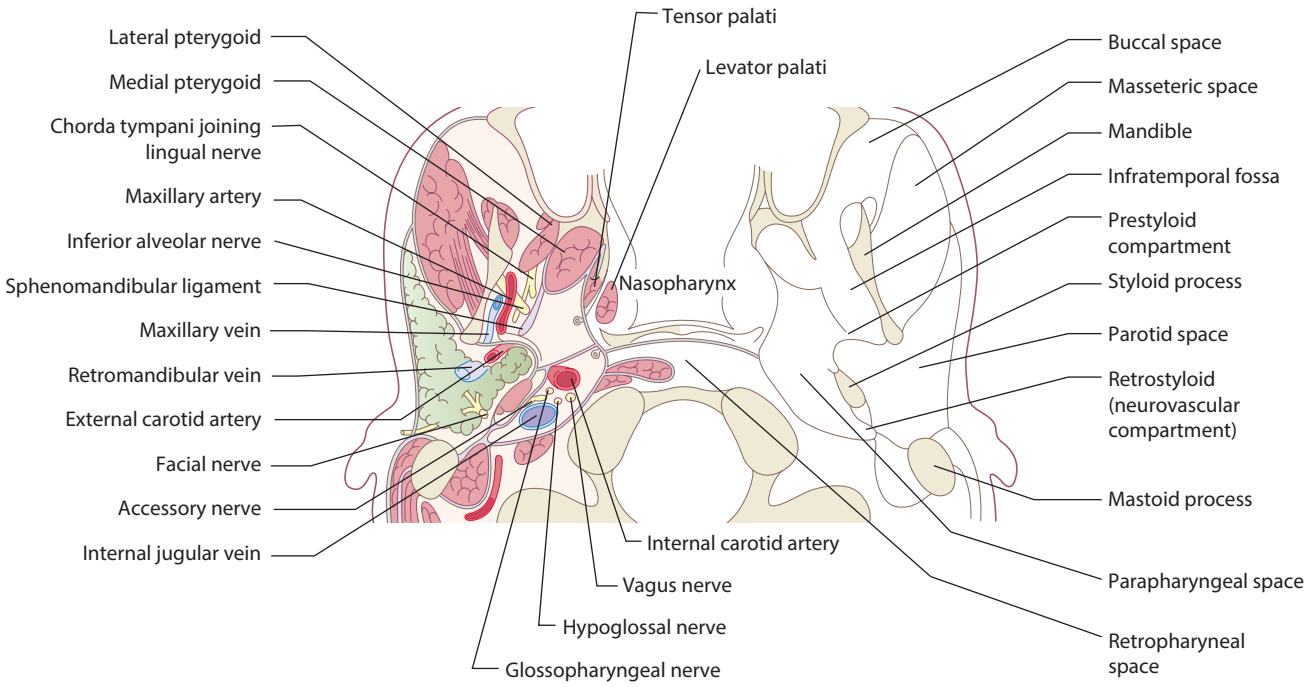


Figure 98.6 The central part of a horizontal section of the head passing through the foramen magnum, between the Eustachian tube and the palate. In the left half all relevant structures have been drawn; on the right, the different compartments are indicated as they appear at this level. Redrawn from van Huijzen (1984), with permission of S. Karger

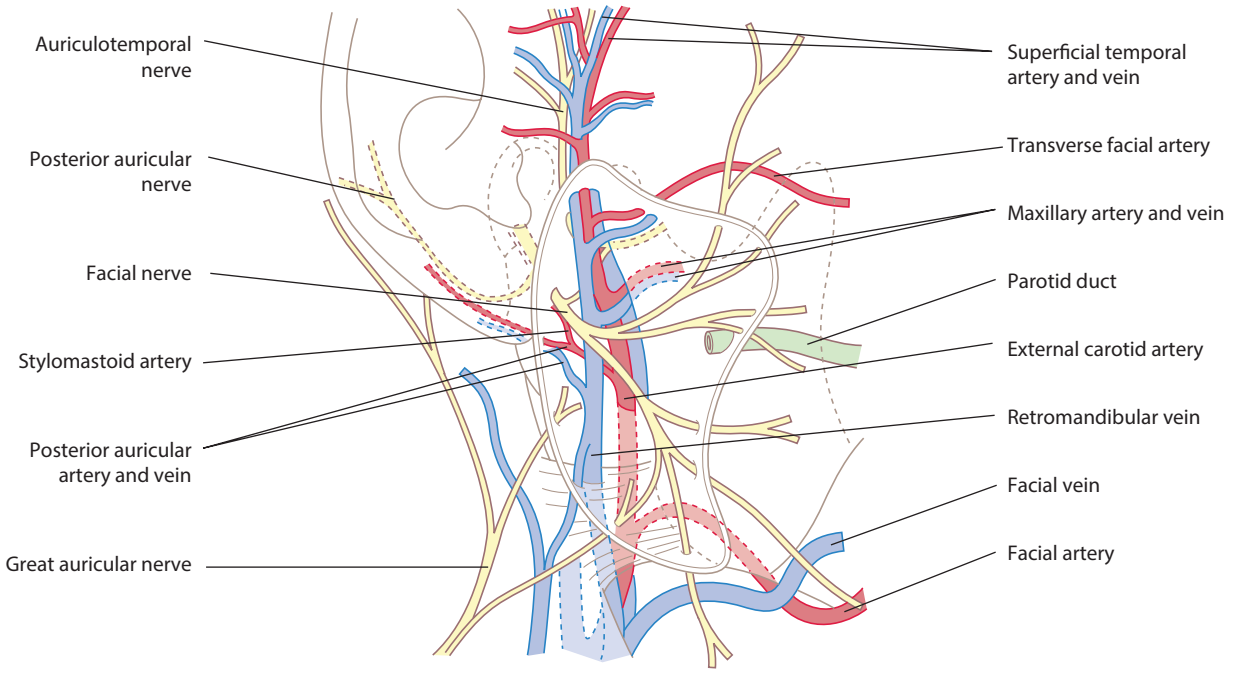


Figure 98.7 The structures of the parotid space, viewed from the lateral aspect. The parotid gland has been removed from its capsule, leaving the vessels and nerves intact. Redrawn from van Huijzen (1984), with permission of S. Karger.

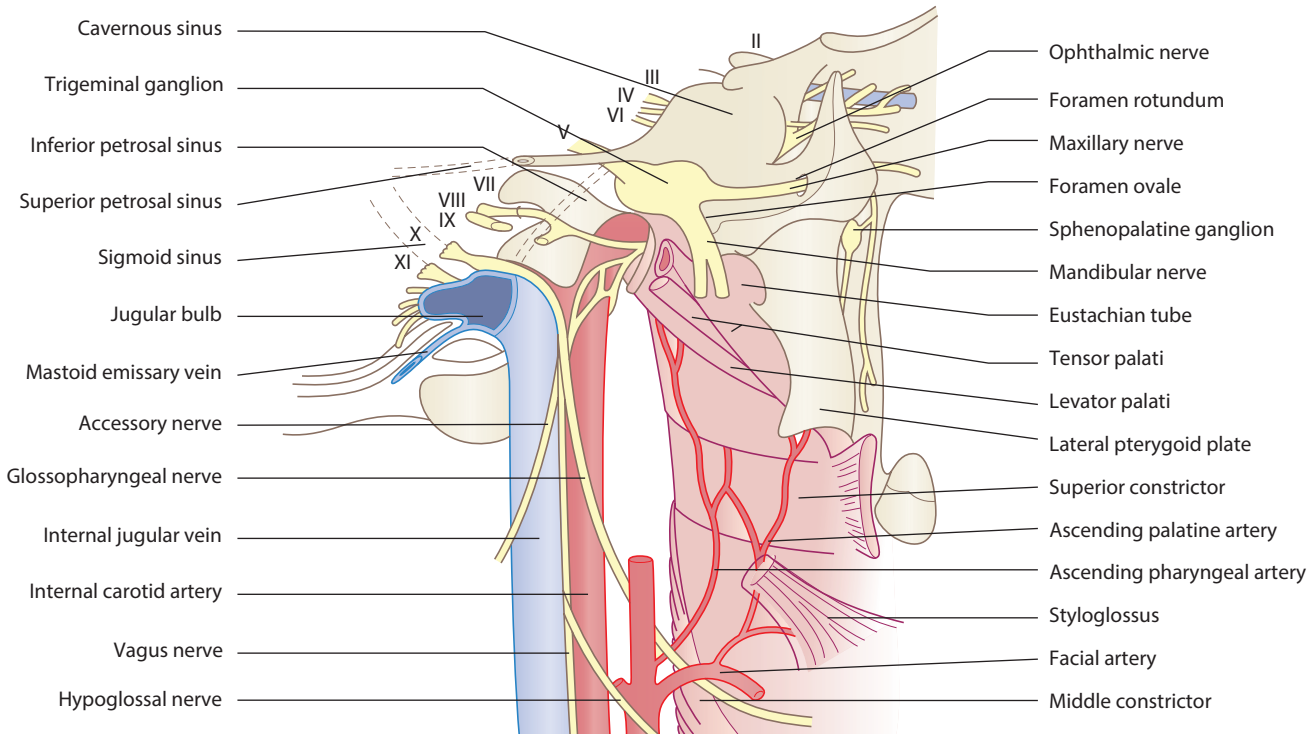


Figure 98.8 The structures of the parapharyngeal space and of the skull base above it, seen from the lateral aspect in a sagittal section passing through the foramen ovale. Redrawn from van Huijzen (1984), with permission of S. Karger.

turn around the hamulus to enter the pharynx, where it broadens into a flat aponeurosis; this triangular sheet blends with its counterparts on the opposite side and is attached to the posterior edge of the hard palate (the crest of the palatine bone). It is supplied by the nerve to the medial pterygoid, a branch of the trigeminal nerve. The action of this muscle is to tense the palate so that other muscles can raise and lower it.

The levator palatini muscle arises from the petrous apex anterolateral to the carotid foramen and from the

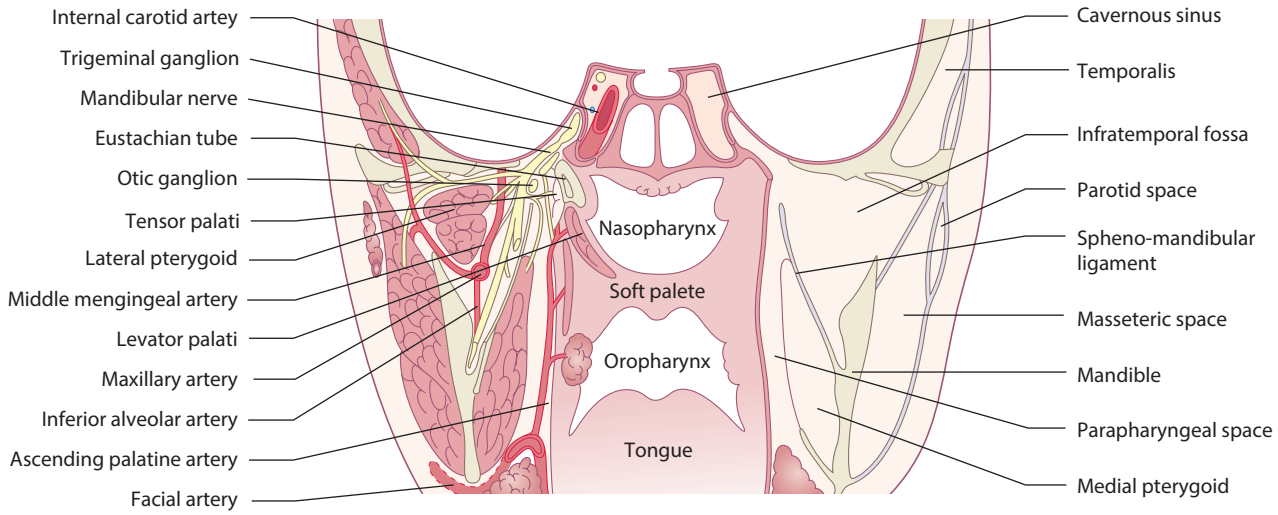


Figure 98.9 Coronal section of the head passing through the foramen ovale. On the left, all relevant structures are illustrated; on the right, the main compartments are shown. Redrawn from van Huijzen (1984), with permission of S. Karger.

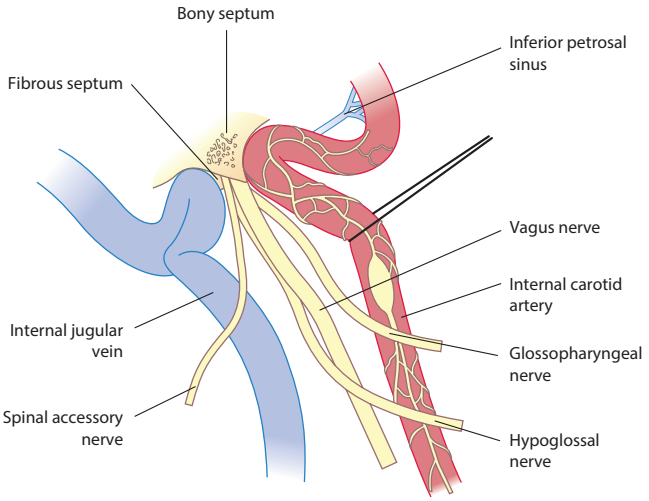


Figure 98.10 The structures in the jugular foramen. Redrawn from Goldenberg (1984), with permission.

medial end of the tubal cartilage and is inserted into the upper surface of the palatal aponeurosis. Supplied by the Xth nerve by way of the pharyngeal plexus, it acts to raise the soft palate and close off the nasopharynx.

The ascending palatine artery, a branch of the external carotid artery, ascends a little more posteriorly along the superior constrictor to supply the pharynx, the middle ear and the meninges. Often it is a major feeding vessel to a glomus tumour (see Figure 98.3).

Retrostyloid compartment

This corresponds to the neurovascular space and contains the carotid sheath.

INFERIOR SKULL BASE

Carotid sheath

The carotid sheath itself is not a membranous fascia, but a dense network of areolar tissue that surrounds the ICA and vagus nerve. It is virtually absent over the internal jugular vein, however, which is thus able to expand greatly during periods of increased blood flow. The carotid sheath is attached to the skull base around the carotid foramen and continues downwards as far as the aortic arch.

In the neck, the carotid sheath, together with the pretracheal fascia, is firmly attached anteriorly to the deep surface of the sternomastoid. Posteriorly, it is not attached to the prevertebral fascia, but is free to slide over it. This means that pus tracking laterally from a parapharyngeal abscess passes behind the sheath and behind the sternomastoid, to point in the posterior triangle.

The ICA passes vertically upwards from the carotid bifurcation in the neck to enter the carotid foramen (see Figure 98.3). It has no branches, but carries with it the carotid plexus of sympathetic nerves from the superior cervical ganglion.

The internal jugular vein descends from the jugular bulb to lie behind the ICA on the lateral mass of the atlas (see Figure 98.4). Just below the base of the skull, it receives the inferior petrosal sinus. As it descends, it passes across on to the lateral side of the ICA, receiving tributaries from the pharyngeal plexus of veins and is crossed on its lateral side by the accessory nerve. The deep cervical lymph nodes also lie on the lateral side of the vein.

The glossopharyngeal nerve (IX) lies lateral to the inferior petrosal sinus as it emerges from the anterior part of the jugular foramen (see Figure 98.5 and Figure 98.10). The nerve passes down on the lateral surface of the ICA and then gently curves forward around the lateral side of the stylopharyngeus, medial to the external carotid artery towards the tongue.

The vagus nerve (X) emerges from its superior ganglion in the middle compartment of the jugular foramen and runs straight down in the back of the carotid sheath between the carotid artery and jugular vein (see Figures 98.5 and 98.10). Just below the skull base, it is dilated into its inferior ganglion, where it receives a connection from the accessory nerve carrying fibres from the nucleus ambiguus.

The accessory nerve (XI) is just lateral to the vagus in the middle compartment of the jugular foramen and runs straight down in the back of the carotid sheath between the carotid artery and jugular vein (See **Figures 98.5** and **98.10**). It immediately begins to curve away posteriorly across the lateral surface of the internal jugular vein, medial to the styloid process and posterior belly of the digastric, giving a branch to the sternomastoid before piercing the muscle to gain the posterior triangle.

The hypoglossal nerve (XII) emerges from the anterior condylar foramen, medial to the carotid sheath and spirals in a lateral direction behind the vagus between the internal jugular vein and ICA (that is, through the carotid sheath) (see **Figures 98.5** and **98.10**). It then swings forwards lateral to the carotid arteries, deep to the styloid muscles and digastric, on its way to the tongue.

The cervical sympathetic trunk lies behind the carotid sheath in front of the prevertebral fascia, just medial to the vagus nerve. It ends superiorly at the superior cervical ganglion. The deep petrosal nerve arises from this ganglion and passes superiorly to join the greater superficial petrosal nerve to form the Vidian nerve.

MUSCLES SUPERFICIAL TO THE LATERAL SKULL BASE

Four muscles that lie lateral to the base of the skull are important in achieving surgical exposure of the area, namely:

1. masseter
2. temporalis
3. sternomastoid
4. digastric.

These are briefly described below (see also **Figure 98.2**).

The masseter muscle arises from the zygomatic arch and is inserted into a wide area on the lateral aspect of the mandible from the angle forwards along the lower border, and upwards over the lower part of the ascending ramus. It is supplied by the Vth nerve by way of the masseteric branch from the anterior division of the mandibular nerve and its action is to close the jaws.

The temporalis muscle arises from the temporal fossa on the side of the skull and from this large origin it converges in the shape of a fan to be inserted into the coronoid process of the mandible. It acts to close the jaws and its posterior fibres also retract the mandible.

The sternomastoid muscle arises by two heads from the manubrium and the clavicle. It is inserted into a curved line extending from the tip of the mastoid process to the superior nuchal line of the occiput. It is supplied by the XI nerve and its main action is to protract the head (moving it forwards while keeping it vertical with a horizontal gaze).

The digastric muscle arises from the digastric notch on the medial surface of the mastoid process. Two muscular bellies (anterior and posterior) separated by an intermediate tendon are described. The posterior belly narrows anteriorly into the intermediate tendon, which passes through a fibrous sling on the hyoid near the lesser cornu, and then expands into the anterior belly, which runs beneath the mylohyoid to its insertion into the digastric fossa on the lower edge of the mandible. The posterior belly is supplied by the VIIth nerve (nerve to digastric) and the anterior belly by the Vth nerve (mylohyoid nerve). Its action is to depress and retract the chin.

Surgical approaches to the following structures may be made via lateral skull base approach:

- middle ear, mastoid and associated structures
- sigmoid sinus and jugular bulb and uppermost part of the internal jugular vein
- middle cranial fossa
- parotid gland
- facial nerve
- inner ear, cochlear and vestibular nerves
- petrous apex
- infratemporal fossa
- carotid artery
- IX, X, XI and XII
- Eustachian tube
- clivus
- basiocciput
- basisphenoid
- nasopharynx.

KEY POINTS

- Intimate knowledge of the course of the facial nerve through the temporal bone and its relation to the lateral semicircular canal is essential for safe mastoid surgery.
- The relationship of the sigmoid sinus, jugular bulb, carotid artery and inner ear structures must be understood for extended mastoid exploration, such as towards the petrous apex.
- Identification of the bulbar nerves and their relationship to the carotid sheath and jugular foramen prevent morbidity in paraganglioma surgery.
- Detailed understanding of the course of the carotid arteries and optic nerves in the lateral walls of the sphenoid sinus are essential in extended endoscopic sinus surgery.

FURTHER READING

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CHAPTER 99

EVALUATION OF THE SKULL BASE PATIENT

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: otalgia, CSF otorrhoea, hearing loss, pulsatile tinnitus, vestibular schwannoma, cerebellopontine angle and skull base, with the use of wildcards.

INTRODUCTION

This chapter aims to provide a simple framework for the assessment of patients with skull base lesions. It is difficult for it to be all embracing and therefore the more common conditions have been covered discussing typical symptoms, signs and investigations in such patients. In writing the chapter, the major difficulty has been that most of the literature deals with skull base lesions in terms of aetiology (e.g. studies of vestibular schwannomas (VS)) rather than the incidence of specific symptomatology (e.g. deafness). It has been necessary to focus on the few studies that have looked at clinical manifestations and collate these with findings from other studies. Due to the relatively low incidence of skull base lesions, most studies are of low impact (i.e. level 3 or 4 evidence).

The skull base has an intricate, three-dimensional conformation that is closely associated with and penetrated by numerous vital neurovascular structures. In order to understand the complexity and clinical manifestations of specific lesions it is extremely important to have a thorough understanding of the anatomy of the skull base. The skull base can be broadly sub-classified into three distinct areas: anterior skull base, central skull base and posterior skull base.[1] The anterior skull base is formed by the posterior wall of the frontal sinus (anterior border); lesser wing of the sphenoid bone and anterior clinoid processes (posterior border); cribriform plate of the ethmoid bone (midline) and nasal cavity, ethmoid sinus and orbits (inferior border); and orbital plates of the frontal bone (lateral border). The central skull base is mainly formed by the sphenoid bone and the temporal bone anterior to the petrous ridge.[2] The central skull base is further divided into midline sagittal, off-midline parasagittal, and lateral compartments.[2] The midline sagittal compartment includes the body of the sphenoid and the portion of the clivus anterior to the basisphenoid. The sella turcica is a depression in the superior surface of the body of sphenoid bone for the pituitary gland. The parasagittal compartment contains important components, which include carvernous sinus, superior orbital fissure, foramen rotundum, vidian canal and foramen lacerum. The carvernous sinus forms the superior and medial boundary of the parasagittal compartment while the parapharyngeal and masticator spaces are along the inferior aspect.[2] The sphenoid triangle, squamous part of temporal bone, and temporomandibular joint forms the lateral compartment of the central skull base. The posterior skull base is formed anteriorly by the posterior surface of the clivus, laterally is formed by the posterior surface of the petrous temporal bone superiorly and the condylar part of the occipital bone inferiorly. The mastoid temporal bone and the squamous occipital bone form the posterior portion of the posterior skull base.

The skull base is composed of a vast number of different tissues and cell types, and consequently can be affected by many different disease processes that include inflammation, trauma, benign and malignant neoplasia, and congenital abnormalities. The more common skull base lesions are shown in **Table 99.1**.

The symptoms produced by any skull base lesion are determined by its anatomical location. Anterior skull base disease may produce hyposmia, diplopia, blindness and

TABLE 99.1 The more common lesions found in different areas of the skull base

Anterior skull base	Central skull base	Posterior skull base
Mucocoeles	Pituitary adenoma	Vestibular schwannoma
Inverted papilloma	Craniopharyngioma	Meningioma
Juvenile angiofibroma	Cavernous sinus meningioma	Cholesteatoma
Olfactory neuroblastoma	Chordoma	Paraganglioma
Nasopharyngeal carcinoma	Chondrosarcoma	Squamous cell carcinoma
Lymphoma	Plasmacytoma	Schwannoma
Encepholocele	Encepholocele	Fibrous dysplasia
Meningioma	Meningioma	Metastasis
Schwannoma	Schwannoma	Endolymphatic sac tumours
Fibrous dysplasia	Fibrous dysplasia	
Metastasis	Metastases	

Modified from Policeni & Smoker, 2015; Borges, 2009; and Raut et al., 2012.[1–3]

frontal headaches. Central skull base lesions may cause facial numbness, in addition to headaches and diplopia. If the greater wing of the sphenoid is also involved, central and vertex headaches, loss of the corneal reflex and trismus can develop. In general terms, posterior skull base lesions usually produce deafness and tinnitus at an early stage, associated in some cases with vertigo and disequilibrium. Facial palsy is a characteristic, though typically late, feature of posterior skull base lesions. It can also cause neck stiffness, difficulty swallowing and hoarseness.

Different disease processes may produce different symptoms at the same location; for example, irritation or invasion of the dura by a neoplastic process is more likely to produce pain than benign lesions such as cysts. So, the nature of a lesion is important in determining the symptoms and signs that it may produce, as well as the site and extent of the lesion concerned.

EPIDEMIOLOGY

Posterior skull base lesion, in particular, cerebellopontine angle (CPA) tumours, predominate in any typical skull base practice and the literature reflects this with little epidemiological information available on other conditions. Within the CPA, VSs are the most common lesions and therefore the management of these tumours forms a major part of any skull base surgeon's work. In a series of 1354 CPA lesions, VS accounted for 91.3%, meningiomas 3.1%, epidermoids (cholesteatomas) 2.4%, facial nerve tumours 1.2% and other cranial nerve tumours 0.2%.[4] Less common lesions included intrinsic brain tumours, metastatic tumours, dermoids and lipomas. In another study of 305 CPA tumours, VS comprised 80%.[5] Smaller studies have shown much greater incidences of rare CPA tumours. Kartush et al.[6] reported two patients with rhabdomyosarcoma and one patient with a chondrosarcoma out of a total of 82 cases. Bozorg Grayeli et al.[7] reported 18 patients with paragangliomas and 18 other patients with malignant lesions that included 8 epidermoid carcinomas and 3 chondrosarcomas in a series of only 81 patients. Undoubtedly, the disease spectra reported in the smaller series were skewed by the effects of local factors and personal practices of individual clinicians.

The incidence of VS based on the Danish data has shown a steady increase of VS from 7.8 VS per 1 million population per year in 1976[8] to a peak of 123 VS per 1 million population per year in 2004. From 2004, the incidence seems to have plateaued to 19 per 1 million population per year in 2008 and may reflect the approximate true incidence of VS.[9]

SYMPTOMS OF SKULL BASE DISEASE

Hearing loss

The hearing loss can be conductive, sensorineural or mixed, depending on the precise site of the abnormality. For example, otitis media with effusion may develop as a result of Eustachian tube obstruction or compression by a tumour. Deafness caused by VS is usually of a high frequency sensorineural type and develops in 80–90% of patients,[10] but low frequency sensorineural loss (500 Hz) is characteristic of larger tumours.[10] In the modern era, due to the wide availability of magnetic resonance imaging (MRI) and the heightened awareness of these lesions, VS are generally detected at an early stage when unilateral sensorineural deafness is the only clinical manifestation. The typical history is that of a gradual hearing loss over the course of years, perhaps even decades, as these tumours grow very slowly. A survey of 580 VS patients found 84% of respondents had hearing loss worse in one ear. Of these, 64.8% had progressive hearing loss, 14.7% had sudden hearing loss, and 13% had both progressive and sudden hearing loss.[11]

Sudden sensorineural deafness has been reported as the presenting feature in 6.5–10.2% of patients.[12] The presumed aetiology maybe labyrinthine artery vascular occlusion, a rapid expansion of the tumour due to haemorrhage, oedema or cyst formation, or alterations in inner ear biochemistry.[13] Typically, 30% of VS that present with sudden hearing loss have caused total loss of function in that ear by the time they are diagnosed compared with only 16% of VS with progressive deafness.[14, 15] Patients who present with sudden hearing loss may have symptoms of an upper respiratory tract infection and sometimes also with vertigo. Labyrinthine function tests in these patients often show reduced or absent caloric responses. When other neurological symptoms and signs are present, the true diagnosis is often considerably delayed as clinicians are misled by the plethora of abnormalities. Similarly, the screening of patients with idiopathic sudden sensorineural deafness by MRI, has found a large number of VS. In one series of 295 patients with sudden onset sensorineural hearing loss, VS was found in 4% of patients.[16] In another

series, there were 10 cases (1.85%) of VS diagnosed in 542 cases of sudden onset sensorineural hearing loss.[17]

Almost 90% of skull base paragangliomas present with a conductive hearing loss.[18] A glomus tympanicum may present early with conductive deafness; whereas an advanced glomus jugulare may present with a mixed deafness when the middle and inner ears are both involved. Fifty to 80% of CPA meningiomas produce auditory symptoms, a much lower incidence than in VS.[19] When confronted with a CPA lesion in a patient with normal hearing, pathology other than a VS should be suspected.

Otorrhoea

Infected otorrhoea is such a common symptom that its presence does not immediately suggest serious underlying pathology unless persistently tinged with blood. For this reason, a temporal bone tumour may be overlooked in these cases and delay in diagnosis is common. Extensive temporal bone cholesteatomas and paragangliomas can present with otorrhoea and is reported in 61% of external auditory canal cancers.[20]

Cerebrospinal fluid (CSF) otorrhoea can be caused by bony erosion or insufficiency as a result of trauma, prior surgery, chronic ear infection, or destructive processes such as cholesteatoma or tumour, leading to temporal bone encephaloceles and/or CSF fistula. However, over the last two decades, there has been a significant increase in the number of spontaneous cases, where no discernible cause can be found. Several studies have demonstrated a strong link between obesity, empty sella syndrome and elevated intracranial pressure among these patients. In one series of 89 cases, nearly 40% of the cases occurred without antecedent trauma, chronic ear disease or surgery, and were considered spontaneous.[21] The mean delay between symptom onset and diagnosis was nearly 3 years, and over 10% of patients had symptoms over a decade,[21] as the majority of these patients present with persistent otorrhoea and hearing loss, mimicking chronic otitis media.

Tinnitus

Tinnitus may be either subjective (only audible to the patient) or objective (the clinician can hear the sound). Subjective tinnitus commonly occurs secondary to hearing loss. Less than 10% of tinnitus is due to pulsatile tinnitus,[22] also known as pulse synchronous tinnitus, which is produced by (i) a hypervascular tumour, for example a paraganglioma; (ii) compression of a major vessel by a tumour, for example a jugular foramen schwannoma; or (iii) an arteriovenous malformation or fistula. It is often possible to identify the cause of pulsatile tinnitus with careful examination and imaging, but in up to 30% of cases no cause is found.[23] **Table 99.2** lists the causes of pulsatile tinnitus. Unilateral subjective tinnitus may be the only presenting symptom of VS and warrants further investigation similar to unilateral or asymmetric sensorineural deafness. The incidence of tinnitus with VS can vary from 11% to 63%.[24, 25] Glomus tumours usually present with pulsatile tinnitus (50%) and deafness (30%), but they can occasionally cause otalgia (7%), a feeling of fullness within the ear (4%) and persistent otorrhoea (3%).[26]

TABLE 99.2 Causes of pulsatile tinnitus reported in the literature

Type of lesion	Aetiology
Arterial lesion	Extracranial arteriovenous malformation
	Dural arteriovenous fistulae
	Carotid cavernous fistulae
	Aneurysm of internal carotid artery or vertebral artery
	Fibromuscular dysplasia of internal carotid artery
	Dissection of internal carotid artery
	Atherosclerosis
	Vascular anomalies of ear (persistent stapedial artery, carotid-cochlear dehiscence)
	Vascular compression of VIIIth nerve
	Migraine
Venous lesions	Jugular bulb anomalies (high riding jugular bulb, enlarged jugular bulb, jugular bulb diverticulum)
	Abnormal condylar/mastoid emissary veins
	Diverticulum of sigmoid or transverse sinus
	Stenosis, stricture of segmentation of transverse sinus
Skull base, temporal lesions	Paragangliomas
	Temporal bone tumours (metastasis, basal meningiomas, haemangiomas, Heffner tumours)
	Labyrinthine fistula
	Meningocele/meningoencephalocele
	Otosclerosis
	Superior canal dehiscence
	Cholesterol granuloma
	Paget's disease
	Histiocytosis X
Miscellaneous	Anaemia
	High cardiac output
	Hyperthyroidism
	Benign intracranial hypertension

Data from Hofmann et al., 2013 and Callander, 1920.[22, 27]

Vertigo and dysequilibrium

True vertigo and dysequilibrium affect between 11% and 50% of patients with VS.[24, 25] The character of the vertigo or dysequilibrium produced by VS is extremely variable and tends to differ from those caused by more common vertigo-inducing syndromes in that nausea is absent in up to 63% and described as mild in 18%.[10] However, vertigo or dysequilibrium is the presenting symptom in 32% of intratemporal lesions.[7] A worryingly large number of patients with VS, as many as 10%, may be labelled as having Menière's disease because of the presence of sensorineural deafness, unilateral tinnitus, episodic vertigo

and pressure sensations within the ear.[14] In order to avoid diagnostic delay, all patients with such symptoms require further investigation in the form of MRI.

There have been a number of reports in the literature of patients with skull base and intracranial tumours who have presented with symptoms and signs of benign positional paroxysmal vertigo (BPPV) (e.g. meningiomas, VS, gliomas, lipomas and CPA cholesteatomas).[28] Non-benign positional vertigo should be suspected in patients with: (i) the presence of other signs or symptoms of neurological disorders (e.g. headaches, double vision); (ii) appearance of nystagmus without dizziness in positional testing; (iii) atypical nystagmus, especially downward-beating vertical nystagmus; (iv) poor response to therapeutic manoeuvres; and (v) recurrence of symptoms on at least three occasions.[29] It is therefore recommended that these patients should be investigated by MRI scan.

Tullio phenomenon is sound-induced episodic vertigo and dysequilibrium and has been associated with a number of conditions, including superior semicircular canal dehiscence (SSCD),[30] perilymph fistula[31] and middle ear osteoma.[32] In a series of 65 patients with SSCD, 60 patients had vestibular manifestations and Tullio phenomenon was noted in 90% of patients.[30] Oscillopsia is an unpleasant blurring and jumping of the external world during active and/or passive head movements. If oscillopsia is only present during head movement, the likely underlying cause is bilateral defect in the vestibulo-ocular-reflex (VOR). The more common causes are post-meningitic vestibular failure, gentamicin toxicity or bilateral idiopathic vestibular failure. If oscillopsia comes in brief attacks and is unrelated to head movements, it is usually due to irritative VIIIth nerve and brainstem lesions.[33]

Headache, otalgia and facial pain

The presence of localized cranial or facial pain and neurological symptoms should alert the clinician to the possibility of a skull base lesion. These symptoms may also suggest more advanced disease. Lesions with an intracranial, inflammatory component are more likely to cause intense headache (e.g. giant cholesterol cysts and tumours that obstruct sinuses). In one series of skull base lesions, the incidence of headache was 18%.[10]

Otalgia can be classified into otogenic otalgia, which originates from external, middle and inner ear, and referred otalgia, which arises from pathology outside the ear. Referred otalgia is associated with: (i) auriculotemporal nerve (cranial nerve V3); (ii) posterior auricular nerve (cranial nerve VII); (iii) Jacobson's nerve (cranial nerve IX); (iv) Arnold's nerve (cranial nerve X); (v) greater auricular nerve (C2); and (vi) lesser occipital nerve (C3). Severe otalgia is a cardinal symptom of intratemporal malignancy, particularly carcinoma of the external auditory canal or middle ear.[7]

Trigeminal schwannomas may present with facial pain that can be either episodic, like trigeminal neuralgia, or persistent. However, in a series of 120 trigeminal nerve lesions, the presenting symptom, in decreasing order of incidence, was facial hypoaesthesia or paraesthesia, weak mastication, tics and deafness.[34] More than 75% of these lesions also had other neurological symptoms, particularly other cranial nerve deficits, most notably diplopia caused by a lateral rectus muscle weakness. As many as 11% of VS may have an atypical presentation with other cranial nerve symptoms, pain over the mastoid or headache. On the whole, these tend to be larger tumours.[24] In a series of 55 large VS, over 50% of patients had trigeminal hypoaesthesia, while trigeminal neuralgia occurred in about 5% of patients.[35] Other tumours that may mimic trigeminal nerve tumour and present with facial pain include cavernous sinus meningioma, metastasis to skull base, haemangiopericytoma and chordomas spreading to the cavernous sinus.[36]

Ophthalmic symptoms

Diplopia on lateral gaze due to VIth nerve involvement is a characteristic feature of petrous apex pathology. At the tip of the petrous apex, the VIth nerve is within Dorello's canal, which makes it susceptible to various pathologic processes. Blurred vision can result from involvement of the optic tracts, raised intracranial pressure or lesions of the anterior skull base.

Facial palsy

Facial palsy is a very important presenting feature of intratemporal lesions and is established in 30% of patients before diagnosis.[7] The possible underlying pathologies include VS, meningioma, cholesteatoma, facial nerve tumours (schwannoma, haemangioma, neurofibroma), carcinomas (squamous cell carcinoma, adenoid cystic carcinoma) and paragangliomas. Facial nerve schwannoma is the most common neoplasm to cause facial nerve palsy, but it is responsible for less than 5% of all facial nerve palsies,[37] with geniculate ganglion involvement being the most common. Facial nerve haemangiomas, on the other hand, which were previously considered rare tumours, are now as frequent as facial schwannomas.[38] Clinically, haemangiomas present with facial nerve palsy and hemifacial spasm at an earlier stage than schwannomas.[39] Within the CPA, abnormal facial nerve function is found in 10–50% of patients with meningiomas, compared with less than 5% in patients with VS.[19] Among patients with jugular paragangliomas, facial nerve weakness or paralysis is present in 11–17% of patients.[40, 41] Glomus faciale are an exceedingly rare cause of facial nerve paralysis but should be considered in the differential diagnosis. Malignant involvement of the intratemporal portion of the facial nerve from head and neck malignancies may occur. The prognosis of patients with squamous cell carcinoma of the temporal bone who present with facial nerve paralysis is poor and comparable to that of T4 disease, leading to the modification of the University of Pittsburgh staging system in 2000.[42] Unexplained cases of facial palsy or those that fail to show any sign of recovery always require radiological investigation.

Lower cranial nerve symptoms

Jugular foramen tumours that extend medially and anteriorly can present with loss of bulbar function, hoarseness, dysphagia, dysarthria or shoulder weakness. They often cause these deficits long before the development of auditory or vestibular symptoms. Any isolated or combination of lower cranial nerve palsies should be investigated by imaging the skull base. The sequence of images must be extended to include the full length of the relevant nerve(s). Neuralgias of the lower cranial nerve include the uncommon glossopharyngeal neuralgia and the even more rare laryngeal nerve neuralgia. Glossopharyngeal neuralgia is characterized by attacks of excruciating unilateral pain of short duration of the ear, throat or neck. Pain can be triggered by swallowing, chewing, coughing, yawning or head movements and in about 10% of patients it is also associated with syncope due to reflex bradycardia.[43] There are seven reported cases of schwannoma of tympanic branch of glossopharyngeal nerve (Jacobson's nerve).[44]

RELEVANT MEDICAL HISTORY

The acquisition of a past medical history is essential for all patients. For those in whom a glomus tumour is suspected, symptoms or conditions that may be caused by catecholamine excess must be sought, for example, palpitations, labile hypertension, and so on. It is also important to ascertain the general fitness of the patient, with particular emphasis on their medical fitness to tolerate future management.

FAMILY HISTORY

Familial predisposition to some skull base tumours can happen in the hereditary cancer syndromes. Neurofibromatosis type 1 (plexiform neurofibroma), neurofibromatosis type 2 (VS and meningioma), paragangliomas and von Hippel–Lindau syndrome can all have implications for the patient's family. The genetic basis for these diseases is well established now and while some may arise as a result of spontaneous mutations, a large proportion do not.

EXAMINATION

Otoscopy

Otoscopy of both ears may provide valuable information regarding the underlying aetiology. Examination of the ear canal may demonstrate the presence of a mass or ulcer, indicative of a squamous cell carcinoma (SCC), the most common primary malignancy of the external auditory meatus. SCCs make up 82% of all ear canal cancers; others include basal cell carcinoma, adenoid cystic carcinoma, melanoma, adenocarcinoma, lymphoma and metastases.[10] Glomus jugulare tumours often infiltrate the floor of the external auditory canal and can be detected clinically as an area of hypervascularity and, sometimes, obvious, frank tumour.

A red pulsatile mass behind the tympanic membrane may be a glomus tympanicum tumour, but could also be a meningioma or adenoma. If arising from the hypotympanum with the classical appearance of the 'setting sun', a glomus jugulare tumour is the most likely diagnosis. Overall, paragangliomas are by far the most common tumours affecting the middle ear cleft and they can sometimes be made to blanch by pneumatic otoscopy. It is important to perform this examination with a microscope in order to enable the clinician to determine whether or not the tumour extends below the lower margin of the annulus. If it does not, the lesion is probably restricted to the middle ear or mastoid; if it does, significant skull base infiltration is possible and more detailed imaging is required.

Head and neck examination

In suspected malignant disease of the temporal bone, it is important to rule out a mass over the mastoid, squamous temporal bone, the parotid or the neck, as these may signify either direct spread or metastases.[17] Examination of the neck is also important in patients with glomus tumours to identify synchronous paragangliomas or detect direct extension of a large tumour into the neck (e.g. glomus jugulare or vagale). Auscultation should be carried out over the upper neck and mastoid and an audible bruit should be taken as being indicative of underlying pathology.

Neurological examination

A thorough neurological examination is essential as it may demonstrate subtle signs that are indicative of the underlying pathology and its probable extent. The minimum assessment must detail the function of the cranial nerves and the state of the optic discs, and test cerebellar function. A more complete examination, including the peripheral nervous system, may be indicated in some cases with extensive intracranial or coexistent spinal disease (e.g. NF1 and NF2). Similarly, the skin must be scrutinized for signs of freckling or pigmented patches in those suspected of having NF2.

The most useful screening tests for optic nerve disorders are visual acuity, visual fields, pupillary reflexes and fundoscopy. Fundoscopy may indicate the presence of incipient or established hydrocephalus. A careful examination of eye movements will reveal any involvement of the nerves supplying the extraocular muscles.

It is essential to appreciate that asymmetry of corneal sensation may be the only sign of trigeminal involvement. Reduced corneal reflexes, facial hypoaesthesia and weakness in the muscles of mastication are more obvious signs of trigeminal dysfunction. Trigeminal deficits can result from primary trigeminal lesions, petrous apex lesions, extensive infralabyrinthine lesions and CPA tumours. Facial hypoaesthesia is present in up to 4% of patients with skull base lesions[6] and loss of the corneal reflex is an important sign in patients with VS, indicating that the tumour may be more than 2 cm in diameter.

Facial weakness is present in up to 30% of all skull base lesions and clinicians should grade the degree of

weakness according to a recognized scale such as the House–Brackmann (HB) system.[18] The majority of skull base tumours do not present with a complete paresis but an asymmetry, particularly at rest. In fact, only 15% of patients present with a HB grade IV weakness or worse.[6] In VS, only about 7% of patients have abnormal facial nerve function at the time of presentation.[5] A diagnosis of VS in the presence of facial weakness should be made with caution.

Asymmetric palatal elevation or an abnormal gag reflex suggests IXth and Xth cranial nerve palsies. Laryngeal examination must be carried out to assess vocal cord function and laryngeal competence. The tongue should be examined for deviation on protrusion, wasting and fasciculation, all of which are signs of a XIIth nerve lesion. Palsies of the IXth, Xth, XIth and XIIth nerves are usually caused by infralabyrinthine disease, though occasional translabyrinthine lesions can involve the jugular foramen, its contents and the surrounding areas. Parapharyngeal tumours, particularly paragangliomas, may involve the sympathetic plexus around the internal carotid artery and cause a Horner syndrome (ptosis, meiosis, anhydrosis and enopthalmus). In a series of 36 patients with glomus tumours, 30 had deafness and tinnitus, 13 had facial weakness, 13 had dysphagia and hoarseness (IXth and Xth), 12 had shoulder weakness (XIth) and 14 had tongue weakness and fasciculation (XIIth).[45] Lower cranial nerve weakness with associated skull base lesions may occur in particular distributions giving rise to various syndromes, such as Horner syndrome, Collet-Sicard syndrome, Vernet syndrome or Villaret's syndrome (**Table 99.3**).[43]

TABLE 99.3 Syndromes of lower cranial nerves associated with skull base lesions

Syndrome	Definition	Aetiology
Collect-Sicard syndrome	Palsy of the IX, X, XI and XII cranial nerves	Glomus jugulare
		Skull base metastasis (breast, prostate, renal, lung)
		Hypoglossal schwannoma
		Neck fibrosarcoma
		Jugular foramen neuroma
		Skull base osteomyelitis
		Haemangiopericytoma of skull base
		Thrombosis of sigmoid-jugular complex
		Carotid artery dissection
		Head/C1 injury
Vernet syndrome	Palsy of the IX, X and XI cranial nerves	Osteolytic metastatis of petrous pyramid
		Skull base fracture
Villaret's syndrome	Palsy of the IX, X, XI, XII and ipsilateral Horner's syndrome	Paragangliomas
		Carotid artery dissection
		Skull base metastasis

Data from Finsterer and Grisold 2015.[43]

Vestibular examination

Spontaneous and induce nystagmus are common findings in neurotologic disorders. Examination of the eyes demonstrates spontaneous nystagmus in up to 46% of patients with VS.[10] The examination for induced nystagmus includes positional testing (Dix–Hallpike), head shaking and looking for either sound- or pressure-induced nystagmus (Fistula sign). Elimination of optic fixation by using Frenzel's glasses may improve the sensitivity of these tests. Balance and coordination can be tested in the clinic using a variety of tests. Romberg and Unterberger testing can indicate an uncompensated peripheral vestibular lesion. A positive Romberg's test can indicate abnormalities with the dorsal columns, whereas Unterberger's will induce turning towards a paretic and away from an irritative lesion of the labyrinth. Tandem gait may be instructive and any patient who can tandem walk backwards has excellent balance. Cerebellar testing includes coordination tasks, such as finger-nose-finger, heel-shin and rapid alternating motion and the patient is observed for dysmetria or dysrhythmia. The presence of limb dysmetria or dysdiadochokinesia is a useful indicator of cerebellar disease.

INVESTIGATIONS

Audiology

All patients with lateral skull base tumours should have an assessment of their hearing. Air- and bone-conduction pure-tone audiometry is the minimum requirement. The addition of speech audiometry to this protocol is preferable and mandatory whenever hearing preservation surgery is contemplated. It is worth noting that about half (49%) of all skull base patients have severe to profound deafness at the time of presentation and a third (33%) mild to moderate hearing loss.[7] Auditory brainstem responses (ABR) are no longer documented routinely. In the past it was used in a diagnostic role to determine which patients required more detailed investigation. MRI has now superseded that role.

Vestibular function tests

Caloric testing is by far the most common vestibular function test described in relation to skull base lesions and in particular with reference to VS. In general terms, they are non-specific and, like evoked response audiometry, cannot be utilized usefully in the diagnosis or screening for VS. Caloric asymmetry (>25%) may be present in up to 66% of patients with CPA tumours and this can further increase with tumour size.[10] Similarly, electronystagmography (ENG) and videonystagmography (VNG) can demonstrate abnormal function in up to 50% of all skull base lesions,[7] but these tests are seldom employed routinely.

Tests of facial function

Electroneurography (ENoG) has been used both pre- and post-operatively as a predictive test in patients with

skull base lesions. Kartush et al.[6] subjected a series of patients with tumours to ENoG and found that a significant reduction in response did not correlate with post-operative facial nerve function. However, in patients with VS, a correlation was found between pre-operative ENoG amplitude and tumour size. In other situations, a 20% or greater reduction in the amplitude of the pre-operative ENoG correlated well with facial nerve involvement by cholesteatoma or non-VS tumours.[6] Electromyography, maximal stimulation testing and electrogustometry have also been described and used to assess the degree of facial function prior to surgery, but have been shown to be of little clinical relevance.

Radiology

The advent of high resolution imaging modalities has totally revolutionized the investigation and management of patients with skull base lesions. There are four principal reasons for imaging: (i) screening; (ii) investigation of suspicious symptoms or signs; (iii) surgical planning and navigation; and (iv) for monitoring size, extent or recurrence of lesions.

The investigation and targeted screening tool of choice for VS is MRI. At first, gadolinium-enhanced MRI was employed, but this has now been superseded by fast spin echo T2-weighted images. Daniels et al.[46] reported the diagnostic outcome of screening 1070 patients with unilateral sensorineural deafness with MRI. From this group of patients they found 56 VS, 27 other CPA lesions, 29 inner ear lesions and 15 lesions affecting the brain parenchyma. Data from Iceland has shown that, about 10% of VS diagnosed were an incidental finding on imaging.[47] Diffusion-weighted imaging (DWI) can increase the conspicuity of skull base lesion and can be used to differentiate between malignant from benign lesions. DWI has also proven to be useful for identifying recurrent tumours, and differentiating these from post-treatment changes.[48] Non-echo-planar imaging DWI can be used to detect recurrent cholesteatoma and confers a positive predict value of 93 to 100%.[49, 50]

The purposes of imaging are not simply to confirm the presence of an abnormality but also to discern characteristics that might indicate the nature of the problem. Equally important are the assessment of size, relationship to other structures and detection of imminent complications, for example, hydrocephalus. In some conditions, NF2 being the best example, additional scans of the entire neuraxis are required to detect other tumours.

In several instances, both computed tomography (CT) and MRI are complementary and essential. There are a number of good examples to illustrate this point. In the assessment of facial nerve tumours, CT portrays the extent of bone destruction and gives an indication of the speed of the destructive process, while MRI can suggest whether the lesion is a schwannoma or an angioma. Similarly, the assessment of SCC of the temporal bone would be incomplete without both CT and MRI as the combination is highly predictive of the actual operative findings.[46]

MRI and CT are adequate for the evaluation of most patients with skull base lesions, but some may also require carotid and vertebral artery angiography as well. Presently, selective angiography can be undertaken by intra-arterial catheterization and injection with contrast into every feeding artery but, if far less detail is required, magnetic resonance angiography (MRA) gives considerable information in a non-invasive way. The assessment of patients with glomus tumours almost always needs a combination of CT, MRI and angiography. CT demonstrates the extent of temporal bone destruction. Gadolinium-enhanced MRI is exquisitely sensitive and will detect even very small glomus tympanicum tumours, while in larger parapharyngeal tumours flow voids give the characteristic 'salt and pepper ground' appearance that is so suggestive of paragangliomas. Subsequent carotid angiography then confirms the diagnosis, defines the blood supply and determines the integrity of the circle of Willis and potential for cross-flow should the carotid have to be sacrificed. It may also demonstrate the target vessels for pre-operative embolization to minimize intra-operative blood loss.

Cone-beam CT (CBCT) is being increasingly used in anterior and lateral skull base imaging. It is an advancement in CT imaging that provides relatively high isotropic spatial resolution of bony structures with a reduced radiation dose reported to be 60% of conventional CT scans.[51] CBCT provides much better images of the ossicular chain within the middle ear, and inner ear imaging is sufficient to diagnose most malformations and dysplasia, traumatic lesions, labyrinthine wall erosion or dehiscence.[52, 53] A low sensitivity to metallic artefacts makes it the imaging of choice in the follow up of cochlear implants. However, its lacks soft tissue contrast and therefore in cases of tumoral, septic or hematic soft tissue infiltration, HRCT and MRI are mandatory.

Positron emission tomography (PET) and single photon emission computerized tomography (SPECT) can be extremely helpful in certain circumstances where biopsy is difficult or potentially dangerous. PET is useful in identifying metabolically active tissues and can differentiate between post-therapeutic changes, for example, granulations and scars from recurrent and residual disease. By contrast, SPECT is 50% more effective at detecting skull base destruction than CT and also shows specific uptake in glomus tumours followed by rapid 'wash-out' of the radiotracer that suggests a benign vascular tumour.[22] This form of dynamic imaging is not possible with MRI. However, both PET and SPECT have limited resolution and can fail to detect small lesions.[23]

In some circumstances isotope scans can be helpful. The detection of multiple paragangliomas or metastatic disease has been facilitated by radionucleotide scintigraphy with metaiodobenzylguanidine (MIBG) or indium-11-octreotide.

General investigations

For the most part, other investigations are limited to those required to assess suitability or fitness for surgery. However, 24-hour urine collection for excreted catecholamines (vanillylmandelic acid (VMA)) is a wise precaution

in patients with paraganglioma, as it can detect a secreting tumour that could cause problems during surgery. The initial screening for paraganglioma should also include measurements of plasma-free metanephrines and urinary fractionated metanephrines.[54]

BEST CLINICAL PRACTICE

- ✓ The cornerstone of diagnosis remains imaging, which can provide an accurate 'tissue' diagnosis in many instances.
- ✓ Subsequent management, undertaken by a multidisciplinary team in a tertiary referral unit, depends on characteristics of the lesion (aetiology, site and extent) together with patient factors (age, general fitness, severity of symptoms).
- ✓ Management consists of simple surveillance, surgery and/or other therapeutic modalities, such as radiotherapy.

FUTURE RESEARCH

- ➤ Due to the rarity of skull base lesions, most of the literature is level 3–4 evidence. There is a place for larger, multicentre trials, in order to provide level 1 and 2 evidence for the investigation and management of these challenging conditions.

KEY POINTS

- Skull base lesions are infrequently encountered by general otorhinolaryngologists and require a high index of suspicion in order to avoid diagnostic delay.
- They may present with symptoms that could be mistaken for a more common otological pathology.

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CHAPTER 100

VASCULAR ASSESSMENT AND MANAGEMENT

Joe J. Leyon, Kurdow Nader and Swarupsinh Chavda

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: skull base surgery, embolization and interventional neuroradiology. The evidence is generally at level 3 or 4, with some animal studies at level 1 evidence. However, there is always the possibility that the results and conclusions drawn from these animal studies may not be reproducible in humans.

INTRODUCTION

The skull base is anatomically complex, particularly with respect to its blood supply. Many skull base tumours are either intrinsically hypervascular or secondarily involve the arteries and veins of the brain that enter and exit the cranium through the skull base. Angiography and interventional techniques have a pivotal role in the investigation and treatment of these conditions. Pre-operative embolization aims to devascularize hypervascular tumours selectively in order to improve intra-operative conditions while preserving blood supply to surrounding normal tissues. Permanent occlusion of the internal carotid artery (ICA) when possible enables the safe removal of those tumours that have an intimate relationship with the ICA.

It must be appreciated that angiography and intervention carry risks. The potential benefits that they offer must outweigh the risks of their possible complications. These risks differ from operator to operator and can be minimized by the combination of experience and detailed knowledge of relevant anatomy, pathology and procedural techniques. These techniques are certainly not for the occasional operator.

CATHETER ANGIOGRAPHY

Indications and technical considerations

Diagnostic angiography is an essential part of the pre-operative evaluation of skull base tumours, particularly if neurointerventional endovascular treatment is being considered. As well as evaluating the suitability of a tumour for embolization, it also provides the surgeon with information regarding the anatomy of the Circle of Willis and the likely tolerance to potential carotid sacrifice.

Primary assessment is made by computed tomography (CT) and magnetic resonance imaging (MRI) in order to determine the following features:

- exact tumour location
- relationship to surrounding bone, nerves, major blood vessels, brain and dura
- pattern of tumour extension
- degree of vascularity
- presence of intratumoural vessels (MRI)
- vascular territories involved by the tumour.

Diagnostic angiography and subsequent intervention can be performed in one session under general anaesthesia. Owing to the complex nature of these lesions, it is not uncommon to perform diagnostic angiography under local anaesthetic as a separate procedure prior to intervention. A size '4' French sheath and catheter is used and is introduced by the trans-femoral route. Subtraction images, fluoroscopy and a map of the vascular structures – the 'road map' – are acquired. The road map superimposes fluoroscopic images onto a previously acquired image of the vessels. This enables the guidewire and catheter to be imaged in relation to the vessels and facilitates safe navigation.

The angiographic protocol is tailored according to the vascular territory in which the tumour is located. At the very least, both ICAs and external carotid arteries (ECAs) are examined. Vertebral artery injection and selective ascending pharyngeal artery injection may be considered, the latter in view of its extensive supply to the skull base, temporal bone and dura. For any skull base tumour that is related topographically to a segment of the ICA, determination of the intracranial collateral circulation at the level of the Circle of Willis is absolutely mandatory. A comment is always made on the anatomy of the anterior and posterior communicating arteries, which may be best visualized by cross compression. This is achieved by compressing the carotid artery on the contralateral side to the vessel catheterized to visualize the anterior communicating artery, and compressing the ipsilateral carotid artery during a vertebral artery injection to visualize the posterior communicating artery. Temporary impediment to flow encourages flow of contrast across these communicating arteries.

A more detailed angiographic assessment is required for tumours in which embolization is being considered. This includes identification and characterization of all feeding pedicles, a search for collateral supply to the tumour, dangerous arterioarterial anatomoses or any arterial supply to cranial nerves, skin or pinna. In addition, it is also important to assess the vascular composition and angioarchitecture of the tumour as well as its venous drainage or any dural venous sinus involvement. Features of tumour angioarchitecture include compartmentalization, flow characteristics and arteriovenous shunts (**Figure 100.1**).[1]

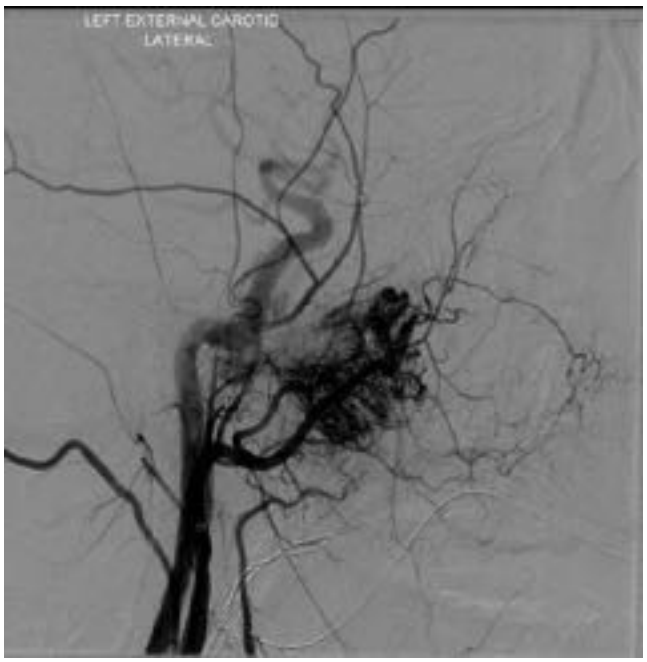


Figure 100.1 External carotid angiogram of an extensive glomus jugulare tumour; superselective angiogram of one compartment of the tumour demonstrating compartmentalization of arterial supply, typical of glomus tumours.

Risks

Carotid angiography carries a risk of permanent neurological deficit of less than 1%.[2] Other complications include arterial dissection, haematoma of the groin and reactions to contrast media that can range from a relatively minor itch to anaphylactic shock. The risk of contrast-induced nephropathy has been shown to be low even in patients undergoing emergency endovascular treatment for stroke.[3] Patients should be warned that it is normal to experience transitory unpleasant sensations or pain during the procedure, particularly following more selective catheterization and contrast injection of ECA branches.

INTERNAL CAROTID ARTERY TEST AND PERMANENT OCCLUSION

Tumours of the skull base may be intimately related to the ICA or may receive significant arterial supply from extradural ICA branches. These features can limit the surgeon's ability to obtain a complete resection. It is in precisely these cases that assessment of the cerebral circulation to tolerate permanent sacrifice of a major vessel is warranted. Given that this is a high-risk procedure, it should only be undertaken if occlusion is intended or likely.

The balloon test occlusion (BTO) is performed under local anaesthetic as this enables assessment of both motor and sensory function, speech and visual fields. Following femoral arterial puncture, a guiding catheter is placed in the ICA. The patient is fully heparinized. A soft micro-balloon is inserted through the guiding catheter into the ICA to the point of anticipated permanent occlusion and then inflated. The occlusion test lasts approximately 30 minutes, during which both clinical and angiographic evaluation is performed, the latter via a second catheter into the contralateral ICA via the contralateral femoral artery. Clinical tolerance of BTO would imply a reduced risk with parent vessel sacrifice, but does not eliminate the risk of stroke, which can happen due to haemodynamic and thromboembolic causes. When crossflow through the Circle of Willis is evaluated, any delay in transit of contrast medium on the side of the occlusion is also assessed. This is best achieved by comparing the appearance of the cerebral veins in the cerebral hemispheres. Adequacy of collateral blood flow can also be assessed by a number of methods such as transcranial Doppler ultrasound, single photon emission CT, xenon CT, pharmacologically induced hypotension, CT or MR perfusion techniques, measurement of arterial sump pressure, EEG and transcranial Doppler ultrasonography.[4, 5] A recently published study in 150 subjects utilizing BTO to assess adequacy of collateral circulation reported a stroke risk of 16% and TIA risk of 8% with parent vessel sacrifice; however, another smaller study in 31 patients reported no neurologic sequelae with parent vessel occlusion in patients who passed both BTO and single photon emission computed tomography (SPECT).[6, 7]

Permanent balloon occlusion of the ICA can be achieved by replacing the non-detachable balloon with a detachable balloon, which is positioned in precisely the same location as the temporary balloon. There are also other devices which can be used to occlude major vessels such as coils, Amplatzer vascular plug (AVP) and the microvascular plug. The AVP can be delivered through the guiding catheter to occlude vessels such as the common carotid artery, the ICA or the vertebral artery while the microvascular plug can be delivered through a microcatheter to occlude intradural vessels.[8, 9]

An external–internal carotid bypass should be considered for those patients who fail the test procedure yet need carotid occlusion. In this way the risk of stroke is reduced after permanent balloon occlusion.[10] In the event that there is doubt about the need to sacrifice the carotid, a balloon occlusion test should be performed prior to surgery and intra-operative permanent ICA occlusion can precede tumour resection if carotid involvement is found during the operation.[11]

EMBOLIZATION OF SKULL BASE TUMOURS

Indications

The main indication for pre-operative embolization of skull base tumours is to reduce intra-operative blood loss and improve visualization of the operative field during surgery. This may translate into shorter operative times and lead to a safer, easier and more successful surgical procedure. Embolization is rarely curative but improves the rate of radical tumour removal and reduces the surgical complication rate and the incidence of recurrence. Other indications for embolization include palliation of symptoms by inducing a reduction in size of the tumour and control of haemorrhage that has been caused by tumour erosion of a vessel wall.

The aim of tumour embolization is complete obliteration of the vascular bed within the tumour. Simply occluding the feeding arteries with emboli may result in the recruitment of a new collateral blood supply and make removal of the tumour even more difficult. Tumours with a rich vascular bed are most suitable, a feature that is usually indicated by the degree of contrast enhancement seen on CT or MRI. This is not always the case as increased contrast enhancement can be produced by accumulation in extravascular intercellular spaces. It does not necessarily indicate high vascularity but certainly cannot be ignored.

Skull base tumours that may benefit from pre-operative embolization include meningiomas, glomus tumours, chordomas, sarcomas, oestrogenic tumours, metastases, olfactory neuroblastomas and juvenile angiofibromas.

Catheters and embolic materials

Microcatheters enable superselective catheterization and embolization of individual feeding arteries and are generally less than 0.02 inches in diameter. Two basic types of microcatheter are used: flow-directed catheters and over-the-wire catheters. Flow-directed catheters take advantage of antegrade blood flow and are therefore more suitable for tumours that have high flow arteriovenous shunts, whereas over-the-wire catheters require the use of a guidewire and are employed in tumours with slower blood flows. While smaller microcatheters can access smaller vessels, their luminal diameter limits the size of the embolic agent that can be injected.[12] Embolic agents can be classified into mechanical agents, particulates and liquids.

Mechanical agents include coils and Gelfoam and are used in vessel occlusion proximal to the tumour. Gelfoam powder is derived from pork-skin gelatin. It is a pliable material that can be cut to appropriately sized particles and is used for more proximal vessel occlusion, often following embolization of distal vessels with particulate material.

Particulate agents achieve penetration into the tumour and can further be classified into non-spherical agents such as polyvinyl alcohol (PVA) particles and spherical particles such as Embosphere® and Embozene®. Spherical particles are the most widely used particulate embolic agents for embolization of skull base tumours and are available in a range of sizes from 40 µm to 1300 µm. Spherical particles offer more predictable embolic penetration compared to PVA.[13] Smaller particles have the ability to penetrate into vessels with a diameter of 40–60 µm. However, the use of particles with sizes in the 40–140 µm range, although more effective in inducing tumour necrosis, is also more likely to cause ischaemia of normal tissue.[14] Evidence also shows that they have a longer occlusive effect.[15–17] Particles smaller than 80 µm may risk cranial nerve palsy, likely due to occlusion of vasa nervorum, while angiographically non-visualized arterial anastomoses would be in the 50–80 µm size range. It is therefore recommended to use particles more than 150 µm.[18]

Liquid embolic agents include dehydrated alcohol, acrylate glues such as N-butyl-cyanoacrylate (NBCA), Onyx® Liquid Embolic System (ev3 Neurovascular, Irvine, CA) and Precipitating Hydrophobic Injectable Liquid (Microvention, Inc, CA). The main application of dehydrated alcohol is the percutaneous treatment of haemangiomatous malformations of the head and neck while other agents are used in embolization of cerebral arteriovenous malformations and dural fistulae. NBCA is also sometimes useful for embolization of tumours exhibiting rapid arteriovenous shunting, in which particles may pass directly though the tumour to the lungs. Liquid embolic agents can also be injected into the tumour upon direct puncture and have been suggested to decrease intra-operative blood loss.[19]

Technical considerations and complications

Embolization is preferably performed under general anaesthesia. This guarantees optimal working conditions by reducing unwanted patient movement, caused by pain,

and enabling haemodynamic monitoring. Local anaesthetic may be adequate for short, relatively painless procedures but requires a cooperative patient.

The vascular anatomy of the skull base is complex. It is important that the likely sources of arterial supply are considered thoroughly, together with any common anatomical variants and potential pathways of communication between the intra- and extracranial arteries, before embolization is attempted. As a general statement, any foramen, especially those carrying a cranial nerve, can be expected to contain a potential site of communication between these circulations. In addition, at each segmental level, residual metameric communications can be expected, particularly between the vertebral arteries and the ascending cervical, deep cervical, ascending pharyngeal and occipital arteries. Unless actively sought, these small vessels are easily overlooked, even on high-quality angiography. Even a small volume of embolic material in these vessels can lead to cranial nerve palsies or stroke. The operator should also be aware that in the course of embolization, as blood flow towards the target decreases, the direction of flow in collateral pathways may reverse and result in flow through extra- to intracranial anastomoses that were not evident on the initial angiogram. Repeated angiograms may have to be performed in the course of the procedure to exclude this possibility.

Other serious complications include blindness and skin necrosis. Blindness can usually be attributed to inadvertent injection of embolic material into the ophthalmic artery through anastomoses with the middle meningeal artery, other arterioarterial anastomoses or unrecognized variant origins. Skin necrosis is caused by embolic occlusion of cutaneous branches of the ECA. The pinna is particularly susceptible, and embolization in the anterior and posterior auricular arteries should be conducted with extreme care.

Three commonly treated tumour types – paragangliomas, juvenile nasopharyngeal angiofibromas and meningiomas – are now discussed in more detail.

PARAGANGLIOMAS

Angiography has several potential roles in the management of paragangliomas. They are:

- identification of the blood supply and flow dynamics to the tumour
- delineation of the venous drainage and demonstration of intraluminal tumour in the internal jugular vein
- assessment of the Circle of Willis for possible carotid occlusion
- detection of synchronous tumours.

Carotid occlusion should be considered when:

- imaging shows extensive destruction of the horizontal portion of the carotid canal (Fisch class C3)
- tumour is present within the foramen lacerum and cavernous sinus (Fisch class C4)
- there is the presence of large caroticotympanic and/or cavernous branches from the ICA.

A number of studies have shown that pre-operative embolization of paragangliomas provides significant benefit. Comparison of surgical data for embolized and non-embolized tumours indicates that pre-operative embolization of paragangliomas of 3 cm or more with PVA is safe, facilitates surgery and results in significantly reduced operative bleeding, shorter operative times and decreased surgical risk.[20–22] Liquid embolic agents such as Onyx or PHIL™ can also be used for transarterial embolization; they can also be injected with direct tumoural pucture.[23, 24] In a study comparing transarterial particulate embolization with direct puncture and percutaneous embolization of carotid body tumours with Onyx, a significant reduction in intra-operative blood loss was observed. Blood transfusion requirement, operative time, and complications were also less in the direct puncture group. Despite the evidence, it is not a universally accepted view and, ultimately, the decision whether to embolize depends on the location and extent of tumour as well as local practice and experience of the surgeon and interventional neuroradiologist.[25–29]

Knowledge of the angioarchitecture of these tumour types is required before embolization. The typical angiographic appearance is that of a tumour with enlarged feeding arteries, an early and intense, slightly inhomogeneous tumour blush, and early appearing draining veins. Histological studies have shown that there is a centripetally orientated system of intratumoural arterioles with a diameter of approximately 90 µm at the tumour periphery and of 300–600 µm in the centre. There are intratumoural arteriolo-arteriolar anastomoses as well as arteriolar-venous shunts.[30] This arrangement of vessels may prohibit the use of smaller particles due to the potential risk of distal migration of emboli into the systemic circulation. NBCA, a polymerizing glue, is indicated in certain cases. The majority of paragangliomas exhibit a multi-compartmental blood supply, with an arterial supply and venous drainage confined to a single area. Separate injections of embolic agent have to be made into each feeding artery to achieve complete transarterial embolization (**Figure 100.2**). Encapsulation of the tumour restricts recruitment of feeders from adjacent territories.[31]

All paragangliomas are supplied by branches of the ascending pharyngeal artery. Its inferior tympanic branch supplies glomus tympanicum tumours, the neuromeningeal branch supplies glomus jugulare tumours and the musculospinal branch supplies glomus vagale and carotid body tumours. The latter acquire an additional blood supply from the carotid body artery that arises directly from the carotid bifurcation. These tumours splay the ICA and ECA. Glomus vagale tumours, on the other hand, displace both ICA and ECA anteriorly and receive additional blood supply from muscular branches of the occipital artery. Contributions from meningeal arteries such as the mastoid artery, a meningeal branch of the occipital artery, indicate intracranial



Figure 100.2 Complete particle embolization of extensive glomus jugulare tumour. **(a)** Pre-embolization; **(b)** post-embolization.

extradural extension. Supply from the anterior inferior or posterior inferior cerebellar arteries indicates intradural spread, and in these cases the risk of posterior fossa stroke precludes embolization.

JUVENILE NASOPHARYNGEAL ANGIOFIBROMAS

Angiofibromas are non-encapsulated fibrovascular tumours that arise in the region of the sphenopalatine foramen. Although benign, they show an aggressive growth pattern and spread through foraminae or fissures. Their vascular components consist of endothelial-lined vascular spaces that are without muscular layers. As a result, these tumours tend to bleed profusely and patients may present with epistaxis.

Pre-operative embolization is an important tool for reducing intra-operative blood loss and is considered by many to be essential. Several retrospective studies, albeit small, have illustrated the effectiveness of pre-operative embolization of these tumours. Prior to the use of endovascular techniques, average intra-operative blood loss was reported to be approximately 2000 mL; this has now been reduced to less than 1000 mL by the routine use of embolization.[32, 33]

Angiographic assessment of juvenile angiofibromas prior to embolization aims to define the blood supply, vascular composition and venous drainage of the tumour as well as any dangerous anastomoses. The distal internal maxillary artery, together with its sphenopalatine and pterygovaginal branches, supplies the tumour at the site of origin in the anterior nasopharynx and posterior nasal cavity. Larger tumours that extend into the sphenoid sinus, infratemporal fossa or parapharyngeal space receive additional supply from further ECA branches, namely the accessory meningeal, ascending pharyngeal and ascending palatine arteries. Further supply from branches of the internal carotid and vertebral arteries are features of advanced tumours and, in some, there may be bilateral blood supply. Other angiographic features of these tumours include an early vascular blush that is intense but inhomogeneous and persists until the late venous phase. Once the feeding vessels have been identified, embolization of the tumour compartments can be performed. Permanent balloon occlusion of the ICA may be indicated in those rare tumours that extend into the cavernous sinus (**Figure 100.3**).[34, 35]

Direct percutaneous punctures may again be done in juvenile angiofibromas for embolization with Onyx prior to surgery. A study comparing transarterial embolization to direct percutaneous embolization with Onyx found significantly lower intra-operative blood loss and red blood cell transfusion requirements.[36]

MENINGIOMAS

Meningiomas are often hypervascular although this feature is somewhat dependent on histological subtype, the angioblastic and transitional types tending to be more vascular than fibroblastic or syncytial types (**Figure 100.4**). Psammomatous subtypes are sometimes almost avascular. Tumoural calcification is more common in histological subtypes associated with less vascularity.

There is usually a dual blood supply to meningiomas. A radial pattern of vessels derived from meningeal arteries penetrate the tumour from its base while an additional supply may be derived from its cerebral surface through pial cortical arteries arising from the ICA. The relative contribution of meningeal and pial arterial supply is variable, ranging from an exclusive meningeal supply to a dominant pial supply. Embolization is most effective when an exclusive meningeal supply is present.

The location of the meningioma determines its blood supply and may also be a good predictor of suitability for devascularization. Some of these tumours present to otolaryngologists or require their input for removal, for example frontobasal meningiomas that arise in the

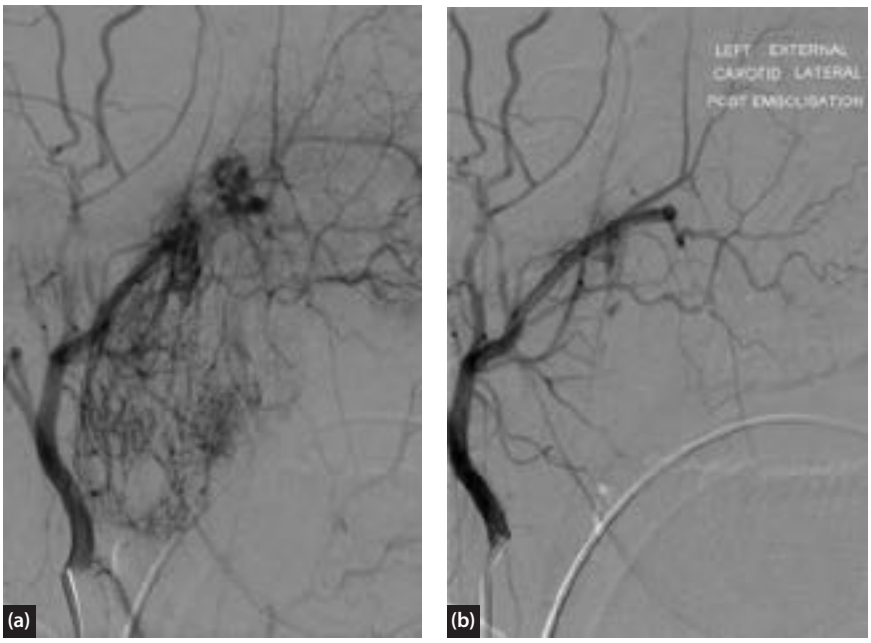


Figure 100.3 (a) Selective angiogram of angiofibroma; (b)post-embolization.

orbital roof, olfactory groove and planum sphenoidale. Orbital roof meningiomas are supplied by the anterior frontal meningeal artery, which arises from the recurrent meningeal branch of the second portion of the ophthalmic artery and from anterior branches of the middle meningeal artery. Meningiomas of the olfactory groove and of the planum sphenoidale receive their dural supply from the anterior and posterior ethmoidal arterial branches of the ophthalmic artery. The small size of these dural branches, the unfavourable vessel geometry and the dangers associated with the ophthalmic artery territory are all factors that limit the role of, although do not preclude, embolization of frontobasal meningiomas.

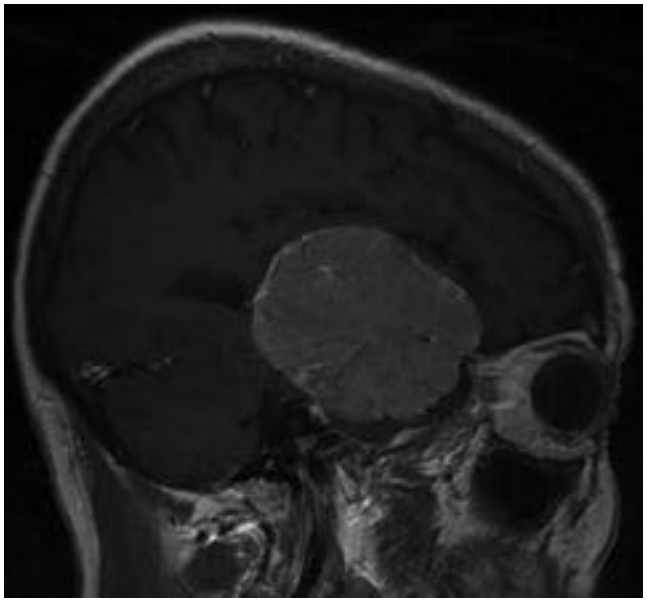


Figure 100.4 Post contrast T1 Sagittal image showing the large vascular skull base meningioma.

The efficacy of embolization can be assessed with gadolinium-enhanced MRI, which may show loss of flow signal void, decrease in contrast enhancement and new areas of non-enhancement indicating tumour necrosis.[37–39] The optimum timing of surgery following embolization is a matter of some debate. Some surgeons prefer to perform surgery within hours of embolization to avoid the effects of acute peritumoural oedema developing, while others prefer to let tumoural necrosis take place, a process that usually takes about four days.[40, 41] It is thought that corticosteroids given immediately before embolization limit tumour swelling.

Many studies have now reported the efficacy of embolization in meningiomas showing effective embolization, reduction in blood loss to tumour volume and improved surgical and functional outcomes (**Figure 100.5**).[42–49]

Complications

In addition to the technical complications already described, there have been reports of tumoural haemorrhage and hemiparesis secondary to tumour oedema.[45, 50] Risk factors include large tumour size and the presence of cysts. Vessel damage and subsequent arteriovenous shunting due to catheter and guidewire manipulation at a sharp bend of a feeding artery has also been reported.[51, 52] A review of 36 studies involving 459 patients reported two mortalities, once again highlighting that these procedures should only be done by experienced interventionalists.[53] It is worth nothing that reported complication rates in meningioma embolization have fallen from as high as 21% to 6% in the more recent literature.[54]

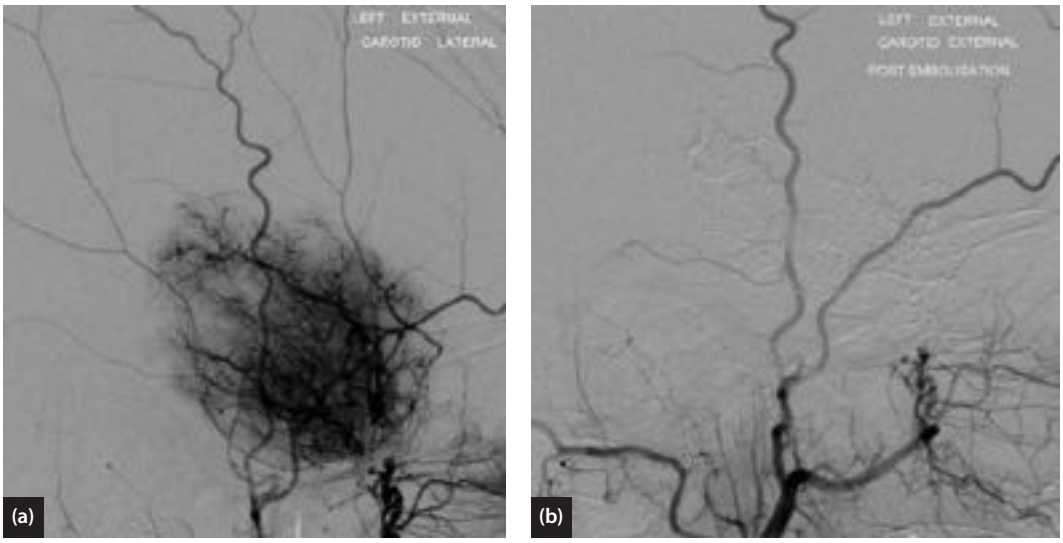


Figure 100.5 Complete particle embolization of extensive skull base meningioma. **(a)** Pre-embolization; **(b)** post-embolization.

BEST CLINICAL PRACTICE

- ✓ Angiography should be undertaken whenever a skull base tumour surrounds or is closely adherent to the ICA.
- ✓ Angiography is mandatory for vascular skull base tumours.
- ✓ Trial balloon occlusion or crossflow studies should be undertaken before any surgery in which the carotid artery might be lost.

KEY POINTS

- Both carotid angiography and embolization carry risks and the patient should be made aware of them.
- The angiographic protocol is tailored to the particular needs of the patient and their tumour type.
- Interventional techniques can make some tumours operable and decrease morbidity.

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CHAPTER 101

NATURAL HISTORY OF VESTIBULAR SCHWANNOMAS

Mirko Tos†, Sven-Eric Stangerup and Per Caye-Thomasen

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SEARCH STRATEGY

Data in this chapter may be updated by a prospective and continuous data collection of data from all patients in Denmark, diagnosed with a unilateral sporadic vestibular schwannoma since January 1976, and supported by a Medline search using the keywords: acoustic neurinoma and vestibular schwannoma (VS): anatomy, pathology, histopathology, epidemiology, incidence, growth and natural history.

INTRODUCTION

Unilateral vestibular schwannoma (VS) (**Figure 101.1**) is a benign tumour arising from abnormally proliferative schwann cells, which envelope the lateral portion of the vestibular nerve in the internal acoustic meatus. At a consensus conference[1] it was determined that the term 'acoustic neuroma', often used in the past to describe this entity, should be replaced by the more accurate term 'vestibular schwannoma'.

The aetiology of VS is not known. Recent advances in molecular biology indicate that a defect of chromosome 22q may be responsible for the development of both the unilateral sporadic VS and the bilateral VS in neurofibromatosis type 2.

Because the tumour develops in the nerve sheath, it compresses rather than invades the nerve on which it arose, thereby leaving a plane between the nerve fibres and the tumour. This feature facilitates dissection of the meatal portions of most tumours at surgery. As the VS grows, it gradually fills all the internal acoustic meatus (**Figure 101.2a, b**) and eventually protrudes out of the porus (**Figure 101.2c**).

Bone resorption is an active, slowly progressive process, caused presumably by increased vascularization, fibrosis and adhesions in the tumour area, where the pressure from the tumour, due to its growth, plays an important role. The degree of bone resorption of the internal acoustic meatus varies in VS. Some large and giant tumours have minor or modest bone resorption, some small- and medium-sized tumours have extensive resorption extending inferiorly as far as the cochlear aqueduct and superiorly to the middle fossa dura. Extra-meatal expansion of the tumour into the relatively large and empty pontine cistern initially develops silently (**Figure 101.3**). Growth and extension in this direction causes some displacement and stretching of the VIIth and VIIIth cranial nerves on the anterior aspect of the tumour and of the anterior inferior cerebellar artery (AICA) on the inferior aspect. Angioneogenesis is visible at surgery, with new small vessels running from the porus to the extrameatal portion of the tumour. After further growth, the tumour expands sufficiently to touch and compress the cerebellum and trigeminal nerve. During this process, the VIIth and VIIIth nerves are thinned or ribboned, become compressed and even more stretched. At the same time, the internal acoustic meatus continues to become more and more widened. Further growth and expansion causes compression and displacement of the brainstem and the fourth ventricle, which leads gradually to hydrocephalus.

CLASSIFICATION OF SIZE

Reporting the size of VS has always been a great problem. The main problem has been the inclusion and addition of the intrameatal element to the overall size of the tumour.

† deceased.

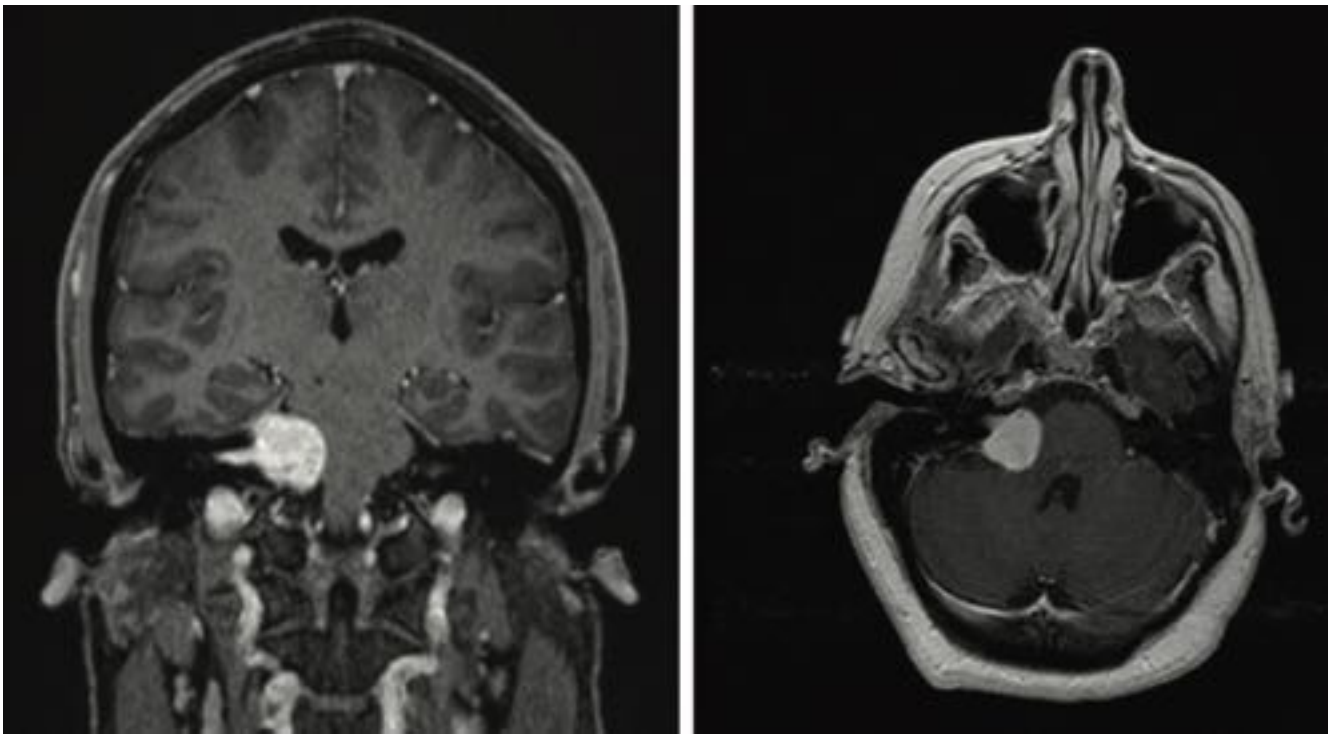


Figure 101.1 MRI scan showing a 3 cm right intra- and extrameatal vestibular schwannoma, touching the brainstem.

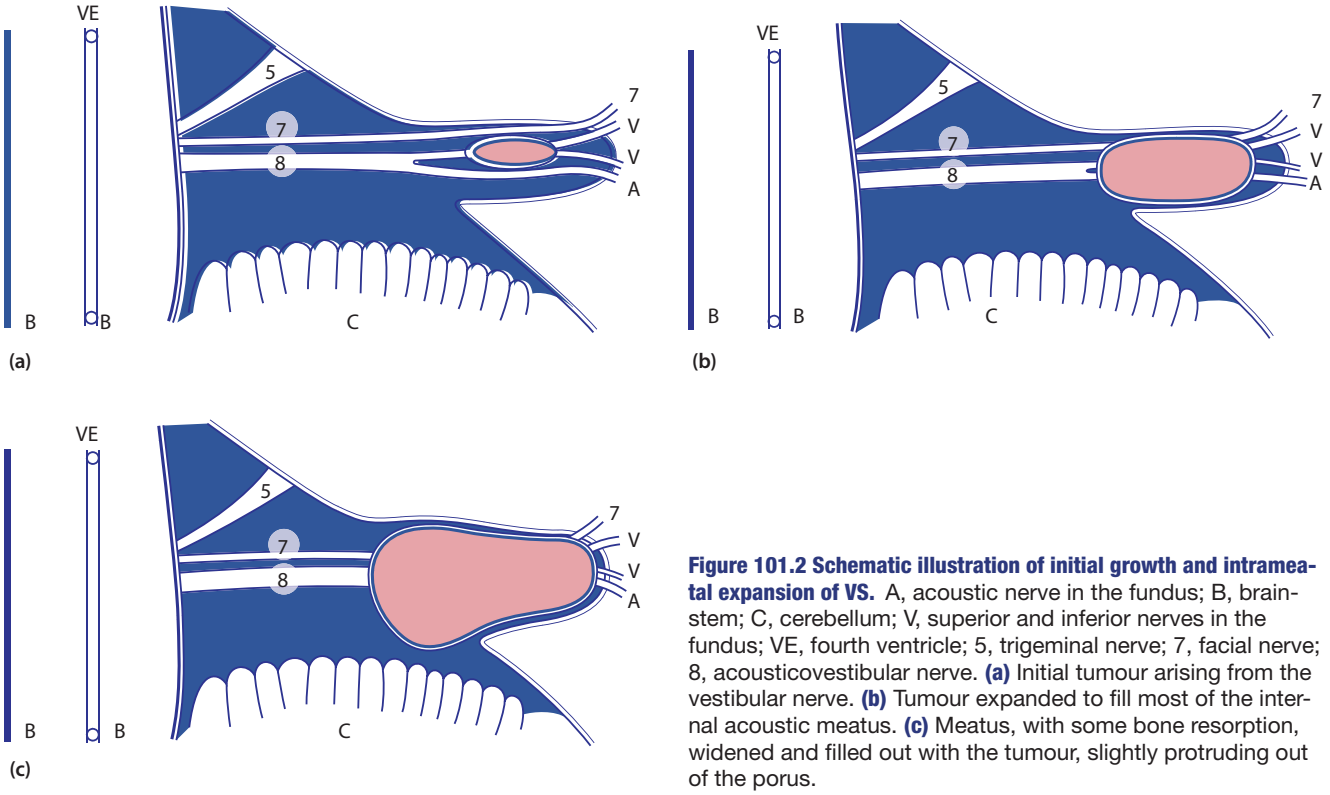


Figure 101.2 Schematic illustration of initial growth and intrameatal expansion of VS. A, acoustic nerve in the fundus; B, brainstem; C, cerebellum; V, superior and inferior nerves in the fundus; VE, fourth ventricle; 5, trigeminal nerve; 7, facial nerve; 8, acousticovestibular nerve. **(a)** Initial tumour arising from the vestibular nerve. **(b)** Tumour expanded to fill most of the internal acoustic meatus. **(c)** Meatus, with some bone resorption, widened and filled out with the tumour, slightly protruding out of the porus.

At the Consensus Meeting on Reporting Systems on Vestibular Schwannoma in 2003,[2] the classification scheme shown in Table 101.1 was proposed and recommended for adoption. It is based on the size of the largest extrameatal diameter and it was further recommended that a note should be made if the fundus is empty or filled by tumour and whether the VS is cystic. If the tumour is entirely within the meatus without any extension out of the porus, the term 'intrameatal' should be used. The extrameatal size of such a tumour is zero.

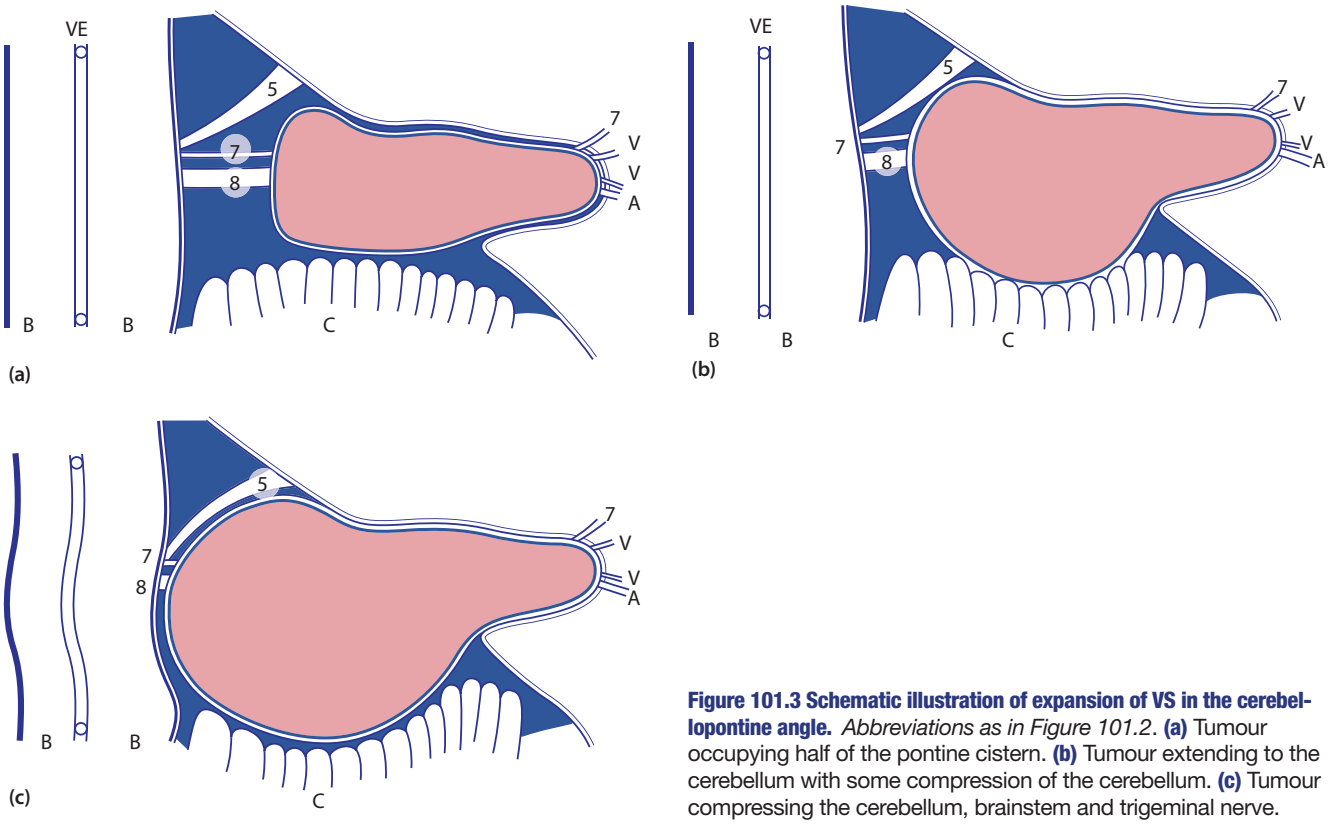


Figure 101.3 Schematic illustration of expansion of VS in the cerebellopontine angle. *Abbreviations as in Figure 101.2*. **(a)** Tumour occupying half of the pontine cistern. **(b)** Tumour extending to the cerebellum with some compression of the cerebellum. **(c)** Tumour compressing the cerebellum, brainstem and trigeminal nerve.

TABLE 101.1 Classification of VS according to size

Classification	Grade	Size (mm)
Grade 0	Intrameatal	0
Grade 1	Small	1–10
Grade 2	Medium	11–20
Grade 3	Moderately large	21–30
Grade 4	Large	31–40
Grade 5	Giant	>40

SYMPTOMS

In more than 90% of patients, the first symptom is unilateral progressive hearing loss with or without tinnitus. In 5–10% of cases, hearing loss is sudden and may be profound. Classically, there is a slowly progressing retrocochlear hearing loss, which is more pronounced in the higher end of the auditory range and is often accompanied by poor speech discrimination. However, it is salutary to note that the hearing was good with normal speech discrimination in 17% of our patients. The caloric test was normal in 8% of our patients, significantly more often (14%) in medium-sized than large tumours. Except for the hearing, symptoms caused by a VS, depend largely on its size. Seventeen per cent had nonacoustic first symptoms[3] such as vertigo, trigeminal or cerebellar symptoms.

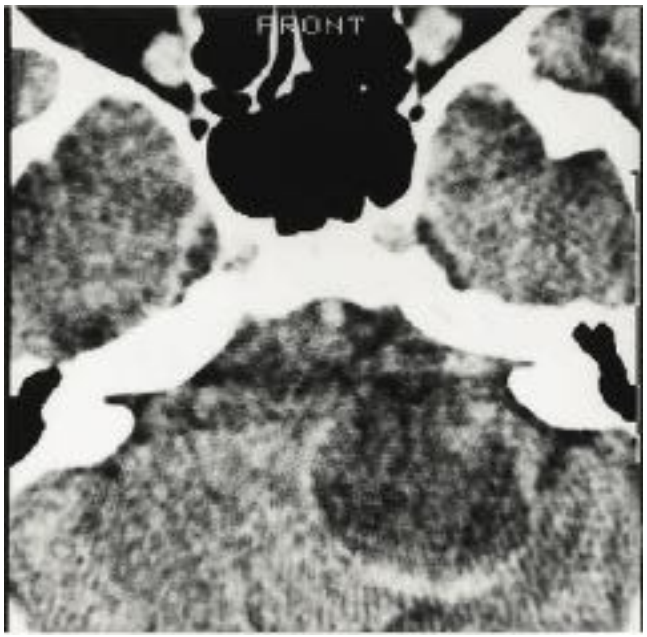


Figure 101.4 A large cystic tumour with a large hypodense area on CT scan.

CYSTIC VESTIBULAR SCHWANNOMA

Cyst formation within VS (Figure 101.4) is seen regularly and is easily detected by MR. This has been thought to represent degenerative change or coalescence

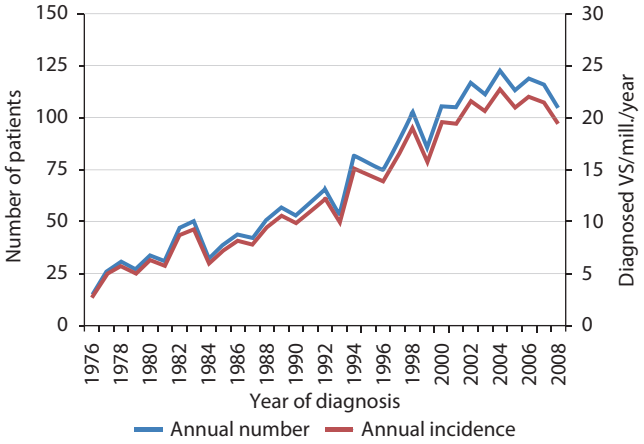


Figure 101.5 Annual number of diagnosed VS and corresponding annual incidence/million/year.

of microcysts in Antoni A tissue. More recently, it has been shown that cystic tumours contain an increased amount of Antoni B tissue that is surrounded by a membrane-like structure composed of Antoni A type cells.[4] Therefore, three criteria are required to be present before a tumour can be termed 'cystic'. First, there must be a hypodense/hypointense area on CT/MR. Second, perioperative identification of the cystic elements must be achieved and, third, there must be histological verification of S-100 positive membrane. Using these criteria, in our series of 773 resected VS, in the period 1976–96, 5.7% were cystic, making an incidence of 0.4 cystic VS per million population per year.

Several studies have shown that the surgical outcome of cystic VS is less favourable than that of solid tumours of comparable size. Furthermore, the cystic elements expand, causing displacement of the brainstem and compression of the fourth ventricle and hydrocephalus. The large size of these tumours at diagnosis, and their cysts, which can increase in size dramatically, have been considered by some to represent a contraindication for treatment by either radiotherapy or a 'wait and scan' policy.

DIAGNOSIS

Until the mid 1980s, diagnosis of VS was based on X-ray, X-ray tomography and computerized tomography. The first magnetic resonance imaging (MRI) scanner became available in most countries from 1980 and over the following years more MRI scanners were introduced. Today, VSs are diagnosed by MRI, except in a few patients with metallic implants, extreme obesity or claustrophobia. At diagnosis, 20% of the patients had a purely intrameatal tumour and in 80% the tumour extended into the cerebello-pontine angle. Nowadays, all patients with unilateral audiovestibular symptoms that cannot be readily explained should proceed to MR imaging with gadolinium enhancement.

Incidence

Several centres have reported an increasing number of diagnosed VS during the last several years.[5,6] In the period from January 1957 to July 1976 the incidence of VS in Denmark was estimated to be 5.4 VS per million per year. This estimate was based on publications from Danish neurosurgical departments.[7,8] Since 1976, the number of diagnosed VS has been constantly increasing from 3 VS per million per year in 1976[9] until an apparent peak in 2004, with 123 diagnosed tumours (23 VS per million per year, **Figure 101.5**).

The increase in the number of diagnosed VS has plausibly been caused by several factors, the most important being continuously improving access to diagnostic equipment (i.e. MRI). Another cause may be heightened symptom awareness amongst the general population and especially among the elderly, as a longer and healthier lifetime may be expected in the developed countries. Better and more widespread audiological testing equipment, as well as easier access to diagnostic imaging, may in addition have heightened the awareness of a possible VS amongst general practitioners and otolaryngologists.

Tumour size at diagnosis

From a mean extrameatal size of about 30 mm in the mid-1970s, the tumour size at diagnosis has decreased continuously over the decades to a mean size of 10 mm in the most recent period from 2003–08. In the 1970s, no purely intrameatal tumours were diagnosed, whereas the large and giant tumours constituted about 40% of all the tumours. Now, the intrameatal tumours constitute 33%, whereas the large and giant tumours constitute about 6% of the diagnosed tumours (**Figure 101.6**).

Age at diagnosis

The age of the patient at the time of diagnosis of the VS has been slowly increasing from 49 years in 1976 to 58 years in 2008 (**Figure 101.7**).

Analyzing the diagnostic age distribution throughout the 33-year period, the number of patients aged 40 years or younger has remained almost unchanged. Thus, the increasing number of diagnosed VS is primarily constituted by patients belonging to the age group older than 50 years.

In the beginning of the period covered, 81% of the patients were 60 years or younger and only 4% older than 70 years. At the end of the period, 59% of the patients were younger than 60 years and 12% older than 70 years.

In the age group of 40 years or younger, the mean tumour size at diagnosis was 23 mm. The size decreased with increasing age, and was 13 mm in the group of patients 70 years or older, even though the mean tumour size decreased throughout the period.

GROWTH PATTERN AND HEARING

The natural history of VS growth is enigmatic. The tumour may grow continuously or only to a certain size,

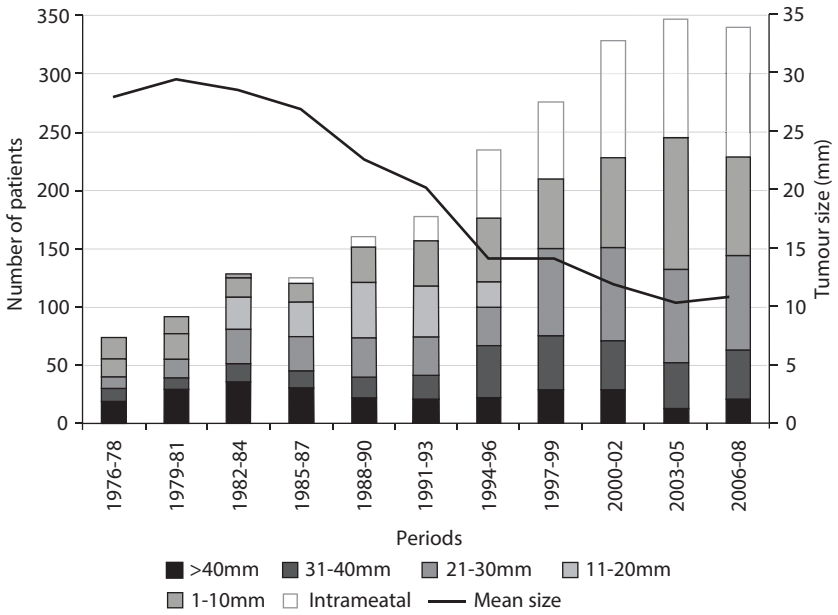


Figure 101.6 Mean size (mm) of diagnosed VS through the period 1976 to 2009.

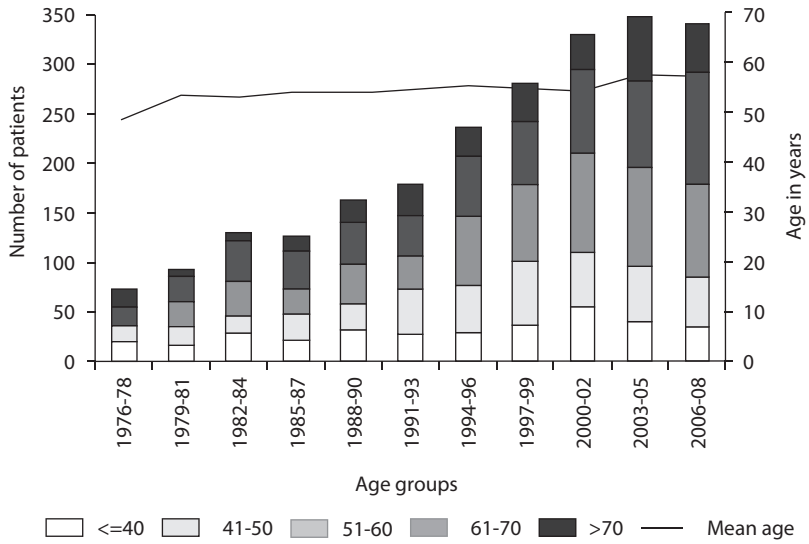


Figure 101.7 Mean age at diagnosis of VS through the period from 1976 to 2009.

followed by stagnation or even shrinkage. Progressive growth in the cerebello-pontine angle will eventually lead to compression of the brain stem and/or the cerebellum, occlusion of the fourth ventricle and subsequently incarceration.

The percentage of growing tumours has been reported to vary from 30% to 90%,[10–27] depending at least in part on the length of the observation period. Most growth observation studies have, however, surveyed a relatively small number of patients and have further been subject to considerable referral bias and patient selection bias, by only including very old patients, patients unwilling to undergo surgery or patients not eligible for surgery due to significant concurrent disease.

Tumour growth

Determined tumour growth rate may depend on the diagnostic tool (CT versus MRI),[13] the method of measurement (number or plane of dimensions assessed)[28] and criteria for the determination for growth (number of millimeters).

The present criterion for growth of a purely intrameatal tumour was growth to extrameatal extension.

For intra- and extrameatal tumours, growth was defined as an increase of at least 3 mm in the largest extrameatal diameter, in order to rule out inter-individual measuring variability and error due, for example, to unaligned scanning images. Largest diameter measurement is adequate when merely questioning absolute growth,[18] which is the

parameter relevant for a clinical assessment and decision-taking, as it is the absolute size that determines the risk of brain stem or adjacent cranial nerve compression. The adequacy of largest diameter measurement has, however, been questioned by one group of investigators, advocating Bayesian tissue classification and partial tumour volume segmentation on MR images for control of tumour growth.[26] Volumetric determination of relative growth rate is definitely mandatory when addressing basic science issues, as a tumour may grow in only one or two dimensions and as, for example, 2 mm growth in a 6 mm tumour is dramatically different from 2 mm growth in a 26 mm tumour, considering, for example, the rate of cellular proliferation.

Growth of intrameatal tumours

Of the intrameatal tumours, 83% remained purely intrameatal during the observation. In 17%, the intrameatal tumour increased in size to extrameatal extension. Of the tumours that grew, 64% grew during the first year, 23% during the second year, 5% during the third year and 8% during the fourth year of observation. No tumour growth occurred after the fifth year of observation (**Figure 101.8**). There were no significant differences in growth between male and female patients or between different age groups.

Growth of extrameatal tumours

Of the extrameatal tumours, 1% decreased in size, 70% remained unchanged and 29% increased in size during observation. Growth was determined during the first year of observation in 62%, during the second year in 26 %, during the third year in 10 % and during the fourth year of observation in 2%. No tumour growth occurred after the fifth year of observation (**Figure 101.8**).

There was no significant difference in the proportion of patients with growth between male and female patients, age groups or diagnostic tumour size. Importantly, the growth occurrence or rate is not related to gender or age, which is in agreement with a recent publication addressing potentially predictive parameters for tumour growth.[29]

Spontaneous change of hearing level

The hearing quality may be evaluated by the pure tone hearing and by speech discrimination.

In order to classify the pure tone hearing, the pure tone average (PTA) is most frequently used. The PTA is calculated as the mean sum of the hearing level (dB) at the frequencies 500 Hz, 1000 Hz and 3000 Hz, or 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz.

The speech discrimination (SD) test is performed in a quiet environment, using word list scoring by phonemes correctly repeated at the most comfortable hearing level.

Over the period 1976–2008, the PTA at diagnosis has improved from 60 dB in 1976 to 50 dB in 2008 (**Figure 101.9**). In the same period the SD at diagnosis has improved from 30% in 1976 to 60% in 2008 (**Figure 101.10**).

Different hearing classifications systems may be used to evaluate the overall hearing acuity.

The AAO-HNS classification

The American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) classification of the hearing level is as follows: class A: PTA < 30 dB and SD >= 70%; class B: PTA < 50 dB and SD >= 50%; class C: PTA > 50 dB and SD >= 50%; and class D: SD < 50% (**Figure 101.11a**).[30] Most authors consider AAO class A as good and preservable hearing.

At diagnosis, 19% of the patients had AAO class A hearing on the tumour ear. The hearing deterioration during observation is seen in **Figure 101.12**. After one year, 26% had lost class A hearing, whereas this was the case for 45% after 5 years and 54% after 10 years.

The word recognition scoring (WRS) classification

The word recognition scoring (WRS) classification[31] has: class 0: designates patients with 100% speech discrimination; class I: SD = 99% to 70%; class II: SD = 69% to 50%;

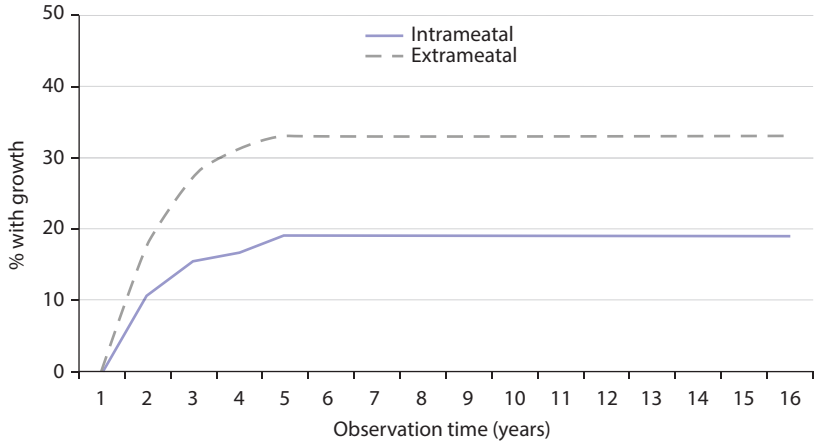


Figure 101.8 Nelson-Aalen curve of growth of intrameatal and extrameatal VS.

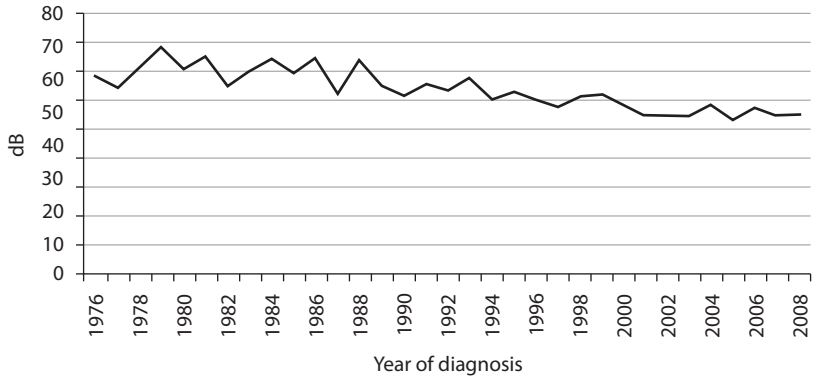


Figure 101.9 Mean PTA (dB) at diagnosis through the period from 1976 to 2008.

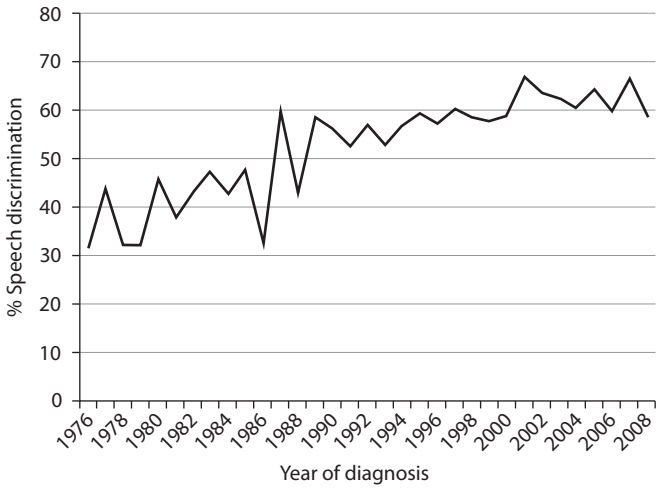


Figure 101.10 Mean speech discrimination at diagnosis through the period from 1976 to 2008.

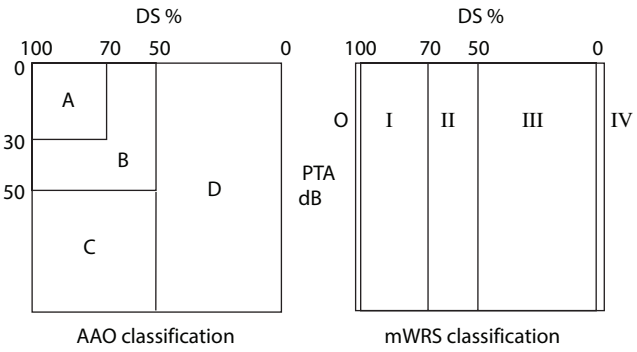


Figure 101.11 AAO and WRS classification of hearing quality.

class III: SD=49% to 1%; and class IV: SD=0% (Figure 101.11b). The hearing is considered good if the SD score is 70% or better (WRS class 0 or I).

At diagnosis, 17% had good hearing (WRS class 0) on the tumour ear, and 36% had WRS class I.[32] In the group with 100% SD at diagnosis (WRS class 0), 3% had lost good hearing after the first year. After 5 years, 12% had lost good hearing and after 10 years 31% had lost good hearing. In patients with even a minor loss of speech

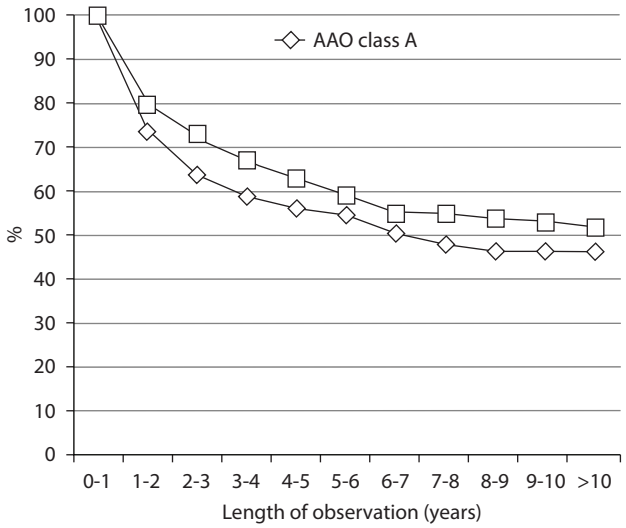


Figure 101.12 Preservation of good hearing (AAO class A or WRS class 0/1) during observation, for patients with good hearing (AAO class A or WRS class 0/1) at diagnosis (*n*=932).

discrimination at diagnosis (WRS class I), 18% had lost good hearing after 1 year, 60% after 5 years and only 38% of the patients with a speech discrimination loss between 1% and 10% maintained good hearing (Figure 101.13).

SPONTANEOUS COURSE OF HEARING AND ACTIVE TREATMENT

Hearing preservation after surgery is usually reported as the results after 1 year, and is reported to vary between 24% and 83%.[33–35] In a study from House Ear Clinic from 2003,[36] the long-term hearing preservation after surgery was evaluated over a five-year period in 38 patients. Of these 38 patients, 61% had AAO-HNS class A-B hearing after surgery. Over the subsequent five-year period, 30% lost class A-B hearing. The great variability in the success rate of hearing preservation after surgery may be explained by difficulties in comparing data, due to variable definitions of good or serviceable hearing and different reporting of the size of the operated tumour. Some surgeons include the intrameatal

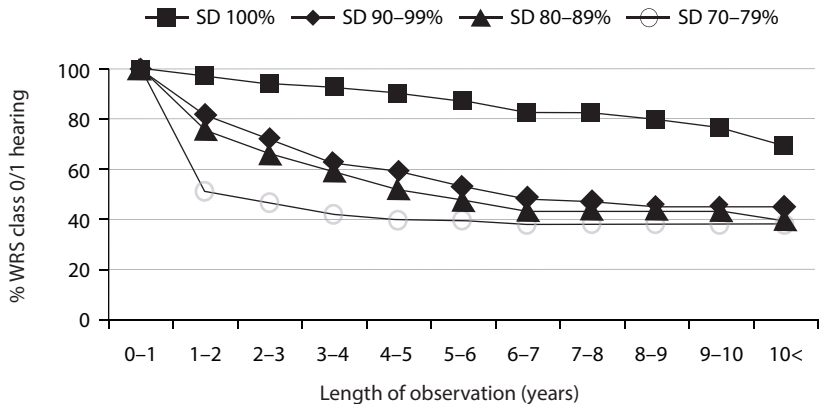


Figure 101.13 Preservation of good hearing (WRS class 1) during observation related to the different SD groups at diagnosis (*n* = 932).

part of the tumour in size measurement, while others measure the extrameatal part only. Most authors agree that the chance of hearing preservation is significantly reduced for tumours with an extrameatal diameter of more than 15 mm, while others have good results of hearing preservation in large tumours.[37] Hearing preservation surgery may be performed by the middle fossa approach, the retrolabyrinthine approach or by the retrosigmoidal approach. Comparing the approaches, it seems that the results are better by the middle fossa approach in small and intrameatal tumours.

The hearing preservation results after radiotherapy is reported to vary between 33% and 79%.[38–40]

During 'wait & scan', 73% of patients with AAO-HNS class A hearing at diagnosis preserve good hearing after one year of observation. According to the WRS classification, 87% of patients with WRS class 1 hearing at diagnosis maintain good hearing. The spontaneous outcome is emphasized further by patients with 100% SD at diagnosis (WRS class 0), in which 99% of tumour ears preserve good hearing after 1 year, whereas 91% of patients preserve good hearing after 5 years of observation, and 68% after 10 years.[32]

The main clinical implication of the hearing results is that the results indicate that it may be possible to identify patients who have a good chance of maintaining good long-term hearing spontaneously, by focusing on the speech discrimination at the time of diagnosis. Thus, a small non-growing tumour with 100% discrimination should be allocated to 'wait and scan', since it is highly likely that the tumour will not grow, and the patient will preserve good long-term hearing spontaneously and thus have an outcome superior to radiotherapy or hearing preservation surgery.

A TREATMENT STRATEGY BASED ON THE NATURAL HISTORY OF TUMOUR GROWTH AND HEARING

As more, primarily small and medium-sized VSs are diagnosed and need to be treated, the medical community is in need of a treatment strategy based on hard data on the spontaneous course of hearing and the growth pattern of these tumours.

Based on the data presented above, our centre has adapted and proposed the following strategy for all sporadic, unilateral VSs smaller than 15–20 mm extrameatal: yearly MRI for 5 years, followed by MRI every other year for 4 years, followed by MRI after 5 years, after which the observation is terminated, if no growth occurs. A rigid data interpretation indicates no reason to follow patients for more than 5 years, as tumour growth only occurred within the first 5 years after diagnosis. We have, however, chosen the above treatment policy as only a limited number of tumours have been followed for more than a decade, and to be on the safe side. If significant growth occurs, active treatment (surgery or radiotherapy) is recommended. Naturally, special considerations may indicate an aberration from this management policy (e.g. observation of old patients with large tumours or surgery for small tumour in patients insisting on a primary operation). However, unless realistic hearing preservation is intended[41] or special reasons (e.g. patient psychology) prevail, there are no available data indicating or substantiating a reason for active treatment of a non-cystic, non-growing VS smaller than 15 mm. Although reasonably surmounted, both surgery and radiotherapy are associated with risks, and the quality of life of our patients appears to be significantly better when their disease is observed.

Primary treatment of tumours larger than 15–20 mm is recommended, as further growth extends the tumour diameter into the range associated with a considerable increase in treatment comorbidity (e.g. damage to the facial nerve function). Cystic tumours are not eligible for radiotherapy and primary surgery is recommended, as these tumours may display sudden and dramatic growth, which implicates a poorer surgical outcome. NF-2 associated VSs are treated individually, as these tumours often display a distinct growth pattern and often are subjects of special consideration.

BEST CLINICAL PRACTICE

- ✓ The size of a VS should be recorded according to the International Consensus Guidelines.
- ✓ Patients allocated to a 'wait and scan' management policy should be observed with annual MRI for at least 5 years.
- ✓ Patients with small non-growing tumours and 100% speech discrimination should be managed conservatively.

KEY POINTS

- The term 'acoustic neuroma' should be replaced by the more accurate term 'vestibular schwannoma'.
- When reporting the size of vestibular schwannomas, the largest extrameatal diameter should be recorded and a note made of whether the VS is cystic.
- Symptoms caused by VS depend largely on its size, but good hearing may be found even in large tumours.
- Trigeminal symptoms and signs together with ataxia indicate a large tumour with significant brainstem compression.
- The precise incidence of VS in the population is not known, but the number of diagnosed tumours is increasing, probably due to easier access to diagnostic tools. The incidence is not less than 25 tumours per million per year.
- Only one fifth of the intrameatal and one third of the extrameatal tumours grow, and in almost all cases within the first 5 years after diagnosis.
- In patients with 100% speech discrimination at diagnosis, most maintain good hearing, in contrast to patients with even a minor impaired discrimination, where about 60% lose good hearing after 5 years observation.

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CHAPTER 102

SURGICAL MANAGEMENT OF VESTIBULAR SCHWANNOMA

Shakeel R. Saeed and Christopher J. Skilbeck

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the following keywords: vestibular schwannoma, acoustic neuroma and acoustic neurinoma.

INTRODUCTION

This chapter introduces the indications for surgical management of vestibular schwannoma (VS), explaining the current management philosophy. The common approaches to the cerebellopontine angle (CPA) are described with explanation of the advantages and disadvantages of each. A review of the current literature with particular focus on developments of adjunctive surgical techniques has been undertaken.

With the advent of high quality imaging and the increased level of awareness amongst clinicians seeing patients with otological complaints, the diagnosis of VS is frequently made earlier.[1] As a result, the tumours are detected at a smaller size and the incidence appears to have increased from the previously quoted 1:100 000 per year to 1:80 000 per year.[1–3] In addition, the epidemiological work of many has shown that a high proportion of patients with VS have static tumours.[4] Although surgery has a role for those with large tumours (>30 mm maximal intracranial diameter), beyond which the role of stereotactic radiotherapy is considered minimal, for smaller tumours, a conservative approach is commonly advised.[5, 6] There is no way of predicting which tumours will grow at the time of initial diagnosis and the majority of patients are offered active monitoring.[7] This active monitoring involves serial scanning to detect any evidence of growth, after which an intervention is offered. Despite this commonly held belief, some growth in small and intracanalicular tumours is tolerated without the need for urgent intervention.[8] Many series have shown 60–70% remain stable with no growth for many years.[9]

Historically the intervention offered was surgery. However, the skull base multidisciplinary team is increasingly offering patients the choice of surgery or radiotherapy, delivered as a single fraction (Gamma Knife) or multiple fractions. This is beyond the scope of this chapter as it is covered elsewhere.

Nevertheless, surgery remains the mainstay of treatment and this chapter deals with the commonly favoured approaches to the CPA. Certain generalizations apply to surgery, whichever approach is employed. Each of the three approaches described has its own advantages and disadvantages and these will be highlighted. The surgical outcomes will be discussed and the complications of surgery mentioned.

HISTORY

It is interesting to look at the history of the two main surgical approaches now in common use, the suboccipital (retrosigmoid) approach and the translabyrinthine approach, and to look at the vitriolic arguments that characterized the debate between the neurosurgeons and the emerging genre of neurotologists in the middle of the 20th century. Going back to the end of the 19th century, it remains unclear whether it was Ballance[10] in London or Annandale in Edinburgh who performed the first successful VS removal. Although Ballance's case was earlier,

Cushing was of the opinion that his case was a meningioma, and said of Annandale's case: 'a brilliant result, the first recorded'.[11] Be that as it may, these operations were carried out though the suboccipital approach by multi-tasking general surgeons before the emergence of neurosurgery as a separate specialty after the First World War. Undeterred by peri-operative mortality of apocalyptic magnitude (Krause in 1903 reported an 84% death rate),[12] surgery of the CPA developed in the hands of the new breed of neurosurgeon, of whom the leaders were the two great Americans Harvey Cushing and Walter E Dandy. Cushing[13] proposed intracapsular debulking of the tumour whereas Dandy[14] was a strong advocate of total removal. Despite their advances it is significant that as recently as the 1950s there still prevailed an attitude amongst many neurosurgeons that surgery should be deferred until the tumour was in fact a threat to life. An article by Pennybacker and Cairns in 1950[15] is worth reading in that it encapsulated much of the thinking of the time.

It was this situation that William House found so unacceptable in the 1960s. He could not see the logic of letting a small or medium-sized tumour become a large or giant tumour before performing an operation that was almost inevitably bound to be associated with a poor outcome or even death. He therefore proposed surgery as soon as the diagnosis could be made and suggested the translabyrinthine approach to the CPA.[16] This approach was first suggested by Panse as long ago as 1904[17] but was dismissed as inappropriate and remained in obscurity for half a century. House endured many hostile confrontations with the neurosurgical community, whose objections were as much due to the fact that otologists were becoming involved with this type of surgery as with the approach itself. Battles raged at international meetings as to which approach was better. It now seems quite clear that the 'best' approach is the approach that gives the best results in the hands of the individual surgeon. Beyond that the argument is sterile. Many developments occurred in the second half of the 20th century that led to improvements in surgical outcomes regardless of approach. There is no doubt that the advent of microsurgical technique was a major breakthrough. So too was the understanding of the importance of the blood supply of the brainstem from the work of Atkinson.[18] Neuroanaesthesia made important strides and enabled surgeons to take many painstaking hours over the surgery (an offer they were happy to accept!). Also, of course, early diagnosis enabled House's vision of early diagnosis and treatment to come a long way to fruition.

SURGICAL APPROACHES TO THE CEREBELLOPONTINE ANGLE

Translabyrinthine approach

This is now the favoured approach for the removal of VS for the majority of neurotologists. Its advantages are the avoidance of cerebellar retraction or resection, and the early identification of the facial nerve at the lateral end of the internal auditory meatus (IAM). Its disadvantages are that it involves destruction of the inner ear and so is not an option for hearing preservation surgery. It has a higher incidence of cerebrospinal fluid (CSF) fistula than other approaches and it is said by its detractors to provide only limited access to the posterior fossa. This criticism is in fact unfounded, and a well performed translabyrinthine approach will allow removal of a VS of any size.[19] It can be extended posteriorly to allow further access to the posterior fossa, jugular foramen, hypoglossal canal and foramen magnum. It can be extended anteriorly to allow access to the petrous apex and clivus (transcochlear approach). It can be extended superiorly to allow access to the middle fossa, and inferiorly to allow access to the jugular foramen and upper neck. Morrison combined the translabyrinthine approach with the middle fossa approach as the translabyrinthine transtentorial approach for large or giant tumours.[20] The technique gives excellent exposure of the tumour and of the brainstem but there is an unacceptable incidence of post-operative epilepsy and occasional temporary dysphasia if the dominant temporal lobe is retracted. The basic translabyrinthine operation is the essential starting point for many lateral skull base operations and must be a routine exercise for all aspiring neurotologists and skull base surgeons.

The key stages in the operation are:

1. Skin and periosteal flaps
2. Extended cortical mastoidectomy
3. Bony labyrinthectomy
4. Skeletonization of the jugular bulb and vertical portion of the facial nerve
5. Skeletonization of the IAM
6. Identification of the facial nerve at the lateral end of the internal meatus
7. Opening of the posterior fossa through the dura of the posterior surface of the petrous bone
8. Removal of tumour using standard neurosurgical techniques
9. Closure with obliteration of the middle ear and petrosectomy defect, usually with abdominal fat.

DETAILS OF THE TRANSLABYRINTHINE APPROACH

Position

The patient is placed on the operating table in the supine position with the head turned 30 degrees away from the surgeon and supported either in a soft head ring or fixed in the Mayfield clamp. Two-channel neuromonitoring for the facial nerve is usually sufficient, but with very large tumours it may be necessary to monitor the lower cranial nerves as well. The anaesthetist should be reminded that neuromuscular blocking agents must not be used after intubation.

Skin incision

A curved incision above and behind the pinna is planned, to allow adequate access for bone removal behind the

lateral sinus and anterior access to the labyrinthine part of the facial nerve. For tumours up to about 2.5 cm intracranial diameter the incision can be about 3 cm behind the postauricular sulcus but for larger tumours the incision should be sited further back to allow exposure of the dura behind the lateral sinus. The anterior limb should extend to a line tangential to the anterior wall of the external auditory canal.

Musculoperiostial flap

It is desirable to create a separate flap that can be used during closure to secure the abdominal fat plug. The flap can be pedicled superiorly or anteriorly. The superiorly based flap has the advantage that, if necessary, it can easily be extended upwards to allow access to the middle cranial fossa.

Cortical mastoidectomy

The secret of the operation is the extent of the bone removal (Figure 103.1). Using cutting and coarse diamond paste burrs, bone is removed up to the middle fossa dura, exposing it widely, both over the floor of the middle fossa and some 3–4 cm up the squamous portion of the temporal bone. If needed, this allows easy retraction of the dura with the instruments during tumour removal. In a similar manner, bone is removed from the sigmoid sinus and from the bone overlying the posterior fossa dura for 2–3 cm behind the sinus. Some surgeons like to leave an island of thin bone over the sinus that can be retracted with the sinus and provides some protection for the sinus. The sinus can thus be compressed backwards to increase access. During preparation of the sigmoid sinus, troublesome bleeding may be encountered from a large emissary vein. If possible it is better to anticipate trouble and identify and control the vein before making it bleed. Its bony canal can be skeletonized and obliterated with bone wax or, alternatively, the vein can be coagulated with bipolar diathermy. Coagulation should not be too close to the main sinus otherwise the manoeuvre may simply convert a small bleed from the emissary vein into a large bleed from the sinus. Care must be taken to avoid damage to the superior petrosal sinus, which runs along the posterior petrous ridge and therefore in the angle created by the bone removal between the middle and posterior fossa dura. The bipolar diathermy, if applied lightly over the dura or the surface of the sigmoid sinus, will make it retract and increase access. Bleeding from the superior petrosal sinus and, indeed, even from the lateral sinus, is easily controlled with pressure and the application of haemostatic mesh (Surgicel). Should more dramatic bleeding occur, it is still possible to apply a tie-over mesh, possibly with the addition of muscle, to avoid tying off the sinus, which is a last resort. Air embolus is only a theoretical risk in our experience.

Attention can now be turned to further bone removal medially. Ensuring the mastoid tip is removed with exposure of the digastric ridge, which aids in identification of the descending facial nerve.

Bony labyrinthectomy

A standard total bony labyrinthectomy is performed (Figure 103.2). Care must be taken in drilling out the ampulla of the posterior canal, which lies medial to the second genu of the facial nerve. The ampulla of the superior semi-circular canal should be retained as it is a landmark for the superior vestibular nerve (SVN). In drilling out the superior canal the surgeon will encounter the subarcuate artery, which runs under the canal and leads to the posterior fossa dura just behind the porus of the internal meatus. The endolymphatic duct can be traced from the vestibule along the line of the common crus where it turns through 90 degrees towards the posterior fossa dura and widens out to become the sac. The bone over the posterior fossa dura between the labyrinth and the anterior margin of the sigmoid sinus should be removed and access is further enhanced, especially in small temporal bone, if bone is

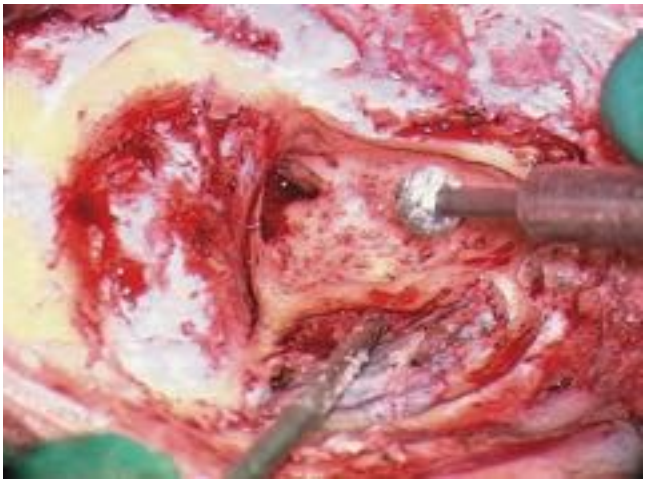


Figure 103.1 Translabyrinthine approach, right ear. Extended cortical mastoidectomy has been performed. Note the wide bone removal over the middle fossa dura and the sigmoid sinus, allowing the dura and the sinus to be retracted and the access improved.

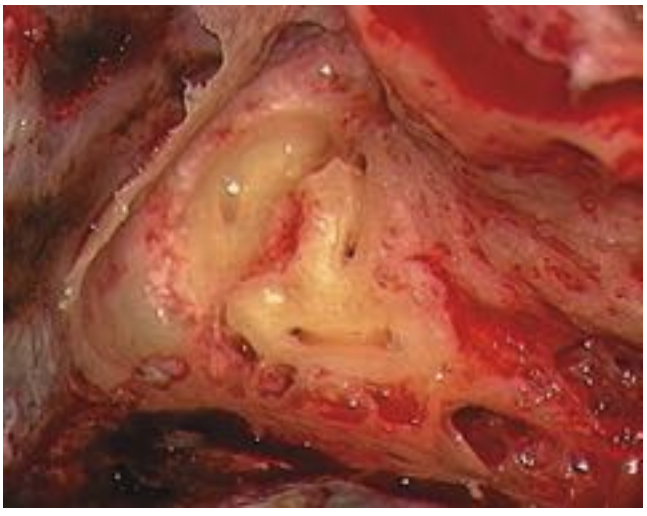


Figure 103.2 Translabyrinthine approach, right ear. Bony labyrinthectomy.

progressively removed from the dura of the middle fossa. It is by removing these bony boundaries of the petrous bone so that the limits of the resection are the soft and compressible dural surfaces that the surgeon gets maximum access to the posterior fossa. This is one of the secrets of success in the translabyrinthine operation. Although opening of the labyrinth almost inevitably leads to total hearing loss there have been attempts to perform a conservative labyrinthectomy with sealing of the vestibule and thus isolation of the cochlea from the labyrinth with preservation of the hearing. This technique was first described by McElveen et al.[21] with a further updates by Magliulo et al.[22, 23] These authors conserved class 1 or class 2 hearing in 7 out of 12 patients treated in this manner.

Others have shown that preservation of the cochlear nerve in the CPA and IAM allows subsequent cochlear implantation.[24, 25] Currently in attempting cochlear nerve preservation, a three-channel intracochlear electrode is inserted during the latter stages of the approach and tumour dissection to allow monitoring of the cochlear nerve function.[26]

Skeletonization of the jugular bulb and the vertical portion of the facial nerve

The jugular bulb is the lower limit of bone removal and in nearly all cases bone should be removed down to its level. The height of the bulb does vary enormously. In some very large, well pneumatized temporal bones with a low bulb and a small tumour it may not be absolutely necessary to expose the bulb. On the other hand it is not at all uncommon for the dome of the bulb to rise up to, and beyond, the level of the floor of the internal meatus, even as high as the middle fossa dura, and in these cases the surgeon must be prepared to mobilize and depress it. This is done by gently freeing the bulb from its bony bed and packing it downwards using haemostatic mesh (Surgicel) and bone wax. Bleeding, sometimes quite brisk, may occur but it is usually easy to control. Bone wax provides excellent protection for the mobilized bulb from the rotating shaft of the drill during the subsequent creation of the inframeatal gutter. The retrofacial air cells are exenterated and bone may be removed over the vertical portion of the facial nerve until the sheath is visible through the bone. The exact extent of bone removal over the nerve depends on the access in the individual temporal bone and the size of the tumour.

Skeletonization of the internal meatus

A U-shaped gutter is drilled below, behind and above the internal meatus (**Figure 103.3**). The extent of bone removal should be approximately 270 degrees round the meatus, and is much faster if the temporal bone is well pneumatized. An extended translabyrinthine approach has been described with removal of bone around the internal meatus to a full 360 degrees by retracting the contents of the meatus inferiorly and carefully continuing drilling towards the petrous apex.[27] This modification is helpful in dealing with lesions of the petrous apex, but is not necessary for the great majority of VSs. It is important to check the degree of meatal expansion on the pre-operative scan. Superiorly bone is removed between the meatus and the dura of the middle cranial fossa, from which the bone should be removed to allow superior elevation of the temporal lobe and easier access. One should constantly keep in mind the position of the facial nerve in the anterosuperior quadrant of the meatus, and remember that in an expanded meatus it may in fact be very close to middle fossa. To guard against inadvertent facial nerve trauma, the inferior meatal gutter is drilled first, allowing the meatal contents to displace inferiorly when the drilling turns to the superior side, where the nerve is immediately under the dura. One should be on the lookout in a pneumatized temporal bone for tumour that has eroded out of the meatus and into the air cell system. In such a situation the facial nerve may be engulfed by tumour and appear to be running through the tumour. Inferiorly one frequently encounters the cochlear aqueduct in a position superomedial to the jugular bulb. It is heartening if a brisk flow of CSF results as this allows the intracranial contents to slacken off and ease the subsequent opening of the posterior fossa. The cochlear aqueduct is a useful guide to the position of the lower cranial nerves, which are just anteroinferior to the duct. Subsequent bone removal round the meatus should be above the level of the aqueduct. When drilling round the porus, especially behind it, one must be aware of the possibility of an arterial loop lurking just under the dura, especially with a large tumour or if CSF has not been run off. There should now be an eggshell of bone over the dura of the internal meatus and the posterior fossa dura adjacent to the porus. At the lateral end of the meatus the transverse crest and the canal for the SVN should be sought. The latter runs from the lateral end of the meatus towards the retained ampulla of the superior semi-circular canal, and is a constant and reliable landmark. As the surgeon looks through the microscope it runs from 12 o'clock to 6 o'clock in the surgical field. Bone should now be picked off the dura of the internal meatus and the posterior cranial fossa if any remains.



Figure 103.3 Translabyrinthine approach, right ear. The internal meatus has been skeletonized and the intrameatal portion of the tumour exposed.

Opening the posterior cranial fossa and internal auditory canal

The dura is opened to make full use of the exposure. The upper limit is close to the superior petrosal sinus, the lower limb close to the jugular bulb. The medial limb is at the level of the porus. The dura is usually thin superiorly but can be very tough inferiorly where it is bilaminar. If CSF has already escaped though the cochlear aqueduct, this step of the operation is easy, because the cerebellum and any important blood vessels have dropped away from the dura. If the intracranial pressure is high, however, this can be a surprisingly difficult exercise, as the cerebellum tries to force its way out, often accompanied by arterial loops. Careful use of neurosurgical patties provides protection until CSF can be released. This is usually done by carefully opening the subarachnoid space at the lower pole of the tumour with a dissector. Alternatively, if a lumbar drain has been inserted the anaesthetist can be asked to run off some CSF. The dura of the internal meatus should be cut from lateral to medial at the level of the transverse crest, with the superior and inferior dural flaps reflected off the tumour, which is usually arising from the inferior vestibular nerve, and the other internal auditory canal (IAC) nerves.

Identification of the facial nerve

The facial nerve is displaced from its normal position by the tumour, but in the majority of cases it is displaced in a fairly predictable way. It runs along the anterosuperior quadrant of the meatus as far as the porus where it is displaced to a variable extent anteriorly and/or superiorly before turning down over the front of the tumour to the brainstem, which it joins just above the pontomedullary junction. Thus in the translabyrinthine approach the tumour is usually between the surgeon and the facial nerve. However, this is not always the case. There are occasions when the facial nerve is rotated backwards in the meatus and comes to lie on the posterior surface of the tumour. This may occur if the tumour arises on the cochlear nerve. It may on occasion be displaced down to the floor of the meatus and run in a more inferior position to the brainstem. If the tumour turns out to be a meningioma, the relationship of the nerve to the tumour may be variable, and it commonly runs over the posterior surface of the tumour. It is therefore essential to establish the relationship of the nerve to the tumour before any tumour is removed. At the lateral end of the meatus the SVN has already been identified. The exposed intrameatal portion of the tumour should be closely examined, both visually and using the facial nerve monitor, to be sure that the nerve has not been displaced on to the posterior surface. Assuming this is negative the nerve should then be sought in front of the SVN both visually and with the monitor. The routine identification of Bill's bar, the vertical crest separating the SVN from the facial nerve, has been abandoned by many surgeons now that reliable monitoring is in use in every case, but it may be useful to do so in cases of doubt. Access to the anterosuperior part of the meatus may be helped by careful debulking of the tumour in the lower half of the meatus.

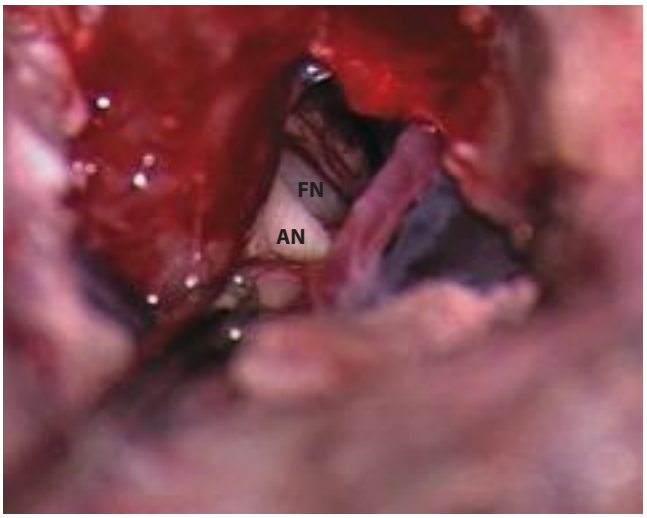


Figure 103.4 Translabyrinthine approach, right ear. The posterior fossa has been opened. The medial pole of the tumour is seen and below it the audiovestibular nerve (AN) and (deeper) the facial nerve (FN) on the brainstem.

It is also useful to try to identify the facial nerve on the brainstem at the earliest opportunity (Figure 103.4). With a small tumour it may be immediately obvious in front of the audiovestibular nerve and usually separated from it by a loop of the anterior inferior cerebellar artery (AICA). With a larger tumour it may not be possible to see it until some intracapsular debulking of the tumour mass has taken place. Once both proximal and distal ends of the nerve have been identified the surgeon starts to form a mental image of the likely course of the nerve in relation to the tumour. This three-dimensional conceptualization of the relationship between tumour and nerve is only acquired with considerable experience and makes tumour removal much more predictable and rapid.

Tumour removal

With tumours confined to the internal meatus or with little intracranial extension, dissection can start at the fundus and proceed medially, keeping to the arachnoid plane, and little difficulty should be encountered, although even small tumours may be surprisingly adherent to the facial nerve just at and medial to the porus, and sharp dissection may be needed (Figures 103.5 and 103.6). With larger tumours, debulking of the inside of the tumour is carried out so that the tumour is converted from a solid ball to a hollow ball. This technique is based on the fact that as the tumour expands all important structures such as the facial nerve and AICA are pushed before the tumour and are to be found in the arachnoid sheath on the outside of the tumour capsule. Dissection that is confined to the inside of the tumour should be safe. A number of techniques and instruments can be used for debulking. If the inside tumour is very soft it is possible to reduce the volume quite rapidly with suction alone. More solid tumours may require the use of the cavitational ultrasonic surgical aspirator (CUSA). The CUSA is certainly effective but one must be sure to use it with great care because it is

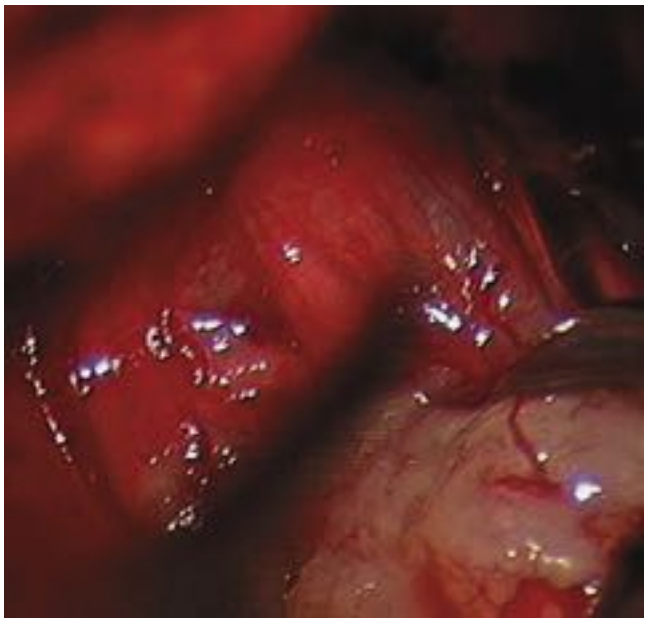


Figure 103.5 Translabyrinthine approach, right ear. The tumour is dissected off the facial nerve (FN) in a lateral to medial direction.

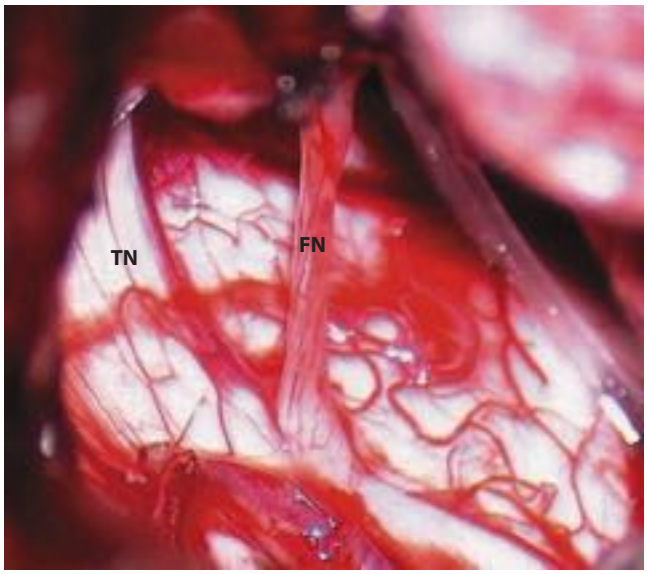


Figure 103.6 Translabyrinthine approach, right ear. Tumour has been removed completely. The facial nerve (FN) can be seen crossing the CPA to the meatus. The trigeminal nerve (TN) is seen more cranially and a loop of AICA inferiorly.

not difficult to penetrate the capsule on the far side of the tumour and risk causing damage to the facial nerve, AICA or the brainstem. It also tends to produce quite a bit of bleeding from the tumour, necessitating frequent coagulation using bipolar forceps. As the tumour bulk reduces it becomes progressively easier to manipulate the tumour capsule, and careful retrograde dissection of the capsule off the brainstem end of the facial nerve may allow the surgeon an increasingly confident image of the path that the nerve is taking. When dissecting at the lower pole one must be careful to protect the lower cranial nerves and AICA, although it must be said that it is not usually difficult to dissect them off the tumour and damage to these structures is rare. With a combination of lateral to medial and medial to lateral dissection the tumour is removed from the facial nerve. The extent to which one can follow the traditional advice to stay in the arachnoid plane varies from tumour to tumour and it is very important that the surgeon knows just where he is in relation to that plane at any moment in the operation. When dissecting the tumour off the facial nerve in the internal meatus he is within the arachnoid plane. When dissecting in a retrograde manner from the stem he is outside the arachnoid plane. Failure to appreciate this subtle difference in location carries the risk of dividing the nerve. In the internal meatus and close to the brainstem the plane between the facial nerve and the tumour is usually quite easy, but at a point at or just medial to the porus it may be almost impossible to identify and sharp dissection may be necessary to get the tumour off the nerve. This is the point where the facial nerve is most likely to be lost. In addition to difficulties with the plane, it is here that the nerve becomes very thin and may be impossible to differentiate visually from the surrounding arachnoid, although the monitor does certainly help. The facial nerve is placed at further risk if the tumour extends far forwards towards the petrous apex carrying the facial nerve with it. The surgeon may in fact decide to leave a small nubbin of tumour on the nerve at this point to reduce the risk to the facial nerve. There is good evidence that these small fragments become devitalized and either disappear on follow-up scanning or at least seem to remain biologically inert.[28,29] Dissection of the capsule off the trigeminal nerve and the brainstem is usually not difficult but some tumours bury their way into the stem and very gentle technique is required to separate one from the other. There may be occasions when the surgeon chooses to leave a fragment of tumour behind, especially if the anaesthetist reports repeated or sustained changes in the pulse or blood pressure during manipulation on the stem. The VIth nerve can usually be seen running up the length of the stem. Large tumours may make contact with this nerve and it must be handled carefully. Even quite gentle dissection can cause a temporary dysfunction of the nerve with transient post-operative diplopia. All blood vessels apart from obvious tumour vessels should be treated with the greatest respect. It is not possible to tell which branches of AICA are essential and it is wise to assume that they all are.

Special attention should be drawn to the unique surgical problems with the so-called medial tumour that arises in the CPA without involving the internal meatus and is usually large at presentation.[30,31] Because they have little attachment to the internal meatus these tumours tend during surgery to be suspended on the VIIth/VIIIth nerve pedicle or even on the facial nerve alone. The surgeon has to be particularly careful to avoid traction on this pedicle if avulsion of the facial nerve is to be avoided.

After tumour removal, haemostasis must be secured. Care must be taken with the use of the bipolar diathermy in the vicinity of the facial nerve. Rather than risk thermal damage to the nerve, one should allow bleeders close to

the nerve to stop spontaneously or use a small fragment of Surgicel to assist haemostasis.

Closure

This is one of the most important steps in the translabyrinthine operation. CSF fistula remains one of the most common post-operative problems, even in large series from experienced centres. To minimize the risk, careful obliteration of the middle ear and the temporal bone defect is essential. Harvest of free autologous fat (and fascia) from the abdominal wall or thigh is performed and prepared for use. The incus is removed and a posterior tympanotomy created. The middle ear, Eustachian tube and vestibule are obliterated with muscle or fascia and bone wax. The supra and inframeatal gutters are obliterated with fat and obvious air cell tracts sealed with bone wax. The temporal bone defect is obliterated with abdominal fat either in strips or in one large piece. Some surgeons first seal off the posterior fossa and drilled anterior surface of the petrous bone with fascia lata from the thigh or fascia from the superficial layer of the external oblique from the anterior abdominal wall. The repair is secured with fibrin glue, although excessive reliance on biological glues is to be regarded with caution. It is possible that they may interfere with the body's natural healing response and, when they are absorbed, actually predispose to CSF fistula.[32] Although predominantly remaining in the surgical bed, post-operative imaging has shown embolic distribution of fat throughout the CSF with no clinical significance.[33] The periosteal flap is then sutured back over the fat and the skin closed in two layers. A firm pressure dressing is applied and kept in place for a week. It should not, however, be so tight that it causes pressure changes in the skin of the forehead. The use of a peri-operative lumbar drain is not routine but is employed in some centres.

Middle fossa approach

The middle fossa approach is one of the possible routes of access for hearing preservation surgery. The internal meatus is approached extradurally from above through a small craniectomy. It has the advantage of allowing good visualization of the lateral extent of the internal meatus. The approach is somewhat cramped, however, and access to the posterior fossa limited, certainly through the standard middle fossa approach. The maximum size of tumour that can comfortably be removed is about 1–1.5 cm in intracranial diameter, which is in fact about the limit beyond which the possibility of hearing preservation recedes. Furthermore there is a small but real risk of epilepsy following extradural retraction of the temporal lobe. Aggarwal et al.[34] described two cases of single ictal events that had the effect of prohibiting the patients from driving for a period of one year. In the extended middle fossa approach (EMFA), more bone is removed in front of and behind the meatus and access to the posterior fossa increased. This approach is more suited to removal of petrous apex lesions such as congenital cholesteatomas or meningiomas, and Wigand et al., who did much to develop this technique, are able to remove VSs with an intracranial diameter of as much 3 cm by this approach.[35, 36]

The key stages in the middle fossa approach are:

1. Skin and soft tissue incisions
2. Middle fossa craniectomy
3. Extradural approach to upper surface of temporal bone and to posterior fossa
4. Skeletonization of internal meatus
5. Identification of facial and vestibular nerves
6. Removal of tumour
7. Closure

DETAILS OF THE MIDDLE FOSSA APPROACH

Position

The patient is supine with the head on a head ring or in a neurosurgical clamp. The essential point is that the intermeatal line should be perpendicular to the floor. This ensures that the internal meatus is in the same plane as the external meatus and assists the surgeon's orientation in identifying the internal meatus. Facial nerve monitoring is routine with auditory monitoring added in cases of attempted hearing preservation.

Incision

A 6–7 cm vertical or gently backward curving incision starts at the level of the zygomatic arch just in front of the pinna. The temporalis muscle is exposed and an inverted T-shaped incision is made though the muscle down to the skull.

Craniectomy

A 5 cm × 5 cm square bone flap is cut with about two-thirds in front of the intermeatal line and one third behind it. The dura over the temporal lobe is exposed. The lower edge of the craniectomy should be at the level of the floor of the middle fossa – it may be necessary to remove further bone down to the floor of the fossa with bone nibblers. Air cells are frequently opened and should be sealed off with bone wax or muscle.

Exposure of upper surface of petrous bone

The dura is elevated off the surface of the petrous pyramid. This is facilitated considerably by the administration of intravenous mannitol at this stage and the dura can be elevated as far medially as the petrous ridge and the superior petrosal sinus. A middle fossa retractor is introduced. As the dura is elevated troublesome bleeding is often encountered from the venous plexus that surrounds the middle meningeal artery in the region of the foramen spinosum. This is controlled with Surgicel packing. As the dura is elevated the greater superficial petrosal nerve is identified running up from the region of the middle meningeal artery to the geniculate ganglion. It is frequently adherent to the dura and may have to be separated from it by sharp dissection. One should also be aware that the geniculate ganglion may be dehiscent in up to 5% of individuals and

at risk of damage as the dura is elevated.[37, 38] The arcuate eminence is the other important landmark to be identified. It corresponds approximately to the superior semi-circular canal.

Location of the internal auditory meatus

There are two favoured approaches to the internal meatus. In the method originally proposed by House, the geniculate ganglion is identified and the facial nerve is followed medially along its labyrinthine segment until the meatus is reached. This method involves drilling between the cochlea anteriorly and the superior semi-circular canal posteriorly. If either of these structures is breached the hearing will be lost. The other approach was suggested by Fisch and others. The angle between the line of the greater superficial petrosal nerve and the plane of the superior semi-circular canal is bisected and that gives the line of the internal meatus. If necessary the superior canal may be blue-lined to establish the exact anatomy of the area, and good quality CT images of the temporal bone will provide the surgeon with important information on the degree of pneumatization that will be encountered as the internal meatus is approached. The internal meatus is skeletonized anteriorly, superiorly and posteriorly. At the lateral end Bill's bar is identified and the ampulla of the superior canal blue-lined. Medially the porus is skeletonized and the dura of the posterior fossa increasingly exposed. Initial drilling of the medial end of the internal meatus is advised, where there is usually more bone overlying the canal, whereas laterally the nerves become more superficial to the middle fossa.[39]

Identification of the facial, cochlear and vestibular nerves

The dura of the meatus is opened longitudinally with scissors as far as the porus and access to the posterior fossa can be gained by opening the dura in front of and behind the porus. The facial nerve is identified in the anterosuperior quadrant of the meatus and is protected under the cut dural edge. The SVN may be seen to be running into the tumour, or alternatively may be seen to be running over the surface of the tumour depending from which branch of the vestibular nerve the tumour arises. The cochlear nerve is concealed under the facial nerve and cannot be seen at this stage. If the tumour does reach right to the fundus, identification of the neural structures lateral to the tumour is easier. Careful positioning of the retractor under the superior petrosal sinus usually provides adequate access into the posterior fossa where the medial pole of the tumour and the facial and vestibulocochlear nerves are identified. It is rarely necessary to divide the sinus. As mentioned previously it takes the surgeon considerable experience to picture these three-dimensional relationships in his or her mind.

Tumour removal

The principles of tumour removal are no different from those outlined in the description of the translabyrinthine approach. The surgeon must recognize that the facial and cochlear nerves lie in the arachnoid plane. Debulking of the inside of the tumour can proceed safely, both inside the meatus and in the posterior fossa. One major difference from the translabyrinthine approach is that the facial nerve lies between the surgeon and the tumour and is thus more vulnerable to damage from instrumentation. When the stage of dissection of the capsule of the facial and cochlea nerves is reached, it is important to remember that the forces applied to the tumour should be in a medial to lateral direction in order to minimize stretching effects on the fibres of the cochlear nerve as they pass through the basilar membrane at the *habenula perforata*.

Closure

The internal meatus is closed with a free muscle plug. A couple of dural hitch stitches are inserted to minimize the risk of an extradural collection, the free bone flap is replaced and secured with non-absorbable ties and the muscle and skin closed in layers.

Retrosigmoid approach

This approach has evolved from the classic suboccipital operation that was favoured by neurosurgeons for the removal of all posterior fossa tumours but particularly for large ones. A very large portion of the occipital bone was removed, from the transverse sinus above to the foramen magnum below and from the sigmoid sinus laterally to the midline. Such a large craniectomy is now rarely necessary and a much smaller retrosigmoid craniectomy of around 5 cm × 5 cm allows good access to the posterior fossa, although the exact amount of bone removal will depend upon the preference of the surgeon and the size of tumour to be removed. The advantage of the retrosigmoid/suboccipital approach is that it allows the possibility of hearing preservation in small tumours. The disadvantage is that, especially for large tumours, considerable cerebellar retraction may be necessary, and even on occasion resection of part of the cerebellar hemisphere. Kim et al.[40] report, however, that the significantly greater cerebellar retraction that is necessary for retrosigmoid surgery does not result in greater long-term balance and disability as compared with those patients who have undergone the translabyrinthine approach.

Post-operative headache is more common with this approach than with the translabyrinthine operation.[41, 42] The mechanism is unclear, although several have been proposed including dural irritation around the IAM, adherence of scalp flap to the dura, extent of dissection of the neck muscles and occipital nerve injury.[43–45] If the facial nerve is lost near the fundus of the internal meatus, it is virtually impossible to perform a primary nerve grafting procedure.

DETAILS OF THE RETROSIGMOID APPROACH

Positioning

The operating position depends on preference. Neurosurgeons will favour the lateral position or park-bench position with or without the use of a clamp.

The sitting position has largely been abandoned in the UK because of the risk of air embolus if the venous sinuses are opened. It does have the considerable merit of enhanced visibility for the surgeon as gravity keeps the field clear of CSF and blood. Neurotologists may find that the supine position with the head turned to the opposite side provides access just as easily. Facial nerve monitoring electrodes will be in place, as will electrodes for intra-operative recording of auditory evoked potentials in cases where hearing preservation is the aim.

Incision

A vertical or slightly curving incision is made about 3 cm behind the mastoid process, from above the level of the transverse sinus to the level of the tip of the mastoid. The soft tissues may be incised down to the bone, but the authors prefer to maintain a superiorly based musculoperiostial flap to assist in the closure.

Craniotomy and exposure of the tumour

A 5 cm × 5 cm craniotomy is made using the drill, taking the mastoid emissary vein as the starting point, and the bone dust is retained for closure. The anterior and superior limits of bone removal are the sigmoid and the transverse sinuses respectively. It is essential to get as close to the sigmoid sinus as possible so that the surgeon's line of sight is along the posterior surface of the petrous pyramid. As the drilling progresses, any mastoid air cells encountered must be closed using bone wax or muscle, to minimize the risk of post-operative CSF leakage. The extent of bone removal required is to some extent determined by the size of the tumour; some advocate completing the craniotomy to the level of the foramen magnum, allowing wider exposure and enabling access to drain CSF. The dura is opened through a U-shaped flap based anteriorly on the posterior edge of the sigmoid sinus and the cerebellar hemisphere is exposed. In order to get good exposure of the tumour, CSF must be run off from the CPA, usually initially by accessing the cisterna magna. This is not always easy as the cerebellum is in the way, but with gentle retraction and reduction of the intracranial pressure by the anaesthetist, this is achievable and an instrument can be passed into the subarachnoid space. Now the cerebellum falls away under its own weight and if the surgery is for a small tumour, as in a hearing preservation operation, little retraction is needed (**Figures 103.7** and **103.8**).

Tumour removal

The previously outlined principles apply. Intracapsular debulking is safe and allows one progressively to handle the capsule of the tumour. It is desirable to identify the facial and audiovestibular nerves on the brainstem as soon as possible, and to note the position of AICA. The intracranial part of the tumour can be dissected off the facial and audiovestibular nerves back to the porus of the internal meatus, but for complete tumour removal the IAM must be drilled out. One of the principles of tumour removal for hearing preservation is that dissection should be in a medial to lateral direction in order to avoid traction on the fibres of the cochlear nerve as they pass from the cochlea through the habenula perforata into the internal meatus.

Drilling of IAM

A dural flap should be elevated over the IAM. This may be based either laterally or medially. The medially based flap has the advantage that it may be turned in over the facial and auditory nerves for protection during the drilling. The internal meatus should be skeletonized above, behind and below, though at least 180 degrees and as far laterally to the fundus as possible. The obstacles to this are the jugular bulb if it is high, and the posterior semi-circular canal.

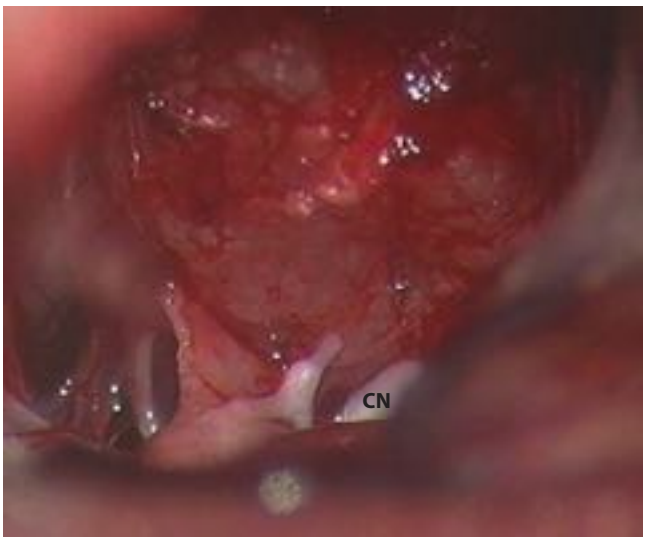


Figure 103.7 Retrosigmoid approach, left ear. Small tumour with cochlear nerve (CN) seen at medial pole.

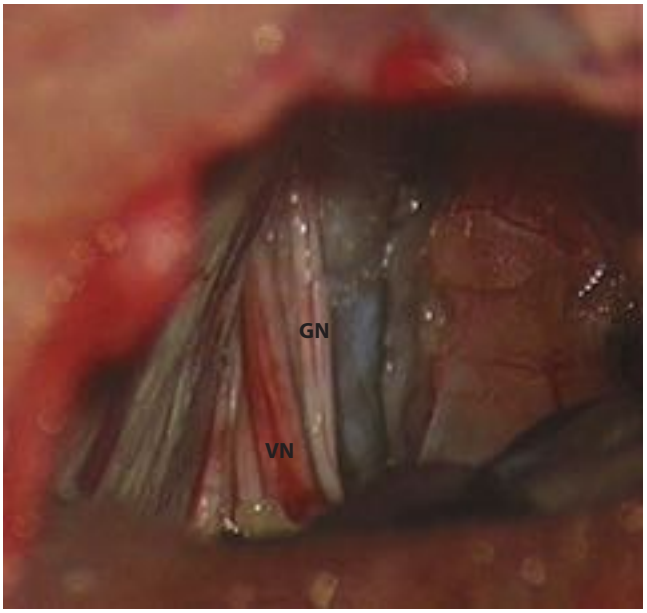


Figure 103.8 Retrosigmoid, left ear. Lower cranial nerves seen below lower pole of tumour. GN, glossopharyngeal nerve; VN, vagus nerve.

A high bulb is more difficult to depress through the retrosigmoid approach than in the translabyrinthine operation. Opening the posterior semi-circular canal is not important unless hearing preservation is intended. The surgeon must look out for the blue line of the canal and avoid it. The combination of a high bulb and an unfavourably placed posterior canal can make the surgical view to the fundus almost impossible. When the bony removal is complete the dura of the internal meatus is opened and tumour removal continues in a medial to lateral direction. If there is a decrease in the magnitude of the auditory brainstem response (ABR), dissection should be halted and local vasodilating agents such as papaverine applied to the vessels in the IAM. As stated above, despite one's best efforts, it may be impossible to see right to the fundus and the last fragment of tumour may have to be removed 'blind'. This manoeuvre clearly carries a risk of damage to the facial and cochlear nerves, and of course there is the risk that tumour may be left behind at the fundus. Some surgeons find it useful to inspect the fundus with a 30 degree fibre-optic rigid endoscope to ensure completeness of removal.[46] Complete endoscopic tumour dissection through a 'key-hole' retrosigmoid craniotomy has also been described.[47]

Closure

After haemostasis is achieved, any remaining air cells are obliterated with bone wax. The dural flap is repaired as far as possible. The repair may be strengthened with fascia or with artificial dura. Steps should be taken to ensure, as far as is possible, that the subcutaneous soft tissues do heal directly on to the dural repair. The authors mix up a pâte of bone dust and tissue glue, which sits on the dural repair and fills the bony defect. A separate periostial flap is then used to cover the pâte repair and the skin and subcutaneous tissues are closed in layers. Hydroxyapatite cement has been used successfully to repair the drilled bony defect in the porus acousticus as a method of preventing CSF rhinorrhoea.[48]

EXTENDED OR COMBINED APPROACHES

There are occasions when extended approaches are applicable, whether via a translabyrinthine approach with transtentorial extension or by utilizing a retrolabyrinthine approach combined with a retrosigmoid and middle fossa bone removal. Occasionally it may be advisable to stage the surgery for very large tumours, with a primary debulking operation and subsequent 'completion'.[49] However, it is quite possible that the 'second stage' may be delivered as single fraction radiotherapy, should the remnant grow.

NOTE ON THE AUDITORY BRAINSTEM IMPLANT

The auditory brainstem implant is increasingly used to rehabilitate patients with neurofibromatosis type 2 (NF2) who are totally deaf and have no functioning cochlear nerves as a result of their bilateral VS or the surgery to remove them. The auditory brainstem implant electrode array comprises 21 small disc electrodes mounted on a Silastic paddle, which is placed onto the surface of the cochlear nucleus. This is found in the floor of the lateral recess of the fourth ventricle, which is entered through the foramen of Luschka. The procedure is usually performed as a combined operation following tumour removal, via either a translabyrinthine or a retrosigmoid approach. The foramen is located by following the glossopharyngeal nerve upwards and the stump of the VIIIth nerve if present downwards. The choroid plexus is seen emerging from the foramen. The taeniae of the fourth ventricle may have to be divided and there is often an arterial loop that has to be moved to one side. The cochlear nucleus is identified by its very white colour and by a fairly constant thin vein that runs over its surface. Intra-operative neural responses using electronically evoked auditory brainstem responses (eABR) are performed to ensure optimal placement of the whole paddle.

OUTCOMES AND COMPLICATIONS

The two key determinants of outcome and complications in VS surgery are the size of the tumour being removed and the experience and surgical skills of the team removing it. Not surprisingly the bulk of the literature on this subject emanates from experienced centres reporting their results: this in effect represents the benchmark for outcomes and complications. Evidence of surgical outcomes from teams undertaking occasional VS surgery are limited. However, the evidence as it exists shows adverse outcomes and higher complication rates when parameters such as death, facial nerve function and CSF leak rates are examined.[50, 51] The evidence for centralisation in NF2 care is certainly strong.[52]

Following enthusiasm from many quarters and the agreement of the British Skull Base Society and the Society of British Neurosurgeons, mandatory data collection for a national audit in VS management is now ongoing in the UK (https://orioncloud.org).[53]

The single most important factor in all studies quoting facial nerve and hearing preservation and extent of resection is the tumour size.[54] Many feel that there is a difference in outcomes between solid and cystic tumours, with cystic ones faring less well with surgery.[55–57] This is by no means universal.[58] It is commonly believed that they are also less successfully treated with radiotherapy.

Facial nerve outcomes are of the utmost importance to the patients, and multiple attempts to improve prognostic information for pre-operative counselling as well as post-operative prediction have been made. Reviewing the pre-operative imaging, the size of the tumour, the anterior extent and the shape have all been correlated with poorer facial function.[59] Intra-operative neurophysiological stimulation has been used with some success to try and predict the degree of facial dysfunction post-operatively.[54, 60–66]

Complications after VS surgery are quite frequent but the vast majority of patients undergoing tumour removal do not suffer any significant long-term sequelae. As complications and outcome are inextricably linked, the two are considered together.

Death, stroke, haemorrhage, brain injury

As indicated earlier in this chapter, the early results of VS surgery were not encouraging, with peri-operative mortality of over 80%.[12] The efforts of Cushing,[13] Dandy[14] and Pennybacker and Cairns[15] brought the death rate down to more acceptable levels, but it was not until the era of microsurgery in the 1960s that it really came down the levels we see today, at around 1% or less in specialist centres.

The actual causes of death have not changed much over the years: vascular events and their effects on the brain and general medical complications associated with major surgery such as myocardial infarction, pulmonary embolus and pneumonia. A meta-analysis including over 30 000 operations for VS focusing on non-audiofacial outcomes showed an overall mortality rate of 0.2%. Approximately 20% of patients experienced one surgically attributable complication.[67] The likelihood of serious vascular events is for the most part related to tumour size and is considered in more detail below.

ARTERIAL BLEEDING

Vigorous arterial bleeding is not a common occurrence during VS surgery. The surgeon must of course take great care to identify and protect the major arterial systems in the posterior fossa, notable the anterior and posterior inferior cerebellar arteries (AICA and PICA) and the superior cerebellar artery (SCA). Gentle handling of tissue, adherence to correct tissue planes and the avoidance of traction are essential. If serious bleeding does occur it must, of course, be controlled with the minimum of damage to the arterial tree, and precise identification of the bleeding point. A small side hole in even a large vessel can often be controlled with skilful and accurate use of the bipolar diathermy. Alternatively, minor degrees of arterial bleeding may be controlled by application of a piece of muscle to the affected site. Serious injury to the main trunk of AICA requiring clamping is of grave significance and carries a high risk of death. It is fortunately excessively rare. Less uncommon is damage to more distal branches of AICA. The extent of brainstem damage in the event of loss of these vessels is variable and depends on the degree of anastomosis from PICA and SCA. It may give rise to fatal infarction of the lateral tegmental pons or the damage may be confined to the cerebellar peduncle, as pointed out by Hegarty et al. (**Figure 103.9**).[68] This may result in serious gait, balance and co-ordination problems. The distal branch in question may loop into and out of the IAM. The vessel must therefore be identified, separated from the tumour and preserved in order to avoid these potential problems. Feeding vessels from branches of AICA to the tumour may be cauterized close to the tumour but, as a rule, every attempt is made to preserve all arterial vessels encountered by remaining in the arachnoid sheath between the tumour and the neurovascular structures of the posterior fossa.

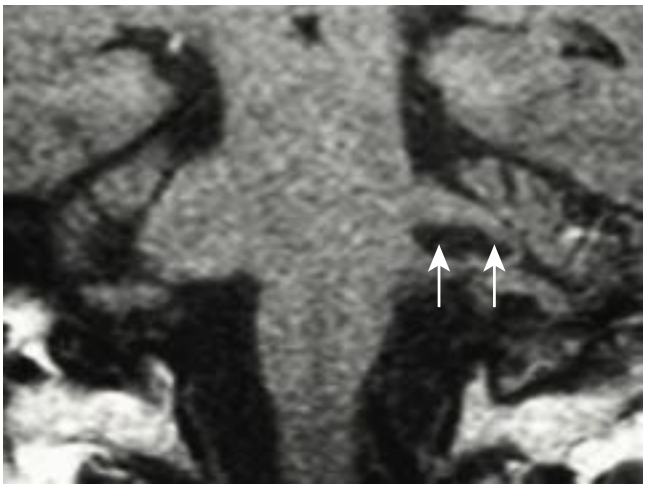


Figure 103.9 Peduncular infarct (arrowed).

VENOUS BLEEDING

Troublesome venous bleeding may occur during the petrosectomy in the translabyrinthine approach and during tumour removal itself. Bleeding from the mastoid emissary veins is readily controlled by a combination of bipolar cautery and the use of bone wax. During the skeletonization of the lateral, sigmoid and superior petrosal sinuses and the jugular bulb, inadvertent injury to the dura of these structures gives rise to dramatic venous haemorrhage. Despite this, careful use of haemostatic mesh (Surgicel) over the tear with compression using bone wax and a neurosurgical cottonoid usually solves the problem and allows the procedure to continue, as the dural sinus veins are a low-pressure system. Care must be taken to prevent air embolism but it should be emphasized that this is an exceptionally rare occurrence, especially since the sitting position for surgery has been abandoned in the UK. Excessive compression of the jugular bulb should be avoided as it may give rise to lower cranial neuropathies. In the experience of the authors it has never been necessary to ligate the lateral venous sinus or the internal jugular vein in the neck to control bleeding from the venous sinuses encountered during the petrosectomy.

During tumour removal itself, the petrosal vein (Dandy's vein) is invariably encountered. This fragile vein drains the brainstem and cerebellar hemisphere and is a tributary of the superior petrosal sinus. It is easily torn during tumour dissection and it is mostly safe to clip or cauterize and divide the vein rather than have to deal with the troublesome back bleeding from the superior petrosal sinus.[69]

Finally, numerous often quite substantial veins are encountered between the arachnoid sheet and the brainstem. These are best dissected away from the tumour and then coagulated if necessary, but the surgeon must be aware of the risk of venous infarction of the brainstem from the indiscriminate sacrifice of these vessels. Overall, while venous bleeding can be troublesome and occasionally dramatic, it is rare for it to lead to hypovolaemia and it is very uncommon to have to transfuse a patient during a VS resection. Finally, the incidence of air embolism during

VS surgery has declined significantly since the almost universal adoption of the supine or lateral position of the patient as opposed to the sitting position.

POST-OPERATIVE HAEMATOMA

The risk of a post-operative haematoma is greatest in the first 72 hours after the operation but continues for about a week. Failure to regain consciousness after surgery is the classic sign of a posterior fossa haematoma and necessitates immediate re-exploration of the operative site. Signs of a delayed haematoma in a patient who has already woken up from the anaesthetic include progressive hypertension, bradycardia, reduction in consciousness level and alterations in pupil size and reactivity. These signs should be recognized by assiduous post-operative neurological observation and recording of the Glasgow Coma Scale. If time permits, a CT scan will confirm the diagnosis but in the rapidly deteriorating patient immediate return to theatre and evacuation of the haematoma is required to save the patient's life. When the translabyrinthine approach has been employed, the wound can be reopened in the ward or the recovery room and the abdominal fat removed. This may bring about a rapid improvement in the patient's neurological status, and he may then be returned to theatre for more leisurely haemostasis.

Ventricular haemorrhage, whether intra-operatively or after surgery, is a rare but very serious complication. External ventricular drainage may help but the condition carries a high risk of death.[70]

In contrast, a small haematoma without neurological sequelae may be managed conservatively, and be left to reabsorb naturally. The incidence of serious post-operative haematoma is approximately 1% and contributes to the overall mortality risk of this type of surgery.[67]

BRAIN INJURY

Cerebellum

The cerebellum is at risk of injury during opening of the dura of the posterior fossa and during tumour removal itself. The mass effect of a large tumour will push parts of the cerebellum against the overlying dura, compressing the cerebellar surface vessels. Minor degrees of venous injury are tolerated without problems but more substantial injury is likely with prolonged cerebellar retraction during retrosigmoid surgery. A degree of encephalomalacia of the superficial lateral part of the cerebellar hemisphere is frequently noted on post-operative MR imaging, though this does not usually give rise to any clinical manifestations.[40] The surface of the cerebellum may become oedematous during removal of large tumours but the historic procedure of resecting the lateral one third of the cerebellum for access and creation of space for post-operative swelling is rarely required now with modern surgical and anaesthetic techniques. Less commonly, parenchymal injury or oedema extends into the deeper parts of the cerebellum. This may signify venous insufficiency of the cerebellum or a cerebellopontine haematoma. This type of injury may well leave the patient with prolonged or permanent ataxia.

Brainstem

Direct injury of the brainstem is avoided by maintaining the subarachnoid plane between the tumour and the brain. In small and medium-sized tumours the plane between the brain and the tumour is usually easily identified and adhesions between the two tend not to be particularly dense and are readily divided. As discussed above, vascular injury is avoided by careful dissection and preservation of arterial anatomy. With larger tumours, however, there is often a degree of malacia of the brainstem due to prolonged compression by the tumour. In these instances the brain is very soft and breach of the pial layer can occur easily. In addition, ischaemia of the brainstem due to traction during tumour removal may give rise to bradycardia or even asystole. Both respond to cessation of dissection of that particular part of the tumour and appropriate intra-operative resuscitative measures. Rarely, the procedure needs to be abandoned due to persistent changes in the vital signs. Direct injury of the brainstem parenchyma is uncommon and the more likely cause of serious or fatal injury is secondary ischaemia consequent to the tumour dissection or injury to vessels such as the AICA as described above.

Temporal lobe and seizures

Seizures after translabyrinthine or retrosigmoid surgery are extremely rare. This, however, is not the case for transtemporal (middle fossa) tumour removal. The middle fossa approach (invariably in an attempt to preserve hearing with a small tumour) involves extradural retraction of the temporal lobe. This carries a risk of seizures, as noted by the authors in two cases.[34] While the fits did not lead to a residual neurological deficit, in both instances the patients were legally obliged to refrain from driving until they were fit-free for a year. Long-standing electroencephalographic changes have been reported[71] in patients undergoing middle fossa VS surgery. In addition, injury to or occlusion of the vein or veins of Labbé, which drain the inferior and lateral temporal lobe, carries the risk of venous temporal lobe oedema and infarction leading to seizures, dysphasia or even loss of life. These veins drain into the distal transverse sinus so are potentially at risk from excessive packing of the proximal lateral venous sinus in order to control bleeding during translabyrinthine or retrosigmoid surgery.

Cranial neuropathies

FACIAL NERVE

Of all the potential sequelae of VS surgery, without doubt the one concern raised by patients above all others is that of post-operative facial function. Most patients expect to survive their operation, be free of disability and be tumour free. It is their facial function that is usually at the forefront of their minds. On this basis, a full and frank discussion with reference to one's own facial nerve outcomes is required in order to secure informed consent for the surgery. Facial nerve preservation refers to

anatomical preservation of the facial nerve, while facial function refers to the physiological function of the nerve at a defined time post-operatively. Both are determined largely by tumour size and experience of the surgical team and, to a lesser but important degree, by the nature of the tumour (solid or cystic)[55–58] and the surgical philosophy of the team. The latter is important. Those surgeons who attempt to remove every last bit of tumour may well find their facial nerve outcomes are less favourable than those who have a low threshold for leaving tumour remnants in order to maintain the anatomical and functional integrity of the nerve.[72–75] It is vital, therefore, when examining facial nerve outcomes, to put the results in context: what is the rate of residual or recurrent tumour in the series that is being studied? In the experience of the authors, if a small nubbin of tumour is particularly adherent to an attenuated facial nerve (often just medial to the porus of the internal meatus) then it reasonable to leave this remnant in order to preserve the facial nerve. Usually, imaging a year later shows the nubbin to have disappeared. If it has not disappeared, serial imaging almost invariably shows the size of the residuum to have remained static.[29]

Facial function is assessed using a grading system, of which the House-Brackmann (HB) system is the most common in general use and relatively easy to use. Nevertheless it is far from perfect and suffers the same criticism that is applicable to any system that tries to fit a dynamic spectrum of movement into a finite number of categories (in the case of the HB system, six categories).

Stratifying the patients by tumour size is helpful in presenting facial nerve results. For intracanalicular tumours and tumours with a maximum intracranial diameter on imaging of less than 1.5 cm, most large series publish facial nerve anatomical preservation rates approaching 100%.[76–78] This is in keeping with the authors' series in which loss of the facial nerve is rare when removing such small tumours. Facial function outcomes for this group is between 80% and 95% HB grade I or II. At this juncture a comment about what constitutes a good facial outcome is required. From the patient's perspective, anything less than normal facial function post-operatively represents a less than ideal outcome. However, the patient will invariably take into account the size of the tumour that he or she presents with (as will the surgeon when counselling the patient) and with larger tumours, HB grade II or even III may be considered satisfactory. When reporting results, therefore, by convention most surgeons consider HB grade I or II as a satisfactory outcome. HB grade III is not a satisfactory outcome for small or medium-sized tumours, though some surgeons fail to appreciate this point when presenting their results.

For medium-sized tumours (maximum intracranial diameter 1.6–2.5 cm), anatomical facial nerve preservation rates fall to around 90% with HB grade I or II outcomes between 80% and 90%.[78, 79] An interesting observation occurs for tumours greater than 2.5 cm intracranial diameter: the facial nerve outcomes decline in an almost inverse linear proportion to the size of the tumour.[80–82] However, this threshold may change with increasing experience of the surgeon. A meta-analysis of more than 10 000 patient outcomes showed a cut-off of 20 mm.[54] Overall, for large and giant (more than 4 cm) tumours, anatomical preservation of the nerve occurs in between 65% and 80% with normal or good facial function (HB I or II) in 50–70%.[83–85]

In assessing facial function, consideration must be given to synkinesis, either the involuntary closure of the eye when the patient smiles or eats or, less commonly, unwanted movement of the corner of the mouth in time with blinking. The phenomenon may detract from an otherwise good facial nerve outcome and cause the patient considerable distress. The judicious use of botulinum toxin may be necessary to minimize this phenomenon. The development of a multidisciplinary facial palsy service in centres offering skull base surgery has allowed improvements in the rehabilitation of patients with facial palsy.[86]

NERVUS INTERMEDIUS

The importance of the function of the nervus intermedius (NI) is perhaps overlooked when reporting the results of VS surgery. Understandably, the nerve is not in the forefront of the surgeon's mind when trying to remove a large tumour and preserve the facial nerve itself. Nevertheless, the morbidity of loss of NI function should not be underestimated. Difficulties with a dry eye (even with normal facial and trigeminal function), altered taste and dryness of the nose and mouth can be very troublesome for the patient.[87] Aberrant re-innervation leading to gustatory tearing can also be troublesome. Attempts should be made to preserve the nerve, though with larger tumours it is often impossible to identify it as a separate entity.

TRIGEMINAL NERVE

Tumours of less than about 2 cm intracranial diameter do not usually come into contact with the trigeminal nerve, which lies antero-superiorly and medial to the tumour. Smaller tumours may stretch the trigeminal nerve as the brainstem is displaced to the opposite side of the posterior fossa. Inadvertent injury to the trigeminal nerve during the removal of small and most medium-sized tumours is rare. For larger tumours, however, there is invariably indentation, stretching and compression of the trigeminal nerve to some degree. This may or may not be associated with trigeminal symptoms pre-operatively. Even large tumours do dissect off the nerve fairly easily in most instances, however, particularly if the surgeon remains within the arachnoid plane between the tumour and the nerve and therefore the incidence of trigeminal symptoms post-operatively lies between 3% and 15%.[88] Such damage can have grave consequences for the eye if there is a concomitant facial weakness, as the loss of corneal sensation with a dry eye (nervus intermedius) and incomplete eye closure puts the unprotected cornea at risk of ulceration leading to loss of vision.

ABDUCENS AND TROCHLEAR NERVES

Palsies of these two oculomotor nerves are uncommon.[84] The abducens nerve may be inadvertently injured during packing of the superior petrosal sinus for control of

haemorrhage from the sinus or from anterior tumour dissection. The resultant paresis invariably recovers over a period of several weeks to a few months. Damage to the trochlear nerve is extremely uncommon although in theory it may be at some risk of injury during anterosuperior tumour dissection towards the free edge of the tentorium cerebelli.

LOWER CRANIAL NERVES

Injury to the lower cranial nerves may cause significant morbidity and a protracted hospital stay, due to the effects on swallowing and the competency of the upper airway. The glossopharyngeal, vagus and accessory nerves are at risk during two stages of surgery: the petrosectomy during translabyrinthine surgery; and during the removal of the inferior pole of the tumour. The relationship of the internal meatus, the cochlear aqueduct, the jugular bulb and the lower nerves has been described above. By keeping above the cochlear acqueduct during skeletonization of the IAM, and by avoiding over-compression of the jugular bulb, damage to these nerves should be avoided.

In small and medium-sized tumours, the intracranial tumour resection puts the lower cranial nerves at almost no risk as long as the nerves are identified early in the procedure. With larger tumours the multiple nerve rootlets of the glossopharyngeal and vagus nerves are stretched and splayed over the inferior pole. Dissection of the tumour off these nerves is usually straightforward and their function is therefore almost invariably preserved. Post-operative lower cranial nerve palsies are uncommon (less than 1%) except in revision cases when fibrosis and distortion of the anatomy can make the dissection more difficult. In such instances, and in larger tumours, electrophysiological monitoring of the vagus using electrodes on the endotracheal tube (NIM TriVantage® EMG Tube) as well as the XIth and XIIth nerves should be considered. Finally, during surgery, manipulation of the IXth and Xth nerves can cause profound but temporary bradychardia and even asystole, and the anaesthetist needs to be warned when dissection of the lower pole of the tumour is taking place.

CSF leakage

Leakage of CSF after VS surgery is the commonest significant post-operative complication. CSF leak rates reported in the literature vary depending on the approach, the size of tumour, the extent of petrous bone pneumatization and primary versus revision surgery.[89–91] The literature is conflicting when comparing the incidence of CSF leakage after translabyrinthine, retrosigmoid and transtemporal approaches – several studies cite no difference and others cite a higher incidence after translabyrinthine surgery, while others cite a higher incidence after the retrosigmoid approach.[42, 67, 90–92] The leak may be classified as minor (requiring no additional surgical procedure to deal with it) or major, necessitating a return to theatre. A subcutaneous scalp collection of CSF with or without leakage through the wound is considered a minor leak, as it is usually remedied with reapplication of a firm pressure dressing and an additional full-thickness scalp suture at the site of leakage, which is often at the bottom end of the wound. Such collections and leaks tend to occur within the first week of surgery and can be dealt with at the bedside, without a need to return the patient to theatre. In addition, continuous lumbar CSF drainage for 3–5 days usually solves this problem. The latter may be used electively after all VS surgery or in response to scalp collections or leaks that persist despite the conservative measures described above. Lumbar drains, however, are not without their own problems. They inherently incur a degree of immobility in the patient at a time when one would wish to encourage mobilization to enhance vestibular rehabilitation and reduce the risk of venous thrombo-embolism. In addition, the drain represents a portal for sub-arachnoid infection and may lead to pneumocephalus if there is entry of air from the nasopharynx through the temporal bone into the posterior fossa as the CSF is siphoned off.[93] Pneumocephalus may lead to a significant neurological deterioration, particularly if the air collects in the ventricles or is under tension. The use of lumbar drains after VS surgery is therefore not universal and evokes debate amongst surgeons who undertake this type of surgery.

It has also been postulated that the inflammation associated with meningeal irritation may result in a spontaneous resolution of CSF rhinorrhoea post-operatively. This has not been our experience and we would advocate early intervention with reoperation and blind sac closure, combined with lumbar CSF drainage if necessary.[94]

Revision surgery and surgery following failed radiotherapy is considered more risky and results in poorer outcomes.[95]

CSF otorrhoea

An intact tympanic membrane at the time of surgery should guard against any leakage of CSF via the external meatus. Any injury to the tympanic membrane or external ear canal skin during VS surgery is rare. CSF otorrhoea has, however, been described in relation to the use of bioglue to seal the Eustachian tube opening and the middle ear.[32] The glue had led to an acute myringitis with perforation of the tympanic membrane and additionally failed to prevent CSF entering the middle ear.

CSF rhinorrhoea

Leakage of CSF through the temporal bone air cells via the Eustachian tube into the nasopharynx remains a troublesome complication that invariably prolongs the patient's hospital stay and often necessitates a return to theatre. Ultimately the leak has to be stopped lest the patient develops intracranial infection. In the retrosigmoid approach the air cell system is most commonly opened posterior to the lateral venous sinus and around the IAM. In both instances most surgeons utilize bone wax to obliterate these cells in an attempt to seal communications between the CPA and the temporal bone. During translabyrinthine surgery the temporal bone surgery is much more extensive

and air cell tracks anterior to the IAM and around the jugular bulb are potential conduits for CSF to enter the middle ear or Eustachian tube directly. In addition, subluxation of the stapes may have the same effect. On this basis several methods to reduce the risk of CSF rhinorrhoea have been described by various surgeons, illustrating that no single method is universally successful. These include using pieces of muscle, fat, fascia, bone wax and tissue glue to seal the areas described. In addition, some surgeons advocate routine lumbar drainage for a few days post-operatively.

Interestingly, there is evidence that despite packing the Eustachian tube at the time of surgery, the middle ear regains ventilation via the tube and, in addition, packing of the tube or waxing opened mastoid air cells didn't result in a reduction of CSF rhinorrhoea.[89, 96] However, like others, it is our practice to ensure the Eustachian tube is tightly packed and the middle ear cleft filled with fat.

Finally, there is the occasional patient who, despite all measures at primary and subsequent surgery, continues to suffer CSF rhinorrhoea. In these instances (less than 1%) the only remaining option is to undertake permanent CSF diversion such as a lumbo-peritoneal or ventriculoperitoneal shunt. It is postulated that in these patients there is a subclinical post-operative hydrocephalus that drives the persistent leak.

Intracranial infection

MENINGITIS, ENCEPHALITIS, CEREBRITIS

Meningitis after VS surgery is one of the more common serious complications occurring in 1% to 5% in the reported larger series.[79, 97] It is invariably associated with CSF leakage (usually rhinorrhoea) and may occur within the first week of surgery or as a delayed event weeks or even months later. In the latter situation the CSF leakage may have passed unnoticed by the patient and the surgeon. Most VS surgeons give prophylactic peri-operative antibiotics empirically as there is no formal evidence that this measure reduces the incidence of post-operative infections. The diagnosis requires clinical vigilance as headache and neck stiffness are not uncommon after VS surgery.[41] In addition, many patients develop low-grade pyrexia within the first week after surgery, which in part may be due to an aseptic meningeal irritation due to blood, air and bone dust in the subarachnoid space. If any doubts exist, a lumbar puncture will confirm the presence of a leucocytosis, though the causative organisms are often not isolated or cultured. The treatment regimen will vary from institution to institution but parenteral Vancomycin and Ceftriaxone are the current first-choice empirical treatment. CSF culture will guide ongoing management and, if sterile after 3–7 days, a diagnosis of aseptic meningitis can be made and the antibiotics stopped. This treatment schedule almost invariably resolves the problem, although rarely the infection may progress to a fulminant encephalitis or cerebritis, both of which carry a high mortality.

OUTCOMES

Tumour extirpation: Residual/recurrence

In the majority of cases undergoing VS surgery, the aim is to remove the tumour completely while maintaining perfect facial nerve function. It was previously thought unacceptable to subject the patient to the inherent risks of this type of surgery and then not remove the tumour in its entirety. However, it is fair to say that this philosophy has changed. While total removal has the obvious benefit of reassuring the patient that their tumour has gone and there is very little chance of recurrence, the evidence is very clear that the facial nerve outcomes are worse when comparing near-total to subtotal, and again in total versus near-total.[75]

There are instances where a planned subtotal removal procedure is reasonable: in patients with large tumours giving rise to hydrocephalus in the elderly; or in those who have concomitant medical problems that necessitate as short a procedure as possible. The residual tumour in these instances can then be monitored with serial imaging and the residuum dealt with by way of further surgery or stereotactic radiotherapy if it grows to a size that once again requires intervention.

The impression of the operating surgeon as to the extent of resection when a 'subtotal resection' has been performed is open to interpretation. It is considered important to document the size of the residual tumour with early post-operative contrast-enhanced MRI.[81] In addition, the post-operative imaging in patients who have undergone incomplete removal often shows no enhancing tissue at all.[28]

Following presumed gross total excision there is a documented rate of recurrence. Despite expecting it to be zero, it has been shown to be in the order of 1–3%. However, it goes without saying that a higher rate of recurrence is expected in situations where a visible quantity of tumour remains, either in subtotal removal or near-total removal, where in both there is lack of clarity as to what exactly is meant. Subtotal removal suggests a solid mass of tumour is left, whereas in near-total removal a linear remnant adherent to the facial nerve is all that remains. One series reporting rates of regrowth showed 3% of patients subjected to gross total excision had regrown, compared to 21% and 22% regrowth rates for near-total and subtotal resections respectively.[72] Choosing to stop tumour dissection short of obtaining a complete resection is usually a consequence of maintaining good facial nerve function. However, in addition to the facial nerve, attempting to preserve integrity of the cochlear nerve and functional hearing may impair a complete resection. This is more often the case in the middle fossa approach because the bone drilling required to visualize this area directly puts the inner ear structures (and therefore the hearing) at risk and tumour removal at the fundus is almost a blind procedure.[98] Intra-operative endoscopy may help in this situation.[46, 99] Finally, there is some debate about the frequency and length of imaging follow-up needed after surgery

before declaring the patient tumour-free. Practice varies from a single scan 1 year post-operatively (as advocated by the authors) to imaging 2, 5 or even 10 years after the surgery.

Hospital stay

The median hospital stay for patients undergoing VS surgery under the care of the authors is 7 days. The literature varies citing a hospital stay of between 5 and 10 days if the immediate convalescence is uncomplicated.[19] The commonest cause of delay in discharge from hospital is CSF leakage, particularly CSF rhinorrhoea. Management of this complication invariably prolongs the hospital stay, particularly if further surgery is required to rectify the leak. One study calculated an additional 13.3 days in hospital in patients who developed post-operative CSF leak.[32] The two causes of a more prolonged hospital stay (several weeks or more) are bulbar symptoms due to brainstem injury or lower cranial neuropathies and the development of meningitis.

Vertigo/balance/return to work or previous physical activity

Many patients with a VS describe a period of vertigo, dysequilibrium or imbalance when questioned directly about pre-operative symptoms. The gradual reduction in vestibular function on the affected side due to the tumour is compensated for by the opposite vestibular end organ, vision, proprioception and the central nervous system such that day-to-day balance is rarely a problem for most individuals before surgery.

Post-operative balance problems depend on the degree of pre-operative impairment, with those with a complete canal paresis on caloric testing seemingly unfazed by the loss of vestibular function. However, those with a functioning labyrinthine system pre-operatively have acute vestibular failure with a paralytic nystagmus and are functionally much worse for a few days until compensation can occur.[100] Other than for initial symptomatic relief, vestibular sedatives should therefore be avoided to allow for this process to occur. In addition, the implementation of vestibular-ocular reflex exercises further accelerates the rate of compensation.[101]

In an attempt to mitigate the impact of acute vestibular failure in patients undergoing translabyrinthine surgery for VS, a chemical labyrinthectomy with intratympanic gentamicin and focused vestibular exercises (prehab) have been shown to reduce vestibular dysfunction immediately after surgery, but also longer term.[102, 103]

In those individuals who have already slowly lost much of their vestibular function due to the tumour, the post-operative vertigo may be minimal. Over the ensuing weeks and months the majority of patients find that their balance recovery is such that they can resume their pre-operative occupation or return to a comparative level of physical activity.[104] However, as expected, an individual with a complete unilateral vestibular deficit cannot be expected to have perfect balance and this may be more noticeable in the dark or with sudden movements. The patient's perception of their balance dysfunction is important, with over 10% perceiving disequilibrium as disabling.[100] Patients with occupations that rely on fine balance therefore need to be counselled in this respect.

Tinnitus

Unilateral tinnitus is one of the cardinal symptoms of a VS. Occasionally it represents the sole presenting symptom.[105] Tinnitus probably remains the most troublesome symptom following surgery for VS. Most clinicians advise that patients presenting with tinnitus are very likely to have persistence of their tinnitus post-operatively and studies support this viewpoint.[106–108] An interesting observation described is that of gaze-evoked or enhanced tinnitus after VS surgery. This is probably a rewiring phenomenon in the brainstem.[107, 109]

Hearing preservation

In discussing the possibility of hearing preservation, a number of issues need to be considered. The commonest presenting symptom of VS is unilateral hearing impairment. As in any hearing impairment, the degree of resultant disability needs to be taken into account with respect to the better, often normal contralateral ear. This is well recognized in reconstructive middle ear surgery such as ossiculoplasty and stapedotomy, where the patient's perception of benefit will only be realised if the middle ear surgery brings the hearing within a defined level of the opposite ear (Belfast rule of thumb, Glasgow benefit plot).[110, 111] On this basis the audiometric criteria for considering hearing preservation surgery advocated by the authors is a pure tone average of 30 dB or better and a speech discrimination score of 70% or better in the affected ear, if the opposite ear is normal (Gardner Robertson class A).[112] This in itself significantly reduces the number of potential hearing preservation candidates. In addition, the tumour should be less than 1 cm diameter intracranially and be well away from the fundus of the internal meatus in order to have a realistic chance of preserving not just a functioning cochlear nerve but also the fine vasculature in the internal meatus that supplies the cochlea. In reality, few patients meet these requirements and in our experience of those that do, the hearing is preserved at the pre-operative level in one in three. In our experience, perhaps the best way to preserve good hearing in a patient with a small tumour is to leave the tumour alone and only intervene of there is evidence of growth on serial imaging.[6, 113] This philosophy of the place of hearing preservation surgery is not uniform by any means.[114] The literature is replete with difficulties when it comes to evaluating this aspect of VS surgery. First, much of the earlier literature fails to define what is meant by good hearing, useful hearing or serviceable hearing in the affected ear. This makes evaluation of hearing outcomes very difficult.[115] Second, many surgeons advocate attempts to preserve hearing at 50 db pure tone and 50%

discrimination scores in the presence of normal contralateral hearing. Some surgeons will even attempt to preserve any measurable hearing, although the utility of this is questionable. While such attempts are acceptable if no additional harm is done, the risk of a higher facial palsy rate (particularly in the transtemporal approach)[116] or a higher incidence of residual tumour in the retrosigmoid approach raises the issue as to whether such hearing preservation attempts are justified.

In attempting to preserve functional hearing, the proponents of both middle fossa and retrosigmoid approaches report good results, even in larger tumours.[117] Vast amounts of evidence exist arguing for one approach over another, although it seems that no one approach confers all the benefits and none of the complications.[118, 119]

Hearing preservation rates vary depending on the size of the tumour, the resultant tumour—nerve interface and the level of hearing pre-operatively.[120, 121] Continuous monitoring of the cochlear nerve during tumour dissection has been shown to improve the preservation of hearing.[122–124] In addition to the actual size of the tumour, the amount of tumour filling of the IAC also has an effect. In cases where there is some CSF lateral to the tumour the rate of preservation is also higher.[125]

Finally, more recent quality of life assessments of patients undergoing VS surgery suggest that the loss of the impaired hearing is not as significant a handicap as one might imagine[126] and, indeed, it is the experience of the authors that the loss of impaired distorted hearing actually allows the patient to gain better overall hearing using the normal contralateral ear alone. This observation is in part responsible for the more recent development in auditory rehabilitation described below.

HEARING REHABILITATION

Complete unilateral hearing loss is an inevitable consequence of translabyrinthine VS surgery and occurs in a large proportion of those undergoing other approaches, including those in which hearing preservation is attempted. Therefore the hearing handicap of single-sided deafness (poor sound localization, reduced intelligibility of speech in noise and overall ease of listening) should be minimized as much as is possible. Advances in hearing aid technology in the form of behind-the-ear aids utilizing wireless contralateral routing of signal have enabled excellent rehabilitation of VS patients at presentation, as well as following intervention.[127] Bone-anchored hearing aid (BAHA) technology has also developed and allows an alternative method of hearing rehabilitation.[128, 129]

As well as accessing the hearing in the contralateral ear, simultaneous or sequential cochlear implantation and translabyrinthine surgery has been performed with good results, both in patients with sporadic tumours and those with NF2.[25]

Quality of life

The patient's perception of their facial appearance, their hearing handicap, their ability to perform routine daily tasks of living and their overall quality of life is of greater importance to them than the surgeons' perspective of success in managing their condition. The emphasis on patient reported outcome measures (PROMs) is reflected across the whole medical literature and VS management is no exception. The development of the first disease-specific quality of life instrument, the Penn Acoustic Neuroma Quality of Life (PANQOL) scale has given the ability for all professionals managing patients with VS to report their outcomes in a similar manner.[130] The UK Skull Base community has adopted this measure as part of the compulsory prospective VS audit that is ongoing[131] (https://orioncloud.org).

At different stages of each individual patient's journey, a change in their perception of quality of life may be anticipated. Diagnosis is a time associated with significant uncertainty and stress and a subsequent reduction in quality of life.[132] Conservative management, where appropriate, provides the highest chance of maintaining a good quality of life. However, there remains an ongoing health and psychological burden in the requirement for regular imaging. Dizziness has the most significant impact on quality of life, with tinnitus also rated as having an impact. Hearing, interestingly, doesn't seem to influence quality of life.[133]

At the stage of intervention, and in particular surgery, the patient is most likely to experience a reduction in quality of life.[134] The potential impact on mobility, balance and facial function is condensed into a short period. This is reflected in the scores in the assessment tool up to 5 years. Longer-term follow-up has shown no significant difference between any of the three groups.[134]

Ongoing collection of quality of life and other surgical outcome data will provide guidance to those professionals involved in the management of VS; with this it is hoped that the standards can be further raised.

KEY POINTS

- The management of a patient with a vestibular schwannoma has evolved over the last 20 years such that many small tumours are managed conservatively.
- Surgery remains the treatment of choice for large tumours and continues to be a viable option for growing small- and medium-sized tumours.
- The outcomes of surgery are largely dictated by the size of the tumour and the experience of the team managing the patient.
- All patients with a diagnosis of vestibular schwannoma must be given the benefit of a multidisciplinary evaluation which includes neuro-otology, neurosurgery, radiation oncology and radiology.

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CHAPTER 103

STEREOTACTIC RADIOSURGERY

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SEARCH STRATEGY

Data may be updated using a PubMed or MedLine search using the following keywords: stereotactic radiosurgery, stereotactic radiotherapy, meningioma, pituitary adenoma and vestibular schwannoma.

OVERVIEW OF STEREOTACTIC RADIOSURGERY DELIVERY TECHNIQUES

Principles of stereotactic radiosurgery

The term 'stereotactic radiosurgery' is applied to techniques involving a well-defined co-ordinate base that enables the precise localization of a tumour and targeting of radiotherapy treatment. Localization may be achieved through the use of a fixed or removable headframe, or using the patient's own anatomy to determine a Cartesian based co-ordinate system. Using this with magnetic resonance imaging (MRI), it can be used to target pathological lesions including skull base tumours. Stereotactic radiosurgery uses ionizing radiation to ablate a volume of tissue, or to alter its biological activity, thus preventing further growth. The dose of radiation can be either delivered in a single treatment (stereotactic radiosurgery (SRS)) or in several fractions (stereotactic radiotherapy (SRT)). The decision of whether to deliver the dose in a single or multiple fractions will be based on the type of delivery equipment, and the requirement to allow nearby healthy tissue to recover in the intervals between each radiotherapy dose fraction. SRS is generally restricted to targets less than 3 cm in diameter and steep dose gradients are essential due to the risk of damaging adjacent normal tissue.

The delivery equipment for SRS can be broadly divided into two categories: modified conventional linear accelerators; and dedicated stereotactic devices. Both categories utilize enhanced imaging to determine tumour location and targeting, and a high-resolution collimation system to achieve sharp dose gradients.

MODIFIED CONVENTIONAL LINEAR ACCELERATORS

Modified conventional linear accelerators have the advantage that they offer flexibility for the workflow of a radiotherapy department, since they can be used to treat a wide range of indications. The equipment is readily available; however, a modification is often required to the machine to enable it for stereotactic use, such as a secondary high-resolution small field multi-leaf collimator (MLC). In order to correctly position the patient, additional stereoscopic X-ray images are often acquired, which, in conjunction with a modified treatment couch and patient fixation system, can achieve sub-mm delivery precision.

DEDICATED STEREOTACTIC MACHINES

Dedicated machines, such as the CyberKnife linear accelerator (Accuray) and the Gamma Knife unit (Elekta), utilize high-precision patient localization and high-resolution radiation beam collimation to deliver dose with sub-mm precision without need for modification.

The high collimation means the units are restricted to treating small volumes. The ability to deliver beams from multiple (several hundred) angles provides the steep dose gradient required to protect against normal tissue damage when using SRS.

The Gamma Knife unit uses a fixed array of 192–201 radioactive cobalt sources to deliver the dose to a patient wearing a rigid stereotactic frame to achieve precise targeting. The Gamma Knife was developed for intracranial SRS several decades ago and the current version has been subject to significant refinement. A CyberKnife unit uses stereoscopic imaging of the patient for precise localization without the need of a headframe (**Figure 103.1**). Since the linear accelerator on the CyberKnife unit is mounted on a robotic treatment arm it is not restricted to any angular position, unlike gantry mounted modified conventional accelerators. The size of the beams can be varied by changing the collimators, and complex dose distributions can be achieved by moving the patient and by blocking sources (Gamma Knife) or by changing the beam angles (CyberKnife). These variables allow treatment plans to be formulated that precisely match even irregular tumour volumes.

The Gamma Knife system uses a surgically attached headframe to enable localization to the machine. The Gamma Knife is dedicated to intracranial or skull base pathology and it is not possible to target disease extending into the neck. A CyberKnife unit uses digitally reconstructed radiographs of the skull from a planning CT scan to produce sub-mm localization. The system is also able to use the spine or fiducial markers to enable extracranial treatment delivery. Intracranial targeting accuracy of a CyberKnife machine is <0.5 mm, and <1 mm extracranially. Intrafractional patient movement during delivery is detected via the stereoscopic X-ray system and corrected by changes to the robotic delivery path, rather than repositioning the patient. Since the system does not require a headframe for positioning, there is no loss in delivery precision if the dose is delivered in one (radiosurgery) or over several (radiotherapy) fractions.



Figure 103.1 CyberKnife unit.

Patient treatment

Prior to any treatment being carried out, several preparation stages are required as well as offering the patient appropriate counselling and support.

Pre-treatment imaging is required for target definition; usually this is MRI but other modalities may be appropriate depending on the pathology of the target. Imaging (often computed tomography (CT)) is also required for localization and this needs to be performed using the treatment immobilization device. For stereotactic frame-based systems (e.g. Gamma Knife) this imaging is performed after application of the frame on the day of treatment. For stereoscopic imaging-based systems (e.g. CyberKnife) this can be done in advance. These images need to be transferred to the planning software. A multistage and multidisciplinary process then ensues, with the images from the various modalities being fused and the target and critical structures defined. A plan is subsequently produced that aims to highly conform the prescribed dose to the target and minimize the dose to the adjacent structures and organs at risk. This plan is subject to a rigorous schedule of checks before treatment can be delivered. The planning process often involves several specialist disciplines dependent upon local set-up and can include radiation oncology, neurosurgery, neuro-radiology and medical physics.

Treatment time depends on the system used and complexity of the target and plan. Typical delivery times are in the order of 1 hour. The patient is positioned on the couch using the system-appropriate immobilization device and localized by use of either a stereotactic headframe or imaging. Once this step is complete, treatment delivery can begin. If the patient moves, this step will need repeating. As with all photon treatments, the patient does not feel anything but can see and hear the machine moving. Treatment is generally delivered as an outpatient and general anaesthesia is not required, but it can be considered for young children.

Further information

For an extensive introduction to skull base and intracranial radiosurgery using all platforms, readers are referred to *Principles and practice of stereotactic radiosurgery*, edited by Chin.[1]

MENINGIOMAS

Role of radiosurgery in meningioma management

The majority of skull base meningiomas are benign and classified as WHO Grade 1.[2] Many are well demarcated; however, they can be difficult to excise completely due to risks of damaging adjacent neurovascular structures such as those within the cavernous sinus. They therefore represent an ideal target for consideration of SRS. Treatment may be considered following partial

resection, either to prevent regrowth or to improve symptoms. As a primary treatment, SRS can be used providing there is a high degree of confidence in the radiological diagnosis and early intervention is warranted. One of the main limitations of SRS for skull base meningiomas are dose constraints to the optic pathway, which is sensitive to the high doses per fraction delivered with this technique. Radiation induced optic neuropathy (RION) is rare if the dose is limited to < 8 Gray in a single fraction.[3] Where it is not possible to achieve safe optic pathway constraints (typically for lesions within 2 mm of the optic nerves/chiasm), fractionated radiotherapy treatment offers similar local control rates without significant risk of RION.

The timing of intervention with SRS or fractionated radiotherapy for skull base meningioma remains controversial. Contrary to surgery, the philosophy with radiotherapy is to treat while the tumour volume is low and prior to clinical deterioration. However, growth kinetics for benign meningiomas can be complex and difficult to predict. Some remain relatively indolent for many years and many small (sub-2 cm) skull base meningiomas do not cause any symptoms within 5 years, supporting an initial period of observation.[4] Given that observation carries a risk of increasing tumour volume, associated with a greater risk of toxicity with SRS, serial MRI scans and clinical examination are essential for active monitoring.

Clinical outcomes

Both SRS and fractionated radiotherapy offer effective treatment for skull base meningiomas with 10-year local control rates typically exceeding 85% (**Table 103.1**).[5–11] However, evidence is confined to retrospective studies and many fail to clearly distinguish outcomes between primary treatment at presentation, treatment immediately following surgery and treatment at progression with or without earlier surgery. In a retrospective multicentre analysis of 3768 patients with benign meningiomas, 5- and 10-year progression free survival (PFS) were 95.2% and 88.6% respectively with a permanent morbidity incidence of 6.6%.[6] Prescribed doses for benign meningiomas are typically in the range of 12–15 Gy with single fraction SRS.[12] Due to increased risk of morbidity SRS is typically used for tumours with volumes less than 8 cubic centimetres (generally < 3 cm). Multisession SRT (up to 5 fractions) using a platform such as CyberKnife is now being successfully used for larger volume tumours although more mature data are awaited.[13] Cranial nerve deficits have been reported following SRS for anterior skull base meningiomas. In one series of 763 patients with sellar/para-sellar meningiomas with mature follow-up, new or worsening deficits were seen in 9.6% of patients, with the trigeminal nerve being most adversely affected.[8]

TABLE 103.1 Selected published long-term local control rates using radiosurgery and fractionated radiotherapy for meningioma

Reference	Patients (n)	Technique	Median dose	Local control
Debus 2001[7]	189	FSRT	56.8 Gy	96% (10 years)
Milker-Zabel 2005[9]	317	FSRT	57.6 Gy	89% (10 years)
Kondziolka 2008[5]	972	GK	13 Gy	87% (10 years)
dos Santos 2011[10]	88	Linac SRS	14 Gy	83% (10 years)
Tanzler 2011[11]	146	CFRT IMRT FSRT	52.7 Gy	96% (10 years)
Sheehan 2014[8]	763	GK	13 Gy	82% (10 years)
Santacroce 2012[6]	4565	GK	14 Gy	87% (10 years)

FSRT, fractionated stereotactic radiotherapy; GK, Gamma Knife; CFRT, conformal radiotherapy; IMRT, intensity modulated radiotherapy; SRS, stereotactic radiosurgery; Gy, Gray.

Optic nerve sheath meningiomas

Optic nerve sheath meningiomas (ONSM) have an intimate circumferential relationship with the optic nerve and can interfere with its vasculature. The natural history of most ONSMs is variable but symptoms of optic pathway compression can occur including painless loss of visual acuity, visual field deficiencies, relative afferent pupillary deficits or proptosis.[14] Observation with serial neuro-ophthalmological assessment to determine rate of symptomatic progression is often considered initially. Presentation with significant optic pathway symptoms and progressive decline in function are considered indications for intervention. Surgical intervention including biopsy is associated with high risk of damage to vision, therefore primary radiation is often considered the treatment of choice. Due to the sensitivity of the optic pathways to high doses per fraction, fractionated radiotherapy is safer than SRS. With the use of highly conformal fractionated radiotherapy, vision commonly stabilizes, and improves in approximately one-third of patients.[15, 16]

Atypical and anaplastic meningiomas

A small proportion of meningiomas are WHO grade 2 or 3 due to atypical or anaplastic pathological features. These tumours have a high propensity for recurrence and can invade surrounding tissue. There remains a paucity of high quality data to guide management. In principle, SRS is generally not suited to tumours with an infiltrating margin. One combined analysis of series using SRS estimated a median 5-year PFS or 59% for Grade 2 and 13% for Grade 3 meningiomas.[17] The definitive role of SRS is unclear although in the authors' experience it has been helpful in selected cases including palliation.

KEY POINTS

- Five-year control rates in excess of 90% with acceptable neurological morbidity may be achieved with SRS for grade 1 meningiomas.
- The timing of intervention with SRS remains debated, given that many grade 1 tumours grow slowly.
- Fractionated radiotherapy is preferable to SRS for tumours in close proximity to the optic pathways or of larger volume unsuitable for resection.

PITUITARY ADENOMAS

Pituitary adenomas are classified by size and ability to hypersecrete hormones (functional versus non-functional adenoma (NFA)). Functional adenomas are typically microadenomas (i.e. <1 cm in size) presenting with clinical seqeulae of hormone hypersecretion while NFAs may be diagnosed incidentally or present with symptoms from local pressure such as visual disturbance.

Therapeutic goals include the reversal of symptoms from pressure or hormone hypersecretion, maintain normal hormone function and ideally prevent regrowth in the future through definitive treatment providing the risks are acceptable. Options available include surgical resection, medical therapy, fractionated radiotherapy, SRS and observation. A multidisciplinary approach is essential.

Non-functional adenomas

Symptomatic non-functional adenomas (NFAs) often require surgery to reverse clinical problems such as visual disturbance caused by optic pathway compression. However, complete resection may not be feasible, particularly if the tumour extends into the cavernous sinus. Furthermore, high late recurrence rates are seen, even in patients thought to have had a complete resection.[18] Despite potential high rates of recurrence, observation following initial surgery is still appropriate in the absence of adverse features, given that most tumours grow slowly and progression can be detected through serial imaging. SRS or fractionated radiotherapy are commonly reserved for recurrence or progression.

Although there is a lack of randomized data, a matched cohort comparison clearly confirmed that early adjuvant radiotherapy improves PFS over surgery alone.[19] A UK series with a median follow-up of 9.1 years reported actuarial PFS of 97% and 96%, at 10 and 20 years respectively, following radiotherapy.[20] However, concerns exist over the use of routine adjuvant radiotherapy, due to the risks of long-term consequences including hypopituitarism, potential increased of stroke and radiation induced cancers.

SRS offers an attractive alternative for low volume inoperable tumours (of an adequate distance from the optic apparatus) and is increasingly used in preference over fractionated radiotherapy (**Figure 103.2**). A retrospective combined analysis of 512 patients treated with SRS reported actuarial PFS of 95%, 91% and 85% at 5, 8, and 10 years respectively.[21] All patients were treated with Gamma Knife and the median follow-up was 36 months with 37.3% of patients completing 5 or more years of follow-up. Tumour volume was the strongest predictor of progression. New or worsened hypopituitarism was seen in 21% of patients. Similar local control rates have been shown with other SRS platforms.[22] The authors are not aware of any data confirming an increased incidence of stroke following SRS; however, dose to the adjacent carotid is often high and carotid stenosis has been documented as a rare event.[23] Steep dose gradients make it possible to reduce the dose to the hypothalamic-pituitary axis with some investigators suggesting safe limits to preserve function; however, mature data are lacking and tumour coverage should take priority.[24] Case reports of second malignancy following SRS do exist; however, one population-based study failed to show any increased risk.[25]

Functional pituitary adenomas

Excluding prolactinomas, where medical therapy is the primary treatment of choice, complete microsurgical resection is often considered the optimum treatment. However, cure through surgical resection may not always be possible due to local invasion and risks of injury to neurovascular structures. SRS is considered a useful adjunct for functional tumours, and may remove the need for ongoing medical therapy.

A review of retrospective data was recently published by Sheehan et al.[21] Although radiological control rates were high, endocrine remission rates varied considerably between series and did not reflect the high rates of local control. The review suggested that SRS was most effective for Cushing's disease where biochemical remission rates were typically in the region of 50% (range 0–100%). This was followed by acromegaly with an overall average endocrine remission rate of 43.6% (range 0–82%). The overall remission rate for prolactinomas was only 30% (range 23.3–41%).

Compared to surgery, there is a latent period of at least a year post-SRS prior to biochemical remission, during which medical therapy needs to continue. Higher doses are required to treat functional tumours; however, morbidity is generally low providing adequate clearance is achieved from the optic pathways.

KEY POINTS

- SRS can be used for low volume (typically <5 cc) recurrent or progressive non-functioning adenomas that are unsuitable for surgical resection.
- SRS is a useful adjunctive treatment in functional pituitary tumours; however, biochemical response rates are variable despite high rates of local control.
- Long-term follow-up is required to monitor for pituitary insufficiency following any radiation to the hypothalamic pituitary axis.

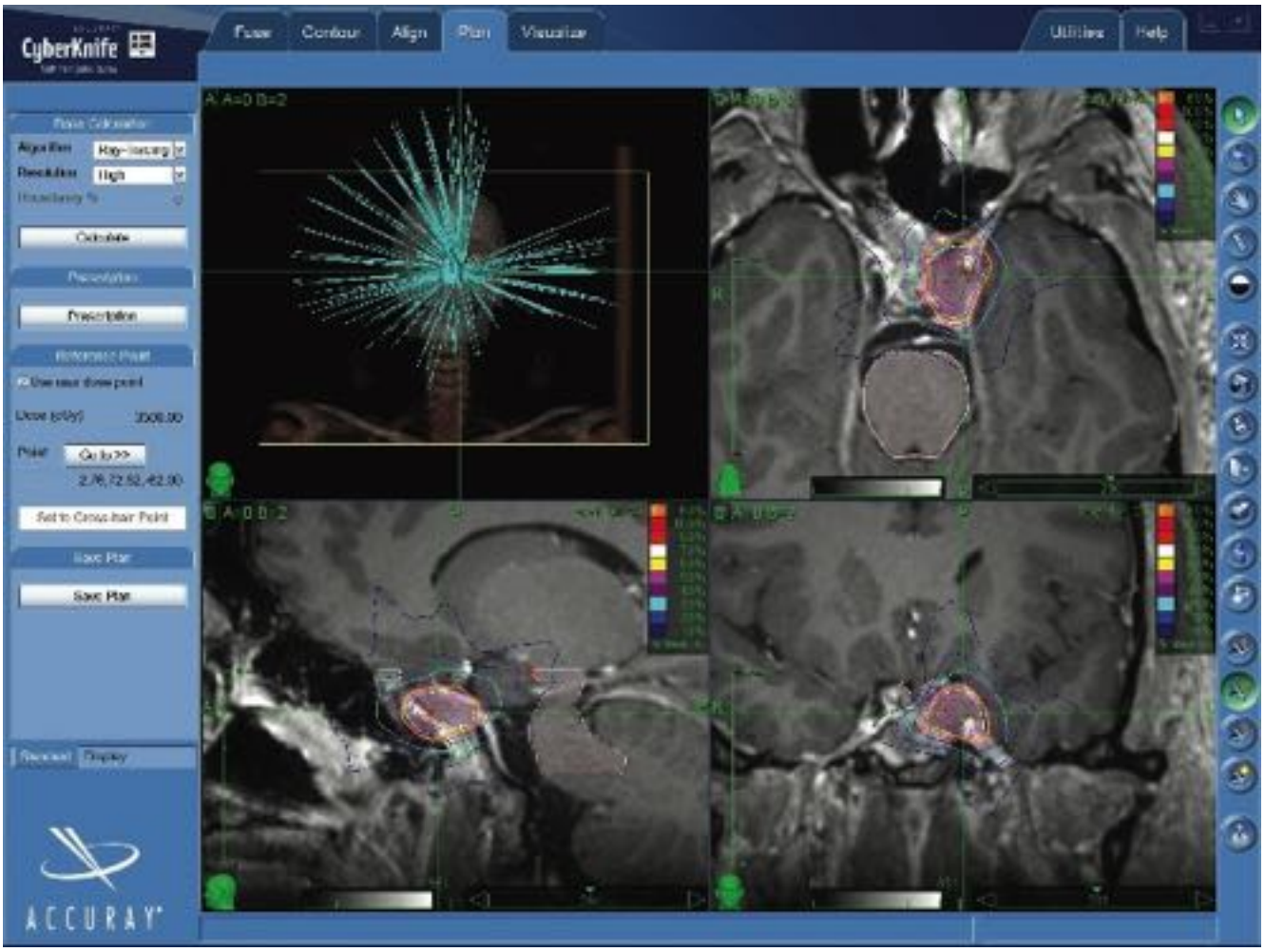


Figure 103.2 Example of pituitary tumour SRS plan (MultiPlan, CyberKnife, Accuray), showing high conformality and steep dose fall off to chiasm and carotids.

VESTIBULAR SCHWANNOMA

Although vestibular schwannomas (VS) are slow-growing, benign tumours, progressive enlargement can cause morbidity. Management strategies for VS include observation with serial MRI (usually indicated for small, newly diagnosed tumours), surgical resection and radiotherapy (both SRS and fractionated). Radiotherapy is used to stop growth (and hence avoid surgery) but is also used in some centres to preserve auditory function. However, the benefits of early intervention with regards to hearing preservation with radiation versus observation remain unproven and this issue continues to be debated.

Numerous published reports of high local control rates (predominantly using Gamma Knife) with minimal toxicities have established SRS as an accepted alternative to surgical resection (**Table 103.2**). [26–28] Similar outcomes have also been reported for other SRS platforms.[29] However, observation with annual imaging and hearing evaluation is believed to have a role in the management of small minimally symptomatic tumours, as SRS or resection can potentially compromise function.[30] Growth can be unpredictable, however, and if significant may limit future therapeutic options. As a result, deciding between early definitive treatment and observation can be challenging.

Currently, most centres prescribe 12–13 Gy to the margin of the tumour (**Figure 103.3**). Over time, the recommended dose has reduced from 16 Gy, which has lowered the incidence of cranial nerve complications, without adversely affecting local control rates.[31]

SRS is generally recommended for tumours < 3 cm in extra canalicular diameter with no significant brainstem compression, as tumour swelling post-radiosurgery can lead to 4th ventricular distortion with resultant obstructive hydrocephalus.

Following SRS, transient enlargement of the tumour followed by stability or even regression (i.e. 'pseudoprogression') is known to occur. In one series, 23% of VS treated with SRS underwent pseudoprogression, most commonly regressing at 24 months post-treatment.[32] As a result, only tumours that begin or continue to enlarge after 24 months post-SRS should be considered as treatment failures, and further intervention (most commonly resection) should not be rushed. The length of clinical and

TABLE 103.2 Selected published outcomes using stereotactic radiosurgery for vestibular schwannoma

Reference	Median follow-up (years)	Patients (n)	Platform	Median marginal dose (Gray)	Local control	Definition of local control	Cranial nerve V preservation (%)	Cranial nerve VII preservation (%)
23	2.9	232	Gamma Knife	15 Gy	97%	No additional surgical intervention	98.5%	99%
24	5.6	216	Gamma Knife	13 Gy	98.3% (10 years)	No additional surgical intervention	94.9%	100%
25	8.1	75	Linac	14 Gy	92%	No change in tumour volume	100%	92%
26	5	103	Gamma Knife	13 Gy	91.1%	No additional surgical intervention	99%	95%

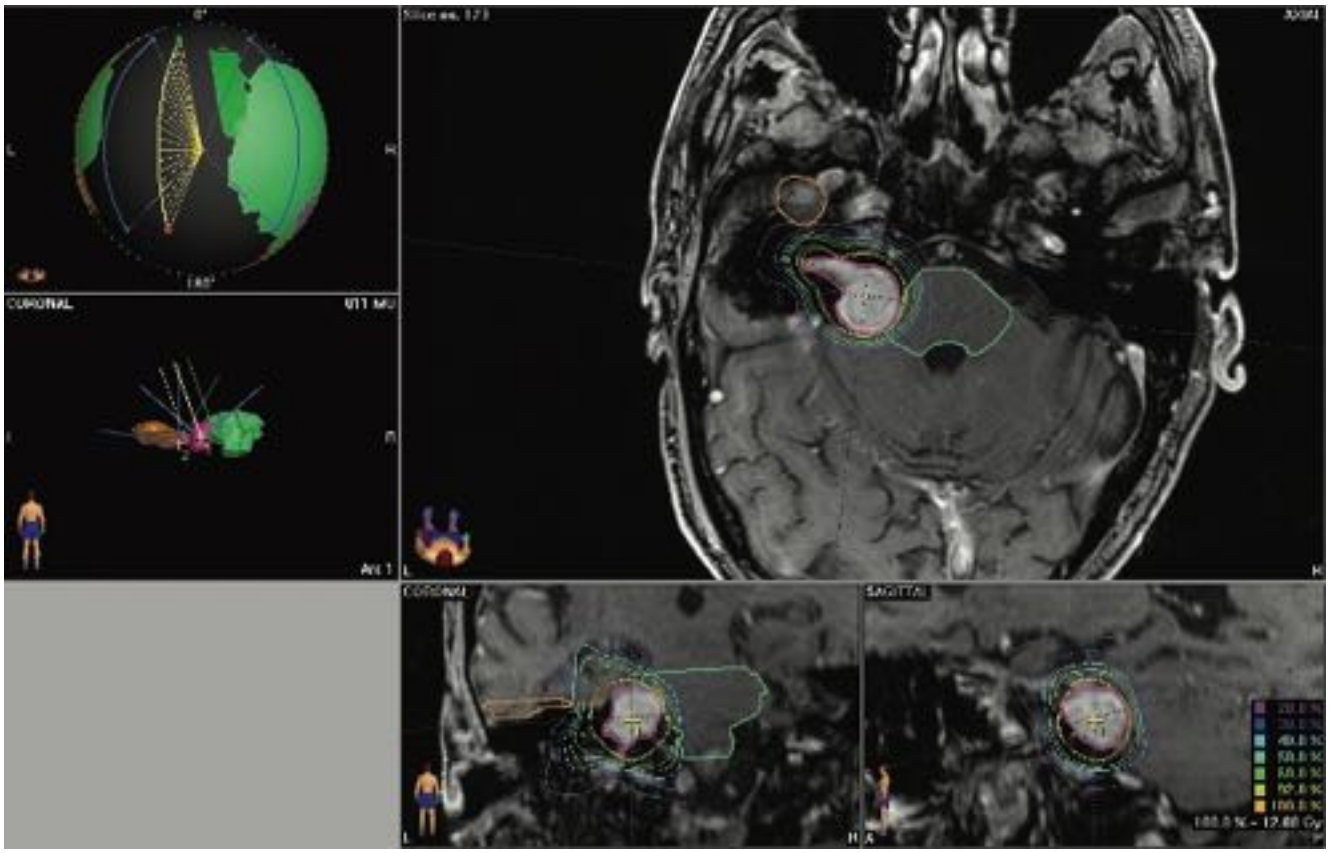


Figure 103.3 Typical dose distribution achieved using BrainLab generated SRS plan (linear accelerator platform).

radiological follow-up required post-SRS is controversial. In the authors' centre, patients are routinely imaged for 10 years post-radiosurgery.

Preservation of cranial nerve function

Following SRS with a marginal dose of 12–13 Gy, published trigeminal nerve preservation rates vary from 78.7% to 100%.[33, 34] The aetiology of trigeminal neuropathy post-SRS is complex and multifactorial. Factors associated with trigeminal dysfunction in published series include: tumour volume; maximum dose received by the trigeminal nerve and brainstem; and length of nerve irradiated.[33] The likelihood of trigeminal toxicity is no doubt higher for patients with tumour in contact with the nerve as a result of post-radiosurgery swelling.

The risk of a persisting facial nerve palsy post-SRS is low with contemporary radiosurgical doses and planning techniques (Table 103.2). Pre-existing facial nerve palsy and hemi-facial spasm is associated with an increased risk of worsening CNVII dysfunction after radiosurgery.[26]

The majority of patients with VS have unilateral sensorineural deafness at presentation. However, for patients with 'serviceable' hearing (Gardner-Robertson Grades I–II), some centres advocate early radiosurgery to preserve auditory function. To date there are no prospective, randomized data to inform practice, and large variations in hearing outcomes are reported between published series. Regis et al. reported prospective non-randomized hearing data for patients with intracanalicular VS managed with observation versus immediate Gamma Knife SRS with a marginal dose of 12 Gy. This series reported improved hearing preservation rates in patients who underwent early radiosurgery (77%, 70% and 64% at 3, 4 and 5 years, respectively) as compared to 75%, 52% and 41% in the observation group.[35] The authors of this chapter therefore support early intervention with SRS in patients with serviceable hearing.

There may be radiobiological advantages of fractionated radiotherapy over SRS in terms of reducing risk of cranial neuropathy and improving hearing preservation. Similar local control rates have also been reported.[36] No prospective comparison has been carried out with SRS to date, however.

Radiosurgery for NF2 vestibular schwannomas

Patients with neurofibromatosis type 2 (NF2) usually have bilateral VS and are therefore at risk of developing bilateral deafness, trigeminal and facial neuropathies at a young age. Results of surgery and radiotherapy for NF2-associated VS are worse than for sporadic unilateral tumours. Tumour control rates are lower and iatrogenic hearing loss is more common.[37, 38]

Plotkin et al. identified that vascular endothelial growth factor (VEGF) is expressed by VS and medical therapy with bevacizumab (an anti-VEGF monoclonal antibody) may improve hearing in some (but not all), as well as reducing tumour volume in the majority of patients with NF2-associated VS.[39] As a result, bevacizumab is increasingly being used as first line management in this patient group when intervention is required.

CHONDROSARCOMA AND CHORDOMA

Small, relatively well-demarcated residual tumours can represent an attractive target for SRS. There are some data reporting use of SRS for small chordomas or chondrosarcomas that are relapsing or remain visible targets after surgery.[40–42] However, series using fractionated radiotherapy with doses in excess of 70 Gy report the highest rates of local control.[43, 44] The local control rates for chondrosarcoma are more favourable than for chordoma. Fractionation permits treatment of a wider region including the presurgical bed. Delivering such high doses of radiotherapy in such close proximity to critical neural structures (in particular brainstem) demands maximum surgery and highly conformal techniques such as proton therapy, fractionated SRT or imaged guided intensity modulated photon radiotherapy. The role of SRS remains uncertain for those patients suitable for resection and high dose fractionated radiation.

GLOMUS TUMOURS

Glomus tumours (also known as paragangliomas or chemodectomas) are rare, benign tumours that can develop in a number of locations including in and around the ear (glomus tympanicum and glomus jugulare). If causing local mass effect on the brainstem, surgical resection is preferred. However, these tumours are often intimately involved with surrounding neurovascular structures and complete excision is usually impossible without significant morbidity. SRS and fractionated radiotherapy are both therapeutic options, given with the aim of tumour control rather than eradication. A meta-analysis, combining results from 276 patients, showed pooled local control following radiotherapy (both fractionated and SRS) as initial, combined and salvage treatment was good, ranging from 79% to 100%.[45] SRS is preferred for relatively small, well demarcated tumours that are in difficult surgical locations. Timing of intervention remains debated given that many tumours will remain relatively indolent for many years.

KEY POINTS

- SRS is an established therapeutic option for VS < 3 cm with no significant brainstem compression with local control rates in excess of 90% with marginal doses of 12–13 Gy.
- It is postulated that early radiosurgery preserves serviceable hearing, although prospective randomized data are lacking.
- Post-SRS cranial nerve preservation is high and treatment-associated complications are low.

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CHAPTER 104

NEUROFIBROMATOSIS 2

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords neurofibromatosis 2/NF2.

HISTORICAL OVERVIEW

The neurofibromatoses consist of at least three distinct autosomal dominantly inherited disorders: neurofibromatosis 1 (NF1), neurofibromatosis 2 (NF2) and schwannomatosis. Historically, these conditions were aggregated as generalized neurofibromatosis (von Recklinghausen disease). NF2 was first described by Wishart in 1822.[1] The heritable nature of NF2 was reported in 1920 by Feiling and Ward,[2] who described a three-generation family with vestibular schwannomas (VS). The autosomal dominant transmission (i.e. a 50% risk of transmission from an affected parent) was confirmed in a large family reported by Gardner and Frazier in 1930.[3] NF1 was delineated by von Recklinghausen in the late 19th century; Harvey Cushing aggregated NF1 and NF2 in 1916,[4] and his scientific stature was such that, despite reports that the conditions were different, many decades were to pass before the distinction between the two diseases was widely recognized. The neurofibromatosis literature prior to 1985 is scattered with cases of NF2 being described as part of von Recklinghausen disease, with cases of bilateral vestibular schwannomas being included in large series of NF1.[5] The conditions were recognized as separate entities only when the *NF1* and *NF2* genes were localized to chromosomes 17 and 22 in 1987 and NF2 was cloned in 1993, respectively. The two diseases were clinically delineated at a US National Institutes of Health (NIH) consensus meeting in 1987.[6] Subsequent studies have indicated that NF2 is a genetically homogeneous condition, with no evidence of exclusion of classical NF2 (bilateral VS) from the *NF2* locus on 22q. Indeed, genetic analysis in Manchester detects aberrations in the NF2 gene in 95% of familial cases. The initial studies on small numbers of families were confirmed in all studies of people with bilateral VS that have been undertaken since the identification of the *NF2* gene in 1993. However, it is possible that there is another closely linked gene that affects NF2 phenotype.

MOLECULAR GENETICS

The initial keys to identifying the *NF2* gene were studies of tumour material.

Chromosome studies of meningiomas highlighted chromosome 22 as the likely location of the *NF2* gene, since many tumours had loss of all or part of chromosome 22. Subsequent cytogenetic studies of schwannomas also confirmed that loss of chromosome 22 or its long arm was by far the most frequent event, which was later confirmed by DNA studies.[7] Seizinger et al. demonstrated loss of constitutional heterozygosity of chromosome 22, with DNA markers being lost in tumours from a person with NF2.[7] Linkage studies then confirmed that all affected members of a large family carried the same copy of chromosome 22.

The *NF2* gene was identified by the simultaneous discovery of constitutional and tumour deletions in a cell membrane-related gene, termed merlin or schwannomin.[8, 9]

Standard mutation techniques, such as single-strand conformational polymorphism analysis or denaturing gradient gel electrophoresis, detect 35–66% of pathogenic mutations. The majority of these mutations are protein-truncating mutations (frameshift or nonsense mutations) and lead to a smaller and probably non-functional protein product. C>T transitions causing nonsense mutations are the most common mutations in the *NF2* gene. Genotype-phenotype correlation studies have found that missense mutations (which result in a complete protein product) and large deletions (which result in no protein product) each cause predominantly mild phenotypes.[10–13] Patients with splice-site mutations have variable clinical manifestations. The more severe phenotype in patients with protein-truncating mutations may be due to a dominant negative effect, with mutant protein dimerizing with the normal product, leaving less wild type protein for tumour suppression. This is supported by a positional effect of mutations (particularly for meningiomas with more severe disease associated with mutations in exons 1–4 and mild disease in the last two exons with mutations).[13]

Some people with mild NF2 are somatic mosaics, in whom a smaller proportion of cells contain the mutated *NF2* gene. One of the clues to the existence of mosaicism in NF2 was that *NF2* mutations were harder to find in blood in sporadic cases than in people who had inherited the disease from an affected parent. In mosaicism, the initiating mutation happens after conception, leading to two separate cell lineages. The proportion of cells affected depends how early in development the mutation takes place. Evidence suggests that as much as 25–35% of NF2 cases without a family history of the disease are mosaic, carrying the mutation in too small a proportion of their cells to be detected from a blood sample.[14, 15] This accounts for the milder disease course in many individuals with unfound mutations, and since only a subset of germ cells will carry the mutation, there is less than a 50% risk of transmitting the disease to their offspring.[15, 16] However, if an offspring has inherited the mutation, they will be more severely affected than their parent, since the offspring will carry the mutation in all of their cells.[17] Mosaicism may be particularly likely in NF2 if the tumours are anatomically localized, for example, limited to one side.[16] The mosaic mutation can be detected by analyzing tumour material from an affected individual. If an identical mutation is found in two tumours from that individual, their offspring can be tested for the presence of the mutation. Other causes (apart from mosaicism) of the low detection rate for constitutional *NF2* mutations using standard techniques are large deletions and rearrangements at the *NF2* locus. The chances of mosaicism depending on age at onset and laterality and the risks to children can be found in recent publications.[15, 16]

NF2 PROTEIN

The NF2 protein (merlin or schwannomin) is a cell cytoskeleton-associating protein of 595 amino acids coded by the 17 exons of the *NF2* gene. The name 'merlin' derived from the sequence homology and shared overall domain structure with ERM (moesin, ezrin and radixin) superfamily of membrane-cytoskeleton linker molecules. Alternative splicing of exon 16 gives rise to two isoforms, which differ by the last C-terminal 11 amino acids. The NF2 protein is expressed in many tissues including neurons, Schwann cells and meningeal cells. Mutant NF2 protein impairs cell adhesion, motility and spreading properties, which are known to be essential for tumour formation. Loss of NF2 protein is the main and possibly the only rate-limiting step in the formation of all schwannomas and most meningiomas. Merlin is localized to the cell membrane/cytoskeletal interface and appears to have a number of different roles involving interactions including the Ras/Raf/MEK/ERK, FAK/Src, PI3K/AKT, Rac/PAK/JNK, mTORC1 and Wnt/β-catenin pathways.[18] NF2 links receptors at the plasma membrane to their cytoplasmic kinases to facilitate contact inhibition. However, NF2 can also interact with a large number of cytoplasmic and nuclear proteins that affect cell cycle progression. NF2 may also, through these pathways, reverse the functional inhibition of conventional tumour suppressor pathways.[19]

EPIDEMIOLOGY

An estimate of the birth incidence of NF2 (1 in 50 000) was made at the 1987 NIH Consensus Conference on the Neurofibromatoses, but this was not epidemiologically based. In the UK, population-based studies have estimated the birth incidence of NF2 as 1 in 33 000 people.[20, 21] A smaller study in southern Finland estimated the birth incidence as 1 in 87 000.[22] Both studies were based on hospital records and cancer registries, and the higher incidence in the UK study is likely more reliable as it is based on a larger area with longer follow-up. Initial estimates of prevalence suggested that as few as 1 per million were affected in the US.[6] The diagnostic prevalence in the UK population-based study is now 1 in 56 000.[21] This has probably increased due to early diagnosis and improved survival. The annual incidence rate for NF2 was estimated as 1 per 2 355 000, [20] equivalent to about 1 case per year for each health region in the UK or over 100 cases per year in the US. The birth incidence is significantly higher than the diagnostic prevalence because many people do not develop features of the condition until the third decade of life or later, and many other people die before this time. The diagnostic prevalence is likely to rise, as the median 15-year survival from diagnosis more than 20 years ago[23] will lengthen due to improvements in early diagnosis and tumour treatment.

Individuals who inherit a pathogenic mutation in the *NF2* gene will almost always develop symptoms by 60 years of age; [23] very occasionally, such people will have apparent non-penetrance (have no features of the disease even late in life). The transmission rate is 50% in the second generation and beyond, but the risk of transmission in apparently sporadic cases of NF2 is less than 50% due to mosaicism.[16, 17] Anecdotal evidence suggested that, in

many NF2 families, the disease course 'breeds true'. More recent research has established that the intra-familial correlation of clinical manifestations of NF2 (age at onset of symptoms, age at diagnosis and number of intracranial meningiomas) is greater than the inter-familial correlation. Stochastic events such as loss of the second *NF2* allele clearly play a role in the natural history of the disease, since the disease course is not identical even in monozygotic twins with NF2.

Initial indications of a maternal gene effect (earlier age at onset in individuals who inherited the *NF2* mutation from their mother) have not been borne out by further study,[20] nor is there evidence for anticipation (an increase in disease severity with successive generations). An apparent worsening of the disease course in affected females is due mainly to meningiomas, not on schwannoma growth and development, and there is no gender difference in risk of mortality.[23, 24]

CLINICAL MANIFESTATIONS, DIAGNOSTIC CRITERIA AND DIFFERENTIAL DIAGNOSIS

Bilateral VS are pathognomic for NF2. Schwannomas of the other cranial, spinal and peripheral nerves are very common. Meningiomas are present in about half of patients, primarily intracranially (including optic nerve sheath meningiomas) but also in the spine, and lifetime risk probably approaches 75%.[13] Less frequently, there are low-grade central nervous system (CNS) malignancies (ependymomas and very rarely gliomas) (**Table 104.1**).[23, 25–29] Individuals may present with cranial meningiomas or a spinal tumour long before the appearance of a VS.

Most individuals with NF2 present with hearing loss (often initially unilateral) that may be accompanied or preceded by tinnitus. Other vestibular presenting symptoms of VS are dizziness or imbalance. About 20–30% of cases present with an intracranial meningioma, spinal tumour or cutaneous tumour. When NF2 presents in early childhood, the first sign is often a non-VIIIth nerve tumour. Adult presentation is therefore quite different from paediatric presentation, in which VS causes only 15–30% of initial symptoms. There have been a number of recent reports of mononeuropathy in NF2, which is most common in people who present at young ages. Mononeuropathy affecting the facial nerve causes facial palsy similar to Bell's palsy, which does not fully recover. Some children present with wasting of muscle groups in a lower limb, similar to polio, which again does not fully recover. In adults, a more generalized polyneuropathy develops in about 3–5% of patients, often associated with an 'onion bulb' appearance on nerve biopsy.[7] This can progress, leading to severe muscle wasting and even death.

Ophthalmic abnormalities are very common in NF2. Between 60–80% of people have cataracts,[7, 10] which are usually presenile posterior subcapsular lenticular opacities that rarely require removal. Cortical wedge opacities are also common and may be present from near birth. Optic nerve sheath meningiomas and retinal hamartomas can cause visual impairment in the first years of life; misdiagnosis of each of these abnormalities as retinoblastoma has led to the eye being removed in the first few years of life.

Skin abnormalities are useful in diagnosis, but cutaneous features of NF2 are much more subtle than those seen in patients with NF1. About 70% of NF2 patients have skin tumours but only 10% have more than 10 skin tumours and there appear to be at least three different types. The most frequent type is a plaque-like lesion, which is intracutaneous, slightly raised and more pigmented than surrounding skin, often with excess hair (**Figure 104.1**). More deep-seated subcutaneous nodular

TABLE 104.1 Clinical characteristics of NF2 patients in four studies

Characteristic	Study			
	Kanter et al.[26]	Evans et al.[23]	Parry et al.[27]	Mautner et al.[28]
Number of cases	73	120	63	48
Number of families	17	75	32	44
Sporadic cases	0	45	17	44
Mean age at onset (years)	20 (of 59)	22	20	17
Intracranial meningiomas (%)	18	45	49	58
Spinal tumours (%)	N/A	26	67	90
Skin tumours (%)	32 (of 73)	68 (of 100)	67	64
>10 skin tumours (%)	N/A	10 (of 100)	N/A	N/A
Café-au-lait macules (%)	42 (of 31)	43 (of 100)	47	N/A
Cataract (%)	N/A	38 (of 90)	81	62
Intracranial astrocytoma (%)	N/A	4.1	1.6	N/A
Ependymoma (%)	N/A	2.5	3.2	6.0
Optic sheath meningioma (%)*	N/A	4.1	4.8	8.0

* In Mautner et al.[29] the frequency of optic nerve sheath tumours is for all histological types (i.e. schwannomas and meningiomas).



Figure 104.1 Plaque-like lesions on the arm of a patient with NF2. These are raised, often slightly pigmented lesions that are also frequently hairy.

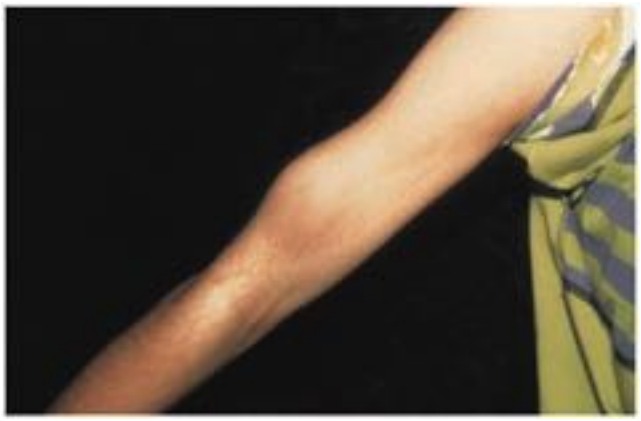


Figure 104.2 Subcutaneous schwannoma on a major nerve in the upper arm in a patient with NF2.

tumours can often be felt, sometimes on major peripheral nerves. These tumours are detected as a fusiform swelling of the nerve with thickened nerve palpable on either side (Figure 104.2). There are also occasional intracutaneous tumours similar to those in NF1. The great majority of these tumours are schwannomas, but occasional definite neurofibromas may be found.

The Manchester (modified NIH) diagnostic criteria for NF2 are shown in Box 104.1. The original NIH criteria have been expanded to include patients with no family history who have multiple schwannomas and or meningiomas but who have not yet developed bilateral VIIIth nerve tumours. Constitutional mutations in the *NF2* gene are found as frequently in patients who fulfil these modified criteria as in sporadic cases with bilateral VS (Box 104.1). This justifies future inclusion of these individuals as having 'definite' NF2, rather than having only one criterion (bilateral VS) for 'definite' NF2 in isolated cases. In addition, the inclusion of criteria for 'probable' NF2 (unilateral VS < 30 years plus other NF2 criteria, or two or more meningiomas plus other NF2 criteria) is a helpful addition. Since 50% of cases are new mutations, the modified criteria increase sensitivity but are unlikely to reduce

BOX 104.1 Diagnostic criteria for NF2 (these include the NIH criteria with additional criteria)

Bilateral vestibular schwannomas or family history of NF2 plus:

- unilateral VS *or*
- any two of: meningioma, glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities.

Additional criteria:

- unilateral VS plus any two of: meningioma, glioma, neurofibroma, schwannoma, and posterior subcapsular opacities *or*
- multiple meningioma (two or more) plus unilateral VS *or* any two of: glioma, neurofibroma, schwannoma, and cataract.

Note: 'Any two of' refers to individual tumours or cataract, not to tumour types.

specificity because chance associations of typical NF2 disease features in people without NF2 are extremely rare. A new scoring-based system for diagnosis, the so-called 'Baser' criteria, has also been developed.[30]

The main possible differential diagnostic dilemmas are in people with multiple non-cranial schwannomas who do not have a family history of NF2. All require a cranial MRI scan. Some of these people develop NF2 and others are somatic mosaics. There are nonetheless a small group of people with tumours largely confined to the spine and subcutaneous nerves, with sparing of the VIIIth nerve, who do not have a constitutional *NF2* mutation detection using conventional techniques.[31, 32] These individuals may pass the condition on to their children, and in families where this happens there is still tight linkage to the *NF2* locus, although *NF2* mutations are found in only a minority of patients with this variant form of the disease.[32] Around 50% of familial cases and 10% of sporadic schwannomatosis cases have now been shown to be due to *SMARCB1* mutations.[32] Confusion with NF1 is unlikely since only 1–2% of NF2 patients have more than 6 café-au-lait macules and Lisch nodules are rare in NF2. Nonetheless, review of tumour histology is a wise precaution in equivocal cases. NF1 is extremely unlikely in a person with a schwannoma who does not meet the NIH criteria for NF1; conversely, NF2 is very unlikely in a person with multiple neurofibromas.

NEURORADIOLOGY

Several groups of individuals are at risk of having NF2 and should be investigated using MRI. These are people with a family history of NF2; people under 30 years old who present with a unilateral VS or meningioma; people with multiple spinal tumours (schwannomas or meningiomas); and people with cutaneous schwannomas.[16] The 'gold standard' in terms of diagnostic precision

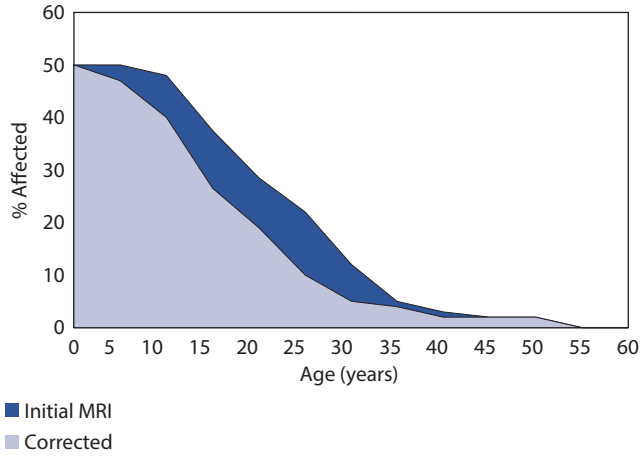


Figure 104.3 Decrease in risk from 50% by age of an individual with a normal cranial scan and an affected parent with NF2.

is magnetic resonance imaging (MRI) with gadolinium enhancement. Initial assessment should include full spinal imaging in addition to a cranial scan. MRI will now detect tumours as small as 1–2 mm in diameter on cranial and spinal nerve roots. Many of these small spinal tumours will never lead to symptoms. Using MRI of the full spine, there are tumours in 80–90% of NF2 patients[28] but only 30% of these patients have symptomatic spinal tumours.[23, 26, 27] Intramedullary tumours, often associated with a syrinx, are mainly found in the upper cervical spine and brainstem. On biopsy, these tumours are usually low-grade ependymomas and the great majority do not progress. Another common finding is schwannomas on other cranial nerves. The Vth nerve is most frequently affected. It is rare for non-VS cranial nerve schwannomas to grow to a size where surgical excision is required. Meningiomas are detected on MRI as enhanced areas on the meninges around the spinal cord, brain or optic nerves. They can form confluent areas on scan or 'meningioma en plaque'. The growth rates of VS are often slow but are extremely variable; on average, growth rates are higher in younger patients.[13] Meningiomas usually have faster growth rates than VS.

CT scans have been largely replaced by MRI due mainly to their poor sensitivity at detecting small VS (**Figure 104.3**). Some NF2 patients have intracranial calcification, but this sign is not useful enough in diagnosis to supplement MRI with CT. Without firm clinical justification, repeated CT scans should be avoided in NF2 due to the tumour-prone nature of the disease and the possibility of radiation-induced tumours.

PATHOLOGY

The main tumour sites, their frequency and pathology are presented in **Table 104.1**. As previously noted, schwannomas can develop at all locations in the body where there are nerves with Schwann cells. The reason for the predilection for the superior vestibular branch of the VIIIth cranial nerve is unknown. Schwannomas are encapsulated tumours of pure Schwann cells, growing around the nerve that may contain blood vessels and have areas of sheets in intertwining fascicles (Antoni A) and looser arrangements (Antoni B). The tumours stain for S-100 protein and vimentin. In NF2, schwannomas tend to be more multifocal and have a more lobular architecture than sporadic tumours.[33] Spontaneous malignant transformation of these tumours to malignant peripheral nerve sheath tumours is recognized, but is more than 10 times as likely to happen after radiation treatment.[34] The background rate of 0.5% for CNS malignancy in NF2 is also very much less than for NF1. A small proportion of nerve-related tumours in NF2 are pathologically delineated as neurofibroma. In these tumours, there is an admixture of cell types (Schwann cells, fibroblasts and mast cells) and the tumour usually has identifiable axons within it. Neurofibromas are mainly found in the skin (where they are still outnumbered by schwannomas by a factor of 5–10) but are also found on the spinal nerve roots. Neurofibromas in NF2 do not develop intracranially. There is currently no evidence of histological or molecular differences between neurofibromas in NF1 and those in NF2. Halliday et al.[35] showed that, in a series of spinal schwannomas and neurofibromas, all spinal tumours in patients with NF1 were neurofibromas, while, with one exception, all spinal tumours in patients with NF2 were schwannomas (one patient had a mixed tumour). In contradistinction to NF2, schwannomas and meningiomas are not found in excess in NF1.[36]

The second most characteristic tumour of NF2 is meningiomas, which usually develop supratentorially in the falx and around the frontal, temporal and parietal regions. Surgical excision of meningiomas around the spinal cord can be difficult. Although there are different histological types of meningioma (meningothelial, fibroblastic and transitional), there is no evidence for a clinical subdivision into NF2-related and non-NF2 related meningiomas. Collision tumours consisting of a schwannoma and meningioma are sometimes seen, particularly in the cerebello-pontine angle. Antinheimo et al.,[22] in a study of all meningiomas and schwannomas in an 11-year period in the Helsinki area, found that 3% of schwannoma patients and 1% of meningioma patients had NF2. A further 2% of schwannoma patients and 4% of meningioma patients had multiple tumours without fulfilling clinical diagnostic criteria for NF2. The great majority of NF2 patients do not present with an isolated tumour, and there is only a small risk of NF2 after a truly isolated VS (no other features of NF2 on clinical examination or scan).[37] However, it is important to recognize that as many as 10% of those presenting in childhood with an apparently isolated meningioma develop NF2.

Low-grade ependymomas and occasionally gliomas also develop; they are very indolent and rarely metastasize. The primary location for these tumours is in the cervical spine and brainstem.

Recently a new era in drug therapy was heralded by evidence that the VEGF antibody bevacizumab had efficacy in shrinking growing schwannomas in NF2.[38]

CLINICAL MANAGEMENT

NF2 presents complex management issues and patients should be managed by a multidisciplinary team consisting of a neurosurgeon, otolaryngologist, audiologist, ophthalmologist, neuroradiologist and geneticist. Surgical results are certainly far better when managed by an experienced team.[39, 40] Indeed there is now firm evidence of a statistically significant reduced risk of mortality for NF2 patients managed at speciality centres in the UK.[25] Radiation treatment can have a role for patients who have particularly aggressive tumours, who are poor surgical risks or who refuse surgery. Teams that are experienced in the positioning of brainstem implants can offer partial auditory rehabilitation to those who are deaf, although results are still behind those achievable for cochlear implants. Because detection of tumours at an early stage is effective in improving the clinical management of NF2, presymptomatic genetic testing is an integral part of the management of NF2 families.

Once a mutation has been identified in an affected individual, a 100% specific test is available for that family. Linkage analysis is still possible in rare families where no mutation is identified. In sporadic cases, testing of a tumour specimen usually identifies the underlying mutation and creates a test for offspring, especially in those with mosaic disease.[15, 16] Age at onset curves aid genetic counselling; for example, it can be seen that the risk of having inherited NF2 for an asymptomatic at-risk individual of 25 years of age, prior to screening, decreases to 25% (see **Figure 104.3**).[16, 41] At-risk individuals who have been shown not to have inherited the mutated *NF2* gene do not need further follow-up.

OUTCOMES

Even with improvements in microsurgery and use of radiation therapy, the great majority of individuals with NF2 become completely deaf. The tumours in NF2 are more difficult to treat than those of sporadic unilateral VS because NF2 VS are often multifocal, appearing like a 'bunch of grapes' around the vestibular nerve in particular. Histologically, NF2 VS are more lobular and less vascular than their sporadic counterpart,[33] which leads to a greater risk of facial nerve damage in NF2. Loss of facial nerve function and the resultant disfigurement is one of the most feared aspects of the condition for many people with NF2, although in good surgical hands this complication is now much less common.[39, 40] Patients may also be severely disabled by a combination of poor balance, visual problems and weakness due to spinal tumours. Indeed, many people with severe NF2 become wheelchair-bound in early adulthood, and many with severe, multi-tumour disease die in the second and third decades of life.

SCREENING PROTOCOL

Children of affected patients are at 50% risk of NF2 and screening for the disease can start at birth. Cataracts can affect vision in early life and other tumour implications are present in the first 10 years of life, particularly intracranial meningiomas. Screening for VS should start at 10 years of age because it is rare for VS to become symptomatic before then, even in severely affected families. Annual audiological tests, including auditory brainstem response, are still a useful adjunct to MRI.[41] Surgery is unlikely to be more successful for tumours <6 mm in diameter than for tumours 6–10 mm in diameter, but VS growth is higher in younger patients. Even in multiple affected patients of similar ages in NF2 families, however, there can be dramatic differences in VS growth rates. For these reasons, MRI screening every 2 years for those under 20 years old and every 3 years for those aged over 20 years should be sufficient for asymptomatic at-risk individuals without tumours. The initial MRI scan can be at about 10–12 years old, or earlier in severely affected families. Once tumours are present, MRI screening should be annual. Spinal tumours are found very frequently on MRI, as discussed previously. While only 30% of patients with spinal tumours have symptomatic tumours that may require operation, a full annual neurological examination is a wise precaution. In most families, it is now possible to develop a genetic test so that only those individuals who have inherited an *NF2* mutation need to be followed.

FUTURE PROSPECTS

Localization and cloning of the *NF2* gene has allowed precise diagnosis when a specific mutation is found in a family. Clinical factors that are closely related to mutation type, such as age at onset or age at diagnosis, predict the risk of mortality and VS growth rate more strongly than the type of constitutional *NF2* mutation. This may be particularly useful in patients with new mutations, in whom insight into the likely speed of tumour progression and risk of other tumours may not be apparent, but it should be noted that such aggregate correlations may be less useful in predictions for individual patients. DNA predictive testing for 70% of families is available with flanking markers or mutation testing, but there is currently little demand for prenatal NF2 diagnosis in the UK. A less controversial option may be pre-implantation diagnosis, which is being evaluated for other genetic diseases such as familial adenomatous polyposis and cystic fibrosis.

Replacement of the tumour suppressor product in the tumours through viral vectors or direct recombination of the *NF2* gene, although requiring great advances in our knowledge, could be very rewarding. Use of newer drugs, such as anti-angiogenesis and drugs targeted at the NF2 pathway, may also offer promise.[42]

KEY POINTS

- NF2 is an autosomal dominant condition caused by mutations in the NF2 gene on chromosome 22q.
- De novo cases have a high chance of having mosaic disease where the genetic mutation is present in only some of the cells and transmission risk is lower to children.
- Although treatment is primarily surgical, newer drug therapies particularly with bevacizumab are showing promise.

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CHAPTER 105

NON-VESTIBULAR SCHWANNOMA TUMOURS OF THE CEREBELLOPONTINE ANGLE

Simon K.W. Lloyd and Scott A. Rutherford

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SEARCH STRATEGY

A Medline search the MESH headings Cerebellopontine Angle OR CPA was carried out. A further search was performed for the following MESH headings: neoplasm, tumour, meningioma, epidermoid cyst, CPA cholesteatoma, arachnoid cyst, glomus jugulare, lipoma, dermoid cyst, facial schwannoma, trigeminal schwannoma, vagal schwannoma, cranial nerve neoplasms, glossopharyngeal schwannoma, jugular schwannoma, chondrosarcoma, chordoma, endolymphatic sac, cochlear schwannoma and haemangioma. A search combining the first and second searches was then performed. Finally, the headings vestibular schwannoma and acoustic neuroma were excluded. Additional searches for other rarer pathologies were also performed.

INTRODUCTION

Lesions of the cerebellopontine angle (CPA) are uncommon, making up 6–10% of intracranial tumours; 80–90% are vestibular schwannomas (VS), with the remaining 10–20% a heterogenous mixture of predominantly benign pathologies, although malignant also occur.[1–9] Pathology may arise from any of the anatomical structures that are found within or adjacent to the CPA. **Table 105.1** summarizes the types of pathology that may occur. Meningiomas and epidermoid cysts are the commonest non-vestibular schwannoma tumours of the CPA, making up approximately 10% and 6% respectively in this location.

SYMPTOMS AND SIGNS OF NON-VS CPA TUMOURS

Lesions of the CPA cause damage to the neurological structures traversing the CPA and it is not usually possible to differentiate between different pathologies based on symptoms and signs. Most present with audiovestibular compromise in the form of sensorineural hearing loss, tinnitus or vertigo.[7, 10, 11] Other cranial nerves may also be affected resulting in altered facial sensation, facial weakness, twitching or spasm and lower cranial nerve weakness depending on the position and nature of the lesion.

Larger tumours also cause brainstem compression that may result in ataxia, headache, hydrocephalus and, in the extreme, may compromise brainstem reflexes, particularly respiratory drive. Onset of symptoms and signs is usually insidious.

It is important to note that the majority of patients with these clinical features have no tumour but have other non-neoplastic pathology such as ischaemic disease, migraine or other neurological conditions.

IMAGING OF NON-VS CPA TUMOURS

Where symptoms and signs are often unhelpful in differentiating between CPA pathologies, modern radiological techniques have, in contrast, revolutionized the diagnosis of CPA pathology. This paradigm shift in the ability to diagnose and differentiate between CPA pathologies has resulted in fundamental philosophical changes in the management of CPA pathology with conservative management and stereotactic radiosurgery becoming increasingly popular in the management of such lesions.

Magnetic resonance imaging (MRI) is the gold standard imaging modality. It provides excellent definition of soft

TABLE 105.1 Differential diagnosis of non-vestibular schwannoma lesions of the cerebellopontine angle

	Benign	Malignant
Lesions arising from the CPA	• Meningioma • Epidermoid cyst • Arachnoid cyst • Trigeminal schwannoma • Facial schwannoma • Lower cranial nerve schwannoma • Lipoma • Dermoid cyst • Tuberculoma • Sarcoid granuloma • Neurenteric/enterogenous cyst • Trigeminal ganglioneuroma • Solitary fibrous tumour • Melanocytoma • Lipomatous glioneurocytoma • Benign glandular peripheral nerve sheath tumour • Neurocytoma	• Metastases (breast, gall bladder, nasopharynx, parotid) • Malignant melanoma • Lymphoma • Neuroectodermal tumour • Malignant peripheral nerve sheath tumour • Haemangiopericytoma
Temporal bone lesions involving the CPA	• Cholesterol granuloma • Glomus jugulare • Haemangioma	• Squamous cell carcinoma • Chondrosarcoma • Chordoma • Endolymphatic sac tumours (Papillary adenoma/adenocarcinoma) • Plasmacytoma
Intra-axial lesions involving the CPA	• Low grade glioma (Ependymoma/Astrocytoma) • Choroid plexus papilloma • Glioependymal cyst • Lipomatous hamartoma • Cysticerosis • Haemangioblastoma • Plasma cell granuloma	• High grade glioma (Glioblastoma/Malignant astrocytoma) • Medulloblastoma • Meningosarcoma • Choroid plexus carcinoma

TABLE 105.2 Table showing the imaging characteristics of the common pathologies affecting the CPA

Lesion	CT	CT + contrast	MRI T1- weighted	MRI T2-weighted	MRI + Gadolinium	Special features
Vestibular schwannoma	→	+	↓	↓/↑	+	'Ice cream cone'; heterogeneous enhancement if cysts
Meningioma	↑	+	→/(↑)	→/↓/(↑)	+	'Dural tail' on post-contrast imaging; may be calcified
Epidermoid	↓	–	↓	↑	–	Bright on DWI b1000 trace; internal structure may be visible on T1-W and T2-W MRI; close to CSF on T1-W and T2-W MRI; not CSF signal on FLAIR MRI
Lipoma	↓/fat	–	↑/fat	↑/fat	–	Complete saturation on T1 fat saturation MRI; chemical shift artefact on T2-W MRI
Arachnoid cyst	↓/CSF	–	↓/CSF	↑/CSF	–	
Glomus tumour	→/↑	+	↓	↑	+	'Salt and pepper'; T1-W MRI, bright haemorrhagic foci; T2-W MRI, dark flow voids
Choroid plexus tumour	→/↑	+	→/↓	→/↑	+	May be calcified; MRI may not distinguish papilloma from carcinoma; children > adults

↓, hypodense (CT)/hypointense (MRI) to brain; →, isodense (CT)/isointense (MRI) to brain; ↑, hyperdense (CT)/hyperintense (MRI) to brain; +, enhancement; –, no enhancement; CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuation inversion recovery.

tissue structures. Axial and coronal T1-weighted imaging with gadolinium enhancement and T2-weighted imaging are widely used. Fat suppression in conjunction with gadolinium-enhanced imaging is also extremely helpful. Diffusion-weighted imaging (DWI) MRI has been introduced in the last decade and is also helpful, particularly in identifying epidermoid tumours.

High-resolution axial and coronal computed tomography (CT) is often a useful adjunct to MRI and provides excellent definition of bony structures.

Table 105.2 summarizes the radiological characteristics of the common CPA pathologies.

Other forms of imaging may also be helpful. This includes MR angiography and traditional angiographic imaging.

These are particularly helpful in delineating vascular lesions such as glomus tumours.

BENIGN LESIONS ARISING FROM THE CPA

Meningiomas

DEFINITION AND PATHOLOGY

Meningiomas arise from clusters of epithelial cells that are present at the tips of arachnoid villi that are concentrated in the walls of venous sinuses, in their tributary veins and at the cranial nerve exit foramina.[11, 12] They may be well circumscribed or, more rarely, *en plaque* when their growth pattern results in a flat lesion. Bony infiltration via Haversian canals can occur and may result in hyperostosis that is demonstrable radiographically. They displace or surround cranial nerves and blood vessels rather than invading them. Nevertheless, they can become strongly adherent to these structures.[10, 12]

Histologically, meningiomas may be graded from 1 to 3 according to the WHO grading system.[10–16] Grade 1 tumours make up 81% and are described as classical. Grade 2 tumours make up 15% and are described as atypical. Grade 3 tumours make up the remaining 4% and demonstrate malignant features including the ability to metastasize either haematogenously or via CSF.[17] Grade 1 and 2 tumours are regarded as benign. Meningiomas often contain 'psammoma bodies', spherical calcifications responsible for a sandy appearance of the tumour surface.

Most tumours are regarded as being idiopathic with the exception of those associated with neurofibromatosis type 1 and type 2. Twenty per cent of adolescents with meningiomas have some form of neurofibromatosis.[13] Some authors have suggested an endocrine aetiology based on high concentrations of progesterone receptors, moderate numbers of androgen receptors and a low level of oestrogren receptors within meningiomas. A recent meta-analysis of the influence of hormone replacement therapy on development of meningiomas in women suggests that there is an association.[18] There may also be an association with androgen use in males.[19] Irradiation to the head is also associated with an increased risk of meningiomas.

EPIDEMIOLOGY

Meningiomas account for approximately 10–20% of all intracranial neoplasms. The incidence increases with age, the average age at the time of diagnosis of posterior fossa meningiomas being approximately 43 years.[13] Between 5% and 10% of all meningiomas arise in the CPA and are more common in middle-aged females. Second to vestibular schwannomas, meningiomas are the most common neoplasm found in the CPA, constituting roughly 10% of lesions in this location.[10–12]

CLINICAL PRESENTATION

Meningiomas differ from vestibular schwannomas in their clinical presentation. Audiovestibular symptoms are common but are often less marked and of shorter duration in patients with meningiomas compared with vestibular schwannomas.[2, 4, 7, 10, 12, 14, 20–23] Hearing loss is present in 41–80% of patients. This is usually sensorineural in nature but may be conductive if the middle ear is involved.[24] Tinnitus is present in about 15–60% of patients and dysequilibrium is a presenting symptom in 20–60% of patients. Other cranial nerve symptoms and signs tend to be more common with meningiomas than with vestibular schwannomas, occurring in up to 30% of patients. Fifth and seventh nerve symptoms are present in up to 20–60% and 10–50% of patients respectively.[4, 7, 10, 12, 14, 22, 23] Cerebellar signs are reported in about 30–90% of patients.[7, 12, 14, 21–23]

DIAGNOSIS

CT scans usually reveal a durally based homogenous tumour that is either iso- or slightly hyperintense. They avidly take up contrast.[10, 11] Peri-tumoural oedema may also be demonstrated, as may bony erosion, hyperostosis and intra-tumoral calcification. CT is superior to MRI in evaluating bone involvement and calcification of the tumour and is also helpful in demonstrating extension into the middle ear.[11, 13]

The gold standard imaging modality for demonstrating meningiomas is, however, MRI. T1-weighted imaging shows a homogenous iso- or hypointense tumour relative to brain parenchyma that is durally based. They take up gadolinium although they often enhance less avidly than vestibular schwannomas (**Figure 105.1**). With gadolinium, a dural tail is seen in around 60% of tumours. It has not been established whether the changes are neoplastic or represent reactive changes in the meninges adjacent to the tumour.[11, 13, 14] They are very variable in intensity on



Figure 105.1 T1-weighted axial MRI scan with gadolinium enhancement showing a large right CPA meningioma.

T2-weighted imaging.[10, 11, 13, 14] Again, MRI may identify significant peri-tumoral brain oedema.

The natural history of untreated meningiomas is generally benign. A systematic review by Sughrue et al. have demonstrated that, over a 4 year period, 50% demonstrate growth. Half of these increase in size by less than 10% per annum.[25]

TREATMENT

For selected cases, particularly for those patients with severe co-morbidities, advanced age or small tumours, observation with serial MRI has become increasingly popular. This reflects the generally benign natural history of meningiomas. This type of management is, however, less effective for meningiomas compared to vestibular schwannomas that demonstrate growth in only 20–30% of cases.

For large or symptomatic tumours, the treatment of choice for meningiomas is surgical excision and the ideal is complete resection of tumour together with involved dura and affected underlying bone. Although complete macroscopic clearance has been described in up to 91% of CPA meningiomas,[26] complete resection is not always possible, particularly if there is extensive bony involvement or strong adherence to neurovascular structures or brain.[27] The extent of resection may be graded using the Simpson criteria.[28] This and the histological grade of the tumour determines recurrence rates. For example, for Simpson grade I tumours, the recurrence rates for WHO grades 1 and 2 respectively are 12% and 41%.[16] **Table 105.3** summarizes the Simpson criteria together with the 10-year recurrence risk for each grade.

Surgical approach is determined by hearing status and the size and location of the tumour, including involvement with neurovascular structures as well as local preferences. The retrosigmoid approach is the standard neurosurgical approach to the posterior fossa and offers the possibility of hearing preservation in appropriate cases.[20, 26, 29, 30] The translabyrinthine approach offers direct access to the CPA and may offer lower mortality and improved facial nerve outcome compared to the retrosigmoid approach, but sacrifices residual hearing.[3, 30–32] A combined translabyrinthine-retrosigmoid approach can be used for tumours greater than 3–4 cm. The transcochlear approach offers anterior exposure to facilitate resection of tumours extending into the region of the clivus, Meckel's cave and the petrous portion of the internal carotid artery, and may be used in combination with a trans-tentorial approach if required.[30, 32] The middle fossa approach may also be used for tumours within the internal auditory canal that have a small CPA component.

Several authors have investigated the potential role of radiotherapy as a primary treatment modality and for recurrent or residual tumours.[33, 34] A number of types of radiotherapy have been used. Historically, external beam radiotherapy was used but this achieved relatively poor control rates of around 85%.[35, 36] Latterly, fractionated stereotactic radiotherapy and stereotactic radiosurgery have been used. For WHO grade 1 tumours, these techniques produce growth control rates of 86–99% although control becomes less likely with increasing tumour volume.[34, 37, 38] Similarly, brachytherapy with iodine-125 seems to be of value in both recurrent and primary skull base meningiomas.[39]

Medical therapies including hormone therapies, temozolomide, hydroxyurea, alpha-interferon, mifepristone and COX-2 inhibitors are currently being investigated but results to date have generally been disappointing.[13, 40, 41] Targeted chemotherapy aimed at blocking specific growth factors or intracellular signalling pathways are currently under investigation.[42]

TABLE 105.3 Table summarizing the Simpson criteria for completeness of tumour removal

Simpson grade	Completeness of resection	10-year recurrence[28]
I	Complete removal including underlying bone and associated dura	5–9%
II	Complete removal and coagulation of dural attachment	15–19%
III	Complete removal without resection of dura or coagulation	12–29%
IV	Subtotal resection	19–40%

Epidermoid cysts

DEFINITION AND PATHOLOGY

Epidermoids or primary cholesteatomas are keratinous cysts that originate from inclusion epithelial cells trapped during neural tube closure between the third and fifth weeks of gestation. In the CPA, they are thought to originate from transplantation of epithelial cell rests by the laterally migrating optic and otic capsules or developing neurovasculature.[2, 11, 43] They are distinguished from dermoids by the absence of skin adnexal components. They increase in size slowly by the accumulation of keratin and cholesterol produced by the desquamation of the squamous epithelial lining of the cyst and their growth rate is similar to that of normal skin and not the exponential growth seen with most neoplasms.[2, 11, 43] They insinuate around neurovascular structures, irritating rather than displacing them, and they fill the cisterns from which they arise following the line of least resistance.[10, 43, 44] Thirty to 40% of epidermoids occur in the CPA but they can be found elsewhere in the brain.[2, 11, 43] Macroscopically, these tumours have a soft texture and a pearly white colour. Microscopically, they are avascular tumours lined by stratified squamous epithelium that surrounds a mass of keratinous debris and, frequently, cholesterol crystals.[10, 43]

EPIDEMIOLOGY AND AETIOLOGY

Epidermoids account for 0.2–1.8% of all intracranial neoplasms and constitute 5–9% of tumours in the CPA.[2, 11, 43, 45] They may be slightly more common in

males than in females. They are not associated with any other congenital abnormalities.[43]

CLINICAL PRESENTATION

Because of their slow growth, CPA epidermoids may be asymptomatic for years.[2, 7, 43] As with meningiomas, hearing loss is less common than with vestibular schwannomas, occurring in 50–80% of cases.[4, 7, 43, 46–48] Fifth and seventh nerve symptoms occur in 30–50% of cases. Cerebellar signs or signs of increased intracranial pressure may also occur.[4, 7, 43, 46–48] Lower cranial nerve symptoms and signs are more rare.[4, 7, 43, 46–48] Spontaneous meningitis without surgery has been reported and an intracranial epidermoid should be suspected in a patient with repeated episodes of aseptic meningitis.[49] Malignant transformation of epidermoids into squamous cell carcinoma has been reported and present with more severe and rapidly progressive symptoms.[50, 51]

DIAGNOSIS

As with other types of CPA pathology, MRI is the imaging modality of choice.[11] On T1-weighted imaging, the lesions are heterogenous and of low signal showing no enhancement with gadolinium, although granulations around the cyst may enhance. T2-weighted imaging is particularly helpful and shows a high signal homogenous lesion that is lobulated, conforming to the shape of the cistern in which it has developed (**Figure 105.2**).[11] Large epidermoids compress adjacent brain. In addition, FLAIR or DWI is usually diagnostic with the lesion having high signal. This is very helpful in differentiating epidermoid cysts from arachnoid cysts.[52]

CT may also be used and shows a lesion with similar signal to CSF. There are not usually any changes within the adjacent bone. CT is often, therefore, not particularly helpful. Atypical MRI and CT appearances have been reported.[53, 54]

TREATMENT

Microsurgery is the treatment of choice with the retrosigmoid approach being the standard approach, although the translabyrinthine and middle fossa approaches may be used if required.[4, 7, 46–48] The goal of surgery is decompression of the cyst and, if possible, removal of the capsule. The interior of the tumour can be easily removed using suction or curettage. The capsule can, however, be very difficult to remove because of the way that epidermoids engulf neurovascular structures, and total removal is associated with a significantly higher morbidity and mortality.[4, 7, 43, 46–48] A comparison of recent major series shows a rate of total removal of between 0% and 97%. Most authors advocate subtotal removal of the tumour rather than compromising neurovascular function. Surgery may be repeated but is often only required every decade or more.[4, 7, 43, 46–48] Post-operative aseptic meningitis may occur in up to 40% of cases and is almost unique to this condition. This complication may be avoided by the use of prophylactic steroid use and minimal intra-operative spillage of tumour. If it occurs, the patient should be treated with antibiotics and steroids.

Even in modern series, recurrence rates of up to 35% have been reported.[4, 7, 43, 46–48] Serial imaging of any recurrence should be performed and a conservative approach taken, given that tumours may not become symptomatic during the patient's normal life span.

Arachnoid cysts

DEFINITION AND PATHOLOGY

Arachnoid cysts are congenital malformations of the arachnoid and are histologically characterized by a cyst wall that resembles arachnoid[55] and a cystic space filled with CSF or xanthochromic fluid.

EPIDEMIOLOGY

Arachnoid cysts make up approximately 1% of all intracranial lesions and the CPA represents the second most

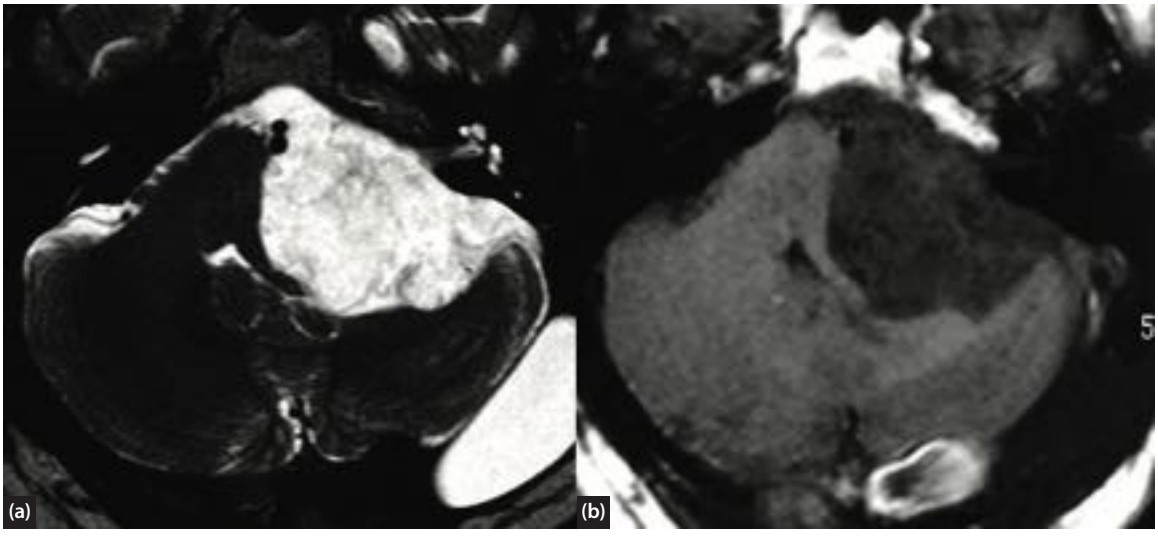


Figure 105.2 Axial MRI scans showing a large left CPA epidermoid. **(a)** T1-weighted scan without gadolinium enhancement. **(b)** T2-weighted scan.

common location after the Sylvian fissure. The aetiology remains unknown, but abnormal CSF flow, trauma or inflammation have been proposed.[56]

CLINICAL PRESENTATION

Eighty-five per cent of cysts are asymptomatic. Symptomatic cysts present with symptoms similar to other CPA lesions, with gradual onset of cranial nerve dysfunction especially of the VIIIth cranial nerve.[56–60] Sudden sensorineural hearing loss has been reported[61] and there have been a number of reports of hemifacial spasm.[62, 63] They may also present with symptoms of brainstem and cerebellar compression, and syringomyelia has been described.[64]

DIAGNOSIS

MRI is the primary diagnostic imaging modality. The cysts are heterogeneous in their appearance but they have the same signal as CSF, being hypointense on T1-weighted images and hyperintense on T2-weighted images (**Figure 105.3**). No enhancement is seen.[10, 56, 60] The cyst wall is smooth and round and the cysts compress or displace adjacent structures. Erosion of adjacent bone may also be seen.[44] They may be confused with epidermoid cysts and diffusion weighted imaging is helpful in differentiating these two pathologies. Only 2% of them demonstrate growth.

TREATMENT

Asymptomatic cysts require no treatment and should be followed by serial MRI scans. For symptomatic cysts, microsurgical decompression and fenestration via the retrosigmoid approach is the most commonly recommended procedure,[10, 11] although some authors have described an endoscopic approach.[65, 66] Sporadic reports of cyst recurrence after inadequate fenestration exist and some authors advocate complete cyst resection.[60] Others suggest cystoperitoneal shunts but these appear to be less effective than fenestration.[56, 60]

Lipomas

DEFINITION AND PATHOLOGY

CPA lipomas are likely to be congenital malformations and not actual neoplasms.[67–70] They may result from the failed dissolution and aberrant differentiation of the meninx primitiva, the mesenchymal derivative of neural crest,[67, 70, 71] which contains mature adipose cells accompanied by a varying degree of fibrovascular tissue. Blood vessels and nerves pass directly through them and are not displaced.

EPIDEMIOLOGY

These are rare tumours with an incidence of 0.08% in autopsy cases.[71, 72] They make up approximately 0.05–0.1% of CPA tumours,[11, 44, 67, 71, 73–78] although this may be an underestimate given that they may be mistaken for vestibular schwannomas.[71, 79] It is thought that only 9% of intracranial lipomas are found in the CPA, with interhemispheric lipomas being the most common.[70] A male preponderance has been reported by several authors.[73, 79, 80] Mean age at diagnosis is around 50 years.[80] Bilateral tumours have also been described.[71]

CLINICAL PRESENTATION

They present clinically with similar symptoms to other more frequent CPA tumours like vestibular schwannomas,[11, 67, 71, 73–75, 77, 79–81] although the onset of symptoms may be more insidious. Hearing loss is the most common presenting symptom followed by tinnitus and dizziness.[71–73, 76, 79, 80] Reports regarding their effect on the facial nerve vary in the literature, with some series showing no effect on facial nerve function and others suggesting that up to 9% of cases have facial nerve weakness.[73]

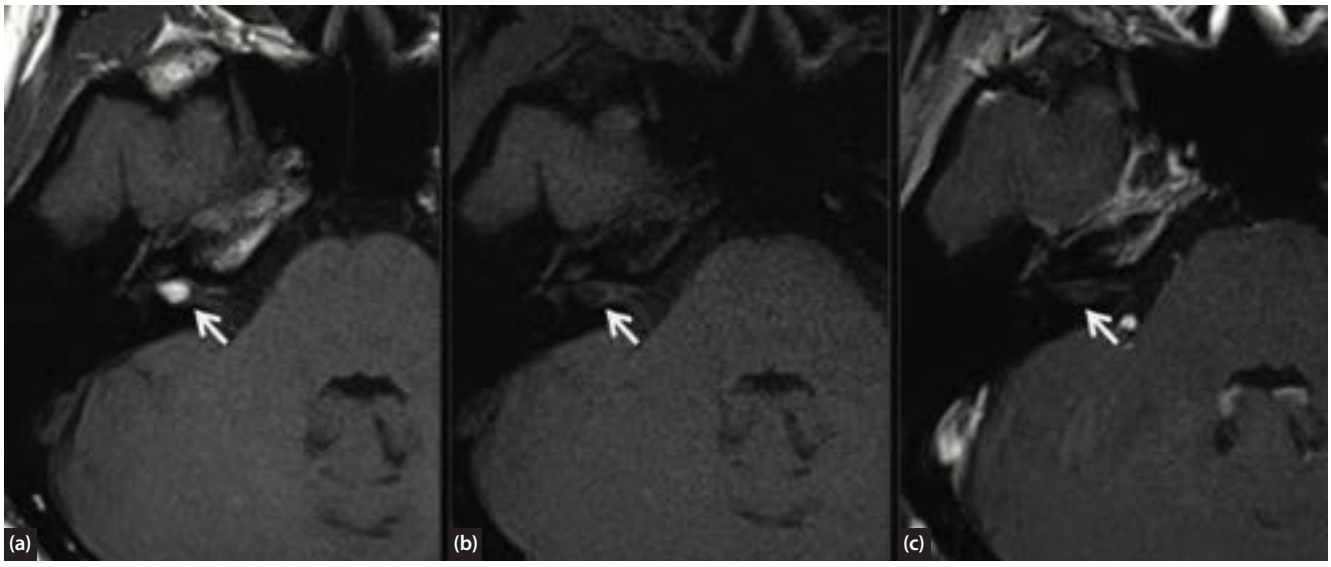


Figure 105.3 An intracanalicular right sided lipoma. (a) Very high signal intensity on axial non-contrast enhanced, T1-weighted imaging. **(b)** Hypointense on axial T1-weighted following fat suppression. **(c)** No enhancement following administration of gadolinium.

Other reported symptoms include hemifacial spasm[82, 83] and trigeminal neuralgia.[68, 84, 85] Weakness of other cranial nerves (with the exception of the vestibulocochlear nerve) has not been reported.

DIAGNOSIS

On MR imaging, lipomas have the same imaging characteristics as subcutaneous fat with high intensity on non-enhanced T1-weighted MRI studies, with progressive iso- to hypointensity with increasing T2 weighting. They produce no signal with fat suppression sequences.[75, 77, 80, 86, 87] The latter is extremely useful in differentiating lipomas from other CPA pathology (**Figure 105.4**). Furthermore, lipomas have also been said to display the MRI phenomenon of chemical shift and this may assist further in confirming the diagnosis. This phenomenon consists of a ring of low signal intensity at the posterior edge of the mass because of mis-registration of the fatty tissue at the interface with soft tissue and cerebrospinal fluid.[71]

Most of the literature suggests that CPA lipomas rarely grow,[11, 71–73, 78–80] with only one documented case of a CPA lipoma demonstrating growth in the current literature.[71] It has, however, been hypothesized that CPA lipomas might fluctuate in size, depending on the patient's weight.[71] This is not a consistent finding in the literature, however.[80]

TREATMENT

Because they are very unlikely to grow, conservative management has become the mainstay of management with some authors suggesting that long-term follow-up is not required.[80] Surgical removal has, however, been performed in cases with symptoms related to compression phenomena, mostly of the cranial nerves[67, 71–73, 79] or in cases of misdiagnosis.[78] In many of these cases, total removal of the lipoma has been very difficult and surgery has been associated with significant post-operative morbidity.[67, 71–73, 79] This is because CPA lipomas tend to be adherent to cranial nerves and the brainstem, making dissection challenging.[71, 73, 78] Most authorities therefore recommend subtotal removal if surgery is indicated. Both the translabyrinthine and retrosigmoid approaches have been described.[11, 67, 71]



Figure 105.4 Axial T1-weighted MRI scan showing a right petrous apex cholesterol granuloma.

Non-vestibulocochlear cranial nerve schwannomas

Schwannomas are the commonest neoplasm of cranial nerves and may develop on the V, VII or lower nerves. Symptoms reflect the nerve involved. Overall, they constitute 2–3% of all CPA tumours. Microscopically, non-vestibular schwannomas cannot be distinguished from vestibular schwannomas.

Facial schwannomas

DEFINITION AND PATHOLOGY

Facial nerve schwannomas (FNS) are rare benign tumours of the Schwann cell sheath of the facial nerve. Tumour may develop at any point along the course of the nerve from the CPA to the muscular branches in the face. Single or multiple segments of the nerve can be involved although the latter is more common.[88] The CPA is involved in 22 to 46% of cases depending on the series reviewed.[88, 89]

EPIDEMIOLOGY

FNS tend to present in the fourth or fifth decades of life[88] and have a male preponderance.[90]

CLINICAL PRESENTATION

In a meta-analysis of 427 patients, the commonest presenting symptoms were facial weakness and hearing loss occurring in 63% and 51% of cases respectively.[91] Facial weakness tends to be more common with tumours involving the extracranial segments of the nerve, especially the geniculate and labyrinthine segments. It can be of variable severity and may be transient or progressive or recurrent.[92, 93] The proportion of patients showing deterioration of facial function following diagnosis ranges from 21% to 38% depending on the series.[88, 94] Audiovestibular symptoms are more common with tumours involving the CPA and internal auditory canal (IAC),[95] although conductive hearing loss may occur if the middle ear is involved.

DIAGNOSIS

The gold standard diagnostic tool for the identification of a FNS is T1-weighted MRI with gadolinium enhancement. This allows identification of multiple segments of the facial nerve, a feature that is highly suggestive of FNS. Nevertheless, it may be extremely difficult to differentiate FNS from other pathologies, particularly if the radiological changes are confined to the CPA or the IAC as the

appearance can be identical to that of a vestibular schwannoma. It may also be difficult to differentiate FNS from other rarer pathologies such as haemangiomas. All CPA tumours should therefore have at least one scan with gadolinium to ensure that there is no adjacent VII nerve enhancement to suggest an FNS rather than a VS.

Tumour growth (>2 mm) has been reported to occur in 14% to 31% of patients.[88, 94]

TREATMENT

In the absence of significant tumour growth, significant brainstem compression or deterioration of facial function to grade 4 or worse, most clinicians recommend conservative management. Over half of tumours are therefore managed conservatively, at least initially.[88, 94, 96]

In those patients not managed conservatively, most undergo surgical excision although stereotactic radiotherapy may also be considered.

For those having surgery, the approach depends on the segment of nerve involved but most often requires a translabyrinthine or transotic approach if the CPA is involved. If there is serviceable hearing a combined transmastoid/middle fossa/retrosigmoid approach may be considered. Facial nerve grafting with great auricular or sural nerves is carried out following tumour removal. The possibility that a CPA tumour could be an FNS rather than a VS should always be considered. Fascicle preservation surgery has also been described with successful preservation of facial function.[97] Bony decompression of the tumour may also be considered under certain circumstances and may avoid deterioration in facial function.

The indications for radiotherapy are, as yet, unclear. A single case report of treatment with stereotactic fractionated radiotherapy has shown that tumour growth can be controlled and facial function not worsened by this modality of treatment.[98]

Trigeminal schwannomas

Tumours tend to involve either the ganglion or the nerve root, or both. Fifth nerve symptoms tend to dominate over VIIIth nerve dysfunction and the patients present with facial pain or numbness.[10] Other symptoms of an expanding CPA tumour may also be present. CT scans demonstrate enlargement of Meckel's cave or foramen lacerum and the tumours tend to be hypo- or isodense and show contrast enhancement. On MRI, the tumours appear iso- or hypointense on T1-weighted images and isointense on T2-weighted images and show bright enhancement as with other schwannomas. Tumour removal is possible through combined posterior, middle fossa or infratemporal fossa approaches.[10, 99] Endoscopic transnasal removal of tumours involving the middle fossa and infratemporal and pterygopalatine fossae has also been described.[100] The use of stereotactic radiosurgery has also been reported.[101]

Lower cranial nerve schwannomas

Lower cranial nerve schwannomas account for less than 1% of all CPA lesions.[45] They develop within the jugular foramen and may extend intracranially or extracranially, often developing a dumbbell shape. Symptoms reflect the nerve involved but may also result in audiovestibular dysfunction or clinical features of brainstem compression if large. Their imaging characteristics are those of any cranial nerve schwannoma. Treatment is by conservative management unless there is significant brainstem compression, in which case surgical resection may be undertaken. The decision to proceed is easier if there has already been loss of lower cranial function. Approaches include retrosigmoid, transcochlear and infratemporal fossa approaches depending on the position of the tumour.[102, 103] Growing tumours with good lower cranial nerve function may be treated with stereotactic radiosurgery.

Miscellaneous tumours

Dermoids are midline cysts and rarely invade the CPA laterally. They contain skin adnexal components, contrary to epidermoids.[45]

Choroid plexus papillomas are rare tumours, representing less than 1% of intracranial neoplasms. They are derived from the epithelial cells of the choroid plexus and demonstrate the structure of the normal choroid plexus when benign. Most often affecting children, they typically arise in the lateral ventricles. In adults, the primary site is the fourth ventricle. Malignant forms are very rare. They may produce signs of a CPA tumour, and signs of raised intracranial pressure are almost always present. Evaluation of CPA choroid plexus papillomas is by CT, MRI and angiography. Their prognosis is excellent when total surgical extirpation is possible. When surgery is not possible, radiotherapy has been evaluated, but results are variable.[104, 105]

Enterogenous cysts[106] are midline cysts that have very rarely been reported within the CPA. They may mimic arachnoid cysts, lipoma, epidermoids or cystic vestibular schwannomas on MRI.[45] They are usually symptomatic and treatment is usually by complete excision.

Neurenteric cysts are cysts derived from notochordal gastrointestinal or respiratory cell rests. They are very rare in the CPA and are usually treated with surgical resection.[107]

Inflammatory disease such as autoimmune or idiopathic pachymeningitis can occur in the CPA and may produce symptoms of CPA pathology due to compression of CPA structures by hypertrophied dura. Similarly, granulomatous diseases, such as tuberculosis and sarcoidosis, may affect the CPA.

The vertebral and basilar arteries and some of their branches pass through the CPA and aneurysms of the vessels, although not true neoplasms, may cause a mass effect on adjacent neural structures.[10, 44, 45]

MALIGNANT LESIONS ARISING FROM THE CPA

Metastatic lesions from either intracranial or extracranial sources account for around 1% of CPA tumours. Sources of extracranial origin are breast, prostate, lung,

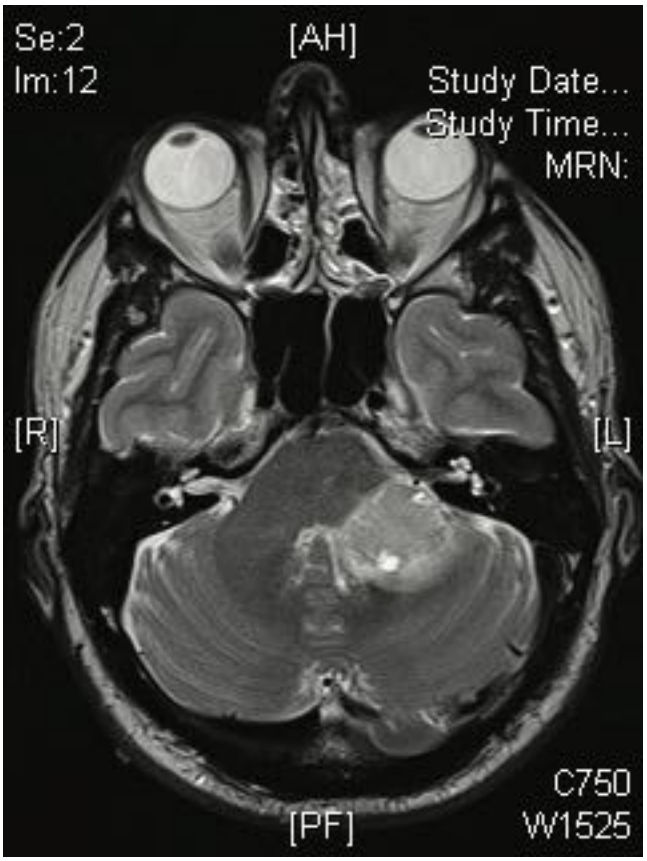


Figure 105.5 Axial T1- weighted MRI scan with gadolinium enhancement showing a left CPA metastasis.

melanoma, thyroid and gynaecological tumours.[45] They usually have similar signal characteristics to schwannomas on MRI (**Figure 105.5**). Diagnosis may be aided by lumbar puncture and CSF cytology. Solitary metastases may be treated with surgical resection or with stereotactic radiosurgery.

Melanomas of the CPA are very rare and may occur as either primary or metastatic tumours, the latter being the most common. Again, they often have similar signal to schwannomas on imaging. Prognosis is poor.[108]

CPA lymphomas are rare and occur as an extra-axial lymphoma, as extension from an intra-axial lymphoma, or as a leptomeningeal lymphoma presenting as a CPA lesion. Aggressive removal is not necessary, but radiotherapy to the lesion should be performed.[109]

BENIGN TEMPORAL BONE LESIONS INVOLVING THE CPA

Lesions originating from the structures of the skull base, especially the temporal bone, may reach the CPA by direct extension.

Cholesterol granulomas

Cholesterol granulomas arise from the apex of the petrous bone and may enlarge to reach the posterior fossa and produce nerve dysfunction (**Figure 105.4**).[44] Symptomatic cases may be decompressed via a transmastoid or endoscopic transnasal approach depending on its position.[110]

Glomus tumours (paragangliomas)

Large jugular foramen paragangliomas (Fisch type D) may present in the CPA by extension from the jugular foramen. Very rarely, primary CPA paragangliomas have been reported.[111] They are usually benign but locally aggressive, and destroy the petrous bone to enlarge to the CPA. Symptoms include pulsatile tinnitus, headache or VIIIth nerve symptoms. Examination may reveal a red pulsatile mass behind the tympanic membrane with a conductive hearing loss. Arteriography should be performed to demonstrate the extent of the tumour and the nature of blood supply. CT appearances are of a well-defined tumour with adjacent bone erosion and marked enhancement after contrast injection. They produce a characteristic 'salt and pepper' image on both T1- and T2-weighted MRI images because of intratumoral haemorrhages (**Figure 105.6**). Glomus tumours enhance intensively after gadolinium administration. Indications for treatment include brainstem compression and significant tumour growth with around 40% demonstrating growth following diagnosis.[112] Radiotherapy effectively controls growing tumours in 90–100% of cases and surgery has become less common as a result.[113–115] It is usually reserved for patients with significant brainstem compression, radiosurgery failure and those patients who already have lower cranial nerve compromise as post-operative cranial nerve deficits are common with unacceptably high morbidity.

MALIGNANT TEMPORAL BONE LESIONS INVOLVING THE CPA

Squamous cell carcinoma of the temporal bone accounts for 0.3% of head and neck malignancies. They are aggressive malignancies that invade adjacent structures.[116, 117] Lymph node metastases occur in 20%. Invasion of the carotid canal, cervical node involvement and poorly differentiated histology are poor prognostic factors. For cases that are operable, radical *en bloc* resection with preservation of the carotid artery, selective neck dissection and post-operative radiotherapy is recommended.[116, 117] It has a disease specific survival ranging from 19% to 48%.

Chondromas and chondrosarcomas are extremely rare and develop from embryonic cartilaginous remnants enclosed in the bones of the skull base.[44, 118] Both lesions are usually treated surgically.

Chordomas are very rare midline tumours arising from notchordal remnants around the vertebral axis. Intracranially they occur at the clivus although primary intradural chordomas have been reported. Whilst they are malignant they are generally fairly indolent in

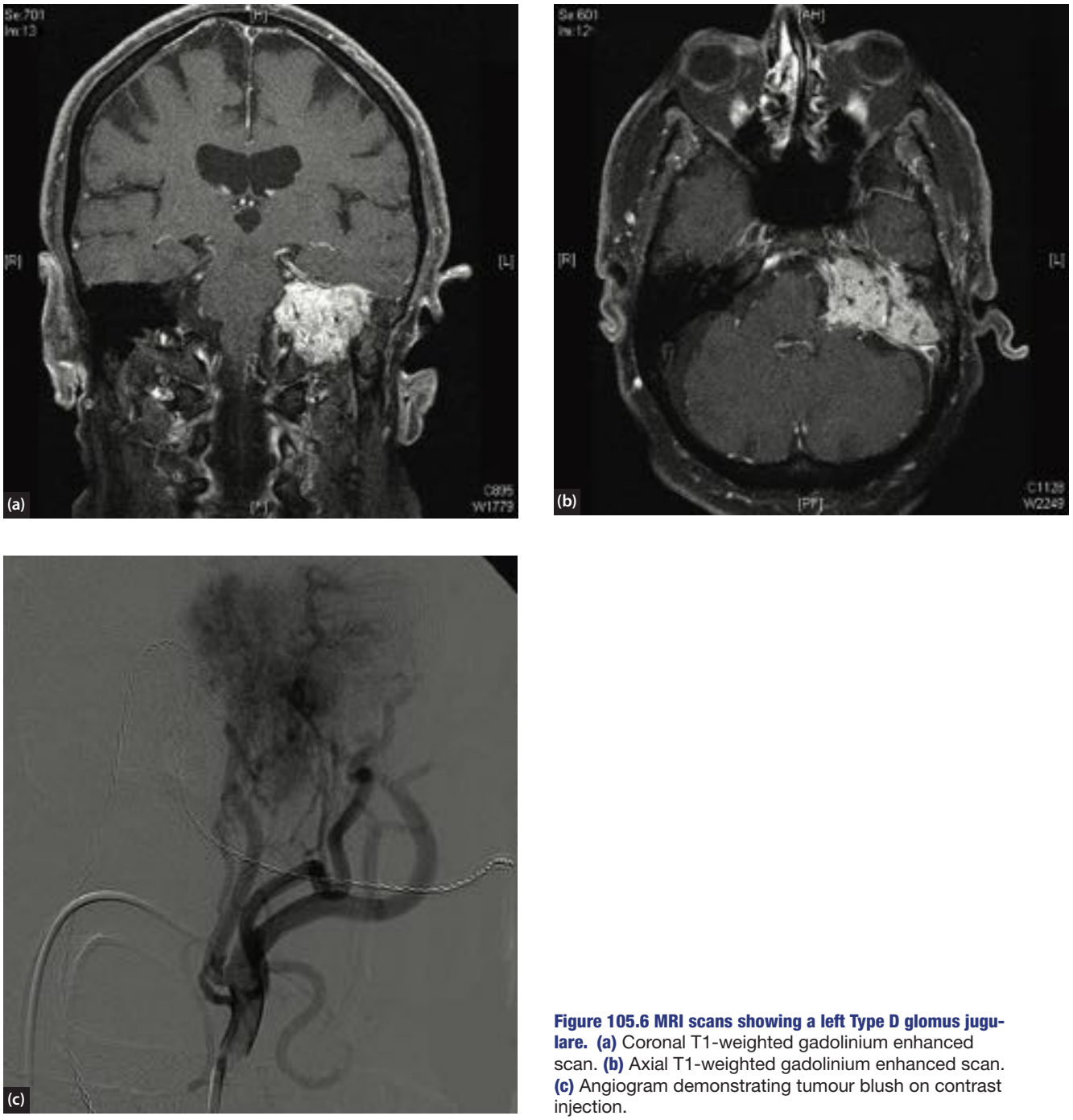


Figure 105.6 MRI scans showing a left Type D glomus jugulare. **(a)** Coronal T1-weighted gadolinium enhanced scan. **(b)** Axial T1-weighted gadolinium enhanced scan. **(c)** Angiogram demonstrating tumour blush on contrast injection.

their behaviour. Treatment is difficult but extended endoscopic endonasal approaches in combination with open approaches have increased the chances of complete resection. This is not always possible, however, particularly if the tumour extends into the inferior clivus.[119, 120] Resection should be followed by radiotherapy with proton beam therapy becoming increasingly the modality of choice. Recurrence rates are high.

Endolymphatic sac tumours are rare low-grade adenocarcinomas of the endolymphatic sac.[121, 122] Twenty per cent are sporadic but most are associated with Von Hippel Lindau Disease (4% of patients with this condition have endolymphatic sac tumours).[123] They are slow growing but locally destructive and rarely metastasize. Their presentation is similar to that of other CPA lesions. CT shows bony destruction centred on the endolymphatic sac. They have heterogenous increased signal on both T1 and T2-weighted imaging with patchy enhancement with gadolinium (**Figure 105.7**). Treatment is by wide local resection via retrolabyrinthine, translabyrinthine or retrosigmoid approaches. Cure can be achieved in 90% of moderate sized tumours but large tumours are difficult to cure. There may be late recurrence. Adjuvent radiotherapy may also reduce recurrence.

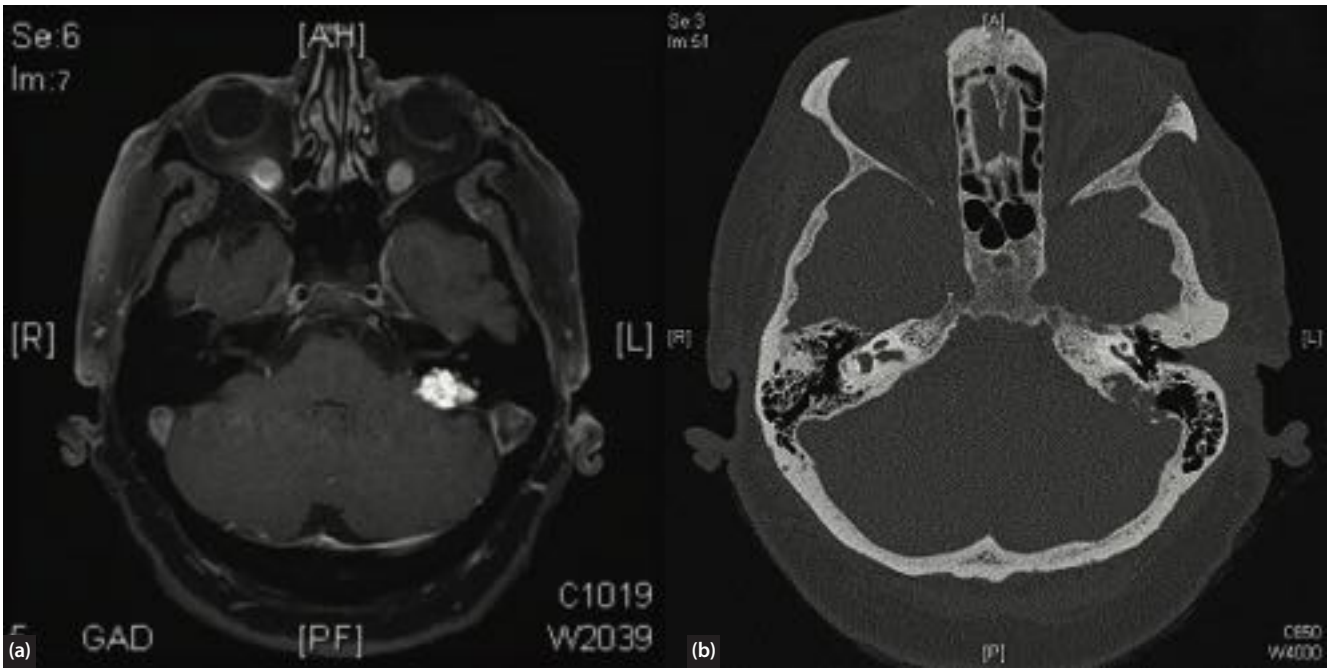


Figure 105.7 MRI scans showing a left endolymphatic sac adenocarcinoma. **(a)** Axial T1- weighted MRI scan with gadolinium enhancement. **(b)** CT scan.

BENIGN AND MALIGNANT INTRA-AXIAL LESIONS INVOLVING THE CPA

Rarely, intra-axial or intra-ventricular tumours invade the CPA. Diagnosis is difficult but subtle image signs, such as narrowing of the cisterns and oedema at the site of tumour origin, as well as the history of the patient, are sometimes helpful.

Primary central nervous system neoplasms

As few as 0.3–2% of the lesions in the CPA originate from primary brain tissue. Presenting symptoms may be typical of a CPA lesion, but an intra-axial lesion may be suspected because of the rate of progression of symptoms and the degree of non-acoustic cranial nerve symptoms.[45] The most common types of primary central nervous system tumours are medulloblastomas, astrocytomas, ependymomas and other gliomas of the brainstem.[124] It may not be possible to distinguish these lesions from vestibular schwannomas by CT although MRI may demonstrate their intra-axial status more reliably. Stereotactic biopsy has an accuracy rate of about 75% in these patients. Treatment regimens include surgery, radiotherapy or a combination of both and in some cases chemotherapy.

BEST CLINICAL PRACTICE

- ✓ All skull base pathology is best managed in a multidisciplinary setting with a core team including otolaryngology, neurosurgery and neuroradiology.
- ✓ Consider diagnoses other than vestibular schwannoma when scans are not typical and hearing loss is not the predominant symptom. All patients should have MR imaging with contrast and, if necessary, fat suppression sequences.
- ✓ Carotid angiography is helpful for certain pathologies, for example glomus jugulare tumours. Pre-operative embolization can reduce morbidity.
- ✓ The aim of surgery should be complete removal pathology but not at the expense of function. Stereotactic radiotherapy or radiosurgery are effective alternatives to surgery for some forms of growing tumour and may be used in combination with surgery in some situations.

FUTURE RESEARCH

Current understanding of the natural growth pattern of non-acoustic CPA tumours and the consequences of watchful waiting is insufficient. Future areas of research should include:

- ➤ assessment of the efficacy of subtotal surgical excision with adjuvent radiotherapy compared with radical excision
- ➤ treatment strategies for residual and recurrent tumours
- ➤ possible alternatives to surgical treatment (e.g. chemotherapy or brachytherapy)
- ➤ possible markers of tumour growth.

KEY POINTS

- One in five CPA tumours is not a vestibular schwannoma.
- Compared with vestibular schwannomas, VIIIth cranial nerve symptoms and signs are less frequent, and other cranial nerve and cerebellar symptoms and signs are more frequent in non-acoustic CPA tumours.
- The number of pathologies in the differential diagnosis of a CPA lesion is large but MRI and CT imaging often demonstrate features leading to correct diagnosis.
- Treatment most often involves surgery but some lesions may be treated conservatively or with radiotherapy.

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CHAPTER 106

MIDDLE FOSSA SURGERY

Raghu N.S. Kumar, Sunil N. Dutt and Richard M. Irving

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: middle fossa surgery and middle fossa approach, combining with cerebrospinal fluid leak, facial nerve surgery, vestibular schwannoma, acoustic neuroma, superior semi-circular canal dehiscence (SSCD) syndrome, petrous apex lesions and vestibular neurectomy.

INTRODUCTION

The middle fossa (MF) approach can be used as an extradural access route to approach the MF floor, the internal auditory canal (IAC), the posterior fossa and the petrous apex. The access through this approach is via a small temporal craniotomy and visualization can be difficult owing to the limited extradural space available and desire not to apply too much pressure on the underlying temporal lobe. The access to the posterior fossa is somewhat limited and it is only when considering the many intra-temporal indications for this approach that the advantages of the MF can be fully appreciated. This chapter will focus widely, considering all the applications of this approach, and will attempt to demonstrate why it is an important skill for all neurotologic surgeons.

HISTORICAL PERSPECTIVE

The earliest description of the MF approach was by William Rose of King's College Hospital, London in 1890.[1] Rose used the approach as an access route to the trigeminal ganglion in cases of trigeminal neuralgia. In 1904, Parry[2] was the first to describe its use to access the IAC. In the early twentieth century, many authors described the use of the MF for surgery of the facial nerve, superior semi-circular canal and petrous apex. Surgical outcomes in the first half of the twentieth century were rather poor and, as a result, the approach was rarely used and fell into disrepute.

The technique was then reintroduced by William House[3] who proposed this as a technique for decompression of the cochlear nerve in cases of otosclerosis. Subsequently, it was popularized again to access and remove small and medium-sized acoustic tumours, as with it residual hearing could be preserved. Significant technical contributions have been made by Fisch,[4] who refined the approach for a variety of conditions, including the treatment of facial nerve lesions. The approach gained further support with the contributions by E and JL Garcia-Ibanez[5] on surgical landmarks in the region in relation to a large case series of vestibular neurectomies. Neurosurgeons and neurotologists considering undertaking this approach are encouraged to consider three-dimensional (3D) computerized tomographic (CT) reconstruction of the temporal bone and middle and posterior fossae prior to surgery, in order to understand the microsurgical anatomy and relations of neurovascular structures, especially where bony landmarks may be absent.[6]

SURGICAL TECHNIQUE

Surgical anatomy

The learning curve to deal with intratemporal pathology via the MF approach involves operating while at the head end of the patient and getting the 3D orientation from above downwards. The most important landmarks in this approach are the middle meningeal artery,

tegmen plate, greater superficial petrosal nerve (GSPN), facial hiatus, arcuate eminence, superior petrosal sinus and the meatal plane. Of these by far the most useful for the surgeon is the GSPN, which serves as a guide not only to the depth of dissection but also to the position of the facial nerve (**Figure 106.1**). Bento et al., in 2002, recommended opening up the tegmen tympani early in the dissection to expose two additional landmarks of importance – the cochleariform process and the tympanic portion of the facial nerve – which could effectively guide the surgeon onto the labyrinthine segment of the facial nerve more directly.[7]

The arcuate eminence has a variable relationship to the superior semi-circular canal as demonstrated by Tsunoda et al.[8] A cadaveric study on 26 temporal bones showed arc-like eminences in 92% of the specimens, but they did not necessarily correspond to the site of the superior semicircular canal. Some of these eminences corresponded to sulci of the temporal lobe, of which most were traces of the occipitotemporal sulcus. It is advisable to use landmarks in addition to the arcuate eminence in order to reach the IAC safely.[8]

There are a number of variations on the MF approach. The transtemporal MF approach as described by Fisch[4] has the advantage of minimizing dural retraction but requires consummate skill. Gjuric et al.[9] described an enlarged MF approach involving the removal of additional bone either side of the IAC and providing greater access to the posterior fossa.

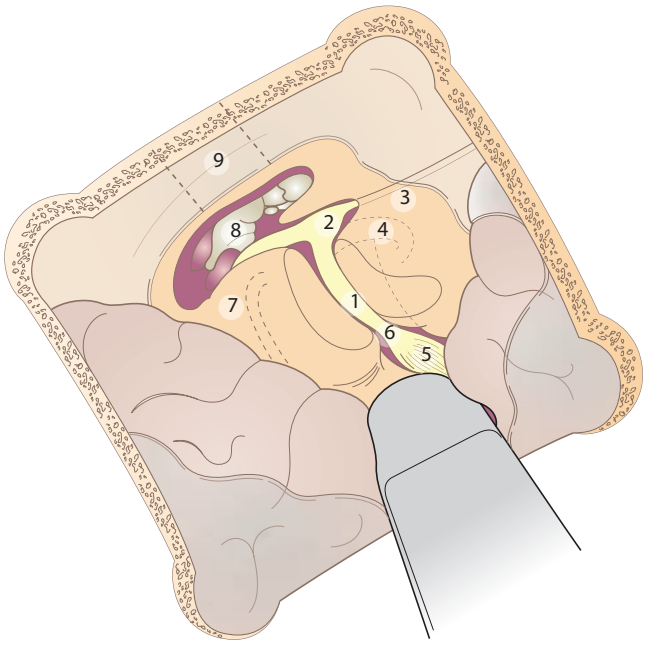


Figure 106.1 Left middle fossa anatomy with facial nerve exposed and internal auditory canal opened. 1, Labyrinthine VII; 2, geniculate ganglion; 3, greater superficial petrosal nerve; 4, cochlea; 5, internal auditory canal; 6, meatal foramen; 7, superior semi-circular canal; 8, removal of tegmen showing heads of ossicles; 9, external auditory canal position.

Patient position

The surgeon sits at the head of the operating table and addresses the floor of the middle cranial fossa from above. This is an unfamiliar orientation for most otologists and will also necessitate a change in the position of the other members of the operating team. The patient lies supine with the head rotated with the pathologic ear uppermost and with the intermeatal line perpendicular to the floor. A head holder is usually not required and a head ring stabilizes the head. Facial nerve monitoring is used routinely and it is advisable to insert a urinary catheter for the patient's comfort. Some, but not all, surgeons give mannitol to reduce intracranial pressure and obtain a larger operative field without undue compression of the temporal lobe.

Incision

This is either an inferiorly based U-shaped flap or a vertical line. It begins 0.5 cm anterior to the base of the helix, at the level of the zygomatic arch, and extends approximately 7 cm superiorly. Branches of the superficial temporal artery that are encountered at this stage should be ligated to avoid post-operative bleeding. The temporalis fascia plane is developed by finger dissection. An incision is placed in the temporalis muscle along its insertion line and it is elevated inferiorly and anteriorly taking care to preserve its neurovascular supply. Elevation of the temporalis exposes the squamous part of the temporal bone. The root of the zygoma indicates the level of the MF floor and it is crucial that the initial exposure adequately identifies this both anteriorly and inferiorly.

Craniotomy

This is sited two-thirds anterior and one-third posterior to the external auditory canal (EAC). An opening of 5 cm × 5 cm is adequate in most circumstances. It is bevelled posteriorly to minimize entry into the mastoid air cell system. The craniotomy can be cut either with an otologic burr or a craniotome to fashion a small bone flap. Utmost care should be taken not to injure the underlying dura during drilling. The opening then needs to be lowered to the level of the MF floor anteriorly and above the root of the zygoma. Any air cells entered should be sealed with bone wax.

Exposure of the middle fossa floor

Under low power of the operating microscope, dural elevation is commenced posteriorly. The superior petrosal sinus and the sulcus at the transverse–sigmoid junction are identified. A self-retaining retractor such as the Fisch, Yasergill's or House-Urban retractor is applied when the dura is sufficiently elevated. Care must be taken not to injure the geniculate ganglion as it can be dehiscent in up to 15% of temporal bones.[10] The arcuate eminence and the GSPN are then identified. It may be necessary to separate the dura using sharp dissection from the GSPN as

it can be densely adherent to it. The middle meningeal artery is anterolateral to the GSPN and dissection here is always bloody and, unless access to the apex is required, may not be necessary. If the vessel is divided, the foramen spinosum will need to be sealed with bone wax. The bone anteromedial to the arcuate eminence and posterolateral to the GSPN is termed the 'meatal plane' and lies above the IAC (Figure 106.2). It is often marked by a shallow depression. The angle between the GSPN and the arcuate eminence is bisected to identify the axis of the IAC, which was popularized by Garcia-Ibanez in 1980.[5]

Finding the internal auditory canal at its medial end (Porus Acousticus)

In medial approaches to the IAC, the dura is elevated over the meatal plane and the retractor is then inserted into the petrous ridge with its tip lodged into the bony groove of the superior petrosal sinus (as illustrated in Figure 106.2). If the ridge is not clearly identified, the placement of the retractor can be too far lateral and there is a risk of entering the inner ear when undertaking the initial bony removal. No identification of the superior semi-circular canal (SSC) is required and the GSPN is exposed only as far as its hiatus. The EAC and IAC are roughly in line, which helps with orientation.

Gentle and careful bone removal is undertaken with a diamond burr over the meatal plane, slowly reducing it over a broad area from the arcuate posteriorly to the limit of the dural elevation anteriorly. The temporal bone is usually pneumatized or filled with bone marrow anterior to the IAC. As the meatal plane is lowered, the IAC becomes visible. Its medial end is then defined and troughs are drilled both anteriorly and posteriorly to give more extensive exposure and sufficient space for safe tumour removal. At this stage, a thin layer of overlying bone is left to protect the dura of the IAC. The IAC is then followed laterally. Great care has to be exercised at this stage to ensure that no inadvertent entry into the cochlea or the SSC happens.[5]

Finding the internal auditory canal at its lateral end (Fundus Acousticus)

The margin of error at the lateral end of the IAC is of the order of 1 mm, representing the distance between the fallopian canal and the cochlea. Very precise identification is an absolute necessity if hearing is to be preserved. The lateral end of the IAC can be identified either by first finding the GSPN as described by House[3] or by using the SSC as advocated by Fisch.[4] In the former technique, the GSPN is delineated and followed proximally through its hiatus to the geniculate ganglion. Then, by tracing the labyrinthine segment of the facial nerve, the IAC is identified (Figure 106.3). A diamond burr with continuous irrigation suction is used to minimize the incidence of traumatic facial paresis post-operatively.[11–12]

The Fisch technique[4] was developed to limit the degree of dural retraction and the risk of damage to the labyrinthine segment of the facial nerve. In his technique the bone of the tegmen is removed and the SSC 'blue lined'. Having identified this, the IAC is then located within an angle of between 45 degrees and 60 degrees subtended from the ampulla of the SSC.

Completion of internal auditory canal exposure

Bone removal in the meatal plane needs to be more extensive in vestibular schwannoma surgery than for vestibular neurectomy. More radical removal of bone is carried out for access to larger vestibular schwannomas and is

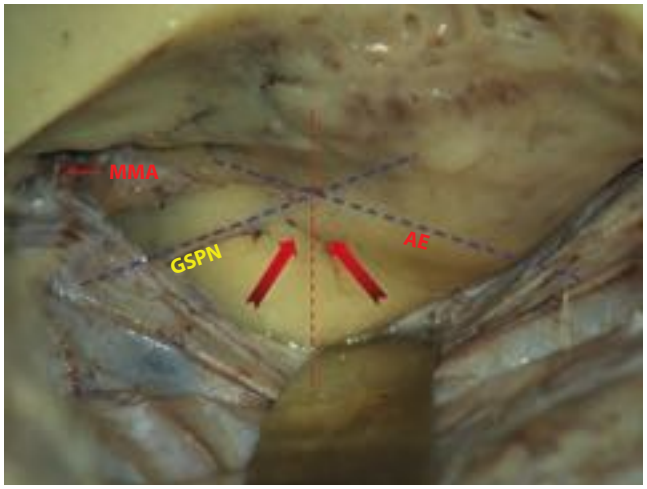


Figure 106.2 Right middle fossa floor: defining the 'meatal plane'. The IAC is identified in a tangent that bisects the angle formed by the superior semi-circular canal, SCC (identified as the arcuate eminence, AE) and the greater superficial petrosal nerve (GSPN). MMA, middle meningeal artery.

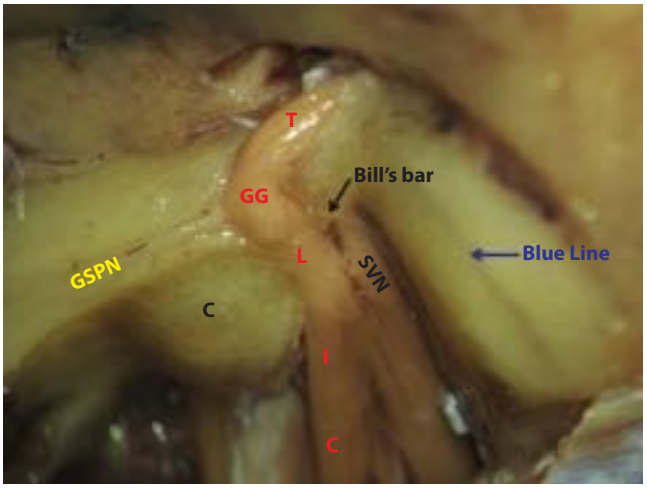


Figure 106.3 Anatomical dissection of the fundus area (right middle cranial fossa). GG, geniculate ganglion; GSPN – greater superficial petrosal nerve; T, tympanic segment facial nerve; C, cochlea; L, labyrinthine segment facial nerve; SVN, superior vestibular nerve. Also demonstrated is the blue line over superior semi-circular canal.

sometimes referred to as the enlarged MF approach.[9] Access can be improved further by division of the superior petrosal sinus.

Approximately three-quarters of the circumference of the IAC at the porous acousticus is exposed. This degree of exposure is not possible at the lateral end of the IAC because of the proximity of the ampulla of the SSC and the cochlea. Bill's bar, the vertical crest of bone separating the facial nerve from the superior vestibular nerve, is identified at the lateral end.

The fine eggshell of bone covering the dura is now carefully removed and the dura incised along the posterior aspect of the IAC, thereby avoiding inadvertent damage to the facial nerve. A dural flap is fashioned and the contents of the IAC identified.[11]

Closure

Any exposed air cell tracts must be waxed and a muscle plug is placed in the IAC. If the tegmen has been removed, it should be repaired with a bone graft or a bone pate slab to prevent dural herniation. The dura can be hitched to the skull by dural sutures to minimize the size of any extradural collection. The temporal bone flap is then fixed back into position.

CLINICAL APPLICATIONS

The indications for the MF approach can be divided into three distinct groups (**Table 106.1**):

- exposure of the MF floor
- access to the IAC and cerebellopontine angle (CPA)
- access into and through the petrous apex to anterosuperior CPA.

Initial elevation of the dura provides good access to the region of the tegmen that is ideal for repair of defects in this region. More medial dural elevation uncovers the cochlea, superior canal and facial nerve, allowing access to these structures. More medial dissection still exposes the meatal plane overlying the IAC. Bone removal in this region will reveal the IAC and can be extended to allow limited exposure of the CPA. In addition, dural elevation more medially and anteriorly exposes the petrous apex from above.[9] Pathology within the apex can be dealt with and if the apex is removed this can provide access to the anterio-superior CPA. This MF-petrosectomy extension can be combined with a posterior fossa craniotomy to access large petroclival lesions preserving inner ear function.

Internal auditory canal/cerebellopontine angle surgery

VESTIBULAR SCHWANNOMA SURGERY

The majority of small tumours are currently managed by either a conservative approach or by radiosurgery. Traditional surgical approaches remain an option in selected cases. The MF approach has been used for the removal of small vestibular schwannomas (VS) and for decompression of the IAC in bilateral tumours. The primary objectives of VS surgery are the control or complete removal of the tumour with preservation of facial nerve function and, where possible, preservation of hearing.[13] Both the MF and retrosigmoid (RS) approaches have been used for attempted hearing preservation in VS surgery. The perceived advantage of the MF approach is better visualization of the lateral end of the IAC when compared with the RS approach. In both the MF and RS approaches, there is a blind spot at the fundus, this being smaller in MF surgery.[14, 15] It is proposed as the hearing preservation approach of choice in tumours extending far into the lateral third of the IAC.[13] The main disadvantage is relatively poor access to the CPA and many surgeons would be hesitant in utilizing this approach for tumours with an angle component greater than 15 mm. In MF surgery, the facial nerve is generally found superiorly between the tumour and the operator. This has the advantage of ease of facial nerve identification but the disadvantage in that greater manipulation of the nerve may be required to remove the tumour. Additionally, control of bleeding in the CPA can be more difficult with the MF approach.[15]

Proponents of the MF approach report excellent results for hearing preservation and claim superiority over the RS in this regard. The reasons why hearing preservation should be better by this route are difficult to understand, but may possibly relate to the direction of tumour dissection. In the MF approach, small tumours can be removed in a medial-to-lateral direction, avoiding avulsion of the fine cochlear nerve endings entering the modiolus of the cochlea. The data on hearing preservation in RS when compared with the MF approach is, however, contradictory. There have been few comparative series[14] and only one prospective randomized study,[15] which reported no advantage of the MF over the RS in terms of hearing preservation. In addition, facial nerve function appears to be worse in the early post-operative period in the MF group.[14]

TABLE 106.1 Clinical applications of the middle fossa approach

IAC/CPA surgery	Middle fossa floor	Petrous apicectomy
Vestibular schwannoma	Repair of CSF leaks	Petrous apex lesions
Resection of IAC/CPA tumours	Superior canal dehiscence	Petroclival tumours
Vestibular neurectomy	Facial nerve surgery	Basilar aneurysms

VESTIBULAR NEURECTOMY

Section of the vestibular nerve can be carried out through a MF, RS or retrolabyrinthine approach. The main advantage of the MF approach is that it offers access at a more distal location where the VIII nerve is naturally divided into its vestibular and cochlear branches. The main indication for this is in patients with incapacitating Ménière's disease, unresponsive to more conservative treatment and with serviceable hearing.[5]

Middle fossa floor

FACIAL NERVE SURGERY

Indications for the MF approach have expanded to address facial nerve pathology in its intracranial, intracanalicular, labyrinthine, geniculate and tympanic segments (**Figure 106.4**). The facial nerve can be accessed through the MF floor for a spectrum of indications, namely: temporal bone fractures involving the intracranial and petrous facial nerve; benign intrinsic tumours involving the supra-tympanic facial nerve segments; nerve decompression in idiopathic recurrent facial palsy; and nerve reanimation by cable grafting it in its internal auditory meatus (IAM) and labyrinthine segments. Such an approach allows direct exposure of the proximal parts of the nerve with preservation of inner ear function, which is otherwise not possible via the trans-mastoid route alone. It is perhaps when considering pathology of the facial nerve that the MF approach clearly exhibits advantages over all others.

The MF approach to the traumatized facial nerve has proven to be a successful route. Bento et al.[16] in 2004 reviewed 220 cases where they advocated a combined MF and transmastoid approach to decompress the facial nerve for injury sustained in an unclear location but presenting with good cochlear reserve. Recently, da Franca Pereira et al. have described in detail the steps of decompression of the tympanic and labyrinthine segments of the facial nerve by middle cranial fossa approach with anatomical measurements in 20 cadavers to conclude that this is a safe, timesaving and reliable technique.[17] Aslan et al. reported a series of 13 patients who underwent facial nerve decompression via MF approach for grade VI traumatic palsy and were able to achieve grade 2 recovery in 7 (58%) patients by decompressing the geniculate ganglion within 1 month of trauma.[18] Cannon et al. have reported a series of 18 patients with traumatic complete paralysis and poor facial prognosis on electrophysiology, all of whom achieved a long-term outcome of HB III or better after MF approach was performed for primary decompression in 11 (64%) patients and repair of the facial nerve by grafting in 7 (36%) patients.[19]

The concept of decompression surgery for facial nerve paralysis of non-traumatic and non-tumorous origin remains controversial. Fisch[20] demonstrated encouraging results with surgical decompression of the nerve in its labyrinthine segment in cases of Bell's palsy and herpes zoster oticus. Marsh and Coker [21] present evidence suggesting that the meatal segment of the facial nerve is the probable site of entrapment. Unimpeded access to this region of the facial nerve can only be achieved via a MF craniotomy. Only one randomized study has attempted to address this issue and it concluded that the outcome in Bell's palsy was improved by MF decompression surgery.[22]

Cannon et al. reviewed long-term outcomes in a series of 14 patients who underwent surgical decompression for Bell's palsy within 14 days of symptom onset from 2000 to 2012.[23] Surgical criteria included greater than 90% degeneration on electroneurography (ENoG) testing and no voluntary electromyography (EMG) potentials. MF

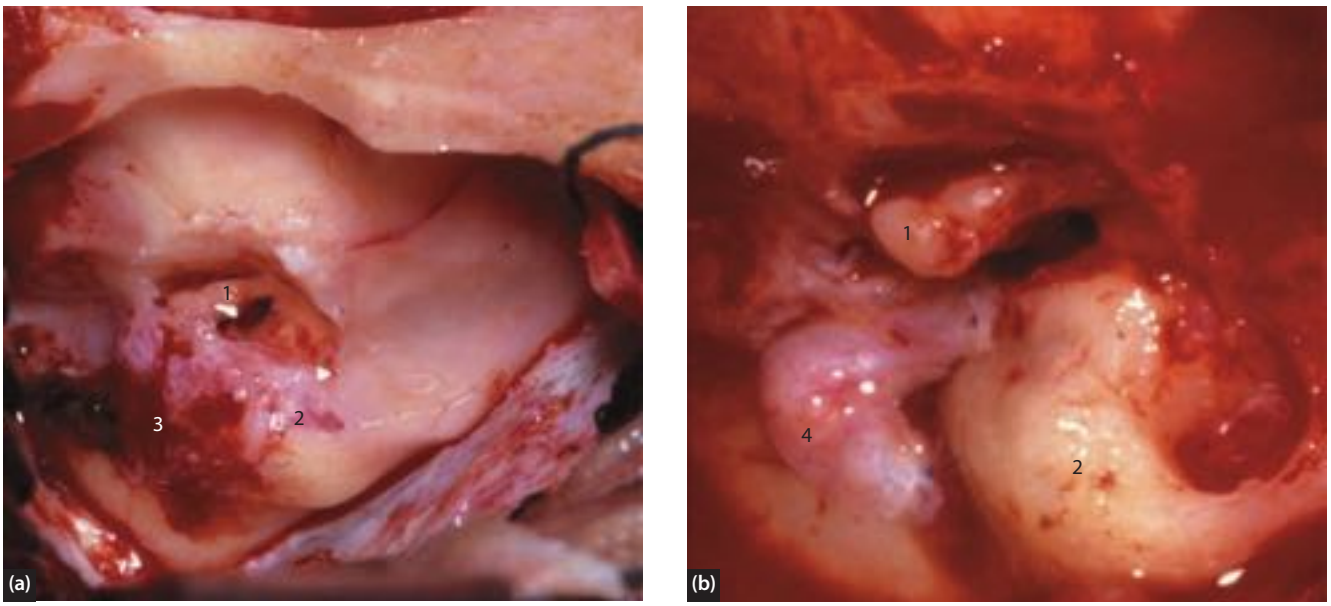


Figure 106.4 View of right middle fossa floor showing facial nerve graft (b) following removal of facial nerve haemangioma (a). 1, Heads of ossicles; 2, superior semi-circular canal; 3, facial haemangioma; 4, facial nerve graft (labyrinthine, geniculate and proximal tympanic segments).

bony decompression of the facial nerve, including the meatal foramen, labyrinthine segment, and geniculate ganglion was performed. Ten patients (72%) had regained normal facial nerve function while four cases improved to HB grade III function, with minimal morbidity in the case series. All these patients had no hearing loss of significance, which suggests MF is a viable route with hearing preservation.[23]

Decompression surgery is particularly appealing in cases of Melkersson–Rosenthal syndrome (MRS) and recurrent facial paralysis of unknown origin. MRS is a triad of recurrent alternating facial paralysis, recurrent facial and labial oedema (cheilitis granulomatosa) and fissured tongue (lingua plicata).[24] The logical conclusion is that the oedematous process affects the entire nerve within a tight bony canal, causing entrapment neuropathy. Total decompression of the entire length of the nerve using a combined transmastoid and MF approach is recommended in cases of MRS where there is a significant increase in frequency, duration and severity of facial paralysis to prevent disabling sequelae, such as synkinesis and residual facial paralysis.[24]

The benefits of MF decompression of the facial nerve in cases of recurrent facial paralysis has been demonstrated by Nyberg and Fisch.[25] They operated on a total of 14 patients, including 11 with acute paralysis with ENoG evidence of more than 90% amplitude reduction within the 10 days following the attack. Their series also included three patients who underwent decompression prophylactically to prevent further recurrences. Graham and Kartush[26] demonstrated excellent results with complete resolution in six patients with recurrent facial paralysis, who underwent total facial nerve decompression. Similarly, facial nerve decompression via MF seems to achieve better outcomes of facial nerve function than conservative treatment according to a recent report by Zhu et al., who were able to prevent further episodes by surgical decompression, providing an HB grades I–II recovery in all their cases.[27] Doshi and Irving[28] provide further evidence to support the effectiveness of MF decompression in recurrent facial nerve paralysis, with no recurrences in four cases with hearing preservation.

There is as yet insufficient evidence to propose facial nerve decompression in Bell's palsy beyond a prospective randomized trial; however, the results of decompression in cases of recurrent paralysis as mentioned above are encouraging.[25–28]

The MF approach provides a route of access to tumours involving the proximal facial nerve. Mowry et al. recommend the MF approach for debulking and decompressing facial nerve schwannomas involving the IAM. They achieved decompression with more than 70% debulking of the tumour via this approach while preserving motor fibres good enough to provide HB grade I function postoperatively at serial follow-up to 1 year.[29] Kusumi et al. also support this fact in their case report where they used a combined extradural and intradural MF approach to remove an intra-petrous GSPN schwannoma involving Glasscock's triangle, while preserving the tumour capsule in the MF floor to safely protect the geniculate ganglion and the main trunk.[30] Decompression alone without tumour debulking is an option for small tumours difficult to separate from the main nerve trunk, and with recurrent facial paralysis, with good medium-term outcomes reported in two cases.[31]

REPAIR OF TEGMEN DEFECTS, CEREBROSPINAL FLUID LEAKS AND MENINGOENCEPHALOCOELES

The conventional approach to repair of tegmen plate defects causing cerebrospinal fluid (CSF) leaks and brain hernias has been the transmastoid approach. The vast majority of spontaneous CSF leaks take place through the tegmen plate, rather than through a posterior fossa defect. Traumatic leaks are more unpredictable and many have both posterior fossa and MF components. Good outcomes are achieved with defects sealed via the MF approach to the tegmen plate when this is the site of the problem.[32–35] The major advantage of the MF approach over the transmastoid is that the repair can be carried out without disturbing the middle ear and ossicles. Also, large or multiple defects can be detected more easily and dealt with by the MF approach.[33]

The procedure can be carried out through a 'mini' temporal craniotomy with a window of less than 4 cm.[22, 23] While drilling, bone dust is collected using a bone-pate collector that is essentially a filter-trap attached to the suction apparatus. After elevation of the dura, all the defects in the tegmen are exposed and sealed with an oblong slab of bone pate mixed with blood and fibrin glue (Tisseel; Immuno, Vienna, Austria). This pliable graft material is insinuated into every defect and crevice in the tegmen using neuropatties. A large free graft of temporalis fascia placed between the dura and the bone-pate slab provides additional reinforcement. Recurrence of CSF leakage has been reported after soft tissue repairs and hence the rationale for using bone pate, which over time is believed to form an adequate layer of viable bone (**Figure 106.5**). More recently, Braca et al. have used autologous dural grafts with synthetic polymer glue to seal successfully tegmen defects with CSF leaks and encephalocoeles in eight patients via the MF approach.[36]

SUPERIOR SEMI-CIRCULAR CANAL DEHISCENCE SYNDROME

Sound- or pressure-induced vertigo caused by a bony dehiscence of the SCC into the middle cranial fossa is a rare cause of otologic symptoms including autophony and vertigo.[37] Disabling vertigo in two of these patients from the initial series prompted plugging of the dehiscent canal via a middle cranial fossa approach with good results.[37] Alternative approaches to address the dehiscence have been subsequently described, including the transmastoid and MF/transmastoid routes. Debate continues as to which is the most appropriate and effective although in some cases, especially where there is an associated encephalocoele the MF approach may be preferred.

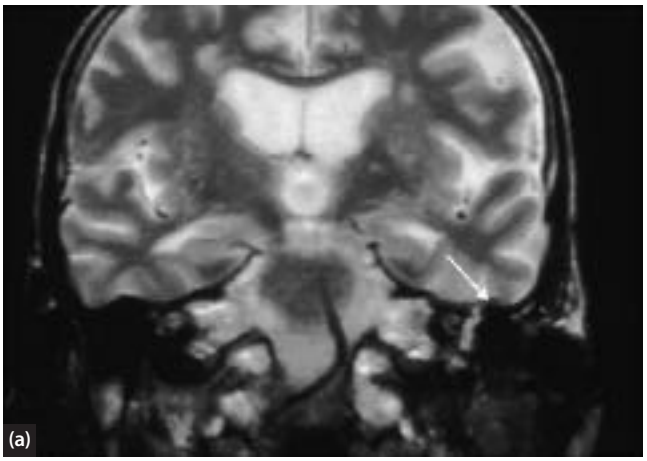




Figure 106.5 (a) Pre-operative coronal T2-weighted image demonstrating a tegmen CSF leak. Arrow shows site of leakage. **(b)** Post-operative coronal CT scan demonstrating bone pate repair. Arrow shows site of repair.

A series with 43 cases of superior canal dehiscence syndrome (SCDS) who underwent surgical plugging by the MCF approach has been reported by Ward et al.[38] Plugging of the canal was performed using fascia strips, bone dust and bone chips, which are gently but securely placed inside the dehiscent canal to obliterate the canal lumen for 2–3 mm beyond either end of the dehiscence. Careful avoidance of unnecessary force on or suction near the membranous labyrinth was observed throughout the procedure. The repair was then covered with hydroxyapatite cement, followed by a layer of fascia and fibrin glue. The authors concluded that low frequency air–bone gap decreases following surgical plugging and appears to be due to both increased bone-conduction (BC) thresholds and decreased air-conduction (AC) thresholds. Surgical plugging via a middle cranial fossa approach in SCDS is associated with mild high frequency sensorineural hearing loss that persists in 25% but no change in speech discrimination.[38–39]

Petrous apicectomy

The MF craniotomy provides the shortest and most direct route to the petrous apex. By elevation of the dura medial and anterior to the IAC, the anterior apex can be exposed as far as Meckel's cave and the ipsilateral cavernous sinus. Primary lesions within the apex, the most common being cholesterol granulomas, chordomas, cholesteatomas and chondrosarcomas, can be approached in this way (**Figure 106.6**). Lesions in Meckel's cave, including schwannomas and meningiomas, when small, can be accessed solely by a MF approach, whereas larger lesions may require an orbitozygomatic craniotomy.[40–42] The bone of the anterior petrous apex conforms to a rhomboid shape bounded by the IAC and cochlea laterally and posteriorly, the intrapetrous carotid anteriorly, and medially by the Gasserian



Figure 106.6 Petrous apex chondrosarcoma with large middle fossa and small posterior fossa components. This large lesion could be removed by a middle fossa transpetrous apex approach.

ganglion. If this rhomboid of bone is removed, the dura of the anterior–superior CPA is exposed and opening this provides limited access to the CPA. Additional exposure can be obtained by transection of the superior petrosal sinus and the mandibular branch of the trigeminal nerve. Access is provided to the ventral surface of the pons and upper clivus. This approach has been used for basilar tip aneurysms and petroclival and Meckel's cave tumours with limited CPA extension.[40–42]

COMBINED APPROACHES

The MF approach can be combined with any of the existing skull base approaches of the anterior, lateral and posterior skull base. While the MF approach is an extradural, subtemporal route consisting of an anterior petrosectomy, an extended approach (combined petrosal) anterior to this is used by neurosurgeons for intradural lesions of the superior CPA and prepontine clivus and cavernous sinus lesions. The 'rule of two fans' technique wherein vascular, nervous, fibrous and osseous structures are localized within two bordering fans, one centred around the geniculate ganglion in the MF floor and one centred around the Gasserian ganglion (perpendicular to the geniculate fan structures) is popular in dealing with lesions such as sphenopetroclival tumours, neoplasms with transtentorial extensions and vertebrobasilar aneurysms.[43]

Combining the MF approach with the transmastoid approach for clearance of extensive lesions is popular and has its advantages. A large defect with CSF otorrhoea after a mastoidectomy is best managed by a combined approach.[44] O'Connell et al. have described a combined transmastoid-middle cranial fossa approach for repair of lateral skull base CSF fistula and encephaloceles using a suture 'pull-through' technique. This method facilitates reliable placement of a composite graft in the centre of lateral skull base defects through a small craniotomy that minimizes temporal lobe retraction.[45]

A middle ear cholesteatoma with intracranial extension would necessitate a MF craniotomy.[46] A giant facial nerve schwannoma extending from the middle cranial fossa to the mastoid region is best cleared by a combined MF and transmastoid approach.[47] In the extended MF and transpetrous approaches, a thorough understanding of the horizontal segment of the petrous internal carotid artery (pICA) (**Figure 106.7**), its normal anatomy with variations and relations to surrounding neural and osseous structures is essential.[48]

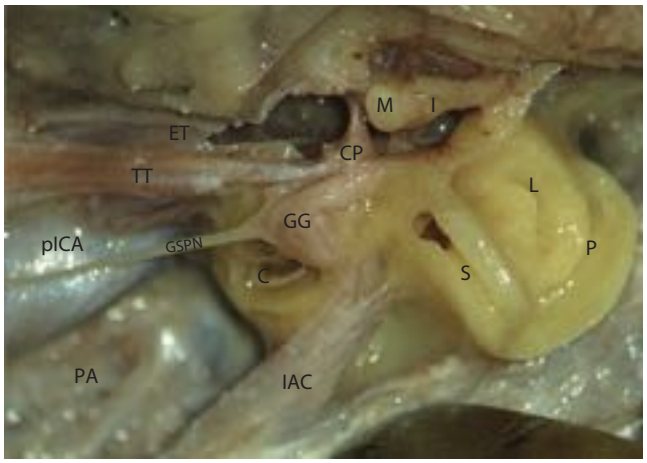


Figure 106.7 Extended dissection of the right middle cranial fossa and petrous region to demonstrate the intrapetrous internal carotid artery (ICA) and its relations. S, superior canal; P, posterior canal; L, lateral canal; GG, geniculate ganglion; GSPN, greater superficial petrosal nerve; C, cochlea; IAC, internal auditory canal; TT, tensor tympani; ET, Eustachian tube; PA, petrous apex; CP, cochleariform process; M, malleus; I, incus.

INFORMED CONSENT IN MIDDLE FOSSA SURGERY

The risks and complications that are discussed with a patient undergoing MF surgery will vary depending upon the precise pathology that is anticipated.

Inadvertent entry into the inner ear, damage to its blood supply or to the VIIIth nerve, can result in hearing loss, tinnitus or balance disturbance. Weakness of the face may develop and be accompanied by damage to the sensory component of the facial nerve. An extradural haematoma may accumulate and can be limited by suspending the dura to the edges of the craniotomy. CSF leakage is less common than in posterior fossa surgery but, nevertheless, can be equally tedious and dangerous as there is a definite risk of infection or meningitis. There has been much debate regarding the possibility of temporal lobe damage following MF surgery. The risk is in the order of 1 in 50 patients having a single early post-operative seizure following a MF exposure of the IAC.[10] Aggarwal et al.[49] described two cases of single ictal events which had the effect of prohibiting the patients from driving for a period of one year. A long-term predisposition to seizures has not been described. Retraction trauma leading to cortical injury, aphasia or hemiparesis has not been described either, but there is some suggestion that temporal lobe function is affected at least temporarily following surgery and may lead to some transient memory loss. There are additional risks in MF transpetrous surgery that include damage to the intrapetrous carotid artery, trigeminal neuropathy and ophthalmoplegia.

KEY POINTS

Middle fossa approaches:

- provide access superior and medial to the otic capsule preserving inner ear function
- provide excellent access to the proximal intratemporal facial nerve
- allow for the repair of tegmen defects with preservation of middle ear function
- small- and medium-sized VS can be removed with preservation of hearing.

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CHAPTER 107

JUGULAR FORAMEN LESIONS AND THEIR MANAGEMENT

Rupert Obholzer

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SEARCH STRATEGY

In this chapter we review the anatomy, pathology, and management options for jugular foramen lesions. Data in this chapter are based on a Medline search using the keywords: jugular foramen and neoplasm (or cancer or tumour), surgery, conservative treatment (or therapy), radiotherapy, radiosurgery and diagnosis.

INTRODUCTION

A number of pathological lesions and conditions can develop in the jugular foramen, all of which are quite rare. There is only a scant amount of data on the incidence and prevalence of jugular foramen lesions, but several hundred cases have been described in the literature. Most are solitary case reports or record small series of patients and emphasize surgical techniques and outcomes. No controlled studies have been undertaken on this subject, so the scientific level of evidence in the body of literature is fairly low. This applies to many aspects of jugular foramen lesions, such as their diagnosis, biological behaviour and therapeutic options. At present, there are no exact or universally accepted management protocols. Surgical intervention in the region of the jugular foramen is often difficult and sometimes hazardous, due to the close proximity of nerves, arteries, veins and intracranial structures.

Surgery should therefore not be the default treatment, but one strategy to be considered in parallel with assessing the merit of conservative management or radiotherapy.

A team approach is often the key to success. Therefore, it is generally agreed that diagnostic examinations, decision-making and treatment should be carried out in a multidisciplinary setting in tertiary referral centres.

ANATOMY

The jugular foramina are the second largest openings in the skull base, after the foramen magnum. Their anatomy varies considerably.[1, 2] The left and right jugular foramina are asymmetrical. Usually the left is smaller than the right, which is presumed to have some relation with the dominance of right cerebral venous drainage. They are extremely important anatomical structures, because they harbour vital vascular and neural pathways.

The lateral part of the jugular foramen is a sigmoid-shaped tunnel, while the medial part looks like a canal in the cephalocaudal direction. The joint between the petrous bone and the occipital bone is part of the petrosphenooccipital suture of Gruber (named after the Russian anatomist Wenaslaus Leopoldovich Gruber) and constitutes the ventromedial aspect of the jugular foramen. The end of the occipital mastoid suture between the mastoid and the occipital bone forms the dorsolateral aspect of the jugular foramen. The incisura jugularis (the curved indentation in the occipital bone) constitutes the dorsomedial wall of the jugular foramen. Its counterpart in the petrous bone forms the ventrolateral wall of the jugular foramen. At the caudal aspect of the jugular foramen, both incisurae jugulares have a so-called intrajugular process. These processes protrude into the lumen of the jugular foramen (**Figure 107.1**) and divide it into

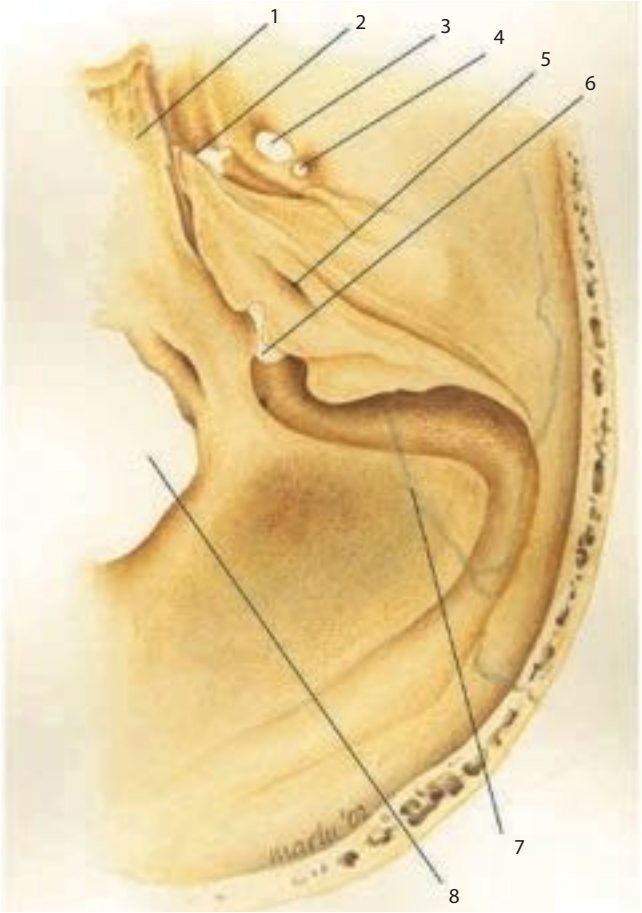


Figure 107.1 Superior view of the skull base (right side) as shown from above. 1, clivus; 2, foramen lacerum; 3, foramen ovale; 4, foramen spinosum; 5, internal auditory canal; 6, jugular foramen; 7, suture of Gruber; 8, foramen magnum.

lateral and medial parts. The lateral part (pars venosa) is filled by the sigmoid–jugular complex, while the medial part (pars nervosa) contains the inferior petrosal sinus, the cranial nerves IX, X and XI, the superior ganglion of the glossopharyngeal nerve and the jugular ganglion of the vagus nerve.[3]

The transverse sinus is an important structure in the venous drainage system of the brain, which opens into the sigmoid sinus. Venous flow proceeds via the jugular foramen through the skull base towards the IJV in the neck. Several venous pathways drain into the sigmoid–jugular complex: the superior and inferior petrosal sinuses, the occipital sinus and the mastoid and condylar emissary veins. The most important is the inferior petrosal sinus that contains the effluence of the cavernous sinus and the basilar plexus. The dome of the jugular bulb is in close contact with the floor of the hypotympanum, the vestibule, the posterior semicircular canal, the vestibular aqueduct and the internal auditory canal. The lateral side of the jugular bulb is close to the mastoid (vertical) segment of the facial nerve. The jugular foramen lies in close proximity to the internal carotid artery: only a small osseous spine separates the vertical part of the carotid canal from the jugular foramen (**Figures 107.2** and **107.3**).

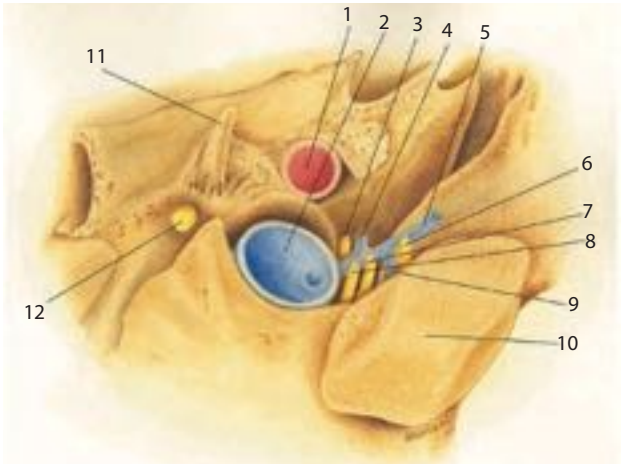


Figure 107.2 View of the jugular foramen (right side) as shown from below. 1, internal carotid artery; 2, internal jugular vein; 3, glossopharyngeal nerve; 4, inferior petrosal sinus; 5, pharyngeal vein; 6, hypoglossal nerve; 7, vagus nerve; 8, spinal accessory nerve; 9, condylar emissary vein; 10, occipital condyle; 11, styloid process; 12, facial nerve.

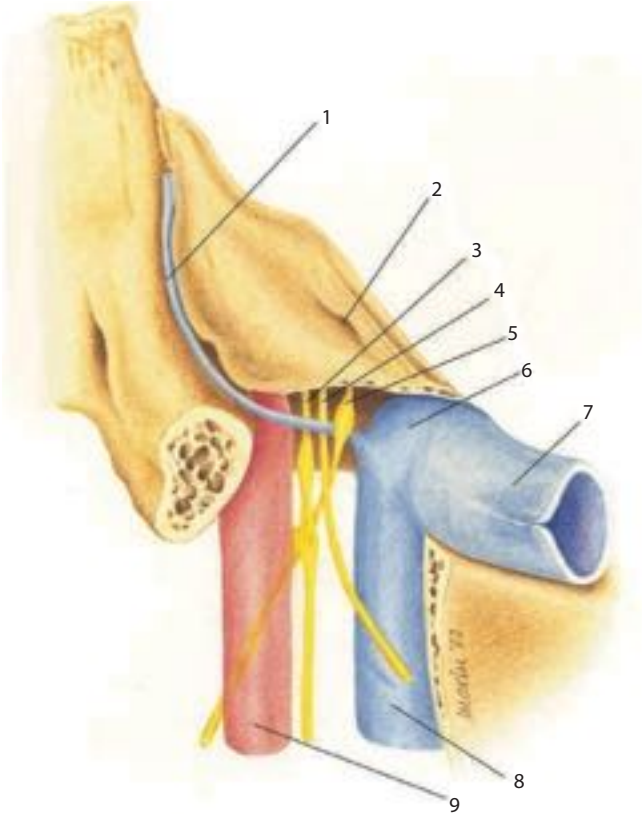


Figure 107.3 View of the jugular foramen (right side) as shown from behind. 1, inferior petrosal sinus; 2, internal auditory canal; 3, vagus nerve; 4, spinal accessory nerve; 5, glossopharyngeal nerve; 6, jugular bulb; 7, sigmoid sinus; 8, internal jugular vein; 9, internal carotid artery.

SYMPTOMATOLOGY

Disease in the jugular foramen causes a variety of symptoms and signs. These are discussed in Chapter 111, Clinical neuroanatomy. In clinical practice, perhaps the

most common is the jugular foramen syndrome, also known as Vernet's syndrome (named after the French neurologist Maurice Vernet). This syndrome comprises paralysis of the cranial nerves IX, X and XI. Obstruction or thrombosis of the sigmoid–jugular complex by tumour or infection may develop and is frequently asymptomatic because the venous drainage system of the brain has sufficient alternative routes or pathways. In rare cases, a thrombosed sigmoid–jugular complex may give rise to retrograde thrombosis of the inferior petrosal sinus and eventually even to thrombosis of the cavernous sinus. This condition then leads to the cavernous sinus syndrome, that is, paralysis of cranial nerves III, IV and VI, oedema of the conjunctiva and upper eye lid, venous congestion in the fundus of the globe and proptosis. Blockage of the cerebral venous drainage through the jugular foramen can also cause increased intracranial pressure and give rise to epileptic seizures and visual obscurations.[4] This is a life-threatening situation that needs urgent attention if multiple neurological deficits are to be avoided.

The symptoms caused by lesions that develop in the jugular foramen are not just confined to their effect on local anatomical structures. Sometimes symptoms are related to more extensive or distant pathology. For example, thrombosis in the jugular foramen is frequently the result of ear pathology, such as chronic otitis media, with or without cholesteatoma. Other factors that might induce thrombosis in the venous structures in the jugular foramen include trauma, various coagulopathies and vessel wall pathology from tumour invasion or systemic vasculitis. Jugular foramen pathology may cause facial nerve palsy and audiovestibular symptoms as a result of the close proximity of the jugular foramen and the vertical part of the facial nerve, cochlea, labyrinth, internal auditory canal and the cerebellopontine angle. Tumours are not the only cause of pulsatile tinnitus; arteriovenous malformations, high jugular bulb or jugular bulb diverticulum are also associated with this symptom. In these latter conditions, the patient should notice a decrease or disappearance of their tinnitus when the IJV in the neck is compressed.

DIAGNOSIS OF JUGULAR FORAMEN LESIONS

Patients in whom a jugular foramen lesion is suspected should undergo a standard triad of diagnostic procedures: first, a clinical examination; second, additional investigations such as audiometry; and third, imaging. The presence of jugular foramen pathology can be substantiated with a high level of probability by the first two steps, but imaging techniques are absolutely necessary to prove the existence and extent of a pathological process.

History and physical examination

The clinical history of patients with jugular foramen pathology is variable. Features to be sought have been discussed in Chapter 99, Evaluation of the skull base patient. Symptoms may result from damage to the contents of the jugular foramen (i.e. cranial nerves IX, X and XI) or to the venous structures of the sigmoid–jugular complex. There may also be symptoms that result from dysfunction of the cochleovestibular system or the facial nerve. For example, paragangliomas of the jugular foramen may present with facial palsy, the insidious development of lower cranial nerve palsies having gone largely unnoticed. In cases with extensive intracranial involvement, ataxia resulting from the compression of cerebellar structures, visual disturbances and vomiting caused by obstructive hydrocephalus may be more prominent features. Infectious disorders of the jugular foramen, such as those caused by chronic otitis media with or without cholesteatoma, may be accompanied by purulent otorrhoea. In some rapidly progressive cases, malaise, fever, headaches and stiffness of the neck may be present and in this situation there should be concern that patients might develop meningitis.

Physical examination should include a complete inspection of the ears, nose and throat and neck. Cranial nerve function must be documented accurately. If the patient has visual symptoms, an ophthalmological opinion is essential.

Additional examinations

Pure-tone and speech audiometry should be performed along with appropriate vestibular tests. Patients with paragangliomas should have their blood pressure checked and either 24-hour urinary collection for catecholamine metabolite assessment or an assay of plasma free metanephrines. This is indicated for two reasons, the identified head and neck paragangliomas may rarely have the capacity to secrete catecholamines, such as noradrenaline and dopamine, and secondly, the patient is at increased risk of having an intra-abdominal paraganglioma or pheochromocytoma, with a greater propensity to secretion.

Imaging

High resolution computed tomography (CT) and magnetic resonance imaging (MRI) are the methods of choice and should be acquired in all patients.[5] T1- and T2-weighted MRI sequences before and after the administration of gadolinium can detect most common lesions in the jugular foramen, such as schwannomas and meningiomas, and portray the precise extent of the tumour both within the infratemporal fossa and intracranially. Paragangliomas, however, require a different policy: besides visualization of the size and extent of the tumour, adequate mapping of vascular structures is a prerequisite to accurate diagnosis. This can be achieved by either magnetic resonance or CT angiography (MRA / CTA) or conventional carotid angiography. MRA with gadolinium enables precise mapping of the vasculature and its relationship with the tumour and surrounding anatomical structures. Moreover, this method accurately displays the size and extent of the tumour. CT images should be made in at least two planes. CT gives more precise information about bone destruction and gives all the information a surgeon would need in relation to temporal bone anatomy if surgery were envisaged.

It is important to visualize the fallopian canal, the middle ear with its ossicles, the absence or presence of a bony lamina between the jugular bulb and the hypotympanum, the position and shape of the internal auditory canal and the carotid canal.

Various scintigraphic techniques may be useful to diagnose some types of pathological condition in and around the jugular foramen. In patients with chronic infections, diagnostic information can be obtained with scintigraphy using radioisotopes, such as technetium-99 methylene diphosphanate and gallium-67 citrate. The former isotope identifies osteoblastic activity, whereas the latter documents the activity of the infectious process. Endocrine activity in paragangliomas can be demonstrated with iodine-123 metaiodobenzylguanidine. Octreotide scintigraphy may contribute to the detection of paragangliomas at multiple locations.

Patients presenting with a jugular foramen paraganglioma should also be screened for other paragangliomas, which are particularly common as manifestations of succinate dehydrogenase gene mutations, typically SDHB or SDHD.[6]

This can be done using positron emission tomography (PET) with 18F-DOPA or 18FDG glucose, although MRI imaging of head, neck, mediastinum, abdomen and pelvis will achieve the same result without radiation exposure, and is therefore the preferred modality for ongoing screening of such patients.

PATHOLOGY

Broadly speaking, pathological conditions involving the jugular foramen can be divided into three categories: neoplasia; infectious conditions; and miscellaneous. The pathological conditions that have been found in the jugular foramen are listed below, the majority being neoplastic disorders. Most of the lesions originate in the jugular foramen or in adjacent structures. The list does not include incidental lesions that originate from more distant head and neck regions and occasionally spread into the jugular foramen, for example, parotid tumours and nasopharyngeal carcinoma, or metastases from distant lesions:

- paragangliomas (also known as glomus tumours)
- schwannoma
- meningioma
- osteoclastoma
- myxoma
- neurofibroma
- haemangiopericytoma
- chondromyxoid fibroma
- angioma
- ceruminoma
- giant cell tumour
- plasmocytoma
- endolymphatic sac tumour
- cholesteatoma
- cholesterol granuloma
- cholesterol cyst
- neurenteric cyst
- amyloidoma
- rhabdomyosarcoma
- adenoid cystic carcinoma
- chondrosarcoma
- sarcoma
- malignant schwannoma.

Neoplasia

Paragangliomas are the most common lesions in the jugular foramen. Schwannomas and meningiomas are the second and/or third most frequent lesions. Schwannomas usually have developed from the cranial nerves IX, X or XI. Meningiomas generally originate intracranially and eventually invade the jugular foramen, although intraosseous meningiomas may occur.[7] Reports of lesions other than paragangliomas, schwannomas and meningiomas are scant and therefore our knowledge of less common jugular foramen lesions is somewhat fragmentary.

PARAGANGLIOMAS

The term paraganglioma is derived from the site of origin of the tumour. In the temporal bone, paraganglia are present in the adventitia of the jugular bulb and along the IXth and Xth cranial nerves, and in the middle ear in association with Jacobsen's plexus. Chromaffin and non-chromaffin paragangliomas have been distinguished according to their intrinsic ability to take up and stain with chromium salts. In the past, a chromaffin paraganglioma was considered capable of producing adrenalin, whereas its non-chromaffin counterpart was not. This distinction between chromaffin and non-chromaffin paragangliomas has since become outdated, as both tumours are now known to synthesize all types of catecholamines. The term chemodectoma should be reserved for tumours that originate from the chemoreceptor system. The paraganglia in the temporal bone do not belong to this histological entity, in contrast with those in the carotid sinus. Therefore, the term chemodectoma is less appropriate for lesions in the jugular foramen and in other parts of the temporal bone.

The term glomus tumour is also inaccurate, because the word glomus means a small, circumscribed histological structure in which arterioles connect directly with veins, a situation found in small cutaneous lesions also known as glomus tumours. However, the term glomus or glomus tumour is commonly used in the historical literature to refer to paragangliomas.

Temporal bone paragangliomas can be divided into one of three categories: jugular paragangliomas; jugulotympanicum paragangliomas; and tympanic paragangliomas. Only the tympanic paraganglioma is confined to the tympanic cavity. These tumours originate in the middle ear, as opposed to jugular paragangliomas, which develop from the adventitia of the jugular bulb. The term jugulotympanic is appropriate for those tumours in which it is impossible to define the site of origin, and for tympanic tumours that have extended to involve the jugular foramen and widely invade the temporal bone.

There is a female predominance.[8] The appearance of the lesion is lobular, pulsatile and red-purple in colour. Its microscopic appearance is dominated by the presence of groups of characteristic neurosecretory cells.

Up to 40% of patients with head and neck paragangliomas have a mutation of the succinate dehydrogenase gene that makes them prone to developing multiple paragangliomas. A proportion of these patients will have multiple tumours at presentation, which may include intra-abdominal tumours with a higher propensity to secrete catecholamines. Paragangliomas are considered to belong to the amine precursor uptake and decarboxylation (APUD) tumours. Consequently, associations have also been described between paragangliomas and a variety of other APUD tumours, such as various forms of multiple endocrine adenomatosis. Moreover, concomitant occurrence has been described with Von Hippel–Lindau disease, renal cell carcinoma, neurofibromatosis and vestibular schwannoma.

Several classifications have been proposed for paragangliomas in the temporal bone, based on symptoms and/or the size and extent of the tumour. Nowadays, staging is performed by means of MR and CT imaging. The most frequently used classification was the one developed by Fisch (**Table 107.1**)[9] in which tumours are classified from A to C based on extension within the temporal bone with tumours that affect the jugular foramen belonging to class C. Class C is subdivided according to the relationship between the tumour and the carotid artery, and Class D is used in addition to the A–C moniker to describe the extent of intracranial involvement where this is present.

The biological behaviour of paragangliomas is usually indolent: it can take many years or even decades for slight growth to become apparent. However, even without any substantial increase in the volume of the lesion, symptoms of progressive cranial nerve deficits may develop, presumably as the result of local erosion and compression by the tumour. In **Figures 107.4** and **107.5**, two illustrative cases are shown.

TABLE 107.1 Classification of paragangliomas in the temporal bone according to Fisch

Classification	
Class A	Limited to the middle ear (mesotympanum)
Class B	In the middle ear (meso- and hypotympanum) and the mastoid
Class C	Tumour originates in the dome of the jugular bulb, destroying the overlying bone; the tumour may spread inferiorly, posteriorly, superiorly, laterally and/or medially; class C is subdivided into four categories, according to the size and extension of the tumour
Class D	Intracranial extension; class D is subdivided into two categories according to the presence or absence of intradural extension; these two categories are subdivided again according to the depth of invasion of the posterior fossa and the degree of medial displacement of the posterior fossa dura, respectively

Reproduced with permission from Fisch.[9]

SCHWANNOMAS

Synonyms for schwannoma include nerve sheath tumour, neuroma, neurilemoma and neurinoma. Nowadays, schwannoma is the generally agreed term because the lesion develops from the Schwann cells in the perineurium. The pars nervosa of the jugular foramen is the site of origin, and the cranial nerves IX, X or XI are primarily affected.

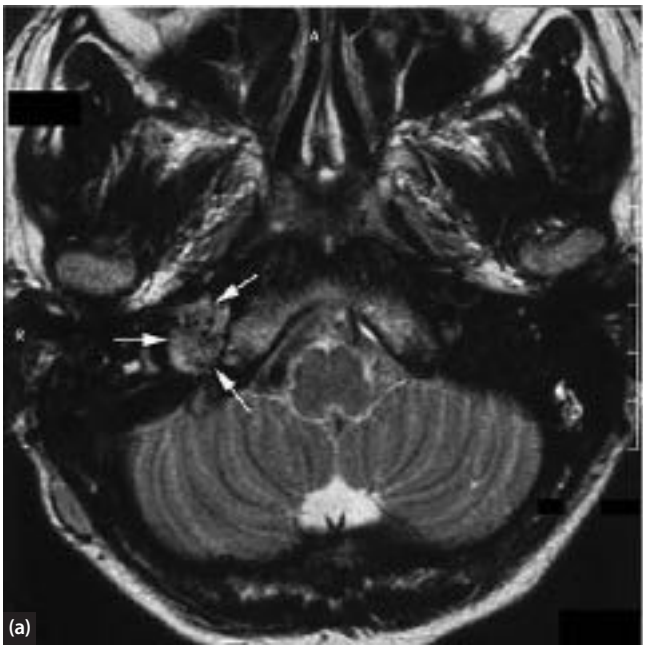
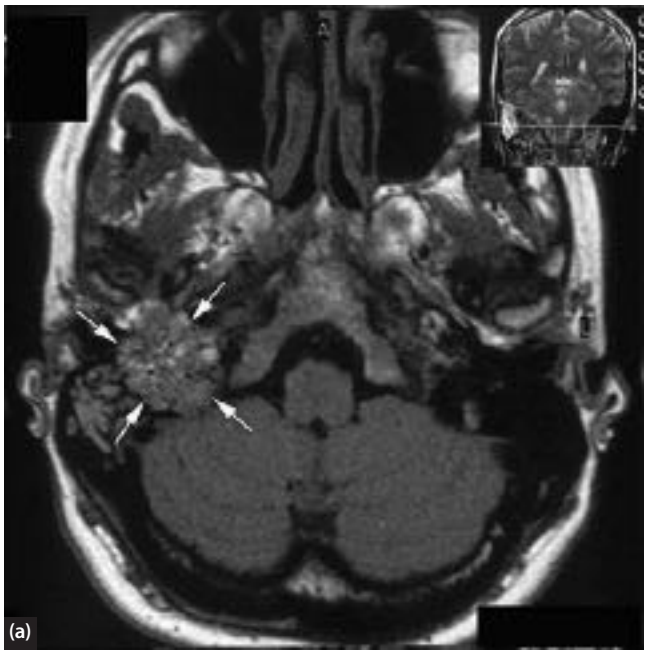




Figure 107.4 A 42-year-old woman presented with a mixed sensorineural-conductive hearing loss of about 50 dB on the right side in combination with a reddish-blue discolouration of the tympanic membrane. (a) T2-weighted axial MRI showing the lesion in the axial plane (arrows). **(b)** T1-weighted coronal slices, showing the involvement of the jugular bulb and the sigmoid–jugular complex (arrows). *(Continued)*



Figure 107.4 (Continued) A 42-year-old woman presented with a mixed sensorineural-conductive hearing loss of about 50 dB on the right side in combination with a reddish-blue discolouration of the tympanic membrane. (c) Subtraction image (that is, T1 with gadolinium minus T1). Diagnosis: Jugular paraganglioma, presumably a class C lesion according to the classification of Fisch.[9]





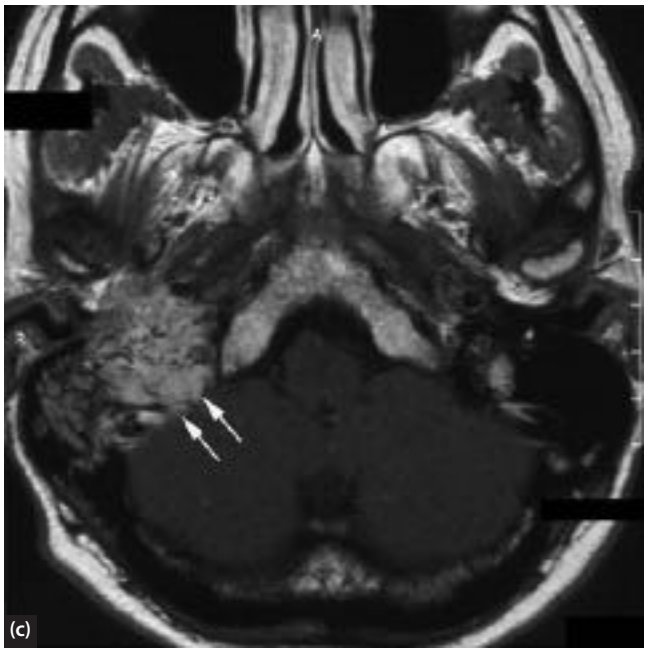
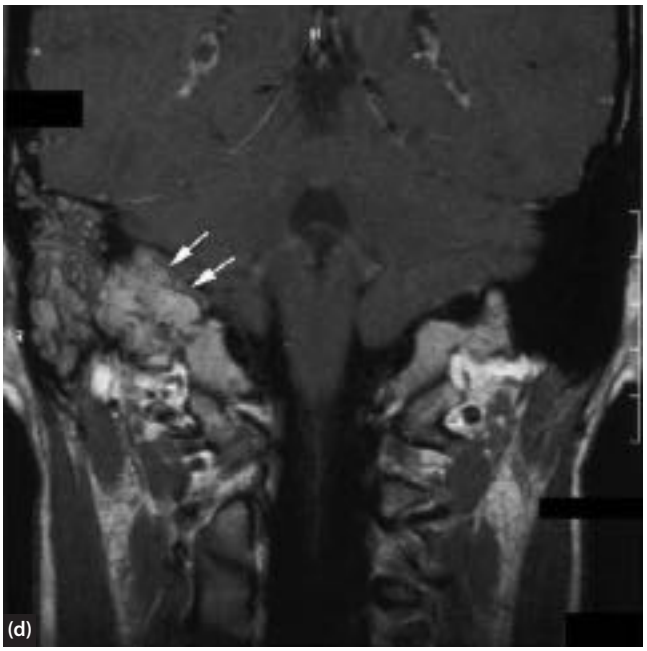
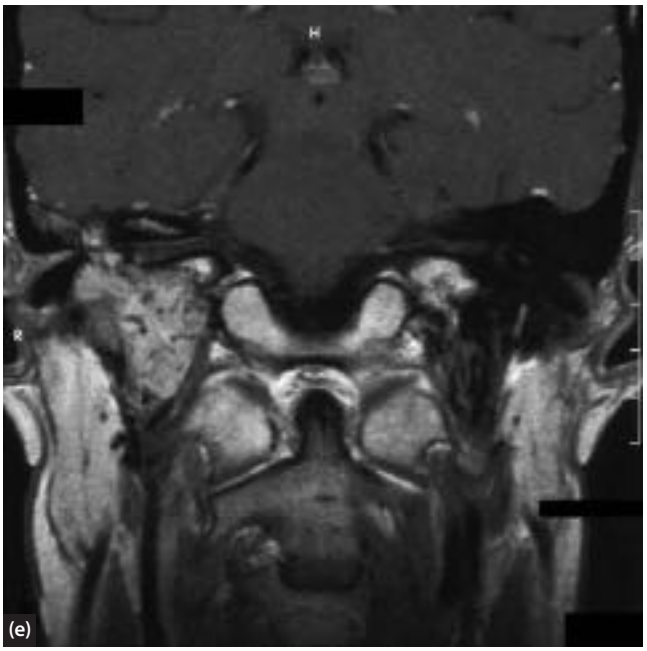


Figure 107.5 A 25-year-old woman presented with right-sided mixed sensorineural-conductive hearing loss of about 60 dB and pulsatile tinnitus. The right tympanic membrane had a reddish-blue discolouration. (a) Axial T1-weighted MRI showing a mass lesion around the right jugular foramen (arrows) with the characteristic appearance of a paraganglioma. **(b)** Coronal MRA; absence of flow in the right sigmoid–jugular complex and internal jugular vein. **(c)** Axial T1-weighted MRI with gadolinium demonstrating involvement of the posterior fossa dura (arrows). *(Continued)*





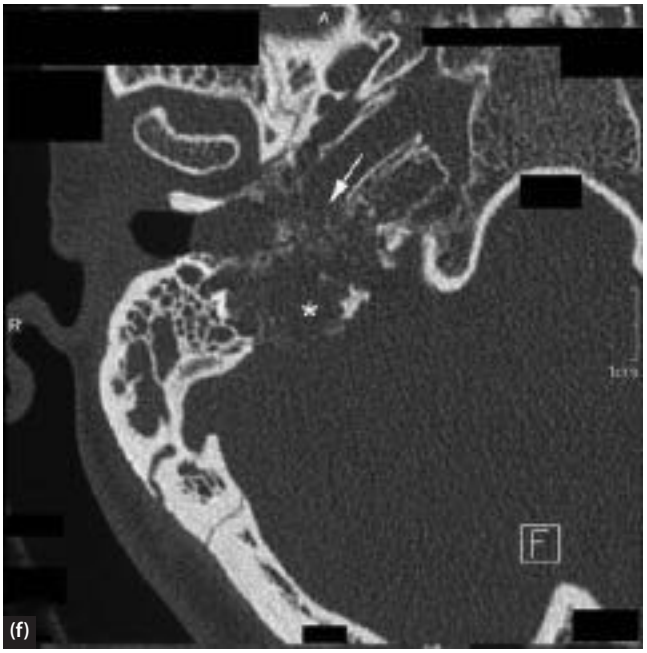




Figure 107.5 (Continued) A 25-year-old woman presented with right-sided mixed sensorineural-conductive hearing loss of about 60 dB and pulsatile tinnitus. The right tympanic membrane had a reddish-blue discolouration. (d) Coronal plane (continued over). **(e)** Demonstrating the tumour in proximity of the internal auditory canal. **(f)** Axial CT scan showing a large defect in the temporal bone (asterisk); note the absence of the bony contour of the internal carotid artery (arrow). **(g)** Coronal CT scan; the tumour extends from the jugular bulb in a cranial direction and has filled the middle ear. Diagnosis: glomus temporale tumour, a class D lesion according to the classification of Fisch.[9]

As a result, a schwannoma is usually localized in the medial part of the jugular foramen. Kaye et al.[10] and Pellet et al.[11] classified jugular foramen schwannomas according to their size and extension (Table 107.2). A further classification has been proposed by Franklin et al. (Table 107.3).[12]

Their histopathological appearance is identical to that of sporadic vestibular schwannomas. Antoni type A and type B tissues can be distinguished. Type A tissue is characterized by densely packed cells, whereas type B tissue is fairly hypocellular with a myxoid stroma. Both types can develop in different proportions. Fatty degeneration, haemorrhage, necrosis and cyst formation may also be seen. The biological behaviour of schwannomas in the jugular foramen does not differ from that in the internal auditory meatus or the cerebellopontine angle, often slow growing or apparently static. Rapid increase in size may be seen and is usually the result of intratumoral haemorrhage and cyst formation.

MENINGIOMAS

Intracranial meningiomas represent about 15–20% of all brain tumours. Basal meningiomas can penetrate the skull base through any of the natural foramina (e.g. the foramen magnum, the optic canal and the jugular foramen). Locally aggressive meningiomas sometimes invade

TABLE 107.2 Classification of jugular foramen schwannomas, according to Kaye et al.[10] and Pellet et al.[11]

Classification	
Type A	Primarily growing intracranially into the cerebellopontine angle
Type B	Growing into the jugular foramen
Type C	Primarily growing extracranially into the neck
Type D	Dumb-bell-shaped tumour, growing from the jugular foramen intracranially and extracranially

TABLE 107.3 Classification of jugular foramen schwannomas, according to Franklin et al.[12]

Classification	
Type A	Confined to the neck
Type B	In the neck and extending into the jugular foramen
Type C	In the jugular foramen and extending along the internal carotid artery
Type D	In the jugular foramen and extending intracranially

Reproduced with permission from Franklin et al.[11]

TABLE 107.4 Meningiomas: World Health Organization classification

Classification	
Grade I (typical)	• Meningothelial (syncytial) • Fibrous (fibroblastic) • Transitional (mixed) • Psammomatous • Angiomatous • Microcystic • Secretory • Clear cell • Chordoid • Lymphoplasmocyte-rich • Metaplastic
Grade II (atypical)	Papillary
Grade III (anaplastic)	Malignant

Reproduced with permission from Kleihues et al.[13]

bone and form new openings (e.g. from the anterior fossa through the cribriform plate into the nasal cavity and from the middle fossa into the temporal bone). About one in five intracranial meningiomas have such extracranial extensions. The histopathology and vascularity of these tumours varies widely. Some classifications have been proposed mainly based on morphological characteristics. The World Health Organization classification is the most generally accepted (Table 107.4).[13] About 10 percent of meningiomas undergo malignant transformation and very occasionally metastasize to the lung, liver or kidney. Females are more frequently affected than males. The peak age of incidence is in the fifth decade.

The medial aspect of the jugular foramen is invaded by meningiomas whose site of attachment lies either anteriorly or at the level of the lower clivus. The lateral aspect is invaded by lesions that originate more posteriorly at the dorsal aspect of the petrous bone. The lower cranial nerves are more susceptible to damage when the medial part of the jugular foramen is involved. Sometimes the tumour also erodes bone and grows through the jugular foramen into the infralabyrinthine bone and tympanic cavity. The tumour can also extend through the jugular foramen into the upper neck, occasionally within the lumen of the internal jugular vein (IJV). Biological activity varies, but slow progression is the most usual pattern.

METASTATIC LESIONS

The common malignancies that arise in the lung, breast, prostate, kidney, stomach and thyroid gland can metastasize to the skull base, including the jugular foramen. Less common malignancies that develop in adjacent structures such as the posterior fossa, temporal bone, infratemporal fossa and nasopharynx, can also spread into the jugular foramen. Some histological types, such as adenoid cystic carcinoma, are more common than others. This tumour may originate in the deep lobe of the parotid gland and spread into the skull base. Metastases from haematological neoplasms and extramedullary plasmocytomas are also seen in the temporal bone and in the jugular foramen, usually as a result of haematogenous spread. Lymphatic spread of malignancies into the jugular foramen is very uncommon. Like many other jugular foramen lesions, metastases make their presence known by causing cranial nerve dysfunction (VII to XII). Erosion of bone usually accompanies metastatic disease and this is clearly seen on CT images as radiolucent areas in bony structures.

Infectious conditions

The most frequent infectious conditions that affect the jugular foramen are:

- acute otitis media
- chronic otitis media
- chronic otitis media with cholesteatoma
- varicella zoster virus
- osteomyelitis
- epidural empyema
- necrotizing skull base osteomyelitis.

The majority are related to otitis media, predominantly the chronic type, with or without cholesteatoma. Intracranial disorders that result in jugular foramen pathology, such as meningitis and epidural empyema, are also frequently related to some type of otitis media.

Miscellaneous disorders

A high jugular bulb is defined as reaching beyond the level of the inferior border of the tympanic annulus. It is a well-known entity that protrudes anteriorly and laterally, and is visible behind the tympanic membrane or in the external auditory canal. It may even reach the ossicular chain and give rise to conductive hearing loss. In patients with a high jugular bulb, myringotomy and tympanoplasty may lead to severe haemorrhage if the condition is not recognized pre-operatively.

Jugular bulb diverticulum is another vascular disorder. The diverticulum develops from the jugular bulb and extends towards the posterior semicircular canal, the internal auditory meatus or the posterior fossa. Vestibular symptoms, sensorineural hearing loss or even facial nerve palsy may be associated with this. The condition can also cause symptoms similar to those in Ménière's disease. In Figures 107.6 and 107.7, two illustrative cases are shown.

MANAGEMENT

The goals of management must be clearly defined in this complex area, and the following discussion pertains primarily to the three commonest pathologies in this area, paragangliomas, schwannomas and meningiomas, all of which typically have a relatively indolent natural history.

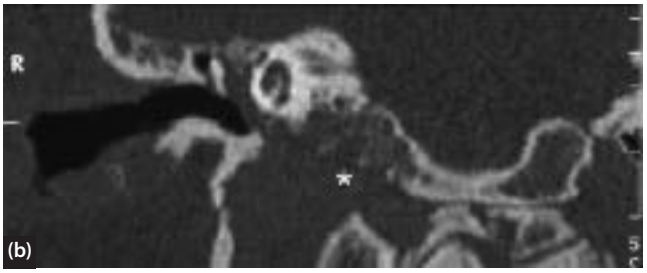
It is generally the case that the gradual onset of venous outflow obstruction is relatively well tolerated, as collateral veins develop, although exceptions occur.

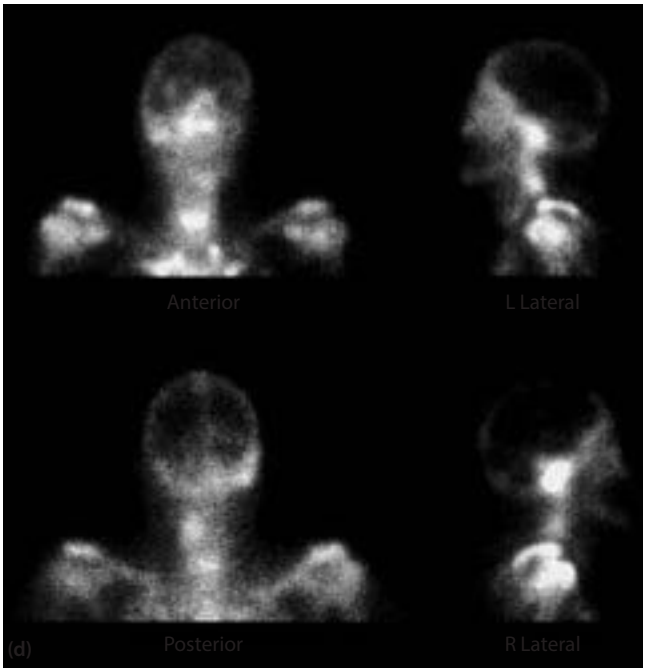
The primary goals of treatment are therefore:

1. to address presenting symptoms
2. the preservation of remaining neurological function (that which has been lost will generally not return)
3. to avoid intracranial disease extension and the associated risk of brainstem compression.

For the majority of processes affecting the jugular foramen, the likelihood of these occurring in the next few years if







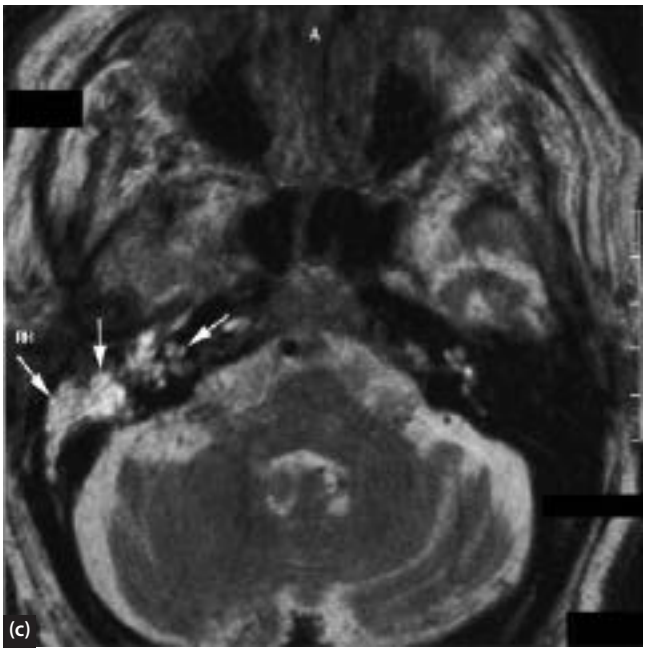


Figure 107.6 A 78-year-old man with a history of diabetes mellitus, polyneuropathy and chronic otitis media presented with right-sided facial palsy (House-Brackmann grade III) and signs of involvement of cranial nerves IX, X and XI. (a) Axial CT scan showing an irregular defect in the right petrous apex (asterisk) extending towards the jugular bulb. **(b)** The coronal plane (asterisk). **(c)** T2-weighted MRI; the right mastoid and some petrous apex cells are filled with fluid (arrows). **(d)** Scintigram (technetium-99m diphosphanate) with signal enhancement in the area of the right temporal bone. Diagnosis: jugular foramen syndrome as a result of petrositis/osteomyelitis of the skull base.

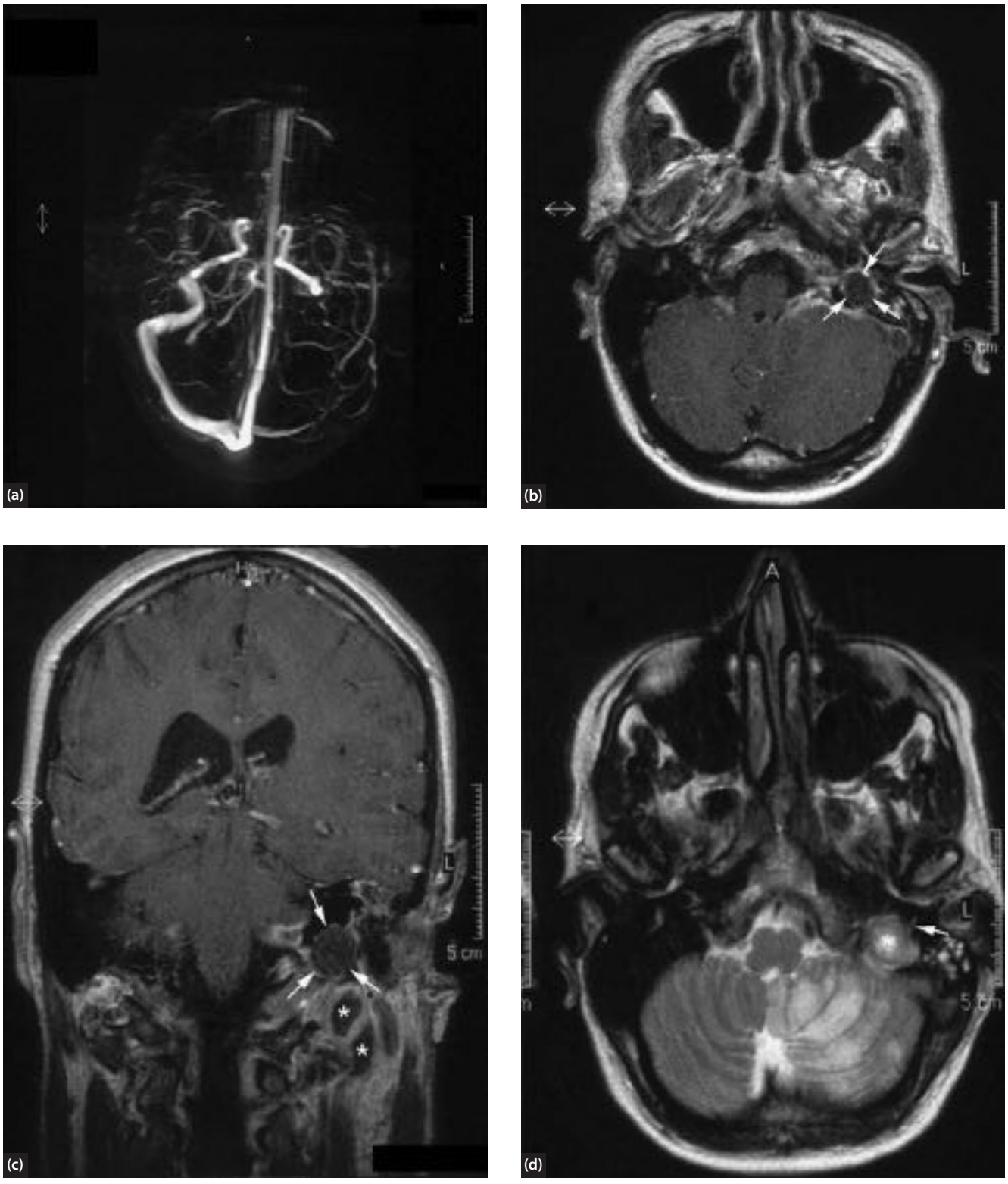


Figure 107.7 A 42-year-old man presented with fever, headache and 40 dB conductive hearing loss on the left side. Moreover, there were clinical signs of involvement of the cranial nerves VII (House-Brackmann II), IX, X, XI and XII. **(a)** MRA showing absence of flow in the left transverse sinus and sigmoid–jugular complex. **(b)** T1-weighted coronal MRI after administration of gadolinium. Mass lesion in the left jugular foramen (arrows). Multiple cystic lesions in the upper neck (asterisks). **(c)** T1-weighted axial MRI after administration of gadolinium. Note mass lesion in the jugular foramen (arrows). **(d)** T2-weighted axial MRI. The lesion in the left jugular foramen is depicted as a hyperintense area (asterisk); a small band suggests the presence of a connection with the middle ear (arrow); this was confirmed during surgery. Diagnosis (made intra-operatively): cholesteatoma in the left jugular foramen with thrombosis of the sigmoid–jugular complex and multilocular abscesses in the upper neck.

the disease is left untreated is low, and it is important that well intentioned intervention does not hasten the onset of disability.

Historically, the presence of a space-occupying lesion once formed sufficient grounds to proceed directly to surgery. It was believed that something that should not be there had to be removed, in view of the threat to adjacent vital structures.

Although the body of literature on jugular foramen lesions still focuses on surgical treatment, much can also be said for non-surgical or conservative management.

Which approach is appropriate depends not only on the nature and extent of the lesion but also on the patient. Advanced age or poor physical condition are contraindications for surgery. As conservative management becomes more widely practised there is also an increasing body of evidence that while paragangliomas, schwannomas and meningiomas may progress rapidly, the majority do not, and spontaneous regression of schwannomas is well recognized. In many cases, progression of the disorder may be extremely slow, sometimes so slow as to be undetectable.

An initially expectant policy may therefore be justified. In general, the choice of surgery, non-surgical or conservative management should not be made until a wide range of aspects concerning the patient and the disorder have been fully considered.

Wait-and-see policy

The size of a jugular foramen lesion can now be accurately measured, monitored and documented with the available imaging modalities of CT and MRI.

In many cases, the lesions do not pose a threat during the whole of the patient's life. However, there are also a number of lesions that show considerable progression and cause progressive neurological deficits and risks to life.

The main problem is therefore to identify those lesions that will progress in the future. Although theoretically histological features of the tumour could provide some insight into its biological behaviour, in most cases taking a biopsy from a jugular foramen lesion is not feasible, and for the commoner pathologies even histology is often unable to distinguish between aggressive and indolent forms of the disease. One potential surrogate marker for future behaviour of paragangliomas is metabolic activity as evidenced by standardized uptake value (SUV) max on FDG PET (fludeoxyglucoze), with higher SUV correlating with an increased tendency to growth.

It is logical to assume that larger tumours are more likely to pose an early threat to the patient than smaller lesions, and one might therefore be more inclined to treat these surgically. However, post-operative morbidity and mortality is also potentially more significant in patients with larger tumours, hence patients with minimal symptoms may be tempted to explore non-surgical options. Conversely, patients with small tumours may tolerate surgery relatively well; however, the risk associated with leaving the lesion is also minimal.

It must be emphasized that these considerations only apply to the three most common jugular foramen lesions. Conditions other than a paraganglioma, schwannoma or meningioma require a different approach, depending on the nature of the lesion. In many of these lesions, it is questionable whether surgery or any other form of treatment will be beneficial to the patient.

Medical therapy

There are very few indications for medical treatment for jugular foramen lesions. Antibiotics are important for all infectious conditions of the jugular foramen, such as those associated with chronic otitis media. Acute sepsis and its complications cannot usually be cured by even the most potent antimicrobial medication, so surgery will invariably be part of the therapeutic strategy. Necrotizing osteomyelitis in contrast is not amenable to surgery, other than to provide tissue for culture, and must be addressed with long term antimicrobial therapy.

Radiotherapy

Conventional fractionated radiotherapy has been demonstrated to be as efficacious as surgery in providing long-term tumour control in jugular and vagal paragangliomas, with a lower risk of iatrogenic cranial nerve damage.[14–16]

The aim is to destroy the microvascular tissue and bring about sclerosis and fibrosis, hence the tumour will not disappear, but may regress over time.

With modern radiotherapy techniques it is relatively straightforward in the vast majority of tumours to limit the dose delivered to the brain to within its tolerance. The cochlea is likely to be affected, however, and treating the middle ear component of a jugular paraganglioma with radiation will invariably compromise the tympanic membrane and risk radiation induced exposure of the bony ear canal floor.

Radiotherapy may be an option for patients whose paraganglioma is impossible to remove surgically (i.e. to patients with extensive class C and D tumours), although in some cases the degree of brainstem compression may present a contraindication, and debulking surgery may be a prerequisite.

In the elderly and those whose life expectancy is limited by other conditions it may be more appropriate not to treat the jugular foramen lesion at all, although a rapidly progressive tumour may be treated with radiotherapy.

The role of radiotherapy in meningiomas is neither sharply delineated nor universally accepted. The indolent nature of these lesions impairs assessment of the contribution that radiotherapy might make to slowing down or stopping progression. Moreover, meningiomas represent a fairly heterogeneous histological group of lesions, which may all react differently to irradiation. A clinical trial randomizing WHO grade 1 meningiomas subtotally resected to either radical radiotherapy or conservative management was instituted by the EORTC clinical trials group but it was abandoned due to low enrolment (EORTC 22021–26021). A similar trial looking at WHO grade 2 and 3 meningiomas is ongoing

but is yet to report results (as of March, 2018, EORTC 22042–26042), although in this cohort of patients radiation is generally considered of more benefit.

In addition, the anatomical localization and extension of meningiomas in and around the jugular foramen differ from one patient to another to a greater extent than for other pathologies, complicating the comparison of different treatments.

All these factors complicate the realistic evaluation of the value of radiotherapy as a treatment for meningiomas.

The jugular foramen lies in close proximity to delicate and vulnerable structures. Therefore, single-dose stereotactic radiosurgery is likely to be chosen in preference to conventional radiotherapy for common benign lesions in the jugular foramen, such as meningiomas and schwannomas.

Stereotactic radiosurgery

Stereotactic radiosurgery is rapidly gaining popularity as a treatment modality for tumours of less than 3 cm maximum diameter. It forms an alternative to microsurgical removal of a variety of benign lesions in the skull base, including those arising in the jugular foramen. The principles of this method of treatment are described in Chapter 103.

Most experience with stereotactic radiosurgery in skull base tumours has been gained on vestibular schwannomas, and for suitable tumours (i.e. predominately solid tumours of less then 3 cm maximum diameter results are excellent). Smaller series of non-vestibular and jugular foramen schwannomas demonstrate similar high rates of tumour control, with a lower incidence of cranial neuropathy than that associated with surgery.[17, 18]

Stereotactic radiosurgery for jugular paragangliomas has been demonstrated to be as efficacious as external beam radiotherapy, with a similar low rate of iatrogenic cranial neuropathy, and has the merit of being a single fraction treatment.[14]

The role of both radiotherapy and radiosurgery in the management of meningiomas throughout the skull base remains ill defined, and this also applies to this subsite. In view of the ambiguous nature of the evidence, clinical trails are now underway that should better define this issue, in particular for WHO grade 2 meningiomas.[19]

Generally, stereotactic radiosurgery can be considered for patients with small volume progressive disease and minimal symptoms, residual disease after surgery, inoperable tumours and in patients of advanced age or with poor physical condition.

SURGICAL MANAGEMENT

Surgical treatment for lesions in and around the jugular foramen is one of the most challenging procedures in head and neck surgery. Various surgical approaches have been described; lateral transtemporal techniques are the most widely used. A major key to success is the surgeon's knowledge of anatomy, particularly in view of the close proximity of a considerable number of important anatomical structures in this delicate area.[20]

The facial nerve nearly always causes a major obstruction to the direct surgical access of the jugular foramen. It goes without saying that it is absolutely imperative to avoid severing or damaging this important nerve. Various surgical approaches have been described, all with the intention of preserving the anatomical integrity of the facial nerve in combination with adequate surgical exposure.[21] During surgery in the region of the jugular foramen, cranial nerves VII–XII are particularly vulnerable. It should be emphasized that any damage to the VII cranial nerve results in far more serious morbidity than impairment of one or more of the other cranial nerves. Therefore, continuous intra-operative facial nerve monitoring should be performed routinely. Monitoring of X and XII nerves is also advisable in cases where pre-operative function is normal.

The internal carotid artery is another major issue for concern. The vertical part of the carotid canal lies close to venous and nervous structures in the jugular foramen. Some lesions invade the petrous carotid artery, which makes preservation of this vessel problematic. In rare occasions pre-operative stenting or balloon occlusion of the carotid may be appropriate.

Pre-operative embolization

Paragangliomas are the most common lesions found in the jugular foramen. If surgical removal is planned embolization should be considered. Selective arteriography is performed and the tumour embolized via branches of the external carotid artery. There is general agreement that pre-operative embolization significantly reduces blood loss during surgery and this facilitates complete removal of the tumour; however, embolization itself carries a small risk of stroke. The timing of embolization is subject to debate, consensus appears to be that it should take place within 48 hours of surgery, although some surgeons advocate waiting 4–6 weeks after embolization prior to surgery.

Similarly, intra-operative haemorrhage is also the main cause of problems during the surgical removal of meningiomas, particularly those that are extremely vascular. Excessive bleeding can lead to incomplete tumour resection, damage to adjacent structures and post-operative morbidity. It is therefore sensible to assess their vascularity by angiography and undertake superselective embolization in selected cases. Thus, two of the most common lesions in the jugular foramen – paragangliomas and meningiomas – should be investigated with conventional angiography and embolization undertaken where indicated.

Permanent balloon occlusion of the proximal and distal petrous carotid artery should be undertaken where it is likely that the artery is not salvageable. In this situation, the tumour can be embolized via the nutrient vessels that branch off the internal carotid artery by means of inserting a catheter proximal to the balloon. This should be done at least a month prior to definitive surgery, to minimize the risk of a watershed cerebral infarct in the event of intra-operative hypotension.

If carotid occlusion is not tolerated the artery can be reinforced with a covered stent, which minimizes the risk of iatrogenic bleeding at the time of tumour resection.

Surgical approach

The requirement of the surgical approach is that it provides adequate exposure of the tumour, and of the key structures at risk in tumour resection. In the management of jugular foramen lesions, these key structures are the facial nerve and the internal carotid artery.

A wide range of approaches has been described, and choice of approach will be dictated by the patient's anatomy and pathology, the goal of surgery (debulking versus complete resection) and surgical preference.

The basic concepts of all the lateral transtemporal surgical approaches described in the literature are fairly similar. A wide retroauricular incision is made to gain access to the lateral aspect of the temporal bone (**Figure 107.8**). This incision is extended downwards into the neck to expose the structures in the infratemporal region. Then, a wide cortical atticomastoidectomy is performed with skeletonization of the sigmoid sinus. A cranially based tympanomeatal flap can be developed if exposure of the tympanic cavity, in particular the hypotympanic region, is required. After detachment of the tendon from the sternocleidomastoid muscle, the mastoid tip is removed. The mastoid segment of the fallopian canal is skeletonized, from the second genu towards the stylomastoid foramen. The bone anterior to this part of the facial nerve is removed and, at the same time, the dome of the jugular bulb is exposed. A diamond burr is used to remove as much bone as possible that covers the sigmoid sinus and the jugular bulb, so that the fallopian bridge is the only structure that overlies the jugular bulb. As a result, the facial nerve may impair adequate exposure of lesions involving the jugular foramen, but the degree of access required also depends on the pathology. In many cases, the vertical segment of the facial nerve has to be transposed, particularly if the lesions are extensive and bulky. There are two ways to deal with this problem. The first method preserves the ear canal, tympanic membrane and middle ear structures, whereas the second method involves performing a subtotal petrosectomy to gain wide access to the facial nerve. Another possibility is not to transpose the facial nerve. Von Doersten and Jackler[22] reviewed the different ways of handling the facial nerve in jugular foramen surgery.

CONSERVATIVE FACIAL NERVE MANAGEMENT

According to some authors, lesions can be removed without any interference to the facial nerve (**Figure 107.9**).[23–25] There is no doubt that this is possible in certain cases. It typically requires the axis of surgical approach to move postero-inferiorly, to the so-called far-lateral approach. However, the anatomical relationship between the mastoid segment of the facial nerve and the jugular bulb varies considerably. When the space between the two is small, it may be difficult to achieve adequate exposure. In patients with a relatively small tumour and sufficient working space between the vertical segment of the nerve and the jugular bulb, it is usually possible to leave the facial nerve undisturbed. The nerve should preferably remain covered

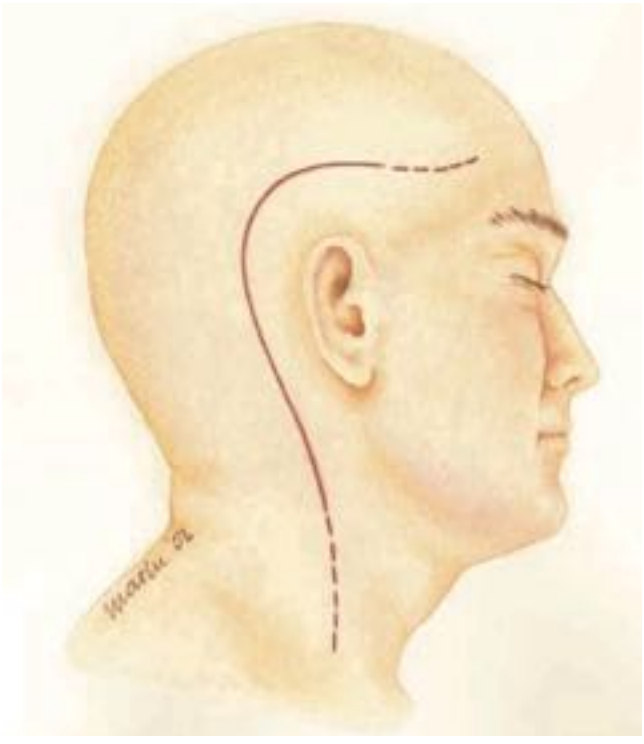


Figure 107.8 The skin incision for the several types of transtemporal approaches to the jugular foramen region.

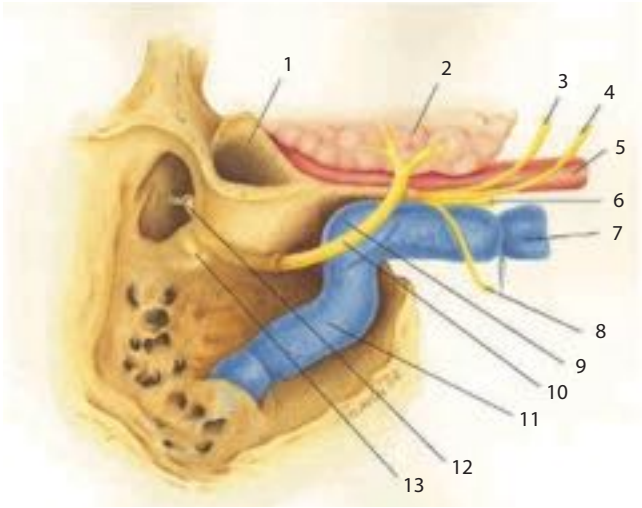


Figure 107.9 Conservative facial nerve management. The right jugular foramen region is exposed without transposition of the facial nerve. After the atticomastoidectomy, the sigmoid–jugular foramen region is exposed. The facial nerve is skeletonized and left *in situ*. The sigmoid–jugular complex is controlled by sutures around the sigmoid sinus and the internal jugular vein. 1, External auditory canal; 2, parotid gland; 3, glossopharyngeal nerve; 4, hypoglossal nerve; 5, internal carotid artery; 6, vagus nerve; 7, internal jugular vein; 8, spinal accessory nerve; 9, jugular bulb; 10, facial nerve; 11, sigmoid sinus; 12, incus; 13, semicircular canals.

by a bony shell (fallopian bridge). In these cases, a large amount of bone anterior to the facial nerve has to be removed to enable wider access to the jugular foramen. Some type of facial nerve transposition may need to be considered if visibility is poor and there is always the risk of incomplete tumour removal.

LIMITED FACIAL NERVE TRANSPOSITION, CANAL WALL UP

This technique involves complete removal of the bony covering of the mastoid segment of the facial nerve, from the second genu down to the stylomastoid foramen. Outside the stylomastoid foramen, the nerve is followed and mobilized over its intraparotid course: first the main trunk and then the temporozygomatic and cervicofacial branches. The subdivisions of these branches are also mobilized and the overlying parotid tissue is removed. Care should be taken to preserve the stylomastoid artery at this stage, to minimize the risk of post-operative facial weakness. After this part of the procedure there is some mobility of the nerve, such that it can be pulled anterolaterally, away from the jugular bulb (**Figure 107.10**). Whether this provides enough exposure is a subject of controversy. It has been stated that this is sufficient for all jugular foramen lesions, but this opinion is not shared universally.[26] According to Fisch,[9] far greater access is needed to achieve adequate exposure and enable total resection of the tumour.

FACIAL NERVE TRANSPOSITION, CANAL WALL DOWN

In order to be able to mobilize the facial nerve more extensively, atticomastoidectomy should be extended to subtotal petrosectomy. This involves removal of the skin of the external auditory meatus along with the tympanic membrane, the malleus and incus, drilling away the posterior canal wall and extensive exenteration of pneumatic cells. As a result, the facial nerve can be uncovered, not only in its mastoid segment, but also in its tympanic part. Then, after mobilization of the intraparotid facial nerve as described above, the nerve can be rerouted anteriorly. The hinge point (pivot) may be located at the second genu, but wider exposure is achieved when the nerve is displaced anteriorly with the hinge point at the first genu (**Figures 107.11** and **107.12**).[22]

MANAGEMENT OF THE SIGMOID–JUGULAR COMPLEX

Damage to the sigmoid sinus or the jugular bulb is a serious risk during jugular foramen surgery. If the vessel wall is punctured, the initial bleeding is fairly simple to control, but retrograde haemorrhage from the IJV may follow. Therefore, the venous blood flow must be blocked at two levels: cranially and caudally to the lesion (i.e. upstream and downstream) (**Figures 107.9–107.12**). It is logical to start with blocking the main flow on the cranial side, the sigmoid sinus. Two methods have been described, ligating the vessel or packing it with Surgicel, both preferably below the level of a preserved mastoid emissary vein. The upper neck can be explored by extending the retroauricular incision downwards. Accordingly, the IJV can be found easily in a later stage of the procedure, after the sternocleidomastoid muscle has been detached from the mastoid process and the mastoid tip has been removed. After identifying the surrounding structures, such as the

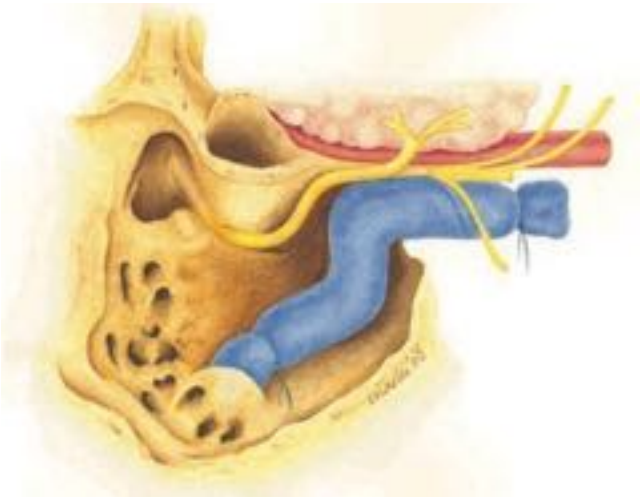


Figure 107.10 Facial nerve transposition, canal wall up. The right jugular foramen region is exposed with a limited transposition of the facial nerve. After an atticomastoidectomy, the mastoidal segment part of the facial nerve is uncovered. The intraparotid part of the nerve is exposed and mobilized. The nerve can then be pulled anteriorly in order to provide access to the jugular bulb. (See also **Figure 107.5**.)

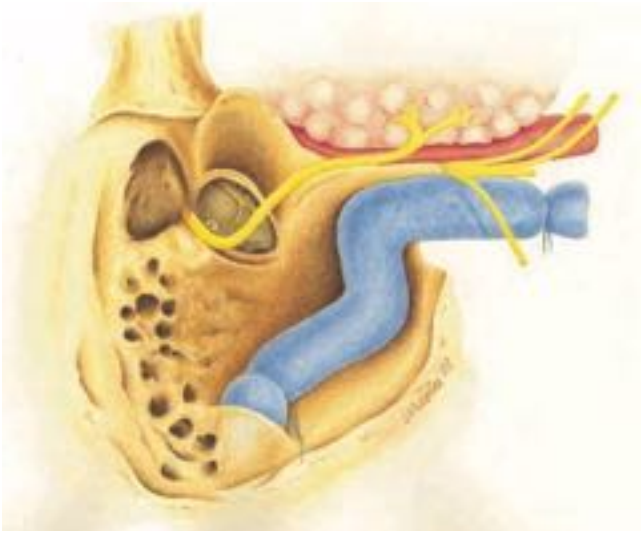


Figure 107.11 Facial nerve transposition canal wall down. The right jugular foramen region is exposed using a more extensive transposition of the facial nerve. After a canal wall down atticomastoidectomy, the tympanic membrane, the malleus and the incus are removed. The facial nerve is uncovered in its mastoidal and tympanic segments. The intraparotid part of the nerve is exposed and mobilized. The nerve can then be rerouted anteriorly with the hinge point at the second genu. (See also **Figure 107.5**.)

internal carotid artery and the cranial nerves IX, X, XI and XII, the IJV should be ligated as high up as possible to avoid bleeding from veins that drain into it in the upper neck. The inferior and superior petrosal sinuses and the mastoid and condylar emissary veins drain into the sigmoid–jugular complex. Usually in a later stage of the procedure, the sigmoid sinus and the jugular bulb have to be opened to remove the tumour. Then bleeding can be expected from these sinuses and emissary veins, which should be dealt with by the use of haemostatic agents.

MANAGEMENT OF THE INTERNAL CAROTID ARTERY

Preservation of the internal carotid artery is of crucial importance during surgery for jugular foramen lesions. The tumour may be attached to the internal carotid artery or be in close contact with it. Visualization of the plane between the tumour and the petrous carotid artery is extremely important. Therefore, the operative field should be as bloodless as possible. All sources of venous haemorrhage must be meticulously controlled, either by ligation or by packing with haemostatic agents. Management of the internal carotid artery is particularly important in patients with paragangliomas. This artery is less likely to be threatened by schwannomas or meningiomas. Paragangliomas may invade the carotid canal, first in its vertical part and eventually along the horizontal part on to the foramen lacerum. They will typically receive part of their blood supply from the petrous carotid artery, via its caroticotympanic or dural branches. In very large tumours, permanent balloon occlusion of the internal carotid artery must be considered, but only if there is sufficient collateral circulation. The latter can be tested pre-operatively during the angiography procedure by temporary occlusion with clinical and radiological surveillance. According to Andrews et al.,[27] permanent balloon occlusion is a safe procedure and does not cause any serious ischaemic deficits, as long as the tolerance test shows sufficient patency of the circle of Willis.

Extensive lesions and malignant tumours may require wide resection with sacrifice of the internal carotid artery. It should also be emphasized that not all patients have sufficient collateral circulation to allow permanent balloon occlusion. In these cases the artery may be stented, with a covered stent to provide reinforcement, or an extracranial–intracranial bypass procedure may be considered.

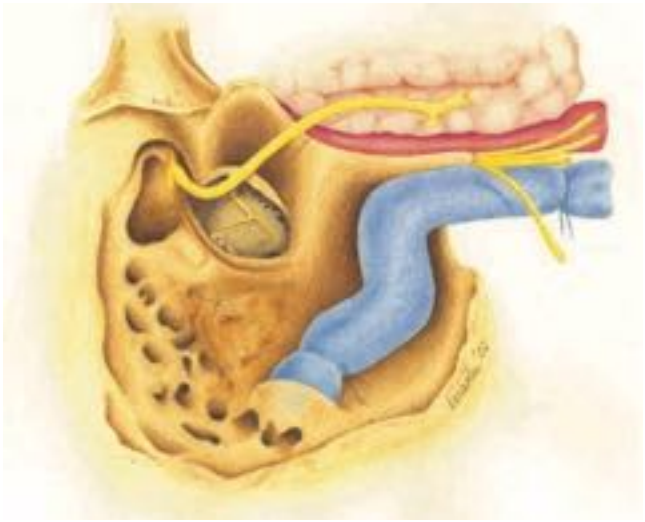


Figure 107.12 Facial nerve transposition, canal wall down. Maximum exposure of the right jugular foramen is achieved by rerouting the facial nerve anteriorly with the hinge point at the first genu. (See also **Figure 107.5**.)

Surgical approaches other than the lateral approach

Although lateral transtemporal surgical approaches are widely accepted, various other surgical techniques have been described (**Table 107.5**).[11, 28–32] These methods invariably involve combinations of well-known neurosurgical techniques. It should be noted that there is not the slightest scientific evidence to suggest that one technique is better than another. Comparative randomized controlled studies have not yet been introduced in this field. Actually, this would hardly be possible for three reasons:

1. the variability and incomparability of pathology in the jugular foramen
2. differences in surgical skills (the human factor)
3. non-uniformity in the way the outcomes are presented. It cannot be expected that this situation will change in the near future.

TABLE 107.5 Surgical approaches other than lateral transtemporal techniques

Approach	Reference
Combined suboccipital and infralabyrinthine–transcervicomastoid approach	Kim et al.[28]
Retrosigmoid suboccipital and combinations with transtemporal approaches	Lee et al.[29]
Extreme-lateral transjugular approach	Salas et al.[30]
Petrooccipital trans-sigmoid approach and combinations with transtemporal approaches	Mazzoni et al.[31]
Widened transcochlear approach	Pellet et al.[11]
Juxtacondylar approach	George et al.[32]
Endoscopic assisted retrosigmoid	Samii et al.[33]

Tumour resection

The close proximity of the internal carotid artery to the jugular foramen seriously complicates the surgical management of a variety of lesions in this area. The aim of all surgical strategies is complete tumour resection with maximum anatomical and functional preservation of nervous and vascular structures. Whether this goal can be achieved depends mainly on the skills of the surgeon and the nature and extent of the pathology. As stated under 'Neoplasia' above, the three most common tumours that affect the jugular foramen are paragangliomas, schwannomas and meningiomas. Paragangliomas usually arise in the lateral part of the jugular foramen (**Figure 107.13**), whereas schwannomas tend to be primarily located in the medial part (**Figure 107.14**). Meningiomas originate in the meninges of the posterior fossa and may eventually fill one or both parts of the jugular foramen, and are likely to encase rather than displace nerves, making functional preservation particularly challenging (**Figure 107.15**). Dumb-bell-shaped tumours are fairly common, because they can extend intracranially as well as into the infratemporal fossa. Factors that play a role in the final outcome of the surgical procedure are control of haemorrhage, appropriate surgical orientation and, last but not least, meticulous microsurgical tissue handling by a skilled surgeon.

Control of venous haemorrhage has been dealt with in Chapter 100, Vascular assessment and management in skull base surgery. Damage to the internal carotid artery is likely to be followed by uncontrollable arterial haemorrhage. This is a serious complication that deserves special attention. Avoiding this situation is a major concern in patients whose tumours infiltrate the carotid canal, such as class C paragangliomas.

After tumour resection, the cavity is filled with abdominal fat. Lumbar drainage may be considered if the resection of a bulky tumour has left a voluminous cavity with wide access to the posterior fossa. Blind sac closure of the external ear canal is performed if the middle ear has not been preserved.

Post-operative management and rehabilitation

In the period immediately following surgery, the patient should be admitted to a well-equipped high dependency care unit for at least 24 hours. Cardiovascular stability must be monitored and safeguarded. Afterwards, the recovery period can be continued in a standard hospital ward. Post-operative care also focuses on the early detection of cranial nerve palsies, because these are the most common complications after jugular foramen surgery. Facial nerve palsy, hearing loss, vertigo, dysphagia and hoarseness are the most obvious symptoms. Functional deficits of cranial nerves XI and XII are usually less embarrassing to the patient. It cannot be expected that function will recover in a nerve that was already compromised pre-operatively.

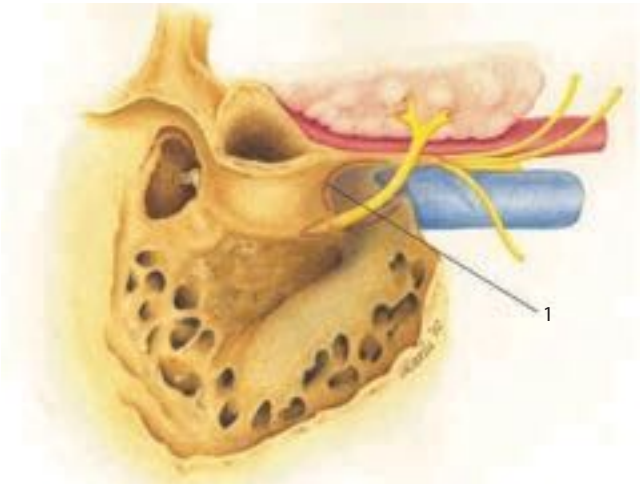


Figure 107.14 1, Right-sided schwannoma in the jugular foramen: localization primarily in the medial part. (See also **Figure 107.5**.)

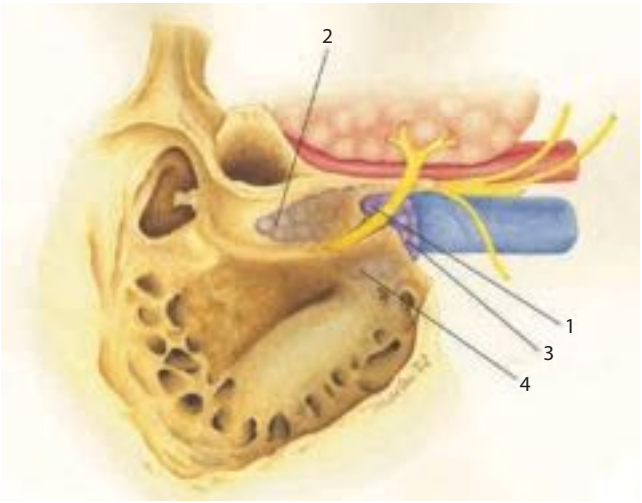


Figure 107.13 1, Right-sided paraganglioma arising from the jugular bulb; 2, extension usually takes place into the hypotympanum; 3, the jugular vein; 4, the sigmoid sinus. (See also **Figure 107.5**.)

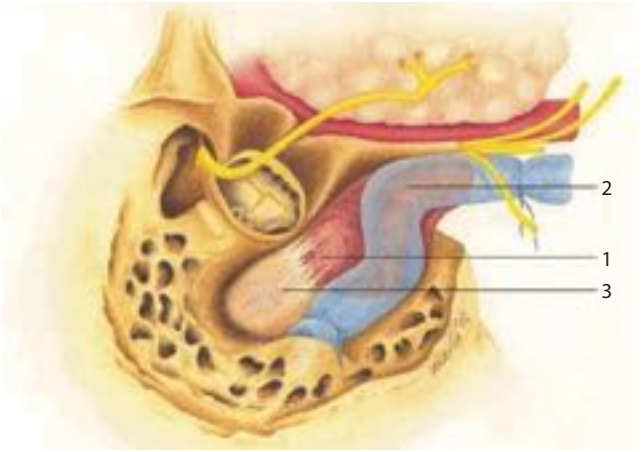


Figure 107.15 1, Right-sided meningioma arising intracranially; 2, extending into the jugular foramen; 3, the facial nerve rerouted and the dura of the posterior fossa exposed. (See also **Figure 107.5**.)

Eye protection is the first step in the care for patients with facial nerve palsy. Lower cranial nerve deficits result in speech and swallowing problems. A specialized multidisciplinary team is required to plan an adequate rehabilitation programme. Depending on the neurological status, a variety of patient-customized measures can be taken.

BEST CLINICAL PRACTICE

- ✓ An in-depth risk versus benefit analysis has to be carried out when deciding on the best management for jugular foramen lesions, in which the risk of progression of the lesion is weighed against the risks of treatment, including surgery.
- ✓ Planning of the treatment should be customized to the patient and to the nature and extension of the lesion. The choice is between radiotherapy stereotactic radiosurgery, microsurgery and a wait-and-see policy, or a combination of these.
- ✓ Only a minority of patients are best served by immediate surgical resection.
- ✓ Among the variety of surgical techniques, the lateral transtemporal approach has received the most attention and widest acceptance. This approach is mostly applied by otologist/head and neck surgeons, because it requires experience with microsurgery on the temporal bone.

FUTURE RESEARCH

- ➤ There are two major issues in the deficiencies of our current knowledge: the biological behaviour of the majority of the jugular foramen lesions and the value of different therapeutic strategies. The best treatment for many jugular foramen lesions is still the subject of controversy. In particular, there are uncertainties about the question whether proceeding to some type of (invasive) therapy is justified or not.
- ➤ There is a need for more knowledge on the biological behaviour of the most common pathologies in the jugular foramen, that is, paragangliomas, schwannomas and meningiomas, to facilitate stratification into those that require aggressive treatment and those that do not.
- ➤ The age threshold at which the long-term risks of radiation to a benign tumour outweigh the immediate risks of surgery remains unclear.
- ➤ The role of radiotherapy and stereotactic radiosurgery in the treatment of meningioma still has to be defined.

KEY POINTS

- The jugular foramen can be involved in a large number of pathological processes. Paragangliomas, schwannomas and meningiomas are by far the most common lesions found in the jugular foramen. All three are characterized by indolent biological behaviour in the majority of cases. However, in the long term, insidious progression may result in serious morbidity and even life-threatening situations.
- The anatomy of the jugular foramen is complex and due to its close proximity to nerves, arteries, veins, meninges, brain tissue and the cochleovestibular system, any treatment modality carries intrinsic risks, particularly surgical treatment.
- Even with regard to the most common lesions, there is no uniformity of opinion and no unequivocal guideline on the best therapeutic approach.
- None of the existing therapies are able to restore functions that have been lost due to the pathological process.
- All the surgical series in the literature describe a considerable risk of functional loss. In selected cases, however, post-operative morbidity is limited to mild inconveniences (e.g. some lower cranial nerve deficits or unilateral hearing loss).
- The skills and experience of the surgeon have a considerable influence on the operative result, while the surgical approach may also play an important role.

ACKNOWLEDGEMENTS

I would like to acknowledge the work of Professor Kees Graamans, who wrote this chapter for the previous edition of Scott-Brown, which was used as the basis for this chapter. I would also like to thank my colleague Professor Michael Gleeson for the time and effort he dedicated to sharing his knowledge of this complex field.

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CHAPTER 108

PETROUS APEX LESIONS

Michael Gleeson

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SEARCH STRATEGY

Data in this chapter are mainly supported by personal experience and the relatively few papers on the subject that have appeared in journals and congress proceedings since 1985.

INTRODUCTION

The petrous apex remains a huge challenge as it is situated at the frontier between otology and neurosurgery. In other words, it is not within the comfort zone of most practising otologists or neurosurgeons. To make matters worse, disease within it or involving it is relatively uncommon, and so few have regular exposure to its access. Added to this is the fact that it contains two very important structures, the cochlea and the horizontal segment of the intra-temporal carotid artery. It also abuts the cavernous sinus anteriorly and the surgeon has to be familiar with the courses of the IVth, Vth, VIth and greater superficial petrosal nerves.

For some considerable time, the petrous apex remained an elusive and relatively silent part of the temporal bone. It was the occasional site of a spreading mastoid infection, signalled by excruciating pain and a VIth nerve palsy – Gradenigo's syndrome. Much less commonly, it was recognized as a potential site of congenital cholesteatoma. Modern imaging techniques have made today's otologist more aware of a wide range of abnormalities and disease processes that are found at this site. Computed tomography (CT) and magnetic resonance imaging (MRI) have given a better understanding of the natural history of many of these conditions and identified those that can be safely watched and those that need to be treated. In recent years surgical techniques to access this part of the skull base have been developed and the expertise to undertake this surgery is being acquired by those designated to work in skull base centres. In this chapter, the issues that surround the management of petrous apex lesions are summarized.

ANATOMY

Situated lateral and adjacent to the clivus, the petrous apex is that part of the temporal bone anterior to the internal auditory meatus that is wedged between the posterior border of the greater wing of the sphenoid and the basilar part of the occipital bones (**Figure 108.1**). The superior surface is part of the floor of the middle cranial fossa, while its posterior face marks the anterior part of the cerebellopontine angle. The two faces are separated by the tentorium, which is attached to the petrous ridge. Its borders and boundaries are marked by major blood

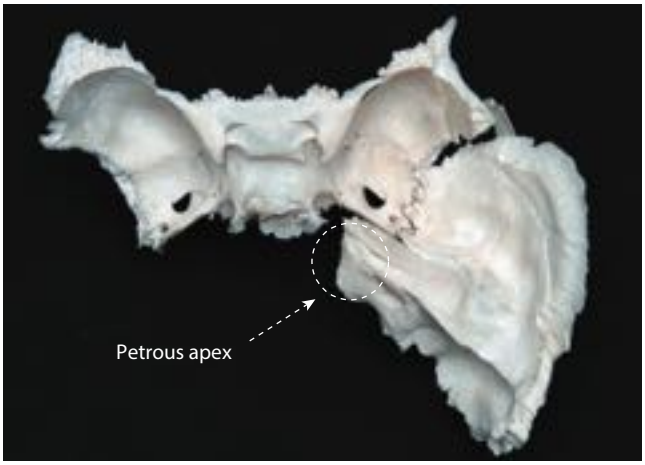


Figure 108.1 The petrous temporal and sphenoid bones. The apex is outlined to clarify its precise position.

vessels and structures, the superior and inferior petrosal sinuses above and below, and the horizontal segment of the internal carotid artery (ICA) and Eustachian tube laterally. Indeed, the apex forms the posterolateral boundary of the foramen lacerum. As an integral part of the petromastoid component of the temporal bone, the apex is preformed in cartilage. The trigeminal ganglion lies in a depression on its posteromedial aspect and the VIth nerve crosses its superior surface beneath the petro-sphenoid ligament. Like other parts of the temporal bone, the degree of pneumatization is variable. The peritubal area is frequently pneumatized, while the rest of the apex is not.

LESIONS AND THEIR PRESENTATION

Infection

As stated previously, in former times the most common disease process affecting the petrous apex was infection. The accumulation of pus or development of an osteitis may give rise to all or part of a triad of symptoms and signs that constitute Gradenigo's syndrome. The full triad of middle ear infection, deep-seated homo-lateral orbital or retro-orbital pain and a homo-lateral lateral rectus palsy may not be present, but will develop in the fullness of time if the infection is not controlled or drained.

Anatomical variants

Defects in the superior surface are occasionally seen and allow the meninges to prolapse into the apex to form a meningocele.

Cysts

Epidermoid cysts (congenital cholesteatoma) may develop in the petrous apex from sequestrated cell rests associated with Seessel's pocket. Mucosal cysts (giant petrous apex cysts) are also found in the apical part of the temporal bone and are thought to develop as a consequence of haemorrhage into the marrow spaces or isolation of a cell tract system with subsequent mucocoele formation. Mucosal cysts are generally found in well-pneumatized temporal bones. Inspection of the CT appearances of the contralateral bone can give some idea of what the state of pneumatization in the affected bone might have been before the development of the cyst. Both epidermoid and mucosal cysts develop over a long period of time, during which constant pressure on the horizontal segment of the ICA causes lateral displacement.

Unilateral hearing loss is the predominant presenting symptom associated with both of these cysts. Patients with cholesterol cysts often have a fluctuating, conductive loss presumably caused by interference with normal Eustachian tube function, while those patients with epidermoids are more likely to have a profound sensorineural deficit acquired in a slow and insidious fashion. Progressive facial weakness or palsy has always been considered the hallmark of epidermoid cysts. In contrast, facial weakness at presentation is uncommon in patients with cholesterol cysts. Regardless of the type of cyst, some patients who present with normal facial nerve function have experienced recurrent episodes of facial weakness or intermittent ipsilateral spasm in the past. Perhaps the most striking distinguishing feature is pain. A large number of patients with mucosal cysts describe a form of trigeminal neuralgia, generalized headache or otalgia and this is most uncommon in patients with epidermoid cysts.[1]

Tumours

Chordomas are derived from notochord remnants and are found in relation to the axial skeleton, most often in the sacrum and skull base. The estimated incidence is 0.5 per million. Both sexes are affected equally and most patients present in the fourth decade of life. Chordomas are slow-growing tumours and so patients often give a long protracted history that starts in a relatively benign fashion with headache or facial pain for which no cause has been found or suspected. Any symptoms are the result of pressure on cranial nerves or dural stretching. Those that develop in the clivus and petrous apex ultimately present with visual disturbance, diplopia, trigeminal deficits or neuralgia, hearing loss, voice disturbance or swallowing problems. These tumours are locally malignant and have a tendency to recur. A few, those with a relatively high proliferative index as assessed by Ki67 staining, are more likely to recur locally than others, often within one or two years of the original resection. Some have the potential to metastasize to regional lymph nodes. Patients with this form of aggressive tumour usually undergo multiple operations and eventually succumb to the disease.

Chondrosarcoma may also develop in the petrous apex, presumably from cartilaginous remnants associated with early development. The tumours are classified according to their mitotic activity and degree of differentiation. Most are low grade and as such have a very slow growth potential and long life expectancy. Like chordoma, with which they were often previously confused, chondrosarcoma produce their symptoms and signs by slow destruction of the temporal bone and its contents, dural stretching and pressure on cranial nerves. Eventually, they break through the cortex of the temporal bone and extend into the cerebellopontine angle, cavernous sinus, middle cranial fossa or into the neck. Those that extend into the cavernous sinus present with trigeminal deficits and diplopia, which is usually caused by an abducens nerve palsy. Chondrosarcomas that extend into the cerebellopontine angle cause trigeminal deficits and varying degrees of hearing loss, while those that break through the base of the skull into the neck are often relatively asymptomatic, possibly found when investigating an isolated hypoglossal palsy.

Meningiomas are the most common intracranial tumour and tend to develop around the venous sinuses. Within the temporal bone, they may develop from meningeal remnants trapped within the bone during development, but may also infiltrate the bone from an

extraosseous site. In the latter situation, they are usually part of an en-plaque tumour that covers a large part of the skull base. The adjacent bone is typically sclerotic as a result of induced osteoblastic activity. Despite their extent, trans-temporal and temporal meningiomas do little harm to the structures that they surround and encase. Growth is usually extremely slow and it may well be decades before any cranial nerve deficit becomes apparent. Some are visible as a mass in the middle ear cavity not dissimilar to, and frequently mistaken for, a glomus tumour.

Other tumours are found in the petrous apex. They are so uncommon that experience of them is largely anecdotal. Among these are plasmacytoma and histiocytosis. It should be remembered also that most of these tumours present in or after the fourth decade of life. For patients of this age, the most common bony tumour is a metastasis. A search for the primary should be undertaken if the scanning features are not characteristic of a defined entity. In the author's experience, renal cell and bronchial carcinomas have both presented in this way before the primary site became symptomatic.

INVESTIGATIONS

The main dilemma that faces the surgeon is the precise characterization of the apical lesion. Only once that is known can an appropriate management plan be devised. Fortunately, many of these tumours have specific characteristics that enable a confident diagnosis to be made from CT and MR images without resorting to open biopsy.[2] Nevertheless, there are occasions when open biopsy is the only option and the surgeon is left with the task of obtaining a diagnostic biopsy without compromising further therapy or inflicting unacceptable morbidity.

For most lesions, a combination of MR and CT imaging will determine the likely diagnosis. CT is pivotal as aggressive bone destruction is suggestive of a malignant process, whereas well-defined expansion is indicative of a benign process. T1-weighted images will distinguish between epidermoid and mucosal cysts. Epidermoid cysts give low signal on T1-weighted images, while mucosal cysts give high signal. Both types of cyst give high signal on T2-weighted images and produce a circumscribed area of bone destruction that can be detected by CT (**Figures 108.2** and **108.3**). High signal in the petrous apex without bone destruction is usually caused by either an effusion or marrow fat. The consistency or uniformity of the signal on T2-weighted images of mucosal cysts can be variable. This probably reflects the contents of the cyst, which may contain large quantities of semi-organized material.

The image characteristics of these cysts still confuse radiologists who are not familiar with the differential diagnosis and protocols necessary to establish their precise nature. Erroneous diagnoses have become more common since the advent of fast spin echo images that are used to screen patients with suspected cerebellopontine

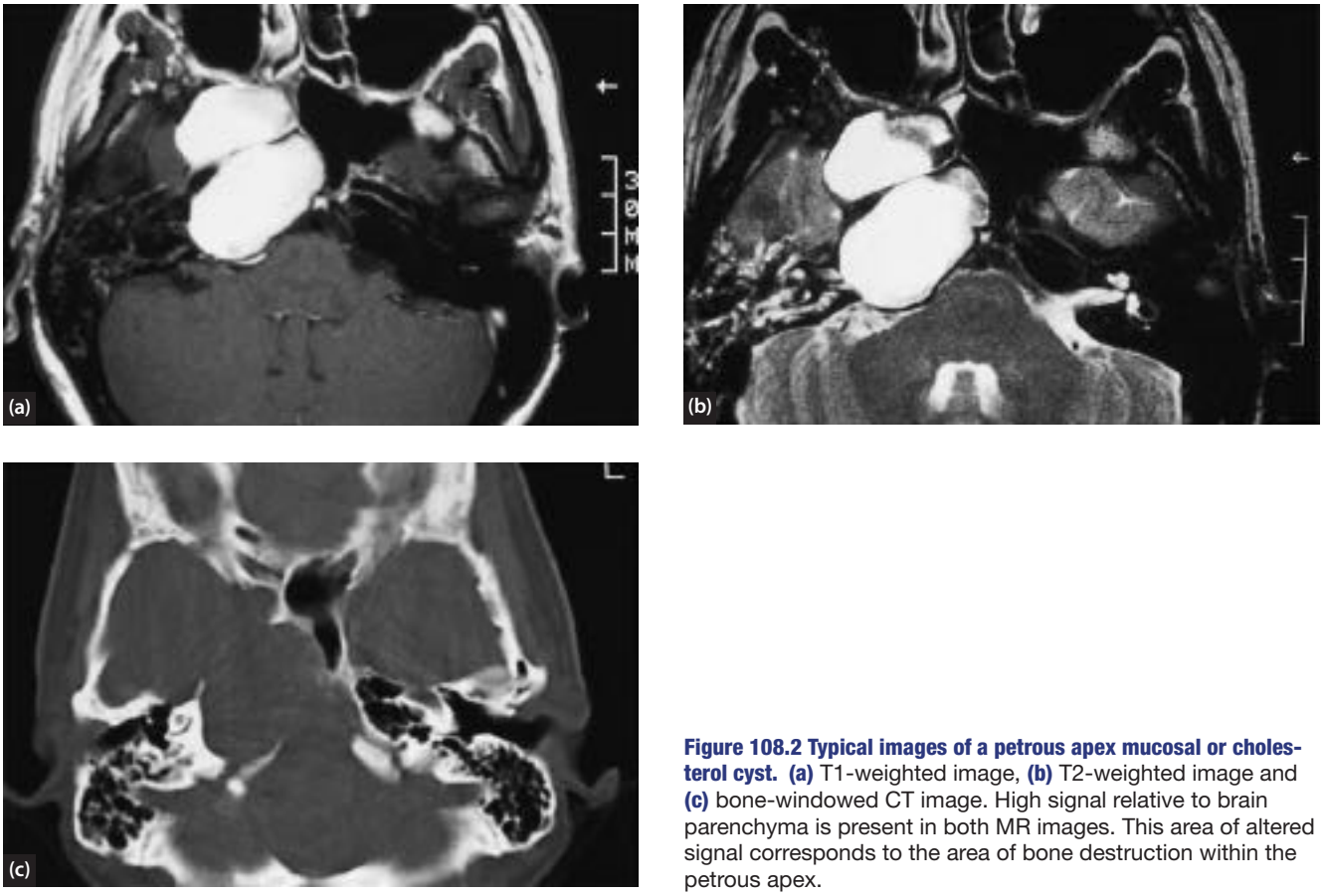


Figure 108.2 Typical images of a petrous apex mucosal or cholesterol cyst. (a) T1-weighted image, **(b)** T2-weighted image and **(c)** bone-windowed CT image. High signal relative to brain parenchyma is present in both MR images. This area of altered signal corresponds to the area of bone destruction within the petrous apex.

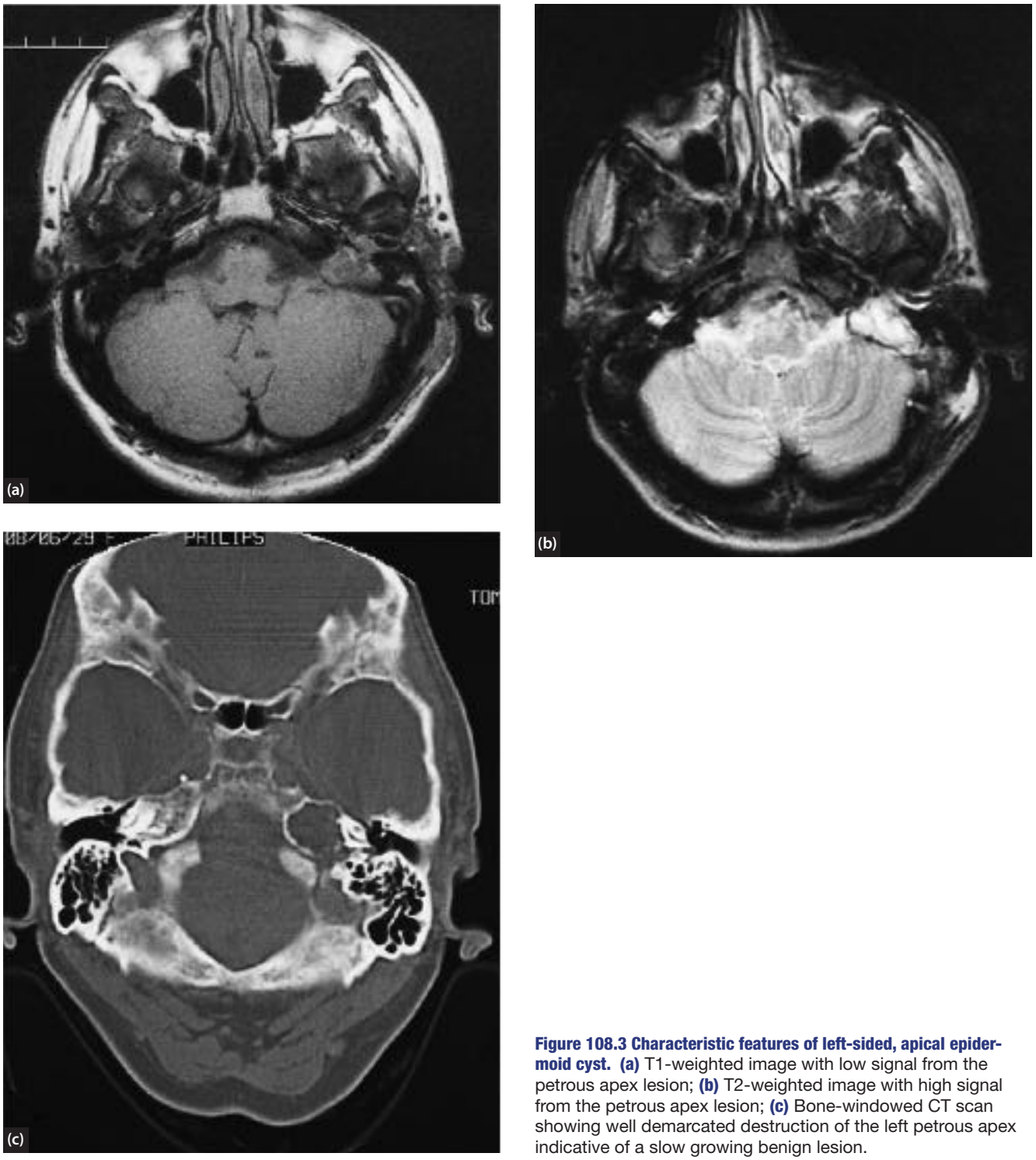


Figure 108.3 Characteristic features of left-sided, apical epidermoid cyst. **(a)** T1-weighted image with low signal from the petrous apex lesion; **(b)** T2-weighted image with high signal from the petrous apex lesion; **(c)** Bone-windowed CT scan showing well demarcated destruction of the left petrous apex indicative of a slow growing benign lesion.

angle tumours. These sequences do not suppress fat and cannot be used in isolation to make any comment about areas of high signal situated within the petrous apex. The diagnosis can only be made with confidence on the basis of T1, T2, inversion recovery sequences and diffusion weighted images.[3, 4]

Bone destruction with foci of calcification within it is typical of chondrosarcoma. Low or iso-intense with brain on T1-weighted images, high signal is obtained on both T2-weighted images and T1-weighted images enhanced with gadolinium (Figure 108.4).

It should be remembered that chordoma almost always arise in the midline, though a few have been described in the petroclival region. Spread from the midline into the petrous apex is common. Chordoma are generally non-homogenous on T1- and T2-weighted images and characteristically have a honeycomb structure on gadolinium-enhanced images.

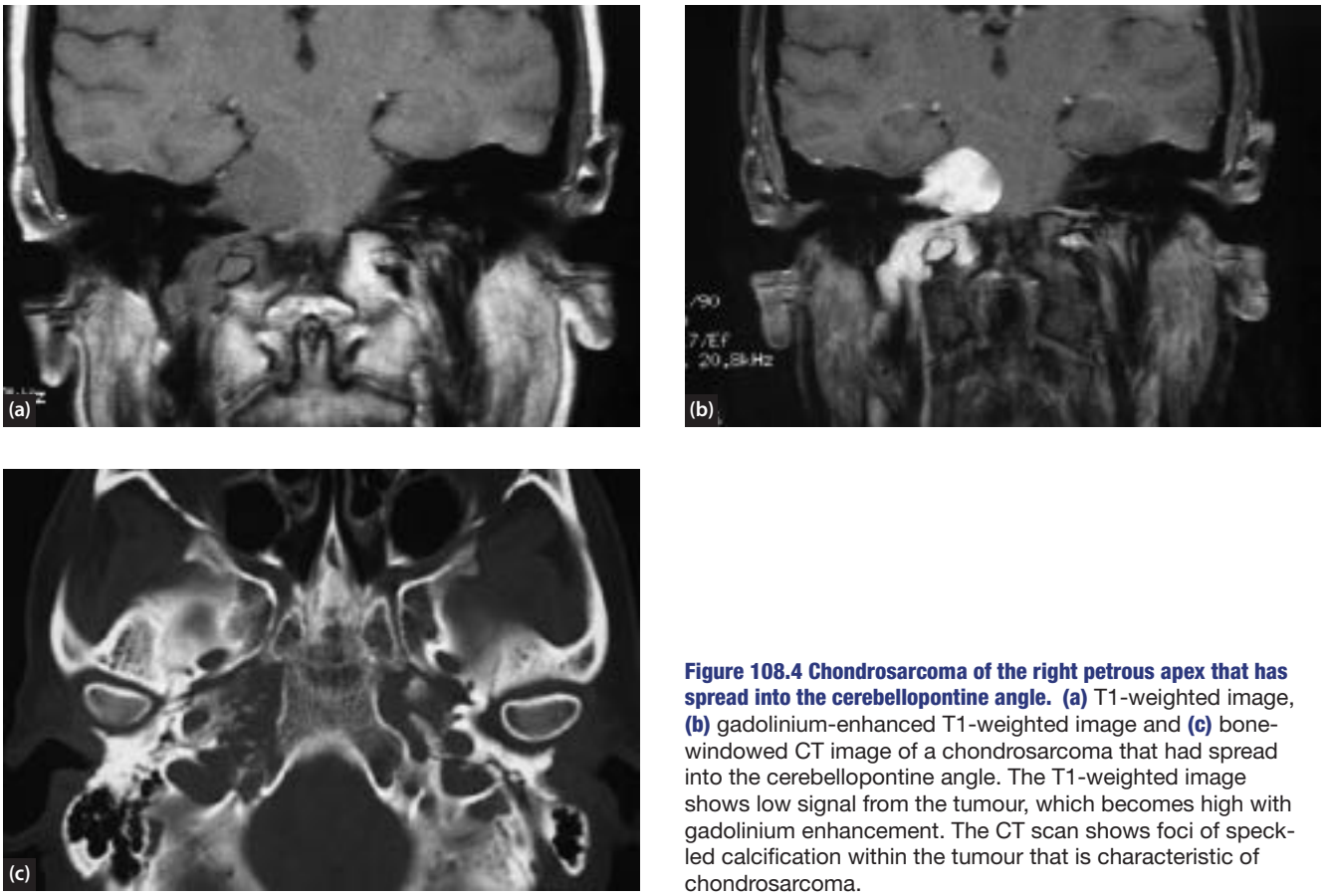


Figure 108.4 Chondrosarcoma of the right petrous apex that has spread into the cerebellopontine angle. **(a)** T1-weighted image, **(b)** gadolinium-enhanced T1-weighted image and **(c)** bone-windowed CT image of a chondrosarcoma that had spread into the cerebellopontine angle. The T1-weighted image shows low signal from the tumour, which becomes high with gadolinium enhancement. The CT scan shows foci of speckled calcification within the tumour that is characteristic of chondrosarcoma.

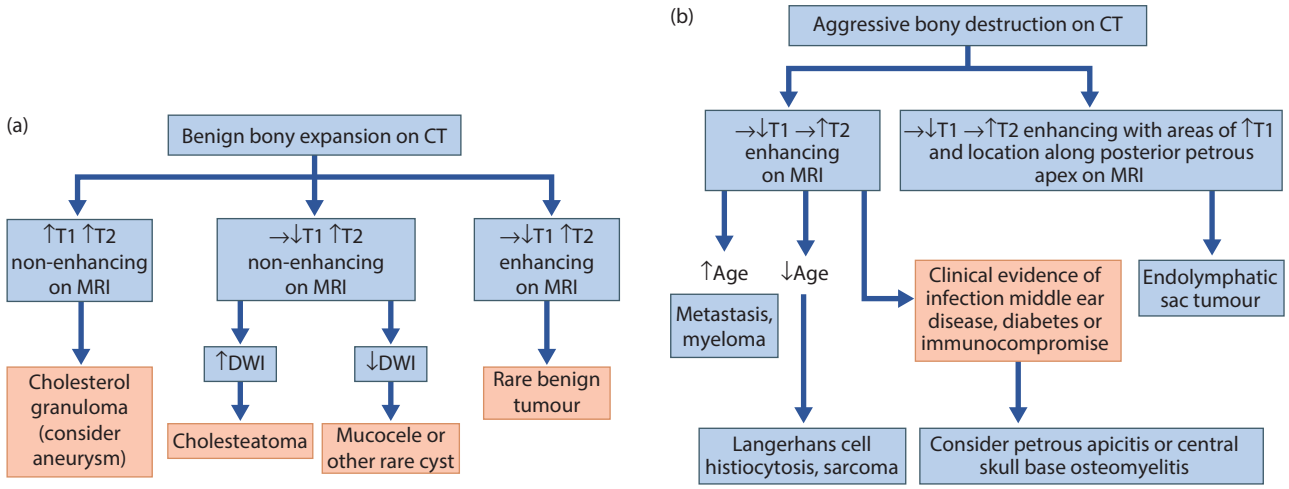


Figure 108.5 Differential diagnosis of petrous apex lesions. **(a)** Benign bony expansion on CT; **(b)** Aggressive bony destruction on CT.

MANAGEMENT

General guidance

The management of infection is dealt with elsewhere in the text (see Chapter 14, Acute otitis media in children). As stated earlier, many cysts and tumours develop over years or decades. A number are probably better observed rather than treated. Growth and its effects can be safely monitored by sequential scans and clinical examination. It is prudent to consider a number of factors before deciding what the optimal and most appropriate management should be for each and every patient. Factors such as the patient's health, their age and life expectancy, the severity of their symptoms and the nature of the cyst or tumour are of prime importance. Ipsi- and contralateral cochlear function must be considered in those where hearing on the side of the lesion might be lost. The temporal bone architecture, in particular the height of the jugular bulb and relationship of the cyst or tumour to the ICA, is also critical.

Epidermoid cysts and tumours can be resected or observed. A third option, drainage, is possible for cholesterol cysts. There is no doubt that for some patients no treatment whatsoever is indicated regardless of the nature of their petrous apex lesion. In general, these are the elderly who are relatively asymptomatic. Neural deficits are rarely reversed by surgery and, if sensorineural hearing loss and tinnitus are the only complaint, a strong case can be made for a policy of 'watchful waiting'. Patients with pain and incipient facial palsy must be considered differently. For them surgical intervention is probably the only solution and each case must be evaluated on its own merits. Figure 108.7 is a flow diagram to guide management of petrous apex cysts.

Approaches

DRAINAGE

The majority of cholesterol cysts can be decompressed by drainage into the mastoid or sphenoid sinuses.[5–7] In this way, serviceable hearing can be retained. The choice largely depends on the height of the jugular bulb when contemplating drainage into the mastoid or hypotympanum. In the first instance, access to the cyst is made through a channel drilled in the space above the bulb, inferior to the posterior semi-circular canal and medial to the facial nerve (Figure 108.8). At best, this measures 4–5 mm in diameter and in patients with high jugular bulbs may not be possible. Similarly, the infra-cochlear route exploits a tract of air cells that runs between the jugular bulb, basal turn of the cochlea and ICA. Again, in patients with large or high bulbs, this potential space may not exist.

The relationship of the ICA to the cyst and posterior wall of the sphenoid sinus are the determinant factors when considering an endoscopic trans-nasal approach. If the ICA is stretched over the anterior surface of the cyst or the posterior wall is too thick, safe or adequate access to the cyst is probably not possible and it would be wiser to explore an alternative option. Serviceable hearing can be maintained by these drainage procedures and this is their main attraction. Unfortunately, some cysts are loculated, others reaccumulate and become symptomatic, while a few become infected. Total resection is then the only alternative for these unfortunate patients.

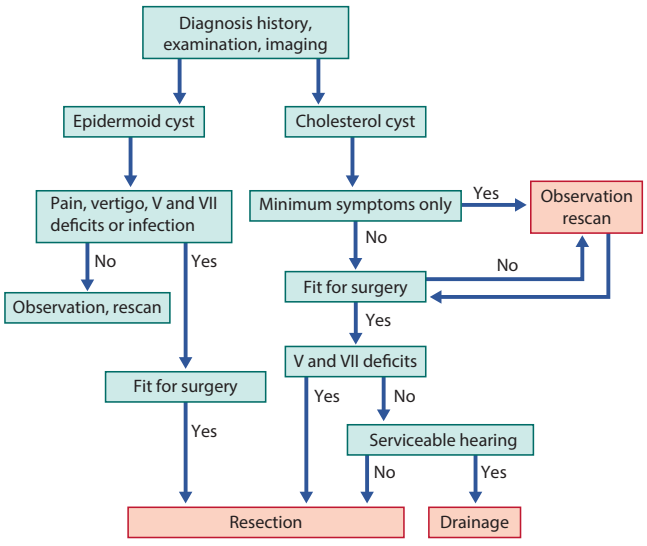


Figure 108.7 Management strategy of petrous apex epidermoid and mucosal cysts.

RESECTION

Drainage procedures are not an option for patients with epidermoids, tumours and cysts that have recurred, become infected or are incipiently inflicting a neural deficit that might be avoidable.

A number of approaches can be used to resect these lesions. Small epidermoids, cholesterol cysts and tumours can be accessed by a subtotal petrosectomy with removal of the cochlea or via the middle fossa. It is impossible to remove the lining of large cysts, epidermoids or tumours completely through these relatively narrow field techniques. For these, a wider exposure as provided by the Fisch type B infra-temporal fossa approach is necessary.[8] In this approach, following a blind sac closure of the external auditory canal, a subtotal petrosectomy is extended anteriorly by inferior displacement of the zygomatic arch, resection of the glenoid fossa of the temporomandibular joint and skeletonization of the vertical and horizontal segments of the intratemporal ICA. In this way, the ICA can be displaced and open access to the apex achieved (Figure 108.9).

The management of patients with chordoma and chondrosarcoma nearly always requires neurosurgical input.[9–12] Staged operations are the rule. For chondrosarcoma, it is probably best to remove disease in the cerebellopontine angle first. Tumour in the petrous bone can be removed at a second stage, after a suitable interval. Chondrosarcoma spreading into the cavernous sinus and sphenoid is probably best managed through a combination of a medial maxillectomy and orbitozygomatic approach. Proton beam therapy has proved successful in a large percentage of patients after radical debulking.[13] Low-grade chondrosarcomas progress very slowly indeed. After initial resection or subtotal resection, it is usually quite adequate to



Figure 108.8 Infra-labyrinthine exposure for drainage of a petrous apex cyst. A channel has been developed beneath the fallopian canal, inferior to the posterior semi-circular canal and above the jugular bulb.

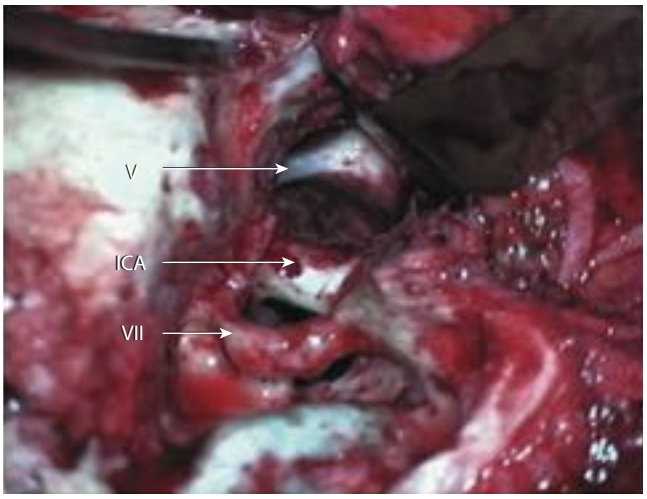


Figure 108.9 Exposure of the petrous apex by the Fisch type B approach. The facial nerve has been skeletonized in the mastoid segment and traced out into the parotid gland. The cochlea has been removed and the ICA exposed. The petrous apex is medial to the ICA and the mandibular nerve can be seen crossing the cavity.

observe clinically with interval scans. Further debulking procedures may become necessary.

Eccentric chordomas are extremely rare and chordoma in the petrous apex is far more commonly the result of spread from the clivus. It is then usually part of an extensive, multifocal tumour. Total eradication is rarely possible and even achieving a reasonable subtotal resection can be difficult. Proton beam therapy (PBT) does have a part to play in the management of this disease and has gained some popularity.[3] Figure 108.10 is a flow diagram that outlines current concepts of chordoma management.

Open cavity surgery is not an option for any of these patients. Leaving a patient with an open cavity after apex surgery is fraught with danger. Infected keratin tends to accumulate in the depths of these cavities and is difficult to remove by suction, as there is often a bottleneck between the deep and superficial portions of the cavities. Furthermore, large areas of exposed dura are usually present on the medial aspect of these cavities and so the risk of recurrent episodes of meningitis is ever present.

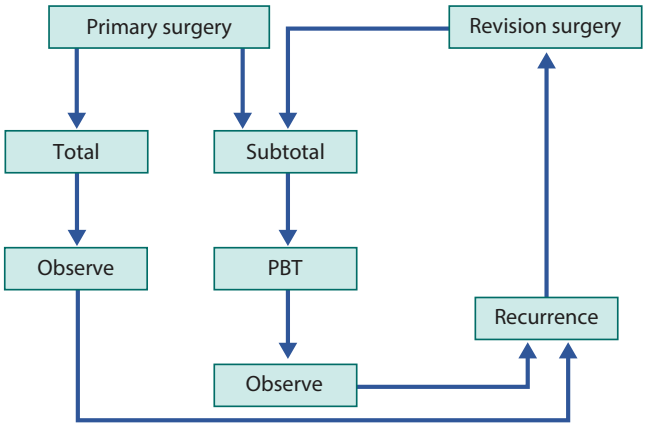


Figure 108.10 Management strategy for chordoma involving the central skull base. Redrawn with permission from Crockard et al.[9]

Complications

Drainage procedures may fail and few ever achieve permanent aeration of the cyst cavity. That the contents reaccumulate is disappointing but in itself is not an indication for further surgery. This is only indicated when the cyst becomes symptomatic.

Open access, trans-temporal access to the apex is always accompanied by a sensorineural hearing loss. This is inevitable and for most this is of no consequence as cochlear function has already been lost. Removal of the glenoid fossa has little impact on the patient and their ability to masticate. It can be reconstructed with a slip of temporalis muscle, which maintains the vertical height of the joint. Most patients experience a temporary occlusal derangement that resolves with the passage of time. Patients are usually able to eat what they like, but choose to eat hard foods on the other side. A temporary weakness of the forehead is acquired by some.

BEST CLINICAL PRACTICE

- ✓ The best exposure to the apex is afforded by the type B infratemporal fossa approach.
- ✓ Open cavity surgery should be avoided and is potentially dangerous. It leaves an inaccessible space medially that accumulates debris that inevitably becomes infected.

FUTURE RESEARCH

- ➤ Long-term outcome studies are required to determine the effect of surgical intervention on patients with low-grade chondrosarcoma, chordoma and cysts.

KEY POINTS

- Many petrous apex lesions have taken years, if not decades to develop. A large number can be managed conservatively by 'watchful waiting'.
- The diagnosis for most lesions can be made on the basis of appropriate CT and magnetic resonance imaging.
- In a middle-aged adult, always consider the possibility of a metastasis.

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CHAPTER 109

APPROACHES TO THE NASOPHARYNX AND EUSTACHIAN TUBE

Gunesh P. Rajan

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Anterior approaches 1326
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SEARCH STRATEGY

Data in this chapter may be updated a Medline search using the keywords: anterior and lateral skull base approaches, extended endoscopic approaches, TORS, Eustachian tube, nasopharynx, outcome, focusing on technique, surgery and results.

INTRODUCTION

In this chapter we describe and discuss the indications for, and surgical access to, the Eustachian tube and the nasopharynx. The approaches we use nowadays are the distillation of the efforts made over the years by countless surgeons who have attempted to remove disease from this particularly challenging part of the skull base. Just the briefest consideration of the passage of the Eustachian tube from its origin in the hypotympanum across the lateral skull base, through the infra-temporal fossa to the nasopharynx gives some insight to the complexity of surgery in this region. Any surgical approach must give safe and wide exposure to achieve removal of disease minimizing the associated morbidity. The last decade has seen tremendous changes with the way we access the skull base; the extended transnasal endoscopic approaches have largely replaced the open procedures to the nasopharynx, midline and paramedian skull base, especially for all benign pathology and selected malignant disease. Recently, the emergence of transoral robotic surgery has again added new possibilities to what we can potentially do in the management of the midline skull base lesions. To do justice to these recent developments we have included the transnasal endoscopic approaches into this chapter. The detailed description of these approaches is provided by Snyderman and his colleagues in Volume 1, Chapter 116, Extended anterior skull base approaches.

What follows is a brief description of the established approaches to the nasopharynx and the Eustachian tube that have withstood the test of time. The strengths and weaknesses of each approach are identified. Each of these approaches can be used in isolation or in combination if necessary.[1–14]

As with various fields in surgery, the new technologies being introduced constantly challenge us surgeons to learn and incorporate new techniques into our surgical armamentarium. This in turn means that training of future skull base surgeons will also have to change with the aim of establishing the competence in open, endoscopic and perhaps robotic techniques. It must be remembered that every patient's needs are different and that treatment has to be planned to suit the individual patient and his/her disease. It should not be forgotten that for patients with a malignant pathology, the surgical resection is the only hope of cure or respite as other therapies are ineffective alone. As with all skull base surgery, a multidisciplinary team approach is essential, utilizing the skills of all the specialities involved.

CLASSIFICATION OF APPROACHES

The aim of the skull base techniques has been to gain maximal surgical exposure while minimizing brain retraction, aesthetic and functional handicaps as far as possible.

There is often more than one way to approach a lesion, each method offering something different. Several approaches to the Eustachian tube and nasopharynx have been described. Most are entirely extradural and extracranial, while a minority access the midline skull base by intracranial and intradural pathways. Numerous surgical variations of each approach have been described but most would agree that each variation can be listed under one of the three categories: the anterior approaches; the anterolateral approaches; or the lateral approaches.

PRE-OPERATIVE ASSESSMENT AND PREPARATION

It almost goes without saying that the evaluation of the stage of disease is absolutely vital. There is no point in subjecting a patient to a major intervention and its morbidities unless there is a reasonable prospect of eradicating their disease or reducing its bulk sufficiently to alter the course of disease. Most tumours in this part of the skull base are intimately involved with the internal carotid artery (ICA) and some displace or infiltrate the cavernous sinus. It is therefore imperative that the relationship of these structures to the tumour is known as precisely as possible and the consequences of damage to the ICA are fully assessed. Most patients will require computed tomography (CT), magnetic resonance angiography (MRA) and balloon occlusion tests. The introduction of neuronavigation has proven to be very useful in this context, enhancing surgical accuracy.

The larger disassemblies of the facial skeleton and the prevertebral skull base are better undertaken after a preliminary tracheostomy. The endoscopic techniques have simplified the sleeve resections of the nasopharynx and adjacent Eustachian tube segments. Dural resection or damage is not infrequent and the possibility of cerebrospinal fluid (CSF) leaks into the nasopharynx is ever present. The addition of a lumbar drainage helps manage the persisting CSF leak post-operatively along with adequate antibiotic coverage. While some patients may be able to take food orally relatively soon after surgery, those in whom extensive osteotomies have been undertaken will not. Another consideration is that the majority of patients with malignant disease will undergo post-operative radiotherapy. For this group of patients, oral feeding may be significantly delayed, therefore considering a pre-operative PEG-insertion.

ANTERIOR APPROACHES

Transnasal extended endoscopic approaches[1, 2]

INDICATIONS

- Tumours of the nasopharynx and anterior infratemporal fossa
- Juvenile neuroangioma
- Access to tumour extension into the clivus and craniocervical junction.

CONTRAINDICATIONS

- Malignant tumours with significant dural invasion and intracranial extension (these tumours can frequently be resected using a combined open–endoscopic approach to minimize morbidity)
- Malignant lesions that require a degree of lateral access, those that extend into the lateral parapharyngeal space, cavernous sinus, posterior infratemporal fossa and posterior peritubal space.

PRINCIPLES OF THE PROCEDURE

Most extended transnasal endoscopic approaches (EEAs) are done with two surgeons using the four-hands technique and the patient in a supine position. Depending on the location of the lesion, various modifications of the transnasal endoscopic routes provide a targeted access to the different midline and paramedian skull base lesions. The transnasal, transmaxillary route with removal of the posterior maxillary wall gives the most lateral trajectory to access the anterolateral infratemporal fossa, the addition of the transpterygoid access opens up the anterior infratemporal and the peritubal compartment, which can be extended posteriorly to access the foramen lacerum and petrous apex (**Figure 109.1**). The classic transnasal pathway after reduction of the vomer and posterior septum provides the workspace to address the nasopharynx and clival lesions.[2] The reconstruction after endoscopic

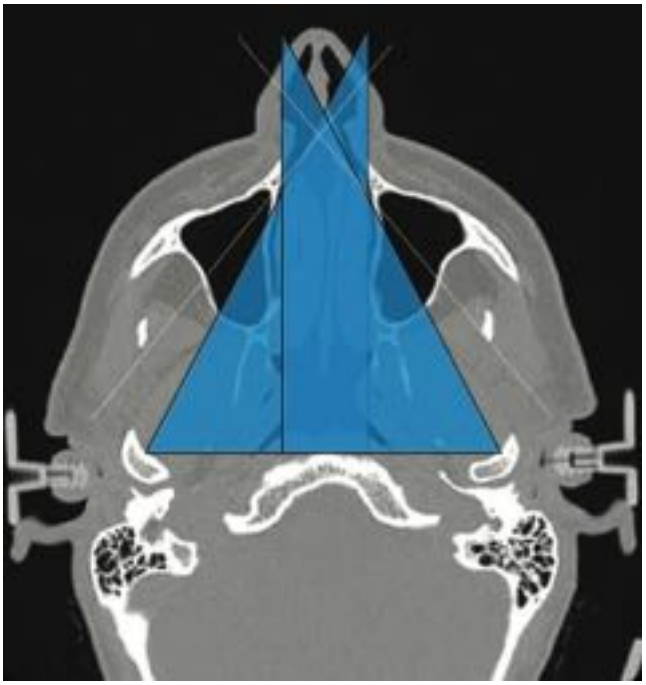


Figure 109.1 Trajectory for the endoscopic access to the anterior Eustachian Tube, peritubal space and medial infratemporal fossa (blue zone). The white lines indicate the lateral extent of the endoscopic access to the infratemporal fossa.

resections in the hostile environment of the nasopharynx and oropharynx in terms of the microbial fauna, saliva exposure and the frequent clearing movements poses a key challenge and is dealt with Volume 1, Chapter 116, Extended anterior skull base approaches. The introduction of the nasoseptal or Hadad flap has certainly simplified the reconstruction of local defects; reliable closure techniques for dural defects are constantly evolving to address this specific weakness of this treatment modality.[2]

ADVANTAGES AND DISADVANTAGES

The EEAs have revolutionized the surgical treatment of midline lesions of the skull base. With the improvement of the scope optics and HD technology, the visualization of the operation field is unparalleled. This together with the increasing portfolio of endoscopic instruments has resulted in the EEA largely replacing the open transoral and transpalatal procedures described below. The EEAs offer direct access and visualization of the pathology and allow for two surgeons to work simultaneously using the four-hands technique. Benign tumours with lateral extension into the parapharyngeal and infratemporal spaces can be accessed by these routes as in most cases the tumour extensions can be medialized into the working field.

KEY POINTS

- Advantages:
  - simple technique
  - direct approach
  - excellent visualization of the operating field.
- Two surgeon – four-hands technique.
- Limitations and drawbacks:
  - limited access to the lateral infratemporal and parapharyngeal space
  - difficult assessment of the margin status in malignant disease
  - limited data of reconstruction outcomes
  - dural reconstruction challenging
  - risk of meningitis due to wound contamination.

Transoral robotic surgery[3]

INDICATIONS

- Benign tumours of the nasopharynx and parapharyngeal space
- Indications are evolving.

CONTRAINDICATIONS

- Malignant tumours with lateral extension, significant dural invasion and intracranial extension (these tumours can frequently be resected using a combined open–endoscopic approach to minimize morbidity)
- Malignant lesions that require a degree of lateral access, those that extend into the lateral parapharyngeal space, cavernous sinus, posterior infratemporal fossa and posterior peritubal space.

PRINCIPLES OF THE PROCEDURE

Transoral robotic surgery (TORS) is the most recent surgical modality that has the potential to further improve surgery in this anatomic region. The range of the 'wrist'-mediated instrument mobility combined with the 3D-visualization of the operating field opens up a new paradigm in our specialty as exemplified by its utility in the management of HPV-positive oropharyngeal tumours. The upcoming introduction of the single-port version of the DaVinci system offers hope in the management of midline lesions. Current limitations of the technology are related to lack of haptic feedback and the lack of instrumentation to remove and remodel bone effectively.

There are several case series reporting excellent outcomes for resections of parapharyngeal tumours with no reported cases of 'first-bite syndrome' so far, which occurs frequently after transcervical removal of these tumours. More recently, salvage surgery for small recurrences of nasopharyngeal carcinoma in the posterior nasopharyneal wall has been performed using TORS with promising outcomes.[3] Detailed descriptions of TORS will be found in Volume 3, Chapter 22, Transoral laser microsurgery.

ADVANTAGES AND DISADVANTAGES

At this stage it is too early to talk about the pros and cons of TORS to address pathologies in the nasopharynx or peritubal space. More clinical data are required to provide any objective interpretation of its utility.

KEY POINTS

- Advantages:
  - direct approach
  - unparalleled instrument dexterity and mobility
  - HD 3D-visualization of the operating field.
- Limitations and drawbacks:
  - high set-up costs
  - utility and indications yet to be defined
  - current case series report on confined lesions of the posterior nasopharyngeal wall and benign tumours of the parapharyngeal space
  - clinical outcomes data evolving.

Transoral and transpalatine approaches[4, 15, 16]

INDICATIONS

- Malignant tumours of the posterior nasopharyngeal wall that are no larger than 2 cm
- Access to tumour extension into the clivus and craniocervical junction.[13, 15, 16]

CONTRAINDICATIONS

- Malignant nasopharyngeal tumours > 2 cm
- Tumours with significant dural invasion and intracranial extension

- Lesions that require a degree of lateral access, those that extend into the parapharyngeal space, cavernous sinus, infratemporal fossa and peritubal space.

PROCEDURE

The patient is placed in the supine position with their head extended as much as possible. Mayfield clamp fixation may be required if neuronavigation is employed or if it is anticipated the cranio-cervical junction might become unstable. There is no doubt that access is easier with the patient's head in a horseshoe rest that permits intraoperative manipulation of the head but this is rarely possible. A preliminary tracheostomy is established so that an unobstructed view of the oropharynx is obtained and to secure the airway post-operatively, as most patients will develop significant lingual and oropharyngeal oedema. Lumbar CSF drainage is inserted if the dura is to be opened. As this approach provides relatively narrow access through a long working distance, appropriate retracting instrumentation is crucial if sufficient exposure is to be obtained. Most surgeons opt for the Crockard wide field retractors and dissecting instruments that have been specially designed for this purpose.

After insertion of the mouth gag and retraction of the oral cavity, the soft and hard palate are infiltrated with 1:200000 adrenaline. The soft palate is split to one side of the midline. The hard palate mucosa is incised along the ipsilateral junction of the hard and soft palate within 5 mm of the maxillary dentition. This mucosal incision is extended along the palatal aspect of the alveolar ridge up to the level of the first molar and then taken in an arc across the palate to the opposite side (**Figure 109.2a**). A mucoperiosteal flap is elevated exposing the bony hard palate. The greater palatine neurovascular bundle is coagulated and divided. Exposure of the nasopharynx is increased by dissection of the muscular insertions of the soft palate from the hard palate. Great care must be taken to maintain the integrity of the remaining greater palatine vascular pedicle while doing this (**Figure 109.2b**). A self-retaining retractor is then inserted to keep the two halves of the soft palate out of the field.

Dissection through the posterior nasopharyngeal wall gives access to the lower clivus. If the lesion extends towards the sphenoid floor or the upper clivus the operative field must be enlarged. In some cases this can be achieved by removal of some palatal vomerine bone. In others, it will be necessary to perform a Le Fort I osteotomy and then split the palate in the midline, displacing each maxilla laterally. This latter approach, known as an 'open door maxillotomy', can offer unrivalled exposure of the entire clivus and cranio cervical junction.

A suitable mucosal flap is raised, hinged either laterally or inferiorly. The length of this flap varies according to the extent of the lesion being removed. The larger the flap, the better the chance of being able to approximate it at the end of the procedure (**Figure 109.2c**). If the lesion is submucosal, it is usually unnecessary to split the prevertebral fascia. But, if it is necessary to access the clivus, the prevertebral fascia and muscles have to be opened and this is best undertaken in the midline. The most helpful anatomical landmark is the anterior arch of the atlas, which is easily palpable. The narrow field afforded by this approach is insufficient for an *en bloc* resection of most tumours, so resection is usually performed in a piecemeal fashion.

Apart from very small dural tears or defects that can be plugged with muscle, primary watertight closure is virtually impossible; however, the advent of new dural sealing materials might alter this condition. The dead space created by tumour resection can be filled with autograft soft tissue secured in place by fibrin glue. It is best covered by pedicled local mucosal or mucoperichondrial flaps raised from the nasal septum and rotated into place. As much as possible prevertebral fascia, musculature and pharyngeal mucosa are reapproximated. The soft palate is readapted, preferably through a three-layered closure. In this way, the chance of an oro-nasal fistula developing is minimized (**Figure 109.2d**). If the maxilla has been split, bone plates are applied for fixation. Removal of the tracheostomy is determined by the clinical progress of the patient in terms of swallowing and resolution of oedema.

ADVANTAGES AND DISADVANTAGES

With the emergence of the EEAs the role of the transoral approaches has slipped into the background. There is much to commend the transoral approaches as they are relatively simple and straightforward to perform. They offer direct access to the lesion and, as a consequence, the surgeon is unlikely to inadvertently stray off target. Inadequacies of exposure can be resolved by local extensions in a stepwise fashion. On the other hand, a covering tracheostomy is required in most cases, the working distance is relatively long and this brings with it difficulties for the surgeon in terms of instrumentation, manipulation and visibility. Tumours with extension laterally into the parapharyngeal and infratemporal spaces cannot be accessed by these routes. Similarly, it is essential that the patient has good mouth opening otherwise a mandibulotomy might become necessary. The repair of the palate can be difficult and, despite every effort, fistulae develop in up to 40% of patients.

KEY POINTS

- Advantages:
  - simple technique
  - direct approach.
- Extendable through the LeFort I-palatal split approach.[13, 17]
- Limitations and drawbacks:
  - tracheostomy requirement
  - narrow working field and long working distance
  - possible palatal dehiscence and oronasal fistula as late complication in 30–40%
  - patients with trismus or impaired jaw opening require transmandibular approach
  - no access laterally to the parapharyngeal and infratemporal spaces
  - risk of meningitis due to wound contamination.

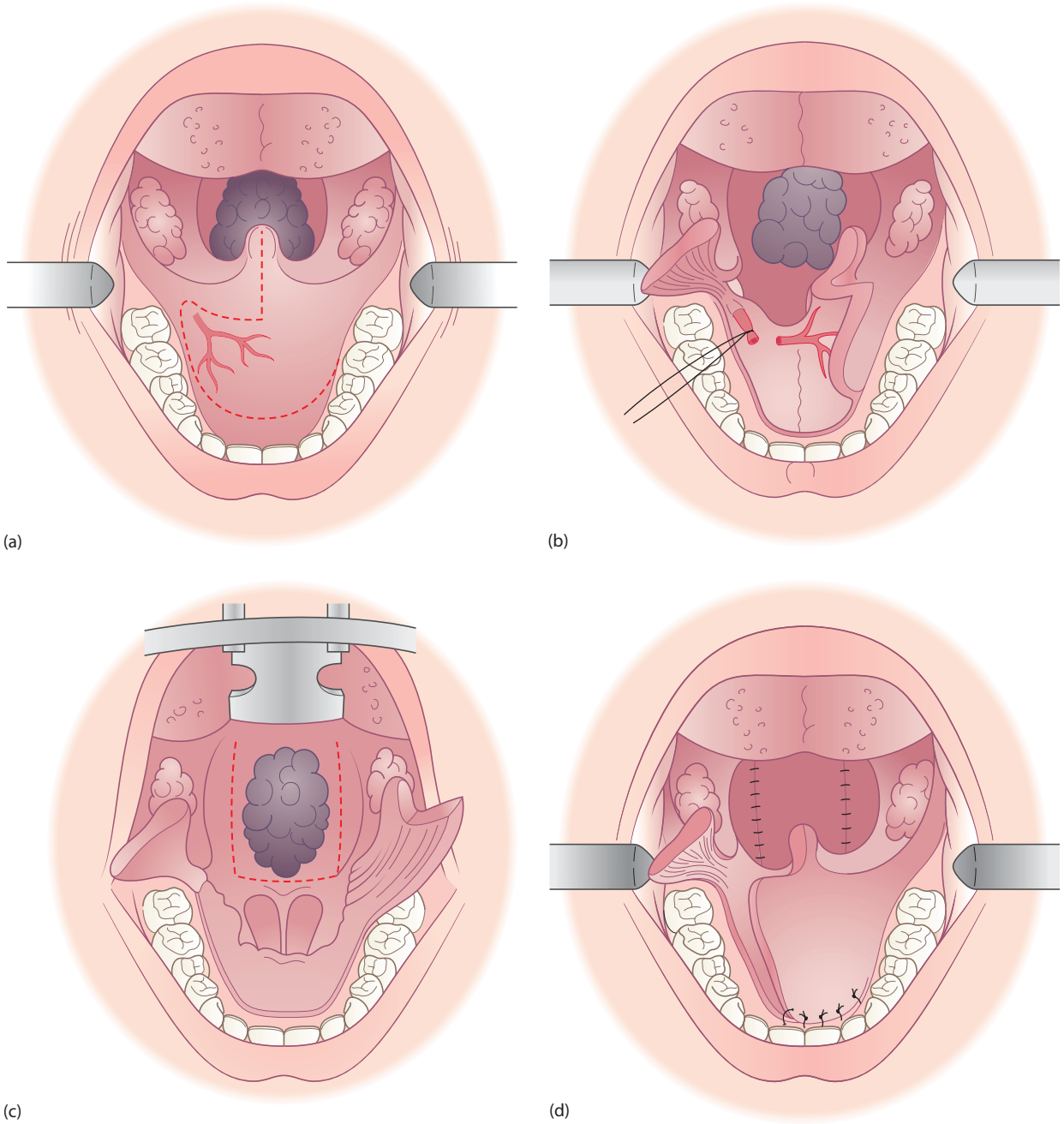


Figure 109.2 Transoral-transpalatinal approach. Redrawn from original illustrations by Margrit Pirker.

Transmandibular-transcervical approach[17, 18]

INDICATIONS

- Nasopharyngeal tumours extending into the anterior infra-temporal fossa.[15, 18]

CONTRAINDICATIONS

- Dural invasion (>2 cm²) and intracranial involvement
- Invasion of the parasellar and posterior infra-temporal region.

PROCEDURE

The patient is placed in the supine position and a tracheostomy established. An extended submandibular incision is made about 4 cm below the mandible from the mastoid tip posteriorly to rise anteriorly and split the lip (Figure 109.3a). The platysma is divided and the dissection directed beneath the submandibular gland. The tendons of the digastric and stylohyoid muscles can be released from their hyoid attachment and reflected superiorly along with the submandibular gland. This aids exposure of the mandible (Figure 109.3b). The great vessels in the carotid sheath are then identified together

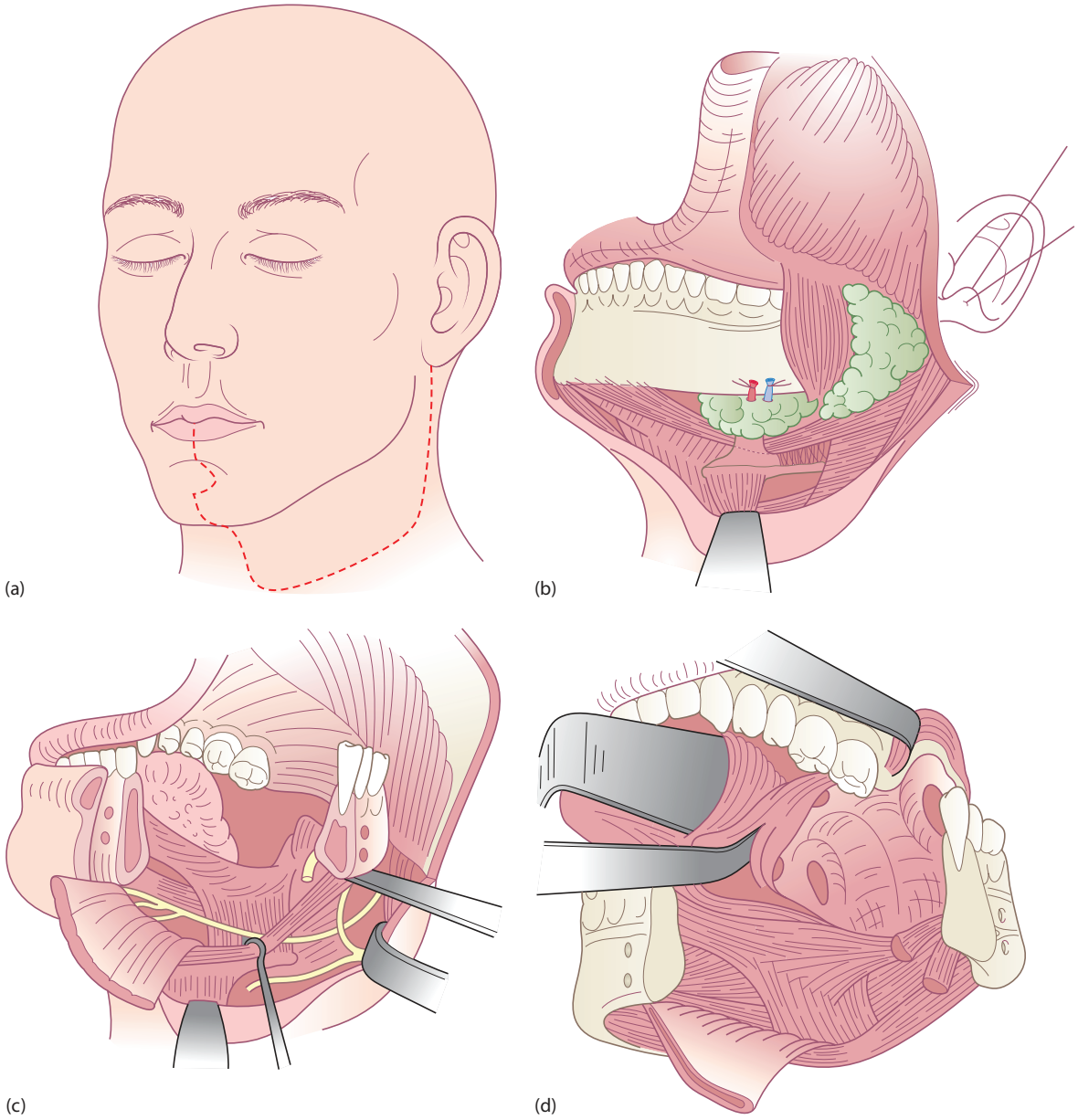


Figure 109.3 Transmandibular-transcervical approach. Redrawn from original illustrations by Margrit Pirker.

with the adjacent cranial nerves. The internal and external carotid arteries are dissected free and followed as close as possible to the skull base. A median mandibular osteotomy is performed after prefitting of mini-plates. Obviously the precise site of the mandibulotomy will be determined by the state of patient's dentition. In patients with poor dental health it is preferable to select an edentulous area (Figure 109.3c).

Dissection then proceeds across the floor of the mouth toward the parapharyngeal space. The tongue is retracted to the opposite side, the mucosa incised, mylohyoid muscle divided together with the anterior belly of the digastric muscle The lingual and hypoglossal nerves are identified and preserved (Figure 109.3c). During this stage of the approach the mandible can be steadily retracted laterally allowing entry into the parapharyngeal space which can then become continuous between the mouth and neck. Additional lateral retraction of the mandible is achieved by ligation of the external carotid artery distal to the lingual artery. By this manoeuvre access to the nasopharyngeal part of the parapharyngeal space and the anterolateral infratemporal fossa is gained (Figure 109.3d). If access to a midline lesion is required the incision is extended upward towards the hard palate and pterygoid plates ending about 1 cm medial to the gingival margin. A hemi-palatal flap is created, thereby producing an 'oropharyngeal sleeve'. Further blunt dissection lateral to and behind the superior and middle constrictor muscles produces a surgical working space (Figure 109.3d). Additional posterolateral division of the styloid musculature and glossopharyngeal nerve together with superior dissection along the retropharyngeal–prevertebral plane

allows release and retraction of the oropharynx to the contralateral side and widening of the retropharyngeal space. The precise position of the ICA should then be established and the tensor and levator muscle of the soft palate sectioned. With this, the pharyngeal and cartilaginous part of the Eustachian tube becomes accessible. Further exposure of the posterior nasopharyngeal wall can be obtained by dividing the tube and releasing the nasopharynx from the skull base at level of the pharyngeal tubercle. In this way, the whole of the pharyngeal sleeve can be displaced to the opposite side and the central skull base is exposed. Further enlargement of the operative field is achieved by removing the posterior portion of the hard palate thus widening access to nasopharynx, choanae and upper sphenoid body.

The intracranial extent of the lesion determines the amount of skull base that needs to be removed. However, if the lesion reaches the posterior aspect of the infratemporal fossa, combination with a lateral approaches may be required to allow *en bloc* resection.

Surgical closure begins with a watertight reconstruction of any dural defects. Smaller defects (< 4 cm²) can be sealed with fascial or pericranial flaps, while larger defects require musculo-fascial or microvascular free flaps. The remaining pharyngeal sleeve is reattached to the pre-spinal muscles at the skull base; exact realignment of the pharynx is achieved by suturing the Eustachian tube around an intratubal splint. The palatal muscles are reapproximated and the mucoperiosteal palatal flap is repositioned and the mucosa sutured. A palatal splint is recommended by some to encourage adherence of the flap to the hard palate. The floor of the mouth is reconstructed with resorbable sutures and the mandible fixed with the pre-fitted miniplates. A large suction drain is placed along the carotid sheath exiting though a separate stab incision in the lower neck. Finally, the lower lip is closed in three layers, taking care to achieve precise approximation of the vermilion border.

The patient should be fed by nasogastric tube for the first week, following which oral alimentation can begin. Removal of the tracheostomy tube is performed after 24 hours of uneventful plugging of the tracheostomy tube. Subsequent build-up of oral feeds is monitored by the speech pathologists.

KEY POINTS

- Advantages:
  - good access to the epipharynx, the parapharyngeal and anterior infratemporal space
  - direct approach
  - good vascular control.
- Limitations and drawbacks:
  - potential infection hazard through oral contamination
  - possible mandibular non-union
  - prolonged need for tracheostomy
  - restoration of normal or adequate swallowing often significantly delayed (mean 7 weeks)
  - temporary PEG frequently required.

ANTEROLATERAL APPROACHES

Maxillary swing technique[19]

INDICATIONS

- Nasopharyngeal tumours with limited extension into the anterior infra-temporal region.

CONTRAINDICATIONS

- Lesions involving the petrous ICA
- Lesions extending into to the petrous apex, parasellar and/or posterior infratemporal region (combination with lateral approach required).

PROCEDURE

The patient is intubated and placed in a supine position and draped. A Weber–Ferguson–Longmire incision is made, extending laterally onto the zygoma (**Figure 109.4a**). The vertical incision limb goes through the upper lip and is continued between the central incisors and onto the hard palate. After reaching the border of the hard and soft palate the incision is curved laterally to run behind the maxillary tuberosity. The facial incision is made through the subcutaneous, muscular and periosteal layers. Gentle, minimal elevation of these tissues exposes the planned osteotomy line (**Figure 109.4b**). The osteotomy is started by separating the zygoma from the maxilla, moving medially along the infraorbital rim until the frontal process is divided from the anterior maxillary wall. Then the medial maxillary wall is separated from the midline nasal complex in an antero-posterior fashion. The posterior wall is released without direct vision using an osteotome inserted through the antrum. The palatal bone is incised and a midline osteotomy fashioned. Finally, the pterygoid plates are separated from maxillary tuberosity by using a curved osteotome (**Figure 109.4c**). The entire maxilla can be swung laterally attached to the cheek flap and the masseter muscle (**Figure 109.4d**). The epipharynx is widely exposed including the cartilaginous Eustachian tubes of both sides, thus allowing *en bloc* resection of confined pathologies in this region.

After the resection has been completed, an ipsilateral turbinectomy provides useful tissue for a free graft that can placed on exposed bone in the epipharynx. Nasal packing keeps the graft in place. Closure is achieved by returning the maxilla to its anatomical position and fixation to the zygoma and contralateral maxilla with miniplates. Exact alveolar ridge alignment can be facilitated by using a pre-operatively fashioned dental splint. The facial and intra-oral incisions are closed in layers. If cartilaginous portions of the Eustachian tube were resected, a grommet should be placed on the affected side in order to prevent a chronic middle ear effusion.

Oral feeding is usually started after 72 hours. Any non-resorbable nasal packs should be removed on the 7th post-operative day and the dental plate after about a month or when all the mucosal wounds have healed.

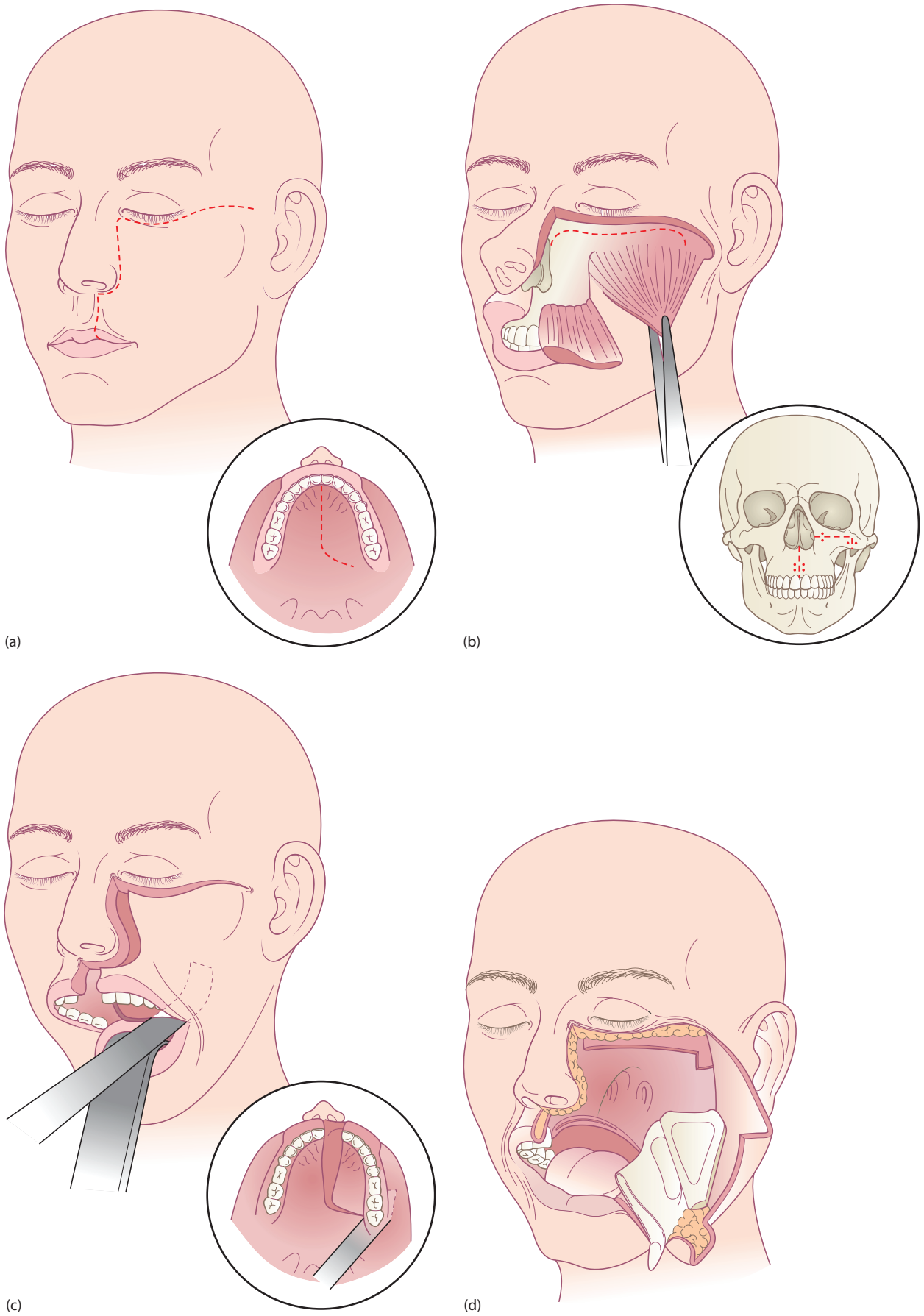


Figure 109.4 Maxillary swing approach. Redrawn from original illustrations by Margrit Pirker.

KEY POINTS

- Advantages:
  - simple technique
  - wide exposure
  - good cosmetic and functional results.
- Limitations and drawbacks:
  - limited parapharyngeal and infratemporal exposure
  - lack of vascular control
  - post-operative trismus
  - necrosis of the maxilla in some cases.

LATERAL APPROACHES

Infra-temporal approach type C[20–22]

INDICATIONS

- Infratemporal fossa tumours that extend into the temporal bone with involvement of the epipharynx
- juvenile angiofibroma Class III b–IV (Fisch)
- nasopharyngeal carcinoma.

If the lesion does not extend to the vertical portion of the petrous ICA, a variation of this approach, the preauricular Type D approach, can be used, thus avoiding blind sac closure and subtotal petrosectomy.

CONTRAINDICATIONS

- Advanced disease with extension into the sella, contralateral middle fossa or anterior skull base.

PROCEDURE

A postauricular C-shaped incision is made that extends superiorly into the temporal region and inferiorly into the neck (Figure 109.5a). The temporalis muscle, mastoid and zygoma are exposed. A periosteal flap is elevated and the external auditory canal is transsected and closed as a blind sac. The pinna and skin flap are reflected anteriorly. As a precaution, the neck is dissected so that control of the carotid and jugular vessels can be achieved. The main trunk of the facial nerve is identified together with its frontal branch so that the zygomatic arch can be exposed and divided anterior to the temporomandibular joint and again just behind the orbital rim without damaging the frontal branch. The zygomatic arch is reflected inferiorly attached to masseter muscle (Figure 109.5b). The temporalis muscle and fascia is elevated from the temporal fossa and reflected inferiorly to expose the superolateral quadrant of the infra-temporal fossa.

A subtotal petrosectomy is undertaken, skeletonizing the sigmoid sinus, ICA and middle fossa dura with preservation of the labyrinth and removal of all vestiges of skin. The temporomandibular joint capsule is exposed followed by excision of the articular disc and subsequent inferior displacement of the mandibular condyle. Additional space can be established by release of the sphenomandibular and stylomandibular ligament. The glenoid fossa is resected to give extensive exposure to infratemporal fossa and this can be enlarged further by division of the mandibular nerve and middle meningeal artery (Figure 109.5c). Access to the anterior third of the Eustachian tube and nasopharynx can be achieved by removal of the pterygoid process with its lateral and medial plates and dissection along the tube. The nasopharyngeal cavity is entered through incision of the pharyngobasilar membrane and nasopharyngeal mucosa.

After completion of the resection, closure of the nasopharynx is accomplished by rotating some of the temporalis muscle into the defect. Alternatively a bulky free flap such as the latissimus dorsi-flap can be used. The temporomandibular joint is reconstructed by interposing temporalis muscle between the condyle of the mandible and the middle fossa dura. The skin and subcutaneous tissue are closed in layers, after drain placement in the infratemporal fossa.

Normal oral feeding can be started on the first post-operative day.

KEY POINTS

- Advantages:
  - wide access to infratemporal, parasellar and temporal region
  - direct approach
  - short working distance.
- Limitations and drawbacks:
  - temporary post-operative trismus and malocclusion
  - hypaesthesia of the lower half of the face and ipsilateral tongue (V3)
  - permanent post-operative conductive hearing loss
  - temporary frontal facial paresis in 30%.

COMBINED APPROACHES

Subtemporal-preauricular infratemporal fossa approach[23]

INDICATIONS

- Large tumours (T4) of the infratemporal space extending into the nasopharynx, the cavernous sinus and the middle cranial fossa.

CONTRAINDICATIONS

- Bilateral involvement of the ICA
- Bilateral involvement of the optic chiasm[24]
- Lesions that extend into the posterior cranial fossa for which a combination with a retrosigmoid or transotic approach is required.

PROCEDURE

A preliminary tracheostomy is performed if resection of the naso-and/or oropharynx is anticipated. The ipsilateral scalp, face, neck, lower abdomen and thigh are prepared and draped. An extended Blair incision is made (Figure 109.6a) and a cervico-facial flap raised. The facial nerve trunk is identified and its major branches

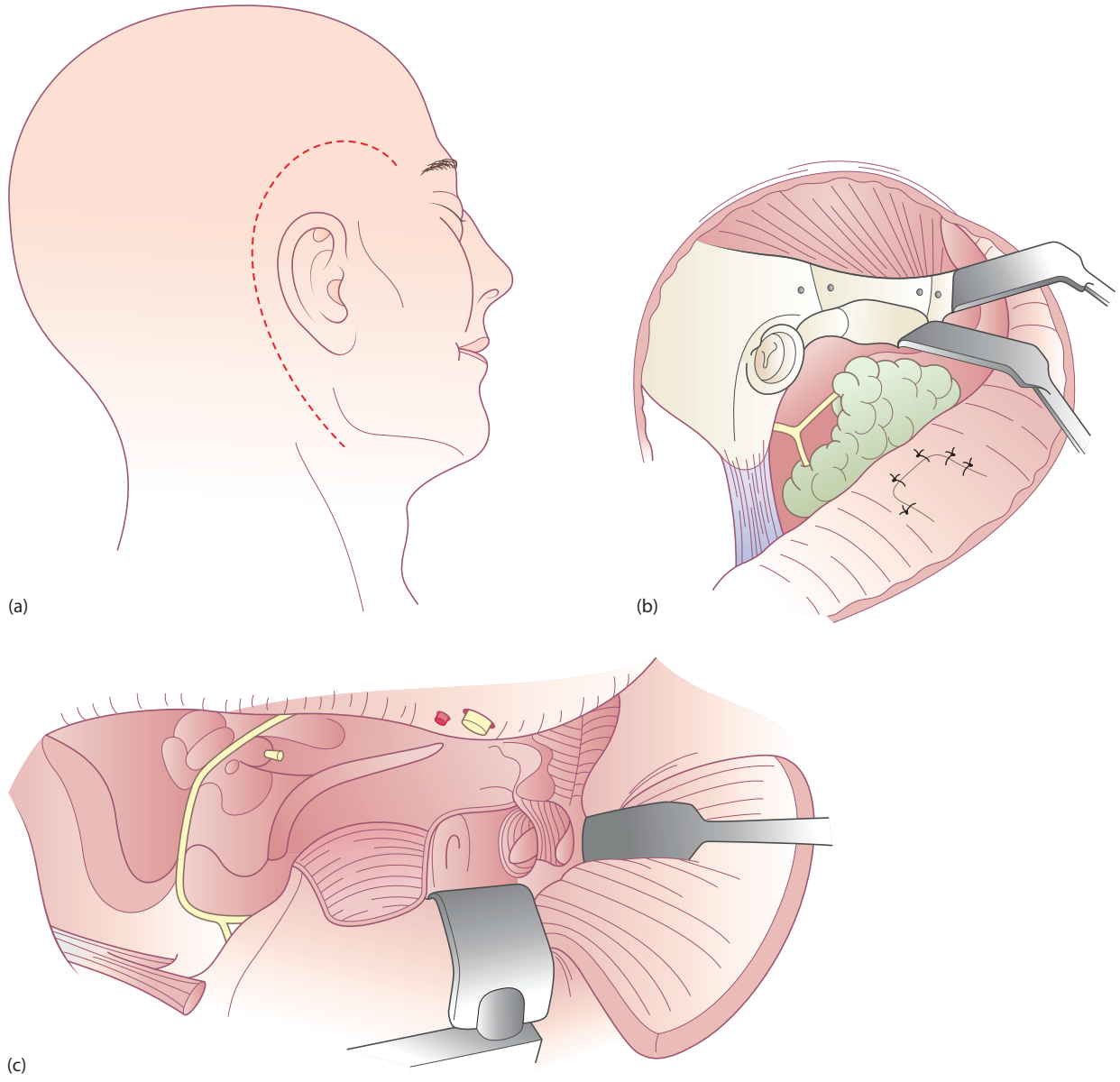


Figure 109.5 Infratemporal approach Type C. Redrawn from original illustrations by Margrit Pirker.

are dissected peripherally. The parotid gland is elevated from the masseteric fascia, the superficial temporal vessels are ligated and the temporalis muscle is elevated from the temporal squama. Osteotomies of the zygomatic arch (Figure 109.6b) permit inferior reflection of the temporalis muscle. A fronto-temporal craniotomy is then fashioned that includes the root of the zygomatic arch, glenoid fossa and the floor of the middle fossa lateral to the foramen spinosum and ovale, extending anteriorly to the pterion (Figure 109.6c).

Using a microscope, further medial dissection elevates the dura to expose the arcuate eminence, greater superficial petrosal nerve, middle meningeal artery and the mandibular nerve (V3). The middle meningeal artery is ligated and divided while the V3 can be retracted if it is not invaded by the lesion. Through this exposure, lesions around the middle third of the Eustachian tube can be addressed. Removal of more bone medial to the glenoid fossa and antero-medially along the greater wing of the sphenoid gives further access to the anterior Eustachian tube and pterygopalatine fossa. Selective removal of the pterygoid process allows access not only to the anterior third and pharyngeal ostium of the Eustachian tube but also to the posterolateral aspect of the nasopharynx. Further dissection along the pharyngobasilar membrane exposes the entire nasopharyngeal soft tissue sleeve allowing circumferential resection. If the lesion extends to the cavernous and petrous ICA, the Eustachian tube is removed completely, which gives access to the horizontal and vertical petrous segments of the ICA. Unroofing the horizontal segment of the ICA exposes the floor of the cavernous sinus. Further exposure of the inferior and medial border of the cavernous ICA is be attained by removal of the pterygoid root and the lateral walls of the sphenoid

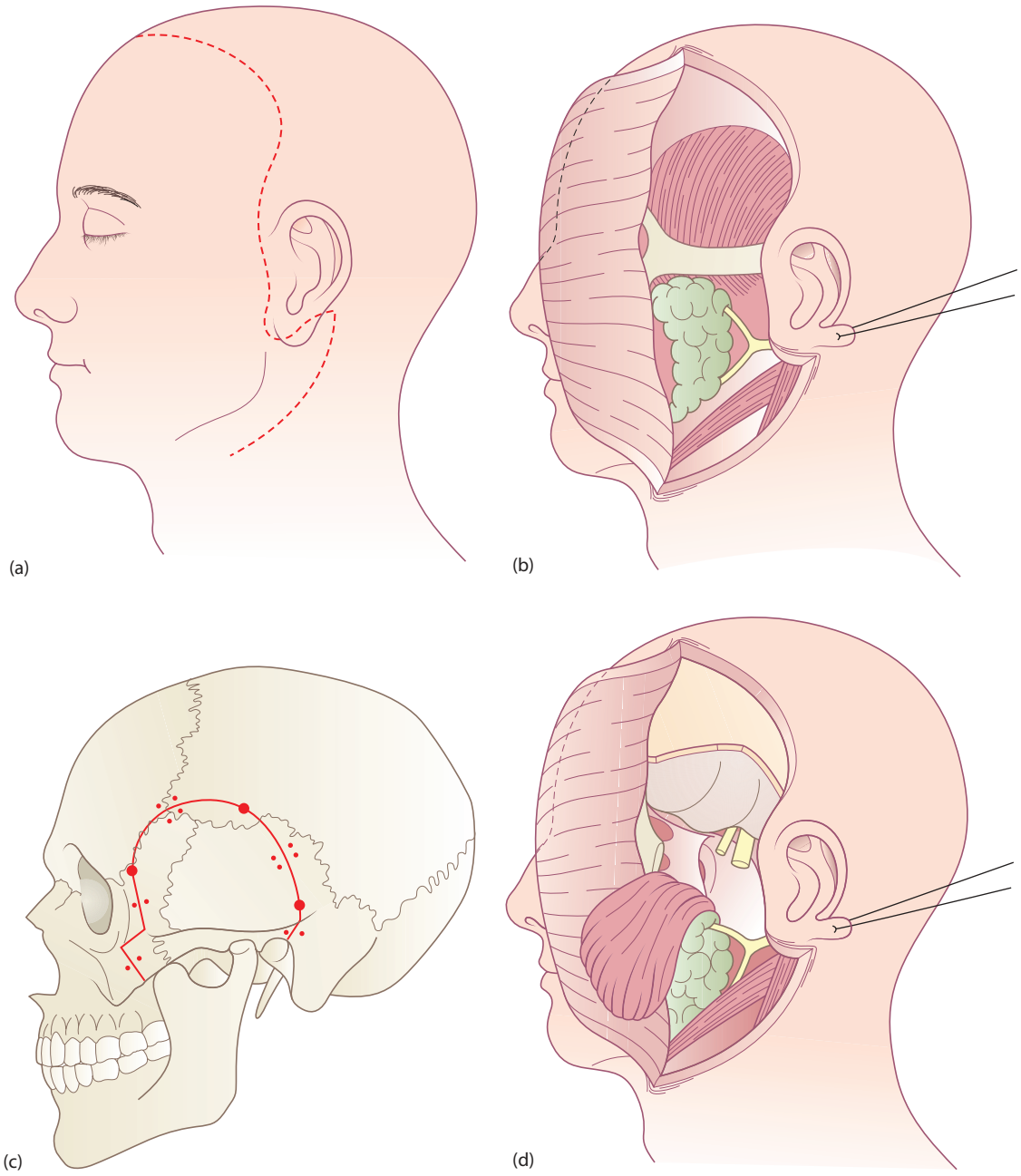


Figure 109.6 Subtemporal preauricular approach. Redrawn from original illustrations by Margrit Pirker.

body; this, however, requires transaction of the maxillary nerve (Figure 109.6d).

After removal of the tumour, dural defects can be repaired with pericranial regional flaps or with autologous fascial grafts such as temporalis fascia or fascia lata. The craniectomy bone flap is replaced and fixed with miniplates. If the defect cavity communicates directly with the nasopharynx, paranasal sinuses or skin, the exposed dura and the major vessel must be sealed off and protected by vascularized musculofascial flaps such as the radial forearm, anterior thigh or latissimus dorsi flap. Simple, passive wound drains are placed and skin closure completed.

Oral feeding can start on the first post-operative day.

KEY POINTS

- Advantages:
  - interdisciplinary approach
  - wide exposure of the infratemporal region, the petrous and cavernous segments of the internal carotid and the cavernous sinus.
  - good access for reconstruction.
- Limitations and drawbacks:
  - craniotomy required
  - CSF drainage required
  - high incidence of post-operative CSF leakage (15–20%)
  - insufficient exposure of the posterior petrous bone and otic capsule.

Facial translocation[24, 25]

INDICATIONS

- Extensive tumours (T4) of the anterior and middle skull base extending into the orbit, paranasal sinus and posterior cranial fossa with intracranial involvement.

CONTRAINDICATIONS

- Bilateral involvement of the ICA
- Bilateral involvement of the optic chiasm.[24]

PROCEDURE

The patient lies supine with the head turned 30–40 degrees to the contralateral side and positioned in an open head rest or Mayfield clamp. The ipsilateral scalp, face, neck, lower abdomen and thigh are prepared and draped. A modified Weber–Ferguson incision is made in order to create a wide cheek flap pedicled on the facial and inferior labial vessels (**Figure 109.7a**). The cheek flap includes the lateral third of the upper lip, the entire cheek soft tissue including the maxillary periosteum, lower lid, facial nerve and the parotid gland. The incision starts from the philtrum of the lip and is continued along the nasal silhouette. It then passes horizontally transsecting the medial canthus, follows the fornix of the inferior eyelid dividing the conjunctiva and the lateral canthus. It then joins the preauricular incision. By necessity, the frontal branches of the facial nerve are transsected and tagged for later reconstructive neurorrhaphy. The soft tissues of the cheek

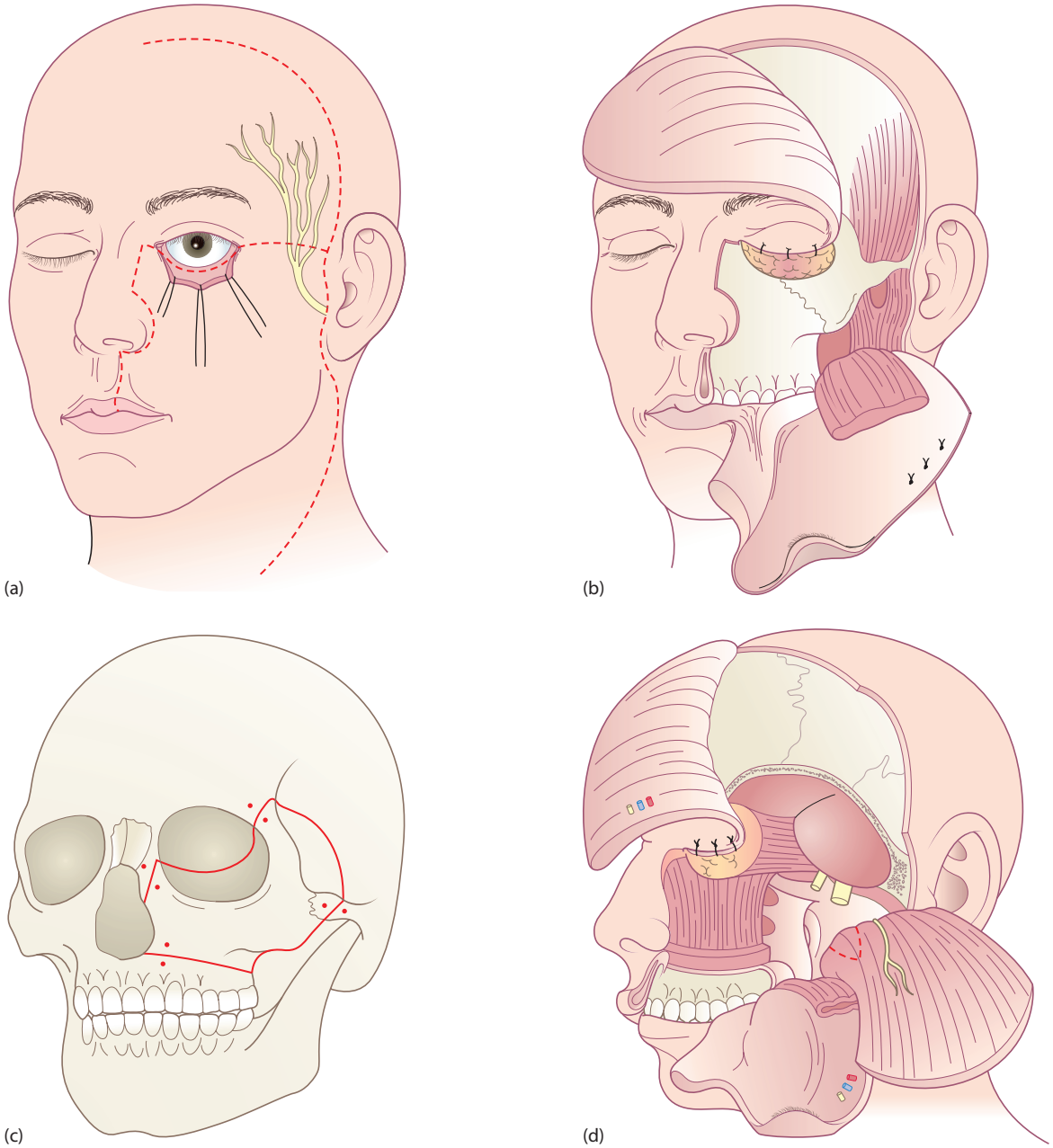


Figure 109.7 Facial translocation approach. Redrawn from original illustrations by Margrit Pirker.

are elevated from the facial skeleton and in doing so the infraorbital nerve is transsected and the masseter muscle is divided just below the zygomatic arch. A bicoronal incision is then made that meets the lateral extension of the previous transfacial incision. This allows elevation of the soft tissues from the temporal muscle and frontal bone thus creating a fronto-temporal scalp flap (**Figure 109.7b**). The latter is reflected towards the midline, while the cheek flap along with transsected masseter muscle are reflected inferiorly to the level of the hard palate. This manoeuvre requires division of the upper lip and extension of the lip incision along the gingivolabial sulcus as far as the last molar tooth (**Figure 109.7b**).

An orbito-maxillo-zygomatic free bone flap is created. Osteotomies pass through the frontozygomatic and temporozygomatic sutures laterally, inferiorly through the maxilla at the level of the nasal floor parallel to the hard palate to reach the pterygopalatine fossa; medially through the orbit in line with the inferior part of the lacrimal fossa and the tip of the inferior orbital fissure; laterally it is continued along the lateral orbital wall to join the transected frontozygomatic suture (**Figure 109.7c**). The posterior wall of the maxilla is freed from the pterygoid plates with a chisel. A subperiosteal osteotomy of the coronoid process and mandibular neck allows the temporal muscle and fascia to be mobilized from the temporal fossa and reflected inferiorly along with the mandible. This gives access to the nasopharynx, the pterygoid process, anterior surface of the sphenoid as well as the infratemporal fossa (**Figure 109.7d**). Further removal of the pterygoid processes and muscles exposes the lateral wall of the nasopharynx and foramen rotundum with the maxillary nerve. If even more access is required, it can be achieved by removal of bone from any of the exposed surfaces and by doing this the entire infratemporal, petroclival and cavernoclival borders can be visualized (**Figure 109.7d**).

Reconstruction follows the previously described steps, starting with watertight sealing of the dura with bulky microvascular free flaps (e.g. rectus abdominis, latissimus dorsi), which also eliminate the dead space and provide a well vascularized barrier between the dura and the nasopharyngeal mucosa. The free bone flaps are replaced and fixed with mini-plates. The cheek flap is realigned and the medial and lateral canthal ligaments reattached with stents being placed in the lacrimal duct. Finally, the frontal branches of the facial nerve are reanastamosed and the skin soft tissue closed in layers. Nasal packings are introduced to prevent obliteration of the nasal airway by encroachment of the reconstructive tissue in the operative defect.

Nasogastric feeding is necessary for a few days but oral alimentation can begin during the first week. Any non-resorbable nasal packs are removed on the eighth day and the lacrimal stents are left in place for 3 weeks.

KEY POINTS

- Careful patient selection and regular unit exposure are crucial for successful outcomes.
- A multidisciplinary management is mandatory.
- The detailed assessment and knowledge about the biology of pathology is the key for approach selection.
- An individually tailored approach decreases morbidity. This can frequently be achieved by a combining an endoscopic with a limited open approach.
- The endoscopic extended approaches have largely replaced the open approaches to benign lesions of the epipharynx and Eustachian tube.
- Swallow and hearing rehabilitation are key factors for quality of life.

FUTURE RESEARCH

Over the last few decades the development of multidisciplinary skull base approaches has rendered previously 'inoperable' lesions operable with minimal peri-and post-operative morbidity. The diseases managed by these approaches are not common and there are few centres with a large experience or with long-term results that would bear any form of analysis.

Improvements in the future may be achieved by:

- the expanding use of endoscopic approaches and procedures and the evolving endoscopic technology, thus further reducing post-operative morbidity and hospitalization length and improving functional outcomes
- TORS for the skull base
- new bone surgery and modelling tools
- new navigational techniques
- new dural repair techniques and products
- establishment of validated, defined indications for the established approaches
- multi-centre case-controlled or cohort studies for the most common skull base pathologies using skull base registries
- employment and evaluation of alternative or adjuvant therapies such as targeted immunotherapy, chemotherapy or Gamma Knife in an attempt to increase local tumour control.

KEY POINTS

- Advantages:
  - direct wide exposure of the anterior and middle cranial base
  - good access for reconstructions
  - radical resection of extensive tumours possible.
- Limitations and drawbacks:
  - complex multi-step surgical technique
  - craniotomy required
  - CSF drainage required
  - reconstruction and tubing of nasolacrimal system required
  - temporary or permanent palsy of the frontal branches of the facial nerve[24]
  - increased risk of post-operative osteonecrosis.

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CHAPTER 110

TUMOURS OF THE TEMPORAL BONE

Marcus Atlas, Noweed Ahmad and Peter O'Sullivan

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Risk factors for the development of temporal bone tumours 1339
Clinical evaluation 1340
Management of temporal bone tumours 1342
Temporal bone tumours in childhood 1346
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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: external auditory canal, middle ear, temporal bone and skull base neoplasm. More specific searches were made on glandular tumours, adenoma, carcinoid tumour, endolymphatic sac tumours, inverted papilloma, haemangioma, haemangiopericytoma, osteoma, chordoma, chondrosarcoma, rhabdomyosarcoma and Langerhans cell histiocytosis, focusing on their presentation, diagnosis and management.

INTRODUCTION

The most common tumours that develop in the temporal bone, glomus tumours and squamous cell carcinomas of the external auditory canal, are discussed in greater detail elsewhere in the text (see Chapter 115, Squamous cell carcinoma of the temporal bone and Chapter 107, Jugular foramen lesions and their management). This chapter is devoted to those tumours that are less common and about which relatively little is known. Some surgeons may never encounter any of these during their career.

There are two key aims of this chapter: first, to provide sufficient information for surgeons so that these uncommon conditions can be suspected at an early stage; second, to provide an overview of what is considered best practice for managing these rare entities.

All three embryonic primordial layers contribute to the normal structure of the temporal bone and, therefore, the spectrum of neoplasms that can develop within it is vast. The difference in growth rate of these tumours, in addition to their sites of origin, account for the varied presentations of these rare tumours. To complicate matters further, initially some may mimic other more common conditions such as cholesteatoma, Wegener's granulomatosis or fibrous dysplasia. Furthermore, the complex anatomical relationships of the temporal bone can make the management of tumours in this region particularly challenging.

RISK FACTORS FOR THE DEVELOPMENT OF TEMPORAL BONE TUMOURS

Genetic

To date, more than 200 mutations of the *NF2* gene have been identified (located on the long arm of chromosome 22–22q12.2). Three separate genes have been identified that are pathogenically linked to hereditary paraganglioma (on chromosome 11q23). An association has also been demonstrated between Von Hippel–Lindau (VHL) disease and endolymphatic sac tumours, the gene for VHL having been identified on chromosome 3p25. The molecular genetics of temporal bone tumours will almost certainly play a key role in the understanding and management of some temporal bone tumours in the future.[1–2]

Radiation

Ionizing radiation has been implicated in the aetiology of temporal bone tumours. Cahan et al.[3] established criteria

that needed to be fulfilled in order to make the diagnosis of radiation-induced sarcoma in bone. Some 50 years later, Lustig et al.[4] defined similar criteria for radiation-induced temporal bone tumours as follows:

- The second neoplasm must develop in the irradiated field.
- A latent period of at least several years must elapse between radiation exposure and the development of a second primary.
- The previous condition must show histological, radiographic and microscopic evidence of neoplasia.
- The second tumour must be of a different histological type from that previously irradiated.

Radiation-induced tumours of the temporal bone are rare, but there are reports in the literature of tumours, such as squamous cell carcinoma, fibrosarcoma and osteosarcoma, which fulfil the above criteria. These tumours are aggressive and tend to metastasize early. Treatment is difficult and management of reported cases has included surgical resection, chemotherapy and adjuvant radiotherapy. Reported outcomes are generally poor with 22–32% of patients surviving 2 years and a 5-year survival of 11–32%.[4]

Chronic suppurative otitis media and papillomatosis

Despite the fact that very few patients with chronic suppurative otitis media (CSOM) develop carcinoma of the temporal bone, a relationship is postulated between the development of squamous carcinoma of the temporal bone and CSOM. Many patients, 68% in one series,[5] have been treated for this condition prior to development of their tumour. The pathogenesis of this association is not understood, but the natural assumption is that cellular trauma must be a contributory factor. Jin et al.[6] isolated human papillomavirus (HPV) 16/18 at both the tissue and molecular levels in patients with carcinoma of the middle ear and associated chronic otitis media. This finding may provide a model to explain the relationship between the two. Although HPV 11 is regarded to be a low-risk variant in the uterine cervix, its behaviour in the head and neck region includes pathogenesis of squamous carcinoma in the temporal bone.[7] The transformation to squamous carcinoma of both benign and inverted papillomas of the temporal bone, recently described, suggests the question whether there should be further genetic analysis of biopsied papillomas to assess their susceptibility to malignant transformation.[8–9]

CLINICAL EVALUATION

Presentation of temporal bone tumours

The presentation of tumours of the temporal bone may be very subtle. Early diagnosis relies heavily on the level of awareness and index of suspicion of the clinician.

The presentation of a tumour can mimic that of less sinister otological conditions, such as otitis externa or CSOM. At the outset, patients present with otalgia, otorrhoea, hearing loss and vertigo. It is not surprising that early diagnosis is difficult and biopsy, the only way to make the diagnosis, is often delayed (or even misleading if taken superficially) until a relatively late stage when other more alarming clinical features such as facial palsy or bleeding have developed. Sadly, only at that stage is the true severity of the patient's pain appreciated by the clinician. Pain caused by these tumours is generally far more severe than that experienced with non-neoplastic conditions. Tumours of the temporal bone described in this chapter tend to spread locally through the Haversian system of the bone and anatomical fissures. These canals contain blood vessels and nerves in the temporal bone and provide additional pathways for tumour spread. Leonetti et al.[10] highlighted a number of ways that this group of neoplasms tended to spread. For example, tumours of the external auditory canal often extend anteriorly into the parotid gland and temporomandibular joint (**Figure 110.1**). Tumours of the middle ear spread anteriorly to involve the Eustachian tube and the postnasal space while extension superiorly rapidly involves the middle cranial fossa (**Figure 110.2**). The otic capsule and the labyrinth become involved by medial growth. Inferior spread involves the jugular foramen and lower cranial nerves. The internal carotid artery not infrequently becomes encased when

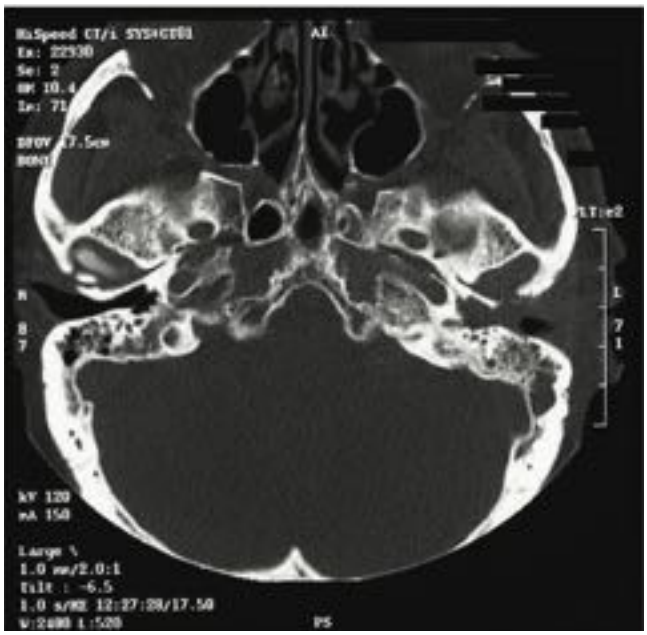


Figure 110.1 Adenoid cystic carcinoma of the left external auditory canal. High resolution axial CT of the skull base revealing soft tissue opacificaton of the left bony external canal with perforation of the anterior wall extending into the temporomandibular joint. There is slight irregularity of the posterior wall of the bony external canal with opacification of the adjacent mastoid air cells. Courtesy of Professor Andy White, Perth Radiological Clinic, Perth, Western Australia.



Figure 110.2 Adenoid cystic carcinoma of the left external auditory canal. Postgadolinium fat saturation T1 cranial scan of the skull base revealing extensive ill-defined enhancing tumour in the left external auditory canal and middle ear cleft. Tumour surrounds the ossicular chain and erodes the tegmen with dural thickening on the undersurface of the left temporal lobe. Courtesy of Professor Andy White, Perth Radiological Clinic, Perth, Western Australia.

tumour extends into the petrous apex. Thus, the clinical features of temporal bone tumours may include:

- trismus
- hemifacial spasm or progressive facial weakness
- lower cranial nerve palsies (IX, X, XI and XII)
- headache and localized pain
- cervical metastases.

Investigation of temporal bone tumours

Multimodality imaging is essential to provide sufficient information to assess the stage of disease from which a sensible management plan can be derived. Thin section computed tomography (CT) will demonstrate bone erosion and gadolinium-enhanced magnetic resonance imaging (MRI) the full extent of soft tissue infiltration. Image merge techniques can contribute much to the assessment of tumour stage. The surgeon must make every effort to evaluate potential dural involvement and extent of spread to the infratemporal fossa.

The tumour should be biopsied for definitive diagnosis based on histological confirmation of tumour type, but this may not be possible until after extirpation of the lesion itself.

Staging of temporal bone tumours

Neither the American Joint Committee on Cancer (AJCC) nor the International Union against Cancer (IUCC) has a system specifically for classifying temporal bone tumours. An AJCC T4 tumour grading applies to both extensive tumours with deep temporal bone involvement and small tumours that superficially invade auricular cartilage – despite what is likely a vast difference in prognosis! A number of alternative staging systems have therefore been proposed that depend on the site and type of tumour.

Stell and McCormick[11] proposed a system for staging carcinoma of the external and middle ear that was subsequently updated by Clarke and Narula[12] (see also Chapter 115, Squamous cell carcinoma of the temporal bone). Arriaga et al.[13] have also proposed a system for staging tumours of the external auditory canal. Fisch, Glassock-Jackson and De La Cruz have all provided systems for the staging of glomus tumours. None of these classification systems have been proven in terms of prognosis, but can be used to aid multidisciplinary discussion and for selection of a suitable surgical approach if appropriate.

Classification of tumours of the temporal bone

Tumour types are summarized in Table 110.1.

TABLE 110.1 Classification of tumours of the temporal bone

Cutaneous neoplasms	Glandular neoplasms	Vascular/ haematological	Paraganglioma	Bone	Neural	Developmental and congenital
Squamous cell papilloma and carcinoma	Ceruminous adenoma and adenocarcinoma	Haemangioma	Glomus tympanicum	Osteoma	V, VII, VIII, IX, X, schwannoma	Chordoma
Basal cell papilloma and carcinoma	Pleomorphic adenoma	Haemangiopericytoma	Glomus jugulare	Secondary tumours	Meningioma	Dermoid
Malignant melanoma	Adenoid cystic carcinoma	Leukaemia	Glomus vagale	Rhabdomyo-sarcoma		Teratoma
	Middle ear adenoma	Lymphoma		Chondrosarcoma		Choriostoma
	Endolymphatic sac tumours	Plasmacytoma		Ewing sarcoma		
		Langerhans cell histiocytosis		Osteogenic sarcoma		

MANAGEMENT OF TEMPORAL BONE TUMOURS

Glandular tumours of the external auditory canal

The glandular components of the external auditory canal consist of sebaceous glands and modified apocrine glands, called 'ceruminous glands'. Previously, glandular tumours of the external auditory canal had been classified under the umbrella term of ceruminoma, but this term is non-specific and should not be used without qualification. There has been some confusion in the literature with no agreed system of nomenclature for these tumours[14] but classification of glandular tumours of the external ear by Wetli et al.[15] is relatively less complicated:

- ceruminous adenoma
- pleomorphic adenoma
- adenoid cystic carcinoma
- ceruminous adenocarcinoma.

CERUMINOUS ADENOMA

Ceruminous adenomas are well-differentiated tumours derived from the ceruminous glands. These tumours exhibit solid, cystic and papillary patterns. Ceruminous adenomas consist of an inner layer of cells that are cuboidal or columnar and are of apocrine origin with an outer layer that is myoepithelial in origin. These tumours should be widely excised because local recurrence is common. Radiotherapy has no role to play in the treatment of this type of tumour.

PLEOMORPHIC ADENOMA

Pleomorphic adenoma should also be excised. Care must be taken to avoid seeding of the local tissues by spillage of tumour during resection. Recurrence may develop many years after resection in much the same way as is seen in the major salivary glands.

ADENOID CYSTIC CARCINOMA

Adenoid cystic carcinoma of the temporal bone may display cribriform, tubular or solid growth patterns surrounded by cystic spaces. Adenoid cystic carcinoma has the propensity for significant local tissue destruction (**Figure 110.1**), perineural and perivascular invasion. It also tends to metastasize to the lymph nodes of the neck. There are no established treatment regimens. This condition is thought best managed by aggressive surgical resection followed by radiotherapy. The long-term prognosis is poor with distant (lungs, lymph nodes, skeletal) metastatic disease developing years later. Bone invasion, perineural spread and tumour extension outside the external auditory canal are considered indicators of poor prognosis.

CERUMINOUS ADENOCARCINOMA

Ceruminous adenocarcinoma is often difficult to distinguish from ceruminous adenoma as it may show very few malignant features apart from evidence of invasion into local tissue. These tumours grow slowly and tend to spread by local invasion. Metastases have been reported. Ceruminous adenocarcinomas are extremely rare and advice on treatment is largely anecdotal. Surgical resection with post-operative radiotherapy is considered to be the appropriate therapy.

In summary, benign glandular tumours of the external ear should be treated by wide surgical excision. The optimum treatment for malignant tumours has not been established and is unlikely to be forthcoming in the near future. Current opinion would suggest aggressive surgical resection followed by adjuvant radiotherapy.[16]

Glandular tumours of the middle ear

Debate continues about the nomenclature, pathology and behaviour of glandular tumours of the middle ear. The distinction between terms such as adenoma, adenomatous tumours, adenocarcinoma and carcinoid tumour of the middle ear has not always been clear, partly because of overlapping pathological features, but also because of uncertainty about the behaviour and natural history of these tumours.

MIDDLE EAR ADENOMA

In 1976, Hyams and Michaels[17] presented 20 primary middle ear tumours with an adenomatous pattern that were strictly confined to the middle ear cleft and thought to be derived from the middle ear mucosa. The tumours described in this series expanded locally. There was no evidence of bony erosion or of distant metastases. All of the patients were treated by local excision. A tympanotomy or mastoid approach was used and no patients were radiated subsequently. Follow-up data were available for 18 patients and all but one was free of tumour 4–24 years after surgery. Similar tumours have been described by other authors,[18] and Torske and Thompson[19] reviewed 48 cases of middle ear adenoma that had been referred to the Armed Forces Institute of Pathology over a period of 25 years. These tumours displayed features consistent with the diagnosis of middle ear adenoma. They lacked features of aggressive malignancy such as mitotic activity, perineural or vascular invasion. The authors suggested that the presence of neuroendocrine markers made these neoplasms indistinguishable from carcinoid tumours. It was argued that the relatively small size of these tumours, together with the relatively poor blood supply of the middle ear, explained the lack of paraneoplastic syndromes. In contrast to other carcinoid tumours, metastatic disease was not seen with middle ear adenoma. It was suggested that 'neuroendocrine adenoma of the middle ear' might be a more appropriate description.

A more recent review by Saliba and Evrard[20] examined the literature on all reported cases, and recommended a new system of classification of middle ear glandular neoplams that may have prognostic significance. Based on the

presence or absence of immunohistochemical markers and metastasis, these lesions are classified into three types:

- **Type I:** neuroendocrine adenoma of the middle ear (NEAME) in 76% of cases (positive immunohistochemistry, negative metastasis)
- **Type II:** middle ear adenoma (MEA) in 20% of cases (negative immunohistochemistry, negative metastasis)
- **Type III:** carcinoid tumour of the middle ear (CTME), only 4% of tumours (positive immunohistochemistry, positive metastasis and/or carcinoid syndrome).

Wide surgical resection is generally recommended and cure can be anticipated. Hearing can often be preserved. It has been suggested that if the tumour is intimately related to the ossicles, removal of the ossicles reduces the possibility of tumour recurrence.[20] Radiotherapy does not have a role to play in the treatment of these tumours.

TUMOURS OF THE ENDOLYMPHATIC SAC

In 1988, Gaffey et al.[18] proposed the term aggressive papillary middle ear tumour (APMET) for adenomatous middle ear tumours that have a primarily papillary architecture. As distinct from the middle ear adenoma described above, these tumours were extremely aggressive locally invading bone and possibly extending intracranially. In Gaffey's series, brain invasion was seen in one patient and no patient had evidence of distant metastases. All of these patients were treated with surgery and, in some, adjuvant radiotherapy. In 1989, Heffner proposed that the middle ear tumour previously described as the papillary middle ear tumour was in fact derived from the endolymphatic sac.[21] Li et al.[22] confirmed their findings in 1993 using similar histochemical and histopathological techniques. Terms such as Heffner tumour, low grade adenocarcinoma of endolymphatic sac origin, and aggressive papillary middle ear tumour are now obsolete and it should be described as endolymphatic sac tumour (ELST) according to the more recently published World Health Organization tumour classification.[23]

Progressive unilateral, sensorineural hearing loss is the most prominent feature of this tumour in addition to tinnitus and vertigo. This neoplasm grows very slowly; the average duration of time between onset of symptoms and diagnosis is 9 years.[21] In the past, some patients have presented with an acute unilateral sensorineural hearing loss and been misdiagnosed as Menière's disease, which is understandable considering the site of the lesion (**Figure 110.3**). The differential diagnosis includes paraganglioma, papillary choroid plexus tumours, ceruminous gland tumours, benign adenomatous tumours and metastatic disease. On microscopy, these tumours demonstrate a papillary ultrastructure, composed of cuboidal or low columnar cells (**Figure 110.4**). Nuclear size and shape may vary, but prominent pleomorphism and mitotic activity is not a feature. They are vascular in nature and invade bone in an aggressive fashion. Metastatic spread has not been reported. Growth and spread to the cerebellopontine angle and posterior fossa is most commonly seen. Extension into the middle and external ear has been reported, as well as into the middle cranial fossa, clivus, cavernous sinus and sphenoid sinus.[24] Mukherji et al.[25] showed a correlation between middle ear spread and the size of tumour. In a radiological review of 20 patients with a diagnosis of ELSTs that included CT imaging, MRI and angiography, eight of nine tumours less than 3 cm in size did not involve the middle ear, and eight of

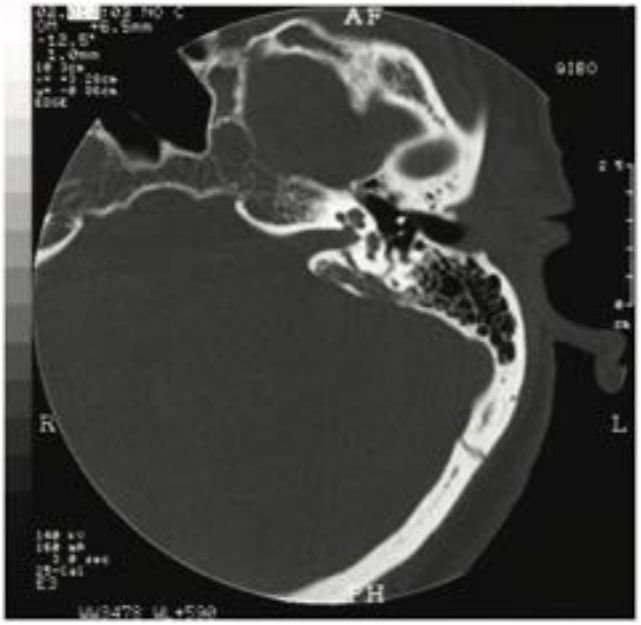


Figure 110.3 Endolymphatic sac tumour. High resolution axial CT of the temporal bone revealing permeative bone destruction along the posterior margin of the left temporal bone along the line of the vestibular aqueduct. Courtesy of Professor Andy White, Perth Radiological Clinic, Perth, Western Australia.

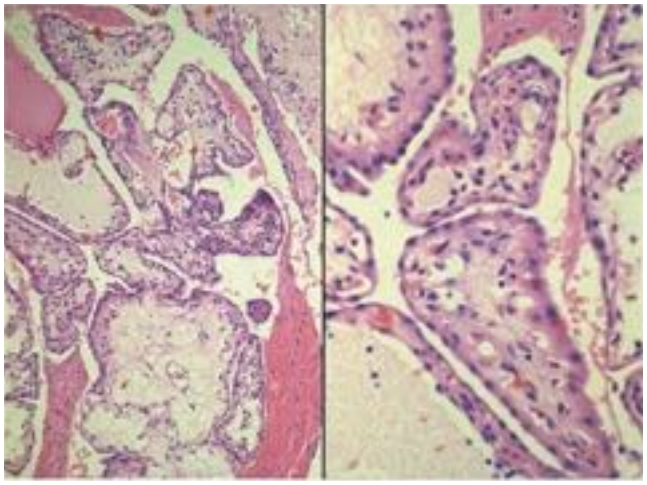


Figure 110.4 Endolymphatic sac tumour. Aggressive papillary middle ear tumour of temporal bone and endolymphatic sac. This tumour occurred in a 35-year-old female. There are papillary formations consisting of oedematous fibrovascular cores lined by a single layer of plump, cuboidal epithelial cells. Courtesy of Drs P Robbins and D Spagnolo, The Western Australian Centre for Pathology and Medical Research, Perth, Western Australia.

nine tumours of at least 3 cm demonstrated soft tissue involvement of the middle ear.[25] It was also demonstrated that the vascularity of the tumour was related to tumour size. Tumours less than 3 cm are supplied solely by the external carotid artery and, as the tumour enlarges, it obtains a blood supply from the internal carotid artery. Ultimately, the tumour may also obtain a blood supply from the posterior circulation (i.e. the anterior and inferior cerebellar arteries).

An association had been established between tumours of the endolymphatic sac and Von Hippel–Lindau (VHL) disease.[24] This autosomal dominant condition predisposes the patient to a number of conditions, including haemangioblastoma of the cerebellum, angiomatous lesions of the retina and renal cell carcinoma. The gene for this condition has been identified in the short arm of chromosome 3 (3p25) and a mutated suppressor gene has also been identified in both abnormal and neoplastic tissues of patients suffering from this condition. Gaffey et al.[18] pointed out that 15% of patients with ELSTs are known to have VHL disease. A review of the literature published in 2012 indicated an earlier age at presentation with ELST in VHL disease (31.3 years versus 52.5 years) with a female preponderance (female-to-male ratio of 2:1 for VHL disease patients versus 1:1 for non-VHL disease patients) and propensity for bilateral ELSTs in VHL disease.[26]

Recent studies have demonstrated an excellent prognosis (in terms of survival and hearing preservation) with early surgical resection without the need for radiotherapy.[27–29] Removal of the tumour is therefore advised (with pre-operative embolization if needed), the extent of the resection being determined by a number of factors that include its size, vascularity, existing neural deficits and those that might be acquired as a result of surgery. Most patients are young adults and incomplete tumour removal can lead to significant long-term morbidity. Partial tumour removal can be justified for some when complete removal might inflict unacceptable morbidity. In this respect, it is worth remembering that this is an extremely slow-growing tumour and the elderly might outlive their disease. Adjunctive radiotherapy has been used in the treatment of these tumours but its role in the treatment of ELSTs is far from established. Radiation therapy may be considered when surgical treatment is not an option or as a palliative measure following partial tumour removal.

Miscellaneous tumours of the middle ear

INVERTED PAPILLOMA

These are extremely rare tumours of the middle ear and are similar to inverted papilloma of the sinonasal system. HPV has been implicated in their pathogenesis. Like its nasal counterpart, surgery is the mainstay of treatment. It is essential that the specimen be examined for evidence of carcinoma as malignant transformation has recently been demonstrated.[9] In those patients with evidence of carcinoma, radical resection with post-operative radiotherapy has been advocated.[30]

HAEMANGIOMA

These benign vascular tumours are derived from arterioles, venules and capillaries. They develop at a number of sites in the temporal bone with the geniculate ganglion being the most common. In the middle ear they have been found coincidentally, but usually present with symptoms of conductive hearing loss. The differential diagnosis includes that of paraganglioma, high jugular bulb and adenomatous tumour. Some haemangioma may regress spontaneously, while others continue to grow and are locally destructive. Surgical excision is the treatment of choice in these cases, but as some tumours may regress spontaneously an expectant approach may be appropriate particularly if surgery might compromise middle ear function.[31]

HAEMANGIOPERICYTOMA

These are rare vascular tumours that consist of proliferating pericytes surrounding capillaries. About 15–25% of haemangiopericytomas develop in the head and neck region. Cases have been reported in the middle ear and temporal bone, although they are extremely rare. Fifty per cent are malignant, although the behaviour of even the benign form is unpredictable. Treatment is by wide surgical excision. Pre-operative embolization may be helpful. These tumours appear to be radioresistant, but it has been suggested that radiotherapy has a role to play if excision is incomplete.[32]

OSTEOMA

These are benign tumours consisting of mature lamellar bone. While well documented in the external auditory canal, they are otherwise very rare in the temporal bone. The most common site of origin appears to be the mastoid with about 20% developing in the middle ear. In half of these, the osteoma causes a conductive hearing loss and the condition is often discovered coincidentally. While easy to remove from the mastoid, an expectant approach is probably more advisable, particularly in the asymptomatic patient with middle ear disease where removal of the osteoma might compromise structures such as the ossicular chain or the VIIth nerve.[33–35]

CHORDOMA

Chordomas are rare tumours that originate from the primitive notochord. A loss of heterozygosity (LOH) study centred on the short arm of chromosome 1 (1p36 region) revealed an high incidence of 1p36 losses among sporadic chordomas.[36] They are subclassified according to site of development: spheno-occipital (35%), vertebral (15%) and sacrococcygeal (7%). Three types of chordoma are recognized: conventional, chondroid and dedifferentiated, the chondroid form being the most common. Chordomas may present more laterally in the skull base, such as at the petrous apex, the carotid canal or the jugular foramen where they are thought to arise from dendritic processes at the cephalic end of the notochord. These tumours may present at any age, but the mean age at diagnosis is

TABLE 110.2 A comparison of symptoms at presentation of chordoma and chondrosarcoma

Symptom	Chordoma (%)	Chondrosarcoma (%)
Headache	67	49
Diplopia	54	70
Intermittent diplopia	25	28
Decreased visual acuity	8	13
Facial numbness	2	23
Decreased hearing/tinnitus	2	9
Facial weakness	2	11
Dysphagia/dysarthria	2	9

Reproduced with permission from Volpe et al.[37]

between 35 and 45 years. The male to female ratio is 2:1. The most common symptoms at presentation are summarized in Table 110.2.[37]

Conventional chordoma has been misdiagnosed as chondrosarcoma in the past. Chondrosarcoma is the main differential diagnosis and despite its name has a less aggressive clinical course. It is essential to achieve accurate histological diagnosis before outlining a management plan for these unfortunate patients. CT-guided fine-needle aspiration may be useful in this respect.

Surgical removal of chordoma is the mainstay of treatment. Complete resection may be difficult but does provide the best long-term survival and lowest risk of recurrence. Successful resection depends on the degree of spread of the tumour and the degree of involvement of vital structures, such as the carotid artery and the brain. A number of skull base approaches have been described, but most fall into the category of anteromidline and lateral techniques. Successful removal also depends on accurate pre-operative assessment of the tumour and the ability of the surgeon but in many cases subtotal resection with post-operative radiotherapy is the only viable management option.

Radiotherapy as an adjunctive treatment has a significant role to play in the management of these tumours. Although a number of delivery techniques have been used, proton beam therapy is now considered the gold standard radiotherapy modality, and a prospective randomized phase III trial is underway comparing it with a newer modality – carbon ion radiation therapy.[38] However, it must be noted that if surgery (such as salvage) is needed after radiotherapy the tumour can be both fibrotic and adherent, making preservation of vital structures particularly difficult.

Crockard et al.,[39] in a review of 42 patients treated over a 12-year period, reported 5- and 10-year survival rates of 77% and 69% respectively, treated by maximum surgical cytoreduction and photon radiation therapy. A smaller, more recent study reported a higher 5-year survival of 82.5%.[40] Stacchiotti et al.[41] have demonstrated a response to chemotherapy in advanced or recurrent chordomas no longer amenable to surgery or radioresistant tumours. Molecular marker analysis of histological specimens could inform prognosis in the future as a study has demonstrated the lack of 1p36 LOH, or the presence of tumour necrosis factor receptor superfamily gene *TNFRSF8* expression, may be associated with a better prognosis.[42]

CHONDROSARCOMA

The precise origin of chondrosarcoma is not known, but one theory is that these tumours may arise from chondrocytes that persist as embryonal cell rests at or about the foramen lacerum. A number of histological types are recognized, such as hyaline, myxoid, clear cell, mesenchymal and dedifferentiated. Immunohistochemistry can help differentiate chondrosarcomas from chordomas.

Hyaline and myxoid types are more common and are sometimes referred to as 'conventional' chondrosarcoma. Evans et al.,[43] in a review of 81 patients with chondrosarcoma from varying sites, graded these tumours I–III, based on their mitotic rate, cellularity and nuclear size. A 5-year survival of 90%, 81% and 43% in grades I, II and III, respectively, has been reported. There was also a correlation between grade and metastatic rates, with a 0% metastatic rate with grade I tumours, 10% with grade II tumours and 71% with grade III tumours.

The common symptoms at presentation of chondrosarcoma of the skull-base tumours are presented in Table 110.2. These tumours grow slowly and have significant potential for local expansion. Before diagnosis, patients may have been treated for many years with non-specific symptoms, such as headaches or non-specific neurological symptoms. The mean age at presentation is in the fourth decade and the male to female ratio is approximately equal, although some studies have shown a male predominance.[44] Chondrosarcomas typically develop around the foramen lacerum, parasellar region, petrous apex and cerebellopontine angle, rather than the midline predilection of the chordoma.

Treatment protocols for chondrosarcoma continue to evolve and are multidisciplinary in nature. Surgical resection is the mainstay of treatment. Complete removal is not always possible but adjunctive radiation therapy, particularly proton beam, is used in the treatment of these tumours and has an increasing role to play in their management. Rosenberg et al., in a review of 200 patients with a diagnosis of conventional chondrosarcoma treated at the same institution, reported a 5-year local control rate of 99% and a 10-year local control rate of 98%. Both 5- and 10-year disease-specific survivals of 99% were reported when surgery was combined with high-dose fractionated proton beam radiation.[45] A recent systematic review with meta-analysis of 560 patients with cranial chondrosarcoma has demonstrated that surgical resection with post-operative adjuvant radiotherapy has the lowest 5-year recurrence rate (9% vs. 19% for radiation alone, $p < 0.011$) and is significantly better than surgery alone (9% vs. 44%, $p < 0.0001$).[46] It should be noted that chondrosarcoma has a much better overall prognosis than that of chordoma, despite similar aggressive treatment protocols.

SECONDARY TUMOURS OF THE TEMPORAL BONE

Secondary tumours of the temporal bone are classified into three types: local spread of a tumour from an adjacent site such as pharynx, parotid or sinus; distant spread of a cancer; and manifestation of a haematological malignancy (e.g. leukaemia). The spread of a tumour from an adjacent head and neck site is dealt with elsewhere (see Volume 3, Chapter 18, Metastatic neck disease). Haematological malignancies have a significant propensity to spread to the temporal bone and are not addressed further in this chapter. Gloria Cruz et al.,[47] in a review of 212 patients with primary non-disseminated malignant neoplasms, found an approximately 22% prevalence of metastases to the temporal bone. The average age of presentation corresponded to the age at which most primary tumours have their onset (i.e. the fifth to sixth decade). There was a slight male to female preponderance.

Table 110.3 summarizes the site of origin of secondary tumours of the temporal bone. The mode of presentation varies from patient to patient and up to 36% of patients have no symptoms attributable to the head, neck or ear. The most common symptom at presentation is hearing loss, followed by vertigo and facial paralysis.[47] Secondary tumours can develop throughout the temporal bone, but the petrous apex is the most common site followed by the internal auditory meatus.[47–48]

The prognosis for patients with secondary temporal bone tumours is poor. Management may involve a number of different modalities and is dependent upon the origin and nature of the original primary. Treatment, therefore, has to be individualized. Diagnosis is difficult, because so many patients are asymptomatic. In their series, Gloria Cruz et al.[47] found that all patients with temporal bone metastases had metastases at other sites. It is important to realize that metastatic disease should be excluded in any patient with a history of a previous malignancy who develops otological symptoms, particularly sensorineural hearing loss.

TEMPORAL BONE TUMOURS IN CHILDHOOD

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is an extremely aggressive tumour of striated muscle origin that has the potential to spread locally and to metastasize. It is the most common soft tumour of childhood. In the head and neck region, RMS of the ear is the third most common site of origin after the nasopharynx and the orbit. Most of these tumours present under the age of 12 years. Four histological types are recognized: embryonal, alveolar, pleomorphic and botyroid.

Table 110.4 summarizes the most common symptoms and signs at presentation. In addition to the normal histological and radiological work up for tumours of the temporal bone, investigations should include a CT scan of the chest, bone scan and a lumbar puncture. Further investigation may then be carried out as indicated.

Definitive treatment of these tumours continues to evolve and consists of a multidisciplinary, multimodality approach that includes chemotherapy, radiotherapy with less of a role for surgery. One study, the Intergroup Rhabdomyosarcoma Study (IRS), was introduced in 1972 to establish the optimum treatment for RMS in general. A summary of the IRS classification system for staging these tumours, as introduced by Maurer et al.,[50] is shown in Table 110.5.

RMS of the temporal bone tends to be diagnosed late due to symptoms that mimic more common conditions. As a result, most patients are staged in group III and included under the umbrella term of 'parameningeal' tumours. The IRS study continued to recruit patients and investigate treatment regimes for RMS, altering the chemotherapeutic regimes and radiation fields as was deemed necessary. IRS results have been reported in every decade since the 1970s. Results of treatment for all groups have improved over the study period with the group III, 5-year survival rates overall improving from 52% in IRS-I to 59% for IRS-II to 65% for IRS-III and 73% for IRS IV.[51–53]

TABLE 110.3 Site of origin: secondary tumours of the temporal bone

Site of origin	Incidence (%)
Breast	25
Lung	11
Kidney	9
Stomach	6
Bronchus	6
Prostate	6

Reproduced with permission from Streitman and Sismanis.[48]

TABLE 110.4 Rhabdomyosarcoma: the most common symptoms and signs at presentation

Symptom	Frequency (%)
Mass in the ear region	56
Aural polyp	54
Ear discharge	40
Bleeding from the ear	30
Ear pain	22
Hearing loss	14
Facial paralysis	14

Reproduced with permission from Prat and Gray.[49]

TABLE 110.5 The IRS classification system

Group	
I	Localized disease completely resected
II	Grossly resected disease, with microscopic residual disease with or without lymph nodes
III	Gross residual disease
IV	Metastatic disease present at onset

Reproduced with permission from Maurer et al.[50]

While still a potentially aggressive and fatal condition, the outcome for childhood RMS of the temporal bone is slowly improving, with the key to survival being early diagnosis through biopsy of unhealthy tissue.

Langerhans cell histiocytosis

Langerhans cell histiocytosis (LCH), formerly called histiocytosis X, is a condition that is characterized by the proliferation of histiocytes that share the characteristic of Langerhans cells (normally located in the dermis). These cells are recognized by the presence of inclusion bodies in the cytoplasm, called Birbeck granules. Proliferation and infiltration of these cells may develop in any organ in the body, including bone, skin, lung, liver, spleen and nervous system. LCH is now the collective name for the following conditions that were previously thought to be three distinct entities, but are now recognized as one condition:

1. **Eosinophilic granuloma:** Generally refers to osseus disease alone and may be unifocal or multifocal
2. **Hand-Schuller-Christian disease:** A systemic disease identified by multifocal osseus lesions, with limited involvement of extraskeletal sites, such as lymph nodes and viscera
3. **Letterer-Siwe disease:** The most serious and rapidly progressive disease, characterized by disseminated disease with multiorgan involvement.

In the series of cases reviewed by Irving et al.,[54] 73% of patients presented with head and neck involvement, 24% of patients had involvement of the skin of the external auditory meatus and 19% had involvement of the temporal bone. The mean age of presentation was 3.2 years and the male-to-female ratio was 1.7:1. These relative percentages of head and neck and temporal bone involvement vary slightly from series to series.[55, 56]

Symptoms and signs of ear and temporal bone involvement are often indistinguishable from that of CSOM and may include a conductive or sensorineural hearing loss. Thirty per cent of patients with temporal bone involvement have bilateral involvement. The characteristic radiological appearance of the temporal bone is that of a 'punched out' or lytic appearance. While extensive destruction of the temporal bone can take place, there are only limited reports of otic capsule involvement with disease often confined to the external and middle ear.

The ultimate prognosis of patients with LCH depends on whether the disease is unifocal, multifocal or disseminated. Age at presentation of less than 2 years with organ dysfunction is an indicator of a much poorer prognosis. Unifocal disease, on the other hand, has a very good prognosis responding to local treatment, which may include local resection or radiotherapy. Most series have a 95–100% cure rate. Multifocal disease also has a good response to treatment,[57] but disseminated disease can be rapidly fatal.[54–56] Involvement of the temporal bone often implies multifocal disease, which is best treated in a multidisciplinary, multimodality fashion with a combination of chemotherapy, radiotherapy and steroid therapy (in order of preference according to current trends). Surgical treatment of temporal bone LCH is now being utilized much more selectively (for isolated disease), recognizing that there is a high risk of complications, particularly to structures such as the facial nerve.

FUTURE RESEARCH

Perhaps because of the rarity of tumours of the temporal bone, there are still large gaps in our knowledge. With some tumours, such as those of the middle ear, there is still uncertainty with regard to their nomenclature, pathology and behaviour.

- ➤ There is no generally accepted system for the classification of temporal bone tumours.
- ➤ While there are staging systems available for some individual tumour types, there is no overall agreed system for staging tumours of the temporal bone.
- ➤ The lack of accurate classifications in addition to the paucity of multicentre trials make treatment guidelines difficult.
- ➤ Randomized, multicentre therapeutic trials should be devised to address these problems and it is heartening to see that these are now taking place in the management of chordomas and chondrosarcomas.
- ➤ It is hoped further advances in molecular biology and immunohistochemistry will advance new therapeutic options.

KEY POINTS

- Temporal bone tumours are exceedingly rare and can be extremely variable in their presentation and prognosis.
- There is often considerable delay in the diagnosis of temporal bone tumours. Biopsy of any unhealthy tissue in the ear is advisable. Early diagnosis and treatment improves outcomes.
- Appropriate radiological investigation is the cornerstone of management.
- The development of unilateral hearing loss in a patient who has had a previous malignancy may indicate a secondary tumour in the temporal bone.
- Management strategies for many of these tumours rely on level 4 evidence.
- Intracranial spread is not uncommon and a multidisciplinary approach is advisable.

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CHAPTER 111

CLINICAL NEUROANATOMY

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SEARCH STRATEGY

Data in the chapter may be supplemented by recourse to the standard textbooks of neuroanatomy e.g. *Gray's Clinical Neuroanatomy: The Anatomic Basis for Clinical Neuroscience*.[1]

INTRODUCTION

A neurological examination is critical in the assessment of patients with skull base disease. In this chapter, applied aspects of skull base neuroanatomy are reviewed and the differential diagnosis of neural deficits considered. In some instances, gross anatomy is of great importance and in others complex central connections require detailed elaboration to illustrate and explain the accompanying clinical disorders. The following account is always biased in the direction of practical applications, and information of limited or uncertain clinical importance has been excluded.

THE CRANIAL NERVES

The cranial nerves fall into three major groupings sharing common anatomical relationships and pathology. Differing patterns of involvement within these groups allows a very accurate differential diagnosis to be advanced, based on both the sequencing and ultimate extent of damage to the nerves in these groups. The advent of computed tomography (CT) and three-dimensional magnetic resonance imaging (MRI) has added remarkably to our ability to confirm or refute clinically suspected diagnosis in what used to be an investigational no-man's land. Scan interpretation still requires a very good knowledge of gross anatomical relationships of the intracranial and extracranial courses of the cranial nerves and these anatomical features form the bulk of this chapter.

The groupings are:

1. Cranial nerves I, II, III, IV, the ophthalmic division of V and VI and the final distribution of the cervical sympathetic
2. Cranial nerves V, VII and VIII
3. Cranial nerves IX, X, XI and XII and the cervical components of the sympathetic chain.

The influence of altered cerebellar, pyramidal, extrapyramidal and corticobulbar function on the nerves and peripheral evidence of disordered brainstem function will be detailed at the end of the chapter, or where appropriate in general discussion.

GROUP 1

In the first group, the close relationship of the olfactory and optic nerves and the varying relationship of the three nerves supplying the extraocular muscles is considered. It is also necessary to include the relationships of the first division of the Vth nerve, which traverses the orbit, to these structures, although the detailed anatomy of this nerve is dealt with in Group 2.

The olfactory nerve (I)

ANATOMY

The olfactory epithelium lies in the olfactory cleft that occupies the upper 10 mm of the nasal septum, the roof of the nasal cavity and down the lateral wall towards the origin of the superior concha (**Figure 111.1**). In humans, its total surface area is some 5 cm^2 and is a yellowish colour. In other species, increasing pigmentation is associated with increased sensitivity to odours. The mucosa is bathed in a lipid-rich secretion from the epithelial Bowman's glands, indicating that lipid solubility may be a critical factor in odour detection. The olfactory receptor cells, some 5 million in all, lie on the basal epithelium and extend vertically to the surface from which the terminal enlargement protrudes and gives rise to 8–20 olfactory cilia. Although these have the standard '9 + 2' fibril arrangement found in mobile cilia in other areas of the body, they are thought to be nonmotile and form a dense mat of fibrils lying on the surface of the epithelium. Pinocytic vacuoles have been demonstrated in the terminal enlargement of the receptor cells, but their functional significance remains uncertain.[1]

The receptor cells are derived from ectoderm and are unique in being replaced from stem cells every 30–50 days. They also enter the central nervous system (CNS) as very thin (0.1–0.4 µm), non-myelinated axons without synapse. These axons become grouped and ensheathed by Schwann cells forming some 20 fasciculi which are invested by pia and arachnoid mater, and pass through the orifices of the cribriform plate to enter the olfactory bulbs lying each side of the crista galli in the floor of the anterior cranial fossa. These axons synapse with dendrites of the large mitral cells of the olfactory glomeruli and each glomerulus receives axons from a wide area of the epithelium. There seems to be no functional grouping of axons. This arrangement allows a relatively small number of receptor cells to distinguish a large number of different odours. The axons of the mitral cells form the bulk of the olfactory tract but centrifugal axons of uncertain origin also pass to the olfactory bulb and undoubtedly modify activity in the olfactory glomeruli, perhaps having both inhibitory and facilitatory actions. The olfactory tracts pass posteriorly and slightly laterally crossing the floor of the anterior cranial fossa, the optic nerves and immediately above the optic chiasm. Just in front of the anterior perforated substance, each divides into medial, intermediate and lateral olfactory striae.

The termination of the medial striae is uncertain. Many fibres decussate to the opposite medial striae and these may become the centrifugal fibres of the opposite olfactory tract noted above, having facilitatory and inhibitory effects on the opposite olfactory bulb. The intermediate striae terminate in the olfactory tubercle but their further functional anatomy is unknown. The lateral olfactory striae synapse with neurons in the lateral anterior perforated substance, the lateral olfactory gyrus, the prepyriform cortex and the medial group of amygdaloid nuclei – the group of tissues that in humans represent the primary olfactory cortex. These are the only sensory pathways in humans that do not relay in the thalamus. The subsequent distribution via the limbic system then contributes to both pleasurable and unpleasant consequences of odour detection at conscious level and the appropriate

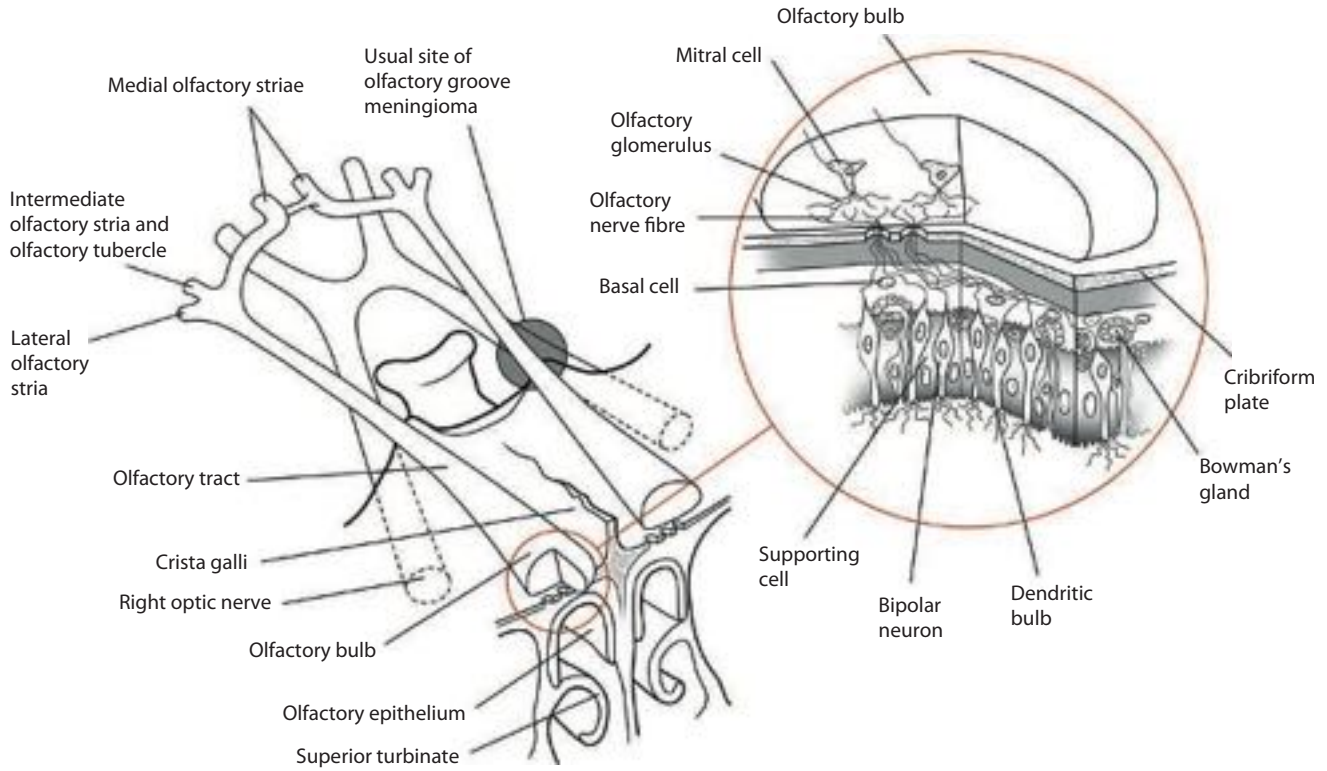


Figure 111.1 The olfactory pathways.

unconscious autonomic responses via the hypothalamus. This is related to activity in the secondary olfactory cortex located in the entorhinal complex, which includes the uncus and a tertiary olfactory cortex in the posterior orbitofrontal cortex. Descending pathways from these areas enter the pontine reticular formation in the brainstem and mediate reflex activity, such as salivation.[2]

There are also ascending projections from the midbrain raphé, the locus caeruleus and the midbrain tegmentum. These may well heighten olfaction in response to hunger and other emotional states, which emphasizes the role of olfaction in behavioural conditions, including sexual and maternal bonding, and in animals recognition of parent and offspring.[3]

PHYSIOLOGY

The receptor proteins lie in the olfactory cilia and it is likely that many different types of protein are involved. An odour must be volatile to enter the nasal cavity, actively sucked into the area of the olfactory epithelium by sniffing, which creates turbulent flow in the nasal passages, and lipid soluble to facilitate access to the fluid-bathed cilia.

Once stimulated, the resulting activity in the neuron is difficult to study. Attempts at single fibre analysis are technically almost impossible and such studies as are available demonstrate no similarities in evoked potentials from similar groups of substances or stimuli.

There is considerable evidence that some odours inhibit as well as excite and to this one must add an anatomical arrangement that allows not only local inhibition and excitation, but also crossed and possibly centrally mediated modulation by both lateral and negative feedback mechanisms. This permits humans to identify some 3000 different odours. The central pathways allow further discrimination and perhaps clarification of odour recognition. In contrast is the remarkable process of adaptation that allows continuous exposure to an unpleasant smell to diminish perception, so that the smell no longer registers. This phenomenon is interesting to consider in those patients who complain bitterly of a persistent unpleasant smell present 24 hours a day – a syndrome that commonly has a psychogenic basis, in striking contrast to patients with severe halitosis who are seemingly unaware of their problem. Further details on the physiology of the sense of smell are found in Volume 1, Chapters 89, Physiology of the nose and paranasal sinuses and 110, Abnormalities of smell.

APPLIED ANATOMY AND PHYSIOLOGY

Of obvious otolaryngological concern are simple mechanical factors interfering with access of the odour to the receptors, with simple airway obstruction, complicated by oedema or drying up of the mucosa as the most common causes of anosmia. Mechanical destruction or blockage of the nasal passages by pathology ranging from allergic rhinitis to complex vascular diseases, such as Wegener's granulomatosis, can occur. Simple polyps, nasal fractures and foreign bodies all have adverse effects on olfaction. Many drugs and generalized medical conditions that can damage or interfere with the function of a highly metabolically active tissue with a 30–50-day turnover rate, can also affect smell. These conditions include generalized metabolic disorders, such as renal failure and hepatic failure, and endocrine disorders, including diabetes, pregnancy and influenza.

Drugs affecting membrane moistness (antihistamines), cell turnover (antibiotics, antimetabolites) and cell function (anti-inflammatory agents, antithyroid drugs) may all affect both smell and taste adversely.[4]

Traumatic lesions of the olfactory fasciculi are usually caused by the shearing effect of brain movement when the head decelerates during a head injury. This complicates some 30% of serious head injuries particularly where immediate anteroposterior forces are applied to the head and a blow squarely on to the occiput is particularly likely to result in this complication. In such cases, little or no recovery can be anticipated. Severe injury of this type may actually tear the arachnoid cuffs and lead to cerebrospinal fluid (CSF) rhinorrhoea with a significant risk of subsequent meningitis.

There is circumstantial evidence that viral infections may gain access to the meninges via the same route in the absence of prior injury, *Herpes simplex encephalitis* being the most notable example. In this condition, the initial localization of the infection in the anterior temporal lobes adds support to this theory of aetiology, the virus presumably gaining access along the olfactory tract, possibly by axonal transport.[5] This is not the whole answer as in 25% of cases the virus isolated from the CSF is a different strain to that found in the oropharyngeal mucosa. Inside the skull, tumours of the olfactory groove, notably meningiomas, can cause unilateral anosmia, often unrecognized by the patient. Due to the local anatomy, progressive visual loss in the ipsilateral eye ensues – also often unrecognized by the patient. It is therefore very important to test the sense of smell in any patient with sudden loss of vision in one eye.

At central level, disorders of smell appreciation are not recognized, although behavioural, endocrinological and biochemical factors undoubtedly modify olfaction, as discussed above. Patients who complain of a continual bad smell are usually suffering from a depressive or psychotic illness. The most readily identifiable centrally based disorder of olfaction is found in uncinate epilepsy, in which an epileptic event originating in the medial temporal lobe is ushered in by the hallucination of an unpleasant smell (and occasionally taste). These olfactory hallucinations are characterized by being both unpleasant and of extremely short duration, usually only a matter of seconds, often insufficient to enable the patient to identify the odour as other than unpleasant – burning rubber or rotting rubbish being the most common descriptions volunteered.

Considerable degeneration of the olfactory glomeruli occurs with age, and olfaction is the first sensory modality to be significantly impaired by increasing age. This probably accounts for the decreasing appetite and loss of interest in food noted by the elderly with their definite tendency to over-season food.[6]

The optic nerve (II)

The orbit is entirely surrounded by structures of otolaryngological significance, only the lateral border being relatively spared from possible infection or invasive pathology other than that arising in the lacrimal gland. The frontal, ethmoid and maxillary sinuses and the lateral wall of the nose bound the orbit superiorly, medially and inferiorly, and are all prone to infection or malignant pathology.

The optic nerve enters the orbit through a tight bony canal, the optic foramen. The nerve is a direct extension of the brain and is invested with glial-derived tissue to the back of the globe, consisting of three membranes. The inner pial sheath invests the nerve and sends septae into the nerve itself, dividing the nerve into a bundle of fascicles. The intermediate arachnoid sheath is very delicate with a potential subarachnoid space inside and a subdural space outside. Both are covered by a thick extension of the dura, which merges with the sclera at the back of the globe. These membranes and enclosed spaces form a direct communication to the intracranial cavity and permit the direct transmission of raised intracranial pressure to the optic disc causing papilloedema, although the exact mechanism of the disc swelling remains uncertain, with venous compression almost certainly playing a major role.

The myelinated fibres of the optic nerve are derived from the rods and cones of the retina. As these cell processes form the most superficial layer of the retina, they are normally non-myelinated until they enter the optic disc. Occasionally, patches of persistent myelination of these fibres produce a characteristic white, fan-shaped lesion in the retina with an associated field defect, which remains unnoticed by the patient, in the same way that one is unaware of the normal blind spot. The most important papillomacular fibres conveying macular vision lie in the medial part of the nerve, only assuming their central position in the nerve as it reaches the optic foramen. In spite of this anatomy, extrinsic compression of the nerve in the orbit and the optic canal preferentially affects these papillomacular fibres, producing a central scotoma rather than a defect spreading in from the periphery, as might be anticipated on purely anatomical considerations (**Figure 111.2**).

There are 1.2 million nerve fibres in each optic nerve, just over half of which decussate in the optic chiasm. The fibres that cross are those derived from the nasal retina, conveying the temporal half field, entering the contralateral optic tract. The temporal half fibres (conveying the nasal field) pass straight into the ipsilateral optic tract.

Lesions within the orbit tend to produce mechanical displacement of the globe with consequent proptosis and diplopia. The optic nerve itself seems remarkably resistant to damage by pressure and displacement in the orbit, although an infective process may be more damaging by vascular mechanisms particularly venous thrombosis.[7, 8]

Lesions in the optic canal readily cause visual disturbance and a central scotoma is often the first evidence of a lesion at this site. This may be followed by extraocular nerve palsies and very much later, proptosis. Meningiomas or neurofibromas are the most frequent tumours arising in the posterior orbit. Neoplastic infiltration from the paranasal sinuses and nasopharynx can occur and metastatic spread from remote sites, such as the prostate in adult males or suprarenal gland in children, are well recognized. In general, the tempo of development of the signs and the presence or absence of pain will indicate the likely diagnosis.[9] The slow painless onset of symptoms usually indicates a benign lesion, while rapidly evolving symptoms, accompanied by pain, indicate a metabolic, neoplastic or infective process in the area.

Involvement of the optic nerve immediately behind the optic foramen can produce bilateral visual problems.

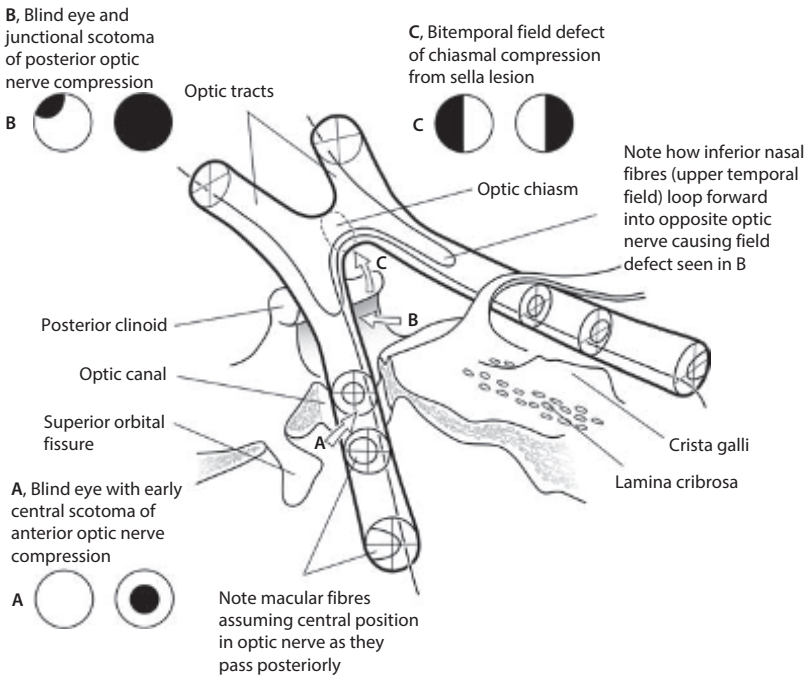


Figure 111.2 The visual pathways.

The inferior nasal fibres of the opposite optic nerve not only cross in the chiasm but also sweep forwards into the optic nerve before turning sharply to head posteriorly into the chiasm and optic tract. They can therefore be damaged by a lesion just anterior to the chiasm. A meningioma of the tuberculum sellae is the most likely lesion to be found at this site. This can produce a blind eye, an upper temporal field defect in the contralateral eye (called a junctional scotoma) and, if large, may cause loss of smell on the same side as the blind eye and eventually papilloedema in the opposite eye, the swelling in the blind eye being prevented by the compressing lesion. This constitutes the well known, but extremely rare, Foster–Kennedy syndrome.

The optic chiasm itself lies more posteriorly than is generally appreciated. It lies above and behind the pituitary gland, not on the sulcus chiasmaticus in front of the pituitary fossa of the skull. Pathological processes in the pituitary region include not only pituitary tumours but neoplasia arising in the ethmoid or sphenoid sinus, mucocoele of the sphenoid sinus and aneurysms arising from the circle of Willis or the great vessels themselves. The importance of excluding vascular anomalies or aneurysms before embarking on the transnasal approach to the pituitary fossa cannot be overemphasized. Lesions extending upwards from the pituitary, damage the underside of the chiasm anteriorly. This produces a bitemporal hemianopia, which starts in and spreads down from the upper temporal field (the lower fibres derived from lower retinal cells – therefore upper field). This field defect is rarely noticed by the patient at this early stage or indeed occasionally even when complete. When testing the temporal visual fields, particular attention should be paid to the upper temporal field to avoid missing a junctional scotoma (see 'Group 1' above and **Figure 111.2**) or the earliest signs of a developing bitemporal hemianopia. In contrast, lesions damaging the chiasm from above and behind tend to affect the lower fields first. These pathologies include craniopharyngiomas, hypothalamic tumours and a dilated third ventricle. Field defects in this area are much more readily identified by the patient as they intrude into all activities, especially reading and walking downstairs.

Because there are many situations in which visual acuity and the visual fields are of help in otolaryngological diagnosis, it is worth describing simple field examination at the bedside. Carefully examined fields, using a red and white hatpin, should be as accurate as screen testing and should only take a few minutes. The examiner should sit in front of the patient (in the traditional otolaryngological position) about 1 m from the patient. The patient should cover one eye. A white 5 mm hatpin, preferably mounted on the handle of a tendon hammer, should be brought into the patient's field of vision on four arcs, upper and lower temporal and upper and lower nasal, respectively. If all are seen at the periphery, no field cut is likely. The pin should then be brought across from the temporal field on the horizontal meridian, the patient keeping the examiner's pupil in view. The blind spot should be detected readily and can usually be compared with that of the examiner, both parties losing the object in the same area. Taking the pin across into the nasal field will detect any small scotoma as the pin will disappear again. The size and shape of the detected scotoma can then be explored and even a small scotoma can be easily confirmed by this technique. At a more sophisticated level, the very earliest evidence of a field defect can be found with the red pin. A 5 mm red pin is used. The visual field is smaller than with a white pin and for reasons that are not clear, the field defect accompanying pregeniculate optic pathway lesions affects red vision first. It is possible to detect a considerable loss of the red field before any intrusion into the white field is apparent. In the early stages, the red object may appear to change to brown or black, but care has to be taken not to confuse the normal loss of brightness of a red object as it passes into the temporal half field, as indicating an early field defect. Ultimately, of course, the red pin will not be detected at all in the affected area.

DIFFERENTIAL DIAGNOSIS OF THE PAINFUL RED EYE

Otolaryngologists are often consulted in cases where blurred vision and diplopia occur in the setting of an inflamed, proptosed eye and may even be the first opinion sought. It is therefore appropriate to consider this diagnostic situation in more detail.[10] Diagnosis falls into four main groups of disorders: inflammatory, vascular, infective and neoplastic.

Inflammatory causes

Acute thyroid exophthalmos

The eye is often injected with chemosis. Lid lag is especially noticeable on downward gaze. There may be diplopia simply due to globe displacement, but actual paralysis of the superior and lateral rectus muscles is a specific feature. In spite of its metabolic basis, the condition is usually unilateral. Vision may be threatened and acute high-dose steroids may be of value in treatment. A CT or MRI scan will usually show marked swelling of the extraocular muscles.

Pseudotumour of the orbit This is an immunologically based inflammatory disorder affecting all tissues in the orbit. It can complicate sarcoid, systemic lupus erythematosus, tuberculosis, Wegener's granulomatosis, polyarteritis nodosa or Tolosa–Hunt syndrome. Proptosis, pain and diplopia associated with a very high sedimentation rate might at first sight all seem to indicate infection. As steroids are indicated, urgent exclusion of infective disease in the paranasal sinuses is vital. CT or MRI scans show normal extraocular muscles in the midst of oedematous orbital contents and will exclude coexistent sinus infection. The condition occurs in two main age groups – between 10 and 30 years and the over 60s.

Vascular causes

Acute caroticocavernous fistula This condition usually follows known trauma with a skull base fracture. Occasionally, an aneurysmal dilatation of the carotid may

rupture into the cavernous sinus producing acute pulsating exophthalmus with marked arterial pulsation visible in the fundal veins. Carotid ligation or embolization is the procedure of choice.

Cavernous haemangioma This condition causes a gradually increasing degree of exophthalmus with proptosis aggravated by bending or straining. There is usually no diplopia or field defect and little pain. The acute proptosis on bending is both dramatic and diagnostic.

Infective causes

Local infections can readily spread into the orbit. Small boils on the nose, eyelids or face in the preantibiotic era had lethal potential and even now are extremely dangerous in diabetics and patients with impaired immunity. Paranasal sinus infection, especially of the ethmoids, can easily extend directly into the orbit. Frontal sinusitis may cause oedema of the eyelid and ptosis. In the diabetic patient, fungal infections, particularly mucormycosis, are a specific problem. The first vesicles of the viral infection *Herpes zoster ophthalmicus* usually erupt in the eyebrow after several days of severe pain and an acute red eye with eyelid oedema is often mistaken for bacterial infection until the vesicles appear.

Neoplastic causes

Any primary or secondary neoplasm may involve the orbit, by direct extension or from remote sites. Chemosis and injection may be minimal. In the elderly, pseudotumour of the orbit can be a presenting symptom of lymphoma and, as always, the importance of a general physical examination must be emphasized, in spite of such a local presentation.

The benign primary orbital tumours most often seen include lipomas, angiomas and haemangiomas. Less frequently, fibromas, myxomas and leiomyomas may be encountered.

Primary malignant orbital tumours are usually rhabdomyosarcomas that are locally invasive and usually occur in childhood. Rarely, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma and haemangioendotheliomas may occur. Lacrimal gland tumours of variable malignancy occur and tend to be locally invasive through the roof of the orbit into the intracranial cavity.

Metastatic tumours in the orbit are secondary to carcinoma of the breast in 50% of cases. Tumours originating in the lung and kidney account for the rest. Malignant melanoma has been reported but is hard to distinguish from a primary melanoma of the ciliary body or retina. In children with neuroblastoma, orbital metastases occur in 20–50% of cases.[11]

PUPILLARY ABNORMALITIES

As the main determinant of pupil size is the incident light, it is appropriate to discuss the major pupillary abnormalities at this stage.

In a blind eye, assuming that the cause of the blindness has not simultaneously damaged the iris mechanism, the pupil will dilate or constrict in proportion to the light falling on the unaffected eye. The direct light reaction will be absent, but the consensual light reflex from the opposite eye will be intact. No consensual reflex in the normal eye will be seen when the affected eye is illuminated. This is a useful check for suspected non-organic visual loss in one eye.

In acute retrobulbar neuritis, which presents as sudden impaired central vision in one eye, the pupil reaction may be sluggish and the pupil may dilate after initial constriction in spite of a constant light source being maintained (pupillary escape phenomenon). In a patient with eye pain, aggravated by movement with blurred vision, this Marcus–Gunn pupil reaction is strongly indicative of demyelinating disease. The postulated mechanism is a decrease in the number of fibres conveying light sensation.

In IIIrd nerve lesions, damage to the efferent pupilloconstrictor fibres produces a fixed dilated pupil even though the patient perceives light normally. Incomplete lesions may merely cause a slightly dilated pupil with a sluggish reaction – an important stage in the evolution of a IIIrd nerve palsy in a patient who is deteriorating following a head injury. A useful clue in a conscious patient developing a IIIrd nerve lesion is the almost invariable accompanying ptosis. This may be followed by diplopia due to paralysis of the superior rectus muscle (see 'The oculomotor nerve (III)' below). Argyll Robertson pupils due to meningovascular syphilis have become a great rarity. This is a small pupil, usually irregular, that does not react to light but reacts normally to accommodation.[12]

A sympathetic nerve lesion (Horner syndrome) will be detected by only the most alert clinician. Due to loss of the less important pupillodilator fibres, the pupil is slightly smaller with a normal light reaction because the light reflex pathway mechanisms are unaffected. A slight and variable degree of ptosis will occur, which rarely droops lower than the edge of the pupil. As the cervical sympathetic pathway courses in and out of otolaryngological territory, a full understanding of the syndrome is essential to the otolaryngologist (see also 'Group 3' below, and **Figure 111.16** under 'The cervical sympathetic' below).[13]

A Holmes–Adie (myotonic) pupil may present as a painful eye as the affected pupil fails to constrict in bright light. The affected pupil may be larger or smaller than the other, depending on the incident light, which produces either a slower constriction or slower dilatation than in the unaffected eye. The light reaction is a very slow, with definite constriction followed by a slow dilatation. This slow myotonic reaction is often best demonstrated by maintained forced convergence for about one minute, which is a much stronger stimulus to pupil constriction. Alternatively, if the patient sits in a dark room, the pupil will become very large, but if they have just come into the clinic from a sunlit room, at first the affected pupil may be smaller than the normal pupil.[14] Vision will be blurred when the pupil is large as close focusing is impossible.

The nerve supply to the extraocular muscles

The three nerves supplying the extraocular muscles and controlling eye movements have complex central control mechanisms and peripheral courses that render them vulnerable both individually and as a group, to a wide range of surgical and medical disorders. They are of special interest to otolaryngologists because of their involvement in local neoplastic disease and in infective processes originating in the paranasal sinuses, nose and nasopharynx.

The oculomotor nerve (III)

The IIIrd nerve exits from the brainstem in the interpeduncular fossa and runs forwards, laterally and slightly downwards in the subarachnoid space towards the roof of the cavernous sinus (**Figures 111.3**, **111.4** and **111.5(a)**). In its distal subarachnoid course, it runs parallel to the posterior communicating artery, hence its unique vulnerability to damage by aneurysms, which commonly arise at either end of this short vessel. It enters the roof and then the lateral wall of the cavernous sinus in between the two layers of dura, dividing into two branches before it enters the superior orbital fissure. In the wall of the sinus it picks up sympathetic fibres from the sympathetic plexus on the carotid artery and additional parasympathetic fibres from the ophthalmic division of the Vth nerve.

The superior ramus supplies the levator palpebrae superioris and the superior rectus muscle. The inferior ramus supplies the medial and inferior recti, the inferior oblique and carries the sympathetic and parasympathetic elements to the ciliary ganglion via the branch to the inferior oblique.

The anatomy of the pupillary fibres within the nerve is of great significance. The fibres at first lie dorsolaterally, then medially and finally inferiorly, but always in the periphery of the nerve. Their blood supply is derived from the pial plexus on the surface of the nerve, while the core of the nerve is supplied by a vasa nervorum. If this latter vessel is occluded by vascular disease (diabetes, arteriosclerosis, arteritis), the pupillary fibres lying peripherally are usually spared. Conversely, if the nerve is damaged by an external compressive surgical lesion (aneurysm, tumour, abscess), the peripheral pupillary fibres are those most easily affected. In a patient who has a IIIrd nerve lesion, the involvement or otherwise of the pupil is a major diagnostic pointer. Furthermore, pain tends to be a feature of surgical lesions, so the painful onset of a IIIrd nerve lesion with pupil involvement is almost certain to indicate a compressive lesion. The absence of pain and a spared pupil is almost certain to indicate a medical cause.[15] The major exception to these generalizations is that a lesion due to diabetes can be both painful and involve the pupil, mimicking a surgical lesion. A serum glucose estimation can be a very inexpensive way of resolving this dilemma.

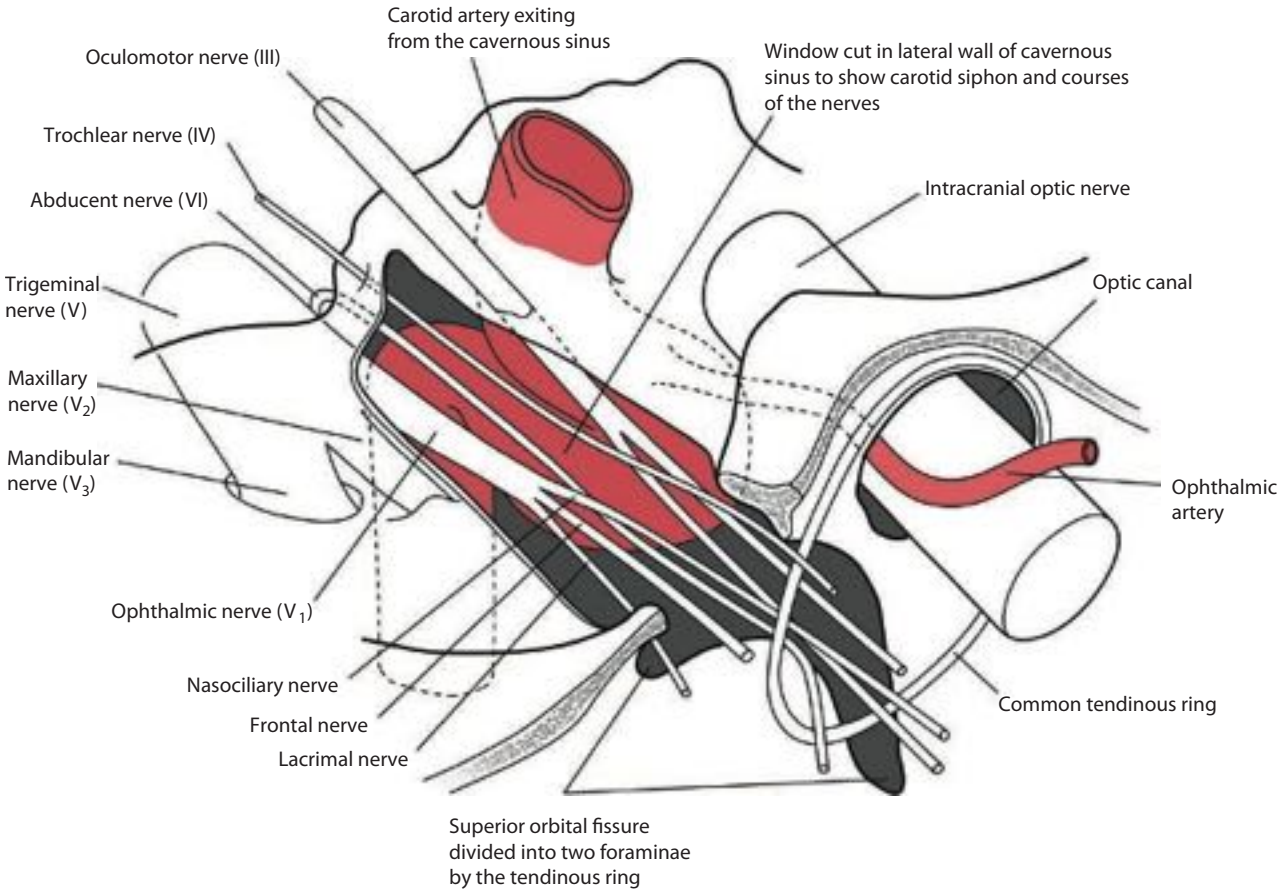


Figure 111.3 The cavernous sinus and orbital foramina.

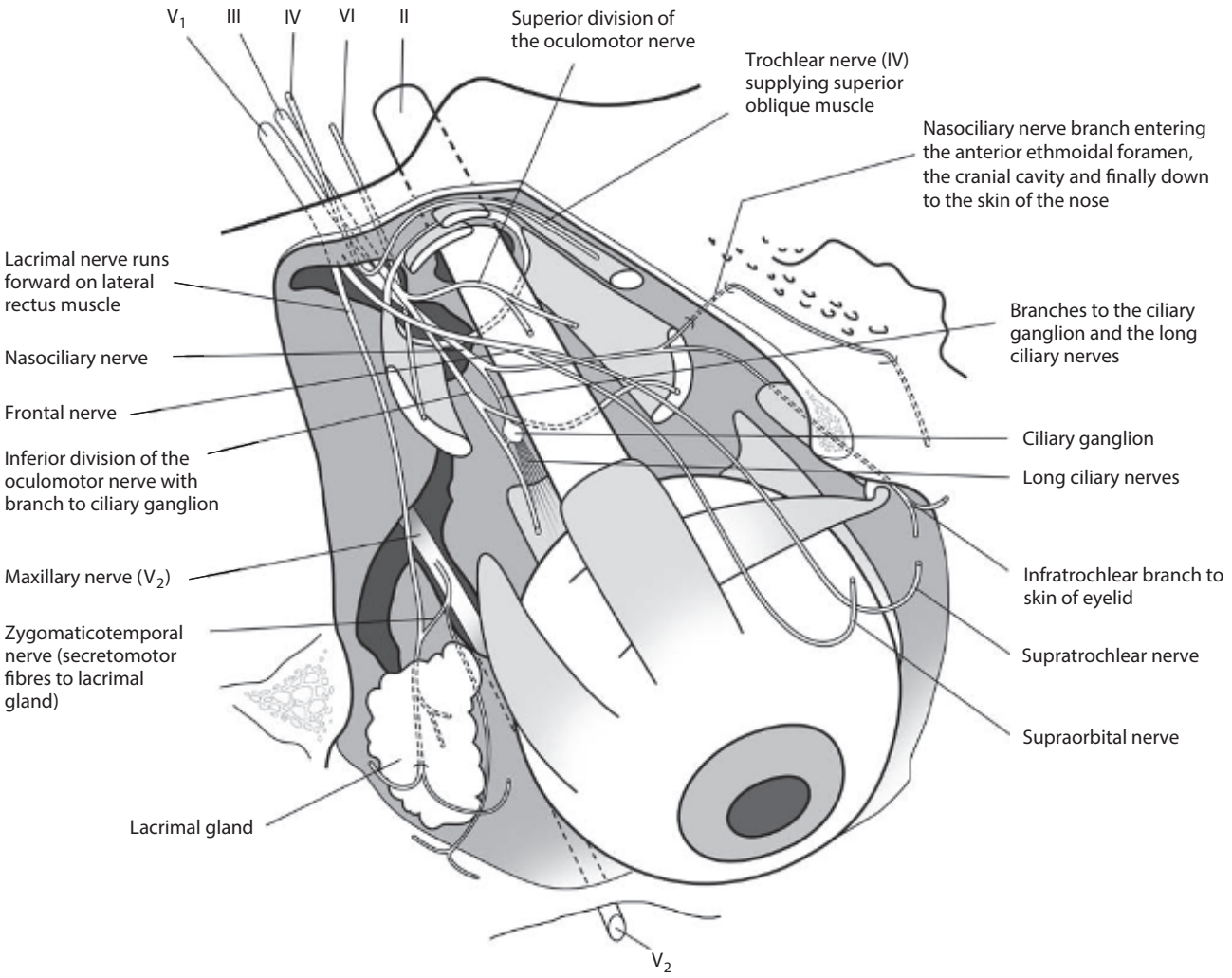


Figure 111.4 The orbital contents (right orbit from above and lateral).

CENTRAL ANATOMY

The detailed anatomical features of the oculomotor nucleus are beyond the scope of the present text. Briefly, the nucleus is shaped like an inverted V, straddling the midline (see **Figure 111.5(a)**). The lateral nuclear columns supply the eyelid and the four extraocular muscles, the superior, medial and inferior rectus and the inferior oblique. The midline nuclei have mainly parasympathetic function especially the upper midline Edinger–Westphal nucleus, which is the main central control mechanism for pupil size. The fascicles of the IIIrd nerve fan out, course towards the anterior midbrain traversing the red nucleus and the substantia nigra, converging to form the main nerve trunk, which emerges just lateral to the midline in the interpeduncular fossa.

The trochlear nerve (IV)

The IVth cranial nerve is unique in several ways. It arises in the dorsal aspect of the brainstem at the level of the inferior colliculus. It then decussates within the superior medullary velum so that the right nucleus supplies the left superior oblique muscle and vice versa (see **Figures 111.4** and **111.5(b)**). It also has the longest intracranial course and is very slender, properties that possibly protect it from damage by extrinsic pressure around the brainstem and in the subarachnoid space. It enters the wall of the cavernous sinus beneath the IIIrd nerve, but crosses it to reach a higher position as it enters the superior orbital fissure to supply the superior oblique muscle. The nerve is rarely damaged in isolation in cavernous sinus lesions, the IIIrd and VIth nerves being much more vulnerable. A vascular lesion of the nerve due to diabetes is the most common cause. Of particular importance to the otolaryngologist is the small fibrocartilaginous loop attached to the trochlear fossa in the upper medial orbit through which the muscle tendon loops. Accidental or surgical trauma in this region may easily damage the tendon interfering with the action of the superior oblique muscle, mimicking a IVth nerve palsy.[16]

The abducent nerve (VI)

The VIth nerve exits from the brainstem anteriorly at the pontomedullary junction (see **Figures 111.3**, **111.4** and **111.5(c)**).

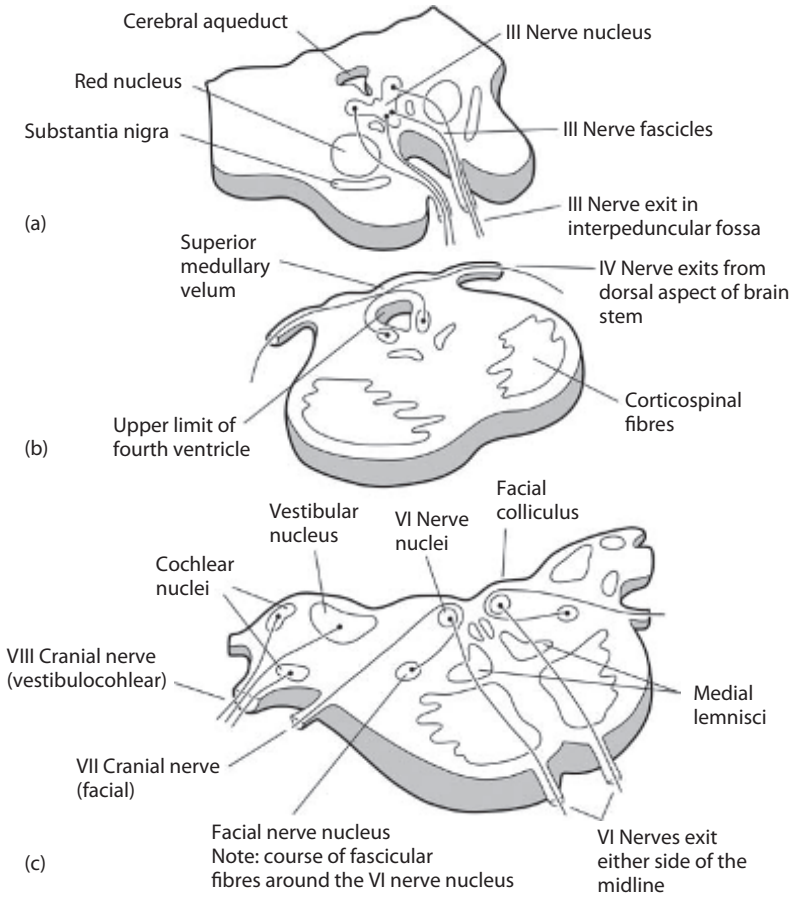


Figure 111.5 Brainstem connections of the extraocular nerves.

It is the most medial of the three nerves which exit from this groove, and ascends on the front of the pons before it angles forwards across the tip of the petrous bone to enter the bottom of the cavernous sinus in which it lies free, in close relationship to the intracavernous portion of the carotid artery. This long subarachnoid and meningeal course adjacent to the meninges renders this nerve particularly liable to damage in acute and chronic meningitis or any other meningeal process. This notably includes the remote or direct spread of malignant disease. The angulated entry into the cavernous sinus renders it vulnerable to stretch when the brainstem is pushed downwards by raised supratentorial pressure, causing the classical false localizing VIth nerve palsy, which may ultimately become bilateral if unrecognized. The nerve may become involved in inflammation of the petrous bone, secondary to otitis media. This may be combined with severe pain in the Vth nerve territory and loss of hearing, which is Gradenigo's syndrome. Inflammatory disease in the cavernous sinus and aneurysmal dilatation of the carotid siphon within the cavernous sinus are particularly likely to involve the VIth nerve, the IIIrd and IVth being involved later by the same process. Nerve trunk infarction secondary to diabetes, arteritis and arteriosclerosis occurs exactly as for the IIIrd and IVth nerves discussed above. Intracranially, both cholesteatomas and vestibular schwannoma could involve the nerve, but such involvement is surprisingly rare. As it enters the orbit it passes laterally to reach its single supplied muscle, the lateral rectus (see **Figure 111.3**). At this point it is particularly liable to damage by carcinoma infiltrating the orbit through the inferior orbital fissure from the nasopharynx.[17]

CENTRAL ANATOMY

The nucleus of the VIth nerve lies in the floor of the IVth ventricle just lateral to the midline (see **Figure 111.5(c)**). The fibres of the facial nerve sweep round it. Although derived from the same nuclear column as the IIIrd and IVth nerve nuclei, it migrates downwards during the massive developmental enlargement of the pons, but remains intimately linked to the other nuclei by the medial longitudinal bundle (see 'Central mechanisms of nerves III, IV and VI' below). The fascicles of the VIth nerve have to traverse the whole depth of the pons to reach their point of emergence at the pontomedullary junction. In its fascicular course, it lies in close relationship to the ascending medial lemniscus and the descending corticospinal pathways.

CENTRAL MECHANISMS OF NERVES III, IV AND VI

The central control mechanisms for eye movement comprise a complex group of pathways that adjust eye position to movement and posture, mainly under the influence of vestibular and extrapyramidal pathways (**Figure 111.6**).

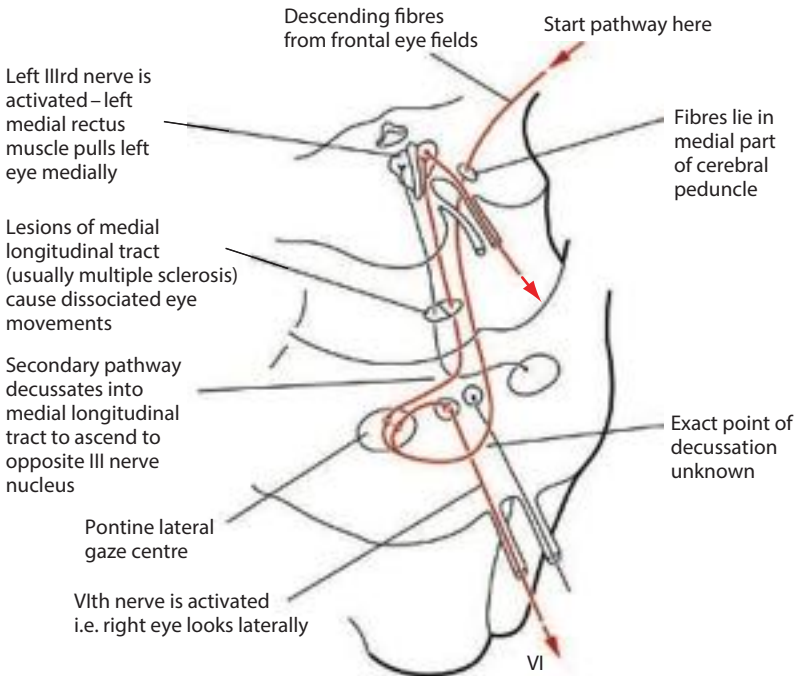


Figure 111.6 The internuclear pathways. Pathway shown moves both eyes to the right side.

There are two forms of voluntarily controlled eye movement:

1. Visual pursuit, where a specific target is fixed and followed, using parietal gaze centres closely integrated with the adjacent visual cortex
2. The ability to select a new target and relocate vision to suit, via frontal gaze centres utilizing direct voluntary pyramidal motor pathway mechanisms.

Damage in either of these areas will cause a conjugate gaze palsy, but because the range of movement of both eyes is identically affected, there is no diplopia. At brainstem level, the need to integrate eye movements controlled by three different cranial nerve nuclei widely spaced in the brainstem requires complex and extremely rapidly conducting internuclear pathways. The most critical of these is the medial longitudinal fasciculus. Damage in this pathway causes internuclear ophthalmoplegias, with disconjugate gaze palsies. These will always cause diplopia as the eyes then move independently.

The cortical influences have final relays in the brainstem in the pons bilaterally, the lateral gaze centres. There are also four gaze centres in the midbrain, two on each side, one to look up and one to look down. Eye movements occur in saccades, a series of little jerk movements without over- or undershoot, until the new position is reached. This is achieved by rapid bursts at 1000 cycles per second by cells in the gaze centres. These bursts are initiated by voluntary information from the frontal eye fields through the anterior limb of the internal capsule. Automatic movements as required in reading are controlled by visual information carried through the optic tract without projection to the visual cortex. Feedback from stretch receptors in the ocular muscles is also of great importance in this type of movement. Tracking movements are integrated in the superior colliculi, once the object to be followed has been located, using stereooptic control.

Vergence mechanisms require the voluntary frontal eye fields to work in conjunction with the parietal cortex simultaneously inhibiting those brainstem mechanisms that normally prevent convergence and divergence. Only animals with binocular stereoscopic vision have the need to converge to focus close objects.

PARIETAL LOBE LESIONS

Poor object following or pursuit gaze problems are often difficult to demonstrate clinically as lesions in these areas also tend to cause a hemianopic field defect, so that the following movement ceases as the object moves into the blind half-field. If, however, the examiner is careful to keep the object in the patient's retained field of vision, a full range of pursuit movement should be achieved if there is no gaze palsy. A tendency to ignore objects on one side in the absence of a hemianopia (an attention field defect) may be related to the inability of the eye to scan peripherally due to lack of visual input.

FRONTAL LOBE LESIONS

An active irritative lesion, such as a tumour or abscess in the frontal pole, will drive the eyes away from the lesion. A right frontal tumour may cause focal epileptic fits preceded by movement of the head and eyes to the left hand side before the patient loses consciousness. An inactive destructive lesion, such as surgical extirpation or a cerebrovascular accident, will permit the eyes to gaze preferentially towards the side of the lesion, due to the unopposed push from the intact side. This phenomenon is most readily seen in a drowsy, anaesthetized or unconscious patient.

MIDBRAIN LESIONS

Midbrain visual mechanisms are mainly concerned with up and down gaze. The classical lesion causing Parinaud's syndrome is a pineal tumour damaging the superior colliculus and the region of the posterior commissure. A lesion here blocks the light reflex relays, producing fixed dilated pupils, impairs upward gaze and causes loss of convergence.

Conversely, lesions of the inferior colliculus will impair downward gaze only. In some instances, the ineffective movements of the extraocular muscles attempting to produce up or down gaze may pull the eyeball in and out of the socket, resulting in the very rare phenomenon known as retractory nystagmus.

Lesions affecting the thalamic nuclei, either structural or pharmacological, may cause fixed deviations of up or down gaze. In patients with postencephalitic Parkinson's disease, episodes known as an oculogyric crisis were a classic feature. This can still be seen in some patients provoked by phenothiazine hypersensitivity, usually young females. Thalamic lesions may cause complex eye movement disorders with divergence with one eye up and one eye down (skew deviation) and see-saw nystagmus on attempted lateral eye movement. A midline haemorrhage between the IIIrd nerve nuclei or acute multiple sclerosis in the same area can produce a divergent squint with both eyes at the extremes of lateral gaze with retained up and down gaze limited only by the mechanical factors operating at this extreme position.

DISORDERS AFFECTING THE MIDBRAIN

Anteriorly, aneurysms of the upper basilar artery or a tortuous basilar artery (basilar ectasia) may damage and distort the emergent IIIrd nerves. Posteriorly, pineal tumours or distortion and dilatation of the posterior end of the IIIrd ventricle due to aqueduct stenosis may cause Parinaud's syndrome. Infiltration of the superior medullary velum by direct spread of a medulloblastoma may cause bilateral IVth nerve lesions and impaired down gaze. Intrinsic lesions due to vascular occlusion, haemorrhage, demyelinating disease and tumour, may all cause an anterior internuclear ophthalmoplegia (i.e. a divergent squint with loss of convergence but preserved up and down gaze).

There are three named vascular syndromes of the midbrain due to combinations of IIIrd nerve lesions and local pathway damage:

1. **Nothnagel's syndrome**: a IIIrd nerve lesion with ipsilateral ataxia due to infarction of the superior cerebellar peduncle
2. **Benedikt's syndrome**: a IIIrd nerve lesion with contralateral cerebellar movement disorder due to a lesion of the red nucleus
3. **Weber's syndrome**: a IIIrd nerve lesion with contralateral hemiparesis due to a lesion of the basis pedunculi.

These syndromes have become extremely rare with the demise of meningovascular syphilis, but are still occasionally encountered in patients with small vessel disease (diabetes, cranial arteritis, lupus erythematosus, polyarteritis nodosa, polycythaemia rubra vera, etc.). Unfortunately, the resurgence of sexually transmitted disease means that these classical syndromes should not yet be consigned to history.

PONTINE LESIONS

The pontine lateral gaze centres are often damaged by vascular lesions and demyelinating disease. This results in loss of gaze to the same side as the lesion, as the descending pathways have already decussated. In a drowsy or unconscious patient, this will result in the eyes deviating towards the unaffected side.

DISORDERS AFFECTING THE PONS

Anteriorly, the VIth nerves are often involved in bacterial, fungal or malignant meningitis due to their long meningeal course. Pontine tumours may involve the nerve nuclei or fascicular fibres and the posterior internuclear pathways. These tumours usually occur in children or adults with neurofibromatosis. Tumours blocking or infiltrating the IVth ventricle cause headache and vomiting due to CSF pathway block and VIth nerve palsies, due to stretching of the nerves by raised intracranial pressure. If the VIth nerve palsy is due to direct tumour infiltration, the VIIth nerve should also be involved, as the VIIth nerve fibres encircle the nucleus. These tumours include ependymoma, medulloblastoma, cerebellar astrocytoma or haemangioblastoma. Multiple sclerosis, haemorrhage and infarction, metabolic disorders (vitamin B deficiency), drug intoxication, fluid balance disturbance, viral infection and *Listeria monocytogenes* infection of the brainstem may all cause conjugate gaze palsies if the damage is in the lateral pons or an internuclear ophthalmoplegia with nystagmus, if the lesion is in the central pons. Vascular occlusive lesions cause strictly unilateral internuclear ophthalmoplegia as the lesion extends only to the midline. There are numerous named vascular syndromes of the pons due to a variety of combinations of damage to the nuclei of nerves VI and VII and their fascicles and the sensory, motor and cerebellar pathways. There is no special advantage in learning these by heart, but the named syndromes include those of Millard–Gubler, Foville, Grenet, Raymond-Céstan, Marie-Foix and Gasperini.[18] As a cautionary note, any hint of variability in diplopia should always raise the possibility of ocular myasthenia gravis. If combined with variable dysarthria or intermittent swallowing difficulty, a brainstem lesion may be incorrectly suspected. This is a very difficult diagnostic trap into which even experienced neurologists may fall.

INTERNUCLEAR LESIONS

Internuclear lesions are typically caused by multiple sclerosis (bilateral) or vascular disease (strictly unilateral unless haemorrhagic) (see **Figure 111.6**). In these instances, the lateral gaze centre is intact and abducts the ipsilateral eye normally. It is the relay to the opposite IIIrd nerve nucleus

that is blocked and the eye that should adduct in unison fails to move beyond the midline. If the lesion is bilateral, neither eye adducts, while the abducting eye moves normally and the mobile eye shows marked nystagmus at full abduction. This syndrome is almost diagnostic of multiple sclerosis. The integrity of the upper brainstem in such cases can be readily demonstrated by intact vertical gaze and convergence.

NYSTAGMUS

Nystagmus is covered in detail in Chapter 49, Physiology of equilibrium; and Chapter 62, Evaluation of balance. From a simplistic neurological point of view, it is a less valuable physical sign than is often thought.

The distinction into the different types (jerk, pendular, rotatory, etc.) is often less easy to make than is suggested in most descriptions. Ultimately, one is seeing the effect of a breakdown in the vestibular mechanisms as they affect the smoothness and stability of eye movements. Weak support from vestibular mechanisms will lead to poor maintenance of gaze (slow phase) and a quick restorative movement (the jerk phase), which is the feature used to define the direction of nystagmus. This is maximal when looking away from the side of a vestibular lesion, be it in the end organ, VIIIth nerve or vestibular nuclear connections.

The controlling influence over vertical eye movements also becomes apparent in the phenomenon of vertical nystagmus, which occurs with structural or metabolic lesions of the brainstem. It is important to note that vertical nystagmus means vertical displacement of the eyes, not side-to-side nystagmus when attempting upward or downward gaze. As defined, vertical nystagmus always indicates brainstem dysfunction.

Another feature of brainstem disease is jelly nystagmus, which is probably due to failure of inhibitory 'pause' neurons, which normally stop the 'burst' neurons from producing visible little saccades. In this condition, the eyes wobble with no clear-cut fast or slow component. Congenital nystagmus produces a similar type of nystagmus – the diagnostic feature being that the patient is quite unaware of it in spite of very dramatic wide amplitude nystagmus.

Cerebellar lesions, especially those affecting the flocculonodular lobes, result in nystagmus due to the loss of the stabilizing effect of input from head posture receptors. In general, the fast and therefore most readily observed phase of cerebellar nystagmus is towards the side of a cerebellar lesion.

GROUP 2

The second major grouping of cranial nerves comprises those lying in the cerebellopontine angle. The medial extent of the angle is defined by the VIth nerve, the upper extent by the Vth nerve and the lower extent by the IXth nerve. The VIIth and VIIIth nerves pass in close proximity across the subarachnoid space to enter the internal auditory canal at the start of their long intraosseous courses.

The trigeminal nerve (V)

The trigeminal nerve is the largest cranial nerve and arises from the middle of the lateral side of the pons and passes forwards and laterally across the subarachnoid space. Its large ganglion lies over the tip of the petrous bone where the nerve divides into its three divisions.

The opthalmic nerve (V_1)

The first division of the Vth nerve lies below the VIth nerve in the lateral wall of the cavernous sinus (see **Figures 111.3** and **111.4**) and is prone to damage by the same pathologies that cause extraocular nerve palsies (see above). Due to its extensive sensory distribution, severe pain in the eye, forehead, nose and scalp, extending back as far as the vertex, may result from such damage. The nerve divides into three branches as it enters the superior orbital fissure:

1. The lacrimal nerve runs along the lateral rectus muscle to supply the lacrimal gland. It also supplies the skin over the lateral eyelid and brow. It picks up secretomotor fibres from the zygomaticotemporal nerve, which it conveys to the lacrimal gland. In the skin, it receives proprioceptive filaments from the facial nerve.
2. The frontal nerve divides into two, the supratrochlear and supraorbital nerves, which supply the skin of the forehead and scalp to the vertex. They are prone to damage by minor injuries over the brow and a causalgic syndrome may follow local trauma.
3. The nasociliary nerve has important autonomic and cutaneous functions:
   a. The main trunk traverses the orbit and enters the anterior ethmoidal foramen into the intracranial cavity, runs forwards across the cribriform plate and exits the skull through a slit in the crista galli to enter the nose. It supplies the mucosa of the nasal cavity and emerges at the lower end of the nasal bone to supply the skin over the tip of the nose, alar and vestibule.
   b. In the orbit, the nasociliary nerve gives off branches to the ciliary ganglion and two or three long ciliary nerves which carry the pupillodilator sympathetic fibres and convey sensation from the cornea. This is of cardinal importance for the protection of the very delicate cornea.
   c. The infratrochlear branch is given off just behind the anterior ethmoidal foramen and lies on the medial wall of the orbit and supplies the skin of the upper medial eyelid and upper side of the nose.

THE CORNEAL REFLEX

It is essential that otolaryngologists know how to elicit this reflex correctly. The afferent limb of the reflex is via the nasociliary nerve, as above, and the efferent limb is via the facial nerve. A pointed wisp of cotton wool should be used. The examiner should ask the patient to look upwards, then, resting the hand on the patient's cheek, the wisp should be applied to the lower cornea but taking

care not to bring it into vision or a blink reflex will result. The patient will flinch, the eyeball will roll up and the eye will attempt to close. Even if the VIIth nerve is paralyzed, the eyeball will roll up and the discomfort will be felt. The opposite eyelid will also close as this is a consensual reflex. Absence of the corneal reflex is often the first clinical evidence of Vth nerve damage and should be tested obsessionally in any patient presenting with symptoms of vertigo, deafness or facial pain.

The maxillary nerve (V_2)

The middle branch of the Vth nerve ganglion lies in the extreme lower lateral wall of the cavernous sinus and exits via the foramen rotundum, passes through the pterygopalatine fossa and enters the floor of the orbit via the inferior orbital fissure (**Figure 111.7**). At first, it lies in a groove in the orbital floor and then enters the short canal and exits on to the face via the infraorbital foramen. It supplies the skin of the cheek, midlateral nose and lateral part of the alar, lower eyelid and the mucous membrane of the cheek and upper lip. In its course, it gives off the following branches:

1. Meningeal branches to the floor of the middle cranial fossa
2. Two branches to the sphenopalatine ganglion, conveying the secretomotor fibres destined for the lacrimal gland
3. The zygomatic nerve, which lies on the floor of the orbit, dividing into the zygomaticotemporal nerve (secretomotor to the lacrimal gland and carrying cutaneous sensation from the temporal area) and the zygomaticofacial nerve which, after penetrating the zygomatic bone, carries cutaneous sensation from the prominence of the cheek
4. The three alveolar nerves convey sensation from the teeth, gums and adjacent palate via the superior

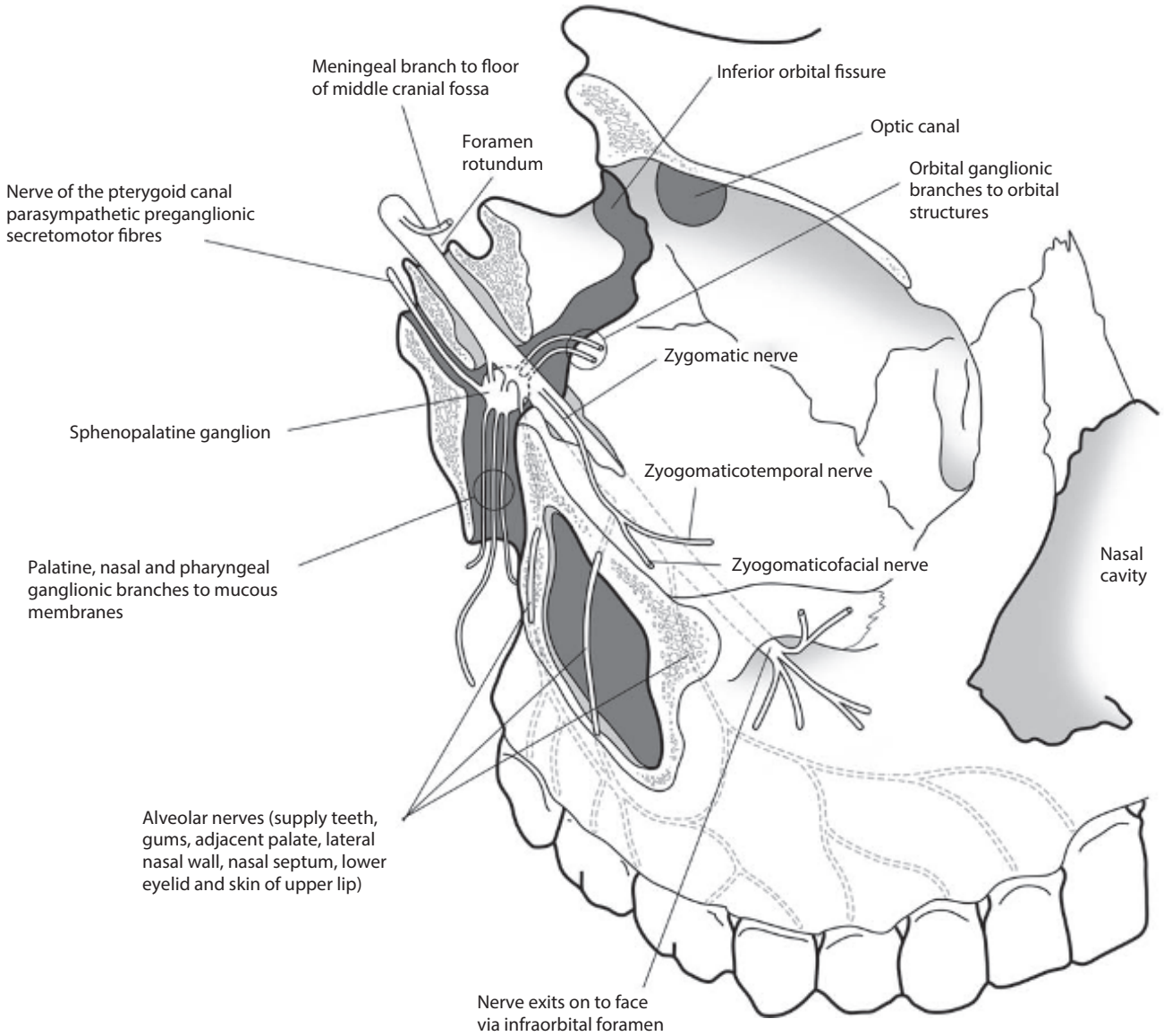


Figure 111.7 The maxillary nerve (V_2).

dental plexus. The anterior superior branch is the largest and supplies not only the incisor and canine teeth, but also the lateral nasal wall, nasal septum, the lower eyelid and the skin of the upper lip.

THE PTERYGOPALATINE (SPHENOPALATINE) GANGLION

This very large ganglion is suspended from the maxillary division, deep in the pterygopalatine fossa. It receives its main contribution from the nerve of the pterygoid canal. This carries preganglionic, parasympathetic fibres derived from the pontine lacrimatory nucleus via the nervus intermedius (VIIth nerve) and sympathetic elements derived from fibres on the middle meningeal artery. Both groups of fibres are then relayed via their subsequent complex course to the lacrimal gland in the lacrimal branch of the nasociliary nerve. The main outflow of the ganglion is via the orbital, palatine, nasal and pharyngeal nerves to the mucous membranes of the orbit, nasal passages, pharynx, palate and upper gums.

The mandibular nerve (V_3)

This is the largest branch of the Vth nerve and includes the motor branch. It exits from the skull base through the foramen ovale, the main sensory trunk being joined by the much smaller motor root, in Meckel's cave, just outside the skull (**Figure 111.8**). A meningeal branch re-enters the skull with the middle meningeal artery through the foramen spinosum and conveys sensation from the lateral, middle and anterior cranial fossae. A small branch, the nerve to the medial pterygoid, supplies medial pterygoid, tensor tympani and tensor veli palatini. The main nerve then divides into anterior and posterior trunks.

The anterior trunk conveys the bulk of the motor root to supply the masseter, temporalis and lateral pterygoid muscles. The main branch of the anterior trunk is the buccal nerve, which merges with the buccal branches of the facial nerve to convey sensation from the skin over buccinator, the mucous membranes of the cheek and the posterior part of the buccal surface of the gum.

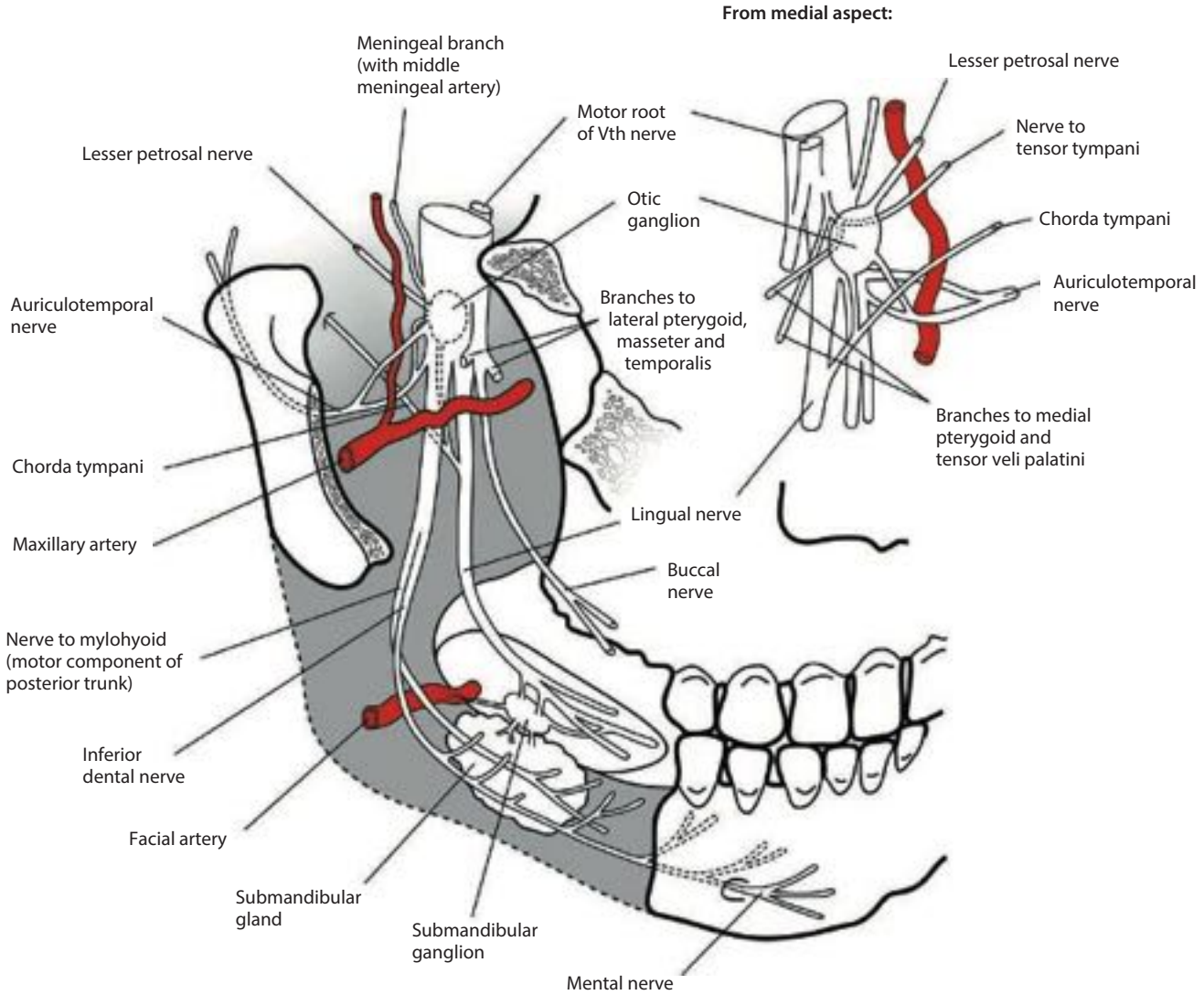


Figure 111.8 The mandibular nerve (V_3).

The posterior trunk is mainly sensory and divides into three main nerves:

1. **The auriculotemporal nerve**, which passes behind the temporomandibular joint to join the facial nerve with which it is distributed to supply the skin over the tragus, helix, auditory meatus and tympanic membrane and, via superficial temporal branches, to the skin over temporalis. It also conveys the secretomotor fibres to the parotid gland and fibres derived from the tympanic branch of the glossopharyngeal nerve via the otic ganglion (see 'The facial nerve (VII)' below).
2. **The lingual nerve**, which carries sensation from the presulcal tongue, the floor of the mouth and lower gums. It also carries the taste fibres of the chorda tympani from the mucous membranes of the anterior two-thirds of the tongue and conveys secretomotor fibres from the submandibular ganglion to the sublingual and anterior lingual glands. It communicates with the hypoglossal nerve.
3. **The inferior alveolar (dental) nerve** enters the mandibular canal running forwards in the mandible to re-emerge on the chin at the mental foramen dividing into the incisive and mental branches, supplying sensory fibres to the skin and mucous membrane of the lower lip, jaw, incisor and canine teeth. The motor component of the posterior trunk leaves the inferior alveolar nerve, just before it enters the mandibular canal, as the mylohyoid nerve supplying mylohyoid and the anterior belly of digastric.

CENTRAL MECHANISMS OF THE VTH NERVE

The central anatomy of the Vth nerve is very complicated. The small motor nucleus lies in a midposition in the upper lateral pons opposite the nerve root. It receives bilateral supranuclear innervation from corticobulbar fibres, which leave the main pyramidal pathways at the level of the nucleus (**Figure 111.9**). Direct connections with proprioceptive fibres in the adjacent main sensory nucleus allow a simple stretch reflex for mastication to operate. The jaw jerk tests the integrity of this pathway and, if greatly enhanced, indicates a bilateral upper motor neuron lesion above midpontine level, the highest stretch reflex that can be elicited.[19]

The sensory nucleus is very extensive. The cell bodies of the sensory fibres lie in the gasserian ganglion overlying the petrous apex. At least 50% of the fibres do not enter the main sensory nucleus but are concerned solely with stretch reflex activity. The other fibres form ascending and descending branches. The ascending fibres enter the mesencephalic nucleus of the Vth nerve. Their subsequent course and exact function is not understood. The descending fibres convey pain and temperature sensation and synapse in the nucleus of the descending tract of the Vth nerve, which lies adjacent to the descending tract itself and extends as low as C2 cord level. The sensory fibres derived from the facial, glossopharyngeal and vagus nerves all join the same tract and relay in the same nucleus. The secondary ascending pathway fibres swing across the brainstem, ventral to the central canal to become the secondary ascending tract of the Vth nerve, which is adjacent to the medial lemniscus,

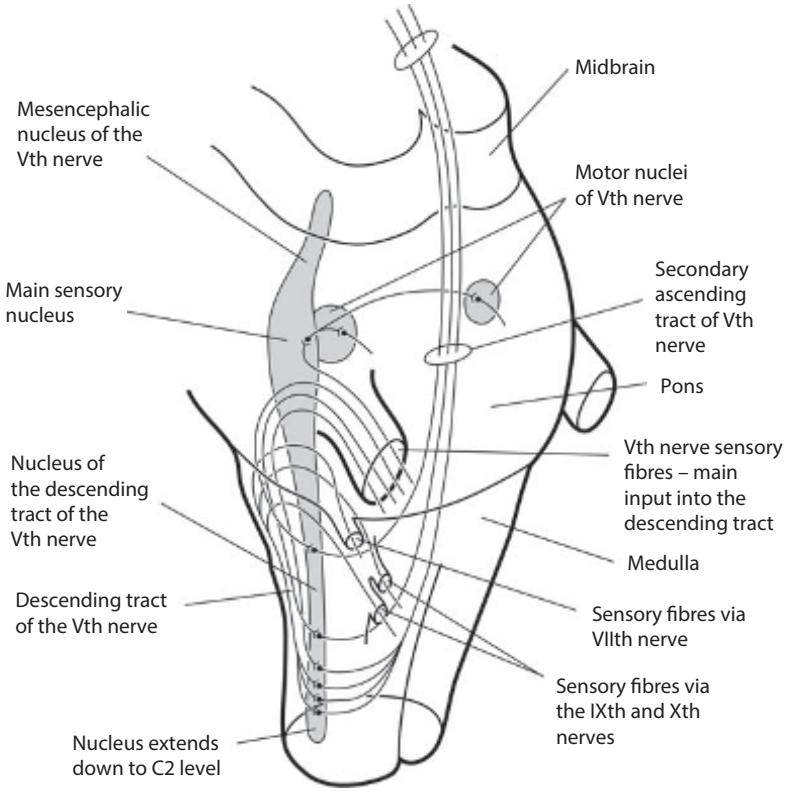


Figure 111.9 Central sensory pathways.

adding sensation derived from the face to that of the arm and leg in the latter pathway. In the decussation, these fibres are very vulnerable to damage by midline lesions, such as syringomyelia and syringobulbia, producing a classical sensory deficit, typically extending forwards from the back of the head. This is the so-called 'onion peel' or 'balaclava' sensory deficit, which may leave sensation intact only over the nose and central face in the final stages of its development.

CLINICAL ASPECTS OF THE VTH CRANIAL NERVE

Damage to the Vth cranial nerve is very important to the otolaryngologist. Branches of the nerve and its associated ganglia lie in areas often involved by otolaryngological disease, especially oropharyngeal and nasopharyngeal neoplasms. Involvement of the motor root of the Vth nerve is quite rare as it seems to be remarkably resistant to pressure or distortion. If damaged, the wasting of the masseter is usually visible and easy to demonstrate by palpation as the patient clenches the teeth. The pterygoids are tested by attempted jaw opening against resistance, the jaw deviating towards the paralyzed side.

Painless or painful loss of sensation over any part of the face, but particularly over V_2, is a very ominous finding and malignant disease in the antrum or nasopharynx is the most likely pathology. Repeated examination under general anaesthesia if necessary and biopsy of the nasopharynx are vital in such cases, to attempt to establish the cause, even if CT or MRI scanning do not clearly indicate an abnormality.

Involvement of V_1 is usually painful and nearly always accompanied by extraocular nerve palsies. It is most often damaged by lesions in and around the cavernous sinus, but may also be involved by malignant disease entering the orbit via the inferior orbital fissure.

Nasopharyngeal tumours most commonly arise in the fossa of Rosenmüller or near the orifice of the Eustachian tube. They are usually squamous carcinomas. Tumours originating in the maxillary antrum or ethmoids are usually either squamous cell carcinomas or adenocarcinomas. Some 40% of such tumours present as neurological problems. In 70% of cases, the Vth nerve is involved; in 50% of cases, the IIIrd, IVth and VIth nerves are involved. Visual pathways are affected in 8.5% of cases, and the lower cranial nerves in 10% of cases. The favourite routes of entry into the skull are through the inferior orbital fissure or via the foramen lacerum alongside the carotid artery.[20]

The maxillary division runs past the mouth of the Eustachian tube and the fossa of Rosenmüller, through the orbital floor just above the antrum and on to the face. Nasopharyngeal and antral carcinomas are particularly likely to damage this division and can cause loss of sensation as frequently as pain. The surface branches of both V_1 and V_2 are easily damaged by blunt trauma around the orbit and cheek, or divided by lacerations.

The mandibular division is involved in oropharyngeal, tonsillar and mandibular tumours and, as noted earlier, painless numbness over the chin may be the presenting symptom, rather than pain. This remains a paradox when we consider that the most common benign condition, trigeminal neuralgia, causes exquisite facial pain and yet the most serious conditions are often quite painless.

Trigeminal sensory neuropathy is a very rare condition in which painless numbness develops over the Vth nerve territory, usually starting in the second division and eventually becoming bilateral. Only the passage of time and continued failure to demonstrate an underlying lesion, allow this diagnosis to be made with certainty.[21]

The sensory root of the Vth nerve is particularly sensitive to distortion and pressure and loss of the corneal reflex is an important early sign of a lesion in the cerebellopontine angle. Rarely, extensive loss of sensation over the face may be the presenting symptom of a vestibular schwannoma, but again it is worth stressing the rarity of pain as the presenting symptom.

TRIGEMINAL NEURALGIA

This is probably the most painful condition known, the cause of which seems to be due to ageing changes in the nerve or seemingly trivial irritation by adjacent aberrant arteries. From a practical, anatomical point of view, the very strict localization of the pain in Vth nerve territory is a vital diagnostic feature. There is no such thing as atypical trigeminal neuralgia and it is not acceptable to allow the pain to radiate behind the ear, onto the neck or across the midline, and the anatomically precise distribution is the linchpin of diagnosis. The pain is usually described in two characteristic distributions. The first runs from the lower canine tooth along the lower jaw to just in front of the ear and sometimes round into the upper jaw (i.e. it involves both V_3 and V_2). The second less frequent type runs from the upper incisor or canine, up the side or inside the nose and encircles the eye, involving both V_2 and V_1. It is probably this spread over two divisions that makes simple surgical section of the peripheral branches unsuccessful in managing the condition long term, although triggering is occasionally reduced. Although it is claimed that transient sensory deficit may follow a spasm of pain, any evidence of sensory loss, impaired corneal reflex or Vth motor weakness should invalidate the diagnosis. Although trigeminal neuralgia may complicate multiple sclerosis, it is very rare as a presenting symptom of this disease.

HERPES ZOSTER OPHTHALMICUS

Most patients with this condition develop very severe pain in the distribution of V_1. The pain lasts between four and five days and during this time the diagnosis of ruptured aneurysm, cranial arteritis or acute frontal sinusitis may all have to be seriously considered. The vesicles usually appear in the inner eyebrow on day five or six and involve the entire distribution of the nerve branch. Severe chemosis of the eye and extraocular nerve palsies may further complicate the initial picture. Often, only the appearance of the vesicles will finally indicate the correct diagnosis.

ANEURYSMAL DILATATION OF THE CAROTID ARTERY

This is the other major condition in the elderly that can cause very severe pain in a V_1 distribution, with chemosis, extraocular nerve palsies and even blindness. This is usually of very sudden onset and typically develops in elderly females with long-standing hypertension.

The facial nerve (VII)

The VIIth nerve is primarily motor to the muscles of facial expression. It also carries the important taste fibres from the anterior two-thirds of the tongue via the chorda tympani and taste from the palate via the nerve of the pterygoid canal (Figure 111.10). A small but clinically important cutaneous supply to the skin of the external ear is mediated in fibres carried from the nerve via the vagus. These sensory fibres are contained in a separate trunk, the nervus intermedius, which runs with the VIIIth nerve rather than the VIIth nerve in the subarachnoid space. The cell bodies of the sensory root lie in the geniculate ganglion. The nervus intermedius also carries preganglionic, parasympathetic secretomotor fibres to the lacrimal, submandibular and sublingual salivary glands. These fibres originate in the lacrimatory nucleus and superior salivatory nucleus.

Several important branches arise from the intrapetrous part of the nerve:

- The greater petrosal nerve arises from the geniculate ganglion, carrying taste fibres from the palate and conveying preganglionic, parasympathetic fibres to the pterygopalatine ganglion, and thence via the zygomaticotemporal and lacrimal nerves to the lacrimal gland. It is joined by the deep petrosal nerve (derived from the sympathetic plexus on the carotid artery) to form the nerve of the pterygoid canal.
- A branch from the ganglion joins the lesser petrosal nerve and is then carried to the otic ganglion. This conveys secretomotor fibres via the auriculotemporal nerve to the parotid gland. It also carries sympathetic fibres derived from the carotid artery to supply the blood vessels of the parotid gland.
- A small twig, the nerve to stapedius, arises 6 mm above the stylomastoid foramen.
- The chorda tympani arises at the same level and runs forward across the middle ear and enters a canal in the petrotympanic fissure, grooves the spine of the

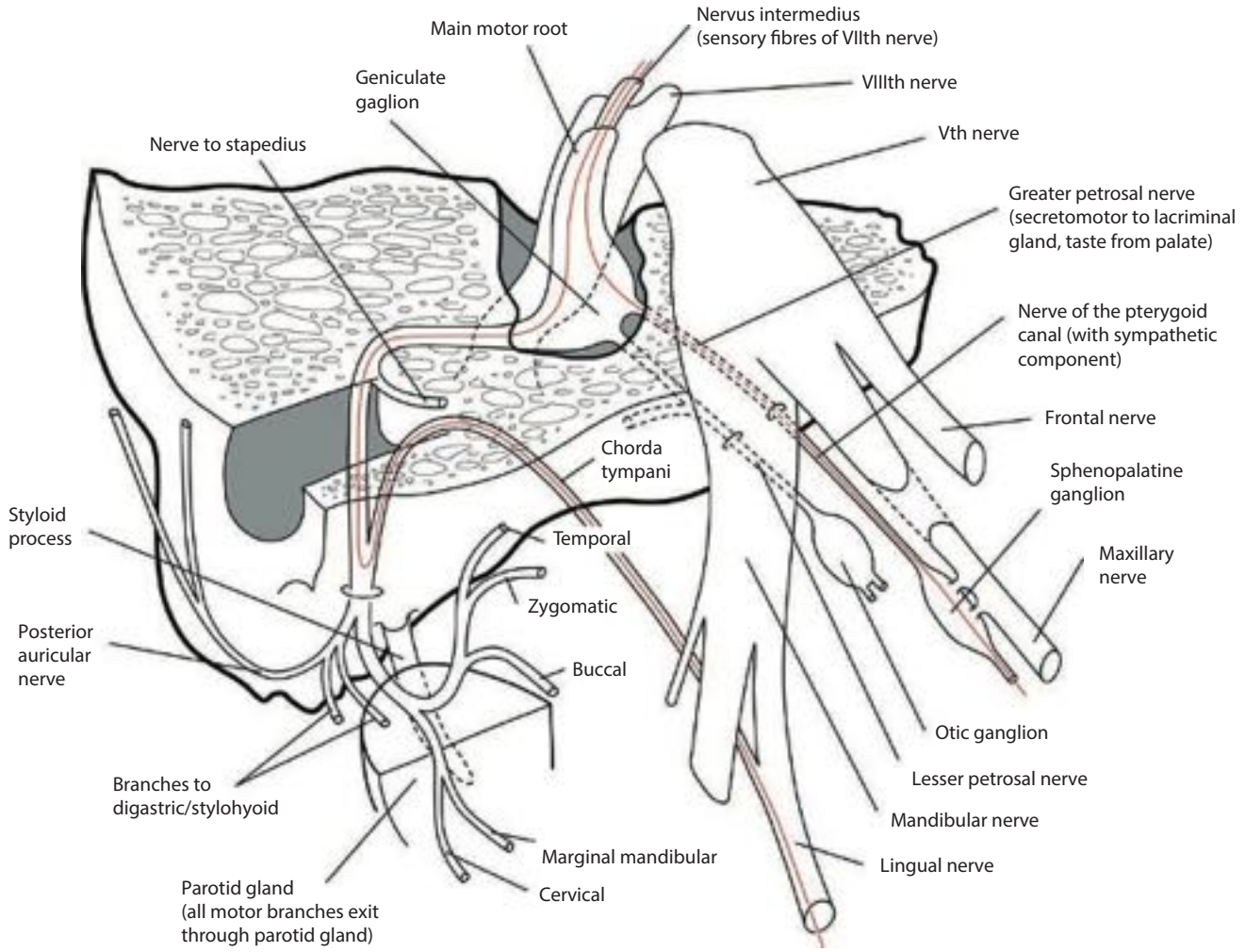


Figure 111.10 The facial nerve.

sphenoid and joins the lingual branch of the Vth nerve with which it is distributed to the presulcal part of the tongue.
- At the stylomastoid, foramen twigs join both the vagus and glossopharyngeal nerve.
- The posterior auricular nerve supplies the muscles of the ear and occipital belly of occipitofrontalis.
- The branches to the muscles of facial expression are, from above down, the temporal, zygomatic, buccal, marginal and cervical. They pass through the substance of the parotid gland before emerging in the skin and are vulnerable to disease in the parotid gland and to local surgical procedures.
- Cutaneous fibres are distributed with the auricular branch of the vagus supplying the skin on both sides of the auricle and part of the external auditory canal and tympanic membrane.

THE SUBMANDIBULAR GANGLION

The submandibular ganglion hangs from the lingual nerve. Its preganglionic fibres are derived from the superior salivatory nucleus and reach it via the facial nerve, chorda tympani and lingual nerve. These fibres are secretomotor to the submandibular and sublingual glands. The sympathetic components are derived from the sympathetic plexus on the facial artery and pass uninterrupted through the ganglion to the blood vessels of the same glands.

THE CENTRAL CONNECTIONS OF THE FACIAL NERVE

The nucleus lies in a deep position in the central pons (see **Figure 111.5**). The dorsal part of the nucleus receives bilateral supranuclear innervation, whereas the lower part of the nucleus receives mainly contralateral supranuclear innervation. This has important consequences for the clinical varieties of VIIth nerve lesions. The nucleus is closely related to the Vth nerve and this proximity is vital for the important corneal reflex and its own reflex activity via the nucleus of the tractus solitarius. The fascicular course of the nerve is unusual in that the fibres course towards the floor of the IVth ventricle, wrap around the nucleus of the VIth nerve, producing a visible enlargement in the floor of the IVth ventricle (the facial colliculus) and then retrace their course across the entire depth of the pons to exit at the pontomedullary junction. This complex arrangement is thought to be due to the embryological migration of the nucleus from its original position in the floor of the IVth ventricle to achieve its close relationship to the nucleus of the Vth nerve and the nucleus of the tractus solitarius.

TASTE MECHANISMS

Taste is mediated via taste buds; some 50 cells arranged in a pear-like cluster. These are found on the tongue, undersurface of the palate, palatoglossal folds, posterior wall of the pharynx, posterior surface of the epiglottis and the upper third of the oesophagus. They are most numerous on the lateral tongue and decrease in number with age by about 1% per annum. Each taste bud opens on the surface of the mucous membrane as a pore. The buds are found in the vallate, fungiform and foliate papillae. The life span of these cells, which are renewed from epithelial cells surrounding the bud, is about 10 days. They are therefore very vulnerable to factors inhibiting rapid cell turnover.

Two main receptor cells have been identified although they are possibly different types of the same cell. Some receptor cells have receptor sites for afferent neurons and small presynaptic vesicles. Others contain larger vesicles and have more definite ciliary processes at their tip just inside the pore. There is evidence of considerable cross-innervation of taste buds, which may indicate inhibitory and facilitatory control similar to that seen in the smell receptors. It is thought that patterns of taste over a wide area of receptors is critical in perceiving different tastes, rather than that there are specific receptors for specific tastes. There is some evidence that sweet is more readily detected on the tip and medial dorsum of the tongue, salt and sour over the lateral tongue and bitter over the posterolateral tongue, where the circumvallate papillae are most numerous.

The neural connections of the taste receptor cells are the unipolar processes of cells in the geniculate ganglion of the VIIth nerve, the inferior ganglion of the IXth nerve and the inferior ganglion of the Xth nerve. The central processes of these cells form the tractus solitarius and they synapse in the adjacent nucleus of the tract. These fibres then ascend in the medial lemniscus to the opposite nucleus ventralis posterior medialis of the thalamus. The final pathway is via the internal capsule to the sensory cortex and insula. Some information from the pons relays direct to the hypothalamus for autonomic reflex purposes.

The anatomy of the peripheral taste pathways is complex, but for practical purposes, the supply to the anterior two-thirds of the tongue is carried by the chorda tympani, but finally distributed via the lingual branch of the mandibular division of the Vth nerve (**Figure 111.11**). The facial nerve also conveys sensation from the taste buds on the palate, through the middle and posterior palatine nerves, via the greater petrosal nerve and the nerve of the pterygoid canal. Taste sensation from the vallate papillae, pharyngeal tongue and palatoglossal folds is conveyed by fibres carried in the IXth nerve. Taste sensation from the lowest part of the tongue, epiglottis and hypopharynx is carried by the vagus in fibres derived from its superior laryngeal branch. Free nerve endings of the Vth nerve are also widespread, conveying somatic sensation from these same areas. They also undoubtedly contribute to the perception of extremely strong taste stimuli, such as curry powder, carbonated drinks and acid substances. Modifications of this pattern of gustatory and simple physical stimuli, such as temperature, can alter taste sensation, heightening the unpleasant features of such highly flavoured compounds. It is clear that taste mechanisms are rather more complex than simple permutations of sweet, bitter, salt and sour. Parallel smell appreciation adds savour to taste. Patients with anosmia describe all food as ‘tasting like cardboard’

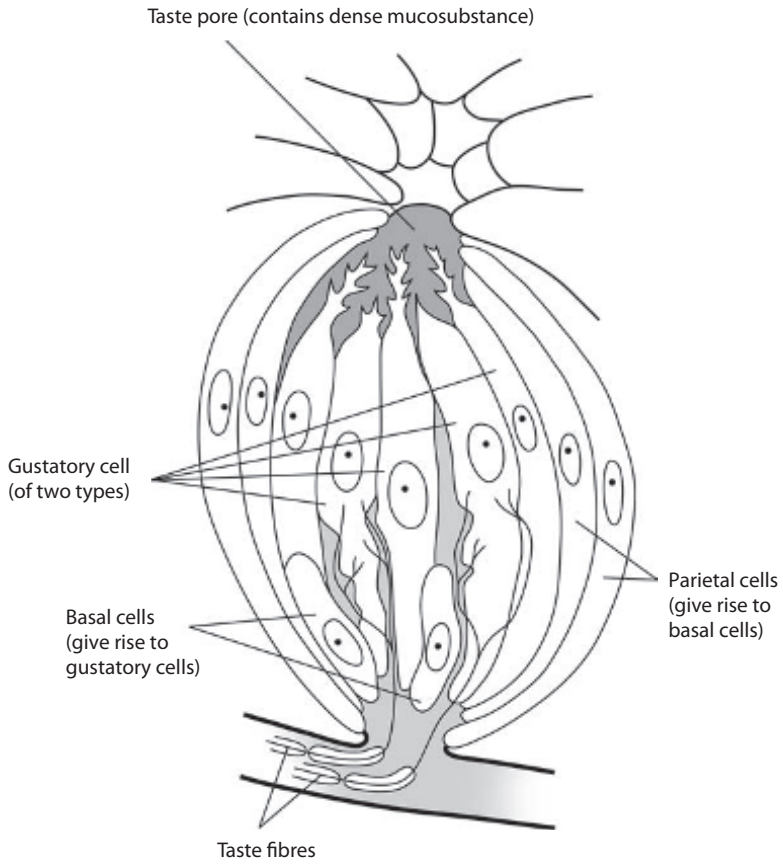


Figure 111.11 The taste bud.

and only highly spiced or flavoured foods make any impact and often not necessarily a pleasant one. Adaptation again plays a role. The modification of fruit juice flavours by the previous use of mint toothpaste, is a universally appreciated phenomenon. Because of the vital role of smell in taste appreciation and the frequent simultaneous impairment of smell, it is difficult to isolate specific disorders of taste. For example, in Bell's palsy, patients identify tastes as having a 'metallic' flavour, in spite of the lesion being strictly unilateral and there being no impairment of the sense of smell. Chemicals and systemic diseases that modify taste and smell are listed under 'The olfactory nerve (I)' above.

The chemistry of taste sensation is described in Volume 1, Chapter 110, Abnormalities of smell.

CLINICAL DISORDERS OF THE VIITH NERVE

The VIIth nerve is frequently damaged by diseases of otolaryngological origin inside the skull, in the petrous bone and in the parotid gland.[22]

For reasons noted above, a cortical lesion affecting VIIth nerve function, such as a vascular lesion or tumour in the motor strip, will cause weakness maximal in the lower face which is almost exclusively contralaterally innervated. The upper face, in particular forehead movement and eye closure, is relatively spared, due to bilateral supranuclear innervation. Thus, upper motor neuron facial weakness is, in many instances, more apparent on spontaneous smiling and speaking than during deliberate attempts to move the face to command.

Lesions affecting the whole facial nucleus or the peripheral part of the nerve should cause total unilateral facial weakness. In some instances, weakness may be more marked in the lower face, which can happen in the early or recovery phase of a simple Bell's palsy and an upper motor neuron lesion may be incorrectly suspected. Much less commonly, a very dense upper motor neuron lesion may mimic a lower motor neuron lesion by affecting all facial movements. These difficulties are stressed as the distinction is of immense diagnostic importance and mistakes are easily made. It is also worth stressing that ptosis of the eyelid is not a feature of either a lower or upper motor neurone facial palsy – a droopy eyelid should never be accepted as part of a facial weakness.

Lesions in the brainstem affecting the VIIth nerve usually also involve the VIth nerve because of the intimate anatomical relationship in the floor of the IVth ventricle. Careful examination may reveal long tract signs, such as brisk reflexes or extensor plantar responses, if the brainstem is distorted or infiltrated by the causative lesion.

The VIIth nerve lies in very close relationship with the VIIIth nerve as they both cross the subarachnoid space to enter the internal auditory foramen. This is in the region of the cerebellopontine angle and a vestibular schwannoma is the lesion most frequently found at this site. Vestibular schwannomas, although inevitably grossly distorting the

VIIth nerve, very rarely present as a VIIth nerve palsy. If there is clinical evidence of a cerebellopontine angle lesion and if the VIIth nerve is involved, alternative pathology is more likely.[23] Permanent damage to the VIIth nerve following surgical removal of a vestibular schwannoma is unfortunately very common and often unavoidable.

In the facial canal, the nerve is liable to ischaemic damage and this is the probable mechanism of Bell's palsy, where the nerve is thought to be damaged by compression, secondary to the inflammatory response to an antecedent viral infection. In nearly all cases very severe pain in the ear is experienced in the 24 hours before the onset of the Bell's palsy, particularly if herpes zoster is responsible (Ramsay Hunt syndrome). The accompanying pain and local swelling may suggest bacterial infection until the vesicles appear three to four days later. The facial paralysis is usually complete on the second day and includes occipitofrontalis and platysma.

In a straightforward Bell's palsy, hearing distortion, due to paralysis of stapedius, and impaired taste, due to simultaneous involvement of the chorda tympani, do not always occur and in mild cases the lower half of the face may be more severely affected than the upper half, mimicking an upper motor neuron lesion, as discussed above.[24] Seventy-five per cent of patients make a good recovery over three to six weeks with or without treatment. Twenty per cent make an acceptable but slow recovery complicated by the development of facial synkinesis. This is due to nerve sprouting with subsequent loss of fine control, which can turn a smile into a snarl and eye closure into a distorted grimace. Five per cent of cases make little or no recovery and may ultimately require plastic surgical repair. In some cases, aberrant regeneration may lead to lacrimation instead of salivation on eating, so-called crocodile tears.[25] It is most important that patients with Bell's palsy are not told that they have had a small stroke. Exclusion of underlying hypertension, diabetes, sarcoidosis and inflammatory arterial disease is important and more recently the recognition of Lyme disease in southern rural England suggests blood tests for *Borrelia burgdorfii* be added to the diagnostic work up in appropriate areas, typically where there is a large deer population.

Middle ear infection carries a considerable risk of damaging the nerve by similar mechanisms. Fractures through the petrous bone are often complicated by facial nerve palsy. Those of immediate onset are usually due to nerve laceration. Those of delayed onset, usually two to three days after trauma, are due to oedema and carry an excellent prognosis. Trauma to the nerve as it emerges from the stylomastoid foramen is a well-recognized complication of forceps delivery.

Benign hemifacial spasm occurs in both sexes at any age, but is most common in elderly hypertensive females. Since the advent of scanning, a surprising number of underlying lesions are found in this condition, such as cholesteatoma, vestibular schwannomas, meningiomas or aneurysms of the basilar artery. CT or MRI scanning should now be regarded as necessary investigations in all cases. The symptoms consist of a constant flickering and twitching of the facial muscles. This usually starts around the eye, producing involuntary winking, and later extends to involve the mouth. It is usually worse in company, but continues 24 hours a day. It may respond to carbamazepine (Tegretol) but if the patient's age and condition permits, posterior fossa exploration to identify vascular irritation by a small vessel may be considered.[26] Excellent control can be obtained using botulinum toxin injections in many cases. At present, the need for repeat injection every two to three months and the expense limits the use of this valuable treatment, but once a gross underlying lesion is excluded, botulinum is the treatment of choice.

CLINICAL TESTING OF THE VIITH NERVE

A standard sequence of movements should be tested. Wrinkling the forehead, followed by forced eye closure will usually detect weakness in the upper half of the face. The ability to flare the nostrils and wrinkle the nose should then be tested, followed by asking the patient to forcibly show the teeth and attempting to blow out the cheeks. Eversion of the lower lip is difficult to achieve, but tests the perioral muscles and produces striking contraction of platysma. It should only take about 30 seconds to perform these tests. Hearing should not be impaired to simple clinical testing, although the patient may report distorted hearing. In the same way, formal testing of taste with standard test flavours may be performed, but often the patient's own perception and description of altered taste will be adequate for diagnostic purposes.

Whenever the VIIth nerve is damaged, it is important to exclude coexistent Vth nerve damage, in particular to confirm the presence of the corneal reflex. Not only will the absence of the corneal reflex exclude a simple Bell's palsy, but the considerable danger to an unprotected and anaesthetic cornea will be identified. Eye movements should be carefully tested to exclude a VIth nerve lesion, which could indicate a brainstem lesion, and simple clinical tests of hearing should be performed, particularly if the corneal reflex is depressed, as simultaneous involvement of the Vth, VIIth and VIIIth nerves would strongly indicate a lesion in the cerebellopontine angle. It should be remembered that herpes zoster may affect several cranial nerves simultaneously and can cause severe pain, which, when accompanied by multiple cranial nerve palsies, can present a very difficult diagnostic situation until the vesicles appear.

The vestibulocochlear nerve (VIII)

The anatomy and physiology of the specialized end organs of the VIIIth nerve are described in Chapter 47, The anatomy of the cochlear and vestibular system: Relating to ultrastructure to function. Discussion here is therefore confined to the role of hearing impairment and balance disorders in the diagnosis of neurological disease.

Due to the anatomical proximity of the VIIth and VIIIth nerves, simultaneous involvement under many circumstances would seem likely. In reality, such damage

is quite unusual, with the exception of acute traumatic lesions of the petrous bone where both nerves are simultaneously lacerated. This peculiarity is of considerable clinical importance.

THE CEREBELLOPONTINE ANGLE SYNDROME

The classical tumour arising in the cerebellopontine angle is a vestibular schwannoma (**Figure 111.12**). Although originating on the vestibular division of the nerve, the rate of growth is usually so insidious that a purely vestibular presentation is extremely unusual. Gradual and often unrecognized impairment of hearing is the rule. Similarly, the VIIth nerve may become grossly distorted but either benign facial hemispasm or weakness as a presenting symptom is similarly unusual. In contrast, minimal pressure on the Vth nerve root as the tumour extends upwards or perhaps stretching of the Vth nerve root as the pons is displaced medially, commonly produces impairment of the corneal reflex. In spite of such distortion, pain or numbness of the face is also very unusual. Obviously, a cerebellopontine angle tumour may present as facial hemispasm, facial weakness, facial numbness or a trigeminal neuralgia-like syndrome, but in all such instances an alternative cause, such as a cholesteatoma or meningioma in the cerebellopontine angle, becomes a more likely diagnosis. If the clinical picture has evolved extremely rapidly, both metastatic carcinoma or lymphoma could be responsible. Less often, and usually in the 5–15-year age group, pontine glioma or cerebellar medulloblastoma can extend into the cerebellopontine angle, to produce this typical combination of nerve lesions.

BALANCE DISORDERS AND VERTIGO

Unsteadiness is a common symptom prompting leading to referral for an otolaryngological or neurological opinion. The most important historical feature to establish is what the patient means by their description using the terms: 'off balance', 'giddy', or 'dizzy'. So often close questioning reveals that they actually mean 'light-headed', 'floaty' or 'woozy', all non-specific symptoms usually due to anxiety. They do not include the obligatory illusion of movement of either themselves or their surroundings, which is necessary to establish that they have true vertigo and therefore justify extensive and expensive otoneurological investigations to define the cause.

Disorders of balance, such as Ménière's disease, vestibular neuronitis and benign positional vertigo, are discussed in Chapters 62–67. The frequency with which vertigo is a symptom in migraine attacks also deserves mention. A feature of all these situations is that the attacks are episodic or provoked by change of position and in the case of migraine often accompanied by or associated with headache. Disorders of balance due to structural organic disease in the CNS tend to produce continuing difficulty with balance and non-stop vertigo. The most frequent causes are multiple sclerosis and cerebrovascular accidents affecting vestibular and cerebellar connections in the brainstem. Pure cerebellar lesions are less likely to produce vertigo, unless they also distort the brainstem. They also tend to produce impaired coordination or a tendency to veer to one side while walking, rather than the drunken reeling in all directions seen in association with vertigo in patients with brainstem lesions.

GROUP 3

The final group of cranial nerves are not only anatomically bunched at their major exit, the jugular foramen, but share common nuclear origins. They also have peripheral cross-connections for final distribution that make for poor physiological distinction of function, as well as complex anatomy. Only the hypoglossal nerve with its discrete nuclear origin

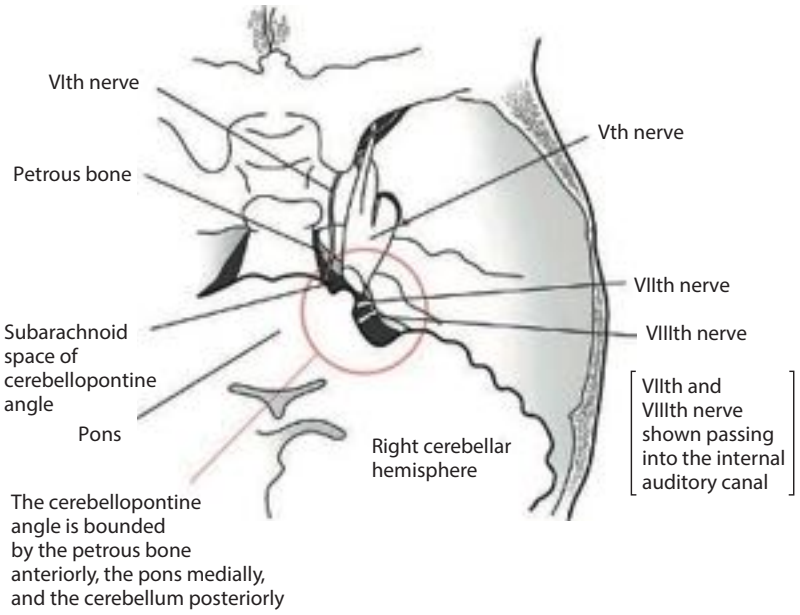


Figure 111.12 The cerebellopontine angle.

and separate hypoglossal canal can be discussed in isolation. Even then, its peripheral course brings it into close anatomical relationship with the other three nerves.

The glossopharyngeal nerve (IX)

The glossopharyngeal nerve has sensory, motor and autonomic components. The sensory ganglion cells lie in the superior and inferior ganglia of the nerve (**Figures 111.13**, **111.14** and **111.15**).

The central processes pass to the nucleus of the tractus solitarius, conveying taste sensation, and to the nucleus of the spinal tract of the Vth nerve, conveying somatic sensation. The motor nucleus lies in the upper part of the nucleus ambiguous, which receives bilateral supranuclear innervation from corticobulbar fibres. This nucleus supplies the stylopharyngeus. The autonomic parasympathetic fibres arise in the inferior salivatory nucleus. These fibres are carried in the lesser petrosal nerve via the tympanic branch to the otic ganglion. The postganglionic fibres are distributed to the parotid gland via the auriculotemporal nerve.

The glossopharyngeal nerve emerges from the brainstem in line with the vagus and accessory nerves and exits from the skull via the jugular foramen. It descends between the jugular vein and carotid artery, picking up sympathetic fibres from the carotid plexus as it loops forwards and medially to reach the soft tissues of the oropharynx, posterior tongue and palate. In its course, it gives off the lesser petrosal nerve conveying the secretomotor fibres for the parotid gland to the otic ganglion. An important nerve, the carotid branch, conveys chemoceptor and stretch reflex information, respectively, from the carotid body and carotid sinus centrally for respiratory and circulatory reflex function. The final branches of the glossopharyngeal nerve are the pharyngeal, tonsillar and lingual branches, conveying general sensation and taste sensation from the posterior third of the tongue and oropharynx.

THE OTIC GANGLION

The otic ganglion lies just below the foramen ovale, attached to the mandibular nerve but functionally carries secretomotor fibres from the glossopharyngeal nerve. These parasympathetic fibres relay in it and supply the parotid gland via the auriculotemporal nerves originating from V_3. Sympathetic fibres derived from the middle meningeal artery pass through the ganglion and are also distributed to the blood vessels of the parotid gland in the auriculotemporal nerve.

GLOSSOPHARYNGEAL NEURALGIA

This is a rare condition that presents at about one-tenth the frequency of trigeminal neuralgia. It consists of excruciatingly severe pain in the palate, throat and external auditory canal, locations demonstrating the somatic sensory distribution of the glossopharyngeal nerve. The pain has the typical burning, electric shock quality of neuralgia and is triggered mainly by swallowing. The incidence of underlying lesions inside the skull is very much higher than in trigeminal neuralgia. Both phenytoin and carbamazepine may control the pain, but MRI scanning would seem a wise precaution in all instances. Intracranial root exploration is necessary if medical treatment fails. Peripheral glossopharyngeal section has little to commend it and can seriously interfere with normal swallowing mechanisms.[27]

The vagus nerve (X)

The vagus nerve (the wanderer) is the most widely distributed cranial nerve, hence only aspects essential to otolaryngologists will be detailed. The central connections are similar to the IXth nerve (see **Figures 111.13**, **111.14** and **111.15**):

- The dorsal nucleus of the vagus contains motor and sensory components. The motor fibres are general visceral efferent to the smooth muscle of the bronchi,

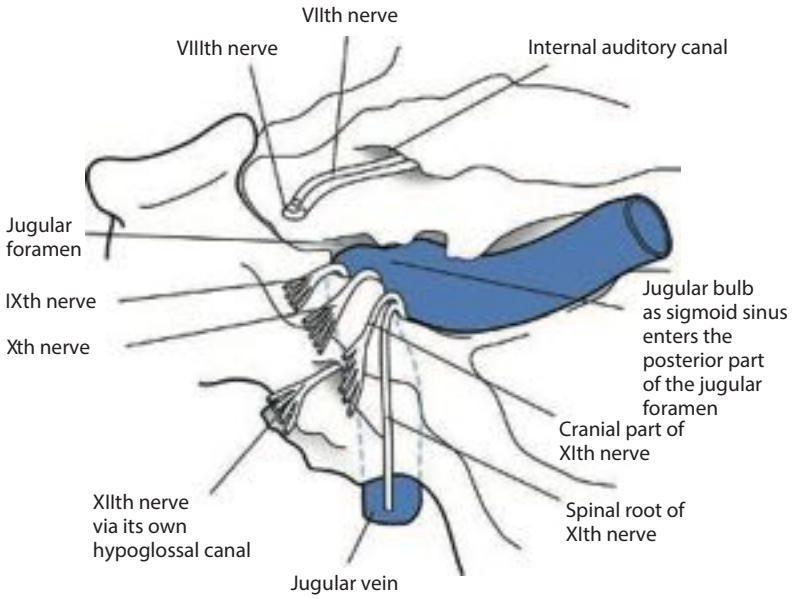


Figure 111.13 Schematic diagram of internal jugular foramen.

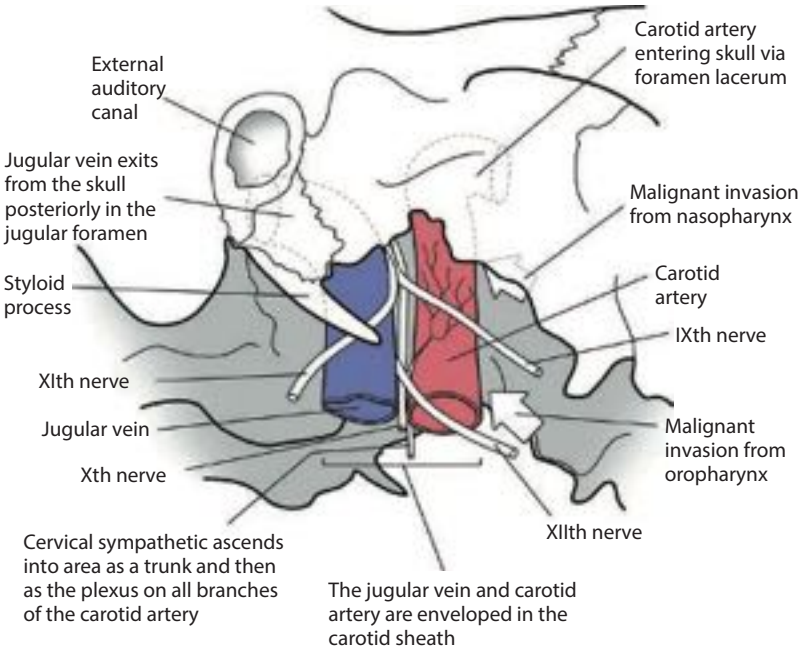


Figure 111.14 Schematic diagram of external jugular foramen. (See also Figure 111.16.)

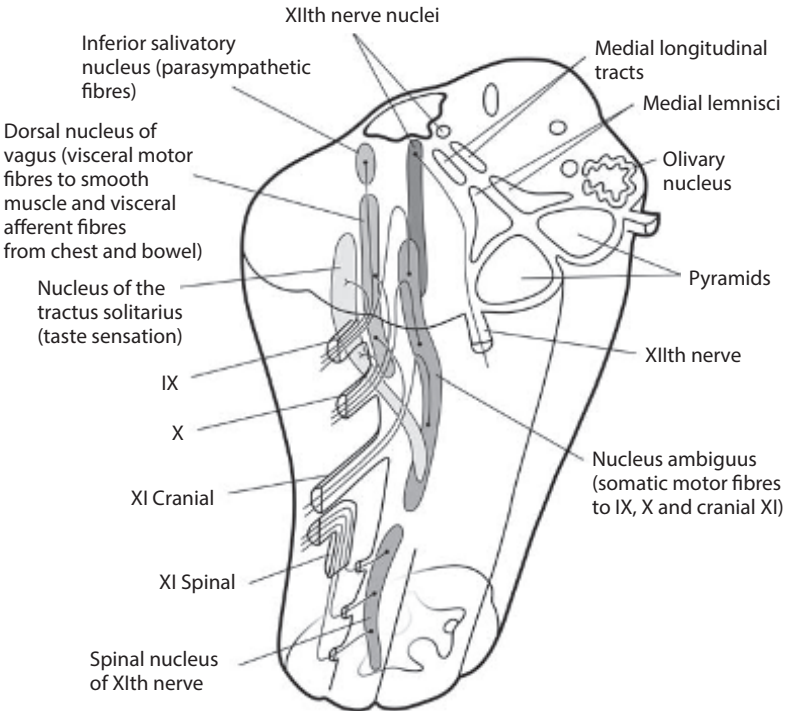


Figure 111.15 Central connections of nerves IX, X, XI and XII, viewed anterolaterally from the right side. (See also Figure 111.9 for central sensory connections via the nucleus of the descending tract of the Vth nerve.)

heart, oesophagus, stomach and intestine. The sensory fibres are general visceral afferent, originating in the oesophagus and upper bowel with cell bodies in the superior and inferior vagal ganglia.

- The nucleus ambiguus gives origin to those fibres controlling the striated muscle of the pharynx and intrinsic muscles of the larynx. It has a bilateral supranuclear innervation.
- The nucleus of the tractus solitarius is shared with the glossopharyngeal nerve and receives fibres from the taste buds of the epiglottis and vallecula.
- General somatic afferent fibres from the pharynx and larynx are found in the nerve and are believed to terminate in the spinal nucleus of the Vth nerve.

Because of these extensive nuclear connections, multiple rootlets emerge from the brainstem and form a flat cord, which enters the jugular foramen.

The superior and inferior ganglia lie in the foramen and just below an identical arrangement to the glossopharyngeal nerve. Both ganglia make connections with the accessory and hypoglossal nerves and the sympathetic

plexus on the carotid artery. Below the inferior ganglion, the cranial root of the accessory nerve merges with the vagus nerve, which then distributes its fibres to the pharynx and larynx.

The vagal branches of practical importance are as follows:

- A meningeal branch supplying the dura of the posterior fossa is given off in the jugular foramen.
- The auricular branch arises from the superior ganglion and is joined by a branch from the glossopharyngeal nerve and conveys sensation from the skin of the external ear with the branch of the facial nerve. These fibres eventually all enter the nucleus of the descending tract of the Vth nerve.
- The pharyngeal branch arises just above the inferior ganglion and distributes the spinal accessory nerve components to the pharyngeal plexus, supplying the pharynx and palate.
- The superior laryngeal nerve comes off the inferior ganglion and divides into two branches: the internal laryngeal nerve, which carries sensation from the mucous membrane of the larynx and conveys proprioceptive information from the neuromuscular spindles and stretch receptors of the larynx; and the external laryngeal nerve, which supplies cricothyroid and contributes to the pharyngeal plexus, which is of considerable importance in speech mechanisms.
- The recurrent laryngeal nerve has differing courses on each side. On the right, it loops under the subclavian artery and on the left under the aortic arch. On both sides it then ascends on the side of the trachea. It supplies all the muscles of the larynx except cricothyroid and carries sensory fibres from the mucous membranes and stretch receptors of the larynx.

The spinal accessory nerve (XI)

The cranial part of this nerve is a detached portion of the vagus and the spinal part is motor to the sternocleidomastoid and trapezius (see **Figures 111.13**, **111.14** and **111.15**).

The cranial portion arises from the lower part of the nucleus ambiguus and a small component from the dorsal efferent nucleus of the vagus. The nerve rootlets emerge in line with the vagus and are joined by the ascending spinal component and run laterally to enter the jugular foramen. The cranial portion merges with the vagus at the level of the inferior vagal ganglion and is then distributed with the pharyngeal and recurrent laryngeal branches of the vagus. These fibres probably supply the muscles of the soft palate.

The spinal root arises from ventral horn cells in the cord between C1 and C5. These fibres emerge from the cord laterally between the anterior and posterior spinal nerve roots to form a separate nerve trunk, ascending into the skull through the foramen magnum. This then exits from the skull via the jugular foramen in the same dural sheath as the vagus. It runs posteriorly as soon as it emerges to supply the sternocleidomastoid and the upper part of the trapezius and receives a major contribution from branches of the anterior roots of C3 and C4, to form the neural plexus, which supplies the cervical musculature. Evidence from surgical procedures suggests that these additional root components make important contributions, as upper cervical root section is required to denervate completely the sternocleidomastoid and trapezius. The peripheral portion of the nerve is easily damaged in lymph node biopsy and other operations in the posterior triangle of the neck.[28]

The accessory nerve is unusual in that clinical evidence indicates that the supranuclear innervation of the motor cells supplying sternocleidomastoid is ipsilateral. In hemiparetic vascular lesions, the weakness in sternocleidomastoid is on the same side as the lesion. In epileptic fits originating in the frontal pole, the head turns away from the side of the lesion (i.e. the ipsilateral sternocleidomastoid is contracting). Failure to recognize this unanticipated distribution may to the novice seem to indicate that a patient with a left hemiparesis also has a right accessory nerve lesion, and therefore a lower brainstem lesion, rather than a typical capsular cerebrovascular accident. This is an easy mistake to make unless this anatomical peculiarity is appreciated and the normality of the upper trapezius on the side of the weak sternocleidomastoid is confirmed.

The hypoglossal nerve (XII)

The hypoglossal nerve arises from a nuclear column lying in the floor of the IVth ventricle and derived from the same cell group as the nuclei of nerves III, IV and VI (see **Figures 111.13**, **111.14** and **111.15**). Like nerves III and VI, the fascicular fibres of XII have to traverse the full sagittal diameter of the brainstem to reach their exit from the ventral surface of the medulla between the pyramid and olive. The numerous rootlets combine and become two main roots with their own dural sleeves and exit the skull via the hypoglossal canal just below the jugular foramen. The nerve therefore emerges deep to the other neural structures and has to course downwards and anteriorly to emerge between the jugular vein and carotid artery, cross the inferior vagal ganglion and then pass upwards and anteriorly on hyoglossus, distributing branches to all the muscles of the tongue. It receives sympathetic fibres from the superior cervical ganglion, some fibres from the vagus and the motor roots of C1 and C2 via the ansa cervicalis. In addition, numerous filaments connect to and are distributed with the lingual nerve.

Motor fibres derived from the hypoglossal nucleus itself supply styloglossus, hyoglossus, geniohyoid and genioglossus. The fibres derived from the C1 components are distributed to sternohyoid, sternothyroid, omohyoid, thyrohyoid and geniohyoid. Although a XIIth nerve lesion paralyzes one side of the tongue as its most demonstrable feature, the larynx also pulls across to the opposite side on swallowing, because the hyoid fails to elevate on the paralyzed side.

The supranuclear innervation of the hypoglossal nucleus is usually bilateral but can be mainly contralateral, so that in some cerebrovascular accidents transient weakness of one side of the tongue may be found. The nerve is

particularly vulnerable to surgical trauma in operations on the submandibular gland and ducts and during carotid endarterectomy.[29] Paralysis following central venous catheterization has also been reported.[30]

THE CERVICAL SYMPATHETIC

Horner's syndrome due to damage to the cervical sympathetic is one of the most frequently missed physical signs in medicine. In the present context, its detection is of vital importance.

The cervical sympathetic originates in the ipsilateral hypothalamus, descends through the entire dorsolateral brainstem to the central grey matter of the cervical spinal cord at TI level (**Figure 111.16**). The sympathetic fibres leave the cord via the ventral root, join the sympathetic chain and ascend through the various ganglia to end as a plexus on the carotid artery, on which they re-enter the intracranial cavity. This ultimately distributes sympathetic fibres to all the cranial nerves innervating the pupil, glands and blood vessels of the head and neck.

The external evidence of Horner's syndrome is said to be fourfold:

1. Enophthalmos is rarely visible and of dubious authenticity.
2. Loss of sweating over the face and forehead is rarely noted, unless specifically tested by warming the patient.
3. Ptosis of the eyelid may be very subtle and somewhat variable, as the nerve endings become sensitized to circulating adrenalin due to denervation hypersensitivity. The lid rarely drops lower than the edge of the pupil.
4. Pupilloconstriction, or more accurately the failure of pupillodilatation, leads to an entirely normally reactive pupil to light and accommodation, but through a smaller range. At rest, the affected pupil is small.

Horner's syndrome may be congenital and this is associated with failure of pigmentation of the iris on the affected side, which remains blue.

The causes of Horner's syndrome are:

- lesions in the dorsolateral brainstem, especially vascular lesions in the medulla, multiple sclerosis at any level or pontine glioma
- lesions in the central cervical cord: syringomyelia, ependymoma, glioma or traumatic damage
- lesions of the TI root: apical carcinoma of the lung, cervical rib, aortic aneurysm or avulsion of the lower brachial plexus
- lesions of the sympathetic chain in the neck: thyroid carcinoma, thyroid surgery, neoplastic lesions, local trauma, accidental surgical damage or surgical extirpation for various vascular syndromes of the arm
- lesions of the carotid plexus: carotid artery surgery, carotid artery thrombosis, migrainous spasm, local neoplastic destruction of the skull base or involvement by aneurysm or malignancy in the region of the carotid siphon or jugular foramen.

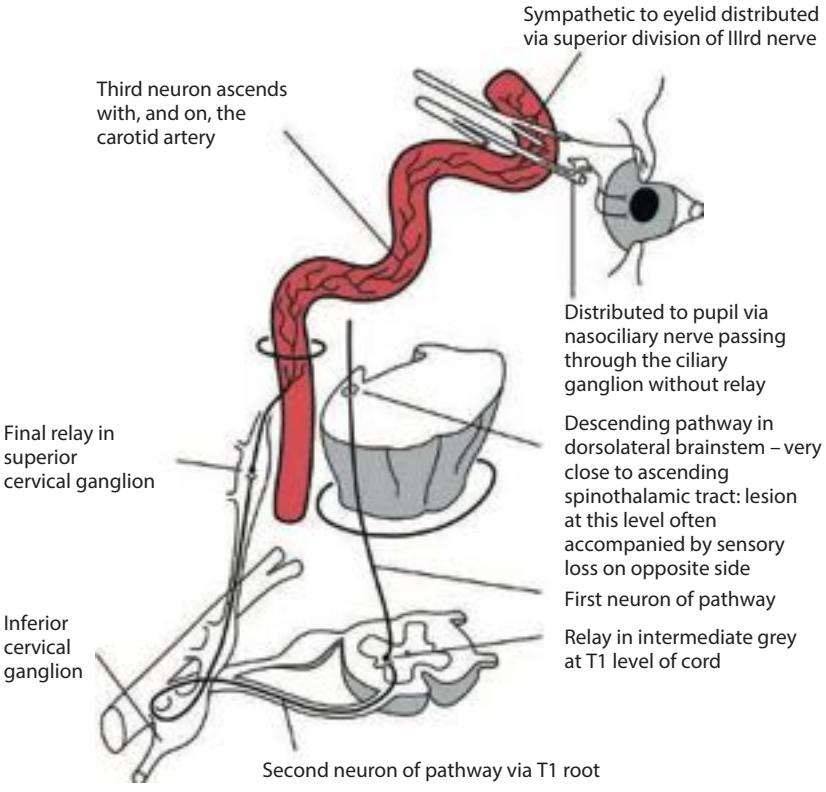


Figure 111.16 Schematic course of the cervical sympathetic nerve.

Clinical evaluation of the last four cranial nerves

Multiple involvement of these nerves is extremely common, so that the symptoms and signs of individual nerve lesions can be difficult to isolate, both from the history and on examination. Disorders of swallowing, speaking, coughing and pain syndromes are the usual presenting symptoms.

A glossopharyngeal nerve lesion will cause impaired taste sensation over the posterior third of the tongue, but this is usually asymptomatic and impossible to test. The loss of somatic sensation over the palate and oropharynx will cause impaired swallowing reflexes as the initial stimulus to deglutition is the arrival of the bolus against the palate. This will lead to occasional choking on food and fluids. Pain in the throat and ear may develop with sensory fibre irritation and then true glossopharyngeal neuralgia may follow. This characteristically will be triggered by swallowing.

Sensation over the palate should be tested by touching the palate with an orange stick and if sensation appears blunted, this can be further explored using a long sharp point. A further check can also be made by touching the posterior pharyngeal wall, while the patient says 'Ah' to elevate the palate.

A vagal nerve lesion at brainstem or jugular foramen level will affect the palate and vocal cords. Unilateral weakness of the palate causes nasal speech and a tendency for food to come back up the nose. Vocal cord paralysis will cause a hoarse, soft voice and prevent explosive coughing. The failure of airway protection when swallowing is initiated, leads to spluttering of food and fluids, with secondary regurgitation through the nasal passages. Pain in the ear may result from irritation of the sensory fibres in the nerve.

In a peripheral recurrent laryngeal nerve lesion, the palate will not be affected, but the voice symptoms will be similar, as will a tendency to choke on fluids. It has also been shown that the external laryngeal nerve with its supplied muscle, cricothyroid, has a greater role in speech than previously realized. Damage causes more severe and lasting speech problems than will result from a recurrent laryngeal nerve lesion.[31]

The integrity of the vagus can be assessed by the patient's voice, ability to cough, direct inspection of the palate and laryngoscopy.

An accessory nerve lesion is really a spinal root lesion, as the cranial part of the nerve is distributed with the vagus. Weakness and wasting of sternocleidomastoid and the upper part of trapezius is readily detected, provided it is carefully sought. Like Horner's syndrome, this is a physical finding that is very easily missed.

A hypoglossal nerve lesion produces paralysis of the intrinsic musculature of the tongue on the supplied side. This causes surprisingly little disability and is often accidentally discovered by the patient or their dentist. Once recognized, some slight difficulty with chewing may then be appreciated by the patient. In an established lesion, on examination at rest, the affected side of the tongue will be shrivelled and fasciculating. On attempted tongue protrusion, the tongue will deviate towards the affected side.

CLINICAL INVOLVEMENT OF IX, X, XI, XII AND CERVICAL SYMPATHETIC NERVES

As the last four cranial nerves lie in close proximity inside the skull and even closer outside the skull (see **Figures 111.13** and **111.14**), multiple involvement is the rule and a variety of named syndromes have been reported. Of immediate practical importance are four major anatomical features:[32]

1. The proximity of the nucleus of nerves IX, X and XI to the spinothalamic tract and descending cervical sympathetic in the brainstem produces a combination of multiple nerve involvement, sparing nerve XII and affecting spinothalamic sensation on the opposite side of the body and associated with an ipsilateral Homer's syndrome. This is seen in Wallenberg's syndrome (dorsolateral medullary infarction).
2. The XIIth nerve lies in a different brainstem vascular territory and the nerve emerges lateral to the pyramid. A vascular lesion of this area will produce a XIIth nerve lesion with contralateral hemiplegia and contralateral impairment of posture, sense and touch. As the nerve exits through a separate foramen, it is often spared by a lesion involving the jugular foramen structures inside the skull.
3. Outside the skull, all four nerves lie so close together that the XIIth nerve is more likely to be involved and is often the first structure affected by lesions infiltrating the area from the oropharynx. Any mass in this region may be palpable.
4. As the cervical sympathetic ascends into the region from below, its involvement (provided there is no evidence of a brainstem lesion, such as a spinothalamic sensory loss on the opposite side) is certain evidence of a lesion external to the jugular foramen.

The named syndromes

Eponymous syndromes have been applied to every conceivable permutation of nerve and tract involvement affecting the last four cranial nerves. Those traditionally accepted are as follows:

- **Vernet's syndrome** (of the internal jugular foramen) is characterized by involvement by nerves IX, X and XI only (an identical syndrome has been attributed to Schmidt).
- **Avellis's syndrome** (of the brainstem) involves only nerve X and the spinothalamic tract (loss of pain and temperature on the opposite side).
- **Tapia's syndrome** involves nerves X and XII. It is difficult to see how this syndrome could occur at either brainstem or peripheral level for anatomical reasons. Presumably this is a chance association.

- **Jackson's syndrome** is characterized by involvement of nerves X, XI and XII. Again it is difficult to see how this combination could develop on any logical basis. Presumably it is also a consequence of a chance combination of peripheral lesions.
- **Collet–Sicard syndrome** (of the posterior lacerocondylar space) is basically the external jugular foramen syndrome involving nerves IX, X, XI and XII, but sparing the cervical sympathetic.
- **Villaret's syndrome** (of the posterior retropharyngeal space). This is involvement of nerves IX, X, XI and XII and the cervical sympathetic and is diagnostic of a complete external jugular foramen syndrome.
- **Wallenberg's syndrome** (infarction of the dorsolateral medulla). This consists of lesions of nerves IX and X, the cervical sympathetic, contralateral spinothalamic loss in the limbs, ipsilateral spinothalamic loss in the limbs, ipsilateral spinothalamic loss over the face and severe vertigo, vomiting and hiccoughs. This is the most classical brainstem vascular syndrome encountered.

Causes (excluding cerebrovascular accidents affecting the brainstem)

- Intracranial lesions:
  - neurinomas of the XIIth nerve, less frequently nerves IX, X and XI, and rarely a vestibular schwannoma may extend down into the internal jugular foramen
  - meningioma of the lateral recess
  - cholesteatoma (particularly likely to affect nerves VII and IX)
  - meningitis (especially malignant or chronic fungal meningitis)
  - fracture of the skull base.
- Extracranial lesions:
  - thrombosis of the jugular bulb
  - metastatic tumour in carotid sheath lymph nodes
  - retropharyngeal abscess or neoplasm
  - carotid body tumour (of the glomus jugulare) may start externally and erode in through the petrous bone or start in the petrous bone and erode out through the skull base.

Clinical symptomatology

The presenting symptoms in these cases may include:

- persistent occipital headache often resembling migraine
- persistent otalgia, which may be worse on swallowing
- hoarse voice, pain in the throat or persistent sore throat
- difficulty in swallowing, choking on fluids or nasal regurgitation.

CT and MRI scanning have revolutionized the investigation of these syndromes. Previously, plain skull films, tomography and carotid angiography were used and often failed to establish a diagnosis. CT scanning will reveal very early evidence of skull base erosion or infiltration by tumour; conversely, MRI scanning can detect even a small neuroma within the jugular foramen – impossible by any other technique.

BULBAR PALSY

The differential diagnosis of lower cranial nerve lesions includes those conditions destroying motor nuclei in the brainstem. Poliomyelitis, previously a common cause, has fortunately become a historical condition, as has diphtheritic bulbar palsy. The most common cause is now bulbar motor neurone disease.

The presenting symptoms consist of a tendency to cough and splutter initially on fluids, but then extending later to include all consistencies of food. Nasal regurgitation and aspiration are common. Speech becomes progressively unintelligible and the patient typically arrives in the clinic clutching a handkerchief to the mouth and a written list of complaints. In the early stages, poor palatal movements, poor tongue movements and weakness of jaw closure and opening may be detected, but the symmetry of involvement may make it difficult to identify mild disability. Fasciculation may be seen in the tongue and facial muscles, or palpated in the masseter. Long tract signs are important and a brisk jaw jerk, increased reflexes and extensor plantar responses would provide strong supporting evidence for the diagnosis.

Myasthenia gravis of the bulbar type is the most important differential diagnosis. Although variability ought to be the hallmark of this disorder, occasionally non-fatiguable and apparently progressive difficulty can produce a confusing picture. This is further compounded by the typical occurrence of bulbar myasthenia gravis in the elderly, the same age group that is liable to develop bulbar motor neurone disease.

PSEUDOBULBAR PALSY

In earlier discussion, the fact that motor cranial nerve nuclei usually have equal, bilateral, upper motor neurone innervation has been emphasized. Only the part of the facial nerve nucleus controlling the lower face shows a major difference in having mainly contralateral supranuclear innervation. Occasionally, both the palate and tongue may be visibly affected by an upper motor neurone lesion, suggesting a variable pattern of supranuclear innervation with mainly contralateral innervation of X and XII in some cases. The accessory nerve is unique in having mainly ipsilateral supranuclear innervation.

The evidence for and the significance of these variations is found in the occurrence of pseudobulbar palsy. This is usually of acute onset consequent upon vascular disease, but is occasionally seen evolving slowly in motor neurone disease and the degenerative condition Steele–Richardson syndrome. These latter conditions produce symmetrical, bilateral, supranuclear degeneration. In vascular disease, a unilateral lesion will usually cause little or no dysfunction of the lower cranial nerves.[33] Occasionally, a patient with a classical, capsular cerebrovascular accident (CVA), in addition to the usual upper motor neurone facial weakness, will demonstrate transient ipsilateral weakness of sternocleidomastoid and upper trapezius and weakness of the palate in the early hours following the onset. Later, a stroke in the opposite internal capsule will acutely deprive

the lower cranial nerves of the residual 50% of their supranuclear innervation. This will result in the instant inability to speak and swallow and is often accompanied by severe emotional lability. In stroke-related disease, these problems will always be of acute onset. In degenerative disease, such as Steele–Richardson syndrome or motor neurone disease of upper motor neurone type, the onset is insidious. In all instances, the end result is pseudobulbar palsy.

EXTRAPYRAMIDAL DISEASE

Fine control of articulation, swallowing and the facial movements associated with speech are achieved by extrapyramidal mechanisms.

PARKINSON'S DISEASE

The loss of spontaneous facial expression and infrequent blinking constitute two of the cardinal features of this disease. In the later stages, hypophonic, tachyphemic speech is characteristic, the short, sharp whispered phrases becoming virtually unintelligible. Chewing food is extremely slowed and the patient may seem to lack the will to initiate swallowing. When one adds the slowness of cutting up and transporting food to the mouth, the cachectic state of a patient with terminal Parkinson's disease is easy to understand. The apparent sialorrhoea of Parkinson's disease actually represents a decreased swallowing rate with a normal production of saliva; it is not due to excessive secretion.

CHOREIFORM SYNDROMES

Choreiform movements of the tongue, palate and mouth conspire to produce spluttering, slurred, explosive speech. This may be seen acutely in Sydenham's chorea as a transient phenomenon or as a severe and progressively disabling problem in Huntington's chorea.

DYSKINETIC SYNDROMES

The so-called buccal–lingual–masticatory syndrome is usually a complication of prolonged neuroleptic therapy, but is also seen in mental subnormality and dementia. In these conditions, the movements do not seem to interfere with speech or swallowing, as the movements subside while speaking and eating. They are mainly a feature at rest.

The oromandibular syndrome (Meige's syndrome) in which slow dystonic opening of the jaw and mouth, in association with tongue protrusion and blepharospasm, is usually seen without neuroleptic provocation. In this condition, attempts to talk and eat aggravate the movements.

Another possibly related dystonic syndrome is spasmodic dysphonia, a disorder characterized by choking of the voice while speaking due to laryngeal spasm, especially on initial vowel sounds. The patient can usually whisper, hum and sing normally. During the choking phase, spasms in the face and neck muscles and blepharospasm may be observed.[34] Treatment with botulinum toxin is a successful form of treatment.

CEREBELLAR DISORDERS

Dysarthria is a feature of generalized cerebellar disease. It typically consists of a slurred, spluttering or scanning type of dysarthria, as breathing mechanisms are desynchronized from speech. It is associated with incoordination of tongue, palatal and facial movements. Inherited cerebellar degenerative disorders and multiple sclerosis are the most common causes, although in the latter condition the disability is often compounded by coexistent spastic dysarthria, producing the typical scanning dysarthria of this disease. Cerebellar neoplasms rarely seem to produce definite speech disturbance.

CONCLUSION

Much clinical material has been included in this chapter to illustrate the functional features of the anatomy and physiology of the cranial nerves in the clinical situation. The coverage is by no means comprehensive. It is hoped that the clinical physiology of cranial nerve function included here will enable the reader to perform a competent clinical examination of cranial nerves in those situations where the symptoms have prompted otolaryngological referral, but have a basis in neurological dysfunction.

KEY POINTS

- Abnormalities of cranial nerve function may be important manifestations of skull base and otological disease.
- A clinical neurological examination is critical in the assessment of patients with skull base pathology.
- In some instances, gross anatomy is of great importance; in others complex central connections require detailed elaboration to illustrate and explain the clinical findings.
- The advent of computed tomography (CT) and magnetic resonance imaging (MRI) has enhanced our ability to unravel suspected diagnoses in what used to be an investigational 'no-man's land'. Scan interpretation requires a very good knowledge of gross anatomy, particularly of the cranial nerves.

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CHAPTER 112

THE FACIAL NERVE AND ITS NON-NEOPLASTIC DISORDERS

Christopher Skilbeck, Susan Standring and Michael Gleeson

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: facial nerve, anatomy, physiology, imaging, Bell's palsy, Ramsay Hunt, trauma, surgery, facial nerve grading system, electrophysiological tests and focusing on diagnosis and management.

INTRODUCTION

Facial palsy is a devastating handicap for our patients and probably the foremost complication that otologic and parotid surgeons fear and try to avoid. Leaving aside the potential medico-legal issues that might flow from a palsy that could have been avoided or the risk of acquiring it reduced, it has a huge negative impact on the quality of life of our patients. In recent years, otologic surgery has expanded into the cerebellopontine angle (CPA) as otologists have worked closer with their neurosurgical colleagues. It is now important that we become more competent and familiar with the management of the facial nerve in the angle as well as the temporal bone and neck. In this chapter, the surgical anatomy of the facial nerve is discussed and demonstrated in fine detail together with the non-neoplastic processes that might affect its function. The management and expected standard of care for patients with facial palsy is detailed including the levels of evidence that underpin current protocols.

SURGICAL ANATOMY OF THE FACIAL NERVE

The facial nerve can be exposed through a number of surgical windows, each of which requires a detailed three-dimensional understanding of the relevant anatomy to avoid causing iatrogenic injury intra-operatively.[1] The nerve contains motor, sensory and parasympathetic axons (Figure 112.1). Cadaveric studies have found that the total number of myelinated axons ranges between 7000 and 9000 in the motor root of the facial nerve and between 3000 and 5000 in the nervus intermedius.[2, 3] Both nerves also contain unmyelinated axons. (For an extensive account of some of the important variations of facial nerve anatomy that have been described in the literature, consult Shoja and Tubbs).[4]

INTRAPARENCHYMAL ELEMENTS, ORGANIZATION AND COURSE

Special visceral/branchial efferent (SVE) motor axons supply muscles derived from the second branchial arch, namely the mimetic facial muscles, buccinator, stapedius, platysma, the posterior belly of digastric and stylohyoid. The axons arise from neurons in the facial nuclear complex in the lateral part of the central tegmentum of the pons just rostral to the pons-medulla transition[5] and run posteromedially through the pons, arching over the abducens nucleus to raise the facial colliculus on the floor of the fourth ventricle (which may be seen in axial MRI sections), before turning anterolaterally to leave the brainstem. Neurons in the face area of the motor cortex (supranuclear neurons) project bilaterally to facial motor neurons that control muscles in the upper face (frontalis, orbicularis oculi) but contralaterally to facial motor neurons that innervate the muscles of the middle and lower face. However, sparing of the forehead in facial paralysis is not necessarily pathognomonic of a central lesion (see 'Physical examination' below). Axons supplying

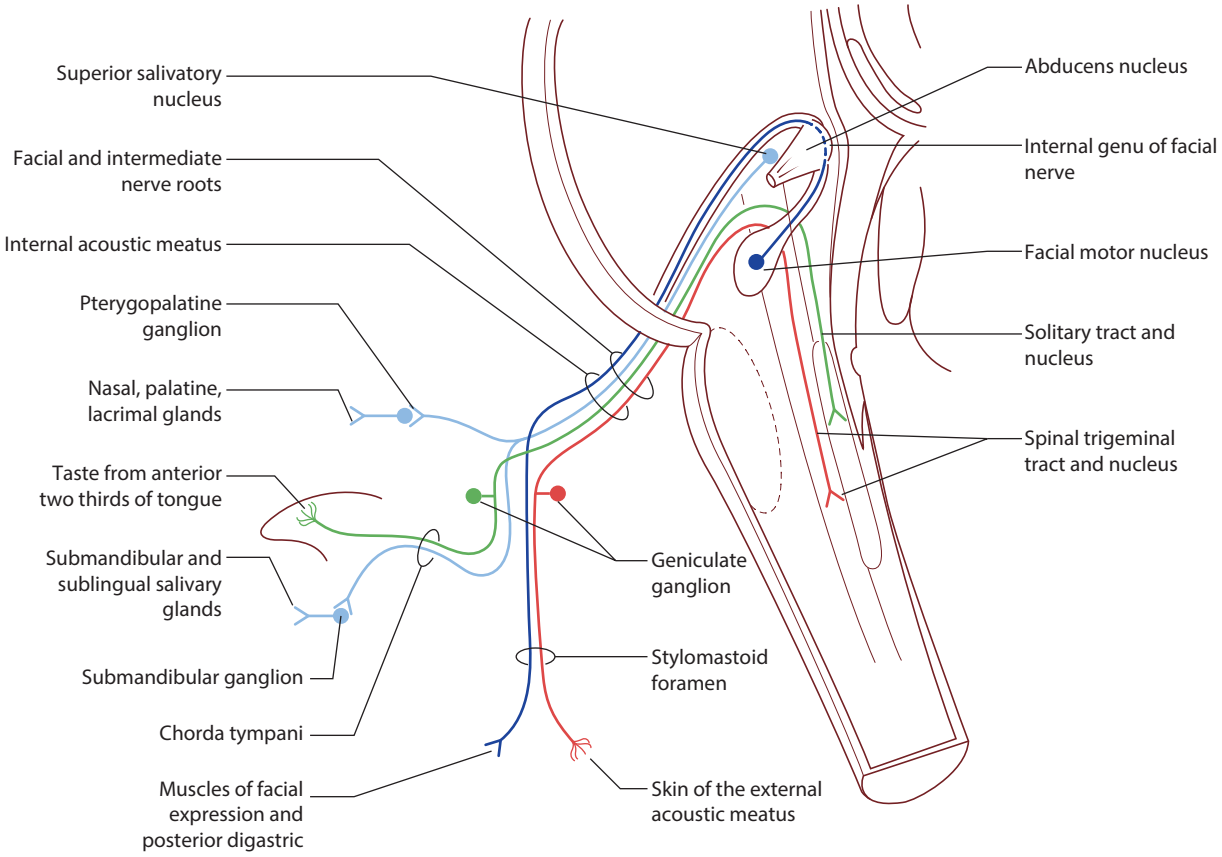


Figure 112.1 GVA axons (nasopharynx, palate, submandibular and sublingual salivary glands) not shown. Cell bodies of origin in the geniculate ganglion, project to more caudal regions of the solitary nucleus. With permission from Haines, D.E. 2013 *Fundamental Neuroscience for Basic and Clinical Applications.*[7]

orbicularis oculi constitute the efferent limb of the corneal reflex. Detailed information about the spatial organization of human stapedial motor neurons is unavailable, but findings in guinea pigs, cats and rats suggest that nerve to stapedius may arise from motor neurons that lie outside the main facial motor nucleus.[6] The stapedial reflex is used to test for topographical assessment of a facial nerve lesion and to assess cochlear function as it is elicited by a sound impulse of threshold + 80 dB.

As they pass through the anterolateral part of the pons the SVE motor axons are joined by general visceral efferent (GVE) preganglionic parasympathetic axons from neurons in the superior salivatory nucleus that will ultimately synapse on postganglionic neurons in either the pterygopalatine ganglion (PPG) or submandibular ganglion.

The facial nerve contains two, possibly three, types of sensory axon. Special visceral afferent (SVA) axons carry taste from the anterior two thirds of the tongue via the chorda tympani. General sensory afferent (GSA) axons carry cutaneous sensation, including pain, from the posterior aspect of the external auditory meatus (EAM),[8, 9] with the caveat that the innervation of this region is complex and largely contributed by Arnold's nerve:[10, 11] these axons are thought to be responsible for coughing during cerumen removal, idiopathic otalgia, Hitselberger's sign[12] and to be the site of vesicular eruptions in Ramsay Hunt syndrome. Several authors have suggested that the nervus intermedius also contains general visceral afferent (GVA) axons mediating pain from the tongue and oropharynx.[13] The evidence appears to be based almost exclusively on Ramsay Hunt's description[14] of the occasional distribution of vesicles on the palate in the region of the anterior pillar of the fauces and on the anterior two-thirds of the tongue in the distribution of the chorda tympani in cases of *herpes zoster oticus*. In 1915, Ramsey Hunt inferred that these clinical findings indicated the *'variable and vestigial intra-oral sensory representation'* of the facial nerve. The craniofacial muscles innervated by the facial nerve typically lack muscle spindles: proprioceptive information from these muscles may be mediated by modified cutaneous mechanoreceptors or capsular corpuscle-like structures within the muscles.[15]

The facial nerve has intra- or extracranial connections with the cutaneous branches of all three divisions of the trigeminal nerve (including branches of the auriculotemporal, buccal, mental, lingual, infraorbital, zygomatic and ophthalmic nerves); with branches of the vestibulocochlear, glossopharyngeal and vagus nerves; and with branches of the cervical plexus (including the great auricular, greater and lesser occipital and transverse cervical nerves). Various functions have been proposed for these connections.[16–18] The cutaneous connections are significant in facilitating the perineural spread of tumours that arise either within the parotid or on the face and explains why some patients

with perineural spread from cutaneous or parotid malignancies may present with vocal cord palsy.[19, 20]

The GVE, SVA, GSA (and GVA) axons form the nervus intermedius (intermediate nerve, nerve of Wrisberg) which was initially described by Heinricus Augustus Wrisberg.[21] The name reflects the fact that the nerve usually lies between the motor root of the facial nerve and the vestibulocochlear nerve as it exits the brainstem (**Figure 112.2**). The axons of the motor root of the facial nerve and the nervus intermedius intermingle within the substance of the pons but emerge separately onto the surface of the brainstem, deep in the pontomedullary sulcus. In a retrosigmoid approach, visualization of the root emerging point is impaired by the lower cranial nerves. The root entry/exit zones (REZ) of the facial nerve and nervus intermedius and the more distal transition zones (Obersteiner–Redlich zones) of these nerves, where central myelin (produced by oligodendrocytes) abuts peripheral myelin (produced by Schwann cells), are both targets in microvascular decompression for hemifacial spasm.[22–24] Surgical landmarks to the REZ on the brainstem are the pontomedullary sulcus; the junction of the glossopharyngeal and vagus nerves with the medulla; the foramen of Luschka and choroid plexus; the cerebellar flocculus (the last three structures are related to the lateral recesses of the fourth ventricle).

The subsequent course of the facial nerve is conventionally divided into intracranial (cisternal), intratemporal and extratemporal portions.

Cisternal portion

The cisternal portion is approximately 24 mm long. The motor root of the facial nerve and the nervus intermedius course anterolaterally through the CPA cistern (pontocerebellar cistern) to the porus of the internal auditory meatus (IAM), accompanied by, and usually anterior to, the cisternal segment of the vestibulocochlear nerve. The nervus intermedius may adhere to the vestibulocochlear nerve for a variable distance.[25] The nerves are ensheathed only by a delicate layer of arachnoid mater: the absence of a more robust connective tissue covering renders them not only extremely vulnerable in CPA tumour surgery but also difficult to identify during dissection of a schwannoma.

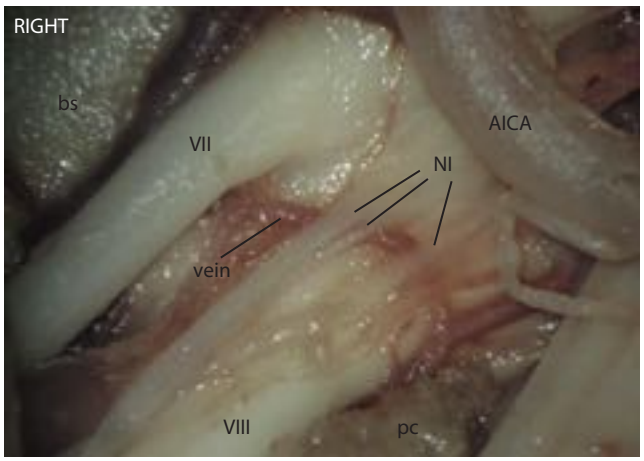


Figure 112.2 Right sided specimen showing the facial nerve (VII), the vestibulocochlear nerve (VIII), the nervus intermedius (NI), and a vein between cranial nerves VII and VIII. In this case, the NI (three bundles) arises separately from the brain stem (bs). The choroid plexus (pc) is located antero-inferiorly to the VII at the entry of the foramen of Luschka. From Alfieri et al. with permission.[22]

Intratemporal portion

The intratemporal portion is 28–30 mm long and subdivided into meatal, labyrinthine, tympanic (horizontal) and mastoid (vertical) segments. The meatal segment runs in the IAM; the labyrinthine segment runs laterally to the geniculum (first turn or genu) and the geniculate ganglion; the tympanic segment runs backwards from the geniculate ganglion to the second genu; the vertical segment runs from the second genu to the stylomastoid foramen; the extratemporal segment runs forwards into the parotid gland where it usually divides into temporofacial and cervicofacial branches. The first three segments do not display any obvious fascicular organization, which may explain why a very selective partial lesion in this part of the nerve is likely to produce a slight overall paresis of the face and also why regeneration following injury usually results in some degree of synkinesis (reinnervation of inappropriate facial muscle groups by regenerating facial axons). These proximal segments are invested by arachnoid mater but lack epineurial and perineurial sheaths, rendering suture technically challenging if not contra-indicated in favour of glue. Arachnoid cysts have been reported within the IAM and facial nerve canal, where they may compress adjacent nerves.[26] Discernible fascicles defined by perifascicular, interfascicular and intrafascicular connective tissue only appear distal to the geniculate ganglion. The number of fascicles increases proximodistally as axons are progressively segregated into specific named nerves. Although the spatial relationship of the fascicles is highly variable,[3] a very selective partial lesion affecting the lower part of the mastoid segment will produce total paralysis of the denervated muscles.

MEATAL SEGMENT

The meatal segment is 5–12 mm long. The motor root of the facial nerve and the nervus intermedius run through the IAM from its porus (medial) to its fundus (lateral wall), accompanied by the cochlear nerve and the superior and inferior vestibular nerves and the labyrinthine artery (**Figure 112.3**). The bundles that make up the nervus intermedius join the facial nerve within the IAM, typically 3 mm from the porus.[22] Different degrees of rotation between the facial and vestibulocochlear nerves have been reported within the IAM.[27] The components of the vestibulocochlear nerve rotate 90 degrees as they travel from the brainstem to the inner ear. The facial nerve remains anterior in its course to the porus acusticus and within the IAM and so lies anterior to the superior vestibular nerve in the lateral end of the meatus.[1] On cross-section, the fundus is divided into four quadrants. It is divided horizontally by a thin bony septum, the crista falciformis (transverse septum) and vertically into anterior and posterior compartments above the crista

by an important bony landmark, Bill's bar (named after **William Fouts House**). The motor root of the facial nerve and the nervus intermedius lie anterior to Bill's bar in the anterior superior quadrant; the superior vestibular nerve lies posterior to Bill's bar in the posterior superior quadrant; the cochlear nerve and inferior vestibular nerve lie below the crista, the cochlear nerve lying anterior to the inferior vestibular nerve (**Figure 112.3**). The close anatomical relationship between the motor root of the facial nerve, nervus intermedius and vestibulocochlear nerve along their cisternal and meatal portions explains the disturbances in lacrimation, taste, salivary flow, hearing, balance or facial motor control that may result from lesions in either the CPA or IAM.

LABYRINTHINE SEGMENT

The labyrinthine segment is the shortest (3–5 mm) and narrowest part of the facial nerve (average diameter of 0.68 mm). It is the only segment of the facial nerve that lacks anastomosing arterial cascades and so is vulnerable to embolic phenomena, low-flow states and vascular

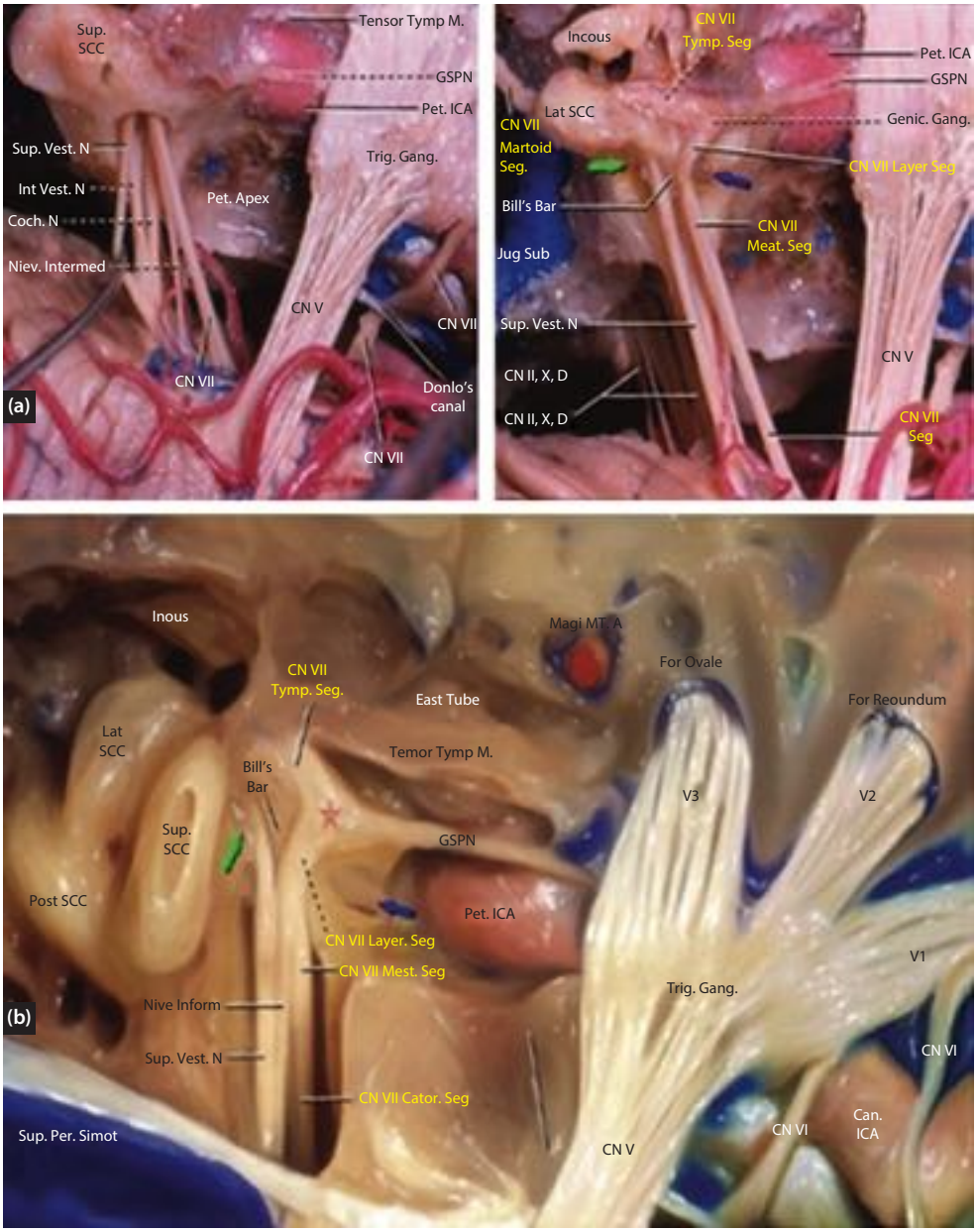


Figure 112.3 When operating using the middle fossa approach, the facial nerve runs laterally, anterior to the superior vestibular nerve and parallel to it within the IAM. This relationship is maintained in a translabyrinthine approach where the facial nerve is found to lie anterior to the superior vestibular nerve and covered by it from the surgeon's perspective, parallel to the cochlear nerve. A significantly different relationship may be encountered in vestibular schwannoma surgery as a result of displacement by tumour. However, it would normally allow the recognition of such a relationship at the level of the fundus when Bill's bar and the crista falciformis become readily identifiable. From Tanriover et al. with permission.[28]

compression: it is most likely to be affected by ischaemia in the event of oedema following trauma or inflammation.

At the distal end of the labyrinthine segment, the geniculate ganglion forms part of a sharp 'hairpin' turn, the geniculum or first genu of the facial nerve, that marks the start of the tympanic segment. At the geniculum, the nerve is cradled by the superior semicircular canal posteriorly and the cochlea anteriorly and inferiorly (**Figure 112.4**). The nerve may be accompanied by the subarachnoid space as far as the geniculate ganglion.[18]

The geniculate ganglion is a sensory ganglion: it does not contain synapses. The central processes of the GSA neurons in the geniculate ganglion carry pain from the EAM and terminate somatotopically in the spinal tract nucleus of V. The central processes of the SVA neurons in the geniculate ganglion that carry taste from the anterior two thirds of the tongue via the chorda tympani terminate somatotopically on second order neurons in the gustatory nucleus (rostral end of the solitary tract) (see **Figure 112.1**). The chorda tympani is thought to modulate trigeminal and glossopharyngeal sensitivity.[29, 30]

Preganglionic parasympathetic axons destined to synapse on postganglionic neurons in either the PPG or submandibular ganglia pass through the geniculate ganglion without synapsing. Those destined for the PPG form the greater petrosal nerve (formerly termed greater superficial petrosal nerve), the first branch of the facial nerve.

The greater petrosal nerve is an important landmark in directing operative approaches through the middle cranial fossa (MCF) to the IAM, petrous apex, trigeminal nerve and petrous portion of the ICA (**Figure 112. 4**).[28, 31] It runs anteriorly and medially from the geniculate ganglion, receives a branch from the tympanic plexus and traverses a hiatus on the anterior surface of the petrous part of the temporal bone to enter the middle cranial fossa, where it runs forwards in a groove on the bone above the lesser petrosal nerve and then passes beneath the trigeminal ganglion to reach the foramen lacerum. Here it is joined by the deep petrosal nerve (which carries postganglionic sympathetic axons from the internal carotid sympathetic plexus), to become the nerve of the pterygoid canal (Vidian nerve) destined for the PPG. Axons travelling in the nervus intermedius pass to the lesser petrosal nerve in the region of the geniculate ganglion. Contrary to their depiction in most anatomical texts, the greater and lesser petrosal nerves are not parallel but usually diverge in the area medial to the geniculate ganglion.[32]

The geniculate ganglion lies in a fossa covered by a very thin layer of bone that separates it from the floor of the MCF. Dehiscences here are not uncommon: when present they render the nerve vulnerable during middle fossa surgery and bring it into direct contact with the meninges. The geniculate ganglion may be injured by bone spicules or directly contused by a shock wave: an enlarged fossa on temporal bone CT strengthens a diagnosis of geniculate ganglion fossa (GGF) fracture in patients with traumatic facial paralysis.[33]

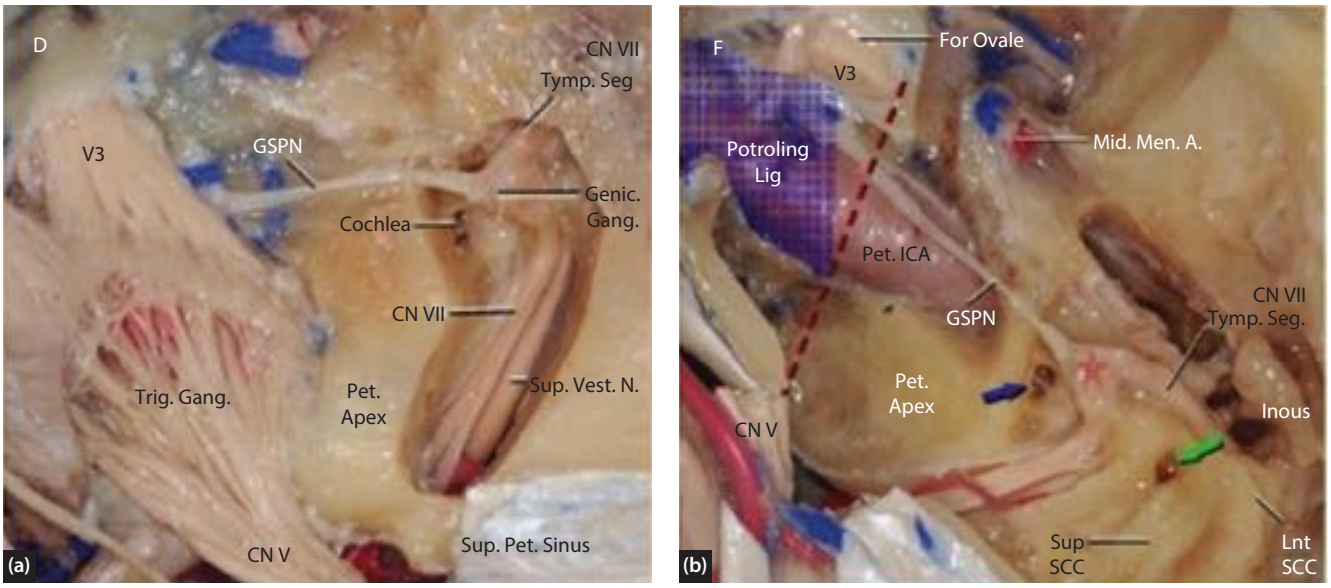


Figure 112.4 **(a)** The superior vestibular and the facial nerves have been exposed within the IAM along with the geniculate ganglion and the cochlea. The cochlea lies below the floor of the middle fossa in the angle between the labyrinthine segment of the facial nerve and the GSPN. The posterior border of the cochlea is the fundus of the IAM, and, posterolaterally, it is related to the geniculate ganglion. The cochlea should not be violated during the exposure of the lateral part of the IAM to preserve the hearing during a middle fossa approach. The bone over the tympanic segment of the facial nerve distal to the geniculate ganglion has been removed. **(b)** The trigeminal nerve has been sectioned to expose the full course of the GSPN and the petrous ICA. The interrupted red line corresponds to the posterolateral limit of the V_3 and the GSPN passes 1.7 cm from this point to the geniculate ganglion (marked with a red star). The cochlea (marked with a blue arrow) and the vestibule (marked with a green arrow) are the main structures to be preserved during the middle fossa approach. The petrous segment of the ICA passes under the petrolingual ligament to enter the cavernous sinus. The petrolingual ligament has been removed; however, the approximate position has been shown in the blue area. From Tanriover et al. with permission.[28]

During a translabyrinthine approach the labyrinthine segment is at risk while drilling along the superior semicircular canal. The ampullated ends of the superior and the lateral semicircular canals (the 'cat's eyes') should be identified; the facial nerve lies just anterior to this area. The labyrinthine segment is the part of the facial nerve that is most likely to be injured in temporal bone fractures, when it is likely to be compressed by bony fragments.

TYMPANIC SEGMENT

The tympanic segment is 8–11 mm long. It runs the length of the superior edge of the medial wall of the tympanic cavity, perpendicular to the long axis of the petrous part of the temporal bone, taking a posterior path that inclines downwards and laterally from the geniculate ganglion to the second genu at the level of the pyramidal eminence.[34] Proximally it passes just above and medial to the posterior edge of the cochleariform process and the tendon of tensor tympani. The cochleariform process is a consistent landmark, when other landmarks are obscured or have been destroyed by pathology. More distally the nerve lies above the oval window niche, just anterior and inferior to the prominence of the lateral (horizontal) semicircular canal before bending at the second genu to enter the bony mass of the styloid complex. The second genu hugs the inferior aspect of the lateral semicircular canal; this relationship is extremely constant. The pyramidal eminence is a useful landmark for the second genu. The retrotympanum contains several small sinuses around the facial canal: the sinus tympani lies medial and anterior to the canal and the facial and lateral tympanic sinuses lie lateral and posterior to the canal.[35–37] The distal aspect of the tympanic segment can be located surgically via a facial recess approach. The chorda tympani nerve and the fossa incudis can be used to identify the nerve when performing a facial recess approach. The second genu of the facial nerve runs inferolateral to the lateral semicircular canal (a relatively constant relationship). The posterior semicircular canal lies just posterior to the second genu: it also marks the superior end of the retrofacial air cells, which are helpful in delineating the medial aspect of the facial canal (**Figure 112.5**).

Developmental dehiscences are not uncommon at this level, making the nerve vulnerable during middle ear surgery, especially around the oval niche.[38–43] A dehiscent or prolapsed facial nerve should always be anticipated in the tympanic segment, especially in patients with congenital ear deformities. The tympanic segment is vulnerable to traction along its axis in longitudinal fractures of the temporal bone.

MASTOID SEGMENT

The mastoid (vertical) segment is the longest of the petrous segments (10–14 mm). It runs vertically downwards in the posterior wall of the tympanic cavity and the anterior wall of the mastoid, from the second genu just distal to the pyramidal process to the stylomastoid foramen on the base of the skull. The digastric ridge (seen on well-pneumatized bones as the medial aspect of the mastoid tip) points to the lateral and inferior aspect of the mastoid segment: a line drawn between the anterior end of the digastric ridge and the tip of the short process of the incus marks the path of the mastoid segment. The nerve may be identified by removing the mastoid tip, skeletonizing the digastric ridge and outlining the inferior part of the vertical segment of the nerve. This is particularly helpful when the extracranial trunk of a functioning nerve is encased in benign tumour recurrences at the stylomastoid foramen.

The nerve travels from the second genu posteromedially to the stylomastoid foramen anterolaterally, which means that expanding a posterior tympanotomy inferiorly in the same plane as it was fashioned could risk injury to the facial nerve. The plane of the facial nerve is almost always lateral to the level of the tympanic anulus, but it may cross it, or lie medial to it in its lower half.[44] The nerve may be damaged when elevating the tympanic anulus or when lowering the mastoid ridge overlying the nerve, as in a modified or radical mastoidectomy.

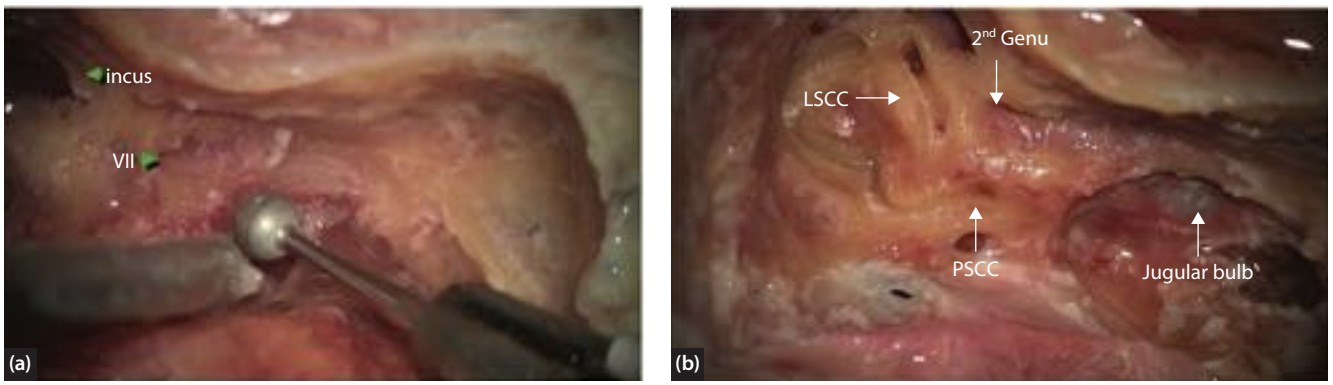


Figure 112.5 **(a)** Right-sided cadaver dissection of the temporal bone. The facial nerve has been exposed in the mastoid segment along an imaginary line from the anterior part of the digastric ridge to the tip of the short process of the incus in the mastoid antrum. **(b)** The semi-circular canals have been skeletonized and opened to demonstrate the relationship of the posterior canal to the second genu (arrowed). If the remaining bone is removed inferior to the lateral semicircular canal, there would be good access to the posterior part of the tympanic segment of the facial nerve.

Most commonly, iatrogenic injury is caused by failure to identify the mastoid antrum properly or being impeded by an overhanging tegmen. It should be remembered that the positions of both the tympanic anulus and the mastoid segment of the facial nerve change during childhood.[45]

The mastoid segment of the facial nerve has three branches, namely the nerve to stapedius muscle, the chorda tympani and the sensory auricular branch. The nerve to stapedius is a small twig given off behind the pyramidal eminence that passes forwards through a small canal to reach the muscle. The chorda tympani is usually given off approximately 5 mm proximal to the stylomastoid foramen and runs anterosuperiorly in a canal to enter the tympanic cavity via the posterior canaliculus. It then curves anteriorly across the pars flaccida of the tympanic membrane between its mucous and fibrous layers, adjacent to the posterior and anterior mucosal folds of the malleus, medial to the upper part of the handle or neck of the malleus and above the insertion of tensor tympani, lateral to the long process of the incus, to reach the anterior wall of the tympanic cavity, where it enters the anterior canaliculus (canal of Huguier) within the medial part of the petrotympanic fissure.[46] Upon exiting the skull at the petrotympanic fissure, the chorda tympani enters the infratemporal fossa where it joins the lingual nerve. A small branch communicates with the otic ganglion. The chorda tympani carries axons mediating taste from the anterior two thirds of the tongue and preganglionic parasympathetic axons that will synapse on postganglionic neurons in the submandibular ganglion. The nerve is a commonly used landmark when performing posterior tympanotomy and serves as the lateral margin of the facial recess. It is sometimes used as the medial limit of lowering the facial ridge when performing a canal wall down technique. Occasionally the chorda tympani may arise extratemporally.[47]

The facial nerve is usually surrounded by thick fibrous tissue at the styolomastoid foramen: to avoid irrevocable damage during anterior transposition of the nerve it is advisable to lift the segment *en bloc* together with fibres of the posterior belly of digastric and slivers of bone around the foramen. On leaving the stylomastoid foramen, the facial nerve initially lies below the tympanic plate, lateral to the bases of the styloid process and the carotid sheath and posterior to the parotid gland. It immediately gives off the posterior auricular nerve which passes upwards behind the ear between the parotid gland and the anterior border of sternocleidomastoid and then in the notch between the EAM and the mastoid process to supply the occipital belly of occipitofrontalis, auricularis superior and the intrinsic auricular muscles. A second muscular branch divides to supply the posterior belly of digastric and the stylohyoid muscle.

EXTRACRANIAL SEGMENT

The main trunk of the extracranial facial nerve enters the parotid gland high up on its posteromedial surface and passes forwards and downwards behind the mandibular ramus. It divides within the gland, usually just behind and superficial to the retromandibular vein and external carotid artery (ECA) into an upper temporofacial trunk and a lower cervicofacial trunk. The relationship between the nerve and vein may vary.[48, 49] In cadaveric studies of adult heads, the length of the facial nerve trunk from stylomastoid foramen to the initial intraparotid bifurcation has been found to range between 8 mm and 22 mm.[50]

The temporofacial trunk contains more axons but fewer fascicles than the cervicofacial trunk.[3] The trunks branch further to form a parotid plexus (pes anserinus) from which five main terminal branches, temporal, zygomatic, buccal, marginal mandibular and cervical, ultimately emerge. These branches diverge within the substance of the parotid and leave the gland via its anteromedial surface, medial to its anterior margin. Numerous microdissection studies have demonstrated considerable individual variations in branching patterns and anastomoses between branches, both within the parotid and on the face.[51–55] While there is no evidence to suggest that a particular classification pattern is associated with increased risk of surgical complications, it is reasonable to assume that nerves that are truly plexiform sustain surgical injury better than those that are not, since accidental division or deliberate sacrifice of a small branch in a plexiform nerve is rarely accompanied by a significant or noticeable facial weakness. While the subsequent distribution of the branches of the facial nerve on the face is variable they retain a relatively constant relationship to soft tissue planes.[4, 56]

Facial nerve injury is the most significant complication of parotidectomy.[57] In addition to intra-operative functional nerve monitoring, a number of landmarks are commonly used to identify the facial nerve trunk during surgical procedures. They include the tragal pointer, the posterior belly of digastric muscle, the junction of the bony and cartilaginous portions of the ear canal, the transverse process of the axis and the tympanomastoid suture. The main trunk of the facial nerve usually lies 1 cm medial and inferior to the tragal pointer (the medial aspect of the tragus which points inward, forming the anterior and inferior wall of the EAM). The trunk can also be identified 6–8 mm below the inferior 'drop off' of the tympanomastoid fissure or by retrograde dissection along the posterior belly of the digastric muscle towards its insertion into the mastoid process: the main trunk bisects the angle between the upper border of the muscle and the EAM. In spite of numerous cadaveric studies there is no general consensus as to which of these landmarks is the most consistent.[58, 59] Landmarks for retrograde parotidectomy, undertaken when the landmarks used in anterograde parotidectomy are not easily accessible intra-operatively, will vary according to which peripheral branch of the facial nerve is being followed retrogradely. The retromandibular vein is a commonly used landmark for the marginal mandibular branch of the facial nerve.[60] The marginal mandibular nerve may also be identified by following the facial vein proximally within the parotid tissue, where the nerve crosses lateral

to the vein. The buccal branch runs parallel and 1 cm below the zygomatic arch and often along the inferior aspect of the parotid duct.

The anatomical course of the facial nerve is subject to variations and anomalies. Because the facial nerve is the nerve of the second branchial arch, any malformations in the derivatives of Reichert's cartilage should raise suspicion of possible anomalies. Otolaryngologists should be cautious when exploring patients with external ear malformations, congenital conductive hearing loss and craniofacial anomalies.

BLOOD SUPPLY OF THE FACIAL NERVE

The arterial supply of the segments of the facial nerve is derived from branches of the vertebrobasilar and ECA systems (**Figure 112.6**).[61, 62] The labyrinthine artery (internal auditory artery) supplies the cisternal, meatal and labyrinthine segments. It usually arises directly from the AICA as it loops between the cisternal segments of the motor root of the facial nerve, the nervus intermedius and the vestibulocochlear nerves, projecting towards and often into the IAM, but it may arise from the basilar, vertebral or superior cerebellar arteries.[63] The greater petrosal nerve is supplied by the petrosal branch of the middle meningeal artery which usually passes through the bone enclosing the geniculate ganglion and tympanic segment of the nerve, less commonly it passes through the hiatus of the greater petrosal nerve: the vessel and nerve are at risk during procedures where the dura is elevated from the floor of the MCF.[64] The tympanic and mastoid segments are supplied by the facial arch, an anastomotic network formed by the superficial petrosal branch of the middle meningeal artery and the stylomastoid branch of either the occipital or posterior auricular arteries, which enters the facial canal via the stylomastoid foramen. The lowest branch from the stylomastoid artery to the facial nerve is given off at the level of the origin of the chorda tympani: collaterals of the stylomastoid artery supply the chorda tympani. Branches from the facial arch anastomose with vessels supplying the bone marrow of the facial canal and with anterior and superior tympanic branches of the maxillary artery, the posterior tympanic branch of the posterior auricular artery, and the inferior tympanic branch of the ascending pharyngeal artery.[65] The posterior auricular and occipital arteries and their branches, including the stylomastoid artery, supply the facial nerve from the stylomastoid foramen to the parotid gland. The temporofacial and cervicofacial branches that exit the parotid gland are supplied by collaterals of the superficial temporal, transverse facial, facial and maxillary arteries.

The labyrinthine portion is supplied exclusively by meatal arteries and therefore more likely to suffer from ischaemic damage than the other segments. That said, any part of the intratemporal portion of the nerve that becomes oedematous is susceptible to compression and subsequent ischaemic damage. Vascular lesions causing pulsatile compression of sensory axons likely produce neuralgia, whereas compression of motor axons will produce hemifacial spasm.

PATHOPHYSIOLOGY OF NERVE INJURY

Peripheral nerves (cranial and spinal) may be injured in a variety of ways, broadly classified as local (trauma, whether blunt or penetrating; compression: chronic traction or acute stretch; local chemical or freeze injury) or systemic (immune-mediated inflammation; diabetes

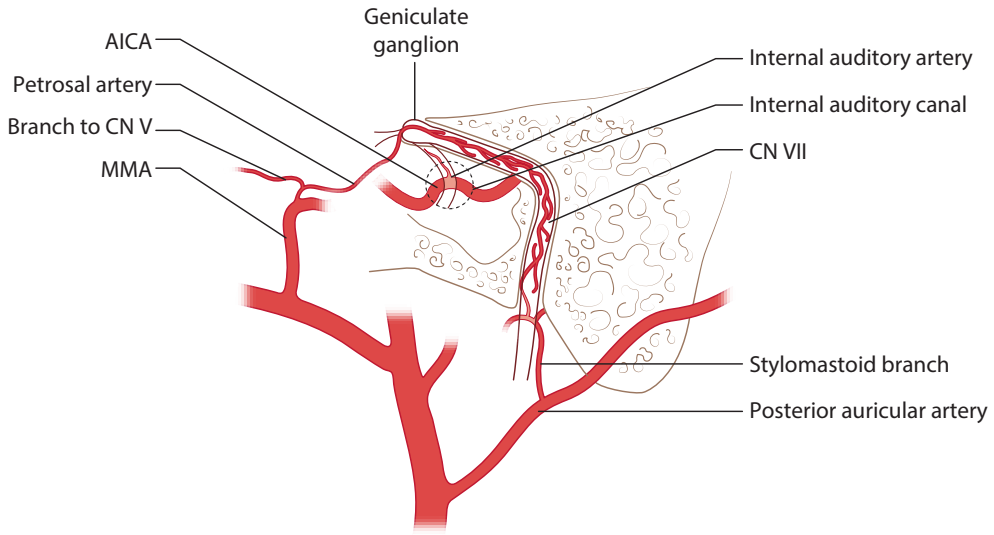


Figure 112.6 The tympanic and mastoid segments of the facial nerve are supplied by the facial arch formed by the petrosal branch of the middle meningeal artery (MMA) and the stylomastoid branch of the posterior auricular artery. AICA, anterior inferior cerebellar artery; CN, cranial nerve. Redrawn from Chen et al.[66]

mellitus; vasculitis; drug-induced). Ischaemia induced by mild pressure may produce transient paraesthesia but no obvious structural changes, recovery is usually rapid and surgical intervention is not required. Prolonged ischaemia or immune-mediated attack may cause specific loss of myelin (primary or segmental demyelination) without loss of axonal integrity, resulting in an increased refractory period of transmission and conduction slowing, followed by conduction block. If the causative agent, such as a spicule of bone or a haematoma, is removed, remyelination typically takes place within 2–4 months, usually with little residual loss of function; surgical intervention is not required. In marked contrast, any injury that physically separates axons from their neuronal cell bodies triggers a programme of molecular and cellular events at the site of the lesion and in distant parts of the injured neurons and their target organs that has a significant impact on outcome. Therapeutic intervention cannot (yet) manipulate responses that happen many centimetres from the injury and that may influence functional outcome months or even years later. Centrally, nerve injury induces reprogramming of synaptic connectivity in the cortex and spinal cord as well as responses in affected sensory ganglia that may mediate the development and maintenance of chronic neuropathic pain. Variable numbers of neurons will die when injury isolates them from their supply of retrogradely transported neurotrophins, particularly if the insult is close to the neuronal cell body. Peripherally, atrophy of chronically denervated sensory end organs and muscles may preclude their reinnervation. (The term 'Wallerian degeneration' refers specifically to the process of degeneration that takes place along a nerve distal to an injury and is named after Augustus Waller: in a seminal report read to the Royal Society of London on February 21, 1850. Waller summarized the degeneration that would come to bear his name, describing the gradual disintegration of the glossopharyngeal or hypoglossal nerves of frogs after axotomy).

The microenvironment of an acutely denervated distal stump facilitates axonal regrowth because it provides a vascularized segment of longitudinally orientated, laminin-rich basal lamina tubes filled with axon-responsive Schwann cells (**Figure 112.7**).[67] However, axonal regrowth is frustrated over time by progressive endoneurial fibrosis and Schwann cell senescence.[68–70] The cardiologists' aphorism 'time is muscle' applies equally to the consequences of delaying nerve repair too long. Early nerve repair results in improved functional outcomes.[71, 72] Surgical intervention, whether direct coaptation of stumps by gluing or suturing; or bridging a long inter-stump gap by either grafting a segment of nerve (end-to-end or end-to-side) or some form of tissue-engineered device; or by nerve transfer, may be required to enable regrowing axons to encounter and interact with Schwann cells. The mitigation of endoneurial fibrosis, muscle and sensory end organ atrophy and Schwann cell senescence remain key clinical challenges.[73]

Based on his wide experience of traumatic nerve injuries, Sir Herbert Seddon distinguished between three types of localized injuries to peripheral nerves and

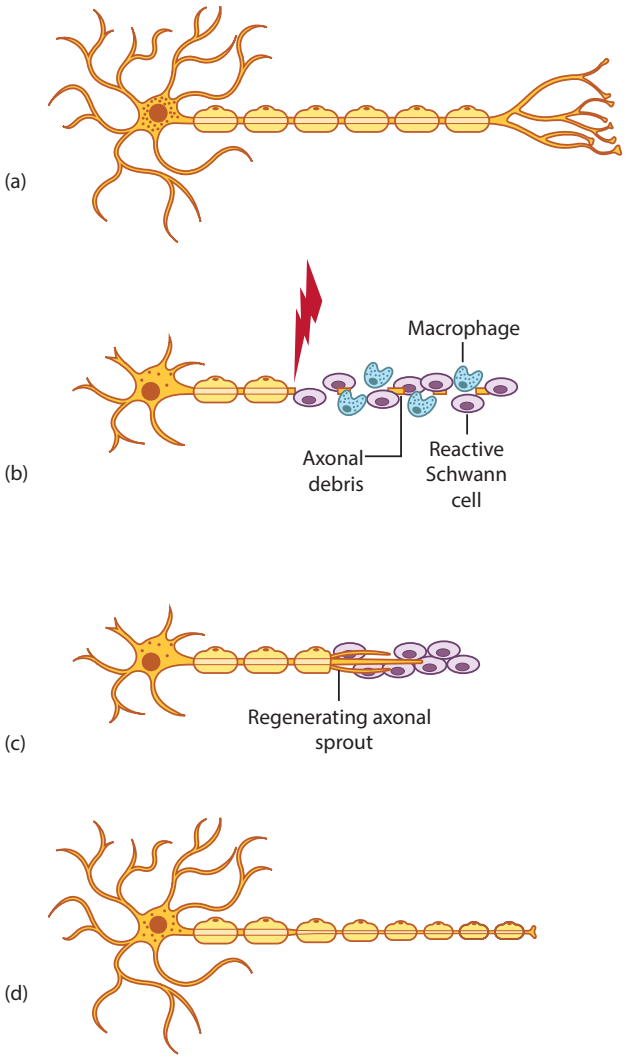


Figure 112.7 **(a)** Normal neuron and nerve fibre. **(b)** Wallerian degeneration. Axotomy results in fragmentation of the distal axon and myelin sheaths. Schwann cells proliferate and macrophages invade the distal nerve segment and phagocytose degrading materials. **(c)** Schwann cells in the distal segment line up in bands of Büngner. Axonal sprouts advance embedded in the Schwann cells and attracted by gradients of neurotrophic factors. **(d)** Axonal reconnection with end organs and maturation and remyelination of the nerve fibre. Re-drawn from Allodi I, Udina E, Navarro X.[67]

introduced the terms neurapraxia, axonotmesis and neurotmesis to describe them.[74] Neurapraxia occurs when compression or stretch produces an anoxic, physiological block of both axoplasmic transport and ion channel functions along affected axons: loss of function is usually temporary and release of the compressive agent usually results in rapid and complete recovery of function and relief of pain. Compression or traction resulting in prolonged ischaemia produces demyelination. Birch[72] points out that … '*the term neurapraxia is best reserved for those situations where electrodiagnosis has conclusively shown that demyelinating conduction block is solely responsible for the neural lesion.*' Axonotmesis occurs when a blunt injury to a nerve results in Wallerian

degeneration distal to the injury, but the connective tissue layers (epi-, peri- and endo-neurium) remain intact. Conduction ceases throughout the distal extent of the nerve within a few days of injury. With the caveat that the distance from injury site to end organ(s) may ultimately defeat successful reinnervation, there is no *a priori* reason why regrowing axon sprouts should not extend to their appropriate targets within the Schwann cell tubes that housed their parent axons: if their progress is unimpeded, recovery progresses proximo-distally (as judged by an advancing Tinel's sign) at a rate of ~1 mm/day. It must be appreciated that even when an axon reaches its target organ, subsequent reinnervation of that target is neither guaranteed nor is it synonymous with full functional recovery. Neurotmesis occurs when a nerve is either completely divided or so badly disorganized by injury that recovery without some form of surgical intervention is impossible. All the connective tissue layers of the nerve as well as the axons are disrupted at the site of injury: a wide inter-stump gap may be produced either by the injury or during subsequent intra-operative wound debridement.

Spontaneous axonal regeneration following this type of injury will be imperfect and disorderly, and may not occur at all. Distance is a significant factor in recovery, particularly after proximal injuries in limb nerves, because regrowing axons may fail to reach their target organs before the latter disappear. Changes in fibre type and loss of striated muscle mass begin within days after denervation; up to 80% of muscle volume may be lost by 4 months and irreversible muscle fibrosis and fatty infiltration occurs after 2 years.[75–77] Some reconstructive surgeons regard functional reinnervation as unlikely beyond 12–18 months. Even after repair, muscles usually exhibit weakness, impaired coordination and reduced stamina; regeneration of the largest diameter axons and coactivation of α and γ efferents may fail. Cutaneous sensory receptors undergo a slow degenerative change after denervation and may disappear after 3 years. Their reinnervation tends to reverse these changes, particularly if the injury occurs close to the end organs and the nerves involved are sensory, however, the longer the period of denervation, the less complete will be the regeneration. Attempts to increase the rate of axonal regrowth in various experimental animal models remain disappointing.

Sir Sydney Sunderland amplified Seddon's category of axonotmesis to describe progressively more invasive levels of injury to the endoneurial contents, perineurium and epineurium, respectively, correlating these new levels with more accurate prognoses of outcomes in axonotmesis injuries.[78] Recovery is typically complete after Sunderland's grade 1 (equivalent to neurapraxia) and 2 (axonal degeneration with intact endoneurium) injuries; grade 3 injuries recover partially; grades 4 and 5 (equivalent to neurotmesis) usually require surgical intervention (**Table 112.1**). Depending upon the level of tissue disruption, misdirection of regrowing axons into modality-inappropriate Schwann tubes in the distal stump is inevitable (For a review of the molecular mechanisms that have been implicated in axonal pathfinding after injury refer to the biology of chronically denervated Schwann cells).[67, 68] Regrowing axons and their associated Schwann cells may form a mechanosensitive neuroma at the end of a proximal nerve stump or a neuroma – in-continuity with the distal stump, phenomena that also compromise recovery. In 1988, MacKinnon

TABLE 112.1 Nerve injury classification and electrophysiological correlates (modified from Birch, 2011)[72]

Seddon	Sunderland	Pathology	Electrophysiological correlate
Neurapraxia	Grade 1	A transient light compression causing endoneurial oedema but no significant morphological changes. A more substantial and prolonged mechanical compression or stretch is most likely to cause a focal demyelination that may be paranodal or affect whole internodes. Anoxia plays a role in the pathogenesis	Conduction block ± conduction slowing. Nerve distal to 'lesion' shows normal conduction
Axonotmesis	Grade 2	Axons degenerate distal to the site of the lesion, irrespective of calibre or modality Endoneurium, perineurium and epineurium remain intact. Schwann cell basal lamina tubes either remain continuous across the lesion or are minimally separated within a morphologically intact perineurium and epineurium	Fibrillation Mild diminution to complete absence of SNAP and CMAP responses, in proportion to degree of axonal loss ± varying degrees of conduction block and slowing associated with demyelination
Axonotmesis	Grade 3	Endoneurium disrupted, axons degenerate distal to the site of the lesion	Fibrillations, absent SNAP and CMAP responses
Axonotmesis	Grade 4	Perineurium disrupted, axons degenerate distal to the site of the lesion	Fibrillations, absent SNAP and CMAP responses
Neurotmesis	Grade 5	Epineurium disrupted, axons degenerate distal to the site of the lesion	Fibrillations, absent SNAP and CMAP responses

'Mixed' is an additional category that combines Grades 2–4 to produce a classification that better represents common clinical scenarios (Mackinnon and Dellon, 1988).[79] SNAP, sensory nerve action potential; CMAP, compound muscle action potential.

and Dellon[79] added a Grade VI injury to Sunderland's classification to better reflect the common clinical scenario of a mixture of crush and transection injury occurring within a damaged nerve. Their classification resonates with an earlier comment by Bowden and Gutmann[75] that … '*In some cases of lesions in continuity there is a mixture of neurotmesis and axonotmesis and if there is much intraneural disturbance, the quality of spontaneous recovery may be poor.*'

The distinction between cases of conduction block (non-degenerative lesions) and those causing axon degeneration is important in prognosis. However, this can be difficult to diagnose early after an injury because Wallerian degeneration usually takes place over several days following injury which means that distal nerve excitability is usually maintained for several days. This timescale has implications on the timing of electrical testing of an injured nerve (see 'Electroneuronography (ENog)' below). In 2016, Hems summed it up well: '*The most important issue is the difference between lesions where the nerve is in-continuity (neurapraxia and axonotmesis) and those where recovery will not occur without surgical repair (neurotmesis).*[80]

Other than a sharp transection, most other injuries or disorders involving the facial nerve will not cause an all-or-nothing lesion, i.e. there is usually a mixture of all three types of injury.

May and colleagues correlated Sunderland's classification with evoked electromyography, histological change, onset of clinical recovery and final recovery according to House and Brackmann's grading.[81] May suggested that the first three degrees of injury can develop with viral inflammatory immune disorders such as Bell's palsy and herpes zoster cephalicus. It is important to remember that the time course for improvement and the extent of recovery is significantly different for incomplete facial nerve paresis compared with total paralysis: 'palsy' includes both entities, whereas 'paralysis' denotes total loss of nerve function.[82] Multiple factors affect the progress of facial nerve regeneration, including the type and severity of the injury and local wound conditions, and more general criteria such as age, nutritional status and comorbidities (e.g. diabetes mellitus).

CLINICAL EVALUATION OF PATIENTS WITH FACIAL PALSY

The history and physical examination are absolutely crucial in the evaluation of a patient with a facial nerve disorder. Every effort must be made to determine the cause. This is particularly the case for patients who present with a facial palsy when their history does not quite fit with an idiopathic palsy (Bell's palsy). In a study of 974 patients referred with a presumptive diagnosis of Bell's palsy, 96 had been misdiagnosed and of these, 47 patients had tumours.[83] Schaitkin and May[84] studied 273 patients who were seen consecutively for evaluation of acute facial nerve palsy. They found that in all cases patients or their families were satisfied if three questions could be answered: (1) what was the cause? (2) when could recovery be expected? (prognosis); (3) what could be done to promote recovery? In most patients who present with an acute facial palsy, these three questions can be answered after a thorough evaluation during the initial office visit.

History

Most patients with a facial palsy consult their general practitioner in the first instance and a large number of them will be assumed to have an idiopathic palsy. Although suggestive, the history of the onset of palsy, whether complete or incomplete, sudden or progressive, is not diagnostic. All these patterns have been noted with idiopathic palsy as well as with infections or neoplasms. Progressive facial nerve palsy over a period of more than 3 weeks, or an incomplete facial nerve palsy that does not start to recover after 3–6 weeks, should make the clinician suspect an underlying neoplasm as the cause and should dictate the need for further investigations.

Ipsilateral recurrent facial nerve palsy is occasionally seen in patients with idiopathic palsy, Melkersson–Rosenthal syndrome and tumours. In fact, the incidence of recurrent facial nerve paralysis in patients with idiopathic palsy is approximately 13% of which 38% are ipsilateral and 62% are on the contralateral side.[85] Pitts et al.[86] reported a mean interval of 9.8 years between recurrences of idiopathic palsy (range : 1 month to 43 years). They also noted that patients with a recurrence were 2.5 times more likely to have a positive family history. Recurrence is common in herpes simplex type I infection but rare with herpes zoster. May and Hardin[87] reported that in 6 of 20 patients with ipsilateral recurrence, a tumour involving the facial nerve was the cause. They recommended that a tumour be suspected in every patient who presented with an ipsilateral recurrent facial palsy. In contrast to recurrent ipsilateral facial paralysis, contralateral recurrence is almost always benign. Alternating recurrent facial nerve palsy is rare and is a feature of Melkersson–Rosenthal syndrome, a condition also characterized by facial oedema, fissured tongue and a positive family history (**Figure 112.8**). Bilateral concurrent facial nerve paralysis is most probably associated with a systemic condition, the most common being Guillain–Barré syndrome, but is also seen in patients with cerebral lymphoma, leukaemic infiltration, sarcoidosis, Lyme disease, rabies, infectious mononucleosis and Moebius syndrome.

Physical examination

A thorough head, neck, otologic and cranial nerve examination is the absolute minimum required when evaluating facial nerve dysfunction. Facial weakness can be extremely subtle, apparent only to a trained examiner and, almost

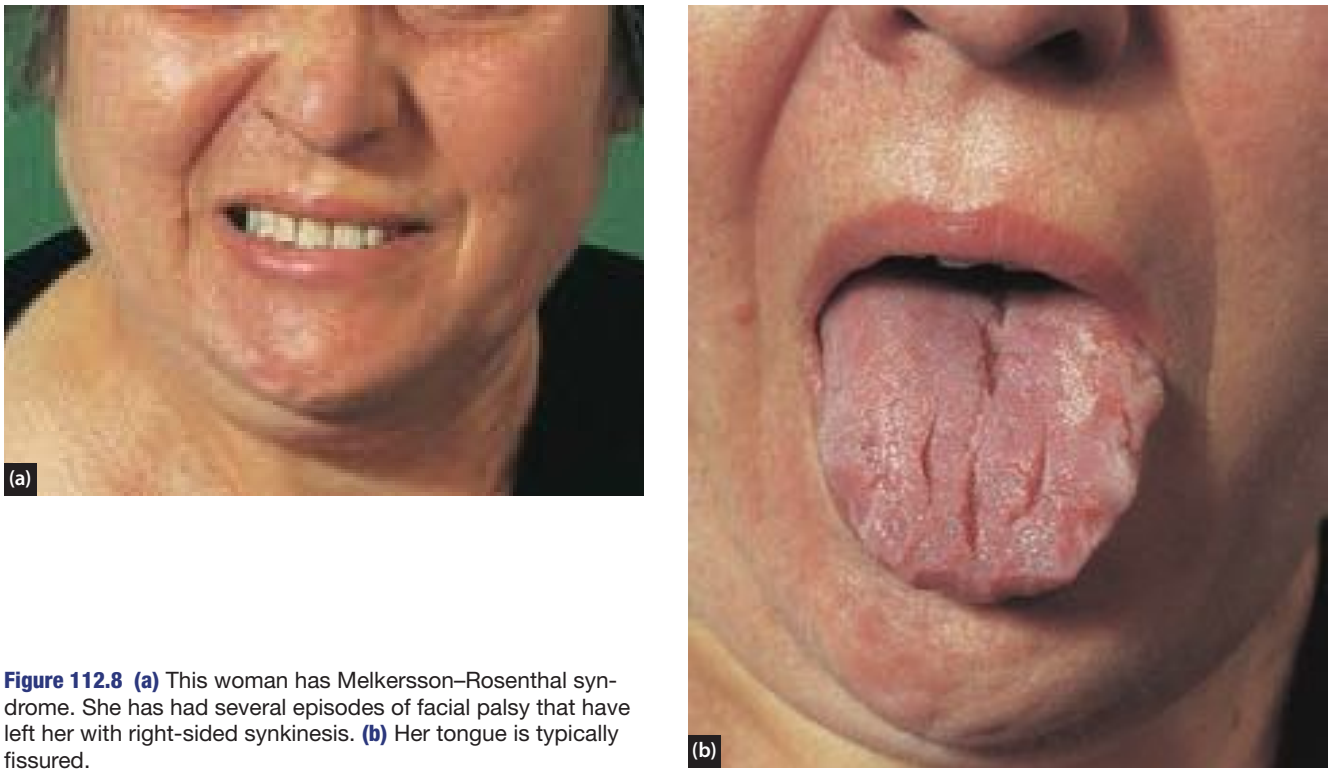


Figure 112.8 **(a)** This woman has Melkersson–Rosenthal syndrome. She has had several episodes of facial palsy that have left her with right-sided synkinesis. **(b)** Her tongue is typically fissured.

certainly, to the patient and their close friends or carers. Examination must be expanded as indicated by the individual patient's history. The degree of facial weakness must be recorded from the outset and an attempt made to localize the precise site of the cause along the course of the facial nerve i.e. intracranial, intratemporal or extratemporal. An open mind to the potential cause is essential since facial nerve palsy may be the first presentation of a systemic illness.

If symptoms or signs of other cranial nerve deficits are present, a central or systemic cause should be suspected. Sparing of forehead movement is considered to be characteristic of a central lesion but is not always the case. Normal movement can be seen in facial nucleus lesions and even peripheral lesions of the temporal branch of the facial nerve. An isolated lower facial palsy is therefore not necessarily indicative of a central lesion. A partial palsy of one or two branches strongly suggests disease localized distal to the stylomastoid foramen and a parotid malignancy should be suspected. If the parotid gland is enlarged and the patient has impaired vision or iritis, sarcoidosis is a possibility.

Facial palsy grading systems

Several systems of clinical measurement of facial nerve function have been described. In 1983, House proposed a six-point scale for reporting the recovery and outcomes of surgery for vestibular Schwannomas. This system was modified and called the House–Brackmann Staging System and has become the most widely used scheme and endorsed by the American Academy of Otolaryngology – Head and Neck Surgery.[81] It has become engrained in clinical practice and will remain so despite its shortcomings as a scientifically accurate assessment tool. In the House–Brackmann system, grade I is normal function, grade VI is complete absence of facial motor function and grades II–V are intermediate (Table 112.2).

As stated above, the House–Brackmann staging system does have limitations with respect to precision and inter-observer error. It emphasizes the characteristics of facial nerve palsy from two assessment domains. The first is gross observation and the second is movement of the forehead, eye and mouth. The fusion of static and dynamic criteria may have contributed to some disagreement between examiners. When only a global score is used, the risk of disagreement among different examiners can range from 13% to 44%.[88, 89] Yen et al.[90] reported the efficacy of the House–Brackmann grading in patients with differential facial nerve function and concluded that a single global grading number was inadequate to describe facial function and primarily reflected the function of the eye. They recommended that regional assessment using the House–Brackmann grading system should be carried out in patients with facial nerve palsy and the result should be reported for the forehead, eye, nose and mouth separately to get a more precise evaluation.

The wide acceptance of the House–Brackmann system has not prevented others from proposing new systems. Burres and Fisch[91] described a method requiring multiple measurements of movement in different parts of the face. Croxson et al.[89] showed the expected correlation between the Burres–Fisch and House–Brackmann systems in 42 patients and found considerable overlap of

TABLE 112.2 House–Brackmann staging system

Degree of injury	Grade	Definition
Normal (1°)	I	Normal symmetrical function in all areas
Mild dysfunction (barely noticeable) (1–2°)	II	Slight weakness noticeable only on close inspection
		Complete eye closure with minimum effort
		Slight asymmetry of smile with maximal effort
		Synkinesis barely noticeable, contracture or spasm absent
Moderate dysfunction (obvious difference) (2–3°)	III	Obvious weakness, but not disfiguring
		May not be able to lift eyebrow
		Complete eye closure and strong but asymmetric mouth movement with maximal effort
		Obvious, but not disfiguring synkinesis, mass movement or spasm
Moderately severe dysfunction) (3°)	IV	Obvious disfiguring weakness
		Inability to lift eyebrow
		Incomplete eye closure and asymmetry of the mouth with maximal effort
		Severe synkinesis, mass movement, spasm
Severe dysfunction (3–4°)	V	Motion barely perceptible
		Incomplete eye closure, slight movement of the corner of the mouth
		Synkinesis, contracture and spasm usually absent
Total paralysis	VI	No movement, loss of tone, no synkinesis, contracture or spasm

This system was proposed by House and Brackmann and adopted by the Facial Nerve Disorders Committee of the American Academy of Otolaryngology, Head and Neck Surgery.

Burres–Fisch scores for House–Brackmann grades III and IV. Murty et al.[88] proposed and tested the Nottingham system of subjective estimation of movement at each of several points on the face. This method correlated better with the House–Brackmann system than did the Burres–Fisch, and it was simpler to perform.

Facial nerve dysfunction includes secondary effects that complicate facial nerve injury. They usually result from aberrant neural regeneration and include synkinesis, hemifacial spasm, contracture, crocodile tears, epiphora, dysgeusia, pain and hyperacusis. These effects do not accompany the primary weakness in an orderly fashion or predictable way and have a significant influence on the patient's perception of disability, handicap and quality of life. Both the Nottingham and Sunnybrook scales have attempted to include these secondary effects in their overall score.[92] To date, none of the current measurement systems have been validated against patient self-assessment in a robust fashion. The ideal system should be user-friendly, reliable and reproducible, reflect patho-physiological events and correlate well with self-assessment.

The advent of computerized technologies prompted more accurate and objective measurements of facial function and secondary effects such as synkinesis, spasm and velocity of facial movement. These techniques have utilized superficial reflective facial fiducials, pixel subtraction techniques, the movement of standardized facial landmarks against registered static points in the midline of the face and even Moiré topography to obtain objective scores or grades. A detailed summary and critique of these techniques has been made by Brenner and Neely.[93] Their conclusion was that computer-based systems offer refinement beyond that available by all other assessment scales. However, they require specialized equipment and considerable investment of time on the part of the clinician, which is almost certainly not possible outside the research setting.

In reality, it is the effect of facial palsy, incomplete recovery and the secondary effects caused by aberrations of regeneration on the patient's quality of life that matter. Functional impairments that include difficulties in eating, drinking, speaking and conveying intimate human information and emotion are simply not captured in any of the surgeon-ranked clinical scales used in practice. Psychological consequences such as decreased self-esteem, anxiety when meeting strangers, depression and social isolation are not even considered. Patient-reported outcomes should be quoted alongside those of surgeon-ranked scales. In a thorough, systematic review undertaken by Ho et al.[94] that analyzed 598 articles indexed by the recognized databases, the Facial Clinimetric Evaluation,[95] the Facial Disability Index[96] and a questionnaire developed to study aberrant facial nerve regeneration[97] were the only instruments that satisfied all inclusion and exclusion criteria. Even these had limitations in domains that addressed self-perception of facial appearance and procedure-related symptoms or satisfaction. Ho et al. concluded that future

research was necessary to develop and validate a new patient-reported outcome instrument.

Topodiagnostic tests

Topodiagnostic evaluation of facial palsy refers to the functional testing of an individual facial nerve branch in an attempt to locate the anatomical level of dysfunction or injury. These tests are of some value but have a slightly limited correlation with the precise site of nerve damage and do not have any prognostic value. These studies are summarized in Table 112.3.

Electrophysiological tests

Electrophysiological tests have been developed to evaluate the degree of dysfunction and assumed viability of the facial nerve in the anticipation that results would provide prognostic information for recovery. This information has been used to influence management, particularly the potential impact of any surgical intervention. These tests are not normally used in the assessment of incomplete paresis, which has a higher probability of full, functional recovery. They are only used in patients with complete established paralysis, when they can aid management decisions concerning facial reanimation. Repair of the facial nerve is contraindicated when the motor end plate muscle units are no longer functional, a process that continues inexorably along with muscle atrophy in the months after total denervation. Reinnervation procedures when no muscle end plate activity can be detected by electromyography are contraindicated because they will not be successful.

The traditional tests using transcutaneous stimulation of the facial nerve to establish the minimum current required to provoke muscle movement, the nerve excitability test (NET), and the current required to achieve maximal muscle response without causing any discomfort to the patient, maximal stimulation test (MST), are rarely used nowadays (Table 112.4). Both these tests compared the response on the normal to the palsied side and could be undertaken at the bedside or in the clinic using a Hilger Stimulator: they had their limitations in terms of accuracy, reproducibility, inter-observer variation and prognostic value (Table 112.4).[98]

The two techniques most commonly used now by otorhinolaryngologists in clinical practice are electroneuronography (ENoG) and electromyography (EMG). A third technique, transcranial magnetic stimulation, also has a role in clinical practice, particularly in neurology, but has yet to be employed widely by otorhinolaryngologists.

ELECTRONEURONOGRAPHY (ENoG)

In ENoG, a supramaximal stimulus is delivered to the facial nerve trunk as it exits the stylomastoid foramen and the evoked biphasic compound muscle action potential (CMAP) is recorded using surface electrodes. The response of the paralyzed side is compared with that of the normal side, which serves as a control, and is expressed as a percentage of the normal. It has been shown that reduction in CMAP correlates well with histological axonal loss.[99] This means that if the CMAP amplitude on the affected side is 10% of the normal side, then it is assumed that



Figure 112.9 Schirmer's test. The patient had sustained a longitudinal fracture of the left temporal bone that had transected the greater petrosal nerve. She had a dry eye as is demonstrated in this test.

TABLE 112.3 Topodiagnostic tests

Test	Nerve branch assessed	Technique considerations	Assessment/ Outcome
Schirmer's test (Figure 112.9)	Greater (superficial) petrosal nerve	Strips of paper are placed in the inferior conjunctival fornix for 5 minutes and the length of paper moistened is compared between eyes	>75% unilateral decrease in lacrimation, or a bilateral decrease in lacrimation (less than 10 mm wetted for both sides at 5 minutes)
Stapedial reflex	Nerve to stapedius muscle	See Chapter 51, Psychoacoustic audiometry	Present or absent
Electrogustometry	Chorda tympani	The tongue is stimulated electrically to produce a metallic taste and the two sides are compared	Threshold of the test is compared between sides
Salivary flow testing	Chorda tympani	Wharton's ducts are cannulated and salivary flow is measured over time following a gustatory stimulus (6% citric acid on anterior part of tongue)	A reduction of 25% is considered abnormal

TABLE 112.4 Comparison of NET and MST

Test	Technique	Outcome measure	Prognostic value
NET	Compares transcutaneous current threshold required to elicit minimal muscle contraction between two sides	>3.5 mA difference is considered significant	Indicates poor recovery
MST	Compares muscle contraction at maximal nerve stimulation (~5 mA) between two sides	Equal response, reduced response or absent response	Loss of response within 10 days is associated with incomplete recovery.

90% axonal loss has been sustained. ENoG is said not to be useful until the fourth day of facial nerve paralysis. Neural conduction disappears quite rapidly after an injury that transects an axon because a degenerating axon is incapable of conducting an action potential, and most axons have at least started to degenerate within 3–4 days of such an injury.

ENoG is considered the most valuable prognostic indicator among current electrophysiological tests and its main indication is acute onset complete facial nerve paralysis. Both the percentage of amplitude reduction and rate of degeneration have been used as prognostic indicators of facial nerve recovery. In idiopathic palsy, degeneration of >90% within 14 days of complete paralysis indicates a probable poor recovery in >50% of cases.[100] ENoG does not appear to be useful in Ramsay Hunt syndrome because of multiple sites of nerve involvement. Fisch has recommended surgical intervention within three weeks in patients where traumatic injury has resulted in >90% amplitude reduction by ENG within 6 days of the injury.[101, 102] Great care has to be taken interpreting these data. Although there is good correlation between the natural history of idiopathic palsy and ENoG findings, there are no definitive data on the natural history of facial nerve injury due to other causes. The assumption that ENoG data is valid regardless of whether the paralysis was of immediate or delayed onset cannot be justified from the literature.[103]

ELECTROMYOGRAPHY (EMG)

EMG records active motor unit potentials of the orbicularis oculi and orbicularis oris muscles during rest and voluntary contraction. EMG can be used to determine:

- if a nerve in question is in continuity (volitional activity recorded)
- if there is evidence of Wallerian degeneration (fibrillation potentials)
- if there are early signs of reinnervation (polyphasic innervation potentials).

Fibrillation potentials typically arise 2–3 weeks following injury, and polyphasic reinnervation potentials may precede clinical signs of recovery by 6–12 weeks.

In cases of acute onset and complete paralysis with unfavourable ENoG recordings (>90% degeneration), the finding of active motor unit potentials indicates that some fibres are intact and suggests a favourable prognosis. As long as some active motor units can be recorded one week following a complete paralysis, severe degeneration is unlikely to take place. EMG has a role in decision making regarding surgical intervention in long-standing paralysis as follows:

- Polyphasic motor unit potentials indicate regenerative processes and surgical intervention is therefore not indicated. In this case, close follow-up studies of nerve regeneration are advocated.
- Fibrillation potentials indicate lower motor neuron denervation, but viable motor end plates. Surgical exploration is therefore indicated with a view to achieving nerve continuity, either by end-to-end anastomosis, interposition grafting, re-routing or re-innervation techniques.
- 'Silence' on EMG (no electrical output) indicates long-term denervation and suggests that muscle has been replaced by fibrous tissue. In this case, static or dynamic (microvascular innervated free muscle transfer or muscle transposition) facial reanimation is indicated.

LIMITATIONS OF ELECTROPHYSIOLOGICAL TESTING

Although electrophysiological testing may provide useful prognostic information and serve as a guide to the management of facial palsy, there are some important shortcomings.

- The electrical impulse can only stimulate normal or neurapraxic fibres and cannot distinguish whether the remaining fibres are in a state of axonotmesis or neurotmesis. Thus, it cannot distinguish between injuries which have different prognoses.
- It provides no useful information in cases of incomplete facial paralysis.
- It fails to provide information on the immediate post-paralysis period (first 72 hours).

An overview of ENoG and EMG is given in Table 112.5 and should be read in conjunction with the Nerve Injury Classification in Table 112.1.

TRANSCRANIAL MAGNETIC STIMULATION

While electrodiagnostic tests provide information about the facial nerve distal to the stylomastoid foramen, transcranial magnetic stimulation is able to stimulate the facial

TABLE 112.5 ENoG and EMG

Study	Measurement	When to measure	Use in acute onset paralysis	Use in long-standing paralysis
ENoG	Evoked CMAP compared to normal site	Between 3 days and 3 weeks	>90% of degenerated fibres suggests poor prognosis	Not useful because of desynchronization
EMG	Active motor unit potentials after voluntary forceful contraction	Complementary to ENoG, after 2 weeks	Presence of active motor potentials in response to voluntary contractions indicates good prognosis	Fibrillation potentials suggest Wallerian degeneration
		In long-standing paralysis		Polyphasic potentials suggest reinnervation

nerve within the cranium. Magnetic impulses induce an electric current within the brain and stimulate neuromuscular tissue in exactly the same way as conventional electrostimulation. The design and type of coil determines the penetration and site of stimulation. A double coil is normally employed for facial nerve studies and has the ability to focus on the infranuclear portion of the nerve, probably at the root entry zone or temporal bone itself. It is this capability that has opened up the potential to clinical and research studies of palsies caused by temporal bone pathologies and link these with information derived from MRI data.[104, 105]

INTRA-OPERATIVE NERVE MONITORING

Intra-operative monitoring is now widely used though yet to be considered a standard of care for every operation at which there is a risk of damaging the facial nerve. A number of devices are marketed that employ continuous EMG monitoring from peripheral facial muscle groups for spontaneous and electrically evoked stimulation of the facial nerve trunk or its branches. Their role in preventing facial nerve injury remains controversial, but there is little doubt that intra-operative nerve monitoring makes the trainees' learning curve safer for the patient. There are no prospective, randomized studies that have proven its efficacy in reducing the incidence of facial nerve paralysis. However, intra-operative monitoring has established itself in CPA tumour surgery, revision mastoidectomy, parotidectomy and in surgery of congenital ear abnormalities. Other considerations should be medico-legal issues that may arise in cases of facial nerve injury when the monitor was not used even though it was available, and the use of monitoring during supervised resident training.

In CPA tumour surgery it is particularly helpful for identification of the nerve at the brainstem, its displacement and distortion around the tumour, where it can be almost invisible, and within the IAM: in other words, throughout the whole of the procedure. Jackler et al.[106] have reported a reduced incidence of complete permanent paralysis following removal of CPA tumours with the use of intra-operative monitoring, while Axon et al.[107] have found a good correlation between intra-operative CMAP amplitude following tumour resection and immediate post-operative facial nerve function. Kirkpatrick et al.[108, 109] reported that intra-operative facial nerve monitoring in CPA tumour surgery appeared to predict eventual facial function accurately in small tumours, but did not predict facial nerve recovery reliably following surgery for larger tumours. Wilson et al.[110] looked at the cost-effectiveness of intra-operative facial nerve monitoring in middle ear or mastoid surgery. They found that a strategy to monitor both primary and revision surgeries had the greatest effectiveness and lowest cost. Noss et al.[111] reported that the absence of monitoring would have led to facial nerve deficits in 1–2% of their cases. Pensak et al.[112] felt that the overall outcome of mastoid surgery was definitely affected in a positive way by the presence of the monitor in 0.4% of cases during residents' training. As far as parotid surgery is concerned, several studies have demonstrated that there is no significant difference in the incidence of permanent paralysis of monitored versus unmonitored groups, but its use may have an effect on the intensity of post-operative palsy and on the recovery time in revision surgery.[113, 114] Only one study demonstrated that intra-operative monitoring led to a significantly decreased incidence of post-operative temporary paralysis (62% versus 44%), although no difference in permanent paralysis was seen.[115] These results support the observation that continuous intra-operative EMG monitoring may not affect post-operative facial nerve outcomes and EMG abnormalities do not predict facial nerve injury in parotid surgery. Pitfalls and caveats are shown in **Table 112.6**.

Blood investigations

While most patients present in a truly idiopathic fashion, some patients do not and the cause of their palsy is far from clear. In retrospect, the following blood tests might have helped to identify or exclude other less common causes: Angiotensin Converting Enzyme titres, Anti-neutrophil Cytoplasmic Antibody profile, HIV serology, Lyme serology and Syphilis serology. Obtaining the results of tests sooner rather than later is wise.

Facial nerve imaging

RADIOLOGICAL IMAGING OF THE NORMAL FACIAL NERVE

Computed tomography (CT) of the temporal bone allows identification of the Fallopian canal from the fundus of the IAM to the stylomastoid foramen (**Figure 112.10a,b&c**). The technique of high-resolution acquisition with overlapping thin sections of 0.6 mm, reconstructed into 0.3–0.4 mm sections, allows equivalent voxels of 0.3 mm^3.

TABLE 112.6 Pitfalls and caveats of intra-operative monitoring

Pitfalls and caveats
Always ask the anaesthetist to avoid neuromuscular blockade
The closer the bipolar electrodes are placed, the fewer the muscle fibres that will be represented in the EMG response
Use transparent drapes for backup
Test the integrity of the system with the anaesthetic nerve stimulator before starting the operation and check the system periodically during surgery
Even after nerve transection, the distal segment can still be stimulated for a few days, creating evoked EMG responses that may be falsely interpreted as evidence of continuity
The mastoid segment is least sensitive to nerve stimulation, so a higher setting is needed (0.5 mA in mastoid surgery as opposed to 0.05–0.1 mA in CPA tumour surgery)

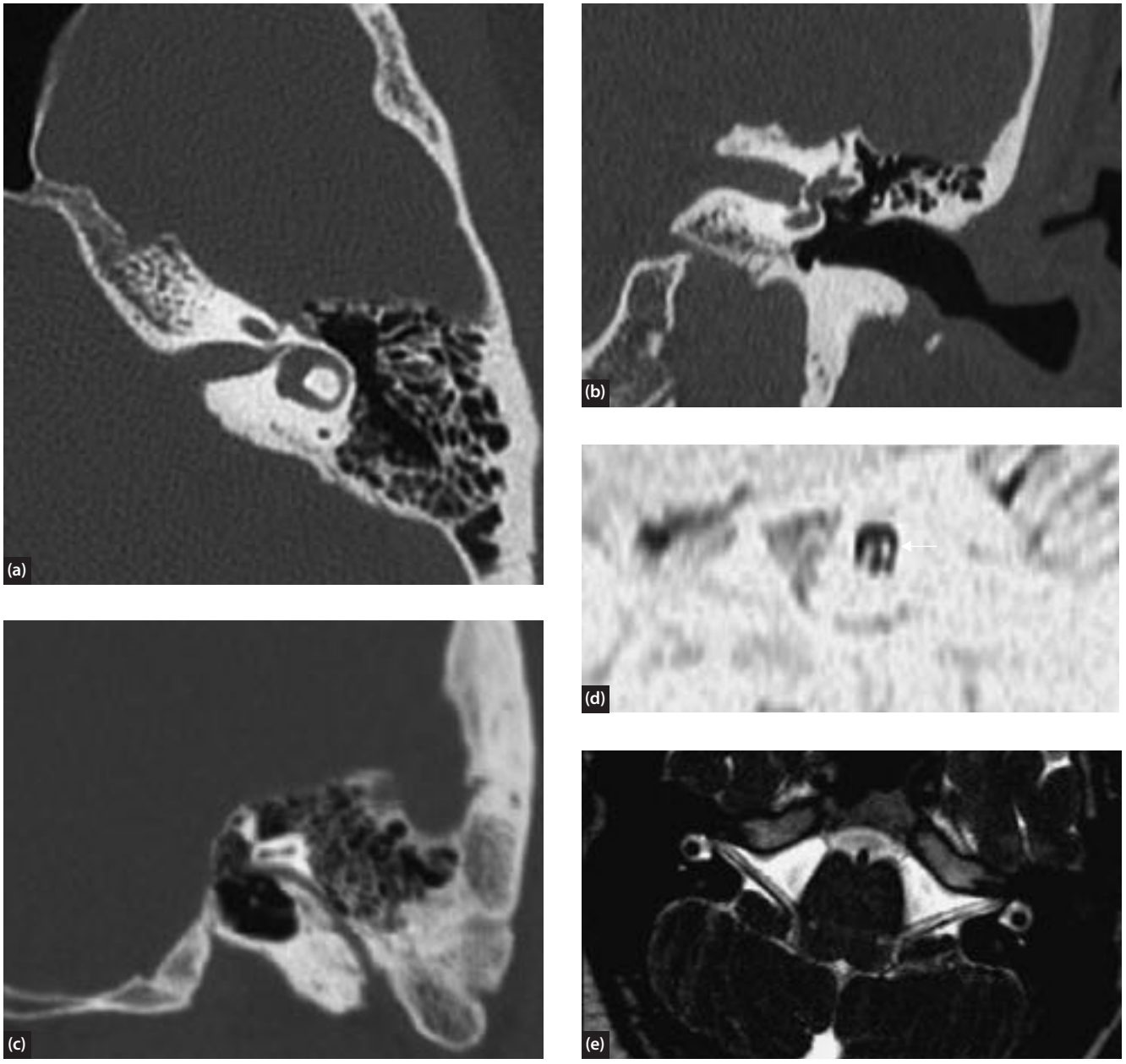


Figure 112.10 **(a)** Axial CT scan of the labyrinthine segment of the facial nerve and first genu; **(b)** coronal CT of tympanic segment of facial nerve which lies just inferior to the lateral semicircular canal; **(c)** oblique sagittal CT view of the mastoid segment of the facial nerve and second genu; **(d)** T2 DRIVE oblique sagittal MRI of facial nerve in the IAM (arrowed); **(e)** T2 DRIVE axial MRI of facial nerve in the IAM running alongside the superior vestibular nerve.

In contrast, the thin collimation performed as part of a trauma sequence CT head/brain may not provide an adequate level of detail to assess the facial nerve canal. The tympanic portion is probably easiest to identify on axial scans at the level of the body of incus and its short process. From there it can be followed proximally and distally towards the labyrinthine and descending segments respectively. The labyrinthine segment is characteristically banana-shaped on axial sections. On coronal images it may be visualized as the medial of the two circular 'eyes' directly above the cochlea. The sulcus for the geniculate ganglion is also well demonstrated in coronal sections. The mastoid segment is best visualized in coronal or sagittal views. In coronal views it is easier to follow the nerve from the stylomastoid foramen to its more proximal part. It is more difficult to identify in axial views, especially in well-pneumatized temporal bones. One way is to try and locate the pyramid or the stapedius muscle; the facial nerve lies immediately behind.[116, 117] Bance and Erb[118] have described the 'B-line': a tangent line extrapolated from the posterior border of the basal turn of the cochlea, which falls within 1 mm of the facial nerve on average. The intra-parotid facial nerve cannot be identified on CT scans. The facial nerve plane is extrapolated as a line connecting the stylomastoid foramen to a point immediately lateral to the retromandibular vein.

The intra-parotid facial nerve is not identified on CT scans. The facial nerve plane is extrapolated as a line connecting the stylomastoid foramen to a point immediately lateral to the retromandibular vein.

Cone-beam CT scanning is becoming increasingly utilized for pre-operative planning for middle ear surgery including cochlear implantation and provides good anatomical detail, particularly in respect of the facial nerve location, while exposing the patient to less ionizing radiation.

The rich perineural arteriovenous plexus which surrounds the normal facial nerve facilitates visualization on contrast enhanced T1-weighted MRI. It is usually observed in more than one segment, more commonly in the geniculate ganglion and the tympanic segments and it may enhance asymmetrically between right and left. Enhancement previously considered pathological has more recently been noted in the fundus of the IAM in normal subjects. Most radiologists believe that the intra-parotid facial nerve cannot be routinely identified on MRI. The linear, low-intensity signal seen on axial T1 scans most probably represents intra-parotid ductal ramification (**Figure 112.10**).

Imaging strategies in facial nerve palsy

The imaging strategy is largely determined by the suspected nature of the lesion. In general, a high-resolution CT (HRCT) enables superior visualization of the intratemporal segment of the facial nerve and is particularly useful in cases of temporal bone trauma, Fallopian canal involvement in chronic suppurative otitis media (CSOM) or temporal bone malignancies. MRI using paramagnetic contrast agents such as gadolinium-DTPA is known to provide better visualization of soft tissues and is particularly useful in neoplastic or inflammatory lesions. It should be remembered that both imaging techniques are complementary and may be used in combination.

IDIOPATHIC PALSY

Imaging of patients with idiopathic facial palsy who present in a typical fashion is not cost-effective. The degree of enhancement on MRI carries no significant prognostic value and the chance of acute facial nerve palsy in a tumour is remote. Imaging is only recommended if the presentation is atypical, an alternative diagnosis is suspected, surgical decompression is planned or recovery is incomplete at 6 months. MRI may be normal in the first 10 days following the onset of palsy. Post-gadolinium enhancement is characteristically asymmetric, diffuse, intense and linear (not nodular). It involves the entire intratemporal segment of the facial nerve, but is more distinct in the fundus of the IAM and labyrinthine segments and may well persist for several months after full recovery (**Figure 112.11**). However, in a case of presumed idiopathic facial nerve palsy the authors consider contrast-enhanced MRI scanning 3 months following the initial weakness if the clinical condition has not improved. In cases where the weakness is progressing, the patient should be scanned earlier.

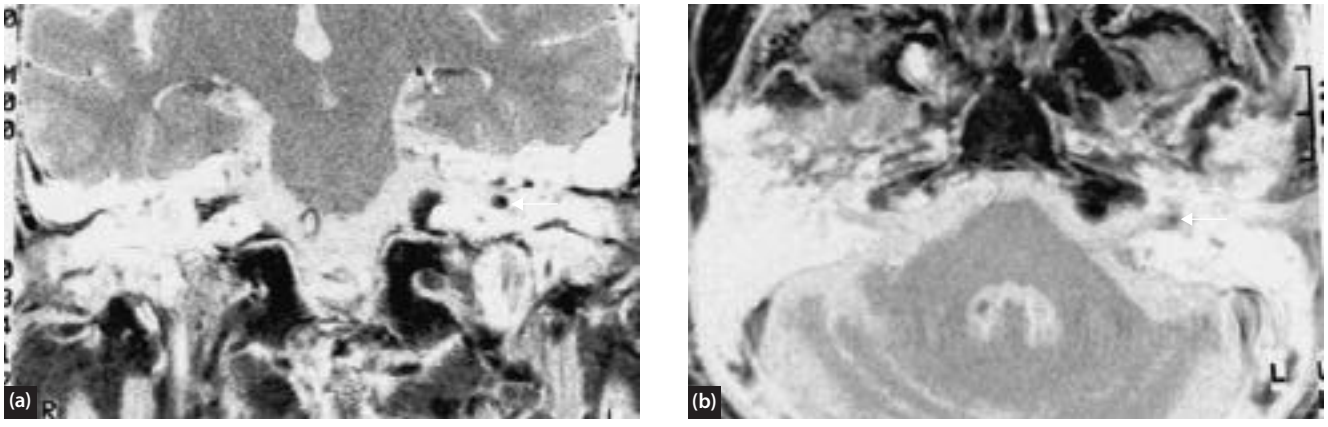


Figure 112.11 **(a)** Coronal and **(b)** axial MRI of a patient with a left-sided idiopathic palsy. Increased signal is clearly visible in the geniculate region (arrowed).

Different departments will employ various imaging protocols to ensure an idiopathic case is not masking a more sinister diagnosis. Pre- and post-contrast T1 sequences through the temporal bone, in combination with T2 sequences of the whole brain and parotid-specific fat suppression imaging can be considered a comprehensive approach.

ACUTE AND CHRONIC OTITIS MEDIA

Imaging in facial nerve paralysis in the presence of acute or chronic otitis media is generally directed towards identifying coexisting intratemporal or intracranial complications rather than the site of nerve damage. A CT scan of the temporal bone can delineate the site of erosion of the Fallopian canal, but MRI cannot differentiate between the increased signal of the facial nerve from that of surrounding inflamed granulation tissue.

TEMPORAL BONE FRACTURE

HRCT is the investigation of choice for temporal bone fractures. Facial nerve injury is usually situated just distal to the geniculate ganglion and the first genu in longitudinal fractures and just proximal to the geniculate ganglion in transverse fractures. MRI has little if any value in these instances. There is no correlation between pathological facial nerve enhancement and ENoG findings and it may be observed up to 2 years post-trauma (**Figure 112.13**).[119]

TUMOURS

MRI is the investigation of choice in these cases. Facial nerve haemangiomas enhance intensely on post-contrast T1-weighted MRI, most commonly in the area of the geniculate ganglion, and also have a typical honeycomb matrix appearance on CT. Facial nerve schwannomas show a strong enhancement with gadolinium on T1-weighted images and, when they grow to the point of filling the internal auditory canal, they cannot be distinguished from vestibular schwannomas (**Figures 112.14, 112.15** and **112.16**). Malignant parotid tumours may track up the facial nerve and a soft-tissue intensity enhancing mass is usually observed extending from the gland through an enlarged stylomastoid foramen to involve the mastoid

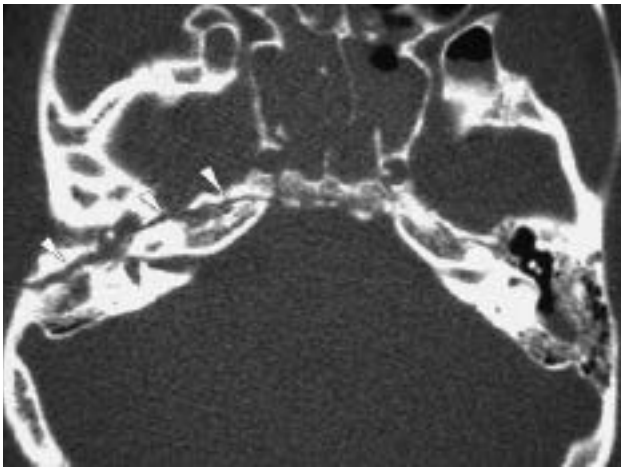


Figure 112.12 Typical CT appearance of a longitudinal fracture of the temporal bone. The fracture line (arrowed) passes anterior to the genu of the facial nerve.



Figure 112.13 CT scan of a transverse fracture of the temporal bone. The fracture (arrowed) passes through the vestibule and across the tympanic segment of the facial nerve.

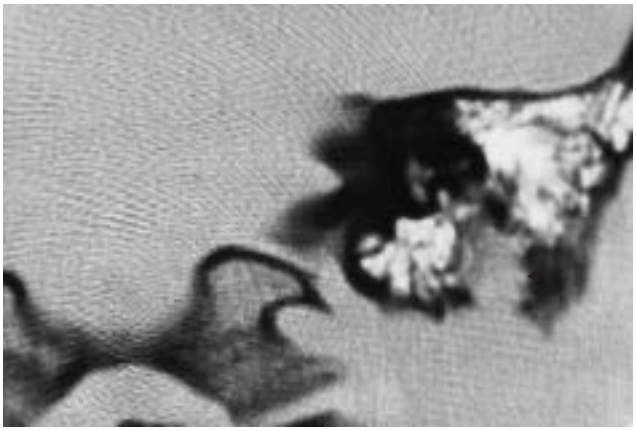


Figure 112.14 CT scan of Fallopian canal containing a facial nerve schwannoma. The canal is expanded and its bony margins are scalloped (arrowed).

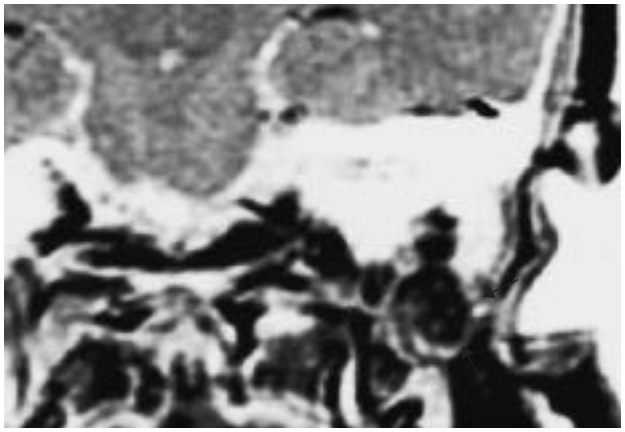


Figure 112.15 T1 gadolinium MRI of facial schwannoma showing increased signal (arrowed).

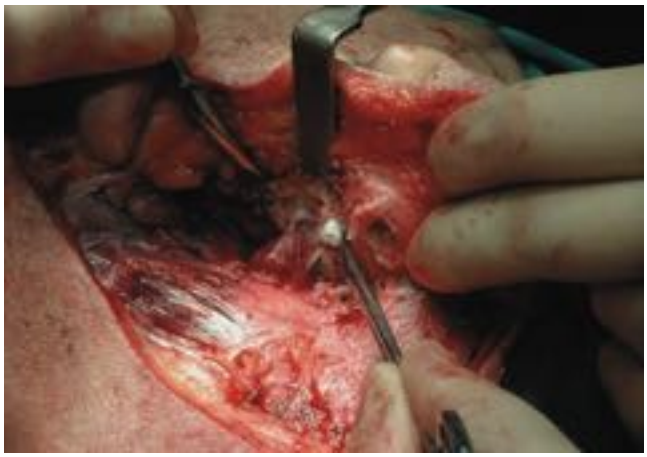


Figure 112.16 Facial nerve schwannoma, imaged in 112.14 and 112.15 seen at surgery pouting from the anterior border of the sternocleidomastoid muscle, entering the parotid gland, just beneath the transected external ear canal.

segment of the facial nerve. There is usually replacement of the hyperintense fat tissue by a hypointense signal in T1-weighted images.

DIFFUSION TENSOR IMAGING TRACTOGRAPHY

Skull base surgeons are well aware of the challenges of functional preservation of the facial nerve at the time of tumour dissection in vestibular schwannoma surgery. Intra-operative EMG is routinely employed to help locate and allow preservation of the often-thinned nerve traversing the tumour capsule. Diffusion tensor imaging (DTI) utilizes multidimensional vector algorithms to derive neural tract directional information. The aligned fibres of neural tissue can be specifically imaged. DTI has been shown to provide the surgeon with additional pre-operative information as to the location of the facial nerve with respect to the tumour within the CPA, potentially increasing the likelihood of a good facial nerve outcome.[120, 121]

MANAGEMENT OF THE PATIENT WITH A FACIAL NERVE DISORDER

As stated earlier, the management of an acute insult causing a facial nerve palsy depends to some extent on the cause, but there are also general points that apply to all (**Table 112.7**). In this section the management issues surrounding palsies resulting from the most common causes are discussed.

EYE CARE

Appropriate eye care, including advice regarding corneal protection with lubrication and patching should be instituted immediately in cases where eye closure is impaired. In those patients with severe facial weakness the blink movement is impaired and the eyelid cannot cleanse and lubricate the corneal surface. In addition, if the nerve injury involves the trunk proximal to the 1st genu, and therefore the origin of the greater petrosal nerve, the secretomotor supply to the lacrimal gland is also impaired thus compounding the problem with corneal lubrication.

Simple guidance regarding the use of large-lens sunglasses can help protect the eye from dust and debris on a windy day. Eye drops should be applied to the corneal surface frequently during the daytime, whilst at night ointment is preferred. Following the application of the ointment the eye should be taped closed. Over time, the unopposed action of levator palpebrae superioris (supplied by the oculomotor nerve) results in shortening of the upper eyelid. Patients should be advised to close their eye manually using a finger as well as attempting to stretch the upper lid to try and prevent this shortening. Upper eyelid weighting with external adhesive skin-tone coloured weights (Blinkeze™) is recommended. More formal surgical weighting or levator-lengthening procedures are used in long-standing cases of impaired eye closure. In some cases, these may be performed acutely as they can be reversed, although this is not the usual practice of the authors.[122, 123]

Idiopathic (Bell's) palsy

The term idiopathic palsy should be reserved for cases of facial paralysis that have signs and symptoms consistent with the disease and in which a diligent search for another cause is negative. The search for a cause should not simply relegate idiopathic palsy to a diagnosis of exclusion, but emphasize the diagnosis based on specific clinical features. In 1959, Taverner[124] outlined the minimum diagnostic criteria for idiopathic palsy, then known as Bell's palsy, that included: paralysis or paresis of all muscle groups on one side of the face; sudden onset; absence of signs of central nervous system disease; absence of signs of ear or CPA disease. These criteria still hold today. Classically, patients present with a prodromal illness which may include periauricular pain and general malaise. Within 72 hours they rapidly develop complete lower motor neuron facial weakness.

The annual estimated incidence of idiopathic palsy is fairly similar throughout the world, ranging between 20 and 32.7 per 100,000 in different studies.[125, 126] The condition affects approximately 1 in 65 people during their lifetime. The incidence reaches a peak between the ages of 15 and 45 years. It has a predominance in women younger than 20 years and a slight predominance in men older than 40 years, although the male to female ratio is more or less equal across the population. Recurrence rates of 4.5–15% and a familial incidence of 4.1% have been addressed in various studies. There may be genetic factors that influence the development of idiopathic palsy but quite what they might be is unclear. Idiopathic palsy is more common in pregnancy with the majority of cases being in the 3rd trimester. It is suggested that the increased incidence in the latter stages of pregnancy relates to changes in fluid balance with increased extracellular fluid leading to oedema of the nerve and subsequent compression within the Fallopian canal.[127]

TABLE 112.7 Causes of facial palsy

Causes	
Birth	Moulding
	Forceps delivery
	Dystrophia myotonica
	Moebius syndrome (facial diplegia associated with other cranial nerve defects)
Trauma	Basal skull fracture
	Facial injuries
	Penetrating injury to middle ear
	Altitude paralysis (barotrauma)
	Scuba diving (barotrauma)
	Lightning
Neurological	Opercular syndrome (cortical lesion in facial motor area)
	Millard–Gubler syndrome (abducens palsy with contralateral hemiplegia due to lesion in base of pons involving corticospinal tract)
Infection	Otitis externa
	Acute otitis media
	Mastoiditis Chronic otitis media
	Chicken pox
	Herpes zoster cephalicus (Ramsay Hunt syndrome)
	Encephalitis
	Poliomyelitis (type I)
	Mumps
	Infectious mononucleosis (glandular fever)
	Leprosy
	Coxsackie virus
	Malaria
	Syphilis
	Scleroma
	Tuberculosis
	Botulism
	Acute haemorrhagic conjunctivitis (enterovirus 70)
	Gnathostomiasis
	Mucormycosis
	Lyme disease
Metabolic	Diabetes mellitus
	Hyperthyroidism
	Pregnancy
	Hypertension
	Acute porphyria
Neoplastic	Facial schwannoma
	VIIth nerve tumour
	Jugular paraganglioma
	Tympanic paraganglioma
	Meningioma
	Haemangioblastoma
	Sarcoma
	Carcinoma (invading or metastatic)
	Anomalous sigmoid sinus
	Haemangioma of tympanum
	Hydradenoma (external auditory meatus)
	Leukaemia
	Cerebral lymphoma
	Teratoma
	Hand–Schüller–Christian disease
	Fibrous dysplasia
	Von Recklinghausen's disease
Toxic	Thalidomide (Miehlke syndrome, cranial nerves VI, VII with congenital deafness)
	Tetanus
	Diphtheria
	Carbon monoxide
Iatrogenic	Mandibular block anaesthesia
	Anti-tetanus serum
	Vaccine treatment for rabies
	Post-immunization
	Parotid surgery
	Mastoid surgery
	Post-tonsillectomy and adenoidectomy
	Iontophoresis (local anaesthesia)
	Embolization
	Dental
Idiopathic	Bell's, familial
	Melkersson–Rosenthal syndrome (recurrent alternating facial palsy, furrowed tongue, faciolabial oedema)
	Hereditary hypertrophic neuropathy (Charcot–Marie–Tooth disease, Déjérine–Sottas disease)
	Autoimmune syndrome
	Temporal arteritis
	Thrombotic thrombocytopenic purpura
	Polyarteritis nodosa
	Landry–Guillain–Barré syndrome (ascending paralysis)
	Multiple sclerosis
	Myasthenia gravis
	Sarcoidosis (Heerfordt syndrome – uveoparotid fever)
	Osteopetrosis

The prognosis for pregnant women with idiopathic palsy is notably better than among non-pregnant women with palsy. Once the child has been delivered, the clinical picture tends to improve. However, there has been reluctance among non-specialists to prescribe corticosteroids for pregnant women with facial palsy. Obstetricians and those involved with the management of pregnant women with facial palsy should be assured of the safety and efficacy of prednisolone in this special group of patients.

The aetiology of idiopathic palsy remains unclear, although microcirculatory failure of the vasa nervorum, ischaemic neuropathy, infectious, genetic and immunologic causes have all been proposed in the past. Of those possible causes, clinical and epidemiologic data lend credence to an infectious origin, which triggers an immunologic response resulting in damage to the facial nerve. Pathogens that have been implicated in the disease process include herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), human herpesvirus, varicella zoster virus (VZV), influenza B, adenovirus, Coxsackie virus and Epstein–Barr virus (EBV). Recently, it has been demonstrated that an inactivated intranasal influenza vaccine increased the risk of idiopathic palsy.[128]

Murakami et al. in 1996 explored the link between herpes simplex virus (HSV) and Bell's palsy.[129] Surgical decompression for facial nerve palsy was performed in 14 patients with Bell's palsy, 9 patients with Ramsay Hunt syndrome and 12 other controls. Viral genomes of HSV-1, VZV and EBV were analyzed in clinical samples of facial nerve endoneurial fluid and posterior auricular muscle using polymerase chain reaction (PCR) followed by hybridization with Southern blot analysis. HSV-1 genomes were detected in 11 of 14 patients (79%) with idiopathic palsy but not in patients with Ramsay Hunt syndrome or in the controls. The authors concluded that HSV-1 is the major aetiologic agent in Bell's palsy. However, these results have not been replicated. Linder et al. identified HSV-1 genomic DNA in 86% of autopsied human geniculate ganglion samples taken from control patients without any previous history of facial palsy.[82] In 43% of the specimens, viral genomic DNA for VZV was found, HSV-2 genomic DNA was not detected. In all 14 geniculate ganglion preparations, either one or even both viral pathogens were found using the highly sensitive nested PCR. HSV-1, HSV-2 or VZV could not be detected in facial muscle biopsy samples taken from acute Bell's palsy patients. Linder et al. also comment, correctly, that current PCR methods are unable to differentiate between a latent and a lytic virus state. [82] To demonstrate that reactivation of HSV virus, or its switch from a latent to a lytic state, causes idiopathic palsy, a reverse transcription PCR aimed at detecting lytic state-specific mRNAs might provide the answer. Until proven otherwise, idiopathic palsy should still be called idiopathic.

Although, the majority of patients with Bell's palsy recover facial movement completely, a significant proportion have long-term issues with facial asymmetry, tightness and synkinesis. Poor prognosis has been related to complete paralysis at onset or incomplete paralysis with late onset of recovery, old age, a dry eye, abolished taste, absent stapedius reflex and postauricular pain.[128] Normal function is usually regained within 3 months in about two-thirds of all patients. No further recovery is expected after a period of 6 months has elapsed.

The pharmacological management of idiopathic palsy primarily involves oral corticosteroid medication. Evidence from the Scottish Bell's Palsy Study[130] showed clear benefit from treatment with prednisolone within 72 hours of onset of the paralysis. There was no evidence of additional benefit from oral antiviral medication in the form of acyclovir. However, other authors have found antivirals provide additional benefit and the most recent evidence from the Cochrane Database concludes that there is evidence that the addition of antiviral medication improved the rates of incomplete recovery and reduces the long-term after-effects of idiopathic palsy.[131] Based on the above evidence, most surgeons would advocate a combination of steroids and antiviral drugs. The usual recommended regime is prednisone 1 mg/kg/day for 10 days and oral acyclovir (400 mg five times daily) for 10 days.

Facial nerve disorders of viral origin

VARICELLA ZOSTER VIRUS (VZV) INFECTION (RAMSAY HUNT SYNDROME)

The strict definition of Ramsay Hunt syndrome is a peripheral facial nerve palsy accompanied by an erythematous vesicular rash on the ear (zoster oticus) or in the mouth (**Figure 112.17**). The mechanism of disease is reactivation of the latent VZV virus in the geniculate ganglion.



Figure 112.17 This patient has a complete left-sided facial palsy and a vesicular eruption in the conchal bowl of her ear which is typical of Ramsay Hunt syndrome.

Other cranial nerves are less commonly involved. The onset of palsy is usually preceded by pain which may persist and be excruciating. In a small proportion of patients, the facial palsy is accompanied by labyrinthine symptoms including tinnitus, vertigo and a sensorineural hearing loss. Diagnosis is clinical but may be confirmed by rising titres of antibodies to VZV. Examination of CSF and gadolinium-enhanced MRI have no diagnostic or prognostic value. PCR to detect VZV in ear exudates is more sensitive than VZV PCR performed on tears or blood mononuclear cells and may be positive before the development of vesicles.[132]

It has been shown that a small proportion of patients diagnosed as idiopathic palsy may in fact have a VZV infection. In 15% of cases vesicles may appear after the onset of palsy, and the diagnosis may be missed. Another reason for missing the diagnosis is the Ramsay Hunt syndrome *zoster sine herpete*. This is characterized by peripheral facial paralysis without ear or mouth rash, and the presence of either a four-fold rise in antibody to VZV or the detection of VZV DNA in skin, blood mononuclear cells or middle ear fluid.[132] Although further research is needed, perigeniculate region VZV PCR may help to distinguish between patients with Bell's palsy and patients with early Ramsay Hunt syndrome.

The prognosis for Ramsay Hunt is worse than idiopathic facial palsy. Persistent weakness is observed in 30–50% of patients and only 10% recover completely after complete loss of function without treatment.[133] Regarding management, the same controversies exist as in idiopathic palsy. Most advocate a combination of steroids and antiviral agents, but for a longer period of time, 2–3 weeks. The largest retrospective Ramsay Hunt syndrome treatment study showed a statistically significant improvement in patients treated with prednisone and acyclovir within 3 days of onset.[134] The recommended regime is prednisone 1 mg/kg/day for 5 days followed by a 10-day taper, as well as intravenous acyclovir (250 mg three times daily), or oral acyclovir (800 mg five times daily). Robillard et al.[135] have shown that patients with Ramsay Hunt syndrome treated with prednisone were less likely to progress to complete facial paralysis than untreated patients. The combination of steroids and acyclovir also seems to reduce otalgia, vertigo and post-herpetic neuralgia. Surgical decompression is not indicated.

OTHER VIRAL CAUSES

A variety of viral diseases have been associated with facial nerve palsy. Guillain–Barré syndrome (acute inflammatory demyelinating polyradiculoneuropathy) presents typically 2–3 weeks after an upper respiratory infection probably caused by an abnormal T-cell response against myelin components. The most prominent feature is ascending symmetrical muscular weakness and autonomic involvement with a maximum effect 2–3 weeks after the onset of illness. Facial nerve paralysis may develop and is often bilateral. Supportive management is of the essence, with attention mainly focused on respiratory support and passive physiotherapy. Steroids have been shown to have no beneficial effect and may even delay recovery. The most effective form of treatment is considered to be intravenous immunoglobulin infusion. Epstein–Barr infection (infectious mononucleosis) is clinically characterized by generalized lymphadenopathy, fever and sore throat and may be associated with facial nerve palsy. The presence of at least 10% of atypical lymphocytes on peripheral tests and positive serology will confirm the diagnosis. Forty percent of the EBV-associated facial nerve palsy cases are bilateral (**Figure 112.18**).[136] Facial nerve paralysis during the course of human immunodeficiency virus (HIV) infection can present at any stage of the disease. The presumed mechanisms of paralysis include local infection of the facial nerve or geniculate ganglion by the HIV, inflammatory demyelinating neuropathy or secondary infection precipitated by immunosuppression with agents such as VZV, HSV or EBV.[137]



Figure 112.18 A young girl with a complete right-sided facial palsy caused by infectious mononucleosis.

FACIAL NERVE TRAUMA

As a general rule, management of facial nerve paralysis following trauma is generally deferred until the patient is both medically and neurologically stable as most cases are associated with more life-threatening injuries. This often delays treatment for a large proportion of patients and for many it dictates that a suboptimal management plan has to be adopted, for example when associated with severe head injuries.

Facial nerve paralysis can result from stab wounds to the face or mandibular fractures. If possible, it is advisable to explore the region within 3 days so that a nerve stimulator can be used to identify the distal segments of facial nerve branches. Transection of the cervicofacial or temporofacial primary divisions should be promptly repaired by end-to-end anastomosis. Mobilization to avoid unwanted tension may be necessary if a short segment of nerve is destroyed. Rarely, an interposition graft is necessary. Injuries to branches distal to the lateral canthus or nasolabial fold are too small for anastomosis and are better approximated and glued in position. This offers a better chance of some recovery without synkinesis. If the wound is dirty, it is advisable to identify and tag the facial nerve branches, clean the wound thoroughly and, in severely soiled cases, repair and close at a later stage. The major problem in knife wounds to the face is that damage to the facial nerve is often multi-segmental with transections at more than one level. With each transection the chance of a good functional outcome is diminished.

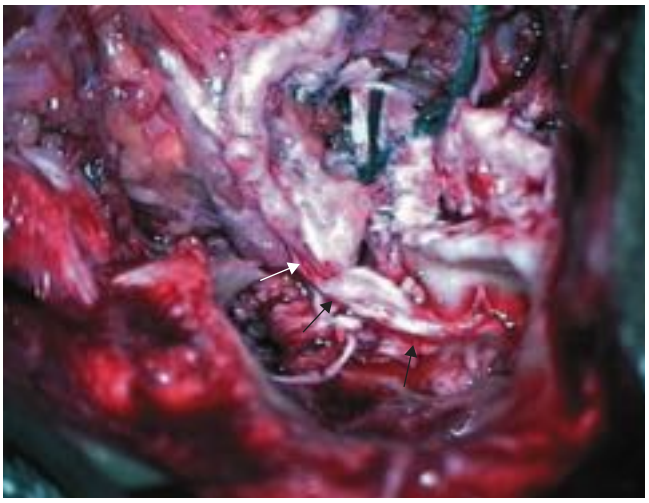


Figure 112.19 This man was shot in the ear and suffered a complete facial palsy. The nerve has been shredded over a significant distance (arrowed).

GUNSHOT INJURIES

Care must be taken when assessing facial nerve function in this type of injury as there is often significant facial oedema and both muscle tone and eye closure appear adequate when in fact they are not. This illusion can last for several days. The mastoid segment of the facial nerve is most commonly affected and often over a long segment. Low-velocity bullets may be found lodged in the mastoid tip.[138] Surgical exploration of the facial nerve should be performed as early as possible. Long delays make identification of the nerve more difficult because of granulation tissue and traumatic neuroma formation. If a segment of the nerve has been destroyed, the proximal and distal ends of the nerve must be trimmed back to a point where healthy fascicles can be seen and then an interval cable graft inserted. Good functional results are rarely achieved and other methods of reanimation should be considered.[139]

There is often considerable bony damage and the potential for subsequent cholesteatoma development should be kept in mind. Open mastoidectomy with a meatoplasty is the surgical technique of choice in this situation as there is a high risk of infection and it may not be possible to find and remove all fragments of skin and bullet (**Figure 112.19**).

FRACTURES OF THE TEMPORAL BONE

Temporal bone fractures are divided traditionally into longitudinal and transverse subtypes, although a significant proportion of these are mixed. Longitudinal fractures are associated with a 20% incidence of complete paralysis and the perigeniculate region is most commonly involved. Transverse fractures have a higher incidence of facial nerve paralysis (50%) and the labyrinthine and mastoid segments are most commonly involved (**Figures 112.12** and **112.13**). Longitudinal fractures are overwhelmingly more common than transverse fractures which is fortunate as outcomes are better. Some authors have recently proposed a different classification according to whether the otic capsule is involved or spared, as this correlates better with the incidence of complications.[140] Patients with otic capsule violating fractures are approximately twice as likely to develop facial nerve paralysis, four times more likely to have a CSF leak and seven times more likely to sustain a profound hearing loss.

The key issues to consider in the management of facial nerve paralysis following temporal bone trauma are (a) if there is an indication for surgical exploration, and if so, (b) when to operate; (c) which is the optimal surgical approach; and (d) which nerve repair technique to use. The use of high-resolution CT scans and ENoG are important in decision-making. If surgical exploration is indicated, the goals are (a) to decompress the nerve to prevent ischaemic injury; (b) to remove bony fragments that impinge on the nerve; and (c) to re-establish continuity in case of transection.

Management in the early post-injury stage

Patients with normal facial nerve function at presentation, regardless of whether they develop delayed palsy or even paralysis, or those with acute onset incomplete palsy without progression, have an excellent prognosis and do not require surgical exploration.[141] Similarly, follow-up with serial ENoG is probably not necessary, although this is not universally accepted. In cases of acute complete paralysis, surgical exploration is warranted if ENoG shows greater than 90% denervation within 6 days of the onset of paralysis and the patient is neurologically stable.[142] The same applies for incomplete palsy that progresses to complete paralysis over time with unfavourable ENoG recordings. In some patients, it is difficult to establish whether the onset of palsy was immediate as the patient may be unconscious at the time of presentation. However, ENoG can be performed on unconscious patients. Lambert and Brackmann[143] have suggested that the indication for surgery should be based on ENoG findings and that time from onset of paralysis should not be taken into account.

Timing of surgery will be dictated by the general condition of the patient: there is no general consensus on the optimal timing, although an early exploration is probably desirable. Chang and Cass[144] suggested decompression within 14 days of injury and May[145] has demonstrated superior results if nerve repair is performed within 30 days of injury. According to Quaranta et al.,[146] recovery of satisfactory facial nerve function can be achieved in more than 75% of cases treated 27–90 days after trauma. It should be noted that there are no studies reporting on the natural history regarding recovery of patients with unfavourable ENoG results.

Management in the late post-injury stage

Owing to trauma-related issues it is not rare to see a patient with facial nerve paralysis many months following injury. As discussed above, ENoG is not helpful after 3 weeks have elapsed. The decision to explore is therefore largely based on CT findings and electromyographic results. The rationale for late exploration is the

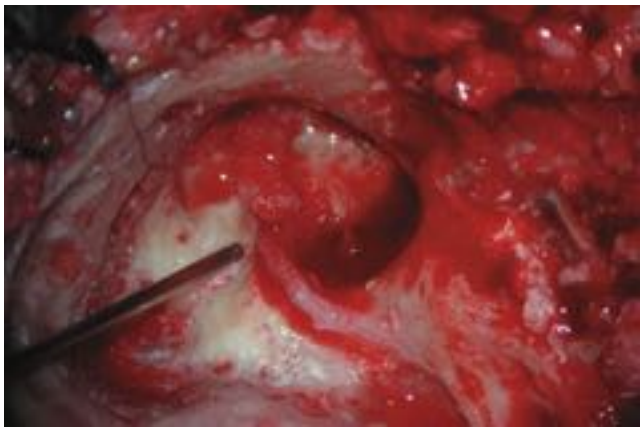


Figure 112.20 This fracture has transected the tympanic segment of the facial nerve. The proximal segment has become fibrotic as a result of organized intraneural haemorrhage and the bone shifts associated with the fracture have made approximation of the ends impossible. An interposition graft was necessary.

need to remove any fragments of bone and fibrosis that may impede regeneration. If no return of facial function is observed 6–12 months after the injury and there are no signs of polyphasic potentials that suggest reinnervation, exploration is indicated with a view to achieving nerve continuity either by end-to-end anastomosis, interposition grafting, rerouting or other reinnervation techniques. If, however, EMG findings suggest long-term denervation (no electrical output), static or dynamic facial reanimation procedures are indicated.

The surgical approach that will be used depends on the site of injury and the hearing status of the patient. In general, a middle fossa approach is preferred for longitudinal fractures in which hearing is preserved. In the very unlikely event of mixed or transverse fractures with serviceable hearing, the same approach may be employed in combination with a transmastoid exploration. In the presence of severe sensorineural hearing loss, a translabyrinthine approach is easier to use and results in less morbidity. Decompression is usually sufficient, although a severely crushed nerve is best resected and primarily anastomosed. If the nerve is transected and if it is possible, an end-to-end anastomosis without any tension on the cut ends is best. Otherwise an interposition nerve graft from the great auricular or sural nerve should be used (**Figure 112.20**). There are no controlled studies on the use of steroids in temporal bone fractures. Administration is based on the assumption that neural oedema is a contributing factor in the progression of nerve injury.

IATROGENIC INJURY

Middle ear and mastoid surgery

The incidence of facial nerve palsy has been reported to be between 0.6% and 3.6%.[146] In the Royal College of Surgeons audit it was found to be 0.8%.[147] The most common site of injury during middle ear or mastoid surgery is the distal tympanic segment including the second genu, followed by the mastoid segment.[148] If an injury to the facial nerve is recognized intra-operatively, exploration with decompression of proximal and distal segments of the nerve should be undertaken. If nerve fibres are found to be herniating, the epineural sheath should be opened with a neurotomy knife or Beaver blade. If more than 50% of the circumference of the nerve has been disrupted it should be repaired with either direct suture or inlay graft.

If facial nerve paralysis is observed immediately post-operatively, it is important to determine whether the facial nerve was identified or its integrity tested intra-operatively. If facial palsy is observed immediately after surgery and the nerve was identified or was not at risk during the operation, a few hours of observation will usually allow for any local anaesthetic-induced weakness to clear. The possibility of a tight mastoid dressing over an exposed nerve should also be considered and it is wise to remove the pack. If the paralysis is incomplete, the patient should be started on oral steroids and observed clinically. In cases of progression to full paralysis, exploration should be considered. Although immediate exploration was advocated in the past, this is no longer justified.[149] Green et al.[150] have not demonstrated a difference between early versus more than 7-day delayed exploration. HRCT imaging should be obtained even though it will probably be subject to artefact from iodine-containing compounds. Perhaps the most important thing is to make sure that a more experienced surgical colleague undertakes the re-exploration or that the patient be transferred to a regional centre where subspecialty expertise is available.

In rare cases, a delayed palsy is observed a few days after uneventful middle ear surgery with a reported incidence of 0.9–1.4%.[151, 152] The aetiology is unclear, although reactivation of HSV or VZV is postulated as the underlying mechanism. Combined use of prednisone and acyclovir should be considered and the overall prognosis appears to be good.

Parotid surgery

The likelihood of temporary facial weakness correlates with tumour location deep to the plane of the facial nerve, previous parotid surgery, previous sialadenitis and the addition of neck dissection to the parotidectomy. All parotid surgery is best undertaken with facial nerve monitoring and at the end of the procedure the main trunk should be stimulated to confirm continuity. If there is no response, the nerve and its branches should be closely inspected for areas of discontinuity. A reduced incidence of facial nerve palsy has been reported with the use of a harmonic scalpel.[153]

Cerebellopontine angle tumour surgery

Post-operative facial nerve function in CPA tumour surgery mainly depends on tumour size and surgical skill. When the facial nerve is lost during dissection, it may be possible to achieve an end-to-end anastomosis or place a cable interposition graft. Unfortunately, this is more often not the case and an expectant approach is probably best lest any fibres have been preserved. A subsequent reanimation procedure can be performed at a later date.

TABLE 112.8 Neonatal facial palsy

Developmental and inherited disorders	Clinical characteristics
Moebius syndrome	Agenesis of VI and VII cranial nerve nuclei. Bilateral facial nerve palsy, abducens palsy, possible involvement of other cranial nerves
Dystrophia myotonica	Progressive familial distal myopathy. Bilateral facial nerve palsy, without abducens palsy at birth. Muscle and extramuscular wasting, swan-like neck (wasting of muscles of mastication and sternocleidomastoids)
Alberg–Schoenberg's disease	Osteopetrosis of bony canals resulting in blindness, deafness and facial paralysis. Present later in childhood, not usually at birth
Melkersson–Rosenthal syndrome	Facial palsy, facial oedema, fissured tongue
CHARGE association	Colobomata, heart defects, choanal atresia, retarded growth, genital hypoplasia and ear abnormalities
Oculoauricular-vertebral syndrome	Abnormal formation of first and second arches
Congenital unilateral lower lip palsy	Hypoplasia of the depressor anguli oris muscle. Cardiac defects in 10%

Neonatal facial nerve injury

The frequency of neonatal facial nerve paralysis ranges from 0.05% to 0.23%.[154] Trauma is the main cause, but other rare congenital conditions should be excluded (Table 112.8). Forceps delivery is associated with a slightly increased incidence of paralysis. The superficial position of the facial nerve at the stylomastoid foramen and the softness of the temporal bone make it vulnerable to injury by this and other presumed mechanisms, such as compression against the infant's shoulder or maternal sacral prominence in cephalopelvic disproportion.[155] Facial nerve paralysis usually involves the entire distribution of the nerve and is usually unilateral. Other signs signifying trauma that may be present include Battle's sign and haemotympanum. EMG responses are present at birth with progressive decline in amplitude over time, as opposed to inherited or developmental disorders where they are absent. Unfortunately, they are rarely obtained and this leaves the surgeon with a diagnostic dilemma. Any child with facial paralysis at birth should also undergo brainstem response audiometry to test hearing as some developmental disorders are associated with cochlear nucleus abnormalities. The prognosis of neonatal facial nerve injury is excellent with more than 90% recovering completely. The indications for surgical intervention are similar to facial nerve paralysis in adults.

Facial nerve paralysis as complications of the ear infection

OTITIS MEDIA

Facial nerve paralysis may complicate both acute otitis media and CSOM. The presumed pathophysiological mechanisms include: direct involvement of the facial nerve by infection through Fallopian canal dehiscences or physiologic canaliculi for neurovascular connections; Fallopian canal osteitis with bone erosion and nerve involvement, inflammatory oedema leading to compression and secondary thrombosis of the vasa nervorum with consequential ischaemia and infarction of the facial nerve, and demyelination of the facial nerve caused by bacterial toxins. The mainstay of treatment of facial paralysis associated with acute otitis media is antibiotic therapy. Steroids may be used, although their efficacy is not supported by any studies. When spontaneous perforation is absent, myringotomy and the insertion of a ventilation tube is generally recommended. Mastoid exploration and facial nerve decompression is essential for patients with CSOM.

MALIGNANT OTITIS EXTERNA

Malignant otitis externa is an invasive *Pseudomonas* or *Aspergillus* infection of the ear canal which may lead to skull base osteomyelitis (Figure 112.21). It mainly afflicts immunocompromised patients, particularly the elderly, insulin dependent and poorly controlled diabetics. Facial palsy indicates advancing infection and invasion through the bony-cartilaginous junction and the fissures of Santorini, under the tympanic ring and posteriorly to the stylomastoid foramen. Ciprofloxacin (750 mg orally twice per day) seems to be the antibiotic of choice and prolonged treatment for a minimum of 6–8 weeks is recommended.[156] However, there are no comparative trials between antibiotics in the literature. Ciprofloxacin has also been safely administered to children with cystic fibrosis and is therefore indicated for treatment of malignant external otitis in the rare paediatric patient. In cases of resistance to ciprofloxacin, antipseudomonal β-lactam agents (ceftazidime, piperacillin, imipenem) with or without an aminoglycoside can be used. Cases attributed to *Aspergillus* infection need systemic antifungal therapy. Surgical management is currently not indicated other than diagnostic biopsies to exclude malignancy. Hyperbaric oxygen has been used on occasion with mixed results and may be considered as an adjuvant treatment for refractory cases although its efficacy remains unproven.[157]

Inflammatory disorders of the facial nerve

Sarcoidosis is an autoimmune systemic disease characterized by non-caseating granulomata mainly developing in the lungs. Facial nerve palsy is the most common otologic manifestation, which can develop either in isolation or with uveitis and parotitis as a component of Heerfordt's disease (uveoparotid fever). A raised angiotensin converting

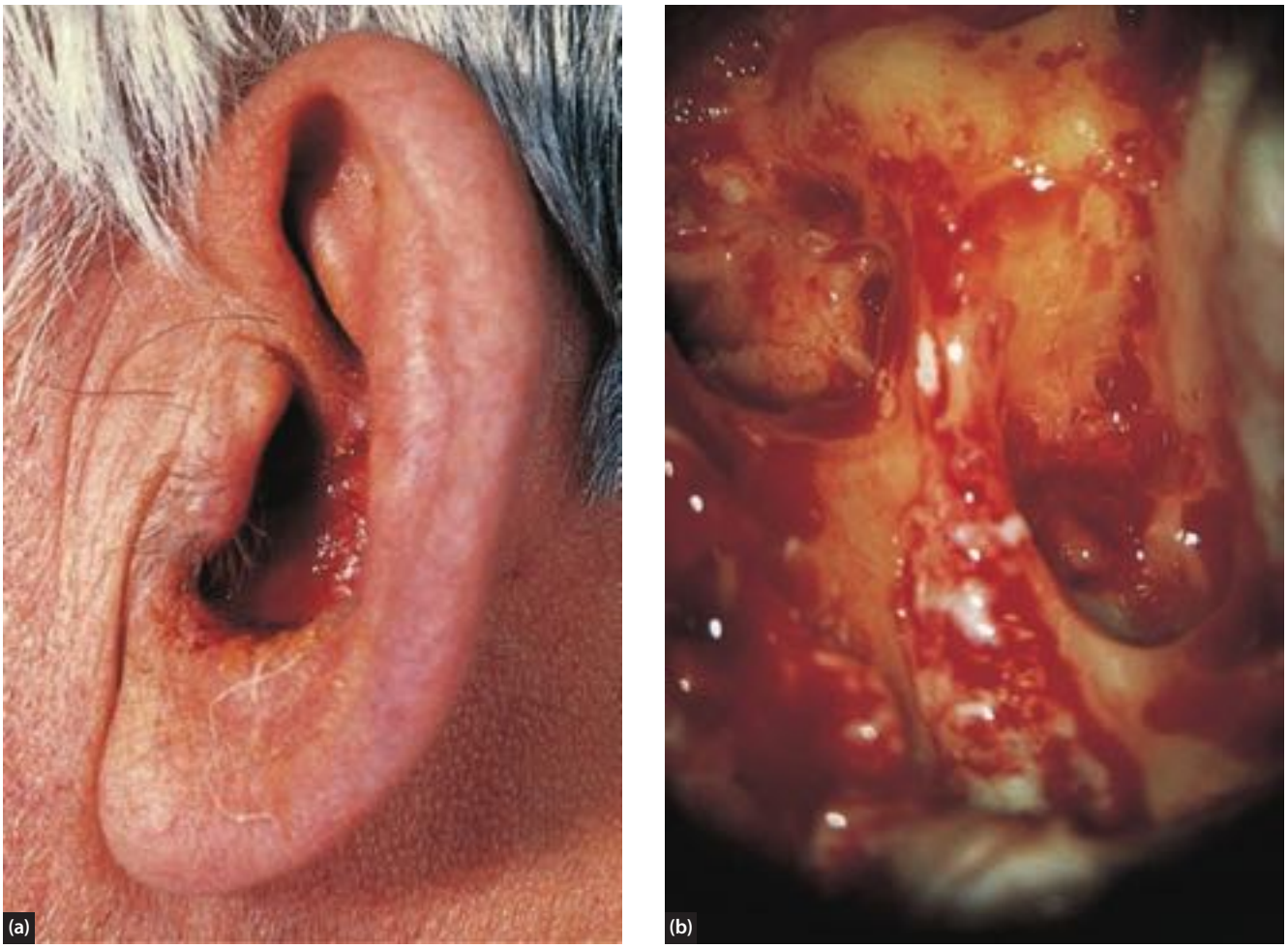


Figure 112.21 Malignant otitis externa. **(a)** discharge from left ear canal; **(b)** on opening at operation, pus was drained from the Fallopian canal. This patient's facial nerve was decompressed at a time well before the introduction of Ciproxin.

enzyme titre helps to confirm the diagnosis. Treatment with systemic corticosteroids is indicated.

Granulomatosis with polyangiitis, formerly known as Wegener's granulomatosis, is an autoimmune necrotizing vasculitis characterized by granulomata of the upper and lower respiratory tracts and kidneys. Facial nerve paralysis may be seen in this condition secondary to middle ear involvement in the presence of a dehiscent Fallopian canal. Clinical suspicion is raised by the synchronous presence of sensorineural hearing loss. Diagnosis is confirmed by elevated circulating antineutrophil cytoplasmic antigen test. Treatment of granulomatosis with polyangiitis includes a combination of cyclophosphamide and steroids. Mastoid exploration and facial nerve decompression is unrewarding and may often aggravate the problem.[158]

Lyme disease is a vector-borne, multisystem inflammatory disease caused by the spirochete *Borrelia burgdorferi*, transmitted to humans by the bite of *Ixodes ricinus* ticks. It is characterized by flu-like symptoms and erythema migrans. Facial palsy can be bilateral and should raise suspicion of the disease, especially in children. Serologic testing can confirm the diagnosis, although sero-conversion can take up to 6–8 weeks. Doxycycline or amoxicillin for 14–21 days is indicated for patients with facial nerve palsy with normal CSF findings. It should be remembered that doxycycline is contraindicated in patients younger than 8 years of age and in pregnant women. Macrolides are suitable alternatives in cases of penicillin allergy.

Multidisciplinary management of established facial palsy

In patients whose facial palsy has not resolved or when recovery is incomplete, the assessment of the degree of impairment and the impact on their physical and psychological well-being is best managed in the setting of a Multidisciplinary Facial Nerve Clinic.[159, 160] Although various models exist, most Facial Nerve MDT clinics comprise surgeons from otolaryngology and plastic surgery and highly specialized facial therapists (physiotherapy or speech and language therapy). Additional support from an oculoplastic surgeon, expert radiologist, clinical photography and psychological services is advised.[161] Patients seen in specialized clinics should expect not only a comprehensive assessment of their facial function and directed management to ameliorate the negative physical aspects of a paralyzed face, but also an attempt at securing

the diagnosis. It is not uncommon for the diagnosis to change once a patient has been seen and assessed under the auspices of the MDT clinic.

PHYSIOTHERAPY FOR INCOMPLETE RECOVERY OF FACIAL PALSY AND SYNKINESIS

Facial physiotherapy techniques for patients with facial palsy vary amongst professionals who specialize in this unique area of practice. A large proportion of the workload is devoted to patients with unresolved idiopathic palsies, although patients with other causes of unresolved facial palsy benefit from the expertise of the therapist.[162, 163] Idiopathic palsy patients may have tightness and shortening of the muscle fibres resulting in a 'frozen face' which may be associated with an aching pain which increases throughout the day. Specific guidance regarding muscle stretches allows the muscles to relax and facial symmetry to improve. Once the muscle length is restored, more active movement is usually achieved.

Given the lack of proprioceptive information from the facial musculature, patients have to relearn to make facial expressions that were previously natural. Facial therapists will spend time guiding the patient in front of a mirror in facial retraining. Novel technologies to engage patients, particularly children, have been developed to help in this regard.

CHEMODENERVATION WITH BOTULINUM TOXIN

Botulinum toxin is utilized as a second-line treatment to further release the over-tightened facial muscles and to facilitate the stretches advised above.[164] In patients with synkinesis, i.e. unwanted muscle contractions resulting from aberrent reinnervation, chemodenervation is helpful in reducing and weakening these unwanted movements.

Occasionally, chemodenervation can be judiciously used to weaken the more active 'normal' facial muscles in order to achieve a more balanced facial appearance and functional benefit for the patient.

FACIAL REANIMATION CONSIDERATIONS

The topic of facial reanimation is beyond the scope of this chapter but some basic principles exist which are considered here. It is generally accepted that a lack of recovery of facial function 12 months following the original insult is considered a permanent deficit. Throughout this period there is a steady loss of motor end-plate units and progressive muscle atrophy, such that after some months reinnervation techniques will have no beneficial effect. Therefore, techniques employing nerve grafting, or nerve transfer are only considered of value if carried out within that first 12-month period and the sooner the better. Historically, ENT surgeons have made use of a hypoglosso-facial anastomosis, providing tone and some active movement in patients with complete loss of ipsilateral facial function. Using an end-to-side neurorraphy or partially opening, rather than transecting, the hypoglossal nerve, it has been possible to preserve good tongue movement.[165] Other cranial nerves may be employed in nerve transfers including the contralateral facial nerve and the nerve to masseter (a branch of mandibular nerve). Whichever technique is employed the patient must expect a long period of rehabilitation and ongoing physiotherapy to achieve the optimum results.

Static reanimation

Given the inability to restore normal facial symmetry and achieve natural spontaneous movement, it is often appropriate for the Facial Nerve MDT to discuss simple small procedures to reduce the burden of facial weakness without the risk of larger more complex procedures. This is particularly the case in older and medically less-robust patient. Periocular surgery, including lower-lid tightening, lateral canthopexy, brow lift and upper eyelid positioning/weighting surgery may be performed under local anaesthesia and can provide benefit for the patient with troublesome eye symptoms.

Various face-lifting techniques can improve the static position of the face. These may be combined with soft-tissue procedures (e.g. wedge resection of the lower lip) to achieve a more balanced facial appearance and more importantly to improve facial function (oral competence).

Dynamic reanimation

In those patients where active movement is desired, particularly in terms of smile, it is usually necessary to bring new tissue to the area. This may be in the form of muscle transfer, for example a temporalis transfer – Labbé procedure[166] or free muscle graft using the gracilis muscle.[167] The latter is preferred in paediatric patients who have the necessary neural plasticity to achieve excellent results following physiotherapy. Depending on the aetiology of the facial nerve palsy, nerve grafting may also form an integral part of this surgery.

PSYCHOLOGICAL ISSUES IN FACIAL PALSY

Facial appearance and non-verbal communication are so central to human interaction that it is no surprise that patients who are unable to eat in public and communicate without embarrassment may suffer significant psychological distress. The development of support networks and groups has enabled patients to benefit from the experience of others and to reduce the isolation associated with living with the effects of facial palsy. Psychological support with counselling is provided in some specialist units and is available through primary care.

The over-arching principle in the management of patients with established facial palsy is to improve facial function, reduce the psychosocial consequences of the facial weakness and improve the overall quality of life for the patient.[168] These aims can be best achieved in a setting where all possible treatment modalities that might be employed in the management of a patient with facial palsy are available.

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BEST CLINICAL PRACTICE

- ✓ Intra-operative facial nerve monitoring is a wise precaution for any surgery around the facial nerve regardless of the surgeon's experience. It is a standard of care in Vestibular Schwannoma surgery.
- ✓ Decompression of the facial nerve in the acute phase after trauma is indicated when paralysis is complete from the outset, there is ENoG evidence of rapid denervation and clear CT evidence of compression or wide displacement of the Fallopian canal.
- ✓ Late exploration of the facial nerve after cranial base trauma is indicated if there is no recovery after 9-12 months and CT evidence of a significant fracture.
- ✓ If a patient awakes from mastoid surgery with an unexpected facial palsy, remove the pack and obtain a CT scan. If no recovery ensues in the first few hours, the ear must be re-explored to establish the integrity of the facial nerve or correct any damage.
- ✓ Antibiotic therapy for malignant otitis externa must be prolonged, often for several months.

FUTURE RESEARCH

- ➤ Although there is some evidence to suggest that Bell's palsy is caused by HSV, definitive evidence is still lacking.
- ➤ Further knowledge regarding aberrant reinnervation and the role of facial therapy in preventing/reducing synkinesis may have a useful benefit for patients.

KEY POINTS

- The commonest cause of facial palsy in adults is an idiopathic palsy.
- Although electrophysiological testing may provide useful prognostic information and serve as a guide to the management of facial palsy, there are some important limitations: it provides no useful information in cases of incomplete facial paralysis and it fails to provide information on the immediate post-paralysis period.
- Ipsilateral recurrent facial nerve palsy or a paralysis with progressive or incomplete recovery should raise the suspicion of malignancy.
- Any facial palsy that does not recover or is recurrent needs further investigation and imaging.

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CHAPTER 113

TUMOURS OF THE FACIAL NERVE

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SEARCH STRATEGY

The data may be updated with a PubMed or MedLine search using the following keywords: facial nerve tumour, schwannoma and neuroma.

INTRODUCTION

Facial nerve tumours are rare. The most common histological type are facial nerve schwannomas (FNS) although facial nerve haemangiomas, malignant nerve sheath tumours and 'skip' lesions from parotid malignancies, amongst others, may also occur.[1] This chapter focuses on FNS, their presentation, diagnosis and management, but will also consider the differential diagnoses for these lesions.

PATHOLOGY

As with other schwannomas, FNS are benign, slow growing tumours arising from Schwann cells within the nerve sheath. Facial nerve neuroma, neurinoma and neurilemmoma are other terms previously used. The classic histology showing Antoni type A and B tissue is indistinguishable from vestibular schwannomas. As such, diagnosis requires correlation with imaging findings and/or intra-operative confirmation of the tumour arising from the facial nerve.

INCIDENCE

Facial nerve schwannomas are rare and thought to account for between 1% and 3% of all cerebellopontine angle (CPA) tumours although are not uncommonly seen as part of neurofibromatosis type 2.[2] A previously reported cadaveric temporal bone study found 5 FNS in 600 specimens, suggesting that these tumours may grow undetected without symptoms.[3]

CLINICAL PRESENTATION

Facial nerve schwannomas can arise from anywhere along the course of the facial nerve from the CPA to the ramifications within the parotid. The presenting symptoms will vary according to the segment involved. The relative frequency of occurrence at each site varies and has been reported to be most common at the geniculate ganglion (68%), labyrinthine (52%) and tympanic (43%) and mastoid segments.[4] In addition, FNS are commonly found to involve multiple segments.[1, 5, 6]

Intratemporal FNS most commonly present with progressive weakness or spasm, although less commonly may present with sudden onset or recurrent facial weakness.[7–8] Tumours affecting purely the internal auditory canal (IAC) or CPA are reported to represent less than 2% of FNS.[9] When isolated to this segment their presentation commonly mimics that of a vestibular schwannoma (VS) with symptoms of hearing loss, tinnitus and imbalance.[9] In these cases diagnostic confirmation of FNS may only occur at surgery thereby presenting an intra-operative management dilemma. This will be considered later in this chapter. Although rare, extra temporal FNS may present simply with a parotid mass.[10]

For FNS that continue to grow and extend intracranially either from the IAC into the posterior fossa or from the geniculate ganglion into the middle fossa, neurological sequelae may develop causing symptoms of brainstem compression/hydrocephalus or seizures.

The natural history of FNS is not as well studied or understood as for VS. However, there is a growing number of published series demonstrating that a significant proportion of FNS do not grow.[5, 11] A recent study of 21 patients with FNS managed with observation for a mean follow-up of 6.4 years (range 4–9) showed that, overall, 43% grew, which corresponded to 10% growth rate in FNS <10 mm in size and 73% growth rate in those >10 mm in size. Furthermore, 18 of 21 (86%) maintained facial function of HB grade III or better.[12]

INVESTIGATIONS

Radiological investigations

The mainstay of diagnosis is with high resolution cross-sectional imaging. A T1 weighted MRI with gadolinium will show an enhancing (often fusiform) lesion at the site of involvement, which may vary in appearance depending on the location. Multiple segment involvement is common and may give a 'beads on a string' appearance.[6,9] Facial nerve schwannomas are classically described as causing smooth bony expansion of the facial nerve canal, which helps to distinguish between contrast enhancement of the facial nerve as seen following a simple Bells palsy and a true facial nerve schwannoma.

Facial nerve schwannomas that are limited to the internal auditory meatus (IAM)/CPA can be difficult to differentiate from VSs (see **Figure 113.1**). However, the advantage of a T1-weighted MRI with gadolinium over other sequences (such as FIESTA) is that it may demonstrate a 'labyrinthine tail' with enhancement of the adjacent facial nerve (see **Figure 113.1**).[6] Involvement of the geniculate ganglion with extension along the greater superficial petrosal nerve makes radiological diagnosis of FNS more obvious (see **Figures 113.2 and 113.3**).

CT of the temporal bones may be helpful in demonstrating smooth bony expansion at the site of the FNS (see **Figure 113.4**). An exception to this well defined appearance has been described when the vertical mastoid segment of the nerve is involved and growth extends into adjacent mastoid air cells giving the suggestion of an aggressive tumour (especially on MR).[13]

Facial nerve schwannomas affecting the tympanic segment of the facial nerve have been described as appearing as a pedunculated mass on imaging but, again, enhancement of the adjacent nerve should help in distinguishing it from other middle ear masses.

Other investigations

Audiometry with a pure tone audiogram and speech audiometry is essential and may influence subsequent management decisions and surgical approaches.

Topographical assessment of facial nerve function (taste, lacrimation and stapedial reflexes) has largely been superseded by other diagnostic modalities and do not usually form part of a standard assessment.

Electroneurography (ENoG) has been advocated as a method for calculating the proportion of facial nerve motor neurons lost to tumour compression. It measures the compound muscle action potential (CMAP) to maximal bipolar stimulation of the facial nerve at the stylomastoid foramen. The investigation is used as an aid in the management of acute facial paralysis because it indicates the severity of Wallerian degeneration in the days after onset of facial weakness. ENoG, however, does have its drawbacks. It relies on comparison of the maximal CMAP derived from the muscles of the affected and normally functioning side and has a poor test–retest reliability. It is particularly inaccurate

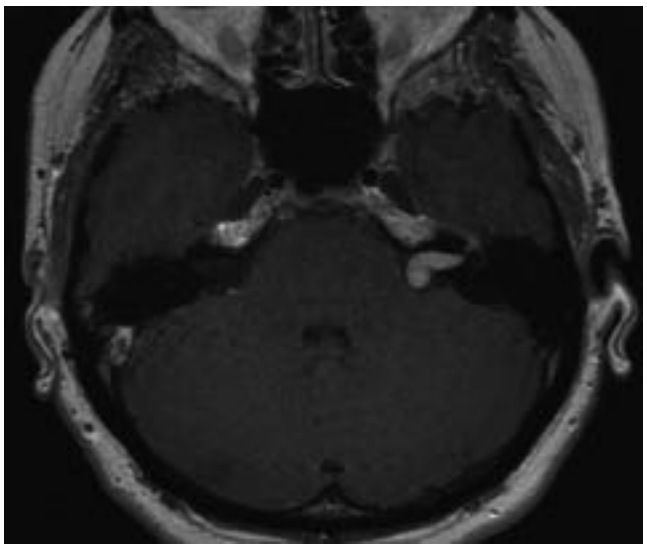


Figure 113.1 Axial T1 weighted MRI of patient who presented with facial weakness showing contrast enhancing tumour of the IAM/CPA with subtle enhancement of adjacent segment producing 'labyrinthine tail'.

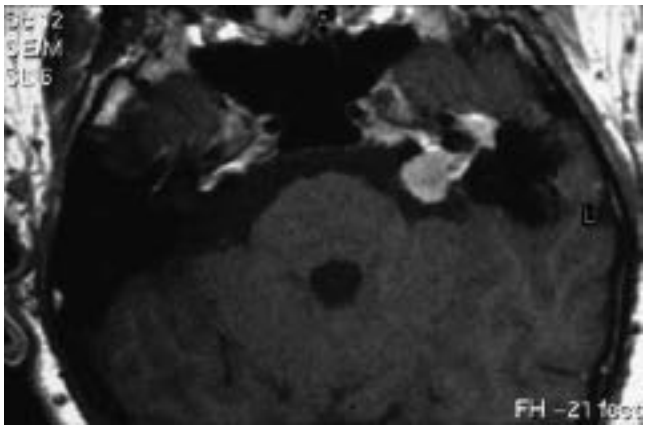


Figure 113.2 Axial T1 weighted MRI with contrast showing facial schwannoma filling the internal auditory meatus and extending along the greater superficial petrosal nerve into the middle fossa.

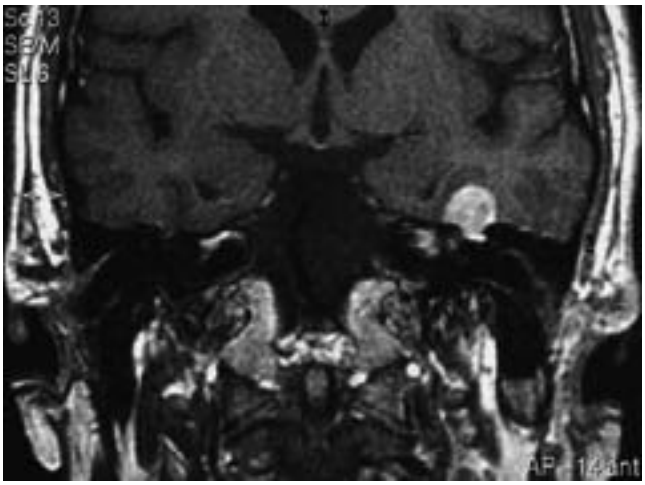


Figure 113.3 Coronal MRI showing a facial schwannoma arising from the geniculate ganglion and extending through the petrosal foramen into the middle fossa, pushing upwards into the temporal lobe.



Figure 113.4 Axial CT of temporal bones at the level of the IAM/geniculate ganglion on the left with a round smooth bony expansion of the geniculate fossa caused by a facial schwannoma. (See **Figure 113.5** for corresponding MRI.)

for assessing longstanding or slowly progressive facial palsy, for two important reasons. First, it is unable to take into account terminal collateral sprouting in response to nerve injury, which increases the number of muscle fibres each motor neuron innervates. Second, it cannot differentiate between motor neurons that are functioning normally across the site of tumour compression and those in conduction block. As such, a clinical assessment of facial function using the House-Brackmann grading system provides a pragmatic assessment for guiding management decisions. Some units do advocate the use of ENoG to monitor for subclinical deterioration in nerve function as an additional factor when considering surgical intervention.[11]

Investigation of intraparotid FNS by fine needle aspiration cytology biopsy has been shown to be unreliable in retrospective analyses.[14–15]

MANAGEMENT

Due to the rarity and heterogeneity of FNS and the inherent problems of conducting prospective trials in this setting (as for VS), management of FNSs remains controversial and lacks good evidence to support any particular treatment algorithm. Overall, however, there does appear to be an evolving philosophy towards a more conservative approach with the paramount aim of preserving optimal facial nerve function for as long as possible.[5, 11] This is in contrast to the previously held wisdom that FNSs should be excised and grafted.[1, 16–17] An acceptance that facial nerve grafting can reach, at best, a House-Brackmann (HB) grade III, has lead to a reluctance to intervene surgically in patients with good facial function (HB I or II).

As for VS, the management options are: observation with serial scanning; radiotherapy (stereotactic or fractionated); and surgery. Management decisions are largely influenced by existing facial nerve function, hearing, tumour location and patient comorbidities.

For patients with an FNS and good facial function (HB I or II), unless there is evidence of significant intracranial extension with mass effect, observation with serial imaging is an appropriate initial strategy for most patients.

For FNSs that have demonstrated growth, the options include stereotactic radiation or surgery (or continued observation). In an effort to prevent deterioration in facial function in FNSs growing within a bony confine or with deteriorating facial function or ENoG, some units advocate bony decompression.[18]

STEREOTACTIC RADIATION

Published reports of stereotactic radiation (SR) treatment for FNS have increased significantly in recent years.[19–21] High tumour control rates of as high as 93% are quoted but these studies include all treated tumours and not just those that have demonstrated growth on serial MR imaging. In a recently published series from Manchester, tumours in only 2 of 11 patients that were managed conservatively with observation grew, giving a growth rate of only 18%.[5] Further larger long-term observational studies are needed to delineate the natural history of these tumours to better measure the true effect size of SR treatment. Nevertheless, given the poor surgical outcomes in terms of facial function, SR remains an attractive option for treating growing FNSs in patients who have good facial function (HB I or II).

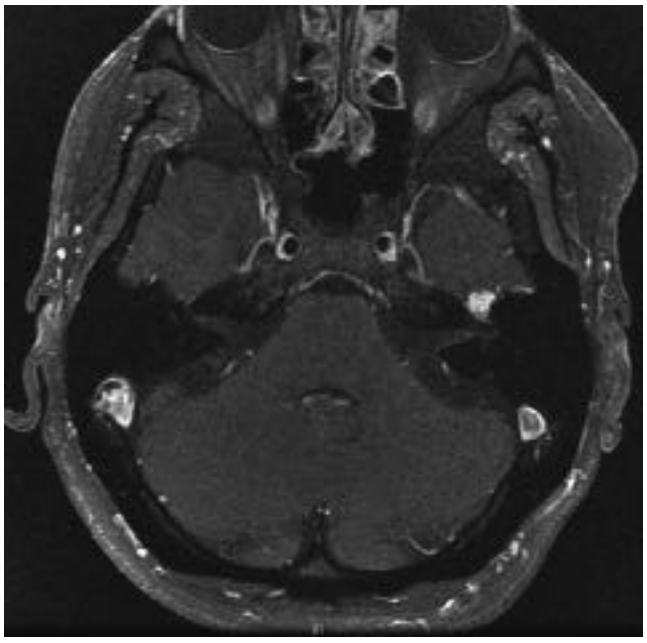


Figure 113.5 A T1 weighted MRI showing enhancing facial schwannoma of the geniculate ganglion from same patient as Figure 113.4.

SURGERY

Surgical intervention is often reserved for growing FNSs that have failed radiation treatment, tumours with significant intracranial extension with mass effect and tumours where facial function has already deteriorated to HB grade III or worse. There is, however, no consensus on the optimal time to intervene or the type of surgical intervention in this scenario. The options include:

- near total/subtotal excision in attempt to maintain nerve integrity with the option of SR treatment if the residual remnant grows
- fascicle preservation surgery/tumour stripping from intact facial nerve
- excision with primary anastamosis, grafting or other reanimation technique.

The choice of surgical approach varies depending on tumour location, levels of hearing and surgeon preference. An FNS involving the mastoid segment of the facial nerve extending through the stylomastoid foramen will require a combined transmastoid/parotidectomy approach, whereas involvement of the geniculate ganglion extending primarily along the superficial petrosal nerve will likely require a middle fossa approach. Tumours extending medially from the internal auditory meatus into the cerebellopontine angle will require a translabyrinthine or retrosigmoid approach depending on surgeon preference. For larger tumours involving multiple segments, combined approaches will be required.

Some units have adopted subtotal excision as a more conservative approach to reduce facial nerve dysfunction. Li et al. published a series demonstrating a regrowth rate of 27% for 15 FNS that had undergone subtotal or near total resection. They concluded that this was not a safe technique despite achieving HB of I or II for 93%.[22] Other centres would consider this acceptable and utilize radiation treatment for growing residual tumour. Fascicle preservation surgery (or tumour 'stripping') has been described as a surgical technique whereby a plane of cleavage can be found between the tumour and the facial nerve, thereby maintaining its integrity.[23,24] Sherman et al. described 5 patients in a series of 10 who had total macroscopic tumour removal leaving an intact facial nerve.[25] All patients achieved HB grade I or II post-operative facial function and one patient had tumour recurrence. O'Donoghue et al. maintained at least 50% facial nerve continuity in 11 of a series of 36 patients undergoing surgery; however, the post-operative results were no better than facial nerve resection and grafting.[26]

For growing FNS where the facial function has already deteriorated significantly, excision of the tumour and involved segment of the nerve offers the best chance of long-term cure. Primary end-to-end anastomosis has the highest success rate and can be performed by mobilization of the nerve when there has been minimal loss of length. More commonly a cable graft is required, such as using the great auricular (or sural nerve if longer length is required). Most would accept that the best outcome possible with this technique is an HB grade III. Techniques vary to achieve the tension free nerve anastomosis but include suturing the epineurium with 8.0–10.0 nylon, using fibrin glue[27] and the use of grafting conduits to aid coaptation such as with autologous vein, tubed fascia or collagen nerve tubules.[18] Clearly, there are many more dynamic and static facial nerve reanimation techniques utilized in this setting that cannot be covered in this chapter.

MANAGEMENT OF THE INTRA-OPERATIVELY DIAGNOSED FNS

As described earlier, the clinical presentation and radiology may not always give the diagnosis of FNS and only at surgery does it become apparent that the tumour is arising from the facial nerve. An index of suspicion in these cases may avoid inadvertent injury. During a translabyrinthine approach to a presumed VS, the finding of a normal superior vestibular nerve overlying a tumour antero-superiorly in the IAM presents a surgical dilemma. At this point the options include: abandoning the procedure; decompression; or some form of partial/total excision as described above. This decision will depend on the individual case, particularly the preoperative facial nerve function, as well as the surgical team's management philosophy.

A middle ear mass arising from the facial nerve identified intra-operatively should not be biopsied as this may cause a facial palsy. Appropriate imaging should be organized post-operatively, which is likely to aid diagnosis, with an FNS often identified on the horizontal facial nerve segment.

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis of an intratemporal facial nerve schwannoma is a facial nerve haemangioma. Clinically these are associated with a significantly worse facial function at presentation, even when relatively small.[28] There may be similar appearances to FNS on imaging but with subtle differences. Bony erosion may not be smooth because haemangiomas do not have a capsule. They do not usually affect multiple segments as FNS do. Haemangiomas have been described as having a 'honeycomb' appearance on imaging.[29] Again, evidence to support management decisions is sparse but given the early loss of facial function and the possibility to resect these keeping the facial nerve intact, some advocate early intervention.[30, 31]

Malignant peripheral nerve sheath tumours can affect the facial nerve and occasionally occur in association with neurofibromatosis type 1. Treatment usually requires radical surgery, often with adjuvant radiotherapy. Other malignant tumours affecting the facial nerve include perineural spread from the parotid gland tumours as seen with adenoid cystic carcinoma and others.

CONCLUSION

FNSs are rare and usually present with disturbance of facial function, with or without audiovestibular dysfunction. Management decisions must be tailored to each patient based on existing facial and audiovestibular function and tumour location but management philosophy varies between units internationally. The primary aim of management is preservation of optimal facial function for as long as possible.

FUTURE RESEARCH

- ➤ Accurate long-term data on FNS managed with observation will provide a better understanding of the natural history of this condition, which will help better counsel patients.
- ➤ The results of long-term data assessing the efficacy of SR treatment are awaited, including the results of subsequent surgery and reanimation in those that fail radiotherapy.

KEY POINTS

- FNS should be considered in all patients with a presumed diagnosis of VS presenting with facial spasm or weakness.
- Surgical excision with facial nerve grafting can achieve a HB grade III facial function at best.
- Most surgeons avoid/delay excision of FNS whilst good facial function is maintained.

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CHAPTER 114

OSTEITIS OF THE TEMPORAL BONE

Cheka R. Spencer and Peter Monksfield

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SEARCH STRATEGY

Data presented in this chapter may be updated by a National Library of Medicine PubMed search of all medical literature using the keywords: skull base osteomyelitis, malignant otitis externa, necrotizing otitis externa, limited to human, English language and full text.

INTRODUCTION

Osteitis is defined as inflammation of bone. It can be due to a number of reasons, the most common of which is secondary to infection. Acute infection of the temporal bone known as acute mastoiditis and chronic mastoid infections coupled with middle ear disease and chronic otitis media are dealt with in other areas of this book.

Temporal bone osteomyelitis, more often called skull base osteomyelitis as it progresses to other bones of the skull base, is the more invasive form of temporal bone osteitis. It usually occurs as a result of otitis externa in immunocompromised individuals. It can cause neuropathy of cranial nerves and is resistant to treatment.

Other inflammatory conditions affecting the temporal bone are rare and much of the literature is limited to case reports rather than case series or larger studies.

SKULL BASE OSTEOMYELITIS

Definition

Skull base osteomyelitis is a rare complication of otitis externa. It is a vicious infection in which the soft tissue pathogens have spread to the periosteum and temporal bone of the skull causing necrosis. This may be associated with involvement of the facial nerve, carotid artery and jugular vein, including the bulbar and hypoglossal nerves. The infection may then progress to other bones of the skull base.

Nomenclature

The condition was first described in 1959 by Meltzer and Kelemen, who named it 'pyocutaneous osteomyelitis of the temporal bone'.[1] Subsequently, Chandler coined the term 'malignant external otitis' in 1968 when presenting his series of 13 patients with progressive osteomyelitis of the temporal bone.[2] He termed it malignant due to the aggressive clinical behaviour, poor treatment outcome and high mortality rate for the patients affected by this disease. This used to be as high as 50% but has significantly reduced with better antibiotic regimens. The term 'malignant' is controversial as many authors feel some may misconstrue the inflammatory process as neoplastic and advocate 'necrotizing otitis externa' instead.[3] It has been suggested that 'necrotizing otitis externa' be used for aggressive soft tissue infection without bony involvement.[4] Otogenic 'skull base osteomyelitis' refers to the more severe clinical entity following spread of infection through the soft tissue and cartilage with histological or radiological confirmed bony involvement.

Epidemiology

Skull base osteomyelitis most frequently affects the elderly and diabetic.[2, 5–18] The national incidence of skull base osteomyelitis, according to the Hospital Episodes Statistics (see **Figure 114.1**), is increasing significantly (from 67 in 1999–2000 to 421 in 2012–2013) out of proportion to the increase of hospital admissions in general[8, 12] This is thought to be due either to the increased number of elderly

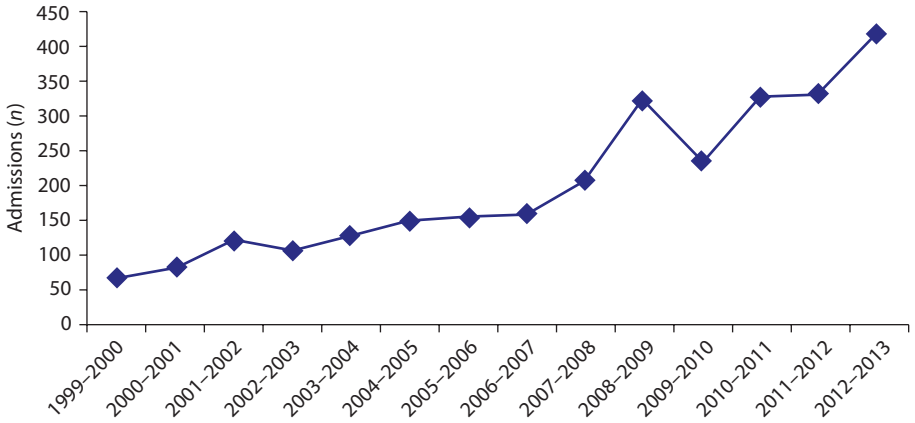


Figure 114.1 Cases of necrotizing otitis externa 1999 to 2013 according to the Hospital Episodes Statistics data.[8]

diabetics or to an increased index of clinical suspicion, and is likely to be both of these factors. The reported prevalence of diabetes in this condition ranges from 65% to 100% of patients.[2, 5, 13] It is postulated that endarteritis, microangiopathy and small vessel obliteration prevalent in the elderly diabetic in addition to their innate defects in humoral immunity, predispose them to this condition.[9, 15] Patients are usually older than 60 years of age and there is a male preponderance with a ratio of 2:1.[12, 17] Conditions causing immunosuppression such as HIV/AIDS, steroid usage, chemotherapy, anaemia, leukaemia, lymphoma, neoplasia and renal transplantation are also predisposing factors to skull base osteomyelitis.[5, 6, 8, 13] The epidemiology of skull base osteomyelitis is said to be changing, with more presentations amongst the immunocompromised.[12]

HIV-affected patients with skull base osteomyelitis tend to be younger than those with diabetes. They are also more likely to have a fungal infection (i.e. *Aspergillus sp.*), particularly when CD4 counts are less than 50 cells/mm.[5]

Skull base osteomyelitis in children is rare. It is most often seen in immunocompromised states such as immunoglobulin A (IgA) deficiency, acute monocytic leukaemia, iatrogenic neutropenia and bone marrow transplantation. Diabetes as a risk factor is not as common in children as in adults.[5, 12, 15]

Pathophysiology

Various factors are said to account for the susceptibility of diabetics to skull base osteomyelitis including their weakened immune response to *Pseudomonas aeruginosa* infection and the high pH of their cerumen.[5, 6, 9, 13–15, 17] In all cases, the infection spreads to the skull base from the external auditory canal through the fissures of Santorini. At the osteocartilaginous junction, the infection spreads medially to the tympanomastoid suture along venous canals and fascial planes invading connective tissue, cartilage, bone, nerves and blood vessels. The inflammatory process alters the morphology of the compact bone of the skull base, changing it to granulation tissue.[5, 9] As the infection progresses to the skull base foramina it causes cranial neuropathies. The facial nerve is most commonly affected due to its close relation to the external auditory canal. The disease can spread medially and subsequently affects nerves around the jugular foramen. Further spread of disease can affect abducens and trigeminal nerves around the petrous apex, and also the optic nerve. Septic thrombosis of the sigmoid sinus and internal jugular vein may also complicate skull base osteomyelitis should the infection spread there. Histologically, new bone formation is observed next to areas where bone has been destroyed. The otic capsule and middle ear structures are very resistant and are rarely, if ever, involved in the disease.[5, 9]

Diagnosis

The diagnosis of skull base osteomyelitis is based on the clinical features, microbiology for culture, radiological changes within the bone of the skull base and histology showing inflammation without neoplasia.[11] Fungal pathogens may also be identified on silver staining of histological sections.[5]

CLINICAL FEATURES

Patients with skull base osteomyelitis are usually elderly diabetics presenting with severe unremitting otalgia, unilateral otorrhoea and a hearing loss. There is usually a history of ear canal trauma, often after irrigation for wax removal.[13] Self-inflicted trauma has also been implicated and a strong relationship between laterarality of skull base osteomyelitis and handedness has been reported.[18] Otalgia that is nocturnal, deep, lancinating and disproportionate to the clinical signs is highly suggestive of osteomyelitis. It is often resistant to analgesics. It is the most common presenting symptom with a prevalence of 75–100%.[6, 7]

Purulent otorrhoea, the second most common symptom and sign, in an exquisitely tender and oedematous ear canal, is found on examination in more than half of the cases.[9] Inspection of the floor of the ear canal may reveal granulation tissue or exposed bone (see **Figure 114.2**). There may also be a polyp or granuloma in the canal obstructing the view of the tympanic membrane. The granulations should be sent for histological analysis to exclude malignancy, histiocytosis and tuberculosis.[6] Patients with HIV infection often lack granulation tissue.[13]



Figure 114.2 Necrotizing otitis externa with granulations of the floor of the right external auditory canal. Reproduced from Carney.[37]

The hearing loss is usually conductive due to external auditory canal obstruction by granulation or oedema. Sensorineural hearing loss is usually due to pre-existing presbycusis.[5]

As bony destruction and inflammation progresses medially through the skull base to the foramina, cranial neuropathies ensue initially with facial paralysis (in up to 25% of patients). This is followed by cranial nerves IX, X, XI, XII and then VI and II. Meningitis, cerebral abscess and sigmoid sinus thrombosis are late signs that are associated with a poor prognosis.[6, 9]

Children with skull base osteomyelitis usually develop facial nerve palsies earlier due to their more medial fissures of Santorini and their underdeveloped mastoid process.[13]

Parotitis and trismus due to masseter myositis and temporomandibular joint involvement is a rare clinical feature that has been described.[9]

A meta-analysis which sought to develop a clinically useful prognostic scoring system found the following factors to have a statistically significant negative effect on outcome: cranial neuropathies, external auditory canal granulations, bilateral symptoms and positive aspergillus cultures.[12]

BACTERIOLOGY

Pseudomonas aeruginosa, a Gram-negative obligate aerobe, is the most common bacteria species in skull base osteomyelitis.[5–7, 12–14] It is opportunistic and only a pathogen when the natural host defences are defective.[9] It has the ability to invade local vasculature and cause a focal coagulative necrosis of the surrounding tissue. Diabetics are susceptible to *P. aeruginosa* infection due to their poor phagocytosis of polymorphonuclear leucocytes. Virulent species have a mucoid surface layer that confers additional protection against phagocytosis. They may additionally produce lytic enzymes (for example, collagenases and elastases) and endotoxins, resulting in a necrotizing vasculitis.[6–9] Some strains also produce neurotoxins, which likely play a role in the development of cranial neuropathies.[6]

Staphylococcus aureus, *Staphylococcus epidermidis*, *Proteus mirabilis*, *Klebsiella oxytoca*, *Klebsiella pneumonia, Burkholderia cenocepacia, Enterobacter cloacae* and *Streptococcus constellatus* are other bacteria that have been implicated in the pathogenesis of skull base osteomyelitis.[5–7, 12]

Fungal infections are more commonly associated with the immunocompromised (e.g. HIV/AIDS) than with diabetics. In contrast to pseudomonal skull base osteomyelitis, these originate more often in the middle ear or mastoid. *Aspergillus fumigatus*, is the most common fungal organism isolated. It is associated with a worse prognosis than *Pseudomonas* when it is the causative agent. Others include *Aspergillus niger, Aspergillus flavus, Candida sp., Malassezia sympodialis* and *Scedosporium apiospermum*.[5–7, 9, 12–15, 17]

RADIOLOGY

All imaging modalities are reliant on the experience and confidence of the radiologist reporting the scans in order to help establish the diagnosis and guide treatment. A high-resolution computed tomography (CT) scan is valuable in diagnosing bony erosion and reduced density in the skull base. However, the value of CT scans is limited due to it only detecting bony demineralization of 30% or greater.[6, 9, 19] A negative CT scan must therefore be treated with caution as a potential false negative, as demineralization may take months to appear.[8, 13] A contrast-enhanced CT scan is useful in evaluating the extent and severity of extratemporal soft tissue involvement. Other features of complicated skull base osteomyelitis, such as abscess formation, mastoid and temporomandibular joint involvement, as well as progression of disease to the petrous apex and carotid canal, can also be demonstrated on CT scanning. However, CT scanning cannot reliably measure treatment response, distinguish between neoplasia and inflammation or show intracranial or bone marrow involvement.[8, 9, 14] It has been shown to depict persistent cortical changes 12 months after initiation of treatment.[11] It is nonetheless useful at the initial evaluation to outline the extent and location of the osteomyelitic process. Magnetic resonance imaging (MRI) is generally good at soft tissue differentiation and in skull base osteomyelitis can depict bone marrow oedema. Nonetheless, MRI is unable to assess response and resolution of disease and has also been shown to depict soft tissue and marrow abnormalities months after treatment has been completed.[6, 9, 11]

Nuclear imaging is useful in diagnosing skull base osteomyelitis, defining its extent and evaluating response to treatment and resolution of infection. Technetium-Tc ^{99m}-methylene-diphosphonate (^{99m}Tc-MDP) or Technetium-Tc 99-hydroxymethylene-diphosphonate (^{99m}Tc-MDP) scintigraphy has almost 100% sensitivity.[5] Its radiotracer accumulates in areas of high osteoblastic activity even in early cases of the disease. It has low specificity as it is also positive in malignancy; and so histological confirmation is important. As it

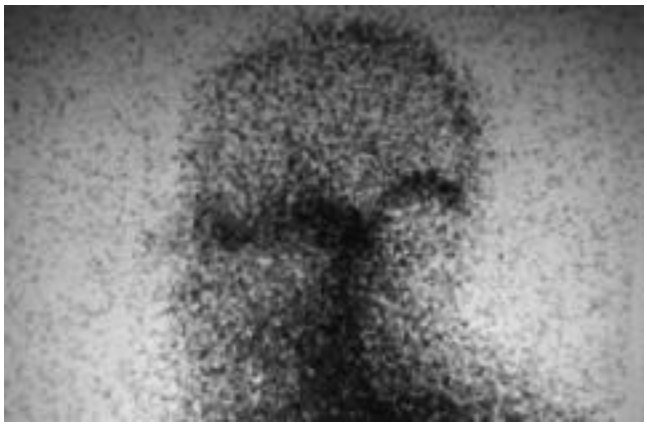


Figure 114.3 Indium labelled white cell scan of a patient with necrotizing otitis externa showing increased uptake in the left temporal bone. Reproduced from from Carney.[37]

cannot distinguish between active infection and bone remodelling, Gallium-67-citrate scanning is often utilized to monitor treatment response.[11, 14] It is based on the propensity of Gallium Ga 67 citrate to accumulate in areas of active inflammation in both soft tissue and bone. As Gallium uptake normalizes with disease resolution, unlike ^{99m}Tc MDP, it is a reliable tool to gauge response to treatment.[6, 9, 11] It should ideally be repeated every 4 weeks to monitor response to antibiotics until it is no longer positive.

Indium 111 (111 In) labelled leucocyte scintigraphy detects neutrophil mediated inflammation (see **Figure 114.3**). Single photon emission computed tomography (SPECT) creates 3-D pictures using Indium 111 or Gallium 67, which optimize anatomical localization.[5]

A meta-analysis of 23 studies seeking to determine which modality was most accurate found that fluorodeoxyglucose positron-emission-tomography (FDG-PET) was most accurate in confirming or excluding osteomyelitis but not significantly better than the combination of ^{99m}Tc bone and leucocyte scintigraphy or Ga67 scintigraphy.[11] Such modalities may not be available in most acute settings.

Treatment

AURAL TOILET

Aural toilet of the external auditory canal, as with uncomplicated otitis externa, is vital. It enables control of granulations and pain. Controversy surrounds the use of topical anti-microbial therapy in these cases as it may make culture of the pathological organism difficult.[4]

CONTROL OF DIABETES

Patients with poorly controlled diabetes are more susceptible to developing skull base osteomyelitis than diabetics with satisfactory control of serum glucose levels.[18] Aggressive glycaemic control in diabetic patients can be as crucial a management strategy as systemic antimicrobial therapy.[5, 13] Achieving good control of serum glucose may be difficult with invasive infection.

SYSTEMIC ANTIBIOTICS

Long-term systemic culture-directed antimicrobial therapy is the mainstay of treatment of skull base osteomyelitis. This is on average continued for at least 6–8 weeks depending on the resolution of symptoms,[5] but in advanced cases could be administered for months. In the ideal setting, antimicrobial therapy should be continued for as long as the gallium-67 scan remains positive. Fluoroquinolones have transformed the treatment of skull base osteomyelitis.[20] They are antipseudomonal, have good bone penetration and good oral bioavailability, and have fewer side effects than such alternatives as penicillins and aminoglycosides. Monotherapy with oral ciprofloxacin (750 mg twice daily) is the preferred initial regimen[5, 21–23] although some experts, with no conclusive evidence, still advocate parenteral antimicrobials converted to oral once the serum C-reactive protein (CRP) and/or the erythrocyte sedimentation rate (ESR) start to decline.[24] The addition of rifampicin (600 mg twice daily) has also been suggested, again with no direct evidence that it confers additional benefit.[25]

The incidence of *Pseudomonal* resistance to fluoroquinolones worldwide is increasing.[16] Cephalosporins active for pyocyanin (i.e. ceftazidime, cefepime), penicillins (i.e. ticarcillin, clavulanate) and aminoglycosides either in combination or as monotherapies are suitable alternatives in the context of resistance.[5, 7] Amphotericin B is the antifungal agent of choice for skull base osteomyelitis of fungal origin.[26] Oral itraconazole may be used after a successful course of amphotericin B.[27]

HYPERBARIC OXYGEN

The use of hyperbaric oxygen as an adjunct to systemic antimicrobial therapy has been debated with reports that it confers a beneficial effect.[27–29] It increases the partial pressure of oxygen, relieving hypoxia and enhancing the oxidative killing of microbes. A Cochrane review, however, found that there was no evidence from randomized controlled trials to support this treatment.[30]

SURGERY

In contrast to the era when the condition was first described, which saw radical debridement advocated to improve survival, surgery has a limited role in the management of skull base osteomyelitis. It is primarily performed to obtain specimens for culture, to locally debride granulation tissue and to exclude malignancy.[17] In selected cases it may be necessary to remove dead sequestra and drain associated abscesses.[5] Facial nerve decompression for complete facial palsies has unproven therapeutic benefit.[16]

OTHER INFLAMMATORY CONDITIONS AFFECTING THE TEMPORAL BONE

Sarcoidosis

Sarcoidosis is a granulomatous inflammatory condition that can affect several organs. It is thought to be due to an

autoimmune response by CD4 lymphocytes and mononuclear phagocytic cells against an unspecified antigen that evolves into a granuloma.[31] The vast majority of patients will have pulmonary involvement but other organs can be affected such as the eyes, spleen, mucous membranes and spleen.

In osseous sarcoidosis, which occurs in 1% to 13% of patients with sarcoidosis, the granulomatous inflammation is within the bone marrow. The petrous apex has been shown to be pneumatized in 30% of temporal bones,[31] with the remaining cases containing bone marrow, which could be a focus for sarcoidosis.

Clinical features have been reported to include otalgia, sensorineural hearing loss, aural fullness, tinnitus, disequilibrium and vertigo. Otomicroscopy is likely to be normal. Neurosarcoidosis, which occurs in 5% of cases, may cause cranial neuropathies with the facial nerve most commonly affected.[31]

Bony involvement exhibits threepatterns of radiographic appearance: lytic, permeative and destructive.[32] ^{99m}Tc-MDP scintigraphy and CT scanning are useful diagnostic tools in identifying bony lesions.[33] Biopsy of accessible lesions is useful when the diagnosis is unclear (e.g. suspected malignancy).[31, 33] There is no consensus on the length of time serial imaging should continue but annual surveillance scanning has been suggested.[31] Oral corticosteroids are the usual treatment modality in sarcoidosis.

Paget's disease

Osteitis deformans, also known as Paget's disease, is characterized by increased osteoclast activity, resulting in bony resorption, followed by osteoblast-mediated disorganized new bone formation. This results in a thickened, hypervascular, hypodense bone that is susceptible to fracture.[34]

It affects 3% of people aged over 40 years, with males more frequently affected.[34] The temporal bone is affected in 65–70% of cases.[35] Hearing loss occurs in 30–50% and vestibular dysfunction in 20–25%.[34] CT scanning demonstrates cotton wool appearance of involved bone due to replacement of marrow with hypodense bone. ^{99m}Tc-MDP scintigraphy is very sensitive in the early stage of the disease process as it is taken up by active osteoblasts.[34] Bisphosphonates that inhibit osteoclast activity are the mainstay of treatment. Zoledronate has been found to be the most potent bisphosphonate in suppressing disease activity.[36]

KEY POINTS

- Skull base osteomyelitis is a severe infection usually arising from otitis externa.
- The incidence of this infection is increasing.
- It affects the elderly, diabetics and immunocompromised individuals.
- Treatment comprises aural toilet, diabetic control and long term systemic antibiotics.

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CHAPTER 115

SQUAMOUS CELL CARCINOMA OF THE TEMPORAL BONE

Liam Masterson and Neil Donnelly

Historical background 1425
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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed, EMBASE and CINAHL search using the keywords: squamous cell carcinoma, temporal bone, external auditory canal, lateral skull base and free tissue reconstruction. The evidence in this chapter is mainly level 3 or 4. The clinical recommendations are predominantly B and C.

HISTORICAL BACKGROUND

Schwartze and Wilde provided the first description of temporal bone carcinoma in 1775, but it was not until the 1880s that Kretschmann, Politzer and Zeroni confirmed the existence of this pathology.[1–3] In 1917, Newhart published the first accurate case series, which consisted of 34 patients with squamous cell carcinoma (SCC) affecting the middle ear cavity, all of whom died after a short period of observation.[4]

The principle of *en bloc* resection emerged in the 1950s after reports by Campbell et al.[5] Using this approach, 20 years later, Lewis published a 25% 5-year survival in a cohort of 100 patients.[6] Modern skull base and reconstructive surgery techniques have improved the treatment of SCC of the temporal bone. Surgery is now more effective due to a greater understanding of skull base anatomy. Imaging techniques such as magnetic resonance (MR) and computed tomography (CT) help produce accurate assessment of the disease extent with particular regard to soft tissue involvement and/or bone erosion. With this approach, recent case series have demonstrated improved control of local advanced (T4) disease with 5-year survival rates ~40%.[7–10]

EPIDEMIOLOGY

SCC is the most common tumour type to occur in the temporal bone. The reported incidence is <6 cases per million per year, which accounts for 0.3% of all cancers within the head and neck. There is a slight predisposition to the male sex and the median age at presentation is within the seventh decade.[11–17]

AETIOLOGICAL THEORIES

Established risk factors for SCC within the epithelium of the temporal bone are chronic suppurative otitis media (CSOM) and previous radiotherapy.[8, 18] Exposure to ultraviolet light may be a risk factor for SCC that originates in the external auditory canal (EAC).[11]

One theory, which may provide a connection for the various predisposing factors, is the establishment of a chronic inflammatory process leading to metaplastic or neoplastic change. No strong evidence exists for occupational exposure to radiation or chlorinated disinfectants.[19]

Chronic suppurative otitis media

Chronic otitis media and cholesteatoma are common in patients with SCC affecting the temporal bone.[8, 20] In recent years several studies[21–23] have suggested an aetiological role for high risk human papillomavirus; however, they are limited to archival samples with disparate methods of collection. As yet, no study has been conducted on a prospective basis with fresh tissue due to the infrequent nature of this condition. It is also not clear if this viral subgroup demonstrates an improved survival after treatment.

Radiation-associated tumours

A past medical history of radiotherapy is relevant and may serve as a red flag at presentation. Goh et al.[24] reported seven patients with temporal bone malignancy, all of whom were initially treated by radiotherapy for head and neck disease. The latency period before symptoms were detected ranged from 5 to 30 years.

Although radiation-associated tumours of the temporal bone occur with a low incidence, their prognosis can be poor.[25] This potential risk should be considered when deciding upon the most appropriate treatment for individuals with tumours of the head and neck – especially if the patient is young and/or the condition is benign (i.e. acoustic neuroma or vascular malformation).

Exposure to ultraviolet light

The most common type of primary cancer in the EAC is SCC. It is suggested that long-term ultraviolet light exposure to the pinna or lateral concha can lead to carcinogenic change that migrates medially.[11] This is more likely in Caucasians, who are more prone to non-melanomatous skin cancers in sun exposed areas. A genetic predisposition to skin cancer may also exist, manifesting as the development of skin cancers in sites not exposed to sunlight (in addition to the more conventional locations).

SURGICAL ANATOMY AND CLINICAL FEATURES

Tumour spread is difficult to predict due to the complex anatomy of the temporal bone. The cartilaginous portion of the EAC provides minimal resistance to malignant invasion and the foramen of Huschke and fissures of Santorini are a source of direct egress to the parotid and temporomandibular regions. Although the bony canal is more resistant to local disease spread, posterior involvement of the mastoid cavity may occur. Medial spread along the EAC can extend through the tympanic ring, allowing entrance to the middle ear cavity and increasing the probability of conductive hearing loss. Invasion of blood vessels of the EAC gives rise to bloody otorrhoea. Once in the middle ear cavity, involvement of the Fallopian canal may result in facial nerve palsy. Extension through the petrous apex and invasion of the internal carotid artery (ICA) is possible but less likely due to the resistant bone of the otic capsule. The Eustachian tube and local neurovascular structures provide a potential method of tumour spread beyond the temporal bone to the nasopharynx, infratemporal fossa or neck. Extension to the inferiorly based jugular foramen may cause dysphonia or dysphagia by involving the vagal, glossopharyngeal or hypoglossal nerves.

Superior invasion through the tegmen tympani is a frequent occurrence and will allow spread to the middle fossa dura and/or the temporal lobe. Less frequently, malignancy within the mastoid will allow direct spread to the posterior cranial fossa.

Node-positive disease is an infrequent finding for early stage tumours (T1–2) but may occur in 10–20% of cases of advanced disease (T3–4).[8, 26] The first echelon lymph nodes are often within the parotid gland and these drain into pre-auricular nodes en route to the jugulodigastric and deep cervical chain of lymph nodes.[27] The integrated pathway of the facial nerve through the temporal bone results in 10–30% of patients with suboptimal facial function at presentation.[7, 8, 14–16] Involvement of the nerve may be found at the stylomastoid foramen/mastoid tip, Fallopian canal, geniculate ganglion or intracranial pathway.

Distant metastases are rarely reported but when present will normally occur in the liver, lungs or bone.[28] Haematogenous spread from other sites to the temporal bone can be possible and should form part of the differential diagnosis.[29]

DIAGNOSIS AND INVESTIGATION

History

The clinical history is relevant if temporal bone malignancy is to be diagnosed at an early stage. Moody et al. showed that the average time from onset of symptoms to the time of primary treatment for cancer was 3.9 years.[26] Common presenting symptoms include otalgia, blood-stained otorrhea and hearing loss. As many patients have associated cholesteatoma or CSOM, a change in clinical pattern can point to the development of a more sinister pathology.[11] If cranial palsies are noted at presentation, skull base osteomyelitis is a more likely differential but a malignancy should be actively excluded.[30]

The frequency of reported symptoms for large contemporary series is reported in **Table 115.1**.

Examination

Clinical examination should include inspection of the pinna, external ear canal and middle ear for scars, ulcers,

TABLE 115.1 Frequency of presenting symptoms (%)

	Gidley[7]	Masterson[8]	Gillespie[16]	Nyrop[13]	Leonetti[15]	Pensak[14]
Otalgia	52	53	53	35	73	74
Otorrhoea	62	55	73	45	69	84
Hearing loss	44	n/a	33	25	69	62
Facial palsy	16	17	13	n/a	30	18

mass lesions or soft tissue swelling. In patients with chronic otitis externa or CSOM, it may be difficult to determine malignant change from inflammation and this fact alone can account for diagnostic delay. An endophytic or exophytic mass within the EAC is likely to be malignant and is a strong indication for an urgent biopsy (**Figure 115.1**). Facial nerve assessment should be meticulously documented along with all other cranial nerves. A complete head and neck examination is performed, looking in particular for enlarged nodes within level II, III and Va.[13] The patient's general medical condition should be evaluated as this may greatly impact treatment options and outcome.

Biopsy and histological confirmation

A trans-canal biopsy is required to determine whether the lesion is malignant or benign. A staging mastoidectomy is not appropriate as this may complicate definitive treatment once a formal diagnosis has been made. Clinically suspicious neck nodes should undergo ultrasound guided core biopsy to improve the diagnostic accuracy of clinical staging and facilitate treatment planning.[31]

Although the majority of neoplastic lesions of the temporal bone are due to SCC, it is important to be aware of a differential diagnosis that can include basal cell carcinoma, melanoma, chondrosarcoma, Ewing's sarcoma, verrucous carcinoma, adenoid cystic carcinoma and metastatic disease.

In view of the strong correlation of SCC with chronic inflammation, it is important to have a high index of suspicion in this group of patients to avoid unnecessary treatment delays caused by misdiagnosis. Deep biopsies are preferable due to the risk of misrepresentative sampling. The middle ear cavity may now also be accessible via CT-guided biopsy. Early results suggest this alternative to direct trans-canal biopsy may increase the probability of a positive biopsy result but at present the majority of the surgical community are sceptical.[32]



Figure 115.1 Early stage SCC right ear canal.

Audiometry

SCC temporal bone carcinoma rarely involves the sensorineural or balance system. However, an audiogram is mandatory before commencing any major ear surgery.[11] This will allow a baseline threshold for future comparison and also investigate the need for hearing rehabilitation as a result of the surgery.

This is important as Kwok et al.[33] identified poor communication in the post-surgical period as a major adverse influence on patient reported quality of life (ranked higher than cosmetic deformity).

Tumour staging

Staging systems are devised to aid classification of patients pre-operatively into groups with similar prognosis. There is now general consensus that the modified Pittsburgh staging system should be used to standardize comparison of outcomes between treatment centres and the differing surgical/non-surgical techniques undertaken.[7, 8, 10, 15, 17, 23, 26]

Arriaga et al. first conceived the Pittsburgh staging system to conform to the American Joint Cancer Committee's TNM classification system.[34] This staging system is based on clinical, pathological, and radiologic evidence. Tumours limited to the EAC are defined as early stage disease, and those that spread from the external canal to invade adjacent soft tissues, the mastoid, middle ear or cranial nerves indicate advanced disease. More recently, this scheme has been modified (**Table 115.2**) again to take into account facial nerve involvement as a prognostic indicator.[26, 35] Complete or partial facial nerve paresis would be classified as T4 regardless of the anatomical area of involvement.

It should be noted that the presence of metastatic lymph nodes in the neck are a poor prognostic indicator and consequently upstage the disease regardless of the T status.

Imaging

Physical examination alone cannot reliably characterize tumour beyond the external ear canal or middle ear cavity. Magnetic resonance imaging is the optimal modality for soft tissue analysis and can help differentiate tumour from fluid or inflammatory mucosa in the middle ear cavity, especially where bony erosion is not present.[32] MR scans with gadolinium DTPA enhancement are better for the assessment of soft tissue disease. Dural and brain involvement, infratemporal disease and perineural spread can be demonstrated when present, which may have great prognostic significance.[34]

High resolution CT (axial and coronal) portrays bone erosion accurately and when combined with MR imaging can improve pre-operative staging and give vital information to the surgical team (**Figures 115.2** and **115.3**).[36] A 1 mm fine-cut CT image is optimal for the temporal bone. The images should be carefully assessed with

TABLE 115.2 Modified Pittsburgh staging system[26,34]

Stage		Description
T Classification	T1	Limited to the EAC without bony erosion or evidence of soft tissue involvement
	T2	Limited to the EAC with bone erosion (not full thickness) or limited soft tissue involvement (<0.5 cm)
	T3	Erosion through the osseous EAC (full thickness) with limited soft tissue involvement (<0.5 cm), or tumour involvement in the middle ear and/or mastoid
	T4	Erosion of the cochlea, petrous apex, medial wall of the middle ear, carotid canal, jugular foramen, or dura; with extensive soft tissue involvement (>0.5 cm, such as involvement of the TMJ or styloid process); *or evidence of facial paresis*
N Classification	N0	No regional nodes involved
	N1	Single metastatic regional node <3 cm in size
	N2a	Single ipsilateral metastatic node 3–6 cm in size
	N2b	Multiple ipsilateral metastatic lymph nodes
	N2c	Contralateral metastatic lymph node
	N3	Metastatic lymph node >6 cm in size
Overall stage	I	T1N0
	II	T2N0
	III	T3N0
	IV	T4N0 and T1-4N1-3

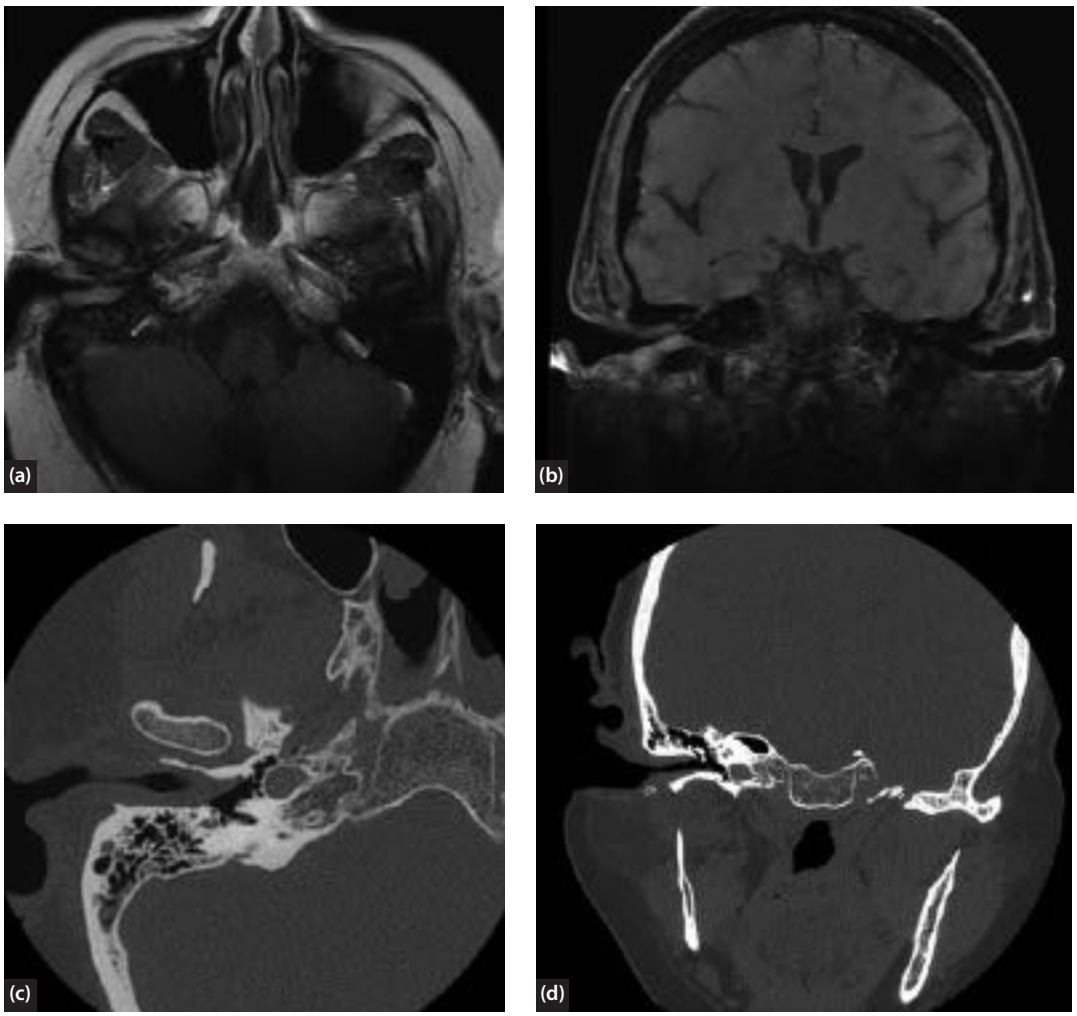


Figure 115.2 MR imaging with gadolinium enhancement showing early stage SCC within the right ear canal (a) MR axial and **(b)** MR coronal. CT imaging reveals that the same disease does not invade the middle ear cavity **(c)** CT axial and **(d)** CT coronal. Images courtesy of Colchester Hospital University NHS Foundation Trust.

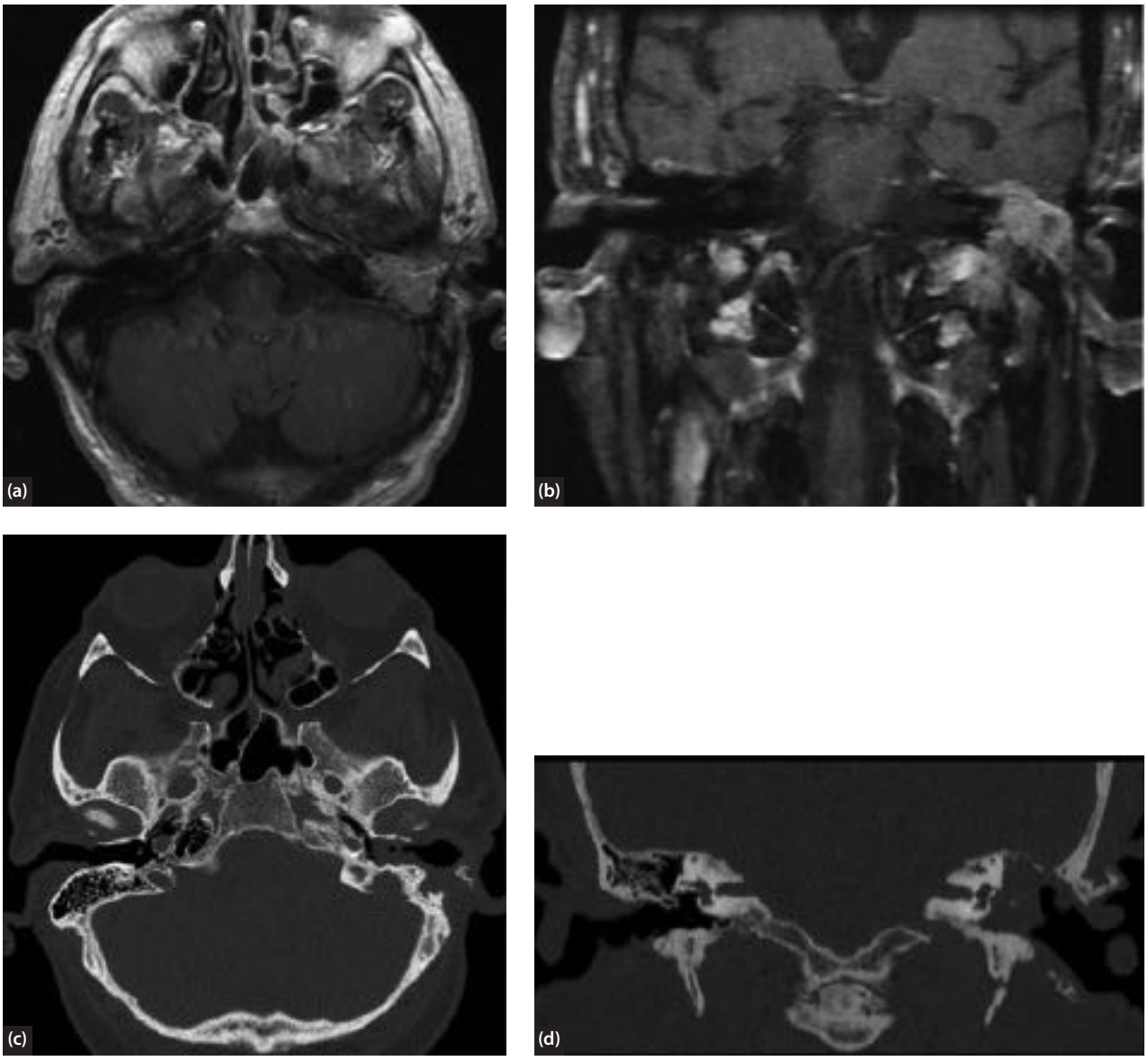


Figure 115.3 MR imaging with gadolinium enhancement (a) MR axial and **(b)** MR coronal, showing late stage SCC in the left mastoid cavity with possible invasion of the temporal lobe. CT imaging reveals that the same disease has eroded through the tegmen tympani and mastoid cavity **(c)** CT axial and **(d)** CT coronal. Images courtesy of Norfolk and Norwich University Hospitals NHS Foundation Trust.

regards to the EAC, middle ear, facial nerve, mastoid, tegmen, middle/posterior fossa dura, sigmoid sinus, jugular bulb and carotid canal. Extra features to review include the parotid gland, TMJ and infratemporal fossa.[37]

If CT or MR raises the possibility of ICA involvement, angiography with balloon occlusion should be considered, as sacrifice of the ICA may be necessary. Angiography with ipsilateral balloon occlusion testing is established to check the patency of cerebral blood flow from the other side. The venous phase is also important to determine the patency of the contralateral sigmoid/jugular system, in case surgery requires sacrifice of the sigmoid sinus or internal jugular vein. In view of the potential consequences of carotid ligation, the multidisciplinary team often makes the pre-operative decision not to sacrifice this major artery unless deemed absolutely necessary.[8, 16]

A staging scan of the neck and chest is routinely performed. CT scanning of the pelvis and abdomen is not required unless the biopsy result suggests an alternative diagnosis to SCC (e.g. lymphoma, melanoma or adenocarcinoma).[35, 36]

TREATMENT

The UK National Institute for Health and Care Excellence (NICE) document, *Improving outcomes in head and neck cancers* was first published in 2004 and subsequently revised in 2012.[38] It provided several recommendations to improve the quality of patient care, for example the establishment of a direct referral pathway and a multidisciplinary team approach (surgeon, oncologist, pathologist and radiologist) to reassess diagnosis and instigate

appropriate treatment plans. Other key recommendations included the provision of a specialist nurse service to enhance co-ordination of care, provide supportive counselling and improve opportunities for participation in clinical trials. The rehabilitation team (audiologist, speech and language therapist, occupational therapist, physiotherapist) is deemed essential to aid the anticipated hearing handicap, balance disorder and speech or swallowing problems.

At present, there is no consensus strategy for operative management of temporal bone tumours. The main surgical approaches are *en bloc* resection combined with adjuvant radiotherapy versus piecemeal resection or radical mastoidectomy with adjuvant radiotherapy.

There appear to be two underlying causes for this. First, a significant proportion of oncological procedures require a degree of piecemeal tumour removal as the main block of tissue is weakened or fragmented by the carcinoma. Second, in some patients the diagnosis is made during mastoid exploration for what seemed to be a routine cholesteatoma or another chronic inflammatory disease. A pragmatic approach entails post-operative radiotherapy alone without further surgical intervention; however, this may adversely affect patient survival.

Notwithstanding the above, recent results suggest that the most favourable survival rates are achieved with *en bloc* extended temporal bone resection and post-operative radiotherapy. This can be demonstrated by analysis of recent results from Yin, Gidley, Bacciu and Masterson et al., which all demonstrate improved survival figures despite treating a cohort of patients dominated by T3 and T4 disease.[7–10, 28]

It is useful to consider each stage or section of the operation separately to give an overview of the management that may arise in individual patients.

Surgical management of the neck

Although nodal metastases are uncommon in early stage disease, a neck dissection will allow accurate staging and provide access to the major vessels for free flap reconstruction. If suspect lymph nodes are found, these are sent for frozen section analysis and, where positive, a modified radical neck dissection is performed. Node-positive disease is associated with a poor prognosis, and neck dissection does not improve survival.[7–9, 26, 34]

Gidley et al. noted that the distribution of pathological nodes within their cohort was largely restricted to levels II/III/Va with the exception being level IV in < 10% of cases.[7] On this basis, a selective neck dissection should incorporate these anatomical zones when performed for node-negative disease. The parotid gland and intraparotid nodes are not only the anterior resection margin of the tumour but also the first echelon nodes draining the EAC. A superficial parotidectomy is routinely performed in early stage disease where a functional facial nerve is present. A total parotidectomy is reserved for advanced stage disease with sub-optimal facial nerve function.

LATERAL TEMPORAL BONE RESECTION

Tumours lateral to the tympanic membrane (T1 and T2) can be resected adequately by a lateral temporal bone resection.[39]

In view of the aggressive nature of this disease, the pinna is only preserved if a wide soft tissue margin (> 1 cm) exists between the lateral aspect of the tumour and the external auditory meatus. Pinna resection will impose a significant handicap to the patient, in terms of both aesthetics and function for those who wear spectacles.

An extended cortical mastoidectomy should be undertaken and the facial nerve identified and preserved as the medial limit of the dissection. The tegmen is followed anteriorly toward the zygoma to allow a suitable bony margin along the anterosuperior canal wall. The facial nerve is skeletonized along its inferior path towards the stylomastoid foramen. The mandibular head may also be transected and the tumour removed *en bloc*. All mucosa is removed from the middle ear cavity to optimize the flap repair and the Eustachian tube is obliterated by scarifying the mucosa and then plugged with muscle, fascia or bone wax.

The anterior border of the malignancy is the posterior limit of the temporomandibular joint (TMJ). The thin bone of the anterior canal wall can be difficult to assess pre-operatively and many studies recommend removal of the articular disc, or at least drill out the glenoid fossa. However, if the condyle is removed, this may give rise to significant dental occlusion deformity. Recent data from Cambridge (UK) would suggest no evidence of microscopic invasion into the condylar head for patients with T1-2 disease.[8] Finally, the primary tumour should be removed *en bloc* with the neck dissection and the superficial parotid gland. This is often not possible due to technical constraints, requiring the neck dissection and parotid to be detached separately.

EXTENDED TEMPORAL BONE RESECTION

An extended temporal bone resection is required when invasion extends medial to the tympanic membrane or into the mastoid (T3/T4 disease). With locally advanced disease, aggressive treatment is required due to the equally aggressive nature of the malignancy. The facial nerve is sacrificed in this procedure and the entire pinna is also removed.

The specimen includes the lateral temporal bone resection (as above) with additional dissection of the medial bony wall of the middle ear, extended mastoidectomy and removal of the otic capsule (**Figure 115.4**). The margins of resection are the ICA anteriorly, middle fossa dura superiorly, sigmoid sinus and posterior fossa dura posteriorly, petrous apex medially and the jugular bulb inferiorly.

In selected patients, resection of dura or brain may be required. A posterior and middle fossa craniotomy is achieved by resecting bone 3 cm above the sigmoid sinus and temporal line. Involved dura is removed with

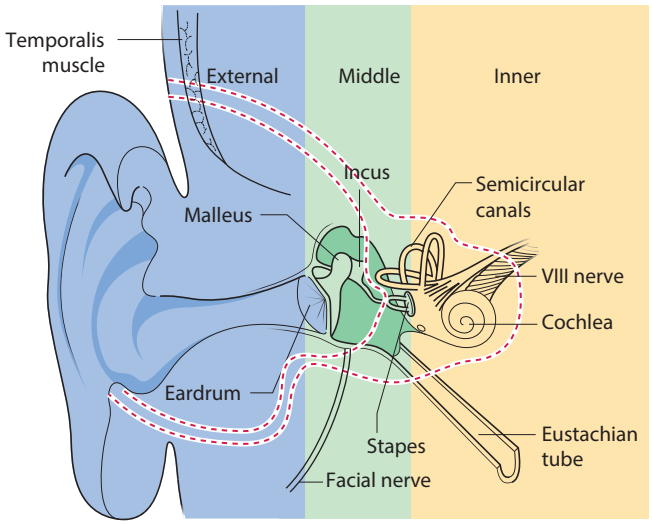


Figure 115.4 Anatomy of the left temporal bone in the coronal plane, showing the extent of a lateral temporal bone resection (outlined in red) and an extended temporal bone resection (outlined in green).

an adequate margin. The jugular bulb and sigmoid sinus are delineated as the resection extends medially. The bony labyrinth and the internal auditory canal are both resected and the intrapetrous portion of the carotid artery exposed. The middle fossa dura is retracted to allow further detailed inspection. Dura and brain, which have macroscopic tumour involvement, are removed as a separate specimen. Frozen sections from all margins of the dura are taken to ensure clear margins. The defect in the dura is then sealed with fascia lata and sutured carefully to avoid a potential cerebrospinal fluid (CSF) leak.

If a radical neck dissection has been performed, the next stage will be to divide and ligate the sigmoid sinus. Wherever possible, the lower cranial nerves (IX, X, XII) are conserved if macroscopic disease is not present. For some, removal of the condyle, coronoid process and the upper two-thirds of the ramus of the mandible together with surrounding soft tissue will be necessary after the masseter has been dissected away. This may allow greater exposure of the infratemporal fossa region to assess disease extension.

The anterior margin of the resection includes the entire parotid gland. Frozen section analysis is employed if there is concern that the surgical margin is not clear. After this stage, the whole temporal bone resection lateral to the ICA together with the neck dissection and parotid gland are removed.

RECONSTRUCTION

Free tissue transfer is routinely used to reconstruct the pyramidal defect that typically remains following ablative surgery. The anterolateral thigh flap is a common choice as it provides skin and fascial covering and can be taken with muscle if more bulk is required.[40, 41] The thigh donor site provides access for fascia lata if required for static slings for simultaneous facial palsy reconstruction. The distant flap donor site allows for concomitant flap harvest and oncological resection, minimizing the duration of surgery. Alternative free flaps, which are less commonly used, include the radial forearm and lateral arm flaps. Pedicled myocutaneous flaps and scalp transposition fasciocutaneous flaps have also been employed with good results, but are usually reserved for the minority of patients who are not good candidates for free tissue transfer due to microvascular disease (e.g. diabetic or peripheral vascular disease patients).[42]

In cases of pre-existing facial palsy or where the facial nerve has been sacrificed, simultaneous facial palsy work can be undertaken including upper eyelid gold weight insertion, browpexy, lateral tarsorraphy and static fascial slings. In patients aged <65 years, and depending on the integrity of the distal facial nerve branches, a nerve graft procedure may be possible (e.g. interposition neurorraphy or transposition of the nerve supplying masseter onto the distal stump of the facial nerve).

Following removal of the pinna and completion of post-operative treatment, patients are routinely offered a prosthesis or, less frequently, a staged autologous pinna reconstruction.

Adjuvant therapy

RADIOTHERAPY

The literature supports a beneficial effect of adjunctive radiotherapy on DSS, but as yet no well-controlled studies have been performed. Most studies report a dose ~60 Gy applied to the temporal bone and upper neck region.[7–10, 15, 43]

The effect of RT may also extend beyond adjuvant therapy based on some retrospective case series. Pemberton et al.[44] revealed a 45% 5-year DSS for 123 patients treated with 55 Gy radiotherapy alone; however, the survival benefit was significantly lower for patients who had advanced disease (T3-4), suggesting primary radiotherapy alone is not appropriate in this subgroup. In the most extreme cases in which contraindications to surgery are present, palliative radiation and/or chemotherapy may be offered.

In patients who have previously undergone treatment with radiotherapy, further doses may be given if the previously irradiated area has been resected and new vascularized tissue covers the defect.[42] Post-operative radiotherapy normally commences 6–8 weeks after surgical intervention to maximize flap viability.

CHEMOTHERAPY

Adjuvant chemotherapy was previously thought to provide little advantage. However, in 2006 Nakagawa et al.[45] reviewed series of patients all treated with either pre-operative chemoradiation or with chemoradiation alone. Four of eight patients treated with chemoradiation (5-Flourouracil + external beam radiation with a dose of 40 Gy), were free of disease at 24–47 months. The same

study also a reported a significant difference in 5-year survival for T4 patients with advanced stage disease treated surgically (75%) and non-surgically (16%). In a similar manner to radiotherapy above, the available evidence would not suggest a survival benefit for primary chemotherapy in advanced stage disease.

TREATMENT OUTCOMES AND PROGNOSTIC FACTORS

Early stage tumours generally have a favourable outcome, with most series reporting an 80–100% survival rate. However, T4 tumours have reduced survival rates even after adequate surgery and adjuvant radiation treatment (Table 115.3).

Prior surgical intervention is often a prerequisite towards making the diagnosis of malignancy, but this can complicate pre-operative staging, disrupt margins and require the surgeon to operate in an inflammatory region.[9] The literature is divided as to whether persistent/residual disease will result in significantly reduced survival when compared to patients who have not received prior treatment.[8, 14–16]

Although true *en bloc* resection is sometimes difficult to achieve because of the complicated three-dimensional nature of the temporal bone and anatomical spread of disease, more recent results confirm that it does offer the greatest chance of successful treatment.[7–10, 16, 28] Advanced stage of disease, node-positive status, dural/brain involvement, facial nerve palsy, poor histological differentiation, positive surgical margins and carotid invasion are all important adverse factors.[7, 8, 16, 17, 28, 36]

Stage of disease

The modified Pittsburg staging system predicts disease outcome by tumour size, local/distant metastatic spread and/or facial nerve involvement. Moody et al.[26] revised the University of Pittsburgh staging system in 2000 by suggesting that temporal bone SCC with evidence of facial nerve palsy should be categorized as T4. Multiple studies have since endorsed this new classification, the best evidence coming from Higgins et al.,[17] who produced a systemic review to determine the impact of facial palsy on survival outcomes. This study selected 21 articles containing information on 348 subjects and found that disease-specific survival (DSS) and overall survival in patients with facial palsy were significantly worse than for subjects without this deficit.

Dural and cerebral infiltration

Extension superiorly through the tegmen with dural and cerebral involvement is considered by some to be a particularly ominous feature. Moody et al.[26] reported that dural involvement was such a poor prognostic indicator that it may render curative surgery futile. This may directly contradict the findings in the larger study by Masterson et al., where 14/60 patients presented with brain involvement and the disease specific five-year survival was not significantly different from the rest of the group (37% versus 44% $p = 0.335$).[8]

Tumour differentiation

For this condition, most studies[7–9, 28] correlate poorly differentiated histology to an adverse prognostic outcome (Figure 115.5). Primary SCC affecting other sites in the head and neck behave in similar manner.

Surgical margins

In those patients with positive surgical margins, recurrent disease is more likely and survival reduced.[10, 16] The judicious use of intra-operative frozen sections can aid detection of safe margins.[8, 14, 18, 34]

Carotid involvement

Carotid involvement is fortunately rare, and also correlates strongly with a poor outcome.[7, 8, 28] Resection of the intrapetrous carotid artery can result in serious consequences and as such should only be attempted with appropriate caution. Malignant invasive disease may sometimes be limited to the adventitia and as a consequence the tumour can be dissected clear without need for ligation and division of the artery.

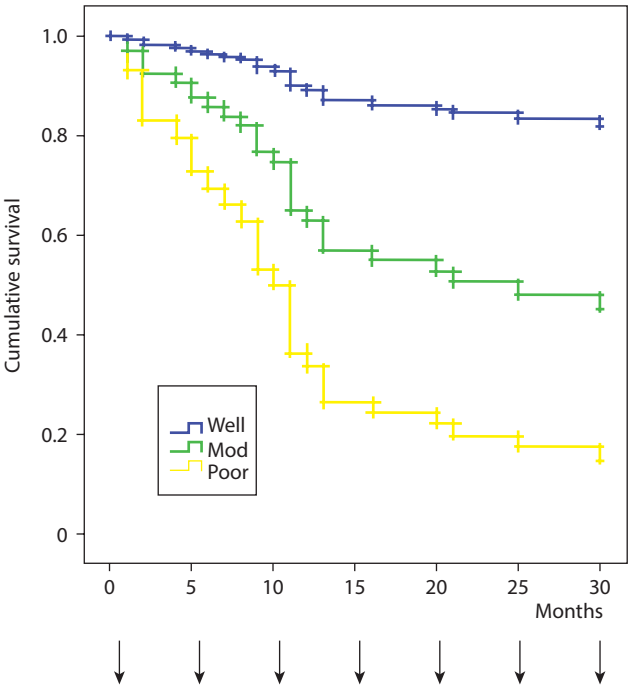
COMPLICATIONS OF TREATMENT

Complications of treatment depend on the extent of resection and the use of adjunctive radiation. Extended temporal bone resection will commonly cause or exacerbate a cranial nerve deficit. Facial palsy will cause both cosmetic

TABLE 115.3 Five-year disease specific survival stratified by stage of disease†

Study	Year	Patient number	Stage I	Stage II	Stage III	Stage IV
*Yin et al.[28]	2006	95	100	100	67.5	29.5
Moore et al.[9]	2007	35	100		53	
Gidley et al.[7]	1020	124	48		28	
Bacciu et al.[10]	2013	45	100	100	86.2	48.7
Masterson et al.[8]	2013	60	n/a	100	62	39.5

† Only studies using the modified Pittsburgh staging system are included;
* Yin et al. report overall survival only



Grade	Number of patients at risk						
Well	12	12	11	10	8	6	6
Mod	32	30	22	15	13	9	3
Poor	14	9	5	4	4	4	3

Figure 115.5 Temporal bone SCC disease specific survival stratified by histological grade (Log-Rank multiple regression analysis p = 0.05; Well, Well differentiated SCC; Mod, Moderately Differentiated SCC; Poor, Poorly differentiated SCC).[8]

and functional disability. Prompt eye care is of vital importance to prevent exposure keratitis.

Post-operative vertigo, hearing loss and other cranial nerve deficits (e.g. V, VIII, IX, X, XI) may also occur. Vagal, glossopharyngeal or hypoglossal nerve palsies may enhance patient risk of poor nutritional input and aspiration pneumonia. Speech and language expertise can be helpful but ultimately some patients will require a gastrostomy and/or temporary tracheostomy.

If the dura was resected and repaired, the risk of meningitis due to a CSF leak can be ameliorated by the use of lumbar drains inserted for 24–72 hours.[46] The main complications of adjuvant radiotherapy include osteoradionecrosis, soft tissue fibrotic change that can mask future recurrent disease, destruction of salivary gland tissue and increased risk of iatrogenic malignancy within the central nervous system (CNS).[16]

CONCLUSION

The gold standard treatment for temporal bone SCC remains undefined because of continued debate regarding staging, adjuvant radiation and the extent and nomenclature of surgical procedures. It is clear that there is a survival advantage to be gained from being managed in a tertiary centre with multidisciplinary expertise in the condition. At present, the number of patients with this condition at each individual institution restricts definitive conclusions. Multi-institutional cooperation is now required to facilitate prospective clinical trials.

Surgery and adjuvant radiotherapy alone are currently insufficient for obtaining adequate survival rates for patients with advanced T4 disease. Induction or concurrent chemotherapy should be investigated as a means of achieving improved survival.

Finally, well-validated outcome measures of quality of life parameters need to be utilized and communicated in the literature. There has been restricted work on patient-perceived outcomes of what is often referred to as disfiguring and debilitating surgery.

BEST CLINICAL PRACTICE

- ✓ Early biopsy of a suspicious lesion in the EAC will avoid diagnostic delays for patients with temporal bone SCC and improve their survival.
- ✓ All patients should have both MR and CT scans to stage their disease and facilitate treatment planning.
- ✓ *En bloc* resection with post-operative radiotherapy is the current treatment of choice.
- ✓ Management by a multidisciplinary team is essential, for example the expertise of the plastic surgeon for reconstruction of the defect, and the skills of the speech and language therapist to overcome speech and swallowing problems.

KEY POINTS

- Temporal bone squamous cell carcinoma is a rare disease that may cause severe morbidity.
- Otitis externa that does not resolve mandates formal biopsy.
- The treatment plan should be informed by careful staging with MR and CT imaging.
- Optimal management involves a multidisciplinary team with specialist expertise in squamous cell carcinoma of the temporal bone.
- The multidisciplinary team should include an otolaryngologist, neurosurgeon, clinical oncologist, reconstructive surgeon, neuroradiologist and rehabilitation team to deal with hearing handicap, balance disorders, speech and swallowing problems.
- Palliative surgery may have a role in advanced cases.

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CHAPTER 116

COMPLICATIONS OF SKULL BASE SURGERY

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: randomized controlled trials, meta-analysis, evidence-based medicine, review literature, skull base (focusing on surgery and complications), skull base neoplasms (focusing on surgery and complications), postoperative complications, vestibular schwannoma (focusing on surgery and complications), cerebrospinal fluid rhinorrhoea (focusing on surgery, complications, prevention and control), cerebrospinal fluid otorrhoea (focusing on surgery, complications, prevention and control), CSF lumbar drainage, antibiotic prophylaxis, meningitis (focusing on surgery, complications, prevention and control), electromyography, intraoperative monitoring, facial nerve and facial nerve injuries (focusing on prevention and control), acetazolamide (focusing on adverse effects and therapy), papaverine (focusing on therapy), intracranial hypertension (focusing on therapy), hydrocephalus (focusing on therapy and drug therapy), CSF pressure, therapeutic embolization, meningioma, angiofibroma. In addition, the Cochrane database has also been searched.

INTRODUCTION

The evolution of skull base surgery has provided an intersection between various surgical specialities including neurosurgery, otolaryngology surgery, ophthalmology, oncology, radiology, head and neck surgery, as well as craniofacial and reconstructive surgery. In addition to this, the last decade has seen dramatic advances in surgical technique, neuronavigation and optics; including the triple chip cameras, endoscopic 3D systems and high-definition screens, providing both precise surgical resection, as well as preservation of surrounding neurovascular structures. Intra-operatively, nerve monitoring has further aided the modern day surgeon when managing varying pathologies within a delicate anatomical region. An improvement in surgical interventions has been coupled with accurate radiological imaging, allowing both appropriate visualization and management of anatomically remote and complex lesions to be safely resected. A collaborative multidisciplinary team, in conjunction with the dramatic advances in surgical technique and technology, has resulted in improved patient care and reduced post-operative complications.

Despite a constant evolution, skull base surgery remains a challenging field of surgery, with important risks. As with any surgical procedure, identification and minimization of complications is essential. Skull base tumours are intimately related to vital neurological structures, cranial nerves (CN), major arteries and venous sinuses, making surgical resection challenging. These problems may be compounded when large tumours directly invade important structures. Dural breaches predispose to cerebrospinal fluid (CSF) leakage and the close proximity to contaminated aero-digestive structures may expose the patient to an increased risk of infection.

In this chapter we will detail both intra-operative and post-operative complications of skull base surgery.

INTRA-OPERATIVE COMPLICATIONS

Vascular

ARTERIAL HAEMORRHAGE

Transection of a major artery is a disastrous but fortunately rare event. Inadvertent excessive manipulation or direct forceful suction of an intracranial artery may lead to vasospasm and cerebral infarction. Gentle handling of vessels using neurosurgical patties for protection with medium/low suction and frequent irrigation with isothermic saline

are mandatory operative techniques. Infiltration of vasoconstrictive agents prior to surgery, as well as local application of patties soaked in vasoconstrictive agents produce lower rates of morbidity intra-operatively.

The primary vessels at risk during lateral skull base surgery are the basilar artery and the anterior inferior cerebellar artery (AICA). The basilar artery may be injured during translabyrinthine or suboccipital approaches to very large vestibular schwannomas (VS). The AICA is frequently in the surgical field during VS surgery. Injury to the AICA may result in Atkinson syndrome – lateral tegmental pons infarction, which is often fatal.

Major vascular complications in anterior skull base surgery primarily affect the carotid within the sphenoid sinus, particularly in transphenoidal surgery for patients with acromegaly. The specific difficulties within this cohort include the sinus being deeper, characterized by more septa and a reduced intercarotid distance, resulting in potential intra-operative surgical difficulties.[1] The intrasphenoid carotid artery can further complicate matters both pre- and intra-operatively. Its presence can mimic a sinonasal mass with variations occurring in approximately 40% of patients, as well as aneurysms of the cavernous portion, which accounts for 2–9% of all intracranial aneurysms.[2, 3] In conjunction with this, there are high rates of dehiscence shown in literature, with multiple other papers finding only a mucoperiosteal covering the intrasphenoid carotid artery coursing through the sphenoid sinus.[3] Sethi et al. described rates of dehiscence as high as 93%, although this paper did not define their criteria.[4] As a result, if the surgeon is not aware of such common variations, a damaged intrasphenoid carotid artery can result in both vascular and neurological complications and potentially death.

Embolization of selected vascular tumours such as meningiomas, paragangliomas and nasopharyngeal angiofibromas may reduce the risk of intra-operative and post-operative bleeding and even the operative time. Unfortunately, studies have yielded contradictory results and, at present, there is no consensus on its use. The majority of studies have been retrospective, and the two prospective studies to date on the preoperative embolization of meningiomas have produced conflicting conclusions.[5, 6] Major complications of such neuroradiological procedures include cerebrovascular accident (CVA), subarachnoid haemorrhage, intratumoral haemorrhage, raised intracranial pressure and CN palsies due to tumour swelling or embolization of the vaso vasorum and even death.

VENOUS HAEMORRHAGE

Venous haemorrhage may be controlled using a variety of methods depending on location and quantity of bleeding. These include bone wax if the bleeding point has a bony perimeter, bipolar diathermy or repair using 6-0 or 7-0 monofilament suture if the vessel wall is easily visible, or placement of haemostatic agents such as oxidized cellulose (Surgicel), microfibrillary collagen (Avitene) or biological tissue glue, typically for more diffuse bleeding. Occasionally, large sinus perforations may require extraluminal packing to achieve haemostasis or even formal ligation. Anatomical studies have shown a unilateral non-functioning sigmoid sinus/jugular bulb is present in only 4% of normal subjects, so adverse post-operative sequelae, such as cerebral oedema or long-term benign intracranial hypertension following ligation, is infrequent.[7]

Air embolus

Air embolus is a rare complication that usually only happens when the patient is in the sitting position. This position leads to a reduction in intracranial venous pressure; if a defect in a venous sinus is created, a pressure gradient favouring the passage of air into the circulation is created.[8] The first sign is a sucking sound or venous crepitation at the site of entry. Later, hypotension, tachycardia, dysrhythmias and diminishing end-expiratory pCO_2 develop. When this complication is detected, inhalation anaesthesia is discontinued and 100% oxygen administered, while the bleeding site is controlled by direct pressure and the jugular veins are compressed in the neck. The patient is placed in the left lateral Trendelenburg position with the head lowered in order to trap the air embolus in the right side of the heart, preventing it entering the pulmonary circulation. The air can then be aspirated through a central venous catheter or, in its absence, needle aspiration of the right ventricle via a subxiphoid approach should be attempted.

Cranial nerve injury

Cranial nerve injuries are among the most debilitating complications encountered in skull base surgery. Most pre-operative CN deficits persist post-operatively if due to tumour invasion rather than compression. Unlike sensory CN deficits, there is a good prospect of some recovery of motor CN function if a primary reanastomosis or cable graft is performed. Microdissection techniques and electrophysiological nerve monitoring enhance the preservation of CN during tumour resection.

OLFACTORY NERVE

The olfactory nerve is at risk and often unavoidable in anterior skull base procedures, specifically ethmoidal tumours or meningiomas of the sphenoid ridge and those involving stripping of the dura from the cribriform plate treated through an open approach. This is due to the position of nerve within the subarachnoid space, with only a meningeal sheath covering.

The olfactory epithelium is present at the apex of the nostrils bilaterally, covering an area of approximately 2–3 cm^2. The epithelium consists of both trigeminal and olfactory nerve fibres, with trigeminal fibres sensitive to irritation and temperature rather than olfaction. Tumours involving the anterior fossa floor often lead to unilateral anosmia, which is usually not perceived; however, it can occasionally cause permanent bilateral anosmia.[9]

Management of patients with anosmia includes safety advice and dietary advice. Smoke and gas detectors should be installed in their homes and they will require advice on healthy eating, as many foods are unappetizing without the sense of smell and this can lead to an unbalanced diet.

OPTIC NERVE

The optic nerve is at risk in anterior skull base surgery, specifically pituitary tumours close to the optic chiasm. Blindness within tumour management may also be secondary to radiotherapy, leading to radiation keratitis, or direct radiation injury to the optic nerve. Visual-evoked potentials should be monitored during surgery. Sharp dissection around the nerve using the appropriate microscopic or endoscopic techniques will lower the risk of injury.

It is interesting to note there is a high level of protrusion and dehiscence of the optic nerve, with over 30% of the population having both protrusion and dehiscence, and various papers reporting rates of protrusion as high as 70%.[3] These differences in variations are attributed to ethnic background.[3] Without careful anatomical dissection it will lead to post-operative visual difficulties, with increased risk of blindness from optic nerve damage within the sphenoid sinus.[3]

CRANIAL NERVES III, IV AND VI

The cranial nerves III, IV and VI are at risk during operations of the petrous apex adjacent to the cavernous sinus and the anterior skull base. The trochlear nerve exits the posterior brainstem and has a relatively long intracranial course, but is well protected in the tentorium and is infrequently injured. Abducens nerve palsy has been reported after lumbar drain placement – it is not known whether this is through an ischaemic or traction injury. Abducens nerve palsy management tends to be symptomatic, with recovery tending to be slow and progressive. In paediatric patients occlusive patch therapy for eyes will help avoid amblyopia, until residual palsy improves. Monitoring of extraocular movements is important in recovery.

TRIGEMINAL NERVE

The trigeminal nerve is at risk during lateral skull base surgery, such as large VSs, temporal bone resection and approaches to the clivus, nasopharynx and parasellar–parasphenoid compartments, when intentional neural section may be necessary for anatomical access. Trigeminal nerve branches are also at risk during anterior skull base procedures. With sensory innervation of the head mainly covered by the trigeminal nerve, except the occipital and maxillary joint area, disorders may lead to severe discomfort for the patient. Various forms of rehabilitation have been hypothesized and researched. With regards to conservative therapy, vitamin B6 is traditionally used as a neurotrophic substance; however, there is little clinical evidence to support its use. Nerve growth factor is a similar neurotrophin, with local use following damage increasing expression of tyrosine receptor kinase A. However, it is currently not available for clinical use and is still within research phases for possible neural repair and reconstruction. Surgically, there have been positive outcomes following reconstructions of the inferior alveolar and lingual branches of the trigeminal nerve, with suggestions that the same theories can be utilized for sensory nerve reconstruction. Possible interposition grafts include the great auricular nerve or the sural nerve for longer graft requirements. Both of these have drawbacks, with permanent sensory deficits over the ear lobe and calf respectively. If reconstruction and rehabilitation is not a realistic option, typically carbamazepine or gabapentin are used as required to treat possible facial pain from trigeminal nerve dysfunction.[10]

FACIAL NERVE

Facial nerve damage frequently leads to decrease in a patient's quality of life, despite successful lesion removal.[11] Pre-operative dysfunction is independently linked to post-operative paralysis, with informed consent essential.[11] Important anatomical variations lead to higher intra-operative complications, with appropriate knowledge of the superficial location of the stylomastoid foramen in infants integral. Other anatomical variations include absence of chorda tympani, lateralization of the vertical portion, duplication in the tympanic segment of the nerve and common bony defects of the fallopian canal. It is, however, important to be aware that the majority of facial nerve injuries in mastoid surgery occur in the presence of an anatomically normal facial nerve.[12] Seventy per cent of iatrogenic injury is located in the pyramidal segment (between tympanic and mastoidal segment) at the second genu.[11]

Orbicularis oculi and orbicularis oris muscles are typically routinely monitored intra-operatively via electromyographic (EMG) monitoring during mastoid procedures. The introduction of intra-operative facial nerve monitoring has facilitated early identification and localization of the facial nerve and is of prognostic value in predicting functional outcome.[13] Feedback from monitoring probably shortens the learning curve, as the surgeon adapts his technique to avoid manoeuvres that produce excessive EMG discharges; however, this does not replace anatomical knowledge and surgical ability.

If the nerve is transected, a primary reanastomosis avoiding tension is the optimum management. If necessary the nerve may be mobilized from the fallopian canal to gain 0.8 cm of length. Removing a portion of the tympanic bone and retracting the parotid gland with a suture can add another 0.9 cm. In total, 1.7 cm of additional length is possible following complete mobilization of the facial nerve for a primary anastomosis.[14] Failing this, the next best option is cable grafting using the greater auricular nerve or the sural nerve. If there is poor or absent facial function one year post-operatively other facial reanimation techniques, such as gold weight upper lid implants, temporalis muscle transfer, cross-facial anastomosis or faciohypoglossal anastomosis techniques may be required. Despite advances, reconstruction techniques are not capable of restoring facial nerve function grade I or II, using the House Brackmann (HB) grading system.[15]

VESTIBULOCOCHLEAR NERVE

Surgical ablation or resection causes a complete loss of audiovestibular function, with symptoms differing depending on pre-operative function. Patients with pre-operative good or near normal auditory and vestibular function will have severe vertigo and noticeable hearing loss. Patients usually achieve satisfactory central vestibular compensation over several weeks, but for some vestibular exercises are invaluable. In addition, customized rehabilitation regimes in the pre-operative phase may facilitate earlier vestibular compensation. Those patients with poor auditory and vestibular function, which is typical in those undergoing nerve resection in VS surgery, or vestibular nerve section for Ménière's, often have a minimal change in symptoms post-operatively.

The auditory nerve has no perineurium, and is therefore prone to damage from mechanical trauma, as well as from vascular injury within the internal auditory canal during tumour resection. Hearing conservation in VS surgery is an option in those with small acoustic tumours and good pre-operative hearing (minimum mean pure tone audiometry 30 dB/70% speech discrimination). It can be performed by a middle fossa or retro mastoid approach depending on tumour location and may preserve useful hearing in 40–79% of cases.[16] The chance of hearing preservation is inversely related to tumour size, with 90% of tumours > 3 cm involving the auditory nerve pre-operatively.[11] Most techniques of intra-operative auditory monitoring only provide delayed feedback to the surgeon and have not improved hearing conservation results in the last decade. Unilateral hearing loss may be rehabilitated by a contralateral rerouting of the signal (CROS) hearing aid or a bone-anchored hearing aid.

LOWER CRANIAL NERVES

The glossopharyngeal and vagus nerves travel closely together throughout most of their course in the skull base and any injuries often happen simultaneously. This may result in a potentially life-threatening complication due to chronic aspiration and recurrent pneumonia. Satisfactory functional recovery often takes place with peripheral lower CN dysfunction, so a temporary tracheostomy and gastrostomy are frequently advisable. However, brainstem dysfunction, especially involving the lower CN nuclei, often results in long-term bulbar problems necessitating laryngeal airway protection. A gastrostomy and tracheostomy will not prevent contamination of the lower respiratory tract. Epiglottopexy and epiglottic plication techniques offer an alternative management option.[17, 18]

Cardiac dysrhythmia

Vagal stimulation can cause a sinus bradycardia and hypotension. Brainstem stimulation may cause tachycardia and hypertension. Fortunately, any adverse cardiac event is invariably transient, although it is usually advisable for the surgeon to switch attention to work on another part of the tumour to allow consolidation of the recovered cardiac status in the patient.

OPHTHALMOLOGICAL COMPLICATIONS

Due to the inherent close relationship of the eyes, as well as their neurovascular supply, to skull base surgery, there are clear risks to vision. Neurovascular injury is especially important in elderly patients with fragile periobital capillaries. In certain scenarios, surgical necessity can lead to visual symptoms, with orbital floor removal producing vertical dystonia, excision of the medical canthal area causing canthal drift, as well as diplopia if two or more extraocular muscles are removed. Rehabilitation for these defects is difficult, with some surgeons opting occasionally for exenteriation of the orbit subsequently or reconstruction following radiation therapy. If reconstruction is sought, the temporalis muscle is most commonly used.[11, 19]

Nasolacrimal duct blockage and the ensuing epiphora can usually be treated effectively with dacrocystorhinostomy. Ectropion and entropions can result from open surgery, with appropriate reconstructive methods extensively used for both cosmesis and corneal surface disorders. Corneal abrasion is the most common cause of post-operative blindness secondary to surgical drape position, foreign body injury or reduced tear production from intra-operative anticholinergic agents.

LATERAL SKULL BASE APPROACH COMPLICATIONS

Lateral skull base approaches require intimate anatomical knowledge, in conjunction with precise surgical exposure of the lesion. To obtain this, an approach through the middle and inner ear may be required, resulting in careful dissection of structures.

Hearing loss can be due to drill-generated acoustic trauma, caused either by direct contact of the burr with the ossicles or endosteal membrane of the cochlea. Avoiding contacting the ossicles and systemic and local application of corticosteroids are the mainstay of protecting the inner ear against trauma.[11] If the inner ear is advertently opened, recognition, repair and avoiding suction of perilymph/endolymph can preserve underlying function.

Whilst the ideal approach to CPA lesions is still debated and will be discussed in Chapter 105, Non-vestibular schwannoma tumours of the cerebellopontine angle, the differing approaches confer different potential complications. Ten to fifteen per cent of CPA surgery procedures are complicated by a post-operative CSF leakage, with the largest risk found in the translabyrinthine approach.[20] Tumour excision through the translabyrinthine approach can either be attempted to be total, with a 57% HB I–II facial nerve preservation rate, or surgeons can perform a functional resection, accepting they are leaving a thin rim of tumour on the nerve, achieving a 77% HB I–II facial nerve outcome.[21] In relation to the retrosigmoid approach, the CSF leak and facial nerve palsy rates are lower (approximately 9% and 6% respectively); however, there is a requirement of cerebellum retraction, which is related to its own complications, and furthermore there is compromised access to the internal auditory canal fundus due to the nature of this technique.[22, 23] Further, the retrosigmoid approach, when compared to

the translabyrinthine approach, is typically used for smaller tumours, which is an independent risk factor for facial nerve outcomes. In comparison the middle fossa approach has greater risks of facial nerve damage (16%), as the anatomical course of the facial nerve may compromise tumour exposure; however, it has higher hearing preservation rates.[23, 24] As a result, although the retrosigmoid approach would seem to provide the most versatile corridor for facial nerve preservation, the middle cranial fossa approach seems safest for hearing preservation for smaller tumours. The translabyrinthine approach would be reserved for larger tumours. Detailed knowledge of potential pitfalls of surgical technique is vital when assessing skull base lesion management, based on position and outcomes desired.

ANTERIOR SKULL BASE ENDOSCOPIC SURGERY RISKS

Within endoscopic surgery, unfavourable results are typically related to learning curve and time taken to adapt to a two-dimensional (2D) environment. With vision of vital importance in surgery, the 2D nature of surgery creates drawbacks, specifically with regard to a lack of stereopsis impairing depth perception. This may impair the surgeon's ability to recognize and manage anatomical structures. With the safety of skull base procedures largely dependent on precise anatomical knowledge, this remains a key concern. Experienced surgeons compensate for this difficulty through the use of visual and tactile feedback, dynamic movements of the scope, light and shadows and detailed anatomical knowledge. Image guidance is another recent advance, with recent studies highlighting a higher number of cases of incomplete resection when image guidance is unavailable.[19, 25, 26]

A further concern with endoscopic surgery is in relation to temperature during surgery. Bone drilling and cauterization within a narrow field delivers significant levels of thermal energy, which can continue despite suctioning and flushing. Incessant increase of the temperature in the intra-operative field can potentially harm neural structures, with temperatures over 42 degrees causing cerebral harm. Regular breaks are important during these procedures.

POST-OPERATIVE COMPLICATIONS

Haematoma

This potentially fatal complication is usually due to inadequate haemostasis. With intradural haematomas, the source of bleeding is invariably vessels adjacent to the tumour. Careful bipolar diathermy effectively controls most bleeding but cannot be used immediately adjacent to important CNs as dysfunction inevitably follows. Surgicel may be helpful in many situations, but many surgeons are reluctant to allow this material to come into direct contact with CNs as increased post-operative neural oedema is possible. On occasions, application of a biological glue such as Tisseal® provides very satisfactory haemostasis in these circumstances. Very occasionally, one will encounter a patient with a previously unknown bleeding diathesis. If the administration of drugs and appropriate blood coagulation products fail, a combination of Surgicel with FloSeal® is effective.

Extradural haematomas may result from failed middle meningeal artery cautery or ligation and more superficially from branches of the superficial temporal artery. They may also arise from haemorrhage at the craniotomy site and require the judicious application of bone wax.

The rate at which neurological deficits develop varies with the location and source of bleeding. Arterial haemorrhage produces a rapid collection of blood. In contrast, venous haemorrhage results in a gradual neurological deterioration, often due to subdural haematoma formation, and may result in secondary hydrocephalus. Depending on the severity and rapidity of the patient's neurological deterioration, management varies from immediate decompression by wound opening at the bedside to surgical exploration in the theatre or computed tomography (CT) imaging. Most haematomas are rapid and precious time should not therefore be wasted on imaging studies.

Cerebrospinal fluid leak

This is the most common complication after VS surgery. CSF leak rates of approximately 10% are reported in the immediate post-operative period. However, late leaks may develop many months or years after surgery and up to 35% of leaks develop 2 weeks after VS surgery.[27] It is likely that neither the surgical approach nor the tumour size affect the post-operative CSF leakage rate and transient post-operative rises in CSF pressure may be responsible.[11, 24, 25, 27] CSF leaks are also the most common anterior skull base complication with reported rates of occurrence between 3% and 19%.[28]

To prevent the development of CSF leaks a peri-operative lumbar drain to lower CSF pressure may be left in place for up to 5 days, during which time the patient is kept on strict bed rest, with the head of the bed elevated at 15–30 degrees. Unfortunately, patients often experience low-pressure headaches.[29] There is no evidence regarding the effectiveness of prophylactic lumbar drainage, but for established leaks it eliminates 50–90%.[29, 30] Known complications of continuous lumbar drainage include brainstem herniation (may present with vagal nerve paresis and vocal cord paresis), Chiari type 1 malformation, infection, pneumocephalus and subdural haematoma.[27, 28] A compression dressing is maintained over the wound to promote watertight healing.

Symptoms of CSF leak include pain or headache (especially positional), unexplained pyrexia and, more seriously, meningitis. Rhinorrhoea may present as a salty taste in the patient's mouth. High-flow CSF leaks lead to clear rhinorrhoea and, less frequently, otorrhoea or wound discharge. A sample should be sent for immunoelectrophoretic assay for beta transferrin, which is both highly specific and sensitive for CSF.

High-flow CSF leaks require surgical exploration and repair. Low-flow CSF leaks may be managed with bed rest and elevation of the head by 20–50 degrees. In addition, a lumbar spinal drain may be used for up to 5 days. Wound

leaks are managed by the insertion of further sutures and the application of a compressive head bandage. Acetazolamide is known to lower CSF pressure by inhibiting the enzyme carbonic anhydrase and by decreasing CSF production. Some units use this therapy but there is no evidence for its efficacy in the treatment of CSF leaks.[31] The use of prophylactic antibiotics remains uncertain. There is some evidence favouring the role of prolonged prophylactic antibiotics in patients with ventricular drains but no studies exist for lumbar drains.[32] Two large meta-analyses have produced conflicting conclusions over the role of antibiotic prophylaxis in the prevention of meningitis in patients with basilar skull fractures and CSF fistulae.[33, 34] The larger meta-analysis found no reduction in meningitis.[35] It is known that prolonged antibiotic use encourages the development of resistant organisms and prophylactic antibiotics in patients with CSF fistulae are probably best avoided, due to poor penetration of the meninges.[34, 36]

Infection

The incidence of wound infections is usually low. Recognized risk factors include tumour size, operative time and haematoma. Anterior skull base procedures performed in a cleaned but previously contaminated environment, where the wound is in close contact with the aerodigestive tract, have a rate of infectious complications of between 0% and 30%.[28, 37] Frontal bone flap osteomyelitis may complicate craniofacial resection for anterior skull base tumours in certain cases.[38] Wound infection may lead to meningitis or a brain abscess. Meningitis is usually associated with a CSF fistula.

The risk of infection is minimized by the liberal use of peroperative irrigation and prophylactic antibiotics (for clean non-implant procedures and for clean contaminated procedures). Prophylactic antibiotics should be given on induction of anaesthesia to ensure high tissue levels at the time of surgery. Antibiotics given more than 4 hours after the end of surgery are not effective, either experimentally or in clinical trials.[39] The Infection in Neurosurgery Working Party of the British Society for Antimicrobial Chemotherapy recommends that surgery for clean and clean-contaminated surgery should be administered as a single intravenous dose on induction of anaesthesia, with additional doses every 3 hours for long procedures.[39] In support of these recommendations, a systematic review in the Cochrane database of prospective randomized controlled trials of patients undergoing major pulmonary, gynaecological, obstetric, urological, pelvic or abdominal surgery, who had been given either single or multiple dose prophylaxis, found no difference in surgical site infection rates.[40] This confirms the findings from an earlier review of similar patient groups.[41] In addition, prolonged antibiotic prophylaxis increases the risk of hospital acquired infection.[40]

Pneumocephalus

Intracranial air is often present after craniotomy and may be seen on CT, but usually resorbs after 7–10 days. The presence of pneumocephalus is pathognomonic for the presence of a CSF leak, with risks of meningitis as high as 30%.[42] It is rarely seen after posterior fossa surgery and is usually associated with surgery at sites that include the aerodigestive tract, as in anterior skull base procedures. Clinically significant pneumocephalus presents in 2–12% of post-operative craniofacial patients.[28] Air accumulating under pressure may create a tension pneumocephalus, which if unrecognized is a potentially fatal condition. The use of positive pressure ventilation and a lumbar catheter drain are risk factors. The lumbar drain creates a vacuum effect by lowering intracranial pressure and drawing air in through the wound. Treatment with needle aspiration via a craniotomy burr hole may be adequate. Surgical exploration to decompress the brain and seal air leaks may sometimes be necessary. About one-third are associated with CSF leaks and a thorough search for a fistula is, therefore, also advisable.

Hydrocephalus

This presents in the early post-operative period with headache, impaired consciousness, gait disturbance and incontinence. It is secondary to cerebral oedema or intracranial haemorrhage. Normal pressure hydrocephalus is due to chronic obstruction of arachnoid villi function. It has been reported following jugular bulb resection in association with unrecognized contralateral cerebral venous drainage insufficiency. The presence of post-operative hydrocephalus is approximately 6% within anterior skull base tumour resection.[43]

Epilepsy

Post-operative seizures may herald the development of haematoma, oedema, infarction or any complication causing mass effect and cerebral irritation. Temporal lobe manipulation carries a special risk of the development of this complication, which is not encountered with posterior fossa surgery. Manipulation or resection of brain parenchyma can result in an irritable epileptic focus. For high-risk procedures, consideration should be given to the use of carbamazepine, phenobarbitone or phenytoin for antiseizure prophylaxis. For post-operative seizures these drugs and diazepam are indicated. One medication is initiated at a time and the dosage increased until the seizure is controlled or the maximum serum level of the drug is reached. Another drug may then be added if necessary.

Headaches

There is a higher incidence of headache with the retrosigmoid approach for VS surgery, which may be debilitating and intractable.[22, 23] This is a feature of VS surgery, with headache not as common using this approach in other posterior fossa tumours. It has been suggested that adherence of the dura to nuchal soft tissue, neck muscle spasm and aseptic meningitis from bone dust or fibrin glue is responsible.[44, 45] It is more common following VS surgery for small tumours, although this may reflect individual psychological

factors, causing patients of a 'sensitive disposition' with mild tumour symptoms to present early and also to be more likely to report local discomfort post-operatively. Intradural drilling of the internal auditory meatus deposits bone dust into the posterior fossa, and alternatively, it is postulated that larger VSs prevent wide distribution of bony debris. The use of cranioplasty techniques with bone or titanium mesh and acrylic reduces the incidence.[44, 45]

BEST CLINICAL PRACTICE

- ✓ **General practice:**
  - performing procedures in a multidisciplinary team, utilizing the strengths of each member
  - regular frequency of surgeries; minimum once every 2 weeks.
- ✓ **Pre-operative management:**
  - otological and audiological examination – pure-tone and speech audiometry
  - vestibular examination – 1/3 of patients with profound sensorineural hearing loss report subjective hearing loss, while twice as many show pathological vestibular signs in caloric testing and/or vestibular evoked myogenic potentials
  - imaging – temporal bone imaging revealed high riding bulb in 32% (which can lead to the presence of bony defects of the hypotympanon), anterior sigmoid sinus in 34%, a low riding dura in 26% and an aberrant carotid artery in 0.02%.
- ✓ **Vascular:**
  - discontinue aspirin and clopidogrel 7–10 days prior to surgery
  - warfarin discontinued 5 days pre-operatively, which is adequate time to reconstitute the coagulation factors. If at risk of thromboembolic event, use low molecular weight heparin 2 days after stopping warfarin or 3 days prior to operation, stopping 24 hours before surgery
  - pre-operative corticosteroid administration – to reduce inflammatory mediators which cause vasodilation, transduction and oedema
  - patient positioning should be reverse Trendelenberg, as head elevation reduces mean arterial pressure in the elevated area. Patient must be tilted in and out of position slowly to avoid sudden shift in blood
  - ventilation technique maintaining normocapnia or mild hypocapnia to minimize bleeding, with some centres using high-frequency jet ventilation
  - highly vascular tumours may require pre-operative embolization and ligation of feeding vessels. Should be performed 24 to 72 hours pre-operatively to provide adequate thrombosis and prior to re-formation of collateral blood supply
  - bleeding is controlled using bone wax, bipolar diathermy, placement of haemostaic agents such as oxidized cellulose (Surgicel), microfibrillary collagen (Avitene) or a biological glue and repair using 6-0 or 7-0 monofilament suture
  - occasionally, large venous sinus perforations require extraluminal or intraluminal packing or even ligation to achieve haemostasis
  - decrease bleeding with controlled hypotensive anaesthesia.
- ✓ **Air embolus:**
  - the first sign of this complication is a sucking sound or venous crepitation at the site of entry
  - later hypotension, tachycardia, dysrhythmias and diminishing end-expiratory pCO_2 develop.
- ✓ **Cranial nerve injury:**
  - microdissection techniques and electrophysiological nerve monitoring enhance the preservation of CN during tumour resection
  - if the facial nerve is cut, primary reanastomosis avoiding tension is best. Failing this, cable grafting using the greater auricular nerve or the sural nerve is the next best option, followed by facial-hypoglossal anastomosis.
- ✓ **Cardiac dysrhythmia:**
  - vagal nerve stimulation can cause a sinus bradycardia and hypotension
  - brainstem stimulation may cause tachycardia and hypertension.
- ✓ **Temperature:**
  - regular flushing of endoscope
  - site of bone drilling to be short and varied to avoid high temperature.
- ✓ **Haematomas:**
  - arterial haemorrhage produces a rapid collection of blood in the extradural space
  - venous haemorrhage results in a gradual neurological deterioration, owing to subdural haematoma formation
  - depending on the severity and rapidity of the patient's neurological deterioration, management varies from bedside wound opening to surgical exploration in the theatre or CT imaging.
- ✓ **Cerebrospinal fluid leak:**
  - immunoelectrophoretic assay for beta transferrin is both highly specific and sensitive for CSF
  - CSF lumbar drainage is effective in eliminating 50–90% of cases of CSF leaks after skull base surgery.
- ✓ **Infections:**
  - there is a good evidence base to recommend a single intravenous dose antibiotic prophylaxis, given at induction of anaesthesia for skull base procedures
  - meningitis is usually associated with a CSF fistula.
- ✓ **Pneumocephalus:**
  - air accumulating under pressure to create an acute elevation of intracranial pressure is potentially fatal.
- ✓ **Hydrocephalus:**
  - this presents in the early post-operative period with headache, impaired consciousness, gait disturbance and incontinence.
- ✓ **Epilepsy:**
  - post-operative seizures may herald the development of haematoma, oedema, infarction or any complication causing mass effect and cerebral irritation
  - temporal lobe manipulation carries a special risk.
- ✓ **Headaches:**
  - there is a higher incidence of headache with the retrosigmoid approach for VS surgery, which may be debilitating and intractable.

FUTURE RESEARCH

Despite the wealth of data on the pathophysiology of disease and our theoretical foundations for treatment, randomized trials have produced somewhat surprising results in the past. Prospective randomized controlled trials, which may need to be multicentred, are required to improve the evidence-base on the following issues:

- the efficacy of neuronavigation technology in reducing complications
- evaluation of newer tumour ablation techniques
- the value of pre-operative embolization of highly vascular tumours, addressing selection criteria, different materials and the timing in relation to surgery
- the efficacy of CSF lumbar drainage for prophylactic prevention of post-operative CSF leaks (How long should the drain remain *in situ*? Should it drain at a certain rate or would a lowered stable CSF pressure setting be more efficacious?)
- the role of antibiotic prophylaxis in clean contaminated skull base procedures, with lumbar drains and in patients with a post-operative CSF leak
- use of novel monitoring techniques, such as four contact adherent systems for glossopharyngeal and vagus nerve monitoring during surgery. Utilize compound muscle action potentials from posterior pharyngeal wall.

KEY POINTS

- The sound of crepitation at the site of a large perforation of a venous sinus and later cardiorespiratory distress should alert the surgeon to the possibility of an air embolus.
- Manipulation of the vagus nerve or brainstem may result in cardiac dysrhythmia and surgery should be halted until sinus rhythm returns.
- Cranial nerve injuries are among the most debilitating complications encountered in skull base surgery.
- Microdissection techniques and electrophysiological nerve monitoring enhance the preservation of CN during tumour resection.
- CSF leaks are among the most common post-operative skull base surgery complications.
- There is a good evidence base to recommend a single intravenous dose antibiotic prophylaxis, given at induction of anaesthesia for skull base procedures.
- Post-operative seizures may herald the development of haematoma, oedema, infarction or any complication causing mass effect and cerebral irritation.
- Most post-operative intracranial haematomas are rapid and require prompt surgical exploration, avoiding the delay of imaging studies.
- There is a higher incidence of headache with the retrosigmoid approach for VS surgery, which may be debilitating and intractable.

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Foreword

The eighth edition of *Scott-Brown* signals the beginning of a new and exciting era for ear, nose and throat surgeons, and also the end of 10 years of very hard work undertaken by John Watkinson and Ray Clarke, the Editors-in-Chief, their team of subeditors and, not least, the publishers. Whatever subspeciality the current generation of trainees decides to follow, they will all have to read and refer to *Scott-Brown* in order to complete their education and gain accreditation. It will be a constant companion and guide throughout their professional lives.

When asked to write the foreword for this edition, I was immediately reminded that I had read John Ballantyne and John Groves's third edition as a trainee, bought the fourth edition as a senior registrar, written chapters for Alan Kerr and Philip Stell in the fifth edition, edited the *Basic science* volume of the fifth edition and was ultimately Editor-in-Chief of the seventh edition. As each edition takes about 10 years to produce, that makes me very old indeed. John and Ray have one final task as Editors-in-Chief: to recommend their successors to the publishers. That was made easy for me as both of them had proved themselves more than capable with the previous edition, and the eighth edition is now their masterpiece. They can enjoy the next 10 years as thousands of surgeons worldwide recognize and thank them for their industry.

This edition reflects the continued expansion of our speciality into fields that Scott-Brown himself could never have imagined. It lays the groundwork for the current generation to make their contribution that will, no doubt, be prompted by technological developments, an evidence base of what is wise and what is not, together with the experience gained by teamwork with other clinicians in today's multidisciplinary approach to patient care.

Simply looking at the table of contents it is clear to see that our role in endocrine surgery has increased dramatically over the last 10 years. The thyroid and parathyroids now account for 30 chapters. How would Scott-Brown have viewed that when the tonsils and adenoids justify just one chapter each, and the sore throat has a mere passing reference? Times have certainly changed and ENT surgery has grown up. We have reflected on our past practices, and the evidence base for our management protocols that was emphasized in the previous edition of *Scott-Brown* has been taken to heart.

I hope that this edition will find its way into every medical library in the world and onto every ENT surgeon's bookshelf. It will serve and guide surgeons throughout the English-speaking world, whether they live in high- or low-income countries. It is said that the tragedy of getting old is that we feel young. Reading these volumes makes me wish that I had my time all over again.

Michael Gleeson



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Preface

When we were asked to head up the editorial team for this, the eighth edition of *Scott-Brown*, we were mindful of Michael Gleeson's towering achievement in bringing the seventh edition to fruition. Michael delivered a much-loved text – conceived in the early post-war years when antimicrobials, the operating microscope and the National Health Service were all in their infancy – in an entirely new format that befitted modern surgical scholarship. Authors, editors and readers alike had become acutely conscious of the need to quote high-quality evidence to guide clinical decisions; the concept of grading clinical recommendations – and, by implication, acknowledging gaps in the evidence base of our practice – was born. Recognizing the enormity of Michael's contribution led us into the trap that has befallen every editor who has come before us; we grossly underestimated the task ahead. We had misjudged the pace of change. What began as an 'update' of some outdated chapters became a complete rewrite to reflect the advances that marked the decade between editions, but we were determined to keep the text to a manageable size. In the end, we have 330 chapters, but with a slightly smaller page count than the seventh edition.

The basic science knowledge that underpins our clinical practice is no longer focused just on anatomy and physiology; genetics, molecular biology, new techniques for auditory implantation, information technology, new medical therapies for many old disorders together with seismic changes in endoscopic technology and in medical imaging have transformed our specialty. Today's head and neck surgery would have been unrecognizable to the early authors and editors. Surgical oncologists have recourse to completely different treatment strategies than did their predecessors and now work as part of multidisciplinary teams. They deal with different disease patterns and vastly changed patient expectations. Thyroid and parathyroid surgery has become almost exclusively the domain of the otolaryngologist. Surgery of the pituitary fossa has come within our ambit, as has plastic and reconstructive surgery of the head and neck as well as aesthetic facial surgery. Neurotology, audio-vestibular medicine, rhinology and paediatric otolaryngology are accepted subspecialties, each with its own corpus of knowledge and skills and each warranting a sizeable section of this text. Contemporary otolaryngology is now a collection of subspecialty interests linked by common 'stem' training and a shared passion for looking after patients with disorders of the upper respiratory tract and the head and neck.

There is a view that a single text – even a multivolume tome of this size – cannot cover the entire knowledge base of modern clinical practice. The subspecialist will, of course, need recourse to supplementary reading. The pace of change shows no sign of slowing down, but there is still a need for a comprehensive working text embracing the whole spectrum of our workload. That was the task we set our authors and section editors; we think they have done our specialty proud.

In the new 'digital' editorial world authors create manuscripts on personal computers. They transmit chapters, figures, amendments and revisions across continents and time zones with a few keystrokes. The bulky packages containing grainy photographic prints and the reams of paper with closely-typed and heavily scored text that accumulated on authors' and editors' desks are a distant memory. References, guidelines and systematic reviews are all available online; the editorial 'red pen' has been replaced by a cursor on the screen. This 'new age' has enabled us to look ever further for expertise. We are proud to have enlisted the support of authors from more than 20 countries for this edition. *Scott-Brown* always enjoyed particular affection and respect in Asia, Australia, Africa and the Middle East. It has been a joy to welcome authors in increasing numbers from many of these parts of the world. We are now a truly global specialty and the eighth edition fully reflects this.

What has not changed is the huge time commitment authors and editors need to make. That time now has to be fitted into an increasingly pressurized work environment. Revalidation, mandatory training, more intense regulatory scrutiny, expanding administrative burdens and ever-expanding clinical commitments leave little time for scholarship. Our section editors are all busy clinicians. They have generously given their time, first instructing authors, cajoling them and then editing their chapters, virtually all of which have been completely rewritten since the last edition. Each author was chosen because of his or her specific clinical and scientific expertise and none has disappointed. Authors and section editors receive no reward other than the satisfaction of knowing that they have made a contribution to teaching and learning in a specialty that has given us all so much professional satisfaction. We are profoundly grateful to them and hope that their endeavours spur the next generation of otolaryngologists to carry on this noble tradition. *Scott-Brown* simply wouldn't happen without this generous and dedicated commitment, unstintingly and graciously given.

It is impossible to produce a book like *Scott-Brown* without the contribution of many individuals working behind the scenes. We would like to express our gratitude to our Publishers, Taylor and Francis, and to the staff who have worked on this project from its early days in 2011 to publication in 2018. In particular we would like to mention Cheryl Brandt who with good humour and patience helped to reel in many of the 330 chapters. Miranda Bromage joined the team in 2016 and her publishing experience and enthusiasm for medical education have helped guide this new edition through its final phases to publication. Finally, we are indebted to Nora Naughton who has dedicated so much more than just her extensive publishing skills to this project. Nora's meticulous attention to detail, combined with her warmth and wisdom have encouraged us all at the end of this endeavour.

We are truly 'passing on the torch' of a huge amount of accumulated knowledge and wisdom; it is this that gives us, the Editors-in-Chief, the greatest pleasure.

Read on and enjoy, our thoughts are yours.

RWC
JCW

I wish to acknowledge the love, happiness and inspiration that have been passed on to me by both my parents and grandparents. I recognise and value the friendship of my dear friend Ray Clarke who has been with me all the way on this rewarding and worthwhile endeavour. I would specifically like to thank Esme, Helen and William, without whom none of this would have been achievable. Their love and support has helped guide me through the years leading up to the publication of this tome, and my final thanks go to Angela Roberts and Sally Holden for their typing and editing skills.

JCW 2018

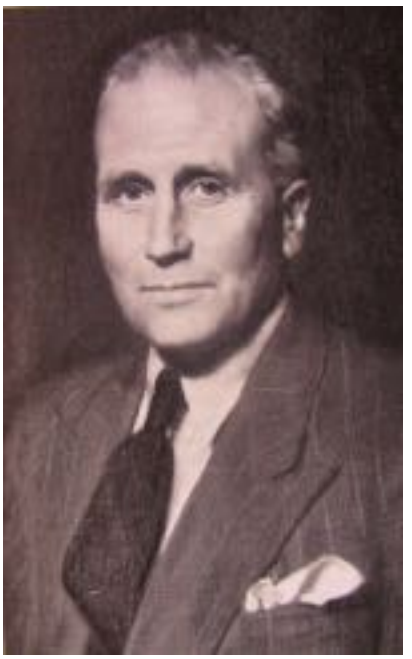
Thanks to my wife Mary for her patience and support. My parents, Emmet and Doreen Clarke, both sadly died during the preparation of this book. They would have been proud to have played a part in such a scholarly enterprise.

RWC 2018



Black Hut on the River Test – Pastel by W G Scott-Brown – circa 1970. Reproduced by kind permission of Mr Neil Weir, who was presented with the original by the artist.

A Tribute to Bill Scott-Brown



Walter Graham ('Bill') Scott Brown. 1897–1987

Walter Graham ('Bill') Scott-Brown was twenty-three when he arrived at Corpus Christi College Cambridge in 1919. One of the generation of young men whose entry to university and the professions was delayed by their participation in the First World War, he had joined the Gunners in 1915 as an 18-year-old. He considered himself blessed to have survived – although wounded – when so many of his contemporaries never returned from the Front. In those early post-WW1 years the medical school at St Bartholomew's ('Barts') in London was keen to attract 'gentlemen'. To this end a series of scholarships – 'Shuter's scholarships' – was established to lure those with humanities degrees from Oxford and Cambridge into medicine. It was via this scheme that the young Scott-Brown qualified MB, BCh in 1925. By now married to Margaret Bannerman, one of the very few women medical graduates of her generation, the two established a general practice in Sevenoaks, Kent. His work here involved looking after children with poliomyelitis, which was then commonplace, and his MD thesis was on polio-related bulbar palsy. It earned him the Copeman Medal for research from the University of Cambridge. While working in general practice, Bill pursued his interest in the then fledgling specialty of otolaryngology, securing fellowships from London and Edinburgh. Postgraduate training was haphazard; there were no structured programmes or even junior posts, so the young Scott-Brown was fortunate to be awarded a Dorothy Temple Cross Travelling Fellowship. Mrs Florence Temple Cross had set up these awards (now administered by the Medical Research Council) in memory of her daughter, who died in 1927 aged thirty-two. They were made available to young physicians to help them travel to overseas centres specifically to study tuberculosis, then rampant and one of the commonest causes of death in young adults. The young Scott-Brown visited the leading pioneers of the day in Berlin, Vienna, Budapest, Stockholm, Copenhagen, Madrid and Venice. Here he developed his considerable endoscopy skills. He reported that his first bronchoscopies were done on a Venetian street entertainer who, for a few coins, would inhale sundry objects that the doctors would then dexterously retrieve from his main stem and segmental bronchi – without of course any anaesthesia!

Times were lean on Scott-Brown's return. Margaret ('Peggy') was now a popular and well-established GP who supported him as his private practice developed. Eventually he secured appointments at East Grinstead, the Royal National and Royal Free Hospitals. He had a thriving Harley Street practice and was the favoured otolaryngologist of the aristocracy. His reputation was such that he become laryngologist to the Royal family, was appointed Commander of the Victorian Order and was a particular favourite of the then Princess Royal, HRH Mary the Countess of Harewood.

By 1938 he was wealthy enough to purchase a farm in Buckinghamshire where he bred prize-winning shorthorn cattle. Ironmongery and blacksmith work were hard to come by during the war years, so Scott-Brown prided himself on his ability to make his own agricultural implements, cartwheels and farm wagons in a makeshift forge he himself established on the farm. He would while away endless hours here at weekends following a busy week in London. An accomplished fly fisherman, he was part of the exclusive Houghton Club whose members fished the River Test in Hampshire, where he numbered aristocrats including the Prince of Wales among his circle.

Scott-Brown's celebrated textbook came about in the early 1950s, when he became ill with jaundice and heart trouble. He was advised to rest, and took 6 months off work. Not satisfied with editing what has become the standard UK textbook, he took up painting as well. He became a celebrated artist whose work is still prized in many private collections. One of his pastels is reproduced on the preceding page.

Bill Scott-Brown lived to be 90. He died in July 1987, six weeks after his beloved Peggy and just as the fifth edition of the celebrated textbook that still bears his name was going to press. His legacy lives on in the pages of this book, and we are proud to continue the tradition of scholarship and learning which he established all those years ago.

We would like to thank Martin Scott-Brown for his help in compiling the biography above.

John C. Watkinson and Raymond W. Clarke
London, 2018

Acknowledgements

We acknowledge our debt of gratitude to the many authors who have contributed to previous editions of Scott-Brown's Otorhinolaryngology, and in particular to authors from the seventh edition, published in 2008. We are also grateful to Neil Bateman who helped with the initial planning of the Paediatrics section.

Chapter 7, Nasal cavity and paranasal sinus malignancy, contains some material from 'Nasal cavity and paranasal sinus malignancy' by Brent A McMonagle and Michael Gleeson. The material has been revised and updated by the current authors.

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Chapter 63, Structural disorders of the vocal chords, contains some material from 'Disorders of the voice' Julian McGlashan. The material has been revised and updated by the current authors.

Chapter 67, Phonosurgery, contains some material from 'Phonosurgery' Meredydd Harries. The material has been revised and updated by the current authors.

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Abbreviations

18FDG	18F fluoro-deoxyglucose
3D	three-dimensional
3D-CRT	3D-conformal radiotherapy
5-FU	5-fluorouracil
A	anterior; *or* asthenia
AASM	American Academy of Sleep Medicine
ABC	aspiration biopsy cytology
AC	anterior commissure
ACC	adenoid cystic carcinoma
AcCC	acinic cell carcinoma
ACE	adult comorbidity evaluation; *or* angiotensin converting enzyme
ACNOS	adenocarcinoma not otherwise specified
ACR	American College of Rheumatology
ACTH	adrenocorticotropic hormone
ACV	Acyclovir
AdCC	adenoid cystic carcinoma
ADD	anteromedial displacement of the disc
ADDR	anteromedial disc displacement with reduction
ADL	additive layer manufacture
AECG	American European Consensus Group
AEWD	automatic endoscope washer-disinfector
AF	ameloblastic fibroma
AFD	ameloblastic fibro-dentinoma
AFDS	ameloblastic fibrosarcoma fibro-dentinosarcoma
AFIP	Armed Forces Institute of Pathology
AFO	ameloblastic fibro-odontoma
AFS	ameloblastic fibrosarcoma
AFTER	Adjustment to the Fear, Threat or Expectation of Recurrence
AFX	atypical fibroxanthoma
AgNOR	argyrophilic nucleolar organizer regions
AHA	alpha-hydroxy acid
AHI	apnoea-hypopnoea index
AHNOGB	Association of Head and Neck Oncologists of Great Britain
AHNS	American Head and Neck Society
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
AKs	actinic keratoses
Allo-HSCT	allogeneic hematopoietic stem cell transplantation
ALM	additive layer manufacture; *or* acral lentiginous melanoma
ALS	amyotrophic lateral sclerosis
ALT	alternative lengthening of the telomeres; *or* anterolateral thigh
amBED	acute mucosal BED
ANA	antinuclear anti-bodies
ANCA	anti-neutrophil cytoplasmic antibody
AOT	adenomatoid odontogenic tumour
AP	anterior-posterior
APC	antigen-presenting cell
APPS	anterior parapharyngeal space
ART	anti-retroviral therapy; *or* adaptive head and neck radiotherapy
ASA	American Society of Anesthesiologists
ASHA	The American Speech and Hearing Association
ASSIDS	Assessment of Intelligibility of Dysarthric Speech
ASV	adaptive servo-ventilator
ATLS	advanced trauma life support
ATM	ataxia telangiectasia mutated
ATP	adenosine triphosphate
ATR	ataxia telangiectasia and Rad3-related
ATSG	adjustable tracheostoma valve
ATSV	adjustable tracheostoma valve
AUG	acute ulcerative (necrotizing) gingivitis
AULS	awake unsedated laryngeal surgery
B	breathiness
BAC	basal cell carcinoma
BAHA	bone-anchored hearing aid
BAHNO	British Association of Head and Neck Oncologists
BCC	branchial cleft cyst; *or* basal cell carcinoma; *or* basal cell cancer
BCW	blue collar workers
BD	Bowen's disease
BDD	body dysmorphic disorder
BED	biologically effective dose
BER	base excision repair
bFGF	basic fibroblast growth factor
BHA	beta-hydroxy acid
BKPyV	BK polyomavirus
BLEC	benign lymphoepithelial cysts
BLEL	benign lymphoepithelial lesions

BMI body mass index
BOT base of tongue
BP blood pressure
BTX-A botulinum toxin type A
BVCMI bilateral vocal cord mobility impairment

CAD/CAM computer-aided design/computer-aided manufacture
CAH clinically assisted hydration
Camp 3',5'-monophosphate; *or* Cyclic AMP
C-ANCA anticytoplasmic autoantibody
cANCA cytoplasmic antinuclear cytoplasmic antibody
CAPE-V Consensus Auditory Perceptual Evaluation of Voice
CAPSO cautery assisted palatal stiffening operation
CAUP coblation assisted upper airway procedure
CBCT cone beam computerized tomography
CBT carotid body tumour
CBTI cognitive behavioural therapy for insomnia
CCC clear cell carcinoma
CCG clinical commissioning groups
CCI Charlson comorbidity index
CCOC clear cell odontogenic carcinoma
CCOT calcifying cystic odontogenic tumour
CD Crohn's Disease
CDK cyclin-dependant kinases
CDKi cyclin-dependant kinases inhibitors
cDNA complementary DNA
CEOT calcifying epithelial odontogenic tumour
CFD colour-flow duplex doppler
CFTCR cystic fibrosis transmembrane conductance regulator
CGF concentrated growth factor
cGVHD chronic graft-versus-host disease
CH cluster headache
CHC Chronic Hyperplastic Candidiasis
CHEP cricohyodoepiglottopexy
CHOP cyclophosphamide, doxorubicin, vincristine, prednisolone
CHP cricohyoidopexy
CI confidence interval
CICO can't intubate, can't oxygenate
CIN cervical intraepithelial neoplasia
CIT complementary integrated therapies
CLH cystic lymphoid hyperplasia
CMV cytomegalovirus
CN cranial nerve
CNAs copy number alterations
CNS clinical nurse specialist; *or* central nervous system
CO_2 carbon dioxide
COAD chronic obstructive airways disease
COF cemento-ossifying fibroma
COMT catechol-O-methyltransferase
COP clinical outcomes publication; *or* carcinoma of occult primary
COPD chronic obstruction pulmonary disease
COS core outcome sets
COSD Cancer Outcomes and Services Data set
COSMIN Consensus-based Standards for the selection of Health Measurement Instruments
CPAP continuous positive airway pressure
CPET cardiopulmonary exercise training
CPG central pattern generator
CQx contact quotient measurement
CRCs colorectal cancers
CRDS Cancer Registration Data Set
CRT chemoradiotherapy
CSA central sleep apnoea
CSCI continuous infusion
CSR Cheyne-Strokes respiration
CSR-CSA Cheyne-Strokes respiration with central sleep apnoea
CSE clinical swallowing evaluation
cT clinical T stage
CT computed tomography; *or* clinical terms
CTA computed tomography angiography
CTCAE common terminology criteria for adverse events
CTLA4 cytotoxic T-lymphocyte-associated protein 4
cTNM clinical (pre-treatment) classification
C-TORS cervical-transoral robotic surgery
CTV clinical target volume
CUP carcinoma of unknown primary
CW continuous wave
CXR chest X-ray

D dose
DA desmoplastic ameloblastoma
DAHNO Data for Head and Neck Oncology
DARS dysphagia-aspiration risk structures
DAT digital audiotape
DB distobuccal
DBCL diffuse B cell lymphoma
DC dentigerous cyst
DCF diced cartilage wrapped in fascia
DCIA deep circumflex iliac artery
DDR DNA damage response
DFS disease-free survival
DFSP dermatofibrosarcoma protuberans

DGCT dentinogenic ghost cell tumour
DID Diagnositic Imaging Dataset
DIEP deep inferior epigastric perforator
DIGEST Dynamic Imaging Grade of Swallowing Toxicity
DILS diffuse infiltrated lymphocytosis syndrome
DISE drug-induced sedation endoscopy
DM diabetes mellitus
dMRI dynamic MRI
DNSI deep neck space infections
DOI depth of invasion
DR drug resistance
DSA digital subtraction sialography
DSB double-strand break
dsDNA double-stranded DNA
DSI dysphonia severity index
DSS disease-specific survival
DVLA Driver and Vehicle Licensing Authority
DVT deep vein thrombosis
DWI diffusion-weighted imaging
DW-MRI diffusion-weight magnetic resonance imaging

EA early antigen
EAM external auditory meatus
EAT Eating Assessment Tool
EBER Epstein-Barr-encoded RNA
EBNA Epstein-Barr nuclear antigens
EBV Epstein-Barr virus
ECD extracapsular dissection
ECM extracellular matrix
ECS extracapsular spread; *or* extracapsular extension
ED ectodermal dysplasia
EDS excessive daytime sleepiness
EEG electroencephalography
EFS event-free survival
EGF epidermal growth factor
EGFR epidermal growth factor receptor
EGG electroglottographic
EIA enzyme immunoassay
ELG electrolaryngography
ELISA enzyme-linked immunosorbent assay
ELR endoscopic laser resection
ELS European Laryngological Society; *or* electrolaryngeal speech
EM erythema multiforme
EMC epithelial-myoepithelial carcinoma
EMG electromyography
EMR endoscopic mucosal resection
EMST expiratory muscle strength training
EMT epithelial-mesenchymal transition
END elective neck dissection
ENE extranodal extension
ENT ear, nose and throat
EOG electro-oculography
EoO eosinophilic oesophagitis
EOR extra-oesophageal reflux
EORTC European Organisation for the Research and Treatment of Cancer
EPAP expiratory positive airway pressure
EPSCC extrapulmonary small-cell carcinomas
ERAS enhanced recovery after surgery
ERCC1 excision repair cross-complementation group 1
ERCP endoscopic retrograde cholangiopancreatography
ERND extended radical neck dissection
ES oesophageal speech
ESR erythrocyte sedimentation rate
ESS Epworth Sleepiness Scale
ESWL extracorporeal shock wave lithotripsy
ET endotracheal tube
EUA examination under anaesthetic
EUS endoscopic ultrasound
EVT Estill Voice Training
EXIT ex utero intrapartum treatment

FA Fanconi's anaemia
FAMM facial artery myomucosal flap
FBC full blood count
FD fibrous dysplasia
FDA Food and Drug Administration
FDG fluorodeoxyglucose
FDG-PET fluorodeoxyglucose positron emission tomography
FEES functional endoscopic evaluation of swallowing
FEESST flexible endoscopic evaluaton of swallowing with sensory testing
FESS functional endoscopic sinus surgery
FEV_1 forced expiratory volume in one second
FFPE formalin-fixed paraffin embedded
FFT fast Fourier transform
FGD fluorodeoxyglucose
FISH fluorescence *in situ* hybridization
FISS fast-interrupated steady state
FK Feyh-Kastenbauer
FLIM fluorescence lifetime imaging
fMRI functional magnetic resonance imaging
FNA fine-needle aspiration
FNAB fine-needle aspiration biopsy

FNAC fine-needle aspiration cytology
FOIS functional oral intake scale
FONA front of neck airway
FoR fear of recurrence
FS Frey's syndrome
FTA-abs fluorescent treponemal antibody absorbed test
FTSG full-thickness skin grafts
FVC forced vital capacity

G glucose; *or* grade
GA general anaesthesia; *or* glycolic acid
GAN greater auricular nerve
GAS group A streptococcus
GBI Glasgow Benefit Inventory
GCS Glasgow coma scores
G-CSF granulocyte colony stimulating factor
GERD gastro-oesophageal reflux disease
GF growth factor
GFR growth factor receptors
GI gastrointestinal
GMC General Medical Council
GM-CSF granulocyte-macrophage colony-stimulating factor
GORD gastro-oesophageal reflux
GPA granulomatosos with polyangiitis
GPU gastric pullup
GRBAS grade, roughness, breathiness, asthenia, strain
GSW gunshot wound
GTV gross tumour volume
GVHD Graft Versus Host Disease

HA hyaluronic acid
HA/ALG hyaluronic acid/mildly cross-linked alginate
HAART highly active antiretroviral therapy
hAdMSCs human adipose-derived MSCs
HANA Head and Neck Audit
HCV hepatitis C virus
HDTV high-definition television
HDU High Dependency Unit
H&E haematoxylin and eosin
HEM heat and moisture exchanger
HES hospital episode statistics
HGF hepatocyte growth factor
HGT high-grade transformation
HHV-8 human herpes virus 8
HIV human immunodeficiency virus
HL Hodgkin lymphoma
HLA human leucocyte antigen
HNC head and neck cancer
HNR harmonics-to-noise ratio
HNSCC head and neck squamous cell carcinoma
HP hyperparathyroidism
HPF high power fields
HPV human papillomavirus
HQIP Healthcare Quality Improvement Partnership
HR homologous recombination; *or* heart rate
HRHPV high-risk human papillomavirus
HRM high-resolution manometry
HRQOL health-related quality of life
HSPL horizontal supraglottic partial laryngectomy
HSV herpes simplex virus
hTERT human telomerase reverse transcriptase expression
HTLV-1 Human T-lymphocytic virus 1
hVFFs human vocal fold fibroblasts
Hz Hertz

I inferior
IBD inflammatory bowel disease
IC induction chemotherapy
ICD International Classification of Disease
ICD-O International Classification of Diseases for Oncology
ICF HNC International Classification of Functioning, Disability and Health for head and neck cancer
ICIDH International Classification of Impairment Disabilities and Handicaps
ICON-S International Collaboration on Oropharyngeal cancer and Network for Staging
ICRT induction chemotherapy followed by radiation
ICS immunochromatographic strip
ICSD international classification of sleep disorders
ICU Intensive Care Unit
IFN-a interferon alpha
IFN-g interferon-g
IgA immunoglobin A
IgG immunoglobulin G
IGRT image-guided radiotherapy
IHC immunohistochemistry
IHNSG International Head and Neck Scientific Group
IJV internal jugular vein
IL-1 interleukin-1
IM infectious mononucleosis
IMPT intensity-modulated proton beam therapy
IMRT intensity-modulated radiotherapy
IOPI Iowa Oral Performance Instrument
IOSGT intra-osseous salivary gland tumours

IPAP inspiratory positive airway pressure
IP-SDM inter-professional shared decision-making
IRIS immune reconstruction inflammatory syndrome
ISH *in situ* hybridization
ISS idiopathic subglottic stenosis
IV intravenous
IVIM intravoxel incoherent motion

KCOT keratocystic odontogenic tumour
KD Kikuchi disease
KFI Kaplan-Feinstein index
KS Kaposi sarcoma
KSHV Kaposi sarcoma-associated virus
KTP potassium titanyl phosphate
KWD Kawasaki disease

L lateral; *or* lower
LADD lacrimal-auriculo-dentodigital
LAUP laser-assisted uvulopalatoplasty
LCH Langerhans cell histiocytosis
LCT long-chain triglycerides
LD laryngeal dysplasia
LDH lactic dehydrogenase
LEMG laryngeal electromyography
LENT SOMA late effects of normal tissue
LFT liver function tests
LGB labial gland biopsy
LMM lentigo maligna melanoma
LMN lower motor neurone
LMRVT Lessac-Madsen Resonant Voice Therapy
LMT laryngeal manual therapy
LOH loss of heterozygosity
LOS lower oesophageal sphincter
LP laryngeal preservation; *or* lichen planus
LPC linear predictive coding
LPR laryngopharyngeal reflux
LRC locoregional control
LSCC laryngeal squamous cell carcinoma
LSE London Speech Evaluation
LSVT Lee Silverman Voice Therapy
LTAS long-term average spectrum
LTB laryngotracheobronchitis
LTR laryngotracheal reconstruction
LTS laryngotracheal stenosis
LVE lymphovascular emboli

M medial; *or* meta-static sites
MAB monoclonal antibodies
mAbs monoclonal antibody drugs
MACH-NC meta-analysis of chemotherapy in head and neck cancer
MAC-NPC meta-analysis of chemotherapy in nasopharyngeal carcinoma
MAGIC MRC adjuvant gastric infusional chemotherapy
MAMS multi-arm-multi-stage
MAPK mitogen activated protein kinase
MAS mandibular advancement splints
MB multibacillary; *or* mesiobuccal
MBS modified barium swallow
MBSImp Modified Barium Swallow Impairment Profile
MC mentocervical
MCC Merkel cell carcinoma
MCII multichannel intraluminal impedance
MCT medium-chain triglyceride
MDADI MD Anderson Dysphagia Inventory
MDR multiple drug resistance
MDSCs myeloid-derived suppressor cells
MDT multidisciplinary team
MEC mucoepidermoid carcinoma
MEK MAPK/extracellular signal related kinase
MEN multiple endocrine neoplasia
MEN-2A multiple endocrine neoplasia syndrome type A
MEP motor-evoked potential
MFR mean airflow rate
MG myasthenia gravis
MGG May-Grunwald-Giemsa
MIO minimally invasive oesophagect
MIP maximum intensity projection
miRNA microRNA
MiSG minor salivary glands
MiSGC minor salivary gland cancer
MIVAT minimally invasive video-assisted thyroidectomy
MLST multiple sleep latency test
MLT micro-laryngoscopy tubes
MMC Mitomycin-C
MMR measles, mumps and rubella
MND motor neurone disease
MPNT malignant peripheral nerve sheath tumour
MPT maximal phonation time
MPTP 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MR magnetic resonance
MRA magnetic resonance angiography
MRC Medical Research Council
MRD marginal reflex distance
MRI magnetic resonance imaging
MRND modified radical neck dissection
MRSA methicillin-resistant *Staphylococcus*

MS median survival
MSA multiple system atrophy
MSC mesenchymal stem cells
MSFo mean speaking fundamental frequency
MSG minor salivary glands
MSLT Multiple Sleep Latency Test
MSM men who have sex with men
MST malnutrition screening tool
MTC medullary thyroid carcinoma; *or* medullary thyroid cancer
MTD muscle tension dysphonia
MUST Malnutrition Universal Screen Tool
MV megavolts
MWT maintenance of wakefulness test

N nodes
NBCCS naevoid basal cell carcinoma syndrome
NBF neutral buffered formalin
NBI narrow band imaging
NBM nil by mouth
NCC nasopharyngeal cancer
NCDB National Cancer Data Base
NCEPOD National Confidential Enquiry into Perioperative Deaths
NCI National Cancer Institute
NCIN National Cancer Intelligence Network
NCRAS National Cancer Registration and Analysis Service
NCWTMDS National Cancer Waiting Times Monitoring Data Set
Nd : YAG neodymium-doped yttrium aluminium garnet
NEED nose, ear, eye and temple
NERD non-erosive reflux disease
NF nasofrontal
NF1 neurofibromatosis type 1
NFc nasofacial
NGF nerve growth factor
NGT nasogastric tube
NHANES National Health and Nutrition Examination Survey
NHEJ non-homologous end-joining
NHL non-Hodgkin lymphoma
NHS National Health Service
NICE National Institute for Clinical Excellence
NK natural killer cells
NM nasomental; *or* nodular melanoma
NMSC non-melanoma skin cancers
NNE normalized noise energy
NNTB number needed to treat to benefit
NOS not otherwise specified
NPC nasopharyngeal carcinoma; *or* nasopharyngeal cancer
NRA nucleus retroambigualis
NRCS National Cancer Registration System
NSAIDs non-steroidal anti-inflammatory drugs
NT nasal length
NTAM non-tuberculosis atypical mycobacteria
NTL near total laryngectomy
NTLP near total laryngectomy with partial pharyngectomy
NTM non-tuberculosis atypical mycobacteria
NZIMES New Zealand Index for Multidisciplinary Evaluation of Swallowing

OAN olfactory neuroblastoma
OCC oral cavity carcinoma; *or* oral cavity cancer
OCT optical coherence tomography
ODI oxygen desaturation index
OF ossifying fibroma; *or* odontogenic fibroma
OFG oto-facial granulomatosis
OFM odontogenic fibromyxoma
OGD oesophagogastroduodenoscopy
OHL oral hairy leukoplakia
OHS obesity hypoventilation syndrome
OI osteogenesis imperfecta
OM odontogenic myxoma
OME otitis media with effusion; *or* oral motor exercise
OMFS oral and maxillofacial surgery
ONS Office for National Statistics
OPC oropharyngeal candidiasis; *or* oropharyngeal carcinoma
OPCS Office for Population Censuses and Surveys
OPG orthopantomogram
OPL open partial laryngectomy
OPSCC oropharyngeal squamous cell carcinoma
OPSE oropharyngeal swallow efficiency
ORF open reading frames
ORL-HNS otorhinolaryngology – head and neck surgery
ORN osteoradionecrosis
OS overall survival
OSA obstructive sleep apnoea
OSAH obstructive sleep apnoea/hypopnoea
OSAHS obstructive sleep apnoea/hypopnea syndrome
OSAS obstructive sleep apnoea syndrome
OSNA One Step Nucleic acid Amplification

P posterior; *or* palatal
PA peripheral (extra-osseous) ameloblastoma
PAA posterior auricular artery

PAC polymorphous adenocarcinoma; *or* parathyroid carcinoma
$PaCO_2$ partial pressure carbon dioxide
PaO_2 partial pressure oxygen
PAG periaqueductal grey matter
PANDAS pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
PAL physical activity level
PARP polymerase
PAS Periodic acid-Schiff
PB paucibacillary
PB-MDT paucibacillary multidrug therapy
PBP progressive bulbar palsy
PCA posterior cricoarytenoid
PCF pharyngocutaneous fistulae
PCI Patient Concerns Inventory
PCL polycaprolactone
PCNA proliferating cell nuclear antigen
PCR polymerase chain reaction
PCU palliative care unit
PD Parkinson's disease
PD1 programmed death 1
PD-L1 programmed death ligand 1
PDT photodynamic therapy
PE pharyngo-oesophageal
PEG percutaneous endoscopic gastrostomy
PES pharyngeal electrical stimulation; *or* progressive elevation of oesophageal pressure
PET positron emission tomography
PET-CT positron emission tomography/computed tomography
PFS progression-free survival
PGL persistent generalized lymphadenopathy
PG-SGA patient generated SGA
PHA polyhydroxy acid
PIOSCC primary intra-osseous squamous cell carcinoma
PIP peak inspiratory pressure
PKB protein kinase B
PLAG1 pleomorphic adenoma gene 1
PLGA polymorphous low-grade adenocarcinoma
PLMD periodic limb movement disorder
PLMS periodic limb movement syndrome
PLS primary lateral sclerosis
PMA progressive muscular atrophy
PMMC pectoralis majory myocutaenous
PNET primitive neuroectodermal tumour
PNI perineural invasion
PNS peripheral nervous system
PORCT post-operative CRT
PORT post-operative radiotherapy
POST post-operative radiotherapy
PPI proton pump inhibitor
PPPS posterior parapharyngeal space
PPS parapharyngeal space
PPV positive predictive value
pRb retinoblastoma protein
PROs patient-reported outcomes
PROMs patient-reported outcome measures
PRSA post-streptococcal reactive arthritis
PRV planning risk volume
PS performance status; *or* pyriform sinus
PSA pleomorphic salivary adenoma
PSG polysomnography
PSGN post-streptococcal glomerulonephritis
PSP progressive supranuclear palsy
PSSHN performance status scale for head and neck
pT pathological T stage
PTA peritonsillar abscess
PTC papillary thyroid cancer
pTNM pathological (post-surgical histopathological) classification
PTV planning target volume

QOL quality of life
qRT-PCR quantitative reverse transcription – polymerase chain reaction

R roughness
RAD radiation-associated dysphagia
RADT rapid antigen detection tests
RARs retinoic acid receptors
RAS reticular activating system
RB retinoblastoma protein
RB1CC1 RB1-inducible coiled-coil 1
RBC red blood cell
RBD REM behaviour disorder
RCR Royal College of Radiologists
RCSLT Royal College of Speech & Language Therapists
RCT randomized controlled trials
RDI respiratory disturbance index
REM rapid eye movement
RERA respiratory effort-related arousals
RF rheumatoid factor
RFA radiofrequency ablation
RFS reflux finding score
RIG radiological inserted gastrostomy
RIS radiation-induced sarcoma
RLN recurrent laryngeal nerve
RLS restless legs syndrome

RMT retromolar trigone
RNA ribonucleic acid
RNA-ISH RNA-based chromogenic *in-situ* hybridization
RND radical neck dissection
ROOF retro-orbicularis oculi fat
ROS reactive oxygen species
RP rapid prototyping
RPR rapid plasma reagin test
RR relative risk; *or* risk ratio
RSI reflux symptom index
RT radiotherapy; *or* radiation therapy
RTA road traffic accident
RTDS Radiotherapy Data Set
RTKs receptor tyrosine kinases
rTMS repetitive TMS
RTOG Radiation Therapy Oncology Group
RTOG-EORTC Radiation Therapy Oncology Group-European Organisation for the Research and Treatment of Cancer
rt-PCR (real-time) polymerase chain reaction
RTPG radiation therapy oncology group
RXRs retinoid X receptors

S superior; *or* synthesis; *or* strain
SACT systemic anti-cancer therapy
SAI supraclavicular artery island flap
SANS subacute necrotizing sialadenitis
sBCC superficial basal cell carcinoma; *or* second branchial cleft cyst
SC sebaceous carcinoma
SCC squamous cell carcinoma
SCCHN squamous cell carcinoma of the head and neck
SCM sternocleidomastoid
SCPL supracricoid partial laryngectomy
SD spasmodic dysphonia
SDC salivary duct carcinoma
SDH succinyl dehydrogenase
SDM shared decision-making
SE sialoendoscopy
SEER Surveillance Epidemiology and End Results
sEMG surface electromyography
SFF speaking fundamental frequency
SFRPs secreted frizzled-related proteins
SGA Subjective Global Assessment
SGC salivary gland carcinoma
SHI Speech Handicap Index
SI signal intensity
SIGN Scottish Intercollegiate Guidelines Network
SIL squamous intraepithelial neoplasia
SLAD–R selective laryngeal adductor denervation–reinnervation surgery
SLE systemic lupus erythematosus
SLN superior laryngeal nerves
SLNB sentinel lymph node biopsy
SLP speech language pathologists; *or* superficial lamina propria
SLS sodium lauryl sulphate
SLT speech and language therapist
SM stomium to menton
SMA solid/multicystic ameloblastoma
SMAS superficial musculoaponeurotic system; *or* subcutaneous musculo aponeurotic system
smTKI small molecule tyrosine kinase inhibitors
SNAP synaptosome associated protein
SNB sentinel node biopsy
SND selective neck dissection
SNE sleep nasendoscopy
SNOMED Systemised Nomenclature of Medicine
SNR signal-to-noise ratio
SNUC sinonasal undifferentiated carcinoma
SO sclerosing osteomyelitis
SOOF suborbicularis oculi fat
SOREM sleep onset REM
SOT squamous odontogenic tumour
SOVT semi-occluded vocal tract therapy
SPECT single-protein emission computed tomography
SPL sound pressure level
SRBD sleep-related breathing disorder
SRI serotonin re-uptake inhibitors
SS Sjögren's syndrome
SSB single-strand break
ssDNA single-strand DNA
SSM superficial spreading melanoma
SSQ Sydney Swallow Questionnaire
SSRI selective serotonin reuptake inhibitor
STA superficial temporal artery
STIR short tau inversion-recovery; *or* short time inversion recovery
STL salvage total laryngectomy
SToPS tracheoesophageal voice auditory-perceptual tool
STPL supratracheal partial laryngectomies
STS split thickness skin grafts; *or* soft tissue sarcoma
STSG split-thickness skin grafts
SUR salivary gland-to-background uptake ratio
SUV standard uptake value
SVR surgical voice restoration
SWAL-QoL swallow-specific Quality of Life questionnaire

T tumour; *or* time
TANIS T and N integer score
TB tuberculosis
TBM tongue base mucosectomy
TCA trichloroacetic acid peel
TCGA The Cancer Genome Atlas
TDC thyroglossal duct cyst
tDCS transcranial direct current stimulation
TdT terminal deoxynucleotidyl transferase
TE tracheo-oesophageal
TEE total energy expenditure
TENS transcutaneous electrical nerve stimulation
TEP tracheo-oesophageal puncture
TGF transforming growth factor
TIC time-intensity curves
TILs tumour infiltrating lymphocytes
TKI tyrosine kinase inhibitors
TL total laryngectomy
TLM transoral laser microsurgery
TLPE total laryngo-pharyngo-oesophagectomy
T-max time to maximum contrast enhancement
TMD temporomandibular disorders
TMJ temporomandibular joint
TMS transcranial magnetic stimulation
TN trigeminal neuralgia
TNE transnasal (o)esophagoscopy
TNM tumour, node, metastasis
TNO transnasal oesophagoscopy
TOLS transoral laser surgery
TORS transoral robotic surgery
TOS transoral surgery
TOVS transoral videoendoscopic surgery
TPF temporoparietal fascia
TPHA *T. pallidum* haemagglutination assay
TPPA *T. pallidum* particle agglutination assay
TRAF TNF receptor associated factor
TSG tumour suppressor gene
TSH thyroid-stimulating hormone
TSP tumour suppression protein
TTA thermal-tactile application
TTLRR time to local-regional recurrence
TVC true vocal cord

U upper
UA unicystic ameloblastomas
UADT upper aerodigestive tract
UARS upper airways resistance syndrome
UC ulcerative colitis
UgFNAC ultrasound guided fine-needle aspiration biopsy
UGCB ultrasound-guided core biopsies
UICC Union for International Cancer Control
UMN upper motor neurone
UOS upper oesophageal sphincter
UPPP uvulopalatopharyngoplasty
US ultrasound
USA United States of America
US-FNAC ultrasound-guided FNAC
USG ultrasonography
USgFNAC ultrasound-guided fine-needle aspiration cytology
USS ultrasound scanning
UV ultraviolet
UW-QOL University of Washington Quality of Life Questionnaire

VA Veterans Affairs
VAPP Voice Activity and Participation Profile
VAS visual analogue scale
VC vocal cord; *or* verrucous carcinoma
VCA viral capsid antigen; *or* vascularized composite allografts
VDRL Venereal Disease Research Laboratory
VEGF vascular endothelial growth factor
VF videofluoroscopy
VFE vocal function exercises
VFSS videofluoroscopic swallowing study
VHI Voice Handicap Index
VHi-10 Vocal Handicap Index 10 item questionnaire
VMAT volumetric modulated arc therapy
VoiSS Voice Symptom Scale
VPA Voice Profile Analysis
VPQ Vocal Performance Questionnaire
VRP voice range profile
VR-QOL voice-related quality of life
VVI Vocal Velocity Index

WCC white cell count
WDTC well-differentiated thyroid cancers
WES whole exome sequencing
WG Wegener's granulomatosis
WGS whole genome sequencing
WHO World Health Organization
WST water swallow test
WUHNCI Washington University Head and Neck Co-morbidity Index

XQ xerostomia-specific questionnaire



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CHAPTER 1

HISTORY

Patrick J. Bradley

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: head and neck surgery, head and neck cancer, head and neck neoplasms and history of head and neck cancer.

INTRODUCTION

The pace of change in the treatment of head and neck tumours has accelerated since the 1950s with a remarkable transition from predominantly ablative surgery to combined therapies focused on preservation of the form and function of the anatomic structures of the head and neck. This chapter will summarize the history of head and neck surgery, with information gleaned from published summaries of this history and original articles.[1–9]

The term 'head and neck surgery' dropped into obscurity from 1906 until 1948, when Hayes Martin used it in one of his early papers.[10] In the same year, Grant Ward published an editorial[11] which defined the future parameters of this 'new' surgical specialty.[9, 10] This surgical discipline was progressed by several groups of surgeons which included Grant E. Ward and James W. Hendrick (1901–1992) of Johns Hopkins Hospital in the United States, who published of their extensive experience in caring of head and neck cancer patients in *Tumors of the Head and Neck in 1950*,[12] with Sir Stanford Cade (1895–1973) General Surgeon and Radiotherapist, Westminster Hospital, Arthur John Gardham (1899–1983) General Surgeon, William Douglas Harmer (1873–1962), Otolaryngologist and Radiotherapist, St Barts. Hospital, Ronald William Raven (1904–1992), General Surgeon and Radiotherapist, St Barts. Hospital and others in Britain, and Henri Redon (1899–1974), Paris and Georges Portmann (1890–1985), Bordeaux who are to be credited with the formation of modern head and neck surgery.[13]

THE MIDDLE AGES

Some of the earliest attempts at head and neck surgery can be credited to Egyptian physicians who attempted ablative and reconstructive procedures of the oral cavity and lip. The 'Edwin Smith Papyrus' (named after the dealer, an American Egyptologist who bought it in 1862), the origins of which are dated at 3000–2500 BCE, contains some of the first descriptions of surgical management of mandibular and nasal fractures, as well as lip tumours.

Arguably, the first documented efforts of reconstructive head and neck surgery are found in the Sanskrit texts of ancient India written approximately 2600 years ago. During this period of Indian history, reconstructive surgery of the nose and ear was highly valued, as invaders from surrounding territories would often stigmatize their victims by amputating the nose or ear. Contained within the publication of Sushruta Samhita (Sushruta's compendium), an ancient Sanskrit text on medicine and surgery, are described numerous surgical techniques for the reconstruction of head and neck defects, dating from the mid-first millennium BCE. Sushruta, regarded as the 'father of Indian surgery', described a variety of pedicle and rotation flaps, similar to many of the techniques utilized in the nineteenth and twentieth centuries. He is reasonably considered the pioneer of reconstructive nasal surgery, having described more than 15 different methods.[14]

Whether Hellenistic or Roman physicians were exposed to the Indian techniques through Alexander the Great's expedition to India in the 4th century BCE is debatable.

Certainly, Roman and Hellenistic physicians described similar techniques to those described in India. Aulus Cornelius Celsus, (c. 25 BC–c. 50 AD), considered to be the greatest of the Roman medical authors and surgeons, also described a variety of techniques similar to those practised in India in his medical text of the 1st century, *De Medecina*, and is credited with one of the first head and neck cancer procedures describing excision of a lip malignancy.[15]

After the fall of Rome in the 5th century and the diffusion of Barbarians and Christianity throughout the Middle Ages, a significant decline in the advancement of all surgery, in particular reconstruction, occurred. This decline was certainly aided by Pope Innocent III (1160b: 1198–1216d Papal Reign), who prohibited surgical procedures of all types. It is interesting to note that physicians of the time considered surgery to be a manual skill and below their intellectual and societal stature. Physicians tended to be academics, working in universities, and mostly dealt with patients as an observer or consultant. Thus appeared the concept of the barber surgeon, and the decline of the role of surgery and surgeons ensued. Despite this, surgery of the head and neck was practised and developed in the Middle Ages but documentation of this is scarce.[16]

The period of Renaissance in the 14th century signalled a rebirth of science, medicine and surgery. In 1442, the Branca family gained prominence in the field of wound reconstruction and, in particular, they reintroduced the previously described Indian methods of nasal reconstruction, using cheek and forehead flaps.[17] Branca's son Antonius modified this technique developing the use of a delayed skin flap donated from the arm. This Italian method, as it became known, was eventually learned by other surgical dynasties (surgical practice at this time in Italy was very much a family affair). Prominent examples include Gasparro Tagliacozzi's (1546–99) work around nasal reconstruction, also using skin donated from the arm. It is believed that Tagliacozzi learned his surgical techniques from members of the Vianeo family from Calabria. Following his own work, he is credited with making significant contributions to facial reconstructive surgery describing and refining the use of distant pedicled flaps for a variety of head and neck reconstructions.[18]

PRE-20TH CENTURY

Oral cavity surgery

Pimpernelle, in 1658, is reported to have been the first who employed a hemiglossectomy to treat macroglossia caused by mercury administration,[1] whilst Marchetti (1589–1673) is credited with the first surgical removal of a malignant tumour of the tongue in 1664.[19] The first published description of a case of lingual cancer was made some 30 years earlier by an Englishman, Alexander Reade (1586–1641), in 1635.[20]

Surgical haemorrhage was a major limitation in the development of head and neck surgery. Accordingly, Germanicus Mirault (1796–1879) in 1813 and Konrad Johann Martin Langenbeck (1766–1851) in 1819 described the ligation of the lingual artery or the use of haemostatic sutures before proceeding with tongue surgery, in an attempt to reduce likelihood of death from exsanguination.[3, 6] A further advance in haemostasis was made by Albretch Middledorpf (1824–68) in 1834, who introduced the galvanic cutting current, the first description of cutting diathermy, to reduce surgical bleeding during incision. Developing this theme, the meticulous approach to haemostasis during surgical dissection proselytized by Emil Theodor Kocher (1841–1917) became the accepted surgical approach throughout the world.[4]

The intra-oral route of excision of tongue lesions was recognized as inadequate for more complicated and advanced tumours and therefore new, open surgical approaches were developed to enhance surgical exposure of lesions of the oral cavity; Joseph H Cloquet (1787–1840) in 1827 and Giorgio Regnoli (1797–1859) in 1838, both Italians used the suprahyoid route to improve access to the base of tongue;[4] Theodor Billroth (1829–94) and Vincenz Czerny (1842–1916) further modified this approach, describing the addition of lateral vertical incisions to the transverse suprahyoid incision. Regnoli went further, describing a retrograde 'pull-through' technique, which was later popularized in the 1860s. However, it was Philibert Joseph Roux (1780–1854) (France) in 1836, followed by James Syme (1799–1870) (Scotland) and Billroth, who described the precursor approach of the lip-split mandibulotomy, which is still commonly used in contemporary head and neck surgical practice, whereby the lip initially is incised in the midline and, deep to this, the mandible is incised through the symphysis, allowing the retraction of the mandibular rami to gain unfettered access to the oral cavity and oropharynx. In 1875, using a variation of the theme, Bernard Rudolf Konrad von Langenbeck (1810–87) divided the mandibular ramus opposite the first molar tooth and ligated the underlying lingual artery prior to removing the enlarged regional lymph nodes in addition to the primary tumour sited in the base of the tongue. Access to the oral cavity from the neck following the raising of a superiorly based musculocutaneous flap as developed by Billroth (1829–1894) of Vienna, was further modified by Kocher of Bern.[20] By the turn of the century Henry Trentham Butlin (1843–1912)[21] and Anton Wolfler (1890–1917) (a member of Billroth's surgical school) had refined the final approaches that established future surgical approaches to the oral cavity, removal of the primary lesion with its regional lymph nodes.[3, 4]

Laryngeal surgery

Visualization of the larynx in life, prior to the invention of the laryngoscope, was not a trivial matter.

An inspection device using mirrors and candles or sunlight for illumination was devised during the early part of the 1800s and almost perfected by John Avery (1807–55), a surgeon at Charing Cross Hospital, London, in 1848 and by Ephraim Cutter (1832–1917) of Boston around 1858. However, Manuel Patricio Rodriguez García (1805–1906),

a Professor of Singing at the Paris Conservatoire who had settled in London, is widely accredited as the first person to view the larynx (his own) in a living human using two mirrors and the sun as a light source.[22] The first clinical application of the indirect laryngoscope was made by Ludwig Turck (1810–68), a neurologist from Vienna, around 1858. By the early period of the 1860s Georg Richard Lewin (1820–96) declared that he had seen more than 60 cases of laryngeal neoplasms and performed surgery using either cutting devices or caustics.[7]

On 23 April 1895 in Berlin, Alfred Kirstein (1863–1922) performed the first direct laryngoscopy, using a modified oesophagoscope.[23] Despite the limitation in visualizing the larynx – and in particular the functioning larynx – there have been a number of reports of larynx tumours being removed 'per viam naturalis'. In 1770, G Koderik, a surgeon in Brussels, reported the ligation of a laryngeal polyp by a snare device. Moreover, the operation of cricothyrotomy and thyrohyoid laryngectomy were devised by French surgeons Felix Vicq d'Azyi (1748–1794) in 1776 and Joseph-François Malgaigne (1806–1865) in 1850 respectively. The first laryngofissure, credited to Ludolph Brauers (1865–1951) of Louvaine in 1833 which was performed without a covering tracheostomy. Laryngofissure was performed under chloroform anaesthetic by Gordon Buck (1807–77) in the United States in New York in 1851, and in London, England by Sir George Duncan Gibb (1821–76) in 1864.[7, 8]

The London laryngologist Morell Mackenzie,[3, 24] (1837–92), having been trained in Vienna and Budapest under Johann Czermak (1828–73), commenced practice in 1862 and is considered the father of British laryngology. As the first English laryngologist, he was the founder of the first hospital for diseases of the throat in the world, which opened in London in 1865. Among Mackenzie's succession of assistants at Golden Square were Lennox Browne (co-founder of the British Rhino-Laryngological Association), Gordon Holmes (author of the first history of laryngology), Felix Simon (Semon's Law), Grenville Macdonald (Professor of Laryngology, King's College Hospital), Norris Wolfenden (co-founder of The Journal of Laryngology and Otology), John Nolan Mackenzie (of Johns Hopkins Hospital), Samuel Johnston (Surgeon to the Baltimore Eye, Ear and Throat Charity Hospital and one of the founders of the American Laryngological Association), Charles Louis Taylor (subeditor of the British Medical Journal), James Donelan (the first laryngologist at the Italian Hospital) and Mark Howell (who assisted during the treatment and attended until the death of Emperor Frederick III June 1888).[7]

The first total laryngectomy was performed by Professor Theodor Billroth (1829–94) of Vienna on 30 December 1873, having excised a laryngeal tumour via a thyrotomy incision, preserving the right vocal cord some weeks earlier. The patient died of local recurrence 7 months following his major surgery. The last success on record was achieved by Enrico Bottini (1837–1903), of Turin. The long survivor was achieved for 15 years after total laryngectomy performed in 1875. Jacob da Silva Solis-Cohen (1838–1927) was the first, in 1884, to perform a total laryngectomy in America – the patient survived 11 years without a recurrence. Based on his contribution to the discipline, it has been proposed that Solis-Cohen be acknowledged as America's first head and neck surgeon.[25]

Paranasal sinuses and nasopharynx surgery

The first total maxillectomy was reportedly performed in 1827 in Lyon, by Joseph Gensoul (1797–1858) without anaesthesia. With further practice, it was said that Gensoul perfected his technique and could complete the procedure in two-and-a-half minutes. A variety of incisions have been suggested over time by various surgeons including Alfred Velpeau (1807–73) of Paris, Karl Otto Weber (1827–67) from Frankfurt, Sir William Ferguson (1808–77) and Thomas Tatum (1802–1879) of London, and James Syme (1799–1870) of Edinburgh. Auguste Nelaton (1807–73) of Paris promoted a transpalatal approach to the nasopharynx in 1859, whilst Pierre Charles Huguier (1804–73), also of Paris, advocated a transmaxillofacial or lateral nasal approach. In 1902, Emil-Jules Mourne (1855–1914) of Bordeaux, published his 'lateral rhinotomy' approach and Alfred Denker (1863–1941) in 1905 described a sublabial approach to the nasal cavity and maxillary antrum.[8]

THE 20TH CENTURY

Following the death of Pimpernelle, in the mid-17th Century, an interval of almost 200 years passed during which it appears from the absence of historical evidence that the development of surgery of the head and neck stagnated.[1] The reasons for lack of significant progress related to the lack of what are now considered fundamental needs for any surgery, such as general anaesthesia, antiseptic techniques, blood banking, antibiotics, surgical pathology and skilled nursing care. The discovery of anaesthesia occurred in the 1840s: ether in 1842; nitrous oxide in 1844; and chloroform in 1847. Local anaesthetic in the form of cocaine was not discovered until 1880.

The introduction of binocular operating microscope heralded the possibility of performing microsurgery of the larynx and other sites. The principal changes in endoscopy have occurred since the 1950s and have been associated with technical improvements in lighting, magnification and instrumentation as well as documentation of clinician findings. Harold Hopkins (1918–94) and Narinder Singh Kapany (b.1926) developed and subsequently introduced the rigid and flexible fibreoptic systems in 1954.[26] Harold Hopkins' solid rods, with their different angles connected to a proximal light source by a fibreoptic cable, have become essential tools for diagnostic and therapeutic procedures in the head and neck. Fibreoptic light sources aided both rigid endoscopy and the flexible fibrescopes, introduced in 1957, allowed improved visualization of the mucosal head and neck subsites and the early detection and diagnosis of cancer in the awake patient. Advancement in pathology, radiology and radiotherapy have expanded the 'team approach' to improve the patient's diagnosis, improved staging of disease

and expanded the options available for the management of patients with head and neck cancer.

Head and neck pathology

The modern era was heralded by the development of the achromatic microscope, which allowed pathologists to first view tissues under magnification.[1, 27] The mid-19th century was dominated by developments in the pathologic description of tumours, including those by the father of modern oncologic pathology, Rudolf Virchow (1821–1902).[28] Virchow, the pioneer of cellular pathology, published the first study of the pathology of tumours in 1858. Surgical pathology, however, only began to develop as a distinct specialty from the 1960s onwards. Two fundamental concepts regarding head and neck cancer were published by Albert C Broders (1885–1964) of the Mayo Clinic in the early 1920s. First, he defined the grading system of squamous cancer of the lip,[29] and subsequently applied it to sites of the head and neck.[30] Broders also described carcinoma *in situ*, although the topic was more firmly established by a subsequent detailed report by John D Crissman and Richard J Zarbo in 1989.[31] Several of the early head and neck surgeons were also experienced pathologists: Joseph H Ogura (1915–83), Barnes Hospital, and John J Conley (1912–99), New York checked their own frozen sections during the weekends.[32] John A Kirchner (1915–2011), Yale, performed serial sections of 100 total laryngectomy specimens in his search for the anatomical pathways by which laryngeal cancer spread.[33] It was at the Centennial Conference on Laryngeal Cancer in 1974 (100 years after the death of Billroth) that the first public interaction between surgeons and pathologists took place and a new era of working practices was established.[34] The appointment of Vincent J Hyams (1924–98) in 1968 as Director of Otolaryngologic Pathology at the Armed Forces Institute of Pathology, Washington and in 1974 the publication of the textbook *Tumors of the Head and Neck* by John G Batsakis (1929–2013)[33, 34] were other landmark events in the development of head and neck pathology. The specialty of head and neck pathology has culminated in the publication, by the World Health Organization, of *A Classification of Head And Neck Tumours* ('The Blue Book'), the most recent edition of which was published in 2017.[35]

Radiology

Computerized tomography (CT) was invented and its early clinical application defined at the Atkinson Morley Hospital, London, England in 1971. The pioneering work of Sir Godfrey Hounsfield (1919–2004) in collaboration with Allan Cormack (1924–98), which underpinned the development of CT, led to both sharing the 1979 Nobel Prize for Physiology or Medicine. Subsequently, magnetic resonance imaging (MRI) was developed by Paul C Lauterbur (1829–2007) of Pittsburg and Peter Mansfield (1933–2017) of Nottingham. Their pioneering work culminated in them sharing the Nobel Prize for Physiology or Medicine in 2003. Continuing the progression of the development of ever more sensitive imaging modalities, in 1999, David Townsend, Ronald Nutt and colleagues in Pittsburg, developed positron emission tomography (PET/CT) for diagnostic use in clinical oncology.[8] This technique is now firmly established in the investigative work-up of patients with head and neck cancer, particularly in patients presenting with occult primary disease or in those where treatment failure is suspected.

Radiotherapy

In the 1920s, ionizing radiation, delivered as an external beam or by the placement of interstitial rods, was first used to treat patients with head and neck cancer. Henri Coutard (1876–1950) described his technique of protracted radiation therapy, which became so popular and accepted in many centres[36] that, for a time, surgery was partially displaced as a primary modality in the treatment of head and neck cancer. Hayes Martin, an admirer of Crile and a pioneer of head and neck surgery, although trained in the use of ionizing radiation, was vociferous in his resistance to the use of radiation for many cancers, primarily because of its toxicity profile and unpredictable ability to effect cure.[37] As outlined above, in these early days, the administration of radiotherapy was limited to orthovoltage generators and radium implants, resulting in a high degree of skin damage, poor cure rates and a myriad of attendant complications. By the 1950s the era of modern radiotherapy had begun with the advent of the linear accelerator and telecobalt units, which generated supervoltage radiation. Early advocates, such as Gilbert Fletcher (1911–92) in the United States,[38] and Manuel Ledermann (1912–84) in the UK,[39] strongly recommended external beam radiotherapy as the primary treatment modality for larynx cancer and cancers of other head and neck sites. The net effect of the work of these early advocates was that radiotherapy as a primary treatment for many head and neck cancers became popular and remains so, even today, in much of Northern Europe, the United States and Canada. The use of post-operative radiotherapy, following definitive surgical resection, became standard care during the 1970s. This combined management, which involved radiotherapy commencing after healing and within 6 weeks of surgery, was shown to definitively improve cure rates when compared with either surgery or radiotherapy alone or when salvage surgery was used after radiotherapy failure.[40] During the late 1980s advancements in computer software and imaging technology led to the development of three-dimensional (3D) image-guided targeting of radiation fields in an attempt to maximize tumour dose whilst minimizing radiation doses to adjacent normal tissues. The introduction of multileaf collimators facilitated an increase in the numbers of beams that could be delivered without a prolonged extension of the treatment time. The result was the emergence of 3D conformal radiotherapy, which allowed further refinement of radiation delivery to image-defined targets. Further improvements to radiation delivery precision occurred throughout the 1990s with the introduction of intensity-modulated radiation therapy (IMRT), which offers a higher degree of dose conformality

to maximize tumour dosing with greater sparing of normal tissue toxicity.[41]

Radiotherapy alone or in combination with cisplatin-based chemotherapy remains today a mainstay of treatment for many cancers of the head and neck in many centres throughout the world – particularly the developed world. Important studies which have led to this situation include the Department of Veterans Affairs (VA) Laryngeal Cancer Study, which, in 1991, demonstrated that response to chemotherapy was an excellent predictor to response to radiation therapy in cases of advanced laryngeal cancer.[42] Many high-quality randomized studies have also shown the utility of concomitant chemoradiotherapy in the management of head and neck cancers. The attraction of this approach is the avoidance of surgery and therefore, particularly for larynx cancer, the potential for preserving laryngeal function. This approach, however, is the subject of much ongoing debate as the treatment is toxic and difficult to tolerate by older patients with poorer performance status. Moreover, it has yet to be firmly established that preservation of the larynx amounts to the same as preservation of laryngeal *function* for the majority of patients treated this way.[43]

Surgery of the oral cavity

By the turn of the 19th century, it had become obvious to surgeons treating oral cavity cancer that treatment failure was most frequently associated with recurrent disease at the primary site and locally in the neck. This prompted surgeons to undertake more radical incisions of the primary tumour and to include removal of the cervical lymph nodes in an attempt to minimize the risk of locoregionally recurrent disease. Polya and von Navratil, in 1902, described the lymphatic drainage of the oral cavity, demonstrating that 50% of the lymphatics traversed the mandibular periosteum [published in German]. This resulted in the development of the concept of *en-bloc* resection and laid the foundations of the original composite (soft tissue and bone) resection for oral cancer. Almost concurrently, in 1906, the American surgeon and pioneer of neck dissection surgery, George Crile (1864–1943) described his approach to head and neck tumours, thus laying the foundation of the present-day approaches to neck dissection surgery.[44] Crile was an extremely creative surgeon, even developing pneumatic suits for patients to maintain their blood pressure during extensive surgical procedures. He also developed a carotid clamp that would reduce but not completely occlude carotid blood flow in an attempt to reduce the technical challenge of surgical bleeding as well as reducing blood loss. In Britain, the pioneering work in head and neck surgery of Henry Butlin (1845–1912) (considered to be the first head and neck surgeon), was continued by John Bland-Sutton (1855–1936) and later St. Clair Thompson (1859–1943) and Alexander Marsden (1832–1902), as well as Wilfred Lewis Trotter (1872–1939).[7] In spite of Crile's efforts to promote ever more radical surgery, the vogue for extensive procedures faded from the scene for a time, because of excessive mortality and apparent indifference in the surgical community.[13, 27]

Neck surgery

In 1927, George Harold Semken (1875–1946) who worked in the New York Skin and Cancer Hospital, excised *en bloc* (later called a composite operation) a primary mouth lesion that involved the corner of the mouth, buccal mucosa and lower jaw and the lymph nodes of the neck. In 1932, Grant E Ward (1896–1958), in Johns Hopkins, performed the first composite *en-bloc* resection, which consisted of a subtotal excision of the tongue, floor of mouth, and mandible in continuity with a radical neck dissection.[1, 45, 46] In 1951 Hayes Martin published a large series of 1450 cases of radical neck dissections, for involved lymph nodes as part of treatment for tumours emanating from all primary sites: so-called therapeutic neck dissection. He did not advocate surgery for the neck in the absence of obviously involved lymph nodes: so-called elective neck dissection.[47]

As an aside, a major innovation in the management of head and neck cancer at this point in time was the description in 1934, by Martin and Ellis, of fine-needle aspiration cytology (FNAC) as a diagnostic tool for enlarged cervical lymph nodes, a development that would dramatically alter the treatment of head and neck malignancy and thyroid disease over the next 75 years.[48]

Neck dissection surgery, the landmark publication by Hayes Martin in 1951,[47] suggested an extension of the surgery previously described by George Crile in 1906 to include resection of the spinal accessory nerve, even when not involved by tumour. In contrast, Crile had recommended preservation of the nerve when not involved by tumour.[46]

Surgical opinion differed about the need for elective neck dissection and those supportive of the approach considered that a radical neck dissection was 'too radical' and clinically unnecessary.[49, 50] This debate continues to this date about the radicality of surgery for tumour positive neck disease. Ettore Bocca (1914–2003) from Italy, popularized the modified neck dissection, where fascial compartment dissection of the cervical lymph nodes with preservation of the non-lymphatic structures (internal jugular vein, spinal accessory nerve and sternocleidomastoid muscle) was performed. Management of neck disease evolved throughout the 1960s and 1970s following the descriptions of selective neck dissection by Osvaldo Suarez (1914–1979) in South America and Ettore Bocca in Italy.[51–53] In 1990 Jatin Shah and colleagues evaluated the histological patterns of lymph node metastasis in patients undergoing elective and therapeutic radical neck dissection, in a series in which all patients underwent a radical neck dissection, irrespective of the primary pre-treatment nodal stage. Based on these data, which showed that the patterns of lymph node metastasis could be largely predicted, elective dissection of selective lymph node levels most at risk was proposed as an alternative to elective modified radical or radical neck dissection.[54]

In addition to the data that show metastatic spread in cervical lymph nodes could be predicted, the spread of tumour within a lymph node to broach the lymph node fibrous capsule – extracapsular spread (ECS) – was identified as an important negative prognostic factor even when

present in small apparently non-metastatic lymph nodes. ECS was identified in 20% of clinically negative necks in patients with supraglottic cancer who underwent elective neck dissection. This finding of ECS and multiple positive lymph nodes, by the Eugene Nicholas Myers (1933b) team from Pittsburgh, became indications for post-operative radiotherapy and currently chemotherapy is also suggested in the context of ECS.[55]

The trend towards modified radical and elective neck dissection was stimulated in an effort to avoid the not insignificant functional and cosmetic consequences of radical neck dissection. Data reported in the 1990s confirmed that selective neck dissection was as effective as modified neck dissection in patients with clinically positive lymph node disease.[56, 57] Identification and removal of the first echelon drainage lymph nodes, so-called sentinel lymph nodes, following the injection of isotope solution into or around the primary oral cancer, is increasingly used to determine whether neck dissection is needed at all.[57–59] It has been proposed and agreed by the International Head and Neck Scientific Group (IHNSG) that a logical nomenclature for the different types of neck dissections be recommended both for clinical and research purposes.[60] Consequently, the IHNSG has summarized the current philosophy in the surgical management for head and neck squamous cell carcinoma.[61]

Reconstructive surgery

The most important surgical innovations of the past 40–50 years have, however, been in the development of approaches to reconstruct ablative defects of the head and neck. In the 1960s, several surgical innovations helped reduce the morbidity of head and neck ablative surgery. In particular the increasing use of very reliable axial pattern flaps to reconstruct large oral cavity and neck defects resulted in decreased morbidity and a considerable shortening of post-operative hospital stay. Foremost among these were the descriptions of the forehead flap for oral reconstruction popularized by Ian McGregor (1921–98) and his wife Mary McGregor[62] and the deltopectoral flap described in the United States by Vahram Y Bakamjian (1918–2010) and colleagues. A H Martin Littlewood (1923–2004), who was a UK Fellow for six months at Roswell Park at the same time (1961), who returned to Warrington and practiced as a plastic surgeon.[63] In the late 1970s, the description of the pectoralis major myocutaneous flap by Stephan Ariyan[64] transformed head and neck oncologic surgery as patients could be offered a single-stage reliable reconstruction with minimal donor site morbidity. In addition, the ease of harvest and transfer of the pectoralis major flap made it a technique that any head and neck-trained surgeon could perform, broadening the scope of reconstructive surgery to other disciplines outside plastic surgery.

The late 1960s and early 1970s heralded the era of reconstructive microsurgery, which has since transformed the practice of contemporary head and neck surgery, to the enormous benefit of patients and healthcare providers. The concept of free-tissue transfer had been developed years earlier, but was limited by the quality and availability of microvascular sutures, appropriate instruments and operating magnification. Jacobsen and Suarez first described the repair of vessels under 2 mm diameter in 1960. The first free-tissue transfer of a composite (soft tissue and bone) flap was performed by G Ian Taylor and Rollin K Daniel in 1973.[65] Subsequent developments in reconstructive microsurgery have resulted in the description of a plethora of free flaps available for head and neck reconstruction championed by a number of extremely gifted reconstructive microsurgeons, including Kiyonori Harii, Harry J Buncke (1922–2008), Ralph T Manktelow, Mark Urken and many others.

Commonly used flaps in contemporary head and neck surgical practice include: the radial forearm flap described by GF Yang in 1983[66] and popularized for oral cavity and oromandibular reconstruction by David Soutar; the composite fibular flap, originally described by G Ian Taylor of Australia in 1977[67] and popularized by David Hidalgo and Alica Rekow for mandibular reconstruction in 1995;[68] and the anterolateral thigh flap described by YG Song et al in 1984[69] and popularized for head and neck reconstruction by Fu-chan Wei et al in 2002.[70] The ubiquitous application and the expansion of training in the use of microvascular free flap techniques has resulted in major changes in the specialty backgrounds of surgeons performing these techniques. Head and neck reconstruction is no longer the preserve of the plastic surgeon, with maxillofacial surgeons and even otolaryngologists/head and neck surgeons assuming pre-eminence in this field.[71, 72]

HEAD AND NECK SOCIETIES AND LEADERS

Hayes Martin (1892–1977) and Grant Ward (1896–1958) in 1952, and 50 selected American general surgeons were invited to serve as founding members of the Society of Head and Neck Surgeons, most were their former residents/students, and practiced in general or plastic surgery. Martin, the first president of SHNS, prioritized his training position for general surgeons, at the exclusion of otolaryngologists. In 1958, a group of otolaryngologists, John Conley (1912–99) the first president, George Sisson (1920–2006) and others conceived the American Society for Head and Neck Surgery, with a desire to foster participation with the American College of Surgeons.[73] Both organizations thrived in parallel for several decades, but as general surgeons waned in their enthusiasm and otolaryngologists became the dominant specialty in head and neck surgery, the two societies merged into the American Head and Neck Society (AHNS – www.ahns.org) in 1998.[74]

In Britain during the 1960s, a similar discussion was had as had been in the US, between a number of general surgeons about setting up a national head and neck society and linking such national societies with an International Association of Head and Neck Oncologists. In late 1967, a decision was taken to set up the Association of Head and Neck Oncologists of Great Britain (AHNOGB) with Mr. Ronald Raven (1904–1992), a London

general surgeon, as President, Professor Brian ED Cooke (1920–2007), an oral medicine and oral pathologist, from the University of Cardiff and Dr Manuel Lederman (1912–1984), a London radiotherapist, both as Vice-Presidents, Mr Douglas Ranger (1916–1997), a London ENT Surgeon as Honorary Secretary, and Mr Michael Harmer (1912–1998), a London general surgeon, as Honorary Treasurer. An additional nine members were invited to join the National Committee, and 78 letters of invitation were sent to doctors working in the field about the formation of a head and neck society. In January 1968, the inaugural meeting was held of the AHNOGB at the Royal Marsden Hospital.[75] In 1995, a decision was made to change the name of the organization to the British Association of Head and Neck Oncologists (BAHNO – www.bahno.org) to more reflect its broader clinician base, multidisciplinary working and membership of the society.

Unlike in many other countries, head and neck cancer surgical services are provided by otorhinolaryngology – head and neck surgery (ORL-HNS) and oral and maxillofacial surgery (OMFS) in an equitable fashion.[2] This resulted in the UK when NHS hospital consultant dentists (BDS) had to admit their patients overnight under the case of a named consultant medical clinician. To remedy that clinical situation, dentists who wished to pursue a career in head and neck surgery, which commenced in the mid-1970s, became doubly qualified both in dentistry and medicine.

It is appropriate that recognition be given to a number of our former UK head and neck surgeons / leaders:

Ian Alexander McGregor (1921–1998) a head and neck plastic and reconstructive surgeon at Cannisburn Hospital Glasgow, Scotland. He graduated from Glasgow Medical School 1944, MRCS and FRCS 1950, and FRCS Glasgow 1962. He studied with Dr. Herbert Conway, New York Hospital in 1955, and set up the West of Scotland Regional Plastic Unit 1959. He authored two major publications Fundamental Techniques of Plastic Surgery and their Surgical Application (1975) which ran for nine editions, and Cancer of the Face and Mouth (1986). He was former President of the Royal College of Physicians and Surgeons of Glasgow 1984–1986, and Presidents of the British Plastic Surgeons and the Association of Head and Neck Oncologists of Great Britain.

Sir Donald Harrison (1925–2003), a London Otolaryngologist, was the first UK Professor of ORL 1963. He published on the Anatomy and Physiology of the Mammalian Larynx, and Tumours of the Upper Jaw. He retired and was knighted in 1990;

Philip Stell (1934–2004), of Liverpool, and when appointed was the second UK Professor of ORL 1979. He did his fellowship with Joseph Ogura, St Louis, USA in 1956. He founded the ORS Society 1978, and the Journal Clinical Otolaryngology 1975. Stell couthored with Arnold Maran the first UK textbook on Head and Neck Surgery in 1972 which is now going into its 6th Edition. A prolific writer and linguist who was fluent in Dutch, German, French and Spanish, Stell translated 11 foreign medical textbooks into English. He retired from clinical practice in 1992 on grounds of ill health. He was awarded an MD on medieval history at York University and was recognized with a MBE by the Queen for his contribution to medieval history.

John Samuel Pattison (Iain) Wilson (1923–2006), a London plastic surgeon who worked at St Georges, Queen Mary's Roehampton, the Westminster and Royal Marsden; he was greatly liked as a teacher by his residents.

Henry Jagoe Shaw (1922–2007), a London Otolaryngologist, appointed surgon in 1962 at the Royal Marsden and St Mary's Hospitals, he did a fellowship with Hayes Martin in New York (1953–1954) and another year at Bellview Hospital, New York.

Barrie Thomas Evans (1946–2015), an Oral and Maxillofacial Surgeon at Southampton General Hospital, appointed in 1988. Developed a major head and neck, skull base surgical service before retiring in 2012 from the National Health Service.He was the first Chairman of the head and neck Interface Training Programme at the Royal College of Surgeons.

Omar Shaheen (1931–2016), an Otolaryngologist at Guy's Hospital, did his fellowship in Iowa, returning in 1963, specialized in thyroid disease, and trained a generation of young surgeons to follow his surgical principles and techniques which resulted in many of the current head and neck surgeons in the UK.

Arnold (Arnie) George Dominic Maran (1937–2017), an Edinburgh Otolaryngologist who when appointed was the third UK Professor of ORL in 1988, he did his fellowship with Brian McCabe, Iowa (1966–1967) before returning to Scotland, and was ultimately appointed at the Edinburgh Royal Infirmary in 1975. Not only was he an expert on head and neck cancer but set up the first voice centre in the late 1980s for which he became dubbed 'the voice doctor'. He was a frequent co-author with his colleague Professor P M Stell in the 1970s including the textbook *Head and Neck Surgery* in 1972. He authored several textbooks on ORL and travelled widely acquiring many accolades. He was elected President of the Royal College of Surgeon of Edinburgh from 1997 to 2000. He was a musician and jazz enthusiast, as well as a golfer – all resulting in publishing books in his retirement, including one on the Sicilian Mafia influenced by his heritage and an incident involving his great uncle.

The European Head and Neck Society (EHNS – www.ehns.org) was formally established in 2006 in Brussels by the signing of the official documents by the founding Board: Jean Louis Lefebvre (France), Rene Leemans (Holland), Jan Olofsson (Norway), Dominique Chevalier (France), Guy Andre (Belgium) and Patrick Bradley (UK). Over several decades the Dutch, British and Scandinavian head and neck societies had met frequently and these gatherings were considered of benefit to all who attended. A decision was made to hold a European Head and Neck

Meeting in Lille, France in 2001, followed by a second meeting in 2003; these suceessful meetings led to a consensus decision to create the European Head and Neck Society. The EHNS is composed of individual persons, national and multi-national societies, and associated study groups oriented towards head and neck cancer research, training and treatment throughout Europe.[74]

The International Federation of Head and Neck Oncologic Societies (IFHNOS – www.ifhnos.org) was established by Dr. Jatin Shah, New York who formed a steering committee at a meeting in London 1987 with representatives of 16 Head and Neck Organizations from around the World.[5] A constitution and bylaws were formulated and Jatin Shah was elected Secretary General. IFHNOS is a global organization established through cooperation of national and regional Societies and Organizations in the Specialty of Head and Neck Surgery and Oncology with membership from national and regional multidisciplinary organizations, representing 65 countries. The purpose of the Federation is to provide a common platform for Specialists in the field of Head and Neck Cancer to interact in professional matters of mutual interest. The Federation has grown with a membership of 43 Head and Neck Oncologic organizations, representing 65 countries. The Federation is able to reach over 5000 specialists. Quadrennial World congresses of the Federation have been held since 1998.

HEAD AND NECK SURGICAL TECHNIQUES

Surgery of the oropharynx

OPEN APPROACH

Over recent decades in the developed world, management of squamous cell carcinoma of the oropharynx, whether human papilloma virus (HPV) associated or not, has become dominated by non-surgical modalities, namely, radiotherapy +/– concurrent cisplatin-based chemotherapy. As a consequence, the surgical management of tumours of the oropharynx involving open access procedures including mandibular osteotomies or lingual release techniques has fallen into abeyance. That said, there are cases where the approach is still used – for example, in patients with advanced stage but still operable disease, who are unfit or too old for primary chemoradiotherapy. In these cases reconstruction of the ablative defect is almost always essential and techniques involving free-flap reconstructive surgery predominate.

TRANSORAL APPROACH

Transoral *en bloc* resection for tonsil tumours was initially described in 1951 by Pierre Charles Huet (1896–1947), a surgeon based in Paris.[77] Current transoral approaches for tonsil cancers in patients with early stage primary disease include transoral laser surgery (TOLS) and transoral robotic surgery (TORS) with integrated neck dissection and risk stratified radiation therapy, pioneered by Heinrich H Rudert, Wolfgang Steiner and Petra Ambrosch (Germany) and Gregory Weinstein (USA), respectively. Such approaches avoid the overall early- and long-term toxicity burden of non-surgical treatments, the morbidity associated with open approaches and free-flap reconstruction, whilst potentially conferring equitable oncological outcomes with better functional outcomes.

Surgery of the larynx

OPEN APPROACH

In 1913, Themistocles Gluck (1853–1942) and Johannes Sorensen (1862–1939) described improved approaches to the creation of the tracheostoma and repair of the pharynx after laryngectomy and arguably became the foundation of modern laryngopharyngeal ablative and reconstructive surgery.[78] It was not until the late 1950s that partial laryngeal surgery was considered an option to treat early stage cancer. The anatomy of the larynx had been studied by Joel Pressman (1901–68) of UCLA and John Kirchner (1915–2011) of Yale, who recognized compartmentalization of the glottis and supraglottis by fibrous bands and ligaments.[79–81] Many partial laryngeal resection procedures have been described over time, providing a wide range of choices of conservation surgical treatments, retaining the goal to cure while preserving laryngeal function in terms of voice and non-tracheostomized breathing. Jean Leroux-Robert described a frontolateral partial laryngectomy for unilateral vocal cord carcinomas, with minimal extension to the opposite side.[82] In 1951, Justo M Alonso (1886–1974) from Uruguay, one of the pioneers of partial laryngeal surgery, described techniques of vertical laryngectomy and horizontal supraglottic laryngectomy.[83] Many variations of this procedure have been described and are all encompassed within the term hemilaryngectomy.

The development of supraglottic laryngectomy was an extension of technique of pharyngectomy (superior and inferior), as described by Wilfred Trotter (1872–1939) in 1920; this resulted in Joseph Ogura (1915–83),[84] Max Som (1904–1990)[86] and Ettore Bocca[81] modifying the technique of supraglottic laryngectomy to that understood by the term today. In the late 1950s a more radical excision of more extensive glottic and supraglottic cancers was reported using a technique of supracricoid partial laryngectomy by Eduard Herbert Majer (1909–1991) and Walter Rieder (1921–1992), surgeons in Vienna, which became popular in Europe.[87] Olivier Laccourreye et al[88] popularized the procedure in the late 20th century in Europe, and Gregory Weinstein from Philadelphia[89] in the United States. A large series of 297 patients from the Institute Gustave-Roussy treated by subtotal laryngectomy between the years 1974 and 1997, reported 3- and 5-year overall survival rates of 92% and 88% respectively.[90] Italian surgeons continued to expand the indications laryngeal sparing surgery, building on the teachings of Italo Serafini (1936–2010) from Vittorio Veneto, who classified open partial horizontal laryngectomy, into three types: supraglottic laryngectomy (Type I); supracricoid

laryngectomy (Type II); and supratracheal laryngectomy (Type III), Type III being indicated for intermediate-to-advanced laryngeal cancers with subglottic extension.[91]

TRANSORAL APPROACH

Francis E 'Duke' Le Jeune Sr. (1894–1977) from New Orleans is credited as a pioneer of the modern era of endoscopic micro dissection of vocal cord cancer, but he had continued the work of Robert Clyde Lynch (1880–1931). The technique of micro laryngeal examination had been first reported by Gustav Killian (1860–1921) from Germany in 1910. Following the publication of the experience of Le Jeune, Charles Vaughan (1926–2014) and colleagues from the United States.[92] Following on from Lejeune, Charles Vaughan (1926–2014) and colleagues from the United States, and Oskar Kleinsasser (1929–2001) from Germany progressed and popularized the developments in minimally invasive surgery of the larynx,[93, 94] initial techniques that have been expanded and popularized by others. For example, M Stuart Strong and Geza J Jako (1930–2015) from Boston are credited with introducing the CO_2 laser for microsurgery of the larynx in the early 1970s;[95] Heinrich Rudert, Wolfgang Steiner and Petra Ambrosch from Germany,[96] published their systematic approach to the endoscopic transoral laser microsurgery (TLM) of laryngeal tumours fundamentally altered the landscape of the management approach for laryngeal malignancy. The introduction of transoral robotic surgery (TORS) in 2007 has further expanded the capabilities of endoscopic surgery.[97] The European Laryngological Society working committee, in an attempt to standardize the reporting of endolaryngeal surgical resection in the clinical and research setting, developed a classification based on the extent of glottic and supraglottic transoral endoscopic resection.[98, 99]

Surgery of the hypopharynx

OPEN APPROACH

Surgery for hypopharyngeal cancer was changed in the 1920s by Wilfred Louis Trotter (1872–1939) from London, and revived in the 1940s by Harold William Wookey (1889–1980) who worked in Toronto. Trotter described a lateral pharyngotomy to gain access, and using local cervical skin flaps to repair the defect, Wookey described the repair of a circumferential defect using a two-layered skin tube to create a neopharynx.[98, 99] who described a lateral pharyngotomy to gain access to the pharynx using local cervical skin flaps to repair the defect, thus avoiding the previously used more extensive pharyngolaryngectomy.[100, 101] As for pharyngolaryngectomy, the transcervical approaches to the hypopharynx may be classified into partial pharyngectomy with partial laryngectomy, total laryngectomy with partial pharyngectomy or circumferential laryngopharyngectomy with or without oesophagectomy.[102] The techniques used for repair of the pharyngeal defect (partial or total) progressed through all of the phases of development of flap reconstruction methods: local skin, pedicle skin, axial myocutaneous and viscus (stomach and colon), free soft tissue +/– bone and free viscus (gastro-omental flap), over a period of 60 years.[103]

TRANSORAL APPROACH

As with larynx cancer surgery, although function-sparing non-surgical treatment is considered standard of care in many centres in the developed world, TLM or TORS has been proposed for the management of hypopharynx cancer with the same aim of reducing the extent of surgery as well as the burden of post-treatment morbidity.[96, 104] The selection of appropriate treatment is of crucial importance in the achievement of optimal functional results and likely survival for these patients.[105]

Surgery of the paranasal sinuses and nasopharynx

OPEN APPROACH

The open approach using the lateral rhinotomy and the Weber-Ferguson transfacial incisions to access tumours of the ethmoid and maxillary sinus was not introduced until the 1970s. In 1963, Alfred Ketcham (1924–2017) first reported a series of patients who had undergone a combined craniofacial approach to anterior skull base malignancies.[106] Other surgeons have since continued and expanded on the trans cranial +/– endoscopic approaches. Noteworthy examples include Victor Schramm, Paul Donald and Dennis Kraus from the USA, Anthony Cheesman from the UK, William Wei from Hong Kong and Sultan Pradham from India. Developments have led to a reduction in post-operative complications and improved survival. As a consequence of the heterogeneous nature of tumours which may occur in this region, histology plays a great role in prognostication. Moreover, tumour extension, particularly intracranial extension, whether dura and/or brain, involvement and positive surgical resection margins all impact negatively on outcome.[107] As an extension of earlier techniques, William Wei from Hong Kong described the anterior-lateral maxillary swing approach in 1998, and reported his long-term results of 246 patients. During surgery, frozen section was used and clear margins were achieved in 78% of cases resulting in a 5-year local control rate of 75%. These were selected patients, however, and did not include patients with erosion at the skull base or invasion of the carotid artery.[108]

TRANSNASAL APPROACH

In the early 1980s, Erik Wigand (b.1931), Wolfgang Draf (1940–2012) and Walter Messerklinger (b.1920) as well as Heinz Stammberger (b.1946)[109] and colleagues from Graz, Austria introduced the concept of functional endoscopic sinus surgery (FESS), thereby providing the technical foundation for the development of minimally invasive nasal surgery. A number of groups around the world, most notably Amin Kassam, Ricard Carrau and Carl Snyderman[110] from the USA, Valerie Lund and Nicholas Spencer Jones from the UK and Giulio Cantu,

Pierro Nicolai and Paolo Casteinuovo from Italy, have extended these concepts and techniques, developing transnasal approaches to the management of anterior skull-base tumours. Endoscopic nasopharyngectomy has been reported to show promising short-term outcomes for early-stage recurrences of nasopharyngeal carcinoma but long-term follow-up is necessary to confirm effectiveness.[111] It is suggested that improvements in technology, robotic-assisted transnasal approaches, and improved suturing techniques and closure devices, will help decrease the rate of CSF leaks and lead to better patient outcomes.[112]

SURGERY OF THE TEMPORAL BONE MALIGNANCIES

Primary temporal bone malignancies are exceedingly rare, squamous cell carcinoma being the most common and are generally the focus of most publications. In a review of 100 temporal bone resections in 1975,[113] John S Lewis (1920–2005) from the Memorial Hospital, New York, published data on 80 patients with these tumours. The death rate reduced from 10% in 1954 to 5% in recent years. The overall 5-year cure rate was 25% for squamous cell carcinoma. Prior to this publication, primary temporal bone cancer was considered incurable, and was treated by radiotherapy alone. Currently, with improvements in disease staging by imaging techniques, surgery remains the primary treatment of temporal bone malignancy, with the use of radiotherapy as an adjuvant to surgery.[114, 115]

HEAD AND NECK SURGERY: THE PRESENT

With great foresight, Hayes Martin, on appointment as Chief of the Head and Neck Service in 1934, set up a weekly head and neck tumour board (multidisciplinary clinic). During the 20th century, this concept was introduced more widely and whilst it was adopted with varying enthusiasm initially, a multidisciplinary team (MDT) approach is now accepted as the 'gold standard' environment within which to manage patients with head and neck cancer (See Chapter 32, Multidisciplinary team working).[116, 117] Case presentations at an MDT, when all things are considered, may affect the treatment offered and will certainly standardize treatment approaches and improve standards of care to the benefit of patients.[118] The problems associated with the occasional head and neck surgeon ('the dabbler') on the treatment outcome was most forcefully highlighted by John ('Jack') J Lore (1923–2004) in a publication of 1987, when he advocated the need for added qualifications and training for future head and neck surgeons, as well as accreditation of the hospital ('dabblice') as being a suitable environment to perform such surgery, and referred to the market place as 'dabbloge'.[119] While the USA, Canada, some European nations (Finland, Netherlands and UK) and Brazil have developed structured additional education and training in head and neck oncology, awarding a 'Certificate of Completion of Fellowship', others have informal training programmes (Italy, Germany and Spain). The concept of such specialist training for future head and neck surgeons has not been universally embraced. Moreover, when instituted, the training programmes need formal assessment of competence on completion of training, overseen by an accrediting body.[120] The modern head and neck surgeon may specialize in a number of parent surgical disciplines including general surgery, plastic and reconstructive surgery, otolaryngology/head and neck surgery, oral and maxillofacial surgery, neurosurgery or endocrine surgery. This confirms the necessity for contemporary head and neck surgeons to assimilate broad but complementary surgical skillsets in order to optimally undertake the complex management of patients presenting with cancers of the head and neck region.

From the early 21st century the training of head and neck surgeons relied on the sheer volume of clinical exposure, rather than specifically designed curricula. In addition, it is recognized that there is a critical mass required to assimilate the necessary expertise to become a competent surgeon, hence the creation of tertiary surgical centres. As in many other surgical specialties and in keeping with the history of surgery, surgical advances are dependent upon advances in technology – and this is increasingly the case in the modern era. Recent developments have resulted on more emphasis being placed on minimally invasive strategies with the aim of maximizing cure whilst minimizing treatment-related short- and long-term side effects. This dynamic environment dictates that surgical training needs to maintain flexibility and relevance.[121–123] Future head and neck surgeons will be trained to work within specialist oncology teams that treat subsites of the head and neck: skull-base surgery, endocrine surgery, endoscopic surgery, laryngology and voice surgery, as well as reconstructive surgery. Additionally, there may be a future need for a head and neck rehabilitation specialist to optimally manage patients coping with adverse effects of treatment.

The era of expanding non-surgical treatment options and precision medicine, and difficulties in recruitment and retention of head and neck surgical trainees has led to commentaries such as 'Has head and neck surgery a real future?'[124] and 'Head and neck surgery in crisis',[125] raising questions about the future of head and neck surgery as a specialty. The modern head and neck surgeon should consider his or her role as a leader and coordinator of the MDT, consider him- or herself as an oncologist, and become an educator, researcher and incorporator of technological advances.[126] The future head and neck surgeon will remain an essential member of the head and neck MDT and accordingly, a stylized job description pertinent for the future head and neck surgeon has been proposed.[127] It is essential that all members of the MDT head and neck cancer team embrace and participate in ongoing research into personalized medicine and targeted therapies, where genomic characterization of tumour tissue or blood is anticipated to play an increasing role in how cancer treatment is selected and individualized.[128]

HEAD AND NECK SURGERY: THE FUTURE

Head and neck surgeons, for the foreseeable future, can rest assured that there will always be a need for their services in the diagnosis and management of patients with cancer of the head and neck. While the indications and selection of treatments fluctuate with time, the success of any cancer treatment is captured by the adage, 'first treatment is always best'. Presently patients with locally advanced disease, (T3 and T4, >N2), of the larynx and hypopharynx, and oropharynx, are treated primarily with chemoradiotherapy. This function-sparing approach has resulted in enhanced organ retention but there is a poor evidence-base to confirm that the retained organ's function in a meaningful way to the extent that overall quality of life is truly enhanced in patients treated this way.

Oral cavity cancers remain best treated by primary surgery, as are other head and neck malignant tumours such as thyroid and salivary glands, skin and temporal bone cancers. The salvage of the failure of organ preservation approaches and for patients treated by minimal invasive surgical strategies represents a difficult challenge for the head and neck surgical oncologist, particularly the selection of patients for whom further treatment will be curative or life enhancing.

Early stage cancers of the larynx and hypopharynx are also best treated surgically with no need for adjuvant treatments.

What is also essential, and which might not have been the case in days gone by, is the need for surgeons to understand the biology of the disease they are treating, to fully appreciate the advantages and limitations of the non-surgical treatments offered to patients, to quality assess and quality control surgical outcomes and validated surgical approaches as part of high-quality, optimally designed and powered randomized clinical trials. Only then will they be able to contribute fully within the multidisciplinary environment to the future management of patients presenting with head and neck cancer.

KEY POINTS

- The term Head and Neck Surgery was reintroduced to surgical specialties in the middle of the 20th century by Hayes Martin and Grant Ward, both general surgeons.
- Oral cancer was described in the 17th century and surgeons mainly concentrated on the removal of mouth and neck tumours. Laryngeal cancer was made more manageable with the introduction of cocaine in the 19th century. The use of radiation therapy was discovered in the late 19th century and was introduced in a formalized therapeutic manner for larynx cancer in the early quarter of the 20th century.
- Early head and neck surgeons were brave, courageous, fearless and speedy in the era before anaesthetic, blood transfusion, and antibiotics.
- Resulting from World Wars, reconstructive procedures were rekindled and rapid progress was made shifting from split skin to axial and regional flaps. The advent of revascularized free transfer of tissue in the late 20th Century, which including muscle and bone, further advanced the surgeon's ability to resect and reconstruct more major and more repair complex defects.
- In the US the Society of Head and Neck Surgeon was established in 1954 by a group of general surgeons, because of an exclusion law, the otolaryngologists formed The American Society for Head and Neck Surgeons in 1956. In 1998, both societies amalgamated into The American Head and Neck Society and agreed a structured training programme for future head and neck surgeons. Similar events have been repeated in other countries.
- While progress was being achieved by performing more major resection on more advanced stage disease and being able to reconstruct the defect, a common event was that the tumour recurred locally, evidence was shown that post-operative radiotherapy reduced such an event happening.
- With advances in diagnostic imaging and anaesthesia it became possible for surgeons to change the extent of surgery from the traditional 'open approach' to a 'closed approach' using endoscopic telescope equipment under radiological monitoring and allowed surgical access to several 'hidden corners', such as the skull-base, parapharynx and temporal bone, inventing the term 'minimally invasive surgery'.
- The introduction of the surgical robot has proven to be an effective technique to safely treat most tumours of the head and neck irrespective of site or access. So far the evidence shows that the functional and cosmetic results are equal if not improved when compared with the standard open surgical approach. The comparison with non-surgical treatment may be difficult due to the inherent selection bias of favourable patients and tumour selected.
- There will always be a role for surgery in the diagnosis and management of head and neck tumours but the role may change over time. It is therefore important that future surgeons be educated as surgeon oncologists and play a major role in the decision-making process for treatment of patients. In time in the developed world at present centralization of head and neck cancer treatment will continue to be advocated and funded to optimize patient survival and minimize morbidity. It is paramount that this role is practiced and enforced within the multi-professional and multidisciplinary clinical group.

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CHAPTER 2

AETIOLOGY OF HEAD AND NECK CANCER

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: head and neck cancer aetiology and head and neck cancer causes.

INTRODUCTION

Squamous cell cancer constitutes the most common head and neck malignancy and is related to tobacco and/or alcohol usage. Non-squamous malignancy includes thyroid cancer, salivary gland cancer and sarcomas. These malignancies are not associated with tobacco and/or alcohol usage.

According to the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) programmes of the United States, between 1975 and 2010 the incidence for most head and neck cancers sites has globally decreased except for tongue, tonsil, salivary glands and thyroid.[1] Estimated new head and neck cancer cases and deaths for 2013 are shown in **Table 2.1**.[2] A decreased incidence of oral cavity cancer has been reported in the last 15 years, widely attributed to a reduction in tobacco use.[3] In contrast, the incidence of oropharyngeal cancer has risen in recent years, a phenomenon that has been linked mainly to the emergence of human papillomavirus (HPV) infection.[4] A more comprehensive treatment of epidemiology of head and neck cancers is discussed in Chapter 3, Epidemiology of head and neck cancer.

SQUAMOUS MALIGNANT TUMOURS

Squamous cell carcinoma of the head and neck encompasses cancer of the oral cavity, oropharynx, larynx and hypopharynx, nasopharynx, nasal cavity and paranasal sinuses. The two most important factors in the aetiology of head and neck cancer are tobacco and alcohol.[5] There is a synergistic interaction between these two agents that is multiplicative for the mouth, additive for larynx and between additive and multiplicative for oesophagus.[6]

TABLE 2.1 Estimated new cancer cases and deaths in United States, 2013

	Estimated cases			Estimated deaths		
	Both sexes	Male	Female	Both sexes	Male	Female
Oral cavity/oropharynx	41 380	29 620	11 760	7890	5500	2390
Tongue	13 590	9900	3690	2070	1380	690
Mouth	11 400	6730	4670	1800	1080	720
Other oral cavity	2460	1790	670	1640	1260	380
Oropharynx	13 930	11 200	2730	2400	1790	610
Larynx	12 260	9680	2580	3630	2860	770
Thyroid	60 220	14 910	45 310	1850	810	1040

A large case-control study from the United States shows good evidence of a dose-response relationship for both tobacco and alcohol.[7, 8] Other factors are also implicated in the aetiology of squamous cell head and neck cancer such as diet, viruses, occupational agents, pollutants and genetic influences, but few case-controlled epidemiological studies have been carried out.

Since the histological distribution and aetiopathological considerations for cancers at various sites within the head and neck are distinct, these tumours will be discussed in more detail under separate anatomic sites.

Cancer of the oral cavity

The main aetiological factors for oral cavity cancer are smoking and alcohol.[7, 8] It is estimated that in 2013 there will be 27 450 new cases of oral cavity cancer in the United States, 14 420 male and 9030 female.[2] In the UK it is the 15th most common cancer among men, and 16th among women.[9] The incidence and mortality increase with age with over 85% cases occurring after the 5th decade. Over the last 30 years there has been a slight increase in oral cancer mainly attributable to the increase in tongue cancer in young women.[10–12] A detailed treatment of the global epidemiology is found elsewhere in the text.

TOBACCO

Tobacco consumption

Tobacco is the most important factor and over 90% of patients have a history of smoking. Tobacco contains over 30 known carcinogens such as polycyclic aromatic hydrocarbons and nitrosamines.[13] There is a synergistic interaction with alcohol due to the increased mucosal absorption of these carcinogens due to increased solubility of the carcinogens in alcohol compared with aqueous saliva. The use of filtered cigarettes reduces this exposure and stopping smoking reduces the risk of head and neck cancer.[14] The risk of oral cancer is reduced by 30% in those who have discontinued for 1–9 years and by 50% for those who have discontinued for more than 9 years,[15] but it is unlikely that it ever returns to the baseline as compared to the rest of the population.[16] Pipe and cigar smokers have an increased risk of oral cancer compared to other head and neck subsites.[17] This is thought to be due to the type of tobacco used. Several reports have shown a progressive decline in tobacco consumption over the last 25 years.[18] It is possible that the decrease in tobacco use accounts for the decrease in oral cancer incidence. Also, a decrease of the prevalence of tobacco use has been reported among oral cancer patients. A recent descriptive report of the prevalence of tobacco use among oral cancer patients has shown a significant decrease of smoking in oral cancer patients.[19] This could suggest that other etiological factors could be responsible for part of patients with oral cancer. Further studies on the aetiology of oral cancer in non-smoking patients are warranted.

Smokeless tobacco

Oral cancer is strongly associated with different forms of smokeless tobacco consumed by chewing. These include Bidi, Chutta, Paan, Khaini and Toombak. This is particularly common in the Indian subcontinent and accounts for the high incidence of oral cancer in these countries. Oral cancer increases in a dose dependent fashion with these agents.[20, 21] There is also a strong association between the subsite of oral cancer and the site where the tobacco is placed. In India and parts of Asia, oral tobacco is mixed with betel leaf, slated lime and areca nut to form a quid called 'paan'. The lime lowers the pH, which accelerates the release of alkaloids from both the tobacco and areca nut. Chewing paan correlates with alveolobuccal cancer.[22] Paan is also strongly associated with a premalignant lesion oral submucous fibrosis.[23] Bidi smoking causes cancer of the oral commissure, oral tongue and also base of tongue. Chutta is associated with cancer of the hard palate and palatine arch in India.[24] Khaini, a mixture of tobacco and lime that is retained in the inferior gingivobuccal sulcus, leads to cancer in this site.[25]

Marijuana

When marijuana is smoked, a wide range of potential carcinogens are released and absorbed including polycyclic aromatic hydrocarbons, benzopyrene, phenols, phytosterols, acids and terpenes.[26, 27] A study from Memorial Sloan Kettering Cancer Center reported an overall risk of 2.6 compared to non-users.[28]

ALCOHOL

Alcohol is believed to act in a synergistic fashion with tobacco.[7, 29, 30] However, some case control and cohort studies have shown an increased risk of cancer even in non-smokers.[31] The precise mechanism by which alcohol causes cancer is not clearly defined as alcohol itself is not a carcinogen. Possible mechanisms include:

- Alcohol may act as a solvent increasing the cellular permeability of tobacco carcinogens through the mucosa of the upper aerodigestive tract.[29]
- The non-alcohol constituents of various alcoholic beverages may have carcinogenic activities.
- The immediate metabolite of ethanol is acetaldehyde and this may have a locally damaging effect on cells.[32]
- Chronic alcohol use may upregulate enzymes of the cytochrome p450 system, which may result in the activation of procarcinogens into carcinogens.
- Alcohol can also decrease the activity of DNA repair enzymes resulting in increased chromosomal damage.
- Alcohol impairs immunity due to a reduction in T cell number, decreased mitogenic activity and macrophage activity.
- Alcohol is high in calories, which suppresses appetite in heavy drinkers. Metabolism is further damaged by liver disease resulting in nutritional deficiencies and therefore lowered resistance to cancer.

DENTAL FACTORS

Poor oral hygiene is associated with oral cancer. This may be due to chronic inflammation of the gingiva.[33]

Alternatively, it may be due to an alteration in the oral microbiome.[34, 35] Painful or loose fitting dentures have also been associated with oral and oropharyngeal cancer.[36] This may also be due to chronic inflammation. There is some evidence suggesting mouthwashes containing alcohol may also be important.[37]

INFECTIONS

In oral cancer, several viruses have been implicated in carcinogenesis including human papilloma virus (HPV), human immunodeficiency virus (HIV) and herpes simplex virus (HSV).

Human papillomavirus

For oral cancer, the pathogenetic relationship with HPV is unclear. Some authors have dismissed a link between oral cavity cancer and HPV infection, based on the very low prevalence rates reported in some studies.[38–40] For instance, in the International Agency for Research on Cancer multicentre study, HPV DNA was detected in biopsy specimens in only 3.9% of 766 cancers of the oral cavity with valid PCR results.[38] In contrast, other authors have reported that the infection of oral cavity cells by HPV is not a rare phenomenon. Analysis of reports focused only on oral cavity cancer have reported a prevalence as high as oropharynx, around 60% or 70%,[41, 42] even in subsites not common for this infection (such as gums or floor of mouth). Therefore, the relationship between oral cavity cancer and HPV infection is not a closed case, and further research is necessary to elucidate its role.

Human immunodeficiency virus

A recent study from New York showed HIV infection in 5% of head and neck cancer patients.[43] In patients under 45, HIV infection was present in over 20%. Due to the depressed immunity in HIV patients, the head and neck cancers observed were more advanced in the HIV group. In addition, HIV infection is more common in inner city populations and certain socioeconomic groups and this will also contribute to the advanced stage at presentation of these patients.[44]

Herpes simplex virus

Several studies have shown that patients with oral cancer have higher antibodies to HSV, but this does not prove a causal relationship.[45] Antibody levels are higher in smokers and even higher in smokers with oral cancer. It is possible that the immunosuppression produced by smoking may lead to a HSV chronic carrier state resulting in raised antibody levels. HSV-type protein has been reported in 42% of patients with oral cancer and 0% in control patients.[46] However, there is little evidence that HSV gene sequences are present in oral cancer cells or any evidence of gene integration. Therefore, there is currently little emphasis on HSV in head and neck cancer.

NUTRITIONAL FACTORS

Several studies suggest high fruit and vegetable intake is associated with a decreased risk of head and neck cancer. This may be due to increased intake of the antioxidants or free radical scavenging vitamins A, C and E.[47–49] La Vecchia et al, estimated that up to 15% of oral and pharyngeal cancers in Europe can be attributed to dietary deficiencies.[50] Some studies have shown an increased risk with red meat intake and salted meat.[51, 52]

GENETIC AND IMMUNOLOGIC PREDISPOSITION

Although smoking is the main risk factor, not all people who smoke develop head and neck cancer. Therefore, genetic and immunologic factors also play a role. There are several genetic conditions that are associated with increased risk. Li-Fraumeni syndrome, an autosomal dominant condition involving mutation of the *p53* gene, has been associated with head and neck cancer in patients with minimal tobacco exposure.[53, 54] Fanconi's anaemia, Bloom syndrome and ataxia-telangiectasia are autosomal recessive disorders associated with increased chromosomal fragility and cancer susceptibility. There is an increased incidence of head and neck cancer in each of these conditions.[55–58] There is a genetic susceptibility in the capacity to metabolize carcinogens and repair consequent DNA damage. This involves polymorphisms in GST genes,[59–61] CYP genes,[62, 63] and the cytochrome *p450* system.[64]

Immunologic factors are also important. Patients treated for bone marrow transplants and organ transplants have an increased incidence of skin cancer and oral cavity cancer. This may be due to the long-term use of immunosuppressive drugs.[65, 66]

Cancer of the oropharynx

Recent studies have shown a dramatic change in the aetiology of oropharyngeal cancer from a cancer caused by smoking and alcohol to a cancer now predominantly caused by HPV.[3] Cancer of the oropharynx is the third most common head and neck cancer after larynx and oral cavity. It is estimated that in 2013 there will be 13 930 new cases of oropharynx cancer in the United States, 11 200 male and 2730 female.[2] In the UK, it has an increasing incidence, reported in near 6% annual percentage change, especially among men.[67, 68] Raised incidence rates are observed in Netherlands, India, France and Italy.[69–71] This increase in tonsil and base of tongue cancer over the last decade is largely due to HPV infection of the palatine and lingual tonsils, and has been called an epidemic of HPV-associated oropharyngeal cancer.[72, 73]

HPV has been extensively studied and there seems to be a definite association between virus and tumour formation.[72, 74] The proportion of cancers with HPV varies with site with a strong association with tonsil cancer.[75,76] Steinberg and DiLorenzo reported HPV infection to be highest in tonsil (74%), followed by larynx (30%), tongue (22%), nasopharynx (21%) and floor of mouth (5%).[77] HPV exists in many different serotypes and specific serotypes are associated with head and neck cancer. For example,

benign lesions such as the common wart are associated with 'low-risk types' and include HPV 6, 11, 13, 32.[78] High-risk types are associated with premalignant lesions and squamous cell carcinoma and include HPVs 16, 18, 31, 33, 35, 39.[78, 79] HPV 16 and 18 appear to be the most common types associated with squamous cell carcinoma. HPV 31, 33 and 35 are more commonly associated with cervical cancer and are not found in oropharyngeal cancer.[80, 81] The E6 and E7 open reading frames (ORFs) of the high risk HPVs are particularly important. They bind to and inactivate tumour suppressor genes *p53* and *pRb* respectively.[82] This allows uncontrolled cell proliferation, which can result in genomic instability and cellular transformation.[83] There is no relationship between clinical stage and HPV status in squamous cell carcinoma of the head and neck. This suggests HPV infection is not a late event in the evolution of head and neck cancer. As mentioned above, the highest incidence of HPV is found in tonsil cancer suggesting that there is a predilection of HPV infection for patients with tonsillar carcinoma.[75, 76] Patients with HPV positive tonsil cancer tend to be young, non-smokers and non-drinkers. The molecular characteristics are completely different to HPV negative tonsil cancers where *p53* is often mutated due to carcinogens in tobacco smoke and amplification of cyclin D1. HPV-positive cancers often have abnormalities in the PIK3/AkT/mTOR pathway resulting in activation of this pathway.[84, 85] Probably due to the different pathogenetic origin, HPV-positive tonsil cancers have shown a better prognosis.[86]

Cancer of the larynx and hypopharynx

The American Cancer Society estimates that 12 260 new cases of laryngeal cancer (9680 in men and 2580 in women) will be diagnosed, and 3630 people (2860 men and 770 women) will die from the disease in the United States in 2013.[2] These numbers are falling by around 2% to 3% a year, mainly because fewer people are smoking.[1, 3] About 60% of larynx cancers start in the glottis, 35% develop in the supraglottic region and the remaining 5% occur in the subglottis.[87]

Cancer of the hypopharynx accounts for 10% of all squamous cell cancers of the upper aerodigestive tract.[87] In the UK, the overall incidence is 1 per 100 000 per annum. There is a high incidence in northern France of 14.8 per 100 000.[88, 89] Subsites of the hypopharynx include pyriform fossa (70%), postcricoid area (15%) and posterior pharyngeal wall (15%).[87] The pyriform fossa is the commonest subsite in North America and France. Postcricoid lesions appear more commonly in Northern Europe. The mean age at presentation is 60 years. Pyriform fossa and post pharyngeal wall have a male predominance of 5 to 20 : 1 in North America[90, 91] with 50 : 1 in France.[92] Postcricoid lesions show a female preponderance 1.5 : 1.[93–95]

TOBACCO AND ALCOHOL

There is a strong association between laryngeal cancer and cigarette smoking. The relative risk of laryngeal cancer between smokers and non-smokers is 15.5 in men and 12.4 in women.[96] Environmental tobacco smoke also increases the risk of laryngeal cancer.[97] The combined use of tobacco and alcohol increases the risk of laryngeal cancer by 50% over the estimated risk if these factors were considered additive.[98–100] Risk is greater for hypopharyngeal cancer than laryngeal cancer.[101] This variation in the risk of alcohol is shown for different sites in the larynx (i.e. supraglottic cancer patients are more likely than glottic and subglottic patients to be heavy drinkers of alcohol).[102, 103]

OTHER FACTORS

Laryngeal cancer is associated with nickel and mustard gas exposure.[104] There may also be association with asbestos exposure.[105, 106] Machinists and car mechanics are at increased risk.[107, 108] Long-term exposure to sulphuric and hydrochloric acid in battery plant workers is associated with an increased risk.[109] Postcricoid carcinoma is associated with previous radiation[93, 110] and sideropenic dysphagia.[93–95] Between 4% and 6% of patients have a history of Patterson-Brown-Kelly or Plummer—Vinson syndrome. Radiation is also implicated in posterior pharyngeal wall carcinomas.[111] Several studies associate high fruit and vegetable intake with a decreased risk of head and neck cancer. This may reflect increased intake of the antioxidants or free radical scavenging vitamins A, C and E.[112, 113] As in oral cavity and oropharyngeal cancer, HPVs may also be a factor in some cases of laryngeal and hypopharyngeal cancers. However, a causative role has been described in only small proportion of patients (5–30%).[114, 115] Laryngeal and hypopharyngeal cancers are also more common in people who are immunosuppressed due to HIV or organ transplantation.[116]

Cancer of the nasopharynx

Nasopharyngeal cancer (NPC) is rare with an incidence in the UK of 0.5/100 000[9], approximately 400 new cases every year.[117] It accounts for 1–2% of all head and neck cancers. In the United States there are approximately 2000 cases per year.[2] However, in southern China and Hong Kong the disease is endemic with an incidence rate of 50 per 100 000.[118] It is also common among Inuits of Alaska and in immigrant groups in the United States, such as recent Chinese immigrants and those from Southeast Asia such as the Hmong. In the last few years the rate at which Americans, including Chinese immigrants, have been developing this cancer has been slowly dropping.

According to the World Health Organization, there are three subtypes:[119] WHO type 1-keratinizing squamous cell carcinoma; WHO type 2-non-keratinizing (differentiated) carcinoma; and WHO type 3-undifferentiated carcinoma. In North America, type 1 accounts for 68% of cases.[120] In the Far East, types 2 and 3 account for 95% of cases.[121]

NPC is the result of interaction of genetic and environmental factors. The association is strongest for WHO types 2 and 3.[122] The genetic association is with different types of HLA types; in ethnic Chinese, NPC is associated

with HLA types A2, B17 and Bw46.[123, 124] HLA B17 carries the same risk as Bw46 and is associated with younger onset disease and poorer prognosis.[124, 125] In addition, family members of people with NPC are more likely to get this cancer. The most important environmental factor is infection by Epstein—Barr virus (EBV). Almost all NPC cells contain EBV.[126] There is a strong association between undifferentiated nasopharynx cancer and positive serology for EBV antigens. Antibody titres to EBV antigens correlate with stage of disease and a fall reflects tumour response to treatment whereas a rise in antibody levels means progression of disease.[126–128]

Dietary factors are also important. People who live in areas of Asia, northern Africa and the Arctic region, where NPC is common, typically eat diets very high in salt-cured fish and meat.[129] Studies indicate that foods preserved in this way that are cooked at high temperatures may produce chemicals that can damage DNA. Ho has reported accumulation of carcinogenic nitrosamines in salted fish.[130] In southeast China, the rate of this cancer is dropping as people begin eating a more 'Western' diet.

Cancer of the nasal cavity and paranasal sinuses

Cancers of the nasal cavity and paranasal sinuses are rare.[131] About 1200 people in the United States develop cancer of the nasal cavity and paranasal sinus each year, representing 3% of head and neck cancers.[132] Men are about 50% more likely than women to get this cancer. Nearly 80% of the people who get this cancer are between the ages of 45 and 85. About 60% to 70% of cancers of the nasal cavity and paranasal sinuses occur in the maxillary sinus, 20% to 30% in the nasal cavity, 10% to 15% in the ethmoid sinuses, and less than 5% in the frontal and sphenoid sinuses.[133]

As in all head and neck cancer, smoking tobacco is a risk factor for nasal cavity cancer. Occupational factors are also important. These include occupational exposure to dust from wood, textiles and leather and even perhaps flour.[134, 135] Other substances linked to this type of cancer are glues, formaldehyde, solvents used in furniture and shoe production, nickel and chromium dust, mustard gas, isopropyl ('rubbing') alcohol, and radium.[136] HPV infection has been reported in patients with benign and malignant tumour of the sinus.[137, 138] HPV DNA type 16 has been detected in over 50% of non-keratinizing carcinomas;[139] it likely represents a distinct histopathologic entity related to HPV infection. However, the clinical significance of these findings is not completely determined.

NON-SQUAMOUS MALIGNANT TUMOURS

Carcinoma of the thyroid

This is more common in women with a ratio of 3:1 and affects mainly young people with nearly two-thirds of cases in the age group 20–55 years. The commonest type is differentiated (80%) which includes papillary (85%) and follicular (15%) cancer. The poorly differentiated cancer accounts for 10% of cases, anaplastic 5% and medullary thyroid cancer 5%.[140] The incidence of thyroid cancer is increasing and this increase is mostly related to papillary carcinoma diagnosis, without any significant difference in the less frequent histologies. The increase is the result of the incidental detection of early thyroid cancer because of increasing use of imaging such as computerized tomography (CT), magnetic resonance imaging (MRI), ultrasound (US) and positron emission tomography (PET).[141] Between 1983 and 2006, the number of subcentimetre well-differentiated thyroid cancers (WDTC) increased five-fold. The incidence of WDTC > 2 cm and also larger WDTCs (> 4 cm and > 6 cm) at least doubled.[142] Therefore, the increase is due to subclinical diagnosis but also due to a true increase in disease incidence. The mortality rates for well differentiated thyroid cancer have remained relatively static and the prognosis is excellent with a 5-year survival of 97% of cases.[143] Thyroid cancer is more common in areas of the world where people's diets are low in iodine, and the opposite in areas with high iodine intake.[144, 145] However, there is not a strong epidemiological relationship between iodine intake and cancer and further studies are warranted.[146] A history of radiation treatment in childhood is a known risk factor. In the past, radiation was used to treat children with acne, fungal infections of the scalp, an enlarged thymus and tonsillar and adenoidal hypertrophy. Subsequent studies showed that there was an increased incidence of thyroid cancer in these children.[147] In contrast, exposure to radiation in adults carries little risk of thyroid cancer. Children exposed to radioactive fallout from nuclear power plant accidents or nuclear weapons also have an increased incidence of thyroid cancer. For example, children exposed to nuclear fallout from Chernobyl have an eight times incidence of thyroid cancer.[148–150]

Inherited medical conditions such as Gardner syndrome, familial polyposis and Cowden disease have an increased incidence of thyroid cancer. Certain families also have an increased incidence of papillary thyroid cancer. Medullary thyroid cancer (MTC), which constitutes approximately 5% of all thyroid malignancies, originates from the parafollicular C-cells, secretes calcitonin and occurs in both sporadic and hereditary forms.[151] Seventy-five per cent of MTC occurs as a sporadic form and 25% as a hereditary form. The hereditary forms can occur in three different settings: as a single component in a hereditary disease (FMTC); in the hereditary syndrome multiple endocrine neoplasia syndrome type A (MEN-2A) associated with parathyroid disease and phaeochromocytoma; and lastly in the hereditary syndrome MEN-2B associated with pheochromocytoma and a specific phenotype characterized by mucosal ganglioneuromas, intestinal ganglioneuromatosis and a marfanoid habitus. Both MEN-2 syndromes are autosomal dominant genetic disorders characterized by mutations in the *RET* proto-oncogene.[152, 153] Patients can now be stratified into high-, intermediate- and low-risk groups according to the type of *RET* mutation.[154]

Salivary gland carcinomas

There are two main types of salivary glands, the major salivary glands (parotid, submandibular and sublingual glands) and the minor salivary glands. About 80% of all salivary gland tumours are in the parotid gland, 10–15% in the submandibular gland and the rest in the sublingual and minor salivary glands.[140] Most tumours of the parotid gland are benign whereas 40% of submandibular gland tumours and 80% of minor salivary gland tumours are malignant. There are several different types of malignant tumours of the salivary glands due to the different types of cells that make up normal salivary glands. These include mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, polymorphous low-grade adenocarcinoma and rare adenocarcinomas such as basal cell, clear cell, salivary duct and mucinous adenocarcinoma. Salivary gland carcinomas are not common and occur with an annual rate of 1.2 per 100 000 in the United States.[1] About one-third-of patients are under the age of 55 years. The incidence of these cancers is increasing but the cause for this is unknown.[155]

Exposure to radiation to the head and neck area for other medical reasons (e.g. radiotherapy for squamous cell cancer) increases the risk of salivary gland cancer.[156] Industrial exposure to radioactive substances and also accidental exposure from atomic bomb blasts also increase the risk of salivary gland cancer.[156] Some studies have also suggested that working with certain metals (nickel alloy dust) and minerals (silica dust) may increase the risk for salivary gland cancer. In men, smoking and heavy alcohol consumption was also associated with higher risk, but these factors were not strongly related to salivary gland cancer in women.[157] Hormonal dependence may also be important; early menarche and nulliparity are associated with increased risk, whereas older age at full-term pregnancy and long duration of oral contraceptive use are associated with reduced risk.[158] Female patients with salivary gland tumours are also 2.5 times more likely to develop breast cancer.[159] Diets low in vegetables and high in animal fat may also be important.[160]

Sarcomas of the head and neck

Sarcomas of the head and neck constitute less than 1% of head and neck malignancies.[161] They are divided into those arising from soft tissue (STS)[161] and those arising from bone (osteosarcoma).[162] STS comprise a heterogeneous group with varied histology and behaviour and include chondrosarcoma, dermatofibrosarcoma protuberans, Ewings sarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumour (MPNT), rhabdomyosarcoma and synovial sarcoma.[162] Rhabdomyosarcoma is rare in adults but is the most common STS in children with over 30% occurring in the head and neck. Dermatofibrosarcoma protuberans is a rare tumour of the dermis that has a high recurrence rate. Malignant fibrous histiocytoma is the most common STS in middle and late adulthood. Only 4% of liposarcomas occur in the head and neck with the neck being the most common site. Synovial sarcomas occur between the ages of 20 and 50 years with the majority arising in the parapharyngeal space. The most common site of chondrosarcoma in the head and neck is the larynx, followed by the maxilla and skull base. Most occur between the ages of 30 and 60 years. The most common site in the larynx is the posterior lamina of the cricoid cartilage (75%). MPNTs are extremely rare but more common in patients with neurofibromatosis type I (NF1).

Osteogenic sarcoma is a rare highly malignant tumour with an incidence of 1 in 100 000 with only 7% occurring in the head and neck region. The majority of these arise in the mandible followed by the maxilla. Head and neck osteosarcoma is most common between ages of 30 and 40 in comparison to long bone osteosarcoma, which is most common in teenage years.

GENETIC PREDISPOSITION

Studies have shown that some groups of individuals are at an increased risk of developing STS.[161, 163] Among them are genetically predisposed individuals, such as those suffering from neurofibromatosis who are at risk of MPNT, individuals with Li-Fraumeni syndrome, and children with retinoblastoma who are predisposed to osteosarcoma, rhabdomyosarcoma, and fibrosarcoma. Other heritable syndromes associated with an increased risk of STS include Gardner syndrome and nevoid basal cell carcinoma syndrome.

RADIATION, VIRUSES AND OTHER FACTORS

Previous exposure to irradiation is another well-documented risk factor[164] for both STS and osteogenic sarcoma. Although radiation-induced sarcoma (RIS) is a well-recognized long-term complication of radiation therapy for other sites, the head and neck is less commonly affected.[165] It is difficult to implicate therapeutic irradiation in the causation of head and neck tumours because of the inherent risk of multiple primary tumours in these patients. In addition, patients with certain types of primary tumours such as retinoblastomas have an increased sensitivity to radiation therapy, but are at increased risk for the development of sarcoma irrespective of the type of treatment.

Environmental carcinogens and chemicals like urethane, ethylene derivatives and polycyclic hydrocarbons have also been reported to increase the risk of STS at sites other than the head and neck.[166]

The role of viruses in the pathogenesis of STS has been investigated, but apart from the association of HIV with Kaposi's sarcoma and the observation that viral oncogenes such as the 'src' in the Rous sarcoma virus can transform cells in culture, no conclusive proof is available for a viral aetiology.[167] Immunosuppression attributable to either HIV infection or antirejection medication in organ transplant recipients may predispose children with latent EBV infection to leiomyosarcoma of the liver.

Patients with chronic lymphedema have an increased incidence of STS formation.[168] Patients with Paget's disease of bone, particularly the skull, are predisposed to osteogenic sarcoma.[169, 170]

KEY POINTS

- Squamous cell cancer is the most common head and neck malignancy, and it is related mainly to alcohol and tobacco use.
- Human Papilloma Virus (HPV) is now the leading cause of cancer of the oropharynx.
- Other malignancies of the head and neck such as thyroid cancer, salivary gland cancer and sarcomas are not related to alcohol or tobacco usage. The main causes of these cancers are less clear. Prior exposure to radiation in the head and neck area is one of the few identified risk factors.
- Genetic predisposition to head and neck cancer is rare and is present in a few inherited conditions such as Fanconi Anaemia and Li-Fraumeni Syndrome. Medullary thyroid cancer is a well-known example of a hereditary thyroid cancer secondary to a specific mutation in RET oncogene.
- There is an important role of head and neck cancer prevention through alcohol and tobacco cessation, HPV vaccination and close follow-up of risk groups such as genetic conditions carriers.

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CHAPTER 3

EPIDEMIOLOGY OF HEAD AND NECK CARCINOMA

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: oral cavity, oropharyngeal cancer, laryngeal cancer, hypopharyngeal cancer, nasopharyngeal cancer, squamous cell carcinoma, HPV, EBV, smoking, alcohol, and/or epidemiology.

INTRODUCTION

Head and neck cancer comprises a diverse array of diseases with distinct anatomical subsites, histopathologic features and risk factors. The most common type of head and neck cancer is squamous cell carcinoma (SCC) of the mucosa of the upper aerodigestive tract (UADT). In 2008, more than 600 000 people worldwide were diagnosed with UADT SCC.[1] The incidence of and risk factors for UADT SCC differ by tumour subsite. The five major subsites are nasopharynx, oral cavity, oropharynx, larynx, and hypopharynx.

Nasopharyngeal cancers are typically related to Epstein–Barr virus, and are a major contributor to the UADT burden in Southern China and Southeast Asia. However, SCCs at this site are relatively rare in other populations. The majority of UADT SCCs worldwide were caused by tobacco and alcohol, and in many countries, public health efforts aimed at reducing tobacco exposure have helped decrease the incidence of UADT SCC. However, in North America, Europe and Australia, there is an epidemic of oropharyngeal SCC (OPSCC) caused by infection with human papillomavirus (HPV), and HPV-positive OPSCC is now more common than tobacco-and-alcohol-associated OPSCC in many of these countries.[2] In contrast, in developing countries where the prevalence of smoking is increasing, the incidence of UADT SCC is also increasing. The rate of oral cavity SCC is higher in South Asian countries than other countries, most likely because of use of oral tobacco and related products, resulting in a global health disparity.

This chapter discusses the incidence of and risk factors for SCC of the oral cavity, oropharynx, larynx and hypopharynx. The shift from tobacco-and-alcohol-related to HPV-related OPSCC is also examined, along with the associated health implications and global variations. A more comprehensive treatment of aetiology is discussed in Chapter 2, Aetiology of head and neck cancer.

SCC OF THE ORAL CAVITY

Worldwide, SCC of the oral cavity is the tenth most common cancer among men, and in 2008, 263 000 people were diagnosed with this disease (171 000 men and 92 000 women).[1] The majority of oral cavity SCCs are related to tobacco and alcohol exposure (61% of oral cavity SCCs in Europe, a higher proportion in India).[3] There is a dose-effect relationship between tobacco and alcohol exposure and risk of oral cavity SCC, and individuals exposed to high levels of tobacco and alcohol have an odds ratio of 7.1 (95% confidence interval [CI], 5.0–10.0) compared to those without tobacco or alcohol exposure.[4] In the United States, because of public health initiatives, the rate of current cigarette smoking declined from 43% in 1965 to 21% in 2004, and in the past three decades there has been a concomitant decrease in the overall rate of oral cavity SCC.[5,6] Globally, as the use of tobacco in developing countries has increased, there has been a subsequent increase in the incidence of oral cavity SCC.[7] Hence, while oral cavity cancer is the tenth most common cancer among men worldwide,

its incidence varies with the prevalence of tobacco use and is higher in many developing countries and lower in many developed countries.

The oral cavity is anatomically subdivided into the oral tongue, floor of mouth and gingivobuccal subsites. In developed countries, the typical patient with oral cavity SCC is a man in the sixth-to-seventh decade of life with a history of smoking and alcohol exposure and a tumour located on the lateral tongue or floor of mouth. These two subsites are the most common subsites of oral cavity SCC; in a National Cancer Database review by Funk et al, 32% of oral cavity SCCs occurred in the lateral tongue and 28% occurred in the floor of the mouth.[8] Oral cavity SCCs are likely to be associated with occult nodal metastasis at presentation, and therefore many patients present with advanced disease.

There is one notable exception to the pattern of decreasing incidence of oral cavity SCC in developed countries: among white patients younger than 40 years in the United States, there has been a 2% annual increase in the incidence of SCC of the oral tongue, though such tumours in young patients are exceptionally rare.[9, 10] Some Scandinavian countries have shown similar increase in incidence of young patients with oral tongue cancer.[11] The explanation for this phenomenon is unclear: not all affected patients have a history of prolonged tobacco exposure, and there is no known viral or other cause for the increase in incidence. Clinical tumour behaviour and survival rates in these young patients with oral cavity SCC mimic clinical tumour behaviour and survival rates in their older counterparts.[12, 13]

Use of smokeless tobacco, tobacco with or without additives that is dipped or chewed, is also a risk factor for oral cavity SCC. Because of global variation in the prevalence of smokeless tobacco use (ranging from less than 5% in the United States to more than 1 in 3 males in India), concurrent smokeless tobacco use and cigarette use, and regional variation in potentially carcinogenic additives, determination of the exact contribution of smokeless tobacco to the risk of oral cavity SCC is difficult.[14, 15] Boffetta et al pooled data from multiple studies and estimated a summary relative risk of 1.8 (95% CI, 1.1–2.9) for users of smokeless tobacco compared to non-users.[15]

Betel nut is an additional risk factor for oral cavity SCC, particularly in developing countries. Betel nut, from the betel or areca palm tree, can be chewed alone or mixed with tobacco and lime and placed in a betel-leaf pouch (in India this is called paan, and there are many variations). Absorption of the red juice produced by the betel mixture results in cholinergic stimulation in the short term but carcinogenesis over the long term. Betel nut use is common throughout South Asia, though exact usage rates are difficult to determine. In India, in 2010, oral cavity SCC was the number one cause of death for men over the age of 30 years, and in 2008, oral cavity SCC was the most common cancer diagnosed in men, in part due to use of betel nut and smokeless tobacco.[16–18]

Oral cavity SCC related to betel nut use most commonly occurs in the buccal mucosa, whereas oral cavity SCC related to tobacco and alcohol use most commonly occurs in the oral tongue or floor of mouth.[19, 20] Betel nut may also cause a benign but devastating submucosal fibrosis of the buccal mucosa, which in severe cases can cause trismus and hinder eating; in some cases, this submucosal fibrosis may be premalignant.[21]

Other risk factors may play a role in oral cavity SCC: multiple studies have examined the role of marijuana as a risk factor; however, no conclusive evidence has been found implicating marijuana use as a cause of UADT SCC at any subsite.[22] These studies may suffer from recall bias, subsite misclassification, confounding due to concurrent tobacco use, and low incidence of heavy marijuana use, and further investigation is needed.[23] Poor oral hygiene has also been identified as a potential risk factor but may be a sign of disease rather than a cause. Defective DNA repair pathways may also play a role in the development of SCC.[24] While HPV plays a strong role in the etiology of OPSCC, there is no evidence that HPV contributes to any great degree to oral cavity SCC.

Patients with Fanconi anaemia are at higher risk than the general population for developing oral cavity SCC.[25] Fanconi anaemia is caused by an autosomal recessive genetic mutation. The disease manifests as congenital anomalies (most commonly skeletal, renal and developmental) and progressive pancytopenia and results in a shortened life expectancy. Leukemia is the most common associated cancer, and there is also an increased risk of head and neck cancers. These occur at a younger age than typical tobacco-related head and neck cancers, most often occur in the oral cavity, and may be aggressive.[25]

SCC OF THE OROPHARYNX

UADT SCC has traditionally been strongly associated with tobacco and alcohol exposure. In the United States, it was expected that the incidence of OPSCC would decrease in parallel with decreasing smoking rates, but in fact, there was only a plateau in OPSCC incidence followed more recently by a dramatic increase.[6, 26, 27] Closer examination revealed that the increase occurred in middle-aged white men, while the incidence of OPSCC in men older than 60 years of all races was decreasing. Furthermore, the middle-aged men who were developing OPSCC often had no history of smoking or were former or light smokers. Because of multiple lines of evidence, the increasing OPSCC incidence in this group is now attributed to HPV.

Two molecularly and epidemiologically distinct types of OPSCC are now recognized, classified according to HPV status. HPV-negative OPSCC is epidemiologically similar to the traditional type of UADT SCC, in which long-term exposure to tobacco and alcohol leads to development of malignancy. The typical patient with HPV-negative OPSCC is a man older than 55 years with a long history of smoking and drinking and a well or moderately differentiated SCC. HPV-negative OPSCC is declining in incidence in the United States, similar to what is occurring with respect to the incidence of other SCCs of the UADT that are caused by tobacco and alcohol but not HPV (SCCs of the oral cavity, larynx and hypopharynx).[2, 28]

In contrast, the typical patient with HPV-positive OPSCC is a middle-aged, non-smoking white man from a higher socioeconomic status and with a history of multiple sexual partners.[29]

HPV-positive OPSCC originates with exposure to high-risk HPV, a sexually transmitted virus, and can develop independently of tobacco or alcohol exposure.[28, 30] HPV is most strongly associated with OPSCC found at the tonsil and base of tongue, and cancers at these subsites account for an increasing proportion of all OPSCCs.[31] Oropharyngeal HPV infection is a necessary event in the development of HPV-positive OPSCC.[30] Although HPV can also be transmitted by less intimate skin-to-skin contact, HPV is transmitted primarily via sexual contact, and the risk of oral cavity/oropharyngeal HPV infection increases with the number of oral sexual partners.[32] The current literature shows that at any given time, approximately 7% of the population has a prevalent oral cavity/oropharyngeal HPV infection.[33, 34] The lifetime oral exposure rate is unknown, but an estimated 65% to 100% of sexually active adults have been exposed to HPV at either anogenital or oropharyngeal sites.[35, 36] Given the high point prevalence of oral/oropharyngeal HPV infection, most such HPV infections are cleared by the immune system and do not progress to cancer. Delayed clearance of oral/oropharyngeal HPV infection may be a risk factor for development of OPSCC, just as prolonged/chronic cervical HPV infections are associated with subsequent cervical cancers.

HPV exposure is so common that the presence of HPV DNA in malignant tissues does not establish causality; for example, a patient with a heavy smoking and drinking history may have a tobacco-induced cancer but also have HPV DNA found in the tumour. However, a cell that has become malignant due to HPV oncogenesis will typically overexpress *p16*. *TP53* is commonly mutated in tobacco-related cancers of the UADT, but *TP53* mutations are not common in HPV-related OPSCC. Therefore, p16 staining and determination of *TP53* mutation status can help distinguish truly HPV-related cancers from cases in which HPV DNA is detectable but the cancer is not HPV-related and cases in which detection of HPV DNA represents a false positive result.

There has been some confusion regarding the role of HPV in UADT SCC at sites other than the tonsil and base of tongue. While HPV DNA has been identified in SCC at other UADT subsites, the causal role of HPV in carcinogenesis at these subsites has not been established, and the proportion of cancers at these other subsites attributable to HPV is likely small. Given the high rates of exposure to HPV, the mere presence of HPV DNA alone cannot support causality. HPV-related oncogenic proteins and downstream events such as *p16* overexpression must be detected as part of proving causality. Additionally, poor classification of the tumour subsite, as well as overlap of some subsites, may also have led to misclassification, particularly in older published studies. For instance, whereas previously some OPSCCs (particularly those of the base of tongue, which are often coded as a generic site 'tongue') were misclassified as oral cavity SCCs, classification of tumour sites has been improving and, in parallel, HPV positivity rates for non-oropharyngeal cancers of the UADT have dropped over time, while HPV positivity rates for OPSCC have risen.[37] Differences in testing methods for HPV may also have contributed to high rates of false-positive findings. Regardless, the rate of HPV-positive SCC has consistently been higher in the oropharynx than in the oral cavity, larynx or hypopharynx.[27]

The incidence of HPV-positive OPSCC is increasing markedly, and it is not hyperbole to call this an epidemic. An estimated 85 000 cases of oropharyngeal cancer occurred worldwide in 2008, and at least 22 000 of these were HPV positive.[38] From 1988 to 2004, there was a 225% population-level increase in HPV-positive OPSCC in the United States (from 0.8 cases per 100 000 individuals in 1988 to 2.6 per 100 000 in 2004) and a concomitant 50% decrease in HPV-negative OPSCC (from 2.0 cases per 100 000 individuals in 1988 to 1.0 per 100 000 in 2004[2, 39] (**Figure 3.1**). In the United States, the percentage of OPSCC cases that were HPV-positive increased from 16% in 1984–89 to over 70% in 2000–04. There has been a 5% annual percentage rate increase in the incidence of OPSCC in the United States and a 6% increase in Finland.[2, 39] Chaturvedi et al estimated that by 2020 the incidence of HPV-positive OPSCC will be greater than

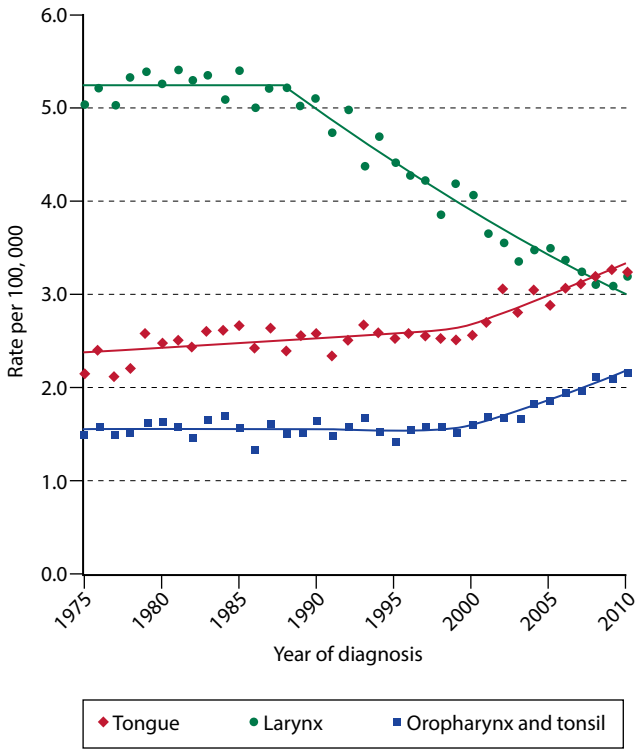


Figure 3.1 Age-adjusted SEER incidence rates by cancer site 1975–2010 (all ages, all races and both sexes). Cancer sites include invasive cases only, unless otherwise noted. Rates are per 100 000 and are age-adjusted to the 2000 US Std Population (19 age groups – Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 4.0.3, April 2013, National Cancer Institute. Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah and Atlanta).

the incidence of cervical cancer, and by 2030, more than half of all head and neck cancers will be related to HPV.[2] The increase in HPV-related OPSCC is well documented in North America, Europe and Australia although marked geographical variation is evident.[2, 40–42] For example, recent data from the UK[43] in a multicentre study involving the HPV typing of tumour samples from ~1400 patients treated between 2002 and 2011, confirmed that whilst the incidence of oropharynx cancer doubled, the prevalence of cases attributable to HPV infection remained stable at ~55% during this decade. Consideration of these, somewhat surprising, data leads to a conclusion that HPV-negative oropharynx cancer has also been increasing in the UK throughout this time period, despite the overall population reduction in tobacco smoking. Why this is, is a matter of conjecture but the authors, citing the parallel increase in oral cavity tumours, suggest a potential role for increased alcohol consumption. Moreover, a similar increase in HPV-positive OPSCC has not been well documented in South America, Africa and Asia, but population-based studies from these regions with careful site classifications and exposure data are limited or non-existent, and different sexual practices and continued high smoking rates may also obscure these trends.

In 2008, using the Surveillance, Epidemiology and End Results (SEER) database (1973–2004), which contains information on a sample of patients in the United States, Chaturvedi et al demonstrated in a landmark study that the rise of OPSCC incidence was occurring specifically among middle-aged white men.[6] There were no significant changes in OPSCC incidence among individuals under 40 years or over 59 years of age, but among middle-aged white men, a 10% annual increase in incidence was seen since 2000.[6] Mehta et al utilized the SEER database to compare the incidence of OPSCC in different age groups during the period from 1973 through 2006.[26] They found that the proportion of patients aged 40–59 years increased from 35% to 45%, while the proportion of oropharyngeal cancer patients aged 60–79 years decreased from 52% to 40%.[26] The increase in OPSCC incidence among Caucasian males is so dramatic as to nearly obliterate a previous racial disparity in the incidence of UADT SCC.[44] In the late 1980s, African American males had more than twice the incidence of OPSCC of white American males; this disparity has been completely eliminated by the increase in OPSCC among white men and continued decrease in OPSCC incidence among African American men.[6]

Patients with HPV-positive OPSCC are less likely to have a history of tobacco exposure; in most series of patients with OPSCC, about 30% of patients in the HPV-positive group are non-smokers, compared with fewer than 5% of patients in the HPV-negative group.[45] Patients with HPV-positive OPSCC are also less likely to use alcohol than are patients with HPV-negative OPSCC patients or those with SCC at other subsites of the head and neck.[46] The past few decades have seen a decrease in the age of sexual debut and an increase in the number of sexual partners, contributing to HPV exposure.[47] However, demographic, exposure and behavioural factors are only somewhat predictive of HPV status in patients with OPSCC and should not replace HPV testing.[48]

Patients with HPV-positive OPSCC are more likely to present with small primary tumours and more extensive and possibly cystic nodal disease.[49] Patients with HPV-positive OPSCC may also present at a younger age than the typical head and neck cancer patient, and thus complaints of neck mass or other symptoms related to the UADT should be carefully evaluated. Finally, HPV-related OPSCC tumour histology is more likely to be basaloid, lymphoepithelial or poorly differentiated.[50] Even though patients with HPV-positive OPSCC are more likely to present with advanced nodal disease, survival is better in patients with HPV-positive OPSCC than in those with HPV-negative OPSCC, which is further discussed in Chapter 13, Oropharyngeal tumours.[49, 51–53]

Over 90% of HPV-positive OPSCC cases are caused by a single HPV type, HPV 16, and few OPSCC cases can be attributed to the other HPV types.[54] This has implications for future public health efforts to decrease HPV-positive OPSCC via vaccination. In the United States, two current Food and Drug Administration-approved HPV vaccines provide strong protection against infection with HPV 16. These vaccines are directed towards the viral capsid L1 or L2, a late protein that is expressed during infection and prior to carcinogenesis. Currently these HPV vaccines are approved in the United States for prevention of cervical cancer and prevention of genital warts and anal cancer in both men and women.[55] There is not currently an indication for prevention of HPV-positive OPSCC, as no studies have been conducted to evaluate the effect of the vaccine on oral/oropharyngeal HPV infection and OPSCC development. Given the decades-long delay between HPV exposure and carcinoma detection, such a study will be difficult and costly. However, because HPV 16 is the cause of the overwhelming majority of HPV-positive OPSCC, it is likely that the vaccine will prevent HPV 16 oropharyngeal infection and subsequent OPSCC development when given to individuals prior to HPV 16 exposure.

SCC OF THE LARYNX

In 2008, 150 000 people worldwide were diagnosed with laryngeal SCC.[1] The majority of patients with laryngeal SCC are men. Laryngeal SCC is strongly related to smoking and alcohol use; multiple studies confirm that the risk in smokers and drinkers is 4–177 times the risk in non-smokers/non-drinkers and that risk increases with duration and frequency of exposure.[3, 56–58] Alcohol or tobacco exposure alone are also significant risk factors for the development of laryngeal SCC.[57] In the United States, the incidence of laryngeal SCC plateaued in 1992 and then decreased 2.8% per year from 1992 through 2009 (to an age-adjusted incidence rate of 3.4/100 000 in 2006–10) as tobacco control efforts began to show an effect, and similar changes were seen across Europe.[27, 59–62] In developing countries, as smoking rates

have increased there has been a concomitant increase in the incidence of laryngeal SCC.[7]

The larynx is divided into supraglottic, glottic and subglottic sites, and the presentation of laryngeal SCC differs by subsite. Supraglottic and glottic carcinoma are the most common and make up over 90% of all laryngeal SCC.[63] Because of their rarity, subglottic cancers are often excluded from analysis. More than 50% of laryngeal SCC arise in the glottis, and such cancers tend to occur in heavy smokers who present early in the course of disease with hoarseness.[56, 58, 64] Because of the paucity of lymphatics in the glottic region, many glottic cancers do not have regional metastasis. Supraglottic lesions make up about 32–35% of laryngeal SCC, tend to occur in people who use alcohol and tobacco and, in contrast to glottic lesions, are more likely to present late with extensive nodal disease due to the rich bilateral lymphatic supply of the supraglottic area and the lack of identifying symptoms associated with small supraglottic lesions.[63–65] Perhaps because of the early presentation of glottic lesions, the survival rate is better among patients with glottic SCC than among those with supraglottic SCC.

Other factors have been implicated in the aetiology of laryngeal SCC, particularly among individuals who do not smoke or use alcohol. Laryngeal SCC may be related to laryngopharyngeal reflux disease or gastro-oesophageal reflux disease, although studies conflict and most are retrospective and may suffer from recall bias and misclassification of reflux disease status.[66–69] Occupational and environmental exposures in the form of inhalation of potentially toxic fumes have also been implicated. These include exposure to diesel exhaust, wood oven smoke, second-hand smoke and asbestos, but the extent of risk is unclear.[70]

SCC OF THE HYPOPHARYNX

The hypopharynx is the least commonly affected of the five major UADT anatomical subsites.[71] Exact numbers of SCCs of the hypopharynx are difficult to determine because in many cancer registries, hypopharyngeal sites are combined with oropharyngeal sites. The hypopharynx is made up of the piriform sinuses bilaterally, the posterior pharyngeal wall and the postcricoid area; the piriform sinus is the subsite most commonly affected. The majority of patients with hypopharyngeal SCC are male (76–80%) and older than 50 years (93–95%) (mean age at diagnosis, 65 years) with a history of smoking and drinking; patients with hypopharyngeal SCC report more excessive use of alcohol than patients with laryngeal SCC.[72, 73] Patients with hypopharyngeal SCC also tend to present late when there is already nodal metastasis, and a Canadian study showed that 80% of patients presented with nodal metastasis and 19% of patients presented with unresectable disease.[73] The distant metastasis rate is higher for hypopharyngeal SCC than for laryngeal or oral cavity SCC: the rate of distant metastasis is 25% at 1 year after completion of initial treatment.[73]

Given the relatively small numbers of patients with hypopharyngeal SCC, as well as the grouping together of multiple pharyngeal sites in reports using data from large cancer databases, there is little published information on hypopharyngeal SCC incidence rates and changes in such incidence attributable to tobacco control efforts. The SEER database shows a slight decrease in the incidence of hypopharyngeal SCC between 1974 and 1999, from 1.0/100 000 to 0.8/100 000.[74]

SUMMARY

The majority of UADT SCCs are related to smoking and drinking, the major exception being HPV-related OPSCCs. In countries where the smoking rate is decreasing, the incidence of UADT SCC is also decreasing. In developing countries, increasing rates of tobacco use are causing a rise in the incidence of UADT SCCs. Tobacco and related products are responsible for oral cavity cancers being the most common cancer in India. Efforts to curb tobacco use should be aimed at high-risk populations. The epidemic of HPV-positive OPSCC necessitates that practitioners be aware of the changing demographics of OPSCC. Future health efforts to increase vaccination against HPV are critical for stemming the increase in OPSCC incidence.

KEY POINTS

- The incidence of laryngeal and hypopharyngeal SCC has decreased after successful implementation of public health efforts aimed at tobacco control.
- In North America, Europe and Australia, there is an epidemic of HPV-positive OPSCC, particularly among middle-aged men, and this epidemic is likely related to sexual behaviours.
- Oral cavity cancer is the most common cancer in India, where the common use of oral tobacco and betel nut is the principal cause.
- The epidemiology of SCC of the UADT differs radically by anatomical subsite.
- HPV is a causative factor for OPSCCs, and these cancers often occur among middle-aged men who do not smoke or drink. There is an epidemic of HPV-related OPSCC in North America, Europe and Australia, and it is most often attributed to prior HPV 16 infection; vaccination against HPV 16 may decrease the incidence of OPSCC in those vaccinated prior to exposure to HPV 16.
- Oral cavity SCC, laryngeal SCC, and hypopharyngeal SCC are most often related to smoking and drinking. Tobacco control efforts are decreasing the incidence of these three cancer types.
- Other risk factors may also play a role in SCC of the UADT, such as environmental exposures, concurrent diseases, and defects in DNA repair mechanisms.

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CHAPTER 4

STAGING OF HEAD AND NECK CANCER

Nicholas J. Roland

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SEARCH STRATEGY

The data in this chapter are supported by a Medline search using the key words staging of head and neck cancer. The author also consulted the International Union Against Cancer booklet TNM classification of malignant tumours, eighth edition[1] and AJCC cancer staging manual, eighth edition.[2] The nature of staging has meant that the data to support the concept have been largely drawn from retrospective and observational studies (level 3). Much of the systems development has been through the opinion of expert panels using these data (level 4).

INTRODUCTION

There are many aspects that affect the outcome of patients with a malignant head and neck tumour. These relate to the tumour (the anatomical site and the clinical and pathological extent of the disease), the host (age, general condition and any intercurrent disease of the patient) and management (treatment options, expertise available, patient preference). Concurrently, there are also many proposed systems that try to evaluate these factors and predict outcomes for an individual patient.

Staging of head and neck cancer is a system designed to express the relative severity, or extent, of the disease. It is meant to facilitate an estimation of prognosis and provide useful information for treatment decisions. Classification by anatomical extent of the disease, as determined clinically and histopathologically (when possible), is that with which the tumour, nodes, metastases (TNM) system primarily deals. The concept is that an orderly progression of disease takes place with enlargement of and invasion by the primary tumour (T) followed by spread to the regional lymph nodes (N) and eventually spread beyond these nodes to distant meta- static sites (M). The stage at diagnosis in the life history of an individual cancer is numerically assigned a TNM classification. These individual TNM classifications are then assembled into four groups – stage groups (stages I–IV), each with similar survival outcomes based on the observation that better survival is anticipated for cancers with less extension.

AIMS OF THE TNM STAGING SYSTEM

There are many benefits to staging, but one of the principal purposes is to provide a method of conveying clinical experience to others without ambiguity (**Box 4.1**).

The strengths of the TNM staging system are its simplicity, low cost, relative accuracy, objectivity, universal acceptance and lack of need for special technology. But the system is not without limitations. Inconsistencies, observer variability and differences in stage method contribute to potential bias. Uniformity in the method of data collection, knowledge of the current TNM system and accurate application of the correct stage are therefore pivotal if meaningful information is to be derived.

BOX 4.1 Objectives of staging

1. To aid the clinician in the planning of treatment
2. To give some indication of prognosis
3. To assist in evaluation of the results of treatment
4. To facilitate the exchange of information between treatment centres
5. To contribute to the continuing investigation of human cancer

HISTORY AND DEVELOPMENT OF STAGING

The TNM staging system has developed with contributions from both sides of the Atlantic.

In Europe, Pierre Denoix developed the TNM system for the classification of malignant tumours between the years 1943 and 1952.[3] During the 1950s the International Union Against Cancer (UICC) appointed a Committee on Tumour Nomenclature and Statistics. Agreement was reached on a general technique for classification by anatomical extent of the disease, using the TNM system. In 1958, laryngeal and breast cancer were the first primary sites to be assigned recommendations on clinical stage and presentation of results.[4] A decade later, the first TNM booklet, the 'Livre de poche', was published.[5] Over the years, series of meetings have been held to update and unify existing classifications as well as to develop new ones.

In the United States, the initial staging system proposed by the American Joint Committee on Cancer (AJCC) in the late 1960s and implemented in the mid-1970s was simply based on a 'consensus' of leaders and experts in the specialty who were members of the working group of what was then called The American Joint Committee for Cancer Staging and End-Results Reporting. They reviewed the available literature of that time and added their own experiences to devise the initial staging system. Subsequent revisions were also implemented based on the observations of the committee members on information available in the literature and from institutional experiences.

In 1983, The American Joint Committee for Cancer Staging and End-Results Reporting became the now familiar AJCC. Since 1996, the current AJCC Head and Neck Task Force has utilized the data from the National Cancer Data Base (NCDB). This is maintained by the Commission on Cancer of the American College of Surgeons and supported by the American Cancer Society as well as data from Surveillance, Epidemiology and End Results Reporting (a database maintained by the National Cancer Institute, which represents 14 cancer registries). In addition to this, data from state cancer registries are also used on occasion. Review of the literature is performed by the task force, who are all selected for their breadth of expertise and depth of knowledge, to incorporate new information and/or new data, which may impact upon revisions on the staging process.

The eighth edition of the UICC and American Joint Committee on Cancer (AJCC) Staging Manual, Head and Neck Section introduces significant modifications from the prior seventh edition. The most significant update creates a separate staging algorithm for high-risk human papilloma virus associated cancer of the oropharynx, distinguishing it from oropharyngeal cancer from other causes. Other modifications include: the reorganization of skin cancer (other than melanoma and Merkel cell carcinoma) from a general chapter for the entire body to a head and neck-specific cutaneous malignancies chapter; changes to the tumour (T) categories for oral cavity, skin, and nasopharynx; and the addition of extranodal cancer extension to lymph node category (N) in all but the viral-related cancers and mucosal melanoma. One other key change from prior editions of the TNM system is the elimination of the T0 category in sites other than the nasopharynx, HPV-associated oropharyngeal cancer, and salivary gland cancers (which can be identified by their unique histology). If no primary lesion can be identified, then the lymph node may have emanated from any mucosal site, so it is considered that there is no rationale to support retaining the T0 designation outside of the virally associated cancers of the oropharynx and nasopharynx.[1, 2, 6, 7] Thyroid staging has been altered with a change in the increased risk age from 45 to 55 years.

The UICC contains rules of classification and staging that correspond exactly with those appearing in the AJCC cancer staging manual and has approval of all national TNM committees.[1, 2]

GENERAL RULES FOR STAGING

The TNM system for describing the anatomical extent of the disease (**Table 4.1**) is based on three components:

- T – extent of the primary tumour
- N – absence or presence and extent of regional lymph node metastases
- M – absence or presence of distant metastases.

All cases should be confirmed microscopically. Two classifications should be documented for each site, namely: clinical (pre-treatment) classification (cTNM), and pathological (post-surgical histopathological) classification (pTNM). The clinical stage is essential to select and evaluate therapy, while the pathological stage provides

TABLE 4.1 The TNM system for describing the anatomical extent of the disease

T – Primary tumour		N – Regional lymph nodes		M - Distant metastasis	
TX	Primary tumour cannot be assessed	NX	Regional lymph nodes cannot be assessed	MX	Distant metastasis cannot be assessed
T0	No evidence of primary tumour	N0	No evidence of regional lymph node metastases	M0	No distant metastasis
Tis	Carcinoma in situ	N1, N2, N3	Increasing involvement of regional lymph nodes	M1	Distant metastasis
T1, T2, T3, T4	Increasing size and/or local extent of the primary tumour				

the most precise data to estimate prognosis and calculate end results. It should be remembered that if there is doubt concerning the correct T, N or M category to which a particular case should be allocated, then the **lower** (i.e. **less advanced**) category should be chosen. Midline nodes are considered ipsilateral except in thyroid cancers. After assigning the cTNM and pTNM categories, the patient should then be classified into a stage group. Once established this must remain unchanged in the medical records. The eighth edition recommends a prognostic factors classification and uses a 'prognostic factors grid' for each subsite.[8] This relates three prognostic factors grouped to relate to the 'tumour' (e.g. T and N stage, level of nodes), the 'host' (e.g. performance status, comorbidity, age) and the 'environment' (e.g. expertise, quality of treatment) under the narrative of essential, additional and new and promising.[1, 2, 8]

The TNM classification applies only to carcinomas and the following sites are included:

- lip and oral cavity
- pharynx: oropharynx (p16-negative and p16-positive), nasopharynx, hypopharynx
- larynx: supraglottis, glottis, subglottis
- nasal cavity and paranasal sinuses (maxillary and ethmoid sinus)
- unknown primary carcinoma – cervical nodes
- malignant melanoma of upper aerodigestive tract
- major salivary glands
- thyroid gland.

Carcinomas arising in minor salivary glands of the upper aerodigestive tract are classified according to the rules for tumours of their anatomic site of origin (e.g. oral cavity). Each site is described, with rules for classification, anatomical sites and subsites where appropriate, the cTNM classification, the pTNM classification, G histopathological grading, stage grouping and a summary. The main aspects are described here, but specific details can be found in the most recent UICC/AJCC TNM booklets.[1, 2]

Histopathological grading

The histological grading of squamous cell carcinoma represents estimation by the pathologist of the expected biological behaviour of the neoplasm. It has been suggested that such information in conjunction with other characteristics of the primary tumour would be useful in the rational approach to therapy.[8] Others have reserved doubts as to the validity of the method because of its subjective nature.[9, 10] Although grading of squamous cell carcinoma of the upper aerodigestive tract mucosa is a common practice, it has not evolved as an important factor in planning therapeutic strategies.

In a systematic review of 3294 patients, it was found that 46% of patients with poorly differentiated tumours had a nodal metastasis at presentation compared with only 28% of differentiated tumours. Distant metastases at presentation were found in 3.4% of poorly differentiated tumours compared with 1.8% of well-differentiated tumours. Primary and nodal recurrence rate rose and survival fell significantly for poorly differentiated tumours.[11] In another retrospective review of more than 1000 patients, grade and distant metastases were considered. It was found that patients with well-differentiated tumours are at low risk of metastases and patients with poorly differentiated tumours are at high risk of distant metastases. It was suggested they should be considered for systemic chemotherapy.[12] Although histological differentiation is subject to inter- and intraobserver error, it is still worthwhile in clinical practice and, therefore, remains an adjunctive part of the TNM system.[1, 2]

The definitions of the G categories apply to all head and neck sites apart from thyroid. They are shown in **Box 4.2**.

BOX 4.2 G = Histopathological grading

GX: Grade of differentiation cannot be assessed
G1: Well differentiated
G2: Moderately differentiated
G3: Poorly differentiated
G4: Undifferentiated

Additional descriptors

When sentinel lymph node biopsy is attempted, designation is now applicable using the suffix 'sn' after N stage. The absence or presence of residual tumour after treatment may be described by the symbol 'R'. A recurrent tumour, when classified after a disease-free interval is identified by the prefix 'r'. The prefix 'a' indicates that classification is first determined at autopsy.

The certainty factor, or C factor, has now been dropped from the introduction rules on staging but is still worthwhile considering during the diagnostic workup. It reflects the validity of classification according to the diagnostic methods employed (C1–C5). C1 is evidence from standard diagnostic means whereas C5 is evidence from autopsy. Pretherapeutic clinical staging of head and neck cancers should be based on a C2 factor, evidence obtained by special diagnostic means such as radiographic imaging (e.g. computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound scan), endoscopy, biopsy and cytology.[1, 2]

Stage grouping

A tumour with four degrees of T, three degrees of N and two degrees of M will have 24 potential TNM categories. It has, therefore, been felt necessary to condense these into a convenient number of TNM stage groups (**Table 4.2**). The grouping adopted is designed to ensure, as far as possible, that each group is more or less homogenous in respect of survival and in addition, that the survival rates of these groups for each cancer site are distinctive. Carcinoma *in situ* is categorized as stage 0, cases with distant metastases as stage IV. The exception to this grouping system are p16-positive oropharyngeal, nasopharyngeal and thyroid cancers (**Tables 4.3, 4.4, 4.5a, 4.5b** and **4.5c**).[1, 2]

TABLE 4.2 Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T3	N0, N1	M0
Stage IVA	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

TABLE 4.3 Stage grouping HPV (p16-positive) related oropharyngeal cancer

Stage I	T1, T2	N0, N1	M0
Stage II	T1, T2	N2	M0
	T3	N0, N1, N2	M0
Stage III	T1-T3	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

TABLE 4.4 Stage grouping for nasopharynx

Stage I	T1	N0	M0
Stage II	T1	N1	M0
	T2	N0-1	M0
Stage III	T1-2	N2	M0
	T3	N0-2	M0
Stage IVA	T4	N0-2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

TABLE 4.5a Stage grouping for medullary thyroid carcinoma

Stage I	T1a, T1b	N0	M0
Stage II	T2, T3	N0	M0
Stage III	T1, T2, T3	N1a	M0
Stage IVA	T1, T2, T3	N1b	M0
	T4a	Any N	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

TABLE 4.5b Stage grouping for differentiated thyroid carcinoma

Papillary or follicular *Under 55 years*			
Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1
Papillary or follicular *55 years and older*			
Stage I	T1a, T1b, T2	N0	M0
Stage II	T3	N0	M0
	T1, T2, T3	N1	M0
Stage III	T4a	Any N	M0
Stage IVA	T4b	Any N	M0
Stage IVB	Any T	Any N	M1

TABLE 4.5C Stage grouping for anaplastic thyroid carcinoma

Anaplastic (all cases are stage IV)			
Stage IVA	T1, T2, T3a	N0	M0
Stage IVB	T1, T2, T3a	N1	M0
	T3b, T4a, T4b	N0, N1	M0
Stage IVC	Any T	Any N	M1

Related classifications

The World Health Organization (WHO) has developed a series aimed at classification of tumours. The WHO International Classification of Diseases for Oncology (ICD-O) is a coding system for neoplasms by topography and morphology and for indicating behaviour (e.g. malignant, benign).[13] This coded nomenclature is identical in the morphology field for neoplasms to the Systemized Nomenclature of Medicine (SNOMED).[14] It is recommended that the WHO Classification of Tumours be used for classification and definition of tumour types and that the ICD-O code be used for storage and retrieval of data.

METHOD OF STAGING

The aim is to define in each patient all the factors relevant to the natural history and outcome of the relevant disease, thereby enabling a patient with cancer to be grouped with other similar cases. The sex and age of the patient, the duration and severity of symptoms and signs, and the presence and severity of intercurrent disease should all be documented.

CT and MRI are now established as the mainstay investigations in the pre-operative workup of patients with head and neck cancer. Not every patient requires a scan but they are useful in delineating the extent and size of the primary tumour, determining the presence (particularly when risk of occult nodes is >20%), number and position of cervical lymph nodes, searching for an occult primary and locating a synchronous primary or distant metastases (particularly in the chest). Appropriate screening for synchronous tumours and distant metastases is particularly important in advanced tumours. Several studies have suggested that a CT scan should be obtained in preference to a plain chest radiograph as this may miss significant lung disease.[15, 16]

Scans to evaluate the primary site should be performed **prior to biopsy** to avoid the effect of upstaging from the oedema caused by biopsy trauma.

Endoscopy and biopsy should be performed by a senior surgeon and in all cases by the head and neck surgeon responsible for any future procedure. For each tumour, this should include a description and diagrammatic representation, and preferably also photographic documentation. Routine panendoscopy (oesophagoscopy and bronchoscopy) is contentious. Proponents point out that these procedures require very little time, and may be performed easily during planned, direct laryngoscopy. A large meta-analysis found a small advantage to panendoscopy in detection of second primary tumours during analysis of multiple prospective studies.[17] Opponents point out that the appropriate use of symptom-directed investigations, in addition to routine chest imaging, have a similar detection rate compared with screening endoscopy and avoid unnecessary risk and expense in asymptomatic patients.[18]

Therefore, panendoscopy is only recommended for symptomatic patients or patients with primary tumours known to have a significant risk of a second (synchronous) primary tumour.

There is a natural desire to confer a stage on the tumour at presentation in the clinic and, certainly, after endoscopy. This should be avoided. It is better to rely on descriptive text to avoid changing the stage as more information becomes available. The cTNM classification based on examination, imaging, endoscopy and biopsy should be clearly documented in the case file only when all the above information is collated. The UICC book should be available in every theatre and clinic to assist in applying the **correct stage**.

Regional lymph nodes

The status of the regional lymph nodes in head and neck cancer is of such prognostic importance that the cervical nodes must be assessed for each patient and tumour. Lymph nodes are described as ipsilateral, bilateral, contralateral or midline; they may be single or multiple and are measured by size, number and anatomical location. Midline nodes are considered ipsilateral nodes, except for thyroid cancers. Direct extension of the primary tumour into lymph nodes is classified as lymph node metastasis.[1, 2]

Imaging for node detection and delineation is advisable if the neck is being scanned as part of the evaluation of the primary tumour, if there is a high chance of occult disease (e.g. supraglottic primary), to assess the extent of nodal disease, to define any deep nodal fixation, or if clinical detection is difficult because of a short, fat or previously irradiated neck.

Lymph nodes are now subdivided into specific anatomical sites and grouped into seven levels for ease of description (**Table 4.6**). The pattern of lymphatic drainage varies for different anatomical sites. However, the location of the lymph node metastases has prognostic significance. Survival is significantly worse when metastases involve lymph nodes beyond the first echelon of lymphatic drainage.[19] It is particularly poor for lymph nodes in the lower regions of the neck (i.e. level IV and level V (supraclavicular area)).

The UICC booklet alludes to the importance of levels in some sites, but does not present any definitions. The AJCC cancer staging manual gives a much more thorough account. It recommends that each N staging category be recorded to show, in addition to the established parameters, whether the nodes involved are in the upper (U) or lower (L) regions of the neck, depending on their location above or below the lower border of the thyroid cartilage.[1, 2]

The definitions of the N categories (**Table 4.7**) are the same for most head and neck sites (oral cavity, p16-negative pharyngeal carcinoma, larynx carcinoma, sinus carcinoma, salivary gland carcinoma). The UICC/AJCC eighth edition recognizes the importance of extranodal extension (previously called extracapsular spread). A patient with evidence of extranodal extension is automatically considered to be N3b reflecting their poorer prognosis. The presence of skin involvement or soft tissue invasion with deep fixation/tethering to underlying muscle or adjacent structures or clinical signs of nerve involvement are classified as clinical extranodal extension.

The latest edition has also introduced two separate staging systems (cTNM and pTNM) for neck metastases for human papilloma virus (p16-positive) oropharyngeal cancer (**Tables 4.8a and 4.8b**). Studies have shown a significant difference in outcome based on the number of pathologically positive lymph nodes, defining two categories: those with 1 to 4 (N1) versus 5 or more (N2) positive nodes. As the number of nodes can only be counted in the neck dissection specimen, a separate N system based on histological assessment of the neck dissection specimen

TABLE 4.6 Nomenclature of anatomical site of lymph node

Level I	Contains the submental and submandibular triangles bounded by the posterior belly of the digastric muscle, the hyoid bone inferiorly and the body of the mandible superiorly.
Level II	Contains the upper jugular lymph nodes and extends from the level of the hyoid bone inferiorly to the skull base superiorly.
Level III	Contains the middle jugular lymph nodes from the hyoid bone superiorly to the cricothyroid membrane inferiorly
Level IV	Contains the lower jugular lymph nodes from the cricothyroid membrane superiorly to the clavicle inferiorly
Level V	Contains the posterior triangle lymph nodes bounded by the anterior border of the trapezius posteriorly, the posterior border of the sternocleidomastoid muscle anteriorly and the clavicle inferiorly.
Level VI	Contains the anterior compartment lymph nodes from the hyoid bone superiorly to the suprasternal notch inferiorly. On each side the medial border of the carotid sheath forms the lateral border.
Level VII	Contains the lymph nodes inferior to the suprasternal notch in the upper mediastinum.

TABLE 4.7 Clinical N stage

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension without extranodal extension
N2	N2a – Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension without extrandodal extension N2b – Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension N2c – Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension
N3a	Metastasis in a lymph node more than 6 cm in greatest dimension without extranodal extension
N3b	Metastases in a single or multiple lymph nodes with clinical extranodal extension

TABLE 4.8a Clinical N stage for HPV (p16-positive) related oropharyngeal cancer

Nx	Regional lymph nodes cannot be asessed
N0	No regional lymph node metasases
N1	One or more ipsilatetal lymph nodes, none larger than 6 cm
N2	Contralateral or bilateral lymph nodes, none larger than 6 cm
N3	Lymph node(s) larger than 6 cm

TABLE 4.8b Pathologic N stage for HPV (p16-positive) related oropharyngeal cancer

Nx	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metasases
pN1	Metastasis in 4 or fewer lymph nodes
pN2	Metastasis in more than 4 lymph nodes

TABLE 4.9 N staging for nasopharynx

N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis, in cervical lymph node(s), and/or unilateral or bilateral metastasis in retropharyngeal lymph nodes, 6 cm or less in greatest dimension, above the caudal border of cricoid cartilage
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or less in greatest dimension, above the caudal border of cricoid cartilage
N3	Metastasis in cervical lymph node(s) greater than 6 cm in dimension and/or extension below the caudal border of cricoid cartilage

Note: Midline nodes are considered ipsilateral nodes, and the supraclavicular triangle is defined by the lines joining the following three points – the superior margin of the clavicle at its sternal and acromial ends, and the point where the line of the neck meets the shoulder.

TABLE 4.10 N staging for thyroid carcinoma

N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis in Level VI (pretracheal, prelaryngeal, paralaryngeal) or upper/ superior mediastinal lymph nodes
N1b	Metastasis in other unilateral, bilateral or contralateral cervical (levels I–V) or retropharyngeal nodes

has been created (pTNM). Recognizing that lymph node size >6 cm does not have a prognostic role in surgically treated necks, no pN3 category exists.

The natural history and response to treatment of cervical nodal metastases from the nasopharynx are different, in terms of their impact on prognosis; thus, they justify a different N classification (**Table 4.9**). Regional lymph node metastases from well-differentiated thyroid cancer do not significantly affect the ultimate prognosis and, therefore, also warrant a unique system (**Table 4.10**).

Pathological classification (pTNM)

The pT, pN and pM categories correspond to the T, N and M categories. The extent of the tumour in terms of the location and level of the lymph nodes should be documented. In addition, the number of nodes that contain tumour and the presence or absence of extranodal extension of the tumour should be recorded. Histological examination of a selective neck dissection specimen usually includes ten or more lymph nodes; a radical or modified radical neck dissection specimen includes 15 or more lymph nodes.[1, 2]

Lip and oral cavity

The oral cavity extends from the skin-vermilion junction of the lips to the junction of the hard and soft palate above and to the line of the circumvallate papillae below. The anatomic sites and subsites are as follows:

- lip:
  - external upper lip (vermilion border)
  - external lower lip (vermilion border)
  - commissures
- oral cavity:
  - buccal mucosa
  - mucosa of the upper and lower lips
  - cheek mucosa
  - retro molar areas
  - buck-alveolar sulci, upper and lower (vestibule of mouth)
  - upper alveolus and gingiva (upper gum)
  - lower alveolus and gingiva (lower gum)
  - hard palate
  - tongue – dorsal surface and lateral borders anterior to vallate papillae (anterior two-thirds). inferior (ventral) surface
  - floor of mouth.

The eighth edition of the staging system recognizes the importance of depth of invasion and this is shown in **Table 4.11**.

(Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumour as T4a).

TABLE 4.11 TNM clinical classification for lip and oral cavity

T – Primary tumour	
T1	Tumour 2 cm or less in greatest dimension and 5 mm or less depth of invasion
T2	Tumour 2 cm or less in greatest dimension and more than 5 mm but no more than 10 mm depth of invasion or tumour more than 2 cm but not more than 4 cm in greatest dimension and depth of invasion no more than 10 mm
T3	Tumour more than 4 cm in greatest dimension or more than 10 mm depth of invasion
T4a	Lip: tumour invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin (chin or nose)
T4a	Oral cavity: tumour invades through cortical bone, into deep/ extrinsic muscle of tongue, maxillary sinus or skin of face.
T4b	Lip or oral cavity: tumour invades masticator space, pterygoid plates, or skull base, or encases internal carotid artery

Pharynx

The pharynx is divided into three regions: nasopharynx, oropharynx and hypopharynx. There have been significant changes in the eighth UICC/AJCC edition to reflect the very different biological and etiological differences between nasopharyngeal carcinoma, HPV-associated oropharyngeal carcinoma and non-HPV-associated oropharyngeal carcinoma, and hypopharyngeal cancer. The eighth edition staging manual has been divided into three separate entities – nasopharynx; HPV-associated (p16-positive) oropharyngeal cancer; and hypopharynx and non-HPV-associated (p16-negative) oropharyngeal carcinoma – to better reflect the variety of diseases arising in the pharynx.[1, 2]

Each region is subdivided into specific sites as summarized below.

OROPHARYNX

The oropharynx is the portion extending from the plane of the superior surface of the soft palate to the superior surface of the hyoid bone (or floor of the vallecula). It includes:

- anterior subsites (glosso-epiglottic area)
- base of tongue (posterior to the vallate papillae or posterior third)
- vallecula
- lateral subsites
- lateral wall
- tonsil
- tonsillar fossa
- tonsillar pillar
- posterior wall
- superior subsites
- inferior surface of soft palate
- uvula.

T categories in both p16-positive, HPV–associated oropharyngeal carcinoma and p16-negative, non-HPV-associated oropharyngeal carcinoma were equally valid from a prognostic standpoint and thus remain the same with two exceptions: the p16-positive classification includes no carcinoma in situ (Tis) (because of the non-aggressive pattern of invasive of p16-positive oropharyngeal carcinoma and the lack of a distinct basement membrane in the epithelium of Waldeyer's ring), and the T4b category has been removed from p16-positive oropharyngeal carcinoma (OPC) (because the survival curves of the T4a and T4b categories prove indistinguishable).[2] **Tables 4.12a** and **4.12b** summarize these changes.

TABLE 4.12a Oropharynx: p16-negative cancers or p16 immunohistochemistry not performed

T – Primary tumour	
T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but not more than 4 cm in greatest diameter
T3	Tumour more than 4 cm in greatest dimension or extension to lingual surface of the epiglottis
T4a	Tumour invades any of the following: larynx, deep extrinsic muscles of tongue genioglossus, hyoglossus, palatoglossus and styloglossus), medial pterygoid, mandible and hard palate
T4b	Tumour invades any of the following: lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base; or encases the carotid artery

TABLE 4.12b Oropharynx: p16-positive cancers

T – Primary tumour	
T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but not more than 4 cm in greatest diameter
T3	Tumour more than 4 cm in greatest dimension or extension to lingual surface of the epiglottis
T4	Tumour invades any of the following: larynx, deep extrinsic muscles of tongue (genioglossus, hyoglossus, palatoglossus and styloglossus), medial pterygoid, mandible and hard palate, lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base; or encases the carotid artery

NASOPHARYNX

The nasopharynx begins anteriorly at the posterior choana and extends along the plane of the airway to the level of the free border of the soft palate. It includes:

- superior wall
- posterior wall: from the level of the junction of the hard and soft palates to the superior wall
- lateral wall: including the fossa of Rosenmuller
- floor: superior surface of the soft palate.

The margin of the choanal orifices, including the posterior margin of the nasal septum is included with the nasal fossa.

There are two changes in nasopharynx T classifications relating to anatomic markers rather than depth of invasion (**Table 4.13**). The previous T4 criteria used synonymous terms 'masticator space' and 'infratemporal', which are now be replaced by a specific description of soft-tissue involvement to avoid ambiguity. In addition, adjacent muscle involvement (including medial pterygoid, lateral pterygoid and prevertebral muscles) are down-staged to T2 based on them having a more favourable outcome.[20]

HYPOPHARYNX

The hypopharynx is that portion of the pharynx extending from the plane of the superior border of the hyoid bone (or floor of the vallecula) to the plane corresponding to the lower border of the cricoid cartilage. It includes the piriform sinuses, the postcricoid area and the lateral and posterior pharyngeal walls. The current staging summary for hypopharynx is summarized in **Table 4.14**.

- Postcricoid area (pharyngo-oesophageal junction): extends from the level of the arytenoid cartilages and connecting folds to the inferior border of the cricoid cartilage, thus forming the anterior wall of the hypopharynx.

TABLE 4.13 Nasopharynx

T – Primary tumour	
T1	Tumour confined to nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal involvement
T2	Tumour with extension to parapharyngeal space and/or infiltration of the medial pterygoid, lateral pterygoid and/or prevertebral muscles.
T3	Tumour invades bony structures of skull base cervical vertebra, pterygoid structures and/or paranasal sinuses
T4	Tumour with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, parotid gland and/or infiltration beyond the lateral surface of the lateral pterygoid muscle

Note: Parapharyngeal extension denotes postero-lateral infiltration of tumour beyond the pharyngo-basilar fascia.

TABLE 4.14 Hypopharynx

T – Primary tumour	
T1	Tumour limited to one subsite of hypopharynx and 2 cm or less in greatest dimension.
T2	Tumour invades more than one subsite of hypopharynx or an adjacent site, or measures 2–4 cm in greatest dimension, without fixation of hemilarynx.
T3	Tumour measures >4 cm in greatest dimension, or with fixation of hemilarynx or extension to oesophagus
T4a	Tumour invades any of the following: thyroid/cricoid cartilage, hyoid bone, thyroid gland, oesophagus, central compartment soft tissue
T4b	Tumour invades prevertebral fascia, encases carotid artery, or invades mediastinal structures

Note: Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.

- Piriform sinus: extends from the pharyngo-epiglottic fold to the upper end of the oesophagus. It is bounded laterally by the thyroid cartilage and medially by the hypopharyngeal surface of the aryepiglottic fold and the arytenoid and cricoid cartilages.
- Posterior pharyngeal wall: extends from the superior level of the hyoid bone (or floor of the vallecula) to the level of the inferior border of the cricoid cartilage and from the apex of one pyriform sinus to the other.

Larynx

The anatomical sites and subsites are:

- supraglottis:
  - suprahyoid epiglottis (including tip, lingual [anterior], and laryngeal surfaces)
  - aryepiglottic fold, laryngeal aspect
  - arytenoid
  - infrahyoid epiglottis
  - ventricular bands (false cords)
- glottis:
  - vocal cords
  - anterior commissure
  - posterior commissure
- subglottis.

Tables 4.15–4.17 detail the T stages for the various laryngeal cancer sites.

TABLE 4.15 Supraglottis

T – Primary tumour	
T1	Tumour limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumour invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g. mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumour limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space and/or with minor thyroid cartilage erosion (e.g. inner cortex)
T4a	Tumour invades through thyroid cartilage, and/or invades tissues beyond the larynx, e.g. trachea, soft tissues of the neck, including deep/extrinsic muscle of the tongue (genioglossus, hyoglossus, palatoglossus and styloglossus), strap muscles, thyroid and oesophagus
T4b	Tumour invades prevertebral space, mediastinal structures, or encases carotid artery

TABLE 4.16 Glottis

T – Primary tumour	
T1	Tumour limited to vocal cord (s) (may involve anterior or posterior commissure) with normal mobility. T1a – tumour limited to one vocal cord T1b – tumour involved both vocal cords
T2	Tumour extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumour limited to larynx with vocal cord fixation and/or invades paraglottic space, and/or with minor thyroid cartilage erosion (inner cortex)
T4a	Tumour invades through thyroid cartilage or invades tissues beyond the larynx, e.g. trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus and styloglossus), strap muscles, thyroid and oesophagus
T4b	Tumour invades prevertebral space, mediastinal structures, or encases carotid artery

TABLE 4.17 Subglottis

T – Primary tumour	
T1	Tumour limited to subglottis
T2	Tumour extends to vocal cord(s) with normal or impaired mobility
T3	Tumour limited to larynx with vocal cord fixation
T4a	Tumour invades through cricoid or thyroid cartilage and/or invades tissues beyond the larynx, e.g. trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), strap muscles, thyroid, and oesophagus
T4b	Tumour invades prevertebral space, mediastinal structures, or encases carotid artery

Nasal cavity and paranasal sinuses

The anatomical sites and subsites are:

- nasal cavity:
  - septum
  - floor
  - lateral wall
  - vestibule
- maxillary sinus
- ethmoid sinus.

Other than the changes to the N stage (consistant with with oral caity, p16-negative oropharynx and larynx) there are no other alterations to sinus tumour stages (**Tables 4.18** and **4.19**).

Salivary glands

The classification applies only to carcinomas of the major salivary glands. Tumours arising in minor salivary glands (mucus-secreting glands in the lining membrane of the upper aerodigestive tract) should be staged according to their anatomic site of origin (e.g. lip). There should be histological confirmation of the disease. The anatomical sites and subsites are (**Table 4.20**):

- parotid gland
- submandibular gland
- sublingual gland.

TABLE 4.18 Maxillary sinus

T – Primary tumour	
T1	Tumour limited to the antral mucosa with no erosion or destruction of bone
T2	Tumour causing bone erosion or destruction, including extension into hard palate and/or middle nasal meatus, except extension to the posterior wall of maxillary sinus and pterygoid plates
T3	Tumour invades any of the following: bone of posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa or ethmoid sinuses
T4a	Tumour invades any of the following: anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate and sphenoid or frontal sinus
T4b	Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve, nasopharynx, clivus

TABLE 4.19 Nasal cavity and ethmoid sinus

T – Primary tumour	
T1	Tumour restricted to one subsite of nasal cavity or ethmoid sinus without bone erosion
T2	Tumour involves two subsites or extends to involve an adjacent site within the nasoethmoidal complex, with or without bony invasion
T3	Tumour extends to invade the medial wall or floor of the orbit, maxillary sinus, palate or cribriform plate
T4	Tumour invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b	Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve, nasopharynx, clivus

TABLE 4.20 Salivary gland

T – Primary tumour	
T1	Tumour 2 cm or less in greatest dimension without extraparenchymal extension*
T2	Tumour more than 2 cm but no more than 4 cm in greatest dimension without extraparenchymal extension*
T3	Tumour more than 4 cm and/or tumour with extraparenchymal extension
T4a	Tumour invades skin, mandible, ear canal or facial nerve
T4b	Tumour invades base of skull, pterygoid plates or encases carotid artery

* Extraparenchymal extension is clinical or macroscopic evidence of invasion of skin, soft tissues or nerve, except those listed under T4a and T4b. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.

TABLE 4.21 Thyroid gland

T – Primary tumour	
T1	Tumour 2 cm or less in greatest dimension, limited to the thyroid T1a – tumour 1 cm or less in greatest dimension, limited to the thyroid T1b – tumour more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid
T2	Tumour more than 2 cm but not more than 4 cm in greatest dimension, limited to the thyroid
T3	Tumour more than 4 cm in greatest dimension, limited to the thyroid or any tumour with gross extrathyroid extension involving only the strap muscles (e.g. sternohyoid, sternothyroid or omohyoid muscles) T3a – tumour more than 4 cm in greatest dimension, limited to the thyroid T3b – tumour of any size with gross extrathyroidal extension invading strap muscles (sternohyoid, sternothyroid or omohyoid muscles)
T4a	Tumour extends beyond the thyroid capsule and invades any of the following: subcutaneous soft tissues, larynx, trachea, oesophagus, recurrent laryngeal nerve
T4b	Tumour invades prevertebral fascia, mediastinal vessels, or encases carotid artery
T4a*	(Anaplastic carcinoma only) – tumour (any size) limited to the thyroid
T4b*	(Anaplastic carcinoma only) – tumour (any size) extends beyond the thyroid capsule

Note: Multifocal tumours of all histological types should be designated (m) (the largest determines the classification).

* All anaplastic carcinomas are considered T4.

Thyroid gland

The four major histopathologic types are:

- papillary carcinoma (including those with follicular foci)
- follicular carcinoma (including Hürthle cell carcinoma)
- medullary carcinoma
- undifferentiated (anaplastic) carcinoma.

In the new UICC/AJCC staging system the definition of T3 has been revised for follicular and medullary carcinomas. In addition, the age for a poor prognosis has changed from 45 to 55 years. The current staging system is summarized in **Table 4.21**.

Unknown primary – cervical nodes

There should be histological confirmation of squamous cell carcinoma with lymph node metastases but without an identified primary carcinoma. It should be appreciated that this is a dynamic concept as eventual discovery of the primary site means that the carcinoma is no longer an unknown primary. Current recommended diagnostic methods include an early PET CT scan with targeted biopsies based on the findings. Transoral laser or robotic excision of the tonsil and tongue base mucosectomy are also recommended in cases which remain as an unkown primary. Histological methods should be used to identify EBV and HPV/p16-related tumours. If there is evidence of EBV, the nasopharyngeal classification is applied. If there is evidence of HPV and positive immunohistochemistry p16 overexpression, the p16-positive oropharyngeal classification is applied.[1, 2] One key change from previous versions of the TNM system is the elimination of the T0 category in sites other than the nasopharynx, HR-HPV–associated OPC, and salivary gland cancers (which can be identified by their unique histology). If no primary lesion can be identified, then the lymph node may have emanated from any mucosal site, so there is no rationale to support retaining the T0 designation outside of the virally associated cancers of the oropharynx and nasopharynx.

Skin carcinoma of the head and neck

This is now presented in a separate chapter in the eighth edition of the UICC/AJCC manuals.[1, 2] The classification aplies to cutaneous carcinaomas of the head and neck region excluding the eyelid (as an antomical site), Merkel cell carcinoma and malignant melanoma. The T stage is presented in **Table 4.22**, and N stage follows the same as nodal metastases from other sites of the head and neck. The following sites are recognized:

- lip
- external ear
- other and unspecified parts of the face
- scalp and neck.

TABLE 4.22 Head and neck skin cancer

T1	Tumour 2 cm or less in greatest dimension
T2	Tumour >2 cm and <4 cm in greatest dimension
T3	Tumour >4 cm in greatest dimension or minor bone erosion or perineural invasion or deep invasion*
T4a	Tumour with gross cortical bone/marrow extension
T4b	Tumour with skull base or axial skeleton invasion including foraminal involvement and/or vertebral foramen involvement to the epidural space

* Deep invasion is defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumour), perineural invasion for T3 classification is defined as clinical or radiographic involvement of named nerves without foramen or skull base invasion or transgression.

Malignant melanoma of the upper aerodigestive tract

The classication in **Table 4.23** applies only to mucosal malignant melanomas of the head and neck region. The regional lymph nodes are staged according to the site in the upper aerodigestive tract of the tumour. As malignant melanoma are aggressive tumours, T1 and T2 are omitted as are stages I and II.

LIMITATIONS OF T STAGING

For most sites in the head and neck, emphasis is placed on tumour size. It is, however, well recognized that T stage alone is of limited prognostic significance in many head and neck carcinomas. It is a significant factor in the presence of nodes on presentation. Patients with larger tumours are more likely to have nodes than those with smaller tumours.[21] In carcinoma of the larynx, the poorer prognosis with increased T stage is explained by the increasing propensity to nodal metastases with larger tumours. If nodal metastases are removed as a confounding factor then T stage per se does not influence prognosis.[22]

Tumours of the larynx are classified according to the number of anatomical surfaces involved. This has led to several problems. For example, a large 3 cm tumour of the supraglottis may remain T1, whereas in the glottis this will almost certainly be a T3. This mitigates against supraglottic tumours in terms of outcome. In addition, depth of invasion is not measured, but is of prognostic and therapeutic importance. For example, a superficial tumour of the vocal cord mucosa would be T1a. The same tumour may be deeply infiltrating into the vocalis muscle and yet the stage will remain T1a.

TABLE 4.23 Malignant melanoma of the upper aerodigestive tract

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T3	Tumour limited to the epithelium and/or submucosa (mucosal disease)
T4a	Tumour invades deep soft tissue, cartilage, bone or overlying skin
T4b	Tumour invades any of the following: brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, mediastinal structures

In the oral cavity and the oropharynx, the size of the tumour is not always easily measured. There is little difficulty in defining a T1 or T4 tumour, but problems can occur when the tumour measures between 1.5 and 3 cm. Furthermore, increasing severity with a T4 tumour is reflected in deep invasion into muscle, bone or adjacent structures. There is then a reliance on the predictive power of radiographic modalities including CT and MRI. The depth of invasion of lesions of the floor of the mouth has been shown to be of prognostic significance and this is similarly difficult to assess by either clinical or radiographic means.[23]

Tumours of the hypopharynx are classified in terms of both their size and anatomical extent. The anatomical boundaries of the hypopharynx have been contentious in the past and it is occasionally difficult to be certain of the exact origin of some of the larger tumours. The dual listing of the aryepiglottic fold in both the supraglottis and hypopharynx sites invokes a problem in trying to classify the site of origin in some situations.

LIMITATIONS OF N STAGING

The reliability of clinical examination of nodes is contentious with studies showing that observers disagree on their presence.[23] Furthermore, palpable nodes do not always harbour tumour. During clinical examination, the size of the node should be measured with callipers, and allowance made for the intervening soft tissues. There is considerable inter- and intra-observer error in estimating the size of the node by palpation alone without a measuring device.[24] Most masses over the size of 3 cm in diameter are not single nodes, but will represent confluent nodes or tumour in the soft tissue compartments of the neck.

One of the main criticisms over many years was the failure of the TNM system to provide a description of the level of nodal involvement. Various studies have confirmed the importance of this parameter[25] and it is now included in the current classification (engaging the Memorial Sloan-Kettering system of lymph node levels).[1, 2]

LIMITATIONS OF STAGE GROUPING

There are now seven stages for head and neck cancers arising at mucosal sites (0, I, II, III, IVa, IVb, IVc) and six stages for salivary gland cancers (I, II, III, IVa, IVb, IVc). Differentiated thyroid cancers also have six stages (I, II, III, IVa, IVb, IVc) with undifferentiated (anaplastic) cancers having three, as all cases are stage IV (IVa, IVb, IVc). Many authorities have concluded that problems exist with the current staging system.[25–28] One of the main criticisms is that the size of some groups defined by the combinations of the TNM classifications is small, preventing accurate prediction from previous experience.

Groome et al.[29] identified four criteria that a stage-grouping scheme should meet:

1. The subgroups defined by the T, N and M that make up a given group within a stage grouping scheme should have similar survival rates (hazard consistency).
2. The survival rates should differ among the groups (hazard discrimination).
3. The prediction of cure should be high (outcome prediction).
4. The distribution of patients across the groups should be balanced (thereby maximizing statistical power in each group).

Compelling arguments have been advanced to show that alternative groupings of the same T, N and M categories will result in an improved system.

The T and N integer score (TANIS) combines the integers of the T and N to create a new score. Thus, a T1N0 would be a TANIS 1, T2N2 would be a TANIS 4, and so on. First reported by Jones et al.,[28] this is an easy to use system evaluated primarily for cancers of the oral cavity and oropharynx. It treats T and N as equivalent with respect to survival. Many authors have studied this system and recommended grouping several TANIS scores to improve hazard discrimination. In their initial report, Jones et al. found little statistical difference between groups 1–3 and 5–7. They recommended pooling TANIS scores 1–3 together as TANIS 1, 4 as TANIS 2 and 5–7 as TANIS 3. Others have tried different groupings based on the TANIS system.[29, 30]

The advantages of the TANIS score are its ease of application, ability to define a reasonable number of groups and ability to be applied retrospectively if the TNM score is known. The main disadvantage is that the concept of T and N equivalence does not hold true. Many studies have confirmed the more significant impact of N status over T status. For example, a T2N0 carcinoma does not have the same survival as a T1N1 at any site although both of these would be categorized TANIS 2. The TANIS system does not account for M1 disease, although most would agree that any M1 would automatically put the patient in the highest TANIS group. It is also apparent that by pooling groups, because there is little difference in survival between them (attempting to improve hazard discrimination), there is an implicit trade-off with hazard consistency.

Others have also tried to improve on the current stage grouping and TANIS system with subtle variations,[26, 31, 32] all claiming that their system is an improvement on any other. It seems that excellent systems have been devised that may improve predictive power, hazard consistency, hazard discrimination and balance over the current UICC/AJCC T, N and M stage grouping system. Lydiatt et al.[33] provide a review of these. They observe that one of the main disadvantages is that the systems are not intuitive and would require a chart for most clinicians to stage their patients. In most publications, analyses comparing the authors' systems with other systems, including the UICC/AJCC, are flawed because the new system under consideration was not externally validated on an independent dataset. Therefore, because the system was created from the dataset, it would naturally perform well. The true test is whether the results from an independent dataset would yield similar results.

The five major sites of the head and neck (oral cavity, oropharynx, larynx, hypopharynx and paranasal sinuses)

share the same system. Arguably, they should be independent of each other. One advantage of an independent system is better groupings within each site. Different systems are in use for the nasopharynx and thyroid, which are sufficiently different with respect to risk factors, behaviour and treatment. In their rebuttal of these views, the AJCC Task Force maintains the opinion that independent systems would create problems for clinicians and investigators not remembering which group was staged by which system. They are of the view that any new system should be comprehensive and easily applicable to all the major sites.[33]

FUTURE RESEARCH

- Definitions of TNM categories may be altered or expanded for clinical or research purposes as long as the basic definitions are recorded and not changed. Changes in the TNM classification should and will only occur, based on the appropriate collection, presentation and analysis of data, in the forum of the UICC and AJCC.
- The TNM system embraces the concept of orderly description of disease with increasing size and extent. While fallible, it is founded on sound principles and relates the combined experience and data from many surgeons and centres. Many of the shortcomings in the system represent the complexity of the disease of head and neck cancer.
- Future versions of the staging system may well incorporate nomograms and personalized approaches; but, for now, the eighth edition strikes a balance between a personalized, complex system and a more general, simpler one that maintains the user-friendliness and worldwide acceptability of the traditional TNM staging paradigm.

KEY POINTS

- Staging of head and neck cancer is a system designed to express the relative severity, or extent, of the disease. It is meant to facilitate an estimation of prognosis and provide useful information for treatment decisions.
- Classification of the anatomical extent of head and neck cancer as determined clinically and histopathologically is called the TNM system.
- Radiological investigations to evaluate the primary site should be performed prior to biopsy to avoid the effect of upstaging from the oedema caused by biopsy trauma.
- The age and sex of the patient, the duration and severity of symptoms and signs, and the presence and severity of intercurrent disease should all be documented. The literature does suggest that symptom severity[34] and comorbidity[35] have a significant impact on outcomes. It is therefore recommended that these data be recorded and this additional information can be used as part of the prognostic grid.
- Assessment by endoscopy and biopsy should be performed by a senior surgeon and in all cases by the head and neck surgeon responsible for any future procedure.
- The clinical (pre-treatment) classification (cTNM) based on examination, imaging, endoscopy and biopsy should be clearly documented in the case file only when all the information is collated.
- Individual TNM classifications should be assembled into four stage groups (Stages I to IV), each with similar survival outcomes.
- The UICC book[1, 2] should be available in every theatre, MDT meeting and clinic to assist in applying the correct stage.

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CHAPTER 5

THE CHANGING FACE OF CANCER INFORMATION

Richard Wight

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the web links given within the reference list.

INTRODUCTION

This chapter describes principles to be followed in capturing high quality cancer data. The principles are transferable to other aspects of otolaryngology. A description is provided of the changing nature of cancer information collection and collation with the National Cancer Outcomes and Services Data Set, unification of cancer registration in England and national radiotherapy and chemotherapy data collection, as well as the National Comparative Audit in Head and Neck Cancer (Data for Head and Neck Oncology, DAHNO).

WHAT ARE DATA?

Data are a collection of directly observed facts, and the storage of these facts in a standardized format and content comprise a database.

For standardization of content, data gathering requires an underlying 'skeleton' of items: a data set. The items need to have defined meaning, standard terminology should be used, and choice of fields should have a consistent coding structure. Use of free text should be avoided. The items are the building blocks from which the construction of information can then subsequently occur. If the data set has been correctly defined and is fit for the purpose, then it should contain all the items needed for the outputs proposed without the need to resort to additional data capture.

WHY COLLECT CANCER DATA?

All clinicians managing patients with cancer have a responsibility to assess the quality of the care they provide.[1] This is reflected in the impact or consequences of the management and treatments they apply to individuals or groups of patients. In order to discharge this responsibility, the prospective collection of data on each patient to derive simple outcomes is a minimum requirement. Potential outcomes are: knowledge of the range of malignancies treated; stage distribution; the types of treatment provided; complications of treatment; survival; and quality of life measures.

Clinicians seek to provide for their patients a prognosis for their disease. This is affected by tumour-specific factors (e.g. stage,[2] pathological features), host factors (e.g. performance status and comorbidities) and environmental factors (e.g. access to services and the availability of treatments).[3] Traditionally, prognosis has been based on anecdote and the 'best of class from the literature' but by routine data capture it can (if sufficient

numbers are obtained) be converted into a true local focus. Customization for an individual's personal circumstances is becoming increasingly important as illustrated by the impact of comorbidities. These are the additional burdens of other diseases present at the time of diagnosis of the index cancer. A series of standardized indexes are available, with the adult comorbidity evaluation (ACE-27) having significant prognostic value.[4]

WHY A MINIMUM DATA SET?

Applying the principle of a minimum data set is based on the fact that the smaller the volume of items the greater the speed of entry, the higher the accuracy and the greater the likelihood of compliance in usage. This has to be balanced against the requirements of components to deliver the necessary outcomes, without additional data entry at a later stage. To produce a minimum data set, each item proposed should be critically examined both in its definition and by it having a defined purpose for inclusion, and these should be reviewed in the light of any piloting.

An ongoing recording of current status in relation to the absence or presence of the index cancer is needed with capture of recurrence or metastasis events, to allow for the censoring of records ultimately in certain types of survival analysis. Creation of a supporting data manual providing an expanded description of each item, its purpose in inclusion and any associated codes and classifications, is of value to support staff, institutions and software writers.

HOW TO DEVELOP CANCER DATA COLLECTION

In commencing an initiative to record cancer data, the goal has to be to collect data at the point of contact with the patient along their care journey (real or near real time data capture). This reduces error and increases likely compliance from health professionals. Duplication is reduced and the data collection process can deliver added value by-products such as referral or discharge letters.

The key steps are shown in **Figure 5.1**. Some items will be derived. For example, it is better to record date of birth and date of an event, then calculate the age at the event subsequently, than it is to enter the age as a free field item. The latter is prone to error, as well as being repetitive if a series of events require age as a factor.

At introduction, for a data set to be successfully collected requires a change in culture by all contributory professionals. A sense of ownership is needed as well as carefully focused drives to ensure data quality on a recurring basis. It is appropriate to validate the data, to ensure all relevant cases have been captured within the geographical target area and particularly where patient care crosses organizations the full record has been collected. Useful sources for cross comparison are multi disciplinary (MDT) meeting lists, pathology, and cytology records. The Office for National Cancer Registration and Analysis service collate the small number of additional death certificate-only registrations.

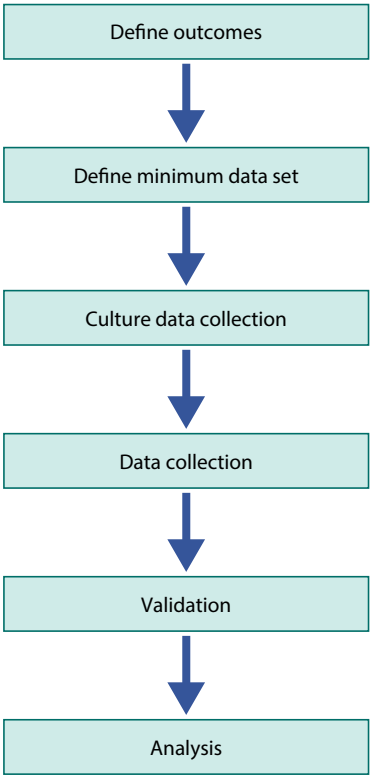


Figure 5.1 The key stages in developing cancer data collection.

When appropriate, data analysis can then occur and this is mostly likely to fail if significant gaps in the data are evident. Only with high quality data can relevant and useful information be assembled.

The data set should not be seen as fixed, but its items should be reviewed on a regular basis both to encompass any changes and confirm that their continued collection remains relevant and of value.

STRUCTURE OF A COMPUTERIZED DATABASE

Each subject on the database requires a unique identifier, and a record of registration is created. In England the mandated identifier is the NHS number. Diagnosis of cancer produces a care spell or event, to which is then tagged each recurrence or metastasis and each treatment plan and treatment. An additional new primary creates a new care spell. A relational database tree is thus constructed.

In selecting database software to support this, a number of factors should be considered:

- local familiarity, including the ability to write in the software to amend for item changes
- flexibility to deliver changes in relationship between events and to support different system packages
- ability to link with other host institutional systems for automated data capture (e.g. link to patient administration systems)
- ability to export data in a number of formats is also of value.

CONFIDENTIALITY – SECURE DATA

Patients expect that information about them will be held in confidence by the health professionals who care for them. Where information is stored in computerized or paper records, it must be effectively protected against improper disclosure at all times.

For the majority of audit purposes anonymized data will meet requirements. If data cannot be used in an anonymized format then permission should be sought from the patient.

Legislation controls confidential information disclosures (Section 251 of the NHS Act 2006) which allow sharing of confidential information in the 'public interest.' It sets a high threshold before the duty of confidentiality can be set aside for the purposes of audit not directly associated with care.[5]

CODING CLASSIFICATIONS

Standardized nomenclature is essential to allow assimilation of data from different units and specialities, and should wherever possible be recognized internationally (e.g. International Classification of Disease (ICD)-10); nationally (e.g. Office for Population Censuses and Surveys (OPCS)-4 operation codes, Systematized Nomenclature of Medicine – Clinical Terms (SNOMED CT)); or national professional (e.g. BAHNO extension codes). Locally derived codes should be avoided wherever possible. To illustrate coding classification structures, some are described briefly here.

ICD-10 tumour site codes

The classification of neoplasms is broken down into categories based on their point of origin and behaviour.[6] Sites for malignant neoplasms are prefixed by C, whilst sites for *in situ* and benign neoplasms are prefixed by D, but grouped into much broader categories (see **Box 5.1**).

For each anatomical site the initial three alphanumeric code is supplemented by a decimal point and an additional digit to identify subsite 0 to 7, or an overlapping site 8 (unless specifically indexed), or unspecified subsite 9 (see **Box 5.2**).

BOX 5.1 ICD-10 tumour site codes (benign and malignant)

C00–C75	Covers specified primary sites (but excludes lymphoid, haematopoietic and related tissues)
C76–C80	Covers ill-defined, secondary and unspecified sites
C81–C96	Malignant neoplasms of lymphoid, haematopoietic and related tissues
C97	Malignant neoplasms of multiple independent primary sites
DOO–DO9	Relates to *in situ* neoplasms
D10–D36	Relates to benign neoplasms
D37–D48	Relates to neoplasms of uncertain or unknown behaviour

BOX 5.2 ICD-10 tumour site codes for the tonsil

CO9	Malignant neoplasm of tonsil (excludes lingual tonsil CO2.4, pharyngeal tonsil C11.1)
CO9.0	Tonsillar fossa
CO9.1	Tonsillar pillar (anterior and posterior)
CO9.8	Overlapping lesion of tonsil (i.e. involves pillar and fossa and not clear which is site of origin)
CO9.9	Tonsil unspecified (i.e. subsite not stated or known)

ICD-O-3 – morphology codes

ICD-10 includes a copy of this coding system to allow it to be used in conjunction with the above site codes, to identify histological type.[7] Morphology codes are prefixed by M. Some histological types of neoplasm are specific to certain sites or types of tissue and C and D site codes are shown after these. For example, M93103 ameloblastoma malignant (C41.0, C41.1) identifies that the morphology only relates to tumours occurring in the maxilla and mandible.

Four identity digits for the histological type of neoplasm, and then a one-digit behaviour code follow:

0 benign
1 uncertain benign or malignant
2 carcinoma *in situ*
3 malignant or primary site
6 malignant metastatic, or secondary site

This system as it applies to squamous carcinoma is illustrated in **Box 5.3**

The morphology section of the Systematized Nomenclature of Medicine – Clinical Terms (SNOMED CT)[8] is similar to ICD-O-3 , but it gives a broader description of pathological terminology to aid coding.

OPCS operation codes

The basic structure of the classification comprises anatomically based chapters, each of which is given an alphabetical code.[9] The next two digits describe the operation group, based on the largest operation first, descending to the smallest, followed by a decimal point and a fourth digit to identify the procedure itself. If the procedure specified does not match these categories, then provided the procedure is recorded a .8 can be added, and where unspecified a .9 can be added. Within the classification, certain codes do encompass multiple procedures, but otherwise the operation needs to be coded from its component parts (e.g. having defined the primary resection procedure, separate codes for type of flap and its site of harvest need to be added). Operations on the salivary glands are illustrated in **Box 5.4**.

BOX 5.3 ICD-O-3 morphology codes for squamous carcinoma

M8070/2	Squamous cell carcinoma *in situ*
M8070/3	Squamous cell carcinoma (not otherwise specified)
M8070/6	Squamous cell carcinoma metastatic (i.e. in a node with an unknown primary)

BOX 5.4 OPCS operation and procedure codes: salivary gland procedures

F44	Excision of salivary gland
F44.1	Total excision of parotid gland
F44.2	Partial excision of parotid gland
F44.3	Excision of parotid gland (not elsewhere classified)
F44.4	Excision of submandibular gland
F44.5	Excision of sublingual gland
F44.8	Other specified
F44.9	Unspecified

NATIONAL CANCER REGISTRATION

Increasingly, cancer data capture is based on national initiatives. In Europe this has focused on registry-based systems,[10] and in the United States registry databases feed to the National Cancer Database.[11]

The Cancer Reform Strategy (2007)[12] identified better information as one of the key drivers to achieve the goal that cancer services in the UK should be amongst the best in the world. The subsequent *Improving Outcomes: A Strategy for Cancer* (January 2011) further supported this concept.[13]

In the UK, 2013 saw completion of the deployment of a National Cancer Registration System (NCRS),[14] in which the individual English cancer registries have been unified into a single online system. Regional registries have become eight regional cancer registration offices. There are also three cancer registries in Wales,[15] Scotland[16] and Northern Ireland.[17] NCRS receives data from a variety of sources including death certification from the Office for National Statistics (ONS) and direct feeds from pathology systems, MDTs and national audits, as well as treatment data on radiotherapy from the National Radiotherapy Data Set (RTDS) and on chemotherapy from the Systemic Anti-Cancer Therapy (SACT) data set. NCRAS is overseen by Public Health England.

CANCER OUTCOMES AND SERVICES DATA SET

In January 2013 the Cancer Outcomes and Services Data Set (COSD) replaced the previous National Cancer Dataset as the new NHS national requirement for reporting cancer in England. It incorporates a revised generic Cancer Registration Data Set (CRDS) and additional clinical and pathology site-specific data items relevant to different tumour types including items specific to head and neck.[18] The latest version of COSD can be found at http://content.digital.nhs.uk/isce/publication/dcb1521.[19]

COSD items are required to be submitted electronically by English NHS trusts to the National Cancer Registration and Analysis Service (NCRAS) on a monthly basis.[20]

COSD is aligned with, and shares data items with, other related data sets such as the National Cancer Waiting Times Monitoring Data Set (NCWTMDS),[21] the RTDS, the SACT data set, the Diagnostic Imaging Dataset (DID)[22] and the national clinical audits.

From 1 April 2009, all facilities providing radiotherapy services in England have been required to return the RTDS, which includes treatments delivered and aspects of fractionation.[23]

Submission of the SACT data set, which covers chemotherapy treatment for all solid tumour and haematological malignancies, including those in clinical trials for all patients receiving cancer chemotherapy in or funded by the NHS in England, commenced in 2013.[24]

NATIONAL CANCER DATA REPOSITORY AND THE FUTURE OF CANCER INFORMATION

By taking multiple data sources such as NCRAS, hospital episode statistics (HES), ONS death data and audit data, and linking these by NHS number, a comprehensive bank of data has been created in the National Cancer Data Repository,[25] which will be of value for national information reporting and analysis, as well as acting as a high quality clinical database for researchers enabling studies of treatments where it is impracticable to carry out randomized controlled studies.

NATIONAL CANCER INTELLIGENCE NETWORK HEAD AND NECK INFORMATION HUB

The National Cancer Intelligence Network (NCIN)[26] is a UK-wide initiative, working to drive improvements in standards of cancer care and clinical outcomes by improving and using the information collected about cancer patients for analysis, publication and research.

The NCIN Head and Neck Cancer Hub provides data and intelligence on head and neck cancers in England.[27] It is aimed at a wide range of professionals working in the field, including NHS providers, commissioners, cancer networks, charities and clinicians. Detailed reports are available on geographic variation, the impact of travel times and changes in head and neck surgery. It also provides information and links for patients and the general public who wish to understand more about head and neck cancers, including data sheet information about incidence and mortality, and past and current trends.

NATIONAL COMPARATIVE AUDIT IN HEAD AND NECK CANCER IN ENGLAND AND WALES

In England and Wales a partnership between the British Association of Head and Neck Oncologists (BAHNO) and the Health and Social Care Information Centre South East Knowledge and Intelligence Team, sponsored by the Healthcare Quality Improvement Partnership (HQIP), delivered Data for Head and Neck Oncology (DAHNO),[28] a national comparative audit for head and neck cancer.

Core issues addressed in the audit were:

- delivery of appropriate primary treatment (including adjuvant therapy) in management of head and neck cancer by an MDT, and delivery of care to agreed standards
- to assess in more detail, care provided by specialist nurses, dieticians and speech and language therapists.

The audit compared reported delivery against clinical standards produced by BAHNO as well as making peer-to-peer comparisons between organizations, MDTs and cancer networks.

The project defined outcomes deliverable by items from the core and head and neck specific COSD data set. The first annual report looking at outcomes related to patients with laryngeal and oral cavity cancer was published in March 2006. Subsequent reports extended across a broad range of anatomic sites, including the pharynx, major salivary glands and most recently the nose and nasal sinuses. More than 54 000 cases have been collated and the tenth annual report, published in September 2015[29] had universal coverage from all hospitals delivering head and neck cancer care in England and Wales.

In a subsequent partnership between BAHNO and a charity Saving Faces, a new national comparative audit in head and neck cancer (HANA) is in development.[30]

EVOLVING SURGEON-SPECIFIC DATA

Publishing of outcomes data by named consultant is well established in a number of countries around the world, particularly in North America. This has now extended to head and neck cancer surgeons in England.

In December 2012, the NHS Commissioning Board (from April 2013 NHS England) published its planning guidance for 2013/14, *Everyone Counts: Planning for patients 2013/14*,[31] commencing a process in which specialist bodies (in conjunction with NHS Choices) were required to publish activity, clinical quality measures and survival rates from 10 national clinical audits, which included head and neck cancer. The aim of using consultant-level data was to drive up quality, facilitate patient choice and support the requirements of professional revalidation. It also aimed to reassure the public that clinical practice is being actively monitored, and that the overall standard of care is very high. Under the Clinical Outcomes Publication (COP), an NHS England initiative, commissioned and managed by HQIP information on aspects of head and neck cancer, including mortality and surgeons' activity, was published openly for the first time at individual consultant surgeon level on NHS choices in 2013.[32] This demonstrated the commitment of BAHNO and the head and neck community to the transparency agenda, and the latest report is now available.[33]

BEST CLINICAL PRACTICE

✓ The measures for improving outcomes in head and neck cancer issued by the National Institute for Clinical Excellence (NICE) support the proposition that clinicians should routinely collect data to assess care.[34]

FUTURE RESEARCH

➤ The relative rarity of head and neck cancer means that, in order to assess and compare results from different treatment regimes and practice and reach statistical significance, it requires comprehensive data collection from as many units as possible across the UK. The goal has to be to achieve high levels of completeness on a regular and systematic basis.

KEY POINTS

- Data gathering requires an underlying 'skeleton' of items – a data set. The items need to have defined meaning, standard terminology should be used, and choice fields should have a consistent coding structure.
- All clinicians managing cancer patients have a responsibility to assess the quality of the care they provide. In order to discharge this duty, the prospective collection of data on each patient to derive simple outcomes is a minimum requirement.
- In commencing an initiative to record cancer data, the goal has to be to collect data at the point of contact with the patient along their care journey.
- Patients have a right to expect that information about them will be held in confidence by the health professionals who care for them.
- The National Cancer Outcomes and Services Data Set (COSD) for England was introduced in January 2013.

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CHAPTER 6

INTRODUCING MOLECULAR BIOLOGY OF HEAD AND NECK CANCER

Nikolina Vlatković and Mark T. Boyd

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SEARCH STRATEGY

The data in this chapter are based on a PubMed searches including the following Medical Subject Headings (MeSH) and keywords: head and neck neoplasms, carcinoma, squamous cell, molecular biology, genome, papillomaviridae and tumour virus infections.

The rule is, jam to-morrow and jam yesterday—but never jam to-day.

Lewis Carroll, *Through the Looking-Glass, and What Alice Found There*

BACKGROUND – INTRODUCTION TO MOLECULAR BIOLOGY

Cancer is a genetic disease. Molecular biology permits the analysis of genes and their function and offers the chance to understand the information we can read in the genome and to predict the consequences for biological and pathological processes.

What is molecular biology? More importantly, why should a clinician or surgeon be interested in it – indeed, should they be at all? The *Oxford English Dictionary* defines molecular biology as 'the branch of science concerned with the formation, organization, and activity of macromolecules essential to life (nucleic acids, proteins, etc.)'. Many diseases arise from errors in biochemical processes (diabetes, for example), and many of these are due to genetic changes or inherited polymorphisms or mutations (cystic fibrosis, for example). (Polymorphism is a common (>1%) variant allele, cf. mutation or mutant allele: a rare <1% or acquired somatic change in nucleic sequence, usually but not always in the coding sequence of a gene.) Moreover, many of the modern treatments for disease, such as some of the monoclonal antibody drugs (mAbs), such as cetuximab (Erbitux®), nivolumab (OPDIVO®) and adalimumab (HUMIRA®) used to treat diseases including cancer and rheumatoid arthritis,[1–3] have been generated using molecular biological techniques (DNA cloning and sequencing). Thus it seems obvious that to understand disease, and to understand many of the treatment options, requires some level of understanding of molecular biology.

If we had tried to write this chapter only 10 years ago, there would have been some amazing technology and some wonderful insights into the nature of the disease, but whilst molecular biology promised much, it had yet to deliver substantially in the clinic, hence the quotation from *Alice in Wonderland* that starts this chapter. Happily that situation is no longer the case, and molecular biology has enabled the development of novel treatments for many types of cancer that are having a dramatic impact on patients, albeit often coming with a heavy financial burden. In the UK, in 2015–16, six of the seven most expensive hospital prescriptions for NICE-approved drugs were produced using molecular biological techniques (either as mAbs or recombinant peptides) and cost the system approximately £1.3 billion. This also highlights the fact that the rate of change is now overwhelming. At the time of writing there are 67 US Food and Drug Administration (FDA)-approved mAbs and in the region of 400 at various stages of testing and development.

Molecular biology is impacting on many aspects of clinical medicine, but for several reasons it has a special relevance to oncology. Essentially this is because cancer is fundamentally a genetic disease, or perhaps it is better to say that cancer is a disease of our genes. No gene

mutations = no cancer, even when a virus is involved as a causative agent! So the use of the technology of molecular biology to analyze tumours has followed hot foot upon the advances in molecular technologies. In the middle of the second decade of the twenty-first century, technology provides us with the potential essentially to identify all of the mutated genes in a biopsy of tissue from an individual tumour site. (There are even tests that reveal their answers in hours, such as One-Step Nucleic Acid Amplification (OSNA), permitting peri-operative information such as nodal involvement to be provided to surgeons.)[4]

From this it follows that if we could understand the function of the mutated genes and how alterations of these impacted on cellular processes, then we could predict the behaviour of the tumour both in terms of its growth and its progression and even how it will respond to a given therapy. However, tumours arise in an individual body, and so the same genetic information, that of the host or patient, should also be able to inform us about the way the patient's body will react to the tumour. So, the potential exists to have a high-resolution image of both the tumour and the body in which it arises, and thus potentially to understand how the tumour will behave, and how the body will respond to that. This particular level of understanding has not yet been reached, but it is clear that the potential is real and seems likely to be substantially achieved sometime during the next decade or so.

In many healthcare systems, there are other limitations to exploiting state-of-the-art technologies, but even for those without access to the very latest technology it remains possible, and increasingly clinically important, to obtain information from molecular analyses that are already being used as part of the routine diagnosis and stratification of patients, with immunohistochemistry for p16 being a good example of a biomarker with particular significance in oropharyngeal squamous cell carcinomas (OPSCC).[5–7]

The aim of this chapter is to review some of the available knowledge and to try to explain the ideas behind our molecular understanding of the basis of cancer, which is also the basis for understanding new diagnostic and therapeutic approaches

We will first briefly mention the technology, then review in more detail the fundamental process of carcinogenesis as it is understood at a molecular level, including how mutations and alterations arise. (For a more detailed treatise on the molecular basis of cancer, both editions of *The Biology of Cancer* by Robert A. Weinberg are highly recommended.)[8, 9] We will then summarize some of the molecular pathways that have been most commonly identified to be altered in head and neck cancers. This will entail a brief discussion of some of the critical tumour suppressors and oncogene networks that are known to harbour mutations and we will briefly describe the normal function of these and the consequences of the observed tumour alterations. Then we will briefly discuss some of the applications of this information and lastly the challenges and limitations facing the effective use of this information for patient benefit.

MOLECULAR TECHNOLOGY

As a practical subject, molecular biology was born following the discovery of restriction endonucleases, enzymes that could cut double stranded DNA at defined sites by recognizing specific sequences in the DNA.[10] The next major developments included the invention of a means to sequence DNA (most often by the di-deoxy sequencing method invented by Fred Sanger)[11] and a process to amplify specific sequences of DNA (the polymerase chain reaction invented by Carey Mullis).[12] However, our understanding of head and neck cancer has been revolutionized by so-called next-generation sequencing of whole genomes and exomes. These technologies vary and have been developed in parallel by several companies. The two most commonly used technologies, Illumina/Solexa and SOLiD, have been used to generate enormous quantities of data. Both approaches enable a high depth of sequence coverage, which is particularly important for studies of cancer since the tumour biopsy may contain a mixture of normal and tumour tissues and, moreover, due to the heterogeneity of cancers, there may be many clones with some common and some distinct mutations. In addition to high depth of coverage sequence analysis, it is now possible to examine the transcriptome (the mRNA products of the genes being actively transcribed) in greater detail and more quantitatively using RNA-Seq.[13] In addition, the application of RNAscope™ is beginning to impact on the analysis of fixed tissue biopsy sections. In particular, this has been used for the detection of human papilloma virus (HPV) gene expression.[14, 15] Much of what we now know about head and neck cancer molecular biology has been generated in the last few years by next-generation sequencing, as will become clear later.

THE MOLECULAR BIOLOGY OF HEAD AND NECK CANCER

Introduction to cancer molecular biology

Cancer is essentially a disease caused by genetic modifications of the information content of the genome such as base mutations and translocations or other chromosomal rearrangements. Indirect effects resulting in altered gene regulation through epigenetic alterations that affect chromatin structure and gene expression may also occur and are important factors in the development of cancer. In all cases, the carcinogenic events typically affect the function of a subset of critical genes regulating processes such as cell survival, proliferation, invasiveness and interactions with the host (the hallmarks of cancer, see **Figure 6.1**). Mutations may be inherited or acquired as somatic mutations (see **Figure 6.2**). However, unlike cancers of the colon and breast, there are no common inherited cancer syndromes that lead to head and neck cancer. Whilst individuals with the rare autosomal recessive disease Fanconi anaemia that affects approximately 3/1 000 000 individuals worldwide[16] do display an increased risk of developing cancers of the head and neck,[17] none of the genes

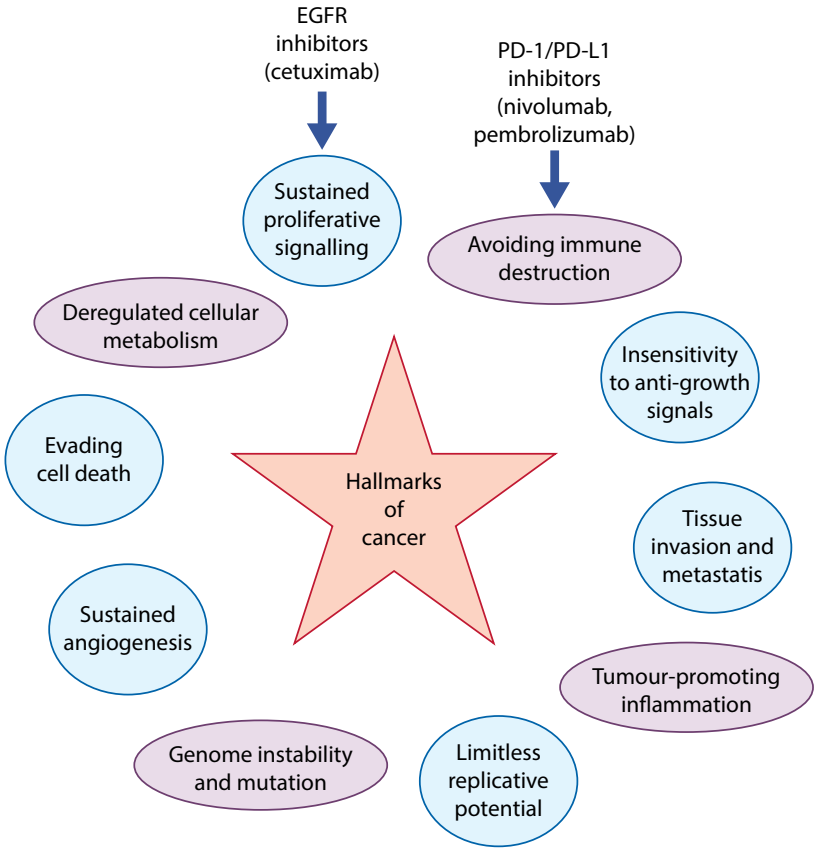
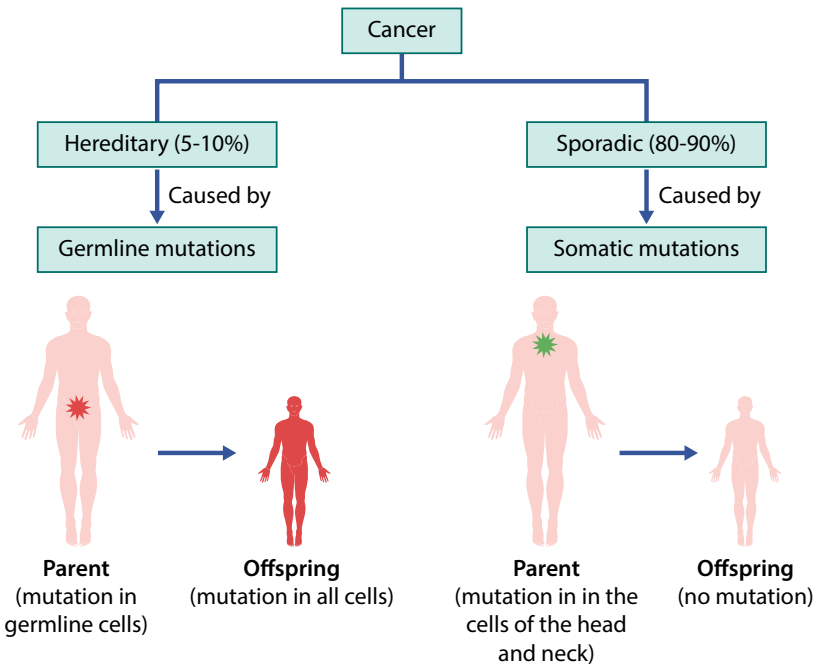


Figure 6.1 The hallmarks of cancer. The illustration shows the six originally proposed hallmarks in addition to the two emerging ones – avoiding immune destruction and deregulating cellular metabolism – and also the two enabling characteristics – tumour-promoting inflammation and genome instability and mutation. Also indicated are drugs targeting some of the hallmarks that are currently in use for the treatment of head and neck cancer (red). Adapted from Hanahan and Weinberg.[79, 80]



- Occur in germline cells: oocytes and spermatozoa
- Are heritable
- Cause cancer family syndromes (e.g. Fanconi anaemia or Li Fraumeni syndrome)

- Occur in non-germline tissues (e.g. head and neck)
- Are not heritable

Figure 6.2 Somatic versus germline mutations. Germline mutations occur in germline cells: oocytes and spermatozoa. They are heritable, and offspring of a person with a somatic mutation will have the same mutation in all cells of their body (e.g. *BRCA1/2* or *RB*, tumour suppressor genes, indicated in red). This increases their chance of developing cancer because only one additional mutation is required to completely inactivate the gene in question (Knudsen's two-hit hypothesis), since most tumour suppressor gene mutations are recessive at a cellular level. Sporadic mutations can occur in any cell in the body (e.g. head and neck cells, indicated in green), spontaneously or as a result of carcinogen exposure. These mutations are not passed onto the offspring unless, by chance, such a mutation occurs in a germline cell. Most cancers are sporadic and are caused by accumulation of somatic mutations. The figures for sporadic and hereditary incidence are for cancers in general. The contribution to head and neck cancer incidence from inherited cancer syndromes is negligible.

implicated in the different complementation groups of this disease have been found to be mutated in sporadic head and neck cancers.[18] (Complementation groups is a genetic term for a situation in which mutations in different genes can cause the same phenotype – in this case, a disease. The term derives from the genetic test for this; if matings between two affected individuals produce healthy offspring, then the mutations cannot be in the same gene. Of course, this only works for a recessive trait.) Other inherited cancer syndromes, including Lynch-II syndrome (genes most commonly implicated include *MSH2, 6* or *MLH1*), Bloom syndrome (inherited mutations in the *BLM* gene), xeroderma pigmentosum (associated with defects in DNA repair genes: *XPC*, *ERCC2* and *POLH*), ataxia telangiectasia (associated with mutations in the *ATM* gene), and Li-Fraumeni syndrome (mutations in the *TP53* and *CHEK2* genes), have also been found to display an increased risk of head and neck cancers.[19–24] However, only the *TP53* and *CHEK2* genes (and the latter only very rarely) have been found to be mutated in sporadic head and neck cancers, and thus none of these syndromes appear to be major contributors to patient numbers or to a better understanding of the disease head and neck cancer.[18] In 1953, Slaughter et al introduced the concept of 'field cancerization' in oral cancers.[25] This notion can now be understood for head and neck cancers at a molecular level, since we know that these cancers are essentially diseases of sporadic mutations arising through a process of sequential mutations and clonal selection. As mutations arise and the populations of cells harbouring the mutations expand with some ultimately becoming cancers (see **Figure 6.3**), populations of cells that arise early on, do not disappear, but may continue to survive and proliferate, ultimately occupying areas outside that of the cancer.[26] These cells can spread and create the 'fields' of abnormal cells harbouring some critical mutations that may provide the raw material for subsequent primary tumours if not removed or killed by treatment. To understand cancer properly at a molecular level, it is necessary to understand the biological process of evolution through natural selection, since the same forces of mutation and selection acting on individual cells harbouring genetic alterations drive the evolution of a tumour during cancer development. **Figure 6.3** illustrates the process of evolution of malignant cells from normal cells through the acquisition of critical genetic alterations that occurs in cases of sporadic carcinogenesis. As cells acquire mutations, the key issue from a cancer perspective is whether any of the mutations that arise by chance in an individual cell provide a selective survival, or clonal advantage (often referred to somewhat imprecisely as a growth advantage or more correctly as a proliferative advantage). What this means is that cells that acquire characteristics that enable that cell, and all of the daughter cells derived from it, to compete more successfully with the surrounding cells and thus have a selective advantage leading to these cells gradually increasing in number. Eventually such cells can proliferate sufficiently to form a pathologically detectable tumour. Since the causes of the mutations in different types of cancer can vary, we will first look at the processes promoting carcinogenesis in head and neck cancers (when we refer to head and neck cancers we mean squamous cell carcinomas of the head and neck). Then

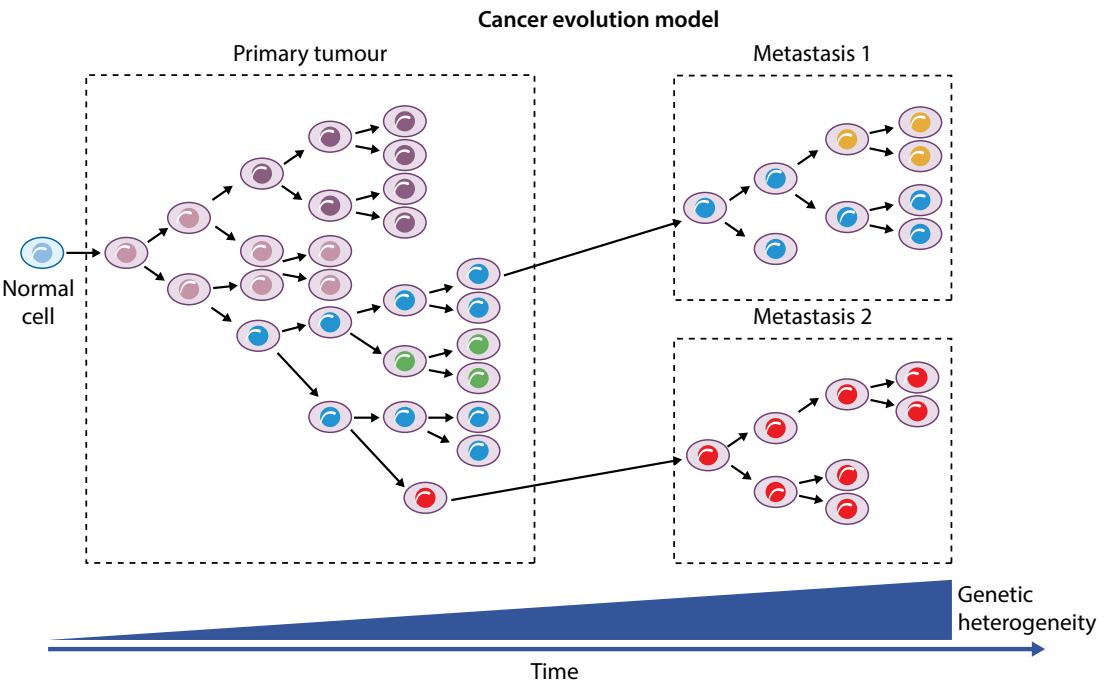


Figure 6.3 Model of cancer evolution. A normal cell (cell with a pale blue nucleus) acquires the initiating somatic mutation giving rise to the founder clone (lavender nucleus). Accumulation of additional mutations will lead to cancer heterogeneity represented by subclones of cells with purple, blue, green and red nuclei. Some of these subclones will acquire metastatic potential (blue and red nuclei) and form metastatic sites (Metastasis 1 and Metastasis 2). Additional mutations can be acquired at any time including post-metastasis (gold nucleus in Metastasis 1). Adapted from Caldas.[27]

we will look at the specific genes that are most frequently altered in head and neck cancers and briefly how these alterations contribute to the disease process.

Mutagenic events, viruses and epigenetic modifications

DNA damage occurs every day in our cells and depending upon the type of damage the frequency can vary from as few as ~10 double stand breaks per cell/day up to ~10^4 bases altered by oxidative damage per cell/day and similar levels of replication errors and single strand breaks.[28] Importantly, much of this DNA damage is repaired and therefore does not lead to stable alterations or mutations. However, DNA damage leads also to mutations being established each day when the damage is not successfully repaired. The most common sources of this DNA damage include normal biochemical processes such as the production of reactive oxygen species (ROS) generated by oxidative phosphorylation through the electron transport chain.[29, 30] Of particular interest for cancers are agents that increase the rates of DNA damage and resulting mutations and thus increase the likelihood of carcinogenesis. In head and neck cancers there are three broadly distinct processes promoting the genetic changes that lead to cancer:

1. Mutations arising from exposure to chemical carcinogens (especially from tobacco smoke and alcohol)
2. Infection by oncogenic viruses (specifically oncogenic strains of HPV), typically leading to loss of tumour suppressor gene (TSG) function
3. Epigenetic modifications, typically leading to loss of TSG expression.

At the present time, the vast majority of data derive from studies from North America and thus the impact of betel quid and asbestos exposure are not being captured by large scale sequencing initiatives, and therefore the undoubted impact of these in some geographical areas remains to be determined by genomic studies.[31, 32]

MUTAGENIC EVENTS

Probably the most significant mutagenic events are those caused by environmental carcinogens, because they affect the most patients and result in cancers with poorer outcomes. The two primary sources of these carcinogens for head and neck cancers are tobacco smoke and alcohol. A critical feature of carcinogenic chemicals is that they often produce chemical modifications, typically of the nucleic acid bases, for which no specific repair pathway exists. This is hardly surprising since the variety of different chemical adducts that smoking alone can cause may exceed one hundred (tobacco smoke contains approximately 50–60 carcinogenic compounds that may display multiple effects on the DNA).[33–35] In contrast, the oxidation of one of the DNA bases, guanine, to 8-oxo-guanine by the endogenous production of ROS – one of the most common chemical modifications of DNA to occur – can be repaired by base excision repair (BER) mechanisms initiated by an enzyme that specifically recognizes this common lesion: 8-oxoguanine glycosylase (OGG1).[36–38]

Alcohol consumption is another major source of risk for developing head and neck cancer.[39–42] Although alcohol may not be chemically as complex a carcinogen as tobacco smoke, the interactions of alcohol with the body are highly complex, ranging from the provocation of an inflammatory response, to mutagenic and epigenetic effects. Alcohol is readily metabolized to acetaldehyde, which is a genotoxin.[43] While most alcohol will be metabolized in the liver, there is good evidence that alcohol is also metabolized in the oral cavity and in the oesophagus.[44, 45] In the oral cavity, the concentrations of acetaldehyde resulting from local alcohol metabolism are estimated to be equivalent to concentrations that have been shown to be mutagenic *in vitro* and, potentially worryingly, this can be achieved by drinks ranging from a single sip of a strong liquor to gargling with an alcohol-containing mouthwash.[46, 47] As with tobacco smoke, the details of alcohol promoted carcinogenesis in the head and neck are too complex to discuss in detail in this chapter. However, to give some idea of the complexities, there is also evidence of carcinogenicity that is not due to the classical ethanol metabolism described above, but rather to additional carcinogenic effects of acetaldehyde that already exists in alcoholic drinks.[48] Further complicating our understanding of this process and the link between alcohol and head and neck cancers is the fact that laryngeal cancer is linked with alcohol as a risk factor,[49–51] but the larynx seems an unlikely site to be directly affected as in normal swallowing action, the alcohol will not come into direct contact with internal laryngeal structures.

Of considerable importance is the interaction between tobacco smoking and alcohol, with several reports suggesting that the interaction leads to a greater than additive effect.[52, 53] It remains unclear how these processes might act synergistically, although it has been suggested that concomitant exposure may alter rates of uptake of some carcinogens and *in vitro* studies support the existence of synergy.[54, 55]

VIRUSES

In the past decade, it has become apparent that a specific subtype of head and neck cancer, with a different biology/molecular biology and significantly different clinical behaviour,[56] has been on the increase. The incidence of OPSCC has risen sharply and this has been particularly apparent in more developed countries.[57–62] This increase has been a surprise, since the smoking incidence has followed a downward trend in most of the developed world,[63] and thus the increase has been observed in the context of a generally stable or even reducing incidence of most head and neck cancers.[64] The most obvious characteristic that distinguishes the vast majority of these patients with OPSCC is the presence of viral DNA derived from the human papilloma virus strain 16 (HPV-16).[57, 65] HPV has long been known as the causative agent of cervical cancers, and so a robust understanding of the oncogenic role of

the virus has been developed.[66] HPV is a double stranded DNA virus (dsDNA); that is, it has a genome that exists as double stranded DNA, and many such viruses (examples include adenoviruses and polyomaviruses) have a strategy to ensure that the infected cell provides the DNA replication machinery needed for viral replication by promoting progression of the cell cycle into S-phase[67] in HPV infection (this involves viral oncoproteins E6 and E7, which are discussed in more detail below). Detailed sequence analysis[18, 68, 69] has shown that HPV+ tumours have fewer mutated genes than similar site of origin HPV– tumours and critically that there are different mutational profiles in HPV+ and HPV– cancers, which may well have important consequences for tumour responses to treatment.[18]

EPIGENETIC MODIFICATIONS

Epigenetic modification of gene expression and function is another major mechanism that promotes cancer in the head and neck. There are many different types of epigenetic changes but the most commonly observed ones with strong links to cancer are the methylation of cytosine residues at so-called CpG islands in the promoter regions of TSGs.[70, 71] (The most common epigenetic modification of DNA is the methylation of cytosine residues to 5-methylcytosine. This occurs predominantly in residues that are 5' to a guanine base, i.e. a CpG site. In many genes the concentration of CpGs is higher in the non-coding promoter regions 'the islands'. Typically, increased methylation of cytosines in CpG islands results in reduced gene transcription; epigenetic silencing.) For example, in head and neck cancers, *CDKN2A (*$p16^{INK4A}$) hypermethylation has been observed to be associated with reduced overall survival in population-based studies.[72–74] Although the enzymes that carry out the methylation of cytosine bases are well known,[75] it is unclear what determines whether a gene will become hyper- or hypo-methylated during the lifetime of an individual. Dietary folate may be one factor, since it ultimately provides the single carbon (i.e. methyl groups) units, but the links between folate levels in diet and gene methylation are complex and often counter-intuitive.[76–78] Some of the genes that are altered in cancers (see below) impact on epigenetic processes, but for the time being, it seems that whilst epigenetic modifications arise, we are not able to say what causes this.

Molecular pathways involved in head and neck cancer

In a recent study from The Cancer Genome Atlas (TCGA), critical and comparatively common mutations were described in 30 genes with mutation frequencies ranging from as high as 80% to as low as 0% for the same gene (this may look like an error, but the gene might be commonly mutated in HPV+ and not mutated in HPV– disease or vice versa), depending on HPV status of the cancer.[18] (HPV+ = HPV positive, i.e. HPV promoted disease, not simply harbouring some HPV DNA; HPV– = HPV negative disease, i.e. disease not driven by HPV, may contain HPV DNA. Whether the disease is driven by HPV or not depends essentially upon whether or not the viral oncogenes E6 and E7 are expressed. Expression of cellular protein $p16^{INK4a}$ is one surrogate biomarker that is linked with HPV+ disease, but it is not 100% specific. See Chapter 13, Oropharyngeal tumours.) In addition, these analyses demonstrated that the majority of tumours harboured copy number alterations (CNAs) with loss of chromosomal regions in 3p and 8p, and gains of 3q, 5p and 8q being the most common.[18] We now know all of the mutations in the whole genome (or in some cases all of the mutations in exon sequences) from several hundred patients with head and neck cancers from a number of studies,[18, 68, 69] and although there is incomplete concordance between studies with respect to the lists of genes identified and the frequency of gene mutations, there is a strong and largely consistent indication of the most frequent and most critical genetic lesions in head and neck cancers. (Exons are the coding parts of gene sequences, in contrast to the introns, which are non-coding and are removed by splicing of the nascent mRNA.) To understand this complex situation, we can simplify the process of carcinogenesis by considering how mutated or silenced genes affect the 'hallmarks of cancer'.

In 2000, Douglas Hanahan and Robert Weinberg published a seminal paper that has been cited more than 14 000 times, introducing their cancer hallmarks.[79] They described how many of the most common mutations that arise in cancers affect six primary, tumour phenotypes or characteristics:

1. Self-sufficiency in growth signals
2. Insensitivity to anti-growth signals
3. Evading apoptosis
4. Limitless replicative potential
5. Sustained angiogenesis
6. Tissue invasion and metastasis.

The significance of this article is that it has provided a clear framework for trying to understand the often complex molecular interactions that have been detected in cancers. The list was augmented in 2011 by the same authors to include enabling characteristics of cancers and two additional emerging hallmarks:[80]

- Enabling characteristics:
  - genome instability and mutation
  - tumour-promoting inflammation
- Emerging hallmarks:
  - Avoiding immune destruction
  - Deregulating cellular energetics.

As we will see, these characteristics are ubiquitous in cancers and understanding the biology that regulates these processes provides a means to incorporate the complex genetic data being generated by the latest technologies.

In 2011, the year that the hallmarks were revisited, an excellent review of head and neck cancer molecular biology was published, based upon a pre-'omic' view of the disease.[26] Considering the 'hallmarks', we can try

to categorize the most frequently mutated genes according to their known roles in these phenotypes. (Note that human gene symbols are typically capitalized and italicized, whereas the protein is not italicized e.g. *TP53* and *MYC* genes encode p53 and MYC proteins. Other species gene symbols usually only capitalize first letters, for example the *Myc* gene in mice or other mammals.) Genes such as *TP53* (p53), *CDKN2A* (p16INK4a), *CCND1* (Cyclin D1), *PIK3CA*, and *MYC*, which were known to be mutated in head and neck cancers, could be identified as having roles in cell cycle regulation (insensitivity to anti-growth signals), cell proliferation (self-sufficiency in growth signals) and cell survival (evading apoptosis). Note though that many commonly mutated 'cancer genes' have roles that impact on more than one hallmark process. So for example, *MYC* is implicated in self-sufficiency in growth signals, insensitivity to anti-growth signals, evading apoptosis and also in acquiring limitless replicative potential, whilst *TP53* has functions that regulate the insensitivity to anti-growth signals, evading apoptosis, acquiring limitless replicative potential, sustained angiogenesis and loss of function has also been linked to tissue invasion and metastasis.[81] If that isn't sufficient, both *MYC* and *TP53* have also been implicated in the deregulation of cellular energetics (see section). In addition, *TP53* has been famously dubbed the 'guardian of the genome' because of its critical role in suppressing one of the 'enabling characteristics': genome instability and mutations.[82] In contrast some 'cancer genes' only appear to impact on one hallmark phenotype. *CDKN2A* is a critical gene for normal cell cycle regulation since it encodes a protein $p16^{INK4a}$ (often simplified to p16),[73, 83] which is a regulator of cyclin dependent kinases that control cell cycle progression (see **Figure 6.4**). Thus mutations or epigenetic suppression of this gene contribute to loss of normal cell cycle control. On its own, this is insufficient to lead to self-sufficiency in growth signals since normal control is retained by the G1-S checkpoint through the *RB* gene, but is sufficient to produce an insensitivity to anti-growth signals that would stimulate p16-mediated G1-S arrest in cells already stimulated to progress through the cell cycle.[85, 86]

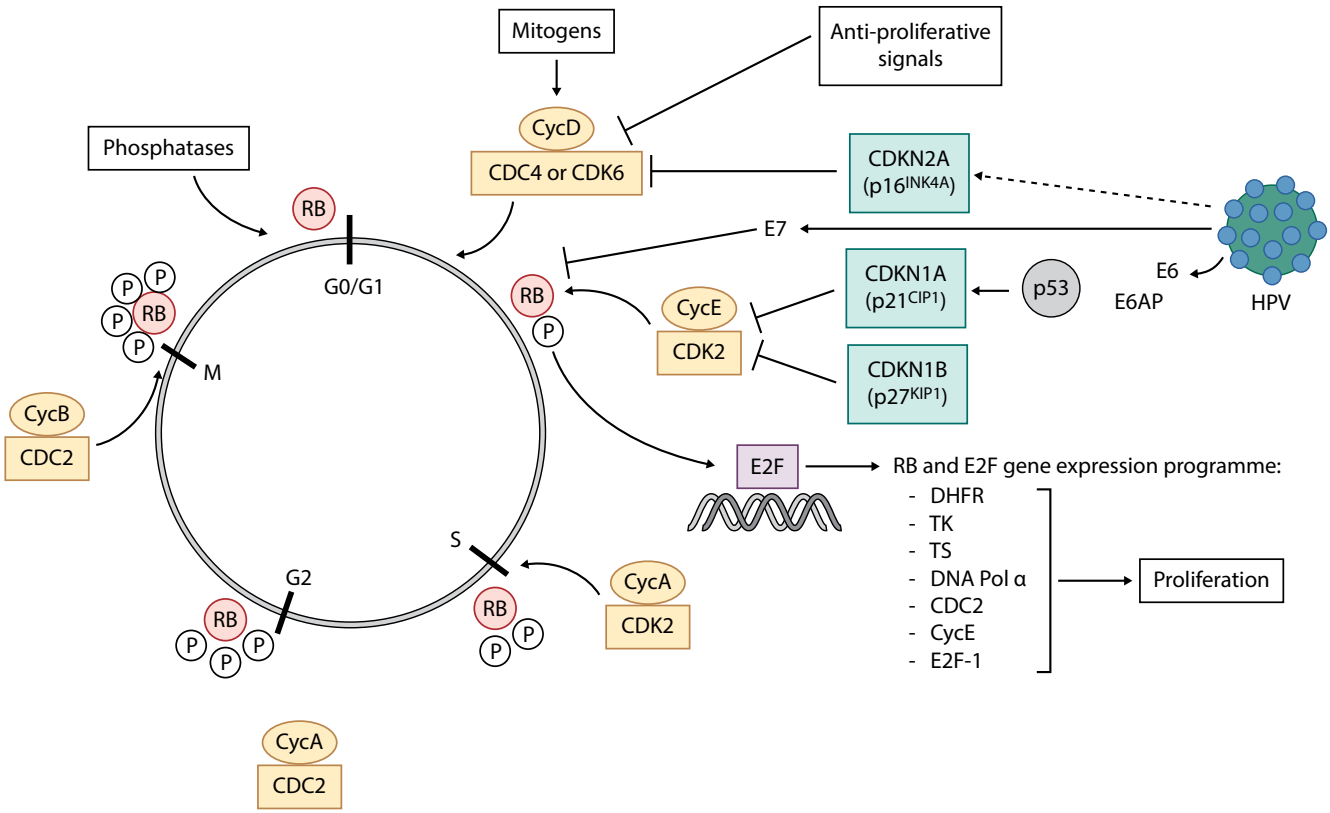


Figure 6.4 Cell cycle regulation. The cell cycle is regulated by coordinated action of cyclins (CycX) and cyclin-dependent kinases (CDKs and CDCs [cell division cycle proteins]) that phosphorylate the RB protein. In the absence of mitogenic signals RB protein is in an under-phosphorylated state and bound to E2F transcription factor rendering E2F inactive. Mitogens activate CycD/CDK4 or CycD/CDK6 complexes that phosphorylate RB protein causing it to release the E2F transcription factor that activates expression of a set of genes that mediate cell cycle progression into S phase, including DNA polymerases and CycE. During the cell cycle RB protein is sequentially phosphorylated by CycE/CDK2, CycA/CDK2, CycA/CDC2 and CycB/CDC2 complexes. Following mitosis RB is de-phosphorylated by phosphatases. Anti-proliferative signals activate $p16^{INK4A}$ protein, encoded by the *CDKN2A* gene that inhibits CycD/CDK4/6 complexes. In response to DNA damage and replication errors p53 protein is activated and up-regulates the transcription of *CDKN1A* gene encoding for CycE/CDK2 inhibitor $p21^{CIP1}$. E6 and E7 proteins, encoded by the HPV genome, target p53 and RB respectively, causing an increase in cellular proliferation. Molecules implicated in head and neck cancer are marked in red. Adapted from Knudsen ES, Knudsen KE.[84]

If the above seems complicated, then the current situation in the now 'omic' era is potentially more daunting because, in the last few years, the amount of genetic data that is available on cancer has been significantly expanded by genomic (and other 'omic') analyses of many different types of cancer. However, whilst the quantity of data has expanded phenomenally, the essential understanding of the disease has not changed too much and in many ways has actually become clearer. Whole genome sequencing (WGS) and whole exome sequencing (WES) of cancer genomes have become fairly routine thanks to the development of so called next-generation or high-throughput/second-generation sequencing technology. As a result, several studies have examined the head and neck cancer genome using a range of different technology platforms,[68, 69] with the most extensive recent studies, already alluded to above, coming from the TCGA consortium.[18]

These studies have confirmed the findings of many older studies that had, for example, correctly identified that the most commonly mutated gene in head and neck cancers was the *TP53* tumour suppressor. In addition, however, these studies identified several genes as harbouring mutations in head and neck cancers that had not been identified by earlier studies.

Another feature of head and neck cancers that has been illuminated by WGS and WES analysis of tumours has been the detection of distinct mutational profiles associated with specific carcinogens or with viral oncogenesis.[18] For example, where smoking and/or drinking contribute to tumorigenesis, then distinctive mutational spectra are observed that are linked with the carcinogen and its mode of action.[87–89] This includes C>A substitutions (identical but complementary to G>T referred to in some of the older of these papers), which are greatly increased in larynx cancers in smokers and it is known that these mutations can be induced by polycyclic aromatic hydrocarbons such as benzo[a]pyrene (for more detail on smoking and mutations induced in cancers, see the excellent recent study by Alexandrov et al[89]). Interestingly, this signature is much less obvious in oral cavity cancers, even though pack years correlate with mutational frequency in oral cancers.[90, 91]

As explained above, epigenetic regulation is an important mechanism contributing to carcinogenesis to the extent that it has been proposed by some as an additional emerging hallmark in cancer development[92–94] (Jones and Baylin, 2002; Muntean and Hess, 2009; Dawson and Kouzarides, 2012). Considerable evidence points to epigenetic alterations playing an important role in the development of head and neck cancers,[70, 95] and data from genomic studies also support this conclusion. For example, the TCGA network found mutations in the histone H3 methyltransferase gene MLL2 in 18% of head and neck cancers studied.[18]

In addition to mutations in genes that catalyse the creation (e.g. methyltransferases) or removal (e.g. demethylases) of epigenetic modifications, other events contribute to this process since gene methylation has been observed to change with time in 'normal' ageing tissues[96] and ageing and cancer are biologically linked processes.[96–99] Whilst it is not known what environmental (such as dietary) factors determine or affect changes in epigenetic regulation, it is clear that some specific genes are modified epigenetically more than others and that this alters the level of expression, typically leading to silencing (down-regulation) of TSGs in head and neck cancers.[70] This occurs in both HPV+ and HPV– carcinogenesis, but the genes that are altered may differ depending on the presence or absence of HPV (see below and also Chapter 13, Oropharyngeal tumours).[18]

The impact of specific genes on the hallmarks of head and neck cancer

Examining the pathways that are affected by mutations in head and neck cancers it is immediately apparent that there are two clearly different patterns of genetic alterations, and which genes are mutated depends to a significant extent upon whether the disease has been promoted by HPV or not.[18, 68, 69] A note of caution needs to be added here: categorization is a human approach to simplifying complex systems; we like to pigeonhole things. But in reality, genes and gene function don't really fit into the neat characteristics to which we want to reduce cancer cell pathways.

LOSS OF CELL CYCLE CONTROL (INSENSITIVITY TO ANTI-GROWTH SIGNALS)

The most common pathway affected in both HPV+ and HPV– disease is loss of normal cell cycle control, which occurs in 90–100% of both types of cancer (genes most commonly implicated: *TP53, RB1, CDKN2A, CCND1, E2F1, MYC, HPV E6*, and *HPV E7*). This pathway primarily regulates the hallmark insensitivity to anti-growth signals, but also impacts upon evading apoptosis and limitless replicative potential and sustained angiogenesis.

TP53

The most common mutations in cancer generally, and in head and neck cancer specifically, affect the *TP53* gene, which has been found to be mutated in approximately 50–60% of all head and neck cancers.[100–109] TCGA network analysis showed that this varied from approximately 80% in HPV– cancers, to 0% in HPV+ cancers.[18] This difference is not surprising, since HPV is oncogenic in part because it can inactivate the p53 protein encoded by the *TP53* gene (discussed below).[18, 110, 111] Importantly, loss of p53 function, typically as a consequence of missense mutations, has been found to be associated with patient outcomes in head and neck cancers with patients harbouring disruptive mutations that compromise p53 function displaying reduced overall survival compared to those with wild-type or non-disruptive mutations.[112, 113] Missense point mutations change the codon such that a different amino acid is encoded (cf. nonsense mutations that introduce a premature stop codon into the sequence). Generally tumour suppressors are inactivated by either nonsense or

missense point mutations, whereas oncogenes can only usually be activated by a very limited number of missense point mutations (not surprisingly, since most amino acid substitutions are more likely by chance to have a negative effect on protein function. Disruptive mutations = non-conservative amino acid substitutions in critical parts of the DNA binding domain. Wild-type = normal, the form of the gene found in the wild, non-disruptive mutations of TP53 = amino acid substitutions that do not disrupt DNA binding or only have a limited effect upon transcription regulations by p53).

The p53 protein functions primarily as a sequence specific DNA binding protein[114] that regulates the expression of a considerable number of genes (estimates range from a few hundred to more than a thousand). p53 protein is a potent inducer of apoptosis (programmed cell death) and so it is not surprising to find that under normal circumstances not one but two genes (*MDM2* and *MDM4*) are responsible for maintaining p53 at low levels in an inactive form. However, following a wide range of cellular stresses, in particular genotoxic stresses (stress induced by damaging DNA), p53 and MDM2 interaction is prevented resulting in an increase in the p53 protein level and a consequent up-regulation of p53 target genes that may mediate cell cycle arrest or apoptosis depending upon the nature of the damage. For more detailed descriptions of the role of p53 and the consequences of loss of p53 function in cancer in general and in head and neck cancer respectively, we direct the reader to Vousden and Lane[114] and Loyo et al respectively.[115]

RB, E2F1 and CDKN2A

RB was the first TSG to be identified and any treatise on the *RB* gene will usually include mention of Alfred Knudsen, retinoblastoma, and the two-hit hypothesis that he proposed.[84, 116, 117] *RB* functions to regulate the G1-S phase transition of the cell cycle and it does this by binding to and inhibiting the activity of a family of transcription factors called E2Fs. As the cell enters the cell cycle at the G1 phase in response to mitogenic signalling (see **Figure 6.4**), the signal passes intracellularly from the activated transmembrane receptor molecules at the cell surface to promote the transcription of cyclins. (Mitogenic signals are induced by mitogens: factors that stimulate mitosis such as growth factors e.g. epidermal growth factor (EGF).) Cyclins that are produced then bind to cyclin-dependent kinases (CDKs) that perform phosphorylation reactions targeting a range of genes, one of these being *RB*.[84] Phosphorylation of RB leads to inactivation of RB since it no longer binds to E2F and as a result, E2Fs promote transcription of their target genes, which *inter alia* includes genes involved in DNA synthesis i.e. S-phase (see **Figure 6.4**). As a consequence, RB not only regulates the cell cycle, but also regulates the cell cycle arrest that is a requirement for terminal differentiation (which is frequently regulated by RB related proteins p107 and p130).[118, 119]

Frequently inactivated in head and neck cancers by promoter hypermethylation, the *CDKN2A* gene encodes two proteins with tumour suppressor activities (p14 [$p14_{ARF}$] and p16 [$p16_{INK4a}$]). p16 inactivation, either through mutation or via promoter hypermethylation has been implicated in many cancers.[120, 121] p16 functions as a negative regulator implicated in many cancers.[120, 121] p16 functions as a negative regulator of G1-S phase progression that acts by binding to and inhibiting the cyclin dependent kinases CDK4 and CDK6.[122] (Some TSGs, including *CDKN2A*, become transcriptionally repressed as a consequence of increased promoter methylation. This can arise as an individual ages, or may be associated with disease. In cancer, changes in methylation of CpG islands (both increases and reductions in methylation) are commonly observed, and loss of *CDKN2A* function either through mutation or increased promoter methylation is a common event affecting more than 50% of HPV– head and neck cancers.)

CCND1 and let-7c

Cyclin D1 is the protein encoded by the *CCND1* gene and this gene has frequently been found to be amplified in a range of cancers including head and neck cancers.[18, 123–125] Cyclins are the critical regulators of the cell cycle and are typically short-lived proteins that are regulated transcriptionally.[126, 127] In the case of cyclin D1, expression is regulated by the MAPK pathway, which is activated following receptor mediated tyrosine kinase activation, by for example, growth factors (EGF binds to the EGF receptor EGFR, see **Figure 6.4**), cyclin D1 associates with cyclin dependent kinases 4 and 6 to promote phosphorylation of target proteins, in particular of the RB TSG leading to its inactivation and cell cycle progression. Thus, gene amplification of *CCND1* provides for constitutively increased cyclin D expression and loss of normal cell cycle regulation at the G1-S checkpoint.[128] let-7c is a microRNA (miRNA) that regulates a number of target genes and that has been found to be down-regulated/deleted in approximately 40% of HPV– head and neck cancers and this was associated with increased *CDK6* expression, anticipated to promote cell cycle progression in combination with *CCND1*.

MYC

The role of the *MYC* gene (also called *c-MYC* or *cMYC* to distinguish it from the viral oncogene originally identified as the v-Myc gene from the avian myelocytomatosis virus and from two other alleles in the human genome: *N-MYC* and *L-MYC*)[129] in cancer has a long and fascinating history due ultimately to the complexity of MYC functions with roles in cell cycle regulation, cell proliferation, cell survival/apoptosis, and more recently identified roles in cancer cell metabolism.[130–135] One of the reasons that *MYC* function has proven difficult to dissect is that MYC has effects on a huge number of genes including *CCND1*, *TP53* and *TERT* (Telomerase – a gene implicated in immortalization of cancer cells).[131, 136] MYC functions as a hetero-dimer to regulate transcription associating with either MAX, leading to activation of gene expression, or with MAD leading to repression of gene expression to regulate control of critical genes that are required for cell

proliferation and survival. More recently it has been found that *MYC* acts not only to regulate the initiation of gene expression similar to many other transcriptional regulators, but also affects other aspects of transcription and post-transcriptional processes such as modulating the stability of newly synthesized RNA molecules and through these additional activities MYC has been revealed to exert an ever greater impact on gene expression.[137] Amplification of the *MYC* locus occurs in over 10% of HPV– cancers, leading to increased MYC signalling and thus promoting cell survival and proliferation.

HPV E6, E7 and E2F1

Human papilloma viruses are doubled stranded DNA viruses that require the host cell DNA replication machinery for viral genome replication.[138] WGS and WES analyses reveal clear differences in the patterns of genetic alterations between HPV+ and HPV– head and neck cancers (note that the vast majority of HPV+ head and neck cancers are derived from the oropharynx).[18, 68, 69, 74, 115] HPV encodes two critical onco-proteins: E6 and E7 that promote S-phase progression in infected cells (see **Figure 6.4**). Together these viral oncogenes inactivate two TSGs, *TP53* and *RB* respectively,[139] with the consequence of promoting S-phase progression in cells.[138]

Normally, this leads to viral DNA replication, and virion assembly and production, which may also lead to cell death. Rarely however, the infection can become abortive, either as a result of recombination leading to integration of part of the viral genome into the host cell genome or as result of the effects of E6 and E7 expressed as episomal genes in a cell that therefore fails to continue to differentiate preventing late gene expression.[140] (Episomal DNA is DNA that can be replicated independently of the chromosomal DNA, typically unintegrated into the genome.) Providing that the infected cell retains both of the oncogenic genes (E6 and E7), this can promote deregulated cell cycle progression through the G1-S checkpoint in the cell, and in all of the daughter cells it produces. The accumulation of a population of cells harbouring such a defect significantly increases the risk of carcinogenesis since two critical TSGs are already inactivated in all of these cells. Another consequence of HPV-mediated TSG inactivation is that fewer additional events are required for tumorigenesis.[68, 69]

E6 functions by binding to the p53 protein and it also binds to a cellular protein E6AP (encoded by the *UBE3A* gene [ubiquitin-protein ligase E3A]), which promotes the poly-ubiquitylation of p53 and thus targets p53 protein to the 26S proteasome for degradation.[141, 142] E7 functions by binding to the RB protein and preventing it from interacting with E2Fs, thus allowing E2F-regulated genes to become transcribed.[143] Recent studies have also identified that binding of E7 to RB also promotes degradation of the RB protein by the ubiquitin – proteasome route.[144, 145] In HPV+ cancers, E6 and E7 expression appear to be ubiquitous, further supporting a role for retaining expression of these to maintain continued cell cycling. In HPV+ cancers, *E2F1* expression was also often increased (in approximately 19% of tumours); this would be expected to result from inactivation of the *RB* and *TP53* genes by E7 and E6 respectively.

Curiously, although we know so much about RB, and we know that loss of RB function resulting from inactivation by HPV E7 protein (see below) leads to upregulation of p16 (*CDKN2A* expression), we do not at the present time know exactly why this is so. Clearly RB represses expression of p16, but since p16 is not known to be a direct target of any of the E2F family of transcription factors that RB suppresses the details remain obscure.

GROWTH AND PROLIFERATION SIGNALLING (SELF-SUFFICIENCY IN GROWTH SIGNALS)

The next most frequently altered pathway identified is the receptor tyrosine kinase (RTK) signalling pathway that regulates the mitogen activated protein kinase (MAPK) signalling pathway. This primarily controls the hallmark: self-sufficiency in growth signals. Genes that regulate this pathway are altered in approximately 60% of head and neck cancers regardless of HPV status (most commonly implicated genes: *PIK3CA, EGFR* and *PTEN* plus *CCND1* and *MYC* listed above).

EGFR, PTEN and PIK3CA

In normal cells the signalling pathway that promotes cell entry into the cell cycle is stimulated in epithelial cells by a soluble ligand mitogen the epidermal growth factor EGF.[146] EGF binds to the extracellular domain of the epidermal growth factor receptor EGFR, a transmembrane receptor protein that has intracellular tyrosine kinase activity (the ability to catalyse the transfer of phosphate onto specific tyrosine residues in substrate proteins). Binding of the EGF receptor ligand causes the receptor to dimerize at the cell surface, which promotes activation of the RTK activity leading it to phosphorylate substrates on tyrosine residues (see **Figure 6.5**). Target proteins that are post-translationally modified by phosphorylation include the receptor itself (auto-phosphorylation) and proteins of the MAPK pathway.[147]

PIK3CA encodes the enzyme phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit (also called p110α), which is the catalytic subunit of a heterodimeric enzyme that catalyses the addition of phosphate from ATP to phosphoinositol lipids that regulate a number of signalling pathways, specifically converting PIP2 to PIP3 and thus activating AKT (also known as protein kinase B or PKB) which plays an important role in cell survival and also regulates several other pathways including ones that control cell movement and metabolism. (PIP2 is phosphatidylinositol (4,5)-bisphosphate; PIP 3 is phosphatidylinositol (3,4,5)-trisphosphate (PtdIns(3,4,5)P3).) This conversion of PIP2 to PIP3 is part of the signalling pathway from RTKs that ultimately controls a wide range of cellular signalling programmes including transcriptional programs that activate progression through the cell cycle and non-transcriptional survival programs such as activating the mTOR pathway that promotes protein synthesis

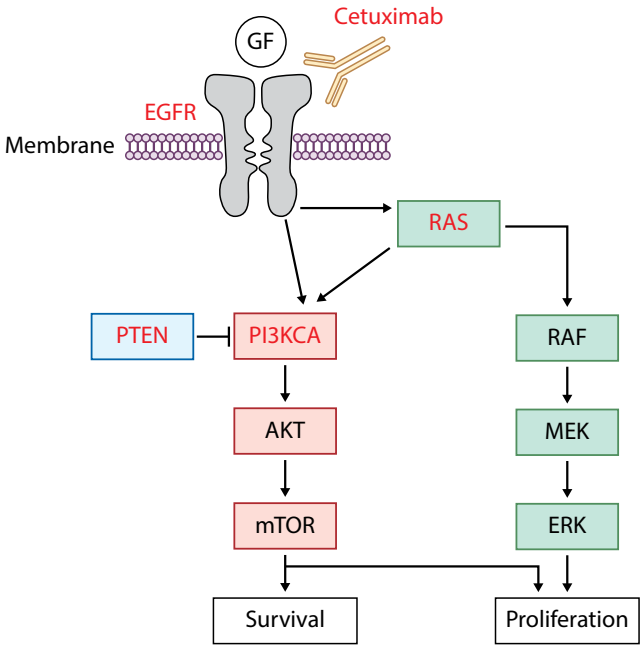


Figure 6.5 Epidermal growth factor receptor (EGFR) pathway. Upon binding of the mitogenic ligand/growth factor (GF) such as EGF (epidermal growth factor), EGFR undergoes dimerization and auto-phosphorylation initiating intracellular signalling via several pathways including the RAS-mediated protein kinase pathway and PI3K/AKT survival pathway. Activation of RAS leads to a signalling cascade involving several mitogen-activated protein kinases (MAPK), including MEK and ERK ultimately leading to cellular proliferation. Activation of the PI3K/AKT pathway is involved in cellular proliferation as well as in apoptosis resistance (survival) via activation of mTOR. PI3KCA is a catalytic subunit of PI3K often mutated in head and neck cancer. Tumour suppressor PTEN is an inhibitor of PI3K/AKT pathway that often undergoes inactivating mutations in head and neck cancer. Cetuximab is a monoclonal antibody that binds to the EGFR that inhibits activation of the EGFR pathway (and recruits antigen directed cell cytotoxicity) and is used clinically for the treatment of metastatic head and neck cancer. Molecules implicated in head and neck cancer are marked in red. Adapted from Ladanyi and Pao.[150]

needed for cell growth as part of the process of promoting cell proliferation and survival.[148, 149] The reverse reaction, converting PIP3 to PIP2, is, interestingly, carried out by the product of the other commonly mutated gene in head and neck cancers, the *PTEN* gene, which encodes an enzyme: the phosphatase and tensin homolog.[151–153]

In head and neck cancers, localized amplifications of the EGFR gene located on chromosome 7 occur in more than 10% of cases and amplification presumably leads to increased signalling from the receptor.[18] Mutations in PIK3CA are common in HPV– cancers (>30% of cases), but are significantly more common in HPV+ cancer (>60% of cases). Typically mutations in PIK3CA were concentrated in three hotspots that are known to lead to constitutive activation of the protein, whereas for PTEN, which functions as TSG to oppose the activity of PIK3CA (and therefore also of EGFR activation), mutations typically inactivate the protein and may be nonsense or missense point mutations. Thus all three of these genes have roles in the same signalling pathway to promote cell growth, proliferation and survival, and mutations in these compromise normal cell signalling and the regulation of cell growth, proliferation and survival.

CELL DIFFERENTIATION REGULATION (LIMITLESS REPLICATIVE POTENTIAL)

The third most commonly affected pathway implicated in between 40% and 60% of HPV+ and HPV– cancers respectively controls cellular differentiation of the squamous epithelium.[18] De-differentiation and the suppression of normal differentiation are prerequisites for immortalization (terminally differentiated cells exit the cell cycle and so do not replicate further) and in the case of HPV+ cancers, arresting differentiation is likely to promote early gene expression at the expense of late gene expression with the predicted consequence of cellular transformation being promoted over viral production.[154] Genes implicated specifically in this pathway include *TP63, NOTCH* and *FAT1*, but also *MYC* which has been shown to upregulate *TERT*,[155] in addition to having a role in cell cycle regulation, cell proliferation and survival.

TP63, NOTCH and FAT1

One of the first new discoveries to come from the early genome wide analyses was that *NOTCH1* (and more rarely other alleles *NOTCH2* and *NOTCH3*) was mutated in a significant percentage of head and neck cancers and moreover that the mutations would be predicted to inactivate NOTCH function.[68, 69] *NOTCH* is best understood because of its role in preventing differentiation of stem cells and through this contributing to their proliferative capacity.[156] Thus mutations that inactivate *NOTCH* would appear to have an anti-proliferative effect and might even promote differentiation. More recently, it has been found that *NOTCH*, and also *FAT1* (also mutated predominantly in HPV– head and neck cancers) negatively regulate the critical *WNT*-gene target β-catenin (encoded by the *CTNNB1* gene) (see **Figure 6.6**).[125, 157] This function might provide an explanation for the presence of *NOTCH* mutations in HPV+ and HPV– cancers (and also for *FAT1*, which is predominantly mutated in HPV– disease). The WNT signalling pathway has been long studied for its role in colorectal cancers (CRCs), and indeed studies of mutations in CRC led to the creation by Bert Vogelstein and his colleagues of what became known as the 'Vogelgram' illustrating the sequence of genetic events and the associated phenotypic changes that commonly occur in CRC as the disease progresses.[158, 159] *TP63* was originally discovered because of sequence homology in its DNA binding domain with that of the p53 tumour suppressor,[160] and subsequent studies have revealed a complex splicing pattern for the gene that can produce p63 isoforms, which display either positive or negative effects on p63 mediated transcription that normally plays a role in squamous epithelial differentiation.[161–163] (Isoforms are two or more forms of a protein that have similar but non-identical sequences (one may be simply shorter), usually

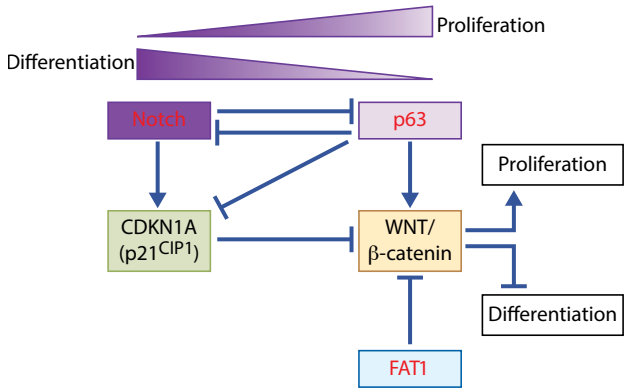


Figure 6.6 NOTCH, p63 and FAT1-mediated regulation of cellular proliferation and differentiation. NOTCH-p63 interplay maintains the balance between cellular proliferation and differentiation. Generally speaking NOTCH promotes cellular differentiation via activation of $p21^{CIP1}$ that suppresses the inhibitory activity of the WNT/β-catenin pathway on the process of differentiation. p63 has the opposite effect by inhibiting $p21^{CIP1}$ as well as by activating WNT/β-catenin pathway that results in an increase in cellular proliferation. In addition, tumour suppressor FAT1 that is frequently inactivated in head and neck cancer inhibits WNT/β-catenin pathway leading to a decrease in cellular proliferation. Molecules implicated in head and neck cancer are marked in red. Adapted from Dotto.[164]

produced by differences in the way that the exons are spliced together or because transcription initiates in different places in the gene.) Thus, changes in splicing would result in altered cellular differentiation and consequently proliferation, with the specific effects depending upon the ratios of expression between splice variants.[165]

CELL DEATH REGULATION (EVADING APOPTOSIS)

The fourth most commonly affected pathway with specific mutations identified in 30–40% of head and neck cancers impacts upon the regulation of cell survival and death, which also impacts upon inflammation and immunity. These disparate responses are partly co-ordinated by the NF-κB pathway.[166–168] Genes implicated in this pathway include *FADD, TRAF3* and *CASP8*, but also the genes *TP53, MYC* and *PIK3CA* already listed above for their roles in cell cycle regulation and survival and cell proliferation signalling. At the present time how these genes contribute to tumorigenesis is not as well understood as the roles of the more extensively studied cell cycle and growth and proliferative pathway genes.

FADD, CASP8 and TRAF3

FADD (fas-associated protein with death domain) has been found to be amplified, predominantly in HPV– cancers, and in several instances, the *FADD* gene was found to be co-amplified with the cyclin D *CCND1* gene, which may suggest an interaction between these.[18] FADD links so-called death receptors such as FAS and TNFR1 (tumour necrosis factor receptor 1), which are transmembrane proteins that connect extracellular signals regulating cell survival and death with the intracellular survival regulatory machinery via NF-κB and also with caspase effectors of apoptosis such as caspase 8 (encoded by *CASP8*).[169] *CASP8* encodes the critical effector caspase 8 for the so-called extrinsic apoptotic signalling pathway and in head and neck cancers. *CASP8* inactivating mutations (found predominantly in oral cavity tumours) were often found associated with wild-type *TP53* (thus p53 is competent to induce apoptosis through the intrinsic pathway but caspase 8 which acts through the extrinsic pathways is not).[170] (There are essentially two main effector pathways for apoptosis: the extrinsic, regulated by cell surface receptor signalling; and the intrinsic, regulated by intracellular stimuli such as DNA damage, hypoxia and metabolic stresses.)[170] *TRAF3* is a member of the TNF receptor associated factor (TRAF) protein family, which mediates signals from transmembrane receptor proteins of the TNF (tumour necrosis factor) such as TNFR1 (which acts via FADD see above). *TRAF3* mutations were almost exclusively found in HPV+ disease, which is interesting since TRAFs have been implicated in anti-viral responses mediated by interferons and several viruses inactivate TRAF proteins.[171, 172]

Inflammation is a known risk factor for promoting carcinogenesis[173, 174] and one of the key regulators of inflammatory responses is the gene *NF-κB*.[175, 176] It seems likely that genes such as *FADD*, *TRAF3* and also *PIK3CA*, *TP53* and *MYC* impact on the regulation of NF-κB activity and thus impact on inflammatory processes.

SUSTAINED ANGIOGENESIS

Tumour hypoxia is a well recognized phenomenon that arises as a consequence of increasing tumour size and poor local vascularization.[177] Hypoxia is linked with radioresistance, and is also an independent predictor of poor prognosis.[178] Tumours typically adapt to combat hypoxia through altering transcriptional programs regulated by the oxygen-sensitive hypoxia inducible factor 1α gene; *HIF1α*.[179, 180] Analyses of head and neck cancer genomes might at first sight appear to reveal only limited genetic evidence of frequent disruption of angiogenic regulatory processes. However, common mutations such as those in *TP53* likely alter angiogenesis; for example, p53 has been reported to regulate expression of angiogenesis suppressor thrombospondin 1 (*THBS1*) and also promotes degradation of HIF1α, and in so doing suppresses neoangiogenesis.[181] In addition, several other genes identified through genomic analyses in head and neck cancers including *FADD*, *TRAF3*, *CASP8*, *PIK3CA* and *MYC* that alter signalling through NF-κB are known to affect angiogenesis[182] (as well as invasion and metastasis, see below), and thus some of the most common mutations that occur in head and neck cancers likely have an impact on angiogenesis.

TISSUE INVASION AND METASTASIS

The ability of cancer cells to invade surrounding tissue and metastasize to distant sites is one of the hallmarks of

cancer (**Figure 6.1**) and is also the leading cause of morbidity and mortality in cancer patients.[80] Metastasis is a complex, multistep process during which cancer cells need to leave the primary tumour site, invade the surrounding tissue, intravasate the lymphatic or vascular circulation, survive in the circulation in order to arrive at the metastatic site where they extravasate and establish a secondary tumour.[183] Epithelial-mesenchymal transition (EMT), a process during which cancer cells acquire mesenchymal phenotype characterized by increased migratory and invasive capabilities, is an integral part of the metastatic phenotype.[184] Several molecular pathways that play a role in metastasis have been identified, including signalling from the TGFβ (transforming growth factor β) pathway that has been shown to be important for EMT in a number of cancers, including head and neck cancer.[185] Indeed, mutations and deletions of *TGFβR2* (transforming growth factor β receptor 2) have been found mostly in oral cavity tumours.[185] In addition, deletions in *SMAD4* (Sma + Mad 4, for 'Mothers against decapentaplegic homolog 4'), a transcription factor that is a member of TGFβ pathway, were identified in particular in HPV–head and neck cancers.[18, 185]

Emerging hallmarks

AVOIDING IMMUNE DESTRUCTION

It has been well documented that the interactions between cancer cells and the surrounding stroma or microenvironment play a role in the initiation and progression of cancer and ultimately determine patient prognosis.[186] Tumour microenvironment consists of a number of components, including extracellular matrix (ECM), blood vessels, immune system cells and fibroblasts. More recently, the immune system and its role in carcinogenesis have come into focus with development of drugs that suppress the ability of cancer cells to avoid destruction by the immune system. In particular, PD-1/PD-L1 interaction inhibitors have shown potential for the treatment of a number of cancers, including lung, metastatic melanoma and kidney cancer.[187, 188] Following positive outcomes in several clinical trials, nivolumab, a PD-1 inhibitor, has been approved by the FDA for the treatment of several cancers including head and neck cancer.[189, 190] In depth analysis of the immune microenvironment has demonstrated that head and neck cancer is characterized by high levels of immune cells infiltration and immunosuppression, regardless of HPV status.[191] In particular, as a result of these studies regulatory T (Treg) and natural killer (NK) cells have emerged as potential therapeutic targets.

DEREGULATING CELLULAR ENERGETICS

As long ago as the 1920s Otto Warburg performed experiments on tumours aimed at determining the metabolic processes used by cells in the tumour, which revealed high levels of glycolysis ('fermentation') as well as respiration typical of normal tissues.[192] However, it was not until the 1950s that more quantitative experiments revealed that tumour cells generate much of their energy from fermentation (i.e. glycolysis) whereas normal cells typically use mostly respiration.[193] This observation has been put to good use in PET-CT using the increased capacity of tumour to uptake a radioactive glucose analogue to image tumours.[194] It seems extraordinary, but it is only in the last decade or so that cancer biology has begun to focus in earnest on the so-called Warburg effect, namely the tendency for cancer cells to obtain substantial amounts of energy from aerobic glycolysis. This effect is so ubiquitous that many are now trying to take advantage of this phenomenon for therapeutic purposes. Many of the genes found altered in head and neck cancers have been implicated in metabolic alterations in cancer cells, chief amongst these being *TP53*,[195] *MYC*[196] and *PIK3CA*,[197] all of which have been shown *in vitro* to modulate cancer metabolic profiles. In the case of *TP53*, studies have already identified potential strategies for therapeutic interventions.[198]

CONCLUDING REMARKS

Ultimately what matters is how the enormous amounts of data now being generated by the research community can be used to impact upon patients, whether it be through developing diagnostics or devising new or more precisely targeted treatments (precision medicine). We now know essentially all of the gene mutations that commonly arise regardless of HPV status, but many of these events present huge challenges for exploitation for therapy. Many of the genes that are activated in cancer cells (oncogenes), have important normal functions in cell growth and proliferation (and survival) and thus selective targeting may prove difficult. Rescuing loss of TSG function is even more challenging. Immunotherapy appears to hold great promise and trials of nivolumab (recently approved by the FDA for treatment of head and neck cancers) and other similar agents are ongoing. Another relatively new area of research that seems likely to lead to novel therapeutic approaches is targeting of tumour metabolism, which is already being used in some other cancers such as renal cancer.[199, 200]

Regardless, what these genomic analyses reveal is that there are identifiable molecular pathways that regulate the key processes, the hallmarks, that are altered in cancers of cell cycle regulation, cell survival and death, cellular differentiation, oxidative stress, immunity and some of these impact also on inflammation, angiogenesis and cell migration (invasion). It seems highly likely that new agents that target aspects of these pathways/molecules will be developed; the problem may be one of availability due to the diminishing returns resulting from the cost of developing so many specialized therapeutic molecules for ever more precisely defined molecular subsets of patients.

KEY POINTS

- Cancer is essentially a genetic disease resulting from an accumulation of somatic mutations (no mutations = no cancer).
- Head and neck squamous cell carcinomas are promoted by carcinogens found in tobacco smoke and alcohol (which act synergistically), or exposure to the HPV (OPSCC), or to other carcinogenic substances such as are found in betel quid.
- Genome wide studies have revealed essentially all of the critical gene mutations that occur in head and neck cancers in North American populations, as well as the changes in gene expression and epigenetic alterations that arise in patients with tobacco smoking/alcohol drinking and HPV-associated tumours (we do not currently have similar detailed data from patients from other high-risk exposure activities e.g. betel chewing).
- The potential exists to obtain genome wide data from individual patient tumours. However at the present time the usefulness of such information is limited.
- Cancer cells display characteristic phenotypes that have been called the 'Hallmarks of Cancer' and we can understand the role of genetic and epigenetic changes in cancer cells in the context of these Hallmarks.
- The most commonly affected cellular genes in head and neck squamous cell carcinomas are: *TP53, PIK3CA, CDKN2A, NOTCH, FADD, let-7c, FAT1, CCND1, PTEN, TP63, EGFR and MYC*.
- In HPV driven disease the viral genes E6 and E7 are critical.

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CHAPTER 7

NASAL CAVITY AND PARANASAL SINUS MALIGNANCY

Cyrus Kerawala, Peter Clarke and Kate Newbold

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SEARCH STRATEGY

Data in this chapter may be updated by a Pubmed search using the generic keywords: 'nasal cavity neoplasms' and 'paranasal sinus neoplasms' but focusing on the diagnosis and management of these conditions.

INTRODUCTION

In this chapter, we discuss the management of malignant tumours that develop in the nasal cavity and paranasal sinuses. Malignant conditions involving the nasal vestibule and external nose are discussed in Chapter 85, Nasal reconstruction.

Sinonasal malignancies are a diverse group of tumours, some of which are unique to the nose. They are uncommon, accounting for less than 1% of all neoplasms. Initially they produce little in the way of symptoms and in the early stages can be misdiagnosed as more common benign conditions such as rhinosinusitis. As a result, the diagnosis is often delayed and only made at a relatively advanced stage when symptoms caused by local disease extension supervene. The average delay between the first symptom and diagnosis is approximately 6 months. By the time of presentation erosion of bone and infiltration of sensory nerves may have produced facial pain and concurrent sensory deficits. Extension of the tumour into the orbit, brain and infratemporal fossa not only produce further symptoms but also have profound implications on treatment and likely outcome in terms of both morbidity and prognosis.

Accurate staging of nasal and sinus tumours remains difficult despite recent advances in endoscopy and almost universal access to refined radiological cross-sectional imaging techniques such as CT and MRI. Current staging systems are only applicable to maxillary and ethmoid sinuses.

Surgery and radiotherapy remain the mainstays of treatment. All treatment regimens inflict considerable morbidity including facial disfigurement, altered mastication and, in some cases, loss of sight. The prognosis for patients with sinonasal malignancies has improved over the last three decades but remains relatively poor compared with other head and neck subsites. Consequently, quality of life issues are of particular importance when considering treatment options, particularly in those presenting with extensive disease.

EPIDEMIOLOGY

Sinonasal malignancies have an incidence of 0.5–1 per 100 000 per year.[1] They account for 0.2–0.8% of all malignancies and 3% of upper aerodigestive tract neoplasms.[2] Most develop in the fifth and sixth decades of life. The incidence in men is twice that of women.[3] The misconception that certain races are more susceptible than others to sinus malignancies is explicable by occupational exposure to carcinogens.[2]

AETIOLOGY

Several carcinogenic compounds have been identified with inhalation of these carcinogens being responsible for around 40% of reported sinonasal malignancies. Foremost among these occupational hazards is exposure to hard woods in the furniture industry. It is thought that biologically active compounds in wood dust impair mucociliary clearance and predispose to carcinogenesis.[4] Acheson et al. reported high rates of nasal cavity and sinus adenocarcinoma in the High Wycombe area and proposed that this was secondary to wood dust exposure.[5] Workers exposed to hard wood have a 70 times increased incidence of sinonasal adenocarcinoma, particularly of the ethmoid sinuses. The UK Government recognizes this as an occupational risk and as such it is a prescribed disease under the 1959 National Insurance Regulations: Reference D6. It remains the duty of a doctor to accordingly inform patients of their rights.

The type of wood is a significant factor. While hardwood exposure increases the risk of developing adenocarcinoma, soft wood exposure is more commonly associated with squamous cell carcinoma (SCC). African mahogany appears to be the most carcinogenic. This wood is often burned by Bantu tribesmen, who have the highest incidence of maxillary sinus cancer in the world. Sinonasal adenocarcinoma that develops in wood-workers has a better prognosis than other nasal adenocarcinomas.[4]

Other occupational hazards include exposure to nickel, which increases risk of developing sinonasal SCC 250-fold. The interval between exposure to nickel and the development of the tumour can be prolonged, with Pedersen et al. reporting a latent interval of between 18 and 36 years.[6] Smoking is also thought to play a role in the development of these tumours, perhaps in a synergistic fashion with wood dust.[4] Other chemicals linked to sinonasal malignancy include chromium, polycyclic hydrocarbons, aflatoxin (found in certain foods and dust), mustard gas and thorotrast (thorium dioxide used in paints for watch dials). Radiation, viral and genetic causes have also been proposed. There is no evidence that chronic sinusitis predisposes to cancer with the incidence of chronic sinusitis in patients with sinonasal malignancies equating to that in the general population.[2]

SURGICAL ANATOMY

The anatomy of the nose and paranasal sinuses is described in detail in Volume 1, Chapter 87, Anatomy of the nose and paranasal sinuses.

General considerations

Sinonasal malignancies spread most commonly by local invasion. The ethmoid and maxillary sinuses are intimately related to the orbit and separated from it by thin bone that is deficient in places to permit the passage of nerves and blood vessels. These anatomical features favour relatively early tumour spread into the orbital contents. The roof of the frontal sinus is similarly thin and this, in combination with perforations in the superior part of the nasal cavity through which the olfactory nerves pass, means that tumours developing at these sites tend to spread intracranially.

In 1933 Öhngren described a line running from the medial canthus of the orbit to the angle of the mandible which he used to separated tumours into two groups, namely those that developed above it and those that developed below it.[7] He suggested that superiorly-based tumours tended to be more aggressive and poorly differentiated, whereas tumours arising inferior to the line were more amenable to treatment and, as a consequence, had a better prognosis. Although this may well be the case, the classification was described before the concept of craniofacial resection was developed. This in combination with the huge advances in radiation oncology that have taken place in the last few decades make Öhngren's suggestion largely of historical interest.

Lymphatic drainage

The lymphatic drainage of the nose and paranasal sinuses is relatively scant. Two lymphatic pathways have been described, the anterior and the posterior. The lymphatics of the anteroinferior part of the nasal cavity and skin of the nasal vestibule drain via the anterior pathway to the first eschelon facial, parotid and submandibular lymph nodes. These in turn drain into the upper deep cervical chain. The remainder of the nose and paranasal sinuses drain through a posterior pathway which runs anterior to the Eustachian tube to first eschelon nodes in the retropharyngeal space and then onwards to the upper deep cervical chain.

PATTERNS OF TUMOUR SPREAD

The advanced stage of tumours at the time of presentation can make their precise origin difficult to determine. Nevertheless, maxillary sinus tumours are the most common (55%) followed by the nasal cavity (35%), ethmoid sinuses (9%) and, rarely, frontal and sphenoid sinuses (1%).

Local invasion

In general, sinonasal carcinomas tend to consume the sinus cavity from which they arise before eroding its bony walls. Periosteum, perichondrium and dura appear to act as a temporary barrier and resist tumour expansion to some extent, a feature possibly explained by the fibroelastic connective tissue component of these tissues.[8] By contrast the bone of the anterior maxilla and orbital floor is very thin and readily destroyed by tumour. Only 25% of maxillary sinus carcinomas are contained within the antrum at the time of presentation.[9] Patterns of local spread are summarized in **Table 7.1**.

Maxillary sinus tumours spread medially from the sinus into the lateral wall of the nasal cavity, laterally into the

TABLE 7.1 Patterns of local spread

Primary site	Anteriorly	Posteriorly	Medially	Laterally	Superiorly	Inferiorly
Frontal sinus	Skin	Anterior cranial fossa, frontal lobes				Ethmoid sinus, nasal cavity
Ethmoid sinus	Skin	Sphenoid, nasopharynx, clivus, pituitary gland	Nasal cavities, cribriform plate	Orbit	Anterior cranial fossa, frontal lobes	Nasal cavity
Maxillary sinus	Cheek, skin	Pterygopalatine fossa, infratemporal fossa, temporal bone, middle cranial fossa	Nasal cavity	Cheek, skin	Orbit	Palate
Sphenoid sinus	Ethmoid sinuses	Clivus, pituitary gland, posterior cranial fossa		Middle cranial fossa, cavernous sinus	Pituitary gland, hypothalamus	Nasopharynx
Nasal cavities	Skin	Sphenoid sinus, nasopharynx		Maxillary sinuses	Anterior cranial fossa, frontal lobes	Palate



Figure 7.1 An advanced carcinoma of the maxillary antrum. The tumour has breached the lateral wall and presents as a swelling in the cheek.

cheek, superiorly through the inferior orbital fissure into the orbit, inferiorly into the palate and posteriorly into the infratemporal and pterygopalatine fossae (**Figure 7.1**).

Tumours that arise in the ethmoid sinus spread medially into the nasal cavity, laterally into the orbit, superiorly into the anterior cranial fossa and inferiorly into the maxillary sinus (**Figure 7.2**).

Frontal sinus tumours extend through the posterior wall into the anterior cranial fossa and frontal lobes, as well as anteriorly into the skin of the forehead and inferiorly into the nasal cavity. Tumours arising in the sphenoid sinus tend to spread laterally into the cavernous sinus and anteriorly into the ethmoids and nasal cavity (**Figure 7.3**).

Regional spread

Lymphatic spread to regional nodes becomes apparent in 25–35% of patients at some time during the course of their disease. Around 10% of patients present with nodal disease, which is usually a marker of locally-advanced disease. The submandibular and jugulodigastric nodes are the most commonly involved. Bilateral lymph node involvement can occur in patients who develop tumours near the midline.

Distant metastases

Distant metastases at the time of presentation are unusual. They develop in around 20% of patients with adenocarcinomas in contrast to just 10% of those with SCCs.[10] When found they are usually associated with local recurrence.[11]



Figure 7.2 An ethmoid carcinoma spreading into the orbit and producing proptosis.

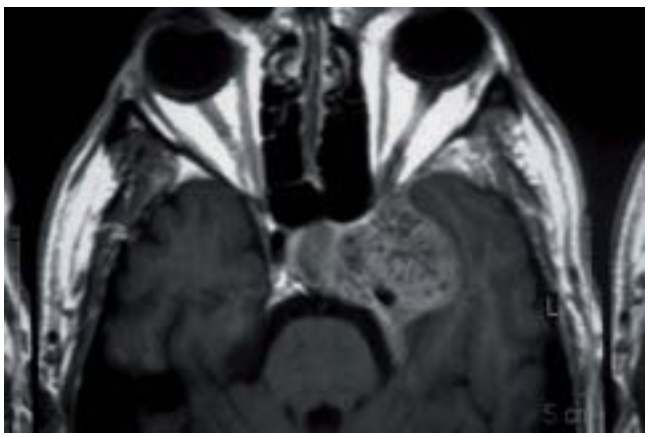


Figure 7.3 MRI of sphenoid tumour that has spread into the cavernous sinus and presented with diplopia secondary to a VIth cranial nerve palsy.

The most common sites for metastases are bone, brain, liver, lung and skin. Unsurprisingly the presence of distant metastases is associated with a poor prognosis except in the small subgroup of patients with metastatic pulmonary adenoid cystic carcinoma (ACC), who can survive for some time if the primary site remains controlled.

STAGING

Staging systems have only been devised for carcinomas of the maxillary sinus, ethmoid sinus and the nasal cavity. These systems are not applicable to mesodermal tumours and have no relevance to olfactory neuroblastoma (OAN) for which separate schemes exist. The TNM classification system for the maxillary sinus (**Figure 7.4**), ethmoid sinus (**Figure 7.5**) and nasal cavity is shown in **Table 7.2**. The staging matrix is presented in **Table 7.3**.[12]

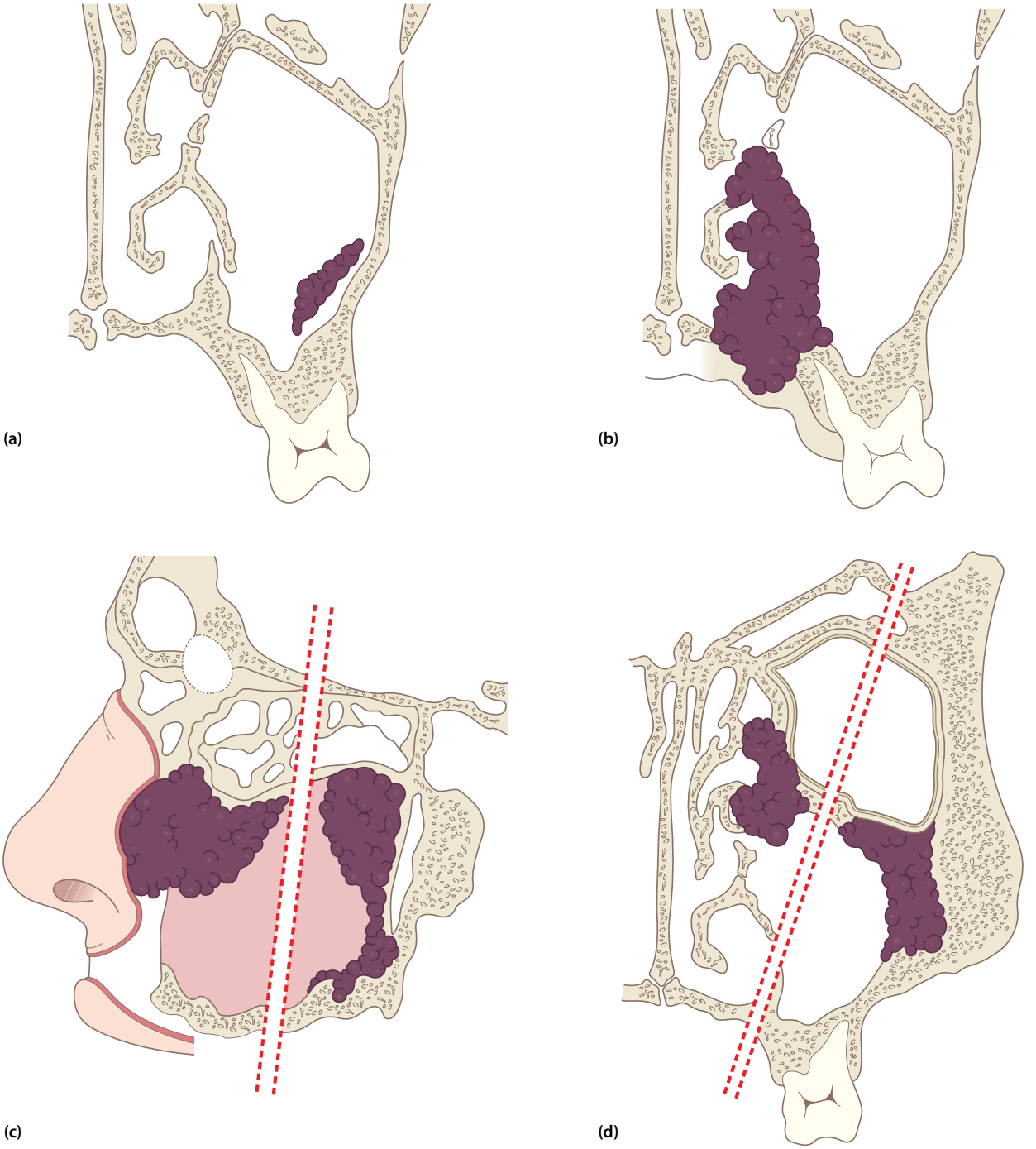
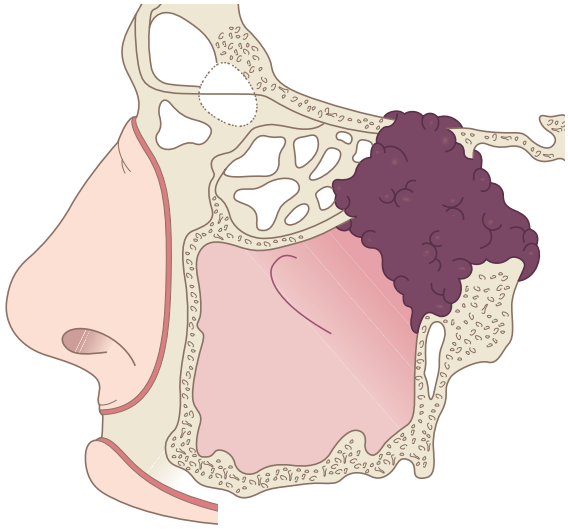


Figure 7.4 TNM diagrams of maxillary sinus carcinoma. **(a)** T1; **(b)** T2; **(c,d)** T3.

(*Continued*)



(e)



(f)



(g)

Figure 7.4 (*Continued*) TNM diagrams of maxillary sinus carcinoma. (e,f,g) T4.

SURGICAL PATHOLOGY

Squamous cell carcinoma

SCC is the most common sinonasal malignancy. The highest incidence is in the seventh decade of life and there is a male preponderance. Most SCCs arise from the lateral wall of the nasal cavity with 50% developing on the turbinates. Two-thirds of septal SCCs are found anteriorly in the region of the mucocutaneous junction. Transformation of Schneiderian papillomas into SCC is a recognized risk. Batsakis reported a 14.6% incidence of SCC in a series of 322 patients with Schneiderian papillomas.[13] Approximately 85% of SCCs are well differentiated tumours. Papillary and exophytic histological patterns are also recognized. It is said that differentiation has little bearing on the ultimate prognosis but this probably reflects the poor overall outcome for these patients and the relative rarity of poorly differentiated forms. Macroscopically some sinonasal SCCs have a polypoid appearance, while others are more obviously fungating, friable and keratinizing.

Adenocarcinoma

Adenocarcinoma accounts for 9% of sinonasal malignancies. Like SCC it too has a male predilection and tends

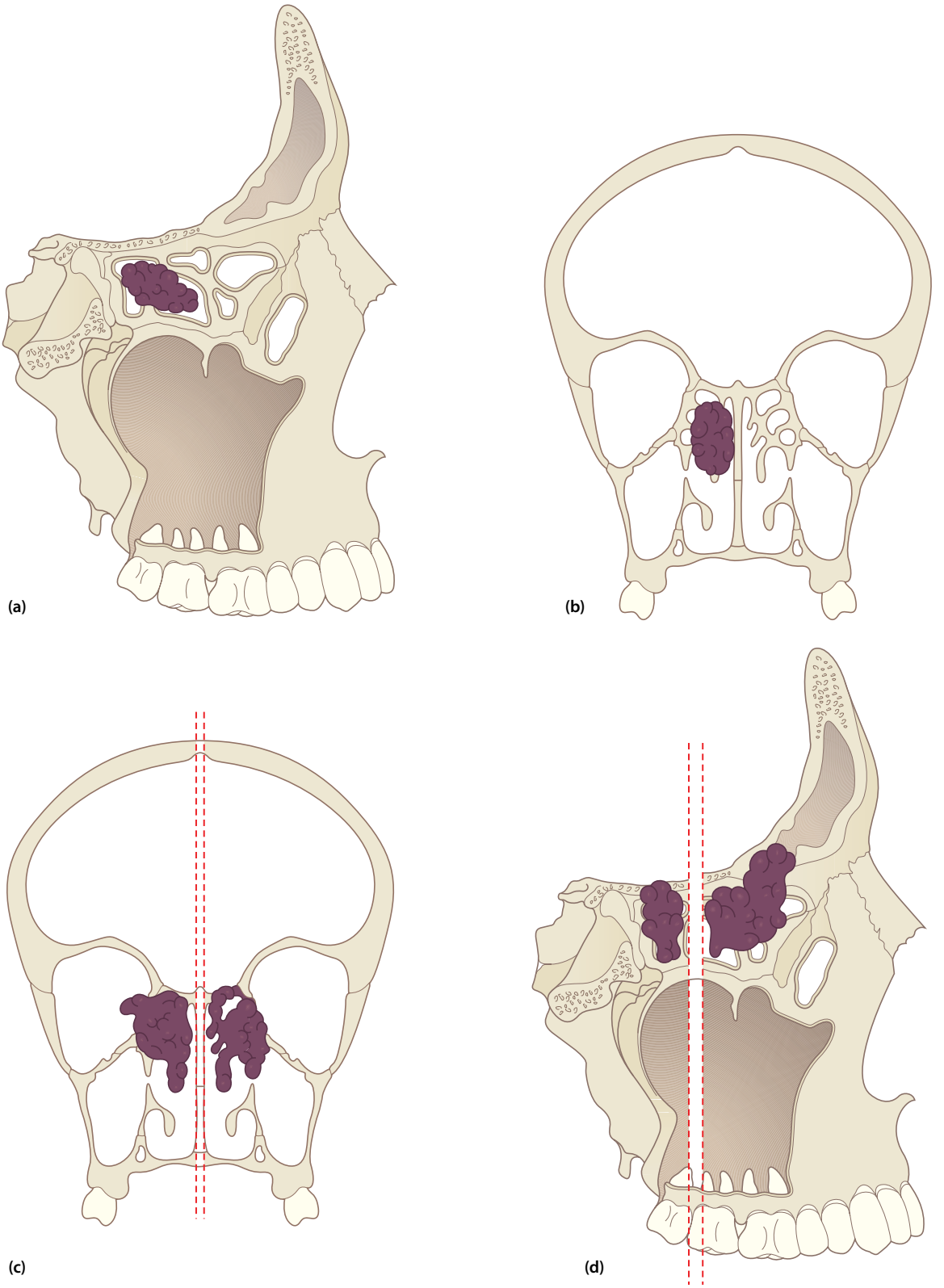
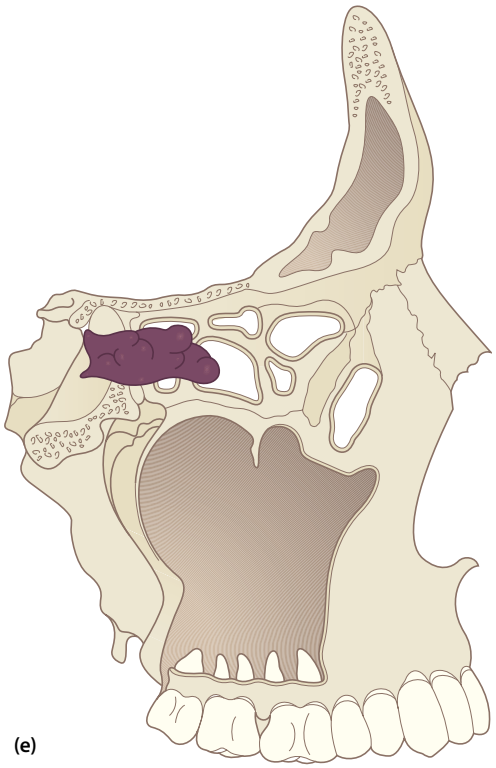


Figure 7.5 TNM diagrams of ethmoid sinus carcinoma. **(a)** T1; **(b)** T2; **(c)** T3; **(d)** T4. (*Continued*)



(e)

Figure 7.5 (*Continued*) TNM diagrams of ethmoid sinus carcinoma. (e) T4.

to affect those in the sixth and seventh decades of life. Adenocarcinomas are generally found in the upper nasal cavity and ethmoid sinuses. They have a slow growth rate and rarely metastasize. Several histological subtypes of sinonasal adenocarcinoma are recognized, namely papillary, sessile, mucoid, neuroendocrine, intestinal and undifferentiated. Papillary adenocarcinomas are the least aggressive form. The intestinal variety is most often associated with woodwork-induced tumours. Sessile and mucoid adenocarcinomas have the worst prognosis.[5]

Adenoid cystic carcinoma

A little less than 5% of sinonasal malignancies are ACCs. As elsewhere ACCs tend to grow slowly but inexorably with early perineurial and vascular spread. All variants of the tumour are seen. The maxillary sinus is the most commonly affected site and patients usually present with a long history of facial pain that can defy diagnosis for many months if not years.

Olfactory neuroblastoma (aesthesioneuroblastoma)

OAN arises from basal cells within the olfactory neuroepithelium. OAN represents less than 5% of all sinonasal malignancies.[14] The incidence of this tumour has a

TABLE 7.2 TNM classification

Stage	Description
Maxillary sinus	
T1	Tumour limited to the antral mucosa with no erosion of bone
T2	Tumour causing bone erosion or destruction, except for the posterior antral wall, including extension into the hard palate and/or middle meatus
T3	Tumour invades any of the following: bone of the posterior wall of the maxillary sinus, subcutaneous tissues, skin, floor or medial wall of the orbit, infratemporal fossa, pterygoid plates, ethmoid sinus
T4a	Tumour invades any of the following: anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b	Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than the maxillary division of V2, nasopharynx or clivus
Ethmoid sinus	
T1	Tumour confined to ethmoid with or without bone erosion
T2	Tumour extends into the nasal cavity
T3	Tumour extends into the anterior orbit and/or maxillary sinus
T4a	Tumour invades any of the following: anterior orbital contents, skin of the nose or cheek, minimal anterior intracranial extension, pterygoid plates, sphenoid or frontal sinuses
T4b	Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx or clivus
Nasal cavity[a]	
T1	Tumour involves one subsite
T2	Tumour involves two subsites or ethmoid
T3	Tumour extends into the anterior orbit and/or maxillary sinus
T4a	Tumour invades any of the following: anterior orbital contents, skin of the nose or cheek, minimal anterior intracranial extension, pterygoid plates, sphenoid or frontal sinuses
T4b	Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx or clivus.

[a] Within the nose, four subsites are recognized, namely septum, floor, lateral wall and vestibule.

TABLE 7.3 Staging matrix

Stage			
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T1/2	N1	M0
	T3	N0/1	M0
IVa	T1/2/3	N2	M0
	T4a	N0/1/2	M0
IVb	T4b	Any N	M0
	Any T	N3	M0
IVc	Any T	Any N	M1

bimodal distribution with peaks at 20 and 50 years of age. Unlike most sinonasal malignancies it is more common in women than men. OAN is a neuroendocrine tumour capable of causing paraneoplastic syndromes by secreting peptides. Patients with OAN causing Cushing's syndrome, inappropriate antidiuretic hormone secretion or hypertension produced by vasoactive peptides have been reported in the literature.

OAN is one of a group of 'small round blue cell tumours' and needs to be differentiated from sinonasal undifferentiated carcinoma (SNUC), neuroendocrine tumour, small cell carcinoma, rhabdomyosarcoma and lymphoma. Expert histopathological review is therefore recommended. OAN typically expresses neuroendocrine markers (neurone specific enolase, synaptophysin and chromogranin) and is negative for keratins. S-100 may show positivity around the periphery of the tumour only, helping to differentiate OAN from sinonasal melanoma. Negativity for vimentin, actin and desmin excludes rhabdomyosarcoma.[15]

Hyams et al.[16] developed a four-point histological grading system for OAN based on such features as the degree of differentiation, the tumour architecture, mitotic index, nuclear polymorphism, fibrillary nature of the matrix and tumour necrosis. This tumour can either be extremely aggressive (grade 4) or relatively indolent (grade 1). There are little data for the role of cytogenetics in the diagnosis of OAN.

Survival for more than 20 years is not unusual while others are less fortunate, succumbing to highly aggressive disease with widespread metastases within a few months.[17] Up to 25% of OAN invade the dura and anterior cranial fossa. In 5% of patients metastases to cervical nodes are evident at the time of presentation and distant metastases are already present in around 7% of patients.[17]

OAN can often be predicted from imaging characteristics, based on its location focused on the cribriform plate (**Figure 7.6**).

Disease-specific staging systems have been devised for OAN. The most useful and commonly used systems are those attributed to Kadish et al,[17] Morita et al.[18] and Dulguerov and Calcaterra[19] (**Tables 7.4** and **7.5**).

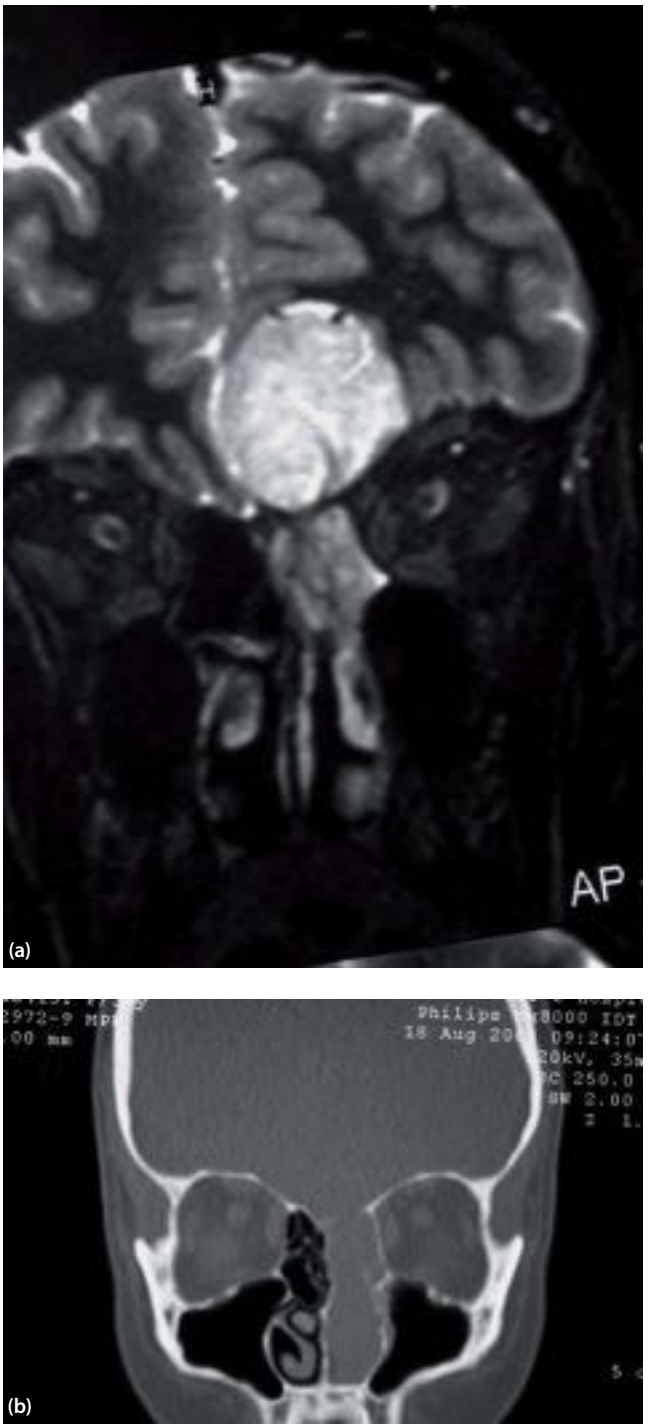


Figure 7.6 (a) MR and (b) CT scan of a patient with a Kadish C olfactory neuroblastoma. The tumour is characteristically centred on the cribriform plate.

TABLE 7.4 Kadish staging system[17] (with Morita's modification)[18]

Stage	Characteristic
A	Limited to nasal cavity
B	Involving nasal cavity and sinuses
C	Extension beyond nasal and paranasal sinuses cavities
D	Tumour with metastasis to cervical nodes or distant sites

TABLE 7.5 Dulguerov staging system[19]

Stage	
T_1	Tumour involving the nasal cavity or paranasal sinuses (excluding the sphenoid sinus) sparing the most superior ethmoidal cells
T_2	Tumour involving the nasal cavity or paranasal sinuses (including the sphenoid sinus) with extension to or erosion of the cribriform plate
T_3	Tumour extending into the orbit or protruding into the anterior cranial fossa without dural invasion
T_4	Tumour involving the brain
N_0	No cervical lymph node metastases
N_1	Any form of cervical lymph node metastases
M_0	No metastases
M_1	Any distant metastases.

Reproduced from Dulguerov et al.[1] with permission.

Sinonasal undifferentiated carcinoma

SNUC was described relatively recently by Frierson et al.[20] It is otherwise known as anaplastic carcinoma and can be hard to distinguish from high-grade OAN. It is a highly aggressive and invasive tumour commonly containing areas of necrosis but, paradoxically, often produces few symptoms despite its extensive nature. Typically SNUC is negative for Epstein–Barr virus, helping to distinguish it from WHO Type 3 nasopharyngeal carcinoma.[21]

Melanoma

Melanoma accounts for 3.6% of all sinonasal malignancies.[22] It is more common in women than men and tends to affect the elderly. The nasal cavity and the septum are usually the sites of origin. Appearances vary from a polypoid mass to an area of ulceration. While some are pigmented, others are not. Immunohistochemistry shows positivity for S100 and HMB-45.[23] Sinonasal melanoma metastasizes less frequently to regional cervical lymph nodes than melanoma that develops elsewhere, but more often to the lungs and brain.[24]

Haemangiopericytomas

These are rare neoplasms that develop from pericytes within the outer capillary wall. They account for less than 5% of all sarcomas. Within the head and neck 20% of all haemangiopericytomas develop in the nasal cavity or sinuses.[25] They have been associated with steroid therapy, coincidental trauma, hypertension and pregnancy. Macroscopically they appear as red-grey, firm, polypoid lesions. Haemangiopericytomas rarely metastasize. Complete surgical excision is necessary as they are relatively radioresistant. There is a 10–60% recurrence rate.

PRESENTATION

Tumours of the nasal cavity cause progressive unilateral stuffiness and blockage, sinus outflow obstruction, bleeding or spot nasal secretions. Distortion of the nose occurs late. The presentation of most sinus malignancies is usually delayed until the sinus of origin is filled with tumour with symptoms being caused by erosion of its walls and extension beyond.



Figure 7.7 Spread of tumour into the cavernous sinus can result in lateral rectus palsy.

Maxillary sinus carcinomas cause facial pain with or without progressive sensory change within the skin of the cheek secondary infiltration of the infraorbital nerve. Erosion of the medial wall is associated with epistaxis and epiphora caused by obstruction of the nasolacrimal duct. Destruction of the posterior wall and spread into the pterygopalatine and infratemporal fossae results in progressive trismus as well as maxillary and mandibular trigeminal nerve deficits. Destruction of bone inferiorly leads to oral masses and teeth mobility. Spread of a tumour superiorly into the orbit gives rise to proptosis and diplopia. A visible swelling or distortion of the cheek develops when tumour breaches the anterolateral wall.

Ethmoid sinus carcinomas usually present with unilateral nasal obstruction and epistaxis. Epiphora, orbital swelling, proptosis or diplopia are not uncommon (**Figure 7.7**). Orbital symptoms and signs also prevail with frontal sinus tumours. Tumours that develop in the sphenoid sinus usually invade the cavernous sinus and infiltrate the contained cranial nerves to produce diplopia and facial pain.

CLINICAL EVALUATION

Endoscopy

A thorough endoscopic examination of the nasal cavity is mandatory in anyone suspected of having a malignancy. While the appearance of some tumours can be obvious with an ulcerative growth others are less conspicuous. It is not unusual for tumours to produce a polypoid reaction in the overlying mucosa. Some of this will be infiltrated but a casual biopsy in the outpatient setting may well be non-diagnostic (**Figure 7.8**).

Imaging

A combination of both computed tomography (CT) and magnetic resonance imaging (MRI) is commonly required for patients with sinonasal malignancies since the former alone may be insufficient for accurate evaluation and staging purposes particularly if it has been adversely affected by amalgam artefact. CT reconstruction gives accurate detail of bone erosion and potential involvement of the skull base. Both axial and coronal views are necessary.

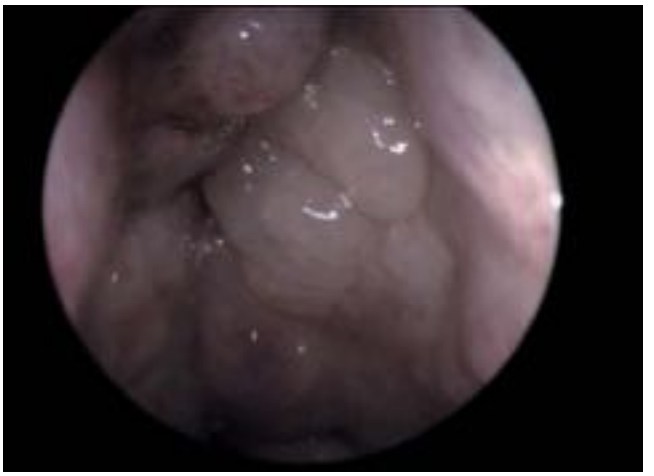


Figure 7.8 Endoscopic view of an extensive SNUC.

Unparalleled information concerning the soft tissue component of tumours is derived from MR imaging. Gadolinium-enhanced MR imaging provides tumour detail that can include flow voids suggesting intense vascularity. It will also detect dural or cerebral infiltration and give an accurate assessment of orbital invasion. T2 and diffusion-weighted sequences are useful in distinguishing between retained secretions, tumour or mucosal thickening (**Figure 7.9**).

Arteriography is rarely required but might be undertaken if pre-operative embolization is being considered to facilitate removal of a vascular tumours such as haemangiopericytoma. FDG positron emission tomography (PET)/CT is not usually necessary for staging the primary tumour but may be helpful in excluding distant disease, for example in melanoma, or in identifying a primary site if there is concern that the disease is metastatic in nature.

Biopsy

Tissue diagnosis is a mandatory part of tumour evaluation. A number of sinus tumours can be excessively vascular and if biopsies are attempted in the outpatient setting facilities should be available to arrest any haemorrhage that might ensue. Biopsies performed under general anaesthesia reduce the rate of non-diagnostic samples and provide the opportunity to sample from within the sinus itself. A Caldwell–Luc approach should be avoided if it is felt this would seed tumour or potentially compromise a subsequent resection (**Figure 7.10**).

TREATMENT

General principles

Malignancies of the nose and paranasal sinuses are rare in contrast to their presenting symptoms. As such many patients still present with advanced disease and there will inevitably be some who are incurable from the outset. Likewise, in some elderly patients concurrent general medical conditions might preclude any major intervention. At initial consultation it is therefore essential that all necessary investigations

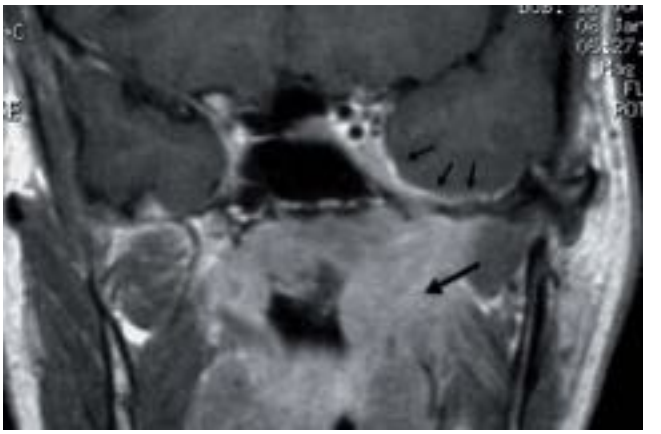


Figure 7.9 MRI and CT scans are complementary and help distinguish between tumour, retained secretions and dural infiltration. This patient had an extensive tumour that had spread into the cavernous sinus, infiltrated the dura of the temporal lobe (small arrows) and the infratemporal fossa (large arrow). The MRI, shown here, shows the true extent of the disease. The spread was not apparent on the CT scan, which had shown a relatively small tumour affecting the sphenoid.

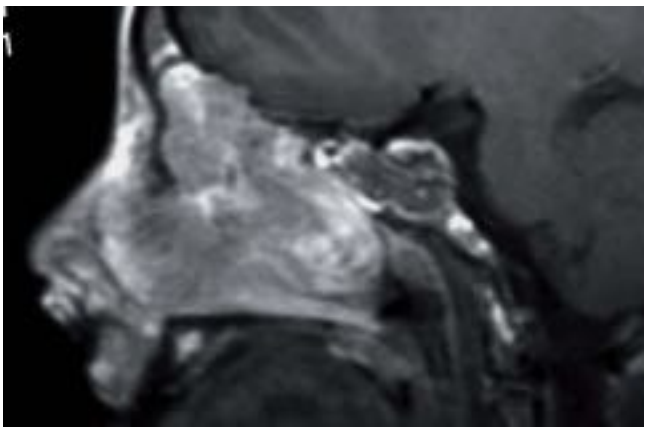


Figure 7.10 This patient lost two litres of blood after a biopsy was taken.

are arranged so that the tumour can be staged accurately and an appropriate treatment plan formulated.

In general, cases should be carefully discussed in a multidisciplinary forum to determine treatment approach and also to facilitate smooth and timely transfer between specialities, so avoiding unnecessary delays in adjuvant therapy. A high quality prosthetic rehabilitation service is an essential component of the MDT. With a palatal resection the defect must be sealed with either an obturator fitted with teeth to restore both speech and normal deglutition or by composite free flap and microvascular techniques. Orbital resections leave an obvious cosmetic deformity but titanium implants have revolutionized the construction and retention of facial prostheses. Radiotherapy is not a contraindication to their use.

There is usually a choice between curative and palliative treatment. In contemplating the latter, it is necessary to balance symptoms and their impact on their life along with the extent of the disease and the potential for distant metastases. Surgery for these patients is both morbid and can raise hopes unrealistically and palliative radiotherapy

might be considered. There are instances, however, when palliative surgery can be useful. Patients with advanced malignant melanoma, for instance, may have a significant reduction in local symptoms with debulking surgery and post-operative radiotherapy. While treatment is likely to be only palliative in patients with large adenoid cystic tumours that have a long natural history, it is often possible to achieve significant periods of good quality survival with local debulking of tumour and adjunctive radiotherapy.

Patients who present early with T1 maxillary tumours may be cured with surgery alone but the majority of patients will require combination therapy. For those patients who are potentially curable most centres recommend a combination of radiotherapy and surgery with the addition of chemotherapy in selected cases. Intensity modulated radiotherapy techniques are generally adopted in order to achieve tumour coverage whilst meeting organ at risk constraints. Post-operative radiotherapy should start within 6 weeks of surgery with 60–65 Gy delivered over 30 fractions. OAN is treated with a combination of surgery and postoperative radiotherapy. Chemotherapy has been used in more advanced cases.[26,27] Multimodality therapy (surgery, radiotherapy and chemotherapy) has generally been demonstrated to be the most effective approach in the treatment of SCC and SNUC.[28–30] The optimal sequencing of those modalities is not clear but if operable surgery followed by post-operative radiotherapy with concomitant platinum-based chemotherapy is the most common approach. In large volume tumours initial non-surgical treatment with (chemo)radiotherapy or chemotherapy alone followed by chemoradiotherapy appears to give better results. Recent evidence based reviews and guidelines support this approach.[31,32] There is increasing experience with proton beam radiotherapy where available, with the possibility of reducing radiation-related morbidity.[33]

There is no role for chemotherapy in the initial treatment of mucosal melanoma, the mainstay of which is surgical resection followed by radiotherapy. In the absence of phase III data it is difficult to draw definitive conclusions regarding the optimal sequencing of treatment modalities in these rare tumours. Topical application of 5-fluorouracil has been advocated by Knegt et al. for adenocarcinoma of the ethmoid sinus.[34]

Other than the stage of disease, patient's wishes and concurrent comorbidity, there are relatively few contraindications to treatment. Local invasion of the anterior cranial fossa and skull base are not necessarily contraindications given the development of modern surgical techniques. Distant metastases confer a poor prognosis and by definition render such patients incurable. Involvement of the facial skin is likewise not a contraindication to treatment and in practice many such patients do well. The involved area is best excised and repaired with either a rotation flap or free flap. Concerns that radiotherapy interferes with healing are less with modern radiotherapeutic regimens.

Surgery for maxillary tumours

A variety of operations has been described, the choice of which is determined by the extent of the tumour and amount of bone that needs to be removed.

PARTIAL MAXILLECTOMY

This entails partial removal of the upper jaw skeleton. Two variants are in common use:

- **medial maxillectomy**, which involves clearance of the lateral wall of the nose including the ethmoid sinuses
- **palatal resection** along with the adjacent alveolus, which is used for tumours of the oral cavity that involve the hard palate. In its simplest form this is called a fenestration although this term is technically incorrect since palatal fenestration was originally described for placing radium implants into the cavity of the antrum. Most partial maxillectomy defects are nowadays reconstructed with free flaps, but for some patients there is still some advantage with the less sophisticated procedure of obturation since this obviates a donor site and allows visualization of the treated cavity during surveillance for recurrence.

TOTAL MAXILLECTOMY

This entails the total removal of the upper jaw, preferably as a bony box containing the tumour.

EXTENDED MAXILLECTOMY

An extended maxillectomy is required when the tumour extends beyond the upper jaw. If this involves the skull base the term craniofacial resection is used.

Surgical approaches

To facilitate the various bony resections it is necessary to use the appropriate soft tissue access procedure, of which three are commonly described:

- **Lateral rhinotomy**. Although this approach is usually attributed to Moure[35] it was originally described by Michaux[36] some 50 years earlier in 1854. It gives excellent exposure of both the nasal cavities and medial maxilla with a cosmetically acceptable incision in the lateral nasal crease (**Figure 7.11**).



Figure 7.11 Extended lateral rhinotomy incision to include the lip. In most cases division of the lip to gain additional lateral exposure is unnecessary.



Figure 7.12 Weber–Fergusson incision.



Figure 7.13 Midface degloving exposure.

- **Weber–Fergusson**. This approach is incorrectly attributed to both Fergusson and Weber and was instead originally described by Gensoul in 1833 (**Figure 7.12**).
- **Midfacial degloving**. Casson et al.[37] described the addition of intercartilaginous incisions to the sublabial incisions advocated by Converse[38] to allow elevation of the soft tissues of the midface. This has been popularized in the UK and well described by Howard.[39] The sublabial incisions should extend from maxillary tuberosity to the contralateral tuberosity to gain maximum exposure. The soft tissues of the cheek are elevated in the subperiosteal plane to the infraorbital nerves. Incisions into the nasal fossa are then made along the piriform aperture on both sides. Bilateral intercartilagenous incisions are extended to a transfixion incision and the skin elevated over the dorsum of the nose using standard rhinoplasty techniques. The incisions are then connected to allow complete elevation of the midface to the infraorbital nerves and medial canthi. With division of the infraorbital nerve the whole of the anterior face of the maxilla to the inferior orbital rim can be exposed. Relevant osteotomies permit varying degrees of maxillectomy. As well as access to the maxilla, pterygopalatine fossa and nasal fossa midface degloving can give wide access to the central skull base and with a Le Fort I osteotomy can be extended to allow better access to the clivus (**Figure 7.13**).[40, 41] The selection of the specific approach depends on the pre-operative assessment, but generally if the anterior ethmoids, frontonasal duct, orbit or zygoma is involved a different approach is indicated. In most other tumours a lateral rhinotomy or midfacial degloving approach will usually give good access for medial maxillectomy and requires little rehabilitation. Extensive tumours require some form of craniofacial approach.

ANAESTHESIA

Skilled anaesthesia is essential. Topical anaesthesia of the nasal mucosa with a decongestant solution along with hypotensive general anaesthesia are of considerable benefit to the surgeon. An oral tube (or tracheostomy) is required for a midfacial degloving.

Maxillectomy

SOFT TISSUE APPROACH

The maxilla is best exposed by the Weber–Fergusson incision. The transverse limb should be placed close to the lid margin to maintain cosmesis, commonly in the first crease. Any lateral extension into a crow's foot should likewise run in an inferolateral direction to minimize post-operative oedema. In the medial canthal region, where the potential for skin loss as a result of radiotherapy is greatest, it is helpful to curve the incision forward over the nasal bones for additional support. An incision along the crest of the philtrum and stepped on the lip is more acceptable than a midline incision. The mucosal incision along the midline of the hard palate turns laterally at the junction with the soft palate passing behind the maxillary tuberosity and then round the alveolus anteriorly. The facial skin flap is raised in a submuscular plane and all the soft tissue incisions are gently dissected free of the bone to allow the subsequent osteotomies (**Figure 7.14**).

OSTEOTOMIES

The body of the zygoma, midline of the palate and pterygoid plates need to be divided. The palatal osteotomy is placed in the floor of the nasal cavity and is most easily carried out using power tools. The pterygoid plates are best separated from the maxilla with a curved osteotome and subsequently dissected free from the muscles. Osteotomies are made medially through the ethmoid cells and then frontal process of the maxilla, the latter after dividing the lacrimal sac. The maxilla is separate from the skull above by osteotomies through the frontal process of the maxilla. Laterally the osteotomy is made through the body of the zygoma. In tumours that are laterally placed, and in which the zygoma needs to be included in the resection then the osteotomy is best made in the lateral orbital wall below Whitnall's tubercle and through the zygomatic arch (**Figure 7.15**).

The remaining bony attachments in the posterior ethmoid cells and antral roof break readily on mobilizing the maxilla. Soft tissue remnants are then divided with Mayo scissors and the maxilla removed. Bleeding from the internal maxillary artery is controlled by packing,

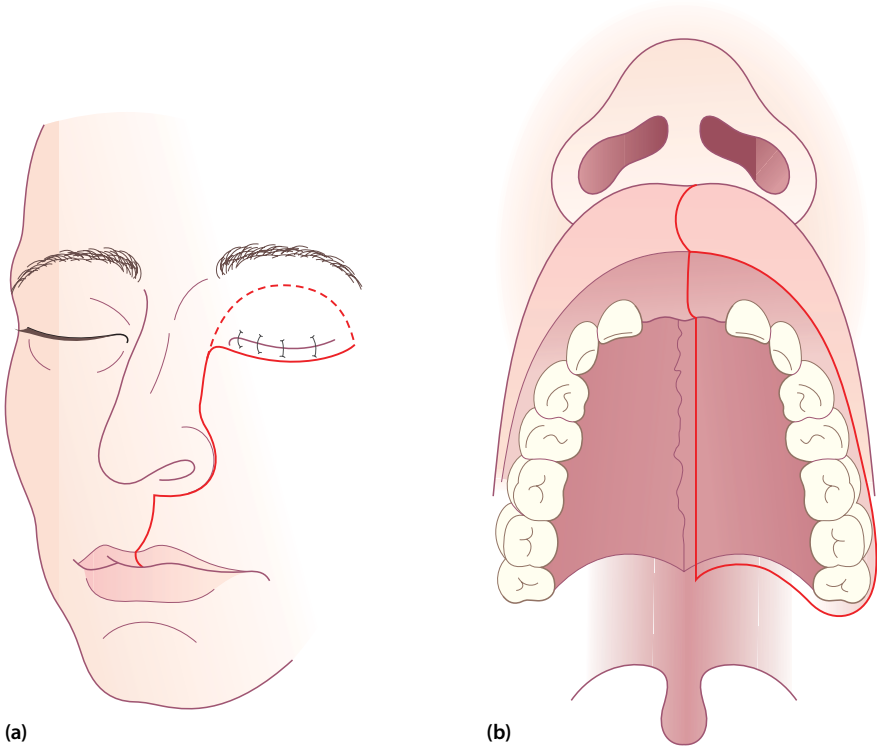


Figure 7.14 Classic maxillectomy. **(a)** Weber–Fergusson incision; **(b)** palatal incision.

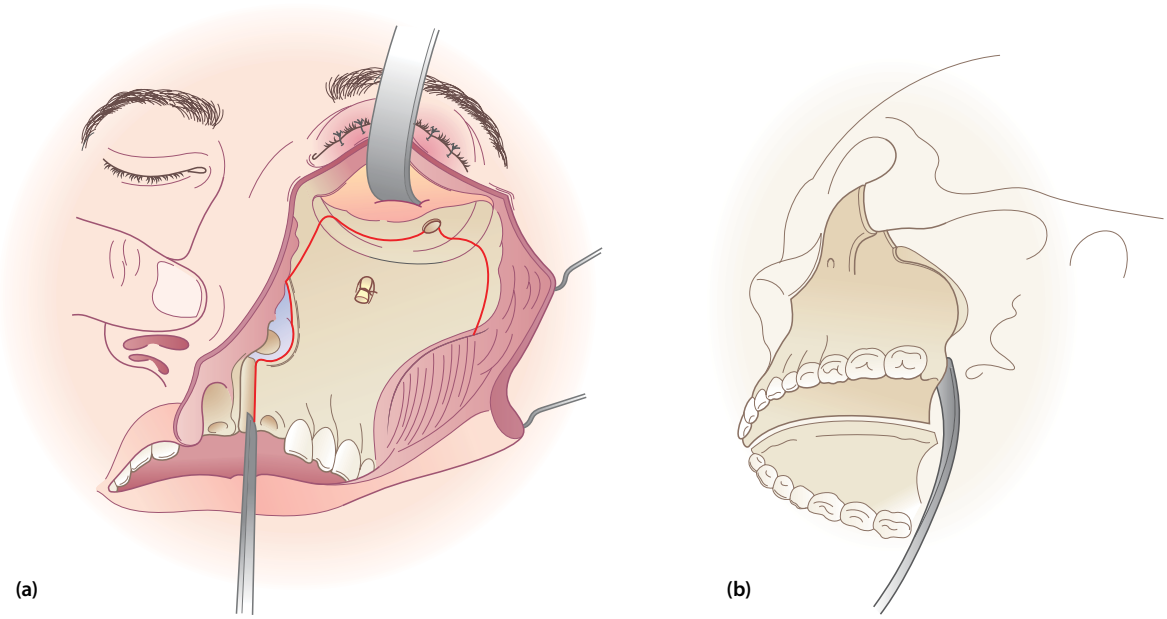


Figure 7.15 Classical maxillectomy. **(a)** Following the elevation of the facial flap, the maxilla is freed with osteotomies through the zygoma, palate and frontal process of the maxilla; **(b)** freeing the pterygoid plates.

Ligaclip application, diathermy or haemostatic matrices, are often used in combination.

COMPLETION OF THE RESECTION

Following removal of the maxilla, further tissue removal is often necessary to promote drainage from the remaining sinuses. The ethmoid cells should be exenterated completely and both the sphenoid and frontal sinuses opened widely. If there is obvious involvement of the orbital periosteum then exenteration is generally indicated. The support of the globe is complex and virtually all the medial and inferior orbital walls can be removed without enopthalmus developing. However, the removal of Whitnall's tubercle laterally results in lack of support for the eye, which can be corrected by transposing the temporalis muscle medially. Orbital exenteration is achieved by an extraperiosteal dissection and transection of the muscle cone at the apex with

Mayo scissors. Bleeding from the ophthalmic artery can be stopped by applying local pressure or bipolar coagulation. Following orbital exenteration the eyelids are preserved but the lid margins and tarsal plates sacrificed, so producing a smooth skin-lined cavity onto which an onlay prosthesis can be fitted.

NECK DISSECTION

Some controversy remains about management of the neck in SCC of the paranasal sinuses. Unlike the plethora of information that exists regarding elective neck dissection in other head and neck sites there are few reports of the use of elective selective neck dissection for management of the maxillary sinus. The rate of occult metastasis is less than 10% with no suggestion in retrospective reviews that elective selective neck dissection contributes to an improved rate of neck control or overall survival.[42]

RECONSTRUCTION AND REHABILITATION

Patients requiring midface reconstruction for malignant disease have undergone extensive ablative surgery and most will require post-operative radiotherapy. This type of facial reconstruction attracts controversy not only because of the many reconstructive options available but also because dental and facial prostheses can be successful in selected cases. Careful rehabilitation, be it biological or prosthetic, aims to ensure a good cosmetic and functional outcome with separation of the nasal and oral cavities. [43, 44]

Low defects not involving the orbital adnexae can often be successfully treated with dental obturators. For the more extensive maxillary defects there is consensus that a free flap is required. Composite flaps of bone and muscle harvested from the iliac crest with internal oblique or the scapula tip with latissimus dorsi can more reliably support the orbit and cheek than soft-tissue free flaps and non-vascularized grafts, and also enable an implant-borne dental or orbital prosthesis. Nasomaxillary defects usually require bone to augment the loss of the nasal bones, but orbitomaxillary cases can be managed more simply with local or soft-tissue free flaps.

In cases where a dental obturator is used, healing of the bony cavity can be rapid but it is advantageous to apply a split-skin graft to the under surface of the facial skin flap. After resuturing the facial incision, the cavity should be immediately fitted with a temporary prosthesis to cover the palate and restore normal facial contours. The prosthesis can be secured with either circumzygomatic wires attached to cleats or more simply fixation screws inserted into any remaining aspect of the hard palate. This primary prosthesis is changed after some 14 days and appropriate adjustments made. This process is repeated several times over the subsequent weeks until such time as it is judged that the cavity has healed and a final prosthesis can be constructed.

Medial maxillectomy using the lateral rhinotomy approach

This approach gives good access to the nasal cavities, the ethmoids, nasopharynx, sphenoid and the pterygopalatine fossa (**Figure 7.16**). For more extensive tumours an en bloc resection can be achieved by combination with an anterior craniofacial approach. The incision is cosmetically acceptable as it passes along the lateral border of the nose to the upper edge of the alar margin. For more extensive resections the incision can be continued into the nasal cavity without compromising the final cosmetic outcome. The upper end should start just above the level of the medial canthus. The orbital periosteum is elevated as for an external ethmoidectomy and extended laterally over the maxilla to the infraorbital nerve. The lacrimal sac and duct are exposed by removing the overlying bone. The orbital contents can then be completely freed medially by dividing the sac low down, clipping and dividing the anterior ethmoidal artery and also by freeing the insertion of the trochlea by sharp dissection. Access to the nasal cavities, ethmoids and antrum is achieved by extending the bony window as required with little cosmetic defect. The mucosa of the nose, antrum and ethmoids can be resected along with the entire lateral nasal wall. The view obtained following the removal of this main block of tissue is excellent and the resection can be extended into the sphenoid and frontal sinuses or alternatively into the pterygopalatine fossa. Packing is rarely required after resection.

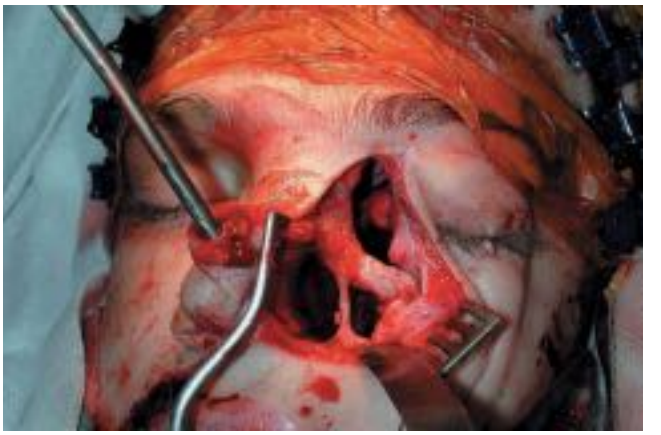


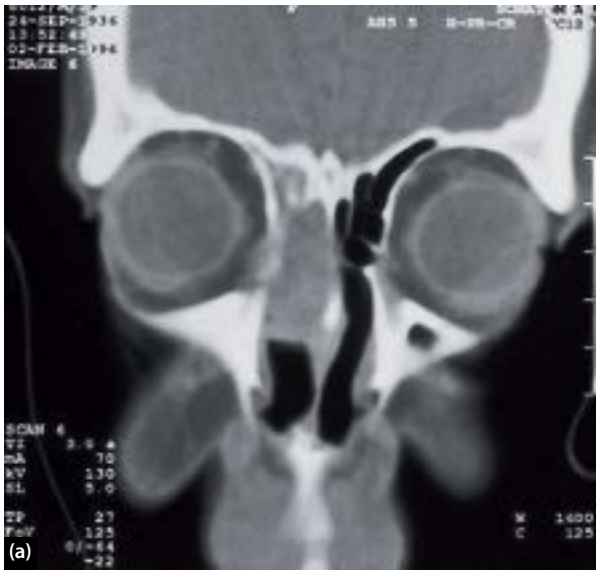
Figure 7.16 Medial maxillectomy approach used to remove a tumour of the ethmoid.

This sort of resection can also be obtained using an entirely endoscopic approach utilizing the appropriate drills and debriders (see below).

Surgery for ethmoidal tumours

Involvement of the cribriform plate region was recognized as one of the major reasons for failure to control ethmoid neoplasms with some of the above approaches. Ketcham et al,[45] Clifford[46] and Cheesman et al.[47] (**Figure 7.17**) described a combined intracranial and transfacial approach that controls and allows resection of tumours involving the cribriform plates, dura and even some tumours invading the frontal lobes. The appropriate selection of approach has been best summarized by Cheesman and Reddy,[48] who subclassified the craniofacial procedures into three types:

- **Type 1: craniofacial (transorbital) resection.** This procedure is essentially an extended medial maxillectomy using a lateral rhinotomy incision. The operation entails careful



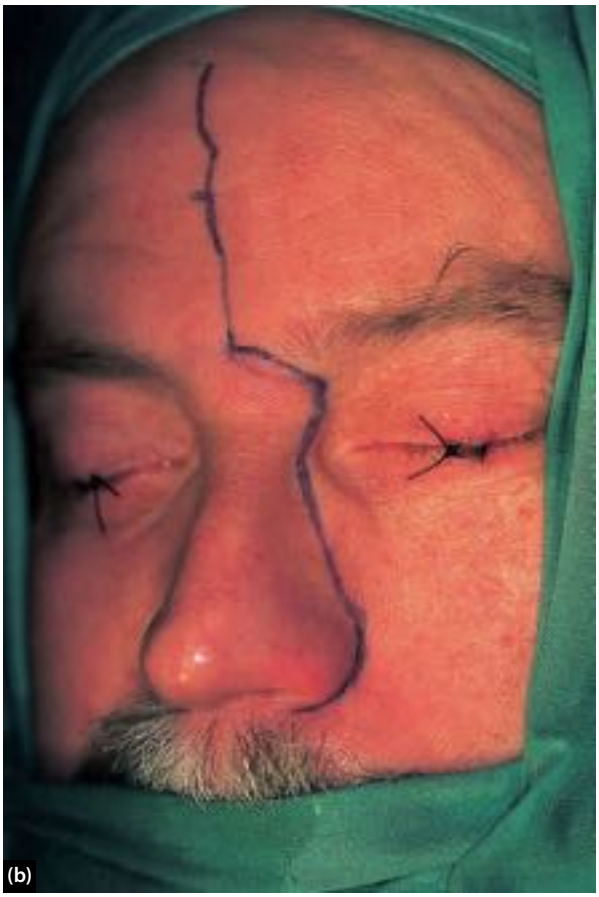










Figure 7.17 Stages of an anterior craniofacial resection.
(a) pre-operative CT acquired face down; **(b–e)** resection; **(f)** post-operative CT.

exploration of the anterior nasal cavities using the operating microscope and frozen section control. The wide exposure allows resection and repair of both the ethmoid roof and orbital periosteum if indicated. A similar approach has been described by Draf and Samii.[49]

- **Type 2: craniofacial (window craniotomy) resection**. In this procedure a lateral rhinotomy approach is used for anterior access and a bicoronal incision utilized to provide a pericranial flap and access to the frontal bone. A small midline 'window' craniotomy usually utilizing the frontal sinus is made giving access to the floor of the anterior cranial fossa. The dura is elevated from the roof of the ethmoids and cribriform plate and the area is encompassed with a cranial osteotomy. This osteotomy, in conjunction with those of the lateral rhinotomy, allows the en bloc resection of both ethmoid complexes. Involved dura and olfactory bulbs can be excised and repaired with fascia lata and pericranium. The window bone flap is replaced and fixed with miniplates. Following soft tissue closure, remarkably little cosmetic defect is evident. The combined approach not only gives excellent visualization of the ethmoid region but also readily allows extensions of the resection into the sphenoid, orbit, pterygopalatine fossae and central skull base.
- **Type 3: craniofacial resection**. This operation is performed in conjunction with a neurosurgeon and combines a transfacial approach with a neurosurgical approach, such as a frontolateral craniotomy, to allow the resection of extensive tumours (**Figure 7.18**). Skull base surgery demands an interdisciplinary approach.

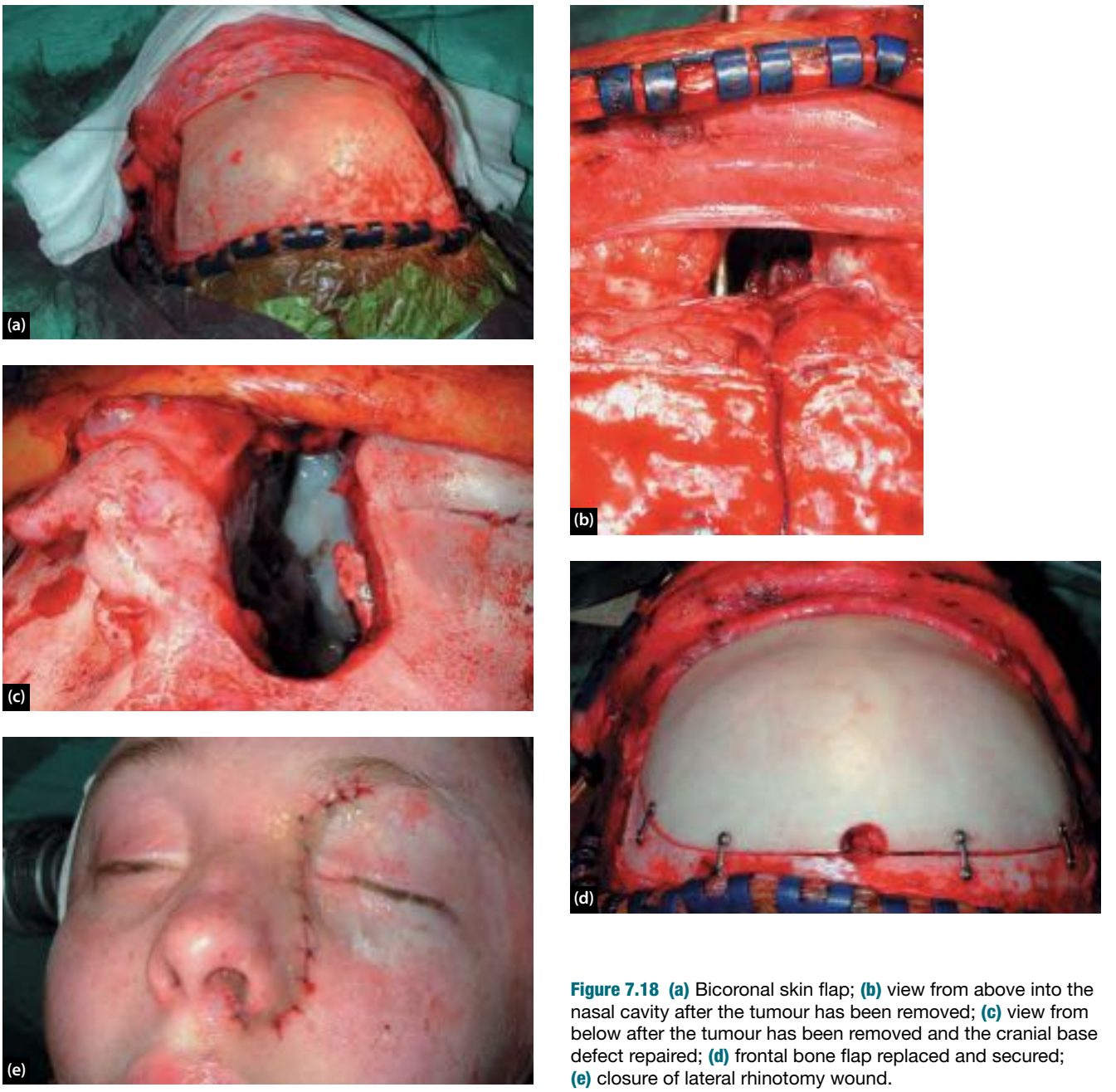


Figure 7.18 **(a)** Bicoronal skin flap; **(b)** view from above into the nasal cavity after the tumour has been removed; **(c)** view from below after the tumour has been removed and the cranial base defect repaired; **(d)** frontal bone flap replaced and secured; **(e)** closure of lateral rhinotomy wound.

There is a trend nowadays for the otorhinolaryngologist to use endoscopic techniques in order to guide the neurosurgeon's osteotomies from below.

Many tumours suitable for Type 1 craniofacial resections can now be approached with endoscopic techniques and extensive tumours requiring a type 3 approach might often be deemed incurable.

Endonasal endoscopic approaches

The introduction and rapid expansion of endoscopic surgery for inflammatory conditions of the sinuses in the 1980s was followed by the extension of these techniques to the skull base and tumour surgery.[50–53] Tumour debulking is usually necessary along with some septal resection for access. The involved sinuses are widely exposed and all bone adjacent to the tumour removed. Resection can continue to include orbital periosteum, dura, crista galli and olfactory bulbs as necessary. Dissection involves drills, debriders and bipolar diathermy as well as standard endoscopic sinus instruments. Neuronavigation and sometimes ultrasonic aspiration are also required especially for intracranial extension. Careful endoscopic repair of dural defects and orbital periosteum with septal mucosal flaps, fascia lata or temporalis fascia complete the procedure. Involvement of the nasal bones, frontal sinus, dura lateral to the ethmoidal roof and orbital contents are contraindications to endoscopic approaches although these may also be combined with transcranial approaches or orbital exenteration where appropriate. A much more detailed treatment of endoscopic resections of sinus tumours is available in Volume 1, Chapter 114, Endoscopic management of sinonasal tumours.

Management of the orbit

Attempts to preserve the orbital contents and reduce mutilation often result in orbital recurrence. If the orbital muscles, globe or orbital apex are involved a lid sparing exenteration is required. The lids provide good skin cover of the defect and can also be used to cover osseointegrated implants, which can be placed at the time of the surgery. However, the orbital periosteum may be involved with tumour while the underlying fat and orbital contents are not, and the use of peri-operative frozen section can determine those patients whose orbits can be safely retained. If frozen section confirms tumour has not penetrated the periosteum it can be resected and repaired without adversely affecting outcome.[54, 55] Orbital involvement despite exenteration significantly affects survival.[56]

PROGNOSIS

The overall prognosis of sinonasal malignancy is directly related to the degree of local control.[1] Absolute local control rates for all malignancies are 50% at 5 years, 31% at 10 years and 21% at 15 years.[57]

Prognosis varies very significantly for different pathologies, however, with very high 5-year survival rates for OAN and ACC and extremely poor prognosis for SNUC and malignant melanoma. For the first two diagnoses in particular, patients may continue to develop relapses for several decades after treatment. In the Memorial Sloan Kettering Cancer Centre series of 166 patients undergoing anterior skull base resection, patients who did experience a recurrence were most likely to fail locally (66.7%). Distant metastases (46.4%) and regional failures were less common (16.7%).[58] Factors associated with prognosis are shown in **Table 7.6**.

TABLE 7.6 Factors affecting prognosis

Factor	Percentage
Anatomical factors: location[1]	
Nasal cavity	77
Maxillary sinus	62
Ethmoid sinus	48
Above Ohngren's line	Worse prognosis
Pathological factors: histological type[39]	
OAN	88
Adenocarcinoma	68
SCC	51
Undifferentiated carcinoma	44
Mucosal melanoma	18
Tumour stage[1]	
T_1	91
T_2	64
T_3	72
T_4	49

5-year actuarial survival.

BEST CLINICAL PRACTICE

- ✓ A combination of CT and MRI scans should be acquired as part of the staging and planning process. These imaging techniques provide complementary information on bone erosion, dural, brain and orbital invasion.
- ✓ Biopsy is most appropriately obtained using endoscopic techniques.

FUTURE RESEARCH

- What is the most appropriate treatment for SCC and SNUC? Are the results for neoadjuvant chemoradiotherapy better than the traditional approach of surgery followed by radiotherapy? Does the addition of chemotherapy improve survival or just add morbidity? Which regimen is optimal? Should the surgical margins incorporate the initial extent of the tumour or just that remaining after chemoradiotherapy?
- Management of the N_0 neck has yet to be determined. Should only N_+ disease be treated or should patients with advanced (T_{3-4}) N_0 tumours also undergo treatment of the neck? Should all histopathological subtypes receive treatment of the N_0 neck or just SCC and OAN? Which levels should be dissected – levels I-III, I-IV or I-V dissection?
- What is the role of surgery for palliation in incurable disease? Is it really justified?
- In reconstruction of the midface, when should an obturator be used and when is a free composite flap appropriate?

KEY POINTS

- Sinonasal malignancies can be difficult to differentiate from non-neoplastic lesions.
- Sinonasal malignancies are uncommon, representing <1% of all malignancies and <3% of all upper aerodigestive tract cancers.
- A large number of sinonasal malignancies are caused by inhaled carcinogens. Risk factors include:
  - wood dust
  - nickel
  - chrome
  - polycyclic hydrocarbons
  - aflatoxin
  - mustard gas
  - thorotrast.
- Maxillary sinus tumours are the most common (55% of all sinonasal malignancies), followed by nasal cavities (35%), ethmoid sinuses (9%) and rarely frontal and sphenoid sinuses (1%).
- Sinonasal malignancies tend to present late.
- The main treatment modalities are surgery and radiotherapy.
- Chemoradiotherapy followed by surgery is advocated for SNUC and advanced ethmoidal SCC.
- Contraindications to aggressive treatment are spread to the sphenoid sinus, middle cranial fossa, optic chiasma, cavernous sinus or prevertebral fascia, as well as the presence of distant intracranial or systemic metastases.
- The prognosis of sinonasal malignancies has improved over the past three decades, but remains poor overall, and is directly related to the degree of local control.
- Absolute local control rates for all malignancies are 50% at 5 years and 31% at 10 years.
- Olfactory neuroblastoma and adenoic cystic carcinoma may relapse after a decade and thus patients should be followed up for at least 15 years

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CHAPTER 8

NASOPHARYNGEAL CARCINOMA

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SEARCH STRATEGY

Apart from the standard textbooks on nasopharyngeal carcinoma, the data in this chapter are based on a Medline search using nasopharyngeal carcinoma against the following keywords: diagnosis, pathology, immunology, treatment and complications.

INTRODUCTION

The nasopharynx is situated deep inside the head and the carcinoma arising in the epithelium of the nasopharynx has a different aetiology, epidemiology and biology compared to other cancers of the upper aerodigestive tract. The deep location of the nasopharynx and the wide spectrum of presenting symptoms make early diagnosis difficult. The distinct tumour biology requires different staging and treatment paradigms compared to other head and neck cancers. Nasopharyngeal carcinoma has been called an enigmatic tumour.[1]

APPLIED ANATOMY

The nasopharynx is the most superior part of the pharynx with the inferior border defined as the lower level of the soft palate. Anteriorly it connects to the nasal cavities through the posterior choana. Superiorly the roof of the nasopharynx is formed by the floor of the sphenoid sinus and slopes down to become the posterior wall, which is formed by the clivus bone. The inferior outlet normally opens into the oropharynx but is closed by the soft palate during swallowing and phonation. The cartilaginous Eustachian tubes on both sides open on the lateral wall of the nasopharynx. A recess extends postero-laterally on both sides of the posterior wall of the nasopharynx to form the lateral recess of the nasopharynx, also known as the fossa of Rosenmüller. The depth of the fossa of Rosenmüller is variable. The posterior cushion of the Eustachian tube opening forms the anterior wall of the fossa of Rosenmüller. Most early stage nasopharyngeal primaries originating from the fossa of Rosenmüller are difficult to detect unless the area is carefully inspected during endoscopy.[2] Cancers arising from the fossa of Rosenmüller therefore frequently invade the Eustachian tube and affect function, leading to the development of otological symptoms.

The nasopharynx is covered with pseudostratified squamous epithelium similar to the mucosa of the nasal cavities and paranasal sinuses. The second layer is the muscular layer formed by the superior constrictor muscles. At the upper part of the clivus and roof, the nasopharynx, the superior constrictor is absent. The pharyngobasilar fascia forms the outermost layer of the nasopharynx wall. The pharyngobasilar fascia anteriorly attaches to the medial

pterygoid plates on both sides. Except for the pterygoid plates in the anterior part of the lateral nasopharynx, the lateral walls of the nasopharynx are devoid of bone. Immediately lateral to the pharyngobasilar fascia are the parapharyngeal spaces with the fat pads and muscles of the soft palate (levator palatini, tensor veli palatini and salpingopharyngeus) on both sides. Cancer of the nasopharynx readily spreads to the ipsilateral parapharyngeal space. Just anterior to the posterior choana, in the posterior part of the lateral nasal wall, is the sphenopalatine foramen. Cancers from the lateral wall can spread to the pterygopalatine fossa via the sphenopalatine foramen. From the pterygopalatine foramen, the cancer then spreads along the foramen rotundum and into the cavernous sinus intracranially, producing ophthalmoplegia. The floor of the sphenoid that forms the anterior part of the roof of the nasopharynx is thin and cancer can easily spread into the sphenoid sinus. From the sphenoid sinus, the cancer can then spread into the orbital apex and cause eye symptoms.

There is extensive lymphatic drainage to both sides of the neck from the nasopharynx. The first echelon of lymphatic drainage is the retropharyngeal lymph nodes (nodes of Rouvière). From the retropharyngeal lymph nodes, the lymphatic drainage continues to the upper jugular nodes, the upper posterior triangle nodes and then further down to the lower neck in a step-wise fashion. The internal carotid artery is located postero-lateral to the fossa of Rosenmüller and is wrapped by the carotid sheath. The carotid sheath extends medially to form the prevertebral fascia. The retropharyngeal lymph node closely abuts the carotid sheath. An enlarged retropharyngeal lymph node caused by cancer metastasis may partially or completely encase the parapharyngeal internal carotid artery. Cancer can also spread along the carotid sheath superiorly into the foramen lacerum and into the intracranial cavity.

EPIDEMIOLOGY

In 2012, there were estimated to be more than 86 000 new cases of nasopharyngeal carcinoma (NPC) worldwide with over 50 000 deaths.[3] The incidence of NPC demonstrates one of the largest geographical variations among all head and neck cancers and the incidence in endemic areas can be 50 times higher than low prevalence areas.

The area with the highest incidence is in Southern China among the Cantonese population of the Guangdong Province. In Hong Kong, where the majority of the population is Guangdong in origin, the age-standardized incidence rate of NPC for men in Hong Kong was once 30 per 100 000 in the 1980s, but it has shown a gradual decline over the last 30 years.[4] Even inside China, there is a large variation in the incidence of NPC in different parts of the country. South China has the highest incidence, followed by Southwest China, Central China, East China, Northwest China and North China. The incidence in South China is three times higher than the second highest region, Southwest China.[5]

Outside China, Southeast Asia has the highest incidence of NPC, especially among countries with significant Malay and Indonesian populations. Populations in North Africa, especially Tunisia and Algeria, also have an elevated incidence.[6] Inuits in Alaska, North Canada and Greenland are another population group with elevated incidence of NPC.[7] Migrants to North America of South Chinese origin also have increased incidence though the incidence decreases among the second and third generation migrants.[8] The Japanese and Koreans, like Western populations, have an annual incidence rate of less than 1 case per 100 000.[7] The marked variation in the incidence of NPC implies that there exists a genetic susceptibility in the high incidence population.

The male to female ratio of the disease is 3 to 1, with a similar ratio observed in endemic areas and among low incidence populations. The peak age group of presentations of NPC in endemic areas is 50–55 years old, and it decreases with increasing age.

In Hong Kong, there has been a gradual decline in incidence of NPC in the last three decades. The incidence decreased by 30% from 38.5 per 100 000 males per year in 1980–84 to 20.2 per 100 000 males in 1995–99. The decreases in incidence in females followed a similar trend.[9] This decrease in not observed in other high-risk populations in Singapore, Malaysia or Guangdong province, People's Republic of China.[10]

AETIOLOGY

The exact sequence of events in the development of NPC has not been elucidated. A complex interplay of genetic susceptibility, Epstein—Barr virus (EBV) infection and environmental factors leads to the development of the cancer.[11]

Genetic factors

The presence of genetic susceptibility to NPC can be implied from the wide variation in cancer incidence across the world. Migrants from high-risk populations who settle in low incidence areas, like Southern Chinese emigrants to North America, have higher incidences than the native population though the incidence reduces in later generations.[8] On the other hand, migrants from low incidence areas do not experience an increased risk of NPC even when they emigrate to high incidence areas, like Indian emigrants in Singapore.[7] About 10% of NPC patients have familial clustering of cases.[12] Although a familial cluster can be explained by genetic factors, members of the same family, especially siblings, may be exposed to similar environmental factors. Therefore, the presence of familial clustering may imply the presence of either genetic or environmental factors, or both.

HLA subtypes and NPC

An early attempt to identify subgroups with genetic susceptibility was to correlate the risk of different human leukocyte antigen subtypes with the risk of developing NPC in high-risk populations in Singapore, Malaysia

and Hong Kong. Recent meta-analysis of the studies on HLA subtypes with NPC showed that HLA A2, B14 and B46 are associated with increased risk of NPC while HLA A11, B13 and B22 are associated with lower risk of NPC.

Recent genetic studies using advanced molecular biology techniques have yielded more information on the role of HLA genes in the development of NPC. A genome wide association study showed that genes at the 6p21 locus within the HLA region are strongly associated with NPC.[13, 14] Other genes in the HLA region were also associated with the development of NPC. The details of these genes are beyond the scope of this chapter. Hildesheim and Wang wrote an excellent review article on the genetic predisposition factors of NPC.[15] Current thinking is that individual HLA subtypes associated with NPC may have impaired immune response to EBV infection and clearance of the virus from the epithelium. The establishment of latent EBV infection in the epithelium of the nasopharynx may lead to pre-malignant changes in the epithelium, later progressing to invasive cancer.

Other cancer-associated genes including *MDM2* and *TP53* and the cell-migration gene *MMP2* have been shown in multiple studies to be associated with NPC, albeit in the later stages of cancer development.[16–20]

Environmental factors

Second and third generation Southern Chinese who had migrated to North America had a decreased risk of developing NPC compared with native Southern Chinese, though the risk was still higher than the local population. This implied that although genetic factors played a role in NPC development, environmental factors might also contribute to the cancer development.

Early studies in the 1970s and 1980s in Hong Kong identified that childhood consumption of salted fish increased the incidence of NPC in early adulthood.[21] Salted fish was shown to be carcinogenic when fed to rats in the laboratory.[22] Consumption of other preserved foods were also shown to increase the risk of development of NPC.[23] The carcinogenic effect of these preserved foods may be due to the high nitrosamine content.[24]

Multiple studies have shown that smoking increases the risk of NPC development and this risk increase is seen in both low and high incidence populations.[25, 26] However, the effect of smoking on NPC development is more pronounced on the well-differentiated type of NPC in the Western population than on the undifferentiated type of NPC in Southern China.[27] Jia and Qin have summarized the effect of environmental factors on the development of NPC in a systematic review.[28]

Epstein—Barr virus

Central to the pathogenesis of NPC is the carcinogenic Epstein—Barr virus (EBV). The virus was first associated with Burkitt lymphoma in sub-Saharan Africa. In the late 1960s, serological studies showed that NPC patients had elevated antibiodies against EBV, similar to levels found in patients suffering from Burkitt lymphoma.[29] Improvement in molecular genetics finally confirmed that EBV DNA sequences were found in the nucleus of the carcinoma cells of NPC.[30, 31] EBV is found only in the poorly differentiated and undifferentiated form of NPC, which is the prevalent histological subtype in high incidence areas.

The exact role of EBV in the development of NPC is still unknown. EBV typically infects B-lymphocytes and produces the acute syndrome of infectious mononucleosis. In the endemic areas, EBV has already infected the majority of the population by early adulthood, yet only a minority develop NPC. The virus does not commonly infect normal nasopharynx epithelium. It is postulated that the combination of genetic susceptibility, environmental factors and EBV infection all contribute to development of NPC. Genetic susceptibility may confer increased risk of a latent EBV infection, while environmental and dietary risk factors may transform the normal nasopharynx epithelium to a premalignant stage, supporting the EBV genome in the transformed nasopharynx epithelium. EBV genome, when incorporated into the nasopharyngeal epithelium, may cause malignant transformation. The virally infected cells may alter the cytokine environment and assist the cancer cells to avoid detection by host immune-surveillance. Tsao et al have summarized the current knowledge of EBV and NPC in a review article.[11]

The association of EBV with NPC can be exploited in the diagnostic process, therapeutic strategies and preventive treatment in NPC. These will be elaborated further later in the chapter.

PATHOLOGY

The commonest type of malignancy in the nasopharynx arises from the epithelium. The World Health Organization (WHO) originally categorized the epithelial malignancies from the nasopharynx into three subtypes: well-differentiated keratinizing squamous cell carcinoma (WHO type 1); non-keratinizing carcinoma (WHO type 2); and undifferentiated carcinoma (WHO type 3). The classification was later revised to two subtypes: keratinizing squamous cell carcinoma; and combining type 2 and type 3 into non-keratinizing carcinoma. The non-keratinizing carcinoma can be further subclassified as differentiated and undifferentiated types. The histology of the keratinizing squamous cell carcinoma is similar to other well-differentiated squamous cell carcinoma in the upper aerodigestive tract. On the other hand, there are some distinctive histological features in the non-keratinizing carcinoma, which is predominant in the high incidence/endemic regions. Histologically, the malignant cells are infiltrated with lymphocytes and plasma cells. These lymphocytes are predominately T-cell and are CD8+.[32] The term lymphoepithelial carcinoma has been coined to describe this histological feature that is different from other undifferentiated carcinoma of the head and neck region like sinonasal undifferentiated carcinomas. Other than the nasopharynx, lymphoepithelial carcinoma

can be found in salivary glands, paranasal sinuses and lungs. When lymphoepithelial carcinoma is found outside the nasopharynx, it is important to distinguish between primary cancer and metastatic cancer from the nasopharynx primary. **Figures 8.1** and **8.2** are histological slides showing a well differentiated NPC (WHO type I) and undifferentiated NPC (WHO type II) respectively.

EBV is ubiquitously found in all the cancer cells in non-keratinizing NPC. Immunostaining for EBV in the cancer cells can help to differentiate between NPC and different types of head and neck cancer, especially in tissue obtained from metastatic lymph nodes by excisional biopsy or fine needle aspiration. Immunostaining for EBV virus encoded small ribonucleic acid (RNA) (EBER) is commonly used to detect the presence of EBV inside the cancer cells.

In endemic areas like Southern China, non-keratinizing type of NPC constitute over 95% of the histological subtype of NPC. In low incidence populations like Japan or USA, non-keratinizing carcinomas still are the majority with only 25% of the NPC being the keratinizing subtype. Basaloid squamous cell carcinoma is a rare subtype of epithelial cancer seen at this site.

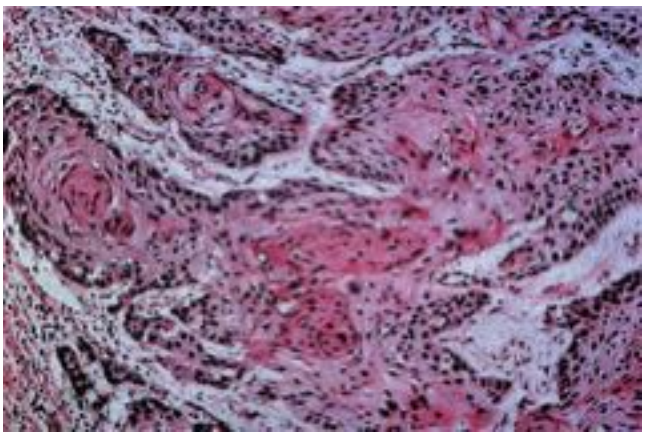


Figure 8.1 H&E stained histological slide of a keratinizing NPC (WHO type I). Note the keratinization.

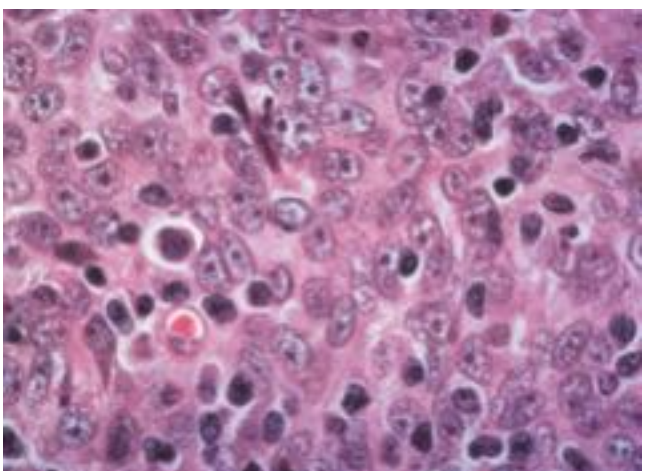


Figure 8.2 High power view of the H&E stained histological slide of an undifferentiated NPC (WHO type III). Note the abundant lymphocytes mixed with the cancer cells.

Salivary gland carcinomas are another important group of cancers that can occur in the nasopharynx, although the incidence is relatively low. The histology and behaviour of salivary gland carcinomas found in the nasopharynx are similar to other minor salivary gland cancers in the head and neck area.

Apart from epithelial carcinomas, soft tissue malignancies can occur in the nasopharynx, including sarcomas, lymphomas and malignant melanomas. Malignant fibrosarcomas and osteosarcomas are the commonest form of radiation-induced sarcomas in the nasopharynx in NPC patients treated with radiotherapy. For radiation-induced carcinomas, the histological subtype is typically well-differentiated squamous cell carcinoma with EBV absent in the cancer cells. Head and neck lymphoma frequently involves the lymphatic tissue in the Waldeyer's ring, including the lymphoid tissue in the nasopharynx. Certain lymphomas like Hodgkin lymphoma and T-NK lymphoma also harbour EBV in the cancer cells. It is important not to misdiagnose lymphoma as undifferentiated type of NPC based only on the presence of EBV in the biopsy. **Table 8.1** lists the types of benign and malignant neoplastic lesions that can occur in the nasopharynx.

TABLE 8.1 WHO classification of tumours of the nasopharynx

I Epithelial tumours	
a Benign	**b Malignant**
1 Papilloma	1 Nasopharyngeal carcinoma
2 Pleomorphic adenoma	2 Adenocarcinoma
3 Oncocytoma	3 Papillary adenocarcinoma
4 Basal cell adenoma	4 Mucoepidermoid carcinoma
5 Ectopic pituitary adenoma	5 Adenoid cystic carcinoma
	6 Polymorphous low-grade adenocarcinoma
II Soft tissue tumours	
a Benign	**b Malignant**
1 Angiofibroma	1 Fibrosarcoma
2 Haemangioma	2 Rhabdomyosarcoma
3 Haemangiopericytoma	3 Angiosarcoma
4 Neurilemmoma	4 Kaposi's sarcoma
5 Neurofibroma	5 Malignant haemangiopericytoma
6 Paraganglioma	6 Malignant nerve sheath tumour
	7 Synovial sarcoma
III Tumours of bone and cartilage	
IV Malignant lymphomas	
1 Non-Hodgkin lymphoma	
2 Extramedullary plasmacytoma	
3 Midline malignant reticulosis	
4 Histocytic lymphoma	
5 Hodgkin disease	

(*Continued*)

TABLE 8.1 (*Continued*) WHO classification of tumours of the nasopharynx

V Miscellaneous tumours	
a Benign	**b Malignant**
1 Meningioma	1 Malignant melanoma
2 Craniopharyngioma	2 Chordoma
3 Teratoma	3 Malignant germ cell tumours
VI Secondary tumours	
VII Unclassified tumours	
VIII Tumour-like lesions	
1 Cysts	
2 Meningocoele/meningoencephalocoele	
3 Granulomas	
4 Amyloid deposits	
5 Others	

Reproduced from Shao et al,[33] with permission.

CLINICAL FEATURES AND MODES OF PRESENTATION

Early cancers of the nasopharynx produce minimal and trivial symptoms that may be neglected by the patients and undetected by physicians. Moreover, the central location of the nasopharynx in the head means that cancer can spread in all directions, affecting many surrounding organs like the ears and eyes, producing symptoms that would not immediately relate to the nasopharynx. Broadly speaking, local symptoms and signs of NPC can be classified in to four categories: nasal; otological; cervical; and neurological. Patients rarely present with exclusive symptoms and signs of systemic metastasis without any local symptoms.

Nasal symptoms and signs

The majority of patients have some form of nasal symptom but may choose to neglect them until more sinister symptoms arise. Around 50% of the patients have suffered from nasal symptoms on presentation when asked directly. The most common symptoms are blood stained nasal discharge or post-nasal drip. If the tumour is large enough to obstruct the posterior choana, the patient may present with nasal blockage. Patients may also report cacosmia or a smell of blood due to bleeding from the tumour.

The nasopharynx is a difficult area to examine without special equipment. Physical examination often cannot identify the presence of the tumour unless the primary tumour has extended into the anterior nasal cavity or down into the oropharynx. Examination of the post-nasal space with a post-nasal mirror may reveal the presence of a tumour but this examination is difficult, especially in patients with strong gag reflex.

Otological symptoms and signs

Between 30% and 40% of NPC patients suffer from some form of ear symptom. Otological symptoms are usually caused by Eustachian tube dysfunction secondary to tumour bulk and/or invasion. Patients complain of recent onset of ipsilateral hearing loss, muffled sound, tinnitus and sensation of ear blockage. Unfortunately, patients and physicians may regard these as transient Eustachian tube dysfunction symptoms suffered during an upper respiratory tract infection, leading to a delay in diagnosis. Otoscopic examination will reveal the presence of a middle ear effusion. The nasopharynx should always be examined in adults with unexplained persistent middle ear effusion.

Neck symptoms and signs

An enlarging upper neck mass is the commonest symptom that prompts patients to seek specialist care. Up to 70% of patients with NPC have enlarged neck lymph nodes on presentation and one third of the patients have bilateral enlarged neck lymph nodes. The most frequently involved nodes are level II (upper jugular) and upper level V (apex of posterior triangle). Lymphatic spread of NPC occurs in an orderly fashion from superior to inferior,[34] with skip metastases being very rare. An isolated enlarged supraclavicular lymph node is almost never a lymph node metastasis from NPC. For patients with lymph node spread down to supraclavicular fossa, the disease is considered as a very advanced type of nodal metastasis, staged as N3b disease.

Occasionally, NPC patients can present with metastatic neck lymph nodes from an unknown primary. In these cases, the primary is usually very small and may not be obvious on endoscopy. New imaging modalities like magnetic resonance imaging and positron emission tomography (PET) may reveal the presence of small cancer in the nasopharynx. Additional investigations like serological testing for EBV and immunohistochemical staining of the cytological material for EBV can also point to a nasopharyngeal primary.

Neurological symptoms and signs

The presence of neurological symptoms usually signals advanced disease. Headache is the most common neurological symptom and is present in up to 20% of patients. The headache is usually localized to the vertex or occiput and caused by the invasion of the clivus bone by the tumour. Facial pain and midface numbness can also be a presenting symptom, caused by tumour invasion into the pterygopalatine fossa and the branches of V2. Cranial nerve (CN) palsies are caused by extension of the tumour into the skull base or intracranially. Common cranial nerves to be involved at presentation are V2, V3 and VI. Involvement of CNIII and CNIV are indicative of cavernous sinus invasion by tumour. Rarely, patients present with ophthalmoplegia, decreased vision and proptosis caused by direct invasion of the tumour into the orbital apex. Trismus is rare unless the tumour has directly invaded the pterygoid

muscles in the masticator space. Horner syndrome can occur if the tumour or metastatic lymph node encases the carotid vessels. This is an uncommon mode of presentation as the carotid sheath is a tough fascia that impedes direct tumour invasion. The presence of Horner syndrome is usually associated with other cranial nerve involvement like CNX and CNXI. Patients from endemic regions with isolated CN palsies should be investigated for the presence of NPC, either by imaging or by nasal endoscopy.

Symptoms of systemic metastasis

NPC presentation with systemic metastasis is uncommon and is usually associated with advanced local or nodal diseases. Common sites of distant metastases are liver, lung and bone, with brain metastasis being rare.

One special scenario that can lead to confusion is the finding of histologically proven lymphoepithelial carcinoma in a lung nodule, which can be a primary lymphoepithelial carcinoma of the lung or distant metastasis from a nasopharyngeal primary. A PET scan can help differentiate between a lung primary and a distant metastasis. If the disease is confined to the lung on imaging, the patient should be treated as appropriate for a primary lung cancer.

Para-neoplastic syndrome

Around 1% of NPC patients develop dermatomyositis as a para-neoplastic syndrome. A study performed in an NPC endemic area showed that up to 12% of dermatomyositis patients developed NPC.[35] Dermatomyositis can develop concurrently with NPC, late after the diagnosis of NPC or months before the NPC is clinically and symptomatically apparent.

DIAGNOSIS

An approach to diagnosis based on the resources and expertise available should be formulated and followed to shorten the time taken for diagnosis. Such a guide to the diagnostic process is especially useful in areas where NPC is endemic. **Figure 8.3** outlines an approach to the diagnosis of NPC in an endemic region.[36] A good history, together with a thorough clinical examination including endoscopy of the nasopharynx, is the basis for making the diagnosis. In most patients, a tumour mass will be found in the nasopharynx and a biopsy should be taken without delay. In less than 5% of patients, the nasopharynx may appear normal and other investigations may then be necessary to confirm or definitively exclude the diagnosis of NPC.

History

NPC should be a differential diagnosis for patient who presents with any of the four groups of symptoms discussed above, especially if they are from a high incidence region. Symptoms of tinnitus, ear blockage or blood stained nasal discharge may seem benign but they should be investigated further if no apparent cause is found. The ancestry of the patient should be inquired about, especially in Chinese patients, who should be asked whether they are from Northern or Southern China. A family history of NPC is also important as 10% of NPC patients have familial clustering of the cancer.

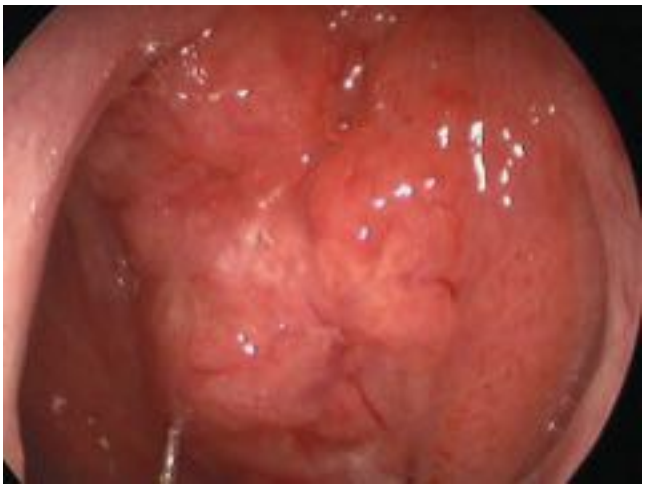


Figure 8.3 View of the nasopharynx through a 0° rigid nasoendoscope. A tumour can be seen obliterating the left fossa of Rosenmüller extending to the right across the midline.

General examination

A full head and neck examination is essential in all patients. Care should be taken to look for otitis media with effusion (OME), CN lesions and cervical lymphadenopathy. When nodes are palpable, their site and size must be carefully assessed as part of the staging process.

Examination of the nasopharynx and nasopharyngoscopy

Traditionally, examination of the nasopharynx was performed by the indirect mirror examination. This technique of examining the nasopharynx is often inadequate due to poor illumination and a strong gag reflex. Additionally, biopsy of any lesion found in indirect mirror examination is nearly impossible in the outpatient setting. Substituting the post-nasal mirror with a 70 degree or 90 degree telescope may solve the problems of poor illumination and poor visualization but the problems of gag reflex and inability to obtain biopsy would still be present.

Antegrade nasopharyngoscopy can be performed with either a rigid telescope or a flexible endoscope. With improvements in technology, the diameter of the new endoscopes is smaller, with improved optics. Both rigid and flexible endoscopes are now available with diameters of less than 4 mm. The choice of using a flexible or rigid endoscope depends on the clinical setting. A flexible endoscope would be more desirable if the larynx and hypopharynx need to be examined in the same setting or if nasal anatomy precludes the use of a rigid telescope. For rigid telescopes, a 0 degree telescope provides a more

direct view but a 30 degree telescope can be turned to examine the lateral wall of the nasopharynx and fossa of Rosenmüller better. **Figure 8.3** shows the view of the nasopharynx with a tumour left fossa of Rosenmüller extending to the left nasopharynx.

Ideally, the nasal cavities should be prepared by the application of local anaesthesia and vasoconstrictor prior to performing nasopharyngoscopy. Traditionally, 5% cocaine was used given its anaesthetic and vasoconstriction properties. However, owing to the disadvantages of being a controlled drug with significant cardiovascular toxicities, other agents are preferred: 2–5% lignocaine with the addition of a vasoconstrictor like 1 : 10 000 adrenaline, 0.5% phenylephrine or 0.1% xylometazoline. The local anaesthetic can be applied by placing cotton pledges soaked with the drug or by spraying the drug into the nasal cavities. The endoscopy should be performed a few minutes later to allow the vasoconstrictors to act so that the nasal mucosa can shrink adequately for better inspection of the nasal cavities and nasopharynx. Occasionally, in patients with deep fossa of Rosenmüller or bulky Eustachian tube cushions, the fossa cannot be adequately visualized. The patient should then be instructed to swallow and then say 'arh'. This will close the velopharynx and pull the Eustachian cushions anteriorly, exposing the deep fossa.

Most of the cancers are readily apparent under endoscopy, presenting as a mass with abnormal capillaries on the surface with areas of ulceration. Occasionally, the tumours are infiltrative and no mass may be seen. However, close inspection will reveal abnormal capillaries in the mucosa; easy contact bleeding is a sign of NPC.[37] Cross-sectional imaging, especially MRI, will pick up this type of submucosal NPC.

Biopsy of the nasopharynx

If an obvious tumour can be seen during endoscopy in the outpatient setting, biopsy of the lesion can usually be performed concurrently. Flexible endoscopes with a biopsy channel for use in nasopharyngoscopy usually have a small biopsy channel; thus, it is advisable to obtain multiple biopsies to avoid inadequate tissue for histological diagnosis. Alternatively, a biting ethmoid forceps used in endoscopic sinus surgery can be passed into the nasal cavity above or below the endoscope under endoscopic guidance for obtaining biopsy (**Figure 8.4**). For procedures using rigid endoscopes, the biopsy technique is similar. Some mild mucosal bleeding can be expected after the biopsy but this should be self-limiting. Patients on anticoagulation drugs should have the coagulopathy corrected before the biopsy procedure.

Biopsy under general anaesthesia may be required if multiple deep biopsies are needed to rule in or rule out the diagnosis of NPC. Patients with metastatic neck lymph nodes with an unknown primary, persistently raised tumour markers and normal nasopharynx on endoscopy or inconclusive biopsy results will be candidates for general anaesthesia. Multiple deep biopsies including biopsies from the roof of nasopharynx, central nasopharynx and mucosa of both fossae of Rosenmüller should be obtained.



Figure 8.4 Biopsy of the left nasopharynx under direct visualization from a 0° nasoendoscopy. The nasoendoscope was introduced through the right nostril while the ethimoid biting forceps was introduced through the left nostril. Alternatively, both instruments can be introduced through same nostril after decongesting the nasal cavities.

DIFFERENTIAL DIAGNOSIS

Several entities may resemble NPC on clinical examination. These include inflammatory disease in the nasal cavities like rhinosinusitis or nasal polyposis, infections in the nasopharynx including viral infections or tuberculosis of the nasopharynx and other rare malignancies, such as T-NK lymphoma (midline lethal granuloma), mucosal melanoma, sinonasal undifferentiated carcinoma and olfactory neuroblastoma involving the nasopharynx.

LABORATORY TESTS

Although biopsy of the nasopharynx remains the gold standard in diagnosis of NPC, several laboratory tests can aid the diagnosis or be useful for monitoring and screening the disease. Blood tests are especially useful for screening purposes as they are less invasive and easier to deploy than endoscopic examination of the nasopharynx.

EBV antibodies serology

The first association of endemic NPC with EBV was found when patients with NPC regularly were found to have elevated levels of EBV antibodies in the serum.[38] IgA antibodies against viral capsid antigen (VCA), early antigen (EA) and EBV nuclear antigen 1 (EBNA1) are commonly used as tumour markers to screen for NPC. On the other hand, serum EBV IgG titre signifies prior infection by the virus and elevated serum EBV IgM titre indicates recent infection. EBV IgG serology and IgM serology are not useful in screening NPC as most adults will have been infected by EBV at an earlier age. EBV IgA VCA is sensitive but not specific for NPC while EBV IgA EA is specific but not sensitive for detecting NPC. Combining both tests

can increase the sensitivity and specificity of the serological tests. A large single centre review of more than 5000 subjects, of which 215 suffered from NPC, showed the sensitivity and specificity of EBV IgA VCA to be 89% and 80% while the sensitivity and specificity of EBV IgA EA was 63% and 95%.[39] A recent meta-analysis of 20 published reports on EBV IgA VCA serology sensitivities in Chinese literature showed a similar sensitivity of around 91%.[40]

EBV serology is not an ideal tumour marker for NPC as the serology has weak correlation with the stage of the disease, unable to reflect the tumour response to therapy and does not show increasing titre in recurrent disease.[41] Despite its deficiency, EBV serology is still widely employed in endemic areas for screening or initial diagnostic work up, due to its low cost.

Plasma EBV DNA titre

EBV genome is found in all cancers cells of the endemic form of NPC and EBV DNA will be shed into the patients' blood stream during cell turnover. More advanced stage NPC will have a higher tumour load and larger cancer cell turnover. Detection of EBV DNA in the plasma could therefore be used as a tumour marker of NPC. Improvements in molecular genetics studies has allowed the number of copies of the DNA in the plasma to be assessed using the quantitative (real-time) polymerase chain reaction (rt-PCR). Establishing a threshold level of plasma EBV DNA can help to differentiate between a genuine case of NPC and low levels of DNA due to reactivation of infection. Lo et al first reported the use of qt-PCR assay of EBV DNA in plasma for the detection of NPC.[42,43] The reported sensitivity and specificity of plasma EBV DNA for NPC detection were 96% and 93% respectively. Studies comparing EBV serology with plasma EBV DNA for detection of NPC have found the latter to be a superior test.[33,41]

Apart from diagnostic and screening purposes, plasma EBV DNA levels can have a prognostic implication.[44,45] A high level of EBV DNA before treatment correlates with the larger tumour load and more advanced stage of the cancer.[46] Plasma EBV DNA levels rapidly decrease to undetectable or very low levels within 1–2 weeks after completion of treatment.[47] Persistently elevated plasma EBV DNA titre after treatment may signify persistent loco-regional disease or development of distant metastasis and has been used as a justification for adjuvant chemotherapy.[48,49] An initial drop of plasma EBV DNA levels after treatment and a later progressive rise in the level may represent tumour recurrence.[49] Plasma EBV DNA titre has also been used for monitoring of treatment response during chemotherapy in lieu of imaging, reducing the cost and inconvenience to the patients.[50] Overall, plasma EBV DNA assessment has proved to be a versatile tumour marker for NPC.

The only caveat when interpreting plasma EBV DNA is that levels will be elevated in any disease associated with EBV, like infectious mononucleosis and EBV-associated lymphoid malignancy.[51] Also, plasma EBV DNA levels lack sensitivity in detecting small local recurrences after radiotherapy.[52]

Nasopharyngeal brushing for EBV DNA

To tackle the problem of elevated plasma EBV DNA in other EBV-associated diseases, direct detection of EBV in the nasopharynx has been devised.[53,54] Brushing of the nasopharynx is performed and the cells obtained are sent for EBV DNA detection with qt-PCR. Theoretically, this test should be more sensitive and specific than plasma EBV DNA level. Although early brush designs fell out of favour due to being impracticable, newer designs of transoral brushing and detection of EBV DNA show promising results. The test is easy to perform and has a very high sensitivity and specificity of 98.9% and 99.3% respectively.

Cytology

When analyzed by an experience cytologist, cytological smears from the fine-needle aspiration of enlarged neck lymph nodes can often differentiate between metastasis from squamous cell carcinoma and undifferentiated carcinoma. With the addition of immunohistochemical staining for EBV RNA (EBER), a definitive diagnosis of NPC with neck lymph node metastasis can be made. Performing fine-needle aspiration avoids open biopsy of the neck lymph node.

IMAGING

Imaging studies are indispensable for staging of the disease and can also aid in the differential diagnosis in cases with atypical presentations. When cost is not a concern, imaging studies are useful for post-treatment monitoring.

Plain radiograph

A plain radiograph of the nasopharynx is neither sensitive nor specific enough for any clinical use and has been superseded by other modalities.[55] A plain chest X-ray can be done as an initial screening for lung metastasis and general health status. Orthopantomogram is often performed by a dentist treating patients prior to radiotherapy.

Computerized tomography

The use of a computerized tomography (CT) scan as a staging modality has been replaced by magnetic resonance imaging (MRI) as more and more centres adopt newer three-dimensional radiotherapy techniques. CT scans are still used by many clinicians as they are more widely available and can clearly show bone erosions in the skull base. Newer scanners can reconstruct the images in any plane with fine details and high accuracy. The new linear accelerators capable of three-dimensional radiotherapy treatments have inbuilt CT scanners, an essential tool for radiation planning.

Magnetic resonance imaging

MRI is the preferred imaging modality for NPC staging and treatment because of its superior soft tissue resolution. For assessment of tumour extent, MRI can better delineate parapharyngeal extension of tumour, perineural spread and marrow infiltration. MRI can also differentiate between tumour infiltration from retained secretions in the paranasal sinuses, and can define better the limits of the optic chiasma, optic nerves and brainstem. Accurate delineation of these structures is important for preservation of these organs at risk in the newer radiotherapy techniques. New generations of radiation planning software systems allow fusion of MRI with CT images for determination of tumour extent and radiation planning, allowing the best of both worlds. Additional imaging modalities like PET-CT can also be fused.

MRI is more useful than CT in monitoring the disease after treatment and imaging recurrent diseases. Post-treatment fibrosis can be difficult to differentiate from recurrent tumour. Traditional MRI sequences may not be much superior to CT[56] but with newer MRI sequences like diffusion weighted images, the diagnostic accuracy of MRI for recurrent disease has increased.[57] The diagnostic accuracy of modern MRI is on par with PET-CT in detecting residual and recurrent disease.[58]

Ultrasound scan

Ultrasound scan is a widely available, inexpensive and non-invasive tool especially suited for investigating neck lymph node metastasis. Ultrasound combined with fine-needle aspiration cytology can achieve a very high sensitivity and specificity for detection nodal metastasis in NPC. In patients with equivocal findings of nodal status on cross-sectional imaging, additional ultrasound guided fine-needle aspiration cytology can provide the diagnosis without resorting to expensive functional imaging modalities like PET-CT scan. The disadvantage of ultrasound scanning is that its accuracy is dependent on the operator. Also, the images and information acquired cannot be fused with other cross-sectional images.

Positron emission tomography

PET is increasingly being used in the management of NPC. A PET scan is a functional imaging study and is normally combined with a cross-sectional imaging modality like a CT scan for anatomical localization. For use in NPC, 18F fluoro-deoxyglucose (18FDG) is the most frequently used isotope. 18FDG is similar to glucose and areas with increased glucose metabolism will be highlighted on PET scans. PET-CT can supplement other imaging modalities in detecting the tumour extent and nodal metastasis but cannot replace MRI scans. PET-CT is less accurate in the delineation of tumour extent in the skull base.[59] Since PET-CT is a whole body scan, it can also detect distant metastases in addition to loco-regional disease extent. Patients with bulky nodal disease have an increased chance of distant metastases, and PET-CT is highly recommended for this group of patients prior to treatment.

PET-CT is very useful in assessing residual and recurrent disease after treatment. Conventional MRI is inferior to PET-CT and the clinician may need serial MRI scans to detect recurrence.[60] PET-CT detects both loco-regional failures and distant failures and is especially recommended in patients with a rising trend of EBV DNA titre after treatment.[61]

STAGING

The biological behaviour and prognosis of NPC is vastly different from squamous cell carcinoma of the head and neck region and the staging system is also different. The modified Ho's stage classification was widely used in the last millennium and was based on the treatment results with conventional two-dimensional radiotherapy techniques. This has now been replaced by the newer International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) staging systems that rely more on cross-sectional imaging for staging and reflect the improved outcomes with newer radiation techniques like intensity modulated radiotherapy and concurrent chemoradiotherapy. The new AJCC eighth edition staging of NPC has several major changes reflecting these improvements.[62] **Table 8.2** sets out the TNM and group stages as per the eighth edition of the AJCC system.

PRIMARY TREATMENT

The non-keratinizating subtype of NPC is a very radiosensitive tumour. Radiotherapy is the mainstay of treatment for primary NPC and surgical treatment is reserved for salvage of radiation failures. The two major advances in NPC management are the introduction of intensity-modulated radiotherapy (IMRT) and the discovery that concurrent chemoradiation improves the efficacy of radiotherapy.

Radiotherapy

Radiotherapy is the cornerstone of loco-regional treatment for all stages of NPC without distant metastases (i.e. from stage I to IVB diseases). Early stage diseases, including stage I and low-risk stage II NPC, can be treated with radical radiotherapy alone. Stage II disease with higher tumour load and stage III, IV disease require combination chemotherapy and radiotherapy.

Intensity-modulated radiotherapy (IMRT) is the standard of care for radiation treatment of NPC. Radiotherapy planning starts with making an individualized immobilization device, usually a thermoplastic cast for the head and neck for each patient. Then, a planning CT scan is obtained with the patient in cast and in treatment position.

TABLE 8.2 AJCC stage classification for NPC[62]*

Primary tumour (T)>		**Regional lymph nodes (N)**	
Tx	Primary tumour cannot be assessed	**N1**	Unilateral metastasis, in cervical lymph node(s), and/or unilateral or bilateral metastasis in retropharyngeal lymph nodes, 6 cm or less, above the caudal border of cricoid carilage
T1	Tumour confined to nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal space involvement	**N2**	Bilateral metastasis in cervical lymph node(s), 6 cm or less above the caudal border of cricoid cartilage
T2	Tumour with extension to parapharyngeal space and/or infiltration of the medial pterygoid, lateral pterygoid, and/or prevertebral muscles	**N2**	Metastasis in cervical lymph node(s) greater than 6 cm in dimension and/or extension below the caudal border of cricoid cartilage
T3	Tumour invades bony structures of skull base cervical vertebra, pterygoid structures, and/or paranasal sinuses		
T4	Tumour with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, parotid gland and/or infiltration beyond the lateral surface of the lateral pterygoid muscle		

Metastatic disease (M)	
M0	No distant metastasis
M1	Distant metastasis present

Stage groups			
I	T1	N0	M0
II	T1 T2	N1 N0, N1	M0 M0
III	T1, T2 T3	N2 N0-, N1, N2	M0 M0
IVA	T4 Any T	N0, N1, N2 N3	M0 M0
IVB	Any T	N3	M0
IV	Compressed previous stage IVB now IVA		

* reprinted with permission[62]

The planning CT scan is used for localization of targets and normal tissues. The required doses to targets and the dose constraints to normal tissues are input into the computer planning system, which will generate the optimal radiation plan that concentrates the radiation dose in targets while minimizing the dose to normal tissues.

There are different treatment targets: gross tumour volume (GTV, both for the primary in NP and for involved neck nodes); clinical target volume (CTV, which includes the GTV and covers for subclinical disease spread around NP and neck); planning target volume (PTV, which includes the CTV with a margin to allow for possible errors in daily positioning and treatment of patient during radiotherapy).

GTVs will include the tumour in NP and any enlarged (>6 mm) retropharyngeal and neck nodes or lymph nodes with necrotic centres. CTV1 includes the GTVs with margin and requires radiation dose of around 70 Gy. The high risk subclinical disease is covered by CTV2, which include CTV1 with margin plus areas at risk of microscopic involvement, including the entire NP, retropharyngeal nodal regions, skull base, clivus, pterygoid fossae, parapharyngeal space, sphenoid sinus, and the posterior part of the nasal cavity/maxillary sinuses that includes the pterygopalatine fossae.[63, 64] CTV 2 requires at least 60 Gy for treatment. The neck is always irradiated together with the primary and the CTV would include bilateral level I through V nodal regions. At levels with nodal involvement, the dose to CTV should be at least 60 Gy. A lower dose, 54–60 Gy, may be given for prophylactic irradiation of uninvolved nodal regions.

IMRT has 'dose-painting' capacity that allows different dose levels to different regions to be applied in the same treatment. For example, in a course of IMRT with 33 fractions over 6.5 weeks, CTV1 may be treated to 70 Gy at 2.12 Gy/fraction while CTV2 can be treated to 66 Gy at 1.82 Gy/fraction. This simultaneous-integrated boost technique allows for a degree of accelerated fractionation in tumour without overdosing the normal tissues. With IMRT, local control rates of over 90% have been reported. The complications from conventional two-dimensional radiotherapy such as hearing loss, xerostomia, temporal lobe neuropathy, trismus and neck fibrosis, are reduced.[65] **Figure 8.5** shows a screen capture from the planning software depicting the dose-painting technique of IMRT.

Chemotherapy

NPC is known to be sensitive to both chemotherapy and radiotherapy. Several studies combining chemotherapy and radiotherapy in treatment of NPC have been published, but the sequence of administration of chemotherapy in relation to radiotherapy and the choice of chemotherapy is important.

The pivotal Intergroup study 0099 established concurrent cisplatin during radiotherapy followed by adjuvant cisplatin and fluorouracil as the standard of care for advanced NPC.[66] The Meta-Analysis of Chemotherapy in Nasopharyngeal Carcinoma (MAC-NPC) showed a survival benefit with the use of chemotherapy in addition to radiotherapy in treatment of NPC.[67] The effect was most significant when chemotherapy was used concurrently with radiotherapy (pooled hazard ratio of death: 0.6). An update of the meta-analysis was reported in 2014

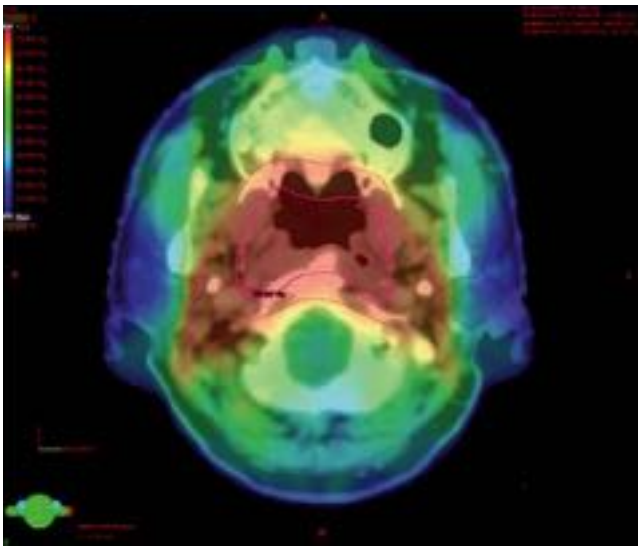


Figure 8.5 Dosimetry plot of IMRT on the nasopharynx. The patient was treated with dose-painting with IMRT: the NP was treated to 70 Gy while the high-risk area was treated to 66 Gy in 33 fractions. The parotids on both sides were treated to 20 Gy or less. Red ~ 65–70 Gy, green ~ 45–50 Gy and blue ~ 20 Gy.

that included additional trials (overall 19 trials and 4798 patients) since the last meta-analysis.[68] There was a significant benefit of chemotherapy in addition to radiotherapy in improving overall survival (hazard ratio: 0.79). There was a significant interaction between treatment effect on overall survival and the timing of chemotherapy, in favour of concurrent chemotherapy with or without adjuvant chemotherapy compared with induction or adjuvant chemotherapy alone.

Cisplatin is the usual agent used concurrently with radiotherapy. Weekly (30–40 mg/m^2) or 3-weekly (100 mg/m^2) cisplatin are acceptable standards of care. A total dose of 200 mg/m^2 administered during radiotherapy is required to benefit survival. The benefit of adjuvant chemotherapy in addition to the concurrent chemoradiotherapy is less certain. Recently, there has been renewed interest in the use of induction chemotherapy, especially in addition to concurrent chemotherapy. The preliminary results of the NPC-0501 study reported from Hong Kong showed that outcomes were not significantly impacted by changing from the concurrent-adjuvant sequence to induction-concurrent sequence with potential benefit of using induction cisplatin and capecitabine in place of cisplatin and fluorouracil.[69]

Unlike squamous cell carcinoma of the head and neck region, epidermal growth factor receptor tyrosine kinase inhibitors like cetuximab had not been shown to be beneficial, either as a single agent for palliative treatment or in addition to chemoradiation for primary treatment. As of 2014, there are no randomized controlled trials on the benefits of adding cetuximab in the treatment of NPC. There are small-scale phase II open labelled trials on the addition of cetuximab with concurrent chemoradiation for treatment of primary NPC[70] or cetuximab with carboplatin for recurrent/metastatic NPC that failed first line chemotherapy.[71] The results showed acceptable toxicities but no definite superiority. Further research is required to develop suitable target therapy for NPC.

With the advancement of radiotherapy and improved local control, distant metastases become the dominant pattern of disease failure. Patients who recur now have usually been exposed to cisplatin and fluorouracil in primary treatment. New chemotherapy agents such as taxanes and gemcitabine have been found to be useful in the treatment of recurrent or metastatic NPC. How best to incorporate these newer agents into the primary treatment of NPC and how to use newer prognostic markers like EBV DNA in selecting high-risk patients for more aggressive treatment are areas of intense research.

MONITORING OF TREATMENT AND FOLLOW-UP PLAN

With the introduction of concurrent chemoradiotherapy, persistence of local and regional disease has dropped to less than 10%. Still, it is prudent to confirm that the disease has fully regressed after treatment. Patients should have endoscopy and biopsy of the nasopharynx to confirm disease resolution after the completion of radiotherapy. This should not be performed too early after radiotherapy as tumour cells continue to undergo apoptosis weeks after completion of radiotherapy. One observational study has shown that patients with a nasopharyngeal biopsy showing tumour cells at 8 weeks after radiotherapy will continue to undergo complete regression by 12 weeks, suggesting that disease should only be considered persistent if biopsy is positive at 12 weeks after radiotherapy.[72]

Long-term follow-up of all patients is essential. Most failures occurs within 2 years of treatment[73] but a small percentage of patients develop local recurrence more than 10 years after the primary treatment.[74] Distant failure can occur several years after treatment and long-term complications of radiotherapy may not be seen until 5 years after treatment. There is no consensus on the optimal follow up schedule. Given the insight from patterns of failure, regular 2–3-monthly follow-up in the first 2 years, increased to 3–4 times per year in the third to fifth years, followed by 6-monthly or yearly reviews is advisable.

SALVAGE TREATMENT

Salvage treatment for NPC is moderately successful but with significant morbidities. A large survey of 200 local failures treated with different modalities showed an overall 3-year survival of 74%.[75] As patients with recurrences have already been exposed to the toxicities of previous treatment, the choice of the salvage treatment would need to consider the tolerance of the normal tissue.

Radiotherapy for local failures

Radiotherapy for treatment of local failures can be delivered by external beam or by local brachytherapy. The main limiting factor in re-irradiation is the tolerance of the vital organs like brainstem, optic chiasma and temporal lobe to radiation. Traditional two-dimensional re-irradiation for local failure had poor results, with one study showing a 5-year survival of only 7.6%.[76] The dismal result was due to the dosimetry constraints to avoid excessive radiation to vital organs. With the development of three-dimensional radiotherapy techniques like 3D stereotactic radiotherapy and IMRT, it is possible to reduce the dose or radiation to these vital organs;[77–79] however, adjacent non-vital organs will still be exposed to higher doses. A small series of 30 patients showed the 5-year overall survival and local control using stereotactic radiotherapy to salvage local recurrence were 40% and 57% respectively.[80]

Brachytherapy delivers a high dose of radiation with limited penetration inside the nasopharynx to treat local failures without deep invasion. The main radioactive sources used are iridium-192 (Ir192) and gold 198 (Au198). Both isotopes emit gamma radiation. Delivering brachytherapy needs special techniques. For Ir192, the radioactive source is loaded into a tailor-made plastic mould fitted into the nasopharynx of the patient beforehand. The plastic mould is placed into the nasopharynx via the oral cavity under local anaesthesia.[81, 82] For Au198, the gold grains are implanted to the nasopharynx after the soft palate is split open under general anaesthesia.[83] Both techniques are only suitable for small tumours less than 2 cm in maximal dimension. The 5-year survival rates for salvaging with this technique is in the range of 50–60%.[84]

Radiotherapy for nodal failures

In the era of concurrent chemoradiation, isolated nodal failure is an uncommon event. Only 5% of patients may suffer from isolated nodal failures.[73] Therefore, it is imperative to investigate for any simultaneous local recurrences in patients who present with nodal recurrence. Patients who have persistently enlarged neck lymph nodes 3 months after completion of radiotherapy should be considered to have persistent nodal diseases and offered salvage treatment.[85] In the era of 2D radiation, re-irradiation of isolated nodal failures showed poor results, with less than 20% 5-year survival.[86] Additional radiotherapy also increases the radiation damage to the soft tissues in the neck; therefore, re-irradiation treatment for salvaging nodal failure is not recommended.

Due to the limited penetration of brachytherapy techniques, they can be used for treatment of nodal failure in conjunction with surgical resection of the nodal metastasis. This will be discussed later in the chapter.

Surgery for local failure

The nasopharynx is notoriously difficult to access surgically. Most routes of access require facial incisions and multiple osteotomies, and transgress a significant amount of normal tissue to expose the nasopharynx. Therefore, surgical resection of the nasopharynx, namely nasopharyngectomy, is only reserved for salvaging radiation failures. The decision to offer nasopharyngectomy for salvaging local failures depends on the location of the tumour and the general condition of the patient. The patient should be fit for a 5-hour operation under general anaesthesia. Tumours that show internal carotid artery encasement, extensive skull base infiltration or intracranial extension are not suitable for salvage surgery. Alternative salvage treatment should be offered instead. Since the introduction of nasopharyngectomy for salvaging NPC local failures in the 1980s, significant experience has accumulated at several large volume centres. Nasopharyngectomy in experienced hands has low peri-operative mortality and acceptable morbidities. The 5-year local control is in the range of 70%. A large case series in treatment of local failures showed that there was no significant difference in terms of overall survival in patients treated with a second course of radiotherapy or surgery but nasopharyngectomy was associated with lower morbidities. Only patients with rT1 and rT2 diseases had survival advantage; patients with rT3 and rT4 diseases showed no improvement in survival with retreatment by either means.[75]

As the nasopharynx is in the central part of the head, various approaches can be used. Below is a brief discussion of various approaches.

TRANSPALATAL APPROACH – INFERIOR APPROACH

This approach is extensively used for salvaging NPC local failures. A mucoperiosteal flap of the hard palate is elevated from the bony hard palate from anterior to posterior to expose the attachment of the soft palate. The soft palate is then detached from the bony hard palate and retracted inferiorly to expose the nasopharynx. The posterior edge of the hard palate can be removed to increase the exposure and the recurrent tumour excised under direct vision. The palatal flap is subsequently re-sutured back to the anterior hard palate mucosa at the conclusion of the procedure. The advantages of the procedure are minimal bone removal and no facial incision; disadvantages include limited lateral access to the parapharyngeal space and risk of palatal fistula. Fee et al reported a series of 37 patients treated with this approach with a 5-year overall survival of 52% and local control of 67%.[87]

TRANSCERVICO-MANDIBULO-PALATAL APPROACH – INFEROLATERAL APPROACH

Morton et al first described this approach for salvaging NPC in 1996.[88] This approach improves the exposure of a transpalatal approach by the addition of the lip-splitting mandibulotomy. The mandible is swung laterally and the floor of mouth incision is extended superiorly along the anterior pillar of the tonsil to divide the soft palate from the hard palate. The nasopharynx can then be visualized from the inferio-lateral fashion. This gives a wider view and can offer access to the ipsilateral parapharyngeal space.

However, owing to disruption of large amounts of normal anatomy, significant long-term morbidities are associated with this technique. King et al reported the morbidity profile in a series of 11 patients who underwent nasopharyngectomy via this approach: eight patients had a palatal defect; six patients suffered from trismus; six patients had dysphagia; and three patients had malunion of the mandible.[89]

MIDFACIAL DEGLOVING APPROACH – ANTERIOR APPROACH

The procedure is similar to the midfacial degloving approach for resection nasal cavity cancers and juvenile nasopharyngeal angiofibromas. To increase the exposure of the nasopharynx and room for instrument manipulation, bilateral medial maxillectomies and posterior nasal septectomy should be performed. In a series of 15 cases, the surgeon was able to achieve clear margins in 12 cases but the long-term oncological outcome was not reported.[90] The obvious advantages of this approach are the lack of facial scar and avoiding the risk of a palatal fistula. Exposure can be poor, even when the medial maxillary walls are removed. There is also limited lateral access with this approach. In one cohort, the oncological outcome of the midfacial degloving approach was significantly worse than the maxillary swing approach.[91] The postulation was that NPC frequently had lateral extension and inability to remove disease in the lateral nasopharynx and parapharyngeal space might contribute to the poor oncological outcome.

MAXILLARY SWING APPROACH – ANTERO-LATERAL APPROACH

The approach starts with a standard incision for radial maxillectomy – the Weber-Ferguson-Longmire incision. Osteotomies are made: at the anterior maxilla inferior to the orbital rim; midline at the hard plate just lateral to the nasal septum; at the anterior zygoma separating the maxilla from the zygoma; and finally between the posterior maxillary wall and the pterygoid plates at the maxillary tuberosity. The maxilla is left attached to the anterior cheek skin and the whole maxilla with the cheek skin is retracted laterally to expose the parapharyngeal space and nasopharynx.[92] This approach provides wide exposure of the nasopharynx and parapharyngeal space, allowing the surgeon to perform resection of the tumour not only in the nasopharynx centrally but laterally in the parapharyngeal space and to the origin of the pterygoid muscles. In addition, the surgeon can localize the parapharyngeal internal carotid artery by palpation during dissection in the parapharyngeal space. After performing the resection, the maxilla is put back and the bony osteotomies fixed with titanium plates. Wei reported his 20 years experience of the maxillary swing approach in 246 patients. The treatment results were very encouraging with a 5-year local control of 74% and 5-year disease-free survival of 56%.[93] The disadvantage of this approach is the presence of a facial scar, risk of trismus and palatal fistula formation.



Figure 8.6 (a) Weber-Ferguson-Longmire incision for maxillary swing approach to the nasopharynx. (b) View of the nasopharynx after swinging the maxilla laterally.

Figure 8.6 shows the facial incision for the maxillary swing approach and view of the nasopharynx after swinging the maxilla laterally.

FACIAL TRANSLOCATION APPROACH – ANTERO-LATERAL APPROACH

An alternative approach is the facial translocation procedure. In this approach, the whole maxilla, including the floor of the orbit, lateral orbital rim, malar prominence and zygomatic arch, is removed. Part of the coronoid process is also removed to provide exposure to the infratemporal fossa and masticator space. The maxilla is detached from the cheek flap and is replaced back to the facial skeleton as a free bone graft, secured with titanium plates. Hao et al report in a 53-patient cohort using this approach a 5-year local control rate of 53.6% and a 5-year overall survival rate of 48.7%, comparable to the maxillary swing approach.[94] The facial translocation approach has better

lateral exposure than the maxillary swing approach at the expense of jeopardizing the blood supply to the maxilla bone. This lateral exposure is usually not required in small recurrent tumours in the nasopharynx and a maxillary swing approach should suffice for resection of most locally recurrent NPC.

LATERAL SKULL BASE APPROACH – LATERAL APPROACH

This approach is based on neurotological principles.[95] Via an extended post-auricular incision, the external auditory canal is closed as a blind sac and the whole auricle is retracted anteriorly with the flap. An extended mastoidectomy and total parotidectomy are then performed to allow the rerouting of the facial nerve. The zygomatic arch is removed and the temporalis muscle is then divided so that the base of the middle cranial fossa can be accessed. To improve the exposure, the condylar process of the mandible can be removed. The mandibular branch of the trigeminal nerve has to be divided and the pterygoid muscles removed from the attachment to the lateral pterygoid plate. The internal carotid artery is then identified and retracted. The tissue in the parapharyngeal space including the cartilaginous Eustachian tube can be resected *en bloc* with the tumour in the nasopharynx.

The advantage of this approach is the early identification and protection of the internal carotid artery. The major disadvantage is the extent of mobilization of normal tissues that needs to be performed to expose the tumour and subsequent morbidity. The visualization of the midline of the nasopharynx and access to resect lesions extending anteriorly to the nasal cavity and paranasal sinuses is poor. Of the 13 patients treated with the approach by Fisch et al, six patients with small recurrences had good local control.[96] Few other reports exist of the use of this approach for resecting recurrent NPC, given that other simpler approaches provide more direct exposure.

ENDOSCOPIC APPROACH

Endoscopic endonasal approach to the anterior skull base is now an established surgical approach to resect tumours in the nasal cavities, paranasal sinuses and anterior skull base.[97] Employing the endoscopic approach to resect nasopharynx tumour is a natural extension of application. Since the first decade of the 21st century, several case series on using the endoscopic approach to resect recurrent NPC have been published. Most of the cases were small tumours with short follow-up periods. The oncological results of endoscopic nasopharyngectomy are respectable, with most series having a 2-year local control of over 80%.[98] The endoscopic approach causes no damage to normal structures of the facial skeleton and minimal loss of function.

An extension of the endoscopic approach is the application of the da Vinci surgical robot (Intuitive Surgical Inc., Sunnyvale, USA) to assist the minimally invasive nasopharyngectomy. The da Vinci surgical robot has been successfully applied to resection of early oropharyngeal, laryngeal and hypopharyngeal cancers. The advantages of the surgical robot include 3D optics, superior manipulation of surgical instruments in tight space, motion scaling and tremor filtration. The nasopharynx is a confined space and endoscopic surgery suffers from lack of space for triangulation of instruments. The da Vinci surgical robot can allow complex movements like suturing, blunt and sharp dissection to be performed in the confined space of the nasopharynx similar to open procedure. Ozer and Waltonen in 2008 first reported a cadaveric experiment on using the da Vinci surgical robot to perform nasopharyngectomy[99] and Wei and Ho in 2010 reported the first clinical case of robotic assisted nasopharyngectomy.[100] Tsang et al have reported a case series of 12 patients who underwent robotic assisited nasopharyngectomy and the 2-year local control was 86%, comparable to other endoscopic nasopharyngectomy series.[101] The advantage over open nasopharyngectomy included shorter hospital stay and less blood loss. **Figure 8.7** is a screen capture from the da Vinci surgical robot performing a robotic nasopharyngectomy.

SURGERY FOR NODAL FAILURES

The poor results and high complication rate for salvaging nodal failures with re-irradiation means alternative management options should be sought for treating nodal failures. Radial neck dissection is considered as the standard of care for management of nodal failures.[85] The rationale for performing radical neck dissection instead of a lesser operation is based on several clinical observations on nodal failures in NPC. First, there are usually multiple nodes that are involved in NPC, even if pre-operative imaging suggests only single-node involvement. Second, extra-capsular involvement is high, reported as high as 70% in one study.[102] As further radiation may not be possible, sparing structures like the internal jugular vein or sternocleidomastoid muscle may leave behind microscopic disease that would not receive post-operative radiotherapy. The spinal accessory nodes are frequently involved in

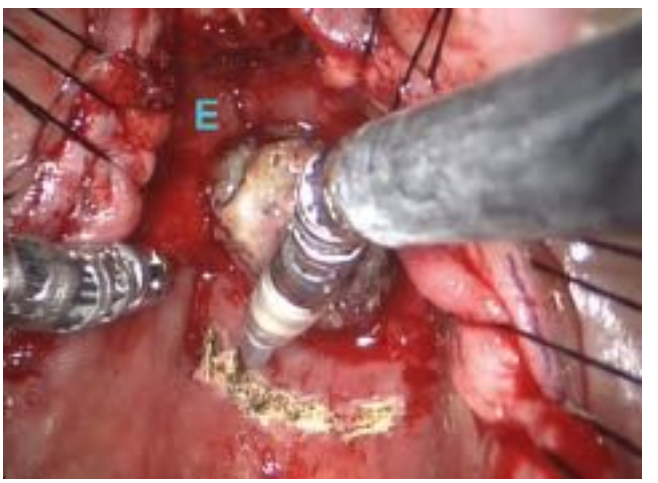


Figure 8.7 Screen capture from the da Vinci surgical robot performing robotic nasopharyngectomy. The soft palate was split in the middling to facilitate placement of the robotic arms.

NPC metastasis and together with the high risk of extracapsular spread, a type I modified radical neck dissection is still suboptimal. However, recent studies have shown that level I lymph nodes are rarely involved and can be spared in the neck dissection.[103]

For advanced nodal disease where the tumour may invade vital structures like the brachial plexus or fully encases the carotid artery at the skull base level, complete excision with sacrifice of these structures may not be advisable. If appropriate, surgery with palliative intent can be offered, as long as realistic goals for the procedure are set. The patient can then be prepared for brachytherapy with after-loading of radioactive source. Special plastic nylon tubes can be placed across the affected area 1 cm apart (**Figure 8.8**). The overlying skin should be removed as it may undergo necrosis after the re-irradiation. The skin defect can then be covered with an appropriate reconstructive option based on patient factors and the expertise available. After the completion of the brachytherapy, the plastic tubes can be removed at the bedside.

Salvaging nodal recurrent disease with radical neck dissection has a 5-year local control rate of 66% and 5-year overall survival of 37%.[104] In one series, the 5-year overall survival and 5-year local control for salvaging advanced nodal disease with radical neck dissection and brachytherapy were 72% and 48% respectively, comparable to less advanced disease treated with neck dissection only.



Figure 8.8 Salvage neck dissection for nodal recurrence in NPC. Plastic tubes were placed 1 cm apart for insertion of radioactive sources during brachytherapy. The overlying skin was involved and resected. A pectoralis myocutaneous flap was used to cover the defect.

TREATMENT OF METASTATIC DISEASE

Treatment for oligometastasis

Traditionally, distant metastases were not treated with surgery. With successful surgical resection and long-term survival for solitary metastasis from colon cancer, interest in curative treatment of distant disease in head and neck cancer has been renewed. A large single-centre review showed that 34% of patients with metastatic disease had single organ metastasis, and 16% with solitary metastasis at the time of diagnosis.[105] Options for treatment of oligometastasis include surgical resection, radiofrequency ablation and radiotherapy.[106–108] Although reports are usually case series and prone to selection bias, addition of curative treatment shows significantly better survival than chemotherapy alone in cases where the metastasis can be completely ablated. This area is now a focus of additional research and may redefine our current definition of incurable disease.

Chemotherapy for distant metastasis

Survival of over 6 months after development of distant metastasis was once considered a rarity. With increasing choice of new chemotherapeutic agents, there are now more options for continuation of palliative chemotherapy should one regimen fail. Traditional first-line chemotherapy for metastatic NPC is a combination of cisplatin and 5-florouracil and the medial overall survival is around 12 months. Second-line drugs include gemcitabine, docetaxel, capecitabine and paclitaxel. The newer agents have reported response rates of 50–70% and are well tolerated.[109] Palliative chemotherapy should be offered unless the patient's general condition is not fit.

PROGNOSIS

The treatment results of NPC have shown remarkable improvement in the last 40 years. The age standardized mortality rate for NPC in Hong Kong in 1983 was 9.8 per 100 000, dropping to 7.4/100 000 in 1993 and 3.0/100 000 in 2012. This threefold reduction in mortality is partly caused by 30% reduction in incidence but, more importantly, by the improvement in curative treatments. The two main reasons for improvement are the introduction of IMRT and concurrent chemoradiation as a standard of care in Hong Kong. Most contemporary studies report locoregional control rates of over 90% at 2–5 years and distant disease accounts for most failures. A large series from Hong Kong with more than 2600 patients showed a 5-year distant recurrence rate of 19%.[73]

Analyzing the survival, with the AJCC eighth edition stage classification, of more than 900 patients from 1998–2007 treated with 3D conformal radiation or IMRT with or without chemotherapy, Lee et al reported the 5-year disease-specific survival for stage I was 100%, stage II 90%, stage III 67%, stage IVA 67%, stage IVB 68% and stage IVC 18%.[110] This is a remarkable improvement as in the last edition of this book, the quoted 5-year survival for stage IVA-B was in the range of 20–40%.

COMPLICATIONS OF TREATMENT

Radical radiotherapy for NPC inevitably exposes normal tissue in the vicinity of the tumour to a damaging dose of radiation. Acute, subacute and late complications are well recognized and reported in the literature. A useful source of information on the subject can be obtained from the comprehensive review of Lee.[111]

As the mucosa of the head and neck region is the radiation volume, mucositis of the oral cavity, oropharynx and hypopharynx occurs to a varying degree during treatment. The mucositis can be severely aggravated if concurrent chemotherapy is given. Up to 90% of patients may need enteral feeding via a gastrostomy or nasogastric tube. Salivary function will be decreased during radiotherapy and depending on the dose to the major salivary glands, the salivary function may or may not recover. With IMRT, it is now possible to reduce the dose to the contralateral parotid gland in T1-T2 tumours and reducing the incidence of lifelong xerostomia.[112]

Otological complications frequently occur after radiation. OME, acute otitis media and otitis externa are common complications. The treatment of OME should be conservative as current evidence shows that the use of a grommet during or soon after radiotherapy is associated with a high incidence of persistent perforation and purulent otorrhoea.[113] Late complications of radiotherapy to the ears include sensorineural hearing loss and osteoradionecrosis of the temporal bone. A minor proportion of sensorineural hearing loss patients may lead to complete deafness but, fortunately, most can be salvaged by cochlear implants. Minor osteoradionecrosis of the external auditory canal can usually be managed conservatively with frequent cleaning and antibiotic ear drops. Significant osteoradionecrosis of the temporal bone can lead to deafness, facial nerve palsy and intracranial infection. The necrotic bone may need to be debrided and the defect covered with a local temporalis muscle flap or a vascularized free flap.[114, 115] With the introduction of IMRT and limitation of the radiation dose to the cochlea and temporal bone, the incidence of temporal bone complications are expected to reduce.[116]

Olfactory dysfunction, nasal crusting, rhinosinusitis and intranasal adhesions are common nasal complications. Olfactory dysfunction, usually transient, occurs in quite a number of patients towards the end of radiotherapy and slowly recovers over the next few months. Nasal crusting and symptoms of rhinosinusitis (thick nasal catarrh and foul smelling nasal discharge) are very common following radiotherapy. Regular saline nasal douching in the first few years after radiotherapy with courses of antibiotics may be needed for adequate control. Minor nasal adhesions between septal spurs and the nasal turbinates are quite common and need no treatment. Occasionally, marked scarring at or close to the choana (**Figure 8.9**) may occur, particularly in patients with more advanced local disease requiring a higher local dose of radiation through afterloading brachytherapy. These adhesions should be removed to facilitate future endoscopic assessment of the nasopharynx.

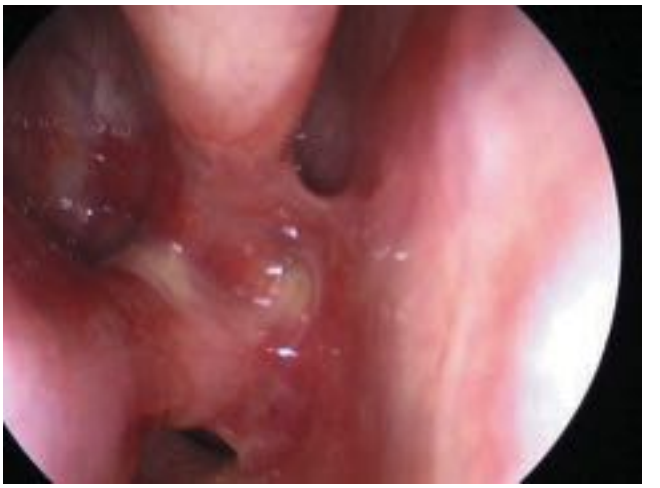


Figure 8.9 Early intranasal adhesions after radiotherapy as seen through a 0° rigid nasendoscope situated inside the right nostril. Note the adhesions around the posterior ends of the middle and inferior turbinates and the nasal septum.

The latent interval of late complications can vary from several months to many years after irradiation, owing to irreversible damage. Tissues that have poor powers of regeneration, such as sensory and neural tissues, are particularly prone. Apart from the total radiation dose, the dose fractionation and timing of delivery will affect the occurrence of late complications.

With the old 2D radiotherapy techniques, the reported incidence of late complication can be more than 30%.[117] Data on long-term complications with the modern IMRT is still lacking but as the dose to the normal tissue is reduced, hopefully we will see a reduction in the long-term complications in the future. On the other hand, the addition of concurrent chemotherapy increases the long-term toxicity of radiation. Swallowing problems in NPC patients treated with radiotherapy is very common and can occur early after treatment.[118] Late dysphagia can affect up to 50% of the head and neck cancer patients treated with concurrent chemoradiation[119] and this increase in late dysphagia is also seen in NPC patients.[120, 121] Dysphagia not only affects quality of life[122] but can also lead to life-threatening aspiration pneumonia.[123]

Radiation-induced fibrosis is another late complication that can lead to neck stiffness and trismus. Apart from osteoradionecrosis of the temporal bone, the skull base and mandible are also at risk for this complication.

Initial treatment including local debridement and hyperbaric oxygen is helpful, but some patients may need definitive resection of the involved bone segment and reconstruction with a free osteocutaneous flap. Osteoradionecrosis of the skull base and radiation fibrosis can lead to lower cranial nerve palsies.[124, 125] The differential diagnosis of late lower cranial nerve palsies is local recurrence and can be difficult to differentiate from osteoradionecrosis or post-radiation fibrosis. Hypothalamic-pituitary dysfunction may result in a range of hormonal deficiencies requiring lifelong replacement therapy. The symptoms and signs of hormonal dysfunctions are subtle and require a high index of suspicion for their diagnosis. Temporal lobe necrosis can develop in patients that were treated with the old radiation techniques but, with modern IMRT, the dose to the temporal lobe is minimal, unless it is for re-irradiation. The symptoms and signs of temporal lobe necrosis are subtle, including personality changes, memory loss and loss of cognitive function. The overt cases may present with epileptic attacks and the more severe cases with symptoms and signs of raised intracranial pressure.

Radiation-induced malignancies mostly develop beyond 5 years after radiotherapy and occur in around 0.3–3% of patients. Radiation-induced malignancy is more important in NPC than other head and neck cancers as patients are younger and coupled with the high cure rate, more patients can survive long enough to develop a radiation-induced cancer. Radiation-induced malignancies can be broadly divided into mucosal squamous cell carcinomas and radiation-induced sarcomas. Unlike atomic bomb survivors, radiation-induced thyroid malignancy is rare in NPC patients. Mucosal squamous cell carcinoma commonly can occur in the edge of the radiation field, including the external auditory canal, middle ear, paranasal sinuses, oral tongue, oropharynx and hypopharynx. It can also occur in the nasopharynx, which needs to be differentiated from local recurrence. Radiation-induced sarcomas are often of the fibrosarcoma or osteosarcoma subtype and usually occur in patients who have received a high dose of radiation. Radiation-induced sarcomas are often difficult to diagnose and can be confused with radiation fibrosis or radionecrosis.[126] Curative resection with clear margins is still the best treatment for radiation-induced malignancies. The prognosis of radiation-induced malignancy is often poor due to the delay in diagnosis, inability to deliver further multimodality treatments and poor performance status of the patients as they suffer from other complications of radiation.[127]

Internal carotid artery aneurysm is a rare life-threatening complication after radiotherapy for NPC. The typical patient will present with minor sentinel bleeds followed by massive epistaxis a few hours to a few days later. Treatment includes prompt airway control followed by endovascular stenting of the internal carotid artery to exclude the aneurysm or ligation of the affected internal carotid artery with vascular bypass. A high index of suspicion is required to diagnose the condition before the patient develops massive rupture of the aneurysm.[128]

CONCLUSION

NPC is a unique disease with a highly variable geographical distribution, distinct viral aetiology interplaying with individual genetic susceptibility and environmental carcinogens. The last two decades have seen a remarkable advance in the treatment in all fronts; from 2D radiation to IMRT, single agent chemotherapy to targeted therapy and open surgery to endoscopic resection. Future developments in in the basic science of the disease include a vaccine for EBV, better understanding of the molecular genetics and newer tumour markers for screening and monitoring of the disease. Newer radiotherapy techniques including image-guided radiotherapy, adaptive radiotherapy and proton radiotherapy are available and may become the mainstream treatment modality. Technological advancements may enable surgeons to perform more endoscopic or robotic surgeries as salvage, reducing the morbidity from open resection.

BEST CLINICAL PRACTICE

- ✓ Nasopharyngeal biopsy under endoscopy should be the first and definitive investigation to establish the diagnosis.
- ✓ NPC is highly radiosensitive; radiation is the first-line treatment for all primary NPC.
- ✓ Radiation delivered in the form of IMRT with up to 66–72 Gy to the gross tumour and involved lymph nodes. 60 Gy of radiation should be given to clinically negative cervical lymph nodes. IMRT will enable delivery of adequate radiation to target the tumour while reducing the radiation dose to adjacent normal structures.
- ✓ Radiation with concurrent chemotherapy is the gold standard for more advanced disease, including stage II disease with bulking lymph nodes and all stage III and stage IV diseases. Cisplatin, delivered either weekly at 40 mg/m^2 or 3-weekly at 100 mg/m^2, is the gold standard.
- ✓ Patients should be followed up regularly after treatment to detect recurrence and complications from treatment.
- ✓ Salvage surgery should be considered for local or regional recurrence as surgery can spare the significant morbidity from re-irradiation.
- ✓ Effective new chemotherapeutic agents are now available for patients with disseminated disease and can offer useful palliation and prolong overall survival.

FUTURE RESEARCH

- The exact role of EBV in the carcinogenesis of endemic form of NPC.
- What are the exact genetic factors in the carcinogenesis of NPC and can these genes be used to define high-risk patients?
- Can the development of a successful EBV vaccine reduce future NPC development in an endemic population?
- What is the best strategy to deploy a mass-screening programme in endemic areas that is cost-effective and improves treatment outcome?
- How can long-term morbidities from chemoradiation, especially in terms of late dysphagia, be further minimized? Can we further reduce the radiation dosage to normal tissue without jeopardizing disease control?
- What is the role of minimally invasive surgeries like endoscopic surgery and robotic surgery in salvaging local recurrence?
- The development of target therapy and newer chemotherapeutic agents with similar or better efficacy than the current line of chemotherapy but with less toxicities.

KEY POINTS

- Nasopharyngeal carcinoma is unique among all head and neck cancers because of wide geographical and ethnic variation in incidence rates. The annual incidence rate in areas with high prevalence of the disease can be up to 50 times higher than low prevalence areas.
- The highest incidence is found in Southern China, including Taiwan, Hong Kong and Macau. Migrants originating from high incidence areas also have a high incidence of developing NPC, though the risk decreases in second or third generation migrants.
- Populations from Malaysia, Indonesia, Arabia, North Africa, Thailand and the Philippines, and Inuits (from Canada and Greenland), have intermediate incidence of NPC.
- Caucasians and populations from Northern China and East Asia (Japan and Korea) have a low incidence of NPC.
- The commonest histological form of NPC in an endemic area is the poorly differentiated type or undifferentiated type (WHO types II and III). The endemic form of the cancer is associated with EBV, and EBV genomes are found in all cancer cells.
- The peak incidence of NPC is around the fourth to fifth decade, a decade earlier than other head and neck squamous cell carcinoma.
- Consumption of salted fish and preserved foods, especially at a young age, are considered as aetiological factors. Smokers also have a moderate increase in risk.
- The aetiology of NPC is the result of a complex interplay of genetic factors, early latent infection by EBV and its subsequent reactivation and exposure to environmental carcinogens. The carcinogenesis of NPC is probably a multistep process.
- Serum EBV IgA antibiodies against viral capsin antigen (VCA), early antigen (EA) and Epstein—Barr nuclear antigens (EBNA) are elevated in patients suffering from NPC and can be used as a tumour marker for screening the cancer. These serological markers are not useful for monitoring of treatment efficacy and screening for recurrence.
- Plasma EBV DNA is a more sensitive and specific tumour marker for NPC. It is also useful for prognostication, monitoring of treatment response and screening for tumour recurrence.
- Symptomatology of NPC can be vague, easily ignored and confused with other conditions. Physical examination often cannot pick up the diagnosis. A high index of suspicion is required to avoid delaying the diagnosis, especially if the patient ethnicity is from an endemic area.
- The most common complaint at presentation is the presence of upper neck swelling: unilateral neck swelling is most common, but bilateral neck metastases are not infrequent. Cervical lymphadenopathy is the presenting complaint in almost 50% of patients. A significant proportion of patients presenting with other complaints also have cervical lymphadenopathy on examination.
- 30% of patients present with nasal symptoms, including blood-stained nasal discharge, nasal obstruction, postnasal drip or even frank epistaxis.
- Approximately 20% of patients present with aural symptoms, including deafness, tinnitus and otalgia. A retracted tympanic membrane or OME is a very common clinical finding. This finding usually correlates with the side of the nasopharynx that has bulkier disease. Adult patients with unexplained unilateral persistent OME should be screened for the presence of occult NPC.
- Neurological complaints include headaches or cranial nerve symptoms. Headaches are a common complaint, occurring in almost 20% of patients, but they may be referred pain when distal branches of the trigeminal nerve are invaded by the tumour in the nasopharynx or nose. However, they can also be the result of bony erosion of the skull base. Cranial nerve symptom(s) may be isolated or multiple. In either case, it occurs late in the disease from the spread of the tumour through the foramina of the base of the skull or with parapharyngeal involvement of the last four cranial nerves. Cranial nerves V and VI are the most commonly involved. When cranial nerves III–VI are affected together, cavernous sinus involvement is the cause. Horner syndrome is rare, but if present is typically accompanied by paresis of one or more of the last cranial nerves.
- MRI is the imaging of choice for delineating the extent of disease in the skull base. CT scan is useful in detecting cortical bone erosion in the skull base but cannot often differentiate between normal structures and tumour invasion in the skull base. PET CT is a useful adjunct to delineate the extent of disease, nodal metastasis and distant metastasis.
- The nodal staging of NPC is different from other head and neck squamous cell carcinoma. The number of lymph nodes involved is not considered in the nodal staging. The laterality (bilateral = N2), size (>6 cm) and inferior location (extends below caudal border of cricoid cartilage) are the considerations in nodal staging.

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CHAPTER 9

BENIGN SALIVARY GLAND TUMOURS

Jarrod Homer and Andrew Robson

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search of publications that focused on the pathology, aetiology and management of benign salivary gland tumours.

INTRODUCTION

There are a number of important issues to address in patients with tumours of the major salivary glands. Accurate and rapid pre-operative diagnosis is imperative, in order to diagnose malignancy. There is some controversy in the choice of correct operation of the commonest type and location of tumour: a pleomorphic adenoma of the parotid gland. The anatomical relationship of a tumour to the facial nerve (or branch) in the parotid gland is nearly always intimate and the potential for a catastrophic cosmetic handicap can make surgery challenging. In is interesting to observe that, whist there has been a great deal of commentary regarding adequate workload in, for example, thyroid surgery, there has been almost none regarding parotid surgery; and yet the consequences of suboptimal surgery that includes incomplete tumour resection and facial palsy are potentially catastrophic for the patient.

In this chapter, these issues and others are addressed and guidelines for the management of benign salivary gland tumours are established.

EPIDEMIOLOGY AND DISTRIBUTION

Bradley and McGurk[1] analyzed the incidence of salivary gland tumours in a defined population in Nottinghamshire, UK between 1988 and 2007. They reported an incidence of benign parotid neoplasms of 5.3–6.2 per 100 000 population and 0.5–0.55 per 100 000 of benign submandibular tumours. The distribution between sites conformed to the traditional teaching of approximately 80% within the parotid gland, and 10% within the submandibular and minor salivary glands respectively. From these data, there does not appear to be a change in annual incidence of benign salivary gland tumours over the 20-year reporting period in the paper.[1]

All age groups are affected with a peak incidence in the sixth decade. There is a female preponderance, with the exception of Warthin's tumours, which are more common in males.[2]

Table 9.1 compares information from Bradley and McGurk[1] (1065 cases including malignant tumours) with a 1985 publication of British Salivary Gland Tumour data of 2410 cases.[2]

The distribution between histological types is shown in **Table 9.2**.

TABLE 9.1 Frequency of epithelia salivary gland tumours and malignancy analyzed by site

	Benign vs malignant (%)	
Site	**Eveson & Cawson[2]**	**Bradley & McGurk[1]**
Parotid	85	91
Submandibular	64	75
Sublingual	14	0
Minor glands	54	60

TABLE 9.2 Histological types of benign tumour by site in a Nottingham population 1988–1997 and 1998–2007

	Major salivary glands						Minor glands		Total		
	Parotid		Submandibular		Sublingual						
	88–98	98-07	88–97	98–07	88–97	98–07	88–97	98–07	88–97	98–07	Cumulative
Pleomorphic adenoma	275	263	31	36	–	–	28	18	333	318	651
Warthin's tumour	100	100	2	1	–	–	–	–	102	101	203
Oncocytoma	3	6	1	0	–	–	–	–	4	6	10
Monomorphic, NOS	9	0	1	0	–	–	–	–	10	0	10
Basal cell carcinoma	6	13	1	0	–	–	–	2	7	15	22
Canalicular adenoma	–	–	–	–	–	–	3	3	3	3	6
Cystadenoma	3	0	–	–	–	–	1	–	4	0	4
Myoepithelioma	1	5	–	–	–	–	–	4	1	9	10
Fibromyoma	–	–	–	1	–	–	–	–	0	1	1
Lipoblastoma	–	–	–	2	–	–	–	–	0	1	1
Total	397	387	36	36	–	–	32	27	464	454	918

AETIOLOGY

Whilst radiation can induce malignant salivary gland tumours, the evidence that it can induce benign tumours is much weaker; restricted to a possible association with Warthin's tumours.[3] In recent years, public concern has focused on the use of mobile telephones and the development of regional malignancies, induced by electromagnetic fields. However, there is no evidence of an increased risk of salivary gland tumours.[4] It has been speculated that human papillomavirus 16 (HPV16) may be associated with pathogenesis of benign salivary tumours, but there is no convincing evidence for such.[5, 6]

PRESENTATION

Most parotid and submandibular gland tumours grow slowly over a long period of time without causing symptoms. A very small number cause discomfort by obstructing salivary flow. Most benign tumours will be smooth, relatively mobile and painless to palpate. The following symptoms and signs suggest the tumour may be malignant or be undergoing malignant transformation:

- pain
- paraesthesia (especially adenoid cystic carcinoma)
- rapid growth or an increase in rate of growth
- facial nerve palsy/other nerve palsy
- skin involvement
- fixity
- irregularity.

A further consideration is the age of the patient and the site of the tumour. Malignancy is relatively more likely in younger patients and in submandibular tumours (40% malignant).

The patient with a parotid tumour eventually becomes aware of a firm mass that is steadily getting bigger behind the angle of their jaw in the retromandibular region, in front of the tragus or in the cheek (**Figure 9.1**). Deep lobe parotid and parapharyngeal space tumours may displace the tonsil and palate medially and are often impalpable

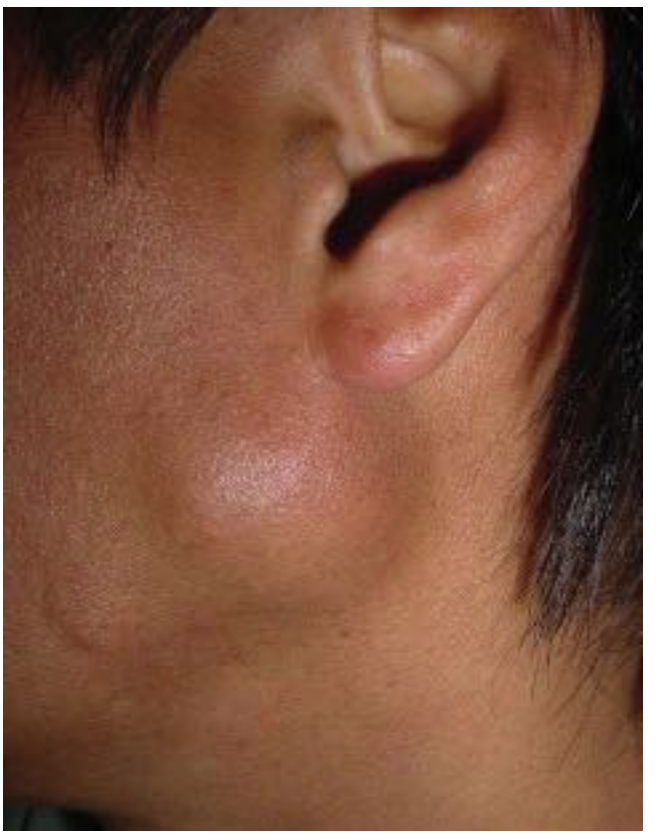


Figure 9.1 Typical presentation of a pleomorphic adenoma of the parotid gland, a retromandibular swelling.

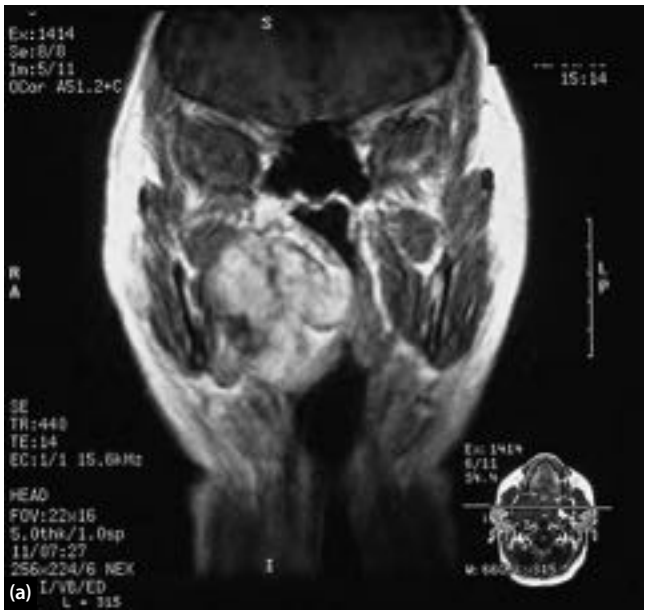




Figure 9.2 **(a)** MRI of a very large deep lobe parotid tumour that had caused Eustachian tube dysfunction, altered the quality of voice and resulted in obstructive sleep apnoea; **(b)** typical intraoral appearance of a deep lobe tumour with medial displacement of the right tonsil.



Figure 9.3 A pleomorphic adenoma of the submandibular gland presenting as a swelling in the submandibular triangle.



Figure 9.4 Unilateral swelling of the left side of the palate, typical of a minor salivary gland tumour.

from outside. Very large parapharyngeal salivary tumours cause stertor, sleep disordered breathing, affect the quality of the patient's voice and may even interfere with Eustachian tube function (**Figure 9.2**). Increasing numbers of salivary gland tumours are being detected as incidental findings on CT, MRI and PET-CT scans performed for other indications. These tumours are asymptomatic and their management poses unique challenges.

Tumours arising in the submandibular gland present as swellings in the submandibular triangle which can be sometimes localized more accurately by bimanual palpation of the floor of the mouth (**Figure 9.3**). It is sometimes difficult to differentiate a tumour arising in the posterior aspect of the submandibular gland from one that is in the tail of the parotid gland and, in turn, either can be mistaken for a lymph node. Benign tumours in the minor salivary glands of the oral and pharyngeal mucosa present as firm submucosal swellings (**Figure 9.4**). Ulceration is rarely if ever seen unless there has been local trauma and, in the absence of that, malignancy should be suspected.

INVESTIGATION

Imaging

In general, every patient with a major salivary gland tumour requires some form of imaging. The arguments for routine imaging are:

- Ultrasound scan can be done at the time of fine-needle aspiration cytology (FNAC), ideally in the setting of a neck lump one stop clinic. FNAC is more accurate if ultrasound-guided.
- Diagnostic information to complement FNAC; if FNAC suggests benignity, imaging may or may not be commensurate with this. If not (i.e. benign cytology but imaging shows, for example, an irregular margin), the cytology should either be repeated and/or the excision performed sooner rather than later.
- If the FNAC is non-diagnostic, imaging may assist in diagnosis and plan urgency of resection.

- If FNAC is non-diagnostic or false negative, and tumour is then found to be malignant, the imaging performed pre-operatively will help to stage the tumour and plan further treatment if necessary.
- Distinguishing:
  - a parotid lump from either high-level 2 lymph node
  - a parotid lump from diffuse parotid enlargement
  - a submandibular lump from an adjacent level 1 (anterior) or level 2 (posterior) lymph node
  - a submandibular tumour from a tumour of the tail of parotid.

Ultrasound imaging can be performed at the time of an initial clinic visit, and fulfils most of the requirements of imaging.[7] It can also demonstrate sialolithiasis and sialectasis very clearly. However, axial (MR or CT) should be performed under the following circumstances:

- tumours that are large (e.g. > 3 cm)
- deep lobe/parapharyngeal space involvement (note that an ultrasound scan may well miss a 'dumbbell' (**Figure 9.5**) tumour in which the greater component of the tumour lies in the parapharyngeal space)
- suspicion of malignancy.

MR is generally preferred because it gives better definition of tumour–normal salivary gland interface.[8] It also is not affected by dental artefact.

Imaging features (on any modality) that suggest malignancy include an irregular capsule, or extracapsular invasion, hypervascularity and imaging features consistent with necrosis.

Fine-needle aspiration cytology and needle core biopsy

Malignant tumours must be detected pre-operatively wherever possible because the staging, workup and surgery may differ. Most salivary gland tumours are investigated by FNAC, at least initially. The accuracy for the diagnosis of benignity or malignancy in most large series is around 80–90%[9, 10] and on systematic review, and concordance with histology for 80% in cancers and 95% in benign tumours.[11] The accuracy will vary from centre to centre. The use of core biopsy can improve the accuracy of diagnosis further. Whilst more invasive, there is no evidence that there is a greater chance of tumour seeding with core biopsy.[12] Some authors advocate the use of core biopsy primarily instead of FNAC. An alternative view is to use core biopsy as a second-line investigation, or when FNAC shows possible malignancy. Such a protocol has been shown to give rise to a sensitivity of 100% and specificity of 92%.[13] The use of ultrasound (a) increases FNAC and core biopsy 'hit rate' and (b) gives useful diagnostic information.[7]

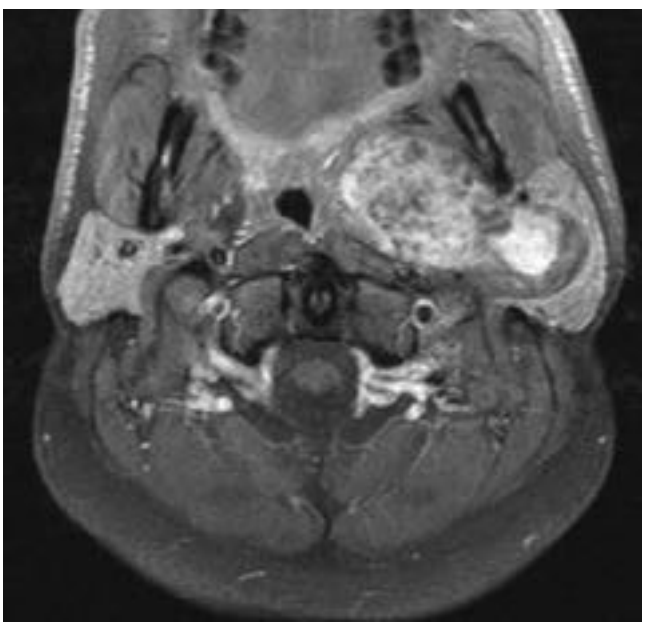


Figure 9.5 MR scan of dumbbell tumour.

THE MANAGEMENT OF COMMON BENIGN TUMOURS

Pleomorphic adenoma

Most patients with a pleomorphic adenoma should be offered and advised to have surgery on the basis of:

1. definitive histology
2. continued growth if left untreated
3. small chance of malignant transformation (see below).

Most parotid pleomorphic adenomas are within the superficial lobe but a small but significant proportion arise either within the deep lobe or involve it by direct growth. Pleomorphic adenomas, left untreated for many years, can attain a large size (**Figure 9.6**). Pleomorphic adenoma can also arise from accessory parotid tissue along the line of the duct (**Figure 9.7**). If far enough anteriorly in this area, they then may only be visible when the mouth is opened and the tumour is pushed outward by the forward movement of the coronoid process of the mandible. Pleomorphic adenomas can also arise in the submandibular gland, or minor salivary glands (e.g. soft palate, see **Figure 9.4**).

The firmness of these tumours varies with the nature and amount of the stromal component and thus ranges from soft, in the case of the more mucinous tumours to hard in the case of tumours with an extensive chondroid or collagenous component.

The myxoid stroma of pleomorphic adenomas is one of its most characteristic features. It can form the major part of the tumour and can bulge into the normal gland parenchyma without any capsule intervening. The almost mucoid nature of many pleomorphic adenomas makes them extremely fragile so that they can rupture at operation. Rupture of the tumour inevitably seeds the operative field and significantly increases the chance of later recurrence.

The cartilage of pleomorphic adenomas, though often termed 'pseudo-cartilage', does not appear distinguishable in any way from true cartilage. Calcifications or bone



Figure 9.6 A large pleomorphic adenoma.

formation are unlikely to develop in any other salivary gland tumour and may be seen clearly in scans. Their presence in a salivary gland or a parapharyngeal mass strongly suggests that the tumour is a pleomorphic adenoma.

It is widely accepted that pleomorphic adenomas are derived from intercalated duct and myoepithelial cells which differentiate into epithelial and connective tissue structures. The epithelial cells are interspersed by stromal elements. Squamous metaplasia with keratinization is common and does not imply malignant change.

It is critical to understand that, in virtually all pleomorphic adenomas, the capsule is exceptionally thin (<20 micron) in at least one area and incomplete in about 50%, more so in the mucoid type which are therefore much more prone to potential spillage during surgery.[14]

The relevance of this and the choice of operation is discussed in the next section.

Another critical feature that influences management is the risk of malignant change. It has always been known that a small percentage of pleomorphic adenomas can undergo malignant transformation. The risk is essentially unknown in terms of x% over y years and historically a figure of about 1–5% in 10 years has been adopted. However, it is known that that only 0.15% of pleomorphic adenomas have features of malignant change[15] and so the actual risk of transformation is probably very low.

CHOICE OF OPERATION

Pleomorphic adenomas of the submandibular gland are treated with excision of the gland. This should be extra capsular and, as a result, there is a higher rate of marginal mandibular facial nerve injury.[16] Pleomorphic adenomas

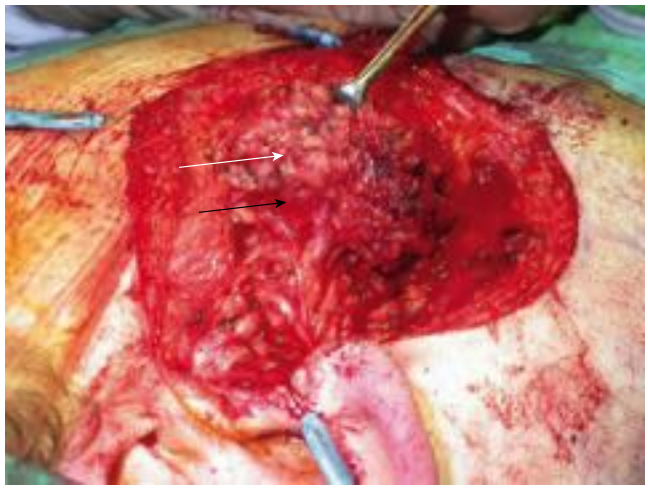


Figure 9.7 Despite taking a cuff of normal tissue, at least one aspect of the tumour capsule is adjacent to the facial nerve/branch. Partial parotidectomy with cuff. White arrow shows cuff but note black arrow show that narrowest margin is capsule only where tumour is adjacent to buccal branch of facial nerve.

of the minor oral salivary glands is treated by wide local excision.

The controversy in management of these tumours largely applies to the parotid gland. As a result of poor encapsulation and a tendency to rupture during resection, enucleation frequently results in subsequent recurrence and is an unacceptable historic practice. However, there is controversy regarding the extent of parotidectomy, from total superficial parotidectomy, through to a partial superficial parotidectomy (the tumour and a cuff of normal tissue) through to extracapsular dissection. The most common practice in the UK is partial superficial parotidectomy.[17]

The key theoretical argument for taking a cuff is the incomplete and thin capsule. However, most tumours, with the exception of very small tumours at the tail of the parotid, will be near the facial nerve or a significant branch thereof. This is the point demonstrated in **Figure 9.8**, i.e. there will almost always be one margin in which the tumour capsule is next to a facial nerve branch, no matter what type of operation is performed. Indeed, histological analysis shows that, even with 'standard' superficial parotidectomy, 81% had some degree of capsule exposure and this was >50% of the surface in 60%.[18]

Therefore, a less invasive approach using careful extracapsular dissection, when possible, can be justified on that basis. The majority of evidence shows at least similar rates of recurrence and facial nerve injury, with many showing lower rates of these complications and others.[19–21] These findings are not universal, but it should be noted that much evidence to the contrary involves analysis of very old data (e.g. going back to the 1960s–1980s).

If there is to be a cuff, there is no consensus as to the amount required. Many surgeons, in effect, will compromise between the two approaches, taking a narrow cuff (e.g. 1 cm) around the tumour. There is not much point in taking a large cuff e.g. a 'superficial' parotidectomy when at least one margin is likely to be negligible next to a nerve branch (see **Figure 9.8**).



Figure 9.8 Clinical photograph showing recurrent pleomorphic adenoma presenting as multiple nodules. Note the scar from the previous surgery.

The salient argument arguments in favour of each approach are shown in **Table 9.3**.

DEEP LOBE TUMOURS

Deep lobe tumours generally require total conservative parotidectomy. However, for some smaller tumours, access via a limited superficial partial parotidectomy may facilitate an approach to the tumour inferior to the facial nerve, mobilizing just the inferior branches to access the tumour in order to perform an extracapsular dissection. This is the same approach (cervico-parotid) as for parapharyngeal tumours (which may include the deep lobe), except that division of the digastric muscle and styloid process ligaments may not be required.

PARAPHARYNGEAL SPACE PLEOMORPHIC ADENOMAS

These can be excised via a cervico-parotoid approach or, if too big and too anterior for this, via a transmandibulotomy/ transpharyngeal approach. Transoral robotic surgery offers an alternative approach, especially instead of the latter, and can be combined with a cervical approach if necessary.[22]

RECURRENCE OF PLEOMORPHIC ADENOMA

The overall recurrence rates of pleomorphic adenomas are in the region of 2% and occur typically about a decade after original surgery,[20, 23] although data from a Dutch national pathology database showed a 6.7% recurrence rate over 20 years.[15] Most recurrences are multi-centric (see **Figure 9.8**). A number of recurrences arise as a result of previous per-operative rupture or spillage of the tumour and seedlings may have been spread over a wide area, although this is probably much less the reason for recurrence than has been previously been cited anecdotally.[24]

An MR scan is the imaging of choice, both to characterize the identified recurrence(s) and detect further foci. It will also determine how much parotid tissue has been left behind after the primary surgery (which will often have been done in another institution).

Assuming the recurrence is still benign, the key issue for the surgeon to assume that this represents the last good opportunity for 'cure' with a good chance of facial nerve preservation without radical salvage surgery. In general, all remaining parotid tissue should be resected with the recurrences and the resection should be carried out mindful that there is a small but significant chance of the recurrent tumour being malignant. The necessary skills that may be required include retrograde nerve branch dissection; identification of facial nerve in mastoid; and nerve repair and cabling by micro-anastomosis. In some cases with, for example, superficial recurrence(s) only, there may be a role for limited surgery of these on the basis that this may be preferable to the significant chance of facial

TABLE 9.3 Arguments in favour for extracapsular dissection and partial parotidectomy with cuff in the surgical treatment of parotid pleomorphic adenoma

Extracapsular dissection	Partial parotidectomy with cuff or superficial parotidectomy
Recurrence rates are the same in this method as in superficial parotidectomy	On histopathology, the tumour capsule is incomplete and tumour cells extend through into adjacent tissue. Therefore, a cuff of tissue is necessary to achieve microscopic clearance and reduce chance of recurrence
Less cosmetic deformity	If the histology demonstrates an unexpected malignancy then clearance may still be adequate (if a low-grade tumour)
Lower incidence of Frey's syndrome	
There is no possible cuff in the tumour adjacent to one significant facial nerve branch in most cases	Dissecting close on the capsule may cause rupture (although when this does happen, it tends to be when dissecting capsule off facial nerve branch (i.e. no scope for a cuff here anyway)
If revision surgery is required (e.g. malignant on histopathology) then the tissue planes used to dissect and identify the main facial nerve and some braches are virginal	

nerve injury that may be inherent in formal revision parotidectomy surgery.

After a comprehensive resection, consideration of postoperative radiotherapy should be given. Radiotherapy is effective in reducing further recurrence of pleomorphic adenoma.[25]

It should be also emphasized that there is a much higher chance of malignant change within recurrent tumours, about 3%.[15] In the assessment, it is essential to

- repeat the FNAC (do not rely on the original histology)
- formally image with MR (mandatory regardless because of possible multifocality)
- get the original histology reviewed by a head and neck pathologist.

Further surgery for a second recurrence after radiotherapy is challenging in terms of minimizing morbidity and will be for disease which is, by definition, aggressive. Fortunately, these cases are rare but might include temporal bone resection, mandibulectomy and reconstruction for the resultant tissue defects as well as facial nerve reconstruction or reanimation (see **Figure 9.10**). This underlies the importance of aggressive treatment of recurrent disease at a point when it can be done in a non-mutilating fashion (i.e. at the first recurrence).[26]

Recurrent tumours of the submandibular gland should be treated with a selective neck dissection (1–3), which will remove the soft tissue that harbour recurrent disease.[16]

The management issues in recurrent disease are not straightforward and involve a working relationship between surgeon, pathologist and radiation oncologist – an example of benign disease that should be managed by a head and neck cancer multidisciplinary team.

Warthin's tumour

This tumour is also known and referred to as either adenolymphoma or papillary cystadenoma lymphomatosum. The latter terms are slightly ambiguous and tend not to be used. It accounts for 20% of benign parotid tumours. It is rare outside of the parotid gland.

The peak incidence of Warthin's tumours is in the seventh decade. Formerly, it was thought that these tumours predominantly developed in men, series quoted a 10:1 incidence ratio. More recent series suggest that this was either a misconception or that the sex distribution is becoming more equal with a male:female ratio of just 1.6:1.[27] There is a strong association between the development of Warthin's tumours and smoking and secondly a racial association in that it is comparatively rare in afro-caribbeans.[28, 29]

Warthin's tumours are comprised of lymphoid stroma and oncocytic epithelium. The lymphoid stroma suggests it arises from intra-parotid or peri-parotid lymph nodes, explaining why it is so rare in the submandibular gland, which contains no lymphoid tissue.

There is some controversy as to the exact nature of Warthin's tumours. Some studies have suggested a polyclonal origin for the epithelium, which would suggest a non-neoplastic origin for these lesions. This has led to a conclusion that Warthin's tumour arises from salivary duct inclusions within intra parotid lymph nodes, in a similar manner to the hypothesis of branchial cysts arising from epithelial inclusions within cervical lymph nodes.[30] However, other work suggests a clonal origin associated with a fusion oncogene transformation.[31]

These tumours typically grow slowly to form soft, painless swellings, usually at the lower pole of the parotid gland. They are not infrequently bilateral. A few may undergo rapid expansion possibly caused by cystic change.

Carcinomatous change in Warthin's tumours has only exceedingly rarely been reported and may, in some cases, be secondary to irradiation. Onder et al. have reported a case of poorly differentiated adenocarcinoma in a Warthin's tumour with severe dysplasia of the oncocytic cells in other areas. They have also summarized the features of 14 previous reports in the English literature. These show that the carcinomas can be adenocarcinomas, squamous cell or undifferentiated.[32] This may not represent malignant transformation as such, but represent dual pathology, or erroneous pathology.

The treatment of Warthin's tumour is generally through surgical excision. FNAC will often be diagnostic or at least suggestive of the diagnosis and most tumours are managed through a partial superficial partotidectomy. However, bearing in mind these tumours may not grow, are not associated with a significant chance of malignant transformation and often occur in the older age group, patients with Warthin's tumours can be managed conservatively with observation only, given a diagnostic FNAC result.[33]

Myoepithelioma

Myoepithelial cells are a prominent component of pleomorphic adenomas. Tumours derived solely from myoepithelial cells are rare. Myoepitheliomas are considered to be variants of pleomorphic adenoma that are characterized by overwhelming myoepithelial proliferation. A carcinomatous variant is also recognized. This tumour has no distinctive clinical characteristics. The average age at presentation is 40 years but both children and the elderly can be affected. There is no apparent predominance in either sex and all salivary glands can be affected. Management is essentially the same for pleomorphic adenomas.

Oncocytoma (oxyphilic adenoma)

Oncocytomas are rare tumours. They are predominantly tumours of those over middle age. Women, usually in the seventh or eighth decade, are more likely to be affected. The parotid glands are by far the most frequent site. These tumours are slow growing and may rarely be bilateral. Oncocytomas are benign and excision is curative. There have been occasional reports of recurrences and this is likely to be due to other nodules of tumour tissue in the gland.[34]

SURGERY

Parotid gland

Removal of the tumour within an appropriate part of the superficial lobe of the parotid gland (partial parotidectomy) is adequate treatment for the majority of tumours. Those extending into the deep lobe demand a total conservative parotidectomy, although small tumours of the deep lobe may not necessitate removal of the entire superficial lobe (but there is potential concern regarding first bite syndrome – see 'Cervico-parotid approach' below). There is growing evidence in support of extracapsular dissection, yet it still remains a minority practice for parotid tumours.[33]

INFORMED CONSENT AND MANAGEMENT OF COMPLICATIONS

Prior to superficial or total conservative parotidectomy the patient should be warned about the following serious or frequent complications.

Facial weakness

The risk of temporary or permanent facial weakness must be carefully explained as it has a very significant impact on quality of life. The risk of facial nerve damage is related to the extent of the disease, the type of resection and the experience of the surgeon. Neuropraxia usually recovers within 4–6 weeks. More severe injuries cause some degree of degeneration and recovery may never be complete and take 6–12 months or even longer to take place. The risk of permanent facial palsy is in the region of 1–2%.[20] There is a lack of clear data regarding more detail on facial nerve outcomes after parotid surgery, with grading data for example.

Sensory loss

A degree of sensory loss in the distribution of the greater auricular nerve, over the angle of the mandible and inferior two-thirds of the pinna, is unavoidable. Most patients learn to accept this deficit and few are severely troubled by it. The area of sensory loss generally decreases in the first 12 months post-operatively. If the posterior branch of the greater auricular nerve can be preserved at surgery, there may be less reduction of sensation, both long term and short term.

Cosmetic defects

The cosmetic appearance of the incision rarely causes huge concern, because the most visible components of a Blair's incision (if used) are in skin crease lines. Loss of bulk behind the ramus of the mandible may be visible, more so in thinner patients. This can be mitigated with fat transfer.

Frey's syndrome

Gustatory sweating or flushing (Frey's syndrome) is a socially embarrassing complication of parotidectomy (see **Figure 9.9**). Although it is a problem only in a minority of patients, nearly all patients have some evidence of it if tested with Minor's starch iodine test. The frequency of this complication is sufficient to warrant pre-operative explanation together with the reassurance that it is rarely significantly disconcerting. When it does emerge as a problem, simple preventive measures such as the application of



Figure 9.9 Frey's syndrome. (a) Classical facial blush elicited by eating flavoured crisps; **(b)** gustatory sweating demonstrated by painting the side of the face with iodine. After this had dried the face was dusted with starch powder. As soon as salivation was stimulated, sweating caused the characteristic starch-iodine reaction.

an anti-perspirant can be used. Otherwise, the standard of care is subdermal injections of botulinum toxin. These need to be repeated at 6–12 monthly intervals.

The risk of Frey's syndrome is decreased by more conservative surgery and the restoration of integrity of the superficial muscular aponeurotic system (SMAS) layer. The use of interpositional flaps (e.g. sternomastoid) can be effective, although the frequency of this complication as a major issue probably does not warrant this as a matter of routine.

Salivary fistula or collection (sialocoele)

Except in total parotidectomy, there will always be a cut surface of the parotid gland from which saliva will leak. This saliva can form a collection (sialocoele) (**Figure 9.10**) or leak through the incision (fistula). When this occurs, it tends to occur within a few days of the surgery. A collection can be quite tense and painful, especially when eating. Collections are aspirated in clinic and this may need to be repeated on several occasions. A leak will need appropriate dressing and maintenance of wound hygiene. Antibiotics should be considered to prevent or treat secondary infection that can occur. Both leaks and collections almost always settle, but it can take 1–2 weeks. Quite why salivary fistulas are not more common is unknown. It could be speculated that those with a significant volume of residual gland, perhaps with an extensive cut surface are more prone to the complication. If there has been ligation of the duct, then it will always happen. Hyoscine patches can be used to reduce saliva production. The next line of treatment when the fistula does not settle conservatively is to inject Botulinum toxin into the main/residual parotid gland (under ultrasound control) and this essentially stops saliva production within a few days and reverses with time (2–3 months).



Figure 9.10 Sialocoele after parotid surgery.

Stump neuroma of the greater auricular nerve

When the greater auricular nerve is cut, its end can form a painful neuroma. When this happens, it is often several months/over a year post-operatively. It presents as a very localized tender nodule just anterior to the superior part of the sternomastoid muscle. It can be managed by simple local excision and burying of the fresh nerve end in the muscle. The latter manoeuvre may avoid the complication. If the posterior branch of the nerve is preserved, this may also mitigate against this complication also.

OPERATIVE PROCEDURE

The fundamental principle of superficial parotidectomy is exposure of the facial nerve and then removal of the gland and diseased tissue from around it. The surgeon should be aware that the branching pattern of the facial nerve can be quite varied and that the nerve may have been displaced from its normal position by tumour. Deep lobe tumours may displace the nerve laterally. Identification of the facial nerve and safe manipulation of the tissues around it can be significantly aided by the use of a facial nerve monitor.

Superficial / partial parotidectomy (**Figure 9.11**)

The patient should not be paralyzed (or at least short-acting agent used only) and be placed in the reverse trendelenberg (head up) position.

Most tumours can be removed through a 'lazy S' (or modified Blair) incision. However in some cases a modified facelift incision is satisfactory and avoids a scar on the anterior (visible) part of the neck. Infiltration of the area with 1:100,000 adrenaline reduces haemorrhage and makes identification of the facial nerve slightly easier. Skin flaps are raised which contain the subcutaneous tissue superficial to the parotid fascia, including SMAS layer. The parotid is then mobilized from the cartilage of the tragal cartilage superiorly and adjacent muscles, the sternocleidomastoid and posterior belly of digastric muscles. It is at this point of the dissection that section of the greater auricular nerve becomes necessary, but preservation of the posterior branch of this nerve should be performed if possible. Wide exposure from superior to inferior, dissecting the gland off the tragal cartilage completely, mastoid tip and sternomastoid with judicious use of traction will aid identification of the facial nerve. When the tumour is around this area, the surgeon should be wary of applying too much traction, as this can cause capsule rupture.

Tragal cartilage, mastoid tip and sternomastoid with judicious use of traction and counter traction will aid identification of the facial nerve.

The facial nerve trunk is then identified. A number of anatomical landmarks facilitate this part of the procedure:

- **The inferior portion of the cartilaginous external auditory canal (tragal pointer)**. The facial nerve lies 1 cm deep and inferior to its tip. The tragal pointer is slightly mobile when retracted so care must be taken when using this as a landmark.

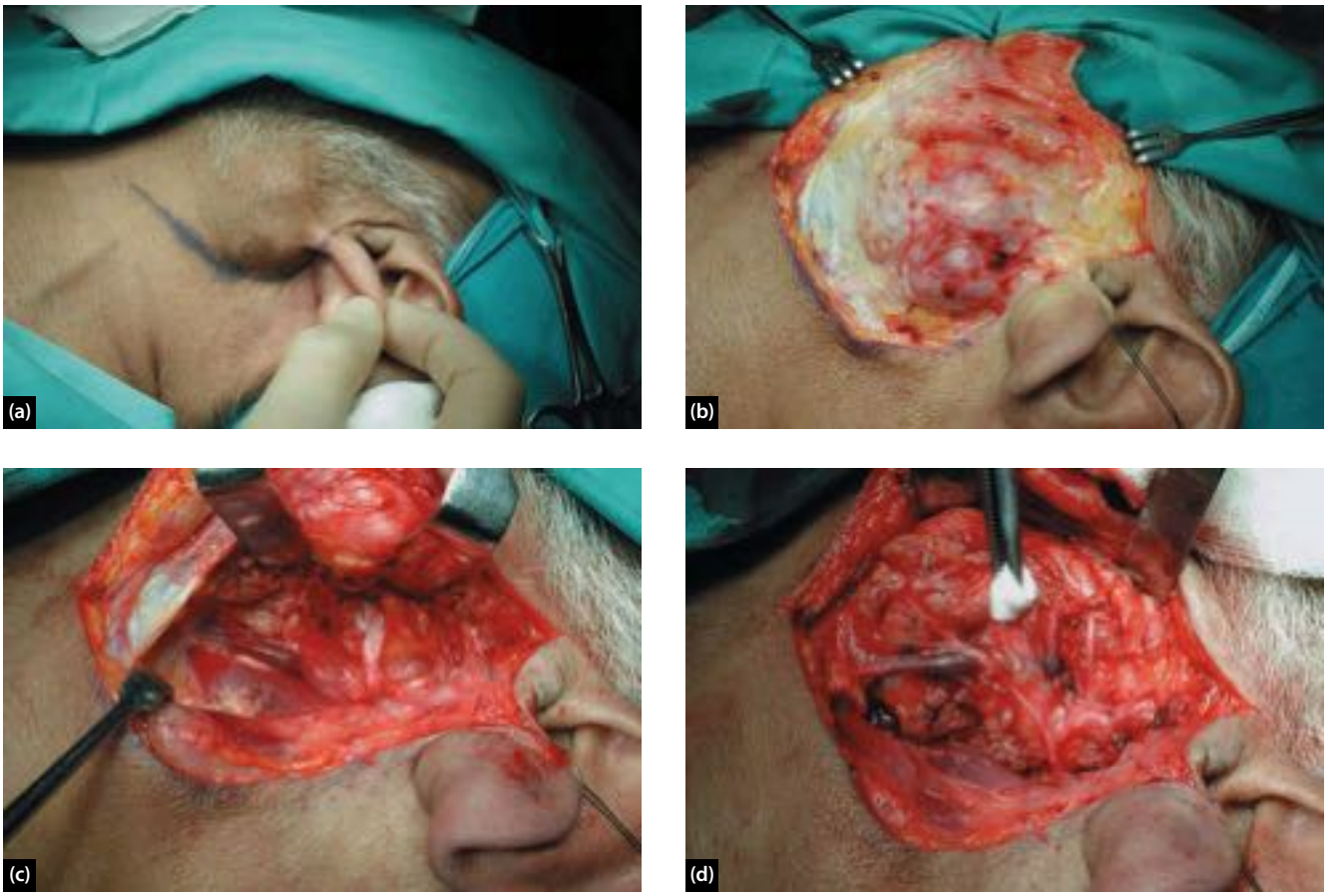


Figure 9.11 Superficial parotidectomy: (a) skin incision; **(b)** identification of posterior branch of greater auricular nerve **(c)** identification of the facial nerve; **(d)** completed dissection.

- **The tympanomastoid suture**. The facial nerve lies immediately deep and inferior to this at its point of exit from the skull. This groove is very easy to feel; and this is an extremely reliable landmark. The surgeon can, literally, get a 'feel' for where the nerve is expected to be.
- **The anterior border of the posterior belly of the digastric muscle**. The facial nerve leaves the skull immediately anterior to the attachment of this muscle. The facial nerve can be exposed by careful dissection in the area immediately anterior to the posterior belly of the digastric in the region of the mastoid process.
- **Care is needed in using the styloid as a landmark**. Whilst easy to palpate it lies deep to the exit of the nerve from the skull so dissection onto the styloid may increase the risk of facial nerve damage.

Rarely, for example in those with large or soft tumours immediately overlying the main trunk of the nerve and in surgery for recurrent disease, it is neither possible nor wise to access the facial nerve trunk at the skull base at the outset of the operation. In these cases it is better to locate and identify one of the major branches and dissect it in a retrograde manner from there. The mandibular branch can be found at the angle of the mandible, as it lies superficial to the facial vessels. The cervical branch of the nerve can be located at the point where it pierces the deep fascia below the body of the mandible. The zygomatic and temporal branches of the upper trunk cross the zygomatic arch anterior to, and within 1–2 cm of, the superficial temporal artery.

In summary, there are a variety of landmarks that can be used to aid identification of the facial nerve and its branches. With experience, the surgeon learns how and when to use this information. Whilst there is no evidence that the routine use of facial nerve monitoring for parotid surgery prevents permanent facial nerve injury[35] and UK practice is variable in this regard, most surgeons would advocate its use in difficult or revision cases.[33] Familiarity with nerve monitoring is therefore essential and it is arguably this, more than any other consideration, that makes a compelling case for its routine use in parotid surgery.

The superficial lobe, or relevant part of the parotid gland and tumour, are then dissected off the divisions and branches of the facial nerve. By this means, the superficial lobe (or part of) is separated from the deeper and other parotid tissue.

In the event of tumour rupture, which, for the reasons explained earlier, can occasionally occur despite good technique, the spillage should be contained and the tissues immediately deep to it removed, including the adjacent aspect of the deep lobe. In this way tissue contamination and seeding is minimized. There is controversy surrounding the traditional teaching of copiously irrigation with

water (not saline) in these situations. That teaching centres on the hypotonic effect on any spilled cells. However, it can also disperse the tumour cells over a wide area.

Haemostasis is then achieved and the wound closed. Drains are usually used, but may not be necessary for lesser resections especially if haemostatic tissue glue is used. Care should be exercised when placing vacuum drains, particularly if there are sections of unsupported facial nerve within the field, as they can be the cause of inadvertent neuropraxia.

Extracapsular dissection (ECD)

The principle of this operation is that the facial nerve is not formally identified. The same incision is made for a standard parotidectomy, and the tumour assessed for suitability for ECD after raising of flaps. Use of the facial nerve monitor is essential. Mobile lesions in the parotid tail are most suitable for ECD, or smaller tumours fairly superficial within the superficial lobe. Inflammatory lesions, large tumours and those extending into the deep lobe are unsuitable for ECD, as are those where malignancy is suspected. An incision is made through the fascia over the lesion and careful bloodless dissection is made down to the region of the tumour. A plane is developed between the capsule of the tumour and normal parotid tissue, with the aid of traction and counter traction from an assistant. The nerve stimulator is used prior to dividing tissue. Care should be taken if retraction distorts normal anatomy, for example if the nerve is inadvertently pulled laterally putting it at risk of damage. If there is doubt about the position of the nerve conversion to a partial parotidectomy with formal nerve identification should be undertaken.

Total conservative parotidectomy (Figure 9.12)

It may be necessary to remove the deep lobe of the gland when either tumour has developed within it or extends into it. Spillage of tumour during superficial parotidectomy is another indication for local resection of the deep lobe. In the latter case, segments of parotid tissue deep to and in between the branches of the facial nerve must be removed and this can be achieved in a piecemeal fashion.

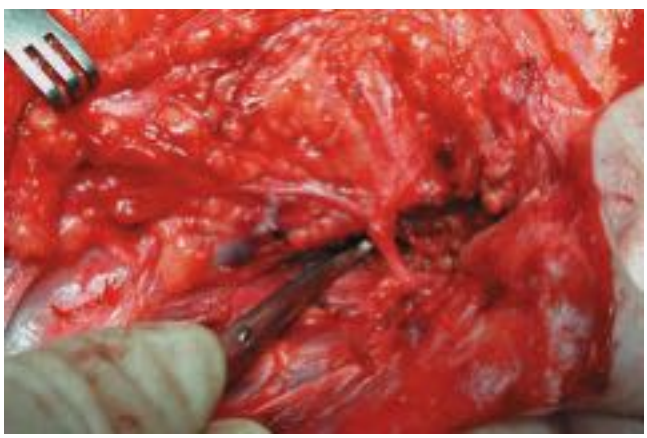


Figure 9.12 Total conservative parotidectomy: the entire gland both superficial and deep to the facial nerve has been removed.

In the case of a deep lobe tumour, usually a superficial parotidectomy is performed. This can be restricted to the inferior. The facial nerve must be mobilized with care. A plane deep to the main trunk is developed followed by more peripheral mobilization. The tumour is removed with all remaining parotid tissue, although this is scant and loose. Hence, the resection generally amounts to an extracapsular dissection.

Cervico-parotid approach to parapharyngeal space adenomas (Figure 9.13)

A complete superficial parotidectomy is not generally required. The lobe portion inferior the main facial nerve trunk and lowest main branches needs to be removed. The facial nerve can then be partly mobilized superiorly. The deep lobe is then removed (unless it is contains part of the tumour (e.g. a dumbbell tumour), in which case it is part of the resection. Access to the parapharyngeal space is then easily established, involving division of the posterior belly of digastric and all of the muscles/ligaments that attach to the styloid process. This should be done accurately, being mindful of the nearby glossopharyngeal nerve. If the process is long, gentle fracture of it can help with access. These manoeuvres allow the ramus of the mandible to be retracted anteriorly, opening up access to the parapharyngeal space.

First bite syndrome

A number of patients develop "first bite syndrome". This is intense pain in the parotid gland when just about to eat and it quickly passes after beginning to eat. There is little published literature on the subject. It probably occurs as a result of sympathetic dennervation of remaining parotid tissue. In the author's experience, treatment with botulinum toxin into the parotid gland can be effective as can high dose gabapentin or Pregabalin. However, this syndrome can be quite debilitating although patients can be reassured that it is generally self-limiting. There is a theoretical argument for performing total parotidectomy at the time of the cervico-parotid approach in order to avoid it, but this would be at the expense of cosmesis and salivary gland function.

Transmandibulotomy/transpharyngeal approach (Figure 9.14)

This is rarely needed. The cervico-parotid approach will facilitate excision of most parapharyngeal space adenomas and this can be combined with transoral robotic access if necessary.

The essential operative steps are as follows:

- Incision – skin crease with lip split. This can be curved alongside the mental skin crease, straight, or angled – all have their advocates.
- Dissection deep and under submandibular gland onto digastric/hyoglossus muscles.
- Identification of hypoglossal nerve.

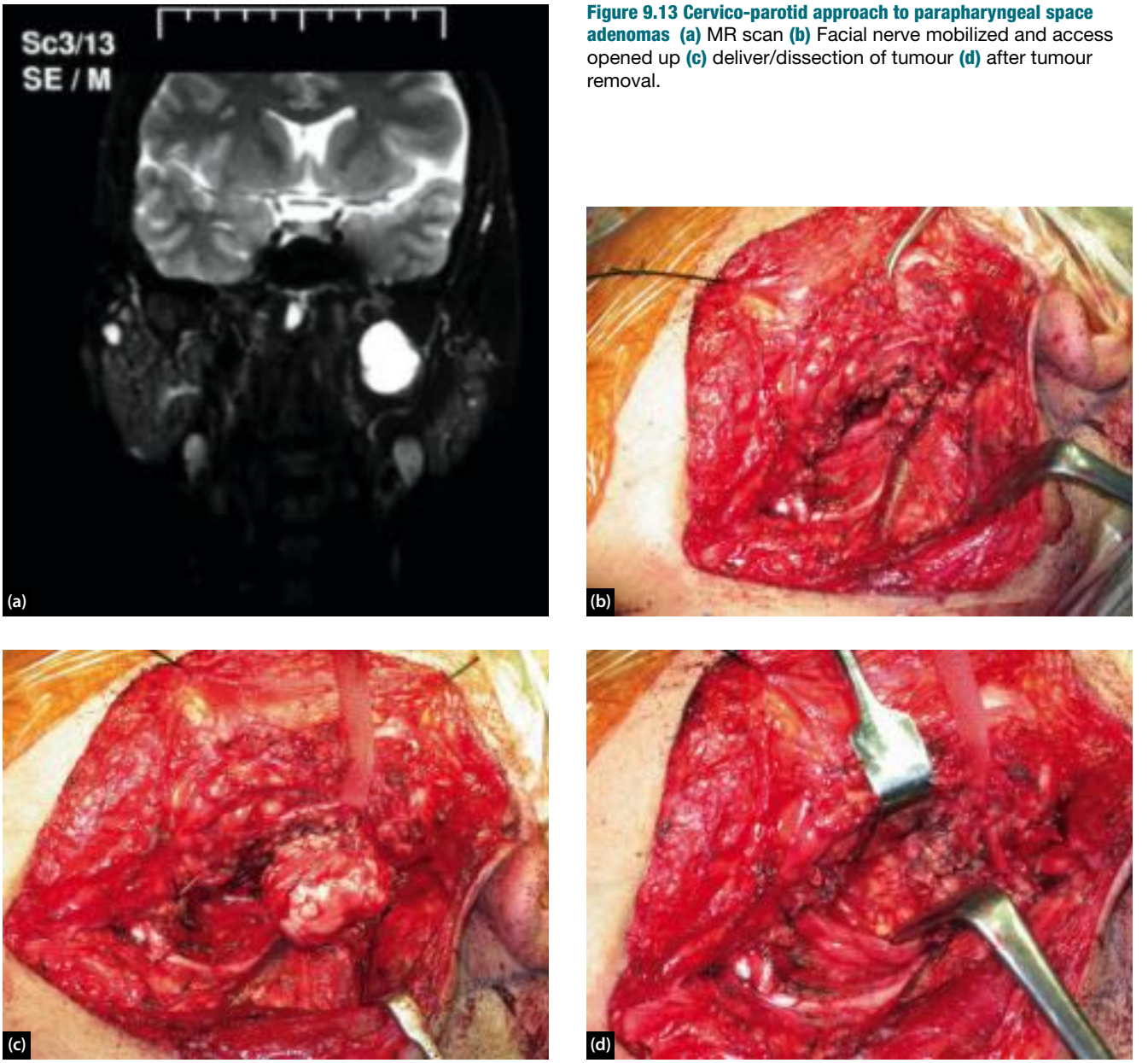


Figure 9.13 Cervico-parotid approach to parapharyngeal space adenomas **(a)** MR scan **(b)** Facial nerve mobilized and access opened up **(c)** deliver/dissection of tumour **(d)** after tumour removal.

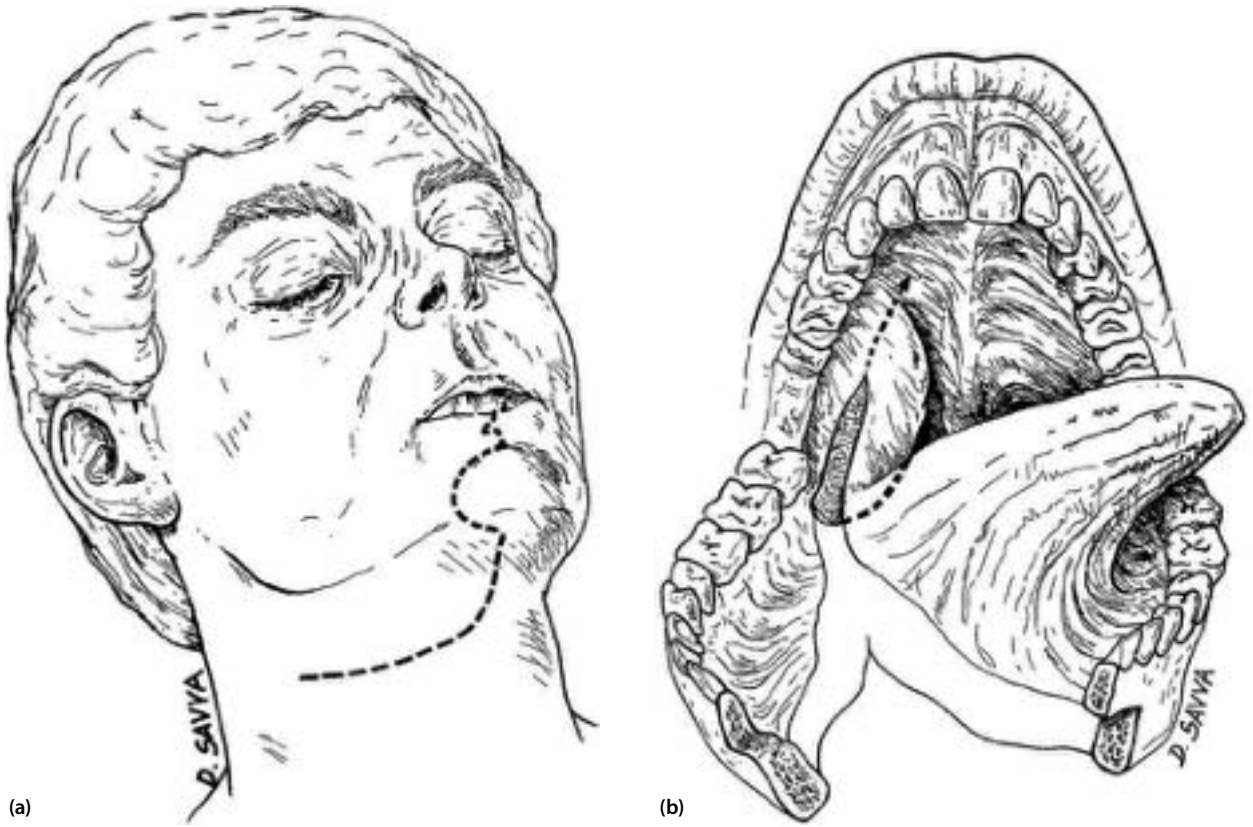
- Paramedian mandibulotomy with pre-plating (2 plates usually). A site between divergent teeth roots can be chosen but sometimes an extraction will be necessary to create the space required).
- The mandible is then retracted laterally so that the incision can be extended between the papillae of the submandibular ducts, along the floor of the mouth and up the anterior faucial pillar to the superior pole of the tonsil. During this part of the exposure the lingual and hypoglossal nerves should be identified and displaced medially, but not overstretched or cut if possible. While it is relatively simple to preserve the hypoglossal nerve, this is not the case with the lingual nerve, which is frequently damaged. Because of this, the patient must be forewarned of the probability of hemilingual anaesthesia following surgery.
- At this stage the exposure is complete and the tumour may be mobilized and removed by blunt dissection. This technique provides excellent exposure of the medial and superior aspects of the tumour which, by any other method, have to be approached blindly. However, caution should be used when dissecting the posterior aspect of the tumour, which is not infrequently adherent to the styloid process/deep parotid lobe. Traction here can cause capsular rupture.

Submandibular gland

Unlike the parotid where only a part of the gland is removed, total resection of the submandibular gland is always indicated for tumours of the submandibular gland.

INFORMED CONSENT

The patient should be warned about the following serious or frequent complications:



(a) (b)

Figure 9.14 Transpharyngeal approach to deep lobe tumours: (a) outline of skin incision; **(b)** osteotomy and opening of floor of mouth and parapharyngeal space. Figures drawn by Despina Savva.

- **Damage to the marginal branch of the facial nerve.** This may result in either a temporary or permanent weakness of the angle of the mouth that will be most noticeable on smiling and puckering the lips. The incidence of this as a permanent complication is around 2–3%.[36]
- **Lingual and hypoglossal nerve damage.** Neuropraxia of the lingual and hypoglossal nerves is unusual but possible. It is more likely to be sustained when the gland is removed for chronic sialadenitis rather than tumour as, in these cases, the gland is likely to be densely tethered to adjacent structures that become more difficult to identify and preserve. This complication is a common source of litigation and so must be included in the consent process. Motor dysfunction of the tongue initially impairs articulation and mastication but the patient rapidly compensates. Ultimately, the tongue muscles waste on that side but without further symptomatic deterioration. The incidence of these complications should be significantly less than 1%.
- **Cosmetic defects.** The patient should be reassured that a properly placed skin incision is unlikely to leave a cosmetically unsightly scar, but that this remains a possible outcome in any patient.[3]

OPERATIVE PROCEDURE

The incision is made in or parallel to a natural skin crease approximately 2.5 cm below the lower border of the mandible and extending for approximately 10 cm anterior to sternomastoid muscle (**Figure 9.15**). It is deepened through the platysma muscle and flaps developed in the fascial plane immediately beneath it. Care must be taken in development of the superior flap as the marginal mandibular branch of the facial nerve runs in the same tissue plane. This nerve enters the neck 1 cm in front of the angle of the mandible, loops over the facial artery and vein 2 cm below the lower border of the body of the mandible before sweeping superiorly to the angle of the mouth. The mandibular branch of the facial nerve can be protected from inadvertent damage by one of two manoeuvres. The facial vessels can be transected at a low level on the surface of the submandibular gland and reflected superiorly. The nerve, which lies lateral to the facial vessels, can then be lifted out of the operative field by traction on the transected end of the vessels. Alternatively, the capsule of the gland can be opened at the level of the hyoid bone and dissection continued beneath it. The elevated capsule protects the nerve in a similar fashion to the first technique. Occasionally, it is very difficult to identify the mandibular branch, and in these cases a nerve stimulator or monitor is extremely helpful.

The superficial part of the gland is mobilized by either blunt or sharp dissection and retracted posteriorly in order to expose the deep portion that lies on the hyoglossus muscle and is partly covered by the mylohyoid muscle. Retraction of the mylohyoid anteriorly, together with posterolateral traction on the gland, brings the lingual nerve, duct and more proximal part of the facial

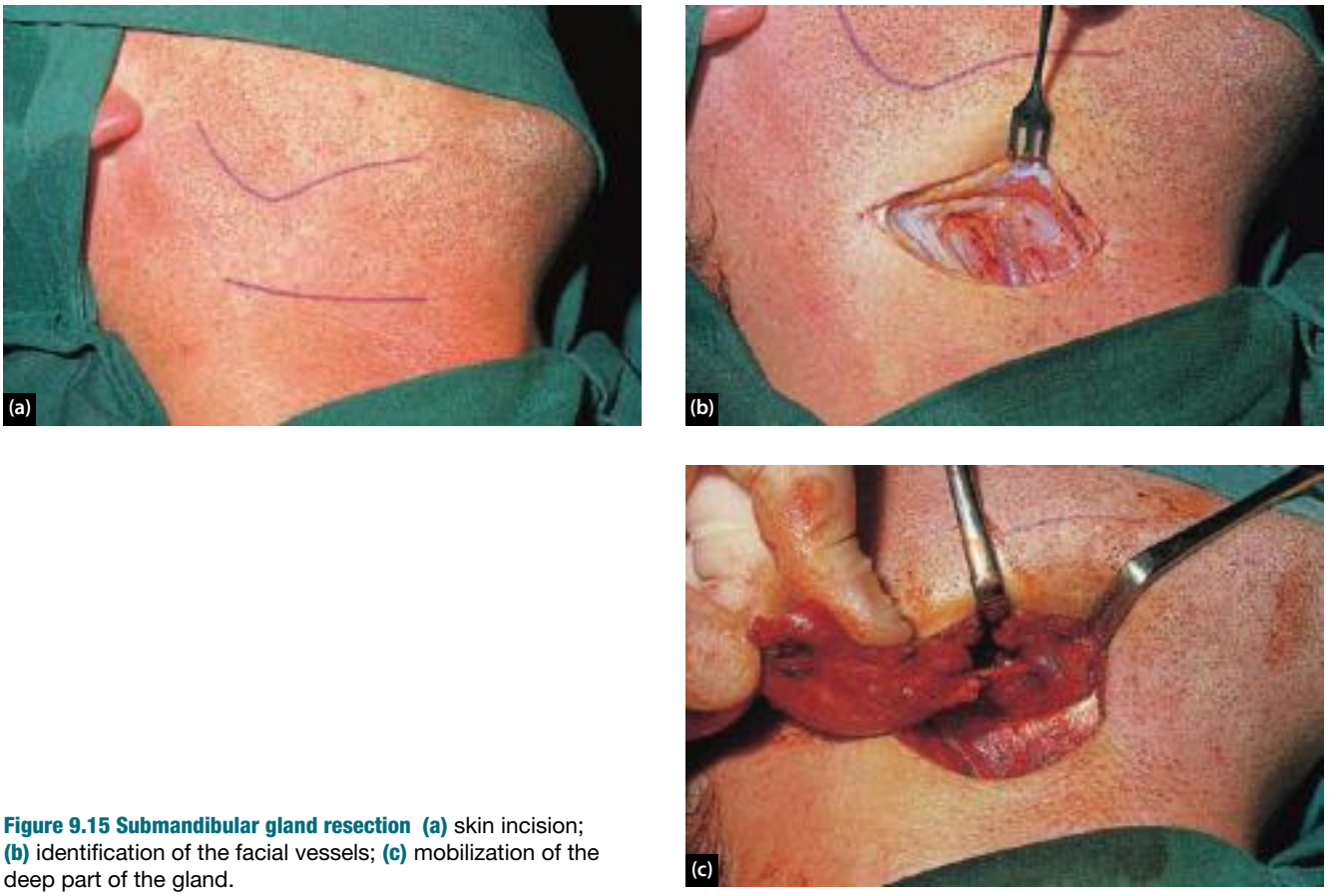


Figure 9.15 Submandibular gland resection **(a)** skin incision; **(b)** identification of the facial vessels; **(c)** mobilization of the deep part of the gland.

artery into the operative field. The lingual nerve appears as a ribbon-like band loosely attached to the body of the gland by a few fibres – the parasympathetic secretomotor supply. Section of these fibres releases the nerve from the gland and permits it to assume a more superior relation. At this stage the hypoglossal nerve may be seen inferior and parallel to the lingual nerve but is sometimes partially covered by the posterior belly of the digastric muscle. The proximal part of the facial artery is usually ligated at this point. The gland is then further mobilized from the hyoglossus muscle about its duct so that this may be ligated and transected as far anterior as possible. A small vacuum drain is inserted and brought out through the skin posteriorly. The wound is closed in two layers.

POST-OPERATIVE FOLLOW-UP

Long-term follow-up for all cases with surgically treated benign disease is unnecessary.[18] For pleomorphic adenoma, the chance of local recurrence is small; when it does occur, the median to recurrence is around a decade; and it is the patient who usually detects the recurrence.

Patients in whom long-term follow-up is advisable include those with:

- incomplete resection (as distinct from completely excised but with incomplete capsule)
- tumour rupture/spillage at operation
- complications that need management
- recurrent disease.

BEST CLINICAL PRACTICE

- ✓ A retromandibular fossa or cheek mass should be considered a salivary gland tumour until proven otherwise.
- ✓ Undertake fine-needle aspiration biopsy on all suspected salivary gland tumours, preferably under ultrasound guidance.
- ✓ Image all deep lobe tumours, those in which malignancy is suspected, congenital tumours and those patients with recurrent disease.
- ✓ Undertake an appropriate parotidectomy every time and never an enucleation.
- ✓ Use facial nerve monitoring in parotid surgery.

FUTURE RESEARCH

- ➤ There is a lack of multi-institutional prospective outcome data for benign parotid surgery.

KEY POINTS

- The incidence of salivary gland tumours is around 6–7 / 100 000 / year.
- Most of these develop in the parotid gland and are pleomorphic adenomas.
- Around 75% of salivary gland tumours are benign.
- The chance of malignancy is higher in submandibular gland and minor salivary gland tumours.
- Most benign salivary gland tumours present in an insidious fashion, growing slowly over a long period of time with little else in the way of symptoms.
- Imaging is performed in most patients. Ultrasound is the primary and initial imaging modality for benign tumours. Cross-sectional imaging should also be performed for larger tumours and complicated cases, such as suspected deep lobe extension or malignancy.
- Fine-needle aspiration biopsy should be undertaken in all salivary tumours, preferably under ultrasound control. Tru-cut biopsy is an alternative, but is usually reserved as a second line investigation.
- The degree of encapsulation of pleomorphic adenomas varies between and within tumours. Areas of deficient or complete absence of capsule are common and this predisposes these patients to recurrence.
- Some pleomorphic adenomas are extensively mucinous and consequently soft and fragile. These rupture easily if not handled with care.
- Recurrence of pleomorphic adenomas may develop many years (typically around one decade) after primary surgery and occurs in around 2% overall according to most data.
- The incidence of malignant change is low in primary disease (around 1/1000) but greater in recurrent disease (around 3%).
- Synchronous or metachronous tumours are more frequently associated with Warthin's tumours than any other salivary tumour.
- Parotid tumours can be managed by an appropriate parotidectomy (with a safe margin of normal tissue around the tumour where possible and with reference/dissection of the facial nerve) or, when possible, by extracapsular dissection (ECD).
- Submandibular gland tumours are managed by total extracapsular gland excision.

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CHAPTER 10

MALIGNANT TUMOURS OF THE SALIVARY GLANDS

Vincent Vander Poorten and Patrick J. Bradley

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SEARCH STRATEGY

The data in this chapter may be updated by a Medline and Pubmed using the following keywords: salivary gland neoplasms, parotid gland, submandibular gland, minor salivary gland, carcinoma, review, management, molecular biology, pathology, surgery, radiotherapy and chemotherapy.

INTRODUCTION

The broad pathological classification of malignant tumours of the salivary gland comprises epithelial tumours, being the most frequently encountered (>80%), mesenchymal tumors which are a very mixed group (<20%), and haematolymphoid tumours (lymphoma and plasmacytoma) making up the remainder of the 2017 WHO classification. Epithelial salivary gland malignancies form one of the most complex diseases in head and neck oncology, due to their low incidence and heterogeneity, both in microscopic appearance and clinical behaviour. A distinction should be made between the paired major salivary glands (parotid, submandibular and sublingual) and the minor salivary glands. The latter are unencapsulated seromucinous glands distributed throughout the entire upper aerodigestive tract, numbering between 500 and 1000, with the majority (<90%) being located in the oral cavity and oropharynx.[1]

INCIDENCE

Epithelial tumours account for the majority (95%) of malignant salivary gland tumours, but are infrequently encountered. Malignant salivary gland tumours are diagnosed in 4 to 135 new patients per million in the population per year, the highest incidence being found in the Inuit community of Greenland and the Canadian Arctic.[1,2] The incidence in the United States of America (USA) is 10 new patients per million per year.[3] For Europeans, the incidence is lower; a Danish population-based study reported a comparable crude incidence of 11 per million per year,[4] with lower incidences reported elsewhere in Europe (with Belgium, the Netherlands, the UK and Finland having about 6–7 new cases per million per year).[5–8] Ethnicity and geographical location presumably account for the observed differences in incidence.[2] Interesting data on the 'population impact' of these cancers were published in the Netherlands in 1995, where 89 new salivary gland carcinomas were diagnosed

that year on a population of 15.5 million inhabitants (Netherlands Interdisciplinary Demographic Institute). When spread across the healthcare sectors, it was estimated that a General Practitioner would see one such patient in 50 years of practice, an Otorhinolaryngologist would see about one or two patients a year, and an average Head and Neck Oncology Centre about ten new patients a year.[6]

As these malignancies occur at different anatomical locations, incidence data are reported by anatomical site. Up to 70% arise in the parotid gland[4–6, 9] and typically 1–3% of all head and neck carcinomas are reported to be parotid carcinomas.[10] The World Standard Population age-adjusted incidence of parotid carcinoma in Belgium in the period 2004–2005 was 6 for men and 4 for women per 10^6 person-years, accounting for 3.9% of Belgian head and neck cancers.[5] Ten to 25% of salivary carcinomas arise in the minor salivary glands.[4, 11] The rest are submandibular carcinomas, with sublingual carcinomas being very rare. An example of the proportion is given by the population-based incidence per 10^6 person-years in the Southern Netherlands of 3.2 parotid carcinomas for men and 1.9 for women, as compared to an incidence of 1.0 for men and 0.4 for women for submandibular and sublingual malignancies.[6]

RISK FACTORS FOR DEVELOPMENT OF SALIVARY NEOPLASMS

The influence of environmental and nutritional factors on incidence has been studied in detail. Follow-up of atomic bomb survivors in Japan and atomic disaster survivors in Chernobyl[12] reveals an increased incidence of both benign (Warthin's tumour and pleomorphic adenoma) and malignant (mucoepidermoid carcinoma) salivary gland tumours.[13] The incidence of Warthin's tumour is doubled and multicentric in smokers.[14] Epstein—Barr Virus (EBV) has been implicated in the genesis of bilateral Warthin's tumours and undifferentiated parotid carcinoma.[15, 16] Cytomegalovirus (CMV) infection may have a tenuous link to the development of mucoepidermoid carcinoma, both in mice and in humans.[17] An inverse relationship exists between a diet rich in polyunsaturated fatty acids and the registration of salivary cancers.[18–23] A Danish study found an increased risk of salivary cancer in workers involved with livestock feed processing, possibly related to naturally occurring mycotoxins produced by *Aspergillus spp.* and are described as one of the most carcinogenic substances known.[24]

KEY POINTS

- The incidence of malignant salivary gland neoplasms in the western world is 7 to 12 per 1,000,000 person-years.
- Salivary malignancy increases with exposure to environmental factors, low-dose ionizing radiation and aflatoxins.
- Smoking of cigarettes is related to development of Warthin's tumours.
- EBV infection may predispose to the development of Warthin's tumour and undifferentiated carcinoma.

HISTOGENETIC THEORIES FOR TUMOURIGENESIS

The normal histology of the salivary gland differs according to their anatomical location (major and minor glands) and consists of different combinations and proportions of the basic components, the acini and the ductal system (**Figure 10.1**). Whereas the major glands have a true excretory ductal system, the minor salivary glands are composed of unencapsulated acini with a short or absent ductal system.[11]

Serous acinus cells predominate in the parotid and the submandibular gland, and form only a minority of acini in the sublingual gland. Mucous acinus cells are the main source of saliva in the sublingual and submandibular glands, and are the only source of saliva in minor salivary glands.

The duct system consists of, in increasing diameter, intercalated ducts, striated ducts and excretory ducts. The luminal cells in the ducts are well-differentiated epithelial cells. Abluminal cells, those not in contact with the lumen, consist of myoepithelial cells that are also found at the abluminal side of the acini, and pluripotent basal cells.[25, 26]

Two theories have been proposed to explain the histogenesis of the complicated appearance of normal salivary gland tissue and the complex 'multicellular' histological appearance of salivary gland tumours. The 'multicellular theory' favours a transformation of the entire

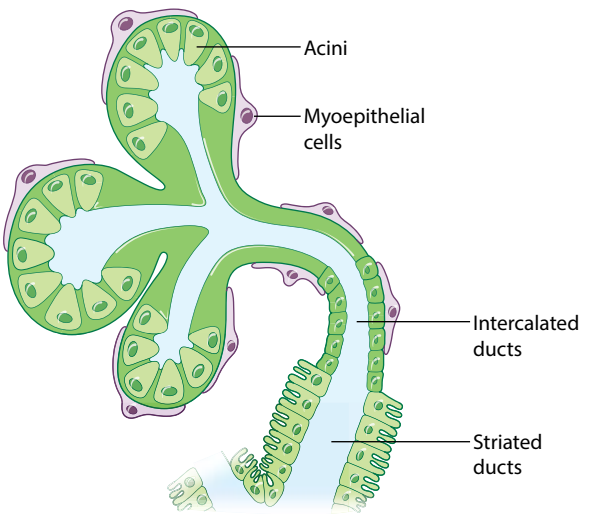


Figure 10.1 Diagram of the normal salivary gland unit. One layer of myoepithelial cells invests the terminal secretory ductoacinar unit – the intercalated duct and the acinus. Source: Tucker AS. Embryology and Clinical Anatomy. *Salivary Gland Disorders and Diseases: Diagnosis and Management*. Bradley PJ, and Guntinas-Lichius, (ed.) Reprinted by permission of Thieme Publishers.

ducto-acinar unit and requires the various 'differentiated' cells to become 'de-differentiated', deranged in their growth pattern, resulting in the microscopically different components observed in the various types of salivary gland tumours.[25] The 'reserve cell theory' states that both the normal salivary gland unit and the different tumour types are the result of differentiation of undifferentiated pluripotent precursor cells, and tumour cells originate from a problem in the normal differentiation process. The earlier in differentiation that a problem occurs, the more undifferentiated and 'high-grade' is the resulting salivary malignancy.

The role of the precursor or 'stem' cell is attributed to the 'epithelial basal ductal cells' that rest on the basement membrane at the abluminal side of the ductal system. Originally, the 'reserve cell theory' was called the 'bicellular' reserve cell theory, distinguishing two types of reserve cells, one at the abluminal side of the intercalated ducts and another at the abluminal side of the excretory ducts.[26–28] The tumours originating from the intercalated duct reserve cells are adenocarcinoma not otherwise specified (ACNOS), acinic cell carcinoma (AcCC), adenoid cystic carcinoma (AdCC), mixed malignant tumour and oncocytic tumours); those said to originate from the excretory duct reserve cells are mucoepidermoid carcinoma (MEC), squamous cell carcinoma (SCC) and salivary duct carcinoma (SDC). The reserve cell theory is supported by recent research indicating the common origin of both the epithelial, myoepithelial and the mesenchymal components of pleomorphic adenoma in exactly these epithelial basal ductal cells.[29]

CLINICAL PRESENTATION AND IMAGING WORKSHOP

The majority of tumours (64–80%) arise in the parotid glands, of which 15–32% are malignant. Seven to 11% arise in the submandibular glands with 41–45% being malignant. Less than 1% occurs in the sublingual gland, where the majority (70–90%) are malignant. Minor salivary gland tumours account for 9–23%, with +/– 80% being malignant.[1, 30]

Parotid gland

The majority of parotid tumours present as asymptomatic, discrete pre-auricular or infra-auricular lumps. With 80–90% of parotid salivary tissue being located lateral to the facial nerve (VIIN), a similar proportion of all neoplasms (benign and malignant) arise in the superficial lobe. A small percentage present only as a swelling of the soft palate or lateral oropharynx,[31] and 1% arise in the accessory parotid gland (along the Stensen duct).[32]

About 1 in 4 parotid tumours are malignant[33] and a diagnosis of a malignancy is suggested by a rapid increase in size, pain, associate cervical lymphadenopathy, fixation of the salivary mass to deep structures or facial skin (**Figure 10.2**), or the presence of VIIN dysfunction.[30] Of patients presenting with parotid cancer, 44% have pain[34]



Figure 10.2 Parotid cancer with skin invasion. Source: *Prognosis in Head and Neck Cancer*, Robert J Baatenburg de Jong, editor. V. Vander Poorten: Prognosis in patients with parotid carcinoma; Chapter 21, p 356. Reprinted by permission of Taylor and Francis.

and 25% have VIIN paresis or paralysis which is independent of the tumour size.[30, 34–41] Rarely, the presentation can be insidious. The incidence of parotid carcinoma has been estimated to be as high as 6% in patients presenting with a lower motor neuron VIIN paralysis where no aetiology has been identified after initial MRI scans. This is more likely if the paresis has been slow in onset, progressive in nature, shows no evidence of recovery, affects only isolated branches of the VIIN and if facial tics are present.[42, 43]

The evaluation should include the size, extent, location and the likelihood of the mass being benign or malignant. Imaging is strongly advised when the tumour mobility is impaired, the tumour >4 cm, the VIIN is clinically involved, and there are palpable cervical nodes.[30, 44, 45] Magnetic resonance imaging (MRI) is superior to computerized tomography (CT) in evaluating parotid tumours and allows better demonstration of the retromandibular parotid, the stylomastoid foramen area, VIIN invasion and possible perineural extension.[43, 44, 46] Conventional MRI is complementary to fine-needle aspiration cytology (FNAC) in the pre-operative assessment of a parotid mass.[47] Diffusion weighted MRI (DW-MRI) is considered to have superior diagnostic efficacy in identifying malignancy based on a specific diffusion pattern.[48] Where malignancy is suspected, appropriate imaging should be performed to exclude distant metastases.[49] Positron emission tomography/CT (PET-CT) imaging has high false-positive rates in differentiating benign from malignant salivary disease as common benign tumours (Warthin's tumours and pleomorphic adenomas) demonstrate an increased FDG uptake.[50]

Submandibular gland

Most patients present with a slow-growing, painless mass or swelling under the jaw or occasionally present with distortion of the floor of the mouth, accompanied in exceptional cases by skin invasion or ulceration or even more rarely with local nerve paresis or paralysis. The hypoglossal nerve is most at risk, followed by the trigeminal nerve and then the mandibular branch of the VII nerve. Thirty percent of patients complain of local pain suggesting local tissue extension.[51] Cervical lymphadenopathy is present in 25% of patients. The median symptom duration in the patient group of The Netherlands' Cancer Institute was 13.5 months, ranging from <1 month to >27 years. The median duration of complaints may range from 3 years for low-grade malignancy to 6 months for high-grade malignancy.[52–56] Evaluation of submandibular gland malignancies by radiological imaging is similar to the principles for the parotid gland.

Minor salivary glands (MiSG)

As MiSG are found throughout the entire upper aero digestive tract, the signs and symptoms depend upon the anatomical site involved. The majority of patients diagnosed are in the 5th to 6th decade, but tumours have been documented in children.[11, 56, 57] Fortunately, when diagnosed in children MiSG cancers are low-grade and can frequently be excised with clear margins.[58] Akin to the normal distribution of salivary glands, the most frequent sites of MiSG cancer development are the oral cavity and oropharynx. The most frequent primary site is the hard palate, where MiSG density is highest. The classical presentation is as a painless submucosal swelling, with fixation of the tumour to the overlying mucosa. There may be a small central area of ulceration. Some patients present complaining of their dentures not fitting comfortably as the tumour alters the positioning of the dentures (**Figure 10.3**). When MiSG tumours present in the nose and pharynx, most patients present with obstructive symptoms. Pain or paraesthesia as a complaint has been recorded in >26% of patients[11, 59] and, when present, MRI is required to evaluate named nerve invasion.[60, 61] The presence of regional metastasis is reported in 1 out of every 6 patients.[11, 62, 63]

To estimate the anatomical involvement of the disease process aiming to predict the likelihood of surgical management it is mandatory that CT +/– MRI is performed. Recent reports suggest that the T-max (time to maximum contrast enhancement) in contrast to enhanced MRI scanning is helpful in differentiating benign from malignant MiSG tumours.[64] DW-MRI, which is of value for the pre-operative identification of malignancy based on the tissue-specific diffusion pattern of major salivary gland tumours, has not been studied specifically for MiSGC.[48]



Figure 10.3 (a) and (b) MiSGC of palate with ill-fitting denture. Source: *Squamous cell cancer of the neck*, Robert Hermans (ed). V. Vander Poorten: Epidemiology, pathology and clinical presentation: Chapter 1: p. 15. Reprinted by permission of Cambridge University Press.

It can be questioned however whether this complex imaging will yield any additional information, when, for MiSG tumours, an incisional diagnostic biopsy is necessary and will provide the histological information needed to plan further treatment. As stated above for major salivary gland cancers, PET with or without CT is useful for the exclusion of metastatic disease.[65]

STAGING OF SALIVARY GLAND CANCERS

All patients should be staged as per the TNM system used for major salivary gland cancers following evaluation (**Table 10.1**).[66] Minor salivary gland cancers are staged as per the anatomic site they originate in.[11, 56, 59, 63, 67–69] The use of a uniform classification system, such as the TNM, allows comparison of outcomes following different treatments to similar tumour stages. TNM components also have an independent prognostic role as shown by numerous studies, which help define and refine guidelines for treatment.[10, 37, 41, 70–73] Similar to major salivary gland cancer, the TNM components and stage groupings for MiSG cancers have been found to be the strong prognostic factors,[11, 56, 63, 74–76] and many studies report that TNM overrules the histological grade.[11, 56, 63, 68] Carrillo attributed an additional independent prognostic value to grade for oral and oropharyngeal MiSG cancers, in addition to anatomical extent as reflected in UICC stage.[57, 77]

KEY POINTS

- The smaller the salivary gland, the less frequent a tumour is likely to manifest, but when it does the more likely is the tumour to be malignant.
- Parotid tumours
  - rapid increase in size or volume, the presence of pain, enlarged neck lymph nodes, fixation to deep structures or skin, or VIIN dysfunction should alert a likely diagnosis of malignancy
  - tumour imaging aims to estimate the extent (summarized in the TNM classification), location and probability of malignancy
  - MRI scanning is mandatory to evaluate invasion of the VIIth nerve, fixation to the deep structures, location at the stylomastoid foramen or deep lobe with the use of CT imaging to evaluate suspected bone invasion.
- Submandibular tumours, although frequently symptomless, are often malignant.
- MiSG tumours commonly present at an advanced disease stage and their extent is summarized as per the TNM classification for that anatomic location.

PRE-TREATMENT HISTOPATHOLOGY TYPING

Accurate characterization of the histology of any malignant tumour is a crucial part of the diagnostic workup. This will confirm true salivary origin of the tumour and permit appropriate treatment planning.

TABLE 10.1 8th Edition (2017) UICC TNM classification and stage regrouping for major salivary gland malignancies

T – Primary Tumour			
Tx	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Tumour 2 cm or less, without extraparenchymal extension*		
T2	Tumour >2–4 cm, without extraparenchymal extension		
T3	Tumour >4–6 cm, and/or extraparenchymal extension		
T4a	Tumour invades skin, mandible, ear canal and/or VIIth nerve involvement		
T4b	Tumour invades base of skull, and/or pterygoid plates and/or encases carotid artery		
N – Regional Lymph Nodes			
N1	Metastasis in a single ipsilateral node, 3 cm or less in greatest dimension, without extranodal extension		
N2a	Single ipsilateral node >3–6 cm, without extranodal extension		
N2b	Multiple ipsilateral nodes <6 cm		
N2c	Bilateral or contalateral nodes <6 cm		
N3a	Node(s) >6 cm, without extranodal extension		
N3b	Single or multiple nodes, with extranodal extension**		
M – Distant Metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
Stage Grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IVa	T4A,	N0, N1, N2M0	
	T1, T2, T3, T4a	N2	M0
Stage IVb	T4B	any N	M0
	Any T	N3	M0
Stage IVc	Any I	any N	M1

* extraparenchymal extension is clinical or macroscopic invasion of soft tissues or nerve, other than those listed under T4a and T4b. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes. Reproduced with permission.[66]

** The presence of skin involvement or soft tissue invasion with deep fixation/tethering to underlying muscle or adjacent structures or clinical signs of nerve involvement is classified as clinical extra nodal extension. Midline nodes are considered ipsilateral nodes.

Fine-needle aspiration cytology

FNAC is an important tool in the diagnosis of salivary neoplasms. Accurate tumour typing is not to be expected as a routine, but when performed by an experienced cytologist, FNAC is safe, associated with minimal morbidity and is a reasonably accurate way to differentiate between malignant and benign lesions (accuracy 79%).[78–80] This information aids with the prioritization and timing of

treatment, with the planning of the excision and possible reconstruction, and allows for appropriate counselling. Performing FNAC with ultrasound guidance (UgFNAC) not only helps with diagnosis of the primary tumour but also aids with synchronously staging of the neck and is to be recommended.[46] Immediate on-site processing and evaluation of the cellular quality of the aspirate should be provided, and if the aspirate is deemed unsatisfactory the FNAC can be repeated; this results in higher diagnostic accuracy.[44, 81, 82] The real-life performance of this technique can be deduced from a large French series of 1355 salivary gland FNACs which were correlated with subsequent histological assessment, showing an 80.5% true positive rate, 4.6% suspicious lesions, 11.9% false negatives and 3% of uninterpretable samples.[78] Even if the FNAC suggests benign disease, removal of the tumour for further histopathology analysis remains mandatory.[83] Diagnostic accuracy of FNAC could be improved in the future by implementing high throughput techniques such as cDNA microarrays on the aspirate to give a tumour-specific overview of overexpressed oncogenes and underexpressed tumour suppressor genes.[84]

Incision biopsy

For MiSG tumours, FNAC can often correctly classify the tumour as benign or malignant, but may be unable to distinguish between subtypes or provide tumour grading. Whereas incisional biopsy is not recommended for the diagnosis of major salivary gland tumours (except for large tumours with skin ulceration or infiltration), it is appropriate for MiSG locations, where the mucosal tumour is readily accessible for biopsy and will not interfere with subsequent definitive treatment. Excisional biopsy of MiSG tumours has a high rate of positive margins, makes orientation and margin assessment of the definitive resection specimen more difficult and is not to be recommended.

The most important factor in the pre-operative evaluation is to obtain an accurate histopathologic subclassification of the MiSGC (**Table 10.2**) and, when possible, an indication of the tumour grade.[85] The caveat to interpreting these biopsies is that many salivary gland tumour types have overlapping histological features. Without seeing the interface between the tumour and the surrounding normal tissue, invasion cannot be adequately assessed which complicates differentiation between benign and malignant tumours. Similar issues are encountered in interpreting FNAC where less information is to be obtained from individual cells, without the architecture.[86] Some tumours at presentation will be at an advanced stage and the biopsy may be the only tissue sample obtained. Additional histological prognostic features, such as perineural growth (**Figure 10.4**), lymphovascular invasion, and involved margins, can usually only be obtained from a resection specimen. Increasingly, molecular biological studies are performed, and many can be carried out also on the incisional biopsy material.

TABLE 10.2 The WHO* 2017 Histologic Classification of Malignant Salivary Gland Tumours[204]

Type WHO	Abbreviation
1. Mucoepidermoid carcinoma	MEC
2. Adenoid cystic carcinoma	AdCC
3. Acinic cell carcinoma	
4. Polymorphous adenocarcinoma	PAC
5. Clear cell carcinoma	CCC
6. Basal cell adenocarcinoma	BAC
7. Intraductal carcinoma	
8. Adenocarcinoma, NOS	
9. Salivary duct carcinoma	SDC
10. Myoepithelial carcinoma	
11. Epithelial-myoepithelial carcinoma	EMC
12. Carcinoma ex pleomorphic adenoma	
13. Secretory carcinoma	
14. Sebaceous adenocarcinoma	
15. Carcinosarcoma	
16. Undifferentiated carcinoma	
17. Large cell neuroendocrine carcinoma	
18. Small cell neuroendocrine carcinoma	
19. Lymphoepithelial carcinoma	
20. Squamous cell carcinoma	
21. Oncocytic carcinoma	
22. Sialoblastoma (uncertain malignant potential)	

* WHO: World Health Organization. Modified from the WHO publication to include only the malignancies.

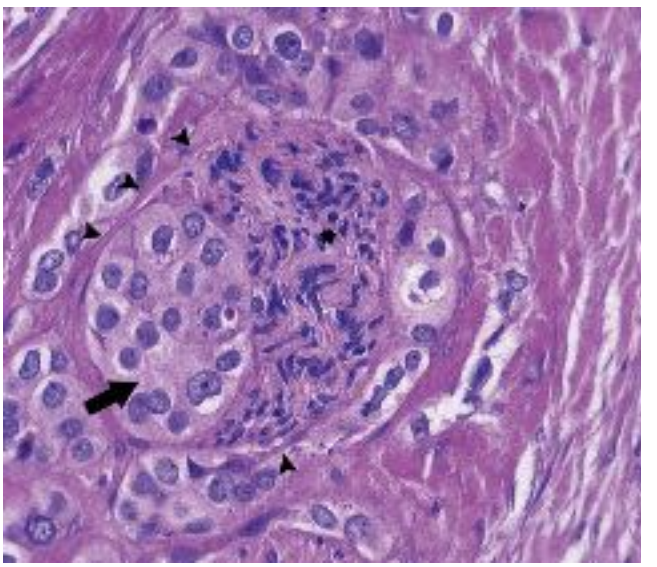


Figure 10.4 Perineural spread of salivary cancer. Arrowhead demarcates perineurium, distended by tumour cells (arrow), compressing the nerve bundles (asterisk). Source: Hermans R. (ed.). *Head and Neck Cancer Imaging*, Vander Poorten V. Epidemiology, risk factors, pathology and natural history of head and neck neoplasms; Chapter 1, p. 13.

Core biopsy

There have been several recent reports discussing the added value of ultrasound-guided core biopsies (UGCB) in salivary gland tumours, with some stating that GCB is so much more accurate than FNAC, that it should become the new standard.[87, 88] There is, however, a theoretical increased risk for complications in the form of tumour seeding (not clearly reported in the literature – but probably strongly underreported) and, especially for parotid tumours, the risk of facial nerve damage (not reported, but in the practice of one of the authors, two patients were documented with VIIth nerve frontal branch damage following UGCB). As these complications are probably poorly reported, and follow-up is frequently too short to know the real effect of tumour seeding, a recent meta-analysis finding no difference between FNAC and USCB, has probably limited bearing.[89] A balanced attitude is probably that, in clinical units where FNAC is quite accurate, USCB can be utilized when FNAC is equivocal or non-diagnostic.[90, 91]

KEY POINTS

- Pre-treatment cytological assessment should be performed for major salivary gland tumours should be performed using FNAC; in selected instances UGCB can be performed, and UGCB or incisional biopsy can be considered when there is associated skin ulceration.
- Incisional or punch-biopsy for MiSG tumours is the standard of care.

SURGICAL TREATMENT

Parotid cancer

PRIMARY SITE

There is strong evidence that primary surgical excision of parotid cancer is the treatment modality providing the best chance of cure.[9, 71, 92] The extent of primary surgery is determined by the size of the lesion, the relationship to the VIIN and extraparotid tissue invasion. The majority of parotid cancers (80%) are located in the superficial or lateral parotid lobe, with a normal functioning VIIN. Performing the standard superficial or lateral parotidectomy would appear to be adequate in the majority of small cancers. Until a prospective randomized evaluation proves the oncological benefit of removing the deep lobe to address occult metastatic disease, to date very little local recurrence has been observed in tumours that are well localized in the superficial lobe and that are adequately removed. It is very likely that the use of post-operative radiotherapy will also aid with the control of possible located microscopic deep lobe lymph node deposits.[93]

Tumours <4 cm, located in the parapharyngeal or deep lobe, or with VIIN involvement should have a more extended surgical procedure, such as a total or radical parotidectomy (**Figure 10.5**). The reasoning for a total parotidectomy is that in locally advanced, high-grade parotid malignant salivary tumours, intraparotid lymph nodes may harbour metastatic disease and be overlooked or not resected should a lesser procedure be performed.[33, 94, 95] Indeed, Armstrong et al. showed that the parotid lymph nodes are involved in 53% of elective neck dissections.[96] Most pre-operatively intact nerves can be dissected macroscopically free from the tumour. VIIN branches are only to be resected when pre-operatively paralyzed or peri-operatively invaded by or surrounded by tumour.[97] More sensitive than clinical examination is electromyography and this can be performed in suspected malignant tumours to support in counselling the patient on the possible need for nerve resection and reconstruction.[98] There is consensus that microscopic disease left behind on a spared nerve branch can be controlled by the use of post-operative radiotherapy.[38, 71, 83, 97, 99, 100] Nerve sacrifice in these instances often induces disproportionate morbidity at the expense of minor gain in tumour control.[39, 97, 100] When the facial trunk or branch resection has been performed, frozen section of the cut margins is recommended to avoid the possibility of leaving tumour skip metastases. Immediate cable grafting results in optimal functional outcomes. The greater auricular nerve (GAN) combines easy access, good diameter and adequate arborization; [101, 102] for longer defects the same donor nerve can be traced back to include cervical sensory branches. The sural nerve is a good alternative.[98] Electromyographic (EMG) signs of reinnervation appear after 4.5 months, followed by the first movements about the 6th month. It can be up to 2 years before the final function is realized, usually a House-Brackman grade III to IV.[98, 101, 102] Factors that negatively impact on the final result of nerve grafting include age >60 years and the presence and duration of the pre-operative VIIN dysfunction.[98] Radiotherapy does not impair the final results of cable grafting: Brown et al. reported a House-Brackmann grade III or IV in 69% of irradiated patients versus 78% of non-irradiated patients (p = 0.54), and replicated previous reported experimental findings of 80% axon recovery in both irradiated and non-irradiated facial nerves.[102, 103]

NECK DISEASE

N+ neck

Parotid cancer related cN+ disease requires a comprehensive (modified radical) neck dissection, removing levels I to V.[104] Where appropriate, based on invasion or proximity to the metastatic disease, the non-lymphatic structures (nerve XI, jugular vein or sternocleidomastoid muscle) may need to be sacrificed.[105] Recent studies corroborated this 'old knowledge': pN+ involvement in a recent study from the Memorial Sloan Kettering Cancer Center reached 52% in level I, 77% in level II, 73% in level III, 53% in level IV and 40% in level V.[106] Also a comparable Korean study reported pN+ rates of 43% in level I, 90% in level II, 40% in level III, 57% in level IV and still 43% in level V.[107] In pN+ patients, post-operative adjuvant radiotherapy to the parotid and the ipsilateral neck doubles locoregional control and improves survival.[73, 105, 108–110]

N0 neck

In patients with a cN0 neck at presentation, performing an elective neck surgery depends on the presence of the



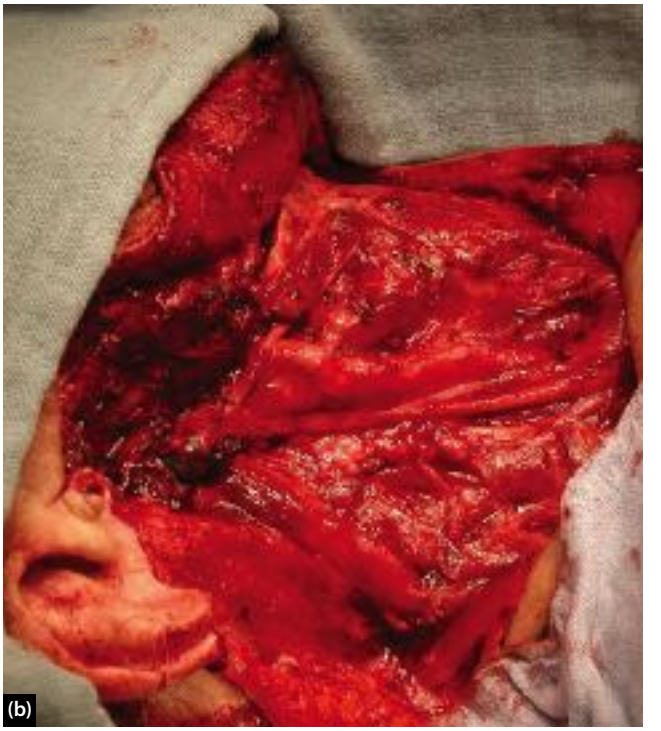








Figure 10.5 Extended radical parotidectomy with free flap reconstruction. **(a)** Outline of the resection for the patient referred to in Figure 10.2. **(b)** Following radical parotidectomy and radical neck dissection (modified type I). **(c)** Monobloc resection specimen including skin and pinna. **(d)** Static facial nerve reconstruction using temporalis fascia – temporoparietal fascia. **(e)** Gracilis free flap reconstruction.

risk factors for occult neck disease, but the alternative of using elective radiotherapy is also shown to be effective in controlling neck disease.[109] The authors routinely perform frozen section of level II nodes at the commencement of the procedure and if these contain macrometastases, we consider the neck as cN+ and proceed with a neck dissection.[41, 80, 83, 92] The recognized risk factors for the presence of occult neck disease are tumour size >4 cm and histology with clinical high-grade behaviour, implying a 20% and 49% risk for occult nodal metastasis respectively.[96, 109, 111] Age >54, perilymphatic spread and extraparotid extension, together correspond to a 95% risk.[111] These high-risk patients require elective neck treatment, be it neck dissection or radiotherapy. Parotid AdCC rarely causes lymph node metastasis, so an elective neck dissection is not really indicated in this high-grade malignancy.[92]

Some authors propose a routine elective neck dissection of for all parotid carcinoma patients; using this strategy Zbären finds a 22% occult rate and a better 5-year locoregional control as compared to that of 'an observation policy', but the patients in this series did not receive radiotherapy.[112, 113] Stennert reports even a 45% occult rate in a large series of patients all of whom underwent neck dissection.[33] A Brazilian study reported a 37% occult metastases rate predicted by T-classification, severe desmoplasia and histology (adenocarcinoma, undifferentiated carcinoma, high-grade MEC, SDC and SCC, together resulting in a 68% occult rate).[114] The surgical approach to the N0 neck can be fine-tuned using pre-operative USgFNAC of the neck and the use of peri-operative frozen section.

The MD Anderson strategy is elective radiotherapy to the N0 neck in high-risk patients, relying on definitive histopathology of the resected primary; this is appealing because the indications for elective neck treatment concur with the indications for post-operative radiotherapy to the primary, and also because pre- and peri-operative typing of salivary carcinomas is very difficult (accuracy 51–62%).[111, 115] This means that the information required to pre-operatively classify a parotid tumour as high risk is often not available during elective surgery and at the time of decision to perform a neck surgery.[44, 105, 115] Furthermore, radiotherapy may still be indicated if a cN0 neck turns out to be pN+.[93, 110] Only conducting a prospective randomized trial will answer the question whether an elective neck dissection (followed by radiotherapy if indicated) provides a better result than elective radiation alone to the cN0 neck.

Submandibular gland cancer

The standard treatment in the last decades has shifted from a rather aggressive and extended surgery as monotherapy[52, 63, 107, 116] to more limited and functional surgery, tailored to the local pathological involved anatomy, supplemented by post-operative radiotherapy.[53–55, 71, 117, 118] The typical standard operation included the submandibular gland in a radical neck dissection, often with *en bloc* excision of the floor of mouth and lower rim of the mandible.[52, 116] The move over time toward conservation surgery was illustrated by Spiro et al.,[71] who described the use of level I-II-III neck dissection for none of the patients in the period 1939–1965 to 38% of the surgeries in the study period 1966–1982. In the Netherlands' Cancer Institute, the level I-II-III dissection comprising the submandibular gland was used, in the cN0 neck and absence of invasion of bone or floor of mouth, and accounted for 66% of operative procedures in the period 1973–1983 and for 71% of the procedures between 1984 and 1994.[55] The current agreement is that for early stage, low-grade disease, the minimal procedure that should be performed, should be complete excision of the gland within a levels Ia and Ib lymph node dissection. For most other disease that is further cN0, a level I-II-III elective dissection encompassing the submandibular gland is the recommended extent of surgery. This operation should only be extended beyond the boundaries of the supraomohyoid dissection, if the local extension of the disease dictates so.[53] Commonly there is cN+ disease, and then a comprehensive neck dissection is mandated.[119]

Sublingual gland cancer

AdCC is the most common malignant tumour of the sublingual gland (72%), followed by MEC, however other SGC have also been reported, usually as case reports. The initial treatment should be surgery, performed after confirmation of histology and imaging, to encompass the extent of the primary tumour. Tumours <2 cm in size and mobile may be resected intraorally but it is also recommended that the ipsilateral submandibular gland or level I be removed, as the submandibular duct is likely to be resected. Tumours >2 cm should receive an *en-bloc* resection, possibly using a 'pull through' procedure or a mandibulotomy approach. Performing an elective neck dissection (levels I–IIa) may facilitate such a surgical procedure in the N0 situation. In the N+ neck, a therapeutic neck dissection such as a modified radical neck dissection should be performed. Adjuvant post-operative radiotherapy is indicated for patients with advanced stage disease (stage III/IV, high-grade tumours, perineural involvement, positive surgical margins, >2 N+ lymph nodes and/or pathological evidence of extracapsular extension.[120]

KEY POINTS

- The preferred treatment of parotid and submandibular gland cancer treatment is surgery.
- VIIN-preserving parotidectomy (allowing for microscopic remnant disease if unavoidable – followed by radiotherapy) in a patient with a pre-operatively functioning VIIN is considered the standard of care.
- Gross tumour involvement of the VIIN requires nerve resection followed by immediate cable grafting.
- The N+ neck requires surgery, the N0 neck should be treated electively surgically or by radiotherapy, depending on the risk factors.
- Post-operative radiotherapy improves locoregional control depending on the prognostic factors present.
- For submandibular gland malignancy, the minimally required surgery is a gland resection within a level I-II-III neck dissection (selective neck dissection); the indication for post-operative radiotherapy follows that for parotid gland malignancy.

Minor salivary gland cancer (MiSGC)

GENERAL CONSIDERATIONS

The primary

The treatment of choice for MiSGC is wide local resection with tumour-free margins. Resectability is determined pre-operatively, based on clinical and imaging findings, the anatomical site of origin, the histology and the available surgical expertise. These factors also determine the extent of resection necessary and the functional implications of a resection. In all reported series, resection margin status is one of the most important survival outcome prognostic factors that correlate strongly with both anatomical extent and histological type.[11, 121, 122]

The neck

Currently, surgical treatment of the neck is only indicated when 1) there is clinical or radiological evidence of regional metastasis (N+), or when 2) the risk of subclinical disease in a clinically negative neck exceeds 15–20% and when 3) the neck is surgically entered as an approach to the primary.

Clinical N+ disease occurs in about 15% of patients.[11, 123] Except in patients with high-grade cancers such as high-grade mucoepidermoid carcinoma, the occult metastasis rate is too low to justify elective surgical treatment.[124, 125] Nasopharyngeal salivary cancers are also an exception, where a high rate of occult disease has been reported following elective neck dissection in a series of patients amenable to surgery.[126] For patients with pN+ disease, post-operative radiotherapy improves locoregional control and survival.[73, 110]

SITE-SPECIFIC CONSIDERATIONS[122]

Oral cavity

The most common subsites are the palate, buccal mucosa, retromolar trigone and upper lip, accounting for +/– 75% of cases. The palate is the most common site (55%) with +/– 60% of these being malignant. In a series from the Netherlands' Cancer Institute, 78% of minor salivary gland cancers were located in the oral cavity.[11] In 149 patients with palatal MSGT seen over a 46-year period at the MD Anderson Cancer Center, malignant tumours were found in 116 patients (78%), with 50% of these tumours on the hard and the other 50% on the soft palate.

The majority (up to 90%) of the oral cavity MiSGC are MEC, AdCC and PAC.[122, 127] Akin to the growth pattern, patients with MEC tend to have localized space-occupying lesions, which present at an earlier stage compared to patients with AdCC, which display an infiltrative submucosal and perineural growth and are at an advanced disease stage when diagnosed. In the MD Anderson series, extensive disease diagnosed locally by radiological imaging showed: local bone invasion 31%, the sinonasal cavities 31%, the sinonasal cavities 31%, the pterygoid muscles 5%, the nasopharynx 3%, and intracranially 3%, but only 3% presented with detectable cervical lymphadenopathy.[75] The latter group need a therapeutic neck dissection in combination with wide excision of the primary. Resection of the primary palatal tumour may require a palatal obturator or free-tissue reconstruction, depending on the size and location of the surgical defect.

Oropharynx

There are few series focusing specifically on the oropharynx, but the tongue base is the most common site of origin. In the Netherlands' Cancer Institute series of patients the posterior tongue was the only oropharyngeal subsite involved.[11] Like in the oral cavity, the most frequent histologies are AdCC and MEC (up to 60%), followed by ACNOS. Treatment – if feasible – is surgery, ranging from transoral laser microsurgery or transoral robotic resections for smaller circumscribed lesions, to suprahyoid release or mandibulotomy and free-flap reconstructions for the larger tumours. Most resected tumours will require post-operative radiotherapy, which is detailed in 'Post-operative radiotherapy' below.

Larynx

MiSGs are found in the submucosa of the subglottis, glottis (floor of the ventricle and the undersurface of the anterior commissure) and supraglottis (especially in the aryepiglottic folds, and petiole of the epiglottis) and account for about 1% of all tumours of the larynx, both benign and malignant. The most frequent laryngeal MiSGC is subglottic AdCC, followed by MEC. Typically, these laryngeal MiSGC are diagnosed at an advanced disease stage when diagnosed, due to their submucosal growth and large size at the time of presentation. The treatment of choice is surgical resection, with endoscopic resection, open partial and total laryngectomy being the options. Post-operative radiotherapy should be considered in all patients especially when unfavourable prognostic factors are present, or in the case of cartilage, perineural or vascular invasion. Laryngeal MiSGC patients frequently develop distant metastasis, usually to the lungs.[128, 129]

Nose, paranasal sinuses and nasopharynx

AdCC is the most frequent MiSGC found in the nasal cavity and paranasal sinuses and due to its advanced stage at presentation results in a worse prognosis than in any other site of the head and neck, implying local recurrences and early perineural and hematogenous spread; around 50% present with distant metastases. Locoregional control is better in those patients receiving more radical primary surgery, with or without post-operative radiotherapy, but there is little data to support radical management over a more conservative approach. Recent progress in surgery, including endoscopic resection, facilitates local surgical radicality and improved surgical reconstruction that allows for timely and optimum post-operative radiotherapy. Use of the gamma knife for residual or recurrent disease optimizes the chances of cure and improves remaining quality of life. A significant number of patients have unresectable

disease at presentation and are treated with primary radiotherapy, explaining why the proportion of MiSGC at this subsite is overrepresented in reported series of AdCC from radiation oncology centres (e.g. 40% in the University of Florida series).[63]

For MiSGC located in the nasopharynx, the most common histology is AdCC (94%), and rarely MEC (6%). AdCC comprised 48% of a large surgical series (n = 23 accumulated during 12 years), MEC 35% and ACNOS 17%. Like MiSGC located in the nose and paranasal sinus, nasopharyngeal MiSGC presents late, typically at an advanced stage of disease with invasion of the skull base, cranial nerve paralysis and intracranial invasion. Complex surgical resections (varying approaches have been described such as lateral infratemporal middle fossa, subfrontal, midfacial degloving, lateral rhinotomy, transoral palatal or maxillary swing approach), possibly transposing or resecting the carotid artery, resection of dura and dissection of cancer from the cavernous sinus, are only possible in a minority of cases. These complex resections demand that expertise for a wide variety of reconstructive options be available, ranging from dural repair using temporalis fascia or a pericranial flap to vascularized flaps. Exceptionally for MiSGC, elective neck dissection reveals occult metastatic disease in about 50% of the patients with tumours in the nasopharynx.[126] Post-operative radiotherapy is always required and will be detailed in 'Postoperative radiotherapy' below. This strategy carries 5- and 10-year disease-specific survival (DSS) rates of 67% and 48% respectively. In non-resectable nasopharyngeal AdCC radical primary external-beam photon radiation seems a good option with a reported local control rate of 45% at 5 years and 5- and 10-year survival rates of 78% and 49%, respectively. Long-term complications may be serious and are less expected with modern IMRT techniques.

KEY POINTS

- The optimum curative treatment for minor salivary gland tumours is surgery.
- The surgical approach and resection should be dictated by the site of origin and can encompass the entire spectrum of head and neck surgical resective and reconstructive procedures.
- Meaningful clear-margin surgery is often impossible to achieve at certain sites because of the extensive local anatomical invasion by tumour at diagnosis (skull base and perineural invasion); in these instances, primary radical radiotherapy may be the first and only choice of treatment available.

RESECTED SPECIMEN: HISTOTYPING, GRADNG AND MOLECULAR STUDIES

Salivary malignancies are categorized as per the 2017 WHO classification (featuring 22 different phenotypes: **Table 10.2**). The characteristics that will also be reported include the tumour grade, and describe negative features such as perineural, vascular and perilymphatic invasion and the margins status. Increasingly, molecular biological markers are being identified and studies suggest that their usage may aid with a more accurate histologic diagnosis and prognosis.[130, 85]

Histologic typing: Light microscopy and immunohistochemistry

The primary histological diagnosis of SGCs is challenging, as can be seen in the 29% reclassification rate resulting from a new histological classification system reported by van der Wal et al.[4, 122, 123, 131] and by a substantial inter-observer variability between pathologists.[60, 132] The Netherlands' Cancer Institute series displayed a 22% reclassification rate.[11] Reclassification, interobserver variability, geographical variation and referral bias all contribute to disparities in the published literature. Only a population-based study can give an accurate idea of the incidence of different histological types.

A clear relationship between histological type and biological behaviour is often lacking, as commented by Spiro[30] and Leivo.[134] In population-based studies, most major SGCs are AcCCs (15–17%), AdCCs (16–27%), and MECs 14.5–19.2%).[8, 40] All 22 malignant salivary tumour types have been described across most sites. In most studies of MiSGCs, AdCC (32–71%) and MEC (15–38%) account for the majority of histological types and far outnumber the other histological variants.[11, 56, 57, 59, 60, 63, 67, 68, 73, 76, 134–137]

The most critical aspect of pathological examination is differentiating these tumours from benign entities, which can demonstrate overlapping histologic features. The proportion of benign to malignant varies across series; those with a higher percentage of malignant disease may suffer from referral bias seen at tertiary centres that are more likely to publish their results.[30, 63, 138]

Grading

Grading is a standard procedure that is performed as a surrogate marker for the biological behaviour within tumours of the same histological type. However, grading suffers from poor inter- and intra-examiner consistency and low independent prognostic power.[11, 56, 131, 132, 139] A clear relationship between histological grade and biological aggressiveness is thus often lacking.[133, 140] In addition, grading often has no therapeutic relevance as most salivary gland cancers are treated similarly with surgery and post-operative radiotherapy, with the exception of completely resected low-grade, low-stage MEC and polymorphous low-grade adenocarcinoma, where post-operative radiotherapy is not required.[44]

Clinical grading combines information from histological type and grade

To facilitate clinical use, the different histological subtypes are divided into low, intermediate and high grades as shown in **Box 10.1**.

BOX 10.1 Grading of salivary gland malignancies based on clinical behaviour

Low:	AcCC, PAC (formerly PLGA), and low-grade MEC
Intermediate:	AdCC and epithelial myoepithelial carcinoma
High:	High-grade MEC, SDC, carcinoma expleomorphic adenoma, ACNOS and undifferentiated carcinoma

When one chooses to work with two groups the intermediate group is clubbed with the high-grade group for the following reasons: AdCC is hard to cure often with a protracted clinical course, and epithelial myoepithelial carcinoma is linked to a recurrence rate of 40% and a DSS of only 60%.[141, 142] It must be noted that this grade assignment does not always parallel clinical behaviour.

Despite these limitations, grading is still an essential part of the workup and decision-making for the three most commonly encountered SGCs: AdCC,[140, 143–145] MEC[132, 139, 146–150] and AcCC.[85, 151, 152] As clinical grading is strongly associated with other consistent prognostic factors such as age[11] and TNM-stage,[56, 140] it is often not retained in the final model in multivariate analysis.

Molecular biology[92, 122, 153]

Protein products of various genes and their corresponding genes in salivary gland cancers have been intensively studied to identify potential prognostic factors and treatment targets.

PROGNOSTIC FACTORS

Cell cycle-based proliferation markers likely represent the endpoint of the accumulation of genetic and epigenetic events that induce deranged growth, reflecting the number of cells going through the cell cycle. The first subject to interest cell biologists in SGC were silver-staining or argyrophylic nucleolar organizer regions (AgNOR); an increased AgNOR cluster to nucleolus volume reflects proliferative activity and correlates with the degree of malignancy. Other intensively studied factors include Ki-67 expression (anti-apoptotic nuclear antigen in proliferating cells), proliferating cell nuclear antigen expression (PCNA, co-factor of DNA polymerase delta), human telomerase reverse transcriptase expression (hTERT) and TUNEL [terminal deoxynucleotidyl transferase (TdT)-mediated dUTP-biotin nick end labelling identifying DNA breaks in apoptotic cells] assays. In SGC, these proliferation markers correlate with optical grading and have prognostic power in AdCC, AcCC, SDC and MEC. Importantly, their contribution is proven by remaining independent factors in multivariate models that include classical clinicopathological factors. The advantage of these proliferation indices is that they are not too expensive, widely applicable, correlate well with prognosis and thus could improve prognostic grouping. In this respect, Ki-67 staining is probably the best studied and most readily available supplementary examination to aid in locating a specific SGC on the scale of biological aggressiveness.

Some of these proliferation markers have also been investigated as therapeutic targets and these are tabulated in **Table 10.3**. What follows is an overview of major advances in SGC molecular biology.

Growth factor receptor proteins and their ligands

Stem cell factor receptor (c-KIT, a transmembrane tyrosine kinase), angiogenesis-related growth factor receptors (VEGFR, PDGFR, bFGFR, IL-8, PlGF , TGFβ), nerve growth factor (NGF), the ErbB/HER family of human epidermal growth factor receptors (EGFR, also named HER-1 through -4 or ErbB-1 through -4), insulin-like growth factors IGF–I/II and receptor IGF-1R, and fibroblast growth factors 1 and 2 and fibroblast growth factor receptor 1 belong to this category. c-KIT is detected in 80–94% of AdCC and in 100% of lymphoepithelial-like SGCs and myoepithelial carcinomas, and in a subset of other tumours as well. In AdCC, the relation between high c-KIT expression (> 50%) and grade remains unresolved. In one study this feature was significantly more common in solid type AdCC but Freier et al.[154] found the opposite: high expression only in cribriform and tubular AdCC. As for angiogenesis-related growth factor receptors, Lim et al.[155] describe a prognostic value for vascular endothelial growth factor (VEGF) expression in many SGC. In multivariate analyses, VEGF expression was associated with advanced stage and with worse DSS. EGFR identification and overexpression parallels aggressiveness in MEC, SDC, and AdCC. HER-2 has been found overexpressed in adenocarcinoma, undifferentiated carcinoma, AdCC, SDC and in 30% of MEC. Furthermore, it is a negative prognostic marker in multivariate analysis, independent of histopathological grade, tumour size and regional metastasis. On the other hand, in a recent study, ERBB1/CCND1/PIK3CA co-amplification was the most consistently observed pattern (29%). EGFR amplification correlated with distant metastasis, and the co-amplification pattern translated into a reduced survival. Aggressively behaving AdCC also displays HER-3 expression. Recently increased expression of NGF has been described in AdCC, possibly accounting for its neurotropism. Fibroblast growth factors 1 and 2 and fibroblast growth factor receptor 1 are all overexpressed in salivary gland SGC.

TABLE 10.3 Molecular targets and corresponding therapies studied in salivary gland carcinoma

Molecular target	Salivary gland carcinoma type	Molecular therapy
c-KIT	AdCC	imatinib
ErbB-1	All types	cetuximab gefinitib
ErbB-2	All types	trastuzumab lapatinib
VEGF -family	AcCC	axinitib
NFκB – proteasomes degrading its inhibitor (I-κB)-α	AdCC	bortezomib

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Cell cycle oncogenes

The above-mentioned growth factor-receptor interaction activates cell cycle oncogenes. These include sex-determining region Y-box 4 (SOX-4), nuclear factor κB (NFκB), human rat sarcoma viral oncogene homolog (H-RAS), phosphatidylinositol 3 phosphate kinase/serine-threonine protein kinase Akt (PI3K/AKT), sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (Src), signal transducer and activator of transcription 3 (STAT3), mammalian target of rapamycin (mTOR, activated by AKT regulates protein synthesis depending on nutrient availability), peroxisome proliferator-activated receptor gamma (PPARgamma), and cyclin D1. In a large microarray analysis of AdCC, Frierson et al. found that SOX-4 was the most significantly overexpressed cell cycle oncogene.[156] Furthermore, increased apoptosis following SOX-4 knockdown suggests that this oncogene exerts its activity via down-regulation of inhibitors of the NFκB pathway (inhibitor protein (I-κB)-α) and by up-regulation of apoptosis inhibitors such as survivin. Mutations of H-RAS are observed in carcinoma ex-pleomorphic adenoma, in adenocarcinoma and in almost half of MECs, where the frequency of H-RAS mutations parallels tumour grade. Cyclin D1 seems frequently overexpressed in AdCC and MEC and correlates with prognosis. In MEC, high-cyclin D1 expression follows inactivation of secreted frizzled-related proteins (SFRPs) by hypermethylation. Nuclear pSTAT3 expression seems to play a role as tumour suppressor in the absence of EGFR, HER-2, and survivin in SGC. RUNX3, a tumour suppressor gene that, when active, facilitates TGF-beta to play its apoptotic role, appears silenced by hypermethylation in AdCC. RB1-inducible coiled-coil 1 (RB1CC1) is a positive regulator for the retinoblastoma tumour suppressor (RB1) pathway, and its expression in SGC implies better prognosis, analogous to observations in breast cancer. Efforts are underway at targeting the PI3K/AKT pathway by blocking mTOR with temsirolimus.

Pleomorphic adenoma gene 1 (PLAG1) is a specific proto-oncogene found in a large percentage of pleomorphic adenomas and is transcribed and overexpressed following a t(3;8)(p21;q12) chromosome translocation resulting in β-catenin-promoter swapping. This causes deregulated expression of PLAG1 target genes by the IGF-II/IGFIR mitogenic signalling pathway. Another fusion oncogene, MEC translocated 1 gene with exons 2–5 of the mastermind-like gene (*MECT1-MAML2*), t(11;19)(q14-21;p12-13) is transcribed into a fusion protein that was initially thought to be exclusive for low-grade MEC. However, high-grade fusion-positive MEC cancers associated with advanced-stage lethal disease have now been described. For AdCC, a recurrent reciprocal translocation of t(6;9)(q22-23; p23-24) resulting in fusion gene partners comprising *MYB* gene and the transcription factor NFIB (previously reported in AdCC of breast and, lacrimal and ceruminal glands) has now been described. In both fusion-positive and a subset of fusion-negative AdCCs, high expression of the transcript Myb was found, suggesting this to be a potential target for new therapies.

Proteins involved in DNA damage repair

p53 and ERCC1 (excision repair cross-complementation group 1) belong in this category. p53 expression and p53 mutations in AdCC are generally associated with worse outcome, but a large Finnish multivariate analysis failed to confirm additional value over a clinicopathological multivariate model. This large study however did not focus on the AdCC subgroup but studied all histological types.

Proteins involved in apoptosis

The Bcl-2 group contains pro-apoptotic proteins such as Bax, Bad and Bak and anti-apoptotic proteins such as Bcl-2, Bcl-xL and survivin. Low expression of Bcl-2 corresponds to higher apoptosis and thus better prognosis, whereas high Bcl-2 expression in SGC relates to poor prognosis and advanced T and N classification. Nuclear survivin expression indicates SGC with worse prognosis.

Proteins involved in cell-cell adhesion (hemidesmosome proteins B180 and B230, E-cadherin, CDH12, α-catenin), migration (matrix metalloprotease, heparanase) and epithelial-mesenchymal transition (NBS-1 and snail) Estrogen, progesterone and androgen receptors

Estrogen receptors have been described in AdCC, whereas androgen receptors are the target of hormonal therapy in SDC.

Microarray technology gives a tumour-specific overview of over- and underexpressed tumour genes, and can be used as a prognostic blueprint of a tumour.

This guides treatment for other tumours such as breast cancer, but to date there have been only limited efforts in SGC. An application of this strategy in AdCC resulted in the identification of a novel oncogene in salivary gland oncogenesis, AQP1, the transcription of which seems epigenetically regulated by (hypo-)methylation status.

Viral aetiology

EBV has been implicated in the genesis of bilateral Warthin's tumours and undifferentiated SGC. CMV infection in mice and in humans seems related to MEC development. This awaits further validation in larger series, but the authors found the CMV protein expressed in almost all cases studied.[17] Other viruses implicated in this disease are HPV, human herpes virus 8 (HHV-8).

SPECIFICS OF THE MAIN HISTOTYPES

In population-based studies of parotid carcinoma, the majority of carcinomas are AcCC (15–17%), followed by AdCC (16–27%) and MEC (14.5–19.2 %).[8, 40] The distribution in submandibular gland cancer and MiSGC is different, with an emphasis on especially AdCC, more than MEC and ACNOS (**Table 10.4**).

TABLE 10.4 Distribution of the major histological tumour types in minor salivary gland carcinomas[122]*

Authors	No. of patients	AdCC %	MEC %	ACNOS %	CAN %	Others %
Spiro et al.[56]	378	34	34	21	1	10
Sadeghi et al.[76]	117	59	25	15	0	1
Garden et al.[67]	160	71	16	11	1	1
Anderson et al.[68]	95	43	26	26	3	0
Parsons et al.[63]	95	60	15	22	–	–
Chou et al.[59]	256	32	38	16	3	14
Jones et al.[135]	103	70	19	–	1	9
Le et al.[58]	54	59	13	28	–	–
Vander Poorten et al.[11]	55	40	16	16	6	16
Terhaard et al.[73]	157	42	23	22	6	6
Pires et al.[136]	546	15	52	9	9	15
Loh et al.[158]	171	47	23	19	–	–
Kruse et al.[159]	27	48	30	22	–	–
Kakarala et al.[160]	639	26	50	22	2	–
Carrillo et al.[57]	77	45	30	15	4	6
Li et al.[137]	103	47	36	–	3	15

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Acinic cell carcinoma (AcCC)

AcCC usually presents as a painless parotid lump and forms some 15–17% of parotid malignancies, yet they account for only 3% of all salivary gland tumours, indicating a clear parotid predilection.[162] Macroscopic pathology commonly shows a solitary encapsulated lesion but multilobulation does occur. This tumour arises from the acinic cells, but in 75% of AcCC more than one cell type is seen and the histological patterns described include solid microcystic, papillary cystic and follicular. All of these patterns may be seen in one individual tumour.[162] AcCC is generally considered low grade and is considered to have the best survival rate, but a high-grade aggressive subgroup (papillary cystic variety) has poorer prognosis.[71, 152, 161] AcCC has a long natural history and long-term follow-up is mandatory. Spiro found that the cure rate continued to drop from 76% at 5 years to only 55% at 15 years and other authors have found the same.[156] Clearly, this can be an aggressive tumour that should be treated accordingly – early attempts at enucleation yield disastrous survival figures.[163, 165] It is generally accepted that one should not hesitate to use post-operative radiotherapy, which can only be omitted for low-stage AcCC in absence of adverse prognostic factors.[83, 92, 110]

Mucoepidermoid carcinoma (MEC)[122]

Whereas AdCC is the most frequent MiSGC overall, MEC is the most frequent type at the intraoral subsite. MEC represents about 16–37% of all MiSGCs, but about 36–59% of intraoral MiSGCs. As in many salivary malignancies the tumour is formed of several cell types, in MEC there are mucus-secreting cells, epidermoid cells and intermediate cells. The prognosis of MEC is mainly influenced by clinical stage, histological grade, and surgical margins, all strongly interrelated factors. In grading MEC, two- and three-tiered systems have been advocated. Batsakis et al.[162] follow the suggestion of Healey et al.[148] for a three-tiered system, based mainly on the involved cell types. Healey found in univariate analysis that recurrence rates of low- and intermediate-grade carcinomas are quite similar with a recurrence rate of 6% and 20% for low- and intermediate-grade MEC respectively, vs. 78% for high-grade carcinomas. The Armed Forces Institute of Pathology (AFIP) also proposed a three-tiered grading system, based on different criteria, and promoted a more quantitative approach but the clinical data supporting this complicated grading system are not convincing. Brandwein et al. showed a good correlation of these AFIP grades with stage and local control, but revealed a significant grading disparity among five experienced oral pathologists using the 'standard AFIP grading criteria'.[132]

More appealing to clinicians are simpler two-tier grading systems. Evans[150] suggests that >90% solid tumour in MEC indicates a high-grade histology, with only univariate analysis supporting this; Ciccolallo et al. suggest that >90% epithelial cells should be interpreted as high-grade histology, supported by the observation that patients with low-grade tumours have a 5-year survival of 96% whereas high-grade tumours show a death rate 10 times this. Recent large studies find no prognostic difference between low- and intermediate-grade MEC.[167] To summarize, in clinical practice only the low-grade subgroup without further negative prognostic features should be managed with surgery alone. In the intermediate-grade MEC group many patients will have additional negative prognostic factors (e.g. involved surgical margins or soft tissue invasion) that will be an indication for adjuvant radiotherapy.

Adenoid cystic carcinoma (AdCC)[122]

AdCC demonstrates insidious growth over many years, with a tendency for local recurrence and distant metastasis despite aggressive therapy at the primary site. Some patients have severe pain due to nerve invasion, and in the parotid gland VIIN palsy may be evident. In a study from Liverpool dealing with 108 patients with AdCC, nearly one-third occurred in the major salivary glands, and most of the remainder involved the minor glands.[168] Forty per cent of patients had oral cavity tumours and half of these were in the hard palate. Of all tumours 41% were locally advanced at presentation and 11% had distant metastases. Interestingly, revision of the pathology slides led to 15% reclassification as PLGA. In the Netherlands' series, 17% of the parotid cancers were AdCC, as were 40% of the cancers of the submandibular gland.

AdCC thus mainly occurs in the MiSG, where it is the most common subtype (32–71%) and, as shown in **Figure 10.2**, occurs mostly in the palate followed by the paranasal sinuses (14–17%). This tumour will often be diagnosed at an advanced stage, and due to the complex anatomical area in the skull base region, complete excision is frequently impossible[169] and further complicated by the propensity of AdCC for perineural extension, both in the MiSG, and in the parotid and submandibular glands, where large nerves are closely adjacent to the tumour. This perineural growth is notorious for skip lesions, for example, in the VIIN, isolated AdCC deposits can be observed several centimetres from where tumour invasion apparently terminated, both on frozen section and on later paraffin-section histology. The feature 'perineural growth' implies a worse prognosis.

A study from the University of Michigan showed 80% positive margins in operated skull base AdCC cases, even with tumours where experienced surgeons pre-operatively had the feeling they could resect the tumour with clear margins.[166] Every AdCC should be considered a 'clinically high-grade malignant neoplasm': the behaviour of AdCC is relentless and the long-term course is marked by multiple local recurrences, uncommon regional and yet frequent distant metastatic spread to the lungs and bones. It is often said that cure is never achieved in this disease. Sometimes optimistic 5-year survival rates are reported (e.g. 92% in an Australian series),[169] but 10- and 20-year survival rates continuously drop (e.g. in a UK series 40% at 20 years and continuing to drop until 30 years; the actuarial primary site recurrence rate in that study was 100% recurrence at 30 years,[168] and 54% in the Australian series). In a large European study, 10 years survival was 65%.[171]

AdCC uncommonly presents with lymph node metastasis, and recently an interesting hypothesis has been developed to explain this phenomenon. AdCC does produce only very limited amounts of VEGF-C, which translates into very few lymphatic vessels within the tumour due to a reduced interaction with VEGFR-3.[172]

AdCC frequently metastasizes to bone and liver, but most frequently to the lung, in approximately 70% of patients in most series. The latter metastases, although alarming to the oncologist and the patient, frequently grow slowly. A Japanese study analyzed 30 patients where 21 had pulmonary metastases, 4 of these at presentation and 17 during follow-up, and showed a cumulative incidence of distant metastasis in 100% of patients followed for longer than 5 years, regardless of grade and initial stage.[173] The average tumour doubling time of a metastatic deposit was just over one year, which is very slow, compared with lung metastases from other cancers. This tumour doubling time suggests that distant metastasis is often present long before the initial diagnosis of the primary salivary gland tumour, and this obviously puts in perspective the limits of ablative surgery for AdCC in the head and neck.

As stated above, AdCC can be graded histologically. The scheme proposed by Szanto et al.[144] indicates a primarily cribriform or tubular tumour as grade I; tumours with less than 30% solid component are grade II and tumours with greater than 30% solid component are grade III. In patients treated similarly, a solid histological pattern of AdCC carries a worse prognosis in terms of distant metastases and long-term survival on univariate analysis. In multivariate analysis, when including stage at presentation, this prognostic effect is less clear, yet a Brazilian study recently confirmed solid histology as an independent prognostic factor.[174]

Polymorphous adenocarcinoma (PAC; formerly polymorphous low-grade adenocarcinoma (PLGA))[122]

PAC, prior to 1983 considered a low-grade variant of AdCC and initially also referred to as terminal duct adenocarcinoma, has a less aggressive biological behaviour compared to other types of adenocarcinoma. About 75% of these tumours arise from MiSGs. Major salivary gland involvement is relatively unusual. It most frequently arises on the palate. Despite the better prognosis, local recurrence even with negative margins, regional recurrence and distant metastasis have all been described. Recurrence can occur very late in follow-up: in one series, local recurrences occurred at 15 years and regional recurrence occurred at 20 years after initial treatment. Therefore, the term 'low-grade' is omitted in the most recent WHO classification, which now talks about 'Polymorphous Adenocarcinoma'. There are four histological patterns: tubular, cribriform, papillary and lobular, and because of this variable appearance, P(LG)AC may be mistaken for pleomorphic adenoma or other benign tumours, and for AdCC, due to comparable growth patterns and to the presence of neurotropism. Immunohistochemical and molecular biological studies may help to differentiate these two lesions.

Adenocarcinoma NOS

This histology also forms a large subgroup in major series (8–18% of parotid carcinoma), but this proportion

depends on the effort by pathologists to revise the material. A substantial part of the tumours initially classified as adenocarcinoma not otherwise specified (ACNOS) can be specified as one of the subtypes in **Table 10.2** upon revision using modern histopathological techniques.[34, 40, 73] Nonetheless, frequently the remaining ACNOS are aggressive, with advanced locoregional extension at diagnosis and frequently implying perineural growth and positive resection margins.[41]

Carcinoma ex-pleomorphic adenoma

These tumours account for up to 5–25% of all SGC and tend to arise in the major glands.[9, 37, 112, 175] The risk of developing this carcinoma within a pre-existing pleomorphic adenoma increases with the time a pleomorphic adenoma exists, to as much as 10% by 15 years. Carcinogenesis seems associated with frequent earlier attempts at removal of a recurrent benign pleomorphic adenoma, the reason why optimal initial surgery is so much stressed upon in trainee surgeons.[177–179] The tumour may be malignant from onset or carcinomatous transformation can occur.[179] In recurrent pleomorphic adenoma, the rate of carcinoma found ranges from 7% to 16%.[177, 178, 180] In the 2005 WHO classification, for the previous term 'carcinoma ex-pleomorphic adenoma' a distinction is made between carcinoma in pleomorphic adenoma (which can be a nidus of non-invasive carcinoma in pre-existent pleomorphic adenoma or a true invasive carcinoma), the very rare and aggressive carcinosarcoma, and the metastasizing mixed tumour, in which metastases contain typical benign structures. The prognosis of a carcinoma in pleomorphic adenoma is poor: the MSKCC cause-specific survivals for this disease are 40% at 5 years, 24% at 10 years and 19% at 15 years.[181]

KEY POINTS

- The histopathological workup of SGC, i.e. typing and grading, is among the most complex areas in histopathology.
- This holds for the light microscopic, immunohistochemical and molecular biological aspects of the histopathological workup.
- Enormous advances in SGC molecular biology in the last two decades have resulted in better prognostic fine-tuning, but to date have not resulted in advances in treatment, nor in improved treatment results.

POST-OPERATIVE RADIOTHERAPY

Parotid and submandibular salivary gland malignancies

Following resection and classical histological and molecular biological workup, post-operative radiotherapy is frequently indicated in patients with salivary gland cancers. In the past, these cancers were believed to be 'radioresistant'. As an example, for submandibular gland carcinomas, Conley stated in the early 1970s[52] that there was no indication that irradiation should be given when an adequate operation has been performed; thus, only 12% of his patients were treated in a combined fashion, and there are reports of series advocating radiotherapy in less than 3% of surgically treated patients.[116] In contrast, in the Netherlands' Cancer Institute series, 67% received combined treatment, as did 59% of patients in the Princess Margaret Hospital series, Toronto, with significant reported improvement in locoregional tumour control.[54] Post-operative radiotherapy to the primary tumour used to be delivered by conformal wedged-pair beams to a dose of 60 Gy[44, 73, 110, 182, 183] but has been replaced by 3-dimensional (3D) conformal radiotherapy and lately intensity-modulated radiotherapy (IMRT), which is now considered the 'standard of care'.[184, 185]

Radiotherapy is indicated in advanced stage disease (stage III and IV) and in the presence of histopathological adverse prognostic factors. Lacking randomized trials, the evidence for this approach comes from retrospective reports, with a bias of selecting prognostically negative patients for combined therapy, yet demonstrating improved locoregional control in the combined treatment group.[51, 70, 110, 185–187] The study of the Dutch Head and Neck Oncology Cooperative Group illustrates this by a relative risk (RR) for local recurrence in surgical patients being 9.7 times the risk of patients receiving combined surgery and radiotherapy. These findings are consistent with the older matched pair analysis by Armstrong et al., describing a significantly improved DSS and local control in patients with stage III and IV disease treated with radiotherapy following resection.[108] Post-operative radiotherapy can only be omitted for stage I-II lesions in AcCC and low-grade MEC if complete resection does not reveal other adverse pathological factors (close surgical margins, perineural or perilymphatic invasion, or recurrent disease).[41, 55, 83, 92] For high-risk major salivary gland carcinomas, two reports recently documented the benefit of a post-operative platinum-based concomitant chemoradiation scheme.[188, 189]

Minor salivary gland cancer

Once the MiSGC has been resected and pathologically staged and graded, post-operative radiotherapy to the primary site is recommended for most patients. Only in 'clear margin' early stage disease (stage I and II) without lymphovascular or perineural invasion (a set of conditions usually restricted to low-grade variants), can post-operative radiotherapy be omitted without loss of disease control[11, 73, 110, 122, 125] Adverse prognostic factors, such as positive or close surgical margins,[67, 76, 125, 131] a high-grade histology,[60, 67, 125] perineural growth (particularly 'named' nerve invasion),[75, 125, 190, 191] bone and muscle invasion, paranasal sinus localization, and high T- and N-classification,[11, 67] are indications for post-operative radiotherapy. In addition to what has been said for the major salivary gland cancers, for MiSGC, proton-beam radiotherapy may be considered to reduce the risk of damage to the brain and visual apparatus in patients with

cancers involving the nasal cavity and paranasal sinuses. Improved locoregional control does not invariably lead to higher survival rates. Spiro et al.[56] were unable to demonstrate a survival benefit for patients receiving post-operative radiotherapy after matching for stage, site and histology. The unaffected incidence of distant metastases is the probable explanation: 36% of patients in the series by Garden et al, with good local control following combined treatment, eventually developed distant metastases.[67]

RADIOTHERAPY AND CHEMOTHERAPY IN UNRESECTABLE DISEASE[92, 122, 192]

Primary radiotherapy is indicated for patients who are inoperable, who refuse surgery, or who have an unresectable tumour. Unresectable SGC or resectable cancer in poor surgical candidates is controlled by conventional photon radiotherapy, with disease control rates from 17 to 57% at 10-year follow-up. The percentages at the upper limit of this range are found in series dealing with mainly early stage disease. Newer techniques such as IMRT promise better results, especially in combination with non-photon radiation, such as proton or carbon ion boost, where locoregional control seems to improve and toxicity remains limited.

Neutron radiotherapy reaches 5-year local control in up to 75% in unresectable disease, especially for AdCC, and this is ascribed to a reduced oxygen-enhancement factor, less variability of sensitivity through the cell cycle and decreased repair of sublethal cell damage. This option remains unattractive because of a lacking survival benefit (distant metastasis occurs in 40% of these patients after 51 months) and severe late side effects, including cervical myelopathy, sensorineural hearing loss, and necrosis of the soft tissues, the mandibular and temporal bone and the temporal brain lobe. Recently, the University of Washington neutron irradiation team reported even better long-term local control after giving a boost using the gamma knife at the end of neutron radiotherapy. Reports have also been published on the use of concurrent chemo-radiation for unresectable disease, showing good tumour control but with acceptable morbidity. Unfortunately, these are reports of small series and not randomized clinical trial data. For recurrent MiSGC, there have been reports on combining re-irradiation with concomitant chemotherapy, resulting in locoregional control of 72% at one year and on combining re-operation with intra-operative radiotherapy.[192]

Currently, chemotherapy remains of palliative use only in salivary gland cancer. A temporary complete remission in about 20% seems the best achievable at the moment. In metastatic ACNOS, high response rates are observed with cisplatin, doxorubicin and cyclophosphamide. Unfortunately these responses are generally short-lived. **Table 10.4** lists the explored targeted therapies that have so far been used clinically; unfortunately, none has significantly improved results. A recent high-quality meta-analysis focusing on AdCC reaches the same conclusion. In this study the activity of cytotoxic drugs given in combination was studied in 143 patients enrolled in 17 trials. In 14 studies, cisplatin-based regimens led to objective responses in 29 of 118 patients (response rate 25%). Response duration ranged from 6 to 77 months.[195] Recent phase II studies explored the combination of cytotoxic and targeted therapy (imatinib and cisplatin, and bortezomib and doxorubicin) in AdCC and concluded that the results warrant further investigation of this approach.

KEY POINTS

- Post-operative radiotherapy is a proven adjunctive treatment to surgery in the management of SGC and has a proven effect on locoregional control in most patients.
- Of all head and neck neoplasms, for SGC treatment, the recent (r)evolution towards IMRT has probably its greatest merits in improving dose delivery to the target volume, while minimizing 'collateral damage' to the non-involved surrounding healthy tissues.
- In SGC, cytotoxic chemotherapy and targeted therapies remains experimental and should be tested in clinical trial settings; to date most are of a palliative use only.

TREATMENT RESULTS AND PROGNOSIS ACCORDING TO SITE

Major salivary gland cancer: Parotid[92]

Treatment results in major treatment centres have to be appreciated in their specific context of stage, percentage high-grade, treatment period and corresponding treatment regimens, patient inclusion criteria and adequacy of follow-up (**Table 10.5**). The decision to exclude palliative intent patients in the 1999 Manchester series,[99] results in a patient cohort with relatively low stage (1 in 5 patients in Stage III-IV) and high DSS as opposed to the 1999 Amsterdam series that includes palliative patients, increasing the proportion of advanced stage disease (1 in 4 in stage IV), reflected in a lower overall DSS.[41]

Many univariate and multivariate statistical analyses have focused on identifying prognostic factors in SGC. Variables such as histological subtype,[72, 195] grade, stage, age, gender, pain, skin invasion and VIIN dysfunction, resection margins and comorbidity have been identified as statistically significant prognostic factors. Several outcomes have been used as the dependent variable, including overall survival, DSS and recurrences. However, it is difficult to meaningfully communicate the data from these disparate studies in a clinical setting.

To empower the consultation and enable effective communication of prognosis, the authors have designed a prognostic index combining several important patient and tumour-specific prognostic factors, appropriately weighted, to provide a point estimate of tumour recurrence. We constructed such an index from the Dutch

TABLE 10.5 Disease-specific survival (DSS) for parotid carcinoma

Research group	Publication year	Number of patients	DSS 5 y	DSS 10 y
Spiro[9]	1986	623	55%	47%
Spiro et al.[71]	1989	62	63%	47%
Kane et al.[10]	1991	194	69%	68%
Poulsen et al.[205]	1992	209	71%	65%
Leverstein et al.[38]	1998	65	75%	67%
Therkildsen et al.[205]	1998	251	76%	72%
Renehan et al.[99]	1999	103	78%	65%
Vander Poorten et al.[41]	1999	168	59%	54%
Harbo et al.[207]	2002	152	57%	51%
Godballe et al.[208]	2003	85	52%	
Vander Poorten et al.[40]	2003	231	62%	
Lima et al.[209]	2005	126	72%	69%
Mendenhall et al.[210]	2005	224		57%
Vander Poorten et al.[34]	2009	237	69%	58%
Guntinas-Lichius et al.[211]	2015	295	82%	82%

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patient population for the situation before (PS1) and after (PS2) surgical treatment. When the requisite data is input into the prognostic equation, the resultant score places the patient in one of four prognostic groups. This prognostic index has been validated in a nationwide and in an international database, indicating its usefulness in parotid carcinoma patients in general. It is available online at (www.uzleuven.be/parotid).[34] A recent validation effort in a Brazilian population did not show the index to have similar prognostic accuracy, but a critical analysis of the population and the methods used identified several reasons for this lack of concordance.[196]

Since the discovery of molecular biology in salivary gland research, it is likely that this new information will contribute to the prognosis. Batsakis rightly commented 26 years ago that critical multivariate assessment of putative molecular biological, clinical and pathological factors with rigorous validation will be needed.[140] Ideally this exercise should be done on a large multicentre datasets.[171]

Submandibular salivary gland

With the use of adjuvant radiotherapy, treatment results for submandibular gland cancer have improved in recent publications.[9, 116] The 5-year survival rate of 50% and the 10-year survival rate of 36% in the series of the Netherlands' Cancer Institute are comparable to the results of a nationwide analysis[6] showing a 5-year survival rate of 52%.[117, 118] An exceptionally high figure was described by Weber et al, who reported a 5-year survival rate of 69% in a population with a surprising majority of T4b disease.[53] The 5-year DSS of 61% and the 10-year DSS of 51% in Amsterdam are almost similar to the findings in Toronto with a 5-year DSS of 60% and a 10-year DSS of 48%. In the past, submandibular gland cancers were ascribed a worse prognosis than their parotid counterparts.[9, 116, 197] Recent studies[51, 70, 71, 198, 199] and our own experience[55] do not support this stance.[122]

Negative prognostic factors for survival, DSS and locoregional control are increasing age at diagnosis,[54, 55] TNM stage,[53, 54, 116–118] extra-glandular soft-tissue extension[53–55] and perineural growth.[55] As for other sites, the finding of a better locoregional control in patients with negative prognostic factors treated with surgery and adjuvant radiation evidence for the efficacy of post-operative radiation.[51, 53, 54, 70, 108, 198]

MiSG cancer[122]

Published overall survival rates vary widely, with 5-year survival ranging from 66% to 80% and 10-year survival ranging from 56% to 70%. This wide range is attributed to differences in non-tumour related deaths, referral bias and selection bias. Selection bias occurs when comparing overall results of all localizations to those of only oral or palatal MiSGCs, known to present at lower stages. Short follow-up periods do not capture long-term treatment failures. In the Netherlands' Cancer Institute series recurrences appeared up to 139 months after treatment (median 23 months). All recurrences after 5 years were in patients with AdCC. Bias can also be caused when patients with prior treatment or delayed referral, or distant metastases are excluded.

Initial tumour control after therapy is expected to be 56–62%. Distant metastasis from MiSGC in patients who are M0 at presentation seems to follow a '1 in 5 rule'. i.e. 20% of patients will develop M+ disease during follow-up.[11, 56, 76] MiSGCs overall do not imply a worse prognosis than their submandibular and parotid counterparts,

although specific involvement of subsites (e.g. the skull base) are associated with a worse outcome.

Clinicopathological prognostic factors[122]

Many univariate and multivariate statistical analyses have focused on prognostic factors in MiSGC to relate the individual's prognosis to the overall results. For example, decreasing overall survival parallels increasing age at diagnosis, but this difference is less clear for DSS where patients dying of other causes are not considered as treatment failures. Also for tumour control, the studies that include age as a prognostic parameter do not retain it as having a prognostic effect, so age alone should not determine treatment policy. In a cohort that also includes major SGC, comorbidity remained an independent factor.[201] As stated before, when a MiSGC arises in the nose, paranasal sinuses, or nasopharynx, very poor treatment results have been observed. This relationship of site to prognosis is most likely confounded by stage. Treatment of late-stage skull base MiSGC is complicated by poor surgical access. UICC Stage determines prognostically separate groups for survival, DSS and tumour control. T-classification alone also predicts all outcomes, as does increasing N classification and M1 classification.

Histologically, soft-tissue invasion including perineural and vascular invasion by the primary tumour are negative prognostic factors, as is the strongly related factor radicality of resection. The problem of surgical access to MiSGC results in a high percentage of close or positive margins, ranging from 23% or 27%[11, 137, 201] up to 40%.[67] When looking at specific sites for specific types, margins are reported in up to 80%.[170] In a homogenous series of 67 patients with oral MiSGC, multivariate analyses showed that clinical T-status, anatomical subsite and margin status were independent predictors for overall survival; T-status and margin status were independent predictors for locoregional recurrence-free survival.[202] Histopathological high grade is strongly correlated with these features. Independent prognostic power is sometimes lost due to its strong interrelationship with other negative prognostic factors. The most frequent histological type, AdCC, is considered a clinically high-grade tumour by most authors. According to da Cruz Perez et al,[199] clinical stage, solid-growth pattern and expression of p53 were the most important prognostic factors in children with AdCC. It is unclear whether grading of AdCC is useful in patient management. There is morphological overlap between solid conventional AdCC and high-grade transformation, and the transition from conventional AdCC to high-grade transformation is often gradual. Basically, the aggressive features common to both variants are more exaggerated in high-grade transformation, while solid conventional AdCC shows only slight deviation from tubular or cribriform patterns.[85, 203] Costa et al have studied the genetic profile of AdCC with high-grade transformation (HGT) versus solid type, and concluded that AdCC-HGT may not necessarily reflect a more advanced stage of tumour progression, but rather a transformation to another histological form in which the poorly differentiated forms presents a genetic complexity similar to the solid AdCC.[204] Although not frequently encountered, neck metastasis also heralds poor DSS. All of previously mentioned clinicopathological factors have been considered for their ability to predict the outcome 'positive neck disease' in a recent large-scale analysis of the Surveillance, Epidemiology, and End Results (SEER) database. The analysis yielded a simple prognostic index including the factors male gender, T3-T4 classification, pharyngeal origin of the MiSGC, and high-grade for adenocarcinoma and MECs. However, this index still needs validation.[123]

KEY POINTS

- Treatment results for both major and minor SGC are comparable and in the range of 60–70% 5-year survival and 50–60% 10-year survival.
- For an individual patient, this expected treatment result varies highly depending on an extensive list of patient-, tumour-, and treatment-related prognostic factors.
- For parotid cancer, prognostic estimates can be performed using validated online calculators.
- For submandibular and MiSGC, the clinician is dependent on the published literature to 'guess-timate' the expected outcome following treatment.

COMPLICATIONS OF TREATMENT

Parotid gland surgery[205]

The typical complication for parotid surgery is temporary or permanent facial palsy, but in experienced hands, normal function can be achieved in 96% of patients after superficial parotidectomy. Further complications are haemorrhage, infection, skin necrosis, Frey syndrome and salivary fistula.

Frey syndrome is rarely encountered in parotid cancer patients, as most of them receive radiotherapy, inhibiting its development. Treatment of this condition with topical anticholinergics is usually unsuccessful owing to poor compliance. The current treatment of choice is chemodenervation using botulinum toxin type A. The median effectiveness is 8–11 months and the treatment can be repeated. Interposition grafts that have been proposed as preventive strategies include the sternocleidomastoid muscle flap. Although there are opponents, this flap is considered effective by most clinicians. In malignant pathology there is a drawback to its use as it complicates revision surgery if needed. The same remark holds for the superficial musculoaponeurotic system (SMAS) flap, reported to be quite effective in prevention of Frey syndrome. Interposed foreign material has an unacceptable rate of complications (haematoma, seroma and salivary fistula).[206]

Paresthesia in the GAN area occurs in 57% of patients after sectioning the GAN, but 90% of patients do not report this to be cumbersome with no impact on quality of life is reported.[208] Recent evidence suggests that the posterior branch of the GAN can be saved in 2/3 of patients undergoing parotidectomy, at the expense of little extra

surgical time, resulting in sensibility returning to normal in 80–100% of patients. Furthermore, the preserved GAN can be a good interposition graft for VIIN reconstruction in surgery for malignant disease.[92]

Submandibular gland surgery

Typical surgical complications of submandibular gland cancer relate to the nerves that may have to be sacrificed in the removal of the submandibular gland for malignancy. Nerves at risk are the mandibular and cervical branches of the facial nerve, the hypoglossal nerve and the lingual nerve. Normally, the lower facial branches should not be damaged unless they loop particularly inferiorly to the mandible or a wide excision of soft tissue is necessary. Neuropraxia resulting from traction is the commonest cause of this problem; recovery is rare. Sacrifice of the hypoglossal nerve leads to paralysis of one side of the tongue but functional adaptation is good and rarely causes severe problems. Damage to the lingual nerve is less likely as it is high up behind the mandible but if damage does occur it is potentially a serious problem as the loss of sensation allows repeated trauma to the tongue from dentition. Repair tends to be unsuccessful.

Radiotherapy

Radiotherapy complications include mucositis, skin ulceration, hair loss, mandibular and temporal bone osteoradionecrosis, fibrosis, cerebral radionecrosis, hearing loss (sensorineural and conductive due to refractory external otitis) and xerostomia. With the advent of IMRT some of these complications can be abrogated.[122]

CONCLUSION

Salivary gland cancer is a particularly demanding tumour for both patient and the multidisciplinary team. Every step in the management algorithm is complicated: the clinical and radiological evaluation, the histological diagnosis, the ablative and reconstructive surgery, the adjuvant radiotherapy and the management of complications. The best care can undoubtedly be provided when these patients are centralized in specialized tertiary referral centres.

KEY POINTS

- The incidence of malignant salivary gland neoplasms in the Western world is 7 to 12 per 1,000,000 person-years.
- Salivary malignancy increases with exposure to environmental factors, low-dose ionizing radiation and aflatoxins.
- Smoking of cigarettes is related to development of Warthin's tumours.
- EBV infection may predispose to the development of Warthin's tumour and undifferentiated carcinoma.
- The smaller the salivary gland, the less frequent a tumour is likely to manifest, but when it does the more likely is the tumour to be malignant.
- Parotid tumours
  - rapid increase in size or volume, the presence of pain, enlarged neck lymph nodes, fixation to deep structures or skin, or VIIN dysfunction should alert a likely diagnosis of malignancy
  - tumour imaging aims to estimate the extent (summarized in the TNM classification), location and probability of malignancy
  - MRI scanning is mandatory to evaluate invasion of the VIIth nerve, fixation to the deep structures, location at the stylomastoid foramen or deep lobe with the use of CT imaging to evaluate suspected bone invasion.
- Submandibular tumours, although frequently symptomless, are often malignant.
- MiSG tumours commonly present at an advanced disease stage and their extent is summarized as per the TNM classification for that anatomic location.
- Pre-treatment cytological assessment should be performed for major salivary gland tumours should be performed using FNAC; in selected instances UGCB can be performed, and UGCB or incisional biopsy can be considered when there is associated skin ulceration.
- Incisional or punch-biopsy for MiSG tumours is standard of care.
- The preferred treatment of parotid and submandibular gland cancer treatment is surgery.
- VIIN-preserving parotidectomy (allowing for microscopic remnant disease if unavoidable – followed by radiotherapy) in a patient with a pre-operatively functioning VIIN is considered the standard of care.
- Gross tumour involvement of the VIIN requires nerve resection followed by immediate cable grafting.
- The N+ neck requires surgery, the N0 neck should be treated electively surgically or by radiotherapy, depending on the risk factors.
- Post-operative radiotherapy improves locoregional control depending on the prognostic factors present.
- For submandibular gland malignancy, the minimally required surgery is a gland resection within a level I-II-III neck dissection (selective neck dissection); the indication for post-operative radiotherapy follows that as for parotid gland malignancy.
- The optimum curative treatment for minor salivary gland tumours is surgery.
- The surgical approach and resection should be dictated by the site of origin and can encompass the entire spectrum of head and neck surgical resective and reconstructive procedures.
- Meaningful clear-margin surgery is often impossible to achieve at certain sites because of the extensive local anatomical invasion by tumour at diagnosis (skull base and perineural invasion); in these instances, primary radical radiotherapy may be the first and only choice of treatment available.
- The histopathological workup of SGC, i.e. typing and grading, is among the most complex areas in histopathology.
- This holds for the light microscopic, immunohistochemical and molecular biological aspects of the histopathological workup.
- Enormous advances in SGC molecular biology in the last two decades have resulted in better prognostic fine-tuning, but to date have not resulted in advances in treatment, nor in improved treatment results.

- Post-operative radiotherapy is a proven adjunctive treatment to surgery in the management of SGC and has a proven effect on locoregional control in most patients.
- Of all head and neck neoplasms, for SGC treatment, the recent (r)evolution towards IMRT has probably its greatest merits in improving dose delivery to the target volume, whilst minimizing 'collateral damage' to the non-involved surrounding healthy tissues.
- In SGC, cytotoxic chemotherapy and targeted therapies remains experimental and should be tested in clinical trial settings; to date most are of a palliative use only.
- Treatment results for both major and minor SGC are comparable and in the range of 60–70% 5-year survival and 50–60% 10-year survival.
- For an individual patient, this expected treatment result varies highly depending on an extensive list of patient-, tumour-, and treatment-related prognostic factors.
- For parotid cancer, prognostic estimates can be performed using validated online calculators.
- For submandibular and MiSGC, the clinician is dependent on the published literature to 'guess-timate' the expected outcome following treatment.

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CHAPTER 11

TUMOURS OF THE PARAPHARYNGEAL SPACE

Suren Krishnan

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SEARCH STRATEGY

The data in this chapter are based on a search using the following keywords: parapharyngeal tumours, carotid body tumours and paragangliomas.

INTRODUCTION

The parapharyngeal space is an intriguing compartment of the head and neck. Although it is the site of only 0.5% of all head and neck masses, the unusual pathology and proximity to vital anatomy attracts the special interest of surgeons, radiologists and pathologists.

Early reports of these rare tumours were made by McIlrath[1] in 1963 and subsequent reports by Maran[2] in 1984, Som and Biller[3] in 1981 and Pensak and Gluckman[4] in 1994, who had series that averaged three or four cases per year. The definitive literature on the topic, describing the anatomy, pathology and surgical treatment was published by Olsen[5] in 1994. Riffat et al.[7] published a systematic review of the international literature examining the experience with 1143 parapharyngeal space tumours reported over a 20-year period in 2014.

Lesions of the parapharyngeal space may involve a wide spectrum of primary pathologies.[5,6] Pre-operative diagnostic accuracy has improved with the advent of multi-planar radiological imaging including fine-sliced computerized tomography (CT) with contrast and magnetic resonance imaging (MRI) with fat suppression sequences and gadolinium for contrast. Image-guided fine-needle aspiration cytology has improved histological diagnosis. This allows for a better understanding of the nature of these lesions and a better plan for the surgical approach to them.

There has been increasing interest and use of transoral robotic surgery (TORS) in the treatment of benign and malignant tumours of the oropharynx. TORS has the approval of the US Government's Food and Drug Administration (FDA) for use in early oropharyngeal cancers and benign lesions of the head and neck since 2009. The da Vinci surgical robotic system (Intuitive Surgical Inc., Sunnyvale, California) provides three-dimensional, high-resolution visual access with magnification as well as tremor filtration and motion scaling of robotic instruments. This allows for delicate dissection and addresses previous concerns leveled against transoral approaches to the parapharyngeal space with respect to controlled dissection around vital neurovascular structures and tumour spillage.

ANATOMY

The parapharyngeal space is a potential neck space filled with fat and areolar tissue. A variety of names have been ascribed to this space including pterygomaxillary space, pharyngomaxillary space, pterygopharyngeal space and lateral pharyngeal space. However, the term parapharyngeal space is generally accepted.

The parapharyngeal space is classically described as an inverted pyramidal-shaped potential space (**Figure 11.1**). Its base lies superiorly at the skull base and comprises

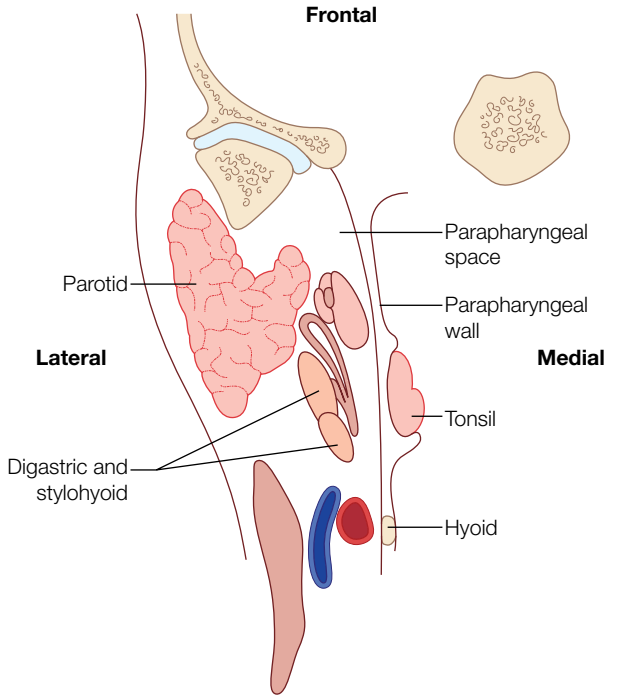


Figure 11.1 The parapharyngeal space resembles an inverted pyramid. Used with permission from Olsen KD. Tumors of the parapharyngeal space. *Laryngoscope* 1994; **104**(5) Suppl 63, Fig 1, p. 2.

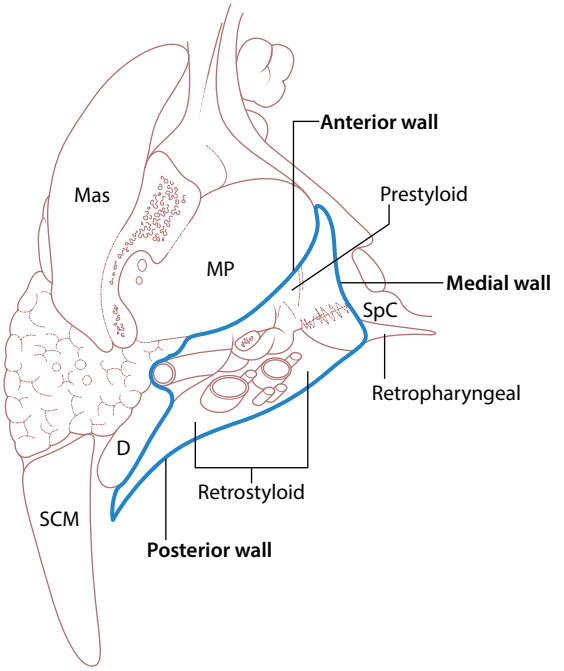


Figure 11.2 Pre-styloid and post-styloid (retrostyloid) compartments separated by condensation of fascia – the aponeurosis of Zuckerkandl and Testut. P, parotid gland; D, digastric; MP, medial pterygoid; Mas, masseter, SCM, sternocleidomastoid. Used with permission from Olsen KD. Tumors of the parapharyngeal space. *Laryngoscope* 1994; **104**(5) Suppl 63, Fig 3, p. 4.

the sphenoid and temporal bones. This area includes the jugular and hypoglossal canal and the foramen lacerum. Its apex lies inferiorly at the greater cornu of the hyoid bone. It has three sides, medial, lateral and posterior and an anterior leading edge which is the pterygomandibular raphe.

The medial surface is distensible and comprises the superior pharyngeal constrictor muscle, the buccopharyngeal membrane and the pharynx. The lateral surface, which is relatively immobile, comprises the medial pterygoid muscle, the ramus of the mandible, and the deep lobe of the parotid gland, and below the level of the mandible, the lateral aspect is bordered by the fascia of the posterior belly of the digastric muscle. It has a posterior surface which is part of the prevertebral fascia, bordered by the carotid sheath posterolaterally and the retropharyngeal space posteromedially.

Two fascial condensations in the parapharyngeal space are of surgical importance. First, the parapharyngeal space is divided into two parts by the fascial condensation called the aponeurosis of Zuckerkandl and Testut (**Figure 11.2**). This fascia joining the styloid process to the tensor veli palatini divides the parapharyngeal space into the pre-styloid and post-styloid compartments. The pre-styloid compartment contains adipose tissue, lymphatics, ectopic salivary gland tissue and small nerves and vessels, a small branch of the trigeminal nerve to the tensor veli palatini muscle and branches of the ascending pharyngeal artery and pharyngeal venous plexus. It is related to the retromandibular, deep aspect of the parotid gland. The post-styloid compartment is posteromedial and contains the internal carotid artery, internal jugular vein, cranial nerves IX to XII, the cervical sympathetic chain, lymph nodes and glomus bodies.

Second, a condensation of cervical fascia forms a band which extends from near the apex of the styloid process of the temporal bone to the angle and posterior border of the mandible (**Figure 11.3**). This stylomandibular ligament, lying posteriorly and the posterior border of the mandible, lying anteriorly, form the stylo-mandibular tunnel. The tunnel is a deep relation of the deep lobe of the parotid gland. Tumours of the deep lobe can extend into the parapharyngeal space through this tunnel giving rise to a dumbbell shaped tumour.

PATHOLOGY

As mentioned above, parapharyngeal space tumours account for 0.5% of all head and neck masses. In a comprehensive review of the literature on parapharyngeal space tumours, Riffat et al. identified approximately 70 different histological subtypes of lesions.[7] Of these 82% were benign and 18% malignant. The most common tumours were of salivary gland origin, accounting for 45% of all lesions. These arose in the pre-styloid compartment. The vast majority (75%) were benign and of these 64% were pleomorphic adenomas. Adenoid cystic carcinoma and muco-epidermoid carcinoma were the commonest reported malignant lesions.

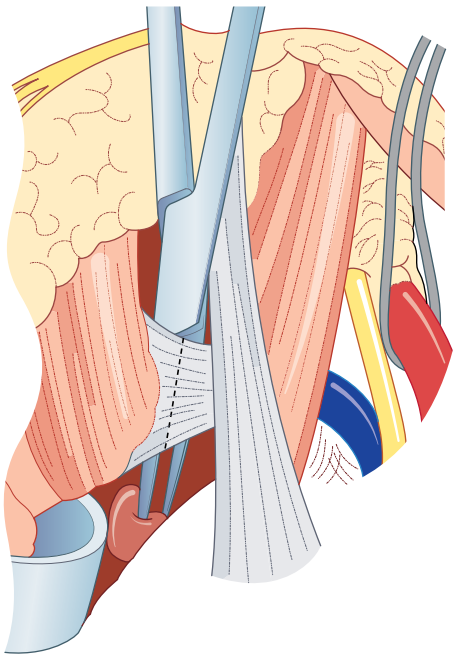


Figure 11.3 Stylomandibular ligament of the left neck from styloid process to posterior border of mandible forming the stylomandibular tunnel. Used with permission from Olsen KD. Tumors of the parapharyngeal space. *Laryngoscope* 1994; **104**(5) Suppl 63, Fig 10, p. 21.

Neurogenic lesions accounted for 41% of lesions in the parapharyngeal space. The majority of these lesions are benign and of these 52% were paragangliomas, 27% were schwannomas and 9% were neurofibromas.

Malignant lesions accounted for 5% and the majority were of neurogenic origin arising in the post-styloid space and the major subtype was malignant peripheral nerve sheath tumour.

A variety of miscellaneous lesions account for 12% of parapharyngeal space tumours. These include internal carotid artery aneurysms, branchial cleft cysts, haemangiomas and meningiomas. Metastatic lesions account for 3% of lesions and 2% of lesions are of lymphoid origin.

Salivary gland tumours

These are the most common neoplasms of the parapharyngeal space. The majority are benign and of these, the majority are pleomorphic adenomas arising from the deep lobe of the parotid gland. A small number arise from ectopic salivary glandular tissue lying in the parapharyngeal space. It is important to distinguish the difference. Tumours arising from the deep lobe of the parotid are generally not suited to contemporary transoral resection using endoscopic or transoral robotic approaches. These tumours may well require a partial parotidectomy and a transparotid and transcervical approach for resection. Parapharyngeal space pleomorphic adenomas, independent of the deep lobe of the parotid gland and arising from ectopic salivary glandular tissue, are amenable to transoral resection and despite their size are suitable for blunt dissection mobilization of the tumour from the skull base. The importance of imaging using both CT and MRI is elaborated in 'Imaging and other investigations' below. In summary, to plan surgical resection, it is important to assess the tumour's relationship to the deep lobe of the parotid gland and to understand if the tumour has a cystic component and the relative thickness of the tumour capsule.

Other benign salivary gland tumours in the parapharyngeal space include Warthin's tumours, basal cell adenomas, monomorphic adenomas, myoepitheliomas and benign lymphoepithelial lesions.

Malignant salivary gland tumours of the parapharyngeal space include adenoid cystic carcinomas, mucoepidermoid carcinomas, squamous cell carcinomas, adenocarcinomas, acinic cell carcinomas and myoepithelial carcinomas. These generally require a parotidectomy with sparing of the facial nerve dependent on pre-operative nerve function with a transcervical approach. The surgical resection may need to be extended to encompass the tumour by means of mandibulotomy for access or mandibular resection if bone is involved in the tumour or access may need to be improved by mastoidectomy or infra-temporal fossa approaches.

Paragangliomas

Paraganglia are groups of cells of neural crest origin belonging to the extra adrenal chromaffin and nonchromaffin cell system (**Figure 11.4**). They are believed to play a role in chemoreception. Paragangliomas are tumours that arise from paraganglia and head and neck paragangliomas may occur from paraganglia along the arterial vasculature and cranial nerves from the skullbase to the aortic arch. About 30% of these tumours are believed to have a genetic origin related to the *Succinyl Dehydrogense* (*SDH*) gene locus. The *SDHA*, *SDHB* and *SDHC* genes are particularly associated with familial head and neck paragangliomas. Head and neck paragangliomas may also be associated with the multiple endocrine neoplasia (MEN) syndromes MEN2a and MEN2b.

Most of these tumours present as an asymptomatic neck mass or an intraoral mass by means of medial displacement of the superior pole of the palatine tonsil. These tumours are believed to be present for months to years prior to the onset of the symptoms and many are the result of an incidental diagnosis. About 10% of paragangliomas are multicentric and should have imaging such as whole body MRI to assess other sites such as the aortic arch and adrenal. About 3% may be secretory and present with systemic symptoms associated with catecholamine release. All patients with paraganglioma should be assessed for catecholamine secretion prior to surgery to avert anaesthetic complications from catecholamine release potentially occurring during surgical manipulation of the tumour. Paragangliomas are slow-growing benign tumours and the decision to perform surgery needs to be well considered. The surgical complications from lower cranial nerve

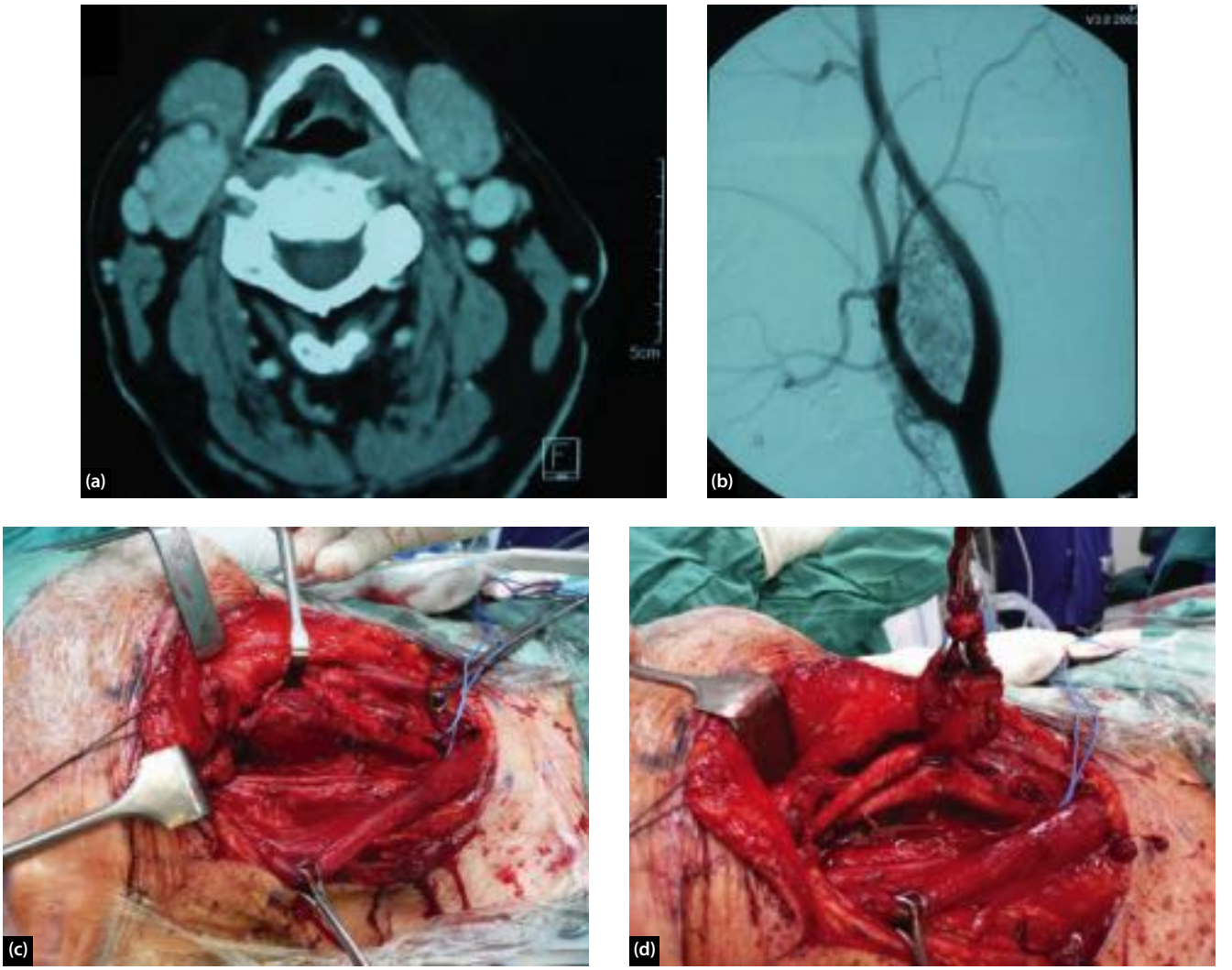


Figure 11.4 **(a)** CT neck showing vascular right carotid body tumour lying between internal and external carotid arteries. **(b)** Angiogram showing vascular right carotid body tumour splaying Internal and external carotid arteries – the 'Lyre' sign. **(c)** Right carotid body tumour. **(d)** Right carotid body tumour dissected off internal and external carotid arteries.

palsies may be more distressing than the lesion and high-vagal paraganglioma may not be amenable to complete resection without significant risk to the vagus, glossopharyngeal, accessory and hypoglossal nerves. The usual indications are suspected malignancy as evidenced by multiple lesions, erosion of adjacent bone or involvement of adjacent cranial nerves or associated regional lymphadenopathy. Surgery may also be indicated if increasing tumour size causes pressure effects on surrounding vascular and neurological structures.

It is difficult to discriminate between benign and malignant paraganglioma unless histological assessment is performed. Both malignant and benign tumours are comprised of the same two major cell types that comprise the paraganglia, these being epithelioid chief cells and sustentacular supporting cells. Together these two cell types form clusters of cells (Zellbalen), which are surrounded by extensive vascular sinusoids. Histological markers such as central necrosis, vascular invasion, and mitosis or nuclear atypia do not appear to be correlated with metastasis or true invasion.[8]

Paragangliomas have characteristic imaging features including demonstration of vascularity, the so called 'salt and pepper' appearance and in the case of carotid body tumours, a displacement of the angle between the internal and external carotid arteries known as the 'Lyre' sign Surgical resection for large lesions requires careful planning and may need transmastoid and infratemporal fossa approaches (**Figure 11.5**).

Schwannomas

Schwannomas are benign neurogenic tumours considered to originate from either Schwann cells or fibroblasts supporting the nerve. They present in patients between 30 and 70 years of age. They usually arise from either the vagus nerve or the sympathetic trunk. The vagus nerve is reported to be the origin of 50% of parapharyngeal

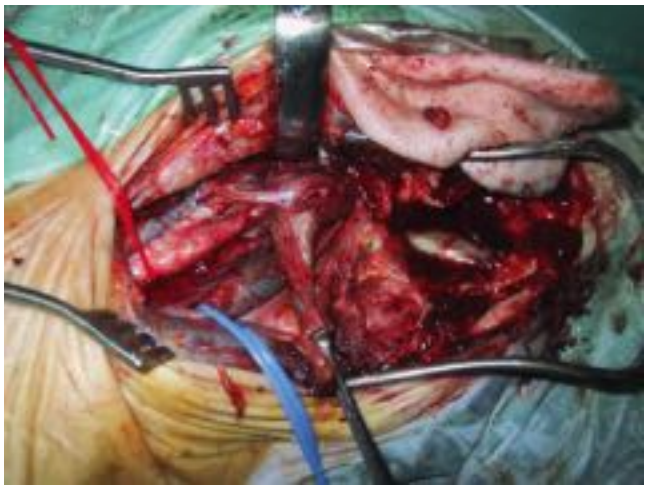


Figure 11.5 Transcervical with transmastoid approach to resect a left vagal paraganglioma. Tumour grasped by Allis forceps. Red ligature loop around carotid artery, blue ligature loop around internal jugular vein and sigmoid sinus on view in mastoid cavity.

schwannomas and cervical sympathetic chain is the next common source. Generally, schwannomas are characterized by slow and asymptomatic growth. However, progressive growth in the parapharyngeal region may result in pressure effects and cause dysphagia and hoarseness of voice. The pre-operative evaluation is critical, with imaging modalities like CT and MRI determining the diagnosis[9] and may indicate the nerve of origin.[10] These tumours are usually fusiform along the long axis of the nerve or may be round. They are of heterogenous signal intensity with hypointense, isointense and hyperintense areas on CT and MRI. Transcervical or transoral biopsy of parapharyngeal space schwannomas is usually associated with unique pain not usually reported by patients undergoing fine-needle aspiration biopsy and may be complicated by haemorrhage, infection and rarely cranial nerve injury.

Metastases to the parapharyngeal space

The parapharyngeal space contains lymph nodes and these drain the mucosa of the upper aero digestive tract and viscera of the neck. It is important to assess the nodal status of the retropharyngeal and parapharyngeal nodes when assessing metastatic neck disease in head and neck cancer. The retropharyngeal and parapharyngeal nodes are not routinely encompassed in surgical fields. However, they are accessible to both surgery and radiation when identified as being involved with metastases.

The most common metastases to the parapharyngeal space is from nasopharyngeal cancer, said to be involved in up to 30% of cases. These nodes may also be involved in tonsil and tongue base cancers and maxillary sinus cancer. Other potential primary sites include the thyroid and parotid glands. Rarely these nodes maybe involved with distant sites such as breast, colon and prostate cancer.

The parapharyngeal space may be directly invaded by malignancy from the nasopharynx, tonsil, retromolar trigone, palate and tongue base.

While benign tumours of the parapharyngeal space enjoy low levels of recurrence with a 5-year progression free survival rates of 93%, malignant tumours of the parapharyngeal space fare worse with a 5-year progression free survival rate of 61%.[11]

CLINICAL PRESENTATION AND EVALUATION

These tumours are usually asymptomatic oropharyngeal masses, found on incidental examination for innocuous symptoms such as a sore throat. They need to be at least 3 cm before they become apparent and present as a neck mass. They may present with a simple nasal obstruction or snoring, or may present with hearing loss due to Eustachian tube occlusion. Rarely they may present with cranial nerve dysfunction causing hoarseness, dysphagia or cough, which may be due to pressure on or involvement of, the hypoglossal, vagus and glossopharyngeal nerve, or Horner syndrome.

Clinical evaluation requires assessment of the airway, speech and swallowing, a full head and neck examination including cranial nerves examination, nasopharyngoscopy and examination of the middle ear for effusion. Bimanual palpation and ballotment helps assess tumour mobility and size and appreciation of the displacement of the tonsil or the posterior pharyngeal wall provides clues to whether the lesion has its origins from the pre-styloid or post-styloid compartment.[12]

IMAGING AND OTHER INVESTIGATIONS

Accurate imaging of the parapharyngeal space is essential to planning surgical resection. Multiplanar imaging with fine slice CT and MRI provides the detail required. Further information regarding vascularity and relationship to the neurovascular structures can be gained from MR angiography and carotid angiography.[13–15] Therapeutic interventions such as pre-operative embolization or balloon occlusion studies can be performed at the same time.

The parapharyngeal space appears as a small triangular space on axial imaging with an image density or signal consistent with fat. Knowledge about the displacement patterns of fat and the internal carotid artery within the parapharyngeal space will aid in the localization of lesions.

The presence of a fat plane between the parotid and a lesion differentiates a truly parapharyngeal space lesion from an extension of a deep lobe parotid lesion through the stylo- mandibular tunnel into the parapharyngeal space

(**Figure 11.6a–d**). A lesion arising in the pre-styloid space may have a rim of parapharyngeal fat antero-medially, but displaces the parapharyngeal fat and internal carotid artery posterolaterally (**Figure 11.7a,b**). However, a lesion in the post-styloid compartment will displace the parapharyngeal fat and internal carotid artery anteromedially. MRI with fat suppression sequences can help delineate this relationship clearly.

CT scans can show evidence of bony detail and erosion by these tumours and may also show calcification within tumours. MRI scans show soft-tissue extension of these tumours including intracranial extension. MRI scan with gadolinium can also show involvement of nerves and perineural spread.

Some lesions have classic imaging characteristics like congenital cysts which on CT are seen as low attenuation

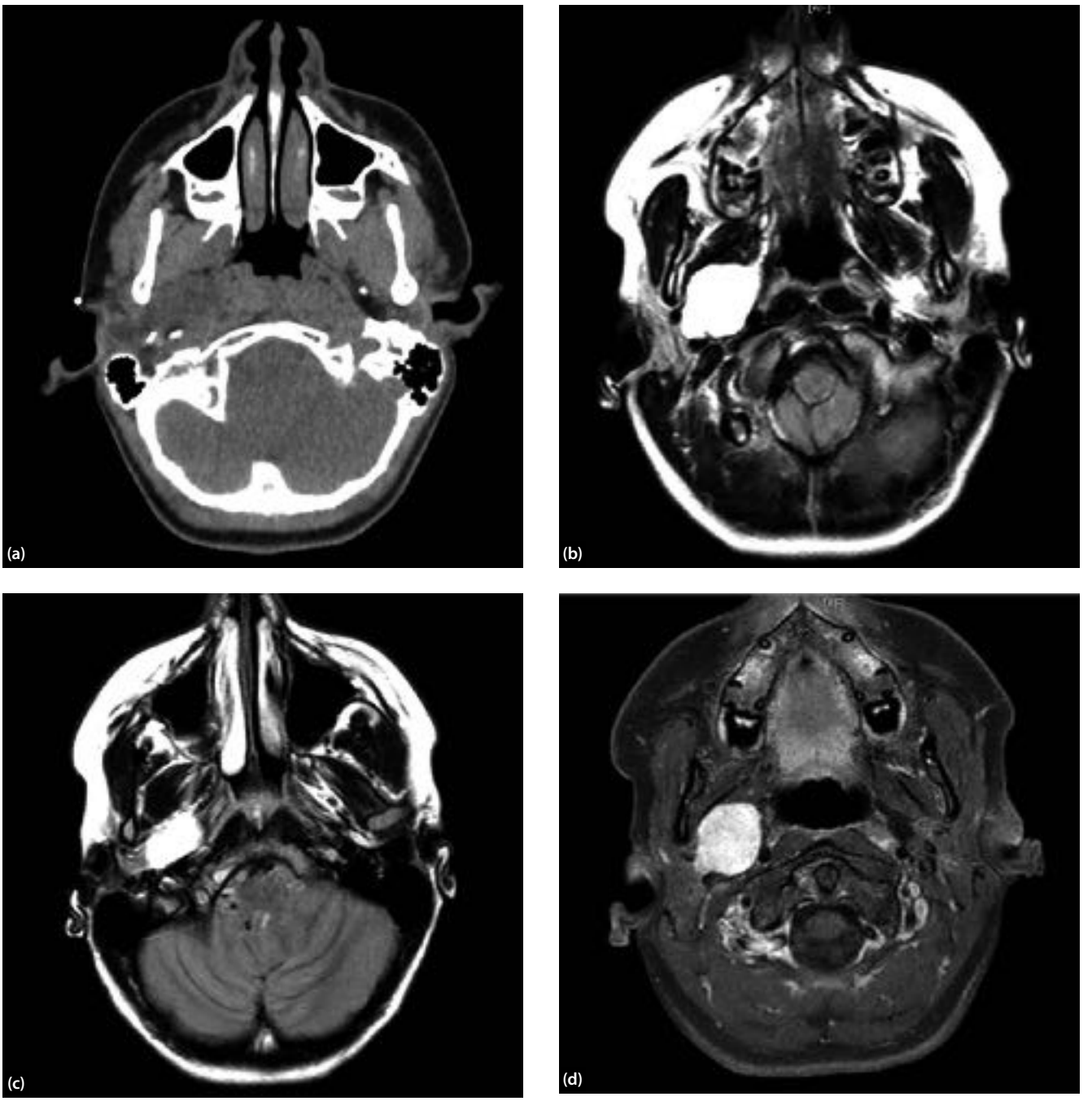


Figure 11.6 **(a)** Right parapharyngeal space tumour on CT shows the mass to be contiguous with the deep lobe parotid. **(b)** The same parapharyngeal tumour on MRI shows the mass to clearly arise from deep lobe of parotid. **(c)** Same right parapharyngeal space tumour on MRI showing limited involvement of deep lobe of parotid. These lesions are ideal for a transcervical – transparotid approach and may be suitable for a combined TORS resection with transparotid identification and protection of the facial nerve. **(d)** T1-weighted MRI with gadolinium and STIR sequence to suppress fat and demonstrate no fat plane in PPS between tumour and deep lobe of parotid.

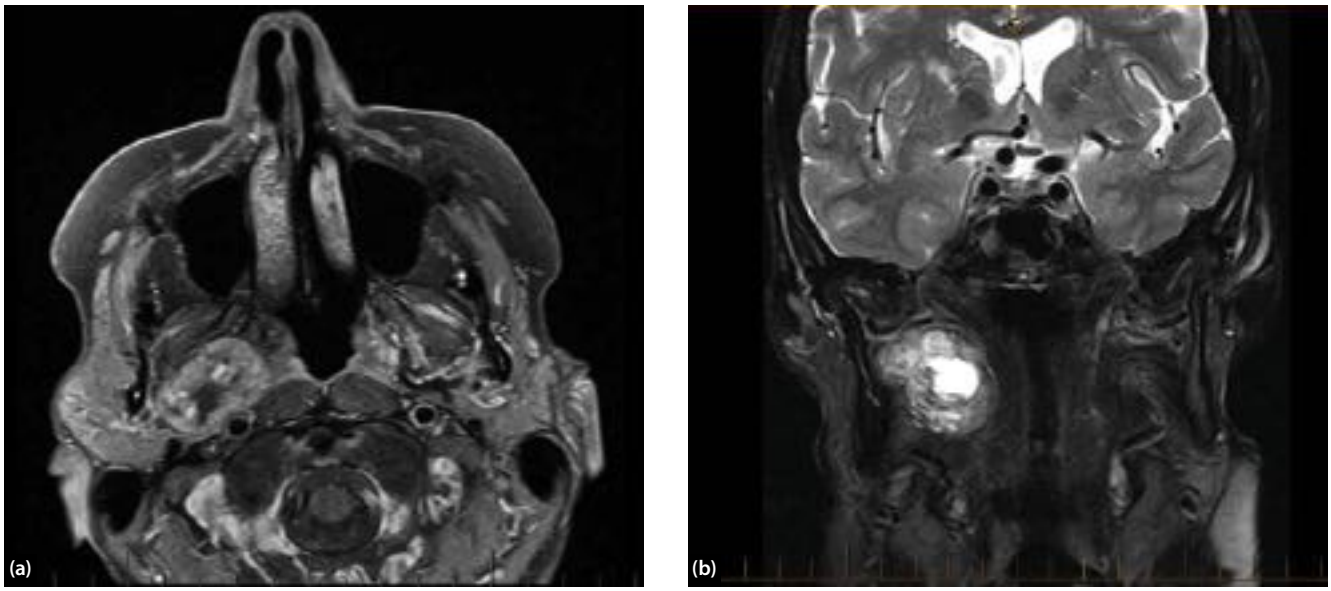


Figure 11.7 **(a)** MRI of right parapharyngeal space tumour. Lesion of the right parapharyngeal space with fat plane between tumour and deep lobe of parotid gland and rim of fat antero-medial to tumour. Lesion of the parapharyngeal space in the pre-styloid compartment displacing the carotid artery posteriorly. This variation is ideal for a TORS approach to resection. **(b)** Right parapharyngeal space tumour displacing carotid artery laterally. Favourable for TORS.

lesions with a thin uniformly smooth wall. On MRI, they appear as T1-weighted hypointense and T2-weighted hyperintense lesions with peripheral enhancement on post-contrast study. Schwannomas are fusiform, sharply circumscribed masses seen on CT as soft-tissue density masses with few cystic areas within. They show uniform enhancement on post-contrast study. On MRI, they appear heterogeneously hyperintense on T2-weighted images and isointense to hypointense on T1-weighted images. There are no flow voids within them which help to differentiate them from paraganglioma. The flow voids in paraganglioma give them the characteristic 'salt and pepper' appearance on MRI. Functioning paragangliomas may require further investigations including 24-hour urine screen for metanephrine.

Image guidance may be required to obtain a transcervical fine-needle aspiration biopsy for lesions not obvious or accessible in the oropharynx by a transoral approach.[15, 16]

Vascular lesions not amenable to resection may be considered for angiography and embolization. Angiography and embolization is also performed 24–48 hours before the excision of vascular tumours. In patients with lesions that encircle the internal carotid artery and who are at risk of trauma or resection of the internal carotid artery, balloon occlusion tests will need to be performed to assess the risk of neurovascular complications and assist in the decision-making process.

SURGICAL APPROACHES

Lesions of the parapharyngeal space are predominantly treated by surgery. In a systematic review of 1293 cases over a 25-year period, Kuet et al.[11] reported that 96% of patients had surgery. The aim of surgery is to remove the lesion with minimal morbidity. Adjuvant radiotherapy is reserved for malignant lesions or recurrent benign lesions with a high risk of recidivism. Chemotherapy is administered when indicated by specific histology such as rhabdomyosarcoma, positive margin status, tumour histology, perineural and lympho-vascular spread. Radiotherapy has also been used in patients who are considered a high surgical risk or for unresectable lesions. There are reports in the radiation literature of observational studies showing long-term control as defined by stable disease or limited regression in patients with paraganglioma undergoing radiation.[17, 18]

External transparotid, transcervical approaches to the parapharyngeal space have traditionally been considered the only safe access. The external approach was initially promoted in the 1950s mainly because of a poor understanding of the nature of these tumours and the surgical anatomical relationships. CT did not arrive until 1972 and was not in general use until 1979; the first MRI scanners arrived in the mid 1980s and were not in general use until the late 1990s. The improved imaging allowed consideration of approaches other than the traditional external approach.

In his treatise on parapharyngeal space surgery, Olsen[5] provides a clear description of the variety of external approaches. These include the transcervical approach which can be carried out in combination with a transparotid approach with or without a mandibulotomy for tumours that extend into the intratemporal fossa. Other combinations including orbitozygomatic, transmandibular and transpalatal approaches have been described. These approaches all involve wide exposure and a significant disruption of the normal anatomy of the

jaw and neck in order to facilitate safe resection of large or malignant neoplasms.

Transoral approaches, in the past, have generally been discredited. This is predominantly related to the risk to adjacent neurovascular structures, the risk of tumours spilled during resection, and the subsequent difficulty in dealing with recurrent tumour and finally the risk of infection from contamination of oral commensals. However, the advent of robotics and modern endoscopic systems have addressed many of these concerns for suitable tumours of the parapharyngeal space.

The choice of surgical technique is dependent on the tumour size, its relationship to the parotid gland and skull base and if the tumour is malignant.

Transcervical approach

The transcervical approach is the most commonly utilized approach, used in about 46% of cases (**Figure 11.8**).[11] It is ideal for small benign tumours independent of the deep lobe of the parotid gland. The procedure is performed under a general anaesthetic with the patient intubated with a nasotracheal tube. This allows an extra centimetre of anterior distraction of the mandible when accessing the parapharyngeal space. The patient is positioned with the neck extended and rotated opposite to the side of the lesion. The excision is performed through a transverse skin crease incision approximately 5 cm below the mandible to spare the marginal mandibular branch of the facial nerve. The platysma is divided and the superficial fascia of the submandibular gland is identified and raised with the superior flap to protect the facial nerve branches. The submandibular gland can be mobilized and displaced anteriorly to get greater access to the parapharyngeal space. The stylomandibular ligament is identified and divided and the mandible is distracted anteriorly. The parapharyngeal space is located between the digastric muscle and the periosteum of the

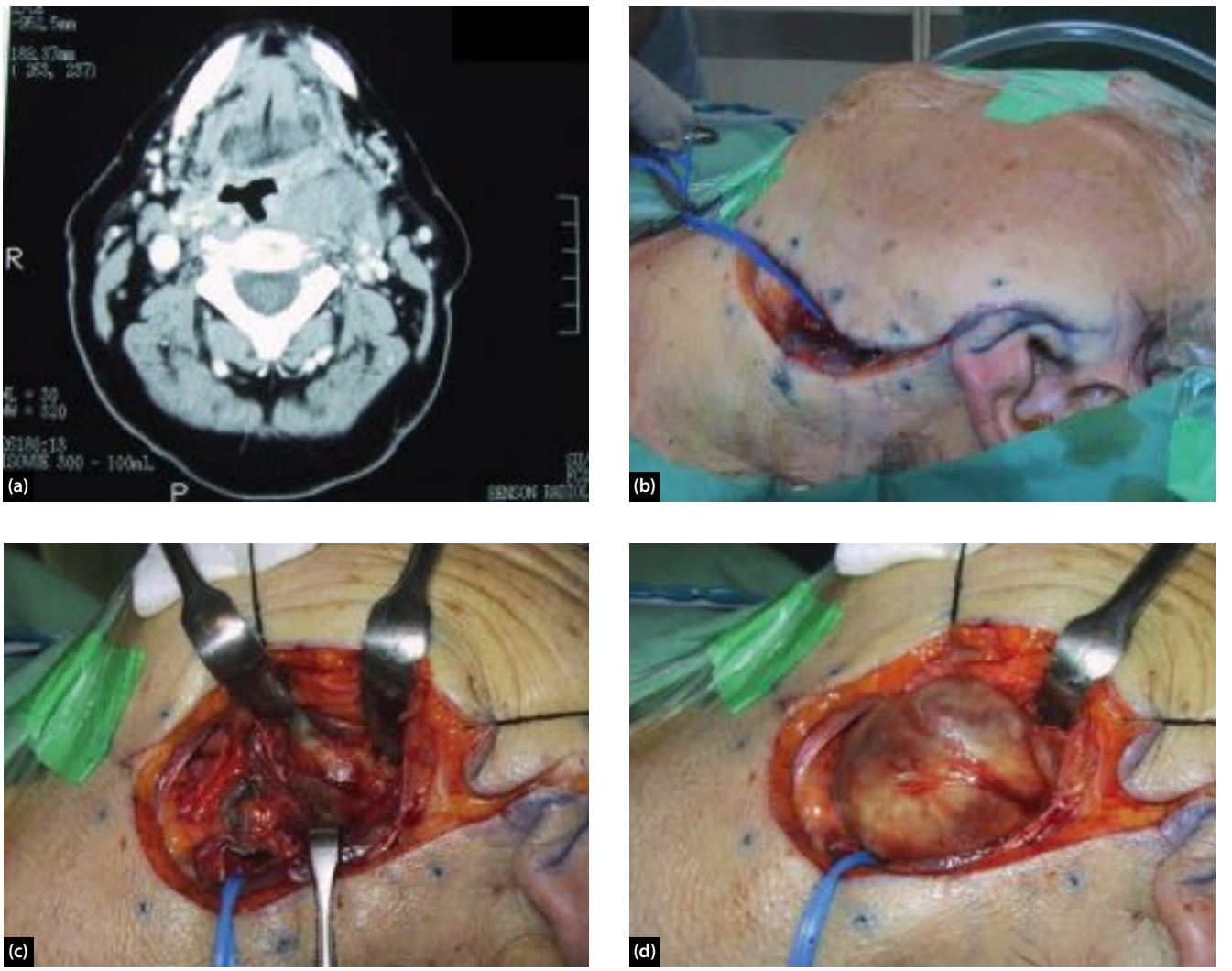


Figure 11.8 **(a)** Large left parapharyngeal space pleomorphic adenoma. **(b)** Large left parapharyngeal space pleomorphic adenoma – transcervical approach incision. **(c)** Large left parapharyngeal space pleomorphic adenoma – transcervical approach: following division of stylomandibular ligament and anterior distraction of mandible, dissection between digastric muscle and mandible provides access to the parapharyngeal space. **(d)** Large left parapharyngeal space pleomorphic adenoma – transcervical approach – delivery of tumour.

mandible and the medial pterygoid muscle insertion into the medial aspect of the mandible. The external carotid artery may need to be ligated to access and remove large tumours. Most of the dissection of the tumour is performed by blunt finger dissection staying close to the capsule of the tumour.

Transcervical – transparotid approach

This is the next most common approach, used in about 27% of cases (**Figure 11.9**).[11] This is well suited for lesions arising from the deep lobe of the parotid gland, for vascular tumours (as it allows access to vessels in the neck) and for the resection of malignant lesions. The operation is performed through a doubly modified Blair's incision as in a routine parotidectomy with a slight anterior extension of the cervical incision. The same procedure as described above for a transcervical excision is performed with an appropriate parotidectomy, identifying and defending the facial nerve.

Mandibulotomy

Transcervical and transcervical–transparotid approaches can be combined with a mandibular osteotomy. This was performed in about 9% of cases in the cumulative literature.[11] This allows access for excision of infiltrating malignancy and multifocal recurrent benign tumours and better visual access to the superior aspect of the parapharyngeal space and the skull base. Mandibulotomy can be performed in the standard paramedian position, or laterally with defence of the inferior alveolar nerve using an

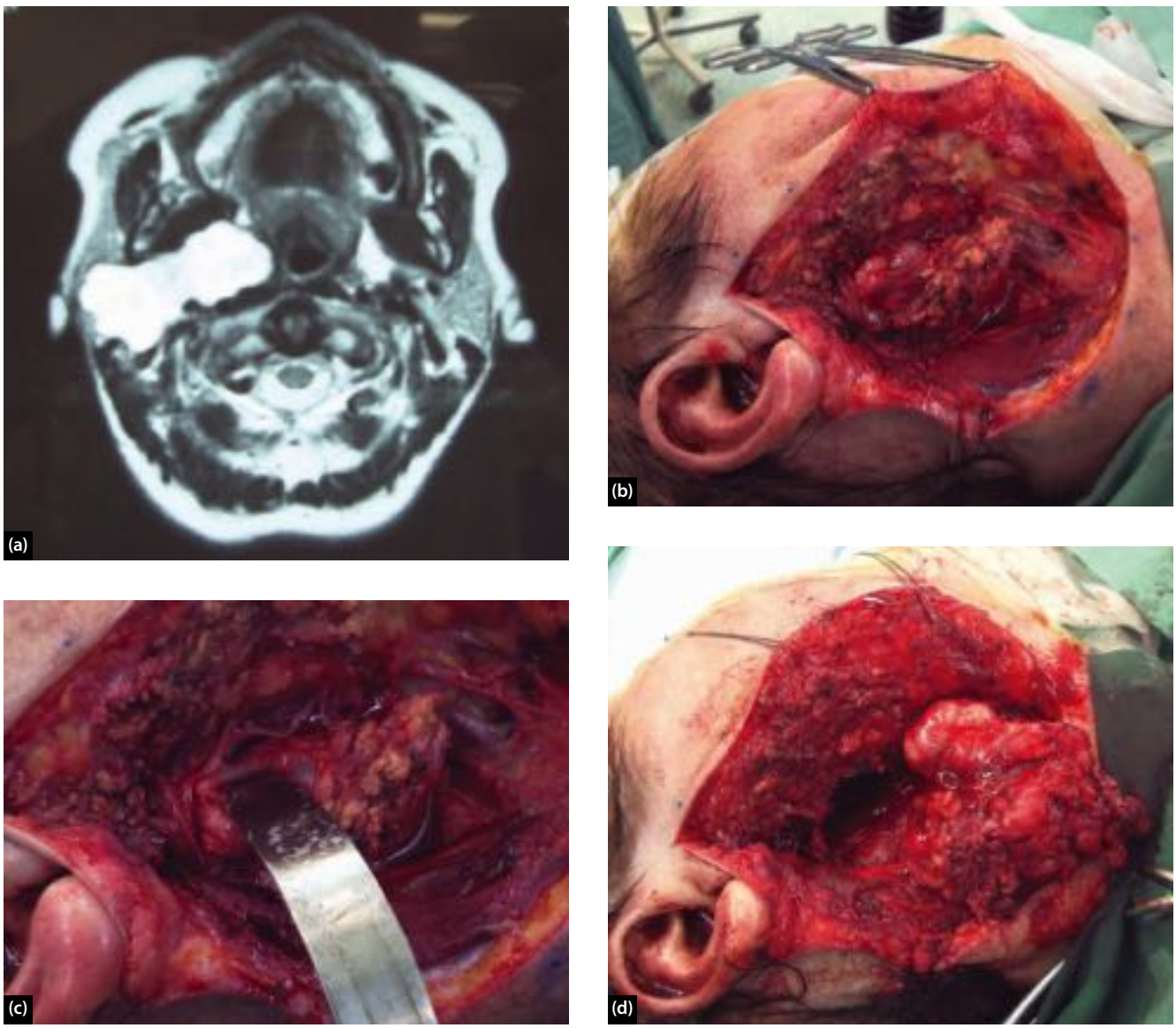


Figure 11.9 **(a)** Large right 'Dumbbell tumour' pleomorphic adenoma in parapharyngeal space. **(b)** Large right 'Dumbbell tumour' removal by transcervical and transparotid approach, superficial parotidectomy performed. **(c)** Large right 'Dumbbell tumour' removal by transcervical and transparotid approach, facial nerve being dissected from tumour. **(d)** Large right 'Dumbbell tumour' removal by transcervical and transparotid approach.

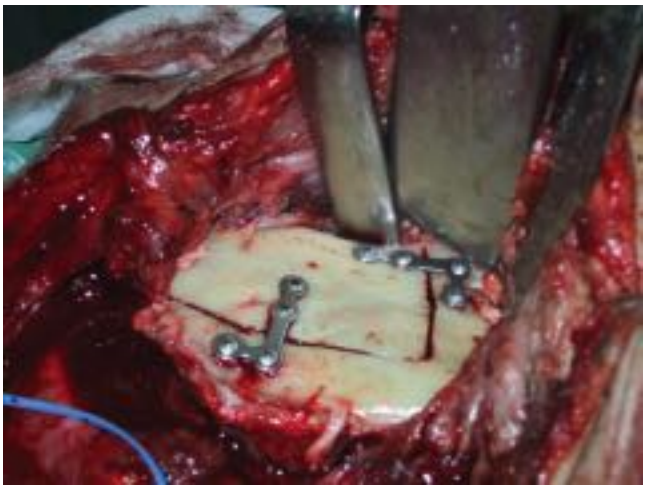


Figure 11.10 'Inverted L' osteotomy left mandible.



Figure 11.11 Transparotid, transcervical and transpalatal approach with paramedian mandibulotomy.

'inverted L' osteotomy[19] or by using a double osteotomy, above the lingula and in front of the mental foramen, again to protect the inferior alveolar nerve. Patients undergoing a mandibulotomy may require a tracheostomy, or may need to be intubated overnight to protect the airway. These patients may have a longer hospital stay, delay in return to normal nutrition and may be subject to complications such as temporomandibular joint dysfunction and malunion (**Figures 11.10** and **11.11**).

Transoral robotic surgery (TORS) of the parapharyngeal space: the paradigm shift (Figure 11.12a–c)

Embarking on TORS of the parapharyngeal space requires addressing the concerns and criticisms of this approach. The first issue is the risk to vital neurovascular structures. The traditional transcervical approaches are mooted as safer. However, in practice these approaches provide clear visualization of the lower cervical component of parapharyngeal space tumours and their relationship to the neurovascular bundle in the neck. The superior component is often difficult if not impossible to visualize. A true inspection of the relationship of tumour to neurovascular bundle would require wide access techniques such as mandibular osteotomy and/or infratemporal fossa approaches. As most tumours are benign salivary gland lesions, the superior aspect of the dissection is often performed with blunt finger dissection and inferior traction of the tumour to displace it off the neurovascular bundle.

The second issue is the risk of tumour spillage. Undertaking a TORS approach requires meticulous study of the imaging and at examination under anaesthesia, evaluating the mobility of the tumour and its lateral, superior and inferior relationships. The surgeon needs to understand the nature of the lesion, whether it is cystic, solid or mixed, whether it is benign or malignant, the thickness of its capsule and its relationship to the adjacent neurovascular structures.

The traditional support for external approach to the parapharyngeal space is based on a number of case series reports.[20–22] However, these are all retrospective, with a limited period of patient follow-up and with mixed pathological type including vascular tumours. These papers still report recurrence of benign tumours and tumour spillage. In practice, it is not uncommon during a standard transcervical approach for lesions to have their capsule disrupted. Sometimes when tumours are displaced inferiorly by pulling down on the tumour, a fragment of tumour may split off from the main mass of tumour. Careful inspection of the parapharyngeal space cavity with a telescope and irrigation of small fragments is required.

In contrast, there are a few papers reporting the results of a transoral approach.[23–25] There have been case reports of neural sheath tumours, neurofibromas, branchial cleft cyst tumours and benign mixed tumours being removed. Ducic et al. reported transoral resection of a series of benign tumours that displaced the carotid artery anteriorly.[24] Since the introduction of CT and MRI scans and a better understanding of the cross-sectional anatomy of the parapharyngeal space, there has been renewed interest in transoral resection of parapharyngeal space tumours.

The advantages of the da Vinci robotic surgical system have also renewed interest in transoral resection of parapharyngeal space tumours. The first reports of transoral robotic resection of parapharyngeal space by O'Malley et al.[28] described resection of a benign parapharyngeal space cyst without complications. The University of Pennsylvania's series reported ten patients, one of whom was converted to an open transcervical approach due to difficulty in finger dissection and to avoid tumour spillage.[29] Dehiscence of the mucosal incision was observed in two patients, none of the patients had residual or recurrent neoplasms at a follow-up on average 19.9 months. Their case series has reached 25 cases at the time of writing, with no recurrences and no patients requiring mandibulotomy or tracheostomy [personal communication]. Several authors have reported their experience with TORS for



Figure 11.12 **(a)** Intraoral view of right parapharyngeal space pleomorphic adenoma. Top of picture is tongue base, tongue displaced to the left. Incision over pterygomandibular raphe exposes tumour capsule. **(b)** TORS removal of parapharyngeal pleomorphic adenoma. **(c)** Tumour bed being inspected; note how the potential space contracts after tumour removal.

parapharyngeal space tumour resection,[36–39] including a systematic review by Chan et al.[40]

Whereas the traditional transcervical approach allows the surgeon access to the inferior aspect of the tumour and a blind finger dissection at the superior aspect of the tumour, a transoral approach allows access to all aspects of the tumour. O'Malley et al. described combining the use of the robot to dissect the inferior and medial aspect of the tumour, with a blunt finger dissection to complete the superior and lateral dissection.[29] Patients at our institution are consented for a transoral robotic approach as well as for possible conversion to a transcervical approach with or without mandibulotomy if the transoral approach is not amenable to safe resection of tumour.

Cross-sectional imaging should distinguish vascular tumours and if necessary appropriate angiographic studies performed. The histological nature of tumours should be identified pre-operatively by fine-needle aspiration either by image control or by direct transcervical or transoral biopsy.

The transoral robotic technique has technical advantages, these being the three-dimensional high-resolution image with magnification, as well as the tremor filtration and motion scaling that allows delicate dissection. For those tumours with a thin capsule or with a significant cystic component, however, consideration must be given to other methods to control the spillage of tumours. This may include blunt finger dissection particularly of the superior and lateral aspects of the tumour, or decompression of the tumour medially by a controlled perforation of the capsule and using either a micro-debrider or coblator wand to evacuate the contents of the tumour within its cystic encasement before lateral dissection is proceeded with. It is important that the lateral aspect of the tumour is dissected bluntly and carefully to ensure that tumour rupture is kept to a minimum.

The transoral robotic approach does address some of the concerns previously leveraged against transoral approaches for parapharyngeal space lesions. The robot provides better visual access to the oral cavity, oropharynx and parapharyngeal space with excellent three-dimensional view with either 0-degree scope or a 30-degree scope which can be used to inspect the superior aspects of the parapharyngeal space up to the skull base, as well as be rotated to inspect the inferior extent of tumours of the parapharyngeal space. It has overcome the line-of-site limitations of the microscope and allows examination of the lateral aspects of the parapharyngeal space including

the stylomandibular tunnel. Scaled movement and tremor filtration also allows for dedicated dissection around the tumour capsule ensuring resection with a margin.

Pre-operative assessment and indication for transoral robotic surgery

The use of TORS for parapharyngeal space resection does require accurate pre-operative assessment. The focus of assessment is the relationship of the tumour to the carotid, tumour extent, tumour pathology and the nature of the tumour in terms of thickness of capsule and if the tumour is cystic or has cystic components. Fine-needle aspiration biopsy done either by image guidance or by transoral biopsy is required as benign and low-grade malignancies are considered suitable for TORS.

The ideal indications for TORS parapharyngeal space resection are benign salivary gland tumours occurring in the pre-styloid compartment, displacing the carotid artery posteriorly and laterally. These are the majority of parapharyngeal space tumours. Schwannomas and other benign neural tumours that are not deforming the carotid artery and not displacing the carotid artery medially are suitable for resection. Cystic lesions such as branchial cleft cysts are suitable for resection.

Relative indications include dumbbell tumours or tumours clearly arising in the parotid gland involving the deep lobe of the parotid gland. Such tumours with limited involvement of the deep lobe can be approached by a combined transcervical and transoral approach as described by Lee et al.[35] An absolute contraindication is tumour that is adherent or involving the carotid artery. Other contraindications include dumbbell tumours arising clearly from the parotid gland with significant involvement of the parotid gland (**Figure 11.13 a,b**), vascular tumours such as paragangliomas, tumours with bony involvement of the skull base, and malignant tumours.

POST-OPERATIVE CARE

All patients are managed in a High Dependency Unit (HDU) overnight for airway observation and for TORS patients, monitoring of potential oral bleeding that may compromise the airway. Patients are usually extubated after surgery with no personal experience or reports of post-operative airway compromise and no patient requiring prolonged intubation or tracheostomy. Patients having an external approach can usually commence an oral diet following surgery. Patients undergoing TORS are kept nil by mouth overnight and allowed clear fluids on the first post-operative day, free fluids on the second post-operative day and a soft diet progressing to a normal diet from the third post-operative day. Patients undergoing an external approach will have a drain *in situ* and when drainage subsides it is removed and the patient is discharged home. Subject to analgesic requirements patients are discharged on the second or third post-operative day.

COMPLICATIONS

The complications reported in surgery of the parapharyngeal space are related to vascular injury, lower cranial nerve injury, tumour spillage and recurrence and 'first bite syndrome'. Correct case selection and meticulous attention to pre-operative imaging with respect to tumour relationship to vessels should prevent risk of vascular injury

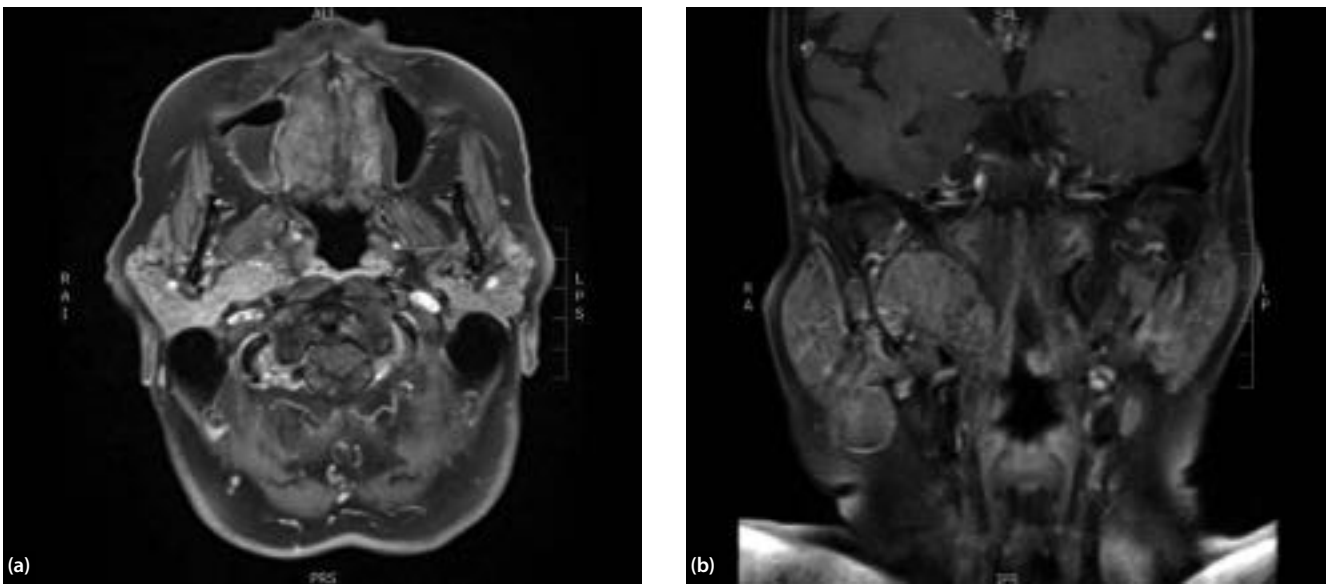


Figure 11.13 **(a)** Axial MRI showing 'Dumbbell' tumour extensively involving the parotid gland with extension through the stylo-hyoid tunnel into the parapharyngeal space. Such tumours are not suitable for TORS resection. **(b)** Coronal MRI showing 'Dumbbell' tumour extensively involving the parotid gland with extension through the stylo-hyoid tunnel into the parapharyngeal space.

including patients selected to undergo TORS for parapharyngeal space tumours. Neurogenic and malignant lesions are associated with greater risk to the facial, glossopharyngeal, vagal, accessory and hypoglossal nerves, with the vagus being the most common to be injured in about 13% of cases.[11] TORS avoids an external incision and avoids parotidectomy, with a reduced risk to the facial nerve and its branches.

It is unclear if tumour spillage will result in definite tumour recurrence. In the Mayo series reported by Hughes et al, tumour rupture was noted in 10 of the 68 cases performed by external approaches. This represents a spillage rate of 15% of pleomorphic adenomas; however, recurrence was only detected in one of those ten ruptured cases.[20] In series reporting experience with transoral resection techniques, Goodwin et al.[23] and Ducic et al.[24] report no tumour spillage seen during transoral resection. Tumuor spillage is not a common occurrence in carefully selected cases with thick capsules and no significant cystic components. In TORS parapharyngeal space tumour resection spillage appears not to be common or worse than with transcervical blunt dissection. The important things are to avoid sharp dissection against the tumour capsule and to use blunt dissection particularly at the lateral and superior and posterior aspects.

There is much debate but no consensus on the actions that need to be taken should the capsule be breached during dissection. The author's practice is to oversew the site of breach after suction drainage of any cystic fluid components within the tumour sac. The operative site should be generously irrigated with sterile water which is hypoosmolar and should promote tumour cell lysis. The role of post-operative radiotherapy is unclear particularly as evidence suggests low rates of recurrence of tumour, despite tumour spillage.[20] The author recommends radiotherapy for large uncontrolled spills with an inability to confirm complete clearance of spilt tumour and for patients undergoing surgery for recurrence with significant risk of facial nerve injury should subsequent surgery be required.

Bleeding can be avoided by meticulous haemostasis using haemoclips and the use of tissue haemostatic agents. Trismus may be present in the early post-operative period but is not a long-term complication, often resolving within 2 weeks of surgery. The other complication reported in external approach surgery is first bite syndrome. As discussed by Chiu et al,[41] it has been theorized to be related to the loss of sympathetic supply to the parotid gland with subsequent increased sensitivity of the myoepithelial cells to parasympathetic innervation. This syndrome has not been reported in transoral resection and is seen as a distinct advantage of transoral resection over external resection.

FUTURE RESEARCH

- More complicated and extended approaches may be required for malignant and complicated tumours involving the carotid artery or extending out of the parapharyngeal space.
- Radiotherapy may have a primary role for high-risk patients unable to have surgery or for select benign vascular lesions where surgery may contribute to significant morbidity from injury to multiple lower cranial nerves.
- Radiotherapy and chemotherapy may have an adjuvant role in some malignant tumours of the parapharyngeal space.
- TORS for parapharyngeal space tumours has advantages for the true pre-styloid benign salivary gland tumour, which is the most common tumour in this space. Its use in other tumours of this space is expanding with better understanding of tumour relationships to vital neurovasculature structures through improved imaging.
- The advent of image guidance and real-time imaging may further enhance the cause of transoral surgery.
- Improvements in robotic instruments, particularly the imminent arrival of single port instruments, will improve access and precision of dissection.
- The introduction of haptic feedback in robotic surgery may contribute to reducing the risk of capsular rupture and tumour spillage.

KEY POINTS

- Parapharyngeal space tumours are a rare subset of head and neck tumours.
- The majority are benign and treated by surgical excision.
- Evaluation of these lesions needs to be meticulous. The use of multiplanar imaging with CT scans with contrast and MRI scans with fat suppression and gadolinium for contrast, when appropriate, can provide accurate details of the nature of the lesion and where it has arisen from.
- Image-guided fine-needle aspiration cytology assists with histologic diagnosis.
- Together, this information helps with planning management of these tumours.
- Some benign vascular and neurogenic tumours are best observed by serial MRI scans, if there is significant risk of debilitating multiple lower cranial nerve palsies from surgery.
- Surgical approaches have to be carefully planned and may include the transcervical approach which can be carried out in combination with a transparotid approach with or without a mandibulotomy.

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CHAPTER 12

ORAL CAVITY TUMOURS INCLUDING LIP RECONSTRUCTION

Tim Martin and Omar A. Ahmed

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SEARCH STRATEGY

Data in this chapter may be updated by a MedLine search using the following keywords: oral cancer mouth cancer, squamous cell carcinoma, neck metastases, tongue cancer and lip cancer.

ORAL CAVITY TUMOURS

Tim Martin

INTRODUCTION

The oral cavity is the uppermost part of the digestive tract. The oral cavity starts at the mucocutaneous junction of the lips (the vermilion border) extending posteriorly to the junction of the hard and soft palate superiorly, anterior fauces laterally and the junction of the anterior two-thirds and posterior third of the tongue inferiorly. Neoplasms of the oral cavity may be classified topographically using the International Classification of Diseases for Oncology,[1] neoplasms of the oral cavity being coded C00–C06 depending on site of tumour (C01 – base of tongue, C05.1 – soft palate and C05.2 – uvula are excluded from this chapter since they form part of the oropharynx).[1]

The oral cavity is lined by stratified squamous epithelium of varying degrees of keratinization. Primary tumours of the oral cavity may be derived from the mucosa, salivary glands, neurovascular tissues, bone or dental tissues. Over 90% of tumours of the oral cavity are squamous cell carcinomas. Globally over 300,000 people are diagnosed with oral cancer each year, it being the eighth most common malignancy.[2] There is considerable geographic variation, the incidence of oral cancer being particularly high in South-East Asia and some Eastern European countries. The incidence of oral cancer in males in England approximates 6 per 100,000 per annum compared to 4 per 100,000 per annum for females. The age-standardized rate for oral cancer in Melanesia is as high as 25 per 100,000 per annum (**Figure 12.1**).

The registration rate for oral cancer has risen by over 20% in the last 30 years in England and Wales, particularly in those under 65 years of age.[3, 4] The increasing incidence of HPV associated oropharyngeal carcinoma may contribute to the reported increase in oral cancer in those publications which do not differentiate between oral cancer and oropharyngeal cancer, however the increase in oral cancer incidence is confirmed in studies specifically isolating the oral cavity site.[5] The author has seen a 10% increase in incidence and 20% increase in prevalence of oral cancer in his own practice between 2000 and 2010, cancers of the oral cavity not being associated with HPV. The increasing incidence of oral cancer has been noted

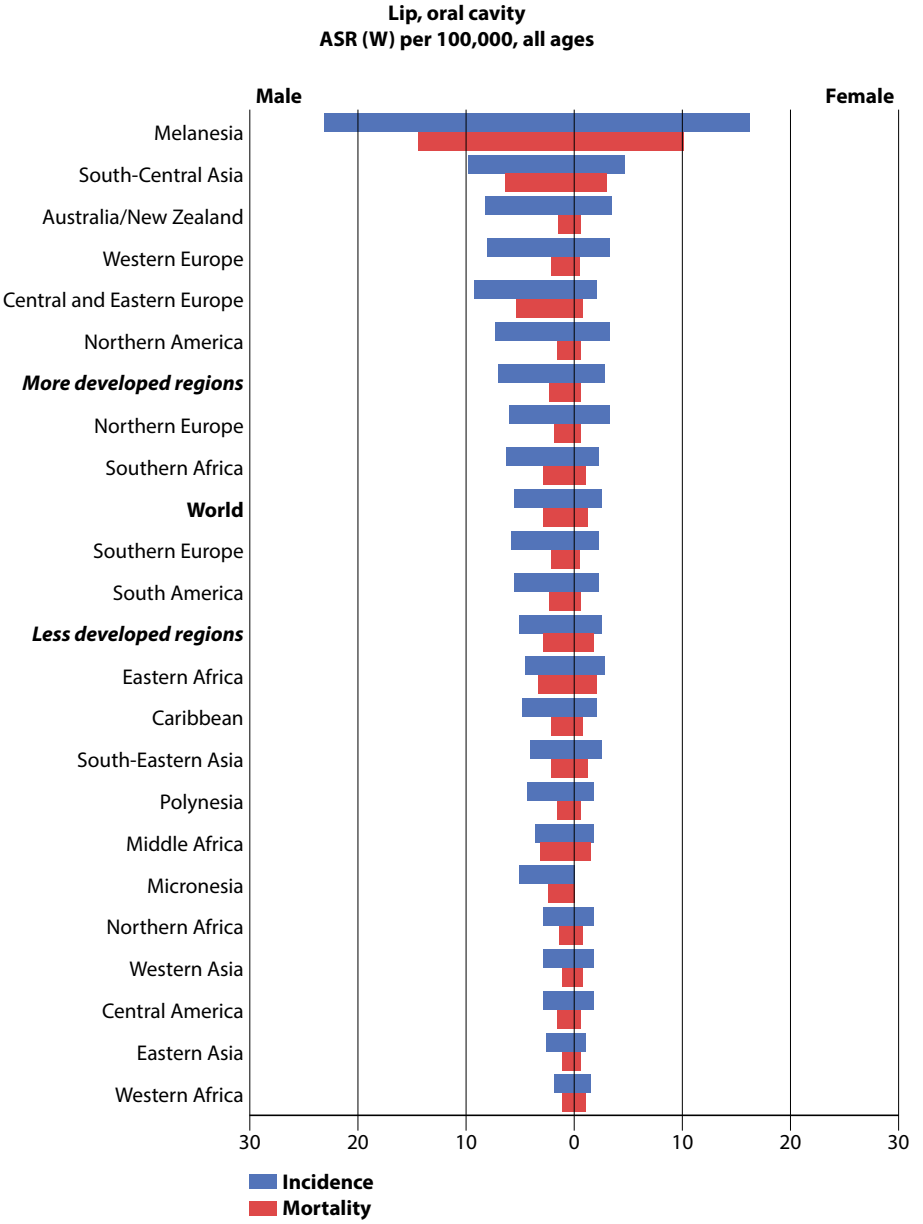


Figure 12.1 Estimated age-standarized rates (World) per 100 000 of lip and oral cavity cancer (Source: GLOBOCAN 2012, http://globocan.fr)

in other populations[6] and may be as a consequence of increasing alcohol consumption. A comprehensive review of international trends in head and neck cancer highlights concerns regarding alcohol consumption.[7] Oral cancer is more common in males, who usually present in the 6th and 7th decade although the incidence of oral cancer in young people seems to be increasing.[8,9] Tobacco and alcohol consumption are the major aetiological factors in the development of oral cancer,[10] oral cancer being considered largely preventable.

If oral cancer is detected when it is confined to the oral mucosa 5-year survival rates exceed 80%, decreasing to 40% for those with regional disease at presentation and 20% if distant metastasis has occurred. Early oral cancer is associated with an improved prognosis and less extensive treatment in attempt to cure the patient. A significant number of patients continue to present with advanced disease and improved public awareness of symptoms associated with oral cancer is a potential solution to this problem.[11,12] Research is required regarding selected or opportunistic screening for oral cancer, but at present there is insufficient evidence to support screening.[13]

The management of patients with oral cancer requires a concentration of medical expertise and resources. For the patient to receive optimal management a truly multidisciplinary approach is required.

WORKUP OF PATIENTS

History

The workup of a patient with suspected oral cancer starts with a detailed accurate history. The patient's symptoms should be documented and a thorough history of each symptom clarified. A short systematic review should be

included, asking specifically for symptoms suggestive of metastatic disease or synchronous aerodigestive tract tumour.

The patient's medical history including medications and allergies should be recorded. A frequently neglected aspect of history taking is the patient's social history. Patients with oral cancer are likely to face the prospect of major surgery, radiotherapy or chemoradiotherapy. The social circumstances of a patient will significantly influence management decisions. Support packages instituted early in the patient's management may help with timely delivery of care and increased patient compliance. If it is anticipated that free-flap reconstruction may form part of the treatment plan then direct questions regarding proposed donor sites should be asked such as hand dominance, intermittent claudication or chronic chest disease.

Examination

While taking a history from a patient the clinician should make note of such things as the patient's mobility when they enter the room, the patients affect, dysarthria or clues to smoking and drinking habits.

The formal examination should ideally be conducted in a dental chair with good lighting. The neck should be systematically palpated for cervical lymphadenopathy, although imaging of the neck in all patients with suspected oral malignancy should be conducted. Using two dental mirrors to help with retraction and visualization, the oral cavity and oropharynx should be examined in their entirety in a systematic manner. All patients should undergo flexible endoscopic assessment of the upper aerodigestive tract mucosa if there is a high index of suspicion for oral cancer. A dental examination should form part of the initial consultation so that dental treatment may be started early in anticipation of surgery or radiotherapy.

Occasionally pain or trismus may limit the examination and in these circumstances an examination under anaesthetic (EUA) should conducted. A restorative dental opinion should be sought before EUA so that necessary dental extractions can be conducted at the same time.

Investigations

Investigations conducted at the initial consultation will depend on the clinician's suspicion that the patient may have oral cancer. Simple investigations that may be conducted at the first appointment include:

- photographs
- incisional biopsy of mucosal lesions
- fine-needle aspiration cytology of suspicious lymphadenopathy
- orthopantomogram
- chest X-ray – if chest CT is not anticipated
- electrocardiogram
- routine bloods – full blood count, urea and electrolytes, liver function tests and clotting.

Biopsy should always be conducted prior to definitive treatment, preferably by a senior member of the team. The timing of a biopsy in relation to other investigations should be carefully considered. If the patient presents with a large tumour where therapeutic or elective management of the neck is anticipated based on primary tumour characteristics, then a biopsy may be safely conducted prior to imaging. If the patient presents with a suspicious small lesion then it is judicious to conduct imaging prior to biopsy to minimize local oedema at the biopsy site or local reactive lymphadenitis, thus upstaging the disease on imaging. Small alveolar tumours should be imaged prior to biopsy since increased marrow signal secondary to inflammation associated with a biopsy may commit the patient to a segmental resection. The biopsy site should be at the periphery of the lesion to include a sample of normal mucosa. A large, deep biopsy may give information regarding depth of invasion and hence the potential necessity to conduct a neck dissection. It has been demonstrated that if tumour thickness on biopsy is >2 mm then the final tumour thickness is usually greater than 3.5 mm,[14] suggesting an elective neck dissection (END) may need to be considered. Unfavourable tumour factors such as perineural spread, vascular permeation and a non-cohesive invasive front are indicators to the probability of positive margins and long-term prognosis. Unfavourable features may lead one to consider wider surgical margins where feasible to reduce local recurrence (accepting that these same features suggest a poorer long-term prognosis) while balancing the quality-of-life issues raised by conducting such a resection.

Once oral malignancy is confirmed histologically additional investigations may be conducted relating to:

STAGING OF THE DISEASE

- CT +/– CT chest
- MRI
- USS (of the neck or primary) +/– USS guided FNA of suspicious lymphadenopathy
- PET.

There has been much debate regarding the extent to which an individual should be screened for second aerodigestive tract tumours or metastatic disease. To subject a patient to major head and neck surgery and an extended hospital stay is clearly inappropriate in the presence of established distant disease, however, extensive surgery may be an excellent mode of palliation. Currently screening for distant metastases is indicated in patients with multiple cervical nodes, recurrence, second primary,[15] or advanced disease.[16] The modality of choice for screening is a CT chest, although ^{18}FDG-PET may have an increasing role.[15] The routine use of panendoscopy in the workup of the patient with oral cancer is not necessarily warranted,[17] although targeted panendoscopy in smokers may reveal synchronous neoplasms in up to 10% of patients.[18] Once the patient has had appropriate investigations the tumour may be staged using the TNM system.[19]

TNM staging

The staging of head and neck cancer will be dealt with in detail in Chapter 4, Staging of head and neck cancer. However, it is worth highlighting recent changes to the TNM staging recommendations published in the American Joint Committee on Cancer (AJCC) 8th Edition Cancer Staging Manual[20] and the Union for International Cancer Control (UICC)[21] which are of particular importance to the staging of oral cavity cancer (OCC). The changes and the rationale behind them are reviewed in detail in Lydiatt et al.[22]

T stage

1. A T0 category is no longer assigned to p16 – OPSCC and other non-HRHPV cancers e.g. larynx, oral cavity and hypopharynx as an exact primary site is, by definition, unable to be established and therefore cannot be assigned to a specific anatomical sub-site.
2. TNM 7th Edition incorporated tumour thickness into the TNM staging criteria as previous data had demonstrated that tumour thickness had prognostic value.[23] However, in TNM 8th Edition tumour thickness has been replaced by an assessment or measurement of tumour depth of invasion (DOI) as this has been shown to be a better prognosticator that tumour thickness.[24]
3. Three DOI groups have been defined: ≤ 5 mm, > 5 mm but ≤ 10 mm and > 10 mm. Each incremental increase in DOI results in an increase in clinical T stage (cT) and pathological T stage (pT) levels.
4. cT DOI relies on clinical examination and measured radiological evidence whilst pT is measured by a perpendicular dropped from a line drawn at the level of the basement membrane (See **Figure 12.1**).[22]
5. These modifications have led to the following revised T stages
   a. **T1:** ≤ 2 cm, ≤ 5 mm DOI
   b. **T2:** ≤ 2 cm, DOI > 5 mm and ≤ 10 mm or > 2 cm but ≤ 4 cm, and ≤ 10 mm DOI
   c. **T3:** > 4 cm or any tumour > 10 mm DOI
6. In addition, 'extrinsic muscle infiltration' is no longer a staging criterion for T4 stage as it has been replaced by DOI.

N stage

1. Extra-nodal extension (ENE) has been added as a prognostic variable in addition to the number and size of metastatic lymph nodes.
2. Radiological evidence alone is insufficient to determine ENE and must be associated with overt clinical evidence of invasion of adjacent anatomical structures (e.g. overlying skin or adjacent nerve).
3. Pathological determination of ENE is subdivided into minor ENE, when ENE < 2 mm beyond the lymph node capsule and major ENE when extension is > 2 mm beyond the capsule +/– soft tissue metastatic deposits are evident. This minor/major distinction is for data collection purpose at this stage and currently, either subdivision is considered ENE positive.

PLANNING OF RECONSTRUCTION

The most appropriate reconstruction will be determined by multiple factors, notably characteristics of the primary site and the anticipated defect, the medical and social history of the patient and potential donor site characteristics. The reconstructive surgeon should have the ability to raise or harvest many different types of local, regional or distant flaps when dealing with head and neck malignancy. For complex bony reconstructions, computer aided planning is invaluable in achieving an optimal cosmetic and functional outcome (**Figure 12.2**).

Focused examination or investigations regarding proposed reconstruction include:

- Allen's test of the vascular supply to the hand if a radial free forearm flap is anticipated
- MRA / angiography of the leg vessels if composite fibula reconstruction is anticipated
- thorough examination of the chest and abdomen if a deep circumflex iliac artery (DCIA) free flap is anticipated
- CAD / CAM models if complex composite reconstruction is anticipated
- dental impressions for all maxillary tumours.

Anaesthetic assessment

It is advisable to liaise with the anaesthetist early in the treatment planning of the patient, especially where a difficult airway is anticipated.

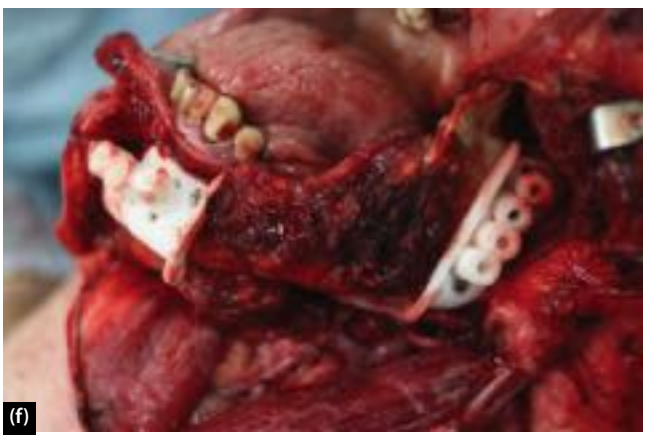
The patient should be seen by the dietician early in their management for dietary advice. Consideration should be given to a percutaneous endoscopic gastrostomy (PEG) to facilitate feeding,[25] however insertion of a PEG is not without morbidity and quality of life issues.[25, 27] A preoperative scoring system has been developed to facilitate decision-making regarding enteral feeding support.[28] Nasogastric feeding may be more appropriate if complex surgery is not anticipated and post-operative radiotherapy (PORT) is unlikely. It is beneficial if the patient meets the speech and language therapist and counsellor prior to starting definitive treatment.

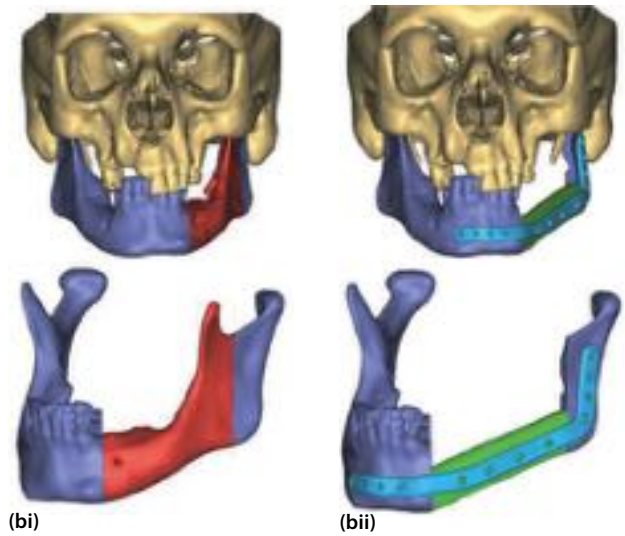
Once the patient has been thoroughly worked up a discussion should occur with the whole Head and Neck team to formulate an appropriate treatment plan. The proposed treatment should then be discussed with the patient and informed consent gained. Informed consent should be tailored to the individual and results achieved in the operating unit. The general success rate of microvascular free-flap surgery is greater than 95%, however 5–15% of patients may require return to theatre for complications such as flap compromise, haematoma or infection. It should be remembered that the peri-operative mortality rate for major head and neck surgery is 1–3%. Patient's age alone should not rule out major surgery and microvascular reconstruction,[29] it being the patient's co-morbidity that primarily influences the incidence of post-operative complications[30, 31] and prognosis.[32] The benefit of major microvascular surgery in patients with significant comorbidity (e.g, an Adult Comorbidity Evaluation Index 27 of Grade 3), should be carefully considered.



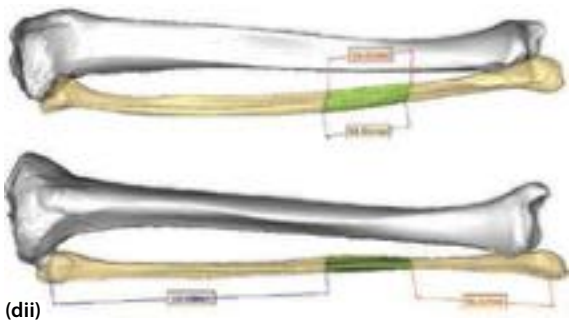












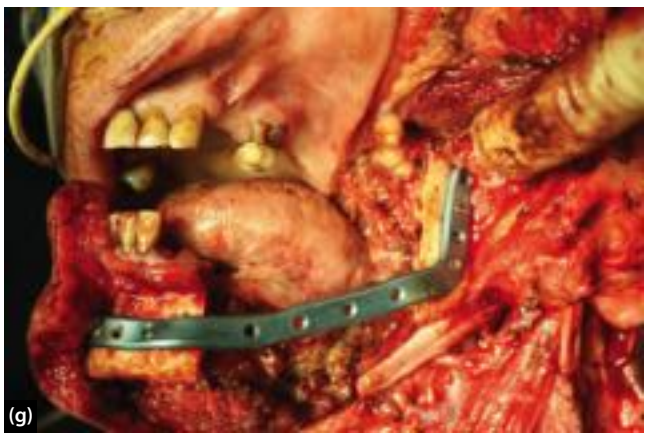


Figure 12.2 **(a)** The primary is a left retromolar trigone ulcer staged T4a, and histologically a squamous cell cancer in a 66-year old male. **(b)** The intended amount of mandible resection is shown in red with the planned donor bone from the fibula in green. Note custom-made pre-bent reconstruction plate. **(c)** Custom-made cutting guides, patient specific implants are 3D printed prior to the operation. **(d)** Computer-aided surgical planning allows 3D printing of cutting guides for the fibula **(e)** Tumour exposed prior to resection. **(f)** Mandible cutting guides in position prior to osteotomy. **(g)** Pre-bent plates anchored in place prior to bony flap inset. *(Continued)*

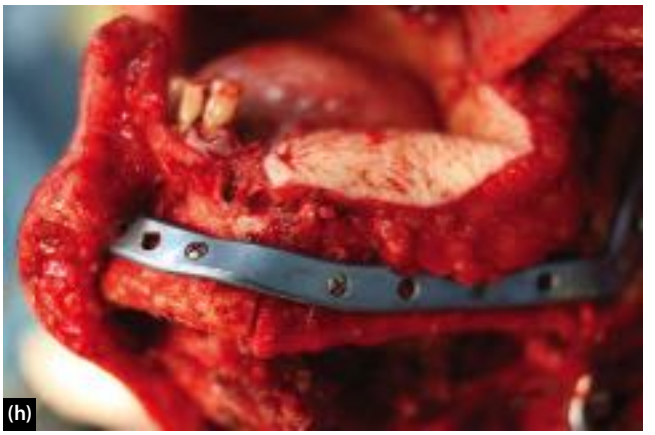


Figure 12.2 (Continued) (h) Donor fibula fixed into the defect using the pre-drilled holes. Note soft-tissue component of the free flap to line the oral cavity. Figures courtesy of Mr James Adams, Newcastle upon Tyne.

SURGICAL ACCESS

The ultimate aim of surgical resection is removal of the tumour with adequate margins. For the majority of oral tumours this may be achieved via a per oral route[33] with good retraction and lighting. Patients with trismus, microstomia, large or posteriorly based oral tumours may require additional access procedures to ensure adequate clearance of the tumour. The role of transoral robotic surgery continues to expand and undoubtedly its application to posterior oral tumours will develop in those institutions able to invest in this technology.

Mandibulotomy

Bone resection is no longer an acceptable method of improving access to oral tumours. A mandibulotomy gives good access to large or posteriorly located tumours. An orthopantomogram (OPG) radiograph is required prior to conducting this procedure to demonstrate the dental anatomy of the area (**Figure 12.3**). Typically, the procedure is accompanied with a lip split. Mandibulotomy without a lip split has been described to minimize facial scars,[34] however access is not as great as when a lip split is conducted. It has been demonstrated that patients have minimal concerns regarding the scar associated with a lip split mandibulotomy.[35]

The neck dissection incision is extended anteriorly to split the lip. Multiple incision designs have been proposed for the lip split.[36] An incision around the chin prominence tends to make the prominence more pronounced, a vertical incision over the chin point producing a more cosmetic result (**Figure 12.4**). Incorporation of a chevron between the chin prominence and vermilion aids closure and breaks up the scar. The intended incision should be marked and temporary tattoos created with needle and ink at the vermilion to ensure accurate reapproximation at the end of the procedure.

The osteotomy should be conducted anterior to the mental foramen to preserve labial sensation. The preferred site for the osteotomy is the paramedian area (between the lateral incisor and canine) since the distance between the tooth roots is greater,[37] dental complications consequently being less than median osteotomies.[38] An osteotomy in the paramedian area preserves the attachments of geniohyoid, genioglossus and digastric to the major segment, only mylohyoid requiring division to mobilize the minor segment. If the distance between the lateral incisor and canine roots is insufficient to accept a saw blade then the lateral incisor should be removed and the osteotomy conducted through the socket to minimize the possibility of osteoradionecrosis should a tooth be damaged. Once the site of osteotomy is established miniplates are adapted and applied to the mandible bridging the proposed osteotomy site. The plates are then removed and the osteotomy conducted using a fine reciprocating saw blade.[39] Application of plates prior to osteotomy ensures maintenance of occlusion at the end of the procedure, although a discontinuity the width of the cutting saw is created. A modified mandibulotomy where only the buccal cortex is cut with a saw, the lingual plate being fractured with a small osteotome, has been described so ensuring bone-to-bone contact at the end of the procedure and may lead to better osseous healing.[40] The mandible and cheek flap may now be retracted laterally and superiorly giving excellent access to the posterior oral cavity and oropharynx.

The non-anatomical position adopted by the temperomandibular joint (TMJ) during this procedure does not give rise to long-term TMJ dysfunction.[41]

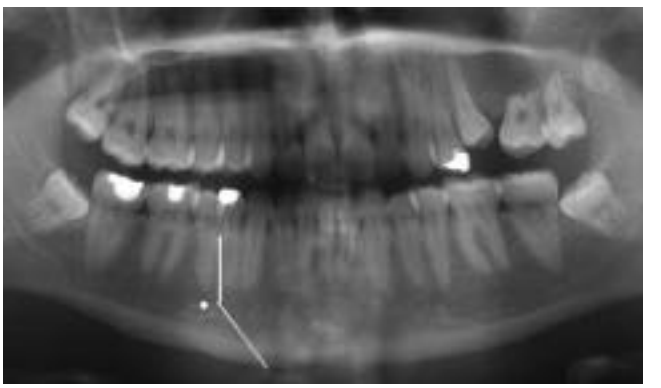


Figure 12.3 OPG showing surgical planning for a planned osteotomy. Figure courtesy of Mr Matt Kennedy, Newcastle upon Tyne.

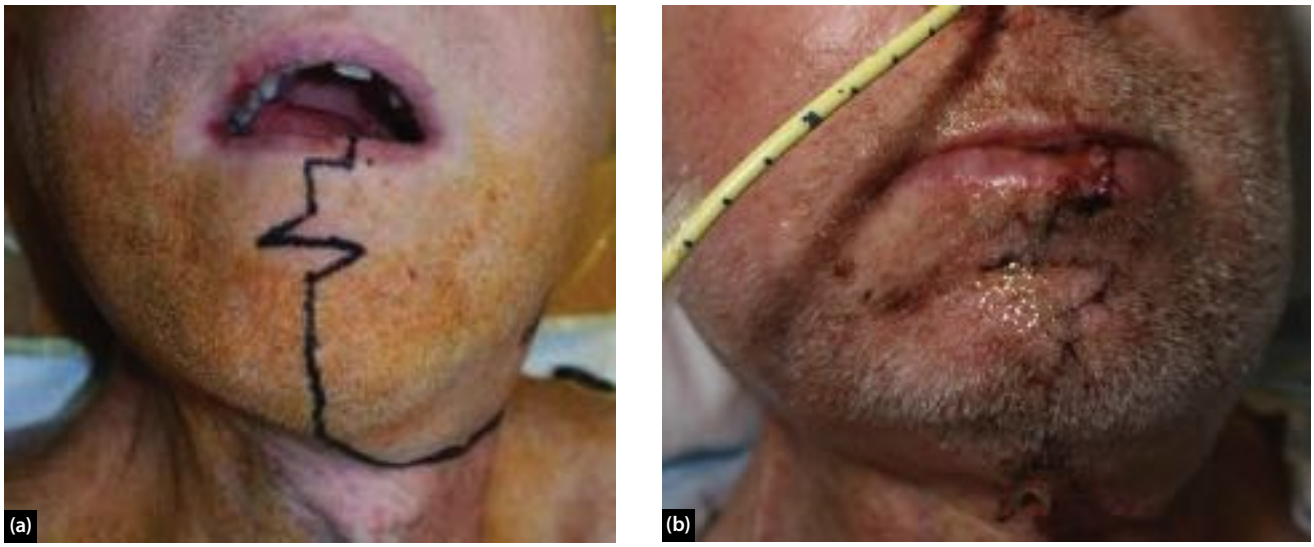


Figure 12.4 Suggested lip split incision that avoids the incision extending around the chin prominence. Figure courtesy of Mr Matt Kennedy, Newcastle upon Tyne.

Visor approach and lingual release

This approach is generally reserved for when bilateral neck dissections are performed. The visor approach may also be appropriate for recurrence or second primary tumours in patients who have received previous radiotherapy to the mandible. The visor approach avoids facial incisions, the incision being located in a cervical skin crease. A mastoid to mastoid visor flap is elevated in the subplatysmal plane to the lower border of the mandible. An intraoral mucosal incision is made in the lingual gingival sulcus from the posterior molar on one side to the posterior molar of the other. In edentulous patients the incision is made on the alveolar crest. The mylohyoid, geniohyoid, genioglossus and digastric muscles are detached from the lingual aspect of the mandible allowing the floor of mouth and tongue to be dropped into the neck. Care should be taken to ensure the lingual and hypoglossal nerves are not injured during the dissection. The reattachment of geniohyoid and genioglossus muscles at the end of the procedure is important to reconstitute the floor of the mouth. This may be facilitated by drilling holes in the lower border of the mandible through which securing sutures are passed. Alternatively, genial muscle reattachment may be facilitated by conducting a small box osteotomy of the lower border of mandible incorporating the muscle attachments and relocating at the end of the procedure with wires or miniplates.

Excellent access may be achieved without the necessity of a lip split, however the expected gain in cosmesis has not been proven and this technique is associated with significantly greater functional deficit post-operatively[41] compared to lip split and mandibulotomy.

Upper cheek flap

The upper cheek flap may be required to augment access to large or posterior maxillary tumours. The cornea of the eye should be protected in all patients. Anterior tumours requiring improved access may be approached via a modified Weber–Ferguson incision without extension. The modified Weber–Ferguson approach is essentially an upper lip split extending into a lateral rhinotomy incision. It is imperative that the incision be marked out accurately and temporary localizing tattoos created prior to starting the procedure. The lip split is usually conducted along the ipsilateral philtral column to the base of the columella. The incision extends laterally along the floor of the nose then follows the alar crease to its superomedial end before continuing to a point 6–8 mm medial to the medial canthus. Locating the vertical limb of the incision on the nose rather than cheek respects the concept of aesthetic facial units and gives a superior aesthetic outcome. The incisions are deepened to bone and the cheek flap raised in the subperiosteal plane, preserving the infraorbital nerve unless it is to be sacrificed on oncological grounds. Elevation of the flap requires a mucosal incision in the gingivo-labial and gingivo-buccal sulcus to a point where the flap incision merges with the resection margins of the tumour. Greater access is afforded by extending the modified Weber–Ferguson incision either with a subciliary incision (Diffenbach extension) or medial canthal incision (Lynch extension). An infraorbital orbitotomy may facilitate access[42] but is not usually required for tumours confined to the oral cavity.

SURGICAL MARGINS

The ultimate aim of surgical resection is adequate clearance of the tumour. Inadequate clearance of tumour results in increased local recurrence and decreased long term prognosis.[43, 44]

Indications for PORT include positive or close margins. However, local recurrence rates following PORT do not approach those in whom adequate clearance is achieved at the primary operation.[44, 45]

Increasing resection margins in the region of the head and neck potentially results in increased functional and cosmetic deficit. Resection margins of up to 2 cm have been advocated, however, such margins may result in significant morbidity following the resection of even the smallest of tumours. One centimetre 3D-resection margins have been demonstrated as acceptable when dealing with oral and oropharyngeal tumours.[46] By adopting 1 cm surgical margins account is taken for the shrinkage of the specimen that occurs following resection and fixation,[47] so ensuring > 5mm pathological margins. A confounding factor that may need consideration when discussing surgical margins is the resecting modality used, differing modalities resulting in variable shrinkage in animal models.[48] It should be remembered that the use of 5 mm as a cut-off point for 'clear' margins is arbitrary and purely represents a margin that is generally considered acceptable,[49] some believing 3 mm is an acceptable histological margin when considering the need for adjunctive treatment.[50] It is vitally important to continually reassess margins visually and by palpation during tumour resection. Adjuncts to assess margin status include intra-operative tissue staining[51] and ultrasound[52, 53] for deep margins and mucosal staining for mucosal margins.[54] If the resection of a tumour is with curative intent then reconstructive considerations should not influence the tumour resection.

Comparison of published data regarding the incidence of positive margins and their influence on survival or local recurrence is complicated by the variable definition of a positive margin.[55] The definition of a positive margin ranges from invasive tumour at the margin,[56] tumour within 1 mm[46] and tumour within 5 mm.[45] The UK Royal College of Pathologists have issued guidelines suggesting clear margins if the histological clearance is > 5 mm, close margins if 1–5 mm and positive margins if < 1 mm.[57]

The incidence of positive margins for tumours of the oral cavity has been demonstrated as being higher than other head and neck sites,[56, 58] potentially due to its complex anatomy and 3D shape. Large tumours, perineural spread, vascular permeation, a non-cohesive invasive front or cervical metastasis are all associated with a greater risk of failing to achieve clear margins.[44, 59] These features suggest that close or involved margins potentially reflect a more aggressive tumour.[44, 46] The incidence of close or involved margins following tumour resection may be greater than 60% depending on tumour site and size, although 15–20% is more representative.

Invariably it is the deep margin that is close or positive.[60] However close deep margins do not necessarily require adjunctive treatment.[61]

Frozen sections are not routinely used by many surgeons,[44, 46] reasons cited being potential cost,[62, 63] inability to reliably prevent positive final margins,[62, 64] failure to influence 5-year survival or primary failure rates[63] and difficulty in identifying the biopsy site should the result be positive.[65] Ninety-nine percent of American Head and Neck surgeons routinely use frozen section intra-operatively, however over reliance on frozen section may result in under treatment of tumours.[55]

When conducting a bony resection a 1 cm margin should be achieved. It has been demonstrated that it is unusual for extension of tumour in bone to exceed the overlying soft tissue extension, consequently the bony resection should be dictated by the extent of soft tissue disease.

BUCCAL CARCINOMA

Surgical anatomy

The buccal mucosa is the mucosal lining of the inner surface of the cheek. The area extends from the oral commissure anteriorly to the retromolar trigone posteriorly. The junction between the buccal mucosa and retromolar trigone is an arbitrary line drawn from the maxillary tuberosity to the distobuccal aspect of the mandibular third molar (or its anticipated position if not present). The inferior and superior boundaries of the area are delineated by the mandibular and maxillary gingiva-buccal sulci respectively. The WHO classifies this anatomical site as ICD-10 C06.0 and C06.1.[1]

The buccal mucosa is not exposed to masticatory loads and so is covered by a lining mucosa with non-keratinizing stratified squamous epithelium. The mucosa is firmly attached to the underlying buccinator muscle. Minor salivary glands are located within the cheek. The parotid duct pierces the buccinator muscle to enter the oral cavity adjacent to the first maxillary molar tooth.

Sensory innervation to the area is via the buccal branch of the mandibular division of the trigeminal nerve. Lymphatic drainage of the site is via the ipsilateral facial and submandibular nodes to the deep cervical chain. The thickness of the cheek, from mucosal lining to external skin, is 1–3 cm.

Epidemiology

The buccal mucosa is the commonest site for oral cancer in South East Asia, up to 40% of oral cancers arising at this site. This contrasts with North America and Western Europe where buccal carcinoma only accounts for 2–10% of oral carcinomas.[46, 66] The consumption of betel quid is socially and culturally embedded in the countries of South-East Asia and is responsible for the difference in site predilection. The ingredients of Betel quid (Paan/Paan Masala) varies throughout South-East Asia. The main ingredients include the Piper betel leaf, slaked lime, spices, tobacco and areca nut. For many years, the tobacco content alone was credited as being the carcinogenic agent in betel quid, however, it is now recognized that the areca nut is also carcinogenic, as well as being the main aetiological agent in oral submucous fibrosis. Individuals who consume betel quid frequently have a preference regarding which side they chew betel, this corresponding to the side of tumour development. There is a strong association with smoking and alcohol consumption in populations where betel chewing is not prevalent.[66–68]

The male to female ratio in Western countries approximates 1:1, however, in South-East Asia the ratio reflects

the consumption of betel quid. In India, the male to female ratio is approximately 4:1 but in the Taiwanese population, where betel quid users are primarily male, the ratio is as high as 27:1.[69]

Buccal carcinoma typically occurs over the age of 40 years, although it may occur in younger patients,[70] particularly when associated with the habit of betel chewing.[71] Oral submucous fibrosis and lichen planus may involve the buccal mucosa, both being considered premalignant conditions.

Presentation

Buccal carcinoma may be described as verrucous, exophytic or ulceroinfiltrative in character. Patients may present with pain, an intraoral mass, ulceration or trismus. Patients who chew betel often have areas of erythroleukoplakia of the buccal mucosa or submucous fibrosis and consequent trismus, making the detection of invasive squamous cell carcinoma difficult. Advanced buccal carcinomas may extend into adjacent sites to include external skin, mandible or maxilla.

It is not unusual for patients to present with advanced disease, 40% or more presenting with Stage III/IV disease,[66, 67, 72] although earlier presentation has been demonstrated in Western populations.[73] Palpable lymphadenopathy on presentation may be as high as 57% for T3/4 lesions. Occult nodal metastasis may be present in 26% of those who are clinically N0 at presentation.[66, 67, 72, 74] It has been suggested that buccal carcinoma associated with Paan chewing is less likely to metastasize to regional lymph nodes, possibly because of local fibrosis associated with submucous fibrosis.[75] Tumours that are greater than T2, are poorly differentiated, have a poor lymphocytic response[74] or are thicker than 5 mm[74, 76] are more likely to demonstrate cervical metastases. Buccal cancers are usually well differentiated.[66, 77]

Workup

Biopsies of buccal carcinomas should be of sufficient depth to help the pathologist give an indication of depth of invasion, since this will help decide on management of the neck. Buccal carcinoma may rapidly extend to adjacent sites, thus accurate imaging is required. Most patients will require MRI/CT imaging, augmented with ultrasound scan if necessary to help in assessment of depth of primary and cervical lymphadenopathy.

Treatment

PRIMARY SITE

Traditional treatment of buccal carcinoma is surgery with PORT for selected patients.[67, 69] T1/2 disease can typically be resected perorally, however, T3/4 disease may require facial access incisions and bony resection of the maxilla and / or mandible.

The primary tumour should be resected with a 1 cm margin,[46] and up to 2 cm if skin is involved.[78] Facial access incisions (upper or lower lip splits) may be required to facilitate access, particularly in patients with concurrent oral submucous fibrosis. The buccinator muscle should be included as the deep margin at the very least.[78] The parotid duct may need to be repositioned or ligated.[77] Ligation of the parotid duct may result in initial parotid swelling which usually subsides as the gland atrophies. External skin should be taken with the specimen if there is any evidence clinically or on imaging that it is involved. Partial maxillectomy or mandibular resection (rim or segmental) may be required.

Small T1 tumours may be resected and reconstructed by primary closure. Healing by secondary intention may be considered, however, post-operative trismus may be anticipated unless vigorous mouth opening exercises are performed. Split-thickness skin grafts may be used with the aid of silicone sheets to stabilize the graft.[79] The use of a skin graft to reconstruct deeper resections may leave a very thin cheek with potentially poor aesthetics. Local flaps such as the buccal fat pad or temporoparietal fascial flap may be used for reconstruction if tumour extension does not compromise their use. Microvascular free-flap reconstruction with a radial-free forearm flap or anterolateral thigh flap[80] restores the thickness of the cheek and if external skin is involved the flaps can be bi-paddled to provide reconstruction of mucosal and skin surfaces. T4 tumours requiring segmental resection of the mandible may require composite free-flap reconstruction. Reconstruction with a radial-free forearm flap has been shown to give better post-operative mouth opening than reconstruction with a split skin graft or buccal fat pad.[81]

Radiotherapy as a single treatment modality for T1/2 tumours has been advocated,[82, 83] however a change of practice from radiotherapy to surgery at Memorial Sloan Kettering was associated with improved prognosis.[84] Brachytherapy or external beam irradiation may be considered.

NECK

Regional spread of disease in buccal carcinoma is usually to the ipsilateral level I and II lymph nodes.[85, 86] Unlike carcinoma of the oral tongue, skip metastases to level IV of the neck are unusual.[75] It has been suggested patients with palpable lymphadenopathy or pathological nodes on imaging should have a comprehensive neck dissection, although if pathological nodes are only located in level Ia level I–III SND may be considered.[87] Nodes in the region of the facial artery as it crosses the mandible should be removed with the neck dissection specimen.

Patients with T2 or greater primary tumours or tumours with a thickness > 5mm should have an END.[67, 88] Some institutions will conduct an END if the tumour is 3–4 mm thick or if histological examination the tumour demonstrates lymphatic infiltration.[67]

PORT

The indications for PORT to the locoregional area are similar to other sites, notably 2 or more nodes in the neck,

extracapsular spread, positive margins or margins less than 3 mm[89] and stage III/IV disease.[72] The beneficial role of PORT in selected patients with buccal carcinoma has been demonstrated by several authors.[90, 91] Some authors suggest that PORT should be considered even in stage I and II disease,[66, 72, 92] or tumours greater than 10 mm thick.[90]

Recurrence

Recurrence rates for buccal carcinoma are 26–80%,[66, 67, 69, 72, 74, 77] usually occurring within 2 years.[67, 69, 77] Involvement of the parotid duct and buccinator have not been found to be significant indicators of recurrence.[66] Factors that influence recurrence include tumour thickness,[74, 76, 93] histological margins less than 3 mm[89] and tumour differentiation.[77] It has been demonstrated that following treatment for buccal carcinoma, distant failure is more common than regional failure compared to tongue carcinoma,[94] although survival rates are similar for both.[94, 95]

Prognosis

Buccal carcinoma is considered by many to be particularly aggressive,[73, 96] but not universally so.[95] Five-year survival figures vary depending on population studied and treatment modality.[67, 72, 97]

Factors that potentially influence survival include regional metastasis,[67, 98] extracapsular spread,[67, 97] tumour thickness >5–6 mm,[74, 76] skin involvement,[69] histological margins less than 2 mm[89, 97, 99] stage[71] and recurrent disease.[74]

KEY POINTS

- Commonest site for oral cancer in South East Asia.
- Associated with Betel / Paan consumption.
- Good surgical reconstruction is required to prevent post-operative trismus.
- Up to 26% have occult nodal metastasis at presentation.
- Consider END (Levels I–III) if tumour >4 mm thick.

FLOOR OF MOUTH CARCINOMA

Surgical anatomy

The floor of mouth is the mucosal lining of the anterior and lateral floor of the mouth. The area is bound anteriorly and laterally by the attached mucoperiosteum of the mandibular alveolus. The lateral floor of mouth is bound posteriorly by the anterior tonsillar pillars. Medially the floor of mouth merges with the ventral and lateral aspects of the tongue. The WHO classifies this anatomical site as ICD-10 C04.[1]

The floor of mouth is lined by non-keratinizing stratified squamous epithelium similar to the buccal mucosa, but with a less dense submucosa. Underlying the mucosa lie minor salivary glands, the sublingual glands, submandibular ducts, hypoglossal nerves, lingual nerves and genioglossus muscles. These structures are located in an area bound by the mylohyoid muscle laterally and hypoglossal muscle medially. The submandibular ducts enter the mouth anteriorly either side of the lingual frenum.

Sensory innervation to the area is by the lingual branch of the mandibular division of the trigeminal nerve. Lymphatic drainage of the lateral floor of the mouth is via the ipsilateral submandibular nodes to the deep cervical chain. Lymphatic drainage of the anterior floor of mouth is via the submental nodes to both the left and right deep cervical chains.[100] Lingual lymph nodes in the floor of mouth, located above the mylohyoid, may have implications in the management of tumours of the floor of mouth.[86, 101]

Epidemiology

The floor of mouth is a common site for oral cancer, 18–33% of oral cancers developing at this site.[46, 102–105] It is thought that the high incidence of cancer at this site may be due to pooling of saliva with dissolved carcinogens or lack of keratinized epithelium.[106] Within this anatomical site tumours are more likely to occur anteriorly.[107–109]

Floor of mouth carcinoma occurs more frequently in men,[104, 105, 108, 110, 111] the age at diagnosis usually being in the 6th–7th decade.[104, 110, 111] Floor of mouth cancer, as does oral cancer at all sites, has a strong association with smoking[106] and the consumption of alcohol.[110]

Presentation

Since the floor of mouth is a relatively small anatomical area, tumours frequently extend into adjacent sites notably the tongue or mandible.[112] Patients may present with a sore lesion, ulceration or obstructive submandibular gland symptoms.[113] Leukoplakia of the floor of mouth may be considered a premalignant condition with an annual transformation rate of 1–2.9%,[114, 115] and it is not uncommon to find a carcinoma focus within an excised leukoplakic lesion.

Stage at presentation varies considerably between institutions, although approximately 50% present with advanced disease.

Cervical lymphadenopathy is present in 17–45% of patients on presentation,[104, 105, 108, 116] up to 22% of those clinically N0 at presentation having occult metastasis.[104, 111, 116, 117] Depending on the location of the tumour up to 28.6% of patients may have bilateral nodal involvement.[105, 116] Many tumours of the floor of mouth are well or moderately differentiated.[108]

Workup

Workup of patients with floor-of-mouth tumours should follow that of any patient with oral cancer. Particularly important in larger floor of mouth tumours is assessment of invasion of the base of tongue or mandible. The loose connective tissue of the floor of mouth presents a poor barrier to local spread.

Treatment

PRIMARY SITE

The need for aggressive treatment of floor-of-mouth carcinomas is well recognized.[118]

Surgical resection with a 1 cm margin should be achieved if surgery is the preferred treatment modality. Even in the best surgeons' hands positive or close margins may be seen in up to 47% of resections,[104, 112] despite the use of intraoperative frozen section.[105] Many floor-of-mouth tumours are infiltrative with indistinct edges, possibly explaining the high incidence of positive margins.[105] Further resection is advocated if margins are positive.[105] Although 1 cm margins are considered by most surgeons to be adequate, extended 2 cm margins have been advocated by some.[119]

The early extension of floor-of-mouth tumours into the tongue or mandible is demonstrated by the fact that many patients require rim or segmental resection of the mandible.[104] Surgical resection of the floor of mouth in the majority of circumstances will involve resection of part of the submandibular ducts. Typically the ducts will be transected at the resection margin, well away from their orifice, although in smaller resections at least 3 mm length of duct proximal to the orifice should be taken to ensure surgical clearance of carcinoma or dysplasia that may extend along the duct.[120] Management of the submandibular ducts is of great importance if a neck dissection is not being conducted with consequent removal of the submandibular gland. Stricture of the duct in the presence of a functioning gland may give rise to obstructive symptoms of the gland and difficulty in differentiating the potential submandibular gland swelling from cervical disease. The ducts should be transected obliquely to minimize stricture formation and repositioned at the margin of resection, ideally being stented.[121] Alternatively, the ducts may be found proximal to the resection margin, a longitudinal incision made and the duct 'marsupialized' to the floor-of-mouth mucosa. Uninvolved branches of the lingual nerve should be identified and preserved.

Small resections may be left to heal by secondary intention or a split-thickness skin graft applied. It has been demonstrated that a better functional outcome is achieved with primary closure, however, this naturally can only be achieved with the smallest of tumours.[122]A more substantial reconstruction may be achieved using local nasolabial[123] or facial artery musculomucosal flaps,[124] but an edentulous segment is required when using both of these flaps to accommodate their pedicle. If a neck dissection is required and surgical facilities allow, microvascular reconstruction provides a far more flexible reconstructive option, without necessarily prolonging operative time if a two-team approach is adopted. The radial free-forearm flap is an ideal reconstructive option for floor-of-mouth defects, easily being converted to a composite flap if segmental resection of an edentulous mandible is required. Prefabricated fasciomucosal free flaps have been described in oral reconstruction,[125] however their role in oncological reconstruction is questioned. The fibula osteocutaneous flap provides superior reconstruction if a segmental resection is anticipated in a dentate patient, but unlike the composite radial free flap, flexibility of the skin paddle is limited. The scapula osteocutaneous flap with two skin paddles, or one skin paddle and muscle left to mucosalize, provides an excellent reconstruction of large defects involving mucosa, bone and external skin.

Radiotherapy techniques (brachytherapy or external beam) for T1/2 primaries have been shown to provide results similar to surgery.[108, 109, 126] The proximity of the floor of the mouth to the mandible is of concern when using brachytherapy since up to 8.5% of patients treated with this modality require segmental resection of the mandible due to osteoradionecrosis within 10 years.[108, 109]

Several units have described a change in practice from brachytherapy to surgery as the primary treatment modality due to the risk of complications.[105, 111, 127] T3/4 lesions are best treated with surgery and PORT.

NECK

Regional spread of disease in floor-of-mouth carcinomas is usually due to the ipsilateral level I to III lymph nodes,[86, 111] with involvement of multiple levels not being unusual. Lesions towards the midline may spread to both sides of the neck, hence bilateral neck dissections should be considered. The presence of lingual lymph nodes has raised the concept of in-continuity neck dissection[128] in an attempt to reduce local recurrence and improve survival. Resection of the tumour accompanied with the complete clearance of the floor of the mouth, preserving mylohyoid, hyoglossus and genioglossus if possible, so clearing the lingual lymph nodes would seem an acceptable method of managing lingual lymph nodes.[101]

The decision to perform an END has been related to tumour size or depth of invasion. Lesions that are T2 or greater should have a I–III/IV selective neck dissection,[104, 129] although ENDs have been advocated for T1 lesions.[108, 129]

Tumour thickness of 4 mm is often used as a 'generic' critical thickness, greater than which an END is indicated, since the risk of occult metastasis is greater than 20%.[130] It has been demonstrated that the risk of cervical metastasis of floor-of-mouth tumours exceeds 20% in tumours as thin as 1.5–2 mm.[131, 132] Using a thickness of 1.5 mm may result in up to 32% of patients requiring END based on thickness criteria.[131]

PORT

The indications for PORT to the locoregional area are similar to other sites, notably two or more involved nodes in the neck, extracapsular spread, positive margins or stage III/IV disease.

The beneficial role of PORT in selected patients with floor-of-mouth carcinoma has been demonstrated.[104, 112, 116]

Recurrence

Recurrence rates for floor-of-mouth carcinoma are 26–55%,[104, 111, 118] usually within the first 2 years.

Factors that influence recurrence include tumour size,[104, 111] margin status[104, 105] and tumour thickness[132] and advanced nodal disease.[111]

Prognosis

Overall 5-year survival for floor-of-mouth carcinoma is 52–76%.[104, 105, 111, 116] Factors that potentially influence survival include nodal status,[105, 116] thickness,[23] margin status and recurrence.[105]

KEY POINTS

- One of the commonest sites for oral cancer.
- Leukoplakia of the floor of mouth has a 1–2.9% annual malignant transformation rate.
- Careful consideration should be given to management of the submandibular ducts.
- Anterior lesions may require treatment of both necks.
- Tendency for cervical metastasis to occur in thinner tumours than other sites.

TONGUE CARCINOMA

Surgical anatomy

The oral tongue is the freely mobile anterior two-thirds of the tongue, demarcated from the base of tongue by the circumvallate papillae posteriorly. The tongue may be subdivided into the tip, dorsum, lateral borders and ventral surface. The WHO classifies this anatomical site as ICD-10 C02.[1] The ventral and lateral surfaces are in continuity with the floor of mouth, having a lining mucosa with non-keratinizing stratified squamous epithelium. The dorsum and tip of tongue are lined by specialized gustatory mucosa, with a thick, primarily keratinized epithelium. The mucosa of the tongue overlies the intrinsic muscles of the tongue, in addition to the four paired extrinsic muscles of the tongue: genioglossus, hyoglossus, styloglossus and palatoglossus.

Motor innervation to muscles of the tongue is via the hypoglossal nerve, except palatoglossus which is supplied by the vagus nerve. Sensation of the tongue is supplied by the lingual nerve, a branch of the mandibular division of the trigeminal nerve. Taste sensation of the oral tongue is supplied by fibres of the facial nerve that run with the lingual nerve before passing to the chorda tympanic branch of the facial nerve.

Lymphatic drainage of the lateral borders of the tongue is to the ipsilateral cervical nodes; however drainage of the midline, tip and base of tongue occurs bilaterally. The blood supply to tongue is provided by the paired lingual arteries, the third branch of the external carotid artery. During resection of posterior tongue lesions the contralateral vascular pedicle should be preserved if the tongue tip is to be maintained. The tongue is a complex structure with an important role in mastication, deglutition and speech.

Epidemiology

In populations where tobacco chewing is not endemic the oral tongue is one of the commonest sites for oral cancer, with 22% to 39% of oral cancers developing at this site.[46, 103, 133]

Within the site most tumours occur in the middle third of the tongue,[134, 135] commonly on the lateral aspect, followed by the ventral aspect of the tongue. Only 4–5% of tongue carcinomas occur on the dorsum of the tongue.[136]

Tongue cancer occurs slightly more frequently in males,[134, 137–140] the age at diagnosis usually being in the 6th–8th decade[134, 138, 139] and 90% of patients are over 40 years of age.[137] The male to female ratio has decreased in recent years, possibly due to increased alcohol consumption by females. Up to 70% report significant tobacco and alcohol use.[134]

Presentation

Patients with tongue cancer may present with several symptoms notably pain, ulceration or a lump on the tongue.[134, 137, 139, 141] Lesions of the oral tongue are more likely to be symptomatic than lesions of the base of tongue but despite this many patients still present with a 4–6 month history of symptoms prior to seeking medical advice.[137, 139, 142] The majority of patients with cancer of the oral tongue present with stage I/II disease,[134, 137, 138, 141] which contrasts significantly with cancers of the base of the tongue that are usually stage III/IV at presentation.[137] Clinically positive cervical lymphadenopathy at presentation is in the region of 21–34%.[134, 138, 140] Occult cervical metastasis has been demonstrated in up to 53% of patients with tongue cancer[134, 139, 142, 143] and may be related to tumour thickness.[144] Tumours arising on the lateral aspect of the tongue tend to be thicker than those of the ventral aspect of the tongue.[140] Up to 4.5% may have occult cervical disease in the contralateral neck.[139] Clinical examination, CT and MRI have relatively poor sensitivity at determining cervical lymphadenopathy.[140, 145]

The majority of tongue tumours are well to moderately differentiated on histological examination.[134, 137, 138, 141]

Workup

As with many sites management of the neck is frequently determined by tumour thickness. Tumour thickness can be assessed accurately with intraoral sonography, or immediate sonography of the resected tumour[52, 146] prior to proceeding to a neck dissection if access to the neck is not required for reconstructive purposes.

Biopsies should endeavour to include the deep margin of the tumour in addition to mucosa at the periphery of the tumour. Deep biopsies may give an indication of tumour depth, but also multifactorial histological malignancy grading of the most dysplastic areas of the invasive front may help in assessing the risk of cervical metastasis.[140]

Treatment

PRIMARY SITE

Resection of the tumour with a 1 cm margin in three dimensions should be conducted if surgery is the treatment of choice. The use of ultrasonography to aid in assessment of surgical clearance has been advocated,[52, 147] particularly for the deep margin. Frozen section is not routinely used in many units. Even with apparently adequate margins during surgery, 10% of resections may demonstrate histologically positive margins.[134]

Resection of tongue tumours using a 'compartmental' approach as adopted by musculoskeletal oncology surgeons has been advocated,[148, 149] with improved outcomes with this technique.[150]

The aim of reconstruction of the oral tongue following resection is to ensure maximum function of the residual tongue tissue, since the complex function of the tongue cannot be replicated with current reconstructive techniques.[151] Preservation of the tip of the tongue, while maintaining oncologically sound resection margins, helps maximize post-operative function.[152]

The use of monopolar electrocautery, 'cutting' through mucosa changing to 'coagulation' when in muscle, or the harmonic scalpel helps reduce bleeding during the resection, however this is at the cost of lack of feel afforded by the use of scalpel or scissors. If both lingual vessels are resected then the viability of the tip of tongue remnant should be carefully assessed. Sacrifice of both hypoglossal nerves results in a non-functioning tongue tip with consequent poor function.

Functional outcomes following reconstruction of the oral tongue are increasingly being scrutinized since many reconstructive methods are increasingly resource intensive.[153, 154] Small lesions may be removed with a laser and allowed to heal by secondary intention. T1 and small T2 primary tumours may be excised with a vertical wedge and the defect closed primarily, if the defect does not extend to significantly include the floor of mouth. Many larger lesions benefit from free-flap reconstruction of the defect, usually with a radial free-forearm flap, although the anterolateral thigh free flap is being used more frequently. The skin paddle of the chosen free flap should be fashioned so as not to restrict residual tongue function and should hopefully augment swallowing. Typically, the reconstruction should be of the same size, or slightly smaller than the defect created by the resection. Care should be taken in the design of the flap when the defect extends to include adjacent sites such as the soft palate or floor of mouth. The mobile tongue and floor of mouth should be 'separated' in the reconstruction to minimize restriction of movement of the residual tongue.[151] Thin radial free flaps may have their bulk increased by extending fascial flaps beyond the skin island, the fascial flaps then being folded and buried underneath the epithelial reconstruction.[151]

Reconstruction of large resections may be accompanied by measures aimed to improve post-operative function such as static laryngeal suspension to the mandible and cricopharyngeal myotomy.[151] Once the specimen is removed it is examined for clearance and orientated for the pathologist, supplemented by a digital photograph.

Radiotherapy as the primary treatment modality has been advocated since it conserves tongue volume and morphology, brachytherapy being considered preferable to external beam radiotherapy.[153] Osteoradionecrosis of the mandible is a recognized complication of brachytherapy of the tongue, up to 9% developing some form of osseous complication.[138] The use of brachytherapy to the primary site requires either surgery or external beam radiotherapy to the neck in an elective or therapeutic manner. When surgery is not used as the primary treatment valuable histological prognostic information is lost. This makes the decision as to whether to conduct an END more difficult. It has been suggested that surgery is superior to brachytherapy in the management of Stage I/II tongue cancer.[154] Surgery as the primary treatment modality ensures that radiotherapy is kept in reserve for either poor prognostic indicators of the resected specimen, for management of recurrence or management of second primaries which may occur at a later date.

NECK

Tumours of the tongue initially metastasize to levels I and II, lateral tongue tumours frequently metastasizing directly to level II nodes.[86] Involvement of level V nodes, in the absence of positive nodes in levels I–IV is rare, however, it is not unusual for nodes in level IV alone to be involved.[140, 155] Hence, in ENDs levels I–IV should be dissected, taking care to manage the thoracic duct appropriately which is the main cause of surgical complication in this area.

Like floor-of-mouth tumours the presence of lingual lymph nodes should be considered and either an in-continuity resection with the neck specimen or clearance of tissue above mylohyoid conducted.[156]

Bilateral neck dissections should be considered in tumours that extend to or beyond the midline, the use of frozen section on ipsilateral nodes having been proposed as method of identifying those in which a contralateral node may be indicated.[157]

The management of the neck in larger primary tumours is usually straightforward since the neck is accessed for microvascular or pedicled flap reconstruction of the primary site. Management difficulties arise with smaller tumours amenable to per oral resection and local closure.[144]

It has been proposed that the increased incidence of nodal metastasis associated with tongue carcinoma may be due to contraction of tongue muscle promoting entry of cancer cells into the lymphatics.[158] It is thought that the mechanism by which tumour thickness is related to cervical metastasis is that thicker tumours have access to wider lymphatics in which tumour emboli can form more readily.

Although tumours arising on the lateral aspect of the tongue tend to be thicker than those of the ventral aspect of the tongue,[140] this may not manifest as a greater risk

of cervical metastasis, since the 'critical thickness' for tumours of the floor of mouth is less than other oral sites.

END or elective neck radiotherapy should be considered for tumours thicker than 3–4 mm,[144, 159, 160] T2 or greater in dimension and T1 tumours that demonstrate poor histological features (poor differentiation, double DNA aneuploidy or degree of differentiation at the advancing front).[135, 160]

A recent randomized trial has largely settled the controversy about elective vs therapeutic neck dissection in the setting of the N0 neck. D'Cruz et al. reported on the oncologic outcomes of 500 patients (245 in the elective-surgery group and 255 in the therapeutic-surgery group), with a median follow-up of 39 months. At 3 years, elective node dissection resulted in an improved rate of overall survival (80.0%; 95% confidence interval [CI], 74.1–85.8), as compared with therapeutic dissection (67.5%; 95% CI, 61.0–73.9). END was associated with a reduced hazard for death in the elective-surgery group (0.64; 95% CI, 0.45–0.92; P=0.01). Patients in the elective-surgery group also had a higher rate of disease-free survival than those in the therapeutic-surgery group (69.5% vs. 45.9%, P<0.001).[159]

Other studies with similar have also demonstrated the survival advantages of END.[142, 143]

PORT

PORT has been advocated for positive margins,[134, 135] multiple cervical nodes,[135] extracapsular spread in the neck,[135] Stage III/IV disease,[134, 135] perineural spread[135] or tumours thicker than 9–10 mm even in the absence of other features.[144, 158, 161] Based on involved margins, ECS of cervical nodes or multiple positive nodes 26–62% of patients receiving surgery as the primary treatment modality may require PORT.[140, 162]

Local failure following PORT to tongue tumours has been demonstrated to be higher than comparable floor-of-mouth tumours, leading some to suggest higher doses of PORT should be considered for tongue tumours.[112]

Recurrence

Recurrence rates for oral tongue carcinoma are 10–50%,[139, 144] usually being locoregional.[134, 140]

Similar to other sites, recurrence usually occurs within the first 2 years.[134, 141]

Factors that influence local recurrence include tumour thickness and the presence of perineural spread.[144, 162] It has been proposed that recurrence of thicker tumours is related to difficulty in assessing deep clearance intraoperatively compared to assessing mucosal clearance.[158]

Patients younger than 40 years have been demonstrated to be significantly more likely to develop locoregional failure, although this does not influence survival.[163] Metachronous second tumours are seen in nearly 10% of patients who have had tongue cancer.[139]

Prognosis

Clinical features of tongue carcinoma remain the most reliable prognostic indicators, although histological characteristics contribute to prognostication.[164] Tumour thickness,[132, 140, 159, 160, 162] the presence of perineural invasion,[144, 162] cervical metastasis[139, 134] or dysplasia at the resection margins[160] have all been demonstrated to influence prognosis. Patients with tumours greater than 9 mm thick have been shown to have a 5-year survival of 66% compared to 100% survival for tumours less than 3 mm thick.[144] It has been reported by several groups that younger patients without usual risk factors have a poorer long-term prognosis.[164, 165]

KEY POINTS

- One of the most common sites for oral cancer.
- Usually presents as Stage I/II disease.
- ENDs should include levels I–IV because of skip metastases.
- Reconstruction should maximize function of the residual tongue.

RETROMOLAR CARCINOMA

Surgical anatomy

The retromolar trigone is a triangular area of mucosa that overlies the ascending ramus of the mandible. The base of the triangle is in the region of the mandibular third molar inferiorly, the apex being adjacent to the maxillary tuberosity superiorly. The area is bound by the buccal mucosa laterally and the anterior tonsillar pillar medially. The WHO classifies this anatomical site as ICD-10 C06.2.[1] The retromolar mucosa is not exposed to masticatory loads and so is covered by a lining mucosa with non-keratinizing stratified squamous epithelium, similar to the buccal mucosa. Sensory innervation to the area is by the buccal branch of the mandibular division of the trigeminal nerve. Lymphatic drainage is to the ipsilateral submandibular and deep cervical nodes.

Epidemiology

The retromolar trigone is a relatively unusual site for carcinoma of the oral cavity, only 6–7% of oral carcinomas arising at this site.[46, 164] The disease is more common in males and like other sites is typically a disease of older individuals.[164–166] Common with other oral sites, there is a strong association with smoking[166, 167] and alcohol consumption.

Presentation

Patients typically present late with pain, trismus, otalgia or lingual parathesia.[164, 167, 168] Since the retromolar tigone is an anatomically small-site tumour which often extends to involve adjacent subsites – buccal mucosa in 84%, oropharynx in 14%, masticator space (medial pterygoid, masseter, temporalis, mandibular branch of the trigeminal nerve) in 22%. Bone involvement of the mandible or maxilla is present in 12–34%[164, 166–169] of retromolar tumours, although a higher incidence of up to 75%

has been reported.[170] The posterior maxilla is more frequently involved than the mandible when bone invasion occurs.[166] Tumour extension into the masticator space or lower pterygoid plates classifies tumours in this area as T4b, however, if resectable outcomes are comparable to T4a tumours.[171]

Retromolar carcinoma usually presents as advanced disease, 55–73% having Stage III/IV disease at presentation.[164–166] Spread to regional lymphnodes occurs in 26–56% of patients at presentation,[164, 166, 172] 8–15% having occult cervical node involvement.[164, 172]

Tumours of the retromolar trigone are usually well or moderately differentiated.[166]

Workup

The complex anatomy of the retromolar region and the frequent extension of retromolar carcinoma make accurate preoperative imaging essential. Clinical examination alone is not reliable at determining underlying bone involvement.[173] CT has been demonstrated to have a high specificity, but low sensitivity for predicting mandibular bone invasion of retromolar carcinomas.[170, 174] MRI is considered the imaging modality of choice for retromolar tumours due to its ability to accurately stage the disease and demonstrate accurately anatomical relationships of the tumour,[175] although mandibular invasion may still be hard to define.

Treatment

PRIMARY

The treatment of choice for retromolar tumours is surgical resection with pre/post-operative radiotherapy or chemoradiotherapy dependant on stage of tumour and histological findings.[164–166, 168, 169, 173] Radiotherapy as a sole treatment modality for retromolar carcinoma has been demonstrated to be associated with significantly worse recurrence rates and disease-free survival,[165, 166] although others have been unable to demonstrate this significance.[167, 176] The debate regarding the use of surgery or radiotherapy as the primary treatment modality is hampered by the lack of data regarding tumour thickness in this anatomical site. It is recognized that tumours in this site may be T3 in size, but superficial in nature.[177]

Resection should be achieved with a 1 cm margin in all planes. It is recognized that the incidence of positive margins following resection of retromolar tumours is higher than other oral sites.[44]

Small tumours of the retromolar trigone may be resected via a transoral route, however, the posterior location of retromolar tumours and frequent extension of disease into adjacent anatomical sites often necessitates a mandibulotomy to facilitate access.[164, 168] Extensive tumours extending into the masticator space may require a cervicofacial incision, parotidectomy, +/– zygomatic osteotomy and preservation of the facial nerve for access, or an anterior approach including maxillectomy.[178]

Defects following the resection of small mucosal tumours may be left to heal by secondary intention, however, larger lesions require reconstruction to prevent trismus. Simple reconstructive methods include use of a split-skin graft or buccal-fat pad reconstruction. Tongue flaps and masseteric flaps have been described,[169] however they lack flexibility and may be compromised in anything but the smallest of tumours.

Given the low-negative predictive value of CT for bone involvement and the high incidence of bone involvement demonstrated in retrospective series, a low threshold for bone resection should be adopted.[173] A posterior marginal mandibulectomy (including coronoid) conducted via a visor or lip split soft-tissue flap is oncologically safe in patients with no history of previous radiotherapy and no radiological signs of cortical bone involvement.[168, 179] Patients demonstrating cortical bone involvement on imaging, or who have previously received radiotherapy, should have a segmental mandibular resection. A posterior maxillectomy should be conducted when indicated.

The combination of mandibulotomy and posterior marginal mandibulectomy for large soft tissue lesions should be avoided in view of the increased risk of osteoradionecrosis; a segmental resection is warranted in these circumstances.[180]

Pedicled myocutaneous flaps such as the pectoralis major flap are stretched to their limit at this anatomical site, often resulting in delayed healing.[168] The use of the radial free-forearm flap or anterolateral thigh flap provides excellent reconstruction of larger soft-tissue defects in the retromolar region. Where the resection involves the soft palate, the combination of free flap and superiorly based pharyngeal wall flap should be considered to minimize nasopharyngeal reflux.

Reconstruction following segmental resection should ideally be with free-tissue transfer such as the fibula, scapula or DCIA flaps. Since radiotherapy will almost certainly be indicated following segmental resection the use of vascularized bone flaps results in more predictable healing with lower risk of non-union or resorption.[168] The use of reconstruction plates and soft-tissue cover alone is particularly prone to failure in the retromolar region.[181]

Large tumours extending into mandible, maxilla, soft palate, tongue base and buccal mucosa require careful consideration regarding reconstructive options. Dual free flaps may provide ideal soft tissue and bony reconstruction but at the increased risk of complications. The scapula flap is versatile enough in thin individuals to be able to reconstruct these extensive defects.

NECK

Lymphatic spread to the neck is usually to levels I and II in the absence of detectable lymphadenopathy, however, involved nodes in levels III–V may occur in the presence of nodes in levels I and / or II.[172]

Unlike tumours at other sites there are little data correlating tumour thickness to incidence of cervical metastasis.

An END (levels I–III/IV) is indicated for any tumour bigger than T1,[164, 168, 172, 179] or where access to vessels in the neck is required for reconstruction.

PORT

Up to 58% of patients may require PORT/chemoradiotherapy,[164] an indication of the typically advanced nature of retromolar carcinomas.

Recurrence

Local and/or regional recurrence may occur in 20–37%,[164–166] depending on primary treatment modality and stage of disease on presentation. Recurrence usually occurs in the first 2 years.[172]

Prognosis

Factors influencing survival are stage, involvement of the masticator space[164] and cervical metastasis,[166, 168, 174] mean survival in patients with masticator space involvement being 38 months.[164] Patients receiving surgery combined with radiotherapy have been demonstrated to have a significant survival advantage over patients receiving radiotherapy alone.[165]

KEY POINTS

- 6–7% of oral carcinomas.
- Frequently presents as Stage III/IV disease with extension into adjacent sites.
- Accurate preoperative imaging is required to determine extent of disease.

MAXILLARY ALVEOLUS AND HARD PALATE

Surgical anatomy

The maxilla comprises the maxillary alveolus and the hard palate. The osseous alveolar process supports the maxillary dentition, being covered by a mucoperiosteum with a stratified squamous epithelium. The maxillary alveolus merges laterally with the buccal mucosa and lips at the gingival sulcus and medially with the hard palate. The alveolar process extends to the upper end of the pterygopalatine arches posteriorly. The hard palate lies within the horseshoe shape of the maxillary alveolus, merging imperceptively with the alveolar mucosa. The hard palate has minor salivary glands located in the submucosa, 33% of palatal tumours being derived from salivary epithelium.[182] Posteriorly, the hard palate merges with the soft palate at the posterior edge of the palatine bone. The WHO classifies these anatomical sites as ICD-10 C05.0 (hard palate) and C03.0 (maxillary alveolus).[1] Sensory innervation to the maxillary mucosa is by branches of the maxillary division of the trigeminal nerve. The nasopalatine nerve supplies the anterior hard palate, passing through the incisive foramen, the posterior palate being supplied by the paired greater palatine nerves that pass through the greater palatine foraminae. Lymphatic drainage is to the ipsilateral cervical nodes via the submandibular nodes or potentially the retropharyngeal nodes in posteriorly located tumours.

Epidemiology

Squamous cell carcinoma of the maxillary alveolus represents 3.5–6.5%[60, 103] of oral cancers, being approximately one-third as common as mandibular alveolar carcinoma. Carcinoma of the hard palate is very unusual representing only 1–3%[183, 184] of oral cancers. Aetiological factors include tobacco use and alcohol consumption. Palatal carcinoma is particularly associated with reverse smoking, a habit practised in parts of India by women.[185–187]

Patients tend to present in their 6th–7th decade of life.[183, 186, 188] There is an even distribution between the sexes, except where reverse smoking is practised when there is a greater frequency in females.[186]

Presentation

Patients may present with pain, ulceration, loose teeth or poorly fitting dentures. Symptoms of advanced disease may include infraorbital parathesia, trismus or nasal obstruction. Most patients present with Stage I or II disease.[183, 188]

Approximately 8% of patients with carcinoma of the hard palate or maxillary alveolus present with cervical lymphadenopathy, a further 27% having occult metastasis.[188]

Workup

The surface extent of a maxillary carcinoma may be relatively easy to determine from clinical examination alone, however, extension into the maxillary antrum and beyond requires additional imaging. Extension of tumour through the pterygoid plates into the masticator space may render a tumour inoperable. CT scans and MRI are complementary in the assessment of maxillary tumours.[189]

Intranasal examination with a nasendoscope should be conducted to determine the extent of tumour through the floor of nose or medial antral wall.

All patients should have impressions taken for the provision of a temporary obturator, even if free-flap reconstruction is anticipated. In the unfortunate situation of free-flap failure the presence of pre-surgical models will make prosthetic salvage considerably easier. If prosthetic reconstruction is to be considered from the outset then early consultation with a prosthodontist is required.

Treatment

PRIMARY

Anaesthesia is usually accomplished with an oral tube, a tracheostomy only being considered for larger resections or free-flap reconstruction. Patients requiring an upper cheek flap for access should have their eyes protected with corneal shields or temporary tarsorraphies.

The surgical goals that apply to hard palate and maxillary alveolar tumours are the same as those at other sites, notably surgical clearance of 1 cm in three dimensions. Small tumours may be approached per orally, however larger tumours may require an upper cheek flap or midfacial degloving to augment access.

Once the mucosal incisions have been completed the soft tissues are elevated in a subperiosteal plane away from the tumour to allow access for bone cuts. Teeth may need to be extracted to allow osteotomy cuts and minimize post-operative complications. The use of a fine reciprocating or saggital saw allows accurate bony resection. Care should be taken to avoid tooth roots. If the margins of resection extend posteriorly the specimen may be disarticulated from the pterygoid plates with a curved osteotome. Posterior dissection may be completed with large curved scissors. The posterior dissection in the region of the pterygoids should be last part of the resection due to the bleeding that occurs in this area. An ipsilateral coronoidectomy should be conducted to minimize impingement of the coronoid on the prosthesis or flap reconstruction. Defects that are to be reconstructed with a prosthesis should be lined with a split skin graft.

Surgical closure of small maxillectomy defects may be achieved with local flaps such as buccal fat pad, temporalis flaps or facial artery musculomucosal flaps. Large defects may require soft tissue[190] or composite free tissue transfer.[191] The use of an appropriate defect classification system[194] allows for planning of reconstruction and communication with colleagues.

NECK

Historically, regional spread from maxillary tumours has been considered low, however this may be due to coregistration of hard palate and alveolar tumours as sinonasal tumours.[182] Cervical metastasis has been demonstrated in 35% of patients with hard palate or maxillary alveolar carcinomas,[188] an elective I–III neck dissection being considered appropriate for lesions of T2 size or greater.[182, 192] Consideration should be given to clearing the facial lymph nodes when conducting a neck dissection for maxillary tumours.

PORT

PORT has been suggested for T3 or greater disease, positive margins, perineural or perivascular invasion or multiple cervical nodes, particularly if they demonstrate extracapsular spread.[182]

Recurrence

Locoregional control of hard palate and alveolar tumours following initial therapy is in the region of 40–45%,[183, 188] increasing to 68% following secondary intervention.[183] Salvage of local recurrence may be achieved in 33% and regional recurrence in 71%.[188] Over 90% of recurrences occur within the first 2 years, similar to other sites.

Prognosis

The 5-year absolute survival for hard palate carcinoma is 57%, 5-year survival for alveolar carcinoma being 49%.[185] Tumour stage and presence of cervical metastasis influence long-term survival.[183] The origin of maxillary carcinoma (oral vs sinus) does not influence long-term prognosis.[193]

Current staging of maxillary tumours categorizes a tumour as T4 if cortical bone is breached. It has been suggested that a more accurate prognostic indication is given if T4 is reserved for tumours that breach the nasal or sinus floor.[194]

KEY POINTS

- Carcinoma of the maxillary alveolus is three times less common than the mandibular alveolus.
- Carcinoma of the hard palate represents only 1–3% of oral cancers.
- Palatal carcinoma is associated with reverse smoking.
- All patients should have dental impressions as part of their workup.
- Some degree of bone removal is nearly always required.
- Selective neck dissection is often indicated.

MANDIBULAR ALVEOLUS

Surgical anatomy

The mandibular alveolus represents that part of the mandible that is 'intraoral'. The osseous alveolar process of the mandible supports the dentition and is covered by a mucoperiosteum. The mandibular alveolus merges laterally with the buccal mucosa/lips at the gingival sulcus and medially with the floor of mouth. The alveolar process extends to the retromolar trigones posteriorly. The WHO classifies this anatomical site as ICD-10 C03.1.[1] Sensory innervation to the mandibular alveolus is by the mandibular division of the trigeminal nerve. Lymphatic drainage is to the ipsilateral submandibular and submental nodes to the deep cervical chain. Lymphatic drainage towards the midline may be bilateral. Following loss of the dentition there is considerable resorption of the alveolar process, leaving only a thin strip of attached mucoperiosteum on the crest of the mandible between the floor-of-mouth and buccal mucosa.

Epidemiology

Squamous cell carcinoma of the mandibular alveolus represents 7.5–17.5%[60, 103, 184] of oral cancers, although it represents up to 30% of oral cancers in the Japanese population.[195] Mandibular alveolar carcinoma is three times more common than maxillary alveolar carcinoma.[196] Rarely primary intraosseous carcinomas may occur, being derived from residues of odontogenic epithelium within the mandible.[197] The use of tobacco, particularly chewing tobacco, and alcohol is associated with alveolar carcinoma.

Patients tend to present later in life in their 7th decade, the disease being slightly more common in males.[195, 196, 198]

Presentation

The most common presenting symptom is pain, occurring in 54–86% of patients.[195, 196, 198] Patients who are dentate may note loosening of teeth while edentulous patients may note a change of fit of their dentures. Labial parathesia may be a presenting feature in up to 14% of patients. Unfortunately patients still present with a history of delayed healing of an extraction socket in up to 28% of cases.[195] The majority of lesions of the mandibular alveolus are located posterior to the canines, extension to the floor-of-mouth or buccal mucosa being common.[196]

Alveolar tumours are staged by their size until there is invasion of tumour through cortical bone into marrow space when the tumour becomes T4. Cervical lymphadenopathy is present in 24–32% of patients at presentation, usually to levels I and II,[195, 196, 198] with 15% of patients having occult metastasis.[196] Up to 94% of patients have evidence of bone involvement clinically.[198] Most tumours at this site are usually well or moderately differentiated.[196, 198]

Workup

The most important aspect of working up mandibular alveolar tumours is to determine the degree of bone involvement since this determines the extent of tumour resection.

Treatment

PRIMARY

Mandibular alveolar carcinoma is considered a surgical disease.[198] Invariably some degree of bone resection is required, 6–7% requiring soft tissue resection only.[196, 198, 199] Small alveolar carcinomas with no clinical evidence of significant bone involvement may be resected via a per oral approach with a marginal mandibulectomy, aiming for a 1 cm soft tissue and bony margin. Larger tumours with obvious bone involvement require segmental resection and extraoral access incisions. Segmental resection should be considered for tumours abutting a mandible previously exposed to radiotherapy, large soft tissue tumours adjacent to the mandible, involvement of the inferior dental nerve or intraosseous tumours (primary or secondary). Marginal mandibulectomy is preferable to segmental resection whenever oncologically acceptable. If a marginal resection is conducted then reconstruction may usually be achieved by primary closure. More extensive mucosal defects may require reconstruction with a skin graft; local flaps such as the FAMM flap, nasolabial flap or buccal fat pad; or microvascular free-tissue transfer to achieve acceptable soft-tissue closure. Segmental mandibular resection should be accompanied with composite microvascular free-flap reconstruction whenever feasible. Small, lateral mandibular defects may be reconstructed with a reconstruction plate and soft-tissue flap only, however central defects or larger lateral defects should be reconstructed with vascularized bone to minimize the risk of complications.[200] The use of a recognized mandibular defect classification helps surgeons plan appropriate reconstruction and communicate effectively with colleagues. The H, C, L, o, m, s classification system[201] accurately describes mandibular surgical defects.

NECK

Regional spread of mandibular alveolar tumours is usually to the ipsilateral level I–III nodes. END is indicated in tumours T2 in size or greater or any tumour with demonstrable bone invasion, clearance of levels I–III being adequate.[202] Lesions overlying the symphysis are thought to be associated with a higher risk of cervical metastasis and may require bilateral neck dissections. It has been argued that a staged neck dissection should be considered if histological examination of the primary tumour demonstrates bone involvement.[202] A more extensive neck dissection should be conducted in the presence of confirmed cervical metastasis, level V requiring treatment.[202]

PORT

Indications for PORT include positive margins (soft tissue or bone), multiple positive nodes or extracapsular spread.[196]

Recurrence

Recurrence rates for mandibular alveolar carcinoma at 2 years are 13–25%.[195, 196, 198] Higher recurrence rates are associated with increasing T stage[199] and positive resection margins.[195, 196]

Prognosis

Overall 5-year survival for lower alveolus carcinoma is 50–60%, disease-specific survival being 73–80%.[195, 196]

Cervical metastasis has been demonstrated to significantly reduce prognosis for lower gingival carcinoma.[202] Increasing T stage and particularly tumours greater than 3 cm,[196] bone involvement (cortical or cancellous),[196] positive resection margins[195, 196] are associated with decreased prognosis.

Tooth extraction at the site of primary tumour does not influence prognosis.[195, 196]

KEY POINTS

- Represents approximately 10% of oral cancers, although up to 30% in the Japanese population.
- 94% of tumours involve bone.
- Alveolar carcinoma is a surgical disease requiring a rim or segmental resection of the mandible.

MANAGEMENT OF THE MANDIBLE

Tumours of the mandibular alveolus, the floor of mouth, buccal mucosa or retromolar trigone may involve the bone of the mandible. Involvement of the mandible has

significant consequences regarding management of the patient.

Squamous cell carcinoma invades the mandible either in an invasive or erosive manner.[199, 203] Invasive tumours demonstrate fingers or islands of tumour advancing deeply into bone with no obvious osteoclastic activity. Erosive tumours have a broad advancing front with osteoclast activity and connective tissue between the tumour and bone, although as the depth of invasion increases they may become more invasive in character. Large, deeply invading tumours are more likely to demonstrate an invasive pattern of spread and involve the mandible.[199, 204]

Tumours enter the mandible at the point of contact,[199, 205] usually the junction of the attached and reflected mucosa, whether the patent is edentulous or dentate. The mandible should be considered at risk at any point where tumour is in contact and this taken into account when planning resection.[206] Clinical fixation of the tumour to bone is not necessary for bone invasion to occur.

It has been demonstrated that it is primarily the size and extent of the tumour that dictates the pattern of spread once in bone rather than anatomical features such as the inferior alveolar nerve or periodontal ligament. Preferential spread within the mandible via the inferior alveolar nerve or medullary space is rare,[199, 207] justifying 1 cm margins.

Tumours demonstrating an invasive pattern of spread are more likely to give rise to cervical metastasis with extracapsular extension,[199] an indication of their more aggressive nature. Pre-operative imaging of the mandible is necessary to determine if bone resection is required, and if so the appropriate type of resection.[208]

At present there is no single investigation that can reliably predict bone invasion. An OPG radiograph should be requested for all cancer patients. This plain radiograph is not only useful for demonstrating bony invasion but also for assessing mandibular height, dental anatomy and dental pathology. It should be remembered that plain X-rays do not detect initial invasion until 30% demineralization has occurred, giving rise to reduced sensitivity.[209] Clinical examination and OPG alone are inadequate for accurate assessment of mandibular invasion.[209]

Axial MRI views with T1 and Short-TI Inversion Recovery (STIR) fat suppression are very sensitive for imaging the primary site of oral cancer with an adequate specificity.[210] Bone scintigraphy or single photon emission computed tomography (SPECT) may be considered in equivocal cases, SPECT being demonstrated to have up to 100% sensitivity in determining bone invasion.[211] When bone involvement is equivocal on pre-operative imaging then periosteal stripping looking for cortical bone disruption at the time of resection may help the clinician plan the resection.

A rim resection/ marginal mandibulectomy should be considered for T1/2 tumours with early invasion (< 5 mm) and adequate bone height of the mandible (dependant on pre-operative imaging, clinical examination and periosteal stripping).[212, 213] Traditionally rim resections have been conducted horizontally, however, with the understanding that tumour may enter the mandible at any point of contact it becomes apparent that the saw cut should be angled to accommodate this.[199] Marginal resections in the retromolar region may include the coronoid process. Every effort should be made to preserve the inferior alveolar neurovascular bundle when conducting a marginal resection in an edentulous mandible so as to minimize the risk of avascular necrosis and iatrogenic fracture. The anterior and posterior margins of a rim resection should be curved so as to minimize the risk of iatrogenic mandibular fracture. Rounding of the edges of the rim resection also minimizes the risk of bone exposure[214] and minimizes the risk of trauma to the pedicle of a microvascular free flap if used for soft tissue reconstruction. If the depth of the mandible following rim resection is less than 10 mm then consideration should be given to converting the resection to a segmental resection.

Segmental mandibular resection and composite reconstruction should be conducted for extensive mandibular invasion or deeply invading soft-tissue tumours that abut the whole depth of mandible. Segmental resection should also be considered in the previously irradiated mandible.[215, 216] The surgeon should aim for a 1 cm margin of the soft tissue tumour, it being highly unusual to get a positive bone margin in the absence of a positive soft-tissue margin.[212]

Usually intra-operative assessment of bony margins is not conducted, however techniques for frozen section analysis of cancellous and cortical bone have been described.[217]

If the planned resection of mandible follows the guidelines set out above then long-term prognosis and recurrence does not differ between marginal resection and segmental resection.[218, 219] The presence of bone involvement, rather than the depth of bone invasion, is the main determining factor of long-term prognosis.[196, 220] It has been proposed that only tumours with an invasive tumour front as opposed to an erosive front be classified as T4 tumours.[220] It is thought that local recurrence following bony resection is usually as a consequence of soft-tissue margin status rather than method of mandibular resection.[221]

Rim resection of the mandible maintains bony continuity and hence is usually associated with an excellent functional and cosmetic outcome. The rim resection in addition to maintaining the structural integrity of the mandible also usually preserves sensation of the lower lip and muscular attachments. With modern reconstructive techniques the Andy Gump deformity should no longer be encountered. Patients' quality of life following mandibular resection is influenced by many factors such as site of bony resection, type of bony resection, the soft-tissue resection, type of reconstruction, adjunctive radiotherapy etc.

It is recognized that whenever oncologically sound, a rim resection should be the resection of choice.[222] However, it has been demonstrated that there is little or no difference in quality of life between a rim resection and segmental resection with composite microvascular free tissue transfer,[226] particularly when the resection is greater than 4 cm.[223]

KEY POINTS

- Bone involvement may be by erosion or invasion.
- Bone involvement occurs at any point where tumour contacts bone.
- MRI, CT, SPECT and periosteal stripping are complimentary in assessing bone involvement.
- Bone margins should be dictated by overlying soft-tissue margins.
- Rim resection should be conducted when oncologically acceptable.

LIP RECONSTRUCTION

Omar A. Ahmed

INTRODUCTION

The lips are complex, highly specialized structures, which are the most mobile elements of the lower third of the face. They serve a critical, aesthetic and functional purpose, which cannot be replicated by any other tissue. Hence it is imperative, wherever possible, to replace lip defects with lip tissue.

The lips are considered to be the beginning of the oral cavity, and they form a fleshy, sensate, highly mobile partition, which separates the intraoral contents from the exterior. They are thus responsible for oral continence, but also play an important role in eating, swallowing, speech, and both verbal and non-verbal communication.

ANATOMY

The lips surround the oral cavity. They are composed externally of skin and internally of mucous membrane. The lips extend from the nose superiorly to the chin inferiorly, and are bound laterally by the nasolabial folds. It is important to have a good knowledge of the anatomical landmarks of the lips (**Figure 12.5**).

The external landmarks of the upper lip are the philtral columns, the Cupid's bow, and the white roll. The philtral columns are a pair of near-vertical ridges, extending from the nasal columella to the vermilion border, which are formed by the underlying orbicularis oris muscles. The philtral columns merge caudally with the white roll, another ridge formed by the orbicularis oris muscle. The philtral dimple is a depression in the central lip between the philtral columns. The Cupid's bow is the curved part of the white roll between the bases of the philtral columns. The main external landmark of the lower lip is the white roll.

A cross-section of the lips reveals the following structures from external to internal: skin and vermilion, subcutaneous tissue, muscle, submucous glands and mucosa (**Figure 12.6**).

The skin of the lips is hair-bearing, with the hair being mostly vellus in women and children. It is rich in sebaceous and sweat glands. Deep to the skin is a significant amount of subcutaneous fat that makes up the bulk of lip thickness. The vermilion extends from the white roll to the wet-dry border, beyond which it transforms into mucosa. It is important to understand the distinction between the vermilion and the mucosa. The vermilion is stratified squamous epithelium with a thin layer of surface keratin. It contains no glands, and is dryer and duller in appearance than mucosa. Mucosa is non-keratinized epithelium that is rich in minor salivary glands and lines the inside of the lip.

The perioral musculature can be classified into three groups based on their attachments (**Figure 12.7**). Group I muscles attach to the modiolus, which is a tendinous thickening at each oral commissure. Group II muscles insert into the upper lip, and Group III muscles insert into the lower lip. Group I muscles include the orbicularis oris, buccinator, levator anguli oris, depressor anguli oris, zygomaticus major and risorius. Group II muscles include the levator labii superioris, levator labii superioris alaeque nasi and zygomaticus minor.

Group III muscles are the depressor labii inferioris, mentalis and platysma.

The paired orbicularis oris muscles are the sphincter muscles of the lips and are essential for oral competence. They also evert and protrude the lips, as in pouting and kissing. They originate at the modiolus, just lateral to the oral commissure. The two muscles insert into a midline raphe in the lower lip, but in the upper lip they cross

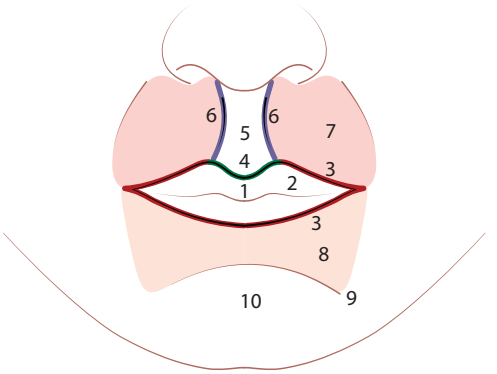


Figure 12.5 Subunits of the lip. 1. Tubercle. 2. Vermilion. 3. Vermilion border. 4. Cupid's bow. 5. Philtrum. 6. Philtral columns. 7. Cutaneous upper lip. 8. Cutaneous lower lip. 9. Labiomental sulcus. 10. Chin.

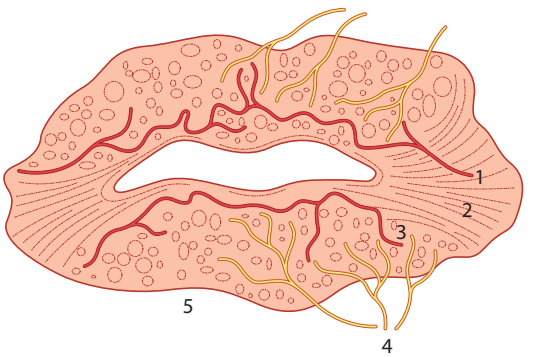


Figure 12.6 Coronal cross-section through lips. 1. Superior labial artery. 2. Muscle fibres. 3. Inferior labial artery. 4. Sensory nerve supply from the infraorbital nerve and motor supply from the lower buccal and mandibular branches of the facial nerve. 5. Fat and subcutaneous tissue.

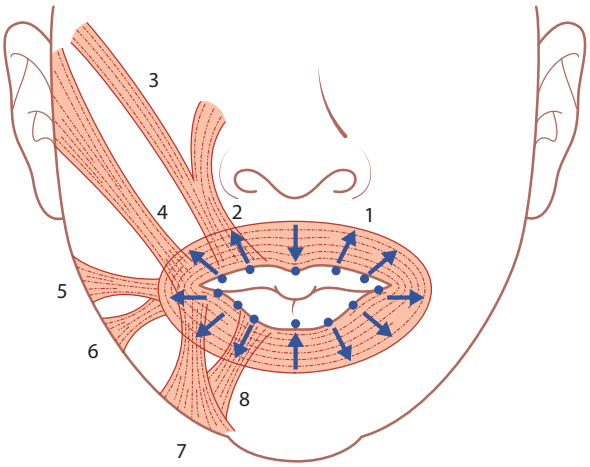


Figure 12.7 Key perioral muscles. Arrows show direction of pull on the lips. 1. Orbicularis oris 2. Levator superioris 3. Zygomaticus minor 4. Zygomaticus major 5. Risorius 6. Buccinator 7. Depressor anguli oris 8. Depressor labii inferioris.

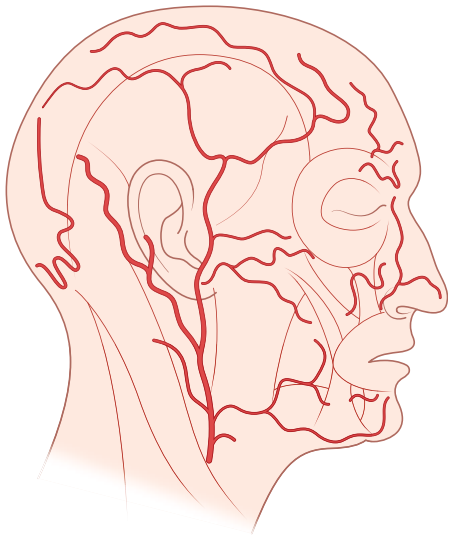


Figure 12.8 Major blood supply to the face.

the midline to insert into the contralateral philtral column. The orbicularis muscles are innervated by buccal branches of the facial nerve. The second most important lip muscles are the paired mentalis muscles, which are the primary elevators of the lower lip. They maintain the lower lip in a correct position at rest, and help maintain oral competence by pushing the lower lip against the upper lip. The mentalis muscles are large trapezoidal muscles that attach superiorly to the mandible just below the attached gingiva and inferiorly to the chin pad below the labiomental sulcus. Each muscle is innervated by the corresponding marginal mandibular branch of the facial nerve.

The depressors of the lip are the depressor anguli oris and the depressor labii inferioris, innervated by the marginal mandibular branch of the facial nerve, and the platysma, whose nerve supply is from the cervical branches of the facial nerve. The elevators of the upper lip include the levator labii superioris, zygomaticus major and minor, and levator anguli oris, which lift the central upper lip, lateral upper lip and commissure respectively. These muscles are innervated by the zygomatic and buccal branches of the facial nerve.

The sensory innervation of the lip is provided by the infraorbital and mental nerves. The infraorbital nerve is a branch of the maxillary division of the trigeminal nerve, which enters the face through the infraorbital foramen and provides sensation to the nasal sidewall, nasal ala and the upper lip. The mental nerve is a branch of the posterior trunk of the inferior alveolar nerve, which arises from the mandibular division of the trigeminal nerve. The mental nerve exits the mandible between the first and second premolar teeth. It provides sensation to the lower lip. Intraoral infiltration of small amounts of local anaesthetic solution around the bony exit points of these two nerves allows for rapid and complete anaesthesia of the lips, making it easy to perform surgical procedures without general anaesthesia.

The lips have a rich vascular supply (**Figure 12.8**). The arterial supply is from the superior and inferior labial arteries, which are branches of the facial artery. Each labial artery communicates with its counterpart across the lip, forming a continuous arterial circle around the oral sphincter. This allows for considerable versatility in local flap design. The arteries lie at the wet-dry border, just deep to the orbicularis oris muscle, and send numerous perforators through the orbicularis muscle to the overlying skin. The blood supply to the labial skin is so rich that local flaps can survive even when they do not include a labial artery. The venous drainage of the lips is more unpredictable than the arterial supply. The labial veins can drain into the anterior facial veins, transverse cervical veins, the superficial temporal veins and the submental veins.

Knowledge of the lymphatic drainage of the lips is important for oncological considerations. Drainage from the upper lip is primarily to the submandibular nodes, but the commissure can drain to the periparotid nodes. Both of these nodal regions subsequently drain to the jugulodigastric nodes. The drainage is mostly to ipsilateral nodes, although the midline of the upper lip can also drain to contralateral nodes. The lower lip also drains to the ipsilateral submandibular nodes with the exception of the midline lip, which drains into the submental nodes. Drainage from the central lower lip frequently crosses the midline. The submental nodes subsequently drain into the submandibular nodes.

HISTORY OF LIP RECONSTRUCTION

A wide variety of techniques have been described to reconstruct the lips. Functional and aesthetic results are best when the lip tissues are oriented in their correct anatomical positions.

Lip reconstruction has been practised for centuries, and most modern techniques are based on older techniques. Sushruta, the great Indian physician and surgeon, provided one of the earliest written records of lip reconstruction in his compendium of surgery (*Sushruta Samhita*), possibly around 600 BC.[228] The Roman

physician Celsus is credited with the original description of the classic wedge excision and primary closure of the lip in the 1st century AD. The Branca family and, later, Tagliacozzi popularized staged tissue transfer techniques in the late 16th century. Tagliacozzi is also credited with writing the first textbook on plastic surgery. In 1818, von Graefe described lip reconstruction in the second textbook on plastic surgery, and was the first to coin the term 'plastic surgery'. Shortly thereafter, in 1834, Dieffenbach described the first cheek advancement flap techniques.[229] The Italian surgeon Pietro Sabattini (1838) came up with the concept of lip-switch flaps,[230] which were popularized in the late 19th century by Abbe[231] and Estlander[232] and are still in common use. In 1853, von Burow[233] applied his principle of skin triangle excisions to facilitate advancement to bilateral cheek advancement flaps for total lip reconstruction. Bernard[234] described a similar technique in 1852. Modifications of the von Burow and Bernard techniques remain useful to this day, especially that of Freeman[235] (1958) and Webster[236] (1960). In the 1920s Gillies introduced the fan flap, which was aimed at restoring a competent oral sphincter. Karapandzic[237] described his elegant neurovascular lip rotation technique for large defects in 1974. Harii and Ohmori were the first to use microvascular free tissue transfer for extensive defects of the lip (1975).[238]

AETIOLOGY OF LIP DEFECTS

The majority of lip defects requiring reconstruction arise from tumours or trauma. Lip tumours can be congenital or acquired. Haemangiomas and vascular malformations are common congenital tumours. Skin cancers make up the bulk of acquired tumours. Basal cell carcinomas tend to occur in the upper lip and squamous cell carcinomas in the more sun-exposed lower lip. Both of these tumours are more common in the elderly. Malignant melanomas also often occur in the lips and can occur at any age. Traumatic lip defects usually occur in young, healthy patients.

PRINCIPLES OF LIP RECONSTRUCTION

1. In order to maintain oral continence, an attempt should always be made to preserve the nerve supply to the reconstructed lip.
2. Muscle-carrying lip vermilion is precious tissue and should also be preserved.
3. Lip tissue should preferentially be used to reconstruct the lip.
4. Whenever possible the muscles of the lip should be correctly orientated.
5. When a lip defect is too large to be reconstructed by remaining lip tissue, adjacent tissues such as the cheeks should be used.
6. Reconstruction by distant tissues, such as free-tissue transfer, should only be performed when there is insufficient local tissue to reconstruct the defect.

Reconstruction of the vermilion

Scars within the vermilion usually heal extremely well. Small vermilion defects can often be closed directly. Lateral superficial defects can be allowed to heal by secondary intention, as long as they are not too close to the white roll. Larger vermilion defects that do not involve the white roll require flap reconstruction, either lip (vermilion) flaps or non-lip (mucosal and tongue) flaps.

Vermilion flaps are best suited for defects close to the white roll and include vermilion advancement flaps or vermilion 'switch' flaps from the opposite lip. Vermilion advancement flaps are reliable flaps based on the labial vessel. The external incision is made directly on the vermilion border and the mucosal incision is made at the corresponding level inside the lip. In vermilion switch flaps the vermilion is cut in similar fashion to a vermilion advancement, but the flap is inset to the opposite lip. If only part of the vermilion is used, the secondary defect is closed directly at the time of inset. If, on the other hand, the full height of the vermilion is used, the defect in the donor lip is reconstructed by vermilion advancement at the time of flap division.

Mucosal advancement flaps are useful for total vermilionectomy defects after cancer resection. In such situations, it is important to carefully raise the mucosal flap in the plane between submucosa and muscle so as to maximize sensory innervation of the reconstructed vermilion. When a lip 'shave' has been performed for dysplasia, resulting in a shallow defect of vermilion, mucosa can be sutured directly to the skin without undermining. Mucosal advancement is also indicated for broad defects that are remote from the vermilion border. These flaps can be raised in V-Y fashion or as bipedicled flaps.

When mucosa is insufficient, tongue flaps can be used. They are usually raised on the lateral border of the tongue and can be anteriorly or dorsally based for vermilion reconstruction. The anteriorly based lateral tongue flap provides more bulk than the dorsally based flap. Tongue flaps are performed in two stages and are best reserved for lateral vermilion defects.

Reconstruction of the upper lip

Superficial defects of the upper lip, with intact orbicularis oris, can often be reconstructed by simple methods. Central defects involving less than half the distance between the philtral columns can either be repaired primarily or with a wedge resection. In all wedge resections, it is essential that the orbicularis muscle be accurately repaired for normal lip movement. If the defect is superficial and involves more than half of the central lip without crossing the philtrum, a full-thickness skin graft can give adequate results. In men, this graft could be taken from hair-bearing preauricular skin to restore hair growth. For superficial lateral defects which are less than half the width of the

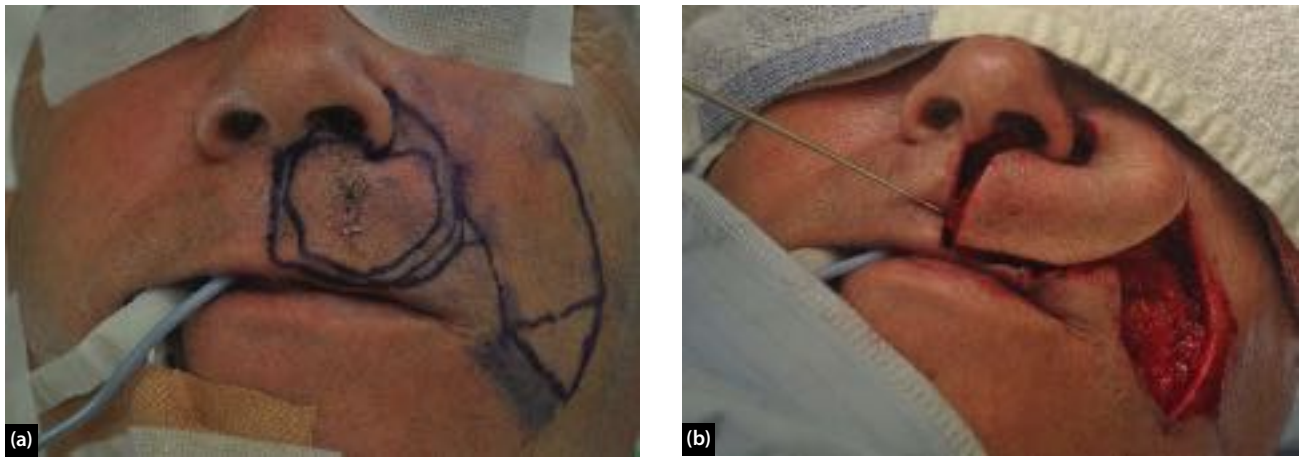


Figure 12.9 (a) Upper lip cancer prior to excision, showing design of a superiorly-based hair-bearing nasolabial flap from left cheek. **(b)** Nasolabial flap being transposed to defect.

lateral lip, wedge resection is a good option. When the defect involves more than half the width of the lateral lip, a local flap from the cheek may be a good option (**Figure 12.9**). Alternatively, a full-thickness graft can be just as acceptable.

The management of full-thickness defects of the upper lip depends on their size and location. Defects up to one-third in width can usually be closed directly, often with the aid of perialar crescentic excisions.[239] If primary closure is employed for central defects it can result in a narrow central lip, but this is usually cosmetically acceptable. When a central defect is greater than half of the upper lip, an Abbe-Sabattini flap from the lower lip is indicated (**Figure 12.10**).

In such situations the whole central lip subunit (from philtral column to philtral column) should be excised. The width and height of the flap should equal that of the upper lip defect. The flap is based on a single inferior labial artery and should ideally be harvested from the central lower lip. It should include the central raphe of the orbicularis oris muscles. When raising the flap, all elements of the lower lip are divided on the non-pedicle side, making a note of the location of the labial artery. On the pedicle side, the artery and a small cuff of mucosa are preserved. The donor defect on the lower lip is generally closed primarily before the flap is inset in layers to the upper lip and columella. The pedicle can be safely divided at 2–3 weeks. This flap is ideal for secondary correction of bilateral cleft lips when there is inadequate upper lip height and volume. A major disadvantage is the two stages required for transfer.

The Abbe-Sabattini flap can also be used to replace lateral lip defects larger than a third if the defect does not involve the oral commissure. If the lip switch flap is combined with perialar crescentic excision and lip advancement, this narrows the lateral upper lip defect so that a smaller flap is required from the lower lip.

For defects of the upper lip greater than 50%, a larger lip switch flap can be used in combination with bilateral perialar crescentic excision and advancement. The large lower lip donor defect can then be closed with the aid of bilateral Schuchardt medial advancement (**Figure 12.11**).

This technique will create microstomia which may require secondary revision. When performing lip-sharing procedures, it is important to maintain a balance between upper and lower lip length.

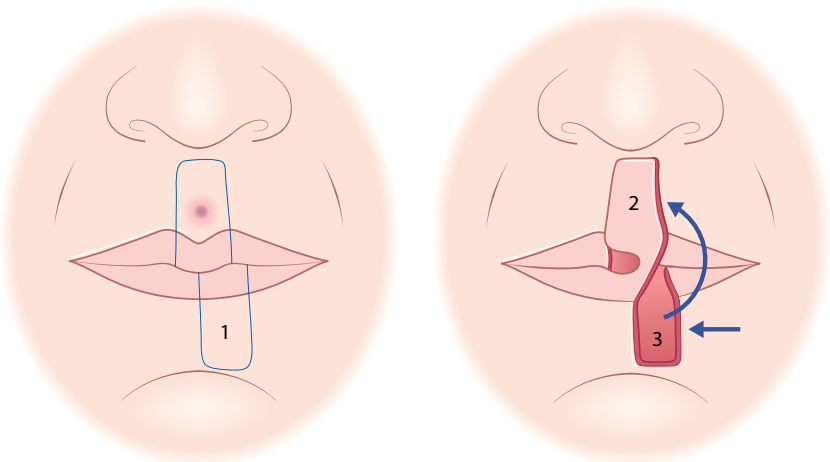


Figure 12.10 Abbe-Sabattini flap. 1. Design of flap and subunit excision. 2. Rotate the flap into the defect on its pedicle. 3. Close the donor site.

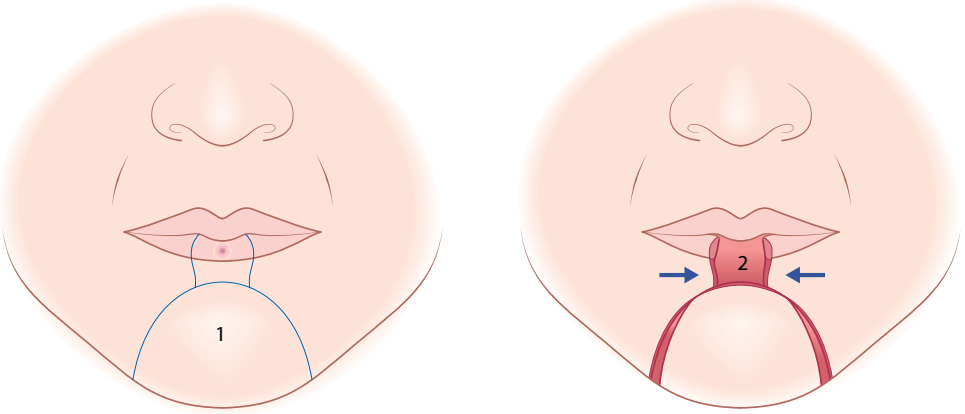


Figure 12.11 Schuchardt bilateral medial advancement flap.
1. Design the full thickness excision and the submental triangles for excision. 2. Advance the lower lip and chin to close the defect.

Subtotal and total upper lip defects are, thankfully, rare and reconstruction with local tissues may not be possible. Fortunately, the upper lip is not as important for oral competence as the lower lip, and static reconstruction with a folded soft-tissue flap, such as a radial forearm free flap, can provide a reasonable total upper lip reconstruction in a single stage.

Reconstruction of the lower lip

Superficial defects of the lower lip are usually best treated by full thickness wedge excision and primary closure, though extensive superficial defects may be simply reconstructed by a full-thickness skin graft, especially if the bulk of lip muscle is still present.

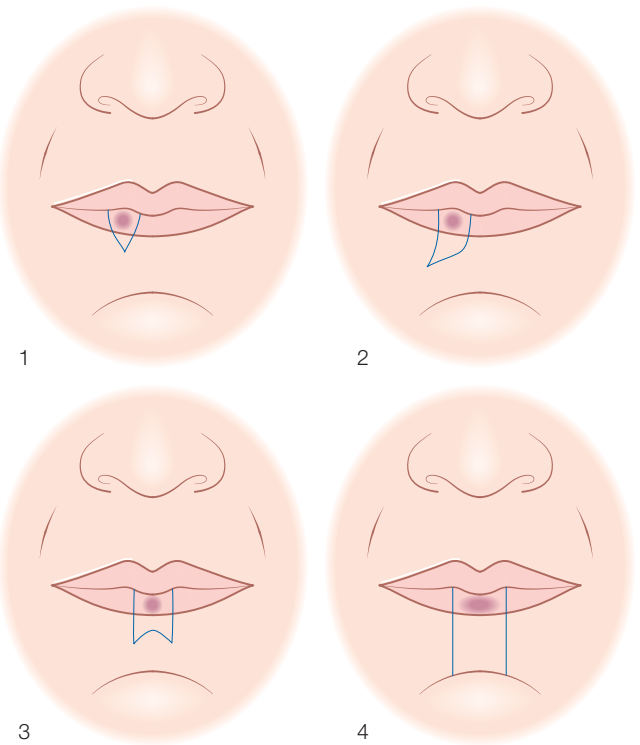


Figure 12.12 Greater than 1/3 lower lip defects closed with (1–3) various wedge techniques or (4) bilateral advancement flap-similar to the Schuchardt reconstruction (see Figure 12.10).

Techniques to reconstruct full-thickness defects of the lower lip can be conveniently classified into three groups, depending upon the size of the lip defect:

1. Defects of up to one-third of the lip width.
2. Defects of between one-third and half of the lip width.
3. Defects greater than half of the lip width.

DEFECTS OF UP TO ONE-THIRD OF THE LIP WIDTH

In the vast majority of cases, up to one-third of the lower lip can be removed by simple wedge excision (**Figure 12.12**) and the resultant defect is then closed primarily in layers. In elderly patients, with greater tissue laxity, this is never a problem (**Figures 12.13a** and **12.13b**).

In a minority of cases the wedge may have to be modified, by extending the incision unilaterally or bilaterally along the labiomental fold and excising skin crescents. This aids in advancing the remaining lip centrally. When the crescents are bilaterally extended as far as the mandibular border, accompanied by mucosal release incisions, this is known as the Schuchardt procedure.

DEFECTS OF BETWEEN ONE-THIRD AND HALF OF THE LIP WIDTH

Rarely, in some elderly patients with lax tissues, it may be possible to primarily close wedge excisions greater than one-third of the width of the lower lip. In the vast majority of cases, however, reconstruction of between one-third and half of the lower lip is best performed by using residual lip tissues, or lip sharing. Lip-sharing techniques preserve lip function and have satisfactory aesthetic results but can cause microstomia.

The Karapandzic technique[237]

This is arguably the best method to reconstruct lower lip defects which cannot be directly closed. This rotation-advancement technique can be used on both lateral and central lower lip (and sometimes upper lip) defects. A unilateral flap can suffice in lateral defects, but for central defects bilateral flaps are required.

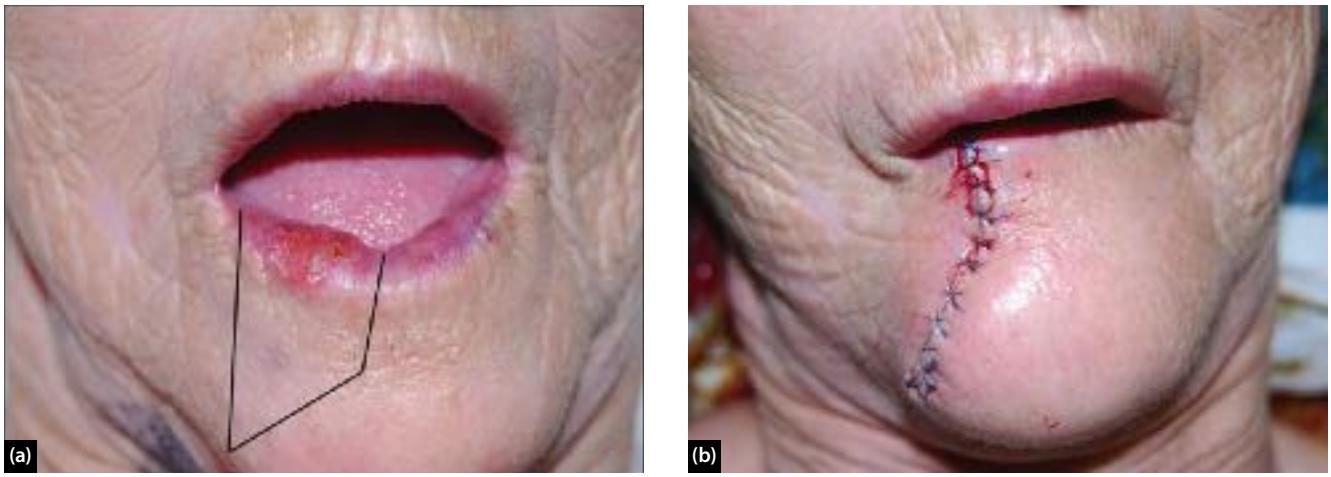


Figure 12.13 **(a)** Modified wedge excision of lower lip squamous cell carcinoma in an elderly patient. **(b)** Closure of wedge excision.

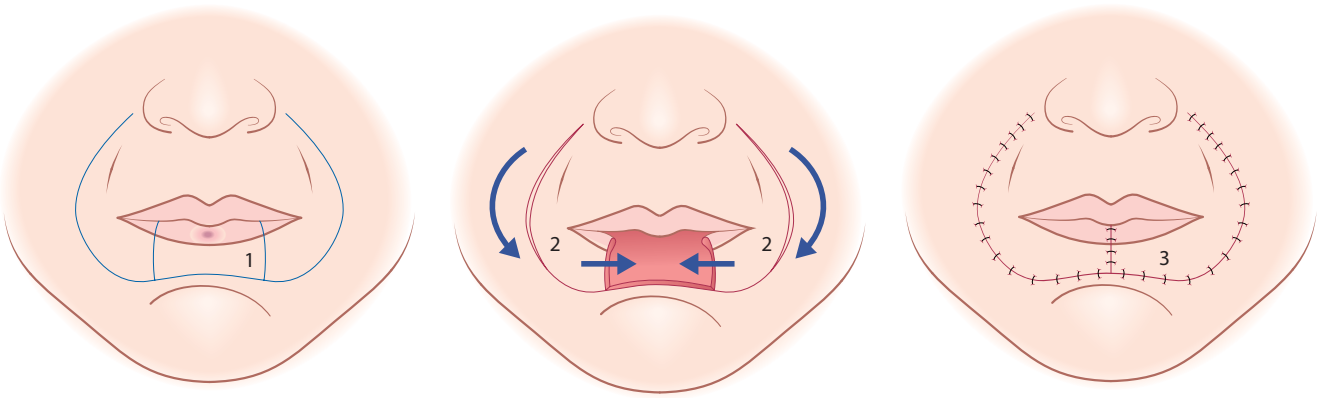


Figure 12.14 Karapandzic technique: 1: Mark out the excision margin and flap. The flap should be the same height as the lip at all points around the flap. 2: After full thickness excision including mucosa, mobilize the crescenteric flaps at equidistance from the free lip margin and full thickness for 2 cm from the postexcisional defect. With scissors the blood and nerve supply around the commissure is preserved. 3: Tension-free rotation of the flaps recreate the lower lip and vermilion.

The Karapandzic technique creates paired full-thickness mucomusculocutaneous lip flaps supplied by branches of the facial artery and preserves the sensory and motor nerves to the lip segment (**Figure 12.14**). It is crucial that the skin incisions are made at a distance from the lip margin equivalent to the height of the lip defect, especially at the commissures, in order to restore normal lip height. It should be noted that the superior incisions are normally placed lateral to the nasolabial creases for this purpose. The mucosal incisions are parallel to the skin incisions but are much shorter: usually about 2 cm on each side. For central lower lip defects, the lip depressor muscles have to be completely divided bilaterally to allow the flaps to move medially. For large defects, the superior incisions are deepened through skin, fat and the superficial layer of facial muscles, with the buccinator and orbicularis oris being preserved. During this manoeuvre, the delicate vessels and nerves to the lip must be carefully preserved. It is important to note that the nerves enter the flaps radially. After flap rotation the superficial muscle layer should be reattached to the orbicularis. For relatively small defects, it is possible to rotate the flaps without necessarily dividing the superficial facial muscles; instead the muscles in the superior incisions can simply be teased or stretched until the flaps are free to advance- the 'cut as you go' approach. After flap rotation, the wounds are closed in layers from within outwards, paying careful attention to the muscle layer. The functional results of this reconstruction are very good, but microstomia is inevitable with large defects (**Figure 12.15**).

Johanson's step technique[240]

This method of lip advancement can only be applied to lower lip defects. The lip lesion is removed as a rectangle and the remaining lateral lower lip segments are advanced medially. To aid this advancement, square or rectangular segments of skin and subcutaneous tissue lateral to the defect are excised in a descending stepwise fashion along the labiomental crease, until advancement of the lateral lip flaps can take place without tension. Each segment excised is approximately half the width of the lower lip resectional defect. The final (caudal) segment to be excised



Figure 12.15 **(a)** Markings for resection of squamous carcinoma of right side lower lip and design of contralateral Karapandzic flap. **(b)** Karapandzic flap assessed for adequate mobilization. **(c)** Karapandzic flap inset. **(d)** Good aesthetic and functional result.

is triangular in shape. As the flaps advance medially, the 'steps' are closed (**Figure 12.16**). The lip should then be closed in layers, with careful reconstruction of the orbicularis. The functional results of this technique are comparable to that of Karapandzic, but the scar can appear unnatural. Reconstruction of larger defects will lead to microstomia.

Lip switch flaps

Defects of the lower lip not involving the commissure can be reconstructed by an Abbe-Sabattini flap from the upper lip (**Figure 12.17**). The flap should be half the width of the lip defect, in order to avoid excess shortening of the upper lip and to evenly distribute tissues between the upper and lower lips.

These flaps lead to an insensate, adynamic segment of lip, and, though a degree of reinnervation eventually occurs, are better suited for upper lip reconstruction. Their main advantage is that they do not blunt the oral commissures.

Defects close to the commissure can be reconstructed in a single stage by the Estlander flap (**Figure 12.18**). This technique is similar to the Abbe-Sabattini flap but reconstructs the oral commissure, though the new commissure is blunted.

The functional results of lip switch flaps are satisfactory, but not comparable to the Karapandzic or Johanson techniques.

DEFECTS GREATER THAN HALF OF THE LIP WIDTH

For larger defects, lip-sharing procedures such as the Karapandzic lip reconstruction can be used when tissue laxity allows (**Figure 12.19**). This preserves lip function, but a degree of microstomia will inevitably occur and secondary revision will usually be required. When the lip defect is greater than three-quarters, in the majority of cases there will be insufficient lip tissue for a satisfactory reconstruction. In such cases, the next best option is to use adjacent tissues. Such reconstructions can achieve satisfactory aesthetic results, but function is always suboptimal.

The Freeman modification of the Bernard-von Burow procedure

The Bernard-von Burow procedure reconstructs the lower lip by medially advancing the cheeks (**Figure 12.20**). Cheek advancement is facilitated by the excision of full-thickness

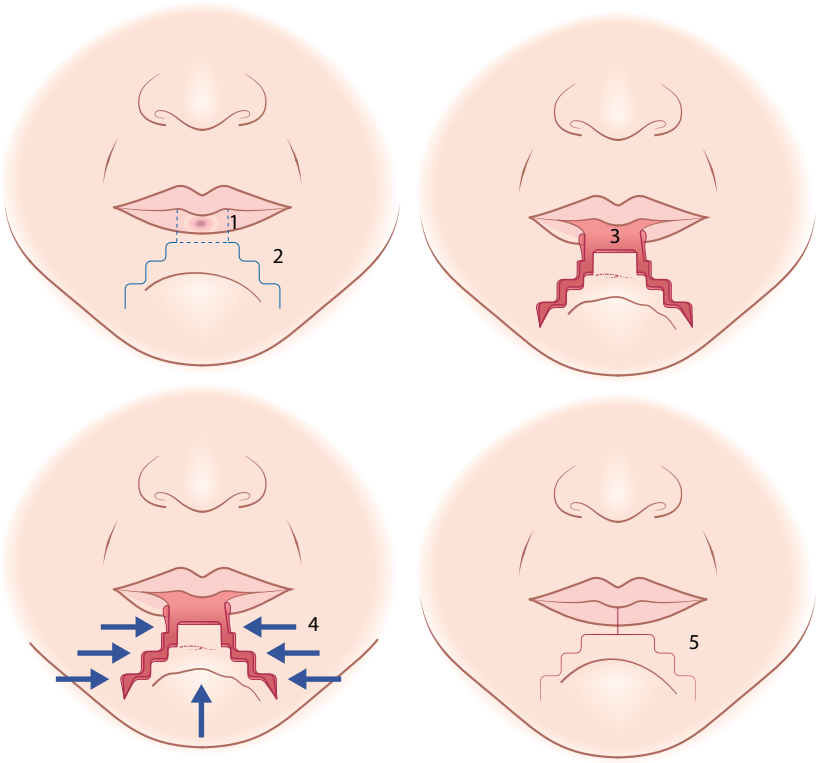


Figure 12.16 Johanson step technique for central defects of the lower lip. 1. Mark out the lesion. 2. Plan the step incision around the labiomental sulcus/chin subunit. 3. Full thickness excision of lesion and incise the step reconstruction full thickness. 4. Bring the medial lip excision margins together and advance the step flaps. 5. Closure.

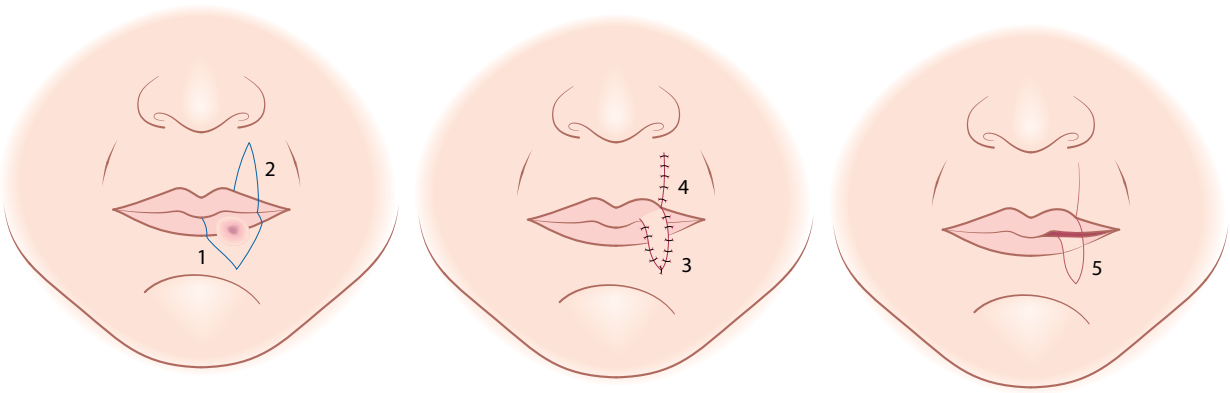


Figure 12.17 Reversed Abbe-Sabattini Flap to one-third lower lip lesion. 1. Lesion marked out for excision 2. Flap design; 3. Full thickness incision of the upper lip flap with the medial free margin of the upper lip inserted in the lateral margin of the lower lip excision. 4. Donor site closure. 5. The medial pedicle is divided and inset at 7 days.

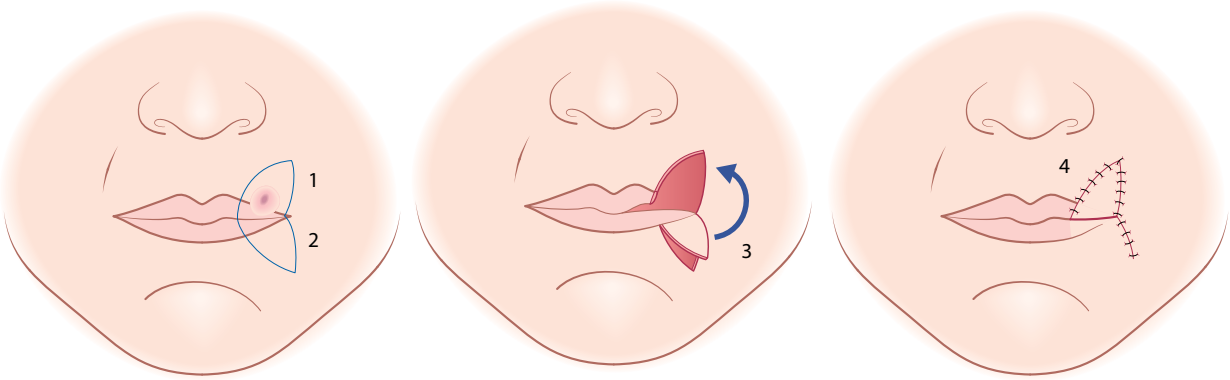


Figure 12.18 Abbe-Estlander Flap for partial commissure reconstruction: 1. Lesion marked out. 2. Corresponding flap marked to allow the medial lower lip pedicle to become the new commissure. 3. Rotate the flap into the defect. 4: Inset and closure of donor site.



Figure 12.19 **(a)** Melanoma of central lower lip and design of bilateral Karapandzic flaps. **(b)** Bilateral Karapandzic flaps inset.

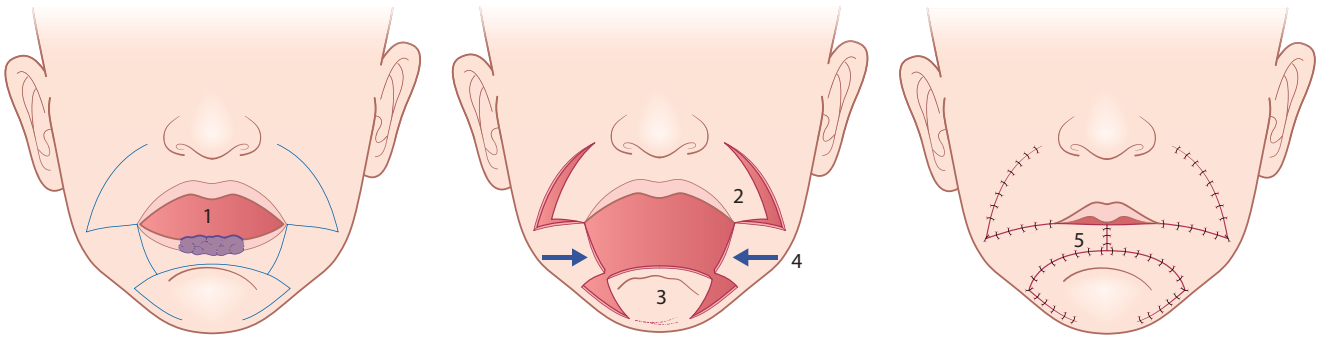


Figure 12.20 Modified Bernard-von Burow technique for up to total lip reconstruction. 1. Lesion marked out and flap with two superior and two inferior Burow's triangles marked out. 2. Burow's triangles are excised into subcutaneous tissue lateral to nasolabial folds. 3. Around the labiomental fold Burow's triangles are excised to allow medial rotation of the lower cheek flaps. 4. Medial advancement of the cheek flaps. 5. 3-layered closure of the midline with a mucosal flap reconstruction of the vermilion.

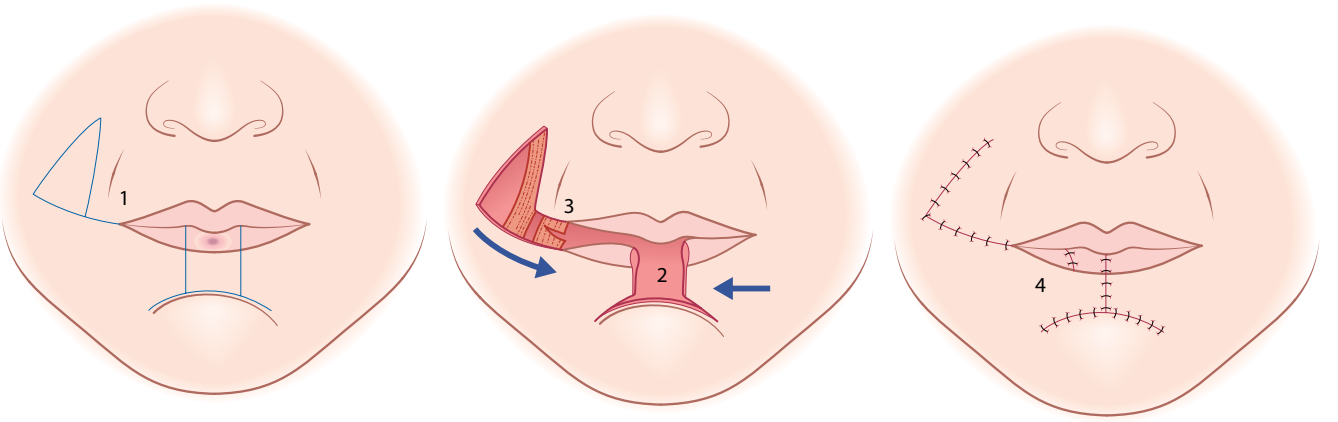


Figure 12.21 Unilateral Freeman modification of the Bernard-von Burow procedure. 1. Mark out excision margin and lateral nasolabial triangle. 2. Advance lower lip into defect. 3. Excision of tissue superficial to the muscle will allow lateral advancement whilst incision of the muscle lateral to the commissure will facilitate a commissuroplasty.

triangles of cheek tissue above and below the defect at the nasolabial fold. The width of the triangular excision is equal to the width of the defect. When both cheeks are advanced, the base of each triangle is half the width of the lip defect. The vermilion is reconstructed by tongue flaps. Webster's modification of this technique mobilizes cheek mucosa to reconstruct the vermilion.

The Freeman modification of the Bernard-von Burow operation is probably the best current cheek advancement technique (**Figure 12.21**).

Freeman converted the lower incision of the Bernard-von Burow operation from a horizontal one to a curved one, following the natural junction between the lip and chin. Only skin and fat is removed in the triangular



Figure 12.22 **(a)** Subtotal defect of the lower lip, with left cheek advancement performed and right Karapandzic flap designed. **(b)** Intra-operative appearance. **(c)** Immediate post-operative appearance. **(d)** Appearance at 3 months.

excisions, in contrast to the full-thickness tissue excision of the older procedure.

Bilateral cheek advancements can be used for total lower lip reconstruction, but there can be significant facial scarring. For the best function, it is important to reconstruct the orbicularis muscle. An alternative for total or subtotal lip reconstruction is to combine unilateral cheek advancement with a contralateral Karapandzic flap (**Figure 12.22**).

The 'bandoneon' technique[241]

A bandoneon is a type of concertina, which is particularly popular in Argentina as an accompaniment to Tango. A mucomusculocutaneous flap from the lower lip can be stretched like a 'bandoneon' and advanced to reconstruct lower lip defects up to two-thirds in width. A zigzag incision through skin, muscle and mucosa is made laterally from the lip defect as far as, or just beyond, the contralateral oral commissure. The incision is placed at the junction of lip and chin. The lower lip flap is then completely freed and stretched towards the lateral border of the lip defect and sutured in three layers (**Figure 12.23**). The zigzag incision facilitates this stretching, akin to the stretching of a bandoneon. In central defects, bilateral flaps can be raised.

Because the orbicularis oris is preserved in the flap, functional outcomes of this reconstruction are good. The oral commissure is shifted medially, however, and microstomia can result from large reconstructions.

The steeple flap[242]

This is an island flap of full-thickness tissue from the cheek. The lower lip defect is first converted to a rectangle. The lower line of excision is then extended laterally for a distance equal to the height of the resectional defect. Two vertical lines are drawn cranially from this line for a distance equal to the length of the lip defect. Thus, a rectangular island flap is marked out to the same dimensions as the rectangular lip defect. A triangle is marked on top of the proposed island flap – this will allow straight-line closure of the wound. The facial artery and its branches are marked with the aid of a hand-held Doppler probe. The flap is then incised full-thickness on its superior, medial and inferior margins. On the lateral margin, the facial artery and a small cuff of soft tissue are preserved. Depending upon the site of entry of the facial artery into the flap, the flap is transposed into the lip defect with either its lateral or medial border forming the upper border of the reconstructed lip. An excess of mucosa is cut

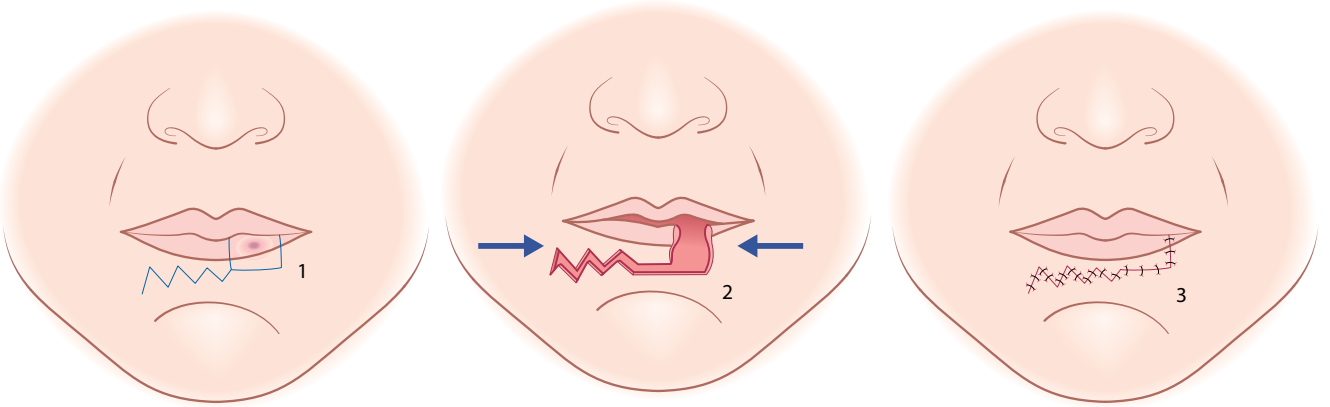


Figure 12.23 Bandoneon flap. 1. Mark out the excision margin and from the lower border of the excision extend a multiple w-plasty just past the commissure following the labiomental junction. 2. Full thickness excision of the lesion and full thickness incision along the lateral zig-zag markings through skin, muscle and mucosa. 3. Advance the lower lip to close the defect.

with the flap; this is used for vermilion reconstruction. For total lower lip reconstruction, bilateral steeple flaps can be used.

This technique avoids significant microstomia, but motor and sensory recovery may be delayed or incomplete.

Microsurgical reconstruction[238]

Subtotal and total reconstruction of the lower lip can be performed by free-tissue transfer, especially when there is scarring or inadequate laxity of the cheeks. Such reconstructions are never natural looking and have poor functional results and should only be used as a last resort. A folded free flap, such as the radial forearm flap, is the best option. The height of the reconstructed lip can be maintained by using the palmaris longus tendon to suspend the flap. This helps with oral continence. Should a sensate reconstruction be required, the lateral antebrachial cutaneous nerve can be anastomosed to the mental nerve.

KEY POINTS

- Lip tissue is precious and should never be discarded unnecessarily.
- Remaining lip tissue is the best option for reconstruction of small to medium lip defects.
- When a lip defect is too large to be reconstructed with remaining lip tissue, adjacent tissue such as the cheeks should be used.
- Reconstruction by distant tissues, such as free-tissue transfer should only be performed when there is insufficient local tissue to reconstruct the defect.

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CHAPTER 13

OROPHARYNGEAL TUMOURS

Terry M. Jones and Mererid Evans

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SEARCH STRATEGY

The data in this chapter are based on a search using the following keywords: head and neck cancer, oropharynx cancer, human papillomavirus, transoral laser surgery, transoral robotic surgery, intensity-modulated radiotherapy (IMRT) and clinical trials.

INTRODUCTION

The rapid increase in the incidence of Human papillomavirus – associated oropharyngeal carcinoma (HPV+OPSCC) seen in many countries of the developed world over the last several decades has resulted in a major healthcare problem which requires a major reassessment of the way oropharyngeal carcinoma is diagnosed and treated.

This discrete and novel disease entity presents in younger, fitter, more affluent patients who drink less alcohol and smoke less tobacco compared with patients who present with HPV negative (HPV-) squamous cell carcinoma of the head and neck. Paradoxically, their tumours, which typically present with clinicopathological features (multiple cervical lymph nodes with a high prevalence of extracapsular spread) traditionally considered as harbingers of poor outcome, respond more favourably to treatment.

Whilst this is to be welcomed, contemporary treatments result in high levels of early and long-term toxicity, particularly impacting negatively on swallowing function. As a consequence, greater numbers of younger patients, whilst being cured of their disease, are left with poor swallowing function which has a major impact on health-related quality of life.

Although most patients with HPV+OPSCC do well, a subgroup of patients, who are currently undetectable prior to treatment, together with patients with HPV-OPSCC, still do poorly. This dichotomy in presentation and outcome has resulted in a clinical conundrum for those clinicians treating patients with OPSCC. Whilst, on the one hand there is an urgent need to find novel de-intensified treatments which maintain the advantageous survival outcomes but confer better swallowing outcomes for patients with HPV+OPSCC, there is also a need to define treatments which will improve survival for patients with HPV-OPSCC.

This quest for novel treatments, as well as renewed interest and use of transoral surgical approaches, has re-opened the debate regarding the role of surgery in OPSCC.

Moreover, a better understanding of the biology of HPV+OPSCC is essential if truly novel treatments and accurate methods of risk-stratification are to be developed – particularly in this exciting era of emerging immunotherapeutic interventions.

Prior to any attempt to de-intensify treatment or to accurately prognosticate, there is a need to develop assays with high specificity to ensure HPV status is accurately determined. This necessity has resulted in significant research efforts over recent years to define the most appropriate assays and testing algorithms.

As well as simply trying to understand the emergence of HPV+OPSCC, the advent of prophylactic vaccination and its role in the prevention of HPV+OPSCC has resulted in an urgent need to understand the epidemiology

of HPV+OPSCC better and, in particular, to define better the apparent wide geographical variation seen between and within countries.

Furthermore, in order to address the void of high-quality data relating to the management of HPV+OPSCC, several groups around the world have developed exciting clinical trials, the results of which are awaited with interest.

These issues, which will be discussed in greater detail in the following chapter, conspire to make it a fascinating and potentially rewarding time to be involved in the treatment of patients with HPV+OPSCC.

SURGICAL ANATOMY OF THE OROPHARYNX

The pharynx is a fibromuscular tube forming the upper part of the respiratory and digestive tracts. It extends from the base of the skull to the level of the sixth cervical vertebra at the lower border of the cricoid cartilage where it becomes continuous with the oesophagus. It is divided into three parts: the nasopharynx, oropharynx and hypopharynx. The oropharynx is bounded superiorly by the soft palate, inferiorly by the upper surface of the epiglottis (the lingual surface of the epiglottis to the tip is included in the oropharynx), anteriorly by the palatoglossal arches and the vallate papillae of the tongue and laterally by the pharyngoepiglottic folds. It follows that the posterior third of the tongue, including the vallecula, is included in the oropharynx as are the palatine tonsils situated in the lateral walls between the palatoglossal arches anteriorly and the palatopharyngeal arches posteriorly (previously called the anterior and posterior faucial pillars). The lateral wall, and therefore the tonsil, takes most of its blood supply from the facial artery. Laterally, there is a rich plexus of paratonsillar veins, which may be the source of serious venous bleeding during surgery. The section of posterior pharyngeal wall included in the oropharynx lies anterior to the vertebral bodies of C2 and C3 and extends from a horizontal line drawn through the hard palate cranially to a horizontal line drawn through the hyoid bone caudally.

The oropharyngeal wall comprises four layers. The inner mucosal lining is surrounded by the submucosa. Outside the submucosa is the muscular layer made up of the superior and inferior constrictor muscles, together with the stylopharyngeus, paltopharyngeus and salpingopharyngeus muscles. These, in turn, are surrounded by the outermost buccopharyngeal fascia layer which is separated posteriorly from the prevertebral fascia by the potential retropharyngeal space which is functionally important, allowing free movement of the pharynx on the vertebral column during swallowing, respiration, speech and exercise. The space itself, and the retropharyngeal lymph nodes contained within it, are also of importance in disease when considering the spread of oropharyngeal infection and malignancy.

Surgical access to the structures of the oropharynx may be achieved transorally, anteriorly via mandibulotomy or inferiorly and laterally from the neck. The route chosen will be determined by the anatomical site and/or nature of the pathology as well as the surgical aim.

Microscopic anatomy

The oropharynx, like the remainder of the pharynx, is predominantly lined with stratified squamous epithelium which is predominantly non-keratinizing although islands of keratinizing epithelium may be seen and become more numerous with age, presumably as a consequence of repeated mucosal trauma / irritation. Interspersed through the mucosa are numerous mucous secreting cells as well as minor salivary glands which are most concentrated on the oral surface of the soft palate.

The oropharynx also contains an abundance of lymphoid tissue, in particular the palatine and lingual tonsils which form the anterolateral components of Waldeyer's ring. It is important to appreciate that these aggregates of lymphoid tissue are covered by pharyngeal mucosa which, particularly in the case of the palatine tonsil, form epithelial crypts which extend deep towards the centre of the tonsils. A particularly large crypt is seen at the boundary of the caudal 2/3 and cranial 1/3 of the tonsil. This intratonsillar cleft is the remnant of the embryonic second pharyngeal cleft.

An appreciation of the histology of the structures of the oropharynx is important when considering the histiogenesis of the various tumours which may arise.

FUNCTIONS OF THE OROPHARYNX

The oropharynx is involved in three primary functions, namely swallowing, speech production (articulation) and host defence against ingested or inspired pathogens.

The movements of the muscular wall, base of tongue (BOT) and soft palate are critical in the former two activities, described in greater detail in Chapters 48, Physiology of swallowing and 60, Voice and speech production, whilst the lymphoid tissue of Waldeyer's ring is the primary effector of the latter.

TUMOURS OF THE OROPHARYNX

Benign

Whilst benign tumours may originate from any of the structures of the oropharynx, apart from mucous retention cysts of the vallecula and tonsil, they are extremely rare. Papillomas are the most common benign tumour and are often found incidentally on routine examinations of the throat.

In almost all instances where intervention is decided upon, surgery is the treatment of choice, the nature of which is dictated by the size, position and histology of the tumour.

Deep lobe parotid tumours, most commonly pleomorphic salivary adenomas, whilst not strictly tumours of the oropharynx, may present as an asymmetric mass protruding into the pharynx and/ or soft palate. Surgical excision as part of a partial or total parotidectomy procedure is usually recommended. In most cases, complete excision is achieved by a solely lateral approach as for a total parotidectomy although, on occasion, a combined approach, involving a lip-split mandibulotomy for access, may be necessary for larger or less accessible tumours.

Malignant

LYMPHOMA

Lymphomas arising in the oropharynx, whilst rare, are not uncommonly seen by otolaryngologist – head and neck surgeons. They are almost exclusively non-Hodgkin lymphomas and arise in the lymphoid tissue of the palatine tonsil or BOT. They particularly present in younger patients (45–55 years) and whilst diagnosed by biopsy, are thereafter treated by haemato-oncologists and accordingly their management is beyond the scope of this chapter.

MINOR SALIVARY GLAND TUMOURS

Salivary gland cancers account for up to 6% of all head and neck malignancies and therefore are rare. Approximately 20% of all salivary gland cancers arise in the minor salivary glands (MiSG) and in contrast to the parotid most (80%) tumours of the MSG are malignant. The hard and soft palate are the commonest sites for MSG cancers.

The World Health Organisation lists 24 different malignant histological subtypes, the four most common of which are mucoepidermoid carcinoma, adenoid cystic carcinoma, adenocarcinoma and salivary duct carcinoma.[1]

Surgical resection with adequate surgical margins is the primary treatment of choice. The surgical approach used for MSGs of the oropharynx will depend on the site and size of the mass and the likely functional deficit following resection, and may range from a transoral resection to a major open resection with microvascular free-flap reconstruction. Post-operative radiotherapy is often used, particularly in patients with high-risk factors, although the radiosenstivity of MSG cancers is highly variable. There is no evidence for the use of post-operative chemoradiotherapy Chemoradiotherapy (CRT) and elective treatment of the N0 neck is controversial. A recent systematic review, whilst accepting the lack of availability of good quality data, recommended the following:[2]

- Complete surgical resection should remain as the mainstay treatment.
- A therapeutic neck dissection should be used to treat patients with clinical or radiological evidence of cervical lymph node metastasis.
- An elective neck dissection for patients with no evidence of cervical lymph node metastasis should probably be reserved for patients with advanced stage or high-grade tumours, particularly for mucoepidermoid carcinoma and adenocarcinoma.
- Post-operative radiotherapy (RT) should be recommended for patients with adverse prognostic features such as T3 or T4 tumours, close or involved resection margins, high-grade, perineural or perivascular invasion and N+ disease.
- The use of PORT for T1-weighted and T2-weighted tumours in the absence of adverse prognostic features is not supported.
- For patients with inoperable disease, or who refuse surgery, primary RT should be considered.
- The value of targeted therapies for advanced and/or metastatic disease has yet to be confirmed.

OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

Epidemiology

Squamous cell carcinoma (SCC) is the commonest malignancy presenting in the oropharynx. Over recent decades, across the developed world, there has been a substantial increase in the incidence of oropharyngeal squamous cell carcinoma (OPSCC) affecting the tonsils, tongue base and soft palate. The incidence of OPSCC in the UK underwent a 2-fold increase between 2002 and 2011 [age-standardized rate 2002: 2.1 (95% confidence interval (CI), 1.9–2.2); 2011: 4.1 (95% CI, 4.0–4.3)].[3] (**Figure 13.1**) Whilst alcohol and tobacco use have been well documented as individual or synergistic risk factors for the development of SCC of the head and neck,[4] over the last three decades accumulating evidence has confirmed

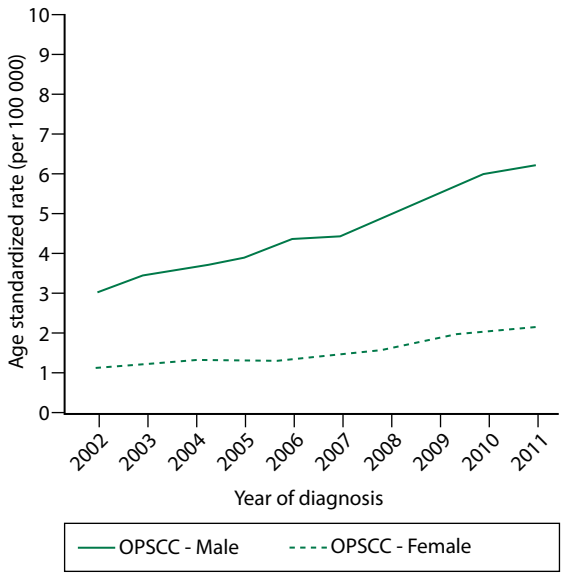


Figure 13.1 Age standardized rate of OPSCC in the UK, 2002–2011. Reprinted from Schache et al, *Cancer Res*; 2016 by kind permission AACR publications.[3]

that human papilloma virus (HPV) – specifically genotype 16 – is an additional, independent, risk factor for OPSCC.[5]

In a recent UK multicentre, cross-sectional study the HPV status of archival tumour tissue blocks collected from 1602 patients diagnosed with OPSCC between 2002 and 2011 was determined. The overall proportion of HPV-positive OPSCC was 51.8% [95% CI, 49.3–54.4] and this remained unchanged throughout the decade [unadjusted RR = 1.00 (95% CI, 0.99–1.02)]. In view of the doubling in incidence, it was concluded that the absolute number of both HPV-positive and HPV-negative cases in the UK was increasing (**Figure 13.2**).[3]

These UK data contrast with published data from other parts of the world where substantial variation has been reported in the proportion of OPSCC attributable to HPV between countries and time periods. This is likely to be a reflection of variations in multiple factors, which may include sexual behaviour and rates of genital HPV infection, as well as tobacco and alcohol consumption and highlights that trends in the aetiology of OPSCC must be considered in a population-specific manner.

Non-HPV associated OPSCC

HPV-OPSCC shares the same risk factors as other SCCs of the head and neck and the pathogenesis of malignant transformation is thought to be similar. Detailed consideration of the pathogenesis of non-HPV-associated OPSCC is therefore, provided in Chapter 6, Introducing molecular biology of head and neck cancer.

In contrast, HPV-associated transformation is limited to the oropharynx and is therefore considered in greater detail below.

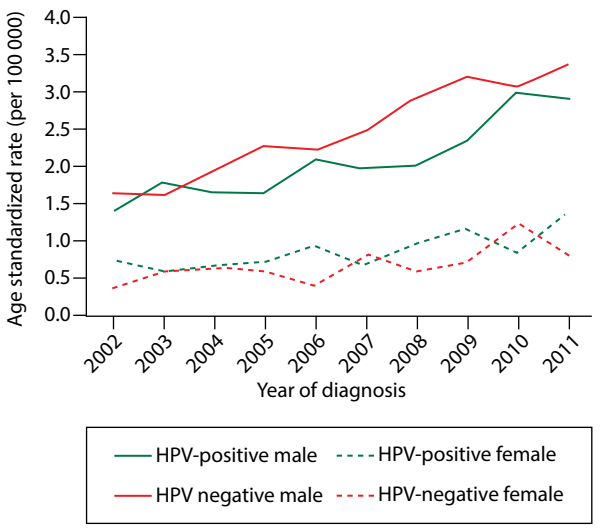


Figure 13.2 Estimated age standardized incidence of HPV-positive and HPV-negative OPSCC in the UK, 2002–2011. Reprinted from Schache et al, *Cancer Res.* 2016 by kind permission AACR publications.[3]

HPV-associated OPSCC

ORAL HPV INFECTION

Prevalence rates

An obvious risk factor for the development of HPV-associated OPSCC (HPV+OPSCC) is an oral infection with high-risk HPV (HRHPV). It follows therefore that an understanding of the epidemiology of HPV oral infection is important when trying to understand the development of HPV+OPSCC and this is comprehensively reviewed in Chung et al.[8]

Data from the US suggest that the prevalence of oral HPV infection is much lower than the prevalence of genital HPV infection: epidemiological studies involving a variety of US populations confirmed a genital infection rate ranging from 27% to 43% in females aged 14–59 years, compared with an oral HPV infection rate ranging from 0.9% to 7.5% in 13–30 year-old men and women.[9–14]

Systematic review data[15] which included 18 studies published between 1997 and 2009 involving ~4500 healthy individuals concluded that the rate of oral infection with any HPV genotype was 4.5% in comparison with 3.5% for infection with any HRHPV genotype and 1.3% for infection with HPV-16.

Similar rates were confirmed in a landmark National Health and Nutrition Examination Survey (NHANES) published in 2012.[9] This cross-sectional study, conducted in 2009–10, involved a general US population comprising ~5500 US men and women. All participants provided mouthwash samples from which DNA was extracted and tested for the presence of one or more of 37 HPV genotypes. Overall prevalence of HPV infection was 6.9%, whilst infection with HRHPV was 3.9% and infection with HPV-16 was 1%.

Whilst similar to the data obtained from the systematic review highlighted above, the overall prevalence identified in the NHANES study was higher, perhaps reflecting the fact that the NHANES data were collected some years later than much of the data included in the systematic review.

Whilst the 'snap-shot' infection rate with HPV-16, at 1%, is low, it is important to reflect that this amounts to >2 million US citizens with an oral HPV infection at any given point in time.

Interestingly, in common with anal and penile HPV infection rates, the prevalence of oral HPV infection has a bimodal distribution with respect to age. The first and smaller peak (~7%) is seen in patients in their early 30s whilst a second peak (~11%) is seen in patients, particularly men, in their early 60s.

Risk factors

Sexual activity appears to be a prerequisite of oral HPV infection as studies have shown that HPV infection coincides with sexual debut. There is also some evidence that vertical transmission, from infected birthing mother to child, is possible resulting in neonatal oral HPV infection.

Whilst an increased number of oral sexual partners have been demonstrated in most studies to correlate with oral HPV prevalence, some studies do not support this assertion.

The NHANES study confirmed that oral HPV infection is increased 8-fold in sexually active individuals compared with individuals who had never had sex (7.5% vs 0.9%). The data also showed that the prevalence of oral HPV infection increased with the number of lifetime sexual partners (vaginal or oral) and with recent sexual activity, with the highest prevalence (>20%) seen in patients reporting >20 lifetime sexual partners.

However, as sexual practices are co-linear, it is difficult to ascertain with precision which sexual practice may result in transmission in any given situation. This is perhaps reflected in the data published by Kreimer et al,[16] which confirmed, in a multi-national study of healthy men, that men who reported never performing oral sex had a similar rate of oral HPV infection to those who reported performing oral sex (3.8% vs 4.1%).

It has been hypothesized that auto-inoculation (oral infection transmitted from infected genitalia in the same individual) may be a significant route of oral HPV infection. There is however, scant evidence to support this. As well as the wide discrepancy between genital and oral infection rates in the same individual, meta-analysis data confirm only a 27% HPV type-specific concordance between genital and oral infection in dually infected women.[17]

It is also clear that additional risk factors are important in the development of oral HPV infection. The NHANES study confirmed that male gender and tobacco use were also important risk factors, as 10% of men were infected in comparison with 3% of women and individuals smoking >21 cigarettes per day had a 20-fold increased risk of oral HPV infection compared with non-smokers. Kreimer et al[16] also established that current tobacco use resulted in a doubling of the odds of an oral HPV infection.

Natural history

As with the epidemiology of oral HPV infection, detailed knowledge of the natural history is also lacking. Existing data suggest that the vast majority of oral HPV infections are cleared within 1 year of infection. For example, Kreimer et al,[18] showed that 85% of incident infections were cleared within 1 year which is similar to the data reported by Moscicki et al,[19] for cervical cancer where they reported that only 10% of women had persistent infection 2.5 years after initial detection.

Link between oral HPV infection and OPSCC

As might be expected, oral HPV infection and other common risk factors have been shown to be associated with the development of OPSCC. For example, HPV-16 DNA is found in ~50% of oral rinses provided by patients with diagnosed OPSCC[20] and patients with OPSCC are 12 times more likely than patients without OPSCC to have an oral HPV infection, a risk which increases 15-fold when HPV-16 infection alone is considered.[21] Moreover, patients with HPV+OPSCC report an increased number of sexual partners.[9]

As well as being a risk factor for oral HPV infection, tobacco use is also associated with an increased risk of HPV+OPSCC.[22, 23] Although median tobacco use is less for patients with HPV+OPSCC compared with those patients with HPV-OPSCC, the majority of patients presenting with HPV+OPSCC are still current or past smokers.[22, 24]

What is clear from increasing numbers of studies is that tobacco use is a dose-dependent risk-stratifier of outcome for patients with HPV+OPSCC, accepting the fact that tobacco use is a likely surrogate of underlying tumour genome mutation load and genetic instability.[6, 7]

Molecular biology of human papillomavirus infection

Virology

The link between HPV and OPSCC was first postulated as early as 1983 by Syrjanen et al[25] A subsequent and increasing volume of clinical data have confirmed its association and HPV-16 is now considered a causative agent.[5]

HPV is a member of the family of papillomaviridae, a virus family recognized in 2004 by the International Council on Taxonomy of Viruses.[26]

The papillomaviridae, together with polyomaviruses, are non-enveloped and contain a circular double-stranded DNA genome. Instead of a phospholipid bilayer envelope derived from the host membrane on infection, they comprise icosahedral capsids in the absence of an envelope.[27] They are obligate epitheliotropic human pathogens in that they have a predilection for infecting human epithelium.

The double-stranded DNA (dsDNA) HPV genome is approximately 8 Kb long and contains eight genes, six of which are expressed early in an infection (*E1, 2 & 4–7*) whilst two are transcribed later in the viral infection cycle (*Ll & 2*). *E1* and *E2* are regulatory genes, controlling the transcription of the remaining genes.[28] Of particular note, *E5–7* are involved in host-cell transformation, and are therefore potentially oncogenic, *L1* and *L2* are structural proteins necessary for the formation of the viral capsids.[29]

Currently, over 200 different genotypes of HPV have been identified. More than 150 have had their genomes completely sequenced and of these 12 have been designated 'high-risk' due to their propensity to provoke malignant transformation of the epithelial cells they have infected.[30] Of these, HPV-16 and -18 are the most important, causing ~70% of HPV-related cancers of which, in addition to oropharynx, the most common are cervix, vagina, vulva, anal and penile.

In OPSCC there is a greater dominance of the HPV-16 genotype compared to cervical cancer (~95% vs ~60%). Why this might be unclear, it may reflect the fact that the different mucosal environments may support the infection of specific genotypes. Conversely, it may reflect a difference in local genotype-specific mucosal immune response.[31]

HPV induced transformation

Little is known about the mode of transmission, route of infection or life cycle of HPV in the epithelium of the oropharynx. Accordingly, much reliance is placed on data derived from cervical cancer research for our current understanding of HPV infection, life cycle and oncogenesis.

Whilst extrapolation of this knowledge to the situation in the oropharynx is necessary as alternative data currently do not exist, this should be done with caution as although there are many similarities in the mucosal structure of both anatomical sites, there are also many differences.

In the transformation zone, between columnar and stratified squamous epithelium in the cervix, the squamous epithelium is stratified, organized in layers of increasing cellular differentiation from deep to superficial. The specific epithelial layers are the basal, para-basal, stratum spinosum and the most superficial desquamating strata.

The basal layer is in contact with the basement membrane and has a low turnover rate. In contrast, the para-basal layer has a high mitotic rate and therefore a rapid turnover of cells.

In the cervix it has been established that microabrasions of the surface epithelium facilitate virus particle infection of the basal and para-basal layer of cells (**Figure 13.3**).[32]

Following infection, the dsDNA viral genome remains in its circular, episomal form in the cytoplasm of the host cell. The virus harnesses the transcriptional and translational machinery of the host cell to instigate viral gene expression followed by viral replication, thereby completing its life cycle.

Transient infections are the norm in the cervix, however, a minority of individuals are unable to clear the initial infection resulting in a chronic inflammatory state. It is assumed that an even smaller percentage of these individuals then progress to develop cervical intraepithelial neoplasia (CIN) prior to developing invasive malignancy. It is important to note that no premalignant lesion similar to CIN has ever been detected in the oropharynx.

For the majority of the cases (85%) proceeding to malignant transformation, viral integration into the host genome is a critical step which results in disruption of the transcriptional repressor gene (*E2*) with the subsequent unregulated expression of the viral oncogenes *E6* and *E7*.[33] The mechanisms by which the remaining 15% of cases in which the dsDNA genome remains in its episomal form, yet still mediates malignant transformation,

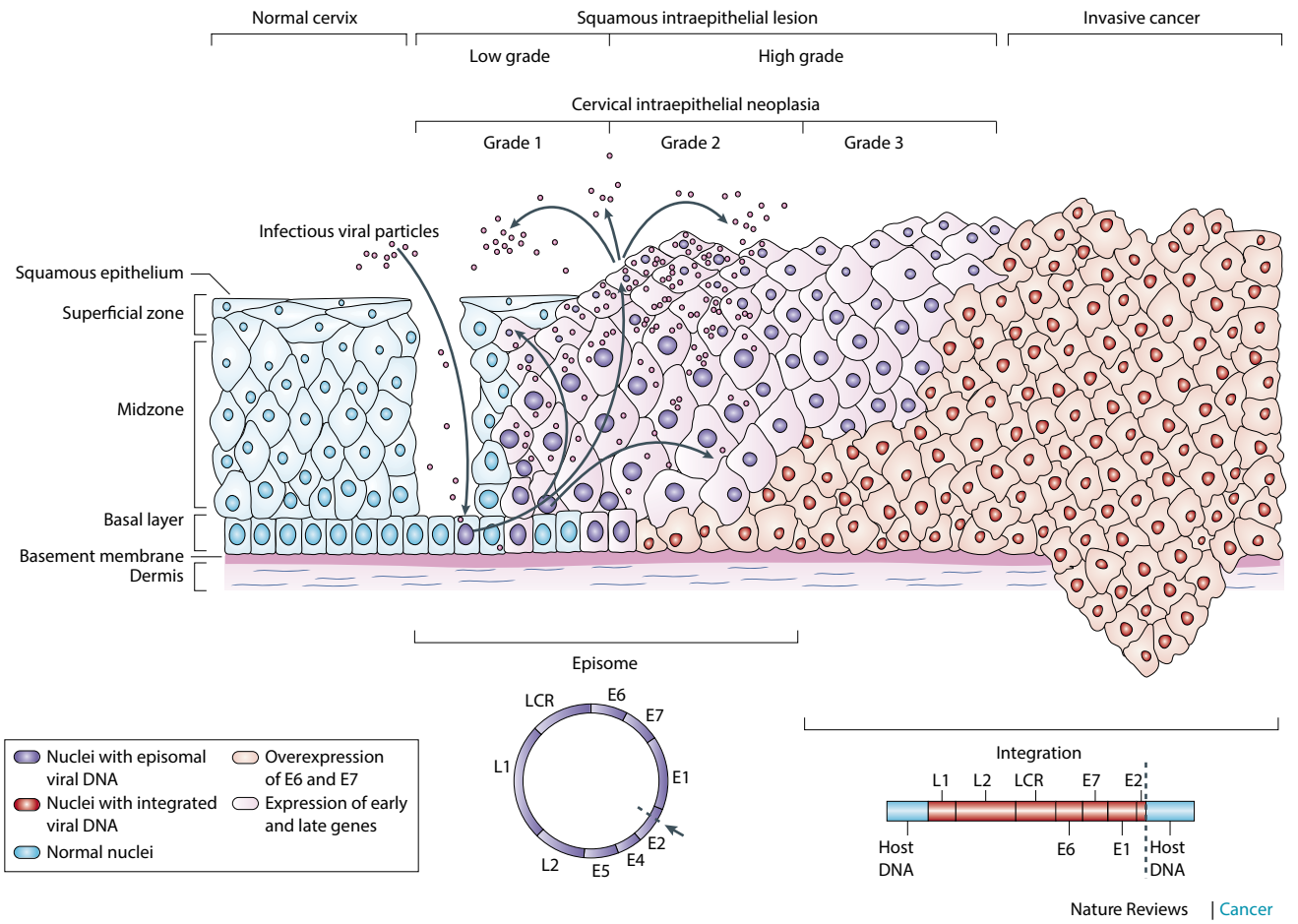


Figure 13.3 A schematic representation of (1) HPV virus infection of the basal layer of cervix mucosa as a consequence of the development of microabrasions. (2) The natural history of the virus life cycle, with virion production which is dependent upon and coincident with the differentiation of the mucosal epithelium prior to release as consequence on epithelial desquamation at the mucosal surface. **(3)** In contrast, the integration of viral genome into host genome resulting in basal cell immortality and cellular progression through dysplasia to invasive neoplasia. Reprinted Woodman CBJ, et al. The natural history of cervical HPV infection: unresolved issues. *Nat Rev Cancer* 2007; **7**: 11–22.

is the subject of ongoing research.[34] A simple model of integration defining the start of a transition to malignancy seems less likely when consideration is made of the relatively low (21–43%) viral integration rates seen in OPSCC.[35] However, epigenetic regulation of the viral Long Promoter Region, from which *E2* transcription is regulated, has been implicated.[36]

The genomes of all eukaryotic organisms are under tight transcriptional control.[37] Whilst certain genes act to switch other genes on to potentiate cell growth and division, antagonistic pathways exist to ensure the regulation of cell growth and division. In order for a cell to grow and divide it needs to advance through the cell cycle. There are four main periods of the cell cycle. G1 is a period of quiescence before the onset of S phase DNA replication. Following completion of DNA replication, S phase is followed by another gap phase, G2, in which cells prepare themselves for mitotic division during M phase. The eukaryotic cell cycle is tightly regulated and various molecular checkpoints exist throughout the cell cycle. At each checkpoint competing growth promoting and growth inhibiting signals are assimilated by the cellular molecular machinery and a 'decision' for the cell to proceed to the next stage of the cell cycle or for progression to become impeded is made. Tumour suppressor protein (TSP) expression is critical for the coordinated progression of the cell through each cell cycle checkpoint. Any perturbation of this checkpoint control mechanism will result in disordered cell cycling and aberrant cell growth, including the ultimate development of cancer.

Two of the most well understood TSPs are p53 and the retinoblastoma protein (pRb). p53 has been called the 'guardian of the genome' in light of its many varied roles in ensuring that cell growth and division does not continue unchecked as a consequence of DNA damage. Broadly, when a given cell is exposed to cellular stress and/or DNA damage, p53 is able to mediate cell cycle arrest followed by either DNA repair or programmed cell death if DNA repair proves impossible.

In contrast, pRb exerts its influence in late G1. If pRb is not phosphorylated it binds to and suppresses the E2F family of transcriptional activators. However, if pRb is phosphorylated it releases its inhibitory grip on the E2Fs allowing them to invoke the transcription of downstream genes whose actions are necessary for the cell to progress from G1 to S phase. Thus pRb is essential in preventing unregulated progression of cells from G1 to S. A notable product of downstream gene transcription is the expression of $p16^{INK4a}$ a protein, as will be seen below, whose expression is utilized to infer 'active' HPV infection.

It is via interactions with p53 and pRb that HPV exerts its primary oncogenic effects. Amongst other mechanisms, *E6* is able to bind p53 whilst *E7* binds pRb. In both cases this results in the degradation of both TSPs by the proteosome. Any cell losing the actions of these two key TSPs is well on the way to becoming a cancer. The effects of their loss will be subsequently augmented by a trend towards genetic instability and ultimately tumourigenesis promoted by the loss of their regulatory pathways (**Figure 13.4**).

HPV detection in clinical practice

HISTOPATHOLOGY

It has been well established that HPV+OPSCC presents with characteristic histopathological features. In contrast to HPV-SCCs which are typically moderately differentiated and keratinizing tumours arising from dysplastic epithelium, HPV-associated tumours are non-keratinizing, display a poorly differentiated predominantly basaloid morphology, are not associated with surface dysplasia but are associated with a high level of tumour infiltrating lymphocytes (TILs), the density of which have been shown to have prognostic value (**Figure 13.5**).[38] Although characteristic, these features are not diagnostic and a combination of molecular testing is required to establish a diagnosis of HPV-associated OPSCC in the oropharynx. Issues relating to the diagnosis of HPV+OPSCC is comprehensively reviewed in Robinson et al.[39]

MOLECULAR TESTING FOR HPV STATUS

It is insufficient to simply detect the presence of HPV DNA within a given tumour cell as a positive result may simply reflect a previous or bystander infection which resulted in inconsequential viral genome integration into the host genome or potential contamination with HPV DNA. Therefore, a necessary requirement for HPV testing is, in addition to demonstrating the presence of HPV DNA, to demonstrate some evidence of downstream HPV-driven biological activity. This is a particularly important issue when de-intensification of treatment – typically in the context of clinical trials (see later section) – is considered for patients with HPV+OPSCC.

TESTS FOR HPV DNA

Two types of diagnostic strategy are commonly used to detect the presence of HPV DNA within tumour cells.

In-situ hybridization (ISH)

This method relies on the use of a DNA probe labelled, for example, with a chromogen, the nucleotide sequence of which is complementary to the DNA sequence or gene under investigation. When applied to formalin-fixed paraffin embedded (FFPE) tumour samples, the probe will bind to the complementary sequence within the DNA of that tissue sample, thereby confirming its presence. The chromogen label allows the visualization of the bound probe by light microscopy. Kits are commercially available for the detection of HRHPV genotypes in FFPE tissue and are typically designed to detect the specific *L1* gene sequences, variations of which determine the specific genotype. A positive test result is confirmed by the presence of a blue dot under light microscopy (**Figure 13.6**). This technique allows localization of the HPV DNA to the host cell nucleus and whilst a punctate staining pattern is suggestive of HPV DNA integration it does not amount to categorical proof of this.

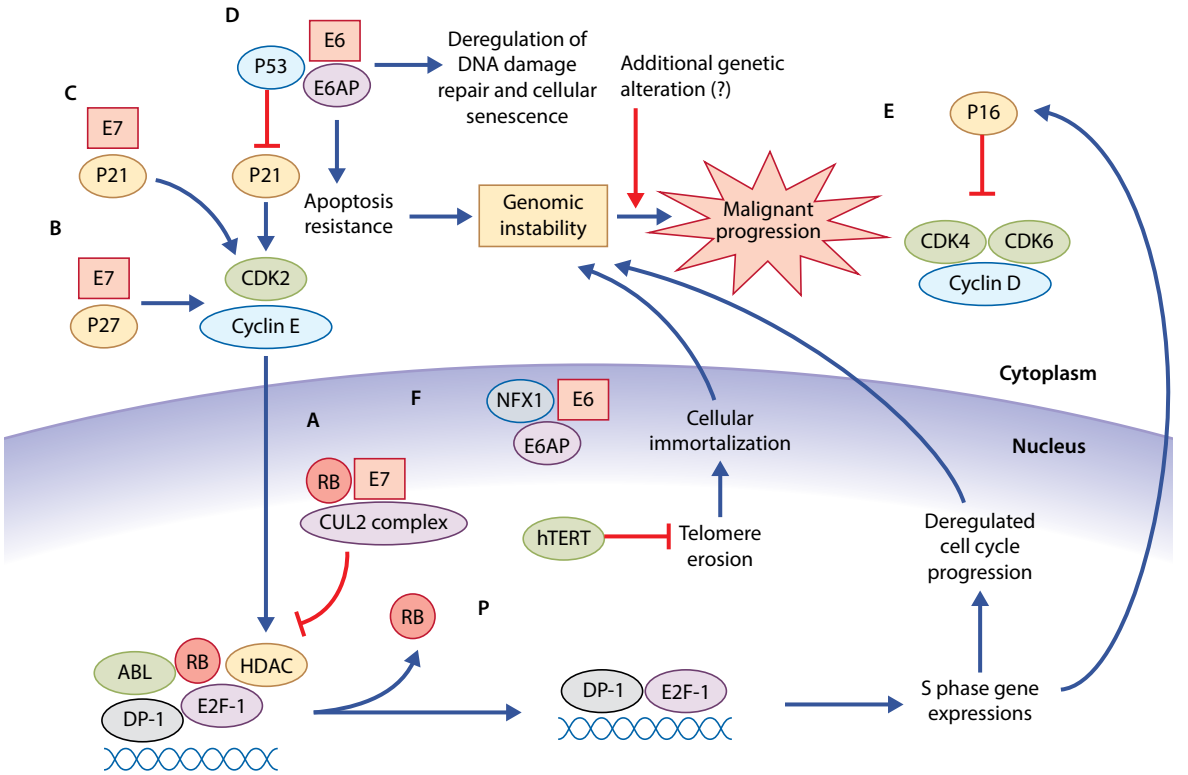


Figure 13.4 A schematic representation of the molecular pathways contributing to E6 and E7 mediated malignant transformation of normal keratinocytes. (A) Proteasomal degradation of retinoblastoma tumour suppressor protein (RB) as a consequence of binding by HPV oncoprotein E7 in association with the cullin 2 ubiquitin ligase complex. (B) Interaction between E7 and p27 resulting in inhibition of cell-cycle arrest. (C) Interaction between E7 and p21 resulting in inhibition of cell-cycle arrest. (D) Proteasomal degradation of p53 TSP as a consequence of binding by HPV oncoprotein E6 in association with the ubiquitin ligase E6AP. (E) Increased expression of $p16^{INK4A}$ as a result of loss of E2F repression which in turn results from RB degradation. (F) E6 and E6AP degradation of NFX1 resulting in the loss of repression of hTERT and a consequent reduction in telomere erosion thereby contributing to the development of cellular immortality. (Source adapted from Chung, CH & Gillison, ML.)[29]

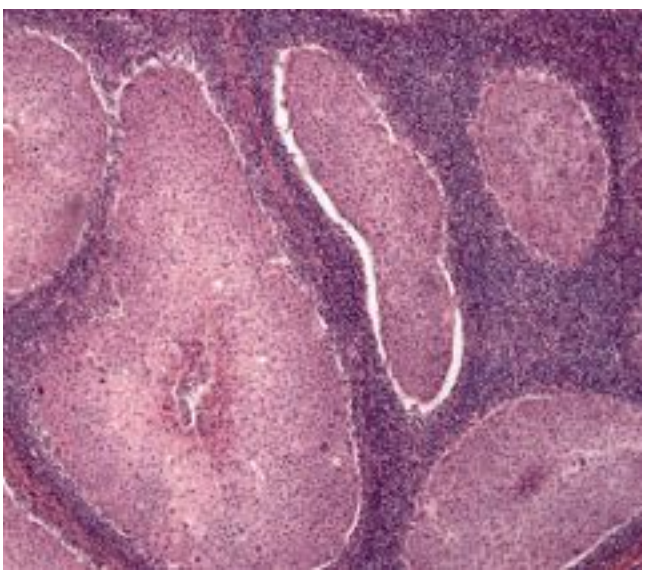


Figure 13.5 Image shows an H&E stained section of an oropharyngeal SCC. Tumour islands are surrounded by a dense infiltrate of lymphocytes. Magnification x50. By kind permission, Professor Gareth Thomas, University of Southampton.

Polymerase chain reaction (PCR)

This is a standard laboratory technique used to amplify short sequences of DNA. It is a highly sensitive technique which is able to augment a single copy of a given DNA sequence. Following the separation of double-strand DNA (dsDNA) into single-strand DNA (ssDNA), the presence of HPV DNA is detected using small targeted DNA sequences (primers) which are designed to bind to complementary DNA sequences on either side of the DNA segment (gene) under investigation: It is common to attempt to detect the presence of the HPV *E6* gene. Repeated cycles of the PCR will exponentially augment single copies of the specific gene under investigation allowing its detection with ease. This technique can be used on FFPE tissue although the best results are achieved using fresh tissue. Consensus PCR simply detects the presence of HPV DNA whilst real-time PCR is able to quantify viral load.

TESTS TO DETERMINE BIOLOGICAL ACTIVITY

Again two strategies are commonly used.

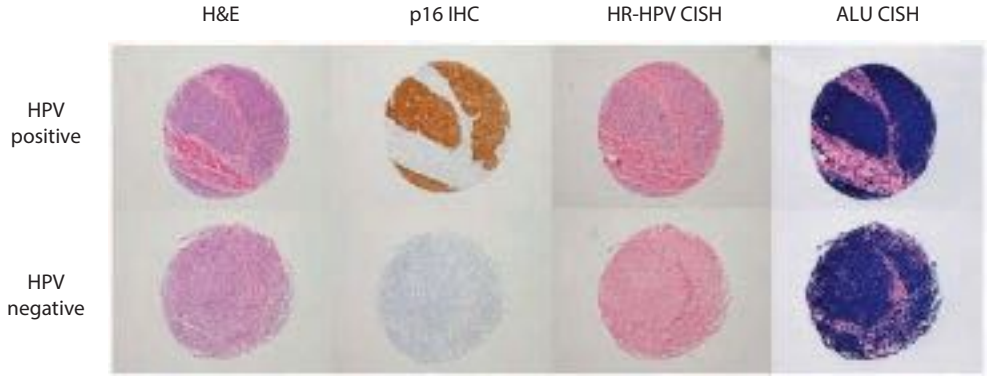


Figure 13.6 Panel of routine diagnostic tests applied for HPV status determination in OPSCC in the UK. **Columns from left**; Haematoxylin & Eosin (H&E), p16 immunohistochemistry (IHC), High-risk HPV chromogenic in situ hybridization (HR-HPV CISH), positive control (ALU CISH). **Top row** HPV positive OPSCC (p16 positive, high-risk HPV positive). **Bottom row** HPV negative OSPCC (p16 negative, high-risk HPV negative). (0.6 mm tumour cores). (By kind permission, Mr Andrew Schache, University of Liverpool).

Direct detection of E6 and E7 transcription

Quantitative Reverse Transcription – Polymerase Chain Reaction (qRT-PCR): Direct detection of E6 and E7 mRNA moves beyond merely detecting the presence of HPV DNA and aims to show HPV DNA is being transcribed resulting in the expression of E6 and E7 mRNA which have oncogenic properties and are presumed to be involved in tumorigenesis. The method most commonly used is quantitative reverse transcription PCR (qRT-PCR) by which complementary DNA (cDNA) is synthesized using the E6 or E7 mRNA transcript as a template. Thereafter, PCR, utilizing primers to the E6 and/or E7 cDNA sequence, is used to amplify the copy number of the cDNA transcripts. This technique is costly and labour intensive and has traditionally been restricted to frozen tissue. However, it constitutes the current gold standard assay for determining HPV biological activity.[24]

RNA-based Chromogenic In-situ-hybridization (RNA-ISH): This is a technique which also overcomes the dual testing requirements to firmly establish HPV status by detecting HPV specific E6/7 mRNA transcripts. This technique, which detects the presence of HPV E6 & E7 mRNA without the need for reverse transcription, is readily applied to the analysis of FFPE tissue. Therefore, in contrast to PCR techniques, it is potentially far easier to use in routine clinical practice. RNA-ISH performed on arrayed FFPE tissue cores has been shown to have a high level of sensitivity (97%) and specificity (93%) when compared with 'gold-standard' qRT-PCR performed on matched frozen tissue samples (**Figure 13.7**).[40] It is anticipated that RNA-ISH will become the routine standard for HPV testing in the foreseeable future. Commercial kits are readily available which contain probes for the E6 & 7 mRNA sequences of multiple HR HPV genotypes.

Surrogate markers

The surrogate marker most often used to detect HPV-induced transformation in the oropharynx is over-expression of $p16^{INK4a}$ using immunohistochemistry (**Figure 13.6**). It has been well established that the loss of $p16^{INK4a}$ is an early event in the development of tobacco and/or alcohol induced squamous cell carcinoma of the head and neck (SCCHN). However, by contrast, in HPV-associated SCCHN $p16^{INK4a}$ is typically intact. In non-transformed cells $p16^{INK4a}$ is negatively regulated by pRb. Consequently, when the effects of pRb are ameliorated by the actions of E7, $p16^{INK4a}$ levels are overexpressed.[41]

Immunohistochemistry to detect $p16^{INK4a}$ overexpression is easily performed on FFPE tissue samples. It is cheap, with well-established protocols and is widely available.

However, whilst its overexpression correlates well with clinical outcome[7] it is has low specificity for HPV infection as $p16^{INK4a}$ may also- be overexpressed by mechanisms other than the HPV-mediated inhibition of pRb in a minority (10–15%) of cases[24] for example Rb itself may be mutated.

Diagnostic algorithm

The Johns Hopkins Medical Institution diagnostic approach outlined by Westra[42] is one of the most widely accepted diagnostic algorithms in current use.

Using FFPE tissue, an initial screening of tumour tissue using IHC for $p16^{INK4a}$ is performed. Following this, all $p16^{INK4a}$ positive tumours undergo HPV-16 specific in-situ hybridization. All HPV-16+ / $p16^{INK4a}$+tumours are therefore designated as HPV-16+ve. The remaining minority of tumours which are $p16^{INK4a}$+/HPV-16 –ve then undergo further testing with an *in-situ* probe which is able to detect the presence of DNA of other HRHPV genotypes.

Such an algorithm is currently necessary in light of the variable sensitivity and specificity of the commonly employed individual tests and the need to demonstrate the presence of 'biologically active' HPV infection, and to ensure that tumours are correctly ascribed as being HPV+ve or not in the most cost effective and clinically convenient way.

CLINICAL PRESENTATION

Tumours which originate in the tonsil represent ~60% of all OPSCC tumours (**Figure 13.8**). In the context of HPV+OPSCC they are typically relatively small and

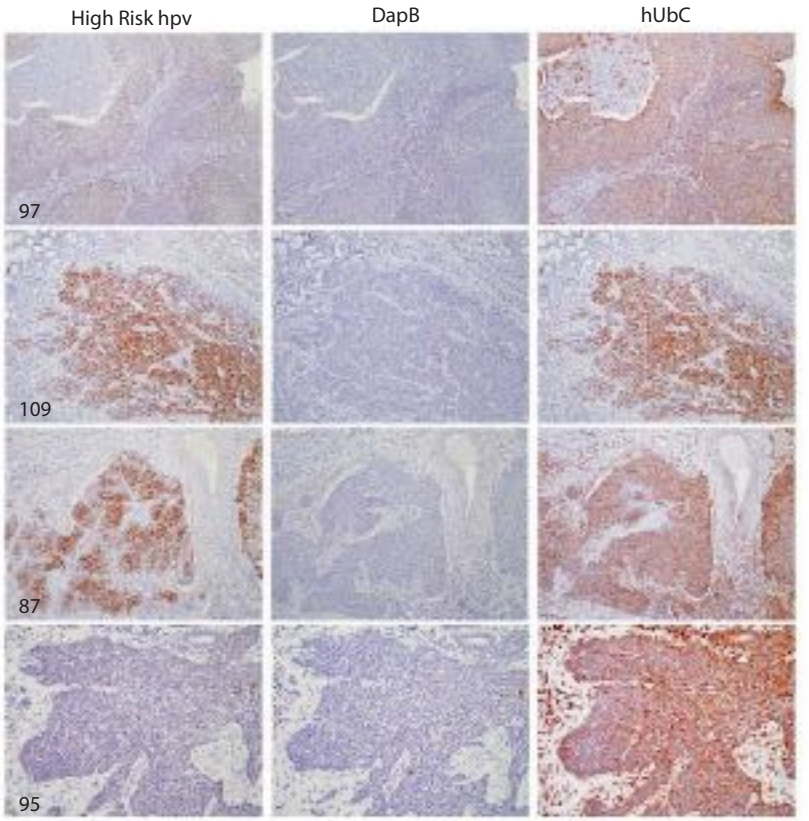


Figure 13.7 Photomicrographs of OPSCC stained using RNAscope with probes for high-risk HPV, dapB (negative control) and UBC (positive control). The cases demonstrate a range of positive staining patterns for high-risk HPV. Cases 109 and 97 showed strong and moderate staining, respectively, and contained HPV-16 E6/E7 mRNA by qRT–PCR. Case 87 showed strong staining and contained HPV-18 E6 mRNA by qRT–PCR. Case 95 showed weak staining and was negative for HPV-16 E6/E7 mRNA, HPV-18 E6 mRNA and HPV-33 E6 mRNA by qRT–PCR (false-positive result). Scale bars are equivalent to 200 mm for cases 109 and 87, and 50 mm for cases 97 and 95. (By kind permission, Mr Andrew Schache, University of Liverpool).



Figure 13.8 Intra-operative photograph of a T2 carcinoma of the right tonsil.

asymptomatic and patients present with cervical lymphadenopathy. They are also the most common site of primary tumours in the context of carcinoma of unknown primary origin (CUP).

As they enlarge, tonsillar tumours extend outside the confines of the tonsillar fossa. Their direction of local extension is unpredictable but can be cranial and medial onto the soft palate, caudal into the tongue base, posterolateral across the posterior pharyngeal wall, anterosuperior towards the retromolar trigone or laterally to involve the pterygoid musculature and other closely related structures in the neck, such as the carotid sheath. Disease which extends laterally and inferiorly may totally envelope the carotid sheath becoming contiguous with involved cervical lymph nodes. The extent of the local extension will obviously dictate the presenting symptoms which will range from being totally asymptomatic to having severe and intractable pain, often referred to the ipsilateral ear.

Base of tongue (BOT) make up ~30% of all OPSCC tumours. As with tonsillar OPSCC it is not unusual for BOT tumours to be asymptomatic or apparently occult, only coming to light during investigation of enlarged cervical lymph nodes. Local extension is typically towards and across the midline as well as into the intrinsic and extrinsic musculature of the tongue. Inevitably the greater the local extension the more likely symptoms relating to the tumour will be evident. Such symptoms can include odynophagia, persistent pain, including referred otalgia, dysphagia, altered speech, impaired tongue movement and bleeding.

Tumours of the oral surface of the soft palate make up the majority of the remaining 10% of OPSCC with posterior pharyngeal wall tumours presenting relatively rarely.

Soft palate OPSCC may present as a painful ulcerative lesion. Progression will result in involvement of the nasal surface of the soft palate, the superior tonsillar pole and/or the hard palate. These tumours not untypically present

as relatively small primary tumours with bilateral cervical lymphadenopathy. They are more likely to be HPV compared with OPSCC of the tonsil and BOT and accordingly typically behave in a more aggressive fashion with poorer outcomes.[3, 43]

Posterior pharyngeal wall tumours, which are also more likely to be HPV-, typically present late with symptoms of odynophagia, persistent sore throat and / or referred otalgia or dysphagia. They are notorious for presenting with widespread submucosal spread in all directions and as such are often underestimated on initial clinical assessment. The potential space between the pharyngobasilar and prevertebral fascia often acts as a barrier to deep spread and so tumour fixation as a consequence of deep spread to involve the prevertebral fascia is a very poor prognostic sign.

Patients presenting with oropharyngeal carcinoma present, broadly, in one of three ways:

- With symptoms related to the primary tumour with an enlarged cervical lymph node(s) which is/are usually painless and present at lymph node level II.
- With symptoms related to the primary tumour in the absence of an enlarged cervical lymph node(s) which is/are usually painless and present at lymph node level II.
- With an enlarged cervical lymph node(s) (usually painless and at level II) in the absence of symptoms related to a primary tumour (CUP).

It is well recognized that the presentation of patients with HPV+OPSCC differs significantly from the presentation of HPV-OPSCC.

HPV+OPSCC typically, although not exclusively, presents with a small primary tumour with multiple, enlarged, cystic cervical lymph nodes with a high prevalence of extracapsular spread (ECS). In contrast, HPV-OPSCC presents as a more typical head and neck cancer with larger primary tumours and relatively lower tumour burden in cervical lymph nodes.[6, 44, 45]

Symptoms relating to the primary tumour (soft palate, palatine tonsil, BOT or posterior pharyngeal wall) may vary quite considerably.

It is not unusual for patients to present with quite sizeable tumours in the absence of any obvious symptoms. In this patient group the primary tumour may be discovered incidentally following self-inspection or inspection of the mouth and oropharynx by a general medical or general dental practitioner, often in the context of seeking advice following a newly discovered neck lump. This is particularly the case for exophytic tumours of the palatine tonsil or BOT which have not invaded underlying musculature.

In contrast, ulcerative lesions which may be relatively small, may present initially with a sensation of sore throat with odynophagia. Larger lesions particularly of the BOT, posterior pharyngeal wall and tonsil may present with continuous pain exacerbated on swallowing and associated with referred otalgia and even dysphagia.

Incidental discovery of a painless enlarged cervical lymph node(s) whilst engaged in a routine task such as shaving or showering is a very common presentation for patients with OPSCC, especially HPV+OPSCC. If solitary, the presenting lymph node is almost invariably situated in lymph node level II whilst multiple lymph nodes will present typically as a chain extending from lymph node level II through III and IV, depending on the number and size of involved lymph nodes.

The presence of contralateral lymph nodes is not uncommon, especially if the primary tumour originates from the midline soft palate, midline BOT or midline posterior pharyngeal wall or is a non-lateralized tumour of the tonsil or BOT (i.e. a tumour encroaching or crossing the midline).

CLINICAL EXAMINATION

Oral cavity, pharynx and larynx

For patients presenting with signs and symptoms of an oropharynx cancer, a thorough examination of the head and neck should be undertaken as similar symptoms may result for tumours arising in one of several different anatomical sites of the upper aerodigestive tract (UADT).

The oral cavity should be carefully examined with the aid of a good light and tongue depressors. Inspection should include the buccal mucosa and lips, the palate, the tongue and floor of the mouth, all surfaces of the teeth and gums, opening and closing of the mouth and dental occlusion. Patients should be asked to elevate the tongue to the roof of the mouth and protrude the tongue towards both the right and the left. If tolerated by the patient, gentle intraoral palpation may be required to examine any swellings – this is particularly pertinent if a tumour of the BOT or tonsil is suspected as it is not unusual for tumours at these sites to be predominantly submucosal. Intraoral palpation may be combined with extra-oral palpation of the submental and submandibular lymph nodes and salivary glands to aid the characterization and/or localization of any swelling detected.

Following examination of the oral cavity, the oropharynx is then inspected with the tongue depressor placed firmly onto the dorsum of the tongue to depress it maximally. The anterior and posterior faucial pillars, the tonsil, retromolar trigone and posterior pharyngeal wall should all be inspected for colour changes, ulceration and swelling.

Pain and trismus arising as a consequence of pharyngolaryngeal or neck pathology may add to the difficulty of the examination but are significant clinical findings in their own right.

Following this initial inspection of the oral cavity and oropharynx, examination with a flexible fibre-optic endoscope passed through the nose, with or without topical anaesthesia, is essential. This will facilitate a high-resolution examination of the entire nasopharynx, oropharynx, larynx and often the hypopharynx. A camera attached to the endoscope permits the taking of high-quality photographs to record and present pertinent clinical findings.

Apart from the clinical scenario of an apparent CUP, an oropharyngeal tumour is usually readily detectable on clinical examination.

The neck

Even in the absence of an obvious neck node, it is essential to undertake a thorough examination of the neck if an oropharyngeal carcinoma is suspected. In order to do this the patient should be examined in the sitting position with the whole neck exposed so that both clavicles are clearly seen. The neck is inspected from the front and the patient asked to swallow, preferably with the aid of a sip of water. Movements of the larynx and any swelling in the neck are noted. The neck is then examined from behind with the chin flexed slightly downwards to remove any undue tension in the strap muscles, platysma and sternocleidomastoid muscles.

On examination for a lump in the neck, it is often helpful to ask the patient to point to any lump they have noticed first. Ask if the lump is tender. The neck is palpated bilaterally in a sequential manner comparing the two sides of the neck. All five palpable neck node levels (I-V) should be examined systematically as well as parotid and pre- and post-auricular nodes.

If a node is clinically obvious, either on inspection or on palpation, clinical examination should concentrate on ascertaining whether the node is solitary or whether there are multiple enlarged lymph nodes prior to estimating their size, determining their consistency (and whether they trans illuminate) and finally, whether they are mobile and therefore, by inference, amenable to surgical resection.

INVESTIGATIONS

1. **Patients presenting with a clinically evident primary tumour and an enlarged cervical lymph node(s) require the following investigations:**
   a. Ultrasound imaging of both sides of the neck followed by ultrasound guided fine-needle aspiration cytology (FNAC) of any neck nodes which are suspicious, on size and/or morphological criteria, of being involved with metastatic disease.
   b. Cross-sectional imaging (CT or MR) of the head and neck. Which imaging modality is employed is usually decided on the basis of local multidisciplinary team (MDT) preferences.
   c. A CT scan (or PET-CT scan) of the thorax and upper abdomen, in order to establish the absence (or presence) of a synchronous primary bronchogenic carcinoma or pulmonary and/or hepatic distant metastases.
   d. An examination under anaesthesia (EUA) of the UADT including a biopsy of the presenting primary tumour.

      Occasionally, it may be possible to biopsy an exophytic oropharyngeal tumour in the outpatient setting. Despite this, an EUA is still recommended if there are no contraindications in order to assess fully the extent and potential operability of the primary tumour.
2. **Patients presenting with a clinically evident primary tumour in the absence of enlarged cervical lymph nodes require the following investigations:**
   a. Cross-sectional imaging (CT or MR) of the head and neck. Which imaging modality is employed is usually decided on the basis of local MDT preferences.
   b. A CT scan (or PET-CT scan) of the thorax and upper abdomen, in order to establish the absence (or presence) of a synchronous primary bronchogenic carcinoma or pulmonary and/or hepatic distant metastases.
   c. An EUA of the UADT including a biopsy of the presenting primary tumour.

      As above, occasionally, it may be possible to biopsy an exophytic oropharynx tumour in the outpatient setting. Despite this, particularly if surgery is a treatment option and as long as there is no contraindication, an EUA is still recommended in order to assess fully the extent and operability of the primary tumour.
3. **Patients presenting with a clinically occult primary tumour with a clinically N+ neck (CUP), require the following investigations:**
   a. Ultrasound imaging of both sides of the neck followed by ultrasound guided FNAC of any neck nodes suspicious, on size and/or morphological criteria, of being involved with metastatic disease. This will, in most cases, confirm the diagnosis of metastatic SCC. If sufficient material is available, HPV testing of FNAC specimens is increasingly being advocated as detection of HPV in an enlarged metastatic cervical lymph node, strongly indicates that the primary site will be in the oropharynx – in particular the tonsil or BOT.[46, 47]
   b. In the absence of evidence of an obvious primary tumour on clinical examination, cross-sectional imaging (CT or MRI) of the head and neck is the usual next investigation of choice in many head and neck cancer centres.

      If the MRI scan confirms the presence of an obvious primary tumour then further investigation may proceed as outlined above with
   c. A CT scan (or PET-CT scan) of the thorax and upper abdomen, in order to establish the absence (or presence) of a synchronous primary bronchogenic carcinoma or pulmonary and/or hepatic distant metastases followed by
   d. An EUA of the UADT including a biopsy of the presenting primary tumour.

If, however, the MRI or CT scan of the head and neck does not delineate a likely primary tumour, then instead of proceeding with a CT scan of thorax and upper abdomen, a whole body PET-CT scan is the investigation of choice as has greater sensitivity for detecting primary tumour site,

whilst simultaneously investigating the presence of distant metastases.

If the PET-CT identifies, on the basis of increased FDG uptake, a likely primary site then and EUA should take place, to enable targeted examination and biopsy of the putative primary site.

In contrast, if PET-CT fails to identify a putative primary site an EUA should still be undertaken to allow a detailed inspection of the UADT taking particular note of the ipsilateral tonsil and BOT as these are the most likely sites of a small primary tumour. In the absence of an obvious primary tumour of the tonsil or BOT, the ipsilateral post nasal space and piriform fossa should be inspected.

If a primary tumour is still not revealed, at least the ipsilateral tonsil should be removed and either biopsies or a formal mucosectomy of the ipsilateral BOT should be performed and sent for histological assessment. Some clinicians would also advocate taking biopsies of the mucosa of the fossa of Rosenmüller and the ipsilateral piriform fossa.

Removal of the contralateral tonsil +/- a contralateral BOT mucosectomy is advocated by some clinicians.[48–50] However, this is a subject of much debate which revolves around the likelihood of detecting a tumour in the contralateral tonsil or tongue balanced against the morbidity of the procedures. To date, robust data do not currently exist to mandate this approach.

In all cases, biopsy of primary site tumours should be subjected to HPV testing. At the very least, this should involve immunohistochemistry for $p16^{INK4a}$ overexpression as described above as this has prognostic significance. If, however, as part of a clinical trial, de-intensified treatment is an option, then serious consideration should be given to additional testing for HPV DNA as outlined in the diagnostic algorithm above. Taking this dual testing approach minimizes the risk of de-intensifying treatment for the small proportion of patients who have tumours which overexpress $p16^{INK4a}$ but which are, in fact, HPV-.

Ultrasonography +/– fine needle aspiration cytology of a cervical lymph node

High-resolution ultrasound scanning (USS) has an established role in the contemporary management of head and neck cancer as the enumeration and characterization of cervical lymph nodes which contain metastatic tumour has a profound impact on outcome. It is common for USS +/- FNAC to be offered as part of a 'one-stop' neck lump diagnostic service in many head and neck centres.[51, 52]

Although USS and FNAC are operator-dependent and therefore should only be undertaken by specialists in the technique, it has been established that USS is more sensitive than palpation in the detection of enlarged cervical lymph nodes (97% vs 73%) and provides high specificity when combined with FNAC in the diagnosis of nodal metastases (93%). Moreover, ultrasound-guided FNAC is more accurate than non-image-guided FNAC.[53]

Magnetic resonance imaging (MRI)

MRI is used in many centres as the primary imaging modality of the head and neck. Continued development of MRI software and hardware ensure the ongoing improvement in MRI to distinguish pathology from normal anatomy. MRI is performed according to defined sequences. Three sequence parameters form the basis of head and neck imaging. T1-weighted images provide a high degree of spatial resolution of normal anatomy. T2-weighted images in contrast preferentially detect water content and therefore pathology. A short tau inversion-recovery (STIR) sequence also preferentially detects water content but in addition, suppresses the fat content of adjacent tissue to further enhance the contrast of pathological lesions. Intravenous gadolinium enhances the imaging of the vascular attributes of a tumour which adds to the contrast of a STIR sequence which may be of particular advantage when imaging apparently occult disease (**Figure 13.9**).

Accordingly, the soft tissue contrast features of MRI are superior to CT and therefore, in the absence of any contraindications (for e.g. inability to tolerate the increased scanning duration and/or intolerance to gadolinium), MRI is the preferred imaging option for oropharynx pathology.

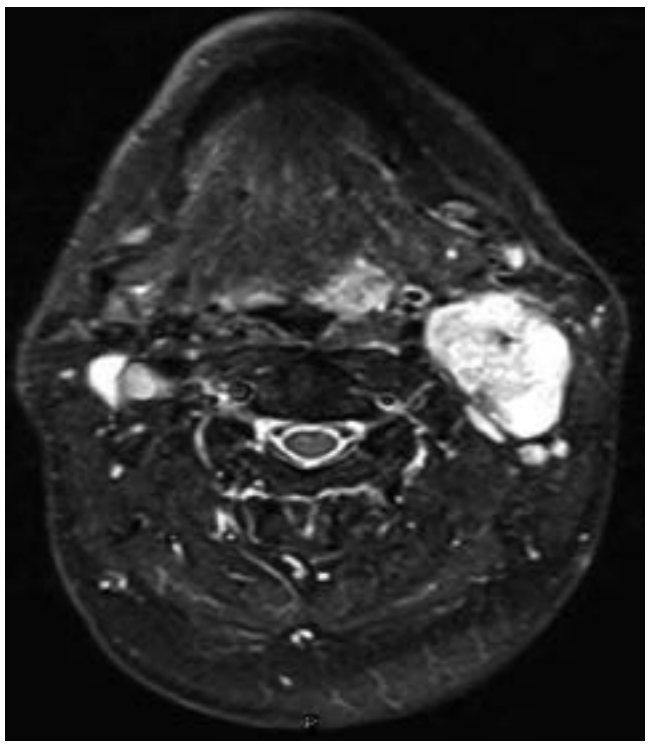


Figure 13.9 An axial short tau inverted-recovery (STIR) sequence magnetic resonance image (MRI) of a T2N2b carcinoma of the left base of tongue.

Computed tomography (CT)

Despite the widespread use of MRI in the staging of locoregional disease volume, CT is possibly the mainstay imaging modality for head and neck disease in most centres as it is widely available and its use in the staging of head and neck cancer is firmly established. It also facilitates imaging of the head and neck at one sitting which has obvious advantages for the patient and healthcare provider. Current imaging protocols ensure that imagine acquisition is rapid thereby reducing movement artefact as well as providing an advantage for patients unable to tolerate the more prolonged imaging sequence required for MRI. It is preferable to MRI if bone imaging is required but soft tissue resolution, particularly when staging soft tissue tumour extent, is comparatively inferior. Contrast-enhancement, using iodine-based contrast medium, based on a more rapid opacification of normal soft tissue than tumour provides added discrimination between tumour and normal. Contrast enhancement is contraindicated in patients with renal impairment. Contemporary CT software allows the high-resolution reconstruction of images to provide highly detailed 3D reconstruction which may be of considerable value when planning bony cuts, resection or reconstruction. The main downside of CT is the significant radiation dose incurred.

Positron emission tomography combined with CT (PET-CT)

The principle upon which this technique is based is the differential uptake, by cancer cells, of various labelled tracers, the pattern of which can then be fused with conventional CT images to create a functional map of the tumour. 18 fluoro-deoxyglucose (18-FDG) is the most commonly used tracer in clinical practice. Cancer cells rely preferentially on glycolysis, rather than aerobic respiration, for energy production (the Warburg effect). Accordingly, glucose derivatives, including 18-FDG, are preferentially transported into malignant cells and trapped. This differential transport is not exclusive to cancer cells as uptake is also greater in metabolically active cells such as inflammatory cells or active muscle. In light of this, PET-CT has to be undertaken in a quiet environment, when the patient is relaxed and preferably prior to the taking of diagnostic biopsies. Despite these precautions, PET-CT has a relatively low specificity with a high false-positive rate.[54, 55] Following administration and uptake, the labelled glucose tracer is detectable with a gamma camera. Metabolic activity is then accurately co-registered with the anatomical location defined by the CT images, thereby creating the functional map. In the context of OPSCC, PET-CT is most commonly used in the context of CUP, as recommended in the UK Royal College of Radiologists Guidelines published in 2013 (**Figure 13.10**).[56]

Examination under anaesthesia (EUA)

An EUA is highly recommended for all patients presenting with OPSCC, even if the primary tumour is evident on clinical examination in the outpatient department. The aims of EUA are typically threefold.

- To take a diagnostic biopsy of the primary tumour, and/or to assess the presence of a primary tumour in cases where a primary tumour is not immediately evident on clinical examination in the outpatient department.
  (A biopsy of the primary tumour is essential for subsequent treatment planning – surgical or non-surgical – even if a positive FNAC diagnosis of a cervical lymph node has been previously obtained. Only in the relatively rare cases when an EUA is contraindicated (usually on the basis of patient fitness) should treatment proceed on the basis of an FNAC result alone.)
- To assess the locoregional extent of the tumour and its relationship to adjacent anatomical structures. This is particularly pertinent if surgery is being considered.
- To exclude the presence of a synchronous second primary tumour.

Following anaesthetic induction, the patient is placed in a supine position with the neck extended assuming there is no contraindication. The sequence of events may vary depending upon operator preference but the following steps are mandatory.

1. Palpation of the BOT and vallecula if access is possible as well as palpation of the lateral walls of the oropharynx and postnasal space.

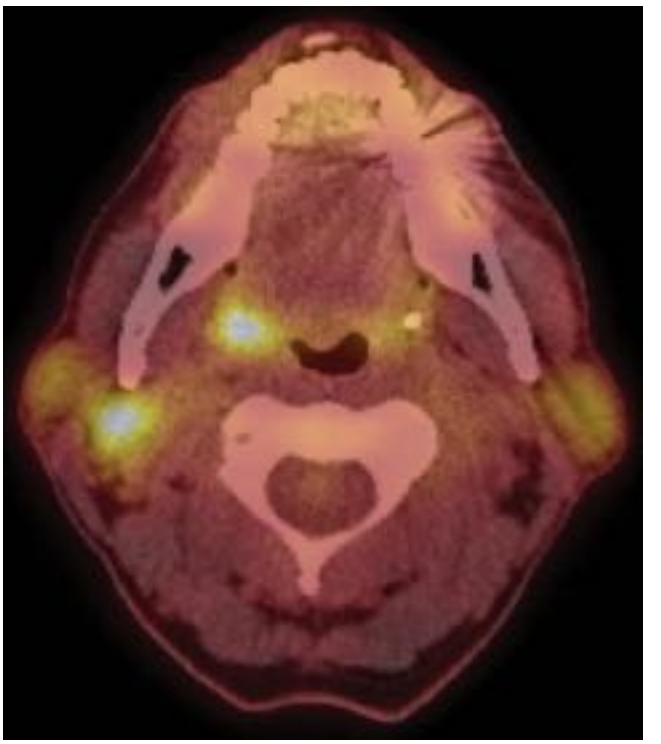


Figure 13.10 A fused axial section of an 18-fluoro-deoxyglucose (18-FDG) PET-CT scan showing increased 18-FDG uptake in the left tonsil and a left metastatic cervical lymph node.

2. An examination of the hypopharynx and cervical oesophagus, using rigid pharyngoscopes +/– a rigid fibre-optic light source.
3. A direct or rigid fibre-optic light source-assisted laryngoscopy.
4. Visual inspection of the oropharynx using an oropharyngeal gap and headlight.
5. A biopsy of any obvious or suspicious primary tumour.

Tonsil biopsy versus diagnostic tonsillectomy

If a primary tumour of the tonsil is evident then it is sufficient to take a representative biopsy to establish histological diagnosis.

If, however, following examination, it is considered that a likely primary tumour is contained within one tonsil a potential dilemma exists, particularly if transoral surgery is a primary treatment option. Traditional teaching would dictate that a diagnostic tonsillectomy is undertaken. However, this may compromise the reporting of surgical margins, complicate revision transoral surgery and adjuvant treatment decision-making. If transoral surgery is a primary treatment option then it may be preferable to either i) simply taking a representation diagnostic biopsy from the centre of the tonsil, avoiding the margins or ii) performing a tonsillectomy according the principles of TLM or TORS surgery. Adopting the former approach ensures that subsequent transoral surgery is not compromised whilst adopting the latter approach ensures that a diagnostic biopsy and appropriate resection are undertaken at the same time and adjuvant treatment decision making is not compromised.

In a third scenario, on EUA of a patient presenting with CUP, if the ipsilateral tonsil appears normal, undertaking the tonsillectomy according to TLM or TORS principles ensures that resection is appropriately completed in the context of a primary tumour being diagnosed on subsequent histological examination and appropriate adjuvant treatment decision-making can proceed unhindered following the completion of an ipsilateral selective neck dissection on a separate occasion.

STAGING

The staging of head and neck cancer will be dealt with in detail in Chapter 4, Staging of head and neck cancer. However, it is worth highlighting recent changes to the TNM staging recommendations published in the American Joint Committee on Cancer (AJCC) Cancer Staging Manual 8th edition[45] and the Union for International Cancer Control (UICC)[57] which are of particular importance to the staging of OPSCC. The changes and the rationale behind them are reviewed in detail in Lydiatt et al.[47]

1. In contrast to the AJCC 7th edition which considered staging of cancers of the naso-, oro- and hypopharynx in one chapter, the AJCC 8th edition divides pharyngeal cancers into three separate chapters which consider the staging of nasopharynx, p16+HRHPV associated OPSCC (p16+OPSCC)* and p16–non-HRHPV associated OPSCC (p16–OPSCC) together with hypopharynx cancers.
2. In the 8th edition, T stages for p16+OPSCC and p16–OPSCC remain the same apart from two exceptions for p16+OPSCC.
   a. The Tis classification has been removed because a premalignant lesion has yet to be identified in p16+OPSCC and because of the absence of a basement membrane in Waldeyer ring epithelium, the presence of which is essential for a diagnosis of Tis.
   b. T4b has been removed as the outcomes for T4a and T4b categories are indistinguishable when considering p16+OPSCC. Consequently a single T4 category remains in the 8th edition.
3. A T0 category is no longer assigned to p16–OPSCC and other non-HRHPV cancers for example larynx, oral cavity and hypopharynx as an exact primary site is, by definition, unable to be established and therefore cannot be assigned to a specific anatomical subsite. In contrast, cytology specimens following FNAC of an enlarged lymph node in which the presence of metastatic carcinoma is confirmed can be subjected to testing for HPV and Epstein—Barr virus (EBV) status. (In this context and in contrast to the recommendation above, both HPV ISH and p16 overexpression is necessary for the confirmation of HPV status whilst the presence of Epstein Barr Encoded RNA (EBER) determines EBV association.)

   It is considered that demonstration of HPV status or EBV status safely allows the primary site to be determined as oropharynx or nasopharynx respectively and therefore, classification systems for p16+OPSCC and nasopharynx maintain T0 categories. (As does salivary gland because primary site can be determined on cytological findings).
4. As p16+OPSCC may be treated with primary surgery or primary RT +/– chemotherapy, separate clinical and pathological staging systems have been stipulated.
   a. The clinical, or cTNM, classification is designed for patients before treatment (regardless of the intended form of treatment) and employs information from physical examination and imaging.

* Importantly and contentiously, HPV status determined according to the diagnostic algorithm described earlier in the chapter is not mandated as HPV-ISH is not widely available in centres throughout the world and its interpretation is often difficult. Instead, p16 overexpression as assessed by immunohistochemistry (>75% expression with at least moderate staining intensity) is considered sufficient to allow re-classification of OPSCC into p16+HRHPV associated OPSCC (p16+OPSCC) and p16 – non-HRHPV associated OPSCC (p16–OPSCC).

In this classification system, the presence of one or multiple involved ipsilateral cervical nodes, all < 6 cm, is classified as N1. The presence of bilateral or contralateral involved nodes < 6 cm, is classified as N2, whilst the presence of any node > 6 cm is classified as N3.

b. The pathological, or pTNM classification is designed only to patients managed with primary surgery. When surgical data were considered, lymph node size, even > 6 cm, or the presence of bilateral or contralateral lymph nodes was not discriminatory. Instead, the number of involved lymph nodes appeared critical. Accordingly, the presence of one to four lymph nodes is classified as N1 whilst five or more positive lymph nodes of any size are classified as N2.

Why the presence of lymph nodes > 6 cm is discriminatory in cTNM staging but not pTNM staging is not clear.

5. Consideration of T and N staging together has led to the publication of three separate stage groupings for OPSCC: separate clinical and pathologic groupings for p16+OPSCC and combined clinical and pathologic groupings for p16−OPSCC. The separate p16+OPSCC clinical and pathologic stage groupings each have three categories (I, II, III and IV) whilst the p16−OPSCC combined clinical and pathological stage grouping has six categories, as per the 7th edition, (I, II, III, IVA, IVB and IVC). Stage II and IVC are reserved for the presence of distant metastatic disease in each classification respectively.

It is important to stress that although the TNM 8th edition is useful for prognostication currently, it should not be used to inform treatment decision-making as its role in treatment allocation requires prospective evaluation in randomized clinical trials or similarly robust studies. Therefore, the management principles for OPSCC described in subsequent chapters have not been modified for TNM 8th edition.

MANAGEMENT

The management of oropharyngeal carcinoma represents an increasing clinical challenge, both because of its rising incidence, particularly in younger patients as a result of HPV infection, and because of the significant technological advances that have occurred in radiotherapy and surgery over the last 10–20 years which have increased treatment options for patients, with little robust evidence yet of their relative merits.

This situation is further complicated by the clinical paradox that has been created following the emergence of HPV+OPSCC. HPV status is highly prognostic in OPSCC patients treated with CRT. In a landmark study, Ang et al retrospectively analyzed the outcomes of patients with stage III/IV OPSCC treated with CRT in the RTOG 0129 study by HPV status: 3-year overall survival was 82.4% in HPV+patients, compared to 57.1% in HPV-patients ($p < 0.001$). Similarly high survival rates for HPV+OPSCC have been demonstrated in patients treated with primary RT/CRT and surgery.[7, 24, 58–62]

However whilst patients with HPV+OPSCC, in general, do better in survival terms than patients with HPV-OPSCC, it must also be borne in mind that a sub-set of patients with HPV+OPSCC also do badly. Whilst high T-stage and number of involved lymph nodes are associated with poor outcome in this subgroup, smoking habit, which is assumed to be a surrogate of underlying tumour mutational load and / or genetic instability, also appears to be of importance.[6, 7, 43]

Currently HPV+ and HPV- OPSCC are managed according to the same treatment protocols, but the improved prognosis associated with HPV-positivity has raised the possibility that they could be managed differently. In particular, there is a need to continually strive for novel intensified treatments which will enhance survival in patients with HPV-OPSCC and the subgroup of patients with HPV+OPSCC who will do badly, whilst potentially considering de-intensified treatment strategies for patients with HPV+OPSCC who will do well, with the aim of maintaining their current good survival outcomes whilst reducing the frequency and severity of short- and long-term post-treatment adverse events.

There is an absence of randomized studies comparing primary surgical and non-surgical approaches in the management of OPSCC, resulting in a global lack of consensus between surgeons and oncologists as to how these cancers should be managed. The options are:

- For T1-T2 N0: Radical radiotherapy or transoral surgery and neck dissection(with post-operative (chemo) radiotherapy if there are adverse pathological features on histology).
- For other stages: primary CRT or surgery and adjuvant (chemo) radiotherapy.

Open surgery and microvascular reconstruction followed by post-operative adjuvant treatment was the historic treatment of choice for OPSCC and is still offered by some units. However, a 2002 retrospective review of 6400 patients with OPSCC in 51 studies showed similar rates of locoregional control, overall survival and cause-specific survival for patients treated with open surgery and post-operative RT (PORT), compared with those treated with primary RT +/− neck dissection, but a significantly higher rate of severe or fatal complications in the surgery group, together with worse functional outcomes.[63] These data raised concerns regarding the continued use of this approach and when combined with high-quality level I and meta-analysis data confirming that benefit of radiotherapy +/− cisplatin-based chemotherapy[7, 64] in the management of OPSCC, a major shift away from open surgery to CRT in the developed world has occurred.

This shift is reflected in UK data from successive National Head and Neck Cancer (DAHNO) audits which confirm that by the 10th audit, CRT was given more than twice as frequently as RT alone.[65] Similarly, data from the US has shown a linear rise (from 20% to > 60% of cases) in the use of CRT for the management of OPSCC from

1998 to 2009 with a concurrent decrease in the use of surgery and radiotherapy alone.[66]

Radiotherapy (RT)/concurrent chemoradiotherapy (CRT)

The primary rationale for the use of RT or CRT in treating OPSCC is organ preservation and also, importantly, to preserve function whilst achieving high cure rates. Data from randomized trials, such as RTOG 0129,[67] comparing CRT schedules confirm that this approach can result in good oncological outcomes, particularly in HPV+ OPSCC. However, it is worth reiterating that high-quality data comparing surgical and non-surgical approaches do not exist, despite RT and CRT becoming the accepted standard of care in many centres throughout the world for early and late stage OPSCC respectively.

Early stage T1-T2 N0-N1 OPSCC can be effectively treated with RT alone.[68] For radical treatment, RT is commonly delivered at a total dose equivalent of 70 Gy in 35 fractions and this may be delivered as a hypofractionated schedule of 65–66 Gy in 30 fractions.

For more advanced T and/or N stage (stage III/IV, TNM 7th edition) OPSCC, CRT is the standard of care, with a RT dose equivalent of 70 Gy delivered in 35 fractions together with concurrent cisplatin at a dose of 100 mg/m^2 given on days 1, 22 and 43 of the RT schedule. The GORTEC 94-01 study demonstrated a ≥20% 3- and 5-year survival benefit for the addition of chemotherapy to RT, albeit in the setting of low overall survival figures (3-year overall survival 51% vs 31%, p = 0.02, disease-free survival 42% vs 20%, p = 0.04 and locoregional control 66% vs 42% p = 0.03).[69] Furthermore, meta-analysis data in 17 346 patients confirmed that, for HNSCCs as a whole, concurrent chemotherapy confers an overall survival benefit of 6.5% at 5 years (p < 0.0001), compared to RT alone.[64] The benefit of adding chemotherapy to RT for the management of OPSCC specifically was confirmed in an additional systematic review.[70]

Weekly administration of low-dose cisplatin (40–50 mg/m^2) is an alternative to 3-weekly high-dose cisplatin which has become increasingly used in clinical practice in an attempt to improve tolerance and compliance. A recent meta-analysis of 4209 patients in 52 studies concluded that there was no difference in treatment efficacy, as measured by overall survival or response rate, between the low-dose weekly and high-dose 3-weekly cisplatin regimens.[71] The weekly regimen was associated with a higher compliance rate and was significantly less toxic with regards to severe (grade 3–4) myelosuppression, nausea and nephrotoxicity. The authors concluded that the weekly regimen needed to be prospectively compared with the standard 3-weekly regimen before being adopted into routine clinical practice. In the meantime, clinicians will continue to choose between regimens, based on institutional protocols, personal experience and patient fitness. In patients for whom cisplatin is contraindicated, concurrent carboplatin chemotherapy (3-weekly at area under the curve (AUC) 5 or weekly at AUC 2) is an alternative that is associated with less ototoxicity and nephrotoxicity.

Concurrent weekly cetuximab (a monoclonal antibody targeting the epidermal growth factor receptor (EGFR) may be given with RT if there is a contraindication to platinum chemotherapy. In a randomized trial, the combination of cetuximab and RT improved median locoregional control (24.4 vs 14.9 months) and median duration of overall survival (49 vs 29.3 months) after a median follow-up of 54 months[72] and this survival difference was maintained on long-term follow-up. The addition of cetuximab to concurrent CRT did not improve outcome compared to CRT alone in a subsequent trial.[73] The results of randomized studies conducted in the USA (RTOG 1016: NCT01302834) and UK (DE-Escalate: NCT01874171) comparing the efficacy and toxicity profile of RT with concurrent cisplatin vs RT with concurrent Cetuximab in HPV+OPSCC are awaited and may change the future standard of care for the non-surgical management of this disease.

Radical RT may be given alone for patients with advanced disease who are not fit for concurrent treatment, particularly if >70 years of age when the benefits of concurrent chemotherapy and cetuximab are reduced.

Induction (or neoadjuvant) chemotherapy

The use of induction chemotherapy (IC) may be beneficial in selected patients. The MACH-NC meta-analysis[64] showed an overall survival advantage for cisplatin and 5-FU chemotherapy compared to local therapy alone for the management of HNSCC, and IC had a relatively more pronounced effect on distant metastasis rate than concurrent CRT. The benefits of using IC prior to concurrent cisplatin-based CRT have not been convincingly shown: a recent meta-analysis which included all types of HNSCC showed that IC increases toxicity and does not improve OS compared to CRT alone.[74]

In the context of OPSCC, including HPV+OPSCC, the use of IC has been advocated for patients with advanced (T4, N3, N2c) disease to reduce the risk of distant metastases.[44] High-quality prospective evidence of its efficacy in these indications is currently not available.

IC with the TPF regimen (taxotere, cisplatin and 5-FU) is recommended, based on a higher response and survival rates and reduced locoregional and distant failure rates compared to PF (cisplatin and 5-FU) in a meta-analysis of five studies.[75] The regimen is associated with higher acute toxicity (neutropenic sepsis and non-haematological toxicities) and therefore is only suitable for patients with good performance status and minimal comorbidity.

Radiotherapy planning and delivery

PRE-TREATMENT EVALUATION

All patients should undergo the following assessments before starting RT:

- **Dental assessment:** including orthopantomogram (OPT) for dentulous patients if the upper or lower jaw is likely to be in the radiation field. Dental treatment,

particularly extraction, should be carried out prior to starting RT (ideally 2 weeks before) to reduce the risk of osteoradionecrosis.

- **Nutritional assessment:** dietetic input prior to the start of treatment is important to start patients with pre-existing weight loss (>10%) on supplementary feeding prior to treatment and to identify patients who are likely to require a feeding tube to support their nutritional requirements during and after treatment. The choice between feeding gastrostomy tube (proactive or reactive) or nasogastric tube depends upon local preference, expertise and availability of resources.
- **Speech and swallowing assessment:** to assess speech and swallowing function and educate patients on proactive swallowing exercise to be repeated daily prior to and during treatment in order to minimize swallowing difficulties in the short and long term.

RADIOTHERAPY PLANNING

Intensity-modulated radiotherapy (IMRT) is now the accepted standard of care for RT treatment planning and delivery for OPSCC (**Figure 13.11**) – the conformal dose distributions achieved allow sparing of normal tissues and organs at risk, potentially reducing toxicities and improving quality of life (QOL). The UK phase III PARSPORT study demonstrated that parotid-sparing IMRT reduces the incidence of grade 3–4 xerostomia (dry mouth) compared to conventional RT, from 83% to 29% 24 months after treatment ($p = 0.0001$).[76]

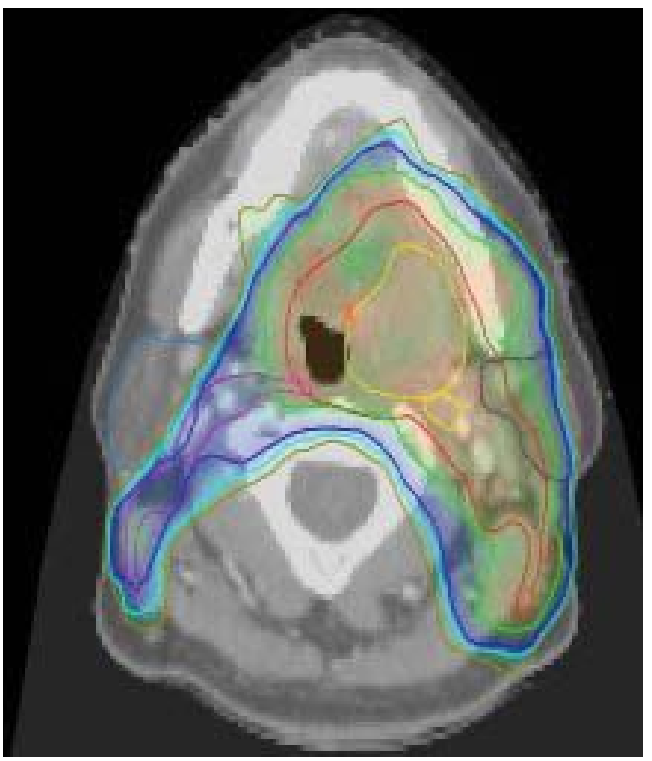


Figure 13.11 Intensity-modulated radiotherapy (IMRT) plan for left tonsillar carcinoma. Gross tumour volume (GTV) for left tonsillar primary and retropharyngeal node (yellow): Clinical target volume (CTV1) for radical dose RT (red): CTV2 for prophylactic dose RT (purple): 62.7 Gy, 51.3 Gy and 48 Gy isodose lines (shown in green, blue and mustard respectively).

Intensity modulation is delivered using a step and shoot technique or more recently, with dynamic arc therapy, either volumetric modulated arc therapy (VMAT) or tomotherapy.

Prior to target volume delineation, the primary tumour should be defined as lateralized or non-lateralized, depending on the site of the primary, T stage and extent of involvement of midline structures, as follows:

Lateralized tumour: tumour confined to the tonsillar fossa/lateral pharyngeal wall extending onto or into the adjacent BOT and/or soft palate by < 1 cm and with > 1 cm clearance from midline.

Non-lateralized tumour: tonsillar/lateral pharyngeal wall tumour that involves the adjacent BOT and/or soft palate by ≥ 1 cm or with ≤ 1 cm clearance from midline.

OR

A tumour that arises from a midline structure (BOT, soft palate or posterior pharyngeal wall primary tumour).

This will determine whether contralateral neck irradiation is required in cN0 cases (see 'Management of the neck' below).

Target volume definition

Patients will require a custom-made thermoplastic immobilization shell to ensure a reproducible position for accurate radiotherapy delivery. A 5-point immobilization system is normally used which includes the head, neck and both shoulders. Target volume delineation is carried out on a contrast-enhanced planning CT scan, often co-registered with the staging MRI and/or PET scan to enhance target volume definition. Target delineation requires a detailed knowledge of cross-sectional anatomy as well as detailed knowledge of tumour location and extent from the staging investigations. The following volumes are defined:

Gross tumour volume (GTV): the primary tumour (GTVp) and involved lymph nodes (GTVn) are delineated.

Clinical target volume (CTV): the CTV is a margin for microscopic disease and is usually divided into 2 or 3 volumes.

CTV1 (the high-dose CTV): typically, CTV1 includes a 1 cm isotropic margin around the primary and nodal GTVs and the whole of the involved nodal level in the neck. The isotropic margin may vary from 0.5 cm to 1.5 cm depending on local protocols and the certainty with which a tumour can be defined from the staging investigations.

CTV2 (the intermediate dose CTV): an optional volume which may include the whole involved nodal level in the neck (if not included in CTV1) and/or an additional isotropic margin around CTV1.

CTV3 (the prophylactic dose CTV): includes the 'at risk' nodal levels. For node negative OPSCC, this typically includes levels II–IVa. For node positive OPSCC, this typically includes levels Ib–V(b or c).

Internationally agreed consensus guidelines for the delineation of at risk nodal levels are used to guide outlining of the prophylactic CTV.[77]

Planning target volume (PTV): a margin (typically 3–5 mm) that is automatically added by the planning system to ensure the CTV is adequately covered on every day of treatment.

Organs at risk, including the spinal cord, brain stem, parotid glands and swallowing related structures are also outlined and also given a planning margin called the **Planning risk volume (PRV)**.

Defining the objectives for target volume coverage and constraints for the organ at risk doses, as well as the relative priorities of each, is then required prior to inverse treatment planning.

TOXICITIES OF RT/CRT

Radiotherapy can result in significant acute (< 90 days) and late (> 90 days after treatment) toxicities and late toxicities, particularly affecting salivary gland function, dentition and swallowing, may be permanent. CRT increases the risk of late toxicity[78, 79] and in the pre-IMRT era, up to 43% of HNSCC patients could develop grade 3–4 late toxicities following CRT.[80] The key late toxicity affecting QOL is swallowing dysfunction.[81] Swallowing is a primary concern for patients,[82] affecting their physical health and well-being, and is a major cause of distress and burden for family members[83] since dysphagic patients often require long-term supportive care.

Whilst the PARSPORT study demonstrated reduced rates of xerostomia in patients treated with IMRT compared to conformal RT, late dysphagia can still be an issue, even in patients treated with IMRT. Feeding tube dependence, a crude measure of swallowing dysfunction, has been reported in 8.6% of OPSCC patients at 1 year and 4.4% at 2 years after modern chemo-IMRT in a multi-institution pooled analysis.[84] Furthermore, a significant deterioration in patient-reported impairment in swallowing function, measured using the MD Anderson Dysphagia Inventory (MDADI), score, is seen in most patients 12 months after treatment and a deterioration of at least 20 points is still detectable in 15% of patients 24 months after treatment.[85,86] Aspiration, which can result in life-threatening episodes of pneumonia, may arise as a consequence. A US study identified > 3500 patients > 65 years who had been treated with CRT for head and neck squamous cell carcinoma (HNSCC) from the SEER-Medicare database (2000–2009) – it showed that > 25% of OPSCC patients had experienced at least one episode of aspiration pneumonia 10 years after treatment.[87]

Late dysphagia correlates with mean radiation dose to the swallowing-related structures (pharyngeal constrictor muscles, glottic and supraglottic larynx, oral cavity and cervical oesophagus), with the correlation being highest for the superior pharyngeal constrictors.[88, 89] The normal tissue complication probability curve for the pharyngeal musculature is sigmoidal in shape and increasing mean radiation doses between 50 and 60 Gy are in the critical range for late dysphagia.[88] The potential of dysphagia-optimized IMRT to reduce dysphagia rates, by reducing radiation doses to swallowing-related structures, holds significant promise and is being prospectively evaluated by a number of investigators and in an ongoing UK randomized controlled trial (RCT) (DARS ISRCTN: 25458988). Omitting chemotherapy could also potentially reduce the risk of dysphagia in selected patients, as concurrent chemotherapy increases late dysphagia rates compared with IMRT alone[89] and, as outlined above, the results of studies comparing the use of cetuximab instead of cisplatin with RT, in the context of good prognosis HPV+OPSCC, are awaited. Furthermore, prospective studies to determine whether intensity modulated proton beam therapy (IMPT) can reduce toxicity compared to IMRT by sparing non-target tissue in the head and neck are being planned.

Post-operative (adjuvant) RT/CRT for OPSCC

Evidence for the role of adjuvant RT after (open) surgery in head and neck cancers was provided by the RTOG 73-03 trial which showed that post-operative RT improved local control.[90] Subsequent studies helped to establish the optimum dose of post-operative radiation and recommended a minimum dose of 57.6 Gy to the primary site with up to 63 Gy to areas of ECS.[91] Prophylactic treatment for microscopic disease was established by a study showing that a dose of 50 Gy in 25 fractions was sufficient to control microscopic disease in over 90% of cases.[92] Patients should start their post-operative RT as soon as possible after surgery, ideally within 5 weeks (35 days) and no later than 6 weeks (42 days) to avoid reduced local control and survival due to protracted treatment beyond a total of 11 weeks (for surgery and RT combined).[93]

The indications for post-operative RT and CRT for OPSCC depend on pathological risk factors for recurrence common to most HNSCCs. These include: primary tumour factors (close (1–5 mm) or positive (< 1 mm) margins, T3–4 stage, perineural and/or lymphovascular invasion) and nodal factors (ECS of nodal disease and/or N2-N3 nodal stage). RCTs conducted by the RTOG and EORTC and a meta-analysis of their results confirmed that patients with ECS and/or microscopically involved (< 1 mm) surgical resection margins around the primary tumour experience significant benefit in terms of overall and disease-free survival from post-operative CRT compared to RT alone.[94] However, post-operative CRT results in significant toxicities (including a 2% death rate) and is not generally recommended in patients > 70 years of age and/or those with significant co-morbidities and poor performance status.

Transoral surgery

In light of accumulating retrospective data of efficacy and following the FDA approval of TORS for the management of OPSCC, there has been a resurgent interest in the transoral surgical management of OPSCC, with a 4.4% increase in the use of primary surgery in the US between 2009 and 2012,[95] a trend that is only likely to continue.

Transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) are minimally invasive surgical techniques for OPSCC, which have the potential to excise T1-T3 tumours with considerably less long-term functional deficit than open surgery. Transoral surgery (TOS) of the primary tumour is usually performed in conjunction with a neck dissection, either carried out at the same time, or as a staged procedure. Although early stage (T1-T2 N0-N1) OPSCC can be effectively treated with surgery alone,[62] adjuvant treatment is required in most patients, usually due to advanced nodal disease.

It is important to note that whilst TLM and TORS employ a transoral approach for tumour resection, there are important practical and philosophical differences between the techniques which is often not appreciated by the uninitiated. The most important difference is that whilst the technique of TLM dictates that the extent of surgery, in an attempt to minimize the removal of uninvolved tissue adjacent to the tumour, is governed by the specific anatomy of the tumour and so differs from case to case, TORS is predicated on the advisability of undertaking a standard procedure avoiding transtumoral resection and attempts to adhere to the principles of traditional *en bloc* surgical resection.

Transoral laser microsurgery (TLM)

(For more information regarding the role of TLM in general, please see Chapter 22, Transoral laser microsurgery)

TLM is conducted according to the principles proposed by Wolfgang Steiner and Petra Ambrosch.[96]

As per the standard technique, tumours are removed in several (at least two) planned pieces following transtumoral resection. Transtumoral resection is necessary for two primary reasons: primarily, it eases the technical burdens of removing large tumours which is of particular importance when resection is taking place down a distending endoscope as is usual when resecting tumours of the BOT. In addition, it facilitates greater appreciation of the 3D orientation of the tumour allowing greater resection precision. In an attempt to confirm complete surgical removal representative marginal biopsies should be taken from the tumour bed and examined histologically.

Marginal biopsies should be taken from all peripheral mucosal regions when this is technically feasible, together with representative marginal deep biopsies from the tumour bed.

The technique of TLM resection for OPSCC is best described when considering resection of a primary tonsil tumour.

Most tonsil tumours considered amenable to TLM are T2 in size. Resection will typically involve removal in two parts, following an initial transverse laser cut through the centre of the tumour which divides it into superior (cranial) and inferior (caudal) halves. Thereafter, each half is removed separately. Following in continuity removal of a given half, it is usually orientated and pinned to a cork board. On removal of the other half, this too is orientated and pinned to the same cork board, to recreate the anatomical arrangement of the primary tumour.

It is from this pinned primary specimen that histological margins around the primary tumour will be determined.

Having removed the two halves of the primary tumour, marginal biopsies are then taken. Marginal biopsies, as far as anatomically possible, should maximally represent the mucosal regions adjacent to the primary tumour and the deep tumour bed (**Figure 13.12**). It is usual therefore to take up to eight marginal biopsies following a standard TLM of a tonsil tumour, namely:

- a superior marginal biopsy involving the mucosa adjacent to the superior pole of the tumour
- an anterosuperior marginal biopsy, from the mucosa anterior to the superior half of the tumour (in many cases this amounts to the mucosa covering the region of the anterior faucial pillar)
- a posterosuperior marginal biopsy, from the mucosa posterior to the superior half of the tumour (in many cases this amounts to the mucosa covering the region of the posterior pharyngeal wall)
- a superior deep marginal biopsy which includes a representative sample of constrictor muscle deep in the bed of the superior half of the tumour
- an inferior marginal biopsy involving the mucosa adjacent to the inferior pole of the tumour
- an anteroinferior marginal biopsy, from the mucosa anterior to the inferior half of the tumour (in many



Figure 13.12 A tonsillar carcinoma, resceted in two portions as per the TLM principles described by Steiner and Ambrosch. Each section is anatomically re-orientated and pinned to a cork board (orange needles). A mucosal marginal biopsy is also anatomically orientated adjacent to the superior edge of the superior specimen. The superior pole of the tonsil is marked with a blue needle.

cases this again amounts to the mucosa covering the region of the anterior faucial pillar)
- a posteroinferior marginal biopsy, from the mucosa posterior to the inferior half of the tumour (in many cases this too amounts to the mucosa covering the region of the posterior pharyngeal wall)
- an inferior deep marginal biopsy which includes a representative sample of constrictor muscle deep in the bed of the inferior half of the tumour.

The biopsies should be labelled as above prior to sending to the pathology laboratory. The taking of marginal biopsies around soft palate and BOT tumours is more difficult to mandate as, in keeping with the philosophy of TLM, to tailor the resection to the tumour extent, there is often no standard procedure for removing these tumours. However, the guiding principles of marginal biopsies – to maximally represent adjacent mucosal boundaries and the deep tumour bed of resected tumours – should be adhered to at all times.

If all marginal biopsies are free of microscopic disease, then resection of the primary tumour is considered to be complete and allocation of adjuvant treatment depends, *inter alia*, on the depth of the resection margin around the main tumour specimen(s).

Re-resection is usually undertaken in a case when one or more initial marginal biopsies are found to contain microscopic disease.

Transoral robotic surgery (TORS)

(For more information regarding the role of TORS in general, please see Chapter 80, Rhinoplasty following nasal trauma)

For tonsil and BOT tumours, it is usual for the neck dissection be performed prior to the TORS procedure, either during the same general anaesthetic or at a previous sitting, during which the ipsilateral lingual and facial arteries are identified and ligated in continuity.

The resection involves *en bloc* removal of the tumour as per the principles outlined in the da Vinci Transoral Surgery Procedure Guide, which can be accessed via the following link.[97] https://oto.med.upenn.edu/education/62-2/.

The resection is performed primarily with the monopolar cautery. Where facilities are available to couple a laser to the robotic arm, this may be used for the resection.

Tonsil tumours: Resectability of the tonsil tumour is confirmed based on imaging. Extension to the parapharyngeal space and pterygoid musculature are relative contraindications to the procedure. Retropharyngeal location of the internal carotid artery is also a contraindication for this procedure and the scans should be very carefully studied to ensure this is not the case. The resection specimen is essentially a lateral oropharyngectomy, where the constrictor muscles of the tonsil bed are removed along with the tumour. If any concerns arise regarding the adequacy of the margins during the resection, the margins can be extended. Following removal, the tumour is grossly inspected to ensure that adequate margins are obtained. This may involve cutting though the tumour with a blade if the expertise and facilities exist. If any concerns are raised about the margins following resection (this usually occurs at the inferior aspect, where the tonsil meets the tongue base), the areas are marked with methylene blue (to identify the surface of interest to the pathologist) and a further margin harvested. The specimen is orientated on a suitable mount and sent for histological examination.

Tongue base tumours: Resectability of the tongue base tumour is also confirmed on imaging. Tumour extending across the midline is a contraindication for the procedure. Resection of the ipsilateral tongue base is performed as described in the procedure guide above. If any concerns are raised about the margins following resection (this usually occurs at the deeper aspect of the BOT), the areas are marked with methylene blue (to identify the surface of interest to the pathologist) and a further margin harvested. The specimen is orientated on a suitable mount and sent for histological examination.

Tumours involving both the tonsil and BOT: These tumours usually do not involve the entire tonsil and thus, it is sufficient to cut through the tonsil and the constrictors at least 5 mm away from the tumour edge and proceed with the resection of the tonsil tumour in the usual fashion, leaving the cranial part of the tonsil. Once the tonsil tumour is completely mobilized down to the styloglossus, the tongue base cuts can be made and the entire tumour removed *en bloc*. As above, further margins are resected on the table if concerns exist. The specimen is orientated on a suitable mount and sent for histological examination.

As outlined above, in contrast to the principle of TLM, primary tumours are removed *en bloc* using TORS in the vast majority of cases. As a result, surgical margins after TORS can be assessed and measured using standard pathology reporting protocols and the taking of marginal biopsies does not apply to tumours resected in this way. However, transtumoral resection and the taking of marginal biopsies – as described for TLM - may also be appropriate when employing a TORS approach and in such cases the same criteria for assessing resection as outlined for TLM above, should be employed.

In the specific instance that *en bloc* resection has been attempted but histological examination confirms a positive (involved) resection margin or margins, the following recommendations apply.

- If the positive margin(s) is mucosal then further resection to confirm complete excision is permitted. In this case, risk group allocation will rely on the histological status of the re-resected mucosal margin(s).
- If the positive margin is deep, then in keeping with the principles of TORS, re-resection is not recommended due to the anatomical limitations of undertaking further resection lateral to the constrictor muscles or deep to the prevertebral fascia. In such cases, patients will automatically be categorized as pathologically high risk.

A retrospective US study of 204 patients with stage III-IV OPC treated with primary TLM and neck dissection reported 3-year rates of local control, overall survival and disease-free survival of 97%, 86% and 82% respectively,

which were higher in HPV+patients.[59] A retrospective series from Liverpool, UK of 153 patients with T1-T3 OPSCC (66% were HPV+) treated with TLM and neck dissection, reported 3-year rates of disease-specific survival, overall survival and disease-free survival of 91.7%, 84.5% and 78.2% respectively, again better in patients with HPV+ disease.[60]

Similarly good outcomes have been reported following TORS: a cohort study of 410 patients from 11 centres treated with TORS, +/- adjuvant RT/CRT, reported 2-year rates of locoregional control, disease-specific survival and overall survival of 91.8% (95% CI, 87.6–94.7%), 94.5% (95% CI, 90.6–96.8%) and 91% (95% CI, 86.5–94.0%) respectively.[98]

No randomized studies have yet compared outcomes following transoral surgery and RT/CRT for OPSCC. Nevertheless, a recent meta-analysis on early stage OPSCC reported comparable 5-year disease-specific survival rates of 90.4% (95% CI, 85.6–95.2%) for RT and 89.6% (95% CI, 81.8–97.3%) for TOS in early stage OPSCC.[27] Furthermore, a systematic review comparing the effectiveness of IMRT and TORS for T1-T2 OPSCC[28] reported similar survival outcomes in 1287 IMRT patients (2-year overall survival 84–96%) and 702 TORS patients (2-year overall survival 82–94%). A different profile of adverse events were reported for IMRT and TORS, which for IMRT included gastrostomy tubes (43%), oesophageal stenosis (4.8%) and osteoradionecrosis (2.6%) and for TORS as described below.

Transoral surgery for early and intermediate stage OPSCC is generally well tolerated, with a median length of hospital stay after surgery of approximately 4.4 days.[59] Acute complications include haemorrhage (2.4%) and fistula (2.5%). Temporary tracheostomy tubes are needed in 12% of patients at the time of surgery but most are decannulated prior to discharge.[99] Temporary nasogastric tubes are required in up to 47% of patients post-operatively but most patients can manage an oral diet without a tube by 4 weeks following surgery.[100, 101] Long-term functional outcomes after TOS appear favourable in small studies: in a study of 30 patients with early (mainly T1-2 N0-N1) OPSCC treated with TORS and neck dissection (without adjuvant treatment), all patients were taking a full oral diet without a feeding tube after a median follow-up of 2.7 years.[62]

However, in most reported series of TOS, the majority of patients also undergo adjuvant therapy, either with post-operative RT (PORT, 21–58% of cases) or post-operative CRT (POCRT, 16–62% of cases.[60, 61, 101–103] It is clear that adjuvant treatment increases acute and late toxicity associated with transoral surgery. In the largest TLM series,[60] adjuvant treatment doubled gastrostomy tube use from 17% to 33% and 19% of patients remained gastrostomy tube dependent 12 months after treatment. In 66 OPSCC patients treated with TORS,[101] 97% were tube free and managing an oral diet 4 weeks after surgery, but 27% (18/66) required a gastrostomy tube during their adjuvant therapy and 3 (4.5%) remained gastrostomy tube dependent more than 2 years after treatment. In 81 patients treated with TORS,[104] all patients were discharged post-operatively on full oral diet, but 13 (16%) required gastrostomy tube placement during adjuvant treatment; of these, five remained in place for over a year. Eating domain health related quality of life (HRQOL) scores were also significantly worse in patients who underwent adjuvant treatment compared to those who did not. Increasing age (>55 years) and extent of TORS resection predicted the need for a gastrostomy tube and high T stage (pT3/pT4) predicted the need for permanent tube feeding. Not surprisingly, functional outcomes following POCRT appear to be worse than after PORT. In 38 OPSCC patients, speech, diet and eating (PSS-H&N) scores at 6 and 12 months following treatment were significantly better following TORS alone compared to TORS followed by PORT which were, in turn, better than after TORS and POCRT.[105] Furthermore, a systematic review of TORS for OPSCC showed clear demarcation in swallowing outcomes across a variety of outcome measures in patients who received PORT compared to POCRT.[106]

It is clear that current adjuvant treatment protocols limit the use of TOS as a potential means of improving long-term function, whilst maintaining good oncological outcomes, in patients with OPSCC. This issue has been raised in particular in the context of HPV+OPSCC. However, adjuvant treatment decisions are based on pathological risk factors for recurrence established >20 years ago in studies which included a heterogeneous group of HNSCCs, most of which were treated with open (not transoral) surgery and none of which were tested for HPV[107, 108] and their relevance to the selection of adjuvant therapy regimens and doses in the context of HPV-positive disease have been questioned. A National Cancer Institute Head and Neck Cancer Steering Committee Clinical Trials Planning Meeting on transoral resection of pharyngeal cancer called for these parameters to be re-evaluated for HPV+ disease in controlled, prospective surgical trials with clinical-pathological correlation of outcomes.[109] US and UK clinical trials, ECOG 3311 and PATHOS (described in more detail later), are currently recruiting in an attempt to address this lack of data.

Management of the neck

The role of the neck dissection in the treatment of oropharyngeal cancer is well standardized and outlined in detail in the UK Head and Neck Cancer Multidisciplinary Management Guidelines 2016.[52]

CLINICALLY NO NECK

The prevalence of micrometastatic nodal disease in OPSCC patients presenting without clinical or radiological evidence of nodal disease is estimated to be between 10% and 30% accordingly, in most cases, elective treatment of the neck is recommended. Surgery, in the form of a selective neck dissection or radiotherapy, is a valid option. Which is chosen is typically predicated on the choice of treatment used for the primary tumour as the aim in early stage disease is for single modality treatment.

NECK DISSECTION

In patients with a lateralized tumour – see 'Radiotherapy planning' above for definition – an ipsilateral neck dissection suffices.

In patients with a non-lateralized tumour – see 'Radiotherapy planning' above for definition – then the contralateral neck should also be dissected if only for pathological staging purposes.

A selective neck dissection including the dissection of, at least, lymph node levels II and III and possibly level IV should be performed. There is also some evidence to recommend the dissection of level I in the case of anterior disease extension.[110] There is no evidence which mandates the dissection of level IIB in the context of clinically N0 disease.

Particularly when TORS is used for primary tumour resection, as described above, it is common for the neck dissection to be carried out as a staged procedure some 2 weeks prior to the primary resection. This is primarily recommended as a strategy to reduce the rate of pharyngocutaneous fistula (PCF) although in practice a staged approach is often dictated by local logistics relating to robot availability. The opportunity is taken, during the neck dissection, to ligate the branches of the external carotid artery which supply the lateral oropharynx (ascending pharyngeal, lingual and facial arteries). This is performed to reduce the local blood pressure with the aim of reducing major haemorrhage following primary tumour resection.

In contrast, when TLM is used for primary tumour resection, it is usual to perform the neck dissection, including the ligation of the external carotid artery branches, during the same anaesthetic. Which is performed first is a matter of personal choice. The risk of PCF is extremely small, especially if lymph node level I is not dissected. It the case where a PCF does occur, repair using local tissues such as the digastric or sternomastoid muscle, followed by a 5-day period of nasogastric feeding, is usually sufficient to allow successful PCF healing.

Although the goal for the treatment of early stage disease is single modality treatment, pathological findings (close or involved surgical margins, pN+ disease +/- ECS) following surgical resection may mandate the need for adjuvant RT +/- chemotherapy. It is for this reason there has been resistance to the use of surgery (to the neck and primary site) for the treatment of OPSCC, particularly in the HPV era. If adjuvant RT is required it should be planned according to the principles used for radical RT (see 'Radiotherapy' below), but a reduced dose of 60 Gy in 30 fractions is usually recommended.

RADIOTHERAPY

Prophylactic radiotherapy should be given to the ipsilateral cervical lymph nodes for lateralized (e.g. tonsillar) tumours and to both sides of the neck for non-lateralized tumours (see 'Radiotherapy planning' above). Radiotherapy to levels II/III/IVa is recommended; level Ib may also be included in cases with anterior extension of tumour and/or involvement of the anterior tonsillar pillar. Neck node levels should be outlined according to the DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines and the associated on-line atlas.[76]

Treatment of the node positive neck

NECK DISSECTION

If the neck is considered operable and surgery is the primary treatment modality then an N+ neck should be treated by selective neck dissection including, at least, levels IIA, III and possibly IV. Additional nodal levels may be dissected as indicated by the volume and level of apparently involved lymph nodes. It is usual to dissect level IIb in the N+ neck and again, level I may be dissected in some instances where anterior extension of the primary tumour is marked. Whether, or which, adjuvant treatment – RT +/– chemotherapy – is required will be dictated by the surgical pathology although avoidance of adjuvant treatment, at least to the primary site, is highly unlikely in the context of T3 or T4 disease.

RADIOTHERAPY/CHEMORADIOTHERAPY (CRT)

The principles of radiotherapy outlining and planning are as described for earlier stage disease. Neck nodes should be included in the treatment fields depending on their probability of involvement and according to the DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines and atlas which were updated in 2013.[77, 111] Radiotherapy to levels Ib–IVa, V(a,b) and the retropharyngeal nodes (level VIIa) at the level of the oropharynx is generally recommended in a N+ neck. The retrostyloid space (level VIIb) is included when level II is involved and the SCF (level IVb and level Vc) is included when level IVa or V are involved. The nodal levels to be included are summarized in **Table 13.1.** Radiotherapy should be given to at least the ipsilateral cervical lymph nodes for lateralized tumours and to both sides of the neck for non-lateralized tumours. The issue of whether the contralateral neck should be treated in patients with lateralized oropharyngeal tumours and advanced (N2+) nodal disease remains controversial and will depend on local practice.[111]

A recently reported phase III RCT that patients with N+ OPSCC can be effectively treated with CRT, without the need in most cases for a neck dissection. The PET NECK trial[112] confirmed that a post-treatment PET-CT surveillance policy, with neck dissection only being performed for patients who have FDG positive or equivocal residual nodal disease on PET-CT scanning at 12 weeks after completion of CRT, results in equivalent survival and regional control rates compared to a planned neck dissection, with a significant reduction in morbidity (by avoidance of surgery in 4 out of 5 patients) and improved cost effectiveness.

TREATMENT FAILURE

The landmark study by Ang et al,[7] which retrospectively considered outcomes of patients with stage III/IV OPSCC, treated with one of two CRT regimes and for whom HPV status had been established confirmed the improved survival outcomes seen for patients presenting

with HPV+OPSCC compared with patients presenting with HPV-OPSCC. The follow-up data also confirmed that significantly more patients in the HPV-OPSCC group had relapsed locoregionally than those in the HPV+OPSCC group (35.1% (95% CI, 26.4–43.8%) vs 13.6% (95% CI, 8.9–18.3%)), although the rate of distant metastasis did not differ significantly between the groups. Patients with HPV-OPSCC and a subset of patients with HPV+OPSCC also have less favourable outcomes in studies where patients were managed with primary surgery.[60, 61]

A retrospective cohort analysis of 185 patients with OPSCC treated with RT and cisplatin +/– tiranzapine by Rischin et al[113] also confirmed that locoregional recurrence was more likely in the HPV- group (14% vs 7%) although the rates of distant relapse were similar in each group.

Similar data were published by Posner et al[114] in a study of 111 patients with local advanced OPSCC. They, too, confirmed an increased rate of locoregional relapse in patients with HPV- tumours at 5 years compared with HPV+patients with similar rates in distant relapse in each group.

Huang et al,[115] in a study which included 624 OPSCC patients similarly concluded that locoregional relapse was statistically more likely in patients with p16- disease compared to those with p16+ disease (21% vs 6%), whilst distant relapse rates were similar.

Collectively these data confirm that locoregional relapse, in contrast to distant relapse, is statistically more likely in patients with HPV+OPSCC, but that the rate of relapse (locoregional and distant) in the HPV+ group is not insignificant and represents a subgroup of patients with HPV+ disease who do badly.

Although the rates of distant relapse appear similar between HPV+ and HPV- patient groups, other data[116, 117] reporting on the pattern of post-treatment distant metastatic spread at relapse in patients with OPSCC confirm obvious differences between HPV+ and HPV- groups.

Whilst the most common pattern of distant spread to the lung, bone and liver is similar between the groups, a subgroup (~30%) of patients with HPV disease develop metastases at unexpected anatomical sites including brain, skin and intra-abdominal lymph nodes. Moreover, it appears that these atypical patterns of spread are harbingers of aggressive tumour behaviour with patients experiencing rapid deterioration following diagnosis.

Despite this subgroup of patients with atypical spread which do extremely badly, overall patients with HPV+OPSCC still fare better after relapse than patients with HPV- disease although the magnitude of beneficial impact in the relapse setting is much smaller than the effect of HPV positivity in the primary disease setting.[115, 116, 118, 119]

Currently, predictive biomarkers of outcome are not available and so identification of the subgroup of HPV+patients destined for poor outcome is currently not possible. Furthermore, as things stand, it is unclear how best to treat patients at relapse and additional high-quality clinical trials designed to address this need are urgently needed.

THE FUTURE

Optimizing treatment for OPSCC: ongoing clinical trials

As explained previously, the emergence of HPV+OPSCC as a discrete disease entity has resulted in the need to identify novel de-intensified treatments for HPV+OPSCC which will maintain the current advantageous survival outcomes whilst reducing the acute and long-term adverse effects of current treatments. In contrast, the quest to identify tolerable intensified treatments for patients with HPV-OPSCC in an attempt to improve current modest survival outcomes, is ongoing. Moreover, there still remains an absence of level I evidence comparing surgical vs non-surgical treatment strategies.

Ongoing clinical trials are attempting to address these voids in our current clinical knowledge.

An EORTC phase III randomized study (EORTC 1420, 'Best-Of' NCT02984410) comparing late function (MDADI at 12 months following treatment) after TOS and IMRT in patients with (HPV+ and HPV-) T1-T2 N0 M0 OPSCC is currently recruiting in several European countries, including the UK and could inform future practice for early stage disease by providing much needed level I evidence following a head-to-head comparison of surgical vs non-surgical treatment.

Similarly, the currently recruiting Canadian ORATOR phase II clinical trial (NCT01590355) will attempt to address the same problem.

Patients with T3-4 OPSCCs, which are not transorally resectable, should undergo primary CRT as the standard of care. Dysphagia optimized IMRT, aiming to minimize radiation dose delivery to swallowing-related structures, and/or the use of cetuximab instead of cisplatin with RT, are being studied in ongoing UK clinical trials (DARS, ISRCTN: 25458988 and De-ESCALaTE-HPV, NCT01874171 respectively), as means of reducing toxicities in these patients.

In addition, The Quarterback Trial (NCT01706939): A Randomized Phase III Clinical Trial Comparing Reduced and Standard Radiation Therapy Doses for Locally Advanced HPV Positive Oropharynx Cancer, has completed recruitment and is in follow-up.

As an alternative approach, the UK phase II/III PATHOS study (ClinicalTrials.gov NCT02215265) (40), and the US study ECOG 3311 [NCT01898494]) are currently exploring transoral surgery (TLM or TORS) +/– de-intensified adjuvant as a potential means of improving long-term function, whilst maintaining good oncological outcomes, in patients with HPV+OPSCC.

PATHOS[120] (see **Figure 13.13** for trial schema) is currently recruiting patients with HPV+OPSCC who will undergo transoral surgery and a neck dissection. Post-surgical pathology will allow stratification into three distinct risk

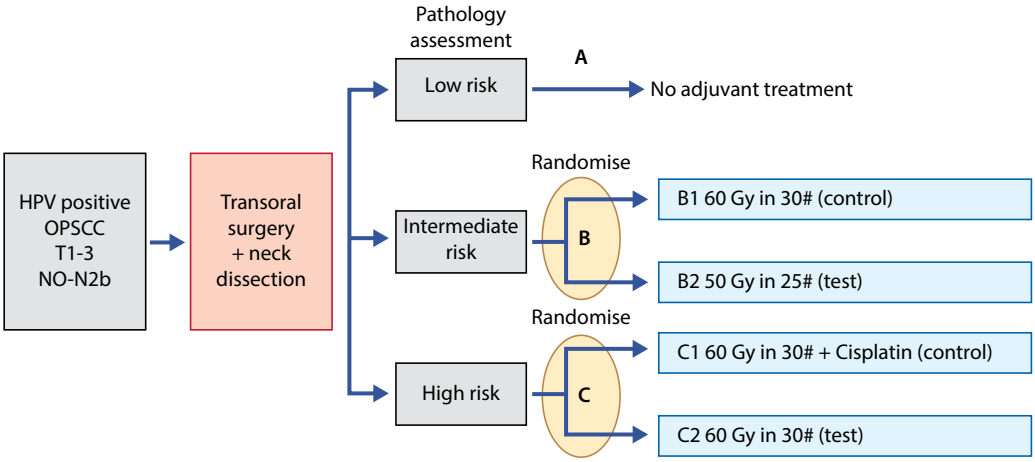


Figure 13.13 PATHOS (Post-operative adjuvant treatment for HPV+OPSCC study schema. Patients with T1-2 N0-N2b HPV+OPSCC undergo transoral surgery and a neck dissection before being stratified into groups (A, B and C) based on pathological risk factors. Group A (no risk factors) have no adjuvant treatment. Group B (N2, close margins, perineural /vascular invasion) are randomized to 60 Gy (control arm) or 50 Gy (test arm) of IMRT. Group C (ECS and/or high risk margins) are randomized to POCRT (control arm) or 60 Gy PORT only (test arm). Primary endpoint, Overall survival; Secondary endpoint, swallowing function, as measured by a multi-instrument swallowing panel, at 1 year post-treatment.

groups. Whilst a low-risk Group A will receive no adjuvant treatment an intermediate risk Group B will be randomized between standard and reduced dose adjuvant IMRT and a high-risk Group C will be randomized between adjuvant CRT and standard dose IMRT alone. A European phase III extension to the ongoing UK phase II is planned to investigate whether de-intensified adjuvant treatment schedules for patients with intermediate stage HPV+OPSCC, undergoing transoral surgery, results in non-inferior survival outcomes and improved swallowing function.

In contrast, poor prognosis OPSCC, including HPV+ current smokers[22] with advanced disease and patients with HPV-disease, may benefit from treatment intensification and an ongoing multi-arm, multi-stage (MAMS) UK study (COMPARE, UKCRN Study No: 18621) is exploring this possibility.

Translational research

What is clear is that many questions relating to the epidemiology and natural history of oral HPV infection and its relationship to the development of HPV+OPSCC remain. Some of the more pressing questions which are currently the basis of ongoing research include:

- Why do a small percentage of infected individuals fail to clear the initial HPV infection and why do a proportion of these then go on to develop HPV+OPSCC?
- Is the mechanism of infection and virally mediated transformation the same for OPSCC as for cervical cancer and why is HPV-16 the predominant genotype involved in OPSCC whilst HPV-18, together with HPV-16, has a more significant role in the development of cervical cancer?
- Why is OPSCC more responsive to treatment than cervical cancer despite presenting with clinicopathological features traditionally associated with poor outcome?
- Does an as yet undetected HPV+OPSCC premalignant lesion exist?
- Why is there a significant male:female gender bias?
- Why has this new discrete disease entity only emerged in the last 3–4 decades?

Moreover, there is an urgent need to identify robust predictive risk-stratifying biomarkers which will identify the subgroup of patients with HPV+ disease. The identification of such biomarkers is planned as a translational programme of research allied to several of the clinical trials highlighted above e.g. RTOG 1420, PATHOS, De-Escalate and COMPARE.

Following on from this, there is also an urgent need to identify novel treatments which will reduce rates of treatment failure and/or enhance life-expectancy in patients who relapse.

Of particular note in this context is the publication of the CheckMate 141 clinical trial.[121] This randomized, open-label, phase III clinical trial, randomized 361 patients with recurrent SCCHN, whose disease had progressed within 6 months of receiving platinum based CRT in a 2:1 ratio to receive nivolumab or standard single-agent systemic therapy. The primary end-point was overall survival. Overall survival was significantly longer in the group that received nivolumab compared with the group treated with standard systemic therapy (7.5 months vs 5.1 months: HR for death = 0.70; 97.7% CI 0.51–0.96%). A post-hoc exploratory analysis of 178 patients with OPSCC for whom p16 status was known confirmed that among the patients with p16+ tumours OS was 9.1 months in the nivolumab group vs. 4.4 months in the standard therapy group (HR for death = 0.56; 95% CI 0.32–0.99%), suggesting that PD-1 blockade may have a discriminatory advantage in patients with HPV+OPSCC in the recurrent / metastatic setting.

Prophylactic vaccination

Vaccination of girls against HPV has been implemented in many countries throughout the developed world with the aim of protecting women against cervical cancer. Gender-neutral vaccination for boys, with the aim of preventing HPV related cancers to which males are exposed, anal, oropharynx and penile, is more contentious. Currently, only the United States, Austria, Canada and Australia recommend vaccination for boys but only Australia has implemented a comprehensive nationwide vaccination programme for boys aged 12–13 years.

The main reason against widespread introduction of gender neutral vaccination is cost-effectiveness. Assessing cost-effectiveness is a relatively complex process as underpinning the successful protection of males is the effectiveness of herd-immunity which is predicated on vaccine take-up in girls. Modelling data confirm that if vaccine coverage in women exceeds 80% then herd-immunity will be sufficient to ensure the protection of males. This argument, however, is based on two main assumptions.

- A high level of vaccine coverage is uniform and sustainable in the long term across the whole female population being vaccinated.
- Males only have sex with vaccinated females.

If each of these assumptions are correct, then population-based vaccination of boys is arguably not cost-effective. Campaigners for the introduction of gender-neutral vaccines propose the following counter arguments:

- That uniform and sustainable vaccination of girls in any given country cannot be guaranteed and that there are areas and populations in all countries – London and certain ethnic and religious groups in the UK for example – where vaccination rates will be far less than 80% so that herd immunity is not guaranteed.
- In an increasingly globalized world men will not only have sex with women from countries where comprehensive vaccination programmes are in place and neither does this assumption take into account the men who have sex with men (MSM) – a group at particularly high risk of developing HPV-related cancers.
- Cancer inequalities will be augmented as males from more affluent backgrounds will be vaccinated privately.
- That choosing to vaccinate only one gender when it is known that the non-vaccinated gender is at risk of harm, albeit not to the same extent, is discriminatory.

Debates such as these are playing out in most developed countries in the world and certainly the proponents for gender neutral vaccination now have the support of high-profile scientific and medical opinion leaders.

Whatever the outcome, it is clear that any positive effect of prophylactic vaccination on the incidence of HPV+OPSCC is likely to be delayed for several decades and in the intervening time it is incumbent upon all involved to continue to strive to improve the outcomes for the patients unfortunate enough to develop this devastating condition.

KEY POINTS

- Globally, the incidence of oropharynx cancer is increasing rapidly in a geographically variable pattern.
- Most of this increase is attributable to a rise in Human papillomavirus related disease (HPV+) although non-HPV related disease (HPV-) appears also to be increasing in some countries.
- HPV+ oropharynx cancer (HPV+OPSCC), constitutes a discrete disease entity, presenting in patents who are younger, fitter and more affluent than patients presenting with HPV- disease.
- Despite presenting with clinicopathological features (N+ with ECS) usually associated with poor disease outcome, HPV+ tumours respond better to treatment.
- In light of this, attention has turned to the potential for de-intensified treatment strategies for HPV+OPSCC, in order to maintain advantageous survival outcomes whilst reducing treatment-related early and long-term toxicity.
- Despite a widespread perception that HPV+OPSCC is a defined sexually transmitted disease, this has yet to be confirmed.

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CHAPTER 14

TUMOURS OF THE LARYNX

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SEARCH STRATEGY

The data in this chapter are based on searches of Medline, EMBASE and the Cochrane Library using the keywords: laryngeal cancer, squamous cell cancer, laryngeal dysplasia, diagnosis, treatment. The articles referenced by these authors were also reviewed. The data are supplemented by further searches of specialized books.

INTRODUCTION

Laryngeal carcinoma is the most common site of malignancy in the head and neck worldwide. The effects of the disease process and the treatment can have significant impact on voice and swallow function and quality of life. Recent advances in the surgical and non-surgical management options, with a burgeoning evidence base, have led to a sea change in the management of laryngeal cancer in the last decade. This chapter will deal with the principles of assessment, diagnosis and management of laryngeal precancer and cancer. The finer aspects of endoscopic, open and robotic surgery for laryngeal cancer merit detailed treatment and are dealt with elsewhere in the book.

EPIDEMIOLOGY

Worldwide, laryngeal tumours account for 156 000 new cases per year and 83 000 deaths. The incidence is higher in men worldwide, with an estimated 138 000 men being diagnosed each year compared to 18 000 women. There are significant variations in incidence across the world.[1] Laryngeal tumours are most common after the age of 60 and less common under 40.[2]

In the UK, the age standardized incidence of laryngeal cancer is estimated to be 3/100 000. Within the UK there are wide variations in incidence with the highest incidence in the north of the country. Overall, the incidence of laryngeal cancer has decreased by 20% since 1990 and appears to have plateaued between 2002 and 2006. This has largely been attributed to a reduced incidence of smoking. Yet other factors such as changes in the industrial landscape and decline in heavy industry could also have contributed. Concurrent with a drop in incidence, the survival following a diagnosis of laryngeal cancer has continued to improve in the UK; between 2002 and 2006 the figures improved from 82.75% to 85.33%. However, the 5-year relative survival rates have remained unchanged over the same period at 65% for the most recently diagnosed cases.[3]

Data from the United States also suggest that there are significant variations in incidence between racial groups, with the majority of tumours occurring in Caucasian patients.[4] A detailed treatment of epidemiology can be found in Chapter 3, Epidemiology of head and neck squamous cell carcinoma.

AETIOLOGY

Smoking remains the most common aetiological factor for cancers of the larynx, with alcohol an independent risk factor for developing laryngeal cancer in the absence

of smoking. The combination of smoking and alcohol appears to be a multiplicative risk.[5] The risk of developing laryngeal cancer is highest in current smokers and increases with the number of cigarettes smoked. There is a reduction in relative risk of developing laryngeal cancer after stopping smoking and drinking with the risk reduction reaching the level of never smokers after approximately 20 years.[5, 6]

While sexual behaviours and HPV infection have been strongly linked with tumours of the oropharynx, there is little epidemiological evidence linking these with tumours of the larynx.[7, 8] Unlike oropharyngeal cancer, existing retrospective studies do not identify a favourable prognostic impact for HPV positive laryngeal tumours.[9, 10]

Other known risk factors include occupational toxic agents such as asbestos, polycyclic aromatic hydrocarbons, wood dust, coal dust and cement dust.[11, 12] Lower socioeconomic status and manual 'blue-collar' occupations also experience a higher risk of developing laryngeal cancer.[11]

Certain genetic syndromes, such as Fanconi anaemia[13] and congenital dyskeratosis[14] are also associated with a higher risk of developing laryngeal tumours in addition to tumours in other parts of the body. A detailed treatment of aetiology of laryngeal cancer can be found in Chapter 2, Aetiology of head and neck cancer.

PATHOLOGY

The most common type of laryngeal cancer is squamous cell carcinoma; however, many other histological types of cancers can be seen in the larynx. A detailed discussion of the various pathological entities in the larynx can be found in Chapter 26, Head and neck pathology.

Optimal pathological assessment of specimens requires a co-ordinated approach between the pathologist and surgeon or oncologist. The Royal College of Pathologists in the UK have published guidelines for the dataset required to report cases. Important factors including the type, size and grade of the primary carcinoma, the pattern of invasion and proximity of carcinoma to resection margins. All have been shown to be important prognostic features.[15] It is crucial that small specimens resected via transoral approaches are oriented prior to pathological analysis to allow accurate reporting of the margins. Several options exist for mounting specimens, which is discussed in detail in 'Transoral laser microsurgery' below. To maintain clear lines of communication, the authors' preference is to send pictures of the resected, mounted specimen, which is then marked, to the pathology team. In cases where a total or partial laryngectomy has been performed, whole organ section analysis is usually performed to consider patterns of spread and resection margins. HPV testing is not considered routine but may be important in a subset of patients.

PATHWAYS OF CANCER SPREAD

Laryngeal squamous cell carcinoma has characteristic patterns of spread depending on the site of origin. Local spread is along tissue planes, while lymphatic spread is guided initially by the boundaries between embryological anlagen (arches III–VI), notably at the free edge of the glottis. Yet, despite long-held beliefs, there is no true anatomical barrier to check spread between the supra- and subglottis, as was shown as long ago as 1969 by Kirchner's laborious whole organ dissections.[16]

Historically, glottic cancer spreading to the anterior commissure (AC) was feared, because early invasion through Broyle's ligament directly into cartilage was thought inevitable. This was perceived to be due to the lack of an inner perichondrium in that area. However, recent work has shown that the ligament is in fact an effective barrier, but it is extension superiorly and inferiorly (via subglottic wedge and hence cricothyroid membrane) that worsens prognosis. Direct spread may continue via the AC to the opposite cord, or may extend posteriorly to invade the arytenoid cartilage. Glottic tumours may be confined to Reinke's space by the embryological boundary superiorly and the conus elasticus inferiorly. To reach the paraglottic space and thence gain an easy passage cranially and caudally, tumours need to transgress both the vocal ligament and vocalis muscle. The laryngeal skeleton is relatively resistant to invasion, though ossified areas appear less so. Nonetheless, external extension directly through the cartilages is regularly seen.

Lymphatic spread of glottic cancer is less common than at other subsites. It has been suggested that the lack of submucosal lymphatics in this area is responsible. However, detailed studies of mucosal cell trafficking have not yet been performed to confirm this. Spread, when it occurs, is to levels II, III, IV and VI. Estimates for the incidence of macroscopic lymph node metastasis by disease stage are: <5% (T1), 7% (T2), 14% (T3) and 33% (T4). The so-called 'Delphian' node (also known as the midline anterior metastatic node or Poirier's pre-laryngeal ganglia node) is very rare, but is thought to be associated with T3 or T4 tumours with significant subglottic extension.

Supraglottic cancers tend to remain locally confined (even with pre-epiglottic or nodal spread) to their subsite until relatively late. As a result, supraglottic laryngectomy is often a viable option even for bulky tumours. However, as noted above, there is no real anatomical barrier to inferior spread. Indeed, the routine use of angled Hopkins rods during staging procedures to examine the cavity of the laryngeal ventricle reveals a steady transmucosal progression of tumours similar to other subsites and permits the precise selection of patients suitable for supraglottic partial laryngectomy. Overall, several studies have shown that approximately 50% of supraglottic cancers spread to the glottic region. The presence of foramina within the epiglottic cartilage makes this less of a barrier to spread than that presented by the other cartilages. However, invasion of the hyoid is rare (2–4%), meaning that it can often be retained during operative clearance. 'Suprahyoid supraglottic' carcinomas tend to invade the pre-epiglottic space and the deep muscles of the tongue and spread mucosally into the piriform fossae rather than into the paraglottic space. Supraglottic tumours also have a propensity for bilateral nodal metastasis. In reports of

advanced disease, supraglottic carcinoma has a positive nodal rate of over 60%, compared with much lower rates of 20% in advanced glottic cases. This has a major influence on the decision to perform elective neck dissections for these patients (see Chapter 36, Clinical examination of the neck).

Subglottic carcinoma tends to extend caudally and circumferentially. Fifty percent invade the cricoid and 75% have already extended outside the larynx by the time of diagnosis. Despite this, clinically detectable nodal metastasis is surprisingly uncommon, although a microscopic incidence of one in three puts this disease into the category of requiring elective nodal dissection. Due to the propensity for inferior extension, nodal dissection for subglottic cancer should include the paratracheal/mediastinal nodes.

Transglottic cancer is defined by spread, both superficially and into the paraglottic space to span all three laryngeal subsites. True primary transglottic cancer is said to originate in the laryngeal ventricle, though in practice it is impossible to be precise about the original epicentre. It is, by definition, at least T3 at presentation and subsequent consideration will therefore be alongside advanced cancers.

Tracheal squamous cell carcinoma is exceedingly rare, with approximately eight cases per annum in the UK and one in Holland, despite being theoretically exposed to the same carcinogens as the larynx. Interestingly, the trachea has the highest density of immunologically active cells suggesting that mucosal immunosurveillance may be a crucial factor in defence against airway mutagenesis. A rule of thumb for spread in each site is given in **Table 14.1**.

Thyroid gland invasion has been studied in resected specimens and the incidence of this has been studied in a systematic review by Kumar et al.[17] Pooling data from 1287 patients, this study showed that the overall incidence of thyroid gland invasion is 10.7% (95% CI 7.6–14.2). Patients with primary subglottic tumours (relative risk 7.5; 95% CI 4.3–13.0) and disease extension into the subglottis (relative risk 4.3; 95% CI 2.5–7.2) have a significantly higher relative risk of thyroid gland invasion. Other sites did not confer this higher risk. As the overall incidence of thyroid gland invasion is low, thyroidectomy can be reserved for cases considered to be at risk as opposed to a being a routine measure for all total laryngectomies.

TABLE 14.1 Spread of laryngeal carcinoma

Primary site		Look for involvement of
Supraglottis	Epiglottis	Pre-epiglottic space
	Epiglottic petiole	Anterior commissure
	Intralaryngeal mucosa, false cords	Paraglottic space
	All	Vocal fold
		Laryngeal cartilage
Glottis	Anterior cord	Anterior commissure/ contralateral cord
	Posterior cord	Thyroid cartilage and cricothyroid membrane
	All	Arytenoid cartilage/ cricoarytenoid joint/ posterior commissure
		Paraglottic space
		Supraglottic/subglottic spread
Subglottis		Trachea
		Thyroid gland
		Cervical oesophagus

CLINICAL PRESENTATION

As with other cancers, laryngeal cancer may present with local symptoms or those due to metastatic spread to nodes or beyond. Occasionally, patients present with general systemic signs, such as weight loss or anaemia, but in laryngeal cancer these are rare in the absence of local symptoms. Paraneoplastic phenomena such as peripheral neuropathy and rashes are very rare. As a result, it is possible to provide primary care workers (and indeed the general population) with a fairly accurate idea of 'warning/red flag' symptoms that require urgent referral to an otolaryngologist.

Glottic cancer

It is fortunate that even the earliest glottic cancer alters the voice by affecting wave pattern forms over the vocal cord. Since normal voice production depends on the integrity of a six-cell thick epithelium and a delicate, jelly-like superficial lamina propria, even carcinoma *in situ* may produce significant voice change. Thus, any person with hoarseness persisting for 3 weeks or more (some would say even less time than this) should be referred urgently to an otolaryngologist for examination. The National Health Service in the UK has implemented a fast-track protocol to aid this. With increasing lesion size, maximum phonation time decreases and with the onset of cord fixation, breathiness may be superimposed, with variable degrees of aspiration. Advanced lesions may lead to airway obstruction causing progressive dyspnoea and stridor. Haemoptysis is usually associated with larger tumours. Referred otalgia (via the vagal complex) is a sinister sign suggesting deep invasion. Dysphagia and odynophagia are rare in uncomplicated glottic cancer. Neck nodes are rarely the presenting complaint; if present, they signify deep invasion and extension into the supraglottis.

Supraglottic cancer

Voice alteration is different in quality from that seen with glottic and subglottic cancer. Small supraglottic lesions not extending to the glottis may present with globus or foreign body sensation and parasthesia. If exophytic, they may cause haemoptysis. As tumour bulk increases, phonation is altered, with a 'hot potato' voice. If tumours extend to the cords, then hoarseness ensues as for glottic disease.

Further extension laterally may cause referred otalgia, odynophagia and true dysphagia. However, lesions may be asymptomatic until quite large and, as a result, first presentation with a neck lump due to cervical nodal metastasis is common.

Subglottic cancer

Again, early symptoms can be vague, with a feeling of 'globus' or foreign body sensation in the throat. Any involvement of the glottis or recurrent laryngeal nerves results in hoarseness. With paralysis, diplophonia may occur with a shortened maximum phonation time. Therefore, this diagnosis should always be considered in the possible differential causes of 'idiopathic' cord paralysis, especially in high-risk cases. Circumferential progression leads to progressive dyspnoea and stridor, with markedly shortened maximum phonation times and rapid vocal fatigue. Direct extension into the thyroid may mimic a thyroid isthmus lesion.

ASSESSMENT AND STAGING

Outpatient setting

In the outpatient setting, the larynx is best assessed using the flexible nasal laryngoscope. The procedure should be explained to patients beforehand, and in the authors' experience, the vast majority of adults tolerate the procedure very well. In most patients, a decongestant spray with a lubricated endoscope will suffice. If due care and attention is used while inserting the endoscope and the examiner ensures minimal contact with the nasal walls and stays in the lumen of the nose, the patient experiences minimal discomfort. Others may need topical anaesthetic spray to reduce the discomfort associated with the procedure. Significant information can be gained via endoscopy that will aid the decision-making process. The value of this examination should not be underestimated as this information is often complementary to what is gained during rigid endoscopy. The latter will not provide information such as cord mobility and a panoramic view of the larynx, and undue reliance should not be placed on the subsequent general anaesthetic procedure to examine the larynx.

Some centres prefer to perform outpatient endoscopy of the larynx using rigid telescopes for the superior view it provides. This requires special topical anaesthetic preparation and is less well tolerated. However, with the increasing availability of modern high-resolution flexible endoscopes that allow simultaneous recording, there is less need to use rigid telescopes for assessment. The outpatient endoscopic assessment can also direct the examiner towards additional investigations if necessary. For example, the finding of salivary pooling in the pyriform sinus in the setting of a small glottic tumour should trigger concern and prompt examination of the hypopharynx and upper oesophagus.

Laryngeal dysplasia (LD) is commonly seen in the glottis, but can be seen virtually anywhere in the larynx. The clinical appearance is that of an inflamed, erythematous larynx, with leukoplakia or erythroleukoplakia. However, clinically abnormal areas in the larynx do not always exhibit histopathological evidence of LD and LD can be detected under the microscope in clinically normal appearing epithelium. Cancers present as proliferative, infiltrative lesions or a mix of both. These are easily recognized as abnormalities on endoscopic examination. Uncommonly, malignancies, usually non-squamous cancers, can present as submucosal masses. The abnormality caused by these lesions can be subtle and may be missed on casual inspection.

Imaging

Imaging for laryngeal mass lesions should include as a minimum cross-sectional imaging for all tumour stages. Options include computed tomographic (CT) or magnetic resonance imaging (MRI), with the chest being imaged too. This is dealt with in greater detail in Chapter 37, Imaging of the neck. MRI scans have higher sensitivity than CT scans in assessing cartilage invasion. Both imaging modalities have their own advantages and drawbacks and this is also discussed in detail in Chapter 37, Imaging of the neck.

Assessment under general anaesthesia

Rigid endoscopic assessment should not only assess the extent of the tumour and take a biopsy, but also be done by a surgeon who can make the decision as to whether the tumour can be resected transorally. Anatomical constraints may make even small tumours not easily resectable. In addition, the judgement about whether special anaesthetic measures may be needed during the surgery (e.g. jet ventilation) will also need to be made and it is often helpful to do this with an anaesthetist who will be able to provide the service.

Submucosal and subglottic mass lesions can be difficult to biopsy. In these instances, an incision on the mass using microlaryngeal instruments, or preferably with a laser, will open into the abnormal tissue enabling a representative biopsy.

All excised samples should be appropriately labelled and if necessary, mounted on suitable media and orientated for the pathologist.

Staging

The staging of laryngeal cancer is discussed in detail in Chapter 4, Staging of head and neck cancer.

LARYNGEAL PREMALIGNANCY

LD has a reported incidence of between 2 and 10 lesions per 100 000 population.[18] The clinical significance LD, also known as laryngeal intraepithelial neoplasia, lies in its propensity for malignant transformation.

The 4th edition of the *World Health Organisation Classification of Head and Neck Tumours*, published in 2017, has adopted a two-tier system, based on

the morphological criteria of the amended Ljubljana Classification, where the lesions are called Squamous Intraepithelial Lesions (SIL): low-grade SILs and high-grade SILs.[19] Reported malignant transformation rates vary between 11% and 25%, but identifying which patients will transform is impossible. Given the above issues with clinical and pathological diagnosis, there is no universal consensus in the investigation and treatment of this condition. Therefore, management practices vary significantly.

The British Association of Otolaryngologists Head and Neck Surgeons have generated consensus on the management of this condition through a national survey and a joint meeting between surgeons and pathologists. The following sections will summarize these consensus guidelines, while recognizing that high-level evidence does not exist and that practices will differ based on local service arrangements and geography.

In larger centres, it is preferable if there is a nominated or a defined number of surgeons providing LD management service. It is also desirable that surgeons managing this condition have received appropriate training in laryngology. Severe dysplasia is preferably managed by personnel with expertise in head and neck cancer management.

All efforts should be made to reduce risk factors. Patients should be counselled regarding tobacco use, especially smoking in this setting. Patients who have symptoms of laryngopharyngeal reflux should also be counselled about anti-reflux measures; this may or may not include proton pump inhibitors.

LESIONS THAT HAVE NOT BEEN PREVIOUSLY TREATED

In patients who have been diagnosed to have LD following an initial biopsy, but have had no previous treatment, these are suggested management principles.

1. The overall appearance of the lesion (single, multiple or confluent) should be the most important factor in deciding management.
   - All visible single and multiple foci should be completely excised.
   - Widespread, confluent leukoplakia should be mapped using multiple biopsies. Following mapping, a staged resection should be offered if feasible. There should be a low threshold for re-biopsy in the presence of widespread disease.
   - All biopsies, including from multiple foci, should be mounted on suitable media for orientation before sending for pathological examination.
   - The general fitness of the patient will play a role in decision making.
2. Documentation in theatre
   - Intra-operative photographs should be performed before surgery and of the post-operative larynx.
   - Assessment during general anaesthesia should include palpation of the vocal cord.
   - Where possible, the intra-operative photographs should be shared with pathologists.
   - The details of type of biopsy (incisional or excisional; if mapping biopsies, identify them in the pictures) should be stated.
   - The technique and extent of resection should be documented.
   - The procedure should be categorized according to the European Laryngological Society classification.
3. Excision technique
   There is no gold standard in the tool used to resect the LD lesion. However, cold steel or laser resection is recommended over monopolar cautery
   - If laser excision is contemplated, carbon dioxide laser is recommended owing to the laser properties enabling minimal penetration, thus reducing collateral damage.
   - Laser ablation (i.e. laser used on the surface of the lesion to destroy the epithelium rather than excising it) is discouraged as no specimen will be available for diagnosis and there is a higher risk of damage to the voice.
   - Vocal cord stripping is not recommended at all owing to the high risk of damage to the vocal cord.
   - Radiotherapy should be offered only in rare circumstances for patients where there is very high risk/suspicion of conversion to malignancy and surgical resection is not possible owing to patient or tumour factors.
4. The histology should be studied in the context of the clinical findings post-operatively. If there is a report of severe dysplasia and the follow-up endoscopy shows a proliferative lesion, the patient should be re-biopsied at the earliest opportunity. The presence of dysplasia at the margins should not be of great concern, especially in mild dysplasia. This is not an indication for a repeat excision.

Figure 14.1 shows an algorithmic approach that summarizes the above points.

Management of persistent or recurrent lesions

The management of these lesions should follow the general principles and the treatment of the initial presentation as discussed above. Additional considerations are:

- Localized mild or moderate local dysplasia should be offered re-excision.
- Widespread mild or moderate widespread dysplasia may be observed or excised.
- The decision to excise should be based on a change in appearance (heterogenous texture; erythroplakia; proliferative features) or change in symptoms.
- The effect of further resections on the patients' voice should also be taken into consideration.
- Recurrent focal severe dysplasia should be managed as a T1 laryngeal carcinoma with surgical resection (e.g. cordectomy) where possible. Radiotherapy may

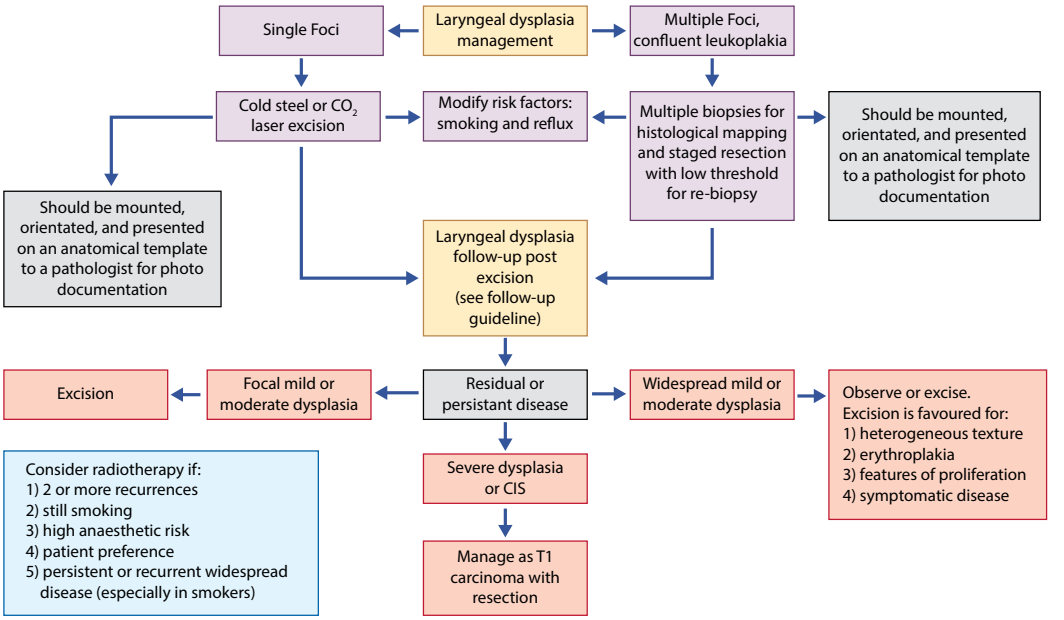


Figure 14.1 Algorithmic approach for the management of laryngeal dysplasia based on a multiprofessional consensus. (Redrawn from Cosway B, Paleri V. Laryngeal dysplasia: an evidence-based flowchart to guide management and follow up. *J Laryngol Otol*. 2015; **129**(6): 598–9.)

be considered in special circumstances only, on a case-by-case basis. Examples include patients who have had two or more recurrences, who continue to smoke, have high risk of anaesthetic complications or have poor access to the larynx.

- For persistent or recurrent widespread severe dysplasia, radiotherapy should be considered as an option.

Follow-up strategies

The recommended frequency and duration of follow-up is set out in **Figure 14.2**.

1. The ENT-UK guidelines recommend that all patients should be followed up as per the following standards:
   - Use of a flexible nasendoscope to view the larynx.
   - Colour photo documentation in the patient notes is essential.
   - Document continuing risk factors if present.
   - Stroboscopy is helpful if available, but is not necessary.
   - Follow-up of low-risk lesions can be performed by General ENT surgeons in peripheral clinics. High-risk lesions are preferably followed up by an ENT surgeon with a special interest in Head and Neck surgery or laryngology.
2. Outcomes should be assessed at baseline, 6 months and 12 months
   - Outcomes include recurrence and progression to cancer.
   - Voice outcomes should also be assessed using a patient-reported voice questionnaire.

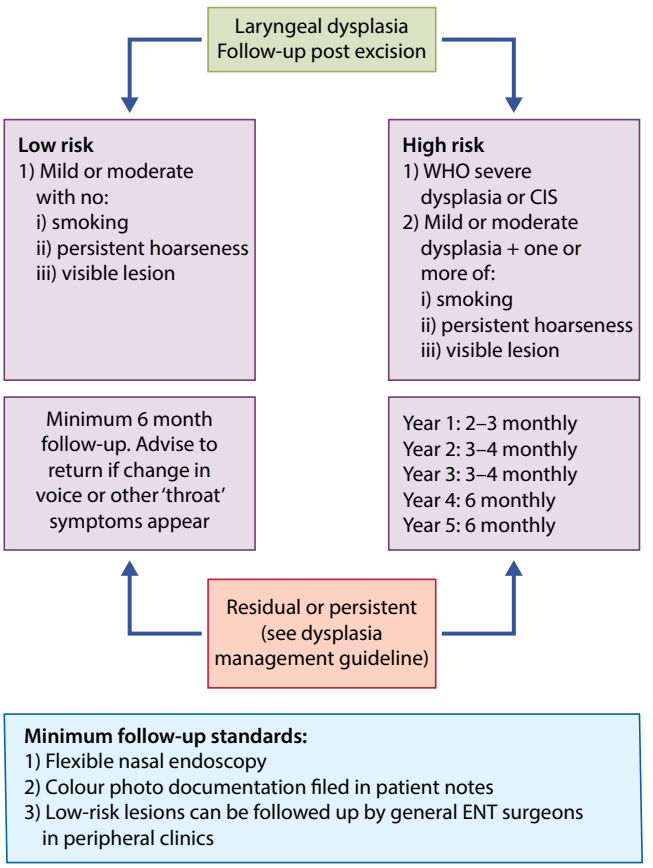


Figure 14.2 Algorithmic approach for the follow-up of laryngeal dysplasia based on a multiprofessional consensus. (Redrawn from Cosway B, Paleri V. Laryngeal dysplasia: an evidence-based flowchart to guide management and follow up. *J Laryngol Otol* 2015; **129**(6): 598–9.)

LARYNGEAL MALIGNANCIES

Decision-making

As there is evidence base to support surgical and non-surgical treatment, all decisions for management are best made in a multidisciplinary setting. The benefits of multidisciplinary working are set out in Chapter 32, Multidisciplinary team working. A multidisciplinary discussion allows the entire treating team to assess the clinical findings, radiology and pathology, along with information provided by allied healthcare personnel about the patients' function, current quality of life, preferences, comorbidity and psychosocial context. In combination, all the above are invaluable in making the appropriate treatment choice.

Management of early stage laryngeal cancers

TREATMENT PHILOSOPHY

Function and survival

Although randomized data do not exist, most practising surgeons and oncologists believe that voice outcomes are comparable for T1 glottic cancers treated by either modality, and for mid-cord lesions, this should rarely be the basis for treatment selection. Even in patients who undergo resections that are type III cordectomy or more advanced, vocal function routinely returns to pre-operative levels following the initial healing period.[20] In a meta-analysis of 362 patients with a mean follow-up time of 47 months, where voice outcomes measured using the Vocal Handicap Inventory, no significant difference in post-treatment VHI scores were detected between radiotherapy and surgery.[21] Systematic reviews have identified no advantages in voice outcomes for patients with T1 glottic cancer treated by radiotherapy (RT) compared to transoral laser microsurgery (TLM).[21–23]

In the UK, the EaStER (Early Stage glottic cancer: Endoscopic excision or Radiotherapy) feasibility trial was set up to compare TLM with RT in laryngeal cancer staged T1, but failed to recruit the required number of patients. A detailed qualitative analysis[24] identified several reasons for failure. These included lack of consensus among investigators regarding the primary outcome, non-adherence to eligibility criteria and lack of equipoise in presenting trial information. However, the ultimate reason resulting in the failure to recruit was that patients declined to be randomized because of the largely practical benefits of TLM over RT. In particular, patients favoured TLM over RT as TLM was completed as a day-case procedure whilst RT involved several weeks of daily treatment. Moreover, recovery following TLM in T1 glottic cancers is rapid with no impact on swallowing, rapid return to normal activities and minimal impact on the voice. Given the above reasons, mid-cord lesions are largely excised by TLM and larger lesions, especially when the impact on voice is considered to be greater, are treated by RT.

It is commonly believed that in early cancers, surgery or RT as a single treatment modality, offer equivalent survival outcomes. As there is less anatomical disruption to the larynx following RT, the voice quality following treatment is superior, especially when the tumour involves the AC or extends across two sites. Thus, the choice of treatment is based on patient choices and the likelihood of advantageous voice outcomes following treatment. Warner et al.[25] updated their systematic review comparing RT, open surgery and endolaryngeal excision (with or without laser) for early (T1, T2a) glottic laryngeal cancer. Although one trial that satisfied inclusion criteria was identified, it was associated with a high risk of bias. The review concluded that all are presently accepted modalities of treatment and the published large case series of each treatment suggest that they confer similar survival advantages. In an assessment of voice quality after treatment of early vocal cord cancer, a randomized trial comparing laser surgery with radiation therapy concluded that overall voice quality between the groups was rated similar, but voice was more 'breathy' and the glottal gap was wider in patients treated with laser surgery than in those who received radiation therapy. Patients treated with radiation therapy reported less hoarseness-related inconvenience in daily living 2 years after treatment.[26, 27] The equivalence of the two modalities has been questioned by some new data. In a population-based analysis of 10 429 patients with localized laryngeal cancer (90% T1 and T2; 10% T3) from the SEER database between 1995 and 2009, Misono et al.[28] observed that while single modality treatment increased over the years (radiation or local surgery), combined modality treatment decreased, with these changes being statistically significant. Survival was analyzed by treatment modalities. Compared with radiation only, which was the reference category, patients who underwent 'local surgery only' or 'local surgery and radiation' had lower hazards of death ($P<.0006$ and $P<.0001$, respectively), with the survival differences persisting beyond 5 years of treatment. Whereas the 5-year disease specific survival rates for the 'local surgery' and 'local surgery and radiation' groups were 91% and 90% respectively, the 5-year survival rate for the 'radiation only' group was 83%.

Similar results have been produced in a database analysis for supraglottic cancers alone. Arshad et al.[29] analyzed outcomes in 2631 patients with early stage supraglottic cancer from the Surveillance, Epidemiology and End Results (SEER) database in the United States. In patients with T2N0 cancer, partial laryngeal surgery and neck dissection led to significantly better 5-year disease specific survival (86% vs 60%; HR = 0.31, $p<0.001$) and overall survival (77% vs 45%; HR = 0.36, $p<0.001$) compared to radiation therapy. These data go against the common perception that in early cancers, either modality offers equivalent survival.

Such retrospective reports, despite large numbers, have associated bias, but are hypothesis generating and clearly indicate the need to look for differences between these treatment methods in a controlled setting. However, it is highly unlikely that an adequately powered randomized controlled trial will be performed in the near future. Given the above data, the authors believe that if expertise is available and all else being equal, all patients should be offered

both treatment options with early stage cancers. The volume of data supporting better survival for the surgical arm is compelling and should be shared with patients.

ORGAN PRESERVATION AS AN ARGUMENT FOR PRIMARY SURGERY FOR EARLY LARYNGEAL CANCER

This is an important issue that is not often discussed during the decision-making process when treatment is planned for early laryngeal cancer, especially stage II. It should be recognized that T2 cancers, despite being categorized as 'early disease', have a significantly higher risk of local recurrence. This has been demonstrated in several studies. Organ preservation following the use of RT in a series of 260 patients with T2 laryngeal squamous cell carcinoma (LSCC) was 81% and 74% for T2a and T2b tumours respectively.[30] McCoul et al.[31] have shown in a meta-analysis of 21 studies (published between 1967 and 2007) that for T2a and T2b laryngeal tumours treated by radiation therapy, mean local control at 5 years was 76.2% (SD 10.2%) and 64.4% (10.2%) respectively. When four of the 21 papers from this study (n = 653) that were published in the last decade are considered separately, local 5-year control rates range between 70% and 80%, indicating no significant improvement in control rates. In a single centre[32] series of 1615 patients with laryngeal cancer of all stages, the 3-year risk of recurrence for T2 cancer was 27.3%. Thus, at least 25% and up to 30% of patients will suffer local disease recurrence when primary RT is used to treat T2 LSCC. These figures have been replicated in large population cohort studies.[33] In the patients who develop disease recurrence following RT, organ preservation is usually not feasible due to tumour and patient factors and total laryngectomy is often required, although open partial laryngectomy (OPL) (see 'Open partial laryngectomy (OPL) below) may be feasible in selected cases. Consequently, most patients who develop local recurrence of T2 LSCC following initial treatment with RT are treated with total laryngectomy, with the inevitable costs to voice and swallowing function as well as overall quality of life.

Prospective datasets suggest that between 7% and 15% of patients treated with transoral procedures for early laryngeal cancer will suffer local disease recurrence. Unlike in patients who recur following RT, a greater repertoire of re-treatment options is available (OPL, repeat TLM/TORS and/or RT) in an attempt to preserve a functioning larynx. This is demonstrated by three large case series with more than 100 patients each of T2N0 disease, with organ preservation rates of 84% to 96% are observed for T2N0 tumours.[33–35] As expected, survival rates are not different across the two modalities. A recent systematic review 48 papers pooled data from 1156 patients treated by TLM and 3191 treated with RT, showed similar local control rates.[36]

Similar high rates of laryngeal preservation are seen in series reporting the outcomes of surgery for T3 tumours of the larynx (73–83%)[35, 38] providing further support for the efficacy of this sequential organ preservation approach. As a result of these and other data, a recent review concluded that there was higher chance of laryngeal preservation if surgery was used as the initial treatment modality in T2 tumours.[39] While studies suggest that the voice outcome may be poor in surgically treated patients,[40] there is no doubt that the poorest voice results when a patient loses their larynx. It follows that the discussion to be had with the patient is whether an initial potential reduction in voice quality is acceptable to retain a fully functioning larynx.

HEALTH ECONOMICS AND EARLY GLOTTIC CANCER

Surgery for early stage laryngeal cancer has been shown to have superior cost-utility compared to RT in a meta-analysis.[41] A recent analysis compared TLM against RT in the management of early stage (T1a, T1b and T2) glottic cancer to identify the most cost-effective treatment modality within the UK National Health Service.[42] A Markov decision model was populated using data from updated systematic reviews and meta-analyses, with attributable costs from NHS sources. The study concluded that over a 10-year time horizon, RT as the initial treatment strategy was more expensive (£2654 vs £623) and less effective (quality adjusted life year (QALY) reduction of 0.141 and 0.04 in T1a and T1b-T2 laryngeal cancer respectively) than TLM. The dominance of TLM for T1a cancers was unchanged on sensitivity analysis in most modelled scenarios, while for T1b-T2 laryngeal cancers, RT became more cost-effective when TLM costs were increased and when a QALY gain was assumed for RT. In the UK, TLM is recommended as optimal treatment for T1a glottic tumours, unless robust contraindications exist.

A cost-effectiveness analysis considering the Canadian healthcare system[43] found TLM to dominate RT with higher QALYs and lower costs. A study of the itemized average costs of RT and TLM in the American healthcare system in 2001 showed RT to be 15.5 times more costly.[44] Using the 5-year survival rate as the 'effect' in a cost-effectiveness analysis, Diaz-de-Cerio et al.[45] found that TLM offered a saving of €1342.68 per year in the Spanish healthcare setting, concluding that TLM was the dominant option for T1 and T2 glottic cancers.

TREATMENT OPTIONS

There has been a significant expansion in the repertoire of surgical procedures used to treat early laryngeal cancer.

Transoral partial laryngectomy

Newer developments permit partial laryngectomy to be performed through transoral approaches. TLM is very commonly used for early cancer of the laryngeal glottis and the supraglottis, with widespread expertise and has also been shown in several controlled series to provide excellent oncological and functional outcomes,[35] comparable to OPL.[46] Centres with expertise in this procedure have moved to a stage where they offer patients with this stage of disease only surgery, with consistently excellent long-term results.[35, 47, 48] TLM is discussed in detail in Chapters 22, Transoral laser microsurgery and 23, Anatomy as applied to transoral surgery. The other

method to perform transoral partial laryngectomy is with the assistance of a robot, used primarily for supraglottic cancers; transoral robotic surgery is dealt in greater detail in Chapter 29, Applications of robotics in head and neck practice.

Open partial laryngectomy (OPL)

Although OPL has been in use in Europe (especially France and Spain) for many years, this procedure has not gained wide acceptance in many countries. Reasons include easier access to radiation therapy services and concerns about post-operative function, which has consequently led to loss of expertise. However, recent publications confirm good to excellent long-term functional and oncological outcome for these procedures,[49] and refinement of the procedure[50] that leads to consistent results. A more detailed treatment of OPL can be found in Chapter 27, Open conservation surgery for laryngeal cancer.

RADIATION THERAPY

RT as a single modality offers an alternative to organ preserving surgical options in the treatment of early LSCC (glottic and supraglottic). The long-term local control rates for early glottic carcinomas are similar to organ preserving surgical approaches (TLM). RT is preferred in most centres in the UK and the United States, where the tumour involves AC and in T2 glottic tumours, largely due to better functional outcomes and to a lesser extent due to the low availability of surgical expertise. This modality is also the preferred option in patients with poor access for surgery and/or high risk for general anaesthesia.

The long-term local control rates following RT alone for early supraglottic carcinomas are also similar to surgery with 5-year local control rates of 100% for T1 and 86% for T2.[51] With increasing expertise in minimal access surgery, the proportion of patients treated with surgery is likely to increase.

TREATMENT PRINCIPLES

Transoral laser microsurgery

Glottic cancers: The standard of care for surgical treatment of mid-cord glottic cancers is TLM. For mid-cord lesions staged T1a, TLM excision has a very high cure rate[23, 27] with the undeniable advantage of higher laryngeal preservation rates[27, 52] and is commonly recommended in most MDTs where expertise exists. TLM to excise T1a lesions is easily taught and learnt, and the treatment process is rapid and preferred by patients,[24] with health economic benefits.[42]

TLM is less commonly used for T1 cancers that involve the AC and for T2 cancers as the impact of surgical resection on the voice is considered to be greater, although cure rates are at least equivalent, if not higher than those achieved by radiation therapy (**Tables 14.2** and **14.3**). The suitability of AC lesions for TLM has been debated in the literature, with some reports suggesting that AC location has an impact on prognosis,[53–56] while others do not.[57] A systematic review[58] of T1b tumours treated by either modality showed a trend towards improved local control when treated with RT, with the caveat that this finding was based on a limited number of published outcomes (n = 194).

All glottic cancers resected by the TLM approach should be classified as per the European Laryngological Society (ELS) system,[59] which describes six types of cordectomy based on the extent of resection of the vocal cord and the adjoining structures (**Table 14.4**).

It is well recognized that AC lesions can exhibit cartilage invasion in up to 20% of cases at presentation.[60, 61]

It is important that the resection specimens are orientated for the pathologist; small specimens sent in a fixative solution can cause shrinkage and curling of the tissue hindering accurate histological interpretation. The techniques used to orientate larger specimens are not effective and thus should be mounted and orientated on suitable media. A popular

TABLE 14.2 Literature review of post-treatment status for anterior commissure SCC – a comparison between surgical outcomes versus radiotherapy

Study (Anterior commissure SCC)	Primary Treatment	Local control rate	Laryngeal preservation rate	Disease-free survival	Overall survival
Mendelsohn et al.[20]	LASER	83.3%	93.3%	96.7%	96.7%
	RT	NA	NA	NA	NA
O'Hara et al.[58]	LASER	76.8%	NA	NA	NA
	RT	86.2%	NA	NA	NA
Taylor et al.[62]	LASER	95%*	100%*	88.7%*	94.1%*
	RT	85.9%*	85%*	85.9%*	94.8%*
Kerr et al.[40]	LASER	99%	100%*	99% +/-2%	91% +/- 3%
	RT	99%	79%*	99% +/- 1%	90% +/- 4%
Bradley et al.[63]	LASER	84%^	93%^	73%*^	NA
	RT	90%	NA	NA	NA

RT – radiotherapy; * - p values>0.05; NA – 'non-applicable' as the authors did not have any considerations for these criteria; ^ - Steiner et al, 2004.

TABLE 14.3 Literature review of post-treatment status for early glottic SCC – a comparison between surgical outcomes versus radiotherapy

Study	Primary Treatment	Local control rate	Laryngeal preservation rate	Disease-free survival
Wilkie et al.[64]	LASER	92%	98%	86%
	RT	NA	NA	NA
Kerr et al.[40]	LASER	NA	100%	99%
	RT	NA	92%	99%
Hartl et al.[65]	LASER	94%	96%	89%
	RT	NA	NA	NA
Peretti et al.[66]	LASER	92.7%	97.1%	81.3%
	RT	NA	NA	NA
Chera et al.[30]	LASER	NA	NA	NA
	RT	94%	95%	97%
Schrijvers et al.[52]	LASER	71%	95%	NA
	RT	73%	77%	NA
Krengli et al.[67]	LASER	96%	96%	95.9%
	RT	90%	91.2%	91.3%
Smith et al.[68]	LASER	NA	97.4%	76.9%
	RT	NA	96.3%	88.9%
Ambrosch et al.[34]	LASER	99%	98.8%	NA
	RT	NA	NA	NA
Spector et al.[69]	LASER	77%	90.2%	77%
	RT	90%	85.1%	85%
Rosier et al.[70]	LASER	88%	NA	83.9%
	RT	90%	NA	90.2%
Foote et al.[71]	LASER	NA	92.5%	87.7%
	RT	NA	94.5%	94.7%

option is to use dehydrated cucumber as a mount with the specimen anchored to it by tissue glue (**Figure 14.3**).[72]

It should be recognized that for the specimens resected by TLM will have much smaller margins than traditional open surgery, with margins of the order of a millimetre being appropriate, which should not be misinterpreted as close or positive margins. Thus, the pathologist should be fully apprised of the nature of the resection and there should be clear channels of communication between the surgeon and the pathologist for appropriate reporting of the resection margins. The authors cannot emphasize enough the importance of clinico-pathological correlation in transoral resections. This is often an area of contention and guidelines for management after TLM have been published by the British Association of Otolaryngologists — Head and Neck Surgeons.[73] These are summarized in **Box 14.1**.

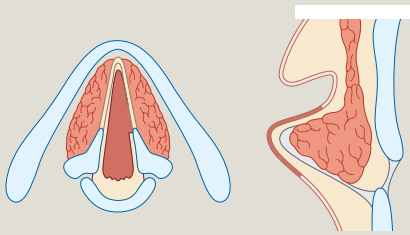
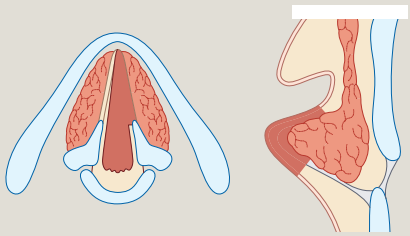
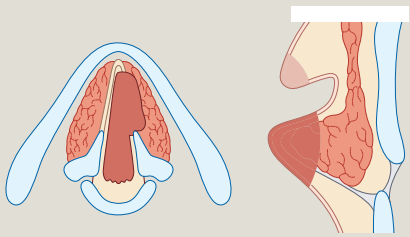
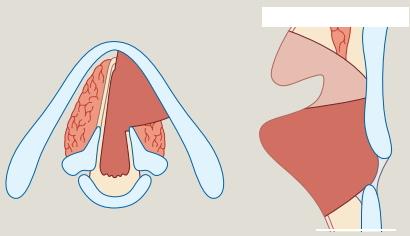
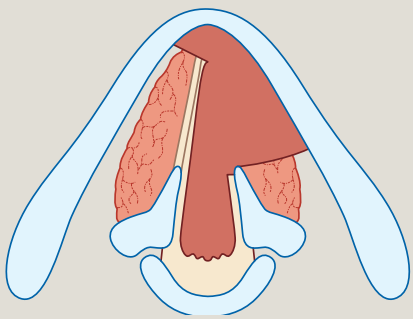
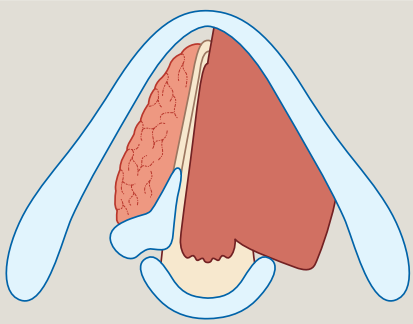
Supraglottic cancers: All supraglottic cancers resected by a transoral approach should be classified as per the ELS system,[74] which describes four types of supraglottic laryngectomy based on the extent of resection (**Table 14.5**). As stated earlier, it is important that all resections be orientated for the pathologist. Unlike glottic cancer, where possible, a conscious effort should be made to achieve surgical margins of at least 5 mm during resection. Further patient side biopsies can be sent for confirmation of the margin status.

Unlike glottic cancers, patients following transoral resections for supraglottic tumours can be expected to have significant swallowing dysfunction in the early stages, even up to 6 weeks at times. Appropriate swallow assessment, therapy and supplemental feeding may be necessary. However, the author's experience and the literature suggest that the swallow outcome is invariably favourable and patients achieve very good functional swallow.[75, 76]

Open partial laryngectomy

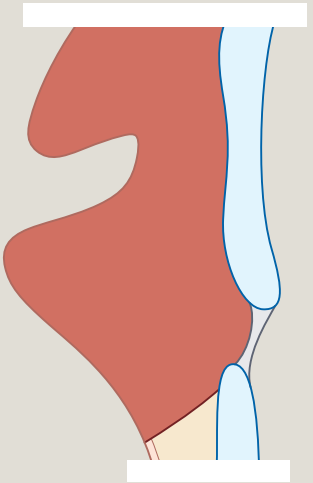
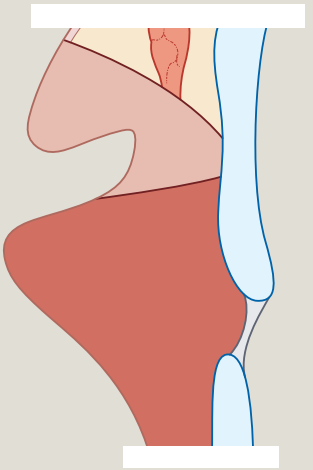
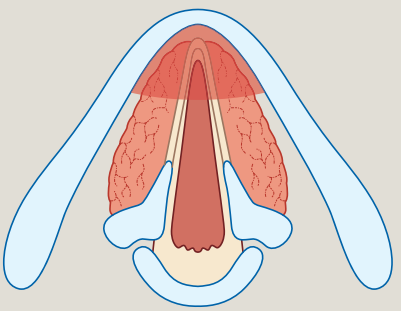
There is little debate about the oncological efficacy of OPL as primary treatment for early laryngeal cancer. The relatively poor functional outcome has been the deterrent to wide use of this procedure. A systematic review by Thomas et al.[49] on the outcome of surgically treated laryngeal cancer showed a pooled local control rate at 24 months from 5061 patients to be 89.8% (95% CI 88.3–91.2), a pooled overall survival of 79.7% (n = 3967; 95% CI 76.5–782.8) and pooled mean disease-free survival of 84.8% (n = 2344; 95% CI 80.6–88.7). These figures are comparable to any other treatment modality, despite the fact that a substantial proportion of the cohort in the study had T3 disease. Some of the studies with large cohorts from high-volume centres are

TABLE 14.4 European Laryngological Society classification of cordectomies for glottic carcinomas[59]

Definition	Type	Description
Subepithelial cordectomy	I 	Resection of the vocal fold epithelium passing through the superficial layer of the lamina propria
Subligamental cordectomy	II 	Resection of the epithelium, Reinke's space and the vocal ligament
Transmuscular cordectomy	III 	Resection of the vocal fold down through vocalis muscle
Total cordectomy	IV 	Resection of the cord, which extends form the vocal process to the anterior commissure. The depth of the surgical margins reaches or includes the internal perichondrium of the thyroid ala
Extended total cordectomy	Va 	Resection includes the contralateral vocal fold and the anterior commissure
	Vb 	Resection includes the arytenoids

(Continued)

TABLE 14.4 *(Continued)* European Laryngological Society classification of cordectomies for glottic carcinomas[59]

Definition	Type	Description
	Vc 	Resection includes the subglottis
	Vd 	Resection includes the ventricle and false cords
Anterior commissurectomy	VI 	Resection of the anterior commissure with bilateral anterior cordectomy; may include the subglottic mucosa and the cricothyroid membrane

summarized in the table below. OPL has been used in the past for supraglottic cancers with significant success rates.[49] It is recommended that the ELS system of classification of open horizontal laryngectomy be used by surgical practitioners to collate data and report on this technique.[77] However, as the procedure involves disruption of the neck musculature and also sensory supply to the pharynx, functional outcomes were even less predictable than with resections for glottic cancer. With the emergence of transoral approaches, OPL is less used as a primary procedure.

Transoral robotic surgery (TORS)

Glottis: Early experience with this modality suggests equivalent oncologic control rates as for TLM.[78, 79] However, the advantages of a TORS approach for glottic tumours are yet to be defined.

Supraglottis: TORS has been a useful addition to the surgical armamentarium in the management of supraglottic tumours. The high-definition three-dimensional vision of the operating field, wristed movement with 7 degrees of freedom and the ability to work without the target

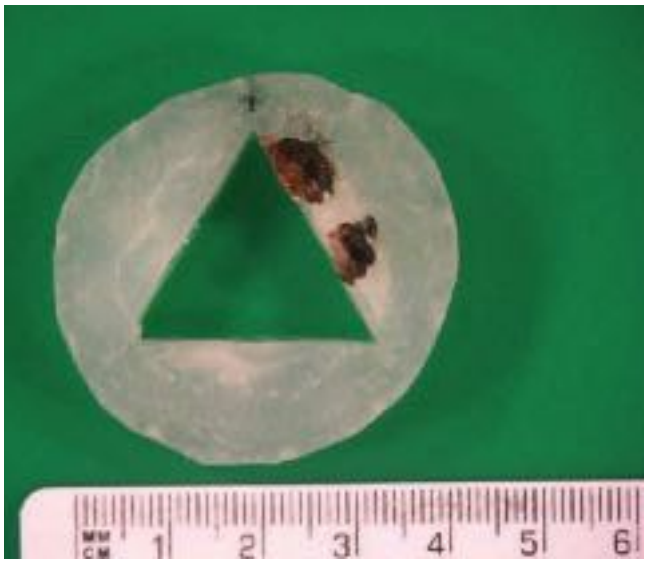


Figure 14.3 Cordectomy specimen mounted on dehydrated cucumber.

being in line of sight (as for laser microsurgery) has made robotic supraglottic laryngectomy a procedure that can be taught and learnt with greater ease than TLM procedures (**Figure 14.4**). As for TLM procedures, support systems for the post-operative swallowing dysfunction should be in place. As **Table 14.7** suggests, outcome data are comparable to those performed by the established TLM techniques.

Neck management

T1 glottic cancer usually presents with no metastatic lymphadenopathy and the risk of occult nodes are very small. Thus, treatment for the primary site alone will suffice. T2 tumours also are less prone to metastatic spread, but given the risk of occult spread of ~7%, there is no consensus on whether the neck should be treated in this setting.

With supraglottic, unlike glottic cancers the neck will almost always need to be addressed even if there is no clinical or radiological evidence of disease. The incidence of occult neck metastases is well over 15%. Exceptions to this rule might be small cancers of the tip of the epiglottis with minimal invasion, or for salivary malignancies in this region.

Radiation therapy

Glottic carcinoma: RT is delivered using megavoltage photons (4 to 6MV), the target volume encompasses the primary tumour. The regional lymph nodes are not treated due to low risk of lymph node metastasis. The treatment is usually delivered using two lateral fields covering the laryngeal skeleton from thyroid notch superiorly to the inferior border of cricoid. The field size ranges from 4 × 4 cm to 5 × 5 cm, with larger field size for T2 tumours, depending on the extent of tumour. The most commonly used fractionation regime in the UK is 50 to 55 Gy in 16 to 20 daily fractions over 3 to 4 weeks. Yamazaki et al. reported a prospective randomized trial in patients with T1N0M0 glottic carcinoma receiving definitive radiation treatment. The study compared two different doses per fraction (2 Gy/fraction Vs 2.25 Gy/fraction). The 5-year local control rates were 77% after 2 Gy per fraction and 92% after 2.25 Gy per fraction with no difference in either acute or late toxicity.[84]

BOX 14.1 Post-resection management following cordectomy for early laryngeal cancer

1. All specimens must be orientated and mounted for histological analysis.
2. Terminology such as 'complete excision', 'close margins' and 'incomplete excision' are misleading. It is advisable for the pathologist to precisely specify the sites on the orientated specimen where the margins are less than 1 mm. This will help in planning a second look and during follow-up.
3. Based on the pathologist's report, the following actions are recommended:
   (i) If the resection margins are considered surgically adequate and are clear by a millimetre or more on histology, no second look is warranted. Routine clinical monitoring will suffice.
   (ii) If the surgical margins are not in doubt but the histology shows tumour at the margins, a second look is recommended 6–8 weeks later.
   (iii) If the surgeon has concerns about resection margins and residual tumour is confirmed on histological analysis, the feasibility of further TLM resection should be considered.

Future management should be discussed at the MDT meeting and careful consideration given to alternative non-endoscopic treatment options.

Supraglottis: The target volume for radiation treatment encompasses the primary tumour and lymph nodes bilaterally (Level II–IVa) due to high risk of microscopic lymph node metastasis. The at risk nodal levels are treated to a reduced dose (prophylactic dose). The fractionation regime commonly used is as for glottic carcinomas. Alternatively, a regime of 65 Gy in 30 fractions over 6 weeks is used.

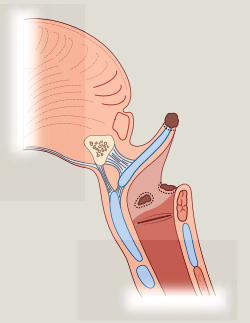
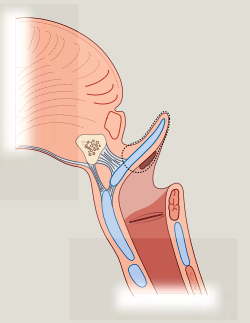
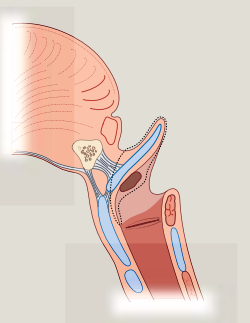
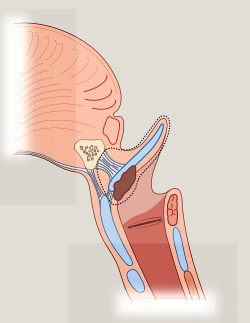
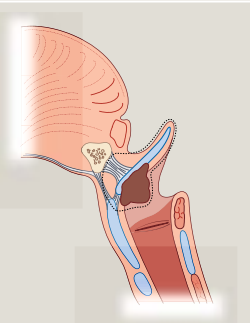
Management of T3 laryngeal cancer

TREATMENT PHILOSOPHY

Functional issues

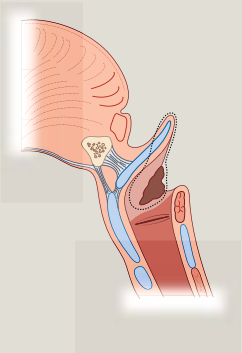
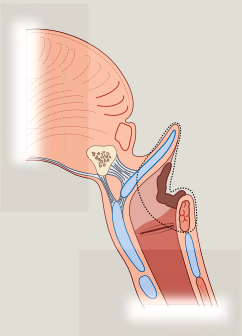
Physicians treating laryngeal cancer have always assumed that laryngeal preservation is a priority for all patients. In 1981, when total laryngectomy was the standard of care, McNeil et al. published a landmark study[85] scrutinizing the trade-off between quantity and quality of life faced by patients diagnosed with locally advanced laryngeal cancer. The utility analysis was performed on 37 healthy volunteers based on the assumption that RT was associated with a poorer survival, but a better voice outcome, while laryngectomy achieved an improved survival at the expense of an artificial voice. The study showed that not everyone valued survival at any price and that survival may not be the most important outcome for all patients. This study has no doubt contributed to the organ preservation

TABLE 14.5 European Laryngological Society classification of transoral resections for supraglottic carcinomas[74]

Definition	Type		Indication and Description
Limited excision	I		Excision of small superficial tumours anywhere on the supraglottis
Medial supraglottic laryngectomy with partial resection of the pre-epiglottic space	IIa		Tumours of laryngeal surface of epiglottis located above the hyoid bone: resection includes the suprahyoid epiglottis
	IIb		Tumours extending below the hyoid: resection includes a total epiglottectomy
Medial supraglottic laryngectomy with resection of the pre-epiglottic space	IIIa		Tumours extending to petiole of epiglottis: resection must include the pre-epiglottic space
	IIIb		Tumours of the infrahyoid epiglottis extending to the ventricular fold: resection includes ventricular folds dissected from the thyroid cartilage

(Continued)

TABLE 14.5 *(Continued)* European Laryngological Society classification of transoral resections for supraglottic carcinomas[74]

Definition	Type		Indication and Description
Lateral supraglottic laryngectomy	IVa		Tumours of the threefolds' region: resection of free edge of the epiglottis, the aryepiglottic fold, the pharyngo-aryepiglottic fold and the ventricular fold
	IVb		Tumour extending to arytenoids: resection includes the arytenoids and inner/medial or anterior wall of the pyriform fossa

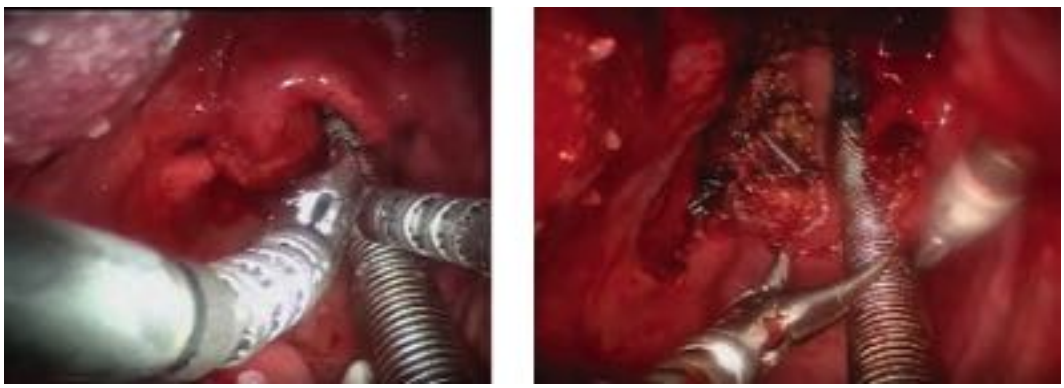


Figure 14.4 Transoral robotic supraglottic laryngectomy for a T2N0 lesion.

TABLE 14.6 Recommended treatments for early glottic cancer

T stage	1st choice	2nd choice	3rd choice
T1a	TLM	RT	OPL
T1b	RT or TLM*	OPL	-
T2a	RT or TLM*	OPL	-
T2b	(C)RT	TLM	OPL

* based on patient choice, local expertise, tumour and patient factors.

trials in the 1990s and the first decade of this millennium (see below). Although quality-of-life comparisons between patient groups treated with total laryngectomy or chemoradiation show differences in functional subscales, the overall QOL scores of both groups seem similar.[86, 87] Clearly significant clinical experience has been accrued since the organ preservation protocols have been implemented across the world. When Laccourreye et al.[88] polled 163 otorhinolaryngologists about the percentage chance of cure that they would be prepared to trade-off to preserve their larynx when faced with advanced stage laryngeal cancer, the professionals were almost equally

TABLE 14.7 Literature review of post-treatment status for early supraglottic laryngeal SCC – a comparison between surgical outcomes versus radiotherapy

Study (early supraglottic SCC)	Primary Treatment	Local control rate	Laryngeal preservation rate	Disease free survival	Overall survival
Swanson[80]	LASER	86%	NA	NA	NA
	RT	70%	NA	NA	63%
Canis et al.[81]	LASER	85%	96%	92%	76%
	RT	NA	NA	NA	NA
Motta et al.[82]	LASER	63%	85.4%	94%	88%
	RT	NA	NA	NA	NA
Ambrosch et al.[83]	LASER	89%	NA	83%	76%
	RT	NA	NA	NA	NA

TABLE 14.8 Recommended treatments for early supraglottic cancer

T stage	1st choice	2nd choice
T1	RT or TLM/TORS*	OPL
T2	RT or TLM/TORS*	OPL

* based on patient choice, local expertise, tumour and patient factors.

divided between total laryngectomy and larynx preservation. These authors[89] also performed a similar questionnaire survey on 269 patients attending the otolaryngology service for various problems and concluded that laryngeal preservation is not a major objective of treatment shared by patients filling a questionnaire devoted to the choice of treatment when facing an advanced laryngeal cancer.

Hamilton et al.[90] replicated the work by McNeil et al.[85] in a more robust fashion. They developed four health state descriptors representing total laryngectomy or chemoradiotherapy with either optimal outcome or with complications. They recruited 114 participants demographically matched to the head and neck cancer population, and asked them to rank the outcome scenarios, assign utility values to each health state using time trade-off and rate the importance of survival on treatment choice. This study concluded that the functional outcome of treatment was a greater determinant of a laryngeal cancer health state utility value than treatment modality and that in many individuals, larynx preservation may not be the primary consideration for treatment selection. This puts in perspective the discussion in the next section on treatment choices for these patients.

RECURRENCE, SURVIVAL AND CONTROVERSY AROUND TREATMENT CHOICES

In the latter part of the 20th century, the standard treatment for T3 laryngeal cancer was total laryngectomy. Indeed, no study has shown improvements in local control and survival compared to total laryngectomy. The landmark Veterans Affairs study[91] compared induction chemotherapy followed by radiation to total laryngectomy and is to date the only study to have compared surgical management with non-surgical management. The study recruited 332 patients with stage III or IV laryngeal squamous carcinoma who were randomized to either three cycles of chemotherapy followed by RT or surgery and RT. In the non-surgical arm there was an assessment after two cycles of chemotherapy. Patients who did not clinically respond crossed over the surgical arm and were treated by total laryngectomy. The study reported comparable survival in both groups of 68% at 2 years. Overall the laryngeal preservation group was 64% in those treated in the non-surgical arm. This study was the first to suggest that non-surgical treatment was a valid option for stage III and IV laryngeal tumours. The Veterans Affairs study had a higher proportion of supraglottic tumours compared to glottic tumours (208 vs 124). The majority were T3 (216) tumours, with a Karnofsky score of >80 in 253 of the patients. Patients who eventually needed a laryngectomy in the non-surgical arm had glottic tumours, fixed vocal cords, gross cartilage involvement and stage IV or T4 cancers. The above factors should be taken into consideration when interpreting the results.

The Intergroup Radiation Therapy Oncology Group (RTOG) 91–11 trial[92] randomized 547 patients to one of the three study groups, which included RT only, induction chemotherapy followed by radiation (ICRT) and radiotherapy with concurrent cisplatin (CRT). The study found that at 2 years, a statistically higher proportion of patients who received CRT had an intact larynx after RT (88%) compared to ICRT (75% P = 0.005) or RT (70%, P<0.001). The rate of locoregional control was also significantly better with CRT (78 percent, vs 61 percent with ICRT and 56 percent with RT only). This trial showed that in suitably selected patients, the addition of chemotherapy concurrently to RT enhanced chances of laryngeal preservation significantly, while not showing a decrease in the overall survival. Subsequently, longer term outcomes for this study with a median follow up of 10.8 years have been published.[93] The long-term study confirmed that both chemotherapy regimens significantly improved organ preservation. Although overall survival did not differ significantly across the groups, there was a trend towards a worse outcome with CRT relative to ICRT. In addition,

the study also demonstrated a statistically significant higher percentage of deaths not attributed to larynx cancer or treatment in the CRT arm (30.8%) than the ICRT (20.8%) or the RT arm (16.9%). The toxicity of the CRT was not insignificant. The CRT arm experienced a 43% rate of severe late complications, including an 18% rate of pharyngeal dysfunction, a 25% rate of laryngeal dysfunction, a 7% rate of death due to the treatment protocol and a high rate of complications following salvage laryngectomy.

Since the publication of the above two studies, several commentators have expressed concerns about the generalization of the trial results to all patients with advanced laryngeal cancer[94, 95] without a full appreciation of the caveats of this approach. The undoubted advantages to organ preservation should be placed and understood in the context of the inclusion criteria to this trial, which have been discussed in an elegant editorial.[96] Over 40% of the patients in the two studies had mobile vocal cords (48% in the VA study and 42% in the RTOG 91–11 study); it is well recognized that cord fixity has an adverse prognosis compared to mobile cords and these patients would have needed a total laryngectomy anyway. The trial participants included a proportion of T2 patients, who could potentially be treated by partial laryngectomy, thus avoiding a permanent stoma. The lack of a surgical arm has been a drawback of this trial, especially given the long-term follow-up data suggesting more causes of non-cancer deaths in the CRT arm. It is important to recognize that several studies[47, 49, 97, 98] showing comparable mature outcomes in patients with T3 cancer who received open or transoral partial laryngectomy as the primary management.

Large database analyses have suggested that a primary non-surgical treatment may have an adverse effect on survival. Hoffman et al.[99] analyzed data from 158 426 cases of laryngeal squamous cell carcinoma (excluding verrucous carcinoma) diagnosed between the years 1985 and 2001 from the US National Cancer Data Base. This review of data showed decline in the 5-year relative survival between the 1985–1990 period and the 1994–1996 period among glottic and supraglottic cancers classified as T3N0M0. Initial treatment of T3N0M0 laryngeal cancer (all sites) in the 1994–1996 period resulted in poor 5-year relative survival for those receiving either chemoradiation (59.2%) or irradiation alone (42.7%) when compared with that of patients after surgery with irradiation (65.2%) and surgery alone (63.3%); there was no difference during this period for the subset of T3N0M0 glottic cancers initially treated with either chemoradiation or surgery with irradiation. In a subsequent SEER analysis, Chen et al.[100] showed that between 1985 and 2007, the use of CRT increased from <7% to 45%, whereas the use of total laryngectomy decreased from 42% to 32% in patients with advanced staged cancer. The 4-year survival rates for patients with advanced laryngeal cancer treated with total laryngectomy, CRT, and RT were 51%, 48% and 38% respectively despite patients receiving CRT being used in younger patients from higher socioeconomic groups.

Megwalu et al.[101] studied a cohort of 5394 patients who received a diagnosis of stage III or IV laryngeal squamous cell carcinoma between 1992 and 2009. Data were extracted from the Surveillance, Epidemiology, and End Results (SEER) Database in the US. They found that patients who received surgical therapy had better 2- and 5-year disease-specific survival (70% vs 64% and 55% vs 51%, respectively; $P < .001$) and 2- and 5-year overall survival (64% vs 57% and 44% vs 39%, respectively; $P < .001$) than patients who received non-surgical therapy. The difference in DSS and OS between treatment groups remained statistically different after stratification by year-of-diagnosis cohorts. Multivariate analysis showed non-surgical patients to suffer worse hazard of disease-specific survival (1.33 [95% CI, 1.21–1.45]) and overall survival (1.32 [95% CI, 1.22–1.43]) after adjustment for other variables. The authors concluded that surgical therapy leads to better survival outcomes than non-surgical therapy for patients with advanced laryngeal cancer. A further analysis[102] of 487 patients with T3 laryngeal tumours alone from the SEER registry and Medicare databases showed adjusted hazard ratio for OS of 0.68 (95% CI, 0.49–0.94) for patients receiving surgery alone vs non-surgical management and 0.75 (95% CI, 0.57–0.98) for patients receiving surgery plus adjuvant treatment vs non-surgical management.

The above analyses could be considered to favour surgery on the basis of less comorbidity in the surgical group. However, in an investigation into the prevalence of comorbidity in surgical vs non-surgical patients in 16 489 cases of advanced laryngeal cancer from the national cancer database, Zhu et al.[103] found that patients with comorbidity were less likely to receive chemoradiation than subtotal or total laryngectomy, with a risk ratio (RR) of 0.84 (95% CI, 0.81–0.87) for patients with one or more comorbidities compared with those without any comorbidity, after controlling for factors such as tumour stage, age, race/ethnicity, insurance and socioeconomic status. A recent systematic review[104] echoes the above points about heterogeneity in staging, anatomical subsite and heterogeneity in patient cohorts, concluding that CRT should not be used as a 'One size fits all' approach for T3 cancers.

The above discussion brings to the fore the question that surgery has not been directly compared to various forms of primary non-surgical therapy. Organ preservation can only be considered for an organ which is fulfilling its functions. Thus, a dysfunctional larynx where the airway is compromised, or where the tumour bulk causes significant dysphagia needing tube feeding are circumstances where organ preservation strategies should not be considered, even if the tumour stage and extent makes it suitable. These are echoed by the recommendations of the Larynx Preservation Consensus Panel.[105]

While the VA trial showed no improvement in survival following primary surgery for patients with stage III and IV laryngeal cancers, there is broad consensus in the literature that primary surgery for T3 tumours offers the best chance for locoregional control. Two single centre studies[106, 107] of stage III or IV laryngeal SCC with

substantial numbers have shown that surgical treatment was associated with statistically significant superior locoregional control rates (16% to 20%), but not in overall survival with a primary surgical option. In a single-centre large series of 1615 patients with laryngeal cancer of all stages,[32] the 3-year risk of recurrence was highest for T3 (35.8%) laryngeal cancer. Of the 368 patients with recurrent disease, 271 (74%) were managed by RT as primary treatment.

However, a meta-analysis[108] of outcomes following primary surgery vs non-surgical treatment for advanced-stage laryngeal cancer arrived at different conclusions. Data from 16 retrospective studies involving 8308 patients (4478 in the TL group and 3701 in the non-surgical group) showed that TL had better 2- and 5-year overall survival (OR 2.79, 95% CI 1.85–4.23 and OR 1.52, 95% CI 1.09–2.14). Interestingly, there were no significant differences between TL and NOP for 5-year local control. This indicates the heterogeneity in the patient population that is categorized as T3 laryngeal cancer. There is an acute need to re-evaluate treatment options for T3 laryngeal cancer. The authors would favour an individualized approach to the management of these patients and advise caution in advocating a primary non-surgical approach to all patients with this disease stage.

TREATMENT OPTIONS (TABLE 14.9)

Non-surgical treatment

Radiation therapy in combination with systemic therapy with either concurrent chemotherapy or Cetuximab (monoclonal antibody which competitively inhibits the cell-surface Epidermal Growth Factor Receptor-EGFR) or alone offers organ preservation in a proportion of appropriately selected patients without compromising survival. The landmark VA study[91] showed that in patients responding to induction chemotherapy, the laryngeal preservation rate was 64% at 2 years with similar survival rates at 2 years (68%) compared to surgery followed by RT. Salvage laryngectomy rates were significantly lower for T3 compared to T4 disease (29% vs 56%). A higher proportion of patients with glottic cancer (those with fixed cord) compared to supraglottic cancer underwent salvage laryngectomy.

A subsequent trial by the Intergroup RTOG 91-11[92] demonstrated that laryngeal preservation rates with concurrent chemoradiotherapy (CRT) was superior to sequential induction chemotherapy followed by RT and to RT alone (88% vs 75% vs 70%) with similar survival rates. The use of concurrent CRT in advanced laryngeal cancer is also supported by the tumour site specific meta-analysis and offers a 5.4% absolute benefit with the addition of chemotherapy at 5 years.[109] This benefit decreases with age and is non-significant above 70 years of age and therefore less appropriate in patients above this age. Combined modality treatment is associated with significant toxicities. The grade 3/4 toxicities related to treatment were 24% in ICT arm, 30% with CRT and 36% for RT arm with treatment related death of 3% in the ICT and RT arm and 5% in the CRT arm.[93] Robust data relating to laryngeal function preservation following CRT are lacking. The consensus panel now recommends the primary end point to be survival and function for future studies. A meaningful functional end point defined is laryngo-oesophageal dysfunction-free survival at 2 years.[105]

It must be emphasized that in the 91–11 trial the radiation therapy delivery was mostly unplanned or using 3D forward-planning technique whilst most centres now use the modern state of the art radiation therapy delivery intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) which allows to conform the radiation doses to the target volume, minimize hot spots and spare dose to adjacent normal structures thereby potentially reduce the associated toxicities.

Standard concurrent chemotherapy regimens include cisplatin (100 mg/m^2) on day 1, 22 and 43 of RT and carboplatin/5 FU on weeks 1 and 5 during RT. In patients where chemotherapy is contraindicated, cetuximab, monoclonal antibody could be considered as an alternative in patients with performance status 0 or 1 during RT. The addition of cetuximab during RT has been shown to improve local control (3-year LRC 47% vs 34%) and 5-year overall survival by 10% (46% vs 36%) compared to RT alone (27% of patients are advanced laryngeal cancer).[111] The toxicities associated with cetuximab include acne form skin rash and hypersensitivity reactions and does not increase the rate of radiation induced mucosal toxicities.

Induction chemotherapy regimens include combination cisplatin and 5FU (PF) given every 3 weeks to a total of 2 to 3 cycles. This in selected patients may improve survival and reduce distant metastasis but its role is not proven prior to concurrent CRT. The addition of docetaxel to above drugs has shown a higher overall response rate and larynx preservation rate compared to PF in patients with stage III/IV laryngeal cancer and may improve survival.[111–115]

Standard fractionation RT alone may be used as a single modality treatment in patients over 70 years of age or where comorbidity precludes the use of concurrent chemotherapy or cetuximab. The outcomes are suboptimal compared to CRT and should only be considered in patients who are selected or chose to receive RT alone.

Altered fractionation regime improves local control and survival at the cost of higher mucosal toxicities but the outcomes are better than RT alone but are still suboptimal compared to concurrent CRT. Altered fractionation with hypoxic modifiers, namely nimorazole, is currently being studied in a UK clinical trial, NIMRAD (a randomized placebo-controlled trial of concurrent nimorazole vs RT alone in patients with locally advanced squamous cell carcinoma not suitable for concurrent chemotherapy or cetuximab).

The potential role of concurrent chemotherapy and dose-escalated RT in laryngeal and hypopharyngeal cancer has been studied in a phase III trial, ART DECO. The early results demonstrated no improvement in local control in the dose-escalated arm and an increased incidence of acute toxicities in the dose-escalated arm.

Primary non-surgical treatment with concurrent CRT remains the preferred treatment option in patients with the following: good performance status, minimal or no comorbidity, disease is limited to the confines of larynx with no cartilage invasion, functioning larynx with no airway compromise to achieve the best possible outcome of organ and function preservation.

Radiation Technique: Most centres in the UK and US routinely use IMRT for treatment (**Figure 14.5**). This allows the dose to be conformal around the target and minimize dose to the adjacent normal structures. This technique also allows the delivery of differential dose to the primary site, involved nodes and uninvolved at risk nodal levels simultaneously. Centres use either two- or three-dose levels for definitive treatment. The two-dose levels are 65-66 Gy for gross disease and 54 Gy for microscopic disease in 30 fractions. A dose of 60 Gy is used for regions at high risk of microscopic disease in centres where three dose levels are used.

In a node-negative patient, the nodal levels at risk for microscopic spread are bilateral level II to IVa and are treated to prophylactic dose of 54 Gy in 30 fractions. The levels are outlined using consensus guidelines.[116]

In a node-positive neck, in addition to level II to IVa, level Va, Vb are also at risk. In patients with level IIa involvement, level Ib and level VIIb (retrostyloid space) are at risk of microscopic spread and are treated to a prophylactic dose as above.

The management of residual neck nodes in patients with higher neck stage (N2b, N2c and N3) following CRT is guided by the results of PET scan done at 10–12 weeks post CRT. A salvage neck dissection is done in patients with positive or equivocal PET uptake.[117]

Open partial laryngectomy (OPL) and Transoral partial laryngectomy

As discussed above, several studies[47, 49, 97, 98] show comparable mature outcomes in patients with T3 cancer who received OPL or transoral partial laryngectomy as the primary management. In the systematic review by Thomas et al,[49] pooled local control rate at 24 months following primary open partial laryngectomy for 5061 patients; 832 patients had T3 or T4 cancers; despite this the LC and DFS rates were excellent. There will be an inevitable selection bias when these treatments are offered, and these are often single-centre series where pockets of expertise exist. A recent systematic review[104] of surgical and non-surgical organ preserving options showed that both OPL and TLM seem to be efficient organ preserving methods for the treatment of T3 squamous cell laryngeal cancer. However, comparisons between surgical and non-surgical treatments were not feasible in this study due to population heterogeneity; recognizing the above bias, some of the best organ preservation and survival rates and lowest recurrence rates were seen with OPL. The authors do not recommend organ preservation surgery for T3 cancers outside of a registered institutional protocol.

Total laryngectomy

Total laryngectomy is a bona fide treatment for T3 laryngeal disease, especially in patients who have laryngopharyngeal dysfunction or a fixed cord. For endolaryngeal tumours with no pathological evidence of neck disease, a total laryngectomy with adequate margins will be all that will be needed. These patients will not need reconstructive interventions as adequate pharynx will be available to create an adequately wide neopharynx.

T4 disease

There is general agreement that laryngeal cancer which extends outside the framework of the larynx should be treated by primary surgery.[118] The reasons for this consensus are that tumours invading the cartilage do not respond well to radiation, and even if tumour control is achieved, patients may be left with a non-functional larynx (poor airway with aspiration) and chondronecrosis, both of which will need surgery for management. There is also a high risk of gastrostomy dependence if this group of patients is treated with CRT.[119, 120] As discussed above, these hark back to the contraindications for organ preservation as discussed by the Larynx Preservation Consensus Panel (**Table 14.9**).

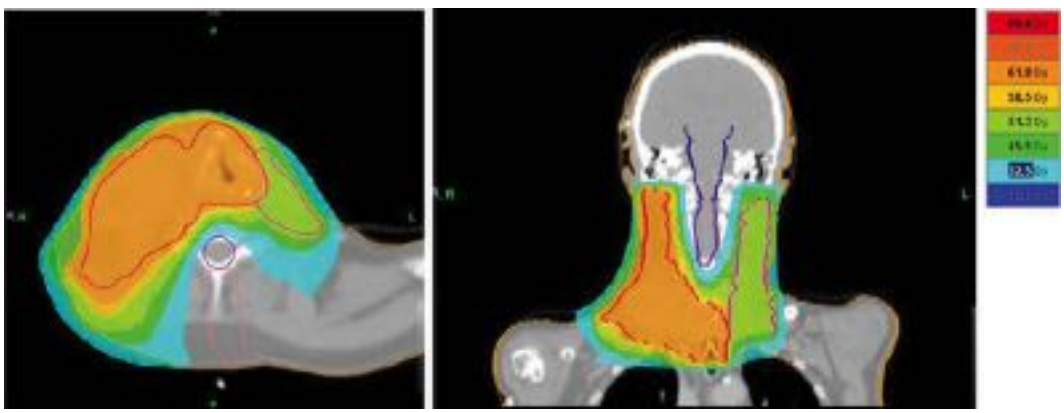


Figure 14.5 Axia and coronal section of an IMRT plan for a patient with T2N2b disease. The prescription dose (orange) encompasses entire larynx and involved nodal levels. The contra lateral at risk nodal level is treated with a prophylactic dose (green).

In an analysis of patients in the United States National Cancer Data Base diagnosed from 2004 to 2012 with T4N0 laryngeal cancer, Stokes et al. showed that overall survival among patients undergoing surgery with adjuvant radiation therapy (n = 1559) was superior to that of patients treated with concurrent CRT (n = 1597)[121] and single-centre reports support this position.[119]

Surgery usually takes the form of total laryngectomy, but for smaller selected tumours, open partial laryngectomy may be an option.[49] There are also reports supporting TLM resection for these tumours with good control rates,[122] but these have not been reproduced outside of experienced hands. Professional opinion on managing this disease is in favour of primary surgery followed by adjuvant therapy. Virtually all these patients will need the neck addressed based on the extent of neck disease; N0 necks will need bilateral levels II-IV neck dissection.

Adjuvant treatment

Post-operative RT to the tumour bed and/or neck in patients at risk of locoregional recurrence can improve locoregional control and survival. The risk factors are pT4 tumours, close or involved resection margins, involved node measuring more than 3 cm, multiple positive nodes and extracapsular spread. Other relative factors are perineural invasion and vascular invasion.

Concurrent chemotherapy and post-operative RT improves locoregional control and disease-free survival compared to post-operative RT in patients with risk factors for locoregional recurrences at the expense of increased mucosal and haematological toxicity. It improves overall survival in patients with positive resection margin and/or extracapsular spread and should be considered in patients with these risk factors for relapse.[123, 124]

TABLE 14.9 Recommended treatments for advanced laryngeal cancer

T stage	1st choice	2nd choice	3rd choice
T3	CRT	OPL/TLM/TORS*#	TL*#
T4a	TL#	CRT	OPL/TLM*#

* based on patient choice, local expertise, tumour and patient factors.
may need adjuvant radiation based on pathological findings.

RECURRENT LARYNGEAL CANCER

Recurrent early laryngeal cancer

Residual or recurrent laryngeal cancer (hereafter referred to as recurrent cancer) following RT is a difficult clinical problem as the disease is more aggressive and carries a poor prognosis. Although several treatment options exist for patients with laryngeal cancer at first presentation, options for those with recurrent cancer will be limited based on the initial treatment received and the stage of the recurrent disease. Cancers that recur after radiation therapy often demonstrate aggressive behaviour, arise in a field where lymphatic drainage is unpredictable, and are associated with poor control rates. Salvage total laryngectomy (STL) is an often recommended option, even for early radiorecurrent cancers, because it is technically easy, and the outcomes are predictable.[124–126] Recognizing that recurrent head and neck squamous cell carcinoma has an aggressive course, and concerns about the higher incidence of complications in the irradiated neck, surgeons have been reluctant to adopt less radical procedures. However, total laryngectomy has far-reaching consequences for the patient in terms of function and quality of life.

OPL

OPL in recurrent cancer has withstood the test of time in instances where the tumour extent and patient are suitable for the procedure, and has been demonstrated to have very good outcomes in the recurrent setting too (**Figure 14.6**). Paleri et al.[128] performed a systematic review and a meta-analysis to study the role of open conservation (partial) laryngeal surgery in radiorecurrent laryngeal cancers. The pooled estimates of oncological outcomes were as follows: local control rate at 24 months for 560 patients was 86.9% (95% CI, 84%–89.5%), the disease-free survival rate for 352 patients was 91.2% (95% CI, 88.2%–93.9%), and the overall survival rate for 360 patients was 83.1%

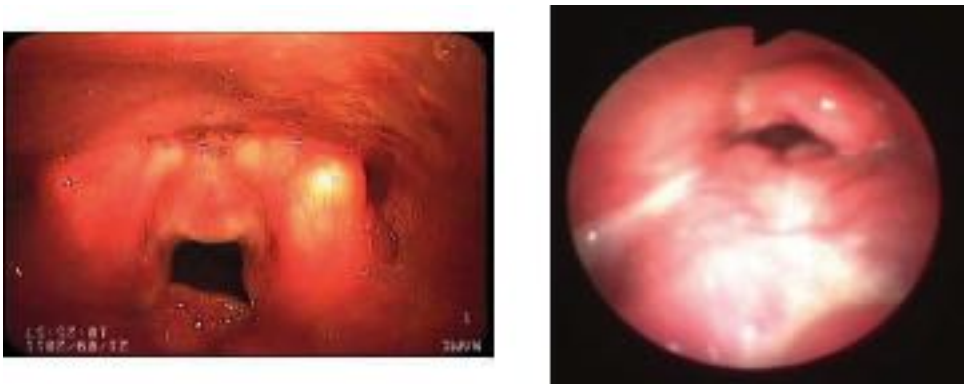


Figure 14.6 Two examples of salvage supracricoid laryngectomy. The patient on the left had both arytenoids and epiglottis preserved, while the one on the right had removal of epiglottis and the right arytenoid. In carefully selected patients and meticulous attention to operative detail, excellent function can be achieved.

(95% CI, 79.1%–86.7%). Since the review, further studies have demonstrated the efficacy of this approach in the radiorecurrent setting.[129]

TLM

As shown above, TLM has a well-defined and proven role in the management of primary laryngeal cancer with several advantages. It is therefore intuitive to try and exploit these advantages to early recurrent laryngeal cancer. However, there are several caveats to this approach. The conventional margins employed during TLM resection in the treatment of primary laryngeal cancer may well not be applicable in the radiorecurrent setting.[130] There is considerable difficulty in identifying peri-operative tumour margins accurately in a previously irradiated larynx, even in the most experienced hands. This is borne out by de Gier et al.[131] who reported a 58% recurrence rate after the first laser resection. Steiner et al.,[132] whose series included recurrent advanced tumours, reported only 38% remained free of disease after the first laser procedure. This improved to 71% following repeat TLM. Studies by Roedel et al.[133] and Ansarin et al.[134] revealed that recurrent tumour was typically clinically understaged and was later found to display a higher stage on pathological examination. This has also been demonstrated in other studies where whole organ sectioning has been employed, where pre-treatment clinical and radiological staging accuracy for recurrent tumour is around 50%, with more than 90% being understaged.[130] Ramakrishnan et al.[135] performed a systematic review of the use of salvage TLM and identified that although it was oncologically sound with a high larynx-preservation rate, there was a distinct trend towards inferior local control rates compared to OPL. The pooled mean estimate of local control at 24 months after first TLM (n = 249) was 56.9%, a full 30% less compared to the 24-month local control rates for OPL in recurrent cancers. This remained the case even when the improved LC following repeat TLM is taken into consideration. The relatively lower mean larynx preservation rate of 72.3% for TLM vs 84% for OPL[128] is a reflection of the higher locoregional failure following TLM and the lower threshold for resorting to a total laryngectomy. The authors believe that where suitable, patients should be offered OPL in preference to TLM for recurrent tumours, unless the cancer is limited to the mid cord and there is little concern about submucosal spread. In cases not suitable for OPL due to patient factors, total laryngectomy should be offered.

Recurrent advanced laryngeal cancer

Patients who recur following CRT are rarely candidates for anything less than a total laryngectomy. Recurrent T3 and T4 cancers with partial or limited erosion of the thyroid cartilage may be suitable for OPL, and there are data to support the oncological efficacy of this approach in carefully selected patients.[128]

Pharyngocutaneous fistulae (PCF) are known to occur in nearly a third of patients after STL.[127] PCF has severe impact on duration of admission and costs, quality of life and can even cause severe complications such as bleeding, infection and death. Paleri et al.[136] performed a meta-analysis of the benefit of vascularized tissue repair in reducing the risk of PCF following STL. Using data from 591 patients across 7 studies, the pooled incidence of PCF for 332 patients who underwent flap reconstruction was 22.2% (95% CI 17.9 to 26.8%), but 31.2% (95% CI 25.8 to 36.9%) in 259 patients who underwent primary closure. The absolute risk reduction in PCF rates of 9% indicates that 11 patients will need a flap to prevent one fistula. The pooled relative risk derived from 591 patients was 0.63 (95% CI: 0.47 to 0.85), indicating that patients who have flap reconstruction/reinforcement reduced their risk of PCF by a third. Another study by Sayles et al.[137] on the same subject, albeit with different inclusion criteria, published almost concurrently, arrived at similar conclusions. They concluded that relative risk of fistula was 0.57 (95% CI 0.37–0.85, $P < 0.001$) for STL with flap reinforced closure compared to primary closure of the pharynx alone and the number needed to treat to prevent one fistula was 6. These pooled analyses suggest that there is a clear advantage in using vascularized tissue from outside the radiation field in the laryngectomy defect (**Figure 14.7**).

Neck management in recurrent laryngeal cancer

A handful of studies have specifically looked at the utility of offering neck dissection to patients who present with recurrent laryngeal cancer.[138–145] Current imaging techniques to assess the post-treatment neck offer a high-negative predictive value (~96%) increasing clinical confidence. Given the increased complications associated with neck dissection in the salvage setting,[142] consideration should be given to conservative management of the neck



Figure 14.7 Endoscopic view of pharyngeal lumen augmented using a free cutaneous flap in a patient who underwent salvage laryngopharyngectomy.

in clinically node-negative patients, especially in patients who have received elective irradiation to the nodal basins. It should be noted that a similar philosophy has significant support in the post chemoradiated neck, where surgical salvage treatment is planned based on imaging findings. Following a comprehensive review of the question, Sanabria et al.[146] offered some recommendations on the subject. In patients with glottic tumours classified originally as early cancer (T1–2) and who recur with tumours of similar stages (rT1–2), an observation policy for the untreated neck is appropriate, if the imaging shows no neck disease. For recurrent early supraglottic cancers, it is very likely that the neck would have been previously treated and a neck dissection is not warranted if there is no clinical or radiological evidence of neck disease. For more advanced laryngeal tumour recurrences (rT3–4), the recommendation was for elective neck dissection (bilateral for supraglottic cancers), particularly if previous radiation fields did not include the lateral neck. It should be noted that if a free-flap reconstruction is to be performed for pharyngeal reinforcement or augmentation, limited dissection of at least one side of the neck may be necessary to site the microvascular anastamosis.

RARE CANCERS (SW)

While the majority of tumours of the larynx are squamous cell carcinomas a number of other pathologies can occur in the larynx. These include neuroendocrine, connective tissue, salivary gland, epithelial cell, malignant melanoma and immune cell derivatives. In a review of these in both the supraglottis and glottis the majority were in men in their 7th decade of life. In the supraglottis, neuroendocrine, small cell and lymphomas predominated. While in the glottis spindle cell, sarcomas and small cell tumours were more common. Limited data exist due to the relative rarity of these tumours to guide treatment.[147]

Neuroendocrine tumours are the most common non-squamous tumours of the larynx. Current consensus classifies them into paraganglioma, typical carcinoid tumour, atypical carcinoid tumour and small cell neuroendocrine carcinoma. Precise diagnosis is essential as natural history treatment and prognosis vary depending on the category. Surgery is the mainstay of treatment for typical and atypical carcinoid. Atypical carcinoid is considered more aggressive and therefore elective neck dissection is advocated, and adjuvant CRT should be considered. Paraganglioma is a benign entity and can typically be treated with surgery alone with an excellent prognosis. Small cell neuroendocrine carcinoma carries a poor prognosis (<5% 5-year survival) and surgery has been shown to offer no benefit when compared to CRT alone.[148]

Primary laryngeal lymphoma is extremely rare, and there is debate in the literature as to whether it constitutes an unusual presentation of non-Hodgkin lymphoma rather than being a separate disease entity. Treatment is targeted at the histological subtype of the lymphoma rather than the site at which it presents, and therefore surgery has a very limited role.

Laryngeal small-cell carcinoma is a subtype of the extrapulmonary small-cell carcinomas (EPSCC) carrying a generally poor prognosis when compared to pulmonary small cell carcinoma. EPSCC is usually a fatal disease, with a 13% 5-year survival rate. In a small percentage of patients, surgery can be curative if the tumour is small and confined to the organ of origin. Because of the poor overall outcome, one needs to consider the possible use of adjuvant chemotherapy in appropriate circumstances if surgery is to be employed. In most patients with limited disease, the combination of chemotherapy and radiation as the primary treatment can be as effective as surgery. EPSCC is responsive to commonly employed regimens for small-cell lung carcinoma; however, the responses are short-lived. The extent of disease at diagnosis represents the most sensitive predictor of survival.[149]

LARYNGEAL CANCER IN YOUNG AGE GROUPS

Laryngeal cancers in young people are much less common. In the US it is estimated that 26% of laryngeal cancers present under the age of 40.

There are a number of studies considering head and neck cancer in young adults, typically defined as younger than 45. In general, this age group has a lower proportion of alcohol drinkers and or smokers. For many subsites there appears to be an inverse relationship with fruit and vegetable intake.[150, 151] HPV infection may be more important in this age group, although epidemiological studies thus far have not shown a strong link as they have in oropharyngeal cancer.

A higher proportion are associated with genetic abnormalities, such as Fanconi's anaemia (FA), than in the older cohort. FA is a rare autosomal recessive inherited cancer syndrome is associated with defects in DNA repair. It is clinically characterized by congenital malformations, progressive bone marrow failure, and increased incidence of malignancies, especially acute myeloid leukemia and squamous cell carcinomas of the head and neck (HNSCCs). On a cellular level, typical features of the disorder are a high degree of genomic instability and an increased sensitivity to bi-functionally alkylating agents. Cisplatin-based chemotherapy, in combination with RT cannot be used in FA patients due to their propensity for increased toxicity. Surgery is the most important treatment option for HNSCC in FA patients, who also merit frequent screening for early detection of malignancies.[152]

Infection with the human immunodeficiency virus (HIV) has been positively linked with rare malignancies of the head and neck, such as Kaposi's sarcoma (KS), non-Hodgkin lymphoma, and more commonly squamous cell carcinoma. Head and neck involvement of KS is not unusual. However, laryngeal involvement is rare. Most patients have had AIDS-related KS, although HIV-negative persons with laryngeal KS have also been

noted. Of the AIDS cases reported, the majority (91%) were males of mean age 35 years (range 24–56 years), with advanced HIV disease, that were antiretroviral naïve. This may explain why many afflicted persons also had oropharyngeal, as well as cutaneous and visceral KS. Care should be taken when performing biopsy of these lesions as they are very vascular and can be associated with brisk, potentially fatal bleeding. Therapeutic options for this scenario include low-dose local irradiation, intralesional chemotherapy or laser ablation, and systemic therapy, particularly if there is disseminated KS. For laryngeal KS lesions producing acute or impending airway obstruction urgent intervention is necessary. However, depending on the location of the KS lesion, tracheostomy may contribute to mortality as a result of fatal haemorrhage. Therefore, cricothyroidotomy has been recommended by some authors as an alternative approach to life-threatening emergencies in this setting.[153]

It is rare to see these cancers in children (those under 18), however cases do occur, particularly in those with a genetic cause. Management will be multidisciplinary and should additionally involve the paediatric oncology teams. Treatment principles however are generally the same, and should be led by tumour histopathological type and subsite, as for adult patients.

KEY POINTS

- A binary grading system for laryngeal dysplasia is currently espoused.
- Management of laryngeal precancer is driven by consensus and logistics as high-level evidence is lacking.
- Transoral laser microsurgery is the preferred option for most T1a and some T1b lesions, based on clinical and cost-effectiveness analysis.
- For locally advanced tumours that have not caused laryngeal dysfunction, radiation therapy allows organ preservation, which is supported by high-level evidence.
- Good evidence exists to support local laryngectomy for T4a disease.
- Management of the neck should be based on the site and the stage of the primary tumour, the presence or absence of disease in the neck, with the treatment modality influenced by the treatment planned for the primary site.

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CHAPTER 15

REHABILITATION AFTER TOTAL LARYNGECTOMY

Yvonne Edels and Peter Clarke

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: surgical voice restoration, laryngectomy and tracheo-oesophageal speech.

INTRODUCTION

Enormous advances in the treatment of cancer of the larynx have occurred since Theodor Billroth performed the first successful laryngectomy in Vienna in the year 1873.[1] Whilst removal of the malignancy and preservation of life remain the primary goal, attention is now directed at achieving functional outcomes for breathing, swallowing and speech to provide optimal quality of life. Management decisions are best made within designated head and neck units by the multidisciplinary team (MDT) of professionals who pool their individual specialist knowledge for the benefit of the patient. The weekly MDT meeting provides the forum for discussion of cases allowing all members to contribute to patient management.[2] Core MDT members include the surgeon, clinical oncologist, pathologist, plastic surgeon, staff nurse, dietician, speech and language therapist (SLT), clinical nurse specialist (CNS), physiotherapist and psychologist.

BACKGROUND

In the presence of advanced disease or recurrence following initial treatment with radiotherapy or chemoradiotherapy, total laryngectomy is often the only available treatment option, with the intent to remove the entire larynx and the cancer. This is major life-changing surgery and the news is almost never welcome. Patients and their close relatives need time and the opportunity to ask questions, and should be offered counselling to understand the considerable implications of a total laryngectomy;[3] these include the formation of a permanent neck stoma, changes to breathing, swallowing and of course the loss of the vocal cords and normal voice production (**Figures 15.1** and **15.2**). This role generally falls to the SLT, the CNS or both. It can take repeated explanations aided by information sheets, diagrams, photos and videos before patients absorb the information. They should be offered the opportunity to also meet other carefully selected laryngectomies. Hence, the rehabilitation starts prior to surgery and enables patients to have realistic expectations.

In addition to the above, counselling should also include detailed information about the various options for voice production. These are oesophageal speech, the artificial larynx and surgical voice restoration (SVR). The latter involves the creation of a tracheo-oesophageal puncture (TEP) at the time of primary surgery or at a later date. The TEP is a fistula through the posterior tracheal wall into the oesophagus. This TEP is stented open with a Foley catheter or a one-way valve made of medical grade silicone. Air can pass into the oesophagus for voice production when the stomal exit is temporarily covered, but food and fluid are not aspirated (**Figure 15.3**).

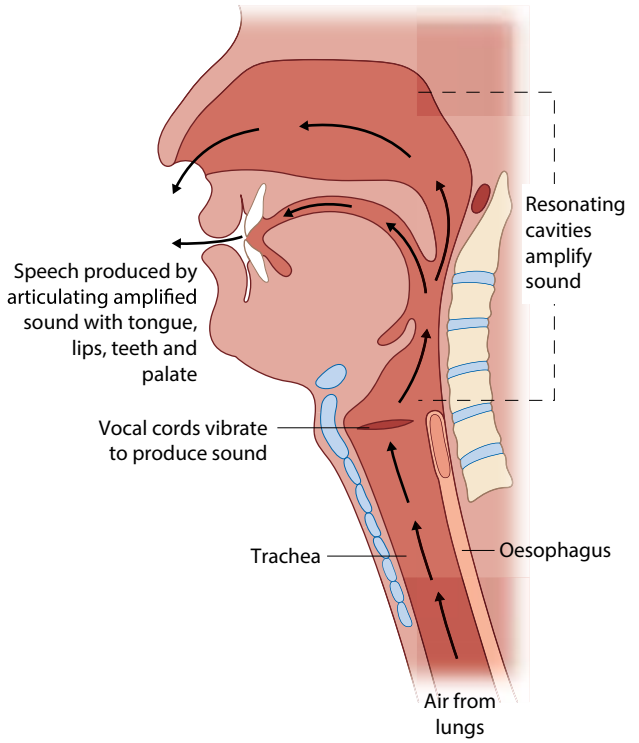


Figure 15.1 Laryngeal voice production.

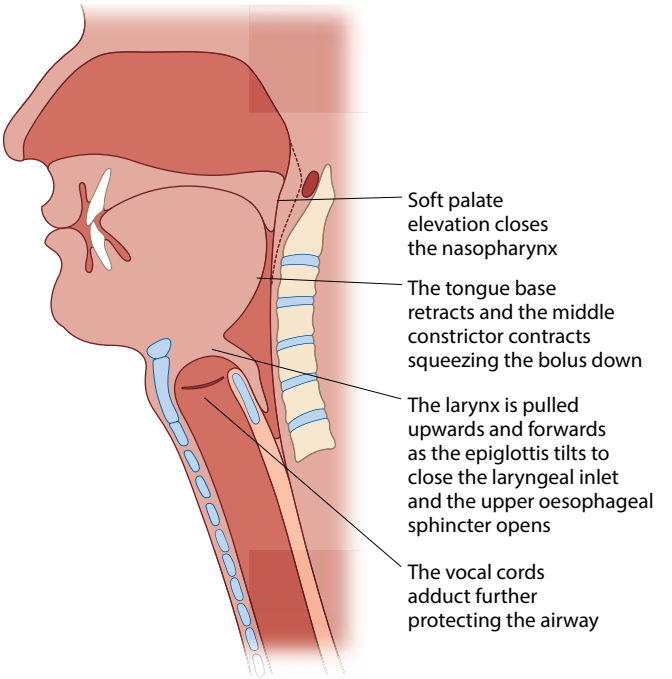


Figure 15.2 Normal laryngeal swallow.

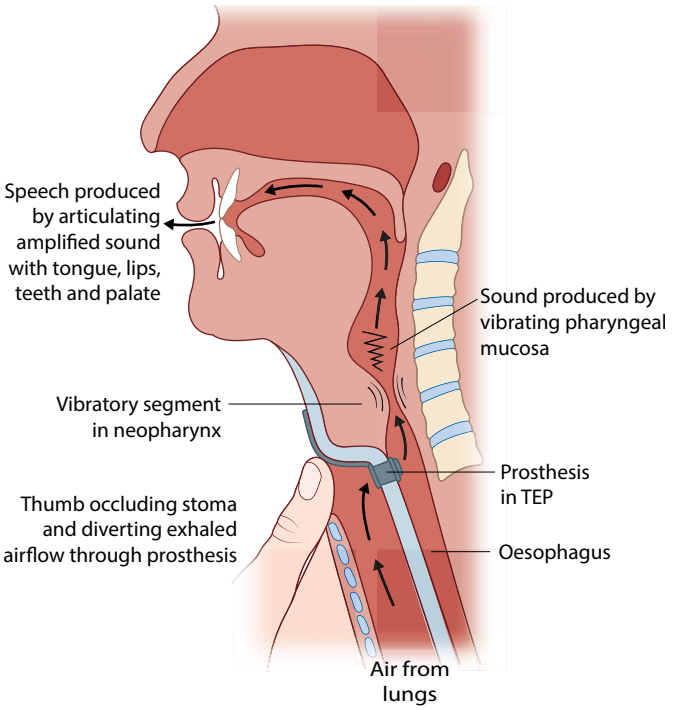


Figure 15.3 Surgical voice production.

SURGICAL TECHNIQUE TO OPTIMIZE SPEECH AND SWALLOW

Tumour resection

Of prime importance is the need to resect all diseased tissue to provide good oncological results. There are, however, a number of fundamental steps that improve the voice and swallowing results and these should be undertaken if they do not compromise the oncological resection.

The laryngectomy is carried out in the usual fashion conserving as much pharyngeal mucosa as possible, particularly over the postcricoid region, the piriform fossae and the valleculae, provided safe clearance from the tumour is obtained. The thyropharyngeus and cricopharyngeus muscles should be dissected off the thyroid laminae on both sides preserving as much muscle as possible (**Figure 15.4**). For hypopharyngeal tumours the mucosa of the uninvolved piriform fossa is carefully preserved to minimize the need for flap reconstruction. Ideally a transverse, unstretched mucosal width of at least 6 cm at the narrowest point is necessary to enable adequate swallowing and effortless tracheo-oesophageal speech. Augmentation of the pharynx with a flap is preferable if the residual mucosal strip is less than 6 cm to avoid pharyngeal stenosis and functional impairment. Irrespective of the available mucosal width, vascularized tissue reconstruction is preferred in the setting of the salvage laryngectomy after chemoradiotherapy, as this strategy reduces the risk of pharyngocutaneous fistula formation by a third.[4]

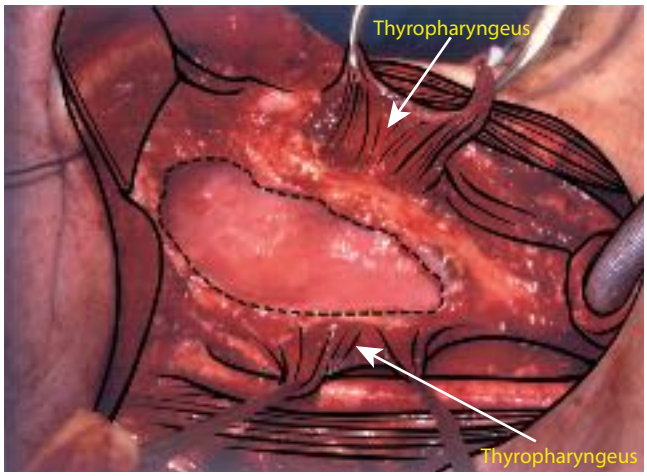


Figure 15.4 Preservation of thyropharyngeus for later muscle repair.

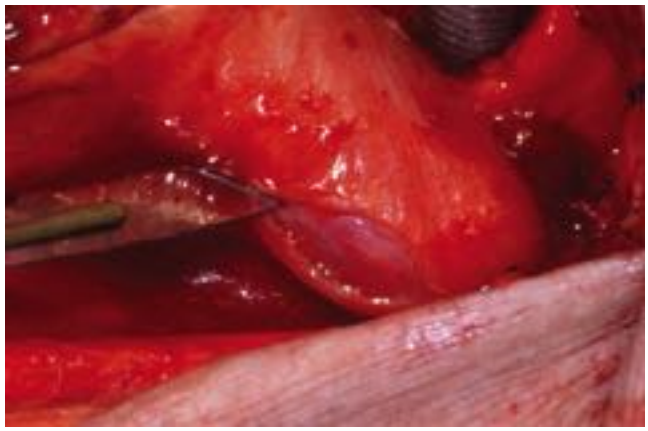


Figure 15.5 Myotomy through upper oesophageal muscles to underlying mucosa.

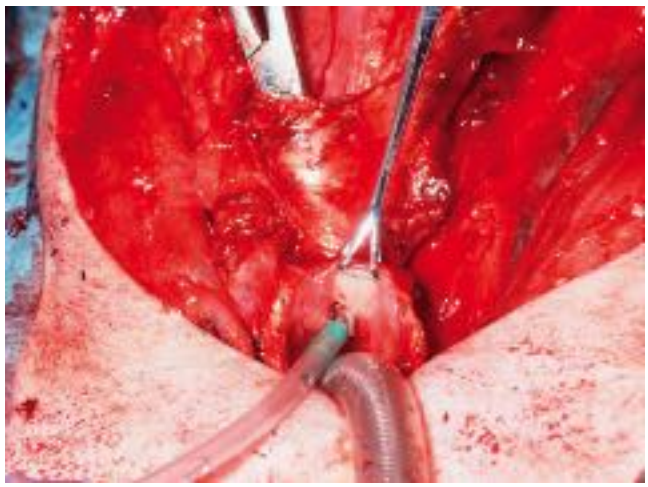


Figure 15.6 Tracheo-oesophageal puncture.

Cricopharyngeal myotomy

Once the larynx is removed, a myotomy of the upper oesophageal sphincter is carried out. This is important to avoid hypertonicity and spasm of these muscles during attempted phonation, and to allow expansion of the upper oesophagus providing an air 'reservoir' below the pharyngo-oesophageal (PE) segment. Hypertonicity or spasm will interrupt the flow of air to a varying degree, restricting or completely stopping voice production. This spasm appears to be caused by reflex contraction of cricopharyngeal and constrictor muscles when the upper oesophagus is distended with air, and is a cause of TEP speech failure in 10–12% of patients.

A short posterior midline myotomy is carried out with a scalpel over a distance of 4–5 cm starting from just below the level of the TEP site, extending cranially into the fibres of the thyropharyngeus. This divides the circular muscle fibres in the upper oesophagus and the cricopharyngeus. It is important that all muscle fibres are cut (**Figure 15.5**). It is unclear whether assessment of the upper oesophageal sphincter with a finger can predict the development of spasm and there seems little contraindication to doing a myotomy on all patients as it may also improve swallow. One of the conclusions of the European multicentre audit of speech and swallowing results after laryngectomy was that myotomy improved voice outcomes.

A unilateral pharyngeal plexus neurectomy has been advocated in the past as an alternative method of constrictor relaxation. Three to five branches of the plexus entering the lateral wall of the pharynx are exposed and identified with a nerve stimulator before division with cautery. This technique has not gained widespread use.

Tracheo-oesophageal puncture

The puncture is positioned in the midline about 10–15 mm below the cut edge of posterior tracheal wall. The tip of a pair of curved artery forceps is inserted through the pharyngeal defect and advanced into the upper oesophagus just as far as the puncture site, tenting up the mucosa. A scalpel is used to incise minimally and horizontally through the mucosa and muscle onto the tip of the forceps, which are then advanced into the tracheal lumen and opened to grasp the tip of a 14 NG tube or Foley catheter (**Figure 15.6**). The forceps and the catheter are then withdrawn through the fistula tract and the tip of the catheter is passed distally down the oesophagus. The catheter is anchored to the skin above the stoma at the end of the procedure. Absorbable sutures between the oesophageal wall and the posterior aspect of the trachealis on either side of the proposed position of the puncture secures the party wall and avoids inadvertent separation. An alternative technique is to insert a valve at the time of surgery through the newly created puncture.

Pharyngeal closure

The pharyngeal defect can be closed using an interrupted or continuous absorbable mucosal suture; A horizontal closure is considered to produce a wider pharynx above



Figure 15.7 Horizontal pharyngeal closure.

the PE segment and may improve resonance for speech (**Figure 15.7**).[5] An alternative technique is the 'T' closure.

Based on how much constrictor muscle is available, an interrupted closure of the muscle is appropriate It is hypothesized that the constrictor muscle closure creates a suitable, 'tonic' PE segment at the optimal site in the pharynx with a good reservoir below it and a wide resonating pharyngeal segment above.[6] Whilst the upper oesophagus needs to be relaxed so that it does not respond to air being injected through the valve by going into spasm, the neopharynx or PE segment needs to provide an area where the mucosa is in apposition to allow it to vibrate efficiently and produce strong voice. Repairing the thyropharyngeus provides this vibratory segment. Conversely, if the muscles or PE segment wall are hypotonic (e.g. after total pharyngolaryngectomy and reconstruction or if thyropharyngeus is not repaired) the voice will be weak because there is minimal or absent muscle in the wall to create a PE segment. However, others[7] have recommended 'half-muscle closure technique', where only one side of the remnant constrictor muscles is used to reinforce the primary closure, with the advantage of reducing pharyngoesophageal spasm. Significant resection of the hypopharynx will necessitate a flap reconstruction.

Repair of the suprahyoid muscles

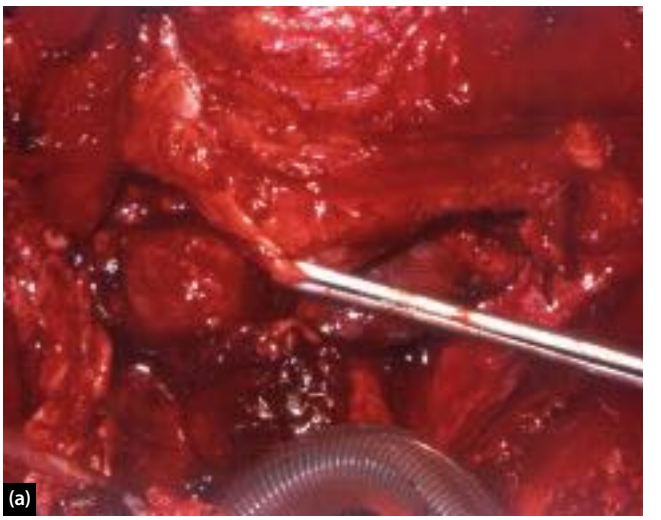
Following repair of the thyropharyngeus it is important to suture the suprahyoid muscles down to the thryopharyngeus. This strengthens the mucosa above the repair, so avoiding a pseudoepiglottis and anterior pouch that may affect swallow, and also reattaches the middle constrictor and other suprahyoid muscles which are important in the swallow reflex (**Figure 15.8**).[8]

Stoma reconstruction

The size, shape and contour of the stoma and surrounding skin are important to aid digital occlusion of the stoma and help ensure optimal adhesion of the base plate for the tracheostoma valve housing. In order to avoid unnecessary tracheal retraction, care should be taken during the laryngectomy not to transect the trachea too low; if necessary, the margins of the trachea can be sutured to the medial margins of the sternomastoid muscle to secure it near the skin. If the tendons of the sternomastoid muscle are prominent, they can be safely divided to ensure a flatter area around the stoma for better base plate adhesion.

Post-operative care

Post-operatively the patient must be fed enterally either naso-gastrically or via a catheter placed through the TEP or the prosthesis, and then directed into the stomach. After an appropriate healing period, which may be significantly longer after chemoradiotherapy, oral feeding is reintroduced, beginning with water and quickly building



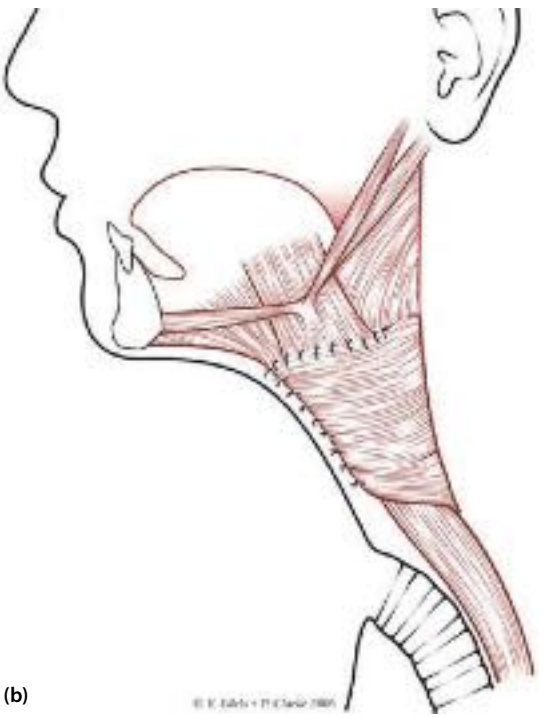


Figure 15.8 Closure of the suprahyoid muscles.

to pureed food, soft food and ultimately a normal diet. Work on voice production begins when adequate healing has taken place. If phonation begins too early, excess pressure during voicing can lead to suture line breakdown.[9] Patients not yet fitted with a voice prosthesis must be sized and fitted at this point. There is increasing support for early feeding, commencing as early as the second post-operative day in patients who have undergone laryngectomy as the primary treatment, as there is no good evidence that this increases the risk of pharyngocutaneous fistula formation.[10]

SECONDARY VOICE RESTORATION

The technique of TEP with prosthetic valve and voice restoration was originally developed for those patients who had failed to achieve adequate oesophageal speech. However, present day indications are mainly for patients who have complex resections and reconstructions, or those undergoing salvage surgery.

Laryngectomies need a tonic PE segment to provide a satisfactory vibratory source for tracheo-oesophageal speech. The first step in assessing patients who present for secondary voice restoration after laryngectomy, when they have failed oesophageal speech acquisition, should be an assessment of PE segment tonicity. A preliminary videofluoroscopy will determine whether it is necessary to inject botulinum toxin into the cricopharyngeus. If the end tracheostoma is too narrow for valve maintenance, a stoma revision may also be indicated at the time of the TEP. The patient should be judged to have adequate lung function to open the valve and produce voice.

Timing of valve placement varies, with the choices being placement of a sterile prosthesis either during surgery or post-operatively once healing has occurred. Either way, the length of the TEP must be carefully measured with a sizing gauge and the overall form and function of the site assessed before selecting an appropriate prosthesis from the extensive range available. One size does not fit all; thus the Blom-Singer and Provox prostheses range include valves of different diameters, lengths, opening pressures and design as well as custom-made varieties, so rarely is it not possible to find an appropriate one. Ex-dwelling prostheses can be self-changed by the patient or carer, freeing the patient from regular hospital attendance, while indwelling prostheses are to be changed by the healthcare professional only, and can remain *in situ* over extended periods.

HEAT AND MOISTURE EXCHANGE

Essential areas for rehabilitation include respiration, swallowing and voice production. Nasal functions of air humidification, filtration and warming are lost when air is taken in via the stoma.[11] The loss of the height from nose to stoma reduces air resistance within the lungs leading to less optimal gaseous exchange. A heat and moisture exchanger (HME), works as an artificial nose, reducing mucus over-production due to loss of nasal humidification, warming and filtering the air thus reducing coughing and assisting sleep. The HME consists of a small filter contained in a cassette, attached in front of the stoma either by a base plate stuck to the parastomal skin or inserted into a laryngectomy tube. Different designs exist, with specifications for daily activity, sleep and exercise. Ideally, an HME should be provided within a few days of surgery to minimize the risk of becoming accustomed to the reduction in respiratory pressure, which can be difficult to re-educate later. Failure to use an HME is mostly related to getting it to attach and remain attached. Difficulties may be due to post-treatment effects on the neck tissue or because the sternocleidomastoid muscles were not divided at laryngectomy to provide a flattened parastomal area for successful attachment. The increased need for pedicled or free flap reconstruction of laryngectomy defects after chemoradiotherapy also distort the anatomy around the stoma making the use of standard base plates difficult. Products exist to clean, moisturize and assist with better base plate attachment, often after a certain amount of trial and error. Several randomized studies have shown clear benefit from HME use in reducing pulmonary symptoms and improving lung function.[12, 13]

SWALLOW

Removal of the hyoid bone and larynx during laryngectomy and separation of the trachea and oesophagus into discrete systems destroys the normal sequential muscular swallow sequence. All laryngectomies have a modified swallow, and the differences between laryngeal and alaryngeal swallow are identified in **Table 15.1**. The key aspects of pharyngeal reconstruction that contribute to a good swallow are discussed above.

SPEECH

Oesophageal speech requires air to be taken into the top of the oesophagus either by injection or inhalation,[14] and then forced out again causing the newly reconstructed pharynx, the PE or vibratory segment, to vibrate in response to the flow of air and produce sound. As in normal laryngeal voice production, this sound is amplified by the resonating cavities above and modified into speech by the articulators, tongue, teeth, lips and soft palate. The electrolarynx produces a sound that is then transmitted into the resonating cavities either by direct pressure of the machine against the skin of the upper neck or through a tube directly into the oral cavity. SVR has largely replaced these other methods, being easier to learn and producing better quality voice (**Table 15.2**).

SVR voice is produced when the stoma is temporarily sealed by a finger placed in front of it or over the HME cassette. Later, the patient may use an adjustable tracheostoma valve (ATSV) allowing hands free speech (**Figure 15.9**). The ATSV seals when the expiratory breath

TABLE 15.1 Differences between laryngeal and alaryngeal swallow

	Oral	Pharyngeal	Laryngeal	Top of oesophagus	Oesophagus
Laryngeal swallow	Lips seal. Teeth, tongue, hard and soft palate form bolus and pass it to the back of the mouth	Soft palate elevates to close nasal port. Back/base of tongue and posterior pharyngeal wall close together. Stripping action propels bolus onward. Swallow sequence fires	Suprahyoid's contract, elevating and tilting larynx forwards and tucking it under the tongue. This action also pulls on the cricopharyngeal muscles helping them to relax and open the top of the oesophagus. The epiglottis biomechanically tilts over, sealing the tracheal entrance and the laryngeal sphincters close together to protect the airway.	Oesophageal entrance opens. Negative pressure created as oesophagus widens helps to draw the bolus in. The bolus enters the oesophagus.	Gravity and the sequential peristaltic wave carry the bolus to the stomach. Lower oesophageal sphincter relaxes and opens to allow bolus to pass.
Alaryngeal swallow	Lips seal. Teeth, tongue, hard and soft palate form bolus and pass it to the back of the mouth.	Soft palate elevates. Tongue back/base approximates posterior pharyngeal wall. Partial/reduced stripping action of posterior pharyngeal wall due to surgery and denervation. Bolus transits pharynx under gravity and power created here. Swallow sequence follows.	Reattached suprahyoids contract, pulling on the top edge of the reconstructed thyropharyngeus muscles and possibly also helping to lift the reconstructed pharynx. Reconstructed thyropharyngeus (and possibly cricopharyngeus) are stretched and relax, helping to open the entrance to the oesophagus. Bolus, under reduced pressure from tongue base/posterior pharyngeal wall contraction, exerts pressure from above. Reduced stripping action together with gravity move bolus on.	Oesophageal entrance opens. Bolus under pressure from above and gravity enters the oesophagus.	Gravity and the sequential peristaltic wave carry the bolus to the stomach. Lower oesophageal sphincter relaxes and opens to allow bolus to pass.

TABLE 15.2 Comparison of speech production before and after laryngectomy

Physical requirements	Normal laryngeal voice production	Oesophageal speech production	Surgical voice production
Initiator	Moving column of air from the lungs	Moving column of air from the oesophagus	Moving column of air from the lungs
Vibrator	Vocal cords	Vibratory/pharyngo-oesophageal (PE) segment	Vibratory/pharyngo-oesophageal (PE) segment
Resonators	Resonating cavities: nose, mouth, pharynx	Resonating cavities: nose, mouth, pharynx	Resonating cavities: nose, mouth pharynx

is strong enough to close its valve and remains shut as long as this pressure is maintained. Once the air pressure falls the ATSV reopens and a new breath is taken in. Regardless of method, once the stoma is sealed, air passes via the voice prosthesis into the oesophagus making the walls of the vibratory segment (i.e. the area between the top of the oesophagus and the base of the pharynx) vibrate to produce sound. This basic tone is again amplified by the resonating cavities above (pharynx, nose and mouth) and modified into speech by the articulators. Outcome measures for post-laryngectomy speechg are evaluated by Deore et al.[15]

TONICITY

For optimal outcomes, the newly created reconstructed/vibratory segment must dilate on swallow and vibrate for voice. This area must be surrounded by tonic muscles to produce optimum voice.[16] If the neopharynx is too loose (hypotonic), the swallow is functional but voice quality is low, weak, whispery and often wet; if it is too tight (hypertonic), swallowing requires increased pressure and the voice is high pitched, effortful and difficult or impossible to maintain.

Hypotonicity is managed using digital pressure against the outside of the neck, artificially increasing the tone. Less severe hypertonicity is managed with a low opening pressure prosthesis but when insufficient, other measures must be considered.

Stretch receptors located within the muscles at the top of the oesophagus respond to being dilated by clamping down, preventing the free passage of air for voice production.[6, 17] By interfering with this mechanism hypertonicity and spasm can be avoided. This is effectively managed at the time of surgery by performing a myotomy[18–20] or neurectomy.[21] A myotomy should cut through all the muscles in the lower third of the reconstructed segment extending down to the level of the puncture (**Figure 15.10**). The upper two-thirds of the vibratory segment is spared leaving these muscles tonic for good voice production.

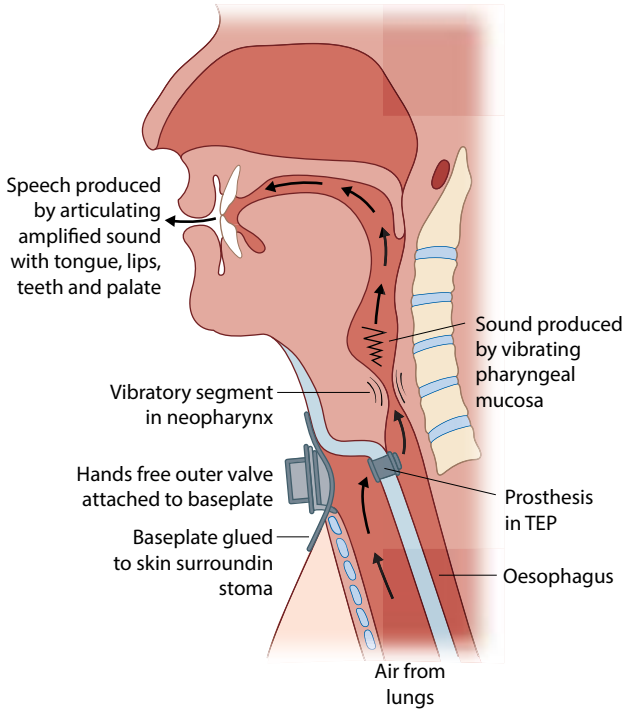


Figure 15.9 Hands-free surgical voice production.

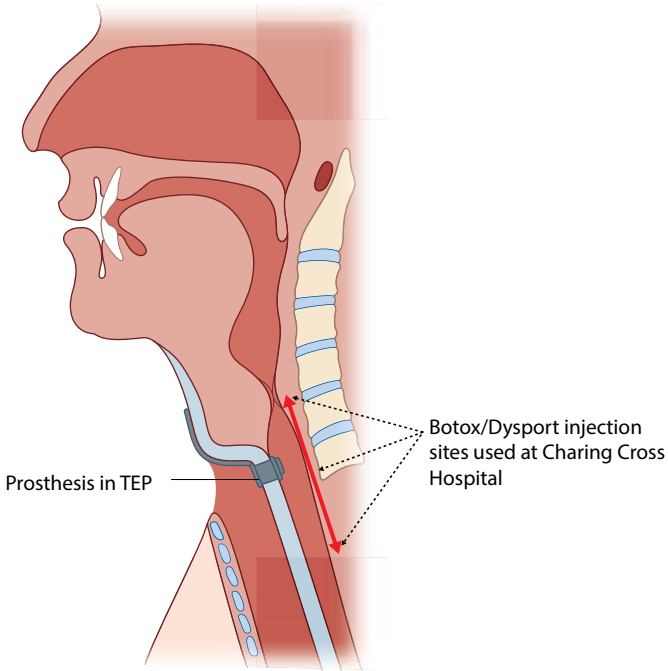


Figure 15.10 The myotomy is made posteriorly from the level of the cricopharyngeus down to below the level of the tracheo-oesophageal puncture. Botox/Dysport injection sites used at Charing Cross Hospital.

Hypertonicity/spasm that develops post-operatively can be managed with an open myotomy or chemical neurectomy. Since the introduction of botulinum toxin,[22] myotomy involving reopening the neck and dividing all the muscles including those of the reconstructed/vibratory segment is rarely performed, as it may cause hypotonicity and involves the risk of perforation.

A full videofluoroscopic assessment of swallow and voice should be carried out followed by a lignocaine injection to confirm the diagnosis.[23] Botulinum toxin is injected unilaterally at three sites along the same short myotomy line (**Figure 15.10**). The dosage administered is influenced by the degree of hypertonicity, neck fibrosis and stricture, whether a primary myotomy was performed and the surgical reconstruction. Injection of botulinum toxin can be repeated, though a single treatment is often sufficient to allow continued tonic voice.

PROBLEM-SOLVING

Problems occur both with the TEP and prosthesis.

Candida albicans

Candida spp. thrive in warm moist environments with a pH near 6.5 (e.g. oesophagus).[24, 25] A voice prosthesis acts as a foreign body within the TEP, becoming covered by a biofilm of bacteria and yeasts, forming plaques (**Figure 15.11**). *Candida albicans* interferes with the prosthesis valve mechanism, causing leakage and aspiration or increasing airflow resistance such that the prosthesis becomes non-functional.[24, 26–28] *Candida* spp. can also develop on the outside of the prosthesis burrowing into local tissue and causing an allergic type reaction (granulation tissue; see 'Granulation' below) (**Figure 15.12**).[24]



Figure 15.11 New prosthesis and one covered in a biofilm bacteria and yeats.

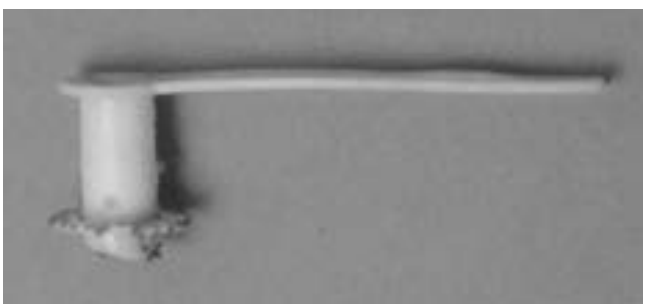


Figure 15.12 Candida species adherent to prosthesis.

Patients should brush and flush their prosthesis daily *in situ*,[29] possibly including a liquid antifungal (e.g. nystatin).[30] Exdwelling prostheses should be regularly removed, washed and sterilized overnight in 3% hydrogen peroxide.[31] If the estimated prosthesis lifetime[32] is too short, the prosthesis should be sent for mycological analysis and the results will indicate the appropriate antifungal to prescribe. Prostheses impregnated with antifungals are available at a cost. Fungal resistant materials are being developed;[33] meanwhile, dietary adjustment including the addition of probiotics should be considered.[34–36]

Granulation

Granulation is connective tissue thought to occur as an acute inflammatory response to a complex interaction between the prosthesis, *Candida* spp and the patient's tissue.[24] Removal of the voice prosthesis can cause bleeding and the open wound acts as a source for further infection. Small areas can be cauterized using a silver nitrate stick but larger areas require surgical removal (**Figures 15.13** and **15.14**). Prosthesis function may be disturbed and lead to TEP closure. Managing the *Candida* colonization is essential to prevent it recurring.



Figure 15.13 Excess granulation tissue being removed from tracheo-oesophageal puncture site.



Figure 15.14 Granulation tissue removed from around prosthesis.

Reflux

Reflux causes oesophagitis and heartburn, and encourages *Candida* spp growth, granulation tissue formation and TEP dilation.[25] Its influence has been under-recognized.[25] Management of reflux is discussed in detail in Chapter 77, Reflux disease.

Central leakage

Candida interfering with prosthesis valving function is the most common cause of prosthesis central leakage.[27] This results in aspiration and increases the risk of chest infections. Other causes include prosthesis fouling against the posterior oesophageal wall while swallowing or negative pressure created within the oesophagus leading to inappropriate valve opening. Alternative prostheses with more appropriate sizes should be selected.

Peripheral leakage

This happens when the tissue around the TEP no longer beds down snugly onto the prosthesis barrel and allows saliva or liquid to penetrate around the prosthesis and hence aspirated into the trachea causing coughing or chest infections. Peripheral leakages should be managed prophylactically, anticipating and preventing this problem.

Reported reasons for peripheral leakage include:

- an oversized prosthesis pistoning within the TEP, suctioning the bolus through[31]
- a thinned or weakened party wall (below 8 mm), associated with a wider diameter prosthesis *in situ*[37, 38] often in patients with concurrent comorbidity (e.g. diabetes).[39]

Prevention can be achieved by the following measures:

- minimizing trauma by avoiding dilation of the TEP[37] and reducing the number of changes
- when changing the prosthesis, one option is to cut the *in situ* prosthesis in half, removing the anterior portion and allowing the posterior portion to pass out through the patient[40]
- hand-load the prosthesis into a smaller gel cap for placement.

Additional options include:

- injecting a filler to bulk the party wall[39, 41]
- using successively smaller diameter catheters to shrink the TEP (e.g. from a 20 FG to 16 FG)[42]
- using a snugly fitting extended flange prosthesis to cover the gap (**Figure 15.15**)[39]
- purse string suture procedures, reported to have poor success rates.[43]



Figure 15.15 Extended flange prosthesis and pushing device to help placement into the gelcap.

KEY POINTS

- Management decisions about rehabilitation after laryngectomy should be made within dedicated head and neck units by the multidisciplinary team.
- Surgical voice restoration should be offered to patients undergoing laryngectomy.
- Attention to surgical detail and long-term speech and language therapist input is required to optimize speech and swallowing after laryngectomy.
- Patients should commence wearing heat and moisture exchange devices as soon as possible after laryngectomy.

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CHAPTER 16

MANAGEMENT OF HYPOPHARYNGEAL CANCER

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SEARCH STRATEGY

A search of PubMed with MeSH headings hypopharynx, piriform fossa, postcricoid,posterior pharyngeal wall, tumour, cancer, squamous cell carcinoma, gastric pull up, free jejunal graft, radiotherapy, chemotherapy,Trans Oral Videoendoscopic Surgery,Transoral Laser surgery, pharyngectomy, laryngopharyngectomy, near total laryngectomy in various combinations was carried out.

INTRODUCTION

Hypopharynx is the caudal part of the pharynx, also called laryngopharynx, extending from the hyoid bone to the lower margin of the cricoid cartilage. It is a dynamic conduit between the oropharynx and oesophagus and has three subsites – pyriform sinus, post-cricoid area and posterior pharyngeal wall. Laryngeal and hypopharyngeal cancers are often clubbed together due to their anatomic proximity. However, hypopharyngeal cancers are distinctly different from laryngeal cancers in terms of presentation, management and prognosis.

EPIDEMIOLOGY

Hypopharyngeal cancers are rare, and account for less than 0.5% of all cancers and 3–5% of head and neck cancers.[1–3] They have a large geographical variation, being relatively rare in Eastern Asia, Africa and Northern Europe (incidence under 0.5:100,000) and more common in India, Brazil, Central and Western Europe (incidence of 2.5:100,000). The incidence in India and France are substantially higher at 8–15 cases per 100,000 population in males.[4]

Hypopharyngeal cancers occur in individuals above 50 years of age, with a peak incidence in the sixth and seventh decades.[5] The most common site of origin is the pyriform sinus followed by the posterior pharyngeal wall and the postcricoid area. Pyriform and posterior pharyngeal wall lesions are more common in males, whereas postcricoid cancers are predominant in females.[6–9] The most common histology at this site is squamous cell carcinoma.

SURGICAL ANATOMY

The hypopharynx lies below and behind the base of tongue and larynx. It extends from the level of the hyoid bone to the lower border of the cricoid cartilage. It is comprised of three subsites: pyriform sinus, postcricoid area and posterior pharyngeal wall.

The pyriform sinus is a funnel-shaped lateral channel on either side of the larynx beginning at the level of the pharyngoepiglottic fold. It has a lateral wall which is contiguous with the posterior pharyngeal wall, a medial wall that forms part of the aryepiglottic fold converging into the postcricoid mucosa medially, and opens posteriorly into the lumen of the pharynx.

The pyriform sinus is bound laterally by the thyrohyoid membrane and medially by the aryepiglottic fold. The tumours tend to spread through this membrane beyond the larynx without cartilage destruction, keeping the laryngeal function somewhat intact. This is relevant in treatment planning.

The pyriform apex lies at the junction of the medial and lateral walls, deep and inferior within the pyriform sinus. It is related laterally to the thyroid cartilage, medially to the cricoid cartilage and lies inferior to the paraglottic space. Tumours involving the pyriform apex can easily spread superiorly into the paraglottic area causing vocal cord fixity. Tumours of the pyriform apex are in close proximity to the cricoid cartilage and oncological removal necessitates removal of the cricoid cartilage. This has implications when considering conservation laryngeal surgery. Tumours from the pyriform apex can also escape via the cricothyroid membrane early on beyond the laryngeal framework and need careful evaluation.

The postcricoid area lies behind the larynx and is located below the level of the arytenoid cartilages and extends to the inferior border of the cricoid cartilage. It continues below into the cricopharynx which lies at the upper end of oesophagus. Tumours in this region often involve the cricoarytenoid joints causing vocal cord fixity and/or aspiration. Being a junctional region, obstruction to the passage of food occurs early on and tumours often extend into the oesophagus inferiorly, mandating evaluation of the lower extent of tumour spread.

The posterior pharyngeal wall is the part of the hypopharynx between the lateral walls of the pyriform sinuses extend from the hyoid above to the level of the arytenoids below. It is separated from the prevertebral muscles by the prevertebral fascia. Tumours in this region can spread in either direction and even involve the prevertebral fascia and muscles early on in their spread.

The wall of the hypopharynx consists of four layers – 1) lining formed by non-keratinized stratified squamous epithelium; 2) pharyngobasilar fascia; 3) muscular layer formed by the lower fibres of the middle constrictor and the inferior constrictor muscles and 4) buccopharyngeal fascia. The hypopharynx derives its major blood supply from the superior thyroid arteries along with collaterals from the lingual and ascending pharyngeal vessels. Care should be taken not to devascularize the remnant pharynx during surgery to avoid pharyngocutaneous fistulae. Motor and sensory supply is provided by the pharyngeal plexus, formed by branches of the glossopharyngeal and vagus nerves. The vagus nerve via Arnolds nerve provides sensory innervation of the external auditory canal and is responsible for referred otalgia in hypopharyngeal cancers. Further description of the hypopharyngeal anatomy can be seen in Chapter 58, Anatomy of the larynx and tracheobronchial tree.

The hypopharynx has a rich lymphatic drainage (**Figure 16.1**). The pyriform sinuses drain to the deep cervical chain – the jugulodigastric and jugulo-omohyoid nodes. The pyriform sinus apex as well as postcricoid area drain into the paratracheal nodes while the posterior pharyngeal wall drains into the retropharyngeal nodes.[10] Careful evaluation of the tumour location and its draining lymph nodes is important in treatment planning in context of lymph node dissection and radiation therapy planning (**Figure 16.1**).

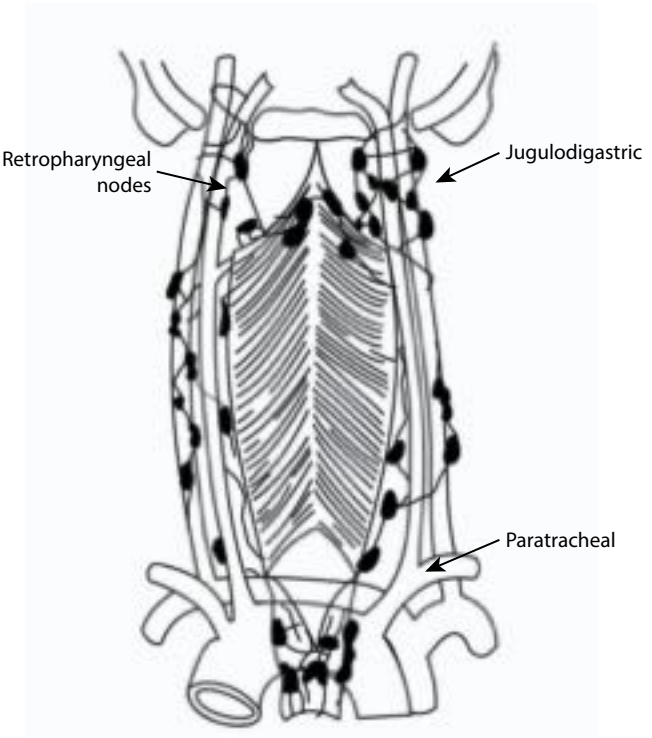


Figure 16.1 Lymphatic drainage of the hypopharynx.

AETIOLOGY

Hypopharyngeal cancers have multifactorial aetiology, predominantly associated with tobacco and alcohol usage. Air-cured tobacco is associated with a higher risk than the flue-cured one of developing laryngo-pharyngeal cancer.[11] Current smokers have a 8.53 higher incidence rate as compared to never smokers.[12] Early initiation of smoking and increase in the number of cigarettes consumed per day increases the cancer risk.[4] There is also a dose–response relationship with bidi smoking;[13] a multicentric case-control study showed bidi smoking to be a strong risk factor for developing hypopharyngeal cancer (odds ratio – 6.8) and supraglottic cancer (odds ratio – 7.5).[14] Smoking cessation is important as it decreases the risk of developing head and neck cancers.[15] Alcohol consumption with direct and indirect carcinogenic actions is also associated with hypopharyngeal cancers. Alcohol not only acts as a solvent for carcinogens like tobacco but also makes the mucosa more permeable to them. Wine, beer and liquor have similar risk of developing head neck cancers.[13, 16–18] There is a dose–response relationship between alcohol intake and

hypopharyngeal cancer[19] with a meta-analysis showing heavy drinkers (>4 drinks/day) having a relative risk of 9.03 compared to occasional or non-drinkers.[20] Those consuming dark liquors have been found to have 4.4 times relative risk compared to light liquors.[21]

HPV related cancers, though more common in the oropharynx, are seen in 10.9% of hypopharyngeal cancers with pyriform fossa having the highest association.[22, 23]

Diet and weight have a bearing in development of cancers. Lower body mass index (BMI) (<18.5) is associated with a greater risk of developing hypopharyngeal cancers.[24] and this seems to be particularly strong among current smokers.[25] Fruits, raw vegetables, and whole grain and dietary fibre intake have an inverse relationship with pharyngeal cancer while higher meat and fried food intake seem to increase the risk of developing hypopharyngeal cancers.[26–29] Post-cricoid tumours are commonly seen in women and are associated with sideropenic dysphagia (Paterson–Brown–Kelly syndrome/Plummer–Vinson syndrome). Certain occupations such as construction workers, potters, butchers, barbers and those exposed to formalin fumes, coal dust, steel dust, iron compounds and fumes are at a higher risk of developing hypopharyngeal carcinoma.[16, 30, 31]

MOLECULAR BASIS OF HYPOPHARYNGEAL CANCERS

Molecular changes causing hypopharyngeal cancers are similar to those at other head and neck sites. However, there are certain specific molecular factors that impact the prognosis of hypopharyngeal cancers. The hypopharynx cancer-specific literature identifies a correlation with amplification of oncogenes (*CCND1*, *FGF3* and *FGF4*) in the region of 11q12, and surprising lack of correlation with loss of tumour suppressor gene.[32] On the contrary, *p53* overexpression was seen in 66% of hypopharyngeal tumours and the overexpression or stabilization of *p53* was significantly associated with improved survival.[33] Cyclin D1 overexpression, apart from being predictive of multiple neoplasms, correlates with advanced clinical stage, tumour extension and relapse prediction after primary radiotherapy and survival.[34] Ki-67, a marker of cell proliferation, is indicative of poor survival.[35, 36] Amongst various factors such as p53, p21, Rb and Cyclin D1 studied in laryngeal and hypopharyngeal cancers, only Cyclin D1 has independent prognostic value for cancer-specific survival.[37] Amongst the growth factor receptors, EGFR was found to be overexpressed in 30% of hypopharyngeal cancers.[38] These may translate into biomarkers for early detection or treatment planning in the quest for personalized medicine.

HISTOLOGY

Most cancers of the hypopharynx are squamous cell in origin and tend to be moderately or poorly differentiated tumours, especially in the pyriform sinus. Non-squamous malignancies are rare and tend to arise from the minor salivary glands (mostly adenoid cystic carcinomas) or are mesenchymal in origin.

ROUTES OF SPREAD

Due to the lack of well-defined spaces as in the larynx, tumours of hypopharynx do not have a very well-defined pattern of spread within the laryngopharynx. With absence of barriers these cancers tend to grow and disseminate long before the patient is symptomatic.

Local extension

Tumours involving the lateral wall of the pyriform sinus most often invade the thyroid cartilage, with ossified cartilages being more prone to tumour invasion. Tumours involving the medial wall of the pyriform sinus extend antero-medially into the paraglottic space and impede vocal cord movement either by mass effect or by invasion of the intrinsic muscles. The apex of the pyriform sinus being inferior to the paraglottic space, tumours tend to involve the paraglottic space early causing cord fixity. Tumours at the pyriform apex can also escape through the cricothyroid membrane and involve the thyroid gland (**Figure 16.2**).[39] Tumours at the pyriform apex do not lend themselves to any form of partial laryngo-pharyngectomy that preserves speech as well as nasal respiration, since the oncological resection would entail removal of the cricoid cartilage. The proximity to the intrinsic laryngeal muscles, the cricoarytenoid joint and the recurrent nerve leads to early impairment of the vocal cords by the tumours.[40, 41]

Post-cricoid area tumours tend to invade the cricoid and tracheal cartilages,[42] thus involving the airway and causing obstruction. The tumour may infiltrate the posterior cricoarytenoid muscle and cricoarytenoid joint causing cord fixity and even precipitate aspiration. Post-cricoid tumours also tend to extend exolaryngeal through the cricothyroid membrane to involve the thyroid gland (**Figure 16.4e**).



Figure 16.2 Right hypopharyngeal cancer with thyroid gland invasion presenting as a thyroid mass.

Anterolateral spread from a predominantly submucous infiltrative post-cricoid cancer may present with a swelling in the region of the thyroid and may be misdiagnosed as goitre, especially in cases where the dysphagia is minimal. It must be pointed out that both these conditions, i.e. post-cricoid cancer and goitre, are commonly seen amongst young females. There have been instances when such mistaken diagnosis has led to exploration of the neck for thyroidectomy causing a lot of embarrassment to the surgical team (**Figure 16.2**).

Post-cricoid lesions have significant submucosal spread which is more pronounced inferiorly than superiorly.[43] The extension of the disease into the cervical oesophagus is common with occasional skip lesions in the oesophagus due to the submucosal lymphatic plexus. This mandates careful pre-treatment evaluation and planning as it can alter the treatment plan.

Lateral spread (parapharyngeal) is in the vicinity of the carotid sheath and extralaryngeal spread from the hypopharyngeal and supraglottic cancers often encases the carotid vessels which needs careful evaluation to differentiate from nodal disease (**Figure 16.3**).

Posterior pharyngeal wall tumours are relatively less common and have not been studied extensively. The tumours tend to be exophytic and are frequently large at the time of diagnosis. In spite of this, invasion of the prevertebral fascia occurs late. The tumour usually involves adjacent areas when first diagnosed. The tumour may extend superiorly to the base of the tonsil and laterally to the oropharyngeal wall, or spread inferiorly into the post-cricoid region and cervical oesophagus. Synchronous tumours along the pharyngeal wall should be evaluated due to the continuous mucosa and extensive lymphatics.

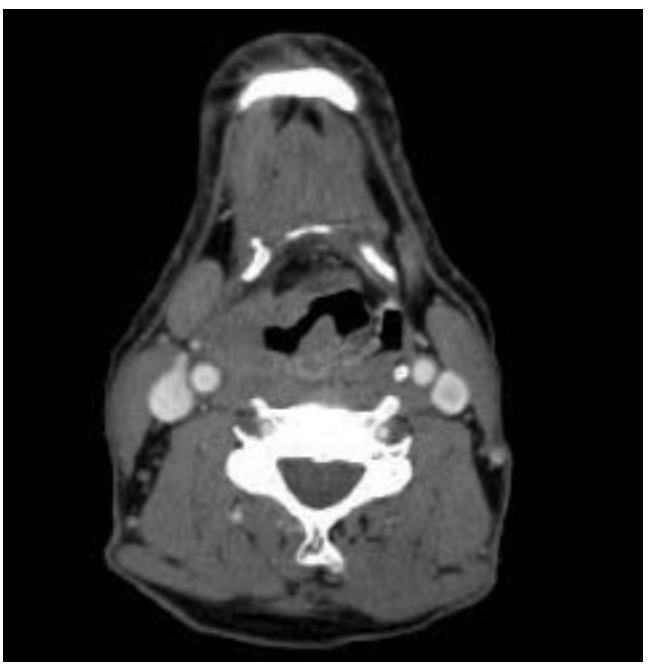


Figure 16.3 Right hypopharyngeal cancer demonstrating extralaryngeal extension.

Regional spread

Hypopharyngeal tumours have the highest propensity for early lymph nodal metastases. Up to 70% of patients may have lymph nodal metastases particularly to levels II and III at presentation and there is a high incidence of occult nodal metastases, which will influence the investigations, staging and treatment.[44] Paratracheal and paraoesophageal i.e. level VI metastases are more common in lesions involving post-cricoid or pyriform sinus apex while retropharyngeal nodes can be involved in posterior pharyngeal wall cancers.[45, 46] When patients have unilateral clinically positive neck disease, the incidence of contralateral occult lymph node metastases is at least 50%.[47] Bilateral occult lymph node metastases in patients with clinically negative neck are most frequently associated with cancers of the pyriform sinus (**Figure 16.1**).[47, 48] In patients with clinically positive neck disease, more than 20% have involvement of the lower nodal stations (level IV and V).[48]

Distant spread

Among all head and neck cancers, hypopharyngeal primaries have the highest incidence of distant metastases at presentation (17–24%)[49, 50] and during follow-up, with more than 50% of failures due to distant metastases.[51] Pulmonary metastases are most common followed by skeletal and liver metastases. The average survival is usually less than 1 year once distant metastases have been diagnosed.[52] Development of distant metastases at some time following initial treatment is associated with tumour recurrence locoregionally.[53]

CLINICAL PRESENTATION

Symptomatology

Hypopharyngeal tumours are detected late as the patients are asymptomatic in the early stages, especially those involving the pyriform sinus. The cardinal symptoms are odynophagia, dysphagia, hoarseness, otalgia, weight loss or a neck lump. The earliest symptom may be that of mild non-specific throat discomfort. In fact, globus sensation may be the only presenting complaint with normal clinical findings.[54] Dysphagia to solid food may be an early presentation in post-cricoid cancers, but is generally seen late in pyriform cancers. Significant weight loss is especially seen in post-cricoid area and oesophageal tumours. Unilateral referred otalgia, is another common symptom and may indicate involvement of Arnold's nerve (X) as explained before. Occasionally, in advanced cases, where the disease extends superiorly to involve the tongue base, referred otalgia may be present deep in the ear, mediated via the glossopharyngeal nerve, the pharyngeal plexus and the Jacobson's nerve in the middle ear. Hoarseness of voice may be a late presentation in pyriform and post-cricoid cancers while 'hot potato' speech signifies involvement of the base of the tongue. As discussed before, a significant

proportion of patients may present to the clinic with palpable neck lymphadenopathy as the only complaint on initial clinical examination.

Clinical examination and signs

A careful and detailed history taking and examination of the patients with suspected hypopharyngeal cancers must be done in the clinic. Most of these patients tend to be elderly males except those with post-cricoid tumours, which is seen predominantly amongst females. A history of tobacco and alcohol consumption must be elicited and recorded with respect to quantity and duration. Counselling services must be offered for tobacco and alcohol cessation, if the patient is continuing with the habit. Patients with advanced disease may look unwell, with significant weight loss. Halitosis may be present. The patients may appear to attempt swallowing with discomfort frequently and a noticeable lump may be present in the neck on inspection. Hoarseness of the voice and history of aspiration must be recorded in every case. In advanced disease, there can be airway compromise with stridor on presentation.

On examination, the presence of exolaryngeal spread with widening of the thyroid cartilage must be assessed. Loss of laryngeal crepitus (Trotter's sign) and restriction of neck extension may imply involvement of the prevertebral fascia. The neck must be carefully palpated for nodes and their size, level of involvement and laterality recorded meticulously. In case of large nodes, movement of the node in vertical and horizontal axis, fixity to the carotid sheath and consistency of nodes (solid or necrotic) must be noted. Skin and platysma involvement must be documented. The root of neck at the suprasternal space of Burns needs to be evaluated for tracheal displacement as well as palpable disease or lymph nodes which would suggest unresectability.

On laryngeal examination, either with a Hopkins rod telescope or mirror, the presence of a growth should be observed. Pooling of saliva may obscure the growth especially in pyriform cancers. If a growth is noted, the extent of disease and involvement of hemi-larynx should be noted. A fibre-optic endoscopic examination under local anaesthesia would give additional visualization and help document the disease extent especially in posterior pharyngeal and pyriform growths. Additionally, a biopsy may be taken with use of the flexible forceps passing through the biopsy channel. However, the flexible endoscope may not be adequate to visualize the inferior extent of the disease, particularly the apex of pyriform sinus and post-cricoid area. In these cases, rigid pharyngoscopy should be performed under general anaesthesia. Treatment decisions are guided by the tumour map, which highlights the importance of a good clinical and laryngoscopic evaluation. In case of circumferential lesions of post-cricoid going down into the cervical oesophagus, a flexible oesophagoscopy may be better than a rigid oesophagoscopy to document the inferior extent of disease as well as to look for a second primary in the oesophagus. A checklist used at the time of the evaluation is important to avoid missing details and has implications for treatment planning (**Table 16.1**).

DIAGNOSIS AND STAGING

Investigations

Barium oesophagogram is an effective screening tool for hypopharyngeal cancers and synchronous cancers in the oesophagus. Barium swallow helps determine the lower limit of a post-cricoid cancer, information that is very vital in the treatment planning.[55] Current practice in most centres involves a flexible transnasal oesophagoscopy to map the lesion, determine its lower limit and proximity to the cricopharynx, assess oesophageal involvement and evaluate synchronous primaries in the oesophagus. This supersedes barium imaging.

Direct laryngoscopy under general anaesthesia helps obtain a biopsy and assess the extent of the lesion for treatment planning. In case of a palpable neck node, biopsy confirmation may be obtained with fine-needle aspiration cytology (FNAC). Open biopsy must be avoided.

Compared to endoscopy or manual examination, CT imaging has higher sensitivity for defining the T stage of the primary tumour (size of tumour, relationship to critical deep structures). Adequate imaging includes contrast enhanced CT (CE-CT) performed with a multidetector CT scanner with bone window reformats (for cartilage assessment).[56] For assessment of cartilage invasion, MR imaging seems to be more sensitive than CT (sensitivity up to 96%). However, CE-CT is the first choice for imaging with MR reserved for trouble shooting. Both CT and MRI over diagnose posterior tumour spread in advanced hypopharyngeal disease and should be correlated clinically. The imaging reporting should be synoptic to avoid missing critical information. The synoptic essentials are covered in **Table 16.2**. **Figure 16.4** illustrates the range of radiologic findings in hypopharyngeal primaries.

A chest X-ray should be performed as a part of screening for distant metastasis while a CT chest is indicated in all patients with advanced stage tumours and/or bulky neck disease.[57] In borderline-resectable disease, positron emission tomography (PET) along with CT scan (FDG-PET/CE-CT) as a single-staging investigation may be considered for evaluation of the primary disease status and excluding any occult distant disease.[58–61] FDG PET/CE-CT is a useful imaging modality in the assessment of laryngeal and hypopharyngeal cancers, especially in post-radiation residual/ recurrent disease where it is often very difficult to prove the presence of active disease and differentiate it from post-radiation oedema.[62]

Staging

Staging of hypopharyngeal cancer is carried out according to the TNM classification, (**Table 16.3**). For the larynx and hypopharynx the only change from the previous staging has been the renaming of T4a resectable as T4a (moderately advanced) and T4b unresectable as T4b (very advanced).

TABLE 16.1 Checklist for direct laryngoscopy under anaesthesia

Subsite evaluated during endoscopy	Disease status	Implication
Oropharynx		
Vallecula /base tongue	Involved / free If involved lateralized or crossing midline	If lateralized resectable If crossing midline, decision-making for glossectomy with laryngectomy vs. chemoradiation
Inferior tonsil pole	Close / involved / free	Close – resectable but will need pharyngeal reconstruction Involved – to evaluate for resectability with superior and lateral extent of lesion into parapharyngeal space
Hypopharynx		
Pyriform apex	Involved / free	No conservation laryngeal procedure feasible as cricoid cannot be oncologically preserved
Cricoartyenoid joint	Involved / free	
Arytenoid cartilage	Involved / free	If cricoarytenoid joint is mobile, consider replacing posterior glottic bulk if conservation laryngeal procedure is planned
Cricopharynx	Free / involved / extending to oesophagus	Involvement indicates circumferential pharyngeal resection requiring reconstruction with free jejunum or free radial artery flap Oesophageal involvement indicates need for gastric pull-up
Lateral pyriform wall	Involved / free	Pharyngotomy approach and pharyngeal reconstruction
Posterior pharyngeal wall	Involved / free If involved lateralized or crossing midline	Crossing midline – pharyngeal reconstruction needed
Pharyngeal mucosa	Mobile / fixed	Mobile – consider TLM / RT Fixed – non-surgical modality
Post-cricoid	Involved / free	Near-total laryngectomy is not feasible and may require patch pharyngoplasty
Glottis / supraglottis		
Vocal cords	Mobile / impaired / fixed	Mobile cords – TLM/TORS,/OPL/ RT Fixed cords – organ preservation
Pre-epiglottic space	Involved / free	Free TLM/TORS/ OPL / RT Involved – organ preservation
Paraglottic space	Involved / free	
Anterior commissure	Cords mobile and pre-epiglottic space free	Supracricoid laryngectomy/hemipharyngectomy
Subglottis	> 1 cm anteriorly	No conservation laryngeal surgery possible
	< 5 mm posteriorly	
Inter-arytenoid	Involved	Conservation laryngeal surgery and near-total laryngectomy not feasible.

TABLE 16.2 Synoptic radiological report

- Tumour volume
- Locoregional extent of the disease
  - Superior – Oropharynx
  - Inferior – Cricopharynx, oesophagus
  - Transglottic
  - Crossing midline – anterior commissure, post cricoid
- Pre-epiglottic space and paraglottic space
- Exolaryngeal spread – thyrohyoid membrane, cricothyroid membrane, straps muscles
- Thyroid and cricoid cartilage involvement
- Cricoarytenoid joint
- Visceral spaces (prevertebral fascia, carotid space)
- Metastatic lymph nodes - Levels II-V, Paratracheal, Retropharyngeal

FACTORS DETERMINING TREATMENT IN HYPOPHARYNGEAL CANCER

Treatment decisions in cancer are guided by the biology of the disease and the peculiarities of the organ affected. Tumour and nodal factors, performance status (PS) of the patient, resources and available technical expertise dictate the management.

Tumour factors: Squamous cell cancers are biologically more aggressive in the hypopharynx due to its rich vascularity and lack of barriers to the spread of tumour. Hypopharyngeal tumours uniquely have substantial submucosal spread well beyond the mucosal limits of the tumour and are seen up to 20 mm.[63] Whole organ studies of hypopharyngeal cancer specimens showed submucosal spread in 60%, most being in the inferior direction followed by lateral and superior. The submucosal spread is not obvious macroscopically and is more often seen in post-irradiated patients.[64] Surgical margins should be critically assessed to contain this submucosal spread.

Proximity of hypopharynx tumours to the larynx causes them to affect laryngeal functions.[65] Surgical organ preservation procedures should be planned based on structural and functional integrity of the larynx without compromising oncologic safety.

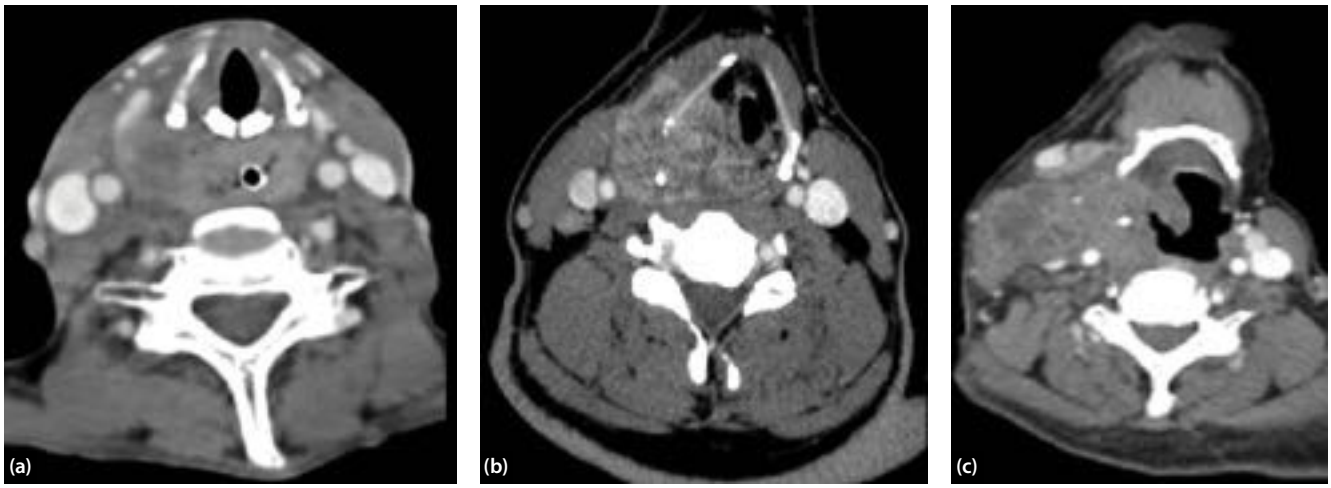


Figure 16.4 **(a)** Extension into post-cricoid region with extralaryngeal component: T3. **(b)** Involving the outer cortex of thyroid cartilage with extralaryngeal spread that surrounds less than 180° of the carotid artery. **(c)** Extralaryngeal spread with involvement of prevertebral fascia and splaying of carotid vessels: T4b.

Nodal factors: Hypopharynx is rich in lymphatics with a high incidence of metastasis to the jugular paratracheal and retropharyngeal group of lymph nodes even in early stages of the disease which may result in the nodal disease as the primary manifestation in 65% to 80% and occult metastasis in 30% to 40% of N0 necks.[43, 48, 66–68] Hence treatment of neck nodes is mandatory in all hypopharyngeal cancers.[69]

Performance status: PS is a measure of general condition of the patient. It takes into account their general wellbeing and ability to carry on daily life activities. Usually the PS scales are the Karnofsky score or the WHO / ECOG / Zubrod scale.

PS in hypopharyngeal cancers is important estimate of treatment outcomes:

- Conservative surgery both open and transoral methods will alter laryngeal anatomy and physiology, resulting in alteration of laryngeal protection mechanisms, thus increasing the probability of aspiration and dysphagia. PS is an important estimate of the ability of the patient to withstand sequelae of the surgery.
- More than 75% of patients present in advanced stages III and IV and will go on to receive multimodality treatment. If PS is low, the possibility of withstanding and completing treatment is lower.
- In the palliative care setting, PS helps determine if the patient will benefit from either chemotherapy or radiation or is best suited for only supportive care.

Resources and technical expertise: Transoral surgery in select cases is technically demanding as well as resource heavy. Transoral laser and robotic surgery require intensive training and mentorship. The goal is to reduce morbidity of multimodal therapy without compromising oncological outcomes; hence achieving proper clearance of disease through transoral access is paramount. Resources such as a fully equipped microlaryngeal setup with laser or a transoral robotic setup are required and may not be feasible at all centres.

Partial laryngopharyngeal resection requires proper case selection and training in laryngeal conservative surgery and reconstructive techniques.

Radiation therapy and chemotherapy are challenging in patients who are nutritionally depleted, who will experience higher grade toxicity with concomitant chemotherapy regimes, resulting in noncompliance with treatment schedule and poorer outcomes. Expertise in delivery of these technically demanding therapies is required for optimal outcomes.

TREATMENT OF EARLY HYPOPHARYNGEAL CANCERS

Early cancers are potentially curable and the goals of treatment should be maximizing chances of cure with function preservation. In hypopharyngeal cancers, these goals are impeded by the proximity of the larynx and occult metastatic nodes, even in early staged tumours.

Treatment of T1 and T2 hypopharyngeal cancers can be with either radiation therapy or conservation surgery. Decision-making in early hypopharyngeal cancers depends on the tumour location and the ability of the patient to withstand treatment. Oncological safety and functional preservation are important decision-making criteria while choosing treatment.

Larynx conservation surgery

Surgical considerations are similar to those in laryngeal cancers where preservation of speech and larynx protection mechanisms is paramount. Patient age and respiratory function are very important selection criteria because hypopharyngeal resection combined with partial laryngectomy alters voice and increases risk of aspiration and airway compromise. Hence patients with tumours involving

TABLE 16.3 UICC staging 8th edition

Primary tumour	
T1	Tumour limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension
T2	Tumour invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest dimension without fixation of hemilarynx
T3	Tumour more than 4 cm in greatest dimension or with fixation of hemilarynx or extension to oesophagus
T4a	Moderately advanced local disease. Tumour invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue (includes prelaryngeal strap muscles)
T4b	Very advanced local disease. Tumour invades prevertebral fascia, encases carotid artery, or involves mediastinal structures
Regional lymph nodes (N)	
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension without extranodal extension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension without extranodal extension
N2b	Multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension without extranodal extension
N2c	Bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension without extranodal extension
N3a	Metastasis in a lymph node, more than 6 cm in greatest dimension without extranodal extension
N3b	Metastasis in a single or multiple lymph nodes with clinical extranodal extension*

Stage grouping			
Group	**T**	**N**	**M**
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1, T2, T3	N1	M0
IVA	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

* Presence of skin involvement or soft tissue invasion with deep fixation / tethering to underlying muscle or adjacent structures or clinical signs of nerve involvement is classified as clinical extranodal extension. Midline nodes are considered ipsilateral nodes.

the pyriform apex or post-cricoid area and those with poor pulmonary function should not be considered as candidates for partial pharyngolaryngectomy. Gastrostomy tube and tracheostomy tube dependence is also a real possibility with alteration of laryngopharyngeal anatomy with surgery and post-operative radiation therapy.

The larynx conservation surgery for early hypopharyngeal cancers can be via two approaches: conventional external and transoral approaches.

EXTERNAL APPROACH – PARTIAL LARYNGOPHARYNGECTOMY

Indications

Conservation surgical procedures are considered for early lesions of the hypopharynx:

- Tumours less than 4 cm (T1–T2)
- Pyriform apex and post-cricoid mucosa free of disease
- Mobile vocal cords
- No erosion of the thyroid cartilage
- No paraglottic spread.

Types

The choice of conservation surgical techniques depends on the location and the spread of the tumour. Depending on the proximity of the lesion to the larynx the procedure can be either partial pharyngectomy, or partial pharyngolaryngectomy.

Partial pharyngectomy: When the tumour arises on the pharyngeal component of the hypopharynx and spares the medial wall of the pyriform sinus and the apex, it is suitable for partial pharyngeal resection. Approached through a lateral pharyngotomy, the involved pharyngeal wall is resected and reconstructed with either pectoralis major myocutaneous flap or free flap. The pharyngeal reconstruction restores continuity of the upper aerodigestive tract and with it, normal speech and swallow.

Partial pharyngolaryngectomy: When the tumour involves the medial wall of the pyriform sinus and extends onto the supraglottic structures of the larynx it necessitates partial resection of the hypopharynx and the larynx. Partial pharyngectomy can be either an extended supraglottic partial laryngectomy or supracricoid hemilaryngopharyngectomy. It is a functional procedure involving resection of the hemilarynx above the level of the cricoid and the medial aspect of pyriform sinus and the ipsilateral supraglottic structures (**Figure 16.5a**). The laryngeal functions are impeded with loss of sensation due to resection of superior laryngeal nerve and removal of supraglottic structures. These need to be reconstructed to prevent aspiration, stridor and dysphagia.

RECONSTRUCTION FOLLOWING PARTIAL LARYNGOPHARYNGECTOMY

Following partial laryngopharyngectomy, the goals of reconstruction are to restore not only the anatomical continuity but also the functionality of the larynx viz airway protection, airway preservation and the ability to voice. The pharyngeal defect is reconstructed with either the pectoralis myocutaneous flap or the free flap usually the radial forearm flap (**Figure 16.5b**). The laryngeal

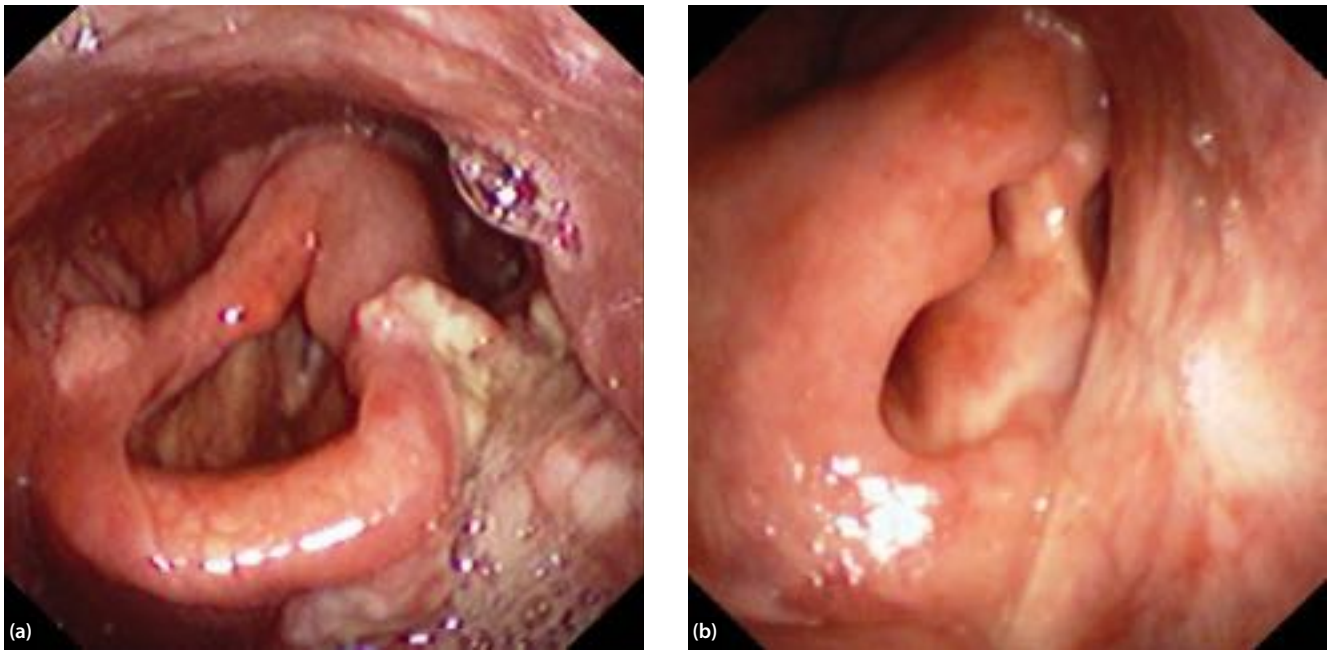


Figure 16.5 **(a)** Early hypopharngeal tumour treated by open partial laryngopharyngeal resection and free radial forearm flap reconstruction, **(b)** shows a healthy pyriform at two years with minimal disruption of anatomy. Note lack of pooling indicating good swallowing function (Courtesy of Prof. Rudolf Hagen, Germany).

structures will be reconstructed ingeniously using parts of the epiglottis and hyoid. Microvascular free-flap expertise has tremendously improved outcomes as compared to the 1960s and 1970s with lower rates of morbidity.

Oncological outcomes

Several studies analyzed the results obtained with partial surgery in patients with early pyriform sinus carcinoma.[49, 70, 71] with 5-year overall survival rates ranging from 55% to 59%. The local control rates have often been excellent ranging from 77% to 97% while regional recurrences occur in 15–23% and distant metastases in 28%. In most series, the incidence of distant metastasis increases as the local control rates improve. Survival is better in patients with T1 disease, those with good surgical margins and in those receiving post-operative radiation.[72–74] Extension to the apex of the pyriform sinus is fraught with local failure while distant metastases occur in patients with two or three wall involvements.[49] Amongst the contemporary series, Chung et al[75] reported 58 patients who underwent partial pharyngectomy with reconstruction, showing 5-year overall and disease specific survival rates of 78% and 77.6% respectively. Level VI metastasis confirmed by histopathological analysis, close (< 5 mm) histologic margins, advanced nodal stage and posterior pharyngeal wall tumours were significant independent factors associated with poor disease-specific survival.

Functional outcomes

Conservation surgery entails removal of structures involved in laryngeal protection. The long-term functional issues are aspiration, tracheostomy and gastrostomy. The published literature suggests that the majority of patients achieve deglutition without aspiration. However, there is a real possibility of aspiration leading to pulmonary infection and death. Even from experienced centres a 3.7% post-operative mortality is reported.[76] Aspiration-free swallowing is generally restored in two-thirds of cases by the end of the first month and in the rest up to 1 year after surgery. However, 3–5% of cases either die of aspiration or undergo completion total laryngectomy or a permanent gastrostomy. With microvascular free-flap reconstruction, the contemporary series show better results. Chung et al[75] in their series of 58 patients reconstructed the pharynx in 72%, majority with free-radial forearm flap. Post-operative pharyngocutaneous fistula developed in 10.3% of which two required PMMC reconstruction for closure. Oral feeding was achieved in 86.2% patients within a mean of 26 days while 13.8% required percutaneous endoscopic gastrostomy tube. Eighty-eight per cent could be decannulated within a mean of 44 days post-operatively. Hence proper patient selection and use of appropriate reconstruction of the laryngopharyngeal defect is important to succeed with the intended functional laryngeal preservation.

TRANSORAL APPROACHES

The transoral approach for surgical resection of the hypopharyngeal cancers can be undertaken either with transoral laser microsurgery or transoral robotic surgery. A new technique, transoral videoendoscopic surgery, has recently been described.

Indications are similar to the open approaches

- tumours less than 4 cm (T1–T2)
- pyriform apex and post-cricoid mucosa free of disease

- good exposure
- mobile vocal cords.

Contraindications:

- oral submucous fibrosis
- full thickness involvement of the pharyngeal muscles
- thyroid cartilage involvement
- base tongue and arytenoid involvement
- cervical oesophagus involvement.

Advantages over open approach:

- avoid disruption of laryngeal skeleton and soft tissues
- avoid tracheostomy
- preservation of innervation
- prevention oro-cervical fistula formation.

Transoral laser microsurgery (TLM)

This transoral approach uses CO_2 laser coupled to the microscope to resect hypopharyngeal tumours. The advantages of laser are precise resection with minimal collateral thermal damage. With minimum alteration of anatomy, there is negligible aspiration and early restoration of oral feeding. Case selection for organ conservation in hypopharyngeal cancers is based on the amount of margin possible with preservation of structures to retain a functional larynx. Besides the larynx, the pharyngeal resection should not expose neck structures requiring additional surgery.

Oncological outcome

The efficacy of TLM in hypopharyngeal cancers should be analyzed in terms of organ preservation and local control. In Steiner's series,[77] transoral CO2 laser surgery was performed on 172 patients, of whom 33 were stage I and II pyriform sinus carcinoma. The 5-year local control was 84% for T1, 70% for T2, 75% for T3 and 57% for T4a tumours. The 5-year recurrence-free survival was 73% in stage I and stage II disease, 59% in stage III disease and 47% in stage IVa disease. Rudert et al[78] in their series of 29 hypopharyngeal cancer patients treated with TLM reported a 5-year overall survival of 71% in stage I and stage II tumours and 47% in stage III and stage IV tumours. In these series, the highest local control rate was achieved in tumours involving the lateral hypopharyngeal wall. In the final analysis, the outcome is significantly dependent on the lymph node involvement as in most head and neck squamous cell cancers. While deciding on the treatment options, functional preservation and oncological safety are important considerations, especially when a lesser morbid treatment option is available. TLM of hypopharynx shows comparable results with open surgical procedures and is superior to radiotherapy alone in terms of organ preservation and local recurrence rate.

Functional outcomes

Post-operative recovery following endoscopic resection of even large hypopharyngeal cancers is surprisingly smooth. If the arytenoid is preserved, most patients are on oral feeds from the first post-operative day. Aspiration depends on preservation of structures and innervation. The healing process is rapid and usually is not a major problem. Hence the procedure is feasible even in the elderly and those with chronic obstructive pulmonary disease (COPD). Mild to moderate discomfort on swallowing may persist for about a week.

Following resection of a large tumour, the resultant raw area necessitates tube feeding for a few days. If the arytenoid is resected, aspiration may be a problem in the post-operative period. In most series[79, 80] functional preservation was seen in 80% of patients. More than one-third of patients do not need nasogastric feeding following TLM, while in the rest the tube feeding remains for around 10–14 days. Post-operative aspiration pneumonia is seen in less than 12% of patients and the need for tracheostomy arises in 5% of patients.

Steiner and Ambrosch report two patients out of 129 cases of pyriform sinus cancer where oral feeding could not be resumed because of persistent aspiration.[77] Pradhan et al[81] have reported persistent aspiration necessitating a feeding gastrostomy in two patients where the arytenoid was resected out of 109 cases of early hypopharyngeal and supraglottic tumours. Both these were cases of recurrent disease in the pyriform sinus 5 years and 13 years following treatment with radiation therapy.

Transoral robotic surgery (TORS)

Another transoral approach which has evolved in the past decade is TORS. It is technologically improved on the standard microscopic and endoscopic techniques in terms of 3D-vision, magnification and ability to operate outside the line of sight. The TORS facilitates two- to four-handed surgery without tremors and improved dexterity. A transoral resection is performed with electrocautery tip similar to open surgery with the added advantage of transoral route with minimal anatomical changes.

TORS is currently done with the da Vinci robotic system® with three arms, one for the camera which has full HD capability with two endoscopes and a 10 x magnification (**Figure 16.6**). TLM is limited with the need for line of sight for firing the laser beam. This is overcome with angled vision and the degrees of freedom for the wristed robotic arms. There is also the advantage of active control of larger blood vessel bleed with use of electrocautery and two-handed approach. The use of TORS for hypopharyngeal cancers has begun recently and long-term results are awaited.

Park et al[82] from Yonsei University, Seoul, Korea published their results of 23 patients managed by TORS with an overall survival of 89% and disease-free survival of 84% at 3 years. On objective evaluation, serious aspiration or delay of swallowing was not observed during the pharyngeal stage of the swallowing process. Overall, 96% of the patients showed favourable swallowing abilities.

There are also reports of combining fibre CO_2 laser with the robotic arm to get that additional advantage of reduced collateral thermal damage as compared to the electrocautery. However, it remains to be seen if the TORS

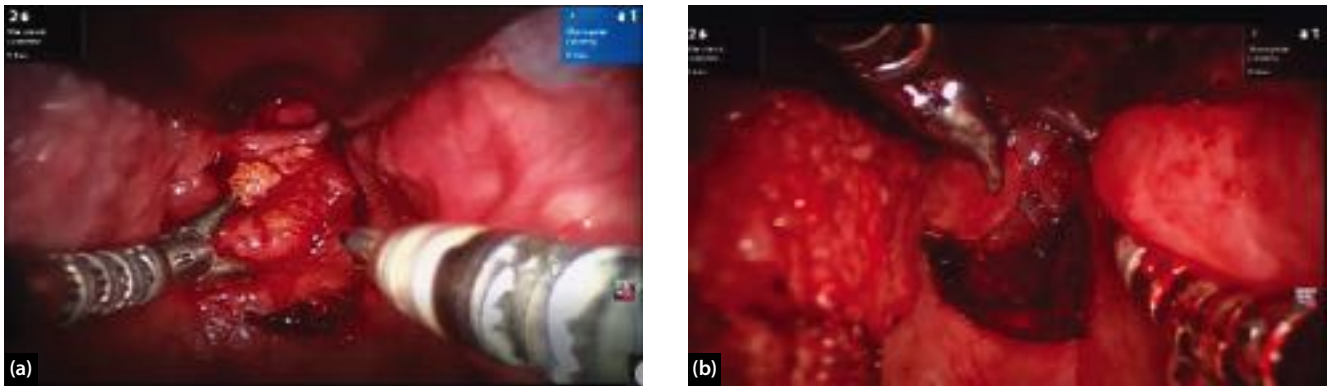


Figure 16.6 Transoral robotic resection of a posterior pharyngeal wall tumour **(a)** the defect is left to heal by secondary intention **(b)** (Image courtesy of Prof. Vinidh Paleri, London).

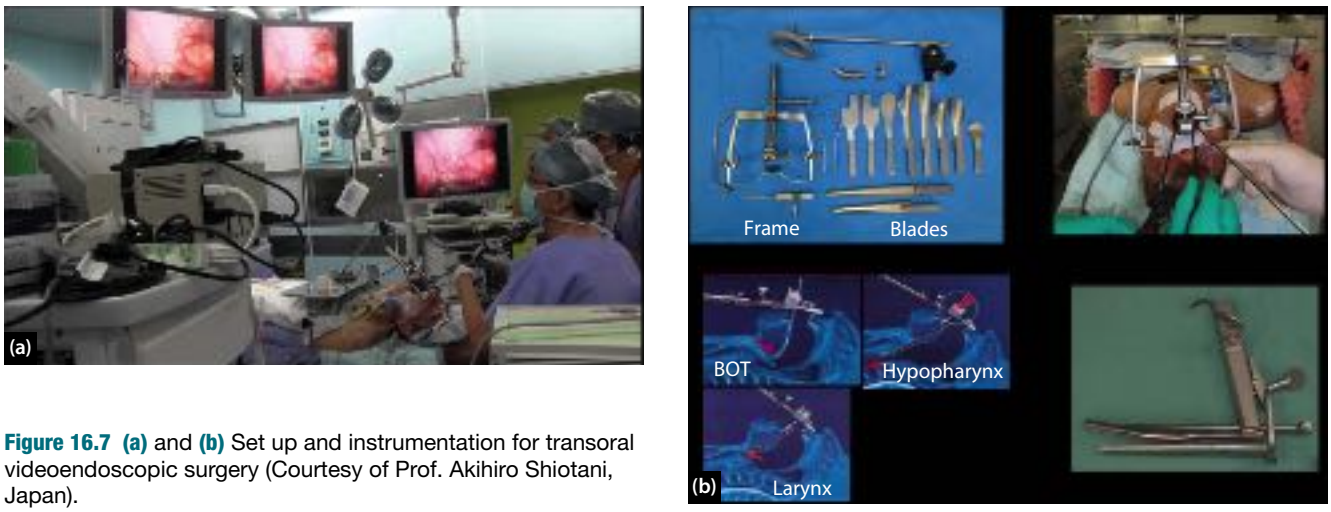


Figure 16.7 **(a)** and **(b)** Set up and instrumentation for transoral videoendoscopic surgery (Courtesy of Prof. Akihiro Shiotani, Japan).

scores over TLM in oncological and functional outcomes besides ease of surgery and the morbidity of the procedure.

Transoral videoendoscopic surgery (TOVS)

TOVS uses flexible video endoscope to visualize the lesion through a suspended larynx similar to microlaryngoscopy (**Figure 16.7**). The difference is the utilization of the video endoscope to visualize the lesion and use of curved instruments with electrocautery for resection. The inspiration for TOVS comes from the endoscopic mucosal resections carried out in the oesophagus by the gastrointestinal surgeons, which, akin to early cancers of the hypopharynx, are predominantly mucosal diseases. The procedure is relatively new and early results are promising. The Japanese series show promising early results with technical feasibility, use of available equipment and outcomes. The long-term oncological outcomes are awaited with early reports from Shiotani et al showing 95% 3-year disease-free survival[83, 84] and good voice and swallowing outcomes.[85, 86]

MANAGEMENT OF THE NECK

All patients should be assessed with CT scan and ultrasonography (USG) as complementary tools to discern metastatic nodes. Patients with pT_1N_0 tumours are either followed up with a wait and watch policy for the neck, with regular US every 2–3 months in the first 2 years, then every 6 months or undergo ipsilateral selective neck dissection of levels II, III and IV. In patients with suspected occult metastatic neck nodes on imaging, unilateral or bilateral neck dissection is performed, depending on the imaging and site of primary. The neck dissection is usually a selective neck dissection of levels II, III and IV and evaluated on frozen section; if disease is found to be positive a modified radical neck dissection is performed. Where facilities for frozen section do not exist, further adjuvant treatment is based on histological report of the neck dissection specimen. In patients with larger tumours (T3–T4) Martin et al[87] recommend a bilateral neck dissection.

In open partial surgery, with the neck exposed for access, the ipsilateral levels II and III that are at the highest risk of occult metastasis are dissected. If they are obviously metastatic or on frozen section they appear involved, then a comprehensive neck dissection of levels II to V is carried out. In case of clinically palpable cervical lymph node metastasis, bilateral comprehensive neck dissection is performed.

ADJUVANT THERAPY FOLLOWING TRANSORAL APPROACHES IN EARLY CANCER

Following resection of T1/T2 hypopharyngeal cancer adjuvant radiation therapy is advised for tumour factors

such as positive margins, where re-resection is not suitable and for metastatic neck node disease. Fields of radiation include the primary tumour as well as both sides of the neck.

It must be highlighted here that TLM of hypopharyngeal cancer should not be performed to merely debulk the tumour. The intent must always be to achieve a complete resection with tumour-free margins.

Radiation therapy in early hypopharyngeal cancers

The goal of radiation therapy as a single modality in early hypopharyngeal tumours is to achieve an oncological cure with minimal toxicity, preserving both organ and function. Conventional external beam radiotherapy (EBRT) is usually delivered over a period of 6–7 weeks, with daily fractionation, 1.8–2 Gray (Gy) per fraction, 5 days a week, over a period of 6–7 weeks. Conformal radiotherapy with 3D planning or intensity-modulated radiation therapy (IMRT) is preferred to minimize radiation to normal structures and reduce xerostomia (**Figure 16.8**).

An analysis of 101 patients with T1–T2 carcinoma of the pyriform sinus treated at the University of Florida[88] with radiotherapy (RT) with or without a planned neck dissection for organ preservation demonstrated 5-year local control rates of 90% for T1 cancers and 80% for T2 lesions. The absolute survival rates for stage I and II were 57% and 61% respectively. Moderate to severe long-term complications developed in 12% of patients. RT alone or combined with a planned neck dissection can result in local control with larynx preservation in a high proportion of patients. The chance of cure is comparable to that observed after conservation surgery, and the risk of major complications is low.

A multi-institutional Japanese study[89] of 115 patients (39 Stage I and 76 Stage II) was carried out where 98 patients were treated with conventional fractionation RT and twice-daily RT in 17 patients. Chemotherapy was combined with RT in 57 patients. With a median follow-up of 47 months the 5-year overall and disease-specific survival rate for 95 patients without synchronous malignancies was 66.0% and 77.4% respectively. The 5-year disease-specific survival rate was 95.8% for T1 and 70.1% for T2 disease. Local control with laryngeal voice preservation was achieved in 87% of T1 lesions and in 73.6% of T2 lesions. Synchronous or metachronous cancers developed in 56.5%. Early hypopharyngeal cancers tend to have a good prognosis with RT. However, second malignancies have an adverse effect on the overall outcomes of patients with early hypopharyngeal cancer.

TREATMENT OF ADVANCED HYPOPHARYNGEAL CANCERS

Advanced hypopharyngeal cancers pose a challenge for the treating oncologists. Many of them present with severe dysphagia, weight loss and malnutrition that needs active intervention by insertion of feeding tubes and dietary supplementation, prior to starting any therapy. It is important to make a proper assessment of the patient's PS and ability to tolerate and withstand major surgery and/or chemoradiation. The choice of initial therapy is based not just on age, PS, medical comorbidity but also on tumour characteristics such as extent of disease, presence of aspiration,

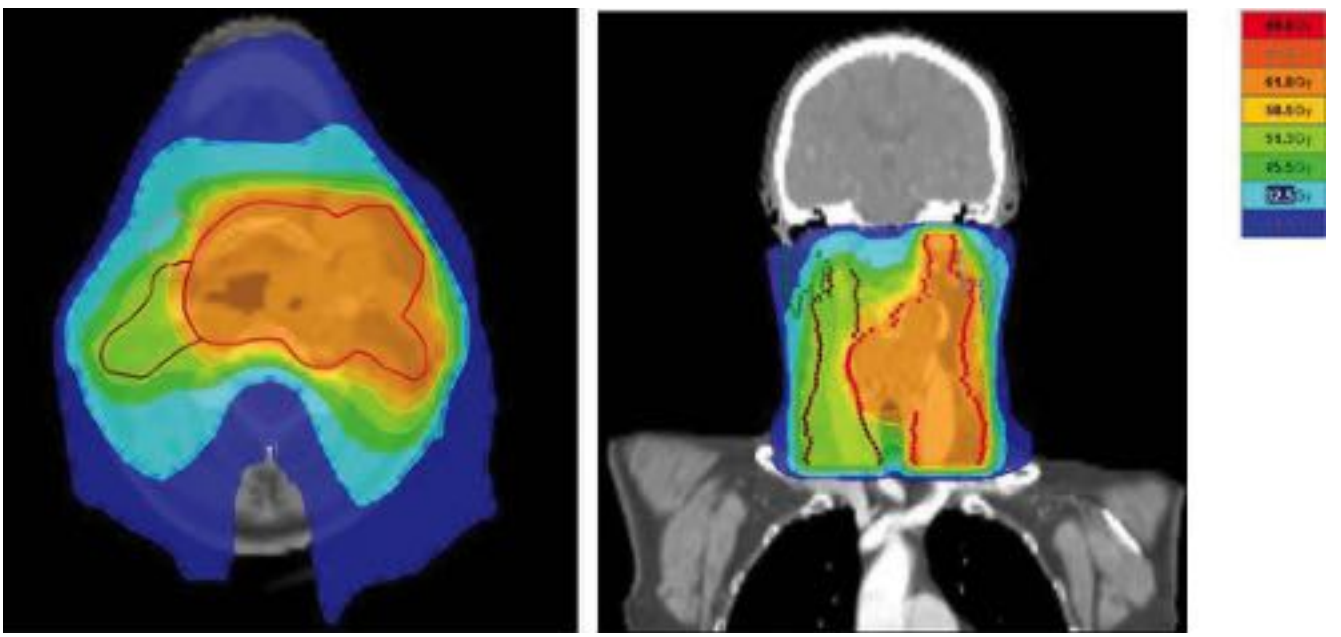


Figure 16.8 Axial and coronal section of an IMRT plan for a patient with T3N2b disease of the left pyriform fossa. The prescription dose (orange) encompasses entire larynx and involved nodal levels. The contralateral at-risk nodal level is treated with a prophylactic dose (green).

function of vocal cords as well as technical expertise and availability of treatment facilities. A multidisciplinary approach should involve surgical, radiation and medical oncology experts as well as speech and language therapists. The patient and caregivers must be counselled about available treatment options. The treatment is based on patient preference and tailored accordingly.

In advanced hypopharyngeal cancers with cord fixity and/or cartilage erosion (T3/T4a), the main issue is treating the disease whilst preserving the laryngeal form and function. In patients with good PS, no comorbidities as well as intact laryngeal framework and function (T1-3N0-2c) the standard of care is concurrent chemotherapy with radiation. In patients with compromised laryngeal framework (T4a) or function, the standard treatment is a total or near-total laryngectomy with a partial or circumferential pharyngectomy along with adjuvant radiation therapy. Lastly, in those patients with intact laryngeal function but exolaryngeal spread through the membranes without cartilage involvement, neoadjuvant chemotherapy with response assessment may be considered for chemoselection for organ preservation.

Surgery for advanced hypopharyngeal cancers

Surgery for hypopharyngeal cancer involves the larynx as well as the hypopharynx. The larynx is usually entirely removed unless the lesion is lateralized. The pharynx is usually resected either partially or circumferentially and most patients will need appropriate reconstruction to restore pharyngeal continuity. Adjuvant radiation / chemoradiation is an essential part of the multimodal therapy for treatment of stage III / IV hypopharyngeal cancers treated surgically.

INDICATIONS

- good general condition
- compromised laryngeal function
- involved laryngeal framework
- salvage surgery following radiation or concurrent chemoradiation.

CONTRAINDICATIONS

- poor general condition
- disease extension
  - Involvement of root neck
  - Prevertebral involvement presents with inability to extend the neck and absence of laryngeal crackle
  - Superior extension into the oropharynx
  - Lateral extension involving carotid artery
- Metastatic disease

Types of surgical procedures

- near-total laryngectomy with partial pharyngectomy
- total laryngectomy with circumferential pharyngectomy
- total laryngo-pharyngo-oesophagectomy (TLPE) with gastric pull-up (GPU).

Near-total laryngectomy with partial pharyngectomy (NTLP)

Voice conservation procedures preserve voice as well as nasal respiration while total laryngectomy sacrifices both functions on the other extreme. The near-total laryngectomy (NTL) falls midway, preserving voice but not nasal respiration.

Indications for NTLP are advanced but lateralized hypopharyngeal cancers where the lesion does not involve the post-cricoid mucosa or the interarytenoid region; the contralateral vocal cord and arytenoid can be preserved and used to form a biological shunt between the trachea and the neopharynx.

This innervated laryngotracheal remnant is fashioned into a tube which, though inadequate to serve as an airway for breathing, is large enough to act as a dynamic shunt by diverting air from the trachea to the pharynx for voice production. The patient therefore has a permanent tracheostome for breathing as in a total laryngectomy which when occluded diverts air through the shunt to produce speech. The innervated dynamic shunt with its sphincteric action protects the airway, preventing aspiration.

The procedure of NTLP offers preservation of excellent lungpowered speech and may be suitable in almost 20% of advanced, operable, pyriform cancers – the most common site amongst hypopharyngeal cancers.

NTL is contraindicated in the following situations:

- Interarytenoid or post-cricoid involvement, which makes preservation of the contralateral arytenoid oncologically unsafe.
- Mucosal involvement of more than one-third the length of the contralateral cord. This does not allow preservation of sufficient laryngeal remnant for shunt formation.
- Prior radiation therapy is a relative contraindication especially if the tissues are oedematous.

Total laryngectomy with partial pharyngeal resection

In hypopharyngeal lesions involving the inter-arytenoid and post-cricoid mucosa, the entire larynx needs to be sacrificed along with the involved pharynx preserving part of the pharynx after adequate resection.

Total laryngectomy with circumferential pharyngeal resection

Indicated in hypopharyngeal lesions involving the post-cricoid mucosa where there is no option of preserving any pharyngeal mucosa. The lesion should however be limited above the level of the cricopharynx ensuring that the cervical stump of oesophagus is normal.

Total laryngo-pharyngo-oesophagectomy (TLPE)

In post-cricoid lesions or hypopharyngeal lesions extending beyond the cricopharynx, an oncological safe margin

requires total laryngopharyngectomy with removal of the entire oesophagus.

RECONSTRUCTION OF PHARYNX FOLLOWING PHARYNGEAL RESECTION

After partial pharyngeal resection, the remnant pharynx is evaluated for mucosal adequacy at the oropharynx, mid-pharynx and the cricopharynx as well as its texture and vitality. If the width is less than 3 cm unstretched or the remnant pharynx is not pliant and oedematous a reconstruction should be considered. The long-term study from Queen Mary Hospital, University of Hong Kong, by Hui et al, showed that a 3 cm unstretched pharyngeal remnant ensures a normal swallow in patients.[90] There are three varieties of defects created:

Partial pharyngeal defects

This requires reconstruction with a pliant tissue similar in thickness of the pharynx. For partial defects, radial artery free flap or anterolateral thigh free flap are suitable. Alternatively, pectoralis major myocutaenous (PMMC) pedicled flap can be used.

Circumferential defects

In our experience, circumferential pharyngeal defects are ideally reconstructed with free jejunal graft. Skin-lined tubed reconstruction, if done, should preferably be a free radial forearm flap. Tubed PMMC is a possible but poor alternative.

Gastric pull-up (GPU)

Following a TLPE, the defect is reconstructed by mobilizing the stomach along with a segment of the duodenum which allows the stomach to be brought into the neck and is sutured to the oropharynx at the fundus. GPU offers a reliable, single-stage vascularized reconstruction with anastomosis in the neck, minimizing the risk of stricture, fistula and post-operative mediastinitis. The GPU is however fraught with higher morbidity in the post-operative period.

MANAGEMENT OF NECK

In stage III and IV either the patient has manifest neck nodes (N1-N3) or has advanced primary (T3/T4) tumour. With manifest neck nodes the surgical plan will usually be bilateral neck dissection levels II–V. In patients with advanced primaries and no neck nodes, the surgical plan will entail bilateral levels II to IV neck dissection.

FUNCTIONAL OUTCOMES

In advanced hypopharyngeal cancers treated surgically, the functional outcomes are related to swallowing and speech. The pharyngeal remnant and the effect of adjuvant radiation will determine the ease of swallow. Generally, patients undergoing primary closure with an adequate pharyngeal width (more than 3 cm unstretched) will experience swallow outcomes close to normal. During neopharynx formation, only mucosal closure vs mucosal and overlying pharyngeal muscle closure has been shown to affect swallowing. Propulsion of the bolus with pharyngeal muscle approximation is more effective while the amount of bolus swallowed is better with only mucosal closure. Thus, during closure the surgeon should ensure that the pharyngeal remnant is adequate and avoid a tight pharyngeal muscle closure. Swallowing is similar in NTLP to TLP with a pharyngeal stenosis rate of 10% caused either by a narrow pharyngeal remnant or radiation-induced stenosis.[91] The pharyngeal reconstruction with a vascularized patch does not alter the function of swallowing and speech in a major way. The only issue remains the amount of functional pharyngeal remnant which can preserve peristalsis. Disordered motility can cause stasis and is more common when the major part of the pharynx is reconstructed.[92] The main concern in gastric pull-up is the gastric emptying. The patient would have to remain upright for fear of regurgitation on lying down after eating. The issue is less with a proper pyloroplasty and most patients have good swallowing albeit with reduced food volume and occasional regurgitation within the first 3 months.

Speech is determined by the pliability of the pharyngo-oesophageal segment. With a remnant pharyngeal mucosa, the speech restoration with tracheo-oesophageal prosthesis is successful in more than 90% of patients. When the laryngeal remnant is preserved as in a NTLP the patients acquires an intelligible, lung-powered speech. Almost every patient will speak following this procedure unless there is a shunt breakdown or stenosis, which is uncommon and is usually technique related, which can be minimized with experience. Results from most published series demonstrate success rates ranging from 74% to 100%.[93–97] Occasionally, a patient may not develop speech or may have to strain while talking. The commonest cause of this is NTL shunt stenosis. This can be overcome by dilatation of the tract using simple gum elastic bougies.

ONCOLOGICAL OUTCOMES

In properly selected cases, the locoregional control rates with near-total laryngectomy are comparable to those with total laryngectomy. In our own series consisting predominantly of T3 / T4 cancers, local recurrence rate is less than 7% with a median survival of 57%.[91] A national analysis of over 1500 patients in the UK showed a 5-year survival of 57% for those treated with pharyngolaryngectomy.[98]

MORBIDITY

The morbidity of surgical treatment in hypopharyngeal cancers is related to the integrity of the neopharynx. Salivary leaks occur more commonly in patients who undergo primary pharyngeal closure for hypopharyngeal cancer surgery compared to those for laryngeal cancers[94]

and may be related to the remnant pharyngeal width. The pharyngeal leak rates are higher in post-irradiated patients, seen in almost 50%. Salvage surgery following concurrent chemoradiation tends to have a higher chance of salivary leak, the incidence rates of which can be reduced by a third using vascularized tissue to reconstruct the defect.[99] In circumferential pharyngo-oesophageal defects, reconstruction with free anterolateral thigh flap seem to have higher success rate (96% vs 93%) compared to free jejunal flap reconstruction, achieving best functional outcome with minimal donor-site morbidity.[94]

The mortality in surgically treated hypopharyngeal cancers is a reality. Nouraei et al have reported the average hospital mortality rate for laryngopharyngectomy around 6% with the gastric pull-up group having the highest incidence at 11%. Those that have had a reconstructive failure tend to have an odds ratio of 6:2 for in-hospital death as well as a worse prognosis.[98]

ADJUVANT THERAPY

Following surgery in advanced stage III and IV hypopharyngeal cancers, adjuvant therapy with either radiation therapy or concurrent chemoradiotherapy is an essential part of the treatment protocols. The factors warranting adjuvant treatment are advanced primary cancer (T3/T4), close- or positive-cut margins, presence of perineural invasion (PNI), lymphovascular embolii (LVE), extension/invasion to adjacent structures like cartilage, muscle, soft tissues, multiple nodal involvement and finally the presence of extra-capsular extension (ECS) in the nodes. There is conclusive evidence for use of concurrent chemotherapy with radiation in cases with positive margins and extra-capsular spread.[100, 101]

Non-surgical organ preservation strategies for advanced hypopharyngeal cancers

Non-surgical organ preservation aims for good locoregional control with function preservation i.e. no aspiration or need for tracheostomy and feeding tubes after completion of treatment. However, careful patient selection is essential to ensure optimal results.

CHEMORADIATION FOR ADVANCED HYPOPHARYNGEAL MALIGNANCIES

The evidence for concomitant chemoradiation in hypopharyngeal cancers comes from the recent update of the MACH-NC with subgroup specific analysis. In the MACH-NC update including 87 trials and 16485 patients, Pignon et al compared locoregional treatment with or without chemotherapy.[102] The hazard ratio of death was 0.88 ($p < 0.0001$) with an absolute benefit for chemotherapy of 4.5% at 5 years and a significant interaction ($p < 0.0001$) between chemotherapy timing (adjuvant, induction or concomitant) and treatment. Concomitant chemotherapy was found to be better than induction chemotherapy. For the 50 concomitant chemoradiation trials, the hazard ratio was 0.81 ($p < 0.0001$) and the absolute benefit was 6.5% at 5 years. The meta-analysis showed benefit for concomitant chemotherapy irrespective of type of radiation (conventional or altered fractionation). The study also concluded that multi-agent chemotherapy did not provide a significant benefit over single-agent cisplatin in the concurrent setting and compared to any other chemotherapeutic agent, platinum-based chemotherapy was significantly efficacious. There was a decreasing effect of chemotherapy with age suggesting that this strategy may be less beneficial in patients over the age of 70 years.[102]

In the MACH-NC comprehensive analysis by tumour site[103] there were 2767 patients with hypopharyngeal cancers. The study suggested that addition of chemotherapy has an absolute 5-year overall survival benefit of 3.9% in the definitive setting with concomitant chemoradiation, both with conventional and altered fractionation.

Non-surgical treatment is used in resectable advanced hypopharyngeal malignancies for organ preservation and when medical comorbidities preclude surgery. Chemoradiation is generally accepted as the gold standard of treatment in advanced laryngeal cancers without frank cartilage erosion. This has been extrapolated to hypopharyngeal cancers despite there being greater risk of both acute and chronic toxicities.[104]

Larynx preservation with concomitant chemoradiation

Chemoradiation scores over surgery with its ability for larynx preservation. However, there have never been any randomized trials comparing chemoradiation vs surgery followed by radiation in hypopharyngeal cancers. The only evidence we have today are single-arm studies, which

TABLE 16.4 MACH-NC UPDATE [Hypopharynx subset] Hazard Ratio of death and 5-year OS

	Timing of chemotherapy			Test of interaction	OS Hazard ratio
	Adjuvant	Neoadjuvant	Concomitant		
HR [95% CI]	1.06 [0.82; 1.38]	0.88 [0.75; 1.02]	0.85 [0.75; 0.96]	$p = 0.31$	*0.88*
5-year abs benefit [CI]	–2.3% [–13.7 9.1]	+5.3% [–0.8; 11.4]	+4% [–1.1; 9.1]		

have shown encouraging results with respect to larynx preservation.

In a study by Huang et al[105] on 33 patients with advanced resectable hypopharyngeal cancers treated with IMRT and concomitant chemotherapy, the laryngeal preservation rate was 67% with a 5-year overall survival (OS) of 44%. A similar study by Liu et al[106] on 27 patients showed laryngeal preservation rates of 63% and 5-year OS rates of 35%. The only randomized controlled trial[107] comparing induction chemotherapy followed by radiotherapy to concomitant chemoradiotherapy for laryngeal preservation in T3M0 pyriform sinus carcinoma, found significantly better laryngeal preservation rate of 92% at 2 years in the concomitant chemoradiation arm as compared to 68% for the induction chemoradiotherapy group.

INDUCTION CHEMOTHERAPY FOR ADVANCED HYPOPHARYNGEAL MALIGNANCIES

When induction chemotherapy is used in conjunction with concurrent chemoradiation in HNSCC, the treatment is referred as sequential chemoradiation. The rationale underlying the use of induction chemotherapy is based on the expectation that drug delivery is better in untreated well-vascularized tumour, and the eradication of micrometastatic disease may be achieved because of high response rate and better tolerance to induction chemotherapy in treatment-naive HNSCC patients.[106]

The approach generally used is to use two to three cycles of induction chemotherapy followed by response assessment. Responders are continued with definitive chemoradiotherapy whereas non-responders are offered surgery. The earliest randomized evidence in favour of induction chemotherapy came from the EORTC 24891 trial[108] conducted in patients with tumours that would require total laryngectomy. This trial randomly allocated patients to induction chemotherapy with cisplatin and 5-florouracil (5-FU) followed by definitive radiation vs primary surgical resection and post-operative radiation. With a median follow-up of 10 years, this trial demonstrated no significant difference in 5- or 10-year OS or progression-free survival.[109] Of note, two-thirds of living patients in the chemoradiotherapy arm were able to retain their larynxes. Thus, PF became the standard induction chemotherapy regime. This is the only randomized controlled study for hypopharyngeal cancer patients and it needs special emphasis that the organ preservation rate in this study was 42% at 3 years with no difference in overall survival.[109]

The only randomized trial comparing induction chemotherapy followed by radiotherapy to concomitant chemoradiotherapy in T3 pyriform cancers showed larynx preservation rates which were lower for the induction arm (68% at 2 years), but there was no difference in the event free survival rates.[107]

The MACH-NC data showed no benefit of multiagent chemotherapy regimes. However, this was a meta-analysis of earlier trials.[102] The later studies evaluated the addition of docetaxel (T) to the backbone of cisplatin and 5FU (PF) to facilitate organ-preservation in locally advanced laryngeal or hypopharyngeal cancers. A randomized French study on 213 patients demonstrated that TPF induction chemotherapy (compared to PF induction) results in superior tumour response rates (80% vs 59%) as assessed by laryngoscopy and CT or MRI.[110] Those with response to induction chemotherapy were treated with organ-preserving (chemo)radiotherapy, while non-responders received laryngectomy and post-operative (chemo)radiation. The higher response rates in the TPF arm allowed for higher rates of laryngeal preservation (70% vs 57% at 3 years), without a detriment in OS (60% at 3 years in both arms). The superiority of TPF was reconfirmed in their long-term follow-up with 10–year larynx preservation at 70.3% vs 46.5% ($p = 0.01$) in the TPF vs PF arm respectively.[111] However, no difference was seen in overall survival, disease-free survival or locoregional control rates between the two arms.

The TAX-324 study utilized similar induction chemotherapy arms (TPF vs PF), followed by concurrent chemoradiotherapy with carboplatin in locoregionally advanced cancers.[112] Five-year survival in the TPF arm was 52% vs 42% receiving PF, while no increased rates of gastric feeding tubes or tracheostomies were noted between groups. A subgroup analysis of larynx and hypopharynx patients demonstrated improved survival in these patients, as well as higher rates of laryngectomy-free survival.

Thus, for advanced hypopharyngeal cancers which have intact laryngeal framework and function, induction chemotherapy (multi-agent TPF) followed by chemoradiation in responders seems to be superior in preservation of larynges and triaging out patients for surgery. Morbidity of the therapy is high and should be kept in mind while selecting a suitable patient for organ preservation.

ALTERED FRACTIONATION FOR ADVANCED HYPOPHARYNGEAL MALIGNANCIES

Another method of organ preservation is by intensification of radiation therapy. Altered fractionation radiotherapy modifies the dosage or fractionation schedules of conventional fractionated radiotherapy. Altered fractionation has been found to improve locoregional control with a potential for organ preservation. A meta-analysis of radiotherapy in carcinomas of the head and neck (MARCH) established the survival benefit of altered fractionation, especially with hyperfractionation having an 8% absolute benefit at 5 years over conventional radiotherapy.[113] A multicentric randomized control trial, comparing accelerated (6 days per week) compared to conventional (5 days per week) showed a 12% 5-year locoregional control advantage.[114] However, there were few hypopharyngeal cancers in most of these studies.

There are a few retrospective series looking at the role of altered fractionation in hypopharyngeal cancers. Niibe et al[115] reported the results of 42 patients with

hypopharyngeal carcinoma who were either inoperable or refused surgery treated with curative intent radiation therapy. Hyperfractionated radiation therapy was used in 23 whilst 19 were treated with conventional fractionation. They found significantly better 3-year local control rates (61.5% vs 18.4%), pharyngolaryngectomy-free-survival rates (64.7% and 5.3%) and a relatively better overall survival rate (69.3% and 31.6%, $p = 0.075$) with hyperfractionated RT with acceptable toxicity. Kawashima et al[116] used a 'chemotherapy enhanced accelerated radiotherapy' regimen to improve control rates in T2–T4 hypopharyngeal cancers; 35 patients received 40 Gy/4 weeks to the entire neck followed by boost RT administering 30 Gy/2 weeks (1.5 Gy twice-daily fractionation). Cisplatin and 5 fluorouracil were administered concomitantly only during the boost RT. They reported encouraging results with overall survival and local control rates at 3 years being 91% and 88% respectively, without significant effects on swallowing.

Salvage surgery after organ preservation

The premise of offering organ preservation is based on the ability to salvage if the treatment does not succeed. This is critical in the counselling of the patient whilst planning treatment.

RESIDUAL LOCAL DISEASE

The hypopharynx is at the highest risk for locoregional and distant failure following standard treatment protocols. Organ preservation strategies for advanced hypopharyngeal cancers are generally applied in Stage III/IVa cancers. However, control rates after primary radiotherapy/chemoradiation are low, with around 30–50% of patients having residual/ local recurrences.[117–119] Most of these patients tend to be unresectable with recurrences involving the prevertebral fascia or carotid artery. When salvageable, the surgery for most cases would be a laryngopharyngectomy with pharyngeal reconstruction.[120–122] In a retrospective study,[119] the successful salvage rate was 17.1% (7/41 patients who recurred locally after radiotherapy). None of the patients who had a primary T4 disease could be successfully salvaged. In a similar study on salvage laryngectomy post-chemoradiation for laryngeal and hypopharyngeal cancers, only 10% of patients with recurrent hypopharyngeal carcinoma underwent salvage surgery.[123]

Salvage laryngopharyngectomies have an increased rate of complications especially pharyngocutaneous fistulae which may occur in up to 50%.[117] Concomitant chemoradiotherapy with radiation doses more than 64 Gy increase this risk considerably. Pharyngocutaneous fistulae in turn increase the incidence of carotid artery blowouts. With a low salvage potential and high rate of complications it is imperative to carefully choose patients for organ preservation, and the surgical team should have a low threshold for using vascularized tissue from non-radiated areas to reconstruct or buttress the pharyngeal repair.

RESIDUAL NECK DISEASE

Limited neck disease (N1) tends to respond well to chemoradiotherapy. Large volume nodal disease (N2 or N3), however, has a poor response despite chemoradiation. In case of palpable or radiologically obvious remnant neck node, salvage neck dissection is done. Generally, a modified neck dissection levels II–V is performed. In case neck nodes are not palpable but picked up on PET-CT scan at 12 weeks in the surveillance scan, a neck dissection is performed on those findings.[124] Larger neck nodes have a reduced salvage potential and increased morbidity and the same caution should be exercised before deciding on organ preservation.

MANAGEMENT OF RECURRENT AND METASTATIC DISEASE

Patients with recurrent disease should be triaged into locoregional and distant metastasis. The management of recurrences depend on recurrent staging, interval between completion of treatment and recurrence (disease-free interval), patient's PS, presence of comorbidities, patient's willingness for further treatment, 'salvageability' potential and durability of control.

Prior treatment has an immense bearing on the salvage treatment. Potential for durable response to treatment improves if surgical salvage is followed by adjuvant radiation/chemoradiation received. In a previously irradiated patient the fields of radiation and the potential for re-irradiation should be discussed prior to salvage surgery.

Many patients with hypopharyngeal cancer develop distant metastases at some point in their clinical course. When this occurs, long-term survival is rare and the treatment intent is palliative in nature. The median overall survival for patients with metastatic head and neck cancer is 6–10 months. Palliative treatment should be planned to improve the remaining quality of life and includes symptom control with appropriate pharmacological interventions, radiation therapy, chemotherapy and best supportive care.

Pain alleviation with narcotic pain medication is invaluable. Palliative radiation therapy is suitable in patients with local pain or bleeding. Palliative chemotherapy can be considered in patients with good PS and disseminated disease. Single-agent cisplatin has been shown to improve overall survival in head and neck cancer patients.[125] Historically, combinations of cytotoxic chemotherapies do not improve survival in comparison to cisplatin alone and are not used routinely. Recent randomized evidence supports the use of a triple drug regimen (cisplatin or carboplatin, 5 fluorouracil and the anti-epidermal growth factor receptor monoclonal antibody cetuximab) in recurrent or metastatic head and neck cancer,[126] with addition of cetuximab to platinum and 5FU significantly improving OS from 7.4 to 10.1 months. However, patients with poor PS should be offered best supportive care and pain medications.

FOLLOW-UP OF PATIENTS

Patients treated for hypopharyngeal cancers should be followed up to check their functional status as well as look out for recurrence. Functional status includes swallowing and speech apart from morbidity related to surgery and radiation therapy.

Follow-up schedule

The standard follow-up schedule is bimonthly for the first 2 years, quarterly in the third year and biannually in the fourth year. From the fifth year, annual check-ups are done with a high index of suspicion for second primary cancers.

Speech

Patients treated with radiation/chemoradiation should undergo periodic speech assessment and therapy to counter the effects of radiation on the vocal cords. Over time the muscle tends to atrophy and the patients are counselled to do regular speech therapy. The speech therapy should be initiated during the treatment itself to inculcate proper vocal 'hygiene' habits in the patients. This includes vocal exercises, vocal naps, hydration and taking care of gastro-oesophageal reflux.

In those rehabilitated with a tracheo-oesophageal prosthesis, careful evaluation for any signs of leakage either through or around the puncture site is carried out. Care of the prosthesis with antifungal application as well as regular cleansing is to be reiterated. This will be further elaborated in the chapter on speech rehabilitation Chapter 34, Speech voice and swallow rehabilitation after chemoradiation.

Swallowing

During radiation/chemoradiation active swallowing and speech therapy is advocated. This must be evaluated at every follow-up appointment. Proactive intervention during the treatment process and continuation thereafter may prevent the fibrosis that sets in which impedes restoration of a normal swallow. Use of saliva substitutes improves swallowing.

A consult with the speech and language pathologist prior to treatment initiation is important. The patients should be counselled to persist with the oral swallowing to reduce the amount of radiation induced fibrosis. On treatment completion the patients are evaluated for signs of aspiration and pharyngeal stenosis which needs dilatation and active therapy.

Dental check-up

Dental check-up for carious teeth and damaged crowns should be done diligently prior to radiation. During follow-up, fluoride gel application is advised regularly to strengthen the enamel and prevent dental carries. Hydration and its importance in preventing halitosis, periodontitis should be impressed on the patients.

Thyroid status

The thyroid gland is either removed partially or completely during surgery and/or radiated following surgery. In either case the patient may turn hypothyroid following treatment for hypopharyngeal cancer. The thyroid function tests should be done when symptomatic or routinely at 6 months following completion of radiation. Thyroxine replacement is started if hypothyroidism sets in and replacement is based on body weight at 1–2 mcg per kg.

Disease surveillance

The patients should be monitored for second primary cancers in the upper aerodigestive tract which are seen in up to 50% of patients. The risk of new cancer development increases by 1% annually. The patients who continue to abuse tobacco and alcohol have a 15–20% increased recurrence risk and should be counselled to desist.

PET-CT scan should be done between 10 and 12 weeks for optimum benefit following radiation in those treated with organ preservation. The negative predictive value of PET-CT is above 95% and is an important indicator of disease control.

SUMMARY

Hypopharyngeal cancer is a high-risk cancer. There are fewer barriers to spread of disease and a good lymphatic network yields a high incidence of occult nodal metastasis. The chance of synchronous tumours is 15% and distant disease at presentation is known. The long-term overall survival in stage III & IV cancers is low. Treatment of hypopharyngeal cancers is fairly morbid affecting speech and swallowing and is requires multidisciplinary planning. Careful evaluation of laryngeal and pharyngeal function in treatment planning is of paramount importance. Organ preservation in advanced hypopharyngeal cancers requires careful case selection. Surgery with adjuvant therapy still remains the gold standard in the management of advanced hypopharyngeal cancers.

KEY POINTS

- Accurate staging is essential. Workup should include evaluation for synchronous primaries and distant metastasis.
- Laryngeal function should be accurately evaluated prior to treatment especially while considering organ preservation.
- Radiation therapy is recommended for Stage I and II disease.
- Multimodality treatment is recommended for Stage III and IV disease.
- The overall 5-year, tumour-specific survival is less than 30%, although the survival of treated patients rises to 50%.

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CHAPTER 17

NECK METASTASES FROM AN UNKNOWN PRIMARY

Ricard Simo, Jean-Pierre Jeannon and Maria Teresa Guerrero Urbano

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search as well as the websites Cancerlit and Cancer Net using the keywords: neck mass, carcinoma of occult primary (COP), carcinoma of unknown primary (CUP), head and neck neoplasm, imaging, and focusing on diagnosis, surgery and management. The evidence in this chapter is mainly levels 3–4 with some level 2 evidence. The clinical recommendations are predominantly B and C.

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) that presents as carcinoma of unknown primary (CUP) represents a difficult challenge for the practising clinician. With improvements in diagnostic techniques such as cross-sectional imaging, molecular diagnostics, robotics and positron emission tomography (PET) scanning, clinicians are now able to identify a higher proportion of primary sites in patients presenting with CUP than before. The most common presentation of CUP in the head and neck is in the context of human papillomavirus (HPV)-associated oropharynx (HPV+OPSCC) carcinoma. As the year-on-year numbers of HPV+OPSCC are increasing in the developed world, it is likely therefore that the incidence of CUP is also increasing.[1–3]

DEFINITION AND HISTORICAL BACKGROUND

The term carcinoma of unknown primary (CUP) represents a heterogeneous disease entity characterized by the presence of clinically overt metastatic disease in the absence of a clinically or radiologically obvious primary tumour. In the head and neck, the definition of a true unknown or occult primary carcinoma is the presentation of metastatic neck lymphadenopathy without the development or manifestation of an index primary tumour within a subsequent 5-year period.

CUP is diagnosed in a patient who presents with biopsy-proven squamous cell carcinoma (SCC) in one or more cervical lymph nodes and in the absence of an obvious primary tumour despite rigorous clinical examination, appropriate cross-sectional imaging and examination under anaesthesia including an ipsilateral tonsillectomy and biopsy of tongue base mucosa (or formal mucosectomy) +/– biopsy of the mucosa of the post nasal space and/or ipsilateral piriform fossa.

It is important to distinguish between true CUP cases in which a primary site tumour never becomes evident and the case where, on initial presentation, a primary tumour is present but remains undetected.

In the latter case, it is presumed that there has been early metastasis from a small primary tumour following which the growth of the cervical metastasis has proceeded at a considerably faster rate than that of the primary tumour. It is inevitable that, left untreated, the primary tumour would eventually become clinically evident. However, as will be seen later, the sites at highest risk of harbouring a

primary tumour are often treated in any case such that the primary tumour never becomes clinically evident.

It follows therefore, that quantification of the true rate of CUPs is not possible with any accuracy.

One of the first explanations of CUP was suggested by Volkmann in 1882 and widely accepted until the 1940s. He believed that the neck mass resulted from the degeneration of a 'branchiogenic cyst' into carcinoma. In 1940, Martin and Morfit revisited this hypothesis in a study of 55 CUP patients; as only eight met Volkmann's criteria, this theory was dismissed.[4–9] Since then several theories have been proposed in an attempt to explain this clinical phenomenon.

Two hypotheses currently predominate, although neither are proved. In the first hypothesis proposed, as explained above, the microscopic primary tumour lies undetected in the mucosal folds of Waldeyer's ring and is too small to be detected by conventional diagnostic methods and is ultimately successfully treated either by design or coincidental (by inclusion in radiation fields designed primarily to treat the neck).

The second hypothesis, which attempts to explain the existence of 'true' CUPs, supposes that the primary tumour is removed by the patient`s innate or adaptive immune system, but not before early metastasis to the cervical lymph nodes has occurred with subsequent evasion of the host immune response.[10–13]

INCIDENCE

The incidence of CUP in HNSCC has reduced significantly over the last two decades (**Table 17.1**). In the 1970s and early 1980s, prior to the universal availability of cross-sectional imaging, the incidence ranged between 10% and 30%. Many of these historical cases may have been incorrectly diagnosed as CUP as they represented distant metastases from lung and abdominal primaries.[14]

The incidence reported in the literature subsequently plateaued over the last decade to around 5% of HNSCC due to standardized diagnostic protocols.[15–28] Our own single-centre experience at Guy's & St Thomas' NHS Trust has also seen a reduction in the incidence of CUP over the last 10 years from 8% to 4% of new HNSCC cases.[29] It is increasingly recognized that high-risk HPV related HNSCC tends to present with regional disease and clinically unrecognized primary focus, and most patients with CUP presentation will have a primary site in the oropharynx.

NOMENCLATURE

The staging of head and neck cancer is dealt with in detail in Chapter 4, Staging of head and neck cancer However, recent changes to the TNM staging system published in the American Joint Committee on Cancer (AJCC) 8th edition Cancer Staging Manual and the Union for International Cancer Control (UICC) included changes which involve the staging of CUP.

A T0 category is no longer assigned to p16 – OPSCC and other non-HR HPV cancers e.g. larynx, oral cavity and hypopharynx. This is because, in these tumours an exact primary site is, by definition, unable to be established. In contrast, cytology specimens following fine-needle aspiration cytology (FNAC) of an enlarged lymph node in which the presence of metastatic carcinoma is confirmed can be subjected to testing for HPV and Epstein–Barr virus (EBV) status.

It is considered that demonstration of HPV or EBV status safely allows the primary site to be determined as oropharynx or nasopharynx respectively and therefore, classification systems for p16 + OPSCC and nasopharynx maintain T0 categories (as does salivary gland as primary site can be determined on cytological findings). The molecular biological and pathological aspects are discussed in Chapters 6, Introducing microbiology of head and neck cancer and 26, Pathology of head and neck malignancies respectively. The management of HR HPV oropharyngeal cancer can be found in Chapter 13, Oropharyngeal tumours.

EVALUATION AND DIAGNOSIS

Clinical assessment

Patients presenting with metastatic lymphadenopathy with an occult primary should undergo a structured diagnostic workup, as recommended by evidence-based guidelines. A thorough history is essential. A history of excessive alcohol consumption and heavy smoking may suggest a primary tumour outside the nasopharynx, while a history of multiple sexual partners and orogenital contact may suggest a primary tumour within the oropharynx.[14] Clinical examination should include fibre-optic nasolaryngoscopy with special attention to sites where a small primary focus can be missed, such as the nasopharynx, tongue base, the infrahyoid epiglottis and the pyriform sinus. The site of the node is an indicator of the primary site. For instance, level I nodes are almost never seen with nasopharyngeal primaries

TABLE 17.1 Treatment recommendations by ENT-UK Multidisciplinary Treatment Guidelines (2016)

Stage	Surgery	Radiotherapy	Chemotherapy
T0N1M0 (No ECS)	SND or MRND	No unless for mucosal sites	No
T0N1M0 (ECS)	SND or MRND	Yes to neck	Should be considered
T0N2M0	SND or MRND	Yes – ipsilateral but contralateral should be considered	Should be considered
T0N3M0	MRND or RND	Yes – ipsilateral but contralateral should be considered	Should be considered

and level V nodes never with laryngeal cancer. Based on epidemiological data and lymph node distribution, nomograms have been created to predict the primary site.[30]

Novel endoscopic techniques, used in the clinic setting, have shown use in this scenario. Narrow band imaging (NBI) is based on the modification of the standard white light endoscope in which white light is transmitted through optical filters absorbing all but two wavelengths; one band centred at 415 nm and another at 540 nm. The former wavelength penetrates the superficial mucosa and highlights submucosal capillaries as a brown colour while the latter penetrates through the submucosal layer and identifies prominent vessels as cyan in colour. As SCCs arising from the upper aerodigestive tract mucosa are accompanied by neoangiogenesis, NBI identifies neoplastic tissue at an earlier stage than conventional endoscopy. A meta-analysis[31] of four studies where NBI was performed on 115 patients with CUP demonstrated a high level of diagnostic accuracy(sensitivity (74.1%; 95% confidence interval [CI] 52.5%–100%) and specificity (94.1%; 95% CI 5 23.7% –100%)).

This should be followed by cross–sectional imaging such as multi-planar computed tomography (CT) or and magnetic resonance imaging (MRI) and FDG PET-CT before the patient is subject to an assessment under general anaesthesia.[32] If the primary is not identified following the above sequence of investigations, then the patient should undergo pandendoscopy under general anaesthesia which should include biopsies based on the results of the core biopsy and imaging. Sites to be sampled include the nasopharynx, tongue base and ipsilateral tonsillectomy.[33] Using this protocol, most CUP cases turn out to be either tonsil or tongue base primary cancers.[14, 29]

RIGID ENDOSCOPY GUIDED BIOPSY OF THE NASOPHARYNX

Blind biopsies of the nasopharynx have proven to be unsatisfactory as they often provide a poor yield of primary site diagnosis.[30] It is therefore recommended that biopsies on this site should be guided using rigid telescopes,[14] especially where abnormalities have been noted on imaging. In instances where high-resolution imaging does not identify pathology, even telescope-guided biopsies are unlikely to pick up a malignant focus.

BILATERAL TONSILLECTOMY

There is evidence from selected series that bilateral tonsillectomy should be employed as the primary resides in the contralateral tonsil in up to 10% of cases.[34–36] In the high-risk HPV era, there is greater recognition that these tumours can be multifocal at presentation,[37] providing further basis for a bilateral tonsillectomy (**Figure 17.1**). It has been suggested that bilateral tonsillectomy could reduce the need for bilateral irradiation to the neck, thus leading to reduced morbidity. In patients who have undergone previous tonsillectomy but they have tonsillar remnants, the search for the primary should also include the excision of the remnants as primary tumours can be found within them.[38, 39]

TONGUE BASE BIOPSIES

Blind biopsies of the base of tongue (BOT) are often unsatisfactory as occult carcinomas rarely arise from the mucosal surface. It is therefore advisable to target the deep tissue of the BOT. The superior manoeuvrability and access provided by transoral robotic techniques have led to the design of the procedure called tongue base mucosectomy (TBM, **Figures 17.2** and **17.3**). This procedure samples the entire tongue base mucosa and has been shown to identify a primary site in over 50% of patients who are PET negative and have no primary site in the tonsil. Interestingly, around 10% can be contralateral foci. However, the morbidity of this procedure cannot be underestimated, with the risk of bleeding, need for tube feeding and the very small risk of pharyngeal stenosis.[40, 41]

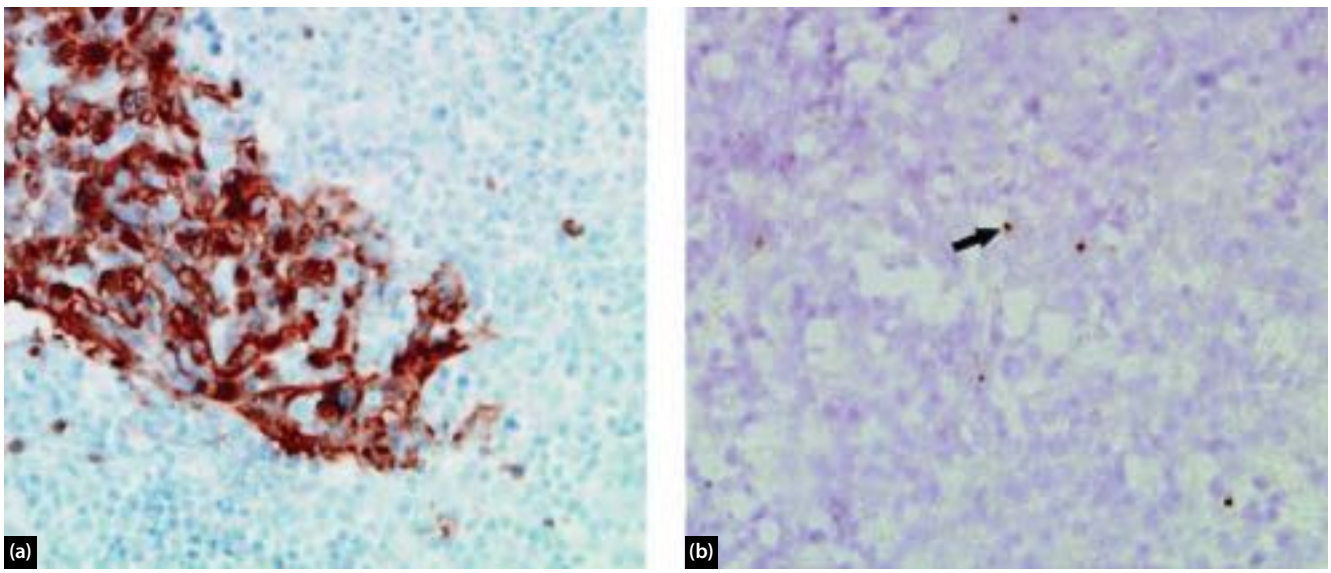


Figure 17.1 Photomicrograph showing immunohistochemistry positivity to p16 in a lymph node of a patient with metastatic HNSCC of unknown primary suggesting a tonsil origin. (a) P16 positivity in the tonsil **(b)** identified malignant cells in the tonsil.

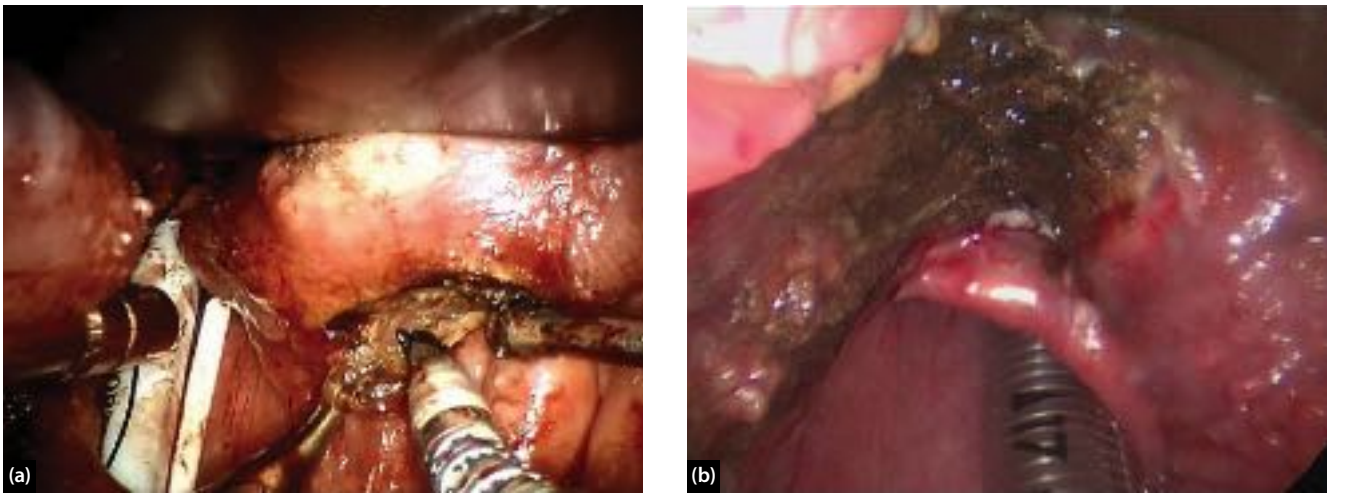


Figure 17.2 **(a)** A robotic tongue base mucosectomy in progress and **(b)** completed procedure.

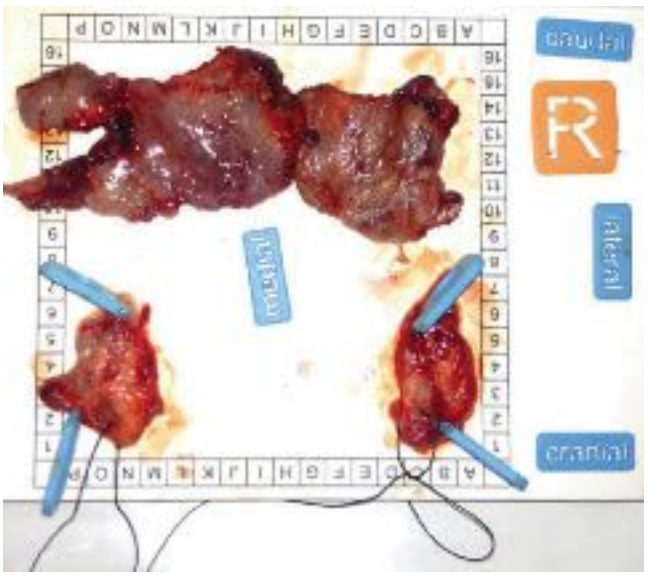


Figure 17.3 A bilateral tonsillectomy and robotic tongue base mucosectomy specimen orientated and mounted for pathological examination.

POSITRON EMISSION TOMOGRAPHY (PET) SCANNING

Fluorodeoxyglucose[18] (G) positron emission tomography (FDG-PET) scanning is now a key modality in the evaluation of the unknown primary. It is combined with a CT scan to provide anatomical localization of the avid lesion (fusion or co-localized PET scanning).

A recent meta-analysis of FDG-PET-CT from the Netherlands has reported data from 11 studies including 433 patients with CUP. Overall primary detection rate was 37%, with equal sensitivity and specificity of 84%. A negative PET-CT result does not preclude the requirement for panendoscopy and multiple site biopsies.[42, 43] Other studies have identified the sensitivity and specificity of PET scanning in identifying the primary in HNSCC to be as high as 87% and 92% respectively.[32–39]

It should be noted that this investigation is only useful if it is performed before the panendoscopy and biopsies, as the post-biopsy inflammatory response may increase the uptake of the FDG tracer, causing a false positive result (**Figure 17.4**).

NICE RECOMMENDATIONS

The pathways for assessment of neck lumps vary across different healthcare settings. Based on low- to high-quality evidence from retrospective studies, an original systematic review, meta-analysis of diagnostic parameters and the experience and opinion of an expert panel, the National Institute for Health and Care Excellence (NICE) made the following recommendations for people with a neck lump that is thought to arise from a head and neck cancer[44] (NICE terminology uses 'offer' to reflect a strong recommendation and 'consider' for a recommendation where the evidence of benefit is less certain):

1. Consider adding ultrasound guidance to fine-needle aspiration cytology or core biopsy.
2. Consider having a cytopathologist or a biomedical scientist to assess the adequacy of the cytology sample.
3. Consider a FDG PET-CT scan as the first investigation to detect the primary site.
4. Consider using NBI (in clinic or during general anaesthetic assessment) in cases where PET-CT has filed to identify a primary site.
5. Offer surgical diagnostic assessment if the FDG PET-CT does not identify a primary site, including guided biopsies, tonsillectomy and TBM.

These have been summarized in an algorithmic fashion in **Figure 17.5**.

CLINICAL MANAGEMENT

Management of CUP continues to generate controversy in multidisciplinary tumour board and scientific meetings.

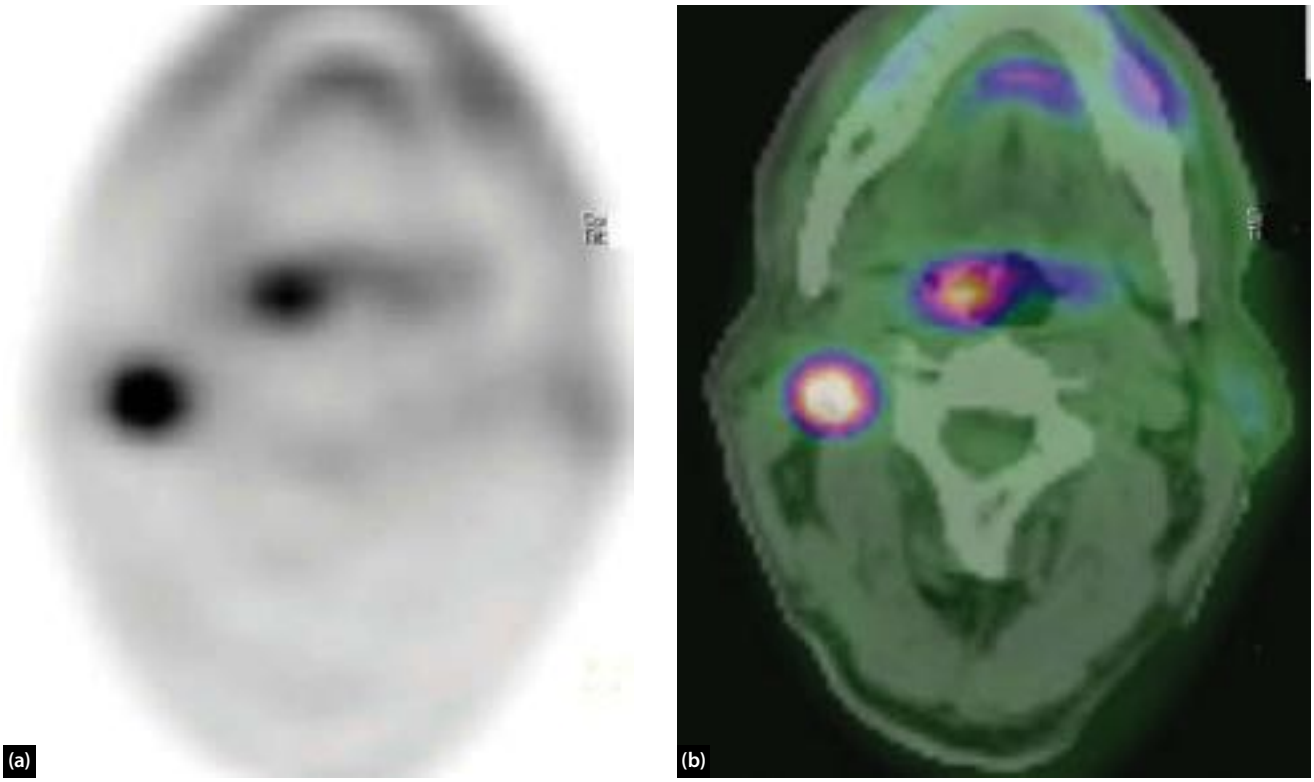


Figure 17.4 FDG-PET-CT scan demonstrating uptake tracer in the right oropharynx in a patient presenting with metastatic SCC of the right neck performed before panendoscopy and biopsy.

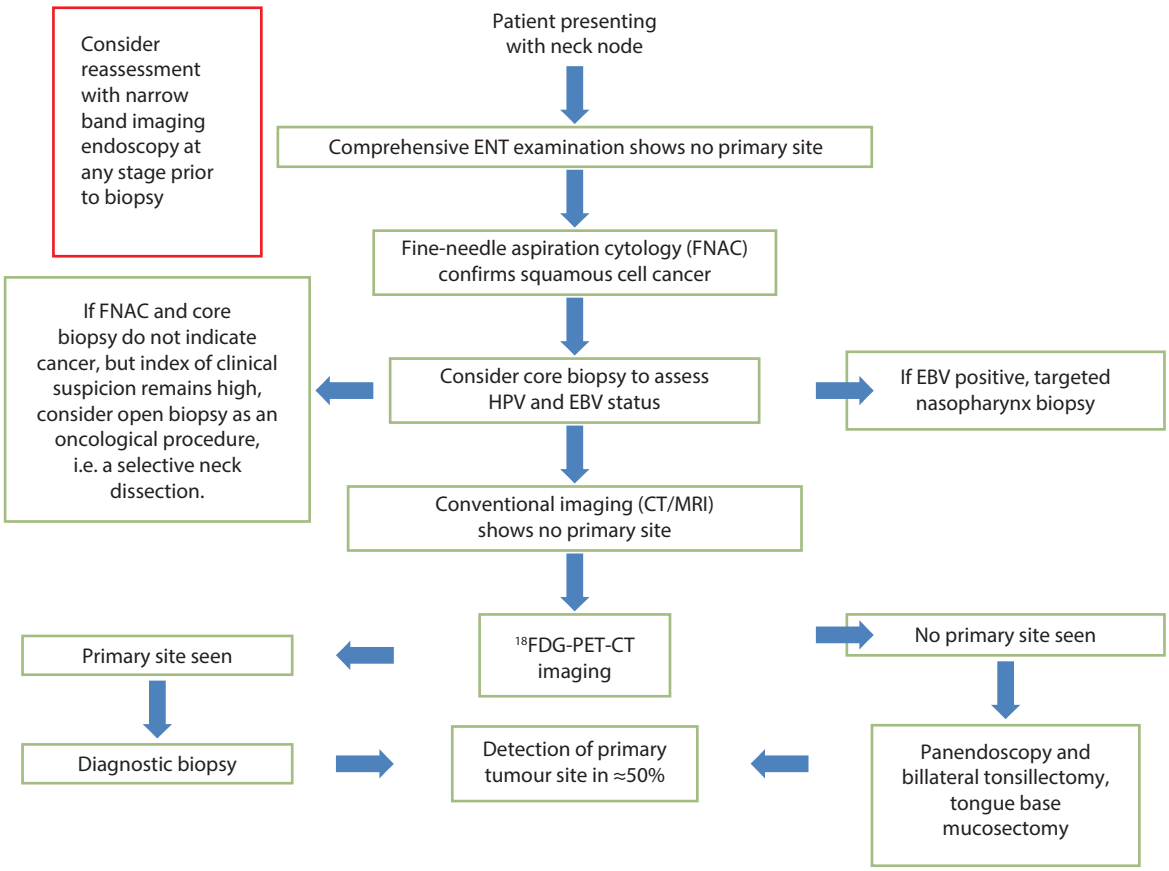


Figure 17.5 Suggested algorithm for the management of the unknown primary.

CUP management can be organized into the treatment of early disease (N1 with no extracapsular spread) and advanced disease (extracapsular spread, N2 and N3).[42, 43] In early disease, single-modality therapy can be considered in the form of neck dissection alone or radiotherapy alone. Radiation therapy alone has been reported for small N1 stage disease with some success and can be considered in patients with comorbidities that can pose a high surgical risk.[40] Similarly, some authors have adopted neck dissection surgery alone without radiotherapy for N1 neck disease with a 'watch & wait' approach to the primary.[41] Advanced cases require combined modality therapy.[45–47] In the absence of high-level evidence, management is largely based on institutional protocols.

Surgical management of the neck

Traditionally, either radical neck dissection or modified radical neck dissections have been employed in the management of CUP. Selective neck dissection has been suggested as a valid option for patients with N2a and N2b disease as the risk of metastases in levels I and V has proven to be rare in patients with CUP unless they present with N3 neck disease.[29, 44]

Traditionally, most units favour neck dissection upfront followed by either RT or chemoradiotherapy (CRT) as indicated. This allows adequate pathological staging of the neck and therefore tailoring treatment accordingly. There is also an advantage of performing surgery in a non-irradiated neck and therefore minimizing morbidity. This approach could potentially cause a treatment delay if any unexpected complications from the surgery occur. Primary RT or CRT will reduce the need for but may render surgery difficult and with an increased risk of complications.

However, recent randomized trials[48] have reported that PET-CT-guided active surveillance after radical CRT showed similar survival outcomes to upfront neck dissection followed by CRT and lead to considerably fewer NDs, fewer complications and lower costs. Although this is in the setting of the known primary, the data is robust enough to warrant a re-examination of current approach for primary surgery in CUP, especially when a firm diagnosis of the neck lump can be established by non-surgical means.[45, 46]

Management of the violated neck

In the past many patients underwent excisional and incisional biopsies as first-line diagnosis. Earlier reports identified poor prognosis in these patients, which has been attributed to inadequate definitive treatment and advanced stage at presentation. With current, centralized, multidisciplilnary team (MDT) driven practices, smaller numbers of patients with lateral neck masses undergo open surgical interventions for diagnosis, primarily due to non-diagnostic FNAC or owing to suspicion of non-SCC pathology such as lymphoma. In the era of adequate surgical management of the neck and good (chemo)radiation practices, open cervical biopsy does not signify a poorer prognosis provided adequate and timely treatment is given.[49] A high proportion of HPV positive oropharyngeal tumours may also explain the favourable outcomes observed.[50] The treatment of the violated neck can be upfront surgery or CRT followed by PET-CT surveillance and surgery as needed.

Branchial cyst carcinoma

The evidence for the existence of branchial cyst or branchiogenic carcinoma is tenuous. Many reported series have failed to meet the criteria set by Hayes Martin and in many cases elective tonsillectomies were not performed. Many patients with CUP may present with lateral neck cystic masses mimicking branchial cysts. There is enough evidence to recommend that all patients over the age of 35 years with lateral cystic masses must be presumed to have cancer until proven otherwise. The authors recommend that these people should be entered into a CUP investigation protocol even if the FNAC is not suggestive of metastatic SCC.[51]

Radiation therapy to the neck and the putative primary site

The external beam radiotherapy (EBRT) fields recommended remains controversial, with some centres offering unilateral radiation to the neck and ipsilateral likely primary sites, whilst others propose bilateral neck treatment, so-called 'total mucosal irradiation'.

Results for bilateral neck irradiation tend to show improved local control rates and disease-free survival compared to unilateral neck treatment. The improvement on overall survival however is not always seen.[43, 45–50]

Unfortunately, the superior survival results seen with bilateral EBRT are at the expense of increased morbidity in terms of pain, xerostomia and long-term dysphagia with increased feeding tube dependence.[46]

Intensity-modulated radiotherapy treatment (IMRT) with bilateral neck radiation has the potential for reduced acute and late toxicity as the parotid glands may be spared, with robust data to suggest that IMRT significantly reduces morbidity.[52, 48] IMRT is currently the standard of care for head and neck cancers in several countries. For CUP patients receiving total mucosal radiation, IMRT appears to provide improved radiation coverage of the mucosa including the nasopharynx with significant reduction of dose to the parotid gland contralateral to the involved neck and therefore reducing the risk of severe xerostomia.[53]

RECOMMENDED TREATMENTS[47, 54]

bcT0N1M0

cT0N1M0 WITHOUT ENE FOUND ON HISTOPATHOLOGICAL OR RADIOLOGICAL STUDIES

Patients can be treated with single-modality treatment either with selective neck dissection or involved field

radiotherapy alone. If treated surgically, the upper aerodigestive tract mucosa should be carefully inspected during surveillance visits.

PT1N0M0 WITH ENE

Patients should be treated with post-operative RT if ENE is identified.

T0N2M0 AND T0N3M0

Patients should be treated with primary CRT followed by PET-CT guided surveillance or combined modality treatment including neck dissection followed by RT or CRT.

TREATMENT OUTCOMES

Most series show improved overall and disease-free survival with combined modality treatment. Survival results are dependent upon the N stage at presentation with worsening outcome observed with increased stage. The outcome and survival of patients with CUP has been variable as the published series are mainly retrospective and represent diverse patient populations. We would however expect a 5-year survival of between 70% and 100% for N1 stage cancers and 30% and 60% for stage N3.

The overall 5-year survival for all stages of HNSCC with unknown primary site would be in the range of 52% and 75%.[39–49] A 10-year single-centre uncontrolled retrospective case series of 25 patients with complete records, from the authors' institution, showed an excellent overall survival for N1 disease of 100% and a 60% survival for patients with N2 and N3 neck disease.[29] (**Figure 17.6**)

In a recent series of patients with CUP treated with IMRT by the Memorial Sloan Kettering Cancer Center showed 2-year regional progression-free survival, distant metastases-free survival and overall survival of 90%, 90% and 85% respectively.[55]

PATTERNS OF FAILURE

The pattern of failure largely depends on the initial treatment protocol. If EBRT is used, disease recurrence is usually in the neck and in form of distant metastasis. Recurrent disease is often difficult to diagnose and it often shows extracapsular spread and presents in advanced stages. FDG-PET-CT scan is probably the best method of detection and diagnosis of recurrences. Distant metastases often occur within a year of treatment completion and are most common in the lung.[51, 52] The incidence of recurrence in the potential primary sites is extremely variable and may occur from 0% to 66%. It occurs mainly in those patients treated initially with surgery alone. The emergence of a primary tumour often occurs within the first 24 months and usually presents in the oral cavity, oropharynx and nasopharynx.[53]

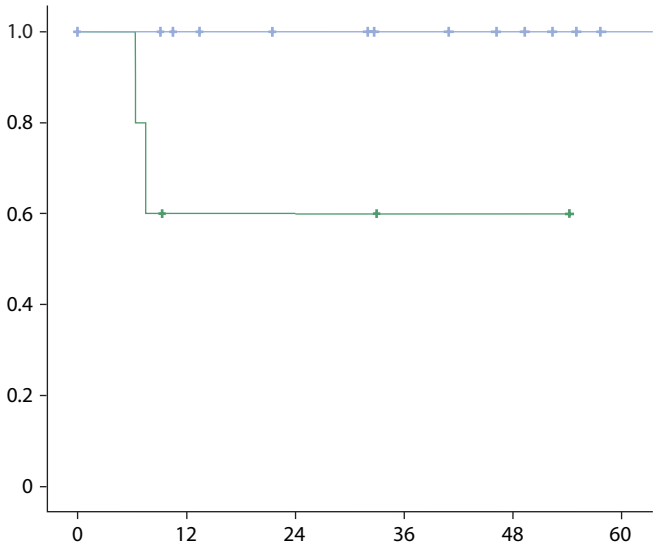


Figure 17.6 Kaplan – Meier Survival Curve for Guy's & St Thomas' series of patients with occult primary carcinoma of the head & neck *n* = 25 (2000 to 2011).

CONCLUSION

The unknown primary in HNSCC is becoming an increasingly rare entity due to better diagnostic protocols and now accounts for fewer than 5% of cases. However, the raw numbers may be on the increase owing to the higher number of HPV-positive cancers. The diagnostic workup should include panendoscopy, bilateral tonsillectomy, biopsies of nasopharynx, tongue base and any other potential suspicious lesions in the upper aerodigestive tract. Investigations should employ cross-sectional imaging CT and or MRI as well as PET-CT imaging; the latter must be performed before the biopsies are taken. Recent modalities being used in the clinical and operative setting allow for a higher primary pickup rate. Most of these cases identify the primary in the oropharynx.

Treatment of CUP should be based on the stage of the disease process, with single modality sufficing for patients with early stage disease. A combination of neck dissection and EBRT may be needed for patients with advanced disease. Bilateral neck irradiation increases overall and disease-free survival at the expense of increased morbidity.

Molecular analysis of the metastatic cervical neck nodes can potentially locate previously occult oropharyngeal or nasopharyngeal primaries.

The survival outcomes are generally good for early and late-stage disease but whether less intensive or single-modality therapy could be adequate in patients who are HPV-positive is yet to be determined.

BEST CLINICAL PRACTICE

- ✓ There is no level 1 evidence for guidance in the management of CUP. Data are at best level 2.
- ✓ PET-CT has shown to have a key rode in the management of patients with CUP and should precede multiple biopsies.
- ✓ Primary surgical management of the neck is preferred to radiotherapy in patients with operable disease.
- ✓ Post-operative selective or total mucosal radiotherapy is indicated for most patients with advanced operable disease.
- ✓ Strategies for the use of new treatment technologies, IMRT and modified radiation fractionation, are largely based on extrapolation of data accumulated for the treatment of known sites of HNSCC.

FUTURE RESEARCH

The management of CUP remains controversial. With the current lack of adequate randomized controlled clinical trials and the decreasing incidence due to improved diagnostic tools, the management of patients with CUP will continue to be challenging.

Most of the current evidence is provided by retrospective single institution studies. With increasing data to suggest that HPV related cancers can be multifocal, further work is needed to define this problem better.

Several questions in the aetiology and management of CUP remain unresolved. These include:

- ➤ Is definitive neck dissection sufficient for patients with N1, N2a and selected N2b disease, avoiding the need for elective total mucosal irradiation?
- ➤ Should definitive RT or CRT should be offered as a primary modality of treatment with salvage neck dissection for persistent disease?
- ➤ Which extent of neck dissection patients should have for each stage?
- ➤ What are the optimal fields for elective irradiation? Ipsilateral, versus bilateral vs total mucosal unilateral or bilateral irradiation.

KEY POINTS

- CUP is an increasingly rare clinical scenario and accounts for only up to 5% of patients with head and neck malignancy.
- Involvement of nodal levels I to IV is almost exclusively associated with occult upper aerodigestive tract primary SCC with level II being the most common site
- Patients should be evaluated with CT, MRI or FDG-PET-CT prior to biopsy in order to guide biopsy site and to avoid imaging artefacts or false positive results with PET-CT.
- FDG-PET-CT has now a clear role on the management of CUP and should be employed whenever possible.
- The only tumour marker of clinical value is Epstein–Barr virus serology as will indicate origin from the nasopharynx. HPV16 status can be determined in tumour cells aspirated from the necks of patients with metastatic HNSCC and its presence is a reliable indicator of origin from the oropharynx.
- Bilateral tonsillectomy may be recommended as diagnostic tool in the evaluation of CUP. Transoral laser and transoral robotic mucosectomies of the tongue base have showed promising results in detecting primary tumours at this site.
- Definitive neck dissection should be performed in all patients with CUP. The extent of the neck dissection requires further evaluation especially on those patients with N1, N2a and limited N2b disease where selective neck dissection could be considered.
- Total mucosal irradiation has demonstrated a reduction in primary site recurrence without any improvement in overall survival. Associated mucositis and xerostomia rates are high.
- Radiotherapy-related morbidity can be reduced if selective mucosal irradiation is undertaken, most commonly by exclusion of nasopharynx especially in patients presenting with II to IV nodal disease.
- IMRT should be considered as the optimal technique for radiation dose delivery.
- For total mucosal irradiation, a dose of 50 Gy in 25 daily fractions, five fractions per week is sufficient for control of occult primary disease.
- Nodal stage is the most important risk factor for local recurrence.
- CRT in patients with CUP should be considered in N3 disease and in those patients with definitive ECS or when resection margins are positive for example around the common carotid artery.

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CHAPTER 18

METASTATIC NECK DISEASE

Vinidh Paleri and James O'Hara

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SEARCH STRATEGY

Data in this chapter may be updated by a search on Pubmed and Medline using the keywords: neck nodes, cervical lymphadenopathy, metastatic lymphadenopathy, neck dissection, occult neck metastases, neck levels and radiation therapy to the neck.

INTRODUCTION

One of the most important prognostic factors in head and neck cancer is the presence or absence, level and size of metastatic neck disease. Many tumours of the head and neck will at some stage metastasize to lymph nodes and a number of factors control the natural history and spread of disease.

Several controversies exist about the management of malignant neck disease, with varying practices on choice, timing and combination of treatment modalities. This is primarily due to the paucity of high-level evidence to many treatment paradigms, but this trend has been reversed with randomized controlled trials and systematic reviews published more recently. However, many organizations have generated guidelines following rigorous evidence gathering exercises, suggesting best management practices based on available evidence in many countries.

This chapter identifies the evidence base and discusses the principles of management of metastatic head and neck squamous cell carcinoma (HNSCC) at initial presentation, residual and recurrent neck disease. It also outlines major clinical controversies regarding the management of the neck in relation to when to treat, how much to treat and which modality to use. It reviews the various rationales for assessment as well as methods for elective and therapeutic treatment and focuses on quality-of-life (QOL) issues. The management of tumours other than HNSCC (i.e. salivary gland and thyroid tumours) are not covered in this chapter.

CLINICAL IMPLICATIONS OF METASTASES

The presence of regional lymph node metastases acts as an indicator of the ability of the primary tumour to metastasize locally and to distant sites, rather than acting as an instigator of distant metastases on their own. This is because lymph node involvement indicates a host response which is permissive for the development of metastases, not only in the regional lymph nodes but also to distant sites. (The molecular mechanisms that promote or prevent metastases is discussed in greater detail in Chapter 6, Introducing the molecular biology of head and neck cancer.) Therefore, the degree of lymph node involvement should be regarded as an indirect index of the systemic tumour burden. Elective removal of regional lymph nodes

serves as a staging procedure to ascertain whether or not metastatic disease is present and to identify high-risk patients who might benefit from systemic adjuvant therapy, but is not expected to diminish the metastatic potential. Akin to breast cancer, tumour-free survival depends more on the biology of the tumour present at the operation rather than at the extent of surgery. This explains why patients with metastatic lymph nodes in HNSCC have a significantly reduced chance of survival when compared with those who have no lymph node metastases.[1]

It has long been recognized that systemic spread can occur early in many solid tumours and this includes HNSCC. Traditional teaching has been to offer wide margin radical surgery to the neck, with the premise that patients who have a large number of occult positive nodes achieve better survival since these nodes are discovered earlier. This philosophy is now being questioned as locoregional disease can be cured with locoregional treatments in a greater proportion of patients, who are now living longer only to die more frequently of second primaries or distant metastases. Overall survival has not changed.

It becomes clear from the above discussion that the spread of HNSCC to the regional lymph nodes indicates an aggressive tumour where the tumour–host balance has swung in favour of the tumour. While there are structural and immunobiological mechanisms that may affect tumour lysis within the lymph node itself, in a certain proportion of cases, systemic spread occurs early on. This can take place by lymphatic or haematological routes. These processes of spread and tumour arrest can be affected by previous treatment. As the systemic immunosuppressive effects of multimodality head and neck cancer therapy are taken into consideration, both the number and the complexity of modalities that are used become ever more important.

NECK LEVELS

It is useful to introduce the concept of neck levels here. The Memorial Sloan-Kettering Hospital published, in 1981, a number of levels or regions within the neck which contain groups of lymph nodes representing the first echelon sites for metastases from head and neck primary sites.[2] These levels have been widely accepted and currently six neck levels are recognized, with level VII being outside the neck and referring to the chain of paratracheal nodes below the suprasternal notch to the level of the innominate artery. These neck node levels (**Figure 18.1**) along with their respective boundaries are described in **Table 18.1**.[3] Levels I, II and V can be further subdivided into (a) and (b). These subdivisions were introduced to recognize certain areas in the neck that have a biological significance independent of the larger zone that they lie in. For instance, Level Ia is rarely involved in malignant processes excluding the lip, anterior floor of mouth and midface. The prognostic significance of level Vb involvement is grave and thus merits the subdivision. The rationale behind subdivision of level II is discussed in 'Elective surgery' below.

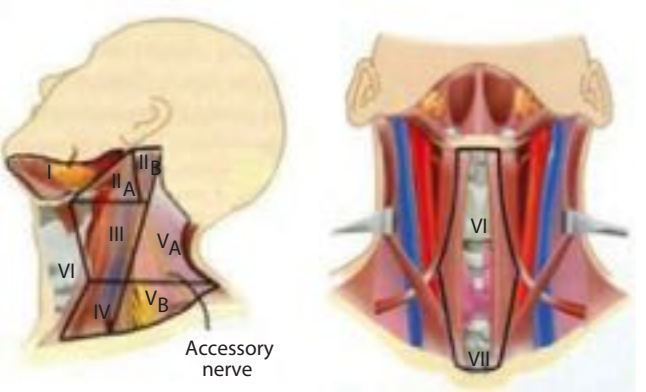


Figure 18.1 The lymph node levels of the neck.

NECK DISSECTION TERMINOLOGY

Standardized neck dissection terminology that was first produced by the American Academy of Otolaryngology and Head and Neck Surgery in 1991 has been updated by the Committee for Neck Dissection Classification of the American Head and Neck Society in 2002 and is widely used (**Table 18.2** and **Figure 18.2**). There is an increasing trend to divide neck dissections into two broad types with subdivisions: comprehensive (removal of levels I–V) and selective (SND) (less than five levels).

The previous division of SND into named subtypes has been superceded by recommendations that the levels or sublevels removed during SND be precisely stated in the operation notes.[4] The term elective neck dissection (END) is used to describe any type of neck dissection that is performed on the clinically and radiologically negative neck (cN0, see below). However, a neck dissection may not fall into one of these standard types, especially in the salvage setting. Recognizing that the current neck dissection terminology will not be appropriate in several post-treatment scenarios, the International Head and Neck Scientific Group has proposed a new classification system for neck dissections.[5]

REGION SPECIFIC LYMPHATIC DRAINAGE

There are approximately 150 lymph nodes on either side of the neck. The normal range in size is from 3 mm to 3 cm but most nodes are less than a centimetre. Within the upper deep cervical nodes in level II, the largest node is often called the jugulo-digastric node and is situated within the triangle formed by the internal jugular vein, facial vein and posterior belly of the digastric muscle. It is important because it receives lymph from a wide area which includes the submandibular region, the oropharynx and oral cavity. The jugulo-omohyoid nodes are situated at the junction between the middle and lower cervical group (low level III/high level IV) where the omohyoid muscle crosses the internal jugular vein and receives lymph from a wide area which includes the anterior floor of mouth, oropharynx and larynx. It is important to realize that contralateral

TABLE 18.1 Neck levels as defined by the American Academy of Otolaryngology-Head and Neck Surgery[6]

Level	Clinical location	Surgical boundaries	Radiological boundaries
Ia	Submental triangle	S: Symphysis of mandible I: Hyoid bone A (M): Left anterior belly of digastric P (L): Right anterior belly of digastric	Nodes above the level of lower body of hyoid bone, below mylohyoid muscles and anterior to a transverse line drawn through the posterior edge of submandibular gland on an axial image
Ib	Submandibular triangle	S: Body of mandible I: Posterior belly of digastric A (M): Anterior belly of digastric P (L): Stylohyoid muscle	
IIa	Upper jugular	S: Lower level of bony margin of jugular fossa I: Level of lower body of hyoid bone A (M): Stylohyoid muscle P (L): Vertical plane defined by accessory nerve	Superior and inferior limits as described under surgical boundaries Nodes posterior to a transverse plane defined by the posterior surface of submandibular gland and anterior to a transverse line drawn along the posterior border of the sternomastoid. NOTE: Nodes lying medial to the carotids are retropharyngeal and not level II
IIb	Upper jugular	S: Lower level of bony margin of jugular fossa I: Level of lower body of hyoid bone A (M): Vertical plane defined by accessory nerve P (L): Posterior border of SCM	
III	Mid Jugular	S: Level of lower body of hyoid bone I: Horizontal plane along inferior border of anterior cricoid arch A (M): Lateral border of sternohyoid muscle P (L): Posterior border of SCM or sensory branches of the cervical plexus.	Superior and inferior limits as described under surgical boundaries Nodes anterior to a transverse line drawn on each axial scan through the posterior edge of the SCM and lateral to the medial margin of the common carotid arteries
IV	Lower jugular	S: Horizontal plane along inferior border of anterior cricoid arch I: Clavicle A (M): Lateral border of sternohyoid muscle P (L): Posterior border of SCM or sensory branches of the cervical plexus.	Superior and inferior limits as described under surgical boundaries Nodes anterior to a transverse line drawn on each axial scan through the posterior edge of the SCM and lateral to the medial margin of the common carotid arteries
Va	Posterior triangle	S: Convergence of SCM and trapezius muscles I: Horizontal plane along inferior border of anterior cricoid arch A (M): Posterior border of SCM or sensory branches of the cervical plexus P (L): Anterior border of trapezius muscle	
Vb	Posterior triangle (supraclavicular)	S: Horizontal plane along inferior border of anterior cricoid arch I: Clavicle A (M): Posterior border of SCM or sensory branches of the cervical plexus. P (L): Anterior border of trapezius muscle	Nodes posterior to a transverse line drawn on each axial scan through the posterior edge of the SCM
VI	Anterior compartment	S: Hyoid bone I: Sternal notch A (M): Common carotid artery P (L): Common carotid artery	
VII	Superior mediastinum	S: Sternal notch I: Innominate artery A (M): Common carotid artery P (L): Common carotid artery	

S = superior; I = inferior; A = anterior; P = posterior; L = lateral; M = medial; SCM = sternocleidomastoid.

TABLE 18.2 Classification of neck dissection techniques

Radical neck dissection (RND)	Removal of levels I–V, accessory nerve, internal jugular vein and SCM
Modified radical neck dissection (MRND)	Removal of levels I–V dissected; preservation of one or more of the accessory nerve, internal jugular vein or SCM (types I, II, III respectively)
Selective neck dissection (SND)	Preservation of one or more levels of lymph nodes.
Extended radical neck dissection (ERND)	Removal of one or more additional lymphatic and/or non-lymphatic structures(s) relative to a radical neck dissection, e.g. level VII, retropharyngeal lymph nodes, hypoglossal nerve

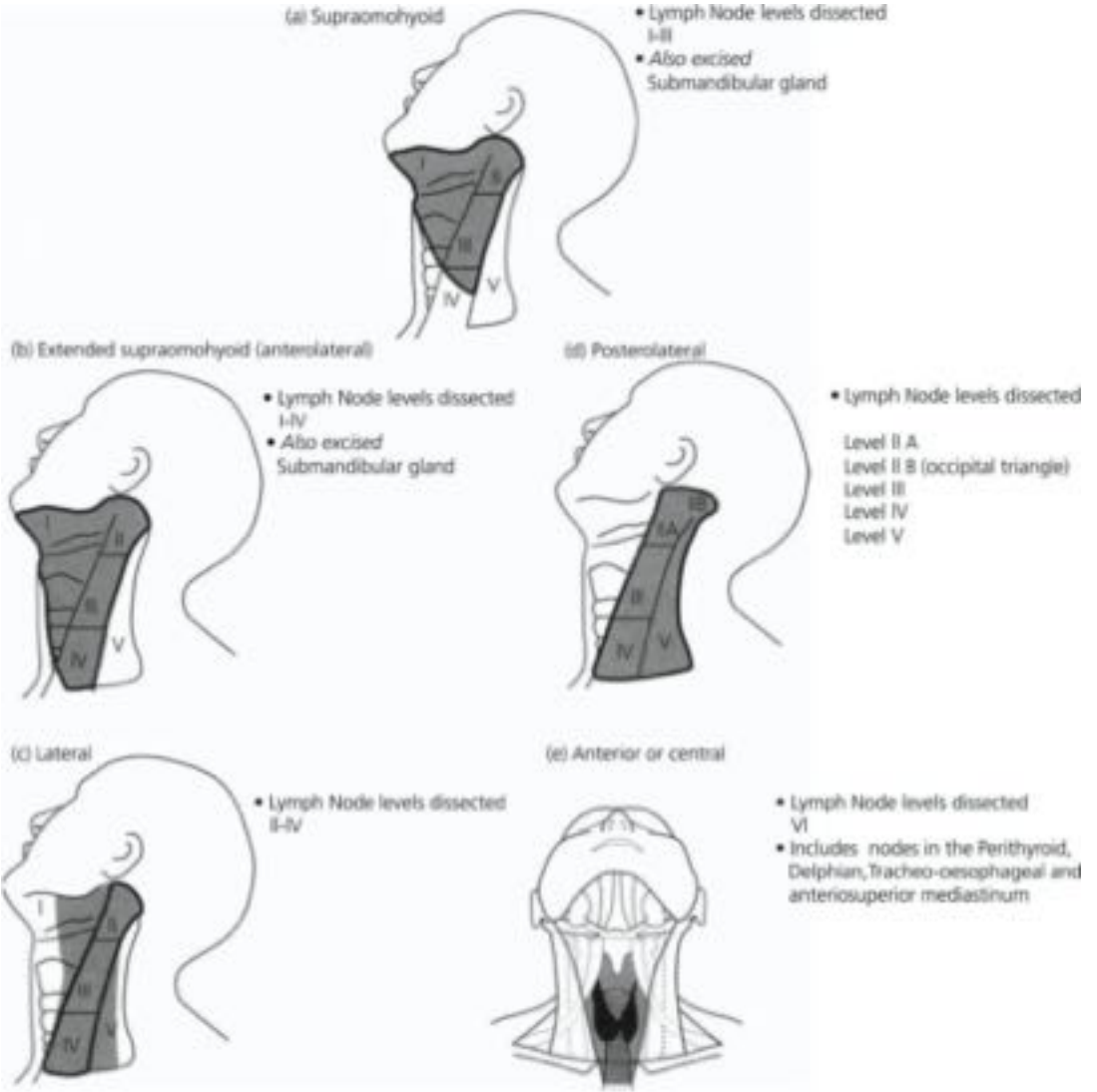


Figure 18.2 Types of selective neck dissection **(a)** Levels I-III (supraomohyoid); **(b)** levels I-IV (extended supraomohyoid; **(c)** levels III-IV (lateral); **(d)** levels III-IV (posterolateral); **(e)** level VI-VII (anterior/paratracheal).

neck spread may occur early in those tumours situated in or near the midline.

- The nasopharynx, nasal cavities and sinuses drain via the junctional nodes into the upper deep cervical nodes (levels II and III) having passed through retropharyngeal or submandibular lymph nodes.
- The oropharynx similarly drains into the upper, middle and lower deep cervical nodes (levels II, III and IV) again either directly or via the retropharyngeal nodes. Within these areas of deep lymph node collections in the neck, certain nodes can reach quite large proportions.
- The oral cavity has a wide area of drainage and this is important because there is often free communication between the two sides of the tongue. The posterior parts of the oral cavity either drain directly into the upper deep cervical nodes (level II/III) or indirectly via the submandibular nodes (level Ib). More anterior parts of the oral cavity and tongue also drain to these nodes but, in addition, may drain to the submental nodes (level Ia) or directly to the jugular nodal chain (levels II to IV). The tongue especially is known to cause 'skip metastases' to level IV.
- The larynx drainage is separated into upper and lower systems based on their embryological origins, with a division that occurs at the level of the true vocal cord. The supraglottis drains through vessels which accompany the superior laryngeal pedicle via the thyroid membrane to reach the upper deep cervical nodes (levels II/III), with a greater tendency for bilateral nodal drainage. The lower system drains directly into the deep cervical nodes (levels III/IV) through lymphatics which pass through or behind the cricothyroid membrane and also into the prelaryngeal, pretracheal or paratracheal nodes (level VI) before reaching the deep cervical nodes. Because the vocal cords are relatively avascular, they have an extremely sparse lymphatic drainage and, as such, lymph node metastases from small carcinomas at this site are uncommon.

- The hypopharynx is similar to the supraglottic larynx, and both may have contralateral spread, particularly in those areas that are either close to the midline or have significant communications across the midline such as the epiglottis, posterior pharyngeal wall and postcricoid region. Drainage is to levels III, IV, VI and VII.

The region-specific drainage translates well into clinical practice and it is possible to predict the site of a primary tumour based upon the distribution of cervical metastases and vice versa. In a landmark study of 1155 patients with previously untreated HNSCC published by Lindberg in 1972,[6] the topographical distribution of clinically evident cervical metastases was set out. This identified distinct patterns of spread to the neck based on the primary site. Histological proof of this concept was produced in 1990 by Shah[7] in a series of 1119 neck dissections.

It is widely accepted that patterns of subclinical microscopic metastases follow a similar distribution. The high incidence of occult metastases in tumours of the oral cavity, pharynx and the supraglottic larynx forms the basis for SND and removal of the echelon lymph nodes which are the most likely sites of initial metastatic deposits. The echelon nodes for each site are as follows: levels I, II and III for the oral cavity, levels II, III, IV for the oropharynx, larynx and hypopharynx and levels IV, VI and VII for the thyroid gland. For the parotid gland, the first echelon lymph nodes are the pre-auricular, periparotid and intraparotid lymph nodes along with those in level II, III and the upper accessory chain (level Va). For the submandibular and sublingual gland, the echelon lymph nodes lie in levels I, II and III.

METASTATIC BEHAVIOUR IN THE PREVIOUSLY TREATED NECK

Treatment modalities can affect tumour–host equilibrium in unpredictable ways and these include surgery, radiotherapy and chemotherapy.

Surgery can undoubtedly mechanically alter the locoregional tumour environment. Considerable gaps between lymphatics mean that collateral channels form, and the ability to do this relates to the nature of connective tissue through which the lymphatics must grow. These mechanical effects can alter patterns of lymphatic metastatic spread and divert lymph flow to the contralateral neck and sometimes even cause retrograde spread. Surgical scarring can trap tumour cells although this may not always ultimately lead to established local recurrence.[8] It seems sensible to suggest that gentle handling of cancer tissues may decrease the amount of exposure that a surgical wound gets to free cancer cells and as such minimize the potential for any growth.

There is evidence in the literature that the systemic cellular immune response is significantly compromised following locoregional radiation therapy (RT) in head and neck cancer patients.[9] Radiation is associated with changes in the regional lymph nodes and lymphatics in general. Thus, within a few days of starting RT, there is a decrease in the numbers of lymphocytes within lymph nodes and thickening of the walls of both lymph nodes and blood vessels can be noted. Some of these changes explain why previous RT can cause lymphatic obstruction and shunting of lymph both into the subdermal vessels and also to the contralateral neck. All of the above lead to unpredictable changes in the pattern of lymphatic drainage, and thus, the echelon levels described above for the various sites will not be applicable to disease recurrence following treatment.

OCCULT NODAL DISEASE

The term occult disease is used to describe the presence of metastases in the neck nodes that cannot be clinically or radiologically identified. This falls into two categories: occult metastases that can be identified on light microscopy and micrometastases measuring less than 2mm that need special histological techniques (immunohistochemistry, step serial sectioning and molecular analysis) for identification. The incidence of occult disease as assessed by routine histological examination varies by the site and stage of tumour (**Table 18.3**), but use of molecular techniques to look for metastatic disease will increase the incidence rates.

TABLE 18.3 The probability of cervical metastases (N) related to primary (T) staging in patients with HNSCC

Primary site	T-Stage	N0%	N1%	N2–N3%
Floor of mouth	T_1	89	9	2
	T_2	71	18	10
	T_3	56	20	24
	T_4	46	10	43
Oral tongue	T_1	86	10	4
	T_2	70	19	11
	T_3	52	16	31
	T_4	24	10	66
Retromolar trigone Anterior faucial pillar	T_1	88	2	9
	T_2	62	18	20
	T_3	46	21	33
	T_4	32	18	50
Nasopharynx	T_1	8	11	82
	T_2	16	12	72
	T_3	12	9	80
	T_4	17	6	78
Soft palate	T_1	92	0	8
	T_2	64	12	24
	T_3	35	26	39
	T_4	33	11	56
Base of tongue	T_1	30	15	55
	T_2	29	14	56
	T_3	26	23	52
	T_4	16	8	76
Tonsillar fossa	T_1	30	41	30
	T_2	32	14	54
	T_3	30	18	52
	T_4	10	13	76
Supraglottic larynx	T_1	61	10	29
	T_2	58	16	26
	T_3	36	25	40
	T_4	41	18	41
Hypopharynx	T_1	37	21	42
	T_2	30	20	49
	T_3	21	26	54
	T_4	26	15	58

The natural history and the clinical significance of occult metastases is an important, yet largely unanswered question. Neck dissection may arrest progress of some cancer cells. However, a lymph node may be negative on examination because either cancer never reached it or if it did, it was not retained or indeed was destroyed. This has led to several controversies in the management of the occult neck. It is important to address this question because this affects whether or not the disease needs to be treated and by what method. Observational data suggests that the conversion rate from the N0 to the N+ neck without neck treatment is similar to the incidence of pathological positive nodes in END specimens (around 30%).[8] There is no doubt that occult neck disease does have the potential to manifest itself, but it is impossible to predict with reasonable certainty in individual patients. This is one of several arguments that justify the elective treatment of the occult neck. The clinical significance is discussed in depth in 'The N0 neck' below.

MICROMETASTASES

Micrometastases are deposits of cancer cells less than 2 mm in size.[10] Presence of micrometastases upstages the neck status. One of the many goals of translational research in cancer has been to refine disease prediction by detecting tumour-specific molecular alterations in histological normal tissues either at resection margins or identifying 'sub-pathological' metastases in regional lymph nodes. Specific clonal genetic changes seen in tumour cells can be used as molecular markers for their detection in lymph nodes. However, the heterogeneity seen in HNSCC, like other solid cancers, precludes the use of a single tumour specific marker. Thus, these studies are dependent on the amplification of less specific epithelial genes or a panel of their transcripts.

Several molecular markers have been used to identify the presence of 'sub-pathological' metastases in lymph nodes. Using immunohistochemistry, micrometastases can be detected in between 5% and 25% of tumour-positive ENDs of clinically N0 necks,[11, 12] with upstaging occurring in up to 12% of patients.[13, 14] Using techniques such as quantitative reverse transcriptase-polymerase chain reaction (QRT-PCR) results can be obtained within two hours of tissue harvesting. An isolated tumour cell is a further category of micrometastases; equating to single cells or clusters of cells no more than 0.2 mm in size. Where identified, they are still classified as N0. However, isolated tumour cells are classified as N1 in cutaneous malignant melanoma and Merkel cell carcinoma.[15]

The clinical significance of micrometastases is undetermined. Prospective studies have used different markers and techniques to assess micrometastases and have arrived at diametrically opposite conclusions. In the absence of a universally acceptable marker or a battery of markers, it will be difficult to design clinical trials. Because of the unknown prognostic significance of micrometastases or indeed implications for additional post-operative treatment, the extra work involved in discovering it on a routine basis is not currently justified.

CYSTIC NECK METASTASES

Cystic neck metastases are usually of oropharyngeal origin, with the most common sites being the tonsil or tongue base. Human papilloma virus (HPV) related tumours are more often associated with cystic metastases than HPV negative tumours.[16] These lymph node metastases tend to have a better prognosis than their non-cystic counterparts. This has been reported as branchiogenic carcinoma in the past. Any diagnosis of branchiogenic carcinomas should be viewed with scepticism.[17, 18] The majority of branchiogenic carcinomas are in fact cystic metastases from oropharyngeal carcinoma and not true carcinomas arising in a branchial cleft cyst. Given the exponential rise in HPV positive oropharyngeal carcinoma throughout the world, any cystic level II neck mass in an adult should be considered as a potential metastasis and should be investigated as recommended in Chapter 17, Neck metastases from an unknown primary, that deals with the investigation and management of carcinoma from an unknown primary.

PROGNOSTIC NODAL FEATURES

There are a number of features of metastatic cervical nodal disease which indicate a poor prognosis (**Box 18.1**). However, much of the data used to arrive at these conclusions is retrospective and readers should consider whether primary surgical or non-surgical treatments were used in the descriptive observational case series. Surgery accurately stages disease and primary radiotherapy will not upstage occult neck disease or define extranodal extension (ENE), previously known as extracapsular spread. Lefebvre et al[19] looked at the impact of various regional factors on regional recurrence and distant metastases. This study with 1330 patients showed that irrespective of T staging, ENE, three or more positive nodes and positive level IV nodes doubled the risk of regional recurrence and trebled the risk of distant metastases. In the era of HPV-induced oropharyngeal SCC (OPSCC), there is emerging evidence that the number of involved nodes may have greater prognostic significance than ENE.[20] Matted nodes identified on pre-treatment imaging, defined as three nodes abutting one another with loss of an intervening fat plane replaced by ENE, is another factor that may confer a worse prognosis for patients with HPV OPSCC undergoing CRT.[21]

Extranodal extension

ENE occurs when the cancer has penetrated and infiltrated beyond the lymph node capsule. There is a consensus that the presence of ENE in a lymph node is associated with a poor prognosis.[8, 22–26] Both prospective and retrospective evidence

BOX 18.1 Prognostic nodal features

- Site, size and number
- Low neck nodes
- Extracapsular spread / Matted nodes
- Morphology
- Bilateral and contralateral spread (N2c disease)

suggests that ENE decreases survival rates by approximately half compared to those patients whose tumour was confined to the nodes. Also, patients who have occult involvement of nodes but ENE statistically do worse.[8, 27] A recent meta-analysis concluded that perinodal spread adversely affected 5-year survival, with a summarized odds ratio of 2.7.[28] Some workers have noted that invasion of the soft tissues of the neck by tumour lowers treatment success rates by 80%. Other studies show that patients with ENE are at increased risk of local recurrence, distant metastases and that the time to recurrence is shorter. Indeed, it has been suggested that stratification of disease by the presence or absence of ENE would offer a more accurate prognosis than the current TNM system.[29] It is likely that ENE may have a differential impact depending on the primary sites. For instance, Oosterkamp et al[30] showed that ENE adversely affected survival in laryngeal cancer by increasing the risk of metastases nine times, compared to a three times greater risk in patients without this finding.

Currently, it is not clear whether or not ENE represents increase in tumour burden or an increase in tumour aggressiveness. Toker[31] demonstrated that a primary rest of tumour emboli within the node capsule may lead to ENE occurring quite early in the metastatic process and as such may represent an anatomical variation rather than an aggressive tumour. In addition, not all nodes within a neck dissection specimen show ENE and there may be a threshold volume of ENE above which the prognosis is poor.

The literature almost universally recommends that the standard treatment if ENE is detected following surgery is to add post-operative radiotherapy or chemoradiation, even for those who have only one node involved.[8, 32, 33] In the presence of ENE, there is level 1 evidence in support of concomitant cisplatin with post-operative radiotherapy for patients fit enough to receive this.[33] However, there are some questions raised over how this evidence relates to the particular population of patients with HPV related OPSCC, following primary surgical management. This is discussed below.

Retropharyngeal nodes

Tumours that are associated with these nodes include primary disease of the oropharynx, paranasal sinuses and pyriform sinus as well as advanced primary tumours at any site together with massive unilateral or bilateral neck disease, which presumably involves retropharyngeal nodes due to shunting from obstructed lymphatic ducts or channels. Retropharyngeal node invasion is almost always a radiological diagnosis (**Figure 18.3**). There are a number of reports in the head and neck literature that associate the presence of retropharyngeal nodes with a very poor prognosis,[8, 34, 35] but a study of 51 patients concluded otherwise.[36]

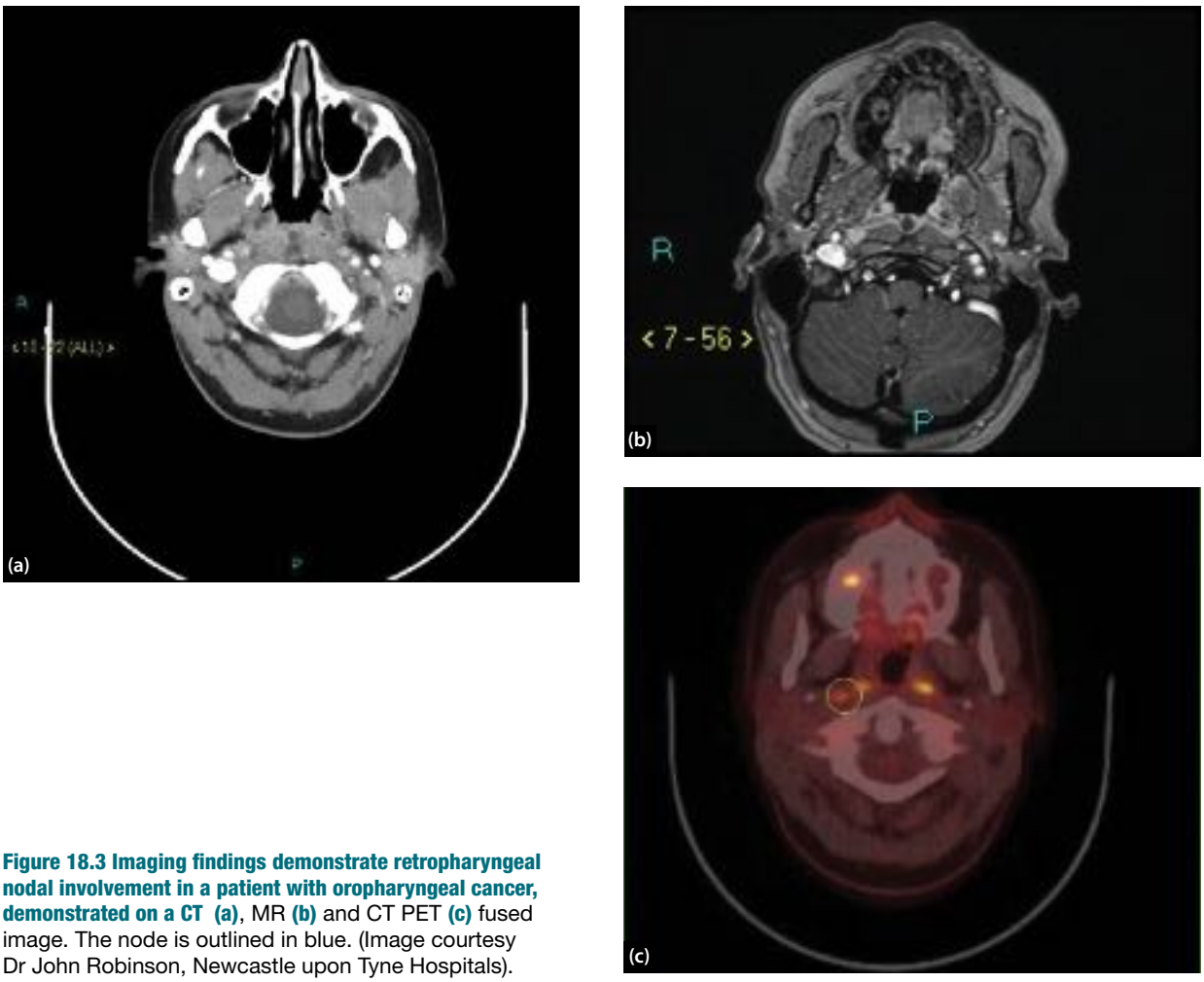


Figure 18.3 Imaging findings demonstrate retropharyngeal nodal involvement in a patient with oropharyngeal cancer, demonstrated on a CT (a), MR **(b)** and CT PET **(c)** fused image. The node is outlined in blue. (Image courtesy Dr John Robinson, Newcastle upon Tyne Hospitals).

CLINICAL STAGING

A classification system is essential for documentation of disease extent, comparisons of results between centres and stratifying patients for inclusion into trials. This is based not only on the presence or absence of cervical lymphadenopathy but also the size, number and laterality of the lymph nodes. The joint UICC and AJCC classifications for regional cervical lymphadenopathy have had substantial changes made to them, in the latest 8th edition (**Tables 18.4–18.6** and **Figures 18.4** and **18.5**). They now take into account ENE status

TABLE 18.4 Clinical N staging for cervical metastases[5, 15]

N category	Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE-negative
N2a	Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE-negative
N2b	Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative
N3b	Metastasis in any node(s) and clinically overt ENE-positive

ENE = Extranodal Extension. Defined as: The presence of skin involvement or soft tissue invasion with deep fixation/tethering to underlying muscle or adjacent structures or clinical signs of nerve involvement is classified as clinical extra nodal extension.

TABLE 18.5 Clinical N stage for Human Papillomavirus (p16) positive associated oropharyngeal carcinoma[5, 15]

N category	Criteria
NX	Regional nodal status cannot be assessed
N0	No regional lymph node metastases
N1	One or more ipsilateral lymph nodes, none larger than 6 cm
N2	Contralateral or bilateral lymph nodes, none larger than 6 cm
N3	Lymph node(s) larger than 6 cm

TABLE 18.6 Pathological N stage for Human Papilloma virus associated oropharyngeal carcinoma[5, 15]

P category	Criteria
NX	Regional nodal status cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in 4 or fewer lymph nodes
N2	Metastasis in more than 4 lymph nodes

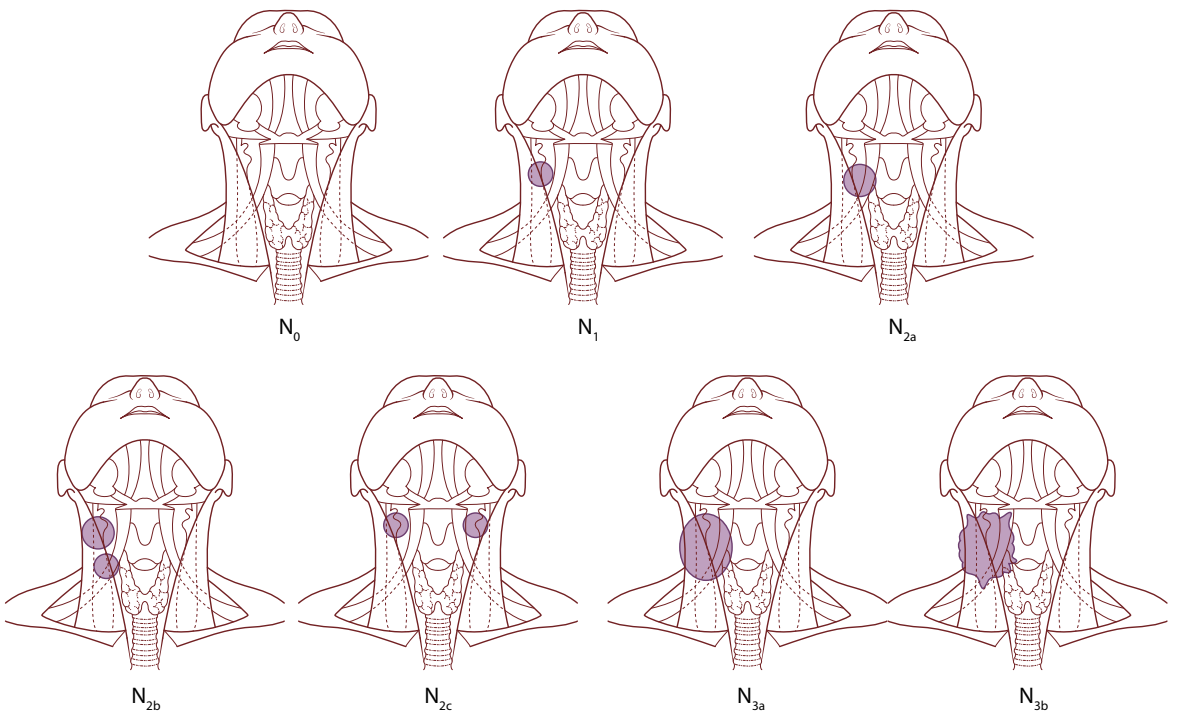


Figure 18.4 Clinical N staging for non-human papillomavirus associated oropharyngeal carcinoma.

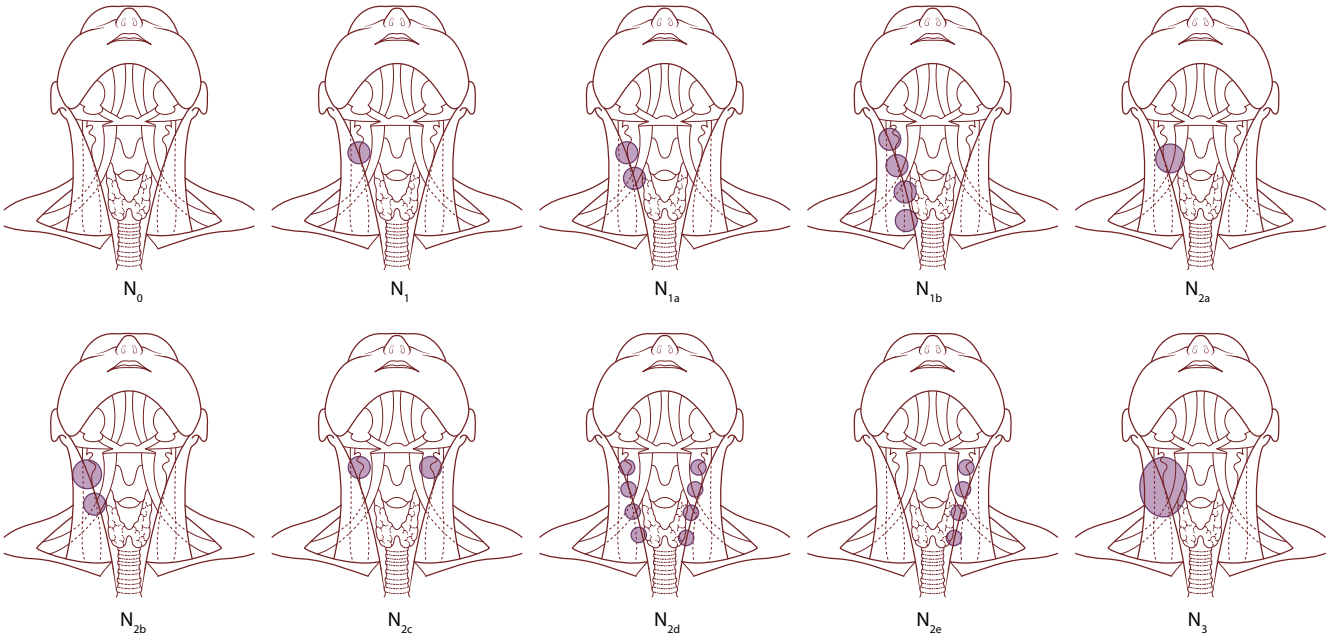


Figure 18.5 Clinical N staging for human papillomavirus associated oropharyngeal carcinoma.

and HPV (P16) status, and split the staging into distinct clinical and pathological classification. This is covered in detail within Chapter 4, Staging of head and neck cancer.

A retrospective analysis of 1190 patients between 1985 and 2007 demonstrated that the inclusion of ENE status in addition to the N-stage offered more accurate survival prognosis than the previous TNM staging system.[29] The 8th edition of the TNM staging recognizes a clinical staging group for ENE in p16 negative SCC, called N3b, diagnosed unambiguously on clinical examination alone (e.g. invasion of skin, infiltration of musculature/dense tethering to adjacent structures, or dysfunction of a cranial nerve, the brachial plexus, the sympathetic trunk, or the phrenic nerve) and supported by radiological evidence (**Figure 18.4**). This represents far more advanced disease than many patterns of ENE identified in neck dissection specimens.

The International Collaboration on Oropharyngeal cancer and Network for Staging (ICON-S) has developed[37] and validated[38] a model for HPV related OPSCC, with neck disease resembling the N-staging for nasopharyngeal carcinoma, but without the lower neck disease variable. This work has shaped the 8th edition of the TNM staging systems. There was recognition that 5-year overall survival was similar for N1, N2a and N2b subgroups, the rationale for these stages being grouped together as N1 disease (**Figure 18.5**). The separate TNM staging system for p16 positive cancers is due to the more favourable prognosis of HPV OPSCC, with previously defined advanced disease now being more appropriately classified to fit with the prognostic evidence. There is an anticipated psychological benefit for these patients, in which many previously stage IV tumours will now be stage I.[39]

CLINICAL PRESENTATION OF NECK DISEASE

The pattern of spread of malignant disease to the neck depends upon both patient and tumour factors. These are identified in **Box 18.2**. The site of the primary tumour is important with some sites having a higher incidence of metastases, both palpable and otherwise, at presentation (**Table 18.3**). Neck metastases usually present as neck masses, usually firm to hard on palpation. They may be mobile or fixed to surrounding structures, usually determined by the degree of ENE.

ASSESSMENT OF CERVICAL LYMPHADENOPATHY

Any patient with a head and neck primary tumour requires careful assessment of the neck. This begins with a full clinical examination which may be supplemented by an examination under anaesthetic. Further assessment of the neck with fine needle aspiration / core biopsy cytology and radiological imaging can help confirm or refute the diagnosis. Occasionally, an open biopsy may be required.

BOX 18.2 Factors implicated in pattern of metastatic nodal disease

- Tumour site
- Tumour size
- Tumour thickness
- Previous treatment
- Tumour recurrence

Clinical examination

Clinical examination remains an important initial method of assessing regional lymph nodes and is covered in more detail in Chapter 36, Clinical examination of the neck. Clinical examination of the neck has a variable diagnostic accuracy.[40, 41] Based on a systematic review,[42] physical examination has a sensitivity of 74%, specificity of 81% and an overall accuracy of 77%. This can be particularly difficult in necks that are difficult to examine i.e. following radiotherapy, previous surgery or in short, stocky necks. Nodes in these instances may go unnoticed until they reach a considerable size. In addition, some regions are inaccessible such as the retropharyngeal area.

Fine needle aspiration cytology

In the presence of palpable disease and a proven primary, treatment will usually be directed towards the assessment of the neck disease rather than confirming that a metastasis is present by fine-needle aspiration cytology (FNAC). Few surgeons would ignore a clinically palpable node in the presence of proven primary disease even if the FNAC shows no evidence of malignancy. The technique is particularly useful in the assessment of a palpable node when searching for an unknown primary as the cytological aspirate (which may require a core biopsy according to institutional practice) can be subjected to tests that may help in the search for the primary tumour. For example, evidence of HPV or Epstein–Barr virus transcripts (or their surrogate markers) will point to a primary site in the oropharynx or nasopharynx respectively. The possibility of anaplastic carcinoma or lymphoma usually makes a core-biopsy or open biopsy mandatory. The FNAC technique is easy to perform, can be reported immediately (particularly if a cytopathologist is present in the outpatient clinic) and has overall accuracy rates exceeding 90%.[43] There is, however, a well-recognized learning curve associated with the technique.

Ultrasound scan

This technique can detect the presence of malignant cervical lymph nodes with sensitivity rates between 70% and 90%. When combined with FNAC, this figure increases to 90%. However, the technique requires an expert ultrasonographer to be present in the outpatient clinic, is operator dependent and labour intensive. The addition of power Doppler to assess vascular flow[44] and molecular analysis of the aspirate[45] does improve on these figures. It should be noted that there are no absolute criteria for differentiating benign from malignant disease, but absent hilar echoes and increases in short axis length are generally considered to be features of metastatic neck nodes. Sonoelastography is a new imaging technique where low-amplitude, low-frequency shear waves are propagated through internal organs, while real-time Doppler techniques are used to image the resulting vibration pattern.

The decrease in vibration amplitude caused by the presence of inhomogeneity, such as a tumour within a region of soft tissue, is measured. This has shown promise in the evaluation of neck nodes.[46] There is also an increasing vogue for adding ultrasound with or without guided FNAC to follow up neck disease in patients after chemoradiation.[47]

CT

The diagnostic accuracy of CT scanning in detecting malignant cervical lymphadenopathy is higher than clinical examination. The range of non-malignant cervical lymphadenopathy is 3 mm up to 3 cm, but most authors recognize that nodes greater than 1 cm in size on CT may contain metastatic disease. The criteria used for categorizing metastatic deposits include lymph nodes with short axis diameter larger than 1 cm, cluster of three or more borderline enlarged nodes larger than 0.8 cm, and nodal necrosis or patchy enhancement within the nodes.[48–50]

A meta-analysis of CT vs physical examination with 647 neck dissections showed CT to have a sensitivity of 83% with a specificity and overall accuracy of 83%.[42] This figure has remained stable in a more recent meta-analysis.[51] The detection of malignant disease is based on the fact that as cancer invades the lymph node, its size, shape and characteristics change so that as it enlarges, its centre dies and appears necrotic and there is a thin rim of inflammation around the edge which shows up on scanning as rim enhancement.

It is important to realize that the two most difficult areas in imaging head and neck cancer are the detection of low-volume neck disease and residual and recurrent disease following surgery and irradiation. Based on the above imaging criteria, it is possible to miss a metastatic deposit in an 8 mm cervical lymph node, at which stage, the lymph node would contain 10^8 malignant cells. With increasing use of organ preservation modalities, conventional imaging (CT and MRI) and nuclear medicine imaging have assumed an important role in the assessment of treatment response after chemoradiation.

However, it is important not to rely on imaging alone and management decisions must be made after correlating the clinical findings. Indications for neck imaging are set out in **Box 18.3**.

MRI

This technique can detect cervical lymphadenopathy with overall similar accuracy rates to CT although meta-analyses have found CT to perform better than MRI.[51, 52]

BOX 18.3 Indications for anatomical neck imaging

- Primary tumour assessment
- Careful monitoring of N0 necks (Ultrasonography more likely)
- Assess treatment response
- Assess the difficult neck
- Re-staging recurrent tumours

However, MRI may be better in evaluating the N0 neck and in the presence of deep invasion. Similar criteria for malignancy are used in both techniques. Initial experience with ultrasmall paramagnetic iron oxide-enhanced MRI has shown this modality to have superior diagnostic efficacy compared to conventional imaging.[53, 54]

PET with CT

PET using [18F]-2-fluoro-2-desoxy-d-glucose (^{18}FDG) as a radioactive tracer has proven efficacy in the functional imaging of solid tumours. Tumour cells metabolize more glucose compared to normal tissue and the increased uptake of the glucose analogue FDG can be imaged. However, the major drawback of this technique is the limited morphological information, making the exact anatomical localization of an area of increased glucose metabolism difficult. On its own, ^{18}FDG-PET has inferior sensitivity and specificity compared to conventional imaging,[55] but has been shown to have the ability to change the management in up to 15% of patients when used prior to commencing treatment.[56, 57]

Co-registered anatomical and functional imaging techniques using dual modality PET-CT scanners lead to accurate image fusion, thus harvesting the advantages of both techniques. With relevance to metastatic neck disease, PET-CT has been investigated in the following settings: initial staging, radiotherapy planning, and evaluation of response to radiation or chemoradiation.

There are calls for using this modality in routine practice to stage patients prior to treatment planning, as apart from diagnosis, this may have an impact on the treatment; for example, the presence of distant metastases otherwise not detected on conventional scanning may be picked up on PET imaging, leading to a more palliative approach. For this reason in the UK, recent national guidelines have recommended offering patients PET-CT staging for all T4 hypopharynx and nasopharynx disease, and all N3 neck disease.[58] This can help more treatment resources to be directed to those who are more likely to do well following locoregional treatment.[59] High sensitivity (90–95%) and specificity (95–99%) rates have been observed in the pre-treatment setting.[60–62] PET-CT detection rate for nodes less than 1 cm is reported at 71%.[63] Thus, this modality has poor detection rate (0–30%) in the setting of the N0 neck.[64–66]

Currently the widespread role of PET-CT is confined to detecting the occult primary, detecting unknown distant metastases in certain clinical settings, and for assessment of residual and recurrent disease following irradiation. If a primary site is not immediately apparent on clinical examination, all efforts must be taken to identify the primary site. A detailed discussion of the assessment of the unknown primary can be found in Chapter 17, Neck metastases from an unknown primary.

It is worth noting that false positive results with PET-CT are common in the first few weeks after primary chemoradiation treatment and scans should be deferred until at least 10–12 weeks after completion of treatment.[67] The scan has a high sensitivity (100%) and negative predictive value (98–100%)[68, 69] in the evaluation of the post-treatment neck, and these figures are consistent on meta analyses.[70] Based on this finding, its use has been recommended to avoid salvage neck surgery (see below).

Open biopsy

In general, this diagnostic procedure is best avoided as an initial diagnostic modality. However, in situations where FNAC is not available, equivocal or non-diagnostic, or when the results suggest either a lymphoma or an anaplastic carcinoma, it may be necessary. When a primary site cannot be identified through exhaustive investigations and diagnostic cytology cannot be achieved from a suspicious neck node (most commonly a cystic lesion), the open biopsy should be performed as an oncological procedure, namely as a SND. There is no evidence in the literature that an open biopsy alters the prognosis, as long as correct treatment is instigated within 6 weeks.[32] Any incision should be made to facilitate the removal of the scar via a subsequent standard neck dissection incision and previous surgery may mean that vital structures such as the sternomastoid muscle may have to be sacrificed due to scar tissue.

Sentinel node biopsy

The sentinel node biopsy (SNB) is a diagnostic technique used to assess the presence of occult metastatic disease in the N0 neck. The SNB concept is based on the principle that identification of the echelon nodes and assessing them for metastatic spread will provide information regarding the status of the rest of the neck. Using radioactive probes and/or blue dye around the tumour site, the first to third echelon nodes are identified with the help of gamma cameras and peri-operative hand-held probes; these nodes are subsequently harvested and analyzed for tumour deposits. From a pathological point of view, these nodes undergo a much more comprehensive analysis (step-serial sectioning, immunohistochemistry) as missing a small deposit in the node could result in a wrong decision to not treat the neck. The assumption here is that if these echelon nodes are negative for secondary deposits, it is unlikely for the rest of the neck to have metastases, thus avoiding further treatment to the neck.

It has been shown in patients with early-stage malignant melanoma that selective lymphatic dissection performed after confirmation of positive sentinel node(s) is therapeutically equivalent to elective lymphatic dissection. Although the technique is considered standard for melanoma, breast cancer and other and non-head and neck sites, there have been some concerns regarding the technique in the head and neck. The head and neck lymphatic drainage can be variable with skip metastases, collateral channels are often present and the technique potentially involves the violation of oncologic principles. In addition, the technique is operator dependent with a recognized learning curve[71, 72] and there is an inherent risk of facial nerve damage when assessing parotid nodes. Its role would

appear to be mainly in the treatment of disease within the oral cavity and oropharynx. Injection of the tracer around laryngeal tumours may be cumbersome and satisfactory injection all around the tumour is difficult. Despite these concerns, meta-analysis shows very good sensitivity of SNB for this difficult site.[73] When considering the SNB evidence, the sensitivity of the test would seem most valuable, indicating the risk of false negative results which could lead to under treatment of neck disease. A pooled meta-analysis of non-randomized trials demonstrated that SNB had a sensitivity of 93% for oral cavity cancer.[71] The implications of this are discussed in the section on management of N0 disease below.

Pathology

The head and neck pathologist has the final say in the assessment and staging of cervical lymphadenopathy. Following neck dissection, the specimen should be pinned out on a board and orientated as to the levels, or the specimen separated into respective levels before presenting it to the pathologist. It will then be examined to assess the total number of lymph nodes in the specimen, the number that are positive, the levels that are involved along with the presence or absence of ENE, neural, vascular and lymphatic permeation. Standardization of pathological reporting is essential in order to compare data across centres and to facilitate comparative audit and there is currently a standardized reporting form, which has recently been updated by the Royal College of Pathologists. A detailed treatment of the pathological aspects can be found in Chapter 26, Pathology of head and neck malignancies.

DRAWBACKS IN THE LITERATURE WHEN ASSESSING TREATMENT OUTCOME

The majority of papers published in the literature which relate to HNSCC are retrospective, and because of this some of the controversies that existed fifty years ago have yet to be resolved. Retrospective data suffers from several biases. These include variation in treatment protocols caused by factors relating to the patient, the tumour and treating physician. Diagnostic and treatment expertise varies between centres and therapeutic schedules applied in various ways and at various times. Data collection may require perusal of the notes, which are often incomplete and studies that report different end points are not strictly comparable. For example, survival is the usual end-point reported by head and neck surgeons but when studying the efficacy of any type of neck treatment, locoregional control is more important.

When assessing any single or combination treatment with regards to the control of neck disease, it is important that the study meets the requirements set out in **Box 18.4**. Prospective randomized therapeutic trials control for all these variables but unfortunately there is a paucity of surgical trials in the current head and neck literature, although this situation is improving with several recently published trials and many trials registered and recruiting currently.

BOX 18.4 Prerequisites for studies reporting outcomes of treatment for neck disease

- Homogeneity in disease presentation (untreated necks, recurrent disease, etc)
- Method of treatment should be standardized
- The primary site should be controlled
- Nodal status verified by rigorous histological examination where possible
- Standardized assessment of treatment response
- Clear presentation of regional control rates and disease specific survival
- Adequate follow-up period

TREATMENT OF METASTATIC NECK DISEASE

After controlling for patient and tumour factors, the treatment of metastatic neck disease is usually decided by the stage of neck disease as identified by the joint UICC and AJCC classifications for regional cervical lymphadenopathy.[5, 15] The following section discusses treatment of neck disease for each N stage. It is worthwhile identifying the broad areas where there is a lack of high-level evidence and controversy exists (**Box 18.5**). Most of these topics are being actively investigated and the treatment paradigms are evolving.

It is worth reiterating a few important general principles regarding neck spread when discussing the surgical management of metastatic neck disease. 1) In the untreated neck, patterns of spread may be predictable. 2) In the N0 neck, occult disease is usually found within the first echelon lymph node drainage basin. This permits the principle of SND. 3). Previous treatment alters drainage patterns significantly. 4) Patients with palpable neck disease are more likely to have non-palpable spread in other levels.

BOX 18.5 Controversies in the management of metastatic neck disease

- Significance of occult disease in cervical lymph nodes
- Clinical significance of micrometastases
- Treatment of the N0 neck: elective vs therapeutic
- Role of selective neck dissection in N1 disease
- Role of the sentinel node biopsy in N0 disease
- Role of chemoradiation in advanced neck disease
- Role of superselective neck dissection in the irradiated neck
- Role of neoadjuvant chemotherapy in neck disease
- Optimal treatment for suspected or established bilateral neck disease
- Management of the difficult, inoperable or untreatable neck
- Use of salvage surgery and re-irradiation in recurrent neck disease
- Quality of life following single and multimodality treatment for neck disease

The N0 neck

Historically, evaluation and treatment for the N0 neck has been one of the great dilemmas in head and neck surgery and its treatment today is still controversial. The problem that faces the head and neck oncologist is whether or not to treat the neck electively. The rationale for elective treatment to the N0 neck is the finding of high incidence of subclinical disease in elective RND specimens at the following subsites: the oral cavity, pharynx and supraglottic larynx. As shown in **Table 18.3**, the likelihood of there being involved nodes depends not only on the site of the primary disease but also on tumour size and histological differentiation. The controversy extends to when and how the N0 neck should be treated.

There are a number of treatment options for the N0 neck. These include the following:

- elective surgery
- elective radiotherapy
- adopting a policy of 'wait and see'
- elective neck investigation.

ELECTIVE NECK TREATMENT

Proponents of elective neck treatment maintain it prevents some cancer-related deaths because untreated neck disease can shed tumour into the vascular or lymphatic system and produce distant metastases. Unfortunately, only distant metastases which are seeded from developing nodal disease can be prevented by elective neck treatment and since spread can occur by other routes, or at inception of tumour, then quite clearly the argument for elective treatment is weakened. The evidence for elective neck treatment vs observation is discussed.

Oral cavity

Early stage oral cavity SCC is a common tumour for head and neck surgeons to encounter. There is no controversy; primary surgical management is the treatment of choice for the primary tumour.[75] There has always been great interest in the question of END for cT1-2 N0 oral cavity disease. The other common early stage tumour, glottic cancer, is rarely associated with cervical metastases and as such elective neck treatment is not considered. A recent large RCT has provided significant evidence in support of END for early oral cancer, and is the basis for the UK NICE guidelines recommending END or SNB for this disease.[58] In 2015, D'Cruz et al published outcomes for 500 patients in the New England Journal of Medicine.[76] Patients were randomized into END (level I–III with levels IV and V cleared for obvious or frozen section proven disease) or observation of the neck with therapeutic neck dissection (MRND) for regional recurrence. The primary outcome measure of 3-year overall survival was 80% for the END group and 68% for the therapeutic ND group (p = 0.01). Disease-free survival was also significantly different at 3 years: 70% vs 46%. Ultrasound was used to stage the neck disease pre-operatively. Suspicious disease was noted in less than 1%, indeterminate nodal disease in 7–8% and normal nodal structure found in approximately 92%, with similar results in both treatment groups. The rate of occult nodal disease in the END group was 30%. It could be argued that this is a reason for END in itself, but the authors rightly point out the disparity in ultrasound findings and occult disease. Improved pre-operative imaging could have the potential to correctly identify more patients with involved nodes. Nodal relapse in the therapeutic ND group was 45%, markedly higher than the 30% occult nodal rate in the END, and nodal relapse was more advanced and was associated with a higher rate of ENE in the therapeutic ND group. The authors reasonably suggest the benefit of END could be higher for a population of patients who may not be as rigorously followed up as in this trial. Subgroup analysis suggested the benefit of END may not exist for tumours with a depth of 3 mm or lower.

Prior to this major publication the evidence was less clear; four randomized prospective trials that have examined the issue of elective neck treatment are summarized in **Table 18.7**. Three compared surgical clearance of the neck,[77–79] and one elective neck irradiation,[80] with observation. Only one trial[78] favoured elective neck treatment. Careful 5-year follow-up detected no difference in survival between the two groups in the French trial,[77] but in the delayed treatment group, tumour problems or the patient's general condition precluded an operation when nodes were palpable in two patients, one of the objections to adopting a policy of

TABLE 18.7 Randomized controlled studies in management of the N0 neck

Study	Treatment arms	Number of patients	Positive necks	Disease-free survival	Follow-up (years)	Difference
Pointon and Gleave[80]	ENI	100	–	80%	2	NS
	OBS	105	–	65%		
Vandenbrouck et al[77]	END	39	19	NA	5	NS
	OBS	36	19	NA		
Kligerman et al[78]	END	34	7	72%	3	p = 0.04
	OBS	33	13	49%		
Fakih et al[79]	END	30	10	63%	1	NS
	OBS	40	23	52%		
D'Cruz et al[76]	END	245	81	70%	3	p < 0.001
	OBS	255	146	46%		

ENI = Elective neck irradiation; OBS = Observation; END = Elective neck dissection; NA = Not available; NS = Not significant.

'wait and see' for N0 disease. In addition, more than 50% of patients in both arms received radiation, which may have contributed to the lack of difference. Although the trial by Fakih et al[79] showed no difference in control rates between the arms, it must be noted that the results reported were 1-year survival data, despite median follow-up period of 20 months. Careful perusal shows that patients who underwent elective treatment did well in all comparisons, without achieving statistical significance. It must also be noted that all these studies are not adequately powered. Many retrospective studies and recently, other prospective non-randomized studies, including an evidence-based review,[32] that have looked at the treatment of the N0 neck in oral cavity carcinomas,[81–85] suggested improved outcome when the neck was electively treated. A recent large multicentre trial of 415 patients showed the sensitivity was 86%.[86] Patients with early stage T1-2N0 appeared to have no oncological compromise, despite only 94 of the 415 undergoing neck dissection. The evidence base pertaining to both END and SNB were assessed by the National Institute for Health and Care Excellence in 2016. Based on a systematic review and an original health economic model, the NICE guidelines made two explicit recommendations pertaining to the management of N0 disease in T1 and T2 oral cavity cancer:

- surgical management of the neck should be offered to all patients
- sentinel lymph node biopsy should be offered instead of END unless they need cervical access at the same time (for example, free-flap reconstruction).[58]

Other head and neck primary sites

A 'wait and watch' policy will result in 25–35% of patients presenting with overt disease, needing therapeutic neck treatment, although the results from the randomized trials quoted above suggest a much higher conversion rate. Control rates in this scenario approximate 30–50%, leading to around 15% of patients who have progressive disease. This figure is still higher than the widely accepted 5–7% failure rate where the neck is electively treated. In the absence of high-level evidence for a watch and wait policy, the general consensus in the literature is to err on the side of caution and it is prudent to treat the neck when the risk of occult spread is more than 15–20%. This figure is derived from a rather simplistic decision analysis model performed in the 1990s[87] which showed that at a threshold occult metastatic rate of 20%, the morbidity of treatment is offset by its benefit, and is widely accepted. It must be noted that the surgical treatment considered in the model was radical neck dissection (RND). Many surgeons and oncologists would perform elective neck treatment for lesser probability (5–15%) of occult metastases.[88] The Scottish Intercollegiate Guidelines Network and UK National Multidisciplinary Guidelines also espouse elective treatment of the neck in this scenario.[67, 89]

Currently both END and irradiation are viewed as prophylactic treatments. If one recognizes the significance of occult neck disease as a marker of the ability of any individual tumour to metastasize, thereby providing a significant prognostic indicator of eventual distant metastases and the possible need for systemic adjuvant chemotherapy, then only surgery can provide the histological data to give this information.

BOX 18.6 Indications for elective neck treatment

- 15–20% chance of subclinical neck disease
- Vigilant follow-up not possible
- Clinical evaluation of the neck is difficult
- Access to the neck for reconstruction

CHOICE OF TREATMENT MODALITY FOR THE N0 NECK

Although there are no prospective trials, retrospective data from studies with large numbers suggest that END and irradiation are equally effective in controlling subclinical disease.[90] The choice of treatment modality is dictated by numerous factors including physician and patient choices, QOL issues and how the primary site is managed. When the primary tumour is being treated with radiotherapy, then elective treatment should be with radiotherapy to at least the first echelon lymph nodes (or the whole neck) and where midline extension occurs, treatment should be bilateral. If the primary tumour is being treated with interstitial brachytherapy then the neck may be treated electively with either surgery or irradiation. When the primary tumour is treated with surgery, then elective neck surgery should be carried out since it provides further information for clinical staging, lymph nodes in the area are cleared to give access to vessels for reconstructive purposes, local recurrence rates may be reduced and survival enhanced. The appropriate levels to be dissected out in an SND are based on the site of the primary tumour and this is discussed later. **Figure 18.6** summarizes our recommendations for management of the ipsilateral N0 neck.

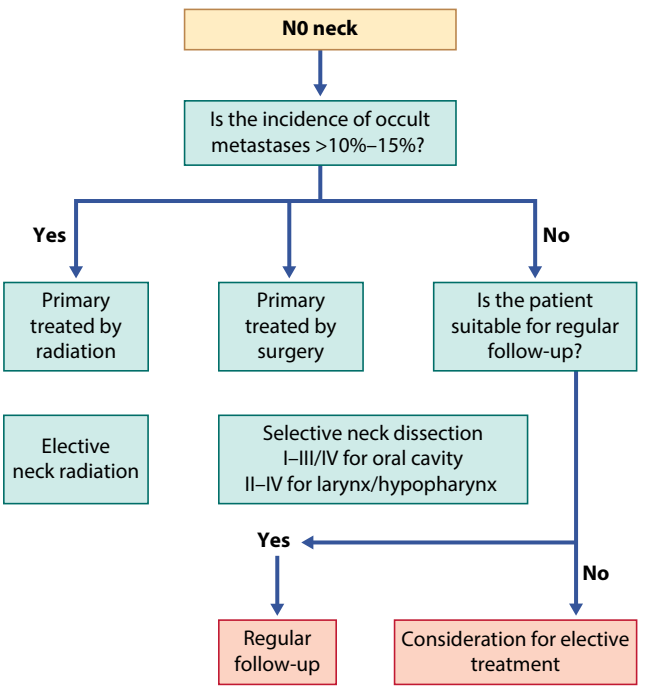


Figure 18.6 Algorithm for management of the N0 neck.

Elective surgery

The pros and cons of elective neck surgery are set out in **Box 18.7** and **Box 18.8** below.

The concept of therapeutic equivalence of SND and comprehensive neck dissection for elective treatment of the neck is widely accepted[91] and based on prospective studies, there is little justification for a comprehensive neck dissection in this setting.[92, 93] Levels II–IV need to be cleared for laryngeal and hypopharyngeal cancer.[93] For patients with oral cavity cancer, SND of at least levels I–III should be carried out, with the addition of level IV for tongue cancers.[92] Levels II–IV are recommended for oropharyngeal cancers.[94] There appears to be little advantage in dissecting level V for any of the mucosal primaries electively.[95–97] Excellent local control rates can be obtained with SND, with recurrence rates around 5% with the primary controlled.

Current work focuses on selecting the levels that need to be dissected in the elective setting. For example, clearance of level IIb during SND involves dissection in a relatively narrow field and significant retraction of the sternomastoid muscle is needed. It is likely that the accessory nerve can be subjected to traction injury and segmental devascularization, causing shoulder dysfunction. Prospective studies[98] have shown that SND causes a small but significant impairment to the shoulder function. The incidence of isolated metastases in this level is very low at 0.3%.[99] Prospective studies have shown little oncological benefit in clearing this level in laryngeal cancer as the occult metastatic rate is low at 0.4%,[99, 100] but higher incidence rates are seen in oral cavity (3.9%) and oropharyngeal (5.2%) cancer. Whether preservation of level IIb necessarily leads to improved shoulder outcomes needs to be verified in prospective studies.

END can undoubtedly serve to pathologically stage the neck, and offer a subsequent indicator of the risk of systemic disease. Local neck and distant metastases are manifestations of the same process and represent the ability of the tumour to metastasize in an individual host.

BOX 18.7 Arguments for elective neck surgery

- The high incidence of occult metastatic disease
- Selective neck dissection has a low morbidity and mortality
- Routine clinical follow-up will not detect the earliest conversion of the neck from N0 to N1 in all patients
- Untreated neck metastases can increase the incidence of distant metastases
- The control rate for neck dissection is decreased if gland enlargement occurs or multiple nodes appear
- Elective neck surgery can be performed during primary surgery
- Anatomical reasons preclude proper neck examination
- Patient compliance for follow-up cannot be assured
- The pathological neck node status from pathology can be used to prognosticate
- The presence of multiple occult metastases will dictate adjuvant irradiation

BOX 18.8 Arguments against elective neck surgery

- Control rates are no lower when a 'wait and see' policy is followed and therapeutic neck dissection is performed
- Careful clinical follow-up combined with imaging has the potential to detect early conversion from N0 to N1
- Radiation is as effective as neck dissection for non-palpable disease
- Elective neck dissection results in a large number of unnecessary surgical procedures associated with inevitable morbidity
- Elective neck dissection removes the barrier to the spread of disease and may have a detrimental immunological effect
- Elective neck dissection can cause a scarred, hypoxic field that can reduce radiation kill.

Elective neck irradiation

Retrospective evidence suggests that external beam radiation of approximately 40–50 Gy to the clinically N0 neck will control occult metastases in up to 90–95% of cases.[101, 102] In addition to the prospective study identified,[80] other retrospective studies evaluating its role in the treatment of patients with SCC of the oral cavity and tongue[103] did show that elective neck irradiation improves locoregional control and may prolong survival in some cases. This is based on the observed rate of conversion of N0 to N+ necks after elective neck irradiation (3–15%) and the expected rate of appearance of nodes when the neck is observed, based on a 20–40% histological incidence of occult neck disease. However, this assumes that all occult lymph node cancer deposits are clinically significant and evidence from other studies suggests this is not necessarily the case.

Elective neck investigation

Another option in the N0 neck is to consider elective neck investigation. Could a radiological investigation such as CT, MRI or ultrasound demonstrate malignant cervical lymphadenopathy at the subclinical stage and if so, could a treatment plan be adopted based on these scans?

It would seem that many of the arguments levelled against neck dissection could be levelled against elective neck imaging.[104] If false positive results are inevitable in the presence of inflammatory neck nodes and false negatives do occur, then imaging could play no role in the routine evaluation of the N0 neck. Treatment should be based upon the understanding of the natural history in question and currently it is probably cheaper and as effective to offer elective treatment to those high-risk patients who need it and 'wait and see' in the others. This will avoid large numbers of unnecessary CT scans and subsequent inevitable inappropriate surgery. It is perfectly reasonable to adopt a policy of 'wait and see' in low-risk necks, i.e. carcinoma of the glottis or the gingiva, but for those that are high risk, waiting for the neck to develop from N0 to N1 may have a detrimental effect on the patient should not to be recommended in current clinical practice.

One recent study[105] evaluated the outcome of observing the clinically N0 neck in high-risk patients (mainly oral carcinoma) using ultrasound-guided FNAC (US-FNAC) for follow-up after transoral excision. Patients were followed up for between 1 and 4 years using palpation and US-FNAC. The high salvage rate (71%) was attributed to a strict follow-up policy using US-FNAC and concluded that a policy of 'wait and see' was justified. Although the authors did not identify the T staging of the primary tumour, some neck failures might have been prevented by elective treatment rather than elective investigation.[106, 107]

THE CONTRALATERAL N0 NECK

In the setting of a unilateral primary and ipsilateral metastases, traditional data suggest that the contralateral neck has a very high incidence of occult metastases, between 30% and 70%, especially in supraglottic,[108–110] hypopharyngeal[111–114] and oropharyngeal tumours.[94, 115] In the presence of advanced primaries at high risk of occult spread, contralateral neck treatment is warranted. Recurrence in the untreated contralateral neck has been shown to be the commonest cause of failure in supraglottic cancer, with improved local control and 2-year survival when dissected.[116–119] There is no benefit in clearing level IIb in the contralateral N0 neck.[99, 120]

The management of the contralateral cN0 neck has again gained prominence as a discussion point, with the rise in popularity and interest in transoral surgical techniques in managing oropharyngeal carcinoma. This technique particularly lends itself to the common scenario observed in HPV positive OPSCC; small-volume lateralized primary tumours, with ipsilateral nodal disease. With this clinical presentation of disease, the most common treatment modality would be primary chemoradiotherapy. Radical treatment dose would be given to the primary site and ipsilateral neck, with prophylactic dose (commonly 54 Gy) to the contralateral neck. The authors offer transoral robotic surgery for this disease and have routinely performed a contralateral staging SND as part of the surgery. They have observed a lower than expected rate of contralateral occult nodal disease in this population. Only 5 out of 60 patients were found to have occult nodal disease, upstaging them to N2c and altering their adjuvant radiotherapy dosage (currently unpublished data). Adjuvant radiotherapy to the contralateral neck was avoided in 55/60 patients. Three of the five patients had HPV negative disease, and it would appear that the risk of occult contralateral nodal disease is higher in the HPV-negative setting. It must be stressed, that the patients treated in this way had lateralized OPSCC, more than 1 cm lateral to the midline of the tongue base, and were highly selected. Nevertheless, these data would suggest that the traditional risk of contralateral occult disease in OPSCC may not be so relevant to this common clinical pattern of disease. Head and neck clinicians should consider how reduced morbidity of treatment can be achieved by avoiding radical treatment to the contralateral neck. Options could consider a staging SND as described, sentinel lymph node biopsy, or serial monitoring with US.

The N+ neck

Management of the N+ neck is continuously evolving as more and more data are accrued. Traditionally, advanced neck disease has needed a combination of surgery and RT for control of disease. The treatment offered to the neck often depends on the modality used to treat the primary site, as seen in the suggested algorithms for patients undergoing primary chemoradiation (**Figure 18.7**) and primary surgery (**Figure 18.8**).

SINGLE PALPABLE METASTASIS IN THE IPSILATERAL NECK LESS THAN 3 CM IN DIAMETER (N1)

Similar to the N0 neck, the choice of modality is usually dictated by the treatment to the primary site. Where the primary is treated with irradiation, the neck is covered as well in the field. ENE is less common in this stage and since the survival figures are good, conservation neck surgery is feasible. In palpable neck disease, traditional teaching is for all five levels to be dissected to clear occult disease; however, it is rare for level I to be involved in primary sites other than the oral cavity. In most cases, the accessory nerve can be preserved, enabling MRND. Based on assessment of the best available evidence,[32] there is no evidence that RND achieves better survival figures than MRND.

It is widely accepted that single-treatment modality gives good control rates for N1 neck disease,[121] although review of large databases suggest that there may be survival advantage in offering adjuvant RT following surgery even for N1 necks.[122] As approximately 50% of clinically N1 necks are upstaged after pathological assessment, many patients subsequently require post-operative radiation. Single modality usually suffices to control N1 neck disease, with both radiation and surgery having equivalent control rates.

Selective neck dissection in the N1 neck as primary treatment

The role of SND in the N+ neck is controversial. There is no doubt that the morbidity of a neck dissection arises largely from level V dissection and there is a low incidence of nodal involvement at this level unless two or more levels (especially level IV) are involved.[32, 123] There is a clear pathological basis for SND in N1 and N2a disease. The proponents for a 'less than five level' neck dissection for N1 disease argue that the distribution of metastases within first echelon lymph nodes in non-palpable disease can be applied to early palpable disease. However, this sort of surgery requires considerable expertise and is not recommended for the trainee surgeon. With experience, a 'conservative MRND' can be performed for N1–N2b to include the entire levels II–IV, with dissection under sternocleidomastoid (SCM) to pull through a significant volume of level V, and to encompass any level IB nodes superficial to the submandibular gland. Careful preservation of the marginal mandibular nerve, the accessory nerve, and

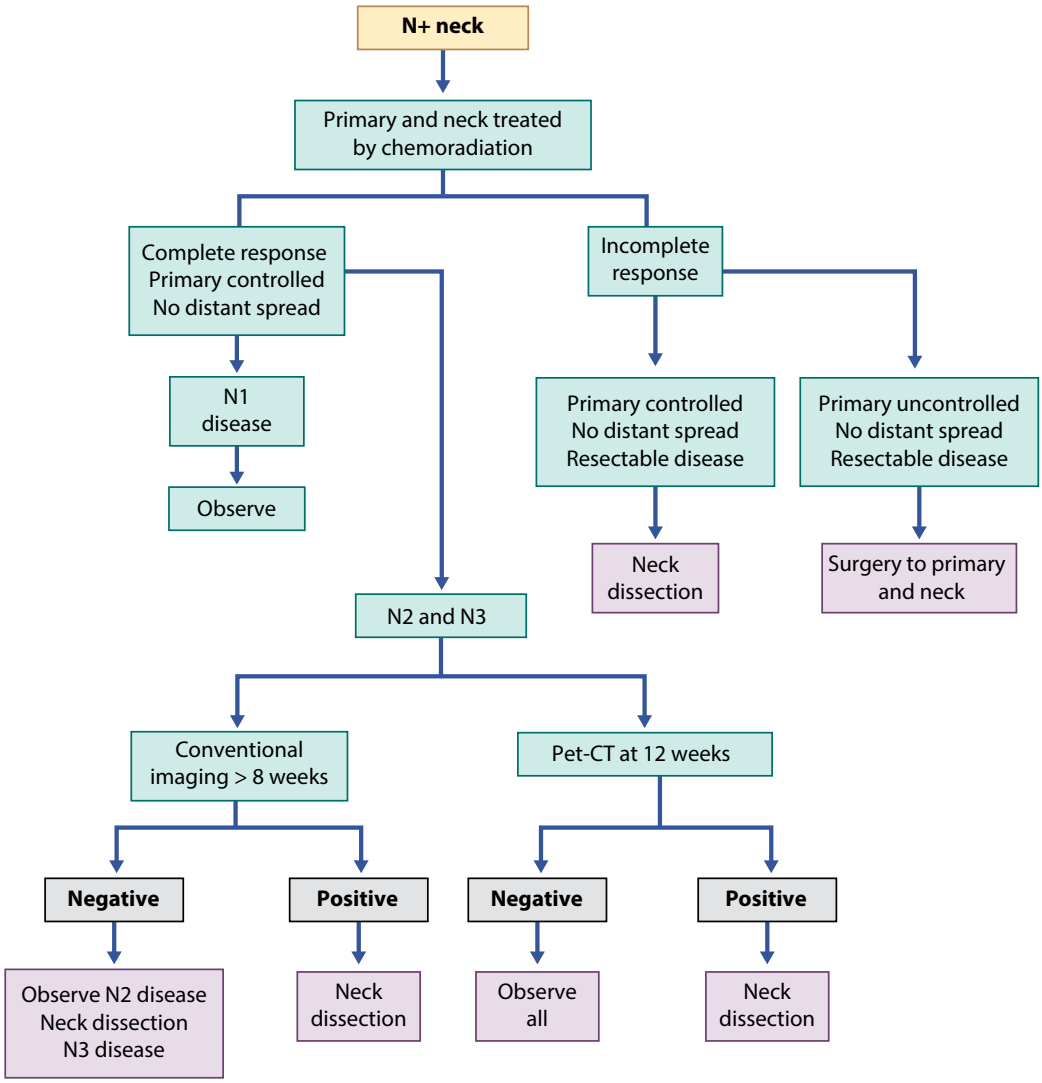


Figure 18.7 Algorithm for management of the N+ neck when chemoradiation is the primary modality.

importantly the small cervical plexus branch that joins to the accessory nerve lateral to the posterior border of the SCM should be performed if considering a conservative approach such as this. Whilst unproven, this sort of conservative approach over a traditional MRND for tumours with predictable nodal metastatic spread may be reasonable, especially if adjuvant therapy can be anticipated to the neck.

Byers et al[124] looked at the outcomes of SNDs in 517 patients. They found that recurrence rates in patients with N1 disease were 5.6% and 35.6% with and without post-operative radiation respectively. Other retrospective studies also vouch for the efficacy of the SND alone in the N1 neck, as long as adjuvant treatment is provided if the disease is upstaged following surgery or other adverse factors exist.[125–130]

Prospective studies are yet to be performed to evaluate this further, but on the basis of a large body of retrospective evidence, it can be concluded that SND may be sufficient treatment for N1 disease confirmed on pathological examination. We recommend that where there is doubt regarding the spread and extent of disease, it is better to perform a comprehensive procedure the first time around.

Concurrent chemoradiation therapy for the N1 neck

Concurrent chemoradiation (given for treating the primary site) offers excellent control rates.[131, 132] No treatment is required in the event of a complete response, but partial responders merit a neck dissection. The type of neck dissection for partial responders is discussed below.

IPSILATERAL LARGE NODE (>3 CM TO 6 CM; N2A) OR MULTIPLE UNILATERAL NODES (N2B)

The treatment depends on the management of the primary and if deemed operable, the neck should be treated with comprehensive neck dissection. If possible, an MRND sparing the accessory nerve gives equivalent control rates to a RND.[32, 133, 134] Larger neck nodes are at a greater risk of ENE, and following primary surgery

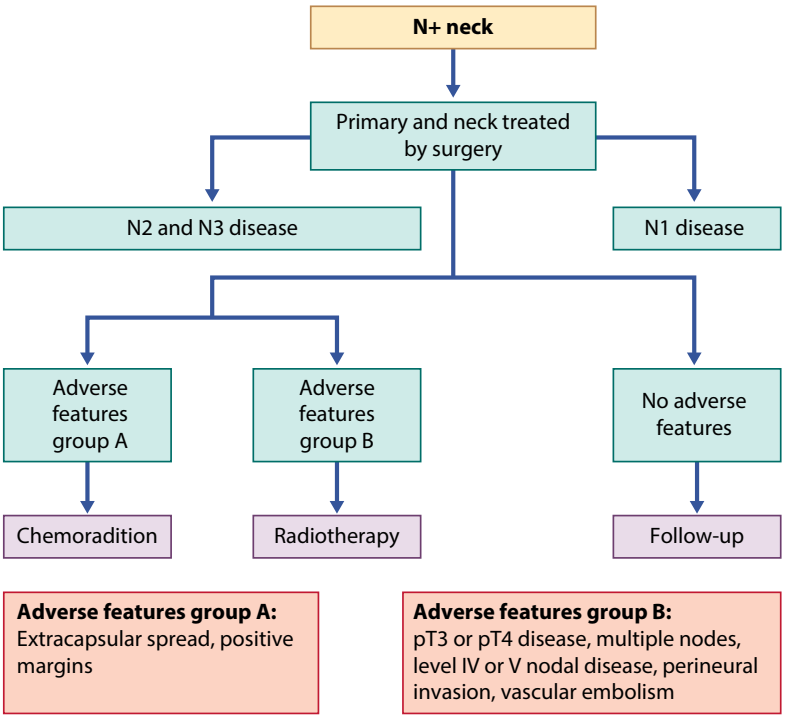


Figure 18.8 Algorithm for management of the N+ neck when surgery is the primary modality.

are best treated by post-operative adjuvant treatment. Analysis of large databases show that adjuvant RT confers a 10% absolute increase in 5-year cancer-specific survival and overall survival for patients with lymph node-positive HNSCC compared with surgery alone.[135] Recent randomized controlled trials performed in Europe and the United States confirm the clear benefit provided by adjuvant chemoradiation in the presence of ENE.[33, 136, 137] If the primary site is being irradiated, and incomplete response ensues, a neck dissection is warranted. Patients who achieve a complete response do not need surgical salvage and the rationale behind this is discussed in more detail in the section on the chemoradiated neck. This group represents advanced disease and retrospective and prospective studies clearly show that if primary surgery is performed, post-operative adjuvant therapy is required to achieve good regional control rates.

BILATERAL AND CONTRALATERAL NODES (N2C)

Patients with bilateral neck nodes are uncommon and occur overall in about 5% of head and neck cancers. As discussed above, N2c disease is more common if the primary sites involved are the tongue base, supraglottic larynx and hypopharynx. Conventionally, the presence of bilateral neck disease was thought to be a grave prognostic sign and this was indicated historically in its staging. However, subsequent careful pathological studies have shown that, in certain instances, this is not so. The prognosis is determined more by the size, number of nodes and by the presence or absence of ENE within the neck rather than by pure laterality. This is particularly true for the supraglottic larynx and in those patients where the bilateral nodes do not feature massive and multiple nodes, treatment can be worthwhile using conventional surgery[138] or chemoradiation. Conservation neck surgery may be possible on the less involved side and post-operative radiotherapy will usually be administered.[1, 139] The decision to treat will often be helped by the location and size of the primary site. Laryngeal tumours with extralaryngeal spread and bilateral nodes are often eminently treatable with laryngectomy and appropriate neck dissection. Patients with bilateral nodes when one side is fixed are usually incurable.

BOX 18.9 Indications for postoperative adjuvant treatment

- Extracapsular spread
- Two or more positive nodes
- N2–3 stages
- Residual disease

MASSIVE NODES (GREATER THAN 6 CM; N3)

The presence of massive nodes is again an uncommon event occurring in patients with head and neck cancer. Only 5% of all patients will present with N3 neck disease in the UK. It is important to realize that many nodes that do reach 6 cm in size are often fixed to the skin and/or underlying structures. The decision whether or not to operate depends upon the stage and site of the primary site, presence or absence of fixation, what the node is fixed to, the experience of the surgeon and the needs of

the patient. The incidence of true fixation of neck masses is often difficult to determine from the literature and varies from series to series with figures from 23%[140] going up to 30%.[141] Fixation to the mandible, sternomastoid muscle or muscles in the midline may not represent as much of a problem as fixation to the brachial plexus or carotid artery. These patients are at high risk of distant metastases and may present a special group where PET-CT scans may be warranted to fully evaluate this problem. Long-term control rates are poor and the benefit of treatment must be carefully weighed against the morbidity caused by it, including the chances of control at the primary site. In many patients, palliation will be the best option. Combined modality therapy leads to better control rates.[142]

THE DIFFICULT NECK

The scenarios that present a difficult neck are set out in **Box 18.10.**

Careful clinical assessment with mandatory radiological imaging will help to assess operability and some of these patients will be helped by extended RND. Fixation to the skull base and brachial plexus is certainly a contraindication to surgical treatment, but fixation to the skin may be treated by wide resection and flap repair.

BOX 18.10 The difficult neck

- Difficult to assess
- Short stocky neck
- Retropharyngeal nodes
- Recurrent disease
- Involvement of vital structures

Carotid invasion: In current day practice, most tumours that present with clinical and radiological signs of carotid invasion are likely to be radiorecurrent.[143] Indications for considering carotid resection include clinical evidence of fixation of the tumour to the carotid, invasion confirmed on imaging, and encroachment of tumour which encompasses more than 270 degrees of the vessel wall. Luminal invasion is rare and pathological evidence of invasion, limited to the adventitia, is seen in only 40–50% of resected arteries.[144–146]

The plan to resect the carotid should always be a pre-operative decision and almost never should a situation arise where this is contemplated for the first time peri-operatively. Pre-operative work up is essential to plan the resection. Balloon occlusion of the artery with single photon emission computer tomography (SPECT) is performed to prognosticate the possibility of neurological deficit following resection. If the test shows adequate cross-flow and does not cause symptoms, there is a lesser need to shunt the artery during resection. If the cross-flow is inadequate, the internal carotid artery should be shunted for the duration of the resection. In all cases, we recommend reconstruction of the artery using an appropriate graft to reduce chances of neurological complications. Most studies report using the saphenous vein graft (**Figure 18.9**). Intra-operative ligation without reconstruction is fraught with a high risk of complications owing to the haemodynamic instability that can occur. This is likely even in those patients who demonstrate good cross-flow and a stump pressure of more than 70 mmHg.

A high-operative morbidity (33% hemiplegia) and mortality (12%) has been quoted from work done in the 1980s, but recent studies where resection and reconstruction of the carotid artery is performed have shown much lower figures.[147, 148] A review of 148 patients published between

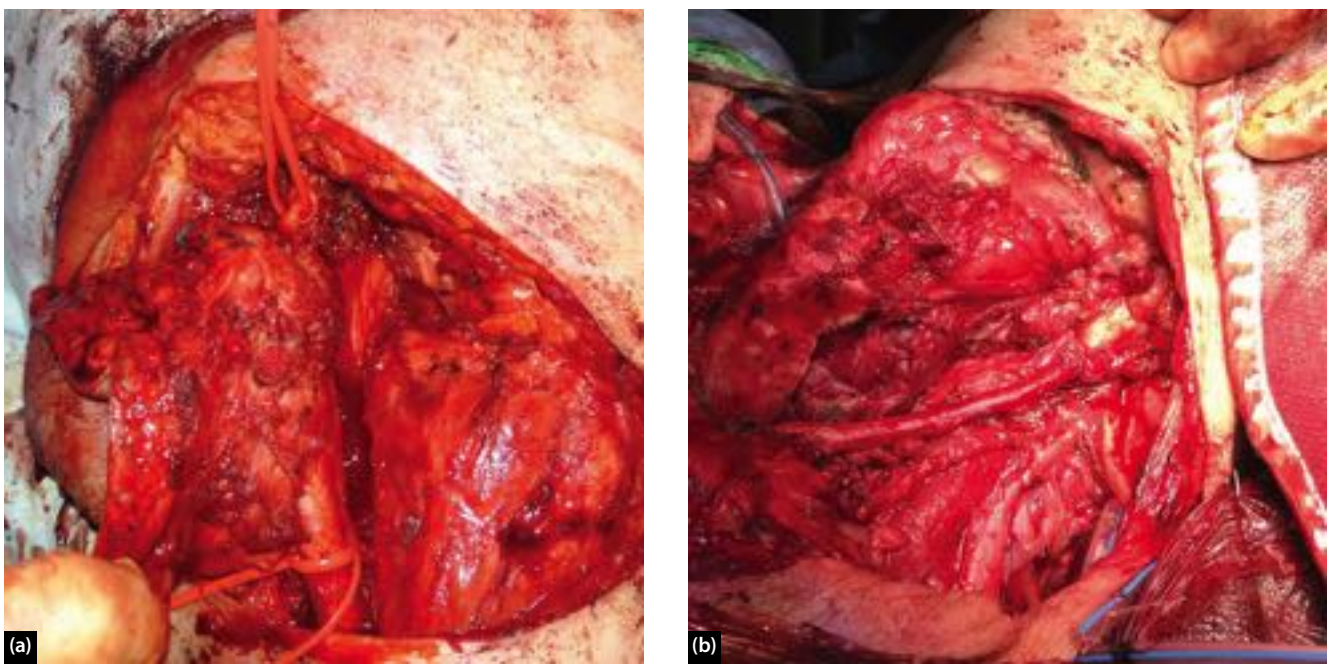


Figure 18.9 (a) A carotid resection in progress. **(b)** The artery has been replaced by a saphenous vein graft.

1987 and 1998 demonstrated combined major neurological morbidity and mortality rates of 10%.[149]

It is well recognized that in untreated patients with HNSCC, the carotid artery may not often be involved even when massive disease is present in the neck and that neck dissection may be possible. However, in the presence of radiological evidence of invasion, surgeons have traditionally opted to resect the carotid. In a review of 90 patients with documented radiological evidence of invasion, Ozer et al[143] showed that this need not be the case and in over 70% of cases dissection of the carotid is feasible and the tumour can be removed without recourse to carotid resection.

Traditionally, carotid resections were regarded to be unrewarding in HNSCC from the point of either achieving locoregional control or improving survival. A review of the literature in 1992[146] reported a 2-year survival rate of 22% following carotid artery resection. This study has been criticised for failing to identify those patients who had been treated previously, for not distinguishing between the treatment of isolated neck recurrence compared with recurrent disease at the primary site as well as the neck. Aggressive disease in a radiated neck may be associated with residual tumour following resection and there is high risk of systemic disease; thus resection of the carotid artery was thought not to affect the natural history of the disease. Papers published in the last decade suggest that poor outcomes are especially seen in patients who have had previous radiation. Those patients with demonstrable carotid invasion who undergo primary surgical resection with or without reconstruction of the carotid may have a much superior outcome, with control rates between 30% and 50% at 5 years.[143, 148–150] There may be a subgroup of patients who present with bulky neck disease and carotid invasion, who are best managed by primary resection and reconstruction with adjuvant radiation.

This is often a difficult scenario and decision should be made after careful consideration of the morbidity and mortality of the procedure, patient expectations and the expertise of the treating team.

THE IRRADIATED N0 NECK WITH RECURRENCE AT THE PRIMARY SITE

Very few studies[151–153] have addressed this question, but they have arrived at the same conclusion. There appears to be no increased risk of occult metastases in this setting and SND is oncologically adequate to clear the neck.

MANAGEMENT OF THE NECK FOLLOWING PRIMARY CHEMORADIATION

Organ preservation protocols have established a firm place in head and neck oncological practice. Using concurrent chemoradiation, they aim to avoid resection and thus sacrifice of the organ where the primary is sited, even for advanced primaries. The following discussion assumes that the primary site has been controlled in all instances.

Although histological evidence of nodal residual disease has been demonstrated in only 40–45% of partial responders, few centres would argue against salvage neck surgery in this setting. The extent of the procedure remains a point of controversy as it is rare to find viable disease in levels that are clinically negative.[154, 155]

Until recently, there had been no universal agreement on how the advanced neck should be dealt with following chemoradiation when a complete response is obtained. Pathological examination of neck dissection specimens has revealed residual disease in up to 25% of patients who have achieved a complete response,[131, 156] but the presence of tumour cells does not indicate that they are viable. Some studies show a clear benefit in regional control when planned neck dissection is undertaken even in the presence of complete response.[131] However, prospective studies of patients with a complete response as assessed radiologically have mature long-term clinical follow-up and show very low regional relapse rates that are comparable to the regional failure rates reported in planned neck dissections series.

Several studies have demonstrated the high sensitivity and negative predictive value of PET-CT imaging to assess residual disease in complete,[68, 157, 158] and partial responders,[68, 69] performed at least 8 weeks after treatment. Earlier scanning increases false positive results and is not recommended. A meta-analysis showed that highest sensitivity results are seen in studies performing PET-CT 10 weeks after treatment.[70] This has been used as a decision-making tool in recommending neck dissection after chemoradiation, with surgery being limited to cases where there is evidence of uptake (**Figure 18.10**). The literature has slowly shifted towards non-surgical management for patients who experience a complete response[159–161] with some international groups endorsing this in consensus statements.[162] Emerging data suggest some role for an SND or even a lesser procedure (superselective neck dissection) in this setting when a complete response is obtained.[163–166]

In 2016, Mehanna et al published the primary outcome results of the PET-NECK trial;[167] 564 patients were randomized to have either an END following CRT, or surveillance of the neck with PET-CT 12 weeks following completion of CRT. Patients were included with N2 or N3 disease at presentation, with primary nasopharyngeal disease excluded from entry to the trial. Patients in the PET-CT surveillance arm underwent ND for residual disease. The trial demonstrated equivalent overall survival between the groups at two years (85% in the surveillance group and 82% in the END group), with fewer neck dissections in the surveillance group (54 vs 221) and a cost saving of approximately £1500 ($2200) per patient undergoing PET-CT surveillance.

The authors make a very important comment following their analysis in suggesting it would be reasonable to monitor residual enlarged neck nodes following CRT, if they are PET-CT negative, in HPV-positive disease. They suggest that in HPV-negative disease, equivocal but enlarged nodal disease on PET CT at 12 weeks should undergo neck dissection (**Figure 18.11**).

In light of this recent level 1 evidence, we recommend that necks staged N2 and N3 undergo PET-CT imaging at 12 weeks (the TNM 8th edition clinical staging[5, 15] does

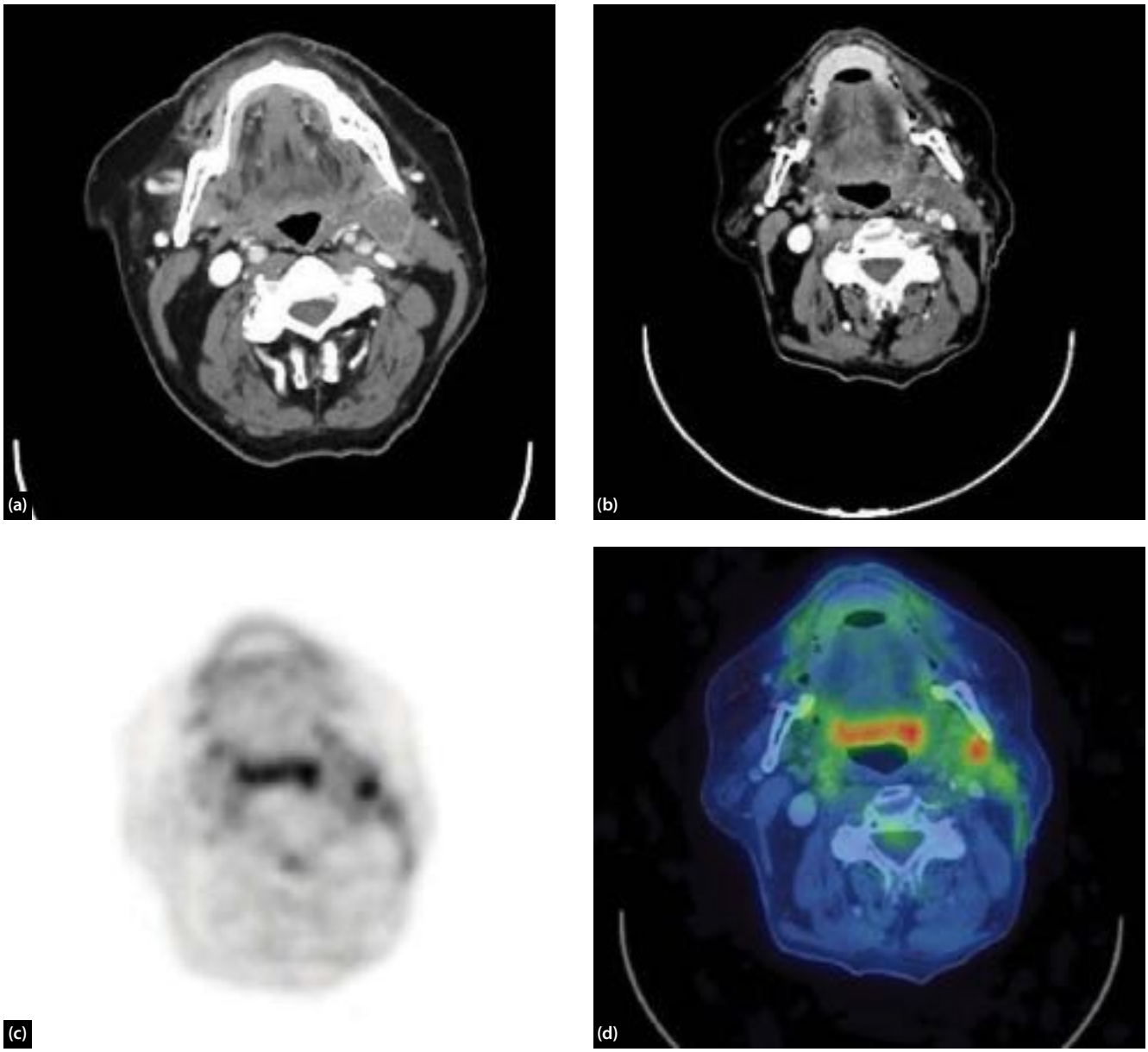


Figure 18.10 **(a)** The pre-treatment CT scan demonstrating a cystic metastasis. Post-treatment CT component of PET-CT scan **(b)** at 14 weeks shows residual nodal swelling that is avid on the PET **(c)** and the fused PET-CT images **(d)**, indicative of residual disease. This patient underwent a neck dissection that confirmed residual disease (Image courtesy Dr Tamir Ali, Newcastle upon Tyne Hospitals.

not allow distinction of a single <3 cm HPV positive node – hence all N1-3 disease should undergo PET-CT imaging at 12 weeks). Complete responders can be observed. Where there is no access to PET-CT, conventional imaging should be performed at 12 weeks. Salvage neck dissection should be considered for residual enlarged nodes.

The PET-NECK trial data has now clarified that complete neck responders can be safely observed.[167] Patients with equivocal PET-CT uptake will be considered partial responders and should be offered neck dissection. Of course, not all of these patients will have pathologically viable tumour. It is the authors' experience that many equivocal neck findings on PET-CT will ultimately turn out to be negative on pathological examination. As discussed above, there has been a move towards SND or even super-SND following CRT, with the recognition that neck morbidity is reduced with less levels dissected. For equivocal responders on PET-CT or more concerning residual findings on PET-CT, what should the extent of neck dissection be? The evidence for this question predates the emergence of PET-CT scanning as a reasonable predicator of response, and comes from series in which many more patients more routinely offered post-CRT neck dissection. However, the series of 177 post-CRT neck dissections described by Robbins et al[166] offers convincing data to support a limited SND in patients with residual disease. Having utilized CT imaging post-CRT, of the 54 patients with pathological residual disease, only two

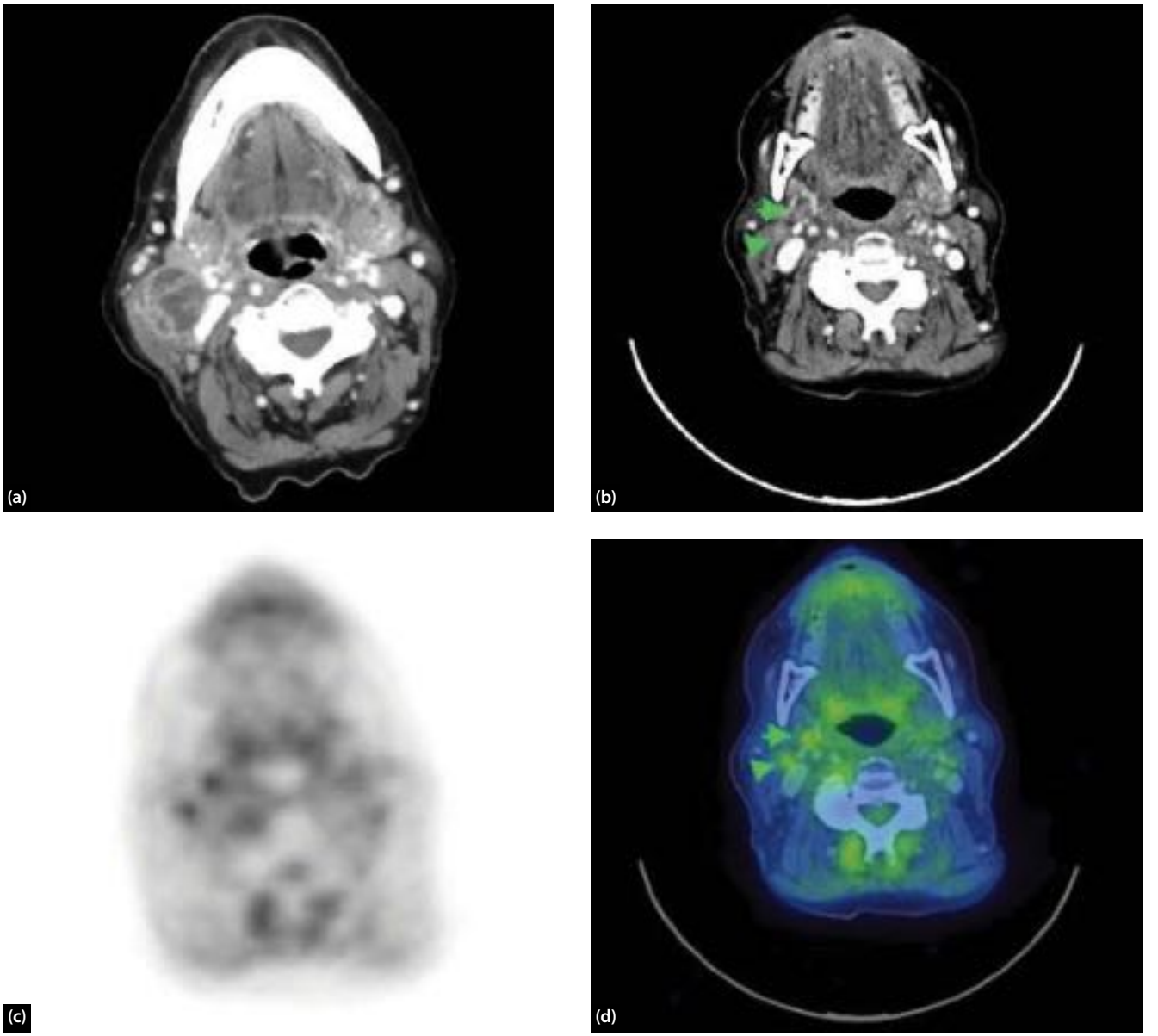


Figure 18.11 **(a)** The pre-treatment CT scan demonstrating a metastatic node in the right side of the neck. Post-treatment CT component of PET-CT scan **(b)** at 12 weeks shows small residual nodal swelling (green arrowheads). The PET **(c)** and the fused PET-CT **(d)** images show equivocal standard uptake values. The decision was made to follow up this patient without surgical intervention (Image courtesy Dr Tamir Ali, Newcastle upon Tyne Hospitals).

patients had disease beyond the clinically predicted single neck level. Only one of these patients would not have had their disease appropriately removed with a limited SND.

The timing of neck dissection after chemoradiation has not been systematically assessed. Nodes tend to regress at variable rates after irradiation. Bataini[168] suggested an interval of at least 8 weeks for nodes 6 cm and less and longer periods (16–20 weeks) for those more than 6 cm. Pathological studies have shown that metastatic disease can be demonstrated in 30% of necks after chemoradiation despite clinical and radiological evidence of complete response, but this does not correlate with the clinical outcome of low (5%) recurrence.[169–172] This may be due to non-viable cells and the fact that many of the neck dissections were done 4–6 weeks after treatment. The neck is best assessed between 8 and 12 weeks as discussed above and salvage offered following this. Surgical procedures on necks after chemoradiation necks are associated with more complications.

NECK DISEASE ASSOCIATED WITH HUMAN PAPILLOMAVIRUS

Enormous research interest lies in head and neck cancer caused by HPV, as it continues to increase in incidence in many parts of the world and as it represents a distinct type of head and neck cancer. The overwhelming majority of HPV-induced cancer is found in the oropharynx.

Most patients who present with HPV-induced OPSCC, do so with advanced disease, often with nodal metastases. Currently, there is no recommendation that HPV-induced OPSCC should be treated any differently to all other non-HPV-induced head and neck cancer with nodal disease. The recognition that patients with HPV-induced OPSCC have better survival outcomes has led some to question whether their management can be better tailored to reduce treatment-related morbidity, whilst maintaining treatment efficacy. As many patients with HPV-induced OPSCC present with small volume, discrete primary tumours, lacking field cancerization change, in combination with nodal metastases, there has been a growing interest in offering transoral surgery to these patients. However, the major stumbling block in offering transoral surgery over primary non-surgical management is the debate around management of the neck disease. Patients with HPV-induced OPSCC have a high rate of ENE within nodal metastases. Based on the current level 1 evidence, any patient with ENE found in their neck dissection, completed as part of their primary surgical management, should be offered adjuvant chemoradiotherpy.[33] There are arguments against such aggressive adjuvant therapy for this particular group of patients: whilst the evidence in support of adjuvant chemoradiotherapy is incontrovertible for ENE, especially for OPSCC, the data on which the conclusions are drawn are somewhat dated and may pre-date the rapid rise in HPV-induced OPSCC. As such, it is possible that only a minority of patients in the two RCTs had HPV-induced OPSCC.[136, 137] We have no data to demonstrate what the survival advantage may be for patients with HPV disease who receive chemotherapy in addition to adjuvant radiotherapy. A large multicentre study assessing the outcomes of transoral laser surgery in 204 patients with advanced stage OPSCC demonstrated no survival difference using multivariate analysis in those patients with or without ENE.[173] In this series, 74% had HPV-induced disease, 63% had ENE and only 16% received adjuvant chemoradiotherapy. A further study of patients undergoing primary surgery demonstrated that whilst ENE was an independent factor in disease-specific survival in oral cavity cancer, ENE did not affect disease specific survival in the 133 OPSCC patients (57% p16 positive). A phase II randomized trial is currently recruiting in the UK to assess the functional outcomes of a reduction in adjuvant therapy, prior to the proposed phase III study to assess survival, for patients with HPV-positive OPSCC treated with primary transoral surgery and neck dissection. Within this trial, patients with ENE are randomized to either adjuvant radiotherapy alone or adjuvant chemoradiotherapy.[174] A similar randomized trial is ongoing in the USA.[175]

TREATMENT OUTCOMES

Regional control rate in the pN0 neck is consistently good with failure rates between 3% and 7%, largely irrespective of the modality of treatment. Recurrence rates following therapeutic neck treatment will vary depending on other factors such as control of the primary site, ENE and the stage. Where the primary tumour has been controlled, overall recurrence rates range from approximately 10% for N1 disease without ENE, 20–30% for N2 disease and up to 85% for N3 disease although some small series quote better results,[1, 142, 176] In many cases of N3 disease, the primary site remains uncontrolled.[8]

Recurrent neck disease

Recurrence in the neck following previous treatment carries a poor prognosis. However, there will be instances in which further treatment is appropriate to control the disease and relieve symptoms, accepting the ultimate lack of curative intent. In accordance with the natural history of HNSCC, the majority of recurrences occur within the first 2 years of treatment. Various considerations including status of the primary site, extent and nature of recurrence, distant metastases and comorbidity dictate the treatment. Thus, a comprehensive investigation of the general status of the patient and distant metastases should be performed. Many of these masses will be fixed to vital structures which will negate extensive surgery. In patients who present with unresectable disease, re-irradiation with or without chemotherapy should be considered, particularly in those who present more than 2 years since their previous treatment. Evidence of partial repair of RT-induced spinal cord subclinical damage and newer RT delivery techniques (IMRT, tomotherapy, protons) that allow better sparing of neurological structures at risk make this a realistic option in a larger number of patients. If surgery is possible, wide resections should be undertaken and post-operative re-irradiation considered. About one-third of patients will be untreatable at presentation.

RECURRENCE IN THE IPSILATERAL UNTREATED NECK

In this situation, neck dissection is usually the preferred treatment with or without post-operative radiotherapy based on the histology. This group of patients do relatively well and local control rates between 50% and 60% can be expected. Alternatively, irradiation with surgical salvage may be used along the principles described above.

RECURRENCE IN THE CONTRALATERAL UNTREATED NECK

A proportion of patients in whom metastases occur on the untreated contralateral side of the neck sometime after a dissection on the other side may be salvaged, provided there is no recurrence at the primary site. In a retrospective review of 2550 patients, Spector et al[177] concluded that delayed metastases occurring on the untreated contralateral side were associated with significantly better salvage rates (42.5%) than the ipsilateral previously treated neck (17%).

RECURRENCE IN THE PREVIOUSLY TREATED NECK

Radical radiotherapy can be used if there is recurrent disease in the neck developing after previous surgery, which was not followed by post-operative irradiation. Owing to scarring from previous treatment, the neck stage is often N2a or more at presentation and ENE occurs in the vast majority of patients.

A multi-institutional review[178] studied 77 patients with cervical recurrence on the treated side, in the setting of a controlled primary. The review found that attempting salvage was useful in selected patients, giving a 33% control rate at 3 years. Results were better when surgical salvage was performed, but this probably reflects the low disease volume. Salvage rates were significantly better in the previously irradiated neck rather than the neck treated by previous surgery, with disease-free intervals being 46 months and 8 months respectively. The use of a pedicled pectoralis major flap or free flap should be seriously considered when embarking on salvage neck dissection, to reduce wound healing complications.

NODAL RECURRENCE AFTER COMBINATION TREATMENT

The prognosis is extremely poor in those patients who suffer a neck recurrence following previous surgery and radiotherapy, with median disease-free intervals of 4 months.[178] This clinical situation is often associated with distant metastases. However, the presence of such disease in the neck causes distressing symptoms such as pain or bleeding, together with offensive fungation and in selected cases further treatment may be appropriate. This includes wide excision of the tumour and the overlaying skin, flap reconstruction and brachytherapy. In very selected cases, re-irradiation may be an option. Evidence of partial repair of RT-induced spinal cord subclinical damage and newer RT delivery techniques (IMRT, tomotherapy, protons) that allow better sparing of neurological structures at risk make this a realistic option in a larger number of patients.

IMPACT OF NECK TREATMENT ON QUALITY OF LIFE

The issues that relate to quality of life (QOL) and the treatment of metastatic neck disease are discussed below.

Elective surgery versus irradiation of the N0 neck

There are no studies comparing (QOL) between these two treatments and there is very little morbidity associated with a well-executed SND. This is because vital structures are preserved and level V is not usually dissected. In contrast, a strategy of uniformly irradiating both sides of the neck to try and decrease the likelihood of occult cancer growth may be associated with numerous problems since radiation does not always control occult neck cancer, the fate of recurrent cancer in an electively irradiated neck is much more difficult to salvage and isolated recurrence in the contralateral neck is extremely unlikely.[8] In addition, treatment options for second primary tumours are diminished when wide-field radiotherapy has been applied to both sides of the neck and there are no prospective randomized studies which demonstrate a survival disadvantage when the N0 neck is observed. In summary, the QOL issues relating to elective irradiation appear less transparent than those for elective surgery and should not be underestimated when prescribing its use. Further studies are awaited.

Impact of neck treatment on the shoulder

Neck surgery for node positive disease usually involves a 5-level dissection and there are QOL issues that relate both to the extent of the dissection and which tissues are sacrificed (i.e. accessory nerve, sternomastoid muscle and the internal jugular vein). Shoulder problems are greater in patients undergoing a RND as opposed to a MRND.[179, 180] Despite preserving the accessory nerve in MRND, dysfunction occurs due to the nerve being devascularized and stretched. The least problems are seen in patients undergoing an SND.[98] It is noteworthy that SNDs that clear levels II– IV can also affect the shoulder by stretching the accessory nerve during dissection of the submuscular recess (level IIb).[181] Quite clearly if level V is not dissected, this may improve QOL. However, it must be noted that the trade-off for not dissecting all five levels may be the subsequent morbidity of post-operative radiotherapy, which does contribute to shoulder dysfunction.[126]

The use and extent of radiotherapy to the neck

While the effects of neck surgery are confined to the neck, radiotherapy fields often include the salivary glands and some of the viscera, leading to side effects such as mucositis and xerostomia. Use of intensity-modulated radiation therapy (IMRT) has allowed parotid-sparing techniques. Results from randomized controlled trials indicate that IMRT does improve quality of life, at least in the early years.[182] In addition, the evidence that both sides of the neck need to be irradiated in well lateralized primaries post-operatively is flimsy since the incidence of contralateral neck disease is relatively uncommon in certain tumours, as discussed earlier.[8] Unfortunately, many oncologists continue to routinely prescribe bilateral post-operative radiotherapy to the neck.

In our efforts to improve quality of life and reduce the traumatic psychosocial impact, a number of specialist centres are now in the process of balancing science with ethics and the human experience with a surge of QOL research and, hopefully, an evidence-based rationale to guide us in the future. Until a major therapeutic breakthrough takes place, reducing physical treatment morbidity, improving patients' overall QOL and minimizing the psychosocial impact of therapy will continue to present our greatest challenge in the practice of head and neck surgery.

FUTURE RESEARCH

The quality and quantity of randomized trials for metastatic neck disease is acknowledged to be limited, but this has improved significantly in recent years. Particularly in the UK, the improved structure of research trial coordination has led to the successful completion of a number of surgical trials, most notably the PET-NECK trial. As a result of this successful trial a number of clinical trials have been funded and are now recruiting well. Further research should involve the integration of modified randomized trials with prospective audit and quality control studies.[183] The following are areas where further work needs to be addressed.

- Imaging of low volume disease
- Significance of occult cancer in the neck
- Molecular detection of occult neck disease and its significance
- Sentinel node biopsy for occult neck cancer, in non-oral cavity cancer
- Selective neck dissection for palpable disease
- Superselective neck dissection for residual disease after chemoradiation
- Management of the contralateral neck
- Quality of life should be investigated following various treatment modalities
- Centralization with specialization and appropriate data collection should improve research, audit and quality control.

KEY POINTS

- Head and neck squamous cell cancer is a systemic disease.
- Tumour-host interaction has a major role to play in the outcomes of treatment.
- Metastatic cervical lymphadenopathy is the most important prognostic factor in head and neck squamous cell carcinoma.
- Patterns of neck metastases are altered by previous treatment.
- Subclinical neck disease is not early cancer.
- Selective neck dissection is adequate in the management of N0 necks.
- Elective neck dissection should be considered for all T1-2 N0 oral cavity SCC, and should be performed for tumours with a depth of over 3 mm.
- Modified radical neck dissection is as good as radical neck dissection in regional control.
- Adjuvant radiotherapy or chemoradiotherapy is indicated for surgically managed N2 and N3 disease and for N1 disease with poor prognostic features.
- Where there is access to it, PET-CT should be performed 12 weeks after primary chemoradiotherapy for N2 and N3 disease. The results should guide the need for subsequent neck dissection.
- In selecting treatment options, QOL issues are important considerations.

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CHAPTER 19

PRINCIPLES AND PRACTICE OF RADIOTHERAPY IN HEAD AND NECK CANCER

Sara Meade and Andrew Hartley

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline Search using the following keywords: head and neck, radiotherapy, intensity-modulated radiotherapy, linear quadratic equation, therapeutic ratio and radiobiological modelling.

INTRODUCTION

Radiotherapy as a single modality or combined with synchronous chemotherapy is capable of high rates of tumour control. A local control rate of 90% at 5 years would be expected both when radiotherapy is administered as the sole treatment for a T1-glottic carcinoma and when HPV-associated oropharyngeal cancer is treated with synchronous chemoradiation in patients without a significant smoking history.[1–6]

However, these high rates of local control come at considerable cost to the patient. Acute side effects can include mucositis which often requires the use of strong opioid analgesia, taste disturbance, hair loss, acute xerostomia, dysphagia requiring the use of temporary tube feeding and skin reactions. Long-term side effects can include the risk of osteoradionecrosis, xerostomia and the risk of stricture formation and fibrosis necessitating long-term tube feeding. There is no strong evidence that prophylactic treatment of these side effects is effective other than the use of intensity modulated radiotherapy to avoid late xerostomia.[7–10] On the contrary an adverse effect on local control was observed in one study when patients were randomized to receive prophylactic granulocyte-colony stimulating factor (G-CSF) during irradiation with no improvement in the rate of acute mucositis, a finding with possible implications for prophylactic G-CSF use during chemoradiation.[11] Death during or within 8 weeks of completion of treatment, when actually reported in randomized trials, occurs in 0–7% of patients undergoing radiotherapy alone and 0–14% with chemoradiation. Deaths definitely ascribable to treatment are reported in 0–3% and 0–5% of patients respectively.[11–23]

It is therefore essential that this therapeutic ratio i.e. the benefit to the patient (altered chance of cure) vs the detriment to the patient (altered chance of mortality/morbidity) is considered in detail when any modification to the radiotherapy or chemoradiotherapy schedule is made.[24–28] In this chapter the physical, chemical and biological processes involved in radiotherapy delivery will be briefly considered to enable an appreciation of the way in which these processes have already been or may be modified in the future to affect this ratio. The radiobiological modelling of such modifications will then be considered.

Basic physical, chemical and biological processes

Photons for use in head and neck radiotherapy, normally of energy of 6 megavolts (MV), are produced in a linear accelerator by accelerating electrons into a target. The photon beam produced can be shaped by using a series of collimators in the head of the machine (multi-leaf collimators) which are able to move permitting intensity-modulation between the delivery of multiple beamlets (step and shoot

intensity-modulated radiotherapy (IMRT)) or during the delivery of the beam (dynamic IMRT). The gantry of the linear accelerator can also move around the head of the patient to deliver photons from different beam angles. If the IMRT is only delivered while the gantry is stationary from a number of set-beam angles (normally 5 or 7 in head and neck IMRT) the treatment is known as fixed-beam step and shoot IMRT. If the IMRT is delivered while the gantry is rotating about the patient the treatment is known as dynamic arc IMRT.[24, 29, 30] Intensity Modulated Proton Therapy (IMPT) may be considered in the future for certain head and neck tumours due to the ability to reduce the 'low dose bath' with this modality (**Figure 19.1**).

Photons cause ionization in normal tissue resulting in the formation of secondary electrons which cause further ionization resulting, in the presence of oxygen, in free-radical formation. The principal target of radiotherapy at a cellular level is deoxyribonucleic acid (DNA). Radiation causes cell death primarily through single- or double-strand breaks in DNA. Single-strand breaks are mostly due to the effects of hydroxyl radicals (OH^-) formed as described above. Double-strand breaks are directly proportional to the dose of radiation delivered and may result from direct interaction by the photons or secondary electrons with the DNA double strand.[31–34]

In general it is the double-strand breaks that are crucial for the lethal effects of radiation. Irreparable DNA damage causes sterilization of the tumour cell with loss of proliferative capabilities, also known as cell kill.[35] However, single- and even double-strand breaks can be repaired by complex repair processes.[36, 37] It must be remembered that both tumour cells and the varied normal tissues which surround the tumour are affected by radiation. It is the differential response between tumour and normal tissues in their ability to repair DNA lesions and their response to the amount of radiotherapy delivered per treatment (fraction size) which the head and neck radiation oncologist utilizes in order to maximize the therapeutic ratio.[25]

Radiobiological modelling

There have been many randomized studies of altered fractionation in head and neck cancer and thus it has been possible to test in the clinical setting models of tumour cell kill and normal tissue response originally derived from the irradiation of cell lines.[38–45] An understanding of the relatively straightforward calculations involved in such modelling together with an appreciation of the limitations of such models is essential for radiation oncologists and helpful for other members of the multidisciplinary team.

Linear quadratic equation and biologically effective dose (BED)

Since 1989 the linear quadratic equation and the concept of BED has been proposed as a model for comparing the biological effects from different dose schedules in radiotherapy:[46–49]

$$E = \alpha nd + \beta nd^2$$

Where:

- E = biological effect
- n = number of fractions of radiotherapy in a course
- α = linear component of cell kill or intrinsic radiosensitivity or lethal hit component of cell kill in units of $Gray^{-1}$ (Gy^{-1}). One Gray (Gy) is equivalent to 1 Joule of energy deposited per kilogram of tissue.
- β = quadratic component of cell kill or component of cell kill resulting from combined sublethal hits in units of Gy^{-2}
- d = dose per fraction

In the mode of action of radiotherapy discussed above the alpha component of cell kill might be considered to be related to the number of double-strand breaks and the beta component related to the number of combined single-strand breaks. The beta component is inversely

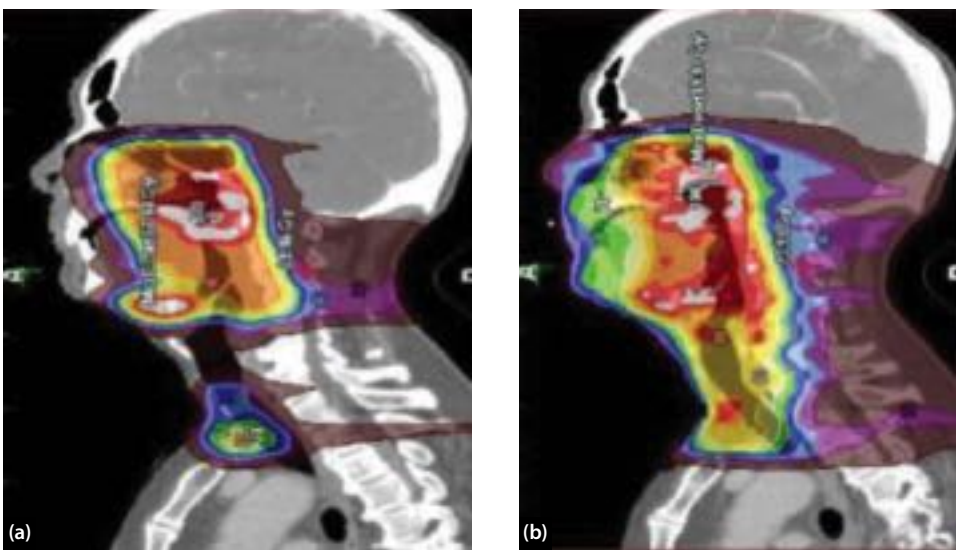


Figure 19.1 Sagittal plane of **(a)** an Intensity Modulated Proton Therapy (IMPT) plan and **(b)** an Intensity Modulated Radiotherapy (IMRT) plan illustrating potential sparing of the posterior fossa of the brain and posterior cervical musculature (Images courtesy of Mr. Trevor Williams).

proportional to the repair ability of the tumour or tissue under consideration. To make this model useful clinically, the concept of BED has been defined. This permits the comparison of different dose fractionations. Two different dose fractionations which result in the same specific biological effect in a defined tissue (which might be a particular tumour or normal tissue) will have the same BED.[46]

BED is derived by dividing the above equation by the intrinsic radiosensitivity parameter alpha:[46–48]

$$\frac{E}{\alpha} = BED = \frac{\alpha nd}{\alpha} + \frac{\beta nd^2}{\alpha} = nd + \frac{\beta nd^2}{\alpha} \tag{19.1}$$

Factorizing gives:

$$BED = nd\left(1 + \frac{\beta}{\alpha}d\right) = nd\left(1 + d\Big/\frac{\alpha}{\beta}\right) \tag{19.2}$$

Number of fractions (n) times the dose per fraction (d) = D = total dose:

$$BED = D\left(1 + d\Big/\frac{\alpha}{\beta}\right) \tag{19.3}$$

Where $\frac{\alpha}{\beta}$ is known as the alpha beta ratio and reflects the sensitivity of different tumours or normal tissues to changes in the dose per fraction d or fraction size. For example the $\frac{\alpha}{\beta}$ for squamous cell carcinoma of the head and neck is considered to be around 10 Gy and for the acute musocal reaction seen during radiotherapy also around 10 Gy but for late mucosal damage around 3 Gy.[50–52] From the above equations, it can be seen that the lower the $\frac{\alpha}{\beta}$ of the tissue the greater the sensitivity to changes in fraction size.

If two treatment regimes used for squamous carcinomas, 55 Gy in 20 fractions (#) and 70 Gy in 35# are considered in terms of likely late mucosal toxicity it is possible to calculate the BED for late mucosal toxicity for both regimes using equation 3. In this example it is necessary to use an $\frac{\alpha}{\beta}$ of 3 Gy. For the first regime with total dose (D) of 55 Gy and dose per fraction (d) of 2.75 Gy, the BED is 105 Gy. For the second regime with D = 70 Gy and d = 2 Gy the BED is 117 Gy i.e. higher rates of late mucosal damage might be expected with the second regime. Although there is a higher dose per fraction in the first regime, the decreased total dose offsets this. In calculations such as these the BED may be reported as $105\,Gy_3$ and $117\,Gy_3$, the subscript reflecting that the dose has been calculated using an $\frac{\alpha}{\beta}$ of 3.[53, 54]

Equivalent dose in 2 Gy fractions (EQD2)

Often BED is converted into equivalent dose in 2 Gy fractions (EQD2) as in the conformal era normal tissues and tumours often received a homogenous dose. Therefore, radiation oncologists were used to working with both tumour doses and normal tissue tolerance in 2 Gy per fraction.[47, 51, 52, 54] This is less relevant in the IMRT era as both total doses and dose per fraction differ greatly between tumour and normal tissues. If needed the conversion can be made:

$$EQD2 = \frac{BED}{\left(1 + 2\Big/\frac{\alpha}{\beta}\right)} \tag{19.4}$$

A similar calculation can be performed for the response of tumour using an $\frac{\alpha}{\beta}$ of 10 Gy. For the two regimes considered above this results in tumour BEDs of $70\,Gy_{10}$ and $84\,Gy_{10}$ and EQD2s of $58\,Gy_{10/2}$ and $70\,Gy_{10/2}$ (the subscripts now indicating that the calculations have been made for a tissue (in this case a tumour) of $\frac{\alpha}{\beta}$ of 10 Gy but that the dose is quoted as if it were delivered in 2 Gy fractions).

The effect of time on biologically effective dose

From the above calculation it would be expected that the second regime (70 Gy in 35) would be associated with a higher rate of tumour control but, in reality, control rates seen with these regimes are similar. In several studies prolonging the overall treatment time over which a fractionated course of radiotherapy is delivered for squamous cell carcinoma of the head and neck results in reduced tumour control.[55–58] This is thought to occur due to an increase rate of cell proliferation in surviving cells once radiotherapy has commenced. In most recent radiobiological studies this accelerated repopulation is modelled to commence at around 21 days known as the kick off time or T_k.[58–62] For squamous cell carcinoma during radiotherapy, the cell turn over time or T_p is modelled at 3 days. A modified equation for BED to take into account overall treatment time has been derived for overall treatment time (T):[51–52]

$$BED = D\left(1 + d\Big/\frac{\alpha}{\beta}\right) - \left(\frac{\ln 2}{\alpha} * \frac{(T - T_k)}{T_p}\right) \tag{19.5}$$

Repeating these calculations for the two regimes above having T of 25 days and 46 days respectively, using a value for alpha of $0.3\,Gy^{-1}$, gives BEDs of $67\,Gy_{10}$ and $65\,Gy_{10}$ suggesting more similar tumour controls. The reliability of these models for tumour control will be discussed in 'Altered fractionation' below.

Such calculations are useful not only in the design of randomized studies but for devising revised schedules when an unintended gap in treatment occurs.[63–66] Such gaps should be avoided where possible but may be compensated for by altered fractionation following the gap. It is important to note that for late side effects such as late mucosal damage or neurological damage there is no correction for time when calculating BED. Late responding tissues appear dependent on total dose and fraction size only and typically have a low $\frac{\alpha}{\beta}$ ratio.[67]

The same calculations as performed for tumour can be performed for BED with respect to the rate of acute grade 3 ucosal reactions which has been considered the dose limiting acute toxicity in head and neck cancer. Tolerance models for the acute mucosa for different radiotherapy schedules have been devised.[50, 68, 69] When calculating BED for acute mucosa the values for $\frac{\alpha}{\beta}$, α, T_p and T_k used are 10 Gy, 0.35 Gy^{-1}, 2.5 days and 7 days. In the simplest of three published models based on published studies of radiotherapy as sole modality in head and neck cancer, Fowler et al. suggest that schedules with an acute mucosal BED (amBED) greater than 61 Gy_{10} were unlikely to be tolerable due to severe acute mucositis.[51] Such models should again inform the design of future randomized studies although it is important to note that they are based on data from the conformal era and that mucosal sparing achievable with IMRT or IMPT may not be taken into account.[70, 71] A recent study has suggested that these tolerance models may be used in the chemoradiation setting (**Figure 19.2**).[72]

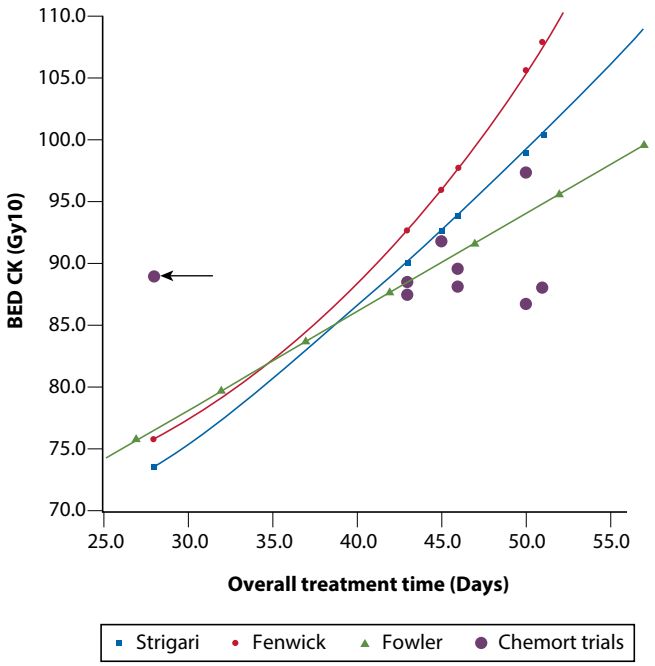


Figure 19.2 Plot of biological effective dose cell kill (BED CK) including contribution from chemotherapy against overall treatment time to illustrate how radiobiological modelling can predict mucosal tolerability. The arrowed trial is predicted to be above the levels of tolerability of 3 published models and indeed was shown to have a grade 3–4 mucositis rate of 77%.

CLINICAL PROCESS FOR A PATIENT UNDERGOING CHEMORADIATION FOR HEAD AND NECK SQUAMOUS CELL CARCINOMA

Radiotherapy for head and neck cancer offers numerous possibilities for modifications to the treatment schedule which might affect the therapeutic ratio. Before considering these and the ways in which their effect might be modelled, a typical patient pathway will be outlined. If the example of a locally advanced squamous carcinoma with p16 positivity invading the base of tongue to midline with no neck nodes or distant metastases in a patient without a significant past smoking history is taken, this patient might expect to be treated in the following way:

Preparation: The patient's case will have been discussed in a multidisciplinary meeting with surgeons, radiation oncologists, histopathologists, radiologists, dieticians, speech therapists and clinical nurse specialists present. The acute and late side effects of the treatment would be discussed with the patient and the patient would give consent. The patient would be offered a choice between having a prophylactic or a reactive feeding tube placed. Dental assessment would be arranged.

Immobilization: The patient's head and shoulders would be immobilized in an immobilization device known as a shell or mask which is subject to regular departmental audit. The data from such audit would be used to inform the planning target volume (PTV) margins below.

Imaging: The patient would have 2 mm slice CT scanning with intravenous contrast in the immobilization device with diagnostic MRI imaging fused to these images.

Target volume definition: The head and neck radiation oncologist would define the GTV based on MRI and CT. A small margin to allow for microscopic spread and the limitations of fusion and the imaging employed (5–10 mm) would be added to form the high-dose clinical target volume (CTV) to receive 70 Gy in 35 fractions. Adjacent areas of oropharynx and nodal regions felt to be at high risk of harbouring microscopic disease may be included in a prophylactic CTV to receive 56 Gy in 35 fractions. PTV margins based on in-house data derived from audit of image guided radiotherapy (IGRT) normally 3–5 mm are added to both CTVs.

Organs at Risk definition: The minimum organs at risk defined for a case such as this would include the spinal cord, brainstem, contralateral parotid, brain and mandible. Other organs that might be contoured but constraints would normally be achieved with ease include lens, optic nerves, chiasm. Other volumes which may be contoured in an attempt to reduce toxicity include oral mucosal volume, laryngeal framework, brachial plexi, cochlea and swallowing muscles.

Peer review of contours: The CTV defined by the radiation oncologist should where possible be peer reviewed particularly in complex cases (skull base, post-operative and following neoadjuvant chemotherapy).

Treatment planning: The departmental dosimetrists would produce an IMRT plan which is reviewed quantitatively and qualitatively by the radiation oncologist and then subjected to rigorous quality assurance.

Delivery: The above plan would be delivered over 7 weeks (number of treatment days 35 but overall treatment time 46 days). Each day the patient would be imaged using cone

beam CT scanning or megavoltage imaging to check positioning and assess any changes in contour due to weight loss or tumour shrinkage which might affect dosimetry (IGRT).

Chemotherapy: Provided the patient was less than 70 and there were no contraindications the patient would receive cisplatin 100 mg/m^2 on the Monday of week 1, 4 and 7 of radiotherapy.

Supportive care: The patient would be reviewed weekly during treatment and till the mucosal reaction has settled by a multidisciplinary team of radiation oncologist, radiographers, speech therapists, dieticians and nurses.

At nearly every point of the example pathway described above there are alternatives or points of controversy. Many of these will be discussed in detail in other chapters. From the literature it is clear that for the most fundamental component of radiotherapy delivery, target volume definition, there is considerable heterogeneity between clinicians.[73, 74]

Altered fractionation

As an illustration of how the linear quadratic model can be used both to model changes in the therapeutic ratio and to clarify terminology associated with radiotherapy fractionation schemes, altered fractionation as an alternative to chemoradiation will be considered.

Although 70 Gy in 35 fractions (overall treatment time 46 days (7 weeks)) has been defined as the standard above, prior to chemoradiation being accepted as standard treatment several different fractionation schemes had been the subject of randomized studies.[39–45] In describing such schemes certain definitions need to be understood. Acceleration is a reduction in the overall treatment time below the standard 46 days. Hyperfractionation is the use of less than 2 Gy per fraction. Conversely hypofractionation is the use of more than 2 Gy per fraction. Dose escalation is an increase in the total physical dose above 70 Gy. The schedules tested in randomized trials include hyperfractionated dose escalated schedules e.g. 84 Gy in 70# over 46 days with 2 fractions delivered twice a day. In this case, dose escalation is made possible because the fraction size is reduced and thus late side effects which depend only on total dose and dose per fraction are not enhanced (late BED for 84 Gy in 70# is 118 Gy_3; for 70 Gy in 35# is 117 Gy_3 (equation 3). Other examples include pure accelerated schedules e.g. 68 Gy in 34# delivered over 38 days (DAHANCA schedule) where the total dose is only dropped minimally and overall treatment time is reduced.[43] Finally, very accelerated schedules were tested such as the CHART regime 54 Gy in 36 fractions over 12 days where 3 fractions a day were administered over 12 continuous days (no weekend breaks).[41] To make very accelerated regimes tolerable to the acute mucosa it was necessary to drop the total dose. A meta-analysis of trials of altered fractionated grouped trials into these three groups as described above and found that an overall survival benefit was only found in the hyperfractionated dose escalated group.[38, 75] This survival benefit is approximately the same as that seen with the addition of synchronous chemotherapy to standard radiotherapy. Unfortunately, this benefit was not seen in patients aged over 70 and so dose-escalated hyperfractionated radiotherapy is not an evidence based alternative to chemoradiation in this cohort.

Using the randomized trials considered in this meta-analysis, one study has shown a strong correlation between BED calculated for each regime using the parameters described above and the proportional change in local control, rate of acute grade 3 mucositis and late mucosal damage seen between study arms.[67] Studies indicate a 1.2% change in local control for a 1% change in BED in the dose range considered. This finding supports the use of the linear quadratic equation as a guide to predicting both tumour and toxicity endpoints in radiotherapy studies.

The therapeutic ratio: dose-escalated radiotherapy or synchronous chemoradiotherapy

The addition of synchronous chemotherapy to radiotherapy has been associated with an 8% survival advantage.[76] As the same benefit can be achieved with dose escalation of radiotherapy alone, modelling studies have looked at the effect on the therapeutic ratio of the addition of synchronous chemotherapy.[24, 77, 79] Initially such studies calculated the effect of chemotherapy on local control as an additional radiotherapy dose in terms of BED using knowledge of the dose response. Such studies suggest that the addition of chemotherapy to radiotherapy is equivalent to the addition of three–four 2 Gy fractions in terms of local control.[24, 77–79] A similar calculation can be performed for the rate of grade 3 mucositis and an approximate mucosal sparing of two 2 Gy fractions for the use of synchronous chemotherapy rather than dose escalated hyperfractionated radiotherapy was proposed.[24] That is, synchronous chemotherapy is beneficial to the therapeutic ratio if the principal benefit of local control and the principal dose limiting side effect of grade 3 mucositis are considered.

However, two recent trials of accelerated fractionation chemoradiation versus conventional fractionation chemoradiation have cast doubt on such modelling.[80, 81] In both these studies the expected increase in local control with accelerated chemoradiation predicted both by previous radiobiological modelling and meta-analysis was not observed.[82] One hypothesis for the lack of benefit for acceleration in these studies is that accelerated repopulation may be compensated for by synchronous chemotherapy. Alternative modelling has been proposed where the dose lost from accelerated repopulation is reduced when synchronous chemotherapy is used by increasing the value of T_p for both tumour and mucosa in equation 19.5 above.[83, 84] Interestingly, a therapeutic loss is predicted for the addition of chemotherapy when this modelling is employed.

While the above serves as an example of how radiobiological modelling can be employed, such an analysis of the therapeutic ratio is limited as it ignores overall survival and the many other early and late toxicities experienced

by patients. It is also largely based on data from the conformal radiotherapy era and toxicity sparing from IMRT is not taken into account.

CONCLUSION

A basic understanding of the mechanism of action of radiotherapy, the radiotherapy preparation and delivery process, the linear quadratic equation and the rationale for the use of chemoradiation or altered fractionation radiotherapy as described above can be beneficial to all members of the multidisciplinary team treating head and neck cancer patients.

KEY EVIDENCE

- Parotid sparing radiotherapy reduces late xerostomia.
- Dose-escalated hyperfractionated radiotherapy increases overall survival by 8% at 5 years compared with conventionally fractionated radiotherapy alone.
- The addition of synchronous chemotherapy to radiotherapy increases survival by 8% at 5 years compared with conventionally fractionated radiotherapy alone.
- Two randomized trials have failed to show evidence for a survival benefit of synchronous chemotherapy and accelerated radiotherapy over synchronous chemotherapy and conventionally fractionated radiotherapy.

KEY POINTS

- Prolonging the overall treatment time reduces the efficacy of radiotherapy.
- The Linear Quadratic Equation can be used to predict the results from future randomized studies.
- The Linear Quadratic Equation can be used to devise compensation schedules following unscheduled gaps in radiotherapy.

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CHAPTER 20

QUALITY OF LIFE AND SURVIVORSHIP IN HEAD AND NECK CANCER

Simon Rogers and Steven Thomas

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: Quality of Life, head and neck cancer, patient reported outcomes, questionnaires and survivorship.

INTRODUCTION

The aim of this chapter is to outline important aspects of quality of life and survivorship following head and neck cancer. The chapter is divided into five sections that take the reader from the definition and measurement of quality of life through to survivorship.

There are two million people living with or beyond cancer in the UK. This figure is set to rise to four million by 2030. It is a cause for celebration that more people than ever are surviving after diagnosis, but we know the impact of cancer does not suddenly stop when treatment is over.[1] There is considerable focus on survivorship through programmes such as the National Cancer Survivorship Initiative – improving the ongoing services and support for those living with and beyond cancer.[2] Survival is improving following oral cancer[3] and with advances in medical care, refinements in treatments and changes in the clinical characteristics of head and neck cancer patients, improved survival is expected in head and neck cancer (HNC) patients. Survivorship focuses on the health and life of a person with cancer from the completion of treatment until the end of life. It covers the physical, psychosocial, and economic issues of cancer, beyond the diagnosis and treatment phases (**Figure 20.1**). Survivorship includes issues related to access to healthcare and follow-up treatment, late effects of treatment, second cancers, and quality of life. It is recognized that family members, friends and caregivers are also part of the survivorship experience.[4] Quality of life

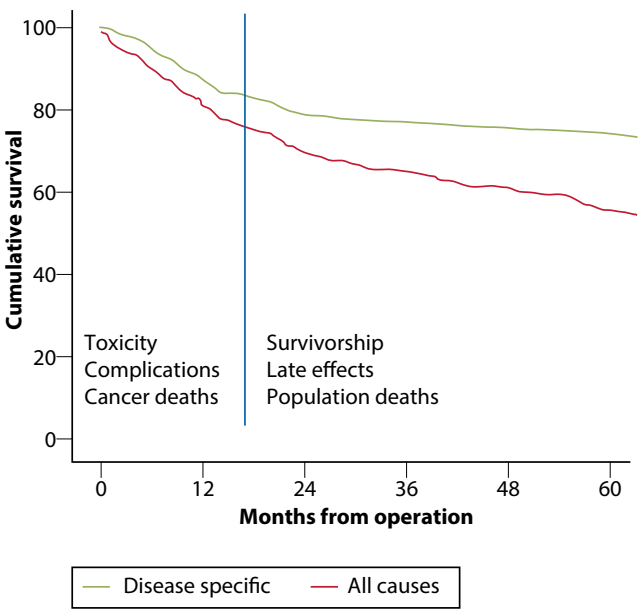


Figure 20.1 Transition from early post-treatment to longer term survivorship following HNC.

(QoL) for HNC patients is a crucial field in which interest has developed in the last two decades and there is now a considerable body of information available to clinical teams concerning QoL outcomes. There are several review articles summarizing the issues related to QoL.[5–9]

WHAT IS HRQoL AND HOW IS IT MEASURED?

Quality of life (QoL) is considered as a multidimensional concept. The World Health Organisation (WHO) defines quality of life as an '*individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns*'.[10] QoL is present in both the positive and negative aspects of different life domains. There are different theoretical models to help explain how QoL is constructed (**Figure 20.2**).[11, 12] In a simplistic model, cancer and its treatment has a consequence. The detrimental extent of this 'consequence' has a direct bearing on 'quality of life', for example, loss of tongue function after surgery or dry mouth following radiotherapy. How patients respond to that 'consequence' has many influences such as their ability to adapt and cope; however, the perceived consequence will influence the patient's ability to accept the situation. This has a direct bearing on their experienced QoL. Finally, in this theoretical model the patients' sense of cure and control over the cancer will impact on their perception of QoL. Hence, if patients are cured this has a positive impact on their QoL.

Health-related quality of life (HRQoL) is regarded as a subcategory of QoL and its coverage can be categorized into four areas related to physical functioning, psychological functioning, social functioning and symptoms from the disease and treatment.[9] The cross-cultural aspects and wide applicability of HRQoL has resulted in the availability of various validated translation questionnaires. Translations have to be carefully undertaken as it is possible that words or phrases differ between languages and cultures.[13] HRQoL is not usually considered to include expected acute toxicity.

HRQoL should not be limited to an outcome in research, but should make a vital contribution in the treatment and management careplan involving both patients and healthcare professionals.[8] HRQoL has a major role in treatment decisions in several but not all situations. For example, when different treatments have a good chance of cure, HRQoL will influence decison-making. The priority given to the best chance of cure often outweighs HRQoL outcomes for indiviual patients, treatment protocols and trial designs. Patients set cure and survival as priority and there is individual patient variability related to the side effects of treatment.[14–17] Another area where HRQoL has an important role is when treatments have equivalent survival outcome but the HRQoL outcomes are different. There might be a trade off with the degree of dry mouth, trismus, pain and swallowing difficulties depending on the modality of treatment used. Also, when the cancer treatment is very unlikely to be curative or the intention of treatment is palliative, there is a strong focus on treatments that maintain HRQoL for the remaining time available. Finally, some treatments result in such a poor HRQoL that even if cure is possible, the adverse impact on the patient HRQoL is too great to consider such treatment. Studies show that long-term survivors of advanced HNC accept major surgical procedures, with over 90% of 273 patients stating that 'I would undergo the same treatment'.[18] There is also strong agreement between patients, their companions and members of the multidisciplinary team (MDT) with regards to priorities in HNC outcomes and low post-treatment regret for patients and their companions. These results suggest that the patients' companions and members of the MDT are able to exercise good judgement when it comes to supporting patients in decision-making.[17] In spite of the enormity of the diagnosis and treatment, relatively few patients feel that they regret treatment. This, of course, may not reflect the reality of the personal experience that can be hidden from the healthcare profession.

HRQoL is usually measured by a patient's self-completed questionnaire. Questionnaires can be complemented by objective measures such as swallowing, speech and shoulder movments. There is no gold standard questionnaire that is best.[7, 19] The choice of questionnaire will depend on the context in which it is being used, based on the hypothesis being tested, such as general cancer issues (pain, depression), HNC-specific items (shoulder, appearance) or function-specific assessment (xerostomia, swallowing, speech).[20] **Table 20.1** gives common examples of the different questionnaires by group. The choice of questionnaire will be influenced by whether they are used in audit or research. The British Association of Head and Neck Oncologists and the British Association of Otorhinolaryngologists Head Neck Surgeons both recommend that HRQoL should be longitudinally recorded. Questionnaires are one of the ways to measure HRQoL and give a structured insight into the patients' point of view.[21] The most commonly used questionnaires[22] are the European Organization for Research and Treatment for Cancer (EORTC),[23] and the University of Washington quality of life (UW-QoL).[24]

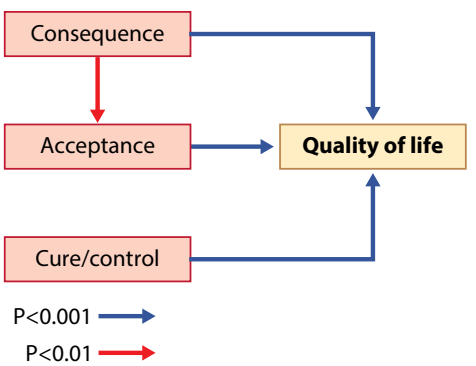


Figure 20.2 Theoretical framework: the interaction between the consequences of treatment and QoL.

TABLE 20.1 Examples of HRQoL questionnaires (Handle-On-QoL)

Group	Questionnaire name	Reference
General	EQ-5D	https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/
General cancer	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)	http://groups.eortc.be/qol/eortc-qlq-c30
	Functional Assessment of Cancer Therapy (FACT)	http://www.facit.org/facitorg/questionnaires
Head and neck cancer specific	EORTC H&N 35 and QLQ-H&N43 revision	http://groups.eortc.be/qol/eortc-qol-module-head-and-neck-cancer-qlq-hn43-revision-eortc-qlq-hn35
	FACT	http://www.facit.org/facitorg/questionnaires
	University of Washington Quality of Life Questionnaire (UWQOL)	http://www.hancsupport.com/professionals/quality-life/qol-questionnaires/university-washington
H&N cancer function specific	Voice related QOL (VRQOL)	Hogikyan ND, Sethuraman G. Validation of an instrument to measure voice-related quality of life (V-RQOL). J Voice 1999;13:557-69.
	MD Anderson Dysphagia Inventory MDADI	Chen AY, Frankowski R, Bishop-Leone J, Hebert T, Leyk S, Lewin J, Goepfert H. The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M. D. Anderson dysphagia inventory. Arch Otolaryngol Head Neck Surg. 2001 Jul;127(7):870-6.
	Sydney Swallow Questionnaire (SSQ)	Dwivedi RC, St Rose S, Roe JW, Khan AS, Pepper C, Nutting CM, et al. Validation of the Sydney Swallow Questionnaire (SSQ) in a cohort of head and neck cancer patients. Oral Oncol 2010;46(4):e10-4.
	The London speech evaluation (LSE) Scale	Dwivedi RC, Rose SS, Chisholm EJ, et al. Development and validation of first-ever speech-specific perceptual speech evaluation tool for patients with head and neck cancer: The London speech evaluation (LSE) Scale. Head Neck 2012; 34(1): 94–103.
Other	Hospital Anxiety and Depression Scale (HADS)	Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983 Jun;67(6):361-70.
	Beck Depression Inventory (BDI)	Beck AT, Ward C, Mendelson M. Beck Depression Inventory (BDI). Arch Gen Psychiatry. 1961 4 (6): 561–571.

TREATMENT DECISIONS AND OUTCOMES IN THE CONTEXT OF HRQoL AND SURVIVORSHIP

The epidemiology of HNC in the UK is changing. The oral cavity is now the most common subsite and there has been a 51% rise in human papillomavirus (HPV)-related oropharyngeal cancers between 1989 and 2006[25] (The HPV-related cancers appear to affect younger people and may respond better to chemoradiotherapy with or without surgery.[25, 26] Organ-preserving therapies are favoured for laryngeal cancer.[27] The choice of treatments available is also changing. These choices are informed by recommendations made in MDTs and following discussion with patients.[28] It is desirable that treatment decision-making should be shared between patients and doctors.[29] Shared decisions involve the doctor learning about the patient, in particular the extent of their understanding, their circumstances and ultimately their wishes, and the patient learning from the doctor about the nature of the treatment and the prognosis.[30, 31] The patient may have to make a decision early in their treatment path which could have important implications for their HRQoL.[32] Shared decision-making improves patients' satisfaction with the consultation, leading to better quality of life.[33–35] Related to shared decision-making is the process of informed consent where an autonomous person has understanding of the treatment and intentionally authorizes the proposed action.[36–38] The view of what a 'reasonable patient' might expect outweighs standards being set from a 'reasonable doctor's view point'.[39] The exchange of information underpins both informed consent and shared decision-making, and there is evidence that patients want detailed information on the effect treatment will have on survival and quality of life.[40] QoL may include specific issues such as the effect on speech and swallowing as well as general issues including pain, fatigue and anxiety.[15, 41, 42] Information needs to be defined by the individual patient and not by the diagnosis or treatment.[36–38, 43, 44] Too much information can result in reduced recall and anxiety, too little information and it is unlikely that patients will be able to reach understanding.[31] Healthcare professionals need to disclose a core set of information about a treatment.[43] The development of a core information set for informed consent will improve the effectiveness of these processes for both patients and doctors.

As with 'Core Disclosure Sets', there is an increasing need for the development of 'Core Outcome Sets' to

enable standardization of outcome reporting in clinical trials. These would define a minimum set of outcomes that should be measured in clinical trials for any given condition. The purpose of core outcome sets is to improve the quality of research by emphasizing the importance of including relevant stakeholders, especially patients, in decisions about which outcomes should be measured and reported and reducing reporting bias by clear definition of outcomes.[45] Outcomes used in clinical trials of head and neck HNC frequently focus on objective measures of function and survival outcomes, but little is known about which outcomes are important from the patients' and carers' perspective.[44] Prognosis research in cancer often fails to report suffering from symptoms, functional status and QoL. Mortality may not be the most important outcome to the patient, nor is it necessarily a good proxy for other outcomes. A range of outcome predictors should be considered: the social and healthcare environment, psychosocial factors and health behaviours as well as biological factors.[46]

HRQoL AND SURVIVORSHIP

The MDT need to be aware that some patients will tend to report a much worse HRQoL. These patients might be helped by additional support through treatment and into survivorship. The types of patients most at risk of poor HRQoL outcome are given in **Table 20.2**.[8,47] Poor HRQoL has been identified as an independent predictor of survival[48–50] but this association may be influenced by various cancer-related, personal, biological, psycho-behavioural, physical, lifestyle-related and social factors.[51]

The main inflences of HRQoL are site, stage and treatment.[5–9, 52] There are much smaller differences by age and gender and these tend to be item-specific such as appearance. Older patients cope remarkably well[53, 54] and with careful selection and support, their expectations are less than younger patients and they can adapt remarkably well to the deficits after cancer therapy. Younger patients can experience more negative impacts related to family, employment, finance, and the the gap between the reality of what they have as a consequence of the cancer and the hopes and expectations for their lives. However, patients' ability to adapt and cope cannot be underestimated.[55]

TABLE 20.2 Common factors associated with worse HRQoL outcomes

Alcoholism: Pre exiting comorbidity and poor coping mechansim
Age: Young patients have much more to lose in terms of life expectation, finance.
Combined treatments: Surgery and radiotherapy, Chemoradiotherapy
Deprivation: Lower socio-economic background
Personality: Negative, nihilistic
Pre-existing distress: Anxiety related conditions, mental health
Single: Lack of support
Site: Oropharynx and hypopharynx
Stage: Advanced disease
Unknown: What clinical experience gives clinicians

SITE

Thyroid

A better understanding of HRQoL following thyroid cancer has developed over recent years and thyroid cancer-specific questionnaires are now available.[56] Awareness of these specific determinants of HRQoL could help healthcare practitioners to provide better supportive care. Long-term thyroid cancer survivors experience more symptoms and deteriorated HRQoL compared to the normative population. Thyroid cancer-specific neuromuscular, sympathetic, concentration and psychological symptoms are stronger associated with HRQoL than clinical and sociodemographic factors alone.[57]

Surgical, radiotherapy and hormonal aspects have been considered.[58–61]

Oral cavity

In most institutions, oral cancer tends to be treated by primary surgery. Conventional surgery with or without adjuvant treatment gives better HRQoL across most domains compared to chemoradiotherapy for oral cavity squamous cell carcinoma[62] including those issues considered most important to patients: chewing, swallowing, saliva and speech.

The HRQoL is better in patients treated with laser excision or primary closure compared to free tissue transfer reconstruction.[63] However, the extent of tumour ablation and the need for reconstruction will depend on the stage of disease. Reconstruction of the tongue and floor of mouth using local methods can provide good function outcomes and shorten operating time, and surgical morbidity.[64] There are a variety of soft tissue free flaps for reconstruction and the choice of flap has relatively little influence on most HRQoL domains. There will be differences in donor site morbidity.[65] For example, with mandibular resection, the need for adjuvant radiotherapy is a more important influence on HRQoL rather than whether a segmental or rim resection is performed or a composite free flap is used.[66] The survival advantage needs to be balanced against increased treatment toxicity. Post-operative radiotherapy (PORT) can be associated with reduced global health status, increased xerostomia and marginally increased levels of fatigue at 6 months post treatment for oral cavity cancer.[67] Adjuvant radiotherapy has a significant effect on HRQoL mainly because of dry mouth.[68] The patients' ability to cope with oral cancer is remarkable; the HRQoL in people who survive more than 5 years, when assessed with the SF-36 questionnaire was similar to those of the general population, even exceeding these reference values in some dimensions.[69]

Maxilla

Debate continues around the importance of obturation or free tissue transfer on HRQoL for the maxillectomy defect.[70] Obturator prosthesis is a highly positive and non-invasive approach to improve the quality of life of patients with maxillectomy defects.

There is an element of patient preference, however, with the large complex resections (palate, maxilla, sinuses, orbital content) HRQoL outcome is arguably better with microvascular reconstuction.[71] It is likely that edentulous obturated patients have worse outcomes than dentate patients, and although the size of the maxillectomy defect might have relatively little bearing, adjuvant radiotherapy results in worse mouth opening and self-reported oral and swallowing problems.[72]

Oropharynx

The oropharynx site brings into focus the debate around organ 'preservation' (non-surgical treatments) and surgery combined often with radiotherapy.[73] The stage[74] and treatment[75, 76] are key determinants of HRQoL outcomes. There is some evidence that there is a tendency for improved HRQoL among patients with oropharyngeal carcinoma treated surgically compared to advanced stages of disease managed with primary chemoradiotherapy.[77] There has been considerable interest in HRQoL as treatment affects aspects of social function for the patients such as speech and swallowing. There have been different treatments advocated such as transoral laser surgery, transoral robotic surgery with risk stratified adjuvant radiation or chemoradiotherapy. With radiotherapy, there is a body of evidence developing in support of intensity-modulated radiotherapy (IMRT). The association with HPV has raised the possibility of treatment de-escalation with better HRQoL and equivalent survival. T stage, tumour involvement of the tongue base, professional status and emotional and social functions can be considered as the main determinants of HRQoL,[78] while HPV status itself is not a main determinant.[79] Early disease can be treated with high long-term HRQoL by surgery alone. Primary surgery with PORT in selected patients with limited primary tumours and advanced neck disease renders excellent HRQoL. IMRT is superior to former radiation techniques with regard to HRQoL, and should be considered as standard of care in patients undergoing RT for oropharyngeal squamous cell carcinoma (SCC).[79] Further efforts to reduce swallowing dysfunction are likely to yield additional gains in HRQoL.[80]

Larynx

The outcomes of patients with early stage glottic cancer report significantly better HRQoL and function specific patient-reported outcome measures (PROMs) than those with more advanced stage disease. When attempting to make comparison between voice handicap and QoL after radiotherapy versus endoscopic laser resection (ELR) for T1a-glottic carcinoma, results should be interpreted in light of the biases inherent in retrospective studies. There is little difference with T1-laryngeal disease treated with ELR and radiotherapy.[81] Laoufi et al.[82] concluded that long-term subjective voice-related quality of life was worse after ELR, with no difference in other domains and larger T2 tumours might have better speech outcome with primary radiotherapy. However, T2 tumours, in particular T2b, and continuing smoking after radiotherapy correlated significantly with poor local control and worse voice handicap index.[83]

Partial laryngectomy procedures such as vertical or horizontal partial laryngectomies, have a role in attempting to optimize function and hence HRQoL. Modified supracricoid laryngectomy seems to improve quality of voice and QoL in patients with early laryngeal cancer.[84] The HRQoL benefits for extended vertical hemilaryngectomy and reconstruction with a neovascularized tracheal autograft for advanced unilateral laryngeal tumours need further evaluation.[85]

TOTAL LARYNGECTOMY

Following laryngectomy, areas that tend not to recover to baseline level are physical functioning, role functioning, social functioning, fatigue, dyspnoea, appetite loss, financial difficulties, senses, speech and social contact. Rather than age, sex, education and tumour site predicting HRQoL outcome, it is tumour stage, recurrent disease, radiotherapy and mental health.[86] Patients can be more accepting of, and find less troublesome, anticipated sensory impairments, cough and dyspnoea, than more general side effects such as constipation and nausea/vomiting.[87] Despite common belief, many patients who have undergone total laryngectomy (TL) maintain a good overall QoL.[88] There are potential difficulties in returning to work after TL. Influencing factors include age < 50 years, being self-employed or a clerical employee, good physical functioning, good speech intelligibility, high motivation to go back to work, and support from colleagues.[89] There is evidence around the impact on HRQoL and primary and secondary tracheo-oesophageal puncture (TEP).[90] Primary TEP provides almost immediate and satisfactory voice rehabilitation. Chemoradiotherapy and patient age do not seem to affect voice quality with either procedure.[91]

Comparison between TL and concurrent chemoradiation for function and long-term QoL outcomes in pharyngolaryngeal carcinoma patients shows no significant difference concerning feeding-tube, oral supplements and respiratory related HRQoL items. Differences are encountered in aspects such as smell and taste (surgical) and with dry mouth and weight loss (with chemoradiation).[92]

Skull base

There is a relative lack of HRQoL outcome data related to skull-base cancer. The development of an Anterior Skull Base Surgery Questionnaire (ASBS-Q) has improved our understanding of the PROM following skull-base cancer.[93] The overall QoL of patients

following endoscopic extirpation of skull-base tumours is good. Endoscopic skull-base surgery is considered a minimally invasive surgical modality with less morbidity and patient discomfort. It appears that endoscopic approaches are not associated with a detrimental long-term effect on sinonasal-related QoL. Short-term impairments of sinonasal-related QoL are predictable and self-limited.[94] Comparison of the impact of the open and endoscopic skull-base surgery on HRQoL revealed that patients who have endoscopic surgery reported significantly better scores in the physical function and impact on emotion domains than the patients who have open subcranial surgery.[95]

STAGE

Stage of disease is consistently one of the main influencing factors for HRQoL outcomes.[5, 9] Stage is related to the extent of the cancer, radicality of treatment, and associated functional deficits. The clinically meaningful significant differences in HRQoL between early stage and late stage HNC is reflected in most papers on this subject. The implication of this finding is that promoting early cancer presentation would make a significant difference not only on survival (patients' first priority) but also HRQoL.

TREATMENT

In general, single modality treatment, radiotherapy or surgery alone, confers much better HRQoL.[96] Transoral robotic surgery might be a way of preserving functional anatomy without compromising surgical resection margins and could have a positive impact on HRQoL,[97, 98] The advantage of less invasive surgery on HRQoL (e.g. transoral resection versus open resection and free-flap reconstruction[63] or rim mandibulectomy versus segmental resection)[66] is lost if primary surgery has to be followed by adjuvant radiotherapy. Avoiding radiotherapy after primary surgery has substantial benefits for patients in terms of HRQoL as long as optimal survival is maintained.[68, 99] There is evidence that reducing the dosage of radiotherapy can make a substantial difference.[100] In addition, IMRT has much better HRQoL outcomes compared to 3D-conformal radiotherapy (3D-CRT).[101]

Outcomes for overall HRQoL are similar for surgery with reconstruction compared to radical radiotherapy,[102] and for radical surgery and radiotherapy compared to chemoradiotherapy. There are functional differences in these comparisons such as greater impairment of speech and shoulder function after surgery whereas after chemoradiation, patients suffer from greater pain, xerostomia, difficulty swallowing and problems chewing.[103] Although the short-term side effects of treatment may differ between the groups, long-term QoL is remarkably similar whether the patients choose primary chemoradiation or surgery with post-operative radiation.[104, 105] Global QoL scores might be associated with slightly better functional outcome with surgery, and from the perspective of functional outcomes, either surgery or chemoradiation seem appropriate treatments for advanced HNC[106] but better long-term HRQoL scores are seen in patients undergoing concurrent chemoradiation.[107] Osteoradionecrosis (ORN) of the mandible is a severe complication of radiation therapy and has a detrimental impact on HRQoL. Surgery for ORN can result in an improved HRQoL; however, lack of improvement, despite the restoration of an intact mandible, relates to the persistent effects of chemoradiotherapy.[108, 109]

Treatment intent

To date there is a relative paucity of information concerning HRQoL in patients treated with palliative intent and further clinical outcomes research is needed.[110, 111] The published studies have tended to be qualitative in design due in part to the absence of a suitable HRQoL questionnaire specific to palliative care in HNC.[112]

Clinical trials

In the literature the evidence base concerning HRQoL is limited in respect to clinical trials. HRQoL questionnaires are a component of a clinical trial often included as a secondary outcome, and not explicitly driven by hypothesis.[113, 114] In the future there will be an increasing number of trials and interventions specifically aimed at evaluating HRQoL differences such as a study to assess the effect of low-level laser therapy on PROMs of oral mucositis and QoL in HNC patients receiving chemoradiotherapy.[115] IMRT will continue to be the subject of trials' research for the foreseable future until it becomes a standard of care (see 'Xerostomia below').

HRQoL ISSUES

There is a diverse range of patient and carer needs and concerns after completion of HNC treatment.[106, 116, 117] The variety of HRQoL issues are reflected in **Table 20.3** and will be mentioned individually below. Issues include pain, skin reactions, mucositis, nutritional status, swallowing, voice and speech, hyposalivation and xerostomia, dental health, trismus, shoulder and tissue fibrosis, sleep, fatigue, anxiety and depression, body image and social isolation, taste and smell, cognitive function and work status. However, the most frequent issue that patients wish to talk about is fear of recurrence (FoR).[116, 118–124]

Carer support

The benefit of carer support is a key issue in terms of patients' HRQoL. The use of support services differs over time. During the treatment phase and in the early period following interventions, there is a need for a wide range of supportive care expertise, including dental hygienists, physical therapists, specialist dietician and speech

TABLE 20.3 The vast array of different aspects to HRQoL following HNC

Alphabetical list
Carer: positive carer support
Coping: social support seeking good, avoidance bad
Dental status: eating- social interaction-coping
Disfigurement: appearance, body image, intimacy
Emotion: anxiety pre-treatment, depression is treatable, mood
Fatigue: common in year 1, poor sleep, low energy
FoR: does not lessen over time
Financial / work: employment, benefits, retirement
Information: various amounts, in various ways, at various times
Nutrition: low weight, diet, PEG feeding
Oral rehabilitation: chewing / eating – expectations + trade-off
Pain: need for opiates, poor sleep, depression
Personality: optimism and HRQoL + survival, high neuroticism
Self-esteem: low self-esteem associated with poor QoL
Sociodemographic: children, social support, ethanol abuse,
Speech: laryngeal speech / isolation
Swallowing: presence of feeding tube most significant
Shoulder: shoulder discomfort and neck tightness – selective
Trismus: poor difficulty in mouth opening – diet/social/intimacy
Xerostomia: profound impact on social function, IMRT
Unknown: clinical art of the individual not a precise science

therapists; long-term supportive care is more focused on aspects such as dental hygiene, speech therapy and physical therapy. Patients pecieved HRQoL deficits will influence their need for supportive care services.[125] Increased social isolation may be a risk factor for poorer physical recovery from, or adjustment to, treatment-related side effects. Social support may be an important target for psychosocial interventions for patients who face challenging treatment side effects.[126] Patients might view themselves as not being a burden to their carers but there is evidence emerging as to the demanding role placed on carers and family.[127] Carers see the patients as they are 'day-to-day' and not just at the review clinic episode. They are often more able to identify needs than the patient themselves recognize.[128] There are potentially many unmet supportive care needs and changes to the needs before and after treatment.[129, 130] Family caregivers report significant stress and needs themselves,[131] and the need for more information and healthcare services support. There is merit in devloping a tool to identify carer needs and caregiving training programs.[132]

Coping

The types of coping strategies patients adopt are important in terms of HRQoL recovery and adaptation.[133–135] Negative coping strategies need to be avoided as they are associated with poorer psychological state (higher incidence of depression, anxiety or low mood) and a reduced HRQoL. Post-laryngectomy avoidant coping strategies (both cognitive and behavioural escape) were among the strongest predictors of poor HRQoL.[136] To enable patients to implement positive coping strategies such as fighting spirit, coping with emotions and benefit finding is important.[137] Coping is part of a complex psychological construct linking QoL, coping styles, optimism and anxiety and depression.[138] Self-efficacy is also shown to positively influence social distress. Formal or informal support for HNC patients on how to cope effectively with disease can increase their resilience and perhaps reduce their reliance on a support network.

Dental status

Chewing and eating are part of social interaction. The significance of dental function cannot be underestimated with patients reporting chewing and eating being one of the most common issues they wish to discuss in clinics irrespective of the site (larynx, oropharynx, oral) or stage (early, advanced) of cancer.[122] The value of oral rehabilitation is not just in chewing, but also in self-esteem and well-being.[139] Oral rehabilitation is discussed in detail below.

Deprivation

Deprivation influences the incidence and outcome of patients with HNC. The more deprived the background of the patient, the worse the HRQoL outcome.[140] The relationship between deprivational and HRQoL is complex and is influenced by social support, lifestyle, comorbidity and coping strategies.

Disfigurement

Disfigurement embraces concepts such as appearance, body image and intimacy. It can be associated with shame and stigma[141] and social and emotional distress.[142, 143] The issue of body image disturbance has been addressed in a review by Rhoten et al.[144] There is a need to screen for appearance problems so that suitable advice and interventions can be offered.[145]

Emotion

The emotional impact of being diagnosed and treated for cancer cannot be underestimated, and certainly not least in HNC.[146]

There is a range of emotional distress syndromes but the main two components are anxiety and depression.[147–149] Anxiety is highest pre-treatment compared to depression, whilst depressive symptoms peak at the end of treatment and persist into survivorship for a proportion of patients.[150–152] Poorer survival has been associated with anxiety, depression, and worse HRQoL.[153] It is possible to screen for anxiety and depression in routine clinics[154, 155] and then to access a variety of interventions.[156, 157]

Fatigue

Fatigue, poor sleep and low energy are well-recognized symptoms during and following treatment, particularly in the first year. Depression and fatigue symptoms correlate negatively with HRQoL.[158] Fatigue-related items are common to several head and neck questionnaires but recently a Modified Brief Fatigue Inventory has been developed to measure intensity and frequency of fatigue specifically in HNC patients.[159] Comorbidity, cancer stage and adjuvant radiotherapy were associated factors. The excess fatigue reported in the IMRT cohort may, at least in part, be attributed to the dose distribution to the posterior fossa, cerebellum and brainstem.[160] Post-treatment hypothyroidism or subclinical hyperthyroidism induced by levothyroxine is associated with alterations in the HRQoL, reduction in the muscle function of upper limbs, and higher degree of fatigue.[59] The benefit of exercise is still to be defined in HNC, whereas it might be of benefit in other cancer sites.[161]

Fear of recurrence

FoR following treatment is common and significantly influences HRQoL.[116, 162] FoR is a major patient concern but is infrequently discussed in outpatient settings and may cause significant detrimental effect on the patient's psychological well-being.[118] Some patients experience intermittent and consistent levels of significant FoR, which do not improve with time and it is difficult to predict those based on clinical characterists.[163] There is merit in screening as this can lead to both informal and formal interventions.[164, 165]

Finance

Financial, work, employment benefits and retirement are factors in HRQoL for this patient group. For some, the cancer can be a time of positive readjustment moving to a slightly earlier retirement that planned. However, for those employed and with financial commitments the treatment and aftermath of cancer can be a substantial cause for concern and stress. Return to work is influenced by the type of job with 'white collar workers' such as professional, managerial, or administrative more likely to return than 'blue collar workers' (BCWs) for example involved in skilled or unskilled manufacturing. Considerably more severe impairments were reported in the self-administered questionnaires for BCWs and a poorer HRQoL.[166] Singer et al.[167] report that only a few laryngectomees return to work and they stress that return to work is important for many patients. Patient consultations should consider possibilities to support vocational rehabilitation before offering to apply for retirement. Survivors who perceived greater negative consequences of their cancer and worse physical functioning took longer to return.[168] In a study by Rogers et al,[169] 57% had suffered financially since diagnosis and QoL had decreased in 53% as a result of the financial impact of the disease. This was most common in the unemployed (64%), and in those whose work was affected by cancer (83%). Two-thirds had applied for benefits after diagnosis. Patients with worse physical and emotional functioning experienced more notable financial burden, more difficult life circumstances in the past month, greater financial difficulty and loss of income due to their condition in the previous week, more dissatisfaction with how well they took care of their own financial needs and were more likely to have sought statutory benefits.[170]

Gastrostomy

Although gastrostomy tube and swallowing, nutrition and function are covered in other parts of this chapter, this deserves individual mention because of the significant association with HRQoL.[171, 172, 173] Clinical stage, tumour site, patient age and nutritional parameters are all associated with the gastrostomy tube placement.[173] Patients with gastrostomies reported multiple deficits in HRQoL and a much poorer QoL. The presence of a feeding tube interferes with family life, intimate relationships, social activities and hobbies, in additon to the practical considerations of local discomfort, leakage or blockage. Permanent gastrostomy is a suitable surrogate indicator for HRQoL outcome.

Information

Patient and their carers need differing amounts of information, delivered in various ways, and at various times. Anxiety and supportive care needs are paramount during the diagnostic phase of the cancer journey.[174, 175] Anxiety and unmet needs are highest in those patients who experience a delay in diagnosis, treatment commencement, poor information and lack of psychological support.[175] Information provision needs to be tailored and include material about illness, treatment, side effects, function, physical fitness, impact on functioning, duration of recovery time, impact on QoL, support groups, where to go for financial advice and the long-term effects of treatment on ability to work.[41, 176] The internet has an important role for patients in providing information and support about their cancer, although other sources are still very important especially in the elderly and those early school leavers.[177]

Intimacy

Problems with sexuality and intimacy in HNC are under reported and have a detrimental imapct on HRQoL. Around one-third of those willing to answer intimacy and sexuality questions report substantial problems with sexual interest and enjoyment, and one-quarter problems with intimacy. The problem is particularly common in the under 55-year old age group.[178] The issue is complex and involved concepts such as 'personal identity', 're-establishing social networks' and 'intimate relationships', and is related to patients' perceived changes to self-esteem and image.[179] There is scope for intervention and pscho-sexual counselling but the concern is difficult to identify in clinical practice as discussion of this tends to be taboo.[180]

Nutrition

Malnutrition is common among HNC patients and negatively impacts on survival and QoL.[181] Unintended weight loss of more than 10% seems to be the most reasonable definition of malnutrition. More than 10% weight loss during and directly after radiotherapy has a significant impact on social eating, social contact, and HRQoL.[182] Chemotherapy and low body mass index at diagnosis are strong predictors of malnutrition.[183] Individualized dietary counselling on nutritional status is beneficial, compared to no counselling or standard nutritional advice and makes a positive impact on HRQoL. The effects of oral nutritonal supplements and tube feeding seem inconsistent in the literature.[184] Nutritional advice is still necessary years after chemoradiation.[185] Novel ways to encourage appetite should be considered.[186.]

Oral rehabilitation

Oral rehabilitation is a basic consideration for all HNC patients due to the importance that chewing, teeth and oral function have on HRQoL and well-being.[121, 139] Oral function influences swallowing, appearance, chewing, trismus, drooling and food clearance.[187] Oral rehabilation improves masticatory efficiency and this impacts positively on both food choice and social life. Consumption of solid, semisolid and overcooked food can be considerably better with the prosthesis.[188] After rehabilitation there is less worry about maxillary prostheses falling out, less embarrassment while conversing, less worry about losing self-confidence from embarrassment caused by dentures and fewer drooling problems.[189] The positive treatment outcome of oral rehabilation is not always predictable as some local effects following soft-tissue resection or radiotherapy cannot be significantly improved by prosthetic rehabilitation leading to functional and emotional disability.[190]

Pain

Pain is a major factor that influences a patient's QoL in relation to HNC. It is a common item in most HRQoL questionnaires.[7] Pain levels relate to HRQoL, the need for opiates, poor sleep and depression.[191] Different questionnaires are used to measure the extent and intensity of pain; however, further research needs to be undertaken to create a better objective, validated pain-related questionnaires.[192] Screening for pain in clinic can allow for intervention and when necessary, onward referral to a specialist pain team.[193]

Personality

Personality, ways of coping, mood and distress all have a bearing upon HRQoL. High neuroticism, avoidance focused coping, drinking to cope and high alcohol consumption are associated with worse distress.[135, 194, 195] Moreover, personality types and coping choices can correlate to survival.[196] The link between HRQoL and coping means that clinicians should be aware of the various positive and negative coping strategies and enlist the help of a clinical or health psychologist.[197]

Self-esteem

Low levels of self-esteem are linked to poor HRQoL and are influenced by issues such as shame and stigma,[141] oral function,[139] intimacy,[179] disfigurement,[142] support needs and family.[132] There are significant differences in anxiety and depression between those patients who have high self-esteem compared to those with low self-esteem. Ideally, patients with low self-esteem need pre-treatment and ongoing intervention.[198] The evidence relating to psychosocial interventions is considered later in this chapter.[157]

Sociodemographics

In a study by Rodriguez et al,[199] the most important contributor of overall HRQoL for people recently diagnosed with advanced cancer was social support. It was followed by general health perceptions, energy, social function, psychological function and physical function. In another study, patients with more support reported less anxiety and depression and better HRQoL in the mental health domain, independent of demographic and medical variables.[200] The degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate healthcare decisions (health literacy) is important. Beitler et al.[201] found that patients who underwent TL had a high chance of being lost to follow-up as well as having inadequate healthcare literacy. When assessing the impact of treatment in respect to HRQoL outcomes it is essential to consider the individual, his or her background and their context for the cancer and survivorship.

Shoulder

The morbidity associated with radical neck dissections and the impact of shoulder dysfunction and pain is well recognized.[202, 203] Where possible selective neck dissections should be performed as the function and HRQoL is much better.[204] There is little subjective morbidity associated with shoulder dysfunction after a unilateral 3 or 4 level neck dissection compared with patients undergoing primary surgery without a neck dissection.[205] Also following selective dissection, patients usually rate poor shoulder function of less importance than other items such as swallowing, speech, dry mouth, chewing and appearance.[206] If level IIb can be safely spared there is some evidence that the accessory nerve function is better.[207] Identifcation of a 'sentinel node' offers potentially the least morbid approach and early reports show HRQoL benefit, for example, less appearance dysfunction related to marginal mandibular nerve weakness and scarring.[208, 209]

Speech and voice

Speech is one of the main HRQoL issues following HNC[121] as it impacts on social function,[210] and contributes to isolation.[5] Radical treatment can have a significant impact on speech, voice and communication outcomes. The assessment is complex and lends itself to specific questionnaires.[211–215] Voice and speech impairment are prevalent;[216] for instance, over two-thirds of surviving oropharyngeal cancer patients will have speech impairment. The main clinical correlates associated with adverse patient and observer-rated speech and voice outcomes are tumour stage, combined treatment (surgery and radiotherapy) and free-flap reconstruction.[217] Local flaps (pharyngeal flap) can improve function and HRQoL in more than half soft-palate resections.[218] Following endoscopic resection or radiotherapy for early glottic cancer HRQoL and voice appear similar despite the two different treatments,[219] and based on functional outcome, patients can have a choice of treatment for early glottic cancer.[220] Voice restoration following TL is an important part of patients' rehabilitation and long-term QoL. Primary TEP provides almost immediate and satisfactory voice rehabilitation. However, it may not be ideal in all clinical scenarios and secondary TEP may be needed. Chemoradiotherapy and patient age do not affect voice quality with either procedure.[91] Voice-related quality of life (V-RQoL) outcomes for patients using tracheo-oesophageal speech had similar V-RQoL outcomes compared to oesophageal speech (ES), and both performed significantly better than electrolaryngeal speech (ELS). For ELS, the total V-RQoL score was better with longer time after surgery and older age.[221]

Swallowing

The importance of swallowing in HRQoL outcomes cannot be underestimated. In this chapter there is only space for a cursory summary of key concepts. The link between nutrition, social function and carers is important and there is the association of permanent gastrostomy with poor HRQoL.[171, 222] It is essential that patients and caregivers attend pre-treatment clinics to discuss nutritional support via the artificial route; their QoL can be enhanced if guided through a specialist support pathway based at the clinical site where they initiated their care, with links to key agencies.[223] Prophylactic gastrostomy insertion can be associated with significantly earlier start and longer use of enteral nutrition, fewer malnourished patients over time, and improved HRQoL at 6 months after start of treatment but there has to be a drive to assist the patient to achieve an adequate swallow to allow the feeding tube to be removed wherever possible.[224] Advanced T-stage, free-flap reconstruction, younger age and base of tongue tumours have a negative impact on post-treatment swallow function and related HRQoL in these patients.[100, 225–228] Swallowing dysfunction following chemoradiation is a major cause of morbidity and reduced HRQoL related to early and late toxicity.[229] More clinical outcomes research is a priority in this area through prospective and randomized studies, robust cohort studies comparing types of feeding and treatment, and interventions.[230, 231] Screening in clinic allows the opportunity for patients and carer support.[232] For more detailed assessment, questionnaires should be accompanied by objective measures and there can be differences between the two evaluations.[232] Long-term dysphagia is influenced by mean radiation doses to the constrictor muscles and there is potential advantage in reducing the RT dose to swallowing structures to avoid severe dysphagia.[233–235]

Taste

Alteration of taste (dysgeusia) is a relatively common complication of head and neck radiotherapy and has a detrimental effect on HRQoL.[236, 237] Taste alteration can influence patients' enjoyment and choice of foods[238] and their dietary energy intake.[239] Consumption of sugary foods (cariogenic) places dentate patients at risk of radiation related caries.[240]

Trismus

Trismus (limited mouth opening) is a common symptom and the incidence is in the region of one-tenth at presentation, one-third at 6 months and one-quarter at 1 year after treatment.[241] The incidence can be higher depending on the criteria used to define trismus.[242, 243] Trismus severely impairs HRQoL through issues such as pain, eating, chewing, taste, saliva, social functioning, social contact and dry mouth.[241–243] Structured exercise with jaw mobilizing devices can improve mouth opening on trismus and have a positive effect on trismus symptomatology and HRQoL.[244]

Xerostomia

As previously mentioned, the severity of of xerostomia correlates with oral discomfort, difficulty chewing/swallowing/speaking, altered taste and low mood.[245] Sticky saliva and profund dryness at night can be major issues.[246] Prevention is better than measures aimed at symptom control; hence there have been technological advances in the delivery of radiotherapy and this has led to less salivary gland hypofunction with sparing of the partoid glands and a potential improvement in HRQoL.[247, 248] IMRT is a technique that allows delivery of lower doses of radiation to normal tissue, while maintaining or increasing the tumour dose, compared with two-dimensional radiotherapy (2DRT) or 3D-CRT. Patients treated with IMRT experience statistically significant improvements in several important HRQoL domains.[249] IMRT had significantly better outcome in various scales such as global QoL, physical functioning, swallowing, senses (taste/smell), speech, social eating, social contact, teeth, opening mouth, dry mouth, sticky saliva and feeling ill.[101, 250] Adaptive head and neck radiotherapy (ART) is a new concept in which there is dose avoidance to anatomical structures. A timed

replan can achieve dosimetric improvement and needs further outcomes research.[251]

Unknown

In spite of the many issues impacting on HRQoL reflected in this chapter, there is still a lot we do not know. HRQoL is a clinical art of the individual and not a precise science. The patient response is not all negative and it is possible, from their experience, to get a different perspective and have a profound influence on the person's QoL.[252] Survivors benefited from support and understanding offered by family, friends and healthcare professionals. This difficult situation can serve as a catalyst for deeper human change. In spite of the major changes such as following laryngectomy, the support of family, friends and healthcare professionals can encourage a successful transition to recovery.[253]

HRQoL IN FOLLOW-UP

Routine assessment

It is very important to adopt a holistic approach to patients' care throughout their follow-up. Patients can report distress at differing time points. Distress negatively impacts on HRQoL.[254] HRQoL screening may permit early identification of problems that influence HRQoL outcomes and may also facilitate timely intervention.[255] HRQoL questionnaires are limited for holistic assessment in routine clinic.[193] Consequently, some of the patients' concerns will be under-recognized and this will lead to unmet needs, poor communication, delayed recovery, further distress and dissatisfaction. The Patient Concerns Inventory (PCI) has been developed to help patients raise issues in their consultation that would otherwise be missed and also to request the opportunity to see or be referred on to other members of the MDT.[256] Despite the PCI comprising of 57 items, it has been shown not to delay the consultation, as there is evidence that both the clinician and the patient focus on what they wish to say in the consultation more efficiently.[257, 258] As an indicator of quality of care and helping to reflect the patients' experiences, the PCI has been included in the national HNC mandatory audit (DAHNO).[259] Advances in information technology and patients' familiarity with computers and the internet will in the future allow for a much more integrated approach to HRQoL assessment and intervention.[260, 261]

Interventions

As our understanding of the HRQoL outcomes of patients has increased in recent decades this has led to a focus on intervention. There are many different interventions reflecting the scope of HRQoL in the post-treatment patient. Semple et al.[157] published a review of psychosocial interventions. Evidence for interventions is limited by the small number of studies, methodological problems and poor comparability. Future interventions should target HNC patients who screen positive for clinical distress and be integrated into standard care.[156] Certain groups of patients might be more suitable for targeted interventions, such as those having chemoradiotherapy, where the HRQoL outcomes are worse.[262] A nurse-led intervention around the time of discharge from hospital, based on informational needs, has potential benefits to HRQoL and satisfaction.[263] Early provision of psychotherapy might reduce post-traumatic stress disorder, anxiety and depressive symptoms, and prevent chronic psychopathology.[264] Interviewing patients to allow them to express their concerns has merit.[265] In the work stemming from the PCI, FoR has been found to be the commonest concern that patients wish to talk about at outpatient consultations.[118] The AFTER (Adjustment to the Fear, Threat or Expectation of Recurrence) intervention has been developed [266, 267] and needs further evaluation. Acupuncture as an intervention has been evaluated. It has been used in the prevention and treatment for radiation-induced xerostomia.[268] When given concurrently with radiotherapy and compared with sham acupuncture it significantly reduced xerostomia symptoms and improved HRQoL.[269] In a randomized crossover study by Simcock et al.[270] eight sessions of weekly group acupuncture compared to group oral care education showed significantly better relief of symptoms in patients suffering from chronic radiation-induced xerostomia. Holistic alternative approaches have also been investigated; examples include intra-oral low-level laser therapy for patients receiving radiotherapy and complementary and integrated therapies (CIT) such as relaxation massage.[271, 272] There is scope for other interventions such as for secondary lymphoedema to help in the management of associated symptom burden, functional loss and psychosocial impact.[273]

Lifestyle

There is a risk associated with continued smoking and alcohol consumption after diagnosis and this affects survival outcomes.[274, 275] Patients with HNC are at considerable risk for other chronic conditions, such as coronary heart disease, causing around one-quarter of deaths. Also, secondary cancers are prevalent.[276] Comorbidity impacts on survival[277, 278] and HRQoL,[279–281] hence it is important to include staging and outcome analysis.[282]

CONCLUSION

HRQoL is now an integral part of the management of the head and neck patients and their carers. In the future, it is likely that enhancements in information technology will allow HRQoL to be routinely integrated into the patient pathway. Also, as our understanding of the patients' perspective of outcome increases, so treatment selection will become more refined and aftercare determined by the needs of the patient.

KEY POINTS

- HRQoL is an essential component when reporting outcomes following head and neck cancer.
- HRQoL is usually measured by questionnaires. The choice of questionnaire is an important consideration and depends on the reason for collecting the patient reported outcomes.
- Many factors impact on HRQoL and relate to the physical/functional, social and emotional consequences of treatments.
- HRQoL questionnaires can be augmented by using prompt lists such as the Patients Concerns Inventory in order to give a more holistic approach to clinical care.
- Advances in computer technology will make a substantial difference in helping to collect HRQoL outcomes and allow this to be use on an individual patient basis for interventions.

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CHAPTER 21

PALLIATIVE CARE FOR HEAD AND NECK CANCER

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the following keywords: palliative and end-of-life care.

THE ROLE AND CHALLENGES IN PROVIDING PALLIATIVE CARE TO HEAD AND NECK CANCER PATIENTS

Head and neck cancer accounts for around 8000 cases per year in England and Wales and up to half of all these patients will die from their illness and will require palliative support.[1] The World Health Organisation (WHO) defines palliative care as being the 'total active care of patients whose disease is not responsive to curative treatment'.[2] The fundamental principle of palliative care is that it should 'offer a support system to help patients live as actively as possible until death and....help the family cope during the patient's illness and in their own bereavement'.[3] The care should be both patient-focused and family-centred and encompass physical, psychological, social and spiritual aspects of care.

With this holistic approach to care and treatment, the overall goal is the achievement of the best quality of life for patients and their families, a parameter recognized to be as important to patients as actual survival and avoidance of recurrence.[4, 5] Patients with head and neck cancer represent a complex group, in part related to the unique properties of the disease itself and the impact the illness and treatments have on different organ systems essential for human functioning e.g. communication, swallowing and breathing.[1, 4] The resulting functional deficit and symptoms that arise can be challenging to treat[6] and can have an impact on the patients' psychological well-being due to resulting social isolation and depression.[4] Additionally, the focus and type of treatment can contribute to the care challenges; those who undergo potentially curative surgery for advanced or recurrent cancer can still have significant morbidity and a limited prognosis and may be considered by some to be palliative.[7] The concept surrounding the terms 'radical' and 'palliative' treatment are challenged when caring for head and neck cancer patients.[8] An ideal palliative treatment is defined as one which provides symptom relief without producing significant morbidity; radiotherapy doses given to induce tumour regression and relieve symptoms are in the range used for cure and can cause painful mucositis and xerostomia; surgical intervention can be accompanied by disfigurement and functional loss.[8] The diagnostic difficulties raise a further challenge; sometimes, due to previous treatments, it can be difficult to obtain histological confirmation of disease recurrence causing uncertainty regarding appropriate referral for palliative care input.

Since the inception of the modern hospice movement by Cicely Saunders in the 1960s, palliative care has expanded.[9] Specialist palliative care units (or hospices) traditionally operated outside the National Health Service (NHS) and were funded by voluntary donations. Since the 1980s however, this situation has been changing with many hospices entering into financial partnerships with the NHS. Palliative Medicine became a recognized speciality in the UK since 1987[10] and increasing numbers of multidisciplinary palliative care support teams have been established within hospitals and the community. Multidisciplinary teams (MDTs) both within hospices and as advisory teams are an integral and key part of specialist

palliative care services and aim to bring together different healthcare professionals with the knowledge and expertise to ensure the appropriate treatment and care is given to each individual patient.[2]

Generally, when assessing the need for palliative care input and support, the decision for referral should be based on need rather than diagnosis, although clear explanations to both the patient and palliative care colleagues may be required regarding roles and responsibilities. Within the last decade, there has been recognition of the need to move palliative care 'upstream' in the disease trajectory and integrate more with curative and rehabilitative therapies rather than the more traditional involvement immediately prior to death (**Figure 21.1**).[9, 11]

Timon and Reilly[13] estimate that approximately 20% of head and neck cancer patients would qualify for palliative care input at the time of initial diagnosis, with an average survival of 5 months within this cohort. Shuman et al[11] suggest the following situations for review regarding the need for palliative care:

- unresectable locoregional disease and/or distant metastasis at initial presentation
- patients with recurrent unresectable locoregional disease and/or distant metastasis after treatment
- patients unable to have anticancer treatments due to disease stage, comorbidity, functional status and/or individual preference.

While this is a useful principle, it may not always be as clear-cut in practice as symptom burden or needs may indicate that palliative care involvement would be beneficial. Many principles of palliative care management are applicable earlier in the course of the illness, often in conjunction with anticancer treatment.[8] Generally, improved patient outcomes can be achieved by a proactive approach with the involvement of palliative care colleagues for advice about symptom control, joint discussion and decision-making and advanced care planning. There is a lack of data, evidence and outcomes regarding the needs and management of end-of-life for patients with head and neck cancer.[6] Further research is needed in this area to guide patient management and improved outcomes.

COMMON PALLIATIVE PROBLEMS IN HEAD AND NECK CANCER

Common symptoms that arise with head and neck cancer patients include pain, dysphagia, fatigue, weight loss and breathing difficulties[6, 14] although many other symptoms and concerns can arise (**Table 21.1**). A retrospective review of 93 terminal head and neck cancer patients showed that patients had a mean number of 4.7 (+/– 2.67) symptoms in the last 6 months of life.[14]

Within this section, an overview will be provided of the following issues: pain, respiratory tract secretion management, communication difficulties, and emergencies including terminal haemorrhage and airway obstruction. For more specific details about other symptoms and specific medications, reference to specialist palliative care textbooks such as the *Oxford Textbook of Palliative Medicine*[18] and the *Palliative Care Formulary*[19] is advised.

Pain

In head and neck cancer patients, pain is a common symptom with studies estimating the prevalence to be between 62% and 99% (**Table 21.1**). Pain can be sub-divided into two main categories:

- Nociceptive pain: arising due to ongoing activation of primary afferent nerves by noxious stimuli (nociceptors)[20]
- Neuropathic pain: due to dysfunction or disease affecting the peripheral and/or central nervous system.[21]

Within clinical practice, there can often be a mixture of both nociceptive and neuropathic pain which can arise either due to the cancer itself (local compression or invasion) or related to previous treatments.

The principles of effective pain management are governed using the WHO pain ladder which remains a useful, practical approach to managing cancer pain (**Figure 21.2**).[22] This step-wise approach advocates the use of non-opioids first-line (e.g. regular paracetamol); then the addition of a weak opioid such as codeine; then proceeding on to substitute the weak opioid for a strong opioid. Generally, the opioid of choice for moderate to severe pain remains morphine.[24]

The concept and understanding of opioid-induced neurotoxicity has become increasingly recognized due to accumulation of opioid metabolites.[25] Clinically, the patient will present with symptoms such as myoclonus, peripheral shadows, hallucinations, confusion and drowsiness. In this situation, the following should be considered:

- Can the current dose of the opioid be reduced (if pain is controlled)?

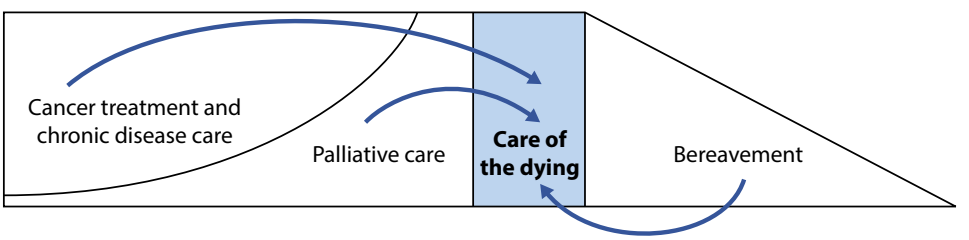


Figure 21.1 Involvement of palliative care within disease trajectory.[12]

TABLE 21.1. Symptom prevalence in advanced head and neck cancer

Author	Talmi et al.[15]	Price et al.[14]	Ethunandan et al.[16]	Ying-Li et al.[17]	Forbes[8]
Year	1995	2009	2005	2011	1996
Setting	Hospice, Israel	Mayo Clinic, USA	Hospital, hospice, home, nursing home, UK	Palliative care unit (PCU) within hospital, Taiwan	Hospice, UK
Method	Last hospice admission before death	Review of clinic notes in 6 months prior to death	Review of case notes for last week of life	Review of charts on admission to PCU	Last hospice admission before death
Patient numbers	67	93	32	94	38
N (%) with symptoms					
Pain	66 (99) 52 (77%) had severe pain	58 (62)	27 (84)	91 (97)	30 (79)
Dysphagia	Not reported	42 (45)	20 (63)	85 (90)	28 (74)
Fatigue/weakness	Not reported	36 (39)	Not reported	Not reported	Not reported
Weight loss/anorexia	63 (94)	40 (43)	Not reported	92 (98)	30 (79)
Breathing/airway difficulties	15 (22)	48 (52)	Not reported	41 (44)	11 (35)**
Feeding difficulties	22 (32)	Not reported	Not reported	84 (89)	28 (74)
Bleeding	6 (9)	13 (14)*	5 (16)	30 (32)	18 (47)

* This includes bleeding from tumour; haemoptysis; mucosal bleeding and bleeding from stoma.
** Problems with secretions.

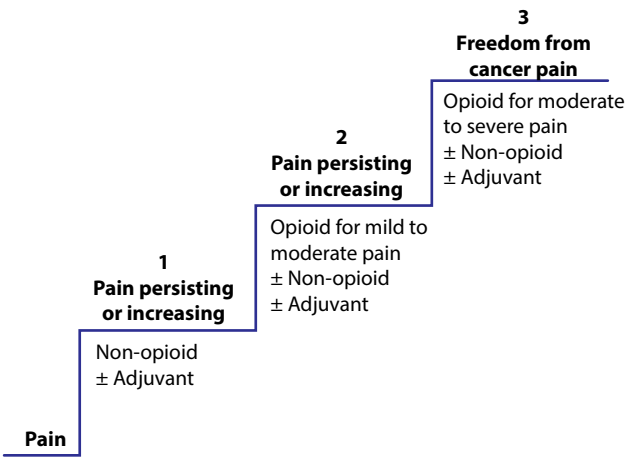


Figure 21.2 WHO pain relief ladder[23]

- Is the patient's renal function stable (as metabolites are more likely to accumulate if opioid is renally excreted)?
- Does the patient require an opioid switch?

In the latter situation, the current opioid medication should be switched to an alternative such as morphine to oxycodone or hydromorphone. If there is evidence of renal impairment, using opioids which are not excreted by the kidneys is beneficial e.g. alfentanil.[26]

In terms of addressing neuropathic pain, in addition to using the WHO ladder, the first-line approach to treatment is either using an anti-convulsant (e.g. gabapentin) or anti-depressant (amitryptiline) medication. If there is evidence of nerve compression, a trial of corticosteroids (dexamethasone) could be considered. Other therapeutic interventions would include the use of methadone, ketamine and potentially interventional pain procedures, and the involvement with specialist palliative care teams would be beneficial for this advice.

There have been more recent developments in the concept of 'breakthrough pain'. The Association of Palliative Medicine within the UK defines this as 'a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain'.[27] Usually, in this situation a short-acting preparation of morphine is given e.g. oramorph or oxynorm. There are newer formulations of strong opioids (fentanyl) which can be administered via sublingual, buccal and intranasal routes, for this type of pain. They have been shown to have equal efficacy compared with traditional oral medications,[28] quicker onset of action but are more expensive. In practice, they tend to be reserved for pain related to a particular event e.g. movement or pain that is sudden in onset and short-lived. It is noteworthy that prior to use, patients should be on at least 60mg of oral morphine or the equivalent.

Particular challenges that arise for patients with head and neck cancer include the route of administration as often the oral route cannot be used. Where a gastrostomy tube is in place, medications can be given this way. It is particularly noteworthy, however, that sustained release preparations of opioids should not be crushed or opened when administered via this route. There are modified-release granules (Zomorph) and suspension (MST Continus) that can be used safely.

The transdermal method of delivery remains an alternative way of delivering opioid medication e.g. fentanyl

patch but it is important to be mindful of the following key messages related to their use:

- transdermal patches should only be used when pain control has been established and is generally stable
- transdermal patches tend to be changed every 72 hours so they do not have as much flexibility in terms of dose titration
- some forms of the buprenorphine patch (e.g. BuTrans) have a maximum dose range (up to 20 mcg which is equivalent to just under 50 mg oral morphine.[29]

The administration of subcutaneous medication given via a continuous infusion (CSCI) is often associated with care of a dying patient. They can be used, however, earlier in the disease trajectory for head and neck patients and this would include as a temporary measure until a gastrostomy is inserted.

Respiratory tract secretion management

When considering the use of anti-secretory medications, the three main drugs are glycopyrronium, hyoscine hydrobromide and hysocine butylbromide. Comparison of these drugs has mainly been undertaken in studies looking at their efficacy in managing retained respiratory tract secretions associated with the last days of life. There is a lack of conclusive evidence about comparable efficacy, although due to the reduced likelihood of agitation and sedation, glycopyrronium may be preferred.[30] The balance needs to be reached between trying to reduce the amount of secretions and not making them too tenacious. If the oral route is not available and a gastrostomy (or equivalent) is not in place, transdermal hyoscine hydrobromide (Scopoderm) patches could be considered.

Communication difficulties

For patients with head and neck cancer, as the disease progresses, there can be increasing difficulties with speech. Alternative methods to aid communication can be using devices for artificially generated speech or using written communication, but the loss of the subtleties of communication can have a profound psychological effect on patients.[8]

Generally, it can be challenging to discuss the complexities of care and decision-making at any time, but with the additional impact of head and neck cancer on communication, this is even more heightened. It also highlights that advance care planning is even more pertinent for these patients while they are able to do so. Having open-ended discussions about the goals of care, potential future complications and issues and being proactive in screening for unmet information needs is an important principle to adopt within the management of these patients.[8]

Terminal haemorrhage

Care for head and neck cancer patients is especially challenging in the terminal phase of illness (the last weeks and days of life) due to the perceived risk of acute catastrophic events such as having a terminal haemorrhage[1, 11] or 'carotid blow out'. The actual occurrence of a terminal haemorrhage (defined as 'bleeding from an artery which is likely to result in death within a period of time that may be as short as minutes')[31] is low with rupture of the carotid artery system occurring in an estimated 3–5% of patients who have undergone major head and neck resections.[32] However, the anxiety and distress associated with the risk of this potential event should not be underestimated. With the increasing numbers of patients who wish to be able to die in their own home, there is the potential for terminal haemorrhage to occur in this setting.[33] Although it is important to be able to prepare the patient and family for this possibility, the benefit and burdens of such discussion need to be carefully balanced in order to avoid unnecessarily escalating distress about an event that may not occur.[33]

Certain factors can increase the risk of a terminal haemorrhage occurring including:

- tumour-related factors – proximity to carotid artery
- treatment-related factors – previous radical neck dissection and radiotherapy; post-operative healing problems
- systematic factors – coagulopathy; age >50 years; 10–15% loss of body-weight; and comorbidities e.g. diabetes mellitus.[33]

Sometimes there can be a herald or warning bleed which precedes the life-threatening haemorrhage or evidence of a ballooning or visible pulsation of arterial vasculature.[34] Trying to minimize the risk of terminal haemorrhage occurring is important. This includes reviewing the patient's current medication to ensure that anti-coagulants (warfarin, heparin) are stopped and other medications which effect platelet function or the coagulation pathway are reviewed and potentially discontinued e.g. non-steroidal anti-inflammatory medications, aspirin, selective serotonin reuptake inhibitor (SSRI) anti-depressants. In several cases arterial embolization by interventional radiologists following a sentinel bleed can delay a bleed or abrogate an ongoing bleed.

Ubogagu and Harris[33] published guidelines about the management of terminal haemorrhage. Although these were specifically for patients at risk of a terminal haemorrhage in their own home, the principles apply for other settings. The key principles include:

- somebody should stay with the patient (and family if present) to help reduce the anxiety and distress associated with the event
- dark towels should be used to reduce the visibility of blood
- an anxiolytic should be given e.g. 10 mg of midazolam given via deep intra-muscular injection due to its rapid onset and short duration of action.

The midazolam should be pre-emptively prescribed, although often in view of the rapidity of the event it is not needed, and certainly is secondary to the need to stay

with the patient. The aim of giving the midazolam is to reduce the patient's awareness and hence distress of the event. Additionally, it provides retrograde amnesia so that if the patient did recover, they would not have recollection of the event. Opioids are generally not needed in this situation unless the haemorrhage is not terminal and the patient is reporting pain. Providing sufficient support to both the family and the healthcare professionals involved is a key factor after the event.

Management at home is more challenging and ideally needs to include a full MDT discussion so that the community healthcare professionals are involved in care planning, the ambulance service are prepared (as they may provide acute support during immediate distress of the event) as well as having appropriate discussions with the patient and family.

Airway obstruction

A further complication that can lead to an acute catastrophic event is airway obstruction. Compromise of the airway can arise due to retention of secretions or by tumour encroachment into the airway or tracheostomy. Preparation for the patient, family and healthcare professionals that this event could occur is of key importance[11] although again the likelihood is thought to be rare. Decision-making about the appropriate level of escalation of treatment in the event of an acute airway obstruction is pertinent. Palliative surgical options include tracheostomy or debulking of the tumour within the airway if deemed appropriate.[35] In the palliative situation, pre-emptive prescription of an anxiolytic, such as midazolam, is appropriate for a terminal event. If there is clinical evidence of stridor, high dose (8 to 16 mg) dexamethasone[36] given via subcutaneous injection may be beneficial.

HOLISTIC CARE FOR THE HEAD AND NECK CANCER PATIENT

Spiritual issues

Spirituality can be interpreted as how an individual finds meaning, purpose and value in their life.[37] Although this meaning may be found within a religious context, it can also relate to achieving life goals, being at peace with oneself[38] or finding particular aspects of life worthwhile.[37]

As a routine part of the palliative care consultation, issues relating to this should be explored. For example, asking questions such as 'how are you coping?'; 'what gives you hope and strength?'; and 'do you ever question "why" this illness has happened to you?' This will enable a patient to share key concerns and the healthcare professional to explore the patient's priorities and wishes for their future care.

Depression

Depression is common in head and neck cancer patients, and as it can independently predict poorer quality of life, requires prompt diagnosis and treatment.[39] Additionally, head and neck cancer patients are noted to have a disproportionately higher suicide risk compared with the cancer population as a whole.[40] Part of this may be due to the higher prevalence of head and neck cancer among male patients and the association with tobacco and alcohol consumption, all of which have been associated with depression and suicide. Additionally, these patients may have more limited social support networks, impacting on their ability to cope.[11]

Brief screening measures can be useful for identification of depression in particular asking about anhedonia (loss of interest or pleasure in doing things) and low mood[41] as many of the traditional physical symptoms associated with depression occur commonly with advanced cancer e.g. weight loss, fatigue, reduced appetite. Treatment with both psychotherapy and anti-depressant medications should be discussed with patients and medication commenced where appropriate. Generally, SSRIs are often considered first line compared with tricyclic anti-depressants due to the latter often being poorly tolerated.[42] It is noteworthy, however, that SSRIs do have the potential to increase the risk of bleeding from the gastrointestinal tract which is a particular consideration for head and neck cancer patients. Mirtazepine is a noradrenergic and specific selective serotoninergic anti-depressant and may be associated with weight gain and sedation. Both of these may be acceptable side effects for cancer patients, particularly if the medication is taken at night.

Ethical issues

The four general principles of ethical decision-making include:[43]

- respect for autonomy – the individual's right to decide what is best for them
- beneficence – duty to act in a way that provides benefit
- non-maleficence – duty to act in a way that does not cause harm
- justice – the fair use and distribution of resources.

These principles form a useful framework to guide decision-making and care planning. Key to good practice is ensuring patient-centred decisions are made and providing explanations about the burdens and benefits of treatments to the patient. Particular ethical issues that arise for head and neck cancer patients include decisions relating to the provision of nutrition and hydration, especially those approaching end of life. Healthcare professionals should consider the individual values and wishes of patients and their families when undertaking decision-making. In view of the likely communication difficulties already highlighted, forward planning and discussions about these issues is pertinent to patient-centred care. Advanced care planning is defined as a 'process of discussion between an individual, their care provider, and often those close to them about future care' and most patients welcome the opportunity to have these types of discussions.[44] Ideally, these should be serial discussions, over a period of time and at intervals when the patient's

condition is relatively stable. Detailed evidenced-based national guidelines have been published within the UK.[45]

The General Medical Council (GMC) within the UK provides specific guidance about decision-making about hydration and nutrition by focusing on both patients 'approaching the end of life' (defined as those likely to die within the next 12 months), and those for which death is thought to be imminent and expected within a few hours or days.[46] A Cochrane review of clinically assisted hydration (CAH) (defined as providing fluids via the intravenous or subcutaneous route) in palliative care was unable to provide any firm recommendations about the use of CAH in dying patients due to the lack of good quality studies.[47] There is limited evidence that CAH may improve sedation and myoclonus,[48] but no evidence to suggest it will improve thirst, delirium or fatigue. Again, although the evidence is limited, CAH may exacerbate symptoms caused by fluid retention e.g. peripheral oedema and ascites. Overall, the review concluded that clinical decisions regarding CAH in the care of dying patients needed to be directed by the perceived benefits and harms on an individualized basis. Additionally, although CAH is regarded in law as a medical treatment,[49] many patients and families consider CAH to be a principle of basic care. This potentially creates tension and a point of ethical contention when making a decision to engage, withhold or withdraw fluids.

In practical terms, patients with advanced head and neck cancer often have a gastrostomy inserted as part of their earlier treatment and, if appropriate, this can be used as a route for hydration and nutrition. If the patient's overall condition deteriorates, the volume of fluid and feeds should be reviewed. For patients who are actively dying (i.e. in the last hours or days of life), often the desire for food or fluid reduces and is seen as a part of the dying process.[44] For those able to take sips of fluid, this should be continued and for all patients good oral hygiene promoted, appreciating that access may be more limited if there is local malignant disease. For most patients, CAH or nutrition is not required at this stage of their illness but a discussion with the patient (if able) and family members is often required to explain that they are dying from their illness rather than from a lack of hydration or nutrition. If concern is raised about this decision, the subcutaneous route can be used to provide fluids and is less burdensome compared with the intravenous route. It is not without complications, however, and these include local site reactions (pooling of fluid or cellulitus) and potentially more systemic problems with symptoms of fluid retention including retained respiratory tract secretions. If a decision is made to commence fluids in this way, regular daily review of the burdens and benefits of the treatment should be considered.

CARE OF THE DYING FOR HEAD AND NECK CANCER PATIENTS

Prognostication i.e. predicting when death will occur remains extremely difficult, with doctors often tending to overestimate prognosis in those with an incurable illness.[50] The recognition and documentation of particular disease trajectories has aided this process e.g. cancer tends to have a comparatively predictable trajectory with a steady decline and a recognized terminal phase (**Figure 21.3**).[48] Patients with head and neck cancer challenge this trajectory to an extent, however, as there is the risk of different modes of death occurring, e.g. acute complications such as terminal haemorrhage or from comorbidities such as chronic obstructive pulmonary disease (COPD).

End-of-life care policies for a number of countries focus on trying to enable more people to die in their preferred place of care which generally is at home.[51, 52] The majority of patients, however, continue to die within the acute hospital setting [53–55] and it is likely that patients with head and neck cancer are no exception to this trend. The provision of palliative care within the acute hospital sector, however, is not without its shortcomings. A recent national survey

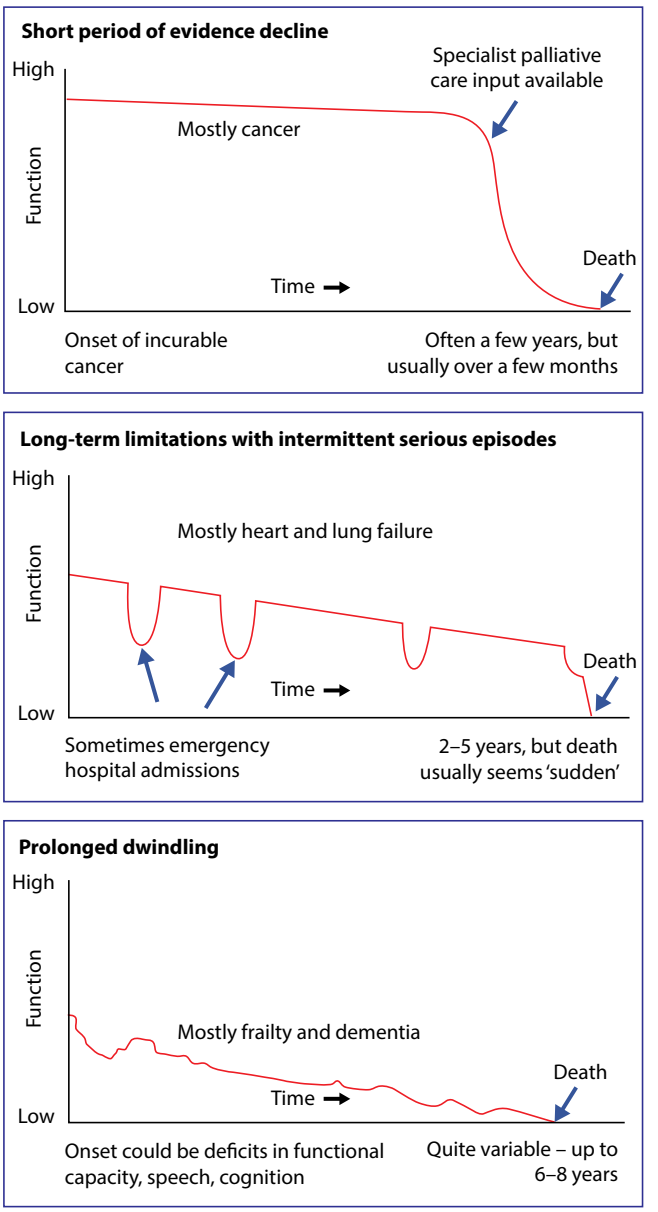


Figure 21.3 Typical illness trajectories for people with progressive chronic illness.[47]

BOX 21.1 The Priorities for Care are that, when it is thought that a person may die within the next few days or hours[58]

1. This possibility is recognized and communicated clearly, decisions made and actions taken in accordance with the person's needs and wishes, and these are regularly reviewed and decisions revised accordingly.
2. Sensitive communication takes place between staff and the dying person, and those identified as important to them.
3. The dying person, and those identified as important to them, are involved in decisions about treatment and care to the extent that the dying person wants.
4. The needs of families and others identified as important to the dying person are actively explored, respected and met as far as possible.
5. An individual plan of care, which includes food and drink, symptom control and psychological, social and spiritual support, is agreed, co-ordinated and delivered with compassion.

of bereaved people in the UK perceived that the quality of care for dying patients was not as high as the level provided at home, within the hospice or care home setting.[56] Recommendations have included increasing accessibility to specialist palliative care teams and mandatory training about care for dying patients for all healthcare professionals.[56] The most recent National report for 'End of Life Care Audit – Dying in Hospital' based on data collected in 2015, however, demonstrated that there were improvements compared with a similar audit undertaken in 2013: a higher proportion of patients were appropriately recognized to be dying in a timely manner and for 95% of these, there was a documented discussion about this recognition with those individuals identified as important to the patient.[57]

In terms of national guidance within the UK about the principles of providing care for those who are dying, the 'One chance to get it right' report identified five 'priorities for care'.[58]

'Individualized end-of-life care plans' are recommended and the subsequent publication of the NICE guidelines for end-of-life care has helped provide a framework for best clinical practice.[59]

Issues specifically related to care of head and neck cancer patients who are actively dying include the provision of adequate pain control. It is not generally recommended that transdermal fentanyl patches are commenced at this stage due to difficulty with titration. If the patient is already established on this method of analgesia, however, it should be continued and in the first instance, as needed injections of opioid used to help control pain. Depending on the amount of extra opioid needed, a continuous subcutaneous infusion (CSCI) should then be commenced in addition to the fentanyl patch.[60]

CONCLUSION

Caring for patients with advanced head and neck cancer is a complex area which raises unique challenges compared with other malignant diseases. Close collaborative working between head and neck cancer teams and specialist palliative care teams is important in addressing patients' needs and achieving high quality of care for the patient and their family. A pro-active approach to management of physical and psycho-social symptoms is needed to best meet patients' changing needs and providing best supportive care.

KEY POINTS

- Head and neck cancer patients have especially complex needs due to the impact the illness and treatment have on communication, swallowing, and breathing.
- Patients often have multiple symptoms including pain, fatigue, retained respiratory tract secretions as well as psychological distress causing depression.
- Advance care planning is important due to the potentially different modes of deterioration and subsequent death from this illness.
- Individualized care plans, incorporating a holistic assessment of needs, should support those who are actively dying.

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CHAPTER 22

TRANSORAL LASER MICROSURGERY

Mark Sayles, Stephanie L. Koonce, Michael L. Hinni and David G. Grant

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SEARCH STRATEGY

The initial search strategy involved PubMed, EMBASE, and Google Scholar database enquiries using the search term *transoral laser microsurgery*. The Cochrane database of systematic reviews was also searched for relevant articles. Additional articles were identified by manually searching reference lists.

INTRODUCTION

Transoral laser microsurgery (TLM) is a minimally invasive surgical approach to functional organ preservation for cancer of the upper aerodigestive tract. It involves tumour resection using specialized endoscopic instruments, microscopes and lasers, with the wound bed often left to heal by secondary intention.[1] The term TLM was first coined by John Salassa of Mayo Clinic in the 1990s to distinguish this technique from the more generic endoscopic laser surgery by virtue of using an operating microscope to closely examine the host-disease interface following principles established by Wolfgang Steiner.[2] This affords the advantage of binocular vision and stereoscopic depth perception, combined with the superb optics of modern microscopes, making it truly a microsurgical technique. In contrast to non-surgical radiation and chemoradiation-based protocols, TLM places no limit on treatment options in the event of recurrent, persistent or second primary disease and avoids the long-term iatrogenic sequelae of definitive radiotherapy. TLM differs from traditional surgical oncology by departing from the classic Halstedian principle of *en bloc* resection. Instead, tumour is often divided with the laser and the tumour margin followed under the microscope, with frozen-section control, allowing piecemeal resection via the endoscope. The aim is to ensure a tumour-free margin in all dimensions with minimal excision of normal tissue. TLM also has a diagnostic element, as it precisely defines tumour extent at the time of surgery and provides maximal tissue for pathological assessment. Transoral minimally invasive techniques will likely become more widespread in the future as advances in technology continue to improve endoscopic access to the pharynx and larynx. This chapter describes the current state of surgical laser technology, its application to head and neck cancer, and provides a framework for the TLM approach to tumours at each major head and neck subsite.

LASERS

Production of laser light

An appreciation of the quantum physical basis of electromagnetic radiation is important for any surgeon wishing to understand the adjustable parameters of laser equipment. 'Laser' is an acronym for light amplification by stimulated emission of radiation. A laser consists of three key components: the lasing medium (e.g. carbon dioxide [CO_2]); an excitation source (e.g. alternating electrical current); and a resonant chamber with a mirror at either end to create positive optical feedback.

Laser energy is the result of electrons in the lasing medium transitioning from high to low energy states. Electrons are negatively charged subatomic particles that can be thought of as orbiting around a nucleus of protons and neutrons. Each orbit can be thought of as an 'energy level'. Electrons transition between discrete energy levels by either absorbing (low-to-high energy transition), or emitting (high-to-low energy transition) a packet of energy. Energy is emitted as a 'photon' of light, the wavelength of which may or may not be in the visible part of the spectrum. Electrons prefer to be in the lowest possible energy level, known as 'ground state'. The transition of an electron from a high energy level to ground state either occurs spontaneously or is stimulated by the collision of the atom with an incident photon. In the stimulated case, one photon collides with an atom and a second photon is emitted. The first photon is not absorbed and continues on its path. Therefore, the total number of photons is increased and the light is amplified.

The lasing medium is contained within the resonant chamber with a mirror at either end. The lasing medium is first excited ('pumped') with an input energy, usually an electrical current. This energy promotes electrons from their ground state to an excited state. Some electrons will then spontaneously fall back to ground state, emitting photons of light with a characteristic wavelength dependent on the lasing medium. These photons are reflected from the mirrors at the ends of the resonant chamber, back into the chamber. The photons will then collide with the lasing medium, producing stimulated electron transitions to ground state, and therefore stimulated photon emission. The stimulated emission has the same wavelength and travels in the same direction as the incident photon. For there to be net amplification of light, there needs to be more lasing medium molecules in the excited state than in the ground state at any one time. This state is known as 'population inversion' and is achieved by pumping with input energy. At one end of the resonant chamber the mirror is partially reflective and partially transmissive. Thus a portion of the light can escape the chamber as a 'laser beam'. The remaining light remains in the chamber, stimulating more photon emissions. The chamber rapidly reaches an equilibrium and the process continues as long as the excitation source maintains population inversion. The result is a beam of light that is monochromatic (of a single wavelength), collimated (travelling in one direction), and both temporally and spatially coherent (photons oscillate in phase, and are distributed equal and parallel across the wave front) (**Figure 22.1**).

Laser parameters

The adjustable parameters of surgical laser systems relate to the laser power, the size and shape of the focused beam (the 'spot'), the power output pattern (continuous wave (CW) or pulsed), and in some cases the equipment allows the user to specify a penetration depth. It is important to realize there is no single 'best' set of parameters: the most appropriate settings vary widely according to the clinical situation, the preferences of the individual surgeon, and between different laser delivery systems.

WAVELENGTH

The wavelength of laser light is dependent on the lasing medium. The CO_2 laser has been the workhorse of TLM since the inception of this approach to treating laryngeal carcinoma because of the excellent tissue cutting and coagulation properties.[2, 3] Other lasers such as Thulium-YAG and Holmium-YAG have been used for TLM and transoral robotic surgery.[4, 5] Each laser has a different wavelength and in turn different absorption characteristics in living tissues. The wavelength of the CO_2 laser is relatively long at 10.6 µm, placing it in the mid-infrared part of the electromagnetic spectrum. Therefore, CO_2 laser light is invisible. It is usually combined with a co-axial He-Ne red aiming beam. The CO_2 laser has a high coefficient of absorption by water, and its action is independent of

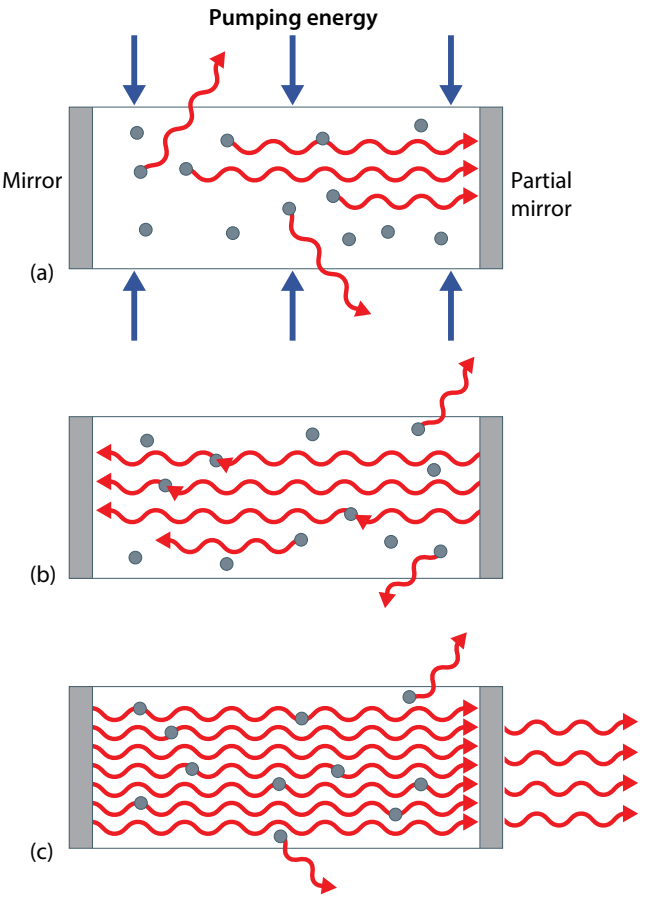


Figure 22.1 Laser physics. **(a)** Pumping of the CO_2 and start of the population inversion. **(b)** The reflected photons traverse the cavity and stimulate other CO_2 molecules to emit photons: the beam is amplified. **(c)** Almost the complete medium contributes to the stimulated emission. The laser beam is transmitted via the partially reflective mirror.

tissue colour. The energy of the CO_2 laser is therefore absorbed by all water-containing tissues.

POWER

Laser power (in watts) is a measure of energy (in joules) emitted per second. Increasing the power increases the amount of energy transferred to the target tissue per second. However, to predict the effect of a given power, the size of the focused beam and the pattern of power output must be known. That is because for a given power the effect on target tissues will be greater if the beam is focused onto a smaller spot (i.e. the energy is more concentrated in space). For this reason, it is sometimes useful to talk about 'power density' (in watts per cm^2) rather than power *per se* as means of comparing different laser set-ups. Similarly, for a given total amount of energy the effect is greater if it delivered over a shorter time period (i.e. the energy is more concentrated in time). Fluence (in joules per cm^2) is power density multiplied by the exposure time, and measures the *total* amount of energy delivered per unit area of exposed target tissue; the 'dose' of electromagnetic radiation. Some laser systems allow the user to specify a penetration depth. It is crucial to realize this is based on the *average* absorption of CO_2 laser light by living tissues. Based on this assumption of average energy absorption and knowing the size of the focused beam, the software calculates the power output required to make the selected incision depth. Therefore, by selecting an incision depth, the user is allowing the software to vary the laser power to produce a predicted surgical effect. The user should be aware that the system is by no means measuring the depth of the incision made, and the actual depth cut will depend on a variety of factors unique to each case.

FOCUSED BEAM 'SPOT' SIZE

The laser beam is passed through a lens to focus the energy on a spot which is typically 0.2–2.0 mm in diameter. The diameter of the focused beam exists over a range of distances around the focal length of the lens, the 'depth of focus'. By defocusing the beam the spot size at the target surface is increased and the laser energy is spread over a wider area. This effect can be exploited for haemostasis of small vessels up to 1 mm in diameter.[6] Larger vessels require careful identification and endoscopic clip application and/or cautery. As well as the manual microscope-mounted micromanipulator laser beam used in a standard 'dot-to-dot' approach, some surgeons use the AcuBlade™ system (Lumenis Inc., Santa Clara, CA., USA). This automatic scanning micromanipulator system produces either linear or curvilinear incisions or circular areas of tissue ablation by rapidly scanning the laser beam back and forth along a pre-determined path.[7]

POWER OUTPUT PATTERN

Lasers energy can be delivered through intermittent pulses, repeated pulses, as a continuous wave (CW) or as very rapid (< 1 ms) pulses in the form of UltraPulse of SuperPulse mode. CW mode produces surrounding tissue damage from thermal spread of laser energy. To produce the desired effects of cutting and coagulation with adequate haemostasis of small vessels and limited char formation, specialized CO_2 laser pulsed modes have been developed: SuperPulse and UltraPulse. These are used with the laser in CW mode, with the energy output pattern modulated into a SuperPulse or UltraPulse pattern. Pulsed modes deliver high peak power density in repeated short duration (< 1 ms) pulses. The difference between SuperPulse and UltraPulse is subtle and clinical outcomes are largely equivalent, although incisions are marginally finer with UltraPulse mode.[7] Superpulse has higher peak energy, less total energy per pulse and more rapid pulse repetition compared to UltraPulse.[6]

Delivery systems

Until relatively recently the CO_2 laser was limited to line-of-sight delivery via a reflecting mirror driven by a micromanipulator mounted on an operating microscope in the manner first used by Strong and Jako in 1971.[3] Restrictions in the physical workspace available via the transoral route, and/or in laryngeal exposure limited the circumstances in which the CO_2 laser could be used. Hollow waveguide systems have been developed to allow the CO_2 laser to be delivered via flexible guides to an increased range of upper aerodigestive tract subsites. These flexible waveguides can be used freehand using a variety of hand pieces, linked to a transoral robotic system, or used via flexible endoscopes in an outpatient setting.[8–15] The first hollow core flexible waveguide system was developed by OmniGuide (Boston, MA., USA) using a photonic band-gap fibre assembly, and is now marketed as BeamPath™. Subsequently, Lumenis (Santa Clara, CA., USA) have developed the FiberLase™ system.

Laser interaction with tissues

When laser light hits tissues, a proportion of the energy is reflected from the surface, a proportion is scattered, a variable amount is absorbed, and the remainder is transmitted. Reflected energy is effectively lost for the surgical purpose of cutting and coagulation and can cause unwanted thermal injury to adjacent tissue. Scattering is dependent on the optical properties of the tissue and the wavelength of light. Shorter wavelengths are scattered more than long wavelengths; hence the commonly used CO_2 laser in TLM is only minimally scattered. Absorption requires a chromophore (a molecule to absorb energy at a particular wavelength). In the case of the CO_2 laser the chromophore is water. The intensity of laser energy decreases exponentially from the tissue surface, hence the absorption (and therefore the heat generated) is maximal at the tissue surface. The thermal penetration of the CO_2 laser is much shorter than other lasers; several micrometres compared to several millimetres for Nd-YAG, Argon, or KTP-YAG lasers.[16, 17] Laser energy is rapidly converted

to heat, resulting in tissue vaporization and precise cutting. Compared to other lasers, the CO_2 laser causes much less thermal spread to adjacent tissues.[18] It is important to maintain appropriate tissue traction and counter-traction when working with the CO_2 laser, to allow visualization of the cut tissue surface and to avoid excessive char formation. In contrast to tumour excision by cutting with a CO_2 laser, there has been some early success with photoangiolytic therapy for early glottic carcinoma.[19–22] In this technique, a KTP laser or other angiolytic lasers that use haemoglobin as a chromophore are exploited to selectively destroy the microvasculature of early glottic cancers.

OPERATING ROOM SET-UP

Trans-oral techniques require a number of highly specialist pieces of equipment including the operating microscope, endoscopes, lasers and endoscopic graspers, diathermy probes and clip applicators. The arrangement of the room is an important consideration since the microscope and laser are bulky and there are specific safety concerns regarding the laser and operating room personnel. **Figure 22.2** is a schematic representation of the typical operating room set-up. It is important to have a selection of endoscopes available (**Figure 22.3**). A good endoscope has a wide proximal aperture to allow instruments to be introduced and manipulated to achieve optimal tumour exposure and tissue retraction. Some endoscopes have inbuilt smoke extraction ports whilst others require an additional smoke extraction unit to be mounted. For oropharyngeal and some hypopharyngeal tumours, the Feyh-Kastenbauer retractor (Invotec) may be used (**Figure 22.4**). This is a highly versatile system, and provides excellent exposure in the majority of cases. Several laser delivery systems are available, each with their own specific advantages and disadvantages over others. The most commonly used systems include the microscope-mounted micromanipulator and more recently flexible hollow core delivery systems (**Figure 22.5**). In all cases, the back table is set up with a selection of endoscopic graspers and diathermy probes (**Figure 22.6**). For dental protection, we prefer to use customized guards for each patient, made from thermoplastic (**Figure 22.7**).[23]

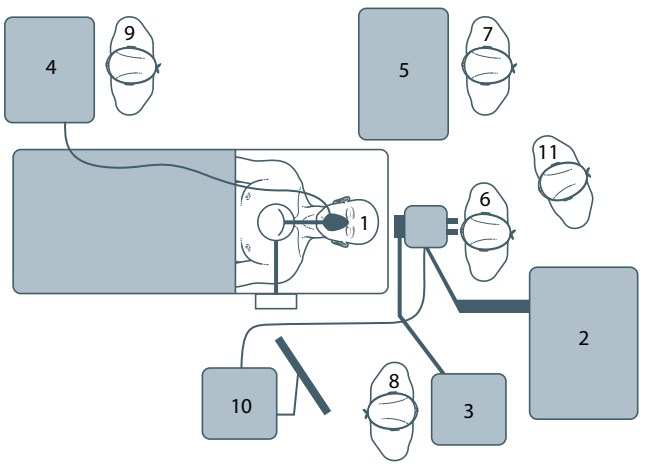


Figure 22.2 Operating room layout. 1, Patient positioned on operating table, with laryngoscopy suspension in place. 2, Operating microscope. 3, Laser coupled to the microscope-mounted micromanipulator. 4, Anaesthetic machine. 5, Back table. 6, Operating surgeon. 7, Operating room nurse at the back table. 8, Operating room nurse controlling the laser. 9, Anaesthetist. 10, Endoscopy 'stack' with camera coupled to the microscope. 11, Trainee surgeon.

HANDLING THE PATHOLOGIC SPECIMEN

A fundamental concept in TLM that distinguishes it from traditional surgical oncology is resection by tumour division. There is now extensive clinical and experimental evidence showing no compromise of local oncologic control with a systematic TLM piecemeal resection compared to the traditional *en bloc* approach.[2, 24–26] The host–disease interface is carefully examined under the operating microscope and the tumour removed piecemeal through the endoscope. For early glottic carcinoma, UK TLM surgeon consensus agreement is for circumferential or *en bloc* resection where feasible with the philosophy of a second-look surgery in the event of uncertain or positive margins.[27] As the indication for TLM evolves to include larger tumours in more inaccessible subsites the paradigm for dealing with resection margins is also changing. The complete excision of tumour to negative histopathological margins at the primary site is key to local disease control.[28, 29] Positive margins on permanent section at the end of TLM are associated with significantly increased rates of local recurrence, distant metastasis, and necessity for salvage surgery, as well as lower overall survival rates.[26, 30] However, an advantage of TLM is that there is usually no need to reconstruct the surgical defect, so the tumour bed is left exposed and readily accessible for second or even third resections to achieve negative margins. There is no negative effect on local recurrence or survival if the negative margin requires two or more attempts.[28, 29]

Hinni et al. recently coined the term 'margin mapping' to describe their approach to the pathological specimen in a series of 128 TLM oropharyngeal cancer resections.[31] This technique involves the surgeon inking the margins of each section of the tumour removed in the operating theatre followed by careful pathological assessment of the margin by intra-operative frozen section. Overall, the positive deep margin rate in the permanent section was 1% for previously untreated palatine tonsil squamous cell carcinoma. There were no local recurrences in the previously untreated group. The piecemeal removal of tumour in the lateral oropharynx is therefore oncologically sound. This is despite what some would term 'close' margins, with the mean smallest margin of 1.98 mm. Hinni et al. relate the size of the deep margin to the width of the lateral oropharyngeal wall musculature in healthy volunteers as assessed by magnetic resonance imaging and conclude

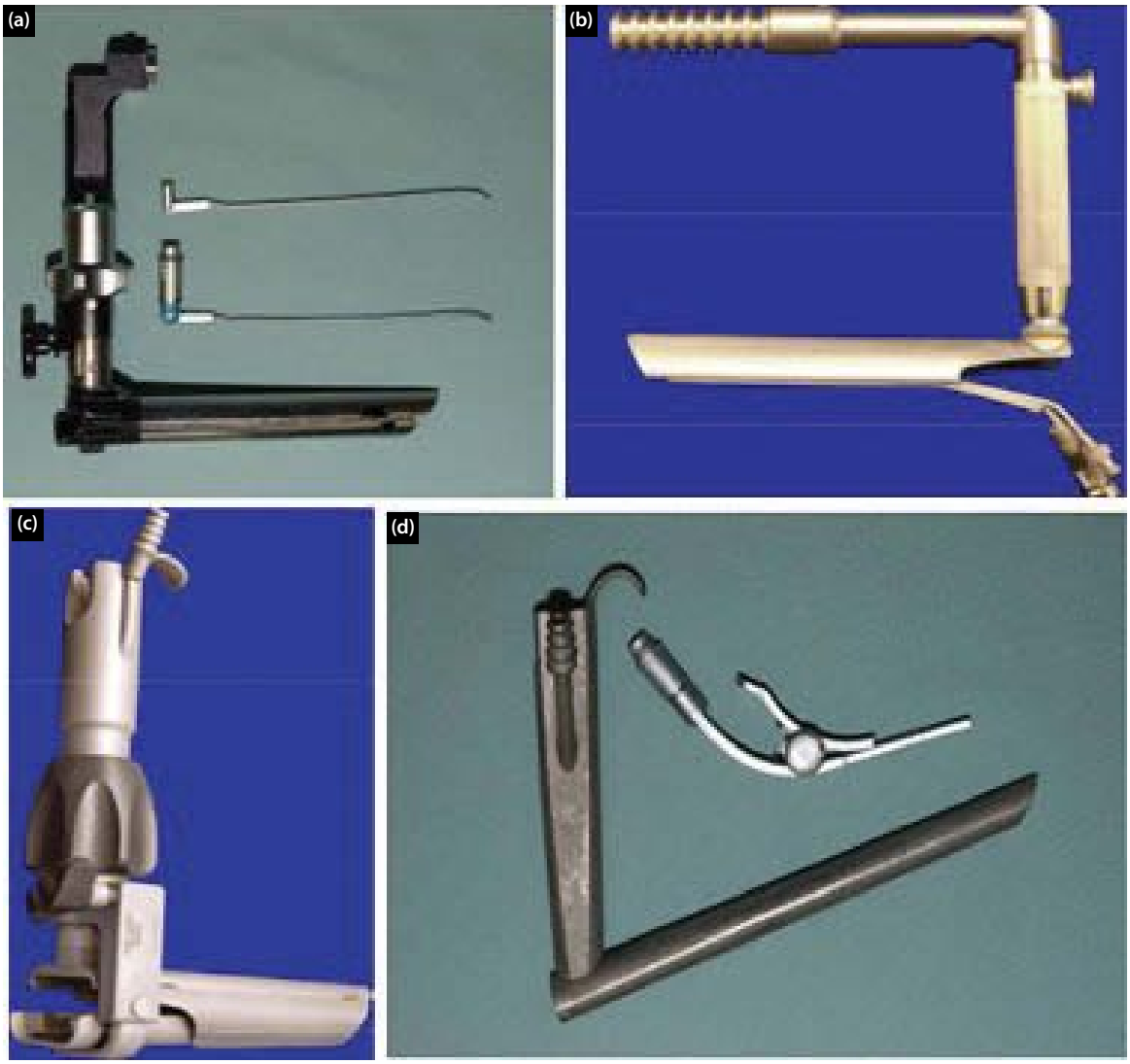


Figure 22.3 Endoscopes used in TLM. **(a)** Steiner distending laryngoscope. **(b)** Zeitels universal modular laryngoscope. **(c)** Steiner distending oropharyngoscope (supraglottiscope). **(d)** Steiner laryngoscope.

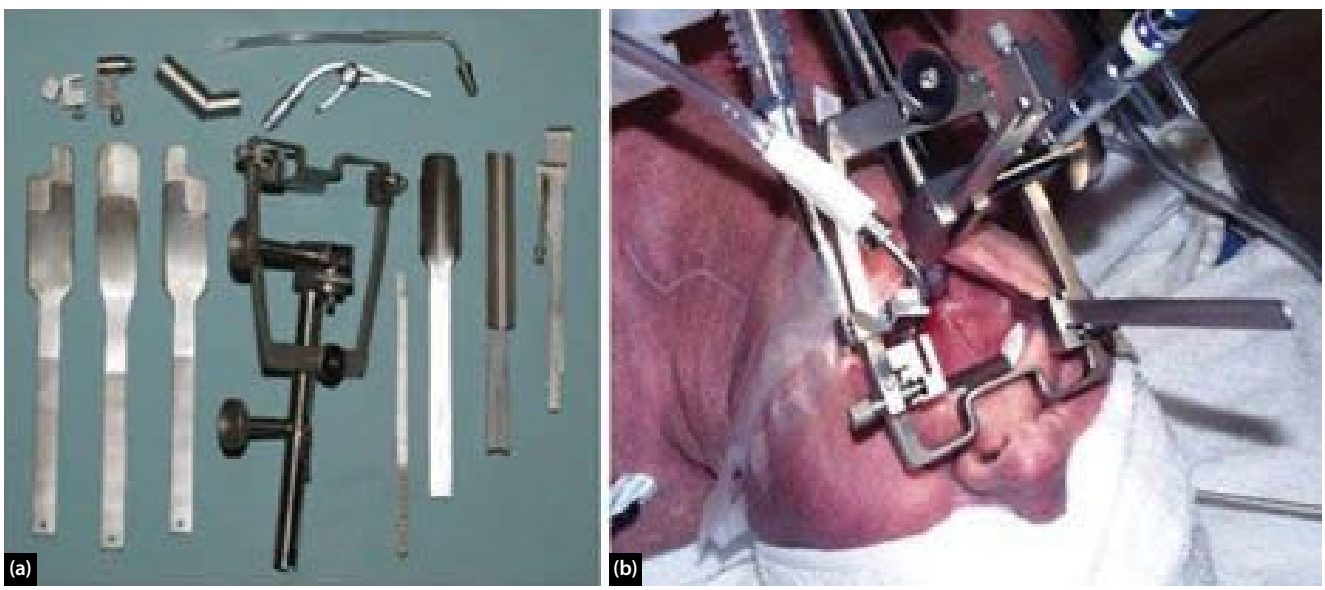


Figure 22.4 Feyh-Kastenbauer retractor set. **(a)** Retractor set **(b)** Retractor placed in the mouth prior to a transoral resection. Assembled *in situ*.

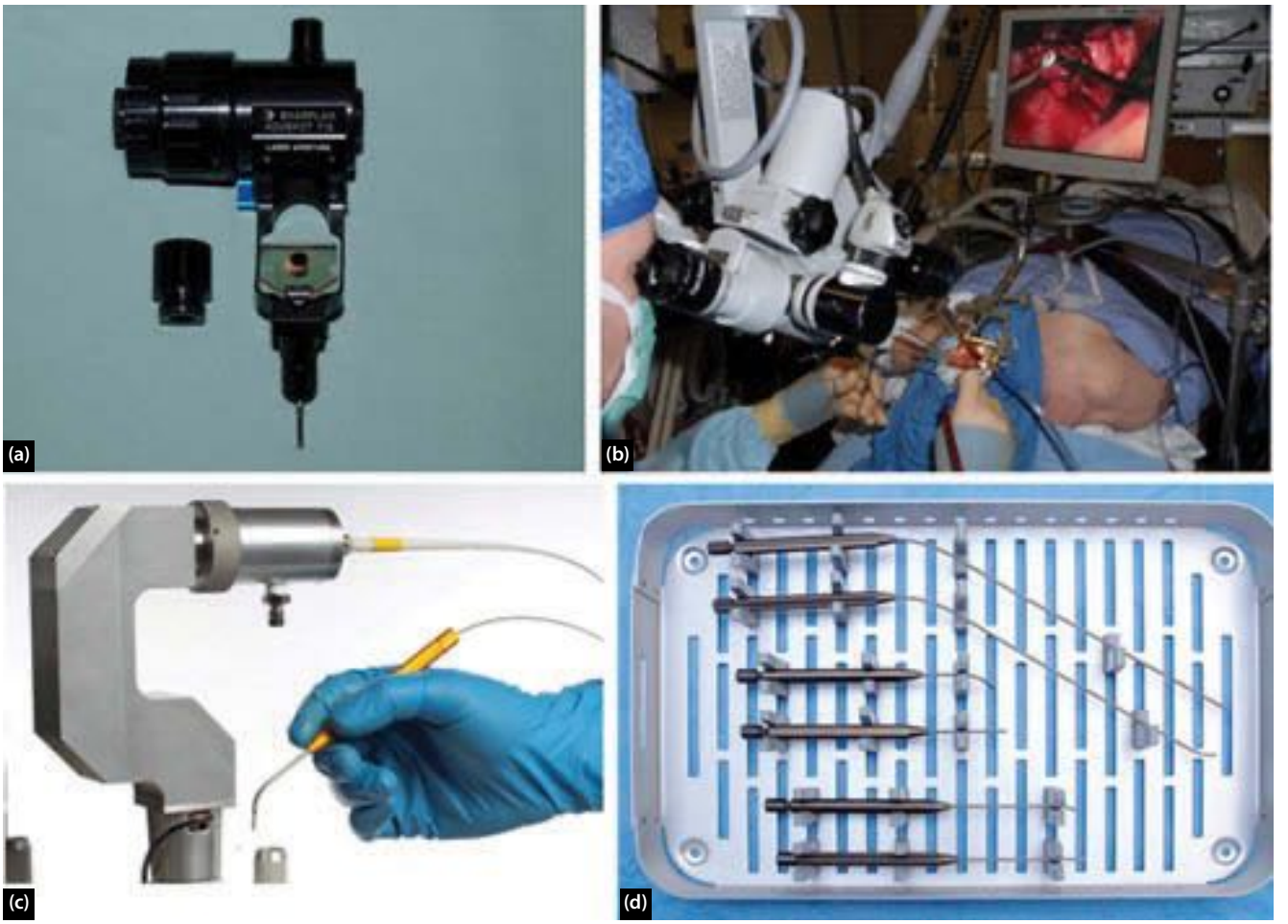


Figure 22.5 Laser equipment. **(a)** Microscope mounted micromanipulator. **(b)** The micromanipulator in use. **(c)** Hollow core flexible waveguide (Omniguide Inc.). **(d)** A selection of handpieces for the flexible laser delivery system.



Figure 22.6 The back table. The set-up includes a variety of graspers, diathermy probes and an inking set for intra-operative margin marking.



Figure 22.7 Custom dental protection. We favour the use of custom-made mouth guards in thermoplastic.

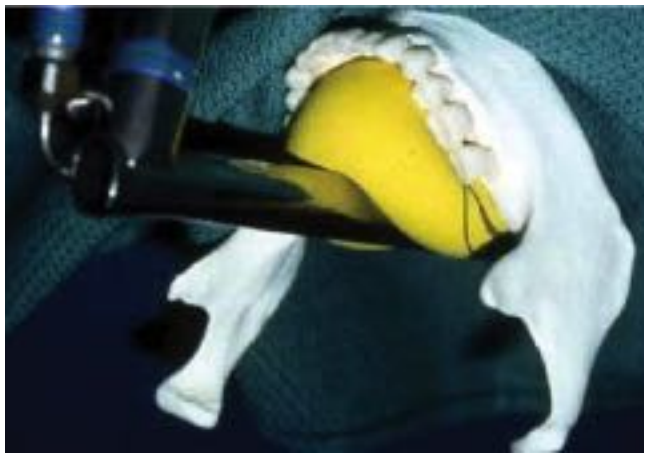


Figure 22.8 The tongue is non-compressible. Illustration of the difficulty of endoscopic exposure imposed by a large tongue, here using a tennis ball as the 'tongue'.

that since the superior constrictor width is 2.4 mm, it is unlikely that larger margins would be obtainable. They point out that inferiorly in the tonsillar fossa, deep to the superior constrictor muscle, is a space between styloglossus and stylopharyngeus muscles filled with parapharyngeal fat. This fat is unlikely to represent a barrier to tumour spread and is of no use as a frozen section margin. It should be emphasized that this detailed microscopic 'margin mapping' approach requires close collaboration between the surgeon and pathologist for intra-operative frozen section analysis and reporting. In some institutions limited resources mean this is simply not practicable.[32] It is also important to remember that frozen sections do not always correlate with permanent pathology.[33]

OPERATIVE TECHNIQUE

General considerations

The optimal patient for TLM is edentulous, with a wide mandible and no limitation of neck extension. Patient selection is key to the success of the technique, as inadequate endoscopic access to facilitate satisfactory oncologic resection is the main contraindication to TLM. It is important to realize that it is often necessary to adjust the set-up at least once during the procedure. Be prepared to change the endoscope and to move position to facilitate tumour exposure and extirpation. The tongue can be a source of significant difficulty in achieving the optimal exposure, as it is non-compressible (**Figure 22.8**). In addition, prolonged retraction and compression of the tongue can result in post-operative complications such as lingual and hypoglossal nerve palsies, and tongue oedema necessitating tracheostomy. In short, the usual caveats of endoscopic exposure apply to the TLM technique: think of the five Ts, Tongue, Trismus, Teeth, Tumour and Tilt (neck extension). To some extent, the development of flexible hollow-core waveguide systems for CO_2 laser delivery has allowed the endoscopic surgeon to work around corners; however, the microscope-mounted laser is limited to line-of-sight view. Therefore, appropriate tissue retraction and positioning of endoscope blades is essential for efficient and effective surgery. The optimal technique involves retracting the tumour into the field of view, applying tension to the specimen and cutting with the laser along the host–disease interface. The use of robotic techniques partially obviates this limitation, but sacrifices the magnification benefits of the TLM procedure.

As with any technique, experience is an important factor in the outcome. In particular, the ability to operate on larger tumours with the TLM approach is experience-dependent. There is a significant learning curve that affects both oncologic outcome and the incidence of operative complications.[34, 35] The authors recommend gaining experience on small tumours before attempting more complex resections using TLM. Locally-advanced hypopharyngeal tumours are often beyond the surgical expertise of even the most experienced TLM surgeons.

Laryngeal carcinoma

The aim of TLM is to preserve as much normal tissue as possible, thereby maximizing the potential for functional recovery. Small superficial T1a glottic tumours may be excised *en bloc* with the CO_2 laser.[27] More complex glottic and supraglottic tumours (T1b, T2-T3) benefit from an initial cut through tumour to assess depth of invasion (**Figure 22.9, Figure 22.10,**). The way in which the laser cuts through normal tissue and tumour is very different and can be appreciated under the operating microscope Normal tissues under tension will spring apart with a 'clean' appearance. Tumour tends to be firmer, less elastic and chars more when cut with the laser. Once the deep margin of the tumour is identified, the host–disease interface is followed with the laser and the tumour removed piecemeal. For large exophytic tumours, the authors recommend initially debulking the tumour to allow accurate assessment of the tumour footprint and its interaction with the host tissues. Assessment of the tumour should take into account the functional consequences of resection.

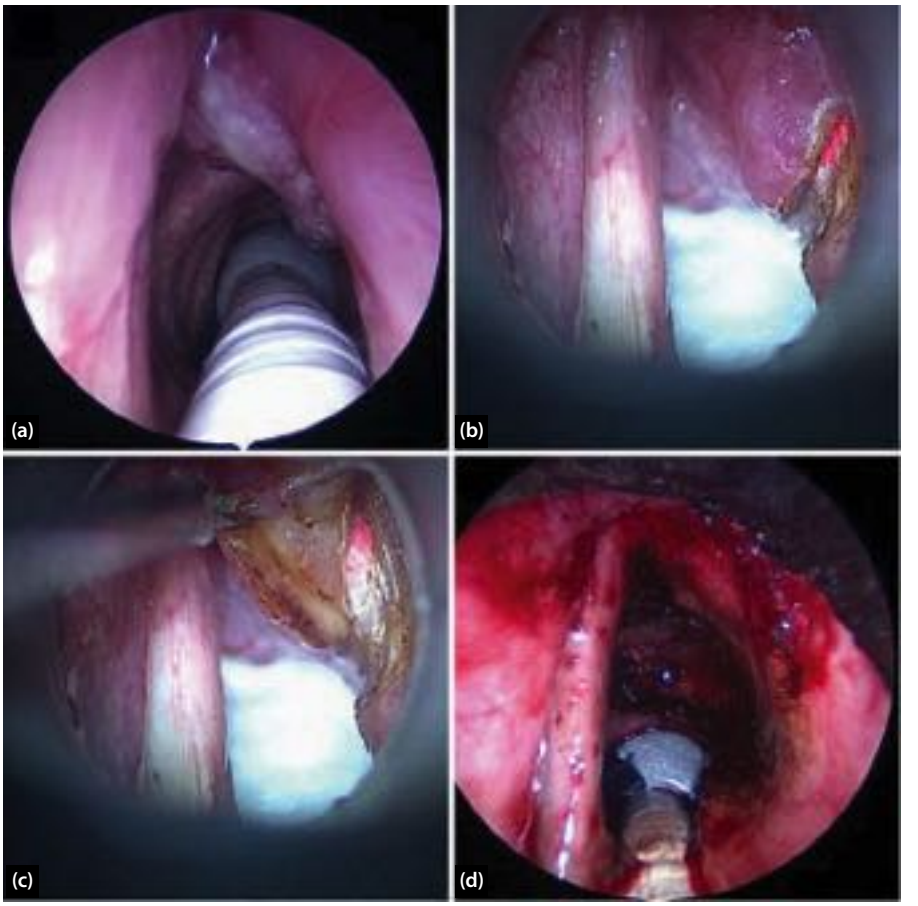


Figure 22.9 TLM for T1a N0 glottic carcinoma. **(a)** Tumour is confined to the right vocal cord. **(b)** The tumour is first divided with the laser to assess the depth of invasion. **(c)** The deep margin of the tumour is followed with the laser, applying tension to the specimen. **(d)** Appearance at completion of resection.

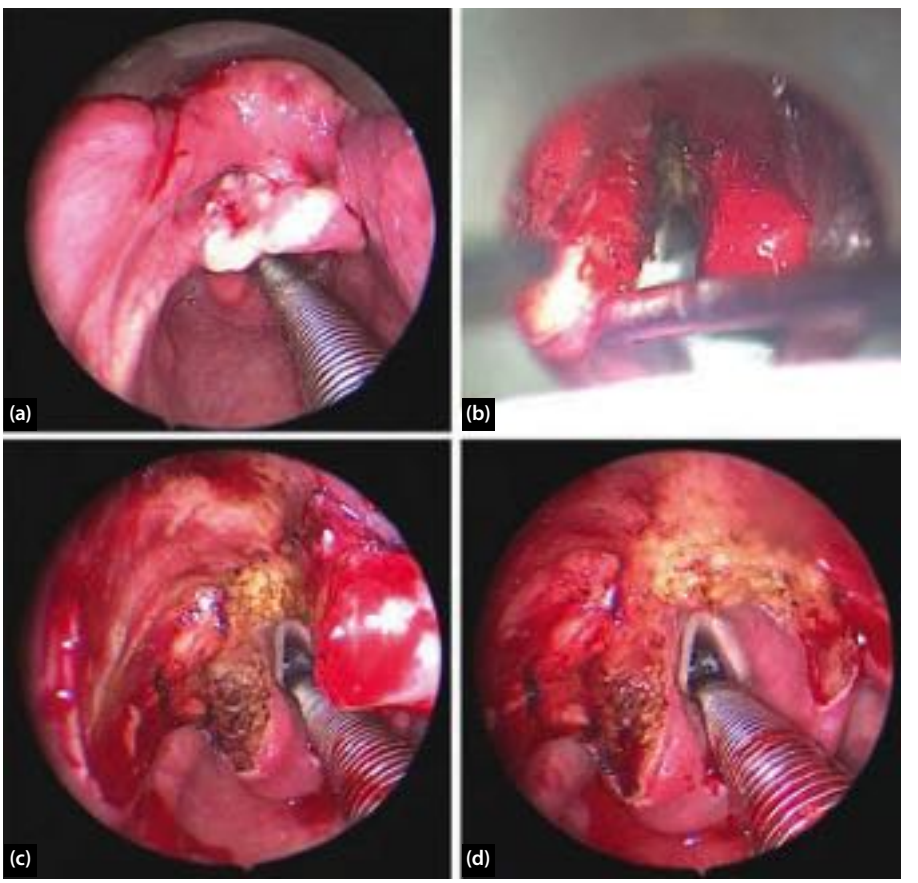


Figure 22.10 TLM for T2 N0 supraglottic carcinoma. **(a)** T2 tumour involving the epiglottis. Both arytenoids are free of tumour. **(b)** The epiglottis is first divided vertically to split the tumour in two to assess depth of invasion. **(c)** The left supraglottis is removed first. The arytenoid is spared. **(d)** Appearance at completion of resection.

To prevent significant functional impairment at least one competent arytenoid complex should be preserved.

The major limiting factor in TLM is surgical access. It has been the experience of the authors that laser excision of the false cord is useful for endoscopic access to the underlying glottis in some cases. Almost any laryngoscope can be used, and several different scopes may be needed during one resection. Very small diameter scopes such as the Hollinger laryngoscope may afford only a monocular view. Deployment of the laser in this situation is difficult. Laryngoscopes with matt finishes are preferable, as this limits reflections from the microscope. For glottic and supraglottic laryngeal carcinoma TLM, the authors prefer the use of suspension with the Göttingen table (Karl Storz). This modular system allows great flexibility and is ideal for laser laryngeal surgery (**Figure 22.11**).

Oropharyngeal carcinoma (OPC)

The use of TLM as a treatment for OPC was first reported by Steiner et al;[36] however, its use was been widely adopted until recently when evidence emerged of its potential benefits in treating OPC with the aim of achieving improved post-treatment swallowing function.[37–39] This is particularly pertinent in this era of HPV16 + OPC as TLM has the potential to contribute favourably to treatment de-intensification strategies. (See Chapter 13, Oropharyngeal tumours)

Transoral access to the lateral oropharynx and the soft palate is relatively straightforward using either a standard Boyle Davis tonsillectomy gag or, more usually, a Feyh-Kastenbauer retractor (**Figure 22.4**) or equivalent. In contrast, access to the tongue base is challenging. Access, if secured at all, is usually achieved using a bivalved distending oropharyngoscope (**Figure 22.3a**). Even then, due to the line-of-sight constraints, complete exposure of the tumour is not the norm and tumour resection has to proceed in a superficial to deep direction, appreciating the 3D orientation of the base of tongue and vallecula. In addition, it may be difficult, even for experienced surgeons, to distinguish tumour from normal base of tongue lymphoid tissue. In such cases, frozen section assessment may be helpful.



Figure 22.11 Göttingen suspension table. Adjustable laryngoscopy suspension table used for TLM resections. This offers maximal flexibility.

When resecting a tonsil carcinoma, following adequate exposure, it is usual to start by transecting the tumour in the axial plane at the mid-point, immediately separating the tumour into a superior and inferior portion.

Each portion is then resected completely, paying particular attention to the mucosal and deep margins whilst considering the trade-off between normal tissue resection and complete tumour removal.

It is important to appreciate, as highlighted above, that there is an anatomical limitation to the extent of deep resection margin that can be achieved in many cases.

Following resection of the main tumour specimen – which is typically orientated and pinned to a cork-board – and in the absence of frozen section availability, representative marginal biopsies are taken from the mucosal edges and deep tissues of the tumour bed. These marginal biopsies are separately assessed for the presence of residual tumour. There should be a zero tolerance for positive marginal biopsies and further resection should be mandated for the infrequent cases where one or more marginal biopsies are positive for tumour.

Similar resection margins are taken following the resection of tongue base tumours although the position from which the marginal biopsies are taken is less proscriptive and is tailored to the position and extent of the primary tumour resection. Despite this, the same zero tolerance for positive marginal biopsies should be maintained.

Hypopharyngeal carcinoma

The same principles of TLM apply when using it to treat cancers of the hypopharynx. As highlighted above, the management of large hypopharyngeal tumours using TLM is contraindicated in all but the most experienced hands. However, TLM removal of smaller tumours (T1/2) is often surprisingly straightforward and results in highly favourable swallowing function outcomes. Assuming there are no anatomical limiting factors relating to the jaw and dentition, access to tumours in the hypopharynx, using a distending oropharyngoscope, is often more straightforward than accessing the more constricted and anteriorly placed larynx – particularly if the tumour is anteriorly placed within the larynx.

An absolute contraindication to TLM in the hypopharynx includes tumour invading through thyroid cartilage into the tissue of the neck and relative contraindications include large tumours, the resection of which will also include the hemilarynx.

COMPLICATIONS

As the indications for TLM to treat laryngeal and pharyngeal malignancies have increased, so too has the number

of complications.[35] Although there are many advantages of TLM over traditional open surgical approaches, such as a decreased need for tracheostomy and gastrostomy with improved post-operative speech and swallowing function, it is not without risk of significant intra-operative and post-operative complications. Routine laser safety precautions are observed to reduce the risk of inadvertent burns to the patient and operating theatre staff. The patient's eyes and face must be covered with wet towels soaked in saline and all operating theatre personnel (with exception of the operating surgeon) must wear protective eye-glasses. It is common practice to display notices outside the operating theatre to warn staff the laser is being used.[40] The major procedure-associated risks are intra-operative airway fire, post-operative haemorrhage and aspiration pneumonia.

Upon contact with living tissue the energy in the CO_2 laser is immediately converted to heat, reaching temperatures up to 450 °C. The incidence of airway fire in large series is 0.4–1.5%.[41] The time to ignition of fat when lasing in oxygen concentrations of > 50% and with a power greater than 5 W is less than 5 seconds.[41] TLM is typically performed with FiO_2 < 30%, especially if an open ventilation system such as high-frequency jet ventilation is used, to avoid significant risk of airway fire.[6, 41, 42] It is routine practice to use laser-compatible endotracheal and jet ventilation tubes, and to cover the cuff of the endotracheal tube with saline-soaked patties to reduce the chance of tube damage and airway fire.[43] Smoke exhaustion should always be used, as the combustible particles in smoke significantly increase the chance of ignition at the site of lasing.[41] In the event of an airway fire the endotracheal tube is removed, the airway re-secured, bronchoscopy is performed and the procedure is terminated.

The most worrisome post-operative complication following TLM is catastrophic haemorrhage in the presence of impaired swallowing and airway protection. In this scenario patients are at risk of death from both torrential aspiration and exsanguination.[35, 44, 45] Rates of post-operative bleeding in large series are 1.4–10%.[1, 44, 46] The majority of bleeds occur within 7 days of surgery, but late secondary haemorrhage occurring up to 17 days post-operatively has been reported.[44] Bleeding is more likely in lateral pharyngeal wall and supraglottic resections compared to resections limited to the endolarynx or oral cavity.[44] Post-operative haemorrhage after TLM highlights the need for modern head and neck surgeons to be familiar with neck vascular anatomy from an inside-out perspective, in contrast to the traditional outside-in view (**Figure 22.12**). Larger vessels should be carefully identified, and clipped and cauterized before division. Vessels identified as the source of major post-operative secondary haemorrhage include the superior laryngeal artery, lingual artery and anterior facial artery.

It is preferable for the TLM surgeon to manage any post-operative haemorrhage. The principles are those of securing and preserving the airway and controlling the source of bleeding. If a surgeon other than the TLM surgeon is managing the emergency situation it may be safer to tie off the external carotid system in such cases, or consider endovascular embolization. Small bleeds should be considered sentinel bleeds. A careful and thorough endoscopic examination under anaesthesia in theatre by the TLM surgeon with equipment available to deal with a major haemorrhage (large clip applicators, large-bore suction, and monopolar and bipolar diathermy) may be required.

ADDITIONAL CONSIDERATIONS

Compared to traditional open surgery, TLM greatly reduces the need for tracheostomy and tube feeding.[47, 48] Temporary tracheostomy may occasionally be necessary for some patients undergoing extensive resections in whom significant aspiration is expected in the immediate post-operative period and who have marginal pulmonary function. Other indications for tracheostomy in TLM cases include patients with high risk of post-operative haemorrhage, and those who have received prior radiotherapy and undergo concurrent neck dissection at the time of TLM resection. Tracheostomy may also be necessary on occasion to improve endoscopic access to the tumour by obviating the oro-tracheal tube. It must be borne in mind, though, that tracheostomy impairs swallowing function in the immediate post-operative period. In the setting of post-operative complications necessitating a return to the operating room, it may be preferable to perform a tracheostomy, to avoid trauma to the healing surfaces by intubation and subsequent extubation by an oro-tracheal route.

Feeding tubes are generally not required in TLM resections. In some extensive oropharyngeal and supraglottic resections it may be necessary to place a nasogastric tube temporarily. This is best done by the operating surgeon under direct vision at the time of TLM resection. In the presence of large open wounds with multiple vascular clips the patient should remain nil by mouth for a period after surgery to reduce the risk of post-operative haemorrhage. In patients requiring post-operative radiation therapy and predicted to require a feeding tube for a prolonged period, the naso-gastric tube should be converted to a percutaneous gastrostomy tube if possible. Early involvement of a specialist speech and language therapist is of benefit for patients with swallowing impairment.

Other considerations include elective intensive care unit admission and the use of antibiotic prophylaxis during healing. Generally, ICU admission should be considered in patients at high risk of post-operative haemorrhage and those requiring tracheostomy. Some TLM surgeons favour the use of post-operative antibiotics in selected cases. It is our routine practice to avoid the use of antibiotics in the majority of patients.

CONCLUSIONS

The continued development of endoscopic and laser equipment has enabled significant advances in minimally invasive surgical approaches for head and neck cancer. TLM offers an alternative to traditional open surgical approaches, with minimal reconstruction (and the associated morbidity)

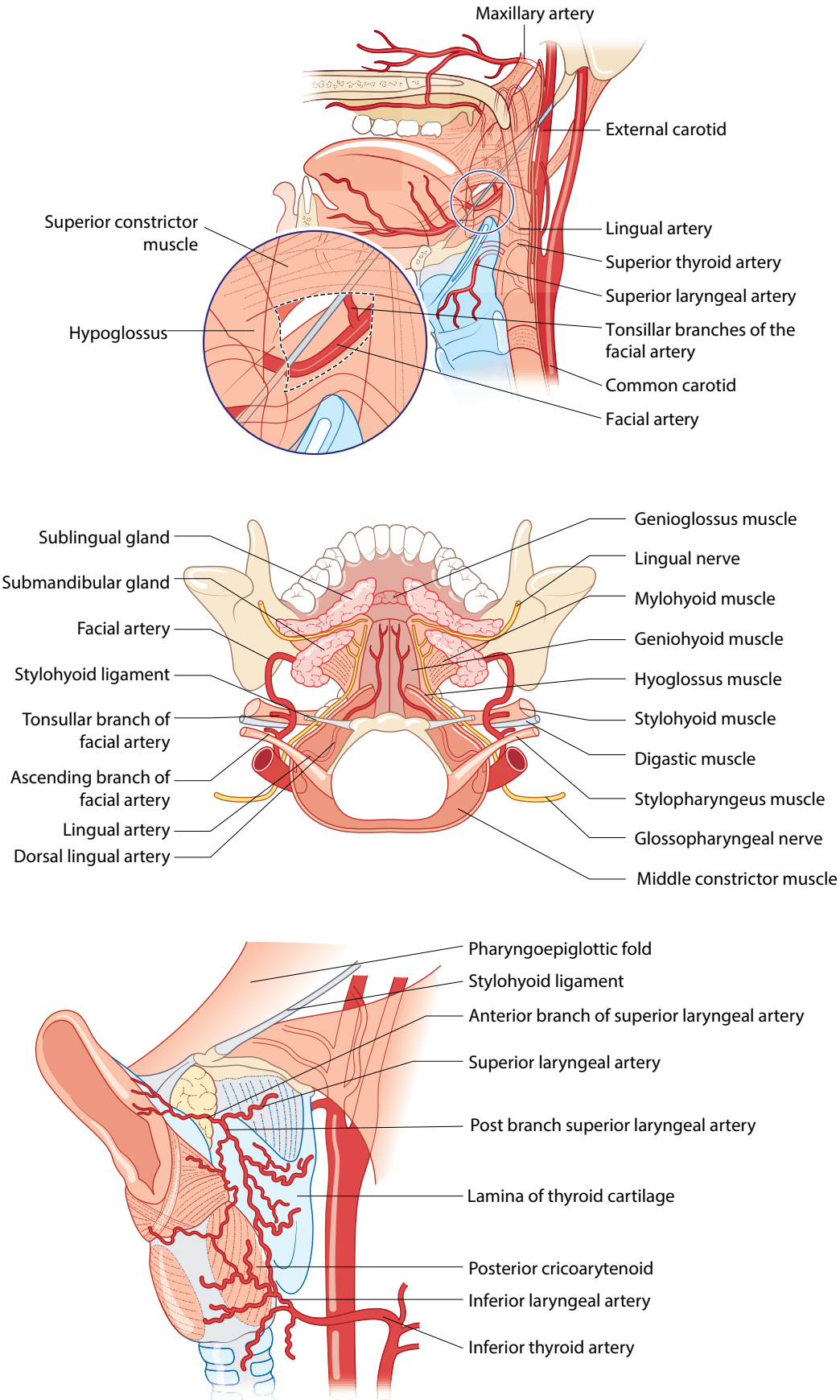


Figure 22.12 Vascular anatomy for TLM.

required in the majority of cases. Since its introduction in the 1980s the use of TLM has expanded to include all head and neck subsites. This is the result of technological advances in both endoscopic access and methods of delivering laser energy to the tumour site, combined with a developing surgical experience and expertise throughout Europe and North America. An understanding of the equipment required to achieve optimal surgical access and the pertinent factors influencing patient selection are key for the practice of TLM. Surgeons of the future need to familiarize themselves with the operating room set-up and operative technique of TLM throughout their training to offer this approach as part of a modern and integrated multidisciplinary head and neck cancer service.

KEY POINTS

- Transoral laser microsurgery is a proven technique in the management of the primary site for a variety of cancer subsites in the upper aerodigestive tract.
- This technique offers significantly less morbidity compared to open approaches.
- The technique requires surgeons to have an excellent appreciation of the anatomy from inside out.
- Significant research is ongoing on transoral surgical techniques with improvements in instrumentation and increased experience.

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CHAPTER
23

ANATOMY AS APPLIED TO TRANSORAL SURGERY

Mark Puvanendran and Andrew Harris

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SEARCH STRATEGY

The data in this chapter is supported by a Medline search using the keywords: transoral surgery, tongue, pharynx, and larynx.

INTRODUCTION

Anatomy is traditionally taught through an outside-to-inside approach. Transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) challenge this classical view, necessitating a 3-dimensional appreciation of the relevant anatomy from a counter-intuitive, inside-out approach. This is particularly important as tumour and/or surgical instrumentation such as retractors or endoscopes distort the normal anatomy. While other chapters within this reference text offer the conventional anatomic approach, the aim of this chapter is to focus on head and neck anatomy relevant for TLM and TORS, with special relevance to the vascular anatomy as seen from a transoral perspective.

TONGUE BASE

The tongue base refers to the posterior portion of the tongue (oropharynx), separated from the anterior, oral cavity segment by the terminal sulcus. This area is derived from the second, third and fourth branchial aches. The tongue base contains the lingual tonsils and the pharyngoepiglottic and glossoepiglottic folds (**Figure 23.1**).

Muscles

The tongue is composed of intrinsic and extrinsic muscles, the muscles on each side are separated by a dense fibrous midline band. The intrinsic muscles from superficial to deep are: superior longitudinal, inferior longitudinal, transverse and vertical. These muscles generally serve to alter the shape of the tongue, the intrinsic muscles are all innervated by the hypoglossal nerve.

The intrinsic and extrinsic muscles of the tongue and their relationship with the oral cavity can be appreciated in **Figure 23.2**.

There are four extrinsic tongue muscles, originating from outside the tongue and inserting within the substance of the tongue. They are styloglossus, hyoglossus, genioglossus and palatoglossus. These are paired muscles which move the main body of the tongue. A detailed breakdown of the actions of the muscles is in the **Table 23.1** below.

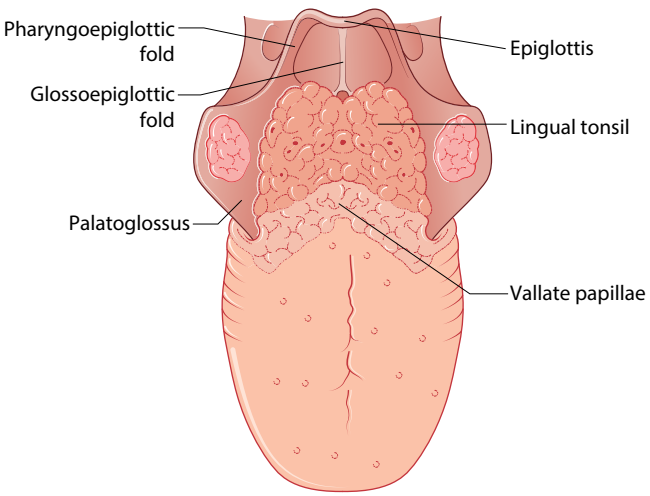


Figure 23.1 Tongue surface anatomy.

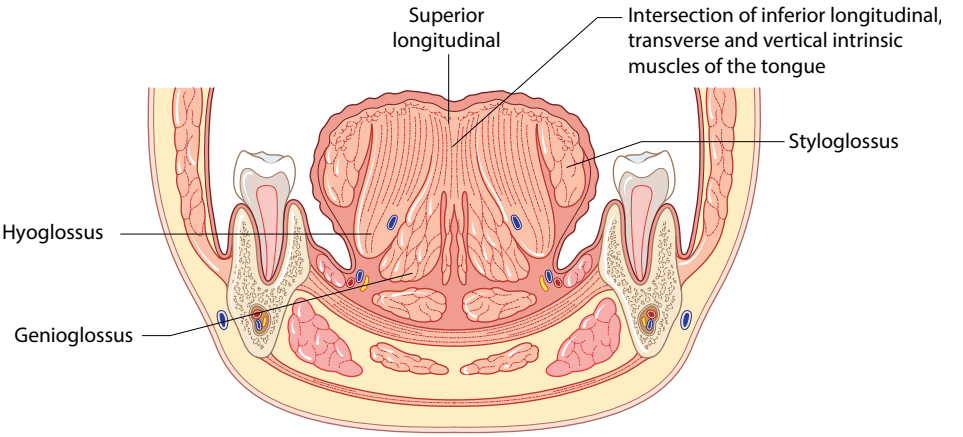


Figure 23.2 Cross-sectional anatomy of the tongue highlighting the muscles of the tongue.

TABLE 23.1 Anatomy, innervation and action of tongue muscles

Muscle	Type	Origin	Insertion	Action
Superior Longitudinal	Intrinsic	Lingual septum and submucous fibrous layer	Margins of tongue	Elevates tip and sides of tongue; shortens tongue
Inferior longitudinal	Intrinsic	Body of hyoid and base of tongue	Apex of tongue	Curls tip inferiorly; shortens tongue
Transverse	Intrinsic	Lingual septum	Submucous fibrous layer	Narrows and lengthens tongue
Vertical	Intrinsic	Superior surface of the tongue	Inferior surface of tongue	Flattens and broadens tongue
Genioglossus	Extrinsic	Mental spine of mandible	Lateral and inferior tongue	Depresses and protrudes tongue
Hyoglossus	Extrinsic	Body and greater horn of hyoid	Lateral and inferior tongue	Depresses and retracts tongue
Styloglossus	Extrinsic	Styloid and stylohyoid ligament	Lateral and inferior tongue	Retracts tongue
Palatoglossus	Extrinsic	Palatine aponeurosis	Lateral tongue	Elevates posterior tongue

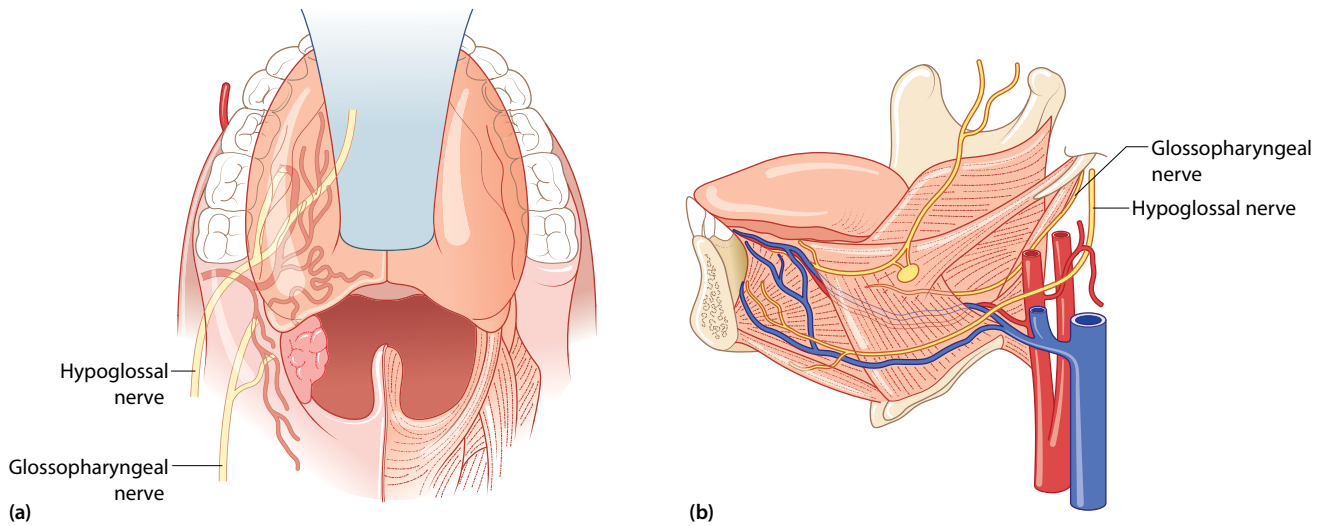


Figure 23.3 Transoral and lateral view of the nerves of the tongue.

Nerves

All the tongue muscles are innervated by the hypoglossal nerve apart from the palatoglossus, which is supplied by the pharyngeal plexus.

The hypoglossal nerve passes through the hypoglossal canal travelling alongside fibres from C1–2, then passing over the internal and external carotid arteries. It is seldom seen during transoral surgery for tongue base pathology (**Figure 23.3a** and **b**). It passes deep to the lingual nerve, along the genioglossus towards the tip of the tongue, and small off-shoots supply the intrinsic and extrinsic muscles apart from palatoglossus.[1]

The glossopharyngeal nerve supplies taste to the posterior 1/3rd of the tongue via the lingual branch. These fibers travel to the inferior glossopharyngeal ganglion and ultimately to the pons/hypothalamus.

Vascular

The principal artery encountered during transoral surgery of the tongue base is the dorsal lingual artery which arises from the common lingual artery. The common lingual artery is usually a branch of the external carotid artery (78%) but in 20% of cases it may arise from a common lingo-facial artery trunk.[2]

The artery has been divided into four segments by Shangkuan et al,[2] the original segment, the segment within the hyoglossus, the ascending and the horizontal segments (**Figure 23.4**).

The original segment consists of the root of the lingual artery which ascends medially then descends anteriorly, it consistently lies 3 to 4 mm supero-lateral to the greater horn of the hyoid bone. This artery is encountered when skeletonizing the greater horn of the hyoid bone deep to hyoglossus muscle.

The segment within the hyoglossus passes obliquely from posterosuperiorly to anteroinferiorly under the posterior border of the hyoglossus muscle and medial to the hypoglossal nerve; prior to entering the intrinsic muscles of the tongue, it runs lateral to the genioglossus.[1] The dorsal lingual artery, the first branch of the lingual artery arises approximately 0.7 cm from the anterior border of the hyoglossus. The vascular territory of the dorsal lingual artery stretches from the root of tongue, 5 mm behind the terminal sulcus, to the glossoepiglottic folds, the glossopalatine arch and the epiglottis.

The ascending segment of the lingual artery ascends in a tortuous manner along the anterior border of hyoglossus. The sublingual artery arises 0.8 cm above the hyoid bone at the origin of the ascending segment passing forward between genioglossus and the sublingual gland. The vascular territory of the sublingual artery includes the ventral side of the tongue, the anterior and lateral floor of the mouth and the vestibular and lingual gum.

The horizontal segment of the lingual artery becomes the deep lingual artery which runs forward with many upward and downward tortuosities between the longitudinal muscle of tongue and the genioglossus of each side, extending to 1cm from the tip of the tongue. The vascular distribution includes the dorsal side of the tongue, the lateral side and part of the ventral side.[3]

VASCULATURE ENCOUNTERED DURING SURGERY FOR TONGUE BASE TUMOURS

The position of the lingual artery within the tongue base is 2.7 cm inferior and 1.6 cm lateral to the foramen cecum (**Figure 23.5**). Dissection within the intrinsic muscles of the tongue tends to be safe, the main trunk lies on the lateral surface of the genioglossus muscle.[4] Intra operative and post-operative bleeding can be controlled with electrocautery or haemostatic clips. More severe bleeding may require transcervical ligation of the lingual and facial arteries.[5]

The veins of the tongue mirror the arteries in name and in their passage through the tongue.

LATERAL PHARYNGEAL WALL

The pharynx is a musculomembranous tube shaped like an inverted cone. It extends from the cranial base to the lower border of the cricoid cartilage, where it becomes continuous with the oesophagus.

Muscles

The muscles of the pharynx are three circular constrictors and three longitudinal elevators. The constrictors may be thought of as three overlapping cones which arise from

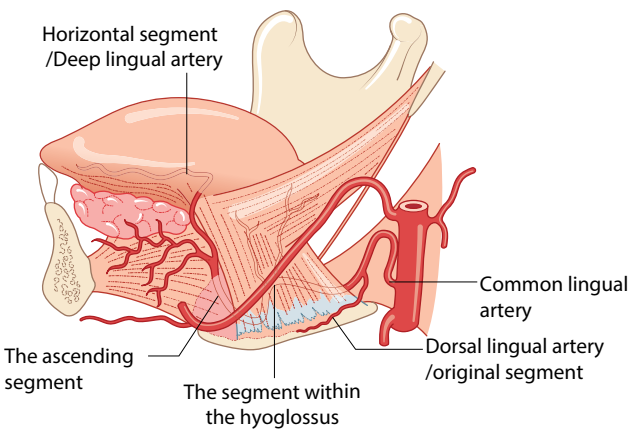


Figure 23.4 Blood vessels of the tongue.

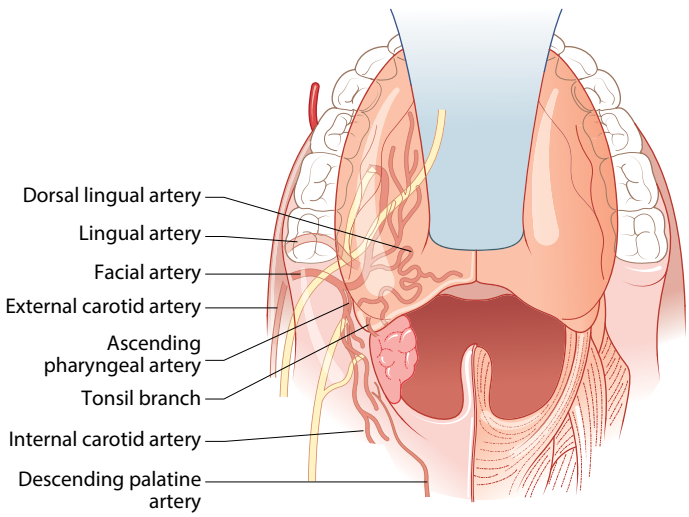


Figure 23.5 Transoral view of the blood vessels of the tongue.

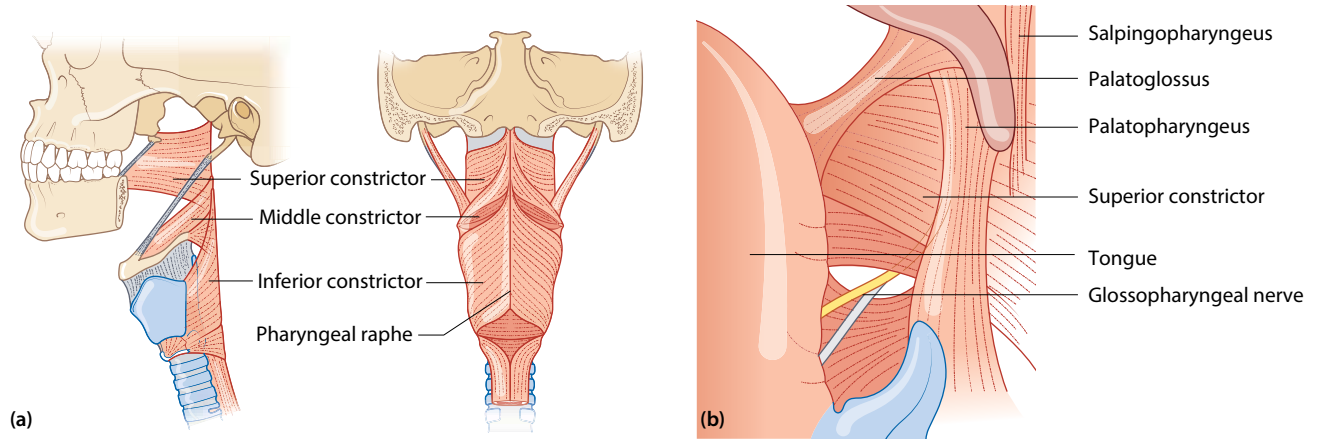


Figure 23.6 **(a)** Pharyngeal constrictors **(b)** Anatomy of the Superior lateral pharyngeal wall.

structures at the sides of the head and neck and pass posteriorly to insert into a midline fibrous band, the pharyngeal raphe (**Figure 23.6a**).

The tonsil is the most medial structure of the lateral pharyngeal wall. It lies between the palatoglossus (anterior faucial pillar) and palatopharyngeus (posterior faucial pillar) muscles. Superiorly these muscles unite with the levator and tensor palatine muscles; inferiorly they are attached to the tongue and pharyngeal wall respectively merging with the superior constrictor.

Deep to the tonsil lies the first of the circular constrictor muscles, the superior constrictor, which originates from the posterior midline pharyngeal raphe and attaches to the pterygomandibular raphe. The constrictors (superior, middle and inferior) overlap each other and all attach to the pharyngeal raphe posteriorly. They act in unison to propel the food bolus into the oesophagus by contracting the lumen.

Continuing to move laterally through the neck the two muscles encountered are styloglossus and stylopharyngeus (**Figure 23.6b**). The styloglossus, an extrinsic tongue muscle, is located superior-anteriorly compared to the stylopharyngeus. These are longitudinal muscles that shorten and widen the pharynx, and elevate the larynx during swallowing.

Nerves

The pharyngeal plexus is responsible for the majority of the innervation of the pharynx. The pharyngeal plexus is comprised of branches of; the glossopharyngeal nerve (CN IX), the vagus nerve (CN X) and sympathetic fibres of the superior cervical ganglion.

The sensory supply to the oropharynx is via the glossopharyngeal nerve (CN IX) and the laryngopharynx is supplied by the vagus nerve (CN X). The glossopharyngeal nerve is located between the styloglossus and stylopharyngeus which in turn lie between the superior and middle constrictors. The glossopharyngeal nerve is consistently identified at the junction of the posterior tonsillar pillar and the tongue base.

The motor supply for all the muscles of the pharynx is the vagus nerve except for stylopharyngeus, which is innervated by the glossopharyngeal nerve.

Vascular

The vascular supply for the lateral pharyngeal wall originates from the external carotid. The upper part of the pharynx receives blood from the pharyngeal branch of the ascending pharyngeal artery and descending branches of the lesser palatine arteries. The lower part of the pharynx is supplied from inferior thyroid artery and superior thyroid artery. The rest of the pharynx receives blood from the ascending palatine and tonsillar branches of the facial artery as well as from the maxillary artery (**Figure 23.7**).

The vascular supply to the tonsil is via tonsillar branches of the ascending pharyngeal and facial arteries, occasionally there may also be a branch from the lingual artery. The tonsillar vessels are commonly found on the medial surface and running through the superior constrictor.

Vasculature encountered during surgery for tonsil tumours

The space between the stylopharyngeus muscle and the superior constrictor muscle contains an irregular and complex venous network called the pterygoid venous plexus, which is partly hidden behind the belly of the stylopharyngeus muscle. Beyond the pharyngeal plexus antero-medially along the superior constrictor the ascending pharyngeal artery and the ascending palatine artery, a branch of the facial artery can all be visualized. The facial, lingual and ascending pharyngeal branches of the external carotid artery lie approximately 5–8 mm deep to the styloglossus.[6,8]

Venous drainage of the superior aspect of the pharynx is via the retromandibular and facial veins which drain into the internal jugular vein. The inferior aspect of the pharynx venous drainage is through the pharyngeal plexus. The pharyngeal plexus can drain either into the internal jugular vein or brachiocephalic vein via the inferior thyroid vein (**Figure 23.8**).

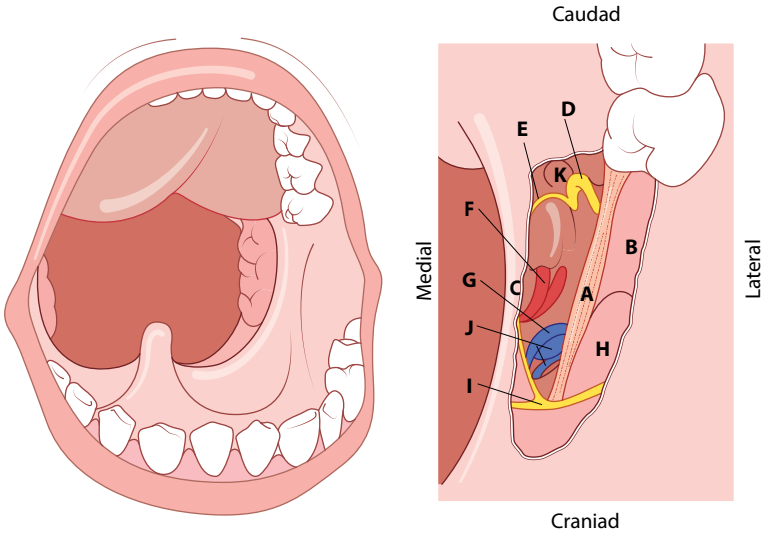


Figure 23.7 Transoral view of the right tonsillar fossa. A, Styloglossus muscle, B, medial pterygoid muscle, C, palatoglossus muscle, D, lingual artery, E, tonsillar branch of the lingual artery, F, tonsillar branch of facial artery, G, tonsillar branch of ascending pharyngeal artery (middle pharyngeal branch), H, superior constrictor muscle, I, tonsillar branch of descending palatine artery, J, tonsillar venous plexus, and K, submandibular gland.

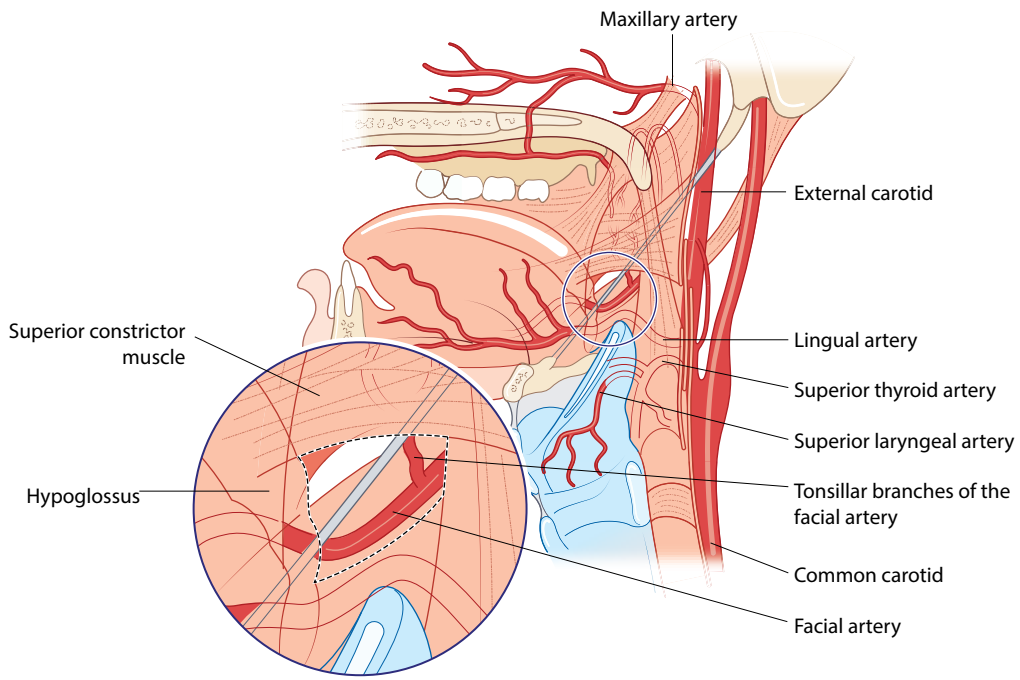


Figure 23.8 The arterial supply to the oropharynx from the external carotid artery.

LARYNX

The main laryngeal framework is composed of the hyoid bone, the thyroid cartilage; a fusion of two quadrilateral shaped laminae, and the cricoid cartilage (**Figure 23.9**). The larynx is suspended from the hyoid bone by two membranes (also termed ligaments), the medial and lateral thyrohyoid membranes.[1]

Cartilages

The thyroid cartilage attaches anteriorly to the cricoid cartilage through the cricothyroid membrane and posteriorly through the cartilaginous cricothyroid joints. Inferiorly the lower border of the cricoid cartilage is attached to the trachea by the cricotracheal ligament. The medial and lateral thyrohyoid membranes along with the cricotracheal

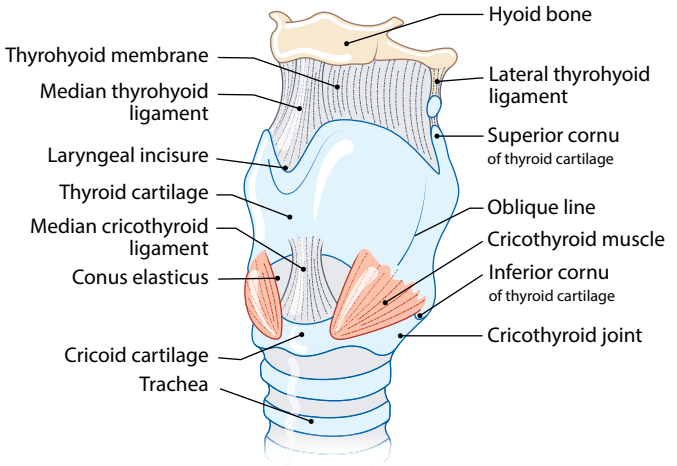


Figure 23.9 A topographical over view of the larynx.

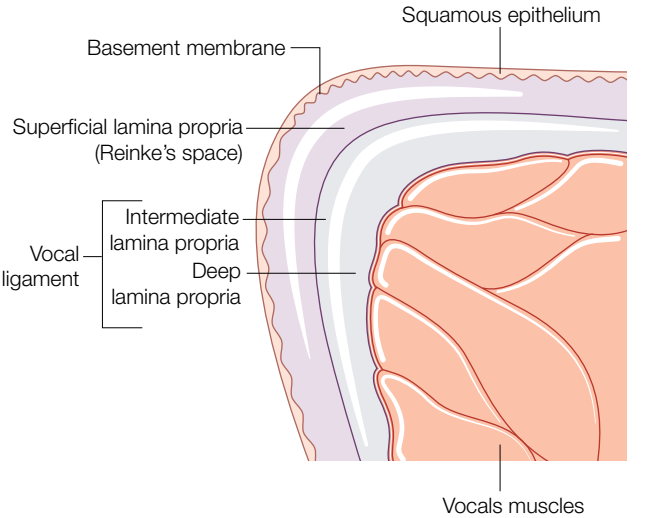


Figure 23.10 The superficial and deep layers of the true vocal cords

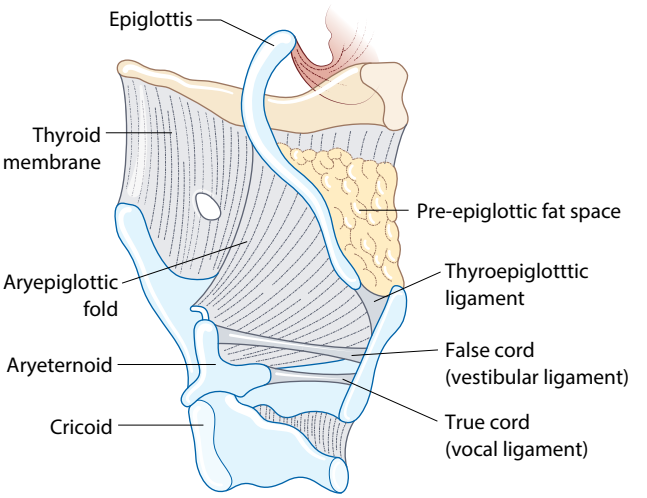


Figure 23.11 Schematic diagram of the larynx in the sagittal plane demonstrating the pre-epiglottic space.

membrane are termed extrinsic ligaments of the larynx. Within the thyroid cartilage, the endolarynx is supported by intrinsic ligaments which lie beneath the laryngeal mucosal membrane forming an internal framework and connecting the internal laryngeal cartilages together.[2] There are two intrinsic fibro-elastic membranes divided by the laryngeal ventricle; the quadrangular membrane, stretching from the arytenoid cartilage to the epiglottis, the free superior border being named the aryepiglottic fold, and the inferior free border forming the ventricular or false vocal fold. The inferior membrane, called conus elasticus, has attachments below to the upper border of the cricoid cartilage, to the mid-point of the thyroid prominence of the thyroid cartilage anteriorly and the vocal process of the arytenoid posteriorly. The free superior edge of the conus elasticus forms the true vocal ligament.

The true vocal cords extend from the angle of the thyroid cartilage to the vocal processes of the arytenoid cartilages. The vocal cords are layered structures with a surface layer of non-keratinizing, stratified squamous epithelium (**Figure 23.10**).

The fusion of the two vocal cords anteriorly produces the anterior commissure tendon. The anterior commissure is an important area for transoral surgery as the epithelium reaches within 1 to 2 mm of the cartilage, there is no perichondrium at this site, and it is a difficult area to expose during surgery. Superior to the anterior commissure the thyroepiglottic ligament attaches the epiglottis to the thyroid cartilage. The epiglottic cartilage extends superiorly and posteriorly forming an important anatomical space within the larynx, the pre-epiglottic space. The pre-epiglottic space is bounded anteriorly by the thyrohyoid ligament, the hyoid bone, and posteriorly by the epiglottis, and superiorly by the hyoepiglottic ligament, connecting the epiglottis to the hyoid bone (**Figure 23.9**).

Posteriorly the vocal cords attach to the vocal process of the arytenoid cartilages (see **Figure 23.11**). The arytenoid cartilages are pyramidal in shape, having a forward projection already mentioned, the vocal process, and a lateral projection, the muscular process to which the posterior cricoarytenoid and lateral cricothyroid muscles attach. These paired cricoarytenoid units are the main functional elements of the larynx involved in speech and swallowing and thus at least one unit must be preserved if meaningful laryngeal function is to be maintained. Two corniculate cartilages articulate with the apices of the arytenoid cartilages. Within the aryepiglottic folds sit two small cuneiform cartilages.

Between the vocal and vestibular ligaments there is a horizontal slit which opens into a recess, the laryngeal ventricle. A diverticulum of the laryngeal ventricle termed the laryngeal saccule extends vertically between the vestibular ligament and the thyroid cartilage. The saccule contains numerous mucous secreting glands to keep the vocal cords lubricated.

The vestibular folds are thick mucus membranes enclosing the vestibular ligament; this being the lower border of the quadrilateral membrane, the superior edge being the aryepiglottic fold (**Figure 23.12**).

Another important anatomical space in laryngeal oncological surgery is the paraglottic space which lies laterally to the conus elasticus and medial to the thyroid cartilage, having the pyriform sinus mucosa as a posterior border (**Figure 23.13**).

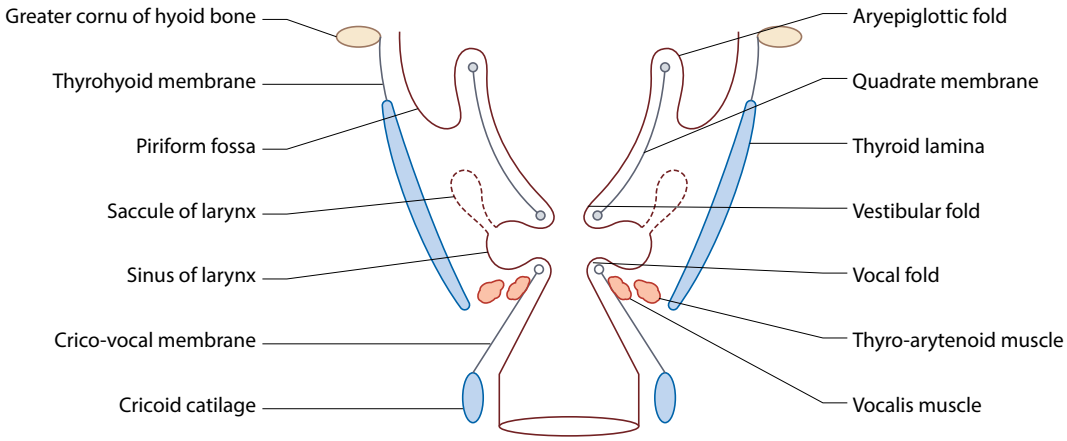


Figure 23.12 Schematic illustration of the endolarynx with the intrinsic membranes, the vestibules and the saccules.

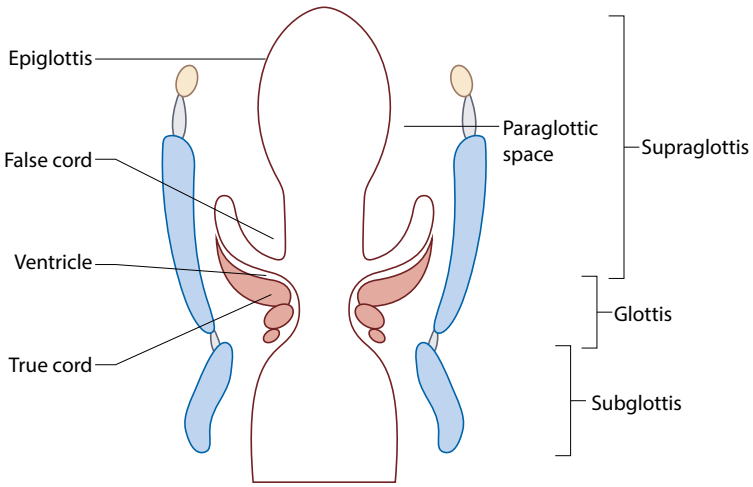


Figure 23.13 Schematic diagram of the larynx demonstrating the paraglottic spaces.

Muscular

The internal laryngeal muscles move the laryngeal cartilages relative to one another, affecting tension and position of the true vocal cords. The thyroarytenoid muscle is a broad flat muscle lying deep to the free edge of the vocal ligament, originating from the thyroid prominence and cricothyroid ligament and inserting in to the vocal process and anterolateral surface of the arytenoid cartilage. The medial portion of the thyroarytenoid muscle is termed the vocalis muscle. The extrinsic portion of the thyroarytenoid muscle inserts anteriorly in to the anterior commissure as thick fibrous tissue known as Broyle's ligament. The intrinsic muscles of the larynx are depicted in **Figure 23.14**.

Vascular

The blood supply to the larynx is derived from the superior and inferior thyroid arteries. The superior laryngeal artery (a branch of the superior thyroid artery) is the artery of main concern regarding post-operative bleeding in TLM / TORS. The superior laryngeal artery courses deep to the thyrohyoid muscle and pierces the thyrohyoid membrane along with the internal branch of the superior laryngeal nerve to enter the larynx.

RELEVANT VASCULATURE ENCOUNTERED DURING SURGERY FOR SUPRAGLOTTIC TUMOURS:

The pharyngoepiglottic fold is important in transoral surgery due to the presence of the neurovascular bundle, comprised of the superior laryngeal artery, superior laryngeal vein and the internal branch of the superior laryngeal nerve (**Figure 23.15**).[3] The artery travels within the pharyngoepiglottic fold to then divide in to five branches:[4] an ascending branch supplies the epiglottis which anastomoses with branches from the lingual artery within the vallecular,[5] other branches supply the ventricle, post-cricoid region, false vocal cords and the thyroarytenoid muscle (**Figure 23.16**). There is a consistent branch of the superior laryngeal artery which runs from posterior to anterior within the undersurface of the false cord. The superior laryngeal artery can generally be found in the superior portion of a triangle formed by the anterior commissure, the vocal process of the arytenoid cartilage, and the attachment of the aryepiglottic fold to the epiglottis.[6,7] Variations of the anatomy of the superior laryngeal artery course exist with a potential for this named vessel being found within the paraglottic space.

The inferior laryngeal artery arises from the inferior thyroid artery and courses with the recurrent laryngeal nerve on the trachea, entering the larynx beneath the

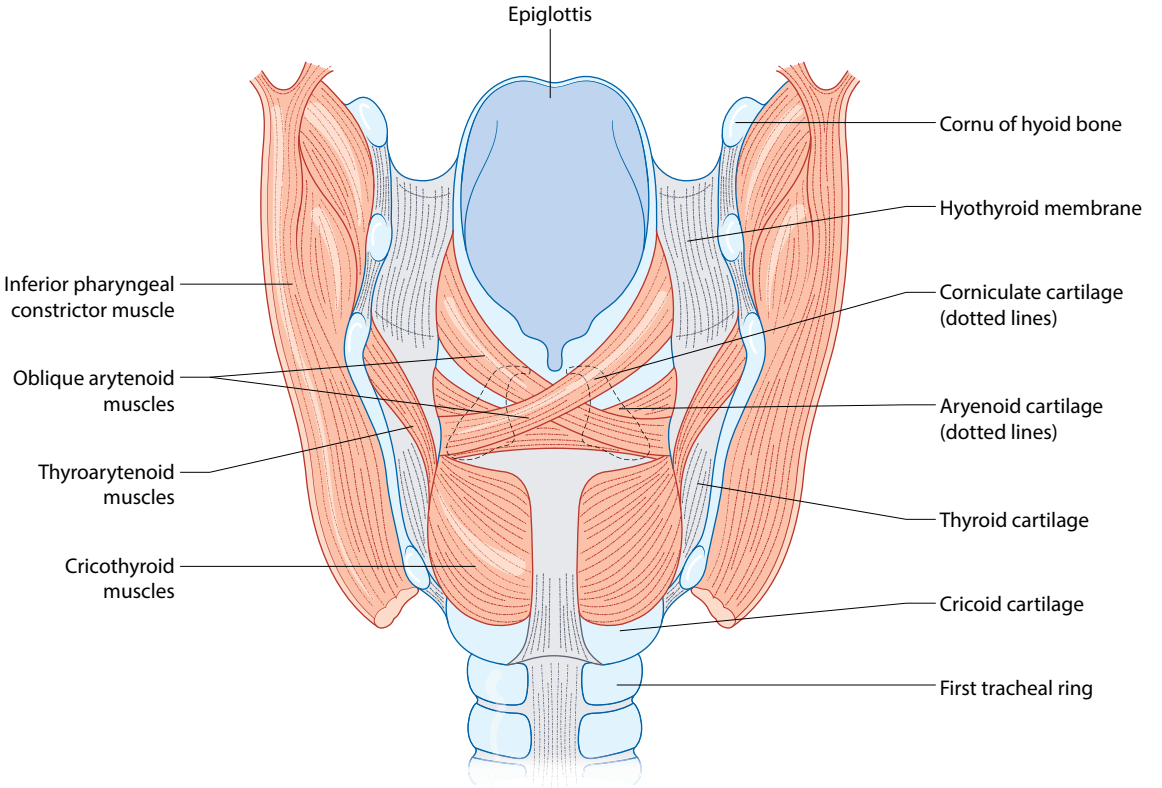


Figure 23.14 A posterior view of the larynx showing the intrinsic muscles of the larynx.

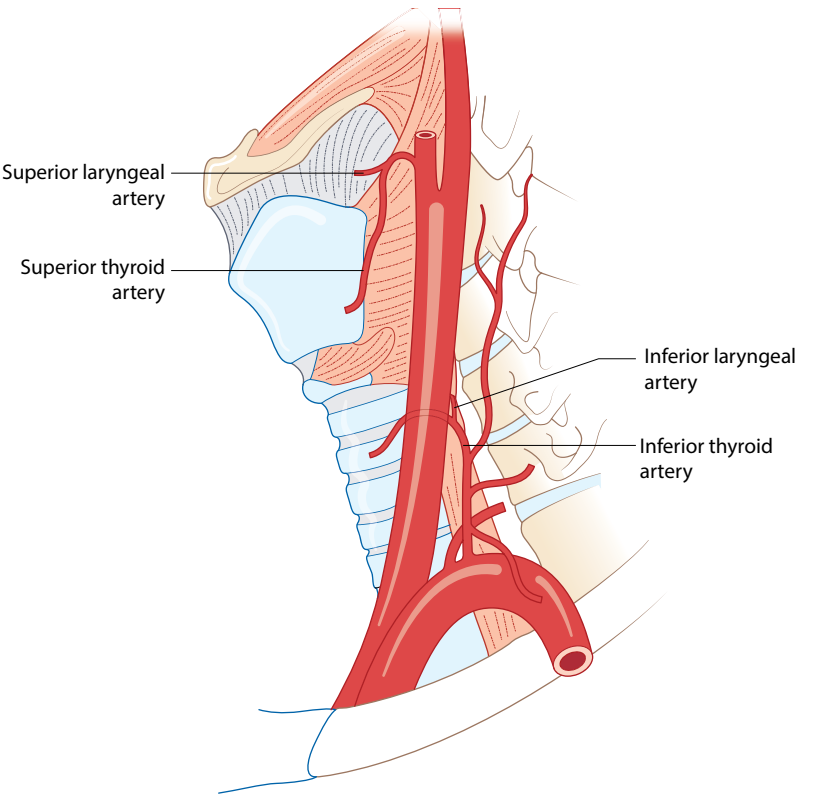


Figure 23.15 The origin and course of the superior laryngeal artery.

lower border of the inferior constrictor. The cricothyroid artery is a branch of the superior thyroid artery and passes across the upper part of the cricothyroid ligament.

Neurological

The motor and sensory supply to the larynx is derived from the vagus nerve. At the level of the greater cornu of the hyoid bone, the superior laryngeal nerve divides in to internal and external laryngeal nerves. The internal branch pierces the thyrohyoid membrane just above where the superior laryngeal artery enters the membrane. The internal laryngeal nerve gives sensory and secretomotor supply to the larynx above the level of the vocal cords (**Figure 23.17**). The branch terminates by piercing the inferior constrictor and uniting with an ascending branch of the recurrent laryngeal nerve; this anastomosis is termed Galen's anastomosis. The internal branch of the superior laryngeal nerve is intimately associated with the superior laryngeal artery and this is an important consideration in oncological resection. This nerve generally splits in to two branches; one which supplies the mucosa above the ventricle and one which supplies the mucosa below the ventricle.[7] If the mucosa superiorly is to be removed as in excision of a supraglottic lesion then preservation of the superior branch is irrelevant. Preservation of the inferior branch which supplies the mucosa below the vestibule along with the hypopharynx could potentially help with the cough reflex preventing aspiration.

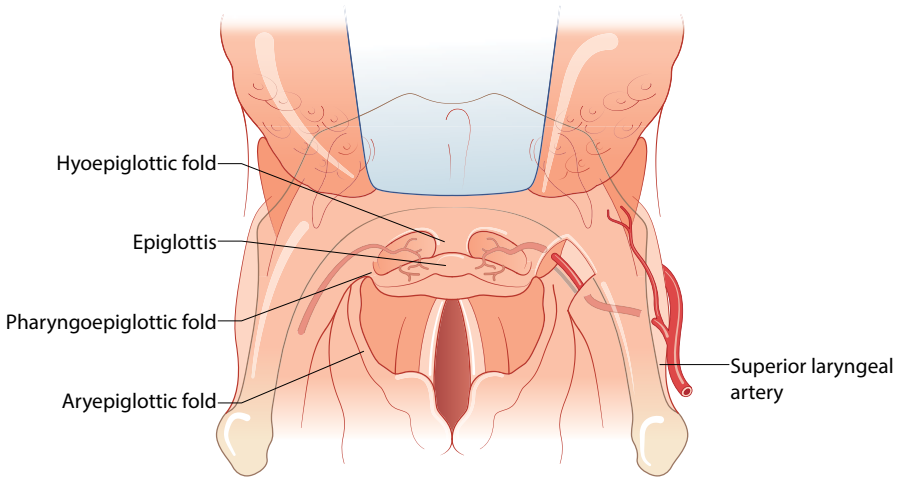


Figure 23.16 The course of the superior laryngeal artery.

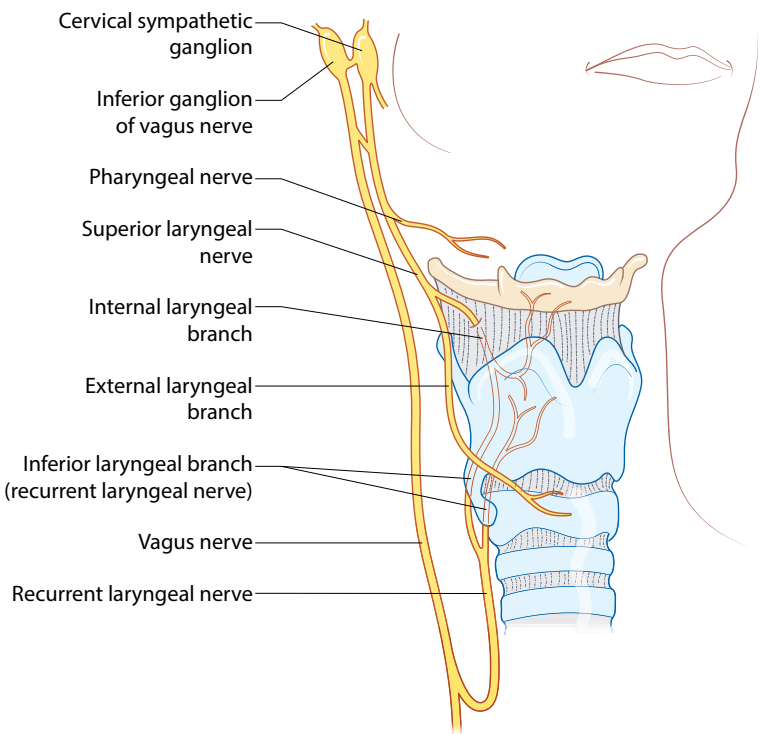


Figure 23.17 The course of the recurrent laryngeal nerve and the superior laryngeal nerve.

KEY POINTS

- A detailed knowledge of the oropharynx, hypopharynx and larynx is essential for all head and neck surgeons.
- The complexities of trans oral surgery turns the conventional anatomy 'inside out', this alternative viewpoint needs to be appreciated before embarking on transoral surgery.

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CHAPTER 24

PRINCIPLES OF CHEMOTHERAPY

Charles G. Kelly

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: chemotherapy, induction chemotherapy, concurrent chemotherapy, radiosensitizers, targeted biological agents, recurrent head and neck cancer, metastatic head and neck cancer and EXTREME trial.

INTRODUCTION

Chemotherapy alone cannot cure head and neck cancer. It is used in conjunction with other treatments, surgery and radiotherapy, to improve outcomes such as better local control, organ preservation with continued organ function and decrease the incidence of subclinical micrometastatic spread. Chemotherapy is given for its direct tumouricidal effect, at both the local primary and distant metastatic sites. If given with radiotherapy it can have a radio-sensitizing effect, making cancer cells more susceptible to radiotherapy and increasing the cancer cell kill.

If the cancer has already caused organ destruction and there is no future option to maintain organ function, then surgery with or without adjuvant radiotherapy may give the best chance of cure and long-term survival. Organ preservation is pointless if the patient is left with a non-functioning organ, especially if it may lead to future problems such as aspiration. Chemotherapy can be used in this situation as well. It may be used as induction chemotherapy to shrink the advanced primary tumour or shrink and render fixed cervical nodes mobile, potentially enabling technically easier surgery.

In locally advanced head and neck cancer, chemotherapy can be used at different points in the patient pathway. Chemotherapy is not given routinely for early primary T1/T2 disease, without nodal involvement. It can be used as induction or neoadjuvant treatment before the primary treatment, be that surgery or radiotherapy; but if used for induction this is almost always before radiotherapy rather than surgery as its use would inevitably delay surgery. However, the preparatory processes before radiation therapy, such as manufacturing an immobilization device and creating a radiotherapy plan, consume time and these can take place while the patient is having induction chemotherapy, thereby bringing forward the initial treatment start date.

If induction chemotherapy is used, further chemotherapy is usually given with subsequent radiotherapy, and this is known as concomitant chemotherapy, which is more commonly used; only a minority of patients receive induction regimens.

Adjuvant chemotherapy, which is treatment given after the principal treatment, is not used as a sole modality after radiotherapy, as it has not been shown to have benefit in this setting; however, when given with adjuvant radiation, it has been shown to improve local control and increase survival where primary surgery has been the definitive treatment. This benefit is seen in patients who have a higher risk of recurrence with positive surgical margins, nodal involvement, especially multiple nodes involved or extra capsular spread.

CHEMOTHERAPY AND HPV-POSITIVE TUMOURS

Human papillomavirus (HPV) is known to have an aetiological role in introducing head and neck cancers, especially in the oropharynx where HPV infection may be linked to 50–80% of tumours. There is also some growing evidence for HPV associated non-oropharyngeal tumours.[1] HPV-positive and -negative head and neck cancers are thought to represent distinct diseases with differing natural histories and prognosis. There is evidence from several studies, for example RTOG 0129, that outcomes are better following treatment in patients with HPV-positive tumours.[2] However, much of this evidence is retrospective, with completed trials being re-interrogated for patients' HPV status, often without complete data being available for all patients entered into these trials. As prospective evidence builds, HPV-positive patients do appear to have better outcomes following treatment when compared to HPV-negative patients. There is also growing evidence that continuing to smoke negates the benefit of the better prognosis given by HPV positivity.

Despite this growing evidence that HPV-positive patients have better outcomes, at present there are not enough robust data to alter chemotherapy or indeed radiotherapy treatment regimens depending on the patient's HPV status, outside of the context of a clinical trial.

There is considerable interest in reducing treatment for patients with HPV-positive tumours and multiple trials are underway worldwide addressing this question.[3–5]

INDUCTION (NEOADJUVANT) CHEMOTHERAPY

As interest in organ function preservation grew, induction chemotherapy was considered to have the potential for several benefits.

If induction chemotherapy could shrink primary tumour volumes before the principal treatment of radiotherapy or chemoradiotherapy, this might allow better blood flow into the tumour allowing a greater tumouricidal dose of drugs to be delivered and decrease the volume of hypoxic areas, which would decrease the radioresistance that hypoxic cancer cells show. If induction chemotherapy could improve local control, there would be a greater chance of functional organ preservation. Since surgery and radiotherapy are both locoregional treatments, induction chemotherapy could theoretically treat distant subclinical metastatic disease.

The response to neoadjuvant chemotherapy could give important prognostic information, as it can act as a surrogate marker for response to later treatment. This latter advantage was used in one of the earliest trials of neoadjuvant chemotherapy for organ preservation, the Veterans trial, in which the patients were given two cycles of cisplatin and 5-fluorouracil followed by response assessment; if there was a response to chemotherapy, patients went on to have chemotherapy and radiotherapy but if there was no response, the patients went directly to laryngectomy.[6]

Most patients who have had induction chemotherapy go on to have concurrent chemotherapy as well. There is a risk that patients undergoing induction chemotherapy may be more at risk of not completing or having breaks in the subsequent definitive radiotherapy treatment because of the morbidity induced by induction chemotherapy, which would result in poorer outcomes.

One of the main evidence sources for the use of chemotherapy in head and neck cancer is the meta-analysis of chemotherapy in head and neck cancer (MACH-NC), which was originally published in 2000 and updated in 2007 and 2009.[7–9] These overviews reviewed more than 90 trials containing data on more than 16 000 patients, with overall survival as the primary endpoint. The analysis failed to show an overall survival benefit from the use of induction chemotherapy when compared to primary surgery or radiotherapy alone, although cisplatin and 5-fluorouracil (5-FU) as a combination did show some benefit. However, these reviews did suggest that induction chemotherapy may reduce the incidence of distance metastases, more effectively than concurrent chemotherapy.

There is still debate as to whether induction chemotherapy followed by concurrent chemoradiotherapy is more beneficial than concurrent chemoradiotherapy alone. Some large trials have shown no benefit[10] while others have shown some.[11] Interest was rekindled in induction chemotherapy when two trials, one European and one from North America, 'TAX 323' and 'TAX 324' showed benefit by including a taxane, such as docetaxel or paclitaxel in the induction chemotherapy regime in addition to cisplatin and 5-FU.[12, 13] Response rates and survival outcomes were higher with taxane-containing regimens but toxicity was considerably higher and chemotherapy-related deaths were also increased with these regimens. Such sequential regimens are offered to patients with good performance status and fewer comorbidities, and those with bulky nodal disease, stage N2b and above, and where surgery is not appropriate.

CHEMOTHERAPY REGIMENS USED IN INDUCTION CHEMOTHERAPY

The standard regimen was formerly cisplatin 100 mg/m² and 5-fluorouracil, 1 g/m² per day for 4–5 days via a chemotherapy infusion bottle. This was given 3-weekly for two to three cycles, before definitive treatment. The definitive treatment is almost always concurrent chemoradiotherapy, except in a few cases where induction chemotherapy can be used in the hope of converting inoperable locoregional disease to more surgically manageable disease.

The European TAX 323 and the North American-based TAX 324 trials[12, 13] produced evidence that adding a taxane, such as docetaxel or paclitaxel to cisplatin and 5-FU (i.e. TPF vs PF) did improve survival in the TPF arm, but at a cost of much higher toxicity, both

haematological with myelosuppression and neutropenia and non-haematological, especially increasing mucositis.

In TAX 323, no concurrent chemotherapy was given with subsequent radiotherapy and in TAX 324, concurrent carboplatin was used. This has led to some criticism that the most optimal concurrent chemotherapy available was not given in the studies. The TPF doses were also different in each of these trials. Both studies did show TPF gave better overall survival than cisplatin and 5-FU alone.

The most effective, optimal and least toxic sequential chemotherapy regimen is still debated and more recent publications have been less encouraging. The TREMPLIN study by Lefebvre et al[14] used induction chemotherapy followed by chemoradiotherapy or by cetuximab plus radiotherapy. There was no difference in outcome with regard to larynx preservation. The PARADIGM trial,[15] which compared sequential chemotherapy versus concomitant chemotherapy alone, showed no overall survival difference in locally advanced head and neck cancer. The DeCIDE trial[16] also found no overall survival difference in patients with nodal stages N2/N3 disease, where induction chemotherapy was added to concomitant chemo-radiotherapy compared with concomitant chemotherapy alone.

These disappointing induction trials are reviewed by Garden[17] in an editorial suggesting that the evidence to date does not suggest that induction chemotherapy is beneficial in head and neck cancer.

CONCURRENT OR CONCOMITANT CHEMOTHERAPY

Concurrent or concomitant chemotherapy given with radiotherapy is more frequently used than induction or sequential chemotherapy. It is given for its direct cell-killing effect and for its effect in sensitizing cancer cells to the effects of radiotherapy. It probably has less effect in suppressing micro-metastatic distant spread than induction chemotherapy. Its main advantage is that when used with radiotherapy, without induction chemotherapy, there is less chance of patients having to stop treatment because of toxicity, and have breaks in radiotherapy, which can be detrimental to treatment outcome.

In the meta-analysis of chemotherapy on head and neck cancer (MACH-NC),[7–9] the overview looked at concurrent chemotherapy in 16 000 patients and showed that it gave a survival benefit when added to radiotherapy alone, giving a 6.5% decrease in mortality at 5 years, in absolute terms. This benefit was not seen in patients over 70 years of age, but patients over 70, formed a very small number of the total patients reviewed.

The most commonly use concurrent chemotherapy regimens are cisplatin 100 mg/m² at days 1, 22 and 43 of radiotherapy, either alone or with 5-FU, 1 g per day on days 1 to 4. Although this regimen is commonly used, there are few direct comparisons with other concomitant chemotherapies within randomized controlled trials.

Increased toxicity produced by adding platinum chemotherapy to radiotherapy can be considerable with more marked mucositis, dysphagia, nephrotoxicity, ototoxicity, myelodysplasia and neutropenia. A significant proportion of patients do not receive all three cycles of chemotherapy because of toxicity, but one study has shown no survival difference in patients receiving two cycles of cisplatin rather than three cycles; however, the radiotherapy delivered was not identical within the arms of this study.[18] Chemotherapy toxicity can also interfere detrimentally with radiotherapy delivery causing breaks and treatment which are associated with poorer outcomes.

While high-dose cisplatin, 100 mg/m², 3-weekly may be optimal for younger patients with good performance status and fewer comorbidities, many head and neck patients are not in this category and other dose regimens may be better tolerated. Cisplatin, 40 mg/m², capped at a total of 70 mg given weekly, may allow for more flexibility with the ability to reduce or omit a weekly dose in response to changes in the patient's tolerability and individual toxicity. Daily cisplatin at a dose of 6 mg/m² is also an occasionally used regimen. Weekly and daily regimens may be easier to administer in an outpatient or day ward setting. High-dose cisplatin at 100 mg/m² may require inpatient admission for prehydration and monitoring.

If cisplatin is contraindicated because of renal function status, the presence of neuropathy, tinnitus or deafness, or where there is a danger of fluid overload with the necessary pre-hydration used in cisplatin administration, carboplatin can be considered as it causes less nephrotoxicity, ototoxicity and peripheral neuropathy but is more myelosuppressive. It is not thought to be as tumouricidal as cisplatin and for this reason it has now been largely overtaken by the epidermal growth factor receptor (EGFR) inhibitor, cetuximab in clinical practice when cisplatin is contraindicated.

CONCURRENT RADIOSENSITIZERS

It is known that tumour cell hypoxia induces radioresistance, and there has been renewed interest in giving hypoxic cell radio-sensitizing drugs during radiotherapy. The two most common in use are the anti-helminthic drug nimorazole, which is extensively used in some parts of Europe, and tirapazamine, an anticoagulant that is activated in hypoxic environments. Although established in some parts of the world, trials are ongoing with these agents to establish efficacy and with nimorazole, patient tolerability.

TARGETED BIOLOGICAL AGENTS

Targeted therapy in head and neck cancer developed with the recognition that EGFR is overexpressed in most head and neck cancers, up to 90% in some studies, and is associated with a poorer prognosis. When a growth factor attaches to its receptor on the cell surface, cells are stimulated to divide and consequently tumours grow. If the receptor is abnormal because of a mutation the stimulation to divide may even occur without growth factors interacting with the receptor. Cetuximab is a

mouse–human chimeric monoclonal antibody that binds to the extracellular portion of EGFR and turns this signalling system off.

In the initial innovative cetuximab trial by Bonner et al,[19] patients with advanced cancers of the oropharynx, larynx or hypopharynx were randomized to receive radical radiotherapy with or without cetuximab. At 3 years, survival was better in the patient group who had received cetuximab, 55% vs 45%; and local control was also better, 50% compared to 41%.[20] Subset analysis, with its inherent limitations, suggested that cetuximab may have more effect in younger patients under 65 years, in those with oropharyngeal cancer and in those with better performance status, broadly reflecting the response with non-targeted standard chemotherapy regimens.

While these initial results with cetuximab were encouraging, a major drawback to the study was that, since it had started, radiotherapy alone as used in this study has been overtaken as a standard of care by chemoradiotherapy for advanced head and neck tumours. Thus, comparing radiation alone versus radiation plus cetuximab is much less relevant in the context of contemporary standard practice.

Despite initial hopes that cetuximab would give less toxicity than standard chemotherapy, and could therefore be given to older patients and those with a poorer performance status, it has been shown to have a different, although not necessarily more gentle toxicity profile. It does show less morbidity with nephrotoxicity, ototoxicity and peripheral neuropathy but it gives patients a more intense grade 3 and grade 4 radiation dermatitis.

Patients may also develop an acne-like rash predominantly over the face, neck and trunk with a more eczema-like condition at the fingertips and elbows, and paronychia may develop. In a minority of patients this reaction can be so severe that cetuximab may need to be stopped but these side effects can usually be managed by increasing the treatment interval and supportive care with topical medications. There is some suggestion that patients who develop this rash also have a better tumour response with improved overall survival.[21]

While receiving cetuximab, infusion-related side effects are not uncommon with headache, flushing, pyrexia, urticaria, swelling of the lips and tongue or bronchospasm. Patients, therefore, usually receive steroids 24 hours before starting a cetuximab infusion. Cetuximab may have a role to play in the treatment of metastatic disease (see below), as shown in the EXTREME trial, but that role is still to be fully defined.

Other targeted EGFR monoclonal antibodies are under investigation, such as panitumumab[22] or zalutumumab,[23] but to date with less encouraging results, showing no improvement in overall survival. Another target further down this biological pathway, offering a different mechanism of action is used by erlotinib, a small molecule inhibitor of EGFR tyrosine kinase. In one phase II trial of erlotinib given alone or combined with cisplatin, unfortunately it did not show any benefit in outcome for the combination. Despite this, other targets in the EGFR pathway are being investigated.[24]

This emerging modality and immuno-oncology are discussed in greater detail in Chapter 30, Biologically targeted agents in head and neck cancers.

CHEMOTHERAPY FOR RECURRENT OR METASTATIC HEAD AND NECK CANCER

Chemotherapy or targeted biological agents may be indicated for patients with recurrent and/or metastatic disease but patients with metastatic disease have a median survival of approximately 6–12 months in most studies.

Appropriateness of chemotherapy depends on several factors, such as: extent and burden of disease; whether symptoms are present or not; and whether failure of control has taken place at the primary site only, there is metastatic disease only, or both. Often, the most important consideration is the fitness and performance status of the patient and whether they could tolerate the proposed chemotherapy, and how much it would reduce their pre-treatment quality of life, for whatever limited survival they have.

LOCOREGIONAL FAILURE

This has been reported in up to 50% of patients with head and neck cancer. Prognosis in this patient group is typically poor and salvage treatments can be limited by the extent of the recurrent disease, the time interval since original treatment and the type of primary treatment.[25]

In this group of patients, if other salvage surgery or re-treatment with radiotherapy and chemoradiotherapy is being considered, it is important to assess the presence of distant metastatic disease, and also to confirm that the locoregional recurrence disease is not a second primary. Discovering that metastatic disease is also present is not an absolute contraindication to salvage treatments at the primary site, as locoregional failure and metastatic disease can be considered as two separate problems in the patient's management plan. If good palliation at the primary site or local regional control can be achieved relatively easily by a salvage procedure, the presence of metastatic disease, especially small volume metastatic disease, should not necessarily stop treatment to the primary or locoregional site. The patients who do better with salvage treatment are those with smaller volumes of recurrence, a longer disease-free interval and fewer comorbidities. Some head and neck subsites, such as the larynx, also have better outcomes than other subsites.[26]

DISTANT METASTASES

Chemotherapy is often indicated here as part of a best supportive care package but has not been shown to significantly extend survival. The presence or absence of symptoms will influence when they receive chemotherapy. The therapeutic window for giving chemotherapy in this

situation would be when the patient still has an appropriate performance status to receive and benefit from chemotherapy, with the trade-off being an improved symptom state for the inevitable morbidity caused by the chemotherapy. Giving chemotherapy to the patient with no symptoms to palliate and little hope of extending survival, while giving some treatment side effects and increased hospital attendances, may well decrease the patient's quality of life by a factor greater than any symptoms alleviated by the chemotherapy. A shared decision-making approach where the patient and his family are given as complete information as possible on the potential benefits and morbidities of having chemotherapy with its likely effect on symptoms, positive or negative effects and prognosis and treatment morbidity may let the patient make a more fully informed decision.

If chemotherapy is to be given for distant metastatic disease, the most appropriate regimen depends on several factors including the performance status, comorbidities present, renal function and the physiological reserve of the patient. Additionally, the regimens the patient has had before and the length of the interval since last chemotherapy was given, may be important.

The most common regimens used are cisplatin or carboplatin with 5-FU. These give an expected response rate of approximately 40%.[27] Carboplatin is used more often in this palliative metastatic setting than with induction or concurrent regimens, because although deemed slightly less effective than cisplatin, it is less toxic and is considered to be more appropriate in the palliative setting.

Elderly patients do appear to respond to platinum-based chemotherapy in the metastatic setting,[28] in contrast to a lack of benefit in the elderly when used in primary chemoradiotherapy regimens. There does, however, appear to be more toxicity using chemotherapy in an elderly patient population than the standard patient population.

Other more toxic chemotherapy regimens have also been investigated using platinum and a taxane (docetaxel or paclitaxel) in combination. These have not been shown to improve survival compared to the standard of care combination of cisplatin and 5-FU, although some studies have found a high response rate but with the cost of higher toxicity.

Cetuximab with cisplatin and 5-FU, which has become a more commonly used regimen, can increase both response rate and improve short-term survival slightly, as shown in the EXTREME trial,[29] but a 5-year follow-up published recently in abstract form shows very low survival for patients in both arms of the study. The EXTREME study did not allow crossover between regimens so similar results might be achieved by the use of cisplatin and 5-FU followed by cetuximab used sequentially. In patients who have become refractory to cisplatin and 5-FU, cetuximab as a single agent does have a low response rate of approximately 10–15%.[30–32]

KEY POINTS

- Concurrent chemoradiotherapy is at present the standard of care for treatment of locally advanced head and neck cancer with a confirmed absolute survival benefit of 6.5% at 5 years.
- Single agent cisplatin, which in the past has been shown to be as effective as multiple drug regimes, is now being challenged by the introduction of the use of taxanes.
- Targeted biological agents, such as cetuximab, have a role to play in both advanced head and neck cancer and recurrent or metastatic disease but those roles are still being established.
- At present HPV status does not alter management regimens, although there are multiple studies underway, examining if less intense treatment, both with radiotherapy and chemotherapy, could be given to achieve the same outcome but with less toxicity.
- The potential benefit of neoadjuvant or induction chemotherapy is being re-examined.
- Elderly patients benefit least in terms of survival advantage with the use of concurrent chemotherapy.

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CHAPTER 25

CYSTS AND TUMOURS OF THE BONY FACIAL SKELETON

Julia A. Woolgar and Gillian L. Hall

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: odontogenic cyst, jaw cysts, non-odontogenic cysts, and jaw neoplasms.

INTRODUCTION

The maxilla and mandible – the upper and lower jaws, respectively – form an important part of the bony facial skeleton and are unique in that they consist, in part, of the alveolar process which has the sole purpose of supporting the teeth. The teeth develop within the deeper part of the jaws and erupt up through the alveolar process, coming to lie within the tooth socket, suspended by the periodontal ligament which lies between the bony tooth socket and the cementum of the tooth root. The crown of the erupted tooth is cuffed at the neck by gingival mucoperiosteum and this junction of hard and soft tissues is a potential source of infection and inflammation. The inflammation can stimulate odontogenic epithelial remnants left after tooth development leading to the inflammatory radicular cyst, the most common type of cyst affecting the jaws. In addition, other types of odontogenic epithelial residues may give rise to developmental odontogenic cysts. The odontogenic cysts, being unique to the jaws, form a major part of this chapter. Also covered are the non-odontogenic cysts which arise from embryonic epithelial residues found within canals running through the facial bones or entrapped at lines of bone fusion. The non-odontogenic cysts are less common but important in the differential diagnosis of cystic lesions. Non-epithelialized bone cysts are also covered since, although they are rare within the jaws compared to the long bones, they are important in the differential diagnosis of cysts of the facial skeleton.

The second part of the chapter focuses on fibro-osseous lesions, a diverse group of bone conditions that can cause 'tumour' or swelling of the bones, drifting of teeth and radiological appearances that mimic cysts and neoplasms. Some are unique to the jaws and their diagnosis requires detailed clinicopathological correlation. The third part of the chapter deals with 'tumours' ranging from developmental anomalies to true neoplasms beginning with an overview of lesions arising from bone cells. Emphasis is given to the clinical and radiological presentation and any ways in which jaw/facial lesions differ from lesions elsewhere in the skeleton. The odontogenic tumours are covered in detail since they are unique to the jaws and both the diagnosis and management can be challenging. Finally, intraosseous salivary gland tumours, miscellaneous lesions and metastatic tumours are briefly considered.

CYSTS

A simple definition of a cyst is 'a cavity, generally lined by epithelium, filled with fluid or semi solid contents but not formed by the accumulation of pus'. As outlined above and summarized in **Table 25.1**, cysts of the jaws and bony facial skeleton arise from several types of epithelial residues. These residues probably exist within the jaws and covering alveolar/gingival mucoperiosteum in all individuals but the factors which lead to cyst formation are poorly understood.

TABLE 25.1 Classification of cysts of the bony facial skeleton

Lining of cyst lumen	Category of cyst	Subcategory	Source of epithelial lining
Epithelialized	Odontogenic	Developmental and inflammatory (see Table 25.2)	Residues of the tooth-forming organ
Epithelialized	Non-odontogenic	Nasopalatine duct cyst and variants	Remnants of nasopalatine duct (Jacobson's organ)
		Intraosseous dermoid and epidermoid	Entrapped epithelium at lines of embryonic closure
Non-epithelialized	Solitary bone cyst		
	Aneurysmal bone cyst		
	Staphne's idiopathic bone cavity		
	Focal marrow-containing jaw cavity		

TABLE 25.2 Odontogenic epithelial remnants, their origin and associated cyst(s)

Odontogenic epithelial residue	Source of odontogenic epithelial residue	Associated odontogenic cyst(s)
Reduced enamel epithelium	Fusion of inner and outer enamel epithelia of enamel organ	Dentigerous (follicular) and eruption cysts
		Paradental cyst
Rests of Malassez	Root sheath of Hertwig	Radicular (apical and lateral) and residual cysts
Rests (glands) of Serres	Dental lamina	Dental lamina cysts of the newborn (Bohn's nodules)
		Lateral periodontal, botryoid odontogenic cysts and gingival cyst of adults
		Keratocystic odontogenic tumour (formerly, odontogenic keratocyst)

Epithelialized cysts

ODONTOGENIC CYSTS

The odontogenic cysts arise from remnants of the tooth-forming apparatus.[1] There are three distinct types of epithelium which persist once odontogenesis is complete (**Table 25.2**). First, the dental lamina, which, in the developing embryo, is the downgrowth of surface oral epithelium that extends into the underlying developing mesenchymal tissue and gives rise to the enamel organ (**Figure 25.1**). Once tooth formation is complete, this structure fragments, but its persistence as small, rounded islands of epithelium within the bone and alveolar soft tissues, the rests (glands) of Serres, is well recognized (**Figures 25.2–25.4**). These dental lamina residues give rise to the developmental lateral periodontal and gingival cysts (and the keratocystic odontogenic tumour, formerly the odontogenic keratocyst). Second, once enamel formation is complete, prior to eruption, the tooth is covered by a layer of reduced enamel epithelium, formed by fusion of the two layers of inner and outer enamel epithelia. This is the source of epithelium for dentigerous (follicular), eruption and inflammatory paradental cysts. The third epithelial residue is the rests of Malassez within the periodontal ligament between the tooth root and the bony tooth socket which results from the fragmentation of Hertwig's root sheath on the completion of root formation, and gives rise to the inflammatory radicular cysts. The classification of odontogenic cysts used in this chapter (**Table 25.3**) is based on that recommended by the World Health Organisation.[2]

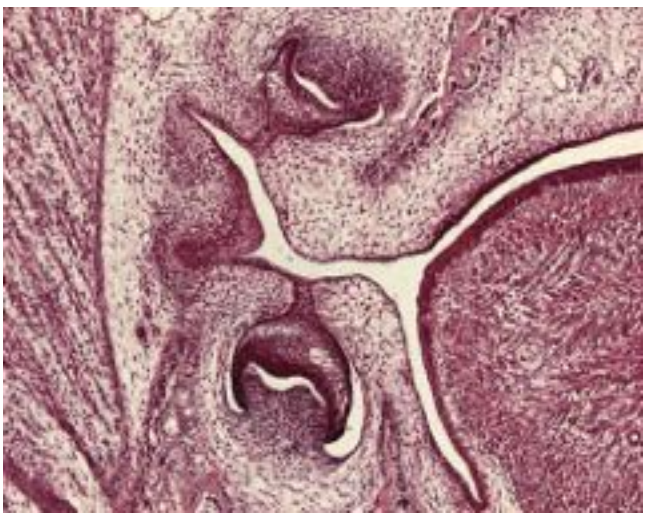


Figure 25.1 Photomicrograph depicting developing tooth germ arising from down growth of oral cavity lining surface epithelium, the dental lamina.

Developmental odontogenic cysts

DENTIGEROUS (FOLLICULAR) AND ERUPTION CYSTS

These account for around 15–18% of jaw cysts. Dentigerous cysts, formed by expansion of the dental follicle, the soft tissue covering the crown of an unerupted tooth, are attached to the cemento-enamel junction. Teeth most commonly affected are those more likely to remain

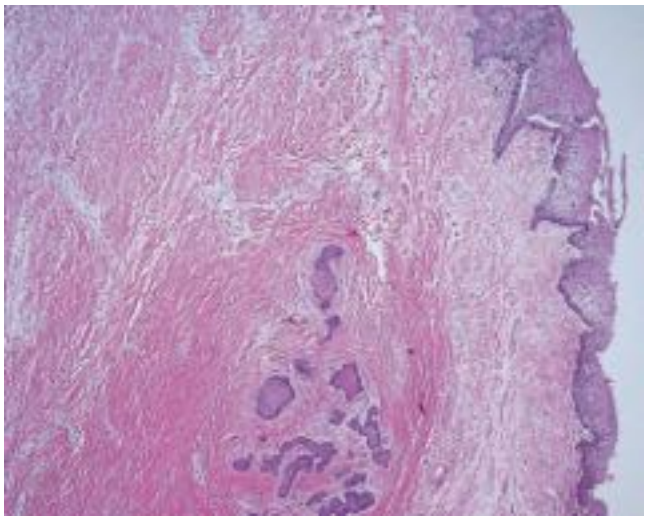


Figure 25.2 Photomicrograph showing remnants of fragmented dental lamina, odontogenic epithelial rests, in an adult within alveolar connective tissues.

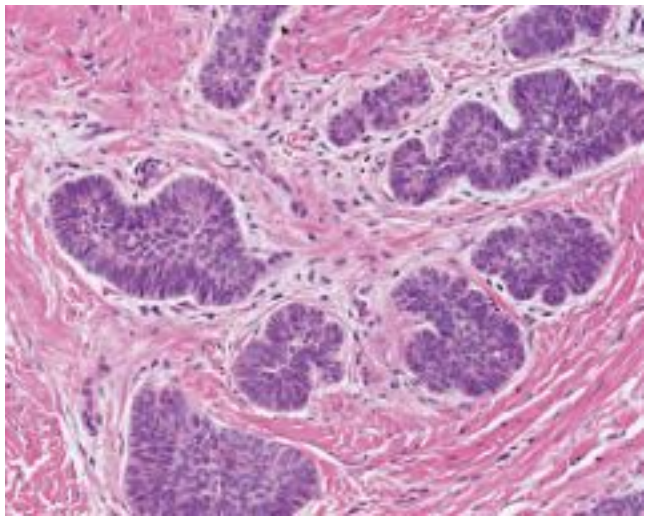


Figure 25.3 Photomicrograph showing remnants of fragmented dental lamina, odontogenic epithelial rests, in an adult within alveolar connective tissues.

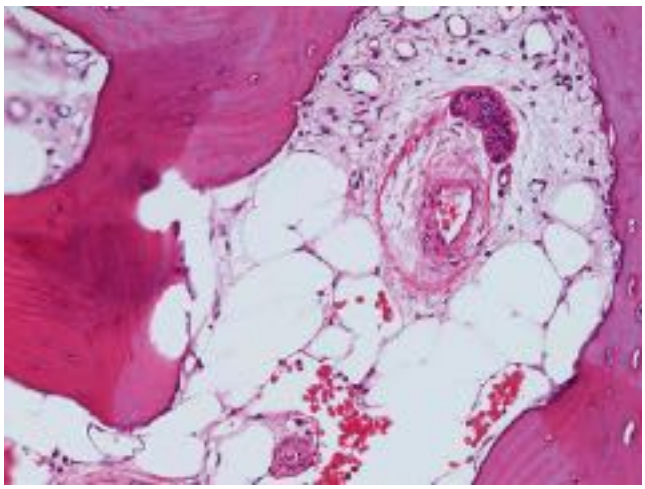


Figure 25.4 Odontogenic epithelial remnants within bone.

unerupted, typically, in order of decreasing frequency, mandibular third molars ('wisdom' teeth), maxillary canines, mandibular second premolars and maxillary third molars. Peak age of presentation is second to third decades but they can be diagnosed later in adulthood. Some present with swelling, displacement of teeth and symptoms resulting from secondary infection but many are found on radiological assessment of a missing tooth. Dentigerous cysts can reach up to 5 cm in radiographic diameter, and the clinical differential diagnosis of larger lesions includes keratocystic odontogenic tumour and unicystic ameloblastoma, two more aggressive lesions that can present in a dentigerous relationship (see below).

Radiographically, dentigerous cysts typically present as unilocular radiolucencies connected to the cemento-enamel junction (**Figures 25.5** and **25.6**). They have a greater tendency than other non-neoplastic cysts to cause root resorption in adjacent teeth[3] possibly because resorption of the deciduous predecessor is a normal function of the follicle.

Histological diagnosis is generally straightforward especially when accurate clinical and radiographic information are provided on the request form. The epithelial lining is thin, either simple cuboidal, columnar or non-keratinized stratified squamous, although metaplasia may result in focal keratinization and scattered mucus and ciliated cells.

TABLE 25.3 Classification of the odontogenic cysts

Pathogenetic category	Cyst type	Subtype	Dental relationship
Developmental	Dentigerous (follicular)	Eruption	Cover the crown of an unerupted tooth; attached to cement-enamel junction
	Lateral periodontal	Gingival cyst of adults	Lateral to root of vital tooth
		Botryoid odontogenic	
	Sialo-odontogenic (glandular odontogenic)		
Inflammatory	Radicular (dental)	Apical	Root apex of non-vital tooth
		Lateral	Lateral root canal of non-vital tooth
		Residual	Within jaw after removal of associated causative tooth
	Paradental		Lateral aspect of partially erupted tooth

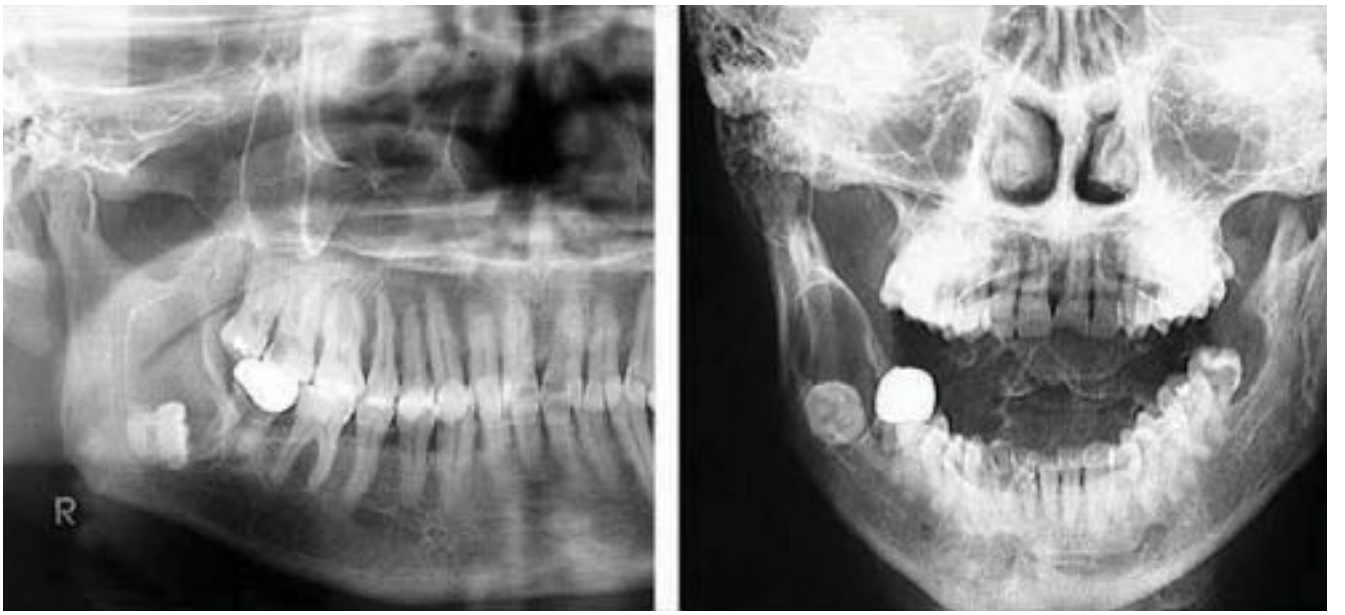


Figure 25.5 Bilateral dentigerous cysts seen radiologically.



Figure 25.6 Macroscopic image of dentigerous cyst and associated lower premolar (impacted) noting relationship to cemento-enamel junction.

Numerous pathogenetic theories have been proposed but why only a minority of patients with unerupted teeth develop dentigerous cysts remains poorly understood. In one study, 29.6% of maxillary third molars were impacted but the frequency of cyst formation was only 5.4%;[4] and other studies have estimated the ratio of cyst:unerupted tooth to be 1 in 150 and 1.44 in 100, respectively.[5, 6]

The eruption cyst[10] is a superficially located dentigerous cyst, presenting as a bluish swelling of the gum overlying an erupting tooth. They are most commonly seen in children, typically affecting the mandibular first molar and maxillary incisor teeth. Cyclosporin therapy is a recognized predisposing factor.[7, 8]

Depending on the type and position of the associated tooth, many dentigerous and gingival cysts can be treated by marsupialization which generally results in full eruption of the tooth.

LATERAL PERIODONTAL AND BOTRYOID ODONTOGENIC CYSTS

Developmental lateral periodontal cysts are rare (accounting for only 0.7% of jaw cysts). They typically present in older adults and mainly affect mandibular premolars, presenting in a lateral position but not related to pulpal or periodontal inflammation.[9] They are generally asymptomatic and detected incidentally on routine radiological examination. Removal for histological diagnosis is usual. The histological features are distinct: thin, non-keratinized epithelium with focal plaque-like thickenings. The debate on the epithelial source of the lateral periodontal cyst is ongoing. Enucleation is the treatment of choice and recurrence is rare. In contrast, the botyroid odontogenic cyst, the multilocular / multicystic variant, has a propensity to recur and complete surgical removal is the preferred treatment.[10]

GLANDULAR ODONTOGENIC CYST (SIALO-ODONTOGENIC CYST)

Accounting for less than 1% of jaw cysts, the glandular odontogenic cyst is of interest to both clinician and diagnostic pathologist due to its propensity to recur and potentially puzzling histological features. With a peak presentation in elderly males, most cases arise in the anterior mandible, presenting as a slow-growing, painless swelling, and on radiology, a unilocular or multilocular radiolucency. Histologically, the cyst is lined by cuboidal or columnar epithelium with scattered goblet cells and characteristic intra-epithelial gland-like crypts. Important differential diagnoses include botryoid odontogenic cyst, intra-osseous mucoepidermoid carcinoma and metaplasia within a dentigerous cyst. The glandular odontogenic cyst shows more aggressive behaviour than other odontogenic cysts and multilocular lesions have a particular propensity to recur and should be treated by complete excision.[11, 12]

Inflammatory odontogenic cysts

RADICULAR (DENTAL) CYSTS: APICAL, LATERAL, RESIDUAL

These are by far the most common jaw cysts, accounting for 65–70%[13] and ones for which there is a clearly defined etiological agent. They occur in both sexes and over a wide age range. Inflammation at the root apex of a tooth, either as a result of extension of pulpal inflammation and/or necrosis due to deep dental caries, or triggered by loss of tooth vitality following trauma, can lead to proliferation of the epithelial rests of Malassez within the periodontal ligament. Radicular cysts may arise in association with any damaged tooth but there is a tendency for the maxillary incisor teeth to be involved more frequently than other sites.[13]

Many factors are involved in cyst initiation and progression. Cytokines and growth factors released by the inflammatory cells cause epithelial proliferation and also lead to soft-tissue destruction and osteoclast-mediated bone resorption, thus allowing space for an established cyst to grow by expansion. Bacterial endotoxins may also stimulate epithelial proliferation. Within the mass of proliferating epithelium, intercellular oedema and degeneration of the more centrally located cells leads to cavitation. The presence of abundant proteinaceous debris within the resulting lumen leads to increased osmolarity and drawing in of fluid leading to further expansion of the established cyst.

A radicular cyst may present with acute symptoms of pain and swelling but many are asymptomatic and seen as a radiolucency at the root apex on routine dental radiological examination (**Figure 25.7**). The associated tooth is, by definition, non-vital. Some teeth have additional communications between the root pulp canal and the periodontal ligament – one or more lateral canals – and these are the origin of lateral radicular (lateral dental) cysts.

The main differential diagnosis of a radiolucency at, or close to, the apex of an obviously carious or damaged tooth is that of granulation tissue without cyst formation, commonly referred to a periapical granuloma. The size of the radiolucency can be used as a diagnostic guide since radiolucencies greater than 20 mm are highly likely to be cysts and ones below 5 mm are likely to be granulomas.[14]

Theoretically, adequate endodontic treatment with elimination of necrotic, infected and inflammatory debris within the pulp canal should lead to resolution of the cyst but many persist and require surgical removal via apicectomy or tooth extraction. Cysts that persist after removal of the associated tooth are referred to as residual cysts (**Figure 25.8**).

Pathological diagnosis is usually straightforward. Characteristically, the fibrous wall is thick with active acute and chronic inflammation, and the epithelial lining is non-keratinized stratified squamous with areas of hyperplasia and focal ulceration. There are, however, some potential pitfalls. First, it is not unusual to find areas of epithelial metaplasia, with mucous-secreting and ciliated cells leading to a resemblance to respiratory-type epithelium and misdiagnosis as antral mucosa or a sialo-odontogenic cyst; or keratin-forming cells and misdiagnosis as a keratocystic odontogenic tumour. Second, a developmental cyst or even a cystic odontogenic neoplasm may become secondarily inflamed and lose its characteristic appearances and acquire features that can be indistinguishable from a radicular cyst, especially if only a small



Figure 25.7 Radiological image of radicular cyst upper lateral incisor with typical location.



Figure 25.8 Residual cyst; unilocular radiolucency, several years post extraction of a tooth with apical pathology.

portion of the lesion is submitted for histological examination. Submission of any cystic lesion of the jaws should always be accompanied by a brief description of its location in relation to the roots and crown of adjacent teeth; the status of the teeth; and the size, shape, margins and radiodensity of the lesion. A further potential diagnostic pitfall concerns periapical granulomas and radicular cysts following successful endodontic treatment when the inflammation has largely resolved, and there is little, if any, active inflammation. Such lesions should be diagnosed as periapical scar tissue and generally are found as a symptomless radiolucency and probably arise due to a lack of bony infilling following successful endodontic treatment.

PARADENTAL CYST

This inflammatory cyst arises in association with a vital tooth, usually on the lateral aspect, and results from inflammation within a periodontal pocket. The commonest site of occurrence is following pericoronitis around a partially erupted mandibular third molar. Hence, the peak age of presentation is young adults (18–25 years) and males are affected more than females. Paradental cysts account for around 3–5% of jaw cysts. The epithelial origin may be the reduced enamel epithelium or the epithelial cell rests of Malassez in the periodontal ligament.[15] The histological features are similar to the radicular cyst and the correct diagnosis depends on accurate clinical and radiological information. Enucleation is curative.

Non-odontogenic epithelial-lined

NASOPALATINE DUCT (INCISIVE CANAL), MEDIAN PALATINE, MEDIAN ALVEOLAR AND PALATINE PAPILLA CYSTS

The nasopalatine duct cyst and its variants are the most common non-odontogenic cysts accounting for 5–10% of jaw cysts.[16] They arise from epithelial remnants of the vestigial Jacobson's organ (part of the olfactory system in some mammals) within the nasopalatine canal which runs from the nasal septum to the palate in the anterior maxilla immediately behind the maxillary central incisor teeth. The nasopalatine duct cyst presents in the midline of the anterior maxilla. The median palatine and median alveolar cysts are posteriorly and anteriorly located variants, and the palatine papilla cyst is superficially located within the soft tissue of the incisive papilla.

The nasopalatine duct cyst and its variants are seen over a broad age range, peaking in middle-aged adult males. They may present with swelling and pain and may be associated with a salty taste. Many are asymptomatic and identified on routine radiography. The radiolucency is typically symmetrical and heart-shaped with a sclerotic border but may resemble periapical pathology of the incisor teeth. Testing the vitality of the incisor teeth is an important diagnostic step, but in the presence of diseased/non-vital teeth, pathological examination may be necessary for definitive diagnosis. A small nasopalatine duct cyst can be difficult to distinguish from the anterior palatine fossa and asymptomatic lesions less than 10 mm should be observed rather than removed.

The typical histological appearance of the nasopalatine duct cyst is a thick-walled sac, with a lumen lined by both squamous and respiratory type epithelia and often sizeable neurovascular bundles (branches of the long sphenopalatine nerve and vessels) within the collagenous wall. Secondary infection and ulceration may mask the characteristic features making accurate clinical and radiographic information essential. When symptomatic or large, the cysts can be managed by simple enucleation and recurrence is rare.

INTRAOSSEOUS DERMOID AND EPIDERMOID CYSTS

Dermoid and epidermoid cysts[17, 18] generally arise within the soft tissues from entrapped epithelium at lines of embryonic fusion. Rarely, they arise within the bone – in the midline mandible or lateral to the orbit being the most common sites. They generally present in children and young adults, as asymptomatic, well-defined radiolucencies. Histologically, they contain laminated keratin and are lined by orthokeratinized epithelium. Dermal appendages characterize the dermoid cyst and often hairs are found within the lumen. Enucleation is curative.

Non-epithelialized primary bone cysts

SOLITARY (SIMPLE, TRAUMATIC, HAEMORRHAGIC) BONE CYST

Although this is the most frequent of the non-epithelialized bone 'cysts', it occurs mainly in long bones and is uncommon in the jaws. It occurs almost exclusively in the mandible, mainly the molar/premolar regions. Peak incidence is in the second decade.[19] Most are asymptomatic and discovered on routine radiography. Typically, the well-defined radiolucency is scalloped around the roots of the teeth.[20] Around 25% result in bony expansion. Lip paraesthesia is exceptional.[19] Surgical exploration may be necessary for confirmation and reveals an empty intrabony cavity with no obvious soft tissue lining. Curettings consist of delicate loose, vascular fibrous tissue containing scattered osteoclasts and haemosiderin pigment. The favoured pathogenetic theory proposes traumatic intramedullary haemorrhage is followed by failure of organization and subsequent lysis of the blood clot. The interval between trauma and discovery ranges from months to years and the apparent relationship may be spurious. Careful curettage, avoiding damage to tooth roots and neurovascular structures, results in fresh intramedullary haemorrhage, organization of the clot and bony in-filling. Some lesions may resolve spontaneously.

ANEURYSMAL BONE CYST

This rarely affects the jaws with only 60–70 reported cases, mainly in teens/young adults with a slight female predilection.[21] Most arise in the mandibular posterior molar/angle and present as a firm, expansile swelling with



Figure 25.9 Multilocular radiolucency body of mandible: differential includes keratocystic odontogenic tumour, ameloblastoma, odontogenic myxoma, giant cell lesion and haemangioma.

facial deformity and often, pain. Radiographs reveal a uni- or multilocular, balloon or soap-bubble-like radiolucency (similar to ameloblastoma and odontogenic myxoma, **Figure 25.9**). Surgical exploration leads to the characteristic welling-up of blood. The curetted tissue consists of numerous blood-filled spaces without obvious endothelial lining. Multinucleated giant cells and haemosiderin are frequent within the fibrous septae. The pathogenesis is uncertain. In some, a translocation involving chromosome 17 and the oncogene USP6 can be demonstrated suggesting they are neoplastic.[22] Other cases may be associated with an intramedullary haemodynamic disturbance and 20–30% appear to complicate central giant cell granulomas or other fibro-osseous lesions.[23] Curettage is generally curative.

STAFNE'S IDIOPATHIC BONE CAVITY

This uncommon mandibular developmental anomaly may be mistaken as a jaw cyst on radiography[24] when a symptomless round/oval, well-demarcated radiolucency of the premolar-angle region is discovered (**Figure 25.10**). It is located beneath the inferior dental canal and may be bilateral. The appearance is due to a saucer-like concavity of the lingual plate occupied by submandibular salivary gland tissue. Anterior lesions related to the sublingual gland are rare. Sialography is helpful in confirming the diagnosis and can prevent unnecessary surgical exploration.



Figure 25.10 Radiology of Stafne's bone cavity; well-defined radiolucency below the level of the ID canal.

FOCAL MARROW-CONTAINING JAW CAVITY (FOCAL OSTEOPOROTIC BONE MARROW DEFECT)

Haemopoietic marrow, typically in the maxillary tuberosity and mandibular ramus/condylar neck, may be mistaken for a cyst radiographically.[25] Histological assessment of curetted tissue is diagnostic.

FIBRO-OSSEOUS LESIONS

These form a diverse group of conditions with differing aetiologies but similar histology (**Figure 25.11**). Normal bone is replaced by variably cellular fibroblastic stroma within which pathological ossification and/or calcification gradually occurs.[26] Diagnosis requires clinical and radiological correlation as well as good knowledge of subtle histological differences. The fibro-osseous spectrum[27–29] includes lesions with a clear developmental aetiology and known genetic mutations, inflammatory/infectious conditions and benign neoplasms. A helpful classification, proposed by Eversole et al,[30] is shown in modified form in **Table 25.4**.

Bone dysplasias

FIBROUS DYSPLASIA

In most cases, fibrous dysplasia (FD) is monostotic and maxillary cases are more frequent than mandibular.[30–33] Maxillary lesions that involve contiguous areas of the zygoma and sphenoid (craniofacial FD) are restricted to a defined anatomical region and generally regarded as variants of monostotic rather than polyostotic FD.[27]

Monostotic FD usually presents in children and young adults or on reactivation of quiescent lesions in adults (for example, during pregnancy) as a painless, slow-growing facial asymmetry or swelling. The smooth, fusiform enlargement is more marked buccally than palatally.[32] Teeth may be displaced or fail to erupt. Involvement of the maxillary sinus and zygomatic process results in exophthalmos and proptosis. Radiographically, the ill-defined

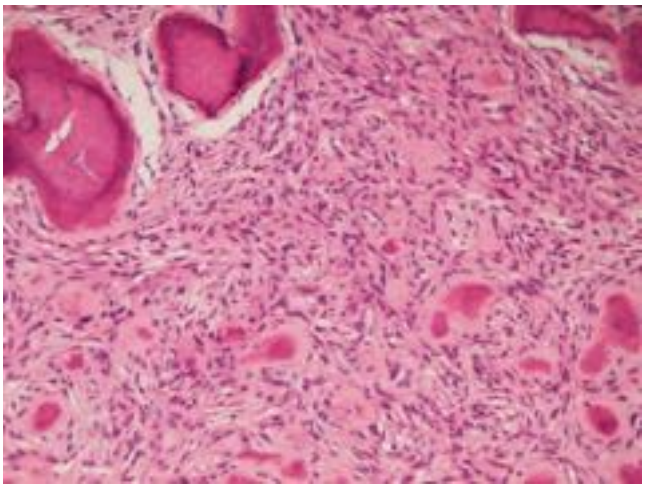


Figure 25.11 Pathological image of a fibro-osseous lesion. This could be an ossifying fibroma or one of the cemento-osseous dysplasias and distinction would require close clinical and radiological correlation.

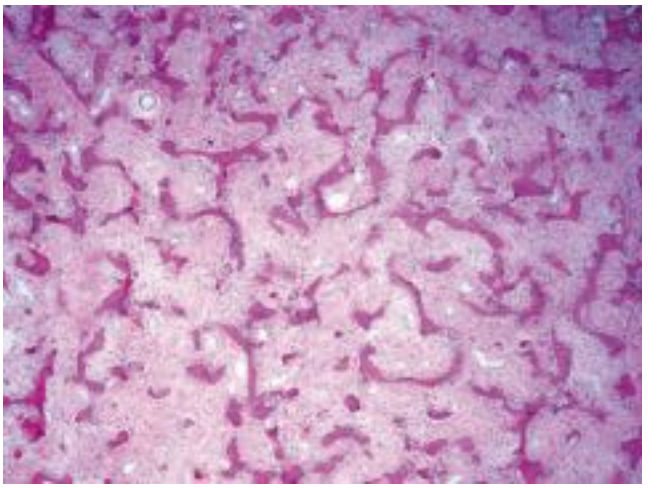


Figure 25.12 Histological picture of typical fibrous dysplasia; cellular fibrous stroma in which so called 'Chinese' character-like trabeculae of bone are deposited.

TABLE 25. 4 A modification of the classification of fibro-osseous lesions of the craniofacial complex proposed by Eversole et al[30]

Pathological process	Disease / condition	Sub-type
Bone dysplasias	Fibrous dysplasia	Monostostic (including craniofacial variant)
		Polyostotic
		Polyostotic with endocrinopathy (McCune–Albright syndrome)
	Osteitis deforms (Paget's disease)	
Cemento-osseous dysplasias	Focal cemento-osseous dysplasia	
	Florid cemento-osseous dysplasia	
Inflammatory / reactive processes	Focal sclerosing osteomyelitis	
	Diffuse sclerosing osteomyelitis	
	Proliferative periostitis	
Metabolic bone disease	Hyperparathyroidism	
Genetic	Cherubism	
Neoplastic	Ossifying fibroma	Ossifying fibroma NOS
		Juvenile ossifiying fibroma (trabecular and psammonatoid types)
		Gigantiform cementoma

lesions merge with normal bone. Early radiolucent lesions pass through mottled and ground-glass/orange-peel stages becoming opaque as bony trabeculae increase in number and size, extending to and distorting, but not crossing, suture lines.

Polyostotic FD mainly affects females (M:F ratio, 1:3), often affecting one side of the body. Most cases present in childhood with bony deformities and pathological fractures, occasionally with skin pigmentation and precocious puberty in females (McCune–Albright syndrome).[32]

Histology depends on the developmental stage of the lesion. Classically, the delicate trabeculae of newly-formed, woven bone resemble Chinese characters and are gradually remodelled to lamellar bone as the lesion ages (**Figure 25.12**).[32] The margin merges with surrounding normal bone, an important distinction from ossifying fibroma (see later).

FD is a sporadic (non-inherited) developmental disorder caused by mutation of somatic cells in fetal (polyostotic FD) or postnatal (monostotic FD) life resulting in alterations in osteoblast growth/differentiation due to faulty expression/signalling of the *GNAS1* gene which encodes for a stimulatory protein.[32] Lesions tend to become quiescent and management is mainly aesthetic reduction of deformity. Lesions are not radiosensitive. Radiotherapy is contraindicated and may increase the risk of transformation to fibro-/osteosarcoma.

OSTEITIS DEFORMANS (PAGET'S DISEASE OF BONE)

This occurs mainly in older adults and many cases are subclinical.[30, 34] Skull involvement is common and often associated with jaw lesions (mainly maxillary). Presentation includes bone pain and deformity, spacing

of teeth, difficulty with dentures, and motor/sensory deficit due to cranial nerve compression. In early lesions, increased bone vascularity results in post-extraction haemorrhage. Hypercementosis and ankylosis, common in later stages, make for traumatic extractions, thus exacerbating poor healing due to late-stage ischaemia. Radiographically, lesions are ill-defined, initially osteoporotic, gradually becoming osteosclerotic ('cotton-wool patches'). Histologically,[34] osteoclastic activity dominates early lesions. Resorbed bone is replaced by vascular, cellular fibrous tissue. Gradually, trabeculae of new bone are deposited and remodelled with prominent resting and reversal lines (mosaic bone). Serum alkaline phosphatase is raised in active disease and useful in monitoring treatment.[34]

Osteitis deformans results from osteoclast dysfunction.[34] Aetiology is unclear, possibly involving paramyxovirus infection and genetic predisposition (on chromosome 18q). Treatment is with calcitonin and/or bisphosphonates. Osteosarcoma is a rare complication mainly affecting cases with widespread lesions.

Cemento-osseous dysplasias

These non-neoplastic proliferations are subdivided into focal and florid based on differences in location and number of lesions (**Figure 25.13**).[34–37] COD is more prevalent in females than males (M:F ratio, 1:10), and in Blacks with most cases presenting after 30 years. Focal COD[36] is more common, and seen as multiple periapical lesions of mandibular incisors which are asymptomatic being discovered on routine radiographs. Early lesions are rounded radiolucencies, which become increasingly radiopaque (maintaining a narrow radiolucent rim) as bone/calcified acellular cementum-like tissue is deposited.[38] Related teeth are vital (in contrast to periapical granulomas/radicular cysts). Florid COF[36] affects all four quadrants and may cause jaw expansion or symptoms related to ulceration/infection. Gigantiform cementoma[37, 38] is a rare familial variant sometimes categorized as neoplastic. Histologically, in CODs, new bone and rounded cementum-like globules are increasing deposited within the fibrocellular stroma eventually leading to a solid, bone-like mass. COD is self-limiting and treatment (for cosmesis or infection) is rarely needed.

Inflammatory/reactive processes

SCLEROSING OSTEOMYELITIS (SO)

This is a form of non-suppurative chronic osteomyelitis[33, 34] and is usually a localized reaction to low-grade periapical inflammation or infection although bacteria are not readily cultivable. Focal lesions affect mainly the mandibular premolar/molar region in children and young adults and present as a localized, uniform radiodensity

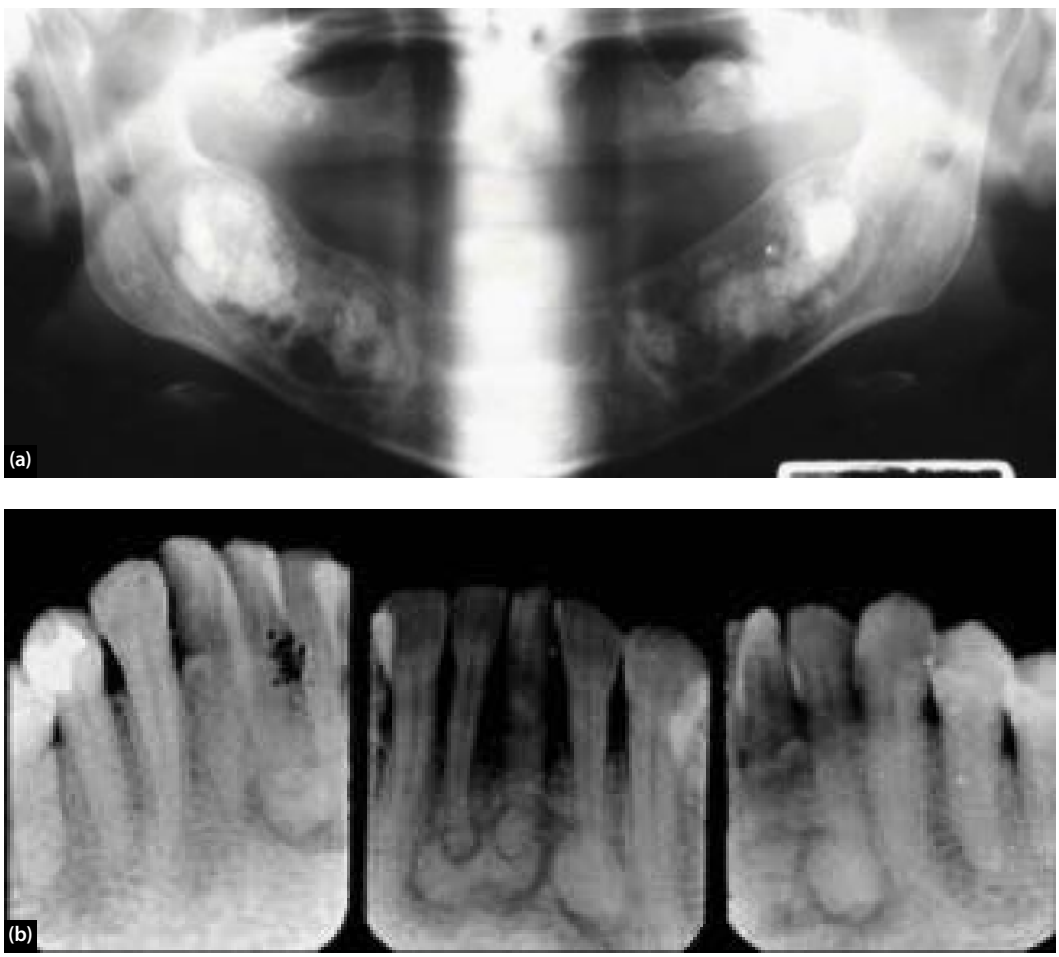


Figure 25.13
(a) Radiological appearances of florid cemento-osseous dysplasia and **(b)** periapical cemento-osseous dysplasia **(b)**.

related to the tooth root apex without jaw expansion. Histologically, dense sclerotic bone with scant fibrous connective tissue or inflammatory cells is seen. The diffuse form of SO affects adults[33, 34] and resembles florid COD radiographically. Treatment of SO is elimination of the source of inflammation by extraction or endodontic therapy. Sclerotic areas may remain radiographically.

PROLIFERATIVE PERIOSTITIS (GARRE'S OSTEOMYELITIS)

Mainly affecting adolescents, this form of chronic osteomyelitis results in onion-skin thickening and swelling of the mandibular lower border due to periosteal reaction to periapical inflammation.[30, 34] Histologically, highly cellular, woven bone is arranged in parallel layers. The bone gradually remodels 6–12 months following elimination of infection.

Metabolic bone disease: Hyperparathyroidism

The jaws may be affected as part of the multifocal replacement of bone by brown tumours, collections of osteoclasts within a vascular, haemosiderin-rich stroma.[30, 33, 34] Primary hyperparathyroidism (HP) due to parathyroid hyperplasia or adenoma mainly affects post-menopausal females. Radiolucent cyst-like lesions may be seen together with loss of lamina dura around tooth roots. Blood biochemistry is essential in interpreting the histological features which are indistinguishable from a giant-cell granuloma. Bone lesions due to the secondary HP associated with chronic renal failure are more common. The bone lesions of HP reverse on treatment of primary HP and respond to oral vitamin D in secondary HP.

Genetic: Cherubism

This is inherited as an autosomal trait (mapping to chromosome 4p16.3), but due to weaker penetrance in females, the phenotype is more common in males.[30, 33, 34] Onset usually occurs before the age of 7 years, presenting with swelling of the mandibular angles and in severe cases, the posterior maxillae, resulting in chubby face, interference with speech and swallowing, displacement/loosening of teeth and cervical lymphadenopathy (due to reactive hyperplasia). Maxillary involvement results in the eyes appearing to turn upwards. Radiography reveals multilocular radiolucencies with fine bony septae. Histologically, early lesions resemble giant cell granulomas with focal collections of multinucleated giant cells within cellular and vascular fibrous tissue. Vessels may show a hyaline cuff. Older lesions show increasing bony repair. Initial rapid growth slows on puberty and lesions gradually regress. Treatment by curettage or paring down is rarely needed.

Neoplastic: Ossifying fibroma and cemento-ossifying fibroma

Although neoplastic, traditionally ossifying fibroma (OF) and cemento-ossifying fibroma (COF)[30, 33] have been categorized with the fibro-osseous jaw lesions, and are considered part of a spectrum rather than two separate lesions. They present slowly as an expansile, well-circumscribed, painless swelling mainly affecting the mandibular premolar or molar regions. Females are more commonly affected than males with a peak incidence between 20 and 40 years of age. Radiographically, lesions are well-defined, initially radiolucent but with increasing calcifications centrally and eventually becoming mainly radiopaque with a narrow radiolucent rim. Roots of related teeth may be displaced. Histological appearances match the radiographic appearances being initially fibrous and cellular, later developing trabeculae of woven bone with peripheral osteoblasts, dystrophic calcifications and rounded cementicles.[38] The calcifications fuse with maturation eventually forming a dense calcified mass with a peripheral fibrous zone which allows the lesion to shell out from the adjacent bone during surgical enucleation.

Juvenile active (aggressive) OF affects the maxilla in children and adolescents[39] and histologically[40] the stroma is often highly cellular and the calcification pattern either trabecular (mainly osteoid with plump osteoblasts) or psammomatoid (compact, rounded calcifications). Some lesions are locally aggressive with a tendency to recur, but most respond to conservative surgery.

TUMOURS (NEOPLASMS)

Tumours arising from bone cells

OSTEOMAS

Osteoma, a benign neoplasm of bone, is subclassified into 'compact' (cortical) and 'cancellous'.[34] They can be situated on the surface of the bone and present as hard swellings (exostosis) or alternatively, can exist purely within the substance of the bone (enostosis, dense bone island) and in the latter location would likely be an incidental radiological finding. Some probably represent developmental anomalies or reactive hyperplasias rather than true neoplasms, common examples being mandibular tori (bilateral exostoses on the lingual aspect of the mandible in the premolar region) and palatine torus (a mushroom-like swelling in the midline of the palate). The most common site for a true osteoma is in the paranasal sinuses. Generally, tori present in childhood and grow slowly, and can be removed for cosmetic reasons or before fitting a denture. Multiple osteomas may be the presenting features of Gardner syndrome (**Figure 25.14**),[41] often leading to the diagnosis (and management by prophylactic colectomy) before adenocarcinomatous transformation of the familial colonic polyps.

OSTEOID OSTEOMA, OSTEOBLASTOMA

These are benign neoplasms of bone with 80% involving long bones and only 1% involving the jaws.[34] Most present in young adult males with severe pain which is relieved by aspirin. Osteoid osteomas are typically <2 cm in size while osteoblastomas are larger and more likely to present with swelling.[34] Radiography reveals a radiolucency

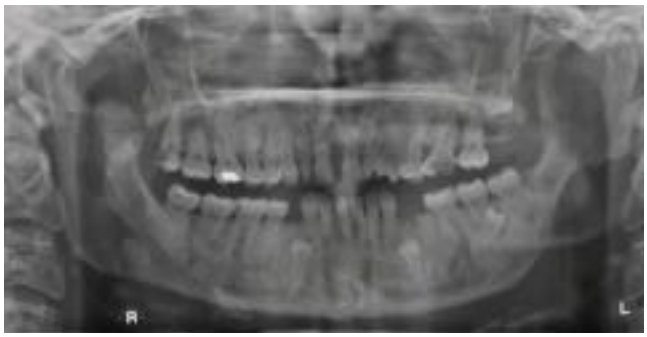


Figure 25.14 Gardner syndrome patient: multiple osteomas seen as radiodensities along with unerupted and supernumerary teeth.

with sclerotic rim and intralesional speckled calcification. Surgical exploration reveals a gritty lesion with well-defined boundaries, which shells out easily.

Histologically, a loose fibrovascular stroma containing abundant trabeculae of osteoid rimmed by plump osteoblasts and mineralized trabeculae is evident. Diagnosis of bony lesions should only be made when clinical and radiographic details are known since the plump osteoblasts could lead to an erroneous diagnosis of osteosarcoma especially when only curettings are available.

OSTEOCHONDROMA

This cartilage-capped exostosis is rare in the jaws, occurring mainly in the mandiblular condyle and coronoid process.[34] Differentiation from condylar hyperplasia can be difficult. Peak presentation is in females in the 4th–5th decade.[42] The slow-growing swellings cause progressive deformity. Histologically, both the overgrowth of bone and its cartilage cap are entirely benign. Any cellular atypia, especially within the cartilage, may indicate development of a secondary chondrosarcoma, a rare but well-documented occurrence.[33]

OSTEOSARCOMA

This is a malignant bone-producing tumour,[34] with only 6–10% of cases involving the jaws.[43–47] The average age at presentation of jaw lesions is 30–40 years, a decade more than for lesions at other sites. Most develop sporadically with no obvious aetiological factors. 'Secondary' osteosarcomas arise following radiotherapy or in Paget's disease of bone, FD, and in association with hereditary retinoblastoma, Ollier disease and Li-Fraumeni syndrome.

Swelling, pain, paraesthesia, ulceration and loose teeth are common presenting features.[46, 47] The radiographic appearance depends on the proportion of radiolucent soft tissue to radiopaque malignant bone matrix. The classical 'sunray' appearance results from the perpendicular spicules of periosteal new bone. Widening of periodontal ligament spaces and the inferior alveolar canal are other classical changes. Histological diagnosis requires the demonstration of osteoid and bone by overtly malignant cells. The architecture of the malignant bone is abnormal ('lace-like'). A high proportion of jaw lesions also contain malignant cartilage (chondroblastic osteosarcoma) while bone is scanty in some (fibroblastic osteosarcoma).

Osteosarcomas arising on the bone surface present specific characteristics and behaviours.[34, 46, 47] The parosteal osteosarcoma is a low-grade neoplasm which can mimic osteochondroma if a cartilage cap is present and also end-stage FD, highlighting the need for close radiological correlation and submission of reasonable quantities of lesional tissue for pathological diagnosis. The malignant cells are generally bland but some focal atypia should be demonstrable. Periosteal osteosarcomas are exceptionally rare and although generally clinically indolent, display more overt malignant cytological features and often abundant cartilage admixed with the malignant bone.

Surgery is the mainstay of treatment with the aim of achieving clear margins.[59] The 10-year survival is 59% in one series[45] with local recurrences more frequent than distant metastasis (31% versus 21%). Pre-surgical or adjuvant chemo- and radiotherapy may offer some benefits. The rarity of jaw osteosarcoma makes it difficult to assess the effectiveness of the well-defined protocols that exist for long-bone osteosarcoma. Overall, it is considered that the prognosis of osteosarcoma of jaws is better than long bones with 40% 5-year survival for jaw lesions compared with 20% at other sites.[43, 44]

CHONDROMA, CHONDROSARCOMA

These are rare in the jaws; the most common sites being the anterior maxilla and mandibular condyle, presenting mainly in middle age with pain, swelling and loosening of teeth.[34, 48, 49] Histologically, the chondroma is a cytologically benign tumour forming mature cartilage. A high degree of cellularity, multiple chondrocytes occupying a single lacuna and plump/binucleate cells are suspicious of well-differentiated chondrosarcoma.[34, 48] Demonstration of invasion is also important. Less well-differentiated chondrosarcomas exhibit more obvious cytological features of malignancy. Calcification and endochondral ossification may occur in both benign and malignant lesions and accounts for the variable radiographic appearances. The outline may be well- or ill-defined or multilocular. Signal characteristics typical of cartilage matrix can best be seen on CT scanning. As in osteosarcoma, the rarity means evidence-based treatment protocols are not yet established. Surgery is the mainstay of treatment with 60% 5-year survival.[49] Mandibular compared to maxillary lesions, small tumour size and high degree of differentiation are favourable prognostic features, the first two presumably reflecting the importance of achieving surgical clearance.

Odontogenic tumours

Odontogenic tumours, a spectrum of lesions unique to the jaws, are derived from tooth-forming apparatus.[50] They range from hamartoma-like dental malformations (odontomas) through to benign neoplasms, locally invasive growths, malignant neoplasms with metastatic potential

TABLE 25.5 Classification of odontogenic tumours (a modification of WHO classification[50])

Benign odontogenic tumours	
Arising from odontogenic epithelium only	Ameloblastoma
	Squamous odontogenic tumour
	Calcifying epithelial odontogenic tumour
	Keratocystic odontogenic tumour (formerly, odontogenic keratocyst)
Including odontogenic epithelium as well as ectomesenchyme with or without hard tissue formation	Ameloblastic fibroma
	Ameloblastic fibro-dentinoma and fibro-odontoma
	Complex and compound odontoma
	Calcifying cystic odontogenic tumour
	Dentinogenic ghost cell tumour
Arising from odontogenic ectomesenchyme only	Odontogenic fibroma
	Odontogenic myxoma
	Cementoblastoma
Malignant odontogenic tumours	
Odontogenic carcinomas	Metastasizing (malignant) ameloblastoma
	Ameloblastic carcinoma • Primary type • Secondary type (dedifferentiated)
	Primary intraosseous carcinoma • Solid type • Arising from keratocystic odontogenic tumour • Arising from other odontogenic cysts
	Clear cell odontogenic carcinoma
	Ghost cell odontogenic carcinoma
Odontogenic sarcomas	Ameloblastic fibrosarcoma
	Ameloblastic fibro-dentino-sarcoma and fibro-odontosarcoma

to primary intraosseous carcinomas with few, if any, odontogenic features. An abbreviated form of the WHO classification,[50] based on behaviour and pathogenesis, is shown in **Table 25.5**. Odontomas account for around one-third. Of the true neoplasms, excluding the keratocystic odontogenic tumour, recently redesignated as an odontogenic tumour, the ameloblastoma is as common as all other types combined. Diagnosis depends on clinical and radiological features as well as the precise histology, hence, accurate information on location, relationship to teeth, circumscription and radiodensity should be submitted to the reporting pathologist.[51] Odontogenic tumours tend to reflect morphological features and inductive interactions of normal tooth germs and histological distinction between some tumours relies on subtle features. The rarity of many lesions, and hybrid forms, add to the diagnostic challenge.

BENIGN ODONTOGENIC TUMOURS

Ameloblastoma

Although the most common odontogenic neoplasm,[52] ameloblastoma only accounts for around 1% of oral biopsies.[53] Based on clinical, radiographic, histological, behavioural and prognostic features, four subtypes[52] can be distinguished (**Table 25.6**). In addition, two malignant forms and a benign variant in which dental hard tissues develop are recognized (**Table 25.6** and see later).

Solid / Multicystic (Conventional) Ameloblastoma

Solid/multicystic (conventional) ameloblastoma (SMA), the most common type of ameloblastoma, displays benign but locally invasive growth with a high recurrence rate if not removed adequately.[52, 54] It is derived from rests of the dental lamina but trigger factors are unknown. The most common site is mandibular molar-ramus and the mandibular: maxillary ratio is around 5:1. All age groups are affected (mean, 37 years) with a M:F ratio of 1.2:1. SMA is centrally located within the jaw and hence, there are few clinical signs in early stages. Later, there may be increasing facial deformity, loosening of teeth, eggshell crackling, bone perforation and spontaneous jaw fracture. Radiographically, multilocular destruction of bone creates a soap-bubble (honeycomb) appearance (**Figure 25.9**). The scalloped margin may incorporate tooth roots typically showing resorption. Some SMA occurs in a dentigerous relationship with an unerupted tooth. At operation, the tumour appears as a greyish-white mass replacing bone. The cut surface is variously solid and cystic. Histologically,[52] the lesion consists of odontogenic epithelium within a fibrous stroma. The odontogenic epithelium shows two

TABLE 25.6 Classification of ameloblastomas and related odontogenic tumours

Benign odontogenic neoplasm	Subtype	Histological variants / key features
Ameloblastoma	Classic solid/multicystic (SMA)	Follicular
		Plexiform
	Unicystic (UA)	Luminal type
		Intraluminal type
		Intramural type
	Peripheral (extra-osseous) ameloblastoma (PA)	
	Desmoplastic ameloblastoma (DA)	
Odontoameloblastoma		Growth features are similar to SMA but contains dysplastic dentine and enamel
Malignant odontogenic neoplasms		
Metastasizing ameloblastoma		A retrospective diagnosis: typical histology but distant metastases occur
Ameloblastic carcinoma		Cellular atypia present

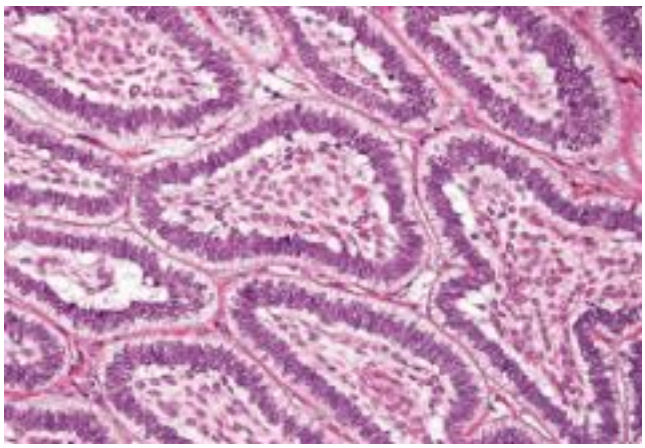


Figure 25.15 Histological image of follicular ameloblastoma. Tumour islands exhibit typical peripheral palisading, reverse polarity and there are central more loosely cohesive stellate reticulum like cells.

main patterns, follicular and plexiform, but many lesions comprise both. Each follicle/strand consists of outer, columnar ameloblast-like cells and inner stellate reticulum-like cells (**Figure 25.15**). Cysts may develop within the stellate cells (especially in the follicular pattern) or within the stroma (especially in the plexiform pattern). The stellate reticulum-like cells are more obvious in the follicular pattern and may display features of the spindle cell, basal cell, granular cell, acanthomatous (squamous), ghost cell or other, less common, histological variants.[52] The tumour infiltrates within the cancellous bone leading to poorly defined margins. The preferred treatment is *en bloc* resection since cancellous infiltration may extend 5mm or more beyond the radiological limits. A conservative approach (enucleation, curettage and burring the bone cavity followed by close review of healing) may be considered for small mandibular lesions. All maxillary lesions should be treated radically since the consequences of recurrence involving the skull base are severe with a mortality of up to 60%.[52, 54]

Unicystic Ameloblastoma

Unicystic ameloblastomas (UAs)[52] account for 5–15% of all ameloblastomas.[55] The term should be reserved for well-defined, monocystic lesions with a lining focally composed of ameloblastomatous epithelium (type I, luminal UA). The inner surface of the cyst lumen may show one or more polypoid, pedunculated masses (type II, intraluminal UA) or intramural nodular growths (type III, intramural UA). Types I and II tend to be in a dentigerous relationship although on removal, the involved tooth is displaced by the cyst rather than projecting into the lumen. Pathogenesis is controversial, theories including an origin from a pre-existing odontogenic cyst, ameloblastic transformation of reduced enamel epithelium, and cystic degeneration and subsequent fusion of microcysts within a SMA. The posterior mandible is the most common site (maxilla: mandible ratio, 1:5). Teens and young adults are mainly affected without an obvious gender distribution. Usual presentation is a painless swelling. Radiographically, UA may be unilocular or multilocular. Root resorption is common. Diagnosis requires assessment of the complete cyst and categorization based on findings in both the epithelial cyst lining and fibrous cyst wall. Types I and II are usually treated conservatively by enucleation and curettage. Type III shows a greater tendency to recur and is generally managed as SMA.

Peripheral (extra-osseous) ameloblastoma (PA)

These comprise 2–10% of all ameloblastomas and are thought to arise from extra-osseous residues of dental lamina (glands of Serres) or the basal layer of the oral mucosa.[52, 56] Around 70% affect the mandible, mainly premolar region. All ages are affected (mean, 52 years) with a M:F ratio of 1.9:1. PA presents as a painless, sessile, firm, 1 cm gingival/alveolar growth. The surface may be smooth, granular or warty. Colour varies from normal to deep red. Masticatory trauma may result in ulceration or frictional keratosis. In most cases, there is

no radiological evidence of bone involvement but large lesions may cause superficial saucerisation. Many PA are removed as suspected fibrous or inflammatory epulides. Histological features resemble SMA. PA are rare and the histological differential diagnosis includes peripheral odontogenic fibroma, squamous odontogenic tumour and odontogenic gingival epithelial hamartoma. PA does not invade bone and recurrence is rare after conservative supraperiosteal surgical excision with adequate (disease-free) margins.

Desmoplastic Ameloblastoma (DA)

This variant[52, 57] of SMA (accounting for 4–13%) exhibits locally infiltrative growth. In contrast to the other ameloblastoma categories, maxillary lesions are as common as mandibular. Lesions present over a wide age range. Males and females are equally affected. Initial usual clinical complaint is a painless swelling, 1–8 cm in size. Radiographically, the borders are ill defined (in contrast to other ameloblastomas) and around 50% are mixed radiolucent/radiopaque potentially leading to a pre-operative diagnosis of fibro-osseous lesion. Resorption of tooth roots is common. The tumour appears as a solid, white infiltrative growth. Histologically,[58] the irregularly shaped islands and cords of odontogenic epithelium are embedded in a densely fibrous stroma often with osseous metaplasia. Focal peripheral pallisading is seen but central areas are hypercellular, whorled spindle or acanthomatous cells rather than stellate reticulum-like. Radical resection is favoured and recurrence rates resemble those for SMA.

Squamous odontogenic tumour (SOT)

This rare benign, locally infiltrative tumour[59, 60] develops from the rests of Malassez within periodontal ligament of vital, erupted teeth and mainly affects the mandible. A wide age range, slight male predominance, and occasional multicentric lesions are reported. Tooth mobility, local pain, gingival swelling/erythema and bony expansion are typical presenting features. Radiographically, a unilocular (or in larger lesions, multilocular) rounded or triangular radiolucency between the roots of adjacent teeth is usual. Histologically, rounded islands of well-differentiated squamoid epithelial cells are embedded in a fibrous stroma. The differential diagnosis includes ameloblastoma, intra-osseous squamous cell carcinoma and 'squamous odontogenic tumour-like islands arising within the walls of odontogenic cysts'. Recurrence is rare after complete, conservative surgical treatment.

Calcifying epithelial odontogenic tumour (CEOT, Pindborg tumour)

CEOT,[61, 62] a locally invasive epithelial neoplasm, accounts for around 3% of odontogenic tumours. The mandibular: maxillary ratio is 2:1. Peak age of presentation is 40 years with most cases presenting between 20 and 60 years. There is no gender predilection. Usual presentation is asymptomatic, slow-growing expansile jaw mass. Radiographically, the unilocular/multilocular, mixed radiolucency-radiopacity may be associated with an unerupted tooth, most often a mandibular third molar. The tumour is solid and histologically consists of islands and sheets of polyhedral cells with conspicuous intercellular bridges embedded within a fibrous stroma. Important diagnostic features include the marked nuclear pleomorphism including giant/monster forms but lack of mitotic figures (unless the tumour has undergone malignant change); and the eosinophilic hyaline material within or around the tumour cells which is positive with stains for amyloid and frequently shows concentric rings of calcification. Differential diagnosis includes intraosseous squamous cell carcinoma, metastatic carcinoma, and, if clear cells are evident, a salivary gland neoplasm. Attention to cellular details such as the lack of mitotic figures and the amyloid globules should prevent a misdiagnosis. CEOT is locally invasive and local resection is needed except for small lesions where enucleation may be sufficient. The overall recurrence rate is around 15% but is higher after enucleation, in larger tumours and in the clear cell variant.

Adenomatoid odontogenic tumour (AOT)

This slowly progressive odontogenic epithelial lesion[63, 64] accounts for around 3% of odontogenic tumours and may be harmatomatous rather than neoplastic. It predominantly affects the maxilla (maxilla:mandible ratio, 2.1:1), females (M:F ratio, 1:1.9), and younger ages (90% < 30yrs). Most cases arise in association with the follicle of an unerupted canine presenting as a painless palpable bony-hard swelling and radiographically as a well-defined unilocular 'dentigerous' radiolucency often with discrete radiopaque foci. Intraosseous periapical and interdental, and peripheral (gingival) variants are less common. Histologically, the tumour is well circumscribed and encapsulated, consisting of variably sized nodules of cuboidal and columnar odontogenic epithelium, some with a characteristic glandular formation, embedded within a sparse fibrous stroma with droplets of eosinophilic amorphous material. Enucleation or curettage is curative. Recurrence is rare.

Keratocystic odontogenic tumour (KCOT), formerly odontogenic keratocyst

Formerly called 'odontogenic keratocyst', the KCOT[65] was renamed at the WHO Consensus Conference, 2003,[50] to reflect its neoplastic nature.[66–68] It is now designated a benign, uni-/multicystic odontogenic tumour with potential aggressive, infiltrative behaviour.[69] It is one of the most common odontogenic tumours, peaking in the 2nd and 3rd decades, with a M:F ratio of 1.6:1. Around 75% occur in the mandible, mainly in the molar-angle-ramus region. Many cases are asymptomatic presenting radiographically as a radiolucency, either small and round-ovoid, or larger with scalloped border (**Figure 25.16**). Large lesions may present with pain, swelling, discharge, pathological fracture and if cortical bone is penetrated, soft tissue involvement.



Figure 25.16 OPG of patient with Gorlin Golltz syndrome demonstrating three distinct radiolucencies: LLQ, LRQ and ULQ.

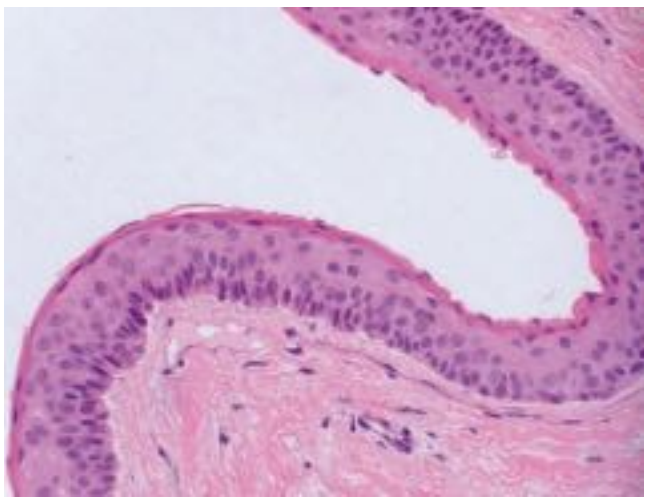


Figure 25.17 Parakeratinized epithelium characteristic of keratocystic odontogenic tumour.

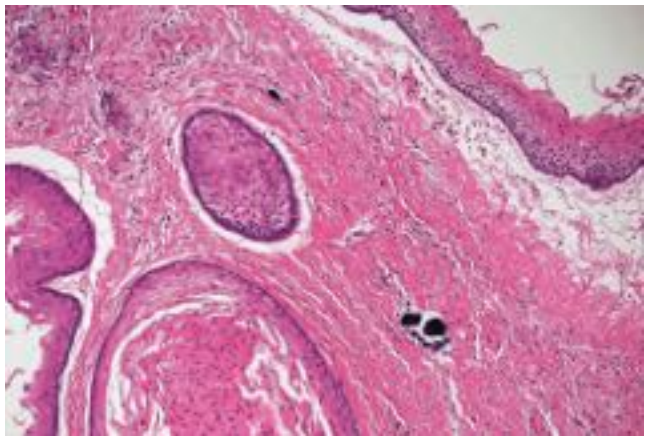


Figure 25.18 Daughter or satellite cysts in keratocystic odontogenic tumour from syndromic patient.

TABLE 25.7 The most common features of naevoid basal cell carcinoma syndrome

Features of naevoid basal cell carcinoma syndrome
Multiple keratocystic odontogenic tumours – either simultaneous or sequential
Basal cell carcinomata - multiple, often in non-sun-exposed skin sites
Frontal and temporoparietal bossing, hypertelorism, mandibular prognathism
Calcification of the falx cerebri
Bifid or deformed ribs
Medulloblastoma, abdominal neoplasms

Adjacent teeth may be displaced but root resorption is rare. The cyst lumen is full of creamy material – keratin squames – and the cyst wall is thin and lined by a thin, parakeratinized epithelium (**Figure 25.17**).

Odontogenic epithelial residues are frequent in the cyst wall and may give rise to satellite cysts (**Figure 25.18**). Budding of the cyst lining is less common but can give rise to daughter cysts. Mitotic figures may be present within suprabasal layers of the epithelial lining and other dysplastic features are occasionally seen and may herald malignant transformation.

Multiple KCOT (either simultaneous or sequential) are an important part of the inherited naevoid basal cell carcinoma syndrome (NBCCS, Gorlin Syndrome, Gorlin and Goltz Syndrome).[1, 70] **Table 25.7** shows the more common clinical features of the syndrome, and notable differences between non-syndrome sporadic and syndrome KCOT are shown in **Table 25.8**.

TABLE 25.8 A summary of clinical and histological features of keratocystic odontogenic tumours in non-syndrome and naevoid basal cell carcinoma syndrome patients

Non-syndrome KCOT	NBCCS KCOT
Single	Multiple – either simultaneous or sequential
Maxilla:mandible ratio, 1:3	Maxilla:mandible ratio, 1:1
Peak age, 20–40 years	Peak age, 15–30 years
Radiographically, generally small round-ovoid and unilocular	Radiographically, frequently large and multilocular
Few proliferating odontogenic epithelial residues and satellite cysts	Proliferating epithelial residues (some 'ameloblastomatous') and frequent satellite cysts
Rarely budding of main cyst lining or presence of daughter cysts	Occasional budding of main cyst lining and presence of daughter cysts
Recurrence rare after complete removal	Recurrence and further new cysts expected

The source of odontogenic epithelium giving rise to the KCOT is uncertain. The dental lamina and its remnants are favoured but there is some evidence for extensions of basal cells from overlying oral epithelium – the original source of the dental lamina in the embryo/infant.[1, 76] The genetic basis of KCOT[1] lies in the NBBCCS or PCTH gene, a tumour suppressor gene on chromosome 9q22.3-q31 which may suffer allelic loss leading to over-expression of bcl-1 and TP53. Over-expression and amplification of genes located in 12p may also be involved.

KCOT has a tendency to recur and the rate depends on the original treatment (overall recurrence rate, 20–25%). Local resection and enucleation with peripheral ostectomy and Carnoy's solution are curative while enucleation with peripheral ostectomy, enucleation alone, marsupialization and enucleation with Carnoy's solution are associated with increasing risk of recurrence (18%, 26%, 40% and 50% respectively in a recent systematic review).[71]

Ameloblastic fibroma, ameloblastic fibro-dentinoma, ameloblastic fibro-odontoma (AF, AFD, AFO)

AF is a rare, benign neoplasm of both odontogenic epithelium and ectomesenchyme.[72, 73] The presence of dentine or other dental tissues leads to the designation ameloblastic fibro-dentinoma[73] (AFD) and ameloblastic fibro-odontoma (AFO),[73, 74] respectively.

Most AF are found in the posterior mandible, presenting as painless swelling or on investigation of disturbed tooth eruption. The peak age is 15 years and there is no sex predilection. Radiographically, a well-demarcated, uni- or multilocular radiolucency with a sclerotic rim is typical. Histologically, strands and islands of odontogenic epithelium forming knots with peripheral palisading (each knot resembles a normal developing tooth germ) are embedded in a cell-rich ectomesenchyme resembling dental papilla. Differential diagnosis includes ameloblastoma (in which the stroma is mature and fibrous rather than immature, cell rich and myxoid); enlarged/hyperplastic dental follicle (scanty epithelium; typical location overlying unerupted tooth); and when hard tissues are evident, the AFD and AFO. Enucleation and curettage is generally curative. Recurrence may follow incomplete removal and rarely, progression to malignancy (ameloblastic fibrosarcoma) is reported.[72]

Odontomes

Odontomes[75–77] are dental hamartomas rather than neoplasms, and range from malformed teeth at one end of the spectrum through to masses of haphazardly arranged enamel, dentine and cementum (composite odontomes). A malformed tooth may replace one of the normal series in either the deciduous or permanent dentition and well-recognized forms include the dens-in-dente (dilated gestant), geminated, and taurodont. The diagnosis of a mature malformed tooth is obvious on radiography but immature forms are radiolucent with variable focal radiopacities (increasing as maturity is reached). Treatment depends on symptoms, location and dental factors and most cases require surgical removal.

The **compound odontome**[75, 76, 78] consists of a varying number of miniature teeth (denticles/odontoids) within a fibrous sac. The anterior maxilla is the usual site but they are found in any tooth-bearing area of both jaws. They are diagnosed mainly in children and adolescents, show no sex predilection, and are one of the most common odontogenic hamartomas/tumours. Once fully mature, growth ceases (generally at 1–2 cm in diameter) and jaw swelling is unusual. Most cases are diagnosed when they impede eruption of a nearby tooth or cause displacement of an erupted tooth. Multiple compound odontomes may be sporadic or part of Gardner syndrome.[34, 79] Radiologically, the denticles and surrounding fibrous sac (radiolucent peripheral zone) are usually obvious. Macroscopic assessment of the specimen may be sufficient to make a definitive diagnosis. Demineralized sections show the denticles, and depending on maturity, immature enamel, dentinoid, cementoid and variable amounts of odontogenic epithelium, dental papilla and reduced enamel epithelium. Enucleation is curative and recurrence does not occur.

The **complex odontome**[80] is also common in children and adolescents of both sexes. The most frequently affected tooth bearing site is posterior mandible. They tend to grow to 3–6 cm in diameter and generally present as slowly increasing, painless swelling, often associated with impairment of eruption or displacement of adjacent teeth. The typical radiographic appearance of a maturing lesion is a spherical/ovoid radiopacity with a radiating periphery and surrounding radiolucent zone. Local enucleation is generally curative but recurrence may follow incomplete removal of an immature lesion. Histological assessment of mature complex odontomes shows variable amounts of enamel, dentine and cement, haphazardly arranged and surrounded and supported by a collagenous capsule containing strands and islands of odontogenic epithelium. Developing lesions show more unmineralized dental tissues and cellular areas of soft tissue. The distinction from the compound odontome is not clear cut.[81] Immature forms may contain AF-like areas leading to uncertainty about the true nature of the AF and its variants which some workers consider represent immature odontomes.[72, 73]

Odontoameloblastoma

This extremely rare tumour[82] is similar to an SMA but contains hard dental tissues. Most lesions present in the posterior mandible, in teens and young adults. The M:F ratio is 2:1. Radiographically, a well-defined uni-/multilocular radiolucency containing variable amounts of radiopaque material (either denticles or a central, solid mass) is seen. Growth characteristics, management and prognosis are similar to SMA.

Calcifying cystic odontogenic tumour (CCOT, keratinizing and calcifying odontogenic cyst, calcifying odontogenic cyst, Gorlin cyst)

This is a rare cystic benign neoplasm,[81, 83] occurring mainly in the anterior region of either jaw, over a wide age range and without sex predilection. Most cases are asymptomatic and present radiographically as a well-circumscribed unilocular radiolucency containing variably-sized calcified bodies. Adjacent erupted teeth frequently show root resorption or divergence and unerupted teeth may be displaced. Histologically, the cyst shows similarities with UA but the stellate-reticulum-like cells are transformed to eosinophilic ghost cells. Ghost cells frequently calcify and dentinoid-like material may be deposited within the fibrous cyst wall. Enucleation is usually curative and recurrence is rare.

Dentinogenic ghost cell tumour (calcifying ghost cell odontogenic tumour, odontogenic ghost cell tumour) (DGCT)

This tumour[81, 84] used to be considered a solid variant of the calcifying odontogenic cyst but is now classified as a locally invasive neoplasm with features resembling ameloblastoma but characterized by keratinization, ghost cells and dentinoid.[50] The tumour occurs in any tooth-bearing area of either jaw (but mainly premolar), affecting a wide age range with males more frequently affected than females. Small lesions are generally asymptomatic but larger lesions cause bony expansion or perforation, and tooth displacement and mobility. Radiographically, the lesion is generally well demarcated, radiolucent or mixed radiolucent/radiopaque. Histologically, an infiltrative margin is seen and the presence of ghost cells and dentinoid are critical in distinguishing the lesion from an ameloblastoma. Distinction from a CCOT can be difficult. The presence of mitoses is suspicious of transformation to odontogenic ghost cell carcinoma. The infiltrative nature of DGCT dictates wide local excision as the treatment of choice.

Odontogenic fibroma

Controversy exists over the concept and definition of this rare tumour.[85, 86] Currently, odontogenic fibroma (OF) is applied to two histological types:[50] epithelium-poor (formerly known as simple type) and possibly derived from dental follicle, and epithelium-rich (formerly known as complex or WHO type) and possibly derived from periodontal ligament. The intraosseous lesion, most common in the premolar region of the mandible, is mainly epithelial-rich and affects adults with a M:F ratio of 1:3. The usual presentation is a slow-growing, painless jaw swelling with cortical expansion. Radiographically, most cases present as a unilocular radiolucency with a well-defined sclerotic border. Larger lesions may have a scalloped margin and sometimes, spotted radiopacities are evident. Histologically, the epithelial-rich type is composed of cellular, fibroblastic connective tissue containing islands and strands of inactive-looking odontogenic epithelium and foci of calcified material (metaplastic cementum/osteoid/dentine). Differential diagnosis includes hyperplastic/enlarged dental follicle and fibromyxoma. OF is well circumscribed and simple enucleation is curative.

Odontogenic myxoma (OM), odontogenic fibromyxoma (OFM)

This benign, locally infiltrative tumour[87, 88] accounts for 3% of odontogenic neoplasms. Pathogenesis is uncertain and the name was originally based on location, resemblance to dental papilla/follicle, and sporadic presence of odontogenic epithelium. Ultrastructural and immunohistochemical studies have not confirmed an origin from ectomesenchyme of the developing tooth and suggest a non-odontogenic origin from myofibroblasts and/or histiocytes. The tumour is more common in females, typically 15–35 years, and two-thirds occur in the mandible (mainly posterior). Typical presentation is a slowly increasing, painless swelling or asymmetry of the affected jaw but growth may be rapid and associated with tooth mobility, root resorption, and in maxillary lesions, nasal obstruction and exophthalmus. Radiographically, a multilocular, soap-bubble (honeycomb) appearance is seen (as in ameloblastoma, KCOT and haemangioma). Macroscopically, the cut surface is white, mucoid and sticky. Histologically, tumour infiltrates bone marrow spaces and consists of cytologically bland rounded, spindle-shaped or angular cells evenly spaced within abundant mucinous matrix. The matrix is finely fibrillar and may contain scattered small islands of odontogenic epithelium, sometimes with a hyaline cuff. More collagenous examples are designated fibromyxoma. The differential diagnosis includes enlarged (hyperplastic) dental follicle, and myxomatous degeneration in fast growing neoplasms such as chondrosarcoma and liposarcoma. Recurrence ranges from 10% to 33% and is more common after conservative surgery. Currettage with frozen-section assessment of margins is generally adequate for smaller lesions but radical resection may be necessary for large, diffuse lesions. Metastases do not occur.

Benign cementoblastoma

This is a benign neoplasm[89, 90] arises from cementoblasts and is fused to a tooth root. The mandibular first molar in young adults (peak, 20 years of age) is most frequently affected. There is no sex predilection. Most present with painful swelling of the buccal and lingual alveolar ridge over a vital tooth. Radiographically, a well-defined, rounded, radiopaque or mixed-density lesion, replacing the apical third of the root, is surrounded by a narrow radiolucent zone (**Figure 25.19**). Histologically, dense



Figure 25.19 Periapical radiograph of benign cementoblastoma, typical relationship to root of molar tooth, radiodense with lucent rim.

masses of acellular cementum (similar to Pagetoid bone) are supported by a fibrovascular stroma often with scattered multinucleated cells. A zone of unmineralized cementoid is seen peripherally. The dental origin is key to distinguishing it from an osteoblastoma and osteosarcoma. Extraction of the associated tooth and complete enucleation are recommended. Recurrence is common after incomplete removal.

MALIGNANT ODONTOGENIC TUMOURS

These are rare.[50] Some appear to be the malignant counterparts of benign odontogenic tumours. Others arise by malignant transformation of epithelial residues or the lining of odontogenic cysts. Aetiology is unknown. Odontogenic carcinomas[91] are more frequent in the elderly while odontogenic sarcomas affect younger age groups. Clinical features include swelling, pain, bleeding, mucosal ulceration, tooth mobility, paraesthesia, and pathological fracture. Radiographically, extensive jaw destruction with ill-defined borders, sometimes with patchy radiopacities, is typical. In carcinomas, metastasis to local lymph nodes and distant sites may occur early and prognosis is generally poor even after resection with tumour-free margins.

Metastasizing (malignant) ameloblastoma

This is a diagnosis made retrospectively when a histologically typical ameloblastoma gives rise to metastases (mainly lung).[92]

Ameloblastic carcinoma (primary type)

This rare tumour, an ameloblastoma with atypia,[92] presents mainly in the posterior mandible and shows no obvious sex predilection. Differential diagnosis includes ameloblastomas with occasional mitotic figures (and no other cellular/architectural atypia), other odontogenic carcinomas and metastatic carcinoma. Pulmonary metastases are present at initial diagnosis in around one-third of maxillary lesions but mainly follow local recurrence in mandibular lesions.

Ameloblastic carcinoma, secondary type (de-differentiated)

This very rare lesion arises within a pre-existing, and often long standing/recurrent, benign ameloblastoma.[92] Cellular atypia and nerve invasion are characteristic changes. Size and proximity to skull base and other vital structures dictate the adequacy of surgical resection and survival.

Primary intra-osseous squamous cell carcinoma (primary intra-osseous epidermoid carcinoma)

This is a central jaw carcinoma derived from odontogenic epithelial residues.[93] Once the tumour destroys the cortex, it may merge with the surface mucosa and be difficult to distinguish from squamous cell carcinoma (SCC) of mucosal (and antral) origin.

Primary intra-osseous squamous cell carcinoma (PIOSCC), **solid type,**[94] invades marrow spaces and induces osseous resorption. The aetiology is unknown. It is derived from odontogenic epithelial residues such as the periradicular rests of Malassez within the periodontal ligament and the reduced enamel epithelium surrounding impacted unerupted teeth. Dedifferentiation from a benign ameloblastoma is a further (rare) possibility. Most arise in later adult life with a M:F ratio of 2:1). Most are located in the body and posterior mandible. Maxillary cases tend to involve the anterior region. The lesion is often discovered as an incidental irregular, non-corticated radiolucency following routine jaw radiography. Large lesions may cause facial swelling and paraesthesia. Histologically, PIOSCC, solid type, is generally moderately differentiated and without specific features. Metastatic SCC must be excluded by clinical and radiological examination. Surgical resection is frequently followed by local recurrence, regional and distant metastases and prognosis is poor.

The other rare subtypes of **PIOSCC**, derived from **KCOT**,[94, 95] and **PIOSS**, derived from **odontogenic cysts**,[94] show SCC in association with a KCOT or odontogenic cyst and generally affect older adults, with a M:F ratio of 2:1. The mandible is much more affected than the maxilla. The SCC may be discovered on histological assessment of a suspected benign tumour/cyst or may present with pain, swelling, loose teeth, non-healing tooth socket, paraesthesia and regional lymphadenopathy. Radiographic appearances range from a typical cyst to an ill-defined radiolucency to gross cortical destruction and soft-tissue extension. Histologically, well differentiated SCC is seen merging with KCOT or the lining of the odontogenic cyst which may show dysplasia or features of verrucous hyperplasia/carcinoma. Differential diagnosis[93] can include keratoameloblastoma, SOT, central mucoepidermoid carcinoma and metastatic tumour. Based on small numbers,

the prognosis is thought to be more favourable than PIOSCC, solid type.

Clear cell odontogenic carcinoma

The rare clear cell odontogenic carcinoma (CCOC)[95–97] predominantly affects the mandible of older females, presenting as jaw swelling with loosening of teeth and radiographically, as an ill-defined radiolucency with root resorption. Histologically, a biphasic pattern of sheets of clear cells and irregular cords of basaloid cells supported by fibrous septae is typical. Many of the tumour cells contain diastase-degradable PAS-positive granules. Differential diagnosis includes salivary gland neoplasms, clear cell variant of CEOT, metastatic renal cell carcinoma and malignant melanoma. Surgical resection may be followed by local recurrence, regional and distant (lungs, bone) metastases and prognosis is poor for large lesions. Post-operative radiotherapy should be considered especially if there is cortical erosion/perforation.

Ghost cell odontogenic carcinoma

This rare neoplasm[81, 98] shows features of CCOT and/or GCOT and mainly affects the maxilla in adult males. Clinical symptoms include swelling and paraesthesia. Radiographically, a poorly demarcated radiolucency with patchy radiopacity and root displacement or resorption is typical. Histologically, the malignant component consists of rounded, mitotically active, epithelial islands in a fibrous stroma and lies adjacent to, or admixed with, typical benign GCOT. Prognosis is unpredictable. Some recur locally and metastasize.

Ameloblastic fibrosarcoma, fibro-dentinosarcoma and fibro-odontosarcoma

Ameloblastic fibrosarcoma (AFS) is the initial diagnosis in around two-thirds of cases while the remainder develop within a pre-existing AF.[99] AFS[100] has a mean age of 28 years (compared to 15 years for AF) and M:F ratio of 1.6:1. Posterior mandible is the most common site. Histologically, benign epithelial nests and cords are present in a highly cellular, cytologically malignant ectomesenchyme. Scattered areas of dentine and enamel, dentine and cementum are present in the ameloblastic fibro-dentinosarcoma (AFDS) and fibro-odontosarcoma (AOFS),[100] respectively. Surgical resection is treatment of choice and the tumours are generally low grade, and with few metastases and a better survival than other jaw sarcomata.

INTRA-OSSEOUS SALIVARY GLAND TUMOURS

Salivary-type carcinomas may occur in the jaws as primary central tumours,[101] but this is very rare compared to the more common jaw involvement by direct spread from an extra-osseous site (mainly, parotid or retromolar). Mandible is affected more often than maxilla and mucoepidermoid and adenoid cystic carcinoma are the most common histological types. Intra-osseous salivary tissue may result from entrapment during embryonic development, surgical manipulation, or metaplastic odontogenic epithelium.[100] Central intra-osseus salivary adenocarcinoma with non-specific/not otherwise specified histology, is very rare and imaging and monitoring clinical progress are important adjuncts to immunohistochemistry in reaching the correct diagnosis. Intra-osseous salivary gland tumours (IOSGT) are usually managed by radical surgical excision, often supplemented by radiotherapy.

MISCELLANEOUS NEOPLASMS

Ewing sarcoma

This is rare in the jaws, mainly affecting the mandibular body in children and young adults.[102] Progressive bone swelling, followed by pain, loosening of teeth and mucosal ulceration is usual. Systemic symptoms of fever, leucocytosis, raised ESR and anaemia indicate a poor prognosis. Histologically, the neuroectodermal Ewing sarcoma cells resemble enlarged lymphocytes and form sheets separated by fibrous septae. Wide excision, followed by radiotherapy and combination chemotherapy, is the usual treatment but may be unsuccessful due to distant spread to the lungs, other bones and lymph nodes.

Haemangioma of bone

Haemangioma of the jaws is uncommon.[34, 79, 103] Solitary lesions mainly affect the mandible, and females, but involvement of the maxilla is an important part of Sturge–Weber syndrome (together with facial port-wine stain and epilepsy). Progressive, painless swelling is the usual presentation. Pulsation indicating resorption of the overlying bone, and loosening teeth with gingival bleeding may be seen with larger lesions. Radiographically, the honeycomb locularity can be difficult to distinguish from ameloblastoma, KCOT and OM. Fresh blood on attempted aspiration is an important diagnostic clue. Histologically, most intra-osseous haemangiomas are of cavernous type. Wide surgical resection may be the only practical treatment but selective arterial embolization may be useful if there are well-defined feeder vessels.

Melanotic neuroectodermal tumour of infancy (Progonoma)

This is a rare tumour of neural crest origin that involves the anterior maxilla either congenitally or in the first few months after birth.[76, 79, 104] It presents as a painless, bluish swelling which occasionally grows rapidly. Radiographically, there is ragged bone destruction and displacement of developing teeth. Histology shows the characteristic clusters and strands of melanin-pigmented and non-pigmented epithelial cells supported by a fibrous stroma. The tumour is benign but non-encapsulated.

Curettage or conservative surgery is curative and recurrence is rare.

Multiple myeloma (myelomatosis), solitary plasmacytoma

Multiple myeloma, a monoclonal immunoglobulin-producing neoplasm of plasma cells, may present with multiple 'punched-out' radiolucencies (typically of the skull vault and areas of red-marrow) on routine radiography or with bone pain/tenderness or signs of bone marrow replacement (anaemia, infections and thrombocytopenia).[34, 79, 105] Peak incidence is 50–70 years of age. Histologically, sheets of neoplastic plasma cells may be well or poorly differentiated with bi- and multi-nucleated forms. Immunohistochemistry for kappa and lambda chains and Ig class shows the monoclonal nature and monoclonal 'M' band seen on serum electrophoresis is confirmatory. Healing may follow combination chemotherapy but relapse is common and 5-year survival is only 20%. The solitary plasmacytoma[106] is managed by radiotherapy and has a good 5-year prognosis but the majority of patients succumb to multifocal disease after 10 or more years.

Langerhans cell histiocytosis (histiocytosis X), eosinophilic granuloma

Langerhans cells, the antigen-presenting histiocytes of epithelia, occasionally give rise to bone tumours. Langerhans cell histiocytosis (histiocytosis X) (LCH) of bone may present as a single 'eosinophilic granuloma'; or multifocally within bone and other organs, or with generalized disseminated multiorgan disease.[34, 79, 107] Multifocal involvement of the craniofacial bones, orbit and posterior pituitary presents with skull defects, exophthalmus and diabetes insipidus (Hand-Schuller-Christian syndrome). The most severe form, disseminated Letterer–Siwe disease, occurs mainly in infants and has a high mortality. Unifocal and multifocal eosinophilic granuloma typically occur in older children/young adults with a 2:1 M:F ratio. The cranium and jaws, in particular the mandible, are common sites. Radiographically, the lesions are osteolytic, rounded and indistinct. Multiple jaw lesions result in the classic 'teeth floating in air' appearance. Loosening and exfoliation of teeth is a common presentation. Involvement of the temporal bone can present as otitis media mastoiditis. Histologically, collections of histiocytes admixed with eosinophils are seen. Immunohistochemical demonstration of the Langerhans cells surface antigen, CD1a, and S-100 protein is diagnostic and has largely replaced the electron microscopical detection of Birbeck granules. Generally, eosinophilic granuloma heals after curettage and some regress spontaneously. More disseminated disease is unpredictable. Genetic studies have shown LCH represents a clonal proliferation and the neoplasm may progress despite irradiation and/or chemotherapy.[107]

METASTATIC TUMOURS

Metastatic carcinoma to the jaws may be from a known or as yet undiagnosed primary carcinoma.[48, 106, 142] Elderly men and women are mainly affected and haemopoietic marrow within the posterior mandible is the most commonly involved site. It is not known whether healing extraction sockets and/or subclinical chronic inflammation which result in foci of increased vascularity encourage deposition of metastatic tumour at other sites within the jaws. Clinical presentation varies from asymptomatic to mobile/drifting teeth, pain, swelling and pathological fracture. Radiography typically reveals an ill-defined or mottled radiolucency. For men, the most common origins of the primary carcinoma are lung, prostate and adrenal glands; and for women, breast, adrenal glands, colon and rectum, genital tract and thyroid.

Details of the immunohistological profiles for the cytokeratins and transcription factors that are useful in the histological diagnosis of the source of the metastatic carcinoma, and the limitations, are discussed by Woolgar et al[102] A logical approach to identify an undifferentiated/poorly differentiated neoplasm begins with a basic screening panel including markers for epithelial, mesenchymal and haemopoietic lineages, and malignant melanoma. This is then followed by staining for cytokeratin profiles and specific antigens or transcription factors (useful in poorly differentiated neoplasms) and in suspected adenocarcinomas, mucosubstance histochemistry. Limited confirmatory staining only is necessary if the existence of a primary tumour is already known and declared on the pathology request form. Management is palliative and depends on factors related to the primary tumour, number and site of metastatic deposits and general patient factors. Even when the prognosis and life expectancy are poor, localized radiotherapy can help control symptoms such as jaw pain particularly when referred to the ear.

KEY POINTS

- The bones of the facial skeleton, by virtue of their association with dentition, can be the origin of a unique group of bone cysts and tumours.
- Owing to the complex embryologic origin, significant epithelial remnants can be trapped within the jaw bones, leading to the high prevalence of cysts in the human body.
- Additionally, other osseous benign and malignant pathology seen elsewhere in the body, can also arise in the jaw bones.
- While clinical presentation and radiologic findings may indicate the nature of the pathology, histologic examination is almost always required to make the diagnosis owing to the wide array of pathologic processes.
- Specialist pathologic expertise is needed as some of the entities are rare and the classification of these lesions is constantly evolving.
- Malignant and systemic diseases affecting the jaw bones will need the input of a multidisciplinary team.

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CHAPTER 26

HEAD AND NECK PATHOLOGY

Ram Moorthy, Adrian T. Warfield and Max Robinson

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: head and neck, biopsy, pathology, cytology, histopathology, histochemistry, immunohistochemistry, *in situ* hybridization, tumour, neoplasia, salivary gland tumour, squamous cell carcinoma, nasopharyngeal carcinoma, lymphoma and neuroectodermal tumour.

INTRODUCTION

The head and neck comprises a complex anatomical region composed of diverse tissues. Consequently many of the diseases that occur are challenging to diagnose and require careful clinico-pathological correlation. Some of the diseases are unique to the site and specialist knowledge is required to derive a differential diagnosis and pursue the appropriate investigations leading to a definitive diagnosis and effective management. Furthermore, some of the diseases are rare and require evaluation by specialist pathologists with the requisite experience to render an accurate diagnosis.

For neoplastic disease, the pathologist has a significant role in assessing whether the tumour has been completely eradicated. For malignant disease, parameters such as tumour grade and stage are important prognostic indicators and determine adjuvant treatment. Furthermore, the evolution of molecular pathology in recent years has led to the emergence of tests that can be used to tailor treatment for individual patients. Biological treatments, such as trastuzumab for breast cancer, require 'companion diagnostic tests' to select the right patients. This strategy ensures that patients have access to the most effective treatment and the best chance of cure. Whilst targeted treatments for head and neck disease remain elusive, this is likely to change over the next decade.

PATHOLOGICAL EVALUATION

There are a number of techniques available to obtain a biopsy specimen for pathological evaluation. The choice of technique mainly depends on the size and location of the lesion (**Table 26.1**).

Fine-needle aspiration biopsy

Fine-needle aspiration biopsy (FNAB) is the first-line investigation for patients presenting with cervical lymphadenopathy or with a lesion in the major salivary glands or thyroid gland.[1] FNAB is highly accurate, especially when the evaluation is restricted to determining non-neoplastic vs. neoplastic and benign vs. malignant.[2] Furthermore, the procedure is acceptable to patients and there is minimal morbidity. The technique is simple to perform and relatively inexpensive. FNAB can be performed 'free-hand' by palpation; however, the use of ultrasound guidance increases the yield of relevant material. It may be possible to get support from a cytologist to determine the adequacy of the specimen in the clinic. Some units provide a 'one-stop' head and neck lump clinic with immediate cytological diagnosis.[3] It is important to emphasize that a negative result on FNAB does not exclude disease and that 'triple assessment' (clinical, imaging and cytolopathology) is essential to arrive at the correct diagnosis.

Fixed smears should be immersed in fixative, usually alcohol-based, without delay and are typically stained with the Papanicolau (Pap) method or sometimes haematoxylin and eosin (H&E). Air-dried smears are best subjected to assisted air flow and are usually stained with a Romanowsky-type stain, commonly May-Grünwald-Giemsa (MGG) or Diff-Quik variants (**Figure 26.1**). Needles and syringe

TABLE 26.1 The advantages and disadvantages of commonly used tissue sampling techniques

Type of sample	Advantages	Disadvantages
Fine-needle aspiration biopsy (FNAB)	• Simple technique • Inexpensive • Can be undertaken in clinic • Relatively risk free • Does not usually compromise future management • Highly accurate, especially when the evaluation is restricted to determining non-neoplastic vs. neoplastic and benign vs. malignant	• Primary cytological diagnosis by FNAB must be confirmed by histology prior to radical treatment for head and neck cancer • Diagnostic yield is both lesion-sensitive and operator-dependent and there can be a high non-diagnostic rate, but this may be improved with the use of ultrasound guidance • Requires an expert cytopathologist • Clinicians must be aware of inherent limitations including a risk of false positives and false negatives • FNAB is of limited help in the diagnosis of lymphoma. Flow cytometry may be helpful in excluding a diagnosis of lymphoma
Core biopsy	• Simple technique • Inexpensive • Can be undertaken in clinic • The diagnostic yield is higher than for FNAB and the sample undergoes histopathological analysis, and therefore specific cytopathological expertise is not required • The complications of the procedure are relatively minor, the most common being haematoma formation • By contrast to FNAB, a core biopsy sample permits a greater chance of sub-classification of a lymphoma and may obviate the need for an open biopsy	• Appropriate precautions are required for patients taking anticoagulation therapy to prevent bleeding and haematoma formation • There is a theoretical risk of tumour seeding associated with the larger needles used in obtaining a core biopsy, but published case series have rarely encountered this complication
Incision biopsy	• Can provide definitive histological diagnosis	• Can affect definitive management of the tumour • Can require admission as a day case • May require a general anaesthetic • Higher complication rate than FNAB or core biopsy • Costlier than FNAB or core biopsy
Excision biopsy	• Can provide definitive histological diagnosis • Can be definitive treatment of the tumour	• Higher risk of complication compared to other biopsy techniques • Can require admission • May require a general anaesthetic • Costliest method of obtaining a biopsy

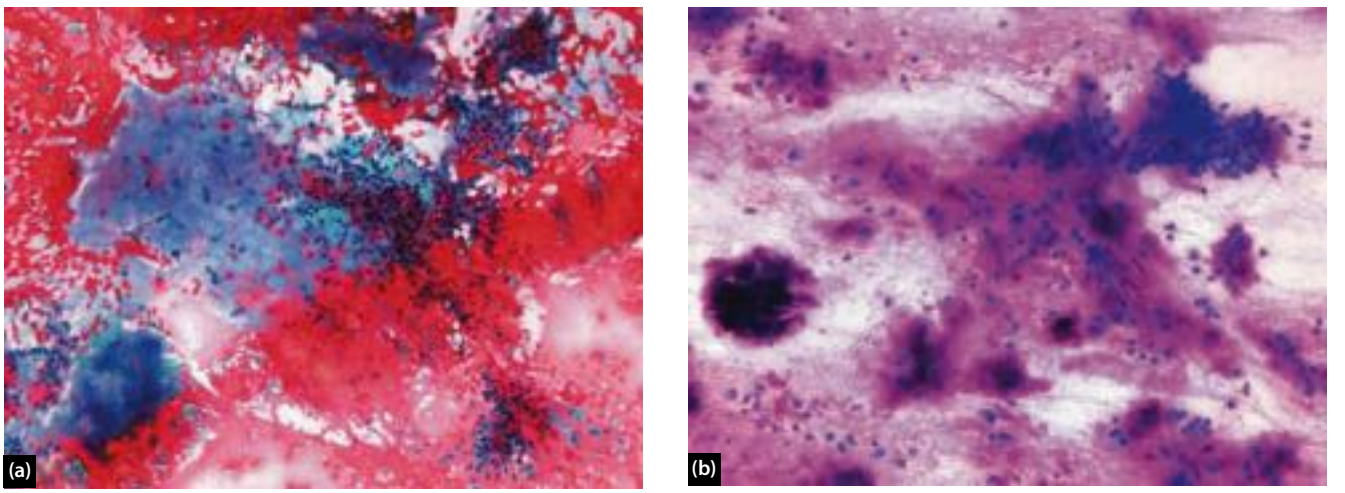


Figure 26.1 Fine-needle aspiration biopsy (FNAB) preparations from a pleomorphic salivary adenoma. (a) This alcohol-fixed slide shows weakly stained, feathery stroma admixed with loosely cohesive, isomorphic epithelioid and spindle cells (Pap stain, medium magnification). **(b)** This air-dried slide from the same tumour at the same magnification highlights the intensely stained myxoid ground substance, which obscures cytological detail in areas (May-Grünwald-Giemsa (MGG) stain, medium magnification).



Figure 26.2 Resection specimen orientation utilizing a corkboard. **(a)** Radical neck dissection specimen pinned to cork block, inverted and immersed to float in formalin. **(b)** The fixed specimen as received in the laboratory, ready for trimming and block selection. This was accompanied by separate annotation by the surgeon. Alternatively, the surgeon may prefer to separate the levels in theatre and place them individually in labelled pots.

hubs may be rinsed in transport medium or proprietary liquid-based cytology fluid (e.g. SurePath, BD or, ThinPrep, Hologic) in an attempt to maximize the cell yield. The resultant 'needle washings' may be handled in the laboratory, by a variety of cell concentration techniques, such as filtration or centrifugation dependent upon local preferences and the reliance upon liquid-based cytology. Any clot material is best processed using conventional histology, because free-floating cells tend to be sequestered in such clots and valuable material may otherwise be discarded.

Core biopsy

A core biopsy is performed using a specific large calibre needle (e.g. Tru-Cut, BD) and will yield a cylinder of tissue that can undergo histological analysis. The clinical utility of a core biopsy is limited by the requirement for local anaesthesia, patient discomfort and the risk of damage to local structures.[4] The use of ultrasound guidance reduces the risk of inadvertent damage to a large calibre blood vessel.[5] The amount of tissue harvested and the preserved tissue architecture increases the diagnostic utility and there is also the possibility of yielding sufficient material for immunohistochemical analysis. It is particularly useful for metastatic disease, where the primary tumour location is unknown. In these circumstances, immunohistochemical tests can be used to indicate the most likely anatomic site of the primary tumour.

Incision biopsy

Incision biopsy involves taking a representative sample or wedge of a lesion for histological analysis. This is a suitable technique for obtaining a diagnosis in accessible tumours affecting the oral cavity, pharynx, larynx or hypopharynx. However, in lesions affecting the major salivary glands or in cervical lymphadenopathy, incision biopsy may compromise further treatment so is used as a last resort.

A sufficient sample of tissue must be obtained to allow histopathological analysis. Thermal artefact and mechanical disruption, either crushing or stretching, during handling or processing of the specimen can make analysis difficult and occasionally impossible. Certain tissues (e.g. lymphoid tissue) and tumours (e.g. neuroendocrine carcinoma) are more susceptible to this than others. It must be noted that a thick biopsy does not necessarily equate to a deep biopsy; it is often the interface between the lesion and the underlying connective tissue that is critical when seeking evidence of invasion and a thick sample from an exophytic epithelial proliferation may still be too superficial to adequately assess this feature.

Excision biopsy

Excision biopsy involves complete removal of the lesion and provides a definitive histological diagnosis. This can range from the removal of a small vocal cord polyp to a major *en bloc* resection. Where appropriate, the specimen should be orientated by the surgeon using sutures or marker clips in appropriate positions. Annotated diagrams or digital photographs aid communication. Specimens can be pinned or clipped on to a cork board or a foam sheet (**Figure 26.2**). Dehydrated cucumber slices are a suitable medium for laryngeal biopsies, which are held in place with tissue adhesive (**Figure 26.3**).[6] Resection planes or other structures of particular clinical concern ought to be brought to the pathologist's attention, especially if these may not be immediately obvious following inevitable distortion induced by fixation. It should always be borne in mind that there will be a reduction in measured specimen margins when a fixed, processed, stained and mounted tissue section is compared to the intra-operative state due to shrinkage inherent in tissue preparation for microscopic examination.

Sentinel lymph node biopsy

This technique is recommended for patients with clinically T1/T2 N0 oral cavity squamous cell carcinoma.[7]

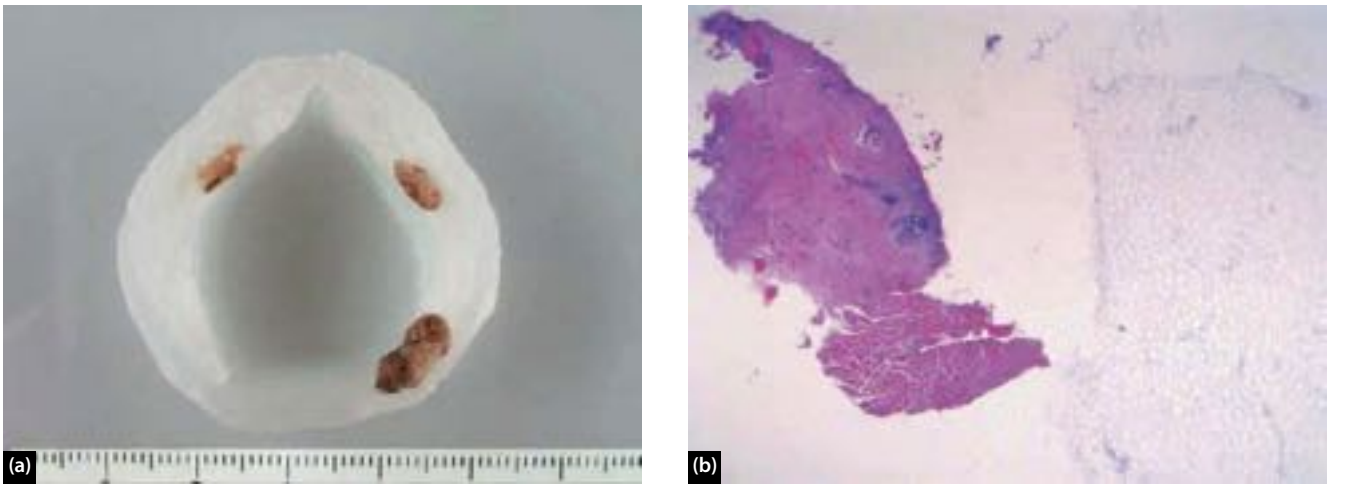


Figure 26.3 Biopsy orientation using a biomount. (a) Three laryngoscopic biopsies glued to a dehydrated cucumber biomount in order to maintain correct orientation in the laboratory. An accompanying endoscopic digital photograph further assists handling of such small biopsies. These may be further inked and/or sliced prior to processing. **(b)** A correctly embedded, though heavily thermalized, laryngeal biopsy on the left with anucleate cucumber biomount to the right (H&E stain, ultralow magnification).

Prior to surgery, four sites around the oral carcinoma are injected with a radioactive-labelled colloid tracer. The tracer enters the lymphatic system and drains to the first echelon lymph nodes. The radioactive lymph nodes can then be mapped by imaging. The surgeon uses a gamma radiation detection system to confirm the location of the sentinel lymph nodes and harvests them using a small incision in the neck. Up to four sentinel nodes may be found. Each 'hot node' is then processed in the pathology laboratory using a protocol that samples the entire lymph node at 125 µm intervals. Immunohistochemical staining for cytokeratins (pan-cytokeratin cocktail, AE1/AE3) is used to increase the sensitivity of the test. A negative sentinel lymph node biopsy has a high negative predictive value (95%) and the neck can be monitored, avoiding elective neck dissection. A positive lymph node requires a completion neck dissection, which is performed at a second operation.

Request form

When requesting pathological analysis of a specimen, it is vital that the pathologist is provided with all relevant information to enable a full assessment of the specimen. Ideally the information should include:

- patient identification and demographics
- clinician responsible
- relevant details of lesion (duration, symptoms, etc.)
- clinical photographs of the lesion can also help
- differential diagnoses
- relevant medical history and medications
- history of tobacco, alcohol and drug use
- previous treatment surgery and/or radiotherapy
- type of biopsy (FNAB, core biopsy, incision biopsy or excision biopsy)
- site of biopsy (if biopsies are taken from multiple sites, each site should be clearly labelled and allocated a separate specimen pot).

If the specimen has been orientated, then an annotated diagram or photograph should be included with the request.

Tissue preparation

Tissue specimens are ideally fixed immediately in theatre by immersion in 10% neutral buffered formalin (NBF), which is the routine fixative of choice. This effectively stops metabolism and arrests autolysis and putrefaction, thereby preserving the tissue structure. The apocryphal maxim is that the minimum ratio by volume of NBF to specimen should be 10 to 1, although this is somewhat arbitrary and if this was ever evidence-based, it is likely to be influenced by intangible factors, such as type of tissue, temperature, agitation and so on – as a rule, more liberal volumes of fixative are preferable. On rare occasions, alternative fixatives, such as glutaraldehyde or alcohol, may be employed if specialized studies (e.g electron microscopy) are required. Fresh unfixed material intended for intra-operative frozen section examination, direct immunofluorescence, molecular studies or microbiology must be despatched without delay to the laboratory, cognizant that it constitutes a biohazard.

Upon receipt in the laboratory, the specimen identity is corroborated and a unique accession number is allocated. Following an appropriate period of fixation (24–48 hours), either the pathologist or senior biomedical scientist staff will describe the specimen macroscopically, and dissect and submit representative tissue slices for examination. These slices are inserted into proprietary sealable cassettes appropriately labelled.

After a further period of fixation, the tissue slices undergo cycles of dehydration, clearing, infiltration and embedding in preparation for microtomy (section cutting). During dehydration, alcohol replaces the aqueous fixative within the tissue. Clearing replaces the alcohol with an antemedium, such as xylene. Molten paraffin wax then replaces the clearing agent and infiltrates the tissue. The tissue is

subsequently embedded by encapsulation in paraffin wax in a mould to provide a rigid support for microtomy. The additional step of decalcification may be instituted in mineralized tissue, which might otherwise hinder sectioning. Automatic tissue processors enhanced by pressure, vacuum, heat and microwave facilities in a self-contained, microprocessor-controlled, programmable unit are used in many modern laboratories, tailored to local conditions.

The pre-chilled, hardened paraffin wax-embedded tissue block is then sliced, typically at 3–5 µm thick on a microtome. The thin sections are then floated on a warm water bath prior to transfer on to a glass slide. The sections are then dried on a hotplate.

The sections may now be stained, typically with H&E and mounted under a glass or self-adhesive plastic film coverslip to form a permanent preparation. Haematoxylin stains nuclei dark blue and tissue glycoproteins light blue. Eosin stains the cytoplasm and collagen pink. The H&E stained slides are then made available to the pathologist for examination. A wide repertoire of additional histochemical and/or immunohistochemical stains may be required, on additional sections, to render a diagnosis. The majority of biopsies are reported within 7 days; however, it is possible to reduce the 'turn-around time' for urgent specimens to 24 hours. Large resection specimens that include bone require a decalcification step, which extends the processing time to around 2 weeks.

Histochemistry

Histochemistry is used to highlight a variety of biological substances in the tissue. Sometimes referred to as 'special stains', there are numerous methods based on chemical reactions that can be visualized by a specific colour change in the tissue sections. For example, Periodic acid-Schiff (PAS) stain can be used to highlight carbohydrates, which stain deep purple; pre-treatment of the tissue section with the enzyme diastase removes simple carbohydrate moieties leaving mucins, which are found in glandular secretions and fungal hyphae. Elastic van Gieson stain is used to appreciate tissue architecture, especially blood vessels; elastin fibres stain black and collagen red. Ziehl Neelsen stain is used to detect bacteria and identify acid-fast bacilli in tuberculosis.

Immunohistochemistry

The principle underpinning immunohistochemistry (IHC) is the demonstration of an epitope or antigen via its binding to a specific antibody, which in turn is conjugated to a label that can be visualized by microscopy. A variety of reporter and linkage systems to produce a visual signal have been developed based on fluorescent molecules and enzyme-generated chromogenic substrates.

In general, monoclonal antibodies are more specific than their polyclonal counterparts. Importantly, no antibody is 100% sensitive and specific – immunophenotyping is best performed using a panel of expected positive and negative antibodies. Expected staining can be checked by examining 'internal controls' (tissue elements that are positive for the antibody) and 'external controls' ('on slide' analyte control material such as cell lines or tissue/tumours with known protein expression patterns). It is important to be mindful of aberrant cross-reactivity, spurious co-expression, false positives, false negatives and vagaries of technical quality. Correlation with conventional morphology is imperative.

Among the broad categories of commercially available diagnostic markers are antibodies directed against intermediate filaments (e.g. cytokeratins, desmin, neurofilament, vimentin), epithelial markers (e.g. Ber EP4, epithelial membrane antigen), structural proteins (e.g. calponin), storage granules/products (e.g. calcitonin, chromogranin, synaptophysin, thyroglobulin), hormone receptors (e.g. oestrogen, progesterone), nuclear epitopes (e.g. p16, thyroid transcription factor-1), lympho-reticular epitopes (e.g. CD3, CD20, CD79a), cell proliferation (e.g. Ki67), apoptosis molecules (e.g. bcl-2, p53) and infectious agents (e.g. cytomegalovirus, herpes simplex virus 1/2, human herpes virus 8, varicella zoster, LMP-1 for Epstein–Barr virus (EBV)).

In-situ hybridization

In-situ hybridization (ISH) is similar to IHC, but instead of using antibodies to detect a protein, a DNA probe is designed to hybridize (stick) to either a complementary sequence of RNA or DNA. RNA ISH is used to detect EBV and kappa and lambda light chains in B lymphocytes. DNA ISH can be used to identify low-risk and high-risk human papillomavirus infection. Chromosomal abnormalities, such as amplifications, translocations and deletions, can be identified by fluorescence ISH.

Molecular tests

More recently, molecular biology techniques have been used to generate high resolution genetic profiling of tumours, by either DNA sequencing and/or gene expression arrays. Such molecular information is currently used in the management of breast cancer (e.g. Oncotype DX breast cancer test). It is likely that these types of test will become available for head and neck cancers in the not too distant future. Projects like the US Cancer Genome Atlas (TCGA) aim to accelerate the understanding of the molecular basis of cancer and facilitate molecular diagnosis.[8] One of the aims of the 100 000 genomes project (Genomics England) is to create a new genomic medicine service for the National Health Service for the benefit of patients.[9]

Multidisciplinary diagnosis

The cytological and histopathological analysis is a complex process. It cannot be overemphasized that reaching a final conclusion depends on many factors, including detailed site-specific knowledge coupled with experience of normality, familiarity with the manifold appearances of many disease processes at various stages in their natural history, awareness of mimics and artefacts plus cognizance of the limitations of the technique, in conjunction with patient-specific details and the clinical context.

Without consideration of these and appropriate correlation with clinical, radiological and other relevant background information, a pathological slide is in danger of becoming a two-dimensional, brightly stained artefact, which may be as misleading as it can be potentially helpful.

Subsites of the head and neck

The head and neck region is divided into a number of subsites as outlined in **Table 26.2**.

TUMOURS OF THE HEAD AND NECK

Tumour typing

There is a multitude of benign and malignant tumours that affect the head and neck region. Benign and malignant tumours can be classified according to the proposed tumour cell origin (histogenesis) and/or its differentiation pathway (**Table 26.3**). This section is not intended to be an exhaustive account of the pathology of benign and malignant tumours affecting the head and neck region, which can be found in any head and neck pathology text.[10–12] We will cover those benign and malignant tumours that are more commonly encountered in clinical practice, and are exemplars of their type.

BENIGN TUMOURS

Benign epithelial tumours

SQUAMOUS CELL PAPILLOMAS

Squamous cell papillomas are benign epithelial lesions that can affect the oral cavity, larynx, sinonasal tract and nasopharynx. They are typically polypoidal or verrucoid lesions arising from the epithelial surface and can be solitary or multiple lesions depending on site and subtype.

TABLE 26.2 Head and neck cancer sites and subsites

Head and neck site	Subsite
Oral cavity (from lips to anterior tonsil fauces)	• Lips • Anterior tongue • Buccal mucosa • Retromolar trigone • Floor of mouth
Oropharynx (from level of hard palate to hyoid bone)	• Tongue base • Tonsils • Lateral and posterior pharyngeal wall
Hypopharynx	• Pyriform fossa/sinus • Post-cricoid region • Posterior pharyngeal wall
Larynx (from epiglottis to lower border of cricoid cartilage)	• Supraglottis: epiglottis to false cords • Glottis: false cords to 5–10 mm below true cords • Subglottis: 10 mm below true cord to lower border of cricoid cartilage
Nasal cavity and paranasal sinuses	• Nasal cavity • Maxillary sinus • Frontal sinus • Ethmoid sinus • Sphenoid sinus
Nasopharynx	
Ear	• External auditory canal • Middle ear • Inner ear
Salivary gland	• Parotid gland • Submandibular gland • Sublingual gland • Minor glands
Thyroid gland	
Parathyroid glands	
Neck	• Level I, submandibular IB and submental IA nodes • Level II, upper jugular nodes divided by spinal accessory nerve into IIA and IIB • Level III, middle jugular nodes • Level IV, lower jugular nodes • Level V, posterior triangle nodes divided by spinal accessory nerve into VA and VB • Level VI, anterior compartment
Skin	

TABLE 26.3 Classification of tumours

Cell type		Examples	
		Benign	**Malignant**
Epithelial		• Squamous cell papilloma • Pleomorphic adenoma • Warthin's tumour	• Squamous cell carcinoma • Mucoepidermoid carcinoma • Acinic cell carcinoma • Adenocarcinoma • Adenoid cystic carcinoma
Mesenchymal	• Nerve • Vascular • Smooth muscle • Skeletal muscle • Fibrous • Adipose tissue • Bone • Cartilage • Immune system	• Schwannoma, neurofibroma • Angioma • Leiomyoma • Rhabdomyoma • Fibroma • Lipoma • Osteoma • Chondroma	• Malignant peripheral nerve sheath tumour • Angiosarcoma • Leiomyosarcoma • Rhabdomyosarcoma • Fibrosarcoma • Liposarcoma • Osteosarcoma • Chondrosarcoma • Lymphoma
Neuroectodermal			• Malignant melanoma • Olfactory neuroblastoma • Neuroendocrine carcinoma

TABLE 26.4 Pathological features of oral squamous cell papillomas[12]

Subtype	Squamous cell papilloma or verruca vulgaris	Condyloma acuminatum	Multifocal epithelial hyperplasia (Heck's disease)
HPV status	• Approximately half are associated with HPV infection • Squamous cell papilloma HPV6 and 11 • Verruca vulgaris HPV2, 4, 40 and 57	• Associated with HPV6 and 11 • Transmission is venereal or autoinoculation and there is an association with genital condyloma	• HPV13 and 32. • Disease of children, adolescents and young adults
Macroscopic appearance	Wart-like exophytic lesion	Dome-shaped exophytic nodules, which are usually larger than squamous cell papillomas	Multiple clusters or patches of soft, plaque-like lesions

Oral cavity and oropharynx

The pathological features of oral cavity and oropharynx papillomata are outlined in **Table 26.4**.

Larynx

Squamous cell papilloma (and recurrent respiratory papillomatosis) is the most common benign epithelial neoplasm affecting the larynx. It has a bimodal distribution with a peak before the age of 5 and a second between 20 and 40 years of age. There is convincing evidence that recurrent respiratory papillomatosis is due to human papillomavirus (HPV) infection, with HPV6 and 11 as the dominant subtypes.[13] Macroscopically, the lesions are exophytic or sessile with a fine lobular surface that can be prone to bleeding when subjected to even minor trauma. Microscopically, the lesions have a typical papilloma appearance with hyperplastic squamous epithelium covering fibrovascular cores. Branching papillae covered by thin squamous epithelium may be seen, associated with a basal and parabasal cell proliferation. Koilocytes are often focally present in the upper and superficial zones and contain perinuclear halos. IHC and other studies can be used to confirm evidence of HPV infection, but are not required for diagnosis, treatment or to predict clinical behaviour.

Sinonasal tract

Unlike the oral cavity and the larynx, papilloma of the sinonasal tract is relatively uncommon. Sinonasal papillomas arise from the ectodermally-derived ciliated epithelium of the nasal cavity, termed the 'Schneiderian membrane'. There are three morphologically distinct types of papilloma:[14]

- *Exophytic sinonasal papilloma* typically arises on the septum around the nasal vestibule. It closely resembles verruca vulgaris and is associated with HPV6 and HPV11 infection. Malignant transformation is uncommon (**Figure 26.4a**).
- *Inverted sinonasal papilloma* may present anywhere within the nose and paranasal sinuses, occasionally elsewhere within the upper aerodigestive tract (e.g. larynx, lacrimal apparatus). It shows a complex, arborescent exo-endophytic growth pattern with primary, secondary and tertiary ramifications into underlying stroma. Numerous intra-epithelial microabscesses are characteristic and stain for macrophage

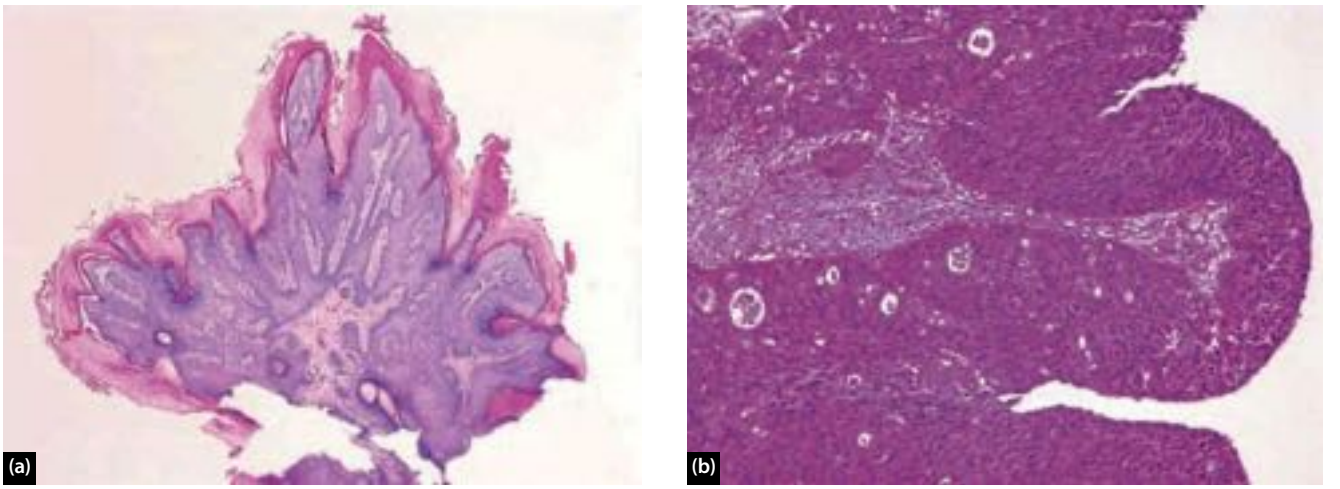


Figure 26.4 Sinonasal papilloma. (a) Exophytic sinonasal papilloma characterized by its radially symmetrical, hyperkeratotic outline (H&E stain, ultralow magnification). **(b)** Inverted sinonasal papilloma illustrating a papillary surface. The tumour is composed of non-keratinizing squamous and transitional epithelium with scattered intra-epithelial microabscesses (H&E stain, medium magnification).

markers (CD68). The epithelium may be squamous (usually non-keratinizing), respiratory, glandular, transitional cell-like or a mixture in any combination or permutation. Varying rates of HPV infection are reported, around a third are considered to be HPV-positive, usually with HPV6 and HPV11. The tumours may be synchronously or metachronously multicentric and because it is difficult to achieve adequate surgical clearance, there is a risk of persistence/recurrence. With each recrudescence, the likelihood of malignant transformation increases (**Figure 26.4b**).

- *Oncocytic sinonasal papilloma* (cylindrical cell papilloma) is not associated with HPV infection. It comprises exophytic fronds of bi-layered, well polarized, oncocytic epithelium supported by a fibrovascular stroma. Microabscesses confined to the epithelium are invariable. There is a predilection for persistence/recurrence if incompletely excised. A small proportion (3–17%) of oncocytic sinonasal papillomas harbour a carcinoma, consequently judicious sampling of the biopsy material is essential.

Benign salivary gland tumours

Benign salivary gland tumours are classified according to WHO and are listed in **Table 26.5**.

PLEOMORPHIC SALIVARY ADENOMA

Pleomorphic salivary adenoma (PSA; benign mixed tumour) is the most common tumour affecting the salivary glands. The annual incidence is reported as 2.4–3.05/100 000. It comprises approximately 50% of all salivary gland tumours, 65% of parotid tumours and 40% of intra-oral minor salivary gland tumours.[15]

Macroscopic appearance

PSA tends to be well demarcated, round or ovoid with broad-based surface bosselations. There may be areas of cystic change and also calcification. They are variably encapsulated and, where present, the capsule may be thick and fibrotic or attenuated and incomplete. The cut surface may either be homogeneous or variegated, dependent upon the precise histological pattern (**Figure 26.5**). Protuberant peri-capsular nodules may be seen, sometimes attached to the main body of the tumour by a slender pedicle. Simple enucleation of the body of a pleomorphic adenoma risks detaching these nodules, which remain behind forming a nidus for recurrence. Predominantly myxoid examples may be semi-fluid and fluctuant – peri-operative capsular rupture and spillage may seed tumour throughout the operative field, increasing the risk of recurrence. Such recurrences are typically multifocal (**Figure 26.6**).

Microscopic appearance

The basic components of a PSA are ductal elements and myoepithelial cells embedded in a chondromyxoid matrix. The appearances vary widely both between PSAs and within the same tumour. A panoply of other changes may be superimposed or even predominate, for example, metaplastic changes (squamous, lipomatous, osseous, neuroid, angiomatoid), degeneration (cystic change, infarction, mineralization, hyalinization, elastosis), specific growth

TABLE 26.5 WHO classification of benign epithelial salivary gland tumours[12]

Benign epithelial salivary gland tumours
• Pleomorphic adenoma • Myoepithelioma • Basal cell adenoma • Warthin's tumour • Oncocytoma • Lymphadenoma • Cystadenoma • Sialadenoma papilliferum • Ductal papillomas • Sebaceous adenoma • Canalicular adenoma

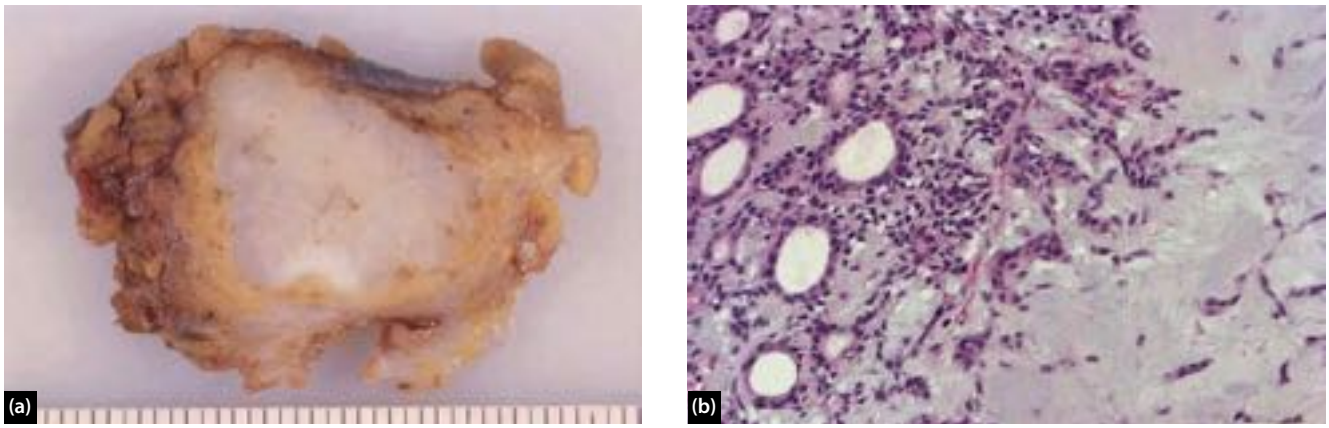


Figure 26.5 Pleomorphic salivary adenoma. (a) Cut surface of the tumour displaying a solid blue/grey hue characteristic of chondromyxoid matrix. **(b)** Histology showing double layered ducts and strands of myoepithelial cells invested by a myxoid matrix (H&E stain, medium magnification).

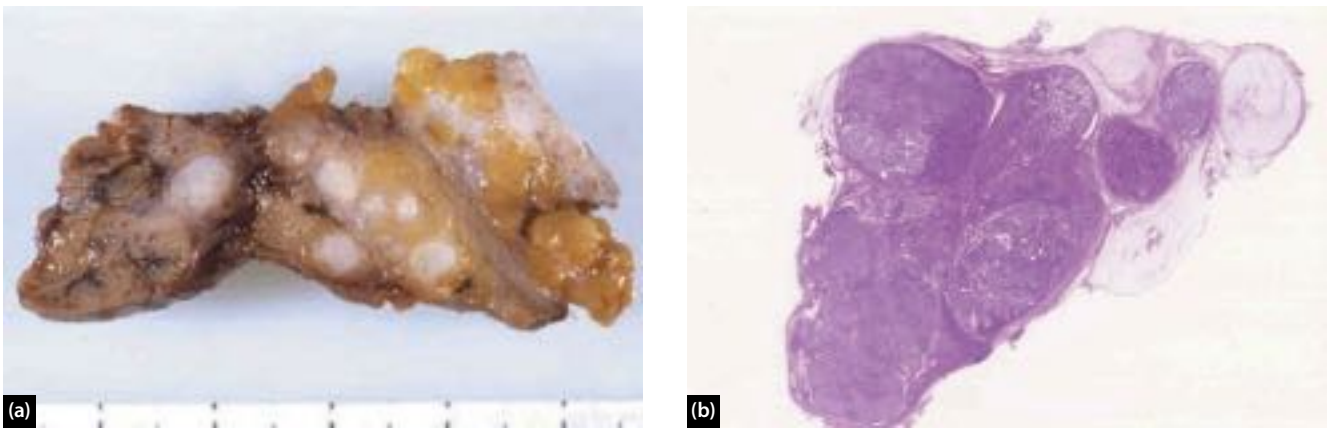


Figure 26.6 Recurrent pleomorphic salivary adenoma. (a) Excision of multi-focal recurrence of pleomorphic salivary adenoma encompassing the original surgical field. **(b)** Whole mount section of another local recurrence showing secondary seeding of fat, residual salivary gland and fibrous tissue. The nodules are clearly of differing composition despite having arisen from the same parent lesion [H&E stain, ultralow magnification].

patterns (e.g. adenoid cystic carcinoma-like, clear cell, epithelial-myoepithelial carcinoma-like, basaloid, giant cell, spindle cell, acinar, plasmacytoid, oncocytoid) and crystal deposition. This heterogeneity can occasionally make diagnosis difficult, especially from limited samples derived from FNAB or core biopsies.

Risk of malignant transformation

PSA has a risk of malignant change, around 6%. Clinical features that are associated with an malignant transformation include:[12, 15, 16]

- older patient age
- male patient
- long duration of tumour
- multiple recurrences
- deep lobe parotid location.

WARTHIN'S TUMOUR

Warthin's tumour (adenolymphoma, papillary cystadenoma lymphomatosum) is the second most common tumour of the salivary glands.[17] It is exclusive to the parotid gland and para-parotid lymph nodes and can be multicentric and/or bilateral in 4–10% of cases. It comprises between 3.5% and 30% of primary epithelial salivary gland tumours with geographical variation. It occurs in Caucasians and Asians with a lower incidence in African-Americans and Black Africans. It can occur over a wide age range, but is common in the sixth decade for women and seventh decade for men. It is more common in males but the male:female ratio has reduced over the last few decades. There is a link between Warthin's tumour and cigarette smoking.[18]

Macroscopic appearance

The tumour is a circumscribed, often thinly encapsulated soft mass that contains multiple cystic and solid/papillary areas, which is white to brown in colour. There may be coagulated tan exudate in the cystic spaces (**Figure 26.7a**).

Microscopic appearance

Warthin's tumour is composed of ciliated, bi-layered oncocytic epithelium supported by reactive lymphoid

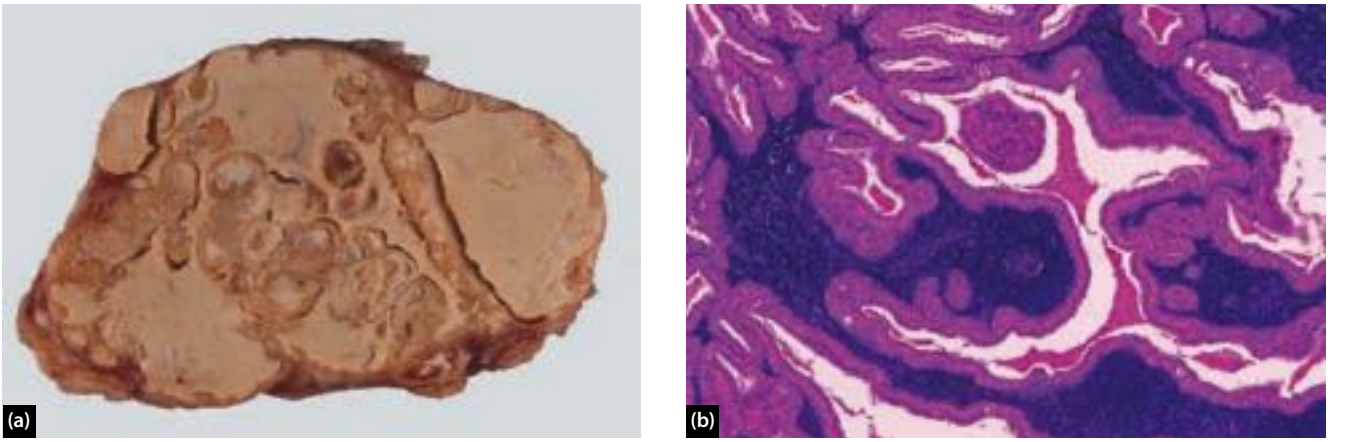


Figure 26.7 Warthin's tumour. (a) The characteristic papillary-cystic cut surface appearance of Warthin's tumour. Oncocytic epithelium is typically mid-brown. The light tan micronodules correspond to reactive lymphoid follicles. **(b)** Papillary-cystic tumour composed of fronds of oncocytic epithelium supported by hyperplastic lymphoid stroma (H&E stain, low magnification).

stroma (**Figure 26.7b**). The cystic areas contain amorphous debris. Warthin's tumour can undergo infarction or degeneration and metaplastic change either spontaneously or secondary to manipulation (e.g. FNAB, core biopsy). Benign oncocytic epithelial inclusions are commonly seen in intraparotid and para-parotid lymph nodes. These inclusions probably account for Warthin's tumour's propensity for multicentricity and bilaterality. Malignant transformation, either carcinomatous or lymphomatous, is rare.

Benign mesenchymal tumours

SCHWANNOMA

Schwannomas (neurilemmomas) are benign encapsulated tumours that originate from the Schwann cells of the peripheral nerve sheath. Schwannoma in the head and neck may arise from the cranial nerves including Vth and VIIth–XIIth, sympathetic chain, cervical or brachial plexus. It is the most common neoplasm affecting the temporal bone, vestibular Schwannoma, and a common site of occurrence is the neck, but it is rare in the oral cavity.[19] The NF2 gene is inactivated in 67% of Schwannomas.[20,21] Approximately 2% are due to neurofibromatosis 2, which is an uncommon autosomal dominant condition characterized by the presence of bilateral vestibular Schwannomas and an increased incidence of extra- and intracranial meningiomas.

Macroscopic appearance

Schwannomas are typically encapsulated, but those affecting the temporal bone tend to be non-encapsulated (**Figure 26.8**). The tumour is usually attached to an identifiable nerve and is firm and rubbery with a tan-white to yellow colour. At operation, it may be mistaken for a lymph node and excised without seeking to preserve or repair the nerve, thereby sustaining unexpected neurological damage.

Microscopic appearance

The tumour consists of a mixture of Antoni A and Antoni B areas. Antoni A areas are formed by short fascicles of closely packed monomorphous spindle cells with fibrillar cytoplasm. The cells sometimes form a palisaded arrangement around acellular, collagenized foci known as Verocay bodies. Antoni B areas are composed of the spindle cells haphazardly arranged within a loose myxoid stroma. Secondary areas of vascular wall hyalinization, microcystic degeneration, haemorrhage, foam cell infiltration and calcification may be seen. Focal bizarre, hyperchromatic and multinucleate giant cell transformation is sometimes encountered. In the absence of increased numbers of mitoses, abnormal mitotic spindles, necrosis or other atypical features, this is designated ancient change, probably a degenerative phenomenon, which is of no known clinical relevance. On IHC, Schwannomas are strongly S100-positive; neurofibromas tend to be weakly positive and also contain neurofilament positive fibres. However, occasionally distinction between Schwannoma and neurofibroma is problematic, invoking the rubric 'benign peripheral nerve sheath tumour'.

MALIGNANT TUMOURS

Malignant disease of the head and neck is the sixth most common form of cancer worldwide with around 300 000 new cases per annum. In the UK there were 11 449 cases of head and neck cancer in 2014 and 3225 deaths, equating to an incidence of 25 per 100 000 (7918 cases) in males and 11 per 100 000 (3531 cases) in females.[22] The majority (90%) of head and neck malignancies are squamous cell carcinomas arising from the epithelial-lining of the upper aero-digestive tract.

Tumour staging

Cancer of the head and neck, due to the diversity of pathology and the variation in progression at different anatomical subsites, cannot be meaningfully staged by a single, generic schema. The tumour, node, metastasis (TNM) staging system, developed and maintained by both the American Joint Committee for Cancer (AJCC) and the International Union Against Cancer (UICC), is the most



Figure 26.8 Schwannoma. **(a)** Encapsulated Schwannoma from the parapharyngeal space giving a smooth surfaced nodal appearance, although the capsule is deficient at one pole. **(b)** The cut surface displays a variegated texture.

widely used method for staging.[23, 24] There are international expert committees that keep the system under review and the 8th edition was published by both the AJCC and UICC in 2017.[24] There have been major changes in TNM staging of the head and neck cancer, when compared to the 7th edition published in 2010,[23] and it remains to be seen how widely this will be adopted and implemented by the head and neck oncology community.

The basic principles of the TNM staging system are:

- *Clinical*. cTNM or TNM is based on clinical findings (physical examination and imaging) and assigned prior to starting first definitive treatment.
- *Pathological*. pTNM is based on the cTNM modified by further information obtained from surgery and subsequent pathological examination.
- *Autopsy*. aTNM is used when the cancer is only classified from the results of post-mortem examination and no evidence of cancer was evident prior to death.

Other descriptors of TNM may occasionally be used and include:

- the 'm' suffix, which is used when there is more than one primary at a single site, pT(m)NM
- the 'y' prefix, which is used when classification is performed during or after initial multimodality therapy, ycTNM or ypTNM.

Tumour differentiation refers to how well developed or mature the malignant cells are. Well-differentiated cells resemble normal cells and tend to grow and spread at a slower rate. There is often morphological heterogeneity, however, both between different tumours of the same type and within the same tumour. Conventionally, tumours are histologically subtyped according to their differentiated components. They are graded with reference to their worst differentiated elements on the premise that it is these that will behave most aggressively, and thereby be the major determinant of prognosis:

- Gx – grade cannot be assessed
- G1 – well-differentiated
- G2 – moderately differentiated
- G3 – poorly differentiated.

The presence or absence of residual tumour is classified as:

- Rx – the presence of residual tumour cannot be assessed
- R0 – no residual tumour is present
- R1 – microscopic residual disease
- R2 – macroscopic residual tumour.

The UICC or AJCC TNM atlas provides detailed descriptions of T-, N- and M-categories for each anatomical sub-site. TNM provides an indication of the amount and spread of the disease. The TNM categories are then used to assign a stage grouping, which relates to prognosis.[23, 24]

Carcinomas

SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma (SCC) and its variants represent by far the most common malignant tumour affecting the head and neck region, accounting for approximately 95% of all primary tumours of the oral cavity, oropharynx, hypopharynx, larynx and sinonasal tract. By contrast, SCC is uncommon in the major salivary glands and thyroid, although these may be affected by direct contiguous invasion from neighbouring structures or metastatic spread. Head and neck squamous cell carcinoma (HNSCC) may also arise from skin. Typically, HNSCC spreads by direct invasion or via regional lymphatics, although haematogenous spread, especially to the lungs, is possible.

Squamous epithelial dysplasia

SCC of the oral cavity and larynx is well known to arise from epithelial precursor lesions, which may be localized or represent wider areas of 'field cancerization'. The precursor lesions harbour varying degrees of epithelial dysplasia, defined by the accumulation of architectural and cytological abnormalities. By convention, epithelial dysplasia is graded and numerous systems have been suggested.

The most recent WHO classification recommends that laryngeal dysplasias are assigned low and high grade categories, whereas oral dysplasia are assigned mild, moderate and severe dysplasia (though there is an option to use a high and low grade categories as well).[12] Grading is known to be subjective and prone to inter-observer variation; nevertheless it is still used to guide management. The more severe the dysplasia, the greater the risk of transformation into malignant disease. A meta-analysis of oral dysplastic lesions indicates a malignant transformation rate of 12% and a mean time to transformation of 4.3 years.[25] Similar transformation rates are quoted for laryngeal precursor lesions.[12] It is clear from these data that progression to invasive malignancy is not inevitable, which implies that such lesions may remain stable over time or possess the capacity to regress – indeed most lesions do not proceed to invasive carcinoma within the time period of the studies conducted. Clinically, these lesions are irregular, circumscribed lesions with a white (leukoplakia), red (erthyroplakia) or variegated appearance (erythroleukoplakia). In reality, dysplasia is a dynamic process manifest as a continuous morphological spectrum. Therefore, the rigorous application of discrete categories, whatever their arbitrary histological basis, is destined to be problematical. IHC, molecular and other biomarkers are presently of limited assistance in resolving this issue.

Aetiology

The main risk factors for HNSCC are tobacco and alcohol abuse, which either alone or combined, are implicated in 75% of all HNSCC.[26] Tobacco alone increases the risk of cancer occurrence two- to three-fold, but acts synergistically with alcohol leading to a multiplicative rather than additive increase. Increased duration of exposure to tobacco and/or alcohol increases the risk of developing HNSCC. Tobacco contains a number of known carcinogens (e.g. polynuclear aromatic hydrocarbons), which cause DNA damage leading to gene mutations. Alcohol causes DNA damage and gene mutation by a number of mechanisms. These include the effect of acting as a solvent for other carcinogens, nutritional deficiencies, acetaldehyde (a by-product of alcohol metabolism) and the direct effect of ethanol. Increasingly, it is recognized that HPV, especially HPV16, is an important cause of oropharyngeal SCC.[27] HPV-positive tumours typically affect non-smokers, non-drinkers and younger patients. Patients with HPV-related oropharyngeal SCC have a better overall survival than those with HPV-negative disease.[28] HPV infection at other subsites is less frequent (< 5%) and consequently the data around survival are less convincing. SCC of the lip is associated with sun exposure and pipe smoking. Sinonasal SCC is linked to nickel and chromate exposure and woodworking. Dietary deficiencies have also been linked to the development of HNSCC, especially vitamins (A, C and E), foods (fruit, vegetables and dairy) and elements (e.g. iron especially when associated with iron-deficiency anaemia of Plummer–Vinson (Paterson–Brown–Kelly) syndrome, which is associated with hypopharyngeal SCC). Oral cavity SCC is particularly common in India where a third of all cancers originate in the head and neck. The widespread chewing of betel nut and paan, which causes both oral submucous fibrosis, a recognized oral potentially malignant disorder, and oral cavity SCC has been implicated. HNSCCs are typically sporadic, but a familial inheritance has been noted in some cases. The risk of HNSCC is also increased in patients with any syndrome associated with an increased risk of cancer. Patients with Fanconi's anaemia have a 700-fold increased risk and the cancer is usually diagnosed in the third decade.

Pathogenesis

HNSCC is a heterogeneous disease, but a hypothetical progression model has been proposed.[26] Histological progression from normal epithelium to hyperplasia, dysplasia and finally invasive carcinoma is related to a number of factors, including genetic changes causing genetic instability leading to cellular change.[29] Genetic changes include the sequential inactivation of tumour suppressor genes and activation of proto-oncogenes. Carcinogens produced by tobacco, which include nitrosamines and benz-(a)-pyrene, produce mutations in p53 associated with HNSCC. The molecular changes are due to a number of genetic alterations, which include loss of heterozygosity (LOH) of 9p21, seen in 70–80% of HNSCC. Other abnormalities include LOH 3p, 17p, 11q and 13q. In HPV16 infection the E6 and E7 viral oncoproteins cause inactivation of tumour suppressor molecules, pRb and p53. Loss of pRb causes uncontrolled cell proliferation. Loss of p53-mediated response to DNA damage leads to genomic stability. There is also reactivation of telomerase driving cell immortality.[27, 29]

Macroscopic appearance

HNSCC appearance varies depending on subsite, but can be an exophytic or ulcerative lesion. On the skin, it typically looks like a non-healing scab or ulcer, which can intermittently bleed. On mucosal surfaces, lesions typically start as whitish or reddish plaque-like lesions (leukoplakia or erthyroplakia), which then progress to ulcerated or fungating masses with irregular indurated borders (**Figure 26.9**).

Microscopic appearance

The histological appearance of SCC is very similar across all sites in the head and neck. Well-differentiated and moderately differentiated SCC characteristically shows evidence of keratinization and intercellular prickles (desmosomes) (**Figure 26.10a**). Poorly differentiated SCC lacks evidence of keratinisation and immunohistochemical analysis may be required to support the diagnosis (**Figure 26.10b**).

Malignant squamous cells display some or all of the following features:

- irregular shape and orientation
- increased and abnormal mitoses



Figure 26.9 Laryngeal squamous cell carcinoma. **(a)** Total laryngectomy specimen opened in the posterior sagittal plane to show advanced, fungating carcinoma effacing much of the supraglottic larynx with local extension on to the left true vocal cord. **(b)** Transverse section through the specimen confirms bilateral midline tumour herniating through the anterior commissural ligament into anterior strap musculature.

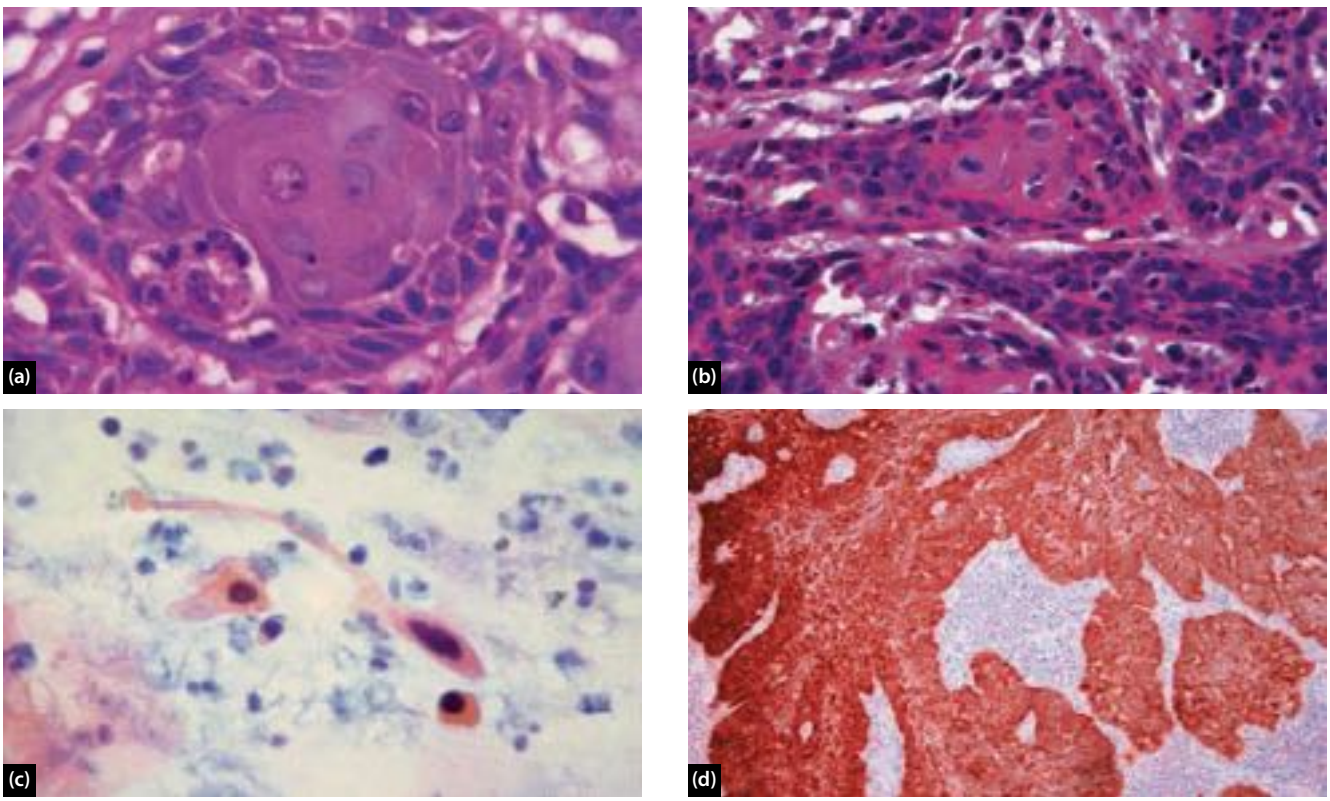


Figure 26.10 Squamous cell carcinoma. **(a)** Moderately differentiated SCC illustrating a focus of keratinization. Note the disordered cell polarity, nuclear pleomorphism (variation in size, shape and intensity of nuclear staining), coarse chromatin and prominent nucleoli (H&E stain, high magnification). **(b)** Poorly differentiated SCC lacking keratinization (H&E stain, medium magnification). **(c)** Cytology preparation from an SCC showing several atypical squamous cells amidst a necrolytic background. Note the large, binucleate caudate ('tadpole') cell, intermediate-sized obovate ('comet') cell and the smaller hyperkeratinizing orangeophilic ('carrot') cell. Other forms commonly seen include fibre ('snake') cells, acanthocytes ('spider') cells and bizarre giant ('monster') cells. Anucleate squames, dissociated keratotic debris, parakeratotic scale ('sprigs') and keratin whorls ('pearls') may accompany these (Pap stain, high magnification). **(d)** Immunohistochemistry showing strong and diffuse nuclear and cytoplasmic p16 expression in an HPV-associated SCC (p16 IHC, medium magnification).

- nuclear hyperchromatism
- coarse and clumped chromatin
- nuclear pleomorphism
- increased nucleus–cytoplasmic ratio
- prominent nucleoli
- premature keratinization (dyskeratosis)
- loss of keratin production
- disordered cell polarity
- disorganized growth.

Cytologically, SCC may be so well differentiated that it is impossible to reliably discriminate it from non-neoplastic squamous epithelium; for example, an FNAB from an inflamed branchial cyst may mimic a cystic metastasis and vice versa. Obviously, the context is all-important and, in experienced hands, FNAB from a cervical lymph node containing abnormal squamous cells against a background of proven SCC may be reasonably taken as presumptive evidence of a secondary deposit until otherwise proven (**Figure 26.10c**). For these reasons, only under exceptional circumstances should radical cancer treatment be undertaken on the basis of a primary diagnosis reached by FNAB without more definitive tissue diagnosis and even then rigorous clinico-radiological correlation must be exercised.

The defining feature of SCC is breach of the subepithelial basement membrane allowing malignant cells to infiltrate into the normal underlying connective tissue, thereby gaining access to lymphatics, blood vessels and nerves. Typically, areas of dysplasia will surround invasive SCC, although this is by no means invariable. The phenomenon of 'field cancerization' reflects the long-term exposure of head and neck mucosa to carcinogens causing genetic alterations, which enable multifocal tumours to arise due to independent genetic events.[29]

The microscopic description of an SCC includes:

- histological subtype
- histological grade (well-, moderate-, poorly-differentiated)
- invasive front (cohesive or non-cohesive)
- vascular invasion
- neural invasion.

The terms 'superficial invasion', 'minimally invasive carcinoma' and 'micro-invasive carcinoma' are sometimes used to denote SCC with limited infiltration. However, these presently have no agreed, validated definition and are, therefore, potentially confusing. It is more helpful to measure tumour depth and/or thickness and overall dimensions, and place this within the recognized TNM schema with any relevant subjective descriptive comments. It is also important to assess for the presence of malignant cells within lymphovascular channels and also neurotropism, signifying vascular or neural invasion respectively, both of which are associated with an unfavourable prognosis.

Immunohistochemistry

For poorly differentiated tumours, IHC is required to render an accurate diagnosis. The initial panel of IHC is directed at identifying broad groups of tumours: carcinoma, melanoma, lymphoma and sarcoma. A pan-cytokeratin cocktail is used to demonstrate cytokeratin intermediate filaments, which is positive in virtually all carcinomas. S100, MelanA, HMB45 and Sox10 can be used to identify melanoma. CD45 (leucocyte common antigen), CD79a (B cell marker) and CD3 (T cell marker) are used to identify lymphoma. Sarcomas are more variable and panels are formulated based on morphological clues. Antibodies for desmin and vimentin are often used to start the process of investigation.

For poorly differentiated carcinomas, cytokeratins 5, 6, 14, and staining with the nuclear proteins p40 and p63, are used to support a diagnosis of poorly differentiated SCC. The results of these panels of IHC are usually described in the pathology report.

For oropharyngeal SCC, HPV testing is recommended.[30] Tests are carried out for prognostication and for entry into clinical trials. Typically, testing is carried out using a combination of p16 IHC and high-risk HPV DNA ISH (**Figure 26.10d**).[31] Other HPV specific tests, such as polymerase chain reaction (PCR)-based tests have also been validated. Tumours that harbour oncogenic HPV show increased p16 expression. There is strong and diffuse, nuclear and cytoplasmic staining in more than 70% of malignant cells. p16 is a recognized surrogate marker of oncogenic HPV infection; the test is highly sensitive but lacks specificity. By contrast, high-risk HPV DNA ISH is highly specific but lacks sensitivity. The combination of both tests provides a satisfactory classification for the majority of oropharyngeal SCC (95%). The significance of p16-positive, HPV-negative SCC is controversial; in some studies p16 is an independent marker of good prognosis, whereas in other studies p16 positivity alone does not confer a favourable prognosis.[32, 33]

For the clinical scenario of an enlarged cervical lymph node that turns out to be metastatic SCC, HPV and EBV tests (see below) are useful in locating the putative primary site. HPV-positive SCCs are usually located in the oropharynx, whereas EBV-positive SCCs are typically discovered in the nasopharynx. A similar strategy can be used to link a distant metastases to an index primary tumour in the head and neck region.

HNSCC variants

A number of morphological variants of SCC are recognized, which include: verrucous carcinoma (VC); spindle cell carcinoma (sarcomatoid carcinoma); papillary SCC; adenosquamous carcinoma; and basaloid SCC.

- VC is a controversial manifestation of well-differentiated SCC, typically occurring in the oral cavity but rarely said to occur in the larynx (1–3% of all laryngeal malignancies), hypopharynx, sinonasal tract and nasopharynx, plus other sites outside the head and neck. Clinically, VC is a warty, exophytic lesion that arises from a broad base. It has a superficial spreading growth, but can be deeply destructive extending

into muscle, cartilage or bone. Histologically, VC lacks significant cellular atypia and is characterized by blunt incursions and an expansile advancing margin sometimes eliciting brisk lymphocytic response. If adequately sampled, approximately 20% of VCs contain areas of conventional SCC, although often very localized, and it is these elements that determine overall prognosis. Incision biopsy diagnosis of VC is problematic as its predominant bland morphology may be indistinguishable from benign squamoproliferative lesions on superficial or limited volume material. Typically, three or four biopsies are required, or even excision biopsy, before the overall architecture is appreciated and the diagnosis is seriously considered. A high index of pathological suspicion and clinical persistence are thus prerequisites.

- Spindle cell carcinoma (sarcomatoid carcinoma) (**Figure 26.11**) occurs in the upper respiratory tract or, less commonly, in the oral cavity. Patients are typically elderly males and a significant number will have had previous radiation. Spindle cell carcinoma usually has a polypoidal, exophytic configuration with either a broad base or narrow pedicle that can occasionally auto-amputate and be expectorated by the patient. The surface tends to be ulcerated. It is usually a bi-phasic lesion with areas of SCC, and/or high-grade dysplasia, associated with bizarre spindle cell and/or giant cell proliferation of sarcomatoid appearance. The squamous component can be difficult to identify due to the ulceration and the sarcoma-like component predominates. IHC may be helpful, although the spindle cells are often negative for epithelial markers and a significant minority paradoxically co-express aberrant positivity for mesenchymal markers.
- Papillary SCC is an uncommon variant.[34] It may affect most anatomical subsites of the head and neck, including the larynx and hypopharynx. Macroscopically, the tumour is similar to VC, but lacks the typical surface keratinization. Microscopically, the lesion is composed of obviously atypical squamous cells overlying fibrovascular papillary stromal cores. The tumour behaves in a similar manner to conventional SCC and management is therefore similar.
- Adenosquamous carcinoma is an uncommon variant of HNSCC, which is considered aggressive and associated with a poor prognosis.[35] It predominantly affects males in the sixth or seventh decade. The larynx, and occasionally the hypopharynx, is the most commonly affected site. Macroscopically, the tumour resembles a typical HNSCC. Microscopically, the tumour is characterized by the presence of conventional SCC admixed with a variable proportion of true glanduloductal elements indicative of divergent differentiation. Mucin histochemistry and keratin immunoprofiling may aid distinction from acantholytic SCC with pseudoglandular growth and also from mucoepidermoid carcinoma.
- Basaloid SCC is a high-grade aggressive variant of SCC typically found in middle-aged male patients, affecting the oropharynx, larynx and hypopharynx.[36] Macroscopically, these are firm to hard tumours with central necrosis and superficial ulceration. Microscopically, the tumour is infiltrating and deeply invasive and presents a typical basaloid appearance consisting of pleomorphic cells arranged in a lobular configuration with palisading. Cystic degeneration with central comedonecrosis is often a feature. There may be minimal objective evidence of squamous cell differentiation.

Other variants include acantholytic, small cell, clear cell, giant cell and lymphoepithelial carcinoma. In practice, many SCCs are heterogeneous in pattern at least focally.

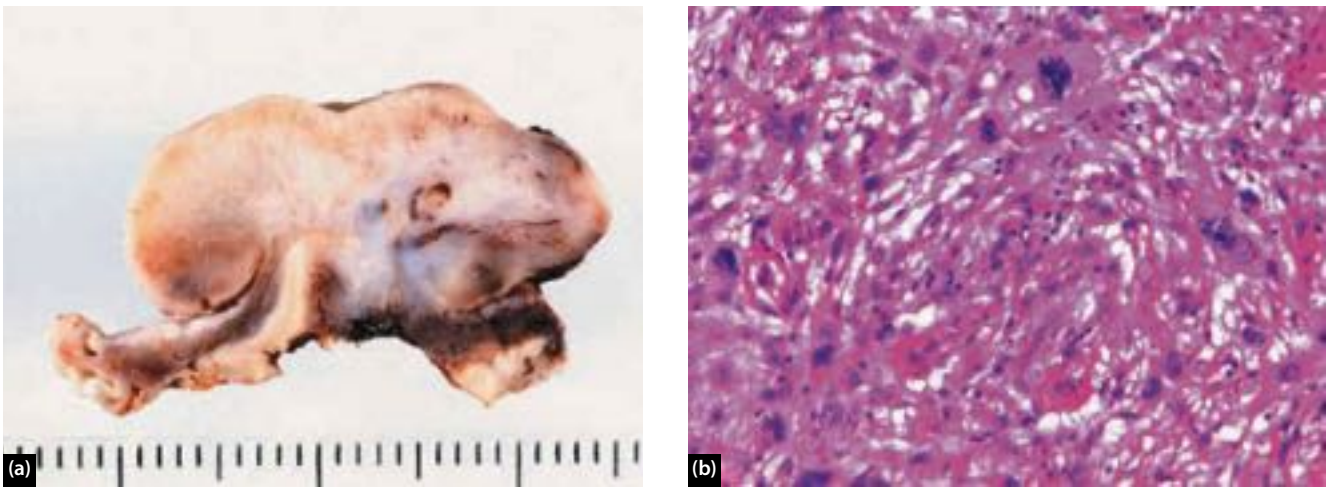


Figure 26.11 Spindle cell carcinoma of larynx. (a) Cross-section of epiglottic resection specimen. This is ulcerated and polypoidal, but also infiltrates deeper, penetrating into and through epiglottic cartilage. **(b)** Representative field beneath the tumour surface exhibiting highly pleomorphic spindle and bizarre giant cells with abnormal mitoses reminiscent of undifferentiated pleomorphic sarcoma (H&E stain, high magnification).

NASOPHARYNGEAL CARCINOMA

Nasopharyngeal carcinoma (NPC) is a distinct type of SCC arising in the nasopharynx.[37] Worldwide, NPC is an uncommon disease with an incidence of less than 1 per 100 000, but has a very distinct geographical distribution. In China, 18% of all adult cancers are NPC and it is especially common in northern provinces, Kwantung and Taiwan, but is uncommon in children (2%). By contrast, 10–20% of all paediatric cancers in northern and central Africa are NPC. Ethnic groups with intermediate risk include Greenland Inuit and the Maghrebis of Northwest Africa, but Caucasian populations have the lowest risk. Other factors implicated in the development of NPC include EBV and dietary factors, especially a high intake of salted fish and preserved vegetable products. Clinically, the tumour can be a bulging, exophytic and lobulated, or ulcerative mass. Occasionally, there may be no visible tumour, necessitating blind biopsy of the nasopharynx.

Microscopically, NPC is classified according to the WHO system, which is dependent on the presence or absence of keratinization. Around a quarter of tumours contain more than one type and are then classified according to the dominant type:

- Keratinizing NPC represents approximately 25% of all NPC in North America, but only 2% of Chinese patients.[37] This type is rarely found in patients under 40 years of age. Like HNSCC in other sites, this type of NPC can be classified as well, moderately or poorly differentiated. The cells grow in well-defined nests with easily demonstrable intercellular bridges and keratin pearl formation. The stroma undergoes a desmoplastic response to invasive growth.
- Non-keratinizing NPC, which is associated with EBV, can be divided into differentiated or undifferentiated, but is of no clinical or prognostic significance:
  - Differentiated non-keratinizing NPC is the least common subtype, accounting for 12% worldwide (2% in China).[37] As the name suggests, there is little or no evidence of keratinization, vague intercellular bridges and it may undergo cyst formation. There is no desmoplastic response to invasive growth.
  - Undifferentiated non-keratinizing NPC is the most common subtype, accounting for approximately 63% of cases, rising to 95% in China,[37] and is the most common type to affect children. The cells possess round nuclei, prominent eosinophilic nucleoli, and/or dispersed or microvacuolated chromatin with scant cytoplasm. There is generally a prominent non-neoplastic intra-tumoral and peri-tumoral lymphoid cell infiltrate. When there is a diffuse, non-cohesive growth pattern, such malignant cells are easily overlooked on cursory inspection. Other recognized growth patterns include cohesive or nested cells. There is no desmoplastic response to invasive growth.

EBV infection can be reliably detected in biopsy specimens using ISH for EBV encoded early RNA (EBER) (**Figure 26.12**). The majority (90%) of Asian NPCs are EBV-positive. There is emerging evidence that some of NPCs are HPV-positive, typically those that occur in Caucasian patients.[38]

MALIGNANT SALIVARY GLAND TUMOURS

Malignant salivary gland tumours are very uncommon and represent approximately 0.5% of all malignancies,

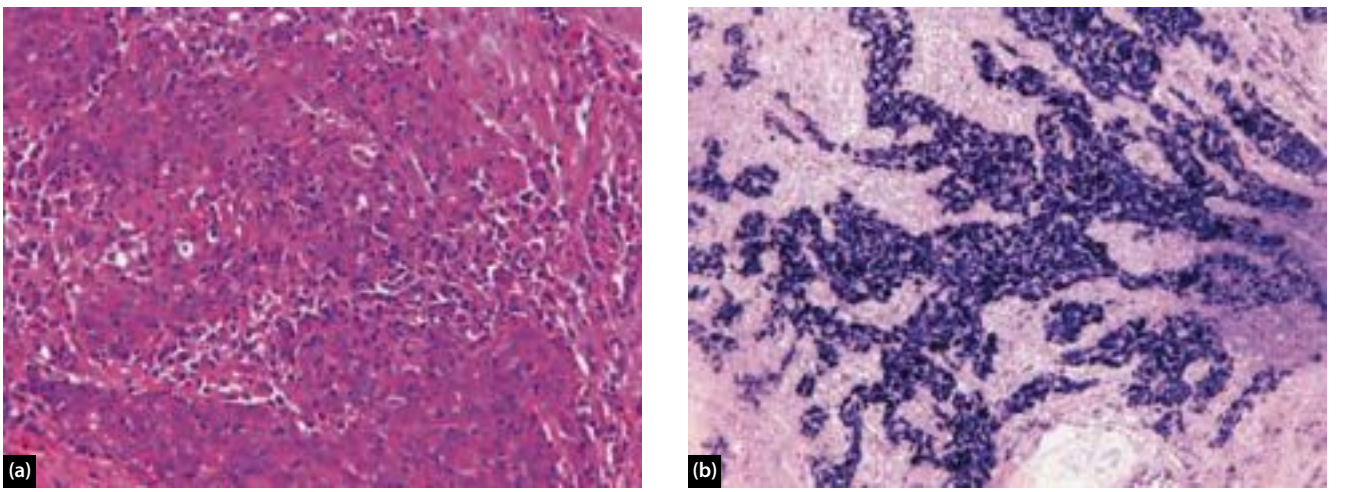


Figure 26.12 Epstein–Barr virus (EBV)-associated undifferentiated carcinoma of nasopharyngeal type. (a) Sheets of poorly differentiated, non-keratinizing malignant cells with ill-defined cytoplasmic borders imparting a syncitial appearance. The nuclei are variously vacuolated or nucleolated. Small lymphocytes are present within and surrounding the tumour cells (H&E stain, medium magnification). **(b)** *In situ* hybridization (ISH) for EBER confirms a diffusely positive signal indicating EBV infection (EBER ISH, medium magnification).

TABLE 26.6 WHO classification of malignant epithelial salivary gland tumours[12]

Malignant epithelial salivary gland tumours
• Mucoepidermoid carcinoma
• Acinic cell carcinoma
• Adenoid cystic carcinoma
• Adenocarcinoma NOS
• Carcinoma ex-pleomorphic adenoma
• Polymorphous adenocarcinoma
• Clear cell carcinoma
• Basal cell adenocarcinoma
• Intraductal carcinoma
• Salivary duct carcinoma
• Myoepithelial carcinoma
• Epithelial/myoepithelial carcinoma
• Secretory carcinoma
• Sebaceous adenocarcinoma
• Carcinosarcoma
• Poorly differentiated carcinoma
• Undifferentiated carcinoma
• Small cell neuroendocrine carcinoma
• Large cell neuroendocrine carcinoma
• Lymphoepithelial carcinoma
• Squamous cell carcinoma
• Oncocytic carcinoma
• Sialoblastoma

5% of all head and neck cancers and an incidence in the Western world of 2.5–3/100 000/year.[13] Despite the low incidence, over 20 named malignant salivary gland neoplasms are recognized (**Table 26.6**). This section will describe the pathological characteristics of the more common malignant neoplasms and the authors recommend reference to a specific head and neck pathology atlas for information regarding less common tumours.[11, 12]

MUCOEPIDERMOID CARCINOMA

Mucoepidermoid carcinoma typically affects the parotid gland, but may also occur in the minor salivary glands. The tumour is triphasic comprising goblet cell mucocytes, epidermoid cells (usually with no keratinization) and non-descript cells of intermediate size and shape.

Epidemiology

Mucoepidermoid carcinoma is the most common malignant salivary gland neoplasm (12–29% of all salivary gland malignancies).[11, 12] It is found more frequently in female patients and can present at any time between the first and ninth decade, but peaks in the fifth decade. The major risk factor for development is previous therapeutic radiation exposure with a latent period of 7–32 years.[11, 12]

Macroscopic appearance

The tumour has a variety of appearances. It can be circumscribed or infiltrative. Tumours are predominantly solid, tan-white to pink masses, often cystic filled with a viscous brown fluid. Areas of scarring can also be present and may occasionally prevail.

Microscopic appearance

The tumour consists of varying proportions of admixed mucinous, epidermoid and intermediate cells (**Figure 26.13**). Low-grade tumours are macrocystic and microcystic with plentiful mucocytes, fewer epidermoid cells and infrequent intermediate cells. Extravasated, dissecting mucin pools may be seen. There may be a sclerosing/fibrosing component. Reactive tumour-associated lymphoproliferation is characteristic. High-grade tumours are more solid and contain fewer mucinous elements with a preponderance of atypical epidermoid cells. High-grade tumours are easily mistaken for SCC and recourse to exhaustive sampling augmented by a panel of mucin histochemistry may be diagnostic. This diversity makes FNAB interpretation challenging. The behaviour of mucoepidermoid carcinoma is very varied and various systems have been proposed to attempt to grade tumours and hence predict outcome. A commonly used system is outlined in **Table 26.7**.[39]

ACINIC CELL CARCINOMA

Epidemiology

Acinic cell carcinoma accounts for 7–17.5% of all malignant salivary gland neoplasms. Approximately 80% arise from the parotid gland, with the remaining 20% arising mainly from the minor salivary glands or submandibular glands, and only 1% from the sublingual gland. There is a male preponderance and they usually present in the third decade of life.[11, 12]

Macroscopic appearance

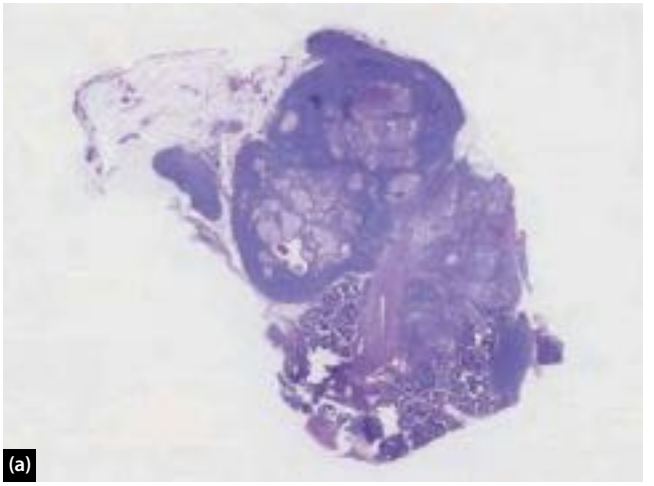
Macroscopically, the tumours are of a firm to rubbery consistency and range in colour from a tan-grey to yellow or pink mass. They are usually rounded, well circumscribed and can be encapsulated. They can contain areas of haemorrhage or cystic change. Recurrent tumours tend to be less well demarcated and can appear multinodular.

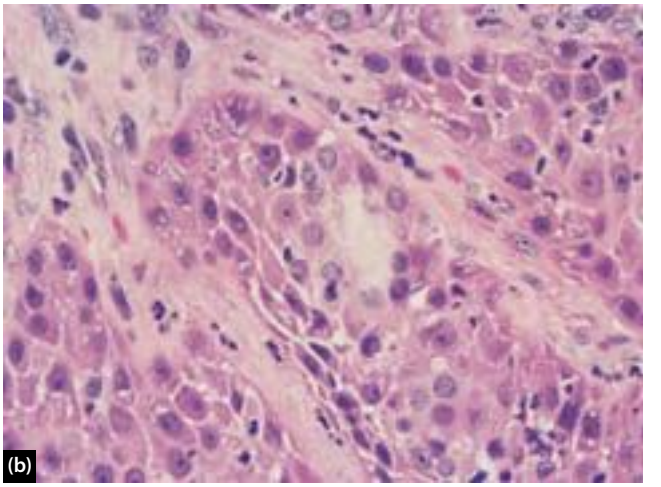
Microscopic appearance

Acinic cell carcinomas recapitulate the serous acinar cell of normal salivary gland tissue. There are a number of recognized growth patterns, which can coexist in a single tumour (**Table 26.8**). Histochemical stains are used to demonstrate zymogen granules in serous acinar cells; in some tumours these cells are sparse, making diagnosis challenging (**Figure 26.14**). Reactive lymphoid tissue is characteristic of acinic cell carcinoma and may mimic lymph node involvement.[40]

ADENOCARCINOMA NOT OTHERWISE SPECIFIC

Adenocarcinoma not otherwise specified (NOS) refers to malignant tumours with glandular or ductal differentiation that do not have specific histologically defining features to enable further sub-classification as a recognized subtype.





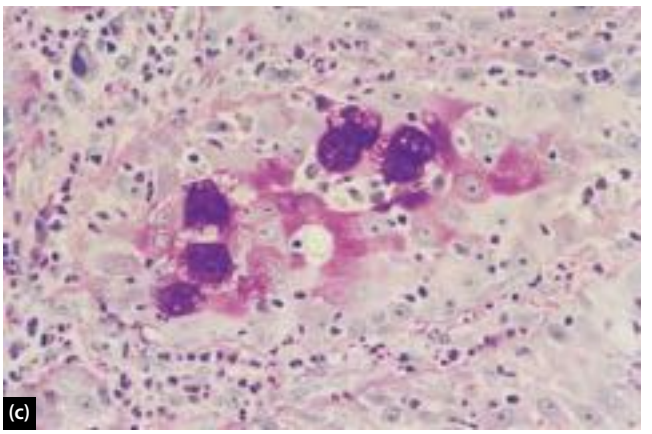


Figure 26.13 Mucoepidermoid carcinoma. **(a)** Whole mount slide of a low-grade mucoepidermoid carcinoma illustrating an expansile multilobulated architecture, substantial macrocystic and microcystic growth plus peripheral lymphoid tissue response (H&E stain, ultralow magnification). **(b)** Intermediate-grade tumour depicting epidermoid cells surrounding a rudimentary tubuloductal lumen lined by goblet cell mucocytes, characterized by abundant microvacuolated cytoplasm (H&E stain, high magnification). **(c)** The same tumour stained for neutral mucosubstances demonstrates mucocytes (dPAS stain, high magnification).

TABLE 26.7 Grading system for mucoepidermoid carcinoma[39]

Parameter	Point value	
Intracystic component <20%	2	
Neural invasion	2	
Necrosis	3	
Mitoses (>4 per 10 HPF)	3	
Anaplasia	4	
Grade	**Total score**	**Overall survival (10 years)**
Low	0–4	90%
Intermediate	5–6	70%
High	7–14	25%

HPF, high power fields.

TABLE 26.8 Growth patterns of acinic cell carcinoma[11, 12]

Growth pattern	Features
Solid	Cells aggregate into sheets forming lobules or nodules
Microcystic	The tumour has a sieve-like appearance due to the presence of microcysts
Papillary–cystic	The tumour contains prominent cysts with intraluminal papillary projections
Follicular	Contain multiple variable-sized cysts loosely resembling thyroid parenchyma

Epidemiology

Adenocarcinoma NOS is the third most common malignant salivary gland neoplasm. It is more common in women and frequently seen in the fifth to eighth decade with a mean age of diagnosis of 58 years, and it is rarely seen in adolescents or children. Sixty per cent occur in the major salivary glands, usually the parotid, and 40% occur in the minor salivary glands.[11–13]

Macroscopic appearance

Macroscopically, tumours appear as a firm tan-white mass, which can be circumscribed to poorly demarcated with an irregular periphery and potentially infiltrative appearance. There may be areas of haemorrhage, cystic change or necrosis.

Microscopic appearance

Adenocarcinoma NOS is a diagnosis of exclusion and therefore tumours that fall within this category can display a variety of features. Common to all tumours in this group is the presence of glandular or ductal features, an invasive

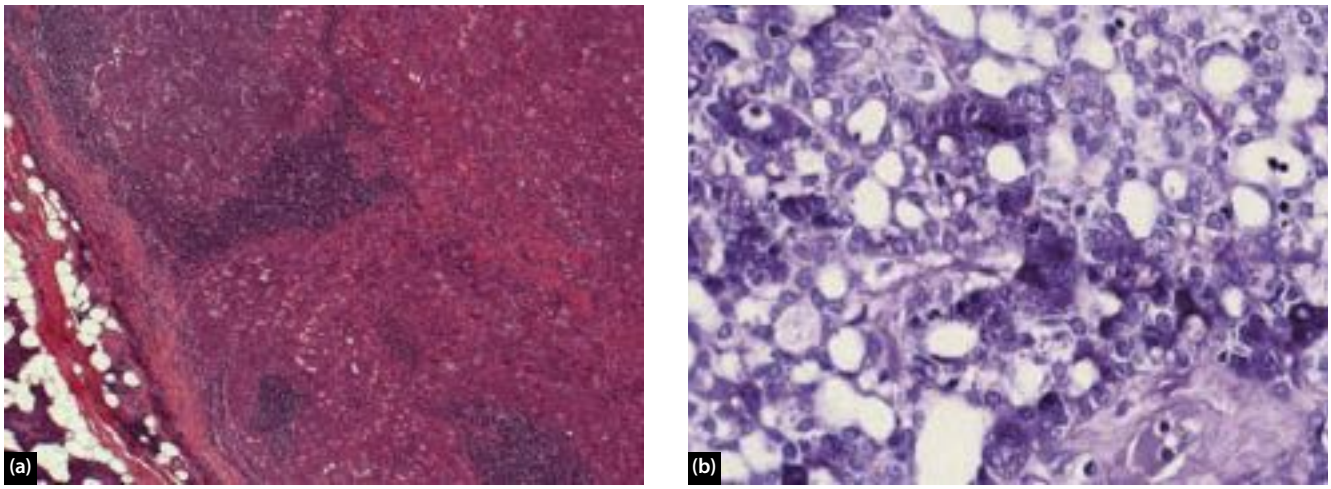


Figure 26.14 Acinic cell carcinoma. **(a)** Sheets of serous acinar cells arranged in a lobular pattern, note the lymphoid stroma (H&E stain, low magnification). **(b)** Microcystic pattern acinic cell carcinoma, there are a few serous acinar secretory cells containing purple zymogen granules (dPAS stain, high magnification).

growth pattern and the lack of histological characteristics of other salivary adenocarcinomas. The malignant epithelium can display various architectural features including glandular, ductal, papillary, solid and nest-like. There may be clear cell change and/or mucinous differentiation. The tumours can also be graded into low, intermediate and high, based on the degree of gland formation, cellular pleomorphism and mitotic count:

- Low-grade tumours have easily identifiable gland and duct-like structures. There is usually a single cell type with small nucleoli, abundant cytoplasm, distinct cell borders and little nuclear pleomorphism with few mitoses. This can occasionally lead to a benign diagnosis if the invasive growth is not identified.
- Intermediate-grade tumours also have easily identified gland and duct-like structures. Unlike low-grade tumours, there is greater nuclear pleomorphism with more mitoses.
- High-grade tumours tend to be solid, with areas of haemorrhage and necrosis. Unlike low- and intermediate-grade tumours, the gland and duct-like structures are much sparser. The cells are much more abnormal and varied. Cellular features include frequent atypical mitoses and enlarged, hyperchromatic, pleomorphic nuclei.

ADENOID CYSTIC CARCINOMA

Epidemiology

Adenoid cystic carcinoma (ACC) accounts for approximately 10–12% of all malignant salivary gland tumours and is the most common malignant tumour of the submandibular gland. It represents approximately 5% of parotid neoplasms and 30–50% of minor salivary gland neoplasms. There is no sex predilection and it is usually seen in patients in their 40s to 60s, rarely in patients under 20 years old. [11–13]

Macroscopic appearance

The tumour is usually a poorly circumscribed solid white tumour. ACC infiltrates into surrounding soft tissue, muscle and bone, sometimes directly through lymph node capsules.

Microscopic appearance

There are often two recognizable malignant cell subpopulations representing epithelial and myoepithelial components. Three growth patterns have been described but many tumours are mixed.

Tubular pattern represents the most differentiated form of ACC.[41] Small nests of cells form few true glandular or tubule-ductal spaces and occasional cords.

Cribriform pattern is the most common pattern and most tumours will contain areas displaying this pattern even if not the predominant type. In addition to true gland lumina containing secretions, cells group to form multiple pseudocysts (pseudolumina) containing mucoid basement membrane material. The overall pattern resembles 'Swiss cheese' (**Figure 26.15**). This architecture represents an intermediate level of cellular proliferation and biological aggressiveness.[41]

Solid pattern is the least common type and unlike the other two types there are few glandular spaces. Cells in the solid type tend to be larger and more pleomorphic with mitoses, interspersed with areas of necrosis. A biphasic cell population may not be apparent and without at least some better-differentiated fields, it may be impossible to arrive at the diagnosis.

ACC may be graded according to the predominant growth pattern:[11–13]

- Grade I, mostly tubular with some cribriform elements
- Grade II, either entirely cribriform or cribriform/tubular with less than 30% solid component
- Grade III, any tumour with more than 30% solid growth.

Low-grade ACC pursues a pernicious course typified by relentless, troublesome local recurrence, ultimately presaging

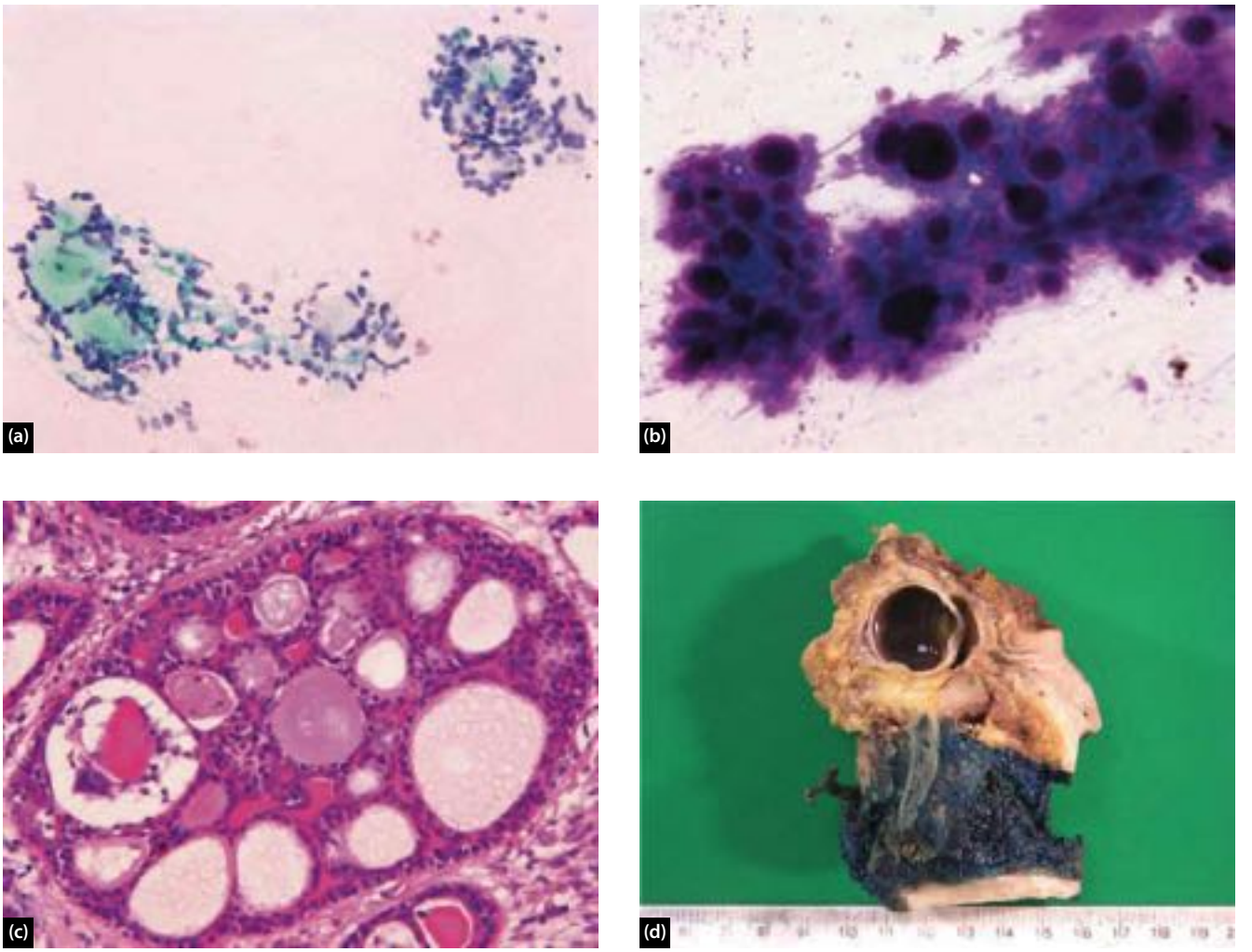


Figure 26.15 Adenoid cystic carcinoma (ACC). **(a)** FNAB illustrating cribriform microbiopsies. The characteristic hyaline basement membrane globules are pale in this preparation (Pap stain, medium magnification). **(b)** Cytology showing similar features albeit with striking intense staining of the hyaline globules (May–Grunwald-Giemsa (MGG) stain, medium magnification). **(c)** Classical cribriform ACC demonstrating pseudolumina filled with variably dense basement membrane type droplets, together with true gland lumina, either empty or containing sparse secretions (H&E stain, high magnification). **(d)** Right maxillectomy and orbital exenteration, for recurrent ACC.

wider dissemination after a prolonged interval of years or even decades. Many malignant salivary gland tumours show a propensity for perineural growth, though this is characteristic for ACC, the latter commonly visualized microscopically some considerable distance beyond what would be regarded as adequate surgical clearance. This neurotropism may radiate in a tentacular fashion well beyond the main body of the tumour. Positive surgical resection planes are, therefore, sometimes an unexpected and unwelcome feature of pathology reports, as this signifies inevitable local recurrence. Obversely, the histological suggestion of surgical clearance is not particularly reassuring. High-grade (solid) ACC is an aggressive, destructive malignancy.

CARCINOMA EX PLEOMORPHIC SALIVARY ADENOMA

Carcinoma ex-pleomorphic adenoma arises from within a pre-existing PSA or at the site of a previous pleomorphic adenoma.

Epidemiology

Carcinoma ex-pleomorphic adenoma is not uncommon and accounts for approximately 12% of all salivary gland malignancies and 6.2% of all pleomorphic adenomas.[42] Risk factors for malignant transformation of a pleomorphic adenoma include older age of patient (mean, 61 years), male sex, prolonged duration of tumour and multiple recurrences.[12, 43] It commonly affects the parotid gland and, rarely, the sublingual gland.

Macroscopic appearance

Carcinoma ex-pleomorphic adenoma tends to be larger than its benign counterpart. Tumours tend to be poorly circumscribed, firm, tan-white and extensively infiltrative masses. They can occasionally be well circumscribed and appear encapsulated. The 'ghost' of a pre-existing adenoma is often identified, sometimes alluded to by a dense, occasionally mineralized, scar. The malignant component tends to radiate centrifugally from this nidus, if present (**Figure 26.16**).



Figure 26.16 Carcinoma ex-pleomorphic salivary adenoma. Cut surface of a longstanding adenoma seen centrally forming a discrete, cream, elastotic scar with focal calcification. This is part-circumferentially surrounded by peripheral lobules of tan carcinoma ex-adenoma.

Microscopic appearance

The malignant element of a carcinoma ex-pleomorphic adenoma typically comprises high-grade adenocarcinoma or salivary duct carcinoma often with squamoid differentiation, but other specific subtypes of salivary carcinoma are seen and these may on occasion be monotypic rather than mixed. The benign pleomorphic adenoma component can be difficult to identify, may require extensive sampling and in some cases it may never be identified. The association of pleomorphic adenoma, carcinoma and sarcoma (carcinosarcoma, true malignant mixed tumour) is very rare. Invasion of tumour through the original lesion's capsule carries prognostic significance and has been classified as:[11–13]

1. Intracapsular carcinoma
2. Minimally invasive carcinoma (less than 4–6 mm invasion)
3. Widely invasive carcinoma.

In principle, (1) and (2) have a favourable prognosis compared to (3), although the precise cut-off point to define a category of invasion with minimal metastatic potential is controversial. Ordinarily, pleomorphic adenomas may show peripheral permeative growth, lymphatic tumour embolus, necrosis and focal internal cytonuclear atypia without signifying malignant transformation. Caution should be exercised in the interpretation of such features if prior FNAB has been attempted. Such tumours are sometimes termed 'atypical pleomorphic adenoma' and generally behave no differently from their more typical counterparts.

MOLECULAR PATHOLOGY OF SALIVARY GLAND TUMOURS

In recent years, a number of genetic alterations have been associated with salivary gland neoplasms.[12] Specifically, the presence of chromosomal translocations and their gene fusions have been used to aid diagnosis (**Table 26.9**).

TABLE 26.9 Chromosomal translocations in salivary gland tumours[12]

Salivary tumour	Fusion oncogene	Diagnostic utility
Pleomorphic adenoma	PLAG-1 fused to CTNNB1, TCEA1 or others	*PLAG-1* abnormality in 30% of tumours
Mucoepidermoid carcinoma	CRTC1-MAML2 (>80%) CRTC3-MAML2 (<10%)	Present in low and intermediate grade tumours
Adenoid cystic carcinoma	MYB-NFIB MYBL1-NFIB	Present 80–90% of tumours
Secretory carcinoma	ETV6-NTRK3	Defines the entity

These molecular alterations can be detected by fluorescence *in situ* hybridization (FISH), PCR or DNA sequencing. Recently, secretory carcinoma, a low grade salivary gland carcinoma, has been described and is defined by a translocation (12;15)(p13;q25) leading to formation of an ETV6-NTRK3 fusion oncogene. In the past, these cases were likely diagnosed as acinic cell carcinomas. It is hoped that such molecular information will facilitate accurate diagnosis and produce new insights into the management of these interesting and rare tumours.

Lymphomas

Lymphoma is the second most common primary malignancy occurring in the head and neck region. Approximately 25% of all extra-nodal lymphomas occur in the head and neck. Thus, although in the UK the overwhelming majority of haematolymphoid tumours, predominantly lymphomas and leukaemias, are managed by specialist haemato-oncology multidisciplinary teams, head and neck surgeons are frequently involved in the initial diagnosis of lymphoma. It is, therefore, important that the head and neck pathologist possesses a sound working knowledge of lymphoproliferative conditions and their differential diagnosis.

It is beyond the scope of this chapter to delve into the complexities of lymphoma diagnosis and the interested reader is referred to the comprehensive World Health Organisation (WHO) classification of tumours of haematopoietic and lymphoid tissues (4th edition, 2008), which is internationally recognized, periodically reviewed and updated.[44,45] This takes a multiparameter approach to classification incorporating clinical, morphological and immunophenotypical features plus genetic studies into account with the expectation that the schema will continually evolve and be refined over time. Lymphomas are broadly divided into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). HL is characterized by Reed–Sternberg cells and is subdivided into classical HL (incorporating nodular sclerosing, mixed cellularity, lymphocyte-rich and lymphocyte-depleted subtypes) and nodular lymphocyte predominant HL, according to site of involvement, clinical features, growth pattern, presence of fibrosis, composition of cellular background, number and/or degree of atypia

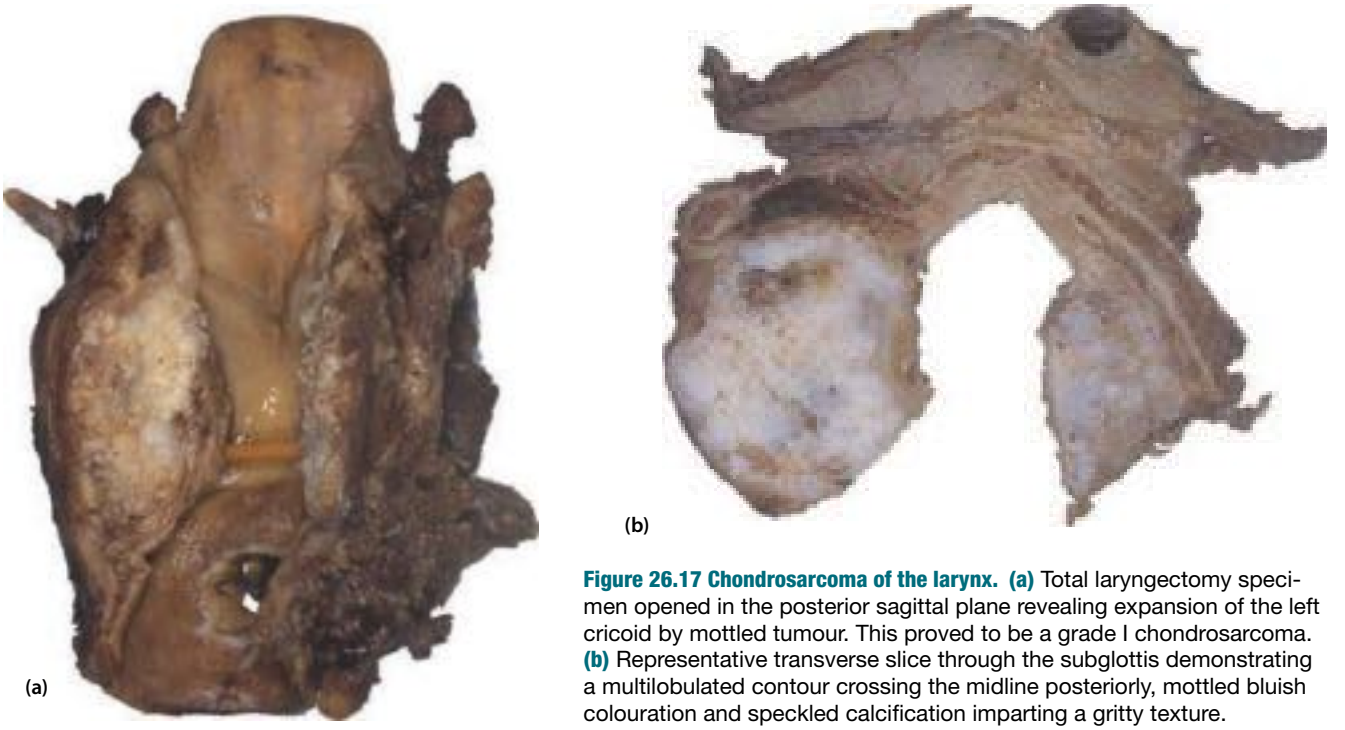


Figure 26.17 Chondrosarcoma of the larynx. (a) Total laryngectomy specimen opened in the posterior sagittal plane revealing expansion of the left cricoid by mottled tumour. This proved to be a grade I chondrosarcoma. **(b)** Representative transverse slice through the subglottis demonstrating a multilobulated contour crossing the midline posteriorly, mottled bluish colouration and speckled calcification imparting a gritty texture.

of the tumour cells and frequency of EBV infection. The immunophenotype of the neoplastic cells in these classical HL subtypes is identical. Around 85% of NHLs are B-cell lymphomas, which include chronic lymphocytic leukaemia/small lymphocytic lymphoma, follicular lymphoma, marginal zone lymphoma, the latter often extranodal involving the mucosa-associated lymphoid tissue of Waldeyer's ring. Diffuse large B-cell lymphoma is the most common aggressive NHL. Mantle cell lymphoma and Burkitt lymphoma are aggressive NHLs sometimes seen in the head and neck region. Plasma cell neoplasms, most commonly plasma cell myeloma and extramedullary plasmacytoma, are occasionally encountered in the head and neck region. Cutaneous T-cell NHLs (e.g. mycosis fungoides) may affect head and neck skin, but are rarely seen at mucosal sites. Extra-nodal NK/T-cell lymphoma is strongly associated with EBV infection and shows a predilection for the upper aero-digestive tract, typically the nasal cavity. Its angiocentric and angio-destructive nature may mimic the histological features of granulomatosis with polyangitis.

Malignant mesenchymal tumours

Malignant mesenchymal tumours (sarcomas) are uncommon in the head and neck region, but include:

- fibrosarcoma
- malignant fibrous histiocytoma
- leiomyosarcoma
- rhabdomyosarcoma
- liposarcoma
- angiosarcoma
- Kaposi sarcoma
- malignant peripheral nerve sheath tumour
- synovial sarcoma
- chondrosarcoma (**Figure 26.17**)
- mesenchymal chondrosarcoma
- osteosarcoma
- chordoma.

Neuroectodermal tumours

MUCOSAL MALIGNANT MELANOMA

Mucosal malignant melanoma is a rare tumour that originates from neuroectodermal-derived melanocytes.[46] Between 15% and 20% of malignant melanomas arise in the head and neck region, but the vast majority, over 80%, are of cutaneous or upper aerodigestive tract origin. Mucosal malignant melanoma represents merely 0.5–3% of malignant melanomas from all sites.[10] Common sites for mucosal malignant melanoma include the sinonasal tract and the oral cavity, particularly the palate. It is more common in men, but this finding is not consistent, and the tumour affects a wide age range (20–80 years).

Macroscopic appearance

Mucosal melanomas are usually pigmented and colour ranges from a light tan to black depending on the amount of melanin production, though amelanotic examples do occur.

TABLE 26.10 Hyams' grading classification of olfactory neuroblastoma[14]

Histological feature	Grade I	Grade II	Grade III	Grade IV
Architecture	Lobular	Lobular	May be lobular	May be lobular
Mitoses	Absent	Present	Prominent	Marked
Nuclear pleomorphism	Absent	Present	Prominent	Marked
Neurofibrillary matrix	Prominent	Present	May be present	Absent
Rosettes	Homer–Wright rosettes	Homer–Wright rosettes	Flexner–Wintersteiner rosettes	Flexner–Wintersteiner rosettes
Necrosis	Absent	Absent	Present	Prominent

Microscopic appearance

They typically comprise epithelioid and/or spindle cells. Plasmacytoid, rhabdoid, small cell, giant cell, balloon cell, neurotropic and desmoplastic variants are recognized. The cells are markedly pleomorphic and may contain pigment. Nucleoli are conspicuous and intra-nuclear inclusions are typical. An adjacent inflammatory infiltrate and necrosis can also be present. Melanocytic atypia or melanoma *in situ* may be observed in the background mucosa.

With few exceptions, the cells show nuclear and cytoplasmic immunoreactivity for S100 protein. MelanA, HMB-45 and SOX10 are usually positive. Epithelial markers are negative, although up to 10% of melanomas may show focal cytokeratin reactivity. The desmoplastic variant of melanoma may be negative for all these markers. Mucosal melanomas usually do not harbour BRAF v600E mutations and consequently are unlikely to benefit from vemurafenib targeted treatment.[12]

OLFACTORY NEUROBLASTOMA

These are uncommon malignant tumours of the upper nasal cavity affecting specialized olfactory mucosa and arising from the superior turbinate, cribriform plate and superior one third of the nasal septum. The reported incidence is four cases per million with a bi-modal distribution in the second and sixth decade, and no sex or racial predeliction.[12]

Macroscopic appearance

Macroscopically, olfactory neuroblastoma appears as a soft, polypoidal, highly vascular mucosa-covered mass.

Microscopic appearance

The malignant cells are uniform, with small round nuclei, scant cytoplasm and possess finely stippled (salt and pepper) chromatin. Hyams' classification system divides olfactory neuroblastoma into four types (**Table 26.10**).[14] The better-differentiated (grade I and II) examples are sometimes termed 'aesthesioneuroblastoma'. Homer–Wright pseudorosettes are formed by cells mantling

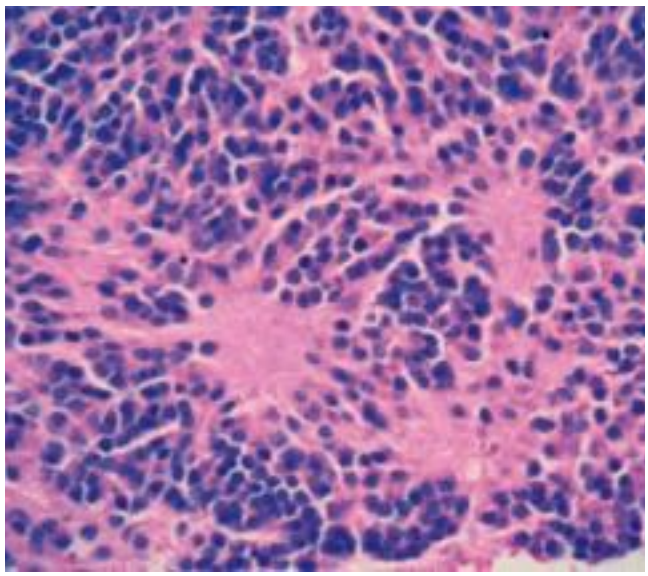


Figure 26.18 Grade I/II olfactory neuroblastoma. Loosely cohesive, uniform, small cells including two Homer–Wright pseudorosettes centred on fibrillary neuropil material. Mitoses are inconspicuous. There is no necrosis (H&E stain, high magnification).

solid, fibrillary neuropil stroma (**Figure 26.18**). Flexner–Wintersteiner rosettes consist of cells surrounding an empty pseudolumen. Other tumours may form perivascular rosettes encircling blood vessel lumina. IHC may aid discrimination between this and other primitive neoplasms (so-called round blue cell tumours), such as lymphoma, Ewing's tumour, melanoma, Merkel cell tumour, rhabdomyosarcoma, nephroblastoma, retinoblastoma and primitive neuroectodermal tumour (PNET).[47] There is, however, no single specific positive marker.

Metastases to the head and neck region

Uncommonly, a primary tumour at another body site may metastasize to the head and neck region. The most commonly encountered are carcinomas of the lung, colon, breast, prostate and kidney (**Figure 26.19**).[11]

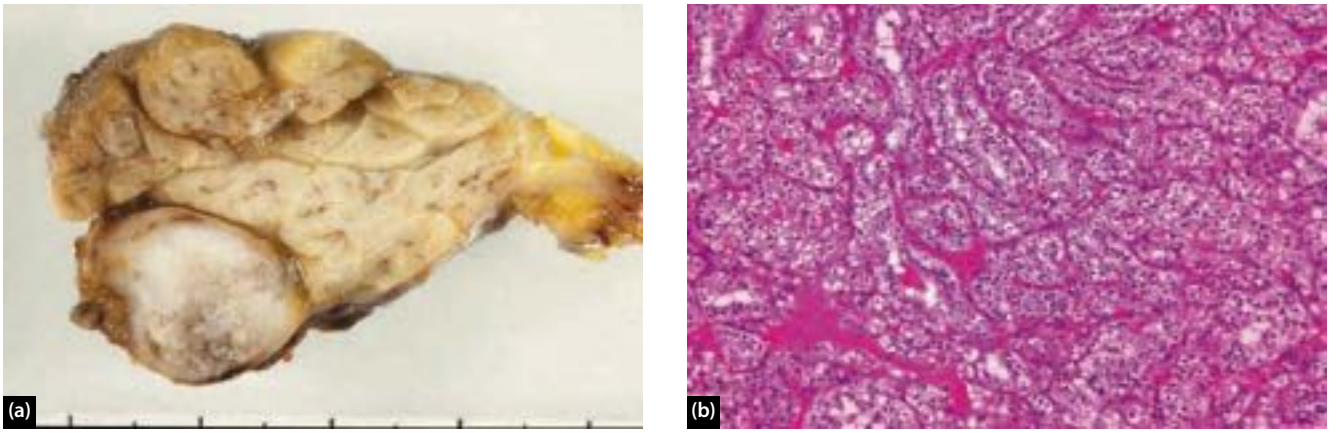


Figure 26.19 Metastatic disease in the head and neck. **(a)** Cut surface of a metastatic deposit effacing a para-parotid lymph node. **(b)** Metastatic clear cell carcinoma from an occult renal primary tumour (H&E stain, medium magnification).

KEY POINTS

- Meticulous and judicious pathological evaluation of head and neck biopsies is essential for effective clinical management.
- Morphological assessment by light microscopy constitutes the cornerstone of cytological and histological diagnosis, supplemented by immunohistochemical and molecular tests, where relevant.
- Fine-needle aspiration biopsy (FNAB) is a comparatively low-risk, cost-effective preliminary investigation in the management of head and neck lumps.
- The histocytopathological diagnostic process is historically heuristic in nature, correlating clinical, pathological, radiological and treatment outcome observations using population and individual case study evidence.
- The head and neck pathologist must be an accomplished practitioner familiar with perhaps the widest range of organ/tissue-specific diseases out of all the anatomically defined site-specific specialities.
- Tumour site, type, grade and stage are major determinants of survival in head and neck cancer, which is influenced to a lesser degree by a variety of other patient-specific and tumour-specific factors. These are accommodated in the UICC/AJCC TNM classification.
- Squamous cell carcinoma in its numerous manifestations accounts for upwards of 90% of all malignant head and neck tumours with lymphoma as the second most common malignancy.
- Fine-needle aspiration biopsy (FNAB) is an established first-line investigation for suspected head and neck cancer. It is rapid, comparatively atraumatic, requires minimal specialized equipment and in experienced hands offers good clinical efficiency, as long as awareness of its inherent limitations and pitfalls is maintained by all concerned.
- The application of immunohistochemistry and molecular markers with deeper understanding of their genetic basis continues to yield insight into the pathogenesis of many head and neck tumours. Their routine use in diagnosis, treatment and prognostication is likely to become more widespread in the future.

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CHAPTER 27

OPEN CONSERVATION SURGERY FOR LARYNGEAL CANCER

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SEARCH STRATEGY

Data in this chapter may be updated by a searching using the following keywords: laryngeal squamous cell carcinoma, conservation laryngeal surgery, laryngeal preservation and functional outcome.

INTRODUCTION

Cancer of the larynx is a debilitating disease associated with significant functional morbidity (breathing, speech, swallowing) and mortality. The preferred treatment choice for laryngeal cancer patients provides the optimal balance between disease control prospects and likelihood of treatment-related functional, aesthetic and psychological side effects.[1] Total laryngectomy (TL) with or without post-operative radiation treatment (PORT) offers the best chances for cure across all types and stages of laryngeal cancer.[2] However, TL is associated with severe functional sequela (**Table 27.1**), significant reduction in quality of life (QOL) and low patient acceptance. As such, it is now mostly applied to clinical scenarios in which TL is the sole viable treatment option, such as advanced (T4a) tumour stage, or in cases of locally recurrent disease after radiation treatment. The majority of laryngeal cancers can be treated with more conservative treatment alternatives that provide an improved risk-benefit ratio compared to TL.[3]

Primary radiation therapy can be applied for definitive treatment of early (T-stage 1/2) laryngeal cancers, yielding local control and larynx preservation rates of 85–95%, acceptable voice outcomes, and the possibility for surgical salvage in cases of failure.[4] However, in advanced stage III/IV laryngeal cancer, its efficacy is considered too low (40% local control), even in the setting of intensified radiotherapy protocols (accelerated, hyperfractionated, or intensity-modulated RTx).[5] The efficacy of radiation therapy for advanced laryngeal cancer can be improved significantly with the addition of cisplatin-based chemotherapy.[5] Evidence from several randomized controlled trials suggests that chemoradiation treatment of advanced laryngeal cancer provides control rates that approximate those of TL, while larynx preservation can be achieved in 66–84% of these patients.[5,6] Although the introduction of primary (chemo) radiation has revolutionized the treatment of laryngeal cancer, increasing follow-up data demonstrate a progressive accumulation of significant treatment sequela over time.[7,8] These include laryngeal oedema, fibrosis,

TABLE 27.1 Sequela of total laryngectomy

Communication	• Loss of normal speech quality and quantity
Airway closure	• Loss of airway protection • Loss of effective cough • Loss of ability to strain
Nasal airflow	• Loss of nasal air conditioning • Loss of smell and taste • Loss of normal nasal homestasis and immunity
Swallowing	• Loss of normal constrictor muscle anatomy • Loss of normal sensory and motor innervation • Fibrosis of constrictor muscles • Loss of upper esophageal sphincter
Psychological	• Body image issues with stoma

TABLE 27.2 Comparison open partial laryngectomy (OPL) and transoral laser microscopic laryngectomy (TLM) and (chemo)radiotherapy (C)RTx for laryngeal cancer

	OPL	TLM	(C)RTx
Oncologic results	Equivocal	Equivocal	Equivocal
Speech quality	Poor	Good	Good
Swallowing	Normal	Normal	Impaired
Complications	Respiratory	Rare	GI ,respiratory, systemic
Feeding tube	Temporary – 1 month	No	5–10%
Tracheostomy	Temporary – 1 month	No	Occasional
Treatment duration	1 day	1 day	7 weeks
Costs	Medium cost	Low cost	Expensive
Repeated treatment	No. Only salvage TL or RT	Yes. Repeated laser possible	No. Only salvage TL

laryngeal neuropathy, dysphagia, vocal cord (VC) dysfunction and airway insufficiency. Surgical salvage is required in a significant number of cases with these complications.

Conservation partial laryngeal surgery may provide the best balance between cure and complications for a significant proportion of laryngeal cancer cases.[2, 9] Traditional partial laryngeal surgery is performed through an open transcervical approach, but recent technical developments (refinement of medical laser applications, introduction of endoscopes, microscopes and image guidance systems) have led to the development of less invasive transoral laser microsurgery (TLM) (**Table 27.2**). In early laryngeal cancers, partial laryngectomy provides local control and laryngeal preservation (LP) rates that are at least equivalent to primary radiation therapy, and acceptable functional outcome.[9] In advanced laryngeal carcinomas, open partial laryngectomy can be applied in selected cases and the role of TLM is increasing, both showing oncologic and functional efficacy that may outperform chemoradiation.[9] With appropriate patient selection, partial laryngectomy can be applied in approximately 30–50% of radiorecurrent laryngeal cancers as well, providing surgical salvage and avoiding TL in these patients.[10] Although transoral laser surgery has now largely replaced open partial laryngectomy, several indications for open partial laryngectomy remain, and mandate comprehension and inclusion into the armamentarium of the head and neck surgeon. This chapter will focus on the open conservation surgical approaches for laryngeal cancer, while transoral laser partial laryngectomy will be discussed in Chapter 23, Anatomy as applied to transoral surgery.

SURGICAL GOALS OF OPEN PARTIAL LARYNGECTOMY

The goal of open partial laryngectomy is complete tumour removal, while preserving the functional integrity and separation of larynx and pharynx. This delicate balance requires a detailed understanding of anatomical relationships, a high level of surgical finesse and familiarity with different conservational surgical options, as well as experience on the part of the surgeon.

Complete tumour removal is defined by acquisition of microscopically negative margins of resection upon pathological examination. Chances of local control are decreased significantly in the absence of pathologically negative margins after conservation laryngeal surgery. Survival may be compromised in this setting as well, as the altered post-surgical anatomy and tissue plane boundaries both facilitate unconventional tumour spread, and hamper early detection of tumour recurrence, making salvage treatment more complicated. In recurrent laryngeal cancers after (chemo)radiation, microscopic complete tumour removal is clearly critical, as adjuvant treatment options are limited. In radiation-naive laryngeal cancers amenable to conservation laryngeal surgery, the treatment plan is generally geared towards avoidance of alternative larynx preservation strategies including primary (chemo) radiation treatment and its sequelae, and this focus can only be maintained upon confirmed negative margins. For these reasons, conservation laryngeal surgery should only be attempted when acquisition of negative margins can be anticipated with confidence.

Successful functional outcome after conservation laryngeal surgery is dependent on three factors that need to be addressed during surgery: (i) establishment of an adequate airway with functional (neo)glottic valve; (ii) recreation of adequate post-operative pharyngeal anatomy for optimal swallowing; and (iii) maintenance of an optimal laryngopharyngeal coordination between motor input and sensory feedback to guarantee airway protection and adequate swallowing.[12] Airway patency after conservation laryngeal surgery may be reduced due to post-operative oedema, fibrosis, redundant mucosa and poorly positioned laryngopharyngeal anatomical constituents, all of which may lead to delayed decannulation, upper and lower airway complications, and need for reoperation. All of these potential issues need to be carefully addressed during surgery and in the post-operative period. Moreover, preservation of a competent (neo)glottic valve is critical for

successful conservation surgery, as it decreases aspiration, improves subglottic pressures and coughing ability, and optimizes speech.

The cricoarytenoid unit is the basic functional unit of the larynx. The cricoarytenoid unit consists of an arytenoid cartilage, the cricoid cartilage, the associated musculature and the nerve supply from the superior and RLNs for that unit. It is the cricoarytenoid unit, not the vocal folds, that allows for physiologic speech and swallowing without the need for a tracheostoma. Preservation of at least one functional unit allows organ preservation laryngeal surgery.[11] Careful preservation of the RLN, which can be placed at risk during dissection in the area of the cricothyroid joint, is one critical aspect of an intact cricoarytenoid unit. Scarring in and around the cricoarytenoid joint should be prevented, as it increases chances for arytenoid fixation. Also, scarring of key intrinsic laryngeal muscles such as the lateral cricoarytenoid muscle should be prevented. In some cases, arytenoid resuspension may be necessary to optimize its anatomical position.

Optimal pharyngeal anatomy is critical for successful swallowing after partial laryngectomy, and although this is in part dependent on wound healing, it can be influenced intra-operatively. Important aspects of this goal are optimal resuspension of the larynx to the tongue base, in a fashion that takes into account the delicate balance between airway protection by a posteriorly 'overhanging' tongue base and airway obstruction by the same. In addition, the shape and position of the pyriform sinuses are vital to unobstructed food passage and reduction of aspiration risk. The normal configuration of the pyrifom sinuses is disrupted by partial laryngectomy and often, resuspension of the pyriform sinuses is needed. This recreates the anatomic funnel shape of the hypopharyngeal inlet and decreases the chance for obstruction by redundant mucosa after the procedure. Cricopharyngeal myotomy can further help facilitate unobstructed food passage and can be considered in case the constrictor lumen feels narrow on finger dilatation.

Proper neurological coordination is also vital for adequate swallowing, not only in terms of intact motor function of swallowing muscles but also in terms of intact sensory feedback of the passing food bolus. Therefore, a detailed knowledge of the neurological anatomy is critical for surgical success. The bulk of laryngopharyngeal sensation above the VCs is provided by the inner branches of the SLNs. These enter the laryngopharynx through the thyrohyoid membrane and, once inside, run in the pharyngoepiglottic fold from lateral to medial direction. Next, they give off two major branches on each side of the larynx, which run in the laryngopharyngeal submucosa in an inferior direction towards the pyriform sinuses and VCs and form an anastomosing bilateral network. Although many laryngeal extensions of the SLN will be sacrificed during partial laryngectomy, great care should be taken to leave the main trunk of the nerve, and the pharyngeal extensions intact. During partial laryngectomy, there are several procedural steps at which the SLN may be at risk. These include: (i) separating infrahyoid muscles from hyoid, in which too much lateral dissection will damage the nerve; (ii) trans-vallecular pharyngotomy, in which too much lateral dissection will damage the nerve; (iii) freeing the superior horn of the thyroid cartilage where the SLN lies just superolateral to the tip of the thyroid horn; and (iv) releasing inferior constrictor and pyriform sinus mucosa from the paraglottic space. Experience and careful surgical technique contribute significantly to optimized functional outcome after partial laryngectomy.[12]

TYPES OF OPEN PARTIAL LARYNGECTOMY

Open partial laryngectomy was first performed by Theodor Billroth in 1874, and several different modifications have since been developed. These procedures can be applied to both glottic and supraglottic disease, and they include vertical and horizontal oriented procedures. Procedures that can be applied to glottic disease include several vertical hemilaryngectomy modifications and horizontal supracricoid laryngectomy with cricohyodoepiglottopexy (CHEP). For supraglottic disease, supraglottic laryngectomy and supracricoid laryngectomy with cricohyoidopexy (CHP) have been developed, both of which are horizontally oriented procedures.

Vertical partial laryngectomy

This procedure may be an anterolateral, frontolateral or anterior vertical partial laryngectomy.

ANTEROLATERAL HEMILARYNGECTOMY

Anterolateral hemilaryngectomy has been developed for glottic tumours that do not involve the anterior commissure. This procedure involves exposure of the thyroid cartilage below the strap muscles, and the ipsilateral perichondrium overlying the thyroid cartilage is lifted in order to preserve it. Next, vertical cuts through the laryngeal cartilage in a midline laryngofissure fashion are performed (**Figure 27.1**). The majority of the ipsilateral thyroid cartilage, true VC, portions of the subglottic mucosa and false cord are removed. The extent of resection depends on the pre-operative and intra-operative assessment of tumour extent. The strap muscles are closed over the residual perichondrium to form a pseudocord. A tracheostomy and feeding tube are generally required for 3–7 days.

If the anterior commissure is involved, a frontolateral or anterior partial laryngectomy can be done.

FRONTOLATERAL HEMILARYNGECTOMY

In frontolateral vertical laryngectomy (**Figure 27.2**), the vertical cartilage cut in the thyroid is performed 1 cm paramedian from the anterior midline on the contralateral thyroid ala. This procedure is preferred if the tumour involves the VC on the ipsilateral side, the anterior commissure and up to one-third of the contralateral VC.

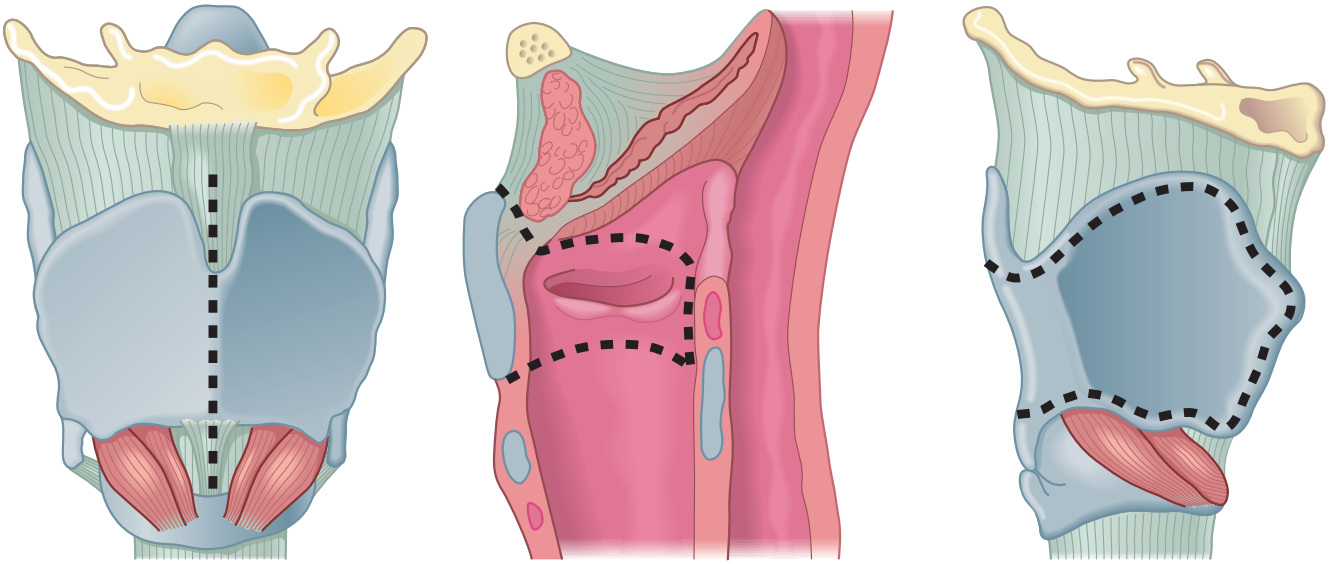


Figure 27.1 Anterolateral midline hemilaryngectomy.



Figure 27.2 Frontolateral and anterior hemilaryngectomy.



Figure 27.3 Silastic keel.

ANTERIOR VERTICAL LARYNGECTOMY

Anterior vertical laryngectomy makes use of two paramedian thyroid cartilage incisions, each positioned approximately 1 cm paramedian from the anterior midline. This procedure may be preferred for an anterior commissure tumour that involves no more than the anterior third of one or both VCs. After tumour removal, the remnant posterior VCs are reattached to the anterior aspects of the remnant thyroid ala that are approximated in the midline. Formation of anterior laryngeal web is avoided with the use of a silastic keel, positioned at the anterior commissure between the VCs (**Figure 27.3**), which is removed endoscopically after 4 weeks.

Supracricoid partial laryngectomy (SCPL) with cricohyoidoepiglottopexy (CHEP)

Glottic tumours that extend across the midline through the anterior commissure are not suitable for vertical hemilaryngectomy if they involve more than the anterior third

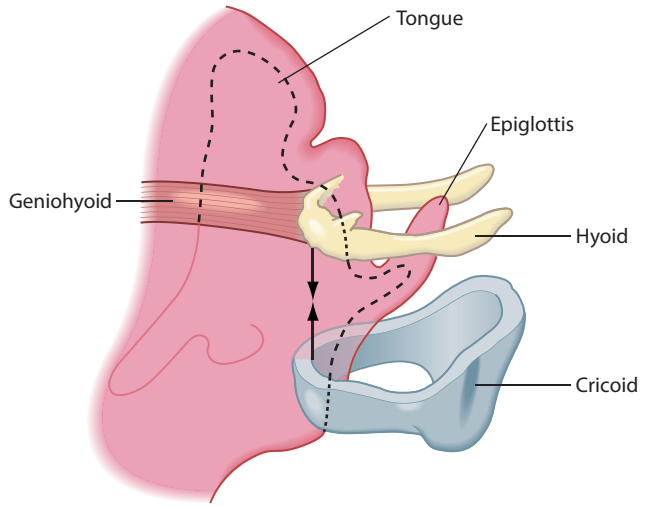


Figure 27.4 Supracricoid laryngectomy.

of the opposite VC. Supracricoid partial laryngectomy offers the possibility for resection of both true cords, both false cords, the entire thyroid cartilage, paraglottic spaces bilaterally, and a maximum of one arytenoid (**Figure 27.4**). Essential goals of this operation include careful preservation of the bilateral superior laryngeal nerves (SLNS) for optimal sensation during swallowing, functional preservation of at least one recurrent laryngeal nerve (RLN) for airway closure during attempted speech and swallowing, and adequate recreation of a functional neoglottic valve.[12, 13] The best functional results are achieved when both arytenoids are functionally and anatomically preserved. However, functional separation of the airway and the alimentary tract is possible provided at least one arytenoid is preserved.[14] Reconstruction is achieved by approximation of the hyoid bone to the cricoid with three absorbable sutures: one in the midline and two sutures placed 1 cm paramedian (to avoid suturing the lingual arteries, hypoglossal and SLN nerves). Also, the suprahyoid epiglottis is preserved and reapproximated to the cricohyoidopexia. Essential in the understanding of the post-operative functional status, is the fact that the orientation of the airway has undergone a 90% turn in the horizontal plane, from its anatomic slit-like antero-posterior orientation to a transverse or T-shaped orientation of the neoglottic valve. The latter can be closed sufficiently by the mobile arytenoid(s). A temporary tracheostomy is required, and most patients can be decannulated early. A nasogastric feeding tube is used in most patients, and can be removed in 4–6 weeks in most patients, provided that stringent swallowing therapy is in place. A PEG tube is advocated in older patients, patients with a single preserved arytenoid, patients with a history of radiation, or hypoglossal, SLN or RLN dysfunction. Quiet aspiration is present in most patients, and stringent oral hygiene is a prerequisite for pulmonary health.

Supracricoid partial laryngectomy (SCPL) with cricohyoidopexy (CHP) for supraglottic cancer

This operation is suitable for supraglottic carcinomas not amenable to horizontal supraglottic laryngectomy due to: (i) glottic level involvement through the anterior commissure or ventricle; (ii) pre-epiglottic space invasion; (iii) decreased cord mobility; (iv) limited thyroid cartilage invasion; or for glottic carcinomas with epiglottic or pre-epiglottic extension. The operation is essentially the same as described above, but an essential difference is the absence of the epiglottic remnant for reconstruction. Naturally, post-operative swallowing is delayed, and the rate and intensity of long-term aspiration is increased.

Horizontal supraglottic partial laryngectomy (HSPL)

In this procedure, the epiglottis, (part of the) hyoid bone, pre-epiglottic space, thyrohyoid membrane, upper half of the thyroid cartilage, aryepiglottic fold and part of the false cords are removed (**Figure 27.5**). The vallecula

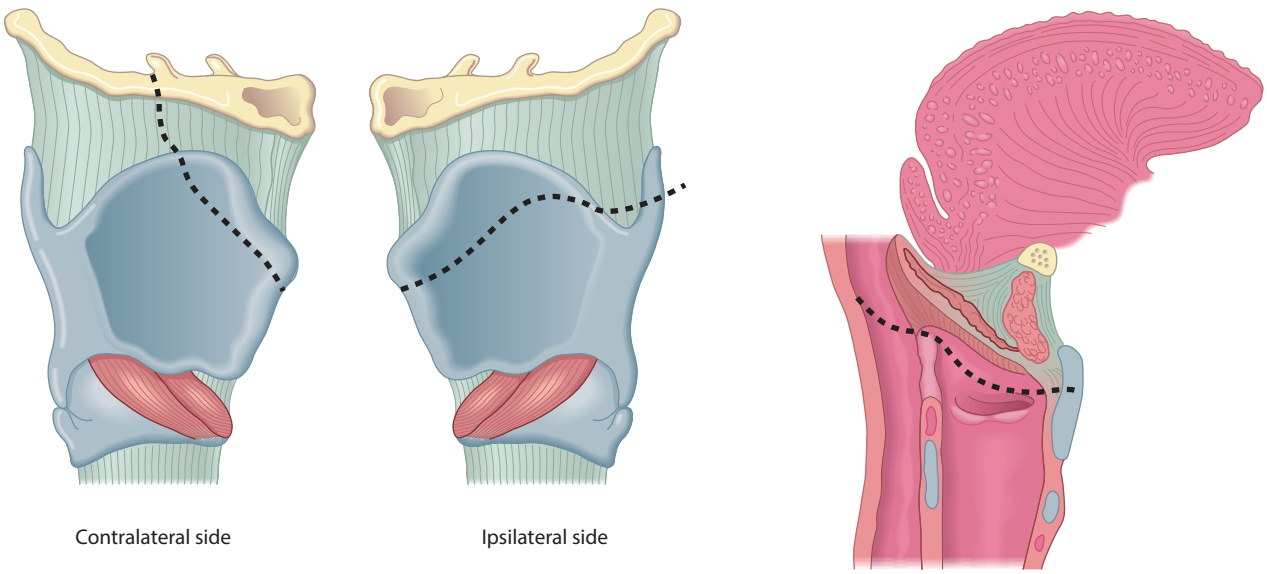


Figure 27.5 Horizontal supraglottic laryngectomy.

is transected superiorly, the ventricles inferiorly and the aryepiglottic folds laterally. Closure is by approximating the base of tongue to the lower half of the thyroid cartilage and closing the posterior false cord mucosa to the medial pyriform sinus mucosa. A temporary tracheostomy is required. Bilateral selective neck dissection is carried out at the same time, for the high rate of (contra) lateral neck metastasis from supraglottic cancers. In this procedure it is important to identify and preserve the internal and external branches of the superior laryngeal nerve. The tongue base sutures are placed in the midline and 1 cm off the midline to avoid damage to the hypoglossal nerves and lingual arteries.

Extended vertical hemilaryngectomy and reconstruction with a neovascularized tracheal autograft

Delaere et al.[15] described this two-stage technique for extended hemilaryngectomy defects involving up to half of the cricoid cartilage. Stage 1 involves tumour resection, following which reconstruction is performed using the cranial 4 cm of the cervical trachea, which is wrapped with the fascial part of a free vascularized fasciocutaneous flap from the forearm. After 4–8 weeks, the enveloped tracheal segment acquires sufficient vascular connections between the fascial soft tissue flap and trachea to allow interruption of the intrinsic blood supply, and thus grafting of the isolated segment of the trachea to the hemilaryngeal defect. Outside of select centres,[16, 17] this technique has not found widespread use; however, favourable oncologic outcomes have been reported. Significant refinements of the procedure have been presented since its original description.

Supratracheal laryngectomy

Laccourreye et al.[18] described a modification of conventional SCPL for tumours with anterior subglottic extension by removing the cricoid ring for anterior glottic tumours, which paved the way for 'functional' supratracheal partial laryngectomies (STPL), whose current version was described in 2006 by Rizzotto et al.[19]

This is aimed at laryngeal cancers with subglottic extension: this procedure involves resection of the entire glottic and subglottic sites along with the thyroid cartilage sparing both or at least one functioning cricoarytenoid unit (i.e. half of the posterior cricoid plate, with the corresponding arytenoid and the intact inferior laryngeal nerve on the same side). Inferiorly, the limit of resection encompasses the cricoid reaching the first tracheal ring. The resultant operation can be a tracheohyoidopexy – subtotal removal of the larynx maintaining one or two cricoarytenoid units and subsequent 'pexy' of the hyoid to the first tracheal ring or tracheohyoidoepiglottopexy – resection with preservation of the suprahyoid epiglottis and maintaining one or two cricoarytenoid units, followed by suspension of the tracheal ring to the epiglottis and hyoid bone.

Succo et al.[20] have detailed the indications and technique in detail; 5-year outcomes for 142 patients are as follows: overall survival from 71% to 85% and disease-specific survival from 86% to 95% based on tumour stage. Experience with this procedure has not been forthcoming from other centres.

INDICATIONS FOR OPEN PARTIAL LARYNGECTOMY

Since most laryngeal tumours are amenable to multiple different treatment options that are equally effective, the choice of therapy is determined by patient- tumour- and physician-related factors, as summarized in **Table 27.3**. In the case of untreated early laryngeal cancers, the treatment choice is typically made between primary radiation and conservation laryngectomy. Although no randomized trials have been completed, retrospective data suggest that surgical therapy may be superior with regard to local control, larynx preservation and disease-specific survival.[8, 9] When surgical treatment of early laryngeal cancers is preferred, TLM has now largely replaced open partial laryngectomy due to its lower morbidity, better voice quality, better swallowing and lower cost. Specifically, retrospective data indicate that the improved voice outcomes after TLM are similar or superior to that after primary radiation therapy.[9] Open partial laryngectomy for untreated early laryngeal cancer is indicated in select patients in whom a strong surgical preference exists, patients that fit the criteria for open partial laryngectomy (see 'Patient factors' below) but cannot be operated by TLM due to transoral inaccessibility or lack of expertise with transoral resections. In the case of advanced laryngeal cancer, a choice exists between upfront TL, (chemo) radiation and conservation laryngectomy. Although no randomized controlled trials of primary surgery vs

TABLE 27.3 Factors impacting upon choice of treatment in laryngeal cancer

Tumour factors	• Anatomic location • Extent • Volume • N-stage • M-stage
Patient factors	• Age • Comorbidity • Pulmonary reserve • Alcohol/tobacco exposure • Other cancers • Occupation • Expectations • Social support system • Motivation • Intellect • Preference • Travel distance
Physician factors	• Availability of resources • Availability of physician • Experience/skill • Comfortability • Preferences/beliefs

chemoradiation treatment have been completed, observational data and incomplete trial data indicate that TL is superior to chemoradiation in terms of oncological outcomes, whereas functional outcome data are immature at this time.[2, 6, 7, 21, 22] In well-selected patients, oncological outcomes of partial laryngectomy in this setting are similar to that of TL, and functional outcomes are better.[9, 23–25] As the experience with TLM for advanced laryngeal cancer is relatively immature, and performed routinely only in a few expert centres around the world, a choice for conservation laryngeal surgery in these patients would entail open partial laryngectomy in most instances. In advanced laryngeal cancers, open partial laryngectomy would thus be indicated in patients that fit the criteria for open partial laryngectomy, reject TL, and are unfit for or reject chemoradiation. In the setting of radiorecurrent laryngeal cancers, TL is the standard of care used by most centres. However, retrospective evidence indicates that 30–50% of patients could be safely managed by open partial laryngectomy, using stringent selection criteria.[10, 26–28] The experience with TLM in the radiorecurrent setting is immature, as retrospective evidence suggests local control rates are significantly inferior to those obtained using open partial laryngectomy.[29] Specific criteria that guide the consideration of open partial laryngectomy are described below. Careful consideration of these factors is important to minimalize the incidence of positive surgical margins, conversion to TL, and poor functional or medical outcome after surgery.

Patient factors

Stringent patient selection is critical for successful open partial laryngectomy. Patients undergoing partial laryngectomy are at increased risk of (clinically significant) post-operative aspiration, and resultant (life-threatening) pneumonias.[11, 30] This risk is exacerbated by poor wound healing, local infection and fistula formation. Although the risk and severity of aspiration varies between different types of open partial laryngectomy, patients with poor pulmonary function such as severe COPD, asthma or restrictive lung disease are poor candidates for partial laryngectomy.[12] Pre-operative assessment of lung function is mandatory in all patients considered for open partial laryngectomy but, as a general rule of thumb, the risk of pulmonary complications is well predicted by a patient's (in)ability to walk two flights of stairs.[12] Patients suffering from chronic microvascular or immunologic diseases that may impair wound healing (e.g. transplantation patients or diabetes mellitus) are also poor candidates for open partial laryngectomy for reasons described above. In patients with previous definitive radiation therapy to the cervical region, anticipation of significantly delayed wound healing should be incorporated as a factor into the treatment consideration. However, carefully selected patients may benefit from conservation surgery provided that post-operative support is stringent. The extent of the radiation portals and the total dose received are vital pieces of information that may help predict the extent of post-operative wound healing issues. For example, patients with locally recurrent T1/T2 laryngeal SCC that have been treated with standard 70 Gy IMRT-based radiation therapy and a limited glottic radiation therapy portal are expected to be better candidates for partial laryngectomy than patients treated with accelerated radiation therapy, chemoradiation, and patients with extensive base of tongue and supraglottic laryngeal carcinomas whose radiation plans have included skull base-to-clavicle type of portals. Finally, patient non-compliance is a major contraindication for partial laryngeal surgery. Successful outcome of partial laryngectomy is influenced by adequate pre-operative counselling, management of patient/family expectations, and early involvement of the speech and swallowing pathology department. Patients must be able to understand the complexities of conservation laryngeal surgery, and must be able to understand the implications of and give consent for intra-operative conversion to TL. The post-operative course after conservation laryngectomy is long and intense, and the patient (and family) should be willing and able to play an active role in speech and swallowing rehabilitation, and be available for frequent oncologic follow-up.

Tumour factors

Tumour factors that influence the choice for partial laryngectomy are primarily related to tumour location and extent within the laryngopharyngeal complex. Histological factors do not influence the choice for partial laryngeal surgery much, and most histological subtypes of laryngeal cancer can be managed successfully by this procedure. The anatomical boundaries of successful partial laryngectomy vary per type of laryngectomy, as listed in **Table 27.4.** These criteria are general guidelines, but they are not absolute and the extent of and the indications for the operation expand as the experience of the surgeon increases.

Application of vertical hemilaryngectomy is generally limited to tumours on one side of the glottic larynx, or at least not extending beyond the anterior third of the contralateral VC. The lesion should preferably not involve more than the vocal process or antero-superior part of the ipsilateral arytenoid in order to gain sufficient margin. Subglottic extension should not be more than 5 mm posteriorly, and 10 mm anteriorly (because of sufficient margin at the cricoid cartilage), whereas cranial extension should not exceed beyond the upper limit of the lateral extension of the sinus of Morgagni. Involvement of the epiglottis is a contraindication because it increases risk for pre-epiglottic space invasion. Selected patients with fixed VCs due to paraglottic extension or arytenoid fixation may benefit from hemilaryngectomy, but involvement of the RLN as a cause of cord fixation is a contraindication for hemilaryngectomy. Cartilage invasion is a contraindication to hemilaryngectomy, although microscopic erosion may not be. Hemilaryngectomy can also be applied to highly selected hypopharyngeal tumours that originate from the medial or lateral walls of the piriform sinus with secondary laryngeal extension, provided that the piriform sinus apex is free.

TABLE 27.4 Anatomic boundaries impacting on selection of open partial laryngectomy approach

	Vertical partial laryngectomy	Supracricoid laryngectomy	Supraglottic laryngectomy
Anterior	AC or anterior one-third opposite cord	Pre-epiglottic space	5 mm margin from AC
Posterior	Ipsilateral vocal process	Inter-arythenoid region	Inter-arythenoid and post-cricoid region free
Cranial	Upper limit of sinus of Morgagni	Base of tongue	Base of tongue
Caudal	Subglottic extension < 5 mm (posterior)/ < 10 mm (anterior)	Subglottic extension < 5 mm (posterior)/ < 10 mm (anterior)	Entrance sinus of Morgagni
Medial	Tumour does not cross midline (except anterior)	NA	NA
Lateral	Ipsilateral thyroid ala	Thyroid cartilage	Thyroid cartilage
General (relative) contraindications	• Epiglottic involvement • RLN involvement • Cartilage invasion • Piriform sinus apex involvement	• Extension to pharyngeal wall, vallecula, or base of tongue • Cartilage invasion • Bilateral arythenoid involvement • Bulky pre-epiglottic space involvement	• Bilateral arythenoid involvement • Cord impairment • Cartilage invasion • Tumour > 3 cm • Piriform sinus apex involvement • Impaired tongue mobility

The basis for successful supracricoid laryngectomy is that the tumour can be removed with sufficient margin, while preservation of the cricoid cartilage and at least one functioning arytenoid will provide the basis for rehabilitation. In practice, supracricoid laryngectomy results are improved significantly when both arytenoids can be preserved and sacrifice of one arytenoid should only be attempted in highly selected patients. Limitations of supracricoid laryngectomy success include gross thyroid cartilage destruction, gross pre-epiglottic space involvement, interarytenoid, bilateral arytenoid involvement, one fixed arytenoid (indicating cricoarytenoid joint invasion), subglottic extension exceeding 5 mm posterior or 10 mm anterior, and extension to pharyngeal wall, vallecula or base of tongue.

HSPL is indicated for supraglottic tumours, within the confines of parameters described in **Table 27.4**. Contraindications include less than 5 mm margin from the anterior commissure, impaired VC mobility, interarytenoid or bilateral arytenoid involvement, cartilage invasion, impaired tongue mobility, pyriform sinus apex involvement, or lesion size greater than 3 cm. HSPL may also be applied to the treatment of highly selected patients with primary tumours of the base of the tongue, medial wall of pyriform sinus and pharyngeal wall tumours, that exhibit secondary extension to the supraglottic larynx.

In patients with tumour recurrence after radiation therapy, careful assessment of tumour dimensions is even more critical, as most radiorecurrent laryngeal tumours recur with higher T-stage disease compared to the original tumour.[9] The majority of such patients require salvage TL to circumvent tumour dimensions. But salvage partial laryngectomy is possible in approximately 30–50% of patients with radiorecurrent glottic carcinomas who do not progress on therapy or who recur within the original tumour confines.[10, 26, 27] Such patients require careful endoscopic and radiologic assessment with CT scan to exclude tumour progression beyond the original tumour confines. Zbaren et al. provided a pathologic basis for this paradigm.[31] These authors showed that recurrent tumours in pathologic salvage laryngectomy specimens often exhibited dispersion of microscopic tumour deposits far beyond the original tumour confines. This observation emphasizes the underestimation of recurrent tumour dimensions on clinical and radiological examination and explains the local failure after removal of radiorecurrent tumours despite reported negative margins. Based on these findings, we recommend intra-operative frozen section analysis to help delineate the boundaries of the recurrent tumour and the need for intra-operative conversion to TL should margins be positive. Salvage supracricoid laryngectomy with CH(E)P is an alternative for larger lesions, which can give local control rates of 83.3%.[28, 32]

Of those with supraglottic carcinoma treated with radiotherapy who fail, only 30% may still be suitable for salvage conservation surgery.[9, 10, 27, 33] For supraglottic cancers, salvage partial laryngectomy by horizontal supraglottic partial laryngectomy or supracricoid partial laryngectomy and CHP is possible if the tumour has not extended beyond the original site as assessed endoscopically and by CT imaging. However, in contrast to glottic carcinomas, supraglottic tumours after RT have usually received a significant radiation dose to the base of tongue, pharyngeal constrictors and neck. This increases poor healing and fistula complications as well as post-operative swallowing problems due to fibrosis. An exaggeration of this situation is provided by (chemo)radio-recurrent base of tongue tumours with supraglottic extension (or supraglottic tumours with base of tongue extension), in which removal of the base of tongue in conjunction with HSPL in the setting of significant post-radiation fibrosis and wound healing issues increases the risk of post-operative swallowing and aspiration problems to unacceptable levels. Poor oncologic results have also been observed in supraglottic carcinomas, especially after salvage HSPL.[9, 10, 27, 33] As a result of these factors, salvage surgery for supraglottic cancer often requires a TL.

ONCOLOGICAL OUTCOMES OF OPEN PARTIAL LARYNGECTOMY

Most laryngeal carcinomas amenable to conservation laryngeal surgery can be treated with TLM or (chemo)radiation therapy with equal efficacy. Randomized controlled trials comparing different treatment modalities have not been completed. Recently, a British and an Australian trial were closed early due to accrual issues, suggesting that randomized data to answer the question will not be available within the near future.[9] Data on the outcome of partial laryngeal surgery are available from several large retrospective studies, and can be compared to that of patients treated with (chemo)radiation or TLM. Local control and LP are the primary aim of the different treatment modalities, as disease-specific death from early laryngeal cancer is approximately 1–3%. Therefore, they are primary clinical endpoints of interest in scientific analyses of oncologic results.

A systematic review of 53 articles[33] including 5061 patients treated with open partial laryngectomy reveals that pooled local control rate at 24 months was 89.8% (95% CI: 88.3–91.2%). The pooled larynx preservation rate (assessed in 3171 patients) was 90.9% (95% CI: 8.8–92.7%). These overall data compare favourably with (chemo)radiation results and suggest that partial laryngeal surgery should be offered as an alternative treatment option to patients who qualify for organ preservation treatment.[9, 33] However, the outcome of laryngeal treatment is heavily influenced by disease stage, and anatomic location within the larynx and should therefore be analyzed within the context of these factors.

Glottic carcinomas

Treatment with open partial laryngectomy gives local control and LP rates in T1 SCC between 92% and 100%.[9] In T2 tumours, local control is between 69% and 93%, but LP after salvage surgery still reaches 93%.[9] TLM in T1 tumours achieves 85–95% local control rates and 95–99% LP after 5 years, whereas in T2 tumours, 65–85% local control rates and 83–96% LP after 5 years can be obtained.[9] Retrospective data suggest that the oncologic efficacy of primary radiation treatment may be similar to surgery, with local control between 85% and 93% and LP 89–96% for T1 tumours, and local control 57–80% and LP 73–82% for T2 laryngeal SCC.[9] Adversaries of radiation treatment further argue that the RT efficacy for early laryngeal cancers may be significantly overestimated, due to the fact that up to 30% of patients that qualify for and are included in primary RT treatment protocols, may have been cured by their pre-RT biopsy already.[9]

Factors that influence outcome in the early laryngeal cancer setting include anterior commissure (AC) involvement and VC mobility impairment.[9] Although tumours with AC involvement are unlikely to harbour a more aggressive clinical course, AC involvement does complicate surgery, which may account for decreased survival rates.[9] Steiner et al. suggested that local control may be 10–15% worse when AC is involved, and LP may be 5% worse overall.[34, 35] Their results were confirmed in a follow-up study of 444 patients.[34, 35] Laccourreye et al. reported 23% local failure after vertical partial laryngectomy in 416 cases of AC involvement.[36] When SCPL-CHEP was applied, local failure was improved to 98%, but most patients had also received an induction chemotherapy regimen in their series.[37, 38] No differences were found when open vs TLM approaches were compared in cases with AC involvement.[9] On the other hand, Peretti did not find differences in local control with or without AC involvement.[39] A literature review by Herranz suggests that all three treatment options have similar results when involvement of the AC is present.[9, 40]

Impairment of VC mobility is also an adverse predictor of outcome in early laryngeal SCC. T2 tumours with impaired VC mobility exhibit reduced local control and LP that is more akin to that of T3 carcinomas with VC fixation.[9] Local control rates in cases with true vocal cord (TVC) impairment or fixation treated with open partial hemilaryngectomy ranges between 52% and 76%.[9] However, local control and LP can be improved to 95% in this patient population with the application of supracricoid laryngectomy as per French data, but the majority of these patients received induction chemotherapy and many received post-operative RTx.[9] Studies using TLM have shown that local control was 74% in T2b, and 68% for T3 tumours, whereas LP was 85% in both groups.[9] Ultimately, 5-year local control was 87%, and disease specific survival (DSS) was 62% in both groups. Three large case series with more than 100 patients each of T2N0 disease, with organ preservation rates of 84–96%, are observed for T2N0 tumours.[41–43]

Limited literature data exist on TLM for more advanced laryngeal carcinomas. Recently, Steiner et al. published on 226 cases of T3 SCC showing a local control and LP rate of 71.4% and 87% respectively.[23] Radiation therapy reaches local control in TVC impairment between 60% and 76%, and LP is 70–80%.[9] The collective data suggest that the oncologic efficacy of open partial laryngectomy is similar to that of TLM, but superior to primary RTx.

Supraglottic carcinomas

In the case of supraglottic carcinomas, high local control rates are obtained for selected early tumours treated with open partial laryngectomy.[44] HSPL has local control of 90–100% for T1 tumours, and 80–97% for T2 tumours.[9] For T3 SCC, local control rates are 71–94%.[9] In T4 lesions, local failure is approximately 67%.[9] Therefore, HSPL should be considered with extreme caution in T3 and T4 lesions. Literature data suggest that application of supracricoid laryngectomy with CHP may improve these figures slightly,[9] where local control can be as high as 96% of patients, at the expense of significant aspiration. The reason for these favourable results is the *en bloc* resection of bilateral paraglottic spaces, pre-epiglottic space and thyroid cartilage. However, it should be noted that a majority of patients in these studies received induction chemotherapy before supracricoid laryngectomy, which may influence the data. Several small studies describe the results of TLM for supraglottic tumours showing similar results to the open approach.[9] Radiotherapy results show that T1 supraglottic tumours have local control of 75–100%, and

T2 have local control of 62–83%.[9] T3 supraglottic carcinomas are rarely treated with RT alone, following the demonstration of improved local control with the addition of concurrent chemotherapy in the 91–11 trial.[5] Comparable to the data on glottic tumours, these retrospective data suggest that open partial laryngectomy as primary treatment for supraglottic cancers achieves equal success rates compared to TLM, but is superior to primary RT.

Radiorecurrent carcinomas

Radiorecurrent tumours treated with partial laryngectomy are virtually all T1 and T2 tumours, as more advanced lesions typically require TL. A recent meta-analysis of the English language literature reported a pooled local control rate of 86.9% (95% CI: 84–89.5%), identified from 26 articles including 560 patients undergoing open partial laryngectomy for radiorecurrent disease.[10] The pooled mean larynx preservation rate derived from analysis of 502 patients was 83.9% (95% CI: 80.7–87%). When excluding patients with supraglottic tumours, the pooled salvage laryngectomy rate was 9.2% (95% CI: 7.4–11.1%) in 253 patients, and the pooled laryngectomy rate for aspiration was 4.4% (95% CI: 2.2–7.4%) in 224 patients. For 159 T1 ($n=124$) and T2 ($n=35$) tumours treated with vertical hemilaryngectomy the pooled local control rate was 84.4% (95% CI: 84.4–84.4%), and the mean LP rate was 85%. Virtually all total laryngectomies were performed for oncologic salvage. One hundred and forty-nine patients treated with supracricoid laryngectomy had pooled local control 93.9% (95% CI: 91.8–95.8%), and mean LP rate was 83.1%; 2.6% of patients required a TL for aspiration. Disease-free survival was similar between these treatments, approximately 80–85%. Few studies have analyzed the efficacy of supraglottic laryngectomy for radio-recurrent laryngeal SCC. These studies suggest that the local control rates are significantly lower than observed for the other procedures.[10, 27, 32] The experience with TLM for radiorecurrent disease has thus far been small, and insufficient for adequate comparison. Altogether, the literature suggests that approximately 30–50% of patients with radiorecurrent SCC may benefit from salvage open partial laryngectomy, with control rates equal to TL in these patients.

COMPLICATIONS AND FUNCTIONAL OUTCOMES OF OPEN PARTIAL LARYNGECTOMY

Post-operative complications

Complications after conservation laryngeal surgery can be categorized into local (wound infection, dehiscence, fistula, chyle leak), swallowing (dysphagia, stricture), airway (aspiration pneumonia, laryngeal stenosis, laryngeal oedema, granuloma formation, surgical emphysema, perichondritis, CH(E)P breakdown) and systemic (cardiac, pulmonary, renal, infectious, metabolic). The rate of overall complications after partial laryngectomy is approximately 20%.[11, 29, 45, 46] Of these, local complications are most common, and occur between 8% and 11%. The fistula rate after partial laryngectomy is between 2.5 and 4%. Prior RT is the most important predictor of local complications including fistula formation. Local complications after salvage partial laryngectomy have been described to occur in 24% of patients, and fistula formation after salvage partial laryngectomy occurs in approximately 14% of cases. Ganly et al. found that prior RT was associated with a 13-fold increase in local complications and fistula formation after partial laryngectomy, an increase that was statistically significant.[45] Several authors have suggested that the type of partial laryngeal surgery is a predictor of complications, with more extensive laryngeal surgery such as supracricoid laryngectomy associated with increased complication rates in univariate statistical analysis.[11, 29, 45, 46] It is currently unclear whether type and extent of open partial laryngeal surgery is an independent predictor of the complication rate in multivariate analysis, but it is clear that partial laryngeal surgery using TLM is associated with significantly lower rate of complications due to less extensive dissection, and absence of need for tracheostomy and percutaneous feeding tube in most patients.[9]

Functional outcomes

Functional outcome of partial laryngeal surgery is influenced by pre-operative factors (patient age, comorbidity, pulmonary status, tumour stage and pre-operative radiation), intra-operative factors (location and extent of resection) and post-operative factors (patency of airway, patency and mobility neoglottic valve, patency and mobility of (oro) pharynx, laryngopharyngeal sensation and the position of the laryngeal remnant in relation to the base of the tongue). Although functional recovery after partial laryngectomy can be qualified in several ways, decannulation rate, time to permanent decannulation, permanent gastrostomy rate, and need for TL for intractable aspiration (functional laryngectomy) are some of the more objective parameters to describe it.[22] Also, these parameters are unequivocal, objective, and allow for reliable comparison with other treatment modalities. Parameters to objectify voice outcomes are less well defined, although this is obviously also a critical outcome parameter after partial laryngectomy.

A recent meta-analysis of primary open partial laryngectomy outcomes[33] found that the pooled decannulation rate among 3955 patients derived from analysis of 42 studies was 96.3% (95% CI: 94.9–97.6%). The permanent gastrostomy rate among 2000 patients derived from 20 studies was 2% (95% CI: 0.9–3.6%). The functional laryngectomy rate was 1.7%. Although the authors excluded salvage partial laryngectomy patients, they did not stratify their data by type of partial laryngectomy. Functional outcome data from individual series demonstrate that tracheostomy and nasogastric feeding tubes can generally be removed within 1–2 weeks from vertical partial laryngectomy, and (temporary) gastrostomy tubes are generally not necessary after this type of procedure.[38, 45, 47, 48] Voice outcome data after VPL have not been reliably assessed. In the case of HSPL and SCPL, post-operative aspiration and airway issues are

generally more severe, and temporary but clinically significant aspiration (Pearson grade 2–3) has been described in 10–20% of patients, while aspiration pneumonia has been reported in 10% of patients after SCPL.[11, 29, 46, 49, 50] Time to decannulation and nasogastric feeding tube removal approaches 1–2 months in most patients, but most patients will require 6–12 months to approach their normal eating habits. Prophylactic gastrostomy tube placement is recommended in a proportion of high-risk patients after SCPL and HSPL. Predictors of clinically significant aspiration include arytenoid sacrifice, advanced age, radiation therapy and CHP reconstruction. However, the rates of permanent gastrostomy, tracheotomy and functional laryngectomy are below 5% in experienced hands and well-selected patient populations. SCPL causes an inevitable change in voice quality, which can adversely affect the QOL, especially in female patients.[51, 52] The functional outcome after salvage partial laryngectomy has been described in a recent meta-analysis.[10] The pooled mean decannulation rate among 315 patients was 95.1% (95% CI: 92.6–97.2%). Eleven studies reported a mean or median time from surgery to decannulation that ranged from 7–31 days. Other functional outcome data could not be reliably extracted from the included studies. In comparison to open partial laryngectomy, the functional outcomes of TLM partial laryngectomy are significantly better.[9] This can be attributed to avoidance of tracheotomy, preservation of hyoid bone and supra/infrahyoid muscles and pharyngeal muscles, and preservation of the extralaryngeal portions of the SLNs. Functional outcomes after RT and chemo-RT are not well described. Recently, publication of the long-term data of the RTOG 91–11 trial[7] demonstrated that 43% of patients had severe late complications, including an 18% rate of pharyngeal dysfunction (significant swallowing problems in 17–25% in concurrent CRTx group, and 13% of the induction chemotherapy and radiation alone groups), and 25% rate of laryngeal dysfunction. In addition, a 7% unexplained death rate was observed in the chemoradiation treatment arm, in addition to a high rate of complications associated with salvage TL after chemoradiation treatment. These data suggest that partial laryngeal surgery is superior to (chemo)radiation in terms of functional adequacy after treatment.

CONCLUSION

Organ preservation management for laryngeal cancer is a desirable treatment avenue. Although no phase III trials have been completed, our best available evidence suggests that conservation laryngeal surgery is a safe approach in selected patients, and is superior to primary (chemo) radiation in these patients in terms of oncologic efficacy and functional outcome. Although TLM is the preferred approach for conservation laryngectomy patients due to its less invasive nature and lower rate of complications, a specific indication for open partial laryngectomy still exists in selected patients who qualify for conservation laryngeal surgery. These include transoral inaccessibility of the tumour, salvage after radiation treatment, and lack of expertise with TLM. For these specific indications, the skill of open partial laryngectomy is important and should remain in the armamentarium of the head and neck surgeon.

KEY POINTS

- Total laryngectomy offers the best chance for cure across all laryngeal cancer types and stages but has the poorest functional outcome.
- Conservative organ-preservation laryngeal cancer treatments include (chemo)radiation and conservation surgery including transoral laser-assisted microsurgery (TLM) and open conservation laryngeal surgery.
- Conservation laryngeal surgery offers better oncologic and (long-term) functional outcomes than (chemo)radiation in properly selected patients.
- TLM offers similar oncologic outcomes but has decreased complication rates and superior functional outcomes to open conservation laryngeal surgery.
- The spectrum of open conservation laryngeal surgery encompasses several different procedures categorized by their anatomic focus (glottis or supraglottic disease), anatomic extent and surgical orientation (horizontal or vertical).
- Indications for open conservation laryngeal surgery are guided by well-defined patient, tumour and physician factors.
- Functional pulmonary reserve is the most common limiting factor for successful conservation laryngeal surgery, as most laryngeal cancer patients feature significant degrees of COPD.
- The surgical goals of open conservation include attainment of negative margins and optimization of functional outcome through preservation of (a) structurally and functionally adequate airway, alimentary tract and neuromuscular coordination.
- Oncologic and functional outcomes of open conservation laryngeal surgery support its application in properly selected (chemo)radiation-naïve and (chemo)radio-recurrent laryngeal cancers.

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CHAPTER
28

MEASURES OF TREATMENT OUTCOMES

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SEARCH STRATEGY

A search strategy, developed for PubMed, combining MeSH terms for head and neck cancer, patient reported outcomes, treatment outcomes, health-related quality of life, voice, speech and swallowing was used.

INTRODUCTION

Outcome assessment constitutes an integral part of patient management. Modern healthcare systems demand robust outcome measures, which should be disease specific and reflect the concerns of the patient. Their measurement is compounded by the fact that patients, carers and healthy 'observers' have different opinions as to what constitutes the most favourable outcome.[1]

Historically, the success of head and neck cancer (HNC) treatment and treatment in general has often been described in terms of survival rates and disease control. However, since patients seek treatment on the basis of their symptoms rather than the underlying diagnoses, one can argue that survival alone cannot be considered truly reflective of the outcomes as it omits measures of function. This can often lead to a paradox of excellent results in medical terms, but unsatisfactory/unacceptable outcomes from the patient's perspective.

Outcomes can therefore be divided into survival outcomes and functional outcomes, which ultimately determine the quality of life (QOL) of a patient. QOL, which is another important concept in the arena of outcomes is discussed at greater length in Chapter 20, Quality of life and survivorship in head and neck cancer.

SURVIVAL OUTCOMES

Undoubtedly, survival remains the cornerstone of outcome assessment for HNC. Analysis of survival has the advantage that there can only be two categories: alive or dead and this outcome cannot be misrepresented. However, this measure is insensitive in diseases with low mortality and there are many inaccuracies in recording the cause of death. Most importantly it disregards functional outcomes and QOL.

'Time-to-event' analysis

Survival analysis is based on scientific fundamentals and techniques of statistics, which analyze 'time to event' and can be used for many outcomes apart from death (**Box 28.1**).

Two key facts should be recognized in time-to-event analyses. The distribution of the data is mostly non-parametric and thus appropriate statistical techniques should be used for analyses. Some patients do not experience the event either because they are lost to follow-up or they were still alive at the end of the study. These patients represent censored events or censored observations.[2]

The Kaplan–Meier survival curve is the most common means of expressing survival and other such binary events in a study group.[3] It is used to estimate survival rates and hazards from such incomplete data assuming that those censored subjects have the same prospect of survival as uncensored subjects. The median survival time is the time at which the cumulative survival is equal to 0.5. The log rank test provides methods for comparing two or more survival curves, but is only appropriate where relative mortality does not change over time (proportional hazards assumption).

BOX 28.1 Survival analysis

PARAMETERS OF SURVIVAL

- **Overall survival (OS)** – The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive.
- **Disease-free survival (DFS)** – The length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer. Also called *relapse-free survival.*
- **Progression-free survival (PFS)** – the length of time that a patient lives with the cancer, but it does not get worse.
- **Disease-specific survival rate** – The percentage of people in a study or treatment group who have not died from a specific disease in a defined period of time. The time period usually begins at the time of diagnosis or at the start of treatment and ends at the time of death. Patients who died from causes other than the disease being studied are not counted in this measurement.
- **Median survival (MS)** – The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that half of the patients in a group of patients diagnosed with the disease are still alive. Also called *median overall survival.*

ANALYSIS OF SURVIVAL

- **Kaplan-Meier survival curve** – Most common method used to estimate survival rates and hazards assumes with incomplete data, as seen with survival, that those censored subjects have the same prospect of survival as uncensored subjects.
- **Log rank analysis** provides methods for comparing two or more survival curves, but is only appropriate where relative mortality does not change over time (proportional hazards assumption).

FUNCTIONAL OUTCOMES

Functional outcomes define anatomical and physiological impairment, disability and handicap that occur secondary to a disease process or the treatments for these and can, ultimately result in a poor QOL.[4]

Functioning, disability and health

The World Health Organisation has classified functioning, disability and health based on the ICF (International Classification of Functioning, Disability and Health). This is a classification looking at the loss/limitation of function. Disability underscores the consequences arising from this loss of function and health, reflects the disadvantages experienced by the patients as a consequence of the impaired functions and disabilities and highlights the interaction with and adaptation to their environment and in relation to their peer group and society in general.

Treatment for HNC is likely to affect some of the most basic human functions – verbal communication, social interaction, eating and breathing. It is easy to see how speech and swallowing can be affected in patients undergoing resection for large oral cavity or oropharyngeal lesions and in the most extreme case of the laryngectomy. However, with the use of concurrent chemoradiotherapy showing approximately the same long-term survival, much emphasis has been placed on organ preservation.[6] Therefore, the clinical trade-off is no longer the length of life, but functional outcome and QOL. It should be noted that anatomical preservation does not guarantee function and patients experience several debilitating side effects with organ sparing treatment paradigms, where voice quality is reduced and swallowing problems are common due to the stiffening of tissues in the pharynx and upper oesophagus. A disease-specific QOL survey covering five domains (speech, eating, aesthetics, pain/discomfort and social/role functioning) demonstrated that speech and eating had the most impact on well-being.[7] It is estimated that as high as 35–75% HNC patients suffer from speech and swallowing problems after such treatment.[8]

Which measures to choose?

Currently, there are no outcome reporting standards for clinical practice or trials in HNC. The World Health Organisation (WHO) recommended as early as 1981 that as a minimum standard, oncology clinical trials should measure tumour and metastasis response, duration of response and adverse effects.[9] Furthermore, the publication of the International Classification of Functioning, Disability and Health for head and neck cancer (ICF HNC) provided a framework for classifying health and health-related domains for measuring health and disability at both individual and population levels.[10] Whilst survival outcomes are critical, health-related QOL and functional outcomes are given less consideration and measured in a far less consistent or rigorous manner.[11] As survival rates improve, however, survivorship issues become increasingly relevant.[12–16]

In the majority of cases, clinicians and trialists make decisions about which outcomes of treatment should be measured. As a result, the data collected and measured may not reflect outcomes of importance to patients, and the lack of standardization makes comparison of outcomes difficult, if not impossible. Small numbers, tumour heterogeneity and incidence of post-treatment functional deficits provide particular challenges when choosing outcomes for patients with SCCHN. For systematic reviewers and guideline developers, disparate outcome measurement precludes the synthesis of individual trial data in

meta-analyses, and much research thus fails to contribute to the evidence base.[17]

Core Outcome Sets (COS) have been proposed by the COMET initiative to ensure that outcomes important to both patients and clinicians are measured consistently, thus facilitating the synthesis and/or comparison of outcomes.[18] A COS is a minimum outcome reporting standard for use primarily in clinical trials, but also in audit and clinical practice that is specific to a clinical condition or area of healthcare.[19] The use of a COS does not preclude the measurement of other outcomes, rather it ensures that 'core' outcomes are measured consistently, allowing for the collection of more rigorous outcomes data.[18]

A COS has been developed for clinical trials in oropharyngeal squamous cell carcinoma (OPSCC) and is in the pre-publication phase.[20]

Once the outcomes to be included in a COS have been chosen, research to establish the best instruments for measuring the outcome must be undertaken. The **Co**nsensus-based **S**tandards for the selection of Health Measurement Instruments (COSMIN) initiative make recommendations about '*how*' the identified outcomes should be measured.[21] The COSMIN checklist can be used to appraise the methodological quality of studies on measurement properties and to check whether all important design aspects and statistical methods have been clearly reported.[21]

Multiple outcome measurement tools abound but there appears to be no consensus among clinicians regarding what to use and when. Choosing the most appropriate outcome measure is essential to evaluate both the effectiveness and efficacy of any treatment and rehabilitation. Outcome measurements may be subjective or objective, patient rated or clinician rated, and may take the form of questionnaire or instrument-based assessment. Ideally, specific, validated tools should be chosen.[22]

Increasingly, patient reported outcomes (PROs) are used. They measure how a patient feels or functions and are collected directly from the patient without interpretation by a clinician. They are often collected using measurement tools (PROMs) that assess the patient's view of their symptoms, functional status or QOL.[23] One could argue whether objective or subjective measures are more valuable, indeed there is poor correlation between objective and subjective measures of xerostomia in this patient population.[24]

MEASURES OF TREATMENT TOXICITY

A variety of scoring systems are used to measure toxicity, and the time points at which these are measured vary. Both acute and late toxicities are encompassed by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Effects.[22] Version 3.0 largely superseded the Late Effects of Normal Tissue (LENT SOMA) and Radiation Therapy Oncology Group- European Organisation for the Research and Treatment of Cancer (RTOG-EORTC) scales, and was updated to version 4.0, June 2010.[25] Late effects are generally accepted as those occurring 6 months beyond the end of treatment.

Xerostomia

Xerostomia is an acute and late adverse effect of radiotherapy to the head and neck, and is most often graded according to the toxicity criteria described above or as part of HR-QOL tools. Patients consider dry mouth to be a top priority after treatment for HNC. Eisbruch et al[26] implemented an 8-item self-reported xerostomia-specific questionnaire (XQ) in patients receiving parotid sparing IMRT. The XQ was found to be reliable and valid in measuring patient-reported xerostomia.

Shoulder dysfunction

Like xerostomia, shoulder dysfunction is most often measured as part of HR-QOL measures. No specific PROM exists.[26]

Voice or speech?

Voice and speech represent different ends of the same spectrum, explained by the source-filter theory. The larynx serves as the source of phonation thereby producing voice, while the vocal tract (oral cavity, oropharynx, nasopharynx, nasal cavity and paranasal sinuses) acts as a filter thereby altering the voice and shaping speech. Speech is the final outcome of voiced sound, which is characterized by resonance, nasality and articulation.[27] Cancers or treatments involving these sites will affect speech and not the voice.

MEASURES OF VOICE OUTCOMES

Voice is predominantly affected by laryngeal cancers or treatments affecting the larynx, directly or indirectly. There are numerous tools used for the evaluation of voice throughout the world (**Box 28.2**), but there exists no widely accepted voice outcome measure. Some of the commonly used tools are described in **Box 28.2.**

Questionnaire-based measures

Voice Handicap Index Voice Handicap Index (VHI)[28] is a validated, self-assessment scale that measures patient perception of the impact of dysphonia on various aspects of routine living. It is one of the most widely used voice questionnaires. It consists of 30 statements on voice-related aspects in daily life each with a scores ranging from 0 to 4. The maximum score is 120, values above 60 indicate a severe disability, those between 40 and 60 moderate disability and less than 40 mild or no disability. The questions are divided into three subscales or domains: physical, functional and emotional, with ten questions in each.

It has been used extensively as an outcome assessment tool in laryngeal cancer in both patients with a laryngeal and alaryngeal voice. VHI-based comparative voice outcomes following laryngeal cancers treated with either

BOX 28.2 Tools available for the assessment of outcome of voice

QUESTIONNAIRE BASED MEASURES

- Voice Handicap Index (VHI)[28]
- Voice Symptom Scale (VoiSS)[29]
- Voice Activity and Participation Profile (VAPP)[30]
- Voice Prosthesis Questionnaire[31]
- Vocal Handicap Index-10[32]
- Vocal Performance Questionnaire (VPQ)[33]

PERCEPTUAL MEASURES

- GRBAS rating scheme[34]
- Perceptual evaluation of alaryngeal speech

INSTRUMENT-BASED MEASURES

- Stroboscopy[35]
- Acoustic analysis of voice using inverse filtering and linear predictive coding[36]
- Electroglottographic (EGG)[37]
- Electromyographic analysis[38]

surgery or radiotherapy,[39] transoral laser excision of early laryngeal cancers,[40] endoscopic laser versus open resection,[41] supracricoid partial laryngectomy,[42, 43] alaryngeal voice[44] and chemoradiotherapy[45] and have all been published in the literature.

Voice Symptom Scale The Voice Symptom Scale (VoiSS)[29] is one of the most rigorously evaluated voice questionnaires. It contains 30-items to assess three aspects of voice: impairment, emotional and physical symptoms. The VoiSS is becoming more widely used in HNC patients to assess voice.[46, 48] In a study looking at patients with early glottic cancer treated by endoscopic resection or radiotherapy similar results were produced for the VHI, VoiSS or VPQ. The exception was the emotional subscale of the VoiSS, which gave better results for those treated with radiotherapy and in addition reflected the concurrent pharyngeal symptoms.[47]

Voice Activity and Participation Profile Voice Activity and Participation Profile (VAPP)[30] is a 28-item questionnaire validated in number of languages. It consists of five sections: self-perception of voice, effect on job, effect on daily communication, effect on social communication and effect on emotion. Each item uses a visual analogue scale 10 cm long ranging from not affected to always affected.

Voice Prosthesis Questionnaire The Voice Prosthesis Questionnaire[31] has been locally validated and looks specifically at the surgically voice-restored laryngectomee. It is a self-administered 45-point questionnaire and has sections relating to speech, leakage, valve changing, maintenance, QOL, humidification and hand-free issues.

Short-form self-assessment questionnaires

Long questionnaires can be time consuming to complete and the score may provide a degree of redundant information. They are useful research tools, but in the clinical setting concise, clinically useful self-report questionnaires are of more use. Two short-form, rigorously evaluated, voice-related scales are available, the Vocal Handicap Index-10 item questionnaire (VHI-10) and the Vocal Performance Questionnaire (VPQ).

Vocal Handicap Index-10 item questionnaire Item analysis of VHI by patients with voice disorders and controls identified the 10 most robust VHI items resulting in the creation of the Vocal Handicap Index-10 item questionnaire (VHI-10).[32] Similar to the VHI, a five-point item scale is used with scores ranging from 0 to 4, resulting in a total score of between 0 and 40.

Vocal Performance Questionnaire The VPQ[33] is a 12-item questionnaire which examines the physical symptoms and socio-economic impact of the voice disorder. The patient selects a statement that best answers each question. The statements are graded in terms of severity of vocal performance. A numerical score of 1–5 is assigned to each answer and these are summed to provide an overall score of vocal severity – maximum score 60 and minimum score 12.

These two short-form voice related scales (VPQ and VHI-10) use a single total score and correlate highly with one another.[48]

Perceptual measures

GRBAS The GRBAS rating scheme[34] is considered as a practical minimum standard for the perceptual rating of voice.[49, 50] It consists of five domains: grade (representing overall voice quality), roughness (which looks at fluctuations in F0, indicative of vocal edge abnormalities), breathiness (which assesses air escape), asthenia (a general decrease in power of or weakness of the voice) and strain (which assesses hyperfunctionality). All are assessments of laryngeal function.

Assessment is made on a recording of a voice reading an established phonetically balanced passage, such as the 'rainbow passage' or on current conversational speech. Each aspect of the GRBAS scale is given a score of 0–3, where 0 is normal, 1 shows slight deviance, 2 moderate deviance and 3 severe deviance. This scale has been shown to be reliable across all parameters except strain.[51]

The GRBAS scale has been used in the assessment of voice in the HNC population, including partial laryngeal surgery, in the comparison of radiotherapy and laser excision in the treatment of early glottic lesions. It has also been used as a tool to assess alaryngeal speech[52, 53] Interestingly little correlation has been shown between self-assessment using VHI and clinician-rated GRBAS assessment with severely dysphonic supracriciod laryngectomy patients scoring mean values of 29.9 on VHI.[42]

Perceptual evaluation of alaryngeal speech Although attempts have been made to develop a scale for perceptual evaluation of alaryngeal speech, a reliable, reproducible perceptual rating system does not seem to exist for the laryngectomee. Van As et al[54] report the use of a semantic

bipolar seven-point scale (e.g. ugly–beautiful, deviant–normal, low–high), for both untrained and trained raters. Eadie and Doyle report the use of direct magnitude estimation (continuous) and equally appearing interval scales for the auditory perceptual rating of naturalness, severity, acceptability and pleasantness of tracheoesophageal voice.[55–57] Hurren and Miller report no current evidence to support the use of acoustic instrumental measures in terms of validity. They show preliminary data support for the validity of a new tracheoesophageal voice auditory-perceptual tool the SToPS, for professional and native raters.[58]

Instrument-based measures

A number of instrument-based measurements of voice can be used to diagnose and evaluate the nature and severity of dysphonia. Only a few are useful in measuring changes in voice quality with time. Most have little use in the assessment of outcome in the HNC patient. The more common and potentially useful measures are mentioned in **Box 28.2.**

Acoustic measures of voice Acoustic analysis[36] is widely used in testing vocal function because it is objective and reproducible, as long as the same equipment is used on each occasion. A voice sample is recorded on to digital audiotape (DAT) and acoustic measurements of the voice/speech signal can be made such as maximal phonation time (MPT), frequency, fundamental frequency (the lowest tone in the harmonic), Jitter 1st (the pitch perturbation or frequency variability in percentage), Jitter 2nd (the average of the differences between successive differences in the frequencies of successive periods in percentage) and Shimmer (the amplitude perturbation or intensity variability in dB from the acoustic waveform).

The main use of acoustic measurements in HNC patients has been to compare outcomes of treatments for early glottic tumours,[59, 60] in the assessment of voice after supracricoid laryngectomy[61] and in the assessment of speech therapy following treatment for such lesions.[62] These measurements have also been assessed in the laryngectomee in which the voice is often aperiodic, and makes the assessment of these acoustic measures even more challenging.[63] A detailed treatment of acoustic measures can be found in Chapter 62, Evaluation of the voice.

MEASURES OF SPEECH OUTCOMES

Normal speech is clearly intelligible, well articulated and has adequate nasal components due to oro-nasal separation.[64] Tumours or treatments involving the vocal tract can alter speech.[65] Speech as a function is generally ignored and poorly investigated in HNC patients.[27] Measures currently in use for assessment of speech outcomes are summarized in **Box 28.3.**

Questionnaire evaluation of speech

Speech Handicap Index (SHI) The speech handicap index (SHI) was developed in 2008 by Rinkel et al[67] Recently an English version was validated.[27] It consists of 30 questions to evaluate the patient's speech and speech-related psycho-social functions. Scoring of SHI is based on a Likert five-point scale with response categories as never (0); almost never (1); sometimes (2); almost always (3) and always (4). Total SHI score is summed and higher scores indicate worse speech-related problems. In addition, there is a global question which rates the patient's overall speech quality, this has four responses: excellent; good; average and bad which are scored as 0, 30, 70 and 100. Higher scores again indicate a greater speech problem.

Perceptual evaluation of speech

This is considered gold standard for speech evaluation and involves speech rated by professionals for different speech parameters.

The London Speech Evaluation 'LSE' scale This has recently been developed and validated for use in HNC patients.[64] It evaluates five speech parameters, intelligibility, articulation, rate, nasality and asthenia and overall grade of speech impairment. Scoring of the instrument is based on a Likert four-point scale ranging from 0 to 3. Higher scores indicate greater impairment.

Assessment of Intelligibility of Dysarthric Speech The Assessment of Intelligibility of Dysarthric Speech (ASSIDS)[66] is used by speech and language therapists and contains assessment of intelligibility of speech. It requires a recording of either 50 single words or sentences of 5–15 words selected at random. Each sample is judged by a pool of scorers (one scorer can be used if improvement is being sought in an individual patient). The recording is listened to and transcribed by the scorer and an intelligibility score given as a percentage of responses that were correct. In addition to percentage intelligibility, scores can be calculated for speaking rate, rate of (un)intelligible speech and a communication efficiency ratio. These calculations are based on a healthy person speaking a 220-word paragraph at a rate of 190 words per minute.

Instrument based measures

Acoustic evaluation of speech Acoustic evaluation of speech measures acoustic parameters like fundamental

BOX 28.3 Tools available for the assessment of outcome of speech

QUESTIONNAIRE BASED MEASURES

- Speech Handicap Index (SHI)[27, 66]

PERCEPTUAL MEASURES

- The London Speech Evaluation 'LSE' scale[64]

INSTRUMENT BASED MEASURES

- Assessment of Intelligibility of Dysarthric Speech (ASSIDS)[66]
- Acoustic analysis of speech signal using linear predictive coding[36]

frequency (F0) and formant frequencies. These are the natural resonance frequency of vocal tract for certain sounds and vowels in particular can be identified by their formants. There are several formants but only the first (F1), second (F2) and third (F3) formant frequencies are of use in speech evaluation of HNC. F1 and F2 are related to tongue position and F3 to size of oral cavity. Formants are extracted through linear predictive coding (LPC). Formant frequencies objectively measure approximation between various portions of the oral cavity and the oropharynx.[68] Currently, acoustic analysis of speech is still in its infancy and is predominantly used as a research tool.

MEASURES OF SWALLOWING OUTCOMES

Dysphagia assessment requires a multimodality approach (**Box 28.4**) and falls broadly into two categories: those that assess the severity of the swallowing disorder and those that try to establish its cause.

Causation generally relate to the biomechanics of the altered swallow mechanism, whether sensory or motor. The choice of examination depends largely on the clinical questions to be answered and the presentation of the patient.

Questionnaire evaluation of swallowing

Sydney Swallow Questionnaire (SSQ) This tool is for evaluation particularly of oral and-pharyngeal dysphagia;[73] it has been recently validated for use in the HNC patients.[74] It consists of 17 well-structured questions for the assessment and quantification of patient reported difficulties with swallowing.[73] It uses a visual analogue scale; the total score is calculated and ranges from 0 to 1700 with higher scores indicating a more severe swallowing impairment.

SWAL-QoL and SWAL-CARE SWAL-QoL[75] is a validated swallow-specific QOL questionnaire to assess oropharyngeal dysphagia. It consists of 44 questions grouped in several subsections to evaluate 10 different QOL domains related to swallowing, based on a 5-point scale. It remains the most comprehensive assessment of swallow performance to date. The SWAL-CARE is a 15-item tool relating to quality of care and patient satisfaction.

MD Anderson Dysphagia Inventory (MDADI) The MDADI[76] is one of the most commonly used swallowing questionnaires for HNC patients. It is a self-administered 20-item questionnaire divided into four domains (Global, Emotional, Physical and Functional). The Emotional, Physical and Functional domains consist of 6, 8 and 5 questions respectively, which are scored on a scale of 1 to 5. All (but one) questions are summed, and a mean score is then calculated. This mean score is multiplied by 20 to obtain a score, with a range of 0 (extremely low functioning) to 100 (high functioning). A higher MDADI score represents better day-to-day functioning and QOL.

The Functional Intraoral Glasgow Scale This is a self-assessment questionnaire for the assessment of speech, chewing and swallowing, validated in oral cancer patients. It consists of an ordinal five-grade scale marked for speech as: always understandable (5), needing repetition sometimes (4), needing repetition many times (3), understandable only by relatives (2), incomprehensible (1); for chewing as (5) any food, no difficulty (4) solid food, with difficulty (3) semisolid food, with no difficulty (2) semisolid food, with difficulty (1) cannot chew at all, and for swallowing as (5) any food, no difficulty (4) solid food, with difficulty, (3) semisolid food only, (2) liquids only (1) cannot swallow at all. This very simple scale showed good correlation with a conversational understandability test performed by speech and language therapists and with an objective computer-based method of speech analysis.[77]

BOX 28.4 Swallowing outcomes

QUESTIONNAIRE BASED MEASURES
- Sydney Swallow Questionnaire (SSQ)[69, 70]
- SWAL-QOL and SWAL-CARE[71]
- MD Anderson Dysphagia Inventory (MDADI)[72]

PERCEPTUAL MEASURES
- Blue dye test
- Water swallow test

INSTRUMENT-BASED MEASURES
- Videofluoroscopy
- Functional endoscopic evaluation of swallowing (FEES)
- Flexible endoscopic evaluation of swallowing with sensory testing (FEESST)
- Electromyography

PERFORMANCE SCALES
- Performance Status Scale for Head and Neck
- The Functional Intra oral Glasgow Scale

Perceptual measures

The simplest assessments are direct bedside clinical assessments.[78] However, these are not standardized and offer poor reliability when used alone. The use of a defined volume of water – 30 ml and looking for abnormal voluntary cough, post-swallow cough or throat clear or voice has been shown to have about a 50% sensitivity and 80–92% specificity for aspiration,[69, 70, 79] and is a useful adjunct to instrumental testing.[71] In the HNC population, water swallow test (WST) using 100 ml has been found to be 67% sensitive but less specific (46%).

Instrument based assessment of swallowing

Videofluoroscopy Videofluoroscopy remains the most frequently applied assessment of complex swallow problems as it allows assessment of anatomy and co-ordination in movements of the oropharyngeal and oesophageal stages of swallowing. It is, however, a relatively expensive and time-consuming investigation involving a multiprofessional

team from radiology, SLT and ENT. There are therefore limited opportunities for repeat assessments.[72, 80, 81] Assessments of the reliability of videofluoroscopy show superior accuracy for aspiration than for determination of pathophysiology. The situation is improved with group discussion. The application of protocols and use of frame-by-frame analysis seems inconsistent.[82–84]

In the most expert of hands, semiquantitative estimates of swallow performance can be made. The most usual of these is the oropharyngeal swallow efficiency (OPSE) calculated using the formula:

> % bolus transfer to upper oesophagus/oropharyngeal transit time.

Efficiency as a measure of swallow is based on the maximum estimated percentage (proportion) of bolus left in the pharynx and can be measured on different textures.

The penetration–aspiration scale (**Box 28.5**) assesses the presence and depth of invasion of material entering the airway, and the patient response to the aspiration and the ability to eject any misdirected material.[85, 86] Traditionally, patients aspirating more than 10% of any bolus should be restricted from taking the relevant consistency orally. Manoeuvres can be tested to reduce aspiration. Ongoing aspiration is seen in 44% patients non-laryngectomy survivors of HNC at 5 years and is associated with lower scores on a number of QOL scales.[87]

DIGEST (Dynamic Imaging Grade of Swallowing Toxicity)[88] is a validated tool for SLT to grade dysphagia after radiotherapy. It combines an assessment of efficiency (E 0–4) and of safety (S 0–4), using maximum percent of pharyngeal residue and maximum penetration–aspiration scale score. A DIGEST grade is given to the dysphagia in line with the CTCAE (common terminology criteria for adverse events) scoring D 0–4.

BOX 28.5 Penetration–Aspiration Scale[89]

Score	Criteria
1	Material does not enter the airway
2	Material enters the airway, remains above the vocal folds, and is ejected from the airway
3	Material enters the airway, remains above the vocal folds and is not ejected from the airway
4	Material enters the airway, contacts the vocal folds and is ejected from the airway
5	Material enters the airway, contacts the vocal folds and is not ejected from the airway
6	Material enters the airway, passes below the vocal folds and is ejected into the larynx or out of the airway
7	Material enters the airway, passes below the vocal folds and is not ejected from the trachea despite effort
8	Material enters the airway, passes below the vocal folds and no effort is made to eject

Fibre-optic endoscopic evaluation of swallowing (FEES)

Fibre-optic endoscopic evaluation of swallowing[90] has emerged over the past two decades as not only a complement to videofluoroscopy, but as a useful investigation in its own right. This test can be performed at the bedside and is best if a digital recording is made. Different textures of foodstuffs can be given, which can be dyed with food colouring to enhance visibility. Bolus flow during swallow, laryngeal penetration and aspiration and post-swallow residue should be assessed. The main disadvantage of FEES is that swallowing dynamics are obscured by obliteration of the view as the endoscope tip opposes pharyngeal and laryngeal musculatures during hyolaryngeal excursion.

Assessment of FEES using the penetration aspiration scale developed for videofluoroscopy can achieve good agreement between raters in 97% of cases.[91] Sharing the video image with the patient offers additional therapeutic opportunities through visual biofeedback as the patient observes the impact of swallowing manoeuvres or head positions on their swallow performance. Endoscopic swallow evaluation is relatively cheap, yet only a small minority of speech and language therapists have access to the procedure.[80] FEES should be incorporated into follow-up for HNC patients, as it can be performed by the speech and language therapist and allows for assessment of recurrence and function.

Flexible endoscopic evaluation of swallowing with sensory testing (FEESST) allows more specific assessment of sensory and motor components than in a standard endoscopic evaluation. Patients with absent pharyngeal motor function combined with poor pulmonary reserve and diminished or absent laryngeal sensation are expected to aspirate. Patients with completely insensate laryngopharynx are at extremely high risk of aspiration. Moderate sensory deficits will also result in aspiration if there is a coexisting motor dysfunction.[89]

Electromyography Surface electromyography (sEMG) signals have been used to identify swallow events.[92] The full application of sEMG has yet to be established. At least in the short term, the principal value of the technique in head and neck patients probably is as an adjunct to biofeedback and rehabilitation manoeuvres.

Performance scales designed specifically for the head and neck patient population

Performance Status Scale for Head and Neck Cancer Patients The Performance Status Scale for Head and Neck (PSSHN)[93] is a clinician-rated scale, designed specifically for the head and neck population and the unique areas of dysfunction experienced by this group of patients. It has three domains: (1) understanding of speech, (2) normalcy of diet and (3) eating in public. There is a score from 0 to 100 for each domain. A higher score correlates with better functional ability. There is strong correlation between the PSSHN and MDADI at multiple time points.[94]

BOX 28.6 Instruments to assess comorbidity

- Kaplan–Feinstein Index (KFI)[96]
- Adult Comorbidity Evaluation (ACE-27)[97]
- Charlson Comorbidity Index (CCI)[98]
- Washington University Head and Neck Co-Morbidity Index (WUHNCI)[81]
- American Society of Anesthesiologists (ASA) Risk Classification

COMORBIDITY

Comorbidity refers to disease that coexists with and is unrelated to the index disease, and has been shown to play a major role in the treatment, outcome and prognosis of a number of malignancies. While comorbidity is used to predict outcome and may play a role in decision-making for treatment, it does not strictly qualify as an outcome measure. However, it has a significant influence on oncological and functional outcomes and is thus included in this chapter.

In 1948, the first attempt to quantify the performance status of patients with advanced cancer was made by Karnofsky.[95] Since then, a variety of instruments have evolved to measure comorbidity (**Box 28.6**).

Kaplan–Feinstein index

The Kaplan–Feinstein index (KFI) was developed for assessment of comorbidity on outcome in diabetes mellitus and has been used to study the impact of comorbidity in several cancers.[96] Information is taken from notes review and specific diseases are classified and a score given of mild, moderate or severe according to severity of organ decompensation. Where multiple comorbidities are present, an overall score is assigned according to the highest ranked illness, and where there are two or more moderate outcomes the overall score is defined as severe.

Adult comorbidity evaluation

Adult comorbidity evaluation (ACE-27)[97] is a modification of the KFI, validated and especially designed for patients with cancer. An overall score of 1, 2 or 3 is assigned according to the highest ranked single condition, except where two or more grade 2 illnesses occur in different organ systems where a score of 3 is given. The National Cancer Intelligence Network in the UK recommends the collection of ACE-27 for all cancer patients.

Charlson comorbidity index

The Charlson comorbidity index (CCI)[98] is a weighted sum of the presence or absence of each of 19 conditions. Each condition is assigned a weight from 1 to 6, where a higher value indicates more severe disease. The index is the sum of all the weights.

Washington University Head and Neck Comorbidity Index

The Washington University Head and Neck Comorbidity Index (WUHNCI)[98] is a head and neck specific tool. It takes into account seven common comorbid conditions based on their relative prognostic significance in HNC patients.

Comorbidity and HNC

HNC patients have a high prevalence of comorbidity (21–35%) due to the long-term effects of smoking and alcohol, second only to lung cancer (40%). Several studies have shown the importance of comorbidity on outcome and the prognosis of HNC.[99–103] It is an independent prognostic indicator even when age and TNM stage have been controlled for.[97]

The KFI has been found to be most successful in stratification of survival analysis in HNC patients when compared with the CCI.[100] The CCI is simple to use and has been used to evaluate comorbidity in laryngeal cancer[104] and thyroid cancer,[105] and has been validated against the ACE-27 for use in HNC.[106] However, because answers evaluate the presence or absence of disease rather than severity, it has been found to be less sensitive than the ACE-27 in assessing comorbidity.[107, 108] Comorbidity assessed through the ACE-27 has been shown to have a direct impact on HNC survival especially in the early years after survival where the greatest impact is seen in the younger patient. Comorbidity is associated with an adverse influence on disease-free survival, a higher risk of more severe complications of treatment, has an adverse effect on QOL and increases the cost of treatment.[109–112]

Comorbidity data add valuable prognostic information that may influence treatment modality. Use of single sources alone may result in some misclassification of comorbidity. Enhancing data extracted from notes with a patient self-report questionnaire can improve the accuracy of comorbidity grading.[113]

PATIENT PRIORITIES FOR TREATMENT OUTCOMES

An early classic paper on the cost utility analysis of the treatment of advanced laryngeal cancer by radiotherapy and laryngectomy presented a trade-off of QOL (retention of laryngeal speech) vs quantity of life (improved survival after primary laryngectomy) to a group of healthy (non-medical) volunteers. In order to maintain natural speech, approximately 20% of those questioned would have chosen radiation instead of surgery.[114] This paper was innovative and influential in suggesting that for some people quality, not quantity, of life was more important. But in a very recent study in a population demographically matched to HNC patients, many participants indicated that larynx conservation was not their primary consideration in treatment choice. Thirty-eight per cent of participants opted for a primary laryngectomy and the functional outcome of treatment had a greater effect than treatment modality on the utility value assigned to laryngeal cancer health state outcomes.[115] In contrast, in a paper by DeSanto et al 20% of patients expressed themselves willing to accept a reduced life span in order to preserve their larynx and QOL.[116] However, 46% of the healthcare professionals questioned had felt that the patients would accept this trade off. A study published by List et al showed that both

patients and nonpatients ranked 'being cured of cancer', 'living as long as possible' and 'having no pain' most frequently in the top three of 12 statements.[117]

There are also differences in the perception of the relative importance of different categories of symptom between patients and carers. In 1992, Mohide et al[1] demonstrated that carers ranked impaired communication and self-image/self-esteem as the two most important QOL outcome domains following laryngectomy. The patients themselves ranked the physical symptoms of tracheal mucus production and interference with social activities as the two most important items. It is important to bear this lack of correlation between patient and carer priorities in mind when counselling patients about treatment options.

Blanchard et al[118] performed a systematic review of patient preferences in HNC, defined by the subsite of the primary cancer. This study showed that whilst there was homogeneity in the methods and conclusions of studies of laryngeal preservation, studies of other subsites suffered from significant heterogeneity, thus making it difficult to draw conclusions about patient priorities. However, survival consistently trumped functional outcomes, underscoring the importance of high survival rates in contemporary or experimental treatments, whatever the subsite.

HNC are heterogenous in their biological nature, and therefore tumour behaviour and response to treatment. Furthermore, the incidence and severity of adverse effects of treatments is highly variable between patients. In their analysis of RTOG 0522 Ang et al[119] support a strategy of refining study populations, for better biologically defined HNC entities. The identification, selection and reporting of disease-specific and appropriate endpoints is therefore a research priority.

BEST CLINICAL PRACTICE

- ✓ Measurement of Base line and post-treatment swallow outcomes using a combination of clinical and instrumental assessments and validated patient outcome measures such as MDADI or PSSHN and instrumental assessments such as 100 ml water swallow test and FEES.
- ✓ Measurement of voice outcomes following treatment for early laryngeal cancer using questionnaires such as VHI short-form 10 or VoiSS.
- ✓ Collection and recording of comorbidity data WHO and ACE 27 in all head and neck cancers registered (as per National Cancer Intelligence Network guidance in UK).
- ✓ Recording of early and late toxicities associated with treatments for head and neck cancer to allow for the comparison of interventions when there is equipoise for survival.

FUTURE RESEARCH

- ➤ Development of a tool to assess xerostomia following treatment in HNSCC with a view to identifying if new treatments reduce this debilitating side effect.
- ➤ Development of a PROM for evaluation of shoulder dysfunction following treatment for HNSCC.
- ➤ Standardization of outcome measurements collected to allow for useful comparison and evaluation.
- ➤ Development of a validated scale for perceptual evaluation of alaryngeal speech.

KEY POINTS

- Outcome measures are integral to the management of patients with HNC and can relate to survival or function. Choice of appropriate outcome measures is essential.
- Numerous tools exist for assessment of voice. Self-assessment questionnaires are most commonly and easily obtained. These can be combined with perceptual and acoustic measures; the latter are commonly used as research tools.
- It is important to distinguish voice from speech since these are different concepts, thus needing different measures.
- Dysphagia is perceived by patients to be one of the most important functional outcomes of HNC treatment. Assessment should be embedded in routine practice and form part of follow-up. This should include questionnaire-based tools such as MDADI or PSSHN and instrumental assessment with FEES. VF is an outcome tool in the research setting, but also valuable in managing patients with swallowing problems.
- Comorbidity assessment using ACE-27 is recommended by NCIN for all cancer patients.

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CHAPTER 29

APPLICATIONS OF ROBOTICS IN HEAD AND NECK PRACTICE

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SEARCH STRATEGY

Data in this chapter may be updated by a search of MedLine and PubMed using the following keywords: head and neck cancer and transoral robotic surgery.

TECHNOLOGY AND OTOLARYNGOLOGY

Surgical innovation and skillfully adapting new technology to improve patient care has been part of the fabric and culture of otolaryngology, head and neck surgery since its inception. As such, there is a long history of otolaryngologists creating and embracing new surgical technology, dating back to 1921, when Dr. Carl Nylen, a Swedish otolaryngologist, used the world's first monocular operative microscope, for the treatment of chronic otitis media.[1] The next year, Dr. Gunnar Holmgren, Dr. Nylen's chief, introduced the first binocular microscope by attaching a light source to an existing Zeiss dissecting microscope.[1] In the 1970s, Dr. Walter Messerklinger and his protégé, Dr. Heinz Stammberger in Graz Austria pioneered the technique of endoscopic sinus surgery, later popularized and refined by Dr. David Kennedy in the US.[2] These noble traditions shows that otolaryngologists, head and neck surgeons are endoscopic surgeons, pioneering new techniques to improve surgical outcomes and patient care.

Recently, the introduction of surgical robotics has transformed the practice of surgery. With robotic surgery, the surgeon and his hands are physically separate from the patient. Real surgery is performed in a virtual environment, allowing the surgeon to interact with surgical anatomy with a novel perspective, in otherwise inaccessible places and in ways that would not be possible without this innovation. In 2007, the Society of American Gastrointestinal and Endoscopic Surgeons and the Minimally Invasive Robotic Association defined 'robotic surgery' as 'a surgical procedure or technology that adds a computer technology-enhanced device to the interaction between a surgeon and a patient during a surgical operation and assumes some degree of control heretofore completely reserved for the surgeon.'[2]

Currently, the daVinci® Surgical System (Intuitive Surgical Inc., Sunnyvale, CA) is the most popular platform for robotic surgery. It consists of three parts: a 'patient-side' cart deploys surgical instruments placed by the surgeon within the patient's body including a binocular 12 mm endoscope with dual zero or thirty degree optics, and a 'surgeon's console' which is remotely placed where three-dimensional surgical anatomy is recreated and linked to instruments in a virtual environment. The surgeon's console consists of a three-dimensional display, a seat for the surgeon, foot pedals to control cautery and other instruments, and hand controls linked to instruments placed in the operative field. The three-dimensional display affords the surgeon unprecedented perspective and visualization of surgical anatomy along with the ability to operate with 540 degrees of wristed instrumentation at zero or thirty degree angles. Motion scaling increases precision by eliminating tremor and fatigue while also reducing greater hand movements. The 'vision cart' houses the video processor and screens to project the procedure, primarily used by the operating assistant and the other observers.

ROBOTIC SURGERY

Transoral robotic surgery

Melder and McLeod performed the first robotic procedure in otolaryngology at the Walter Reed Army Medical Center in 2003, removing a vallecular cyst.[3] With the first generation 'standard' DaVinci® Surgical System (Sunnyvale, CA),

Hockstein, Weinstein, and O'Malley presented a series of landmark papers beginning in 2005 defining the field of transoral robotic surgery (TORS).[4–7] Whereas Melder and McLeod placed robotic arms through a slotted laryngoscope, Hockstein et al. placed the robotic arms through the oral retractors, moving from laryngoscopes to the Feyh-Kastenbauer (FK), Crowe-Davis, McIvor, or Dingman, which provided excellent exposure for the oropharynx but even allowed access to the supraglottic larynx and occasionally the hypopharynx. Different combinations of retractors, laryngoscopes, endoscopes and microsurgical instruments were used to identify the optimal setup for robot-assisted head and neck surgery. Hockstein found that placing the robotic arms through a tubed laryngoscope, such as the Lindholm, significantly limited range of motion, but that an oral and oropharyngeal retractor, such as the McIvor, provided relatively free motion of the surgical instruments and endoscope for procedures of the oropharynx, supraglottis and hypopharynx.

The operative arms carry interchangeable 5 or 8 mm diameter instruments including atraumatic forceps, monopolar cautery, bipolar cautery, among other manipulators and dissectors. The most common cutting device is the monopolar electrocautery spatula, which doubles as a dissector. Lasers have recently been adapted to work with the robot manipulators and have been a popular addition. Fibre laser technology couples the unsurpassed visualization with a more precise cutting device with nominal thermal damage and reduced tissue necrosis when compared to the monopolar electrocautery. In addition to two operative arms, either an 8.5 or 12 mm binocular stereoendoscopy or camera provide a high-definition three-dimensional view of the anatomy of the laryngopharynx (**Figure 29.1**).



Figure 29.1 A bird's eye view of the da Vinci Si system docked in the mouth prior to TORS.

O'Malley et al. in 2006[8] demonstrated the use of TORS in cadaver and animal models. Once they had demonstrated adequate exposure with these models, they proceeded with 3 tongue base cancers on human subjects under an institution review board approved human trial. They concluded 'TORS provided excellent three-dimensional visualization and instrument access that allowed successful surgical resections from cadaver models to human patients'.[8]

Multiple studies emerged demonstrating the feasibility of transoral robotic surgery for patients with laryngopharyngeal cancer. Moore et al. reported on the feasibility of robotic surgery in a prospective case study of 45 patients with previously untreated oropharyngeal squamous cell carcinoma.[9] His case series included T1–T4a tumours with simultaneous unilateral or bilateral neck dissection. Margins were all negative, operative time improved as operative experience developed, and all 14 patients who underwent tracheostomy tube placement were decannulated. All 30 patients who had either a nasogastric or gastrostomy feeding tube placed eventually had their tubes removed. Weinstein et al.[10] in a multicentre prospective case series reported on the safety, feasibility and adequacy of surgical margins for transoral robotic resections. A total of 192 patients were initially screened and 177 were finally included, as 13 were excluded for inadequate exposure with TORS and 2 who were switched to an open approach. Most cases were oropharyngeal followed by laryngeal squamous cell carcinoma. In regard to safety, there were no intra-operative mortality or deaths in the immediate post-operative period. Blood loss averaged 83 mL and no patients required transfusions. Twenty-nine patients (16%) experienced serious adverse events requiring intervention or hospitalization. Twenty-two patients (2.3%) had a tracheostomy tube at last follow-up visit and the gastrostomy tube dependence rate was 5.0%. The positive margin rate was 4.3%. This multicentre study concluded that TORS was safe and feasible.

White et al. reported on the 1- and 2-year survival rates after transoral robotic surgery.[11] Eighty-nine patients from 2 institutions were included, mostly with oropharyngeal squamous cell carcinoma followed by laryngeal squamous cell carcinoma. T-stage ranged from T1 to T4 with most being T1 or T2 and most were overall stage III or IV. At last follow-up and after a median follow-up of 26 months, 82 had no evidence of disease, 2 died of disease, and 4 were alive with disease. The 2-year recurrence free survival rate was 86.5% and none of the patients were gastrostomy tube dependent.

Despite multiple studies and meta analyses[12] supporting the use of transoral robotic surgery, there are no randomized studies comparing surgical management of oropharyngeal carcinoma to chemoradiation. **Table 29.1** summarizes ongoing trials worldwide, aiming to identify the role of transoral surgery (with the laser or the robot) in this setting on TORS in the world, 4 of which are randomized trials. The RTOG 1221 randomized trial has been designed to compare transoral resection of p16- oropharyngeal carcinoma followed by risk-based adjuvant therapy (60 Gy IMRT with or without weekly cisplatin)

TABLE 29.1 TORS trials currently ongoing (as of January 2017)

Name of trial	Identification number	Inclusion criteria (disease specific)	Comparative arms	Primary outcome measure	Negative margin threshold
'CompARE' Phase III randomized controlled trial comparing alternative regimens for escalating treatment of intermediate and high-risk oropharyngeal cancer	ISRCTN41478539	• OPSCC in base of tongue and tonsil with MDT recommendation for treatment with definitive concurrent chemoradiotherapy • Intermediate risk [HPV +ve OPC with N2b+ disease and greater than 10 pack year history of smoking] or high risk (HPV–ve OPC) as per Ang classification	**Arm 1 (control):** Concomitant chemoradiotherapy (70 Gy in 35# and cisplatin) +/– post- treatment neck dissection **Arm 2:** Induction chemotherapy (docetaxel, cisplatin and 5-FU), followed by arm 1 **Arm 3:** Dose-escalated chemo radiotherapy (64 Gy in 25# and cisplatin) +/– post- treatment neck dissection **Arm 4:** Resection of primary and selective neck dissection plus post-operative chemoradiotherapy (T1/2 transoral surgery, T3/4 transoral or open surgery)	• Overall survival (OS) • Disease-free survival (DFS)	not specified
'PATHOS' A phase II/III trial of risk-stratified, reduced intensity adjuvant treatment in patients undergoing transoral surgery for HPV +ve OPC	NCT02215265	• Stage T1–T3, N0–N2b SCC of the oropharynx • HPV +ve	Post-operative risk stratification 1. Low risk: no adjuvant treatment 2. Intermediate risk: randomized to: • 50 Gy in 25# • 60 Gy in 30# 3. High risk – randomized to: • 60 Gy in 30# • 60 Gy in 30# with cisplatin	• Patient-reported swallowing outcome	> 5 mm
'ADEPT' Post-operative adjuvant therapy de-intensification trial for HPV-related, p16+ oropharynx cancer	NCT01687413	• Patient must have histologically confirmed p16 positive SCC of the oropharynx (OPSCC). • Patient must have undergone transoral resection of their T1–4a oropharynx primary to a negative margin, and a neck dissection(s). • Patient's disease must be pathological N-stage positive. • Patient's disease must show ECS in their nodal metastasis verified by central pathologist's review. • Patients with synchronous primaries are included. • Patients with unknown primaries are included if the diagnosis and resection of a primary site in the oropharynx is made from an endoscopic or robotic surgical procedure(s)	Post-operative randomization **Arm 1:** 60 Gy in 30# **Arm 2:** 60 Gy in 30# and cisplatin	• Disease-free survival (DFS) • Locoregional control	not specified

(Continued)

TABLE 29.1 ***(Continued)*** TORS trials currently ongoing (as of January 2017)

Name of trial	Identification number	Inclusion criteria (disease specific)	Comparative arms	Primary outcome measure	Negative margin threshold
'ORATOR' A phase II randomized trial for early-stage SCC of the oropharynx: radiotherapy vs transoral robotic surgery	NCT01590355	• Histologically confirmed SCC primary tumour site in the oropharynx • Tumour stage: T1 or T2, with likely negative resections at surgery • Nodal stage: N0, N1, or N2, without extranodal extension on pre-randomization imaging	**Arm 1:** Radiotherapy +/– chemotherapy **Arm 2:** Transoral Robotic surgery and neck dissection +/– adjuvant radio(chemo)therapy based on pathological findings	• Quality of life	>2 mm
'ECOG 3311' Transoral surgery followed By low-dose or standard-dose radiation therapy with or without chemotherapy in treating patients with HPV Positive Stage III-IVA oropharyngeal cancer	NCT01898494	• SCC or undifferentiated carcinoma of the oropharynx; patients must have been determined to have resectable oropharyngeal and neck disease • Patients must have AJCC TNM tumour stage III, IV a, or IV b (with no evidence of distant metastases) • Nodal stage N1-N2b • p16 (HPV) positive disease	Post-operative risk stratification 1. Low risk: no adjuvant treatment 2. Intermediate risk: randomized to: • 50Gy in 25# • 60Gy in 30# 3. High risk: chemoradiotherapy	• Progression free survival rate • Accrual rate • Risk distribution • Incidence of grade 3–4 bleeding events during surgery and positive margins after surgery	>3 mm
A single-arm phase II Study of post-transoral robotic surgery (TORS) alone to the primary tumour site and SND followed by adjuvant radiation therapy (+/– chemotherapy) to the regional nodes for advanced stage, HPV positive, oropharyngeal cancer	NCT02159703	• Histologically confirmed diagnosis of SCC of the oropharynx, stage IVa, p16-positive on immunohistochemistry • Pathologic T1 or T2 disease, resected with negative margins (2 mm) • Pathologic N2a, N2b, or N2c disease		Number of adverse events	>2 mm
Robotic surgery for oropharyngeal SCC	NCT02225496	• Patients with a previously untreated, T1 or T2, N0-N2b transorally resectable (as determined by the treating surgeon), histologically proven HPV positive, SCC of the oropharynx		Time to local-regional recurrence (TTLRR)	>5 mm
Transoral robotic surgery in treating patients with benign or malignant tumours of the head and neck	NCT01473784	• Patient must present with indications for diagnostic or therapeutic approaches for benign and/or malignant diseases of the oral cavity or laryngopharynx		Determine the feasibility of the TORS in patients with oral and laryngopharyngeal benign and malignant lesions	not specified

SCC, squamous cell carcinoma; SND, selective neck dissection, HPV, human papilloma virus; ECS, extracapsular spread.

to standard chemoradiation therapy (70 Gy IMRT with weekly cisplatin); owing to reduced numbers of HPV- disease, this trial failed to meet recruitments targets, and has been closed. In the UK, the CRUK funded ComPARE trial will recruit surgically resectable intermediate and high-risk patients as per the stratification data published by Ang et al.[13] and has a surgical resection followed by platinum based RT as one of the arms.

Additionally, while HPV-associated oropharyngeal carcinoma has been clearly shown to have improved prognosis compared to HPV negative oropharyngeal carcinoma, no trials have yet been conducted on de-escalation of therapy. Accrual for ECOG 3311 is currently underway, which is a phase II randomized trial comparing low-dose radiation (50 Gy) vs standard post-operative dose of radiation (60 Gy) after transoral resection of of p16+ oropharyngeal squamous cell carcinoma with intermediate risk factors (< 3 mm margins, < 1 mm ECS, and 2–4 metastatic lymph nodes). Patients with low-risk features (T1–T2, N0-1, and negative margins) will receive no post-operative adjuvant therapy and patients with high-risk features (> 1 mm ECS, > 5 metastatic lymph nodes, or positive margins) will receive standard 66 Gy IMRT with weekly cisplatin.

In the UK, the PATHOS trial will recruit patients with low and intermediate staged HPV positive oropharyngeal cancer, managed by transoral excision followed by risk stratified radiation therapy. This trial aims to establish whether the de-intensification of adjuvant treatment in patients undergoing TLM/TORS for HPV-positive OPC, by reducing radiation dose or omitting chemotherapy, will confer improved swallowing outcomes at 1-year post-treatment whilst maintaining high cure rates. Thus, the treatment of this disease is rapidly evolving and significant changes can be expected in the next decade. A summary of these trials can be found in a recent review[14] TORS has also been shown to have a clear role in resection of supraglottic[15, 16] and hypopharyngeal cancers.[17–19] A new role has been defined for TORS in diagnosing the unknown primary, using tongue base mucosectomy, where pick-up rates of between 50% and 60% have been demonstrated,[20] even in patients who show no avidity on CT-PET imaging.[21]

Transoral robotic surgery versus transoral laser microsurgery

Transoral laser surgery has been shown to be effective in the management of tonsil tumours and is discussed at length in Chapter 22, Transoral laser microsurgery. The principles of this procedure involve resection of the tumour by following its extent, tailoring resection to each patient. Assessment of the depth of the tumour is achieved frequently by transecting the tumour until the 'normal' tissues are reached. The cutting characteristics of the laser mean this is clearly demonstrable. However, margins on the specimen are frequently reported as close and marginal biopsies are therefore used to assess status. While this approach is oncologically safe, it can present practical concerns in deciding if adjuvant therapy is needed.[22] Nevertheless, the significant amount of work in the TLM literature has paved the way to establish TORS for tonsil tumours as *bonafide* management with firm long-term oncological outcomes.

The principle of TORS surgery is *en bloc* resection with a clear margin (**Figure 29.2**). The foundations for *en bloc* resection of tonsil cancers via a transoral route had been laid back in the 1950s when P-C. Huet described this procedure.[23] This involved transoral resection of the tonsil and the superior constrictor muscle deep to the parapharyngeal space. Holsinger et al.[24] reported good outcomes for tonsil tumours with this technique. *En bloc* resections of the tonsil, although feasible with the TLM approach, are not easy due to the line of sight working and instrumentation. The advent of TORS has allowed surgeons to perform *en bloc* resections at this primary site. The superior optics and manoeuvrability combined with the ergonomics have meant that the learning curve for transoral robotic radical tonsillectomy is not as shallow as that of transoral laser microsurgery (**Figure 29.3**).

Robotic thyroidectomy

Transoral endoscopic head and neck surgeons rely on access through the mouth and axilla which provides ample opportunity for innovation and improvement in minimally invasive techniques for the treatment of laryngopharyngeal tumours. However, robotic surgery may also play a role for the management of tumours of the thyroid and parathyroid.

Advances in minimally invasive thyroid surgery date back to 1996 with the first endoscopic parathyroidectomy performed by Gagner.[25] The operative setup resembled that of laparoscopic surgery utilizing 5 mm laparoscopic instruments placed between the platysma and strap muscles with the operative space maintained with CO_2 insufflation. Subsequent advances involved minimally invasive video-assisted thyroidectomy (MIVAT) in which the thyroid gland is removed with or without gas insufflation via cervical, axillary, or anterior chest wall approaches.[26, 27] Multiple Asian studies have emerged reporting on endoscopic transaxillary thyroidectomy.[28–30] Chang et al. reported their experience with a combined endoscopic-robotic transaxillary approach for thyroidectomy.[31] Kang et al. reported on 200 patients who underwent transaxillary robotic thyroidectomy utilizing the DaVinci® Surgical System.[32] The combination of minimally invasive thyroid surgery utilizing the DaVinci® Surgical System provides many advantages for the endoscopic head and neck surgeon. The three-dimensional display employing 30-degree optics along with the 540 degrees of wristed instrumentation improve operative dexterity along with operative field exposure and visualization.

Terris et al.[33] demonstrated the use of robotic-assisted thyroidectomy via a facelift incision. In 2012, he demonstrated the feasibility of the facelift approach, comparing it favourably against transaxillary robot-assisted thyroidectomy. Specifically, in his series of 15 patients, he demonstrated decreased operative time and outpatient thyroidectomy

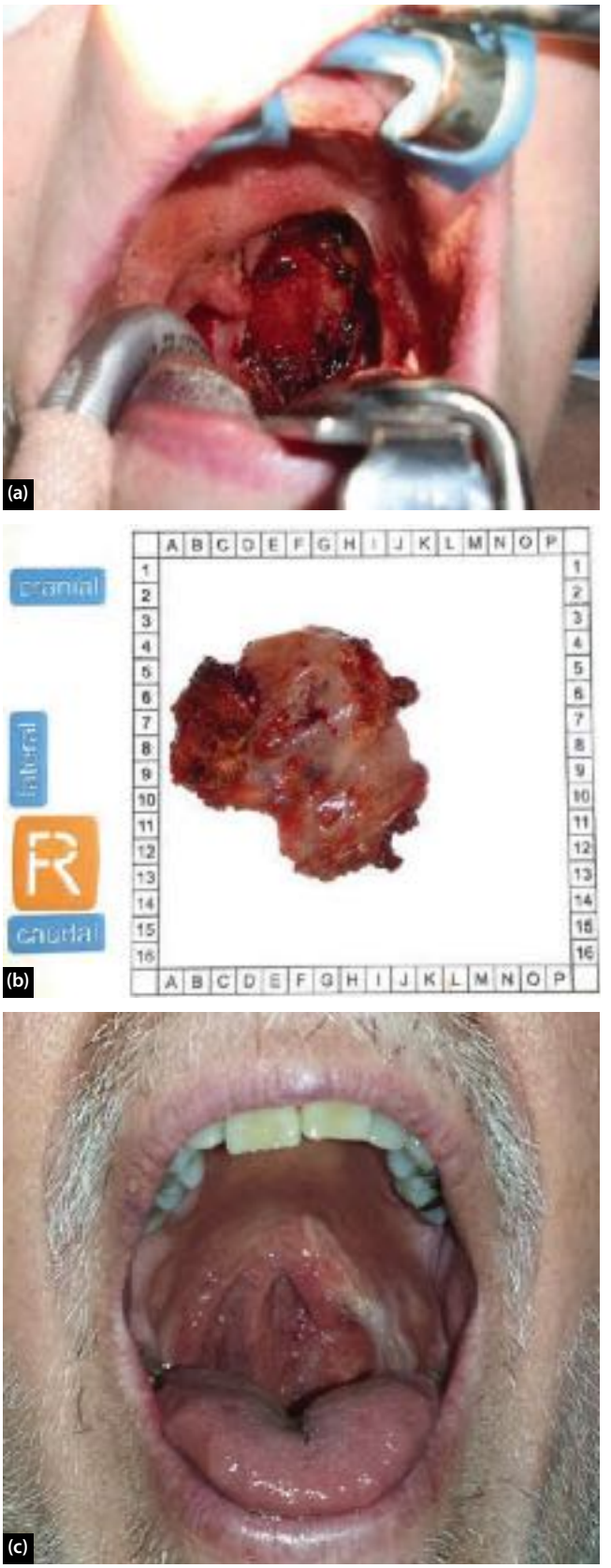


Figure 29.2 **(a)** is the view following transoral robotic *en bloc* resection of a T2 tonsil cancer. **(b)** is the specimen with the cancer in the middle and demonstrates adequate macroscopic margins. **(c)** shows a fully healed lateral oropharygectomy defect.



Figure 29.3 Photograph shows robotic surgery in progress, with dual surgical consoles. The two console surgeons share the same view and can swap control of the instruments, which facilitates training and allows rapid acquisition of skills.

without drain placement in robotic facelift thyroidectomy compared to transaxillary thyroidectomy. A recent meta-analysis of 5200 patients showed an equivalent adverse event and complication rate for robotic thyroidectomy compared to conventional approaches, generating confidence in wider adoption of the technique.[34] Many, however, remain sceptical of robotic-assisted techniques in thyroidectomy given that the time-honoured approach of conventional open thyroidectomy remains safe and effective.

Robotic neck dissection

The neck dissection has undergone significant changes from the radical neck dissections to functional and selective neck dissections without compromising oncologic principles and outcomes. This has led to a decrease in the morbidity of neck dissection. Now, authors have demonstrated minimally invasive combined endoscopic-robotic approaches to neck dissection in human cadaver models.[35] In 2004, Werner et al.[36] successfully demonstrated management of cervical lymphadenopathy using an endoscopic approach for squamous cell carcinoma in the setting of sentinel lymph node biopsy. Also, Kang et al. demonstrated the feasibility of robot-assisted neck dissection for well-differentiated thyroid carcinoma.[37] Furthermore, in 2010 Moore et al. demonstrated the use of transoral robotic surgery for retropharyngeal lymphadenectomy in papillary thyroid carcinoma.[38] Comparative studies of open and robotic neck dissections via a retroauricular/facelift route have shown equivalent functional and oncologic outcomes, with the robotic approach taking greater time, which could be ascribed to the learning curve.[39–41]

Robotic sleep apneoa surgery

Obstructive sleep apneoa (OSA) is a serious public health problem, as it is an independent risk factor for hypertension, myocardial infarction, and stroke. Sleep surgery has

a long history of improving quality of life for patients with OSA but has been limited by exposure of the posterior oropharynx as well as longevity in post-operative improvement scores. Given the success of robotic-assisted techniques in head and neck surgery, sleep medicine seemed an appropriate extension of the previously described techniques. Many surgeons were performing base of tongue resections for malignant disease with great precision and minimal complications, thus base of tongue resections for benign disease also seemed to be an appropriate use of the robot. In 2010, Vicini reported on his experience of 10 patients who underwent transoral robotic surgery for the management of OSA due to tongue base hypertrophy.[42] He resected the base of tongue in a piecemeal fashion, starting medially and subsequently resecting laterally. Vicini had confirmed in a cadaveric anatomic study that no significant neurovascular structures were present in the midline of the base of tongue, thus beginning resection there was quite safe.[43] All surgeries were successfully completely solely with TORS and there were no serious peri-operative complications. In the preliminary novel experience, Vicini routinely performed tracheostomies prior to the tongue base resections for every patient. Mean blood loss, operative time, setup time, pre-operative Epworth Sleepiness Scale, and pre-operative AHI was 25 mL, 45.5 min, 41.4 min, 12.4, and 38.3 respectively. Post-operative Epworth Sleepiness Scale and AHI were 6.9 and 20.6 respectively. There was a mean follow-up of 6 months. Vicini successfully demonstrated the feasibility of robotic-assisted sleep surgery.

In 2012, Friedman followed up on Vicini's work by performing midline posterior glossectomies for OSA without first performing a tracheostomy.[44] He included 40 patients who underwent TORS for obstructive sleep apneoa-hypopnoea syndrome and compared them to 2 cohorts: patients undergoing radiofrequency treatment or submucosal coblation. He reported that the TORS patients took longer to recover with a longer time to resume normal diet; TORS patients also took longer than the radiofrequency treated patients to resume regular activity. But that is where TORS' weakness stopped. Reduction in AHI for TORS patients averaged 60.5% while radiofrequency treated and coblated patients experienced average reductions of 32% and 37% respectively; both of these differences from TORS were statistically significant. Furthermore, only the TORS group achieved a statistically significant improvement in minimum oxygen saturation. Friedman noted no airway or bleeding complications. Once again, the feasibility of TORS for sleep surgery was confirmed.

Not satisfied with his results for in OSA outcome compared to open tongue base reduction with hyoid epiglottoplasty as described by Chabolle, Vicini wanted to apply the concept of geniohyoidpexy with transoral robotic surgery. In 2011, Vicini reported on the success of this technique in the cadaver model.[45] The hyoid bone was identified via transoral resection through the base of tongue and subsequently dissected free of its suprahyoid attachments. With minimal further dissection, the medial inferior border of the mandible is identified and two holes are drilled. One to two stitches are placed through those holes and then around the hyoid bone under slight tension, allowing for geniohyoidpexy and successfully demonstrating TOR access to the hyoid bone, which can be useful for many other applications.

Robotic skull base surgery

In 2007, Hanna et al. published on robotic-assisted anterior and central skull base surgery in a cadaver model.[46] Hanna used bilateral sublabial incisions with bilateral Caldwell-Luc antrostomies and posterior septectomy in order to gain access to the cribriform plate, fovea ethmoidalis, medial orbits, planum sphenoidale, sella turcica, suprasellar and parasellar regions, nasopharynx, pterygopalatine fossa, and clivus. The ability to perform two-handed endoscopic closure of dural defects was a major advantage of this approach. Kupferman et al.[47] described reconstruction of the skull base following robotic resection via a bilateral translabial Caldwell-Luc approach. They undertook a robotic-assisted suture based technique for reconstruction of dural defects suggesting that traditional suture techniques can be implemented after robotic resection using robotic instrumentation.

O'Malley et al.[48] developed a transoral approach to apply robotics for the treatment of tumours of the parapharyngeal space and infratemporal fossa. Beginning with pre-clinical studies on cadaver and animal models, O'Malley demonstrated the feasibility of TORS in this setting. In February 2007, the findings from this pre-clinical work led the way to perform a robotic resection of an infratemporal fossa cystic neoplasm in a live patient, as part of a prospective human trial. The robotic approach afforded adequate and safe identification of the internal carotid artery and cranial nerves. They achieved complete resection, excellent haemostasis and there were no peri-operative complications. In the prospective study, O'Malley et al. enrolled 10 patients with benign parapharyngeal space tumours without carotid encasement and found that 9 of the 10 patients were successfully completed with TORS with acceptable blood loss and no significant peri-operative complications.[48] His approach involved dissection intraorally through the pterygomandibular raphe. Seven of the patients were treated for pleomorphic adenoma, one of these required conversion to an open approach. They noted capsule disruption in 2 and pharyngeal disruption in 2. The 7 patients with pleomorphic adenomas were tumour free during the follow-up period ranging from 16 to 37 months. The other 3 patients were treated for benign cysts. Kim et al.[49] also provided support for use of TORS for benign tumours of the parapharyngeal space and infratemporal fossa in their series of 3 patients with pleomorphic adenomas. The disadvantage of this technique is adequate exposure, ensuring complete surgical resection, which is a serious consideration when considering malignant disease.

Blanco et al. also assessed the feasibility of the DaVinci® Surgical System for infratemporal fossa and anterior skull base lesions using a cadaver model.[50] They gained access to the infratemporal fossa using a maxillary window and the anterior skull base using a maxillary window and a nasal corridor. Although they deemed the robotic-assisted approach to the skull base was feasible, they felt the DaVinci

instruments need to be redesigned to be smaller and with distal articulating tips prior to clinical application.

Robotic approaches to the anterior and midline skull base via a transoral approach was assessed in a pre-clinical trial for TORS. O'Malley et al.[51] performed 10 procedures on cadaver and animal models. While they were able to access the canine skull base using a transoral approach, for the human cadaver they noted the standard transoral approach did not provide adequate access to the midline and anterior skull base. They developed a new technique deemed cervical-transoral robotic surgery (C-TORS), which successfully provided access to the anterior and midline skull base. For the C-TORS technique, standard robotic trocars are inserted at the posterior border of the submandibular gland with the robotic instruments directed cranially, parallel to the long axis of the spine. The camera was placed transorally, however, for the end effector instruments, a 3 mm cut was made through skin and platysma at the posterior border of the submandibular gland bilaterally, then standard plastic introducers and round-tip dilators were passed through those incisions and traced upward in a circular dissecting fashion until they were visualized intraorally using the camera. The introducers pierce the pharynx at the level of the lateral hypopharynx. They describe how using their technique they do not injure arteries, veins or nerves. McCool et al.[52] also described a transcervical approach along with a transoral approach for infratemporal fossa lesions using 4 cadaver models. While O'Malley described ports posterior to the submandibular gland, McCool placed a midline suprahyoid port, which pierces into the vallecula. He reported excellent visualization into the infratemporal fossa with a 30 degree scope.

Additionally, Ozer et al. described multiple approaches involving different placement of the camera and end effector instruments along with utilization of 0 degree and 30 degree scopes in order to achieve adequate visualization of the skull base.[53] They applied transoral, transnasal, transpalatal, and transcervical approaches to determine optimal visualization. Transnasal approaches required posterior septectomies while transpalatal approaches required elevation of a mucoperiosteal flap posterior to the molar teeth and resection of a portion of the hard palate and vomer. They concluded that the transoral camera and instruments with a 30 degree endoscope provide good control over the posterior and lateral nasopharynx without good control over the roof of the nasopharynx or posterior choana. The transnasal camera (0 degree) with transoral instruments provided great visualization but with cumbersome instrumentation. Overall, they felt the transpalatal approach was the best compromise of visualization and instrumentation for the nasopharynx, clivus and anterior skull base. Transcervical ports provided superior range of motion and use of instrumentation with the camera in any of the possible configurations.



Figure 29.4 TORS free flap inset in progress following resection of a recurrent oropharyngeal cancer of the tonsil and the tongue base. A medial sural artery perforator flap was used, and the pedicle fed into the neck via the oropharyngeal defect (Courtesy of Prof Vinidh Paleri, London).

Free flap inset via TORS

TORS has allowed removal of complex tumours from the oropharynx. As acceptability of the recognition of the safety and efficacy of the procedure has evolved, larger and more complex tumours are being treated. This has increased the need to reconstruct the oropharynx to provide velopharyngeal competence and reduce fistula risk. A number of algorithms have been proposed depending on the site and size of the defect. These range from allowing healing by secondary intent to velopharyngoplasties with local flaps, local flaps alone or in larger defects regional and free-flap reconstruction. Robotic assisted mobilization and inset of the flaps have been described in extending the range of options for these patients (**Figure 29.4**).[54, 55]

CONCLUSION

Robotic technology has demonstrated great promise in the field of otolaryngology. As the technology becomes refined and instrumentation is developed for the specific purpose of head and neck surgery, robotic surgery may have an even greater impact on minimally invasive surgical outcomes.

KEY POINTS

- Significant global expertise exists in transoral robotic surgery (TORS).
- TORS is primarily used for oropharyngeal and supraglottic primaries.
- Several ongoing randomized trials on transoral surgery will clarify the role of this modality in head and neck cancer treatment.
- Improvements in technology mean that transoral surgery is here to stay.

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CHAPTER 30

BIOLOGICALLY TARGETED AGENTS IN HEAD AND NECK CANCERS

Kevin J. Harrington and Magnus T. Dillon

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: head and neck cancer, oncogene, tumour suppressor gene, growth factor, epidermal growth factor receptor, tyrosine kinase inhibitor, monoclonal antibody, cell cycle control, DNA damage repair and immunotherapy.

INTRODUCTION

Cancer is a genetic disease that develops when the information in cellular DNA is corrupted or wrongly decoded. This leads to altered patterns of gene expression and derangement of normal protein function. Simply stated, genetic changes leading to cancer mediate two general effects: (i) overactivity of genes that stimulate cell growth, survival and spread; and (ii) underactivity of genes that repress these processes. Through these changes, cancer cells acquire properties that allow them to grow in an uncontrolled fashion, invade adjacent normal tissues, recruit their own blood supply, avoid immune detection and destruction, spread to distant sites and develop resistance to anticancer treatments. By understanding these processes, we have an opportunity to design and implement new classes of so-called targeted therapies that will exploit the fundamental biological differences between malignant and normal cells.

ONCOGENES AND TUMOUR SUPPRESSOR GENES

The functions of two classes of genes (oncogenes and tumour suppressor genes) are central to understanding cancer biology.[1] Oncogenes represent mutated versions of normal cellular genes (called proto-oncogenes) encoding proteins that control cell proliferation, survival and spread. In normal cells, the expression of proto-oncogenes is tightly regulated but, in cancer, abnormal proto-oncogene function causes uncontrolled cell division, enhanced survival (even during anticancer treatment) and dissemination. A single mutated copy of a proto-oncogene can promote cancer (so-called phenotypic dominance). Such mutations are rarely associated with inherited cancer syndromes: *ret* proto-oncogene mutations are associated with multiple endocrine neoplasia (MEN) syndromes (types 2A and 2B) and germline mutations in *H-ras* can cause Costello syndrome (high birthweight, cardiomyopathy and cancer predisposition). Oncogenes are activated in three ways to cause cancer:

- gene mutation can change the genetic code and enhance the function of the encoded protein (e.g. *RAS* mutation)
- gene amplification results in multiple additional copies of a normal gene being present in the genome (e.g. *EGFR* amplification)
- gene translocation, which is important in salivary gland cancers, involves movement of genetic material from its normal chromosomal locus to a new position which is usually on a different chromosome.

In contrast, tumour suppressor genes (TSGs) are normal cellular genes whose function inhibits cell proliferation and survival. The function of both copies of a TSG must be lost in order to promote cancer (so-called phenotypic recessiveness). Mutated TSGs are responsible for the majority of inherited cancer syndromes, although this is not a significant cause of head and neck cancers.

THE HALLMARKS AND ENABLING CHARACTERISTICS OF CANCER

Eight key changes that drive the malignant process have been described: these 'hallmarks of cancer' are: growth factor independence; evading growth suppressors; avoiding apoptosis; maintaining replicative potential; angiogenesis; invasion/metastasis; reprogrammed energy metabolism; and evading immune destruction (**Figure 30.1**).[2] In addition, two so-called enabling characteristics of cancer (genomic instability and inflammation) have been defined.[3] These processes are described briefly below.

Growth factor independence

In normal health, activation of growth factor receptors (GFRs) is very tightly controlled, as is the synthesis and release of the ligands that stimulate them. Cancer cells overactivate normal GFR signalling pathways to promote unrestrained cell division through three main strategies: (i) they make and release growth factors to stimulate their own receptors (autocrine signalling) and those on neighbouring cells (paracrine signalling); (ii) they modify the number, structure and/or function of surface GFRs to increase the rate and duration of receptor activation (even in the absence of ligand); (iii) they deregulate signalling pathways downstream of GFRs so they are permanently turned on (constitutively active).

Insensitivity to anti-growth signals

Anti-growth signals can force cells into quiescence (G0 stage of the cell cycle) or induce their terminal differentiation, which represents a state in which they will no longer multiply. Anti-growth signalling is mediated by cell surface ligand-receptor interactions, especially through transforming growth factor beta (TGF-β) binding to TGF-β receptor. Anti-growth signalling pathways mainly control cell progression and mediate their effects through retinoblastoma protein (Rb), cyclins, cyclin-dependent kinases (CDK) and their inhibitors (CDKi). Loss of normal anti-growth signalling pathways is extremely common in head and neck cancers.

Avoidance of apoptosis

Normal cells constantly audit the balance between incoming survival and death signals. They require constant 'reassurance' from their environment in order to prevent them from activating signalling pathways that would result in their committing suicide. In normal cells, DNA damage (including that induced by radiotherapy or chemotherapy) leads to a block in proliferation (cell cycle arrest) and an evaluation of the cell's capacity for repair. If the damage exceeds the repair capacity, the balance of survival and death signals swings in favour of the death signals and the cell commits to programmed cell death (apoptosis). This mechanism guards the genome against persisting DNA damage and prevents mutations being passed to the daughters of cell division. Loss of normal apoptotic pathway signalling is an extremely common event in cancer. Indeed, the best known cancer-associated gene (*p53*) is intimately involved in controlling apoptosis and is functionally inactivated in the majority of head and neck cancers.[4,5] By circumventing normal apoptotic signalling, cancer cells are better able to sustain DNA damage without its causing cell death and are more likely to be intrinsically resistant to anticancer treatments.

Sustained angiogenesis

In normal tissues, growth of new blood vessels (angiogenesis) is held very tightly in check by a balance between stimulatory (pro-angiogenic) and inhibitory (anti-angiogenic) signals, which normally favours inhibitory signalling.

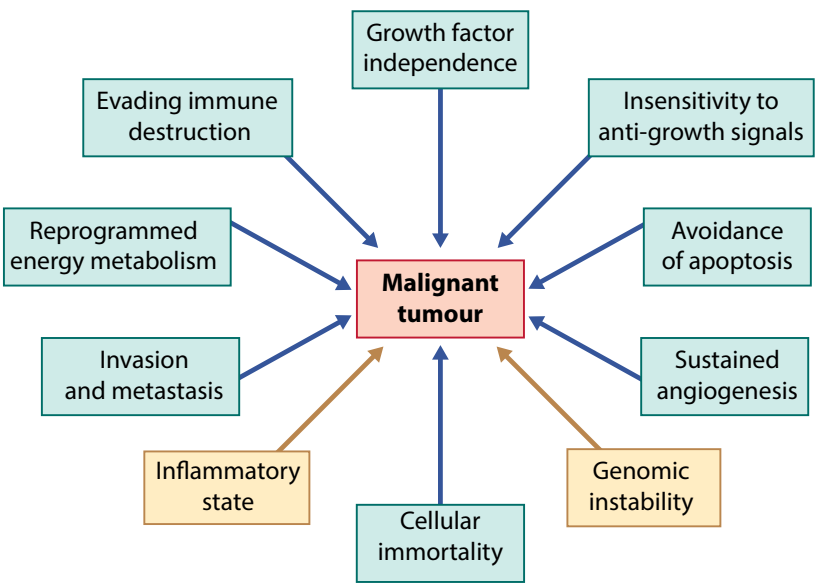


Figure 30.1 The eight hallmarks (blue boxes) and two enabling characteristics (yellow boxes) of cancer.

The growth of cancer deposits is linked to their being able to secure a dedicated blood supply. The diameter of growing cancer deposits is restricted to 60–100 μm by the diffusion limit of oxygen and nutrients from blood vessels. If a nascent tumour is to exceed this limit, it must develop its own blood supply. Cancers recalibrate the balance between pro- and anti-angiogenic factors and activate the so-called 'angiogenic switch'. To do this, they increase production of pro-angiogenic proteins, such as vascular endothelial growth factor (VEGF), and/or decrease production of anti-angiogenic proteins, such as thrombospondin-1.

Cellular immortality

Normal somatic cells can complete a finite number of cell divisions (Hayflick limit) before they permanently arrest their growth in a process of replicative senescence. This process occurs because cells cannot fully replicate the telomeric terminal portions of chromosomes at each cell division. Over time, telomeres shorten progressively, effectively behaving like molecular clocks that count down a normal cell's lifespan. In contrast, stem cells and malignant cells achieve immortality by maintaining the length of their telomeres. In most tumours, this process involves upregulation of cellular telomerase, but in 10–15% of cases a different mechanism called alternative lengthening of the telomeres (ALT) is responsible.

Invasion and metastasis

Distant metastases cause 90% of cancer deaths. A series of complex biological processes must be co-ordinated in order that metastasis can occur:[6] (i) disengagement from cellular and stromal attachments at the local site; (ii) degradation of the extracellular matrix followed by specific directional motility; (iii) invasion of blood/lymphatic vessels and tumour embolization; (iv) survival in the circulation until arrival at the metastatic site; (v) adherence to endothelium of blood vessels at the metastatic site and extravasation from the vessel; (vi) proliferation and invasion at the new location and recruitment of a new blood supply. The patterns of metastasis to specific organs are not random, but appear to be driven by expression of chemokine receptors by tumour cells that allow them to 'seek' a suitable environment in which to establish a colony.[7] Interestingly, the patterns of metastasis of human papillomavirus-positive (HPV+ve) and -negative (HPV-ve) head and neck tumours appear to be different and the underlying mechanisms of this phenomenon remain to be elucidated.

Reprogrammed energy metabolism

Chronic, uncontrolled cancer cell proliferation requires a reconfiguration of the way in which cancer cells metabolize glucose.[8] Normal cells process glucose, initially in the cytoplasm by glycolysis to yield pyruvate, and then in the mitochondria by oxidative phosphorylation to generate carbon dioxide and water. In contrast, even under oxygenated conditions, cancer cells tend to switch their metabolism to preferential use of glycolysis with generation of lactate (the so-called Warburg effect). As a consequence, they generate only two adenosine triphosphate (ATP) molecules per glucose (as opposed to a maximum of 38 via oxidative phosphorylation). As yet, the reasons for this apparently profligate use of glucose are not entirely clear but seem to provide proliferating cancer cells with a means of generating large amounts of essential metabolic precursors. This reprogramming is driven by mutations in key oncogenes and TSGs and this suggests that it is an important underlying principle of cancer biology.

Evading immune destruction

The relationship between a tumour and the immune system of the host in which it grows is immensely complex. According to the theory of immune surveillance, the immune system mounts a constant vigil against the emergence of premalignant and frankly malignant cells. The most frequently cited evidence for this comes from the observation that chronic immunosuppression (e.g. after kidney transplantation) is associated with a marked increase in specific cancers, especially those of viral origin. The immune system also appears to present a significant barrier to non-viral cancers in immunocompetent patients. However, it is clear that this function of the immune system frequently fails, as shown by the occurrence of malignant tumours. A paradigm that has been proposed to explain the interplay between an evolving tumour and the host's immune system over time is the so-called Elimination-Equilibrium-Escape model.[9] This model supposes that the immune system is frequently able to eliminate mutant precancerous/cancerous cell clones such that they never become clinically apparent. However, in some instances, the emerging tumour cells are able to suppress antitumour immune responses sufficiently to allow them to establish a state of equilibrium in which they can persist, albeit as microscopic, dormant deposits of malignant cells. Ultimately, some nascent tumour deposits will accumulate other changes (e.g. loss of tumour-associated antigens or major histocompatibility complex proteins) that will allow them to escape from immunosurveillance and emerge as clinically apparent malignancies. As part of this process, it is thought that selection of less immunogenic cancer cells (through immunoediting) and active recruitment of immunosuppressive components of the immune system (e.g. regulatory T-cells (T_{reg}) and myeloid-derived suppressor cells (MDSCs)) to some cancers allows tumours to develop and spread without becoming targets for immune clearance.

Although it is currently impossible to validate this paradigm, it provides a useful framework in which to approach the development of novel immunotherapies that may be able to target all aspects of the cancer-immune system interaction.

Enabling characteristics of cancer

The roles of genomic instability and inflammation in enabling carcinogenesis have recently been highlighted.

Genetic instability defines a state in which cancer cells lose control of the integrity of their genetic material. As such, they acquire an increasing repertoire of mutational changes that progressively alters their biology and promote the hallmarks of cancer. The second enabling characteristic describes the common situation in which premalignant and frankly malignant lesions excite an inflammatory state through the recruitment and activation of components of the immune system that promote and support tumour growth and spread.

BIOLOGICALLY TARGETED AGENTS

Huge improvements in our knowledge of the biology of cancer have opened up the possibility of developing novel targeted therapies for head and neck (and other) cancers. In this section, the review will focus on three specific themes that, at the time of writing, appear most promising. These areas are: (i) targeting growth factor independence; (ii) developing molecularly targeted drugs that enhance the response to radiotherapy (radiosensitizers); and (iii) enhancing antitumour immune responses using immunomodulatory monoclonal antibodies (MAB).

Targeting growth factor independence

Squamous cell cancers of the head and neck (SCCHN) very frequently display upregulated epidermal growth factor receptor (EGFR) signalling. EGFR is a member of the c-erbB family of transmembrane type I receptor tyrosine kinases. These receptors, comprising four members (EGFR/c-erbB-1/HER1, c-erbB-2/neu/HER-2, c-erbB-3/HER-3, c-erbB-4/HER-4),[10, 11] consist of a glycosylated extracellular ligand-binding domain, a hydrophobic trans-membrane component and an intracellular domain with tyrosine kinase activity (**Figure 30.2**). Binding of the cognate ligand to the specific ligand-binding domain on the extracellular component of EGFR leads to a cascade of intracellular secondary messengers that lead to altered patterns of gene expression, such that the binding of a protein on the cell surface is able to influence the cell's behaviour. Normally, activation of EGFR is tightly controlled, as is the synthesis and release of the ligands (transforming growth factor alpha and epidermal growth factor) that bind to it.

SCCHN achieves growth factor independence by: manufacturing and releasing growth factors that stimulate its own receptors (autocrine signalling) and those of neighbouring cells (paracrine signalling); altering the number, structure or function of the surface growth factor receptors that it displays; and by deregulating the signalling pathway downstream of the receptor. In contrast to certain tumour types where EGFR gene amplification or mutation is implicated, overexpression of the receptor, without gene amplification, is the dominant process whereby EGFR influences the pathobiology of SCCHN. A mutated form of EGFR (EGFR variant III) was reported to be present in 42% of head and neck cancers,[12] but recent reports have suggested that it does not play a major role in head and neck cancer biology.[13] The contribution of c-erbB-2 and c-erbB-3 expression to the biology of SCCHN remains unclear, but it is known that c-erbB-2:c-erbB-3 (HER2/HER3) heterodimers are potent inducers of the PI3-kinase anti-apoptotic pathway.[14]

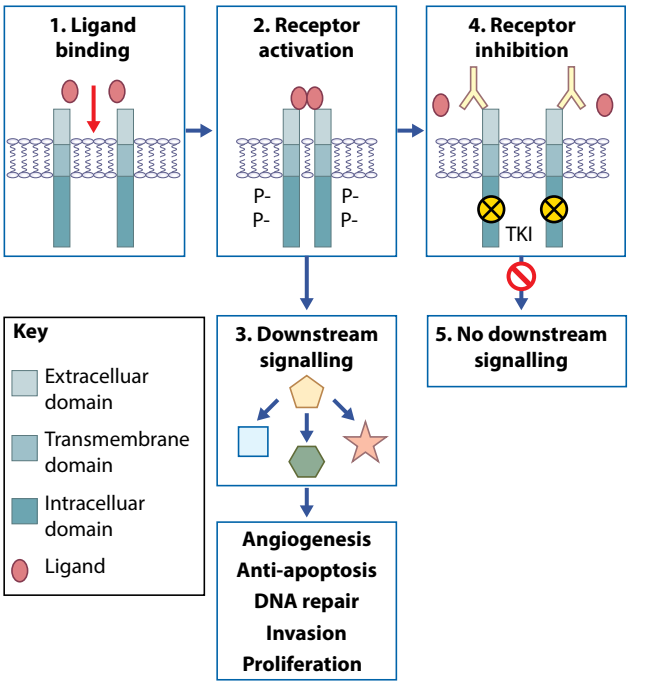


Figure 30.2 Growth factor independence can lead to sustained signalling in pathways that control essential biological functions, such as growth, apoptosis, angiogenesis, invasion and DNA damage repair. Ligand binding **(1)** leads to receptor dimerization and activation **(2)** through phosphorylation of tyrosine residues on the intracellular domain. Downstream signal transduction **(3)** activates important biological functions necessary for tumour growth, survival and spread. This process can be blocked **(4)** by monoclonal antibodies (MAB) that target the extracellular domain of the receptor or by small molecule tyrosine kinase inhibitors (TKI) that interact with enzymatic activity in the intracellular part of the receptor. These inhibitors are able to switch off downstream signalling events **(5)**.

c-erbB receptors are attractive therapeutic targets in SCCHN. Two classes of drugs, MAB and small molecule tyrosine kinase inhibitors (smTKI) have entered clinical trials. MAB are directed against the extracellular domain of the receptor, while smTKI inhibit the intracellular kinase domain of the receptor.

ANTI-EGFR MAB

Anti-EGFR MAB in the curative setting

A number of EGFR-targeted MAB have been tested in the clinic. They differ in terms of their species of origin (murine, chimeric (part human/part murine) or fully human) and the part (epitope) of the EGFR protein that they target. Cetuximab (C225, Erbitux) is a human-murine chimeric MAB. *In vitro* studies showed antitumour activity through anti-proliferative effects, direct cytotoxicity and potentiation of the effects of chemotherapy or radiotherapy.[15–18] In addition, *in vivo* experiments

demonstrated anti-angiogenic effects.[19] Early stage clinical trials confirmed the efficacy of cetuximab in combination with chemotherapy or radiotherapy.[20–24]

In a phase III study of 424 subjects with locally or regionally advanced SCCHN, locoregional control (median 24.4 vs. 14.9 months; hazard ratio: 0.68; P = 0.005) and overall survival (median 49.0 vs. 29.3 months; hazard ratio: 0.74; P = 0.03) were significantly prolonged in patients receiving radiotherapy and cetuximab compared to those treated with radiotherapy alone.[25] Cetuximab was associated with a higher incidence of rash and infusion reactions, but otherwise the grade 3 and greater toxic effects were the same in the 2 groups. Further analysis of the data showed that the occurrence of skin reaction represented a biomarker of favourable outcome in this group of patients.[26] The clinical importance of these findings, especially in an era in which concomitant chemoradiotherapy (not radiotherapy alone) is the standard-of-care, has been questioned. As a result, the Radiation Therapy Oncology Group (RTOG) conducted a follow-on study (RTOG-0522) in 940 patients with locoregionally advanced disease in which they tested radiation plus cisplatin versus radiation, cisplatin and cetuximab. Disappointingly, there were no significant differences in 2-year progression-free or overall survival rates.[27] The triple combination of bio-chemoradiotherapy was associated with significantly worse grade 3 and 4 mucosal/skin reactions. In a different approach, the phase II TREMPLIN study randomly assigned patients with locally-advanced laryngo-hypopharyngeal cancers, who had had a > 50% response to induction taxane-based triplet chemotherapy, to either concomitant cisplatin-based chemoradiotherapy or cetuximab-RT.[28] Of 153 patients who enrolled in the study, 116 were randomized after induction chemotherapy (i.e. they had a sufficiently good response to treatment). There were no differences in outcomes between the two treatment groups in terms of larynx preservation or overall survival.

Similar findings have been reported with a human MAB, zalutumumab, from the DAHANCA-19 study in which 619 patients were enrolled to receive modestly accelerated radiotherapy, the hypoxic cell sensitizer nimorazole and cisplatin (if indicated), with or without zalutumumab.[29] The majority of patients had stage III/IV disease and 70% received concomitant cisplatin. Treatment was well tolerated, but almost all (94%) patients in the zalutumumab arm reported a skin rash (grade 3–4 in 29%). No difference was seen between the study arms in terms of locoregional control at 3 years (78% in the zalutumumab arm and 79% in the control arm, (hazard ratio 0.8; 95% confidence interval 0.6–1.2). The data for disease-free and overall survival rates also failed to show a difference between the zalutumumab and control arms.

In addition, two studies with panitumumab (Vectibix), a fully human anti-EGFR monoclonal antibody have yielded negative data.[30, 31] The CONCERT-1 study randomized patients with previously untreated stage III-IVb disease to chemoradiotherapy or chemoradiotherapy plus panitumumab.[30] Of the 150 patients treated, 63 received standard chemoradiotherapy and 87 received chemoradiotherapy plus panitumumab. Locoregional control (LRC) at 2 years was non-statistically significantly better for standard chemoradiotherapy (68% vs. 61%) and the overall comparison for LRC showed a hazard ratio of 1.33 (95% confidence intervals (95% CI) 0.77–2.30). Data for progression-free and overall survival also showed no benefit from the addition of panitumumab (hazard ratios 1.15 (95% CI 0.68–1.96) and 1.63 (95% CI 0.88–3.02), respectively). The combination with panitumumab was significantly more toxic, with increased grade ≥ 3 dysphagia (40% vs. 27%), grade ≥ 3 mucosal inflammation (55% vs. 24%) and grade ≥ 3 radiodermatitis (31% vs. 13%). The CONCERT-2 study had a different design and evaluated platin-based chemoradiotherapy vs. radiation plus panitumumab (without platin chemotherapy) in patients with unresected stage III–IVb disease.[31] Of the 151 patients treated, 61 received standard chemoradiotherapy and 90 received radiation plus panitumumab. As with CONCERT-1, there was a non-statistically significant difference in LRC with radiation plus panitumumab performing worse (hazard ratio 1.61 95% CI 0.98–2.66), p = 0.06). A similar trend was also seen in terms of overall survival (hazard ratio 1.59 95% CI 0.91–2.79). Radiation plus panitumumab showed a statistically significant detriment for progression-free survival in this study (hazard ratio 1.73 (95% CI 1.07–2.81). Again, grade ≥ 3 radiation-induced toxicities were more common in the patients who received panitumumab.

Taken together, these data indicate that, in the curative setting, anti-EGFR MAB therapy should be restricted to the use of cetuximab plus radiotherapy. The precise indications for how this should be used, to replace cisplatin in patients who will not tolerate standard chemoradiotherapy or as a less toxic treatment in human papillomavirus positive oropharyngeal cancers (HPV+ OPC), remains to be defined precisely. In the latter case, a number of studies are ongoing to define the role of cetuximab plus radiotherapy combinations in HPV+ OPC [RTOG 1016 NCT01302834, UK De-Escalate HPV NCT01874171 and Trans-Tasman Oncology Group NCT01855451].

Anti-EGFR MAB in the palliative setting

Cetuximab has also been shown to improve the outcome of first-line palliative chemotherapy. In the EXTREME study, 442 eligible patients with untreated recurrent/metastatic SCCHN received cisplatin (100 mg/m^2) or carboplatin (area under the curve of 5 mg/mL/min) plus 5-fluorouracil (1 g/m^2 per day for 4 days) every 3 weeks for a maximum of 6 cycles. Cetuximab (400 mg/m^2 loading dose, then 250 mg/m^2 per week) was administered to 222 randomly selected patients. Patients in the cetuximab arm who showed stable disease were permitted to continue with maintenance cetuximab until disease progression or unacceptable toxicity. This study showed that the cetuximab/platinum/5-fluorouracil combination prolonged median overall survival from 7.4 months to 10.1 months (P = 0.04). There were also increases in the median progression-free survival time (3.3 to 5.6 months; P < 0.001) and the response rate (20% to 36%; P < 0.001).[32]

A similar trial design was employed for the SPECTRUM study, which evaluated the humanized MAB panitumumab. Patients in both groups received up to six 3-weekly cycles of intravenous cisplatin (100 mg/m^2) and 5-fluorouracil (1 g/m^2 per day for 4 days), while those in the experimental group also received intravenous panitumumab.[33] As in the EXTREME trial, patients randomized to panitumumab could continue maintenance MAB treatment. A total of 657 patients were randomized and the median overall survivals were 11·1 versus 9.0 months (hazard ratio 0·873; P = 0·1403) in the panitumumab and control groups, respectively. Despite this negative finding for overall survival, there was a statistically significant improvement in median progression-free survival in favour of panitumumab (5.8 vs. 4.6 months, hazard ratio 0·780; P = 0·0036). In sub-group analysis, the median overall survival in patients with p16-negative, but not p16-positive, tumours was prolonged in the panitumumab group (11.7 vs. 8.6 months; hazard ratio 0·73; P = 0·012). A number of toxicities, including rash and biochemical abnormalities were more common in the MAB-treated group.

Single-agent zalutumumab has been assessed in a 2:1 randomized phase III study versus best supportive care (including methotrexate) in 286 patients with platinum-resistant SCCHN.[34] The median overall survivals in the zalutumumab and control groups were 6.7 and 5.2 months (hazard ratio 0.77; P = 0.065), respectively. There was a statistically significant improvement in progression-free survival for zalutumumab (hazard ratio 0.63; P = 0.0012). As for previous studies, rash was more common in the group randomized to the anti-EGFR MAB.

Therefore, it appears that triple-agent therapy with platin/5-fluorouracil and cetuximab may be beneficial for patients as first-line therapy for relapsed/metastatic disease. In practice, many patients do not receive the triple therapy because of concerns about the additional toxicity of adding cetuximab to standard treatment. Although single-agent cetuximab is licensed for use in the USA, its use is not approved in Europe. Other single agent anti-EGFR MABs should not be used in relapsed/metastatic head and neck cancers.

SMALL MOLECULE TYROSINE KINASE INHIBITORS

Small molecule tyrosine kinase inhibitors in the curative setting

Gefitinib (ZD1839, Iressa) is a low-molecular weight smTKI that is highly specific for EGFR. By competing with ATP on the intracellular domain of EGFR it has been shown to prevent receptor autophosphorylation with resultant anti-proliferative effects observed in a variety of human xenograft models. Furthermore, combining gefitinib with cytotoxic chemotherapy increases growth inhibition and apoptotic cell death.[35–37]

It has been reported that gefitinib can be safely combined with chemoradiotherapy both with standard cisplatin-based chemoradiotherapy and with a rather unconventional split-course, twice-daily schedule with 5-fluorouracil and hydroxyurea.[38, 39] Results for erlotinib in this context have been disappointing with no improvement in treatment outcomes and increased toxicity when combined with chemoradiotherapy in a randomized phase II study.[40]

Lapatinib is an oral dual smTKI with action against both EGFR and c-erbB2/(HER-2).[41] It has demonstrated activity both *in vitro* and *in vivo*, as well as showing tolerability in phase I clinical trials.[42] A placebo-controlled randomized window-of-opportunity biomarker study has been performed with this agent in patients with advanced SCCHN. A single agent response rate of 17% was reported, with biomarker evidence of significantly reduced proliferation and receptor phosphorylation in the lapatinib treated group.[43] A phase I dose escalation study of lapatinib administered during radical chemoradiotherapy has been completed in patients with stage III and IV head and neck cancer.[44] Patients were enrolled in three cohorts of escalating lapatinib dose: 500 mg, 1000 mg and 1500 mg/day. Patients received one week of lapatinib alone followed by 6.5 to 7 weeks of the same dose of lapatinib plus radiotherapy 66–70 Gy and cisplatin 100 mg/m^2 on days 1, 22 and 43 of radiotherapy. The most common Grade 3–4 adverse events were radiation mucositis, radiation dermatitis, lymphopaenia and neutropaenia. The recommended phase II dose was defined as lapatinib 1500 mg/day with chemoradiation. Based on these findings, randomized phase II and III studies of lapatinib plus chemoradiation were initiated.

The randomized phase II study assessed the activity and safety of concurrent chemoradiotherapy and lapatinib followed by maintenance treatment in locally advanced, unresected stage III/IVA/IVB head and neck cancer.[45] Patients were randomized 1:1 to concurrent chemoradiotherapy and placebo followed by placebo or concurrent chemoradiotherapy and lapatinib followed by lapatinib. Treatment continued until disease progression or study withdrawal. Primary endpoint was complete response rate by independent review 6 months post-chemoradiotherapy. Sixty-seven patients (median age 56 years; 97% Eastern Cooperative Oncology Group performance status ≤1; 82% stage IV) were recruited. Lapatinib combined with chemoradiation was well-tolerated. Grade 3/4 toxicities during CRT were balanced between arms, with the exception of an excess of grade 3 diarrhoea (6% vs. 0%) and rash (9% vs. 3%) and two grade 4 cardiac events in the lapatinib arm. Complete response rate at 6 months post-chemoradiotherapy was 53% with lapatinib versus 36% with placebo in the intent-to-treat population. The progression-free survival and overall survival rates at 18 months were 55% vs. 41% and 68% vs. 57% for the lapatinib and placebo arms, respectively. The difference between study arms was greatest in p16-negative disease (median progression-free survival >20.4 months [lapatinib] vs. 10.9 [placebo]). These data led to the instigation of the randomized phase II TRYHARD study (NCT01711658) in patients with HPV-ve disease.

A randomized phase III study of lapatinib administered concomitantly with chemoradiotherapy and as maintenance monotherapy in patients with high-risk surgically-treated SCCHN has also been reported.[46] Patients with

resected stage II-IVA SCCHN, with a surgical margin ≤ 5 mm and/or extracapsular extension in metastatic cervical nodal disease were randomized to chemoradiotherapy (66 Gy total dose and 100 mg/m^2 cisplatin administered on days 1, 22 and 43) plus placebo or lapatinib (1500 mg/day) prior to and during chemoradiotherapy, followed by 12 months of maintenance monotherapy (either placebo or lapatinib). Six hundred and eighty-eight patients were enrolled; 346 received lapatinib and 342 received placebo. With a median follow-up of 35.3 months, the study was terminated early due to the apparent plateauing of disease-free survival events. Median disease-free survival was 53.6 months and not reached for lapatinib and placebo, respectively; hazard ratio 1.10 (95% CI 0.85–1.43). No significant differences in disease-free survival by HPV status, or overall survival, were observed between the two treatment arms. Similar numbers of patients in both treatment arms experienced adverse events, with more patients in the lapatinib arm experiencing serious events (48% vs. 40%). This study demonstrated that adding lapatinib to chemoradiotherapy and its use as long-term maintenance therapy did not offer any efficacy or safety benefits compared with placebo, in patients with surgically-treated high-risk SCCHN.

Afatinib is an irreversible inhibitor of EGFR, c-erbB2/HER2 and c-erbB4/HER4 that is being investigated in a number of settings in SCCHN. In the primary treatment setting, it is being tested in combination with chemoradiation (NCT01732640), and as adjuvant therapy after definitive chemoradiation in high-risk patients (phase III LUX2 study NCT01345669) or after surgery (GORTEC 2010-02, EudraCT 2010-023265-22). As yet, data are not available to permit a judgement of the potential role of this agent in the curative setting in patients with SCCHN.

Overall, despite significant clinical trial activity, there is no clear indication for the use of a smTKI in the treatment of newly diagnosed SCCHN. This is most clearly true in the case of combinations of smTKI with definitive chemoradiotherapy, but the existing data also suggest that there is no clear role in the adjuvant setting. Further trial data will become available in the coming years and this situation may change.

Small molecule tyrosine kinase inhibitors in the palliative setting

Gefitinib was evaluated in phase I trials that included a number of patients with head and neck cancer.[47–50] It was well-tolerated at doses from 150 to 800 mg/m^2, the most frequent grade 1 or 2 toxicities were diarrhoea (47–55%), asthenia (44%) and an acneiform follicular rash (46–64%). Antitumour activity, including both partial responses and cases of prolonged stable disease, was observed at all doses. Clinically meaningful stable disease was achieved in 50% of patients with SCCHN, and quality-of-life ratings also remained stable during treatment, except in one study where they improved significantly over time.[50]

A phase II study has evaluated oral gefitinib (500 mg/day) as first- or second-line monotherapy in 52 patients with recurrent or metastatic SCCHN most of whom had previously received combination chemotherapy or radiotherapy.[51] Forty-seven patients were evaluable for tumour response and an objective partial response rate of 10.6% (one complete response) was demonstrated. Disease control, defined as objective tumour response plus stable disease, was achieved in 53% of patients and was sustained for more than 6 months in 13% of patients. The response rates and survival times of patients who received gefitinib as first-line therapy were not significantly different to those of patients who had received prior chemotherapy. Overall, the median times to progression and death were 3.4 months and 8.1 months respectively, with an estimated 1-year survival of 29%. There was only a single case of grade 4 toxicity (hypercalcaemia), a 4–6% incidence of grade 3 toxicity (anorexia, diarrhoea, nausea and hypercalcaemia), grade 1 or 2 skin rash in 48% and grade 1 or 2 diarrhoea in 50%. A second study using single-agent gefitinib at a dose of 500 mg/day has also been reported.[52] Clinical, symptomatic and radiological response, time to progression, survival and toxicity were recorded. Forty-seven patients were treated and the observed clinical response rate was 8% with a disease control rate (complete response, partial response, stable disease) of 36%. Thirty-four percent of patients experienced a symptomatic improvement. The median time to progression and survival were 2.6 and 4.3 months, respectively. Acneiform folliculitis was the most frequent toxicity observed (76%) but the majority of cases were grade 1 or 2. Only 4 patients experienced grade 3 toxicity of any type (all cases of folliculitis). The 250 mg/day dose was also tested in phase II trial and appeared to be less active than the 500 mg/day dose.[53]

Subsequently, a randomized phase III study was conducted to compare survival in patients with recurrent or metastatic SCCHN treated with gefitinib 250 or 500 mg/day or standard-of-care single-agent methotrexate.[54] Four hundred and eighty-six patients were randomized to oral gefitinib 250 mg/day, gefitinib 500 mg/day, or intravenous methotrexate 40 mg/m^2 weekly. Neither of the gefitinib doses improved overall survival compared with methotrexate (hazard ratios 1.22 (95% CI, 0.95–1.57 and 1.12 (95% CI, 0.87–1.43), respectively. The median overall survivals were 5.6, 6.0, and 6.7 months for gefitinib 250 mg/day, gefitinib 500 mg/day, and intravenous methotrexate, respectively. Interestingly, gefitinib therapy appeared to be associated with an increased risk of haemorrhagic events. These data do not support the use of gefitinib as a palliative therapy in relapsed/metastatic SCCHN.

Afatinib has been assessed in the phase III LUX head and neck-1 study in patients receiving second-line therapy for relapsed/metastatic SCCHN.[55] A total of 583 patients were treated with afatinib (322 patients) or methotrexate (161 patients). Afatinib significantly increased median progression-free survival (2.6 vs. 1.7 months, p = 0.03) but did not improve median overall survival (6.8 vs 6.0 months) relative to methotrexate. The overall response rates of the two study arms were low – 10.2% and 5.6%, respectively. In an integrated analysis of quality of life, afatinib showed a delay in deterioration of global health status, pain and

swallowing problems (all $p \leq 0.03$). The profile of toxicities was markedly different between the two treatments, with afatinib causing more rash and diarrhoea and methotrexate causing more stomatitis and leukopenia. A randomized phase II comparison of afatinib and cetuximab has also demonstrated that afatinib has similar antitumour activity to cetuximab, as assessed by tumour shrinkage on treatment.[56] It remains to be seen if, on the basis of these data, afatinib finds a place in the treatment process for patients with relapsed/metastatic SCCHN.

Molecularly targeted radiosensitizers

Radiotherapy is an extremely effective therapy for SCCHN. Sophisticated modern 3-dimensional conformal planning techniques allow us to target tumour volumes more accurately than was the case with previous conventional methods. In addition, advanced delivery systems, such as intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT), offer the prospect of higher rates of tumour control with reduced toxicity.

In tandem with the development of advanced radiotherapy techniques, a parallel track of preclinical and clinical studies has evaluated combinations of radiotherapy with cytotoxic drugs in an attempt to enhance radiation-induced cytotoxicity in cancer cells.[57] As a result of meta-analyses of a large number of small- to medium-sized randomized trials, we now recognize radiotherapy delivered with concomitant platin monotherapy as the standard-of-care for locally advanced SCCHN.[58]

As discussed earlier, there is an increasing understanding of the molecular pathways leading to malignant transformation in normal cells. DNA damage, which is an inevitable consequence of cellular metabolism and proliferation, can also be caused by exogenous agents including ionizing and non-ionizing irradiation and environmental chemical toxins. Clinical and medical oncologists exploit these agents, in the form of radiotherapy and chemotherapy, to inflict DNA damage on cancer cells. However, cancers frequently have a deranged DNA damage response and, as discussed earlier, this leads to a state of genomic instability that can drive the evolution of more aggressive cellular clones within the tumour. Importantly, the loss of key components of the DNA damage response may also constitute a cancer-specific molecular 'Achilles' heel' that is vulnerable to therapeutic exploitation with a new generation of targeted radiosensitizing agents.[59] Development of radiosensitizers designed to target the DNA damage response (DDR) will require very careful clinical trial design, because of the potential risks of unwanted and unacceptable normal tissue toxicity arising from damage to normal cells.[57, 59]

CELL CYCLE CONTROL AND DNA DAMAGE REPAIR

Cell division is an essential component of development, growth and tissue repair. Since this process involves replicating the cell's genetic material, it is not surprising that it is tightly regulated to ensure that each daughter cell receives an accurate copy of the genome. Failure to copy the cellular DNA faithfully exposes the daughter cells to the risk of inheriting mutations. During the cell cycle, there are opportunities for the cell to slow down or pause while it assesses genomic integrity and corrects errors in the sequence of DNA. Cells can also slow down or stop in the cell cycle when they experience DNA damage, including that inflicted by radiotherapy and/or chemotherapy. Overall, there are 4 cell cycle checkpoints: at the G1/S transition, during S phase, early in G2 phase and late in G2 phase. Two of these are particularly relevant to the cellular response to radiotherapy. The G1/S checkpoint allows diploid (2n, 46 chromosomes) cells to pause before entering synthesis (S) phase, during which the entire DNA complement is duplicated to create a cell with 4n DNA content before mitosis. The TSGs *TP53* and retinoblastoma (*RB1*) play central roles in the G1/S checkpoint. *TP53* pathway mutation or inactivation is extremely common in many tumours, including head and neck cancers. In fact, smoking-induced SCCHN demonstrates almost universal loss-of-function mutations of the p53 pathway, with 84% of tumours showing *TP53* mutation in The Cancer Genome Atlas Network analysis.[4] In contrast, only 3% of HPV-positive SCCHN showed mutations of *TP53*, but these tumours inactivate the pathway through interactions between viral E6 and E7 proteins with p53 and Rb proteins, respectively.[4] As a result of this very frequent aberrant status of the G1/S checkpoint, most SCCHN have become highly reliant on a functional G2/M checkpoint.

Ionizing radiation induces a number of lesions in DNA, ranging from purine and pyrimidine lesions to single-strand (SSB) and double-strand breaks (DSB) in the DNA. DSB are potentially the most lethal DNA lesions induced by radiotherapy and therapies that can prevent their repair/resolution have the potential to be profoundly radiosensitizing. As might be expected, there are specific mechanisms to detect and repair radiation-induced abnormalities in DNA structure: DSBs are repaired by non-homologous end-joining (NHEJ) repair during G1 phase of the cell cycle and by high-fidelity homologous recombination (HR) in S and G2 phases; SSBs and base damage are repaired through the base excision repair pathway.[60]

Different types of radiation-induced DNA damage are sensed by mechanisms that activate specific DDR kinases: ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR), which phosphorylate the checkpoint kinases, Chk1 and Chk2. In turn, these proteins transfer the signal to different effector molecules. The specific pathways involved are illustrated in **Figure 30.3**.

RADIATION-INDUCED CELL DEATH AND SYNTHETIC LETHALITY

Radiation-induced cell death requires cells to attempt to divide with unrepaired, damaged DNA. This is thought to result in cell death through mitotic catastrophe, in which a cell is unable to complete mitosis successfully and dies in the process.[61, 62] Alternatively, radiation can induce a state of replicative senescence in which the cell permanently loses

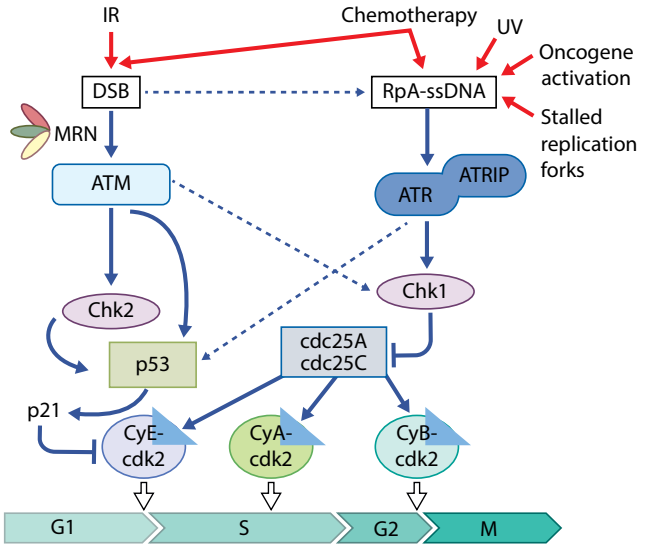


Figure 30.3 Schematic representation of the DNA damage response. The ATM pathway is activated strongly by DNA double-stranded breaks (DSB), causing activation of Chk2 and p53 with subsequent G1 cell cycle arrest. Diverse inputs converging on RpA-coated single-stranded DNA (ssDNA) activate the ATR-ATRIP complex, with downstream phosphorylation of Chk1, amongst other targets, resulting in G2/M arrest. The ATR pathway also plays an important role in S-phase progression and replication fork stabilisation. There is evidence of substantial crosstalk between these pathways (indicated by the dotted arrows).

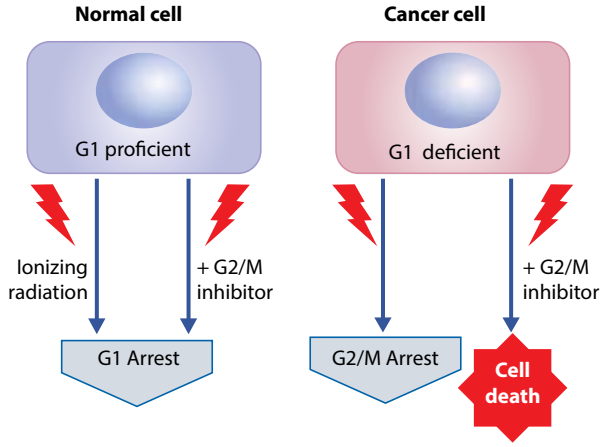


Figure 30.4 G1 checkpoint-deficient cancer cells rely heavily on radiation-induced G2/M arrest to survive after irradiation. Inhibiting the G2/M checkpoint in cancer cells will abrogate all checkpoint function in cancer cells, while intact G1 checkpoint arrest allows DNA repair in normal cells. This synthetically lethal interaction underpins interest in the G2/M checkpoint as a target for radiation-drug combination therapies.

the ability to divide and, thus, becomes non-clonogenic (and, therefore, no longer a threat to the host).[63] As discussed above, the majority of SCCHN (both HPV-ve and HPV+ve) lack a normal p53-mediated G1/S checkpoint and are highly dependent on the ATR-Chk1 pathway to mediate S and G2/M arrest to allow repair of DNA damage following irradiation. Thus, G2/M checkpoint control has been viewed as a particularly attractive target for cancer-specific radiosensitization.[59] Irradiated cancer cells that are defective in p53 pathway signalling will be unable to stop at the G1/S checkpoint and will be highly vulnerable to drugs that inhibit the G2 checkpoint.[64] Such cancer cells will proceed into mitosis before they have been able to repair their radiation-induced DNA damage and, as a result, will run a significant risk of mitotic catastrophe and cell death. This activity of G2/M checkpoint inhibitors in p53-defective tumour cells is an example of a so-called "synthetic lethal interaction" with ionizing radiation and represents a promising prospect for developing cancer-selective radiosensitizing drugs (**Figure 30.4**).

TARGETED DRUGS AS RADIOSENSITIZERS

ATR inhibitors

ATR inhibitors can radiosensitize cancer cells through disruption of the intra-S and G2 checkpoints and, perhaps, by disrupting ATR's roles in the DSB response, replication fork stabilization and the cellular response to hypoxia.[65,66] Small molecule inhibitors of ATR kinase have been tested in preclinical studies in combination with genotoxic chemotherapy or ionizing radiation. Thus far, there have been no publications on ATR inhibitors in patients with cancer, although early phase clinical trials have been initiated.

VE-821 (Vertex Pharmaceuticals, UK) is the most extensively studied ATR inhibitor to date. It caused cell death and growth inhibition in cancer cell lines and synergized with DNA-damaging agents, such as ionizing radiation.[67] The role of p53 pathway function in determining cellular sensitivity to VE-821 is, as yet, unclear.[65] A related molecule, VE-822 (Vertex Pharmaceuticals, UK) sensitized pancreatic cancer cell lines to both radiation and gemcitabine *in vitro*, without significant toxicity in normal cell lines. It also demonstrated efficacy in pancreatic tumour xenografts, with inhibition of radiation-induced Chk1 phosphorylation and a reduction in tumour growth when combined with radiation or gemcitabine-based chemoradiation in comparison to untreated or single-agent treated controls. Importantly, VE-822 did not cause any additional in-field gastrointestinal radiation-induced toxicity in animal models.[68] Specific studies in head and neck cancer models are not yet available, but it is reasonable to hypothesize that the data generated thus far should be relevant in the context of SCCHN.

AZD6738 (AstraZeneca plc) is a potent ATR inhibitor which can inhibit Chk1 pathway signalling.[69] The agent caused dose- and time-dependent induction of replication stress (measured by S-phase cell cycle accumulation by flow cytometry), increased DNA-strand breaks formation (measured by γH2AX focus formation) and growth inhibition/cell death *in vitro*. When combined with ionizing radiation *in vitro*, AZD6738 showed significant enhancement of growth inhibition activity compared to radiation or drug treatment alone in head and neck cancer (and other) cell lines. AZD6738 is currently being tested in phase I clinical trials, both as monotherapy and combined with either radiotherapy or chemotherapy [NCT02223923, NCT02264678].

Chk1 inhibitors

Chk1 is directly downstream of ATR in the DNA damage response signalling cascade and is phosphorylated by it. A number of Chk1 inhibitors have been tested preclinically,[70] but few have entered clinical trials. UCN-01 showed enhancement of radiation and genotoxic chemotherapy-induced cytotoxicity that was selective for p53-dysfunctional cells.[71] It was tested in phase I trials as monotherapy[72] and in combination with DNA-damaging agents such as platinum,[73] topoisomerase inhibitors[74] and nucleoside analogues.[75, 76] In phase II studies, UCN-01 was tested combined with DNA-damaging chemotherapy but its development was aborted due to lack of clinical efficacy.[77–79]

AZD7762 is a combined Chk1 and Chk2 inhibitor which radiosensitized tumour cells *in vitro* and *in vivo* in preclinical trials. Although it was initially suggested that this activity was p53-dependent, these data were not entirely clear-cut.[80, 81] In pancreatic cancer cell lines *in vitro* and in xenografts, AZD7762 sensitized to radiation alone and radiation in combination with gemcitabine, with abrogation of the radiation-induced G2/M checkpoint and inhibition of HR repair.[82] AZD7762 was tested in a clinical trial as a single-agent and in combination with gemcitabine (NCT00413686). Unfortunately, its development was terminated prematurely because of concerns about toxicity (especially cardiovascular effects which were manifest as significant reductions in cardiac ejection fraction).[83]

Other Chk1 inhibitors have been developed, including PF-00477736,[84, 85] MK8776 (otherwise known as SCH900776)[86] and SAR-020106.[87] The latter agent, SAR-020106, was shown to be a potent radiosensitizer both in *in vitro* and *in vivo* models. The drug inhibited radiation-induced G2/M arrest and reduced clonogenic survival in p53-deficient, but not p53-competent, tumour cells. Importantly, SAR-020106 promoted mitotic entry after irradiation in all cell lines: p53-deficient cells were likely to undergo apoptosis or become aneuploid, while p53 wild-type cells experienced a post-mitotic G1 arrest followed by subsequent normal cell cycle re-entry. Following combined treatment with SAR-020106 and radiation, HR-mediated DNA damage repair was inhibited in all cell lines. However, a significant increase in pan-γH2AX-stained apoptotic cells was observed only in p53-deficient cell lines. Efficacy was confirmed *in vivo* in a clinically relevant human head and neck cancer xenograft model.[87] The lack of oral bioavailability of this agent has arrested its clinical development. However, an orally bioavailable Chk1 inhibitor (CCT245737)[88] is entering clinical studies in a range of solid cancers and it is hoped that its development will include combination studies with radiation in disease subtypes that will include head and neck cancers.

Other G2/M-targeted checkpoint inhibitors

The Wee1 kinase regulates entry into mitosis, by negatively controlling CDK1 and 2. In a similar fashion to ATR and Chk1, it is active during normal unperturbed cell division, playing a role in the maintenance of genome integrity. A Wee1 kinase inhibitor (AZD-1775, formerly MK-1775) has been shown to sensitize p53-deficient tumour cell lines to radiation, with abrogation of radiation-induced G2 arrest and premature entry into mitosis.[89] The drug has also been shown to potentiate DNA-damaging agents *in vitro* and *in vivo*,[90, 91] and has reached a number of phase I trials. Cdc25 phosphatase is another G2 checkpoint target[92] and inhibitors have been developed that have shown activity against tumour cells and xenografts.[93]

Targeted immunomodulation as an anticancer strategy

In recent years, after decades of negative studies and false hopes, immunotherapy has emerged as a major new modality in the treatment of many solid cancers.[94] This change in the fortunes of immunotherapy has been underpinned by huge advances in our understanding of the fundamental biological principles that guide the activity of the immune system. In particular, a number of specific immune checkpoints have been discovered that are integral components of normal immune responses. In normal health, these checkpoints function to inhibit T-cells and prevent them from becoming chronically activated or aberrantly targeted against normal tissues. Effectively, they function as negative regulators or 'brakes' on the normal immune response. Many cancers subvert these inhibitory pathways in order to break free from immunosurveillance. Therefore, by activating brakes on the immune system, cancer cells are able to emerge from elimination/equilibrium phase and escape from immune detection and/or immune-related attack.[9]

Proteins that are expressed on activated T-cells, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed death 1 (PD1), are key players that allow many cancers to evade anti-tumour immunity by interfering with the activation and effector phases of immune responses, respectively. CTLA4 is an important control mechanism that influences the activation phase of the immune response. As shown in **Figure 30.5**, when a specific tumour-associated antigen is presented by an antigen-presenting cell (APC) to a T-cell that expresses a T-cell receptor capable of recognizing it, there are two possible outcomes. In the first case, if the T-cell also receives a co-stimulatory signal via B7 on the APC binding to CD28 on the T-cell, the T-cell will become activated and capable of mediating an antitumour effect. However, in becoming activated, the T-cell upregulates CTLA4 on its surface and this is able to out-compete CD28 for binding of B7 on the APC. The net effect is that the T-cell can be switched off or anergized. Therapeutic MAB that target CTLA4 are able to block this negative interaction and enhance T-cell activation. In the effector phase of the immune

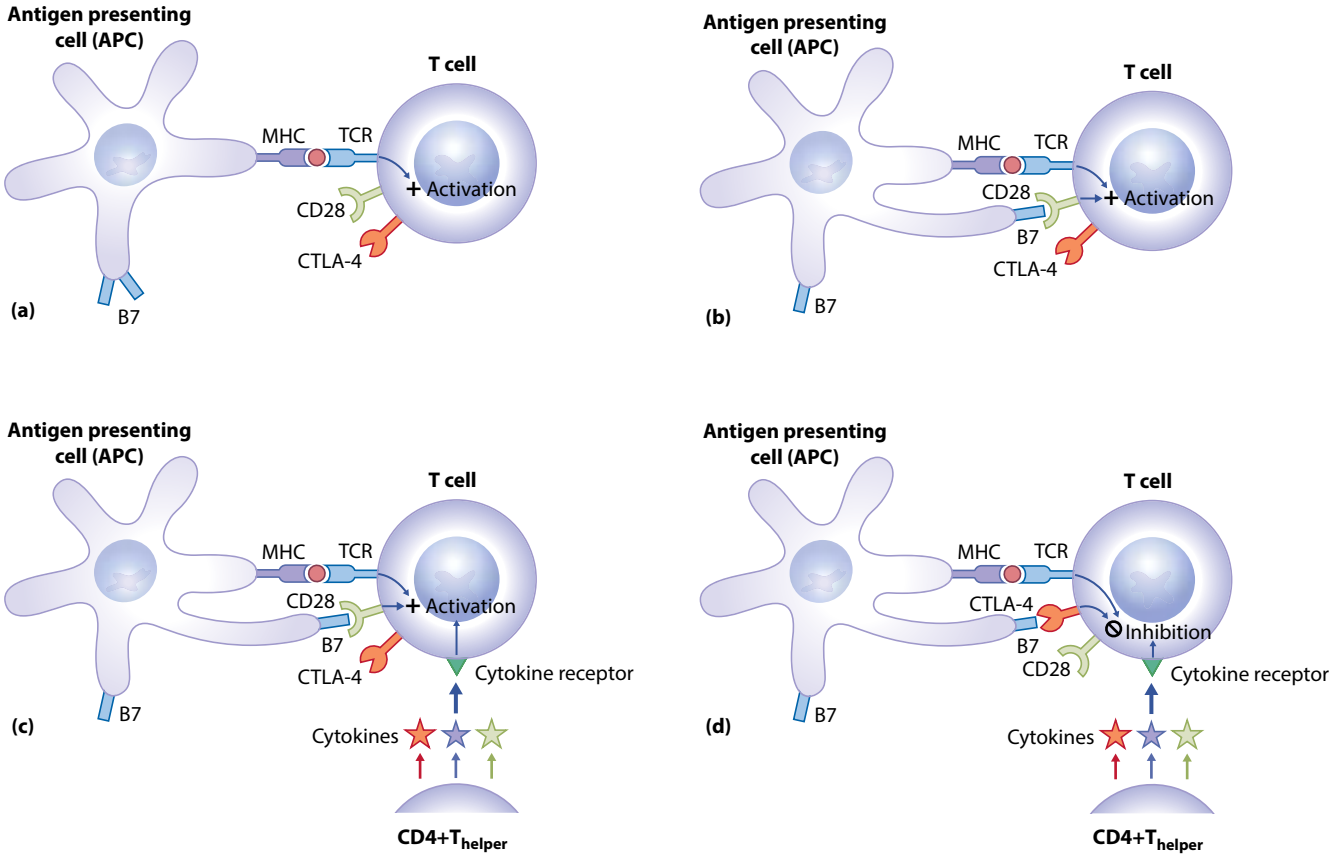


Figure 30.5 The activation phase of the immune response can be switched off by the T-cell protein CTLA-4. **(a)** Presentation of a tumour-associated antigen (TAA) on a major histocompatibility complex via a T-cell receptor leads to a positive signal (signal 1) to the T-cell; **(b)** To become fully activated, the T-cell must also receive a further signal (signal 2) when B7 on the APC binds to CD28 on the T-cell; **(c)** Activation is reinforced by cytokines released by CD4+ T_{helper} cells that bind to cytokine receptors on T-cells (signal 3); **(d)** Activation can be inhibited and the T-cell can be inactivated if CTLA-4 on the T-cell out-competes CD28 for binding of B7 on the APC (shutting off signal 2 and sending a negative message to the T-cell).

response (**Figure 30.6**), an activated T-cell can be prevented from engaging with and killing a tumour cell if the tumour cell expresses the negative regulatory ligand programmed death ligand 1 (PD-L1) on its surface (either constitutively or in response to interferon-gamma secreted by an activated T-cell). This negative interaction between T-cell and tumour cell can be interrupted by administration of specific MAB that block either PD-1 on the T-cell surface or PD-L1 on the tumour cell surface.

In addition to these two pathways, a large number of other checkpoints have been described at the immune checkpoint (e.g. TIM3, LAG3, OX40, GITR). Some of these checkpoints lead to inhibition and others to activation of immune responses. A large number of new therapeutic agents are currently in preclinical or clinical development and it is likely that some of these will reach the clinic in the next few years.

CLINICAL EXPERIENCE WITH CHECKPOINT INHIBITORS

Both anti-CTLA4 and anti-PD1/PD-L1 MAB have demonstrated significant activity in a range of non-SCCHN tumour types, including melanoma,[95–99] lung,[100] bladder[101] and mismatch repair-deficient bowel cancer.[102] Intriguingly, it appears that the likelihood of a patient deriving benefit from immunotherapy may correlate with the mutational burden and, hence, the neoantigenic load carried by their tumour.[103] This mutational load appears to be greatest in melanoma, but head and neck cancers (especially HPV-ve tumours) are also associated with a significant number of mutations.

In the context of SCCHN, there have been initial reports of single-agent activity in patients with relapsed/metastatic disease. The largest experience has accrued with single-agent therapy with the anti-PD1 monoclonal antibody, pembrolizumab. In the KEYNOTE-012 (NCT01848834) study, patients with PD-L1-positive (>1% staining of tumour cells) tumours were divided into HPV+ve and HPV–ve cohorts and treated with 10 mg/kg of pembrolizumab every 2 weeks. Treatment beyond disease progression was permitted, as long as the patient was judged to be deriving clinical benefit from therapy. Overall, 26 of 51 patients had a reduction in tumour burden and 20% satisfied standard radiological criteria (RECIST v1.1) for response.[104] In a subsequent study, a larger group of 132 patients was treated with a fixed dose

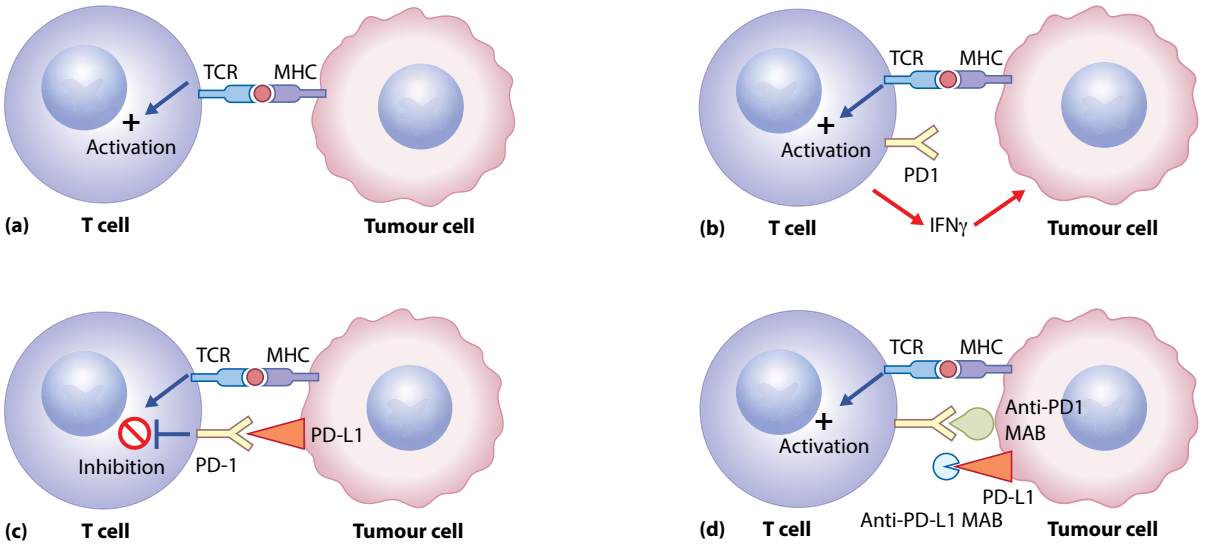


Figure 30.6 PD-1/PD-L1-mediated immune evasion by cancer can be reversed by immune checkpoint-inhibiting monoclonal antibody (MAB) therapy. **(a)** T-cells are frequently capable of recognizing tumour-associated antigens loaded on major histocompatibility (MHC) class I molecules. **(b)** In doing so, T-cells become activated and express programmed death 1 (PD-1) receptors on their surface and secrete interferon-γ (IFN-γ). **(c)** In response, tumour cells can upregulate expression of programmed death ligand 1 (PD-L1), which can bind to PD-1 on T-cells and switch them off. **(d)** Treatment with either anti-PD-1 or anti-PD-L1 MAB can block the interaction between PD-L1 on tumour cells and PD-1 on T-cells and as a result, anti-PD-1 or anti-PD-L1 MAB can reactivate T-cell activation against tumour cells.

of pembrolizumab (200 mg) every 3 weeks. Patients were included irrespective of PD-L1 status. The treatment was well tolerated with only 7.6% of patients experiencing a grade 3 or greater adverse effect. Of 99 patients who were evaluable for preliminary analysis, 18.2% showed a response (all partial responses) and 31.3% of patients had stable disease.[105] There are a number of ongoing randomized phase II and III clinical trials with both anti-PD1 and anti-PD-L1 agents (pembrolizumab [KEYNOTE-040 NCT02252042, KEYNOTE-048 NCT02358031], nivolumab [CHECKMATE-141 NCT02105636], durvalumab/MEDI4736 [HAWK NCT02207530, EAGLE NCT02369874] in patients with relapsed/metastatic disease that are likely to be reported in the next 2–3 years.

The clinical responses to immunotherapy tend to occur rather more slowly than with conventional cytotoxic chemotherapy and may be preceded by a period of disease progression – so-called pseudoprogression. In addition, the side effects of immune checkpoint inhibitors are entirely different from standard chemotherapeutic agents. In particular, by taking the brakes off the immune response, these agents are associated with significant auto-immune adverse reactions, such as skin rash, colitis, hepatitis and endocrinopathy (thyroid, adrenal and pituitary dysfunction). These effects appear to be more common with anti-CTLA4-targeted drugs rather than anti-PD1/anti-PD-L1 agents, but in all instances, require specialist management because they can evolve into serious, even life-threatening, conditions.

COMBINATIONS OF CHECKPOINT INHIBITORS AND RADIATION

There is evidence from both the laboratory and the clinic that radiation therapy can cause immunogenic cell death.[106–108] Furthermore, there are both preclinical and clinical data to demonstrate that immune checkpoint inhibition may enhance this effect and lead to systemic activity of a local therapy (e.g. radiation).[109, 110] These observations, combined with the excitement over single-agent activity of immune checkpoint inhibition, have led to a number of clinical studies that are combining immune checkpoint inhibitors with ionizing radiation. At present, there are no substantial reports of this approach in the literature, but it is likely that studies evaluating palliative hypofractionated radiotherapy and radical standard fractionation (with and without platin-based chemotherapy) will be reported in the coming years. This strategy certainly seems to hold promise, especially as a means of using intensive locoregional therapy as a means of generating systemic activity (and protection) against metastatic disease recurrence.

KEY POINTS

- An increasing understanding of the fundamental biological processes involved in cancer cell formation has resulted in the development and clinical use of drug strategies to treat head and neck cancer.
- Of note, Epidermal Growth Factor Receptor Inhibitors, Tyrosine Kinase Inhibitors, drugs which arrest cell cycle progression and sensitize cancer cells to the effects of radiotherapy have been used in various treatment regimens.
- Exciting improvements in treatment have resulted from the use of drugs which modulate the host immune system.

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CHAPTER 31

PROSTHETIC MANAGEMENT OF SURGICALLY ACQUIRED ORAL AND FACIAL DEFECTS

Chris Butterworth

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: maxillectomy, maxillary obturator, rhinectomy, facial prosthesis, dental assessment, dental implants, zygomatic implants and dental rehabilitation.

INTRODUCTION

This chapter deals with the planning and application of maxillofacial prosthodontic and prosthetic techniques for patients requiring prosthetic rehabilitation for surgical defects of the mouth and face. The text will primarily refer to the management of patients with oral, maxillary and mid-facial tumours.

Complex oral and facial rehabilitation aspects of treatment should be led by the maxillofacial prosthodontist in conjunction with the other core members of the multidisciplinary team (MDT) as well as additional extended members such as the dental hygienist and specialist dental/facial prosthetic technicians (See Chapter 97, A combined prosthetic and surgical approach). Where patients are dentate, ongoing liaison with the patient's primary dental care practitioner is also of utmost importance.

Osseointegrated implants are a very important tool in the management of complex oral and facial defects and the appropriate expertise should be available in the MDT to allow their application where clinically indicated either at the time of primary surgery or as part of definitive secondary rehabilitation. An appropriate funding stream for such treatment is also required due to the complexity and cost of these individual bespoke rehabilitative treatments.

Oral and facial rehabilitation treatment seeks to help address, or in many cases palliate, the patient suffering from the negative unwanted effects of surgical and oncological treatment modalities (**Box 31.1**).

BOX 31.1 Negative effects of treatment for H&N cancer

- Altered oral and facial anatomy
- Maxillary and facial defects
- Trismus
- Xerostomia
- Altered dental occlusion
- Bulky soft-tissue flaps
- Altered facial sensation
- Speech and swallowing problems

PRE-SURGICAL ASSESSMENT

All patients with oral, oro-pharyngeal, maxillary and mid-face tumours should be seen and assessed by the maxillofacial prosthodontist at an early stage in the patient journey, especially where there are good reasons to undertake early prosthetic rehabilitation. Dental pathology is extremely common in this group of patients and

appropriate dental management is required for the majority of patients.[1] All dentate patients should have a screening panoramic dental radiograph in conjunction with a detailed oral examination with appropriate decision making regarding dental extractions, restorations and definitive planning for prosthetic rehabilitation in terms of osseointegrated implant placement to support any definitive prosthesis that may be required.

Following a detailed assessment of the patient's dentition, a final decision regarding the definitive treatment plan should be made in the light of the patient's oral and general motivation, whilst taking into account the likely effects of the proposed oncological treatment strategy. Ideally, risk factors such as smoking and alcohol consumption should be addressed where they exist pre-treatment if complex rehabilitative treatments are to be considered. The overall proportion of head and neck cancer patients receiving osseointegrated implant treatment has been reported to be quite low.[2] Careful patient selection is required to ensure that the patient receives the appropriate benefit of the treatment especially where implants are placed primarily at the time of primary oncological surgery.

MANAGEMENT OF THE MAXILLECTOMY DEFECT

Prior to the advent of predictable free vascularized tissue transfer, the management of many maxillectomy defects was via prosthetic obturation. The use of prosthetic obturation has subsequently decreased considerably in modern surgical practice but still has a useful role in the management of patients who cannot receive complex autogenous reconstruction, where the access for subsequent surveillance is deemed to be an advantage or for small well-defined maxillary defects.

The use of a classification based approach to decision-making is a useful one and such classifications such as those by Brown[3] and Okay[4] are helpful in this respect. Brown's surgical-based classification has been widely adopted when considering the decision to reconstruct the maxilla and mid-face surgically whereas Okay's work is more directed to the maxillofacial prosthodontist and is very helpful in the design of maxillary obturator prostheses depending on the remaining dental configuration following surgery.

The decision-making process should be a joint one between the surgeon, the prosthodontist and the patient. It is clearly a multifactorial process and has to take into account the size and location of the tumour, the tumour subtype and histological features, the perceived prognosis for the patient and their fitness for surgery, their current dental status, mouth opening and desire for future dental rehabilitation.

In general terms, the more extensive maxillary defects should be surgically reconstructed with free tissue-transfer techniques. When the defect extends out of level 2,[3] the overall facial result tends to worsen and is more difficult to maintain with a prosthetic obturator (**Figure 31.1**). Defects involving the orbital floor should also ideally be reconstructed wherever possible to prevent the inferior displacement of the globe which results in a poor aesthetic facial appearance (**Figure 31.2**).

Preparation for a maxillectomy combined with prosthetic obturation must begin in advance of the operation with an outpatient visit with the maxillofacial prosthodontist. A clear and detailed surgical treatment plan should be provided to allow adequate planning and prescription for the surgical obturator prosthesis. Specifically, the planned alveolar margins of the resection in the dentate patient are very important to the accuracy of fit of the prosthesis at surgery (**Figure 31.3**). Dentate patients will always require pre-operative impressions for models and prosthesis construction whereas the edentulous patient may not, depending on whether they are currently wearing a well made and extended prosthesis. Often the surgical obturator prosthesis can be constructed with appropriate tooth replacement included but where there are significant time constraints prior to surgery or for the non-denture wearing edentate patient, a simple clear acrylic cover plate can



Figure 31.1 Lip contracture following level 2 maxillectomy and obturation.



Figure 31.2 Significant drop in right globe position following maxillectomy involving the orbital floor.



Figure 31.3 Marking the cast prior to maxillectomy.

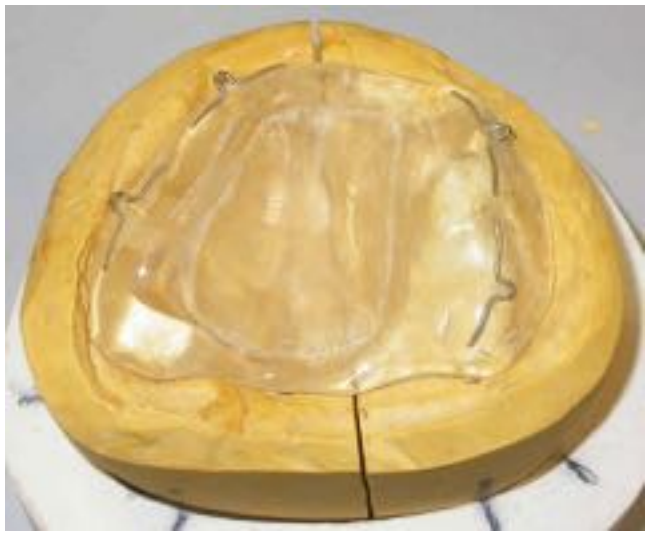


Figure 31.4 Surgical obturator with loops for circum-zygomatic wires.

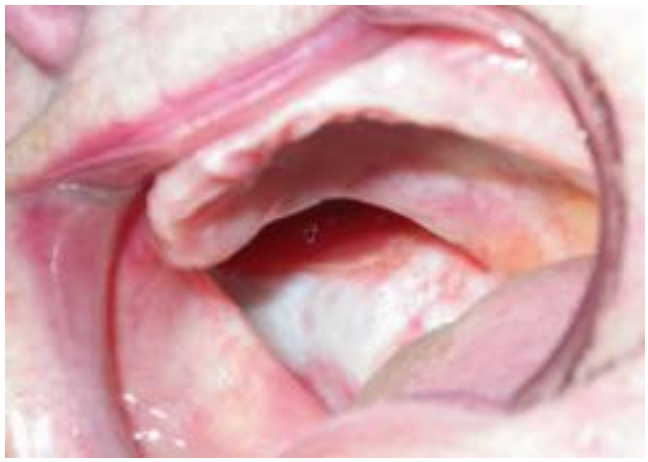


Figure 31.5 Healed split-skin graft in the cheek producing retentive scar band for obturator prosthesis.

be constructed. Depending on the size, extent and location of the proposed maxillectomy defect, the prosthesis should contain appropriate elements designed to assist with the retention of the appliance such as dental clasps or circum-zygomatic loops (**Figure 31.4**). Where ongoing retention difficulties are foreseen by the maxillofacial prosthodontist, specific plans for the concomitant insertion of osseointegrated implants at the time of surgery should be made.

A clear explanation of the various stages of treatment should be given to the patient, including the need for regular follow-up visits with the prosthodontist following surgery, together with what they should expect from the prosthetic obturator.

SURGICAL MODIFICATIONS TO FACILITATE OBTURATOR PROVISION

Where possible, bone cuts through the maxillary alveolus should be undertaken through an edentulous region or through the middle of a dental extraction socket following the removal of the required tooth to facilitate this. This ensures that any remaining abutment teeth have uncompromised periodontal bone support for the future which is so important in their ongoing role in supporting the obturator prosthesis.

The incisions through the hard palate mucosa should ideally be made laterally to the bone cuts to create a keratinized mucosal flap which folds over the cut edge of the palatal bone. This provides a cushioning effect for the future prosthesis which tends to move about this axis to some degree during masticatory function.

The cheek defect should be grafted with a carefully sutured split-skin graft. This results in the production of a scar band within the cheek which helps to retain the obturator prosthesis (**Figure 31.5**). This is essential where a conventional obturator is being provided and this is one of the few areas where retention can be gained. Its use is less important where other forms of retention such as osseointegrated implants are to be used to assist with prosthesis retention.

Where exposed into the resulting defect, the inferior turbinate(s) should be removed to provide more vertical space for the obturator elements of the prosthesis and to prevent future trauma. Once the resection has been completed, the surgical obturator prosthesis should be relined and fitted prior to extubation of the patient. A variety of materials have been advocated to obturate the surgical defect including black gutta percha, silicone putty impression material and foam-based products. The author favours the use of addition-cured silicone putty as it is readily available, easy to use and provides rigid support for the cheek as well as the ability to engage undercuts in the defect which can assist in the overall retention of the prosthesis in the immediate post-operative period. It can



Figure 31.6 A screw retained surgical obturator relined with silicone putty.



Figure 31.7 A simple maxillary obturator prosthesis with integral soft bung to engage defect undercuts.

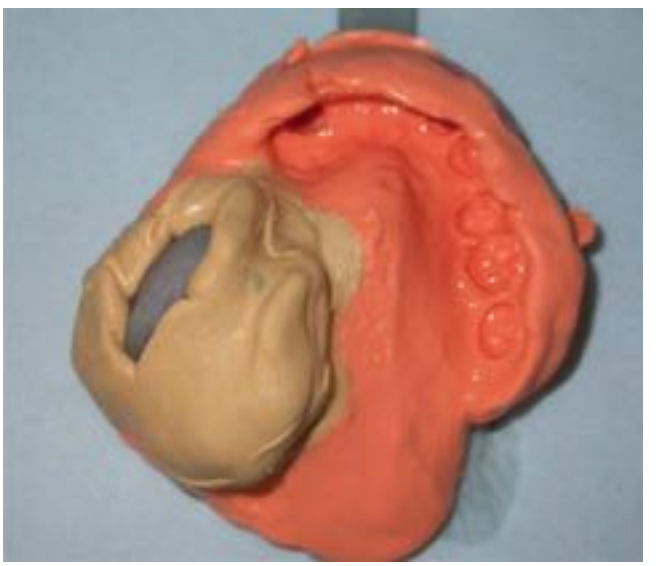


Figure 31.8 A multi-part dental impression.

also assist with haemostasis where there is residual oozing from within the defect.

The fixation of the surgical obturator will depend on the defect size as well as the presence of remaining teeth and residual alveolar bone in the maxilla. Where the defect is small and there are plenty of remaining teeth, dental retention utilizing clasps will usually suffice. In larger defects, additional retention is often required utilizing bone screws and/or circum-zygomatic wires (**Figure 31.6**).

Post-operatively the surgical obturator will require removal and modification as the defect heals and begins to change in dimensions. Smaller defect cases can often be managed in the outpatient clinic whereas larger defects may require a return to the operating room especially where circum-zygomatic wires have been employed as a means of retention. The surgical obturator is generally left *in situ* for 1–3 weeks before it is modified and relined to improve its oro-nasal/oro-antral seal and general comfort for the patient. The patient is instructed on how to remove, clean and replace the prosthesis. The patient is followed up on a regular basis with further modifications being made to the prosthesis until such time as further impressions can be made to construct a more definitive obturator.

Figure 31.7 demonstrates the definitive obturator prosthesis for a patient with a low-level partial maxillectomy. The soft silicone bung material assists in the retention of the prosthesis by engaging the natural undercuts in the defect by means of the surgical technique.

MULTI-PART MAXILLARY OBTURATORS AND THE USE OF OSSEOINTEGRATED IMPLANTS

Many patients experience significant trismus following maxillectomy especially where surgery is combined with radiotherapy.[5] This factor must be taken into account when planning prosthetic obturation of maxillary defects and may lead to the decision to remove further teeth to allow access for the obturator. In partially dentate patients, significant trismus can lead to difficulties in the access for impression making and indeed in the placement and removal of the prosthesis. In many cases, impressions need to be taken in several parts (**Figure 31.8**) and the definitive obturator can also be fabricated with a separate obturator component which is joined intra-orally with the dental prosthesis component. **Figure 31.9** demonstrates this approach for a low-level maxillectomy defect in the posterior maxilla. The obturator component is inserted directly into the defect initially and attaches to the overlying dental prosthesis by means of a magnet embedded into the acrylic surface of the obturator component which combines with another magnet in the intaglio surface of the dental prosthesis.

Where more extensive maxillary defects are to be obturated or in the edentulous patient where retention



Figure 31.9 A 2-part obturator with magnet linkage.

difficulties are anticipated, the use of osseointegrated dental implants may be employed. Mostly these retention aids should be placed at the time of resection especially if radiotherapy is to be utilized post-operatively. **Figure 31.10** demonstrates the use of zygomatic implants to retain a large maxillary obturator in an edentulous patient. These implants achieve very high initial stability and can be used at a very early stage to support the obturator. In this case, the implants are splinted together with a retentive bar to retain the obturator. In such cases, the extent to which the prosthesis needs to engage into the defect is much reduced as this is not required for its retention.

PROSTHETIC MANAGEMENT OF FACIAL DEFECTS

The use of facial prostheses to reconstruct surgical or congenital defects of the nose, mid-face, orbit and external ear is well established and is reviewed very nicely in a recent review article by Ariani et al.[6] The use of silicone-based facial prostheses is a highly effective way of providing the patient with an aesthetic tissue replacement in situations where surgical reconstruction with autologous tissue would be extremely challenging or not possible due to anatomical constraints or patient fitness. The construction of such bespoke prostheses requires great skill on the part of the prosthetic technician and careful planning on the part of the surgical team and maxillofacial prosthodontist to provide a defect of adequate dimensions and with appropriate retentive elements. Whilst the use of skin adhesive products together with the use of mechanical features such as defect undercuts and spectacle frames were the main methods to retain facial prostheses, the last 30 years has seen a shift to retention of facial prostheses with osseointegrated implants.[7-9] Whilst conventional adhesive retained prostheses still have their role, patients find them difficult to locate, subject to dislodgement during daily functions as well as suffering from skin irritation.[10]

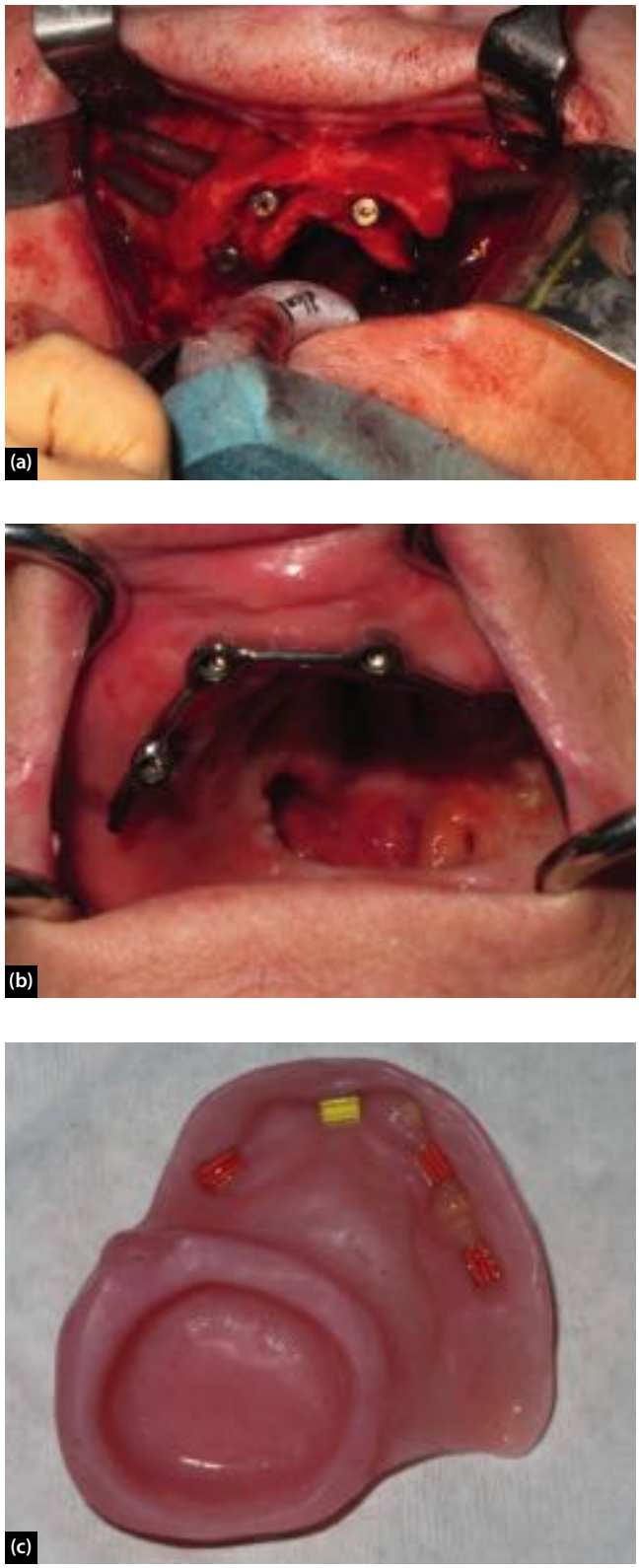


Figure 31.10 The use of zygomatic implants to retain a maxillary obturator prosthesis. (a) Multiple zygomatic implants placed at the same time as a left-sided maxillary resection. **(b)** Zygomatic implant retained bar to provide improved support and retention for the removal of the maxillary obturator. **(c)** Maxillary obturator with ink-well obturator componenet and retentive components to fit onto zygomatic implant bar.

A number of pre-prosthetic surgical techniques are widely accepted in order to maximize the benefit from the facial prosthesis[11] depending on the area concerned. Small areas of unsupported tissue should be removed, where possible, to provide a solid margin to support the periphery of the prosthesis. A suitable cavity should be provided to accommodate the prosthesis and this is especially true in mid-face and orbital cases. If possible, the bulk of vascularized flaps in this area should be kept to a minimum or subsequently debulked prior to prosthesis construction. Sharp bony margins of the resection should be smoothed and the use of split-skin grafts is encouraged especially within the orbit as, once healed, they can provide a stable, hair free, and drier surface.

Where rhinectomy is undertaken, preservation of the nasal bones, when oncologically safe, is advantageous as it provides useful vertical support for the prosthesis and for spectacle wear. Reduction of the projection of the nasal septum helps create space within the defect for implant frameworks, where these are employed, and also helps reduce secretions in the area of the prosthesis.

A variety of endosseous implant types have been successfully employed to retain facial prostheses ranging from very short (3–5 mm) 'extra-oral' implants, conventional 'dental' implants and very long (30–55 mm) zygomatic implants.[9]

Figure 31.11 demonstrates the use of horizontally placed zygomatic implants to retain a large mid-face prosthesis.



Figure 31.11 Horizontally placed zygomatic implants used to retain a large mid-face prosthesis.

DENTAL ACCESS SURGERY TO ASSIST TRANS-ORAL PROCEDURES

Trans-oral surgery is increasingly used in the management of benign and malignant processes. However, access for such techniques can be hampered significantly by a range of factors such as trismus, a class 2 skeletal profile and the presence of maxillary anterior teeth. Alternative trans-oral techniques have been reported for pharyngeal pouch repair in patients with trismus[12] as open surgery is perceived to hold higher morbidity for patients. The use of dental extractions to facilitate trans-oral ENT procedures is rarely reported but should be considered in conjunction with the maxillofacial prosthodontist as a means of facilitating surgical access.[13] Tooth replacement with fixed or removable dental prostheses can be subsequently provided depending on the patient's presenting dental status and wishes.

RESTORATION OF THE DENTITION FOLLOWING ABLATIVE SURGERY

Patients presenting with head and neck cancer often present with significant dental issues at time of presentation.[14] There are high levels of dental phobia and anxiety reported in this population of patients and this often results in a degree of dental neglect. Many patients are elderly and a significant proportion of patients are edentulous at the time of presentation. In addition, resective surgery for malignant tumours within or adjacent to the maxillary and mandibular alveolar bone require the removal of sections of the dentition either as a rim or segmental resection to achieve oncologically safe margins. The resulting post-surgical condition of oral cancer patients is therefore highly varied and each one presents a range of challenges in respect to successful dental rehabilitation. Soft and hard free-tissue reconstruction techniques can often lead to the presence of residual bulky soft tissue skin flaps overlying the jaws obstructing the dental envelope (**Figure 31.12a**).

However, there is little doubt that the use of composite free flaps to reconstruct segmental jaw defects has very much improved outcomes for patients and can usefully provide a foundation for osseointegrated implant insertion in selected cases.[4]

Decisions regarding the dentition need to be made prior to surgery to ensure that the patient's subsequent oral function is maximized and that untreated dental pathology does not remain untreated. The patient's wishes and motivation regarding their dentition and subsequent rehabilitation should be taken into account along with their habitual risk factors, the site, extent and behaviour of their presenting tumour and their predicted prognosis. Where radiotherapy is to be used as an adjuvant treatment, the dose, fields and fractionation of treatment and their likely effect on the remaining dentition should be carefully considered when arriving at a suitable treatment plan for the dentition.

Where dental rehabilitation is to be provided, the aims, advantages and limitations of treatment should be

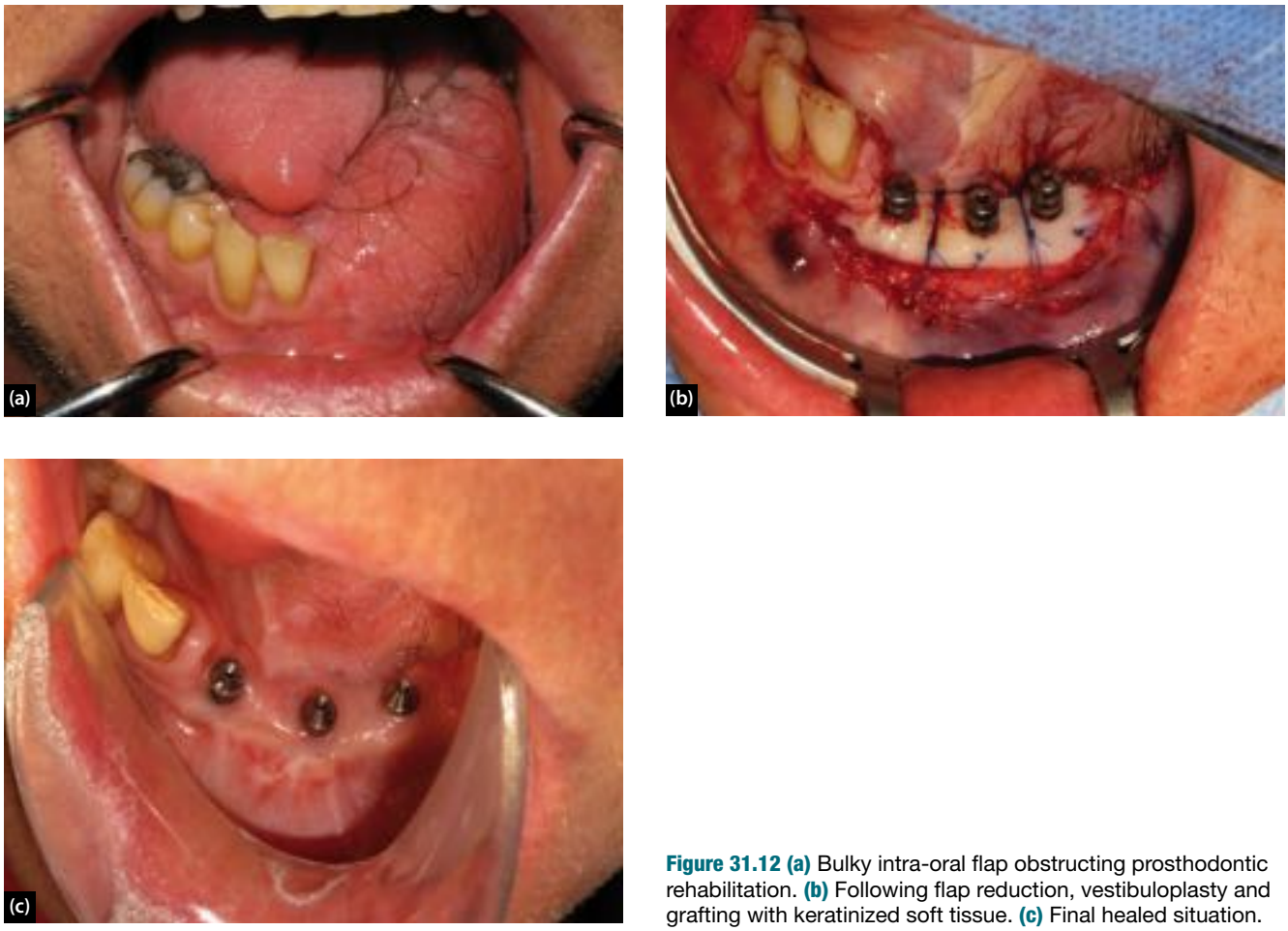


Figure 31.12 (a) Bulky intra-oral flap obstructing prosthodontic rehabilitation. **(b)** Following flap reduction, vestibuloplasty and grafting with keratinized soft tissue. **(c)** Final healed situation.

acknowledged with the patient. Whilst patients can benefit enormously from the cosmetic improvement in appearance following prosthodontic treatment, they are often left with functional problems associated with chewing and swallowing and these are to a large part associated with the degree to which their overall tongue function has been affected by the cancer treatment modalities. In addition, patients always tend to favour chewing on their non-resected side following jaw resection so restoration following a small posterior mandibulectomy is often not required if the patient has a good complement of remaining functional natural teeth.

A small number of patients can receive, tolerate and function reasonably well with conventional fixed and removable dental prostheses following surgery but the majority of patients who have undergone reconstructive procedures within the mouth are often left with aberrations in intra-oral anatomy that are difficult to overcome with simple dental prostheses alone. It is in this context that the maxillofacial prosthodontist relies on the use of osseointegrated implants to overcome these difficulties.

Primary dental implant placement

In some carefully selected patients, there will be a case for the immediate installation of osseointegrated implants at the time of primary resective surgery in order to provide a future effective prosthetic dental rehabilitation within a reasonable timescale (**Figure 31.13**). The placement of implants at the same time as the resective surgery has a number of advantages and potential disadvantages (**Table 31.1**) although a recent systematic review[15] has shown that this is a highly effective treatment in facilitating dental rehabilitation with high levels of implant survival, despite subsequent post-operative radiotherapy.[16] The majority of patients (75%) go on to complete their dental rehabilitation and show improvements in their quality of life (QOL). Not surprisingly, patients receiving post-operative radiotherapy report poorer QOL scores than their counterparts who did not require radiotherapy.[17]

The use of primary osseointegrated implants has been reported mainly in patients with intact mandibles who are undergoing soft-tissue oral resections although there are smaller case reports/case series with placement directly into composite flaps[18] (mainly fibula flaps for mandibular resections) as well as into the maxilla and zygomatic complexes for patients undergoing maxillectomy.[19] Implants should be placed by or in close conjunction with the maxillofacial prosthodontist to ensure that the best prosthodontic result is obtained. The placement of implants into composite free flaps at the time of jaw reconstruction is however fraught with difficulty and there is evidence to suggest that such patients should be treated secondarily.[20]



Figure 31.13 Insertion of dental implants into the anterior mandible simultaneously with tumour resection from the floor of mouth.

TABLE 31.1 Advantages and disadvantages of primary osseointegrated implant placement

Advantages	Disadvantages
Early rehabilitation	Unknown prognosis for patient
Implants placed before radiotherapy	Unknown oral function post surgery
Psychological patient benefit	Anatomical difficulties for placement
Reduced number of surgeries	Cost implications if implants not used

Rohner et al.[21] described the use of 'pre-fabricated' fibula flaps into which implants are installed by means of CT-based computerized planning and guided surgical techniques with their subsequent transfer to the defect and immediate restoration with a dental prosthesis.. This technique however is not yet in widespread use and is not yet applicable to routine jaw resections required for malignant disease.

Secondary dental implant placement

For many patients, any decisions regarding dental rehabilitation should be left till the patient has fully recovered from the effects of the cancer treatments, their functional deficits identified and their response to the treatment in terms of disease control established. Their motivation for treatment should be ascertained and detailed prosthodontic planning undertaken prior to intervention. CT-based computerized planning techniques are useful where composite reconstructive techniques have been used as they assist in establishing whether adequate bony union has been established following surgery, the presence and position of osteosynthesis plate and screw materials, localized anatomy and the relationship of the proposed prosthesis to suitable implant positions. The use of stereolithographic surgical drilling guides can be helpful in transferring





Figure 31.14 (a) The use of a stereolithographic surgical template to guide placement of orbital rim implants. **(b)** Dental implants positioned in the orbital rim according to the pre-operative computer planning.

detailed computer-based planning to the clinical situation (**Figure 31.14**).

Management of the peri-implant soft tissue is another important aspect of care as inevitably excess tissue is present prior to treatment. Reduction and tailoring of skin flap tissue overlying the jaw around the implant fixtures is recommended to allow easy access to the implant, to produce immobile tethered peri-implant tissue and where possible to fashion a new buccal sulcus adjacent to the implants, to facilitate future oral hygiene measures (**Figure 31.12b**). Where radiotherapy has not been used, more aggressive reduction of the soft tissues is possible in conjunction with soft-tissue grafting using palatal mucosa[22] or split-skin grafts[23] to obtain ideal results often with the use of an implant retained dressing plate. In the irradiated patient, simple thinning of the overlying tissues is often all that can be done without risking mucosal breakdown and potential bone exposure.

Implant placement in irradiated jaws

The use of dental implants in the management of irradiated oral cancer patients has been a controversial subject over many years with reports of poor implant survival (as low as 50%) being reported within the literature in some centres.[24, 25] Clearly, radiotherapy is a significant risk factor for failure in these patients and must be carefully considered when planning treatment strategies. However, more recent data are much more encouraging with a recent comprehensive meta-analysis demonstrating an overall mean survival of 83% (range 34–100%) with a mean follow-up of at least 5 years.[26] This study demonstrated no statistically significant differences in survival between implants in irradiated and non-irradiated native jaws but highlighted poorer survival for implants placed into irradiated grafted bone. Changes in implant design, 3-dimensional prosthodontic planning as well as improved / minimalized surgical techniques may account for this improvement in outcomes.

The use of hyperbaric oxygen treatment prior to placement in the irradiated jaw has received much attention with varying results in the literature. Currently there is inadequate information to support its routine use for this indication.[27]

KEY POINTS

- Patients requiring prosthetic rehabilitation for oral and facial defects should be seen pre-operatively with a maxillofacial prosthodontist and anaplastologist.
- Patients requiring a facial prosthesis invariably benefit from osseointegrated implant insertion together with surgical modifications of the resulting defect to maximize the success and aesthetics of the final prosthesis.
- Carefully selected patients should receive osseointegrated implants at the time of resective surgery to maximize dental rehabilitation.
- Osseointegrated implants have high success rates and contribute significantly to improved QOL outcomes in oral, dental and facial prosthetic rehabilitation.
- Radiotherapy reduces implant success and reduces QOL gain from dental prostheses but the use of implants is still of great value in patients who have received radiotherapy.

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CHAPTER 32

MULTIDISCIPLINARY TEAM WORKING

Andrew Davies, Nigel Beasley and David Hamilton

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: interdisciplinary communication, cancer, decision making, communication, head and neck neoplasms and personal autonomy.

INTRODUCTION

The Oxford English Dictionary defines multidisciplinary as 'combining or involving several academic disciplines or professional specialisations in an approach to a topic or problem'.[1] The UK Department of Health has defined the multidisciplinary team (MDT) as a 'group of people of different health-care disciplines, which meets together at a given time (whether physically in one place, or by video or teleconferencing) to discuss a given patient and who are each able to contribute independently to the diagnostic and treatment decisions about the patient'.[2]

Before the early 1990s only a relatively small proportion of cancer patients benefited from their care being managed by a MDT of cancer specialists. Such teams had existed for decades for some cancers in some hospitals but this was the exception not the rule. In the last 15 years MDT working has been deemed to be the standard of care in the management of all types of cancer. In the UK, the drivers for the development of MDT working were the 'Calman-Hine report',[3] the 'The NHS Cancer Plan',[4] the National Institute for Clinical Excellence's Improving Outcomes Guidance,[5]and the ongoing cancer peer review process.[6]

MULTIDISCIPLINARY TEAM WORKING

Multidisciplinary team (MDT) working is seen as the modern standard of care in cancer treatment decision-making.[5] This means that every cancer treatment decision in the UK should be made under the auspices of an MDT. A survey of 2000 MDT members in September 2009 found that there is an overwhelming consensus that MDTs are beneficial to patient care and should remain the cornerstone of cancer treatment.[7] MDTs bring together staff with the necessary knowledge, skills and experience to ensure high quality diagnosis, treatment and care for patients with cancer. MDT working has been advocated in each of the NICE Improving Outcomes Guidance reports and is strongly supported by clinicians.[8]

Despite this enthusiasm from clinicians, the evidence base for MDT working is weak, with most studies looking at outcomes before and after the introduction of the MDT. These studies are confounded by increasing sub specialization, centralization of care and improvements in diagnosis and treatment. However there is increasing evidence that MDTs do improve some clinical outcomes, patient experience and the working lives of team members. The challenges faced when assessing the impact of MDT working on survival in cancer was outlined by Hong et al. in their systematic review on this subject.[9] The definition of MDT is applied variably across centres and any benefits demonstrated may reflect a selection bias of patients with a better prognosis, rather than a real effect.[9] Hong's review included 21 studies which were categorized broadly into retrospective studies and those with cohorts before and after the introduction of an MDT, usually

in a single centre: it was not able to demonstrate a link between MDT working and survival.

There are no randomized controlled trials of MDT working, as it is now ubiquitous. However, in Glasgow, MDT working was introduced into one health board (the 'intervention area'), before other health boards in the west of Scotland (the 'non-intervention area'), allowing a comparison between two similar populations.[10] Before MDT working was introduced, breast cancer mortality was 11% higher in the intervention area than in the non-intervention area. After MDT introduction, breast cancer mortality was 18% lower than the non-intervention area. There was also a reduced variation in survival between hospitals in the intervention area. This study used cancer registry data on 13 722 patients, and the authors adjusted for temporal trends. This large study was published after the systematic review above and the authors provided detail about the definition of MDT working used. Although only one single study in one cancer, the size of the effect is noticeable and it provides the strongest evidence of a positive effect of MDT working on cancer survival to date.[10] Despite this, given the overall weight of evidence, it is not known if MDT working has an effect on cancer survival. Importantly, however, there is equally no convincing evidence of a negative effect. However, even if MDT working did improve survival, the aspect of the process which was responsible for such effects is not known.

MDT working is popular amongst the members of staff who attend it.[7] Specifically in head and neck cancer, a qualitative study of 33 professionals in four focus groups found that the team provided an inclusive environment for planning care. Staff members reported that the team gave support, a chance to stay up to date and an opportunity for discussing difficult cases.[11] However, MDTs are also expensive: best practice guidelines estimate that a radiologist will take 2 hours and a pathologist 2.4 hours to prepare for each hour of team meetings[12] putting the estimated cost of all UK MDT meetings at £50 million a year for preparation and the same amount again for attendance.[13]

MDTs that work well are characterized by clear aims and a shared understanding of goals, clear systems and processes for managing communication and conflicts, and responsive and proactive leaders who run effective team meetings, provide access to resources and reward excellence. These teams can improve patient outcomes and cost effectiveness in a range of settings from primary care to complex hospital care including stoke, cardiac and musculoskeletal conditions. However, MDTs must be supported to work effectively together. The Interdisciplinary Professional Education Collaborative have suggested the following interventions to support MDTs:[14]

- encourage teams to invest time in developing a shared aim
- develop team skills through practice and reflection
- pay attention to internal team relationships
- identify changes in the educational infrastructure required to help sustain interprofessional learning
- use multiple methods of communication to bridge barriers of schedules and geography.

While it is recognized that the evidence base for the value of for MDT team working in clinical decision making is diverse and of limited quality, studies have concluded that time pressures, a lack of information, a lack of nursing input and poor team leadership can have a negative impact on team decision making. Lamb et al. suggest that the 'inclusion of multidisciplinary cancer teams, preparation time into team-members job plans, making leadership skills training available and obtaining more extensive input from nursing personnel should be considered at the national policy level'.[15]

Effective MDT working should result in the outcomes outlined in **Box 32.1**. These outcomes are expected to be more likely in MDTs with a focus on[16]

- teams with the right membership, good attendance, strong effective leadership and opportunities for personal development and training
- good preparation for well organized meetings in the right physical environment with appropriate technology to support effective communication
- patient-centred clinical decision-making
- good team governance and support, with regular data collection and discussion of patient outcomes.

MULTIDISCIPLINARY TEAM WORKING IN HEAD AND NECK ONCOLOGY

In the UK, the National Institute for Clinical Excellence's Improving Outcomes Guidance for Head and Neck Cancer[5] endorses MDT working, together with centralization of

BOX 32.1 Putative benefits of multidisciplinary team working[16, 17]

- treatment and care being considered by professionals with specialist knowledge and skills in the relevant aspects of that cancer type
- patients being offered the opportunity to be entered into high quality and relevant clinical trials
- patients being assessed and offered the level of information and support they need to cope with their condition
- continuity of care, even when different aspects of care are delivered by different individuals or providers
- good communication between primary, secondary and tertiary care
- good data collection, both for the benefit of the individual patient and for the purposes of audit and research
- improved equality of outcomes as a result of better understanding and awareness of patients' characteristics and through reflective practice
- adherence to national and local clinical guidelines
- promotion of good working relationships between staff, thereby enhancing their job satisfaction and quality of life
- opportunities for education/professional development of team members (implicitly through the inclusion of junior team members and explicitly when meetings are used to devise and agree new protocols and ways of working)
- optimization of resources – effective MDT working should result in more efficient use of time which should contribute to more efficient use of NHS resources more generally.

cancer services at regional cancer centres (serving a population of over one million people). Moreover, the guidance states that patients should be managed by MDTs treating at least 100 related cases per annum. Studies suggest that such centralization of services is associated with improved outcomes in head and neck cancer.[18] The guidance recommends that specialized MDTs manage patients with thyroid cancer, patients with salivary gland tumours and patients with skull-base tumours. In addition, the guidance recommends that patients with a sarcoma of the head and neck region should be managed in conjunction with the regional sarcoma MDT.

Box 32.2 shows the suggested core membership for a head and neck cancer MDT in the UK;[5] the guidance characterizes the role of each member of the core team for example clinical nurse specialist, speech and language therapist, dietician. The diverse membership of the core team is essential as almost all patients with head and neck cancer require assessment and management of the airways, speech, nutrition, appearance and pain. **Box 32.3** shows the suggested extended membership for a head and neck cancer MDT in the UK.[5] The members of the extended MDT are there to manage certain patients and, as such, are not required to attend all MDT meetings (in contrast to the members of the core MDT). Specialized MDTs managing thyroid, salivary and skull-base tumours have a different membership to head and neck cancer MDTs. For example, the thyroid cancer MDT should include endocrinologists and nuclear medicine specialists.[5] A national audit published in 2003 highlighted that a high level of attendance was not always being achieved in head and neck cancer: although over 95% of meetings were attended by an oncologist and/or a surgeon and 80% were attended by a speech and language therapist, fewer MDTs had access to other specialists. Only around half included dietitians and/or clinical nurse specialists, and the role of other specialists was even more variable, with teams having a mix of plastic surgeons, restorative dentists and palliative care physicians.[19]

BOX 32.2 Recommended core members of the head and neck cancer multidisciplinary team[5]

Core members

- Surgeons (≥ 3) – the surgeons are likely to be ear, nose and throat (ENT), maxillofacial, or plastic surgeons
- Clinical oncologists (x 2)
  - Restorative dentist
  - Pathologists
  - Radiologist
  - Clinical nurse specialists
  - Speech and language therapist
  - Senior nursing staff from the head and neck ward
  - Palliative care specialist
  - Dietitian
- Team secretary
  - Data manager
  - MDT co-ordinator – the co-ordinator may also take the role of team secretary and/or data manager

EVIDENCE-BASE FOR MULTIDISCIPLINARY TEAM WORKING IN HEAD AND NECK CANCER

The evidence-base for MDT working in head and neck cancer is as diverse as that for other MDTs, with the same enthusiasm from clinicians, but similar problems with study design and confounding variables such as increasing subspecialization. The primary problem with assessing the effectiveness of the MDT is deciding what the measure should be and from which viewpoint it should be measured. A survey of head and neck cancer MDT members from the UK reported that 90% thought MDT discussion resulted in improved timeliness of tests and treatment, 74% thought MDT discussion resulted in improved patient choice, 71% thought that MDT discussion resulted in improved patient involvement in decisions, 95% thought that MDT discussion results in an increase in proportion of patients staged, and 90% thought that MDT discussion results in improved survival rates.[20]

Wheless et al. reported on a prospective study of the effect of MDT meetings on the management of patients with benign and malignant head and neck tumours.[21] Patients were initially assessed by the 'referring attending physician', and the diagnosis, stage of disease and treatment plan recorded. Subsequently, patients were reviewed at the multidisciplinary 'tumour board', and the diagnosis, stage of disease and treatment plan again recorded. The MDT meeting resulted in a change on diagnosis in 1% patients with cancer (6% patients with benign tumours), a change in stage in 12% patients with cancer, and a change in treatment in 24% patients with cancer (6% patients with benign tumours); in the patients with cancer, the treatment was escalated in 15% cases, de-escalated in 5%

BOX 32.3 Recommended extended members of the head and neck cancer multidisciplinary team[5]

Extended members

- Other specialist surgeons
- Anaesthetist
- Gastroenterologists, radiologists, surgeons and other health professionals with expertise in gastrostomy creation, feeding tube placement and support for patients who require tube feeding
- Ophthalmologist
- Pain management specialist
- Nuclear medicine specialist
- Therapeutic radiographer
- Maxillofacial/dental technician
- Dental hygienist
- Social worker
- Benefits advisor
- Liaison psychiatrist
- Clinical psychologist
- Counsellor
- Physiotherapist
- Occupational therapist

cases and changed to a different modality in 4% instances. In a similar study, Brunner et al. found that in almost a third of cases the treatment plan of the referring clinician was changed by the MDT.[22] Treatment plans were more frequently altered if the original plan from the referring clinician did not include surgery or if the histology was not squamous cell carcinoma or skin malignancy. Kee et al. attempted to ascertain if, when a clinician presents their patient at the MDT, the ensuing discussion changes the reported preference of the clinician.[22] In a similar proportion of cases (39%) the preference of the referring clinician did not match the final decision of the MDT. Interestingly however, they also showed that in only 26% of cases where the team and individual clinician disagreed did the referring clinician finally concur with the decision of the team and present it to the patient.[23]

Kelly et al. reported on a retrospective study of the effect of MDT working on so-called 'clinical quality indicators' associated with the management of patients with head and neck cancer.[24] The introduction of the MDT was associated with an increase in PET scanning as a staging investigation, an increase in pre-treatment dental assessments, an increase in pre-treatment nutritional assessments, an increase in the use of chemoradiotherapy for locally advanced cancer, and a decrease in the time period between surgery and post-operative radiotherapy. Birchall et al. reported on a re-audit of the effect on implementing 'consensus standards' (including multidisciplinary head and neck clinics) on the 2-year survival of patients with head and neck cancer.[25] The study compared patients managed in a number of hospitals during two time periods (1996–1997 and 1999–2000). The authors reported that the proportion of patients seen in an MDT increased from 46% to 74% between the two audits and the number having pre-treatment imaging and accurate staging work-up also increased. The overall survival between the two cohorts was not significantly different (64.1% increased to 65.1%), but analysis revealed that those patients were assessed in an MDT had a statistically significantly better survival than those who were not.[25] Although MDT working could have improved the 'non-temporal' standards such as pre-treatment imaging, the correlation between MDT working and increased survival cannot be assumed to be causative. The authors discussed that survival data was probably incomplete, as the deaths reported did not match those of death registrations in the area. Also, temporal trends were not accounted for and confounding factors such as patient selection were not acknowledged.[25]

Similarly, Friedland et al. reported on a retrospective study of the effect of MDT working on the 5-year survival of patients with head and neck cancer.[26] The study compared patients managed by the MDT vs patients managed outside of the MDT within the same hospital over a 12-year period. There was no difference in survival in patients with stage I–III disease, but there was statistically (and clinically) significant improvement in survival in patients with stage IV disease who were managed by the MDT. The authors suggested that the improvement in survival was primarily related to an increase in the use of multimodal therapy, and specifically the use of concomitant chemotherapy and radiotherapy. However, the allocation to management within or outwith the MDT was not randomized, but chosen by the referring clinician; also the MDT patient group had a higher age and more advanced disease. Most importantly however, it is not made clear why some patients were selected to be managed by the MDT whilst others were managed by individual clinicians.

OTHER ISSUES

Patient autonomy

The MDT lacks one important voice, that of the patient.[27] There are little data documenting the patient experience of involvement in MDTs, as it is rarely routine practice: small studies have concluded that patients attending their own MDT allows for better information giving but not necessarily improved involvement in decision-making. Many teams adopt a 'democratic forum model', whereby patients are informed of the decision of the MDT and can accept or decline the treatment proposed. This lacks patient involvement. Shared decision-making (SDM) is a process in which both clinicians and patients work together choosing treatments based on the best available clinical evidence and the patient's preferences. Patients are given information about options, outcomes and uncertainties, and after discussion agree a treatment plan.[28] This concept has been used by Sharma et al. in creating the 'MDT approval model' (**Figure 32.1**).[29] This involves patients in the decision-making process at the very first visit with the patients views taken to the MDT for discussion by the clinical team. Nevertheless, the area of Inter-Professional Shared Decision Making (IP-SDM) is in its infancy as the majority of the research on SDM concentrates on the physician/patient dyad.[30, 31] In two recent systematic reviews of measures to help the implementation of SDM, only 3/40 studies focused on the interdisciplinary approach.[32, 33] Stacey et al. performed a large literature review and theory analysis which identified no models of SDM in the interprofessional context.[34]

Omitting, or not incorporating, patient preference information into the treatment discussion potentially has an effect on decision implementation. In three studies of the implementation of the MDT recommendation in the clinic 'patient choice' caused a change in, or rejection of the MDT recommendation in between 2% and 5% of cases.[35–37] At the same time, patient-centred care is important to MDT members. In the NCAT Survey of MDTs, 95% of respondents felt that 'patient views should always inform the decision-making process' and 'patient views/preferences should be presented to the MDT by somebody who has met the patient'.[7] When the free-text responses from the NCAT survey were analyzed, lack of information about the patient or lack of knowledge of the patient views were seen as the main reason for MDT decisions not being implemented.[38]

Various quantitative measures have attempted to measure the 'patient centredness' of the MDT discussion.

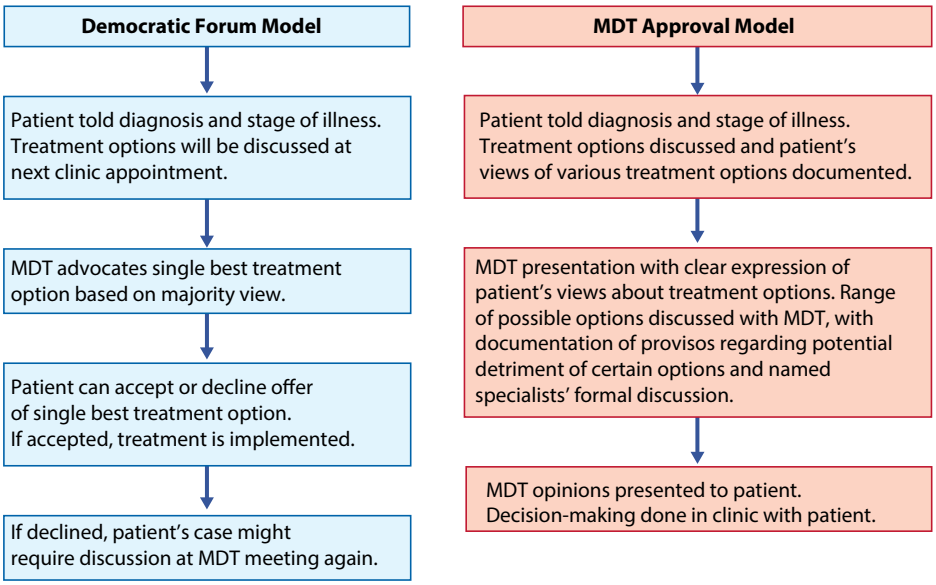


Figure 32.1 Democratic forum model and MDT approval model of decision-making.[29]

Taylor et al. measured the patient-centredness of the MDT decision by counting the number of cases where there was a mention in the MDT discussion of patient-based information.[39] Patient-based information in this study was defined as patient demographics, comorbidities, supportive needs or patient and family preferences. Eight out of the ten observed meetings scored 'poor' or 'very poor' for patient-centred care. The patient information which was included was frequently confined to demographics and most teams rarely considered other patient-based factors. Lamb et al. developed a tool which used Likert scales to quantify 11 aspects of MDT team discussion, including information about the patient, contribution of members of the team and the incorporation of patient views.[15] Teams scored highly in the amount of information given about the clinical history, and radiological information. Teams were found, using this scale, to incorporate patient views into the discussion quite poorly. Moreover, the self-assessment questionnaires completed by the team members suggested that they overestimated the 'patient-centredness' of their decisions.

Qualitative studies have gone further in analyzing how MDT discussions include the patient. Kidger et al. conducted observations and interviews of MDT members and found that the consideration of patient-related factors such as comorbidity information, psychosocial issues and patients' wishes was unstructured when compared with the very structured manner in which the biomedical information was presented.[40] MDT members recognized the importance of 'seeing' a patient rather than an objective representation through information; however information about patient preferences was only really presented when these were strongly held, or ran counter to the recommendation of the team. The team exhibited uncertainty about when and how this kind of information should be incorporated into the discussion. In a similar study, Lanceley et al. reported that the biomedical details of the patient were at the forefront of the discussion, packaging patients into a semi-predictable 'case' which consisted mainly of their biomedical data.[41] Although information such as the ethics of treatment selection or the individuality of the patient was sometimes presented, the team struggled to incorporate this into the 'case' and therefore into the decision. The authors observed that this often led to two strands of narrative about a single patient, which the team had significant difficulties combining.

Clinical decision support systems

Clinical decision support systems are defined as 'systems that are designed to be a direct aid to clinical decision making in which the characteristics of an individual patient are matched to a computerized clinical knowledge base, and patient-specific assessments or recommendations are then presented to the clinician(s) and / or patient for a decision'.[42] Clinical decision support systems have been reported to useful in the MDT, but further research is needed before such technology is introduced into routine clinical practice.[43, 44] Additionally, 'decision aids' are designed to be used before, during or after a clinical consultation by the patient with or without a clinician. In a systematic review of 115 randomized controlled trials, the use of a decision aid was associated with improved patient knowledge, lower decisional conflict, a decreased proportion of patients who were passive in decision-making and fewer patients remaining undecided. There was also a reported increase in patient satisfaction with the decision-making encounter and improved perception of risk.[45] However, most of these studies analyze the use of the decision aid in the context of the clinician-patient dyad rather than an MDT.

MDT working does however allow a new role to be incorporated into the team: that of a decision coach. A decision coach's role is to assess the decisional needs of the patient and then support the patient through decision making, using decision aids and adjuncts if available.[45] Decision coaching can be provided by a member of the team who

is 'trained in decision support and [is] supportive but relatively neutral in the decision'.[46] Decision coaches can help to improve confidence in decision-making and prepare for the decision consultation with positive effects on knowledge, information recall and participation in decision-making.[47, 48] However, in a recently published systematic review, only 10 randomized controlled studies were identified and thus conclusions about the effectiveness of decision coaches were limited. The authors found that although decision coaching can improve patient knowledge, it is difficult to unpick how much of this improvement is due to decision coaching, and how much to the decision aid which is often simultaneously used. The effect on other outcomes such as cost effectiveness, values-choice concurrence and patient satisfaction varies, with some studies reporting a positive effect, and others reporting no difference.[49]

Medico-legal issues

The discussion of a patient at a MDT meeting amounts to a referral to the members of the MDT, and so extends a 'duty of care' to the clinicians within the multidisciplinary care team.[50] As a result, the clinicians are accountable for decisions related to their area of expertise, irrespective of whether or not they contributed to the treatment discussion, and irrespective of whether or not they subsequently treat, or even meet, the patient. It is, therefore, imperative that team members voice any concerns about treatment decisions during the MDT meeting, and ensure that these concerns, and recommendations about alternative treatments, are formally recorded in the documentation relating to the MDT meeting. In such cases, the MDT should inform the patient about the alternative treatment option as well as the 'consensus' treatment option.

CONCLUSION

The creation of formal MDTs ensures that patients are cared for by clinicians with a range of skills, facilitates communication between team members allowing continuity of care, and creates an opportunity for the team to learn together and review patient outcomes against other teams using nationally published datasets.[13]

MDT working is the standard of care in cancer decision-making, however if it is to remain so, the limitations of decision-making in this setting should be acknowledged and overcome. MDT working presents barriers to the incorporation of patient-centred information (such as values, preferences and treatment priorities). If these factors are not taken into account, this may lead to decisions not being implemented, or to a predominance of a paternalistic decision-making style.

Despite the weak evidence base, MDTs are enthusiastically supported by their members and there is increasing evidence that they play an important role in improving patient outcomes and patient experience along with the working lives of team members. Tools are available for teams to reflect on their performance and drive improvement, with a particular focus on regular review of patient outcomes and team relationships.

While there is a recognition that patients with head and neck cancer should be cared for by specialized teams treating large numbers of patients, it is important to emphasize the need to provide care for patients closer to home where possible. Multidisciplinary networks of care providing access to assessment, diagnostics, follow-up and end-of-life care close to home will be vital before further centralization of complex services is considered.

The simple act of bringing together expert clinicians from a wide range of professions and disciplines to discuss and review individual patients and share successes and failures has brought about a revolution in patient management. The head and neck is a diverse and complex cancer site where continuity of care when considering issues with the airway, speech, nutrition, appearance and pain have all been supported by MDT working. Review of outcomes and recruitment into trials will be critical to improving patient outcomes and experience in the future and will all be supported by effective MDT working.

KEY POINTS

- The majority of head and neck cancer decisions in the UK and worldwide are made through a multidisciplinary team (MDT).
- MDT working encourages the involvement of allied health professionals in the assessment, management and rehabilitation of head and neck cancer patients.
- MDT working improves a range of clinical outcomes (such as appropriate staging and clinical trial entry), however, its effect on survival is harder to measure.
- Effective patient involvement in MDT decisions is a challenge and clinicians should develop ways of working which encourage shared decision making.

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CHAPTER
33

NUTRITIONAL CONSIDERATIONS

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SEARCH STRATEGY

Data in this chapter is supported by a Medline search using the following keywords: nutrition, screening, assessment, malnutrition, weight, nutritional intervention, immunonutrition, enteral tube feeding, gastrostomy, PEG, RIG, nasogastric tube (NGT), swallow, dysphagia, xerostomia, quality of life, rehabilitation, survivorship and feeding.

INTRODUCTION

This chapter will look at the nutritional considerations from diagnosis, throughout treatment to rehabilitation and survivorship in patients with head and neck cancer. The chapter aims to provide information on several areas of nutrition including nutritional screening, nutritional interventions during surgical and non-surgical oncology treatments, nutritional support, rehabilitation and survivorship.

THE ROLE OF NUTRITION IN HEAD AND NECK CANCER

It is common for patients with head and neck cancer to report difficulties with eating and drinking at presentation due to tumour location. In addition, dietary habits and lifestyle factors may have further compromised their nutritional intake prior to diagnosis.[1] Studies have estimated that between 44% and 57% of patients experience difficulties in eating or unintentional weight loss prior to commencing treatment.[2, 3] Treatment for head and neck cancer can have negative effects on eating and swallowing which can lead to deterioration of nutritional status.[4] These effects will be intensified with multi-modality treatments. In the surgical patient, weight loss can lead to increased complication rates, such as impaired wound healing, reduced immune function and decreased tolerance to treatment.[5] For patients undergoing radiotherapy, weight loss is associated with increased treatment toxicities, more treatment interruptions, poorer quality of life (QOL) and reduced overall survival.[6–8]

It is widely accepted that weight and Body Mass Index (BMI) alone are inadequate measures of nutritional status. The loss of muscle mass that occurs during cancer-related malnutrition is understood to be the major contributor to reduced functional status, increased mortality and other negative outcomes associated with malnutrition.[9] Nutritional intervention for patients with head and neck cancer aims to identify, prevent and treat malnutrition from the point of diagnosis through the entire cancer pathway. Regular dietetic counselling and weighing may help to motivate patients and improve nutrition outcomes and QOL.[10, 11] A specialist head and neck dietitian should be a key member of the multidisciplinary team (MDT) treating patients with head and neck cancer.[1]

Defining malnutrition

Malnutrition is a state of nutrition in which a deficiency or excess (or imbalance) of energy, protein and other nutrients causes measurable adverse effects on tissue/body form (body shape, size and composition) and function and clinical outcome.[12]

Malnutrition may be defined as:

- a BMI < 18.5 kg/m^2
  OR
- a combined unintentional weight loss of > 10% over 6 months (or > 5% in 3 months), in combination with a reduced BMI or low fat free mass index (age and sex specific).[13]

The definition of malnutrition in cancer patients is complicated by emerging terminology such as cachexia and sarcopenia of which there are no universally accepted definitions. These terms attempt to recognize the loss of lean body mass which is compounded by the systemic inflammation and metabolic disturbances which may arise in patients with cancer.[14] Although not routinely used in clinical practice at this time, such terms are appearing more in the oncology literature as the complex mechanisms involved in cancer-related malnutrition become better understood.

Nutritional status has been recognized as a long-term prognostic factor in patients with head and neck cancers for almost 30 years.[15] Malnutrition in patients with head and neck cancer can have a significant adverse impact on clinical, cost and patient-centred outcomes.

Malnutrition has been associated with:

- delayed wound healing and increased risk of post-operative complications and infections[16]
- impaired cardiac and respiratory function due to muscle weakness
- treatment interruptions[16, 17]
- decreased response rates to chemotherapy
- increased risk of loco-regional failure[18]
- increased length of hospital stay
- depression and poor QOL[19]
- increased mortality rate. [8, 20]

Nutritional screening

Nutritional screening aims to identify patients who are malnourished or who are at risk of becoming malnourished during treatment as early as possible. Patients with head and neck cancer should be nutritionally screened using a validated nutritional screening tool.[10, 21] Whilst there is limited good-quality evidence for screening tools specifically for patients with head and neck cancer, there are several validated for use with cancer patients.[10] These include Subjective Global Assessment (SGA) Tool, Patient Generated SGA (PG-SGA) Tool and Malnutrition Screening Tool (MST).

The SGA assesses nutritional status based on features of a patient's nutritional history and physical examination. The PG-SGA is an adaptation of the SGA for assessing nutritional status and is patient generated. Scores identify patients who are well nourished and those who have developed or are at risk of developing malnutrition during treatment and follow-up.[22] The MST consists of two questions relating to weight history and appetite; it is quick and simple to use and compares favourably with PG-SGA. The Malnutrition Universal Screen Tool (MUST) is used widely in healthcare settings across the UK, however it is not validated in cancer.[12] Early identification of high-risk patients and referral to a specialist head and neck dietitian for assessment should be included as part of the planning for every patient with head and neck cancer when treatment options are being considered.[23, 24] Screening should be repeated at regular intervals during the patient pathway.

TABLE 32.1 Factors to consider for nutritional assessment

Diagnosis, specifically regarding tumour site and staging
Nutritional implications of previous treatments
Aim of current treatment plan: cure vs palliation
Single or multimodality treatment plan
Performance status and comorbidity factors
Physical activity level and functional impairment
Medical history that can affect nutritional intake, e.g. diabetes
Current ability to chew and swallow and the likelihood of further impairment due to treatment
Weight history and % weight loss. If not available, signs of weight loss e.g. ill-fitting clothes/dentures
Measurement of muscle mass and recent changes (e.g. hand grip strength)
Changes to appetite, reduced food intake
Modified eating habits or techniques to make it easier to swallow
Avoidance of foods or drinks that are difficult to chew or swallow
Avoidance of eating meals with others or eating in public
Access to food, food preparation facilities and cooking skills
Lifestyle factors, alcohol, smoking, recreational drug intake
% of energy intake from alcohol
Fluid intake
Employment and financial status
Social support network / support at home

Nutritional assessment

Following screening, a full nutritional assessment should be undertaken for patients identified as nutritionally 'at risk'. This should include consideration of a range of factors, illustrated in **Table 32.1**. Assessment should be completed within a pre-treatment clinic and should be repeated at regular intervals during treatment. It is imperative that patients with head and neck cancer are assessed by a specialist head and neck dietitian, and advised and monitored up to the point of surgery and/or non-surgical treatment with respect to their nutritional status. This enables the best possible outcome from treatment interventions in this

high-risk group and should form an integral part of clinical practice for head and neck MDTs.[4]

Pre-treatment optimization

It is essential to optimize patients with head and neck cancer who are malnourished at presentation. Even patients who are managing reasonably normal intake may struggle to reach their energy and protein requirements without individualized dietetic intervention and/or supplementation in some format. Vital factors to be considered when determining appropriate nutritional intervention for patients are:

- Is there evidence of pre-existing malnutrition, indicating the need for pre-treatment nutritional intervention?

Evidence suggests that correcting nutritional deficiencies before surgery reduces the incidence of post-operative complications.[16] Pre-operative feeding for 7–14 days should be offered to patients who present with severe malnutrition and are planned for major surgery, even if the surgery must be delayed.[25, 26]

- Does the patient have a safe swallow?

If the patient is displaying signs of aspiration they should be referred for assessment by a specialist speech and language therapist (SLT).[27] Dysphagia at baseline is a risk factor for requiring earlier and prolonged enteral tube feeding during treatment and should be considered in the pre-treatment stage.

Nutritional requirements

Cancer itself does not have a consistent effect upon either resting energy expenditure (REE) or total energy expenditure (TEE).[9, 28] Indirect calorimetry to determine REE has a high degree of accuracy however it is not usually feasible in clinical practice. Guidelines suggest the use of standard formulas for healthy subjects for estimating REE with the addition of standard values for physical activity level (PAL).[14] Alternatively, standard equations for energy requirements based on healthy subjects (25–30 kcal/kg/day), may be used.

It is suggested that a protein intake of at least 1–1.5 g/kg/day can help to maintain or restore lean body mass. Intakes up to or above 2 g/kg/day are considered safe in patients with normal renal function.[9, 14]

Requirements for fluid and micronutrients are calculated based on daily recommendations for healthy populations.

Nutritional requirements are summarized in **Table 32.2**. Estimations may be less accurate for severely malnourished, morbidly obese and surgical patients.

TABLE 32.2 Estimated nutritional requirements[9, 14]

Energy	25–30 kcals/kg/day depending on activity level, can increase further if major complications
Protein	1–1.5 g/kg/day
Fluid	30–35 mls/kg/day, this increases in presence of infection or excessive fluid losses
Vitamins and Minerals	As per recommended daily allowance for healthy populations unless considered deficient

TABLE 32.3 Criteria for determining people at high risk of developing refeeding problems[21]

Patient has one or more of the following:

- BMI < 16 kg/m^2
- unintentional weight loss > 15% within the last 3–6 months
- little or no nutritional intake > 10 days
- low levels of potassium, phosphate or magnesium prior to feeding

Or patient has two or more of the following:

- BMI < 18.5 kg/m^2
- unintentional weight loss > 10% within the last 3–6 months
- little or no nutritional intake > 5 days
- a history of alcohol abuse or drugs including insulin, chemotherapy, antacids or diuretics.

Refeeding syndrome

Refeeding syndrome may occur when nutrition support is reintroduced in severely malnourished or starved patients. The syndrome is characterized by metabolic disturbances including hypophosphataemia, hypokalaemia, hypomagnesaemia, altered glucose and lipid metabolism, thiamine deficiency and abnormal fluid balance.[29] These effects may result in life-threatening disturbances of organ function and metabolic regulation.

There are no data on the incidence of refeeding syndrome in patients with head and neck cancer although it is a recognized risk in this population due to the high incidence of malnutrition, history of excessive alcohol intake and requirement for artificial nutrition support. The identification of refeeding syndrome may be problematic in this patient group as their underlying clinical condition and oncological treatment may also result in deranged serum electrolyte levels.

The National Institute of Clinical Excellence (NICE) guidelines on nutrition support, 2006, define criteria for patients at risk of refeeding syndrome (**Table 32.3**).

Although the NICE guidelines provide a useful framework for identifying patients at risk of refeeding syndrome, it is acknowledged that their sensitivity and specificity is low and should be interpreted with caution by healthcare professionals with adequate training in nutrition support.[30] In a patient with head and neck cancer for instance, low concentrations of serum potassium, magnesium or phosphate may be related to chemotherapy and is unlikely to represent risk of refeeding in the absence of other nutritional risk factors, i.e. prolonged starvation. Conversely normal electrolyte levels should not be interpreted as an indication of low refeeding risk as due to homeostatic mechanisms, serum concentrations of potassium, magnesium and phosphate may be within normal parameters prior to feeding, even in the starved patient. The advice is to commence oral, enteral or parenteral nutrition cautiously, starting at a maximum of 10–20 kcal/kg/day for

high-risk patients and less for severely high-risk patients (5–10 kcal/kg/day).[21, 30] Introduction of nutrition support should be accompanied by vitamin supplementation and monitoring of electrolyte levels, with repletion of electrolytes as necessary.

NUTRITIONAL INTERVENTIONS AND TREATMENT

Surgery

It has long been recognized that surgical outcome, in any speciality, can be robustly linked to the nutritional status of the patient. Malnourished patients have a higher risk of post-operative complications and long-term adverse effects on QOL. In head and neck surgery, post-operative morbidity and mortality is mediated by poor wound healing, higher risk of flap failure, impaired immune function and a general decreased tolerance to stress of major surgery in those who are nutritionally compromised.[5, 31, 32]

Patients requiring surgery for head and neck malignancy will often have advanced disease and require procedures that will, frequently, further interfere with their ability to maintain an adequate oral intake. It is important when counselling patients about their treatment options that surgeons are realistic with them, their families and the allied healthcare professionals in the treating team about potentials for oral intake both immediately after surgery and in the longer term.

Patients need to be fully informed about the effects of surgery on their swallowing. Studies have shown that swallowing consistently remains one of the top priorities for patients following treatment for head and neck cancer.[33] Patients may already have difficulty swallowing due to the site or stage of their tumour. The effect of tumour resection in the oral cavity, oropharynx, hypopharynx and larynx should be explored at pre-treatment assessment by an experienced MDT. Therefore, the patient expectation should be kept realistic and the functional outcomes explained fully in conjunction with the SLT. Options for maintaining nutrition should be discussed in conjunction with a specialist head and neck oncology dietitian and an individualized management plan formed.

For those patients who are malnourished at presentation, early dietetic input is invaluable in the time leading up to surgery. This allows optimization of their nutritional status and early intervention. If patients are clearly unable to meet their nutritional requirements with oral intake due to dysphagia, odynophagia or aspiration, despite optimization of analgesia and SLT input, an early decision regarding enteral nutrition is required to prevent further nutritional decline. Whether this is via a nasogastric tube (NGT) or a gastrostomy tube is a patient-centred decision, based on the following factors: patient preference, tumour stage, the site of the primary tumour (more likely for oral cavity/oropharynx, less likely for larynx), the likely need for post-operative radiotherapy +/– chemotherapy, the predicted length of time to achieve oral intake of a normal consistency or quantity and institutional expertise.[28]

It is imperative to ensure that patients are assessed, advised and monitored up to the point of surgery with respect to their nutritional status. This enables the best possible outcome from surgery in this high-risk group of individuals. Post-operatively, patients should have a form of enteral nutrition available that can be commenced within 24 hours of their surgery.[10] Depending on pre-operative discussions and the nature of surgery, an NGT may be all that is required if early return to oral diet is anticipated. However, if recovery is more likely to be protracted a prophylactic gastrostomy may be more appropriate. If unforeseen complications occur or recovery is slower than anticipated a reactive gastrostomy is also a possibility. In all instances, an appropriate feeding regimen should be prescribed by a specialist head and neck oncology dietitian to stop any delay in post-operative feeding.

Early oral feeding (day 1–7 post-operatively) in primary laryngectomy patients should be considered as studies indicate no evidence of increased fistula rates when compared with standard protocols for commencing oral intake, traditionally > 7 days.[6] Similarly, early oral feeding protocols following oral cavity surgeries are gaining popularity due to evidence suggesting favourable outcomes such as earlier tracheostomy decannulation and reduced length of stay without an increase in morbidity.[34]

Enhanced recovery after surgery (ERAS)

Enhanced recovery programmes have gained popularity over the last 15 years amongst many surgical disciplines. Historically there have been little data pertaining to head and neck surgery, however a consensus based ERAS protocol for the management of patients undergoing head and neck surgery with free flap reconstruction has now been developed.[35]

There are three main aspects of operative care to ERAS:[36]

- **Pre-operative:** assessment, education and counselling about the procedure and its recovery, avoidance of premedication, same day admission/limited hospital stay, attention to fluid balance, minimization of fasting and carbohydrate loading, nutritional optimization.
- **Intra-operative:** minimally invasive surgical techniques, regional anaesthesia, standardized anaesthetic protocol with the use of short-acting anaesthetics, goal-directed fluid therapy, avoidance of drains and high inspired oxygen concentrations.
- **Post-operative:** early mobilization, early removal of drains, catheters and lines, early oral/enteral intake, optimized pain relief, nausea and vomiting prophylaxis and use of prokinetics/laxatives/chewing gum.

The practice of keeping all patients nil by mouth (NBM) from midnight prior to surgery may contribute to an abnormal physiological state thereby slowing down

recovery after major surgery; the abnormal physiology can be further exacerbated by delayed post-operative feeding. In ERAS protocols, patients are not placed NBM from midnight but are given carbohydrate rich fluids up to 2 hours before surgery (carbohydrate loading).

In patients undergoing colorectal surgery it has been demonstrated that pre-operative carbohydrate loading results in shorter hospital stay, less loss of muscle mass and earlier return of bowel function with no increase in risk of aspiration.[37] In some hospitals in the UK, pre-operative carbohydrate loading has been introduced to patients undergoing head and neck surgery with no concerns.[38] Pre-operative carbohydrate loading involves the administration of 100 g of carbohydrate the night before surgery and 50 g carbohydrate up to 2 hours before surgery. Carbohydrate is provided in specialized nutritional supplements. ERAS programmes often recommend commencing nutrition post-operatively within 4 hours of surgery.[39] Current European nutrition guidelines suggest starting enteral feeding within 24 hours.[26]

The mere presence of a pathway with nutrition as an integral part ensures that this is not a neglected facet of peri-operative care. One of the main ways that ERAS is beneficial is by reducing the 'metabolic stress' of major surgery. This manifests as rising levels of insulin resistance post-operatively, related to the magnitude of the operation performed. Insulin resistance lasts for several weeks following surgery and affects all parts of the body's metabolism. There is reduced glucose uptake in body cells leading to loss of lean body mass and reduced muscle function. Pre-operative carbohydrate loading and early post-operative feeding can help reduce the catabolic response to surgery and thus patients recover quicker with fewer complications.[40] Major head and neck surgery does in fact lend itself to many of these general principles of ERAS.[35] Early dietetic assessment, as discussed earlier, and intervention pre-operatively for life-changing surgery is required to ensure realistic outcomes for patients, which is similar to the fundamental principle of ERAS. Most patients can be admitted on the day of surgery. Nutrition is just one part of ERAS pathways. Early mobilization and optimization of post-operative analgesia are also important.

Immunonutrition

Also known as immune enhanced nutrition, immunonutrition is feed containing various additives in the form of amino acids, nucleotides and lipids. Much of the research concentrates on the substances omega 3 (fatty acids from fish oil) with arginine or glutamine.[41] These additional constituents are thought to upregulate the host immune response, modulate the inflammatory response and improve protein synthesis after surgery.[42]

Many randomized controlled trials and several meta analyses have shown that administration of enteral arginine, omega 3 fatty acids and nucleotides reduce infection rate and length of hospital stay in patients with upper or lower gastrointestinal cancer with the greatest benefit seen in malnourished patients.[42]

Arginine alone promotes healing and modulates inflammation and can be used in an enteral feed in isolation. A recent systematic review and meta-analysis showed that the administration of an arginine-enriched feed reduced both the development of fistulas post-operatively as well as the overall length of stay in hospital.[43] Previous studies have also found that arginine may improve fistulas and wound complications in patients with head and neck cancer.[44] Other studies have found similar tendencies with improved wound infection rates but less convincing effects on fistulas.[45]

With the increasing amount of evidence in the literature, post-operative immunonutrition appears to be emerging as another technique in our armamentarium to reduce length of hospital stay. However, the mechanism remains unclear, as other clinical benefits such as reduced complications and infections have not been consistently demonstrated.[10]

CHYLE LEAKS

An uncommon, but major complication of head and neck surgery is a chyle leak or chylous fistula, particularly if surgery involves the left supraclavicular fossa region. The literature suggests an incidence of 0.5–1.4% for thyroidectomy and 2–8% for neck dissection.[46]

Chyle is a by-product of the absorption and digestion of fat. Fat digestion begins in the duodenum with pancreatic lipase, which hydrolyses triglycerides into monoglycerides and free fatty acids. These in turn interact with bile salts and form micelles. The micelles transport the monoglycerides and free fatty acids across the brush border of the villi of the small intestine. Most of the fat absorbed into the epithelial cells combines with cholesterol, phospholipids and lipoproteins to form chylomicrons. These then enter the lacteals of the villi as milky-looking lymphatic fluid (chyle).

The lacteals coalesce to form the cisterna chyli, which traverses the diaphragm to run superiorly as thoracic duct in the posterior thoracic cavity behind with the oesophagus. As the thoracic duct enters the neck it crosses between the internal jugular vein (IJV) and the anterior scalene muscle. It either terminates at the junction of the left IJV and left subclavian vein or drains directly into the IJV. For this reason, the majority of chyle leaks are on the left, although approximately 5% will occur on the right from the right lymphatic duct.[47]

About 2–4 litres of chyle flows through the thoracic duct on a daily basis. Flow rates vary with the amount of dietary fat consumed. Chyle leaks are classified as low output (< 500 mls/24 hours) or high output (> 500 mls/24 hours). Conservative management is appropriate for low-output leaks; high-output ones are more likely to require definitive intervention. Chyle leaks cause local problems with tissue loss and wound healing as well as systemic effects related to fluid loss and electrolyte dysfunction. Early recognition and treatment is essential to reduce morbidity.

The mainstay of all management strategies is nutritionally based. It is based on the theory that reducing

formation of chyle slows down the flow and thus allows the fistula to heal. A triglyceride level >110 mg/dl is diagnostic of a chyle leak. If the triglyceride level is <110 mg/dl further analysis is required to demonstrate the presence of chylomicrons. A triglyceride level <50 mg/dl usually rules out a diagnosis of a chyle leak unless a patient is malnourished or has been fasted.

The principal aims of nutritional management are to reduce the flow of chyle whilst maintaining nutritional status, ensuring adequate fluid balance and replacing electrolyte losses. Normally, when dietary fat is consumed long-chain triglycerides (LCTs) enter the blood-stream via chyle, medium-chain triglycerides (MCTs) are absorbed directly into the portal system. This important differentiation forms the basis on which nutritional management is based. Therefore, the nutritional management is to use a fat-free or high-MCT product. MCT is recommended because it is directly absorbed into the portal system resulting in less chyle production. Many patients with low-output leaks will respond to this intervention alone, thus making early dietetic input essential.[48] To date, no consensus exists on how to nutritionally manage chyle leaks, how long nutrition management should be pursued, or what constitutes an acceptable amount of chyle output. The nutritional intervention is usually dependent on clinician preference.

If dietary manipulation is unsuccessful parenteral nutrition may be required. This should not be used as first line management except in extreme cases, for example, very high volume leaks (>1000 mls). Further alternative treatments include Octreotide, Orlistat or recourse to surgical intervention.

RADIOTHERAPY +/– CHEMOTHERAPY

Patients should be offered pre-treatment assessment before commencing radiotherapy +/– chemotherapy to ensure

- full assessment of baseline nutritional status
- appropriate dietary advice is provided before commencing treatment to correct nutritional deficiencies
- information is provided on the nutritional implications of treatment, including anticipated need for enteral tube feeding support.

It is recognized that radiotherapy can cause side effects that may limit oral intake and lead to weight loss.[11] The addition of chemotherapy during radiotherapy has been shown to lead to increased locoregional control and an 8% improvement in overall survival, but this has been at the cost of increased toxicity.[49] Chemotherapy agents act as radiosensitizers. Unfortunately, the sensitizing effects are not selective for tumour cells and therefore normal tissue in the radiation field is also subject to more toxic radiation. Addition of chemotherapy to radiotherapy schedules is known to significantly increase grade 3 or 4 mucositis in most patients (~88%) compared to only 20–30% of patients treated with radiotherapy alone.[50] Monoclonal antibody treatments (e.g. cetuximab) given in conjunction with radiotherapy will also increase the incidence of mucositis and other toxicities effecting nutritional intake and hence patients should be managed in the same way as for conventional chemoradiotherapy.[10]

The impact of neoadjuvant chemotherapy schedules on nutritional status and oral intake is poorly understood due to limited studies in this area.[10] It is advised that nutritional status is assessed at regular intervals during neoadjuvant chemotherapy cycles to prevent nutritional decline prior to future radiotherapy treatment.

Intensity-modulated radiation therapy (IMRT) is the most commonly used technique to deliver radiotherapy to the tumour and regions at risk. Whilst the benefits of IMRT include the ability to limit radiation toxicity to the salivary glands and critical pharyngeal structures required for swallowing, thus reducing the chronic toxicities of dysphagia and xerostomia, residual toxicity remains with a high rate of weight loss, mucositis and continued need for nutritional support. Independent predictors of severe toxicity with concurrent chemoradiotherapy have been shown to be older age, advanced T stage, primary site in the larynx/pharynx and neck dissection after radiotherapy + chemotherapy.[51]

Radiotherapy side effects start to impact on the patient between the second and third week of treatment with this reaction continuing and increasing during the fourth, fifth and sixth weeks. Side effects peak approximately 1–2 weeks after treatment finishes.[52] Supportive care during chemoradiotherapy is demanding and often requires extensive oral and skin care, opioid medications, antiemetic medications and intensive nutritional support. Chemoradiotherapy can profoundly affect nutritional intake and swallowing physiology thereby causing significant morbidity and diminished QOL.[53] This impairment of oral food and fluid intake as a result of treatment may further exacerbate pre-existing malnutrition.[54]

Ongoing nutritional assessment and counselling by a specialist head and neck oncology dietitian should be part of the patient's treatment plan with patients being reviewed weekly during treatment.[10, 55] Odynophagia and oral pain when eating may lead to a reduction in the types and selection of foods consumed, often at the expense of adequate nutrition. Modifying the texture and consistency of foods is common during treatment. Increasing the frequency of meals and fortifying with nutrient dense foods will minimize nutrient deficiencies by increasing calories and protein. As treatment progresses, many patients will move to pureed or liquid diets and be more reliant on oral nutritional supplements to meet their nutritional requirements. Some patients may require enteral tube feeding to meet their nutritional needs.

Long-term side effects of chemoradiotherapy are more severe than for radiotherapy alone. Dysphagia, pain and dependence on feeding tubes are more common with chemoradiotherapy compared to radiotherapy alone and have negative effects on QOL.[51, 56] Dysphagia usually improves in the first year following treatment but in some cases swallowing dysfunction may be permanent.[57] In addition, the late effects of chemoradiotherapy can include osteoradionecrosis (destruction of bone within the

oral cavity), dental decay, trismus (reduced mouth opening), hearing loss and pharyngeal or oesophageal stenosis. Most late effects of chemoradiotherapy can impact on a patient's ability to eat and drink. It is important to assess nutritional status and oral intake at review appointments even many years after treatment and refer to a specialist head and neck oncology dietitian for advice if oral intake is compromised.

PALLIATIVE CARE

The specialist head and neck oncology dietitian plays a key role in the palliative care team due to the high incidence of weight loss, dysphagia and enteral tube feeding amongst patients with head and neck cancer.[10]

Collaborative assessments and reviews with an SLT can aid in determining the level of nutritional intervention required based upon the nature, severity and likely progression of dysphagia. Although previous goals for maintaining weight and energy intake may no longer be appropriate, patient comfort and QOL should be optimized, for example providing oral or tube feeding to avoid feelings of hunger or thirst during end-of-life care.[9] It is essential that nutritional care is patient-centred, taking into account the holistic needs of the patient whilst being guided by prognosis and medical management.

NUTRITION SUPPORT METHODS

There are three main methods of nutrition support for patients with head and neck cancer. These are oral nutrition support, enteral tube feeding and parenteral nutrition.

The aims of nutrition support are to[58]

- improve the subjective QOL
- enhance anti-tumour treatment effects
- reduce the adverse effects of anti-tumour therapies
- prevent and treat undernutrition.

Oral nutrition support

Healthcare professionals should consider oral nutrition support to improve nutritional intake for people who can swallow safely and are malnourished or at risk of malnutrition.[21] Oral nutrition support involves providing nutrition to improve intake by several methods. These include

- fortifying food with macronutrients including energy, protein and fat as well as vitamins and minerals
- changing the frequency of meals and types of foods consumed
- using oral nutritional supplements.

Previous therapeutic diets, for example, lipid lowering diets, are also often relaxed to prevent further nutritional decline. Oral nutritional supplements are used extensively in patients with head and neck cancer and there are large varieties available. The type used depends on a patient's current nutrition intake, need and preference. The dietitian initiates oral nutritional supplements when there is a deficit in nutritional intake and/or the patient continues to lose weight even when following a high calorie/protein diet.[58]

Enteral tube feeding support

General nutrition support guidelines recommend enteral tube feeding for patients who are malnourished or at risk of malnutrition and have inadequate or unsafe oral intake and a functional gastrointestinal tract.[21] In the post-operative patient, enteral tube feeding is recommended if it is expected that the patient will be unable to eat for more than 5 days post-operatively or unable to maintain at least 50% of recommended intake orally for more than 7 days.[26] In patients undergoing radiotherapy +/– chemotherapy, the benefits of initiating enteral tube feeding when oral intake is inadequate have been demonstrated in terms of improving nutritional intake and minimizing weight loss.[10]

Enteral tube feeding can be delivered via the nose into the stomach or jejunum (nasogastric or nasojejunal tube), or directly into the stomach or jejunum (gastrostomy or jejunostomy tube). **Table 32.4** details the different types of feeding tubes available. The choice of feeding route depends on the expected duration of feeding, site of tumour, treatment plan and intent and patient choice. **Table 32.5** highlights some of the advantages and disadvantages of enteral feeding tubes. In patients with head and neck cancer the preferred route for enteral nutrition is either a nasogastric and/or gastrostomy tube as the stomach is usually accessible. In some circumstances jejunal feeding may be required, for example, patients who have undergone a pharyngolaryngectomy with gastric pullup.

Nasogastric intubation is a procedure involving the insertion of a polyurethane tube (NGT) through the nose, past the throat, down the oesophagus and into the stomach. Tubes are usually placed at bedside but if placement is difficult fluoroscopic or endoscopic placement may be required. There is a risk that the tube can become misplaced into the lungs during insertion, or move out of the stomach at a later stage. It is essential to ensure that the NGT is in the stomach to prevent any complications. pH testing of the NGT aspirate is used as the first-line test method, with pH between 1 and 5.5 indicative of correct

TABLE 32.4 Enteral tube feeding routes and indications

Insertion route	Tube type	Indication
Nose	Nasogastric	Short-term feeding <4 weeks
	Nasojejunal	Short-term feeding when feeding into the stomach is not possible or indicated
Stomach	Gastrostomy	Long-term feeding >4 weeks
Jejunum	Jejunostomy	Long-term feeding when feeding into the stomach is not possible or indicated

TABLE 32.5 Advantages and disadvantages of enteral feeding tubes

Tube type	Advantages	Disadvantages
Nasogastric	• Usually easy to place at bed side • Inexpensive to place • Ideal for short term (< 4 weeks feeding) • Easy to remove when no longer required	• Easy to dislodge • Tube tip position must always be pH checked and a pH of ≤ 5.5. obtained prior to using tube to ensure that tube tip is in stomach • Highly visible • Tubes can block easily with medication due to small diameter of tubes • Laryngeal irritation • Gastro-oesophageal reflux • Nasal sores and erosion • Risk of feeding into the lungs if tube tip position is not in the stomach
Gastrostomy	• Ideal for long-term feeding (>4 weeks) • pH testing not required to check tube tip position as tube tip inserted and secured in stomach • Discrete as located directly in stomach • Unlikely to be dislodged	• Expensive to place compared to NGT insertion • Cannot be placed at bedside • Risk of infection, bleeding and peritonitis from insertion technique • Major complications can impact on ability to deliver oncological treatment
Nasojejunal	• Non-invasive • Ideal for short term (< 4 weeks feeding) • Easy to remove when no longer required • pH checking not required as tube is placed post-pylorically	• Requires placement under X-ray guidance, in interventional radiology or endoscopy • Easy to dislodge • Not feeding into stomach therefore feeding rates are required to be slower due to no gastric reservoir • Feeding times maybe prolonged due to slower feeding rates • Highly visible • Tubes can block easily with medication due to small diameter of tubes and length (> 130 cm) • Laryngeal irritation • Nasal sores and erosion • Potential GI disturbances • With certain medication there is a risk of reduced medication absorption as bypassing stomach
Jejunostomy	• Ideal for providing post-pyloric feeding • Discrete as located directly in jejunum	• Delivery rate of feed less than feeding into stomach due to lack of reservoir • Small diameter of tube increases risk of tube blocking with medication and/or feed • Tube easily dislodged • Requires operation to insert tube

TABLE 32.6 Characteristics of PEG and RIG tubes

Tube type	Characteristics
PEG	• Usually inserted with a 'pull technique'. Tube is pulled through the mouth into gastrointestinal tract endoscopically • Bumper retained • Usually made of polyurethane • Tube must be advanced and rotated at least once a week 2–4 weeks after initial insertion to prevent buried bumper syndrome • Tube life is usually a number of years • Tube is difficult to dislodge
RIG	• Tube usually inserted with a 'push technique'. Tube is inserted directly into the stomach radiologically • Usually balloon retained • Usually made of silicone • Water in balloon must be checked and replaced weekly after the first 1–2 weeks and tube must be rotated • Tube life is usually 3–4 months • Tube may become dislodged if balloon fails

placement in the stomach. A chest X-ray is used only as a second-line test when no aspirate can be obtained or pH indicator paper has failed to confirm the location of the NGT.[59]

There are two main methods of gastrostomy insertion: endoscopic and radiological placement. A gastrostomy that is placed in endoscopy is known as a percutaneous endoscopic gastrostomy (PEG) and one that is placed in radiology is known as a radiologically inserted gastrostomy (RIG). The key characteristics of PEG and RIG tubes are shown in **Table 32.6**. Grant et al.[60] have shown that procedure-related mortality and other complications are higher in patients with head and neck cancer when compared to mixed populations as well as RIG complications being greater than PEG complications. Clinician experience of tube related complications and what services are

available within a head and neck unit generally determine the method of gastrostomy placement.

NGTs are frequently used after surgery as patients often require non-oral feeding for just a few days to weeks. If oral intake is likely to be impaired for longer than 4 weeks after surgery, a patient may have a gastrostomy placed.

For patients with head and neck cancer being treated with chemoradiotherapy, a feeding tube is either placed prior to treatment (prophylactic) or during (reactive). Studies have suggested that a prophylactic gastrostomy leads to improved nutritional outcomes with less weight loss and may improve QOL during and post-treatment compared to reactive NGT.[10] Conversely, prophylactic gastrostomy tubes may have a negative impact on swallow outcomes and lead to tube dependency,[61] though the association of early gastrostomy tube feeding and long-term swallow impairment has been inconclusive.[62, 63] To date there is no consensus on the optimal route (NGT vs gastrostomy) or timing (prophylactic vs reactive) of tube feeding during oncological treatment for head and neck cancer, meaning this is largely determined by clinician and patient preference.[64]

ENTERAL TUBE FEEDING INSERTION CONTRAINDICATIONS

Before inserting any form of enteral feeding tube, the clinical situation, diagnosis, comorbidities, prognosis, possible contraindications, implications for QOL as well as the patient's wishes should all be considered.[64] Both NGT and gastrostomy placement carry risks and in certain situations their placement is contraindicated.

NGT placement may be contraindicated in the following situations:

- severe facial trauma resulting in fractures to the skull base, cribriform plate, and sphenoid sinus, due to the possibility of inserting the tube intracranially[66]
- significant coagulopathy
- oesophagogastric surgery/injury (e.g. gastrectomy/oesophagectomy/oesophageal perforation)
- distal bowel obstruction, perforation or fistula
- competent patient refusal to consent to procedure.

Gastrostomy tube placement may be contraindicated in the following situations:[65]

- significant coagulopathy
- interposed organs (e.g. liver, colon)
- enlarged liver, portal hypertension, confirmed varices and/or ascites
- peritoneal metastasis/carcinoma/dialysis
- peritonitis
- gastroparesis
- gastric outlet obstruction (unless venting gastrostomy indicated)
- small bowel obstruction
- oesophagogastric surgery (e.g. gastrectomy / oesphagectomy)
- hiatus hernia
- acute / uncontrolled psychosis
- advanced dementia
- clearly limited life expectancy
- competent patient refusal to consent to procedure.

The above contraindications may be absolute or relative and their presence makes tube insertion high risk or unfeasible. Specialist input from the MDT (dietitian, gastroenterologist, radiologist and clinical team), should be sought to determine suitability for tube placement where one of more contraindications are identified.

TYPES OF FEED AND DELIVERY METHODS

Dietitians assess the most appropriate type of enteral feed to give patients with head and neck cancer based on their nutritional requirements, their condition, their previous diet, their mobility and lifestyle and their desire to be fed continuously (via a pump) or in smaller volumes (bolus). For patients with head and neck cancer it is usual to use polymeric feeds (whole protein) with or without fibre. Feeds range from 1 kcal/ml to 2.4 kcal/ml with varying levels of protein.

Continuous and bolus feeding

Bolus and continuous feeding are two ways to deliver nutrition to patients who are tube fed. Bolus feeding is defined as the administration of liquid feed (primarily oral nutritional supplements) by syringe or bolus feeding set. A prescribed volume of feed (typically 100–400 ml) is given at regular intervals throughout the day, for example, four times per day. In contrast, continuous feeding involves the administration of a liquid feed via a feeding pump and pump set. The feed is usually run at a set rate, for example, 125 ml/hr for a set period of time; this can be intermittent, for example, overnight feeding, or continuous over 24 hours.

There are advantages and disadvantages of both feeding methods. The choice of feed delivery method is usually determined by patient preference and enteral feed tolerance. In addition, due to the flexible and intermittent nature of bolus feeding, patients with head and neck cancer are generally able to be more mobile with this type of feeding. This is particularly useful if the patient is attending the hospital daily for treatment. Once a patient has completed treatment, bolus feeding may facilitate a quicker transition back to a pre-morbid lifestyle, (returning to work and social activities) as it physiologically mimics a typical eating pattern.

Bolus feeding may be easier to undertake with a gastrostomy tube rather than an NGT as repeated administration of feed boluses requires increased pH testing with a NGT. It can be poorly tolerated by some patients due to

the volume of feed being delivered over a short period of time. In addition, a primary disadvantage of bolus feeding is that it requires manual dexterity and strength. As such this method of feeding may not be suitable for patients with poor manual dexterity, for example, arthritis of the hands. In such instances, continuous feeding using a pump would be the preferred method.

Continuous feeding is often used when commencing patients on enteral tube feeding to assist gastrointestinal tolerance, particularly for patients immediately post head and neck cancer surgery. This is because it allows the lowest possible hourly feed rate to meet nutritional requirements. It is also advantageous if patients are at home and rely on community nursing to administer their enteral feed as it usually requires only two nursing visits a day to set up and disconnect. It is also useful if patients wish to be fed overnight whilst sleeping. A disadvantage of continuous feeding is attachment to the feeding pump. This can lead to decreased mobility, which may affect QOL, however many feed companies provide carry bags to allow portable pump feeding.

Parenteral nutrition support

Parenteral nutrition is rarely required in patients with head and neck cancer as most patients have an accessible and functioning gastrointestinal tract. National data suggests an incidence of <1% for patients with head and neck cancer.[67] Parenteral nutrition may be used as a temporizing measure in patients with head and neck cancer who have obstructive tumours, making placement of an enteral feeding tube impossible. It may also be used for patients who have a chyle leak that has not responded to oral or enteral diet modification. Parenteral nutrition should be considered for individuals who are malnourished or at risk or malnutrition and have inadequate or unsafe oral/enteral nutritional intake and have a non-functional, inaccessible or leaking gastrointestinal tract.[21] Parenteral nutrition can be stopped once adequate oral or enteral nutrition is tolerated and withdrawal should be planned and stepwise with a daily review of the patient's progress.

REHABILITATION

Rehabilitation has been defined as 'the restoration, to the maximum degree possible, of an individual's function and/or role, both mentally and physically, within their family and social networks and within the workplace where appropriate'.[68] Following treatment for head and neck cancer, patients may have long-term side effects of their treatment which affect their ability to eat, drink and communicate. Due to the very nature of multimodality treatment, side effects can vary significantly between patients with regards frequency, timing, severity and impact on QOL.[69] Surgical intervention may permanently alter the texture of diet that a patient can consume and in some instances result in permanent feeding tube dependency. Patients who have had chemoradiotherapy are at high risk of developing both late and long-term side effects such as xerostomia, dysphagia, odynophagia and trismus. One year post-treatment reports suggest that the majority of patients still experience eating problems due to persisting side effects of treatment.[70]

Studies have identified that pain is a significant problem for patients following radical radiotherapy, often leading to a reduction in dietary intake.[71] Patients suffering from reduced laryngeal elevation, reduced cricopharyngeal opening and non-functional swallow on at least one swallow with any bolus type are significantly more likely to require a texture modified diet and have an intake of less than 50% of estimated nutritional requirements.[72] It has been suggested that up to 50% of patients who have undergone head and neck cancer treatment experience dysphagia and up to 60% report severe xerostomia following treatment with an estimated 10% requiring long-term enteral nutrition.[73–75]

Multidisciplinary rehabilitation programmes involving a specialist head and neck dietitian and SLT have the potential to improve outcomes for oral intake. Guidelines recommend that patients with head and neck cancer receive fortnightly reviews by a specialist head and neck dietitian for at least 6 weeks after treatment. In addition, dietetic support should continue for up to 6 months, or for as long as they require management of long-term side effects, weight loss and enteral nutrition.[10] Further research is required to examine the benefits of these proactive rehabilitation programmes in reducing tube dependency in patients with head and neck cancer.

The level and nature of support between patients will vary, as well as being dependent on local resources and guidance. The nutritional status of patients should be closely monitored so that dietary intervention can be adjusted in a timely manner. Locally, support groups such as 'Back to Eating' should be established to provide patients with an encouraging environment to try new foods during the rehabilitation phase. Patients may be discharged by the dietitian once rehabilitation goals have been achieved, however, there should be an agreed process in place to re-access specialist head and neck dietetic services should this be required.[4]

SURVIVORSHIP

As the incidence of cancer increases, alongside recent improvements in cancer treatment, it is expected that patients with head and neck cancer are living well and beyond their cancer diagnosis and treatment.

Ensuring that good survivorship care, incorporating nutrition, is provided to patients with head and neck cancer may lead to a reduction in future mortality by

- reducing the risk of cancer recurrence
- preventing or managing comorbidities such as diabetes, cardiovascular disease and other cancers
- earlier identification of recurrence.

There is limited evidence available detailing specific dietetic support for patients with head and neck cancer in

survivorship as the long-term consequences of treatment are unknown. Patients are encouraged to follow general health promotion recommendations including dietary advice on maintaining a healthy weight (BMI 18.5–25 kg/m^2), limiting alcohol and eating a balanced diet once they have reached a stable weight and are able to meet their nutritional requirements from food. There have been reports that patients with head and neck cancer suffer increased levels of emotional distress, physical limitations, altered body image and relationship difficulties.[76] It is essential that services for survivorship are developed that support and enable them to cope with these needs and allow them to lead a good QOL for as long as possible.

Some patients may continue to require medical led follow-up long term. However, with younger people being diagnosed with head and neck cancer, because of the association of human papillomavirus (HPV) and oropharyngeal cancer, there are a growing number that can be educated and supported to self-manage at home with remote access and timely re-access to clinics.[69] Many survivorship initiatives are recommending structured holistic recovery packages that incorporate the following:

- holistic needs assessment and care planning
- treatment summaries
- health and well-being events
- advice and schemes supporting physical activity.

The specialist head and neck dietitian plays an integral part in the delivery of such survivorship packages by providing nutritional advice tailored to the needs of the patient with head and neck cancer.

CONCLUSION

A specialist head and neck dietitian is an integral part of the head and neck MDT. There is clear evidence to support the benefits of nutrition throughout a patient's head and neck pathway which starts with nutritional screening and pre-treatment optimization. Nearly all patients undergoing treatment will require nutrition support, most commonly oral or enteral tube feeding interventions. The expected impact of treatment on nutrition as well as potential for long-term difficulties with eating and swallowing should be discussed thoroughly at pre-treatment stage. The decision to provide a nutritional intervention such as insertion of a feeding tube should be patient-centred and consider the impact on QOL. It is especially important to consider the individual patient needs for those having primary chemoradiotherapy where optimal route and timing for enteral tube feeding is not certain. Nutrition intervention usually ends in the rehabilitation and survivorship stage of a patient's treatment pathway and more research in this area is required.

KEY POINTS

- A high proportion of patients with head and neck cancer present with malnutrition due to disease site and process, pre-existing dietary issues and psychosocial factors. Identifying malnutrition with a validated screening tool is recommended early in the treatment pathway.
- Nutritional assessment by a specialist head and neck oncology dietitian is advised prior to treatment to allow optimization of nutritional status.
- Pre-operative feeding for 7–14 days should be offered to malnourished patients who are planned for major surgery, even if the surgery must be delayed.
- ERAS protocols in head and neck surgery are likely to improve outcomes and nutritional aspects include prevention of long fasting times pre-operatively, carbohydrate-loading and early enteral and oral feeding post-operatively.
- All patients undergoing (chemo)radiotherapy for head and neck cancer will require weekly nutritional assessment by a specialist dietitian due to the impact of treatment toxicities on swallow and oral intake.
- Nutrition support methods during treatment typically include oral (texture modification, food fortification, nutritional supplements) or enteral tube feeding (reactive or prophylactic via NGT or PEG).
- Following treatment for head and neck cancer, patients are at risk of developing late and long-term side effects, such as xerostomia, dysphagia, odynophagia and trismus which may impact nutritional status.
- Multidisciplinary rehabilitation programmes which include a specialist dietitian and SLT have the potential to improve outcomes for oral intake and facilitate early enteral tube feeding removal.
- It is essential that survivorship services are developed for patients with head and neck cancer as they may suffer increased levels of emotional distress, physical limitations, altered body image and relationship difficulties following treatment.
- Nutritional interventions during palliative care should aim to maximize patient comfort and QOL.

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CHAPTER
34

SPEECH VOICE AND SWALLOW REHABILITATION AFTER CHEMORADIATION

Justin W.G. Roe and Katherine A. Hutcheson

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: chemoradiation, head and neck cancer, swallowing, voice and functional outcomes.

INTRODUCTION

Radiotherapy for head and neck cancers (HNC) can impart devastating effects on swallowing and communication abilities. Impaired communication and swallowing functions have significant consequences on health and well-being, and limit activities and participation in social situations.

Adverse effects of tumour on swallowing ability prior to treatment are well documented, largely in patients with advanced stage (T3–T4) primary tumours.[1–3] Cancer treatment in most cases, compounds baseline tumour-associated functional deficits. Historically, functional impairments were largely attributed to major surgery. In the last two decades, however, radiotherapy and chemo-radiotherapy regimes have become the main treatment modality to improve locoregional control and offer functional organ preservation for many advanced stage HNC that would have previously required ablative surgery. Despite comparable survival rates after non-surgical organ preservation,[4, 5] it has become increasingly clear that 'organ preservation' does not necessarily result in function preservation, particularly with regard to swallowing mechanics.[6, 7]

Dysphagia is the most commonly cited functional problem after non-surgical organ preservation for HNC, and may ultimately cause aspiration pneumonia, nutritional and hydration compromise, and subsequent reliance on tube feeding. Patients themselves report that swallowing is a top concern before and after treatment with organ-preserving radiotherapy with or without chemotherapy, hereafter referred to as (chemo-)radiotherapy.[8, 9] Speech and voice outcomes are less commonly reported after non-surgical modalities for locoregionally advanced HNC, and pre-treatment data are often lacking in published reports.[10] Nonetheless, recent studies have identified that changes in voice quality are present up to 1 year following organ preservation treatment for HNC,[10] and these changes are also present in those who have been treated for non-laryngeal cancers.[11, 12]

This chapter includes a brief overview of the communication issues experienced by patients with locoregionally advanced HNC treated with non-surgical organ preservation. A review of voice changes after (chemo-)radiotherapy for early glottic cancer is beyond the scope of this chapter. The primary focus of the chapter is an evidence-based review of swallowing outcomes after non-surgical treatment. Swallowing outcomes reported in published literature will be summarized. Predictive factors will be highlighted, in particular, baseline clinical predictors of swallowing. Preventative strategies will be reviewed, including the potential benefits of highly conformal radiation treatment aiming to reduce bystander doses to swallowing-critical structures and swallowing status during radiotherapy. Finally, this chapter will cover the emerging evidence for rehabilitation strategies implemented both prophylactically and following non-surgical treatment for HNC.

COMMUNICATION FOLLOWING CHEMORADIATION FOR HEAD AND NECK CANCER: ASSESSMENT AND MANAGEMENT

Communication outcomes, and in particular voice outcomes, are increasingly relevant in contemporary practice. With changing demographic towards a predominance of HPV-related head and neck disease, patients are now younger at diagnosis with better prognosis for long-term survival. More likely to be employed at diagnosis, impaired communication may well impact on a successful return to work in modern HNC survivors. Organ-sparing chemoradiotherapy preserves, in most cases, the agility of the articulators, and a minimal effect on speech intelligibility should be expected. Nevertheless, both acute and chronic effects of radiotherapy may impart normal tissue effects that cause perceptual differences in speech and voice. Acute toxicities such as ulceration and oral mucositis will impact on comfort when speaking, but resolve in the months following treatment. In addition, radiotherapy fields that include the larynx will inevitably result in voice changes to some extent. Voice is produced by the larynx, which is particularly vulnerable to the effects of radiation. Treatment effects include oedema, fibrosis and hyperemia and erythema.[13] A recent study highlighted that concurrent chemoradiotherapy for non-laryngeal cancers can have a significant, long-term impact on voice production across patient-reported, instrumental and perceptual assessment methods.[11]

A number of assessments are available to assess vocal functioning. Patient reported outcomes can be collected using the Voice-Related Quality of Life (VR-QOL),[14] the Voice Symptom Scale (VoiSS)[15] and the Voice Handicap Index (VHI).[16] Perceptual voice evaluation is usually rated using the GRBAS scale[17] or the CAPE-V. Instrumental evaluation of voice can be conducted for example using laryngeal videostroboscopy. Videostroboscopy assesses symmetry and degree of true vocal fold motion, and vibratory patterns during phonation.

Speech intelligibility is a broader construct of communication, impacted by voice quality, resonance and articulation. A simple, global assessment of intelligibility includes the Understandability of Speech scale as part of the 3-item Performance Status Scale for Head and Neck Cancer.[18] While there are numerous patient reported voice measures, there are few designed specifically for speech. The Speech Handicap Index (SHI) has been validated for use in the HNC population in Dutch and English.[19, 20] Both the VHI and SHI which have been translated and validated for use in a number of languages.[19–21, 27]

Voice therapy after (chemo-)radiotherapy for advanced stage HNC is largely unstudied. Efficacy of behavioural voice therapy has been reported after radiotherapy for early stage glottic cancer,[28] but it is not clear if there is comparable benefit after radiotherapy for advanced HNC. Vocal hygiene (i.e. laryngeal hydration, gentle vocalization) is also empirically recommended to minimize vocal trauma, abuse or maladaptive hyperfunction during the course of radiotherapy and in acute recovery. The role of the speech language pathologists (SLP) during and following radiotherapy is to instruct the patient in vocal hygiene and to prevent maladaptive strategies employed to overcome radiation-induced dysphonia. Following treatment, patients are likely to experience voice difficulties resulting from the oedema and dryness. In the latter stages of treatment and early recovery phase, fundamental frequency be reduced due to greater vocal fold mass and *en bloc* vibratory patterns from bulky, stiff vocal cords. Along with a harsh or rough quality of voice, disturbed frequency of voice contributes to the perceptual changes reported in published studies. Patients may also report vocal fatigue after long periods of talking. Voice problems may persist due to permanent treatment-related changes or vocal abuse resulting from attempts to compensate for transient dysphonia during early recovery.[29]

FUNCTIONAL ASSESSMENT OF SWALLOWING AFTER CHEMORADIOTHERAPY

In recent years, there has been a significant rise in the number of studies reporting swallowing outcomes after organ preservation. To understand the impact of cancer therapy on swallowing function, it is essential that researchers use a range of measures that are sufficiently standardized to allow for future meta-analysis as well as immediate interpretation. One of the challenges in interpreting published data is the heterogeneity of swallowing outcome measures reported in published studies.[30] Much of the radiation oncology literature reports toxicity according to clinician-rated scales such as the Common Terminology Criteria for Adverse Events (CTCAE).[31] While these scales provide invaluable data in relation to a broad range of toxicities, the CTCAE rates dysphagia as function of dietary restrictions, dysphagia symptoms, and enteral/parental nutrition requirements, and lacks sensitivity or specificity to aberrant oropharyngeal swallowing physiology.[6] The broad criteria that define toxicity grades for dysphagia are, unfortunately, not sensitive to physiologic disturbances, asensate dysphagia (e.g. silent aspiration), or specific to pharyngeal dysfunction and downstream effects of dysphagia on quality of life.

Comprehensive dysphagia assessment requires a multidimensional panel of measures, incorporating instrumental examinations of swallowing such as the modified barium swallow (MBS) study (videofluoroscopy) or Fibreoptic Endoscopic Evaluation of Swallowing (FEES), along with clinician-rated and patient-reported outcome measures (PROM). The importance of multidimensional swallowing evaluation has been reinforced by a recent study evaluating swallowing outcomes following radiotherapy. In this longitudinal study of chemoradiotherapy for HNC, it was found that using different methods of swallowing evaluation resulted in complementary, but distinct normal toxicity complication probabilities.[32] The importance of including a broad range of swallowing measures has been further highlighted in the radiation oncology literature with specific guidance to incorporate these multidimensional assessments of swallowing function in Phase III organ preservation trials.[33]

Standardized functional assessments are a critical component of comprehensive clinical care and outcomes research. Functional assessments can include 1) clinician-driven appraisals (e.g. physical examination, instrumental and imaging studies and clinician-rated scales) and 2) patient-reported outcome measures (PROMS) (e.g. quality-of-life questionnaires, symptom inventories). Clinical examinations by speech and language therapists (SLTs – also known as speech language pathologists (SLPs in the USA) include a cranial nerve examination, oral motor assessment, perceptual motor speech and voice ratings, and the clinical examination of the swallow. Observations from these clinical assessment protocols provide the foundation of the functional assessment and offer the advantage of observing speech, voice or swallowing in a more natural environment (e.g. swallowing natural food rather than a contrast agent, or voicing without an endoscope in the mouth or nose), but clinical assessments lack the sensitivity of instrumental studies.

Instrumental examinations and imaging studies are therefore considered the gold-standard because they directly observe the physiology and competency of swallowing, speech or voice production. Instrumental examinations include the MBS study (or videofluoroscopic swallowing study), FEES, and laryngeal videostroboscopy. Indicators of functional status can also be rated as an adjunct to clinical and instrumental studies according to standardized tools such as the Performance Status Scale-Head and Neck (3-items: Normalcy of Diet, Understandability of Speech, Eating in Public), toxicity grading scales European Organization for Research and Treatment of Cancer (EORTC), CTCAE, or simply by record of the presence or absence of gastrostomy or tracheostomy. Functional status scales provide uniform nomenclature for simple, surrogate measures of functioning routinely ascertained in clinical encounters. Each type of functional measure is detailed in the following sections.

Clinical evaluation of swallowing

The importance of the clinical swallowing evaluation is that it provides a baseline on which performance measures can be taken (ideally) before treatment and may predict outcome.[34] A clinical swallowing evaluation is comprised of a number of measures. After completion of a detailed medical history, the clinical examination will include an oromotor evaluation to assess the integrity of the cranial nerves pertaining to swallowing. In addition, swallowing trials will be undertaken to establish the presence of clinical signs of aspiration or overt signs of difficulty. Recent studies have reported on the benefits of the 100 mL Water Swallow Test (WST) as a component of the conventional clinical swallowing evaluation.[35] Offering a low cost quantifiable endpoint from clinical examination, the WST measures swallowing speed, capacity and volume. The WST is easily repeatable at follow-up appointments to monitor changes in swallowing performance. In addition, clinicians can observe for clinical signs of aspiration as is the case in any standard clinical swallowing evaluation. In combination with information gleaned from history taking and oromotor examination, these data signpost referral for a detailed instrumental evaluation of swallowing. The use of a simple, validated tool such as the Performance Status Scale for Head and Neck Cancer (PSS-HN)[36] or Functional Oral Intake Scale (FOIS)[37] should be used in adjunct to the conventional examination to quantify the functional status of the patient with regard to feeding tube dependence and level of oral intake.

Instrumental evaluation of swallowing

A number of instrumental methods are available to examine swallowing function (i.e. physiology, safety or airway protection and efficiency or bolus clearance) in detail. These include solid-state and high-resolution manometry,[37–42] scintigraphy,[43–46] ultrasound,[47–54] transnasal (o)esophagoscopy (TNE),[55, 56] cine magnetic resonance imaging (MRI)[57–59] and advanced computed tomography (CT) techniques.[60, 61] Each of these techniques provides a unique insight into specific features of the deglutition process, however, the most commonly reported technique in the radiation oncology and oropharyngeal dysphagia literature is videofluoroscopy[62] and FEES.[63]

During videofluoroscopy, patients are imaged in lateral and anterior-posterior planes and presented with a range of liquid and food boluses that have been infused with contrast agents, typically barium sulfate. Videofluoroscopic examination of swallowing, commonly referred to as the MBS, allows for visualization and analysis of the oral, pharyngeal and oesophageal stages of the swallow. A number of observations can be made from MBS, including the presence of penetration of material in to the laryngeal airway and tracheal aspiration (quantified per the validated Penetration-Aspiration Scale[64]) and swallowing efficiency (quantified by Oro-Pharyngeal Swallowing Efficiency (OPSE)[45]). More recently the Modified Barium Swallow Impairment Profile (MBSImp) was introduced to comprehensively assess 16 critical components of the oropharyngeal swallow and provide a standardized profile of the physiological swallowing impairment.[45, 65] Based on findings from the MBS, the SLP can establish the nature and extent oropharyngeal dysphagia and develop an individualized rehabilitation plan. Efficacy of tailored swallowing strategies, such as change in posture or modification of the swallowing pattern, can be examined in real-time on the MBS. DIGEST is another method recently developed to measure the severity of pharyngeal stage dysphagia in a manner compatible with CTCAE toxicity grade (1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening/profound) based on the results of the MBS study.[66]

FEES also allows for detailed evaluation of swallowing. While the oral stage cannot be observed and there is white out during the swallow, it provides valuable information on the pharyngeal stage of the swallow and is a useful biofeedback tool, particularly for therapeutic benefit.

Patient-reported outcome measures (PROMS) of swallowing

The patient's perception of their swallowing impairment and how it impacts on their everyday life is arguably a critical outcome of cancer therapy. To that end, PROMs have

gained popularity in recent decades. PROMs complement clinician-rated assessments by quantifying the patient's perceived level of handicap or impairment, and its impact on daily activities and quality of life. More recently, the PROMs have been augmented by carer-reported outcomes to add how dysphagia might impact on quality of life and participation in social situations.[67]

A number of assessments are available that enable clinicians to understand patient's perceived swallowing outcomes following HNC treatment. Specific to HNC, these include, among others, the University of Washington Quality of Life Questionnaire (UW-QOL),[68] the European Organization for Research and Treatment of Cancer (EORTC HN-35),[69] and the MD Anderson Dysphagia Inventory (MDADI).[70] UW-QOL and EORTC are general QOL inventories that include swallowing-specific items, whereas the MDADI is a 20-item inventory focused exclusively on swallowing-related QOL.

The UW-QOL is particularly useful for assessment of multiple domains of functional impairment, and it offers the unique feature of prioritization of key issues for the patient. Research has shown that up to 48% of patients select swallowing as being a priority concern for them 1 year after treatment with 3D-conformal radiotherapy treatment.[8] A recent study of patients treated with parotid-sparing intensity-modulated radiotherapy (IMRT) has found that 40% of patients report swallowing as being a priority concern at 12 months.[9] Popular multi-symptom inventories that include dysphagia symptom items include the MD Anderson Symptom Inventory-Head and Neck module (MDASI-HN)[71] and the Vanderbilt Head and Neck Symptom Scale (VHNSS).[72]

Questionnaires are available to ascertain more details on swallowing-specific quality of life including the MDADI and the SWAL-QOL.[73] Among these, the MDADI was specifically developed and validated for use with HNC patients. Other questionnaires designed to ascertain swallowing symptoms and ability include the EAT-10[74] and the Sydney Swallow Questionnaire (SSQ) that have both been validated for use in HNC.[75] There is consensus that PROMs and clinician-rated measures should be used in concert, because discordance that is recognized between patients' perception of their handicap and clinician-rated observations.

DYSPHAGIA AFTER CHEMORADIOTHERAPY

Outcomes

During (chemo-)radiotherapy, acute damage occurs to the mucosa and soft tissue in the radiation treatment volume leading to an inflammatory reaction and subsequently, mucositis and oedema of the soft tissues.[13, 76, 77] While some improvement of acute symptoms can be expected by 3 months, this is not universal. Persistent, longer-term difficulties have been reported after treatment, months or even years later.[78–81] Commonly reported problems impacting on swallowing safety and efficiency include reduced pharyngeal contraction, reduced base of tongue retraction, incomplete epiglottic deflection, incomplete or delayed laryngeal closure and hyolaryngeal excursion, and abnormal oesophageal opening and stricture.[78, 82–86] While mainly seen in the high dose volume, stricture has been observed in areas that have not been treated in the high dose radiation field, leading authors to suggest that decreased swallowing frequency during treatment may also increase the risk of fibrosis.[83] Jointly, however, current data suggest that aforementioned impairments in laryngopharyngeal physiology are the primary contributors to radiation-associated dysphagia (RAD) rather than stricture. This is particularly the cases for late-RAD, driven often by profoundly impaired pharyngeal propulsion coupled with delayed lower cranial neuropathies.[87] A recent systematic review reported the overall risk of stricture after non-surgical HNC treatment was 7.2% over published series from 1989 to 2008. Interestingly, the rate of stricture was elevated in IMRT series (16.7%) perhaps reflecting intensified regimens of chemoradiation in contemporary organ preservation publications or early methods of IMRT not sufficiently controlling laryngeal and esophageal inlet dose.[88]

A primary observation from instrumental assessment is the presence or absence of aspiration. Penetration of material into the upper airway may be spontaneously cleared by patients, however for some, cumulative penetration or inadequate clearance of airway pharyngeal residue may result in delayed aspiration after the swallow. Aspiration is often silent in upwards of 50% of post-radiotherapy aspirators, and the false negative results of clinical examination in silent aspirators can lead to potentially life threatening aspiration pneumonia. Aspiration is common in patients with HNC. Authors have cited data reporting aspiration rates ranging from 18% to 81% after chemoradiation to all head and neck sites and 18% to 54% in the case of oropharyngeal cancers.[89]

Predictors

Tumour and treatment burden are the most notable clinical predictors of functional outcomes after organ preservation.[90] While data suggest the prognostic significance of the primary and nodal staging per TNM criteria, T-stage appears the most consistent staging variable that impacts the severity of dysphagia, gastrostomy dependence, and aspiration after HNC treatment. Likewise, among sites of HNC treated with radiotherapy or chemoradiotherapy, hypopharyngeal tumours confer the highest risk of developing chronic dysphagia and stricture. Population-level data from the US suggest that patients with oropharyngeal primary tumors have the second highest risk of dysphagia (after hypopharyngeal), followed closely by laryngeal primary tumours.[91] Laryngeal cancers may have performed differently in this study, if small glottis cancers had been stratified out from advanced stage laryngeal cancers that are more likely to manifest dysphagia after treatment.

Treatment intensity significantly impacts functional outcomes. Intensification strategies, whether accelerated fractionation schedules, dose-escalation, or via the addition of systemic agents to radiotherapy regimes, have all been associated with greater toxicity and functional effects in clinical studies. Radiotherapy dose-distribution predicts the degree of swallowing impairment across a variety of

outcome measures.[32] Thus, conformal plans using IMRT have been proposed as a strategy to reduce the burden of dysphagia.[86] It is important to note, however, that swallowing-specific dose-constraints have not historically been included in IMRT algorithms. In fact, unintended elevated bystander doses have been observed in certain swallowing-critical regions of interest including the brainstem, anterior oral cavity (inclusive of critical suprahyoid musculature), and larynx when not optimized in IMRT plans.[92, 93] It follows that the maximal benefit of IMRT on swallowing function may be realized only with swallowing-specific OARs are considered in treatment plans. Significant efforts have been made in the last decade to delineate these regions, and consensus is largely to reduce dose to the pharyngeal constrictor muscle region (particularly SPC) and the larynx , with emerging reports suggesting suprahyoid muscles in the floor of mouth regions as a previously undetected swallowing region of interest.[94–97] Favourable results have also been reported with the sparing of dysphagia-aspiration risk structures (DARS) using IMRT.[89] Given recent reports regarding lower aspiration levels in patients receiving split-field IMRT techniques,[98] potential benefits over whole-field techniques have been discussed in the literature.[94] In addition, de-escalation of total radiotherapy dose is currently proposed in several cooperative group trials in HPV-associated HNC populations who have favourable locoregional control and the potential to live decades with late effects of treatment. Examples of two multicentre studies which have incorporated a dedicated dashboard of multidimentional swallowing measures to explore these areas include the PATHOS and DARS studies.[99, 100]

Likewise, cytotoxic chemotherapy sensitizes tumour and normal tissue to effects of radiotherapy. Thus, treatment intensification by the addition of chemotherapy typically increases swallowing toxicity. Acute and chronic dysphagia is most likely exacerbated when chemotherapy is delivered concurrently with radiotherapy, whereas adverse effects of induction chemotherapy on swallowing function are not established. In fact, induction chemotherapy was found to impart improved local symptoms (diet per PSS-HN, MDADI, and pain scores) prior to definitive local therapy in a trial of oral tongue cancer patients.[101] Favourable long-term swallowing outcomes have also been observed in longitudinal follow-up of patients with locally advanced HNC treated with an induction approach.[102]

Baseline functional status significantly predicts function after treatment. Aspiration, vocal fold paresis, feeding tube dependence and tracheostomy prior to treatment have all been reported as adverse prognostic indicators of functional recovery.[90] That is, organ preservation should not be expected to restore function to the impaired organ. While data suggest that roughly half of patients with vocal fold fixation prior to chemoradiation may recover some mobility, the functional translation of this recovery is not clear.[103, 104] Moreover, aspiration of thin liquids sufficient to necessitate dietary modifications prior to treatment significantly predicts for unsafe oral intake requiring NPO status in long-term survivorship after laryngeal preservation.[85] For these reasons, among others, pre-treatment referral to SLTs for baseline functional assessment has recently been recognized as best practice in patients receiving non-surgical organ preservation by the Triological Society[105] and in the National Institute for Clinical Excellence's Improving Outcomes Guidance for Head and Neck Cancer.[106] It is also a 'top-ten' recommendation from the British Association of Head and Neck Oncologists.[107]

One of the important changes in clinical practice that may contribute to improved swallowing outcomes is the implementation of an individualized approach to tube feeding placement in patients undergoing organ-preserving HNC treatment.[94, 108] As discussed earlier, it is clear that some people may require nutritional support by way of tube feeding simply due to cancer related dysphagia. However, there has been a shift in the clinical practice trends from implementing *prophylactic* gastrostomy feeding in all patients to individualizing decisions on the basis of pre-treatment functioning, nutrition, and tumor burden.[109] Systematic reviews agree that the evidence base regarding optimal tube feeding route is limited at this time.[110] Variation has been reported in approaches to tube feeding in the UK and Australasia.[111, 112] Two primary considerations are timing of placement (prophylactic versus reactive) and the type of tube (nasogastric versus gastrostomy).

Historically, gastrostomy tubes were placed prophylactically in all (or most) patients with locally advanced HNC dispositioned to receive radiotherapy. Recent data, however, suggest that reactive rather than prophylactic feeding tubes are associated with favourable swallowing outcomes and the feasibility of this approach has been established in comprehensive systems that allow for close monitoring of nutrition, hydration and swallowing status during radiotherapy.[113] Rather than placement of prophylactic gastrostomy tubes in patients who may ultimately continue with oral intake during treatment,[114] the use of reactive nasogastric feeding has also been proposed in the literature.[115] Despite more frequent tube displacements, no difference has been reported in patient reported assessments of physical condition or quality of life between those who had nasogastric or gastrostomy feeding.[116]

Prevention and rehabilitation

Improved outcomes in modern trials may be influenced also by more active involvement of rehabilitation professionals such as SLTs and dietitians in recent years. However it is clear from surveys of UK, US and Australasian service delivery that the timing and nature of SLT provision to HNC patients is still variable.[112, 117, 118]

Several studies have examined the potential benefit of prophylactic swallowing therapy for HNC patients, including three randomized clinical studies.[119–121] Proactive swallowing therapy encourages maximal use of the swallowing musculature during radiotherapy. In effort to discourage disuse atrophy, two goals can be outlined in proactive swallowing therapy: eat (that is, continue oral intake during radiotherapy) and exercise (that is, perform targeted swallowing exercise during radiotherapy). Observational data suggest the benefit of maintaining oral intake throughout radiotherapy on long-term diet

outcomes and PROMs.[122, 123] In addition, four institutions have published a range of favourable functional outcomes associated with swallowing exercise during radiotherapy. Prophylactic swallowing exercise has been associated with better swallowing-related quality of life scores,[124, 125] superior base of tongue and epiglottic movement,[126] lower gastrostomy rates,[113] shorter gastrostomy dependence,[113] better post-radiotherapy diet levels[120] and superior muscle composition on post-radiotherapy MRI.[121] Despite many hints of efficacy in these studies, a recent Cochrane review found inconclusive evidence on the benefit of swallowing exercise in this population in large part related to underpowered single institution trials and variable methodology precluding meta-analysis.[128] Data also suggest independent positive associations with both prophylactic swallowing therapy goals: *eat* and *exercise*. That is, patients who both eat and exercise during radiotherapy have the best swallowing outcomes, and patients who either eat or exercise have better swallowing outcomes than those who do neither.[127, 128] Importantly, it has also been raised in the literature that despite fairly uniformly positive findings, studies of proactive swallowing exercise vary in how therapy was delivered and practicalities in individual clinical settings.[94] More recently, there has been interest in the potential of Expiratory Muscle Strength Training (EMST) in the rehabilitation of HNC treatment-related dysphagia. Reduced maximum expiratory pressures have been found in patients with chronic radiation-associated aspiration. Initial findings in the HNC population suggest improved expiratory muscle strength and improved swallowing function following therapy with EMST.[129, 130]

CONCLUSION

In this chapter we have described the impact of disease and treatment effects contributing to communication and swallowing problems following organ preservation protocols for HNC. The SLT is a vital member of the multidisciplinary team. Based on the available evidence, we propose the following key points to optimize functional outcomes.

KEY POINTS

- Refer patients for multidimensional swallowing assessment *before* treatment to tailor proactive swallowing therapy and identify high risk patients.
- Standardize multidimensional swallowing assessments to include clinical swallowing evaluation, instrumental swallowing examination and PROMs.
- Use psychometrically validated, quantitative metrics of swallowing function.
- Implement prophylactic swallowing therapy prior to and during treatment – including targeted swallowing exercise and promotion of oral intake throughout treatment.
- Instruct patients in vocal hygiene during treatment and in the immediate post-treatment phase to prevent secondary voice problems due to vocal hyperfunction.
- Advocate a collaborative approach to care during treatment to minimize side effects such as pain that may impact on the ability to continue swallowing.
- Individualize decisions regarding tube feeding during (chemo-)radiotherapy, with preference towards reactive rather than prophylactic tube placement.
- Establish resources and clinical pathways to work towards tube removal as soon as possible following treatment.
- Implement evidence-based swallowing therapy to address impairments based on instrumental swallowing evaluation.
- Consider highly conformal techniques such as IMRT optimized to spare swallowing critical structures, when possible.
- Consider an individualized approach to treatment de-escalation when possible to reduce toxicity and improve swallowing outcomes.
- Consider the profound effect on health-related quality of life that some HNC survivors may encounter and encourage psychological support to deliver a holistic rehabilitation programme when indicated.
- Ensure systems are in place to monitor and provide interventions for patients with persisting swallowing difficulties after treatment and importantly, late radiation associated dysphagia that can occur even years after functional swallowing.

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CHAPTER 35

SURGICAL ANATOMY OF THE NECK

Laura Warner, Christopher Jennings and John C. Watkinson

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SEARCH STRATEGY

This chapter is a basic science chapter with information from anatomy texts and scientific papers concerning head and neck anatomy, identified through Medline searches. The anatomical evidence is supported by cadaver dissection studies, as well as the medical literature.[1] The clinical evidence is observational.

INTRODUCTION

> 'Anatomy is to physiology as geography is to history; it describes the theatre of events'
>
> Jean Fernel 1497–1558 France.

A sound appreciation of the intricate anatomy of the neck is essential for any surgeon embarking upon operations in the neck. This chapter provides a detailed and clinically focused synopsis of neck anatomy; covering developmental anatomy, surface anatomy and the triangles of the neck, fascial layers, neck musculature and deep neck spaces, as well as the important structures encountered within in the neck such as major blood vessels, lymphatics and important cranial and cervical nerves. Details of the viscera of the neck, such as the larynx, pharynx, oesophagus, trachea, thyroid, parathyroid and salivary glands are discussed elsewhere.

DEVELOPMENTAL ANATOMY

Structures in the neck that are innervated by the cranial nerves are derived from the branchial apparatus. The six branchial arches begin to emerge from 4 weeks' gestation. Each arch has its own cranial nerve, cartilage and artery. The fifth arch obliterates soon after all the branchial arches become apparent. Between the arches sit internal pouches and external clefts or grooves (**Figure 35.1**). The arches, clefts and pouches give the appearance of a series or slit-like grooves, resembling the gills of fish, hence the term 'branchial' which is derived

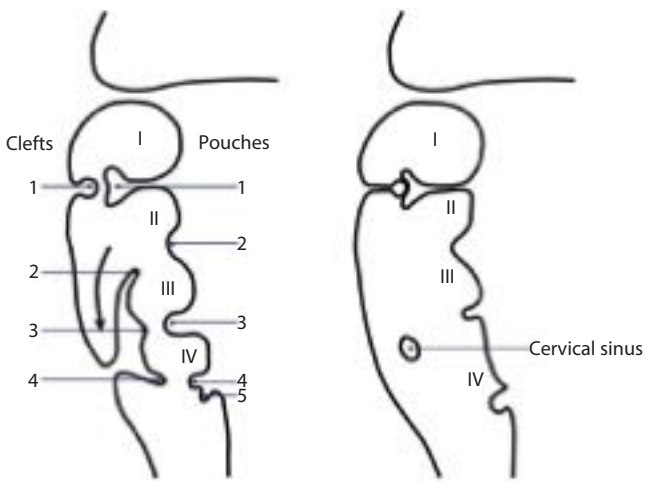


Figure 35.1 Schematic diagram of the branchial apparatus *in utero*.

from the Greek word for gills. The structures derived from the branchial system are outlined in **Table 35.1**.

Congenital abnormalities of the branchial arches can lead to absence or malformation of the head and neck structures arising from the branchial apparatus. This may result in microtia, hearing loss and facial asymmetry and can occur in isolation or as part of a syndrome. Developmental anomalies of the branchial clefts lead to cysts, sinuses or fistulae found in the neck (**Table 35.2**).

First branchial cleft abnormalities are caused by embryonic duplication of the first cleft or first arch and cleft, classified by Work in 1972 into type I and type II respectively.[2] These are rare, representing approximately 5% of branchial cleft anomalies. First branchial cleft abnormalities present as an external fistula tract opening located anterior and inferior to the tragus (type I) or as a fistula tract between an anterior opening close to the angle of the mandible with a posterior opening found in the ear canal or conchal bowl (type II). The fistulae tracts are present from birth and may be asymptomatic or can present with recurrent skin or ear discharge. Treatment is with complete surgical excision of the tract, taking care not to injure the facial nerve. This is particularly relevant with type II lesions which have an inconstant relationship to the facial nerve which may run either deep or superficial to the fistula tract.

Second branchial cleft abnormalities are the most commonly encountered, representing approximately 95% of all

TABLE 35.1 Branchial derivatives

Arch	Nerve	Cartilage	Muscle	Artery	Internal pouch	External cleft
1 Mandibular	Trigeminal (Mandibular branch V3)	Meckel's: Maxilla Malleus Incus	Mylohyoid Anterior digastric Tensor tympani Tensor veli palatini Muscles of mastication	1st aortic arch: maxillary artery	Eustachian tube Middle ear cleft Medial surface of tympanic membrane	External auditory meatus Lateral surface of tympanic membrane
2 Hyoid	Facial	Reichart's: Lesser cornu + upper body of hyoid Stapes superstructure Styloid process	Muscles of facial expression Posterior belly of digastric Platysma Stapedius	2nd aortic arch: stapedial artery	Palatine tonsil	Grows over remaining grooves
3	Glosso-pharyngeal	Greater cornu + lower body of hyoid	Stylopharyngeus Superior & middle constrictor	3rd aortic arch	Inferior parathyroid glands Thymic duct	Obliterated
4	Vagus – Superior laryngeal nerve	Thyroid lamina	Cricothyroid	4th aortic arch: arch of aorta	Superior parathyroid glands	Obliterated
6	Vagus – Recurrent laryngeal nerve	Cricoid Arytenoid cartilages	Inferior constrictor Intrinsic muscles of larynx	6th aortic arch: ductus arteriosus	Ultimobrachial body (forms parafollicular C cells of thyroid)	Obliterated

TABLE 35.2 Congenital branchial abnormalities

Branchial cleft fistula		% of cases	External opening	Internal opening	Associated structures	Symptoms	Management
1st	Work Type I	5%	Anterior and inferior to tragus	External ear canal or middle ear	Lies superficial to facial nerve	Skin or ear discharge	Surgical excision of fistula tract with CN VII monitoring
	Work Type II		Posterior to angle of mandible	Conchal bowl or external ear canal	Inconstant relationship with facial nerve	Skin or ear discharge	Surgical excision of fistula tract with CN VII monitoring
2nd		90%	Anterior border of sternocleidomastoid	Tonsillar fossa	May pass between internal and external carotid artery, runs deep to hypoglossal nerve	Skin discharge associated with upper respiratory tract infections	Surgical excision of fistula tract
3rd and 4th		<5%	Anterior border of sternocleidomastoid muscle, lower neck	Piriform fossa (3rd superior and 4th inferior to superior laryngeal nerve)	4th tract may be associated with thyroid gland	Skin discharge or abscesses, Recurrent thyroiditis (4th)	Surgical excision of tract or endoscopic ablation of internal opening

branchial anomalies. Second cleft fistulae or sinus tracts are found along the anterior border of the sternocleidomastoid muscle, with a tract extending cranially along the carotid sheath which can pass between the internal and external carotid arteries and may run deep to the hypoglossal nerve. The internal opening of a second branchial cleft fistula is found in the tonsillar fossa. Patients present with recurrent skin discharge, often associated with upper respiratory tract infections. Management is with complete surgical excision of the tract, taking care to avoid injury to the carotid arteries or hypoglossal nerve.

Third and fourth branchial cleft abnormalities are rare and are difficult to differentiate clinically so are described together. Third cleft fistulae have a skin opening anterior to the sternocleidomastoid muscle in the lower third of the neck, with an internal opening in the piriform fossa, above the level of the superior laryngeal nerve. Fourth cleft fistulae have similarly located skin openings, however, the internal opening in the piriform fossa is located below the level of the superior laryngeal nerve. Clinical features of third and fourth branchial cleft abnormalities include recurrent skin infections and abscesses. Recurrent thyroiditis is a potential feature of fourth cleft abnormalities as the fistula tract may be closely related to the thyroid gland.[3] Traditional management entails complete excision of the tract, although, more recently, endoscopic ablation of the internal opening within the piriform fossa has been described.[4, 5]

Branchial cysts typically arise from the second branchial cleft, which grows caudally, eventually obliterating the third and fourth clefts in normal development. This creates a potential space known as the cervical sinus, hypothesized to be a site of trapped epithelium which develops into a branchial cleft cyst. Branchial cysts are often asymptomatic and go unnoticed until they enlarge secondary to upper respiratory tract infection. A popular alternative theory for branchial cyst development is cystic degeneration within a lymph node, hypothesized because lymphoid tissue, as well as epithelium, is found within the walls of brachial cysts.[6]

KEY POINTS

- Knowledge of the developmental anatomy is key to understanding neck anatomy.
- Abnormalities of the branchial clefts may present with fistulae, sinuses or cysts.
- Definitive treatment of 1st and 2nd branchial cleft fistulae is complete excision of the tract together with the openings.
- 3rd and 4th branchial cleft abnormalities may be managed with endoscopic ablation of the internal opening.

SURFACE ANATOMY AND TRIANGLES OF THE NECK

Understanding of the surface anatomy of the neck and the structures that can be palpated is essential for surgeons to differentiate pathology from normal anatomy in neck examination. Furthermore, the means to determine the exact location of pathological masses encountered assists with diagnosis. The neck is classically divided into anterior and posterior triangles, which can be further divided into other triangles as described below, helping to compartmentalize the complex anatomy of the neck.

Surface anatomy

The superior border of the neck is defined by the mandible with the deep limits of the floor of mouth anteriorly and skull base posteriorly. The inferior limits of the neck are formed by the upper aspect of the first rib and the first thoracic vertebrae.

MANDIBLE

The lower border of the mandible forms the upper limit of the neck and the division between the neck and the face. The superficial lobe of the submandibular gland is palpable inferior to the lower border of the body of the mandible, just anterior to the angle. The tail of the parotid gland is palpable just posterior to the angle of the mandible.

MASTOID PROCESS

The tip of the mastoid is palpable posterior to the lobule, where the sternocleidomastoid muscle inserts. Anterior and inferior to this the transverse process of the atlas may be palpated.

HYOID BONE

The hyoid is an important bony landmark in the neck. Sitting in the midline of the neck, superior to the thyroid cartilage, the hyoid is a horseshoe-shaped bone with a central body and paired greater and lesser cornus. The greater cornu acts as a guide to the lowermost extent of the marginal mandibular branch of the facial nerve and the level of the hyoid divides nodal levels II and III. The hyoid bone has many muscular attachments; the mylohyoid, geniohyoid and hyoglossus insert onto the superior aspect of the body of the hyoid, whereas the omohyoid, sternohyoid and thyrohyoid muscles insert onto the inferior border. Fibres of the middle constrictor muscles insert into the greater cornu and the stylohyoid ligament attaches to the lesser cornu. Inferiorly the thyrohyoid membrane connects the body of the hyoid to the thyroid cartilage.

Laryngeal cartilages and trachea

The cartilaginous framework of the larynx consists of the thyroid cartilage and cricoid cartilage, which are palpated in the midline of the neck. The arytenoid cartilages lie posteriorly and are not palpable. The thyroid cartilage is shield shaped and is notched superiorly forming a laryngeal prominence that is generally more significant in males than in females. Provided there is no lateral displacement of the larynx the notch can be a helpful surface landmark of the midline of the neck. Inferior to the thyroid cartilage sits the signet ring-shaped cricoid cartilage which is

easily palpable in thin individuals. The cricoid cartilage is at the level of the sixth cervical vertebrae and represents the border between the larynx and trachea, being the first and only complete tracheal ring. It is an important surface landmark to guide placement of the transverse incision used for elective tracheostomy, which is typically between the suprasternal notch and the lower border of the cricoid cartilage in an extended neck.[7] The thyroid and cricoid cartilages are joined by the cricothyroid membrane which is palpable in the midline as an area of cartilage deficiency between the lower border of the thyroid cartilage and the cricoid. This membrane forms an important landmark for emergency front of neck access as it is a relatively avascular plane where temporary airway access can be gained via needle or scalpel cricothyroidotomy. Inferior to the cricoid the cartilaginous rings of the cervical trachea can be palpated.

Thyroid

The isthmus of the thyroid gland can be palpated overlying the second and third tracheal rings. The lobes of the thyroid are located deep to the lower third of the sternocleidomastoid muscles and are not palpable unless enlarged.

Sternocleidomastoid muscle

The sternocleidomastoid muscle has a sternal head which arises from the manubrium and a fan-shaped clavicular head that arises from the medial part of the clavicle. The sternocleidomastoid divides the neck into anterior and posterior triangles, as outlined below. The carotid sheath runs deep to the sternocleidomastoid muscle, the bulk of the muscle provides a degree of protection to the major vessels from penetrating neck injuries. The lymph nodes of the jugular chains are located deep to the muscle. Turning the patient's head towards the side of the neck being palpated relaxes the muscle to allow palpation of the deeper lymph nodes.

Trapezius muscle

The trapezius forms the posterior border of the posterior triangle and the posterior limit of the nodal basins of the neck. Posterior to the trapezius lies the para-spinal musculature and the vertebrae.

Marginal mandibular branch of the facial nerve

The path of the marginal mandibular nerve is important to consider during many neck procedures to avoid inadvertent injury. It originates from the lower division of the facial nerve after the stylomastoid foramen and courses anteriorly and inferiorly from the lower aspect of the parotid gland, extending to the level of the greater cornu of the hyoid at its lowest point.[8] Whilst the exact course of the nerve and number and location of branches may be variable, it is reliably located at the point where it crosses the mandible to leave the neck, running with the facial artery, from which a palpable pulse may be located just anterior to the angle of the mandible. Incisions should be placed below the level of greater cornu of the hyoid, typically two finger breaths below the lower border of the mandible, to avoid injury to the nerve. Many surgical strategies exist to avoid inadvertent injury during neck dissection. Some surgeons advocate raising the flap in the immediate subplatysmal plane and locating the nerve before incising fascia inferior to it to retract the nerve above the level of the mandible, some suggest ligating the facial vein inferior to the lower border of the submandibular gland and retracting the vein and fascia upwards to protect the nerve as the marginal mandibular nerve is reliably located superficially to the facial vessels.

Spinal accessory nerve

The course of spinal accessory nerve is important to appreciate as it can be accidentally injured in procedures in both the anterior and posterior triangles of the neck. After exiting the skull via the jugular foramen, the spinal accessory nerve courses inferiorly and laterally in the neck to provide motor supply to the sternocleidomastoid muscle, which it passes through, and the trapezius. The nerve can be reliably located over the transverse process of the atlas, palpable anterior and inferior to the mastoid tip. It then enters the sternocleidomastoid muscle, typically at the junction of the superior and middle thirds and exits the posterior border of the sternocleidomastoid 1 cm above Erb's point where the cervical plexus nerves emerge from the posterior border of the muscle.[9] The accessory nerve then follows a variable course across the posterior triangle to enter the trapezius muscle at the junction of its middle and lower thirds. The spinal accessory nerve is an important landmark in sub-dividing lymph node levels IIa and IIb.

Carotid artery

The pulse of the carotid artery is most easily palpated at the level of the carotid bifurcation, located between the angle of the mandible and greater cornu of the hyoid, found at the anterior border of the sternocleidomastoid muscle.

Jugular veins

The internal jugular vein (IJV) runs with the carotid artery and vagus nerve in the carotid sheath. The surface marking of the IJV is parallel and slightly lateral to the common carotid artery. The external jugular vein is often visible, running inferior from the angle of the mandible, crossing at the mid-point of the sternocleidomastoid muscle and extending deep to the posterior border of the clavicular head of sternocleidomastoid to meet the internal jugular and anterior jugular veins. The anterior jugular veins run para-midline, superficial to the sternohyoid and thyrohyoid muscles.

Root of the neck

The root of the neck is defined by the manubrium, the sternoclavicular joints and the clavicles, which articulate with the acromion laterally. Above the sternal notch is the suprasternal fossa, also known as Burns space.[10] Chassaignac's triangle (**Figure 35.2**) is the space between the longus colli muscle, the anterior scalene muscle as it attaches to the C6 tubercle (Chassaignac's tubercle) with the subclavian vein as the inferior border. The scalene lymph nodes are located in this space, which should be explored during neck dissection. Lymphadenopathy in this location frequently represents metastasis either from the thyroid or from a primary site below the clavicles which may be of breast, lung, stomach or ovarian origin. The thoracic duct is encountered here, either on the left as a main trunk, or as a network of smaller lymphatic channels on either side. Care must be taken to avoid injury to these vessels to avoid chylous fluid leak during neck dissection.

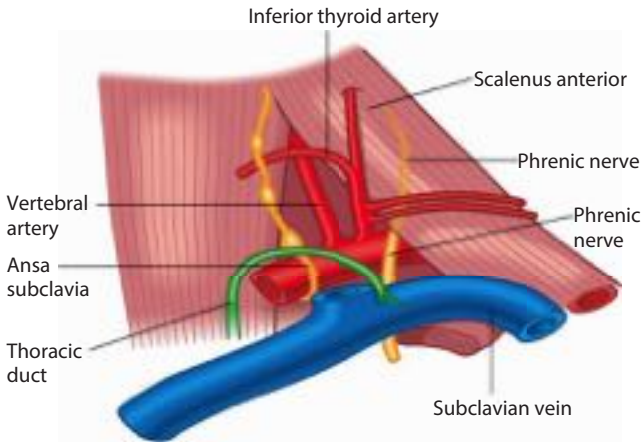


Figure 35.2 Chassaignac's triangle.

KEY POINTS

- Surface anatomy of nerves and vessels must be considered when planning incisions.
- The marginal mandibular branch of the facial nerve can run as low in the neck as the greater cornu of the hyoid; incisions should be placed below this level to avoid injury to both this nerve and the cervical branch of the facial nerve.
- The spinal accessory nerve runs in the roof of the posterior triangle; all important structures lie caudal to the nerve.

Triangles of the neck

The neck is classically divided into anterior and posterior triangles (**Figure 35.3**), by the posterior border of the sternocleidomastoid muscle. These triangles can be further sub-divided into distinct anatomical triangles known as the submental, submandibular, carotid, muscular and subclavian triangles.

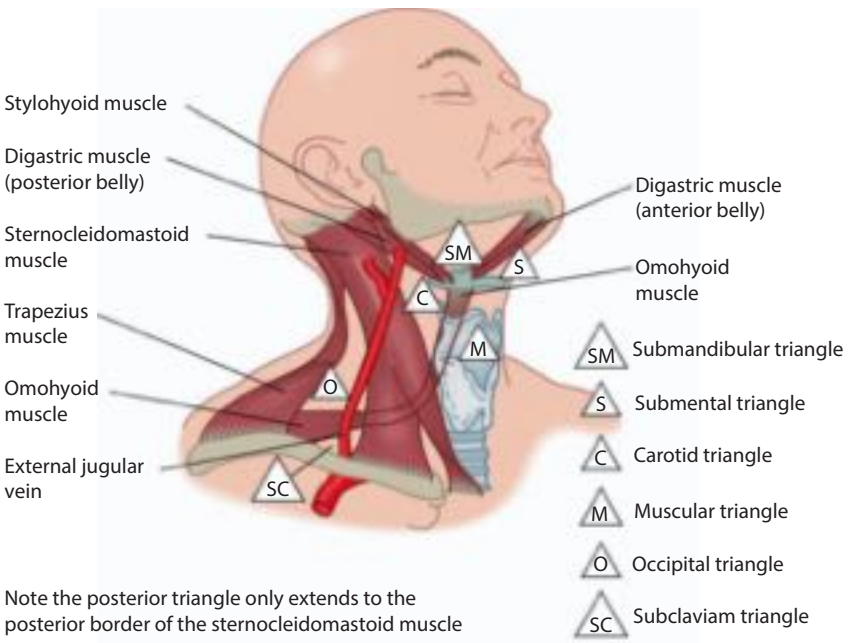


Figure 35.3 Triangles of the neck.

TABLE 35.3 Summary of the contents of the anterior triangle

Muscles	Vessels	Nerves	Viscera	Other
Digastric	External carotid artery and branches (except posterior auricular)	Internal and external laryngeal nerves	Thyroid and larynx	Jugular chain of lymph nodes
Stylohyoid and mylohyoid	Internal and anterior jugular vein and tributaries	Nerve to mylohyoid	Submental and submandibular glands	
Superior belly of the omohyoid		Hypoglossal nerve		
Strap muscles				

ANTERIOR TRIANGLE

The anterior triangle is defined by the midline anteriorly, the inferior border of the body of the mandible superiorly and the posterior border of sternocleidomastoid. The majority of the anatomical structures of the neck of importance to the head and neck surgeon are found within the anterior triangle, as summarized in **Table 35.3**. The anterior triangle is further divided into the submental, submandibular, carotid and muscular triangles.

SUBMENTAL TRIANGLE

The submental triangle is a single midline triangle located inferior to the mental process of the mandible in the upper neck, as opposed to the other triangles which are paired on each side of the neck. The boundaries are the anterior bellies of digastric laterally and the body of the hyoid bone inferiorly. The mylohyoid muscle forms the floor of the triangle. The contents include fatty tissue, level Ia lymph nodes and small veins that drain into the anterior jugular veins.

SUBMANDIBULAR TRIANGLE

The submandibular triangle (**Figure 35.4**) is also known as the digastric triangle as it lies between the anterior belly of digastric, which forms its anterior limit and the posterior belly of digastric which acts as the infero-lateral border with the stylohyoid muscle. The superior limit is formed by the inferior border of the body of the mandible. The floor is formed by the mylohyoid muscle anteriorly and the hyoglossus posteriorly. The submandibular triangle contains many important anatomical structures including the facial artery and veins, the marginal mandibular branch of the facial nerve, the submandibular salivary gland and lymph nodes of level Ib.

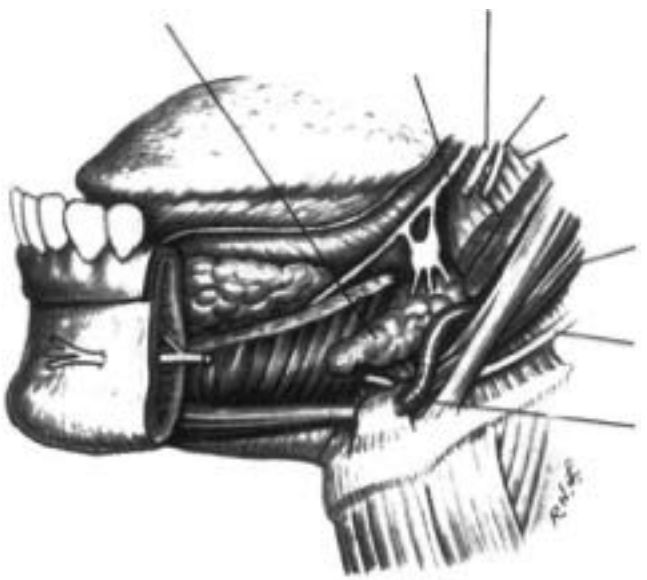


Figure 35.4 Submandibular triangle.

CAROTID TRIANGLE

The carotid triangle is bounded by the posterior border of sternocleidomastoid muscle laterally, the posterior belly of digastric superiorly and the superior belly of omohyoid medially. The contents include the superior part of the carotid sheath, containing the common carotid artery, the carotid bifurcation and the internal and external carotid arteries. The proximal superior thyroid artery, ascending pharyngeal artery, lingual artery, facial artery and occasionally the occipital artery may be found in this triangle. The corresponding veins drain into the jugular vein within the carotid triangle. The vagus nerve, running deep to the vessels in the carotid sheath, the hypoglossal nerve, the superior root of the ansa cervicalis, the superior laryngeal nerve branching from the vagus nerve are all found within the carotid triangle, with lymph nodes of the jugular chain.

MUSCULAR TRIANGLE

The muscular triangle is defined by the lower posterior border of the sternocleidomastoid muscle infero-laterally, the superior belly of omohyoid supero-laterally and the midline. The contents include the lower part of the carotid sheath, the sternohyoid and thyrohyoid muscles, the thyroid and parathyroid glands and the upper aerodigestive tract.

POSTERIOR TRIANGLE

The posterior triangle is bounded by the posterior border of the sternocleidomastoid muscle anteriorly, the anterior border of the trapezius posteriorly and the clavicle inferiorly. The floor is formed by the splenius capitus, levator scapulae and the posterior, middle and

TABLE 35.4 Summary of the contents of the posterior triangle

Muscles	Vessels	Nerves	Other
Omohyoid	Occipital, transverse cervical, suprascapular and subclavian arteries	Cervical and brachial plexus	Lymph nodes
	Transverse cervical, suprascapular and external jugular veins		

anterior scalene muscles respectively from superior to inferior. These muscles are covered by prevertebral fascia and represent the deep limit of resection during neck dissection procedures. The accessory nerve runs across the roof of the posterior triangle, with all other important anatomical structures and lymph nodes positioned caudal to it. Posterior to the trapezius muscle is the cervico-occipital area which contains paraspinal musculature, without lymph nodes or any other anatomical structures of relevance in head and neck surgery. The contents of the posterior triangle are summarized in **Table 35.4**.

SUBCLAVIAN TRIANGLE

The boundaries of the subclavian triangle are the inferior belly of the omohyoid, the clavicle and the posterior border of the sternocleidomastoid muscle. It contains the branchial plexus, emerging between the anterior and middle scalene muscles, the transverse cervical artery and suprascapular artery, which are branches of the thyrocervical trunk. The domes of the pleura with the overlying supra-pleural fascia and the subclavian artery and vein are also found within the subclavian triangle so care must be taken not to injure these structures during neck dissection if retro-clavicular dissection is necessary.

KEY POINTS

- The anatomical triangles of the neck help to compartmentalize the anatomy of the neck.
- The travel from one triangle to another facilitates the concept of neck dissection.
- Sound knowledge of both triangles and contents converts two-dimensional knowledge into three-dimensional surgical reality.

SKIN

Skin of the neck

The relaxed skin tension lines of the neck (**Figure 35.5**) run perpendicular to the fibres of the underlying platysma. These lines create skin creases that run transversely when the skin is not under tension.[11] Wherever possible, surgical incisions should be placed within these skin creases to create cosmetically acceptable surgical scars.

Vascular supply of the skin

The blood supply to the neck skin is derived from branches of the facial, posterior auricular, occipital and subclavian arteries. These arteries, with accompanying veins, form a network within the platysma muscle that supplies the overlying subdermal plexus, from which the overlying skin draws its blood supply. This is an important point to consider during neck surgery as skin flaps should be raised in the subplatysmal plane to preserve the blood supply to the skin, thereby avoiding skin necrosis.

The anterior cervical skin is supplied by branches of the superior thyroid artery and the transverse cervical artery. The posterior cervical skin is supplied by branches of the occipital artery and the deep cervical branches from the costocervical trunk. The superior neck skin derives its blood supply from the occipital artery through its branch to the sternocleidomastoid, the superior fibres of which insert into the upper neck skin. The submental and submandibular branches of the facial artery supply the anterior upper neck. The transverse cervical and suprascapular

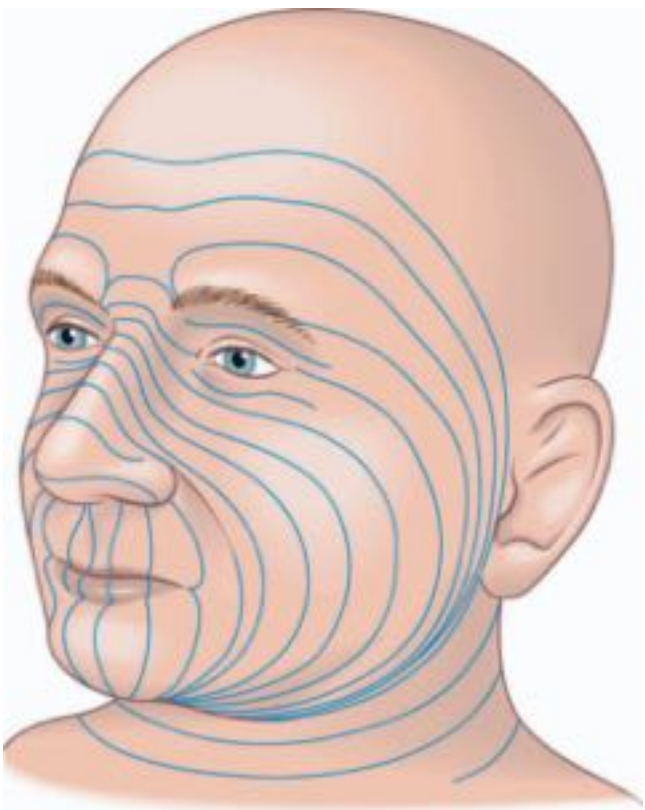


Figure 35.5 Relaxed skin tension lines.

branches of the subclavian artery via the thyrocervical trunk supply the skin of the inferior neck. The venous drainage follows the arterial supply, ultimately draining into the internal and external jugular veins.

Lymphatic drainage of the skin of the neck

In general, the lymphatic drainage of the skin drains into the superficial cervical lymph nodes in closest proximity, with division between anterior and posterior neck zones (**Figure 35.6**). The occipital, post-auricular, supraclavicular and posterior triangle lymph nodes drain the posterior head and neck, including the scalp, whereas the neck skin areas drain into the anterior nodal groups.[12] The anterior neck skin inferior to the hyoid bone drains into the lymph nodes related to the anterior jugular vein, which then drain into the deep cervical chain. The skin above the hyoid bone drains superiorly into the submental and submandibular lymph nodes. Parotid lymph nodes are a common site for occult nodal involvement in skin cancers so parotidectomy should be considered for any neck dissection procedure for skin cancer.

KEY POINTS

- Skin incisions placed within relaxed skin tension lines leave cosmetically acceptable scars.
- Skin flaps should be raised in the subplatysmal plane to avoid skin necrosis.
- Lymphatic drainage of the skin is to the closest superficial nodes; anterior neck and facial skin drains to anterior nodal zones and posterior lymphatics drain posterior neck and scalp.
- The parotid lymph nodes are a frequent site for metastasis from head and neck skin malignancy.
- Skin flap movement is facilitated by elastic properties; these are affected by age, sun exposure and smoking, as well as the presence of infection or previous radiotherapy.

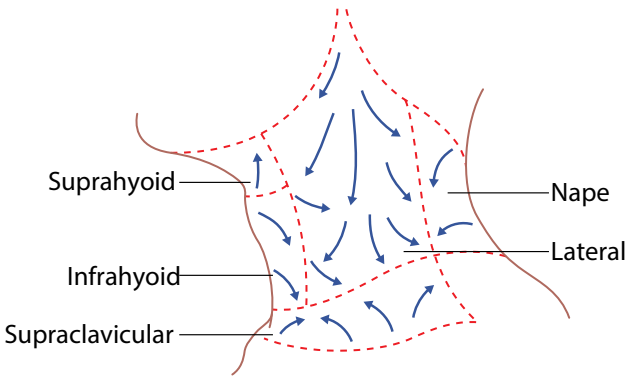


Figure 35.6 Lymphatic drainage of the skin of the neck. The lymphatics of the skin in the suprahyoid region drain to level I, the submental and submandibular lymph nodes. The lymphatics of the skin of the rest of the neck drain to levels II, III and IV, apart from the posterior lateral neck skin lymphatics which drain into the spinal accessory nodes in the posterior triangle.[13]

FASCIAL LAYERS

The neck has superficial and deep fascial planes which encase the structures of the neck (**Figure 35.7**). The deep fascial layer has three distinct layers; the superficial investing layer, the visceral layer and the deep layer. An understanding of the fascial planes of the neck assists in neck surgery as identification of the fascia allows dissection within a safe and relatively bloodless plane.

Superficial cervical fascia

This thin layer of fascia invests the platysma muscle and is penetrated by small vessels supplying the skin, therefore skin flaps are raised in the subplatysmal plane to preserve the blood supply to the skin, as mentioned previously. Inferiorly this creates an aponeurosis that either attaches to skin of the neck or continues inferiorly, becoming continuous with the fascia of the deltoid and pectoralis major muscles.

Deep cervical fascia

INVESTING LAYER

The superficial layer of the deep cervical fascia, also known as the investing layer, forms a fascial cylinder that contains most of the structures of the neck, including all of the nodal stations. Arising from the ligamentum nuchae and the spinous process of the cervical vertebrae posteriorly this layer invests the entire neck, dividing to enclose the sternocleidomastoid, omohyoid, infrahyoid and trapezius muscles. The investing fascia attaches superiorly at the superior nuchal lines and to the mastoid tip and zygoma. The fascia splits to enclose the parotid gland as the parotid fascia, the deep layer of which fuses with the fascia of the internal carotid artery (ICA). Anteriorly the investing layer of fascia attaches to the hyoid bone and to the acromion, clavicle and sternum inferiorly.

CAROTID SHEATH

The carotid sheath is derived from the investing layer of deep cervical fascia, medial to the sternocleidomastoid muscle. It encloses the common carotid artery and the internal and external carotid arteries after the bifurcation, the IJV and the vagus nerve. It is thicker around the arteries, but loose around the IJV allowing expansion during times of increased venous flow. The carotid sheath is connected to other fascial layers by loose areolar tissue.

PRETRACHEAL FASCIA

This middle layer of the deep cervical fascia, known as the pretracheal or visceral layer of cervical fascia, is again derived from the investing layer. It attaches to the hyoid bone superiorly and can be considered as having two parts: the muscular compartment encasing the infrahyoid

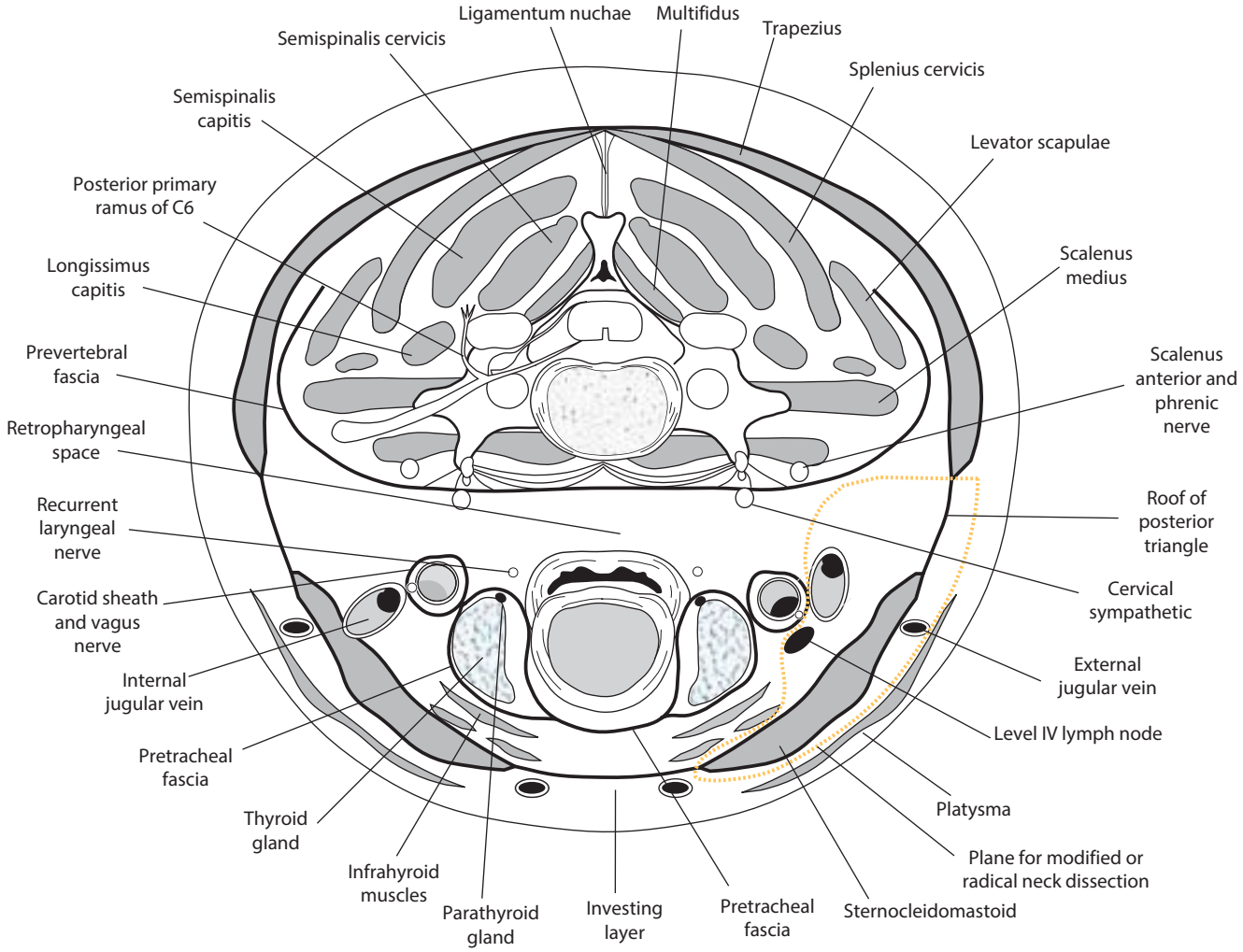


Figure 35.7 Fascial layers of the neck.

muscles and the visceral compartment containing the trachea, the thyroid gland, the pharynx and upper oesophagus. Inferiorly it fuses with the fascia of the superior mediastinum around the great vessels and the fibrous pericardium. Laterally it connects to the carotid sheath by loose areolar tissue.

PREVERTEBRAL FASCIA

The deepest layer of cervical fascia is also known as the prevertebral fascia as it encompasses the posterior neck muscles, the scalene muscles and the vertebrae. It forms the floor of the posterior triangle and represents the deep limit of neck dissection and the plane between the cervical vertebrae and the upper aerodigestive tract, allowing the pharynx to move freely during deglutition. The alar fascia is a supplementary layer of fascia anterior to the prevertebral fascia, extending from the skull base to the posterior mediastinum to the level of the second thoracic vertebra. The danger space, described in 'Retropharyngeal space' below, lies between the prevertebral fascia and the alar fascia.

KEY POINTS

- The fascial planes of the neck form dissection tunnels which can be followed to surgically unlock the neck.
- The investing layer of deep cervical fascia encases all of the nodal zones of the neck.
- The prevertebral fascia is the deep margin of neck dissection surgery, protecting the phrenic nerve and branchial plexus which run deep to the fascia.
- Access and definitive surgery through the fascial planes of neck is best facilitated with tissues under tension and sharp dissection.

NECK SPACES

Between the fascial layers of the neck are several anatomical compartments, containing only loose areolar tissue in healthy subjects. Whilst fascial layers limit the spread of infection, these inter-connected spaces can act as routes of transmission of infection or neoplasia.

Submental space

The borders of the submental space correspond to the submental triangle, as described above, with a superficial limit of superficial cervical fascia and the deep limit of the mylohyoid and geniohyoid muscles. The lymph nodes of level Ia are found within this space.

Submandibular space

The submandibular space is of key clinical significance as it is a route of spread of infection between the neck and floor of mouth. The superior limit of the submandibular space is the mucosa of the floor of the mouth, inferiorly it is defined by the investing layer of deep cervical fascia from the mandible and the hyoid bone. The anterior and posterior bellies of the digastric muscle form the antero-inferior and postero-inferior boundaries respectively. The superficial limit of this space is the investing layer of deep cervical fascia which wraps around the submandibular gland, forming a tough membrane that supports the gland. The mylohyoid muscle runs through the middle of the submandibular space, dividing it into superior and inferior compartments, which communicate around the free posterior edge of mylohyoid.[14] The superior space, also termed the sublingual space, contains the sublingual gland, the deep portion of the submandibular gland and the lingual nerve. The inferior space holds the superficial lobe of the submandibular gland. Both areas contain lymph nodes and branches of the facial vessels.

Between the submandibular gland and the mylohyoid muscle is the loose and distensible epimysium. The deep fascia does not split to enclose the submandibular gland so swelling in this space is limited by the attachments of the mylohyoid muscle and deep fascia. Subsequently distension of this space occurs in a cephalic and medial direction.[15] Ludwig's angina is a life-threatening airway complication of submandibular space infection, characterized by rapid onset of cellulitis of the floor of mouth tissues, causing swelling, induration and tongue elevation resulting in a compromised airway. Submandibular space infections are most commonly odontogenic in origin but can occur secondary to submandibular sialadenitis, lymphadenitis, trauma or after surgery.

Peritonsillar space

The potential space between the palatine tonsil and the superior constrictor muscle is known as the peritonsillar space. The condensation of the pharyngobasillar which forms the tonsillar capsule may be breached by bacterial infections of the tonsil, resulting in abscess formation in the peritonsillar space, also known as a quinsy. Untreated peritonsillar infections may spread to involve the parapharyngeal space.

Parapharyngeal space

The parapharyngeal space (**Figure 35.8**) is an inverted pyramid-shaped space, extending from the petrous temporal bone superiorly to the level of the hyoid. The space is bounded by the superior constrictor muscle medially and the pterygoid muscles, the parotid salivary gland and the mandible laterally. The styloid process and its attachments pass through the space, dividing it into pre-styloid and post-styloid compartments.

The pre-styloid compartment contains fat, connective tissue, the maxillary artery, the inferior alveolar nerve, the lingual nerve and the auriculotemporal nerve. The post-styloid compartment contains the carotid sheath and its contents, the glossopharyngeal and hypoglossal nerves, the sympathetic chain and lymph nodes. The determination between pre- and post-styloid involvement and displacement of the parapharyngeal fat pad are key radiological features which aid in diagnosis of parapharyngeal

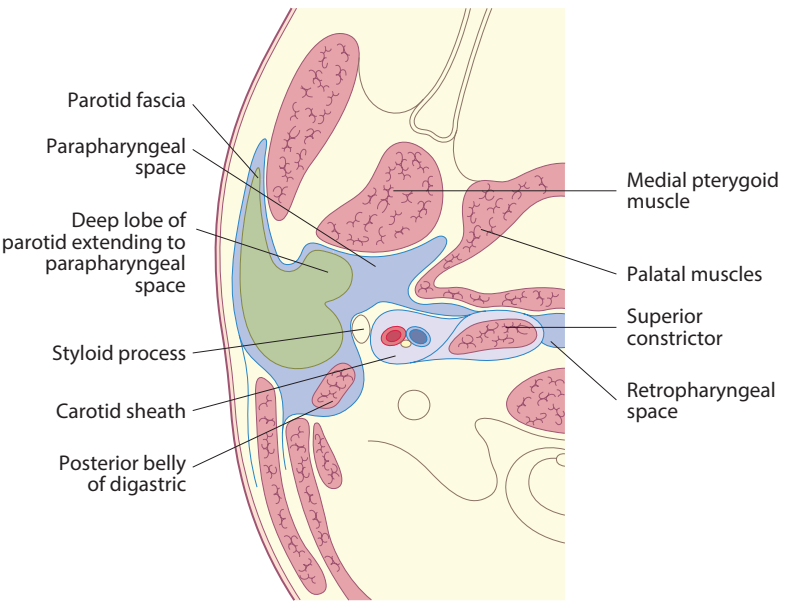


Figure 35.8 Parapharyngeal space.

space neoplasia. Pre-styloid lesions are most commonly associated with the deep lobe of the parotid gland and will deflect the carotid sheath and parapharyngeal fat posteromedially. Lesions in the post-styloid compartment are frequently of neuroendocrine origin, arising from the carotid sheath as carotid body tumours or vagal schwannomas, or neuromas of the sympathetic chain. Post-styloid lesions displace the parapharyngeal fat pad anteriorly. Surgical access to the parapharyngeal space can be challenging and may require mobilization of the parotid gland or lip split mandibulotomy.

The parapharyngeal space is a central connection for other deep neck spaces and as a result is a common site for deep neck abscess formation.[16, 17] Abscesses of the parapharyngeal space may occur because of spread from the submandibular space secondary to oro-dental causes, or from the peritonsillar space. Parapharyngeal space abscesses readily result in airway compromise if untreated. Medial displacement of the tonsil and lateral oropharyngeal wall will be seen but neck swelling or asymmetry may or may not be present. Trismus may also occur secondary to inflammation of the pterygoid muscles. The two parapharyngeal spaces communicate with the retropharyngeal space posteriorly and infection may readily spread into this compartment.

Retropharyngeal space

Between the two parapharyngeal spaces is the retropharyngeal space which is continuous with both. The superior limit of the retropharyngeal space is the skull base and it is continuous inferiorly with the posterior mediastinum, down to the level of the carina. The anterior boundary in the neck is the buccopharyngeal fascia which encases the pharyngeal constrictors, the posterior limit is the alar fascial component of the prevertebral fascia. The only contents of this space are the retropharyngeal lymph nodes, which typically regress by adulthood but can represent a route of metastatic nodal spread from midline or posterior tumours of the pharynx. Radiological evidence of retropharyngeal lymphadenopathy in adults should therefore raise the suspicion of head and neck malignancy.

Infection of the retropharyngeal space may occur indirectly, tracking from the parapharyngeal space or directly secondary to perforation of the pharynx or cervical oesophagus. Retropharyngeal abscesses are more commonly seen in children than in adults, secondary to bacterial infection of the upper aerodigestive tract and may result in airway obstruction due to anterior displacement of the airway.

The alar space, known colloquially as the 'danger space' is a further potential space located posterior to the retropharyngeal space, between the alar fascial component of the prevertebral fascia and the prevertebral fascia itself, extending to the level of the diaphragm. This space is only visible radiologically if distended due to collection within this area. The name 'danger space' refers to the potential for neck infections to readily spread into the thorax and cause mediastinitis.

Prevertebral space

The prevertebral space is the potential area posterior to the prevertebral fascia and anterior to the vertebral column and para-spinal musculature. Spread of infection to this area may occur as a result of traumatic perforation of the pharynx or oesophagus, or because of a breach of prevertebral fascia from retropharyngeal infection. Infection in the prevertebral space can cause spinal osteomyelitis and spinal cord compression. Prevertebral space invasion in head and neck malignancy is a feature which often signifies inoperable disease.

Carotid space

The carotid space is a potential space within the carotid sheath, which is itself formed from a condensation of all three layers of deep cervical fascia. It contains the common carotid artery, the IJV and the vagus nerve.

Parotid space

The parotid space is formed by the investing layer of deep cervical fascia that splits to encompass the parotid gland and therefore contains the facial nerve, the retromandibular vein and the terminal branches of the external carotid artery.

Visceral space

The visceral space is bounded by the middle layer of deep cervical fascia that envelops the thyroid and the trachea anteriorly and posteriorly by the pretracheal fascia. It contains the larynx, hypopharynx, cervical oesophagus, proximal trachea, thyroid and parathyroid glands and lymphatics of level VI.

KEY POINTS

- The inter-connected neck spaces act as potential routes for spread of infection and malignancy.
- Collections within the submandibular space and deep neck spaces readily result in airway obstruction if untreated and can make endotracheal intubation problematic due to distorted and displaced anatomy.
- Parapharyngeal space infection may occur directly or because of spread from the submandibular or peritonsillar spaces.
- The two parapharyngeal spaces communicate with the retropharyngeal space, from where infection can spread into the mediastinum or into the thorax to the level of the diaphragm via the danger space.

MUSCLES

Knowledge of the muscles of the neck is key to understanding neck anatomy, acting as important landmarks in the neck and forming the boundaries of the triangles of the neck. The muscles of the neck may be divided into groups: the superficial muscles, suprahyoid and infrahyoid muscles and the prevertebral muscles.

Superficial neck muscles

PLATYSMA

The platysma is a thin sheet of muscle that encases the neck. It is covered by superficial cervical fascia and is attached inferiorly to the deep fascia of pectoralis major muscle of the anterior chest wall. Superiorly it attaches to the inferior border of the mandible and is often deficient in the midline, however some fibres cross the midline and interweave below the mentum. Inferiorly it is continuous with the fascia of the pectoralis major muscle. The thinness of the platysma means that it has little functional significance; however, it does play a role in depressing the angle of the mouth as some superior fibres blend with the risorius muscle. The muscle derives its blood supply from a plexus of vessels within the muscle, which also supply the skin, as mentioned previously. The arterial supply is from branches of the facial artery superiorly and the suprascapular artery inferiorly, the venous drainage is via the facial vein and internal and external jugular veins. The innervation is from the cervical branch of the facial nerve which runs deep to the muscle (**Table 35.5**).

STERNOCLEIDOMASTOID

The sternocleidomastoid muscle is the most prominent muscle in the neck and is an important landmark as it divides the neck into anterior and posterior triangles along its posterior border. The muscle is encased by the investing layer of deep cervical fascia and lymph nodal levels II to IV are located deep to the muscle. The upper part of the muscle overlies the cervical plexus and the lower half overlies the carotid sheath and the scalenus anterior.

Inferiorly the sternocleidomastoid has both sternal and clavicular origins as two separate heads. The sternal head arises as a thick tendon, attached to the anterior and lateral surface of the manubrium. The clavicular head is fan shaped, arising from the medial third of the clavicle. Superiorly it inserts into the lateral aspect of the mastoid tip and the superior nuchal line. Although classified as a single muscle the two heads are functionally distinct with most of the sternal head attaching to the superior nuchal line and the clavicular head mainly to the mastoid tip. The action is complex; causing tilting of the head to the ipsilateral side and rotation of the head to the contralateral side. When both sides contract simultaneously it aids in head flexion and can assist in raising the thorax when the head is fixed, acting as an accessory muscle of respiration.

The blood supply to the muscle is in three segments. The superior third is supplied from the occipital artery and the posterior auricular artery. The middle third receives blood from a branch from the superior thyroid artery and the inferior third supply is from the suprascapular artery. Perforators from the sternocleidomastoid supply the skin inferiorly which is the basis for the sternocleidomastoid flap. The spinal accessory nerve, which normally passes through the muscle, provides motor function, with sensation and proprioception supplied by the ventral rami of C2–4.

TRAPEZIUS

The trapezius is a key landmark in head and neck surgery as it defines the posterior limit of the posterior triangle. All lymphatic zones and important anatomical structures lie anterior to the trapezius, with only prevertebral muscles and nerves posterior to the muscle. The trapezius is a broad, diamond-shaped sheet of muscle, arising in the midline from the skull to the lower thorax. The superior origin is from the superior nuchal line and the ligamentum nuchae to the level of the seventh cervical vertebra and inferiorly it arises from the spinous processes and interspinal ligaments down to the twelfth thoracic vertebra. Superiorly it has fibres that insert into the clavicle, with inferior fibres inserting into the spine of the scapula.

The trapezius is the main anti-gravity muscle of the shoulder, providing postural stability, and relieves some of the compression load of the head on the cervical spine. The active movements include tilting and turning the head and shrugging the shoulders. The trapezius elevates, depresses and rotates the scapula.[18] The arterial blood supply is via the transverse cervical artery. The accessory nerve provides motor supply to the trapezius muscle with contributions from the cervical plexus derived from C3 and C4 nerve roots. The cervical plexus branches mainly provide proprioception, however studies have proven a contribution to the motor function of the transverse and ascending parts of the

TABLE 35.5 Superficial neck muscles

Muscle	Origin	Insertion	Innervation	Blood supply
Platysma	Inferior border of mandible	Continuous with fascia of pectoralis major muscle	Cervical branches of facial nerve	Plexus with supply from facial artery superiorly, suprascapular artery inferiorly
Sternocleidomastoid	Manubrium, medial 1/3 clavicle	Mastoid tip, superior nuchal line	Spinal accessory nerve, C2–4	Occipital, post auricular, superior thyroid and suprascapular arteries
Trapezius	Superior nuchal line, ligamentum nuchae down to C7 Spinous processes	Clavicle and spine of scapula	Spinal accessory nerve, cervical plexus from C3, C4	Transverse cervical artery

muscle from the cervical plexus branches. Disruption of the motor supply to the trapezius causes shoulder droop and a winged scapula with difficulty in elevating the ipsilateral arm above the head and weakness when shrugging the shoulder. Chronic neck pain is often a feature of trapezius paralysis.

Suprahyoid muscles

The four suprahyoid muscles lie superiorly to the hyoid bone in the neck and act upon the hyoid, elevating it during swallowing, amongst other functions. This group includes the digastric, stylohyoid, mylohyoid and geniohyoid muscles (**Table 35.6**). Whilst not a suprahyoid muscle, rather an extrinsic tongue muscle, we have also included the hyoglossus muscle as it can be a helpful landmark for structures that pass between the mylohyoid and hyoglossus.

DIGASTRIC

The digastric muscle is named as such because it has two bellies, joined in the middle by an intermediate tendon that passes through a sling attached to the lesser cornu of the hyoid bone. The posterior belly arises from the digastric notch on the medial aspect of the mastoid tip. The anterior belly inserts into the digastric fossa of the medial surface of the mandible near the midline. The anterior belly lies superficially to the mylohyoid muscle. The anterior bellies from each side define the submental triangle and the anterior and posterior bellies define the submandibular triangle as described above. The origin of the posterior belly at the digastric ridge is a landmark for the depth of the facial nerve as it exits the stylomastoid foramen.

The arterial blood supply is from branches of the facial artery anteriorly and the occipital artery posteriorly. The nerve supply to digastric reflects its embryological origins from the first and second branchial arch; the posterior belly is supplied by a branch of the facial nerve, the nerve to digastric and the anterior belly is supplied by the nerve to mylohyoid, from the maxillary division of the trigeminal nerve. The digastric muscle depresses the chin to assist in mouth opening and elevates the hyoid during swallowing.

STYLOHYOID

The stylohyoid muscle is related to the posterior belly of digastric, which it runs alongside. Its function is to elevate the hyoid bone during swallowing. It arises from the styloid process of the mastoid tip and it inserts into the lesser cornu of the hyoid bone. A tendon is formed in the mid portion of the muscle that splits around the sling that the digastric tendon passes through. The innervation of the stylohyoid is from the nerve to digastric from the facial nerve and the blood supply is from branches of the facial and occipital arteries.

MYLOHYOID

The mylohyoid muscle forms the floor of the mouth, its function is to support the weight of the tongue and elevate the hyoid bone during deglutition. It arises from the mylohyoid line, on the inner surface of the mandible and inserts into the anterior surface of the body of the hyoid bone. The two muscles meet at the midline, forming a midline raphe from the hyoid to the mentum. The submandibular salivary gland wraps around the free posterior border of the mylohyoid muscle. The mylohyoid is a muscle of the first pharyngeal arch and is innervated by the inferior alveolar nerve, from the mandibular division of the trigeminal nerve. The arterial blood supply is from the branches of the facial artery.

GENIOHYOID

The geniohyoid muscle arises from the genial tubercle on the inner surface of the mandible at the midline and runs deep to mylohyoid to insert into the upper part of the body of the hyoid bone. Like mylohyoid, the geniohyoid provides support to the floor of mouth and elevates the hyoid, but also acts to depress the mandible during mouth opening. The innervation is from C1 nerve roots that run with the hypoglossal nerve and the blood supply is from branches of the facial artery.

HYOGLOSSUS

The hyoglossus lies posterior and deep to the mylohyoid muscle, with fibres originating from the body and greater

TABLE 35.6 Suprahyoid muscles

Muscle	Origin	Insertion	Innervation	Blood supply
Digastric	Digastric ridge, mastoid tip	Digastric fossa, inner surface mandible	Anterior belly: Trigeminal neve Posterior belly: Facial nerve	Anterior belly: Facial artery Posterior belly: Occipital artery
Stylohyoid	Styloid process	Lesser cornu hyoid	Nerve to digastric from facial nerve	Facial artery Occipital artery
Mylohyoid	Mylohyoid line of mandible	Anterior surface of body of hyoid	Inferior alveolar nerve from trigeminal	Facial artery
Geniohyoid	Genial tubercle	Body of hyoid	C1 nerve roots with hypoglossal nerve	Facial artery
Hyoglossus	Body and greater cornu of hyoid	Inserts into tongue	Hypoglossal nerve	Lingual artery

TABLE 35.7 Infrahyoid muscles

Muscle	Origin	Insertion	Innervation	Blood supply
Sternohyoid	Medial clavicle and manubrium	Lower body of hyoid	C1, C2, C3	Superior thyroid artery
Sternothyroid	Posterior surface of manubrium	Oblique line of thyroid cartilage	C1, C2, C3	Superior thyroid artery
Omohyoid	Lower body of hyoid	Scapula	C1, C2, C3	Inferior thyroid artery
Thyrohyoid	Greater horn of hyoid	Oblique line of thyroid cartilage	C1, C2, C3	Superior thyroid artery

cornu of the hyoid before entering the tongue. The lingual vein passes medially and the lingual artery passes deep to hyoglossus. Several important structures run between the mylohyoid and the hyoglossus muscles; the sublingual gland, submandibular duct, lingual nerve, and the hypoglossal nerve. The innervation is from the hypoglossal nerve and it derives its arterial blood supply from the lingual artery.

Infrahyoid muscles

The infrahyoid muscles, commonly termed the 'strap' muscles, lie inferior to the hyoid bone. This group consists of the sternothyroid, sternohyoid, thyrohyoid and omohyoid muscles which have the common action of depressing the hyoid and larynx to modify resonance during voice production. They oppose the elevators of the hyoid, stabilizing the hyoid during action of the mylohyoid and the digastric. They are all innervated by the ansa cervicalis with fibres from C1, C2 and C3.

STERNOHYOID

The sternohyoid is the most superficial of the strap muscles and the largest. It arises from the medial clavicle, the sternoclavicular joint and the upper manubrium and inserts into the lower body of the hyoid bone. The two muscles are joined in the midline at a midline raphe, a relatively bloodless plane that must be dissected to unlock the central compartment for thyroidectomy and tracheostomy procedures.

STERNOTHYROID

Deep to the sternohyoid is the sternothyroid muscle, arising from the posterior surface of the manubrium and first costal cartilage and inserting into the oblique line of the thyroid cartilage. Deep to the sternothyroid lies the thyroid gland, both the sternohyoid and sternothyroid must be retracted to enable access to the thyroid lobes.

OMOHYOID

The omohyoid muscles has two bellies, joined by a flat tendon at the point where the muscle passes over the IJV. The superior belly arises from the lower body of the hyoid bone and runs inferiorly, just lateral to the sternohyoid muscle and deep to sternocleidomastoid and across the IJV. The inferior belly then travels an oblique course to insert into the scapula posteriorly.

THYROHYOID

The thyrohyoid is the smallest of the infrahyoid muscles and attaches the thyroid cartilage to the hyoid bone.

Prevertebral muscles

Contained within the prevertebral fascia are the prevertebral muscles, a group of weak neck flexors. This muscular group can be subdivided into anterior and lateral groups.

ANTERIOR PREVERTEBRAL MUSCLES

The anterior prevertebral muscles lie deep to the prevertebral fascia and anterior to the spinal column and include the rectus capitus anterior, rectus capitus lateralis, longus capitus, longus colli and splenius capitus. Their combined action is to flex and bow the head.

LATERAL PREVERTEBRAL MUSCLES (SCALENE MUSCLES)

The lateral prevertebral muscles, also known as the scalene muscles, are of more significance in head and neck surgery than the anterior group, due to the many important relations of the anterior scalene muscle. The phrenic nerve runs on the superficial surface of the anterior scalene muscle and the second part of the subclavian artery passes posterior to the scalenus anterior, where it gives off the costo-cervical trunk. The transverse cervical, ascending cervical and suprascapular arteries lie superficial to the muscle. The roots of the brachial plexus arise between the scalenus anterior and scalenus medius and emerge on the lateral border of scalenus anterior. The branches of the brachial plexus carry with them a layer of prevertebral fascia, which also encases the subclavian artery and becomes the axillary sheath.

KEY POINTS

- The superficial neck muscles provide important anatomical boundaries and are covered by layers of cervical fascia.
- The supra-hyoid and infra-hyoid muscles act antagonistically to elevate, depress or stabilize the hyoid for speech and swallowing.
- The anterior scalene muscle and its relationships to the phrenic nerve, brachial plexus and subclavian artery provide vital anatomical knowledge relating to the root of the neck and Chassaignac's triangle.

CERVICAL LYMPHATICS

The lymphatics of the neck are divided into superficial and deep systems. The superficial lymphatics drain the skin and perforate the investing layer of deep cervical fascia to drain into the deep system. When affected by malignancy, these lymph nodes will quickly invade the skin necessitating skin resection to ensure complete excision.

The deep lymphatics are associated with fascial condensations and are in proximity to the vessels, nerves and muscles of the neck. Over 80% of lymph nodes in the neck are closely related to the IJV. The deep lymphatic system is divided into nodal groups as depicted in **Figure 35.9**, or classified into nodal levels, demonstrated by **Figures 35.10** and **35.11**.

Lymphatic flow is typically in a downwards direction and may pass through many nodal zones. In the event of metastatic lymphadenopathy from an unknown primary the nodal zone involved can help to predict the primary site due to the somewhat predictable pattern of lymphatic spread, in the previously untreated patient. In the context of previous neck dissection, the pattern of regional lymphatic involvement is much less predictable and may readily involve any remaining lymphatic areas of the ipsilateral neck, the retropharyngeal lymph nodes and the contralateral neck.

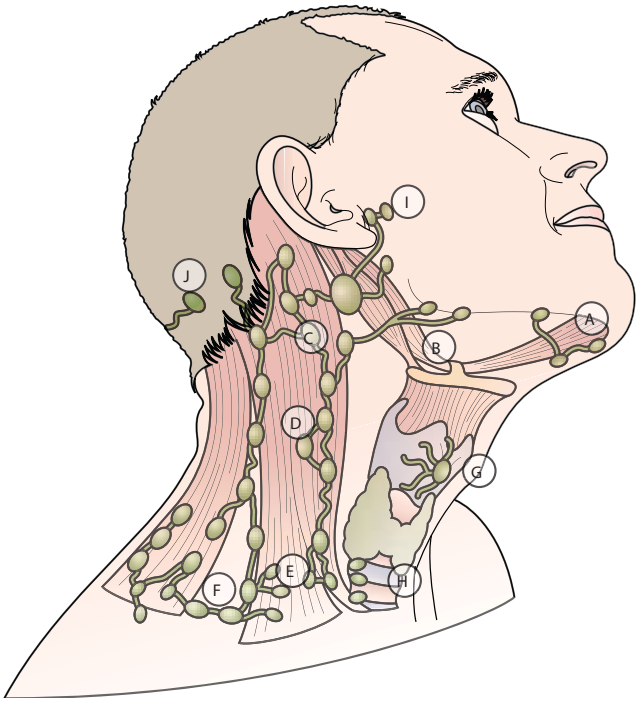


Figure 35.9 Lymph node groups.

Lymph node levels

The classification of lymph node zones into levels originates from the Memorial Sloan Kettering Hospital, New York and was adopted by the American Academy of Otolaryngology Head and Neck Surgery (AAOHNS) in 1991.[19] This clinically orientated classification system was developed by surgeons and radiologists and aims to differentiate nodal areas that drain the visceral structures of the head and neck.

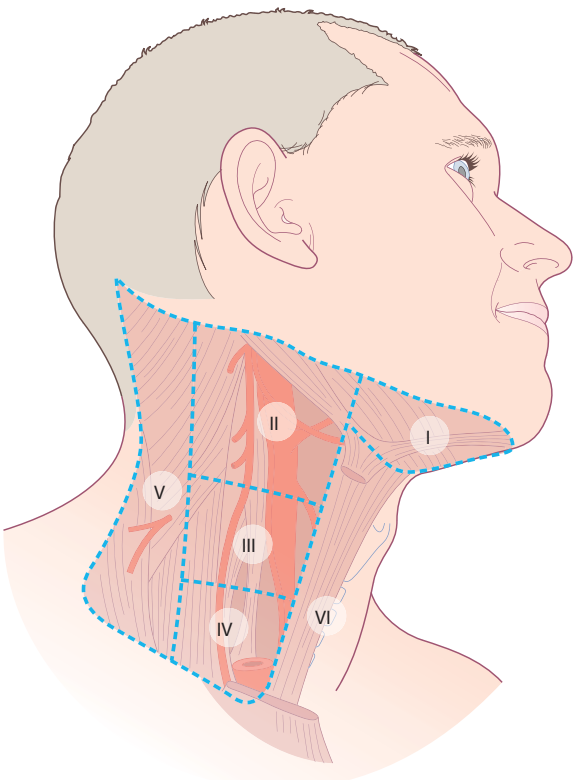


Figure 35.10 Lymph node levels.

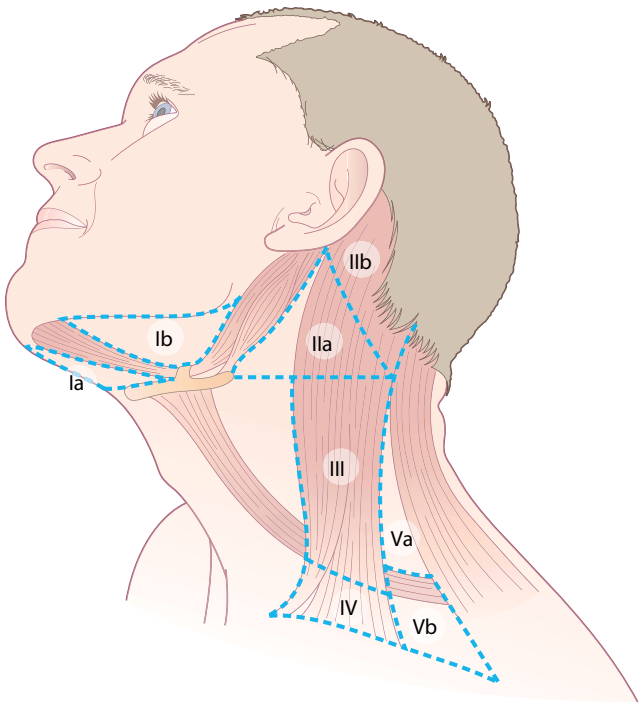


Figure 35.11 Lymph node zones and subzones.

LEVEL IA

This nodal area is a single midline zone, corresponding to the submental triangle, between the two anterior bellies of digastric and the hyoid bone. The submental lymph nodes are located within this level, which provides lymphatic drainage to the anterior floor of mouth, lower lip and ventral tongue.

LEVEL IB

This level is located within the submandibular triangle and contains the submandibular lymph nodes. Drainage from lateral oral cavity structures such as the lateral tongue, floor of mouth and buccal cavity is to these lymph nodes, which are closely related to the facial vessels.

LEVEL II

The lymphatics of level II are the uppermost nodes of the jugular chain, extending from the skull base to the level of the inferior border of the hyoid bone. Level II lymphatics are the first echelon lymph nodes of the oropharynx, but also drain the oral cavity, nasopharynx, hypopharynx and larynx, as well as the parotid gland. Lymphatic drainage from the submandibular and retropharyngeal nodes joins the jugular system at the junctional nodal area, at the lower aspect of level II. The spinal accessory nerve subdivides level II into IIa and IIb as described below.

LEVEL IIA

Caudal to the spinal accessory nerve is level IIa. The presence of nodal disease in IIa mandates dissection of IIb during neck dissection.

LEVEL IIB

Cranial to the spinal accessory nerve is level IIb, also known as Suárez's triangle, named after the Argentinian who first described functional neck dissection in the 1960s. This nodal level covers a triangular area with the apex at the junction of the posterior border of the sternocleidomastoid muscle and the posterior belly of digastric and is bounded inferiorly by the accessory nerve. The occipital artery may be encountered in the superior aspect of this nodal zone.

LEVEL III

Level III refers to the lymph nodes of middle jugular chain, from the level of the inferior border of the hyoid to the inferior aspect of the cricoid cartilage. This zone receives lymphatic drainage from the lower areas of the oropharynx, the hypopharynx and larynx.

LEVEL IV

This zone extends from the level of the inferior border of the cricoid to the clavicle and contains the lymph nodes of the lower jugular chain, which drain the hypopharynx and larynx. The omohyoid muscle crosses the superior aspect of this level. Low in level IV, within Chaissaignac's triangle in the root of the neck, lymph node metastasis may occur from an infraclavicular primary source, typically bronchus or breast. Furthermore, Virchow's node, a supraclavicular lymph node metastasis from upper gastrointestinal malignancy, is located in level IV on the left side of the neck.

LEVEL V

Level V represents the posterior triangle lymph nodes. This zone covers a large area, with a thin layer of fibrofatty tissue over the prevertebral musculature, extending from a superior apex formed by the junction of the trapezius and sternocleidomastoid muscles to the clavicle inferiorly. The anterior limit is the posterior border of the sternocleidomastoid muscle and the posterior limit is the anterior border of trapezius. The spinal accessory nerve runs across the roof of level V and the transverse cervical artery is found in the inferolateral aspect of this zone. The lymphatics of level V receive drainage from all other nodal areas but are also a common location for metastatic involvement from nasopharyngeal or cutaneous scalp primary lesions. Level V is subdivided into Va and Vb by an imaginary horizontal line at the level of the inferior border of the cricoid cartilage.

LEVEL Va

This subzone is the area above the boundary line and contains the lymph nodes related to the spinal accessory nerve, which runs in the roof of level Va. Much of nodal tissue is located caudal to the nerve.

LEVEL Vb

This represents the nodal area below the level of the inferior border of the cricoid cartilage and contains the level V lymph nodes related to the transverse cervical artery and the supraclavicular lymph nodes.

LEVEL VI

This single midline zone, also termed the anterior or central compartment, is located between the common carotid arteries laterally. The superior border is the inferior aspect of the hyoid. The inferior boundary is defined as the innominate artery on the right side of the neck and the corresponding level on the left side.[20] The paratracheal, perithyroid and precricoid (Delphian) nodes are in this zone. Nodal metastasis in this area may arise from primaries in the thyroid, the glottis or subglottic larynx, the apex of the piriform fossa or the cervical oesophagus. Lymph node dissection of the central compartment is commonly performed in conjunction with total thyroidectomy for malignancy or total laryngectomy and may result in postoperative hypocalcaemia because of inadvertent removal of the parathyroid glands which are also located within this nodal zone.

LEVEL VII

This refers to the lymph nodes of the superior mediastinum which may be accessed via the neck, or via an access sternotomy. These lymph nodes may harbour metastasis from thyroid, subglottic or tracheal or cervical oesophageal malignancies. The thymic remnant is also found in this area.

KEY POINTS

- The patterns of lymphatic drainage within the neck are site specific.
- The flow of lymph is from superficial to deep and then from cephalic to caudal direction.
- There are approximately 100 lymph nodes on either side of the neck which range in size from 3 mm to 3 cm with a mean of 1 cm.
- The cervical lymph nodes are divided into levels the dissection of which forms the basis of selective neck dissection.
- Selective neck dissection is based upon site specific drainage and is therefore best suited to the untreated neck.
- Incisions in the neck can alter lymphatic drainage for up to one year after surgery.
- Previous treatment of the neck, in the form of surgery and or radiotherapy, alters lymphatic drainage which can result in unpredictable patterns of metastatic lymphadenopathy, including involvement of the parapharyngeal and retropharyngeal spaces.

NERVES

Knowledge of the anatomy of the nerves of the neck is essential when operating in the neck to avoid unnecessary morbidity from major nerve injury. The important nerves of the neck are the lower cranial nerves, the spinal nerves of the cervical plexus, the cervical sympathetic trunk and the brachial plexus.

Cranial nerves

FACIAL NERVE

The facial nerve is the nerve of the second branchial arch. Its main function is to supply motor innervation to the muscles of facial expression, with smaller branches that also provide motor supply to the posterior belly of digastric and the stylohyoid muscle. After leaving the cranium through the internal auditory meatus and passing through the middle ear space and mastoid, the main trunk of the facial nerve exits the temporal bone via the stylomastoid foramen. It then traverses the parotid gland where it divides into five main branches within the gland. Known as the 'pes anserinus', literally meaning the 'goose's foot', these branches are the temporal, zygomatic, buccal, marginal mandibular and cervical branches; the latter two are the branches found in the neck.

MARGINAL MANDIBULAR NERVE

The marginal mandibular branch of the facial nerve is the main branch of the lower division of the facial nerve. It takes a variable course and may have up to four branches in the neck. The nerve passes antero-medially across the upper neck in the plane just deep to the platysma muscle but superficial to the investing layer of deep cervical fascia. It can extend as low as the greater cornu of the hyoid bone, before passing superficial to the facial vessels and across the mandible to provide motor supply to the depressor anguli oris, depressor labii inferioris and mentalis muscles. Its action is to move the corner of the mouth and lower lip, however the nerve supply to the lower lip is multifactorial, with contributions from the cervical branch of the facial nerve and the platysma muscle, meaning that if any one of these mechanisms is interrupted lower facial asymmetry may occur.

This nerve is most at risk during submandibular gland excision and clearance of lymph node level I for malignant disease. The nerve can be protected by incising the investing layer of deep cervical fascia inferior to the lower border of the submandibular gland or just above the hyoid bone and reflecting the fascia superiorly along with the facial vein, retracting the nerve out of the surgical field.

CERVICAL BRANCH OF THE FACIAL NERVE

The lowest branch of the facial nerve, the cervical branch supplies the platysma muscle. It can be identified travelling antero-inferiorly and may give off multiple branches. Injury to this branch can cause asymmetry of the corner of the mouth due to the contribution of the platysma to the movement of the lower lip.

GLOSSOPHARYNGEAL NERVE

The glossopharyngeal nerve is the ninth cranial nerve and the nerve of the third branchial arch. It exits the skull via the anterior compartment of the jugular foramen, then passes between the IJV and the ICA, before descending anterior to the ICA. It then curves anteriorly around the stylopharyngeus muscle, deep to hyoglossus and either pierces the lower fibres of the superior constrictor or runs between superior and middle constrictor muscles. Fibres are then distributed to the palatine tonsil, mucosa of the pharynx and posterior tongue and minor salivary glands of the oral mucosa and the oropharynx. The glossopharyngeal nerve is historically described as 'the nerve of economy' due to the way it is considered to spread itself thinly between the structures it supplies; providing motor supply to one muscle, special sensory supply to one area, visceral sensation to one organ, parasympathetic fibres to one secretory gland and general sensation to other areas.

The glossopharyngeal nerve has many branches, some of which communicate with other nerves. It sends filaments that communicate with the sympathetic trunk, the vagus and facial nerves. The clinically relevant branches are:

- **The tympanic nerve:** Also known as Jacobson's nerve, this branch supplies the tympanic plexus and is the reason for referred otalgia secondary to pain affecting the oropharynx.
- **The lesser petrosal nerve:** This branch provides postganglionic secretomotor supply to the parotid gland and passes through the infratemporal fossa.

- **Carotid sinus and carotid body branches:** These branches take afferent nerves from the chemoreceptor in the carotid body and baroreceptors from the carotid sinus.
- **Pharyngeal branches:** These branches join the fibres from the vagus nerve and the sympathetic trunk to form the pharyngeal plexus, which sits on the posterior aspect of the middle constrictor muscle. Small nerves from the plexus perforate the muscle fibres of the middle constrictor muscle and innervate the mucosa of the oropharynx. The pharyngeal branches provide somatic sensation. The tonsillar branch anastomoses with the lesser palatine nerves to supply the mucous membrane of the palatine tonsil. Injury to the pharyngeal plexus may lead to swallowing dysfunction.
- **Motor branch:** The main motor branch of the glossopharyngeal nerve innervates the stylopharyngeus muscle.
- **Lingual branches:** These provide common sensation, taste and secretomotor supply to the posterior third of the tongue.

VAGUS NERVE

The vagus nerve derives its name from the Latin word 'vagi', meaning 'roaming', due to the wandering course that it takes from the cranium to the abdomen. It is the nerve of the fourth branchial arch and is the Xth cranial nerve. The vagus nerve leaves the skull via the middle compartment of the jugular foramen. The superior ganglion of the vagus is located just inferior to the jugular foramen and contains cell bodies for afferent fibres of meningeal and auricular branches. Lower in the neck the nerve dilates to form the inferior ganglion which contains afferent cell bodies of the other branches. The accessory nerve contributes a branch to the vagus nerve which provides motor innervation to all of the visceral striated muscle supplied by the vagus. The vagus nerve runs posteriorly in the carotid sheath, between the IJV and common carotid artery. The vagus gives off the following branches in the neck:

- **Auricular branch:** Also known as Arnold's nerve, this branch passes between the mastoid and the tympanic plate to provide sensory supply to the tympanic membrane and skin of the posterior pinna and posterior ear canal; a further mechanism for referred otalgia.
- **Carotid body branches:** This small branch supplements the branches of the glossopharyngeal nerve that supply the carotid body chemoreceptors.
- **Pharyngeal branch:** The vagal contribution to the pharyngeal plexus derives from the spinal accessory fibres that join the vagus nerve before branching off as the pharyngeal branch. These fibres cross the internal carotid to join the pharyngeal plexus, providing motor innervation to the pharyngeal constrictors and soft palate, in combination with the glossopharyngeal nerve and sympathetic trunk.
- **Superior laryngeal nerve:** The superior laryngeal nerve is given off high in the neck and passes inferior to the ICA, before travelling antero-inferiorly towards the larynx. At the level of the hyoid the nerve branches into the internal and external laryngeal nerve. The internal laryngeal nerve penetrates the thyrohyoid membrane superior to the superior laryngeal artery and provides sensory innervation to the laryngeal and piriform fossa mucosa, with some motor contribution to the interarytenoid muscle and motor and sensory supply to the cervical oesophagus and trachea. The external laryngeal branch is much smaller and runs with the superior thyroid artery on the sidewall of the inferior constrictor before piercing it to provide motor supply to the cricothyroid muscle, the only intrinsic laryngeal muscle not supplied by the recurrent laryngeal nerve. The human communicating nerve is an inconstant branch of the external branch of the superior laryngeal nerve, found as a normal variant in approximately 45% of healthy subjects. It is believed to provide additional motor supply to the thyroarytenoid muscle and sensory supply to the subglottic mucosa. This communicating branch may anastomose with the recurrent laryngeal nerve or may directly supply the thyroarytenoid muscle. This branch was first discovered during early anatomical studies of the larynx but later forgotten as it was not felt to have functional significance, however recent histological studies demonstrate positive staining for acetylcholinesterase, thereby proving motor function of this branch.[21]
- **Cardiac branches:** These branches leave the vagus low in the neck to form the cardiac plexus.
- **Recurrent laryngeal nerve:** The path of the recurrent laryngeal nerves differs on each side of the neck. The reason for this asymmetry is rooted in its embryological development as the nerve of the sixth branchial arch. The artery of the sixth arch is the ductus arteriosus which obliterates on the right whilst it descends into the thorax on the left side, taking the left recurrent laryngeal nerve with it. The left recurrent laryngeal nerve leaves the vagus in the lower part of the neck, before looping around the ligamentum arteriosum and arch of the aorta and then ascending back into the neck in the tracheo-oesophageal groove. The right recurrent laryngeal nerve has a more variable path but usually hooks around the subclavian artery before passing medially towards the tracheo-oesophageal groove. The right nerve takes a non-recurrent course in approximately 1% of individuals. The relationship of the recurrent laryngeal nerve and the inferior thyroid artery is variable but of great significance in thyroid surgery as the nerve may run deep to the artery, superficial to it or between its branches, before it perforates the cricothyroid membrane. The recurrent laryngeal nerve provides motor innervation to all the intrinsic laryngeal muscles except cricothyroid and provides sensory supply to the mucosa of the larynx inferior to the vocal folds. A helpful landmark for identifying the recurrent laryngeal nerve is Beahr's triangle (**Figure 35.12**), which is formed by the common carotid artery laterally, the inferior thyroid vessels and the recurrent laryngeal nerve.

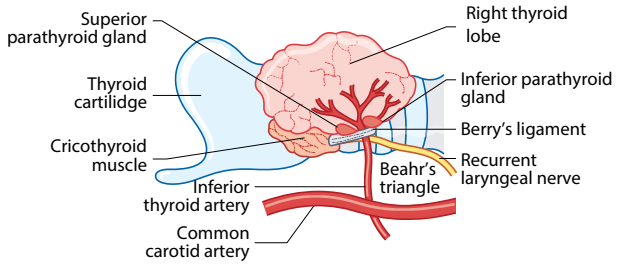


Figure 35.12 Beahr's triangle.

SPINAL ACCESSORY NERVE

The spinal accessory nerve is so called because of the accessory fibres that it contributes to the vagus nerve. This motor nerve constitutes both spinal and cranial origins; fibres from the anterior horn cells in the upper five or six segments of the cervical spinal cord pass intracranially through the foramen magnum to join fibres from the cranial root. The combined fibres then exit the skull via the middle compartment of the jugular foramen, and then pass deep to the styloid process and the posterior belly of the digastric muscle. The nerve then courses across level II, before penetrating the sternocleidomastoid muscle which it supplies, with sensory contribution from the cervical plexus.

The course of the accessory nerve after leaving the sternocleidomastoid varies. It usually leaves the posterior aspect of the muscle one centimetre above Erb's point, where the cervical plexus branches emerge, however the point of emergence is variable and the nerve may not pass through the muscle at all. From the sternocleidomastoid the nerve runs in the roof of the posterior triangle to the trapezius, deep to the investing fascia and superficial to the prevertebral fascia within the fibro-fatty tissue. All-important structures of the posterior triangle are located caudal to the nerve. The nerve reaches the trapezius at the junction of the lower and middle one-third of the anterior surface of the muscle and enters the deep surface of the muscle.

The spinal accessory nerve is thought in most subjects to be the sole motor innervation for the sternocleidomastoid. The trapezius is solely innervated by the spinal accessory nerve in approximately one-quarter of individuals, meaning that in the majority the trapezius also receives a degree of motor innervation from the cervical plexus.[22] In some individuals, the motor branch to trapezius arises from the spinal accessory high in the neck before the accessory nerve enters the sternocleidomastoid muscle so care should be taken in this area to preserve all potential branches. Proprioceptive fibres from the anterior roots of the spinal cord supply the sternocleidomastoid and the trapezius muscles as part of the cervical plexus and may also carry motor fibres. The proprioceptive innervation of sternocleidomastoid is mostly from C2 and C3 and the supply to trapezius is mostly C3 and C4.

The commonest cause of iatrogenic accessory nerve damage is during level V neck dissection, which may be permanent or transient. This leads to denervation of all or part of the trapezius muscle, resulting in difficulty elevating the arm, winging of the scapula and reduced support for the weight of the arm which can lead to intractable cervical nerve root pain.

HYPOGLOSSAL NERVE

The hypoglossal nerve is solely a motor nerve and provides motor innervation to all the intrinsic muscles of the tongue and all extrinsic muscles except palatoglossus, which is supplied by the vagus nerve. After exiting the skull via the hypoglossal canal, the nerve runs deep to the IJV and courses around the vagal ganglion. It then curves around the carotid bifurcation as it heads anteriorly, passing inferior to the greater horn of the hyoid before coursing superiorly, superficial to hyoglossus to reach the tongue. The hypoglossal nerve is susceptible to injury during surgical procedures in the neck, particularly at its lowest point near the hyoid so care must be taken in these areas, to avoid the devastating effect of a hypoglossal nerve palsy on speech and swallowing.

C1 nerve root fibres run with the hypoglossal nerve, giving off a branch known as the descendens hypoglossi that arises at the level of the carotid bifurcation. This branch courses inferiorly, running on the anterior surface of the IJV and joins with cervical plexus branches to form the ansa cervicalis, providing motor supply to the strap muscles.

CERVICAL PLEXUS NERVES

The cervical plexus nerves arise from the anterior rami of the upper four cervical spinal nerves. The cervical plexus lies deep to the prevertebral fascia and passes over the scalenus medius muscle. It has motor and sensory branches (**Figure 35.13**).

The sensory, or cutaneous branches of the cervical plexus emerge from the posterior border of the sternocleidomastoid muscle 1 cm superior to the emergence of the spinal accessory nerve at a point termed Erb's point. These branches provide sensory innervation to the anterior neck, with four named branches:

- **Lesser occipital nerve:** Formed entirely from the C2 root this branch provides supply to the skin posterior to the pinna, up to the superior nuchal line.
- **Greater auricular nerve:** This branch is formed from C2 and C3 nerve roots and runs superiorly from Erb's point, across the sternocleidomastoid muscle towards the parotid gland. It branches into anterior and posterior divisions. The anterior branch supplies sensation to the skin anterior and inferior to the pinna whereas the posterior branch supplies the inferior pinna including the lobule, the skin inferior to the pinna and provides innervation to the parotid capsule. The nerve is often injured during neck dissection or parotid surgery and may have to be sacrificed to enable access to these areas, resulting in insensate lobule and numbness of the upper neck and peri-auricular skin.

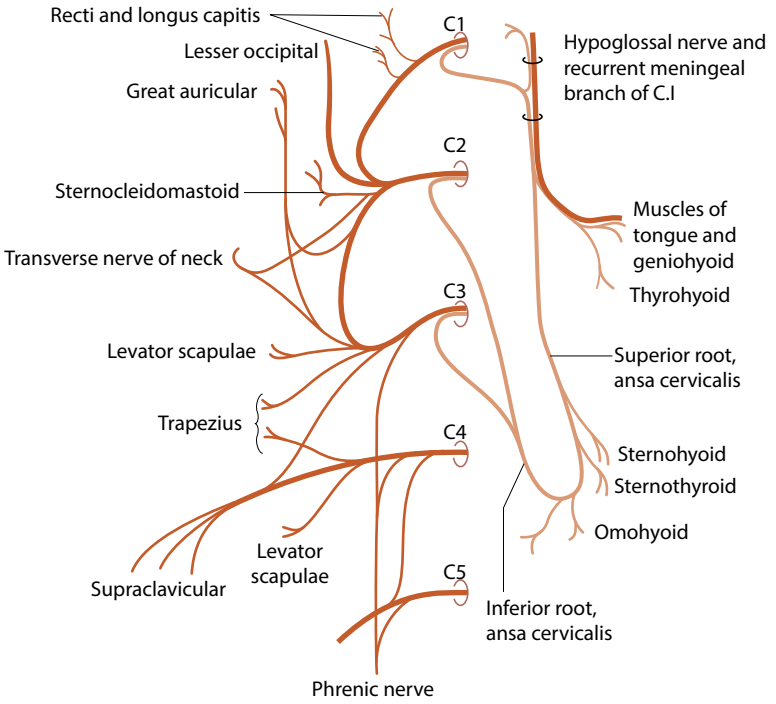


Figure 35.13 Cervical plexus nerves.

- **Transverse cervical nerves:** Fibres from the C2 and C3 nerve roots combine into a single nerve that leaves Erb's point then passes anteriorly and branches multiple times to give sensory innervation the skin of the entire anterior neck.
- **Supraclavicular nerves:** C3 and C4 nerve root fibres combine to form a single nerve which branches after Erb's point into three main divisions. A medial branch supplies an area of skin down to the sternoclavicular joint, the intermediate branch supplies the anterior chest wall skin, down to the anterior axial line. The lateral branch supplies the skin over the deltoid muscle and as far posterior as the spine of the scapula.

The muscular branches are given off segmentally to the prevertebral muscles of longus capitis, longus colli and the scalene muscles. The other muscular branches are the superior and inferior roots of the ansa cervicalis, segmental branches to the sternocleidomastoid and trapezius muscles and the phrenic nerve.

- **Ansa cervicalis:** Named as such from the Latin word 'ansa' meaning 'loop' this nerve is formed from a superior root, the C1 fibres of the descendens hypoglossi and an inferior root from the ventral rami of C2 and C3. The two roots merge over the IJV to form the ansa cervicalis which supplies motor innervation to the infrahyoid muscles: the sternothyroid, sternohyoid, thyrohyoid and omohyoid muscles.
- **Segmental supply to sternocleidomastoid and trapezius muscles:** As previously discussed, whilst the spinal accessory nerve provides the main motor supply to these muscles each also receives motor contribution from the cervical plexus. Branches from C2 and C3 supply the sternocleidomastoid whilst C3 and C4 fibres supply the trapezius. This is evidenced by the preservation of some of the motor supply to these muscles after sacrifice of the spinal accessory nerve during neck dissection. Conversely, shoulder dysfunction may still commonly occur when the accessory nerve is preserved, as a result of injury to the cervical plexus branches that contribute motor innervation to trapezius.
- **Phrenic nerve:** The phrenic nerve is the most significant motor branch of the cervical plexus. Formed from the ventral rami of C3, C4 and C5 the phrenic nerve runs inferiorly on the anterior surface of the scalenus anterior, deep to the prevertebral fascia to provide the sole motor supply to the diaphragm. The phrenic nerve is identifiable as the only structure deep to the prevertebral fascia that runs from lateral to medial. In addition to providing motor supply to the diaphragm it also provides sensory innervation to the central tendon of the diaphragm This is the cause of referred pain to the shoulder tip secondary to diaphragmatic irritation from abdominal or chest pathology that is referred via the C4 root of the phrenic nerve which communicates with the C4 root of the supraclavicular nerve.

CERVICAL SYMPATHETIC TRUNK

The cervical sympathetic trunk runs on the anterior surface of the prevertebral fascia, deep to the carotid sheath. It may have between two and four ganglia but typically has three, the superior, middle and inferior ganglia.

- **Superior cervical ganglion:** This is the largest of the ganglia and provides sympathetic innervation to the skin of the face and neck, including the eyes and eyelids.
- **Middle cervical ganglion:** This ganglion provides parasympathetic supply to the thyroid and parathyroid

glands and has a cardiac branch which supplies the heart, oesophagus and trachea.
- **Inferior cervical ganglion:** Also known as the stellate ganglion when fused with the highest thoracic ganglion, this receives contributions from C7, C8 and T1 and supplies the upper limb, lower neck and the heart.

Injury to the cervical sympathetic trunk may occur during head and neck surgery causing Horner syndrome, characterized by ipsilateral ptosis and meiosis with anhydrosis of the facial skin due to disruption of the oculosympathetic pathway. Horner syndrome is a rare complication of thyroid surgery due to an anatomical variation whereby a communicating branch between the recurrent laryngeal nerve and the cervical sympathetic trunk exists, which is at risk during thyroidectomy.

BRACHIAL PLEXUS

The brachial plexus is formed from the ventral rami of C5 to C8 and T1 and provides motor and sensory supply to the upper limb. It emerges between the anterior and middle scalene muscles and courses posteriorly across the inferior aspect of the posterior triangle, deep to the prevertebral fascia. It is an important structure for head and neck surgeons to appreciate as injury can have a catastrophic effect on the patient. It is most at risk during neck dissection, particularly when operating low in the posterior triangle or if the prevertebral fascia is breached.

KEY POINTS

- Knowledge of the anatomy of cranial and cervical nerves in the neck is key to operating safely in the neck.
- Care must be taken to avoid injury to the accessory nerve in the posterior triangle; all important structures lie caudal to the nerve.
- Supplementary motor supply from the cervical plexus to the sternocleidomastoid and trapezius muscles should be preserved where possible to optimize function.
- During neck dissection, with the fascial layers under tension, the sensory nerves of the cervical plexus travel medially and upwards, allowing sharp dissection away from the important motor nerves of the cervical and brachial plexus.
- There are rare connections between the recurrent laryngeal nerve and cervical sympathetic trunk which, if divided, can result in ptosis following thyroidectomy.

BLOOD VESSELS

The common carotid artery, branching in the neck into the internal and external arteries, provides the main arterial blood supply to the neck, with venous drainage via the jugular venous system.

Common carotid artery

The common carotid artery arises from the arch of the aorta on the left and from the brachiocephalic artery, also termed the innominate artery, on the right side. It does not normally give off branches, however, the vertebral, superior thyroid, inferior thyroid, ascending pharyngeal or occipital arteries may arise directly from the common carotid as normal variants.

The common carotid artery travels in the carotid sheath with the IJV and the vagus nerve. The cervical sympathetic trunk lies deep to the carotid sheath. The common carotid artery branches into internal and external branches at the level of the greater cornu of the hyoid bone. At the point of the bifurcation the artery dilates to form the carotid sinus, which contains stretch receptors innervated by the glossopharyngeal nerve which are the body's main baroreceptors. The carotid body lies deep to the bifurcation and contains chemoreceptors innervated by the glossopharyngeal nerve.

External carotid artery

The external carotid artery gives off multiple branches after the bifurcation which supply the viscera and muscles of the neck and face. The external carotid gives off six branches before dividing into two terminal branches within the parotid gland (**Table 35.8**). Although the superior thyroid artery is the first branch to be encountered, the ascending pharyngeal branch may arise first but is located deep to the main trunk and may not be readily visible. When ligating the external carotid artery for epistaxis, the ascending pharyngeal branch was traditionally preserved, because of its supply to the skull base and dura.

Internal carotid artery

The internal carotid artery (ICA) has no branches in the neck and lies deep and lateral to the external branch after the bifurcation. It runs beneath the posterior belly of digastric to enter the skull via the carotid canal and provides blood supply to the intracranial contents, with the vertebral artery via the circle of Willis. Important relations of the ICA are the IJV which runs antero-laterally to the artery and the pharynx, superior laryngeal nerve and pharyngeal vessels which are situated medial to the artery.

TABLE 35.8 Branches of the external carotid artery

Branch	Location	Supplies
Ascending pharyngeal	Deep	Oropharynx, hypopharynx, skull base, dura
Superior thyroid	Anterior	Thyroid, sternocleidomastoid
Lingual	Anterior	Tongue
Facial	Anterior	Tongue, tonsil, superficial facial soft tissue
Occipital	Posterior	Sternocleidomastoid, occiput
Posterior auricular	Posterior	Pinna, post-auricular skin
Superficial temporal	Terminal	Temporal region, scalp
Maxillary	Terminal	Deep facial tissues, mandible, nasal cavity

The cervical sympathetic trunk and its superior ganglion lie deep to the internal carotid.

Subclavian artery

The right subclavian artery arises from the brachiocephalic artery, whereas the left arises from the arch of the aorta, in a similar arrangement to the common carotid arteries. The subclavian arteries travel laterally towards the arm. The first part of the subclavian artery, from its origin to the medial aspect of the anterior scalene muscle, gives off the vertebral artery, the internal thoracic artery and the thyrocervical trunk, from which the inferior thyroid artery, suprascapular artery and the transverse cervical artery arise. The first part of the subclavian artery lies deep to sternocleidomastoid and the strap muscles but may extend above the clavicle so is at risk during procedures in the supraclavicular fossa. The second part of the artery runs deep to the anterior scalene muscle and gives off the costocervical trunk and the dorsal scapular artery. The third part passes lateral from the edge of the anterior scalene towards the arm and has no branches in the neck.

Internal jugular vein

The lateral or sigmoid dural venous sinus continues into the neck as the internal jugular vein (IJV). The jugular bulb lies within the floor of the tympanic cavity. After exiting the skull via the jugular foramen, the IJV travels inferiorly in the carotid sheath, anterior and lateral to the carotids. The IJV receives tributaries from the inferior petrosal vein, the common facial vein, the pharyngeal venous system and the superior and middle thyroid veins. Important relations of the jugular vein include the carotid arteries as mentioned above and the vagus nerve which runs posteriorly in the carotid sheath. The sternocleidomastoid muscle lies superficial to both the IJV and the carotid arteries, providing protection from penetrating trauma. The posterior belly of digastric and the inferior belly of the omohyoid muscle both cross over the IJV.

Inferiorly the IJV drains into the brachiocephalic veins on both sides, with only one valve before draining into the superior vena cava and eventually into the right atrium. Because of backflow from the right atrium the IJV has a pressure wave. The thoracic lymphatic duct drains into the posterior aspect of the IJV, at the intersection with the subclavian vein in Chassaignac's triangle.

Facial veins

The venous drainage of the face and oral cavity is via the facial and lingual veins which then form a venous plexus in the submandibular triangle. These may drain into the jugular vein with one single tributary that drains into the common facial vein or there may be many tributaries. The common facial vein also receives some drainage from the retromandibular vein which passes through the parotid gland.

Superficial jugular veins

Both the anterior jugular vein and the external jugular vein are part of a variable superficial venous system that drains the face and scalp. They drain into the subclavian vein, where valves exist to prevent backflow; thus the superficial jugular veins have low pressure, unlike the IJV.

KEY POINTS

- It is important to remember the ICA has no branches in the neck and lies deep and lateral to the external carotid.
- Both the internal and external carotid arteries are intimately related to the glossopharyngeal nerve and the pharyngeal and laryngeal branches of the vagus nerve, as well as the vagus nerve itself, the hypoglossal nerve and the cervical sympathetic trunk.
- Access to lymphatic level II is facilitated by retraction of the digastric; when doing so it is important to remember that vital vascular structures lie immediately deep to the muscle.
- When dissecting the hypoglossal nerve difficult bleeding can be encountered from the venae comitantes nervi hypoglossi and from a network of veins draining the thyroid, face and tongue known as the thyroglossofacial confluence which empty into the IJV in this location.
- Division of the common facial vein facilitates access to the hypoglossal nerve.
- When ligating any important vascular structure in the neck given a name, transfixion of the vessel should be considered to avoid haemorrhage.
- During thyroidectomy there are only two structures encountered within the para-carotid tunnel. These are the non-recurrent nerve and the middle thyroid vein; care should be taken when dividing this close to the IJV.

SUMMARY

Preservation of function when operating in the neck is more important than ever in this era of conservation surgery and improved survivorship from head and neck cancer. Functional neck surgery is not possible without a sound understanding of neck anatomy. This chapter covers the clinically relevant surgical anatomy of the neck to highlight the key areas any surgeon operating in the neck should be aware of. Advances in head and neck imaging aids surgeons in planning operations by providing detailed anatomical imaging, however, a sound knowledge of head and neck anatomy from texts and most importantly from clinical experience of operating in the neck remains key to providing patients with the highest standards of surgical care.

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CHAPTER 36

CLINICAL EXAMINATION OF THE NECK

James O'Hara

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SEARCH STRATEGY

Data in this chapter may be updated by a search of PubMed using the keywords: clinical examination AND neck OR salivary glands, Head and Neck neoplasms AND Lymphatic metastases OR Neck metastases.

INTRODUCTION

Clinical examination of the neck should accompany a thorough history and appropriate ear, nose and throat assessment. It is performed in either acute or elective settings, during assessment of a primary upper aerodigestive symptom, primary neck lump complaint or surveillance following treatment.

INSPECTION

The patient should ideally be exposed from the clavicles. Observe for lumps, skin changes and scars. Ask the patient to point to any lump if one is not obvious. Patients with midline lumps should be observed whilst drinking a sip of fluid and protruding the tongue. The thyroid gland is enveloped in pre-tracheal fascia along with the trachea. It will rise with laryngeal elevation during swallowing. Ask the patient to hold the fluid in the mouth before swallowing, giving the examiner time to concentrate on any movement. A thyroglossal cyst will elevate with tongue protrusion, being attached via the thyroglossal duct remnant to the foramen caecum of the tongue. Ask the patient to open their mouth, observe the lump and then ask them to protrude the tongue. Pemberton's sign is elicited by asking the patient to sit and raise the arms.[1] Venous congestion with facial plethora or cyanosis may indicate thoracic outlet obstruction for which a retrosternal goitre is a cause. Examination of the oral cavity to assess the parotid and submandibular ducts should accompany a thorough neck examination.

Examine the relevant cranial nerve function. Metastatic lymphadenopathy in the region of the accessory nerve can cause reduced function. It is important to note this prior to any proposed surgery. Parapharyngeal tumours may cause impairment to the nerves from which they arise, for example, Glomus vagale or Schwannoma of the sympathetic chain, or can cause compression to other lower cranial nerves.

Examine the scalp and external ear closely for lesions where appropriate. Skin conditions often cause level V reactive lymph nodes. Cutaneous squamous cell carcinoma and melanoma, often previously excised, may metastasize to the parotid lymph nodes and cervical nodes.

In the acute presentation, observe the patient for how the neck is held and for neck movements. Acute torticollis in a septic patient, usually a child, is indicative of severe inflammation and pain. Reduced range of neck movement in a septic patient may indicate a deep neck space abscess.

PALPATION

Have a set method that is reproducible. The location of the noted pathology in the neck should lead the examiner to consider a list of differential diagnoses (**Table 36.1**).

TABLE 36.1 Basic differential diagnosis of neck lumps

Lymph node group	Differential diagnosis
IA (submental)	Lymph node Thyroglossal cyst Dermoid cyst Plunging ranula
IB (submandibular)	Submandibular gland pathology Lymph node Cystic hygroma / lymphangioma (both can affect the entire neck)
II (upper jugular)	Lymph node Parotid gland pathology Branchial cyst Parapharyngeal pathology (e.g. Paragangliomata or nerve sheath tumours)
III (mid jugular)	Lymph node Branchial cyst Parapharyngeal pathology Laryngocoele
IV (lower jugular)	Lymph node (including Virchow's node on the left)
V (posterior triangle)	Lymph node Lipoma Cervical rib
VI (anterior compartment)	Thyroid gland pathology Thyroglossal cyst Parathyroid neoplasm Lymph node Direct extension of a laryngeal neoplasm



Figure 36.1 Palpation of the neck.



Figure 36.2 Bimanual palpation of the salivary glands.



Figure 36.3 Palpation of a suspected thyroglossal cyst.

Each side of the neck should be examined individually, not simultaneously as this may cause excessive vagal stimulation through carotid sinus massage. The neck should be slightly flexed with the head tilted to the side of examination. This relaxes the neck muscles, in particular the sternocleidomastoid, allowing palpation of structures deep to it. The flats of the fingers should be used to palpate in a slow sweeping manner and should not resemble piano playing (**Figure 36.1**). The author always starts at level IA, sweeping posteriorly into IB before examining the jugular chain lymph nodes from level II to IV. The fingers then pass from medial to lateral above the clavicle before sweeping superiorly, anterior to the trapezius, towards the mastoid tip, covering level V. The post-auricular region, occipital and parotid regions are then palpated. Bimanual palpation of the salivary glands should be performed for any salivary lump (**Figure 36.2**). A suspected thyroglossal cyst is palpated in the same manner as during inspection (**Figure 36.3**). Finally the thyroid gland is palpated. This organ can be examined with both hands and the swallowing assessment repeated if necessary. Thyroid nodules may be palpable in 4–7% of the population, rising with age.[2] When detected as a part of an examination for other symptoms, thyroid nodules are not classified as 'incidentalomas' (as they are when detected with imaging) since they are by definition palpable. These nodules require investigation with serum thyroid-stimulating hormone (TSH), thyroid ultrasound with fine-needle aspiration where appropriate. Bear in mind normal anatomical structures which may seem pathological; the transverse process of the C2 vertebra, a prominent carotid bifurcation or occasionally patients may be aware of a normal internal jugular vein on voluntary valsalva.

PERCUSSION

Percussion over the sternum may give an indication of the extent of a retrosternal goitre or other upper mediastinal mass.

AUSCULTATION

Auscultation of the carotid arterial flow is often advocated for patients with symptoms suggestive of cerebral insufficiency. A study of 2000 patients found that 'critical auscultation' had a sensitivity of 83% and specificity of 40% in detecting carotid bifurcation lesions.[3] It concluded that auscultation is not capable of excluding carotid lesions. Auscultation over the larynx and trachea may help further characterize stridor, especially helpful in children.

CLINICAL EVALUATION OF CERVICAL LYMPHADENOPATHY

The majority of clinical neck examinations are performed to assess the cervical lymph nodes. The site, size, number, consistency, fixity to surrounding structures and overlying skin appearances should be assessed. For lymph nodes considered to contain metastatic head and neck malignancy, the affected site or sites should be classified according to the level(s) of the neck. The concept of 'levels' of the neck was first proposed by Shah in 1990.[4] Subsequently the Committee for Neck Dissection Classification of the American Head and Neck Society published several consensus documents further defining these levels.[5,6] The most recent anatomical boundaries of the neck levels are summarized in **Table 36.2** (**Figure 36.4**). Physical examination alone has a sensitivity of 81% and specificity of 77% in detecting metastatic lymphadenopathy.[7]

TABLE 36.2 Classification of neck levels

Lymph node group	Anatomical boundaries
IA (submental)	Laterally the anterior belly of digastric muscles, inferiorly the hyoid bone, superiorly the mandible.
IB (submandibular)	Anteriorly the anterior belly of digastric muscle, superiorly the body of the mandible, posteriorly the vertical plane defined by the posterior border of the submandibular gland (updated in 2008). This level includes the submandibular gland.
II (upper jugular – divided into A and B)	Medially the vertical plane defined by the posterior border of the submandibular gland (updated in 2008), laterally the posterior border of the sternocleidomastoid muscle, superiorly the skull base and inferiorly the inferior border of the hyoid bone. The vertical plane defined by the accessory nerve divides level II into A, anterior and medial and B, posterior and lateral.
III (mid jugular)	Medially the medial aspect of the common carotid artery (2008), laterally the posterior border of the sternocleidomastoid muscle, superiorly the inferior border of the hyoid bone, inferiorly the inferior border of the cricoid cartilage.
IV (lower jugular)	Medially the medial aspect of the common carotid artery, laterally the posterior border of the sternocleidomastoid muscle, superiorly the inferior border of the cricoid cartilage, inferiorly the clavicle.
V (posterior triangle – divided into A and B)	Medially (anterior) the posterior border of sternocleidomastoid muscle, posteriorly the anterior border of the trapezius muscle, superiorly the convergence of the sternocleidomastoid and trapezius, inferiorly the clavicle. It is divided by the horizontal plane from the inferior border of the cricoid arch into levels VA, superior and containing the nodes around the accessory nerve and VB, inferior containing the nodes around the transverse cervical vessels. Level VB incorporates the supraclavicular nodes, except Virchow's node in level IV.
VI (anterior compartment)	Laterally the medial aspect of the common carotid arteries, superiorly the hyoid bone and inferiorly the suprasternal notch.

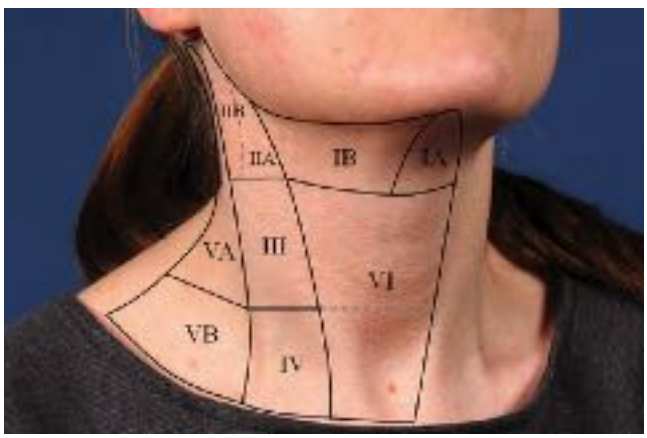


Figure 36.4 Anatomic boundaries of the neck levels.

KEY POINTS

- All patients presenting with head and neck symptoms should undergo a thorough clinical examination of the neck.
- The site of any neck pathology should lead the examiner to consider the potential differential diagnoses.
- Lymphadenopathy secondary to head and neck malignancy should be described according to the involved levels of the neck.

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CHAPTER
37

IMAGING OF THE NECK

Ivan Zammit-Maempel

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: head and neck cancer, head and neck infections, neck masses, imaging, CT, MRI, ultrasound, PET-CT.

IMAGING TECHNIQUES

Various imaging techniques are used in the evaluation of patients presenting with a neck mass or a 'hot' neck and in the staging and post-treatment follow-up of head and neck cancer. These include plain X-rays, ultrasound, CT, MRI, and PET-CT. Radiologists are increasingly being involved in image-guided biopsies, aspirations of collections in the neck, botox injections in selected post-surgical patients to improve speech or reduce salivary flow and embolizing/stenting vessels in patients with uncontrollable bleeding. Contrast studies including videofluoroscopy and angiography have an important role in selected cases.

The ENT surgeon is often unsure as to which investigation to request and this chapter will aim to clarify this based on the currently available evidence in the literature. However, there is no escaping from a meticulous history and examination in reaching a clinical diagnosis and imaging should be used to confirm this diagnosis and not used as a blanket screening examination.

Imaging modalities have been discussed in more detail in the relevant organ-specific chapters but some brief observations are provided below.

PLAIN X-RAYS

The use of plain X-rays in the head and neck is limited to detecting ingested radio-opaque foreign bodies, assessing the dentition in head and neck cancer patients and those presenting with abscesses around the floor of mouth as well as confirming the presence of air (**Figure 37.1**) or evaluating bony hard masses (**Figure 37.2**).

ULTRASOUND (US)

US is quick, non-invasive, readily available, inexpensive and does not use ionizing radiation but is heavily operator dependent. It is widely used in children for evaluating neck lumps, lymph nodes, the thyroid and salivary glands and in guiding fine-needle aspiration (FNA) or core biopsies. US is particularly helpful in evaluating whether a node appears reactive (**Figure 37.3a**) and can therefore be safely ignored or more complex (**Figure 37.3b**), requiring FNA and further investigation.[1–3]

COMPUTED TOMOGRAPHY (CT)

CT is used extensively in staging head and neck cancer patients and for detecting masses or abscesses in the deep

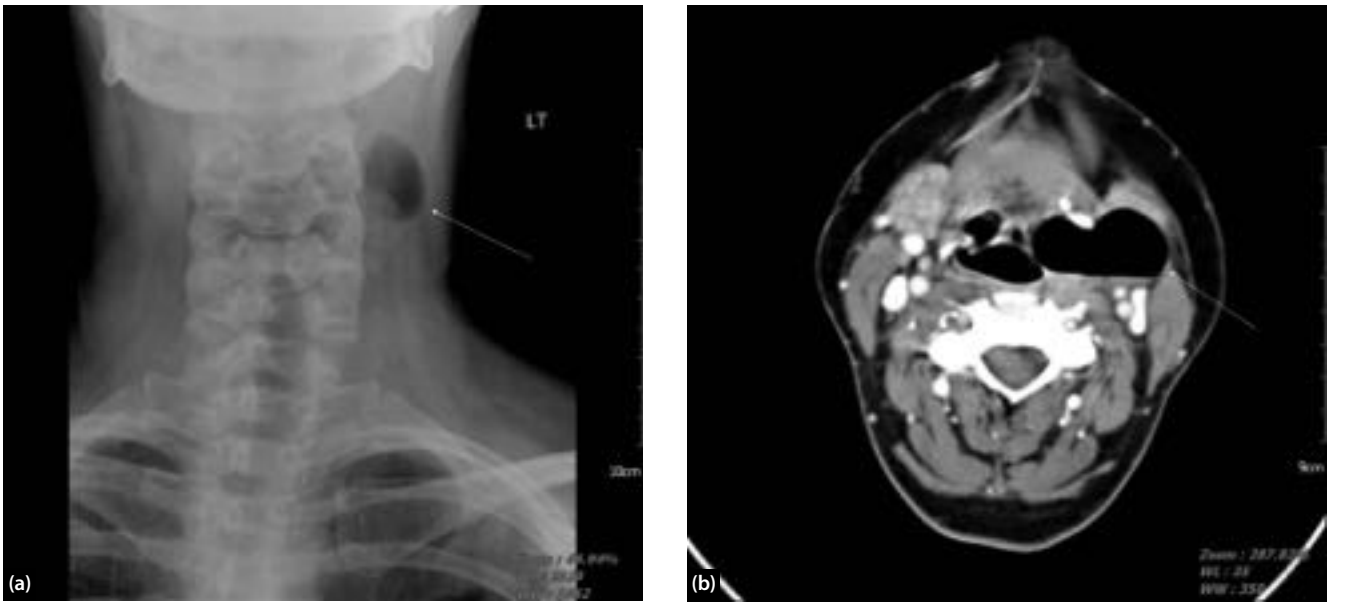


Figure 37.1 Plain X-ray (a) and axial contrast enhanced CT **(b)** showing a left-sided laryngocoele (arrow) in a patient initially referred with a soft swelling for ultrasound.



Figure 37.2 Bilateral cervical ribs, larger on the right: patient presented with a bony hard mass in the right supraclavicular region.

spaces of the neck. With the advent of multi-detector scanners, the entire neck can be scanned in a few seconds and a volumetric data set obtained, allowing reconstructions in any plane. Because of its relatively low soft-tissue resolution, intravenous iodinated contrast agents are necessary. Dual-source scanning is the latest breakthrough in CT technology and early results are promising for imaging the neck.[4] Radiation dose is an important consideration on CT and dose reduction can be achieved by special in-built features in most modern CT scanners as well as manually altering settings such as mAs and KV, without affecting diagnostic image quality.[5, 6] Artefact from dental amalgam can be negated by gantry tilt but the combination of this facility and volumetric scanning is not available on all scanners.[7] Cone-beam CT has an evolving role in head and neck imaging.[8]

MAGNETIC RESONANCE IMAGING (MRI)

MRI produces images with very good soft-tissue contrast and does not use ionizing radiation but is contraindicated in certain patients with pacemakers, ferromagnetic intraocular foreign bodies, cochlear implants, cerebral artery aneurysm clips and valve prostheses. The long acquisition times result in neck images that can be easily degraded by movement and swallowing artefact.

POSITRON EMISSION TOMOGRAPHY (PET)

PET is a functional imaging technique that depicts tissue metabolic activity and all hypermetabolic cells, not just malignant cells, accumulate the tracer resulting in increased activity as measured by standard uptake value (SUV). The commonest tracer used is fluorine-18-labelled 2-fluoro-2-deoxy-D-glucose (FDG), which has a half-life of 110 minutes. The combination of CT and PET allows accurate anatomical localization. PET-CT is especially useful in assessing patients presenting with a metastatic neck node and no overt primary, the so-called cancer of unknown primary, and in the post-treatment patient, where differentiation between post-treatment fibrosis and residual/recurrent tumour can be difficult. Head and neck PET-CT is complicated by the fact that various structures such as Waldeyer's ring (lymphoid tissue of the

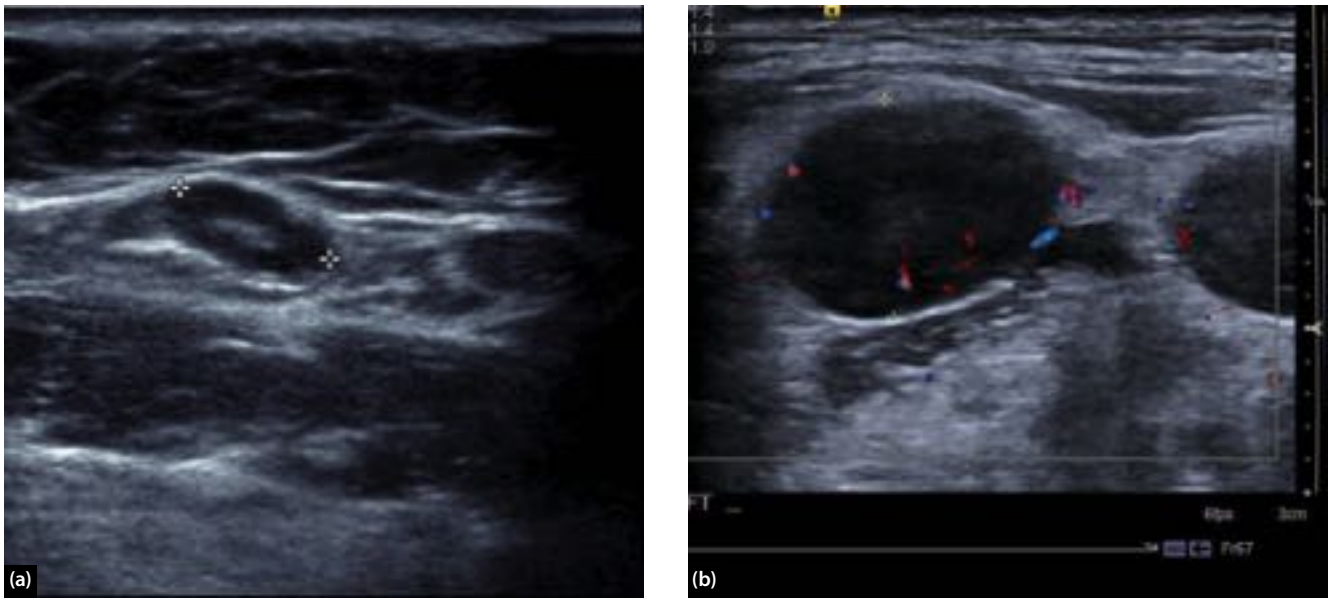


Figure 37.3 US showing a reactive node with a normal echogenic hilum **(a)** and a metastatic node showing loss of its normal architecture and increased peripheral vascularity **(b)**.

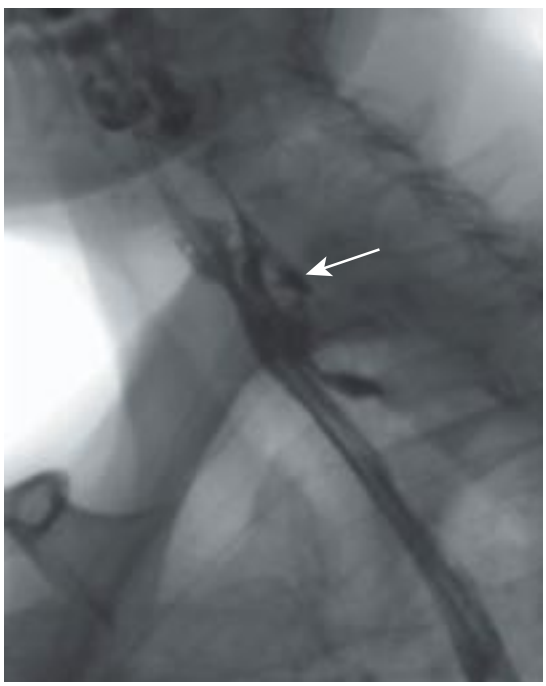


Figure 37.4 Contrast swallow post-laryngectomy showing an inferior leak (arrow) extending into the superior mediastinum.

nasopharynx, tongue base, palatine tonsil, soft palate and posterior pharyngeal wall), the salivary glands, nasal turbinates and cervical muscles normally show FDG uptake. The feasibility of MRI and PET in the staging of head and neck cancer is also being evaluated.[9]

CONTRAST SWALLOW

Contrast swallows are important in assessing for the presence of leaks in the early phase after laryngeal and pharyngeal surgery (**Figure 37.4**) while videofluoroscopy is important in assessing head and neck cancer patients presenting with dysphagia before or after treatment.

HEAD AND NECK CANCER

Imaging plays an important role in assessing the extent of primary tumour and any metastases.[10, 11] Many tumours can initially be staged by CT as the chest and liver can be imaged at the same time as the neck, allowing the detection of distant chest, liver or bone metastases and any synchronous lung or gastrointestinal tumours. MRI is particularly useful for evaluating intracranial spread in nasopharyngeal and other skull-base tumours and the oral cavity in patients where the images are degraded by dental amalgam artefact. Diffusion-weighted MRI is being increasingly used in the head and neck to help with differentiating benign from malignant tumours, squamous cell carcinoma from lymphoma, suppurative lymphadenitis from metastatic nodes, recurrence from post-radiotherapy fibrosis as well as nodal staging.[12–16]

Small mucosal tumours are easily assessed clinically but larger tumours require cross-sectional imaging to assess the size, location and deep extension of tumour, involvement of surrounding structures and presence of distant metastases.

Lymph node status is one of the most important prognostic factors in head and neck cancer and various studies have shown that imaging is more reliable than clinical palpation.[17, 18]

NASOPHARYNGEAL CANCER

The most common cancer of the nasopharynx is undifferentiated or poorly differentiated carcinoma that has a close relationship to the Epstein–Barr virus. Other cancers

that may arise in the nasopharynx include lymphoma, adenocarcinoma, adenoid cystic carcinoma, melanoma, plasmacytoma, chordoma and sarcoma. This chapter will concentrate on nasopharyngeal carcinoma that has a high incidence in the Chinese population, even after they have emigrated.

Nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is different from other head and neck squamous cell tumours in its aggressive local infiltration and propensity for metastatic spread despite apparently early primary lesions. Patients may present with a neck mass, nasal obstruction, blood-stained nasal discharge, headaches, ophthalmoplegia, hearing loss and tinnitus. The aim of imaging is to accurately map the primary tumour and to detect any extension especially to the skull base and deep fascial planes as well as nodal and distant metastases.

CT allows assessment of the primary tumour, neck nodes, chest and liver in one examination but MRI is superior in demonstrating the tumour soft-tissue extent, any intracranial extension and skull-base bone marrow changes.[19–22] Dynamic contrast-enhanced MRI may be useful in characterizing NPC as higher stage tumours show some parameters of increased permeability and perfusion.[23] PET-CT is useful in staging, assessing for recurrence and in evaluating the nasopharynx in patients presenting with neck nodes and no obvious primary.[24–27] Huang et al.[28] showed that intratumoral heterogenicity of FDG uptake across NPC tumours significantly correlated with tumour aggressiveness and predicted patient outcome while various authors have shown a correlation between SUV and outcome.[29–34] Ng et al. suggest a combination of PET-CT and head and neck MRI as the initial staging examinations for NPC patients, with MRI superior in detecting locoregional invasion and retropharyngeal nodes and PET-CT more accurate in determining cervical node metastases.[35] However King et al. showed that the additional use of PET-CT did not upstage or change management when compared to MRI in their cohort of patients.[36] Imaging may allow differentiation of NPC from lymphoma as NPC is often asymmetrical with a propensity to invade widely and deeply into muscle tissue, fat spaces, neural foramina and skull base while lymphoma is more symmetrical, shows homogenous enhancement and has a propensity to involve Waldeyer's ring.[37–39]

An understanding of the pathology of nasopharyngeal cancer is essential in order to correctly interpret imaging at the time of staging and subsequent follow-up.[40] Most nasopharyngeal tumours originate in the fossa of Rosenmuller and tend to spread submucosally with early infiltration of the palatal muscles and obstruction of the Eustachian tube (**Figure 37.5**). The most common spread is laterally with infiltration of the parapharyngeal and masticator spaces with potential involvement of the mandibular nerve and intracranial spread. Anterior spread of tumour into the nasal fossa can result in erosion of the maxillary sinus and infiltration of the pterygopalatine fossa and thence along the maxillary nerve onto the foramen rotundum (**Figure 37.6**). NPC can spread superiorly to erode the clivus (**Figure 36.7**), petrous apex, sphenoid sinus and foramen lacerum. Inferiorly it can extend along the pharyngeal wall to the oropharynx while posteriorly it infiltrates the retropharyngeal space and prevertebral muscles. Nodal metastases (**Figure 37.8**) to all cervical levels including the retropharyngeal group are extremely common and may be the presenting feature but level 2B nodes rather than retropharyngeal nodes appear to be the first echelon nodes in NPC.[41, 42] Tomita et al. showed that primary tumour existence beyond the midline of the nasopharynx was associated with a higher incidence of bilateral lymph node metastases than primary tumour presence within the midline, with incidences of 66% and 18% respectively.[43] Distant metastases to the lung and liver are common.



Figure 37.5 Axial CT on bone settings showing nasopharyngeal carcinoma (white arrow) and retained secretions left mastoid air cells (black arrow) due to Eustachian tube obstruction.

Management of NPC is one of the greatest clinical challenges, with radiotherapy, especially intensity-modulated radiotherapy (IMRT), being the primary treatment and chemoradiotherapy used for locoregionally advanced tumours.[44] The aim of post-treatment imaging is to detect early recurrence. As there is usually tumour resolution by 3 months post-radiotherapy, PET-CT is being increasingly used to ensure no residual activity within the primary site or nodes.[26, 45] Differentiating fibrosis from tumour recurrence is difficult on CT and can also be problematic by MRI but 3T-MRI may be comparable to PET-CT in detecting residual or recurrent NPC and contrast-enhanced MRI is useful in detecting perineural spread (**Figure 37.8**).[46–50] The combined use of MRI and FDG PET-CT is more accurate for tumour restaging than either modality used independently.[51] Some authors have suggested plasma Epstein–Barr virus DNA screening and if positive followed by PET-CT while others have advocated the use of CT perfusion in detecting recurrences.[52–54] A systematic review comparing PET-CT, CT

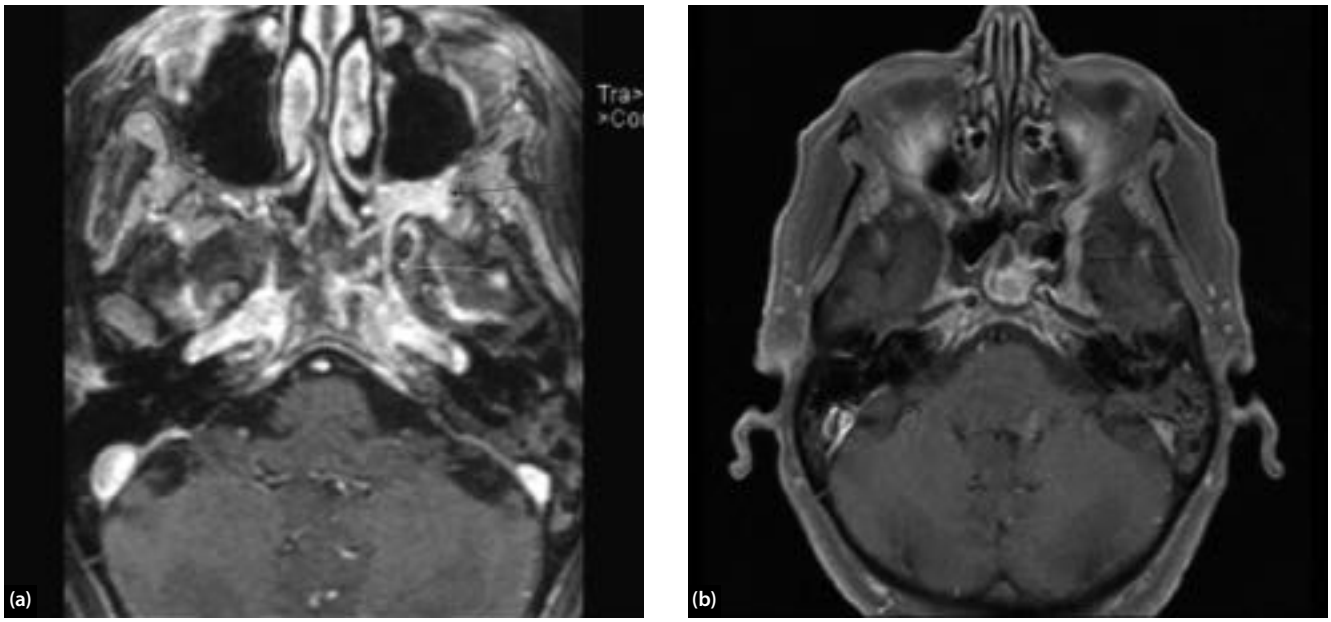


Figure 37.6 Axial VIBE (Volumetric interpolated brain examination) MRI showing left nasopharyngeal cancer (NCC) extending into the pterygopalatine fossa (black arrow) and vidian canal (white arrow) **(a)** and into the foramen rotundum (black arrow) **(b)**.

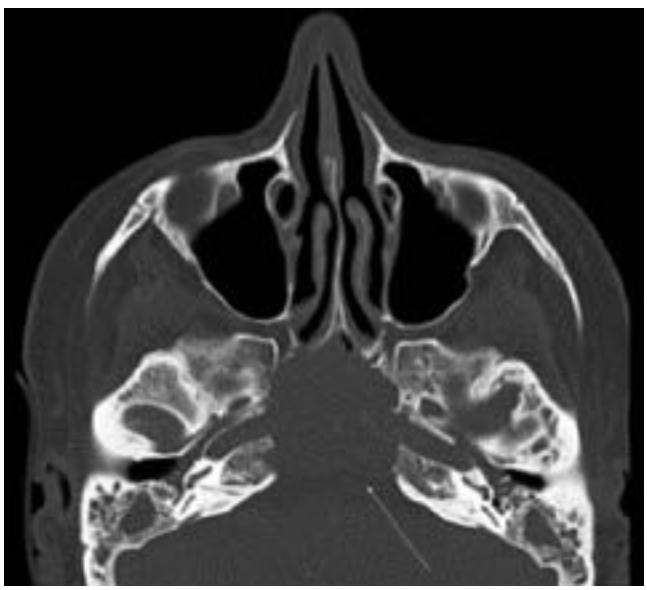


Figure 37.7 Axial CT showing destroyed clivus (white arrow) secondary to NPC.

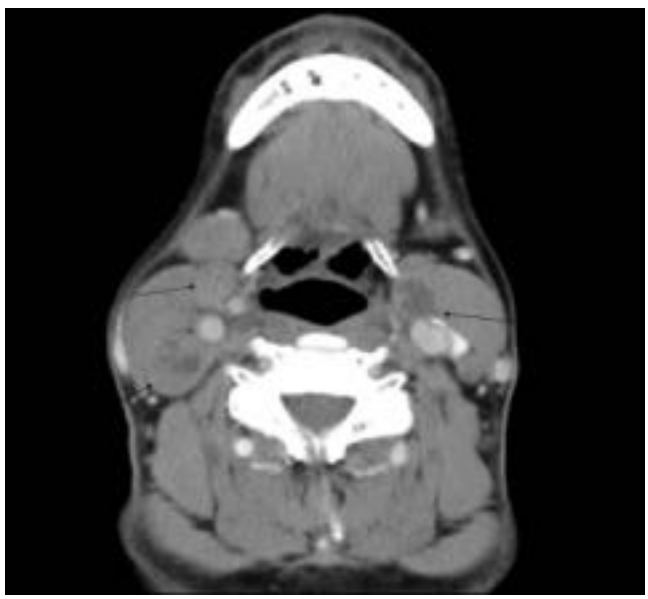


Figure 37.8 Axial contrast-enhanced CT showing bilateral level 2/3 nodes (black arrows) in patient with NPC.

and MR imaging for the diagnosis of local residual or recurrent NPC showed that PET-CT was the best imaging modality.[55] PET-CT should therefore be the imaging modality of choice in the detection of residual or recurrent disease (**Figure 37.9**).

Lymphoma

Non-Hodgkin lymphoma (NHL) is the second most common nasopharyngeal tumour and classically involves Waldeyer's ring.[37–39] Imaging usually demonstrates a well-defined, homogenous, non-necrotic mass that is exophytic rather than infiltrative in nature (**Figure 37.10**).

ORAL CAVITY TUMOURS

The oral cavity is bordered by the hard palate and maxillary alveolar ridge superiorly, the mylohyoid muscle and alveolar mandibular ridge inferiorly, the lips anteriorly, the gingivobuccal region laterally and the soft palate, circumvallate papillae and tonsillar pillars posteriorly. Although the soft palate forms part of the oropharynx, the mucosal layer beneath the hard palate lies within the oral cavity. The centre of the oral cavity is filled by the tongue, the anterior two-thirds of which is part of the oral cavity.

Oral cavity tumours are usually readily apparent clinically and easily amenable to biopsy but challenging for

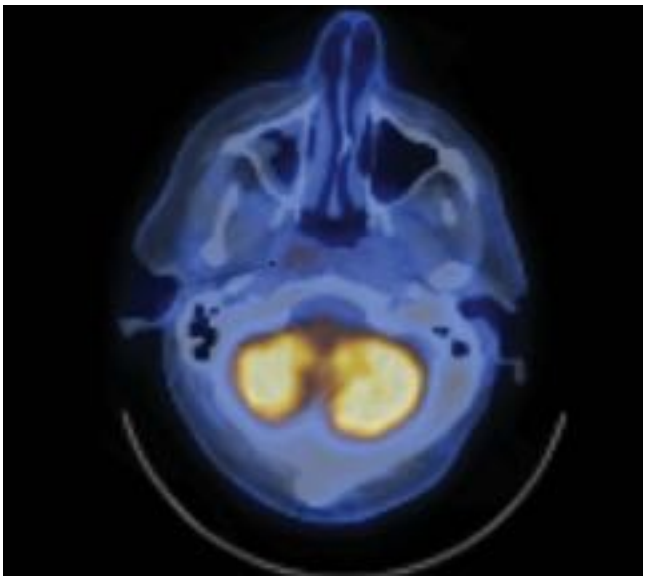


Figure 37.9 Fused axial PET-CT showing activity in the right nasopharyngeal region (black arrow), confirmed histologically to be NPC recurrence.

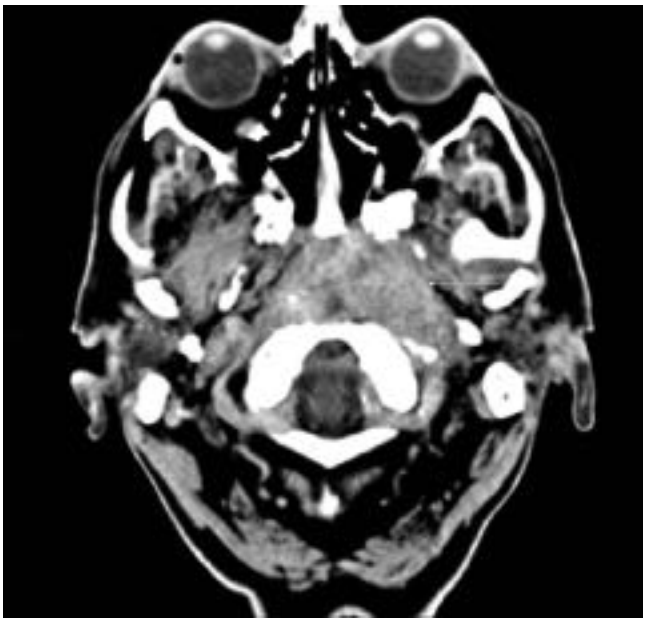


Figure 37.10 Axial CT showing a midline nasopharyngeal mass, biopsy confirmed non-Hodgkin lymphoma.

radiological diagnosis because of the surrounding anatomy and small tumours are often not visualized by imaging. Squamous cell carcinoma (SCC) is the most common tumour that affects the oral cavity and can extend along the submucosa to invade adjacent structures. Despite the invasive character of SCC, bony structures are infiltrated late in the course of disease. The invasion of nerves and vessels is an important aspect in the spread of oral cavity tumours. Vascular invasion results in a greater risk of remote as well as lymph node metastases while perineural extension allows spread far beyond the expected tumour margins. The oral mucosa has bilateral drainage to the level 1 submental and submandibular nodes and any asymmetrically enlarged nodes should be regarded with suspicion. Cervical nodal metastases occur in approximately 50% of patients with SCC of the oral cavity and may be bilateral especially if tumours cross the midline but lymphadenopathy is often occult and not detected clinically or by imaging. The floor of mouth, retromolar trigone (RMT) and ventrolateral tongue are involved in descending frequency by SCC and will be briefly discussed.

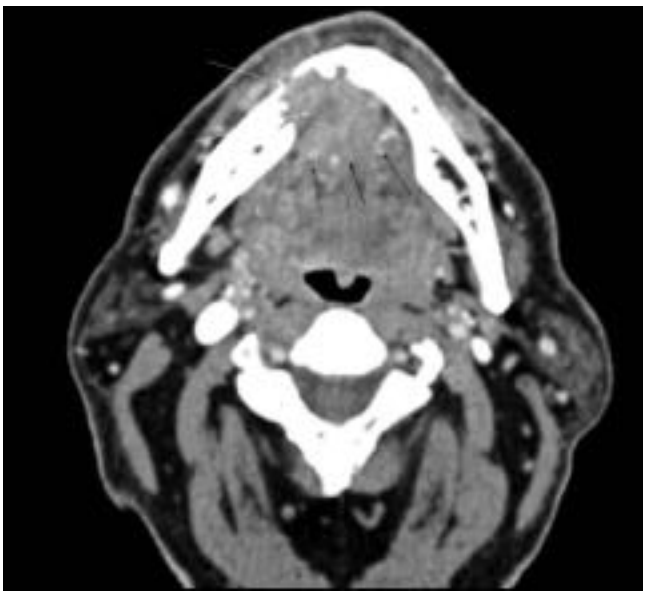


Figure 37.11 Axial contrast-enhanced CT showing anterior floor of mouth SCC crossing the midline (black arrows) with associated destruction of inner and outer cortex of mandible (white arrows).

Floor of mouth cancer

Most of these tumours are easily diagnosed clinically and occur anteriorly, from where they can extend deeply into the sublingual gland, obstruct the submandibular duct and invade the submandibular space. The key points from the imaging point of view include looking for extension posteriorly along the neurovascular bundle and across the midline (**Figure 37.11**).

Retromolar trigone cancer

The RMT is the triangular mucosa posterior to the last molar and tumours are less easily detected clinically. SCC can arise from the RMT (**Figure 37.12**) or spread into the RMT secondarily from the tongue base or tonsil. Tumours may invade the mandible directly, the inferior alveolar nerve or extend posteriorly along the pterygomandibular raphe, a fibrous band beneath the RMT that extends from the hook of the hamulus of the medial pterygoid to the mylohyoid line on the medial border of the mandibular body. As the buccinator, superior constrictors and orbicularis oris muscles all insert into the pterygomandibular raphe, tumours can extend into the lateral floor of mouth, buccal space, tonsillar fossa or nasopharynx.

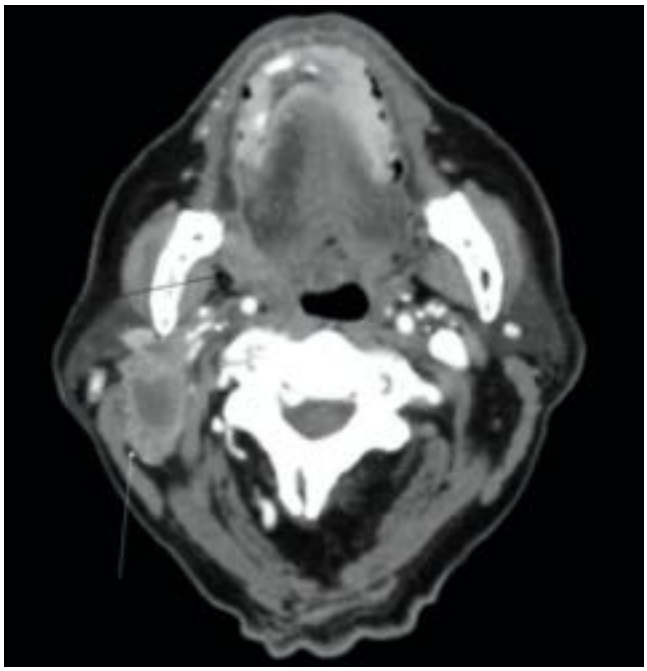


Figure 37.12 Axial contrast-enhanced CT showing a right retromolar trigone tumour (black arrow) with an associated necrotic level 2 node (white arrow).

Tongue cancer

The ventrolateral surface of the tongue is the site most commonly involved by tumour (**Figure 37.13**), which can easily invade the intrinsic muscles. Besides assessing for tumour spread into the floor of mouth, tongue base, tonsils, soft palate and mandible, tumour extension across the midline and to the contralateral neurovascular bundle also needs evaluation.

Hard palate, gingival and buccal cancer

The gingiva is the mucous membrane that covers the alveolar bone processes and is attached to the lingual and buccal surfaces of the mandible and maxilla. Gingival and buccal tumours (**Figure 37.14**) may eventually invade the mandibular or maxillary cortex especially in edentulous patients. Hard-palate tumours (**Figure 37.15**) require close evaluation of the bone, best seen in the coronal plane and can spread perineurally along the incisive and greater and lesser palatine canals to the pterygopalatine fossa.

Modalities available for imaging the oral cavity are ultrasound, CT, cone-beam CT, MRI and PET-CT.[56–63] As in other head and neck cancers, CT provides better evaluation of cortical bone while MRI has the advantage of better characterizing local tumour extent, perineural spread and bone-marrow involvement. Dental amalgam artefact poses a frequent diagnostic problem on CT, while swallowing artefact is also a problem with CT but especially so with MRI because of the long acquisition times. Acquiring CT images with gantry tilt that avoid dental metalwork artefact significantly improves sensitivity in the staging of oral and oropharyngeal tumours.[64]

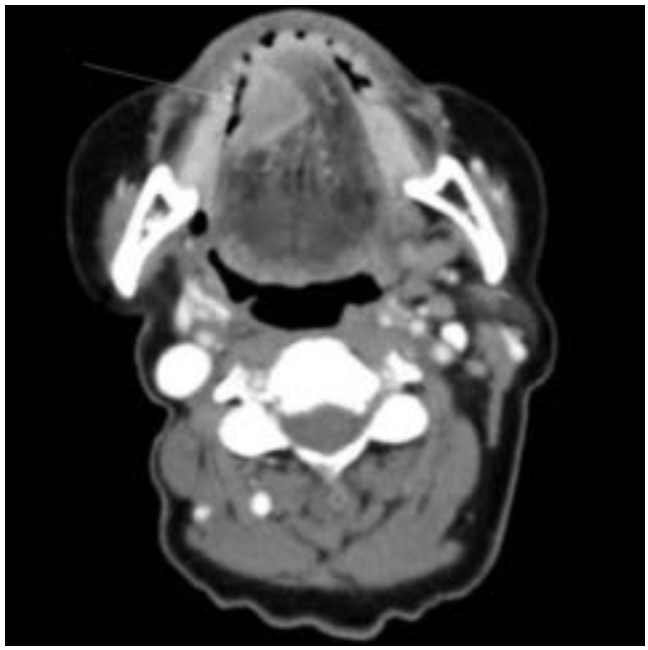


Figure 37.13 Axial contrast-enhanced CT showing right ventral tongue tumour (white arrow) just reaching the midline.

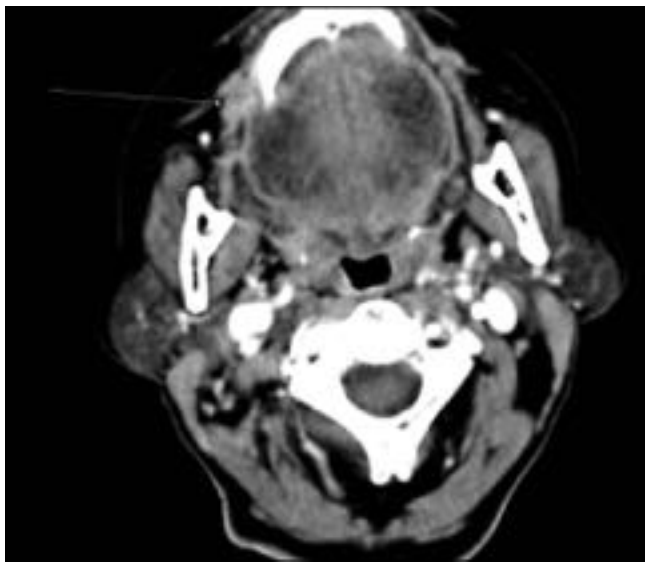


Figure 37.14 Axial contrast-enhanced CT showing right buccal tumour (white arrow).

Various contrast-enhanced CT protocols have been used with a low-flow delayed-phase protocol providing better delineation of the tumour edge compared to a high-flow rate and short-delay protocol but no difference in central tumour enhancement.[65] Intimate apposition of the oral mucosa to the alveolar mucosa makes assessment of small oral tumours particularly difficult with both CT and MRI and cheek puffing has been used as a manoeuvre on CT to separate surfaces.[66, 67] This is not possible with MRI because of long-imaging sequences but the placement of a rolled piece of gauze into the oral vestibule before MRI scanning improves visualization of small tumours.[68]

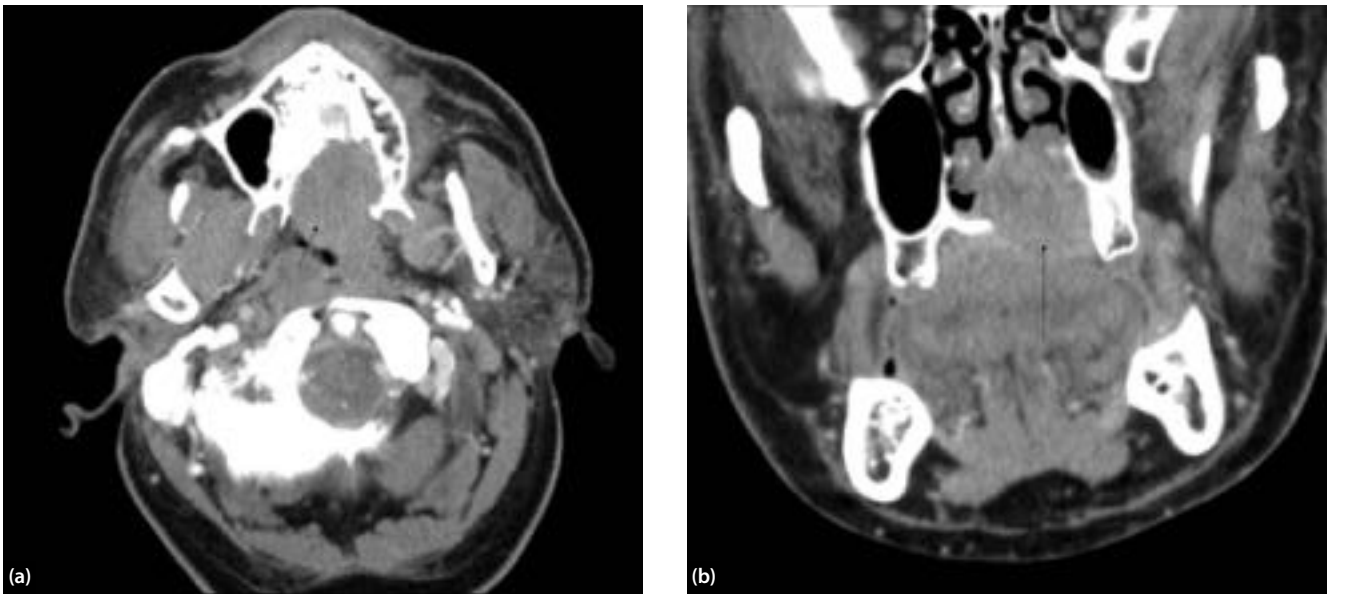


Figure 37.15 Axial **(a)** and coronal reformatted **(b)** contrast-enhanced CT showing left sided destructive hard palate SCC (black arrows) extending into nasal cavity.

MRI is an accurate method for the assessment of oral cavity malignancies, presence of mandibular involvement and the evaluation of depth invasion, with 9.5 mm in one study being the depth cut-off value for determining positive nodes.[69, 70]

In the initial staging of patients with oral cavity tumours, the use of PET with a contrast-enhanced CT is a reliable alternative to the combination of PET/plain CT and a separate diagnostic CT, with a sensitivity of 96% for detecting the primary tumour and a sensitivity of 89% and a specificity of 81% for cervical metastases.[71] An open mouth PET-CT can improve anatomical tumour localization, tumour extent and detection of involvement of adjacent structures when compared to a standard examination.[72] In the study by Seitz et al.[73] PET-CT was not superior to MRI but Baek et al.[74] showed that PET-CT provided further useful clinical information about the primary oral cavity tumour in patients in whom dental artefacts distorted the conventional CT or MRI images. Kim et al.[75] also showed that FDG-PET was more sensitive than CT or MRI in the staging of oral cavity tumours. A SUV nodal maximum of 5.7, either alone or in combination with extracapsular spread, is an independent prognostic indicator for 5-year neck cancer control and survival rates in oral cavity tumour patients with pathologically positive lymph nodes.[76] Furthermore patients with the combination of primary tumour SUV equal to or greater than 19.3 and pathological tumour depth equal to or greater than 12 mm are at greatest risk of poor local control and death.[77] A significant difference has also been shown in maximum SUV on PET-CT between nodes with and without extracapsular spread and a cut-off SUV value of 2.5 is associated with a greater risk of cervical lymph node metastasis.[78] PET and PET-CT however only had a sensitivity of 77.7% and a specificity of 58% in detecting cervical metastases in the primary staging of 473 patients with SCC of the oral cavity.[79] PET-CT and US can be complementary tools in the pre-operative evaluation of patients with SCC of the oral cavity.[80]

Evaluation of whether there is marrow or cortical involvement of the maxilla or mandible by SCC of the oral cavity is crucial for the surgeon to obtain both radical tumour resection and good functional results. In the case of tumours related to the mandible, resection can vary from a shaving of the lingual cortex, rim resection or segmental mandibulectomy. Many surgeons advocate periosteal stripping for tumours adjacent to the mandible at the time of surgery but accurate imaging does help the surgeon plan the treatment options and allows for an informed discussion with the patient prior to surgery. Abd El-Hafez et al. found that PET-CT was more specific than MRI (84% versus 61%) but less sensitive (78% versus 97%) for detection of bone-marrow invasion of the mandible and maxilla, with dental status and tumour origin affecting the diagnostic performance of PET-CT. They concluded that a negative MRI could confidently exclude the presence of bone-marrow invasion while in patients with positive MRI findings, a negative PET-CT was useful in ruling out bone marrow invasion in dentate patients.[81] Gu et al. noted sensitivity, specificity and accuracy of 41.7%, 100% and 84.8% for CT and identical figures of 58.3%, 97.1% and 87% for MRI and PET-CT in the detection of mandibular invasion. The combined use of CT, MRI and PET-CT improved sensitivity to 83.3% without loss of specificity and accuracy but this did not reach statistical significance.[82] Although Vidiri et al. showed that MRI had a higher sensitivity than CT in the assessment of mandibular involvement from SCC of the oral cavity, this did not reach statistical difference.[83] Cone-beam CT (**Figure 36.16**) has been shown to be accurate in predicting bone invasion in patients with oral malignancies, competing well with

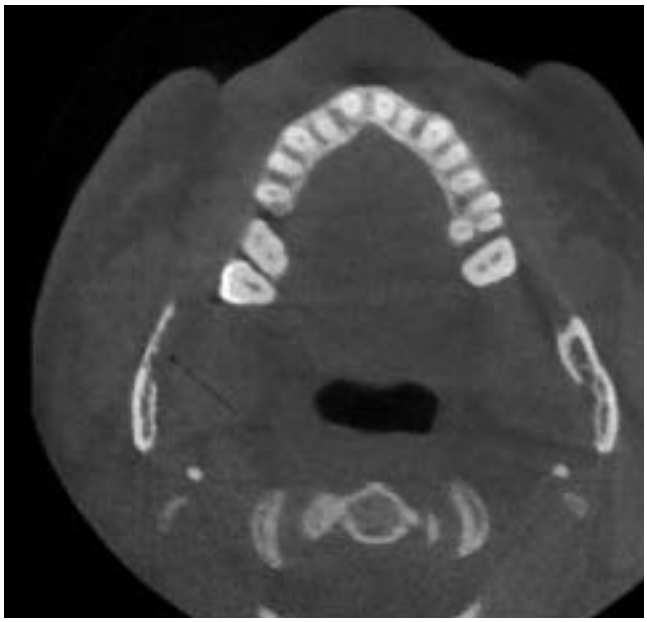


Figure 37.16 Cone-beam CT showing destruction of the inner cortex of the right mandible (arrow) in a histologically proven intraosseous SCC.

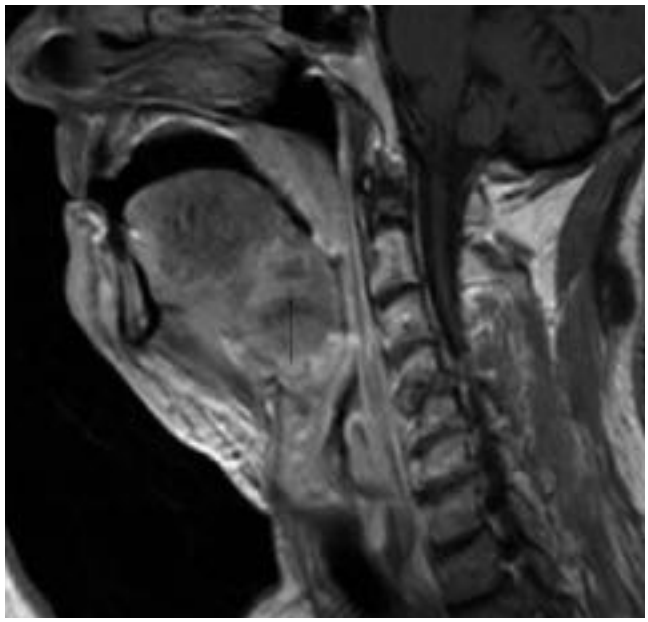


Figure 37.17 Post-gadolinium sagittal T1W MRI showing histologically proven residual tumour (black arrow) six weeks after completing chemoradiotherapy for a large tongue tumour.

CT and single photon emission computerized tomography (SPECT).[84] It therefore appears that CT, MRI and PET-CT all have strengths and weaknesses in assessing bone involvement by SCC and imaging needs to be assessed on a case-by-case basis depending on the site of tumour and local expertise.

Treatment of the clinical N0 neck in SCC of the oral cavity remains a dilemma because of the inability to detect micrometastases on conventional cross-sectional imaging including PET-CT.[85, 86] Although guided FNA seems to correlate best with histological staging for exact N classification compared with CT and PET-CT, it is still not reliable enough to replace elective neck dissection in the N0 neck.[87] The detectability threshold of occult metastases is below the spatial and contrast resolution of CT, MRI and 18FDG–PET in oral cancer patients staged as T1 or T2 and clinically negative neck.[88] Although PET-CT has been shown to perform better than CT or MRI, the sensitivity and specificity of PET-CT in detecting occult cervical metastases varies between 50–64% and 81–97% respectively.[71, 89] There appears to be some value in volume-based PET-CT in patients with clinically node negative oral cancer.[90] Magnetic resonance lymphangiography has limited diagnostic value compared with US with or without fine-needle cytology and CT in the pre-operative staging of the N0 neck.[91] Based on the available evidence, cross-sectional imaging including PET-CT cannot be used in deciding whether to proceed to elective neck dissection or not in N0 patients.

The imaging of post-treatment patients with oral cancer is problematic. The combined use of PET and contrast-enhanced CT for post-treatment monitoring of cancers of the oral cavity has steadily increased in recent years as residual/recurrent disease at the primary site, extent of nodal disease and distant metastases can be assessed. However interpretation of the first follow-up post-treatment PET-CT is challenging and a period of 12 weeks post-treatment is usually recommended to reduce false positive findings.[92, 93] CT or MRI (**Figure 37.17**) rather than PET-CT should be performed during this waiting period of 12 weeks should imaging be required.

OROPHARYNGEAL TUMOURS

The subsites of oropharyngeal tumours include the tongue base and valleculae anteriorly, the tonsils and glossotonsillar sulci laterally, the inferior surface of the soft palate and uvula superiorly and the posterior wall posteriorly.

Tonsillar cancer

Almost all tonsillar tumours originate from the anterior tonsillar pillar (**Figure 37.18**) and commonly spread to the tongue base and soft palate along the palatoglossal muscle and to the pterygomandibular raphe and RMT along the pharyngeal constrictors. Advanced lesions may spread through the pharyngeal wall to the parapharyngeal space (PPS) and along the pharyngeal wall to the nasopharynx superiorly and hypopharynx inferiorly. Once tumour has spread into the PPS it can extend freely to the skull base and into the carotid and masticator spaces.

Tongue base tumours

These tumours are often clinically silent and may spread along the palatoglossal muscle to involve the anterior tonsillar pillar and along the hyoglossal and mylohyoid muscles to the floor of mouth (**Figure 37.19**). Differentiation of

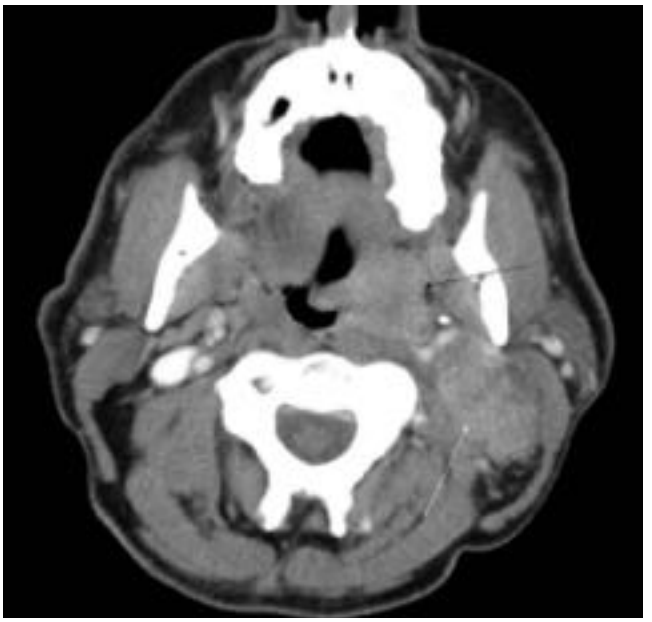


Figure 37.18 Axial contrast-enhanced CT showing large left tonsillar SCC (black arrow) with associated level 2 node (white arrow).

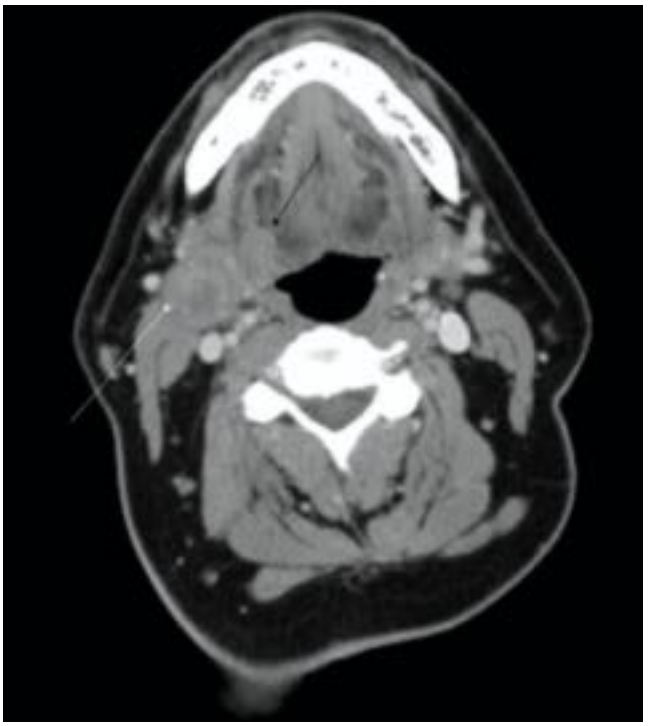


Figure 37.19 Axial contrast-enhanced CT showing right tongue base tumour (black arrow) with associated metastatic right level 2 node (white arrow).

tongue-base tumours from normal lingual lymphoid tissue may be difficult on all cross-sectional imaging.

Soft palate cancer

These tumours usually spread along the tonsillar pillars and in advanced disease on to the nasopharynx.

Posterior oropharyngeal wall cancer

These are rare tumours but more commonly the posterior oropharyngeal wall is invaded by cancers originating from the lateral oropharyngeal wall (**Figure 37.20**). Imaging plays a role in excluding invasion of the prevertebral muscles by demonstrating preservation of the retropharyngeal fat plane with a negative predictive value of 82–97.5% but predicting involvement of the prevertebral space is poor by cross-sectional imaging.[94, 95]

Oropharyngeal tumours spread by direct extension over mucosal surfaces, muscle and bone, along neurovascular bundles and via lymphatic drainage pathways. Imaging needs to evaluate these three routes of spread for accurate staging.[96, 97] Because nodal involvement is the single most important prognostic indicator, accurate assessment of all nodal chains is paramount. Extracapsular spread, detected on imaging by poorly defined nodal margins and surrounding soft-tissue stranding (**Figure 37.21**), is associated with a 3–5-fold increase in local recurrence. US has been shown to discriminate extranodal positive from extranodal negative SCC nodes with comparable accuracy and higher specificity than MRI.[98]

The advantages of staging oropharyngeal tumours with CT are that subtle cortical erosions can be detected

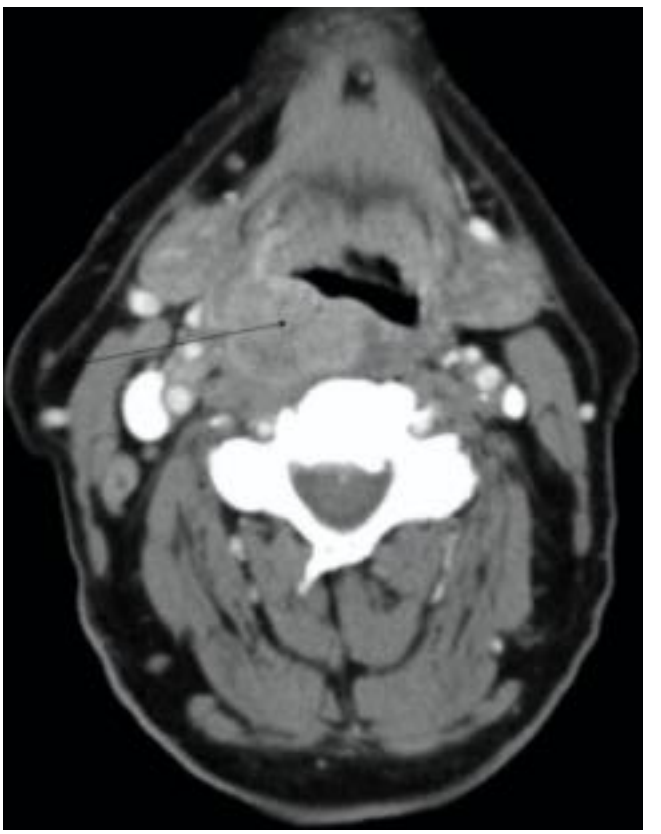


Figure 37.20 Axial contrast-enhanced CT showing large right oropharyngeal tumour involving the posterior oropharyngeal wall (black arrow) and closely apposed to the prevertebral muscles.

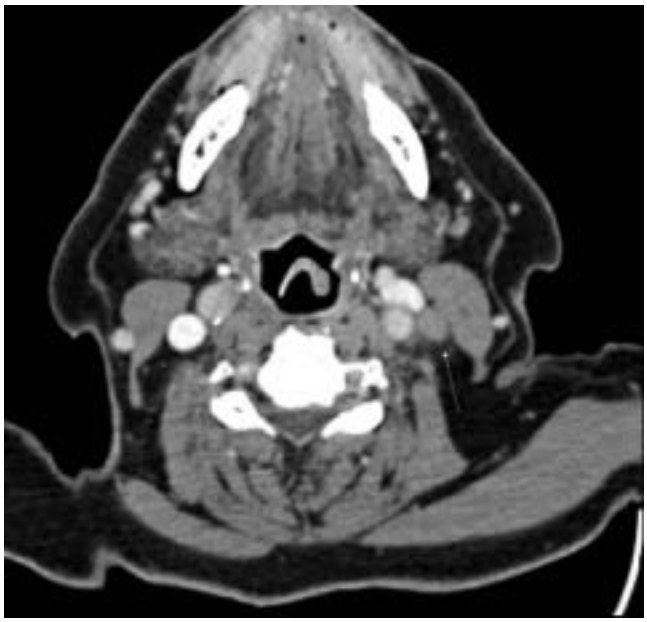


Figure 37.21 Axial contrast-enhanced CT showing a small ill-defined left level 2 node with streakiness to surrounding fat (arrow), histologically confirmed extracapsular spread.

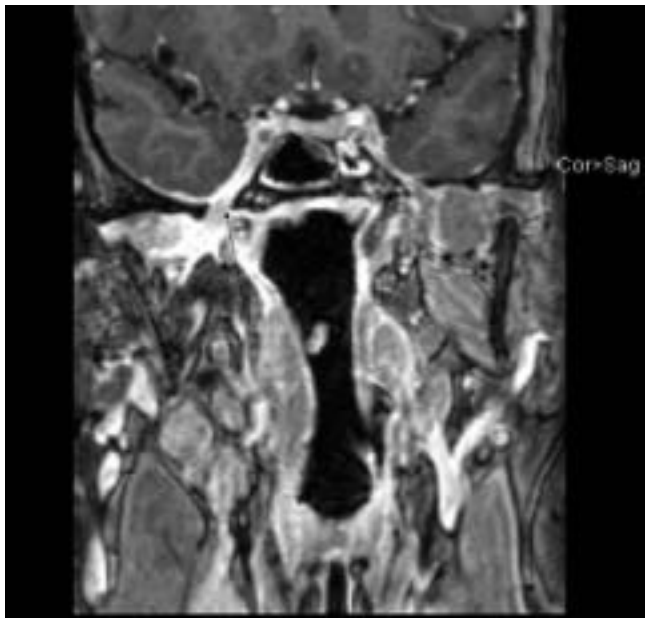


Figure 37.22 Coronal reconstruction of a post gadolinium VIBE (volumetric interpolated brain examination) showing perineural tumour spread along the right mandibular branch of the trigeminal nerve through the foramen ovale (black arrow) and on to the cavernous sinus.

and the chest can be included in the same sitting.[99] MRI is particularly useful in assessing perineural spread (**Figure 37.22**) and bone marrow involvement.[100] It is also an accurate method for measuring tumour invasion depth in the tongue base and this can have a predictive value for nodal metastases, with a cut-off depth of invasion of the tongue base by 14.5 mm for positive nodes.[69]

PET has a higher sensitivity than CT/MRI for detection of primary tumour and cervical metastases but no difference in specificity.[101] The use of a contrast-enhanced CT with conventional PET as a one-step examination has been shown to be a reliable initial staging examination.[71, 102] PET-CT has a higher sensitivity and diagnostic capability than 3T whole body MRI for the detection of distant metastases and second primary tumours.[103, 104] Similarly, PET has been shown to be more sensitive than extended field-multidetector CT for detecting distant metastases albeit with more false positive findings.[105] A pre-treatment PET-CT can be used as a staging tool to aid in treatment planning of SCC of the oropharynx with rates of retropharyngeal and nodal metastases consistent with those in the literature.[106]

Patients often present with a nodal mass and no obvious primary tumour on clinical inspection, the so-called unknown primary, the majority of tumours being in the tonsil and tongue base. PET-CT is particularly good at detecting the unknown primary but is complicated by the normal physiological uptake in these areas (**Figure 37.23**). There is considerable variation in pharyngeal palatine tonsil uptake in normal patients but generally only a small difference between left and right sides and an absolute difference between the maximum SUV between the two sides of 0.83 may be useful in detecting an occult tonsillar carcinoma.[107] Diffusion-weighted MRI is showing some

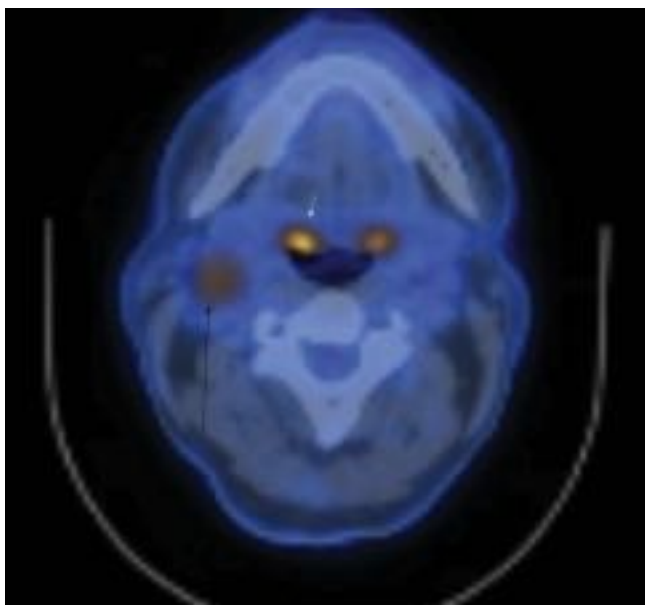


Figure 37.23 Axial-fused PET-CT showing increased activity in the right tongue base (white arrow) in a patient presenting with a right sided neck mass (black arrow) and no apparent primary on clinical examination or conventional CT. Note the normal physiological activity in the left tongue base.

promise in distinguishing between normal lymphoid tissue and SCC of the palatine tonsil.[108]

Oropharyngeal cancer is treated with curative intent by surgery, radiotherapy with or without chemotherapy or a combination of the two. The relationship between tumour volume and local outcome is less pronounced in oropharyngeal cancer compared to other head and neck tumours. However pre-treatment FDG-tumour uptake represents

an independent prognostic factor in patients with oropharyngeal SCC and patients with high FDG uptake may be better treated by surgery followed by radiotherapy with or without chemotherapy.[109] Perfusion CT provides a rapid, reliable and non-invasive technique for assessing tumour vascularity and may predict response to induction chemotherapy and mid-term remission-free survival in patients with advanced oropharyngeal SCC.[110] Treatment of the clinical N0 neck in T1 and T2 oropharyngeal cancer, as in oral cancer, remains a dilemma as CT, MRI and PET-CT all fail to detect the presence of lymph node micrometastases reliably.[86–90]

Response to definitive treatment with radiotherapy with or without chemotherapy is a powerful predictor of outcome.[111] In the post-therapy setting in patients with oropharyngeal cancer, imaging with PET-CT can have considerable influence on clinical decision-making as early detection of residual disease/recurrence enables salvage surgery to be carried out as soon as possible while neck dissection is only performed if there is evidence of residual nodal disease.[112, 113] Accurate assessment of response to treatment is therefore essential to optimize the chance of cure in those patients with residual disease and to minimize unnecessary surgery in patients who have been successfully treated. Several studies have shown that the use of PET-CT is superior to conventional imaging in response assessment as small residual nodes are common following treatment and radiation-induced changes are difficult to distinguish from residual disease using CT or MRI.[114, 115] The sensitivity of PET for detecting residual or recurrent cancer is high, in the range of 84–100%.[116, 117] The timing of PET-CT after treatment is critical to accurately differentiate residual disease from inflammatory changes secondary to treatment and thereby increase specificity. PET-CT performed between 12 and 16 weeks post-treatment has high diagnostic accuracy of response assessment.[118, 119] Should disease progression be suspected in the immediate post-treatment period, then contrast-enhanced CT or MRI and not PET-CT should be performed.[93] Diffusion-weighted MRI 2–3 weeks after completion of treatment has the potential to allow prediction of treatment response at the primary site.[13, 120, 121]

Regular surveillance is especially important in the first 2 years after treatment since the vast majority of disease recurrences are found during this period and PET combined with contrast-enhanced CT can be performed when there is a suspicion of recurrence.[118, 122, 123] However, there does not appear to be a role for blanket surveillance PET-CT at 12 and 24 months for detecting recurrence.[124]

HYPOPHARYNGEAL TUMOURS

Hypopharyngeal cancers are usually SCC and have the worst prognosis among head and neck cancers. They are insidious tumours, commonly presenting with a lump in the neck, secondary to metastatic nodal involvement, or dysphagia, otalgia, weight loss and hoarseness when the recurrent laryngeal nerve is involved. The trend of these tumours to spread in a submucosal fashion makes accurate delineation by cross-sectional imaging of paramount importance in planning treatment. The most important features determining prognosis are the size and local spread of the primary tumour and the extent of nodal involvement.[125]

The hypopharynx extends from the oropharynx to oesophageal verge and is divided into three regions, pyriform sinus or fossa, post-cricoid region and posterior hypopharyngeal wall, with distinct spread patterns of tumours in each region. Tumours arising from the lateral aspect of the pyriform sinus (PS) invade the posterior aspect of the thyroid cartilage and can extend into the paraglottic space and soft tissues of the lateral compartment of the neck (**Figure 37.24**). Tumours arising from the medial aspect of the PS show early laryngeal invasion. Posterior hypopharyngeal tumours (**Figure 37.25**) tend to grow in a cranio-caudal direction while tumours in the post-cricoid region (**Figure 37.26**) tend to invade the posterior aspect of the larynx.

The important points in staging are evaluating all the hypopharyngeal subsites, the larynx, thyroid cartilage, nodal status, distant metastases and any other synchronous primary, especially oesophageal carcinoma.[104, 126,] Imaging usually results in upstaging the tumour.[127, 128] Contrast-enhanced CT performed during quiet breathing is the preferred method of evaluating the hypopharynx due to its shorter acquisition time, facility for multiplanar reconstruction and ability to assess the chest and abdomen in one sitting. Three-dimensional CT laryngography with modified valsalva manoeuvre is informative for the diagnosis of PS apex involvement.[129] CT has also been shown to be a reliable method for assessing tumour volume with CT-based tumour volume being a predictor of outcome after treatment with both radiotherapy and surgery.[130–132]

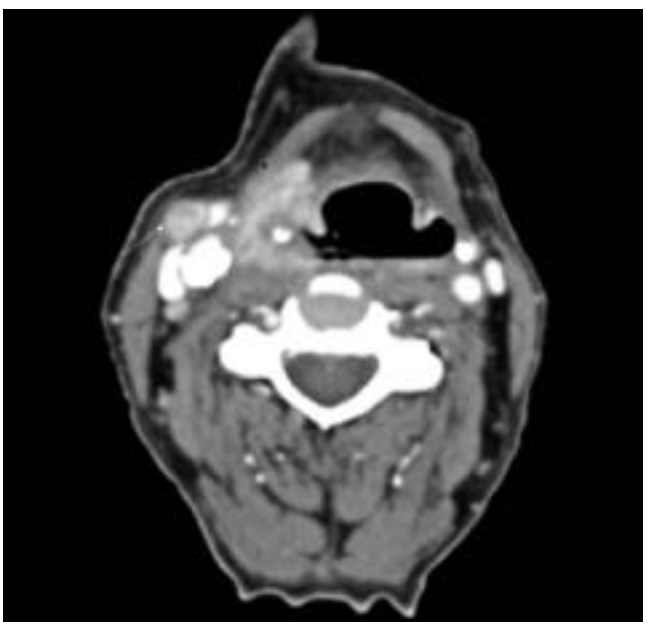


Figure 37.24 Axial contrast-enhanced CT showing right pyriform fossa tumour just extending into the paraglottic space and extralaryngeal soft tissues (black arrow) with associated metastatic level 3 node (white arrow).

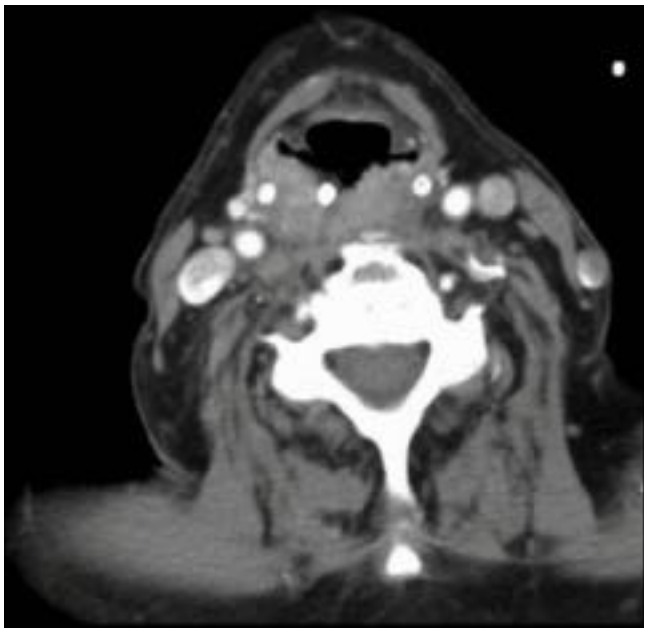


Figure 37.25 Axial contrast-enhanced CT showing a large hypopharyngeal posterior wall tumour extending on to the prevertebral muscles.



Figure 37.26 Axial contrast-enhanced CT showing a post-cricoid carcinoma (black arrow) extending on to the prevertebral muscles.

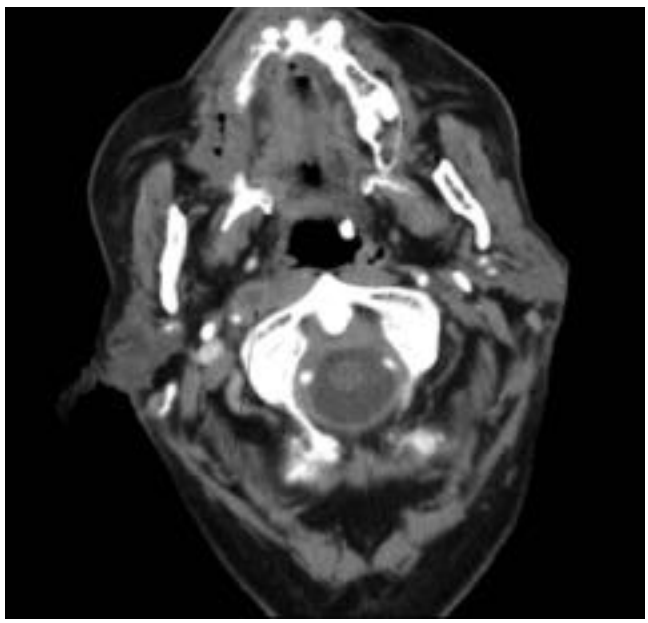


Figure 37.27 Axial contrast-enhanced CT showing a necrotic right retropharyngeal node (black arrow) in a patient with a hypopharyngeal posterior wall tumour.

Correct assessment of nodal status is essential as hypopharyngeal cancer has a high risk for early regional lymph node dissemination and metastatic nodal disease still remains the single most important negative predictor. CT perfusion has been suggested as a way of distinguishing malignant from non-malignant nodes.[133] Deng et al. noted a regional lymph node metastatic rate of 73.9% on CT/MRI images in 88 patients with hypopharyngeal cancer, the highest rates being at level 2 and 3, with bilateral disease a potential risk factor for retropharyngeal node metastases.[134] Tumours originating from the posterior wall of the hypopharynx not only show a significantly higher incidence of retropharyngeal nodal metastases (**Figure 37.27**) as demonstrated by CT and/or MRI than other subsites but have a high incidence of distant metastases resulting in dismal outcomes.[135] FDG-PET has been shown to be helpful in detecting retropharyngeal nodal metastases in hypopharyngeal cancer, which should be suspected in patients with tumours originating from the posterior pharyngeal wall and those with ipsilateral level 5 lymph node metastases.[136]

PET-CT in hypopharyngeal cancer, just as in oropharyngeal cancer, has a higher sensitivity than 3T-MRI or CT for the detection of distant metastases and second primary tumours.[103–105] PET-CT has a high sensitivity for detection of residual and recurrent tumour following surgery and radiotherapy.[125]

LARYNGEAL TUMOURS

Laryngeal carcinoma is the commonest head and neck malignancy, comprising 30–40% of all cases, the vast majority being SCC. Most laryngeal tumours present with hoarseness and less commonly with a neck mass, dysphagia, stridor or haemoptysis. Around 80% of tumours are glottic, arising from the vocal cords, 15% are supraglottic, arising from epiglottis, false cords or aryepiglottic fold (**Figure 37.28**) and 5% subglottic. Some tumours are transglottic involving all laryngeal levels (**Figure 37.29**). Although most laryngeal tumours are mucosal lesions and easily seen endoscopically, cross-sectional imaging frequently demonstrates the limitations of clinical and endoscopic examination in evaluating submucosal disease and cartilage invasion.

Imaging is important to identify the site and size of primary tumour, involvement of laryngeal cartilage and surrounding extralaryngeal structures, state of airway and nodal status.[127, 137–140] Multidetector CT is the preferred modality for evaluating laryngeal carcinoma given its widespread availability and ease of acquisition with

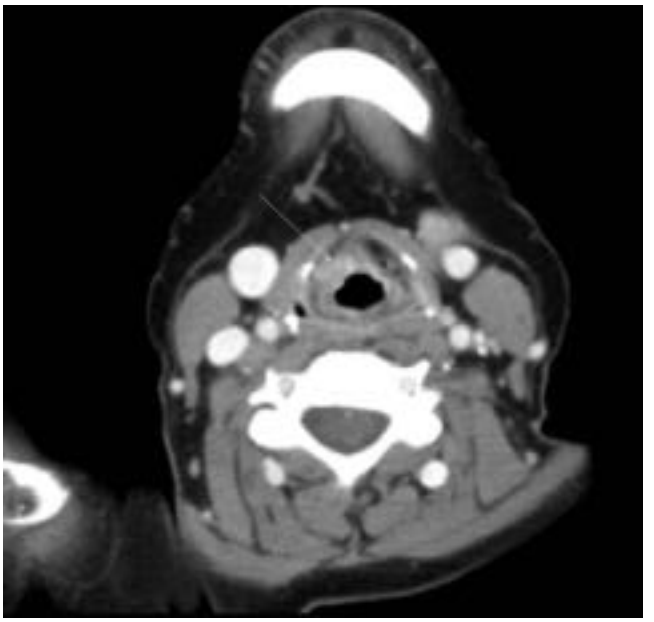


Figure 37.28 Axial contrast-enhanced CT showing a supraglottic tumour (white arrow) involving the epiglottis and right paraglottic space.



Figure 37.29 Axial contrast-enhanced CT showing a large left transglottic tumour (long black arrow) with completely destroyed left arytenoid (white arrow) and sclerotic left cricoid cartilage (short black arrow).

excellent multiplanar reformation while ultrasound, MRI and PET-CT are used as problem-solving tools. Functional imaging of the larynx on multidetector CT in the form of inspiration, phonation and valsalva and virtual laryngoscopy have a questionable role in staging.[141–143] The pretreatment staging accuracy of laryngeal carcinoma by CT has been reported to be between 84.9% and 88.8% on recent studies with problems in distinguishing tumour from peritumoral inflammation, identifying small tumours and predicting cartilage invasion.[142, 144–148] Incomplete ossification of the thyroid cartilage and asymmetric mineralization of the arytenoids make cartilage assessment difficult but the presence of tumour on both sides of the cartilage is said to be a useful imaging finding in predicting cartilage involvement.[149, 150] No statistical difference was seen in a study of 34 patients with laryngeal cancer between MRI and post-surgical pathohistology in tumour extension to the anterior commissure, pre-epiglottic space and subglottis as well as cartilage infiltration but paralaryngeal infiltration was overdiagnosed by MRI resulting in a correct T classification in 76% of those cases.[151] MRI overpredicts thyroid cartilage involvement although there is some evidence that contrast-enhanced MRI may differentiate inflammatory from neoplastic change and demonstrating a normal cartilage signal on MRI is reassuring.[152, 153] MRI is therefore more sensitive but less specific than CT in detecting neoplastic cartilage invasion.

In view of the sensitivity and specificity issues with CT and MRI, US (**Figure 37.30**) is being increasingly used as

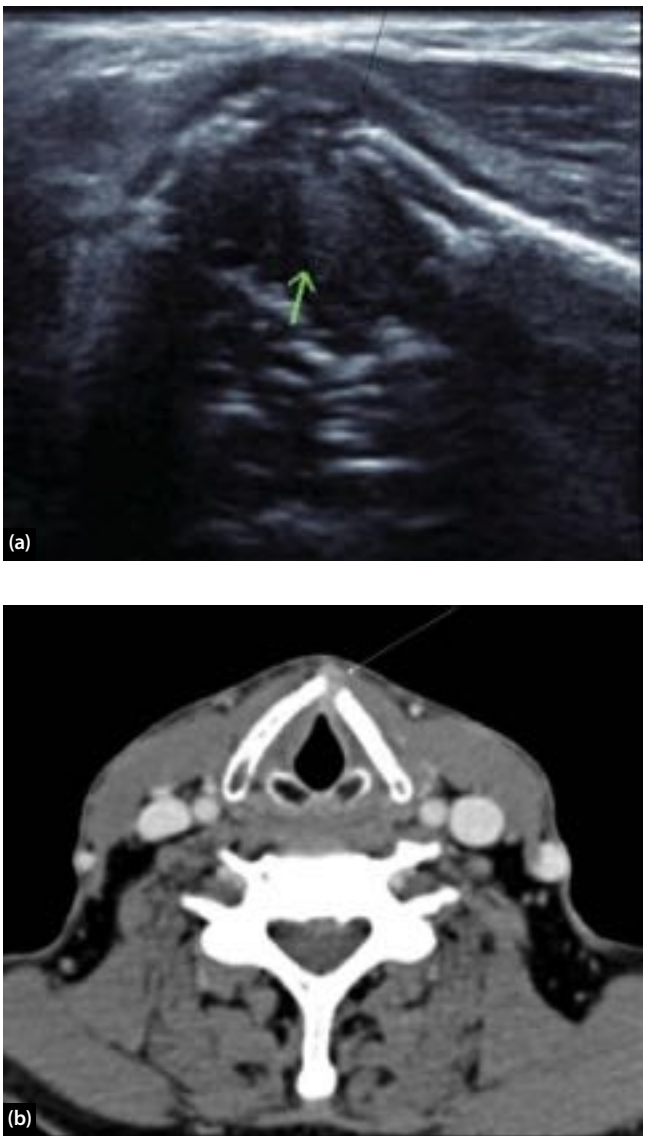


Figure 37.30 US of the larynx (a) showing a sizeable low reflectivity laryngeal tumour (thick arrow) extending through a defect in the thyroid cartilage (black arrow) with the corresponding contrast-enhanced axial CT **(b)** confirming extralaryngeal spread of tumour (white arrow).

a complementary technique in the evaluation of laryngeal cancer, which usually appears hypoechoic on ultrasound.[153] Hu et al. demonstrated an accuracy of 83.3% for US compared to 88.8% for CT and an accuracy of 80% for US compared to 76.5% for unenhanced MRI in the T-staging of glottic cancer, with US only being inferior in demonstrating tumour involvement in the retrolaryngeal structures.[145, 154, 155]

The performance of PET-CT not surprisingly is better than stand-alone PET or CT in patients with cancer of the larynx and can have a major impact on management.[156] However, as in the case of other head and neck tumours, it has no role in predicting the need for surgical neck dissection in the N0 neck.[157, 158]

The treatment of laryngeal cancer consists of surgery including laser resection, total or partial removal of the larynx and radiation therapy, either as a cure or as an adjunct after radiotherapy. Conservative laryngeal surgery preserves a portion of the larynx so that a voice can be produced while obtaining the same local control as that provided by total laryngectomy. Appreciating the normal imaging findings following both partial and total laryngectomy is important in the interpretation of cross-sectional imaging.[159–161] Hemithyroidectomy used to be performed as part of total laryngectomy but this practice is now being questioned and pre-operative evaluation of any thyroid gland involvement is essential in deciding whether to preserve the thyroid gland. [162] Laryngeal oedema following radiotherapy is common, particularly affecting the supraglottis, and may mask recurrence.[163]

Imaging for recurrence following treatment to laryngeal cancer includes CT, MRI and PET-CT.[164] PET-CT is useful in detecting local residual tumour after treatment and has been suggested as a cost-effective means of selecting patients for direct laryngoscopy in suspected recurrence following radiotherapy.[165–167] PET-CT however has too high a false negative rate to warrant deferring neck dissection in the N0 neck in suspected recurrence following treatment.[168]

Lymphoma is a rare tumour of the larynx that classically presents as a large uniformly enhancing submucosal mass showing no necrosis centred in the supraglottis that extends into the glottis. Cervical adenopathy is not usually present and as in SCC, lymphoma may extend into the subglottis, pharynx and laryngeal cartilages.[169, 170] Sarcomas make up about 0.3–1% of all laryngeal malignancies of which chondrosarcomas show specific imaging findings with an expansile defect in either the thyroid or cricoid cartilages (**Figure 37.31**).



Figure 37.31 Axial contrast-enhanced CT showing low grade chondrosarcoma (black arrow) centred around an expanded and remodelled right cricoid cartilage.

NECK LUMPS

The imaging of patients presenting with a neck lump depends on the age of the patient, clinical history and location of the mass.

The majority of neck lumps in children are simply due to reactive lymph nodes secondary to an upper respiratory tract infection, earache or toothache and if small, soft and mobile and associated with an upper respiratory tract infection will usually regress within 3 weeks. In such cases, no imaging is required and the parents are simply reassured and asked to return if the child becomes systemically unwell or if the swelling increases in size. Children with fever, hepatosplenomegaly, weight loss or night sweats and nodes greater than 3 cm should have a chest X-ray, screening blood tests including a full blood count and serology especially for Epstein–Barr virus, and the neck imaged initially by ultrasound.[171] As a general rule, US will differentiate reactive lymphoid hyperplasia from lymphoma and identify abscess formation within nodes[172] and excision biopsy is necessary in only a very small proportion of cases.

Adult lymphadenopathy is more unusual than in children and any adult presenting with a suspicious neck lump should be imaged by US initially and if this appears suspicious or the entire deep extent cannot be ascertained, then CT or MRI are necessary.[173]

In the non-lymphadenomatous neck swellings, can US differentiate between a cystic or solid mass with CT and MRI serving as supplementary examinations in defining the exact anatomy prior to any surgery. The vast majority of cystic masses in children are congenital or developmental in origin and in adults inflammatory or malignant.

Thyroglossal duct cyst (TDC)

This is the most common congenital cystic mass and the second most common benign mass after benign lymphadenopathy. The thyroid primordia migrate down the neck along the thyroglossal duct which runs from the foramen caecum in the base of the tongue to the lower anterior neck and normally involutes in the 8th–10th week of gestation. If any portion of the duct persists, secretions from the epithelial lining may give rise to cysts and as the duct is intimately related to the hyoid bone, most occur either below (65%) or at the level of hyoid bone (15%). Seventy-five per cent of cases occur in the midline and the rest up to 2 cm off the midline.



Figure 37.32 US showing a midline infrahyoid homogenous anechoic cystic mass with posterior wall enhancement (black arrow) in keeping with a thyroglossal duct cyst.

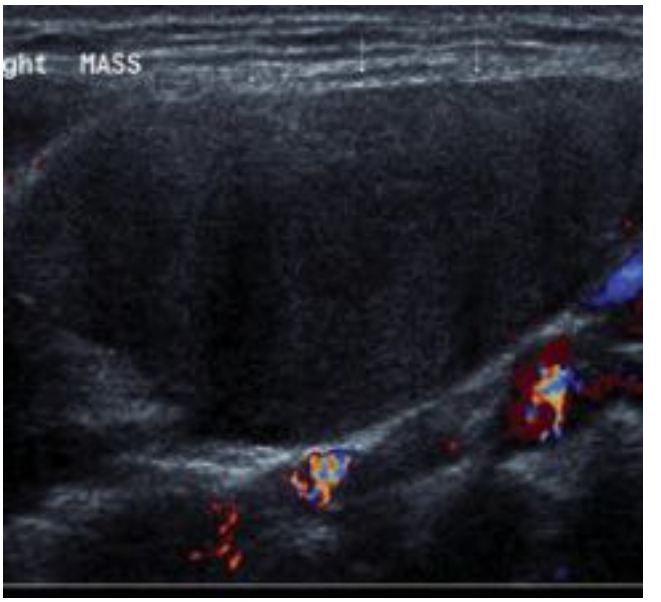


Figure 37.33 US showing an avascular, pseudosolid right level 2 mass in keeping with a second branchial cleft cyst.

On US TDCs (**Figure 37.32**) have a varied appearance ranging from a homogenous anechoic mass with posterior wall enhancement, a pseudosolid mass due to proteinaceous secretions or a mass with a heterogenous echo pattern due to previous haemorrhage or infection. A variable appearance is also seen on CT or MRI depending on the cyst contents but on MRI the cysts are invariably of high T2 signal and variable T1 signal depending on the amount of proteinaceous secretions.

The important imaging points are the relationship of the TDC to the hyoid bone, the presence or absence of normal thyroid tissue and whether any solid material is present within the cyst as there is a 1% incidence of carcinoma, classically papillary thyroid cancer (PTC) within TDC.

Second branchial cleft cyst (BCC)

Second BCCs account for 95% of all branchial cysts, typically occur between 10 and 40 years and classically present as a mass at the angle of the mandible superficial to the carotid sheath, posterior to the submandibular gland and along the anteromedial border of sternomastoid.

The sonographic appearances of second BCCs (**Figure 37.33**) is variable ranging from a classic anechoic simple cyst with posterior wall enhancement to a pseudosolid or heterogenous mass with internal debris and septae.[174] If on US a beak is identified pointing medially, then CT or MRI is warranted to exclude a sinus or fistula. On CT, classic second BCCs appear as homogenous low-attenuation masses with a thin wall and on MRI as masses of high T2 and low T1. On all imaging modalities, BCCs complicated by previous infection or haemorrhage appear as ill-defined, heterogenous, thick-walled masses containing debris and septae (**Figure 37.34**). Such a mass can cause confusion as a completely necrotic node from a head and neck SCC or a PTC may mimic BCC. If the patient is over 40, a smoker and drinks excessive alcohol, then such a mass has to be considered to be a metastatic SCC till proven otherwise and if a primary tumour is not identified clinically or by CT/MRI, then consideration should be given for PET-CT. In a younger patient, the mass is likely to represent a BCC or PTC and it is essential to look for other cystic masses especially around the thyroid gland as the primary tumour is often very small and not necessarily picked up by imaging.[175]

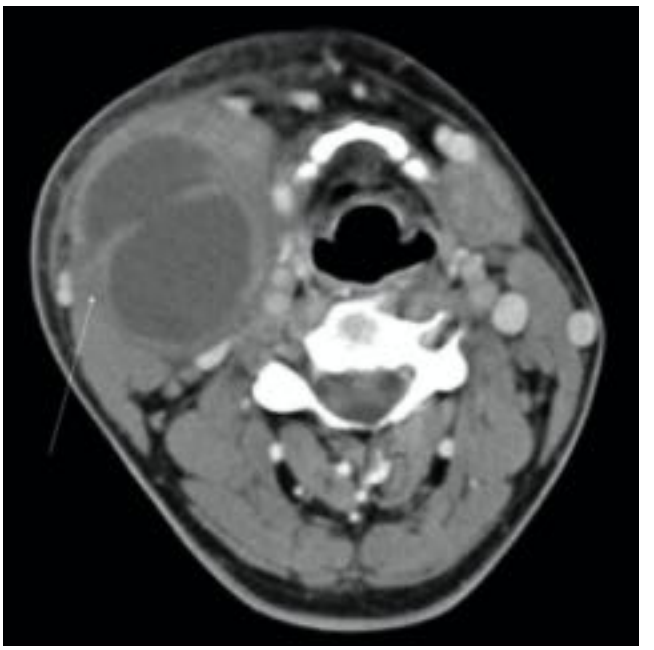


Figure 37.34 Axial contrast-enhanced CT showing a septated thick-walled right level 2 mass (white arrow) displacing the submandibular gland anteriorly and deep to sternomastoid in keeping with an infected second branchial cleft cyst.

Epidermoid/dermoid cyst

The difference between these two entities is histological, the more common dermoid cyst containing skin appendages such as sebaceous glands and hair follicles while an epidermoid cyst is entirely ectodermal. Epidermoids tend to present in infancy with dermoid cysts presenting later and both frequently occur in the submental or suprasternal regions in or close to the midline. These masses are usually well defined on imaging and may have a varied appearance on US (**Figure 37.35a**) varying from an anechoic mass with posterior wall enhancement to a pseudosolid appearance. Fatty content is pathognomic for a dermoid but in its absence, differentiation by imaging is not possible.[176] On CT the central cavity is usually filled with homogenous low-attenuation material (**Figure 37.35b**) but may appear to contain 'marbles' due to fat coalescing into small nodules within the fluid.

Ranula

This is a retention cyst resulting from obstruction of the duct to the sublingual gland and may be simple when confined to the floor of mouth or plunging when extending into the submandibular space. On US a simple ranula appears as a unilocular, well-defined cystic mass in the submental region related to the sublingual gland. It may contain fine internal echoes usually due to the presence of debris from previous episodes of inflammation.[177] On CT a simple ranula will appear as a solitary, low-attenuation, non-enhancing thin-walled mass and on MRI a mass of low T1 and high T2 signal. A plunging or diving ranula (**Figure 37.36**) forms from a ruptured ranula that extends either dorsally or caudally through defects in the mylohyoid muscle, the so-called boutonniere anomaly, into the submandibular space. As these plunging ranulas are effectively pseudocysts, there is usually some associated granulation tissue and may show enhancement on CT or MRI.

Salivary and thyroid gland masses

These will be discussed elsewhere in this section.

Lipoma

The head and neck is a typical site for lipomata which characteristically present as striped or feathery masses on ultrasound, masses of similar low attenuation as the surrounding fat on CT (**Figure 37.37**), and as masses of high T1 and T2 signal and low on fat suppression sequences on MRI.

Nerve sheath tumours

Nerve sheath tumours such as neurofibromas and schwannomas (**Figure 37.38**) may mimic lymph nodes on US as they can appear as diffusely hypoechoic masses with marked vascularity. They can also undergo cystic degeneration and then mimic cystic metastatic nodes.

Vascular malformations

Low-flow vascular malformations are common in the head and neck and comprise venous and lymphatic malformations or a combination of the two.

Venous malformations especially haemangiomas (**Figure 37.39**) are commonly found in the masticator space especially within the masseter muscle and phleboliths are seen in 22% of cases. The aim of imaging is to identify the extent of the lesion and the exact anatomical location.[178, 179] US usually suggests the diagnosis and further cross-sectional imaging is needed to ascertain its extent.

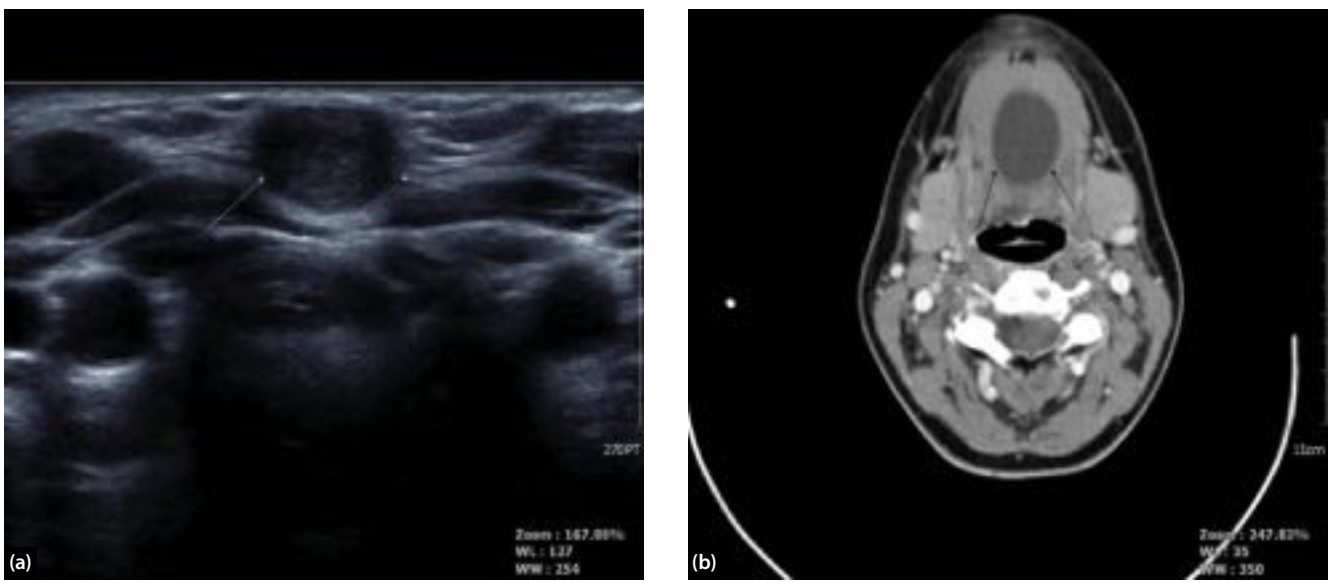


Figure 37.35 US **(a)** showing a midline, infrahyoid mass containing internal echoes (white arrows) in a child, a histologically confirmed dermoid and contrast-enhanced axial CT **(b)** showing a midline cystic floor of mouth dermoid (black arrows) in an adult.

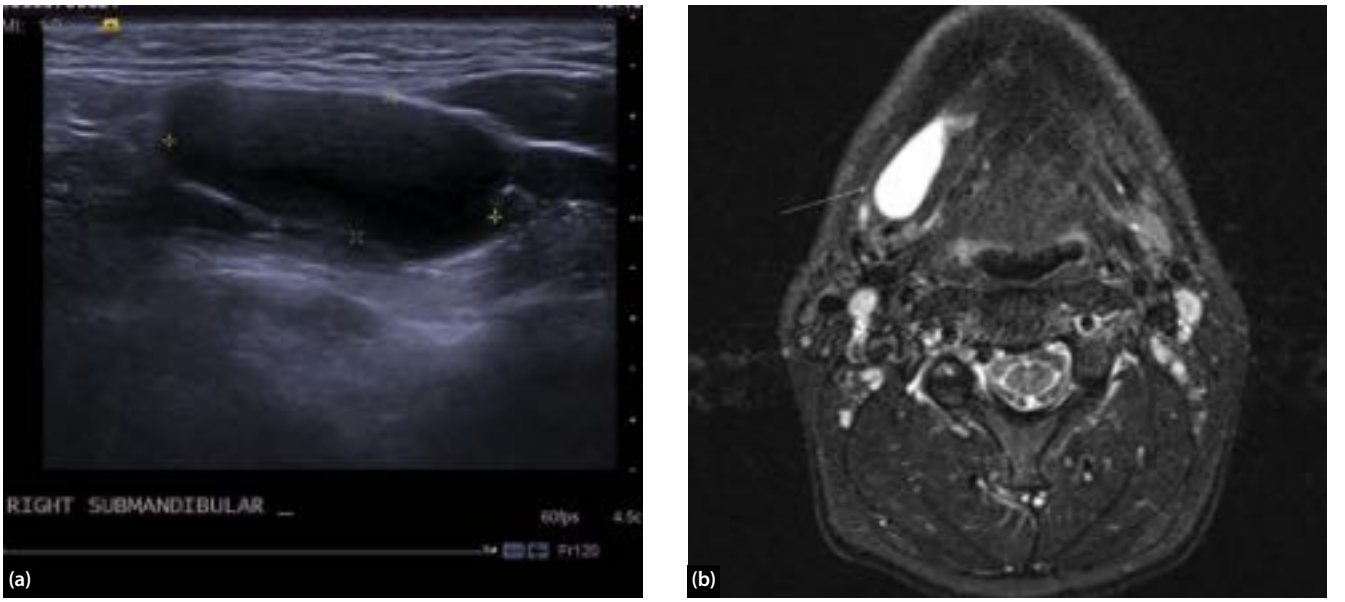


Figure 37.36 US **(a)** and axial STIR (short tau inversion recovery) MRI **(b)** of a cystic plunging ranula (white arrow) extending into the right submandibular space.

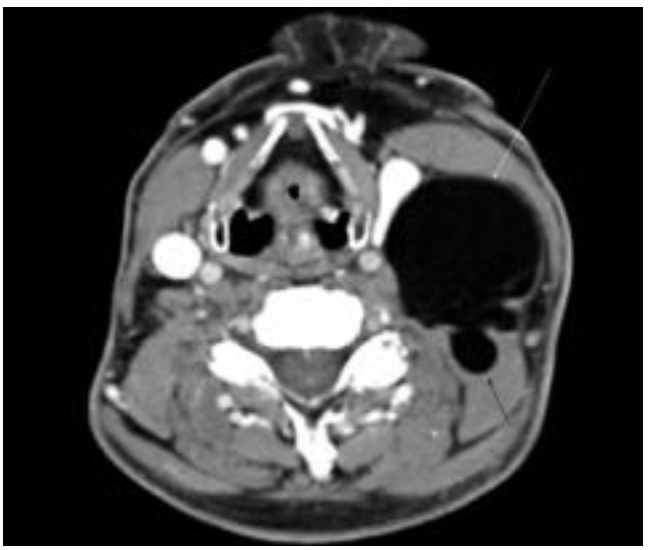


Figure 37.37 Contrast-enhanced axial CT showing a large lipoma deep to left sternomastoid (white arrow) and compressing the jugular vein. Note the small intramuscular component of the lipoma (black arrow) extending into levator scapulae.

US appearances are characteristic with the lesion showing a low reflectivity heterogenous echo pattern with multiple sinusoidal spaces. On MRI (**Figure 37.40**) venous vascular malformations show a striking high signal on T2-weighted sequences, including short tau inversion recovery (STIR). MRI is not as sensitive as CT or US in detecting phleboliths but shows the entire extent of the malformations very eloquently.

Lymphatic malformations or lymphangiomas are congenital abnormalities that arise when developing lymphatics fail to establish communication with developing veins.[180] The most common lymphangioma, also called cystic hygroma, typically presents in childhood as a

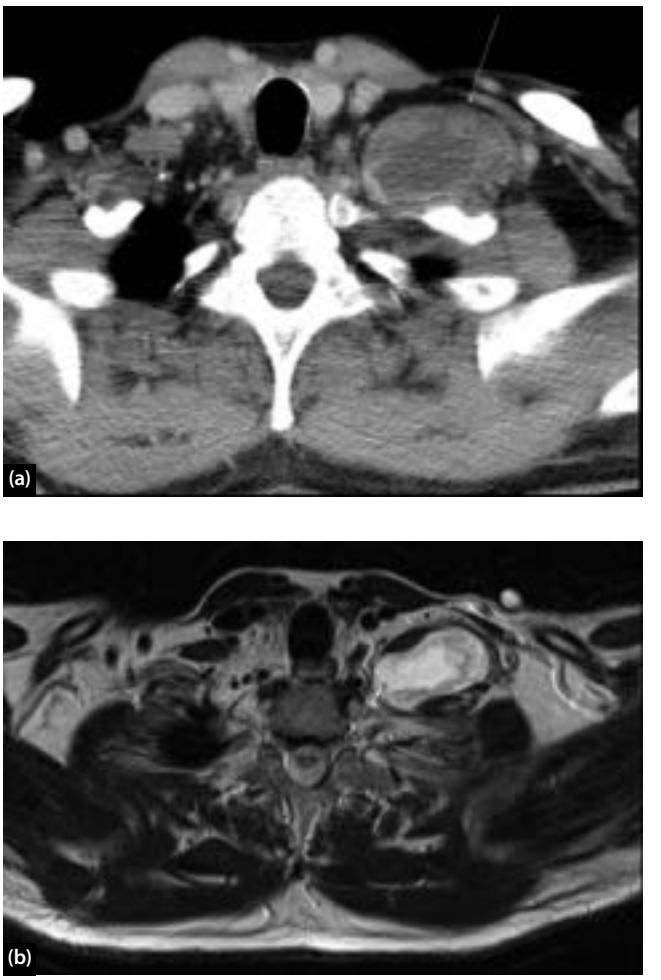


Figure 37.38 Contrast-enhanced axial CT (a) and T2 weighted axial MRI **(b)** showing left interscalene groove schwannoma (white arrows) arising from one of the branches of the brachial plexus.



Figure 37.39 Contrast-enhanced axial CT showing a non-enhancing haemangioma (white arrow) containing several foci of calcification (black arrow) in the right submandibular space.

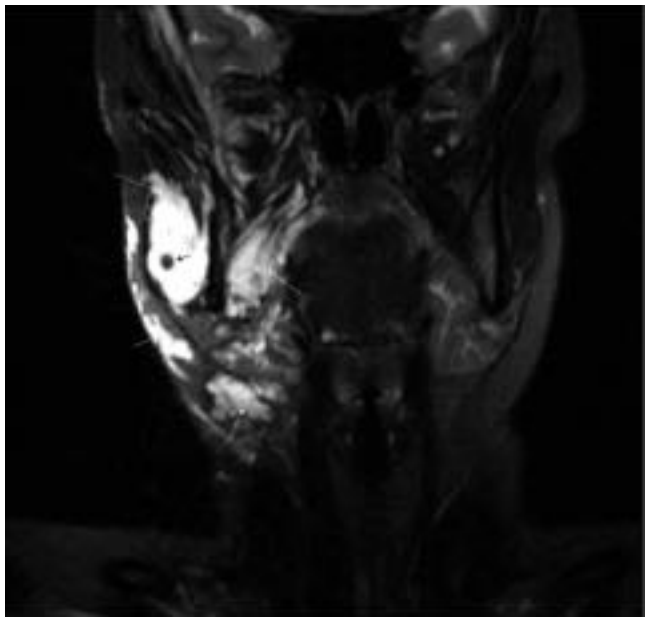


Figure 37.40 Coronal STIR (short tau inversion recovery) MRI showing a multifocal low-flow vascular malformation in the right side of neck involving the skin and several different spaces (white arrows) with a small plebolith (black arrow) within the masseteric component.

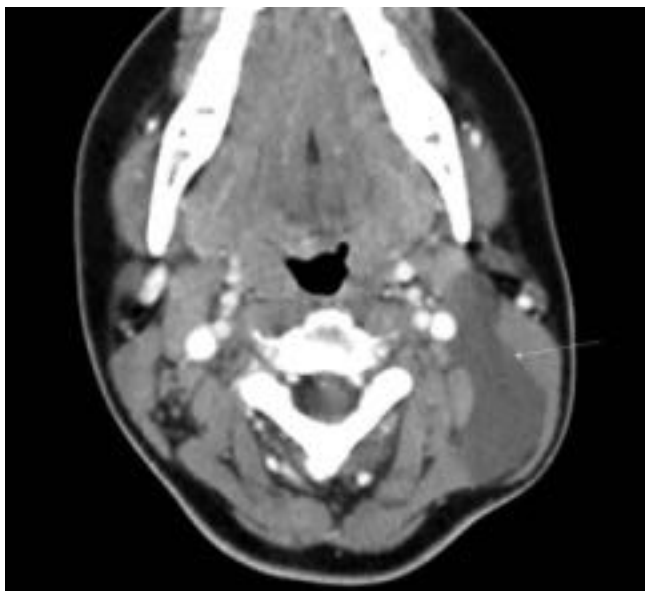


Figure 37.41 Axial contrast-enhanced CT showing a lymphangioma (arrow) within the left lateral compartment of neck deep to sternomastoid and abutting the internal carotid artery.

posterior triangle mass. Imaging usually reveals a multiloculated mass with septa of variable thickness that invaginates between vessels and other normal structures to occupy multiple contiguous spaces (**Figure 37.41**).

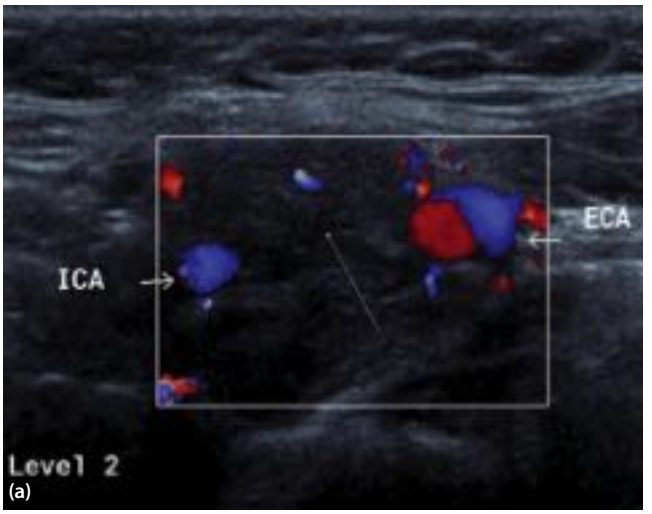
Paragangliomas

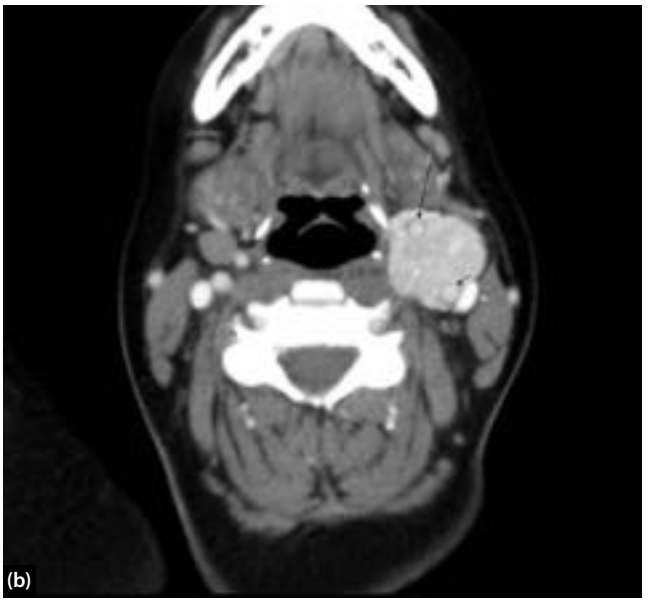
Paragangliomas are benign vascular tumours derived from primitive neural crest and occur anywhere along the carotid sheath as far as the skull base, the most common being the carotid body tumour (CBT).[181] CBT occurs at the bifurcation of the common carotid artery with resultant characteristic splaying of the internal and external carotid arteries (**Figure 37.42**). As the tumour increases in size, it may encase the carotid vessels but does not narrow their calibre.[182] Because of its site a CBT can be mistaken for an abnormal lymph node in the upper cervical chain. Other common paragangliomas are the glomus jugulare and glomus vagale arising from the jugular vein and vagus nerve respectively. The glomus vagale characteristically displaces the internal carotid artery anteriorly or medially and the jugular vein posteriorly. Paragangliomas may be familial and in such cases may be multiple and may very rarely show malignant transformation. On US paragangliomas do not appear particularly vascular despite showing avid enhancement on contrast-enhanced CT and MRI. They may show a characteristic 'salt and pepper' appearance on MRI (**Figure 37.43**) with the 'pepper' or low-signal appearance representing flow voids of feeding vessels.

Tuberculosis

Tuberculosis is commonly seen in the cervical lymph nodes but may occasionally be seen in the larynx or pharynx. The posterior triangle and supraclavicular nodes are frequently affected. In the early stage nodes may simply be enlarged and show homogenous enhancement on CT or MRI but later the nodes adopt the classical matted appearance with central necrosis (**Figure 37.44**).[183]

Atypical mycobacterial cervical adenitis is a cause of a unilateral persistent neck lump in a child under 5-years of age, often associated with an overlying violaceous skin appearance. US (**Figure 37.45**) reveals a marked decrease of echogenicity in the early stages and intranodal liquefaction with sinus tracts in the advanced stages.





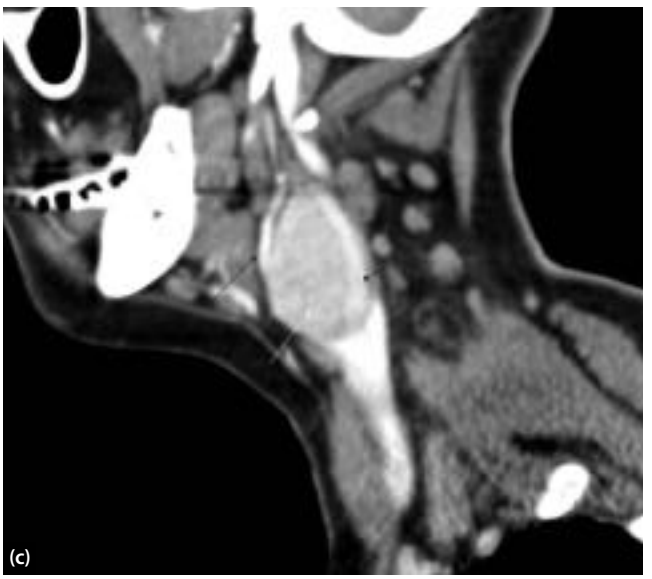


Figure 37.42 US **(a)**, axial **(b)** and sagittal reformatted **(c)** contrast-enhanced CT showing a level 2 mass (white arrows) lying between splayed internal (ICA, short black arrows) and external carotid arteries (ECA, long black arrows) consistent with a carotid body tumour. Note the carotid body tumour is avidly enhancing on contrast-enhanced CT but relatively avascular on US.

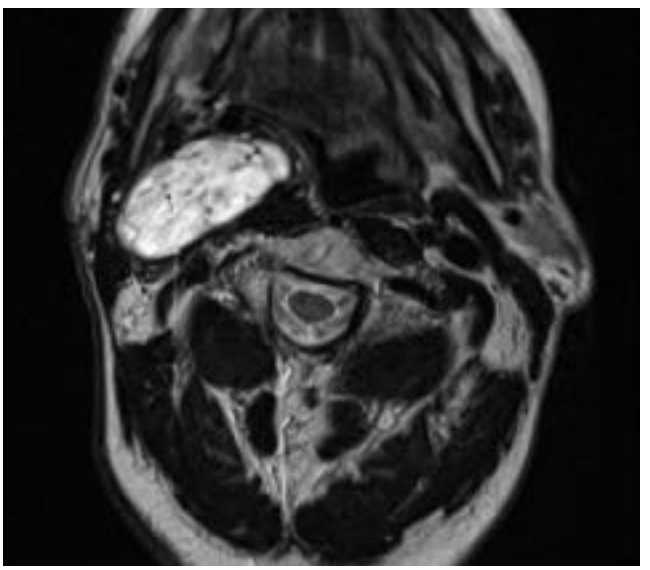


Figure 37.43 Axial T2-weighted MRI showing a high signal right carotid space mass (white arrow) containing several signal voids (small black arrows) consistent with a paraganglioma.

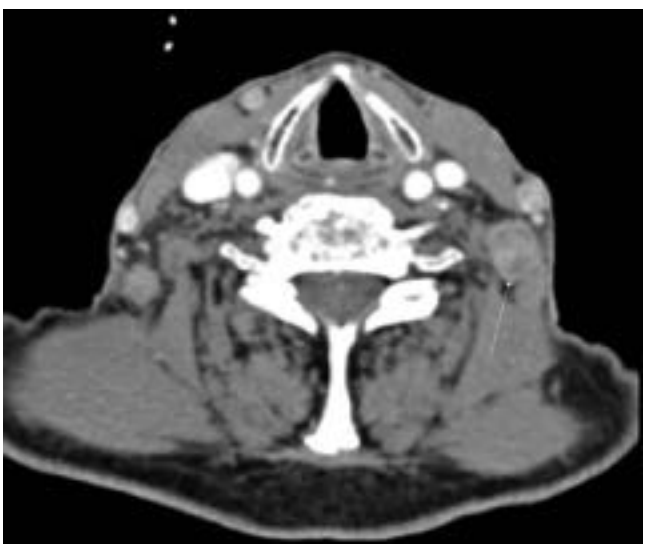


Figure 37.44 Axial contrast-enhanced CT showing tuberculous partly necrotic nodes in the left lower neck (white arrow).

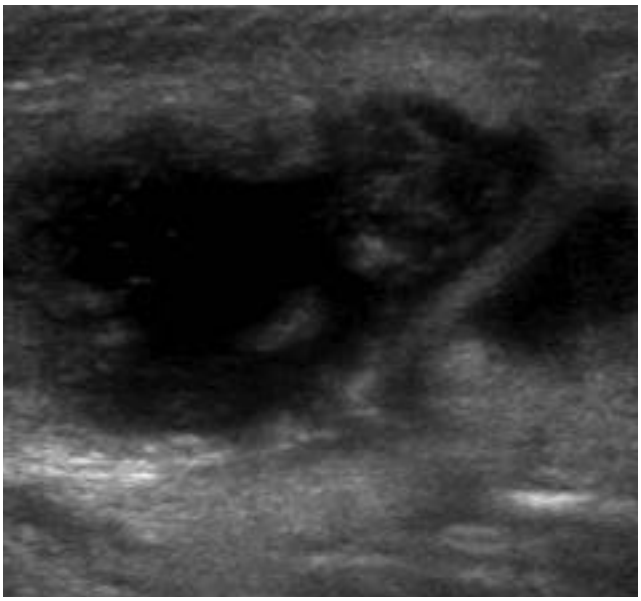


Figure 37.45 US of a child showing an irregular septated mass overlying which clinically was skin violaceous discoloration consistent with mycobacterial cervical adenitis.



Figure 37.46 US in a child, presenting with neck swelling and fever, showing a suppurative node (white arrow).

THE HOT NECK

Patients presenting with fever, pain, swelling, odynophagia, sore throat or trismus have to be considered to have neck sepsis and require imaging to assess whether surgical intervention is required (**Table 37.1**). The commonest sources are tonsillar or odontogenic infection. US should be the first-line investigation in children (**Figure 37.46**) and any superficial infection but contrast-enhanced CT of the neck and mediastinum is the imaging modality of choice to assess the extent of infection and any complications such as airway compromise, vascular thrombosis, neural dysfunction and ultimately necrotizing mediastinitis.[184–187] These complications may be life-threatening and surgery remains the mainstay of treatment but conservative medical treatment is effective in selected cases.[188] The patient's condition usually precludes the use of MRI but is extremely useful if a discitis and prevertebral abscess are suspected.

US is a very reliable diagnostic tool in the diagnosis of pus collections in the neck with a sensitivity of 96% and specificity of 82% and can show small collections to resolve without surgical drainage.[189] However should a parapharyngeal or peritonsillar abscess be suspected clinically, then CT rather than US should be performed.[190, 191] Meyer et al.[192] argue that as duration of localized symptoms of deep neck infection in children does not predict findings of abscess on CT, it is appropriate to obtain a CT scan upon presentation in all children with concerning symptoms for neck abscess. The findings on CT may include inflammatory stranding and loss of fat planes in cases of cellulitis, enhancing inflammatory phlegmon and abscess formation, characterized by a focal low-attenuation area with a surrounding enhancing rim (**Figure 37.47**). However, occasionally fluid collections without wall enhancement have yielded pus on surgical exploration.[193]

TABLE 37.1 Imaging in the Hot Neck, what the surgeon needs to know

Is there an abscess or just inflammatory change?
If an abscess is present, in which space/spaces?
How large is the abscess?
Extent of abscess
Is the mediastinum involved?
Is the airway compromised?
Is there jugular vein thrombosis?

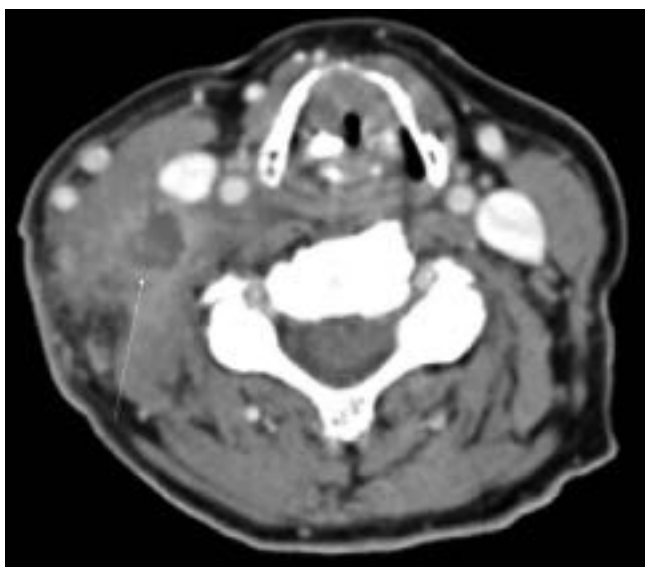


Figure 37.47 Axial contrast-enhanced CT showing a low-attenuation area with surrounding enhancing rim (white arrow) and surrounding inflammatory change consistent with an abscess in the lower neck.

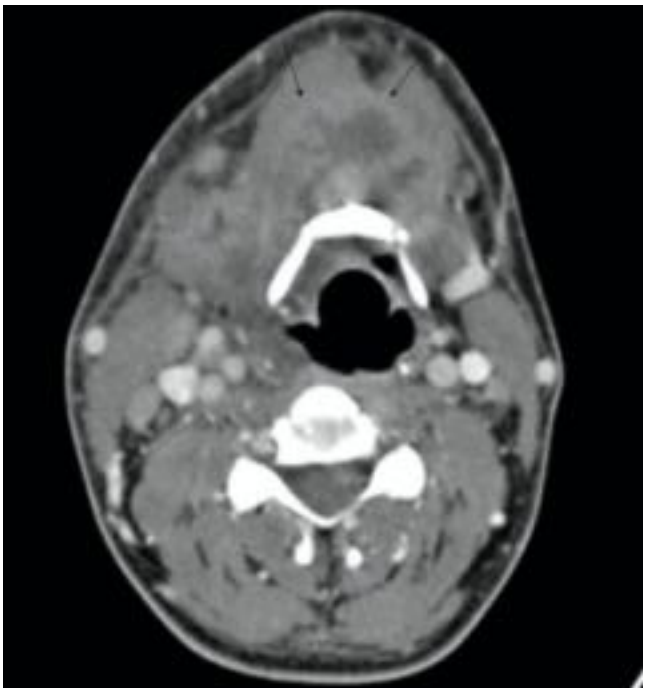


Figure 37.48 Axial contrast-enhanced CT showing an ill-defined phlegmon/abscess (black arrows) in the floor of mouth with an odontogenic source identified in the mandible.



Figure 37.49 Axial contrast-enhanced CT in a child showing an abscess within a retropharyngeal node (black arrow).

Contrast-enhanced CT has a positive predictive value of 79.6–82% for diagnosing deep neck abscesses, increasing to 91.3% when more than one deep neck space is involved but decreasing to 50% in patients with isolated retropharyngeal abscess.[194, 195]

Infections in the sublingual, submandibular and masticator spaces are often odontogenic in origin and these patients should also have an orthopantomogram (OPG) to assess the dentition.[196] Infection originating in the incisors to premolars mandibular teeth usually spread to the sublingual space while infection of the molars spread to the submandibular space (**Figure 37.48**).

Retropharyngeal space infection occurs mainly in children due to suppuration of a retropharyngeal node (**Figure 37.49**) and is usually due to naso- or oropharyngeal infection. Infection from here may track into the posterior mediastinum above the level of the carina.

Tonsillitis is the commonest infection to occur in the pharyngeal mucosal space and usually responds to antibiotics but occasionally patients may develop tonsillar or peritonsillar (quinsy) abscesses that then involve the parapharyngeal and retropharyngeal spaces (**Figure 37.50**).

Cervical lymphadenitis is common in children and refers to inflamed, enlarged and tender cervical lymph nodes, usually due to an upper respiratory tract illness.

It is important to realize that head and neck cancers can present as infection in patients over 40 years with one study quoting a prevalence of 4.9%.[197, 198] In such patients any neck mass that fails to resolve after a course of antibiotics should be further investigated by FNA, endoscopy and cross-sectional imaging.

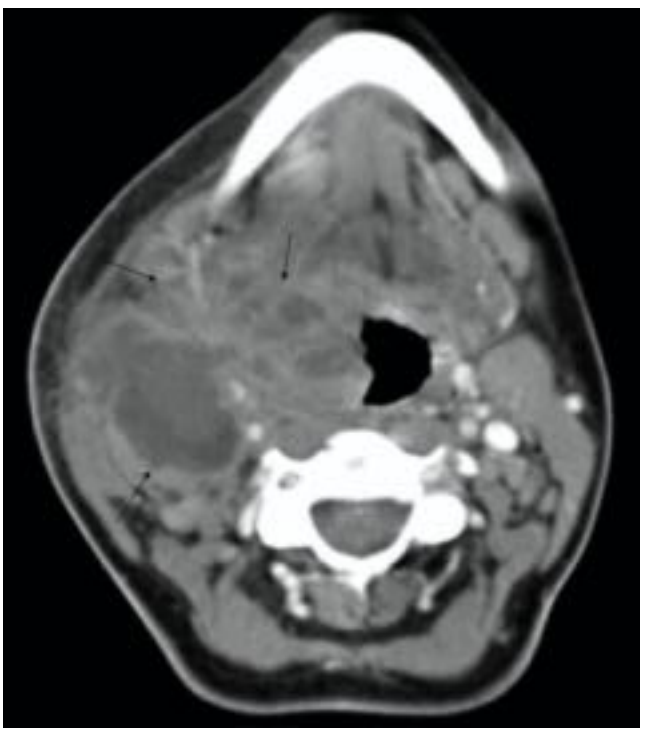


Figure 37.50 Axial contrast-enhanced CT showing a multiseptated abscess (black arrows) occupying multiple spaces arising from untreated tonsillitis.

KEY POINTS

- Imaging of the neck is integral to diagnosis, treatment and follow-up of neck lumps.
- The choice of imaging modalities depends on the clinical scenario and the working diagnosis.
- Dedicated head and neck radiologists can provide invaluable help in diagnosis, especially in complex cases.
- Cross-sectional imaging is mandatory in almost all cases of head and neck cancer.
- Based on the clinical picture, complementary information can be obtained from a combination of imaging modalities.
- All imaging is best done before any surgical intervention to avoid artifacts caused by the surgery.

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CHAPTER 38

NECK TRAUMA

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SEARCH STRATEGY

Data in this chapter may be supported by a Medline search using the following keywords: trauma, cervical, trachea, esophagus, and vascular.

INTRODUCTION

The issue dominating discussion on the management of penetrating neck trauma for the past few decades is whether penetrating neck injuries require mandatory exploration. There has been a distinctive paradigm shift from mandatory exploration towards more selective, conservative management based on clinical evaluation and specialized investigations. Introduction of diagnostic tools such as flexible endoscopy, oesophagography, high-resolution computed tomography (CT), and duplex doppler have improved non-operative evaluation of aerodigestive and vascular injuries. The realization that certain injuries may be treated non-operatively and the management of selected arterial injuries by endovascular techniques have further promoted the concept of selective exploration of the neck.

THE TRAUMA PATIENT: GENERAL PRINCIPLES

Primary survey (survival assessment)

Resuscitation should be performed in accordance with the Advanced Trauma Life Support (ATLS®) principles.[1] The Primary Survey is an initial assessment of factors that cause early deaths in trauma patients. It focuses on factors such as hypoxia, hypovolaemia, tension pneumothorax and head injury.

AIRWAY AND CERVICAL SPINE PROTECTION

The patient is examined for evidence of airway obstruction; this may present as stridor and use of accessory muscles of respiration. The neck should be stabilized with a cervical collar or sandbags until cervical spine injury is excluded. Major facial fractures, in particular mandibular fractures, and large cervical haematomas may compromise the airway. Patients with transcervical gunshot wounds (GSWs) may not have airway problems initially, but must be closely observed as they can rapidly develop airway obstruction. A chin lift and jaw thrust procedure should be done to try to overcome the obstruction. Patients with Glasgow coma scores (GCS) of ≤8 usually require intubation to protect the airway. An endotracheal tube may sometimes be inserted directly into the trachea through a penetrating cervical injury. Cricothyroidotomy must be considered if intubation fails. It should subsequently be converted to a formal tracheostomy within 24 hours, as the small tube is difficult to keep clean, and to prevent subglottic stenosis.

BREATHING

The chest should be examined for chest wall movement and air entry. Tension pneumothorax and haemothorax

are life-threatening conditions; immediate intervention based on clinical diagnosis is mandated before X-rays are obtained. Tension pneumothorax presents with hypoxia, restlessness, hyper-resonance to percussion, decreased air entry, contralateral tracheal shift, and elevated jugular venous pressure. It is decompressed by needle thoracocentesis; a large bore needle is initially inserted through the 2nd intercostal space in the mid-clavicular line, followed by insertion of a chest drain. A large haemothorax is identified by dullness to percussion and decreased air entry, and is also managed with an intercostal drain.

CIRCULATION AND PERFUSION

In the shocked patient, insert two high-flow lines with 14-gauge cannulae in the antecubital fossae. The line should not be inserted on the same side as a vascular injury with massive bleeding, for if there is a venous injury, intravenous fluids will merely bleed out. In the shocked patient, start with two litres of crystalloid; if the blood pressure does not improve, proceed to a transfusion of 0-negative blood, and arrange blood cross-matching. A shocked patient with warm peripheries may have neurogenic shock secondary to spinal cord injury. This would result in low blood pressure and bradycardia, potentially masking a significant vascular injury. Active bleeding from a cervical wound may be controlled with a compressive dressing or digital pressure. Failing this, a large Foley's catheter may be inserted into the wound, the bulb inflated, and the catheter cross-clamped to stop blood pouring through the catheter. This can be a very effective form of haemostasis particularly with bleeding from the subclavian and cervical vessels.[2] Throughout, the patient should remain recumbent, or the neck wound must be covered with an occlusive dressing when the patient sits up, to prevent air embolism.

DISABILITY

The GCS and pupil size and reactivity to light are recorded, and power in the limbs is assessed.

EXPOSURE

All clothing is removed in order to avoid missing associated injuries. The patient is kept warm.

Adjuncts to primary survey

Adequate monitoring, including ECG, pulse oximetry and non-invasive blood pressure monitoring is instituted. A rectal examination to exclude a urethral injury should be performed prior to inserting a urinary catheter. The haemoglobin level, blood glucose and arterial blood gas are checked. Imaging is essential. In a well-resourced trauma centre, this would include cross-sectional CT or MR imaging. Alternatively, cervical spine chest and pelvic X-rays are essential. In a patient with isolated penetrating neck trauma, a chest X-ray and cervical spine X-rays will suffice. Exclude a haemo- or pneumothorax, pneumomediastinum (tracheal or oesophageal injury), and widened mediastinum on chest X-ray. The mediastinal width on a supine chest X-ray should not exceed 8 cm; a widened mediastinum is suggestive of major intra-thoracic injury and must be further investigated with CT angiography. Cervical spine X-ray is used to exclude spinal column injury and prevertebral air (pharyngeal or oesophageal injury). Non-urgent X-rays should be requested only on completion of the secondary survey.

Secondary survey

A detailed head-to-foot examination of the patient is conducted. In firearm injuries, the location of the wounds must be noted and the direction of the tract established so as to determine which anatomical structures may have been injured. X-rays (AP and lateral) are obtained in the absence of an exit wound to locate and determine the tract of the bullet. If the patient has not been intubated, examine the cranial nerves and exclude Horner syndrome. Note the presence of a large cervical haematoma, subcutaneous emphysema, the jugular venous pressure and tenderness over the mandible. If a nasogastric tube has been inserted, the presence of blood in the nasogastric tube should be looked for.

KEY POINTS

- Wounds should not be probed as this may cause massive bleeding from an arterial injury.

Check the peripheral pulses for discrepancy or absence. Examine the distal carotid and superficial temporal artery pulses, and listen for bruits. Again exclude a haemo/pneumothorax and listen to the heart sounds. The abdomen and pelvis should be examined, followed by a full neurological examination during which spinal cord and brachial plexus trauma are excluded. Note the presence of hemiplegia or Brown-Sequard syndrome (hemitransection of spinal cord). The patient should be logrolled in order that the back can be examined for trauma.

History

Take a history with specific reference to the nature of the trauma. Enquire about symptoms pointing to oesophageal injury (haemoptysis, haematemesis, dysphagia, and odynophagia), and recurrent laryngeal nerve or laryngeal injury (dysphonia, stridor). Past medical and surgical history is documented, as well as the time of the patient's last meal.

Further investigations

Any further X-rays that are required after the secondary survey are now completed. Special investigations such as CT scan, ultrasound and gastrografin or barium studies may now be requested in a haemodynamically stable patient.

Full documentation

All injuries are documented and the patient is referred for definitive care.

AETIOLOGICAL CLASSIFICATION

- Penetrating
  - stabs
  - GSW
    - low kinetic energy
    - high kinetic energy
    - shotgun
- blast
- blunt.

Unlike stab wounds and low kinetic energy GSWs, close-range shotgun, rifle, and bomb injuries cause extensive soft tissue trauma.

ZONES OF THE NECK

The neck contains three principal anatomic components i.e. vascular (carotid, vertebral, and subclavian arteries; jugular and subclavian veins), digestive (pharynx and oesophagus) and respiratory (larynx and trachea). Roon & Christensen's classification into three zones is most commonly used for description of the site of cervical trauma (**Figure 38.1**).[3] All three zones contain major vascular, and aerodigestive structures. However injuries to zones I and III are both diagnostically and surgically more challenging.

- Zone I: Sternal notch / clavicle to cricoid cartilage
- Zone II: Cricoid cartilage to angle of mandible
- Zone III: Angle of mandible to base of skull

In a second classification system by *Monson,* the transition between zones I and II is at the sternal notch.[4] Both retrospective and prospective studies and review articles of penetrating cervical trauma fail to take into account these differences in the classification systems used.[4] Although transcervical injuries (injuries that cross the mid-line of the neck) are associated with vascular or aerodigestive injuries in 73–100% of patients, neither classification system takes cognisance of transcervical injuries.

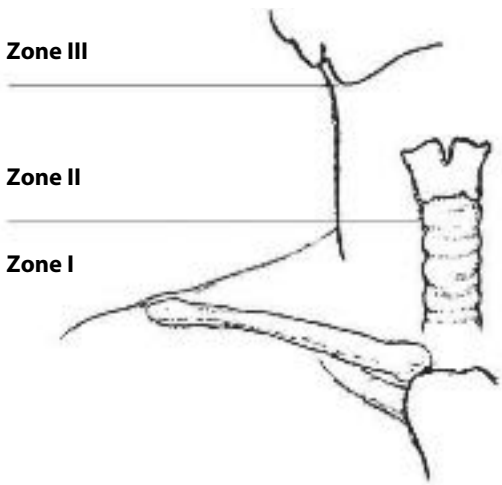


Figure 38.1 Zones I – III: Roon and Christensen classification.

MANDATORY VERSUS SELECTIVE EXPLORATION OF PENETRATING CERVICAL INJURIES

Prior to World War II, non-operative treatment of penetrating neck injuries was associated with a mortality of 15–18%.[5] Following experience in World War II, Bailey in 1944 proposed early exploration of penetrating neck injuries. Coupled with the introduction of antibiotics and tracheostomy, early exploration reduced the mortality rate to 7%.[6] In 1956, Fogelman and Stewart reported that mortality for patients not immediately explored was 35% vs. 6% for those that had been promptly explored. They concluded that all penetrating neck wounds that violated the platysma required surgical exploration.[7] Mandatory exploration of the neck whenever the platysma muscle had been breached subsequently became common practice. In 1963 Stone questioned the need for mandatory exploration for civilian injuries.[8] Ever since that time controversy has reigned about the relative merits of mandatory exploration vs selective exploration for low-velocity gunshot and sharp penetrating cervical wounds. The majority of trauma centres currently advocate some form of selective conservative management.[9]

Mandatory exploration

Proponents of mandatory exploration of stable patients with low-velocity GSWs and stab wounds that breach the platysma muscle consider that the risk of missing an unsuspected vascular or aerodigestive tract injury outweighs the morbidity and expense of negative exploration. They point to the unreliability of clinical evaluation, that diagnostic studies do not have 100% sensitivity to detect oesophageal and vascular injuries, low morbidity associated with negative exploration, additional time and effort associated with expectant observation, and the significant morbidity and mortality associated with delayed detection and repair of oesophageal injury. Yet, vascular and oesophageal injuries can be missed when the neck is explored without the assistance of pre-operative angiography, oesophagography and/or oesophagoscopy.

Selective exploration

Protagonists of selective exploration quote the high rate (36–89%) of negative mandatory exploration,[9–11] good sensitivity and specificity of special investigations such as angiography, doppler, barium swallow, rigid oesophagoscopy, and flexible laryngotracheobronchoscopy; expense of prolonged hospitalization following negative exploration; the fact that many injuries (e.g. thyroid, pharyngeal and certain venous injuries) that are detected at mandatory exploration may be treated conservatively; and that neck exploration leaves an unsightly scar (**Figure 38.2**).

TABLE 38.1 Selective conservative management of penetrating cervical injuries

Series	No of patients	Explored	Endovascular management	Negative explorations	Observed	Mortality
Narrod[12]	77	62 %	NR	15%	29%	0%
Campbell[13]	108	24%	NR	0%	82%	1.2%
Ngakane[14]	109	NR	NR	NR	97%	1.8%
Demetriades[9]	335	20%	NR	15%	80%	0%
Thoma[15]	203	12%	4%	0%	78%	0%
Van Waes[16]	77	8%	1%	0%	90%	0%

NR = not reported.

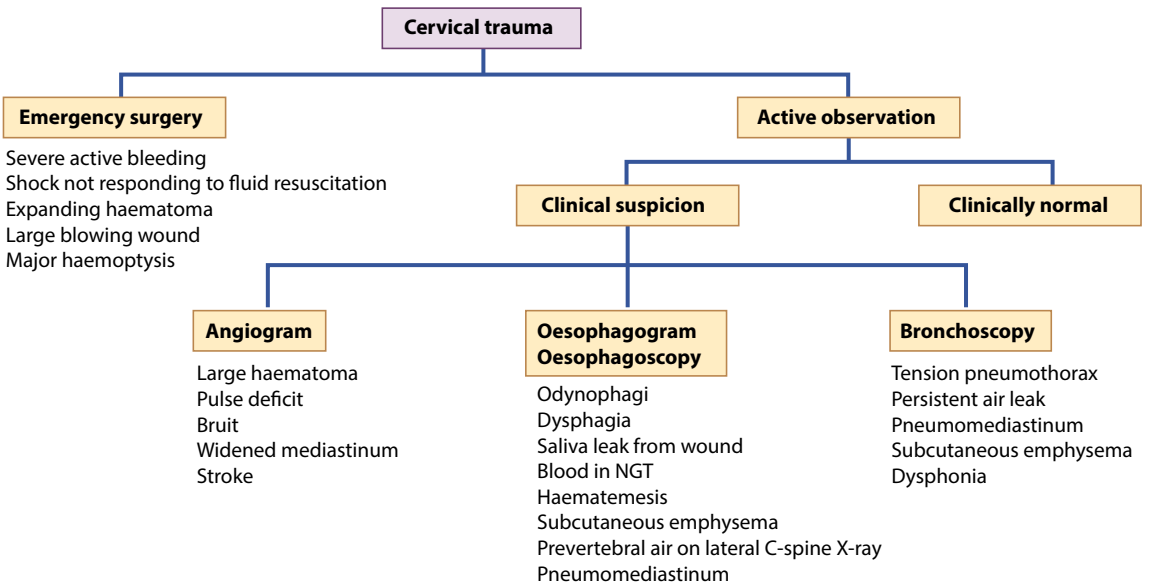


Figure 38.2 Selective surgical exploration algorithm.

Negative exploration in centres practising selective exploration ranges between 9% and 62%.[10–12] The safety of selective conservative management of penetrating cervical injury is apparent from the results of six prospective studies summarized in **Table 38.1**. Mortality in the studies by Campbell[13] and Ngakane[14] was not attributable to cervical injury, but to associated trauma. Two recent prospective studies from our institution have validated the fact that selective non-operative management of penetrating neck injuries is effective and safe.[15, 16]

KEY POINTS

- Indications for emergency surgery with such a selective approach include severe active bleeding, hypovolaemic shock not responding to resuscitation, a rapidly expanding haematoma, a large blowing wound and major haemoptysis.

The remaining patients are assessed clinically and appropriate radiological and endoscopic investigations are done only if there is a suspicion of visceral injury.

While the importance of early diagnosis of occult vascular injury is debatable, delayed diagnosis of oesophageal perforation is accompanied by increased morbidity and mortality.[17, 18] Because of concerns about reliability of physical assessment alone, some protagonists of selective exploration therefore advocate mandatory oesophageal and vascular studies; others have employed active observation with special investigations only if the clinical examination is equivocal.

Active observation with selective special investigations

Demetriades et al. reported in a prospective study of 335 penetrating neck injuries that a combination of clinical and selective investigations yielded a specificity of 85%, and sensitivity of 100% to identify clinically significant vascular and aerodigestive tract injuries. Only 38% of patients with surgical emphysema required exploration. They concluded that selected exploration can be based on careful initial and repeated clinical examinations.[9] They advocate emergency exploration for the absolute indications for neck exploration noted previously. They do not consider soft signs such as shock responding to resuscitation, minor active bleeding, haematoma, dyspnoea,

subcutaneous emphysema, hoarseness, dysphagia or minor haematemesis to be absolute indications for exploration; such patients are assessed individually, taking into account the direction of the injury tract, and the severity of the clinical signs. If the tract courses away from larynx, trachea, oesophagus and carotid sheath, then no further investigations are done. If the tract is directed towards the midline, then contrast oesophagography, and/or endoscopy are done. Chest X-ray is requested if chest pathology is suspected. Hall et al. support this approach in a report on the safety of active observation of children with penetrating injuries in Zone II.[5] Although transcervical gunshots are twice as likely to have visceral/vascular injury as gunshots that do not cross the midline (79% vs. 31%, $p = 0.02$), 80% may be safely managed non-operatively by active observation and selective special investigations.[19]

Spiral CT scanning to evaluate the neck shows promise.[20] When CT scan in the stable patient reveals that the trajectory courses away from vital structures, then employment of invasive studies appears to be superfluous.

SPECIFIC INJURIES

Pharyngeal injury

Hypopharyngeal injury should be suspected in Zone II penetrating injuries, particularly in the presence of dysphagia, odynophagia, voice change, haemoptysis, haematemesis, and surgical emphysema. Flexible nasopharyngoscopy may reveal oedema, blood in the pharynx, or the perforation may be visible if located in the superior hypopharynx. Direct pharyngoscopy should reveal all injuries, but oesophagography is unreliable.[21] In a retrospective study of 47 hypopharyngeal injuries, Stanley et al. reported no complications in supra-arytenoid hypopharyngeal injuries, as opposed to a 22% complication rate for infra-arytenoid hypopharyngeal injuries. They conclude that upper hypopharyngeal injuries may be managed non-operatively; this part of the hypopharynx is capacious, has a low-intraluminal pressure and is enveloped by both the middle and inferior constrictor muscles. The lower hypopharyngeal funnels into the cricopharyngeus segment and is less capacious, has higher intraluminal pressure and is surrounded only by the inferior constrictor muscle; it should explored, repaired and drained like oesophageal injuries.[22]

Oesophageal injury

Early recognition and treatment of oesophageal perforation is the key to favourable outcome. Missed oesophageal injury has high morbidity and mortality. Intervention delays of >12 hours for iatrogenic oesophageal injury has a mortality rate of 40% as opposed to 9% if <12 hours.[17] In a retrospective multicentre study, Asensio et al. compared the outcome of patients that underwent diagnostic studies, with patients taken straight to the operating room. The study revealed a significantly increased oesophageal complication rate (41% vs. 19%), and length of ICU stay with patients having diagnostic studies. They concluded that time delays in instituting active management incurred by investigations associated with selective exploration can lead to increased morbidity and mortality.[18] This report does not however distinguish between the cervical and thoracic oesophagus. Whether their conclusion applies to isolated cervical oesophageal injury is therefore open to question, particularly in view of reports of successful outcome of small cervical oesophageal injuries treated conservatively. However, centres practising selective management of penetrating neck injuries should make rapid diagnosis and definitive repair a priority.

ACCURACY OF DIAGNOSIS OF OESOPHAGEAL INJURY

Dysphagia, haematemesis and odynophagia are symptomatic of penetrating oesophageal injury. Clinical evidence includes surgical emphysema and a salivary leak. X-ray may reveal retropharyngeal air, retropharyngeal oedema, haematoma, tracheal deviation, and a pneumomediastinum. Clinical evaluation has a sensitivity of 80% (50% for stabs, 100% for GSWs), a specificity of 64%, and an accuracy 72%.[17] Sensitivity of barium swallow is 48–100%, and of oesophagoscopy 40–90%.[23, 24] In a prospective study, Weigelt et al. reported 89% sensitivity, 100% specificity and 94% accuracy (AP and lateral views with cineradiography) for barium swallow; flexible oesophagoscopy was unreliable, particularly in the proximal oesophagus as the mucosa cannot be effaced as with rigid oesophagoscopy; rigid oesophagoscopy had a sensitivity of 89%, specificity of 95% and accuracy of 94%; and a combination of oesophagography and oesophagoscopy had a sensitivity of 100%.[17] Wood et al. reported sensitivity of oesophagography of 100% and specificity of 96%, and cautioned that oesophageal and vascular injury can be missed at neck exploration.[25] Flowers et al. and Srinivasan et al. have however more recently reported sensitivities of 100%, and specificities of 96% and 92.4% respectively, for flexible oesophagoscopy to detect the presence of penetrating injury of the oesophagus.[26, 27] Because barium, if aspirated, may induce serious pulmonary problems, it should not be used in trauma patients and an appropriate water-soluble contrast agent (e.g. gastrografin) should be used.

DO ALL OESOPHAGEAL INJURIES NEED TO BE EXPLORED?

Treatment of oesophageal injury varies from observation, to simple repair of the wall +/- drainage of deep neck spaces, to primary diversion of salivary flow to the skin by means of partial or total exteriorization procedures. All high-kinetic injuries should be explored. The management of stab wounds and low-kinetic energy GSWs is more contentious. Wound site, size, mechanism of injury, time delay, associated injuries, availability of and expertise with diagnostic tests such as oesophagography and oesophagoscopy, and availability of theatre time all play a role in determining the management of oesophageal injury. Generally it is recommended that, should barium swallow be positive or equivocal, one should proceed to rigid oesophagoscopy; if positive, then the oesophagus is explored. However, Ngakane et al. concluded from a prospective study of penetrating visceral

injuries of the neck, that should oesophagography reveal minimal leakage of contrast, then patients can be managed conservatively; oesophagography is repeated on day 5, prior to commencing oral feeding.[14] Similarly favourable outcomes of small cervical oesophageal perforations treated conservatively been reported by Mandal et al. and others.[28]

SURGICAL TECHNIQUE

The majority of oesophageal injuries can be repaired primarily. The remainder are repaired by resection and anastomosis, or are simply drained. Intravenous antibiotics and enteral or parenteral nutrition should be instituted. Adequate drainage, suction or dependent, is important as even with a technically sound repair, 13% develop fistulae.[11] If part of the oesophagus has been blown away, if mediastinitis or sepsis is already present, or if oesophageal injury extends into the chest, then a lateral cervical oesophagostomy may be required. There is no evidence to favour a double- or single-layered repair. Local infrahyoid strap or sternocleidomastoid muscle flaps can be used to buttress the repair, or used as an interposition between an oesophageal injury and a vascular or tracheal repair.[29] Barium swallow is done on day 5–7, as 50% of post-operative oesophageal fistulae are asymptomatic and detected only on contrast study.[11] Should a fistula or sinus be present, the drain is retained.

COMPLICATIONS OF OESOPHAGEAL INJURY

Oesophagocutaneous fistulae occur in 9–28% of oesophageal injuries.[29] They occur more commonly with GSWs, but generally close spontaneously. Oesophagotracheal fistulae are repaired with interposition of a muscle flap. More serious complications include abscess formation, mediastinitis, septicaemia and death.

Tracheal injury

Cervical tracheal injury is relatively uncommon, and frequently associated with oesophageal, vascular or spinal injury. Symptoms of tracheal injury include a blowing wound, surgical emphysema, haemoptysis and hoarseness. Chest X-ray may reveal surgical emphysema and pneumomediastinum. The priority is to secure an airway. The trachea can sometimes be intubated through a blowing wound in the neck. Tracheotomy is appropriate in the presence of laryngeal trauma to avoid further injury to the endolarynx, when it is not possible to safely pass an endotracheal tube, or with quadriplegia requiring ventilatory support. Former teaching that nasotracheal or orotracheal intubation should be avoided as it may aggravate an existing tracheal injury or cause a false passage appears to have been overly cautious.[30] Distal tracheobronchial disruptions can be bypassed under direct vision with an introducer passed through a rigid bronchoscope, or by intubating over a flexible bronchoscope. Tracheobronchoscopy can be useful to assess the injury, but the diagnosis is usually readily apparent on exploring the neck for associated injuries. Minor tracheal injuries in patients not otherwise requiring cervical exploration can be managed expectantly. In cases of marked surgical emphysema, a tracheotomy might expedite recovery. Tracheal repair is effected with interrupted sutures. When there is an associated oesophageal or vascular injury, then the repair can be bolstered with a local muscle flap. In selected cases a tracheotomy or an endotracheal tube may be used to protect the tracheal repair.

Vascular injury

The common carotid artery is the most frequently injured major vessel; it accounts for 22% of vascular injuries.[31] Current debate centres on evaluation of the asymptomatic patient, and optimal treatment of vascular trauma. The majority of published series are small, retrospective, and from single centres.

CLINICAL EVALUATION

Hard clinical signs of vascular injury are expanding haematoma, external haemorrhage, absent or diminished distal pulses, ischaemic neurological deficits, or coma. The reported accuracy of clinical evaluation varies widely. Scalafani et al. reported a specificity of 80% and sensitivity of 61%; Meyer et al. reported an accuracy of 68%.[32] Demetriades et al. reported a sensitivity of 100% for clinical detection of significant vascular injury.[33] The widely disparate results may reflect shortcomings of retrospective data collection, and a lack of emphasis placed on clinical decision-making in centres with a bias towards routine angiography or exploration.

INVESTIGATIONS

The gold standard investigation remains 4-vessel arch angiography with selective catheterization. Angiography has the following benefits: identifies the site of injury; identifies subclinical vascular injury including vertebral artery trauma; serves as a roadmap for the surgeon; delineates the extent of crossover circulation through the Circle of Willis; and identifies injuries amenable to endovascular intervention. However, helical CT angiography is largely replacing conventional angiography and has a 90–100% sensitivity and specificity to detect arterial injury.[20] Vascular injuries in Zone II are readily exposed, and with Zone II penetrating injuries, the chance of detecting an asymptomatic arterial injury by angiography is less than 1%, which approaches the complication rate of angiography.[4] With penetrating injuries in Zone II, angiography may therefore be employed selectively for patients with clinical suspicion of a vascular injury, or when the tract of a GSW passes close to vascular structures. Vascular injuries in Zones I and III can however be difficult to assess clinically, and surgical exposure and vascular control are more challenging. Hence pre-operative angiography of suspected vascular injuries in Zones I and III is generally recommended. Demetriades et al. reported that colour-flow duplex Doppler (CFD) imaging, when combined with clinical examination, had a sensitivity of 91% and specificity of 99% to detect vascular injury. CFD only missed an intimal tear which did not require treatment.[33] CFD however requires trained personnel; is not always readily available; is best avoided if there is a suspected cervical column

injury; it may not demonstrate very well the origins of cervical arteries from the aortic arch, the arteries close to the skull base, and the vertebral arteries; and it is difficult to identify individual branches of the external carotid artery.

CAROTID REVASCULARIZATION VERSUS LIGATION

With the introduction of vascular surgical techniques during the Korean War, primary repair of carotid artery injuries was recommended. In 1973 Bradley concluded from two autopsy studies that revealed haemorrhagic brain infarction, that revascularization should not be attempted in patients with severe neurological deficits.[34] Fear about converting an ischaemic into a haemorrhagic infarct by reperfusion and hence worsening the neurological outcome has since been a major concern to vascular surgeons, and has fuelled the dilemma of ligation vs. reperfusion. In 1978 Liekwig and Greenfield showed that patients with severe neurological deficits just short of coma had significantly better results with reperfusion.[35] This was supported by Brown et al. in 1982 who showed that revascularization in patients with pre-operative coma (lack of meaningful response to verbal or noxious stimuli) was indicated when ischaemia had only been present for a short period of time prior to surgery (**Figure 38.3**).[36]

PSEUDOANEURYSMS AND INTIMAL INJURY

Clearly the risk of surgery for pseudoaneurysms (focal, eccentric widening of the lumen extending beyond the arterial wall), intimal defects and intimal flaps, should not exceed the risk of complications developing from the arterial pathology. Pseudoaneurysms, intimal defects and intimal flaps have been managed conservatively.[37, 38] However, studies are small and the safety of a conservative approach particularly with respect to the carotid artery has not been confirmed. Patients managed conservatively should be followed with arteriography to confirm that the lesion does not increase in size.

VERTEBRAL ARTERY INJURY

With the increased availability of angiography, vertebral artery injury is being more frequently recognized.[39] Patients may present with acute bleeding or with late complications of thrombosis, false aneurysms, bleeding, arteriovenous fistulae and stroke. Torrential bleeding may be encountered from a lacerated vertebral artery. Arteriovenous fistulae may present with a bruit, thrill, haematoma, neurological deficits, or cardiac failure. A neurological deficit seldom occurs in the presence of a normal contralateral vertebral artery and intact collateral circulation.[40] Mortality from isolated vertebral artery trauma ranges from 5% to 17% but increases to 50% if there is an associated injury of the carotid artery.[41] The majority of vertebral artery injuries can be managed by angiographic embolization. If the injury is discovered at emergency surgery, the vessel should be ligated. This is fairly simple if the injury is located at a point before the vertebral artery enters the foramen transversarium at the level of the 6th cervical vertebra. Once inside the vertebral canal, ligation may be achieved with ligaclips. Alternately, bone wax should be used to tamponade bleeding, followed by angiographic embolization.

ENDOVASCULAR TECHNIQUES

Endovascular techniques are playing an increasing role in the treatment of both acute and late manifestations of vascular trauma, particularly at the skull base. False aneurysms and arteriovenous fistulae can be treated with covered stents, or by trapping the lesion proximally and distally with balloons or coils, once good cross-flow across the Circle of Willis has been demonstrated (**Figures 38.4** and **38.5**).

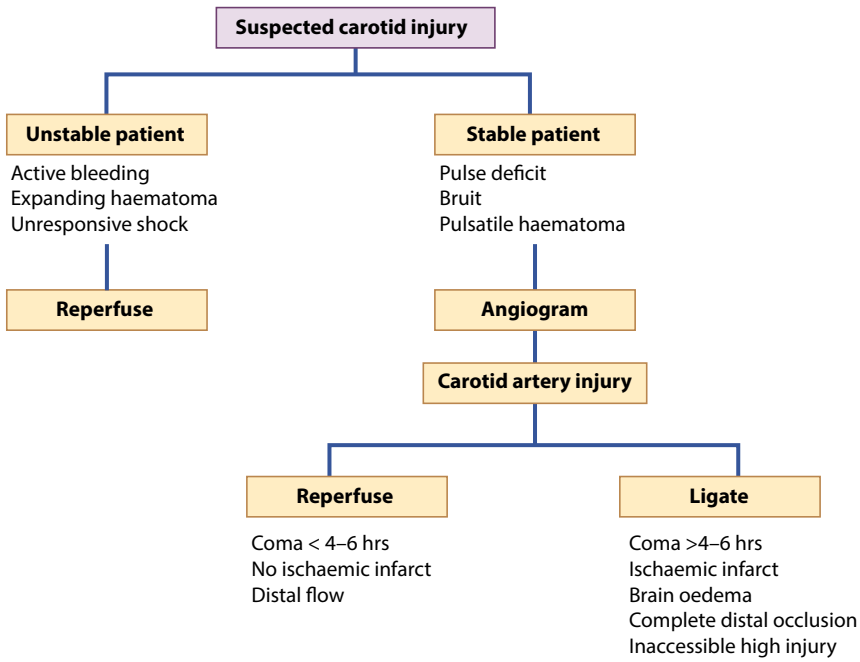


Figure 38.3 Recommended protocol for carotid ligation vs. reperfusion.

Bleeding from branches of the external carotid artery can be controlled by embolization.

VENOUS INJURY

The external jugular vein may be ligated if injured. The internal jugular vein may be repaired by lateral venorrhaphy, or ligated. Should both internal jugular veins have been injured, then at least one vein should be repaired to prevent facial swelling, and sequelae of raised intracranial pressure such as blindness, SIADH and even death. A remnant of the contralateral internal jugular vein or saphenous vein can be used should a graft be required.

Chylous injury

Patients with Zone I injuries rarely develop a chylothorax due to injury to the thoracic duct or right lymphatic duct. Although one can attempt a diet of medium-chain triglycerides, Worthington et al. reported that conservative treatment is uniformly unsuccessful, and advocate early ligation via thoracotomy.[42]

Neurological injury

Significant brachial plexus nerve injury should be repaired within 24–72 hrs.

EXPLORATION OF THE NECK: GENERAL PRINCIPLES

- IVI lines, suction, blood in theatre
- General anaesthesia: crash induction with cricoid pressure
- Airway:
  - nasotracheal/orotracheal intubation
  - cricothyroidotomy or tracheotomy
- Position:
  - supine
  - neck extended, turned to opposite side, if no C-spine injury
- Exposure:
  - chest and face for Zones I and III injuries, to permit additional surgical exposure if required
  - contralateral groin and lower leg to permit harvesting of saphenous vein for grafting
- Approach:
  - localized injury: horizontal skin crease incision, subplatymal flaps
  - wider exploration: long incision along anterior border of sternocleidomastoid muscle
- Additional exposure:
  - Zone I: divide omohyoid muscle; bilateral exploration: apron flap
  - Zone III: anterior dislocation of the mandible.

SUMMARY

Management of penetrating injuries of the neck remains controversial. Reasons for the controversy include paucity of well-designed, large, prospective studies; the uncommon occurrence of oesophageal injury; the variable levels of radiological and surgical expertise at trauma centres confronted with cervical injuries; the wide spectrum of the site and severity of injuries and of aetiological agents, as well as the lack of a uniform classification system when reporting neck injuries.



Figure 38.4 False aneurysm of internal carotid artery, with carotico-jugular fistula following stab wound at base of skull.



Figure 38.5 Trapped false aneurysm and fistula (Figure 38.4), with coils by endovascular technique.

FUTURE RESEARCH

- Significance of delayed repair of cervical oesophageal injury.
- CT scan for initial evaluation of penetrating cervical injury.
- MRI scan for initial evaluation of penetrating cervical injury.
- Endovascular intervention for vascular trauma.

KEY POINTS

- Properly executed, selective management of penetrating injuries of the neck is as safe as mandatory exploration.
- Trauma centres need to design their management protocols in accordance with their investigative and therapeutic capabilities.

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CHAPTER 39

BENIGN NECK DISEASE

Ricard Simo, Jean-Pierre Jeannon and Enyinnaya Ofo

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SEARCH STRATEGY

Data presented in this chapter are based on a Medline search using keywords listed in the chapter. The main terms included, congenital neck masses and acquired neck masses, inflammatory neck masses, and neck abscesses. It included diagnosis, surgery and management. The evidence of this chapter is mainly evidence levels 3 and 4 with some level 2 evidence. The clinical recommendations are predominantly B and C.

INTRODUCTION

Neck masses or swellings are a common occurrence. In the adult population, approximately 75% of non-thyroid neck masses are neoplastic,[1, 2] and of these 80% are metastatic. Around 75% of these metastatic neck masses are caused by a primary tumour located above the clavicle. In children under 15 years, 90% of neck masses are benign and of these up to 55% may be congenital.[1, 3, 4]

Benign neck masses may be classified as congenital or acquired. The latter group are often enlarged lymphadenopathy, but there may be a wide range of different pathologies involved. The introduction of fine-needle aspiration biopsy / cytology (FNAB / FNAC) with or without the use of ultrasound scan (USS) guidance has now become the gold standard investigation.[5–7]

The evaluation and management of patients presenting with a neck lump should include a systematic and uncompromising clinical approach.[2, 8–10] This must include a thorough history, examination of the upper aerodigestive tract and head and neck, followed by relevant investigations, which may include blood tests and radiological imaging.

History

This should include age, sex, past medical history, travel abroad, the mode of onset and duration of neck mass, associated symptoms including dysphonia, dysphagia, odynophagia, sore throat, referred otalgia, nasal obstruction, cranial nerve neuropathies, weight loss, anorexia, malaise and night sweats.

Examination

The examination should include an inspection of the skin over the skull, face, neck, and of the ears, nose, oral cavity and oropharynx. The fibre-optic endoscope should be used to inspect the nasal cavity, nasopharynx, oropharynx, larynx and hypopharynx.[2, 10, 11] The neck should be examined in a systematic fashion and the number, size, site, shape, texture and involvement of the skin and the deep cervical structures noted. Additionally, while concentrating on the head and neck as a source to explain the presence of a neck mass, it is frequently worth extending the general physical examination to include the chest and breasts in women, including the axillae. Examination of the neck is addressed extensively in Chapter 36, Clinical examination of the neck.

Investigations

The investigations of patient with a neck lump should be tailored to each individual case. All patients with neck lumps should as a minimum be considered for: full blood count (FBC), chest X-ray (CXR) and utrasound guided FNAB / fine-needle aspiration cytology (FNAC).

If an inflammatory mass is suspected, especially in a young patient, the above investigations together with an erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Epstein–Barr virus (EBV) and cytomegalovirus (CMV) titres, liver function tests (LFTs), lactate dehydrogenase (LDH), Brucella, *Bartonella henselae* and toxoplasma serology may be advisable.[1, 9]

Once a clinical or tissue diagnosis has been made, it is possible to determine what, if any, further tests or imaging is required. If the diagnosis is infective or inflammatory a plain chest X-ray or no further imaging may be indicated. If a neoplastic lesion is diagnosed, computerized tomography scanning (CT), magnetic resonance scanning (MR) and positron emission tomography (PET) scanning alone or a combination may be performed. See details in Chapter 37, Imaging of the neck.[1]

A basic understanding of the different pathologies presenting as a neck lump is essential to direct adequate investigations and conclude an accurate working diagnosis without compromising the patient's clinical outcome. Occasionally, the clinician needs to be conscious that a working diagnosis may be incorrect;[12] hence it is paramount that patients are reviewed frequently during the early stages, to ensure resolution of the mass, if that is the expected outcome, or referral to a specialist for a second opinion if the anticipated diagnosis has not be confirmed, or doubts in the diagnostic accuracy still persist.

CONGENITAL NECK MASSES

LYMPHANGIOMAS

Lymphangiomas are degenerative lesions arising from lymphatics, and can be classified as: simple lymphangiomas, cavernous lymphangiomas and cystic hygromas.[13–16]

Lymphangioma simplex These are also called capillary lymphangiomas. They are composed of thin-walled capillary-sized lymphatic channels, usually asymptomatic and present as a pale, small vesicle-like lesions visible on the skin or oral cavity.

Cavernous lymphangioma Cavernous lymphangioma represent 40% of all lymphangiomas, composed of dilated lymphatic spaces, often with a fibrous adventitia, typically occurring in the tongue, cheeks and lips, and present as a painless diffuse swelling.

Cystic hygroma Cystic hygroma are composed of cysts and sinuses, varying in size from a few millimetres to several centimetres in diameter, usually presenting as a cystic mass containing eosinophilic acellular lymph fluid.

AETIOLOGY

The lymphatic system arises from five primitive sacs (two jugular sacs, two posterior sciatic sacs and a single retroperitoneal sac) developed from the venous system. Endothelial buds from these extend centrifugally to form the peripheral lymphatic system. Two principal theories have been postulated to explain the origin of lymphangiomas:[17, 18]

- Sequestration of lymphatic tissue derived from segments of the primitive sacs, which retain the proliferative growth potential and bear no connection with the normal lymphatic system
- Endothelial fibrillar membrane proliferation from the walls of the cyst, which penetrate the surrounding tissue along the lines of least resistance between muscles and vessels, canalize and produce more cysts.

CLINICAL FEATURES

Although congenital and in most cases present at birth, sometimes they can manifest for the first time in young adults. They can appear anywhere in the head and neck. On palpation they feel cystic and transilluminate. They may remain static or involute, but in some cases they gradually increase in size and occasionally, especially after internal haemorrhage or infection, can grow rapidly potentially risking life-threatening airway obstruction.[13, 19]

DIAGNOSIS AND INVESTIGATIONS

The diagnosis is usually made on clinical grounds but CT and MRI scanning will more accurately determine the size, exact anatomical location, and relationship with important structures as well as aiding surgical planning.[13, 19]

TREATMENT

The management of these lesions is difficult and challenging and many treatment modalities have been described over the years. The treatment strategy varies depending on the anatomical location, size and involvement of surrounding structures. Observation has been proposed by Broomhead[20] as up to 15% of patients may have spontaneous regression. Repeated aspirations may be helpful in the event of rapid increase in size causing pressure symptoms whilst awaiting definitive treatment. Injection of sclerosants such as bleomycin, tetracyclines and alcohol has been suggested, but internal scarring is reported to be unpredictable resulting in difficulty with any subsequent surgery and it is not currently recommended. The intra-lesion injection of OK-432 (Picinabil) has shown promising results.[21, 22] It causes an inflammatory reaction and thrombosis with subsequent necrosis. Surgical excision remains the treatment of choice but it is challenging and is therefore best undertaken by experienced surgeons in specialist centres.[17] Surgery can be helped by the injection of methylene blue into the lymphatic spaces (**Figure 39.1**).



Figure 39.1 Operative picture of a lymphangioma of the supraclavicular region.

DERMOID CYSTS

Dermoid cysts are classified as epidermoid, true dermoid and teratoid cysts, depending on the types of tissues identified pathologically within them.[23] Twenty per cent of all dermoid cysts are found in the neck and 30% of these in the face. They make up 28% of all midline cysts, with no sex predominance.

Epidermoid cysts contain only skin and no other adnexal structures. They are lined with squamous epithelium with or without keratinous material. These are the most commonly encountered variety.

True dermoid cysts are lined with squamous epithelium and contain skin with appendages such as hair, hair follicles, sebaceous glands and sweat glands.

Teratoid cysts are lined either with squamous or respiratory epithelium. They contain all three embryological elements; ectodermal, endodermal and mesodermal elements such as nails, teeth, brain and glandular tissue.

AETIOLOGY

These lesions develop because of ectodermal differentiation of multipotential cells trapped at the time of closure of the anterior neuropore, especially along the lines of fusion, hence their being located along the midline of the neck. In the head and neck other areas of tissue fusion may present with dermoid cysts, such as external angular dermoids, and the nasal dorsum.[23]



Figure 39.2 Thyroglossal cyst.

CLINICAL FEATURES

The peak age of incidence is usually the second and third decade. They can present as a cystic or solid painless mass, usually in the submental region, above or below the mylohyoid muscle. They may infrequently manifest as an acute inflammatory swelling associated with infection (**Figure 39.2**).

DIAGNOSIS AND INVESTIGATIONS

Diagnosis is suggested by the patient's age, the clinical location, and nature of presentation. Ultrasound-guided FNAC may be useful in the diagnosis of these lesions. Cross-sectional imaging such as a CT and MRI can help delineate the extent of large lesions, and aid surgical planning.

TREATMENT

Complete surgical excision is the treatment of choice.[23]

THYROGLOSSAL DUCT CYSTS

Thyroglossal duct cysts are the most common upper neck midline lesion accounting for almost one-third of all congenital neck masses.[24] They can present as a mass or lump, at any level between the foramen caecum and the upper mediastinum, with the majority presenting about the level of the hyoid bone. They are usually sporadic but a rare familial variant has been documented, identified as an autosomal dominant condition in pre-pubertal girls. Thyroglossal duct carcinoma, although rare, may present and be identified by the pathologist in a thyroglossal duct cyst.[25, 26] This is described in the section on thyroid malignancies.

AETIOLOGY

Embryologically the thyroid gland originates from the floor of the primitive pharynx between the first and second

pharyngeal pouches. In addition to the major median swelling, there are smaller paired lateral pouches, which contribute to the parafollicular or calcitonin-secreting C cells. The median pouch loses its lumen, about the 5th week of gestation and breaks into fragments, the lower end dividing into two portions that become the lobes of the thyroid gland. Thyroglossal duct cysts arise from epithelial cells when they cease to remain inactive. The stalk usually atrophies during the 6th week but should it persist as a patent tract, it becomes a thyroglossal duct along which cysts can develop. It may run from the thyroid gland inferiorly, upwards and in the region of the hyoid bone, and the tract may be located behind, through or in front of the hyoid, ending deeply in the junction of the anterior two-thirds and posterior one-third of the tongue, at the foramen caecum. The mechanisms involved in the development of cystic changes is not fully understood.[27] A fistula usually arises from spontaneous drainage of an abscess or more commonly following attempted drainage of a misdiagnosed midline neck abscess, or as a result of inadequate surgical excision associated with leaving an intact hyoid bone.

CLINICAL FEATURES

The majority (~95%) of thyroglossal cysts present as an asymptomatic cystic mass at or about the level of the hyoid bone. It moves on swallowing or on protrusion of the tongue. Up to 5% of these cysts present as an acute inflammatory episode with an infection, and 15% may have an associated discharging fistula.[28] There is no sex preponderance. The mean age of presentation is 5 years, with a range between 4 months to old age. Ninety per cent are in the midline but 10% may be to one or other side, with 95% of these being in the left side; 75% are pre-hyoid with the remaining 25% located above or below the hyoid, and rarely can be found within the mediastinum[24, 29] (**Figure 39.3**).



Figure 39.3 Right branchial cyst.

DIAGNOSIS AND INVESTIGATIONS

Patients with suspected thyroglossal duct cysts should be investigated with thyroid function test and ultrasound guided FNAC. The TSH and T4 levels will determine the thyroid status of the patient. USS may help with the location and diagnosis of the cyst, and will also confirm the presence of a normal thyroid gland in its expected anatomical position. FNAC will demonstrate cystic contents containing colloid. Isotope scan with either Tc^{99} or I^{123} may be useful if the cyst is located above the hyoid or in the posterior tongue, with a view to identifying or excluding the presence of a lingual thyroid. CT or MRI scanning should be considered in the presence of large cysts, when malignancy is suspected and when the possibility of a lingual thyroid has been considered.[30]

TREATMENT

Surgical excision is the treatment of choice, as there is a high probability the cyst may become infected, resulting in loss of normal tissue planes, or scarring of the neck skin and the occurrence of recurrent cyst enlargement causing patient discomfort.[24, 31] The Sistrunk procedure was described in 1920,[32] which resulted in a permanent cure for the majority of cases. Previously the hyoid bone was not excised resulting in recurrence rates of up to 50%,[33] with associated infections.[34] A modification of the Sistrunk technique is currently employed as the standard surgical procedure, without the need to excise the tongue base epithelium. The excision is performed through a transverse midline neck incision just below the cyst. The lesion is dissected from the infra-hyoid strap neck muscles and the laryngeal cartilages. The dissection then proceeds upwards to the region of the hyoid bone. At this point the suprahyoid muscles, i.e. mylohyoid, geniohyoid and genioglossus, are detached from the hyoid bone, while the middle third of the hyoid bone, between the lesser cornu, is cut and mobilized in continuity with the soft-tissue specimen, which includes the thyroglossal duct cyst. The completion of surgery involves further dissection upwards, into the tongue base, to include a core of tissue that should incorporate the tissue tract or raphe between the mylohyoid muscles, a portion of each genioglossus muscles up to the region of the foramen caecum. The technique as described has resulted in a significant reduction in recurrence rates, when compared with simple excision or removal of the cyst alone (Shalang Procedure) (**Figure 39.2**).[35]

Treatment of recurrent cysts and fistulae

Up to 8% of thyroglossal cysts may recur following adequate surgical excision.[36] If a substandard excision, without removal of the central portion of the hyoid bone, had been performed, the classic Sistrunk procedure should be undertaken. However, further surgery following a Sistrunk procedure may be difficult. In these cases, the previous incision scar should be excised and a central compartment neck dissection performed, with excision of the scar tissue up to the foramen caecum.[37, 38]

BRANCHIAL CYSTS

The word 'branchial' is derived from the Greek '*bragchia*' meaning gills. Branchial cysts appear as a developmental failure of the branchial apparatus. Branchial anomalies account for up to 19% of all paediatric cervical masses.[39] They often manifest in young adults with a peak incidence in the third decade. Cysts are usually lined by stratified squamous epithelium except in 10% of cases that may have respiratory epithelium instead; 80% have lymphoid tissue in the outer wall and contain straw-coloured fluid in which cholesterol crystals are found.

AETIOLOGY

Four theories have been suggested to explain the origin of branchial cysts.[40, 41]

Branchial apparatus theory

This theory suggests that branchial cysts represent remains of pharyngeal pouches or branchial clefts, or a fusion of these two elements. The development of the branchial apparatus extends from the 3rd to the 8th week of gestation. This theory would suggest that cysts should be present at birth, whereas the peak incidence is usually in the 2nd to 3rd decade.

Cervical sinus theory

This theory advocates that branchial cysts represent the remains of the cervical sinus of His, which if formed by the second arch growing down to meet the fifth arch. The second arch mesoderm almost covers the neck entirely and forms the platysma muscle.

Thymopharyngeal duct theory

This theory suggests that the cysts are remnants of the original connection between the thymus and the 3rd branchial pouch from which it takes origin. However, a persistent thymic duct has never been described and there has never been a branchial cyst found deep to the thyroid gland.

Inclusion theory

This theory postulates that branchial cysts are epithelial inclusions within a lymph node. This theory is supported by the fact that most branchial cysts have lymphoid tissue in their wall and have been reported in the parotid and the pharynx. This theory also explains why most branchial cysts have no internal opening, are almost unknown in neonates, while the peak age of presentation is much later in life, compared to that seen for most other congenital lesions.

CLINICAL FEATURES

Sixty per cent are located in the upper third of the neck, at the anterior margin of the sternocleidomastoid muscle, although they have been reported in any site of the neck including the parotid gland (**Figure 39.3**).[39] The presentation is a persistent neck swelling in 80% (with 20% intermittent in nature),[42] with 70% appearing cystic although up to 30% may feel solid. In nearly 40% of cases, a history of upper respiratory tract infection prior to noticing the mass can be elicited. Inflamed cysts may be complicated by abscess formation with the possibility of rupture.

DIAGNOSIS AND INVESTIGATIONS

All patients with a suspected branchial cyst should be investigated with at least a FBC and ultrasound-guided FNAC. Ultrasound-guided FNAC yields acellular fluid with cholesterol crystals on microscopy examination. However cytological findings should be interpreted cautiously, given that squamous debris may suggest malignancy. If lymph nodes are necrotic, as seen in squamous cell carcinoma and tuberculosis, they may be difficult to distinguish sonographically from a second branchial cleft cyst, but FNB is usually helpful. CT and MRI scanning is a useful investigation for large cysts to allow surgical planning (**Figure 39.4**).

TREATMENT

Surgical excision is the treatment of choice.[39] This is indicated as branchial cysts have a tendency to become infected, can increase to a large size causing local discomfort, pressure symptoms and obvious cosmetic deformity. The procedure is initiated by a transverse cervical incision made on the neck skin crease overlying the cyst. The platysma is incised and sub-platysmal flaps are elevated. The cervical fascia is incised over the anterior border of

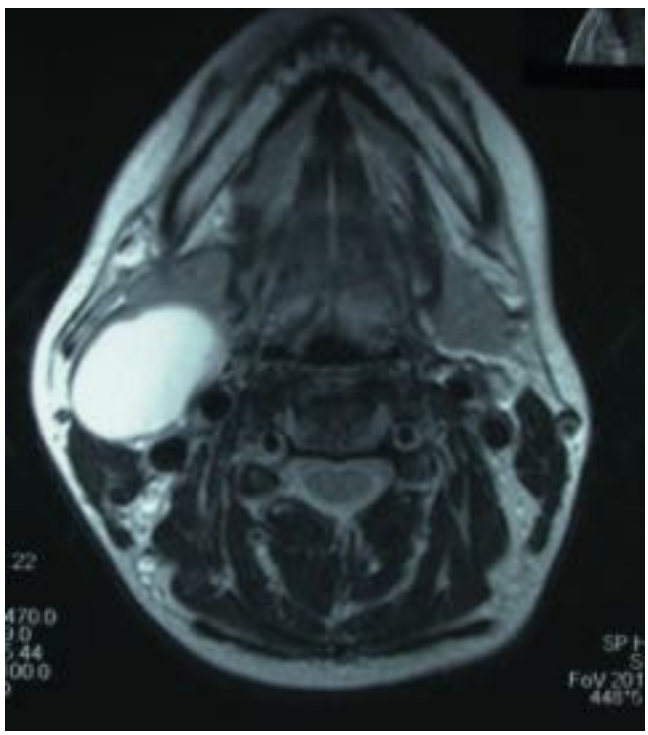


Figure 39.4 MR scan demonstrating a large right branchial cyst.

the sternocleidomastoid muscle, which is retracted laterally. The cyst is then identified and dissected from its fascial attachments and capsule ensuring that the cyst wall is not ruptured. During the dissection the carotid sheath and its contents should be identified and mobilized out of the surgical area. In addition, the marginal branch of the facial nerve, vagus, accessory and hypoglossal nerves should be identified and preserved. The cyst is excised completely and there is usually no need to look for a tract although the tail of the cyst may need to be dissected from the tail of the parotid gland or parapharyngeal space.

KEY POINT

- In patients over the age of 35, cystic neck lumps should be considered metastatic unless proven otherwise. These are usually seen with high-risk HPV-related head and neck squamous cell carcinomas.

BRANCHIAL FISTULAE AND SINUSES

Branchial fistulae are congenital defects consisting of a skin-lined tract, opening internally as a slit on the anterior aspect of the tonsil fossa if it is of second arch origin. The external opening is at the anterior border of the sternocleidomastoid muscle, at the junction of its middle and lower thirds.[27]

Branchial sinuses or branchial pits open along a line between the tragus and the sternoclavicular joint at the anterior border of the sternocleidomastoid muscle but with no internal opening.

AETIOLOGY

They arise from failure of complete development of the branchial apparatus including the first, second, third and fourth arches. During the 4th week of intrauterine life, six branchial arches develop as neural crest cells migrate cranially. During the 5th week, the second branchial arch grows over the third and fourth branchial clefts, forming a cervical sinus. Failure of the cervical sinus to close allows for potential communication with the second branchial pouch in the area of the tonsil fossa, the third pouch in the area of the larynx, and the fourth pouch opening in the pyriform fossa.[27]

CLINICAL FEATURES

Most patients are usually young infants with a discharging sinus, which may or may not have an internal fistulous opening. Clinically, second branchial cleft fistulae are the most common. They have a cutaneous opening along the anterior border of the sternocleidomastoid, usually at the junction of the middle and lower thirds, tracking up between the internal and external carotid arteries ending in the tonsillar fossa. Third and fourth branchial fistulae are rare, opening low in the neck and ending in the pyriform sinus, with an opening that is sometimes visible on endoscopic examination.[43]

DIAGNOSIS AND INVESTIGATIONS

The diagnosis is made on clinical grounds. A contrast swallow or CT fistulogram may be helpful to determine the pathway of the tract, differentiate a sinus from a fistula and aid surgical planning (**Figure 39.5**).

TREATMENT

Surgical excision is the treatment of choice.[44] The excision is performed in a stepladder fashion, removing the mouth of the sinus with an ellipse of neck skin. The tract is followed upwards as high as possible and then another transverse cervical or cervico-facial incision is made. The dissection is then continued to the tonsillar region where the tract usually disappears and should be ligated before it avulses, in order to minimize recurrence of symptoms (**Figure 39.6**).



Figure 39.5 Fistulogram of a left branchial fistulae.



Figure 39.6 Left branchial fistula tract emerging between the constrictor muscles and deep to the omohyoid muscle.

ACQUIRED NECK DISEASES AND MASSES

NON-INFLAMMATORY NECK MASSES

Sebaceous cysts

Sebaceous cysts are skin appendages lesions occurring mainly where there are sebaceous glands and are commonest in hairy skin, particularly in the beard region and scalp.

AETIOLOGY

These cysts develop when the duct of a sebaceous skin gland, responsible for the production of oily sebum protecting the skin, becomes blocked. The retained secretions distend the gland causing progressive enlargement of the cyst.

CLINICAL FEATURES

The lesions can be single or multiple, and of different sizes. They tend to be spherical, smooth and well defined, stretching the overlying skin and the opening of the blocked duct is often visible as a 'punctum'. The cyst may discharge in which case the creamy secreted dry material may accumulate in the centre to form a sebaceous horn, and sebaceous cysts also have a tendency to become infected.

DIAGNOSIS AND INVESTIGATIONS

Sebaceous cysts often display very distinct clinical features and rarely require investigation. They have a non-specific sonographic appearance and FNB/FNAC is not necessary unless there is clinical doubt.

TREATMENT

Surgical excision is the treatment of choice as they are unsightly, have a tendency to grow, burst, get infected and recur. Excision should be done very carefully ensuring that the punctum, and scar if they have been previously incised and drained due to infection, is excised with a small ellipse of healthy skin, to avoid leaving part of the cyst capsule which will lead to the recurrence of the lesion.[45]

Acquired dermoid cysts (implantation dermoids)

Dermoid cysts are usually solitary, with solid and cystic areas containing skin appendages.

AETIOLOGY

Acquired dermoids occur due to a penetrating injury or following surgery resulting in the implantation of dermal or skin structures deep into the subcutaneous tissue.

CLINICAL FEATURES

These cysts present at the site of a penetrating injury and often display solid and cystic areas containing sebaceous material.

DIAGNOSIS AND INVESTIGATIONS

The diagnosis is often made on clinical grounds however ultrasound-guided FNAC may be helpful in some cases where the history of injury is not clear.

TREATMENT

Surgical excision is the treatment of choice. The incision should include the injury tract that should be completely excised in continuity with the cyst to avoid recurrence.[46]

Pilomatrixoma or calcifying epithelioma of Malherbe

Pilomatrixoma is a benign tumour of the prickle cell layer of skin, first described by Malherbe and Chenantais in 1880 as a calcified epithelioma.[47–49] It is most frequently seen in the first two decades of life with two-thirds of these occurring in patients under 10 years of age and is more common in females, with a female preponderance of 3:2. The majority of these tumours (68%) occur in the head and neck region. Malignant transformation has been described but is very rare.

AETIOLOGY

The aetiology is unknown although an episode of local inflammation or trauma may precede their development.

CLINICAL FEATURES

Pilomatrixomas are usually solitary and present as a firm, nodular superficial lesions measuring up to 3 cm in size. There is usually no discolouration but if situated superficially a blue-red colour may be seen.

DIAGNOSIS AND INVESTIGATIONS

Pilomatrixomas have very distinct clinical features. If the diagnosis is suspected, FNAC can be performed. Cytopathological features include the identification of basaloid and squamous cells, calcium deposits and foreign body giant cells.[49]

TREATMENT

Surgical excision is the treatment of choice if the lesion is bothersome or there is doubt about diagnosis. The excision must be carefully performed in the same manner as for an epidermoid cyst as leaving part of the capsule will result in recurrence of the lesion.[50]

Lipomas

Lipomas are benign lesions of the adipose layer. The adipose cells are organized into large lobules divided by loose fibrous septa. Lipomas can be multiple and occasionally can be painful (Dercum's disease). Although the majority of lipomas are sporadic a minority can be familial.[51] The most common familial lipomatosis affecting the head and neck is Madelug's lipomatosis. In the neck region, lipomas may be subfascial or arising within the muscles. They grow very slowly and have a very low risk of malignant transformation.

AETIOLOGY

The aetiology is unknown, however, a history of preceding trauma which leads to breakdown of the adipose layer and abnormal growth has been suggested.[52]

CLINICAL FEATURES

Lipomas usually occur in adults and have a variable size. The tumour has a smooth, lobulated surface with a well-defined edge. They tend to be soft, and as they lie below the dermis, the overlying skin can be moved above the lesion.

DIAGNOSIS AND INVESTIGATIONS

Lipomas have characteristic appearances on USS, and do not require FNAC, unless risk of malignant transformation is suspected. For large lipomas, CT and MRI scanning may be useful in assessing the anatomy and aid surgical planning.[53]

TREATMENT

Surgical excision is the treatment of choice when the lesion is of a large size causing an obvious cosmetic deformity, when there is suspicion of malignancy, or due to patient choice.[53]

INFLAMMATORY NECK MASSES

Acute cervical lymphadenitis

Acute cervical lymphadenitis is common, especially in the paediatric population.[54] It occurs due to viral or bacterial infection in the upper aerodigestive tract, ears, or the skin of the head and neck.

CLINICAL FEATURES

The mass is usually painful and may result in an abscess, in which case the mass appears fluctuant. The patient may be toxic, and the primary infective process is usually evident, although in small children it is not always clear.[55]

DIAGNOSIS AND INVESTIGATIONS

The diagnosis is made on clinical grounds. If the infective episode is severe and the child requires hospital admission, basic haematological and biochemical investigations such as white cell count and CRP levels may aid in diagnosis. Usually, other investigations are not required unless there is clinical suspicion that the patient is developing an abscess, or there are concerns of an underlying neoplastic process. In these situations ultrasound-guided FNAC may aid the diagnosis.

TREATMENT

Treatment is initially empirical, with supportive and broad-spectrum antibiotic therapy, if a bacterial infection is suspected or diagnosed.[56]

Infectious mononucleosis

Infectious mononucleosis or glandular fever is a viral infection caused by EBV that usually affects adolescents and younger adults.[57, 58] EBV infection is also associated with the development of EBV-associated lymphoid or epithelial cell malignancies such as Hodgkin lymphoma, Burkitt lymphoma, nasopharyngeal carcinoma and multiple sclerosis.

AETIOLOGY

EBV is a gamma-herpes virus that infects over 90% of the human population worldwide. It is usually transmitted between individuals in saliva, and establishes replicative infection within the oropharynx as well as life-long latent infection of B cells. Primary EBV infection generally occurs during early childhood.[59]

CLINICAL FEATURES

Primary EBV infection may be asymptomatic or results in a mild self-limiting illness characterized by fever, tonsillitis and lymphadenopathy. If delayed until adolescence or later, it can be associated with the clinical syndrome of infectious mononucleosis, which is characterized by fever, pharyngitis, lymphadenopathy, especially cervical, and malaise. Five per cent of patients develop a maculopapular rash and up to 50% of patients may develop palatal petechiae, acute bacterial tonsillitis usually with a grey fibrinous exudate, splenomegaly and hepatomegaly. In severe cases or in immunocompromised patients, autoimmune haemolytic anaemia, thrombocytopenia, splenic rupture, encephalitis, cranial nerve paralysis and acute

upper airway obstruction as a result of significant tonsillar hypertrophy can develop.[60, 61]

DIAGNOSIS AND INVESTIGATIONS

The diagnosis is made on clinical grounds. The FBC will show more than 50% of mononuclear cells and over 10% atypical lymphocytes. The ESR and CRP will be elevated. Monospot and Paul Bunnell tests will be positive, but may also be negative, especially in the first 2 weeks of the disease. Hepatic enzymes may also be elevated.

TREATMENT

The management is largely supportive with conservative measures, such as rest and hydration. Avoidance of contact sports and heavy lifting is advised for at least 6 weeks, and abstainance from alcohol whilst LFTs remain abnormal.

Broad-spectrum antibiotic therapy may be useful in cases of secondary bacterial infective tonsillitis but ampicillin and its derivatives should be avoided as patients may develop a maculopapular rash. Corticosteroid therapy is advisable in cases of impending airway obstruction, thrombocytopenia and haemolytic anaemia as well as other complications, such as cranial nerve paralysis.[62] Antiviral chemotherapy with acyclovir or famcyclovir has been reported to help in some cases.

Cat scratch disease

Cat scratch disease mainly affects children and young adults with a peak of incidence between 2 and 14 years of age.[63] The disease is more common in the USA where over 24 000 people may be affected every year, but also affects Europe, Africa, Australia and Japan.

AETIOLOGY

Cat scratch disease is caused by the Rickettsia *Bartonella* sp. *Bartonella henselae* is the most common species to cause the widest spectrum of diseases in humans, and cats especially kittens are the main reservoir.

CLINICAL FEATURES

Cervical lymphadenopathy is preceded by erythematous papulae at the site of inoculation. Systemic symptoms such as fever, malaise, anorexia, headache and splenomegaly can occur, but tend to be more common in the immunocompromised patients.

DIAGNOSIS AND INVESTIGATIONS

Serological testing for *Bartonella henselae* is both sensitive and specific for cat scratch disease.[64, 65] More recently polymerase chain reaction RNA of the bacteria has been used for diagnosis.[65]

TREATMENT

Several antibiotics such as gentamicin, rifampicin, ciprofloxacin, and especially azithromycin which is associated with rapid resolution, have been advocated.[65] However, antibiotic use in cat scratch disease without systemic symptoms remains controversial given that infections may resolve without treatment.

Cervical necrotizing fasciitis

This is a rare, but life-threatening infection, which causes progressive necrosis of the skin and subcutaneous tissues.

AETIOLOGY

It results from an odontogenic[66] or tonsillar bacterial infection or may be a complication following deep space neck infections or surgery.[67, 68] *Streptoccocus pyogenes* or *viridans* and mixed anaerobes are the most common aetiological agents.[67]

CLINICAL FEATURES

The diagnosis is made on clinical grounds, with characteristic features such as initial cutaneous cellulitis with disproportionate pain that progresses to necrosis of subcutaneous tissues and skin.

DIAGNOSIS AND INVESTIGATIONS

The white cell count and other inflammatory parameters are raised. An ultrasound or CT scan may show oedema and air pockets of the skin, which are diagnostic features.[67]

TREATMENT

If untreated, cervical necrotizing fasciitis can be fatal, hence early diagnosis and treatment are essential. Intravenous high-dose antibiotic therapy, against aerobic and anaerobic bacteria, with debridement of all necrotic areas, is mandatory.[66, 67]

Chronic cervical lymphadenitis

There is a wide range of chronic inflammatory conditions which may present with cervical lymphadenopathy. They are often associated with systemic symptoms such as malaise, weight loss, anorexia and night sweats, hence the clinical history is very important. These conditions include: HIV and AIDS, sarcoidosis, toxoplasmosis, actinomycosis and tuberculosis (TB). In all cases, excluding TB, lymph node enlargement may be non-specific, hence clinical diagnosis may be difficult.

HIV-AIDS

Acquired immunodeficiency syndrome (AIDS) is a viral disease caused by human immunodeficiency virus (HIV). The infection is classified as:

1. acute infection or seroconversion illness
2. asymptomatic infection
3. persistent generalized lymphadenopathy (PGL)
4. full blown AIDS.

AETIOLOGY

The HIV virus is transmitted via contaminated blood or human secretions. It is prevalent in homosexuals, promiscuous heterosexuals and intravenous drug-abusers.

CLINICAL FEATURES

Up to 30% of seroconverted patients develop PGL and it may be the first manifestation of the disease. As with the acute seroconversion illness, PGL tends to be non-specific and it is characterized by multiple diffuse lymphadenopathy involving two or more extra inguinal sites for <3 months. It may also be an early sign of HIV infection and associated with other manifestations of the disease (**Table 39.1**).[69, 70]

INVESTIGATIONS

When suspected, HIV serology is indicated and diagnostic. FNAC will help the diagnosis of PGL and also assist in elucidating other causes of infection such as TB, Kaposi sarcoma (KS) or non-Hodgkin lymphoma (NHL).

TREATMENT

CD4+ lymphocyte count is the most important reference factor for initiating ART in asymptomatic patients. The large number of available drugs, the increased sensitivity of tests to monitor viral load, and the ability to determine viral resistance, has resulted in a more individualized approach to therapy.[71–73]

Tuberculous adenitis

TB is the oldest documented infectious disease. It is the world's leading cause of death from a single infective agent and is on the increase.[74, 75] Amongst the factors associated with reversal of a previous decline are; increased world travel and a rising incidence of immunodeficiency through HIV infections or intravenous drug abuse. Pulmonary TB is the most common manifestation but extra-pulmonary disease is also increasing in incidence with tuberculous adenitis, or historically named 'scrofula,' being the most common. The word scrofula comes from the Latin 'scrofulae' meaning brood sow. In the middle ages, it was believed that the 'royal touch' of the sovereign of England or France could cure the disease. It was therefore known as the King's Evil. The kings were thought to have received this power having descended from Edward the Confessor, whose legend states he received the power from Saint Remigius. Tuberculous adenitis can affect any lymph node group of the head and neck, including salivary glands and thyroid. Hence it is important to have a high index of suspicion especially in certain ethnic groups where TB may be endemic.

TABLE 39.1 Otorhinolaryngological manifestations of HIV infection

Candidiasis
Hairy leukoplakia
HIV-gingivitis
Necrotizing ulcerative gingivitis
Kaposi sarcoma
Non-Hodgkin lymphoma
Benign lymphoepithelial cyst parotid gland
Benign hyperplasia of the lymphoid tissue
Pneumocystic *carinii neumonia*
Tuberculosis
Opportunistic infections

AETIOLOGY

Mycobacterium TB is an obligate aerobe, non-spore forming slender rod. Humans are the only reservoir and it is usually acquired through contact from a TB infected patient via air-borne transmission. After a short period of replication in the lungs, silent dissemination occurs through the lymphohematogenous system to extra-pulmonary sites including the cervical lymph nodes. This pathophysiological process differs from non-tuberculous atypical mycobacterial adenitis (NTAMA) that is addressed later in this chapter.

CLINICAL FEATURES

Ninety per cent of patients have unilateral involvement mainly of the jugular chain of lymph nodes, followed by the submandibular triangle and the posterior triangle. The lymph nodes are usually firm, painless and present with a characteristic erythematous skin discoloration. If the disease has progressed without being diagnosed, they tend to fistulae, and present with an obvious discharging sinus, or form a 'cold' abscess, which suggests the clinical diagnosis. TB can also affect the ear, nose, pharynx, larynx, salivary and thyroid glands (**Figure 39.7**).[74, 76, 77]



Figure 39.7 Cervical tuberculous adenitis with central necrosis (scrofula).

DIAGNOSIS AND INVESTIGATIONS

Head and neck TB can be very difficult to diagnose, as the clinical features may resemble neoplastic disease, especially when presenting as a single-organ involvement. FBC is non-specific and may be normal. ESR is often elevated. Chest X-ray is mandatory but only up to 20% of patients will have positive changes. Soft-tissue X-rays of the neck may show dystrophic calcification characteristic of TB infection. Mantoux and Heaf test may be non-diagnostic if the patient has been vaccinated against TB, but a grade IV skin reaction on this test may suggest active infection. USS of the nodes will often show multiple, matted nodes but may be non-specific. FNAC can reveal mycobacteria, but is only positive in up to 40% of patients,[78] however, the use of FNAC and polymerase chain reaction allows a quick and accurate diagnosis with high specificity (84%) and sensitivity (100%). Excision biopsy if possible, may be very difficult due to the matted nature of lymph nodes, with an increased risk of bleeding and nerve injury. Alternatively, incisional biopsy of affected nodes should be performed if there is already skin involvement. Samples should be sent for microbiology as well as histological analysis and this should provide the definitive diagnosis. Microbiology analysis may take up to 6 weeks to culture mycobacteria, which may delay treatment. HIV testing is advisable in all patients.[74–78]

TREATMENT

Suspected or proven active tuberculous adenitis is treated with a combination of antibiotics, using a multidisciplinary approach with involvement of respiratory or infectious diseases physicians amongst others.[74, 77] Increasing resistance is currently a significant problem and therefore chemotherapy should be adjusted according to sensitivity. Surgery has a limited role and should only be used as a diagnostic tool or in cases of residual disease.

Non-tuberculous atypical mycobacterial adenitis

Non-tuberculous atypical mycobacteria (NTAM) adenitis is increasingly common in the Western world, and the main difference from tuberculous infection is it tends to affect otherwise healthy immunocompetent children from middle-class families.[79]

AETIOLOGY

Mycobacterium avium and *Mycobacterium avium intracellulare* are the main two pathogens. The route of entry is usually through the oropharynx or the eye, from ingestion of contaminated soil leading to superficial lymphadenopathy in the neck.

CLINICAL FEATURES

Patients affected by NTM are usually young healthy children with multiple cervical lymphadenopathy, but without any symptoms or signs of systemic illness. The enlarged lymph nodes often adhere to skin causing a characteristic red-purple discolouration, with occasional abscess or sinus formation and scarring.[79–81]

DIAGNOSIS AND INVESTIGATIONS

The diagnosis is made on clinical suspicion and confirmation relies on isolating the organisms in culture either through microbiological swabs, FNAC or incisional biopsy.

TREATMENT

Most children may eventually develop their own immunity so a period of observation is advisable especially if the lesion is in the parotid gland. Antibiotic therapy with macrolides such clarithromycin or azithromycin with or without antituberculous therapy has been suggested.[82] In some studies resolution has been achieved in up to 67% of cases, without surgical excision. Surgical curettage with or without antibiotic therapy may be an option and has been used with some success in selected cases especially if full surgical excision may cause significant morbidity.[79] Surgical excision is the ultimate treatment of choice and appears to be more effective than antibiotic therapy alone.[79, 83, 84]

Brucellosis

Brucellosis is primarily a disease of domestic animals and causes contagious abortion or other reproductive problems in cattle (*Brucella abortus*), pigs (*B. suis*), goats (*B. melitensis*), dogs (*B. canis*) and sheep (*B. ovis*). Current pasteurization of dairy products, and other hygienic preventive measures, as well as adequate animal vaccinations has greatly reduced the incidence of the disease in Western countries.[85]

AETIOLOGY

Human spread of *Brucella* spp. occurs by direct contact of infected tissue with the conjunctiva or broken skin, by ingestion of contaminated meat or dairy products, or by inhalation of contagious aerosols.

CLINICAL FEATURES

The clinical features are often non-specific and some infections are subclinical. When the infection is clinically evident, most patients complain of night sweats, chills, undulating pyrexia and malaise. Up to 20% of patients will develop cervical lymphadenopathy and a similar percentage will have splenomegaly.[85]

DIAGNOSIS AND INVESTIGATIONS

When the diagnosis is suspected, blood cultures will often isolate the bacteria and provide a definitive diagnosis. Serology will also provide the diagnosis in those cases where the clinical picture is less obvious.

TREATMENT

This involves combination antibiotic therapy, as single-agent treatment is associated with a 30% risk of relapse. The current WHO recommendation is to use doxycycline 200 mg and rifampicin 900 mg daily for 6 weeks.[86]

Toxoplasmosis

AETIOLOGY

Toxoplasmosis is a worldwide infection caused by *Toxoplasma gondii*, a protozoan transmitted by the ingestion of cysts excreted in the faeces of infected cats, or from eating undercooked beef or lamb.[87]

CLINICAL FEATURES

Congenital infection usually causes hydrocephalus or microphaly. Acquired infections present with generalized malaise, myalgia, fever, cough and a maculopapular rash. If untreated, a chronic phase will develop which may be asymptomatic or present with isolated cervical lymphadenopathy. In immunocompromised patients especially with HIV-AIDS, it may cause encephalitis.[87]

DIAGNOSIS

The diagnosis is made on clinical history and complemented by serology, which will provide confirmation in the majority of cases.[87, 88] The white cell count will show lymphocytosis with atypical mononuclear cells. FNAC may suggest the diagnosis although may be non-specific. Lymph node biopsy will reveal features supporting the diagnosis of toxoplasmosis.[89] CSF analysis may demonstrate the parasite and confirm the diagnosis if there is central nervous system involvement.

TREATMENT

Where treatment is indicated a combination of sulphadimidine, pyrimethamine and folic acid is used.[87] The FBC should be monitored regularly until it becomes normal.

Actinomycosis

AETIOLOGY

Actinomycosis is a bacterial infection caused by *Actinomycosis israelii*, an anaerobic organism which is a commensal in the healthy oral cavity.[90] The organism may become pathogenic when the mucous membrane is injured. Infection is usually associated with severe dental caries and periodontitis.

CLINICAL FEATURES

Patients present with a firm indurated mass with ill-defined edges usually lateral to the mandible. If left untreated the infection may spread to adjacent tissues and may become bony hard. Once the infection is established multiple sinus may develop which discharge pus and watery fluid containing characteristic sulphur granules.

DIAGNOSIS AND INVESTIGATIONS

The diagnosis may be suspected on clinical grounds, which are usually typical. FNAC may show sulphur granules that are diagnostic. Tissue biopsy will again show characteristic colonies with sulphur granules, but the organism may be difficult to culture.[90]

TREATMENT

Therapy is with intravenous benzylpenicillin or cephalosporins in high doses that may be required for at least 6 weeks. However, longer courses of antibiotic treatment for up to 1 year may be necessary in resistant cases or immunocompromised patients. Removal of carious teeth is imperative to eliminate the site of origin of the infection.[90]

NECK ABSCESSES

In this section only the superficial soft tissue neck abscesses will be addressed as the deep neck infections will be addressed in Chapter 40, Neck space infections.

Superficial soft tissue neck abscesses

Cervical abscesses are relatively uncommon in comparison with the number of acute and chronic lymphadenitis that present in the paediatric and adult population. However, small children under the age of 4 years and immunocompromised patients appear to be more susceptible.

AETIOLOGY

Failure of patients to eliminate the organism at the site of attachment to the nasal or pharyngeal epithelium will result of spread of infection via lymphatics causing suppuration. The most common pathogens are: *Staphyloccoccus aureus*, *Streptococcus pyogenes* and in the paediatric population atypical mycobacteria.[56]

CLINICAL FEATURES

The development of the abscess is often preceded by an upper respiratory tract infection although on occasions this may not be obvious from the history, especially in the younger paediatric population.

DIAGNOSIS AND INVESTIGATIONS

Diagnosis is based on clinical suspicion. FBC, ESR and CRP are useful to ascertain the inflammatory origin and monitor progress. USS and CT scanning will be useful to determine whether the mass has a central area of necrosis that may require incision and drainage.

TREATMENT

The treatment involves a combination of supportive therapy, broad-spectrum antibiotics until culture and sensitivity

results are available, plus or minus surgical incision and drainage. Repeated needle aspiration is not usually helpful unless the abscess is arising from a thyroglossal duct cyst in which case incision and drainage is reserved as a last resort after antibiotic therapy and repeated aspiration has failed.[56]

MISCELLANEOUS RARE CAUSES OF NECK MASSES

Organized haematomas

AETIOLOGY

Blunt or penetrating trauma of the neck.

CLINICAL FEATURES

Patients present with a neck mass that usually causes local discomfort and occasionally constant pain.

DIAGNOSIS AND INVESTIGATIONS

A history of trauma is usually present although not always obvious. Ultrasound-guided FNAC will suggest diagnosis but the sonographic appearances depend on the age of the haematoma. If in the liquid state, blood can be aspirated. CT and MRI scanning will display distinct radiological features and determine the anatomical extent. Follow-up USS may be helpful to ensure there is no underlying lesion.

TREATMENT

Surgical excision is the treatment of choice although it may be difficult due to the surrounding fibrosis of the lesions.[91, 92]

Castleman disease

Castleman disease is a rare entity which is characterized by hyperplasia of lymph nodes and capillary proliferation that usually affects adolescents and young adults. Three histological patterns have been described: hyaline vascular type, plasma cell type and mixed type. Two clinical types have been identified; a localized type (ECL) usually of benign clinical course and a multicentric type (ECM) of worst prognosis as it may lead to the development of non-Hodgkin lymphoma.[93–95]

AETIOLOGY

It is unknown, although up to 50% of multicentric variants are caused by Kaposi sarcoma-associated virus (KSHV) a gamma herpes virus that causes KS and primary effusion lymphoma.

CLINICAL FEATURES

Patients usually present with a progressively enlarging lateral cervical lymphadenopathy often associated with an autoimmune iron-deficiency anaemia. ECM may present with B symptoms such as fever, anorexia and weight loss.

DIAGNOSIS AND INVESTIGATIONS

FBC shows iron-deficiency anaemia and the ESR is elevated. FNAC often shows a lymphocytic aspirate that is not normally diagnostic therefore surgical excision is advised for histological diagnosis. Imaging studies are often not useful.

TREATMENT

Anaemia is difficult to treat, as it does not often respond to iron supplements. Surgical excision is usually therapeutic in ECL although it may be difficult in ECM. Treatment with ganciclovir or the antiCD20 B-cell monoclonal antibody, may improve outcome in some patients with ECM. With ECM long-term follow-up is advised, in association with the haemato-oncology team.[93–95]

Kikuchi disease

Kikuchi disease (KD) is a self-limiting disease of lymph nodes that usually affects young women. It is also known as Kikuchi-Fujimoto disease and was first described by Kikuchi from Japan in 1972.[96, 97] Histologically, it is characterized by a histiocytic necrotizing lymphadenitis.

AETIOLOGY

The pathogenesis is unknown, however an autoimmune aetiology has been proposed as some human leucocyte antigen (HLA) class II genes, are more frequent in patients with KD. An association with systemic lupus erythematosus (SLE) has also been reported.

CLINICAL FEATURES

The disease often presents with persistent or intermittent fever as well as tender enlarged cervical lymph nodes. It is self-limiting but it may take up to 3 months to resolve.

DIAGNOSIS AND INVESTIGATIONS

The diagnosis can be confirmed by histopathological analysis of a lymph node following open biopsy.

TREATMENT

The disease is usually self-limiting and does not respond to antibiotic therapy. Supportive therapy with non-steroidal anti-inflammatory drugs may help to alleviate the lymphadenopathy, tenderness and pyrexia.[96, 97]

Kawasaki disease

Kawasaki disease (KWD) is an acute, self-limited vasculitis of childhood although it may also occur in adults. Tomisaku Kawasaki, from Japan, first described the condition in 1967.[98] In some countries, KWD has now surpassed acute rheumatic fever as the leading cause of acquired heart disease in children.

AETIOLOGY

The acute presentation and clustering of cases may indicate an infectious aetiology, however, the exact aetiology is unknown.

CLINICAL FEATURES

The illness is characterized by fever, bilateral non-exudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy. Coronary artery aneurysms or ectasia develop in approximately 15–25% of untreated children and may lead to myocardial infarction and sudden death.[99, 100]

DIAGNOSIS AND INVESTIGATIONS

Diagnosis is based on the recognition of the characteristic sequence of clinical events, none of which are pathognomonic. Establishing the diagnosis may be further complicated by the occurrence of other, seemingly unrelated, clinical features, such as irritability, neck stiffness, sterile pyuria, pneumonitis and hepatitis. There is no laboratory test that can aid in confirming the diagnosis.

TREATMENT

Treatment is with intravenous gammaglobulin therapy and high doses of aspirin.[99, 100]

BOX 39.1 Other rare causes of cervical neck masses

- Sarcoidosis
- Fibromatosis colli
- Rosai–Dorfman disease
- Kimura's disease
- Dermatofibroma
- Prominent transverse process of atlas

KEY EVIDENCE

- This is a heterogeneous chapter addressing multiple benign disorders of the head and neck.
- There is lack of substantive high-level evidence due to the intrinsic nature of the disorders included. In most areas the evidence is at most level 2.
- Troublesome congenital abnormalities of the head and neck region are best treated with surgical excision whenever possible.
- Head and neck tuberculosis is where evidence is higher and should be treated with systemic antituberculous therapy with surgery having a limited role in its management.

KEY POINTS

- Benign disorders and masses of the neck represent a heterogenous group of diseases and its knowledge is imperative for the treating clinician.
- The evaluation and management of the patients presenting with neck lumps should be addressed with a clear systematic and uncompromising approach.
- All patients presenting with neck lumps should undergo ultrasound-guided fine needle aspiration whenever possible.
- The majority of congenital neck masses should be treated with meticulous surgical excision to avoid recurrence.
- Acquired non-inflammatory benign neck masses should be treated mainly with surgical excision to establish the histological diagnosis.
- Acquired inflammatory masses of the head and neck should be treated medically – with antibiotic therapy – and surgery is reserved for diagnosis – if this has not been established clinically or by FNAC – and for incision and drainage of established abscesses.
- Head and neck abscesses can be treated with repeated aspiration if indicated but incision and drainage should be always considered.

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CHAPTER 40

NECK SPACE INFECTIONS

James W. Moor

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SEARCH STRATEGY

Data in this chapter may be updated by a search of Pubmed and Medline using the keywords: deep neck spaces, deep neck space infection, deep neck infection and deep neck space infections.

INTRODUCTION

Neck space infections arise through a variety of aetiological processes and cause a diverse clinical picture. They carry the potential to cause life-threatening complications and death, although in the modern era with availability of broad-spectrum antibiotics, cross-sectional imaging and modern theatre facilities, the mortality rate is low. Nonetheless, appropriate and successful management requires a thorough understanding of the anatomy of the neck, knowledge of usual causative organisms and their sensitivities to commonly available antibiotics, clinical diagnostic skills and formulation of multi-speciality treatment plans with potential input from anaesthetists, microbiologists, oral and maxillofacial surgeons, otorhinolaryngologists, paediatricians and radiologists.

ANATOMICAL CONSIDERATIONS

The cervical fascia invests muscles and organs of the neck thereby limiting and influencing the direction of spread of infection. The relationship of the fascial layers to each other and adjacent structures creates potential spaces and therefore understanding the anatomy of the cervical fascia is key to understanding the anatomy of neck space infections.

The cervical fascia is divided into two layers: the superficial layer that envelops platysma and the muscles of facial expression and the deep layer, which, in turn, comprises superficial, middle and deep layers (**Figure 40.1**).

Superficial (or investing) layer of deep cervical fascia

This is attached superiorly to the superior nuchal line of the occipital bone, the mastoid process, the zygomatic arch, the inferior border of the mandible, the hyoid and the spinous processes of the cervical vertebrae. Inferiorly it is attached to the manubrium, the clavicle and the acromium and spine of the scapula. It forms the roof of the anterior and posterior triangles of the neck.

This layer forms the most superficial fascial boundary of the deep neck spaces and provides a robust barrier to the spread of infection, such that abscesses tend to track deep to it into adjacent, deeper neck spaces, or even into the mediastinum. It is not unusual for compression of deep structures to occur as a consequence of an accumulating abscess contained by the superficial layer of deep cervical fascia even to the extent that airway compromise becomes evident.[1]

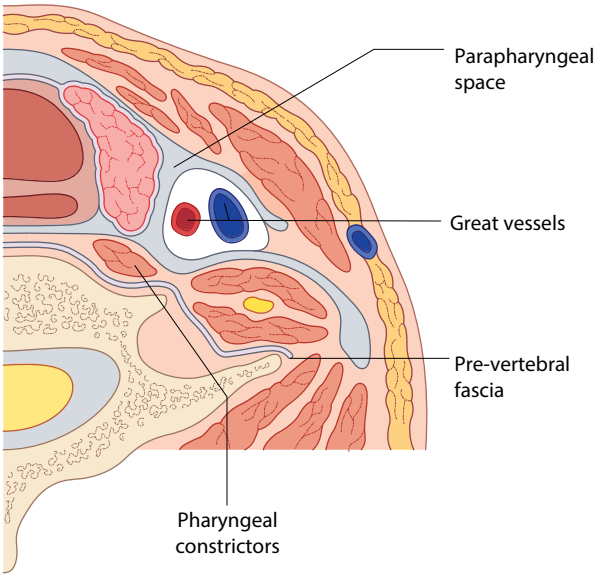


Figure 40.1 Axial section through C7 vertebrae detailing superficial cervical fascia, superficial, investing and deep layers of deep cervical fascia

Middle layer of deep cervical fascia (or pre-tracheal fascia)

This is limited to the anterior aspect of the neck; it splits to invest the thyroid gland, trachea and oesophagus and blends with the carotid fascia laterally. It descends into the superior mediastinum where it blends with the fibrous pericardium. Consequently, it bounds a deep space which extends from the neck into the mediastinum.

Deep layer of deep cervical fascia (prevertebral fascia)

The deep layer of deep cervical fascia (prevertebral fascia) forms part of a fascial sleeve for the prevertebral muscles that surround the vertebral column. It extends from the skull base to the third thoracic vertebra where it fuses with the anterior longitudinal ligament in the posterior mediastinum; it extends laterally as the axillary sheath.

Alar fascia

The alar fascia is a component of the deep layer of deep cervical fascia although it is described separately from it as it lies between the deep and middle layers of deep cervical fascia (**Figure 40.2**).[2]

NECK SPACES

Several deep neck spaces are classically described, created by the boundary layers of cervical fascia described above.

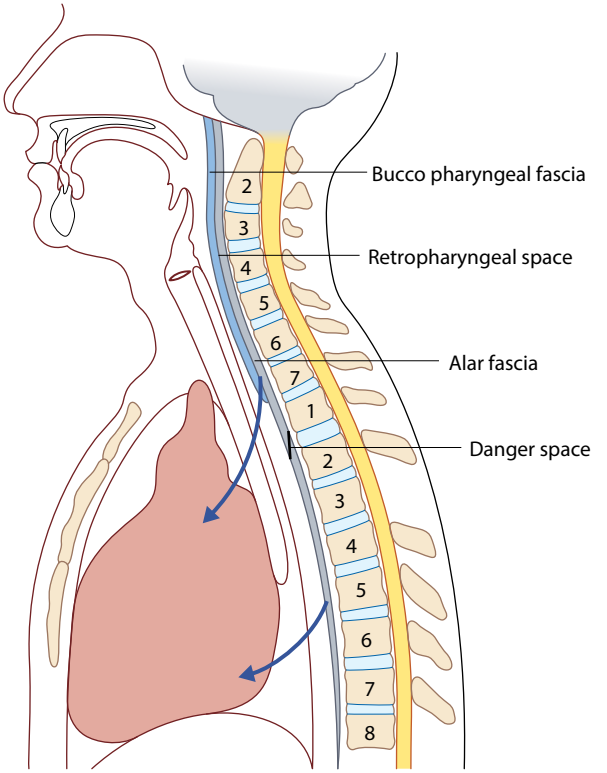


Figure 40.2 Sagittal section detailing retropharyngeal, prevertebral and 'danger spaces'.

Parapharyngeal space (lateral pharyngeal space, pharyngomaxillary space)

The parapharyngeal space (lateral pharyngeal space, pharyngomaxillary space) (**Figure 40.1**) forms an inverted cone with its base bounded by the petrous portion of the temporal bone and its apex at the level of the hyoid. It is crossed by the styloid process and attachments thus dividing the space into pre and post-styloid compartments. The pre-styloid compartment (anterior to the styloid complex) contains fat, connective tissue, the maxillary artery, the inferior alveolar nerve, the lingual nerve and the auriculotemporal nerve. In contrast, the post-styloid (posterior) compartment contains the carotid sheath and its contents, the glossopharyngeal and hypoglossal nerves, the sympathetic chain and associated lymph nodes.

Retropharyngeal space

The retropharyngeal space (**Figure 40.2**), contains lymph nodes and is bounded anteriorly by the middle layer of deep cervical fascia and posteriorly by the alar fascial component of the deep layer of deep cervical fascia. It extends craniocaudally from the skull base to the tracheal bifurcation. A midline raphe is formed by the attachment of the superior constrictor muscles to the alar fascia.

So-called 'danger space'

The so-called 'danger space' is a potential space between the alar fascia anteriorly and the deep layer of deep cervical fascia (prevertebral fascia) posteriorly, which extends craniocaudally from the skull base to the diaphragm.

Submandibular space

The submandibular space (**Figures 40.4, 40.5** and **40.6**), is bounded by the floor of mouth mucosa cranially and the mandible laterally, whilst the anterior and posterior bellies of the digastric muscle form the anteroinferior and posteroinferior boundaries respectively. The mylohyoid muscle lies anteriorly and the stylomandibular ligament posteriorly. The space is divided by the mylohyoid muscle into sublingual and submandibular compartments which contain the sublingual salivary gland and lymph nodes respectively. These compartments are continuous around the posterior free edge of the mylohyoid muscle and the submandibular gland lies within both as it straddles this free edge.

Masticator space

The masticator space, (**Figures 40.7** and **40.8**), lies inferior to the skull base (greater wing of sphenoid and squamous temporal bone) and is bounded by the pharyngeal mucosa medially and the medial surface of the ramus of the mandible laterally. The lateral pterygoid plate, superior constrictor, tensor and levator palatini muscles constitute the posteromedial border and can be subdivided into superficial temporal space superolaterally, deep temporal space superomedially, pterygoid space inferomedially and masseteric space inferolaterally. Communication with the pterygopalatine fossa exists via the pterygomaxillary fissure; the muscles of mastication and the mandibular division of the trigeminal nerve are contained within it.

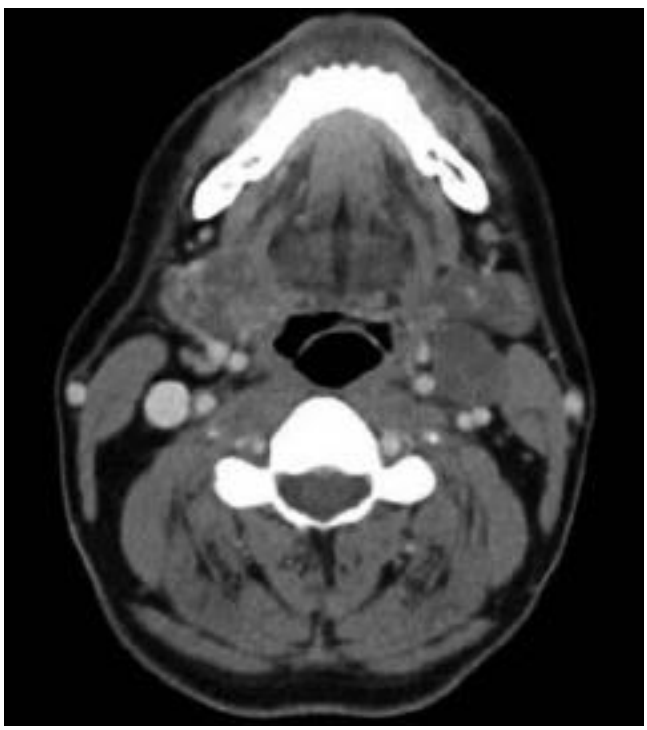


Figure 40.3 Axial contrast-enhanced CT scan demonstrating lymph node abscess in left parapharyngeal space. Note posterior displacement of internal jugular vein and medialization of carotid vessels. Mass effect and mucosal oedema cause subtle asymmetry of the airway at the level of the epiglottis.

Visceral space

The visceral space is formed anteriorly by the middle layer of deep cervical fascia that envelops the thyroid and the trachea, and posteriorly by the deep layer of deep cervical fascia. It contains the larynx, hypopharynx, cervical oesophagus, proximal trachea, thyroid and parathyroid glands.

Carotid space

The carotid space is a potential space formed by the carotid sheath, which is in itself formed from all three layers of deep cervical fascia blending together. It contains the common carotid artery, the internal jugular vein (IJV) and the vagus nerve.

Parotid space

The parotid space (**Figure 40.9**), is formed by the superficial layer of deep cervical fascia that splits to invest the parotid gland and therefore also contains the facial nerve, the retromandibular vein, the external carotid artery and its terminal branches.

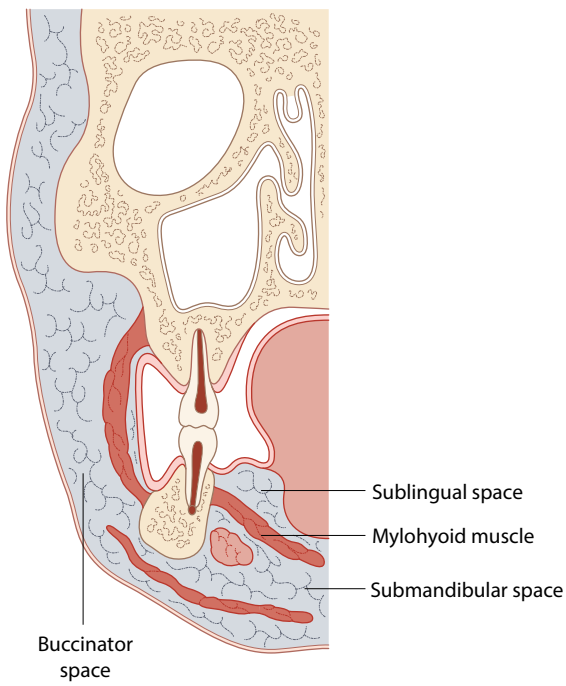


Figure 40.4 Submandibular, sublingual and buccinator spaces.



Figure 40.5 Pointing abscess of the submandibular space.

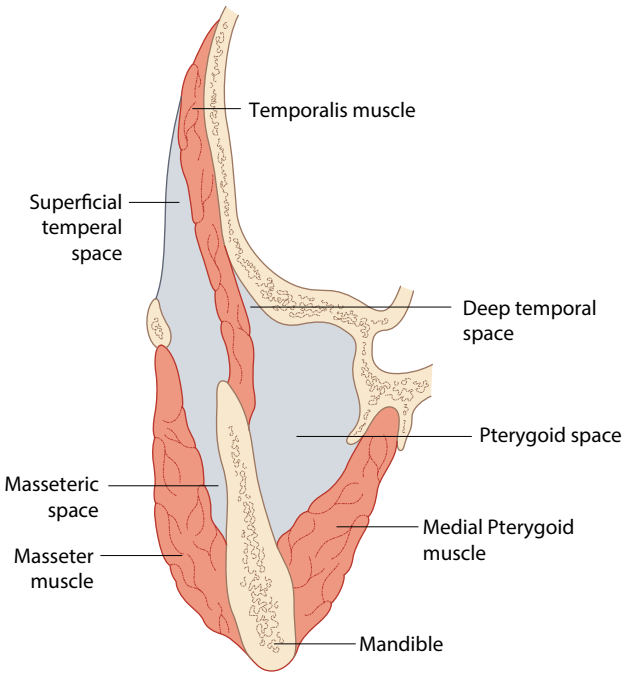


Figure 40.7 The masticator space and subdivisions.

Peritonsillar space

The peritonsillar space lies lateral to the pharyngeal tonsil and medial to the superior constrictor muscle. It contains loose connective tissue and is the site of accumulation of pus in peritonsillar abscess, or quinsy.

It is important to note that direct communication exists between the posterior aspect of the parapharyngeal space and the retropharyngeal space, as well as the anterior parapharyngeal space and the submandibular space. Moreover, peritonsillar space abscess can directly spread to the parapharyngeal space by direct extension, via lymph and/or blood vessels which traverse the superior constrictor muscle.[1–3]

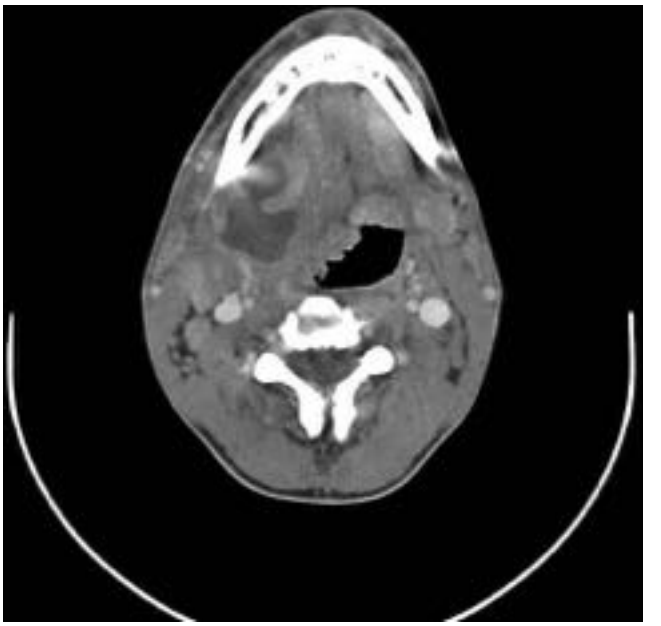


Figure 40.6 Axial contrast-enhanced CT scan showing abscess in the right submandibular space (different patient to Figure 40.5). A large hypodense area medial to the mandible is evident with ring enhancement and oedema affecting the soft tissues superficial and deep to the abscess. The pharyngeal lumen is narrowed and shifted to the contralateral side.

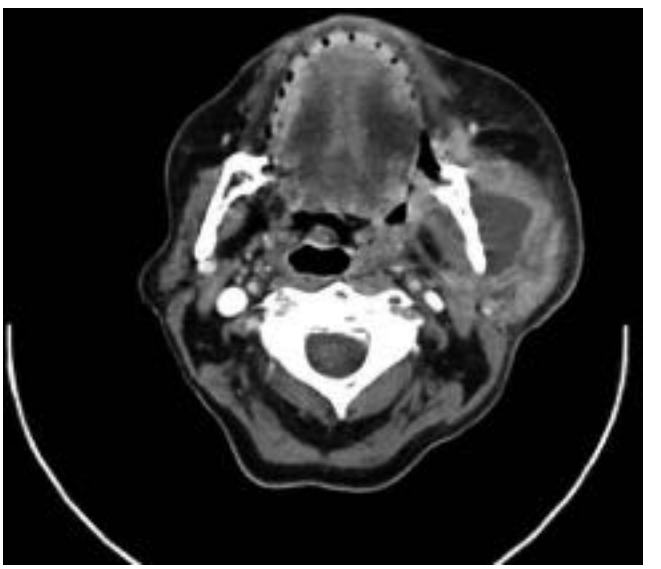


Figure 40.8 Axial contrast-enhanced CT scan showing masseteric space and pterygoid space abscess. Ring enhancement is evident around the hypodense abscess cavity as well as gross soft tissue oedema superficial and deep to the abscess causing asymmetry of the appearance of the external neck and deviation of the pharyngeal lumen contralaterally.

AETIOLOGY

In the pre-antibiotic era, 70% of deep neck space infections (DNSI) were caused by pharyngotonsillitis and 20% by odontogenic infection.[4] Recent published data



Figure 40.9 Parotid space abscess.

demonstrate that odontogenic infection is now the most common aetiological factor causing 31–49% of DNSIs.[5, 6] Peritonsillitis is variably mentioned as the underlying cause in approximately 7–20% of cases[4, 7] whilst in 17–57% of cases the primary source of infection is not clinically apparent.[7, 8]

Retrospective case series which include large numbers of cases describe various aetiological factors including ingestion of foreign body, coexisting Diabetes Mellitus (DM), Human Immunodeficiency Virus (HIV) infection and intravenous (IV) drug abuse although it is notable that the patient demographics from which these series have drawn their cases show considerable baseline variability and it would be inappropriate to extrapolate these findings to groups outwith the study populations. It is worth mentioning other cause of DNSI that have been reported and include mycobacterial infection, mandibular fracture, sialolithiasis, parotitis and thyroid infection.[4, 5, 7, 8]

INCIDENCE

The true incidence of DNSI is unknown. According to Hospital Episode Statistics (HES) data in England during the 12 months to the year ending March 2016 it is recorded that there were 216 admissions for 'drainage of retropharyngeal abscess'. By comparison there were 5246 admissions for 'drainage of abscess of peritonsillar region' during the same period. Other neck space infections are not coded in the data presented.[9]

CLINICAL FEATURES

Pain is the pre-eminent symptom in most patients, and in some published series it is almost ubiquitous.[7] Pain is usually focused at the neck space harbouring the infection, but can also be referred to the ear, cause odynophagia, trismus or torticollis. Other symptoms caused will depend on the site of infection but include dysphonia, dysphagia, sialorrhoea or cough.

The most common clinical signs include swelling in the neck, pyrexia and trismus. Skin fistulae, medial or anterior displacement of the lateral or posterior pharyngeal wall and gingival swelling occur commonly but less frequently.[5, 7, 10, 11]

Most series,[4, 5, 8, 13–16] although not all,[7, 11] demonstrate that males are more commonly affected than females by a ratio of approximately 1.6:1. The majority of patients, male and female, occupy the 20–40 year age range, with an estimated median age in the mid-30s. However, the age range of affected patients is wide and all age groups can be affected. The reasons why patients in their 3rd – 5th decades show the highest incidence of disease, and, why males are more commonly affected is not known. Co existent diseases (see 'Aetiology' above) include dental caries, DM, IV drug abuse and HIV infection.

CLINICAL ASSESSMENT AND INVESTIGATIONS

Assessment begins by taking a full clinical history and performing a thorough examination including fibre-optic nasendoscopy to assess the upper aerodigestive tract mucosa and airway patency simultaneously. Relevant clinical findings will lead the attending clinician to the differential diagnosis and will influence the subsequent lines of enquiry and early / emergent management strategy. Due to the potential for DNSIs to cause significant airway compromise it is essential that the initial assessment of patients is performed with high priority consideration as to whether the patient requires emergency airway management (see 'Airway management' below) or whether the patient is capable of maintaining their own airway for the foreseeable future. This initial assessment is important as it determines whether cross-sectional imaging with the patient in a supine position is safe to undertake. Consequently, it is essential that initial assessment is undertaken by clinicians experienced in the management of patients with airway compromise and who have the necessary clinical skills to be able to achieve a secure airway in the event of sudden deterioration.

When either the airway is secured or it is considered that significant airway compromise is not imminent, then cross-sectional radiological assessment can be undertaken in the form of contrast-enhanced CT as this is considered to be the gold-standard imaging modality.[17, 18] Due to potential communication of the visceral, retropharyngeal, danger and prevertebral spaces with the mediastinum it is imperative to include the mediastinum in the CT scan field. Where there is clinical concern of septic emboli spreading to the brain, lungs or liver these organs are required to be imaged also. Abscesses will demonstrate characteristic rim enhancement on CT imaging and cellulitis may be represented by fluid and fat stranding in the subcutaneous tissues and along fascial planes, whilst

myositis is suggested by enlargement and hyperenhancement of the adjacent musculature. Ultrasound imaging, in contrast, may be helpful to determine whether an abscess has sufficiently liquified to be drained, and may also be useful in targeting attempted drainage.[18] Where the infection is considered to be of dental origin an orthopantomogram is acquired, as it is in the case of infection of unknown aetiology.

Regular observations including pulse rate, blood pressure, temperature and respiratory rate are mandatory – the frequency of such observation being determined by the clinical condition of the patient. Blood is sent for urea, creatinine and electrolytes assays, blood count, including differential white cell count, C-reactive protein and erythrocyte sedimentation rate. Consideration is given as to whether it is appropriate to send blood for microbial culture. Pustulating skin fistulae and obviously infected dental sockets or roots may be swabbed for microbial cultures but routine pharyngeal microbiology swabs **must not** be taken to avoid precipitating an airway crisis as a consequence of triggering the gag reflex. If the clinical condition of the patient dictates it, appropriate venous access should be secured. Finally, it is essential that the patient is managed in a clinical environment commensurate with the severity of their presenting clinical condition.

SPECIFIC NECK SPACE INFECTIONS

- **Ludwig's angina** is considered to be an acute infection of bilateral sublingual and submandibular spaces, and the submental space. It occurs most commonly as a consequence of anterior dental infection.[1] In these patients, as a consequence of the underlying abscess, there is typically gross oedema of the floor of mouth and of the anterior tongue, such that the tongue becomes grossly swollen, protuberant and immobile. The result is significant risk of life-threatening airway obstruction and decision-making with regard to airway management needs to include emergency tracheostomy as a primary treatment option.
- **The parapharyngeal space (PPS), Figures 40.1** and **40.3**, can become infected either primarily or as a consequence of direct spread of infection from the submandibular and/ or the retropharyngeal spaces. A recent study of DNSIs of this space in particular demonstrated different clinical features depending on whether the anterior or posterior parapharyngeal space (APPS and PPPS respectively) is infected. The difference arises due to the anatomical contents of these sub-spaces. The APPS contains fat which in the presence of infection may liquefy, develop into pus and hence abscess formation. The PPPS is rich in lymph nodes and vessels and it is suggested that infection in this space causes lymphadenitis, but is less likely to develop into abscess formation. Consequently, APPS and PPPS infections can have different clinical courses and be managed differently, with a more conservative approach possible in PPPS and aggressive surgical drainage of pus required for APPS.[11] However, the ultimate distinction between the two is made on imaging.
- **Suppurative thyroiditis** – This usually occurs due to abnormal development of the 4th branchial pouch, resulting in a communicating sinus between the pharynx and the thyroid bed; in some cases, a proximal orifice may be identified as a defect in the mucosa of the piriform fossa. Patients with episodic recurrent suppurative thyroiditis need to have this diagnosis considered. Barium swallow examination and/ or cross-sectional imaging with contrast-enhanced CT or MRI may demonstrate the sinus tract, and the orifice will usually be identifiable by careful inspection of the piriform fossa mucosa under anaesthetic using direct pharyngoscopy. There is a preponderance for these affecting the left side of the hypopharynx. Treatment consists of excision of the tract of the sinus including the ipsilateral hemithyroid, although care must be taken to accurately identify the relationship of the sinus to the recurrent laryngeal nerve, as this can be variable.[19, 20] Alternatively, obliteration of the sinus opening in the hypopharynx using monopolar diathermy has been reported to be effective at preventing further infections.[21]
- **Retropharyngeal space abscess** is usually caused in adults by penetrating trauma through the posterior mucosal wall of the pharynx or cervical oesophagus. However, in children it is more commonly secondary to suppuration of retropharyngeal lymph nodes following an upper respiratory tract infection, although retropharyngeal lymph nodes tend to regress after the age of 5 years. Retropharyngeal space abscess is a significant cause of airway compromise, and as a consequence surgical tracheostomy is not uncommonly required.[22, 23] An attempt to intubate the patient using an endotracheal tube by an unprepared anaesthetist may lead to traumatic rupture of the abscess due to pressure from the tip of the intubating laryngoscope and subsequent flooding of the unprotected airway with pus and blood. Once the airway has been appropriately secured the abscess can be drained in a controlled fashion, the incision is made at the most inferior aspect of the collection such that further accumulation of pus will drain through gravity into the pharynx.
- **Masticator space infection** (**Figure 40.9**), usually arises secondary to odontogenic infection or less commonly as spread from infection in the parotid space, submandibular space or peritonsillar space. Trismus is a common clinical finding due to oedema of the adjacent pterygoid muscles.

MICROBIOLOGY AND PHARMACOLOGY

A wide range of aerobic, microaerophilic and anaerobic microorganisms typically colonize neck space infections.[24]

The predominant organism responsible for a given DNSI is influenced by the prime aetiological factor, be it odontogenic infection, penetrating neck trauma, IV drug use etc. The prevalence of these factors may depend on the geography, socio-economic status, and the incidence of predisposing factors such as coexisting DM and HIV infection.

However, there are some similarities reported in the literature with regards to microbiology of DNSIs as *Peptostreptococcus* spp., Viridans Group Streptococci, *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Klebsiella pneumoniae* are commonly present in many reported series.

Typically, broad-spectrum antibiotics are commenced prior to receipt of microbiological results, and in cases of a conservatively managed patient there may be no microbiological input into the case at all. Indeed, even with adequate pus sampling, failure to culture the causative bacteria occurs in approximately 25% of cases, which may be due to the difficulties in culturing anaerobic organisms that are inherently fastidious, or liberal use of antibiotics prior to referral to secondary care facilities.[8] Polymicrobial cultures are commonly seen.[25]

Antibiotic treatment should reflect the diverse nature of the microbiology of the condition, the likely aetiology and consider the possibility of adverse reactions in patients receiving treatment. Broad-spectrum antibiotics are prescribed, either amoxicillin/clavulanate, or 2nd or 3rd generation cephalosporins with metronidazole.[26] Antibiotic prescriptions need to be reviewed in the light of culture results and changed as necessary. Clindamycin and vancomycin are commonly used second-line agents, or potential first-line agents when drug allergy or sensitivity restrict choice. Resistance to antimicrobial agents is rising as evidenced by reported resistance to clindamycin in 11–18%, erythromycin 14%, penicillins 7–8% and aminopenicillins 0–3%[26] of cases.

SURGICAL TREATMENT

The maxim that one should '...never let the sun set on an undrained abscess' has guided management of neck space abscesses for many years especially in an era that predated cross-sectional imaging. Changes in radiological assessment have moved away from plain soft-tissue neck X-rays and now utilize contrast-enhanced rapid acquisition spiral tomographic scanners that permit reconstruction of acquired images in multiple planes and three dimensions. There has consequently been a considerable increase in the sensitivity and specificity of abscess diagnoses on radiological grounds, and with it the opportunity for a more conservative approach to management of selected cases.

Nonetheless, neck space infection is a potentially life-threatening infection; crude mortality rates of up to 2% have been published. The primary responsibility of the treating clinician is to ensure protection of the airway and to consider surgical drainage of pus secondarily. However, not all neck space infections develop into abscesses and even in the presence of an imaging study diagnostic of a small deep-seated abscess there has been a trend towards conservative management ***wherever possible.***[7]

Most published series report the surgical intervention rate, with the reported median confirming that approximately 80% of patients underwent surgical drainage of an abscess – although the range of reported intervention between studies is wide (10–100%)[5, 7, 8, 10, 13, 16, 27] and probably reflects preferred local practice rather than anything else. Usually, in cases without impending airway compromise, surgical intervention follows a period of conservative management of 24–48 hours with a decision taken to surgically intervene if there is a clinical failure to respond (persistent pyrexia, persisting or worsening pain, etc).

If surgical treatment is deemed necessary various treatment options exist. Conventional surgical drainage procedures incise the skin over the area of maximal fluctuance or induration. Following evacuation of the abscess contents, the abscess wall is curetted, and any loculations or boundaries between adjacent and communicating neck spaces (e.g. retropharyngeal, parapharyngeal and submandibular) are broken down – often with digital dissection. In classical Ludwig`s angina it is often necessary to undertake this procedure through multiple transcutaneous stab incisions to ensure that adequate drainage of these spaces bilaterally is achieved. Drains are secured to permit further drainage of pus; it is the author's preference to use soft, non-suction drains that protrude through the incised wound into the abscess cavity, with simple dry gauze dressings adhered distally. The activity of the drain is recorded by the number of dressing changes per 24 hours and they are removed gradually over a period of days. In the case of odontogenic infections the underlying dental infection(s) should be dealt with during the same general anaesthetic.

Consideration has been made of the merits of ultrasound-guided aspiration of pus compared to open surgical drainage and a small prospective randomized trial reported a shorter length of hospital stay (reduced mean length of hospital stay from 5.2 to 3.1 days), a 41% cost reduction and no difference in treatment efficacy or complication rate in the ultrasound aspiration group.[28] Also, microbiology sampling by aspiration rather than by microbiological swabs of an incised abscess has been shown to increase the isolation of anaerobes and reduce the detection of potential skin contaminants.[24, 28, 29]

AIRWAY MANAGEMENT

Maintaining a patent and safe airway is the pre-eminent step in management of patients with DNSI. Mortality can occur as a consequence of asphyxiation and hypoxia as well as delayed septic complications. The widespread use of antibiotics has reduced the morbidity and mortality from pharyngeal oedema and permits a watch and wait policy in selected cases. Conversely, large abscesses causing a precarious airway demand a coherent management

strategy to secure the airway prior to surgical drainage and to maintain the airway post-operatively. The decision as to which management strategy can be adopted is made on a case-by-case basis.

Conventional endotracheal intubation is not always possible due to trismus, reduced neck extension, laryngopharyngeal oedema, mass effect from the abscess and the friable nature of the mucosa that readily obstructs the view due to contact bleeding. It is of utmost importance that induction of anaesthesia does not lead to a situation where neither ventilation nor intubation by conventional means are possible. Algorithms are available online[32] to assist joint anaesthetic/surgical airway management and these should be agreed by the attending teams prior to commencement of any procedure.

Options available to manage the airway are numerous and described elsewhere (see Chapter 72, Upper airway obstruction and tracheostomy).[12, 33] Patients that have impending airway obstruction need to be transferred to a place of safety for airway management. In the UK, this would be to one of the anaesthetic rooms in a hospital operating theatre complex with anaesthetic and surgical staff who have the appropriate experience in attendance. Once a plan of action has been agreed, the surgical and scrub teams prepare the operating theatre in anticipation of the requirement for an emergency tracheostomy in the event of failed intubation and loss of airway. If it is deemed that the patient will tolerate it, it is advisable to infiltrate 2% lignocaine with 1:80000 adrenaline solution into the skin at the site of potential tracheostomy prior to the commencement of the anaesthetic procedure. In the event of an emergency tracheostomy being required, this step does not need to be repeated; the adrenalin will have caused some local vasoconstriction and it lessens the likelihood of flexion/extension reaction from a semi-obtunded patient resultant from the pain of the skin incision.

If there are sufficient concerns that oral or nasal intubation are unlikely to be successful, it is preferable to perform tracheostomy under local anaesthetic as an emergency (as opposed to an emergency 'crash' tracheostomy).

Once the airway has been secured, the abscess can be drained in a controlled fashion as described.

COMPLICATIONS

The incidence of resulting complications reported varies considerably between different published series. Tracheostomy, either planned or 'crash', is reported as necessary in 3–22% of patients[4, 7] and, in general, patients with Ludwig's and retropharyngeal abscess are at higher risk of airway obstruction than those presenting with lateralized abscesses. Other complications include pneumonia, IJV thrombosis, carotid artery aneurysm and rupture, necrotizing fasciitis, skin fistulae and defects, vocal cord and facial palsies, descending mediastinitis, upper gastrointestinal bleeding, iatrogenic bleeding following tracheostomy insertion, septic emboli from IJV thrombosis, sepsis, multi-organ failure and death.

Patients with pre-existing comorbidities are more likely to suffer from complications, as are patients that have infection in more than two neck spaces: in the series published by Kang et al,[34] abscess formation in the retropharyngeal space was always seen in patients that developed mediastinitis. A combined thoracic and cervical exploration may be required to facilitate adequate treatment in those patients.

PAEDIATRIC NECK SPACE INFECTION

It has been reported that neck space infection in children is increasing in incidence[22, 35] although it is not known why. Childhood neck space infection more often results from an upper respiratory tract infection than from odontogenic aetiologies and methicillin-resistant *Staphylococcus aureus* (MRSA) is more frequently isolated from pus samples taken from DNSIs in children than in adults. Two published series have reported positive MRSA cultures in 27% and 42% of cases.[36, 37] There is a rising prevalence in cultures positive for MRSA demonstrated year on year in many other series.[36–40]

The management principles for paediatric DNSI are no different to those required to treat adults; maintenance of the airway is of the utmost importance, appropriate imaging to identify the distribution of affected neck spaces, treatment with broad-spectrum antibiotics until specific sensitivities are known, and a decision made and then frequently reviewed as to whether surgical drainage is indicated, and if so, what form that surgical procedure takes.

Paediatric patients demonstrate different physiological responses to sepsis in comparison to adults and attending clinicians need to understand and respond to alterations in the clinical condition of paediatric patients with rapidity in order to avoid catastrophic deterioration of the airway and/or the cardiovascular system from impending septic shock.

CONCLUSION

Neck space infections are seen in patients of all ages, with and without pre-existing comorbid problems. Assessment and management of the airway is required alongside treatment of the underlying infection with broad-spectrum antibiotics. Life-threatening complications occur frequently which, given the anatomy of the cervical fascia, may be distant to the primary focus of infection. However, mortality is usually an infrequent occurrence with appropriate and timely treatment.

FUTURE RESEARCH

- Ongoing publication of prospectively collated microbiology data pertaining to DNSI to assess changing trends in causative organisms and patterns of antibiotic resistance, ideally across different continents.
- Safety and efficacy of conservative vs. US-guided aspiration vs. surgical management of DNSI in children with small localized abscesses.
- How is the incidence and management of DNSI being influenced by rising incidences of diabetes and obesity?

KEY POINTS

- Understanding of the anatomy of cervical fascial planes is key to diagnosis and management.
- Cross-sectional imaging, where possible, will provide extremely useful information to aid treatment decision-making.
- Generally the mantra 'Never let the sun set on undrained pus' should be adhered to. But, some non-toxic patients with small localized abscesses may be suitable for more conservative management. These patients require very close clinical observation and regular review of their treatment plan in the light of a changing clinical situation.

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CHAPTER 41

ANATOMY AND EMBRYOLOGY OF THE MOUTH AND DENTITION

Barry K.B. Berkovitz

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SEARCH STRATEGY

Data in this chapter may be updated by a search using the following keywords: mouth, dentition, anatomy and embryology.

INTRODUCTION

The importance of the mouth to the otolaryngologist is self-evident. It is the portal of entry for visual examination of the oropharynx, larynx and the opening of the Eustachian tube in the nasopharynx. It is also the portal of entry for many of the surgical procedures undertaken in these regions. Malformations in the mouth, such as cleft palate, may have important consequences for the healthy functioning of the system. Infection or tumours from the mouth may spread to involve the ear, nose and throat. As an example, infection from maxillary teeth may give referred pain to the nasal region, while infection from mandibular teeth may spread to the neck and result in severe (and sometimes fatal) respiratory embarrassment. Due to its close physical (and also evolutionary) relationship to the ear, clinical conditions affecting the jaw joint (temporomandibular joint) may need to be differentiated from those directly involving the ear.

The mouth can be subdivided into the vestibule (external to the teeth) and the oral cavity proper (internal to the teeth). The mouth extends from the lips and cheeks externally to the anterior pillars of the fauces (palatoglossal arches) internally, where it continues into the oropharynx. The roof of the mouth is the palate and separates the oral and nasal cavities. The floor of the mouth is formed by the mylohyoid muscles and is occupied mainly by the tongue. The lateral walls of the mouth are defined by the cheeks and retromolar regions. Opening into the mouth are three pairs of major salivary glands (parotid, submandibular and sublingual) and numerous minor salivary glands (labial, buccal, palatal, lingual).

PALATE

The palate is divisible into two regions: the hard palate in front and soft palate behind.

Hard palate

The skeleton of the hard palate is formed by the palatine processes of the maxillae and the horizontal plates of the palatine bones. The oral mucosa is bound tightly to the underlying periosteum. In its more lateral regions it also possesses a submucosa where the main neurovascular bundles lie (**Figure 41.1**).

The periphery of the hard palate surrounding the necks of the teeth is termed the gingiva and a zone similarly lacking submucosa runs anteroposteriorly in the midline as a narrow, low ridge; the palatine raphe. At the anterior

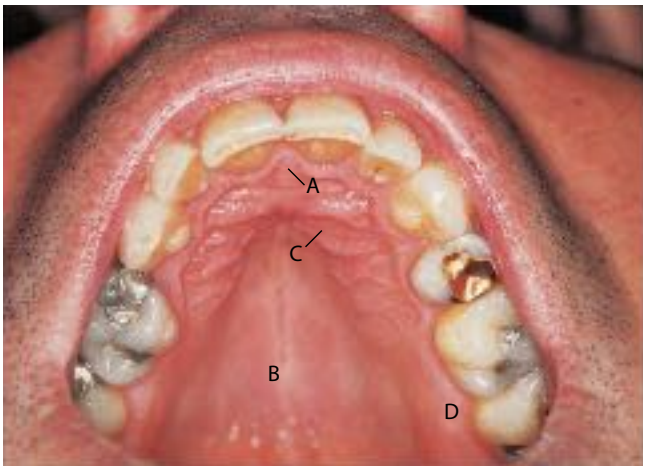


Figure 41.1 The hard palate. A, Incisive papilla; B, palatine raphe; C, palatine rugae; D, alveolus. Reprinted from Ref. 1 by permission from Elsevier.



Figure 41.2 The soft palate and oropharyngeal isthmus. A, Palatoglossal fold; B, palatopharyngeal fold; C, palatine tonsil; D, uvula. Reprinted from Ref. 1 by permission from Elsevier.

extremity of the raphe behind the incisor teeth is a small prominence, the incisive papilla that covers the incisive fossa at the oral opening of the incisive canal. Radiating outwards from the palatine raphe in the anterior half of the hard palate are irregular transverse ridges or rugae. The pattern of rugae is unique for the individual and has been used in forensic science to identify a dead individual.

The submucosa in the posterior half of the hard palate contains minor mucous salivary glands. These secrete through numerous small ducts although, bilaterally, larger ducts collecting from many of these glands often open at the paired palatine foveae. These are two sagittally elongated depressions, sometimes a few millimetres deep, which flank the midline raphe at the posterior border of the hard palate.

The upper nasal surface of the hard palate is the floor of the nasal cavity and is covered by ciliated respiratory epithelium. The lower oral masticatory surface is covered by keratinized epithelium.

Soft palate

The soft palate is a mobile flap suspended from the back of the hard palate, sloping down between the oral and nasal parts of the pharynx (**Figure 41.2**). The boundary between the hard and soft palate may be distinguished by a change in colour, the soft palate being a darker red with a yellowish tint. In its relaxed and pendant position, its anterior (oral) surface is concave, with a median raphe. Its posterior aspect is convex and continuous with the nasal floor. A median conical process, the uvula, projects downwards from its posterior border. Just behind and medial to each upper alveolar process, in the lateral region of the anterior part of the soft palate, a small bony prominence can be felt. This is produced by the pterygoid hamulus, an extension of the medial pterygoid plate of the sphenoid bone.

The soft palate contains an aponeurosis, muscular tissue, vessels, nerves, lymphoid tissue and mucous glands, while some taste buds are situated on its oral aspect.

A thin, fibrous palatine aponeurosis is attached to the posterior border of the hard palate. It represents the expanded tendons of the tensor veli palatini muscles and provides the fibrous skeleton of the soft palate that supports the palatine musculature. The aponeurosis is thick in the anterior two-thirds of the soft palate but very thin further back. The palatine muscles are attached to the aponeurosis.

CHEEKS

The cheeks are covered externally by skin and internally by mucous membrane (buccal mucosa) and have a muscular skeleton, the buccinator. Internally, the pink mucosa of the cheek adheres firmly to the buccinator muscle. Few structural landmarks are visible. The parotid duct drains in the region of a small parotid papilla opposite the maxillary second molar tooth. A whitish line (the linea alba) may be seen at a position related to the occlusal plane of the teeth: this hyperkeratinized line is presumably the result of continuous mild trauma during biting. Yellow patches (Fordyce's spots) representing ectopic sebaceous glands may be evident on the internal surface of the cheek. Their numbers increase in puberty and in later life. Behind the molar teeth, a fold of mucosa can be seen extending from the upper to the lower alveolus, especially when the mouth is opened widely. This fold covers the pterygomandibular raphe that extends from the pterygoid hamulus to the back of the mylohyoid line. The raphe gives origin to the buccinator muscle from its anterior surface and the superior constrictor muscle from its posterior surface. The entrance to the pterygomandibular space lies lateral to the pterygomandibular raphe and medial to the ridge produced by the anterior border of the ramus of the mandible.

Between the lips or cheeks and the teeth lies a slit-like space, the oral vestibule. Where the mucosa covering

the alveolus of the jaw is reflected onto the lips and cheeks, a trough or sulcus is formed which is called the fornix vestibuli. With the teeth in occlusion, a space still exists behind the last molar tooth (retromolar region), allowing for the passage of fluids when the jaws are wired together following fractures. A variable number of sickle-shaped folds containing loose connective tissue run across the fornix vestibuli. The upper and lower labial frena (or frenula) are constant folds in the midline. Other folds may traverse the fornix near the canines or premolars.

LIPS

Like the cheeks, the lips are covered externally by skin and internally by mucous membrane (labial mucosa) that is smooth and shiny and shows small elevations caused by underlying mucous glands. The lips have a muscular skeleton, the orbicularis oris muscle.

The red zone of the lip (the vermilion) is a feature characteristic of man. In the upper lip, the vermilion protrudes externally in the midline to form the tubercle, above which is situated a grooved region termed the philtrum. The lower lip shows a slight depression corresponding to the tubercle.

FLOOR OF THE MOUTH

This comprises a small horseshoe-shaped region beneath the tongue (**Figure 41.3**). Near the base of the tongue in the midline, a fold of tissue called the lingual frenum is seen to extend onto the inferior surface of the tongue. The sublingual papilla is a conspicuous centrally positioned protuberance at the base of the tongue. The submandibular salivary ducts open into the mouth at this papilla. On either side of the sublingual papilla are the sublingual folds, beneath which lie the submandibular ducts and sublingual salivary glands. The muscle forming the floor of the mouth is the mylohyoid muscle.

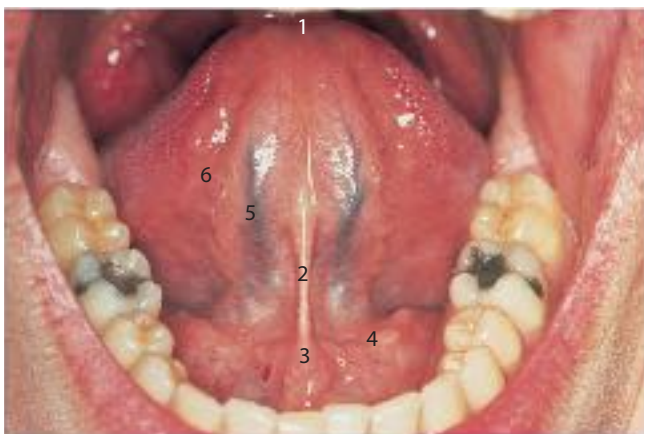


Figure 41.3 The ventral surface of the tongue, related to the floor of the mouth. 1, Tip of tongue; 2, lingual frenum; 3, sublingual papilla; 4, sublingual fold; 5, deep lingual vein; 6, fimbriated fold. Reprinted from Ref. 1 by permission from Elsevier.

OROPHARYNX

The oropharynx extends from the soft palate to the upper border of the epiglottis (see **Figure 41.2**). Its lateral wall consists of the palatopharyngeal arch, with the palatine tonsil lying between this arch and the palatoglossal arch anteriorly. The two arches are also known as the pillars of the fauces. The floor of the oropharynx is occupied by the pharyngeal aspect of the tongue.

The aperture of communication between the mouth and pharynx, the oropharyngeal isthmus, is situated between the soft palate above and the dorsum of the tongue below, bounded on both sides by the palatoglossal arches. Each palatoglossal arch runs downwards, laterally and forwards and contains the palatoglossus muscle with its covering mucous membrane. The approximation of the arches, to shut off the mouth from the oropharynx, is essential to deglutition.

Palatine tonsil

The palatine tonsil is a mass of lymphoid tissue situated in the lateral wall of the oropharynx, where it lies within the tonsillar fossa between the diverging palatopharyngeal and palatoglossal arches. It forms the anteroinferior part of Waldeyer's ring of lymphoid tissue. This ring surrounds the openings into the digestive and respiratory tracts and consists of the palatine and tubal tonsils laterally, the nasopharyngeal tonsil (adenoids) and smaller collections of lymphoid tissue in the intertonsillar intervals posterosuperiorly, and the lingual tonsil inferiorly.

The medial (free) surface of the palatine tonsil projects into the oropharynx and usually presents a pitted appearance. These pits, 10–15 in number, lead into a system of blind-ending, often highly branching crypts, which extend through the whole thickness of the tonsil. The deep (lateral) aspect of the tonsil is covered by the fibrous tissue of the tonsillar hemicapsule that can be easily separated throughout most of its extent from the underlying superior constrictor muscle. An important and sometimes large vein (the external palatine or paratonsillar vein) descends from the soft palate lateral to the tonsillar hemicapsule before piercing the pharyngeal wall. Haemorrhage from this vessel can complicate tonsillectomy.

The size of the tonsil varies greatly and at puberty may be approximately 10–15 mm in transverse diameter and approximately 20–25 mm in the vertical dimension. The tonsil starts to atrophy at puberty so that, by old age, only a little tonsillar lymphoid tissue remains.

A more detailed treatment of the oropharyngeal anatomy can be found in Chapter 44, Anatomy of the pharynx and oesophagus.

TONGUE

The tongue is a highly muscular organ of deglutition, taste and speech. It is partly oral and partly pharyngeal in position. It has dorsal and ventral surfaces and a root and an apex.



Figure 41.4 The dorsum of the tongue. 1, Sulcus terminalis; 2, posterior third (pharyngeal part); 3, lingual follicles; 4, pillars of fauces; 5, epiglottis; 6, vallecula defined by median and lateral glosso-epiglottic folds; 7, anterior two-thirds (palatine part); 8, circumvallate papillae; 9, foramen caecum. Reprinted from Ref. 2 by kind permission of Informa Healthcare.

The curved dorsum of the tongue (**Figure 41.4**) shows an anterior, oral part facing upwards and a posterior, pharyngeal part facing posteriorly, the two being separated by a V-shaped groove, the sulcus terminalis. The sulcus terminalis runs anterolaterally towards the palatoglossal arches from a median depression, the foramen caecum that indicates the site of the embryonic thyroid diverticulum that gives origin to the thyroid gland.

The anterior two-thirds of the tongue in front of the sulcus terminalis is related to the hard and soft palates above and has a tapered tip or apex touching the incisor teeth, and a margin in contact with the gums and teeth. On each side, in front of the palatoglossal arch, are four or five vertical folds, the foliate papillae. The dorsum has a longitudinal median sulcus and is papillated and the three remaining types of papillae representing the filiform, fungiform and circumvallate papillae. Of the papillae, all except the filiform papillae bear taste buds.

The keratinized filiform papillae are the most numerous. They are minute conical or cylindrical projections, arranged in diagonal rows extending anterolaterally, parallel with the sulcus terminalis, except at the apex where they are transverse. They have a masticatory function, appearing to increase the friction between the tongue and food, facilitating the movement of particles by the tongue within the oral cavity. The fungiform papillae appear scattered on the lingual margin but also irregularly on the dorsal surface, where they may occasionally be numerous. They differ from filiform papillae by their larger size, rounded (mushroom) shape and deep red colour (due to their thin, non-keratinized epithelium and highly vascular connective tissue core). The circumvallate papillae are cylindrical structures, 1–2 mm in diameter, varying in number from about 8 to 12 and form a V-shaped row immediately in front of the sulcus terminalis. Each papilla is circumscribed by a groove.

The pharyngeal (postsulcal) third of the tongue lying behind the sulcus terminalis forms the base of the tongue and lies posterior to the palatoglossal arches. It forms the anterior wall of the oropharynx and its mucosa is reflected on to the epiglottis posteriorly by a median and two lateral glossoepiglottic folds. The folds surround two depressions or valleculae. The pharyngeal part of the tongue has underlying lymphoid nodules that produce low-surface elevations collectively termed the lingual tonsil. The ducts of small seromucous glands open on the apices of these elevations.

The ventral inferior surface of the tongue (see **Figure 41.3**) is smooth, purplish and reflected on to the oral floor and gums. Anteriorly is a median mucosal fold, the lingual frenum. Lateral to this fold on either side, a deep lingual vein is visible, and lateral to the vein is a fringed mucosal ridge, the plica fimbriata.

ORAL MUCOSA

The lining of the mouth, the oral mucosa, is continuous with the skin at the vermilion of the lip and with the pharyngeal mucosa at the oropharyngeal isthmus. It varies in structure, appearance and function in different regions of the oral cavity.[1] It can be classified into masticatory, lining and specialized mucosae. Masticatory mucosa covers the gingivae (gums) and hard palate. Its epithelium is keratinized (often parakeratinized) and has a dense fibrous lamina propria. It is pink in colour. A submucosa is absent from the gingivae and the midline palatine raphe, but is present over the rest of the hard palate, especially where it contains mucous salivary glands, and also the greater palatine nerves and vessels. The masticatory mucosa is bound firmly to underlying bone or to the necks of the teeth, forming in the gingivae and palatine raphe a mucoperiosteum.

Lining mucosa covers the internal surfaces of the lips and cheeks, floor of the mouth, soft palate, ventral surface of the tongue and the alveolar processes (excluding the gingivae). It is red in colour, having a non-keratinized, stratified, squamous epithelium overlying a loosely fibrous and elastic lamina propria, and the submucosa contains some fat deposits and collections of minor mucous glands.

Gustatory mucosa covers the anterior two-thirds of the dorsum of the tongue. The vermilion (red zone) of the lip that separates the skin from lining mucosa has been regarded by some as being specialized, as it shares features of both lining and masticatory mucosa.[2] The epithelium that attaches the tooth to the gingiva, the junctional epithelium, also has features that distinguish it from all other stratified squamous epithelia (e.g. internal and external basal lamina).

MUSCLES OF THE ORAL CAVITY

Buccinator muscle

The muscle of the cheek is the buccinator (**Figure 41.5**). Above and below it is attached to the outer surfaces of the alveolar processes of the maxilla and mandible by the side of the molar teeth. Behind, it arises from the anterior margin of the pterygomandibular raphe (a thin band of tendinous fibres passing between the hamulus of the medial pterygoid plate down to the posterior end of the mylohyoid line of the mandible). Additionally, a few fibres arise from a fine tendinous band that bridges the interval between the maxilla and the pterygoid hamulus. From these origins the fibres of buccinator pass forwards towards the angle of the mouth. Here, the central fibres decussate, those from below crossing to the upper part of the mouth, those from above crossing to the lower part. The highest and lowest fibres of buccinator continue forwards to enter their corresponding lips without decussation.

The buccinator muscle compresses the cheek against the teeth and gums during mastication and assists the tongue in directing food between the teeth. When the cheeks have been distended with air, the buccinators expel it between the lips, for example, when playing wind instruments. The buccinator muscle is innervated by the buccal branch of the facial nerve. Its arterial supply is derived from the facial and maxillary (buccal branch) arteries.

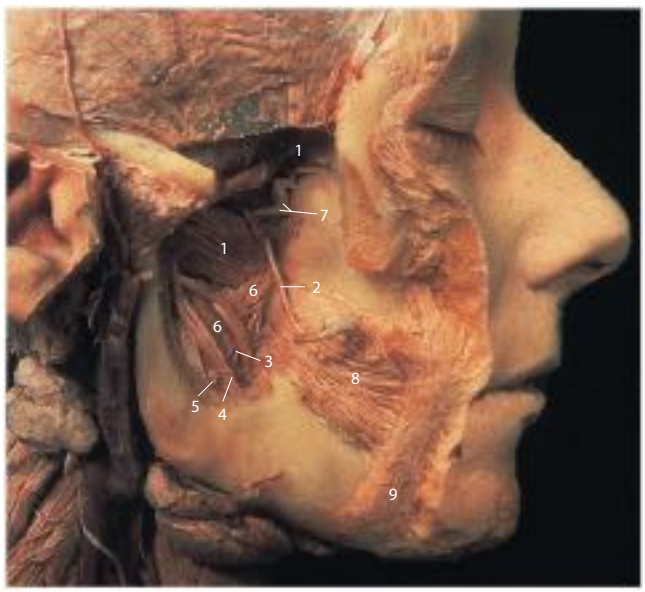


Figure 41.5 The buccinator muscle and the infratemporal fossa. 1, Lateral pterygoid muscle (two heads); 2, buccal nerve; 3, lingual nerve with accompanying branch from maxillary artery; 4, inferior alveolar nerve and artery; 5, mylohyoid nerve; 6, medial pterygoid muscle (two heads); 7, maxillary artery; 8, buccinator muscle; 9, depressor anguli oris muscle. Reprinted from Ref. 2 by kind permission of Informa Healthcare.

Mylohyoid muscle

The main muscle forming the floor of the mouth is the mylohyoid muscle (**Figures 41.6** and **41.7**). Immediately above it is the geniohyoid muscle. The mylohyoid muscle is a flat, triangular sheet attached to the mylohyoid line of the mandible. The posterior fibres pass medially and slightly downwards to the front of the body of the hyoid bone near its lower border. The middle and anterior fibres from each side decussate in a median fibrous raphe that stretches from the symphysis menti to the hyoid bone.

The mylohyoid muscle elevates the floor of the mouth in the first stage of swallowing. It also aids in elevating the hyoid bone or depressing the mandible when the hyoid bone is fixed. The muscle is supplied by the mylohyoid branch of the inferior alveolar nerve and derives its blood supply from three sources: the lingual artery (sublingual branch),



Figure 41.6 The floor of the mouth as seen in a median sagittal section through the head. 1, Hard palate; 2, soft palate; 3, upper lip and superior part of orbicularis oris muscle; 4, edentulous maxillary alveolar ridge; 5, lower lip with inferior part of orbicularis oris muscle; 6, body of mandible; 7, tongue; 8, genioglossus muscle; 9, geniohyoid muscle; 10, mylohyoid muscle; 11, hyoid bone; 12, epiglottis; 13, valeculla. Reprinted from Ref. 2 by kind permission of Informa Healthcare.

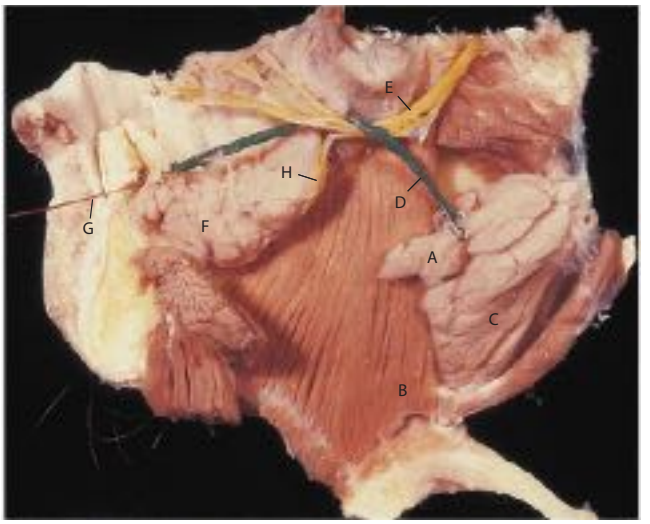


Figure 41.7 Medial view of the floor of mouth showing deep part of the submandibular gland (A) passing around the free border of the mylohyoid muscle (B). C, Superficial part of submandibular gland; D, submandibular duct wrapping around the lingual nerve (E); F, sublingual strand; G, bristle in opening of submandibular duct at the sublingual papilla; H, branches of the lingual nerve to the sublingual gland carrying parasympathetic nerve fibres. Reprinted from Ref. 1 by permission from Elsevier.

the maxillary artery (the mylohyoid branch of the inferior alveolar artery) and the facial artery (submental branch).

Geniohyoid

This narrow muscle lies above the medial part of the mylohyoid (**Figure 141.8** and see also **Figure 41.6**). It arises from the inferior genial tubercle (mental spine) on the back of the symphysis menti. It runs backwards and slightly downwards to attach to the anterior surface of the body of the hyoid bone.

The geniohyoid muscle elevates the hyoid bone and draws it forwards. When the hyoid bone is fixed, the geniohyoid muscle depresses the mandible. The muscle is supplied by the first cervical spinal nerve, through the hypoglossal nerve. The blood supply is derived from the lingual artery (sublingual branch).

Muscles of the tongue

The muscles of the tongue comprise both extrinsic and intrinsic muscles, the former extending outside the tongue and moving it bodily, the latter lying wholly within it and altering its shape.

The **extrinsic** musculature is composed of four pairs of muscles: genioglossus, hyoglossus, styloglossus and palatoglossus.

GENIOGLOSSUS MUSCLE

The genioglossus muscle lies near the midline (see **Figures 41.6** and **41.8**). It arises from the superior genial tubercle (mental spine) behind the mandibular symphysis and above the origin of the geniohyoid muscle. From its origin, the fibres fan out as they pass backwards and upwards. The inferior fibres are attached to the upper anterior surface of the hyoid body near the midline. Intermediate fibres pass backwards into the posterior part of the tongue, and superior fibres ascend forwards to enter the whole length of the ventral surface of the tongue from root to apex, intermingling with the intrinsic muscles.



Figure 41.8 Muscles of the tongue and structures on the hyoglossus muscle in the floor of the mouth. 1, Lingual nerve; 2, hypoglossal nerve; 3, submandibular duct (cut); 4, external carotid artery; 5, lingual artery; 6, glossopharyngeal nerve (cut); 7, hyoglossus muscle; 8, styloglossus muscle; 9, geniohyoid muscle; 10, genioglossus muscle. Reprinted from Ref. 1 by permission from Elsevier.

The genioglossus muscle brings about the forward traction of the tongue to protrude its apex from the mouth. Acting bilaterally, the two muscles depress the central part of the tongue, making it concave from side to side. Acting unilaterally, the muscle helps move the tongue to the opposite side. Genioglossus receives its motor innervation from the hypoglossal nerve. Its blood supply is derived from the lingual artery (sublingual branch) and the facial artery (submental branch).

HYOGLOSSUS

This muscle arises from both the greater cornu and from the front of the body of the hyoid bone (**Figure 41.8**). It runs up to insert into the side of the tongue between the inferior longitudinal muscle medially and styloglossus laterally.

The hyoglossus muscle depresses the tongue. It is innervated by the hypoglossal nerve. Its arterial supply is derived from the lingual (sublingual branch) and the facial arteries (submental branch).

STYLOGLOSSUS

This muscle arises from near the apex of the styloid process (anterolateral aspect) and from the styloid end of the stylomandibular ligament (a fibrous cord extending from the tip of the styloid process to the lesser cornu of the hyoid bone) (**Figure 41.8**). From this origin, the muscle runs downwards and forwards to enter the substance of the tongue, decussating with fibres of hyoglossus.

The styloglossus muscle acts to pull the tongue upwards and backwards. The muscle is supplied by the hypoglossal nerve and derives its blood supply from the sublingual branch of the lingual artery.

PALATOGLOSSUS

Although this muscle is most closely associated with the soft palate in function and innervation, it is described here with the other tongue muscles. The palatoglossus arises from the palatine aponeurosis and passes to the side of the tongue within the palatoglossal arch. Acting bilaterally, the muscles narrow the oropharyngeal isthmus and can also help raise the sides of the tongue. Unlike the other tongue muscles, the palatoglossus is innervated, not by the hypoglossal nerve, but by the cranial portion of the accessory nerve through the pharyngeal plexus. Its blood supply is derived from the ascending pharyngeal and facial (ascending palatine) arteries.

INTRINSIC MUSCLES OF THE TONGUE

These comprise four groups: the superior and inferior longitudinal, the transverse and the vertical muscles.

The superior longitudinal muscle forms a thin stratum of longitudinal and oblique fibres lying beneath the lining of the dorsum of the tongue. The inferior longitudinal muscle is a narrow band of muscle beneath the inferior surface between the genioglossus and hyoglossus muscles. The transverse muscle fibres pass laterally from the median fibrous septum to the submucous fibrous tissue at the lingual margin. The vertical muscle fibres extend from the dorsal to the ventral aspects of the tongue in the borders of its anterior part.

When the superior and inferior longitudinal muscles contract, the tongue tends to shorten. In addition, the superior longitudinal fibres also pulls the apex and sides upwards to make the dorsum concave, while the inferior longitudinal fibres pull the apex down to make the dorsum convex. The transverse muscle contracts to narrow and elongate the tongue while contraction of the vertical muscle makes the tongue flatter and wider. Acting alone or in pairs and in endless combination, the intrinsic muscles give the tongue precise and highly varied mobility, important not only in alimentary function but also in speech. All intrinsic lingual muscles are supplied by the hypoglossal nerve and derive their blood supply from the lingual artery.

MUSCLES OF THE LIPS

The muscles surrounding the mouth and contributing to the lips are derived from two different sources. Neighbouring muscles of facial expression converge on the angle of the mouth and pass through into the lips. For the upper lip, these are chiefly from the buccinator and depressor anguli oris, and for the lower lip, the buccinator, levator anguli oris and zygomaticus major. In addition, an accessory muscle, incisivus labii superioris, is present in the upper lip, arising from the floor of the incisive fossa of the maxilla above the eminence of the lateral incisor tooth and running laterally within the upper lip to the modiolus (a zone of muscle intersection just beyond the corner of the mouth). A similar strip of muscle is present in the lower lip, incisivus labii inferioris, arising from the floor of the incisive fossa of the mandible and running laterally within the lip to the modiolus.

The muscles of the mouth are capable of various movements, including closing, protrusion and pursing of the lips. The muscles are innervated by the facial nerve (buccal and mandibular branches) and derive their blood supply from the facial (superior and inferior labial), maxillary (mental and infraorbital branches) and superficial temporal arteries.

VASCULAR SUPPLY AND LYMPHATIC DRAINAGE OF THE ORAL CAVITY

Arteries

The main arteries to the teeth, palate and cheeks are derived chiefly from the maxillary artery, a terminal branch of the external carotid. The lips are mainly supplied by the superior and inferior labial branches of the facial artery. The floor of the mouth and tongue are supplied by the lingual arteries. The cheek is supplied by the buccal branch of the maxillary artery.

Teeth in the lower jaw are supplied by the inferior alveolar (dental) artery, a branch of the maxillary artery (see **Figure 41.5**). It lies in the infratemporal fossa where it gives off a mylohyoid branch before entering the mandibular foramen. The inferior alveolar artery then traverses the mandibular canal (accompanied by the inferior alveolar nerve) to supply the mandibular molars and premolars and divides into the incisive and mental branches below the premolar teeth. The incisive branch continues below the incisor teeth (which it supplies) to the midline. The mental artery leaves the mental foramen to supply the chin.

Teeth in the upper jaw are supplied by the posterior, middle and anterior superior alveolar (dental) arteries that form a plexus of vessels. The posterior superior alveolar artery usually arises from the third part of the maxillary artery in the pterygopalatine fossa. It descends on the infratemporal surface of the maxilla to supply molar and premolar teeth, adjacent bone and the maxillary sinus, and provides superficial branches that continue over the alveolar process to supply the gingivae. The anterior superior alveolar artery arises from the infraorbital artery that enters the orbit posteriorly through the inferior orbital fissure to run in the infraorbital groove and canal with the infraorbital nerve. It curves through a fine canal (canalis sinuosus) to supply the upper incisor and canine teeth and the mucous membrane in the maxillary sinus. A middle superior alveolar artery is often present and supplies the premolar teeth.

The gingival tissues derive their blood supply from the maxillary and lingual arteries. In the lower jaw, the buccal gingiva posteriorly is supplied by the buccal artery (a branch of the maxillary artery as it crosses the lateral pterygoid muscle) and by perforating branches from the

inferior alveolar artery. Anteriorly, the labial gingiva is supplied by the mental artery and by perforating branches of the incisive artery. The lingual gingiva is supplied by perforating branches from the inferior alveolar artery and by the lingual artery of the external carotid.

In the upper jaw, the buccal gingiva around the molar and premolar teeth are supplied by gingival and perforating branches from the posterior and middle superior alveolar arteries and by the buccal artery. The labial gingiva of the anterior teeth is supplied by labial branches of the infraorbital artery and by perforating branches of the anterior superior alveolar artery. The palatal gingiva around the maxillary teeth is supplied primarily by branches of the greater palatine artery, a branch of the third part of the maxillary artery in the pterygopalatine fossa.

The hard palate derives its blood supply principally from the greater palatine artery, a branch of the third part of the maxillary artery. The greater palatine artery descends (with its accompanying nerve) in the palatine canal. In the canal, it gives off two or three lesser palatine arteries that are transmitted through lesser palatine canals to supply the soft palate and tonsil (anastomosing with the ascending palatine branch of the facial artery). The greater palatine artery emerges on to the oral surface of the palate at the greater palatine foramen and runs in a curved groove near the alveolar border of the hard palate to the incisive canal. It ascends this canal and anastomoses with septal branches of the nasopalatine artery.

The tongue and floor of mouth are supplied mainly by the lingual artery that arises in the neck from the external carotid artery (see **Figure 41.8**). It reaches the floor of the mouth by passing between the hyoglossus muscle and the middle constrictor of the pharynx. Near the tip of the tongue, the lingual artery anastomoses with its fellow from the opposite side. The branches of the lingual artery in the floor of the mouth are the dorsal lingual branches, the sublingual artery and the deep lingual artery.

The dorsal lingual arteries (usually two or three) arise medial to the hyoglossus muscle and ascend to the posterior part of the dorsum of the tongue. They supply the mucous membrane of the dorsum of the tongue, the palatoglossal arch, soft palate, tonsil and epiglottis.

The sublingual artery arises from the lingual artery at the anterior margin of hyoglossus. It passes forwards between the genioglossus and mylohyoid muscles to the sublingual gland. It also provides a branch that enters a small foramen (lingual foramen) on the mandible, situated in the midline on the posterior aspect of the symphysis, immediately above the genial tubercles.

The deep lingual artery is the terminal part of the lingual artery and is found on the inferior surface of the tongue near the lingual frenum.

In addition to the lingual artery, the tonsillar and ascending palatine branches of the facial and ascending pharyngeal arteries also supply tissue in the root of the tongue. In the region of the valleculae, epiglottic branches of the superior laryngeal artery anastomose with the inferior dorsal branches of the lingual artery.

Veins

As with veins elsewhere in the body, the pattern of drainage for the mouth and associated structures is variable and only a generalized account will be given.

The cheek is drained by the buccal vein that leads to the pterygoid venous plexus in the infratemporal fossa. Venous blood from the lips is collected by the superior and inferior labial veins and drains into the facial vein. The veins of the hard palate accompany the arteries and drain largely to the pterygoid plexus.

Veins accompanying the superior alveolar arteries drain the upper jaw and teeth anteriorly into the facial vein, or posteriorly into the pterygoid venous plexus.

Veins from the lower jaw and teeth collect into several inferior alveolar veins. Some of these veins drain through the mental foramen to the facial vein, others via the mandibular foramen to the pterygoid venous plexus.

No accurate description is available concerning the venous drainage of the gingivae, although it may be assumed that buccal, lingual, greater palatine and nasopalatine veins are involved. These veins run into the pterygoid plexuses (apart from the lingual veins, which pass directly into the internal jugular veins).

There are two sets of veins draining the tongue. The deep lingual vein begins near the apex of the tongue and runs back on its ventral surface (see **Figure 41.3**). It joins a sublingual vein from the sublingual salivary gland, to form the vena comitans nervi hypoglossi. This then passes backwards with the hypoglossal nerve and joins the lingual, facial or internal jugular vein. Dorsal lingual veins drain the dorsum and sides of the tongue and join the lingual veins accompanying the lingual artery. They drain into the internal jugular in the region of the hyoid bone.

Lymph drainage

The principal sites of drainage of lymphatic vessels from orodental tissues are the submental, submandibular and jugulodigastric lymph nodes. However, the manner of drainage is so variable that there is no precise and accurate description.

The cheek, upper lip and lateral parts of the lower lip drain to the submandibular nodes. The central part of the lower lip drains to the submental nodes.

The lymph vessels from the teeth usually run directly into the submandibular lymph nodes on the same side. Lymph from the mandibular incisors, however, drains into the submental lymph nodes. Occasionally, lymph from the molars may pass directly into the jugulodigastric group of nodes.

The lingual and palatal gingivae drain into the jugulodigastric group of nodes, either directly or indirectly through the submandibular nodes. Lymphatics from the bulk of the palate terminate in the jugulodigastric group of nodes.

The lymphatics from the tongue drain to three main regions: marginal, central and dorsal. The anterior region of the tongue drains into the marginal and central vessels

and, behind the circumvallate papillae, the posterior part of the tongue drains into the dorsal lymph vessels. Of particular clinical importance is appreciating that more central regions may drain both ipsilaterally and contralaterally.

Marginal lymph vessels of the tongue that arise from the apex of the tongue and the **lingual frenum area descend under the mucosa to widely distributed nodes.**

- Some vessels enter the submental nodes and also pass to the jugulo-omohyoid nodes. Vessels may cross under the frenulum to end in the contralateral nodes, efferent vessels of submental nodes that are median pass to both sides.
- Some vessels drain to submandibular nodes.
- Some vessels end in jugulodigastric nodes, one vessel often reaching the jugulo-omohyoid node.

Vessels from the lateral margin of the tongue may drain into the submandibular nodes while others end in the jugulodigastric or jugulo-omohyoid nodes. Vessels from the posterior part of the lingual margin traverse the pharyngeal wall to the jugulodigastric lymph nodes.

Vessels draining the central region of the tongue may drain to either or both sides into the deep cervical nodes, especially the jugulodigastric and jugulo-omohyoid nodes. Some pierce the mylohyoid muscle to enter the submandibular nodes.

Vessels draining the dorsum of the tongue in the region of the circumvallate papillae and behind them run posteroinferiorly. Those near the median plane may pass to either or both sides, draining to the jugulodigastric and jugulo-omohyoid lymph nodes.

Innervation

The mucosa lining the mouth derives its sensory innervation chiefly from the maxillary and mandibular divisions of the trigeminal nerve. Additional nerves supply the tongue, including special taste sensation. The muscles of the mouth are supplied chiefly by the mandibular, facial and hypoglossal nerves. The salivary glands are supplied by secretomotor fibres derived from the facial and glossopharyngeal nerves. The innervation of the oral musculature is shown in **Table 41.1**.

SENSORY SUPPLY

Cheeks, lips and palate

The sensory supply to the cheek is derived from the buccal branch of the mandibular nerve (see **Figure 41.5**). This nerve arises from the anterior division of the mandibular nerve within the infratemporal fossa. Initially deep to the lateral pterygoid muscle, it emerges between the two heads of the muscle and runs forwards to supply the mucosa of the cheeks.

The upper lip is supplied by the infraorbital branch of the maxillary nerve (**Figure 41.9**). Running along the floor of the orbit in the infraorbital canal, it enters the face at the infraorbital foramen, where its labial branch runs downwards to supply the upper lip. The mental nerve is a terminal branch of the inferior alveolar nerve and exits the mandible at the mental foramen to supply the lower lip (see **Figure 41.9**).

The sensory nerves to the palate are derived from the greater and lesser palatine and nasopalatine branches of the maxillary nerve (**Figure 41.10**) These nerves pass through the pterygopalatine ganglion. The greater palatine nerve descends through the greater palatine canal, entering the hard palate at the greater palatine foramen. It then passes forwards on the bony palate towards the canine tooth, supplying the gums and the mucosa and



Figure 41.9 Infratemporal fossa showing mandibular nerve branches. 1, Auriculotemporal nerve surrounding middle meningeal artery; 2, buccal nerve; 3, lingual nerve (joined by chorda tympani nerve); 4, inferior alveolar nerve; 5, mylohyoid nerve; 6, mental nerve; 7, sphenomandibular ligament; 8, medial pterygoid muscle; 9, infraorbital nerve. Reprinted from Ref. 1 by permission from Elsevier.

TABLE 41.1 Innervation of the oral musculature

Region	Muscle	Nerve
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glands of the hard palate (excluding the anterior teeth). As it leaves the greater palatine canal, palatine branches are also distributed to the soft palate. The smaller lesser palatine nerves descend through the greater palatine canal to emerge through the inconspicuous lesser palatine foramina and give branches to the uvula, tonsil and soft palate. Fibres conveying taste impulses from the palate probably pass via the palatine nerves to the pterygopalatine ganglion (see **Figure 41.10**) and through it to the nerve of the pterygoid canal and then the greater petrosal nerve to reach the facial ganglion, where their somata are situated. Parasympathetic postganglionic secretomotor fibres run in the facial nerve through its greater petrosal nerve to reach the pterygopalatine ganglion to be distributed in the palatine nerves, thereby reaching palatine mucous glands.

The nasopalatine nerves (**Figure 41.10**) enter the palate at the incisive foramen to supply the anterior part of the hard palate behind the incisor teeth.

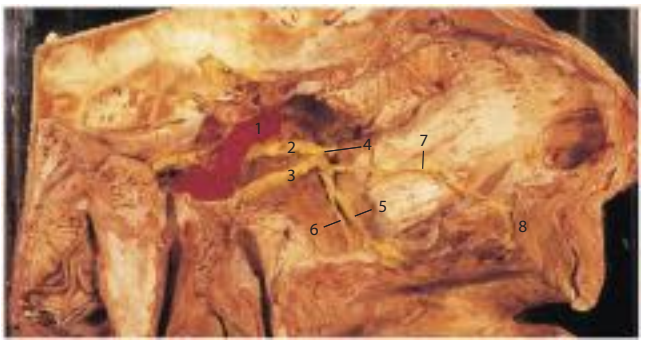


Figure 41.10 The pterygopalatine ganglion. 1, Internal carotid artery; 2, maxillary nerve; 3, nerve of pterygoid canal; 4, pterygopalatine ganglion; 5, greater palatine nerve; 6, lesser palatine nerve; 7, nasopalatine nerve dissected off from nasal septum; 8, nasopalatine nerve at incisive fossa. Reprinted from Ref. 1 by permission from Elsevier.

There is an additional sensory component in the region of the pillars of the fauces derived from the glossopharyngeal nerve which is involved in the gag reflex (see **Figure 41.8**).

The floor of the mouth is supplied by the lingual nerve (see **Figures 41.5** and **41.9**). This nerve arises from the posterior division of the mandibular nerve in the infratemporal fossa.

Teeth and gingivae

The regional supply to the teeth and gingivae is shown in **Table 41.2**. The posterior superior alveolar nerves supply the teeth in the upper jaw, while the inferior alveolar nerve supplies those in the lower jaw.

There are three superior alveolar (dental) nerves that arise from the maxillary nerve in the pterygopalatine fossa or in the infraorbital groove (canal) and these form a plexus of nerves supplying all the upper teeth. The posterior superior alveolar (dental) nerve leaves the maxillary nerve in the pterygopalatine fossa and runs anteroinferiorly to pierce the infratemporal surface of the maxilla, descending under the mucosa of the maxillary sinus. After supplying the lining of the sinus, the nerve divides into small branches that link up as the molar part of the superior dental plexus, supplying twigs to the molar teeth. It also supplies a branch to the upper gingiva and the adjoining part of the cheek.

The variable middle superior alveolar (dental) nerve arises from the infraorbital nerve as it runs in the infraorbital groove, and passes downwards and forwards in the lateral wall of the maxillary sinus. It ends in small branches that unite with the superior dental plexus, supplying small rami to the upper premolar teeth.

The anterior superior alveolar (dental) nerve leaves the lateral side of the infraorbital nerve near the midpoint of its canal and traverses the canalis sinuosus in the anterior wall of the maxillary sinus. Curving first under the infraorbital foramen, it passes medially towards the nose,

TABLE 41.2 Nerve supply to the teeth and gingiva

	Nasopalatine nerve			**Greater palatine nerve**					**Palatal gingival**
Maxilla	Anterior superior alveolar nerve			Middle superior alveolar nerve		Posterior superior alveolar nerve			Teeth
	Infraorbital nerve			Posterior superior alveolar nerve and buccal nerve					Buccal gingival
	1	2	3	4	5	6	7	8	Tooth position
	Mental nerve			Buccal nerve and perforating branches of inferior alveolar nerve					Buccal gingival
Mandible	Incisive nerve		Inferior alveolar nerve						Teeth
	Lingual nerve and perforating branches of inferior alveolar nerve								Lingual gingiva

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turns downwards and divides into branches supplying the incisor and canine teeth. It assists in the formation of the superior dental plexus.

The inferior alveolar (dental) nerve arises from the posterior division of the mandibular nerve in the infratemporal fossa (see **Figures 41.5** and **41.9**). Emerging from beneath the lower head of the lateral pterygoid muscle, it descends to enter the mandibular canal via the mandibular foramen (accompanied by the inferior alveolar artery). Just before entering the mandibular canal, the inferior alveolar nerve gives off a small mylohyoid branch to supply the mylohyoid muscle and the anterior belly of digastric.

In the mandibular canal, the inferior alveolar nerve runs downwards and forwards, generally below the apices of the cheek teeth until, below premolar teeth, it divides into terminal incisive and mental branches. The incisive branch continues forwards in a bony canal or in a plexiform arrangement, giving off branches to the first premolar, canine and incisor teeth, and the associated labial gingivae. The lower central incisor teeth may receive a bilateral innervation, fibres probably crossing the midline within the periosteum to re-enter the bone via numerous canals in the labial cortical plate.

The mental nerve passes upwards, backwards and outwards to emerge from the mandible via the mental foramen between and just below the apices of the premolar teeth to supply the skin of the lower lip and chin (see **Figure 41.9**).

The nerves supplying the gingiva in the upper jaw come from the maxillary nerve via its greater palatine, nasopalatine and anterior, middle and posterior superior alveolar branches. The mandibular nerve innervates the gingiva in the lower jaw by its inferior alveolar, lingual and buccal branches (see **Table 41.2**).

The tongue and floor of the mouth

The sensory supply to the tongue involves both general and taste afferents and reflects the embryological development of the structure. Thus, it can be considered in two portions, the presulcal (anterior two-thirds) and a postsulcal (posterior one-third). The nerve of general sensation to the presulcal part is the lingual nerve, indicating the embryological derivation of this part from the first branchial arch. The lingual nerve also carries taste sensation derived from the chorda tympani branch of the facial nerve. The main nerve supplying general (and taste) sensation to the postsulcal part is the glossopharyngeal nerve, while an additional area in the region of the valleculae is supplied by the internal laryngeal branch of the vagus nerve, indicating the embryological derivation of the postsulcal part from the third and fourth branchial arches.

The lingual nerve originates from the posterior trunk of the mandibular nerve in the infratemporal fossa (see **Figures 41.5**, **41.8** and **41.9**). Here, it is joined by the chorda tympani branch of the facial nerve that supplies taste to the anterior two-thirds of the tongue and parasympathetic fibres that supply the submandibular and sublingual glands via the submandibular ganglion (**Figure 41.9**). Emerging from beneath the lower head of the lateral pterygoid muscle (**Figure 41.5**), the lingual nerve passes forwards medial to the inferior alveolar nerve and is closely applied to the periosteum of the medial surface of the mandible by the side of the roots of the third molar tooth (**Figure 41.7**). Here, the lingual nerve is at great risk during surgical removal of (impacted) lower third molars using a lingual approach. The lingual nerve then passes medial to the mandibular origin of the mylohyoid muscle, which carries it progressively away from the mandible. It passes downwards and forwards on the deep surface of the mylohyoid muscle and then runs below the submandibular duct, which crosses it from medial to lateral (**Figure 41.7**). The nerve next curves upwards, forwards and medially to enter the tongue. The lingual nerve is connected to the submandibular ganglion by two or three branches and, at the anterior margin of the hyoglossus, it forms connecting loops with twigs of the hypoglossal nerve.

Branches of the lingual nerve supply the lingual gingivae, the mucosa of the floor of the mouth and the anterior two-thirds (presulcal part) of the tongue (excluding the circumvallate papillae, which are supplied by the glossopharyngeal nerve).

The glossopharyngeal nerve is present in the neck where it passes around the posterior border of the stylopharyngeus muscle, which it supplies (**Figure 41.8**). It runs forwards on this muscle and either pierces the lower fibres of the superior constrictor muscle or passes between it and the middle constrictor to be distributed to the postsulcal part of the tongue (including the circumvallate papillae). It communicates with the lingual nerve.

The sensory supply to the valleculae of the tongue (the recess between the median and lateral glossoepiglottic folds) is derived from the internal laryngeal nerve. This nerve is a branch of the superior laryngeal nerve and, passing between the superior and inferior constrictor muscles, pierces the thyrohyoid membrane. From here, branches ascend to supply the valleculae.

The parasympathetic innervation of the lingual glands is derived from the chorda tympani branch of the facial nerve that joins the lingual nerve (**Figure 41.9**) and synapses in the submandibular ganglion. Postganglionic fibres re-enter the lingual nerve to the glands. The sympathetic supply to lingual glands and vessels enters the tongue through plexuses around its arteries, arising from the carotid plexus.

MOTOR SUPPLY

The nerves supplying the buccinator and orbicularis oris muscles are derived from the facial nerve that exits the skull at the stylomastoid foramen and then passes into the substance of the parotid gland, where it divides into its terminal branches. The buccinator is supplied by its buccal branch(es) and the lips from the buccal and mandibular branches. The nerve supplying the mylohyoid muscle is the mylohyoid nerve and is seen branching from the inferior alveolar nerve just above the mandibular foramen (**Table 41.1**).

The muscles of the tongue are supplied by the hypoglossal nerve. These muscles develop primarily from occipital

somites that migrate into the developing tongue carrying their nerve supply, the hypoglossal nerve, with them. The hypoglossal nerve is seen in the neck crossing over the internal and external carotid and then the loop of the lingual artery (**Figure 41.8**). It then passes upwards and forwards between the mylohyoid and hyoglossus muscles. Here, the hypoglossal nerve is situated below the deep part of the submandibular gland, the submandibular duct and the lingual nerve. It then passes on to the lateral aspect of the genioglossus muscle, continuing forwards in its substance as far as the tip of the tongue.

The muscular branches from the hypoglossal nerve are distributed to styloglossus, hyoglossus and genioglossus. Numerous slender rami ascend into the tongue to supply its intrinsic muscles.

The nerve to geniohyoid (and to thyrohyoid) arises near the posterior border of the hyoglossus. It is derived from fibres of the first cervical spinal nerve.

TEETH

There are two generations of teeth: the deciduous (primary) dentition and the permanent (secondary) dentition. In the complete deciduous dentition there are 20 teeth – five in each jaw quadrant. In the complete permanent dentition there are 32 teeth – eight in each jaw quadrant. In both dentitions, there are three basic tooth forms: incisiform, caniniform and molariform. Incisiform teeth (incisors) are cutting teeth, having thin, blade-like crowns. Caniniform teeth (canines) are piercing or tearing teeth, having a single, stout, pointed, cone-shaped crown. Molariform teeth (molars and premolars) are grinding teeth possessing a number of cusps separated by fissures. Premolars are bicuspid teeth that are peculiar to the permanent dentition and replace the deciduous molars.

Permanent teeth

There are two incisors, a central and a lateral, in each half jaw or quadrant (**Figures 41.11** and **41.12**). Viewed from the front, the crowns are trapezoid, the maxillary incisors (particularly the central) being larger than the mandibular. They are surmounted by the biting or incisal edges. In side view their labial profiles are convex while their lingual surfaces are concavo-convex (the convexity near the cervical margin being due to a low ridge or cingulum, prominent only on upper incisors). The roots of incisors are single and rounded in maxillary teeth, but flattened mesiodistally in mandibular teeth. The upper lateral incisor may be congenitally absent or may have a reduced form (peg-shaped lateral incisor).

Behind each lateral incisor is a canine tooth with a single cusp (hence the American term cuspid) instead of an incisal edge. The maxillary canine is stouter and more pointed than the mandibular canine. The canine root is single and is the longest of any tooth.

Behind the canines are two premolars, each with a buccal and lingual cusp (hence the term bicuspid). The occlusal surfaces of the maxillary premolars are oval (the long axis is buccopalatal) with a mesiodistal fissure separating the two cusps. The maxillary first premolar usually has two roots (one buccal, one palatal). The maxillary second premolar usually has one root. The occlusal surfaces of the mandibular premolars are more circular or squarer than those of the uppers. The buccal cusp of the mandibular first premolar towers above the very much reduced lingual cusp. In the mandibular second premolar, the lingual cusp is more substantial compared with the first, and frequently presents as two cusps. Each lower premolar tooth generally has one root.

Posterior to the premolars are three molars whose size decreases as one passes backwards. Each has a large



Figure 41.11 Permanent dentition upper jaw. Reprinted from Ref. 1 by permission from Elsevier.



Figure 41.12 Permanent dentition lower jaw. Reprinted from Ref. 1 by permission from Elsevier.

rhomboid (upper jaw) or rectangular (lower jaw) occlusal surface with four or five cusps. The maxillary first molar has a cusp at each corner of its occlusal surface and the mesiopalatal cusp is connected to the distobuccal by an oblique ridge. A smaller cusplet or tubercle (cusplet of Carabelli) usually appears on the mesiopalatal cusp. The tooth has three widely separated roots, two buccal and one palatal. The smaller maxillary second molar has a reduced distopalatal cusp. Its three roots are less divergent and two of them may be fused. The maxillary third molar, the smallest, is very variable in form. It usually has three cusps (the distopalatal being absent) and commonly the three roots are fused.

The mandibular first molar has three buccal and two lingual cusps on its rectangular occlusal surface, the smallest cusp being distal. It has two widely separated roots, one mesial and one distal. The smaller mandibular second molar is like the first but has only four cusps (lacking the distal cusp of the first molar) and its two roots are closer together. The mandibular third molar is smaller still and, like the upper third molar, is variable in form. Its crown may resemble that of the lower first or second molar and its roots are frequently fused. The third molar is often impacted against the second molar, with resultant food packing and inflammation. Third molars are frequently congenitally absent.

Deciduous teeth

The incisors, canine and premolars of the permanent dentition replace two deciduous incisors, a deciduous canine and two deciduous molars in each jaw quadrant. The deciduous incisors and canine are shaped like their successors but are smaller and whiter and become extremely worn in older children. The deciduous second molars resemble permanent ones rather than their successors, the premolars. Each second deciduous molar has a crown almost identical to that of their respective, adjacent first permanent molar. The upper first deciduous molar has a triangular occlusal surface (its rounded 'apex' being palatal) and a fissure separates a double buccal cusp from the palatal cusp. The lower first deciduous molar is long and narrow; its two buccal cusps are separated from the two lingual cusps by a zigzagging mesiodistal fissure. Like permanent molars, upper deciduous molars have three roots and lower deciduous molars have two roots. These roots diverge more than those of permanent teeth, as each developing premolar tooth crown is accommodated directly under the crown of its deciduous predecessor. The roots of deciduous teeth are progressively resorbed by osteoclast-like cells (odontoclasts) prior to being shed.

Eruption

The first deciduous teeth to erupt into the mouth appear at approximately 6 months after birth and, by around the age of 3 years, all the deciduous teeth have erupted. By 6 years of age, the first permanent teeth appear (lower incisors and first molars) and thence the deciduous teeth are exfoliated one by one as they are replaced by their permanent successors. A complete permanent dentition is present when the third molars erupt at around the age of 18–21 years. Information on the sequence of development and eruption of teeth into the oral cavity may be important in forensic medicine and archaeology in helping to age individuals. The data provided in **Tables 41.3** and **41.4** concerning the chronology of tooth development are largely based on European-derived populations and there is evidence of ethnic variation. When a permanent tooth erupts, approximately two-thirds of the root is formed and it takes approximately another 3 years for the root to be completed. For deciduous teeth, root completion is more rapid. The developmental stages of initial calcification and crown completion are less affected by environmental influences than eruption, the timing of which may be modified by several factors such as early tooth loss and severe malnutrition.

Figures 41.13 and **41.14** show the panoramic appearance of the dentition seen with orthopantomograms at 5 and 11 years of age.

For detailed information concerning the structure and function of teeth the reader is referred to standard textbooks.[1]

TABLE 41.3 Chronology of the deciduous dentitions

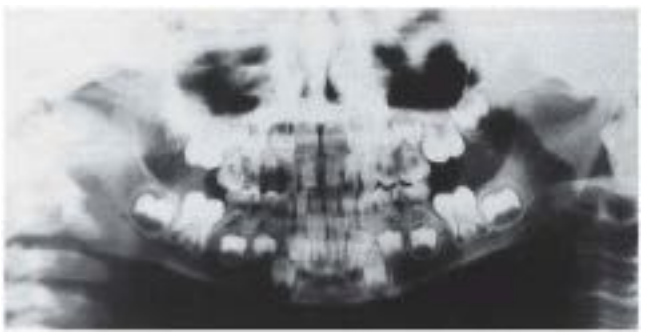
Tooth	First evidence of calcification (months IU)	Crown completed (months)	Eruption (months)	Root completed (years)
Maxillary				
A	3–4	4	7	$1\frac{1}{2}$–2
B	$4\frac{1}{2}$	5	8	$1\frac{1}{2}$–2
C	5	9	16–20	$2\frac{1}{2}$–3
D	5	6	12–16	2–$2\frac{1}{2}$
E	6–7	10–12	21–30	3
Mandibular				
A	$4\frac{1}{2}$	4	$6\frac{1}{2}$	$1\frac{1}{2}$–2
B	$4\frac{1}{2}$	$4\frac{1}{2}$	7	$1\frac{1}{2}$–2
C	5	9	16–20	$2\frac{1}{2}$–3
D	5	6	12–16	2–$2\frac{1}{2}$
E	6	10–12	21–30	3

Unless otherwise indicated all dates are post-partum. IU, *in utero*. The teeth are identified according to the Zsigmondy System. Reprinted from Ref. 1 by permission from Elsevier.

TABLE 41.4 Chronology of the permanent dentitions

Tooth	First evidence of calcification	Crown completed (years)	Eruption (years)	Root completed (years)
Maxillary				
1	3–4 months	4–5	7–8	10
2	10–12 months	4–5	8–9	11
3	4–5 months	6–7	11–12	13–15
4	$1\frac{1}{2}-1\frac{3}{4}$ years	5–6	10–11	12–13
5	$2-2\frac{1}{2}$ years	6–7	10–12	12–14
6	Birth	$2\frac{1}{2}$ –3	6–7	9–10
7	$2\frac{1}{2}$ –3 years	7–8	12–13	14–16
8	7–9 years	12–16	17–21	18–25
Mandibular				
1	3–4 months	4–5	6–7	9
2	3–4 months	4–5	7–8	10
3	4–5 months	6–7	9–10	12–14
4	$1\frac{3}{4}$ –2 years	5–6	10–12	12–13
5	$2\frac{1}{4}-2\frac{1}{2}$ years	6–7	11–12	13–14
6	Birth	$2\frac{1}{2}$ –3	6–7	9–10
7	$2\frac{1}{2}$ –3 years	7–8	12–13	14–15
8	8–10 years	12–16	17–21	18–25

All dates are post-partum. The teeth are identified according to the Zsigmondy System. Reprinted from Ref. 1 by permission from Elsevier.



Teeth erupted Max ABCDE / Mand. ABCDE

Teeth unerupted Max 1234567 / Mand. 1234567

Figure 41.13 Orthopantomogram from patient aged 5 years. Reprinted from Ref. 1 by permission from Elsevier.



Teeth erupted Max 1234E6 / Mand. 1234E6

Teeth unerupted Max 578 / Mand. 578

Figure 41.14 Orthopantomogram from patient aged 11 years. Reprinted from Ref. 1 by permission from Elsevier.

TISSUE SPACES AROUND THE JAWS

The most common cause of infection of the tissues associated with the mouth is dental caries (tooth decay). As infection may spread from the teeth to the head and neck and become life-threatening, a knowledge of the tissue spaces associated with the jaws is of considerable clinical importance.[3–6] The tissue 'spaces' are only potential spaces that are normally occupied by loose connective tissue. It is only when inflammatory products destroy the loose connective tissue that a definable space is produced. The tissue spaces associated with the mouth are primarily defined by muscles (principally the mylohyoid, buccinator, masseter, medial pterygoid, superior constrictor and orbicularis oris muscles). Knowledge of the normal position of the root apices in relation to some of these muscles is important for an appreciation of the treatment of dental abscesses.[7]

Because of the potential of inflammation associated with the tissues surrounding partially erupted, impacted third molars (pericoronitis), the spaces associated with this region are particularly important and, as they are interconnected, inflammation can spread to involve the tissue spaces of the neck. The submental and submandibular tissue spaces are located below the inferior border of the mandible, beneath the mylohyoid muscle, in the suprahyoid region of the neck. The submental space lies beneath the chin in the midline, between the mylohyoid muscles and the investing layer of deep cervical fascia. It is bounded laterally by the two anterior bellies of the digastric muscles. The submental space communicates posteriorly with the two submandibular spaces. The submandibular space is situated between the anterior and posterior bellies of the digastric muscle. It communicates with the sublingual space around the posterior free border of the mylohyoid muscle.

The sublingual space lies in the floor of the mouth, above the mylohyoid muscles. It is continuous across the midline and communicates with the submandibular spaces over the posterior free borders of the mylohyoid muscles (see **Figure 41.7**).

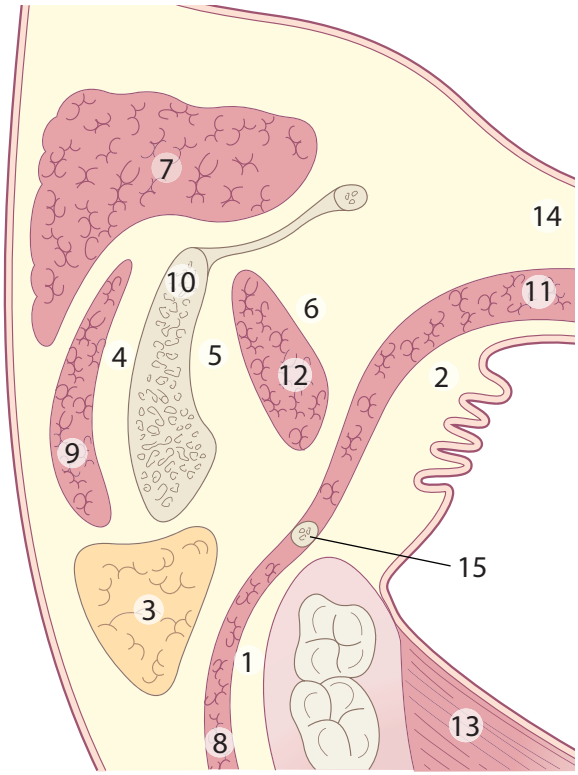


Figure 41.15 Diagram showing the tissue spaces in the retromandibular region. 1, Vestibular sulcus; 2, peritonsillar space; 3, buccal space, filled with buccal pad of fat; 4, submasseteric spaces; 5, pterygomandibular space; 6, parapharyngeal space; 7, parotid space; 8, buccinator muscle; 9, masseter muscle; 10, ramus of mandible; 11, superior constrictor of pharynx; 12, medial pterygoid muscle; 13, mylohyoid muscle; 14, retropharyngeal space; 15, pterygomandibular raphe.

The remaining tissue spaces in the region of the molar teeth are illustrated in **Figure 41.15**. The buccal space is located in the cheek, on the lateral side of the buccinator muscle.

Between the lateral surface of the ramus of the mandible and the masseter muscle is a series of spaces called the submasseteric spaces. These spaces are formed because the fibres of the masseter muscle have multiple insertions on to most of the lateral surface of the ramus.

Between the medial surface of the ramus of the mandible and the medial pterygoid muscle lies the pterygomandibular space.

Behind the ramus of the mandible is located the parotid space, in and around the parotid gland.

The parapharyngeal space is bounded by the superior constrictor of the pharynx and the medial surface of the medial pterygoid muscle. This space is restricted to the infratemporal region of the head and the suprahyoid region of the neck. It communicates with the retropharyngeal space, which itself extends into the retrovisceral space in the lower part of the neck.

The peritonsillar space lies around the palatine tonsil between the pillars of the fauces. It is part of the intrapharyngeal space and is bounded by the medial surface of the superior constrictor of the pharynx and its mucosa.

Most dental abscesses from lower teeth will drain either into the mouth lingually above the mylohyoid muscle (sublingual space) or into the vestibule (above the buccinator) and will have natural drainage. Where, for example, a cheek tooth drains below the buccinator (into the buccal space) or lingually below the mylohyoid (into the submandibular space, especially when involving the second and third mandibular molars), surgical intervention will be required to ensure drainage. As an example, direct spread may involve the submental space and the sublingual and submandibular spaces of both sides, giving rise to Ludwig's angina.

The teeth of the upper jaw have special relevance to ENT surgeons because of their potential close relationship to the maxillary air sinus. The root apices of the maxillary cheek teeth are close to and may even invaginate the maxillary sinus. The permanent tooth most commonly involved is the second molar, followed by the first molar. However, the premolars may also be involved as might the third molar. Following tooth extraction, resorption of alveolar bone and cavitation of the maxillary sinus may significantly increase. During removal of fractured root apices in this region, care must be taken to ensure the root fragment is not pushed into the sinus. Similarly, during root canal treatment, care must be taken not to push any filling material into the maxillary sinus. Routine X-rays may no longer be considered satisfactory in providing sufficient definition of the close relationship between the floor of the maxillary sinus and root apices and cone beam computed tomography may be necessary to provide extra detail (**Figure 41.16**). Due to the close anatomical relationship of the openings of the various air sinuses in the region of the middle meatus, infection of the maxillary sinus may spread to involve other sinuses and vice versa.

THE SALIVARY GLANDS

Salivary glands are compound, tubular, acinous, merocrine glands whose ducts open into the oral cavity. They secrete a fluid, the saliva that, among its many functions, aids in the mastication, digestion and deglutition of food.[8–10]

There are three pairs of major salivary glands: the parotid, the submandibular and the sublingual glands. Numerous minor salivary glands are also scattered throughout the oral mucosa.

Approximately 0.5 L of saliva is secreted per day. Salivary flow rates are approximately 0.3 mL/min when unstimulated, rising to 1.5–2 mL/min when stimulated. During sleep, salivary flow rate is negligible. In the unstimulated state, the parotid gland contributes approximately 20%, the submandibular gland approximately 65% and the sublingual and minor salivary glands the remainder. When stimulated, the parotid contribution rises to 50%.[11]

Parotid gland

The parotid gland is the largest salivary gland. It is a serous gland. The parotid gland is situated in front of the external ear on the face and consequently will not

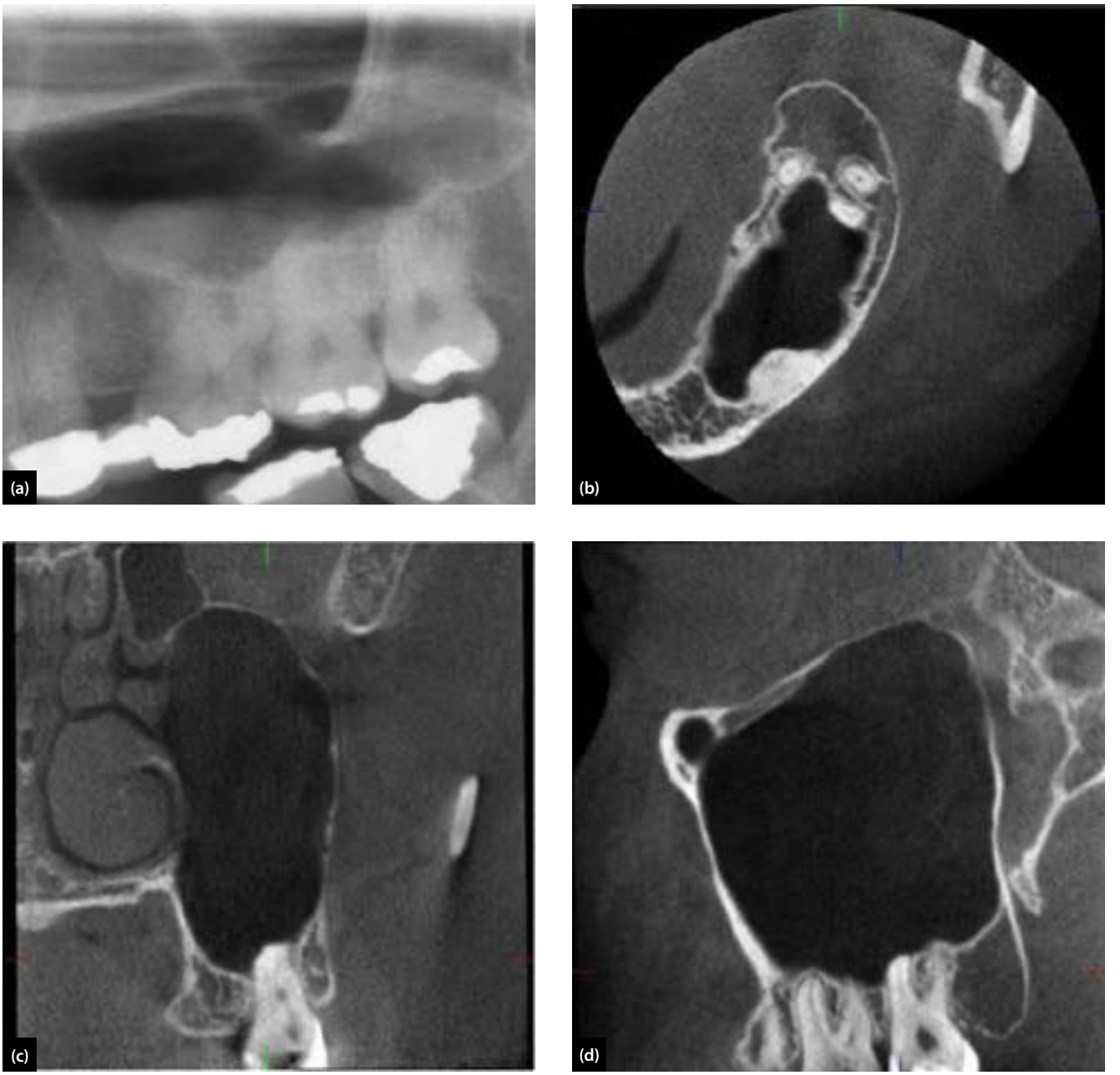


Figure 41.16 (a). Routine orthopantomograph showing roots of the left maxillary molars. The relationship of the root apices to the floor of the maxillary antrum is not clear. **(b,c,d)**. cone beam computed tomography of the same second and third maxillary molar teeth as in A, showing the precise relationship of the root apices to the floor of the maxillary sinus in three-dimensions. **(b)**. Axial image showing the palatal (P), distobuccal (DB) and mesiobuccal (MB) roots of the maxillary third molar **(c)**. Coronal image showing the mesiobuccal root (MB) of the maxillary third molar invaginating the floor of the maxillary simus. **(d)**. Sagittal image showing the mesiobuccal (MB) and distobuccal (DB) roots of the maxillary third molar invaginating the floor of the maxillary sinus. The roots of the adjacent maxillary second molar are also very close to the floor of the maxillary sinus, Courtesy of Dr J Davies.

be described further. The parotid duct runs through the cheek and drains into the mouth opposite the maxillary second permanent molar tooth. Its parasympathetic innervation is derived from the lesser petrosal branch of the glossopharyngeal nerve via the otic ganglion.

Submandibular gland

The submandibular gland is irregular in shape and approximately the size of a walnut. It consists of a larger superficial and a smaller deep part, continuous with each other around the posterior border of the mylohyoid muscle (see **Figure 41.7**). It is partially enclosed between two layers of deep cervical fascia extending from the greater cornu of the hyoid bone. It is a mixed, but predominantly serous, gland. The superficial part of the submandibular gland is situated in the digastric triangle. Above, it extends medial to the body of the mandible. Below, it usually overlaps the intermediate tendon of the digastric muscle and the insertion of the stylohyoid muscle.

The inferior surface, covered by skin, platysma and deep fascia, is crossed by the facial vein and the cervical branch of the facial nerve. The lateral surface is in relation with the submandibular fossa on the medial surface of the body of the mandible and the mandibular attachment of the medial pterygoid muscle. The medial (deep) surface is related anteriorly to the mylohyoid muscle and posteriorly to the styloglossus muscle. In its intermediate part, the medial surface is related to the hyoglossus muscle, separated from it by the styloglossus muscle, the lingual nerve, submandibular ganglion, hypoglossal nerve and deep lingual vein.

The deep part of the submandibular gland lies between the mylohyoid muscle inferolaterally and the hyoglossus and styloglossus muscles medially. It extends forwards to the posterior end of the sublingual gland (see **Figure 41.7**).

The submandibular duct is approximately 5 cm long and emerges from the medial surface of the superficial part of the gland behind the posterior border of the mylohyoid muscle. It passes through the deep part of the gland, runs between the sublingual gland and the genioglossus muscle and opens in the floor of the mouth on the summit of the sublingual papilla at the side of the frenulum of the tongue. On the hyoglossus muscle it is crossed laterally by the lingual nerve, some of whose terminal branches ascend on its medial side (see **Figures 41.7** and **41.8**).

The secretomotor supply to the submandibular gland is associated with the submandibular ganglion. This is a small, fusiform body that lies on the upper part of the hyoglossus muscle suspended from the lingual nerve. The motor, parasympathetic root conveys preganglionic fibres travelling in the facial, chorda tympani and lingual nerves (see **Figure 41.9**) to the ganglion, where they synapse. The postganglionic fibres are distributed to the submandibular and sublingual salivary glands.

Sublingual gland

The sublingual gland, the smallest of the main salivary glands, lies beneath the oral mucosa, which is raised as a sublingual fold (see **Figure 41.3**). The gland lies in contact with the sublingual fossa on the lingual aspect of the mandible, close to the mandibular symphysis. It is narrow, flat, shaped like an almond and weighs 3–4 g. The gland is seromucous (but predominantly mucous). Beneath the gland is the mylohyoid muscle, whilst behind it lies the deep part of the submandibular gland (see **Figure 41.7**). The genioglossus muscle lies medial to the sublingual gland, separated from it by the lingual nerve and submandibular duct. The sublingual gland has 8–20 excretory ducts. From the posterior part of the gland, smaller sublingual ducts mostly open separately on the summit of the sublingual fold. From the anterior part of the gland small rami sometimes form a major sublingual duct (Bartholin's duct), opening with or near to the orifice of the submandibular duct.

Minor salivary glands

The minor salivary glands of the mouth include the buccal, labial, lingual, palatal and palatoglossal glands. The buccal and labial glands contain both mucous and serous elements. The palatal glands are mucous glands. They are located in both the soft and hard palate. The anterior and posterior lingual glands are mainly mucous. The anterior glands are embedded within muscle near the ventral surface of the tongue and open by means of four or five ducts near the lingual frenum. The posterior glands are located in the root of the tongue. Around the circumvallate papillae are serous glands (of Von Ebner). The palatoglossal glands are mucous glands and are located around the pharyngeal isthmus.

TEMPOROMANDIBULAR JOINT

As the temporomandibular joint is closely related anatomically to the external acoustic meatus and clinical conditions of the joint may produce symptoms of pain that must be distinguished from those directly associated with the ear, the joint will be considered in this chapter.

The temporomandibular (craniomandibular) joint (TMJ) is a synovial joint. It is formed by the mandibular (glenoid) fossa articulating with the mandibular condyle. The TMJ has a number of unusual features:

1. The joint space is divided into two joint cavities (upper and lower) by an intra-articular disc.
2. The articular surfaces are not composed of hyaline cartilage but of fibrous tissue (reflecting the joint's intramembranous development).
3. A secondary condylar cartilage is present in the head of the condyle until adolescence.
4. Movements of the joint are influenced by the teeth.

The shape of the mandibular fossa does not conform exactly to the shape of the mandibular condyle and this may partly explain why the joint cavity is divided by an articular disc into upper and lower compartments (**Figure 41.17**).[6, 13] The TMJ allows both gliding (upper joint compartment) and hinge (lower joint compartment) movements.

The condyle joins the ramus through a thin bony projection termed the neck of the condyle, a frequent site for a fracture of the mandible. A small depression (the pterygoid fovea) situated on the anterior surface of the neck marks part of the attachment of the lateral pterygoid muscle. The articular surfaces of the condyle are the anterior and superior surfaces. During the period of growth up to early teens, a layer of hyaline cartilage (condylar cartilage) lies immediately beneath the fibrous articulating surface of the condyle.

The joint capsule

The capsule of the TMJ is attached above to the mandibular fossa, extending anteriorly to just in front of the crest of the articular eminence and posteriorly to the squamotympanic and petrotympanic fissures. Below, the capsule is attached to the neck of the condyle. Being a thin

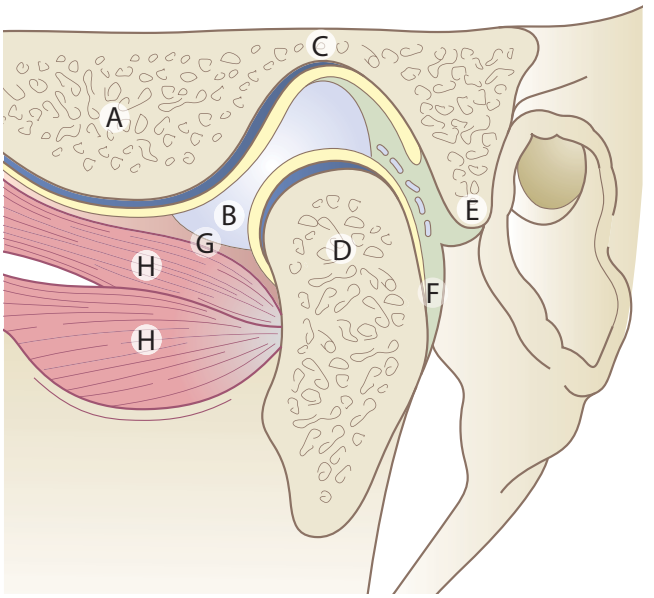


Figure 41.17 The temporomandibular joint showing the articular disc and attachments of the lateral pterygoid muscle. A, Articular eminence; B, articular disc; C, mandibular fossa; D, condyle; E, upper lamina (fibro-elastic); F, lower lamina (non-elastic); G, capsule of joint; H, lateral pterygoid muscle. Yellow layers indicate upper and lower joint cavities, black layers indicate upper and lower fibrous articular surfaces. Redrawn by permission from Ref. 12.

slack cuff, the capsule itself does not limit mandibular movements and is too weak to provide much support for the joint.

The inner surface of the fibrous capsule is lined by a synovial membrane that is reflected over the margins of the articular disc, but the membrane does not cover the articular surfaces of the joint. The synovial membrane secretes the synovial fluid, which occupies the joint cavities and lubricates the joint. Important components of the fluid are the proteoglycans. At rest, the hydrostatic pressure of the synovial fluid has been reported as being subatmospheric, but this is greatly elevated during mastication.[14, 15]

Articular disc

The articular disc (meniscus) is of a dense, fibrous consistency and is moulded to the bony joint surfaces above and below. Blood vessels are only evident at the periphery of the articular disc, the bulk of its central part being avascular. When viewed in sagittal section, the upper surface of the disc is concavo-convex anteroposteriorly and the lower surface is concave. Viewed superiorly, the articular disc is somewhat rectangular or oval in outline. The overall shape of the articular disc is thought to provide a self-centring mechanism, which automatically acts to maintain its correct relationship to the articular surface of the mandibular condyle during mandibular movements. Whereas some regard the functions of the articular disc as helping to spread the joint forces and to stabilize the condyle, others see its function as primarily destabilizing the condyle and permitting it to move more freely.[16]

The central (intermediate) zone of the disc is the thinnest and the collagen fibres are crimped, perhaps evidence that the disc is subjected to tensional, as well as compressional, forces.[17] The margin of the articular disc merges peripherally with the joint capsule. Anteriorly, fibrous bands connect the disc to the anterior margin of the articular eminence above, and to the anterior margin of the condyle below. Medially and laterally, the articular disc is attached to the joint capsule and, just below the medial and lateral poles of the condyle, by triangular zones of connective tissue. Posteriorly, the disc is attached to the capsule by a looser connective tissue, the retrodiscal tissue (pad) that has a bilaminar appearance. The superior lamina is loose and possesses numerous vascular elements and elastin fibres. It attaches to the anterior margin of the squamotympanic fissure. The inferior lamina is relatively avascular, less extensible (as it has few elastin fibres) and is attached to the posterior margin of the condyle. The volume of the retrodiscal tissue appears to increase four to five times as a result of venous engorgement as the jaw is opened and the condyle moves downwards and forwards. The return of the articular disc to its original position may possibly be aided by the elastic recoil of the superior lamella.

Numerous studies have been undertaken to determine the precise attachment of the lateral pterygoid muscle with respect to the articular disc in the hope of explaining any predisposition to TMJ syndrome. Variations in the attachment are seen. The findings indicate that, in the majority of articles (60%), fibres from the superior head of the lateral pterygoid muscle are described as gaining a direct attachment into the capsule of the joint and to the medial aspect of the anterior border of the articular disc (as well as to the condyle). In 30% of articles, only a few muscle fibres are described as inserting into the disc, while in the remaining 10% of articles the superior head of the lateral pterygoid muscle is attached only to the condyle.[18] Very rarely, some fibres from the inferior head of the lateral pterygoid may insert into the articular disc.

Considerable research has been undertaken on the activity of the lateral pterygoid muscle as it is believed by some that impaired activity of the muscle might predispose the joint to developing a pathology. It was originally thought that the two heads of the lateral pterygoid were reciprocal during opening and closing, the inferior head being active in opening the jaw, the superior head during closure, this view has now changed. The superior head has now been demonstrated to be active during opening and the two heads must be considered as acting together as one muscle with functional heterogeneity and with varying amounts of evenly graded activity throughout its range.[19]

Ligaments of the temporomandibular joint

The main ligament limiting lateral movement at the TMJ is the lateral ligament (temporomandibular ligament), which cannot be readily separated from the capsule. It runs

downwards and backwards from the articular tubercle (a bony protrusion on the lateral surface of the articular eminence) to the lateral surface and posterior border of the neck of the mandibular condyle.[19] To help resist posterior movement of the mandibular condyle, the lateral ligament is reinforced by a horizontal band of fibres running from the articular eminence to the lateral surface of the condyle. As there is little evidence of a medial ligament, medial displacement of the TMJ is likely to be prevented by the lateral ligament of the opposite side.

Accessory ligaments of the TMJ are the stylomandibular ligament, the sphenomandibular ligament and the pterygomandibular raphe. However, of these, the only one likely to have any significant influence upon mandibular movements is the sphenomandibular ligament.[20]

The stylomandibular ligament is merely a reinforced lamina of the deep cervical fascia that extends from the tip of the styloid process and from the stylohyoid ligament to the angle of the mandible.

The pterygomandibular raphe is a thin band of tendinous fibres passing between the hamulus of the medial pterygoid plate and the posterior end of the mylohyoid line of the mandible. It gives origin anteriorly to the buccinator muscle and posteriorly to the superior constrictor muscle.

The sphenomandibular ligament runs from the spine of the sphenoid bone to the lingula of the mandible. It represents the remnants of the perichondrium of the cartilage of the embryonic first branchial arch. The sphenomandibular ligament is slack when the jaws are closed, but during jaw movement becomes tense at about the time when the condyle has passed in front of the lateral ligament.[20]

In addition to the above, an additional ligament, the retinacular ligament, has recently been described. This ligament is said to originate from the articular eminence and insert into the fascia overlying the masseter muscle at the angle of the mandible. As the ligament is connected with the retrodiscal tissues, and contains an accompanying vein, it may function in maintaining blood circulation during masticatory jaw movements.[21]

Innervation and vasculature of the temporomandibular joint

Innervation for the joint is provided by the auriculotemporal, masseteric and deep temporal branches of the mandibular nerve. Of particular functional significance are the proprioceptive nerve endings important in the reflex control of mastication.

The vascular supply is derived from the superficial temporal artery and the maxillary artery (anterior tympanic and deep auricular branch). Other branches from neighbouring arteries may also contribute (e.g. deep temporal and transverse facial arteries).

Condylar cartilage

A secondary cartilage is present beneath the fibrous articular surface of the condyle until puberty. Unlike a primary cartilage, this secondary condylar cartilage has less extracellular matrix, the cartilage cells themselves do not undergo cell division and do not align themselves into columns. Although once thought to be a prime causative factor in controlling mandibular growth, the secondary condylar cartilage is now not thought to have any intrinsic growth potentiaton. The condylar cartilage disappears around the age of 16 years.

Clinical considerations of the temporomandibular joint

Estimates indicate that a considerable proportion of the population suffer in varying degrees from TMJ disorders. TMJ disorders are multifactorial in origin, although they may present with common symptoms such as pain in the jaw joint or face, clicking sounds in the joint and limited mouth opening.

Like other synovial joints, the TMJ is prone to inflammatory and degenerative conditions, such as rheumatoid and osteoarthritis. In these situations, damage to the articular surfaces will subject the articular disc to increased friction that may lead to degenerative changes within the disc. The intra-articular disc may gradually become displaced from its normal position between the articular surfaces. With the more usual anteromedial displacement, the posterior part of the disc may end up between the bony articular surfaces and be subjected to abnormal loading. The associated loss of structure may be accompanied by an invasion of blood vessels, with the disc eventually becoming perforated. The accompanying degenerative changes may also result in exposure of bone at the articular surfaces.

Inflammatory changes and increased permeability of the vessels of the synovial membrane may raise the intra-articular fluid pressure and change the composition of the synovial fluid. The synovial fluid in TMJ disorders may show an increased content in molecules such as proinflammatory cytokines (e.g. interleukin, tumour necrosis factor), matrix metalloproteinases and vascular endothelial growth factor. Irrigating and aspirating the joint (arthrocentesis) may reduce symptoms and improve mobility.

TMJ disorders are discussed in greater detail in Chapter 57, Temporomandibular joint disorders.

DEVELOPMENT OF THE FACE AND PALATE

As the neural plate of the embryo invaginates to form the neural tube, neural crest cells (ectomesenchyme) at the margins proliferate and migrate from this site to various parts of the body. There, interacting with the overlying epithelium (epithelial/mesenchymal interactions), the neural crest plays a significant role in normal development, contributing to many systems, such as the nervous system, soft and hard connective tissues. In addition, the cells play a major role in tooth development and give rise to melanocytes.

Development of face

In a 4-week-old embryo, the developing oral cavity (stomodeum) is present as a small, blind-ended pit bounded by five facial swellings (prominences) produced by proliferating zones of mesenchyme lying beneath the surface ectoderm. Much of the mesenchyme is derived from neural crest cells. The five facial swellings are the single frontonasal and the paired maxillary and mandibular processes (**Figure 41.18**). The centrally positioned frontonasal process lies above, the two maxillary processes are located at the sides and the two mandibular processes lie below the mouth. The maxillary and mandibular processes are derived from the first branchial arches. The facial processes are separated by grooves that, in the course of normal development, become flattened out by the proliferative and migratory activity of the underlying mesenchyme. Any disturbance in this process affecting, for example, the number, migration and subsequent differentiation (or apoptosis) and pattern formation of these cells can produce congenital abnormalities such as cleft lip and palate.

At this early stage of development, a membrane (the oropharyngeal membrane) separates the invagination representing the primitive oral cavity from the developing pharynx behind. The oropharyngeal membrane is bilaminar, being composed of an outer ectodermal layer and an inner endodermal layer. This membrane soon breaks down to establish continuity between the ectodermally lined oral cavity and the endodermally lined pharynx. Although not detectable in the adult, the demarcation zone between mucosa derived from ectoderm and endoderm corresponds to a region lying just behind the third permanent molar tooth.

In a 5-week-old embryo, localized thickenings of ectoderm on each side give rise to the optic and nasal placodes. These placodes will invaginate to form the lens of the eye and the olfactory epithelium, respectively. The nasal placodes sink into the underlying mesenchyme, forming two blind-ended nasal pits. Proliferation of mesenchyme from the frontonasal process around the openings of the nasal pits produces the medial and lateral nasal processes. The nasal pits continue to deepen until eventually they approach the roof of the primitive oral cavity, being partitioned from it by oronasal membranes (**Figure 41.19**). By the end of the fifth week, these membranes rupture to produce communications between the developing nasal and oral cavities.

In the 6-week-old embryo, the two mandibular processes fuse in the midline to form the tissues of the lower jaw. Rarely, persistence of a midline groove in this region

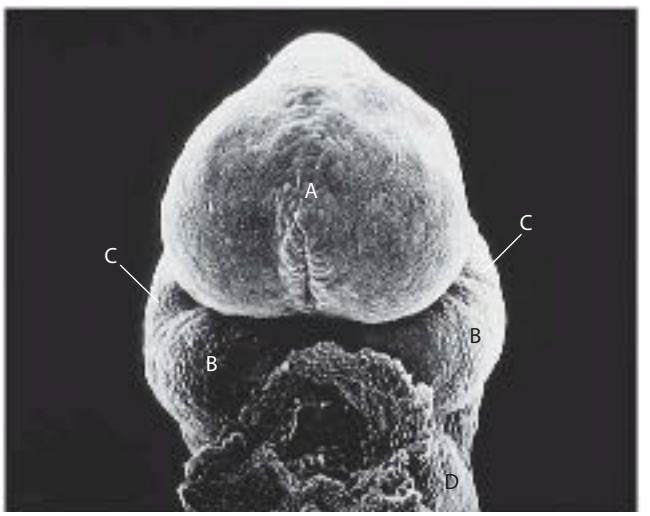
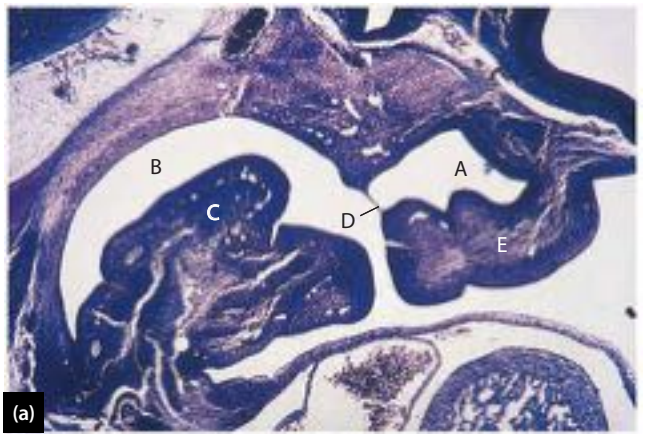


Figure 41.18 Scanning electron micrograph of the face at an equivalent 4-week stage (in the rat). Frontal aspect. A, Frontonasal process; B, mandibular processes; C, maxillary processes; D, pericardial swelling. Reprinted from Ref. 1 by permission from Elsevier.



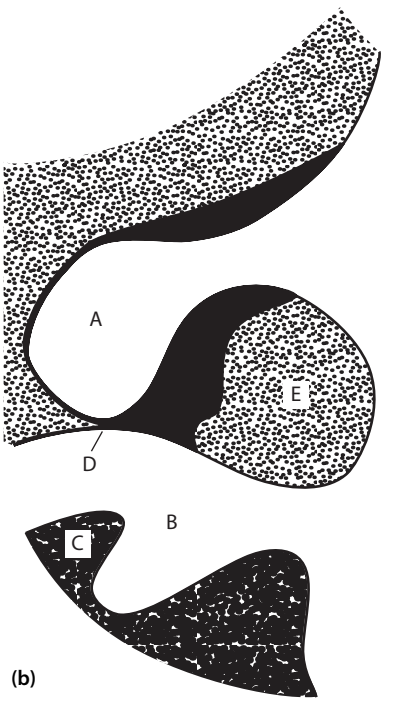


Figure 41.19 (a) Sagittal section through the developing nasal A and oral B cavities to C, developing tongue D, oronasal membrane; E, maxillary isthmus. Toluidine blue ×30. **(b)** Diagram with similar labelling. Reprinted from Ref. 1 by permission from Elsevier.

produces a mandibular cleft. The mandibular and maxillary processes meet at the angle of the mouth (labial commissure), thus defining its outline. Disturbances in this development may give rise to macrostomia (enlarged oral orifice) or microstomia (small oral orifice), or rarely to an astomia (lack of an oral orifice). From the corners of the mouth, the maxillary processes grow inwards beneath the lateral nasal processes and towards the medial nasal processes of the upper lip (**Figure 41.20**). An appreciation of this arrangement helps explain the occurrence of a unilateral or bilateral cleft lip (when the medial nasal and maxillary processes fail to merge successfully) and a median cleft (when the two median nasal processes fail to merge). The severity of a cleft may vary from a barely imperceptible groove to a complete cleft. Between the merging maxillary and the lateral nasal process lies the naso-optic furrow. From each furrow a solid ectodermal rod of cells sinks below the surface and canalizes to form the nasolacrimal duct. Persistence of the naso-optic furrow may produce an oblique facial cleft.

Two differing accounts have been given for the development of the upper lip. One interpretation is that the maxillary processes meet the medial nasal processes, the latter thus forming the middle third of the upper lip. This view is favoured by macroscopic observations of development. The alternative view states that the maxillary processes overgrow the medial nasal processes, merging in the midline to contribute all the tissue for the upper lip. This interpretation is based on the innervation of the fully formed upper lip (i.e. the infraorbital branch of the maxillary division of the trigeminal nerve), the maxillary processes being supplied by the maxillary nerve, the frontonasal process by the ophthalmic nerve. It is of interest to note that, in cases of bilateral cleft lip, the isolated median segment of the lip is innervated by the ophthalmic nerve, although this clearly is a pathological condition. At present, too little is known about the behaviour and any subsequent migration of the mesenchyme of the facial processes and the accompanying nerves after the initial fusion of the maxillary and medial nasal processes. The muscles of the lip, like the other facial muscles, are derived from the mesenchyme of the second branchial arch, and are therefore innervated by the facial nerve.

Fusion between the maxillary and medial nasal processes during the formation of the upper lip involves active epithelial filopodial and adhering interactions, as well as programmed cell death. Slight defects in growth and patterning of the facial mesenchyme or epithelial fusion result in cleft lip with or without cleft palate, the most common and disfiguring craniofacial birth defect. Recent studies of craniofacial development in animal models have identified components of several major signalling pathways, including Bmp, Fgf, Shh and Wnt signalling, that are critical for proper midfacial morphogenesis and/or lip fusion.

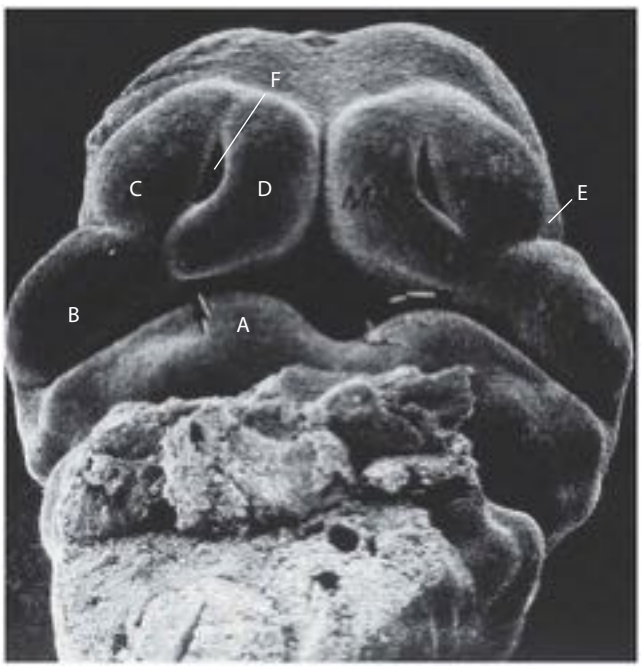


Figure 41.20 Scanning electron micrograph of developing rat upper jaw and lip at an equivalent stage to six weeks in the human showing the merging maxillary and medial nasal processes. A, Mandibular process; B, maxillary process; C, lateral nasal process; D, medial nasal process; E, naso-optic furrow; F, primitive nasal cavity. Reprinted from Ref. 1 by permission from Elsevier.

Development of the palate

As we have seen at 5 weeks of development, the nasal pit deepens and the nasal placode comes to lie in its roof where it will form the olfactory epithelium. The region of the frontonasal process lying between the two nasal pits forms the primary nasal septum, while the tissue beneath the pits and separating them from the stomodeum forms the primary palate. At this stage, the nasal pits are confined only to the anterior extremity of the future oral cavity, the large region behind at this stage forming a common oronasal cavity (**Figure 41.21a**). Subsequent development is designed to extend the primary nasal septum and primary palate backwards by means of a secondary nasal septum and secondary palate.

During the 6th week of development, a secondary nasal septum grows down from the roof of the stomodeum behind the primary nasal septum, thus dividing the nasal aspect of the common oronasal cavity into two. In addition, a lateral palatal shelf grows out from each maxillary process but, due to the comparatively large size of the developing tongue, is prevented from growing horizontally and becomes oriented more vertically (**Figures 41.21b** and **41.22**).

During the 8th week of development, the tongue 'drops' and the vertically inclined palatal shelves can now occupy a horizontal position (**Figures 41.21c** and **41.23**). The reason for the displacement of the tongue is not known. As the tongue is attached to the mandible, it has been suggested that the descent of the tongue is related to mandibular growth. Conversely, reflex movements of the tongue and/or a change in its shape may be implicated. On becoming horizontal, the palatal shelves contact each other

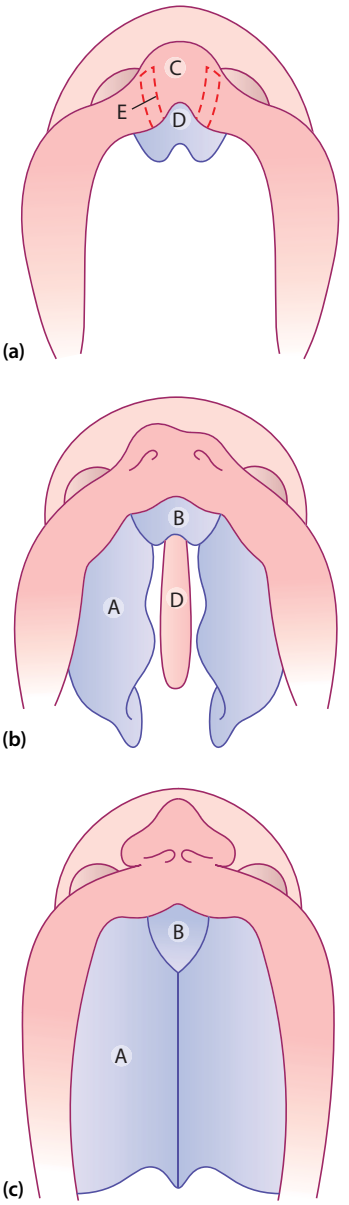


Figure 41.21 Diagram showing the development of the palate (a). By 6th week of intrauterine life; **(b)** during 6th week of intrauterine life and **(c)**. At 9th week of intrauterine life. A, lateral palatal shelves of secondary palate; B, primary palate; C, primary nasal septum; D, secondary nasal septum; E, primitive nasal cavities.

(and the secondary nasal septum) in the midline to form the secondary palate. The shelves contact the primary palate anteriorly so that the oral and nasal cavities become completely separated from each other. After shelf contact, the medial edge epithelia of the two shelves fuse to form a midline epithelial seam. Subsequently, this seam (together with the epithelium separating the palatal shelves from the secondary nasal septum) degenerates, allowing continuity of mesenchyme to be established across the now intact and horizontal secondary palate. Fusion of the palatal processes is complete by the 12th week of development. Behind the secondary nasal septum, the palatal shelves fuse to form the soft palate and uvula.

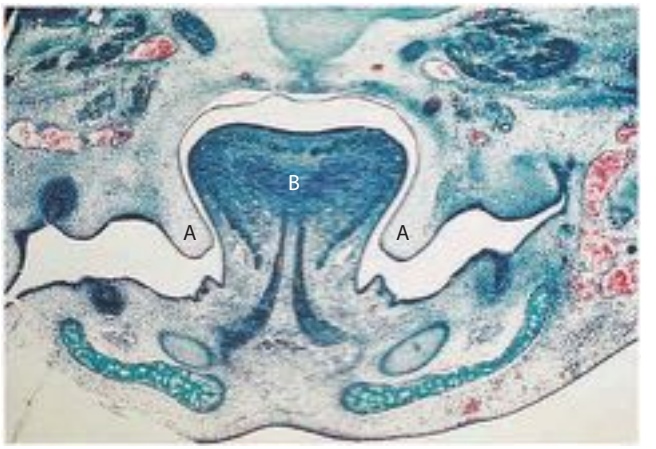


Figure 41.22 Coronal section through the head at an equivalent stage of seven weeks intrauterine development in the human showing the vertically inclined palatal shelves (A). B, Developing tongue. Masson's trichrome ×30. Reprinted from Ref. 1 by permission from Elsevier.

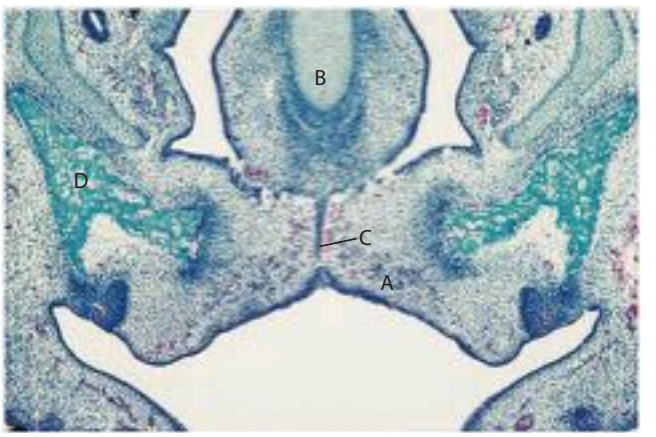


Figure 41.23 Coronal section through developing oro-nasal regions following contact of the palatal shelves (A) and secondary nasal septum (B). C, Midline epithelial seam; D, developing bone of maxilla. Masson's trichrome ×30. Reprinted from Ref. 1 by permission from Elsevier.

The hard palate ossifies intramembranously from four centres of ossification, one in each developing maxilla and one in each developing palatine bone. The maxillary ossification centre lies above the developing deciduous canine tooth germ and appears in the 8th week of development. The centre of ossification for the palatine bone is situated in the region forming the future perpendicular plate and appears in the 8th week of development. Incomplete ossification of the palate from these centres defines the median and transverse palatine sutures. There does not appear to be a separate centre of ossification for the primary palate in man (in other species there is such a centre, forming a separate 'premaxilla').

The muscles of the palate are derived from the lower branchial arches, hence their nerve supply by the pharyngeal plexus. However, tensor veli palatini develops from the first branchial arch, explaining its innervation by the mandibular nerve.

As is evident from the description above, palate formation is a complicated process. The palatal shelves must grow to the appropriate size; the palatal shelves must elevate at the appropriate time on both sides; the medial edge epithelia of the palatal shelves must adhere to form a midline epithelial seam: the midline epithelial seam must degenerate to allow for the establishment of mesenchymal continuity across the midline. Any interference or mistiming of these processes may contribute towards the formation of a cleft palate. Clefts of the palate, like those of the lip, are multifactorial malformations, involving both genetic (polygenic) and environmental factors. Recent research on palatogenesis has concentrated on two main events: palatal shelf elevation and the initial stage of fusion of the shelves.

PALATAL SHELF ELEVATION

This process, during which the palatal shelves move from the vertical to the horizontal position, is thought to occur very rapidly (in terms of minutes and hours rather than days). Although it was once thought that extrinsic forces might be responsible (e.g. forces derived from the tongue or jaw movements), recent research has primarily focused on the search for a force intrinsic to the palatal shelf. Systems which have at one time or another been implicated include differential mitosis, contraction of connective tissue elements such as collagen or mesenchymal cells, changes in vascularity or tissue-fluid pressures. Particular attention has focused on the proposition that the intrinsic shelf elevation force might develop as a result of hydration of ground substance components (principally hyaluronan) in the shelf mesenchyme.[22] In this context, hyaluronan is a highly electrostatically charged, open coil molecule that is capable of binding up to ten times its own weight in water. In support of the possible importance of hyaluronan in palatogenesis, research using organ culture systems have shown that the presence of agents either leading to an alteration in hyaluronan content or size, or that disrupt glycosaminoglycan substitution on proteoglycans, or that alter the balance of matrix molecules secreted via the Golgi complex and hyaluronan produced at the cell surface, all detrimentally affect normal palatogenesis.[1] In addition to hyaluronan, however, other matrix components (including proteoglycans) may also be important during shelf elevation.

FUSION OF THE PALATAL SHELVES

Following palatal shelf elevation, contact is made initially in the middle third of the palate and then extends both anteriorly and posteriorly. The two adjacent medial edge epithelium contact each other and adhere by means of a 'sticky' glycoprotein coating their surfaces. In addition, the epithelial cells develop desmosomes that form a medial epithelial seam. The adherence of the medial edge epithelia is site-specific as palatal epithelia will not fuse with epithelia from other sites (e.g. the tongue).[22]

For normal palatogenesis to proceed, the epithelial seam must be removed for consolidation of mesenchymal tissues across the midline. The signals that are responsible for such a breakdown are not yet fully understood. As a breakdown of medial edge epithelium occurs in single isolated palatal shelves, the process does not depend specifically upon shelf contact.

Factors that may contribute to thinning and then removing the epithelial seam include: growth of the palate (in terms of oronasal height) and epithelial cell migration from the region of the seam on to the oral and nasal aspects of the palate; programmed epithelial cell death (apoptosis); migration of epithelial cells from the epithelial seam into the palatal shelf mesenchyme and their subsequent differentiation into mesenchymal cells (epithelial/mesenchymal transformation).[23] As in other systems, it is thought that signals (e.g. growth factors such as epidermal growth factor and transforming growth factors) emanating from the underlying mesenchyme are ultimately responsible for controlling epithelial degeneration.

CLINICAL AND AETIOLOGICAL CONSIDERATIONS

Malformations of palatogenesis may result in the appearance of clefts. The mildest form of cleft is that affecting the uvula, such a disturbance occurring relatively late in the process of palatal fusion. Disturbances occurring during the early phases of palatal fusion can result in a more extensive cleft involving most of the secondary palate. Should the cleft involve the primary palate, it may extend to the right and/or left of the incisive foramen to include the alveolus, passing between the lateral incisor and canine teeth. Cleft palate may be associated with cleft lip, though the two conditions are independently determined. Dental malformations are commonly associated with a cleft involving the alveolus. A submucous cleft describes a condition where the palatal mucosa is intact, but the bone/musculature of the palate is deficient beneath the mucosa.

As with other situations of epithelial mesenchymal interactions, large numbers of genes, growth factors and their receptors, and transcription factor are involved to ensure that palatal development proceeds normally. These factors have been mapped and show differences at different stages of palatal development, some being more important at the early stages in palate formation, others being more involved at later stages. Their importance in palate development has been shown by experimental manipulation, when their inactivation has been associated with palatal cleft formation. In the early stages of epithelial-mesenchymal interactions, Shh, Fgf10 and Bmp2 and Bmp4 are especially important, as is the orderly release of matrix metalloproteinases (such as those associated with the degradation of versican). During palatal fusion, TGF beta has a prominent role.

With growth of the palatal shelves, there is considerable heterogeneity along the anteroposterior and mediolateral axes of molecules such as Shh, Bmp4, Msx1, Osr1, Barx1. However, the biochemical changes produced by the particular genes, growth factors and signalling molecules are poorly understood.

KEY POINTS

- A detailed knowledge of the anatomy of the mouth and dentition is mandatory for all head and neck surgeons operating in this area.
- For the general ENT surgeon, the anatomy of:
  - **the floor of mouth** is important when dealing with submandibular duct pathology or submandibular duct rerouting, tongue tie, treatment of a ranula and biopsying suspicious lesions;
  - **the buccal mucosa** is important when dealing with parotid duct pathology and biopsying suspicious lesions;
  - **the hard palate** is important when biopsying suspicious lesions;
  - **the soft palate** is important for understanding Eustachian tube pathology, palatal surgery for snoring, and for biopsying suspicious lesions;
  - **the palatine tonsil and lateral pharyngeal wall** are important for tonsillectomy and management of peritonsillar and parapharyngeal abscesses as well as biopsy of suspicious lesions;
  - **the tongue** is important when assessing neurological function after suspected hypoglossal nerve damage or chorda tympani loss, as well as for biopsy of suspicious lesions;
  - **the salivary glands** is important for understanding the principles of parotidectomy and submandibular gland excision;
  - **the temporomandibular joint** is important because of its close relationships to the external ear canal.

For the general ENT surgeon, understanding the development of the face and palate is helpful in understanding a wide range of congenital head and neck abnormalities and cleft palate pathologies in particular.

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CHAPTER 42

BENIGN ORAL AND DENTAL DISEASE

Konrad S. Staines and Alexander Crighton

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SEARCH STRATEGY

Data in this chapter may be updated with a search using the following keywords: dental caries, dental plaque, saliva, pulpitis, apical periodontitis, acute dentoalveolar abscess, pericoronitis, periodontal disease, gingivitis, herpetic oral ulceration, aphthous or aphthous-like ulceration and acute ulcerative (necrotizing) gingivitis, dental trauma, cleft lip and palate, alveolar osteitis, cysts of the jaw, ameloblastoma, oral mucosa, oral mucosa infections, herpes virus, oral candidiasis, aphthous ulcer, lichen planus, pemphigus, pemphigoid, graft versus host, orofacial pain, trigeminal neuralgia, cluster headache and temporomandibular disorders.

COMMON DISORDERS AFFECTING THE TEETH AND PERIDONTIUM

Dental caries

Dental caries is a dynamic, multifactorial, bacterial disease of teeth. The initial stage in dental caries is termed the initial enamel lesion. This typically arises at sites where dental plaque (a microbial biofilm adherent to tooth tissues) is persistent. The underlying process in the initial stages involves acid dissolution of calcified dental tissue creating a dynamic imbalance between demineralization and remineralization in favour of the former.

The pathophysiology of dental caries can be described in terms of the interplay of four factors: dental plaque, dental tissues, saliva and the substrate (**Table 42.1**).

Bacteria within dental plaque, most notably but not exclusively *Streptococcus mutans*, will metabolize substrates generating acid by-products at the plaque–enamel interface. A dynamic process with localized demineralization of the adjacent dental tissues countered by attempts at remineralization driven through saliva, will determine whether caries will develop. Dental plaque creates a microenvironment favourable to demineralization where the protective buffering and remineralization properties of saliva are accordingly diminished. The initial stage of

TABLE 42.1 Factors involved in the development of dental caries

Factor	Action
Salivary factors	Saliva has important cleansing, antibacterial and remineralization functions.
Dental plaque factors	Dental plaque is a microbial biofilm adherent to tooth tissues. Bacteria within plaque, most notably but not exclusively S. mutans, ferment carbohydrate substrates, producing acids that can potentially result in localized demineralization of the adjacent dental tissues. Dental plaque creates a microenvironment favourable to demineralization where the protective buffering and remineralization properties of saliva are accordingly diminished.
Substrate factors	Substrates that can utilized by plaque microorganisms to produce acid are considered cariogenic. Refined carbohydrates especially containing sucrose are examples of such substrates. However, naturally occurring substrates such as those found in fruit are also cariogenic.
Dental factors	Risk factors with regard to dental anatomy are those that favour accumulation of plaque and a favourable environment for caries formation. Examples of such factors include narrow fissures, pits, inadequate interdental contact points that allow food impaction, inadequate dental restoration margins.

dental caries involves the alteration of the enamel surface with acid permeating alongside the enamel prism sheaths causing localized enamel dissolution. This initial stage (with no cavitation or dentine involvement) is considered reversible and amenable to focused preventative treatment.

Should enamel caries progress, eventually, the enamel dentine junction is reached with the ultimate persistence of this process leading to cavitation. Caries may progress involving dentine acid dissolution, proteolysis and bacterial invasion of the dentinal tubules. Once the dental pulp is reached, infection and inflammation of the pulp (pulpitis) will follow.

The clinical diagnosis of caries involves detection and evaluation of the severity of the lesion through clinical examination (predominantly visual and tactile inspection using blunt dental probes) coupled with dental radiographic examination.

Operative treatment of dental caries is required as soon as there is surface cavitation with dentine involvement. The operative treatment of dental caries involves removal of carious tissue and restoring tooth integrity with a restoration. The restoration's function is to restore anatomy and prevent ingress of microorganisms into the restored cavity. Such ingress may, in the presence of other cariogenic factors described above, lead to recurrent caries around the restoration.

Non-carious tooth surface loss (tooth wear)

Tooth wear develops secondary to mechanisms that can be grouped as erosion, attrition, and abrasion occurring independently or in combination. An example of a common exacerbating factor is hyposalivation. The potential consequences of long-standing tooth wear include hypersensitivity secondary to dentine exposure, reduced masticatory function and poor dental aesthetics.

EROSION

Erosion can be defined as the non-plaque mediated chemical dissolution of tooth tissue.

This acid dissolution may be secondary to intrinsically derived acid such as the reflux of gastric acid in gastroesophageal reflux disease or through externally derived acids, with dietary consumption of acid food and drink being the most common cause. Predisposing factors such as hyposalivation may predispose to erosion-mediated tooth wear. Erosion may be a contributing factor to both attrition and abrasion secondary to 'softening up' of the calcified dental tissues.

ATTRITION

Attrition is tooth wear secondary to non-masticatory tooth-to-tooth contact. Bruxist clenching may predispose towards attrition.

ABRASION

Abrasion is tooth wear secondary to friction of exogenous material against the tooth surface. Abrasion may be caused by a variety of mechanisms with an appropriate example being overzealous toothbrushing.

Dental infections

The most common dental infections for which patients seek emergency dental care are pulpitis and apical periodontitis (periapical abscess), pericoronitis and periodontal abscess.

PULPITIS AND APICAL PERIODONTITIS

Pulpitis (dental pulp inflammation) occurs most commonly secondary to microbial infection involving a carious lesion. Less common pathways of infection are through a tooth fracture or in a retrograde manner through the apical foramen. Pulpitis is characterized by inflammation within the confines of the pulp chamber resulting in pressure causing occlusion of the blood vessels and necrosis of the pulp tissue. The pain changes from pain exacerbated by thermal stimuli in reversible pulpitis to a dull, throbbing, persistent poorly localized pain of spontaneous onset in irreversible pulpitis. Ultimately, progressive infection of the pulp chamber is followed by an anaerobic bacterial biofilm colonizing the walls of the necrotic root canals leading to asymptomatic necrosis or acute inflammation. The involvement of the periapical tissues via the apical foramen may elicit an acute inflammatory host response resulting in acute periodontitis. Symptoms indicating the development of apical periodontitis are the development of tenderness on application of pressure of the involved tooth. Dentists typically use the end of a dental mirror handle to tap on the tooth to elicit this. Treatment of pulpitis and apical periodontitis is through root canal treatment or dental extraction. Systemic antibiotics are not routinely prescribed.

Further spread of infection into the periapical tissues and formation of an acute dentoalveolar abscess is accompanied by pain, swelling, erythema and suppuration usually localized to the affected tooth. Surgical treatment is the management of choice for most dental abscesses by drainage of pus and elimination of the source of infection typically through root canal treatment or extraction of the tooth. Antimicrobial use should be mainly limited to spreading and severe infections which are still a cause of hospital admissions.

The host response to involvement of the periapical tissues via the apical foramen is predominantly mediated by T cells and macrophages, leading to a chronic periapical granuloma rather than an acute apical periodontitis. This is typically asymptomatic but may eventually be visible on radiographic examination of the apex of the tooth as a well-circumscribed radiolucency.

PERICORONITIS

Pericoronitis is an acute localized infection which develops around partially erupted teeth, with the most common site being around a partially erupted, impacted wisdom tooth. Presentation is with symptoms of pain aggravated by jaw movement and mastication, trismus and halitosis. On examination an inflamed operculum (gum flap) is invariably present around the affected tooth, associated with localized facial swelling, regional lymphadenopathy and inability to open the jaw to the usual range of movement.

Initial treatment may be limited to irrigation under the operculum with an appropriate topical preparation such as chlorhexidine 0.2%. Indications for systemic antimicrobial treatment include the presence of regional lymphadenopathy, trismus or spreading infection. As gram negative anaerobes are predominantly implicated in pericoronitis, metronidazole is often prescribed.

Periodontal disease (plaque related gingivitis and periodontitis)

The gingivae and the periodontium may become inflamed secondary to a variety of pathological causes ranging from autoimmune to infectious causes (**Figure 42.1**). The generic terms gingivitis and periodontitis are usually applied to plaque-related inflammation of these tissues. The aetiology of chronic adult periodontal disease is multi-factorial, involving interaction between dental plaque, genetic and environmental risk factors. Dental plaque differing in microbial composition, forms above (supra-) and below (sub-) the gingival margin. Periodontitis develops when the plaque-related gingivitis results in an increase in depth of the gingival sulcus by mechanisms involving apical migration of the gingival attachment to the tooth root surface, loss of connective tissue attachment and alveolar bone loss. Examples of clinical parameters used by dental surgeons to assess periodontal disease include placing a periodontal probe in the gingival sulcus, measuring pocket depth which allows an indication of periodontal attachment loss. Bleeding on placement of the periodontal probe tip into the gingival sulcus or periodontal pocket reflects the presence of active gingival inflammation (**Table 42.2**). There has been significant research into the aetiology and association between periodontal disease and systemic diseases such as diabetes mellitus and atherosclerotic vascular disease.



Figure 42.1 Chronic periodontitis.

TABLE 42.2 Causes of gingival bleeding

Local	Systemic
Chronic gingivitis	Any condition causing exacerbation of gingivitis (e.g. pregnancy)
Chronic periodontitis	Leukaemia
Acute necrotizing gingivitis	Human immunodeficiency virus infection
Angioma/telangiectasia	Other causes of purpura
	Clotting defects
	Drugs, e.g. anticoagulants
	Scurvy

GINGIVAL PIGMENTATION

Gingival pigmentation is common in dark-skinned races (**Figure 42.2**). Other common causes include amalgam tattoo and melanotic macules. Smoking, tobacco and betel chewing, and drugs such as hydroxycholoroquine and minocycline may also cause hyperpigmentation. Other causes are listed in **Table 42.3**. See also 'Changes in mucosal colour' below.



Figure 42.2 Gingival racial pigmentation.

TABLE 42.3 Causes of oral hyperpigmentation

Localized pigmentations	Generalized
Kaposi's sarcoma	Addison's disease
Malignant melanoma	Drugs, e.g. phenothiazines, antimalarials, minocycline, contraceptives
Melanotic macules	Ectopic ACTH (e.g. bronchogenic carcinoma)
Naevi	Heavy metals
Syndromes:	Syndromes:
Albright	Complex of myxomas, spotty pigmentation and endocrine overactivity
Laugier–Hunziker	Malignant acanthosis nigricans
Peutz–Jegher	Racial
Tattoos (amalgam or graphite)	Localized irritation, e.g. smoking
	Other rare causes, e.g. haemochromatosis, generalized neurofibromatosis, incontinentia pigmenti

GINGIVAL REDNESS

Chronic gingivitis is the usual cause of gingival redness and is usually restricted to the gingival margins and interdental papillae. More widespread gingival erythema in children is usually caused by herpetic stomatitis but, in adults, desquamative gingivitis (typically seen in lichen planus or pemphigoid) or occasionally allergic responses are responsible.

Localized red areas may represent erythroplasia, carcinoma, Kaposi's sarcoma, candidiasis, lichen planus or lupus erythematosus.

Telangiectasia may be a manifestation of hereditary haemorrhagic telangiectasia, primary biliary cirrhosis, systemic sclerosis, or may follow radiotherapy. Haemangiomas are usually isolated but may occasionally be part of a syndrome.

GINGIVAL SWELLINGS

Localized gingival swellings (epulides) may be of local aetiology (irritation) or can be manifestations of pregnancy, a neoplasm or systemic disease (**Table 42.4**). Generalized gingival swelling is most commonly seen in chronic gingivitis, or caused by drugs such as phenytoin, cyclosporin and calcium channel blockers (**Figure 42.3**) and is occasionally hereditary (hereditary gingival fibromatosis). Gingival swelling may also be seen in herpetic stomatitis, leukaemia, Crohn's disease (CD), orofacial granulomatosis, sarcoidosis, amyloidosis, scurvy and other disorders.

GINGIVAL ULCERS

Neoplasms, herpetic oral ulceration, aphthous or aphthous-like ulceration, acute ulcerative (necrotizing) gingivitis (AUG) and other bacterial infections (e.g. syphilis, tuberculosis) are some of the conditions that cause gingival ulceration.

Dental trauma

Injury to the front teeth is especially common in, but not limited to, childhood. If a permanent incisor is avulsed then reimplantation as soon as possible is advisable. The tooth can be stored in a suitable medium such as milk pending reimplantation. If the deciduous tooth is avulsed then this should not be reimplanted. Fractures of the crown of the tooth should be attended to by a dentist as quickly as possible. If the fractured fragment can be identified it can be reattached to the tooth rather than a restorative filling material being placed. If there is any soft-tissue injury and a missing tooth fragment, the wound should be explored for the fragment before closure. Dental trauma can be a presentation of non-accidental injury in a child and this, together with the pattern of soft-tissue injury and other points from the history should remind the practitioner to consider this aetiology.



Figure 42.3 Drug-induced gingival swelling.

TABLE 42.4 Causes of gingival swelling

Generalized	Localized
Local	
Chronic gingivitis	Abscesses
Hyperplastic gingivitis due to mouth breathing	Cysts
	Pyogenic granuloma
	Neoplasms and warts (various)
Systemic	
Hereditary gingival fibromatosis and associated syndromes	Pregnancy
Drugs: Phenytoin Cyclosporin Calcium-channel blockers	Sarcoidosis
	Orofacial granulomatosis
	Crohn's disease
	Wegener's granulomatosis
Pregnancy	Amyloidosis
Sarcoidosis	Neoplasms (various)
Orofacial granulomatosis	
Crohn's disease	
Leukaemia	
Wegener's granulomatosis	
Scurvy	

DEVELOPMENTAL DISORDERS OF TEETH

Abnormalities of tooth development and eruption may occur either as isolated defects or as part of a wider developmental disorder. Cleft lip and palate is an example of a disorder that may affect both tooth development and eruption. A discussion of other syndromes with associated craniofacial deformity and dental developmental disorders is outwith the scope of this chapter and is discussed in Volume 2, Chapter 6, The child with a syndrome. The effect of trauma may range from root dilaceration of a developing tooth or temporomandibular joint (TMJ) injury.



Figure 42.4 Peg-shaped lateral incisor.

Commonly the last tooth in each dental series may be missing or malformed, more commonly in the adult rather than the primary dentition. This is most often seen by the absence of the third molar tooth, followed by the lateral incisor and finally the second premolar. Multiple missing teeth is termed 'hypodontia' and requires a specialist assessment to plan for a functioning adult dentition. The commonest malformed tooth visible is the upper lateral incisor which is termed a 'peg' lateral incisor (**Figure 42.4**). Adhesive dental restorations, orthodontic tooth movement and dental implants have radically changed the outlook for patients with dental anomalies.

Systemic factors such as hypothyroidism may impact the developing dentition and result in delayed dental eruption. Drugs such as cytotoxic medication may result in delayed eruption.

Discoloured teeth

Teeth most commonly become discoloured through habits such as tobacco use, drinking tea, coffee and red wine (**Table 42.5**). It is important to consider iatrogenic causes of discolouration of teeth such as administration of tetracyclines to a child under 12 years of age or to a pregnant or lactating mother (**Figure 42.5**). Excess systemic fluoride intake in the developing dentition may cause a range of defects from white specks to brownish discolouration and surface irregularities (fluorosis). Chlorhexidine mouthwash especially when used for more than a week can cause discolouration of teeth and dental composite restorations.

Mobile teeth

Causes of early tooth loosening and loss are given in **Table 42.6**. The most common reason for tooth mobility is advanced periodontal attachment loss secondary to chronic adult periodontal disease. When trauma causes mobility, this will be evident from the history. It is important to be aware that in rare cases, malignancy may result in loosening of teeth. Rare systemic disease such as Langerhans cell histiocytosis may also result in localized periodontal attachment loss and tooth mobility.

TABLE 42.5 Causes of discolouration of teeth

Extrinsic	Intrinsic
Poor oral hygiene	Trauma
Beverages/food	Caries
Drugs, e.g. iron, chlorhexidine	Restorative materials, e.g. amalgam
Habits, e.g. smoking or betel chewing	Pink spot (internal resorption)
	Drugs — mainly tetracyclines
	Fluorosis
	Dentinogenesis imperfecta
	Amelogenesis imperfecta
	Porphyria
	Jaundice in neonate or infant



Figure 42.5 Intrinsic dental staining.

TABLE 42.6 Pathological causes of loosening and early loss of the teeth

Local causes	Systemic causes	Others
Trauma	Disorders with some immune deficit	Acrodynia
Periodontitis	Down syndrome	Neoplasms
	Diabetes mellitus	Eosinophilic granuloma
	Leukopenia or leukocyte defects	
	HIV disease	
	Juvenile periodontitis	
	Rapidly progressive periodontitis	
	Papillon–Lefèvre syndrome	
	Hypophosphatasia	
	Ehlers–Danlos syndrome (type VIII)	

Non-neoplastic lesions of the jaws

VARIATIONS OF NORMAL ANATOMY

Bony exostoses (tori) are commonly encountered on clinical examination of the oral cavity. Maxillary tori may be noted of the buccal and labial aspects of the alveolus or in the midline of the palate. Mandibular tori are typically present on the lingual aspect of the premolar regions. The presence of multiple tori within the oral cavity especially if associated with extraoral exostoses may raise a clinical suspicion of syndromes such as Gardner syndrome.

DEVELOPMENTAL BONE DISEASE OF THE JAWS

Osteogenesis imperfecta

Osteogenesis imperfecta (OI) is an autosomal dominant disease, with defective type 1 collagen formation. There are four main types with the main characteristic including bone fragility. OI is associated with dentinogenesis imperfecta which presents with widespread structural defects of the dentition and accelerated tooth wear (**Figure 42.6**).

Infections of the jaw bones

ALVEOLAR OSTEITIS (DRY SOCKET)

Alveolar osteitis is a localized osteitis which develops following a minority of dental extractions and is associated with breakdown of the tooth socket clot. Pain is severe, deep seated and localized to the socket and represents inflammation in the bone rather than infection. The cause is unclear but may represent ischaemia of the tissues as the condition is much more common in smokers. There also seems to be a familial tendency to develop a dry socket.

Clinical examination reveals an extraction socket with no clot with inflammation of the surrounding oral mucosa. Treatment is simply by local curetting of the bone walls of the socket allowing a blood clot to reform. Systemic antibiotics are not indicated.



Figure 42.6 Dentinogenesis imperfecta.

OSTEONECROSIS

Osteonecrosis of the jaws may develop secondary to irradiation to the head and neck. In recent years there has been an increased incidence of medication related osteonecrosis of the jaw secondary to use of antiresorptive drugs such as but not exclusively, bisphosphonates and denosumab.

OSTEOMYELITIS

Both acute and chronic forms may occur in the jaw bones. Causes include spreading dental infection in the presence of a complicating factor such as immunosuppression. Osteomyelitis may also complicate an area of osteonecrosis. Treatment is through systemic antimicrobial therapy and surgical debridement.

Metabolic bone disease of the jaws

PAGET'S DISEASE OF BONE

The maxilla is the more frequently affected site and can be significantly increased in size thus creating occlusal disturbances and denture wear. Specific dental complications of Paget's disease include hypercementosis of teeth with the roots fusing with the alveolar bone resulting in ankylosis.

As in other sites, patients with Paget's disease of the jaws have an increased risk of malignant transformation to osteosarcoma.

Cysts of the jaw

Cystic jaw lesions may be classified using a variety of criteria such as developmental, or inflammatory, epithelial or non-epithelial, odontogenic or non-odontogenic. In adults, radicular cysts, which are inflammatory cysts, are the most common type, followed by developmental cysts such as dentigerous cysts (DCs).

The distribution and characteristics of jaw cysts in children are different from those in adults. In children, there is a relatively high rate of developmental cysts, whereas in adults inflammatory cysts are more common. Clinical presentation may vary depending on the type of cyst, size, site and structures affected. Cysts may also become infected with resultant signs and symptoms developing accordingly. It is important to appreciate that odontogenic tumours, both benign and malignant, may present as cystic lesions. Conversely, malignant change has been described to complicate both inflammatory and developmental cysts.

Odontogenic cysts, by definition, are formed from remnants of the tooth forming dental lamina and consequently involve the tooth-bearing regions of the jaws.

Inflammatory dental cysts

RADICULAR CYST

The radicular cyst is the most common inflammatory odontogenic cyst. This cyst arises around the apex or less commonly the lateral aspect of a non-vital tooth. Together with apical periodontitis, periapical granuloma, it is a

consequence of pulp infection and necrosis. The key to diagnosis is to demonstrate non-vitality of the associated tooth. If the tooth is vital a periapical radiolucency is not secondary to a periapical cyst.

If the culprit tooth is extracted, it is possible that cystic remnants of a periapical cyst will form a 'so-called' residual cyst. Treatment of the smaller periapical cyst is by extraction or root canal treatment of the involved tooth. When the periapical cyst is larger, treatment is as above, accompanied by surgical enucleation of the cyst.

Developmental cysts of the jaw

DENTIGEROUS CYST

The most common developmental odontogenic cyst is the dentigerous cyst (DC) and indeed is the most common cyst of the jaw in the paediatric age group. This cyst arises around the crown of an unerupted tooth with the wall of the cyst attached around the cervical margin of the involved tooth, with significant variation in size. DCs are more commonly unilocular but may also be a multilocular. Radiographically, a dental follicle-related radiolucency around an unerupted tooth should measure less than 4 mm from the surface of the tooth to the outer edge of the follicle; consequently any further increases should raise the possibility of cystic change. It is important to bear in mind that odontogenic tumours such as ameloblastoma and odontogenic keratocyst may involve unerupted teeth and present a diagnostic dilemma.

The treatment options include marsupialization or enucleation, with allogeneic or xenogeneic bone grafting. Harvesting of autogenous bone for grafting should be restricted to cases with large cysts and where bone substitute is not available. Enucleation of a cystic jaw lesion allows the entire surgical specimen and not only a biopsy specimen to be examined histopathologically.

Non-odontogenic developmental cysts

NASOPALATINE DUCT CYST

The embryological remnants of the nasopalatine duct may develop into a cyst. This may be an incidental X-ray finding with a radiolucency noted in this area or alternatively a swelling involving the nasopalatine papillary area is clinically evident coupled with the above-mentioned X-ray findings. The vitality of the adjacent teeth is intact.

Non-epithelial bone cysts

ANEURYSMAL BONE CYST

The aneurysmal bone cyst is controversially not considered a true cyst due to the absence of an epithelial lining. Presentation is most common in the mandible of children and young adults as a unilocular cyst. The size range varies with the potential to involve a significant proportion of the mandible. Radiographically, the radiolucency may have a scalloped appearance extending in between the roots of the teeth. Biopsy confirms the cyst cavity to be devoid of an epithelial lining. Healing may occur without treatment or consequence to an attempt at exploratory diagnostic surgery.

AMELOBLASTOMA

Ameloblastoma is an example of an odontogenic neoplasm that presents as a multicystic or unicystic lesion, locally infiltrative into bone marrow. Depending on the stage at diagnosis, the patient may be asymptomatic or at a later stage present with a swelling extensive jaw expansion. Both clinically and radiographically this tumour may need to be included in the differential diagnosis of a cystic lesion of the jaw. Histopathological confirmation is mandatory.

DISORDERS AFFECTING THE ORAL MUCOSA

Oral mucosal disease can be a reflection of anatomical changes or immunological processes within the oral cavity or an indication of systemic processes within the body. There are also a variety of irritants which produce visible changes in the mucosa on clinical examination.

Examining and recording changes of the oral mucosa

The oral mucosa should be examined using a good light source and suitable retractors, such as dental mirrors. The process should be systematic to ensure that all areas are considered and the recording of the findings presented in a reproducible and easily understood manner. The mucosa should be dried during the examination to allow proper visualization of any lesions. It is important to record negative as well as positive findings to avoid doubt in the future regarding changes in particular mucosal areas. Where appropriate, clinical photographs should be taken to record any lesions, particularly if monitoring is planned.

History taking for oral mucosal diseases

When taking a history from a patient with an oral mucosal disease, the clinician should ensure that the description of the presenting symptom is unambiguous. As an example, patients often refer to 'ulcers' in the mouth to mean any sore area. If the patient is using a word or phrase that has a specific meaning, the clinician must clarify the situation by direct questioning, such as 'Tell me what you mean by an 'ulcer''. Often, patients referred by their doctor or dentist may have no symptoms at all and a change in the expected appearance of the oral mucosa would have been noted by the practitioner as part of a routine oral examination.

Benign oral mucosal changes

A variety of oral mucosal changes may be noted on clinical examination that are either developmental, present as a result of normal oral function or are unexplained.

FRICTIONAL KERATOSIS

This is an adaption of the oral mucosa to increased trauma and results in a white thickening of the mucosal surface which often appears to be 'on top of' the existing mucosa. One common area where this can be seen is the area of the dental alveolus in a patient with missing teeth. This mucosa has increased trauma from food rubbing; an area previously protected by the teeth. The keratosis develops as a reactive change over time to reduce damage to the mucosal surface.

LEUKOEDEMA AND NICOTINIC STOMATITIS

This is a more generalized reactive white change to the oral mucosa, again in relation to generalized rather than focal irritation. Most commonly, this is a change seen in smokers where areas most in contact with the hot smoke are affected. This change can be much more prominent where there is a heavy smoke concentration, such as against the posterior hard palate, producing the changes seen in nicotinic stomatitis. In this condition, the dense hyperkeratosis with inflammation of the opening of the minor salivary gland ducts in the palate appear as red spots against the white background of the palatal mucosa.

FORDYCE SPOTS

The oral mucosa is not part of the developmental gut tube and is derived from the same elements that form the skin of the face. Various adaptations take place including the substitution of minor salivary glands for sebaceous glands. However, in some individuals the sebaceous glands still form in some areas and are visible through the mucosa as small yellow/white spots known as Fordyce spots. These are completely benign (**Figure 42.7**), most commonly seen on the buccal mucosa and the patient is normally unaware of them. They are also found on the lips in some individuals and women in particular, can find them a cosmetic problem.

TONGUE COATING

Many patients complain of having a 'coated tongue'. Occasionally this is a true overgrowth of the dorsal surface papillae and these can become stained to give the appearance of a 'brown hairy tongue' (**Figure 42.8**). More often, it is a slight exaggeration of the normal surface, as can happen when changing to a less abrasive diet or dehydration due to illness. A patient can become quite fixated about the appearance of their tongue, even in the absence of any symptoms.

The condition typically improves if the patient avoids habits or drugs that stain the tongue, such as dark beverages, smoking and chlorhexidine mouthwashes. The appearance can be improved by an increase in oral hygiene efforts and daily cleaning of the tongue dorsum by brushing the tongue with a toothbrush, use of sodium bicarbonate or peroxide mouthwashes, chewing gum or sucking a peach stone for 30–60 minutes each day.

GEOGRAPHIC TONGUE

Geographic tongue is a disorder of epithelial tissue turnover on the tongue dorsal surface. Very occasionally it can be found on other parts of the oral mucosa. Normal epithelial replacement occurs in scattered parts of the tongue mucosa at the same time and is not noticed, but in geographic tongue, adjacent epithelial areas have synchronized turnover with thinning of the mucosa as the existing layers are lost. This thinning makes the red colour of the connective tissue more visible and the patient describes red patches on the dorsum of the tongue which then gradually 'heal' as the new epithelium is produced (**Figure 42.9**). This entire process takes about 10 days but may be progressive over adjacent areas of the tongue which leads to the appearance of the condition 'moving' across the tongue. Although it can be a continuous process, it often occurs at intervals of 2 or 3 months in susceptible individuals. Most patients have no symptoms, but a proportion get sensitivity to highly flavoured or spicy foods due to the thinning of the epithelial barrier. This sensitivity is most noticed



Figure 42.7 Fordyce spots.



Figure 42.8 Brown hairy tongue.



Figure 42.9 Geographical tongue.

by children and can be disabling particularly in the very young. With age, the sensitivity reduces and most symptomatic patients require no treatment other than avoiding irritant foodstuffs. Topical anaesthetics such as benzydamine can be helpful if symptoms are particularly bad, but as the cause for the reduced epithelial proliferation is unknown, no 'curative' treatments are available.

MEDIAN RHOMBOID GLOSSITIS

This is an uncommon condition that presents as a red, depapillated and smooth, rhomboidal area, broadly in the centre of the dorsum of tongue. It is usually associated with an invasive candidiasis which is not pathogenic. Multiple oral lesions may occasionally be present, especially a 'kissing' lesion in the palatal vault. Smoking, denture wearing and, occasionally, immune defects including HIV and diabetes are said to predispose to median rhomboid glossitis, but most lesions are seen in healthy adults. No treatment is required as the lesion is almost always asymptomatic, but a biopsy with PAS stain for candida can be useful for reassurance, particularly when the area becomes raised and lumpy.

MUCOSAL SWELLINGS

Thickening, hypertrophy and lumps of the mucosal structures can be reactive to a variety of local irritants or as a result of benign pathology of the oral or submucosal tissues. All of these lesions are typically painless.

Viral warts can produce thickening of the epithelium and are most commonly seen in children. When these present in an adult, immunosuppression is usually the cause and conditions such as HIV should be considered. Both extra- and intraoral warts usually arise as a result of contact with a skin lesion, such as on the hand or fingers, and all must be eradicated to prevent recurrence.

Fibro-epithelial polyps arise from low-level irritation and can be sessile or pedunculated. They only require removal if they are being subject to trauma, but the cause of the trauma should first be removed to prevent a continued increase in size or recurrence after removal. Multiple mucosal polyps, dental anomalies (hypodontia, enamel defects and taurodontism) and occasionally cleft lip and palate are found together in the rare Gorlin-Goltz syndrome and multiple mucosal papillomas with associated gastrointestinal (GI) and thyroid disease are found in Cowden syndrome.

Benign tumours in the connective tissue such as a neuroma, lipoma or minor salivary tumours such as the pleomorphic adenoma will produce small mobile lesions deep in the tissue. Mucoceles – obstructive minor salivary gland lesions – will usually have a history of waxing and waning on a recurrent basis, but may eventually fibrose to leave a firm connective tissue swelling.

Inflammatory swellings can arise on any part of the oral mucosa but are frequently seen on the gingival margin. The source of the irritation is often not obvious but a broken tooth may be a trigger. Pregnancy predisposes to gingival inflammatory swellings; most are pyogenic granulomas but giant cell lesions are also common. These latter lesions may be isolated localized lesions or part of a more widespread disease such as hyperparathyroidism. An X-ray should always be taken in the area of any gingival swelling to ensure that the soft-tissue lesion is not a bony lesion extending into the mouth.

Mucosal swellings can also arise as part of systemic disease including CD/orofacial granulomatosis, sarcoidosis, Wegener's granulomatosis and amyloidosis. Recurrent lip swelling is found in angio-oedema and orofacial granulomatosis.

Changes in mucosal colour

The oral mucosa is pink but as this is a view of the blood in the connective tissue beneath, the exact colour varies with the thickness of the epithelium and the vascularity of the underlying connective tissue. Consequently, the keratinized areas of mucosa such as the hard palate and gingival tissues appear whiter as there is a thicker barrier between the observing clinician and the connective tissue blood vessels.

White lesions of the oral mucosa are most commonly thickening of the epithelium by acanthosis or hyperkeratosis although reduced connective tissue blood flow can be seen in conditions such as submucous fibrosis (**Table 42.7**). An established squamous carcinoma will appear white as there is increased tissue in the area. White lesions are more

TABLE 42.7 White lesions of the oral mucosa

Local	Systemic
Frictional keratosis	Candidiasis
Smoker's keratosis	Lichen planus
Idiopathic keratosis	Lupus erythematosus
Carcinoma	Papillomas (some)
Burns	Syphilitic keratosis
Skin grafts	Inherited lesions (e.g. white-sponge naevus)

frequent, but are less commonly associated with dysplasia than red lesions. A white sponge naevus is a dominant-inherited developmental condition causing characteristic changes within the epithelium. It usually starts in childhood at the posterior buccal mucosa and spreads slowly anteriorly over years giving a characteristic appearance of a 'shaggy' white lesion covering much of the buccal and palatal mucosa including areas not subject to dental trauma such as the buccal sulcus. It is symptomless and requires no treatment.

Red changes of the mucosa usually reflect thinning of the mucosa making the observer more able to see the blood in the connective tissue but they can also arise as a consequence of increased vascularity of the connective tissue, as in the case of dysplasia or malignancy; thus, unexplained red lesions are of greater concern to the clinician. Inflammation of the tissues will also produce red changes to the mucosa, and commonly candida or other causes of mucosal irritation will give this appearance. Focal red lesions can represent capillary haemangiomas and require no treatment unless bleeding becomes an issue, usually secondary to trauma. Multiple focal haemangiomas are seen in the oral and facial tissues as part of hereditary haemorrhagic telangiectasia.

Pigmented lesions can be localized or generalized (see **Table 42.3**). Brown pigmentation is the result of increased melanin in the tissues. Biopsy can differentiate a melanosis (normal melanocyte numbers producing excess melanin) from a naevus (increased number of melanocytes each producing a normal amount of melanin). A melanoma is a rare primary lesion in the mouth.

Grey/blue pigmentation is seen with foreign bodies such as dental amalgam or heavy metal poisoning with lead or arsenic (**Figure 42.10**). These are best diagnosed on biopsy as the material is seen phagocytosed inside giant cells. X-rays are not reliable to demonstrate the small amount of foreign material and are discouraged as an investigation to reduce radiation exposure. Dark blue and purple lesions are mostly venous malformations such as a cavernous haemangioma or a varicosity and are seen in many elderly patients. If these lesions are raised enough to be subject to trauma and bleeding, they can be surgically excised or ablated with cryosurgery.



Figure 42.10 Amalgam tattoo.

Generalized oral mucosal pigmentation is most commonly racial pigmentation, whilst smoking is the commonest acquired cause. In smokers, the pigmentation fades when the habit is stopped. Medicines are another common reason for mucosal pigmentation with drugs as diverse as hydroxychloroquine, imatinib, minocycline and the oral contraceptive pill all implicated. Pregnancy or hormonal changes where ACTH levels are raised can also result in widespread oral pigmentation. Addison's and Cushing's diseases or some small-cell lung tumours are rare causes; for these reasons, an unexplained increase in pigmentation in the mouth should always be investigated.

Isolated or localized pigmentation can also be caused by any of the systemic causes for pigmentation; the observer may simply be seeing the start of the process. Localized lesions tend to have a local cause such as an amalgam tattoo where a tooth apicectomy has been performed, or post-inflammatory pigmentation in an area of trauma. However, the commonest cause is the simple melanotic macule or freckle but this should be confirmed on biopsy to differentiate it from a naevus or early dysplastic change. Peutz–Jeghers syndrome is an autosomal dominant trait characterized by hamartomatous intestinal polyposis and multiple areas of mucocutaneous melanotic perioral pigmentation.

Oral ulceration

Mouth ulcers are a frequent complaint by patients but the clinician must be clear as to what the patient means by 'ulcer'. This can be a term used to mean any sore spot in the mouth to a patient. A true ulcer is a break in the epithelium and may be preceded by a blistering phase in some conditions. It is important that this is clarified when taking the history. As oral ulceration can be a presentation of malignancy, any ulcer which has been present for more than 2 weeks must be investigated.

The common causes of ulcers include local trauma from teeth or sharp edges on dentures, recurrent aphthous stomatitis, Behçet's syndrome) and viral infections after the initial vesicle has burst. Systemic diseases associated with oral ulceration are given in **Table 42.8**.

The history should clearly differentiate a single continuing ulcer episode from recurrent oral ulcers and multiple oral ulcer lesions that overlap in time. Where an ulcer recurs in a specific area repeatedly a local cause should be considered, although ulcerated forms of lichen planus frequently present in this way.

APHTHOUS STOMATITIS

Aphthae are recurrent oral immunological ulcers that are multifactorial in origin and arise as a result of T-cell medicated damage to the mucosal epithelial basal layer (**Figure 42.11**). They are not potentially malignant lesions, occur throughout the GI tract and are characterized as major, minor or herpetiform depending on the presenting features (**Table 42.9**). All are genetically determined and this tendency may cause ulcers to be expressed spontaneously throughout life, or never at all depending upon the family characteristics. The family history is an important

TABLE 42.8 Oral ulceration associated with systemic disease

Causes	Examples
Microbial disease	Herpetic stomatitis Chickenpox Herpes zoster Hand, foot and mouth disease Herpangina Infectious mononucleosis HIV disease Tuberculosis Syphilis
Malignant neoplasms	Squamous cell carcinoma Lymphoma
Skin disease	Erosive lichen planus Pemphigus Pemphigoid Erythema multiforme Dermatitis herpetiformis and linear IgA disease Epidermolysis bullosa
Systemic triggers for ulcers Blood disorders	Rapid growth periods during childhood Haematinic deficiency (ferritin, folate, vitamin B_{12}) Leukaemia Neutropenia Other white cell dyscrasias
Gastrointestinal disease	Coeliac disease Crohn's disease Ulcerative colitis
Iatrogenic causes	Antirheumatic drug therapy Chemotherapeutic agents Acrodynia Radiotherapy



Figure 42.11 Aphthous ulcer.

predictor of the ulcer pattern in an individual. In addition to the genetic susceptibility are a range of health and environmental modifying factors which can promote ulcer formation; the combination of genetic and environmental triggers determine the individual's susceptibility to aphthae. If an individual has had recurrent aphthous oral ulcers since childhood then the genetic component is likely to be the main ulcer determinant, but if there has only been the occasional ulcer until recently it is more likely that a modifiable environmental or health factor could be at play, leaving the opportunity for successful medical intervention. The most common correctable triggers are haematinic deficiencies, where iron (measured as ferritin), folic acid or vitamin B_{12} levels are low. This can happen in the presence of a normal blood count and the absence of anaemia does not exclude a haematinic deficiency. A haematinic screen together with a coeliac screen should be carried out for all patients with recurrent aphthous stomatitis.

TABLE 42.9 Aphthous ulceration

Type of aphthous ulceration	Clinical features
Minor aphthous ulceration	Most common form of aphthous ulceration Less than 10 mm in diameter Last 2–3 weeks Only on non-keratinized mucosa Heal without scarring Can be multiple but fewer than 10 at a time Usually at the front of the mouth Commonly in areas of mucosal trauma
Major aphthous ulceration	Larger than 10 mm in diameter Can last up to 3 months Can occur on keratinized or non-keratinized mucosa Can heal with or without scarring Usually single but 1–3 ulcers can be present at once Usually towards the back of the mouth
Herpetiform ulceration	Least common form of aphthous ulceration Less than 5 mm in diameter Last for up to 2 weeks Heal without scarring Large numbers of ulcers – up to 100 Coalesce in areas to form large areas of ulceration Arise in keratinized and non-keratinized mucosa Similar in appearance to primary herpetic gingivostomatits

As aphthous ulcers are driven by an immunological reaction, the process can be controlled using immunomodulatory therapy. In some cases, altering environmental factors such as avoiding sodium lauryl sulphate (SLS) containing toothpastes or dietary triggers (benzoate, chocolate, cinnamon) can reduce the triggering of lesions to a level low enough to satisfy the patient. In others, the use of topical immunosuppressants or immunomodulators can successfully alter the clinical course of the disease. As the immunological damage happens some days before the ulcer appears, it is critical that the treatment is started as soon as the patient becomes aware of the lesion. By the time the ulcer appears, it is too late for an immunomodulatory drug to be effective and the patient must rely on analgesic solutions or obturative pastes to manage their symptoms. Treatment options for aphthous ulcers are listed in **Table 42.10**. Systemic immunotherapy should only be used by a specialist with appropriate experience.

Erythema multiforme (EM) is an immunological hypersensitivity reaction that can affect many body systems

TABLE 42.10 Treatment options for aphthous ulceration

Treatment modality	Medication	Instructions
Symptomatic	Benzydamine solution	Spray solution onto ulcer or rinse with the solution for one minute before meals to reduce ulcer sensitivity
	Occlusive paste (e.g. orabase) Lignocaine gel	Apply to the ulcer before eating to give relief from discomfort
Topical episodic	Betamethasone mouthwash	1 mg dissolved in 10 ml water, use as rinse for 2 mins twice daily at the onset of ulcer symptoms until ulcer heals
	Beclomethasone Inhaler 50–200 mcg/puff	Give 2 puffs of the powder three times daily directly onto the area with ulcer symptoms starting at the onset of symptoms until the ulcer heals
Topical preventative (*can be combined into a single mouthrinse*)	Betamethasone mouthwash	1 mg dissolved in 10 ml water, use as rinse for 2 mins once daily each day
	Doxycycline mouthwash	100 mg soluble tablet in 10 ml water used as a rinse for 2 mins twice daily
Systemic preventative	Colchicine Azathioprine Mycophenolate mofetil	Used under the direction of a specialist only

individually or together (Stevens-Johnson syndrome). There may be a genetic predisposition to recurrent erythema multiforme and this is seen most commonly in young men. In the mouth, EM presents in much the same way as a primary herpetic gingivostomatitis with widespread oral mucosal inflammation and multiple areas of coalescing ulceration on both keratinized and non-keratinized mucosa. This may be the only clinical lesion, but in other patients the oral lesions may appear concurrently with skin, genital or nasopharyngeal lesions. EM appears to be a type 3 hypersensitivity reaction where a host antibody binds an antigen in the circulation and lodges in capillary tissue, activating complement and initiating localized inflammation and tissue damage. The labial mucosa is often involved, and a serosanguinous exudate leads to crusting of the swollen lips.

The following are possible triggers for EM: infective agents, particularly HSV and mycoplasma; drugs such as sulphonamides, cephalosporins, aminopenicillins, quinolones, NSAID; food additives or chemicals such as benzoates, nitrobenzene, perfumes, terpenes.

The diagnosis can be difficult and a biopsy of perilesional tissue, with histological and immunostaining examination are essential if a specific diagnosis is required. Supportive care is important; a liquid diet and intravenous fluid therapy may be necessary. EM should be treated with high-dose systemic corticosteroids in the acute phase. Preventative therapy with acyclovir can be helpful if recurrent lesions are suspected to be from a HSV reaction.

Mucositis (mucosal barrier injury) is the widespread erythema, ulceration and soreness which commonly complicates chemo-, radio- or chemoradiotherapy. Mucositis appears from 3 to 15 days after treatment, earlier after chemotherapy and radiotherapy. Mucositis invariably follows total body irradiation and external beam radiotherapy involving the orofacial tissues. Up to 90% of patients on traditional chemotherapy develop mucositis although targeted cancer immunotherapy is less likely to give ulcers. Oral mucositis is particularly severe after haemopoietic stem cell transplant and can act as a portal for infection. Mucositis typically presents with pain which can be intense enough to interfere with eating, and significantly affect quality of life, with ulceration and sometimes bleeding.

Management aims to relieve pain, hasten healing and prevent infectious complications. Pain relief is usually with opioids given by patient-controlled analgesia; additionally, benzydamine rinse or spray can aid relief. Oral cooling with ice chips ameliorates chemotherapy-induced mucositis.

Systemic diseases and the mouth

The oral mucosa is a specialized form of skin bridging the gap between the embryonic gut tube ending and the outside world as the head and brain rapidly enlarge. The mouth therefore has a stratified squamous epithelium lining and the transition to the gut 'proper' happens in the oesophagus. Consequently, the oral cavity experiences a transition of diseases between GI and dermatological conditions and skin appendages can result in visible changes in the mouth in some individuals.

DISEASES OF THE SKIN

The immunobullous conditions pemphigus, pemphigoid and lichen planus are commonly present with findings in the oral mucosa. Others seen more rarely include epidermolysis bullosa and linear IgA disease.

Pemphigus and pemphigoid are autoimmune disorders driven by immunoglobulins, where C3 and IgG binding cause loss of adherence of intercellular desmosomes and hemidesmosomes. They result in separation of the cells of the epithelium from each other (pemphigus) and the epithelium from the basement membrane (pemphigoid). Pemphigoid presents with a combination of intact and ruptured bullae but pemphigus has such fragile intraepithelial bullae that they are frequently not seen other than as a white change in the mucosa which is rapidly lost to reveal a red and inflamed submucosa (**Figure 42.12**). There are variations in these diseases depending upon the epitopes of the antigen



Figure 42.12 Pemphigus.



Figure 42.13 Lichen planus.

targeted by the immune reaction and these small alterations can significantly change the presentation or consequences of the disease processes. There are also differences between the immune target in the skin and oral versions of these conditions such that they can run largely independent courses in the same individual. Pemphigus often will start with oral lesions and later involve the skin whereas pemphigoid can have limited oral and cutaneous versions. Pemphigoid also has a scarring form limited to the mucosa and into the eyes and oesophagus – cicatricial pemphigoid. This is progressive and can be very disabling over time with difficulty opening the mouth and swallowing as well as significant ophthalmological issues.

All patients diagnosed with pemphigoid on the oral mucosa should see an ophthalmologist to manage any conjunctival scarring which may appear with time. Most symptoms from these conditions result from the ulcerative areas left when the bullae burst (pemphigoid) or the epithelium separates internally (pemphigus). This causes widespread discomfort for the patient.

Paraneoplastic pemphigus is suspected when a pemphigus lesion is difficult to manage. It is usually associated with lymphoproliferative disease or thymoma and the oral lesions may be the sole manifestation. A degree of suspicion is needed but an appropriate referral to a general physician for assessment is essential. Biopsies for pemphigoid and pemphigus must be taken from perilesional tissue otherwise no epithelium will be present on the specimen for proper examination.

Lichen planus (LP) is a very common oral condition and in most patients, is asymptomatic. It is a T-cell mediated attack on the basement membrane and basal cell layer of the skin or mucosa and causes a reactive increase in the epithelial width (acanthosis – white appearance) or a reduction in the production of new epithelial cells and a consequent reduction in epithelial width (atrophy/ulceration – red appearance). Both can be present in the same lesion at the same time. On the skin it gives lacy patterns, with itchy purple spots on the wrists, legs and trunk. About 30% of patients have both oral and cutaneous lesions. The oral lesions are frequently asymptomatic and seen as an incidental finding on oral examination. However, oral LP can present in more aggressive ways including atrophic and erosive versions which cause discomfort with spicy and flavoured foods. Lesions tend to be intermittent and recurrent and can be symptomatically confused with recurrent aphthous ulcers. However, LP lesions tend to recur in the same places repeatedly whereas aphthae vary in position. Common sites for LP are the lateral aspects of the tongue and the buccal mucosa (**Figure 42.13**). LP has a low potential for malignant transformation although the individual risks for a lichenoid lesion are not clear. Patients must be made aware of the issue of possible malignancy so that regular monitoring of the lesions can take place. LP is mostly of unknown origin but in some individuals, there is a trigger from amalgam or other dental restorations adjacent to the lesions. This is termed a lichenoid reaction although the lesions on the mucosa are essentially the same as those seen in LP. Drug reactions can also trigger a lichenoid reaction, the commonest of which are ACE inhibitors and beta-adrenergic blockers. Disease-modifying drugs used in connective tissue diseases such as gold, penicillamine and sulphasalazine are used less frequently now but were frequent triggers in the past. Discontinuing these medicines gradually results in an improvement in the condition. Angiotensin-2 receptor blockers do not give this reaction and are a good alternative where an ACE inhibitor is suspected as the cause of the lichenoid reaction.

All three of these dermatoses can also present in limited form in the mouth, affecting the attached gingivae only. This is clinically described as a 'desquamative gingivitis' and the underling condition can be determined by biopsy (**Figure 42.14**).

Management of pemphigus, pemphigoid and LP uses the same algorithmic approach as is used for aphthous ulcers (**Table 42.10**) with the exception of colchicine which has no role in the immunobullous conditions. Additionally, topical clobetasol or tacrolimus as a cream or ointment can be useful for stubborn but localized lichenoid lesions. Tacrolimus as a mouth rinse can be a useful bridge between topical steroids and systemic medication for



Figure 42.14 Desquamative gingivitis.

individuals with widespread lichenoid lesions but is ineffective against pemphigus and pemphigoid in the mouth as they are largely antibody rather than T-cell driven.

Diagnosis of an immunobullous condition in the mouth is by perilesional biopsy with one sample sent for standard histopathology and a second sample for direct immunofluorescence. Indirect immunofluorescence from a blood sample is not accurate as a diagnostic test but can be helpful in monitoring disease activity.

GASTROINTESTINAL DISORDERS

GI conditions are frequently associated with oral symptoms and signs. The consequences for the oral mucosa can be direct disease effects or secondary to nutritional deficiency from GI bleeding or malabsorption. Oral ulcers, candida infections and lichenoid lesions are all exacerbated by haematinic deficiency and thus, blood loss from peptic ulcer disease, inflammatory bowel disease or bowel cancer will impact on the mouth, and may be the presenting symptom.

Coeliac disease is often easy to diagnose in children as there is growth failure. However, adult-onset coeliac is more of a challenge and the nutritional deficiency consequent to malabsorption may exacerbate oral diseases. Commonly ferritin and folic acid levels are reduced when there is small bowel malabsorption and this combination should always raise suspicion. Where necessary a tissue transglutaminase or more specific coeliac test can be run.

Ulcerative colitis (UC) similarly can exacerbate oral conditions that are sensitive to haematinic deficiencies. However, aphthous pattern mouth ulcers can occur during periods of UC activity and the oral lesions tend to settle when the colonic disease is controlled.

Crohn's Disease (CD) is a pan-GI disorder with full-thickness inflammation of the mucosa, lymphatic obstruction and mucosal oedema. Like UC its aetiology is unknown but likely represents a range of aetiologies interacting with the host immune system. First symptoms can commence at any age and localize to any area of the GI tract; akin to UC, exacerbation of oral conditions related to haematinic deficiencies complicates the condition. CD can involve the mouth together with other GI sites and when there is gut disease present the oral features are described as 'oral Crohn's disease'. In children, the oral features may present before GI symptoms.

Oro-facial Granulomatosis (OFG) is a disease which has all the features of CD but is localized to the oral mucosa with no symptomatic GI disease. Over time some will develop GI symptoms and OFG may represent part of the spectrum of CD rather than being a separate entity. As sarcoidosis and tuberculosis can both present in the mouth with similar clinical findings, it is important that these are excluded before a diagnosis of OFG is attributed. The characteristic features of OFG are identified in **Box 42.1**.

Not all of these findings are present in every patient and recurrent or persistent lip swelling usually triggers the referral. These lip swellings are from lymphoedema with the lymphatics obstructed by giant cells. The swelling persists for several days or weeks at a time. Like CD it is likely that the aetiology of the immunological reaction in OFG is multifactorial and varies from patient to patient.

Management of OFG takes two approaches. First, the lymphoedema can be reduced in patients who have a sensitivity to dietary triggers by a 12-week complete exclusion diet. It is not possible to identify these patients other than by the diet and so all OFG patients are started with this regime. The patient needs to exclude benzoate, sorbate, cinnamon and chocolate. This requires a degree of determination by the patient and others in the household if it is to be a success. Advice from a specialist dietician can be helpful. During the exclusion period those patients with dietary hypersensitivity will get progressive reduction of the lip swelling although some of the other intraoral changes will persist. At the end of the exclusion period, the patient can return to a normal diet if exclusion was ineffective or, if it was helpful, individual foodstuffs can be reintroduced one at a time to identify individual items for future avoidance. It is unclear whether these dietary triggers are implicated in the aetiology of OFG or are coincidental issues present in the patient for many years and brought to the fore by the lymphatic obstruction.

The second management approach is to use immunotherapy to eliminate the giant cell reaction and allow the lymphatics to drain freely. This can be tried with topical tacrolimus but usually needs systemic treatment with azathioprine of mycophenolate. Surgical options for OFG management usually produce a poor cosmetic result.

BOX 42.1 Oral features in Crohn's disease

- Lip and/or facial swelling and erythema
- Angular cheilitis
- Oral mucosal tagging
- 'Cobblestone' appearance of the mucosa
- Linear ulcers in the depth of the buccal sulcus
- Non-plaque related full width gingival inflammation

CONNECTIVE TISSUE DISORDERS

Most connective tissue disease affecting the head and neck involves the salivary glands. However, mucosal lesions from lupus erythematosus or loss of tissue elasticity as a result of scleroderma can complicate oral care.

Discoid lupus lesions or those associated with SLE have a clinical appearance like lichen planus but are distinct on biopsy. The lesions are also more commonly found in sites unusual for lichen planus, such as the mucosa of the palate.

Scleroderma either on its own or as part of CREST syndrome poses many challenges for oral care. Once the disease fully takes hold, mouth opening is greatly reduced and dental care including denture provision becomes extremely difficult. When it is clear a patient has oral involvement from scleroderma, an opinion should be obtained from a Restorative Dentistry specialist who can assess the long-term prognosis for the dentition and plan for a future low-maintenance mouth.

GRAFT VERSUS HOST DISEASE

Graft versus host disease (GVHD) is usually the consequence of allogeneic bone marrow transplant but is also seen after autologous stem cell treatment. The oral lesions are similar to a widespread lichenoid reaction and mirror the immunological damage taking place elsewhere in the body. The oral lesions can be painful if erosive or atrophic and can be managed with topical steroids in most cases. However, the patient's physician should be made aware of the oral finding as systemic immunotherapy may be preferred to prevent concurrent damage to other body organs. Herpes simplex virus (HSV) causes primary herpetic stomatitis of the oral and genital areas with oral lesions accompanied by systemic upset and fever. Either HSV1 or 2 can be found in primary or recurrent lesions. Many infections with HSV occur in childhood and are subclinical, often misdiagnosed or passed off as 'teething'. More typically it presents with malaise, anorexia, irritability and fever, anterior cervical lymphadenopathy and a diffuse, purple, boggy gingivitis with multiple vesicles followed by scattered ulcers 1–3 mm in diameter. A full blood picture, white cell count and differential, and viral studies may therefore be required. Specific antiviral agents such as aciclovir are reserved for immunocompromised patients. Recurrent HSV lesions can be seen periorally but can also present as intraoral lesions, most typically on the palate. The patient describes a recurrent 'ulcer' in an area which is unilateral and restricted to a single mucosal nerve branch. Where symptomatic, the intraoral and extraoral lesions can be treated symptomatically. In significant lesions which are disfiguring or persisting, systemic acyclovir is used in preference to topical drug. A continuous low dose of aciclovir can be given each day as prophylaxis against recurrence and can significantly improve the patient's quality of life.

Herpes Zoster virus (HZV) causes similar clinical lesions as found in HSV but the primary infection (chicken pox) has skin lesions as well as the oral vesicles/ulcers and systemic fever. The HZV virus is more neuropathic than HSV and the characteristic difference when recurrent lesions (shingles) appear in the mouth or on the face is pain in the affected area, which may precede the onset of the vesicular rash. Shingles should always be treated with aciclovir to reduce the cumulative nerve damage that can lead to post-herpetic neuralgia. The medication should be started with the onset of pain and continued until the rash has cleared. The dose of aciclovir needed to treat HZV is higher than with HSV and similarly, if daily prophylaxis against recurrent HZV is to be given, the dose must be raised above that used for HSV.

Other herpes group viruses also cause oral mucosal lesions. Epstein–Barr virus (EBV) gives the features of glandular fever during the primary infection and although there is no mucosal recurrent lesion as with HSV, persistence of the virus can be associated with hairy leukoplakia in the immunocompromised and nasopharyngeal carcinoma. Cytomegalovirus (CMV) rarely causes oral issues except in the extremely immunosuppressed patient where widespread atypical oral ulceration can arise, a difficult clinical problem. *HHV8* is associated with Kaposi's Sarcoma oral lesions.

Human papillomavirus (HPV) is present in mucosal warts and multiple wart-like lesions in an adult should raise the suspicion of immunodeficiency. HPV seems not to be associated with oral squamous cell carcinoma although it plays a significant role in oropharyngeal cancer.

Coxsackie viruses can cause hand, foot and mouth disease, and herpangina with oral vesiculation together with systemic symptoms but treatment for the oral lesions is supportive only.

HIV-associated oral lesions have been well documented but with the advent of HAART management these are now rarely seen except in the latter terminal stages of the disease. Consequently, an HIV test should be considered in any patient presenting with an oral condition noted to be associated with immunosuppression (**Figure 42.15**).

FUNGAL INFECTIONS

Candida albicans is the most common fungal organism found in the mouth although other forms such as *C. krusei, C. glabrata C. tropicalis* and *C. dubliniensis* can be



Figure 42.15 Hairy leukoplakia in HIV.

TABLE 42.11 Rare orofacial fungal infections

Infection	Oral manifestations
Aspergillosis	Aspergilloma Rhinocerebral type causes palatal necrosis Disseminated in immunocompromised patients
Blastomycosis	
North American South American (paracoccidioidomycosis) Coccidioidomycosis Cryptococcosis Histoplasmosis Phycomycosis (mucormycosis, zygomycosis)	Oral ulcers, or suppurating granulomas
	Oral ulcers and lymphadenopathy
	Rarely oral ulcers
	Oral ulcers
	Lumps or ulcers
	Antral involvement with palatal ulceration in immunocompromised patients – especially diabetics

TABLE 42.12 Oral *Candida* conditions

Types of candidiasis	Predisposing factors
Acute pseudomembranous candidiasis (thrush)	Local or systemic immunosuppression
Acute atrophic candidiasis (antibiotic sore mouth)	Broad-spectrum antibiotics
Erythematous candidiasis	None, aging
Chronic atrophic candidiasis (denture-related candidiasis)	Denture/appliance-wearing, especially at night
Chronic hyperplastic candidiasis	Tobacco smoking
Median rhomboid glossitis	Tobacco smoking, denture wearing, local immunosuppression
Angular cheilitis	Denture wearing, diabetes, haematinic deficiency, OFG
Chronic mucocutaneous candidiasis	Often immune defect; rarely endocrinopathy

found. These non-albicans species tend to be more resistant to common antifungal agents. Rarer orofacial fungal infections are listed in **Table 42.11**.

Candida spp. is a commensal in many of the population and a swab from the mouth demonstrating *candida* does not denote infection, simply candidial carriage. Quantitative fungal assays can be used where it is important to demonstrate high levels in the mouth. *Candida* can cause a variety of oral infections and appearances (**Table 42.12**). Although acute pseudomembranous candidiasis can produce white lesions in the mouth the clinician will do well to remember that there are many causes of oral white lesions and that every patient with a white lesion should not be assumed to have, and be treated for, candidiasis!

Denture-related stomatitis (chronic atrophic candidiasis) is the most common form of mild, chronic, oral candidiasis. It occurs only beneath a denture or other appliance and, despite its name, is not often sore. Dentures worn throughout the night, or with a dry mouth, favour development of this infection and occasionally there is a mixed infection with staphylococcal species. An accumulation of microbial plaque on and in the fitting surface of the denture and the underlying mucosa predispose to making the clinical appearance persist. This condition is managed exclusively by proper denture hygiene including removing the denture at night, cleaning the denture properly and treating it regularly with an appropriate antiseptic. There is no need for a topical antifungal except in the immunocompromised. If untreated the patient may develop papillary hyperplasia of the tissues beneath the denture which can complicate the provision of a new denture in the future.

Acute oral candidiasis (acute pseudomembranous candidiasis) may complicate systemic, topical or inhaled corticosteroid or antibiotic therapy (**Figure 42.16**). It produces widespread erythema and soreness or the mouth and pharynx, sometimes with thrush.



Figure 42.16 Pseudomembranous candidiasis: 'thrush'.

In some immunocompetent patients, there is persisting erythema in the palatal tissues associated with candida. This is termed chronic erythematous candidiasis and requires no treatment.

Chronic hyperplastic candidiasis (CHC) is a condition that has been considered potentially malignant but the link between CHC and oral cancer is now less clear. Its true nature remains elusive but it is associated with candida invasion into the tissues at the corners of the mouth causing a raised white lesion on the oral mucosa. Histologically, the picture is often that of high-grade dysplasia, but this is a reactive change to the presence of candidial hyphae in the tissues. When systemic antifungals are given, the dysplastic appearance settles and it is essential that where dysplasia is reported in CHC, the patient is given a systemic antifungal and the tissue re-biopsied to ensure that the tissue changes resolve. The fungal invasion and the clinical picture will usually return in time and may need repeated systemic antifungal courses.



Figure 42.17 Angular stomatitis.

Angular stomatitis is a fairly common acute or chronic inflammation of the skin and contiguous labial mucous membrane at the angles of the mouth, bilaterally (**Figure 42.17**). Most cases are in adults and due to mechanical and/or infective causes but, in children, nutritional or immune defects are more prominent causes.

Mechanical factors include dentures with an incorrect facial height, no denture worn in edentulous patients or as a normal consequence of the ageing process in some patients. This can result in overfolding of the mouth corners and leakage of saliva. This is a strong irritant to the skin at the corners of the mouth. Nutritional deficiencies, in particular iron, folate and vitamin B_{12} make this change more likely. It is also seen to be associated with orofacial granulomatosis, diabetes and HIV infection. *Candida spp.* or staphylococci are isolated from most patients and topical miconazole treats both of these organisms. There is a benefit from using a preparation with miconazole and hydrocortisone as it allows for quicker reduction in the inflammation of the skin and the re-establishment of a proper infective barrier. This reduces recurrence of the condition.

Orofacial pain

Most oral pain is from common dental and periodontal inflammatory causes such as pulpitis, periapical periodontitis and pericoronitis. Neurological, vascular and referred causes are less common. Non-dental and idiopathic facial pain are common in specialist settings and present to dentists, general practitioners, neurologists and oral surgeons as well as oral medicine and ENT specialists. Often a patient has multiple referrals to a variety of specialist services from different practitioners and these other specialty contacts must be identified in the history so that collaborative working can take place.

Chronic oral mucosal soreness can arise from persisting ulceration or mucosal atrophy secondary to lichen planus, major aphthous ulceration, geographical tongue and haematinic deficiency states. Other distinct groups of orofacial pain conditions cluster around trigeminal autonomic cephalgias, oral dysaesthesias and temporomandibular disorder.

Glossitis is not a true condition but the term is frequently used. Tongue pain may be related to deficiency of iron, folate or vitamin B_{12}, and may present in association with other deficiency-related oral issues such as angular stomatitis and/or aphthous ulcers. A full blood count and assays of iron (ferritin), folate and vitamin B_{12} are indicated. The clinical appearance of the tongue may show generalized or localized depapillation predominantly of the filiform papillae. The tongue may appear fissured and erythematous but this is a normal variation and not the source of any discomfort reported by the patient. Lichenoid atrophy of the tongue dorsum and candidial invasion of the tongue surface can also give tongue sensitivity and pain and a biopsy is indicated if there is doubt about the cause of the patient's symptoms.

TRIGEMINAL AUTONOMIC CEPHALGIA

The extremes of this group of facial pain and headache conditions are recognized as trigeminal neuralgia and cluster headache. However, it is now clear that this is a spectrum of disorders with any one individual having features closer to either condition or a blend of both. Importantly, patients can move along the spectrum with time changing the presenting symptoms and the treatment needed to remain pain free.

Trigeminal neuralgia (TN) is a condition of unknown origin which causes a characteristic pain on stimulation of a particular sensory nerve area. This is usually on the surface of the face or in the mouth but can be deeper in the tissues and even the teeth and is usually worse over the winter months. If the same condition affects the mucosa of the posterior tongue or pharynx it is labelled glossopharyngeal neuralgia and this has implications for the management options. TN is mostly seen in patients over 50 years of age but there are an increasing number of younger patients presenting. In the classical form TN presents with a trigger area which, when touched, causes a severe but short-lasting pain radiating from the trigger area through the trigeminal distribution. In most cases, this is the maxillary or mandibular divisions of the trigeminal nerve. Usually a single unilateral area is affected. In some cases, the pain may be followed by a burning sensation in the trigger area. Hypoaesthesia in the trigger area should raise suspicion of an intracranial mass lesion such as an acoustic neuroma or a degenerative brain disease, both of which can present with TN. Rarely TN can follow maxillofacial trauma with the trigger in the area of the injury, such as a previous zygomatic or mandibular fracture.

MRI is an essential first investigation when TN is suspected and medical therapy should be instituted quickly. The medication of choice is determined by the patient's other medication, medical and home circumstance and the treating physician's experience with TN patients. Carbamazepine is often the first-line medication but it causes significant sedation, balance disorders, nystagmus and drug interactions. Oxcarbazepine and lamotrigine are effective alternatives with fewer side effects in most patients. Lamotrigine must be introduced over several weeks and is often used once initial symptom control is achieved with carbamazepine.

Surgical treatment for TN is indicated in the young or where the dose of medication is significantly impacting on the patient's quality of life. A microvascular decompression is the treatment of choice where the MRI indicates that a vascular loop is compressing the trigeminal root. This procedure will usually result in a pain-free patient, off medication for several months although lower doses of the anti-neuralgic medicines are needed eventually. Destructive procedures to the trigeminal ganglion are quicker and simpler operations for the less fit patient and stereotactic radiosurgery (gamma knife) requires no operation at all.

Cluster headache (CH) is a condition of unknown origin which has unilateral pain and autonomic efferent features including ptosis, facial erythema/swelling, lacrimation and nasal discharge on the affected side. It has both episodic and chronic forms. The former will give several weeks of daily intense headache and facial pain before terminating abruptly whereas the latter gives daily pain with no respite. In CH the pain lasts several hours, is unbearable for the patient and stops spontaneously after 3–5 hours. It often happens at night or in the evening and there is an association with coffee use. Management is for specialist practice. Inhaled oxygen with the onset of pain can be very effective but triptans have a place in some cases. Chronic CH has been reduced in severity and frequency using verapamil at moderate to high doses; lithium has also been used as a preventative therapy.

ATYPICAL ODONTALGIA

Patients with this condition often have a strange pattern of dental extractions on looking in the mouth. Most often there is a single mouth quadrant where many teeth have been removed in an otherwise healthy mouth. This condition is characterized by intense toothache focused on a single tooth. This usually has no evident disease but the patient is in such intense pain the tooth is eventually root treated and finally extracted. The pain settles but in a few weeks or months returns in the same quadrant of the mouth in an adjacent tooth. The pattern repeats. If, eventually, all of the teeth are removed the pain settles in the edentulous bone with the same characteristic toothache. This appears to be a neuropathic pain problem but even with current medication if can be challenging to treat.

PERSISTENT IDIOPATHIC FACIAL PAIN

This is a diagnosis of exclusion and consequently can reflect the clinician's diagnostic ability as much as the pain problem itself. It is best made by a specialist in oro-facial pain who can exclude some of the rarer but treatable head and neck pain problems. The older term of atypical facial pain should not be used.

ORAL DYSAESTHESIA

Oral dysaesthesias are a group of conditions in which the patient seems to have altered perception of the oral environment such that the mouth feels dry, burning, numb or with a bad taste/smell in the absence of any disease. They are often referred to as burning mouth syndrome although the most common presenting variation is that of a feeling of oral dryness or stickiness in the presence of plentiful oral saliva. These conditions represent a misperception of the normal oral environment rather than a disease of the oral mucosa or supporting tissues. Patients will often have more than one dysaesthesia symptom, such as a burning feeling and a persistent dryness. This condition is often worse as the day progresses, relieved by eating or oral activity and enhanced by stressful life events. Treatment starts by explaining to the patient that there is no disease or oral condition even though this seems to be the case and that the problem is with the 'feeling nerves' in the mouth. It is unclear whether there is a true local neuropathic problem in a dysaesthesia or whether it is an issue with the understanding and interpretation of the neural signals in the brain, as there is some experimental and treatment evidence for both. Very occasionally, similar symptoms can arise from mucosal atrophy as a result of haematinic deficiency and haematinics should be checked if a burning sensation is reported. Where sensory changes are reported, an MRI is a sensible precaution even if there are no cranial nerve deficiencies on testing. Occasionally, dysaesthesia symptoms can result from neuro-degenerative disease. Tricyclic antidepressants are the most effective treatment with nortriptyline having a better side effect profile than amitriptyline. Gabapentin and clonazepam have been used as alternatives. For mild cases, simple oral distractors such as chewing gum are useful. As these conditions are commonly associated with an underlying anxiety disorder, psychological intervention or hypnosis can be useful alternatives.

TEMPOROMANDIBULAR DISORDER

Temporomandibular disorders (TMD) encompass a range of pain and mechanical problems around the TMJ. Patients reporting locking of the joint or indicating pain only in the area of the joint itself have an internal joint derangement and require imaging and surgical assessment.

TMD represents the largest group of non-dental pains presenting in the head and neck. The actual presenting complaint varies from patient to patient but any diffuse head and neck pain which is chronic in nature must have TMD excluded. The core finding in TMD patients is a tendency to anxiety and as such they are a similar demographic to many other medical conditions including burning mouth syndrome, irritable bowel syndrome and fibromyalgia. Indeed, some view TMD as an extension of fibromyalgia to the head and neck with similar symptoms and management strategies.

Pain in TMD patients can be widespread and diffuse, affecting both sides of the face, head and neck or very focused on a single site, such as chronic midface pain, simulating dental pain in the molar teeth. It is characterized by an aching sensation which lasts for many hours or days at a time. In many cases, the pain centres around the masticatory muscles and the patient experiences limited mouth opening with pain when trying to chew. This can be accompanied by clicking of the TMJs and displacement

of the dental occlusion, all of which are compatible with the TMD pain syndrome diagnosis. Focal tenderness of the masticatory muscles is analogous to trigger points found in neck muscle pain or elsewhere in fibromyalgia. The clenching of teeth at night is a common finding in these patients but the muscle pain does not seem to be a direct consequence of this, as many patients clench their teeth and develop no chronic pain.

When the masticatory muscles are the focus for the patient's symptoms a plastic bite splint can be provided by the patient's dentist. If this is combined with a soft diet and supported yawning many patients will get good symptomatic relief. However, if the pain is more diffuse and chronic the use of a tricyclic antidepressant such as nortriptyline at night can aid recovery.

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CHAPTER 43

SALIVARY GLAND ANATOMY

Stuart Winter and Brian Fish

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search (as well as the websites Cancerlit and CancerNet) using the keywords: neck mass, head and neck neoplasm, imaging and fine-needle aspiration cytology, and focusing on diagnosis, surgery and management. The evidence in this chapter is mainly levels 3/4 with some level 2 evidence. The clinical recommendations are predominantly B and C.

INTRODUCTION

Embryogenesis and ultrastructure

The salivary glands share a common embryological development, whether they are the major named glands or the minor mucosal salivary glands.

The major salivary glands develop from the 6th to 8th weeks of gestation as outpouchings of oral ectoderm into the surrounding mesenchyme. The parotid develops first, growing in a posterior direction as the facial nerve advances anteriorly so that eventually, the parotid gland surrounds the facial nerve.

After the parotid glands are formed, the submandibular glands develop at 6 weeks and the sublingual glands at 8 weeks. The minor salivary glands arise from oral ectoderm and nasopharyngeal endoderm.

While the parotid is the first to develop, it is the last to become encapsulated, after the lymphatics develop. This results in entrapment of the lymphatics deep to the capsule in the parenchyma of the gland. Salivary epithelial cells can be included within these lymph nodes and this may be important in the development of Warthin's tumours and lymphoepithelial cysts within the parotid gland. The submandibular glands in general become encapsulated before lymphogenesis and usually do not have intraparenchymal lymph nodes.

The major glands lie distant to the oral mucosa, and are connected to the mucosa by excretory ducts. The minor glands lie within the mucosa or submucosa of the oral cavity and oropharynx and either open directly onto the surface of the mucosa or are connected to it via short excretory ducts.[1, 2]

Microscopic anatomy

Salivary glands are made up of secretory acini and ducts. The acini can either be serous, mucous, or a mixture of serous and mucous. The secretory cells are categorized into three types. Cells containing small granules are serous and secrete salivary proteins and enzymes. Mucin-producing cells are cylindrical in shape and contain larger granules producing mucoproteins. Seromucinous cells have an intermediate ultrastructure.

The acinar ducts coalesce into intercalated ducts and subsequent striated ducts composed of columnar cells, before uniting into the main excretory duct of the gland.

The intercalated ducts are lined by simple low cuboidal epithelium, and surrounded by myoepithelial cells. The striated ducts have a folded basal membrane, enabling the active transport of substances out of the duct, such as water resorption and active secretion into the ducts. The excretory ducts are lined with a tall columnar epithelium.

Within the major salivary glands the acini are arranged into lobules and lobes within the glands. Each lobule has a single excretory duct. The lobules are linked by dense fibrous tissue containing excretory ducts, vessels, lymphatics, nerve fibres and ganglia to form lobes (**Figure 43.1**).

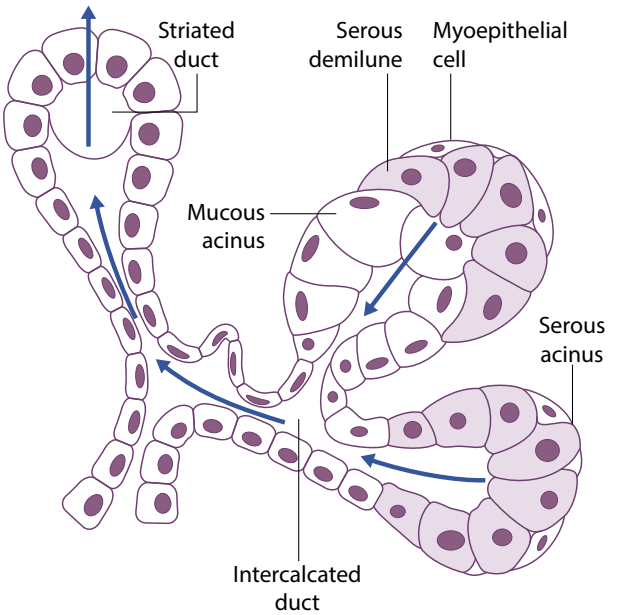


Figure 43.1 Part of a salivary gland showing a serous acinus and mixed serous-mucous acinus.

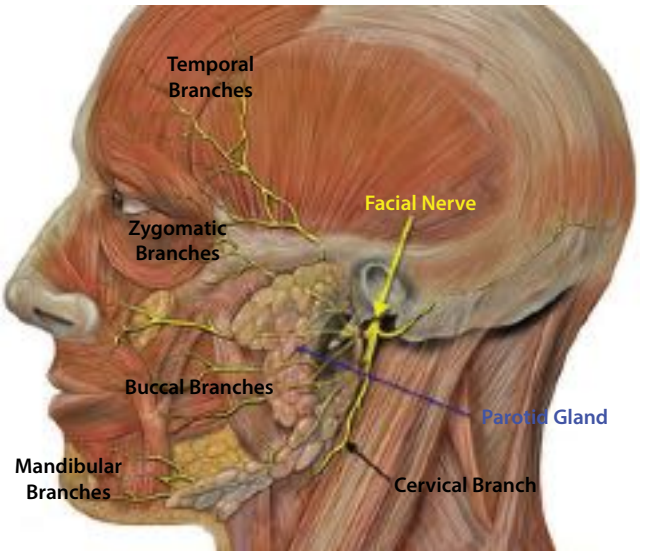


Figure 43.2 Anatomy of the parotid gland.

It is likely that the morphological description is an oversimplification and the products of these cells form an almost continuous series, from serous secretions with negligible amounts of protein-associated acidic carbohydrates, to mucous secretions rich in them.

THE PAROTID GLANDS

Clinical anatomy

The parotid glands are the largest of the salivary glands and are mainly serous, containing only a few mucous acini. Each gland weighs on average 25 g and is irregularly lobulated. It is wedge-shaped on coronal section and laterally extends from the zygomatic arch superiorly to the upper part of the neck inferiorly, where it overlies the posterior belly of digastric and the anterior border of the sternocleidomastoid muscle (**Figure 43.2**). Anteriorly it overlies the masseter muscle and posteriorly it extends below the external auditory canal and onto the mastoid process overlying the lateral process of C1. Medially it fills the gap between the mandible anteriorly the mastoid and the styloid process. It extends close to the lateral wall of the oropharynx and hence the need to examine the oropharynx when assessing the parotid gland (**Figure 43.3**).

The accessory parotid gland is a separate part of the gland usually lying on the masseter muscle between the parotid duct below and the zygomatic arch above.

The superficial (lateral) surface of the gland is concave and covered by the parotid fascia, skin and the posterior border of platysma. Some branches of the great auricular nerve lie superficial to the gland tissue and superficial lymph nodes lie on or deep to the fascia as well as within the gland. The great auricular nerve arises from the cervical plexus and provides sensation to the lower two-thirds of the pinna as well as to the parotid fascia and it is often possible to preserve at least its posterior branch during parotid surgery.

The anteromedial surface lies on the ascending ramus of the mandible and the medial pterygoid muscle as it inserts into the ramus. The gland is wrapped around the temporomandibular joint and joins the superficial surface over the masseter muscle to form the convex anterior border of the gland. The facial nerve and parotid duct emerge from this surface and run forwards deep to the anterior border. As the gland develops from the buccal cavity it grows backwards towards the ear. It envelops the external carotid artery, which divides into the maxillary and superficial temporal artery within the gland. The maxillary artery leaves the anteromedial surface and the superficial temporal artery continues superiorly to exit the gland from its superior surface. The auriculotemporal branch of the mandibular nerve runs deep to the superficial temporal vessels, passes within the capsule adjacent to the neck of the mandible and behind the temporomandibular joint.

The posteromedial surface lies on the mastoid process, the posterior belly of the digastric and the sternocleidomastoid muscles. Medially it overlies the styloid process with its attached muscles (styloglossus, stylohyoid and stylopharyngeus), which separate the gland from the internal carotid artery and internal jugular vein within the carotid sheath. This surface is indented by the external carotid artery prior to its entering the gland. The facial nerve trunk enters the gland high on the posteromedial surface between the mastoid and styloid processes.

Superficial to the maxillary and superficial temporal arteries lie the corresponding veins, which unite to form the retromandibular vein within the gland. The retromandibular vein emerges from the lower pole of the gland and divides into two branches. The anterior branch joins the facial vein before entering the internal jugular vein. The posterior branch joins the posterior auricular vein to form the external jugular vein. The division may occur within the gland and two branches emerge from the lower pole.

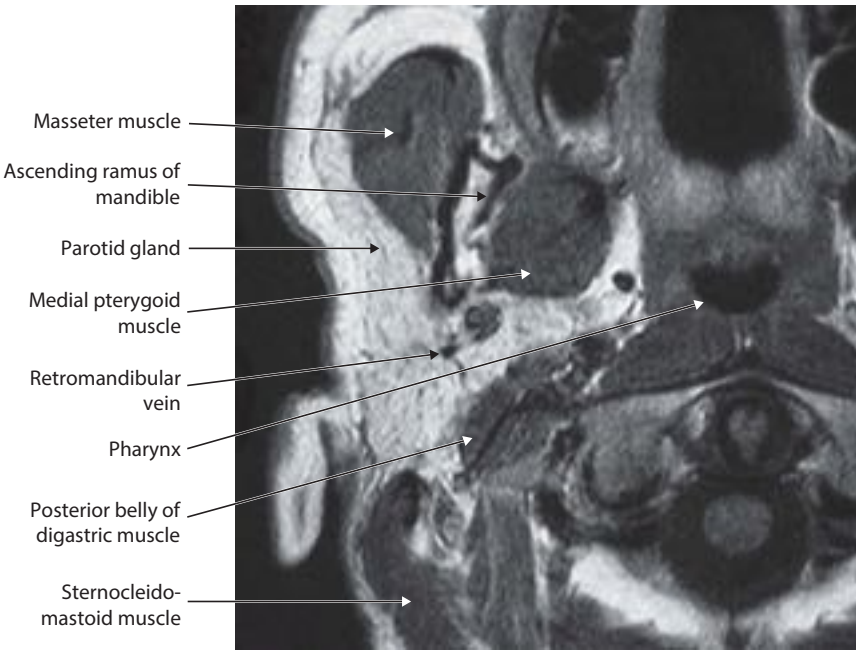


Figure 43.3 Axial MR scan showing the relationships of the wedge-shaped parotid gland, and its division into superficial and deep lobes by the retromandibular vein.

Once the facial nerve enters the gland it divides into two main temporal and cervical divisions. These pass forwards anteriorly dividing further before emerging from the anteromedial surface of the gland. The nerve divides the gland into superficial and deep lobes comprising approximately 80% and 20% of the gland respectively. The nerve lies superficial to the retromandibular vein, which is in turn superficial to the external carotid artery. The vein can be a useful radiological landmark for the nerve.

The capsule

The deep cervical fascia splits to surround the gland and is known as the parotid fascia. It is continuous anteriorly with the fascia covering the masseter as the parotidomasseteric and extends up to the zygomatic arch. Overlying the gland is the superficial musculoapneurotic system (SMAS). This is adherent to the parotidomasseteric fascia in the pretragal area and becomes separate from it as the fascia enters the cheek.[3] The deep part extends to the base of the skull and is thickened between the styloid process and the and the angle of the mandible forming the stylomandibular ligament.

The fascia is largely tough and inelastic but thins anteriorly. Inflammatory oedema pus and rapidly growing tumours contained within the capsule will cause it to stretch and become painful, often in advance of overt enlargement. The relatively thin fascia over the apex of the gland can lead to the spread of sepsis into the parapharyngeal space.

Most parotid tumours arise from the superficial lobe and expand towards the superficial surface but some deep lobe tumours are limited by the stylomandibular ligament and expand into the parapharyngeal space. Tumours arising from adjacent to the stylomandibular ligament may expand both ways to form a dumbbell-shaped mass.

The parotid duct

The parotid duct (of Stensen) is lined by low cuboidal epithelium surrounded by a smooth muscle and fibrous tissue wall. It originates within the gland, enveloped by the deep lobe of the parotid; only small ductules connect the superficial lobe with the duct.[4] It measures approximately 5 cm in length with an internal calibre of about 0.6 mm. It emerges from the anterior border of the parotid gland and travels across the masseter muscle. Having received the duct from the accessory gland it turns medially at the anterior border of the masseter. It pierces buccinator and runs obliquely between buccinator and the oral mucosa before entering the oral cavity at the parotid papilla opposite the second upper molar tooth. The facial nerve and its branches are always observed lateral to the parotid duct.

The surface marking is the middle of a line between the intertragal notch of the auricle and the midpoint of the philtrum, although a recent study suggests it may be lower than this.[5]

The facial nerve

The facial nerve emerges from the stylomastoid foramen just deep to the junction of the cartilaginous and bony parts of the external auditory meatus, usually as a single trunk but rarely as a double trunk. This has been estimated at 3–26.7%. Similar anomalies have been documented in the intratemporal course of the nerve, often associated with other congenital abnormalities. The existence should therefore be especially considered in patients with congenital abnormalities of the pinna or with congenital hearing loss. The main trunk lies approximately 1 cm above the posterior belly of the digastric muscle and it passes downwards and forwards over the styloid process and attached muscles before entering the substance of the gland. This part of the nerve gives off the posterior auricular branch,

which passes upwards to supply the occipital belly of occipitofrontalis, and a muscular branch, which divides to supply the posterior belly of the digastric and the stylohyoid muscles.

On entering the substance of the gland the main trunk divides into upper zygomaticotemporal and lower cervicofacial divisions. Further subdivisions then occur to form five branches – temporal, zygomatic, buccal, mandibular and cervical – supplying the muscles of facial expression. The resulting pattern is known as the pes anserinus. The branching pattern is variable and a number of classifications have been described. McCormack et al. and Davis et al. both described six patterns.[6, 7] Katz and Catalano[8] described five patterns (**Figure 43.4**) and Kwak et al. four, based on the origin of the buccal branch.[9] The cross-innervation between branches and divisions of the facial

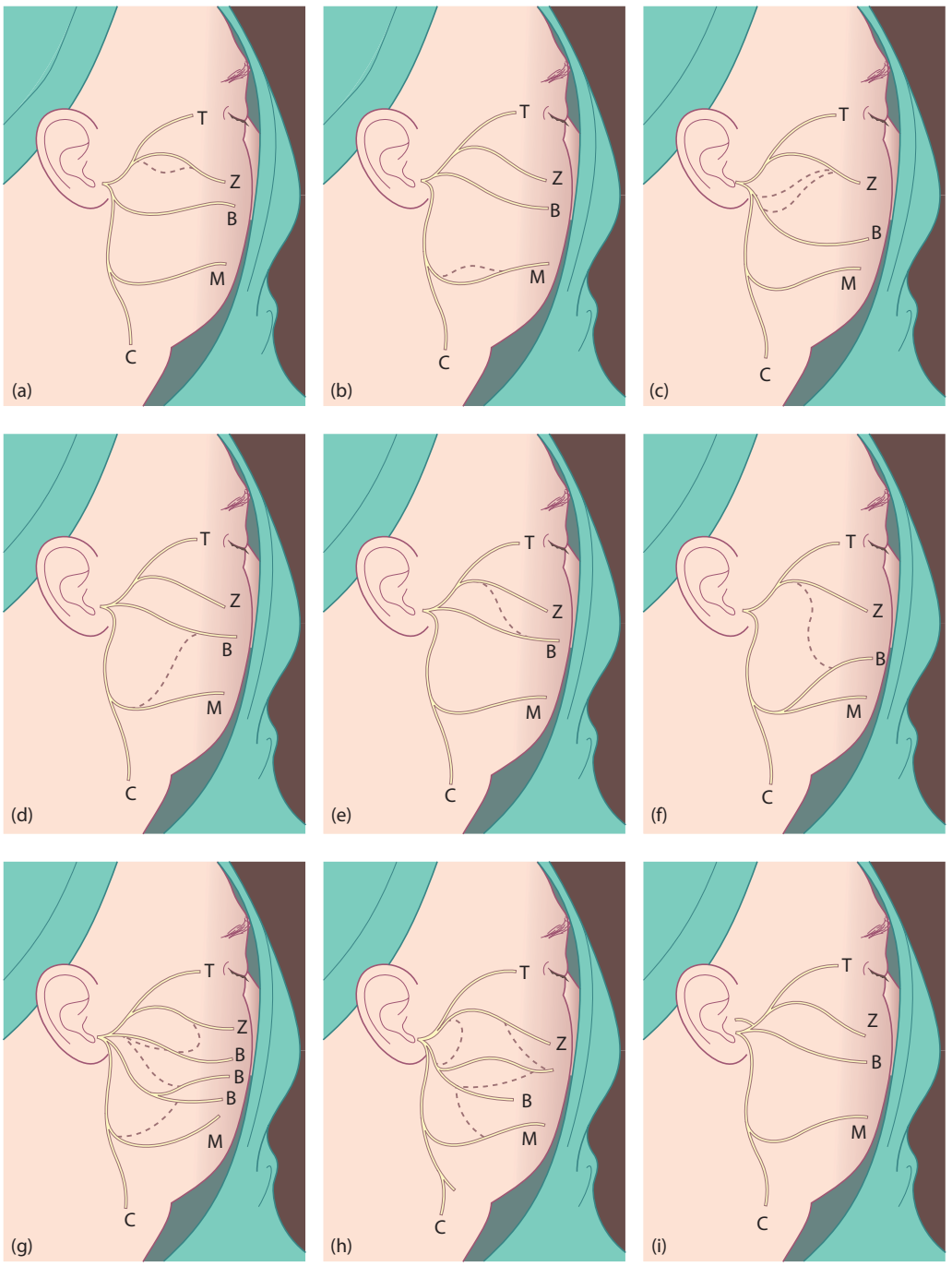


Figure 43.4 Intraparotid branching patterns of the facial nerve. **(a)** and **(b)** Type 1: in this type there is splitting and subsequent reunion of the zygomatic or mandibular branches. **(c)** Type 2: in this type subdivisions of the buccal branch fuse with the zygomatic branch peripherally. **(d)**, **(e)** and **(f)** Type 3: in this type there are major communications between the buccal branch and others. **(g)** and **(h)** Type 4: there are complex branching and anastomotic patterns between the major divisions in this type. **(i)** Type 5: in this type the facial nerve leave the skull as more than one trunk. B, Buccal branch; C: cervical branch; M, mandibular branch; T, temporal branch; Z, zygomatic branch.

nerve is most pronounced between zygomatic and buccal branches and least for the marginal mandibular branch. This explains why significant defects in midfacial movement are rarely seen following injury to the buccal or zygomatic branches and are relatively common following a marginal mandibular injury. An understanding of the variability is essential for those undertaking parotid surgery (see **Figure 43.2**).

Nerve supply

Preganglionic secretomotor fibres are carried from the inferior salivatory nucleus in the medulla along the glossopharyngeal nerve, its tympanic branch, the tympanic plexus and the lesser petrosal nerve to the otic ganglion. Post-ganglionic fibres are carried to the gland via the auriculotemporal nerve.

Sympathetic (vasoconstrictor) fibres are carried to the gland via the plexus on the external carotid and middle meningeal arteries from the superior cervical ganglion.

The gland receives sensory fibres from the auriculotemporal nerve and the fascia receives its sensory innervation from the great auricular nerve (C2).

Vessels

Branches of the external carotid artery supply the gland. Venous drainage is via the retromandibular vein into the external and internal jugular veins.

THE SUBMANDIBULAR GLANDS

The submandibular glands are the second largest of the major salivary glands. They consist of a larger superficial part and a smaller deep part wrapped around the posterior border of mylohyoid. The gland lies in the submandibular triangle formed by the anterior and posterior bellies of the digastric muscle and the inferior margin of the mandible. Each is irregular in shape and weighs 7–16 g.[1]

The lateral surface lies adjacent to the body of the mandible in the mandibular fossa and the origin of the medial pterygoid. The facial artery enters or deeply grooves the gland posteriorly, after emerging from deep to the superior margin of the posterior belly of the digastric. It initially lies deep to the gland before turning anterolaterally to emerge between the gland and the lower border of the mandible.

The superficial part is covered by skin, platysma and a fibrous capsule, derived from the deep cervical fascia. The capsule runs from the greater cornu of the hyoid bone and splits to enclose the gland before blending with the periostium of the mandible along the mylohyoid line medially, and the lower border of the body of the mandible laterally. The fascia is crossed by the facial vein, the cervical branch of the facial nerve and the marginal mandibular branch of the facial nerve.

The medial surface lies on the surface of mylohyoid anteriorly, with the nerve to mylohyoid and submental vessels. Posteriorly the gland overlies hyoglossus, the lingual nerve with its submandibular ganglion, hypoglossal nerve, stylohyoid and posterior belly of the digastric.

The deep part of the gland lies between mylohoid and hyoglossus. It lies between the lingual nerve above and the hypoglossal nerve below.

The submandibular duct

Like the parotid duct, the submandibular duct is approximately 5 cm long. It is formed by the coalescence of numerous ducts within the superficial part of the gland before emerging from the medial surface of this part of the gland, traversing the deep part before running anteriorly along the floor of the mouth between mylohyoid and hyoglossus. It emerges on the summit of the sublingual papilla adjacent to the lingual frenulum after passing between the sublingual gland and genioglossus. Whilst running forwards on hyoglossus, it lies between the hypoglossal and lingual nerves. The lingual nerve crosses the duct laterally at the anterior edge of hyoglossus before branches of the nerve emerge on the medial surface of the duct (**Figure 43.5**).

The size of the duct varies between ducts and along its length. The duct is narrowest at the ostium. In one study the mean duct diameters ranged between 1.5 mm and 0.5 mm.[10, 11]

Vessels and nerves

The arterial blood supply is from the submental branch of the facial artery, a branch of the external carotid.

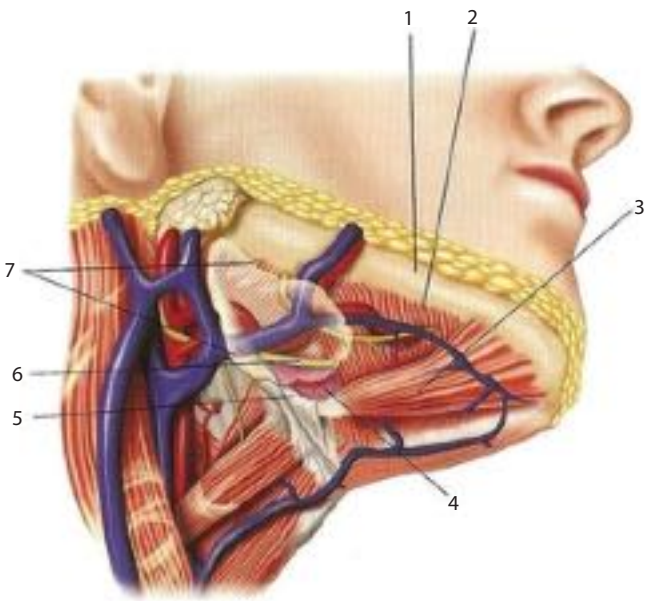


Figure 43.5 Submandibular glands. 1. Mandible. 2. Mylohyoid. 3. Anterior belly of digastric. 4. Submandibular gland. 5. Hyoid. 6. Hypoglossal nerve. 7. Facial artery.

The venous drainage is into the corresponding facial vein. An important anatomical relationship is that the marginal mandibular nerve passes lateral to the vein and, therefore, dissecting deep to the vein, can be used to preserve or identify the nerve.

The submandibular lymph nodes lie adjacent at the medial aspect and anterior end of the superficial part and sometimes within the gland itself. Lymphatics drain into the deep cervical group, particularly the jugulo-omohyoid nodes.

The sympathetic innervation of the gland is from the superior cervical ganglion via the lingual artery. Presynaptic parasympathetic innervation is via the lingual nerve, a branch of the mandibular division of the Vth cranial nerve to the submandibular ganglion. Innervation is initially from the superior salivatory nucleus in the pons passing through the nervus intermedius and carried by the chorda tympani nerve.

Lymphatic drainage goes to the deep cervical and jugular chains of nodes. Perivascular lymph nodes near the facial artery are often involved with cancer originating in the submandibular gland, and these nodes should be removed with submandibular resection.

THE SUBLINGUAL GLANDS

The sublingual glands are the smallest of the paired named salivary glands and unlike the other major salivary glands have no true fascial capsule. Almond-shaped, they lie beneath the mucosa of the floor of the mouth, between the mandible and genioglossus muscle and inferiorly they are bounded by the mylohyoid. The submandibular duct (Wharton's) and the lingual nerve pass between the sublingual gland and genioglossus muscle. Each weighs approximately 4 g.

There is no dominant duct drainage and most of the small excretory ducts (ducts of Rivinus) open directly on the summit of the sublingual fold, but some may open into the submandibular duct itself (Bartholin's duct).[1]

Vessels and nerves

The blood supply is via the sublingual and submental vessels, branches of the lingual and facial vessels. Innervation is similar to the submandibular gland, with sympathetic innervation from the cervical chain ganglia and the parasympathetic supply via the submandibular ganglion.

Lymphatic drainage goes to the submandibular nodes.

KEY POINTS

- The intraparotid portion of the facial nerve has a variable branching pattern.
- The anatomy of the fascial capsules of the salivary glands influences the spread of salivary gland disease.

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CHAPTER 44

PHYSIOLOGY OF THE SALIVARY GLANDS

Mriganke De and T. Singh

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the following keywords: salivary glands; saliva; production; constituents; pathophysiology of saliva.

INTRODUCTION

Salivary glands produce saliva, which plays an important role in the maintenance of oral health. The largest portion of total saliva volume is produced by three paired major salivary glands: the parotid, the submandibular and the sublingual salivary glands. In addition, there are 600–1000 minor salivary glands present in the mucosal lining of the oral cavity and oropharynx that also contribute to total saliva production.[1] Each pair of glands produces saliva of differing consistency. This variation of consistency depends on several factors including blood flow to the gland, which in turn correlates with volume of saliva produced initially. Further modification of saliva properties results from post-secretion modifications that occur within the salivary gland duct unit.

MICROANATOMY OF SALIVARY GLANDS

The secretory unit of a salivary gland consists of the acinus, enveloped by myoepithelial cells, and distally in order away from the acinus, the intercalated duct, the striated duct and the excretory duct (**Figure 44.1**).

The acinus

All acinar cells contain secretory granules, but the secretory product of acinar cells varies between salivary gland types and this is reflected in the different intracellular secretory granules.

In serous glands, the acinar cells are rich in protein (amylase) secreting granules. In contrast, mucous salivary glands are rich in secretory granules, which contain mucin. The relative abundance of secreting granules in the acinar cells dictates the consistency and composition of the secreted saliva.

Three types of acinus have been described:

- Serous (protein-secreting) – spherical cells rich in zymogen granules
- Mucous (mucin-secreting) – tubular shaped cells; mucin granules are washed out on haematoxylin and eosin preparations giving an empty cell appearance
- Mixed – varying proportions of serous and mucous acinar cells.

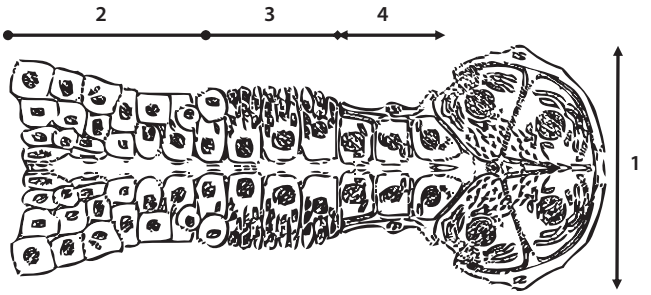


Figure 44.1 Basic salivary duct unit.

Within the acinus, the acinar cells and the cells of the proximal ductal system (intercalated duct) are enveloped by pseudopodia of surrounding myoepithelial cells. They have contractile properties and create the peristalsis action which moves saliva away from the acinus, distally along the salivary duct system.

The lumen of the acinus communicates directly with the lumen of the duct. As seen in **Figure 44.1**, the ductal system, from proximal to distal, comprises the intercalated duct, striated duct and excretory duct.

The intercalated duct

The intercalated duct is lined by low cuboidal epithelial cells rich in carbonic anhydrase. As a consequence, these cells secrete bicarbonate into the lumen and absorb chloride from the lumen. Therefore the intercalated ducts modify saliva composition produced by the acinar cells as it passes to the striated duct. This part of the duct is short and poorly developed in mucinous salivary glands.

The striated duct

The striated duct is lined by simple cuboidal cells that exhibit extensive folding of basal and basolateral plasma membrane. The folds are associated with numerous mitochondria. These cells absorb sodium from the lumen and secrete potassium into the lumen, thereby producing increasingly hypotonic fluid. The faster the salivary flow rate and/or the longer the striated duct, the more alteration of saliva composition will result. Not surprisingly, therefore, striated ducts are short or even non-existent in mucous secreting salivary glands, resulting in minimal or no modification of saliva composition. In contrast, these ducts are well developed in serous glands, resulting in heavily modified salivary composition.[2]

The excretory duct

Excretory ducts are lined by simple cuboidal epithelium proximally and striated cuboidal or pseudostratified columnar epithelium distally. These cells do not perform any modification to the salivary content.

The composition of the duct unit, including the relative abundance of mucin-secreting or protin secreting acinar cells, together with the length of the intercalated and striated ducts, dictate the salivary gland phenotype.

Accordingly the parotid gland is a serous salivary gland with the mucinous to acinar cell ratio 1:1 in the parotid acini. The submandibular glands are mixed but produce predominantly serous saliva. In contrast, the sublingual glands, which are also mixed glands, produce predominantly mucinous saliva.

In addition to the ductal microanatomy, the salivary gland stroma is rich in lymphocytes and plasma cells, which are responsible for the production of IgA, which is secreted into the salivary duct system to be excreted in the saliva.[3]

PHASES OF SALIVARY SECRETION

The production of saliva is an active process occurring in two phases:

1. Primary secretion is produced by the acinar cells and is an active process; the result is a product similar in composition and osmolality to plasma.
2. The primary secretion is then modified as it passes down the ductal system, again by active processes occurring in the cells lining the duct. Broadly, as the primary secretion passes down the duct the primary secretion becomes progressively more hypotonic with decreased sodium and increased potassium concentrations.

In general, saliva comprises 99.5% water, in addition to proteins, glycoproteins and electrolytes. The saliva is high in potassium (7 x that of plasma), low in sodium (1/10 x that of plasma,) calcium, phosphorous, chloride, thiocyanate, and urea resulting in a pH of 5.6–7.[4]

SALIVARY PHYSIOLOGY

The functions of saliva and the associated individual components are detailed in **Table 44.1**.

SALIVARY FLOW

The average volume of saliva secreted from the major salivary gland in a 24-hour period is 1–1.5 litres (**Figure 44.2**). Secretion from the major glands is inducible and most saliva is secreted during mastication. The basal salivary flow rate is 0.001–0.2 ml/minute/gland, while the stimulated salivary flow rate increases to 0.18–1.7 ml/minute/gland. In contrast, the salivary flow from the minor salivary glands is independent of stimulation and constitutes 7–8% of total salivary output. The saliva produced by minor salivary glands is rich in mucin and is primarily responsible for maintaining oral mucosal lubrication.[1]

In an unstimulated state the contribution of measured salivary gland is:

- submandibular gland: 69%
- parotid gland: 26%
- sublingual gland: 5%.

TABLE 44.1 The major functions of saliva

Function		Responsible component
Oral protection	• Lubrication • Antimicrobial • Growth factors • Mucosal integrity • Lavage/cleansing • Buffering • Remineralization	• Mucins, proline-rich glycoproteins, water • Amylase, complement, defensins, lysozyme, lactoferrin, lactoperoxidase, mucins, cystatins, histatins, proline-rich glycoproteins, secretory leukocyte protease inhibitor, statherin, thrombospondin • EFG, TGF-$_x$,TGF-β, FGF, IGF-1 and IGF-2, NGF • Mucins, electrolytes and water • Water • Bicarbonate, phosphate ions, proteins • Calcium, phosphate, statherin, anionic proline-rich proteins
Digestion and speech production	• Alteration of food constituency • Digestion • Taste (Food solute) • Speech (oral cavity lubrication)	• Water, mucins • Amylase, lipase, ribonuclease, proteases, water mucins • Water, gustin • Water, mucins

EGF, epidermal growth factor; FGF, fibroblast growth factor; IGF1 and IGF2, insulin-like growth factor; NGF, nerve growth factor; TGF-α, transforming growth factor-alpha; TGF- β, transforming growth factor-beta.

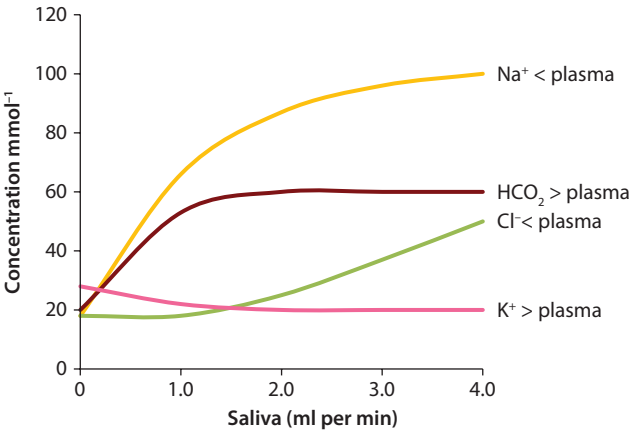


Figure 44.2 Salivary flow rates and changes in ionic composition.

In a stimulated phase the relative contributions of major salivary glands are:

- parotid gland: 69%
- submandibular gland: 26%
- sublingual gland: 5%.

THE AUTONOMIC NERVOUS SYSTEM AND SALIVARY SECRETION

The normal secretion of saliva depends on a centrally coordinated balance of sympathetic and parasympathetic activity. Parasympathetic activity, which is typically tonic, provokes most of the secretion by stimulating exocytosis from the secretory cells and varying the extent of vasodilatation of blood supply of the individual gland as well as stimulating the contraction of myoepithelial cells surrounding the gland acinus and proximal ductal system. In contrast to the tonic stimulation of the parasympathetic system, the sympathetic stimulation tends to be more intermittent and acts in opposition to the parasympathetic input. It is, however, able to modulate the composition of saliva by varying the exocytosis from specific cells lining the duct system.

It follows that the parasympathetic nervous system is the primary instigator of salivary secretion. Interruption of parasympathetic supply to the salivary glands results in glandular atrophy while interruption of sympathetic supply results in no significant change in the gland architecture.

The secretomotor cholinergic parasympathetic fibres for the parotid gland originate in the inferior salivatory nucleus. Fibres travel via the glossopharyngeal nerve initially and then via the lesser superficial petrosal nerve to synapse in the otic ganglion. The post-ganglionic fibres reach the gland through the auriculotemporal nerve. In contrast, the parasympathetic fibres of the submandibular and sublingual glands originate in the superior salivatory nucleus and travel via the hypoglossal nerve originally and then via chorda tympani to the submandibular ganglion; the post-ganglionic fibres release acetylcholine in close proximity to the glands with no true post-ganglionic synapses. In comparison, the adrenergic post-ganglionic sympathetic fibres travel from the superior cervical ganglion in fibres that pass along the external carotid artery and its branches, to reach the glands.[1]

MECHANISMS OF SALIVARY SECRETION

The mechanisms of saliva secretion have been reviewed in detail by Baum.[5] Most of the information presented below comes from the study of rat salivary glands. Little is known of the mechanisms of human salivary secretion, but similarities are assumed to exist in the physiology of salivary secretion across species.

Saliva is produced in response to neurotransmitter stimulation. Both the adrenergic and cholinergic systems have a role in the salivary secretion. Neurotransmitters bind to relevant receptors in the basolateral region of the acini. Noradrenaline, whether from the sympathetic system or circulating following release from the adrenal glands, binds to both α- and β-adrenergic receptors, while parasympathetic derived acetylcholine binds to cholinergic receptors. Secondary message pathways of both types of

receptor depend on guanine nucleotide-binding regulatory protein (G protein) for transduction of the neurotransmitter stimuli. The G proteins that transduce signals following binding of neurotransmitter to the receptors of acinar cells are heterotrimeric molecules consisting of α, β and ɣ subunits. The α subunit is the site of guanine nucleotide binding and probably confers the functional specificity of a given G protein. Binding of a neurotransmitter to a receptor results in conformational change of the intracytoplasmic portion of the receptor, which facilitates association of a G protein. Binding of the G protein provokes replacement of GDP by GTP at the G protein nucleotide binding site and promotes dissociation of the heterotrimer into a free α subunit and a βɣ heterodimer. The resulting GTPase activation of the α subunit catalyzes the hydrolysis of GTP to GDP. The GDP bound to the α subunit then re-complexes with the βɣ complex to restore the original heterotrimeric molecule.

The G protein signal transduction pathways propagate to result ultimately in the generation of cAMP as a result of β adrenergic receptor stimulation and formation of 1,4,5-inositol triphosphate (IP_3) after acetylcholine receptor stimulation. The specific mechanism by which cAMP results in protein exocytosis into saliva remains unclear. However, in rat salivary glands, β-adrenergic receptor stimulation leads to a rise in cAMP levels, and amylase or glycoprotein secretion by the parotid or submandibular glands, respectively.

IP_3 activity is known to result in an influx of extracellular calcium into the acinar cell cytoplasm. The exact mechanism for this effect is unclear, although it has been established that this effect is not voltage activated.

Possible mechanisms for Ca^{++} entry into acinar cells include a direct receptor (IP_3)-gated Ca^{++} channel, a G protein activated Ca^{++} channel or a second messenger activated Ca^{++} channel, but the existence of any of these has yet to be established, although there is some evidence suggesting the synergistic action of IP_3 and its metabolite 1,3,4,5-inositol tetrakisphosphate (IP_4) is important in promoting Ca^{++} influx.

Currently, the most favoured explanation of the mechanism of Ca^{++} entry is termed Capacitative Ca^{++} entry. By this mechanism, dynamic depletion of the intracellular Ca^{++} storage pool provides the concentration gradient that drives sustained Ca^{++} entry. Support for this theory comes from experimental data that show that graded depletion of the Ca^{++} store (using for, for example, the ER uncoupler thapsigargin) have led to similarly graded Ca^{++} entry. Despite this hypothesis, the mechanism of continued depletion of intracellular Ca^{++} is, to date, not established. What is known is that extracellular pH and cytoplasmic Ca^{++} do modulate extra to intracellular Ca^{++} flux.

Acinar cells are water permeable and therefore able to derive fluid from the surrounding blood vessels, the movement of which is, in turn, determined by the vasodilation of the gland microcirculation as well as osmotic and hydrostatic pressure gradients. Whilst acinar cells are permeable the salivary duct system in impermeable to water. That said, active transport processes in the plasma membranes of the cells lining the duct, which result in the removal of sodium and chloride and the addition of potassium and bicarbonate ions as well as proteins, are able to modify the composition of the saliva as it passes along the duct.

MECHANISMS OF ION TRANSPORT IN SALIVARY ACINI

As in all secretory epithelia, fluid transport in salivary gland cells is thought to be driven osmotically by transepithelial concentration gradients. Studies on rat and rabbit salivary glands have suggested three mechanisms that act concurrently resulting in the production of primary salivary fluid secretion.[6]

The first mechanism depends on the combined action of four membrane transport systems (see **Figure 44.3**), namely:

1. a Na^+ -Cl^- co-transporter that is located in the basolateral membrane of the acinar cells
2. a basolateral Ca^{++}-activated K^+ channel (not shown in **Figure 44.3**)
3. an apical conductive pathway for Cl^-, which is presumably a Ca^{++} -activated Cl^- channel
4. a basal Na^+/K^+ ATPase.

In the resting state, K^+ and Cl^- concentration gradients, where the intracellular concentration exceeds the extracellular concentration, are actively created by by a Na^+/K^+ ATPase and a Na^+/K^+ - $2Cl^-$ cotransporter respectively.

Secretory stimulation via the parasympathetic nervous system, as described above, leads to a rise in intracellular Ca^{++} concentration, which, in turn, results in the opening of the basolateral K^+ channel and the apical Cl^- channel.

K^+ and Cl^- then flow along their respective concentration gradients – K^+ into the ECS and Cl^- into the duct lumen – resulting in the accumulation of Cl^- ions into the primary salivary fluid. A consequence of this is a net negative charge of the primary salivary fluid, which promotes the transport of sodium ions from the interstitium into the duct lumen. The resulting osmotic gradient for NaCl, in turn, provokes the transepithelial movement of water from the interstitium to the lumen.

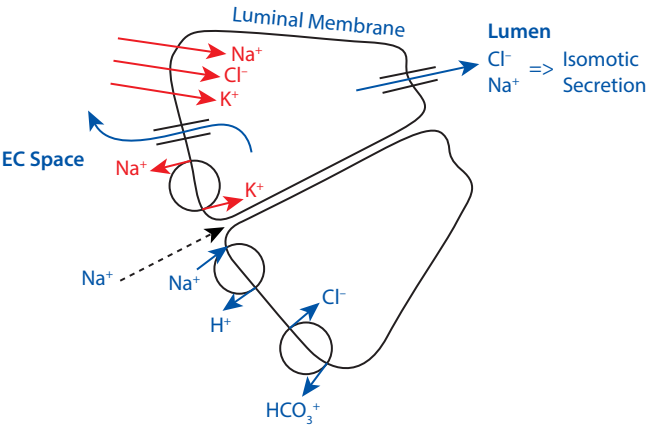


Figure 44.3 The ion exchange that occurs at the salivary acinus via the anion exchange pumps located on the basal and luminal surface of the salivary acinus.

Continued parasympathetic input results in continued transepithelial chloride flux and increased saliva volume. Cessation of parasympathetic stimulus is followed by a fall in intracellular calcium concentration to resting levels, closure of the K^+ and Cl^- channels and the return of the cell to its resting state.

The second mechanism also involves the creation of an intracellular Cl^- concentration gradient. However, in this case this is created by a Cl^-/HCO_3 exchanger acting in tandem with a Na^+/H^+ exchanger. A fall in intracellular chloride concentration as a result of parasympathetically stimulated KCl loss thus leads to entry of more Cl^- in exchange for HCO_3^-. Acidification of the cytoplasm that results from this bicarbonate loss is buffered by the Na^{++}/H^+ exchanger, which uses the extracellular-to-intracellular sodium gradient generated by Na^+/K^+ ATPase, to drive protons out of the cell.

Unlike the first two mechanisms in which chloride is the secreted ion, the third involves active bicarbonate secretion. CO_2 enters the acinar cell across the basolateral membrane and is converted to HCO_3^-, which is lost across the apical membrane via an anion channel, which is possibly the same as the Cl^-/HCO_3 exchanger involved in chloride secretion as described in second mechanism above. Acidification is rectified by the expulsion of a proton by the basolateral Na^+/H^+ exchanger.

FACTORS AFFECTING SALIVARY FLOW

Xerostomia is the term used to describe reduced salivary flow.[7–9] Xerostomia may be subjective or objective. In the former a reduction in saliva is perceived, while in the latter a genuine reduction in saliva flow is detectable. For example, Ship et al. found that, although xerostomia is a common symptom in postmenopausal women, no actual reduction of saliva flow in otherwise normal women is detectable.[7]

In clinical practice, drugs are the most common cause of measurable decreased salivary gland function. **Table 44.2** shows a list of drugs that commonly may affect salivary secretion. Not surprisingly, most of these drugs possess anti-cholingeric or sympathomimetic effects, mechanisms that are known to be essential for normal saliva production. Tricyclic antidepressants and phenothiazine neuroleptics are among the most troublesome as they have particularly strong anticholinergic (antimuscarinic) effects. Ganglion-blocking drugs can also have a similar effect.

Xerostomia may also result from specific disease states that do not involve specific salivary gland pathology. For example, depression and anxiety states and their attendant bystander anticholinergic side effects of the underlying condition may result in measurable xerostomia. Busfield et al. measured the rate of salivary secretion in 42 untreated depressed patients and found it to be decreased in comparison to non-depressed hospital patients and healthy controls. However, there is no relationship between the degree of xerostomia and the severity of depression.[8, 9]

Moreover, xerostomia is an inevitable consequence of dehydration induced by, for example, haemorrhage, diarrhoea, chronic vomiting, polyuria secondary to diabetes and restricted fluid intake or overdose of diuretics.

COLLECTION OF SALIVA

Measuring salivary flow rate facilitates a diagnosis of xerostomia – however, accurate measurement of flow rate is not a trivial matter. Usually, the collection of saliva is performed under three circumstances:

- Unstimulated flow of total saliva
- Stimulated flow of total saliva
- Stimulated or unstimulated flow of an individual gland.

Systemic or local sialagogues may be used to stimulate flow. The archetypal systemic salivary sialagogue is pilocarpine, a parasympathomimetic, although this is rarely used outside research. Local sialagogues are more convenient, with minimal side-effect profiles and are therefore used more commonly in the clinical setting. A commonly used protocol involves the dropwise application of 5% citric acid solution on the dorsum of the tongue. As for collecting saliva, a variety of methods are used. These include spitting, drainage, suction and cotton wool rolls. The particular method used is determined by whether global or individual gland salivary output is the desired endpoint.

For example, saliva produced exclusively by the parotid gland is accurately collected by cannulating the parotid duct with a polythene catheter. Alternatively, a Carlson-Crittenden cup could be used. This device is specifically

TABLE 44.2 Drugs liable to cause xerostomia

Drugs with anticholinergic activity	Drugs with sympathomimetic activity
• Atropine and analogues (hyoscine, ipratropium, etc.) • Tricyclic antidepressives • Monoamine oxidase inhibitors • Phenothiazines and related neuroleptics • Orphenadrine, benzhexol and related anti-Parkinsonian agents • Antihistamines • Ganglion blockers and clonidine • Antiemetics (antihistamines, hyoscine and phenothiazines)	• 'Cold cures' and decongestants containing ephedrine or phenylpropylamine • Bronchodilators (isoprenaline, orciprenaline, etc.) • Appetite suppressants, particularly amphetamines and diethylpropion

designed for the task and involves a collecting chamber that is placed on the buccal mucosa over the ampulla of the duct, which is separated from an outer suction chamber, which ensures that the saliva produced is sucked into the collecting chamber.

Saliva produced by the submandibular and sublingual glands is typically collected using a syringe. Individual gland production is technically impossible due to the close proximity of duct orifices in the anterior floor of mouth or more pertinently by the numerous potential communicating channels between the duct systems of all four glands.

The choice of method used depends on the type of investigation being carried out. In clinical practice, for example in the diagnosis of Sjögren's syndrome, measurement of total salivary flow in the presence and absence of stimulation over a period of 10–15 minutes where saliva is collected by the patient spitting, usually suffices.[10]

SIALOCHEMISTRY

Saliva chemistry may also change in disease and therefore, the chemical composition of normal saliva is an important reference point (**Table 44.3**).

SALIVARY PHYSIOLOGY IN DISEASE

Examples of changes in the concentration of inorganic ions and organic components in saliva in diseased states are shown in **Tables 44.4** and **44.5** respectively. Low flow states, the development of local inflammation and cellular calcified nidi may promote salivary debris (sludge) and calculi formation.

Three diseases that have been studied in terms of sialochemistry in particular detail are Sjögren's syndrome, cystic fibrosis and coeliac disease.

Sjögren's syndrome

The European Community Study Group on Diagnostic Criteria for Sjögren's Syndrome concluded that unstimulated whole saliva flow rate and minor salivary gland biopsy are the two most valuable diagnostic tests. A low resting as well as stimulated flow rate are typical of Sjögren's syndrome. The cut-off values of 0.1 mL/min for resting whole saliva and 0.5 mL/min for stimulated saliva has been considered diagnostic of salivary gland hypofunction and consistent with a diagnosis of Sjögren's syndrome.

Cystic fibrosis

Cystic fibrosis is an autosomal recessive genetic condition that affects 1 in 3000 newborns of Northern European ancestry. Affected individuals are homozygous for mutations of the cystic fibrosis transmembrane conductance regulator (CFTCR) gene. The CFTCR is responsible for regulating chloride ion transport across cell membranes. The net effect of its absence is the formation of exocrine secretions of increased viscosity. That said, the effect on total saliva production is minimal. However, significant

TABLE 44.3 Composition of mixed saliva

	Unstimulated		Stimulated	
Substance	**Mean + s.d.**	**Range**	**Mean + s.d.**	**Range**
Protein (g/L)		1.4–6.4	2.8	1.8–4.2
IgA (mg/L)	194.0			
IgG (mg/L)	14.4			
IgM (mg/L)	2.1			
Amylase (g/L)	0.38 + 0.08			
Lysozyme (mg/L)			108.9 + 29.1	3.7–625
Carbonic anhydrase (K/L)			2100	
Histamine (mg/L)	0.15	0.11–0.18		
Glucose (mmol/L)	0.55 + 0.048		0.056	0.02–0.17
Urea (mmol/L)	3.22 + 2.5	2.33–12.5	2.17	0.1–4.8
Creatinine (mg/L)	0.09	0.04–0.18		
Cholesterol (mg/L)	0.2	0.07–1.3		
Sodium (mmol/L)	6.2 + 0.46		26.4 + 11.8	
Potassium (mmol/L)	21.6 + 1.2		19.7 + 3.9	
Calcium (mmol/L)	1.56 + 0.06		1.48 + 0.04	
Magnesium (mmol/L)	0.21 + 0.01		0.15 + 0.04	
Phosphate (mmol/L)	6.2			
Chloride (mmol/L)	17.4 + 1.4		29.0 + 8.8	
Iodide (umol/L)	0.8	0–3		1–3
Fluoride (umol/L)	1.5 + 0.68	0.5–3	0.56 + 0.25	0.25–1.2

TABLE 44.4 Changes in the concentration of inorganic ions

Condition	Changes in the concentration of inorganic ions
Sialadenitis	Raised Na^+ , K^+, Ca^{++} and P^+ levels
Radiation damage	Raised Na^+, Ca^{++}, Mg^{++} and Cl^- levels
Sjögren's syndrome	Raised Na^+, Cl^- and P^+ in parotid gland saliva
Cystic fibrosis	Raised Na^+, Ca^{++} and P^+ levels. Mandel[10] suggested that the combined Ca^{++} and P^+ concentrations formed a useful diagnostic index
Aldosteronism	Depressed Na^+ but raised K^+ levels. Mandel[10] suggested that the product Na^+/K^+ could form a useful diagnostic index
Hypertension	Depressed Na^+ levels
Alcoholic cirrhosis	Raised K^+ levels
Hyperparathyroidism	Raised Ca^{++} levels
Diabetes mellitus	Raised Ca^{++} levels
Chronic pancreatitis	Depressed HCO_3^- levels
Psychiatric illness	Possibly raised Na^+ levels
Digitalis intoxication	Raised Na^+ and K^+ levels. Mandel[10] suggested that the product, $Na^+ \times K^+$, could form a useful diagnostic index

TABLE 44.5 Conditions affecting the composition of saliva

Condition	Effect on composition of saliva
Sjögren's syndrome	Raised total protein and β_2 microglobulin levels in parotid gland saliva
Cystic fibrosis	Raised total proteins, amylase, lysozyme in submandibular gland saliva and glycoproteins in parotid gland saliva
Cirrhosis	Raised total protein and amylase in parotid gland saliva
Hyperparathyroidism	Raised total protein
Diabetes mellitus	Raised total protein, IgA, IgG and IgM and raised glucose levels
Sarcoidosis	Depressed amylase and lysozyme levels

changes in the salivary chemistry result in a dramatic elevation in the salivary protein and calcium concentrations. The net effect is a predisposition to salivary duct blockage and an increased frequency of salivary calculi, particularly of the minor salivary glands, resulting in a build-up of calculi around the gingival margins.

Coeliac disease

This condition is characterized by malabsorption of gluten in the intestines. One can detect antibodies (IgA–AGA) to gliadin, a major component of gluten, in saliva and serum. Consequently, salivary serology can be used as a screening test for coeliac disease although it lacks the sensitivity of its serological counterpart.[11]

SIALOLITHIASIS

A deleterious increase in the viscosity of saliva (through, for example, dehydration), reduced flow or even stasis, by mucosal obstruction or inflammation of the lining of the salivary unit with retention of cellular or bacterial debris, may precipitate liathiasis (stone formation) and painful salivary obstruction. The biochemical components of salivary stones vary depending on the gland, as do their resulting imaging appearances (for example, due to the relative calcium composition, 90% of parotid stones are radiolucent whilst 90% of submandibular stones are radio-opaque).

THE EFFECT OF CHEMOTHERAPY AND RADIOTHERAPY

Saliva is critically important for dental hygiene and maintenance. Due to the high turnover of the salivary duct unit component cells, these areas are at extreme vulnerability from bystander tissue effects of ionizing radiation and chemotherapeutic agents. Profound xerostomia is therefore the most common short- and long-term adverse event of non-surgical treatment of cancers of the head and neck. The resulting xerostomia has a profound negative impact on swallowing function and quality of life, as well as commonly resulting in severe dental impairment due to the loss of the bactericidal and lubricating properties of saliva.

SALIVA IN CLINICAL PRACTICE

Saliva is a readily available body fluid that can be easily collected with no adverse events, simply by getting a

patient to spit in a sample bottle. Moreover, the constituents of saliva, in particular soluble DNA or protein, have the potential to become either predictive or prognostic biomarkers. As such, a great deal of effort is ongoing in a research setting to establish the effectiveness of several putative biomarkers in clinical practice. Of the numerous examples that have been investigated to date, the presence of human papillomavirus (HPV) DNA and/or antibodies in the context of HPV-related oropharynx cancer and anti-p53 antibodies as a biomarker for oral cavity cancer outcome.[12]

Saliva has also been investigated as a medium for hormone monitoring but some limitations are evident.[13, 14] Ellison et al. have considered certain technical aspects of salivary progesterone assay and its interpretation and reviewed the utility of these assays for clinical purposes.[15] They concluded that this approach has some value because of the ease of obtaining serial samples from the same individual.[16]

SUMMARY

Salivary production and function is a complex biological process. The fine balance of salivary flow rate, volume and salivary biochemistry are all susceptible to modification altered by normal physiology, drugs, therapeutic strategies (radiotherapy and surgery) and disease states.

KEY POINTS

- Saliva, produced by salivary glands, plays an important role in oral cavity and dental health.
- There are three paired major salivary glands that collectively produce the majority of saliva: the parotid, the submandibular and sublingual glands.
- In addition, there are 600–1000 minor salivary glands present in the mucosal lining of the oral cavity and oropharynx, which also contribute to total saliva production.
- Disease and the side effects of treatment for head and neck cancer, particularly radiotherapy, alter salivary gland physiology and saliva volume and constitution.

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CHAPTER
45

IMAGING OF THE SALIVARY GLANDS

Daren Gibson and Steve Colley

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Salivary masses and suspected neoplasms 697
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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: salivary, sialolithiasis and tumours.

INTRODUCTION

The ideal imaging technique would be harmless, widely available, cost efficient, highly diagnostic and reliably repeatable. It should provide excellent multiplanar capabilities and good spatial resolution, while simultaneously identifying all foci of disease involvement that require treatment near and far from the primary presentation site. Unsurprisingly, this single utopian test does not currently exist, although, across a range of modalities in usage, there is a calculated compromise to be struck with individual test strengths balanced against specific weaknesses and side effects (**Table 45.1**). Modern imaging continues to improve and can potentially act as a surrogate marker for pathological tissue diagnoses, select surgical from non-surgical candidates and also help to prognosticate. Through modern electronic radiological systems, today's surgeon is increasingly exposed to these newer diagnostic and interventional practices including guidance systems. In specific instances, image guidance can help to deliver non-surgical efficacious treatments (fluoroscopic salivary intervention, radiofrequency ablation, intra-arterial chemotherapy etc.). Functional imaging methods, such as positron emission tomography/computed tomography (PET-CT) and diffusion-weighted imaging (DWI) for neoplasia, can reflect cell turnover, metabolic consumption, vascular patterning and biological behaviour and this discipline will provide useful adjuncts to conventional anatomical images.

The current salivary gland imaging guidance for UK based clinicians is extracted from the 7th edition of the Royal College of Radiologists (RCR) Guidelines.[1] This document states that 'for salivary gland obstruction, ultrasound (US) or sialography is indicated for intermittent, food related swelling. Occlusal views are useful when US has demonstrated sialectasis but has not shown a calculus. US and/or sialography are also helpful to assess the suitability for minimally invasive management of salivary calculi.' Additionally it goes on to comment that 'for a suspected salivary mass, US is the initial investigation of choice and this can be combined with fine needle aspiration cytology when necessary. US is extremely sensitive and has a high specificity.' When the lesion extends to deeper neck spaces beyond the useful penetration of US, it suggests, 'magnetic resonance imaging (MRI) or computer tomography (CT) should be used, although, increasingly, despite the guideline recommendations, MRI and CT are being used as primary imaging modalities in clinical practice. MRI may be better than CT for malignant lesions in the assessment of local infiltration including perineural spread. Obviously, reliable staging of the thorax, if distant pulmonary metastases were suspected, would require a CT study.' The American equivalent, the similarly structured American College of Rheumatology (ACR) Appropriateness Guidance, currently offers no specific instructions for salivary imaging.

As always, any generic guidance will need to be modified around specific clinical scenarios following a focused

TABLE 45.1 Comparative imaging techniques

	Technique				
	US	**MRI**	**CE-CT**	**Conventional sialography**	**Salivary gland scintigraphy**
Advantages	• Quick examination • Widely available • No patient harm • Possible in poorly cooperative patient • Guides US-guided FNAC/ Trucut[R] • Doppler evaluates vascularity • Elastography for lesion compliance	• Excellent soft tissue contrast • Multiplanar capabilities • No radiation • Less dental artefact • Non-invasive	• Quick • Widely available • Sensitive for calculi • Broad anatomical coverage depicts • 2D and 3D reconstructions in conventional orthogonal planes	• Quick • Widely available • Excellent luminal depiction of glandular duct anatomy	• Quantification of function • Quantification of obstruction • Reproducible • Well tolerated • Easy to perform
Disadvantages	• Highly operator dependent • Non-penetrative at mandible, calculus or air interface • No depiction of deep facial spaces	• Not widely available • Relatively small field of view (cf. CT) • Long examination time (30–45 minutes) • Motion artefact • Contraindications: pacemaker, claustrophobia, non-cooperation of patient	• Radiation dose • Artefact from dental restorations and implants • Iodinated contrast issues around poor renal function and allergies	• Invasive examination (retrograde contrast injection) • Complications: bleeding, traumatic perforation, rupture duct • No information proximal to complete obstruction • Indirect information on parenchymal disease • 4–15% unsuccessful cannulation submandibular duct • Good patient cooperation required • Contraindications: acute sialadenitis, contrast allergy, thyroid disease	• Poor anatomical correlate • Radiation burden (low)

ENT examination. Any subsequent investigation will be primarily symptom-driven.

To this end, the following chapter sequentially considers:

- salivary gland obstruction and sialadenitis
- mouth dryness and glandular hypofunction
- salivary lumps and suspected neoplasms.

SALIVARY GLAND OBSTRUCTION AND SIALADENITIS

Salivary calculi (sialolithiasis), mucus plugs and ductal strictures account for the majority of cases of salivary gland obstruction. The diagnostic route for patients with obstructive symptoms may include plain radiographs (occlusal view or orthopantogram), ultrasound, conventional sialography, CT or MR imaging.

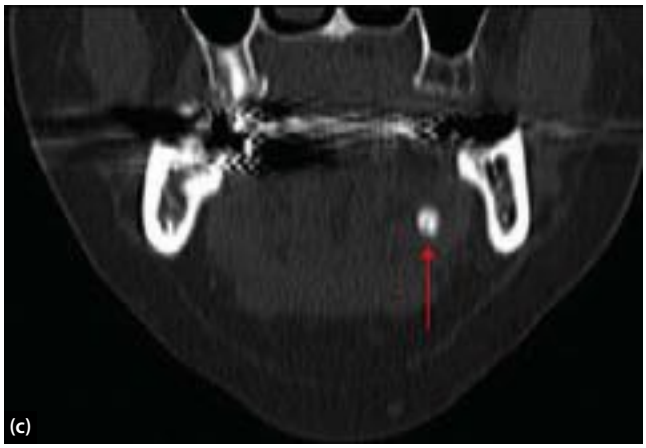
Sialolithiasis

Studies have estimated the lifetime prevalence of symptomatic salivary calculi to be 0.45%.[2] Calculus disease affects the submandibular gland far more commonly than the parotid, with sublingual and minor salivary glands being affected very rarely.

Stones may be diagnosed on plain radiographs, but ultrasound and CT are more frequently used and more sensitive in the detection of smaller calculi (**Figure 45.1**). Up to 15% of calculi are radiolucent and not visible on plain radiographs alone.

Formal sialography is still widely available but is an invasive test that carries a 4–15% failure rate, and a small risk of provoking acute sialadenitis and ostial injuries with scarring for the inexperienced operator. MR sialography is a newer non-interventional, highly T2 weighted (T2W) technique without requiring ductal cannulation or contrast





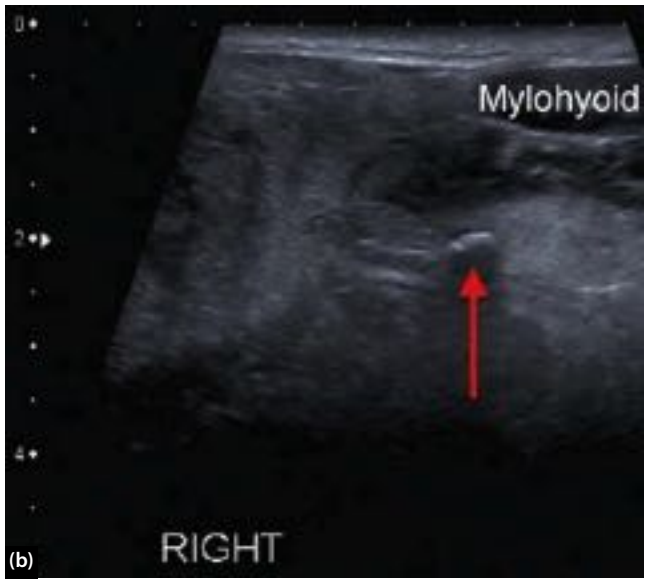


Figure 45.1 Sialolithiasis. **(a)** Orthopantogram demonstrates a right-sided SMG hiloparenchymal calculus projected over the posterior mandible; **(b)** Transverse axial ultrasound image demonstrates an echogenic hiloparenchymal calculus with acoustic shadow; **(c)** A coronally reconstructed, non-enhanced CT image demonstrates a distal left submandibular ductal calculus.



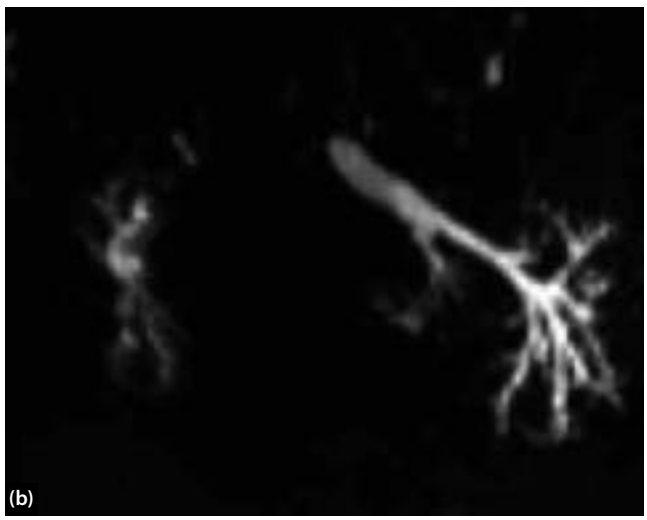


Figure 45.2 MR sialography. **(a)** Highly T2-weighted axial image to illustrate ductal fluid; **(b)** Maximum intensity projection (MIP) to highlight ductal pattern.

media as it relies upon inherent salivary fluid within the ducts to generate recordable signal (**Figure 45.2a** and **2b**). The reported sensitivity for the MR sialography diagnosis of calculous disease varies from 69% to 91%. Its specificity is 88–97%, the positive predictive value is 93–97% and the negative predictive value is 91%.[3–5]

TABLE 45.2 Advantages of CT, sialography and MRI

	Conventional sialography	Computer tomography (CT)	MR sialography
Invasive	Y	N	N
Radiation dose	+	++	N
Detects calculi	+	++	+/–
Detects mucus plugs	+	–	+/–
Detects strictures	+	–	+
Availability	+	++	+
Cost	low	moderate	high
Therapeutic options	Y	N	N

The advantages of CT, sialography and MRI are summarized in **Table 45.2**.[6]

In cooperative patients, digital subtraction techniques used at sialography will effectively remove the overprojected mandible, cervical spine and skull base, thus demonstrating the ductal opacification with iodinated contrast medium (**Figure 45.3**). In specialist centres utilizing stone retrieval devices, balloon sialoplasties and lithotripsy, a diagnostic sialogram remains a relevant and useful test. Dynamic luminal information and emptying patterns are not achievable at MR sialography. With any sialographic technique, the descriptive terminology needs to be locally agreed and standardized.

In mainland Europe, ultrasound (US) is often used as the initial diagnostic choice for obstructive symptoms and, in experienced hands, it can provide as much or more information than CT or MRI.[7] Glandular volumes and textural subtleties are easily appreciated, while the simultaneous use of a sialogogue has the potential to 'pressure test' the ductal system. The main parotid ducts are easily assessed in their entirety. However, due to the obliquity of the distal submandibular duct near the tongue frenulum, it should be remembered that US may fail to identify a small distal calculi, and complementary occlusal views are recommended.

Salivary strictures

Unlike sialolithiasis, salivary strictures preferentially affect the parotid ducts. Nearly two-thirds are a focal 'point' stricture, with the remainder being multiple beaded or long-segment, more diffuse strictures.[8] US, conventional sialography and MR sialography may all depict the site and nature of the stricture; however, due to lack of luminal detail, CT use is limited in this setting.[9]

Ultimately, identification of the type of obstruction, be it stones or strictures, is important in guiding subsequent treatment decisions. Strictures can be dilated, either under fluoroscopic control or at the time of sialoendoscopy.[10] This is generally well tolerated under local anaesthesia in an outpatient setting. With a variety of retrieval basket designs and fluoroscopic control or endoscopy, removal of calculi is a safe and effective method to treat small, mobile calculi up to 6 mm in size. Correct patient selection is vital for success. Determined by both patient factors and local expertise, larger calculi may require combined stone shattering treatments, sialoendoscopy and a transoral open approach.[11]

KEY POINTS

When presented with an obstructed submandibular gland and unilateral symptoms, care should be taken to ensure that this is due to a benign luminal phenomenon rather than extrinsic compression secondary to floor of mouth or sublingual space pathology (**Figure 45.4**).

Sialadenitis

Acute bacterial sialadenitis with sepsis is usually clinically obvious in often susceptible, dehydrated and malnourished elderly individuals. Unless there is trismus or medial tonsillar deviation to suggest deeper parapharyngeal involvement, a parotid abscess is reliably excluded with US. In the subacute setting, the role of radiology is primarily to exclude an obstructive stone, a significant treatable stricture, neighbouring nodal disease or a masquerading salivary neoplasm. More established chronic sialadenitis will eventually destroy the normal ductal architecture with sialectasia and reduce salivary flow. These persistent but low-level symptoms would still merit US evaluation, sialography and/or scintigraphy to determine whether useful gland function can be preserved as the only real surgical alternative would be excision. With these recurrent episodes, the gland becomes progressively atrophied and echo-reflective at US. With swelling and erythema in the submandibular region, odontogenic sepsis is usually excluded with an orthopantomogram (OPG).

Though multifactorial in origin and often unilateral in occurrence, a non-suppurative recurrent juvenile parotitis is a distinct entity. Emerging evidence suggests that early sialoendoscopy and/or therapeutic interventional sialography may avoid glandular destruction, symptom deterioration and the eventual need for gland excision.[12] Punctate sialectasis follows repeated infections and this clouds the initial precipitating aetiological cause. A US examination is contributory to patient workup and often

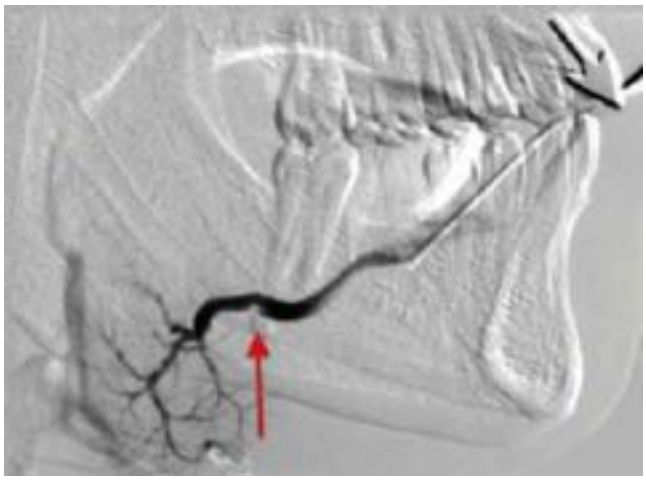


Figure 45.3 Digital subtraction sialography illustrates a right-sided, partially obstructing luminal calculus.

demonstrates a bulky, hyperaemic gland. The ducts may be irrigated with antibiotic and steroid solution at the time of intervention.

Rarer still, TB, actinomycosis, cat-scratch disease, brucellosis and toxoplasmosis can all precipitate acute episodes of sialadenits.

DRY MOUTH AND GLANDULAR HYPOFUNCTION

The clinical presentation of a non-obstructive, non-suppurative multisite glandular swelling or even a unilateral asymmetric, atypical finding may be secondary to a diffuse inflammatory or systemic condition. Although US remains the first imaging modality of choice, it has a limited range of anatomical coverage and the radiologist will need to appreciate that non-mealtime, bilateral salivary

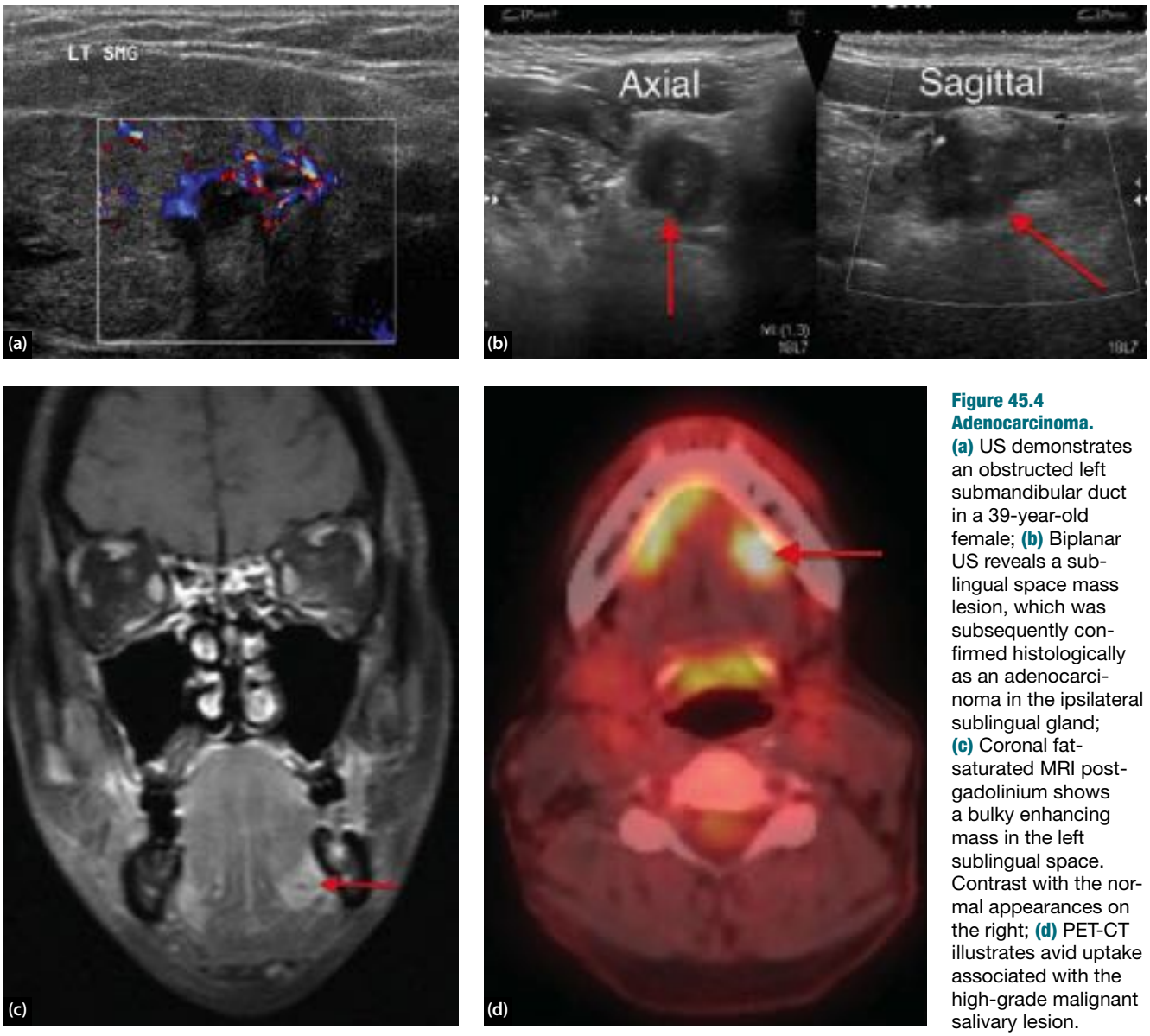


Figure 45.4 Adenocarcinoma. **(a)** US demonstrates an obstructed left submandibular duct in a 39-year-old female; **(b)** Biplanar US reveals a sublingual space mass lesion, which was subsequently confirmed histologically as an adenocarcinoma in the ipsilateral sublingual gland; **(c)** Coronal fat-saturated MRI post-gadolinium shows a bulky enhancing mass in the left sublingual space. Contrast with the normal appearances on the right; **(d)** PET-CT illustrates avid uptake associated with the high-grade malignant salivary lesion.

symptoms with or without constitutional features raises a wider possibility of a more nebulous, potentially multifocal underlying condition.

Sjögren's syndrome

Initially presenting with intermittent swelling of the major salivary glands, primary Sjögren's disease is an autoimmune disorder that will chronically destroy salivary and lacrimal exocrine glands to result in xerostomia and xerophthalmia. With a coexistent systemic arthropathy, such as rheumatoid arthritis, it is termed secondary Sjögren's syndrome. Accelerated dental decay may be seen on an OPG (**Figure 45.5a**). As part of the patient workup, the 2002 American-European Consensus Report revised criteria for the secure diagnosis of Sjögren's disorder includes abnormal sialographic and/or scintigraphy studies with delayed uptake, reduced concentration and/or delayed secretion of tracer material.[13, 14] Scintigraphy involves intravenous injection of approximately 80–100 megabequerels of pertechnetate (^{99}Tc) in an attempt to quantify glandular secretory dysfunction. This tracer is preferentially taken up and secreted via the duct epithelium and counts are acquired over a 30–45-minute period using gamma camera detectors. As a two-phase study, a sialogogue is given midway through the test to define a secretory phase and quantitative time-activity curves are routinely generated. Antibody screening including titration of rheumatoid and anti-nuclear factors as well as anti-Ro (SS-A) and anti-La (SS-B) antibodies may help alongside radiological studies but, ultimately, a labial mucosal biopsy is the most specific diagnostic test.

There are now ample studies documenting the role of US in the non-invasive diagnosis of Sjögren's.

The ultrasonic features described with Sjögren's disease will vary with the stage of presentation with initial hypoechoic, pseudocystic regions and hyperaemia. These 'cysts' may pathologically reflect numerous repeated ductal obstructions due to lymphocytic infiltration and intraparotid nodal hyperplasia.

Chronically, gland volumes are markedly reduced with eventual fatty replacement. Standard fluoroscopic sialography and MRI sialography have been used to evaluate characteristics ductal patterns in affected and the long-established grading system initially proposed by Rubin and Holt[15] is still approximated for both techniques. Larger areas of cavitation, benign lymphoepithelial lesions (BLEL) and parenchymal atrophy will result in globular areas of ductal sialectasia and beading, although, these are not pathognomic features that can also be seen with straightforward chronic sialadenitis. More recently, with MR DW techniques, researchers have attempted to differentiate normal glands from those affected by inflammatory, connective tissue diseases.[16] In longstanding cases, CT will elegantly demonstrate multiple bilateral punctate calcific foci with atrophy (**Figure 45.5b**).

Chronically, with elevated risks of developing marginal zone B-cell lymphomas within parotid or submandibular gland tissue, urgent cross-sectional imaging +/– biopsy is required for an enlarging, painless parotid mass. Currently, no evidence supports interval imaging for surveillance.

With considerations of a wider differential, those having undergone previous head and neck radiotherapy, with occult HIV and adenopathy, with hepatitis C viral infections, occult sarcoidosis or complicating graft-versus-host disease, can all present with similar symptoms and some of these entities will need a high index of clinical suspicion in high-risk individuals.

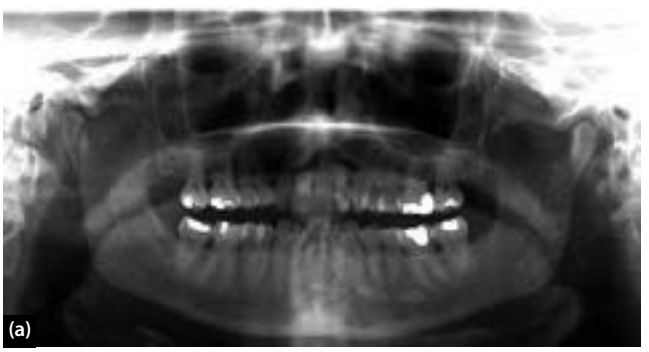




Figure 45.5 Sjögren's syndrome. **(a)** OPG shows multiple small calcific densities projected over both parotid glands; **(b)** Non-enhanced axial CT shows multiple tiny glandular calculi.

Sarcoidosis

With otolaryngological manifestations in around 10% of patients, cervical adenopathy, parotid or submandibular swellings and cranial nerve palsies are the commonest head and neck presentations of this multisystem disorder. Diffuse, intermittent parotid gland enlargement is usually bilateral but, when asymmetric, an ultrasound guided fine-needle aspiration cytology (USg FNAC) can be useful.[17] Notably, conventional sialography is often normal in the presence of florid systemic features whilst biopsy of the affected tissue or nodal excision is usually diagnostic. Eventually, the normal tissue will be replaced by fat infiltration that can have striking appearances on fat sensitive T1W sequences. A brain and skull base MRI with post contrast images is indicated in the presence of cranial neuropathies or meningism. Radiolabelled gallium scans with associated mediastinal and hilar adenopathy can yield a typical 'lambda' or 'panda' sign, which are not entirely specific radiologic findings.

IgG4-related systemic disease

This emerging and obscure condition was first reported in 2003.[18] It has numerous head and neck manifestations that now encompass both Mikulicz syndrome and Kuttner's pseudotumour with initially enlarged lacrimal and submandibular glands. Affected patients can present with a tentative diagnosis of lymphoma or malignancy due to weight loss and adenopathy. A detailed, relevant clinical history may identify prior multi-organ involvement that may include acute pancreatitis and previous renal failure. The eventual, often delayed but highly treatable diagnosis is securely made on the basis of raised serum IgG4 concentrations. CT or MRI imaging demonstrates bilateral cervical adenopathy, glandular swelling and excessive enhancement of salivary and lacrimal tissue in the context of mild SICCA symptoms (**Figure 45.6a, b, e**).

A typical geographic textural abnormality and hypervascularity is seen on US Doppler imaging (**Figure 45.6c, d**). A FNAC or biopsy is often performed to distinguish this highly steroid responsive protean disorder from a parenchymal mass lesion or a lymphoproliferative disorder. More recently, PET-CT has been proposed to stage and monitor aggressive, multi-focal disease.[19]

It is currently a matter of debate as to whether there is an increased propensity for affected individuals to develop complicating lymphomas. Critically, an early diagnosis and immunosuppressant therapy invariably leads to a dramatic clinical improvement and avoidance of life threatening abdominal, renal and vascular complications.

Radiotherapy

Radiotherapy for head and neck cancers can often induce debilitating xerostomia in a dose-predictable fashion. Other than subjective patient reporting of symptoms and salivary flow studies, conventional sialography and/or scintigraphy are the most commonly utilized tests for further documentation of impaired glandular function and stricture formation.

Follow-up CT studies will initially show avid enhancement and global increased density and, over months, this is followed by irreversible dose-dependant reduction in gland volume with ductal ectasia and fibrosis (**Figure 45.7 a–d**). MR sialography may show a correlation between submandibular gland dysfunction and xerostomia.[20] Parotid doses over 60 Gy inevitably lead to irreversible xerostomia, while mean doses below 24 Gy will usually preserve salivary flow. At MRI, Nomayr et al.[21] documented preferentially larger volume losses during treatment in the parotid tissue rather than the submandibular glands. The parenchymal volumes will alter significantly during treatment when compared with baseline imaging.[22]

US studies[23] describe parenchymal heterogeneity, increased duct conspicuity and lowered vascular resistive indices in previously irradiated glands, and these findings are believed to relate to acute inflammatory infiltrates maturing with resultant chronic fibrosis. With the advent of intensity-modulated radiation therapy (IMRT) techniques, reduced dose delivery can be achieved for selected organs at risk. The prospective, randomized PARSPORT trial confirmed that parotid-sparing IMRT plans improved subjective symptoms,[24] salivary flow rates and scintigraphy results. Where IMRT planning is used, it is now the standard of care to use parotid-sparing planning techniques.

SALIVARY MASSES AND SUSPECTED NEOPLASMS

The 2005 World Health Organisation[25] pathological classification for salivary gland tumour subtypes is generally viewed as complex and the evidence-based data around the ideal management of these rare lesions is relatively poor.

Therefore, local, national and international experiential variations in surgical and radiological practice will exist. Workup may involve all or some of the following: US; USgFNAC; core biopsy; CT staging; MRI; frozen section; and/or surgical excision. Obviously, different sampling techniques will provide variable amounts of histopathological tissue with which to secure a reliable pre- or post-operative diagnosis. Excision of the salivary mass as per local protocols ultimately yields the definitive diagnosis. At added expense, functional imaging tests may go on to provide non-invasive methods of tumour characterization with promising initial results.[26]

Ultrasound (US) and ultrasound-guided fine-needle aspiration cytology (USgFNAC)

Ultrasound is the preferred initial test for palpable salivary gland masses. It is tolerated well, cheap, quick

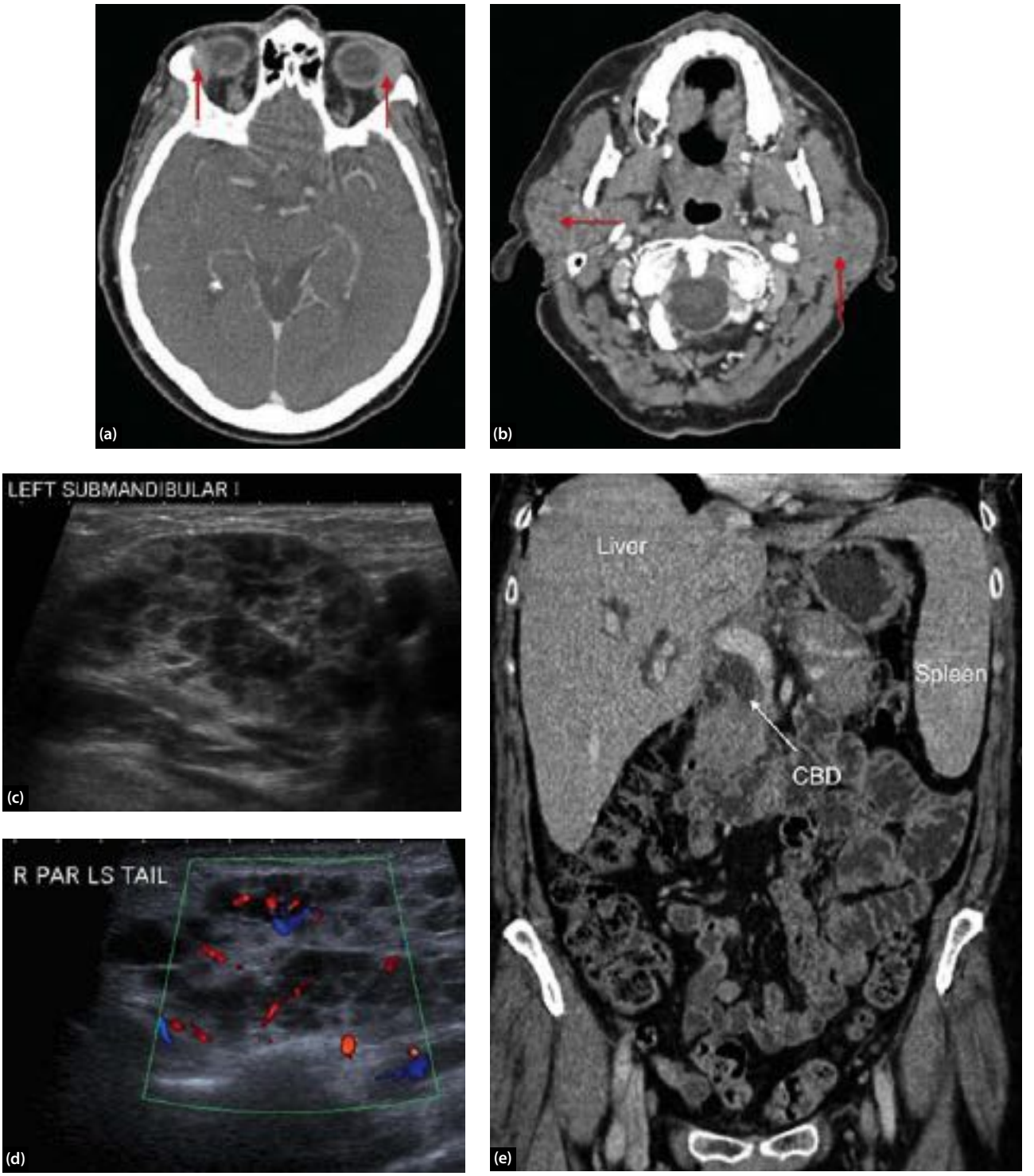
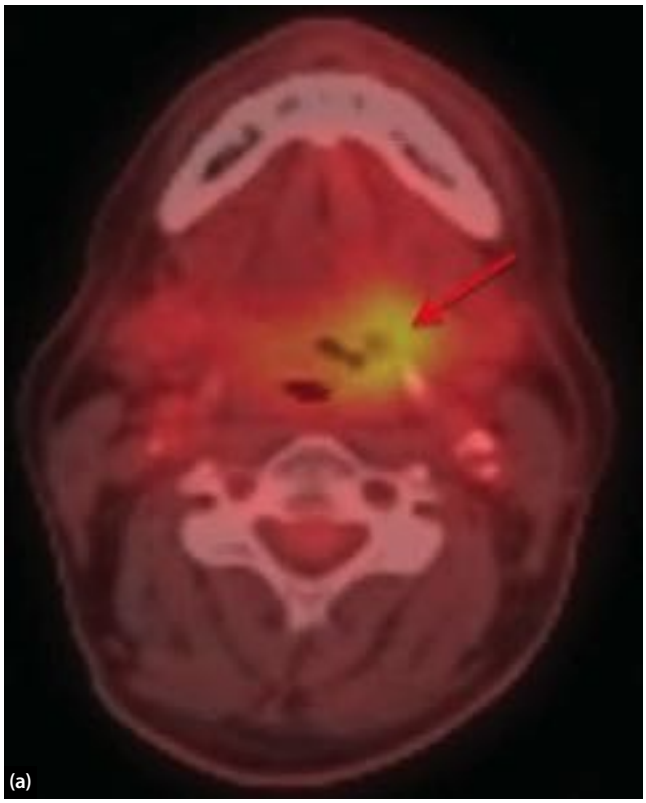


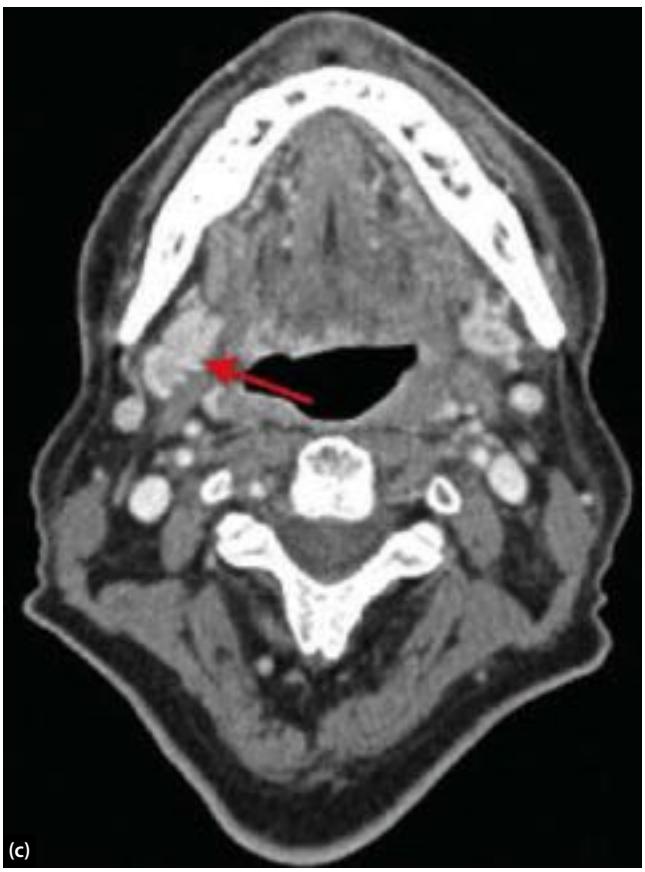
Figure 45.6 IgG4related systemic disease. **(a)** Enlarged, bilateral lacrimal glands; **(b)** Symmetric bilateral parotid gland enlargement; **(c)** Bilateral heterogeneous glands with hypoechoic regions; **(d)** Hyperaemic glandular parenchyma; **(e)** Contrast CT (coronal) shows pancreatitis and hepatosplenomegaly with an obstructed CBD.

and accessible. It allows image guided biopsies and assessment of coexistent pathologies and cervical nodes. It is, however, operator-dependent. Normal variants such as gland ptosis in the elderly and congenital anatomical mylohyoid defects are readily appreciated.

A reliable pre-operative diagnosis facilitates better informed consent, potential conservative management of benign tumours in the frail, and streamlined operative list management. Radical surgical approaches will only be undertaken in the presence of a confirmed malignancy. The drawbacks of freehand FNAC are well-documented[27] and, where feasible, core biopsy should be performed for a definitive histological diagnosis prior to intervention.







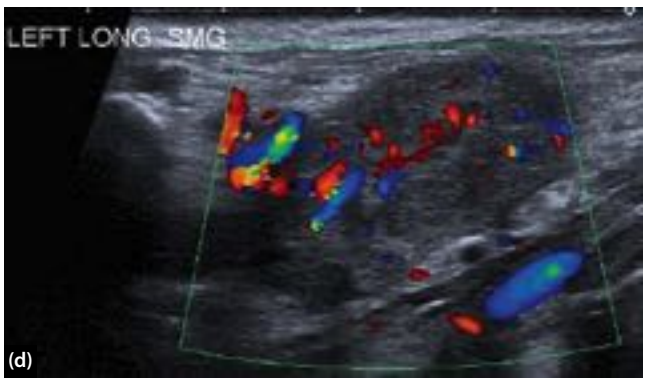


Figure 45.7 Salivary gland changes after radiotherapy. **(a)** PET-CT demonstrates left base of tongue tumour; **(b)** Enhanced CT (sagittal) shows avidly enhancing SMG; **(c)** Enhanced CT (axial) shows avidly enhancing SMG; **(d)** US demonstrates hypoechoic, hypervascular gland.

In 2010, Sriskandan et al.[28] published retrospective data on the accuracy of US alone in discerning benign from malignant lesions for 220 referred parotid lumps. The sensitivity, specificity and diagnostic accuracy for malignancy was 91%, 93% and 93% respectively, with nine false positives and four false negative cases. The majority of pleomorphic adenomas had classic 'benign' appearances; being lobulated, clearly defined, relatively echo-poor and homogenous, however, posterior acoustic enhancement and vascular patterning on Doppler imaging seemed relatively poor discriminators.

Cystic, septated and bilateral disease often correctly suggested benign Warthin's tumours.

As a non-invasive imaging adjunct, sonoelastography uses graduated compressions to assess tissue stiffness. Dumitriu et al.[29] assessed lesional compliance in 74 benign and malignant salivary gland tumours with a histological end point. However, elastography has failed to consistently show significant differences between benign and malignant lesions and is currently unable to eliminate FNA or biopsy from the diagnostic work-up.

USgFNAC without local anaesthetic infiltration is a rapid and safe outpatient procedure with no absolute and a few relative contraindications. Consent will require a discussion of infrequent infective complications, tumour

seeding and haemorrhagic risk. In 1997, the Papanicolaou society[30] published guidelines that estimated that the risk of seeding with small needles (<22 G) was between 0.003% and 0.009%. Standardized cytological categories are: (i) inadequate; (ii) benign; (iii) atypical cells present; (iv) suspicious for malignancy; or (v) overtly malignant.[31] Perhaps unsurprisingly, using pathological correlates, data has consistently shown that the diagnostic accuracy of USgFNAC is most dependent upon the site of aspiration, the number of needle passes, the number of prepared slides submitted and the experience of the individual performing and interpreting the FNAC. It is made more accurate when the individual interpreting the FNAC is the same individual who obtains the aspirate material.[32] It is routinely performed with a 23- or 25-gauge, long bevel needle with a capillary technique as proposed by Zajdela et al.[33] Advantageously, US guidance will avoid hypocellular, necrotic or cystic regions that pose diagnostic challenges. Both air-dried and alcohol-fixed slides are prepared bedside. Flow cytometry and immune-phenotyping techniques or trucut core biopsies will be required if lymphoma is suspected and surgical excision is to be avoided.

Articles concerning USgFNAC yields[34–37] have reported sensitivities ranging from 62% to 98% and specificity ranges from 94% to 100%. For 191 salivary tumours, Howlett et al.[38] conducted a 1-year audit within a rapid-access clinic setting and found a diagnostic sensitivity of 64% and specificity of 100%. Zhang et al. in 2009[39] published data showing that overall accuracy in distinguishing benign from malignant lesions was 79.1% and the sensitivity for salivary neoplasia was 89.4%. In 2011, a retrospective study[40] looked at USgFNAC for 245 parotid and submandibular salivary aspirates without immediate adequacy assessments. A cytological diagnosis was possible in 215 aspirates (87.8%). The sensitivity, specificity and diagnostic accuracy of the test in separating benign from malignant lesions were 75.7%, 100% and 95.8% respectively. In the recent pathology literature, it seems clear that the ideal FNAC is immediately prepared by skilled technicians trained in slide preparation with further on-site 'live' technical expertise available for prompt adequacy assessments; however, this model has significant increased service cost implications. With this model in place, the group quotes an overall accuracy rate for salivary FNAC of between 90% and 95%. The UK National Institute for Health and Care Excellence (NICE) guidelines recommend having a cytopathologist or biomedical scientist to assess the cytology sample adequacy when the procedure is carried out.

In 2007, Howlett et al.[41] considered the additional merits of avoiding surgery for Warthin's tumours in elderly, frail individuals using US-guided core biopsies for 135 superficial parotid lesions. With this same technique, low-grade lymphoma is reliably separated from nodal hyperplasia. The group comments that seeding has only been documented with bigger gauge needles in older studies but, undoubtedly compared with FNAC, there will be an increased risk of haematoma formation and facial nerve injuries.

Benign neoplasms

PLEOMORPHIC ADENOMAS

Given that 90% of parotid pleomorphic adenomas occur within its superficial lobe, these are readily assessed and sampled at USgFNAC (**Figure 45.8a**). Submandibular gland masses and palpable minor salivary gland lesions are also easily sampled. With typical image findings, some authors have proposed that US alone is sufficient prior to surgery.[42] A radiologist's confidence for facilitating a

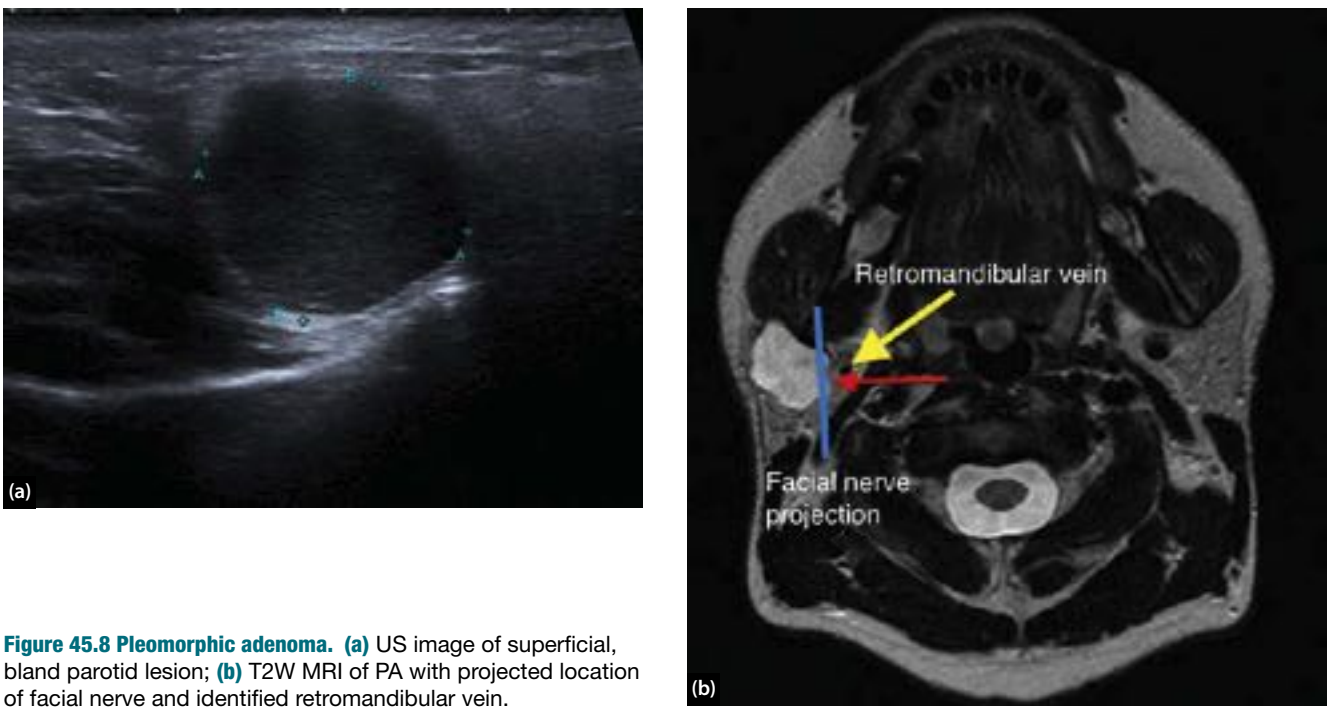


Figure 45.8 Pleomorphic adenoma. (a) US image of superficial, bland parotid lesion; **(b)** T2W MRI of PA with projected location of facial nerve and identified retromandibular vein.

successful superficial parotidectomy or extracapsular dissection is dependent upon the expected position of the facial nerve branches lying lateral to the often-identified retromandibular vein. A commonly used surrogate MR technique to plot the expected facial nerve trajectory from the stylomastoid foramen is described by Ariyoshi et al.[43] using the digastric muscle and the mandibular ramus (**Figure 45.8b**).

Newer T1-like gradient echo sequences (FISP/GRASS and magnetization-prepared rapid acquisition gradient echo sequences) and double echo steady state/reversed FISP sequences have had recent success in actually demonstrating the intraparotid facial nerve.[44, 45]

MRI, with its excellent soft tissue definition and lack of ionizing radiation, is routinely indicated for the rarer deep lobe lesions (**Figure 45.9c** and **d**), ill defined or

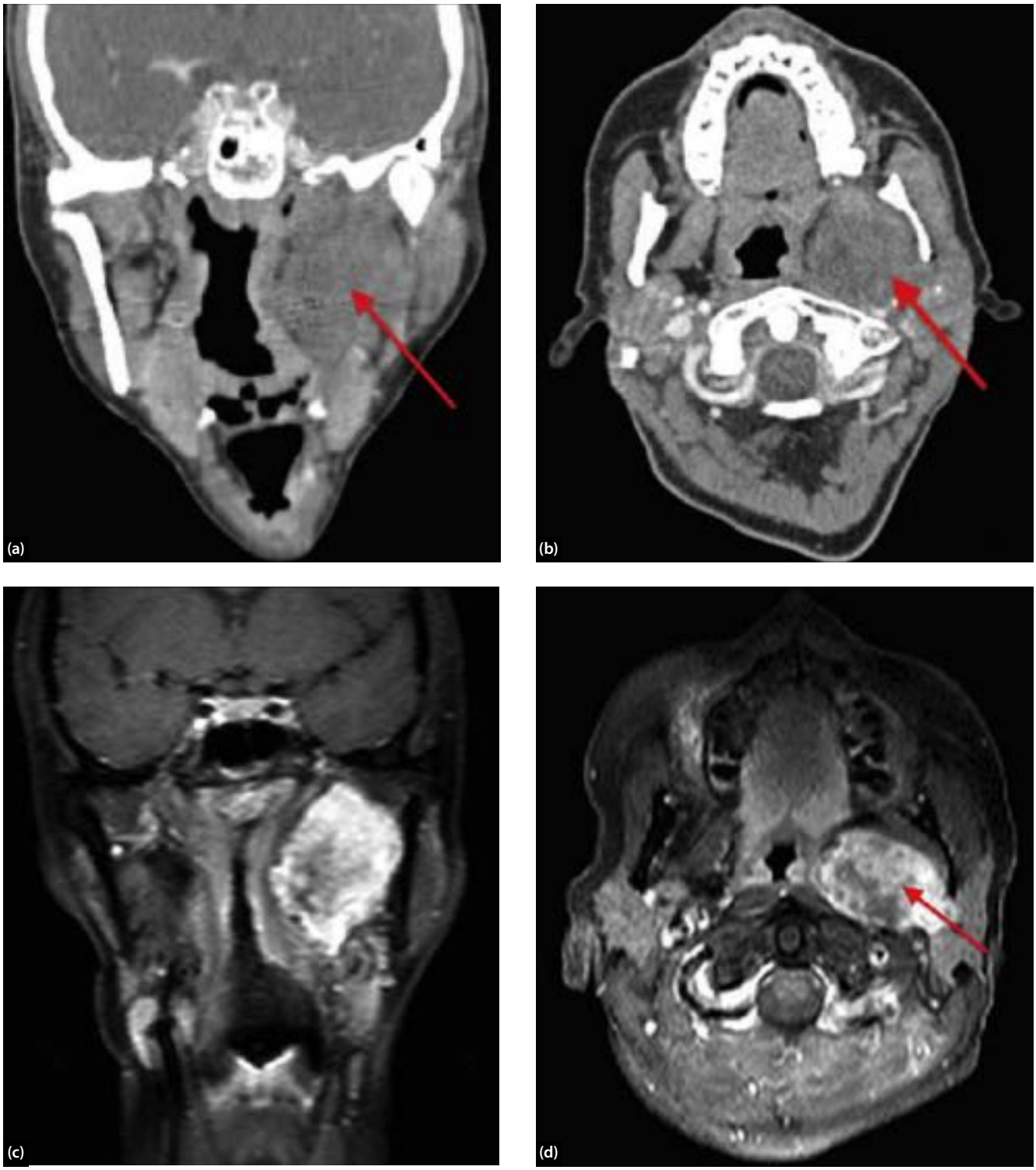


Figure 45.9 **(a, b)** Contrast-enhanced CT images of deep lobe PA; **(c, d)** Post-gadolinium, fat-saturated MR images of deep lobe PA.

infiltrative masses, in the context of facial nerve symptoms or suspected perineural disease and when FNA is suggestive of malignancy. Axial or coronal T2W sequences, fat-saturated contrast-enhanced and DWI are commonly performed. At MRI, pleomorphic adenomas typically follow the signal characteristics of fluid, appearing homogenously low signal at T1W imaging and 'T2 fluid bright'. They demonstrate variable moderate and sometimes delayed enhancement patterns following gadolinium. The thin surrounding capsule and pseudopodia formation of the commonest myxoid/ hypocellular pleomorphic subtype with a relatively higher propensity for recurrence is not visualized at imaging.[46] The less prevalent hypercellular variant is more likely to demonstrate atypical low signal intensity (SI) on T2W images. If a pleomorphic adenoma is managed non-operatively, the risk of malignant transformation is reported to increase with chronicity and this is suggested at MRI with T2W hypointensity (hypercellularity), rapid interval growth, abnormal facial nerve enhancement and ill-defined infiltrative margins. In small case series, DWI shows promising follow-up results.[47]

The literature suggests pleomorphic adenoma recurrence rates of around 1–4% after treatment and these usually occur in the first decade after surgery. In the larger series, two-thirds of recurrent disease is multifocal and the majority should maintain the same benign imaging characteristics of the initial tumour. Recurrent, small subcutaneous nodules are frequently seen and disease can present in a remote site from the operative bed.[48] Routine post-operative surveillance imaging is a costly and contentious issue.

WARTHIN'S TUMOUR

Warthin's tumour is the second most frequent parotid gland tumour with a 10–15% incidence of bilaterality. US highlights a well-defined, somewhat heterogenous, hypoechoic lesion that may be septated and partially cystic. Subacute haemorrhage or proteinaceous material will yield 'T1 bright signal' at MRI and possibly a hypointense signal rim indicative of chronic haemosiderin and blood degradation products. Enhancement is classically poor apart from the vascularized septations and the lesion may have restricted signal on DWI (**Figure 45.10**). A confident pre-operative diagnosis in those with significant comorbidities may avoid surgery altogether.

ONCOCYTOMAS

Oncocytomas most commonly present as solitary lesions in the parotid glands and these rare tumours are difficult to distinguish from benign and low-grade salivary tumours on routine US and MR imaging alone. A case series of nine patients describes a 'vanishing mass' with hypointense and isointense signals on T1 and fat-saturated T2W sequences respectively in eight of the pathologically confirmed lesions.[49] Like Warthin's tumours, these will demonstrate cystic degeneration and have a propensity to bilateral disease (10%).

Malignant neoplasms

The NICE guidelines on improving head and neck cancer outcomes in 2004[50] promoted appropriately set-up and funded fast track 'one-stop' clinical and US assessment clinics to provide same-day tissue biopsies and prompt diagnoses. The most common malignant salivary tumours are mucoepidermoid, adenoid cystic, acinic cell, adeno- and squamous carcinomas. Approximately 20% of all parotid tumours, half of the submandibular gland tumours and more than 90% of sublingual tumours are malignant. Malignant tumours can deceptively show the same imaging characteristics as their benign counterparts.

KEY POINTS

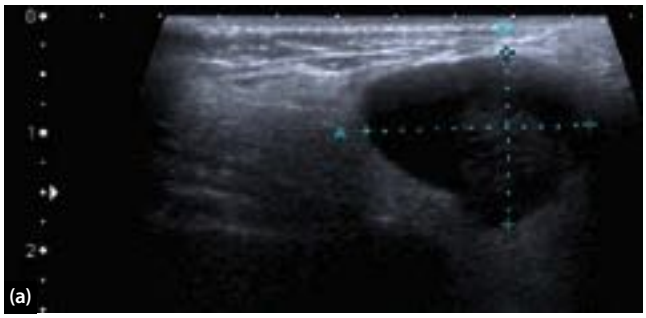
- Common knowledge states that there is an inverse relationship between the volume of the salivary gland and the risk of malignancy.
- It should be remembered that minor salivary glands are present throughout the upper aerodigestive tract including the sinonasal cavity and trachea.
- Intermediate grade and aggressive tumours with metastatic potential are disproportionally more frequent in the sublingual and minor salivary glands.

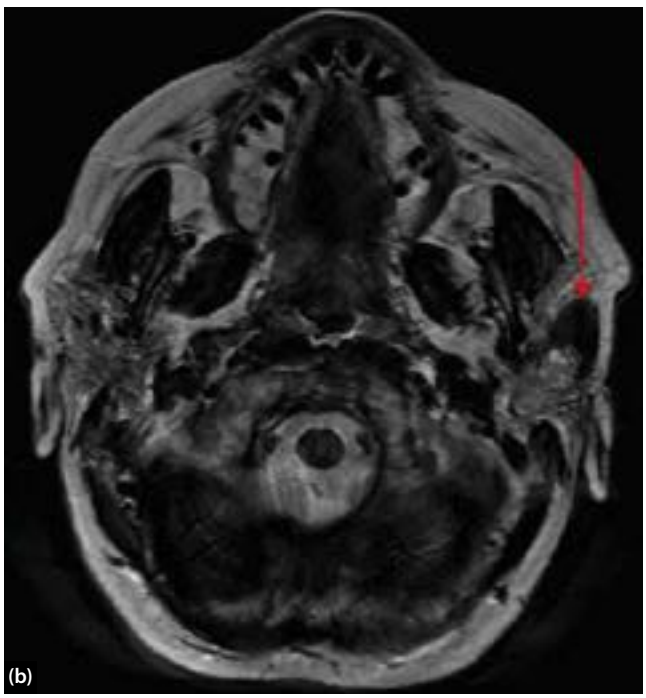
A firm, fixed, painful lesion with rapid growth or possible cranial nerve deficits and local adenopathy strongly suggests malignant characteristics. Image interpretation is primarily focused towards these adverse prognostic indicators.[51] Imaging features more suggestive of malignancy are lesional inhomogeneity, posterior acoustic shadowing and raised inherent vascular flow at US. With a good positive predictive value, ill defined and infiltrative margins imply malignancy. The absence of T2W bright fluid signal with avid enhancement patterns at MRI renders a focal lesion as indeterminate, possibly malignant and this will require prompt surgical excision. MR signal characteristics and tumour grades are poorly correlated. Perineural facial or trigeminal nerve enhancement (best depicted on fat-saturated, post-gadolinium images), obscuration of fat around widened skull base neural foramina, biopsy proven cervical lymph node metastasis, remote lung nodules and destructive bone lesions are highly sensitive indicators of loco-regional and distant metastatic disease.

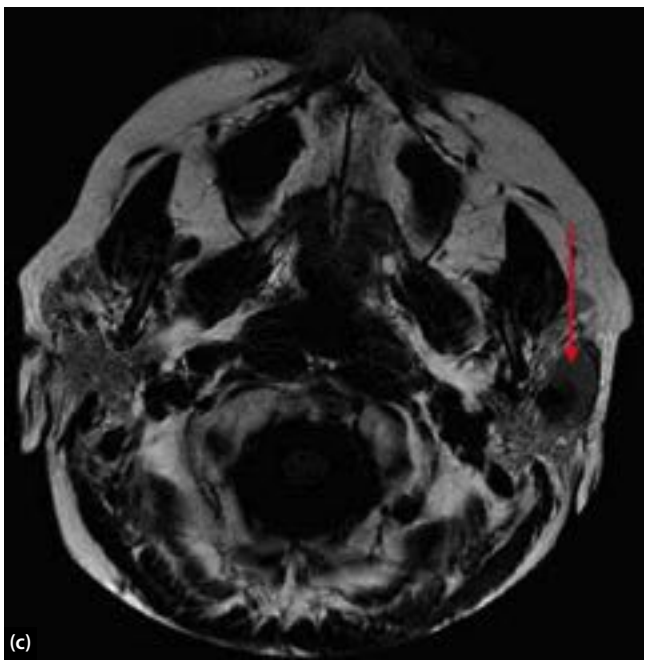
Contrast-enhanced CT is universally used to stage presenting aerodigestive squamous cell carcinomas and it is sensitive in detecting pulmonary metastasis that would generally preclude curative surgery in high-grade salivary malignancies. However, its routine use in evaluating the salivary gland parenchyma is limited due to poor soft tissue characterization. Moreover, salivary gland lesions may be concealed amongst dental amalgam artefact and the surrounding normal avid enhancing gland parenchyma. A skull base and neck CT study would be complementary to MRI when associated bony erosion is suspected.

MUCOEPIDERMOID TUMOURS

Mucoepidermoid tumours are the most common parotid malignancy, and constitute 12–29% of all salivary







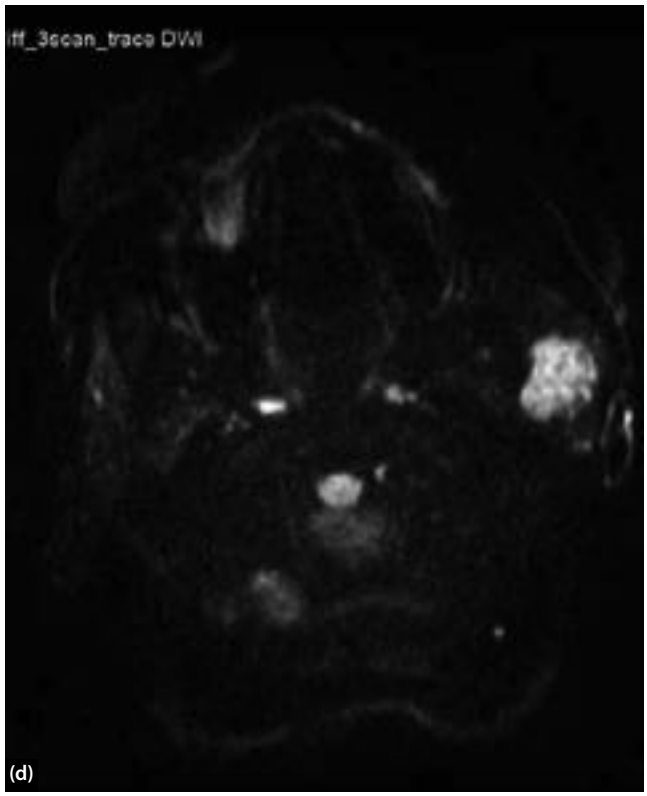




Figure 45.10 Warthin's tumour. **(a)** Axial US of well-circumscribed, heterogenous superficial Warthin's lesion; **(b)** Axial T2W MR of left parotid gland Warthin's tumour; **(c, d)** Diffusion-weighted imaging of a Warthin's tumour; **(e)** matched ADC image demonstrating hypercellularity.

malignancies. Classified into high-, intermediate- or low-grade tumours, they may have abundant fibrous tissue that is hypointense across MR sequences. Cystic change may be present.

ADENOID CYSTIC CARCINOMAS

Adenoid cystic carcinomas are overall the second most common salivary gland lesion but the commonest malignant tumour within the submandibular glands. Cribriform, tubular and solid subtypes exist and cellularity correlates with prognosis. Hypercellular areas tend to yield hypointense signal on T2W sequences and are more common with the solid subtypes.[52] Local perineural spread should be always be sought pre-operatively on contrast-enhanced MR images. Larger tumours may have intralesional bleeds with bright signal foci on T1W imaging.

INTRAPAROTID NODAL METASTASIS: LYMPHOMA, SCC AND MELANOMA

As a drainage pathway to the face, lateral scalp and external auditory canal, occult skin squamous cell carcinoma (SCC) and melanomas may present as parotid masses (**Figure 45.11**). Primary salivary gland lymphomas are more common in immunosuppressed individuals and those with background chronic autoimmune disease such as pre-existent Sjögren's disease. The imaging findings and long clinical histories are suggestive clues. At US, bulky, non-necrotic hypoechoic large intra-parenchymal nodes with distorted hila are also highly suggestive of secondary lymphoma, which will require staged abdominopelvic imaging.

Newer functional techniques

Whilst the overwhelming success of DWI in ENT has been for the evaluation and follow-up of cholesteatomatous ear disease, it has also been studied to differentiate salivary gland tumours. Its spatial resolution is poor but it is always acquired rapidly alongside conventional anatomical imaging. Transient magnetic gradients reflect local intra- and extracellular water diffusion amongst macromolecules, endothelium, cell membranes and hypercellular environments that can characterize pathological tissues in more detail. Quantitative values (apparent diffusion coefficients or ADC values) are obtained routinely and these can be prospectively correlated with subsequent histopathological findings. To dichotomize and oversimplify, high ADC values imply a benign phenotype, while reduced values suggest a greater chance of malignancy. Fluid and vascular flow can confound the validity of results[53] and the different ratios of serous and mucinous salivary glands yield differing ADC values in healthy individuals.[54]

Perhaps less favourable than initial reports, Habermann et al.[55] prospectively considered 136 consecutive parotid tumours and they were significantly and successfully able to separate pleomorphic adenomas and myoepithelial adenomas from other cell types. Despite variation in their biological behaviours, Warthin's tumours, mucoepidermoid, acinic cell and basal cell adenocarcinomas (surgical candidates) were poorly separated with overlapping, somewhat indeterminate results.

The significant histological heterogeneity in salivary neoplasms and small study sizes do not favour the development of these newer techniques. Sumi et al.[56] used intravoxel incoherent motion (IVIM) MR sequences to prospectively study 31 salivary gland tumours with histological correlation and derived parameters that could be successfully used to partition malignant and benign entities. Conceptually, it is thought that densely packed, small malignant cells, with high nuclear : cytoplasmic ratios tend to have poor associated diffusivity.

From the wider arena of oncological imaging, dynamic MRI (dMRI) continues to look at correlating enhancement patterns with angiogenesis and cellular-stromal ratios in pathological tissues. A seminal paper by Yabuuchi et al.[57] describes a promising method. Intravenous gadolinium is delivered via a power injector. Having chosen a region of interest, repeated sequential dynamic images are acquired over a period ranging from 0 to 300 seconds. Time-intensity curves (TIC) are then generated with avoidance of cystic regions and large vessel sampling. Plateau type patterns at dMRI are suggestive of malignant foci with rapid enhancement, fast peak times and delayed contrast wash-out. It is proposed that this latter finding may represent extravasation of contrast material through abnormally permeable endothelium in tumour beds.

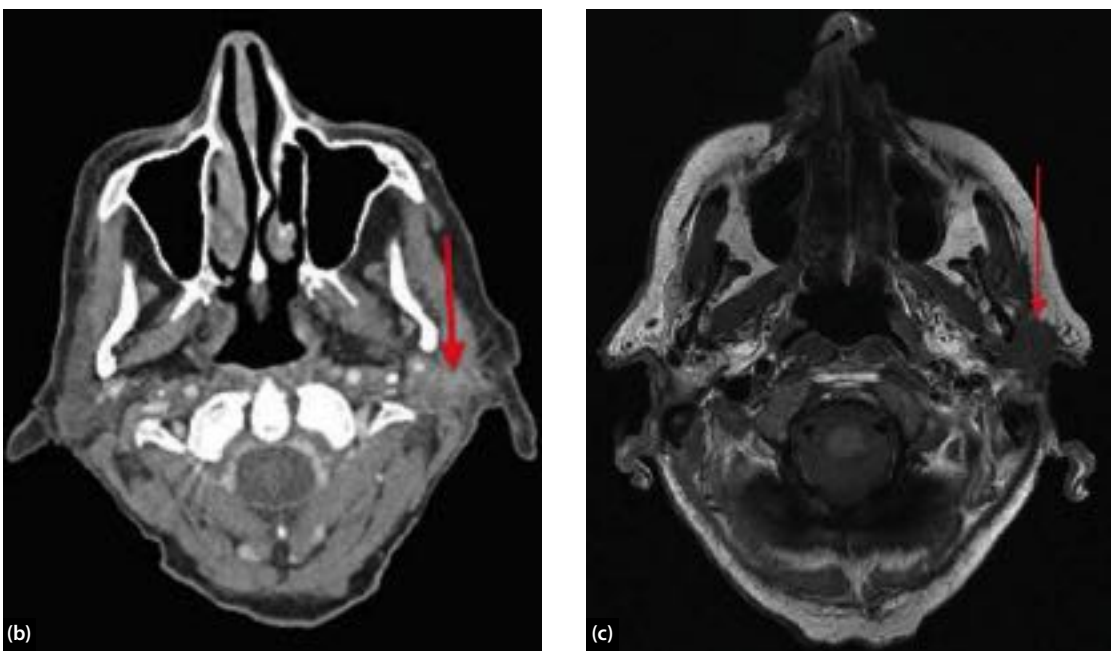
MR proton spectroscopy can be used to characterize choline/creatinine ratios and, in 2005, King et al. showed that larger ratios imply a benign phenotype.[58]

Using combinations of these techniques, researchers are moving towards multiparametric evaluation to anticipate likely tumour behaviour, prognostics and treatment response. In 47 patients with major salivary lesions, Yabuuchi[59] retrospectively considered the added merits of combining DWI measurements with dynamic contrast-enhanced MRI. This revealed further improvements in the pre-operative separation of malignant and benign lesional characteristics with the former group illustrating rapid peak times and delayed wash-out.

At PET-CT, diffuse, supra-normal increased uptake in the salivary glands is occasionally seen incidentally in low-grade asymptomatic inflammatory disorders and connective tissue diseases. PET-CT has a well-defined role in mucosal HNSCC; however, its role in focal salivary glandular pathology is far less clear with small study sizes. The reality is that by this stage of assessment the patient would usually already have had an USgFNAC. The ability to differentiate benign from malignant disease is dependent on glycolytic activity and potential exists to misclassify hypermetabolic, benign lesions (Warthin's tumour, oncocytomas) from intermediate/low-grade malignant tumours with low metabolic activities. The real potential is for a single test to stage high-grade tumours with a propensity for occult bony metastasis.

Figure 45.11 Squamous cell carcinoma left parotid gland. **(a)** Atrophy of temporalis muscle with facial nerve palsy suggests V & VII nerve palsies; **(b)** Contrast-enhanced axial CT shows irregular infiltrative left parotid mass; **(c)** T1W MR demonstrates irregular retromandibular, left parotid gland mass.





KEY POINTS

- A specialist opinion and detailed history directs the appropriate imaging.
- US is the best initial test in most circumstances.
- Fine-needle aspiration of a mass is a robust test when good cytological support is available.
- Facial nerve symptoms or localized nodal disease is likely to signify malignant disease.

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CHAPTER 46

NON-NEOPLASTIC SALIVARY GLAND DISEASES

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SEARCH STRATEGY

A literature search was performed using Medline and included the following keywords: non-neoplastic salivary disorders, benign salivary disorders, as well as all the main subject headings. A few earlier references are included where they are pertinent and only the relevant references have been cited.

INTRODUCTION

A wide range of non-neoplastic disorders of the salivary glands can arise, although the more common are sialolithiasis, mumps, acute suppurative sialadenitis, Sjögren's syndrome (SS) and drug-induced xerostomia. Disease of the glands typically manifests as swelling (**Table 46.1**) and/or oral dryness (**Box 46.1**). The present chapter provides an overview of non-neoplastic disorders of the salivary glands, but also focuses upon the common disorders likely to be of relevance to otorhinolaryngologists.

CONGENITAL SALIVARY GLAND DISEASE

Salivary gland agenesis

Agenesis of one or more of the major salivary glands is uncommon. There can be variation in the number of absent salivary glands and hence the degree of associated xerostomia, dysarthria and/or dysphagia varies accordingly. Lack of saliva predisposes to dental caries, gingival and periodontal inflammation, candidosis and acute suppurative sialadenitis in any existing glands, although in children severe dental caries may be the only initial sign of underlying salivary gland agenesis.[1]

The precise incidence of major salivary gland agenesis is difficult to establish due to the asymptomatic nature of many affected individuals but it may have an estimated incidence of 1 in 5000 live births,[2] with males more likely to be affected than females. Familial clustering of salivary gland agenesis has occasionally been reported but many instances are isolated, non-familial and non-syndromic.[3] Salivary gland aplasia can be associated with other ectodermal defects, in particular lacrimal apparatus abnormalities (the salivary glands and lacrimal puncta both develop at about the 4th to the 8th weeks of embryonic life as a consequence of ingrowths of ectodermal tissue into the underlying mesenchyme).[1] Autosomal dominant aplasia of the lacrimal and salivary glands is due to a defect being loss-of-function mutations in the fibroblast growth factor 10 (*FGF10*) gene at chromosome 5p13-p12125.

TABLE 46.1 Non-neoplastic causes of salivary gland swelling

Unilateral	Bilateral
• Acute suppurative sialadenitis • Recurrent parotitis of childhood • Sialolithiasis and other causes of ductal obstruction • Sjogren's syndrome (and associated non-Hodgkin lymphoma • IgG4-related disease • Sarcoidosis • Chronic non-specific sialadenitis • Xanthogranulomatous sialadenitis • Amyloidosis • Others	• Mumps • HIV salivary gland disease (and related disorders) • HCV sialadenitis • Sjogren's syndrome (and rarely bilateral non-Hodgkin lymphoma) • IgG4-related disease • Sarcoidosis • Sialosis • Pneumoparotitis • Iodine containing contrast media and radioactive iodine • Drugs (rare) • Others

BOX 46.1 Non-neoplastic causes of long-standing reduced salivary output

- Drugs (many)
- Radiotherapy of the head and neck
- Sjogren's syndrome and related disorders
- Chronic graft-versus-host disease
- IgG4-related disease
- Sarcoidosis
- Salivary gland agenesis
- HIV salivary gland disease
- HCV sialadenitis
- Others (e.g. long-standing anxiety, depression)

Associations with hypohidrotic ectodermal dysplasia (ED)[4] and lacrimal-auriculo-dentodigital (LADD; Levy-Hollister syndrome) reflecting defects of *FGF10* gene[5] and ectodactyly-ED syndromes have been reported. Bilateral parotid gland aplasia in a patient with Down syndrome has been reported[6] and agenesis of the major salivary glands in association with an absence of the lacrimal puncta of one side also observed.[7]

The management of children with absence of salivary glands follows that of long-standing oral dryness due to Sjögren's syndrome.[8]

KEY POINTS

- Lack of saliva predisposes to dental caries, gingival and periodontal inflammation, candidosis and acute infective sialadenitis, although in children rampant dental caries may be the only initial sign of underlying salivary agenesis.
- Salivary gland aplasia is rare, may occur in isolation or be associated with other ectodermal defects, in particular lacrimal apparatus abnormalities.
- The management of children with absence of salivary glands follows that of long-standing oral dryness due to Sjögren's syndrome.

INFECTIONS OF THE SALIVARY GLAND

Viral and bacterial infections are the most common infectious disorders of the salivary glands, although very rarely other infectious agents can be involved (**Table 46.2**). In addition the salivary glands may be the site of asymptomatic viral infection – particularly some of the herpes group (e.g. human herpesvirus 6 (HHV-6), cytomegalovirus and perhaps human herpesvirus 8 (HHV-8)), while saliva can contain low amounts of a wide range of infectious agents including hepatitis B virus, hepatitis C virus (HCV), HHV-8 and human immunodeficiency virus (HIV).[9, 10] There is little evidence, however, that saliva is a common fluid for the transmission of HCV or HIV.

Of note, xerostomia is more likely with viral (e.g. HCV and HIV) than bacterial infection of the salivary glands. The infections that can arise in the salivary glands are summarized in **Table 46.2**; however, as some of these are rare and/or have no specific salivary gland features, the present discussion will focus upon the more common infections of the salivary glands.

Mumps (epidemic parotitis)

Mumps is an acute generalized paramyxovirus infection of children and young adults. Mumps typically affects the major salivary glands, although involvement of other structures can occur including the pancreas, testis, ovaries, brain, breast, liver, joints and heart.[11]

Mumps is transmitted via the droplet route, and has an incubation time of approximately 14–18 days. Patients present with initial pyrexia, chills and facial pain. The parotids are typically bilaterally enlarged, although this may initially be unilateral. There is often swelling of the submandibular glands together with lymphadenopathy, giving rise to profound facial and neck swelling. Rarely sublingual swelling may be so profound as to cause elevation of the tongue and dysphagia and dysarthria. The salivary swelling tends to diminish after approximately 4–5 days and may precede more complicated aspects of the illness. There have been a small number of reports of transient facial nerve weakness in association with the parotid gland enlargement in mumps.[12]

Orchitis may develop approximately 4–5 days after the onset of parotitis. Typically only one testicle is affected, though occasionally there can be bilateral involvement. Orchitis tends to arise in post-pubertal boys, and rarely gives rise to serious long-standing disease.

Mumps can give rise to a lymphocytic or viral meningitis, which commences a few days after the development

TABLE 46.2 Infections of the salivary glands

Common	Uncommon
• Acute suppurative sialadenitis • Mumps • HIV-associated salivary gland disease • HCV-associated sialadenitis	• Human T-lymphocytic virus 1 (HTLV-1) • Epstein–Barr virus (EBV) • Cytomegalovirus (CMV) • *Mycobacterium tuberculosis* • Non-tuberculous mycobacteria • Arachna spp • *Haemophilus influenzae* • *Escherichia coli* • *Treponema pallidum* • *Eikenella corrodens* • 'Cat scratch' bacillus • Caffkiya anaerobia • *Actinomycosis israelii* • *Actinomycoses eriksonii* • *Samonella enteritidis* • *Salmonella choleraesuis* • *Histoplasma* spp • *Candida* spp • Cysticercosis

of parotitis. It should be noted that meningitis can occur in the absence of salivary gland disease. Other neurological manifestations include retrobulbar neuritis and encephalitis. Deafness is possible, but rare. Pancreatic infection may give rise to mild upper abdominal pain, but acute and long-term complications are unusual. Likewise, while cardiac, hepatic and joint infection can occur, they are rare and do not generally cause notable complications.

The diagnosis of mumps is typically based upon the clinical picture; however, it may be confirmed by detection of viral-specific immunoglobulin G (IgG) and immunoglobulin A (IgA). Viral culture is possible, but generally unnecessary as serological methods are highly sensitive.

There is no specific treatment for mumps, analgesia and appropriate fluid intake being the mainstays of therapy. It has been suggested that corticosteroids may be effective for severe parotitis, but generally these are not required unless the patients have other systemic symptoms such as orchitis.

Mumps can generally be prevented with appropriate vaccination (measles, mumps and rubella (MMR)). The effectiveness of the MMR vaccine is evidenced by outbreaks of mumps as a consequence of suboptimal uptake of vaccination.[13]

KEY POINTS

- Mumps patients present with initial pyrexia, facial pain, enlarged parotid glands usually bilateral, and swelling of the submandibular glands together with lymphadenopathy and, rarely, sublingual swelling.
- Mumps salivary swelling tends to diminish after approximately 4–5 days.
- Serious and not infrequent complications of mumps include orchitis and viral meningitis.

HIV salivary gland disease

Salivary gland manifestations can arise in up to 10% of adults and children with untreated HIV infection. Clinical syndromes of HIV infection of the salivary glands include HIV salivary gland disease per se, bacterial sialadenitis, intra-parotid lymphadenopathy, primary or metastatic non-Hodgkin lymphoma and Kaposi's sarcoma.[10] There have been rare reports of sialolithiasis possibly secondary to atazanavir (that has also been linked to renal and biliary lithiasis),[14] ranula formation of the sublingual gland[15] and submandibular gland swelling due to cytomegalovirus infection as part of immune reconstitution inflammatory syndrome (IRIS).[16]

HIV salivary gland disease is a distinct disorder characterized by recurrent and/or persistent major salivary gland enlargement and xerostomia. The parotid glands are most frequently affected, there often being profound bilateral enlargement. Submandibular gland involvement is considered to be rare.[17] Salivary gland disease tends to arise in late HIV infection, although occasionally can be the first manifestation. A higher rate of male to female ratio of involvement has been reported, but this probably reflects the epidemiology of the patients that have been previously reported. HIV salivary gland disease may be associated with HLA-DR5, and is part of a more generalized disorder termed diffuse infiltrated lymphocytosis syndrome (DILS) characterized by CD8+ T-cell infiltration of the lungs, salivary glands and lacrimal glands.[3] There is increasing evidence that salivary gland inflammation and cyst formation are driven by infection with BK polyomavirus (BKPyV) and thus, as expected, HIV salivary gland disease is a virally driven opportunistic infection in an immunodeficient host.[18, 19]

The clinical picture of HIV salivary gland mimics that of Sjögren's syndrome; however, there are distinct histopathological and serological differences between the two disorders. Patients with HIV disease generally do not have anti-Ro or anti-La antibodies – but do have hypergammaglobulinaemia. The minor salivary gland histopathology is generally similar to that of Sjögren's syndrome, being dominated by perivascular, periacinar and periductal lymphocytic infiltrates with the formation of CD20+

lymphocyte dominated lymphoepithelial islands/complex and lymphoid follicles.[20]

Multicystic lymphoepithelial lesions, sometimes termed cystic lymphoid hyperplasia (CLH) or benign lymphoepithelial lesion (BLEL) or benign lymphoepithelial cysts (BLEC), may also occur. The exact cause of the lesions is not known but it has been suggested that they are due to ductal ectasia of entrapped salivary gland inclusions arising within lymph nodes.[21, 22] Cystic change can also arise following intra-glandular ductal obstruction by hyperplastic lymphoid tissue. It is estimated that swellings associated with CLH arise in up to 6% of adults and 10% of children infected with HIV. Transformation to non-Hodgkin lymphoma is a rare complication of CLH.

The diagnostic process of HIV salivary gland disease is similar to that of Sjögren's syndrome although, unlike the latter, histopathological involvement of the minor salivary glands may not be evident in HIV salivary gland disease or CLH. Fine-needle aspiration biopsy (FNAB) is sometimes, but not always, helpful for diagnosis as it allows rapid exclusion of malignancy.[20, 23] Radiological imaging (e.g. ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) is essential to establish the cause of any swellings of salivary glands in HIV disease, and in particular to exclude the possibility of malignancy.[17]

There is little information regarding the specific management of HIV salivary gland disease and the associated cystic swellings.[17] Clinical signs are usually non-progressive, and hence therapy is only indicated if there is notable cosmetic deformity or xerostomia. While it has been suggested that anti-retroviral therapy (ART) will reduce the swelling of HIV salivary gland disease, there is more evidence that protease inhibitors of ART may increase swelling (sometimes as a consequence of far accumulation within the gland)[24] and lessen salivary secretion.[25] Other, perhaps less practical, suggested therapies are repeated aspiration, tetracycline sclerosis or surgical removal of an enlarged gland.[26] External radiation (e.g. 8–10 Gy) can cause transient improvement, although higher doses (e.g. 24 Gy) can cause resolution of disease for at least several years – without causing severe xerostomia.[27]

The salivary gland dysfunction of HIV disease increases the risk of caries and lessens quality of life, hence there is a need to lessen the symptoms of xerostomia and provide preventative oral health care.[28]

Xerostomia independent of salivary gland involvement may arise in HIV infection as a consequence of some nucleoside analogue HIV reverse transcriptase inhibitors or protease inhibitors.[25]

KEY POINTS

- HIV salivary gland disease is characterized by recurrent or persistent major salivary gland enlargement, usually of the parotid glands with or without oral dryness. It tends to arise in late untreated HIV infection and can affect both children and adults.
- Clinically it mimics Sjögren's syndrome but there is an absence of anti-Ro and anti-La antibodies in HIV salivary gland disease.

BEST CLINICAL PRACTICE

- ✓ Treatment is only indicated for notable cosmetic deformity or xerostomia.
- ✓ Anti-retroviral therapy (ART) may lessen the onset of HIV salivary gland disease and may reduce swellings.
- ✓ The swellings of HIV salivary gland disease may respond to local radiotherapy. Doses of 24 Gy may cause long-term resolution of swelling without causing severe xerostomia.
- ✓ Other suggested therapies include repeated aspiration, tetracycline sclerosis or surgical removal of an enlarged gland.

Hepatitis C virus infection

Unlike the other hepatotropic hepatitis viruses, HCV frequently gives rise to a wide spectrum of extra-hepatic manifestations that include salivary gland disease. HCV-associated salivary gland disease arises in around 80% of infected patients.[29]

Xerostomia is the predominant symptom of HCV-associated salivary gland disease[30] and objective evidence of reduced unstimulated whole sialometry has been observed in 13–33%, although some groups of patients with HCV disease seem to have normal salivary flow rates – despite the presence of HCV in saliva.[30, 31]

The histopathological features of HCV-associated sialadenitis have similarities to those of Sjögren's syndrome, there being a lymphocytic infiltrate of salivary tissue in both. Whereas the infiltrate is periductal in the latter, in HCV sialadenitis it is pericapillary. In addition there is a more dominant cytotoxic T-cell infiltrate in HCV disease than Sjögren's syndrome.[31–33]

Transgenic mice expressing HCV genes develop sialadenitis, thus confirming the notion that HCV gives rise to salivary gland disease.[34] Nevertheless, the precise pathogenesis of HCV-related salivary gland disease remains unclear, particularly as the presence of HCV RNA in saliva does not correlate with clinical or histopathological evidence of salivary gland dysfunction.[31]

HCV infection may occasionally give rise to non-Hodgkin lymphoma (usually low grade B cell tumours); indeed, the salivary glands are a common site of lymphoma in HCV-infected individuals with 'Sicca' like symptoms. There remains, however, no association between HCV infection and the pathogenesis of Sjögren's syndrome.[32]

As with other disorders that give rise to oral dryness, patients with HCV sialadenitis require treatment of the xerostomia and the associated increased risk of common oral disease such as caries and gingival inflammation.

Acute suppurative sialadenitis (suppurative parotitis; bacterial sialadenitis; bacterial parotitis)

Acute suppurative sialadenitis is an uncommon disorder characterized by painful swelling – usually of the parotid

glands (suppurative parotitis), purulent discharge from the duct of the affected gland, associated dysgeusia and cervical lymphadenopathy. When disease is severe there may be accompanying pyrexia, malaise and a risk of abscess formation.

Acute suppurative sialadenitis can affect children and adults. Prematurity may be a risk factor for disease in childhood, and sialadenitis can occur in newborns.[35–37] The highest incidence is seen in children aged 3–6 years.[38] Immunodeficiency and concurrent illness may predispose to childhood suppurative parotitis. Of interest, an aseptic sialadenitis has been observed in pre-term children receiving long-term orogastric tube feeding.

In adults, it is most commonly seen in elderly, dehydrated, patients although long-standing xerostomia (e.g. Sjögren's syndrome) and radiotherapy-induced xerostomia are additional risk factors, as well as other predisposing factors such as poor oral hygiene, diabetes mellitus, HIV disease, the placement of a Sengstaken-Blakemore tube,[39] endoscopic retrograde cholangiopancreatography (ERCP), continuous positive airway pressure therapy,[40] and the use of total parenteral nutrition. Ductal obstruction (e.g. sialolithiasis, malignancy or foreign bodies), unusual anatomy of Stenson's duct,[41] positioning of the head during long surgical procedures,[42, 43] possibly after implant placement,[44] malar augmentation with poly-L-lactic acid injections,[45] and infection as a consequence of bacteraemia may also predispose to acute suppurative sialadenitis. Coprophagia gave rise to recurrent submandibular sialadenitis in one patient. Rarely infection may be acquired nosocomially[46] and following intra-glandular injection of botulinum neurotoxin for drooling.[47]

The causative organism of acute suppurative sialadenitis is often not found; however, facultative anaerobes, particularly *Staphylococcus aureus* and *Streptococcus viridans* have frequently been reported to be of aetiological significance. In addition a wide range of other bacteria including gram negative bacilli, strict anaerobes such as *Bacteroides* spp, *Fusobacterium nucleatum* and *Peptostreptococcus anaerobius* have been identified in affected individuals.[48, 49] Rare organisms associated with acute suppurative sialadenitis include methicillin-resistant *Staphylococcus aureus*,[50] *Bartonella henselae*, *Treponema pallidum*[51] and *Eikenella corrodens*.[48] There have been rare reports of acute sialadenitis associated with primary mycobacterium tuberculosis,[52] pre-existing *Mycobacterium tuberculosis* and non-tuberculous mycobacterial infection.[53, 54] Other rare infections have included *salmonella* spp,[55] *Neisseria meningitides*, *Fusobacterium necrophorum* (Lemierre's disease)[56] and *Burkholderia pseudomallei* (Meliodosis).[57, 58] **Table 46.2** indicates other possible bacterial infections of the salivary glands.

The diagnosis of acute suppurative sialadenitis is usually straightforward – being based upon the history and clinical picture. Microbiological culture of pus, under both aerobic and anaerobic conditions, may reveal the causative agents, although specific relevant tests may be useful if a particular infection seems likely.

The benefits of sialography for the diagnosis of acute suppurative sialadenitis remain unclear. Some authorities suggest that such investigation is contraindicated (probably when there is notable disease), while others suggest that it may resolve any causative ductal stricture. Sialography may reveal areas of ductal stricture and sialectasis, the latter are most likely with recurrent disease. Scintiscanning is generally unhelpful but may sometimes reveal the underlying cause (e.g. poor salivary gland function). Ultrasound scanning is useful as it may identify sialoliths, ductal anomalies, fluid collections and parenchymal disease of probable Sjögren's syndrome or HIV disease. Additional cross-sectional imaging may be essential if abscess formation is suspected.

COMPLICATIONS

There is a risk of abscess formation as a consequence of duct ectasia, primary parenchymal involvement (most likely with submandibular gland infection) or infection of subcapsular lymph nodes.[38] Facial nerve palsy secondary to parotid abscess formation with sialadenitis is rare, but possible.[59] Extension to the neck spaces is also possible (see Chapter 40, Neck space infections).

THERAPY

Effective hydration and antibiotics are the mainstays of therapy of uncomplicated acute suppurative sialadenitis. Empirical antibiotics used are anti-staphylococcal penicillins (e.g. flucloxacillin, amoxycillin or co-amoxiclav), cephalosporins or clindamycin based on local protocols, but these may change if a causative organism is identified. Intra-ductal injection of antibiotics is unlikely to be of practical benefit. A recent literature review concluded that cephalosporins and fluoroquinolones achieve high levels of concentration in saliva and are likely to exert an effective anti-bacterial action (although, interestingly, phenoxymethylpenicillin and tertacyclines do not).[60]

Surgical drainage should be considered if there is a lack of clinical improvement after 3–5 days of antibiotic therapy, any unlikely facial nerve involvement, any involvement of deep fascial spaces, or abscess formation within the parenchyma of the gland. Superficial parotidectomy may be required if disease becomes recurrent or chronic.[61, 62]

KEY POINTS

- Acute suppurative sialadenitis presents with painful swelling – usually of the parotid glands (suppurative parotitis), purulent discharge from the duct of the affected gland, dysgeusia, cervical lymphadenopathy, pyrexia and malaise.
- Acute suppurative sialadenitis usually affects adults although children may rarely be affected. Risk factors for acute suppurative sialadenitis are centred around causes of persistent obstruction of the ductal system and/or reduced salivary production.

BEST CLINICAL PRACTICE

- ✓ The diagnosis of acute suppurative sialadenitis is primarily clinical with microbiological culture of pus, under aerobic and anaerobic conditions.
- ✓ Ultrasound imaging is probably the most useful diagnostic radiological investigation.
- ✓ Effective hydration and antibiotics are the mainstays of therapy of uncomplicated acute suppurative sialadenitis. Typical antibiotics may include anti-staphylococcal flucloxacillin, amoxycillin (or co-amoxiclav), cephalosporins or clindamycin.
- ✓ Surgical drainage should be considered if there is a lack of clinical improvement after 3–5 days of antibiotics, facial nerve, deep fascial space involvement, or abscess formation within the parenchyma of the gland.

CHRONIC NON-SPECIFIC SIALADENITIS

Chronic non-specific sialadenitis is an uncommon disorder, usually of adulthood, characterized by recurrent and/or persistent enlargement of usually one major salivary gland. The parotids are more commonly affected than the submandibular glands.[63] Patients can have episodes of disease akin to acute suppurative sialadenitis. Affected patients are generally well, have no systemic disease likely to cause sialadenitis, although many have a history of recurrent parotitis of childhood or previous sialolithiasis.

In most instances, chronic non-specific sialadenitis reflects abnormalities of the ductal system – the recurrent infection having caused or worsened any ductal strictures. Likely causes of this disorder are small sialoliths and, less commonly, external pressure and resultant ductal defects due to dentures,[64] congenital ductal defects or radiotherapy-induced salivary gland damage. The strictures have a damming action causing salivary stasis and liability to infection with resultant chronic, and possibility acute, inflammation.

The investigation of chronic non-specific sialadenitis is similar to that of acute suppurative sialadenitis, although often microbiological examination of saliva will be unhelpful clinically. Sialochemistry is not helpful. Sialography will almost always reveal strictures and/or associated distortion of the major ducts, although there can also be variable sialectasis. Imaging studies may reveal small causative sialoliths. Chronic non-specific sialadenitis has no specific histopathological features, although there may be duct dilatation (sometimes with squamous metaplasia), acinar atrophy, interstitial fibrosis and a periductal inflammatory infiltrate comprised predominantly of lymphocytes and sometimes plasma cells and eosinophils.

The clinical course of the chronic non-specific sialadenitis is highly varied; about 50% of patients have eventual spontaneous resolution of symptoms after up to 5 years, but as many as 40% will have symptoms that warrant surgical intervention.[65] Although there is a recent report of parotid duct carcinoma arising within chronic sialadenitis,[66] chronic non-specific sialadenitis does not have any notable malignant potential.

The management of any acute infection associated with chronic non-specific sialadenitis follows that of acute suppurative disease. In addition, sialagogues such as chewing gum, duct and glandular massage, improved oral hygiene and therapeutic sialography have been suggested to be useful, but there are no supporting data.[67] Unless the cause is likely to be a sialolith, subtotal or total surgical removal of the affected gland may be the only useful treatment.[62, 63, 68]

KEY POINTS

- Chronic non-specific sialadenitis is an uncommon disorder, usually of adulthood, characterized by recurrent and/or persistent enlargement of usually one major salivary gland. The parotids are more commonly affected than the submandibular glands.
- Patients can have episodes akin to acute suppurative sialadenitis but affected individuals are well and have no systemic disease likely to cause sialadenitis, although they may have a history of recurrent parotitis of childhood or previous sialolithiasis.
- Clinical course can be highly varied with up to 50% having spontaneous resolution but up to 40% may warrant eventual surgical intervention.

BEST CLINICAL PRACTICE

- ✓ Investigations might include ultrasound scanning, sialography, CT or MRI to define the ductal structure and/or identify the presence of sialoliths.
- ✓ Treat acute episodes as for acute suppurative sialadenitis with hydration and appropriate antibiotics.
- ✓ Sialagogues, glandular massage and improved oral hygiene and therapeutic sialography seem logical but there is no supporting evidence.
- ✓ Subtotal or total gland removal maybe the only useful treatment for the chronic, non-infected state unless sialoliths can be identified.

RECURRENT PAROTITIS OF CHILDHOOD (JUVENILE RECURRENT PAROTITIS)

Recurrent parotitis of childhood is characterized by recurrent parotid inflammation usually associated with non-obstructive sialectasis of the parotid gland. Recurrent parotitis can arise at any age, but the usual age of onset is 3–6 years. Childhood onset disease is usually more common in males, but interestingly, adult onset disease normally arises in females.

The disease is characterized by localized pain and swelling that may last up to 14 days. Fever and overlying erythema are common, and occasionally white mucopus can be expressed from the parotid duct. Recurrent parotitis of childhood tends to be unilateral rather than bilateral.

The number of attacks varies from 1 to 5 per year, but some patients may have up to 20 episodes of swelling per year. The frequency of recurrence tends to peak between 5 and 7 years of age, and up to 90% of patients have resolution of disease by puberty.

Sialography and ultrasonic scans reveal sialectasis, but this feature can also be observed in the non-affected glands of the opposite side. Serum amylase may be elevated.[69] The precise aetiology of recurrent parotitis remains unclear, but certainly almost all affected patients are otherwise well. There is no evidence that viral infection underlies this disorder. No gross immunological abnormalities have been described in large numbers of affected persons and there is no evidence of an associated genetic anomaly.[69]

Analgesia is the mainstay of therapy. Antibiotics do not shorten attacks. Intraductal saline with or without dilatation of Stenson's duct, intraductal antibiotics (or methyl violet to induce sclerosis) have been proposed as have included sialoendoscopy,[70, 71] ductal dilatation with a sialoballoon, but there are no reports of the outcomes of large series of treated patients. A report indicated that sialography with high concentration iodinated oil caused a 100% reduction in recurrence of juvenile recurrent parotitis of 87 patients.[72] Suggested invasive procedures include ligation of Stenson's duct, transection of chorda tympani or transection of Jacobsen nerve in the middle ear. Radical methods such as total or sub-total parotidectomy have also been proposed[72] but as the disease tends to resolve spontaneously there seem little place for such invasive measures. There is a recent report of Huangqi and bear bile capsules or granules reducing the frequency of swellings of recurrent parotitis of childhood.[73]

KEY POINTS

- Recurrent parotitis of childhood is characterized by recurrent painful unilateral parotid swelling usually associated with non-obstructive sialectasis of the parotid gland.
- The cause of recurrent parotitis of childhood is unknown although affected individuals are otherwise well.
- The usual age of onset is 3–6 years. The number of attacks varies from 1 to 5 per year, but up to 20 episodes may occur per year. The frequency of recurrence peaks between 5 and 7, and up to 90% of patients have resolution of disease by puberty.

BEST CLINICAL PRACTICE

✓ Analgesia is the mainstay of therapy. Antibiotics do not shorten attacks. A variety of other non-surgical and surgical therapies have been proposed, sialography or sialoendoscopy being the most promising of these.

IgG4-RELATED DISEASE

IgG4-related disease is a rare fibroinflammatory disorder characterized by elevated serum levels of IgG4 and multiorgan inflammation that can thus manifest with a plethora of possible manifestations. The disease has predominantly been described in Asian patients (particularly in Japan) but affected individuals have been reported in the Western World. Disease onset is usually in the 7th decade with males more likely to be affected than females (other than those with sialadenitis and dacryodenitis where there is an equal gender distribution or slight female predominance). Probable IgG4 sialadenitis has been reported in at least one child.[74]

The salivary glands are commonly affected, and in the past the features were termed 'Mikuliz disease' 'Kuttner tumour' or 'chronic sclerosing sialadenitis'. The submandibular gland is commonly affected, although the parotids, sublingual glands and minor salivary glands can occasionally be affected. The salivary gland features manifest as long-standing and generally asymptomatic swelling, sometimes, but not always, with symptoms of xerostomia.[75, 76]

The (many) other associated features of this disorder are well reviewed elsewhere[76–78] but include:

- lacrimal gland (IgG4 dacryoadenitis): swelling, keratoconjunctivitis sicca (sometimes), other features
- pituitary gland (IgG4-realted hypophysitis): headache, visual field deficits, diabetes insipidus, lactation
- thyroid (IgG4-related thyroiditis): malaise, oedema, neck swellings
- pancreas (Type 1 autoimmune pancreatitis): upper abdominal pain, obstructive jaundice, impaired glucose tolerance
- biliary tract (IgG4-related sclerosing cholangitis): obstructive jaundice
- lung (IgG4-related lung disease): cough
- prostate gland (IgG4-related prostatitis): urinary frequency
- retroperitoneal cavity (IgG4-related retroperitoneal fibrosis): fever, malaise, aortic aneurysm
- lymph nodes (IgG4 lymphadenopathy): lymph node enlargement.

Thus in specialist ENT clinics, patients may present with symmetrically swollen upper eyelids, salivary glands, cervical lymphadenopathy[79] and sometimes symptoms of ocular and/or oral dryness.

Histopathological examination of IgG4-related sialadenitis salivary gland lesions reveals a dense lymphoplasmacytic infiltrate, large irregular follicles with expanded germinal centres and acinar atrophy. Obliterative phlebitis, in which there is obliteration of venous channels by the lymphoplasmacytic infiltrate, is said to be a characteristic feature as is storiform fibrosis,[80] although this last feature may not always be evident in affected salivary glands.[81] Unlike Sjögren's syndrome there is an absence of lymphoepithelial lesions in IgG4-related sialadenitis. Immunohistochemistry of affected salivary gland tissue of IgG4-related disease reveals an abundance of IgG4+ plasma cells that may constitute up to 50% of the plasma cell infiltrate (although this may be absent if there is extensive fibrosis). The normal lobular architecture of the glands are usually preserved and the inflammation may be localized to one site or throughout a gland.[75]

There may be a hypergammaglobulinaemia and serum levels of IgG4 are always elevated and there is an absence

of circulating anti-Ro and anti-La antibodies.[76] In view perhaps of the sometimes non-diffuse nature of the disease within salivary glands, sialography may not always demonstrate any notable ductal abnormalities, although punctate of globular sialectasis may sometimes be observed.[82] Ultrasound scanning may reveal salivary gland enlargement and hypoechoic areas[82] while MRI may similarly demonstrate salivary gland swelling, but may not delineate the nodal (i.e. hypoechoic) areas.

The aetiopathogenesis of IgG4-related disease is reviewed well elsewhere.[76, 78, 80] The precise cause or trigger of this fibrotic disorder is not known although disease is driven by an excess production of type 2 T-helper cells and regulatory T-cell cytokines (e.g. IL-10) and transforming growth factor (TGF) -β, the latter then driving fibrosis.

There are no randomized controlled trials (RCTs) of the management of the oral aspects of IgG4-related sialadenitis and where disease is asymptomatic no therapy may be warranted. Short-term glucocorticoids may cause an increase in saliva production in affected patients.[83] This response contrasts with that of Sjögren's syndrome and may reflect the possibly localized involvement of the salivary glands in IgG4-related disease. Azathioprine or calcineurin inhibitors have been employed for some of the non-salivary elements of IgG4-related disease and, perhaps as expected, rituximab has been reported to reduce the salivary gland swelling of a small number of patients.[84, 85] Surgical excision of an affected gland is often advocated.[86]

Malignancy can arise in patients with IgG4-related disease (including one report of an unspecified cancer of the tongue) but there is no evidence that the risk of malignancy at any likely site of IgG4 related disease is increased in comparison to that of appropriate control populations.[87]

KEY POINTS

- IgG4-related disease is a multiorgan fibroinflammatory disorder that can give rise to painless enlargement, sometimes with dysfunction of the submandibular and other major salivary glands.
- Disease usually arises in middle to late life. The diagnosis typically rests upon the presence of elevated serum levels of IgG4 and histopathological evidence of a lymphoplasmacytic infiltrate with a high percentage of IgG4+ cells and the presence of fibrosis. Ultrasound scanning may demonstrate multiple hypoechoic areas.
- There is no evidence that IgG4 disease increases the risk of malignancy of the salivary or lacrimal glands.

BEST CLINICAL PRACTICE

- ✓ While IgG4-related sialadenitis has some of the clinical features of Sjögren's syndrome, the serological, histopathological and radiological features of the two disorders are distinctly different.
- ✓ Surgical excision of affected salivary glands may be helpful, as may high dose systemic corticosteroids. Patients with multiorgan disease may benefit from systemic immunosuppression. The long-term outcomes of IgG4-related disease are presently not known.

Xanthogranulomatous sialadenitis

Xanthogranulomatous sialadenitis is a very rare disorder manifesting itself as a solitary painless swelling within a major salivary gland.[88] It is histopathologically characterized by the presence of lipid-laden macrophages (xanthoma cells or foamy macrophages) with chronic and acute inflammation as well as non-caseating granulomas. The investigation of this disorder is similar to that of a salivary gland malignancy. It has been suggested that xanthogranulomatous sialadenitis may arise as a consequence of FNAB, but there are few supporting data. Excision would seem to be the logical treatment, particularly in view of the presence of Warthin's tumour in association xanthogranulomatous sialadenitis of one patient.[89, 90]

Sialolithiasis

Sialolithiasis is a common disorder characterized by the formation of a calculus (sialolith) usually within the ductal system of a gland. Sialoliths can arise in both the major and minor salivary glands – indeed, necropsy studies revealed that 1% of submandibular glands can have sialoliths while sialomicroliths (microscopic stones/concretions) are present in almost all submandibular, and some parotid glands. Sialoliths are more common in the submandibular glands (e.g. 83% of one sample) than the parotid (10%) or sublingual (7%) glands,[36] and are more common in females than males, and are much more likely in adults than in children. The minor salivary glands, particularly of the upper lip, can be affected.[91]

Sialolithiasis does not always give rise to clinical signs or symptoms, indeed the presence of sialoliths on ultrasound scans of salivary glands of patients without clinical problems is not uncommon.[72] Obstruction of a major duct will give rise to pain and swelling, typically in the submandibular gland, with gustation or eating. The swelling is diffuse, develops rapidly and is often associated with a burning-like local pain. The swelling is generally non-tender and gradually resolves over a few hours. Longstanding sialolithiasis may give rise to acute suppurative sialadenitis or chronic non-specific sialadenitis. Sialoliths of minor salivary glands give rise to painless hard swellings that rarely form mucoceles.

The likely cause of sialolith formation remains unknown,[92] although stasis caused by sialomicroliths, with resultant inflammation and fibrosis and further stagnation of calcium-rich fluid can be a driver for sialolith formation. However, sialomicroliths need not be the origin of all sialoliths. The sialoliths are composed of both organic and non-organic material, the central medulla being the more organic. The high proportion of sialoliths in the submandibular gland possibly reflects the high alkalinity and calcium content of submandular saliva together with its strong parasympathetic secretory drive. Calcium phosphate is the predominant salt of the calculi, laid down as concentric shells of about 10 micrometres thickness.

It is suggested that sialoliths may be associated with diabetes mellitus, hypertension and/or chronic liver

disease, and possibly nephrolithiasis,[93] but not to water hardness.[94] Patients with hyperparathyroidism may have an increased incidence of sialolithiasis, and individuals with both hyperparathyroid disease and sialolithiasis have a greater risk of nephrocalcinosis than those without sialolithiasis.[93] An association between the anti-HIV agent atazanavir and sialolithiasis has been reported.

INVESTIGATIONS

Plain radiographs (e.g. lateral skull and occlusal views for suspected submandibular stones) may reveal a sialolith – provided it is large and radiopaque. However, as many as 30% of sialoliths, particularly of the parotid glands, are radiolucent. Ultrasound scanning can detect both radiopaque and radiolucent sialoliths (see Katz et al.[72] for useful review). Sialography may also be helpful but can be technically difficult when investigating the submandibular gland. Pan-oral tomograms are not helpful in view of their tomographic nature, although CT and possibly MRI may be of some benefit. Where available, sialoendoscopy (SE) may be a first-line investigative tool.

TREATMENT

When small and accessible, it may be possible to express a sialolith from the submandibular duct by manual palpation, and many sialoliths can also be simply removed via a transoral approach – if within the anterior segment of the submandibular duct.[95, 96] This does, however, carry a risk of stricture formation.[97] Transcervical surgical removal of an affected gland can often be the only effective treatment for calculi in the posterior aspect of the duct or within the gland, particularly when there is lithotripsy and/or sialoendoscopic methods are not available (see below). A submental approach that lessens postoperative scarring, provides good cosmetic outcomes and is no more time consuming than other approaches has also been suggested.[98]

The management of sialolithiasis has been significantly advanced by the introduction of minimally invasive, gland-sparing, therapies, which can often be undertaken under local anaesthesia in children and adults.[99, 100] These methods include interventional SE (that includes endoscopy plus possible laser cutting of intraductal fibrosis), with or without extracorporeal shock wave lithotripsy (ESWL) – although ESWL is not available in the US. Interventional SE may be used for both diagnosis and treatment, and the latter is particularly useful for small distal sialoliths, particularly when there are multiple stones. When SE is unsuccessful for small distal sialoliths, or the sialolith is proximal, mobile or intraparenchymal there may be a need for ESWL followed by SE (with basket retrieval of the fragments). Sialoliths of up to 10 mm will require ESWL and SE and there may be a need for an open surgical approach.[101] Intracorporeal lithotripsy (i.e. sialolith fragmentation with XeClexcimer, flash-lamp pulsed dye, Ho:YAG or erbium:YAG) is now possible as the fibres of the lasers are of small diameter,[102] but the lasers are expensive, the procedure is time-consuming and there is a risk of perforation of the duct and possible abscess formation that will necessitate surgical removal of the gland.[100]

The majority of studies of minimally invasive therapy of sialolithiasis have been of submandibular disease. However, these techniques seem to be equally applicable to parotid sialoliths.[103] The outcomes of interventional sialoendoscopic methods are highly favourable. Surgeon-based results report sialolith removal being achieved in up to 93% of patients and relief of symptoms being reported by up to 95%.[102, 104] Patient-orientated outcomes of minimally invasive procedures report resolution in 86% of patients with sialolithiasis and a significant improvement of quality of life and in the Glasgow Benefit Inventory (GBI).[105] Significant adverse side effects such as upper airway obstruction are rare.[106] Minimally invasive procedures are also applicable to the management of ductal obstruction due to stenosis and mucous plugging.[107–109] Minimally invasive methods are increasingly available across the globe, although the equipment is costly and, as with all new surgical procedures, there is a need for clinicians to be appropriately trained to lessen operating times, minimize morbidity and ensure that surgeon- and patient-reported outcomes are high.

Preliminary data suggest that systemic therapy with the alpha-1-blocker alfuzosin may reduce symptoms associated with ductal stenosis of the parotid gland or post-lithotripsy therapy of parotid sialoliths[110] but there is a need for prospective studies to confirm the exact benefits of this treatment.

KEY POINTS

- Sialolithiasis is a common disorder due to formation of calculi (sialoliths) usually within the ductal system of a gland.
- Sialoliths are more common in the submandibular glands (e.g. 83% of one sample) than the parotid (10%) or sublingual (7%) glands, are more common in females than males, and are much more likely in adults than in children.
- Sialolithiasis presents as pain and swelling, typically in the submandibular gland with gustation or eating. The non-tender swelling is diffuse, develops rapidly, is often associated with a burning-like local pain and resolves over a few hours.
- Long-standing sialolithiasis may give rise to acute suppurative sialadenitis or chronic non-specific sialadenitis.

BEST CLINICAL PRACTICE

- ✓ Investigations include plain radiographs and ultrasound scanning. Sialoendoscopy, where available may also be useful.
- ✓ When small and accessible, manual expression of a stone from the submandibular duct is often feasible, and many can also be removed surgically if within the anterior segment of the submandibular duct, but this carries a risk of stricture formation.
- ✓ Minimally invasive procedures such as sialoendoscopy with or without extracorporeal lithotripsy would seem the highly effective for the removal of many sialoliths.
- ✓ Surgical removal of an affected gland may, however, be the only effective treatment for some cases of sialolithiasis.

OTHER INFLAMMATORY DISORDERS

Chronic sarcoidosis can give rise to xerostomia and salivary gland enlargement in up to 9% of affected patients, which often occurs as part of Heertfordt's syndrome.[111] Parotid gland swelling can also arise (sometimes in association with facial nerve palsy)[112] and while the swelling is usually unilateral, there have been reports of bilateral parotid gland enlargement in sarcoidosis.[113] Reports of Crohn's disease affecting the minor salivary glands[48] are probably unexpected, in view of the widespread nature of oral lesions of the disorder; however, involvement of the major glands is rare. Major salivary gland enlargement due to Wegener's granulomatosis[114] has been reported but again is rare.

DRUG-ASSOCIATED SALIVARY GLAND DISEASE

A wide range of drug-related salivary disorders can arise. These predominantly comprise swelling and/or xerostomia (**Table 46.3**).[115]

Salivary gland swelling due to iodine-based agents

Mild acute sialadenitis (sometimes termed 'iodide mumps') can arise in response to iodine-based contrast media (e.g. for percutaneous coronary interventions).[116–118] This disorder tends to be transient.

Radioactive iodine, used for the treatment of thyroid cancer, can cause transient sialadenitis; indeed, sialadenitis is the most frequent non-thyroid complication of radioactive iodine therapy. This sialadenitis manifests itself as transient xerostomia, and unilateral or bilateral salivary gland enlargement, the parotid being particularly affected.[119] The clinical features develop within 24 hours of iodine therapy and are suggested to resolve within a week. However, inflammation may persist, particularly when doses of radiation have been high, and cause permanent loss of function of one or more glands and give rise to pain and reduced swallowing.[120, 121] One study found that 20% of 852 major salivary glands of 213 patients who had received high dose radioiodine therapy had scintigraphic evidence of reduced function, with good correlation between symptoms of xerostomia and degree of salivary gland dysfunction (particularly when the submandibular glands were affected).[122] The risk of long-term symptomatic sialadenitis secondary to iodine 131 (I-131) may possibly be predicted from sustained high salivary gland-to-background uptake ratio (SUR) of I-131 as demonstrated with scintigraphy of post-therapy glands.[123]

The risk of radioactive iodine-induced sialadenitis can be reduced by use of lemon confectionary – these increase salivary flow, increasing the speed of carriage of radioactive iodine through the glands and hence reducing the time of glandular radiation exposure. There are recent reports of sialoendoscopy being an effective procedure for patients with long-standing sialadenitis of the parotid or submandibular glands secondary to radioiodine therapy, the sialadenitis being due to mucous plugs, ductal debris and/or stenosis.[124] It has been suggested that thymus honey may be a means of lessening sialadenitis of radioiodine, but there is no supportive evidence.[125]

TABLE 46.3 Salivary gland manifestations of drug therapy

Xerostomia	Salivary gland swelling	Sjogren's syndrome	Salivary gland pain	Saliva coloured red
• Atropine and analogues (antimuscarinics) • Tricyclic antidepressants • Serotonin re-uptake inhibitors (SRIs) • Antihistamines • Antiemetics • Tranquillizers (antipsychotics) • Decongestants • Bronchodilators • Appetite suppressants • Amphetamines • Lithium • Omeprazole • HIV protease inhibitors • Disopyramide • Dideoxyinosine • Didanosine • Diuretics • Interleukin-2 • Retinoids • Others	• Anti-thyroid agents • Chlorhexidine • Cimetidine • Clonidine • Ganglion-blocking agents • Insulin • Interferon • Iodides • Isoprenaline • Methyldopa • Nicardipine • Nifedipine • Nitrofurantoin • Oxyphenbutazone • Phenothiazines • Phenylbutazone • Ritodrine • Sulphonamides	• Hydralazine • Levamisole • Practolol • Procainamide • Sucralfate	• Bethanidine • Bretylium • Clonidine • Cytotoxics • Guanethidine • Methyldopa	• Rifabutin • Rifampicin

Salivary gland swelling due to other agents

A wide range of non-iodine-based drugs has been suggested to give rise to transient painful swelling of the salivary glands, and in particular the parotid glands. A recent systematic review of 84 case reports of drug-induced parotitis (i.e. swelling and pain) concluded that l-asparaginase, clozapine and phenylbutazone would seem to be the most likely agents to cause medication-associated swelling of the parotid (and presumably other major) salivary glands.[115] However, many other drugs have probably also given rise to parotitis and include: methyldopa, IFN-α, oxyphenbutazone, ramipril, trimethoprim/sulfamethoxazole, nicardipine, nifedipine, chlormethiazole, methimazole, naproxen, nitrofurantoin, sulfadiazine, captopril, cytarabine, cimetidine, ranitidine and thioridazine.[115, 126] Protease inhibitors of HIV may cause bilateral salivary gland enlargement. Bilateral sialadenitis observed in one adult following naproxen therapy was thought to be allergic in origin as the affected patient also had a cutaneous rash. Salivary gland swelling has been reported in one patient with organophosphorus poisoning.[127]

KEY POINTS

- Mild transient, bilateral, painless sialadenitis may arise with a number of drugs, particularly l-asparaginase, clozapine and phenylbutazone.
- Transient sialadenitis secondary to radioiodine is not uncommon and 20% of patients can develop long-standing symptoms that may warrant sialoendoscopic intervention.
- A wide spectrum of other drugs can cause salivary gland enlargement.

XEROSTOMIA

Dry mouth is a common complaint in many elderly persons.[128–130] This is a probably a consequence of a large number of drugs (more than 500) that can cause xerostomia and the high frequency of polypharmacy in the elderly. The principal mechanism of drug-induced xerostomia reflects anticholinergic or sympathomimetic actions, hence the drugs most commonly implicated in xerostomia are tricyclic antidepressants, benzodiazepines, atropinics, beta-blockers and anti-histamines, and thus it is common in patients treated for hypertensive or mental illness (**Table 46.3**). While often promoted as having less anticholinergic actions than the tricyclics, the serotonin reuptake inhibitors (SRIs) still cause some dry mouth. Some other newer drug therapies, including omeprazole, anti-HIV protease inhibitors, the nucleoside analogue HIV reverse transcriptase inhibitor didanosine, trospium chloride, elliptinium, tramadol and new generation antihistamines, may all cause drug-induced xerostomia.

Some drugs can give rise to primary Sjögren's syndrome-like disease. These include hydralazine, Busulfan, quinidine sulphate and thiobendazole; however, this clinical disease can be transient. In addition, affected patients may not have high levels of immunological markers of Sjögren's syndrome, hence it seems unlikely that this is true Sjögren's syndrome.[131]

KEY POINTS

- There are more than 500 drugs that can cause dry mouth but the principal mechanism of action of xerostomia is anticholinergic and sympathomimetic; therefore, tricyclics, benzodiazepines, atropinics, beta-blockers and anti-histamines are the commonest culprits.
- Drugs may also give rise to salivary gland swellings.

SOME DISORDERS ASSOCIATED WITH ORAL DRYNESS

Radiotherapy-associated salivary gland dysfunction

Xerostomia is the most common complaint of head and neck cancer survivors that have received radiation therapy, with a prevalence of 93% during radiotherapy (RT) and 74–85% following RT.[132] The prevalence of RT-induced xerostomia varies with respect to RT field, dose, regimen and technique. The introduction of intensity-modulated radiation therapy (IMRT) has led to a significant reduction in the prevalence of xerostomia after RT. A recent systematic review comparing the effect of different techniques of RT on xerostomia scores confirmed a significant overall benefit in favour of IMRT with a hazard ratio of 0.76 (95% CI: 0.66, 0.87; $p < 0.05$).[133]

Radiation-induced xerostomia and hyposalivation typically commence early during treatment: during the first week after exposure to 10 Gy, a 30–50% decrease in salivary flow can be observed;[134] after 7 weeks of conventional RT (70 Gy), salivary flow can diminish to approximately 20% of the baseline flow rate.[135] Radiation-induced salivary gland dysfunction is considered irreversible,[136] although a slight recovery of salivary function 12–18 months after treatment completion has been reported.[137]

Two separate mechanisms seem to cause radiation damage to salivary glands. The first mechanism involves selective cell membrane damage resulting in altered intracellular signal transduction and defects in cellular functioning.[138, 139] The second mechanism includes the loss of secretory cells as a result of progenitor cell death.[140]

Whatever the mechanism, the impact of RT-associated hyposalivation upon the mouth and patient well-being can be significant. The rapid reduction in saliva gives rise to dysarthria, dysgeusia, difficult mastication and dysphagia. The inhibition of taste sensation and the impairment of chewing and swallowing can adversely impact upon a patient's nutritional status. Patients may experience intraoral burning sensation and an increased sensitivity to salty and spicy foods. Wearing dentures may be extremely

uncomfortable due to the reduced surface tension between the dry mucosa and the prosthesis.[141] Clinically the lips can become dry, desquamated and fissured, and the oral mucosa atrophic, pale and hyperemic. Patients with long-standing RT-induced xerostomia have an increased risk of caries, oral candidal infections (e.g. acute pseudomembranous candidiasis, angular cheilitis and median rhomboid glossitis) and acute suppurative sialadenitis of the parotid glands.[132, 142, 143]

PREVENTION OF RT-INDUCED HYPOSALIVATION

There remains no means of reversing any RT-induced damage of the salivary glands, although IMRT has reduced the frequency and severity of this complication. Several additional strategies have been proposed to prevent RT-induced salivary damage, particularly the use of the radioprotectant amifostine. A meta-analysis in 2006 of four investigations concluded that amifostine is effective in reducing the chances of developing Grade 2–3 acute xerostomia and late xerostomia by 76% and 67% respectively ($p < 0.05$) compared to placebo.[144] Two later randomized trials confirmed these findings,[145, 146] but two other studies failed to demonstrate a reduction in the incidence of acute and late xerostomia in participants receiving concomitant chemoradiotherapy and amifostine.[147, 148]

Intravenous amifostine can cause adverse side effects such as hypotension (62% of patients) and nausea, which seem to occur less frequently when amifostine is administered subcutaneously.[149] There is no evidence to suggest that amifostine may have a tumour-protective activity and reduce efficacy of anti-cancer therapy.[150] As all of the randomized studies of amifostine involved patients who were receiving conventional RT, is not clear if the addition of amifostine to IMRT is beneficial in reducing xerostomia.

There have been seven randomized double-blind placebo controlled trials investigating the effect of pilocarpine in preventing the incidence of xerostomia when administered during the course of RT and up to 3 months after. Four RCTs showed no significant difference between treatment and placebo groups with respect to xerostomia,[151–154] although a significant improvement in both subjective and objective outcome in treatment versus placebo was observed in others.[155, 156] Scarantino reported a moderate improvement in the average unstimulated salivary flow in the pilocarpine group (P value < 0.05), whereas no difference was noted following parotid stimulation or with regard to subjective outcome.[157] However, detailed information on dose distribution – the most important prognostic factor for developing salivary dysfunction – was generally lacking in the reports of the RCTs. As a consequence, there remains little robust evidence to suggest efficacy of pilocarpine in preventing xerostomia and hyposalivation associated with RT.

A phase II study suggested that following submandibular gland transfer out of the main RT field (to the submental space) 81% of patients had no or minimal xerostomia at the end of RT. Similar results were reported by Zhang et al.[158] A multicentre phase III comparative randomized trial reported better outcomes of submandibular salivary glands transfer with respect to prophylactic pilocarpine[159] in terms of xerostomia reduction. Surgical complication associated with this technique include facial oedema (13.6%), submental swelling (19%), shoulder weakness (4.5%) and neck numbness (6.8%).[160] The long-term efficacy of this approach has been demonstrated in a non-randomized study by Liu et al.[161] However, this invasive procedure is only applicable to patients with cancers requiring surgical resection as part of their treatment and it remains invasive, expensive and time-consuming.[162]

A recent randomized feasibility trial of the potential benefit of acupuncture showed that the individuals receiving acupuncture concurrently to RT had significantly lower xerostomia scores and greater salivary flow rate than the group randomly assigned to receive standard care.[163] The results were in agreement of another small study.[164] At present there remains no good evidence that acupuncture is an effective means of reducing the risk of RT-associated xerostomia.

MANAGEMENT OF RT-INDUCED HYPOSALIVATION

The management of RT-induced salivary gland hypofunction remains challenging, as there is no means of reversing the salivary gland damage. There are a number of promising modalities, but their long-term efficacy requires to be appropriately determined.

Sialagogues

Patients often suck confectionary or chew gum to lessen any oral dryness, but these have only short-term, if any, benefit and can increase the risk of caries if they contain sucrose.

The parasympathomimetic muscarinic secretagogues pilocarpine and cevimeline have been used to treat the xerostomia. Pilocarpine is a relatively non-selective muscarinic receptor agonist whereas cevimeline is an acetylcholine analogue that selectively stimulates the M3 muscarinic receptors in salivary glands.[165]

Cevimeline is not commercially available in Europe but has been shown to increase salivation after head-and-neck irradiation in animal studies and in two RCTs involving human patients. In dosages of 30 mg three times daily, cevimeline-treated subjects had significantly greater increase in the unstimulated salivary flow rate, but not stimulated, than patients receiving placebo. The subjective sensation of xerostomia, assessed via visual analogue scale (VAS) and questionnaire, improved in the cevimeline group but only in one study.[166] In a recent double-blind multicentre, randomized, placebo-controlled study, using the same dosage of cevimeline daily, the investigators observed that the grade of xerostomia decreased for both cevimeline-treated and placebo-treated patients over the course of the treatment.[167]

Six randomized double-blind trials have investigated the efficacy of pilocarpine in the treatment of radiation-induced dry mouth. The majority of these studies reported that pilocarpine (15 mg to 30 mg per day) is effective in lessening the sensation of oral dryness (measured by a VAS) and increasing salivary flow rate in post-RT setting, although adverse side effects are frequent, dose-dependent and can be problematic.[168–173] Topical pilocarpine (spray or lozenge) has been introduced in the attempt to minimize adverse side effects; results of clinical trials were, however, disappointing and did not encourage further investigations.[174, 175]

Oral mucosal lubricant/salivary substitutes

A wide variety of salivary substitutes are commercially available across the globe for the management of xerostomia of any cause. Available salivary substitutes are characterized by different composition and viscosity; they contain mucin, carboxymethylcellulose, hydroxyethylcellulose, xanthan gum, linseed or polyethylene oxide. While these agents may lessen symptoms transiently they have no lasting beneficial effects. The majority of studies of the efficacy of these agents have included a small numbers of patients, have rarely been well-designed RCTs and have had a variety of different end points. As a consequence a recent Cochrane review concluded that no salivary substitute could be recommended for the treatment of long-standing oral dryness of any cause.[176] The major disadvantages of salivary substitutes consist of their transient temporary activity, taste, excessive viscosity and cost. About 40% of patients discontinue the use of saliva substitutes and prefer to sip water as required.[177]

Other strategies

Although some available studies suggested acupuncture could provide symptomatic relief, three independent systematic reviews concluded that there remains insufficient evidence to support acupuncture as a standard treatment for RT-induced dry mouth.[178–180] More recently a multicentre randomized crossover study found that acupuncture, compared with oral care, produced significant reductions in patient reports of severe dry mouth, but no significant changes in either stimulated or unstimulated saliva measurements over the treatment.

A Phase I study of transfer of the *Aquaporin 1* (*Aqp1*) gene via retroductal cannulation of the parotid glands demonstrated an early positive response to adenoviral-mediated *Aqp1* cDNA transfer to a single previously irradiated parotid gland. Six of 11 patients had enhanced parotid flow rates and reduction in dry mouth symptoms.[181]

Electrostimulation of salivary glands via the lingual nerve has been demonstrated to reduce the symptoms of dry mouth and increase salivary flow.[182, 183] The effect of an intra-oral electrostimulating device is presently being assessed in a large RCT of patients with RT-induced salivary dysfunction.

KEY POINTS

- Radiotherapy of head and neck malignancies can cause profound oral dryness and salivary gland acinar destruction when the radiotherapy is directed through the major salivary glands.
- The degree of xerostomia reflects the duration and dose of radiotherapy.
- The xerostomia is irreversible and patients have oral symptoms akin to those of Sjögren's syndrome.

BEST CLINICAL PRACTICE

- ✓ Double blind, randomized controlled trials have conclusively established that oral and perhaps high dose topical pilocarpine may reduce the frequency and severity of radiotherapy-induced xerostomia and associated symptoms.
- ✓ IMRT reduces the frequency and severity of long-term salivary gland hypofunction.
- ✓ Radioprotectants such as amifostine may be of advantage in preventing radiotherapy-induced xerostomia.
- ✓ There remains no effective means of reversing or reducing the effects of established RT-associated xerostomia although a number of potentially promising therapies are presently in trial.

Sjögren's syndrome

Sjögren's syndrome is the second most common autoimmune connective tissue disorder, characterized by xerostomia and xerophthalmia due to profound lymphocytic infiltration into the salivary and lacrimal glands.[184]

Sjogren's syndrome can be broadly classified as primary disease of which there are only symptoms and signs affecting the eye and mouth, and secondary Sjögren's syndrome in which there is xerostomia, xerophthalmia and associated connective tissue disorder – most frequently rheumatoid arthritis or systemic lupus erythematosus. This classification is possibly more simplistic, as many patients with primary Sjögren's have a spectrum of other systemic, and often autoimmune phenomena.

Sjogren's syndrome occurs in 0.2%–3% of populations, seems to have no geographic or ethnic associations but is possibly nine times more common in women than men. Disease is usually detected in the 4th–6th decade of the patient's life, although Sjögren's syndrome can arise in younger adults and occasionally in children under 10 years of age. Sjögren's syndrome probably remains underdiagnosed, possibly reflecting the generally mild nature of the clinical signs in some patients. In addition, there is an increasingly wide range of other disorders that may give rise to clinical features similar to those of Sjögren's syndrome – notably infection with HIV, HCV and chronic graft-versus-host disease. Many asymptomatic people have circulating ANAs relevant to Sjögren's syndrome, but these are generally present in low titre and are not indicative of a future risk of Sjögren's syndrome.

The clinical manifestations of Sjögren's syndrome are well detailed elsewhere[185] and for the purposes of this text, only the oral and salivary features of Sjögren's syndrome

will be discussed. Nevertheless it is important to appreciate that primary disease can give rise to arthralgia (in 75% of patients) and myalgia (45%); that each may arise before the onset of lacrimal or salivary gland symptoms, xerosis (30%), vasculitic and other cutaneous rashes; and that up to 15% of patients may have Raynaud's phenomenon.[185] Thus, like secondary Sjögren's, the primary disease can significantly impact upon the function, well-being and quality of life of affected individuals.

The oral dryness of Sjögren's syndrome (both primary and secondary) can be profound, giving rise to dysarthria and dysphagia. The oral dryness leads to retention of food on the teeth, mucosa and gingiva and thus increases the frequency of caries (particularly cervical disease) and acute gingivitis. Patients with Sjögren's syndrome do not appear to have an increased predisposition to periodontitis per se.

There is an increased liability to candidal infection, notably acute pseudomembranous candidiasis, and median rhomboid glossitis, chronic atrophic candidiasis (denture-associated stomatitis) and angular cheilitis. The long-standing oral dryness of Sjögren's syndrome increases the liability to acute suppurative parotitis.

The poor salivary output can lead to dysgeusia and loss of taste – many affected persons report most foodstuffs taste 'cardboard-like'.

Affected patients may have intermittent swelling of the major salivary glands – notably the parotid glands, this often reflects non-specific inflammatory change within the glands. Solitary enlargement of a salivary gland may reflect chronic sialadenitis, acute suppurative parotitis and, importantly, non-Hodgkin lymphoma.

Sjogren's syndrome is a potentially malignant disorder having a 4.3% risk of malignancy with a standardized incident rate of 18.9. Low-grade marginal-zone lymphoma related to mucosa-associated lymphoid tissue (MALT) is the common lymphoma but others can also be follicle-centre, diffuse B cell lymphoma (DBCL) or lymphoplasmacytoid lymphoma.[186, 187] Risk factors for malignancy in Sjögren's syndrome include splenomegaly, lymphadenopathy, salivary gland enlargement(s), low C4, high β-2 microglobulin, low CD4 T-cells, low IgM and mixed cryoglobulinaemia. Therapy is usually cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) and the outcomes are extremely good, with the 5-year survival rates being 85–100%.

The aetiopathogenesis of Sjögren's syndrome is complex and the precise cause, like many other autoimmune connective tissue disorders, remains unknown. There may be some genetically determined risk factors for its development, but while HIV and HCV infection may give rise to some of the histopathological and clinical features of Sjögren's syndrome, there is no evidence that this autoimmune disorder has an infectious aetiology. Similarly, the malignancies of Sjögren's syndrome are also not thought to be driven by viral or other infections.

DIAGNOSIS

The diagnostic criteria (and hence the relevant investigations) have been subject to considerable debate over the last 10 years. Until recently, there were the American European Consensus Group (AECG) criteria and the American College of Rheumatology (ACR) criteria. A detailed critique of these is available elsewhere[188] but essentially the two systems comprised generally similar diagnostic steps of detection of clinical symptoms and signs of lacrimal and salivary gland dysfunction, specialized investigation of lacrimal and salivary gland structure and function (e.g. radiological and histopathological investigations), the presence of circulating antibodies (anti-Ro and anti-La) and the exclusion of other disorders likely to give rise to a similar clinical picture (e.g. HIV or HCV disease, sarcoidosis, chronic graft-versus-host disease, IgG4 disease and perhaps, although very rarely, amyloidosis).

The AECG classification was the most widely accepted system and formed the basis of the diagnosis of Sjögren's syndrome in possibly the majority of major units across the globe. It was based on the presence of two subjective and two objective criteria of dryness, a salivary gland biopsy grade 3 or 5, and the presence of relevant circulating autoantibodies.[188] Although the AECG classification took into consideration only anti-SSA/-SSB antibodies (Anti-Ro/La), perhaps as expected a number of other autoantibodies are frequently detected in patients with Sjögren's syndrome. The most frequent autoantibodies are antinuclear antibodies (ANA), in up to 80% of the patients, and rheumatoid factors (RF).[189] According to the AECG criteria, salivary gland function could be assessed by unstimulated whole salivary flow, parotid sialography or salivary gland scintigraphy. However, it was shown that the addition of salivary gland ultrasonography can significantly improve the diagnostic performance of the AECG criteria. However in 2016 a unified system was agreed – the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria – that is based upon a scoring system, based upon objective features of LGB histopathology, presence of anti-Ro/La, ocular staining score, Schirmer test and whole saliva flow rate.[190]

Central to the diagnosis of Sjögren's syndrome is the histopathological detection of pathognomonic features within salivary gland tissue. This comprises an infiltrate of mononuclear lymphocytes and other cells of chronic inflammation that are scored as foci of 50 lymphocytes, plasma cells and macrophages (focus lymphadenitis). A focus score of number of foci per 4 mm^2 is determined and for Sjögren's syndrome this must be greater than 1. In addition, unlike IgG4 disease, germinal centres are present in Sjögren's syndrome; indeed, it has been suggested that the presence of germinal centres may be a predictor of non-Hodgkin lymphoma development later in life.[185] As expected there is loss of salivary acini and peri-ductal fibrosis. Histopathological studies are typically performed on labial gland biopsy (LGB) tissue but as might be expected there can be considerable variation in the diagnosis of Sjögren's syndrome by histopathologists from different specialties and centres across the globe.

The classification system(s) may not always be helpful but Sjögren's syndrome is the likely diagnosis when a middle-to-late aged female has signs of ocular and oral dryness, is not on medication or has systemic disease likely to give rise to such a clinical picture and there are some radiological, serological and/or histopathological features suggestive of

such a process. In these circumstances, it would seem to be medicolegally sound to indicate that, while there is a risk that the disease is not Sjögren's syndrome, there is sufficient evidence to warrant the patient and attending clinicians being aware of the possible risk of lymphoma.

TREATMENT

Salivary substitutes

A number of synthetic salivary substitutes are available for the management of xerostomia, a number of them supplemented with calcium, phosphate and fluoride ions in order to prevent demineralization. However, since none of them can completely comply with the highly complex nature of saliva molecules, patients find them generally unsatisfactory – unless the xerostomia is mild. As a consequence of the variable effectiveness of these agents and sometimes their high financial cost to patients, many affected individuals resort to simply sipping water regularly.[189, 190] Moreover, as stated in a comprehensive review by Furness et al,[176] there is no conclusive evidence about their effectiveness for caries prevention.

Chewing gum

Salivary stimulation with sugar-free chewing gum may enhance salivary flow, increasing pH and buffer capacity.[191] The addition of substances such as polyols and carbamide apparently does not improve the caries-preventive effect of the chewing process itself.[192] However, these actions are likely to be transient, and full-denture wearers may be unable to use them – even when the manufacturers state that these agents are suitable for them.[193]

SYSTEMIC AGENTS

Sialagogues

Two muscarinic acetylcholine receptor agonists (pilocarpine and cevimeline) are licensed for the treatment of dry mouth symptoms due to Sjögren's syndrome. These agents stimulate the muscarinic acetylcholine receptors M1 and M3 present on salivary glands, leading to increased secretory function. No study has compared the efficacy and safety of these two drugs.

The clinical benefit of orally administered pilocarpine has been reported in large randomized, placebo-controlled clinical trials. A dosage of 5 mg pilocarpine four times daily resulted in increased whole saliva flow and improved dry mouth, dry eyes, nasal, vaginal and skin dryness.[194–196]

Pilocarpine therapy can also reduce the frequency of oral and ocular symptoms related to xerostomia and xerophthalmia. Data from RCTs have revealed a high frequency of adverse events associated with pilocarpine use, including sweating, increased urinary frequency and flushing (observed in 43%, 10% and 10% of patients, respectively).[197] These data suggest that pilocarpine may be of benefit in the symptomatic management of Sjögren's syndrome, but studies have not included patients with absolute xerostomia, who may have the most severe oral symptoms of long-standing oral dryness.[198]

Several double-blind studies confirmed that cevimeline significantly reduces symptoms of xerostomia and dry eyes in patients with Sjögren's syndrome.[199] The best results in RCTs were achieved with a dose of 30 mg/8 h.[200] The adverse effects of cevimeline mirror those of pilocarpine, with increased gastrointestinal symptoms and rigor but reduced urinary frequency in the case of cevimeline.[201]

Bethanechol, which has both muscarinic and nicotinic agonist actions, was suggested to be of potential use in the management of drug-induced xerostomia, but had never been objectively assessed.[202, 203]

Available data, including that of a placebo-controlled study,[204] suggest that the cholinesterase inhibitor pyridostygmine may be of benefit in the treatment of drug-related xerostomia, although there are no data on the efficacy of this agent in the management of other common disorders giving rise to xerostomia.

Bromhexine (32–48 mg daily) may increase salivary and lacrimal flow in patients with Sjögren's syndrome;[205, 206] however, there are little published data on the precise oral benefits of this therapy other than those of one study and the results of an animal study that suggested that bromhexine does not significantly alter the development or severity of Sjögren's syndrome-like disease.[207]

Biological therapies

Several studies have analyzed the use of biological agents in primary Sjögren's syndrome, including interferon alpha (IFN-a), anti-TNF (tumour necrosis factor) agents and B-cell targeting therapies.

Open label studies suggested that intramuscular (e.g. 1×10^6 IU/week) and parenteral (3×10^6 three times weekly) IFN-a increase the lacrimal and salivary flow of patients with primary and secondary Sjögren's syndrome.[208] Subsequent open and single blinded studies also suggested that IFN-a-containing lozenges (150 IU IFN-a 3 times daily) might reduce the severity of xerostomia in primary and secondary Sjögren's syndrome, clinical benefit being observed in some patients after 9 weeks therapy.[209, 210] Despite the promising results of these preliminary studies, a large RCT – including 497 of the 569 patients treated with IFN-a to date – observed that therapy with IFN-a tended to improve only unstimulated salivary flow and was associated with gastrointestinal adverse events.[211]

Two antiTNF agents, a monoclonal antibody against TNF (infliximab) and a recombinant soluble TNF receptor (etanercept) have been tested as potential therapy for primary Sjögren's syndrome. An openlabel study in 16 patients with Sjögren's syndrome demonstrated the efficacy of infliximab, based on subjective and objective measures.[212] However, the positive results were not confirmed in a subsequent RCT including 103 patients.[213] Etanercept, a recombinant soluble TNF receptor, has been tested in two small studies (one RCT, one prospective) revealing no significant difference in the main sicca characteristics and symptoms associated with Sjögren's syndrome after treatment.[214, 215]

As Sjögren's syndrome is characterized by B-cell hyperactivity, a large number of clinical trials investigated the efficacy of biologic agents with the B-cell depleting antibody rituximab. Two small placebo-controlled

RCTs comprising 47 patients demonstrated considerable improvements in sicca features, salivary flow rate, ocular tests results, fatigue and quality of life scores after treatment with rituximab.[216, 217] More than 10 uncontrolled trials found a reduction in extraglandular features in patients treated with rituximab, compared with placebo.[197] Two large double-blind studies have been undertaken in France and the UK to understand if rituximab can be used in large populations of patients with Sjögren's syndrome. The TRACTISS study in UK should be completed in mid-2014, whereas the results of the TEARS study have been recently published, indicating that rituximab infusions did not produce sustained or substantial alleviation of symptoms or improvement in disease activity in adults with recent-onset or systemic Sjögren's syndrome.[218]

Corticosteroids

While systemic corticosteroids may be beneficial for the management of accompanying connective tissue disorders, there are conflicting data of the precise benefits in reducing the oral or ocular symptoms of Sjögren's syndrome. The results of one randomized study suggested that prednisolone (30 mg on alternate days) was effective[219] in reducing dry mouth symptoms but failed to enhance salivary flow rate. Conversely increased salivary flow rate was demonstrated after corticosteroid irrigation of the major glands (e.g. with prednisolone 2 mg/ml saline).[220] The use of glucocorticoids in clinical practice in primary Sjögren's syndrome is not supported by reliable scientific evidence, since the available studies (all but one uncontrolled) have substantial methodological flaws in their design.[197] Additionally the use of systemic corticosteroids has been associated with a high rate of adverse events, including increased appetite and weight gain,[221] and a twofold higher frequency of diabetes mellitus compared with age-matched and gender-matched individuals without systemic autoimmune diseases.[222]

Antimalarials

Antimalarials such as chloroquine and hydroxychloroquine are widely used for treating Sjögren's syndrome. The main effect seems to be due to inhibition of the antigen-processing ability by macrophages and monocytes, leading to decreased production of interleukin-1 (IL-1), IL-6, TNF-a and interferon-g (IFN-g). Although no large RCTs exist to date, hydroxychloroquine may improve salivary functions by inhibition of glandular cholinesterase with a benefit sustained after 3–9 months of hydroxychloroquine use as reported in a retrospective study.[223–226]

Immunosuppressive agents

The immunosuppressive agents tested in Sjögren's syndrome are cyclophosphamide, azathioprine, methotrexate, leflunomide, mycophenolic acid and cyclosporine A. Unfortunately, present evidence suggests that these agents have limited benefits for sicca features and are associated with an unacceptable rate of adverse events (ranging between 41% and 100%).

The discovery of a soluble ligand of the TNF cytokine family, BAFF/BlyS (B lymphocyte stimulator), which is a prominent factor in B-cell differentiation, homeostasis, and selection, led to consideration of its use as a potential therapeutic target. Very recent data from a two-phase II open-label study on belimumab, a monoclonal anti- body targeting soluble BAFF, suggest this approach may have promise in primary Sjögren's syndrome[227] and further investigation is warranted.

Other strategies

It has been suggested that electrostimulation[228] and acupuncture[229] may increase salivary flow in some patients with Sjögren's syndrome, but good clinical evidence for such claim is lacking. Similarly the *in vivo* potential benefits of gene therapy (utilizing viral vectors of aquaporin) remain unknown. However, a recent study examining the distribution of AQP5 in the labial salivary gland cells concluded that salivary gland hypofunction in Sjögren's syndrome is probably not caused by reduced presence of AQP5.[230]

The results of one placebo-controlled investigation suggested that a herbally-based agent with vitamin supplements (LongoVital®) caused a prolonged increase in unstimulated salivary flow and reduction in Rose Bengal scores in a group of patients with Sjögren's syndrome. It has been suggested that evening primrose oil, rich in fatty acids important in inhibiting 2-series prostaglandins, may enhance salivary flow in some patients with Sjögren's syndrome.[231]

KEY POINTS

Head and neck manifestations of Sjögren's syndrome include:

- xerostomia, which can be profound, giving rise to dysarthria, dysphagia, increased frequency of caries and acute gingivitis but not periodontitis per se
- increased liability to candidal infection – notably acute pseudomembranous candidosis, and median rhomboid glossitis, chronic atrophic candidosis (denture-associated stomatitis) as well as angular cheilitis and acute suppurative parotitis
- dysgeusia and loss of taste – many affected people report most foodstuffs taste 'cardboard-like'
- intermittent swelling of the major salivary glands – notably the parotid glands; this often reflects non-specific inflammatory change within the glands
- solitary enlargement of a salivary gland, which may reflect chronic sialadenitis, acute suppurative parotitis and, importantly, non-Hodgkin lymphoma
- a possible 4% risk of non-Hodgkin lymphoma of major salivary glands.

BEST CLINICAL PRACTICE

- ✓ In treatment of xerostomia in Sjögren's syndrome, there is no evidence at present that systemic and immunologically active agents reduce the oral dryness of Sjögren's syndrome.
- ✓ Therapies such as electrostimulation may be promising therapeutic approaches in the future.

Chronic graft-versus-host disease

Allogeneic hematopoietic stem cell transplantation (allo-HSCT), the transfer of hematopoietic stem cells from one individual to another, is widely employed for the treatment of hematologic malignancies.[232] It has also been used to treat autoimmune or other non-malignant diseases such as immunodeficiency or haemoglobinopathies.[233, 234]

Chronic graft-versus-host disease (cGVHD) is the most important complication in long-term survivors after allogeneic hematopoietic stem cell transplantation, with nearly 50% of patients developing the disease.[235] Symptoms of cGVHD generally present within the first 3 years after HSCT and may affect only one organ or be widespread.[236]

Oral cGVHD can present as oral mucosal lesions (ulcers, lichen-type features and hyperkeratotic plaques) and salivary gland dysfunction. A reduction of the mouth opening due to the perioral deposition of collagen may also occur.[237, 238] The prevalence of oral mucosal lesions after allo-HSCT has been estimated to range between 45% and 83% among cGVHD patients.[239]

Salivary dysfunction of cGVHD has been documented since 1977,[240] and is characterized by Sjögren's syndrome-like manifestations, including hyposecretion of saliva and tears.[241] The early diagnosis of salivary gland dysfunction related to cGVHD is a key factor in the investigation of the cGVHD in other organs, since the clinical features of cGVHD often initially manifest in the mouth.[242]

A recent cross-sectional study revealed that xerostomia was reported by 77% of the patients with cGVHD.[238] Of note, just 27% of these patients had signs of hyposalivation. cGVHD affecting the salivary glands is characterized histopathologically by intralobular periductal lymphocytic infiltration (often with associated fibrosis) and exocytosis of lymphocytes into intralobular ducts and acini.[243] Immunohistochemical studies demonstrate a lymphocytic infiltrate of primarily CD41 and CD81 T lymphocytes as well as the presence of Langerhans cells and CD681 macrophages.[244] Sialochemical changes, with a reduction in the antioxidant capacity[245] and protein content, have also been observed.[246] Oral cGVHD may also be associated with recurrent superficial mucoceles, probably secondary to a damage to excretory salivary ducts.[247]

Patients affected by cGVHD have a higher risk of developing secondary solid tumours, in particular squamous cell carcinoma and salivary gland neoplasms. Kruse et al. reviewed the literature regarding the development of oral malignancy after HSCT over the last 30 years and found that cGVHD was present in 76.6% of cases before they developed the malignancy.[248]

Local therapy of cGVHD of salivary glands is aimed at stimulating the salivary flow with sialagogues and symptoms relief with salivary substitutes. Partially successful therapy is reported for pilocarpine,[249] which, however, can be problematic in patients with graft-versus-host disease involving the gastrointestinal tract for the increased secretion of gastric fluids.[250] It has been reported in a small case-series report that cevimeline treatment might improve xerostomia symptoms in patients with cGVHD.[251]

SOME SALIVARY GLAND SWELLINGS

Sialosis

Sialosis (sometimes termed sialoadenosis) is an uncommon non-neoplastic and non-inflammatory disorder giving rise to bilateral non-painful enlargement of the major salivary glands. Sialosis tends to arise in middle to late life with peak incidence in the 5th and 6th decades, although there have been reports of children being affected.[252, 253] There is a slight female predominance. The parotid glands are typically affected; indeed, often the enlargement is profound. The enlargement develops slowly and there may be some decrease in salivary flow, but xerostomia is not a common or dominant accompanying symptom.

The precise cause is unknown. The underlying pathogenesis is thought to reflect a neuropathy, in particular a neuropathy that results in dysregulation of autonomic control comprising a loss of parasympathetic activity and increased sympathetic drive, leading to an unopposed increase in protein content within the acinar cells.[254] This would thus explain the association of sialosis with diabetes mellitus and perhaps hypothyroidism, malnutrition, and alcoholic and other causes of hepatic cirrhosis. Sialosis has also been described in association with puberty and menopause, and as a reaction to antihypertensive medication. In diabetes mellitus the onset of sialosis seems to be unrelated to the duration or metabolic control of the endocrine disease.[254]

Salivary gland enlargement may affect up to 68% of individuals with bulimia nervosa. The aetiology of increased salivary gland size in bulimia nervosa remains unclear; however, it is suggested that binge eating may result in functional hypertrophy of the salivary glands. Alternatively, mild damage due to passage of fluid into the gland, autonomic neuropathy, endocrine disease or past alcohol use has also been suggested to cause this problem. Of note, a salivary gland enlargement may correlate with the frequency of bulimic symptoms and with levels of serum amylase. There presently remains no specific management for a salivary gland enlargement associated with bulimia nervosa; however, cessation of vomiting is generally associated with resolution of the parotid swelling.

Of interest, oral mucosal disease that affects the opening of Stenson's duct can give rise to painless swelling of one parotid gland, for example if a bulla forms around the opening. There is one report of a patient with pemphigus vulgaris developing recurrent bilateral non-suppurative parotid enlargement secondary to dehydration and possible mucus plug formation secondary to pemphigus vulgaris.[255] Sialosis is histopathologically characterized by acinar cell hypertrophy and atrophy of striated ducts associated with oedema of the interstitial connective tissue. Ultimately there is widespread fatty replacement of acini.

There is no defined therapy for sialosis. Management is typically directed towards correcting any underlying systemic disorder; however, sialosis associated with diabetes

mellitus, other endocrine disorders or hepatic cirrhosis is often resistant to treatment. Rarely, surgical reduction of parotid glands (e.g. superficial parotidectomy) may be required, although this clearly carries some risks. There remains one report of pilocarpine successfully resolving sialosis associated with bulimia nervosa.[256]

KEY POINTS

- Salivary gland enlargement due to sialosis may be associated with diabetes, hypothyroidism, malnutrition, hepatic cirrhosis, puberty, menopause and antihypertensive medication.
- Treatment is often difficult with endocrine and hepatic causes of sialosis being particularly resistant, even if the underlying disorder is addressed. Surgical reduction of the glands may be possible but should be a last-resort intervention

Pneumoparotitis (pneumosialadenitis, wind parotitis)

Pneumoparotitis is characterized by the presence of air within the parotid gland due to the reflux of pressurized air from the mouth into the parotid duct. The swelling may be unilateral or bilateral, and tender or non-tender. There may be crepitus and frothy saliva and air bubbles may emanate from the parotid duct during massage of the gland. The swelling of the parotid gland resolves over minutes to hours, although occasionally may take several days to resolve. Rarely, air may escape from the parotid gland giving rise to subcutaneous emphysema of the face and neck, mediastinum and possible pneumothorax.

Pneumoparotitis is most likely in people where raised intra-oral pressure is common – for example, wind instrumentalists, balloon and glass blowers. There are rare reports of pneumoparotitis secondary to bicycle tyre inflation, dental procedures using air powered equipment, cough associated with chronic obstructive airways disease, cystic fibrosis, whistling, nose blowing and the Valsalva manoeuvre to clear the ears. Occasionally pneumoparotitis may be self-induced, possibly reflecting mental illness. There have been reports of pneumoparotitis due to spirometry and, rarely, pneumoparotitis can arise without an identifiable cause.[257, 258] In most instances there is no associated infection (e.g. acute suppurative sialadenitis) or chronic sialadenitis, but both are possible.[259]

There is often no need for detailed investigation as the history is often suggestive of the cause. Sialography may demonstrate air bubbles within the duct and may also show sialectasis if repeated episodes of pneumoparotitis have resulted in infection and resultant sialadenitis. Ultrasound scanning can demonstrate similar features,[260] as may CT[261, 262] and, presumably, MRI.

Pneumoparotitis rarely warrants active treatment as there are few symptoms, the cause is usually easy to identify and there is a low risk of acute or chronic sialadenitis. Cessation of the factor causing the increase in intra-oral pressure results in generally complete resolution of signs but as this may interfere in the employment of musicians it is unlikely that many will follow this path. Pneumoparotitis is rare.

KEY POINTS

- Any persistent or significant rise in intra-oral pressure may cause pneumoparotitis.
- Management involves avoiding raised intra-oral pressures.

RANULA

Ranulas are cystic lesions that develop from extravasation of saliva, possibly following trauma to the sublingual gland or obstruction of the ducts.[263] The term ranula is the Latin word for a small frog, and it is used for the condition because it causes croaking speech and an oral ranula resembles a frog's belly. Ranulas have a prevalence of 0.2 cases per 1000 people.[264] Ranulas are connective tissue lined swelling of extravasated saliva. They usually manifest as a soft, blue-tinged swelling of the floor of mouth, are detected in the second decade of life and may have a female predisposition – although there are rare reports of ranulas in neonates that have required *ex utero* intrapartum treatment (EXIT). Lesions may be classified as simple (or intra-oral) when they lie above the mylohyoid, and deep or plunging when they invade below this muscle.[265] Plunging ranulas usually manifest as a painless persistent or recurrent neck swelling and, rarely, may spread to the upper chest wall. Respiratory obstruction secondary to a simple or plunging ranula is rare.[266]

A congenital predisposition to the development of plunging ranula has been suggested based on the observation of a larger number of ranulas in some ethnic groups and among siblings.[267] An increased occurrence of ranulas has been documented in HIV-infected individuals, which could be due to a blockage of the salivary gland by inflammation and peri-ductal fibrosis as part of HIV-associated salivary gland disease.[15]

Diagnostic confirmation typically necessitates radiological imaging appropriate for soft tissue swellings, possibly together with cytological examination of FNAB.[268]

Several surgical approaches and techniques for oral and plunging ranulas in paediatric and adult patients have been proposed, with a rate of success that ranges from 0% to 100%.[263] Among these, excision of the sublingual gland is associated with the lowest rate of recurrent disease, although it might give rise to several complications.[269] These include injury to the lingual nerve or Wharton duct, with possible stenosis, obstructive sialadenitis and ductal laceration. Bleeding and hematoma have also been observed following this procedure.[270]

A medical treatment for ranula based on the oral administration of nickel gluconate has been described and tested by Garofalo et al.[271] At low doses, nickel is thought to promote enzymatic functions and tissue-repairing process in salivary glands. The authors reported promising results in their case series, with no recurrence and lower incidence of side effects after medical treatment.[271]

HETEROTOPIC SALIVARY GLAND DISEASE

Heterotopic salivary gland disease is the presence of salivary gland tissue arising outside the normal distribution of the minor and major salivary glands (hence excludes accessory salivary gland tissue and salivary gland material associated with branchial cleft anomalies).[272] Heterotopic salivary gland tissue has been documented in the middle ear,[273] larynx,[274] lower neck,[275] chest wall,[276] sternoclavicular joint, and brain.[277] The exact mechanism of salivary gland heterotopia is uncertain, with a possible explanation being the entrapment of salivary tissue during embryogenesis or heteroplastic changes of epithelial tissue.[278] Generally these are asymptomatic incidental findings, although they can manifest as a mass or draining sinus.

Radiological imaging with or without histopathological examination of lesional tissue are the usual diagnostic procedures with complete surgical excision being the treatment of choice.[276] Neoplastic transformation of heterotopic salivary gland tissue is possible but rare.[279]

LYMPHOEPITHELIAL LESION

Lymphoepithelial lesion is an uncommon disorder that manifests itself as a recurrent or persistent swelling typically of the parotid gland. The submandibular gland may be affected in approximately 15% of individuals. Generally the swelling is non-painful.

Affected patients do not have clinical features of Sjögren's syndrome or features of other disorders likely to give rise to xerostomia, although they do have an increased risk of non-Hodgkin lymphoma. The histopathological diagnosis of BLEL is important as the clinical features mimic those of salivary gland malignancy, and histopathologically there can be some confusion with lymphomas. Surgical excision is the usual treatment of a BLEL.[280]

EXCESS SALIVATION (SIALORRHOEA)

Although excess salivation is uncommon, it can be distressing to both patients and carers. True excess salivation is extremely unusual, although it may sometimes arise following drug therapy. The majority of patients with excess salivation have difficulties in salivary control rather than hypersalivation.

There are no specific investigations for sialorrhoea, and the cause is often established from the clinical history.

There are few controlled studies of possible treatment for excess salivation. Young adults with likely long-term illness such as cerebral palsy may benefit from surgical relocation of the submandibular ducts together with removal of the sublingual glands. Likewise, the parotid ducts may be relocated to pass out in the tonsillar fossa.

Anticholinergic agents such as transdermal scopolamine or benztropine have been suggested to be of long-term benefit but more recently intra-glandular injection of botulin toxin has been found to be of application for the treatment of hypersalivation in adults[281, 282] and children[283] with a myotropic lateral sclerosis, cerebral palsy, Parkinson's disease and other causes of excess salivation.

A lower dose of RT (8–12.5 Gy) has been suggested to be effective for excess salivation of patients with amyotropic RT; indeed, in view of the often shortened lifespan of affected individuals, this may be a useful treatment for this disabling salivary disorder.

DROOLING

Drooling is the unintentional loss of saliva from the mouth,[284] common in normally developed babies but considered abnormal after age 4.[285] Drooling may arise as a consequence of impaired neuromuscular function, though less frequently it can be due to an increased production of saliva (idiopathic or drug-induced). In children, the most common cause of drooling is cerebral palsy, which persists in 37–58% of these individuals.[286, 287] In adults, drooling can be observed in 45% of patients affected by Parkinson's disease.[288] Neurological disorders also associated with drooling are cerebral palsy, amyotrophic lateral sclerosis and facial palsy.[289]

Drooling can give rise to a wide spectrum of clinical and functional complications such as impaired speech and eating, perioral skin breakdown, bad odour and infection. Aspiration-related and pulmonary complications are possible.[290]

Drooling is known to be difficult to treat. Management can be conservative or more invasive. Conservative treatments include changes in diet or habits, oral-motor exercises, intra-oral devices such as palatal training devices, and medical treatments such as botulinum toxin injections. More invasive treatments include surgery or radiation.

Behaviour modification to promote swallowing has been advocated for many decades but results are inconsistent, it requires motivation and is time-consuming.[291] Pharmacological therapy for drooling encompasses the use of anticholinergic agents, such as glycopyrrolate, benztropine andscopolamine to decrease saliva secretion through the parasympathetic autonomic nervous system. A systematic review investigated the efficacy of oral agents in the treatment of drooling concluding that, although effective, no one drug was preferable.[292]

Recently botulinum toxin, a neurotoxin that prevents the secretion of saliva by inhibiting the release of presynaptic acetylcholine, has emerged as a potential treatment for the management of drooling. The effectiveness of botulinum toxin has been reported in several clinical trials. A recent meta-analysis (2013) concluded that botulinum toxin decreases the severity of drooling with statistical significance in both adult and paediatric populations.[293] The duration of effect can vary from 6 weeks to 6 months.[294] However, there remains the need to establish the ideal dose and form of application. Botulinum toxin treatment may cause increased saliva thickness (3.9%), dysphagia (3.3%), xerostomia (dry mouth) (3.3%) and pneumonia (2.2%).[293]

Various surgical procedures have been suggested for treatment of drooling. These procedures all encompass an alteration in the anatomy of the salivary glands and include salivary gland excision, denervation of the salivary glands, and relocation or ligation of the salivary ducts.[295, 296] The most common surgical approach is the submandibular duct relocation. Ranula formation and submandibular duct obstruction have been reported in 8% of patients after submandibular duct relocation.[297] Resection of the major glands are not without their side effects, of course, the most frequent being xerostomia, visible scar and facial nerve weakness.[290, 298]

Radiation is rarely applied for the risk of xerostomia, loss of taste and development of malignancy of the approach.[299, 300] It is typically reserved for elderly patients who are not candidates for surgery and cannot tolerate medical therapies.[301]

KEY POINTS

- Sialorrhoea is uncommon.
- The common causes of drooling include cerebral palsy, amylotropic lateral sclerosis, traumatic brain injury, stroke and Parkinson's disease.
- Persistent drooling leads to angular cheilitis, excoriation of the lower facial skin and wetting of clothes.
- There are no specific investigations for sialorrhoea, the cause often being established from the clinical history.

BEST CLINICAL PRACTICE

- ✓ Young adults with likely long-term illness such as cerebral palsy may benefit from surgical relocation of the submandibular ducts together with removal of the sublingual glands. Likewise, the parotid ducts may be relocated to pass out in the tonsillar fossa.
- ✓ Intra-glandular injection of botulin toxin has been found to be of application for the treatment of hypersalivation in adults and children with amylotropic lateral sclerosis, cerebral palsy, Parkinson's disease and other causes of excess salivation.
- ✓ A low dose radiotherapy (8–12.5 Gy) is useful for patients with shortened lifespan and a disabling salivary disorder.
- ✓ Transdermal scopolamine or benztropine may be helpful

FREY'S SYNDROME (GUSTATORY SWEATING)

Frey's syndrome (FS), also called gustatory sweating or auriculotemporal syndrome, is reported as the most disturbing sequela in patients at more than 5 years after parotid surgery for benign disease.[302] It is characterized by facial warmth, flushing and sweating over the distribution of the auriculotemporal nerve and/or greater auricular nerve, stimulated by any gustatory stimulus.[303] The information found in the literature concerning the incidence of FS shows a great variation, ranging from 2.6%[304] up to 97.6%.[305] Rustemeyer et al.[302] reported that 23.5% of patients undergoing parotidectomy developed FS an average of 12 months after surgery, but only 44% of these patients were symptomatic. Gustatory sweating syndrome secondary to submandibular gland surgery or trauma is also possible, although they do not involve the auriculotemporal nerve.

The aetiology of FS is not entirely known. It is commonly explained as 'misdirected nervous regeneration'. During parotidectomy, the postganglionic parasympathetic fibres of the auriculotemporal nerve, which supplies the parotid gland, and sympathetic fibres supplying local sweat glands are sectioned. During the regeneration process, parasympathetic fibres may grow along the distal ends of sympathetic fibres to the skin vessels and sweat glands. Thus, a gustatory stimulus produces sweating accompanied by flushing and heating.[306, 307] The time necessary to regenerate the postganglionic parasympathetic nerve fibres could explain the latent period between intra-operative facial nerve injury and the onset of FS; in most reports, this interval has ranged from 5 weeks to several months after parotid gland surgery, but unusual cases have presented many decades (30 years) after surgery.[308]

Although this syndrome has been reported primarily after parotid gland surgery,[309] it has also been observed after temporomandibular joint trauma or surgery[303, 310, 311] and carotid endarterectomy.[312] In childhood it can be a complication of forceps injury, frequently misdiagnosed as food allergy.[313]

Minor's starch iodine test, allowing visual confirmation of the blue-black reaction in the sweating area, is thought to be the gold standard of diagnosis.[314]

Many patients with FS do not wish any therapy.[315] Currently, the most effective treatment is the subcutaneous infiltration of botulinum toxin A in the affected area, with a benefit lasting for 1.5 years for 60% of the patients.[316]

Data concerning the efficacy of prevention strategies for FS remain inconclusive. A systematic review concerning the effectiveness of the a surgical approach (sternocleidomastoid muscle flap) to prevent FS after parotidectomy suggests that total prevention is unlikely to be achieved with any technique because FS is found, to some degree, in all treated sample groups.[317]

KEY POINTS

- Gustatory sweating syndrome is a rare sequela of salivary gland surgery.
- Gustatory sweating syndrome presents as facial warmth, flushing and sweating over the distribution of the auriculotemporal nerve following a gustatory stimulus.
- Botulinum toxin injection may be helpful if treatment is needed.

SOME MINOR SALIVARY GLAND DISORDERS

Mucoceles

Mucoceles are probably the most common disorder of the minor salivary glands, typically presenting as single blue or translucent sessile swellings on the lower lip.

Mucoceles occur in both genders and in all age groups, the peak age of incidence being between 10 and 29 years. They are rare in infants, although can occur in neonates.

The lateral aspect of the lower lip is the most common site of recurrence of mucoceles, but other common sites include the floor of mouth and the ventral surface of the tongue. The usual clinical presentation is of a single, recurrent, fluctuant, painless, well circumscribed bluish swelling that ruptures easily to release viscid salty mucus. Occasionally mucoceles can be multiple or develop suddenly at mealtimes.

The majority of mucoceles are the extravasation type, in which duct damage causes pooling of mucus in the adjacent connective tissue. Retention mucoceles, the less common variant, arise after partial or complete obstruction of the excretory duct (e.g. a sialolith – although rarely clinically or histopathologically detected) leading to retention of glandular secretions and dilation of the duct. Extravasation mucoceles may be more frequent in young patients, whereas retention mucoceles may occur most often in middle to late life.

Some mucoceles may resolve spontaneously but large, recurrent or unsightly mucoceles often require to be surgically excised, or removed by laser or cryotherapy. Other therapies of less well proven efficacy include intralesional corticosteroid injections and gamma-linolenic (oil of evening primrose).[318]

Subacute necrotizing sialadenitis

Subacute necrotizing sialadenitis (SANS) is a rare non-specific inflammatory disorder of adults of unknown aetiology affecting the minor salivary glands. It presents as a rapid onset painful, non-ulcerated swelling of minor palatal salivary glands. Almost all reported affected patients have been male. SANS tends to be self-limiting, symptoms and signs resolving within 2 weeks, and is not associated with necrotizing sialometaplasia.[319–321]

Necrotizing sialometaplasia

Necrotizing sialometaplasia is an uncommon disorder that typically affects the minor salivary glands of the palate, although may rarely involve other minor salivary glands and, very unusually, the major salivary glands.[322] It presents typically as a palatal swelling that breaks down to give rise to localized, irregular ulceration.

Lesions can be large – up to 5 cm in diameter – and can give rise to local paraesthesia or anaesthesia; however, they generally heal within 4–90 days. Affected patients may have systemic features such as pyrexia, chills and malaise. Despite the sometimes extensive area of ulceration, bony involvement is rare. There have been rare reports of airway obstruction and excessive bleeding with hypovolaemia due to large areas of sialometaplasia.[323]

Necrotizing sialometaplasia is thought to arise from local ischaemia, possibly caused by direct trauma (e.g. from a denture or as part of an anorexia nervosa bulimia nervosa pattern),[324] placement of dental local anaesthetics, recreational cocaine use, RT, alcohol, tobacco smoking, upper respiratory tract infections, allergic disease, oral intubation and other surgical procedures, or sickle cell disease.

Of note, it may be clinically and histologically confused with malignancies such as a squamous cell carcinoma, mucoepidermoid carcinoma or non-Hodgkin lymphoma. Necrotizing sialometaplasia is characterized histopathologically by acinar necrosis with squamous metaplasia of the ductal epithelium. This latter feature underlies the possible diagnostic confusion between necrotizing sialometaplasia and squamous cell carcinoma.

Necrotizing sialometaplasia is usually self-limiting; however, in view of the possible clinical similarity between necrotizing sialometaplasia and oral malignancy, careful histopathological examination of biopsy material is essential. Any likely causative factors should be identified and removed.[325]

Cheilitis glandularis

Cheilitis glandularis (suppurative stomatitis glandularis) is a rare disorder that usually arises in adults (but can occur in children) manifesting as labial swelling and ulceration. The disease is localized almost exclusively to the lower lip, especially the contact zone between the lips, although there have been occasional reports of the condition affecting the upper lips and palate.[326] Affected individuals usually have swelling, eversion and protrusion of the lower lip secondary to inflammation of the minor labial salivary glands. The orifices of the minor salivary gland ducts are dilated and inflamed, and a mucopurulent secretion may be expelled from the ducts when the lip is compressed.

The precise aetiology remains unknown, although associations with syphilis and other more ill-defined bacterial infections, poor hygiene, tobacco use, actinic exposure and emotional disturbance have been suggested. A genetic predisposition has also been proposed but there are no substantial supportive data. The connection with actinic damage is perhaps supported by 6 of 22 affected patients in one series being albino.[327]

Cheilitis glandularis may be classified into three types based upon the severity of the disease – simplex, superficial suppurative and deep suppurative. The last two types represent a stage where there is bacterial infection, being clinically characterized by increased inflammation, suppuration and ulceration of the lip. The deep suppurative type has also been termed cheilitis apostematosa or myxadenitis labialis, while the superficial suppurative has also been termed Baelz's disease.

The histopathological findings are non-specific but include local chronic sialadenitis, mucous/oncocytic metaplasia and mucin in ducts. Dysplastic epithelial changes may occasionally occur, but although associated carcinoma of the lower lip has been reported, cheilitis glandularis is still considered to be a benign disorder that should be managed by conservative means.[326–328] There are no detailed randomized studies of the treatment and surgery; for example, vermilionectomy has been suggested to be effective. However, albeit rarely, mucoceles can occur following surgery.

The term suppurative stomatitis glandularis has also been suggested to describe cheilitis glandularis. Indeed, the terminology used in the previous relevant literature is confusing. Granulomatous cheilitis is unrelated to cheilitis glandularis, the former being a localized presentation of sarcoidosis, orofacial granulomatosis or Crohn's disease.[329]

Inclusion of salivary gland tissue

Cyst-like areas of radiolucency are seen in the region of the angle of the mandible. Such inclusions are also possibly the origin of rare intraosseous salivary gland tumours.[330]

FUTURE RESEARCH

There are many unknowns in the aetiology and treatment of non-neoplastic salivary gland disease. Perhaps the most relevant areas of investigation for the treatment of such disease remain:

- the establishment of the pathogenesis of HCV-related sialadenitis
- the determination of the aetiology of Sjögren's syndrome
- the development of strategies for the prevention and treatment of radiotherapy-induced salivary gland disease and, indeed, other causes of non-drug-related oral dryness.

KEY POINTS

- Non-neoplastic disease of the salivary glands is dominated by the symptom of oral dryness (xerostomia) and/or the sign of salivary gland enlargement.
- Oral dryness is typically caused by drug therapy or Sjögren's syndrome.
- Enlargement of one submandibular gland is likely to be sialolithiasis, while enlargement of one or both parotid gland(s) has a much wider range of non-malignant causes.
- While the investigation of salivary gland disease has advanced greatly there remains no reliably effective means of lessening oral dryness that is unrelated to drug therapy.

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CHAPTER 47

ANATOMY OF THE PHARYNX AND OESOPHAGUS

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SEARCH STRATEGY

Data in this chapter are based on a PubMed search using the keywords: pharynx, nasopharynx, oropharynx, hypopharynx, laryngopharynx, constrictor, sphincter, elevator, oesophagus, adenoidectomy, tonsils, adenoids, Waldeyer's ring, soft palate, cervical oesophagus, thoracic oesophagus, abdominal oesophagus, Valsalva, tonsillectomy and post-tonsillectomy bleed.

ANATOMY OF THE PHARYNX

INTRODUCTION

Shaped like an inverted cone, the 12–14 cm long musculofascial tube that is the pharynx hangs down from the pharyngeal tubercle at the skull base and fuses with the oesophagus below at the level of the lower border of the cricoid cartilage. It is the continuation of the common pathway for respiration and digestion that begins with the oral cavity.

The pharynx acts as a single physiological structure in its role as the common aerodigestive pathway and its mucosal lining is shared with that of the auditory tubes, the nasal cavity, the oral cavity and the larynx. Functionally, in addition to directing air into the laryngeal inlet and food into the digestive tract, via the auditory tube, it also assists in the equalization of pressure within the middle ear and aids in vocalization of sound to facilitate speech.

An understanding of the anatomy of this region is vital to the otolaryngologist. Inflammatory and neoplastic diseases of the pharynx and oesophagus are common in the general population and form a substantial proportion of surgical work. With the advent of transoral surgery for pharyngeal cancers, in addition to the conventional knowledge of anatomy of this region, there is a need to appreciate the anatomy from 'inside out'.

SUBDIVISIONS OF THE PHARYNX

Anatomically, the pharynx is divided into distinctive subdivisions – the nasopharynx, the oropharynx and the hypopharynx (laryngopharynx) – the boundaries of which are purely arbitrary and based on their anterior communications with the respective nasal, oral and laryngeal cavities (**Figure 47.1**). Each of these subdivisions has a variety of structures within them of clinical relevance. The muscular wall and the layers of the wall, common to all the subdivisions, will be dealt with in separate sections.

Nasopharynx

The superior aspect of the pharynx, the region above the soft palate and behind the choanae, is the nasopharynx. This space has a roof, two lateral walls, a posterior wall and a floor, and it communicates with the oropharynx

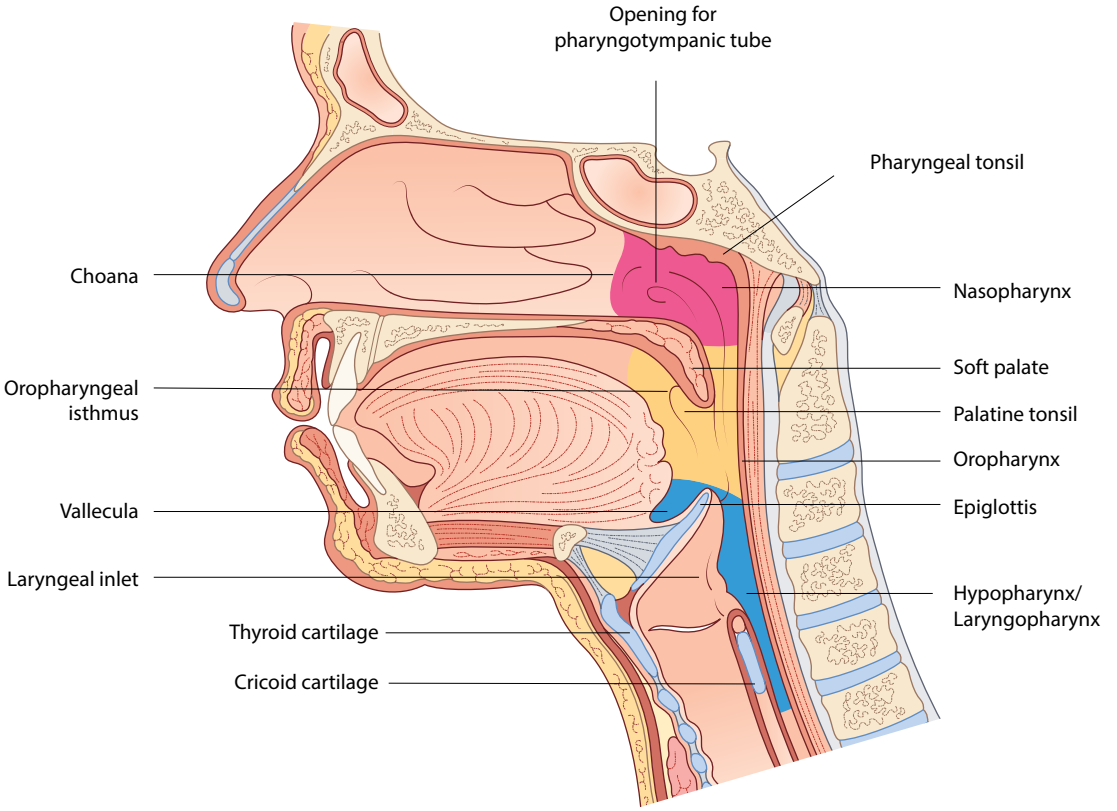


Figure 47.1 Sagittal section of the head and neck.

below via the pharyngeal isthmus posterior to the soft palate and anterior to the posterior pharyngeal wall. The important subsites within this space are the opening for the pharyngotympanic tube (also known as the auditory tube or the Eustachian tube), the pharyngeal recesses and the nasopharyngeal tonsils (or the adenoids).

The nasal cavity communicates posteriorly with this space and, thus, the anterior boundary of the nasopharynx is that formed by the right and left posterior nasal apertures, or the choanae, separated in the midline by the vomer, its bony septum. The posterior ends of the inferior and middle conchae from the lateral walls of the nasal cavity project medially into each choana. With the exception of the soft palate, the walls of the nasopharynx are rigid and the cavity thus always patent, allowing for unhindered flow of air, in sharp contrast to the cavities of the oropharynx and the laryngopharynx, which open and close on swallowing and with respiration.

The roof and posterior wall of the nasopharynx are contiguous due to the sloping nature of the inferior body of the sphenoid bone and the basilar part of the occipital bone, and it continues down to the level of the junction of the hard and soft palate. The bony deep structures within this region are often referred to as basisphenoid. Within the mucous membrane of the roof and posterior walls is a collection of lymphoid tissue known as the nasopharyngeal tonsil, maximal in size during childhood and contributing to the defence of the upper respiratory tract. Unlike oropharyngeal tonsillar tissue, there is no clear plane of cleavage in the nasopharyngeal tonsil, which makes excision less precise and complete during adenoidectomy (see **Boxes 47.1** and **47.2**).

The floor of the nasopharynx is formed by the soft palate (dealt with in detail below). The posterior and lateral walls of the nasopharynx are composed predominantly of the superior constrictor muscle and its overlying mucosa. Within the lateral wall sits the pharyngeal orifice of the pharyngotympanic tube, approximately 1–1.5 cm from the posterior end of the inferior turbinate at the level of the superior border of the palate – or the floor of the nose. This tube connecting the middle ear and the nasopharynx allows, by its transient opening and closing, the equalization of air pressure on both sides of the tympanic membrane. It is formed primarily by fibrous tissue and cartilage but also by bone, and it is more horizontal and approximately half its adult length at birth, allowing for easier spread of infection back and forth from the nasopharynx into the middle ear cavity in this age group. The orifice of this tube is covered with a cartilaginous projection, the torus tubaris, orientated posterosuperiorly, with the longer extension situated posteriorly and extending in a craniocaudal direction, which gives it its comma-shaped appearance. It also forms the anterior boundary of the pharyngeal recess, or fossa of Rosenmüller, situated posterosuperior to

BOX 47.1 Within the nasopharynx: the nasopharyngeal tonsils or adenoids

Size	Rapid growth during infancy, involutes during ages 8–10 and atrophies in later life. At its largest at age 5
Site	Roof and posterior wall of nasopharynx
Shape	Described as a truncated pyramid, with a vertically oriented median cleft, its apex directed towards the nasal septum and its base at the junction of the roof and posterior wall of the nasopharynx
Surface	Free surface has anteriorly and laterally radiating folds from the bursa of Luschka – a median blind recess or the pharyngeal bursa. This extends deep into the tonsil in a posterior and superior direction
Structure	Predominantly respiratory epithelium, ciliated in nature, on its lateral and inferior parts. Also contains occasional patches of keratinized stratified squamous epithelium. Anchored at its superior pole via a connective tissue hemicapsule onto which the tonsillar fibrous framework attaches
Supply	An anastomosis of the following arteries: ascending pharyngeal and ascending palatine arteries, tonsillar branch of facial artery, pharyngeal branch of maxillary artery and artery of pterygoid canal. Occasionally, an emissary vessel (off inferior hypophysial artery) to basisphenoid bone supplies the nasopharyngeal bed – a possible culprit in persistent haemorrhaging post adenoidectomy
Significance	Part of Waldeyer's ring of tonsillar tissue, contributing to the defence system of the upper respiratory tract
Surgical/clinical considerations	Inflammation of this tissue: **adenoiditis**, predominantly in children (peak age 5) when it causes persistent chronic otitis media infections, problems with nose breathing and intermittent sleep apnoea
	Adenoidectomy or the surgical removal of nasopharyngeal tonsils: blind curettage, suction diathermy or suction micro-debridement. During blind curettage, important to avoid hyperextending the cervical spine as arch of the atlas (cervical vertebra C1) may pierce through prevertebral fascia and cause infection and instability of the C-spine

the torus tubaris, which is the site of the tubal tonsils which, when present, constitute an additional component of Waldeyer's ring of tonsillar tissue (**Figure 47.2**). The superior constrictor and overlying mucosa forms its floor while the skull base forms the superior and posterior border. This fossa is the commonest site of the origin of nasopharyngeal carcinomas and should be targeted in biopsies of the nasopharynx in the context of carcinoma of the unknown primary. The fold of mucosa projecting inferiorly from the cartilaginous ridge of the pharyngotympanic orifice is the salpingopharyngeal fold, formed by overlying mucosa and the levator veli palatini and salpingopharyngeus muscles, the latter of which passes inferiorly and laterally to merge with the lateral pharyngeal wall.

Anteriorly, the epithelium of the nasopharyngeal wall is predominantly respiratory in nature, ciliated and pseudostratified, with goblet cells. More posteriorly, non-keratinized stratified squamous epithelium predominates and this continues into the oro- and laryngopharynx. At the point where the two types of epithelium meet – the transitional zone – instead of cilia, columnar epithelium with short microvilli are present, continuing superiorly to meet the nasal septum and laterally the pharyngotympanic tubal orifice towards the soft palate and lateral pharyngeal wall.

The sensory innervation of the nasopharynx is via the pharyngeal branch of the maxillary nerve, transmitted from the middle ear cavity via the pharyngotympanic tube. Posterior to the tubal orifice, the pharyngeal branch of the pterygopalatine ganglion supplies the majority of the mucosa. This branch passes through the palatovaginal canal along with a branch of the maxillary artery, its pharyngeal branch.

Oropharynx

The oropharynx continues caudally from the nasopharynx, connected to it via the pharyngeal isthmus. The boundary between the naso- and oropharynx is the start of the common aerodigestive tract and the site where the oral cavity, larynx and hypopharynx communicate. It therefore has dual functionality, coordinating breathing and swallowing. The space has anterior, lateral, posterior and superior walls and it communicates with the oral cavity via the oropharyngeal isthmus. The clinically relevant anatomical subsites within the oropharynx are the base of tongue and valleculae in the anterior wall, the palatine tonsils, the tonsillar fossae, the tonsillar (faucial) pillars and the glossotonsillar sulci in the lateral walls, and the inferior surface of the soft palate and the uvula in the superior part of the space. In addition to tonsillitis and peritonsillar abscesses within this region, the palatine tonsils and base of tongue are common sites of malignancy, in particular human papillomavirus-associated squamous cell carcinoma. Foreign bodies (typically, fish bones or food debris) may become lodged either in the palatine tonsils or in the valleculae.

The clinical boundaries of the oropharynx differ from those commonly indicated in anatomy textbooks as described above. It is bounded superiorly by a horizontal line drawn at the level of the hard palate, inferiorly by a horizontal line drawn through the floor of the valleculae and anteriorly by a vertical plane defined by anterior boundary of the palatoglossal folds (which contain the palatoglossus muscles and the overlying mucosa) to include the posterior third of the dorsum of the tongue. The posterior wall of the oropharynx is the extent of the posterior pharyngeal wall bounded by the imaginary lines drawn from the superior and inferior limits described above.

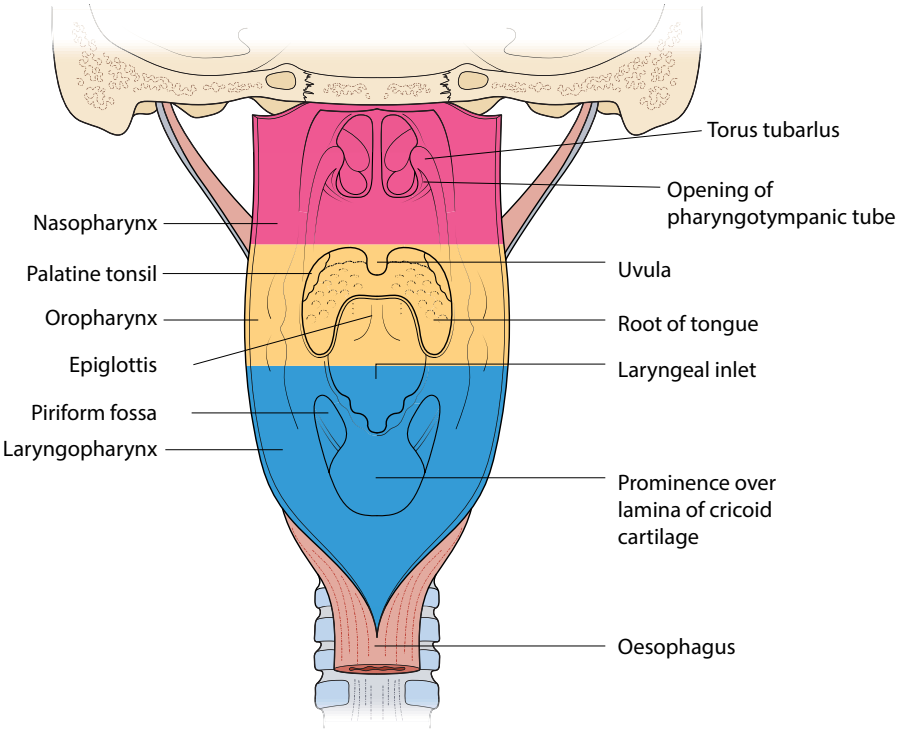


Figure 47.2 Features of the pharynx (posterior view with the pharyngeal wall opened).

The superior boundary of the oropharynx is the soft palate. This structure is suspended from the anterior bony projection of the palatine part of the hard palate and is essentially a mobile flap that opens and closes on swallowing. The point of demarcation between the soft and hard palates can be felt with ease and may demonstrate a change in colour, the soft palate possessing a yellowish discolouration on a base of a darker region than that of the anterior hard palate. Within the thick mucosal fold that is the soft palate, the soft palate muscles – five in total – and the thin and fibrous palatine aponeurosis, the neurovascular structures, the mucous glands and the lymphatics all lie in close proximity. All the soft palate muscles are attached to the palatine aponeurosis, which also encloses the small musculus uvulae muscle close to the midline. In the midline, the conical-shaped uvula containing the small musculus uvulae muscle forms the inferior free border and dangles down to extend into the oropharyngeal isthmus. The lateral aspects of the soft palate wall blend in with the lateral pharyngeal wall.

The lateral walls of the oropharynx have two prominent folds bilaterally, the faucial pillars. The anterior communication between the oral cavity and the oropharynx is via the oropharyngeal isthmus and is demarcated by the bilateral anterior palatoglossal arches, their underlying muscles and the horizontal intrinsic tongue musculature. Situated more posteriorly are the palatopharyngeal arches comprising the palatopharyngeus muscle and its overlying mucosal layer (**Figure 47.3**). Within the space between these two mucosal folds sit the palatine tonsils in the tonsillar fossae, the third component of Waldeyer's ring of lymphoid tissue.

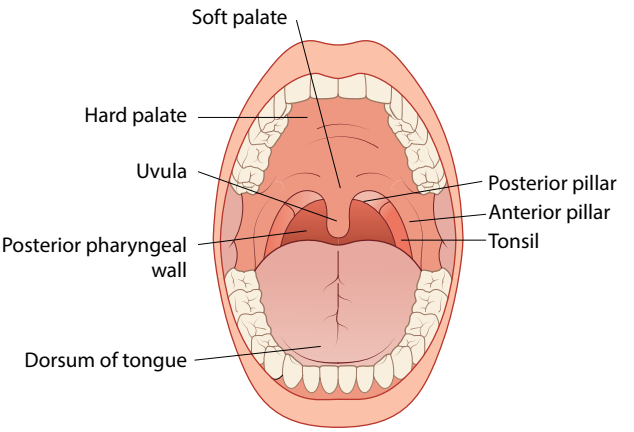


Figure 47.3 Oropharyngeal isthmus and tongue.

The posterior third of the dorsum of the tongue slopes downwards from the sulcus terminalis to form the anterior vallecular wall of the oropharynx (**Figure 47.4**). The nodular appearance of the mucous membrane in this region is largely due to the aggregations of lymphoid follicles – the lingual tonsils – which complete Waldeyer's ring. A midline ridge, or fold, of mucous membrane extending from the tongue to the anterior lingual surface of the epiglottis, the median glossoepiglottic fold, divides the valleculae into two shallow right and left depressions. Similar mucosal folds limit the valleculae laterally. These lateral glossoepiglottic folds extend from the lateral aspect of the epiglottis to the pharyngeal wall, not to the tongue as the name would suggest. These are sometimes referred to as the pharyngoepiglottic folds. The nerve supply in

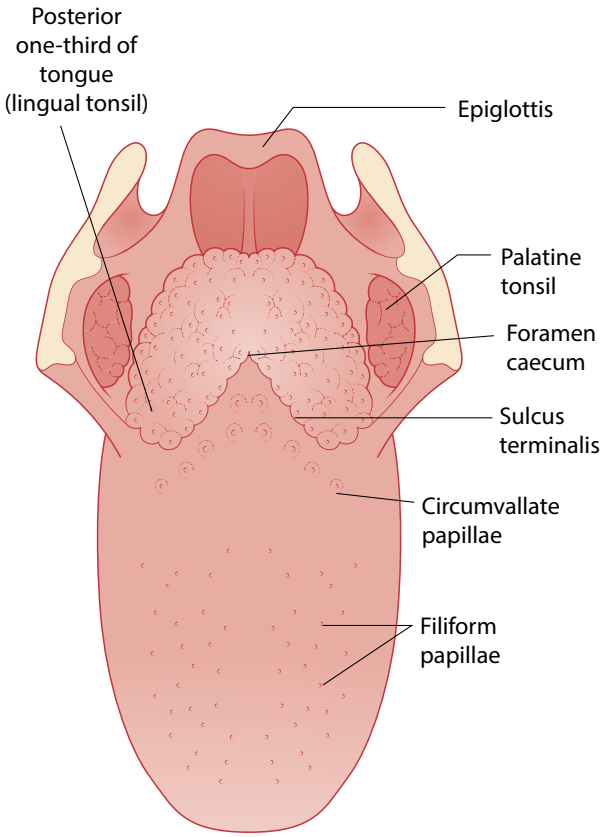


Figure 47.4 Anatomy of the tongue. The posterior third is part of the oropharynx.

this region of the oropharynx is via the internal laryngeal nerve, a branch of the vagus nerve. The mucosa in rest of the oropharynx is supplied predominantly by the glossopharyngeal nerve and to a lesser degree by the lesser palatine nerve.

PALATINE TONSILS

The palatine tonsils (**Box 47.2**) lie in the tonsillar fossa between two tonsillar pillars – the palatoglossal and the palatopharyngeal folds – and can be variable in the depth to which they are embedded between the folds. Previous infections, particularly peritonsillar abscesses, can cause apparent asymmetry of the palatine tonsils. True asymmetry is uncommon and should raise concerns about potential malignancy or parapharyngeal masses pushing the tonsil medially.

Palatine tonsils are characterized by multiple craters on their surface, which are formed by crypts passing deep into the parenchyma of the tonsil. The pitted epithelium of the tonsillar tissue has an intratonsillar cleft within the substance of the tonsil. Histologically unique, the palatine tonsils consist of lymphoid tissue covered by squamous epithelium. Unlike the other components of Waldeyer's ring, the palatine tonsil is encapsulated. This provides a convenient plane of dissection when performing tonsillectomy. The floor of the tonsillar bed is formed by the superior constrictor, and is separated from the tonsil by a thick condensation of pharyngeal submucosa, the tonsillar capsule, which is, in essence, an extension of the pharyngobasilar fascia. This capsule is further separated from the superior constrictor by a thin film of loose areolar tissue.

The palatine tonsils are supplied by the tonsillar artery, a branch of the facial artery that gains access to the tonsil by penetrating the superior constrictor to enter the inferior pole of the tonsil. There is additional arterial supply from the ascending palatine, lingual, descending palatine and ascending pharyngeal arteries. The venous drainage of the palatine tonsils is via a plexiform arrangement, deep to the tonsils, the pharyngeal venous plexus. The large external palatine vein descends from the soft palate and passes close to the lateral surface of the tonsillar capsule; this vein is most commonly divided in tonsillectomy and is the likely culprit in persistent post-tonsillectomy bleeds. The lymphatics of the tonsil drain to the jugulodigastric lymph node area.

The tonsils receive their nerve supply from the tonsillar plexus, a complex meshwork of nerves originating from the tonsillar branches of the maxillary nerve and the glossopharyngeal nerve. The fibres of the maxillary nerve are distributed to the lesser palatine nerves (although they pass through the pterygopalatine ganglion, they do not synapse there) and via these nerves are then combined with the glossopharyngeal nerve to form their plexiform arrangement of nerves around the tonsils. This plexus also supplies the oropharyngeal isthmus and the soft palate. An offshoot of the glossopharyngeal nerve, the tympanic nerve, also supplies the tympanic cavity and the tympanic membrane. Consequently, any pathology affecting the tonsils or the tonsillar fossa may present as pain referred to the ear.

WALDEYER'S RING

The pharynx in its nasopharyngeal and oropharyngeal part has a number of gut-associated lymphoid aggregates that make up what is known as Waldeyer's ring. This circumpharyngeal ring of mucosa-associated lymphoid tissue is at the entry point to the aerodigestive tract and its role almost certainly one of immune maturation and sampling. These include the adenoids posterosuperiorly, the superolateral tubal tonsils, anterolateral palatine tonsils and the anteroinferior lingual tonsils. The tubal tonsils are not always present. As well as these discrete aggregates, there are numerous areas of lymphoid tissue that are sited in the lamina propria just beneath the epithelium as well as collections of this tissue in the intertonsillar intervals. The former collections can often be seen on the posterior pharyngeal wall as small areas of salmon-pink, slightly raised swellings.

Hypopharynx

The hypopharynx (laryngopharynx, in anatomical textbooks) is the junction between the oropharynx and the oesophagus (**Figure 47.5**). Shaped like a funnel with much of its anterior segment missing, it extends from the level

BOX 47.2 Within the oropharynx: the palatine tonsils

Size	Varies according to age and pathological status – increase rapidly in size until ages 5–6 and at maximal size during puberty. Involution starts at puberty. Little lymphoid tissue exists in old age
Site	Within the lateral wall of the oropharynx, located between the palatoglossal and palatopharyngeal folds in the tonsillar bed, and surrounded by the tonsillar capsule
Shape	Ovoid mass of lymphoid tissue associated with the mucosa of the oropharynx and with a fixed position, long axis from superior to inferior to posterior
Surface	Free medial surface has a pitted appearance, with about 10–20 pits in total, which lead into blind-ending crypts that travel through the full thickness of the tonsils. The tonsils sit in a hemicapsule made up of connective tissue
Structure	Varies according to age and pathological status – they may be hypertrophied or inflamed, so difficult to say what is normal. Healthy tonsils have fissure-like crypts that are in contact with each other. The **recessus palatinus**, or **intratonsillar cleft**, is situated within the substance of the tonsil
Supply	Several anastomosing arteries but predominantly the tonsillar artery off the facial artery (a branch of the external carotid artery) Venous drainage is via the paratonsillar vein – external palatine vein – within the tonsillar hemicapsule, and via a plexiform venous drainage system outside the tonsillar hemicapsule Lymph drains to the jugulodigastric node of the deep cervical lymph node group
Sensation	The tonsillar branch of the glossopharyngeal nerve (CN IX) and the lesser palatine nerve (off the maxillary division of CN V2). Diffuse nerve supply
Service	The right and left tonsils are part of Waldeyer's ring of lymphoid tissue that provides first line defence to the upper respiratory tract
Surgical/clinical considerations	**Tonsillitis** refers to inflammation of the palatine tonsils. Pain can be referred to the middle ear due to innervation from different branches of the same cranial nerve (glossopharyngeal nerve). The tympanic branch of the glossopharyngeal nerve also supplies the middle ear, causing **referred pain** to the ear from the tonsils The internal carotid artery is 2.5 cm posterolateral to the tonsils A **peritonsillar abscess** or quinsy occurs outside the tonsillar capsule. Drainage is achieved by directly incising the most prominent bulging part of the collection, usually using topical anaesthetic spray **Tonsillectomy** or the surgical removal of the palatine tonsils: indications are recurrent acute infection of the tonsils, treatment for acute peritonsillar abscesses or for treatment of airway obstruction due to enlarged tonsils. Methods employed are the guillotine method or dissection in the plane of the fibrous hemicapsule, which is followed by electrocautery or ligation of the vessels. Usually performed under general anaesthetic but can be done using local anaesthetic infiltration of the region and/or nerve block. By separating the fibres of the superior constrictor muscle, the glossopharyngeal nerve can be accessed The paratonsillar vein (or external palatine vein) running within the tonsillar capsule is the usual culprit for a **post-tonsillectomy bleed**. This vein is commonly divided in a tonsillectomy

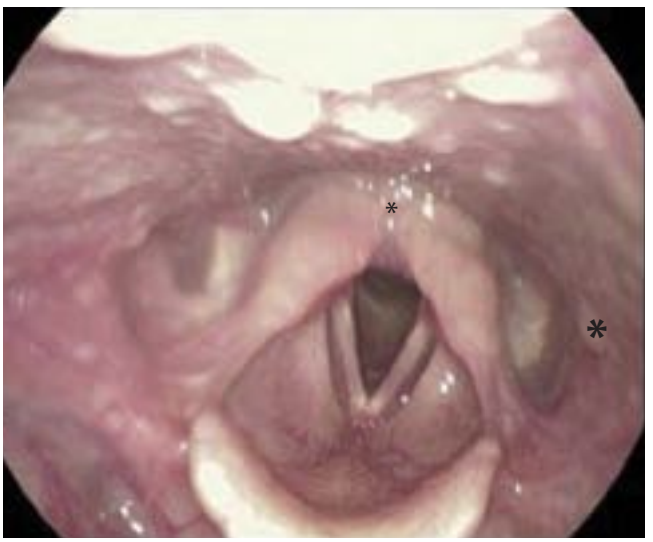


Figure 47.5 Endoscopic view of the hypopharynx during Valsalva manoeuvre allowing assessment of the upper postcricoid area (small asterisk – postcricoid area; large asterisk – pyriform sinus).

of the hyoid bone (or the superior margin of the epiglottis, delineated on either side by the lateral glossoepiglottic folds of the vallecular walls) to the lower margin of the cricoid cartilage at vertebral level C6 where the pharynx terminates and the oesophagus begins. The missing anterior segment corresponding to the laryngeal inlet, the aditus, is the communication between the larynx and the pharynx. This oblique area is bounded superiorly by the epiglottis, the posterior surfaces of the arytenoids and the cricoid cartilage inferiorly and laterally by the aryepiglottic folds. The mucosa in the hypopharynx is predominantly stratified squamous epithelium with goblet cells. Clinically, this region is often demarcated by imaginary lines: a horizontal line drawn posteriorly at the level of the cranial border the hyoid bone divides the hypopharynx from the oropharynx above and a horizontal line at the level of the caudal boundary of the cricoid cartilage indicates the start of the cervical esophagus below.

In its key position behind and to either side of the larynx, the hypopharynx is the crucial area in maintaining a

safe swallow and preventing aspiration of fluids and food boluses. It is made up of a number of subsites according to the International Union against Cancer (UICC) TNM (see Chapter 4, Staging of head and neck cancer) classification and tumours in this region have a poor prognosis due to their vague symptoms and the tendency to enlarge and metastasize prior to detection.

- The **posterior pharyngeal wall** extends from the horizontal line drawn at the level of the superior margin of the hyoid bone (or floor of the valleculae) to the level of the inferior border of the cricoid cartilage, and from the apex of one piriform recess to the other. Three overlapping constrictors form the posterior wall of the laryngopharynx to the level of the vocal cords. Beyond this point, the inferior constrictor is the main component of the wall behind the cricoid lamina and to the level of the upper margin of the cricoid cartilage. As the inferior constrictor is in reality composed of two separate muscles –thyropharyngeus and cricopharyngeus –this fusion point of these muscles, Killian's dehiscence, is a site of potential weakness and the site of pharyngeal pouches. This is discussed in more detail in 'Pharyngeal muscles' below.
- The bilateral **piriform recesses** or fossae extend from either side of the epiglottis from the lateral glossoepiglottic folds to the upper end of the oesophagus. They are broader superiorly and narrower inferiorly, and lie on either side of the laryngeal inlet. The recesses are formed by the larynx bulging into this part of the pharynx, leaving the bilateral anterolateral recesses. They are lined with mucosa and bounded medially by the quadrangular membrane of the larynx. The lateral boundaries are the thyrohyoid membrane superiorly and the thyroid cartilage inferiorly. Foreign objects commonly lodge in the recesses, and tumours can silently expand within the space asymptomatically until metastatic lymphadenopathy manifests.
- The pharyngo-oesophageal junction, or **postcricoid area**, fills out the rest of the hypopharynx. It extends from the level of the arytenoid cartilages and connecting folds to the inferior border or lamina of the cricoid cartilage, thus forming the anterior wall of the hypopharynx. The corresponding mucosa and submucosa extend from the inferior aspect of the arytenoids to the lower margin of the cricoid cartilage, and the lateral margins merge with the medial wall of the piriform recesses at the level at which the cricoid cartilage makes an anterior bend.

PHARYNGEAL WALL

The pharyngeal wall is composed of five discrete layers, two of which are fascial layers. The five layers, from deep to superficial, are the mucous membrane, submucosa, pharyngobasilar fascia, muscular layer and buccopharyngeal fascia or loose areolar sheath.

Mucosal layer

The mucosa of the nasopharynx is typical respiratory mucosa and is made up of ciliated, pseudostratified columnar epithelium. The rest of the pharynx is lined by non-keratinized stratified squamous epithelium. This change occurs at the transitional zone at the lower end of the nasopharynx.

Submucosal layer

Beneath the mucosa is a layer of submucosa, also termed lamina propria, which is made of connective tissue containing elastic tissue. In addition to the mucosal layer, it is host to a number of aggregates of gut-associated lymphoid tissue that forms Waldeyer's ring. The submucosa is thick and blends in with the fibrous pharyngobasilar layer, which also forms the tonsillar capsule.

Pharyngobasilar fascial layer

The pharyngobasilar fascia is the next layer and is firmly adherent to the skull base in the region of the occipital bone and petrous temporal bone. Superiorly, the fascia is thicker and fuses with the buccopharyngeal fascia to form a dense fibrous structure that suspends the pharynx from the base of skull. The muscular wall does not fully reach the skull base and this fascial layer is important in maintaining the integrity of the pharynx.

Muscular layer

The muscular layer is made up of three pharyngeal constrictor muscles that interlock like three cones or flowerpots one inside the other, with each layer overlapping the next layer. Their anterior aspects communicate with the spaces immediately in front of them, the nasal, oral and laryngeal cavities. The constrictor muscles have bilateral anterior attachments to the aforementioned cavities and sweep backwards from there to fuse on the posterior aspect of the pharynx at a midline raphe, the pharyngeal raphe. The muscular framework of the pharynx is dealt with in more detail below.

Buccopharyngeal fascial layer or loose areolar sheath

The final layer of the pharynx is a thin areolar layer covering the pharyngeal constrictors that is also continuous with the covering of the buccinator muscle. This layer contains the pharyngeal plexus of veins and nerves.

MUSCLES OF THE PHARYNX AND SOFT PALATE

The muscles of the soft palate and pharynx work in unison and are therefore dealt with together here.

Pharyngeal muscles

The pharyngeal muscular wall (**Figure 47.6**) is relatively thin and comprises three circular constrictor muscles, all of which act to enable the reflex of swallowing to ensure prompt propulsion of the food bolus by a coordinated peristaltic wave into the oesophagus. They are assisted by three longitudinal muscles, which act as elevators and dilators of the pharynx. The constrictors sit within each other like three stacked cones or cups and overlap on their posterior aspect. Although the framework of the pharynx dangles down from the base of the skull, and from the pharyngeal tubercle in particular, the muscular wall does not originate from the bony skull. Instead, the fibrous submucosal thickening of the pharyngeal wall, the pharyngobasilar fascia, stretches across like a curved but rigid sheet attached to the nasopharyngeal wall and fills the gap between the superior constrictor muscle below and the base of the skull above. In effect, the pharyngobasilar fascia is the fourth cone or cup stacked into the muscular constrictors below and is the main component for maintaining the patency of the nasopharynx in its task of guaranteeing unhindered flow of air for breathing.

All of the constrictors are supplied by the pharyngeal and superior laryngeal branches of the vagus nerve through the pharyngeal plexus.

THE THREE CONSTRICTORS

The superior constrictor is the thinnest of the constrictors and shaped like a quadrilateral sheet slung from one side of the pharynx to the other to form the superior part of the pharyngeal wall. Its function is to constrict the upper region of the pharynx. It arises from the pterygoid hamulus (but occasionally also from the posterior surface of the medial pterygoid plate) and the pterygomandibular raphe running from the pterygoid hamulus to the retromolar trigone, and from the posterior end of the mylohyoid line on the mandible. A few of its fibres originate from the side of the tongue. The pterygomandibular raphe is the fibrous condensation that extends between the buccinator and the superior constrictor muscles. The muscle fibres of the latter run backwards and upwards from their anterior attachments to fuse in the midline on the posterior aspect of the pharynx at the median pharyngeal raphe. Some fibres project upwards and attach to the base of the skull indirectly via the pharyngobasilar fascia, which attaches to the pharyngeal tubercle, a bony projection just anterior to foramen magnum. Posteriorly, the lowermost fibres sit comfortably within the overlapping middle constrictor muscle and reach the level of the laryngeal vocal folds. On the lateral aspect, the superior and middle constrictors do not overlap and a gap exists through which the stylopharyngeus muscle passes downwards to insert into the pharyngeal wall. Through the same gap, the styloglossus muscle as well as two nerves – the glossopharyngeal and the lingual – pass forwards in the direction of the tongue.

The fan-shaped **middle constrictor** arises from the inferior end of the stylohyoid ligament and the greater and lesser horns of the hyoid bone and its fibres fan out in several directions. Most of its fibres wrap around in the same manner as the superior constrictor fibres to join the median pharyngeal raphe while the upper fibres also encircle the lower posterior fibres of the superior constrictor. The lowest fibres of the middle constrictor muscle that angulate downwards in a dorsoventral direction also terminate at the level of the laryngeal vocal cords, along with those of the superior constrictor. The muscular anterior wall here is incomplete between the middle and the inferior constrictors and is covered by the thyrohyoid membrane, which forms part of the anterior wall in the hypopharynx. On the superolateral aspect of this membrane, the internal laryngeal nerve and the superior laryngeal artery and vein pass medially.

The inferior constrictor, the thickest of all the constrictors, is generally described as two muscles, the thyropharyngeus and the cricopharyngeus. Thyropharyngeus originates from the oblique line of the thyroid lamina,

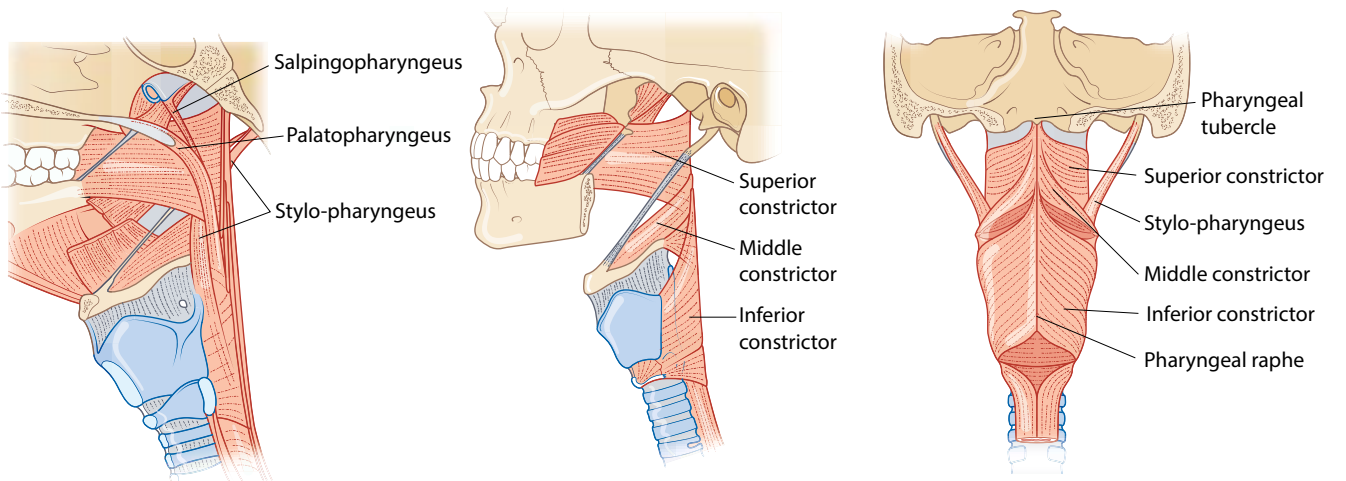


Figure 47.6 Muscles of the pharynx: (a) sagittal section, **(b)** lateral view and **(c)** posterior view.

from a small strip of lamina behind it and a small part of the inferior thyroid horn as well as from a part of the tendinous fascia overlying and looping over the cricothyroid muscle. Its fibres pass upwards posteromedially to join at the median pharyngeal raphe, although some of its fibres cross over the raphe to fuse with the contralateral muscle. Its upper fibres overlap with the middle constrictor fibres. Cricopharyngeus arises from the lateral aspect of the cricoid cartilage, emerging from between the attachment for the cricothyroid muscle and the inferior thyroid horn. It is distinctively different from all the other flat constrictor muscles in that it is thicker and rounder and its fibres pass horizontally to encircle the cricoid arch without fusing in the midline at the pharyngeal raphe. This is the sphincter of the pharynx, which is also continuous with the circular muscular coat of the upper oesophagus below. By default, this sphincter is closed and only opens momentarily during swallowing, and it can thus pose problems when passing an endoscope past this point. Swallowing will overcome any resistance encountered.

The innervation, attachments and functions of the three constrictor muscles of the pharynx are summarized in **Table 47.1**. The attachments are illustrated in **Figure 47.7**.

The inferior laryngeal artery and vein as well as the recurrent laryngeal nerve pass upwards deep to the inferior constrictor's lower margin.

The potentially weak area at the junction of thyropharyngeus and cricopharyngeus has clinical implications. The mucosa between these two muscles has little support from the pharyngeal musculature and is known as the pharyngeal dimple or, more commonly, Killian's dehiscence. The specific site of weakness is on the posterior aspect, in the midline, of the fusion point of these two muscles. This area is important in the pathogenesis of pharyngeal diverticulae, which form as a prolapse of mucosa and submucosa of the pharynx just above the cricopharyngeus muscle at the level of the sixth cervical vertebra. The resulting pharyngeal pouch (**Figure 47.8**) then becomes a convenient reservoir for trapping some or all of the passing food bolus. Halitosis and regurgitation are, unsurprisingly, the hallmarks of the condition. The specific aetiology of a pharyngeal pouch is, however, unknown. It is thought that malfunction of the upper oesophageal sphincter may contribute to the condition.

Despite the initial posterior expansion of any prolapse, prevertebral fascia prevents any further expansion in that direction. Thus, any larger prolapses usually project more laterally and inferiorly, mainly to the left side of the pharynx, which is the more exposed of the two sides. In a progressively enlarging prolapse, the pouch can potentially push the oesophagus to one side and thus sit in line with the rest of the pharynx. Consequently, dysphagia and cachexia may result, and pouch contents are more liable to spill into the larynx causing respiratory infections. The aetiology of the formation of a pharyngeal pouch is thought to involve a sequence of events originating from

TABLE 47.1 Constrictors of the pharynx

Muscle	Innervation	Anterior attachment	Posterior attachment	Function
Superior constrictor	Vagus nerve	Pterygomandibular raphe and adjacent bone on the mandible and pterygoid hamulus	Pharyngeal raphe	Constricts the pharynx
Middle constrictor	Vagus nerve	Greater horn of hyoid bone (upper margin) and adjacent margins on lesser horn of the hyoid bone and the stylohyoid ligament	Pharyngeal raphe	Constricts the pharynx
Inferior constrictor	Vagus nerve	Cricoid cartilage, oblique line of the thyroid cartilage, and the ligament that is between these two attachments and crosses the cricothyroid muscle	Pharyngeal raphe	Constricts the pharynx

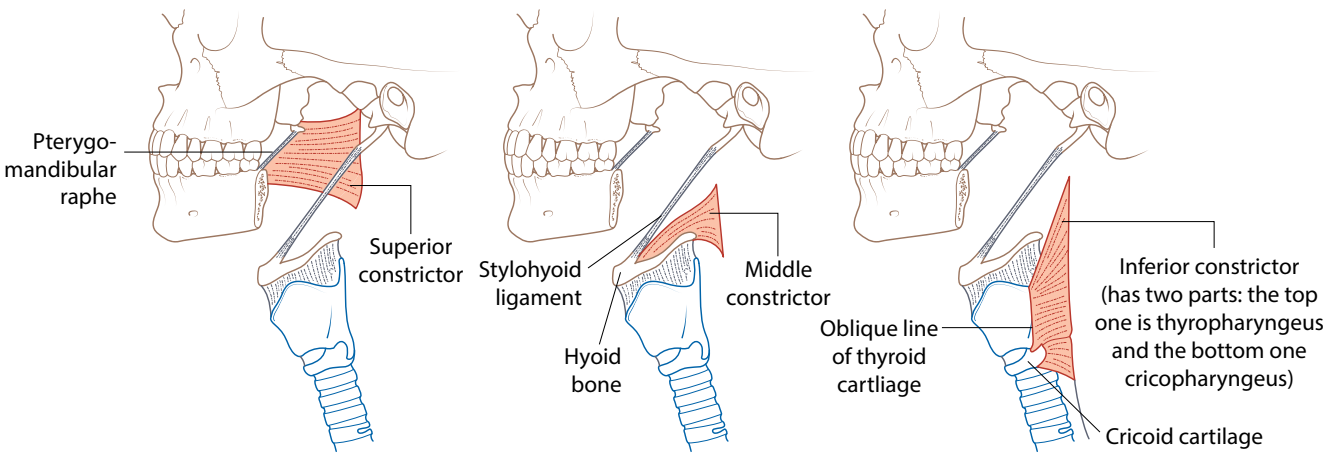


Figure 47.7 Attachments of the constrictor muscles of the pharynx: 1 – superior constrictor, 2 – middle constrictor, 3 – inferior constrictor.

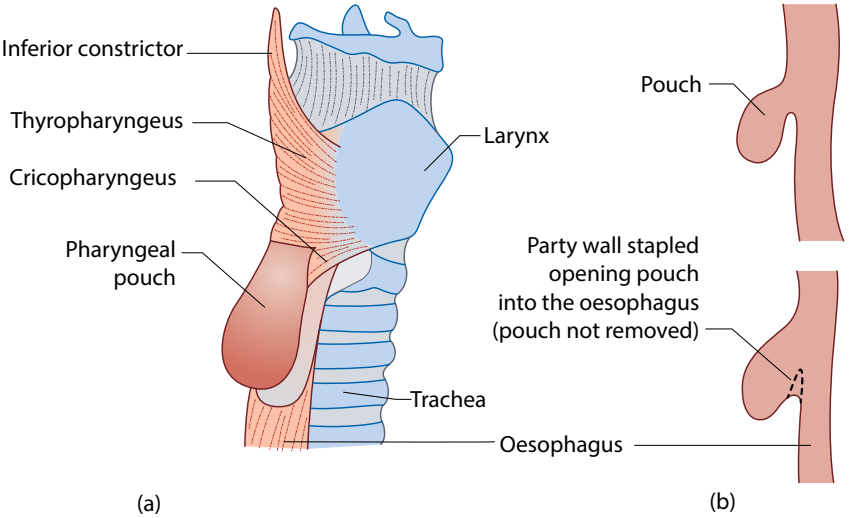


Figure 47.8 Anatomy of a pharyngeal pouch and stapling.

discoordinated swallow which elevates the pressure adjacent to the dehiscence and delays the relaxation of the cricopharyngeus sphincter below.

THE THREE DILATORS AND ELEVATORS

In addition to the three constrictor muscles that form the external muscular wall of the pharynx, three longitudinal muscles act to elevate and dilate the pharynx. These are the stylo-, palato- and salpingopharyngeus muscles. The first two are named based on their origins on the skull base; salpingopharyngeus, in contrast, has a long and slender shape with a wider distal end, the structure of which is reminiscent of the Greek trumpet bearing its name (salpinx).

The stylopharyngeus muscle is a long conical muscle that descends inferiorly between the external and internal carotid arteries. Curiously shaped, it is cylindrical above but flat below, and is markedly slender. It enters the pharynx between the superior and middle constrictors. It originates from the medial side of the base of the styloid process, within the temporal bone, and inserts into the posterosuperior border of the thyroid cartilage alongside the palatopharyngeus muscle. Some of its fibres also merge with the lateral glossoepiglottic folds, the lateral boundaries of the valleculae in the oropharynx. Its action is to raise the pharynx and assist in peristaltic movement of the food bolus. An important relation is the glossopharyngeal nerve which, en route to the tongue, curves from medial to lateral on its posteroinferior border and innervates it. All the other pharyngeal muscles are innervated by the pharyngeal nervous plexus, although cricopharyngeus is also innervated by the recurrent and external laryngeal nerves. Stylopharyngeus elevates both the pharynx and the larynx.

Palatopharyngeus is as much a pharyngeal muscle as it is a muscle of the soft palate. It has two heads and thus two actions. While both heads lie in the same plane, they are separated by levator veli palatini, a soft palate muscle. Its thicker anterior head originates from the posterior border of the hard palate and the anterior and superior surfaces of the palatine aponeurosis respectively. Its posterior head also originates from the superior surface of the palatine aponeurosis, but from further back on it. These two heads fuse at the lateral border of the palatine aponeurosis, are joined by fibres of salpingopharyngeus and arch downwards from here to insert into the posterior border of the thyroid lamina alongside stylopharyngeus and salpingopharyngeus. As it makes its way down as a single muscle covered in submucosa and mucosa, it forms the posterior faucial pillar, or palatopharyngeal arch. This muscle has a dual purpose: it elevates the larynx and pharynx and constricts the palatopharyngeal arch to assist in swallowing and, additionally, enables the concave shape of the oral surface of the palate with its arch.

The fibres of palatopharyngeus originating from the anterior head are horizontal at the level of the first cervical vertebra and form the palatopharyngeal sphincter. Contraction of these fibres lifts up the posterior pharyngeal wall in what is reminiscent of a ridge, Passavant's ridge, which is in direct contact with the superior surface of the soft palate during swallowing. No consensus has been reached on the origins of Passavant's ridge, some sources stating that it could be superior constrictor, and others that a completely different muscle acts as a sphincter at this point. What is clear is that there is a change of mucosal type along the line of this sphincter, from the ciliated, columnar respiratory epithelium above to the stratified squamous epithelium below.

Shaped like a long and slender trumpet, the salpingopharyngeus muscle arises from the lower part of the cartilaginous pharyngotympanic tube and descends internally in the salpingopharyngeal fold and inserts by blending into the palatopharyngeus muscle. The action of this muscle is to elevate the pharynx, although it may also serve to assist the soft palate muscle, tensor veli palatine, in opening the cartilaginous part of the pharyngotympanic tube during swallowing.

The innervation, origin, insertion and functions of the elevators of the pharynx are summarized in **Table 47.2**. Their attachments are illustrated in **Figure 47.9**.

Box 47.3 summarizes the openings in the pharyngeal wall musculature.

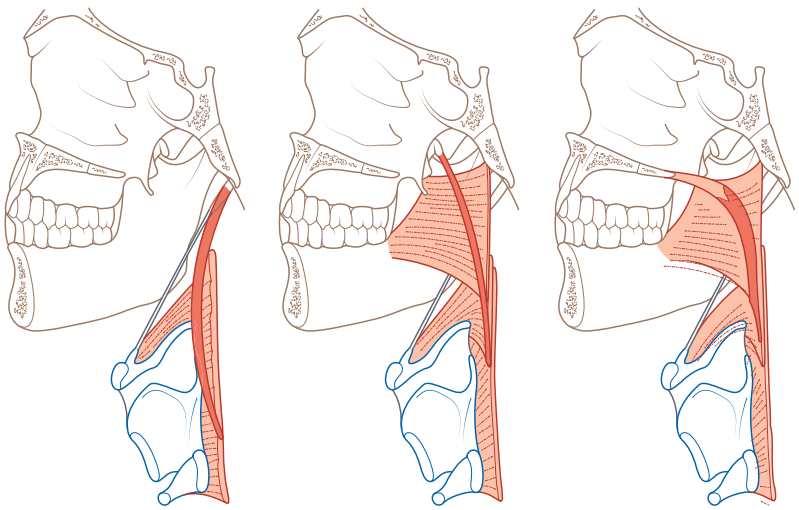
Soft palate muscles

Sloping down from the hard palate into the nasal and oral parts of the pharynx is the mobile flap which is the soft palate (**Figure 47.10**). It is the fibromuscular continuation of the hard palate and acts as a partition between the oropharynx and the nasopharynx. The failure of this structure and the consequences related to this are clearly seen in children born with a cleft palate, who struggle with feeding as well as normal speech production due to velopharyngeal incompetence.

The boundary between the soft and hard palate is easily palpable and is characterized by a subtle change in colour; the soft palate is characterized by a yellowish discolouration on a background of a darker red than that visible in the region of the hard palate. The soft palate is essentially a thick mucosal fold that holds within it an aponeurosis, muscles, neurovascular structures, lymph nodes and mucous glands. In its relaxed state, it is pendulant and a midline raphe is visible on its concave oral surface. The soft palate requires an intact central fibrous aponeurosis

TABLE 47.2 Elevators of the pharynx

Muscle	Innervation	Origin	Insertion	Function
Palatopharyngeus	Vagus nerve	Upper surface of palatine aponeurosis	Pharyngeal wall	Elevates the pharynx and closes the oropharyngeal isthmus
Stylopharyngeus	Glossopharyngeal nerve	Medial side of base of styloid process	Pharyngeal wall	Elevates the pharynx
Salpingopharyngeus	Vagus nerve	Inferior aspect of pharyngeal end of pharyngotympanic tube	Pharyngeal wall	Elevates the pharynx



1 Stylopharyngeus **2** Salpingopharyngeus **3** Palatopharyngeus

Figure 47.9 Attachments of the longitudinal muscles of the pharynx: 1 – stylopharyngeus, 2 – salpingopharyngeus, 3 – palatopharyngeus.

BOX 47.3 Openings in the pharyngeal wall musculature

Where?	Structures traversing
Above the superior constrictor	The cartilaginous portion of the pharyngotympanic tube, the tensor and levator palati muscles and the palatine branch of the ascending pharyngeal artery. All of these structures pass through the pharyngobasilar fascia
Between the superior and middle constrictor muscles	The stylopharyngeus muscle, styloglossus muscle, the glossopharyngeal and lingual nerves
Through the thyrohyoid membrane to enter the piriform fossa	The internal laryngeal nerve and superior laryngeal vessels
Below cricopharyngeus	The recurrent laryngeal nerve and inferior thyroid artery pass superiorly into the larynx deep to the cricopharyngeus muscle

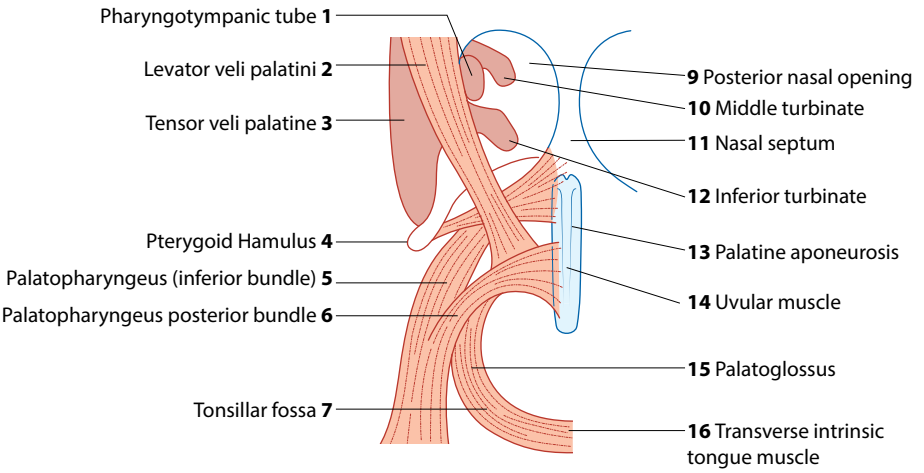


Figure 47.10 Posterior view of the soft palate showing the muscles acting on the left-hand side.

formed by the fused expanded tendons of the tensor veli palatini muscles upon which the muscles attached to the palate can act. The aponeurosis is attached posteriorly to the palatine part of the hard palate and has a midline raphe. The soft palate has a thicker anterosuperior portion near its insertion with the hard palate. As the palate travels posteroinferiorly, it gradually thins out, giving off the characteristic curved lower border appearance as it merges with the palatoglossal muscles which insert into it. In the centre is the conical uvula, part of its free inferior border, which can vary in length (but is typically longer in those who snore or have sleep apnoea) and projects downwards. The uvular muscles are embedded in the aponeurosis which splits to surround them. From the uvula, the two muscles of the pharyngeal arches – palatopharyngeus and palatoglossus – diverge laterally and inferiorly and insert into the intrinsic muscles of the tongue. The mucosa of the soft palate is covered in mucinous glands as well as minor salivary glands, and some taste buds exist on its oral surface.

The muscles of the palate do not act independently but work in unison to facilitate the swallowing reflex to close off the nasopharyngeal sphincter on initiating a swallow. All of the five paired soft palate muscles are attached to the palatine aponeurosis, the latter of which also encloses the small musculus uvulae muscle in the midline. These muscles can be classified according to their anatomical function: tensor veli palatini, levator veli palatini and the musculus uvulae raise the soft palate; palatoglossus (also an extrinsic tongue muscle) and palatopharyngeus (also a pharyngeal muscle) elevate the tongue and pharynx to close off the oropharyngeal isthmus during swallowing.

ELEVATORS OF THE SOFT PALATE

Tensor veli palatini is a veil-thin triangular muscle arising from the scaphoid fossa of the sphenoid bone, the lateral lamina of the pharyngotympanic tube and the spine of the sphenoid. It descends on the lateral surface of the medial pterygoid plate and then forms a tendon that hooks around the pterygoid hamulus to spread out to form the palatine aponeurosis. Its two sides fuse in the median raphe. Upon bilateral contraction, the muscles tauten predominantly the anterior part of the soft palate and depress the arch. Unilateral contraction of the muscles moves the soft palate in the direction of the pull. A primary function of the tensor veli palatini muscle is also presumed to be associated with opening the pharyngotympanic tube during swallowing and yawning to allow for equalization of nasopharyngeal and middle ear air pressure. This explains why patients with cleft palate will almost universally have otitis media with effusion; due to a failure of the midline connection, the tensor veli palatini cannot pull open the pharyngotympanic tube and, so, aeration of the middle ear as well as protecting it from the transmission of infections from the pharynx is negligible. The tensor veli palatini is the only muscle of the palate that is supplied by a branch of the mandibular division of the trigeminal nerve – the nerve to medial pterygoid. The rest are supplied by the cranial part of the accessory nerve via the pharyngeal plexus.

Levator veli palatini is a cylindrical muscle that arises from a small tendon on the inferior, roughened, portion of the petrous temporal bone, known as the quadrate area, situated in front of the inferior opening of the carotid canal. Some of its fibres also originate from the lower part of the cartilaginous pharyngotympanic tube and yet more from the vaginal process of the tympanic bone. It inserts onto the nasal surface of the palatine aponeurosis and sits between the two heads of the palatopharyngeus muscle, forming a rounded belly. The levator muscles pass anteromedially and together they form a V-shaped sling just above and behind the palatine aponeurosis, which allows elevation and slight retraction of the vertical posterior part of the soft palate when closure of the nasopharynx is required. The soft palate then touches the posterior pharyngeal wall, closing off the nasopharyngeal isthmus to prevent nasal regurgitation during speech and swallowing. Additionally, its fibres also pull the lateral nasopharyngeal wall anteromedially to narrow that space. The effects of levator veli palatini on the pharyngotympanic

tube and its role in the equalization of air pressure are controversial. This muscle, along with the palatoglossus, palatopharyngeus and uvular muscle, are all supplied by the cranial part of the accessory nerve via the pharyngeal plexus.

Musculus uvulae lies between the two laminae of the palatine aponeurosis and arises from the posterior nasal spine on the palatine bone as well as from the superior surface of the aponeurosis. It sits above the V-shaped sling formed by the two levator veli palatini muscles and runs backwards above it to insert into the uvular mucosa. Most of this small muscle is fused in the midline. Its function is to act in conjunction with the levator veli palatini muscles to retract and thicken the mid-third of the soft palate, thus closing the nasopharyngeal isthmus. As the two muscle bellies run at 90 degree angles to each other, when they contract, a 'levator eminence' is formed. This helps in the finally sealing off of the nasopharynx during swallowing.

ELEVATORS OF THE PHARYNX AND TONGUE

As a pharyngeal wall muscle, **palatopharyngeus** has been discussed in the section on pharyngeal muscles. Its role as a soft palate muscle is to elevate the pharynx and pull it forwards and medially. Additionally, the muscles acting together also draw the palatopharyngeal arches together and approximate them, enabling closure of the oropharyngeal isthmus.

Palatoglossus is both an extrinsic tongue muscle and a soft palate muscle. It arises from the palatine aponeurosis, on its oral surface, where it is continuous with the contralateral muscle, and projects anteriorly, inferiorly and laterally to the side of the tongue, forming the palatoglossal fold anterior to the palatine tonsil on its way down. A few of its fibres extend into the dorsum of the tongue, while others pass into the parenchyma of the tongue to intermingle with the intrinsic musculature. Unlike the rest of the extrinsic and intrinsic tongue muscles, palatoglossus follows the innervation of the soft palate muscles and is innervated by the cranial part of the accessory nerve and its pharyngeal plexus. Its action is to elevate the root of the tongue and to approximate the two palatoglossal arches when closure of the oropharyngeal isthmus is required.

The innervation, origin, insertion and functions of the elevators of the muscles of the soft palate are summarized in **Table 47.3**. Their attachments are illustrated in **Figure 47.11**.

BLOOD SUPPLY OF THE PHARYNX

The pharynx has a rich vascular supply from a number of branches of the external carotid artery. Much of the superior pharynx is supplied by the ascending pharyngeal artery. This artery arises from the medial external carotid and passes superiorly, giving off branches to the pharynx. A palatine branch passes over the edge of the superior constrictor to supply the soft palate and internal pharynx as well as the pharyngotympanic tube. There are additional supplies from the tonsillar artery and ascending palatine branch of the facial artery as well as, more inferiorly, from the superior and inferior laryngeal arteries.

Venous drainage is via the internal submucosal and the external pharyngeal venous plexus, which sits predominantly on the posterior aspect of the middle constrictor. The venous plexus drains into the internal jugular vein and, to an extent, connects with the pterygoid venous plexus. The venous plexus is a common cause of significant

TABLE 47.3 Muscles of the soft palate

Muscle	Innervation	Origin	Insertion	Function
Tensor veli palatini	V3, mandibular nerve via the branch to the medical pterygoid muscle	Scaphoid fossa of the sphenoid bone, fibrous part of the pharyngotympanic tube and the spine of the sphenoid	Palatine aponeurosis	Tenses the soft palate and opens the pharyngotympanic tube
Levator veli palatini	Vagus nerve via the pharyngeal branch to the pharyngeal plexus	Petrous part of the temporal bone anterior to the opening for the carotid canal	Superior surface of the palatine aponeurosis	The only muscle to elevate the soft palate from the neutral position
Palatopharyngeus	Vagus nerve via the pharyngeal branch to the pharyngeal plexus	Superior surface of the palatine aponeurosis	Pharyngeal wall	Depresses the soft palate, moves the palatopharyngeal arch towards the midline and elevates the pharynx
Palatoglossus	Vagus nerve via the pharyngeal branch to the pharyngeal plexus	Inferior surface of the palatine aponeurosis	Lateral margin of the tongue	Depresses the palate, moves the palatoglossal arch towards the midline and elevates the back of the tongue
Musculus uvulae	Vagus nerve via the pharyngeal branch to the pharyngeal plexus	Posterior nasal spine of the hard palate	Connective tissue of the uvula	Elevates and retracts the uvula and thickens the central region of the soft palate

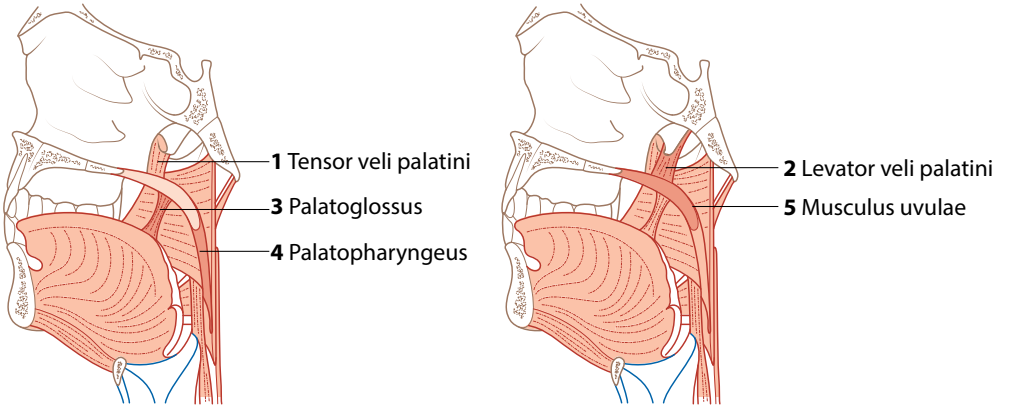


Figure 47.11 Soft palate muscular attachments.

bleeding in operations of the pharynx and can, on occasion, be very difficult to control.

The vascular supply of the soft palate is equally rich, but it mainly originates from the lesser palatine artery of the maxillary artery, and the ascending pharyngeal artery and its palatine branches in particular. These arteries form a complex anastomosis with the ascending palatine artery, a branch of the facial artery.

PHARYNGEAL PLEXUS OF NERVES

The motor and the majority of the sensory supply to both the pharynx and the soft palate come from the pharyngeal plexus. This is a meshwork of interconnecting nerves on the posterolateral surface of the pharynx and it is formed by contributions from the pharyngeal branches of the vagus nerves, the glossopharyngeal nerves and the sympathetic branches of the superior cervical ganglion. Mixed nerves then exit the plexus and either descend or ascend over the external surface of the pharyngeal constrictors, in particular over the middle constrictor, to supply the deeper layers of the pharyngeal wall, the muscles and the mucosal surfaces.

The motor fibres of the plexus originate in the cranial root of the accessory nerve and are carried by the pharyngeal branch of the vagus nerve to supply all of the pharyngeal muscles, apart from the stylopharyngeus muscle (which is supplied by the glossopharyngeal nerve) and the tensor veli palatini (which is supplied by nerve to medial pterygoid, a branch of the mandibular division of the trigeminal nerve). These motor fibres travel between the internal and external carotid arteries to enter the superior margin of the middle constrictor. At this point, it joins the hypoglossal nerve – close to where it curves around the occipital artery – via a miniscule filament, the ramus lingualis vagi. In addition to innervation via the pharyngeal plexus, the inferior constrictor, namely cricopharyngeus, also receives contributions from braches of the vagus nerve, the external and recurrent laryngeal nerves.

Sensory fibres predominantly originate from the glossopharyngeal nerve to provide the sensory supply to the majority of the oropharynx. The valleculae lying within the oropharynx are, however, supplied by the internal laryngeal nerve off the vagus nerve as well as by the lesser palatine nerve, a branch off the maxillary division of the trigeminal nerve. Part of the nasopharynx is supplied principally by the maxillary branch of the trigeminal via the pterygopalatine ganglion. Sensation within the laryngopharynx is via the internal laryngeal nerve.

The sensory supply of the palate originates from branches of the pterygopalatine ganglion, namely the greater and lesser palatine nerves, which travel with the arteries of the same name. The site of their entry into the palate is a useful landmark for performing local anaesthetic blocks, as it enters 1 cm medial to the region of the second molar.

LYMPHATIC DRAINAGE OF THE PHARYNX

The lymphatic drainage of the pharynx is complex due to the length of the structure and the rich lymphatic supply. It is especially important in malignant disease, as metastatic spread is particularly common from cancers affecting the pharynx. Awareness of this pattern of spread is important when assessing which parts of the lymphatics to treat prophylactically.

The nasopharynx lymph drains to the retropharyngeal lymph nodes and deep cervical lymph nodes. In nasopharyngeal cancer, the nodal stations involved are principally the retropharyngeal nodes and level 2 nodes (in approximately 70% of cases), with spread to levels 3, 4 and 5 also occurring to a lesser extent (45%, 11% and 27% respectively).

Lymphatics channels within the oropharynx pierce through the superior constrictor to principally drain into the deep cervical lymph nodes, particularly the jugulodigastric or tonsillar node situated just below the angle of the mandible (level 2). On occasion, lymph can also drain into level 3 and 4 nodes, although drainage to these distant levels without affecting the upper neck nodes is uncommon.

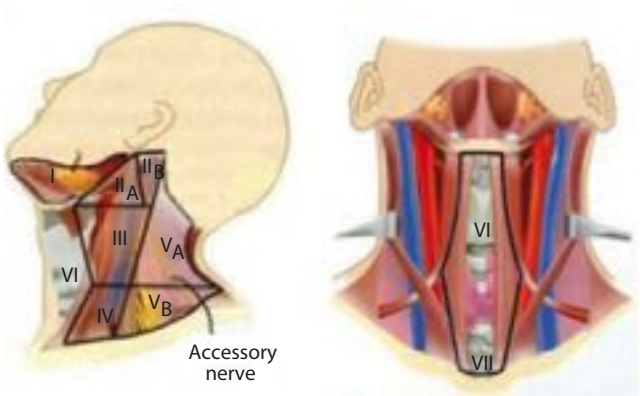


Figure 47.12 The lymph nodes of the neck.

The hypopharynx drains to all levels of the deep cervical nodes, principally to levels 2, 3 and 4. Overall the commonest level of drainage is to level 3 (**Figure 47.12**).

ANATOMY OF THE OESOPHAGUS

INTRODUCTION

The immediate continuation of the pharynx and a conduit for food and fluids into the stomach is the 25 cm long oesophagus, a flattened muscular tube that extends from the level of the inferior border of the cricoid cartilage (sixth cervical vertebra) to the cardiac orifice of the stomach at the level of the eleventh thoracic vertebra. It is the narrowest part of the digestive tract (excluding the appendix) and has three anatomical narrowings along its course. It courses anterior to the vertebral column in the neck and passes through the superior and inferior mediastinal spaces on the posterior aspect of the thorax to the diaphragm, which it penetrates via the oesophageal hiatus at the level of the tenth thoracic vertebra. Thus the oesophagus has a cervical, thoracic and abdominal component. Within the neck, despite originating in the midline, it gradually veers to the left until it reaches the root of the neck. From there it continues again in the midline, and is back to its original vertical orientation. At the level of the fifth thoracic vertebra, it veers yet again to the left but reverts back to being a midline structure. At the level of the seventh thoracic vertebra, it veers to the left again and continues in this course until it pierces through the oesophageal hiatus of the diaphragm. As it descends from the cervical region into the thoracic and then abdominal region, the oesophagus also follows the curvatures of the vertebral column in the anteroposterior plane.

Knowledge of the oesophagus is of considerable interest to otolaryngologists; rigid oesophagoscopy is a relatively common procedure, pharyngeal pouch repair may be complicated with perforations of the oesophagus, foreign bodies routinely lodge within the oesophagus, strictures of the tube require the skilled use of dilators to avoid complications. An intimate knowledge of the anatomical constrictions and oesophageal relations are vital to avoid formation of false passages and inadvertent entry either into the mediastinal cavity or the adjacent pleural spaces and lungs.

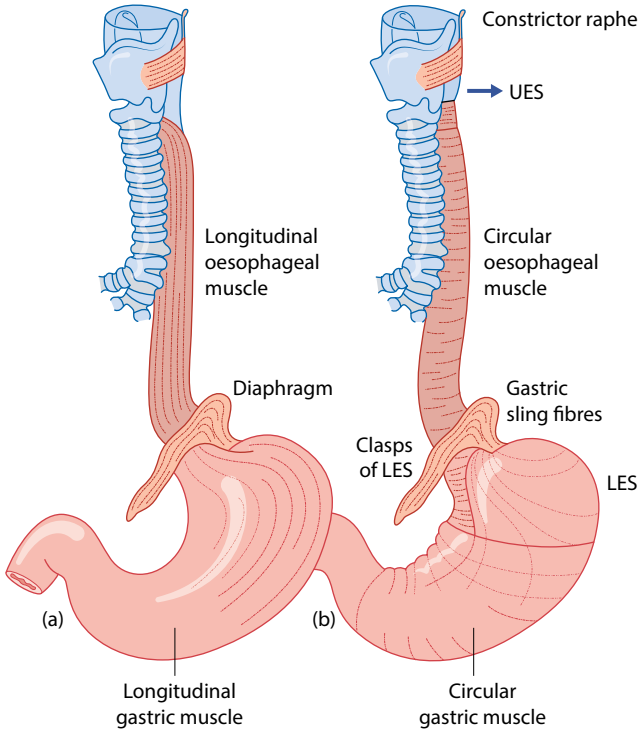


Figure 47.13 Longitudinal and circular muscle in the oesophagus.

Muscles of the oesophagus are shown in **Figure 47.13**.

SUBDIVISIONS OF THE OESOPHAGUS

The oesophagus has three arbitrary subdivisions, primarily based on its course from neck to abdomen as it traverses the neck, the thorax and enters into the abdomen (see above). These are the cervical, thoracic and abdominal oesophagus.

Cervical oesophagus

The superiormost region is the cervical oesophagus. It lies immediately posterior to the trachea and is adherent to the trachea via loose connective tissue. Bilaterally, close to a groove between the two structures, the recurrent laryngeal nerves pass superiorly to pass into the larynx behind the cricothyroid joint to innervate the intrinsic musculature of the larynx. At the level of the thyroid gland, the oesophagus is generally slightly to the left of midline. Posteriorly, the oesophagus rests on the vertebral column formed at this level by the bodies of the sixth and seventh cervical vertebrae and the prevertebral fascia overlying the longus colli muscle. It is flanked on both sides by the common carotid artery, within the carotid sheath, as well as the lower poles of the thyroid gland. To its left, the thoracic duct ascends for a short distance on its way to deposit its contents at the confluence between the subclavian vein and the internal jugular vein.

Thoracic oesophagus

Within the superior mediastinum, the thoracic oesophagus runs slightly to the left of midline initially before passing posterior and to the right of the aortic arch to enter the posterior part of the inferior mediastinum (**Figure 47.14**). Here, it descends to the right of the descending thoracic aorta, although it veers to the left along its course to the oesophageal hiatus of the diaphragm and thus is situated anterior to the descending aorta in the inferior part of the thorax.

In the superior mediastinum, the anterior relations of the oesophagus are the trachea and the left recurrent laryngeal nerve. Its left lateral relations at this point are the terminal part of the aortic arch, the left subclavian vein, the thoracic duct, the left recurrent laryngeal nerve and the left pleura. In the posterior mediastinum, the anterior relations are the left main bronchus, the tracheobronchial lymph nodes, the pericardium and the left atrium. Immediately posterior to the oesophagus are the vertebral bodies of thoracic vertebrae one to four, the thoracic duct sandwiched between the azygos vein and the descending aorta, as well as the right posterior intercostal arteries, and the hemiazygos and accessory azygos veins. At the terminal end of the thoracic part, the descending aorta lies between the oesophagus and the vertebrae.

The left side of the oesophagus lies close to the mediastinal pleura superior to the arch of the aorta except where the thoracic duct and left subclavian artery intervene. The right side of the oesophagus is adjacent to the mediastinal pleura and lung except where the azygos vein intervenes. The thoracic duct enters the thorax through the right side of the aortic hiatus of the diaphragm and runs up along the right side of the oesophagus until, at the level of the fifth thoracic vertebra, it crosses to the left side. From here, it continues up to drain into the junction of the internal jugular vein and the subclavian vein.

The left and right vagus nerves form a plexus that covers the oesophagus, giving off cardiac and pulmonary branches. Lower in the thoracic oesophagus, the plexus once again forms a number of nerve trunks that accompany the oesophagus through the oesophageal hiatus.

CONSTRICTIONS OF THE OESOPHAGUS

The thoracic oesophagus has three constrictions that are not evident in the collapsed oesophagus but can be visualized when air is insufflated into the oesophagus, as is done during oesophagoscopy or when contrast medium is swallowed for radiological examination. The narrowest part of the oesophagus is at the cricopharyngeal sphincter, the commencement of the oesophagus and point of termination of the pharynx. This is generally at approximately 15 cm from the incisor teeth. Below this point, three further anatomical constrictions can be expected along the course of the oesophagus through the thorax and into the abdomen (**Figure 47.15**).

The first constriction within the oesophagus itself is formed when it is crossed over by the arch of the aorta at approximately 22 cm from the incisor teeth. This is immediately followed by a further constriction occurring at approximately 27 cm from the upper incisor teeth and caused by the left main bronchus crossing over it. These two constrictions are often considered as one constriction. The final constriction, at 38 cm from the incisor teeth, occurs as it passes through the diaphragm just prior to the start of the abdominal part of

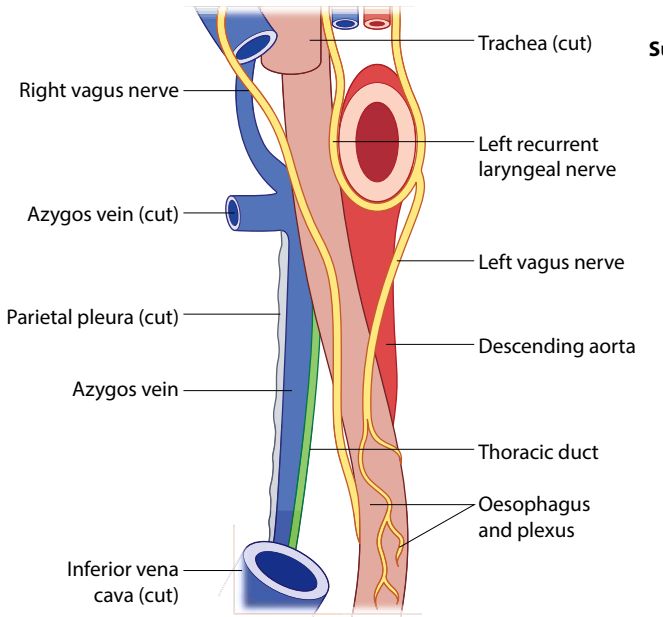


Figure 47.14 The intrathoracic part of the oesophagus.

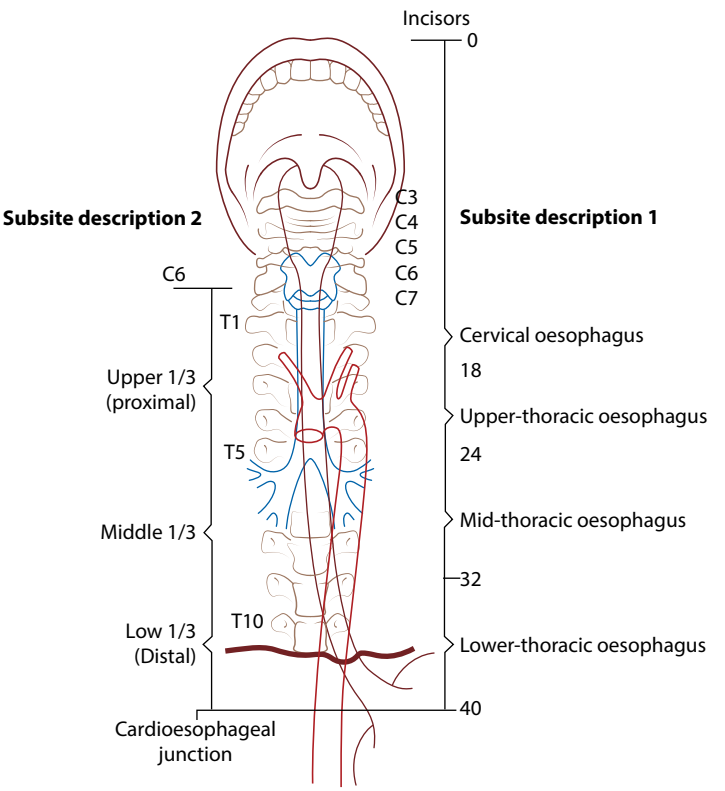


Figure 47.15 Oesophageal constrictions.

the oesophagus. Should the left atrium be enlarged for any reason, it can occasionally cause indentation onto the oesophagus on the anterior aspect just below the left main bronchus.

These constrictions and knowledge of the measurements from the incisor teeth are of considerable importance clinically when instruments are passed through the oesophagus, which can cause serious damage should the functional anatomy of this area not be fully appreciated. All measurements are approximate for an adult.

Abdominal oesophagus

The abdominal section of the oesophagus is the shortest of the three sections and emerges through the right crus of the diaphragm at the level of the tenth thoracic vertebra, left of the midline. It lies in the oesophageal groove on the posterior aspect of the left lobe of the liver before passing to the left to enter the stomach. The right border of the oesophagus continues into the lesser curvature of the stomach in the shape of a truncated cone to become continuous with the cardiac orifice of the stomach. It is covered with peritoneum overlying the lesser sac. The left border of the oesophagus, however, is separated from the fundus of the stomach by the cardiac notch. It is contained within the superior part of the lesser omentum due to the peritoneal coverings that encompass it on its lateral and anterior aspects. On its posterior surface, peritoneum is reflected to the diaphragm. This is part of the gastrosplenic ligament connecting the stomach and the spleen. The oesophageal branches of the gastric artery travel through this ligament to arrive at the abdominal part of the oesophagus. Even further posteriorly are the left phrenic artery and the left crus of the diaphragm. The vagus nerve travels alongside the oesophagus but its relation to the structure is varied as the oesophagus traverses the diaphragm. The left vagus nerve, with its two to three trunks, is usually located on the anterior aspect. The thick, single right vagus nerve is situated posterior to the oesophagus.

OESOPHAGEAL WALL

The oesophageal wall is made up of four discrete layers. These are, from the lumen outwards, the mucosa, submucosa, muscularis propria and adventitial layers. The oesophagus lacks a distinct serosal covering. As a result, direct tumour spread is easily facilitated, often complicating surgical resection. In addition, in the event of oesophageal perforation, the absence of a serosal layer makes repair more difficult.

Mucosal layer

The mucosal layer is lined by a continuation of the non-keratinizing stratified squamous epithelium which has an abrupt change in the lower oesophagus on entering into the stomach at the so-called Z line. This jagged line at the gastro-oesophageal junction is the area at which the mucosa changes to columnar epithelium which lines the stomach. The oesophageal mucosa above is characteristically greyish-pink and smooth; the gastric mucosa below is reddish-pink and has a number of bulges and depressions on its surface. This change is clearly visible at endoscopy. In life, the oesophageal mucosa is thick; superiorly it is more red and thicker. Inferiorly, it is paler. At rest, the mucosa is arranged into longitudinal folds; which disappear upon distension of the oesophagus.

The mucosal layer has three distinct sub-layers: (i) non-keratinizing epithelium which covers the entirety of the inner surface of the oesophagus, with the exception of the lower oesophageal sphincter, at which squamous and columnar epithelium meet and coexist; (ii) a thin layer of connective tissue, the lamina propria; and (iii) the muscularis mucosae comprising irregularly arranged longitudinal fibres of smooth muscle extending from the oesophagus into the rest of the gastrointestinal tract.

Submucosal layer

The submucosal layer loosely connects the mucosa to the underlying muscular layer. It also penetrates into the longitudinal ridges of the lumen of the oesophagus. It contains the larger blood vessels and Meissner's plexus of parasympathetic fibres and numerous mucinous glands, lymphocytes and plasma cells. The oesophageal mucinous glands are small tubulo-acinar glands. These mucous glands have acini arranged like grapes on a stem. Secretion from these glands is important in oesophageal clearance as well as to render the oesophageal tissue resistant to acid. The elastic fibres of the submucosal layer play an important role in closing the lumen after the dilatation caused by peristalsis.

Muscular layer (muscularis externa)

The muscular layer is responsible for oesophageal motor function and is composed of an outer longitudinal and an inner circular coat of muscle fibres. These layers are typical to the intestine. The longitudinal layer forms a continuous coverage of the oesophagus, apart from the upper 4 cm. Here, the fibres diverge posteriorly to form two longitudinal bands which pass in a superior and anterior direction to attach to the cricoid cartilage. The circular fibres are continuous, on the posterior aspect, with the corresponding muscular layer of the constrictor muscle superiorly and the muscles of the stomach. Generally, the longitudinal layer is the thicker of the two layers.

The proximal third of the oesophagus consists exclusively of striated (or skeletal) muscle, whereas the distal third is made up of smooth muscle. Between these two regions is a mixture of both striated and smooth muscle, a zone of transition in which the proportion of smooth muscle increases continuously, so that it, alone, exists in the lower part of the oesophagus. The oesophagus has two physiological sphincters, namely the upper oesophageal sphincter, which is composed principally of the lower

fibres of cricopharyngeus and is therefore anatomically strictly outside the oesophagus, and the lower oesophageal sphincter at the junction of the oesophagus and stomach. The physiological function of these is dealt with in Chapter 48, Physiology of swallowing.

Adventitial or fibrous layer

The external fibrous layer of the oesophagus consists of adventitia and dense connective tissue with elastin fibres and also contains small vessels, nerve fibres and lymphatic channels. This covers the oesophagus and connects it with its neighbouring structures. As mentioned above, the oesophagus is unique in that it has no serosal layer, unlike the rest of the digestive tract.

BLOOD SUPPLY OF THE OESOPHAGUS

The cervical oesophagus gets its main blood supply superiorly from the inferior thyroid artery of the thyrocervical trunk. The thoracic section of the oesophagus gains some of its blood supply segmentally from branches of the descending aorta or by branches of the bronchial and oesophageal arteries. Approximately five oesophageal arteries arise from the aorta anteriorly and these descend to supply the oesophagus by forming a vascular chain on the oesophagus itself. The vascular chain anastomoses with the branches of the inferior thyroid artery above as well as with the branches of the left phrenic and left gastric arteries below. The abdominal oesophagus is thus supplied by the left gastric and left inferior phrenic arteries. A dense blood supply and the anastomotic nature of the oesophageal blood supplying it render the organ virtually immune to infarction.

The venous drainage is initially via a complex network or plexus of veins that lies in the submucosal layer. Drainage from here is into a perioesophageal venous plexus, the point of origin of the oesophageal veins. The cervical oesophagus drains into the inferior thyroid vein via the brachiocephalic veins. The thoracic part of the oesophagus drains predominantly into the azygos veins, but also to a lesser extent into the hemiazygos and intercostal veins in the thorax, as well as to the bronchial veins. Inferiorly, the abdominal oesophagus drains into the left gastric vein. It meets the oesophageal vein at the lesser curvature of the stomach and drains from here into the portal vein. Knowledge of this anastomosis occurring at the level of the central diaphragmatic tendon (vertebral level T8) between the portal and systemic venous system is useful when diagnosing oesophageal varices. Portal obstruction can result in the formation of oesophageal varices in these veins, and throughout the upper gastrointestinal system, which, if ruptured, can result in life-threatening haemorrhaging.

INNERVATION OF THE OESOPHAGUS

The oesophagus also receives its innervation from dual sources. This is traditionally referred to as the sympathetic and parasympathetic supplies, although innervation is received from the vagus as well as the spinal nerves via different pathways and synapsing in different nuclei. Its sympathetic supplies, both motor and sensory, are from the spinal segments of T1–T10. Sympathetic and parasympathetic innervation regulates smooth muscle activity and glandular secretion.

The upper striated muscles of the oesophagus are supplied by multiple small branches arising from the recurrent laryngeal nerves as well as postganglionic sympathetic fibres from the middle cervical ganglia hitching a ride along the inferior thyroid arteries. The more distal smooth muscle fibres of the lower oesophagus are supplied by the oesophageal plexus, a meshwork of parasympathetic and sympathetic fibres hosted by the vagus and recurrent laryngeal nerves below the level of the lung roots.

Intrinsic innervation of the oesophagus is provided by the thin nerve fibres and numerous ganglia of the intramural myenteric and submucosal plexi. Auerbach's plexus (also known as the myenteric plexus) is formed by the ganglia that lie between the longitudinal and the circular layers of the tunica muscularis. Meissner's plexus (also known as the submucous plexus) is formed by those ganglia that lie in the submucosa. Despite their different functions – Auerbach's plexus regulates contraction of the outer muscle layers and Meissner's plexus regulates secretion and the peristaltic contractions of the muscularis mucosae – they are interconnected by a network of fibres.

The perception of pain in the oesophagus is limited and is more likely to be due to stretching of the external muscular coat rather than actual mucosal awareness. This may explain why localization of pain to a site within the oesophagus is very difficult, although referred pain is common.

LYMPHATIC DRAINAGE OF THE OESOPHAGUS

An extensive submucosal lymphatic system exists within the oesophagus. The upper oesophagus drains into the lower deep cervical and paratracheal and upper mediastinal nodes. The thoracic section drains into the posterior mediastinal nodes and the tracheobronchial nodes. The abdominal section drains into the left gastric nodes as well as the coeliac nodes. The lymph drainage, however, does not follow this pattern strictly. Within the walls of the oesophagus, there are lymphatic channels which allow the flow of lymph within the organ itself. Some lymph may pass directly into the thoracic duct.

KEY POINTS

- Within the nasopharynx, the **pharyngotympanic/auditory tube** connecting the middle ear to the pharynx opens out. This connection helps to equalize pressure behind the tympanic membrane within the ear but, as with all connections, it has the potential for spreading infections from one site to the other, predominantly from the nasopharynx to the middle ear.
- Although there is plexiform venous drainage around the tonsillar hemicapsule of the palatine tonsils, the paratonsillar vein (or external palatine vein) runs within the capsule and is the usual culprit for a **post-tonsillectomy bleed**.
- The glossopharyngeal nerve also supplies the middle ear (the tympanic branch) and thus **referred pain** to the ear during an episode of tonsillitis or after any surgical procedure in the peritonsillar area is not unusual.
- Nasopharyngeal tonsils can be problematic when inflamed in **adenoiditis**. The lymphoid tissue here is prominent in children but generally atrophies after puberty. Enlarged adenoids can cause mouth-breathing, and may block the pharyngotympanic tube.
- **Peritonsillar abscesses** – quinsies – occur outside the tonsillar hemicapsule. The internal carotid artery is about 2.5 cm lateral and posterior to the tonsil and this is thus a potential danger zone when incising peritonsillar abscesses.
- The valleculae, between the dorsum of the tongue and the epiglottis, is a common site for **small foreign bodies** to lodge.
- The piriform recesses at the side of the laryngeal inlet are also potential sites where **foreign bodies may lodge**. The space also allows for **malignancies** to grow to a substantial size asymptomatically, at which point they present with metastatic cervical lymphadenopathy.
- Killian's dehiscence, at the junction formed by the two muscles (thyropharyngeus m. and cricopharyngeus m.) forming the inferior constrictor, is a site of potential weakness. A defect or weakness here can result in the formation of a **pharyngeal diverticulum**.
- The cricopharyngeus muscle, which is circular and a sphincter, remains closed most of the time. This can pose problems when an **endoscope** is required to get beyond this point into the oesophagus but is generally overcome by getting the patient to swallow, and thus relax the sphincter momentarily.
- Three anatomical constrictions of the oesophagus, measured by their distance from the incisor teeth to allow for endoscopic examinations, are at 15 cm, 23–27 cm and 38 cm.

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CHAPTER
48

PHYSIOLOGY OF SWALLOWING

Joanne M. Patterson and Stephen McHanwell

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SEARCH STRATEGY

Data in this chapter are based on a PubMed search using the keywords: swallowing, transit times, pharyngeal pressure, bolus formation, mastication and taste.

INTRODUCTION

Swallowing requires the coordinated activity of muscles in three regions of the head and neck: the oral cavity, the pharynx and larynx, and the oesophagus. This complex sequence of motor behaviour is part reflex and partly under voluntary control. It has been extensively investigated using a variety of techniques including videofluoroscopy, endoscopy, radiography, ultrasound, electromyography (EMG) recording and functional MRI, together with observations on individuals with dysphagia. Swallowing as a motor behaviour is so complex that some details have remained difficult to resolve. The literature is often contradictory, particularly the earlier studies based on inferential analysis of radiographic data. Careful analysis of swallowing using newer techniques shows that there is a surprising amount of variation between individuals. This chapter will survey the current state of knowledge concerning the normal anatomy and physiology of swallowing and what might be considered as the limits of normality, essential to the understanding of dysphagia. Neural control and the coordination of breathing and swallowing will also be addressed.

STRUCTURES INVOLVED IN SWALLOWING

Swallowing involves the passage of a bolus of food or liquid from the oral cavity to the stomach via the pharynx and oesophagus. During this passage, the bolus passes over the entrance to the laryngeal vestibule which thus needs to be closed if food or liquid is not to enter the airways (**Figure 48.1**). The musculature involved is extensive, including muscles controlling the position of the lips, elevation and depression of the jaw, position and degree of contraction of the tongue, the degree of constriction and length of the pharynx, closure of the laryngeal inlet, the cricopharyngeal sphincter and the muscles of the oesophagus and oesophageal sphincter. This section will simply outline some key anatomical features and functions of the structures involved. For a more detailed account of the anatomy of the relevant muscles and the larynx, a suitable textbook of anatomy should be consulted.[1]

The elevators and depressors of the jaw play a key role in bolus preparation before the swallow is initiated by grinding and reducing the food between the teeth. Two groups of muscles that move the jaw can be recognized: the supramandibular muscles and the inframandibular muscles. The supramandibular muscles are attached between the mandible and the skull and comprise the muscles of mastication, temporalis, masseter and the medial and lateral pterygoid muscles. As the consequence of their attachments, they principally act as jaw elevators, though the inferior head of lateral pterygoid is active during jaw depression by acting to protract the mandible. The inframandibular muscles are composed of the suprahyoid and infrahyoid muscles of the neck and act indirectly on the mandible through their actions in raising or lowering the hyoid bone. Bolus formation is also a function of the

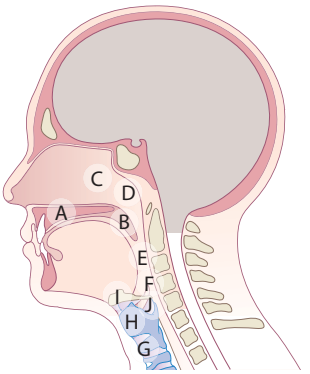


Figure 48.1 A mid-sagittal section of the head and neck showing the location of the major structures involved in swallowing. A, hard palate; B, soft palate; C, nasopharynx; D, pharyngeal isthmus; E, oropharynx; F, laryngopharynx; G, cricoid cartilage; H, thyroid cartilage; I, hyoid bone; J, laryngeal inlet.

muscles of the tongue. Two groups of tongue muscles can be recognized, the intrinsic muscles of which are mainly responsible for changing the shape of the tongue. The extrinsic muscles with one attachment outside the tongue are responsible for altering the position of the tongue in the mouth. The actions of these two groups of tongue muscles are not entirely independent since changes in tongue shape will result in changes in tongue position and vice versa. For example, flattening the tongue by the verticalis muscles will protrude the tongue as its bulk is displaced, while downward movement of the tongue by the hyoglossus muscle will tend to lower the sides of the tongue but not its centre. The actions of the tongue and jaw muscles in bolus formation are aided by that of the sphincter of the lips orbicularis oris in maintaining a seal, the buccinator muscle of the cheek in returning food from the vestibule into the oral cavity and thus ensuring that food remains in place between the occlusal surfaces of the molar teeth, and the soft palate in preventing nasal regurgitation and premature movement of material into the oropharynx. It is now recognized that the palate does not seal off the oropharynx completely during bolus formation (see below).

On leaving the oral cavity, food enters the pharynx, a midline tube approximately 15 cm long, continuous with the oesophagus inferiorly while above the soft palate it is continuous with the nasal cavities anteriorly. The anterior wall of the pharynx below the soft palate is incomplete and composed of the posterior part of the tongue superiorly and the larynx inferiorly, with the laryngeal inlet forming a posterior-facing opening on the anterior wall. As a consequence of these anterior anatomical relationships, the pharynx is divided into three regions: nasopharynx, oropharynx and laryngopharynx, corresponding to those structures that lie anterior to the appropriate part of the pharyngeal tube.

The pharyngeal wall proper is composed, like the whole of the gastrointestinal tract, of four layers or coats which, from the outside in, are the areolar, the muscular, the submucous and the innermost mucous membrane. The muscular layer is composed of circular and longitudinal muscles. There are three circular muscles – the superior, middle and inferior constrictors – with the inferior constrictor being further subdivided into a thyropharyngeus and a cricopharyngeus part. These constrictor muscles are arranged as a triad and are usually described as being arranged in the form of three stacked cups with the inferior constrictor being on the outside and the middle and superior constrictors lying inside. The fibres of the superior and middle constrictors extend inside the inferior constrictor to approximately the level of the vocal folds. With the exception of the cricopharyngeus, the constrictor muscles are paired and attach to a posterior midline raphe. The cricopharyngeus forms a distinct sphincter, the cricopharyngeal sphincter, at the point where the laryngopharynx joins the oesophagus and it contains a high proportion of elastic fibres to aid its sphincteric function. There are two discrete longitudinal muscles on each side, the palatopharyngeus and the stylopharyngeus, which, despite their names, both attach inferiorly to the posterior border of the thyroid cartilage.

The larynx is formed of a series of cartilages in the wall of the upper part of the trachea, the main cartilages being the thyroid, cricoid arytenoid and epiglottis. The thyroid, cricoid and arytenoid cartilages articulate at two synovial joints – the cricothyroid and cricoarytenoid joints – formed between the cartilages of the same name. Movements at these joints result in changes of position of the vocal folds to allow lengthening or shortening, opening or closing. The larynx is suspended from the hyoid bone by the thyrohyoid membrane and thyrohyoid muscle. When the suprahyoid and infrahyoid muscles move the hyoid bone, they also alter the height of the larynx. The epiglottis projects above the hyoid behind the posterior part of the tongue and is attached to the posterior aspect of the thyroid cartilage. The epiglottis is capable of movements to aid in the closure of the laryngeal inlet, although the mechanism by which movements are produced remains unclear (see below). Attached between the epiglottis anteriorly and the arytenoid cartilages posteriorly is the quadrangular membrane, the superior margin of which forms the boundary of the laryngeal inlet. Within this superior border are the aryepiglottic muscles that control the inlet, together with the small thyroepiglotticus muscle that may help to depress the epiglottis to prevent aspiration. Adduction or closure of the vocal cords by the intrinsic muscles of the larynx provides a further line of defence to the accidental ingestion of food or foreign objects.

The oesophagus is a muscular tube continuous with the pharynx. It has a short cervical course before it enters the thorax where it lies posteriorly in the midline and descends, piercing the diaphragm and entering the stomach.

THE SEQUENCE OF EVENTS IN THE NORMAL SWALLOW

In any land-living mammal that does not normally swallow its food whole, different stages of swallowing can be identified as having evolved in order to ensure that food is transported from the mouth to the stomach safely.[2]

Swallowing is a continuous process with overlapping events that may be artificially divided into three distinct phases: oral (preparatory and transit phase), pharyngeal and oesophageal. This evolutionary division is also convenient for descriptive purposes. **Figure 48.2** illustrates the key stages in the swallowing process as traditionally described.

Oral phase for liquids

ORAL PREPARATORY PHASE

In the oral preparatory phase, liquids are taken into the mouth and held either on the floor of the mouth or against the hard palate by the upward movement of the tongue. Throughout this first phase, the soft palate is kept lowered by the contraction of the palatoglossus and palatopharyngeus. The posterior tongue is simultaneously elevated, thus preventing uncontrolled spillage of the bolus into the pharynx. Liquids require minimal processing and are marginally diluted with saliva before swallowing. The airways remain open during this phase. Traditionally, the oral cavity was thought to be sealed posteriorly but this may not always be the case, as described in the following section.[3]

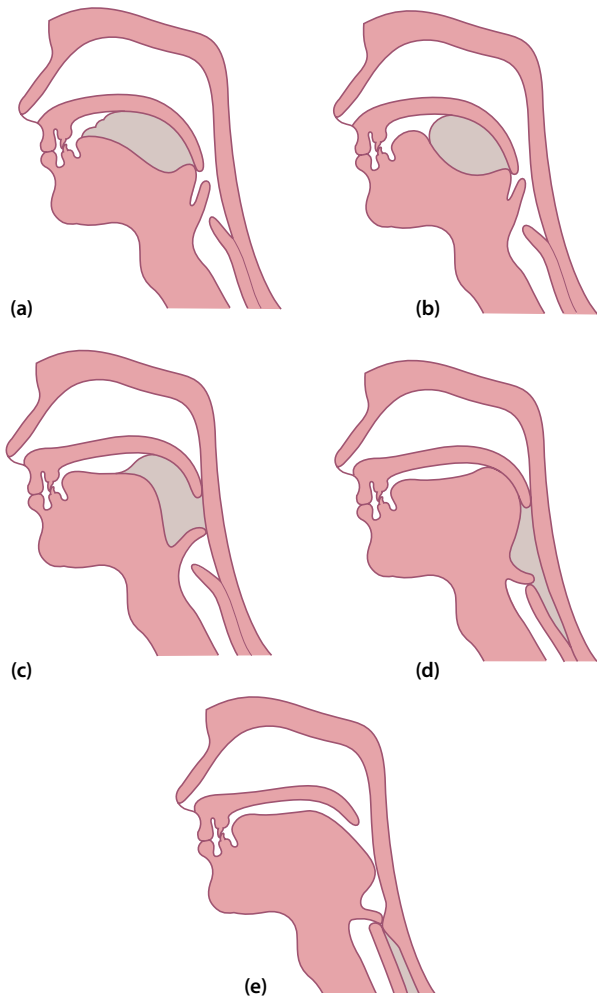


Figure 48.2 Oral and pharyngeal stages of a normal swallow: (a) oral phase, food is reduced and the bolus prepared; **(b)** the bolus is moved to the posterior part of the tongue; **(c)** the bolus contacts the trigger points in the oropharynx and the pharyngeal phase is initiated; **(d)** the bolus is moved past the closed larynx; **(e)** the bolus enters the oesophagus.

ORAL TRANSIT PHASE

The bolus is transported through the palatoglossal and palatopharyngeal arches into the oropharynx. The tongue is moved by the action of the intrinsic muscles together with the genioglossus elevating the tongue tip and blade of the tongue towards the hard palate. Orbicularis oris and buccinator remain contracted, keeping the lips and cheeks taut and the liquid central in the oral cavity. Liquid boluses are accommodated in a shallow midline gutter that forms along the dorsum of the tongue, probably as a result of the styloglossi and the genioglossi, aided by the superior longitudinal and transverse fibres of the intrinsic muscles.

A prerequisite for oral transit is mandibular elevation. Although the mouth does not have to be fully closed during swallowing, it is hard to swallow with the mouth more than a little open. The stabilization and elevation of the mandible is necessary for adequate lingual pressure generation. The proximity of the tongue to the palate helps to compress the bolus. The elevation and fixing of the mandible also assist the suprahyoid muscles in raising the hyoid bone. The elevation of the floor of the mouth is accompanied by lifting the tongue under the action of the stylohyoid. Simultaneously, the tongue is flattened, probably as a result of the contraction of the hyoglossus and some of the intrinsic lingual muscles, thus moving the bolus backwards. Patterns of lingual movement during swallowing can vary but, most commonly, the elevated, flattened tongue pushes the bolus against the hard palate, and the sides of the tongue seal against the maxillary alveolar processes, helping to move it posteriorly. The greatest amount of pressure appears to be generated by the anterior lingual segment.[4] Contraction of the styloglossus and mylohyoid completes the elevation of the back of the tongue. These tongue movements are simplified during sequential swallowing, as the frequency and speed of swallowing increase.[5] As the bolus reaches the back of the tongue, now deeply grooved, the soft palate is elevated by the levator and tensor veli palatini to protect the nasopharynx from the entry of food and to close the airways superiorly.

Oral phase for solids

When swallowing solid food, the process is slightly different. Food is mixed with saliva and reduced to smaller particles by the process of chewing. This can vary in duration considerably, from less than 1 second to as much as 10 seconds. When the bolus has been converted to a suitable consistency to be swallowed, it is transferred to the oropharynx, valleculae and posterior part of the tongue, where it may be retained for a few seconds prior to swallowing, sometimes referred to as ‘retrolingual loading’.[3]

During this time chewing can continue and the bolus is progressively added to, until a swallow is initiated and the pharyngeal phase begins. Thus, the oral preparatory, oral transport and pharyngeal phases overlap when solid food is being swallowed.

Chewing is essential to fragmenting solids, using a combination of shearing and compression forces. The mandible is moved by the action of the jaw elevators – the temporalis, masseter and medial pterygoid – and jaw depressors. Parotid salivary flow is increased in association with this action. The lips maintain a tight seal under the action of the orbicularis oris while the buccinator performs a similar function for the cheeks. In this way the sulci are closed, the vestibule normally remains empty, and any food that enters the vestibule is returned to the oral cavity proper. This, along with lateral and rotatory tongue movements, ensures that the food remains positioned under the occlusal surfaces of the molar teeth. Lateral and rotatory tongue movements ensure that the food is positioned under the occlusal surfaces of the teeth. Lingual forces will differ according to the physical properties of the bolus. These movements are cyclical in phase with movements of the jaw and hyoid bone. As the jaw is depressed, the tongue is also depressed and moves anteriorly. As the jaw is elevated, the tongue is retracted so that it no longer lies under the anterior teeth as they are brought together by jaw elevation. This helps to ensure that the tongue is not bitten during chewing.

It used to be thought that the soft palate was depressed throughout this phase, but it is now known that there is not a tight posterior seal and that the oral and oropharynx remain in communication.[6]

Pharyngeal phase

The pharyngeal phase begins at the point of the bolus leaving the oral cavity to enter the pharynx until it passes into the oesophagus. During this involuntary phase the respiratory and digestive streams cross and so it is important that this reflex behaviour occurs as automatically as possible to prevent blockage of the airways or aspiration into the lungs. As the bolus is moved back by the tongue to enter the pharynx, a sequence of events is initiated that ensures that the airways are protected during bolus transport. Diaphragmatic contraction is inhibited making simultaneous breathing and swallowing impossible under normal circumstances.[7] The nasopharynx is sealed off from the oropharynx by activation of the superior pharyngeal constrictor and contraction of a subset of palatopharyngeal fibres to form a variable, ridge-like structure (Passavant's ridge) against which the soft palate is elevated.

As the bolus enters the oropharynx and touches key trigger points, a patterned response is initiated in which the constrictors relax to dilate the pharynx, while the pharynx and larynx are raised by the longitudinal muscles. Solid boluses are propelled over the epiglottis by the action of the constrictors contracting in sequence. The larynx is then closed by contraction of the muscles of the laryngeal inlet, predominantly those of the aryepiglottic folds. The initiation of swallowing involves contact of the food with the palatoglossal and palatopharyngeal (faucial) arches or with the mucosa overlying the posterior pharynx in the region that is innervated by the glossopharyngeal nerve. Work conducted using simultaneous videofluoroscopy and endoscopy suggests that the 'trigger point' for this initiation may be the 'summation of afferent signals for the entire oropharyngeal sensory field', rather than a single point.[3] However, this may not be the case for the swallowing of secretions, as saliva may gather as deep as the piriform sinuses, until a critical mass is reached upon which a swallow response is triggered. Bolus properties may also influence this timing, for example, carbonated drinks or cold fluid temperature can reduce these latency times.[8] Bolus material is seen in the valleculae and even the piriform sinuses in 60% of liquid and 76% of solid swallows before the swallow is initiated.[3] This calls into question the term 'premature spillage' (where the bolus is viewed in the laryngopharynx prior to a swallow trigger) as an indicator of dysphagia. It is often said that, once the bolus of food has passed the palatoglossal and palatopharyngeal arches, swallowing becomes reflexive. While it is true that swallowing is automatic once initiated, many people can voluntarily delay their swallowing up to a certain point.

Lack of clarity exists around the precise temporal relationships of subsequent events involving movement of the food from the posterior part of the tongue into the oropharynx and airway protection. As the bolus is moved into the oropharynx, a reflex closure of the glottis is initiated in which there are preparatory movements of the vocal folds and the laryngeal inlet prior to a full closure of the larynx.[3] Endoscopic studies have shown that the first swallowing event is arytenoid movement towards the midline.[9, 10] These movements are even seen when the bolus enters the oral cavity.[10] More commonly, the true vocal folds achieve maximal closure prior to laryngeal elevation, but for some the glottis may not be fully adducted until elevation is complete.[10] Furthermore, it appears there may be variance from person to person and from swallow to swallow, with a range of laryngeal closure duration from 0.31 seconds to 1.07 seconds.[11] Events may alter according to bolus consistency and the nature of the swallow. For example, during sequential swallowing of drinks, some individuals retain an elevated laryngeal position; others demonstrate a pattern of laryngeal 'bobbing' with the larynx semi returning to a resting position between swallows. Apnoea onset occurs approximately 0.19 seconds prior to the elevation of the larynx.[7] A completely sealed larynx requires full adduction of the vocal folds and hence glottic closure by medial movement of the arytenoid cartilages. This is achieved by the combined efforts of the thyroarytenoid, interarytenoid and lateral cricoarytenoid muscles. The ventricular folds approximate, tensing of the edges of the laryngeal opening and lowering of the epiglottis.[7]

The bolus enters the pharyngeal space, which is widening as it is raised, said by some to resemble the engulfing of prey by a snake.[2] This is partly due to the relaxation of the pharyngeal constrictors and partly to the anterior

movement of the pharynx as the hyoid bone is drawn forward under the elevating action of the suprahyoid muscles. It is thought that the geniohyoid is largely responsible for displacing the hyoid anteriorly, and the mylohyoid superiorly.[12] Laryngeal elevation also occurs as the suprahyoid muscles move the hyoid bone anteriorly, contributing to pharyngeal dilation. Raising the larynx narrows the laryngeal inlet, moving it towards the pharyngeal surface of the epiglottis as the laryngeal cartilages move anteriorly, tucking under the bulge of the posterior tongue, i.e. out of the path of the bolus. This action helps to expand the hypopharyngeal space and relax the cricopharyngeal sphincter, which is also raised by several centimetres. The bolus moves into the oropharynx, contacting the epiglottis, which then moves downward. This movement is usually described as occurring in two distinct stages, with the first bringing the epiglottis from a vertical to a nearly horizontal position and the second moving the upper third of the epiglottis to below the horizontal to cover the narrowed laryngeal aditus. The precise contribution of active and passive mechanisms to this two-phase closure is unclear. Some authors state that both actions occur passively due to movements of adjacent structures and forces generated by compression of the pre-epiglottic adipose fat pad, and within the ligamentous attachments of the epiglottis, or by a combination of the two.[13, 14] Others claim that the second epiglottic movement is generated actively by the action of the thyroepiglottic and hyoepiglottic muscles.[15] In favour of an entirely passive mechanism, it has been claimed that these muscles are too sparse to generate adequate force and that some of their attachments are not consistent with such an action.[14] Throughout this stage of swallowing, respiration remains suspended.

As the food passes over the posterior part of the curved epiglottis, it is diverted into the lateral food channels and the piriform fossae. Evidence has shown that solids tend to go straight over the epiglottis, while liquids are diverted laterally. This is possibly a characteristic of bolus properties rather than swallow biomechanics.[3] Multiple swallowing post-bolus is often classed as a sign of impairment. Clearance swallows occur in the healthy population even with water, more so with older adults.[16]

The true and false folds guard the entrance to the airways with the true vocal folds adducted to prevent ingress of foreign bodies. The protective cough reflex can then be used to remove the object. This strong expiratory airflow is assisted by abdominal muscles and compression of the lungs.

The pharynx constricts behind the bolus as the superior constrictor muscle contracts. The bolus is carried down the pharynx by a coordinated peristaltic wave in which the three constrictor muscles contract in the appropriate sequence, driving the bolus towards the oesophagus. The head of the bolus moves faster than the wave of the pharyngeal contraction suggesting that the kinetic energy imparted to the bolus as it is expelled from the mouth may be sufficient to carry it through to the pharynx. The tongue driving force is a positive pressure that squeezes the bolus towards the laryngopharynx. It is generated by the upward movement of the tongue pressing the bolus against the contracting pharyngeal wall and requires a tight nasopharyngeal seal. A hypopharyngeal suction pump is caused by the elevation and anterior movement of the hyoid and larynx, which creates a negative pressure in the laryngopharynx, drawing the bolus towards the oesophagus, aided by a more negative pressure inside the oesophagus. The pharyngeal constrictors generate a positive pressure wave behind the bolus. Their sequential contraction may facilitate clearance of any pharyngeal wall or piriform sinus residue.

At the end of this phase, the bolus is propelled towards the cricopharyngeal sphincter. At rest, this sphincter is closed by active contraction. Prior to the bolus arriving and the sphincter opening, the cricopharyngeus relaxes. The sphincter is then opened actively by the combined action of the suprahyoid muscles in moving the larynx anteriorly and superiorly and passively by pressure from the arriving bolus.

Oesophageal phase

The oesophageal phase begins after the relaxation of the cricopharyngeal sphincter has allowed the bolus to enter the oesophagus. This is a true peristalsis in which a relaxation in front of the bolus and a constriction behind the bolus move it towards the stomach. Sequential waves of contractions of the oesophageal musculature subsequently propel the bolus down to the lower oesophageal sphincter, which opens momentarily to admit the bolus to the stomach.

Swallowing timings

The timings of the stages of swallowing have been extensively investigated. Once the food is of a suitable consistency to swallow, transit from the mouth to the oropharynx takes 1–2 seconds, with up to a further second for the bolus to traverse the pharynx to the cricopharyngeal sphincter. The bolus then passes through the oesophagus to the stomach. The time taken for oesophageal transit has been estimated by a variety of techniques. Healthy oesophageal clearance time for a single swallow is estimated at 10–15 seconds,[17, 18] although a shorter time of 3 seconds is needed for liquids.[2] In the preparatory stage, it is unclear what determines when the bolus is to be moved into the oropharynx. An important factor is likely to be bolus consistency as sensed by mechanoreceptors in the oral cavity. The sensory control of swallowing will be discussed below under ‘Neural control’.

NEURAL CONTROL

Neural control of the complex activity of healthy swallowing involves a number of different regions of the central nervous system (CNS). In common with all complex motor behaviours, swallowing is organized and coordinated by a hierarchical series of structures within the brain.

This extends from the motor neurons within the motor nuclei of the brainstem and spinal cord (for ventilation) up to the cortex. The act of swallowing, as with all movement, is regulated by sensory feedback, although the importance of this has only been fully recognized relatively recently.[19] There are probably still some areas of the CNS involved in swallowing that remain to be identified but there is a consensus as to the main regions involved. The initiation of swallowing is normally characterized as being either a voluntary act (volitional swallowing) or a reflex (reflexive swallowing) as the result of stimulation of the appropriate mucosa in the oral cavity. This might occur during saliva accumulation or by the presence of food or liquid. However, it is now recognized that this distinction is not absolute. During mastication, for example, a volitional act, the encountering of a hard object will cause mastication to cease, suggesting a continuum of control between the purely volitional and purely reflex components of swallowing.[20] Although there may be a continuum because of the fact that, as swallowing is partly a reflex activity and partly voluntary, its neural control is divided between two major regions of the brain: the cerebral cortex and the brainstem. Studies have shown that several regions of the cortex contribute to the voluntary control of swallowing. It is also recognized that, as with any voluntary movement, the movements of swallowing are also regulated by the basal ganglia and the cerebellum.[21, 22] Due to the close anatomical and physiological relationships between swallowing, ventilation and mastication, there is also extensive overlap in the brainstem areas controlling these functions. There is an absolute requirement that neural control of these various processes ensures that they are coordinated.

The cortical control of swallowing involves projections to numerous groups of motor neurons. The areas of the cortex that have been most frequently cited as being involved in the control of swallowing include the primary motor and sensory cortices, premotor and supplementary cortices, posterior parietal cortex, cingulate cortex (especially the anterior cingulate gyrus) and the insula and frontal operculum.[23] Corticobulbar projections to motor nuclei controlling muscle groups are bilateral but, in the case of projections controlling pharyngeal muscles, asymmetric so that one can speak of a swallowing dominant hemisphere. As is the case for speech, this asymmetry is not related to handedness but it is the left hemisphere that is usually stated as being swallowing dominant though not with the same high frequency as speech.[24, 25]

Within the cortex, evidence suggests that the frontal swallowing centre is organized somatotopically with different regions controlling different stages of swallowing. This is substantiated by studies employing transcranial magnetic stimulation of the frontal swallowing centre.[24] These studies show that the lower precentral gyrus and posterior inferior frontal gyrus control the oral phase of swallowing. The voluntary initiation of swallowing (oral phases, see above) involves bilateral areas of the prefrontal, frontal and parietal cortices. These include the face areas of both the primary sensory and motor cortex, as well as the prefrontal swallowing areas which are located just anterior to the face region of the precentral gyrus in the primary motor cortex, corresponding to Brodman's area. Stimulation here produces swallowing activity in the appropriate muscles of the oral cavity, pharynx, palate and larynx.[26] Volitional swallowing also activates the cingulate cortex, anterior cingulate gyrus, supplementary motor cortex and insula just prior to the onset of the swallow. It has been proposed that activity in these regions prior to the swallow occurring controls the initiation, including motivation to swallow, and planning of the act of swallowing.[23]

Reflexive swallowing (see 'Pharyngeal phase' above) is thought to involve primary motor cortex, premotor cortex and areas of sensorimotor cortex within the parietal lobe.[27, 28] In most people, swallowing control is asymmetrical with the projection from one hemisphere being larger than the other. It has been hypothesized that this explains both the prevalence of swallowing problems following stroke and the recovery that occurs in most patients over a period of weeks. Damage to the hemisphere that is the source of the greater projection to the swallowing structures in the brainstem would account for the initial difficulty. Recovery then occurs as the intact projection from the undamaged hemisphere is reorganized.[29]

It can be seen that both volitional and reflexive swallowing involve the primary sensory and primary motor cortices consistent with the role, more generally, of these cortical areas in the control of fine distal motor movement. As might be expected, sensory feedback is needed to control swallowing, just as would be the case for any other movement.[19] The satisfactory execution of swallow needs to take account of the properties of the bolus being swallowed such as its size, texture and consistency. These properties are relayed to the primary sensory and motor cortices during the reflexive phase where they influence the intensity and speed of pharyngeal muscle contraction to ensure that the bolus is safely moved through the pharynx and on to the oesophagus.[30, 31] This role of the motor and sensory cortex in controlling force of contraction of muscles is consistent with what has been observed in other volitional movements.

The inference from animal studies is that the control of swallowing is bilateral, but in humans the organization of corticobulbar projections from the cortex to the relevant motor nuclei appears more complex. Cortical projections to the muscles of the larynx, pharynx, palate and upper face are bilateral while projections to other muscles can be either unilateral or bilateral.[32]

Other cortical areas that have been implicated in swallowing include the frontal operculum, the orbitofrontal cortex and the superior temporal gyrus.[24] The insula lies deep to the lateral fissure and is covered by the operculae of the frontal, parietal and temporal lobes and strokes here can induce dysphagia.[33] In addition to its role in swallowing as outlined above, taste is also represented in this region. It has been suggested that the insula may be involved in integrating the taste of a swallow with the movement of swallowing. The superior temporal gyrus has also been identified as a possible region of the cortex involved in integrating taste, but also food imagery, with swallowing.[34] This suggests that cortical control of swallowing

is hierarchical, with precentral areas of the cortex being influenced by deeper and more caudal centres.[24]

Cortical control of movement is regulated by reciprocal projections between the cortex and basal ganglia and between the cortex and the cerebellum. It is becoming evident that these regions of the brain also play a part in the control of swallowing. The evidence that this is the case in humans comes mainly from investigations of swallowing disorders in disease. Connections pass from cortical regions through the basal ganglia and back to the cortex via nuclei in the thalamus in the form of a series of recurrent loops. The basal ganglia were first recognized as having a role in movement because of the very obvious movement disorders that occur in basal ganglia disorders such as Parkinson's disease. However, it is now recognized that the basal ganglia regulate many other aspects of cortical function. Disorders of the basal ganglia affecting movement can be characterized as hypokinetic, with too little movement (e.g. in Parkinson's disease), or hyperkinetic, with too much movement (such as in Huntington's chorea). The effects of Parkinson's disease upon swallowing are consistent with its effects upon movement generally, with hypokinetic tongue movements that impair transport of food into the pharynx, poor bolus formation and poor pharyngeal transport including slower laryngeal movements.[21] The cerebellum also has reciprocal connections with the cerebral cortical regions controlling movement and functions to monitor executions of movements and act as an error detector. Though there are relatively few investigations into the occurrence of dysphagia in cerebellar disease and the results are inconclusive, it would appear that the cerebellum does play a part in motor control of swallowing.[22]

The cortex is crucial in the voluntary initiation of swallowing and integration with movements of the face and associated structures. However, cortical structures are not essential for a coordinated swallow, which can occur in the presence of significant brain damage in these regions. There are important areas within the brainstem necessary for the control of swallowing and these are located particularly within the medulla. Descending pathways project to these medullary swallowing centres from the frontal swallowing areas within the cortex. These probably include pathways in both the dorsolateral and ventromedial descending systems through the ventral and lateral corticobulbar tracts. Whether swallows are volitional or reflexive, the pattern of the swallow is similar because it is the brainstem that executes the patterns of swallowing movements in both cases.

Most of our knowledge of the role of these regions in swallowing control comes from experimental studies in animals. The results of these studies clearly have limitations when one attempts to apply them to humans.[35] Within the medulla there are a number of neuron groups involved in the control of swallowing.[36] Swallowing is initiated by touch sensation or pressure from the liquid or food within the posterior part of the oral cavity, epiglottis or oropharynx. Thus, the nuclei receiving afferent input from these regions, which include the nucleus tractus solitarius and the spinal trigeminal nucleus, are very important. Afferent input from the jaw, muscles of mastication, lips and tongue is also essential to the control of swallowing, not just during the pharyngeal phase as outlined above but also during the oral phase. The oral cavity contains an unusually high concentration of mechanoreceptors. These protect delicate tissues from the high forces generated during mastication, to trigger the reflex and to sense the size and consistency of the bolus, also as part of the trigger mechanism.

The efferent pathways from the medulla and pons to the muscles involved in swallowing involve several cranial motor nuclei. The most important are the nucleus ambiguus for the muscles of the palate, pharynx and larynx, the hypoglossal nucleus for the muscles of the tongue, and the motor nuclei of the trigeminal and facial nerves for the muscles of the jaws and lips. In addition, motor neurons within the cervical spinal cord control the muscles of the neck including the infrahyoid muscles.

Between these input and output pathways are interposed two main groups of neurons that appear to be essential for the coordination and regulation of swallowing by the medulla. The first lies in the dorsal region of the medulla above the nucleus of the solitary tract. A second group lies more ventrally around the nucleus ambiguus. These two neuronal groups are sometimes referred to as the lateral and medial medullary swallowing centres. A variety of evidence, much of it emanating from the laboratory of Jean,[37] supports the view that these two neuronal groups are vital in the control of swallowing. The dorsal group would appear to be the site of convergence of sensory input from the various nuclei and is probably important in the sequencing of swallowing. The ventral group distributes outputs to the various cranial nerve motor nuclei. Outputs from this region are not simply excitatory. In any reflex system, excitation of agonist muscles and their synergists will be accompanied by inhibitory outputs to the corresponding antagonist muscles.

The correct sequencing of events for healthy swallowing is thought to be controlled by a central pattern generator (CPG).[37] CPGs are groups of neurons capable of generating outputs that will ensure the basic sequencing of a movement in time and space in terms of the muscle contractions needed for automatic movements such as swallowing, ventilation and locomotion.[38] The action of many CPGs is based upon pacemaker-type activity of a subset of neurons that is responsible for the initiation of the rhythmic activity.[38] In this respect, swallowing is similar to ventilation, and both of these motor behaviours are linked to masticatory movements.[39] Given the close relationship between swallowing and ventilation, it seems to be inevitable that there will be central coordination of these processes. The idea of a central mechanism coordinating and regulating respiration and swallowing was first hypothesized over 30 years ago.[40] The exact neural organization is still unclear[41] and is one of the many areas for further investigation for a fuller understanding of the control of swallowing.

RESPIRATION AND SWALLOWING

The act of swallowing involves a crossing of the stream of liquid and food with that of breathing and this occurs within

the pharynx. This crossing of the alimentary and ventilatory streams is an evolutionary consequence of the transition in vertebrates from sea to land living. A variety of mechanisms have evolved to ensure that, during normal swallowing or vomiting, no material can be aspirated into the lungs through the larynx. Aspiration can have serious consequences, such as asphyxiation caused by airway blockage, or occult aspiration with resultant complications, although recent work has shown that aspiration can occur, although rarely, in the absence of a swallowing problem.[42, 43]

Respiration and swallowing are inextricably linked, finely coordinated and are under tight neural regulation (see above). Efficient transport of food and drink to the oesophagus has to co-occur with maintenance of a safe airway and prevention of material entering the lower respiratory tract (**Figure 48.3**). The main sphincteric mechanisms protecting the airways are the soft palate, guarding the pharyngeal isthmus, and those guarding the laryngeal aditus. There appears to be an individual swallowing respiration pattern that matures in the teenage years and is remarkably consistent thereafter.[45] Even following laryngectomy, where there is no risk of aspiration, breathing continues to be suspended during a swallow.[46] Furthermore, the length of breathing suspension appears to be longer in this case group, which is thought to be associated with longer pharyngeal transit times, compared to individuals with a larynx.[47]

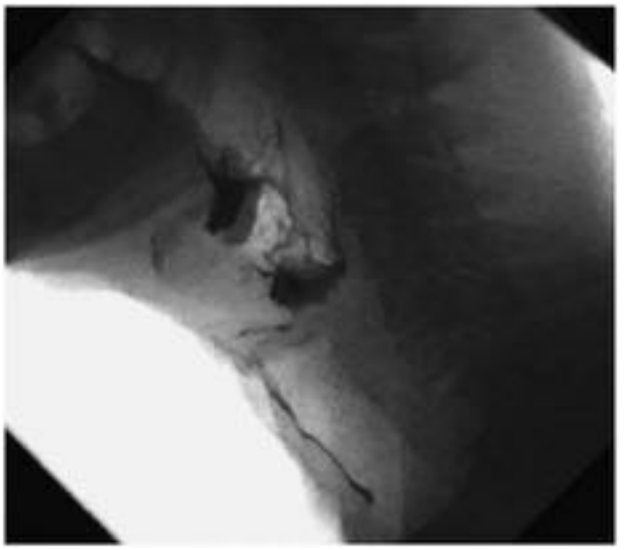


Figure 48.3 Aspiration into the upper trachea. Reproduced by permission of the BMJ Publishing Group from Leslie et al.[44]

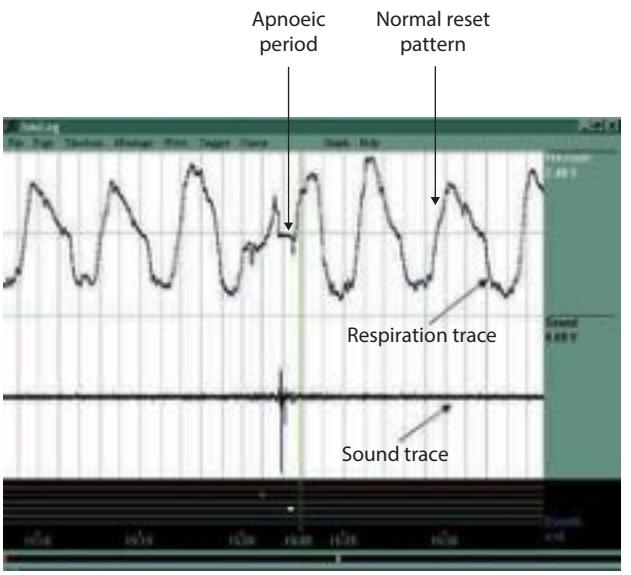


Figure 48.4 Swallow apnoea.

Swallow apnoea

Despite these methodological caveats, some general principles emerge. Clearly, ventilation has to be suspended during pharyngeal transit of the bolus (**Figure 48.4**). This is known as the period of swallow apnoea and is typically less than 1 second in length, corresponding to the duration of the reflex part of the swallow in its pharyngeal phase.[48, 49] The duration of apnoea increases with larger bolus volumes.[45] The effect of bolus consistency is less clear. There is evidence to suggest that solids increase apnoeas with the onset preceding the actual swallow, due to the risk posed by retrolingual loading,[50] but sample numbers are too small to be unequivocal.[49] Gender effects are conflicting, with men having longer durations due to differences in structure[51] and women having longer durations linked to increased cricopharyngeal opening.[45]

Phase of respiration when swallowing occurs

Swallowing tends to occur during the expiration phase of respiration. Expiration on swallowing is longer in duration, compared with quiet respiration.[52, 53] Expiration occurs after 80–100% of healthy swallows.[51, 54, 55] This is likely to be a protective mechanism, as any material left in the laryngeal vestibule post-swallow will be moved to the pharynx rather than sucked into the lungs. The diaphragm is responsible for a downward pull on the trachea and therefore the larynx. On the expiratory phase, at mid to low lung volume, this pull reduces, decreasing resistance and enabling the larynx to elevate during swallowing.[56]

Post-swallow inspiration is more common in populations with impaired swallowing.[55, 57] Furthermore, respiratory disorders such as chronic obstructive pulmonary disease (COPD) can compromise this phase regulation necessary for safe swallowing.[58] Much of the research on the respiratory–swallowing pattern is based on small single boluses of less than 10 mL. This pattern appears to alter with larger boluses, with a greater number of swallows occurring during the inspiratory phase[59] and require a greater lung volume than smaller boluses.[60]

TASTE

Taste buds are the receptors for taste and are located on the surface of the tongue, soft palate and epiglottis.

Each taste bud contains approximately 50–100 cells and has a life span of 10–14 days, and they are under constant regeneration.[61] They mature into one of three types of taste cell: type I detects salt; type II sweet, bitter and umami; and type III sour.[62] Saliva facilitates the movement of taste molecules to the taste bud and its composition is important for taste perception. Taste-related impulses are transmitted via the facial, glossopharyngeal and vagus nerves to the olfactory area of the cortex. The biomechanical swallowing response can alter with different taste flavours. For example, a sour bolus (e.g. lemon juice) may increase oral tongue pressures and tongue-to-palate contact times, although some dispute this.[63, 64] Furthermore, a sour bolus seems to have a longer transit and clearance duration in the distal oesophagus.[65, 66]

AGE EFFECTS

Infancy

In infancy, the anatomical relationships of the tongue, mandible and hyoid bone are much closer, requiring a highly coordinated pattern of suckle–swallow and respiration. Newborn feeding is primarily reflexive, and is dependent on a rooting reflex to latch on to a nipple or teat. Suckling requires the generation of intraoral pressure via lip seal around the source and the posterior tongue moving towards the soft palate. On average, infants generate two to seven tongue pumps per swallow.[67] Jaw movement creates an external pressure on the nipple or teat, encouraging liquid flow into the oral cavity. Swallow apnoea is mainly attributed to the larynx tucking under the tongue base and the arytenoids tilting forwards. Complete epiglottic inversion is not consistently present up until the age of 5 years.[68] From 0–5 months biting is an immature upwards mandible movement. The oral preparatory phase becomes more refined with the maturation of the oral cavity. Preliminary chewing begins with introduction of a more textured diet around 4–6 months. At approximately 1 year, the infant is more able to use grinding chewing movements, which continues to mature up to the age of 16.

Presbyphagia

Presbyphagia is defined as normal age-related changes in swallowing in healthy adults. Sarcopenia is the term used to describe the age-related decrease in muscle mass, strength and coordination. As a consequence of this process, older people have generally weaker oral phase movements, including reduced tongue strength.[69] Although still able to achieve adequate lingual pressures for swallowing, these pressures are generated more slowly than in younger people.[70, 71] Loss of dentition is common, reducing the number of opposing dental units for biting and grinding. Ill-fitting dentures may further hamper the oral preparatory phase. Changes to smell and taste also occur as part of the ageing process, impacting on the pleasure of eating and appetite. The pharyngeal phase is often longer in duration, with prolonged hyolaryngeal excursion. The pharyngeal wall can thin over time, creating a larger vault at rest, consequently reducing maximal constriction and pharyngeal pressure generation.[72–76] Sensory changes may account for a slower swallowing response time.[70]

Breathing and swallowing coordination may also decrease with age, with overall longer periods of apnoea. The combination of these changes may account for the higher incidence of laryngeal penetration of fluids in older individuals.[77, 78] Cricopharyngeal sphincter opening times are longer in duration. There is also a higher incidence of cricopharyngeal bars, which can impede bolus flow.[79] Overall, swallowing transit times are longer, but mean differences between younger and older age groups are small.[75, 76]

WHAT CONSTITUTES THE NORMAL SWALLOW?

Much of the data on the swallowing process comes from observations of populations with impaired systems. Studies of healthy groups are often of small numbers with young age ranges and many of the difficulties in swallowing are linked to age or age-related diseases. As more information emerges, the performance envelope of what constitutes 'normal' is growing. The process of swallowing a series of controlled volume and/or consistency boluses ('command swallows') does not equate with that of eating a meal.[6] When evaluating reports, the reader needs to be clear about age, sex, bolus type and other variables. It is clear that there is uncertainty and some scope for variation in the normal swallow.

KEY POINTS

- Swallowing is a cyclical and irregular process, not a stepwise progression.
- Healthy swallowing has a wide range of parameters.
- Neural control is divided between the cortex and the brainstem.
- Cortical control of swallowing is bilateral, although one hemisphere is usually dominant.
- Airway protection is activated in advance of the pharyngeal stage of swallowing.
- Impaired respiration patterns will affect swallowing and vice versa.

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CHAPTER 49

CAUSES AND ASSESSMENT OF DYSPHAGIA AND ASPIRATION

Helen Cocks and Jemy Jose

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: dysphagia, aspiration and swallowing, with focus on aetiology and diagnosis.

INTRODUCTION

Dysphagia

Dysphagia is a term used to describe difficulty with swallowing solids, liquids or both. It implies impairment of one or more of the phases of swallowing. Dysphagia usually arises as a complication of another health condition. It can be divided into oropharyngeal (high) dysphagia and oesophageal (low) dysphagia.

Dysphagia is common, with epidemiologic studies suggesting that as many as 22% of the population over the age of 50 are affected.[1, 2]

Aspiration

Aspiration is the entry of food or liquid into the airway below the true vocal folds.[3] It may be due to incompetent or inadequate airway protection, ill-timed, uncoordinated events before, during or after the swallow has triggered.[4] Silent aspiration is defined as foreign material entering the trachea or lungs without an outward sign of coughing or attempts at expulsion.

The link between aspiration and aspiration pneumonia remains elusive. Although an association has been identified in stroke patients there are no such data available in head and neck cancer (HNC) patients. In general, aspiration should be kept to a minimum but no clear guidelines exist as to the amount of aspiration that can be tolerated by patients with dysphagia. In a study looking at a mixed group of neurological and HNC patients, only 25% had a history of pneumonia despite over 50% presenting with aspiration.[4] Additional factors may need to be present for pneumonia to develop, such as poor oral hygiene, immobility,[5] neutropenia[6] and malnutrition.

Aspiration pneumonia has been shown to be the most common cause of mortality during hospital admission,[7] followed by nosocomial infections.[8] Prolonged, repeated aspiration of small amounts of material and chronic chest infections has been associated with the development of interstitial pulmonary fibrosis.[9] Diffuse alveolar scarring can occur across a period of time, reducing the ability of lung tissue to transfer oxygen to the bloodstream.

CAUSES OF DYSPHAGIA AND ASPIRATION

Dysphagia can be associated with anatomical, neurological, muscular or psychological causes, with aspiration often developing secondary to dysphagia. This section does not provide exhaustive coverage of possible causes but considers those causes more commonly seen in practice.

Congenital

Most patients present in the paediatric age group, though some may present later in life.

CLEFT LIP AND PALATE

Cleft lip and palate is often associated with nasal regurgitation. The child is unable to suck due to an inadequate seal within the oral cavity resulting from

the lip/palatal defect. This condition is usually picked up intrauterine or at routine neonatal examination soon after birth; however, mild variants of the condition can have a delayed diagnosis.

CEREBRAL PALSY

Cerebral palsy can cause significant oral muscular incoordination resulting in dysphagia, drooling and aspiration as saliva and food pools in the anterior floor of mouth and fails to trigger the pharyngeal phase of swallowing. Assessment involves clinical evaluation of swallow with videofluoroscopy (VF) in cases where there is concern about aspiration. Treatment options include speech therapy or physiotherapy measures, improving posture and relocation of submandibular ducts. Enteral feeding may be required in some patients.

VASCULAR RINGS

Vascular rings around the oesophagus due to malformation of great vessels, usually due to aberrant subclavian artery, double aortic arch or anomalous left pulmonary artery, can cause dysphagia. Extrinsic compression is noted on barium swallow and computed tomography (CT) angiography or magnetic resonance angiography (MRA) is diagnostic.

ATRESIS, CLEFTS AND FISTULA

Laryngeal clefts, tracheoesophageal fistula and oesophageal atresia all present with both dysphagia and airway difficulties depending on the type and severity of the condition. Diagnosis is made at endoscopy.

CONGENITAL VOCAL CORD PALSY

Congenital unilateral vocal cord palsy usually presents with a hoarse cry. There can be swallowing difficulties and aspiration during feeding. Diagnosis is made on endoscopy.

Infective

Infections of the oral cavity, larynx, pharynx and neck spaces can present with dysphagia. These are covered elsewhere in the book (see Chapter 69, Acute infections of the larynx; Chapter 51, Pharyngitis; and Chapter 40, Neck space infections)

Inflammatory

GASTRO-OESOPHAGEAL AND LARYNGOPHARYNGEAL REFLUX

The most common inflammatory process that causes dysphagia occurs secondary to gastro-oesophageal reflux disease (GORD).

GORD can result in erosions, ulcerations and even stricture formation in the lower oesophagus, which cause dysphagia and even food bolus impaction.

Dysphagia and other throat symptoms are also seen with laryngopharyngeal reflux (LPR), which can present with subtle laryngeal findings of erythema and oedema of posterior larynx; however, a recent systematic review has shown poor sensitivity and specificity for these findings, with many being seen in 64–93% of healthy subjects'[10] laryngoscopy findings. Flexible oesophagoscopy, 24-hour pH monitoring and oesophageal manometry studies often aid in making the diagnoses. GORD is discussed in greater detail in Chapter 53, Oesophageal diseases, and LPR in Chapter 77, Reflux disease.

PATTERSON–BROWN–KELLY SYNDROME

Patterson–Brown–Kelly syndrome is the association of dysphagia with atrophic gastritis and iron-deficiency anaemia. It affects mainly middle-aged and elderly women. The dysphagia is due to hyperkeratinization with web formation in the postcricoid region and can be seen on barium swallow, but it may not always be found at rigid endoscopy. The dysphagia and the hyperkeratinization are treated with iron replacement, but the web may need dilatation. The condition is associated with the development of postcricoid carcinoma in a small percentage of patients. Other features of iron deficiency anaemia – smooth tongue, angular stomatitis and koilonychias – may be seen.

EOSINOPHILIC OESOPHAGITIS

Eosinophilic oesophagitis (EoO) is an emerging condition characterized by oesophageal symptoms and infiltration of the oesophageal epithelium with eosinophils for which no other cause can be found. Other causes of eosinophilia need excluding and these include GORD, infection, malignancy, collagen vascular disease and inflammatory bowel disease (IBD). The condition has yet to be fully understood but it is thought that food allergy plays a large role in its development.

It was originally thought to be a form of GORD and a paediatric condition, but it is now known to be most common in middle-aged men. It is most frequently seen in Caucasians and has predominance in developed countries. Prevalence of EoO has increased in the last decade but this may be due to better understanding and detection. A community study in Sweden reported a prevalence of 4 in 1000 in 2016.[11] The British Society of Gastroenterology has set up a national registry.

Presenting symptoms of EoO can vary according to the age of the patient. In children, presentation is with failure to thrive and food refusal. Adolescents can have other symptoms such as chest/epigastric pain and vomiting and in adults symptoms can be of dysphagia, odynophagia and heartburn. Often adults present with food bolus obstruction.

Investigation is with gastroscopy and biopsy, and diagnosis is made on the finding of more than 15 eosinophils per high-powered field at microscopy. Allergy testing with RAST can be helpful in identifying allergens.

Management of EoO involves modification of diet. In severe situations, this involves exclusion of six predominate

food groups (wheat, dairy, fish, eggs, soy and peanuts) and the introduction of an elemental diet to allow improvement. Once improvement is seen at biopsy, food groups can be gradually reintroduced and the effect again judged by mucosal response at biopsy.

Other treatment is with topical steroids, a fluticasone or budesonide inhaler sprayed into mouth and swallowed dry with avoidance of eating and drinking for 30 minutes. A side effect of this is candidiasis.

Gold-standard monitoring of the condition is serial gastroscopies. Absolute blood eosinophil count has been found to correlate significantly with oesophageal eosinophil density and there is some evidence for use of absolute blood eosinophil level as a marker of disease.[12]

Stricture formation can occur as a complication of the condition and dilatation may be required.

SYSTEMIC AUTOIMMUNE DISORDERS

Systemic autoimmune disorders[13] are associated with dysphagia in a large proportion of cases, though the mechanism differs between disease groups. Diagnosis of this group of conditions is based on the clinical picture and autoantibody profile. Control of the disease with steroids and immunosuppressive drugs does not usually improve the dysphagia.

Scleroderma and 'CREST' syndrome

Scleroderma and 'CREST' syndrome (calcinosis, Raynaud's, oesophageal involvement, sclerodactyly, telangiectasis) are progressive disorders of connective tissue. Smooth muscle cells are replaced by collagen fibres, resulting in fibrosis. Anti-nuclear antibodies and anti-centromere antibodies are raised in this condition. The lower oesophagus is often affected, resulting in poor peristalsis, severe GORD with stricture formation and Barrett's oesophagus.

Systemic lupus erythematosis

Systemic lupus erythematosus (SLE) is a progressive systemic inflammatory disease involving skin, joints and internal organs that can affect the oesophagus and can cause oral mucosal ulcerations. The dysphagia tends to be mild.

Dermatomyositis

Dermatomyositis is a diffuse inflammatory condition affecting skin and skeletal muscle associated with underlying malignancy in a high percentage of patients. Dysphagia is seen in up to a third of affected patients and may be secondary to hypopharyngeal and upper oesophageal involvement. It usually presents with symmetrical proximal muscle weakness and skin changes. Diagnosis is made by a muscle biopsy.

Pemphigus, mucosal pemphigoid and epidermolysis bullosa

These conditions are characterized by blistering, either subepidermal (pemphigus) or submucosal (mucosal pemphigoid and epidermolysis bullosa). The oral cavity, pharynx and oesophagus can be involved, leading to scarring and stricture. Diagnosis is made by skin biopsy showing typical antibodies with direct immunofluorescence. Contrast swallow can have a characteristic appearance. There is often a good response to steroids.

Sjögren's disease

Sjögren's disease causes dysphagia due to xerostomia. Anti-Ro (SS-A) antibody levels are raised in 70% of cases and anti-La (SS-B) in 40%. However, a negative blood test does not exclude the condition. Biopsy of the minor salivary glands of the lip will show lymphocyte infiltration and aid the diagnosis.

Traumatic

FOREIGN BODY/FOOD BOLUS OBSTRUCTION

A foreign body in the pharynx or oesophagus is the most common traumatic cause of dysphagia. Patients often present with accompanying drooling. It is important from the history to determine whether it is a sharp foreign body or a soft food bolus obstruction.

A variety of foreign bodies are ingested by children and patients with learning difficulties, the most common being coins. The size and shape of the foreign body will dictate where it lodges, but common sites are the cricopharyngeus, at the level of the aortic arch and at the cardia.

Food bolus obstruction from large pieces of meat (with or without bone) is not uncommon, particularly in those who cannot or do not chew well and in patients with oesophageal stricture. Patients present with painful dysphagia and, if obstruction is complete, there will be drooling of saliva. Laryngoscopy may confirm pooling of saliva. Neck examination may reveal subcutaneous emphysema if pharyngeal or oesophageal perforation has occurred. A lateral soft-tissue radiograph of the neck shows loss of natural lordosis of the C spine, widening of the prevertebral space and often an air bubble in the oesophagus. A radio-opaque foreign body may be seen. Urgent rigid or flexible endoscopy might be required if the foreign body does not pass spontaneously and with sharp foreign bodies. If perforation is suspected, it may be necessary to perform a contrast swallow with a non-ionic contrast, which has the added advantage of not interfering with subsequent oesophagoscopy as it is clear.

CAUSTIC BURNS

Burns due to accidental or deliberate ingestion of acid or alkaline substances cause dysphagia. Initial oedema and ulceration can result in stricture formation and perforation.

HEAD, NECK AND SPINAL TRAUMA

Trauma to the head and neck, chest or cervical spine may be accidental or iatrogenic and may involve blunt trauma, penetrating injuries or compression effects or

a combination of these. Neck injuries may disrupt the swallowing mechanism directly or indirectly by affecting the cranial nerves IX to XII. This is discussed in greater detail in Chapter 38, Neck trauma. Head injuries can produce a variety of neurological defects resulting in paresis, paralysis or loss of coordination of the swallowing mechanism, which may not become apparent until the patient resumes consciousness, starts feeding again and aspiration results.

Neoplastic

Both benign and malignant tumours may cause dysphagia either by mechanical obstruction, intra- or extraluminal, or due to neuromuscular invasion. A number of studies have shown that the severity of dysphagia and its complications depend on tumour size and site.[14–20] One study showed that 50.9% of patients with pharyngeal tumours had dysphagia at presentation compared with 28.6% of patients with laryngeal tumours and 28.2% with oral lesions of stage T2 or more.

In the oral cavity, most tumours are malignant and of these 95% are squamous cell carcinomas (SCCs). The patient may present with a lump in the mouth or with an ulcer that may result in odynophagia. Dysphagia can be caused by tongue fixation. In the oropharynx, most malignant tumours are squamous cell in origin. Dysphagia is often due to pain but involvement of the tongue base and/or soft palate can result in problems with tongue fixation and regurgitation respectively. The tumour is often seen on examination. In the hypopharynx, rare benign tumours such as leiomyomas, lipomas and fibrolipomas can be found which cause dysphagia. The majority of tumours, however, are SCCs, with 60% occurring in the piriform fossa. Large tumours can cause significant swallowing problems with alteration of diet to softer textures. Weight loss is not uncommon and symptoms of aspiration such as cough associated with swallow and recurrent chest infections should be asked about. Small tumours and tumours of the postcricoid region or the cervical oesophagus can be more difficult to diagnose. The patient may only complain of a feeling of 'something in the throat', like a crumb being stuck. At examination it is important to look for pooling of saliva and any localized oedema, which might raise suspicion. In cases where there is a high index of suspicion or an obvious tumour, an assessment of the upper aerodigestive tract (UADT) and staging of the tumour is made, usually under general anaesthetic. Cross-sectional imaging MRI or CT is also helpful.

In the oesophagus, benign leimyomas can be found occasionally but the majority of tumours are squamous carcinomas. Adenocarcinomas may develop at the lower end and may arise from gastric metaplasia, as seen in Barrett's oesophagus. Dysphagia of short duration in an elderly male who smokes and drinks and which progresses from solids to liquids is typical for this type of tumour. Examination may show weight loss and anaemia and cervical lymphadenopathy advanced disease, but there may be little to find in early disease. Oesophageal lesions are best dealt with within the upper gastrointestinal multidisciplinary team and investigated with flexible gastroscopy and cross-sectional imaging.

External compression of the oesophagus due to goitre and thyroid malignancies, thymoma and enlargement of mediastinal lymph nodes, seen in metastatic disease and lymphoma, is not uncommon and investigations primarily involve cross-sectional imaging and tissue diagnosis.

Post-treatment dysphagia

Patients who have undergone treatment for HNC often suffer significant dysphagia and aspiration. Longer oral and pharyngeal transit times, greater amounts of oral and pharyngeal residue, shorter cricopharyngeal opening durations, and poor swallow efficiencies are seen. Swallow function is significantly worse with higher tumour stage, and patients with oral or pharyngeal lesions have worse swallow function than patients with laryngeal lesions.[20, 21] A multicentre study found a much higher proportion of HNC patients aspirated (76%) than did patients with neurogenic, medical, gastrointestinal diseases.[4] These effects are long-standing, with one study reporting that 44% aspirated at 5 years and beyond their original treatment.[22]

Chemoradiotherapy is, in many centres, the standard treatment for locoregional advanced tumours, particularly of the oropharynx, larynx and hypopharynx. Despite the encouraging results in terms of locoregional control and survival, significant functional impairment has been documented. This is discussed in greater detail in Chapter 34, Speech voice and swallow rehabilitation after chemoradiation, but the salient points are covered here.

Common problems include: reduced tongue strength and control, decreased tongue base movement towards the posterior pharyngeal wall, decreased laryngeal elevation, reduced epiglottic inversion, delayed pharyngeal swallow, frequent residue in vallecula and piriform sinuses and frequent penetration of the laryngeal vestibule and frank aspiration.[23] A prospective study found that 30% of HNC patients treated by chemoradiotherapy developed aspiration pneumonia, despite being fed by tube.[24]

The radiation dose delivered to the superior and middle pharyngeal constrictors, longitudinal muscles and palatopharyngeal fold appears to be significantly related to swallowing outcomes.[25] Intensity-modulated radiotherapy (IMRT) is designed to reduce doses to the major salivary glands, constrictor and masticatory muscles and the mandible. While studies have demonstrated improved salivary function,[26] swallowing function is not always improved.[27] This may be because it is impossible to spare key structures such as the tongue base and soft palate due to tumour site. The pharyngeal phase of swallowing depends on precise interaction of these muscles with tongue base movement, pharyngeal contraction and hyolaryngeal excursion. Gastric tube dependence has been noted for 13–33% at long-term follow-up after chemoradiation.[24]

These problems can also occur following surgery, but are perhaps more predictable. Reconstruction using

regional and microvascular flaps along with rehabilitative therapy has been shown to be beneficial, allowing some compensation.[28, 29] A shift in surgical techniques towards transoral resections involving the use of the laser and the robot have resulted in reduced anatomical and functional disruption and in improved swallowing outcomes, even when radiotherapy and chemotherapy are used in the adjuvant setting.[30, 31]

Functional endoscopic evaluation of swallowing (FEES) is very helpful in the post-treatment HNC patient and is easily performed in the outpatient clinic setting. A functional evaluation including a pharyngeal squeeze manoeuvre,[32] forced breath hold, maintenance of glottic closure and dry swallow can be made and a range of fluid and food can be given. Food colouring can be added to improve the view. Bolus flow during swallow, laryngeal penetration and aspiration and pre- and post-swallow residue in the vallecullae, piriform fossa and postcricoid area should be documented.

Oesophageal motility disorders

These disorders can produce severe dysphagia in the absence of visible abnormalities, the diagnosis being made by manometry.[33] However, before the diagnosis of a dysmotility disorder is made, it is important to exclude a tumour or structural abnormality by endoscopy or radiology.

ACHALASIA CARDIA

Achalasia cardia is the classical condition in this group wherein the lower oesophageal sphincter fails to relax and allow food to pass into the stomach. It is caused by degeneration or absence of the ganglion cells (myenteric plexus of Auerbach) in the oesophageal wall. The condition is indistinguishable from Chagas disease, seen in patients from South America and due to infection by *Trypanosoma cruzi,* which destroys the ganglion cells. Patients present with difficulty in swallowing fluids initially and progressively difficulty with solids. Barium swallow will demonstrate a 'bird's beak' tapering on the oesophagogastric junction and dilatation of the lumen above it. Manometry studies can be used to detect failure of the lower oesophageal sphincter to open even before the features on barium swallow appear.

OESOPHAGEAL SPASM

Diffuse oesophageal spasm is a condition characterized by non-effective peristaltic waves of high amplitude in the oesophagus, causing angina-like chest pain. Barium swallow and manometry demonstrate non-propulsive peristaltic waves and incomplete lower oesophageal sphincter relaxation.

PRESBYDYSPHAGIA

Presbydysphagia refers to swallowing difficulties due to ageing which affect all stages of swallowing. The oral phase is affected by loss of teeth and tongue connective tissue, reduced strength of mastication and weakness of the velopharyngeal reflexes. The pharyngeal phase is affected by decreased elevation of the larynx and prolongation of the pharyngeal transit time. In the oesophageal stage, there is prolongation of the upper oesophageal sphincter relaxation time and the oesophageal transit time with ineffective tertiary peristaltic waves. However, these age-related changes and abnormalities, seen on barium swallow, are evident in one-third of otherwise healthy elderly individuals. Therefore, it might be that age-related changes reduce functional reserve such that problems develop more easily when disease or generalized weakness from systemic illness ensues.[34]

Neurological

Neurological causes of dysphagia[35] mostly affect the oropharyngeal phase of swallowing. Usually, the motor, sensory and coordinating centres for swallowing are affected directly by the disease and it is unlikely that the dysphagia would present as an isolated symptom without the other characteristic features of the neurological disease. In general, patients who present with an acute disorder causing dysphagia, such as a stroke, tend to improve with time, whereas patients with chronic neurological disorders will experience progressive swallowing difficulties. Diagnosis of the specific swallowing problem in these conditions is made by a careful assessment including a detailed head and neck examination. Speech and swallowing assessments include water swallow test to help screen for risk of aspiration and VF. Constant re-evaluation is often needed.

CEREBROVASCULAR ACCIDENT (STROKE)

Cerebrovascular accident (stroke) is probably the most common neurological disorder causing Dysphagia, by affecting the cortex or the corticobulbar tracts (pseudobulbar palsy) or by affecting the bulbar nerve nuclei (bulbar palsy). Recovery takes place within the first week in the majority of patients. Factors contributing to the dysphagia include delayed triggering of the swallowing reflex, cricopharyngeal dysfunction and reduced tongue control and pharyngeal contraction and cough. Loss of pharyngeal sensation associated with the dysphagia correlates well with aspiration, aspiration pneumonia being a major cause of death after a stroke. Following a stroke, studies suggest that 25–70% of patients have dysphagia initially, with 10–30% continuing to have dysphagia and aspiration even after recovery.[1, 2]

PARKINSON'S DISEASE

Parkinson's disease is progressive and characterized by the triad of resting tremor, bradykinesia and rigidity, patients having difficulty in starting, performing and stopping a movement. The dysphagia is associated with changes in striated muscle under dopaminergic control and smooth muscle under autonomic control and is mostly due to

abnormalities in the oral preparatory and pharyngeal phases of swallowing. The oral phase of the swallow is affected by rigidity of the tongue musculature with inefficient, non-propulsive, back and forth movement of tongue which prevents food being delivered into the oropharynx. In the pharyngeal phase there is delayed contraction of the pharyngeal muscles. Findings on VF include impaired motility, hypopharyngeal stasis, aspiration and poor movement of the epiglottis.

MULTIPLE SCLEROSIS

Multiple sclerosis is a demyelinating disease affecting the brain and spinal cord. There can be either a relapsing–remitting or a progressive course. Swallowing problems and aspiration tend to occur in end-stage disease in up to a third of the patients. Reduced pharyngeal peristalsis and delayed swallowing reflex are the most common features. However, the demyelinating lesions can occur in a single cranial nerve or cause a general dysfunction of all three phases of deglutition.

MOTOR NEURONE DISEASE

Motor neurone disease (amyotrophic lateral sclerosis) is a progressive disease that affects the corticobulbar and corticospinal tracts. Progressive swallowing difficulties affect mainly the oral and oropharyngeal stage of swallowing. Twenty-five per cent of patients present with swallowing problems and most develop problems as the disease progresses. Swallowing problems together with dysarthria and anarthria account for much of the misery of this disease.

MYASTHENIA GRAVIS

In myasthenia gravis there are antibodies to acetylcholine receptors, impairing the function of the neuromuscular junction of striated muscles. The hallmark of this condition is fatigability. There is bulbar muscle weakness manifested by slow and weak tongue movements, fatigue of swallowing and food residue in the oropharynx. There may be laryngeal penetration and aspiration. The diagnosis is a clinical one supported by the presence of acetylcholine receptor antibodies

RECURRENT LARYNGEAL NERVE PALSY

Isolated recurrent laryngeal nerve palsy can be associated with dysphagia and aspiration of liquids due to decreased pharyngeal gradient pressures and decreased glottic closure, as well as inferior constrictor and cricopharyngeus muscle dysfunction. Combined superior and recurrent laryngeal nerve injury will have a greater impact due to the ipsilateral sensory deficit.

Medication-induced/pharmacological

Drugs can cause dysphagia directly by causing oesophagitis, or as part of their pharmacological action or normal side effects.[36] Swallowing tablets with insufficient water or just before going to bed can cause oesophagitis as oesophageal transit time is longer during sleep. The oesophagus at the level of the aortic arch is most commonly injured by both lack of neutralization by saliva and contact by acid-producing drugs with a pH of less than 3, such as tetracyclines, doxycycline, vitamin C and ferrous sulphate. Broad-spectrum antibiotics and chemotherapeutic drugs may cause secondary viral ulceration or fungal infections. Stevens–Johnson syndrome is a more serious complication of antibiotic therapy with an acute erosive pharyngitis and oesophagitis causing dysphagia as well as delayed oesophageal strictures.

Anticholinergics, tricyclic antidepressants and calcium channel blockers decrease oesophageal peristalsis and tone of the lower oesophageal sphincter. Xerostomia is a common side effect of many medications such as antihypertensives, ACE-inhibitors, anticholinergics, antiemetics, antihistamines, diuretics and opiates.

Miscellaneous

GLOBUS PHARYNGEUS

Variously described as ‘foreign body sensation in the throat’, ‘lump in the throat’ and ‘frog in the throat’, globus sensation in the throat should not be associated with genuine dysphagia. This should be ascertained with a detailed and specific history from the patient. Investigations and management of this condition are discussed in Volume 2, Chapter 34, Foreign bodies in the ear, nose and throat. It is imperative to rule out a lesion in the hypopharynx, remembering especially not to miss an inconspicuous pathology in the postcricoid area. Similarly, a small group of patients with oesophageal malignancy may also present with this symptom.[37] Therefore, flexible nasendoscopy, transnasal oesophagoscopy and barium swallow tests should be used as appropriate in these patients.

PHARYNGEAL POUCH

A pharyngeal pouch is a pulsion diverticulum that occurs at an area of weakness between the two parts of the inferior constrictor at Killian’s dehiscence. The pouch first develops in the midline, but as it enlarges it expands to one side, most frequently the left. Manometric studies suggest that it is associated with high intrapharyngeal pressures with a high resting tone in cricopharyngeus that is slow to relax.[38] Patients first present with dysphagia and regurgitation of undigested food but recurrent chest infections can result from aspiration due to overflow of food into the larynx. Diagnosis is confirmed by a barium swallow. For more information on the aetiology and management of this condition, see Chapter 52, Cricopharyngeal dysphagia.

Box 49.1 lists the causes of dysphagia.

BOX 49.1 Causes of dysphagia

Congenital
- Cleft lip and palate
- Cerebral palsy
- Vascular rings
- Atresis, clefts and fistula
- Congenital vocal cord palsy

Infective
- Acute and chronic infections of pharynx/larynx
- Neck space infections

Inflammatory
- Gastro-oesophageal reflux disease
- Laryngopharyngeal reflux
- Patterson–Brown–Kelly syndrome
- Eosinophilic oesophagitis

Autoimmune
- Scleroderma
- Systemic lupus erythematosus
- Sjögren's syndrome
- Pemphigus, epidermolysis bullosa
- Dermatomyositis

Traumatic
- Foreign body
- Food bolus obstruction
- Caustic burns
- Head and neck trauma

Neoplastic
- Benign tumours
- Malignant tumours

Motility disorders
- Achalasia cardia
- Oesophageal spasm
- Presbyoesophagus

Neurological
- Cerebrovascular accident
- Parkinson's disease
- Multiple sclerosis
- Motor neurone disease
- Myasthenia gravis
- Vocal cord palsy

Miscellaneous
- Post-treatment dysphagia
- Pharmacological
- Globus pharyngeus
- Pharyngeal pouch

ASSESSMENT OF DYSPHAGIA AND ASPIRATION

Assessment of dysphagia typically includes both clinical and instrumental evaluation. **Figure 49.1** provides a suggested algorithm for the clinical assessment of dysphagia.

History

Patients complain of difficulty in swallowing food or liquid easily and there can be a sensation of food sticking. They will often localize the level of this sensation. In high (oropharyngeal) dysphagia, there is difficulty in preparing and transporting the food bolus through the oral cavity, as well as initiating the swallow, and this may be associated with aspiration or nasopharyngeal regurgitation. In low (oesophageal) dysphagia, patients complain of food sticking low in the neck, retrosternally or at the epigastrium. This localization has low diagnostic specificity. Around 30% of oesophageal dysphagia is localized above the suprasternal notch.

The history should include the onset, duration, progression and severity of the symptoms, as well as the types of food that give problems. Typically, malignant dysphagia presents with a short and progressive history, a change to softer textures and more liquid consistency, with associated weight loss. Conversely, in neuromyogenic dysphagia it can be more difficult to swallow fluids.[39]

Patients may complain of a number of other UADT symptoms:

- **Regurgitation**, which can be immediate or delayed, can give an indication as to the level of the problem. Delayed regurgitation of undigested food is typically seen in patients with a pharyngeal pouch.
- Symptoms of **retrosternal discomfort, belching and early satiety** indicate GORD.
- **Odynophagia** (pain on swallowing), is associated with infection, neoplasia or GORD.
- **Hoarseness** may indicate laryngeal fixation due to tumour or vocal cord palsy.
- **Choking or coughing**, during or after eating, or frequent chest infections may suggest aspiration.
- **Referred otalgia** via the IX and X cranial nerves is usually secondary to an UADT tumour and a poor prognostic sign.
- **Associated neurological symptoms** such as bulbar dysfunction, dysarthria, diplopia, limb weakness and fatigability can be seen in motor neurone disease and myasthenia gravis. Tremor, ataxia and unsteady gait are features of Parkinson's disease.

Examination

Examination should exclude any obvious structural cause, and assessment should be made for signs of associated systemic or neurological dysfunction and for signs of complications of dysphagia such as weight loss and malnutrition and pulmonary problems due to aspiration.

The oral cavity and oropharynx should be examined carefully, looking for obvious mucosal ulceration or lesions and oral dryness/xerostomia. Palatal raise and gag reflex and tongue movement are assessed and any wasting or fasciculation of the tongue noted. Asking the patient to say 'la' and 'ka' can assess anterior and posterior tongue elevation. Dentition and the presence and fit of dentures are assessed; oral competency and buccal tension can be confirmed by testing for facial nerve function.

The pharynx and larynx should be examined with flexible nasendoscopy, assessing for an UADT lesion, vocal cord mobility and pooling of saliva in the piriform fossa

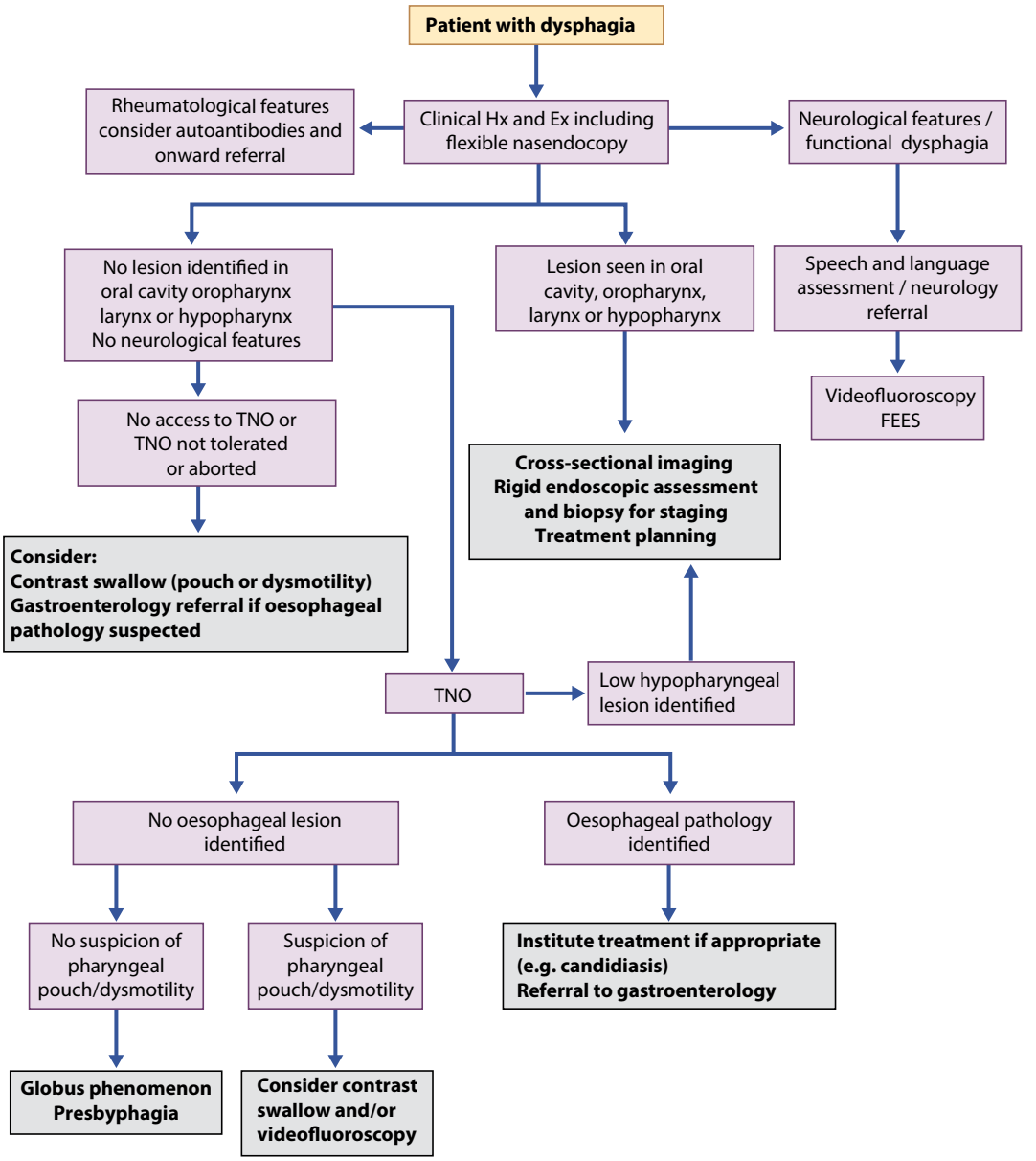


Figure 49.1 A suggested algorithm for clinical assessment of a patient with dysphagia. TNO, transnasal oesophagoscopy; FEES, fibre-optic endoscopic evaluation of swallowing.

or postcricoid area, which is suggestive of an organic cause of dysphagia. Where facilities are available, the flexible endoscopy should be performed using a transnasal oesophagoscope which will enable concurrent assessment of the larynx, pharynx and the entire oesophagus.

Lower cranial nerve function is assessed for loss of tongue movement, wasting and fasciculation, loss of gag and cough reflexes, loss of pharyngeal and laryngeal sensation and loss of vocal cord mobility.

The neck is examined for lymphadenopathy and other neck masses, thyroid enlargement, loss of laryngeal crepitus and the integrity of the laryngeal cartilages.

General physical and neurology examinations should look for evidence of malnutrition, weight loss, chest disease, epigastric tenderness and abdominal swellings, loss of coordination, fasciculation and tremor.

Investigations

Clinical findings dictate further investigations. In the case of upper UADT lesions, investigation is to assess and stage the tumour with panendoscopy and cross-sectional imaging. However, history and examination may not reveal the cause of dysphagia though it may suggest that the cause is either lower than the hypopharynx or has a neurological or functional basis. Further investigations aid examination and assess the function of the swallowing pathway and are also used to assess the risk of aspiration.

BLOOD TESTS

A full blood count and indices should be obtained in all patients to exclude anaemia as a cause or effect of

the dysphagia. Liver and renal function tests together with serum calcium levels should be acquired when nutrition is impaired or metastases are suspected. Thyroid function tests are indicated if dysphagia is caused by a goitre or thyroid malignancy. Creatine kinase levels may be elevated in myopathies.

BEDSIDE ASSESSMENTS

Bedside assessments of swallowing are not standardized and offer poor reliability when used alone. A water swallow test (WST) of a defined volume of water (30 mL) and looking for abnormal voluntary cough, post-swallow cough or throat clear or voice has been shown to have about a 50% sensitivity for aspiration and 80–92% specificity.[40–42] It is used to screen patients with neurological dysphagia at risk of aspiration and is a useful adjunct to instrumental testing.[43] In the HNC population, WST using 100 mL has been found to be 67% sensitive for aspiration but less specific (46%).[20] The value of WST is in identifying patients who require instrumental testing.

Evan's blue dye test[44, 45] is used to assess the presence of and aspiration in the tracheostomized patient. The presence of blue dye from the tracheostomy site is assessed after a test swallow. Detailed treatment of swallow assessment can be seen in Chapter 50, Functional investigations of the upper gastrointestinal tract.

QUESTIONNAIRE-BASED ASSESSMENTS

There are a number of self-reported (University of Washington Quality of Life,[46] M.D. Anderson Dysphagia Inventory[47] and SWAL-QOL[48]) and observer-rated questionnaires that can be useful adjuncts in the assessment of dysphagia in the head and neck population. The most used observer-rated instrument is the Performance Status Scale for Head and Neck (PSSHN).[49] Swallow performance is assessed by: (i) eating in public (scale 1–5) and (ii) normalcy of diet (scale 1–10). These instruments are discussed in greater detail in Chapter 28, Measures of treatment outcomes.

INSTRUMENTAL TESTING

Fibre-optic endoscopic evaluation of swallowing

A fibre-optic endoscopic examination of the UADT should be performed in all cases of dysphagia. The assessment of swallow (fibre-optic endoscopic evaluation of swallowing – FEES)[50, 51] as part of this is very useful in identifying aspiration and secretion management and for visual biofeedback for the patient when trying compensatory procedures to aid swallowing and reduce aspiration. This test can be performed at the bedside and is best if a digital recording is made. Different textures of foodstuffs can be given which can be dyed with food colouring to enhance visibility. Bolus flow during swallow, laryngeal penetration and aspiration, and post-swallow residue should be documented. Endolaryngeal sensation can also be assessed. The procedure is described fully in Chapter 50, Functional investigations of the upper gastrointestinal tract.

Direct pharyngo-oesophagoscopy

This is an examination to visualize and biopsy the pharynx and upper oesophagus under general anaesthetic. It is performed to biopsy and stage all cases of UADT tumour and in patients who complain of food sticking. It allows inspection of the postcricoid area, which is not seen so well during flexible endoscopic assessment of the upper gastrointestinal tract. It is used to examine pharyngeal pouches and to facilitate their treatment.

A major drawback of this assessment technique is the need for a general anaesthetic. In the UK, use of the rigid endoscope to examine the lower one-third of the oesophagus is discouraged owing to the higher risk of complications.

Gastroscopy

Gastroscopy (or oesophagogastroduodenoscopy – OGD) is the endoscopic examination of the oesophagus and stomach. It is used to assess, stage and biopsy oesophagitis, Barrett's oesophagus and tumours. It is poor at detecting disease of the hypopharynx.

Transnasal oesophagoscopy

The relatively new technique of transnasal oesophagoscopy (TNO)[52] uses a narrow-bore flexible scope to assess the oesophagus under local anaesthetic in the clinic setting. It has been shown to be reliable at assessing and diagnosing oesophageal pathology. Studies have shown that around 40% of patients being referred to otolaryngologists with swallowing problems can have concurrent oesophageal pathology, justifying inclusion of this procedure as one of the investigative options for dysphagia.

The major clinical advantage of TNO is the lack of sedation-related morbidity and mortality that is associated with OGD under sedation. It is also more cost-effective than OGD.

Manometry

This is the measurement of oesophageal pressures at rest and during swallowing to diagnose motility disorders.[53] A catheter with pressure transducers along its length is placed in the oesophagus and a multichannel system records the contraction amplitude, duration, coordination and velocity of each peristaltic wave. It is particularly helpful in patients with atypical chest pain and unexplained causes of dysphagia. Conditions with almost pathognomonic manometric findings include achalasia, diffuse oesophageal spasm and scleroderma.

Twenty-four hour ambulatory oesophageal pH monitoring

This is regarded as the most accurate method of diagnosing GORD.[53] It is especially useful when standard investigations such as flexible oesophagoscopy and barium swallow (see below) are normal in a patient with typical symptoms, or in patients with atypical symptoms. A pH sensor placed 5 cm above the manometrically defined lower oesophageal sphincter continually monitors the pH over the test period, while the patient records their symptoms, mealtimes, going to bed and getting up in a

diary card or with an event marker on the pH recorder. Normal oesophageal pH varies between 5 and 7 and GORD is present when the pH is less than 4. The results are expressed as the percentage of time the pH is less than 4 over a 24-hour period – the DeMeester score.[54]

RADIOLOGICAL INVESTIGATIONS

There are two radiological assessments of swallowing that are important in the assessment of dysphagia: contrast swallow and VF.

Contrast swallow

The traditional barium swallow includes both static and dynamic assessment of swallow. The patient is given a cup of liquid barium to swallow and the bolus is followed fluoroscopically to the stomach. Improved visualization of mucosal detail can be obtained by using effervescent granules of barium producing an air contrast study. It is useful to diagnose intrinsic disease (diverticulae, stricture or web, tumour and dysmotility) and extrinsic disease (compression from thyroid or cervical osteophytes). It has poor sensitivity for other pharyngeal disease. It may show reflux disease, but it is not a very sensitive as it fails to pick up 40% of cases.[55] Oesophageal motility is also assessed with swallows in different positions.

Tertiary and disordered contractions can be seen – these patients not uncommonly present with pharyngeal symptoms. The use of barium is contraindicated when there is a risk of aspiration since it can cause pneumonitis. Urgent physiotherapy is necessary in cases of aspiration. In these situations a low molecular weight, non-ionic, water-soluble contrast medium should be used as this is less irritant and should cause minimal complications.

Videofluoroscopy (VF)

VF is a true dynamic assessment of swallowing and is considered to be the gold standard for evaluating the swallowing mechanism.[56] The passage of measured volumes and viscosities – liquid, puréed and solid foods – is observed in both the lateral and anteroposterior plane and a recorded study made. It is a comprehensive test for all phases of swallowing but particularly useful for the oral and pharyngeal phases. The study is interpreted and assessment made of bolus preparation and propulsion. If detected, aspiration can be measured on scales such as the penetration–aspiration scale.[57] Manoeuvres can be tested to reduce aspiration, including swallowing during breath-holding, with or without a chin tuck, and with or without a head turn towards the affected side. VF is particularly useful in patients with neurological disease, and in patients after treatment for HNC.

Computed tomography

Patients with malignant dysphagia should have a CT examination of the neck, chest and abdomen to stage their disease, as should those with dysphagia due to extrinsic compression.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) of the brain or skull base is indicated when a neurological cause of dysphagia is suspected such as multiple sclerosis, cerebral tumours and intracranial extension of a nasopharyngeal carcinoma. It is particularly useful for lesions around the foramen magnum and the brainstem. It is also used to diagnose vascular anomalies.

BEST CLINICAL PRACTICE

- ✓ Be aware of the wide and varied causes of dysphagia in adults and children.
- ✓ Take a detailed current and past medical history to provide clues as the possible aetiology.
- ✓ Comprehensively examine the H&N including the lower cranial nerves.
- ✓ A fibre-optic endoscopic examination of the UADT should be performed in all cases of dysphagia .
- ✓ Look for signs of malnutrition.
- ✓ Perform FBC in all patients with dysphagia.
- ✓ Consider TNO where there is access to this.
- ✓ Consider instrumental assessment of swallowing – FEES and VFSS.
- ✓ Where there is a concern of a malignant cause arrange cross-sectional imaging and UADT assessment under general anaesthetic.
- ✓ Consider a BaSw in cases of pharyngeal pouch and dysmotility.

KEY POINTS

- Dysphagia is common: 22% of over individuals over 50 are affected.[1,2]
- Aspiration pneumonia is the highest cause of mortality associated with hospital admission.[7]
- Stroke is the commonest neurological cause of dysphagia and aspiration.[1, 2]
- 76% of HNC patients have been shown to aspirate. This is higher than those with medical, neurological or GI problems.[4]
- VFSS is considered the gold standard for evaluation of swallow and should be used in conjunction with FEES.[56]
- 30% of patients treated with CRT develop aspiration pneumonia despite tube feeding.[24]
- Radiation dose to the superior and middle constrictor is significantly related to swallow outcome.[25]
- Laryngeal signs show poor sensitivity and specificity for LPR.[10]

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CHAPTER 50

FUNCTIONAL INVESTIGATIONS OF THE UPPER GASTROINTESTINAL TRACT

Joanne M. Patterson and Jason Powell

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SEARCH STRATEGY

Data in this chapter are based on searches of Medline, EMBASE and the Cochrane Library using the keyword Dysphagia, focusing on upper GI functional investigations. The articles referenced by these authors were also reviewed. The data are supplemented by further searches of specialized books.

INTRODUCTION

This chapter seeks to describe functional investigations of the upper digestive tract. A full investigation usually requires multidisciplinary input involving an otolaryngologist, speech and language therapist, radiologist and gastroenterologist, and a focused diagnostic examination with appropriate selection of instrumental assessment. The physiology of normal swallowing has been fully described in Chapter 48, Physiology of swallowing. The underlying aetiology for dysphagia is of anatomical, neurological, muscular or psychological origins. Early diagnosis and effective management of dysphagia reduce the incidence of pneumonia and improve quality of care and outcomes.[1]

INVESTIGATIONS

When to refer for a swallow assessment

Referral guidelines for swallowing assessments have been published for specific conditions. For example, patients with acute stroke should have a swallowing screening test, conducted by a trained healthcare professional before administrating any food, fluid or medication.[1] If a problem is identified, a specialist swallowing assessment should follow within 72 hours. Head and neck cancer patients referred for treatment that will affect swallowing should be assessed by a speech and language therapist and a plan for method of feeding devised.[2] As well as specific conditions, there are certain risk factors that require consideration. For example, a referral for a swallowing assessment is indicated for a tracheostomized patient if there is co-occurring neurological involvement following head and neck surgery, or there are signs of a problem such as evidence of secretions or ingested material on suctioning.[3] However, not all patients with a tracheostomy will have dysphagia.

Patients' perceptions of their swallowing do not always relate to function and therefore symptoms can be underreported.[4] The person may not be aware of a swallowing difficulty, or may attribute their problem to something else. Therefore, healthcare professionals need to be vigilant to the signs and symptoms, taking into account some of the more covert features and refer on for a specialist swallowing assessment as indicated. Some of the signs and symptoms of dysphagia include: coughing during or after eating and drinking, wet-sounding voice after eating and drinking, drooling, repeated chest infections, weight loss and dehydration.

Clinical swallowing evaluation

A clinical swallowing evaluation (CSE) is usually the first step in a functional assessment of the digestive tract and is primarily a screening assessment. The purpose is to identify and differentiate dysphagia symptoms, to assess severity and form a hypothesis regarding the underlying

anatomical and/or physiological causes. Swallow physiology cannot be directly observed if the breakdown is at the pharyngeal or laryngeal level. Sensory changes can mask any outward signs of difficulty such as coughing on swallowing. A CSE typically involves a detailed case history including relevant risk factors such as respiratory status and oral hygiene, an oropharyngeal and oromotor examination and an observation of a swallowing trial.

Currently, there are no published, standardized tests for a CSE. They have been criticized for their poor reliability and sensitivity when used in isolation. Reliability increases with the inclusion of a water swallow test (WST).[2, 3] Testing with measured amounts of water is more reliable than using trial water swallows,[5] probably due to a more defined pass or failed criterion. For example, a systematic review reported that a 30 mL WST could predict pneumonia in a hospital geriatric unit.[6] A combination of features identified on the oropharyngeal examination further increases the sensitivity for the detection of aspiration. For example, the presence of any two features from abnormal voluntary cough, absent gag reflex, dysarthria, dysphonia, post-swallow cough, throat clear or voice change improves validity over single items (sensitivity 92%, specificity 67%) in determining aspiration risk.[7]

A CSE may not be appropriate for certain populations, including patients with dementia or profound learning disability. For such groups, one may be limited to systematic observations of mealtime behaviours. Observations may include specific eating problems such as drooling or food pocketing, ability to self-feed, caregiver feeding skills, body and head positioning, behavioural issues such as agitation, sensory problems such as visual perceptual disorders and distraction by other stimuli. A systematic review of assessment tools for mealtime observations[8] identified two instruments with acceptable psychometric properties; the Minimal-Eating Observation Form-version II[9] and the McGill Ingestive Skills Assessment.[10]

A CSE may also include non-imaging equipment such as cervical auscultation, a cough response test using nebulized citric acid[11] and pulse oximetry. Cervical auscultation amplifies the sounds associated with breathing and swallowing. The flat diaphragm of a stethoscope is placed on the side of the thyroid cartilage. Several acoustic features of the swallow are noted, such as the release of subglottic air and epiglottic movement. There is disagreement over which sound or silent interval corresponds to which feature.[12–14] Swallowing sounds can be influenced by bolus volume and fluid viscosity.[15, 16] Furthermore, it appears that only a proportion of clinicians can achieve high inter- and intra-rater reliability.[12, 17]

Pulse oximetry measures oxygen desaturation. The intricacies of the respiratory–swallow cycle are described in Chapter 48, Physiology of swallowing. Aspiration of material can interrupt this cycle, impacting on arterial blood oxygenation. When used as part of a CSE, baseline measures need to be taken over a sufficient period of time and monitored for any changes following swallowing trials.[6] The sensitivity and specificity for pulse oximetry in identifying aspiration in the stroke population is questionable.[18]

Poor performance or uncertainty based on a CSE will influence the decision to perform a more in-depth, instrumental assessment.

When to refer for an imaging swallowing assessment

Screening assessments aim to identify whether someone has dysphagia, but cannot identify why the dysphagia is occurring. Instrumental tests have an important role in the identification of risk and safe management of aspiration, planning targeted interventions and provide outcomes on the effectiveness of treatment. The American Speech and Hearing Association (ASHA) and the Royal College of Speech & Language Therapists (RCSLT) have published guidelines on the conduct of instrumental swallowing assessments.[19, 20] ASHA's suggested criteria on when a swallow imaging assessment is indicated for assisting in making a diagnosis and/or planning dysphagia management include the following:

- The patient's signs and symptoms are inconsistent with the CSE findings.
- There is a need to confirm a suspected medical diagnosis and/or assist in the determination of a differential medical diagnosis.
- There is either nutritional or pulmonary compromise or a question of whether the oropharyngeal dysphagia is contributing to these conditions.
- Safety and efficiency of the swallow remain a concern.
- The patient is identified as a swallow rehabilitation candidate and specific information is needed to guide management and treatment.

An instrumental examination may be indicated for making the diagnosis and/or planning effective treatment in patients with suspected dysphagia based on the clinical examination and the presence of one or more of the following:

- The patient has a medical condition or diagnosis associated with a high risk for dysphagia, including but not limited to neurologic, pulmonary or cardiopulmonary, gastrointestinal problems; immune system compromise; surgery and/or radiotherapy to the head and neck; and craniofacial abnormalities.
- The patient has a previously diagnosed dysphagia and a change in swallow function is suspected.
- The patient has a communication or cognitive problem and is unable to complete a CSE.
- The patient has a chronic degenerative disease or a disease with a known progression, or is in a stable or recovering condition for which oropharyngeal function may require further assessment for management.

RADIOLOGICAL ASSESSMENTS OF SWALLOWING

There are two distinctly different barium swallows available for the evaluation of dysphagia: the traditional

barium swallow, and videofluoroscopy (also called a modified barium swallow or dynamic swallowing study). Logemann[21] published one of the first articles to describe a videofluoroscopic swallowing study (VFSS) as a diagnostic procedure for oropharyngeal dysphagia.

Videofluoroscopic swallowing study

A VFSS is a recorded radiographic study of the swallowing structures, their movement and coordination. Unlike a barium swallow, it is a dynamic assessment of swallowing. It tracks a radio-opaque bolus from the oral cavity to the upper oesophagus in the lateral or anterior–posterior plane and for this reason it has been deemed the 'gold standard' swallowing assessment. The examination typically involves a speech and language therapist, radiologist and/or radiographer. The presence of a radiologist is considered best practice for paediatric VFSS.[20] Other professionals who may be involved include physicians, surgeons, nurses, physiotherapists and occupational therapists. Specific referral procedures will vary according to local guidelines. Referring sources may include medical practitioners and designated referring speech and language therapists (SLTs). Patients must undergo an appropriate CSE prior to VFSS being undertaken in order to determine suitability and to direct the content of the examination.

PROCEDURE

Patients are not required to fast prior to a VFSS. Where possible, they should be positioned in their usual eating/drinking position. Test boluses are mixed with radio-opaque material to enable visualization. Consideration needs to be given to rheological characteristics, visibility and adherence or coating when adding substances such as barium. Guidelines for mixing the different commercially available radio-opaque substances are available from www.SteeleSwallowingLab.ca.[22, 23]

A VFSS should be systematic to allow for comparison within and between patients. Test boluses are given in increasing volume to minimize the risk of large amounts of aspiration. A range of different food textures may then be assessed, in a graded fashion. The majority of the VFSS is usually conducted in the lateral plane. An anterior–posterior view will give further information about symmetry of laryngopharyngeal movement and laterality of any residue. An oblique head position may be used to further investigate the upper oesophageal area. The number of test items will be limited in order to keep radiation dose to a minimum. The test may include a trial of compensatory strategies, for example an airway protection technique, a chin tuck position. These may then form part of an intervention plan.

Images are recorded digitally, for later analysis and interpretation. Patients may be shown the examination as part of shared decision-making and participation in management plans. If biomechanical movements are to be measured, a metal ring of known diameter (e.g. coin) is taped in the midline to the underside of the chin for calibration. Specific patient safety procedures need to be in place, i.e. access to suctioning in cases of gross aspiration as well as clinician safety guidelines for protection to radiation exposure.

CONTRAINDICATIONS AND RISKS

The examination is conducted in the radiology department and therefore patients need to be medically stable enough to attend and participate in the procedure. The referring clinician needs to consider whether the individual has the ability to cooperate with the examination, such as the ability to maintain the appropriate position and respond to instruction. Caution is needed when gross aspiration is suspected or where there is a history of respiratory distress/arrest due to aspiration. Patient pregnancy is another contraindication due to radiation exposure to the fetus. Needless to say, a VFSS cannot be performed on individuals who have been placed nil by mouth for reasons other than dysphagia (e.g. before general anaesthetic). Reports of adverse reactions to radio-opaque contrast are rare but could be life-threatening and therefore an alternative investigation needs to be found.

ANALYSIS

Interpretation of a VFSS includes a description of bolus flow, reactions to a misdirected bolus, presence of airway invasion, residue and variations from the normal anatomy and physiology. The rater considers the efficiency of bolus preparation and propulsion, and safety or airway protection. An analysis of oropharyngeal swallowing requires a thorough understanding of the normal swallow biomechanics in the context of influencing factors (i.e. gender, age). Typical anatomical abnormalities detected on VFSS include pouches, diverticulae, osteophytes, cricopharyngeal web and fistulae. A number of biomechanical measurements can be derived from the examination such as timing of swallow onset, hyolaryngeal movement, oropharyngeal movements, airway protection mechanisms, upper oesophageal opening. The presence of penetration, aspiration and residue and patients' response to it is recorded.

The reliability and validity of VFSS interpretation has been reported.[24–26] Reliability improves when examinations are group rated, viewed in slow time as well as real time, and judged using validated scales.[27, 28] Examples of rating scales include the MBSImps (a 17-point scale recording oropharyngeal swallowing impairment) and the penetration–aspiration scale (recording the depth of airway invasion and the patient's response to it).[27, 29, 30] Consideration needs to be given to the controlled nature of a VFSS and how much this reflects natural eating and drinking. Stability (i.e. the level of agreement between swallows of the same texture and volume) can vary between bolus consistencies. One study has demonstrated poorer stability for semi-solids than for liquids.[31] The clinician needs to integrate these findings when preparing the report, including recommendations for feeding and an intervention plan.

LIMITATIONS

There are several limitations of this assessment technique:

- Radiation exposure to the patient, especially for repeated or lengthy studies. However, 3 minutes of videofluoroscopy examination gives the equivalent radiation exposure as two cervical spine radiographs.[32] Scattered radiation exposure to the surroundings is within acceptable levels.[33]
- The cost of equipment and involvement of several specialist staff is high.
- There can be difficulties with positioning patients such as those who are bedbound or have difficulty with head control.
- The properties of barium are designed to coat structures, so liquid and food containing barium do not behave in the same way as normal liquids or food.
- Limited or inferred information only is gained about mucosa and secretions, sensation, inter-bolus pressure and glottic closure.

Barium swallow

The traditional barium swallow includes both static and dynamic components to identify intrinsic disease (tumours, diverticula, webs and dysmotility) and extrinsic disease (cervical osteophytes, enlarged thyroid gland). The oesophageal lumen is distended with liquid barium, or coated in thick barium and distended by gas to show intrinsic irregularities and extrinsic impressions. Static imaging with plain radiographs provides information on structural abnormalities (e.g. Zenker's diverticulum, cervical osteophytes), but these static images have little else to contribute to the investigation of dysphagia.[34]

Oesophageal motility is assessed with multiple single swallows in different positions, including recumbent (unlike in a videofluoroscopy assessment of oropharyngeal dysphagia), to assess peristalsis without the effect of gravity. Continuous and single swallows are observed separately as a second swallow obliterates peristalsis of the first.

If oropharyngeal dysphagia and aspiration are suspected, bolus sizes need to be kept small and the investigation should proceed cautiously, or a videofluoroscopy examination should be undertaken instead.

Both the oral and pharyngeal areas should be examined even if the complaint is only oesophageal as 35% of patients have simultaneous disorders of the pharynx and oesophagus[35] and the level of the lesion does not necessarily correspond to the site of the patient's symptoms.[36] Perlman et al.[35] give a comprehensive account of the interpretation of observations and dysphagic characteristics in the oesophageal stages of swallowing.

CT and MRI

These techniques both show structural lesions, for example intracranial disease causing neurogenic dysphagia.[37] More recently, high-speed MRI has been used for dynamic analysis of swallowing in both healthy volunteers and patients with dysphagia.[38, 39] MRI is a non-invasive test that gives both anatomical and functional information on swallowing that can be a useful addition to traditional assessment tools.[40] This technology is costly and still experimental and there is only limited published normal control data for comparison. These tests also require the participant to be supine while swallowing, which does not reflect normal swallowing activity.

ENDOSCOPIC EVALUATION OF SWALLOWING

Fibre-optic endoscopic evaluation of swallowing

A fibre-optic endoscopic evaluation of swallowing (FEES) affords a different perspective from a VFSS. It allows a direct view of nasolaryngopharyngeal anatomy and physiology, assessment of swallowing function and any compensatory interventions to facilitate swallowing performance.[41, 42] The equipment is portable so the test can be conducted at the bedside. This is particularly useful for vulnerable groups such as an intensive care unit setting. The endoscopic view can give specific information on secretion management (an important indication of aspiration),[43] the impact of fatigue (as the scope can be held in position for some time) and laryngopharyngeal sensation. Sensation may be measured quantitatively using FEES with sensory testing (FEESST), which requires additional equipment to deliver air pulses of differing intensity, duration and frequency through an additional port in the endoscope.[44] The patient can view their swallowing simultaneously, which is particularly useful for teaching swallowing manoeuvres.[45] The test may be conducted by an otolaryngologist and/or a trained SLT. In the latter case, any suspicious lesion, dysfunction or pathology needs to be referred back to the patient's medical team. Published guidelines are available from RCSLT[41] and ASHA.[46]

PROCEDURE

Patients are not required to fast prior to a FEES. They should be positioned in their usual eating/drinking position. First, the nostrils are examined using the tip of the scope to assess which side provides the wider access. Local anaesthesia is not routinely administered, to avoid desensitizing the pharyngeal or laryngeal mucosa. Topical anaesthesia or a decongestant may be applied to the nares only, for patients who have difficulty tolerating the procedure. The nasendoscope is coated in a water-based lubricant to ease its passage through the inferior meatus of the nasal passage. Four different views allow observation of anatomy and physiology during swallowing as follows:

- Nasal passage for elevation of the dorsal side of the velum (**Figure 50.1a**).

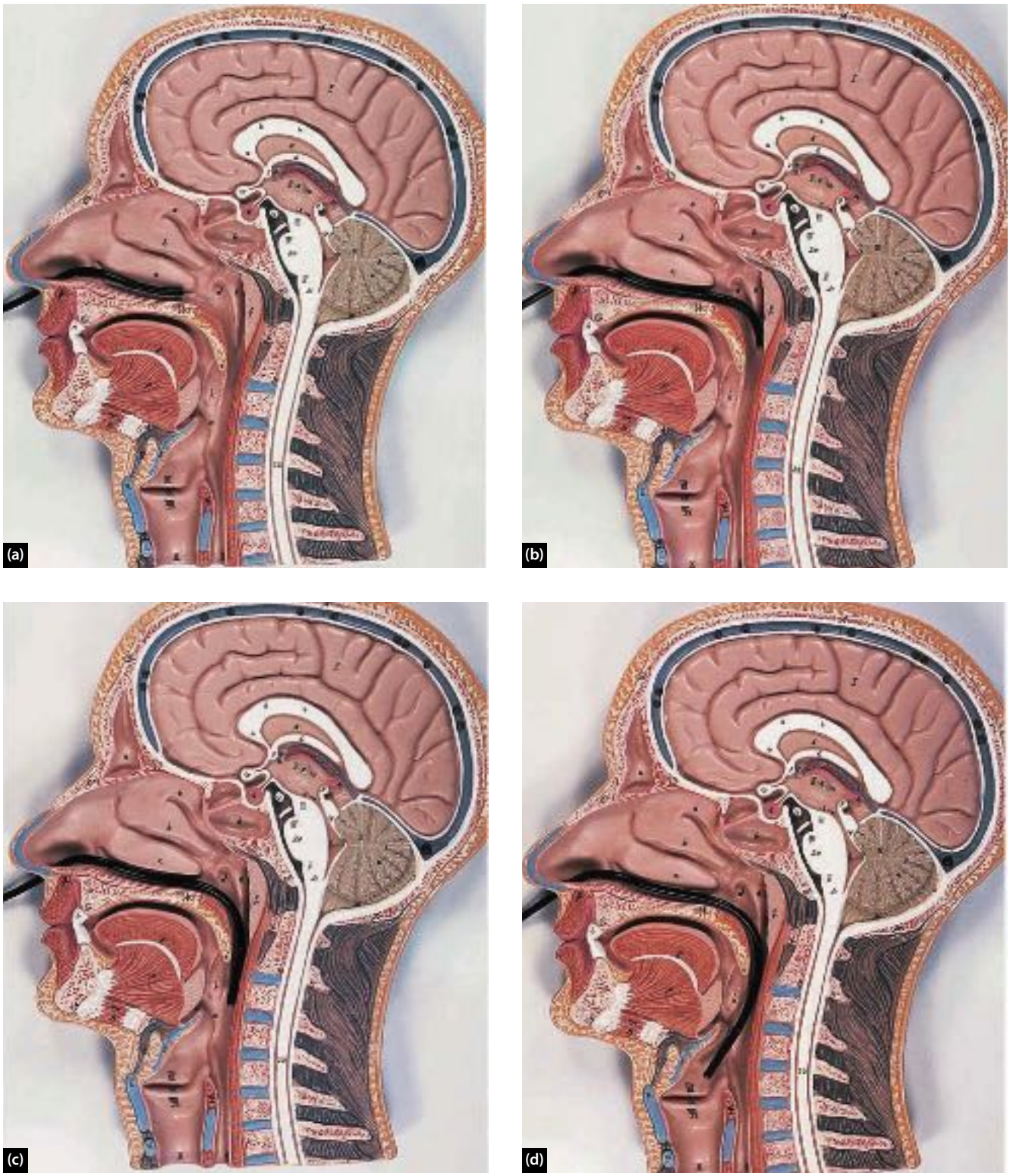


Figure 50.1 Endoscopic evaluation of swallowing. Nasendoscope positioned to view **(a)** dorsal side of velum, **(b)** nasopharynx, **(c)** oropharynx, and **(d)** hypopharynx/laryngopharynx.

- Nasopharynx for velopharyngeal competency, nasal reflux and lateral and posterior pharyngeal walls (**Figure 50.1b**).
- Oropharynx for base of tongue, epiglottis and larynx (**Figure 50.1c**).
- Hypopharynx for pyriform fossae, vocal folds and upper trachea (**Figure 50.1d**).

A functional evaluation is conducted prior to the introduction of any food or liquid. Examples of this include

a pharyngeal squeeze manouevre,[47] forced breath hold to assess maintenance of volitional glottic closure and a dry swallow. A range of fluid and food can be given, without requiring the addition of radio-opaque contrast. Food colouring is added to enhance visibility. For patients with severe dysphagia, the swallow trial may just consist of an ice chip as described by Langmore.[42]

Similar to VFSS, compensatory strategies may be introduced and their effectiveness evaluated. Images are recorded digitally, for later analysis and interpretation. Specific patient safety procedures need to be in place, such as guidelines for epistaxis or laryngospasm. Local guidelines on sterilization and infection control need to be followed.

CONTRAINDICATIONS AND RISKS

FEES has a good safety record, but it may be unsuitable for those patients who are drowsy or are unable to cooperate. Caution is needed in patients with a history of bronchospasm or laryngospasm, vasovagal response, cardiac instability, severe epistaxis or a physical obstruction to the passing of the scope. Adverse reactions to the topical anaesthetic are rare, but clinicians should take an adequate case history, adhere to recommended doses and have resuscitation measures available.

ANALYSIS

Interpretation of a FEES includes a description of bolus flow, reactions to a misdirected bolus, presence of airway invasion, residue and variations from the normal anatomy and physiology. Specific measurements relating to initiation of the swallow (also referred to as 'dwell time') may be taken.[48] The presence of post-swallow residue and airway invasion are recorded.

LIMITATIONS

There are a number of limitations of FEES, including:

- There is no view for evaluation of the oral stage of swallowing.
- There is loss of view ('whiteout') during the swallow due to pharyngeal constriction around the endoscope lens.
- Quantitative measures of structure displacement (e.g. hyoid elevation) are not possible.
- Ability to estimate amount of aspirated material is limited.

VFSS and FEES are widely used as instrumental assessments of oropharyngeal dysphagia in routine clinical practice. They are complimentary functional investigations.[49, 50] The features of each examination are summarized in **Table 50.1**.

Transnasal oesophagoscopy

Transnasal oesophagoscopy (TNO) is now a widely available technique for visualization of the upper digestive tract without the need for sedative drugs. This is discussed in greater detail in Chapter 49, Causes and assessment of dysphagia and aspiration. The role of TNO in functional investigations of the upper digestive tract is mainly in the exclusion of structural pathology, such as strictures or malignancies, and also in the diagnosis of other pathology, such as oesophagitis, through visual assessment and biopsy.[51]

MANOMETRY

Manometry provides additional swallowing information and evaluates pressure changes from pharyngeal and oesophageal muscle activity, particularly in patients with motility disorders.[52]

TABLE 50.1 Comparison of VFSS and FEES

Considerations	FEES	VFSS
Equipment	Nasoendoscope, camera, monitor, digital recorder, microphone	Fluoroscopy, digital recorder, monitor
Personnel	Otolaryngologist and/or SLT	Radiologist and/or radiographer, SLT
Safety	Mild patient discomfort	Radiation exposure
Accessibility	Highly portable, repeatable	X-ray department only; repeated assessment limited by radiation
Oral stage	Not observed	Well seen
Pharyngeal stage	Direct assessment before and after swallowing, not during	Well seen
Oesophageal stage	Not observed	Can be observed
Aspiration/penetration	Accurate assessment	Accurate assessment
Pharyngeal sensation	Sensory response to the scope can be observed	Only inferred
Range of boluses	All ranges of food and drink	Radio-opaque contrasts alter viscosity, texture and taste of food/drink
Fatigue effect on swallow	Easily assessed	Limited by radiation and expense

Pharyngeal manometry

Pharyngeal manometry provides information regarding the amplitude and duration of pharyngeal contractions and upper oesophageal sphincter (UOS) relaxation during swallowing. Rates of pressure change are greater in the pharynx than the oesophagus. Clinically, this test gives an indication of the strength and consequently the efficiency of essential swallowing movements. This can assist in understanding the nature of the swallow breakdown, particularly with motility disorders and post-swallow pharyngeal residue. Manometry can be used in conjunction with the tools mentioned above, i.e. videofluoroscopy (manofluoroscopy) or endoscopy (manovideoendoscopy). It may be used as a stand-alone measure, when the swallowing physiology has already been studied and is known. However, when used alone, it will be susceptible to technical difficulties with accurate sensor placement and reduced inter- and intrareliability.

Three main measures of timing and pressure generation are derived from the procedure:

- base of tongue to pharyngeal wall pressure generation
- lower pharyngeal pressure
- UOS relaxation.

A healthy swallow is characterized by rapid onset of pharyngeal pressure generation, a drop in UOS pressure in response to laryngeal elevation and a return to baseline pressure measurement post swallow.

PROCEDURE

Pharyngeal manometry is moderately invasive, requiring placement of a specialized catheter through the nose and into the oesophagus. This needs to remain in the correct position during swallowing, which can be problematic due to the upward movement of the larynx. The distal tip needs to remain in the UOS, for the assessment of cricopharyngeal relaxation. The proximal end of the catheter is secured with tape against the face. Microcatheters are required if this test is to be performed in children. Patients may require a little time to accommodate to the catheter *in situ*. Measurements are taken at rest and during swallowing.[52]

Research reporting normative data is available. Readings can differ according to age, gender, viscosity and bolus volume[53, 54] so a standardized approach is necessary for comparisons. There is less variation in resting UOS pressures.[53] Measurements appear consistent across swallows, limiting the need for repeated trials.[55, 56] Training is required for interpreting results, with just short training affording high levels of reliability.[57] The measures derived are useful outcome measures for guiding and evaluating treatment.

Oesophageal manometry

Oesophageal manometry provides information on oesophageal muscle activity and can be useful in diagnosing oesophageal motility disorders. The oesophageal peristaltic wave pressure rises slowly to approximately 50 mmHg, and falls rapidly. Secondary peristaltic waves arise locally in response to distension, needed for more solid bolus transportation. Tertiary oesophageal contractions are irregular, non-propulsive contractions involving long segments of the oesophagus.[37]

The 3 cm long lower oesophageal sphincter (LOS) behaves like the UOS, but with a lower tonic (resting) contraction pressure of 10–30 mmHg relative to intragastric pressure. It remains closed except for relaxation when the bolus and peristaltic wave arrive, as swallowing induces inhibition of LOS tone activity. The barrier formed by LOS tonic pressure is lower after meals and tighter at night. Similar to the UOS, measurement of the LOS tonic pressure is complicated by radial asymmetry and a respiratory pressure fluctuation.

HIGH-RESOLUTION MANOMETRY (HRM)

Conventional pharyngeal or oesophageal manometry utilizes a solid-state catheter with sensors spaced at intervals along the catheter. Sensors are unidirectional and record pressure changes shown as pressure waveforms. The enhanced technology of HRM offers several advantages over conventional manometry. The catheter has 36 circumferential pressure sensors, at 1 cm apart, thus providing greater specificity and accuracy. Output is interpreted from a spatiotemporal plot, requiring manual analysis.

PATIENT SELECTION

Manometry is not frequently used as part of a routine clinical assessment in the UK. Robust guidance on who to select for this procedure is still in its infancy. However, the information derived can help to form a more detailed understanding of swallow breakdown. A small number of patients may not be able to tolerate the passage of a nasopharyngeal catheter and this may be contraindicated in those with recent nasopharyngeal surgery. Patients with suspected Zenker's diverticulum will require X-ray guidance, to ensure correct catheter placement into the upper oesophagus. The range of manometric findings for different pathological processes is dealt with in Chapter 49, Causes and assessment of dysphagia and aspiration, and Chapter 53, Oesophageal diseases.

OTHER INVESTIGATIONS

Respiration

Respiratory recordings measure the duration and timing of deglutition apnoea, and direction and rate of airflow and thus a more complete picture of the physiology of swallowing.[58, 59] Several assessment tools have been used and reported in the literature, including intranasal pressure measurements, resistive chest belt, nasal thermistor and respiratory inductive plethysmography.[60–63] Continuous recordings of oxygen saturation by pulse oximetry have also been investigated as a possible marker of aspiration, with conflicting results.[64–67]

Ultrasound

Ultrasonography is a non-invasive technique for soft-tissue imaging during swallow events. The ultrasound transducer with high-frequency sounds (>2 MHz) is placed submentally to produce dynamic images of the soft tissue in the oral cavity and parts of the oropharynx, hyoid motion and changes to hyoid–thyroid distance. The quality of the tongue image for measuring movements is not easy to interpret.[37, 68] It cannot visualize episodes of penetration or aspiration. Patients need to maintain sufficient head control during this examination. There are further methodological issues such as accuracy of transducer placement and reliability of measurements.[69]

Pharyngeal and oesophageal pH monitoring

Prolonged (24-hour ambulatory) pH monitoring is the most reliable method of diagnosing gastro-oesophageal reflux disease (GORD). Recently, the introduction of pharyngeal probes has resulted in the technique being used to diagnose laryngopharyngeal reflux (LPR). Technological advances have led to the, single, dual and even triple lumen sensors that can detect liquid reflux events as well as purported aerosolized acid exposure at various points along the upper digestive tract.[70, 71]

In oesophageal pH monitoring the distal oesophageal pH probe is placed 5 cm above the LOS (position determined by manometry) and the proximal one below the UOS, thus any reflux is measured along the entire length of the oesophagus. The pharyngeal probe is typically placed at the level of the uvula; there is, however, inconsistency in the methodology of pH monitoring in much of the published literature, in particular location of the pharyngeal probe.[72] Further limitations identified in pH monitoring include the impact of diet[73] and the role of non-acidic factors, particularly in LPR.[74] A recent meta-analysis of pH manometry showed that, when techniques were tightly controlled, consistent differentiation of LPR patients from healthy controls was possible.[72] Nevertheless, oesophageal and pharyngeal pH manometry does require specific invasive equipment. This invasive technique prevents some patients from undertaking activities that provoke reflux during the investigation, so it can lead to underestimating their problems.[75]

Scintigraphy

This procedure tracks movement of the bolus over time and quantifies the residual bolus in the oropharynx, larynx and trachea, using radionuclide material with liquid or food, and a gamma camera. It can offer information regarding oesophageal transit.[76] Although it can detect aspiration and reflux, it has poor anatomical definition in comparison to VFSS or barium swallow, and it does not image the biomechanics of swallowing, thus the cause of aspiration cannot be determined.

Lingual pressure recording

Tongue strength and endurance are important components for bolus pressure drive. Three-bulb linear manometric sensor arrays have been used to evaluate the timing and pressure patterns of the anterior, middle and posterior tongue during the oral phase of swallowing. Small pressure sensors are attached to the palate. Most work to date has been experimental.[77]

Electromyography

Surface electromyography (sEMG) measures the amplitude of submental muscle activity from electrodes placed under the chin, in combination with a laryngeal sensor. Activity is recorded from any or all of the submental muscles during swallowing. They are variable in their order of activation both within and between subjects. Preliminary evidence suggests that it may be an important adjunct in identifying aspiration risk in acute stroke patients.[78]

CONCLUSION

Manometry, nasendoscopy and videofluoroscopy are complementary procedures which enhance our understanding of the pathophysiological processes causing symptoms and inform management decisions. Other techniques mentioned are either at experimental stages requiring more research-based data, or are for specific conditions related to dysphagia.

BEST CLINICAL PRACTICE

- ✓ After careful history-taking, evaluation of symptomatology and a clinical swallow evaluation, choosing the most appropriate investigation for any one patient depends on many factors:
  - ✓ specific symptoms of dysphagia
  - ✓ medical condition, cognitive functioning, fatigue level and mobility of patient
  - ✓ invasive nature of investigations and the likely effect(s) this may have
  - ✓ availability and cost of both equipment and trained/experienced professionals.
- ✓ Each investigation has different advantages and limitations, as listed in detail in the chapter.
- ✓ Some patients may require several investigations for a more complete picture but, in general, FEES and/or videofluoroscopy are the first choices for oropharyngeal dysphagia, followed by manometry for motility disorders and to identify candidates for myotomy or dilatation. Barium contrast identifies anatomical and some motor disorders; endoscopy of the oesophagus is the approach of choice for obstructions, taking biopsies for pathologic identification, therapeutic dilatation of a stricture or removal of foreign bodies.
- ✓ The two techniques of videofluoroscopy and FEES are equally effective in discrimination between penetration and aspiration and in guiding management with respect to the outcome of pneumonia.

KEY POINTS

- Functional investigations of the upper GI tract to explore oropharyngeal dysphagia provide information about anatomy, muscular function, mucosal sensation, bolus direction and flow, and the relationships between them. This information is important for devising management recommendations, shared decision-making and evaluating treatment over time.
- Oropharyngeal dysphagia is caused by many underlying aetiologies, producing a wide range of symptoms. The selection of functional assessments will depend on the clinical question needing to be answered.
- Non-instrumental and screening tests are useful to detect the presence of dysphagia. However, functional investigations using instrumentation are more sensitive and specific in accurately detecting aspiration or penetration.
- Instrumental tests, such as videofluoroscopy and FEES, are diagnostic assessments as they can define the swallow disorder in terms of anatomy and physiology causing the problem, and the symptoms in terms of aspiration, penetration, reflux and residue. Such information enables treatment to be directed at the physiological disorder(s) while symptoms are managed by compensatory strategies.
- Technological advancements are allowing for a multitude of further advanced assessments of the upper GI tract and are useful for specific clinical scenarios.

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CHAPTER 51

PHARYNGITIS

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: acute pharyngitis, sore throat, acute tonsillitis, streptococcal pharyngitis/sore throat, bacterial pharyngitis/sore throat, viral pharyngitis/sore throat; peritonsillar abscess alone and with epidemiology, bacteriology, clinical features, differential diagnosis, investigation, treatment and complications; infectious mononucleosis, glandular fever and Epstein–Barr virus, both in isolation and in conjunction with, epidemiology, clinical features, systemic manifestations, associated tumours, serological diagnosis and treatment; chronic pharyngitis/ nonspecific chronic pharyngitis or non-infectious chronic pharyngitis.

In addition, the Cochrane Database of Systematic Reviews and the references in the Scottish Intercollegiate Guidelines Network (SIGN) were reviewed.

DEFINITION

Pharyngitis is defined as inflammation of the pharynx. It can be generalized inflammation of the whole pharynx (**Figure 51.1**) or localized to a specific area of the pharynx (tonsillitis, **Figure 51.2**). The presenting symptom of pharyngitis is usually a sore throat, which is one of the most common presentations for outpatient consultations in primary care.

EPIDEMIOLOGY

Pharyngitis affects both sexes and all age groups, but it is more common in children in late autumn and early winter. The overall incidence of sore throat in all age groups varies widely and different definitions make comparisons between figures difficult. Moreover, most patients with sore throat never or only rarely see their GP. A study demonstrated that only 1 in 18 sore throat episodes led to a GP consultation.[1]

In 2007, the age-standardized patient prevalence rate for acute pharyngitis for all ages in UK was 182 per 10 000.[2]

The cost to the UK National Health Service (NHS) of GP consultations for sore throat, before any treatment or investigation, has been estimated at approximately £60 million per annum.

AETIOLOGY

Most cases of pharyngitis are due to infectious causes (**Box 51.1**). Viruses are isolated in approximately 40–60% of cases and bacterial pathogens in approximately 5–30% of cases. In approximately 30% of cases no pathogen is isolated.

Non-infectious causes include dry air, allergy/post-nasal drip, chemical injury, gastro-oesophageal reflux disease (GORD), smoking, neoplasia and endotracheal intubation.

GABHS BACTERIAL PHARYNGITIS

Group A beta-haemolytic streptococci (GABHS) are the commonest cause of bacterial pharyngitis and are spread via respiratory secretions through close contact. There is



Figure 51.1 Acute pharyngitis with a mucopurulent secretion on the posterior pharyngeal wall.



Figure 51.2 Clinical appearance of tonsillitis with pharyngeal erythema, enlarged tonsils and tonsillar crypts containing necrotic or purulent exudates.

an incubation period of 1–5 days. The risk of contagion most probably depends on inoculum size and the virulence of the infecting strain. Individuals are most infectious in the early stages of the disease. More than 120 M-protein types of GABHS have been isolated, with serotypes 1, 3, 5, 6, 18, 19 and 24 associated with rheumatic fever (i.e. rheumatogenic forms) and others, such as serotypes 49, 55 and 57 associated with pyoderma and acute post-streptococcal glomerulonephritis.

Clinical presentation

The classical history is that of sore throat, fever, chills, malaise, headaches, anorexia, abdominal pains as well as a history of exposure to known carriers. However, all these features are rarely present, but sore throat is present in all those old enough to recognize the symptom (see **Figure 51.1**).

The clinical picture in an individual sore throat is of limited assistance in distinguishing between a bacterial and a viral aetiology. There is no evidence that bacterial sore throats are more severe than viral ones or that the duration of the illness is significantly different in the two types.

BOX 51.1 Causes of pharyngitis

Bacterial	
Common	Group A-beta haemolytic *Streptococcus pyogenes (GABHS)*
Uncommon	*Neisseria gonorrhoeae* *Haemophilus influenza* *Corynebacterium diphtheria* *Moraxella (Branhamella) catarrhalis* Group C and G streptococci *Corynebacterium haemolyticum* *Chlamydia trachomatis* *Mycoplasma pneumonia* *Borrelia* species *Francisella tularensis* *Yersinia* species
Probable co-pathogens	*Staphylococcus aureus* *H. influenza* *Branhamella catarrhalis* *Bacteroides fragilis* *Bacteroides oralis* *Bacteroides melaninogenicus* *Fusobacterium* species *Peptostreptococcus* species
Viral	
	Rhinovirus *Adenovirus* *Parainfluenza* virus Coxsackievirus *Coronavirus echovirus* Herpes simplex virus Epstein–Barr virus (EBV) (mononucleosis) Cytomegalovirus (CMV) Human immunodeficiency virus (HIV) infection
Fungal	*Candida* species
Protozoa	*Toxoplasma gondii*
Non-infectious causes	Dry air Allergy/post-nasal drip Chemical injury Gastro-oesophageal reflux disease (GORD) Smoking Endotracheal intubation

Although no single or combination of physical findings is specific for distinguishing GABHS from viral aetiologies, several features are suggestive (**Box 51.2**).[3]

Specific viral infections have characteristic features: conjunctivitis more commonly with adenovirus infections, infectious mononucleosis (IM) typically is exudative and associated with extensive false membranes; finally, herpangina (usually coxsackievirus A or herpes virus) is associated with papulovesicular lesions. Concomitant vesicles on the hands and feet are associated with coxsackievirus A (hand, foot and mouth disease).

Several scoring systems have been described to provide a rational basis for differentiating GABHS from viral pharyngitis. SIGN guidelines[4] recommend that the Centor clinical prediction score should be used to assist the decision on whether to prescribe an antibiotic but cannot be relied upon for a precise diagnosis.

BOX 51.2 Features distinguishing GABHS pharyngitis from viral pharyngitis

Features suggestive of bacterial pharyngitis	Features suggestive of viral origin
Pharyngeal erythema Enlarged tonsils Tonsillar crypts containing necrotic or purulent exudates Fever Cervical lymphadenopathy Soft palate petechiae Scarlet fever rash (punctate erythematous macules with reddened flexor creases and circumoral pallor), also called 'sandpaper' rash History of exposure 5–15 years age group	Conjunctivitis Sneezing and rhinorrhea Cough Diarrhoea Exanthems or enanthems Papulovesicular lesions

The Centor score[5] gives 1 point each for:

- tonsillar exudate
- tender anterior cervical lymph nodes
- history of fever
- absence of cough.

McIsaac et al[6] developed the modified Centor criteria, which add the age of the patient (+1 if age 3–14, 0 if age 15–44 and –1 if age ≥45), taking into account the fact that GABHS is more prevalent in the age group of 5–15 years.

The likelihood of GABHS infection increases with increasing score, and it is 25–86% with a score of 4 and 2–23% with a score of 1, depending upon age, local prevalence and seasonal variation.[4] The score is not validated for use in children under 3 years.

Studies on sensitivity and specificity suggest that reliance on clinical diagnosis will miss 25–50% of GABHS pharyngitis cases and that 20–40% of those with negative throat cultures will be labelled as having GABHS.

Investigation

Investigations are of limited practical value but may occasionally be of benefit when symptoms are severe or if they persist despite adequate conservative management. Full blood count may show leukocytosis, which is highly suggestive of bacterial infection.

Recommendation regarding routine use of tests for microbiological diagnosis of GABHS varies among national guidelines.

According to US[7,8] and French[9] guidelines, microbiological confirmation is required for the diagnosis of GABHS pharyngitis, and rapid antigen detection tests (RADTs) or throat culture should be routinely performed in suspected cases. However, according to UK guidelines, further studies are required to evaluate the cost-effectiveness and clinical benefit of RADTs and insufficient evidence was identified to support a recommendation (SIGN).

RADTs involve extraction of the group-specific carbohydrate antigen from the GABHS cell wall and identification of the antigen by an immunological reaction. A recent meta-analysis of these tests[10] determined an overall sensitivity of 0.85 [95% CI, 0.84–0.87], specificity was 0.96 [95% CI, 0.96–0.97], likelihood ratio (+) 22.21 [95% CI, 15.12–32.63], and likelihood ratio (–) 0.15 [95% CI, 0.13–0.18].

A well-conducted prospective study showed that the RADT can be a valid diagnostic test for the diagnosis of GABHS in adults with pharyngitis, particularly when combined with the Centor clinical score and should be used in patients with at least two clinical findings suggestive of GABHS.[11]

It has been suggested that a strategy based on clinical scores alone may be associated with higher antibiotic usage as compared with either (i) a combination of clinical score and rapid tests use or (ii) use of rapid tests alone.[12] Rapid antigen detection, however, is not sensitive for group C and G streptococci or other bacterial pathogens.

Throat culture is described as the criterion (gold-standard) diagnostic test for GABHS in the North American literature. Results can take up to 24 hours. Throat culture results are highly sensitive and specific for GABHS but can vary, depending on technique, sampling and media. A positive throat culture for GABHS makes the diagnosis of streptococcal sore throat likely but a negative culture does not rule out such a diagnosis. There are cases where *Streptococcus* is isolated from sore throats but there is no serological evidence of infection.[13] There is also a high asymptomatic carrier rate of up to 40% for GABHS.[14] The flora of bacteria recovered from the surface of the tonsil correlates poorly with that deep in the tonsillar crypts, which is the most likely cause of infection.[15,16] Symptoms also correlate poorly with results of throat swab culture.[17] Throat swabs are neither sensitive nor specific for serologically confirmed infection, increase costs considerably, may medicalize illness and alter few management decisions. **Throat swabs should not routinely be carried out in sore throat.**[18]

Antistreptococcal antibody titres reflect past and not present immunologic events and therefore cannot be used to determine whether an individual with pharyngitis and Group A streptococcus (GAS) in the pharynx is truly infected or merely a streptococcal carrier.

Treatment

Streptococcal pharyngitis usually has a 5–7-day self-limiting course. Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol are more effective than placebo for relief of symptoms.[19] Paracetamol will suffice for mild cases, but in adults NSAIDs such as ibuprofen and diclofenac are considered superior to paracetamol for pain relief.[12]

Although concerns about risks of NSAIDs have been raised, a large double-blinded randomized controlled trial (RCT) showed that ibuprofen is as well tolerated as paracetamol,[20] hence the SIGN guidelines recommend use of ibuprofen 400 mg thrice daily for symptomatic relief of sore throat, fever and headache, in accordance with the

usual contraindications. Ibuprofen should not be given to patients with or at risk of dehydration due to concerns regarding renal toxicity. In patients who have contraindications for ibuprofen, paracetamol 1 g q.i.d. is recommended. However, in children paracetamol should be used as the first choice, with ibuprofen being used as an alternative.

TOPICAL ANALGESIA

A recent placebo-controlled study suggested that chlorhexidine gluconate and benzydamine hydrochloride mouth spray, added to standard antibiotic treatment, significantly alleviate the intensity of clinical signs in patients with streptococcal pharyngitis.[21]

Based on *in vitro* studies, amylmetacresol and 2,4-dichlorobenzyl alcohol (AMC/DCBA)-containing throat lozenges have been thought to produce an analgesic effect by means of its antiseptic action on bacteria and viruses and partly due to sodium channel blocking, i.e. direct local anaesthetic-like effects.[2] However, in the absence of good quality evidence confirming their efficacy or lasting benefit, there is insufficient evidence to support a recommendation of use of topical analgesia.

CORTICOSTEROIDS

According to a recent Cochrane review, in adult patients with sore throat, pain can be reduced and resolution hastened by use of a single dose of oral or intramuscular corticosteroids in conjunction with antibiotic therapy.[22] Two studies which directly compared intramuscular and oral routes found no differences and it is suggested that the oral route is used. Patients taking corticosteroids were three times more likely to experience complete resolution of their sore throat symptoms by 24 hours compared to those taking placebo. The mean time to onset of pain relief was 6.3 hours earlier in participants taking corticosteroids compared to placebo. However, these modest benefits have to be balanced with possible adverse drug effects of steroids,[23] although it is suggested that a short course is unlikely to be harmful.

There was insufficient evidence to recommend steroids in children with sore throat or as stand-alone treatment without the use of concurrent antibiotics.

ANTIBIOTICS

Bacterial pathogens are responsible for only 5–30% of cases of acute pharyngitis.[24] It is therefore illogical to treat all sore throats with antibiotics, and there is a favourable outcome in the majority of cases even when antibiotics are withheld. An open study of prescribing strategy in over 700 patients randomized to antibiotic versus no prescription versus delayed prescription for 3 days showed no difference in the main outcomes.[25]

A recent assessment of Cochrane reviews suggests that, for streptococcal tonsillitis, the use of antibiotics seems to be discretionary rather than prohibited or mandatory. This is because the benefit in terms of symptoms is only about 16 hours compared with placebo.[26] Estimates of the number of people with sore throat who must be treated to resolve the symptoms of one of them by day 3 (i.e. the number needed to treat to benefit (NNTB)) varied between 3.7 and 14.4, with benefit being more pronounced in patients with a positive throat swab for *Streptococcus*.

Role of antibiotics in preventing complications

Although the Cochrane review on the role of antibiotics found that antibiotics reduced the rate of non-suppurative complications such as rheumatic fever to about one-quarter of that in the placebo group and the rate of suppurative complications to about one-third, most of the beneficial effects were seen in studies conducted before 1975. The incidence of rheumatic fever in the UK is extremely low and there is no support in the literature for the routine treatment of sore throat with penicillin to prevent the development of rheumatic fever.[17] Protecting sore throat sufferers against suppurative and non-suppurative complications in high-income countries requires treating many with antibiotics for one sufferer to benefit. This NNTB may be lower in low-income countries as acute rheumatic fever remains a major problem in tropical regions, resource-poor countries and minority indigenous communities, with Aborigines in central and northern Australia showing some of the highest rates of both acute rheumatic fever and rheumatic heart disease in the world. Study of this latter group suggests that group C and G streptococcal organisms as well as the usual group A streptococcal infections may also have rheumatogenic strains.[18] Similar considerations apply to the prevention of glomerulonephritis.[19]

Recommendation regarding role of antibiotics

Most guidelines[4, 12, 27] recommend that antibiotics should not be prescribed for symptomatic management of pharyngitis, especially in patients with less severe presentation (e.g. 0–2 Centor criteria). Antibiotics should be considered in patients with more severe presentations (when three or more Centor criteria are present), but the modest benefit in symptoms from antibiotics should be weighed against increased antibacterial resistance, costs and possible side effects.

Antibiotics need not be started immediately. A Cochrane review evaluated the use of delayed antibiotics (more than 48 hours after presentation) compared to immediate or no antibiotics as a prescribing strategy for acute upper respiratory tract (URT) infections.[28] No significant differences in outcome were observed among the three groups, which led the authors to conclude that, in patients with respiratory infections where clinicians feel it is safe not to prescribe antibiotics immediately, no antibiotics with advice to return if symptoms do not resolve is likely to result in the least antibiotic use, while maintaining similar patient satisfaction and clinical outcomes to delayed antibiotics.

Patient and doctor education on the lack of benefit of antibiotics in routine management of sore throat can have a significant impact on the amount of antibiotics prescribed.[29]

Choice of antibiotics

Penicillin has been the antimicrobial agent of choice for GABHS and is recommended by most guidelines, if an antibiotic is deemed necessary for the management of pharyngitis. The minimal inhibitory concentration of penicillin for GABHS has not shown an increase over at least five decades.[30]

Most trials have compared penicillin with a variety of other antibiotics, notably cephalosporins. Although optimum elimination of GABHS is secured with intramuscular long-acting penicillin, oral penicillin V, 500 mg, four times daily for 10 days (adults) is the recommended dosage[4] and is widely regarded as the gold-standard treatment, with the advantages of being cost-effective and well-tolerated. A 10-day course of penicillin appears to be more effective than a 5-day course in reducing the incidence of bacteriological treatment failure, characterized by the presence of the same seroptype of GABHS in follow-up throat cultures.

Other more expensive antibiotics, mainly cephalosporins, have been shown to be statistically significantly more successful in eradicating the organism although the clinical advantage is much less clear. Some cephalosporins offer a more convenient dosage regimen, but twice and three times daily dosage of oral penicillin V has also been shown to be effective in eliminating GABHS. A 2010 Cochrane review[31] noted that, although there seem to be indications that carbacephems and cephalosporins might have some benefit over penicillin in terms of resolution of symptoms and incidence of relapse, the findings were inconsistent across analysis methods and the NNTBs were substantial. Therefore there is insufficient convincing evidence to alter current guideline recommendations for the treatment of patients with GABHS tonsillopharyngitis.

In patients allergic to penicillin, the alternatives include narrow-spectrum cephalosporins (cephalexin, cefadroxil) or macrolides (azithromycin, clarithromycin).

Doctors need to be aware that IM may present with severe sore throat with exudate and anterior cervical lymphadenopathy, and therefore should avoid prescription of ampicillin-based antibiotics, including co-amoxiclav, as first-line treatment.

When sore throat recurs in patients who have received antibiotic treatment, the reasons may include inappropriate antibiotic therapy, inadequate dose or duration of previous therapy, patient non-compliance/non-concordance, reinfection and local breakdown of penicillin by beta-lactamase producing commensals. Benzathine penicillin, cefuroxime and clindamycin have been shown to be superior to penicillin V in the management of children with this problem, and they may reduce the frequency of episodes.

ROLE OF TONSILLECTOMY IN THE MANAGEMENT OF PHARYNGITIS/TONSILLITIS

Although the non-inflammatory indications for tonsillectomy are reasonably defined with further trials in progress, the indication for tonsillectomy in the setting of recurrent/chronic tonsillitis/pharyngitis is controversial, with varied opinions regarding the relative risks and benefits. The controversy stems from the fact that palatine tonsils are only one constituent of the Waldeyer's ring of lymphoid tissue within the pharynx. Therefore, a patient who has had the tonsils removed can still have inflammation of the surrounding lymphoid tissue leading to recurrent sore throat. Hence, the important clinical question is to differentiate patients with recurrent tonsillitis from those with recurrent generalized pharyngitis presenting with sore throat. The natural history of tonsillitis is for the episodes to become less frequent with time, but there are insufficient epidemiological data for all age groups to allow predictions of this to be made in individual patients.

Various criteria have been proposed to select patients who are most likely to benefit from tonsillectomy. The referral criteria for tonsillectomy in the presence of recurrent sore throat that are used currently in the UK are based on the SIGN guidelines,[4] which are adapted from Paradise et al:[32]

- Sore throats are due to acute tonsillitis
- The episodes of sore throat are disabling and prevent normal functioning
- Seven or more well-documented, clinically significant, adequately treated sore throats in the preceding year *or*
- five or more such episodes in each of the preceding 2 years *or*
- three or more such episodes in each of the preceding 3 years.

Cognisance should also be taken of whether the frequency of episodes is increasing or decreasing.

A 2009 Cochrane review looked at the benefits of tonsillectomy compared with non-surgical treatment in the management of chronic or recurrent acute tonsillitis.[33] In this review, Burton et al observed that good information about the effects of tonsillectomy was only available for children and for effects in the first year following surgery. Children were divided into two subgroups: those who are severely affected (based on specific criteria which are often referred to as the 'Paradise criteria') and those less severely affected. Severely affected children will on average have one rather than three unpredictable episodes of any type of sore throat in the first year post-surgery, at the cost of one additional episode of post-operative pain. In the less severely affected group, surgery will mean having an average of two rather than three unpredictable episodes of any type of sore throat. Although the size of the effect is modest, the authors concluded there may be a benefit to knowing the precise timing of one episode of pain lasting several days; it occurs immediately after surgery as a direct consequence of it.

Several non-controlled studies suggest that tonsillectomy in children leads to an improvement in their general health and well-being.[34, 35]

The Cochrane review cited above found limited evidence of benefit of tonsillectomy in adults. One small well-conducted RCT[36] which looked at the effects of tonsillectomy in adults with proven recurrent group A streptococcal pharyngitis over a very short period

demonstrated a modest benefit; one episode of post-operative pain led to 1.5 fewer episodes of sore throat in the first 6 months.

These benefits have to be assessed keeping in mind that tonsillectomy is associated with a small but significant degree of morbidity in the form of primary and secondary haemorrhage. Patients who choose surgery for themselves or parents who choose it for their child must therefore be fully informed of the benefits and risks of the procedure.

THE CARRIER STATE

Patients exposed to GABHS may continue to carry the organism asymptomatically even after adequate antibiotic therapy. Carriers are recognized as those who demonstrate a positive culture but no rise in antistreptolysin O convalescent titre, and rates reported in the literature vary between 3% and 40% depending on the population studied. Carriers are at little risk of transmitting the disease: only 3.5% produce disease within their families.

Complications

Complications of GABHS pharyngitis can be classified as suppurative and non-suppurative (**Box 51.3**).

SUPPURATIVE COMPLICATIONS

Peritonsillar abscess (quinsy)

Peritonsillar abscess (PTA) is a collection of pus between the fibrous capsule of the tonsil, usually at the upper pole, and the superior constrictor muscles of the pharynx.

Epidemiology

Data from England have suggested that there was an 18% increase in the incidence of PTA in the 10 years to 2012, with 7589 episodes seen in 2009–2010.[37] It has been hypothesized that it could be because of fewer tonsillectomy operations being performed during that same period.

It may happen at any age but the majority of abscesses are seen in young adults between 20 and 39 years of age, which is surprising in view of the fact that the incidence of tonsillitis peaks in childhood, suggesting the aetiology must be more complex.

Several factors are known to increase the predisposition to form PTA. They include age, male gender, smoking, poor dental hygiene and immunodeficiency.

Pathogenesis

Two mechanisms have been proposed to describe the pathogenesis of PTA:[38]

- **A complication of acute tonsillitis.** This has been the most accepted theory, but recently questions have been raised about this hypothesis. This is because of certain studies which demonstrated up to 68% of patients with PTA had no preceding history of tonsillitis.[39, 40] The other factor which goes against this theory is the fact that the incidence of PTA is highest in the 20–39 age group whereas acute tonsillitis has the highest incidence in the 5–15 age group.
- **Weber gland blockage.** Passy[41] introduced the theory that a PTA may also represent a sequela of damage to Weber's glands, which are minor salivary glands located in the supratonsillar space. It has been suggested that the production of saliva by these glands helps to keep the tonsillar crypyts and peritonsillar areas clean. Poor dental hygiene and localized Weber gland infection could lead to blockage of the gland or the draining duct, predisposing this area to abscess formation.[41, 42] The reduction of innate immunity provided by saliva could be a contributing factor.[43]

Bacteriology

Group A beta-haemolytic streptococci and anaerobes such as *Fusobacterium necrophorum* and *Streptococcus milleri* have been clearly identified as causative organisms in PTA.[38]

Powell et al[38] suggested that there seem to be predominantly two pathogenically different PTA subtypes. Type 1 contains a pure culture of a single organism, most often GABHS. Type 2 displays heavy polymicrobial growth, often containing a variety of facultative and obligate anaerobes. Clinically, type 2 PTA often appears to be more severe, probably due to synergistic microbial interactions.

Clinical features

The main feature of the history is the progressive, usually unilateral, sore throat over 3–4 days, odynophagia, dysphagia for solids and eventually liquids, drooling of saliva, trismus, ipsilateral otalgia and headache associated with fever, lethargy and ipsilateral lymphadenopathy. The patient often develops a 'plummy' voice secondary to the oropharyngeal swelling and, on examination, limited mouth opening is virtually pathognomonic.[44] The tonsil is displaced medially by the hyperaemic, bulging mucosa of the anterior pillar over the peritonsillar space (**Figure 51.3**) and, in addition, the jugulodigastric nodes are tender and enlarged. Bilateral quinsies have been reported[45, 46] and in association with IM.[47] PTA arising in patients with IM is not linked to steroids prescribed to relieve upper airways obstruction in these circumstances.[48]

BOX 51.3 Complications of GABHS pharyngitis

Suppurative	Non-suppurative
Peritonsillar abscess Parapharyngeal abscess Retropharyngeal abscess	Rheumatic fever Post-streptococcal reactive arthritis Post-streptococcal glomerulonephritis Scarlet fever Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)



Figure 51.3 Peritonsillar abscess showing tonsils displaced medially and a bulge of the anterior tonsillar pillar.

Investigation

Investigation is not mandatory in clear-cut cases but may be helpful in less straightforward cases.

Needle aspiration of pus is often curative and may also provide useful bacteriology in recurrent or non-responsive quinsies and help clarify the difference between peritonsillar cellulitis and PTA. Bacteriological specimens do not need to be sent to the laboratory routinely after needle aspiration; this should be reserved for patients with a high likelihood of infection by resistant organisms, such as diabetics, immunocompromised patients or patients with recurrent PTAs.[49]

Although traditionally routine screening for IM in all patients presenting with PTA had been recommended,[50] a recent evidence-based review suggests that tests for infective mononucleosis should be reserved for cases were clinical suspicion is high, such as in teenagers and young adults and those with general features that are suggestive of infective mononucleosis.[37]

Transoral ultrasound is used in some countries[51] as an effective non-invasive method of differentiating pus from cellulitis (sensitivity 92.3%, specificity 62.3%).

Dental radiographs or an orthopantomogram may be helpful in the presence of coincidental dental disease or uncertainty as to whether a dental abscess may be involved.

Computed tomography (CT) has been used in the presence of suspected complications such as spread to the parapharynx, retropharynx and mediastinum. If descending necrotizing mediastinitis is suspected, CT of the neck and chest is the investigation of choice, rather than chest radiograph, as it will pick up signs when the chest radiograph is still normal.[52]

Magnetic resonance imaging (MRI) allows better soft-tissue detail and MR angiography may be suitable for suspected vascular anomalies. However, it takes longer and is more expensive and hence used sparingly.

Treatment

Surgical drainage is the mainstay of treatment for PTA. Drainage of the abscess can be performed by either needle aspiration or an incision and drainage. Needle aspiration is the most common treatment in the UK.[53] It is relatively pain-free, significantly contributes to pain relief compared with no aspiration[54] and is not associated with any significant complications. However, complete pus drainage may be less reliable than with a quinsy knife thus potentially predisposing to greater recurrence risks and delayed complications. Quinsy knife drainage is mainly used when needle aspiration has failed but it is more painful than needle aspiration and has, historically, been associated with some disastrous complications. Incision and drainage are less painful if carried out with proper infiltration of local anaesthetic at the site of drainage rather than local anaesthetic spray.[54]

Meta-analysis of success rates for needle aspiration gives a rate of 94 with recurrence rates ranging between 10% and 15%.[55] Since recurrence rates with incision and drainage (~10%)[56] are comparable to those with needle aspiration, clinician experience and patient choice should prevail in decision-making regarding the choice of approach.[37]

Medical management

Although surgical drainage is the mainstay of treatment, antibiotics are recommended for resolution of infection. A combination of benzyl penicillin and metronidazole is the preferred choice of antibiotics.[57] In patients with penicillin allergy, erythromycin/clarithromycin should be used. There is some evidence that benzyl penicillin alone is effective,[58] but, in view of the polymicrobial nature of these infections and variable rates of penicillin resistance, a combination of antibiotics is preferred.[37]

The use of steroids as an adjunctive treatment has been increasing, with one RCT reporting a range of favourable outcomes with steroids with no increase in complications.[59] A single dose of intravenous steroid in addition to antibiotic therapy significantly reduces throat pain, time in hospital, fever and trismus.

Supportive management

Attention should be paid towards adequate analgesia for symptomatic relief in this painful condition. Intravenous fluid resuscitation is important in patients who are unable to maintain adequate oral intake.

Inpatient admission for the above measures is the routinely followed practice in UK in the management of PTA. In the US, most patients are managed as outpatients. Multiple studies[56, 60] have shown that patients can be successfully managed in an outpatient setting with high levels of patient satisfaction. Outpatient management of PTA can be recommended if systems are in place for recognition of patients with risk of airway compromise/dehydration, short-term monitoring, good follow-up protocols and easy access for admission if the condition worsens.

Role of tonsillectomy

Abscess tonsillectomy is a technique with a poor reputation in the UK but it is practised in other countries[61, 62] with good results and minimal morbidity, with the additional advantage of avoiding recurrence and the need for

elective delayed tonsillectomy admission.[63] Moreover, the dissection plane is already created by the pus and prevents fibrosis, which makes interval tonsillectomy difficult. In a paediatric population in which needle aspiration or abscess drainage requires general anaesthesia, abscess tonsillectomy under general anaesthesia may be the treatment of choice.[64] Although concerns have been raised about the incidence of post-operative haemorrhage, comparison of the post-tonsillectomy haemorrhage rates of abscess tonsillectomy versus elective tonsillectomy in age- and gender-matched groups shows no statistically significant difference.[62, 65] However, the presence of trismus and associated intubation issues can increase the risk of GA, which has to be weighed against the advantages of the procedure.

Interval tonsillectomy Elective tonsillectomy after recurrent PTA is recommended. Most surgeons do not recommend surgery after one episode alone, as after tonsil-conserving treatments approximately 11% of cases recur by 5 years and 22% by 17–35 years and the number needed to treat would be 5–10 patients. In this group of patients, a subset with a higher risk (20–39 years, recurrent tonsillitis) may be considered for interval tonsillectomy.

Recurrence is rare after the age of 40 and therefore elective tonsillectomy is not warranted.[66]

Deep neck space infections and mediastinitis have been described in 1.8% of cases.[67] Mediastinitis is a condition with significant mortality (23%) [68] even with aggressive management, i.e. combined neck and mediastinal drainage as well as appropriate antibiotic therapy. If initial mediastinal drainage does not lead to resolution, reoperation including contralateral thoracotomy may be required.

Necrotizing fasciitis following PTAs has rarely been described. Treatments advocated include broad-spectrum antibiotics, abscess tonsillectomy and large-scale debridement of necrotic tissue.[69]

Parapharyngeal abscess and retropharyngeal abscess

Parapharyngeal abscess and retropharyngeal abscess are discussed in Chapter 40, Neck space infections.

NON-SUPPURATIVE COMPLICATIONS

Rheumatic fever

Rheumatic fever results from antibodies to streptococcal M protein cross-reacting with heart muscle leading to pancarditis. It may be associated with migratory arthritis involving the large joints, the erythema marginatum rash, subcutaneous nodules, and choreoathetotic movements of Sydenham's chorea. It typically occurs about 1–4 weeks after the GABHS infection.

Elevated or rising antistreptococcal antibody titres provide reliable confirmation of a recent group A streptococcus (GAS) infection and are of value in identifying a preceding GAS infection in a patient suspected of having rheumatic fever.

Although the incidence of rheumatic fever has decreased significantly in the developing world, it is still a major cause of morbidity, with the global prevalence estimated to be at least 15.6 million cases, with 282 000 new cases and 233 000 deaths each year.[70]

POST-STREPTOCOCCAL REACTIVE ARTHRITIS

Post-streptococcal reactive arthritis (PSRA) is a distinct clinical entity following streptococcal infection, with patients presenting with arthritis but lacking other major criteria for diagnosis of rheumatic fever. While the arthritis of rheumatic fever occurs 14–21 days after an episode of GAS pharyngitis and responds rapidly to acetylsalicylic acid, PSRA occurs about 10 days after the GAS pharyngitis and does not respond readily to acetylsalicylic acid.[7]

Post-streptococcal glomerulonephritis

Post-streptococcal glomerulonephritis (PSGN) is a type 3 hypersensitivity reaction and deposition of immune complexes in the glomerulus leading to an acute nephritic syndrome. It usually occurs 1–2 weeks after the infection. Although the incidence of this condition is also decreasing rapidly, it has been estimated that there are more than 470 000 cases of acute PSGN worldwide annually with around 5000 deaths, 97% of them occurring in less-developed countries.[70] Moreover, the majority of acute PSGN in tropical regions occurs predominantly as a result of skin infections, with the burden of PSGN attributable to pharyngitis being much lower. The prognosis for children with acute PSGN is generally favourable with a mortality of <0.5% and fewer than 2% progressing to end-stage renal failure.[71]

Scarlet fever

Scarlet fever is due to exotoxin production (erythemogenic or erythrogenic toxin) and leads to an erythematous rash and the tonsils and pharynx being covered by a yellow membranous film. Desquamation of the papillae of the tongue leads to a 'strawberry tongue' appearance, which is pathognomonic of this condition.

Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

Paediatric autoimmune neuropsychiatric disorder and acute disseminated encephalomyelitis, which can affect children and adults, have quite recently been recognized as immune-mediated illnesses associated with GABHS infection. Similar to Sydenham's chorea, it is believed to be due to an autoimmune response that cross-reacts with brain tissues and presents as an abrupt onset obsessive-compulsive disorder including hand washing, tic disorders and daytime urinary urgency.

The PANDAS hypothesis has stimulated considerable research, and controversy, but the American Heart Association guidelines state that, based on the current state of knowledge, the concept of PANDAS should be considered only as a yet-unproven hypothesis.[7]

NON-GABHS BACTERIAL PHARYNGITIS

Group C and G streptococci have been noted to be responsible for food-borne and waterborne outbreaks of pharyngitis.[72, 73] Some of these organisms are normal commensals, so differentiating colonization from infection is difficult. They can be cultured in patients with acute pharyngitis with clinical symptoms and examination findings indistinguishable from those of GABHS but generally less severe.[73] Pharyngeal infection with group C and G streptococci can cause acute glomerulonephritis but has never been shown to cause acute rheumatic fever.[74] Penicillin and clindamycin both provide effective eradication when necessary.

Sexually transmitted bacterial infections such as *Neisseria gonorrhoeae* and *Treponema pallidum* can lead to tonsillopharyngeal infections. Anaerobic bacteria can also be copathogens in GABHS infections, with a synergistic effect leading to suppurative complications.

Diphtheria

Diphtheria is a disease which was thought to be almost eradicated in most countries with high levels of vaccination. However, the level of immunity is believed to decline in late childhood and adolescence, depending on the schedule of immunization and the remaining reservoir of the causative organism *Corynebacterium diphtheria* in the population. This fact may lead to gaps in the immunity of the adults and diphtheria outbreaks may occur in subgroups of susceptible individuals despite widespread childhood vaccination.[74]

Diphtheria is caused by *Corynebacterium diphtheriae*, a non-motile, gram-positive pleomorphic bacillus. The characteristic feature is the presence of a fibrinous gray pseudomembrane on the tonsils, sometimes spreading to other areas of the pharynx and larynx, which is usually preceded by sore throat and fever. Attempts to remove the pseudomembrane cause bleeding from the pharyngeal mucosa. Marked cervical lymphadenopathy may lead to the 'bull neck' appearance. Since this condition can rapidly lead to significant airway obstruction or delayed exotoxin-induced myocarditis and neuritis, a high index of suspicion is to be maintained for diagnosis.

DIAGNOSIS

Definitive diagnosis is based on microbiological tests. Culture of swabs is performed on special culture media such as Loeffler medium. Smear morphology shows the classical 'Chinese character' appearance. Confirmation of toxigenicity of the organism was traditionally undertaken by the Elek test, but this test can lead to a delay in diagnosis of more than 48 hours. A rapid immunochromatographic strip (ICS) method for detection of diphtheria toxin has recently been developed.[75] The use of polymerase chain reaction (PCR) for rapid screening of toxigenic *C. diphtheriae* has also been described.[74]

TREATMENT

Treatment consists of rapid administration of antitoxin which can inactivate toxin that has not entered cells. The recommended dose is dependent on the location of the disease and duration of the illness.[51] Antibiotics are also needed to eradicate the organism. Penicillin is the drug of choice and erythromycin can be used as an alternative.

Airway monitoring is important and occasionally intubation/tracheostomy may be necessary to secure the airway. Patients need to be monitored for impending cardiac and neurological complications for up to 3 weeks.

VIRAL PHARYNGITIS

Viral pharyngitis is more common than bacterial and is usually a sequela of the common cold. The viruses that cause common cold (*Rhinovirus, Parainfluenza, Corona*) are the most common etiological agents. Symptoms are similar to those of GABHS pharyngitis, although usually milder, but certain features such as coryza, exanthema and cough are indicative of a viral infection. Treatment is usually symptomatic but can predispose to secondary bacterial infection.

EBV is responsible for the most clinically relevant form of viral pharyngitis, leading to the characteristic picture of IM.

Infectious mononucleosis (glandular fever)

Glandular fever is a common, acute, systemic viral infection presenting typically with the classical triad of sore throat, fever and lymphadenopathy, hence the name glandular fever. The causative agent is the EBV, one of six human herpes viruses isolated from blood, lymph nodes and saliva.

EPIDEMIOLOGY

IM is primarily a disease of young adults but can present in early childhood and older age groups. The current incidence of this condition is estimated at approximately 500 cases/100 000 persons/year with the highest incidence in the age group 15–24 years.[76] Transmission is via saliva, and it has thus been described as the kissing disease. Individuals with the antibody to the viral capsid antigen will not usually develop the disease. The incubation period is normally 5–7 weeks.

CLINICAL FEATURES

There is a prodrome of 4–5 days with malaise, fatigue and headache. The most common symptom is tender cervical adenopathy, usually accompanied by sore throat. Pharyngeal signs range from acute follicular tonsillitis indistinguishable from follicular tonsillitis to a grey membrane lining the oropharynx, petechiae on the soft palate and sometimes a PTA, which can be bilateral (**Figure 51.4**).



Figure 51.4 Infectious mononucleosis (IM) with features of exudative tonsillitis and false membrane.

Occasionally, all the lymphoid tissue of Waldeyer's ring may enlarge and become covered with a membranous slough, with significant risk of respiratory obstruction. Airway obstruction in IM may be aggravated by herpes infection. Rare, head and neck manifestations include periorbital oedema, especially of the lower lids (Hoagland sign)[77] and cranial nerve mono- and polyneuropathies of which facial nerve weakness is the most common. Other cranial nerves including the hypoglossal nerve, oculomotor nerve and vagus have been reported to be involved either in isolation or as a polyneuropathy.

SYSTEMIC MANIFESTATIONS OF EPSTEIN–BARR INFECTION

The systemic manifestations of EBV infection are summarized in **Box 51.4**.

The oncological risks following EBV-related IM include the following:

- Hodgkin disease
- genome-positive Burkitt lymphoma
- lymphoproliferative disorders in immunocompromised patients
- EBV is a cofactor for the development of nasopharyngeal carcinoma.

Recent developments in molecular and immunological diagnostic approaches have suggested that EBV has a causative role in chronic active EBV infection syndrome, EBV-related haemophagocytic lymphohistiocytosis, EBV genome-positive T-cell lymphoma, natural killer cell leukaemia/lymphoma, Hodgkin disease and gastric carcinoma.

A recent study showed that a history of IM significantly increases the risk of multiple sclerosis.[78]

DIAGNOSIS

The diagnosis is made from the clinical picture, together with the finding of mononucleosis on the peripheral blood film. The two clinical conditions with a similar picture are CMV infection and toxoplasmosis. The differential diagnosis of acute pharyngotonsillitis from IM can be aided by flexible nasendoscopy. Lymphoid tissue is present in the nasopharynx of 92% of patients with IM, unlike in patients with acute tonsillitis. The white cell count may be normal in the first week but is usually raised in the second.

Traditionally, the Hoagland criteria have been used to confirm the diagnosis of IM:[79] at least 50% lymphocytes and at least 10% atypical lymphocytes in the presence of fever, pharyngitis and adenopathy, and confirmed by a positive serological test.

It has recently been suggested that a lymphocyte/WBC ratio could be a quick screening tool to differentiate acute tonsillitis from glandular fever.[80] This study concluded that a ratio higher than 0.35 could indicate glandular fever. However, a review of this hypothesis by a large retrospective study involving 1000 individuals who underwent a monospot test revealed that this ratio had a sensitivity and specificity of only 72% and 84% respectively for the detection of this condition.[81] The authors concluded that, although it is a good indicator of IM, using this ratio alone would lead to one in seven of the patients with IM being missed. It has therefore been proposed that the L/WCC ratio should only be used in conjunction with the Hoagland criteria.

BOX 51.4 The systemic manifestations of EBV infection

Common	Rare
Pyrexia usually accompanies the severe form of the disease	Gastrointestinal: acute appendicitis, mesenteric adenitis, pseudoappendicitis
Generalized lymphadenopathy	Genitourinary: genital ulceration, interstitial nephritis
Splenomegaly occurs in 50% of patients with occasional reports of rupture following blunt soft-tissue trauma or splenic infarcts	NS: Guillain–Barré syndrome, meningoencephalitis, myelitis
Hepatomegaly and jaundice occur in 10% of patients and liver function tests are frequently abnormal	CVS: myocarditis, infective endocarditis, pericarditis
Ascites	RS: pneumonitis, bilateral empyema and mediastinitis
Rubelliform skin rash sometimes occurs and almost invariably if ampicillin is prescribed	Haem: severe autoimmune haemolytic anaemia, haemophagocytic syndrome aplastic anaemia and thrombocytopenia and common variable immune deficiency
	Chronic fatigue syndrome following IM with a premorbid history of poor physical functioning being the main predictive factor. The risk of chronic fatigue syndrome postglandular fever has been estimated to be 9–22% 6 months after glandular fever compared with 0–6% following an ordinary URT infection. EBV virus infection may have a role in initiating multiple sclerosis
	Unexpected deaths possibly related to upper airway obstruction

The heterophil antibody test has remained the basis for serological diagnosis since 1932 when Paul and Bunnell discovered that serum from IM patients caused sheep erythrocytes to agglutinate. The monospot test, which uses bovine erythrocyte-extracted antigen to detect heterophil antibodies, is the most commonly performed serological test today. Both of these are screening tests. The sensitivity of this test varies from 63% to 95% whereas the specificity varies from 84% to 100%, based on the various commercial kits available.[82] False positive monospots can occur in healthy controls as well as in a variety of conditions including mumps, systemic lupus erythematosus, Mediterranean spotted fever and diabetes sarcoidosis. These tests are usually positive in the first week of the disease, although approximately 10% never develop a positive test and this figure may be higher in children. Serological tests cannot distinguish between typical and atypical severe forms of IM.

The gold standard includes serological evidence of EBV-specific antibodies, the most useful being immunoglobulin M (IgM) antibody to EBV viral capsid antigen found during acute primary EBV infection. A recent review of new diagnostic modalities suggested that real-time PCR and measurement of EBV viral load may aid in the early diagnosis of IM in cases of inconclusive serological results.[82]

Female patients without tonsillitis and a WCC of less than 10 and an aspartate aminotransferase over 150 are at significant risk of complications and should be carefully monitored.

TREATMENT

Treatment is symptomatic for mild to moderate cases.

Role of antivirals

A lot of interest has been generated in the role of antivirals in treating this condition. Acyclovir (ACV) is the most commonly prescribed antiviral agent. A meta-analysis of five RCTs involving 339 patients with IM treated with ACV concluded that clinical data did not justify use of ACV for the treatment of mild to moderate IM.[85]

On the other hand, there is evidence to suggest that antiviral agents may benefit patients with severe manifestations of IM, especially when used as an adjunct to corticosteroids.[86] This may be increasingly justified for some of the high-risk complications and prolonged fatigue syndromes.

Ampicillin-based antibiotics should be avoided because of the certainty of producing a rubelliform rash.

Role of steroids

The role of steroids is similar to that of antivirals. A Cochrane review concluded that there was insufficient evidence to recommend steroids for routine symptom control in IM.[87]

However, steroids have been indicated in the setting of acute upper airway obstruction secondary to this condition. The role of corticosteroids in managing complications other than upper airway obstruction is less clearly defined but there may be a role in immune-mediated anaemia, thrombocytopenia and interstitial nephritis.

Patients who develop upper airway obstruction seem to be more prone to developing later recurrent tonsillitis, and acute tonsillectomy has the incidental benefit of avoiding this complication. Rarely, tracheostomy may be required if tonsillectomy fails to relieve airway obstruction.

Contact sports should be avoided for 4–6 weeks even in the absence of splenic enlargement because of the risks of splenic rupture.

There is ongoing research regarding the role of novel therapeutic agents including 5-substituted uracyle, azacytosine derivatives, and peptides inhibiting EBV-mediated membrane fusion in the management of IM.[82]

Cytomegalovirus

Cytomegalovirus (CMV; herpes virus 5) is ubiquitous, and most individuals develop antibodies to it due to infection in childhood. Infection in the immunocompetent host rarely results in clinically apparent disease. Infrequently, immunocompetent hosts exhibit a mononucleosis-like syndrome with mild pharyngitis. About two-thirds of adults with heterophil-negative mononucleosis have CMV-induced mononucleosis. Patients with this illness are usually older than those with EBV IM. Symptoms are similar to IM but lymphadenopathy is less common. The diagnosis is made by isolating CMV from the blood or showing a fourfold rise or greater in antibody titre to CMV.

The virus can lead to a significantly more severe infection in immunocompromised hosts, especially in those with HIV infection.

Herpes simplex 1

Type 1 herpes simplex infection primarily involves the oral cavity and oropharynx and usually affects young children, being less frequently found in the late teens and early twenties. It causes severe vesicular and ulcerative stomatitis of the lips, tongue, gums, buccal mucosa and, occasionally, oropharynx. The oropharyngeal involvement may be an isolated pharyngitis without ulceration or vesicles. Children are systemically unwell with pyrexia, tachycardia and cervical adenopathy.

Diagnosis is usually clinically obvious, although it may be confused with Stevens–Johnson syndrome. The condition is infective and may be transmitted to staff. Occasionally, severe ulcerative pharyngitis may be due to type 2 herpes simplex infection contracted by heterosexual orogenital contact. In the virology laboratory virus from an unruptured vesicle can be identified using fluorescent antibody or be seen as intranuclear inclusions on scrapings. Secondary herpetic infection takes place when the herpes virus resides within the posterior root ganglion. Intercurrent illness then results in the appearance of herpetic vesicles, usually in the lips or the angle of the mouth, as a typical cold sore.

The treatment is usually supportive with appropriate analgesics and fluids. Acyclovir is active against herpes virus but does not eradicate it. It is effective only if started at the onset of infection.

Herpes zoster

Herpes zoster pharyngitis probably arises from the reactivation of virus particles in the cranial nerve nuclei after a previous attack of chickenpox, thus it is analogous to shingles or cold sores. It can, though, also appear during an epidemic of chickenpox. In the pharynx, herpes zoster can materialize in the distribution of the Vth, IXth and Xth cranial nerves. It often occurs with herpes zoster oticus (Ramsey–Hunt syndrome). The pharyngeal features may be transient and can easily be overlooked. They may give rise to pain on swallowing, vesicles and shallow ulcers, which heal rapidly, may be seen on the soft and hard palate, tonsil or posterior pharyngeal wall.

Treatment with antivirals should be started within 72 hours of onset of the lesions. Acyclovir has been the drug of choice in the past, but newer drugs such as valacyclovir and famciclovir are equally effective and have more convenient dosing regimens and decreased incidence of post-herpetic neuralgia. A single dose of gabapentin reduces acute pain associated with herpes zoster infection. Herpes zoster vaccination markedly reduces the incidence and morbidity of this condition as well as the likelihood of developing post-herpetic neuralgia.

Hand, foot and mouth disease

This is usually caused by enterovirus 71 or coxsackieviruses, but untypable enteroviruses and mixed cultures may also be responsible. It is characterized by a vesicular eruption in the oral cavity and oropharynx causing dysphagia and dehydration, accompanied by vesicles on the hands and feet. It is normally accompanied by pyrexia, malaise and vomiting. The illness is short-lived and mainly affects young children but has been associated with mortality, for example in the 1998 epidemic in Taiwan. Fulminant enterovirus 71 infection may lead to severe neurological complications, acute pulmonary embolus and cardiopulmonary decompensation. Age younger than 3 years has been associated with higher mortality as have larger families and kindergarten attendance. Hospital admission, careful staging and stage-based management reduce the fatality rate in those with cardiac complications. Initial investigations include stool cultures and a white blood cell count. Currently, hand, foot and mouth disease is not susceptible to antiviral agents or vaccination, and prevention of outbreaks in high-risk areas requires high-level surveillance and public health interventions.

Herpangina

This is a self-limiting vesicular eruption that occurs in the oropharynx and a number of enteroviruses (30 and 71) and coxsackievirus group A have been implicated. Its regular spread to the oropharynx distinguishes it from herpes simplex type 1 infection.

NON-SPECIFIC CHRONIC PHARYNGITIS

Non-specific chronic pharyngitis is a common clinical diagnosis and relies on a history of long-standing throat discomfort of variable severity without any evidence of specific aetiological factors, with often little to find on clinical examination apart from prominent lymphoid tissue, especially lateral pharyngeal bands. Possible aetiological factors include:

- heavy smoking, including passive smoking
- industrial/occupational irritants
- chronic sinusitis with post-nasal drip
- acid reflux
- poor dental hygiene
- psychological stress
- *Chlamydia pneumoniae* infection
- indoor secondary heating sources (which emit NO_2 and SO_2).

Exclusion of malignancy is the most important aspect of managing these patients. This requires a careful history, in particular enquiring about localized pain to one side and earache, progressive dysphagia or weight loss, and careful physical examination of the whole upper aerodigestive tract with a nasendoscope and otoscopy. Direct examination of the oral cavity and oropharynx, paying special attention to the tongue, floor of the mouth, buccoalveolar sulcus region and manual palpation of the tongue, including its base, is required. Finally, the neck must be carefully palpated to exclude lymph node metastases. Usually this is sufficient to exclude malignancy in the absence of unexplained otalgia or progressive dysphagia but, occasionally, further investigations, mainly rigid panendoscopy under general anaesthetic to take biopsies, may be required.

If physical examination bears out evidence of post-nasal drip or significant acid reflux, both should be treated appropriately with intranasal steroids and proton pump inhibitors, although there is little documentation to support this practice.

Strong advice is given about cutting out smoking and alcohol if these are involved and an appropriate dental referral may need to be initiated. In those patients where stress is deemed to be a significant factor, neck and throat muscle relaxation therapies are deemed to be beneficial.

A large variety of non-specific remedies has been used, such as gargles, antiseptic and analgesic throat spray, with no well-defined benefits. Surgery is of no demonstrable help in this situation and operations to remove excess extratonsillar lymphoid tissue are of no proven benefit.

SPECIFIC CHRONIC PHARYNGITIS

Syphilis

This is an infection by the spirochaete *Treponema pallidum* and, apart from the congenital form, is acquired

through sexual intercourse. The disease progresses through primary, secondary and tertiary stages with the secondary stage being most likely to give rise to pharyngeal symptoms. The condition may present with almost any symptom in any organ system and hence is termed the 'the great pretender'. The lesion of primary syphilis is at the site of initial inoculation and the organism can penetrate both normal and mucosal abrasions. After a decade of unprecedented decline in the 1990s, the worldwide incidence of syphilis has been rising since 2000, mainly among HIV-positive men. This has been well-documented in the UK.[88] Patients immunocompromised by HIV have a higher likelihood of developing neurosyphilis.

In primary syphilis, the lesion is the chancre, which develops after an incubation period of 21 days. The most frequent extragenital sites for the chancre are the lips, tongue, buccal mucosa and tonsil. The lesion begins as a papule that breaks down to form a painless ulcer with indurated margins. At the same time there may be non-tender uni- or bilateral cervical lymphadenopathy. Secondary infection of the classically painless ulcer can result in pain. The ulcer usually persists for 2–6 weeks and then heals spontaneously, often despite inappropriate treatment. While the primary lesion is present the patient is highly contagious. It is therefore very important to consider the possibility of primary syphilis in atypical oral or oropharyngeal ulceration.

Secondary syphilis usually occurs several weeks (commonly 4–6 weeks) after the primary lesion and about 30% of patients at this stage will have a healing chancre. The features of the second stage are fever, headache, malaise, generalized lymphadenopathy, mucocutaneous rash and sore throat. The pharynx and soft palate display hyperaemia and inflammation and there may be lesions, which have been described as mucous patches or 'snail track' ulcers. The lesions are more commonly seen in the oral cavity than the oropharynx and are ulcerated and covered with a greyish white membrane, which when scraped off has a pink base with no bleeding. The secondary stage of the disease lasts a few weeks and, again, the lesions in the mouth and pharynx are infectious. About 30% of cases will go on to develop the tertiary stage.

Tertiary syphilis develops 5–25 years after the initial infection and is characterized by lesions that may be widespread throughout the body or restricted to one or two organ systems. In the URT they are due to gumma. This is a granulomatous necrotic lesion that begins as a nodule and then breaks down to form an ulcer. It can arise in the hard palate, nasal septum, tonsil, posterior pharyngeal wall or larynx. The gumma, whether ulcerated or not, is typically painless. There is usually no lymphadenopathy unless the lesions are secondarily infected. When treated with penicillin, the gumma will heal rapidly.

DIAGNOSIS

In the primary or secondary stage of the disease, spirochaetes can be identified by darkfield illumination microscopy in smears taken directly from the lesion. PCR may be used on oral or other lesions where contamination with commensal treponemes is likely. The spirochaetes can also be identified in biopsy specimens using silver stains or fluorescent-labelled antibody. Biopsy of a tertiary lesion provides a typical histopathological picture.

Serological tests for syphilis fall into two main groups: those used to identify non-specific antibodies to cardiolipin (i.e. Venereal Disease Research Laboratory (VDRL)/rapid plasma reagin (RPR) tests) and those to detect specific treponemal antibodies.

There are several tests to detect specific treponemal antibodies. The UK national guidelines[89] recommend using treponemal enzyme immunoassay (EIA) to detect immunoglobulin M and immunoglobulin G (IgG), if primary syphilis is suspected. IgM is detectable towards the end of the second week of infection while IgG is detectable usually in the fourth or fifth week. A positive screening test should be confirmed with a different treponemal test. The other tests include *T. pallidum* haemagglutination assay (TPHA), *T. pallidum* particle agglutination assay (TPPA), fluorescent treponemal antibody absorbed test (FTA-ABS) and *T. pallidum* recombinant antigen line immunoassay. All the specific tests are almost invariably positive in secondary and early latent syphilis.

The guidelines recommend that a quantitative VDRL/RPR test should be performed when treponemal tests indicate syphilis, as this helps stage the disease and indicates the need for treatment. The VDRL tests use an antigen extracted from beef heart in a slide flocculation test. The VDRL reaction starts to become positive during the first or second week after the development of the chancre and 99% of patients with secondary syphilis have a positive reaction.

An immunoblot (*T. pallidum* recombinant antigen line immunoassay) is recommended when the standard confirmatory test does not confirm the positive treponemal screening test result.[90]

TREATMENT

Penicillin is the treatment of choice, with 2.4 mega units i.m. in single or divided doses, being the standard for primary and secondary syphilis. In tertiary syphilis, 7.2 mega units in divided doses of 2.4 mega units at 7- to 14-day intervals are recommended. Azithromycin is recommended as a second-line alternative in primary syphilis.

Full details of treatment regimens can be obtained from the detailed guidelines on the management of early and late syphilis.[89]

Tuberculosis

The pharynx is not a common site for clinically manifest tuberculosis (TB); however, it is the site of primary infection almost always in children and results in an asymptomatic primary focus in the pharynx (usually tonsil or adenoid) with cervical lymphadenopathy.

Secondary TB affects the pharynx, but only in patients with massive positive and usually cavitating pulmonary TB. This is in contrast to laryngeal TB in which lesions do

occur with low-grade or inactive pulmonary disease. The pharyngeal lesions are secondary to coughing up heavily infected sputum and consist of multiple, painful shallow ulcers in the pharynx or oral cavity. Occasionally, the pharynx is involved in patients with widespread military TB and here the lesions may be from blood-borne as well as sputum-borne dissemination of disease. Lupus vulgaris is a low-grade cutaneous form of TB and has been described in the nasal cavities and in the pharynx. Tuberculous otitis media is probably a blood-borne dissemination of the disease but, on occasion, can result from pharyngeal disease by spread from the Eustachian tube.

The resurgence of TB has closely paralleled the epidemic caused by HIV. In both the US and Africa, the areas with the highest rates of HIV infection and high-risk groups, such as intravenous drug abusers, are those that have sustained the highest increase in TB. Poverty, overcrowding and homelessness are the socioeconomic factors common to coinfection with both. HIV-infected individuals are at risk of reactivation of previous TB and to rapid progression of acquired infection. The presentation is often atypical and an increase in extrapulmonary TB has been demonstrated.

DIAGNOSIS

The diagnosis is usually clear because of the association with pulmonary disease, both clinically and radiologically, although pharyngeal squamous cell carcinoma with pulmonary metastases is the obvious differential. Microscopic examination of stained smears for acid-fast bacilli is still one of the most useful tests for the initial diagnosis of TB. Although less sensitive and specific than culture, the sensitivity can be greatly improved by using phenol auramine stain as compared with the older Ziehl–Neelsen technique. Semi-automated and continuous monitoring systems developed specifically for the isolation of mycobacteria include enzyme-linked immunosorbent assay (ELISA) tests to detect antigens and PCR to detect genetic elements.

TREATMENT

Pharyngeal TB requires no special treatment. It will, in principle, be treated at the same time as the pulmonary disease with triple therapy, usually isoniazid, rifampicin and pyrizinamide as first-line drugs. All cases should be treated in association with an interested specialist. Drug resistance (DR) worsens outcomes and may have significant cost implications. Multiple drug resistance (MDR) is found globally. Management relies upon treatment with at least three drugs to which the isolate is susceptible. Directly observed treatment strategy should be used in adults and children where there is a significant risk of non-compliance and is vital to cut down transmission of disease in the community. TB can be controlled if appropriate policies are followed, effective clinical and public health management is ensured, and there are committed and coordinated efforts from within and outside the health sector. Rapid expansion of effective TB control services is urgently required to avert the continued high burden of morbidity and mortality from TB and its effects on the HIV pandemic.

Toxoplasmosis

Toxoplasmosis is a common disease of birds and mammals caused by the protozoan *Toxoplasma gondii*, which was first described in 1908. The parasite has three stages in its life cycle: tachyzoite, oocyst and tissue cyst. The infection can be transmitted to humans (zoonosis) by the ingestion of cysts or food contamination with animal faeces, the incorporation of tissue cysts or tachyzoites from transplanted organs or blood products from other humans with acute or latent toxoplasmosis, and transplacental transmission from a mother who is acutely infected. About 750 cases of toxoplasmosis occur annually in the UK with a mean age of 30 years. The number of cases rises evenly from adolescence with males predominating up to the age of 20 but after this age females prevail. The age distribution has rose over the 1980s. There is no longer any seasonal or geographical distribution.

In immunocompetent humans, acquired toxoplasmosis usually gives rise to no symptoms. Some patients have a sore throat with malaise, fever and cervical adenopathy and, on occasion, a patient will present with cervical lymphadenopathy only. The fever and malaise may last for several weeks and many organ systems, such as lungs, skin, liver, spleen, myocardium, pericardium, liver, brain, eyes and skeletal muscles, may be involved. The disease is usually self-limiting; rarely, symptoms persist for many years due to chronic active infection, but death is most unusual. The differential diagnosis is usually from other glandular fever-type syndromes. Eye disease presents as isolated retinochoroiditis with little systemic or immunological response. Transplacental infection occurs in approximately 45% of women who acquire toxoplasmosis during pregnancy. The effects range from subclinical infection to intrauterine death. Damage to the central nervous system and retinochoroiditis are the most common nonfatal affections. Only 10–20% of congenitally infected infants have clinically apparent disease at birth but most will develop some sequelae in later life, most commonly retinochoroiditis.

Toxoplasmosis in people with impaired immunity has been documented in association with cancer, organ transplantation, connective tissue disorders and HIV infection. Patients with such conditions are more likely to experience reactivation of latent disease than to acquire new infections. Encephalitis and space-occupying lesions in the brain may develop and, if untreated, rapidly progress to disseminated infection.

DIAGNOSIS

The differential diagnosis is usually from other glandular fever-type syndromes. A dye test for the serological diagnosis of toxoplasmosis was described in 1948. This test, in modified form, remains the gold standard although for diagnostic purposes it is restricted on grounds of cost to

reference laboratories. Several tests for specific antibody classes have been developed and used for diagnostic as well as epidemiological purposes. Lymph node biopsy, which reveals follicular hyperplasia and typical epithelioid cells, is sometimes carried out to confirm the diagnosis.

TREATMENT

Treatment is usually unnecessary but in those individuals with severe systemic upset or immunodeficiency a combination of pyrimethamine and sulphadiazine is indicated, although these are associated with significant side effects. A combination of primethamine and azithrimycin with similar efficacy but fewer side effects has been used for sight-threatening ocular toxoplasmosis. A twice weekly, 25 mg pyrimethamine/500 mg sulphadoxine combination is used as effective prophylaxis against toxoplasmosis encephalitis and *Pneumocystis carinii* pneumonia in patients with advanced HIV infection. In an effort to minimize side effects, considerable work is ongoing to develop new drugs or drug combinations for the treatment of severe symptomatic toxoplasmosis. Early studies suggest that macrolides and fluoroquinolones are possibly effective. A Cochrane review demonstrated a lack of evidence for routine treatment of the acute form of toxoplasma retinochoroiditis but weak evidence for treating chronic disease.

Leprosy

Leprosy is a rare condition in the UK, a dozen or so cases per year notified since the 1990s. No definite cases of indigenously acquired leprosy have been reported since the disease became notifiable. Globally, of the 122 countries considered endemic for leprosy, WHO states that 119 have eliminated the disease as a public health problem (defined as 1 case per 10 000).[90] It is a curable, chronic infectious disease caused by the bacillus *Mycobacterium leprae* that mainly affects the skin and peripheral nerves but also the respiratory mucosa and eyes. Leprosy affects all ages and both sexes. It is still a stigmatizing disease and yet, despite its reputation, is not a highly infectious one. Prolonged contact with an untreated person suffering from an infectious form and an inherent immunological susceptibility in the exposed person are normally required for transmission to take place.

Leprosy usually begins as an anaesthetized area in a hypopigmented skin lesion that can arise anywhere within the body. The spectrum of disease that then develops depends upon the degree of cell-mediated immune response mounted by the host. If there is a vigorous host response, tuberculoid leprosy, which is not infectious and clinically must contain fewer than five skin lesions, results. Borderline leprosy can progress to lepromatous leprosy with numerous skin lesions and this is infectious.

Isolated leprosy of the pharynx does not occur. It spreads to the naso- and occasionally oropharynx from the nasal cavities. Lepromatous leprosy can affect the pharynx and gives rise to a combination of granulomatous lesions ulcerating and healing with fibrosis.

DIAGNOSIS

The diagnosis is usually made by biopsy.

TREATMENT

Treatment is with multidrug chemotherapy, which was introduced by WHO in 1982.[91] Under this programme, patients are classified as having one of two types – paucibacillary (PB) or multibacillary (MB) – and receive either the combination of rifampicin and dapsone (known as paucibacillary multidrug therapy or PB-MDT) or the triple drug combination of rifampicin, dapsone and clofazimine (known as multibacillary multidrug therapy or MB-MDT). The rifampicin and part of the clofazimine component are taken monthly under supervision. PB-MDT is given for 6 months and MB-MDT for 1–2 years.[92] Chemoprophylaxis with dapsone and Bacille Calmette-Guérin (BCG) vaccine provide protection for household contacts.

Scleroma

Scleroma is a chronic infective condition caused by *Klebsiella rhinoscleromatosis*. The disease begins in the nose and only secondarily spreads to the pharynx where it produces granulomatous lesions and scarring.

Candidiasis

Oropharyngeal candidiasis (OPC), or thrush, is a common infection typically caused by the yeast *Candida albicans*, which is part of the flora of the oral cavity and oropharynx in 30% of normal individuals. Other *Candida* species such as *C. glabrata*, *C. krusei*, *C. tropicalis*, *C. parapsilosis* and *C. dublinensis* have also often been implicated, especially in immunosuppressed individuals.

In order for these organisms to become pathogenic and symptomatic there must be some local or systemic change in the host. The predisposing factors are listed in **Box 51.5**.

CLINICAL FEATURES

Clinically, candidiasis may be asymptomatic or present with pain and dysphagia. Examination reveals small

BOX 51.4 Predisposing factors for candidiasis

Local	Systemic disease and or immune compromise
Local disease: lichen planus, leukoplakia	Diabetes mellitus
Systemic antibiotics may change local oral flora sufficiently to allow overgrowth of *Candida*	Lymphoma
Radiotherapy to the oral cavity and oropharynx	Immunosuppressive drugs
	AIDS
	Usually *C. albicans*, but increasingly *C. dubliniensis* is becoming the opportunistic infective agent

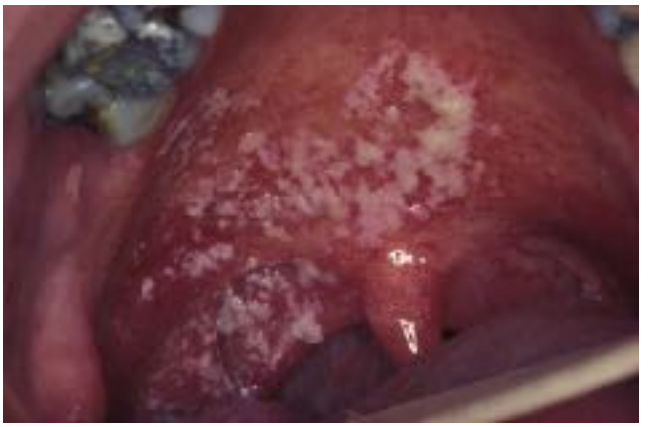


Figure 51.5 White membranous lesions of the soft palate in a man who uses steroid inhalers. This appearance is typical of pseudomembranous candidiasis.

white/creamy-white plaque-like lesions on the tongue, palate, buccal mucosa or oropharynx (pseudomembranous lesions). These can typically be 'wiped' away from the underlying mucosa to leave an erythematous ulcer or an erythematous lesion (**Figure 51.5**). The presentation could also be in the form of chronic hyperplastic candidiasis (i.e. hyperkeratotic white patch), which cannot be removed by scraping or chronic atrophic candidiasis (i.e. erythema without plaque formation).

TREATMENT

Mild disease responds well to local therapy, such as nyastatin drops or lozenges 100 000 units 6-hourly, or clotrimazole troches at a dosage of 10 mg five times daily and there is little risk of developing resistance. For moderate to severe disease, oral fluconazole at a dosage of 100–200 mg (3 mg/kg) daily for 7–14 days is recommended.[93]

Increasing resistance of *Candida* species to fluconazole is becoming a problem, especially in the HIV population. For fluconazole-refractory disease, either itraconazole solution or posaconazole suspension can be used.[93] In severe cases not responding to triazoles, a new class of agents called echinocandins or amphotericin may rarely be required.

Neither primary nor secondary prophylaxis is recommended for most patients exhibiting OPC because of the potential for resistant *Candida* species to develop over time with continued antifungal pressure.[94] Moreover, mucosal disease is associated with very low attributable morbidity and mortality, and acute therapy is highly effective.[95]

HIV and AIDS

Although great progress has been made in the global response to the AIDS epidemic in 30 years, more than 34 million people are still living with HIV infection worldwide.[96] Sub-Saharan Africa continues to be the most affected continent, followed by Eastern Europe and the Caribbean.

Pharyngeal presentation of HIV disease includes the following:

- acute seroconversion illness
- opportunistic infections, especially with *Candida*, but also TB, syphilis, CMV and *Cryptococcus*
- oral hairy leukoplakia (OHL) and Kaposi's sarcoma (KS), both AIDS-defining illnesses, and oral aphthous ulceration
- lymphoid tissue hyperplasia
- neoplastic lesions including non-Hodgkin lymphoma (NHL), KS, SCC of the head and neck, Hodgkin disease, myeloma and leiomyosarcoma in children.

PRIMARY HIV INFECTION/ACUTE SEROCONVERSION ILLNESS

Primary HIV can be asymptomatic or result in severe symptomatic illness. Common symptoms are pyrexia, pharyngitis, malaise, lethargy, maculopapular rash, mucous membrane ulceration, cervical lymphadenopathy and headache. Non-head and neck manifestations of primary HIV infection might include gastrointestinal tract transit disturbances, weight loss, anorexia, abdominal pain, myalgia, arthralgia and neurological features. The differential diagnosis is with glandular fever-type syndromes. A careful sexual history may provide a clue. It can be diagnosed by virology testing (HIV-1 RNA level >50 000 copies/mL) in the absence of HIV-specific antibodies (ELISA and confirmatory Western blot antibody testing). Progression to late-stage disease is influenced by the severity of the symptoms in primary HIV infection, the duration of illness, and the presence of neurological symptoms and oral candidiasis. Currently, the experimental evidence is insufficient to recommend whether those diagnosed with primary HIV infection should routinely receive antiretroviral therapy although it is routinely given in the US. Treatment of primary infection with highly active antiretroviral therapy (HAART) does not prevent establishment of chronic infection. Very early therapy could, potentially, decrease the viral set point, prevent viral diversification, preserve immune function, improve clinical outcome and decrease secondary transmission.

ORAL AND OROPHARYNGEAL LESIONS DUE TO OPPORTUNISTIC INFECTION

Oral candidiasis has been reported as the most prevalent oral lesion. *Candida* species other than *Candida albicans* are more prevalent in HIV disease, including *C. glabrata, C. krusei* and *C. dubliniensis*. Fluconazole is the mainstay of therapy, although resistance is developing. *Penicillium marneffei*, a newly described fungal infection, has been identified in South East Asia.

Oral lesions common in the early years of the AIDS epidemic including KS, oral aphthous ulceration, AIDS-associated oral lymphoma (Figure 51.6) and OHL all contain EBV DNA. Abundant viral replication only occurs in OHL and is due to a previously unknown mechanism involving concurrent expression of prolific, replicative



Figure 51.6 Tonsil hypertrophy presenting as lymphoma in an immunocompromised patient.



Figure 51.7 Papilloma on the uvula seen as a discrete papillary, cauliflower-like lesion.



Figure 51.8 Lymphoid tissue hyperplasia.

and transforming proteins of the gamma herpes virus EBV. KS has also been shown to contain a different herpes virus specific to this lesion, which is now known as KS-associated virus.

Oral lesions, especially pseudomembranous and/or erythematous candidiasis and OHL, which are highly suggestive of HIV infection in individuals of unknown HIV status and those known to be HIV infected, indicate that the battle lines between HIV virion production and destruction of immunologically important cells have been drawn. These observations have led to the almost universal inclusion of oral lesions in HIV staging. Recently, lower frequencies of oral disease due to HAART have been noted, except that oral warts may become more common as the viral load falls and the CD4 count rises. Human papillomaviruses (HPV) are associated with oral warts in HIV-positive individuals (**Figure 51.7**), a diagnosis that is increasing. Types include verruca vulgaris, condyloma acuminatum and focal epithelial hyperplasia. In addition to HPV, herpes simplex virus infection is increasing in this group and may run an atypical course including presentation as an exudative erythema multiforme. In children with HIV infection, additional oral lesions include angular cheilitis, ulcerative gingivitis/periodontitis and enamel hypoplasia, salivary gland disease, linear gingival erythema over-retention and delayed primary eruption of teeth. OHL is much less common in children than adults.

LYMPHOID TISSUE HYPERPLASIA IN THE PHARYNX

Lymphoid tissue hyperplasia (**Figure 51.8**) in the pharynx commonly involves all the tissues of Waldeyer's ring including adenoidal, palatine and lingual tonsils. Adenoidal hyperplasia and hypertrophy may cause Eustachian tube obstruction and otitis media with effusion. Biopsy of this tissue to exclude nasopharyngeal carcinoma and lymphoma is mandatory but radical adenotonsillectomy is to be avoided because of the bleeding risks. HIV viral RNA but no other microorganisms can be identified in this tissue. The complex immunological changes suggest that HIV may be disseminated through the upper aerodigestive tract via target cells. Subsequent presentation of viral antigens to the tonsillar and adenoidal lymphoid tissue results in simulated neoplastic proliferation of these structures, which are highly suspicious of HIV, even in asymptomatic HIV-positive patients.

PHARYNGEAL NEOPLASMS

Pharyngeal neoplasms include KS, NHL and SCC. The outlook for patients with these malignancies has improved significantly with the use of HAART and more aggressive cytotoxic therapies. The relative risk of acquiring these conditions compared with non-HIV-infected individuals is for KS greater than 10 000, B-cell NHL greater than 100, NHL eight and multiple myeloma five. Children also have a high risk of leiomyosarcoma (RR = 10 000). KS appears to result from an uncontrolled expression of latency genes of human herpes virus-8. It is exquisitely sensitive to immune deficiency and its incidence has declined rapidly with the use of HAART while

that of NHL has declined much less so. Patients with head and neck SCC who are HIV-positive in the absence of AIDS, presented at a younger age, more frequently experienced treatment-related complications and had a poorer outcome, suggesting that head and neck SCC may be an AIDS-defining diagnosis. Oral cavity and oropharyngeal tumours in HIV-positive patients respond to radiation therapy but there is a marked difference in the degree of acute reactions to treatment between patients with and without KS.

BEST CLINICAL PRACTICE

- ✓ A combination of Centor Clinical prediction score and Rapid Antigen Detecton test (RADT) should be used to diagnose GABHS pharyngitis.
- ✓ Supportive care with NSAIDs/Paracetamol with delayed antibiotics (48 hours after presentation) or no antibiotics for most patients with GABHS pharyngitis.
- ✓ SIGN guidelines[4] as a criterion for tonsillectomy.
- ✓ Serum Monospot test for patients with suspicion of Infectious mononucleosis.
- ✓ HIV infection to be considered in unusual pharyngeal presentation.

FUTURE RESEARCH

- ➤ Quality-of-Life studies to further ascertain the role of tonsillectomy in adults.
- ➤ Selective vs. Universal use of RADT in patients with pharyngitis.
- ➤ Role of novel therapeutic agents in the management of infectious mononucleosis.

KEY POINTS

- Viruses and not bacteria are the most common cause of acute sore throat, but GABHS is still the most frequent bacterial pathogen.
- Despite some forms of acute pharyngitis being associated with classical presentations, one cannot reliably distinguish between viral and bacterial aetiologies on clinical grounds alone.
- In UK practice there is insufficient evidence to support the use of antibiotics in the management of acute sore throat for symptom relief and prevention of spread, recurrent sore throat or to prevent rheumatic fever, glomerulonephritis or suppurative complications.
- The indications for tonsillectomy in the setting of recurrent/chronic tonsillitis/pharyngitis are controversial with varied opinions regarding the relative risks and benefits. The referral criteria currently used in the UK are based on the SIGN guidelines.
- There has been a steady increase in the incidence of peritonsillar abscess over the past 10 years. Drainage of abscess can be performed either by needle aspiration or an incision and drainage.
- Pharyngeal signs of EBV infection are clinically indistinguishable from follicular tonsillitis and even PTAs may occur as a complication. Screening tests include the monospot and Paul Bunnell tests, but both have false-positives rates. EBV IgM to viral capsid antigens is the gold standard for accurate diagnosis. Treatment is symptomatic in most cases but antiviral agents may be justified in the presence of systemic complications.

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CHAPTER 52

CRICOPHARYNGEAL DYSPHAGIA

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SEARCH STRATEGY

Data in this chapter are based on a Medline search using the keywords: upper oesophageal sphincter, oropharyngeal, dysphagia, cricopharyngeus/cricopharyngeal, pharyngeal pouch, hypopharyngeal diverticulum and Zenker's diverticulum.

INTRODUCTION

This chapter is about difficulty swallowing due to dysfunction of the upper oesophageal sphincter or cricopharyngeus. The applied anatomy and physiology of the upper oesophageal sphincter are first described. The chapter then details the management of cricopharyngeal dysphagia, with and without a pharyngeal pouch. Management of the conditions requires consideration of medical, endoscopic and open surgical approaches. All of these are discussed.

DEFINITION

The terms cricopharyngeus and upper oesophageal sphincter are often used interchangeably. The cricopharyngeus is the most inferior part of the constrictors of pharynx. The upper oesophageal sphincter is the term used to describe the area of the digestive tract at the junction of the pharynx and oesophagus. This term perhaps oversimplifies the functional zone of the lower pharynx and upper oesophagus. Rather than being a simple sphincter made up of a circular muscle lying at the lower border of the pharynx, the functional area is most likely an inverted cone shape with the cricopharyngeus at the lower end of the confluence of the piriform fossae and indented anteriorly by the cricoid cartilage. Opening and closing is a complex function influenced by this circular muscle as well as the position of the cricoid cartilage in relation to the lumen of the upper oesophagus.

Cricopharyngeal dysphagia is difficulty swallowing due to dysfunction of the cricopharyngeal muscle. Dysfunction is failed relaxation due to fibrosis or muscle spasm. This can occur either with or without the formation of a pharyngeal pouch.

A pharyngeal pouch is a herniation of pharyngeal mucosa through a defect (usually posterior) in the pharyngeal wall. The terms Zenker's diverticulum and hypopharyngeal diverticulum are also used.

The most frequent location of the herniation is the posterior wall of the pharynx through an area of natural weakness between the two parts of the inferior constrictor muscle. This area was described by Killian in 1908 and is referred to as Killian's dehiscence.[1]

INCIDENCE

It is difficult to quantify the incidence of pharyngeal pouch in the general population because not all patients present to a specialist. The incidence of presentation to an ear, nose and throat (ENT) specialist has been estimated as

0.47–1 cases per 100 000 per year.[2,3] Pharyngeal pouch is more common in men, with a ratio of approximately 2 : 1. Patients are usually over the age of 50 years with the most common presentation being between the sixth and ninth decades. In an ageing population, it might be expected that prevalence will increase. The condition of pharyngeal pouch affects Caucasians and is rare in Asian and Afro-Caribbean races.

DIAGNOSIS

Patients present with symptoms of variable severity, not necessarily related to the size of the pouch. Most patients present with long-standing symptoms; indeed, it is the insidious onset and slow progression of the symptoms that cause many patients to present with a well-developed pouch and sometimes severe weight loss.

Dysphagia is the most common symptom and is present in virtually all patients. Dysphagia means that the patient must have either a mechanical blockage or neuromuscular incoordination or both. Dysphagia should be distinguished from the sensation of a lump in the throat that typifies the globus syndrome. In a patient with a pharyngeal pouch the early symptoms are of solids sticking in the throat with the need to swallow several times to clear the food. Frequently, the patient attempts to chew every mouthful of food down to small fragments. As the condition progresses, it becomes impossible to enjoy a meal with friends, owing to the excessive length of time taken to eat the meal and the fact that regurgitation sometimes occurs. Eventually, dysphagia with semi-solid foods and then liquids develops. Occasionally, patients present with total dysphagia, unable to swallow their own saliva. Severe weight loss and malnutrition accompany this final state. Painful swallowing in very unusual and should raise suspicion of a malignancy.

Regurgitation of undigested food is a very common presenting symptom. Undigested food may regurgitate into the mouth during a meal, although more often it is after the meal. The regurgitation is more likely to happen when the patient is lying down, and sleep may be disturbed by it. A few patients solve this problem by evacuating the pouch before going to bed by pressing on the side of their neck. Frequently, there is stasis of food in the pouch and this leads to a 'foul taste' and friends or relatives may complain about the patient's halitosis.

Pulmonary complications may arise and result from aspiration of the pouch contents into the larynx. The patient may complain of a persistent cough or throat irritation. The aspiration may lead to chest infections, pneumonitis, lung abscess, bronchiectasis and lung collapse. Hoarseness occurs due to laryngitis caused either by aspiration or gastric reflux, which commonly coexist. The voice might also have a 'wet' quality due to stasis of fluid and soiling of the larynx.

The patient may complain of a lump in the neck that appears intermittently, and gurgling noises in the neck are sometimes noticed (cervical borborygmi). The patient is often aware that food is sticking in the upper throat and frequently will point to the region just below the cricoid cartilage.

Clinical examination may reveal a thin or malnourished patient. The endoscopic view of the larynx and pharynx may be normal although sometimes 'pooling of saliva' can be seen. Rarely, a soft compressible swelling may be found in the neck, usually on the left side in the anterior triangle. The 'rising tide' clinical sign has been described in this setting. During flexible endoscopic evaluation of swallowing using fluids (usually with water or milk with dye), small amounts of swallowed fluid can be seen to rise up from the postcricoid region after the bolus has disappeared from view.

The differential diagnosis includes all motility disorders of the pharynx and oesophagus (globus, scleroderma, achalasia) as well as structural oesophageal disease (neoplasm and strictures) and, finally, neuropathies and myopathies. Gastro-oesophageal reflux disease (GORD) is often present and virtually all motility disorders have been reported in association with GORD. The successful treatment of GORD usually improves the symptomatology of all motility disorders, and is certainly relevant in the treatment of patients with a pharyngeal pouch.

The investigation needed to confirm the diagnosis is either a barium swallow or a contrast video swallow (**Figure 52.1**). The latter provides considerably more



Figure 52.1 Barium swallow showing a pharyngeal pouch.

information about the function of the pharyngeal muscles as well as the presence or absence of gastric reflux.[3] It is essential that the contrast study includes the lower oesophagus and stomach because a lower oesophageal carcinoma can coexist with a pharyngeal pouch.

KEY POINTS

- Incidence is one per 100 000 per annum.
- The condition occurs almost exclusively in Caucasians.
- Dysphagia, regurgitation, hoarseness and pulmonary complications are the main symptoms.
- Differential diagnosis: globus, scleroderma, achalasia, neoplasm, stricture, neuropathies.
- There is a common association with gastro-oesophageal reflux.
- Contrast study is required and a dynamic video swallow is best.

AETIOLOGY

Over the years, many theories concerning the aetiology of pharyngeal pouch have been advanced but no one theory is accepted. There is agreement about the site at which a pouch forms: the posterior wall of the most caudal part of the hypopharynx between the oblique fibres of the thyropharyngeus muscle and the horizontal fibres of the cricopharyngeus muscle. The area between these two muscles is triangular and there are very few muscle fibres in this part of the pharyngeal wall (**Figure 52.2**). This triangular area is called Killian's dehiscence after the man who first described it in 1908. With the advent of more sophisticated and accurate manometric methods for measuring pharyngo-oesophageal sphincter function, one might have hoped for a common consensus on aetiology. On the contrary: even the most popular theories continue to be questioned.

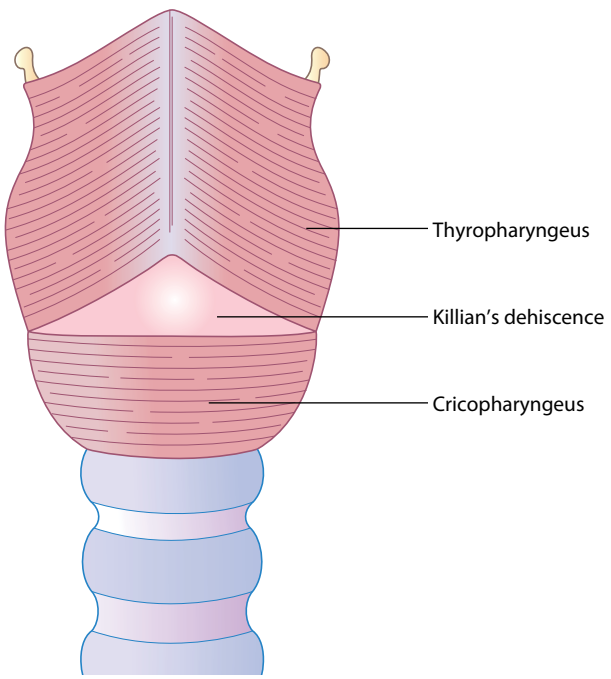


Figure 52.2 Killian's dehiscence.

The three main theories currently proposed to explain the formation of a pouch are:

- that it occurs mainly because of an anatomical weakness in the pharyngeal wall
- spasm of the cricopharyngeus muscle
- various theories that can be labelled as incoordination of the pharyngeal muscles.

Killian's dehiscence; an area of anatomical weakness

Van Overbeek has proposed that anatomical dehiscence is the major cause of pharyngeal pouches.[4] He reasons that, in humans, the larynx is an important structure generally larger than in other animals. In most mammals, the larynx is located just below the skull base, but in humans it has descended to the cervical region. Consequently, the pharyngeal constrictor muscle fibres in humans (with the exception of cricopharyngeus) have assumed an oblique course because the raphe in the dorsal midline is attached to the skull base. However, the cricopharyngeus muscle has horizontal muscle fibres which arise from either side of the cricoid cartilage and not the skull base. Therefore, the 'descent of the human larynx' gives rise to Killian's dehiscence. (It should be noted that pharyngeal pouches do occur in other animals.)

Van Overbeek further proposes that individual variations in anatomy are the cause of a predisposition for hypopharyngeal diverticulum; for instance, some individuals with longer necks might have a larger triangle of Killian.[4] Perrott studied the pharyngeal muscles in cadavers and found several different patterns of fibre arrangement in the gap between thyropharyngeus and cricopharyngeus, and in each individual muscle.[5] He suggested that in some individuals the arrangement of the cricopharyngeus muscle leaves denuded portions, and therefore these individuals were more liable to pouch formation.

To account for the fact that pharyngeal pouches develop after 40 years of age, Van Overbeek suggests that, with advancing age, there is loss of tissue elasticity and a decrease in muscle tone. The large size of the laryngeal skeleton may explain why pharyngeal pouches are more common in men.

That an anatomical predisposition may play a prominent role in pouch formation is also supported by the familial incidence seen with these relatively rare diverticula. In Van Overbeek's series of 545 patients with pharyngeal pouch, nine patients were from four families and three of the nine were brothers from the same family. All 545 patients were Caucasian.[4]

Van Overbeek's manometric studies showed that, in normal people as well as patients with a pouch, there is a high intraluminal pressure in the caudal hypopharynx that peaks during pharyngeal contraction. He proposes that, in individuals with an anatomical predisposition (large or weak Killian's dehiscence), a mucosal prolapse takes place

and over the years the intraluminal pressure produces a pulsion diverticulum that gradually increases in size. He found no significant differences in the maximal contraction pressure in the hypopharynx between patients with a pouch and normal individuals, and thus concluded that the problem is due to an anatomical weakness (Killian's dehiscence).

Failed relaxation of the cricopharyngeus muscle

The cricopharyngeus muscle normally is in a state of tonic contraction, but it relaxes at the end of the second stage of swallowing when the sequential contraction of the pharyngeal constrictors occurs from above downwards. Various functional abnormalities have been suggested to account for pouch formation.

Negus,[6] Sutherland[7] and Belsey[8] favoured the theory that persistent tonic spasm of the cricopharyngeus muscle prevents the downward passage of the bolus and creates a high pressure above the cricopharyngeus that eventually causes herniation through Killian's dehiscence.

Dohlman and Mattson[9] stressed the importance of an intact prevertebral fascial layer that normally supports the posterior wall of the larynx. They reasoned that, with increasing age, the fascia may weaken, allowing the larynx to fall forwards and thus decrease the circumference of the cricopharyngeus muscle, which is normally stretched open during the act of swallowing. A functional obstruction would be produced and, with elevation of intrapharyngeal pressure on swallowing, herniation of mucosa through the weakened posterior triangle, now unsupported by prevertebral fascia, would take place.

Cook[10] has more recently proposed that, rather than spasm of the muscle, the failure to relax is due to fibrosis. Laryngopharyngeal reflux is suggested as one possible cause of this.

Some patients with primary muscle disorders such as inclusion body myositis can have failed cricopharygeal relaxation, initially due to muscle failure and laterally due to fibrosis in the muscle. A pharyngeal pouch may then develop above the disease cricopharyngeal muscle.

Incoordination theories

Ardran, Kemp and Lund[11] used contrast cineradiography to examine 16 patients with pouches of differing sizes and 17 normal subjects. After the initial swallow, the main bolus descended into the pharynx to be moved on by the pharyngeal stripping wave. In patients with pouches they found this to be defective in two ways: the oropharyngeal contraction was weak, and the pharyngeal peristaltic wave was also weak together with early closure of the cricopharyngeus muscle. As a result of their studies they proposed a mechanism of pouch formation. The cricopharyngeus contracts prematurely and, as the stripping wave descends to the prematurely closed sphincter, it pushes the posterior pharyngeal wall down and forwards to meet the back of the cricopharyngeal sphincter. A dimple is produced which, in time, goes on to form a pouch.

Ellis et al[12] came to similar conclusions by measuring the intraluminal pressures in patients with pouches and comparing them with those of normal subjects. The resting tone of the cricopharyngeus was found to be normal in all subjects, but in patients with a pouch the cricopharyngeus was found to contract a fraction of a second before pharyngeal contraction was complete so that the pharyngeal–oesophageal peristaltic sequence was not coordinated.

Lichter et al[13] also supported the incoordination theory. His manometric study showed that, although the sphincter relaxes for the normal amount of time, relaxation begins prematurely and therefore ends prematurely. The effect is the same: high pharyngeal pressures conducive to herniation of mucosa through a muscle-deficient area. Lichter also noted the phenomenon of repetitive pharyngeal swallow, thought to be a result of obstruction to the swallow wave at the upper oesophageal sphincter, since it disappeared following sphincterotomy.

Hunt[14] proposed that gastro-oesophageal reflux may lead to cricopharyngeal spasm or incoordination. The reported incidence of gastric reflux in patients with pharyngeal pouches ranges from 5% to 100%, with the incidence in the normal population being put at 23%.[15] The wide variation in these series could easily be explained by how persistently the symptom of reflux was sought and interpreted. Resouly et al[16] studied 29 patients who underwent surgical correction of pharyngeal pouches. Of these, 19 were found to have reflux and 20 dysmotility. Their findings suggest that many patients with a pouch may have a generalized oesophageal muscle dysfunction and not purely a localized incoordination of the cricopharyngeal muscle.

Rarely, a pharyngeal pouch may form by traction as opposed to pulsion. The adhesions associated with surgery to fuse the anterior cervical spine following trauma can 'pull' a pouch out of the pharynx.[17, 18]

Similarly, pouches (or more correctly pseudopouches) may appear in the presence of large anterior cervical spinal osteophytes over which the pharynx moves, causing an apparent pouch. When examined, such sacs do not herniate through muscle and disappear on removal of the osteophytes.[19, 20]

In summary, opinion concerning the pathophysiology of pharyngeal pouches is divergent. Part of the disagreement may be ascribed to differences in measuring techniques.

CONCLUSION

It is unlikely that there is a single pathophysiological process causing pharyngeal pouch formation. However, in general terms, incoordination between the descending peristaltic wave and failed cricopharyngeal muscle relaxation creating an abnormally high intraluminal pressure subsequently leads to mucosal herniation through the weak area of Killian's dehiscence.

As most agree that failed cricopharyngeal muscle relaxation is involved in the aetiology of pouch formation, a cricopharyngeal myotomy is recommended. With endoscopic techniques this is always carried out because the

cricopharyngeus muscle lies within the bar that divides the pouch from the oesophagus. For operations involving pouch excision, a separate myotomy is required.

KEY POINTS

- Killian's dehiscence is an area of potential weakness between the thyropharyngeus and cricopharyngeus muscle.
- Dysfunction of the cricopharyngeus muscle (or failed cricopharyngeal relaxation) is involved in pouch formation.
- Gastro-oesophageal reflux may contribute.

PATHOLOGY

The histology of an excised pouch shows an epithelial lining of stratified squamous epithelium and submucosa, often surrounded by fibrous tissue. Nearer the neck of the pouch, scanty muscle fibres are found in the wall.

There is evidence of myositis either isolated or as part of a systemic disease (e.g. inclusion body myositis) in some patients.

Carcinoma occurring within a pouch

Carcinoma within a pouch was first described by Vinson in 1927; it is a rare problem with only 47 cases reported in the English literature.[21] Huang et al,[22] in a series of 1249 patients, found four patients with a malignancy arising within the pouch, an incidence of 0.32%. In Van Overbeek's series of 545 patients only two (0.4%) had a carcinoma.[4] However, Bradley et al, in a retrospective review, found that out of 50 pharyngeal pouch excisions, two had carcinoma *in situ* and two had invasive carcinoma.[23]

Carcinoma usually seems to occur in individuals who have had a very long-standing pouch, with the average duration of symptoms in Huang et al's four patients being greater than 7 years. The main predisposing factor is thought to be chronic irritation and inflammation of the pouch lining caused by food retention.

It has been stated that barium studies show a constant filling defect as opposed to the filling defect due to food debris, which may move or alter between films. Symptoms indicating a carcinoma are rapidly increasing dysphagia, pain and/or blood in the regurgitated food. Nodes or a mass in the neck may be found. Patients with a pouch do not normally complain of pain or bleeding and the dysphagia usually progresses slowly. An urgent endoscopy is required in any individual with these suspicious symptoms, whether or not they have had a pouch treated before.

The endoscopic management of a pharyngeal pouch should include a close inspection of the pouch lining with a biopsy of any areas that look suspicious. Close inspection with a Hopkins rod is recommended and it may be necessary to wash the food debris out of the pouch with saline in order to obtain a reliable view of the pouch mucosa.

Carcinoma arising after pouch surgery

At a meeting in 1951, Lodge was the first to question the possibility of a carcinoma arising in the pouch wall following Dohlman's procedure. To this Professor Dohlman replied: 'I suppose the operation, as soon as it relieves the retention in the sac, contributes to a more normal appearance and function in the mucous membrane, and consequently diminishes the danger of cancer.'[24] However, carcinoma certainly can arise in the pouch wall following endoscopic division of the cricopharyngeal bar and after pouch excision (at the junction of pouch and oesophagus). In all reported cases there has been a delay of several years before the carcinoma occurred and often the patient has had persistent symptoms and multiple procedures.[25]

KEY POINTS

- Carcinoma developing in a pouch is rare (0.4%).
- At operation, it is essential to examine the lining of the pouch.
- Carcinoma can rarely occur after pouch surgery.
- Rapid-onset dysphagia, pain or blood-stained secretions should raise suspicion for malignancy.

MANAGEMENT OPTIONS

The management options for patients with a pharyngeal pouch can be divided into three groups: conservative, endoscopic surgery and external approach surgery. Particularly for patients with a pharyngeal pouch, it is essential to consider the overall health of the patient carefully as well as assessing how much effect the pouch is having on the individual's quality of life. A small pouch may cause minimal symptoms, in which case the patient may or may not present to their general practitioner.

Careful consideration of the patient's general health and their specific symptoms needs to be undertaken. When weighing up the decision as to whether to operate or not it is important to consider that the symptoms associated with a pharyngeal pouch usually increase with time whereas the elderly patient's overall health tends to decline. In Zenker's original review, 13 of 22 patients died because of the complications associated with living with a pouch.

The majority of patients undergoing pharyngeal pouch surgery are elderly and frail. The mortality rates observed in some of the published series are a reflection of this frailty. Therefore, the ideal surgical method is one that requires a short anaesthetic and the minimum surgical intervention. The modern endoscopic technique employing stapling fulfils these criteria.

Pouch operations include:

- endoscopic:
  - fibre-optic (flexible) endoscopy and division of cricopharyngeus (diathermy)
  - rigid endoscopy and diathermy division of the cricopharyngeal bar

  - rigid endoscopy and laser division of the cricopharyngeal bar
  - rigid endoscopy and division of the cricopharyngeal bar by a cutting and stapling device
- open cricopharyngeal myotomy
- open excision of the pouch with/without cricopharyngeal myotomy
- inversion of the pouch and cricopharyngeal myotomy.

HISTORICAL COMMENT

Ludlow of Bristol was the first, in 1769, to identify a patient with a pharyngeal pouch.[26] In 1878 the clinical features were reported by Zenker,[27] who described a hypopharyngeal diverticulum as a pulsion diverticulum above the oesophageal inlet.[27]

In 1886, Wheeler[28] reported the first successful excision of a pharyngeal pouch, performed the year before, in 1885. It was an incidental finding while operating on an army officer who had acquired a lateral pharyngocoele from overexercising his voice on the parade ground. This patient recovered completely and his swallowing returned to normal. However, many of the early attempts at excision were unsuccessful, being complicated by sepsis and, in particular, mediastinitis. Other methods were therefore advocated including inversion of the sac and diverticulopexy, in which the fundus of the sac is secured high up in the neck. All types of pharyngeal pouch surgery had high mortality rates until the advent of antibiotics; Stetten,[29] in 1910, reported a 17% mortality rate for pouch excision.[29] Even when antibiotics were available, external excision of a pharyngeal pouch continued to carry significant morbidity and mortality. A high fistula rate meant that in most series of pouch excision the average length of hospital stay was in excess of 12 days.[30] The use of an autosuture stapling device to excise the pouch, while at the same time sealing the wound edges, improved the results for pouch excision considerably.[31, 32]

Inversion of a pharyngeal pouch was first described by Girard in 1895.[33] This technique was developed to avoid the risk of opening the sac, associated as it was with the serious problems of sepsis and fistula formation. Stell repopularized this technique, which, when compared with pouch excision, has a lower complication rate and the patient has a shorter hospital stay.[34, 35]

The principle of endoscopic treatment, in which the cricopharyngeal bar is divided to create a common cavity so that the bolus must pass into the oesophagus, was first described by Mosher in 1917.[36] The common wall between the oesophageal lumen and the pouch was divided with punch forceps. Mosher noted that 'a small cresenteric rim was to be left at the bottom of the pouch to wall off the mediastinum' and that 'should symptoms return, it should be an easy matter to cut the common wall still more'. Six patients were treated successfully until Mosher discontinued the procedure when his seventh patient developed mediastinitis and died.

The concept of creating a common cavity endoscopically was restored to favour by Dohlman and Mattson.[9] Dohlman introduced diathermy for coagulating the common wall prior to cutting it. He pointed out that division of the bar or septum, within which lay the cricopharyngeal muscle fibres, simultaneously produced a cricopharyngeal myotomy. Dohlman carried out 100 diathermy divisions in 39 patients, with no complications and a recurrence rate of 7%. It should be noted that many of his operations involved at least two stages. Other individuals could not achieve his results and this endoscopic procedure using diathermy did not gain universal acceptance because many patients complained of persistent dysphagia after the operation and required revision procedures.[37]

Most retrospective reviews showed that the results for pouch excision and endoscopic cricopharyngeal bar division were similar, with both groups having significant morbidity and a high recurrence rate. However, one individual surgeon's figures did stand out; Van Overbeek's series of patients, all treated endoscopically, is still the largest. The first 328 patients were treated by Dohlman's procedure using diathermy and, subsequently, 216 patients were treated with a microscope coupled with a carbon dioxide laser to divide the bar. Van Overbeek's success rate surpassed all other published series at the time and had the lowest complication rate.

In the early 1990s, developments in laparoscopic surgery produced stapling devices that allowed division and sealing of tissue simultaneously.[38] Collard was the first surgeon to use a cutting stapler to divide the common wall between the pouch and the oesophagus while at the same time sealing the opposing walls of the pouch and the oesophagus.[39] Independently, in 1993, Martin-Hirsch and Newbegin published a case report describing a similar endoscopic technique using a stapling gun.[40] Several centres then developed and refined the technique, so that by the time of a 1996 survey 28% of ENT surgeons in the UK were using a stapling device if they used an endoscopic technique. In the following year, the National Confidential Enquiry into Perioperative Deaths (NCEPOD) in the UK recommended that endoscopic stapling should become the treatment of choice.[41] This enquiry also recommended that there should be one or, at the most, two surgeons within each ENT department who are trained and competent in the surgery of pharyngeal pouches. Following this recommendation there has been a shift away from pouch excision.

Cricopharyngeal myotomy via an external incision still has a role, in particular for patients with a very small but symptomatic pouch.

The indications for excision include the presence of a carcinoma in a pouch and a large perforation if it happens during attempted endoscopic stapling.

Table 52.1 describe the authors' approach to surgery for symptomatic pharyngeal pouches.

CONSERVATIVE MANAGEMENT

There is no evidence that any drug therapies work for cricopharyngeal dysphagia.

Botulinum toxin has been injected both percutaneously and endoscopically. Success is variable, and there

TABLE 52.1 The authors' approach to surgery for symptomatic pharyngeal pouches

Size of pouch	First-line treatment	Recurrence/failure/poor access
Small (less than 2 cm)	Balloon dilation of cricopharyngeus *or* Endoscopic division of the cricopharyngeal bar (LASER)	Endoscopic division of the cricopharyngeal bar (LASER) *or* Open cricopharyngeal myotomy
Moderate (2–4 cm)	Endoscopic stapling	Revision stapling *or* Open excision of the pouch and cricopharyngeal myotomy
Large (greater than 4 cm)	Endoscopic stapling *or* Open excision of the pouch and cricopharyngeal myotomy;	Revision stapling *or* Open excision of the pouch and cricopharyngeal myotomy;

are reports of protracted dysphagia due to dysmotility and also of paralysis (temporary) of the larynx.

OPERATIVE DETAILS OF THE METHODS AVAILABLE FOR PHARYNGEAL POUCH SURGERY

Endoscopic stapling technique

In order to obtain informed consent, a thorough discussion with the patient is required. The following points need to be discussed.

- The possibility of not being able to complete the operation safely exists. During the pre-operative assessment it should be possible to identify the patients in whom access may be difficult. The biggest problem encountered is prominent teeth and this may be combined with retrognathia. These patients should be told that it may not be possible to staple the pouch safely, and an alternative strategy should be discussed prior to surgery.
- Patients should be told that there is a risk of damaging their teeth.
- There is a risk of perforating the pouch during attempted endoscopic stapling. Should this happen, a small tear can be sutured endoscopically or managed conservatively but, if it is a large perforation, it would be prudent to open the neck, find the perforation and excise the pouch. It follows that any surgeon undertaking pouch surgery should be competent in head and neck surgery and the patient should be warned pre-operatively that external surgery is a possibility.
- When quoting figures as part of the informed consent, the optimum arrangement is to quote personal figures if this is possible; if it is not, a conservative interpretation of the outcomes given at the end of this chapter could be used.

Technique: endoscopic

This is a modified version of the technique described by Bates.[42]

The procedure is performed under general anaesthesia with endotracheal intubation (preferably with a microlaryngscopy tube to afford more space). If present, the upper teeth are protected with a gum guard or wet swab; the latter allows a little more room for the scope.



Figure 52.3 A Weerda diverticuloscope.

A rigid Negus pharyngoscope is introduced to identify the cricopharyngeus. At this point any stenosis due to scarring can be dilated with a balloon. A rigid oesophagoscope is then introduced to identify clearly and inspect the upper oesophagus. Then a Weerda distending diverticuloscope (Karl Storz Endoscopy (UK) Ltd, Slough, UK) is introduced (**Figure 52.3**) with confident knowledge of the anatomy of the pouch and any coexisting lesions. (As an alternative, an Oxford Roberts pharyngoscope may be used in a patient with a limited access.) The upper blade of the diverticuloscope is carefully inserted into the oesophagus, with the lower blade simultaneously entering the neck of the pouch. The blades of the diverticuloscope can be adjusted in two directions, and the necessary adjustments are made until a good view of the cricopharyngeal bar is obtained (**Figure 52.4**). The scope is then suspended with a laryngoscope holder. Food debris is gently cleared from the pouch using a sucker and adherent debris can be washed out with saline from a 50 mL syringe.

A Hopkins telescope is used to inspect the lining of the pouch. Any abnormality of the mucosa should be biopsied, although it is rare to have to do this. At times, the lining of the pouch will be inflamed and under these conditions it is important to take extra care, with gentle suction in order



Figure 52.4 The cricopharyngeal bar*.



Figure 52.5 A divided and stapled cricopharyngeal bar.

to prevent any bleeding. The presence of blood impedes the view of the operator.

Once a satisfactory view of the cricopharyngeal bar is obtained, an endoscopic linear cutting stapling gun or similar device is removed from the packet and checked. At this stage, the end of the gun carrying the staples is rotated so that the staples are in the upper jaw, which will be inserted into the oesophagus, with the anvil (lower jaw) going into the pouch. Spare staples should be available. The gun is carefully introduced through the Weerda diverticuloscope until the cricopharyngeal bar lies between the two jaws of the gun. The jaws are closed and locked in place. Visual inspection and gentle traction ensure that there is adequate tissue between the jaws. The gun is fired and this divides the septum and simultaneously seals each of the cut edges with a triple staggered row of staples (**Figure 52.5**). The release button is then pressed to free the jaws and the gun is gently removed, making sure that the jaws are not snagged on any tissue.

Tips and tricks for pouch stapling

MAXIMIZING THE VIEW

It is most important to try to obtain the best view possible prior to placing the jaws of the stapling gun over the cricopharyngeal bar. In edentulous patients with a wide mouth, the Weerda scope affords an excellent stereoscopic view and should be used whenever possible. If a good view can be obtained, the operation is usually straightforward. However, difficult access, and a little trauma and possibly bleeding can convert the situation into one where the surgeon will really struggle. A few simple precautions can ensure the best view possible.

- Use a small endotracheal tube or microlaryngoscopy tube, with minimal cuff inflation.
- Ensure that the patient is totally paralyzed.
- Use the Weerda scope if it will fit.
- Use a wet swab to protect the teeth if the access is limited.
- Be prepared to alter the degree of neck extension.
- Use a sucker with great care to limit mucosal damage and bleeding.
- Wash out any debris with 50 mL of saline.
- Use the Hopkins rod.
- Be extremely gentle with the tissues.

DIFFICULT ACCESS

In about 20% of patients access will be difficult owing to a combination of prominent teeth and retrognathia. The anaesthetist will usually confirm that intubation has been difficult (grade 3 or 4). A stiff or arthritic neck needs care but does not often prevent access.

If it is not possible to obtain a view with the Weerda scope, the Oxford Roberts pharyngoscope, the Negus pharyngoscope or the Steiner pattern bivalved laryngopharyngoscope can be used. Each has advantages and disadvantages, but these unfortunately will probably offer poorer visualization than the Weeda diverticuloscope.

NO APPARENT OESOPHAGEAL OPENING

The oesophageal opening is obviously present, but at times it can be hard to find. The reason is that, as a pouch enlarges, the plane of the neck of the pouch rather that the oesophagus comes to lie directly in line with the hypopharynx so that food (and the endoscope) passes into the pouch preferentially. Finding the opening of the pouch is therefore relatively easy, and once found the oesophageal lumen must lie anterior and behind the larynx. The oesophageal opening may appear as a tiny slit or dimple, but when recognized it can be gently dilated using a balloon until the upper beak of the endoscope can be inserted. It can often be found more easily with the use of a Roberts–Jesberg oesophagoscope as this has a slightly upturned superior lip. Also, a fine bougie can be gently passed with its tip bent slightly upwards to cannulate the oesophagus.

DIVISION OF THE SEPTUM

Ideally, virtually all the cricopharyngeal bar should be divided with only a small rim of tissue remaining. Achieving this result is not always easy. The Hopkins telescope can be used to estimate the depth of the

pouch and, with the Weerda scope, it can also be used to check the placement of the jaws of the stapler. It has been suggested to use two endoscopically placed 'stay sutures' to pull the bar up into the jaws of the pouch.[43] It is not possible for the stapling device to cut completely to the end of the cricopharyngeal bar, because the anvil protrudes further than the cutting surface. It is possible to saw the end of the anvil and/or create a deeper pouch by pushing inwards with the jaws, but both these manoeuvres possibly increase the risk of perforation. Leaving an excessively long bar probably predisposes the patient to recurrence but, if in doubt, it is safer to underdivide rather than overdivide the septum and risk a perforation. It is interesting to note that Dohlman was cautious and most of his patients underwent two separate operations. Some surgeons advocate use of the CO_2 laser to divide this last bit of the bar. This does run a higher risk of perforation, as one would expect.

GUN JAMMING

Failure of the stapling gun is rare but the jaws of the gun can jam if too much tissue is placed between them. This occurs when there is a large pouch and the operator is overambitious in trying to do too much with one stapling. In most published series at least two sets of staples are used in the majority of patients. If the gun does jam, gentle manipulation of the release lever will eventually free the mechanism. Do not pull/withdraw a jammed gun; only withdraw when the jaws have been released.

PREVENTING A TEAR/PERFORATION AND SUBSEQUENT MANAGEMENT

It is relatively easy to create a perforation, especially in the pouch itself! The pouch mucosa may be chronically inflamed and, by definition, there is no protective muscle layer. It is possible to push the beak of the scope through the fundus of the pouch or inadvertently tear the pharynx when the stapling device is removed. Occasionally, the stapling device may fail and, if this happens, a diagonal defect in the tissues of the bar appears. Under these circumstances it is possible that the staples have simply not sealed the edges of the tissues properly.

If a small perforation is identified, it may be possible to suture via the endoscope;[44] several endoscopic needle holders are available, such as the 'Berci' needle holder (Stortz). A nasogastric tube should then be inserted and the patient observed carefully for signs of mediastinitis over the next few days.

If a large perforation is present, it is prudent to open the neck, excise the pouch and repair the oesophagus if necessary. Insertion of a large nasogastric tube and a large wound drain is recommended.

If the procedure is traumatic, it is wise to insert a nasogastric tube. In most large series one or more patients are noted to have had a small perforation in the post-operative period because of the presence of surgical emphysema. Conservative management with parenteral feeding and antibiotics is usually successful.

THE LARGE POUCH

Generally, the larger the pouch, the easier it is to deal with using the stapling technique. With a large pouch there is always a long cricopharyngeal bar and as many sets of staples as it takes to divide the bar are used. A huge pouch that extends into the mediastinum is not a contraindication to the stapling procedure, although there is some evidence that large pouches are more likely to recur.[45, 46] Very large pouches may be better treated by open excision; there is no clear evidence favouring either technique, so this has to be carefully discussed with the patient.

THE SMALL POUCH

A patient with a small pouch presents the biggest challenge whether an endoscopic or external approach is used. Unfortunately, small pouches can be symptomatic and some patients who simply have a prominent cricopharyngeal bar and not even a true pouch sometimes also have significant dysphagia. If there is a sufficient cricopharyngeal bar to fill half the jaws of the gun, then stapling is likely to work, but a bar smaller than this makes stapling impossible. Advocates of CO_2 laser division claim that the laser is able to deal with smaller pouches than the stapling device. While this may be true, the margin for error is small. The other options are to let the patient tolerate their symptoms until a more substantial pouch develops, perform an external cricopharyngeal myotomy or simply perform a balloon dilatation of the cricopharyngeus.

PREVIOUS POUCH SURGERY

If the patient has had a previous pouch excision or inversion and then develops a recurrence, it might be assumed that endoscopic stapling would be difficult; this is not the case. Occasionally, scarring twists the pouch to one side but usually the appearances are the same as a pouch presenting for the first time. Following diathermy, laser or stapling division recurrent surgery is usually straightforward.

RECURRENCE

A significant recurrence rate occurs with all endoscopic procedures but, given the minimal discomfort of the first procedure, most patients are usually willing to undergo a repeat stapling, which is not difficult. The same cannot be said for revision external surgery which is difficult and associated with an increased complication rate.

It is arguable whether contrast studies are helpful if a patient has recurrent symptoms after an endoscopic procedure.[47–49] The contrast coats the pouch wall before passing into the oesophagus and the radiologist invariably reports that there is a recurrent pouch. However, multiple pathologies (such as oesophageal dysmotility) can exist, so the authors would recommend a repeat contrast study if surgery is being entertained.

Post-operative care

The patient should not eat or drink for the first few hours after the operation, giving the surgeon time to check the

patient's general well-being and, in particular, confirm the absence of neck or back pain, tachycardia and surgical emphysema. A nasogastric tube is not routinely required but should be inserted if there is significant mucosal damage. Antibiotics are not routinely required and should be reserved for complications. A sensible approach is to allow the patient to drink water initially and then proceed to a soft diet on the evening of surgery if all is well. Many patients can be discharged on the day of surgery.

It is the authors' practice to recommend a soft diet for a week and then progress to a normal diet. The rationale behind this is that the discomfort that can be associated with swallowing can be minimized with a soft diet. Having been denied a good swallow for months, most patients need little encouragement to move on to a normal diet. It seems logical to treat patients with symptomatic gastric reflux with proton pump inhibitors although there is currently no evidence to suggest that this practice reduces the risk of recurrence.

DIVISION OF THE CRICOPHARYNGEAL BAR USING A CO_2 LASER

The Weerda scope is used and the cricopharyngeal bar identified in exactly the same way as for pouch stapling. Swabs soaked in saline are placed around the mouth. An operating microscope with a 400 mm objective lens and attached laser is used. The cricopharyngeal bar is then divided using a CO_2 laser. A nasogastric tube is not essential and the patient is monitored post-operatively in the same manner as for stapling.

Division of the septum using a laser requires experience because it is often difficult to judge the exact amount of septum that can be safely divided without causing a perforation. Inadequate division, on the other hand, results in recurrence of symptoms, requiring revision surgery.

A potential advantage of the laser over the stapling technique is when access is difficult, necessitating the use of a small scope; a better view is obtained because there is no stapling device in the way. The laser can also be used on a cricopharyngeal bar that is simply too small for the jaws of the stapler; however, division of such a small bar does carry with it an increased risk of perforation.

There has been a report of laser endoscopic myotomy with suture closure of the mucosal defect.[41, 50, 51] Although no high-level evidence exists that this represents a better procedure, with modern instrumentation is appears reasonable to close the mucosal defect routinely.

FIBRE-OPTIC ENDOSCOPIC CRICOPHARYNGEAL BAR DIVISION

Fibre-optic endoscopic cricopharyngeal bar division is a technique that uses monopolar cautery to divide the bar. Although approved by the National Institute for Health and Care Excellence (NICE), there are no comparative trials between this technique and established procedures. There are no long-term results available for its efficacy.

The cricopharyngeal myotomy: sole procedure

The approach through the neck tissues is the same as for pouch excision. The assistant passes an oesophagoscope down to just beyond the level of the cricopharyngeus and then withdraws it slightly and rotates the scope so that the light shines through and highlights the muscle fibres, which are divided with a knife. These fibres often do not look substantial and it is important to divide along a length of at least 4 cm. An alternative method is to use the microscope to identify the fibres although it is still helpful to have a solid object, such as a large nasogastric tube, within the lumen. The authors use a pledget to push the muscle fibres apart such that there is at least a 1 cm gap between them. A nasogastric tube is placed by the surgeon in case of any post-operative problems.

Pouch excision

The operation is performed under general anaesthesia with the patient intubated. A pharyngoscope is passed and the openings to the pouch and the oesophagus are identified. A nasogastric tube is passed down the oesophagus. A large bougie can also be passed down the oesophagus alongside the nasogastric tube and can be helpful in the dissection (see below). Food debris is very gently removed from the pouch. The lining of the pouch is carefully inspected with a Hopkins telescope in order to exclude a carcinoma. The pouch is then packed with ribbon gauze soaked in either proflavin or bismuth iodoform paraffin paste, and the proximal end of the strip of gauze brought out through the mouth. The patient is then finally positioned with a sandbag under the shoulders and the head extended and rotated away from the side of the incision.

Either a horizontal incision (usually left sided, level with the upper border of the cricoid), or a vertical incision (along the anterior border of the left sternomastoid muscle) is made. The authors favour a vertical incision for very large pouches. The deep cervical fascia is incised along the anterior border of the sternomastoid muscle, which is retracted laterally. The anterior belly of the omohyoid muscle is divided. The sternohyoid and sternothyroid are retracted towards the midline. The middle thyroid veins are then ligated and divided and this allows the ipsilateral lobe of the thyroid gland to be turned forwards. The contents of the carotid sheath are retracted laterally while the pharynx and larynx are gently rotated to the right. It is good practice to identify the left recurrent laryngeal nerve. It is in close proximity to the inferior thyroid artery, which may have to be ligated and divided. The recurrent laryngeal nerve enters the larynx just inferior to the cricothyroid joint. The dissection is then carried posteriorly along the anterior aspect of the prevertebral fascia so that the tracheoesophageal groove is identified. The pouch will lie immediately above this and can usually be palpated because of the packing within it. It should also be possible to feel the bougie within the oesophagus. This provides 'a base' on which dissection of the pouch can be carried out and it also helps prevent the excessive excision of oesophageal wall.

Sharp dissection of the connective tissue surrounding the pouch is necessary before forceps (Babcock) can be used to grasp the fundus of the pouch. The anaesthetist is then asked to remove the gauze packing. The pouch is carefully dissected free of the oesophagus and the neck of the pouch is carefully cleaned of muscle fibres at its junction with the pharynx.

The pouch should be completely mobilized so that it can be held at right angles to the long axis of the oesophagus, with its neck dissected down to the point where the mucosal sac protrudes through the muscular defect of the pharynx. Care must be taken not to pull normal mucosa out through the deficiency.

A cricopharyngeal myotomy is completed (see 'The cricopharyngeal myotomy: sole procedure' above), and then a large swab should be placed under the pouch to collect any spillage. The neck of the sac is clamped, the pouch excised and the wound edges sealed, preferably using an autosuture stapling gun. A continuous praline suture can be used to invert the suture line.

Recurrence following pouch excision is not uncommon. Contrast studies may be useful in patients who have recurrent symptoms following pouch excision, although a post-operative contrast study by Zeitoun et al[52] showed a multitude of abnormalities even among those patients who were asymptomatic. Their conclusion was that excision of a pharyngeal pouch does not appear to restore a normal swallow.

OUTCOMES

The result of the majority of published series involving ten or more patients is shown in **Table 52.2**. In some of the series, detailed data were collected at the time of surgery but in many of the publications the collection of data was retrospective and is therefore incomplete.

From the data, pouch excision with or without a cricopharyngeal myotomy is an operation that is usually 90% successful, has a recurrence rate of greater than 10% and is associated with major complications in at least 20% of patients. Lengthy anaesthesia is required and the duration of stay in hospital is usually more than 7 days.

Indications for pouch excision remain, including the patient in whom either the pouch or oesophagus is perforated during an attempted endoscopic procedure or the patient in whom a carcinoma is suspected. Some surgeons also advocate pouch excision for young patients and for those with large pouches.[46] The results are better for pouch excision if a stapling device is used to excise the pouch and seal the edges of the pharynx.[31, 32] Pouch inversion also appears to reduce the complication rate but the number of patients reported in the literature is small.[34, 35]

Endoscopic procedures involving division of the cricopharyngeal bar can be seen to produce good results, in particular when the larger series under the care of one surgeon are considered. Dohlman's figures for the period 1940–1960 remain most impressive, with 39 patients being treated with diathermy, a 90% success rate and no major complications.[9] The majority of Dohlman's patients did, however, require two-staged operations. Similarly, Van Overbeek's diathermy series of 328 patients recorded a success rate of 91.5%, a revision rate of 8% and a relatively small number of major complications.[4] **Table 52.3** shows that, when multiple surgeons, each doing a small number of operations, attempt Dohlman's procedure, the success rate drops to 70% with a revision rate of 19%, and the complication rate rises.

With the advent of the Weerda telescope and the CO_2 laser, Van Overbeek changed to laser division in 1981 and his next 216 consecutive patients showed the same success rate and recurrence rate as diathermy, but there was a reduction in the number of complications. When the results of several large studies using the laser technique are summated, it can be seen that the technique has a success rate of 90% and a recurrence rate of 7%. The complication rate is low but higher than for endoscopic stapling.

The results for endoscopic stapling are impressive, with a success rate of 90%, a revision rate of 12% and a very low complication rate.

Long-term recurrence/failure is possibly greater than with open resection, based on the often short follow-up data in endoscopic stapling papers. However, a big advantage of the endoscopic technique is that, when a recurrence occurs, revision is straightforward.

The criticism that a carcinoma may be missed at the time of endoscopic resection is not borne out by the results. There are no reports of this happening in the literature. Bradley's report[23] of a carcinoma *in situ* being found within the wall of a resected pouch of two patients is of concern, and the advice to inspect the mucosa of the pouch thoroughly with a Hopkins rod at the time of the operation seems entirely appropriate. The reported cases of a carcinoma developing some time after endoscopic resection and, indeed, after pouch excision, underline the fact that, if a patient presents with increasing dysphagia, pain or blood-stained regurgitated fluid, then early investigation is required whether they have had pouch surgery or not.

The NCEPOD enquiry noted that pharyngeal pouch surgery is an uncommon procedure associated with a significant mortality of 1–2%. In the year of the study (1995–1996), there were seven deaths following open surgery and one after endoscopic stapling.[41] The one death that followed endoscopic stapling has been published but the other seven have not. The 1996 survey of pouch surgery in the UK showed that 75% of surgeons were doing less than three operations a year. NCEPOD recommended that, because the majority of patients undergoing pharyngeal pouch surgery are elderly and represent a high risk, specialist head and neck surgeons should perform the surgery and, ideally, there should be one, or at most two, surgeons within an ENT department who are trained and competent in this type of surgery. The summated results from the main published series support this recommendation. NCEPOD further recommended that pouch stapling should be the procedure of choice; the summated results indicate that both stapling and laser division of the cricopharyngeal bar should be the operations of choice at the present time.

TABLE 52.2 Results of all the major published series for pouch surgery involving more than ten patients from 1940 to 2003

No.	Author/ref	Date of surgery	No. of patients	Exclusions	No. abandoned	No. of surgeons	Technique	Success	Recurrence	Complications	Length of service (days)	Follow-up (months: mean, range)
Comparative Studies												
1	Dohlman, Mattsson[9]	1940–1960	100	?	?	1	Dohlman's procedure: staged for large pouches	90%+	7%	No major	?	?
2	Aggerholm, Illum[51]	1989–2001	110				Excision (without myotomy)	100/110 (91%)	18/110 (16%)	Fistula: 7 (6%) Mediostinitis: 2 (2%) RLNP: 10 (9%) Other: 13 (12%) Death: 1 (0.9%) Total: (30%)	Not given	Not given
3	Parker, Hawthorne[25]	1962–1971	24	0		Several	Dohlman's procedure	16/24 (66%)	7%	Neck pain: 1	5–6; 2–8	
			7				Excision – myotomy	3/7 (43%)	4/7 (57%)	RLNP: 1 Pneumonia: 2	9	
4	Todd [30]	1950–1972	9				Excision – myotomy	6/9 (66%)	3/9 (33%)	RLNP: 2 Haematoma: ??? fistula: 2		
			48			18	Excision	42/48 (88%)	6/4	RLNP: 9 (19%) Fistula: 9 (19%) Mediastinitis: 2 (4%) Pneumonia: 5 (10%) Stenosis: 3 (5%) Total: (9%)	~18	
			58				Dohlman's procedure	49/58 (84%)	15/58 (26%)	Fistula: 2 Haemorrhage: 1 Stenosis: 2 Total: (9%)	4	
5	Freeland, Bates[34]	1975–1985	19		0	5	Excision ± myotomy	13/19 (68%)	4/19 (21%)	RLNP: 7 (37%) Fistula: 3 (16%)	16	
			9			3	Inversion ± myotomy	7/9 (77%)	1/9 (11%)			

(Continued)

TABLE 52.2 (CONTINUED) Results of all the major published series for pouch surgery involving more than ten patients from 1940 to 2003

No.	Author/ref	Date of surgery	No. of patients	Exclusions	No. abandoned	No. of surgeons	Technique	Success	Recurrence	Complications	Length of service (days)	Follow-up (months: mean, range)
6	Morton, Bartley[35]	1982–1989	15				Excision	14/15 (93%)	1/15 (7%)	RLNP: 1 (7%) Fistula: 2 (13%) Wound infection: 3 (20%)	9 (5–61)	40
			18				Inversion	18/18 (100%)	Nil	1 death (6%)	3 (1–10)	40
7	Van Overbeek[4]	1964–1982	328			1	Dohlman's procedure: staged for large pouch	91.5%	8%	Perforation: 7 (3.3%) Haemorrhage: 4 (1%) Oes/trach fistula: 1 (0.3%) Stenosis: 8 (2%) Mediastinitis: 3 (1.42%) Death: 1 (0.3%)		
		1981–1992	216			1	CO_2 laser: staged for large pouch	90.6%	16/216 (7.4%)	Perforation: 12 (5.5%) Haemorrhage: 1 (0.4%)		
8	Van Eeden, Lloyd, Tranter[48]		18				ESS	83.3%	1/18 (5.5%)		2.26	Average 10
			19				Various	70.6%	3/19 (17.6%)		4	Average 43
9	Moran, Wilson, Al Muhanna[15]	1967–1984	73	14		?1						
			13			?1	Dohlman's procedure	6/13 (46%)	7	RLNP: 1 (7.5%) Perforation: 5 (38%)		
			36			?1	Excision	26/36 (725)	2/36 (5.5%)	RLNP: 2 (5.5%) Fistula: 4 (11%) Stenosis: 2 (5.5%)		
10	Mirza, Dutt, Minhas, Irving[46]	1989–1999	23			7	Excision	22/23 (96%)	1/23 (4%)	Perforation: 3 (13%) RLNP: 1 (4%) Wound infection: 1 (4%)	8.5 (4–16)	
			20			4	ESS	15/20 (75%)	2/20 (1%)	Perforation: 3 (15%)	3 (1–6)	
			9			2	Dohlman's procedure	7/9 (78%)	1/9 (11%)	Perforation: 1 (11%)	5.8 (3–8)	
			3			1	Inversion	3/5 (60%)		Nil	5 (4–6)	
			3			2	Cricopharyngeal myotomy alone	3/3 (100%)		RNLP: 2 (66%)	6.7 (3–10)	

(Continued)

TABLE 52.2 (CONTINUED) Results of all the major published series for pouch surgery involving more than ten patients from 1940 to 2003

No.	Author/ref	Date of surgery	No. of patients	Exclusions	No. abandoned	No. of surgeons	Technique	Success	Recurrence	Complications	Length of service (days)	Follow-up (months: mean, range)
11	Mackay[54]	1957–1994	42			7	Dohlman's procedure		3/42 (7%)	1 developed carcinoma Mediastinitis: 2 Stenosis: 1 Lung abscess: 1 Perforation: 1 Total: 14%	11+ (5–110)	Not given
			30			13				Fistula: 6 RLNP: 2 Emphysema: 2 Stricture: 1 Glottic oedema: 1 Total: 27%	16+ (5–365)	
			20				Dilatation	Mostly ineffective	High			
laser Studies												
12	Benjamin, Gallager[55]	1987–1992	34	0	2		Laser	30/32 (93.8%)	1/32 (3.1%)	Perforation: 2	4.5	Not given
13	Kresper, Kacker, Remacle[56]	1989–2001	69	Pouch <2 cm and 74 cm	3		Laser	58/67 (86%)	6/69 (8.7%)	Perforation: 3 (4%) Bleeding: 2 (3%) Pneumothorax: 1 (1%)	Not given	Average 4.8 (1–121)
14	Bradwell, Bieger, Strachan, Homer[57]	1085–1993	15				Laser	11/15 (73%)	2/15 (13%)	Perforation: 2 (13%) Bleeding: 1 (6.6%)	4.5+ (2–11)	48–132
15	Nyrop, Svendstrup, Jorgensen[58]	1989–1999	61			3	Laser	53/61 (87%)	6/61 (10%)	Bleeding: 1 (2%) Perforation: 3 (5%) Inflammation: 2 (3%)	3 (2–14)	37 (3–96)
16	Lippert, Benedikt, Heinrich, Werner[59]	1984–1996	70				Laser	66/70 (94%)	3/70 (4%)	Mediastinitis: 1 (1%)	Not given	Not given
ESS (stapling) Studies												
17	Cook, Huang, Richstmeier, Scher [43]	1995–1999	74		6	2	ESS	66/68 (97%)	6/68 (8.8%)	Perforation; 1 Dental: 5	1 (0–4)	9.3 (1.5–25)

(Continued)

TABLE 52.2 (CONTINUED) Results of all the major published series for pouch surgery involving more than ten patients from 1940 to 2003

No.	Author/ref	Date of surgery	No. of patients	Exclusions	No. abandoned	No. of surgeons	Technique	Success	Recurrence	Complications	Length of service (days)	Follow-up (months: mean, range)
18	Jaramillo, McLay, McAteer[47]	1996–2000	32	5	2	1+1 supervised registrar	ESS	13/15 (86%)	2/15 (13%)	Perforation: 1 (3%)	3.17 (2–11)	Results of surgery repoerted on 15 patients to having at least 24/12 follow-up
19	Bates, Steventon[60]	1994–2004	230	0	0	1+ supervised registrar	ESS	197/230 (86%)	41/230 (18%)	Dental: 8 (3%) Perforation: 1 (0.4%)	2.1 (1–6)	60 (3–138)
20	Collard, Otte, Kestens[39]	1992	6	0	0	1	ESS	5/6 (83%)	1/6 (16.6)	Nil	2	2–16
21	Sood, Newbigin[45]	1992–1999	37				ESS	32/37 (86%)	4 (9%)	Perforation: 1 Dental: 3 Death: 1	<2	2–43 (19)
22	Counter, Hilton, Baldwin[61]	1993–1997	28				ESS	16/9 (84%)	6/19 (22%)	Perforation: 3 (11%)	4.1 (1–31)	59 (55–73)
23	Raut, Primrose[62]	1994–1998	25			1	ESS	20/25 (80%)	9/25 (36%)	Perforation: 2 (8%)	3.4	24–60
24	Stoeckli, Schmid[63]	1997–2000	30	0	0	1	ESS	96%	1/30 (4%)	Nil		13.2
25	Thaler, Weber, Goldberg, Weinstein[64]	?–2000	23		7		ESS	14/16 (87%)	2/16 (13%)	Nil		
26	Lüscher, Johansen[65]	1997–1998	23	0	0	Limited	ESS	22/23 (96%)	1/23 (4%)	Perforation: 1 (4%)		12 (4–22)
27	Narne, Cutrone, Bonavina et al[66]	1992–1996	102		4	Limited	ESS	96/98 (98%)	4/102 (4%)	Perforation: 1 (1%)	4	16 (1–45)

TABLE 52.3 Summary of different procedures and outcomes

No. of patients	Method	Success	Revision rate	Complications	Length of stay
278	Excision	255 (91%)	40 (14.3%)	LNP: 35 (12.6%) Fistula: 33 (11.9%) Mediastinitis: 4 (1.4%) Stenosis: 5 (1.8%) Pneumonia: 8 (2.9%) Death: 1 (0.4%) Other: 22 (7.9%)	12+
587	ESS	530 (90%)	63 (12.6%)	Perforation: 14 (2.4%) Dental: 15 (2.6%) Death: 1 (0.2%)	2
463	Laser	417 (90.6%)	34 (7.3%)	Perforation: 17 (3.6%) Bleeding: 4 (0.9%) Mediastinitis: 4 (0.86%) Other: 6 (1.29%)	4
100	Dohlman by Dohlman	90%+	7%	No major	
328	Dohlman by Van Overbeek	91.5%	8%	Perforation: 7 (3.3%) Mediastinitis: 3 (1.42%) Stenosis: 8 (2%) Death: 1 (0.5%) Haemorrhage: 2 (0.52%) Fistula: 1 (0.3%)	
79	Dohlman by multiple surgeons	56/79 (70%)	15/79 (19%)	LNP: 1 (1.26%) Perforation: 6 (7.6%) Mediastinitis: 3 (3.79%) Other: 3 (3.79%)	

CONCLUSIONS

The short-term results with endoscopic procedures are superior to external operations. Endoscopic stapling and laser division are quick and bloodless, are associated with minimal discomfort and avoid the need for a nasogastric tube. Endoscopic techniques permit an early oral intake and early hospital discharge, thus reducing the morbidity and costs traditionally associated with pharyngeal pouch surgery. The long-term recurrence of endoscopic techniques is probably higher than pouch excision. However, revision surgery via the endoscope is relatively easy and successful.

The results for stapling and laser division are similar. Stapling has the theoretical advantage of reducing the risk of perforation and mediastinitis, whereas the laser permits a better view when there is limited access.

Cricopharyngeal myotomy as a sole procedure has a role in the treatment of the very small pouch. There remain some indications for pouch excision. The experience of the surgeon appears to be of the utmost importance. At times, pouch surgery can be difficult and the complications life-threatening. Surgeons who have developed an interest in pouch surgery sufficient to publish large series have the best results.

BEST CLINICAL PRACTICE

- ✓ When operating, strive to obtain a good view.
- ✓ Treat tissues with great respect.
- ✓ Carry out a biopsy for abnormal mucosa.
- ✓ If there is significant trauma, insert a nasogastric tube.
- ✓ For a small perforation, use an endoscopic suture.
- ✓ For a large perforation, open the neck and repair.
- ✓ Post-operative contrast studies are unhelpful.

FUTURE RESEARCH

- ➤ The very small pouch is difficult to treat endoscopically. Changes in the design of the stapling device might help resolve this problem, namely a device that cuts and staples along the whole length of its jaws.
- ➤ Access is difficult in 20% of patients. Improvements in endoscopes and viewing telescopes may reduce the degree of difficulty.

- ➤ The recurrence rate for all types of pouch surgery is high and may be related to persistent gastric reflux. Aggressive treatment of the gastro-oesophageal reflux may be appropriate but the evidence is lacking.
- ➤ Following all types of pouch surgery, patients are rarely completely asymptomatic and it would be useful to have a method for treating these residual symptoms, which are probably due to an underlying neuromuscular incoordination.
- ➤ Randomized controlled trials comparing new techniques with established treatments are justified.
- ➤ In the UK, virtually all pharyngeal pouch surgery is now performed by ENT surgeons. Subspecialization is slowly happening and is to be encouraged so that, within each major centre, only ENT surgeons with a special interest in pouch surgery should manage pouch patients.

KEY POINTS

- Cricopharyngeal dysphagia results from the failure of the cricopharyngeal muscle to relax. It can occur with or without the formation of a pharyngeal pouch.
- Pharyngeal pouch occurs in elderly, sometimes frail, patients.
- Incidence is one per 100 000 per year.
- Diagnosis is made with a barium or video swallow.
- Surgery improves quality of life.
- Endoscopic resection with a stapling device or laser is generally considered the first-line treatment for most pouches.
- Recurrence is easily treated with endoscopic techniques.
- Carcinoma is rare but vigilance is required.
- Surgeons with a special interest in pouch surgery should treat all patients.

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CHAPTER 53

OESOPHAGEAL DISEASES

Shajahan Wahed and S. Michael Griffin

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: gastro-oesophageal reflux disease, Barrett's oesophagus, oesophageal motility, oesophageal achalasia, oesophageal cancer, oesophageal perforation, oesophageal disruption, Boerhaave's, oesophageal foreign body, eosinophilic oesophagitis. The fifth edition of the textbook *Oesophagogastric surgery* was also consulted in preparing this chapter.[1]

INTRODUCTION

A broad spectrum of benign and malignant conditions affects the oesophagus. This chapter concentrates on the main conditions dealt with by upper gastrointestinal surgeons and some gastroenterologists, recognizing that some patients present first to the ENT surgeon depending on the predominant symptoms. Malignant disease and several of the less common benign conditions are managed in specialist oesophagogastric centres in order to improve knowledge, achieve standardization of treatment and, most importantly, improve outcomes.

GASTRO-OESOPHAGEAL REFLUX

Gastro-oesophageal reflux disease (GORD) is extremely common, with symptoms triggered by food, gastric acid or bile from the duodenum travelling back up into the oesophagus.

Presentation

The most common symptoms include retrosternal pain, heartburn, dyspepsia, waterbrash, pain on swallowing, regurgitation and vomiting. Symptoms typically become apparent after meals or when lying supine. A small minority of patients present with atypical symptoms related to proximal reflux. These include voice changes, coughing, sore throat, throat clearing or even sinusitis. Reflux and micro-aspiration might account for worsening of respiratory symptoms in patients with underlying lung disease.

Risk factors include being overweight, smoking, overeating and leaving only a short interval between meals and sleeping. Spicy foods and alcohol are commonly recognized as substances that precipitate symptoms. The underlying mechanisms for developing reflux can include the presence of a sliding hiatus hernia, a reduction in lower oesophageal sphincter pressure, an increase in the number of lower oesophageal sphincter relaxations, abnormal oesophageal peristalsis that fails to clear any refluxate, poor gastric motility and excessive gastric acid production.

Investigation

All patients over 40 with new onset reflux or a change in long-standing reflux symptoms should be referred for urgent flexible endoscopic assessment. This is not only to identify signs of reflux disease but also to exclude malignancy. Endoscopy should be performed while patients are not on any acid-lowering treatment. Appearances might demonstrate oesophagitis, the presence of a sliding hiatus hernia that would predispose to reflux disease, bile reflux or acid-related strictures or they might be normal (**Figure 53.1**).

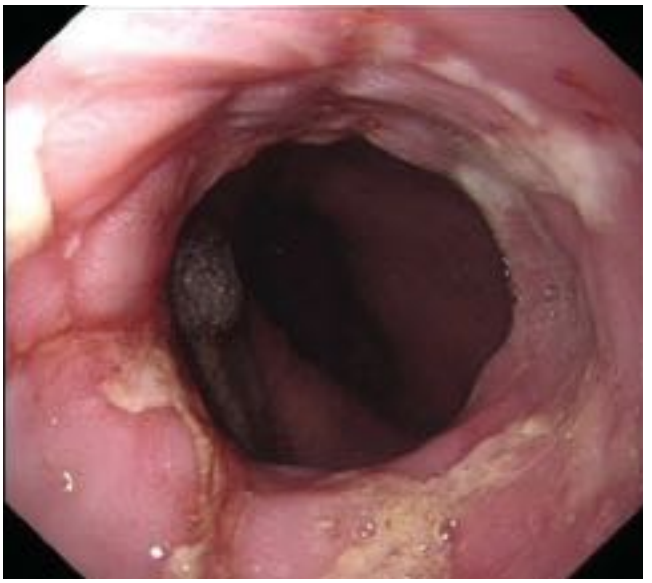


Figure 53.1 Endoscopic view of moderate oesophagitis above a sliding hiatus hernia.

Further investigation is only required in a minority of patients where endoscopic appearances are equivocal in supporting the diagnosis (particularly in cases where non-acid reflux is suspected), if surgery is being contemplated, or in cases of suspected proximal reflux.

Oesophageal manometry assesses the adequacy of peristalsis and can identify any underlying motility disorders. A fine catheter placed in the oesophagus records pressures at rest and during the passage of 10 swallows at various levels along the oesophagus and the oesophagogastric junction. Conventional manometry uses eight channels and displays results as a line graph (**Figure 53.2**). Developments in catheters and software has allowed the introduction of high-resolution manometry, where up to 32 channels can be used to give more detailed information and produces images with contrasting colours to represent differential pressure levels (**Figure 53.3**).

Oesophageal 24-hour ambulatory pH monitoring will reveal whether the oesophagus is exposed to acid content for a pathological length of time (pH<4 for more than 5% of the 24-hour period) and allows for correlation with

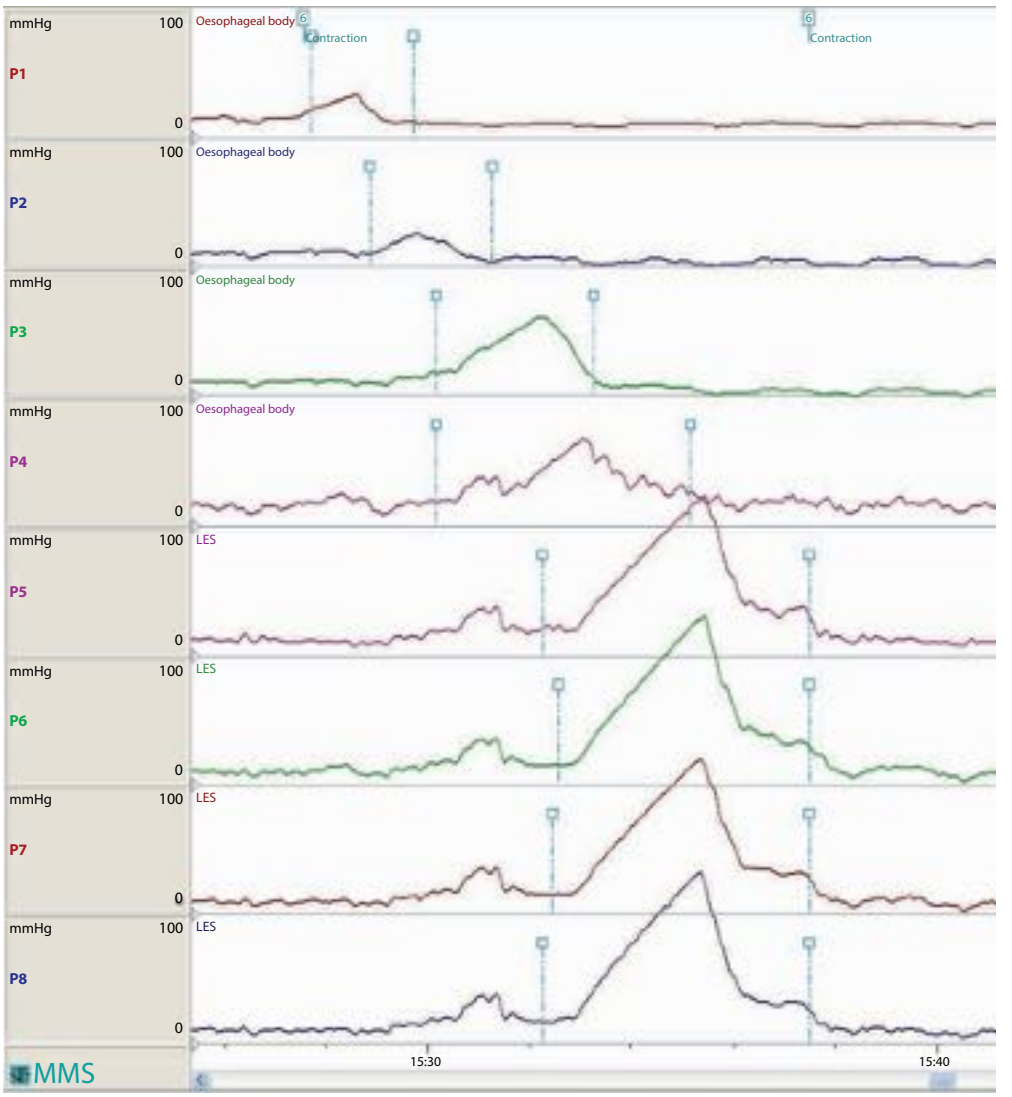


Figure 53.2 Conventional eight-channel manometry demonstrating normal peristalsis within the oesophageal body.

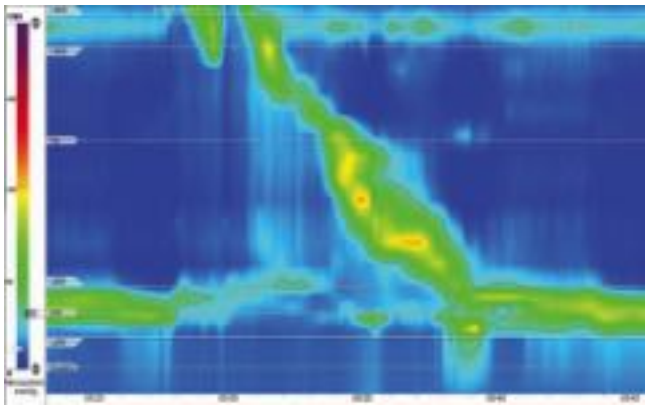


Figure 53.3 Appearances of high-resolution manometry in a normal oesophagus.

any symptoms the patient experiences. Impedance studies are required only in cases of suspected proximal reflux or when non-acid reflux is implicated as the underlying cause. Bile reflux monitoring is possible although is not commonly used. Contrast radiology in the form of a barium swallow can be useful to exclude underlying dysmotility and may also demonstrate reflux.

Management

The overwhelming majority of patients with reflux disease will be managed successfully by addressing risk factors and simple antacids, with proton pump inhibitors required in those with more severe symptoms. The few patients who fail this treatment strategy can be assessed for anti-reflux surgery once the additional investigations have excluded dysmotility and shown evidence of oesophagitis on endoscopy or abnormal acid exposure during 24-hour pH monitoring.[2, 3] Appropriate patient selection is crucial to achieving successful outcomes from antireflux surgery as the potential effects of fundoplication in the wrongly selected patient are disabling.

The standard operation involves a fundoplication where the fundus of the stomach is wrapped around the gastro-oesophageal junction. This is performed laparoscopically in most centres because of reduced post-operative pain and length of hospital stay (often day case) although open surgery perhaps improves the longevity of the fundoplication.[4] A floppy Nissen fundoplication involves a loose, posterior 360-degree wrap combined with tightening of the crura, although variations are practised.[5–8] Whether tailoring of the wrap improves outcomes is not conclusive.[9] Complications from surgery include dysphagia, retrosternal pain, gas bloat, excess flatus and oesophageal perforation. Revisional antireflux surgery is challenging and includes patients with short-term as well as long-term symptom recurrence.[10] Resumption of proton pump inhibitor treatment will suffice in many cases although revisional fundoplication is an option. Subtotal gastrectomy and a roux-en-y reconstruction is reserved as a definitive procedure to relieve intractable symptoms. Newer endoscopic and robotic antireflux techniques remain unproven.[11, 12]

Reflux disease appears to accelerate the development of bronchiolitis obliterans in some lung transplant recipients.[13] This has led to antireflux surgery being considered in such patients.[13] Ongoing research is needed to determine which of these patients are most likely to benefit and to decide upon the optimal timing of such procedures. This mechanism is being extrapolated to patients with other respiratory diseases who do not exhibit symptoms traditionally associated with reflux. In future antireflux surgery might be beneficial in preventing reflux-associated lung damage from microaspiration in this group of patients.

KEY POINTS

- Reflux symptoms are common.
- Upper respiratory tract symptoms are rarely due to reflux.
- Patients over 40 with recent onset reflux symptoms need an endoscopy.
- Most patients with reflux disease are managed with lifestyle modification and proton pump inhibitors.
- Only a minority of patients will require surgery (floppy Nissen fundoplication).

BARRETT'S OESOPHAGUS

Barrett's oesophagus develops when the normal oesophageal lining changes from stratified squamous to columnar epithelium (**Figure 53.4**). It is common in the Western world and has an increasing incidence. It occurs as a result of chronic inflammation secondary to acid, alkaline and bile reflux.[14–16] Genetic factors might also increase an individual's predisposition to this condition and its progression.[17] This metaplastic epithelium increases the risk of developing adenocarcinoma of the oesophagus.[18–20] A formal diagnosis of Barrett's requires the reporting of two separate specimens from a specialist gastrointestinal pathologist. Dysplastic changes within the Barrett's epithelium can occur, subclassified as either low-grade or high-grade. Confirmed low-grade dysplasia increases the risk of progression on to high-grade dysplasia or adenocarcinoma although some will not progress.[21, 22] High-grade dysplasia poses a significant risk of developing adenocarcinoma and, given the subjectivity of biopsies, might indicate that there is adenocarcinoma already present. Patients with a diagnosis of low- or high-grade dysplasia within Barrett's oesophagus should be referred to specialist centres for management.

Surveillance

Enrolment of patients in to an endoscopic surveillance programme improves identification of dysplastic changes before the onset of adenocarcinoma and potentially allows less invasive treatment.[23] Despite the logical advantage of surveillance on an individual basis, definitive evidence of benefit has not yet been produced. A randomized study comparing endoscopic surveillance versus symptomatic presentation designed to determine whether surveillance improves survival in patients with Barrett's oesophagus



Figure 53.4 Macroscopic appearance of circumferential Barrett's oesophagus.

completed recruitment in 2012. Research using less invasive screening devices that could perhaps identify patients needing endoscopy is ongoing.

Management

The development of Barrett's oesophagus does not require treatment other than addressing risk factors for reflux disease, prescribing proton pump inhibitors to reduce acid reflux and endoscopic surveillance. There is no evidence to suggest that antireflux surgery, which will prevent both acid and alkaline reflux, is superior to medication at preventing progression of the condition.[24, 25]

The development of high-grade dysplasia within Barrett's oesophagus requires full staging to exclude an underlying malignancy with computed tomography (CT), flexible videoendoscopy and endoscopic ultrasound (EUS). Endoscopic mucosal resection (EMR) to obtain a more substantial biopsy might be required (see below). The confirmation of dysplasia will trigger consideration of further treatment.

Radiofrequency ablation

Radiofrequency ablation (RFA) is a newer endoscopic treatment used to destroy dysplastic epithelium.[26] It is indicated in high-grade dysplasia when complete assessment and staging have shown an otherwise normal oesophagus with a flat mucosal lining and an underlying adenocarcinoma has been excluded. It is often used following EMR of a nodular area of Barrett's. Long-term results from this treatment are lacking and there remain concerns about occult neoplasia developing beneath the ablated epithelium.[27] Repeated treatment applications are often required with potential complications of perforation and stricture formation. Intensive endoscopic surveillance is required following treatment to detect any recurrence or new dysplasia that require repeat application or repeat staging. Long-term follow-up of this treatment is awaited and prospective registration of all cases should ensure accurate data.[28] Indications for RFA are likely to expand to include low-grade dysplasia to prevent progression.

Surgery

Oesophagectomy still remains the gold standard for high-grade dysplasia in Barrett's oesophagus as it provides definitive cure. It is indicated when nodal disease is evident on staging suggesting undiagnosed invasive adenocarcinoma, the length of Barrett's oesophagus is extensive or multifocal, the oesophagus is otherwise abnormal or the patient is young. Morbidity and mortality have reduced considerably in oesophagectomy and can be performed with a low mortality and acceptable morbidity. In cases of high-grade dysplasia in Barrett's oesophagus, mortality appears even lower, with one review showing a 1% mortality in 530 patients.[29] More limited resection techniques have also been used.[30]

KEY POINTS

- Barrett's oesophagus increases the risk of developing oesophageal adenocarcinoma.
- Endoscopic surveillance should be offered to patients with Barrett's oesophagus.
- High-grade dysplasia within Barrett's oesophagus indicates the need for full staging and referral to a specialist centre.
- Radiofrequency ablation is a new alternative to surgery to treat high-grade dysplasia in selected cases but long-term results are awaited.
- Oesophagectomy remains the gold-standard treatment for high-grade dysplasia in Barrett's oesophagus.

OESOPHAGEAL CARCINOMA

Incidence

Oesophageal carcinoma is the eighth most common cancer worldwide, with an estimated incidence of 480 000 in 2008.[31] The two predominant types are adenocarcinoma and squamous cell carcinoma. Adenocarcinoma and squamous cell carcinoma differ in several of their risk factors, predominant location within the oesophagus, response to chemotherapy and radiotherapy, and overall survival. Rare cancer types include small cell carcinoma, primary melanoma, malignant stromal tumours and leiomyosarcoma.

The incidence of oesophageal carcinoma increases considerably after the age of 40, with a peak between 70 and 74 years of age for men and a continual rise for females. The cancers have a strong preponderance in affecting males more than females in a 2–4 : 1 ratio.[31]

OESOPHAGEAL ADENOCARCINOMA

This histological subtype predominates in the Western world, accounting for over two-thirds of all oesophageal cancers diagnosed (**Figure 52.5**). The incidence of adenocarcinoma in the Western world is continuing to increase and is the source of concern.[32] These cancers have a



Figure 53.5 Appearance of an oesophageal adenocarcinoma after fixation of the specimen.

tendency to occur in metaplastic columnar epithelium of the middle and lower thirds of the oesophagus or at the oesophagogastric junction. There are concerns that adenocarcinoma might increase in the Far East as Western lifestyles and habits spread.[33] There has also been an increase in the number of oesophagogastric junction adenocarcinomas, seemingly a result of oesophageal cancers migrating distally and gastric cancers migrating proximally over time.

The main risk factors include obesity, reflux disease and the presence of Barrett's oesophagus.[18, 34–36] Smoking, excessive alcohol consumption, a family history of gastrointestinal cancer and diets low in fresh fruit and vegetables are all also implicated in increasing risk of developing oesophageal adenocarcinoma.

OESOPHAGEAL SQUAMOUS CELL CARCINOMA

In contrast squamous cell carcinoma of the oesophagus still predominates in the Far East. These cancers tend to occur in the cervical oesophagus and the upper parts of the thoracic oesophagus. Smoking, high alcohol intake, low socioeconomic status, hot drinks and diets low in fresh fruit and vegetables are strong risk factors in developing squamous cell carcinoma.

Presentation

Presentation often occurs late as many of the early symptoms are non-specific and patients often do not seek medical advice. Attempts at increasing awareness of risk factors and symptoms are important as early disease improves chances of offering curative treatment. Many of the symptoms overlap with benign reflux disease and dysmotility (**Box 53.1**). Early flexible videoendoscopy is essential to capture the patients that have cancer as the underlying cause. Respiratory symptoms can occur due to more proximal reflux and microaspiration from obstruction. Surveillance of patients with Barrett's oesophagus and those with significant family history is designed to identify premalignant changes or early disease.

BOX 53.1 Symptoms suggestive of oesophageal cancer

- New onset or worsening heartburn or reflux in patients aged over 40
- Dysphagia
- Early satiety
- Loss of appetite
- Unexplained weight loss
- Vomiting or haematemesis (less common)
- Voice changes or a persistent cough (less common)

Diagnosis and staging

Diagnosis is made by flexible videoendoscopy, following which patients require fitness assessment, staging investigations and formal discussion at a specialist oesophagogastric multidisciplinary team (MDT) meeting (**Figure 53.6**). These are coordinated through centralized units. This MDT meeting involves oesophageal surgeons, medical and clinical oncologists, radiologists, pathologists, specialist nurses, dieticians, palliative care nurses and a coordinator.

Fitness investigations require a thorough history and examination of the patient, an electrocardiogram, spirometry and a timed exercise test. Formal cardiopulmonary exercise testing (CPET) has been introduced to help objectively measure a patient's fitness in order to quantify risks of treatment.[37, 38] CPET can identify undiagnosed cardiorespiratory comorbidity that might be amenable to treatment before any potential surgery although its precise value is yet to be determined.

Oesophageal cancer and oesophagogastric junction cancers that predominantly involve the oesophagus are staged using the seventh edition of the tumour, node, metastasis (TNM) classification[39, 40] (**Table 53.1**).

Precise identification of the location and depth of the primary cancer, the location and numbers of lymph nodes involved, and the total length of disease taking into account involved lymph nodes will determine available treatment options. Staging investigations as a minimum will include endoscopy, and a gastric protocol CT of the chest, abdomen and pelvis (**Figures 53.7**).

Most patients require additional investigations (**Box 53.2**). EUS is better than CT at identifying local nodes and depth of invasion (**Figure 53.8**). Tumours that demonstrate invasion into the muscular layers of the oesophagus (T3) or involvement of nodes require

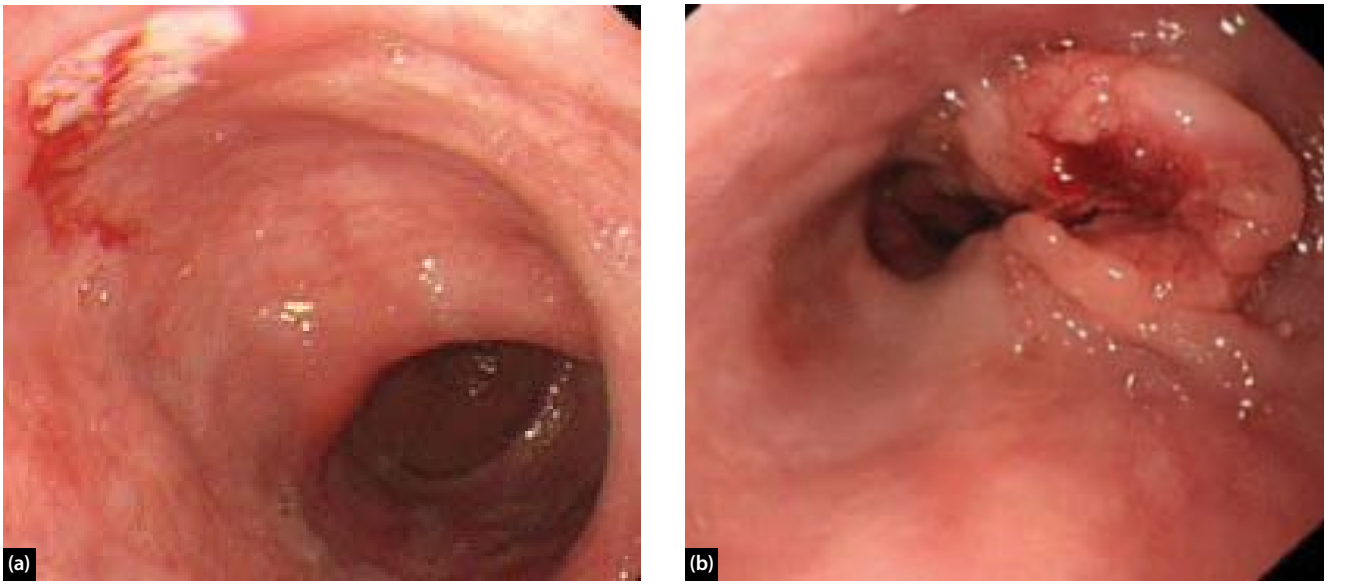


Figure 53.6 The endoscopic appearances of two different oesophageal cancers.

TABLE 53.1 TNM classification of oesophageal cancer

Tis	Carcinoma *in situ* / high-grade dysplasia
T1 T1a T1b	Lamina propria or submucosa Lamina propria or muscularis mucosae Submucosa
T2	Muscularis propria
T3	Adventitia
T4 T4a T4b	Adjacent structures Pleura, pericardium, diaphragm, or adjacent peritoneum Other adjacent structures, e.g. aorta, vertebral body, trachea
N0	No regional lymph node metastasis
N1	1–2 regional lymph nodes
N2	3–6 regional lymph nodes
N3	>6 regional lymph nodes
M0	No distant metastasis
M1	Distant metastasis

additional staging with either bone scan or positron emission tomography (PET-CT) (**Figure 53.9**).

EMR is often required to obtain a more substantial biopsy for small lesions that have inconclusive histology. It may provide a therapeutic option (see below). Neck ultrasound is useful at diagnosing suspicious nodal disease in the neck and can guide fine-needle aspiration cytology. Bronchoscopy and endobronchial ultrasound are occasionally required. Staging laparoscopy is required in patients who have evidence of gastric involvement in locally advanced cancers.

Management

Management is determined by the patient's fitness to undergo radical treatment, the patient's wishes, the stage of the disease and the histological type of cancer.[41, 42] Early cancers include those that are limited to the mucosa,



Figure 53.7 CT images demonstrating the presence of a polypoidal tumour in the lower oesophagus and a hiatus hernia.

BOX 53.2 Staging investigations in oesophageal cancer

All patients require endoscopy and CT. The majority also require endoscopic ultrasound and bone scan or PET-CT. Other investigations are selected on an individual case basis.

- Flexible videoendoscopy
- CT chest, abdomen, pelvis (gastric protocol)
- Endoscopic ultrasound
- Bone scan
- Positron emission tomography (PET-CT)
- Neck ultrasound +/– fine-needle aspiration
- Bronchoscopy
- Endobronchial ultrasound
- Staging laparoscopy
- Endoscopic mucosal resection

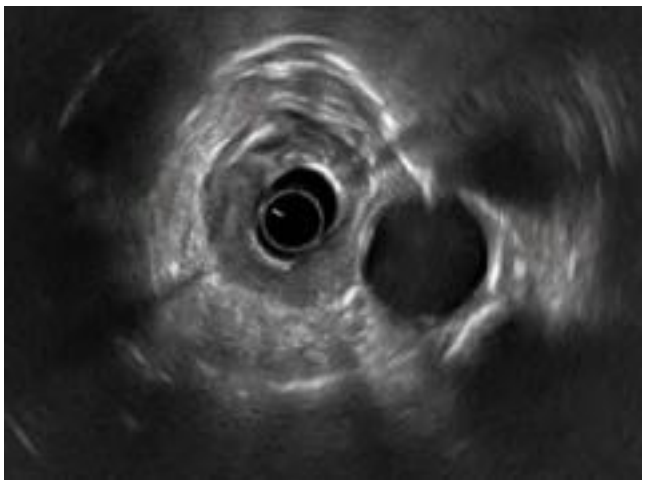


Figure 53.8 Endoscopic ultrasound image demonstrating a T3 oesophageal cancer posteriorly.

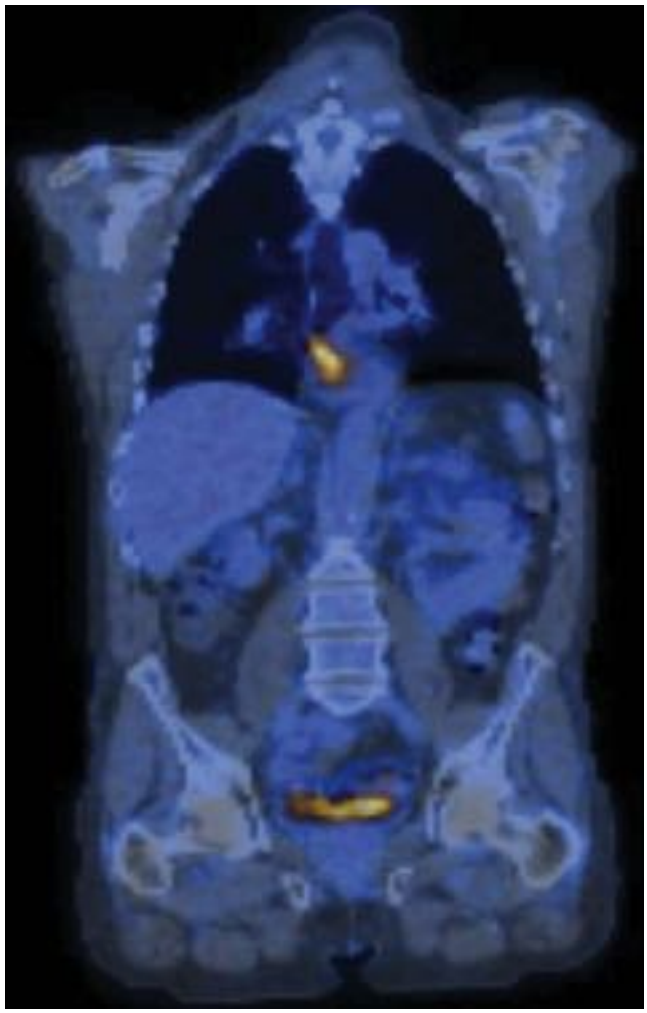


Figure 53.9 A PET-CT image demonstrating high uptake of FDG in a cancer of the lower oesophagus.

submucosa or to the muscularis propria where there is no evidence of nodal involvement on clinical staging (*c*T1/2 N0). Locally advanced cancers can be considered those cancers where there is evidence of lymph node involvement within surgically resectable fields or within the scope of radical radiotherapy in relevant cases of squamous cell carcinoma such that treatment is of curative intent.

NEOADJUVANT AND ADJUVANT CHEMOTHERAPY

For oesophageal cancer that is clinically staged as either reaching adventitia (T3/4) or with nodal involvement (N1-3), neoadjuvant chemotherapy or chemoradiotherapy followed by restaging and surgery is the recognized treatment pathway, with adjuvant chemotherapy then considered following surgery.

The benefit of chemotherapy was originally demonstrated by the Medical Research Council (MRC) OE02 study in which patients were randomized to receiving surgery alone or two cycles of cisplatin and 5-fluorouracil followed by surgery.[43] The patients who received neoadjuvant chemotherapy demonstrated an overall survival advantage of 6% at 5 years.[44] This regimen is currently still used in squamous cell carcinoma in the UK although is likely to be superseded by neoadjuvant chemoradiotherapy based on a similar chemotherapy regimen supplemented with neoadjuvant radiotherapy.

In oesophageal adenocarcinoma, neoadjuvant chemotherapy in the UK is based on the MRC adjuvant gastric infusional chemotherapy (MAGIC) trial that evaluated the benefit of administering three cycles of epirubicin, cisplatin and capecitabine in the neoadjuvant setting followed by a further three cycles in the adjuvant setting.[45] This trial was originally designed for gastric adenocarcinoma but included lower-third oesophageal and oesophagogastric junction adenocarcinoma. It demonstrated a 13% survival advantage at 5 years. A further study (OE05) comparing two cycles of neoadjuvant cisplatin and 5-fluorouracil to four cycles of epirubicin, cisplatin and capecitabine completed recruitment in 2011. A recent meta-analysis has confirmed the benefit of neoadjuvant chemotherapy.[46]

Current trials are assessing whether anti-angiogenic agents confer additional survival advantage, and preliminary investigations evaluating agents targeting growth factor receptor antagonists have also started.

NEOADJUVANT CHEMORADIOTHERAPY

Chemoradiotherapy in the neoadjuvant setting was previously reported in the UK but was abandoned in favour of neoadjuvant chemotherapy after reports of increased morbidity and mortality. Other countries continue to use neoadjuvant chemoradiotherapy, although regimens in each country differ. Newer chemoradiotherapy regimens do not appear to affect morbidity as in the past. Although there are few randomized trials comparing neoadjuvant chemotherapy to neoadjuvant chemoradiotherapy, a recent meta-analysis and a randomized trial suggest there is an additional survival advantage without an increase in morbidity.[47, 48] Squamous cell cancers are recognized as being more sensitive to chemoradiotherapy and most of the benefit highlighted in the recent trial was in patients with squamous cell carcinoma. Neoadjuvant chemoradiotherapy is likely to become the standard for squamous cell carcinoma. Whether the same occurs for oesophageal adenocarcinoma will depend on the outcomes of future appropriately powered studies designed to evaluate whether neoadjuvant chemoradiotherapy offers a survival advantage without additional morbidity to patients over neoadjuvant chemotherapy.

Surgery

The principles of oesophagectomy were established many years ago. Surgery is only undertaken with curative intent, when a complete (R0) resection is expected based on the staging investigations. There is no role for oesophagectomy in a palliative setting. An en bloc resection is performed with a radical two- or three-field lymphadenectomy.[49, 50]

LYMPHADENECTOMY

Current radiological staging investigations are not accurate enough to predict the lymph node status following resection in all patients. A standardized, radical lymphadenectomy is therefore performed in all patients to offer the best chance of cure. Evidence has accumulated that the extent of lymphadenectomy improves disease staging but more importantly improves overall survival and reduces locoregional recurrence rates.[51, 52] Patients in whom there is no evidence of nodal disease within the resection specimen are perhaps overtreated by the lymphadenectomy but this observation can only be made once all the lymph nodes have been examined by a pathologist. Patients with extensive nodal involvement are at high risk of having occult metastases and developing early recurrence. However, without the full lymph node resection for pathological analysis this cannot be determined. It must be remembered that for any given individual it is impossible to predict long-term outcome. The contribution of radical lymphadenectomy to the morbidity of oesophagectomy is difficult to quantify although the overall reduction in morbidity from resection and the improvements in lymph node yields suggest that in the majority of patients the lymph node dissection can be performed without additional burden.

In-hospital mortality following oesophageal resection has reduced to 2.9% in the UK while other major centres in the world also report improvements in mortality.[53, 54] This reduction is the result of a number of factors including earlier diagnosis, improvements in pre-operative patient assessment and selection, peri-operative care, and post-operative recognition and management of complications. Specialist oesophagogastric centres have been established that concentrate expertise and increase hospital and surgeon volume, with good evidence to suggest this approach improves outcomes.[55]

SURGICAL APPROACH[1]

The stomach is the preferred organ to use as the conduit following oesophagectomy. Colon is used in patients with previous gastric surgery rendering the stomach unsuitable or when there is extensive gastric involvement with the cancer. Either the right colon or transverse colon can be used. Colon is not considered as the primary choice owing to its functional deterioration over time. Jejunum can also be considered in certain circumstances.

Open surgery

Several different approaches can be used. For middle- and lower-third cancers, a two-stage transthoracic resection is the preferred approach. An upper midline incision is used, to allow for gastric mobilization with preservation of the right gastroepiploic and right gastric arteries and veins. A pyloroplasty or pyloromyotomy is performed to improve post-operative gastric emptying and reduce the risk of aspiration. Insertion of a feeding jejunostomy is also good practice and can be performed with a low additional complication rate. It allows enteral nutrition access during the recovery period but more importantly in the event of any anastomosis or conduit problems that delay the resumption of oral intake.

A posterolateral right thoracotomy is performed through the fourth or fifth intercostal space. The thoracic duct is removed en bloc along with all tissue dissected from the aorta, pericardium, pleurae, bronchi and right side of the trachea including all the mediastinal lymph node stations (**Figure 53.10**). A supra-azygous dissection is performed for middle-third oesophageal cancers or when staging investigations identify nodes above this level. It is not routinely required in lower-third cancers. The stomach is delivered into the chest, taking care not to twist the conduit. The stomach is divided to excise the cardia and proximal lesser curve with the oesophagus resection ensuring an appropriate margin from the primary tumour. The conduit must not be made too narrow as this will interrupt intramural vascular arcades and increase the risk of ischaemic necrosis of the anastomosis or conduit. The anastomosis is completed with a circular stapling device before closure of the gastrotomy. Hand-sewn anastomoses can also be used and there is no evidence to suggest either method is superior to the other.[56, 57]

A routine three-phase procedure with a neck dissection is not required unless the oesophageal lesion is in the upper



Figure 53.10 *En-bloc* resection of the oesophagus with delivery of the stomach into the chest prior to gastric division.

third or upper part of the middle third of the oesophagus. Routine three-field lymphadenectomy compared to two-field does not outweigh the potential increase in morbidity of the procedure from the extra thoracic dissection and neck dissection. Only minimal additional longitudinal resection is gained by this approach. Proponents highlight that cervical anastomotic problems cause less morbidity than intrathoracic leaks, although considerable reductions in overall anastomotic problems indicate that any such differences account for few patients. A left- or right-sided neck incision or a collar incision can be used to deliver the oesophagus and stomach into the neck and fashion an oesophagogastrostomy. Most surgeons use hand-sewn anastomoses in the neck although stapling techniques are also described.

Localized carcinoma of the hypopharynx or cervical oesophagus can be treated with pharyngolaryngo-oesophagectomy incorporating a radical neck dissection and a transhiatal oesophageal resection. Intraepithelial carcinomas of the upper oesophagus can also be considered for this approach.

Some surgeons approach lower- and middle-third cancers utilizing a left-sided thoracoabdominal incision. This route does not afford optimal access for either the formal abdominal lymph node dissection or the complete mediastinal lymphadenectomy. The transhiatal approach has a role in a selected group of patients. Some surgeons use this approach routinely although the ability to perform a radical mediastinal lymphadenectomy is considerably reduced. The technique has evolved from blind mediastinal dissection to several descriptions of dissection under vision.[58] Randomized trials comparing transhiatal and transthoracic resection have demonstrated improved survival in patients with oesophageal adenocarcinoma undergoing transthoracic resection, particularly in patients with limited nodal disease on histology.[30, 59]

Vagal-sparing resections and limited resections with jejunal interposition have been proposed as suitable alternatives for early disease on clinical staging.[30]

Minimally invasive oesophagectomy

Experience in minimally invasive oesophagectomy (MIO) techniques has increased over recent years, although publication of very few long-term results prevent definitive comparisons with open approaches.[60] It must be remembered that all the same oncological principles apply whether the adopted approach is open or minimally invasive.

Totally minimally invasive techniques involve laparoscopic gastric mobilization with thoracoscopic mediastinal dissection and oesophagus mobilization. Hybrid procedures utilize an open gastric mobilization and thoracoscopic mediastinal dissection, or a laparoscopic abdominal procedure followed by a conventional thoracotomy. The anastomosis can be performed in the chest through a mini-thoracotomy although is more commonly performed in the neck. The belief is that smaller incisions lessen the burden of the surgery on the patient, with less post-operative analgesia requirements, increasing mobilization and reductions in post-operative respiratory complications. One small, randomized trial has demonstrated a reduction in post-operative respiratory complication although it was not powered sufficiently to draw firm conclusions.[61] The UK national audit showed similar complication levels for open and MIO techniques.[54]

There are a few high-volume centres with experienced surgeons who achieve excellent results but this has not been reproduced countrywide. Complications specific to the MIO approach have been recognized including an increased risk of anastomosis and conduit problems. This has led to a refinement in techniques and an increase in the understanding of which patients are potentially suitable for such approaches. Overweight and obese patients create a particular challenge for laparoscopy due to the intra-abdominal fat obscuring tissue planes and the vascular arcade that requires preservation.

Robotic surgery has also been used in a few centres for oesophageal resection although such procedures remain in the remit of trials.[62] It will take many years to decide whether such techniques confer benefit in the recovery period without compromising long-term survival.

Endoscopic mucosal resection

Limited intramucosal disease where there is no evidence of nodal disease on CT or EUS can be resected using EMR. EMR is often performed as a diagnostic procedure but, provided depth of invasion is confined to the mucosa and both deep and lateral margins are clear, it can be considered a curative treatment. The procedure is performed under sedation. The submucosal layer is injected with Volplex®, indigocarmine dye and adrenaline. This lifts the lesion from the underlying muscle layer. The lesion is then removed either by applying suction and cautery with a cap device attached to the flexible endoscope, or by applying suction and a band below the lesion before excision (**Figure 53.11**).[63, 64]

Intensive endoscopic surveillance every 3 months is required with targeted biopsies at the EMR site to diagnose any dysplasia or recurrence as this is a relatively

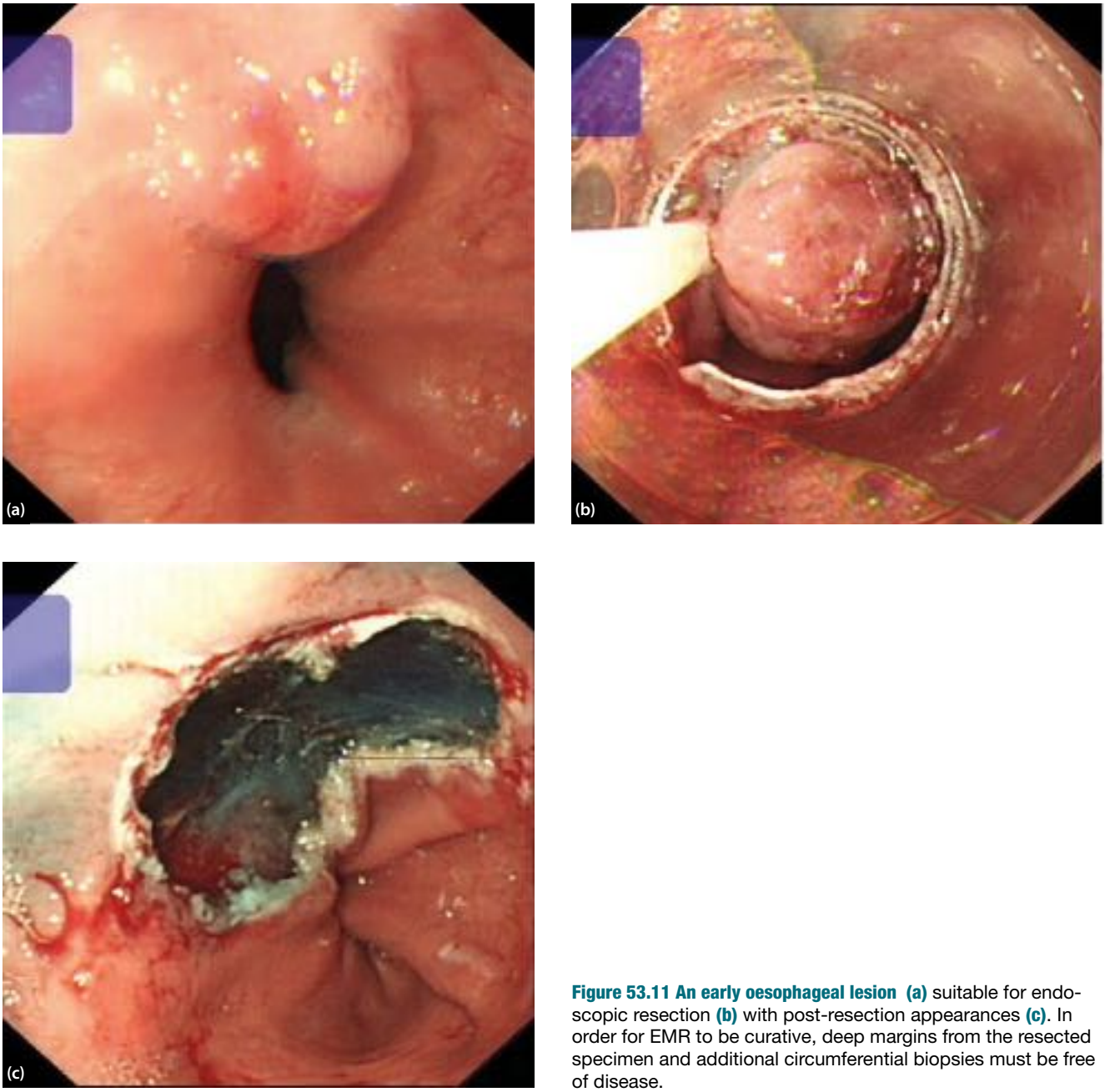


Figure 53.11 An early oesophageal lesion (a) suitable for endoscopic resection **(b)** with post-resection appearances **(c)**. In order for EMR to be curative, deep margins from the resected specimen and additional circumferential biopsies must be free of disease.

new treatment strategy and long-term results are few.[65] Evidence shows that the risk of lymph node metastases in the context of mucosal disease is negligible which is why this strategy has become feasible.[66, 67] If margins are positive, repeat EMR can be performed although surgery should also be considered. If circumferential margins are positive for dysplasia only (low-grade or high-grade) and all visible disease has been removed, the remainder of the oesophagus can be treated with RFA. Surgery should still be considered in young patients with high-grade dysplasia at the margins and in patients where there is evidence of multifocal high-grade dysplasia. Surgical resection is recommended because of the higher risk of lymph node involvement for oesophageal cancer with submucosal involvement although endoscopic submucosal dissection is technically feasible.

Definitive chemoradiotherapy

Definitive treatment with radical, concurrent chemoradiotherapy has been used with curative intent in oesophageal squamous cell carcinoma where total disease length does not exceed 10 cm. The evidence to compare this strategy to neoadjuvant treatment and surgery is sparse. No substantial evidence exists to support such an approach for adenocarcinoma. Often the choice of definitive chemoradiotherapy depends on the local expertise and the discussions between patient, clinical oncologist and surgeon. Patients who are not fit enough to undergo surgical resection might still be fit enough to tolerate definitive chemoradiotherapy. Studies have failed to identify conclusively for which particular patients definitive chemoradiotherapy might be a suitable curative option.

Salvage oesophagectomy remains an option in selected patients treated with definitive chemoradiation who fail to respond completely or demonstrate evidence of locoregional recurrent disease on follow-up.

Palliative treatments

Palliative chemotherapy and chemoradiotherapy can be used in patients with non-curative oesophageal adenocarcinoma and squamous cell carcinoma. External beam or endoluminal radiotherapy can be delivered to reduce tumour burden. Oesophageal stents are inserted to palliate dysphagia in patients with non-curative disease who are unsuitable for or opt against chemoradiotherapy.[68, 69] Stents should not be inserted in operable tumours because of the risks of perforation that would render the cancer incurable and also because of the transmural inflammation that inevitably results.

KEY POINTS

- Oesophageal adenocarcinoma continues to increase in incidence and accounts for the majority of oesophageal cancers in the Western world.
- Centralized units coordinate complete endoscopic and radiological staging with assessment of patient fitness through timed walking tests and cardiopulmonary exercise tests.
- Intramucosal disease might be suitable for endoscopic mucosal resection with follow-up endoscopic surveillance.
- Most patients with potentially curative disease have evidence of nodal disease or at least T3 depth of disease at presentation and receive neoadjuvant or peri-operative chemotherapy prior to surgery.
- Two-stage oesophagectomy with a radical lymphadenectomy has been shown to improve outcomes for lower-third adenocarcinoma.
- Experience with minimally invasive surgery techniques is increasing although a definite benefit has not been demonstrated and long-term outcomes are yet to be reported.
- Definitive chemoradiotherapy is an option in squamous cell carcinoma.
- Palliative treatments include chemotherapy, internal or external beam radiotherapy and endoluminal stents.

OESOPHAGEAL PERFORATION

Oesophageal perforation remains a rare condition and still has high mortality.[70] Spontaneous perforation (Boerhaave syndrome) occurs in an otherwise normal oesophagus.[71] Iatrogenic perforation can occur in a variety of procedures, particularly therapeutic flexible endoscopy, diagnostic or therapeutic rigid endoscopy or during revisional antireflux surgery. Increasing chances of a successful outcome depends upon a high index of suspicion, prompt resuscitation and investigation, with early transfer to a specialist oesophageal unit. The degree of pleural and mediastinal contamination in conjunction with the presence of systemic sepsis determines whether patients require surgery or can be managed non-operatively. Perforations of the cervical oesophagus are more likely to have successful non-operative management provided there is no mediastinal contamination. Non-operative approaches require intensive observation and reassessment of the patient (**Box 53.3**). A feeding jejunostomy can be inserted via a mini-laparotomy and is the preferred option for enteral nutrition access although a nasojejunal tube could also be considered.

BOX 53.3 Non-operative management of oesophageal perforation

- Nil by mouth
- Intravenous fluids
- Intravenous proton pump inhibition
- Intravenous antibiotics
- Intravenous antifungals
- Opiate analgesia
- Prophylactic low molecular weight heparin
- Nasogastric decompression (endoscopically or radiologically placed)
- Consider intercostal chest drain
- Enteral nutrition (feeding jejunostomy or nasojejunal tube)
- Regular reassessment in high-dependency environment

Surgery for perforation involves repair of the oesophageal defect following thorough debridement and lavage of mediastinal and pleural contamination of the mediastinum and pleura. Repair over a T-tube provides a controlled oesophagocutaneous fistula and is a good option in most, although primary repair has been used in some cases with success. Intercostal muscle flaps can be used as reinforcement. Oesophageal stents of varying types have been reported with varying success.[72] Stents are unlikely to hold position in an otherwise normal oesophagus, as there is not a stricture to hold the stent in place. Stents expose patients to complications of migration, bleeding and later stricture formation. They should not be inserted routinely in perforations as there is a lack of evidence to suggest healing rates and outcomes are improved. Many of the publications report on stent use in the context of adjunct drainage procedures. It is difficult to assess whether the control of sepsis through drainage or the stent contributes more to the healing in these situations.

KEY POINTS

- Recognizing oesophageal perforation requires a high index of suspicion.
- Prompt resuscitation, investigation and referral to a specialist centre are advised.
- The choice between non-operative and operative management depends on the degree of contamination and the presence of sepsis.
- Placement of oesophageal stents remains unproven and controversial.

FOREIGN BODY INGESTION

Ingested foreign bodies and food boluses can impact in the oesophagus. Foreign body ingestion is most commonly seen in children but also in patients with psychiatric conditions. Food bolus obstruction can occur in

any patient group. It is sometimes associated with an underlying Schatzki ring, peptic stricture or eosinophilic oesophagitis and occasionally is the first presentation of a malignant stricture. Initial investigations include anteroposterior and lateral plain radiographs, although some radiolucent objects will not be identifiable. CT can also be considered. Airway difficulties, absolute dysphagia, ingestion of sharp objects or button batteries, and prolonged impaction are indications for intervention. Rigid oesophagoscopy in experienced hands is appropriate to locate and retrieve impacted objects in the pharynx and cervical oesophagus. Care must be taken to avoid iatrogenic oesophageal perforation. Flexible endoscopy is the investigation of choice and allows for therapeutic intervention. It has a lower risk of perforation compared to rigid oesophagoscopy. Pushing a food bolus distally without having first passed the endoscope beyond the bolus should be avoided as it increases the risk of perforation.

MOTILITY DISORDERS

Achalasia

Achalasia is an uncommon condition with an annual incidence of 1 in 100 000. It is seen in both men and women, most frequently in middle and older age groups. Achalasia results from degeneration of the ganglionic neurons within the myenteric plexus and is characterized by a failure of relaxation of the lower oesophageal sphincter on swallowing with absence of peristalsis in the oesophagus. This can be associated with a higher resting tone in the oesophagus. Primary achalasia is idiopathic in aetiology while secondary achalasia occurs in Chagas' disease and following antireflux surgery with creation of a fundoplication wrap that is too tight.

PRESENTATION

Patients most often present with dysphagia to liquids and solids. Some present with symptoms of regurgitation or recurrent chest infections resulting from aspiration of stagnant oesophageal content. Retrosternal chest pain is a feature of a specific type of achalasia (vigorous achalasia) as a result of simultaneous, strong peristaltic contractions. Weight loss is a feature of long-standing achalasia.

INVESTIGATION

Investigation should start with a flexible endoscopy. It is important to exclude cancer as the underlying problem as many of the symptoms are common to both diagnoses. Endoscopic appearances in early achalasia can be completely normal. Features supporting a diagnosis of achalasia include a tight oesophagogastric junction, a dilated oesophagus or food within the oesophagus. A barium swallow in advanced cases will demonstrate delay in passage of barium across the oesophagogastric junction, possibly within a dilated oesophagus that fails to show any peristaltic activity (**Figure 53.12**). Confirmation of the diagnosis is provided by oesophageal manometry (**Figure 53.13**).

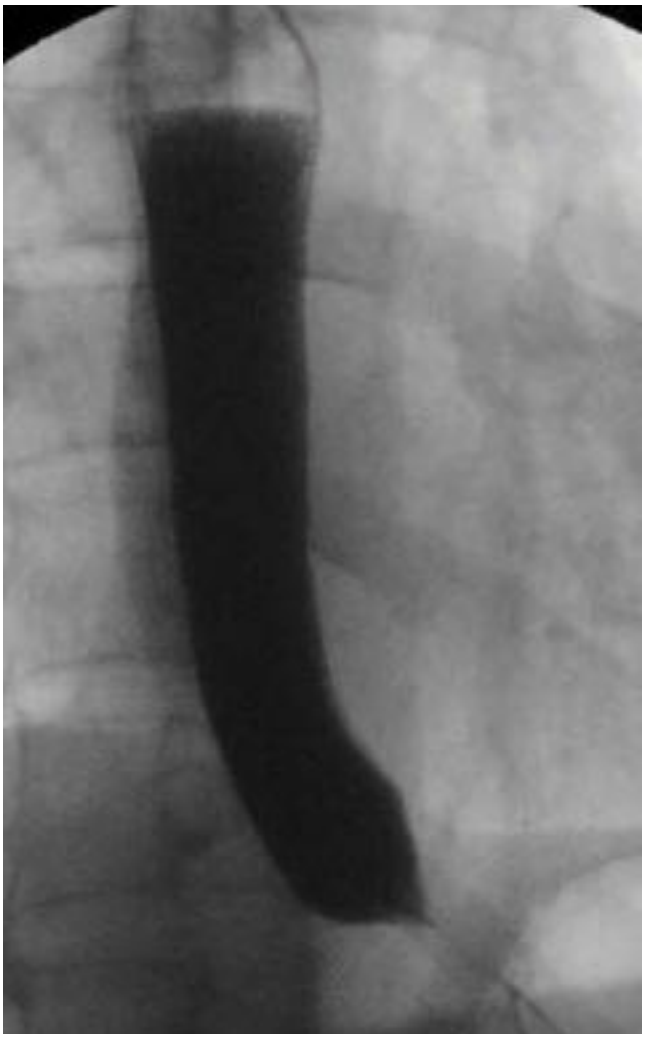


Figure 53.12 Barium swallow showing the classical bird's beak appearance in achalasia with a dilated, non-peristaltic oesophagus tapering towards a lower oesophageal sphincter that fails to relax.

Recent results with high-resolution manometry suggest there are several subtypes of achalasia that may respond differently to treatment.[73]

MANAGEMENT

The two main treatment options are endoscopic balloon dilatation or cardiomyotomy.[74–76] Results from a European multicentre randomized trial did not demonstrate differences in treatment efficacy at 2 years (93% balloon dilatation versus 90% laparoscopic cardiomyotomy) or in the occurrence of gastro-oesophageal reflux after treatment.[77]

Successful and safe balloon dilatation requires experienced endoscopists. The procedure is performed under sedation as a day-case procedure with image intensification used to ensure complete effacement of the balloon waist. The balloons are of fixed diameter with initial dilatation performed with a 30 mm size. Sequential dilatation can be performed if necessary after several weeks with a 35 mm and a 40 mm balloon. The main risk is of perforation and this risk increases with the larger diameter balloons.

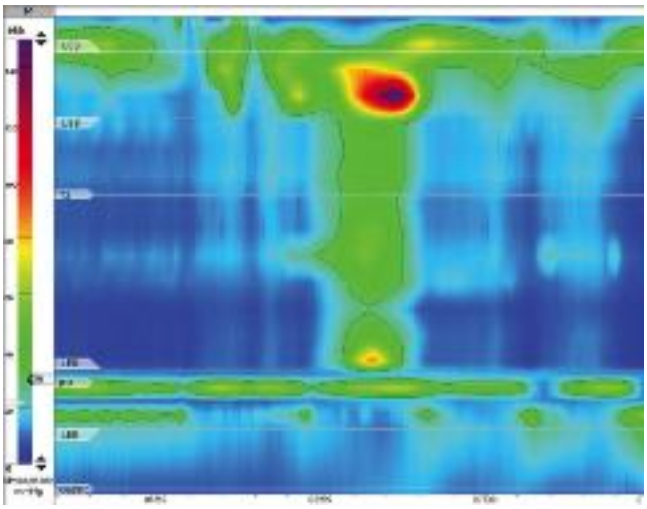


Figure 53.13 High-resolution manometry appearances of achalasia (type 2) with oesophageal compression. Pan-oesophageal pressurization can be seen in the oesophageal body between the higher pressure bands of the upper and lower oesophageal sphincters. The lower oesophageal sphincter fails to relax with swallowing.

Cardiomyotomy is performed laparoscopically and some surgeons combine this with a partial fundoplication intended to reduce the incidence of post-operative reflux.[78] The muscles are split for 5 cm along the oesophagus with the myotomy extended into the cardia for 3 cm. There is a risk of mucosal perforation with the procedure but this can be managed conservatively in most cases.

A newer technique of endoscopic myotomy has been developed in Japan and is being evaluated in randomized trials against balloon dilatation and cardiomyotomy.[79–81] It is performed under general anaesthesia and involves creation of a submucosal tunnel with an endoscope before division of the fibres in the circular muscle layer.

Endoscopic injection of botulinum toxin into the lower oesophageal sphincter is not a long-term solution. It has significant early failure rates and should be considered only in frail patients unsuitable for the other treatment modalities.[82]

SURVEILLANCE

Patients with achalasia should be enrolled on endoscopic surveillance programmes because of the increased risk of developing both squamous cell carcinoma and adenocarcinoma.[83, 84] Whether successful treatment alters this risk is currently not known.

KEY POINTS

- Achalasia requires investigation with endoscopy, barium swallow and manometry.
- Results from balloon dilatation and laparoscopic cardiomyotomy are equivalent so treatment depends on the available expertise.
- Achalasia patients should undergo endoscopic surveillance because of an increased risk of developing oesophageal cancer.

Diffuse oesophageal spasm

Diffuse oesophageal spasm is a rare condition characterized by non-peristaltic high-pressure contractions of increased duration. These occur in the smooth muscle of the lower two-thirds of the oesophagus. Symptoms are predominantly of severe retrosternal pain during swallowing and can occur in conjunction with dysphagia.

INVESTIGATION

Non-oesophageal causes of these symptoms need to be excluded. The diagnosis is evident on manometry when high-amplitude simultaneous contractions are measured within the oesophagus following an apparent normal swallow. This does rely upon patients experiencing symptoms during the 10 swallows of the investigation. Further investigation with ambulatory manometry might be required.[85] Occasionally evidence of such spasm is identified during a barium swallow.

MANAGEMENT

Treatment options aim to induce smooth muscle relaxation and include calcium channel blockers such as nifedipine, nitrates and botulinum toxin although results are variable. Surgery is rarely undertaken in these patients but one option is to perform a long oesophageal myotomy.[86]

Nutcracker oesophagus

This is a rare condition characterized by severe retrosternal pain during swallowing similar to diffuse oesophageal spasm. The diagnosis is made by demonstrating normal peristalsis with higher than normal amplitude contractions on manometry.

Eosinophilic oesophagitis

Eosinophilic oesophagitis is an increasingly recognized condition. Clinical symptoms relate to oesophageal dysmotility. Endoscopic features can include fixed oesophageal rings, luminal narrowing, furrows or exudates evident on flexible endoscopy.[87] Biopsies show eosinophilic infiltration within the oesophageal epithelium. Reflux disease should be excluded as the underlying cause. Treatment strategies are evolving and include topical steroids, avoidance of any identifiable food allergens and cautious dilatation of strictures.

Oesophageal diverticulae

Diverticulae are infrequently found in the oesophagus on flexible endoscopy. These are mostly asymptomatic. Congenital diverticulae are rare. Of acquired diverticulae, these are mostly of pulsion type where incoordinated peristalsis and functional obstruction lead to increased pressure at a specific point in the oesophageal wall. Most such diverticulae occur in the lower parts of the oesophagus and rarely need any specific treatment.

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All endoscopic and operative pictures are courtesy of Professor S Michael Griffin.

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CHAPTER 54

NEUROLOGICAL DISEASE OF THE PHARYNX

Kim Ah-See and Miles Bannister

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: pharynx, pharyngeal disease, neurological disorders and nervous system. Articles are included that are systematic reviews and meta-analyses of systematic reviews from four medical journals: *British Medical Journal*, *Lancet*, *New England Journal of Medicine* and *Journal of the American Medical Association*.

INTRODUCTION

A wide range of neuromuscular diseases can affect the pharynx. The primary function of the pharynx is swallowing. Different phases of swallowing are affected by different conditions, depending on which of the cranial nerves are involved. These diseases can also manifest as difficulties with breathing and speaking. Symptoms may arise in conjunction with anatomical variations, from congenital or acquired diseases.

ANATOMY AND PHYSIOLOGY

The reader is referred to a detailed discussion of the relevant anatomical details and physiology of swallowing in Chapter 47, Anatomy of the pharynx and oesophagus, and Chapter 48, Physiology of swallowing. A good understanding of these concepts is a necessary prelude to understanding management of neurological diseases of the pharynx.

SYMPTOMS

The principal symptoms of neurological dysfunction affecting the pharynx include:

- dysphagia
- odynophagia
- aspiration
- coughing
- choking
- throat clearing
- nasal regurgitation
- 'wet' voice.

Dysphagia is the principal symptom and can be due to a structural problem as well as a neurological one. History taking and physical examination are accompanied by endoscopy. Details of chronology, the effect of different food consistencies, exacerbating and improving factors and particularly past medical history help the clinician formulate a diagnosis. Oral cavity and cranial nerve examination are important in assessing neurological disease of the head and neck. Examination of the face and limbs can elicit muscle wasting and fasciculation.

EXAMINATION

General examination of the patient can yield information about the likely underlying pathology for the reported swallowing difficulties. Paucity of facial expression suggests Parkinson's disease whereas facial weakness and grade of this suggests a stroke and the time elapse since onset. Inspecting for mobility aids (walking stick, walking

frame, wheel chair) and a tracheostomy also provides an indication of disease severity that may relate to the degree of swallowing dysfunction.

Patients' gait patterns may correspond to certain neurological diseases. A festinating gait can be characteristic of Parkinson's disease as can a broad-based gait in cerebellar dysfunction. Fatigability can accompany advanced Myasthenia gravis, though will also be present in patients with advanced osteoarthritis and those with intermittent claudication secondary to peripheral vascular disease.

Certain distinctive patterns of speech may be present in those patients with advanced cases of neurological disease. Dysarthric (slurred) speech is the commonest speech pattern present in neurological disease and is associated with cerebrovascular accidents, cerebellar disease, Parkinson's and motor neurone disease. 'Wet' or 'moist' speech can develop in patients with Parkinson's disease due to poor oral phase control, though this does develop in cases of head and neck trauma and presbyphagia. It is usually associated with aspiration. Patients' suffering with bulbar palsy (affecting the IXth, Xth, XIth and XIIth cranial nerves) can develop a nasal quality to their speech. The aetiology of this condition is primarily a lesion of the medullar oblongata, though local tissue infarction and demyelinating diseases are also causes. Those with pseudobulbar palsy may demonstrate 'Donald Duck' speech due to alaryngeal vocalization using the buccal area.

Formal neurological examination may or may not elicit the signs described later in this chapter. Cranial nerve examination, particularly of the lower cranial nerves, provides the most useful and familiar assessment to the otolaryngologist in this area. Unilateral or bilateral fasciculation or even wasting of the tongue or soft palate, secondary to progressive deinnervation of the muscles will affect the oral and pharyngeal phases of swallowing. Flexible nasolaryngoscopy is useful in identifying these changes in the pharyngeal constrictor muscles and identifies other abnormalities including vocal cord palsy, polling within the pyriform fossae and laryngeal penetration that contribute to the overall assessment of patients' swallowing abilities.

INVESTIGATIONS

Swallowing assessment and endoscopy

Swallowing assessment is complemented by functional endoscopic evaluation of swallowing (FEES). The pharynx and larynx are visualized through an endoscope while boluses of different volumes and consistencies are swallowed. These endoscopies may be performed at bedside, if tolerated by the patient, limiting the need for transport to a radiology department, possibly in a different hospital.[1] Images may be recorded and transferred for discussion and review. FEES may be performed by appropriately trained speech and language therapists. Views of bolus and saliva retention in the hypopharynx can be achieved, which may not be possible in videofluoroscopy.[1] The disadvantages are obstruction of the operator's view due to food and fluid in the pharynx and when the pharynx closes, limiting assessment of the pharyngeal phases of swallowing. The oesophageal phase cannot be viewed either, though the upper oesophageal lumen can be visualized.

Videofluoroscopy

Videofluoroscopy is the gold-standard investigation in assessing neurological disease of the pharynx. Videofluoroscopy was initially developed in 1965 and involves recording fluoroscopic images that appear on a monitor of a patient ingesting a radio-opaque bolus.[2] This demonstrates the dynamics of the swallowing mechanism and allows speech and language therapists to assess swallowing problems and identify techniques for a safer swallow for the patient.

The investigation can identify nasal regurgitation, poor pharyngeal contraction, retention of the food bolus within the vallecula and pyriform sinus, and problems with opening of the upper oesophageal sphincter. Videofluoroscopy is particularly useful in identifying 'silent' aspiration, pre-, intra- and post-deglutitory.[1]

The patient is placed in an anterolateral position and anatomical landmarks are identified. Administration of the bolus begins with minimum quantities to avoid the risk of inhalation and may be increased as the consistency of the patient's swallow is assessed. Liquid, semi-liquid and solid boluses can be provided. An anteroposterior image recording can assess for asymmetry in movement or stasis of the bolus.[1]

Radiation exposure is limited in videofluoroscopy and the recorded images can be viewed repeatedly and transferred between clinicians and centres.[1] It supplements the clinical examination in those patients with reflex mandibular closure and aids treatment planning.[3] 'Reflex mandibular closure' is different from the gag reflex and is a sign of neurological disease, whereby patients are unable to maintain mouth opening, rather than reacting to oropharyngeal stimulation. No direct view of the passage of the food bolus is provided, however, and videofluoroscopy cannot be performed at the patient's bedside, requiring transfer to a radiology department. The general physical state of the patient may prevent investigation and compliance with instructions. Interpretation of the images recorded may vary considerably.[1]

ACQUIRED CONDITIONS

NEUROMUSCULAR DISEASE

Multiple sclerosis

Multiple sclerosis results from inflammatory demyelination of neurons within the central nervous system. Progressive and relapsing–remitting forms of the disease have been identified, the former of which generally has a poorer prognosis. The greatest incidence is in younger adults, particularly those of Western European origin and in areas between latitudes 40 °N and 40 °S. Definite diagnosis requires evidence that two or more areas of the central nervous system are affected on different occasions.

Cerebrospinal fluid testing may reveal oligoclonal bands of immunoglobulin G.

Dysphagia results when the brainstem and/or the corticobulbar tracts are affected. Dysphagia typically presents in advanced cases of the disease, while choking is more a feature of the earlier stages. Percutaneous gastrostomy feeding may therefore be required. Videofluoroscopy reveals a delayed swallowing reflex and loss of pharyngeal peristalsis.

Management includes corticosteroid medicines and β-interferon. While multiple sclerosis itself is not a terminal condition, many sufferers succumb to pneumonia due to poor coughing mechanisms and uraemia as a result of urinary retention and renal failure.

Parkinson's disease

Parkinson's disease results from degeneration of the substantia nigra in the zona compacta, leading to a reduction in the neurotransmitter dopamine within the brain. Symptoms develop around 45–65 years of age. The disease is overwhelmingly idiopathic without any aetiological cause, though manganese, carbon monoxide and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) narcotic can be implicated in its development. Diagnosis is based primarily on the clinical features displayed by patients including rigidity, bradykinesia, tremors and poor posture stability.

Swallowing initiation slows and bolus stasis in the pyriform fossae results.

Levodopa remains a mainstay of treatment as do anticholinergic agents and dopamine agonists. Selegiline and amantadine inhibit dopamine metabolism and improve milder symptoms, respectively. Catechol-O-methyltransferase (COMT) inhibitors reduce levodopa metabolism, prolonging the effect. Deep brain stimulation surgery is available.[4]

Myasthenia gravis

Myasthenia gravis results from autoimmune IgG antibodies developing against acetylcholine receptors at the end plate of the neuromuscular junction. Nerve impulse conduction is slowed and weakened as a result. Voluntary muscle weakness develops with diplopia and ptosis in cases of orbital muscle involvement. Classically symptoms are reported to improve following periods of rest and worsen with periods of repetitive action. Patients may present with dysphagia, dysphonia or nasal regurgitation alone having previously been well and deterioration in symptoms correlates with advancement of the disease. Electrophysiology testing reveals muscle fatigue following stimulation and serum acetylcholine receptor antibodies may be detected.

Videofluoroscopy reveals reduced pharyngeal mobility and aspiration.

Management includes cholinesterase inhibitors, edroponium, corticosteroids and other immunosuppressive agents. Thymus excision may benefit those patients with a thymoma because of the causative effect of the tumour.

Motor neurone disease

Motor neurone disease describes a collection of diseases that affect motor nervous fibres, including progressive bulbar palsy, pseudobulbar palsy, primary lateral sclerosis, amyotrophic lateral sclerosis and progressive spinal muscle atrophy. Difficulties in swallowing, chewing, coughing, talking and breathing develop in addition to limb weakness, limb stiffness, muscle wasting and fasciculation. Motor neurone disease is progressive with death most commonly resulting from pneumonia.

Dysphagia and aspiration result if the corticobulbar tract is affected. The disease is aggressive (death from the amyotrophic lateral sclerosis results within 5 years of symptom onset) and early gastrostomy insertion should be considered to prevent aspiration pneumonia, as dysphagia develops within months of diagnosis or may be the presenting symptom.

Guillain Barré syndrome

Guillain Barré syndrome, also described as acute idiopathic polyneuropathy, results from multifocal demyelination of the cranial nerves and immune cell-mediated damage to nerves, usually following a preceding infection or immunization. Both motor and sensory function deteriorates, usually in an ascending and symmetrical pattern with peripheral regions of the body being affected initially. Motor function deterioration is usually more prominent. Respiration and swallowing function can be affected, though not universally.

Cerebrospinal fluid analysis reveals high protein concentrations. The prognosis is generally good though recovery may be prolonged. Up to 20% of sufferers may be left with residual disability.

Muscular dystrophy

Muscular dystrophy is a collection of myopathic disorders that result in muscle wasting. This leads to continued muscle contraction following withdrawal of the initial nerve impulse producing further muscle weakness. Duchenne muscular dystrophy has the worst prognosis with rapid progression; death results within 15 years of symptom onset due to respiratory failure and pneumonia when the respiratory muscles become affected. Other types are more benign with slower rates of progression. Muscle biopsy and electromyography confirm the myopathic nature of the disease.

The soft palate is usually affected with regard to swallowing, producing dysphagia and nasal regurgitation. Sensation is maintained. Videofluoroscopy reveals muscle paralysis leading to nasal regurgitation and aspiration. No treatment for muscular dystrophy exists though physiotherapy and speech and language therapy maintain function and slow symptom progression.

STROKE

Cerebrovascular events are the commonest neurological disorders of the pharynx. Patients may suffer with

both dysphagia and aspiration. Nerve injury results from infarction or, less commonly, haemorrhage. Patients typically present with sudden onset of neurological deficits, the signs of which reflect the area of the brain affected. Patients commonly have a past medical history of atherosclerosis, hypertension, diabetes mellitus or heart valve disease. Infarction risk is uniform throughout the cerebral vasculature.

Dysphagia can be the sole symptom of an event affecting the brainstem, with videofluoroscopy demonstrating asymmetrical movement and poor bolus transit. CT imaging of the head distinguishes between an infarction and haemorrhage. Management involves anti-platelet therapy and control of risk factors to prevent reinfarction in particular, including statin use to reduce blood cholesterol levels.[5–7] Thrombolysis has an increasing role in treating ischaemic strokes that present sufficiently early. Patients may be suitable for carotid artery surgery if symptoms are transient, which may be offered as an urgent or emergency operation.[8] The overall prognosis for survival is better for those suffering an ischaemic than a haemorrhagic stroke, though the risk of recurrence is greater in such patients, as is the risk of myocardial infarction.

INFECTIOUS DISEASE

Polio

Polio is caused by poliovirus that destroys neurons within the anterior horn cells of the spinal cord. The brainstem may also be affected. Dysphagia develops slowly and steadily when the pharyngeal muscles are affected, often years after the original infection. The disease is rare in the developed world but remains endemic elsewhere, such as in parts of Asia and Africa.

Herpes zoster

Herpes zoster results from *Varicella zoster* virus infection, which remains in the dorsal root ganglia and cranial nerve ganglia in a latent state. Reactivation can lead to palsies of the lower cranial nerves. Disease manifestation is commoner in patients over 60. Treatment includes famciclovir or acyclovir antiviral agents. The disease has equal prevalence throughout the world.

Diphtheria

Diphtheria results from *Corynebacterium diphtheria* bacterial infection, which produces a neurotoxin that can ultimately lead to pharyngeal weakness. Infection of the pharynx may also cause airway obstruction. The treatment includes antitoxin and penicillin antibiotics. A vaccination based on the toxin is available. The disease is commoner in the developing world.

Rabies

Rabies is caused by a viral infection residing in feral animals. The virus infects the neurons of the central nervous system, through which it spreads. Laryngopharyngeal spasm can result as can fasciculation of the pharyngeal muscles. This severely limits the patient's ability to swallow, leading to aspiration. Rabies has been eradicated in much of the developed world but is endemic elsewhere. It can be successfully treated with vaccination and specific immunoglobulin administration.

Botulism

Botulism results from bacterial toxins released from *Clostridium botulinum* that weaken the muscles supplied by the lower cranial nerves. Patients present with dysphagia. The disease can be successfully treated with a specific antitoxin.

NEOPLASTIC DISEASE

Nasopharyngeal carcinomas and particularly skull-base tumours compress and invade the lower cranial nerves producing a variety of symptoms. MRI and CT scanning of the anterior cranial fossa, brain and temporal bone should follow the appropriate clinical examination. Surgery or radiotherapy can then be considered. A variety of jugular foramen syndromes exist, described in **Table 54.1**. A small number of paraneoplastic syndromes have been associated with neurogenic dysphagia including squamous cell carcinoma of the skin, transitional cell carcinoma of the bladder, ovarian cancer, prostate cancer and chronic lymphocytic leukaemia.[9–13]

MISCELLANEOUS ACQUIRED CONDITIONS

Trauma and surgery

Blunt or penetrating trauma to the pharynx can injure the nervous supply as well as cause structural abnormalities through muscle injury. Iatrogenic surgical injury in thyroid, cardiothoracic, anterior cervical spine, carotid and oesophageal surgery can injure branches of the vagus nerve in particular.

TABLE 54.1 Jugular foramen syndromes

Syndrome	Cranial nerves affected	Aetiology
Vernet's	9, 10, 11	Aneurysms or tumours at the jugular foramen
Collet–Sicard	9, 10, 11, 12	Parotid tumours, chemodectomas or metastases at the posterior laterocondylar space
Villaret's	9, 10, 11, 12 Horner's syndrome	Parotid tumours, chemodectomas or lymphadenopathy at the posterior retroparotid space
Jackson's	10, 12 Corticospinal tract	Chordomas, metastases or schwannomas

Glossopharyngeal neuralgia

Glossopharyngeal neuralgia presents with stabbing pain in the oropharynx region innervated by the glossopharyngeal nerve. The cause is unknown but the symptoms may be attributed to Eagle's syndrome. Investigation for skull-base lesions may be required and, while surgery to remove an enlarged styloid process may treat the condition in cases of Eagle's syndrome, symptom control is usually achieved with carbamazepine.

Medication

Medications whose side effects result in depression of the central nervous system can make any dysphagia worse.

Old age

The oral phase of swallowing increases in old age and the first two stages become 'uncoupled', leading to the food bolus passing into the vallecula prior to laryngeal elevation. The food bolus volume necessary to stimulate pharyngeal swallowing may need to increase up to five times. Both these factors increase the risk of aspiration.

CONGENITAL CONDITIONS

A small number of neurodevelopmental disorders affect the function of the pharynx. Compression of nervous tissue is the principal cause of pharyngeal dysfunction.

In Klippel–Feil syndrome, the cervical vertebra fuse during growth, compressing the brainstem and injuring the nuclei of the lower cranial nerves, with concurrent shortening of the neck. In Dandy–Walker syndrome, cerebrospinal fluid flow out of the ventricular system is obstructed, leading to a cyst developing in the posterior cranial fossa that compresses the cortex and brainstem. Compression of the brain by an Arnold–Chiari malformation can cause brainstem herniation and injury. In syringomyelia, a cystic cavity remains in the medulla or upper spinal cord that enlarges to compress and injure the nerve tracts.

TREATMENT

The treatment of neurological disease of the pharynx centres on accurate diagnosis of the underlying cause and treatment of that cause. Specific otolaryngological interventions for those chronic conditions that cannot be treated centres on avoiding aspiration, with resulting pneumonia, and maintaining feeding. Both require a multidisciplinary approach and a crucial role is provided by speech and language therapists.

A variety of techniques can be deployed to these ends. Solid food chewing is preferable to liquid foods that are more easily aspirated. Neck flexion both aids swallowing and protects the airway. The Mendelsohn manoeuvre aids the opening of the pharyngo-oesophageal segment and coughing immediately after swallowing clears food from the laryngeal inlet, preventing aspiration. More detail on the subject of rehabilitation is presented in Chapter 55, Rehabilitation of swallowing disorders.

Support to control sialorrhoea medically is available.[14] Hyoscine (usually in patch form), glycopyrrolate (usually as oral solution) are most commonly used in the United Kingdom and are anticholinergic medications that antagonise the effects of acetylcholine at the muscarinic receptors. Other medications used are atropine, tropicaimide, hyoscyamine and tricyclic antidepressants, which all have anticholinergic properties.[14] Common side effects include xerostomia, urinary retention confusion and sedation and anticholinergic use is contraindicated in glaucoma and in those patients with established dementia.

Botulinum toxin (type A or type B) can be injected into the major salivary glands to reduce saliva production by inhibiting acetylcholine release from axonal endings at cellular neuromuscular junctions.[14] The dosage and duration of effect are variable but can be repeated. Ultrasound guidance improves gland localization, particularly in those that undergo atrophy with age or from repeated injection, and the accuracy of delivery.

Those patients who cannot tolerate swallowing safely will require a feeding tube to be placed. Short-term feeding needs can be satisfied with insertion of a nasogastric tube but patients with chronic or deteriorating swallowing problems with little hope of recovery will benefit more from a gastrostomy placement. Feeding usually takes place overnight for convenience to the patient.

Anxiety and depression must be recognized in patients at every stage of their problems and should be treated accordingly.

There is a specific role for surgery to 'normalize' the phases of swallowing. Vocal cord medialization techniques can aid airway closure in swallowing while cricopharyngeal myotomy or botulinum toxin injection into the muscle will treat spasm of the cricopharyngeus muscle. Tracheostomy insertion abates the risk of aspiration but interferes with the normal process of swallowing by fixing the position of the larynx. Rarely, total laryngectomy may need to be considered to eliminate intractable aspiration.

KEY POINTS

- The aetiology of neurogenic dysphagia and the clinical features of different neurological diseases should be considered when managing swallowing disorders.
- FEES assessment and videofluoroscopy are complementary in the assessment of patients' swallowing function.
- The management of neurogenic dysphagia is multidisciplinary and includes treatment of the principal aetiology, early speech and language therapist input to improve swallowing function and ensure a 'safe' swallow and consideration of additional interventions to prevent aspiration and maintain satisfactory feeding and nutrition.

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CHAPTER

55

REHABILITATION OF SWALLOWING DISORDERS

Maggie-Lee Huckabee and Sebastian Doeltgen

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SEARCH STRATEGY

Data in this chapter are based on several independent literature searches of the PubMed, Scopus and Google Scholar databases, which involved relevant keywords describing each intervention (e.g. effortful swallow, transcranial magnetic stimulation, transcranial direct current stimulation etc.) and outcome measure (e.g. pharyngeal pressure, motor evoked potential etc.). Furthermore, the reference lists of identified studies were searched for additional relevant publications.

INTRODUCTION

The clinical management of swallowing disorders has evolved over the last four decades to include ongoing development of compensatory and rehabilitative interventions designed to increase swallowing efficiency and safety. Initially, the clinical approach to managing swallowing disorders was largely characterized by strategies to compensate for impaired peripheral motor function. Many of these techniques remain a valuable asset in the clinical armamentarium for the short-term management of disordered swallowing. Since then, multidisciplinary clinicians and researchers have developed ever-increasing sophistication and specificity in the diagnosis and treatment of dysphagia. As diagnostic specificity is increasing, we are no longer applying traditional treatment approaches to patients in a 'one size fits all' approach.

Increased specificity will ultimately lead to improved rehabilitative outcomes, for two reasons. First, with greater diagnostic specificity we will be able to tailor compensatory and rehabilitative efforts to directly address the underlying impairment of any given patient. One example of this is the clinical application of a technique known as thermal–tactile application (TTA) of the faucial pillars. This technique was originally developed to facilitate initiation of pharyngeal swallowing[1] and was applied to any patient presenting with preswallow pharyngeal pooling. It stands to reason that only patients presenting with pharyngeal pooling secondary to sensory impairment would benefit from this sensory-based technique, not those presenting with underlying motor impairment. Thus, careful scrutiny of the underlying impairment and consequent selection of the right treatment for the right problem is likely to increase the rehabilitative effectiveness of TTA.

Second, increasing diagnostic precision will improve patient outcomes by decreasing the likelihood for causing harm. For example, the technique of effortful swallow, historically applied as a compensatory technique to facilitate bolus clearance during swallowing,[2, 3] is now increasingly being used as a rehabilitation approach.[4, 5] Repeated swallowing with effort is presumed to strengthen pharyngeal contraction, much like repeatedly lifting weights will increase arm muscle strength. However, studies have now demonstrated that effortful swallowing may in fact impair, not facilitate, anterior hyoid movement during swallowing in some patients due to an imbalance of anterior and posteriorly oriented forces acting on the hyolaryngeal complex during swallowing.[6] A subsequent case study has documented the potential for effortful swallowing to impair movement patterns at the base of the tongue, resulting in nasal redirection.[7] Similarly, the Mendelsohn manoeuvre was originally designed to increase airway protection through volitionally prolonging swallowing-related suprahyoid contraction at the point of maximal hyolaryngeal excursion.[3, 8] Recent evidence obtained using high-resolution pharyngo-oesophageal manometry demonstrates that, while pharyngeal bolus passage may be aided by increased and prolonged pharyngeal pressure generation, proximal oesophageal peristalsis is significantly decreased

during Mendelsohn manoeuvre swallows.[9, 10] Meticulous evaluations of both short- and long-term effects of these manoeuvres, and others, are required.

Our current state of the art in dysphagia rehabilitation is quickly broadening from an almost exclusive approach of peripheral muscle strengthening to incorporate techniques designed to maximize central control mechanisms. This chapter provides a cursory introduction to the established muscle-strengthening techniques for which a supportive evidence base has been reasonably established. Then we look ahead with a preview of exciting new developments in cortical modulation that are likely to move into clinical application once a supporting evidence base is available.

CURRENT REHABILITATION APPROACHES

Oral motor exercises

Speech pathology has a long history of therapeutic efforts aimed at increasing the strength and efficiency of oropharyngeal movements. Originally, these were developed for improving articulatory precision related to speech. Subsequently, these exercises were logically expanded and transferred to swallowing rehabilitation, with the goal of improving oral phase movements and facilitating tongue-driving forces involved in pharyngeal phase swallowing. Although these techniques have been around for decades, only recently has their efficacy for improving functional swallowing been systematically investigated. The development of a handheld manometric device, known as the Iowa Oral Performance Instrument (IOPI), facilitated the evaluation of oral motor exercise (OME) in swallowing rehabilitation. Regular OME using this device and performed prophylactically by healthy elderly individuals can increase swallowing and isometric peak pressures following a 9-week exercise regimen.[11] This was accompanied by an increase in lingual volume. Of note, the beneficial effects of regular OME do not necessarily rely on using the IOPI for training; they can also be achieved by standard tongue strength exercises using a tongue depressor.[12] A study evaluating the effects of OME in patients documented that an 8-week isometric lingual exercise regimen using IOPI as biofeedback modality increased isometric and swallowing pressures for some bolus conditions in patients presenting with dysphagia following stroke.[13] It has also been demonstrated that tongue strength measured using the IOPI is significantly correlated with oral phase dysphagia following stroke[14] and longer meal times in residential age care.[15]

Effortful swallow

First introduced as a compensatory technique by Kahrilas and colleagues,[2, 3] the instructions for this technique are simply to 'swallow hard'. With increased effort resulting in increased pressure on the bolus, this technique was routinely applied to reduce pharyngeal residue in patients with pharyngeal motility disorders. A considerable body of research has documented the potentially positive effects of increased pharyngeal pressure associated with effortful swallowing.[6, 9, 10, 16–24] However, subsequent research now demonstrates that simply 'swallowing hard' is not as benign as it may seem.

A potential complication of the effortful swallow was documented to be decreased anterior hyoid movement during swallowing.[6] Biomechanically, this observation is likely linked to the relative imbalance in the opposing muscles that act on the hyoid during swallowing. Anterior pull of the relatively small floor of mouth muscles may be outweighed by posteriorly oriented forces exerted by the much larger pharyngeal constrictors and suprahyoid muscles (posterior belly of digastric, stylohyoid). Due to the synergistic coordination of the oropharyngeal swallowing process, it is likely that during effortful swallowing, **all** muscles involved in swallowing exert a greater degree of contraction. With regard to the movement of the hyolaryngeal complex, this would lead to a biomechanical imbalance resulting in a stronger net posterior hyoid displacement compared to non-effortful swallows. A further single case study of a young patient with brainstem tumour resection experienced increasing nasal redirection on initiation of effortful swallowing that subsided when the technique was discontinued.[7] In young healthy women, effortful swallowing was shown to increase sympathetic cardiac modulation, a sign of cardiac overload.[25] These studies require replication but should prompt clinicians to understand that, if a technique is powerful enough to effect a positive change, it may also be powerful enough to effect a negative change. It is critical to understand which direction our interventions take on not only the physiological feature of interest but other biomechanical and (neuro-)physiological processes as well.

Mendelsohn manoeuvre

Another technique, which was originally introduced as a compensatory technique but which is now being employed as a rehabilitative approach, is Mendelsohn manoeuvre.[8] Following initiation of swallowing, peak hyolaryngeal excursion is maintained for several seconds before relaxing and completing the swallow. The presumed benefit of this manoeuvre is prolonged suprahyoid contraction, which subsequently results in prolonged upper oesophageal sphincter (UOS) opening for improved bolus flow into the oesophagus. Repeated performance of this manoeuvre is now thought to result in improved cricopharyngeal compliance. In 1990 Logemann and Kahrilas[8] were the first to report the biomechanical effects of the Mendelsohn manoeuvre in a single case report of a patient presenting with dysphagia following lateral medullary infarct. Swallowing efficiency improved greater than twofold over other techniques in this patient. Subsequent basic research identified increased duration of anterior and superior hyolaryngeal excursion that resulted in delayed UOS closure on videofluoroscopic swallowing study. Miller and Watkin[22] later identified similar results using real-time ultrasound, and a further study employing manofluorography suggested that not only the duration but also the

intensity of pharyngeal contraction is increased during this manoeuvre.[26] McCullough and colleagues documented that, following 2 weeks of treatment, 18 patients with dysphagia following stroke demonstrated increased duration of hyoid excursion[27] and increased hyoid elevation,[28] which were not maintained after a subsequent 2-week, non-training period. Of note, two studies employing high-resolution pharyngo-oesophageal manometry in healthy volunteers demonstrated that, while pharyngeal pressures and bolus transfer were increased during Mendelsohn manoeuvre swallows, proximal oesophageal peristalsis was reduced.[9, 10] This phenomenon requires consideration in clinical populations with impaired pharyngo-oesophageal peristalsis and warrants further investigation.

Masako manoeuvre

The Masako, or tongue-hold manoeuvre, is the first potential rehabilitation exercise that was designed to directly address a specific underlying symptom. Fujiu and colleagues initially documented significantly increased anterior bulge of the posterior pharyngeal wall in patients who had undergone base of tongue resection for cancer treatment. [29] The Masako manoeuvre was designed to mimic this disorder by instructing individuals to 'protrude the tongue maximally but comfortably, holding it between the central incisors'.[30] In healthy participants, this manoeuvre resulted in videographically assessed increased anterior bulging of the posterior pharyngeal wall.[30] This manuscript provided a caution, however, about using this technique during bolus ingestion as the anterior tongue placement leaves the airway in a relatively unprotected, vulnerable position. When the technique was translated to a small population of three patients with base-of-tongue resection, the manoeuvre resulted in increased base-of-tongue to posterior pharyngeal wall contact pressures. This finding is remarkable considering that the posterior pharyngeal wall was required to compensate for the anteriorly resected base-of-tongue structures. In a group of 40 healthy individuals, however, oropharyneal and hypopharyngeal pressures did not differ during manoeuvre conditions, while UOS relaxation pressures were significantly reduced.[31] Using high-resolution pharyngeal manometry and intramuscular electromyography, it was similarly demonstrated that, in the absence of posterior tongue movement during tongue-hold swallows, activation of the superior pharyngeal constrictor was increased, resulting in stable pharyngeal pressures.[32]

Head-lift (Shaker) exercise

The Shaker exercise was originally introduced by Shaker et al.[33] and was designed to target floor-of-mouth muscle contraction outside the context of swallowing with the aim of increasing UOS opening during ingestion. Individuals are instructed to lie flat on their back and to raise their head until they can see their feet, without raising their shoulders off the bed. As such, this exercise is purely a muscle-strengthening exercise for the floor-of-mouth muscles involved in both the oral phase (lowering the jaw during chewing) and pharyngeal phase (contraction of floor-of-mouth musculature and subsequent anterior displacement of the hyolaryngeal complex) of swallowing. Importantly, this exercise does not strengthen other muscles involved in swallowing, as is the case with the effortful swallow or Mendelsohn manoeuvre. Research has documented that the Shaker exercise induced signs of fatigue in the floor-of-mouth muscles[34] and increased EMG amplitude during exercises,[35] suggesting an active involvement of these muscle during the exercise. In their initial study, Shaker et al. documented that this exercise resulted in increased laryngeal excursion, increased width and duration of UOS opening and consequently decreased UOS intrabolus pressure in healthy elderly individuals. Similar findings were reported in a subsequent study of stroke patients and patients with specific impairment of UOS opening.[36] After 6 weeks of exercise, all were able to resume oral feeding. Clinically, it is conceivable that this exercise may be a suitable addition to training with the effortful or Mendelsohn manoeuvres as it specifically targets the swallowing musculature and may hence counteract any biomechanical imbalance potentially induced by the latter two manoeuvres (as discussed above).

Expiratory muscle strength training

Expiratory muscle strength training (EMST) is quickly emerging into more widespread clinical practice and is a promising approach for pharyngeal swallowing impairment and airway protection. EMST emerged from the area of respiratory medicine and has since been adapted for speech and swallowing rehabilitation. EMST is designed to strengthen the contraction of the expiratory musculature by directing expiratory airflow through a one-way, spring-loaded valve that remains open in the presence of positive airflow. The resistance of the valve can be adjusted so that increasing valve resistance requires increasing expiratory airflow. Initial work by Sapienza et al.[37] demonstrated that EMST resulted in significantly increased expiratory airflow in young, healthy participants. Proof of concept for a potential application of EMST in swallowing rehabilitation was provided by a study that documented increased activation of floor-of-mouth muscles during EMST. As outlined above, these muscles play a critical role of providing anterior pull on the hyolaryngeal complex during swallowing which biomechanically facilitates UOS opening. Based on the promising early results, several studies of the effects of EMST in neurological populations have since documented that EMST may help recover respiratory muscle weakness in Parkinson's disease[38, 39] with a further study demonstrating greater hyoid movement and penetration–aspiration (P–A) scale scores following a period of EMST training.[40] Positive effects have also been reported in patients with multiple sclerosis on speech production and, importantly, strength of voluntary cough in patients with moderate disability.[41, 42] Similarly, EMST has been shown to increase maximum expiratory pressure and maximum hyoid displacement during swallowing in amyotrophic lateral sclerosis.[43]

EXPANDING THE INTERVENTION REPERTOIRE

As outlined in the previous section, the majority of interventions available for swallowing rehabilitation have traditionally focused on facilitating the recovery of swallowing function through biomechanical modifications that are largely driven by increased muscle strength. The assumption has persisted that, by increasing peripheral muscle strength, there would be consequent increased biomechanical force, which in turn would facilitate effective pharyngeal bolus clearance and airway protection. This approach may well be appropriate in some presentations of swallowing impairment; however, it may also well be inappropriate in others. By focusing solely on peripheral, biomechanical (dys)function, there has been little regard for the central neurological networks that drive human sensorimotor function. This represents a significant shortcoming in common management practices for patients with neurological impairment.

Increased understanding of swallowing neural control – particularly the role of the cerebrum in swallowing neural networks – has brought about a significant paradigm expansion in our collective approach to addressing swallowing impairment. Recent research favours the assumption that, if we can modify the underlying neurological substrates of swallowing, the changes in swallowing biomechanics will be more permanent and robust than what is seen following peripheral muscle exercise alone. Behavioural and non-behavioural techniques for neural modulation are currently under development and provide promise for new approaches to rehabilitation of swallowing impairment. These are briefly outlined below, accompanied by a discussion of ethical and practical challenges that may accompany their transition into routine clinical practice.

Behavioural, cortical modulation: skill training paradigms

Stevenson and Allaire[44] comment that a process of encephalization underlies the ability to modify the reflexive swallowing response seen in infancy to the more mature and variable response seen in adult-like, ingestive swallowing. Inherent in this comment is the suggestion that the 'skill' component of swallowing is acquired through cortical expansion and modulation of the primitive brainstem generated response. Quite unlike our current strength-based, peripheral approaches, relearning or modifying the complex sequence of swallowing events at the level of central control is gaining increasing recognition as a type of skill-based training following neurological impairment.

DEFINITION AND REQUIREMENTS OF SKILL TRAINING

Much of the conceptual research related to skill training derives from physiotherapy. In very brief summary, this research suggests that task-oriented skill-training programmes produce more favourable rehabilitative effects on recovery of motor impairments than strength-training programmes due to greater neuroplastic adaptation in the motor cortex,[45] greater corticomotor excitability,[46] greater functional movement improvements[47] and greater strength gains.[48]

Skill training can be defined as the acquisition of skill through functional repetition and refinement of movement patterns. However, fundamental knowledge of neurorehabilitation demands that mere repetition of a task will not improve skill; several additional criteria must be met. First, skill-based training must incorporate task-specificity to ensure cortical plasticity.[49] Thus any repetitive exercise must replicate the desired task – in this case swallowing. Second, there must be an element of task challenge and problem solving[50] to activate different brain circuits which underlie motor learning, neural and behavioural change.[51] Finally, extrinsic visual and intrinsic kinaesthetic feedback regarding task performance allows for evaluation of movement accuracy and correction on subsequent exercise trials.[52, 53]

EARLY ATTEMPTS AT TRANSLATING TO SWALLOWING RESEARCH

Translated to clinical routines, some of our traditional strength training approaches may indeed satisfy the task-specificity requirement by incorporating repetition of exercise into the context of functional swallowing; this would be the case with effortful swallowing, Mendelsohn manoeuvre, or tongue-hold swallowing. The adaptation required for task execution lends support for their application in skill-based training regimes with the focus on initiation and modulation of volitional swallowing rather than strengthening. Inclusion of ingestive swallowing in the treatment paradigm also meets the criteria for task specificity. However, there is likely to be very little therapeutic benefit from ingestion of a safely tolerated diet as it merely repeats a task with no challenge. The newly described McNeill Dysphagia Therapy Program[54] could be considered a type of skill training as it meets the requirement of task challenge. This protocol uses a hierarchical approach to bolus size and texture, thus systematically challenging oral intake in a controlled therapeutic environment. Another approach using surface electromyography as a biofeedback device has recently been described.[55] Although historically used to provide valuable feedback regarding increased strength of contraction, recent research suggests great benefit of this modality for increasing skill and precision of movement using a targeted, skill-based rehabilitation protocol[55] This protocol meets the characteristics of skill training by requiring repeated execution of skilled swallowing movements, progressive and challenging aims for timing and degree of muscle contraction, and ongoing and delayed feedback regarding task performance.

Proof of concept research in a sample of patients with dysphagia secondary to Parkinson's disease has documented significant improvements in quality of life and functional swallowing after two weeks of daily skill training. Other skill training approaches have been explored using manometry as a biofeedback device to alter timing characteristics of the pharyngeal response[56] and respiratory related feedback to improve swallowing respiratory coordination.[57]

Our past rehabilitation attempts that have focused on strength training may well have inadvertently facilitated recovery by increasing skill, more so than strength. Only recently have clinicians and clinical researchers focused specifically on therapeutic tasks to increase swallowing skill with the exclusion of potential imbalance in the biomechanical system through muscle strengthening. In doing so, rehabilitative outcomes are likely to improve as we develop greater specificity in treatment options.

Non-behavioural or behaviourally augmented central modulation: stimulation paradigms

The development of brain imaging and stimulation techniques has significantly expanded our understanding of the neurophysiological mechanisms of swallowing. Approaches designed to improve swallowing function through extrinsic modulation of central neuronal circuits involved in swallowing motor control have received increasing interest by researchers and clinicians alike. Approaches designed to improve swallowing function through extrinsic modulation of central neuronal circuits involved in swallowing motor control have received increasing interest by researchers and clinicians alike. A growing body of evidence now suggests that harnessing the brain's ability to reorganize its synaptic connections using stimulation techniques may in the future provide superior rehabilitation outcomes in some patient groups compared to 'traditional' behavioural intervention.[58, 59] Techniques developed to assess and promote neuroplastic reorganization in the human motor cortex, including transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and pharyngeal electrical stimulation (PES) will be briefly outlined below. At present, none of these techniques has been sufficiently evaluated in order to be applied in routine clinical practice; however, their evidence base is continuously expanding. Once optimal treatment paradigms have been developed and evaluated, it is highly likely that some, if not many, of these techniques will be available to the judicious clinician.

The reader is directed to Doeltgen and Huckabee[60] for a discussion of some of the practical and ethical considerations that accompany the transition of these techniques into routine clinical application. It is worth noting that several brain stimulation devices are already available for anyone to purchase over the internet.[61] This is likely to speed up the transition of some of these techniques into clinical practice and may challenge their application in an evidence-based framework.

TRANSCRANIAL MAGNETIC STIMULATION

Perhaps the most researched non-invasive brain stimulation technique in the field of swallowing rehabilitation is that of transcranial magnetic stimulation (TMS). Employing a strong but short-lasting electric current that is discharged through a coil of wires placed over a targeted cortical area, usually the primary motor cortex, a magnetic field is generated that painlessly penetrates the intact skull. At sufficiently high intensities, TMS transynaptically activates descending motor output neurons that in turn will generate descending volleys of action potentials. These can be measured at the periphery as a single motor-evoked potential (MEP) using surface electromyography. In its basic application, single-pulse TMS therefore allows assessment of the excitability of targeted motor circuits. Rapid application of up to several hundred TMS pulses, known as repetitive TMS (rTMS), can under certain circumstances modulate the trans-synaptic excitability of the targeted motor circuits and this effect may outlast the stimulation period by several hours.[62] The nature of the neuroplastic changes induced by rTMS heavily depends on its stimulation parameters, including frequency, intensity and stimulus pattern.

Conventional rTMS is applied in rhythmical trains of single stimuli. When applied at low inter-stimulus frequencies of less than 1 Hz, rTMS reduces corticospinal or corticobulbar excitability, whereas higher rTMS frequencies of greater than 1 Hz increase it. For example, in healthy research participants, 1 Hz rTMS applied over the motor projections to the pharyngeal musculature reduces the corticobulbar excitability of these projections, which is accompanied by a reduction in swallowing reaction time of normal and fast swallowing.[63] Although significant in its own right due to its proof of principle nature, this finding may be particularly important for future studies developing this paradigm into a rehabilitation approach for patients who present with delayed onset of swallowing, such as following stroke. Interestingly, when facilitory 5 Hz rTMS was applied to the non-dominant hemisphere, the inhibitory effects of the previous 1 Hz rTMS could be reversed, an effect that was shown to restore swallowing function.[64]

In a group of patients presenting with dysphagia following stroke, 5 Hz rTMS applied over the contralesional hemisphere was shown to increase pharyngeal motor cortical excitability, which was accompanied by a reduction in aspiration scores and pharyngeal residue.[65] In contrast, low-frequency 1 Hz rTMS applied over the ipsilesional hemisphere clinically increased swallowing response time for liquids and reduced aspiration for liquids and residue for paste on videofluoroscopy.[66] Applied at 3 Hz over the lesioned representation of the oesophageal musculature, rTMS resulted in improved clinical presentation of swallowing impairment in cortical stroke patients[67] and patients presenting with lateral medullary stroke or brainstem stroke.[68] Taken together, the findings of these studies suggest that rTMS may hold the potential to assist the recovery of swallowing function in various patient groups, although at present the variability in stimulation paradigms is reflective of the infancy of this approach.

TRANSCRANIAL DIRECT CURRENT STIMULATION

Although it has been developed over a century of invention and research,[69, 70] electrical stimulation of the human

central nervous system has only recently been rediscovered in the form of transcranial direct current stimulation (tDCS). Unlike its relatively painful relative, transcranial electrical stimulation, tDCS employs low-intensity electrical direct currents that modify the excitability of large neuronal assemblies mainly through changes in the transmembrane potential during stimulation. In general, anodal current flow applied over the primary motor cortex increases the excitability of its motor representations, whereas cathodal stimulation has the opposite effect. Originally demonstrated in the corticospinal motor system,[71] the bidirectional effects of tDCS have now also been demonstrated in the corticobulbar motor system involved in the control of swallowing. For example, cathodal tDCS at 1.5 mA intensity for 10 minutes reduced pharyngeal motor excitability, whereas 10 minutes of 1.5 mA or 20 minutes of 1 mA of anodal tDCS increased it.[72] When applied in a cohort of patients presenting with cortical stroke, 2 mA contralesional anodal tDCS applied for 30 minutes combined with effortful swallowing on 5 consecutive days increased functional swallowing based on clinical presentation.[73] Likewise, ipsilesional application of 1 mA anodal tDCS for 10 days[74] or 5 days[75] improved clinical ratings of swallowing function.

Several systematic reviews come to the conclusion that both rTMS and tDCS may hold a promising potential to assist the recovery of swallowing function. The reader is directed to these reviews for an in-depth discussion of the currently available evidence.[76–79] It is worth noting that in these clinical trials researchers evaluated the effects of the various tDCS paradigms on clinical outcome measures that were based purely on observational, clinical rating scales. Future studies are warranted to evaluate neurophysiological and biomechanical outcome measures underlying the reported clinical improvements.

PHARYNGEAL ELECTRICAL STIMULATION

Pharyngeal electrical stimulation (PES) differs from non-invasive brain stimulation techniques in that it is not applied directly to the central nervous system. Instead, a weak electrical current is applied to the sensory receptors of the pharyngeal mucosa via surface electrodes embedded in a catheter.[80] This technique deserves mention as it has been systematically evaluated in several seminal studies in both healthy and swallowing-impaired populations. The cumulative evidence so far suggests that this approach may provide a suitable means of modifying the excitability of corticobulbar projections relevant for swallowing. When applied using optimal stimulus parameters,[80] increased excitability of the pharyngeal cortical motor representation was accompanied by an improvement in dysphagic symptoms, including pharyngeal transit times and aspiration scores.[81] Similarly, a single application of PES in a group of patients presenting with chronic stroke resulted in an increase in corticobulbar excitability of the unaffected hemisphere and was associated with a decrease in aspiration scores.[82] The neuroplastic effects induced by PES appear to have a cortical origin[80] and may be modified by genetic influences.[81] Based on these preliminary findings, PES may be a promising alternative to non-invasive stimulation techniques that are directly applied to cortical neuronal tissues, especially in patients who meet exclusion criteria for these techniques.

NON-INVASIVE BRAIN STIMULATION IN THE CONTEXT OF EVIDENCE-BASED PRACTICE

The transition of any new intervention from the research laboratory into routine clinical practice will naturally need to occur within the framework of evidence-based practice. Sackett et al. define this as the synthesis of external research evidence, internal clinical expertise of the treating clinician and client preferences.[83] As outlined in this chapter, a growing body of external scientific evidence presently outlines the promising potential of peripheral or central stimulation techniques targeting swallowing-related neuronal networks to support swallowing rehabilitation efforts. Further large-scale clinical trials are required to establish optimal stimulation paradigms and to test these for their safety and efficacy. The judicious clinician will eventually be able to incorporate this knowledge into their own clinical reasoning and guide their clients towards making fully informed decisions. In recognition of our responsibilities regarding beneficence and non-maleficence in research and clinical practice, this process will occur gradually and within the framework stipulated by the Declaration of Helsinki (2013).

SWALLOWING REHABILITATION – A RAPIDLY CHANGING LANDSCAPE

As outlined in this chapter, swallowing rehabilitation practices are undergoing a significant and rapid expansion from focusing solely on modification of peripheral biomechanics towards understanding and harnessing the neurophysiological mechanisms that underlie human swallowing. As such, researchers and clinicians are challenged to address the required cultural, ethical and organizational issues that accompany the development of novel skill-training and brain-stimulation techniques. These challenges include questions regarding the provision of neuromodulatory interventions to patients, determination of professional competencies and scope of practice as well as practical implications for patient services.[58] Partnerships between stakeholders across the various professions involved in swallowing rehabilitation will facilitate the development of required institutional frameworks locally and globally. Unrestricted access to information via the internet has accelerated the transition from bench top to routine clinical application in many areas of health services. It is therefore likely that patients will increasingly become more vocal stakeholders in the clinical decision-making process than perhaps has previously been the case. It will be the responsibility of clinical service providers to guide their patients in this process by providing individually tailored, evidence-based advice.

KEY POINTS

- Swallowing rehabilitation practices have traditionally focused on enhancing oropharyngeal swallowing biomechanics primarily through muscle strengthening exercise.
- With increased recognition of the role of the cortex in modulating swallowing behaviour, contemporary approaches to rehabilitation are shifting attention from muscle strengthening to the capacity for control adaptation.
- Skill-based behavioural training approaches are emerging that maximize voluntary volitional control, with early research seeking to define this type of treatment and provide proof of concept outcomes.
- Neuromodulatory approaches that employ cortical and peripheral non-invasive neurostimulation techniques are being actively researched with preliminary evidence to suggest that certain non-invasive brain stimulation protocols can improve some aspects of dysphagia.
- The development of competency and regulatory frameworks will be required to facilitate the transition of novel behavioural and neuromodulatory approaches to clinical practice.

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CHAPTER 56

CHRONIC ASPIRATION

Guri S. Sandhu and Khalid Ghufoor

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: dysphagia, aspiration, unsafe swallow, cricopharyngeal dysmotility, pharyngeal pouch and laryngeal incompetence.

INTRODUCTION

The larynx, trachea and bronchi form the conduit between the lungs and the external environment through which respiratory gases are transported and pulmonary secretions are expectorated. The larynx is also the primary organ of phonation, acts to protect the airway from aspiration during swallowing and provides important sensory feedback and movements that are critical to the control of ventilation.[1] Swallowing is a highly complex process, both voluntary and involuntary, requiring the precise coordination of many different muscle groups through the actions of sensory and motor nerves via the central nervous system.

Charles Darwin noted in *On the Origin of Species* that the human is the only animal whose upper aerodigestive tract fails to adequately serve its principal evolutionary functions of preventing aspiration and acting as the gateway to the lungs.[2] In all mammals, including the human infant, the pharyngeal airway is short and the epiglottis and the soft palate are anatomically related, allowing simultaneous swallowing and breathing. Starting at 4–6 months of age, the larynx descends in man, leading to loss of nasolaryngeal association. The neonate's larynx lies at the level of the 3rd cervical vertebra and the adult larynx lies at the level of the 6th cervical vertebra. This adult position allows humans to meet the requirements of complex speech through resonance and articulation.

Aspiration is contamination of the tracheobronchial tree with secretions, food material and other contaminants. Prevention of aspiration occurs primarily through reflex laryngeal closure, laryngeal elevation and cessation of breathing during swallowing, and any aspirated contents are expelled through coughing. A certain amount of aspiration is normal in humans, especially during sleep,[3] but is tolerated without complications in healthy subjects with normal tracheobronchial ciliary function and normal immunology.

The response to even small quantities of aspiration will depend on the pH of the aspirate, microorganisms present and the person's pulmonary and immunological status. This may lead to cough or in some cases life-threatening pulmonary complications. In cases where the cough reflex is reduced or absent, 'silent' aspiration may occur. Acute severe aspiration of a large bolus may lead to airway obstruction and may prove fatal, whereas chronic small

volume aspiration may risk pneumonia or respiratory failure through chronic pulmonary emphysematous disease or bronchiectasis.

Chronic or intractable aspiration is usually associated with a significant impairment of the normal swallow, especially if there is a dysfunction of the larynx or pharynx.

PRESBYPHAGIA

Although it is widely believed that swallowing function deteriorates with age, the evidence supporting this is inconclusive, especially if one excludes the affects of neurological disorders, diabetes mellitus and connective tissue diseases.[4] The changes in swallow function with age appear to be modest but there does appear to be a reduction in the swallowing function reserve and 'plasticity', lowering the threshold for dysphagia and aspiration, and impairing the success of swallowing therapies, manoeuvres and corrective surgery.

Swallowing is a complex process that requires finely coordinated neurological inputs and is therefore susceptible to a variety of structural and neuromuscular diseases.[5–7]

EVALUATION OF THE 'ASPIRATING PATIENT'

All patients with severe swallowing problems and aspiration should be assessed and managed in a multidisciplinary setting. This team should include an otolaryngologist with a special interest, swallowing therapist, gastroenterologist, neurologist and dietitian, and have access to appropriate radiology and respiratory medicine.

A thorough history from the patient, relative or referring physician will often reveal the cause of the aspiration.

Physical examination is essential and must include examination of the head, neck and upper aerodigestive tract with functional assessment of the cranial nerves.

Flexible nasal endoscopy in the clinic will help exclude tumours and masses as well as determine laryngeal function and sensation. The signs may be subtle, with even small quantities of pharyngeal residue or secretions indicative of a swallowing problem. At the other extreme there may be significant pooling of secretions, bathing an oedematous, asensate larynx and freely entering the airway.

Videofluroscopic (VF) assessment of swallowing should always be performed in conjunction with a swallowing therapist. The investigation provides valuable information about the nature of the swallowing disturbance and degree of aspiration. Ideally it is performed using limited amounts of barium but where there is clinical suspicion of aspiration then a water-based radiological contrast agent should initially be trialled.

Functional endoscopic evaluation of swallowing (FEES) uses dyed liquids, semi-solids and solids, which are sequentially swallowed with nasopharyngeal fibre-optic observation and video recording. Swallowing strategies can be trialled and recorded during the assessment. The technique will diagnose aspiration but has the added advantages that it avoids radiation and can be performed by the bedside. In addition, it can be viewed with the patient, and provides biofeedback to the patient regarding the benefits of swallowing strategies and manoeuvres.

Objective assessment tools for aspiration are available. The Penetration-Aspiration Scale[8] uses data from FEES and VF studies, and the New Zealand Index for Multidisciplinary Evaluation of Swallowing (NZIMES)[9] and the MBS Measurement Tool for Swallow Impairment (MBSImp)[10] rely on data from VF. The most widely accepted subjective score for dysphagia is the Eating Assessment Tool (EAT-10).[11]

PRINCIPLES OF MANAGEMENT

The aims are to protect the airway, avoid life-threatening respiratory complications and achieve adequate nutrition, while also considering the psychological and social aspects of food and feeding. As previously mentioned, these patients should be assessed and treated in a multidisciplinary team environment.

TABLE 56.1 Causes of an unsafe swallow

Neurological and neuromuscular disorders	Auto-immune disorders	Damage to larynx, pharynx or neck	Others
• Cerebrovascular accidents • Head injuries • Hypoxic brain injuries • Parkinson's disease • Amyotrophic lateral sclerosis • Multiple sclerosis • Motor neurone disease • Muscular dystrophy • Myasthenia gravis • Guillain-Barre syndrome • Myopathies • CNS tumours • Neurosurgery or skull-base surgery	• Systemic sclerosis (scleroderma) • Bullous mucosal conditions • Systemic lupus erythematosis • Sjögren's syndrome and salivary gland diseases	• External trauma (RTA or sports injuries) • Internal trauma (caustic ingestion) • Reflux diseases • Post-surgical (conventional and trans-oral laser) • Post-irradiation • Neoplasms • Strictures	• Intoxication or drugs • Eosinophilic oesophagitis • Pharyngeal pouch • Cricopharyngeal muscle discoordination/ spasm • Achalasia • Severe illness or nutritional deficiencies • Amyloidosis

Under the direction of the swallowing therapist, where possible, compensatory techniques, dietary modification and appropriate exercises should be trialled (discussed in Chapter 66, Speech/voice therapy for voice disorders). Medical therapy should be directed at dealing with the underlying cause of the dysphagia. Excessive secretions sometimes respond to the use of anticholinergic patches but these may be associated with unacceptable side effects. Alternatively, ultrasound guided botulinum injections to salivary glands[12] may be considered.

The oral phase of swallowing is quite complex and attempts at surgical restoration, usually following cancer surgery, at best create a mass of tissue to optimize any residual function with compensatory techniques. Surgery for swallowing is generally limited to the pharyngeal or oesophageal phases and even then it can only be directed at specific sites contributing to the dysphagia or aspiration. In many cases surgery is not possible because of the very poor health of the patient or poor prognosis, or because a surgically correctable cause is not identifiable.

Progressive deterioration of swallowing function, leading to aspiration, can be assessed at intervals in the multidisciplinary swallowing clinic and appropriate investigations, therapies or procedures can be directed for the best possible quality of life for the patient. Patients may present acutely with severe aspiration, usually following an acute neurological event. A bedside assessment is usually adequate to identify those in whom oral intake should be discontinued and an alternative route of nutrition provided. Initially this will be via a small nasogastric feeding tube but where recovery is unlikely, or is likely to take many days or weeks, then a gastrostomy feeding tube should be considered. Antibiotics and pulmonary physiotherapy should be commenced where appropriate.

Nasogastric and gastrostomy feeding tubes will not eliminate aspiration of secretions and further consideration needs to be given to airway protection. A tracheostomy tube with a low-pressure cuff allows airway toilet in patients with copious secretions; however, current cuff design does not eliminate the passage of secretions into the lower airway.[13] The tracheostomy tube also reduces laryngeal elevation by 'anchoring' the trachea, and the inflated cuff compresses the oesophagus,[14] resulting in partial obstruction (**Figure 56.1**). In addition the tracheostomy reduces the effectiveness of the cough, and bypassing the normal flow of air through the larynx may reduce laryngeal sensitivity. On intensive care units there is increasing use of tracheostomy tubes with a suction port above the cuff, reducing the risk of secretion aspiration.

A tracheostomy tube is therefore not the ideal solution to chronic aspiration and when used for this purpose will require close attention and frequent suctioning of the oropharynx and tracheostomy, especially in the debilitated patient.

SURGERY FOR CHRONIC ASPIRATION

Patients with palatal incompetence suffering nasal reflux or escape may benefit from prosthetic appliances to elevate the soft palate, or velopharyngeal flap techniques may be considered.[15]

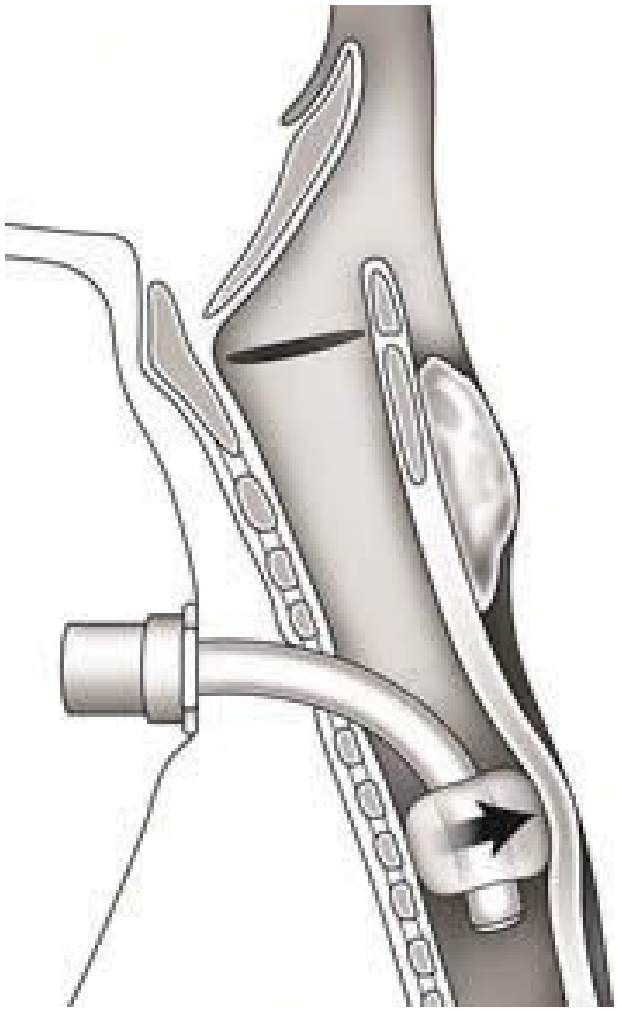


Figure 56.1 A tracheostomy tube can have an adverse effect on swallowing by reducing laryngeal elevation and also by oesophageal compression through direct transmission of cuff pressure.

In cases of dysphagia and aspiration due to parapharyngeal or retropharyngeal masses, then surgical removal of these is likely to be helpful.

It is well recognized that the trans-oral laser approach to removing even small tumours on the posterior pharyngeal wall may result in severe dysphagia and aspiration,[16] even in the younger patient. This is thought to be due to disruption or damage to the pharyngeal plexus. Careful thought should also be given to external surgical approaches to the pharynx and upper oesophagus in the older patient. These patients have minimal swallowing reserve and surgical scarring contributing to tethering of the larynx or pharynx, or damage to the pharyngeal plexus may adversely affect the safety of swallowing.

Sometimes osteophytes from the cervical spine will be seen to overhang the laryngeal inlet and act as a 'ski-slope' for food and secretions in to the airway (**Figure 56.2**). The trans-oral, trans-pharyngeal approach to these will certainly risk exacerbating the swallowing problem. An external approach to the anterior cervical spine, with



Figure 56.2 Osteophyte from cervical spine overhangs the laryngeal inlet and can be associated with secretions dripping into the airway.



Figure 56.3 Fibre endoscopic view of larynx in a patient who has aspiration (milk with green dye during FEES study).

lateral retraction of the larynx and pharynx, is a viable option but may affect swallowing, for the same reasons mentioned earlier in this chapter, and there is potential for injury to the recurrent laryngeal nerve. Sometimes a laryngeal suspension procedure will elevate the larynx away from such an osteophyte and not risk the swallow further.

SURGERY TO THE CRICOPHARYNGEAL SPHINCTER

If flexible nasendoscopy demonstrates pooling of secretions in the hypopharyx (**Figure 56.3**), then based on the medical history and videofluoroscopic imaging it is possible to determine whether this is due to weakness of the pharyngeal musculature, a hypertonic or discoordinated cricopharyngeal sphincter, or both.

In these circumstances it is logical to think about an upper oesophageal myotomy. One cannot always be confident of the results of an external approach myotomy and for this reason the authors prefer a trial of a 'medical myotomy' using botulinum toxin.[17] A total of 80–120 units of botulinum toxin A is administered into cricopharyngeus in three separate injections, dividing the total dose. A short general anaesthesia and direct visualization of this muscle, using a laryngoscope, allows one central and two postero-lateral injections to be placed accurately (**Figure 56.4**). If this treatment is successful it can either be repeated or be followed by an endoscopic CO2 laser myotomy (**Figure 56.5**).[18] Very rarely is an external approach myotomy required.



Figure 56.4 View of cricopharyngeus through a laryngoscope. Botulinum toxin is injected in the three positions (arrows) to produce the effects of a 'temporary myotomy'.

LARYNGEAL INCOMPETENCE

The airway has several levels of protection against aspiration. During a swallow the larynx moves up and forwards to lie under the tongue base, the epiglottis moves to lie above the laryngeal inlet and the true and false cords adduct. If there are residual secretions in the hypopharynx, aspiration can still take place even if the larynx is functioning normally. Even though the larynx elevates during a swallow, as it descends to its resting position retained secretions can enter the airway. Usually this will produce a cough, but this may not be the case in a neurologically impaired patient. In addition, when the larynx has been exposed to chronically retained secretions there is associated oedema of the laryngeal mucosa and diminished supraglottic sensation.

More commonly the cause of laryngeal incompetence is damage to a vagal nerve, high in the neck, which affects both motor and sensory function of the unilateral larynx as well as the associated pharyngeal musculature.

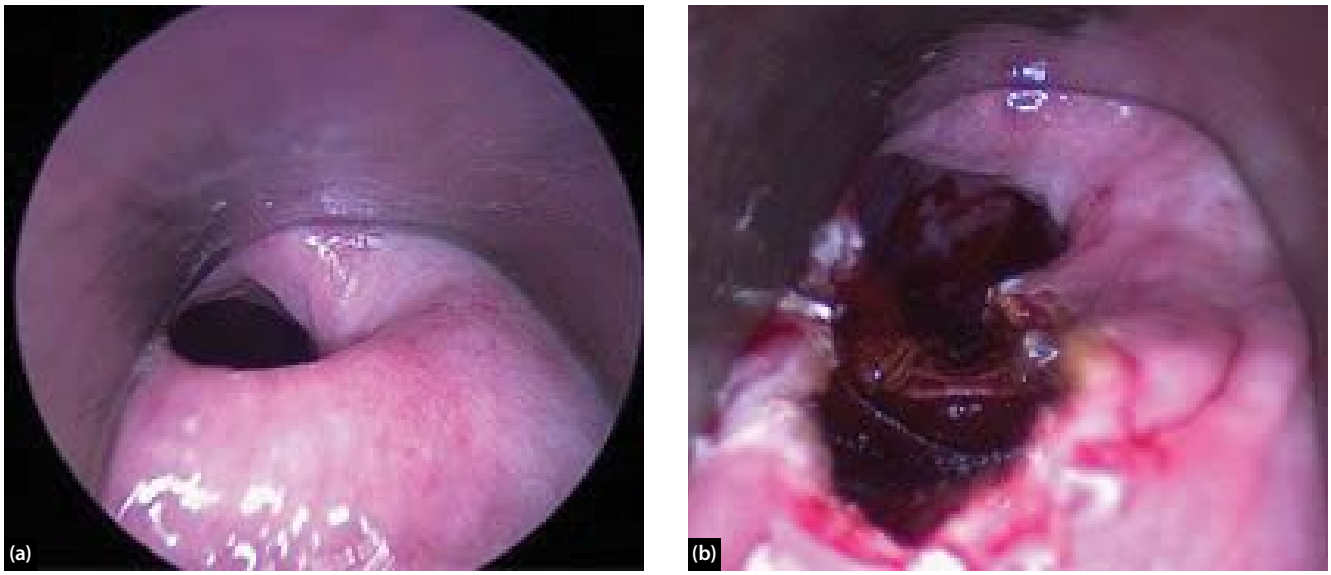


Figure 56.5 Result of endoscopic CO2 laser cricopharyngeal myotomy (right).

Cerebrovascular events, especially if involving the brainstem, and progressive muscle wasting conditions can also lead to impaired laryngeal and pharyngeal competence. A plethora of approaches has been described to deal with this particular problem; the sheer variety, and the absence of large trials, would suggest inconsistent results.

Bilateral vocal fold medialization techniques have been described to deal with this problem. These can consist of injections lateral to the thyroarytenoid muscle. Laryngeal injections can be carried out under local or general anesthesia and most are temporary (see Chapter 68, Movement disorders of the larynx). They are ideally suited for conditions where there is likely to be a recovery of laryngopharyngeal function within a few weeks, or as a test of medialization suitability prior to medialization thyroplasty procedures that are described as permanent. Thyroplasty implants include Gore-Tex ribbon, titanium, hydroxylapatite and silicon. Bilateral medialization thyroplasties were first described for vocal cord bowing[19] as seen with presbyphonia. In these circumstances the posterior edge of the implant needs to sit anterior to the vocal process of the arytenoid so that it does not interfere with normal abduction of the cords. However, bilateral medialization for aspiration requires adduction of the entire vocal cord.[20] The technique works in carefully selected cases of mild aspiration[21] as it does not prevent all aspiration and risks patients requiring a tracheostomy.

Unilateral vocal fold medialization or arytenoid adduction[22] techniques in combination with cricopharyngeal myotomy are described for cases of vagal nerve injury leading to aspiration. In some cases of high vagal injury there is associated hypopharyngeal dilatation leading to excessive pooling of secretions in the pyriform. Denker originally devised a technique for excising the redundant pharyngeal mucosa on the affected side, through an external approach, which others have modified with the use of plication sutures or a stapling device.[23] With these 'hypopharyngeal pharyngoplasty' procedures it is usually necessary to perform a cricopharyngeal myotomy and cord medialization at the same time.

GLOTTIC AND SUPRAGLOTTIC LARYNGEAL CLOSURE

The first glottic closure procedure, performed through a median laryngofissure, was described by Montgomery in 1975[24] and involved stripping the vocal cord mucosa on both sides and suturing the cords together to encourage fibrous union. As an alternative to damaging the vocal cords, a two-layered closure of the supraglottis (**Figure 56.6**) was devised via a pharyngotomy approach.[25] This was later modified by Remacle et al.[26]

The problems with these two approaches are that they run a high risk of breakdown and, as the larynx is closed, the patient is tracheostomy dependent and has no voice. Also these procedures are not easily reversible. In 1975 Biller et al.[27] described a two-layer, vertical supraglottic closure, with a small opening at the tip of the epiglottis (**Figure 56.7**). The procedure was designed to prevent aspiration in total glossectomy patients. Some retained the

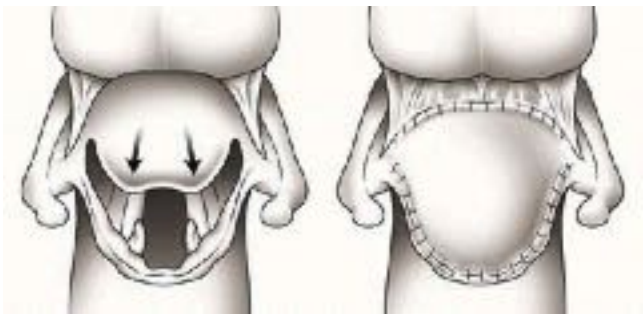


Figure 56.6 Horizontal closure of the supraglottic larynx via a lateral pharyngotomy approach.



Figure 56.7 Biller supraglottic laryngoplasty for treating chronic aspiration in total glossectomy patients.

ability to speak and others could commence oral intake but retained a tracheostomy tube.[28]

LARYNGEAL PROSTHESES

A translaryngeal, closed stent is one means of preventing aspiration and can be placed endoscopically and held in place with trans-cervical sutures.[29] The theoretical advantage is that the stent can be removed if the patient recovers a safe swallow. Unfortunately these stents cause scarring at the level of the glottis, are uncomfortable and do not provide a reliable seal to secretions.[30] With advances in biointegratable materials and the work on implantable larynges[31] there is hope for prostheses that allow voicing, without aspiration, but the patient may still need a tracheostomy.

OESOPHAGEAL MOTILITY DISORDERS

Oesophageal motility disorders can lead to retained secretions in the hypopharynx and risk aspiration. They result from either primary diseases of the musculature or from an imbalance between excitatory and inhibitory innervations. Historically the diagnosis has been based on VF but high-resolution manometry with oesophageal pressure topography has become the current gold standard.

Abnormalities of oesophageal function are common in patients with gastro-oesophageal reflux disease (GORD).[32] Mild cases of dysmotility can be managed by suppressing gastric reflux through the use of proton pump inhibitors, prokinetic antibiotics (macrolides) or prokinetic drugs (domperidone). In severe cases, such as spasm or hypertensive peristalsis, medical treatment with nitrates and calcium channel blockers may prove effective. Endoscopic dilatations and Botox injections may help with more localized problems such as achalasia (lower oesophageal sphincter) or cricopharyngeal spasm (upper oesophageal sphincter). A permanent solution in these patients includes a myotomy.

Secondary motility disorders may be related to neurological or connective tissue diseases, as well as diabetes and rarer disorders such as amyloidosis, Sjögren's syndrome and eosinophilic oesophagitis.

PHARYNGEAL POUCH

A pharyngeal pouch (Zenker's diverticulum) is a posterior pulsion diverticulum occurring, in a natural weakness (Killian's dehiscence), between the fibres of thyropharyngeus and cricopharyngeus. They are associated with an oesophageal motility disorder in the vast majority of cases. The symptomatic patient complains of dysphagia, regurgitation of food, coughing, aspiration or repeated chest infections. Treatment is indicated when symptoms impact on quality of life or pose a risk to the patient's health.

Endoscopic techniques transect the diverticulo-oesophageal wall so that material does not collect in the pouch. This transection also divides cricopharyngeus (**Figure 56.8**) and some upper oesophageal muscle fibres, and quite neatly performs a synchronous myotomy (**Figure 56.9**). Division of this dividing wall has evolved from using electrocoagulation, the CO_2 laser and more recently endoscopic stapling devices.[33] The endoscopic approach is not always feasible if there is poor access

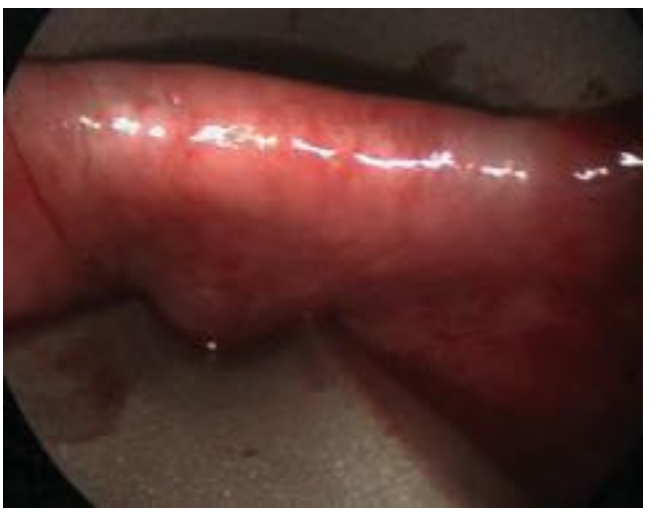


Figure 56.8 Pharyngeal pouch party wall.



Figure 56.9 Pharyngeal pouch party wall divided.

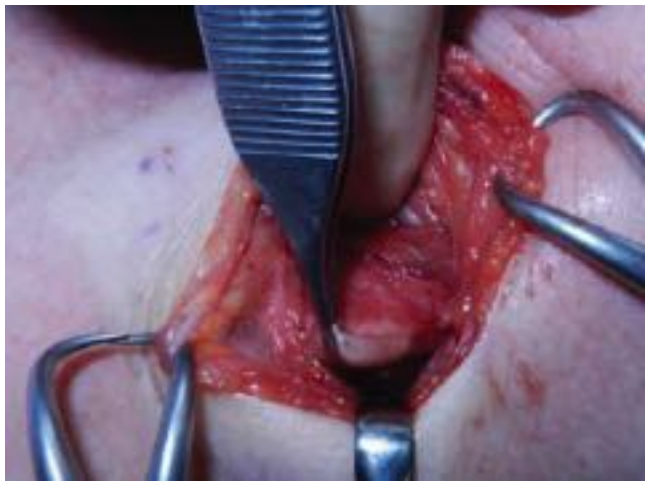


Figure 56.10 Open pharyngeal pouch excision.



Figure 56.11 Proflavine impregnanted ribbon gauze visible in pharyngeal pouch.



Figure 56.12 Mucosal edge of open pharynx and oesophagus with pouch excised.

and it is not always suitable for very small or very large pouches, and there is still a small incidence of post-operative leaks with the risk of mediastinitis.[34] In some cases it is necessary to perform an external approach diverticulectomy (**Figures 56.10–56.12**) combined with a cricopharyngeal myotomy. This does, however, mean a longer hospital stay with increased morbidity (see Chapter 52, Cricopharyngeal dysphagia).

RADIOTHERAPY-RELATED DYSPHAGIA AND ASPIRATION

Radiotherapy to the head and neck is responsible for both early and late changes to the irradiated site. The effects of radiotherapy can vary between individuals even if the dosing is identical. In general the degree of radiotherapy damage depends on: total dose; adjuvant chemotherapy; the extent of the radiotherapy fields at the primary site; and whether the neck has also been treated.

Early radiotherapy therapy changes include mucositis, erythema and pain but also oedematous thickening of soft tissues, weakness of muscles altered taste, altered sensation and reduced oral secretions. Late changes (beyond 6 months) include tissue fibrosis, damage to the blood supply, neuropathic changes, reduced contraction of muscles and joint mobility restriction. The irradiated pharynx will be poorer at clearing secretions and the larynx, if irradiated, may demonstrate poor closure and elevation. In patients receiving radiotherapy for hypopharyngeal or post-cricoid tumours, the scarring and stricture formation may continue for 10 to 20 years after exposure and aspiration may be a very late presentation.

Treatment of post-radiotherapy-related dysphagia and aspiration includes compensatory manoeuvres, dietary

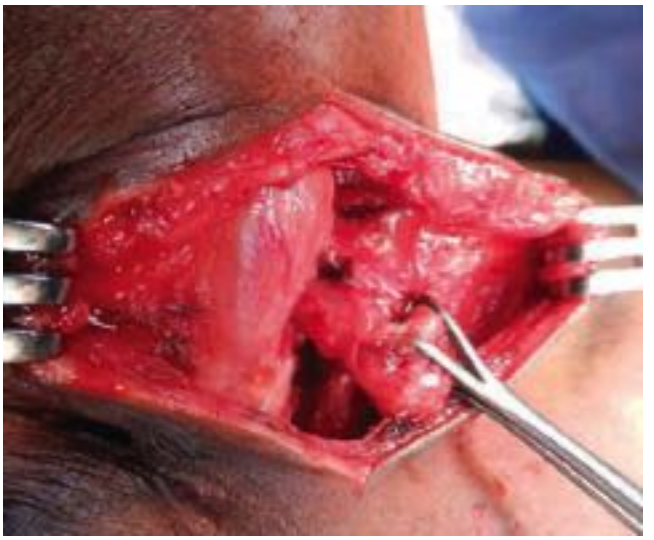


Figure 56.13 Transverse colon transposition in a patient with caustic injury to the pharynx, oesophagus and gastroduodenal areas. Hypopharynx visualized, scarred neck from previous surgery for caustic pharyngeal and oesophageal injury.

modifications and other forms of nutrition. Surgical options are often limited to serial dilatations or ultimately a laryngectomy or laryngopharyngectomy with free flap reconstruction. The authors have used lateral pharyngeal augmentation techniques, with rotational or free myocutaneous or bowel flaps, in cases of hypopharyngeal strictures following caustic ingestion (**Figures 56.13–56.16**), in whom results are more favourable, but the results in radiotherapy patients have been poor.

New radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), can minimize exposure and damage to structures related to swallowing and the salivary glands and are likely to reduce the incidence of these complications.

LARYNGOTRACHEAL SEPARATION

Laryngotracheal separation[35] is described as a simple procedure that allows protection of the airway, while preserving the swallow. The patient's lower airway opens as stoma in the neck and the trachea just below the subglottis is closed as a 'blind-ending' (**Figure 56.17**). As it is reversible it has the potential for restoring voice when the patient recovers. It is however, associated with a high incidence of complications (40%) that include wound breakdown and fistulae, and also airway stenosis at the subsequent tracheal anastomosis; some of the patients go on to require a long-term tracheostomy or laryngectomy.[36]

Tracheo-oesophageal diversion is a modification of the Lindeman procedure described above. The proximal tracheal segment is anastamosed in an end-to-side fashion to an opening in the anterior oesophagus thus eliminating the 'sump' of secretions that results with the former technique. The modification does add to the potential for complications at the primary procedure and when reversed. Both of these procedures make it difficult to be confident



Figure 56.14 Transverse colon mobilized in a heavily scarred abdomen.



Figure 56.15 Transverse colon mediastinal transposition.



Figure 56.16 Pharyngo colonic anastomosis.

of adequate recovery of swallowing function to commit to a reversal, as evidenced by the number of patients requiring subsequent tracheostomies and laryngectomies.[36]

LARYNGEAL AND LARYNGOHYOID SEPARATION

In severe cases of aspiration where there is reduced laryngeal elevation, excessive pooling of hypopharyngeal secretions and reduced laryngeal sensation, or severely discoordinated swallowing, the aspiration poses a significant risk to life. If there is also limited likelihood of recovery of swallow function, yet life expectancy is still

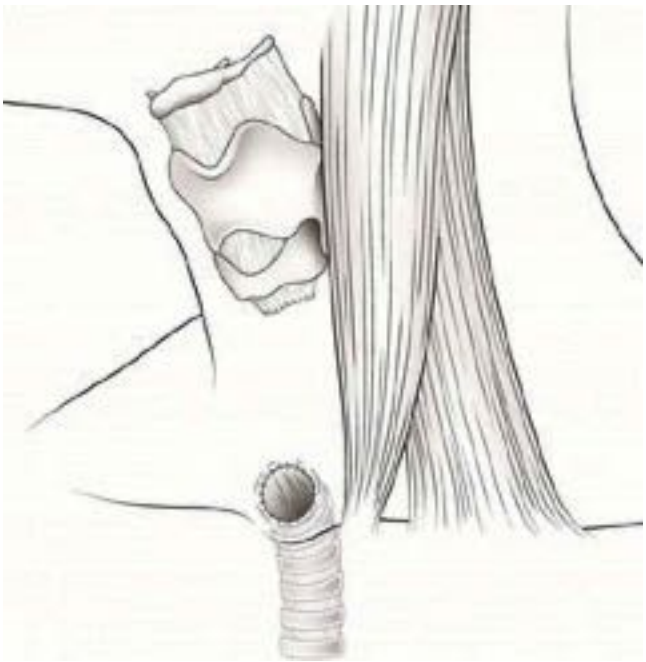


Figure 56.17 Laryngotracheal separation procedure. The airway is closed below the subglottis and the distal trachea is brought out to the skin surface as a stoma.

reasonable, then the safest option is to consider a narrow-field laryngectomy.

There are, however, some intermediate measures to consider before taking such a drastic step. Laryngeal suspension to the hyoid bone is well documented[37] but the results are not always reliable. Part of the problem is that the degree of suspension achieved is fairly limited and often less than 1 cm. The authors have developed an 'enhanced laryngeal suspension' procedure where the thyroid cartilage is removed starting a few millimetres above the level of the glottis, the base of the superior horn of this cartilage is also resected and a more significant thyrohyoid approximation is achieved using braided monofilament sutures. As the sutures in the thyroid cartilage are placed postero-laterally and those in the hyoid near the midline, anterior transposition of the thyroid cartilage is achieved. This technique should be performed synchronously with a cricopharyngeal myotomy and can be combined with a medialization thyroplasty (**Figure 56.18**).

Hans Mahieu[38] performs a standard laryngeal suspension but also suspends the thyrohyoid complex to the mandible (**Figure 56.19**) and includes an upper oesophageal sphincter myotomy. This elevates the larynx away from hypopharyngeal secretions but also pulls open the upper oesophageal inlet.

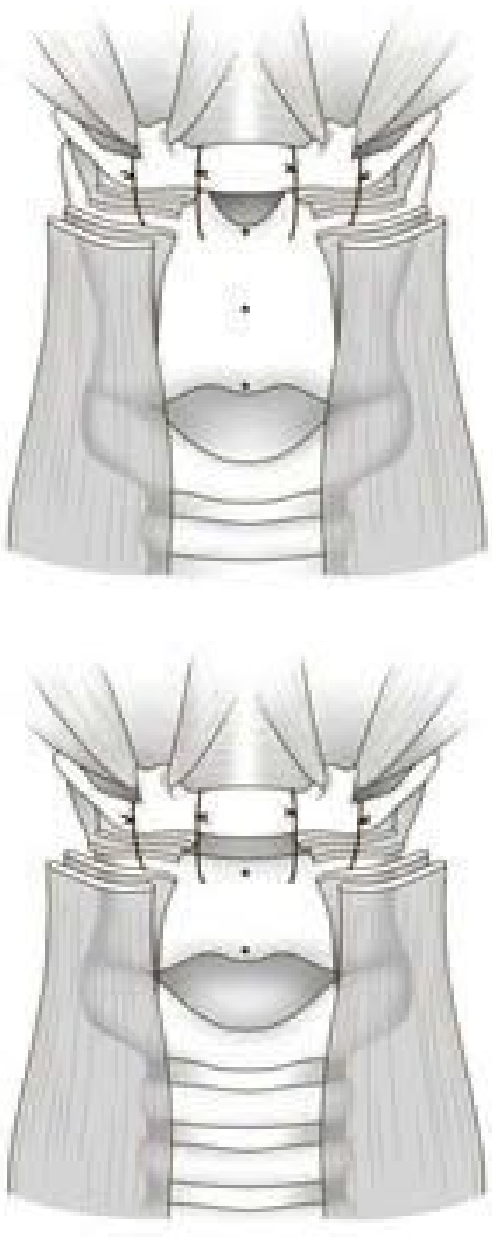


Figure 56.18 (a) a standard laryngeal suspension. (b) an enhanced laryngeal suspension. The thyroid cartilage is excised, from within its perichondrium, above a line representing the level of the glottis (midpoint dot on (a)). The base of the superior horn of the thyroid often needs to be divided to allow successful thyrohyoid approximation.

LARYNGECTOMY

A narrow-field laryngectomy removes the laryngeal skeleton but spares the hyoid, the strap muscles and hypopharyngeal mucosa allowing for a multiple layer closure with reduced incidence of a fistula. Preservation of pharyngeal mucosa also means that pharyngeal closure could be achieved using a linear stapling device[39] and feeding commenced within 5–7 days.

DISCUSSION

The ideal surgical procedure for chronic aspiration would be simple, associated with few complications, allow speech and swallowing, and be easily reversible without long-term sequelae. The majority of patients with a

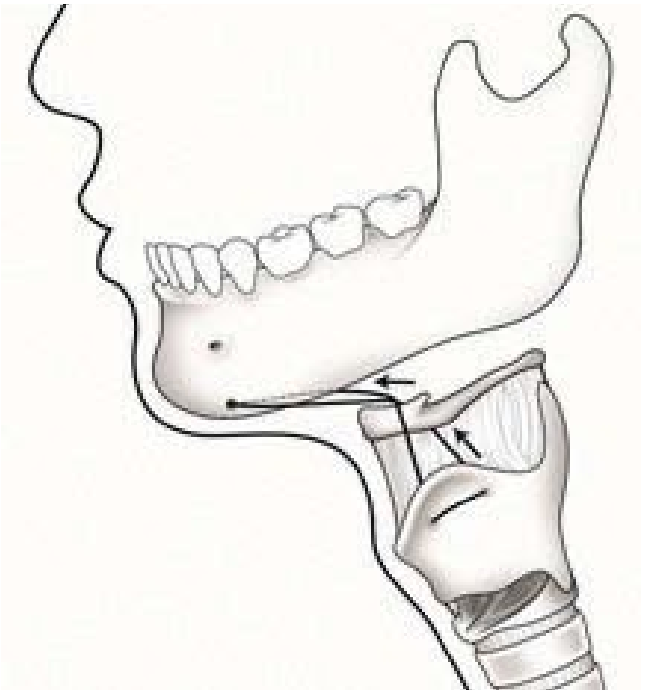


Figure 56.19 Thyrohyoid complex is suspended to mandible.

reversible neurological deficit tend to show recovery within a few months and it is the practice in most units to manage these patients with tracheostomies and feeding tubes even though this may be far from ideal. There are therefore very few indications for reversible procedures. Dysphagia with mild aspiration due to dysfunction of cricopharyngeus, weakness of the hemilarynx or reduced pharyngeal constrictor activity can usually be managed with a cricopharyngeal myotomy, vocal cord medialization with or without excision of the redundant pharyngeal mucosa. Laryngeal or laryngohyoid suspension may be considered in more severe cases.

The difficult decision is in those patients who are not going to recover a safe swallow or who are suffering with either a neurological condition that is progressive, or severe scarring and contracture related to radiotherapy treatment. Supportive procedures described above may be helpful for a period but there will come a time when a laryngectomy may become the procedure of choice. It provides a definitive separation of the respiratory and digestive tracts. Feeding tubes and tracheostomies are avoided and depending on residual dexterity and neurological function surgical voice restoration may be possible.

KEY POINTS

- Swallow disturbances may arise from deranged function in the oral cavity through to the oesophagus.
- Dysphagia patients should be assessed in the MDT clinic.
- Directed dysphagia history will identify the likeliest cause of dysphagia.
- Qualitative questionnaires can help chart management response.
- Swallow therapist instruments for swallow including FEES VFS are necessary before trialling intervention.
- Temporary procedures should be trialled before embarking on irreversible surgical correction of aspiration.
- The larynx is the prime organ for airway protection whilst the pharynx is actively involved in deglutition.

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CHAPTER 57

TEMPOROMANDIBULAR JOINT DISORDERS

Andrew J. Sidebottom

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SEARCH STRATEGY

Data in this chapter are based on a PubMed search using the keywords: temporomandibular joint, temporomandibular disorder, TMJ pain, myofascial pain, rheumatoid arthritis, arthroscopy, arthrocentesis and joint replacement.

INTRODUCTION

Temporomandibular joint (TMJ) problems are a common cause of morbidity with around 30% of the population complaining of problems related to the joint at some stage during their life. Approximately 10% of the population has one or more TMJ symptom or sign at any one time. Differential diagnosis can be confusing and patients are often considered to have 'earache' and referred for ear, nose and throat (ENT) advice. This chapter will aim to provide guidance in the differential diagnosis and primary management of TMJ disorders, with advice when onward referral for subspecialist surgical advice is appropriate.

The most common form of TMJ disorder has various names, including TMJ pain dysfunction, myofascial pain dysfunction and TMJ dysfunction syndrome. Internationally the term temporomandibular disorder (TMD) has been largely introduced from the research and diagnostic criteria. This is a group of disorders of the joint and related masticatory muscles and is best defined as a spectrum from internal derangement (disc-related disorder) to masticatory myofascial pain (purely muscle disorder). The majority of this chapter will deal with this spectrum but will include the other less common disorders affecting the joint.

EPIDEMIOLOGY OF TMJ DISEASE

TMJ disorders present in all age groups, but in the under-40s there is little degenerative disease, unless there is a history of significant trauma or joint surgery. In the over-40s there is increasing evidence of remodelling of the joint (wear and tear or osteoarthrosis) and ultimately degenerative disease (osteoarthritis when associated with pain and inflammation), although this may not be the cause of the patient's symptoms. Symptoms however, present more commonly in the under-40s.

In youths (14–30 years), acute restriction of opening is generally due to a reduction in lubrication within the joint – called anchored disc phenomenon[1] – and this can be dealt with effectively by arthrocentesis (joint washout under pressure; see below). Additionally, acute muscle spasm secondary to clenching or grinding (particularly around the time of examinations or other times of stress) is common in this age group. This problem can also affect older age groups at times of stress as the balance of wear

and tear to repair is tilted towards the former by raised adrenaline levels causing increased muscle spasm, with induction of myofascial type symptoms and consequent compression of the joint.

Women seem to be affected more commonly than men with various ratios from 2:1 to 10:1 being reported.[2] The rationale behind this may be a variance in oestrogen joint receptors although the correlation of this is not fully clear, with raised free radicals also being found in joint aspirates of affected individuals.

Predisposing factors include previous trauma to the joint (macro-trauma) including previous open joint surgery, a history of a clicking joint (present in up to 30% of the population) and a history of clenching in particular, but also grinding (nocturnal bruxism), which causes recurrent microtrauma. There is no conclusive evidence for the role of occlusal/dental factors in induction of disease; indeed, the American Association of Orthodontists devoted significant research into this area in the late 1980s to show that orthodontic management did not induce or reduce the incidence of TMJ disorder or clicking during or after orthodontic treatment. Subsequent Cochrane studies[3] have shown no benefit for occlusal modification in the management of TMJ disorders, as much of the literature on TMD are case series, not randomized studies.

HISTORY OF TMJ DISEASE

The primary symptoms to be elicited from the history (**Box 57.1**) are discussed below.

Pain

Pain from TMD may be from the joint itself (TMJ pain) or in the related muscles of mastication (myofascial pain). The history and examination should distinguish these two prior to definitive management, although initial care is the same for both. Often both are interlinked, giving a spectrum of disease from joint pain at one end to muscle pain at the other. Pain should be recorded using a reproducible pain score, such as a 10 cm analogue scale such that outcomes can be assessed.

Pain localized in front of the tragus of the ear, which can be pointed to with the finger, is likely to be TMJ pain. It is often made worse by function (eating and yawning), and may radiate to surrounding structures. Biting on a tongue spatula on the side of the pain induces the pain in the joint, helping to confirm the diagnosis.

BOX 57.1 Symptoms to be determined from clinical history

1. Pain
2. Joint noises
3. Locking
4. Restriction of opening
5. Disturbance of the bite
6. Alteration in facial appearance
7. Other joint disorders, particularly rheumatological and hypermobility

Myofascial pain is often less well defined with complaints of 'numbness' or aching on the side of the face, which is poorly localized but often in the region of the ramus of the mandible or lateral cheek below the zygomatic process or into the temple. This tends to be worse in the mornings, due to clenching or grinding the teeth at night (a habit that can sometimes be confirmed by the patient's partner), or after particularly 'stressful' situations (e.g. a long drive through heavy traffic or around exam times). Occasionally temporalis pain may be described as headache.

Joint noises

Clicking or cracking of the joint are common. Clicking is related to anteromedial displacement of the disc (ADD) of the TMJ repositioning itself over the joint and predisposes to joint disease (see under 'Internal derangement' below). Click alone does not warrant any treatment other than reassurance that it will reduce with time and does not indicate or lead to 'arthritis of the joint'. Cracking or crepitus again does not warrant treatment but suggests 'scarring' or degeneration within or around the joint. Without associated symptoms the patient can be reassured, although occasionally it can be a presentation of arthritic conditions.

Locking

Locking is the inability to either fully open or fully close the joint. Inability to fully open the joint (confusingly called closed lock) will often be overcome following massage, with a click or crunch restoring full opening. This was considered to be due to anteromedial disc displacement with reduction (ADDR), although it may be due to acute muscle spasm of the lateral pterygoid muscle, which attaches to the anterior portion of the disc, or any of the other muscles of mastication (secondary to myofascial spasm). It may also be due to alteration in the lubrication of the joint (anchored disc phenomenon). Inability to fully close over a period of time (open lock) is usually due to a joint effusion (synovial fluid) or blood (haemarthrosis). Both may be secondary to trauma although the former may also be secondary to the acute synovitis seen in rheumatoid diseases. The frequency of locking should be recorded.

Restriction of opening

Normal range of mouth opening for an adult is above 35 mm inter-incisal distance (with upper and lower dentures in if present). An opening greater than 55 mm suggests hypermobility.

Muscle spasm and disc displacement can both cause restriction, as can ankylosis of the joint, trauma or the spasm associated with cervicofacial infection. Opening less than 25 mm in a young adult without associated systemic illness suggests anchored disc phenomenon, due to loss of joint lubrication. This should be managed urgently

by a maxillofacial specialist with an interest in TMD who will consider early arthrocentesis which is usually curative. Significant delay may lead to a permanent restriction (**Figure 57.1**).

Disturbance of the bite

Collapse of the joint with reduction in height of the ramus will cause a premature contact on the side of the collapse. There may be associated centreline deviation of the chin or teeth towards the side of collapse. If both sides collapse the chin point will move backwards (class 2 deformity) with bilateral loss of ramus height and an anterior open bite (inability of the front teeth to bite together).

Alteration in facial appearance

Collapse of the joint may cause retrusion of the chin if bilateral, or rotation of the chin centreline towards the side of collapse. In addition there will be loss of definition of the angle of the mandible due to loss of ramus height (**Figure 57.2**). The opposite features occur where there is joint overgrowth with centreline deviation towards the opposite side and lengthening of the ramus with possible open bite on the affected side.

Other joint disorders

The TMJ can be affected by rheumatoid joint diseases or hypermobility.[4] Rheumatoid disease often presents with pain and ultimately can lead to joint collapse with a disturbance in the way the teeth bite together (malocclusion) or ankylosis. Ankylosing spondylitis may lead to joint ankylosis with pain and restriction of opening. Psoriatic arthropathy also may cause pain, restriction, ankylosis and occasionally joint collapse.

Hypermobility can lead to joint dislocation. This occurs when the condyle of the mandible is displaced anterior and superior to the articular eminence of the temporal bone. It tends to occur in two age groups – young adults with generally hypermobile joints and the elderly who have loose ligaments and overclosure of the jaw due to lack of teeth. The frequency of dislocations should be recorded. Often patients may complain of 'dislocation' when in fact they are describing a click or locking.

CLINICAL EXAMINATION

The aim of clinical examination is to determine the sites of tenderness and the degree of disorder present. The examination comprises the steps shown in **Box 57.2**.





Figure 57.2 (a) A young woman with juvenile arthritis of the TMJ, demonstrating undergrowth on right side. **(b)** The OPG of the same patient showing condylar under-development on the right side.





Figure 57.1 (a) Limited mouth opening in a young man with psoriatic arthropathy. **(b)** Fixed neck flexion in the same patient due to pseudo ankylosing spondylitis.

BOX 57.2 Clinical examination of the TMJ

- Palpation of the joint for tenderness and noises/crepitus laterally and posteriorly with the mouth both closed and open
- Palpation of the masseter muscles for tenderness and areas of muscle tightness
- Palpation of the temporalis muscles for tenderness and areas of muscle tightness
- Use of a tongue spatula to bite between the teeth on each side
- Measurement of inter-incisal mouth opening in millimetres
- Observation of the opening path of the mandible in relation to the maxillary centreline
- Interdigitation of the teeth (dental occlusion)

Palpation of the joint

The TMJ is palpated just in front of the tragus of the ear. Movement consists of rotation in the lower joint space and glide from the upper joint space over the articular eminence at the base of the zygomatic arch. Tenderness may be elicited over the lateral aspect of the joint while stationary or in motion. The posterior aspect of the joint can only really be felt in wide opening by palpating between the back of the joint and the tragal cartilage or with a finger in the external auditory canal. Tenderness over a joint indicates inflammation in the joint related structures of capsule, synovium and bone.

Noises may be palpated and heard such as a click or crepitus (crunching). Due to the close relation of the joint to the ear, the patient may complain of noises that either are intermittent or cannot be palpated or heard by the examiner. Assume the noise is present if the patient complains of it. Tinnitus is not generally a symptom of TMD.

Palpation of the masseter and temporalis

The masseter muscles lie over the vertical ramus of the mandible up to the base of the zygomatic arch. The temporalis lies above the zygomatic arch, extending behind and above the ear and onto the forehead below the hairline. Tenderness in a muscle during clenching or the palpation of tight bands of muscle indicates myofascial spasm and pain.

Headaches may be a symptom of TMJ disorder when there is associated muscle or joint tenderness, but alone are not indicative of TMJ problems. They may also be associated with stress-related disorders.

Use of a tongue spatula

It is relatively difficult and impractical to determine areas of tenderness in the other muscles of mastication and the author does not feel this is necessary in non-specialist practice. Placing a tongue spatula between the teeth and asking the patient to bite on it will elicit pain in the joint on the ipsilateral side or pain in the lateral pterygoid on the contralateral side, and provides a useful indirect palpation of the muscle.

Measurement of inter-incisal opening

The distance between the upper and lower incisors during maximal mouth opening gives a reliable and reproducible measure of loss of function and outcome. Around 97% of the population has an opening of greater than 35 mm and this provides a useful distance to aim for as a treatment outcome. Some patients with an opening greater than this will have subjective restriction and others with an opening less than this will be normal. Improvement in opening following treatment gives a good measure of outcome.

Observation of opening path

Mouth opening tends to deviate towards the side of pathology. The early phase of opening is a rotation of the condyle of the mandible against the disc in the lower joint space. From 20–25 mm, opening continues with glide between the disc-condyle complex and the glenoid fossa of the temporal bone in the upper joint space. This latter movement causes the joint to move away from the side of the gliding. As much of the joint pathology causing restriction is related to upper joint space problems, muscle spasm restricting disc movement or muscle or joint pain restricting movement, the loss of glide is the most common outcome and therefore the 'normal' joint glides causing the jaw centreline to deviate towards the diseased side. Looking for this particular clinical sign aids confirmation of the side and site of the problem.

Interdigitation of the teeth (dental occlusion)

The way the teeth bite together can be altered by joint collapse. If one joint collapses the fulcrum on that side moves superiorly, causing the posterior teeth to meet prematurely on that side and the centreline to deviate towards that side. If both sides collapse, the front teeth will not meet (anterior open bite) when the patient reports they previously did (**Figure 57.3**).

Conversely, if there is an effusion (inflammatory fluid in the joint) or haemarthrosis (blood in the joint) the joint space increases, lowering the fulcrum, preventing the posterior teeth on the side of the effusion from meeting. Minor variances in the occlusion are usually irrelevant.

INVESTIGATIONS

Plain radiographs form the mainstay of initial examination of the TMJ, although they have little diagnostic value as they only show a section of the joint surface and show nothing of the soft tissues associated with the joint. Other pathologies should be excluded (including dental pain, sinus problems, trigeminal neuralgia etc.) from the history and examination, and often an orthopantomogram (OPG) radiograph is taken to exclude possible

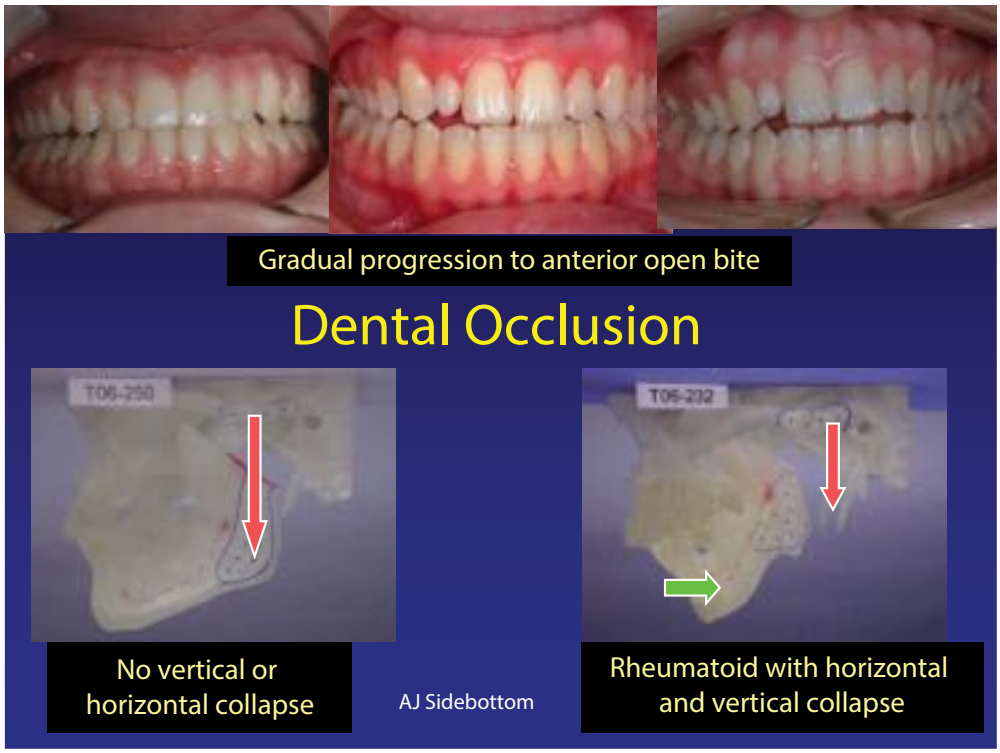


Figure 57.3 These pictures illustrate the development of anterior open bite and ramal collapse in a patient with bilateral temporomandibular joint collapse. The accompanying models of the facial skeleton demonstrate the joint collapse.

dental causes. Transpharyngeal and transcranial views may be requested, as may open and closed views, but they add little to a thorough clinical examination and an OPG showing both TMJs.

Further investigations, where indicated, include an isotope bone scan if hyper or hypoplasia of the condyle is suspected. CT scanning of the joint shows the bony structures well and three-dimensional reconstruction can aid in localizing bony pathology, particularly when joint resection and reconstruction are indicated (**Figure 57.4**). Less dosage but more restricted views can be obtained with cone beam CT (CBCT). The soft tissues are best imaged with MRI scanning, which will help to determine disc displacement, tears and disc movement.

Isotope bone scanning involves injecting the patient with ^{99m}Tc. This circulates the body and is taken up in bone that is actively turning over. Radiographs are taken 2 hours after injection. Uptake is increased at sites of active bone turnover and therefore will show as a 'hot spot' in a hyperplastic condyle. It will also show where there is acute infection (possibly dental). The isotope is largely expelled within 24 hours. Positron emission tomography (PET) is often used at the same time and shows similar results.

CT scans are best placed to show the bony anatomy of the joint and surrounding structures. They are essential in planning for joint replacement, but of little use in assessing the joint soft tissues. The scan itself can be used to generate a three-dimensional computer-aided design/computer-aided manufacture (CAD/CAM) model of the joint to aid planning and reconstruction.

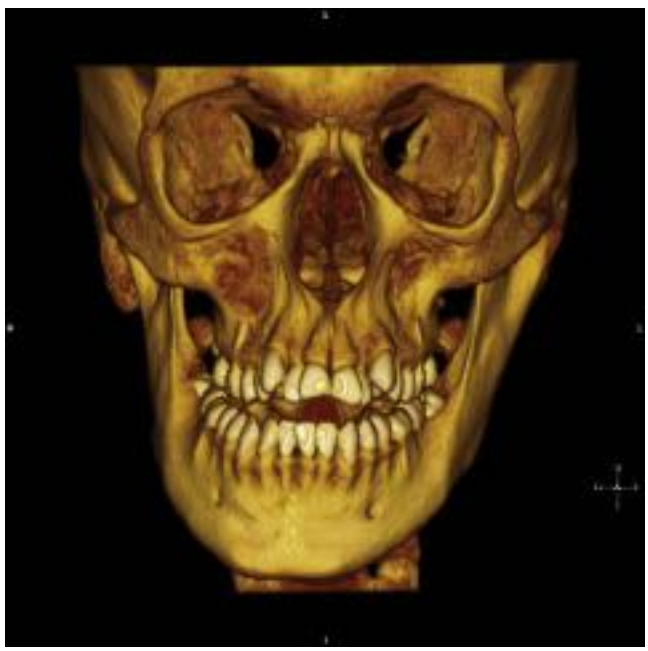


Figure 57.4 3D-CT scan showing left condylar hyperplasia with centreline deviation and lengthening of left ramus.

MRI scanning is increasingly accurate in determining the position and state of the soft tissues around the joint and the position of the disc. Unfortunately these are static scans in the most part and therefore do not look at function. Disc position can be displaced due to pain stopping the disc relocating, lack of intra-articular lubrication

or scarring within the joint holding the disc in position. This cannot be differentiated by an MRI scan and therefore the author tends not to use this modality of assessment as it seems to add little to clinical diagnosis at present. Likewise, the accuracy of the scan lies in the quality of the scan and the quality of the radiologist interpreting it. Even in the best hands, under- and over-diagnosis of disc related disease is made in 50% of cases. The wise surgeon will manage a patient according to the clinical signs and symptoms and not based solely on radiological investigations, which should be an aid to or confirmation of diagnosis.

Arthroscopy, which will be discussed in more detail later (see 'Surgical management of the TMJ' below), in good hands, provides not only a significant aid to diagnosis, but also helps to relieve over 70% of patients of their symptoms.

Open surgical exploration of the joint should only be considered as a last resort and there should be a specific pathology that the surgical treatment is aimed at relieving. It should not be considered as a diagnostic aid.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of TMJ disorders follows the standard surgical sieve. While there are numerous mnemonics for remembering this, the author finds the acronym TINNED VIIM works (**Box 57.3**).

While this surgical sieve is useful, the majority of patients presenting with TMJ symptoms have internal derangement or myofascial pain and these disorders will be dealt with first, followed by the standard surgical sieve.

INTERNAL DERANGEMENT

This condition affects up to one-third of the population at some stage during their lives. Most patients suffer nothing more than a 'clicking joint' and this is so common that some would say it is a normal variant. The clicking may be associated with pain, locking or restriction of movement. Clinical examination should determine if there is tenderness over the joints laterally and posteriorly, whether there is associated muscle tenderness and how much motion the joint can achieve by measuring the inter-incisal distance and lateral deviations. Where in the cycle the click occurs can be useful, but a determination of whether there is any glide (upper joint space movement) is more useful in determining whether there is physical restriction. Movements under 25 mm with no glide (loss of lateral deviation away from the affected side) suggest that the upper joint space is occluded, and the joint spaces are sticking together due to lack of lubrication (anchored disc phenomenon). This can be simply dealt with by early arthrocentesis if 6 weeks of conservative management fail to improve the movement.

There is often overlap of signs and symptoms of internal derangement with myofascial pain. Fortunately the initial management of both of these conditions is the same, namely rest, non-steroidal anti-inflammatory drugs (NSAIDs) and a bite splint[5] (the author uses a lower soft splint as it is cheap and easy to fit) for at least 6 weeks.

BOX 57.3 TINNED VIIM as a surgical sieve

- Congenital lesions
- Acquired lesions:
  - Traumatic
  - Inflammatory
  - Infective
  - Neoplasms:
    - primary
    - secondary
- Nutritional
- Endocrine
- Degenerative
- Vascular
- Idiopathic
- Iatrogenic
- Miscellaneous

INITIAL MANAGEMENT

The primary management of most TMJ disorders initially is reassurance that there is unlikely to be a significant underlying condition, it is unlikely to precede arthritis and the majority of patients can be managed with non-surgical treatment. A significant proportion of patients will have some psychological component to their disease process, whether this is a primary cause or a secondary effect, and the reassurance will go some way to improving their symptoms. Also the placebo effect should effect a 'cure' in around 40%. This explanation should be supported by some form of written leaflet to facilitate retention of knowledge.

Explanation of the disease process along the lines of a 'sprain' of the joint with consequent joint pain due to inflammation and resultant muscle spasm will help to empower the patient and reduce the risk of following internet mis-advice. Initial rest with avoidance of chewy foods (chewing gum and sticky toffees) and tough foods (steaks and crusty bread), and restriction of wide mouth opening (occasionally the pain may have been induced by a long dental visit) will improve symptoms, but this regime must be persisted with for several weeks. The addition of topical non-steroidal anti-inflammatory gels[6] applied to the area of the joint four times daily for 4 weeks will give additional benefit in terms of pain relief and reduction of joint inflammation. Paracetamol as a simple analgesic can additionally be used.

A lower soft full occlusal coverage splint to wear at night should be provided.[5] The patient's dentist should be able to make this. No splint has been shown to be better than any other and since a full coverage lower soft splint worn part-time is unlikely to cause untoward occlusal effects, this method is used by the author. Hard splints should cover all the teeth and make a stable occlusion. They are more costly and time consuming, but are recommended by some restorative experts. The splint helps to reduce the load on the muscles and joint overnight, particularly in those patients who have a clenching habit. It will also help to eliminate the habit. It may take a few nights for the patient to get used to the splint and it may take a few

weeks for symptoms to start to improve. There is no benefit shown by occlusal adjustment of the teeth, although some dentists may feel this is the case.[3] Cochrane analysis has shown that doing nothing is just as effective and is much less harmful.

Although physiotherapy may be beneficial in the short term there is no evidence of its long-term efficacy. Steroid injections to the joint should be avoided and it should be left to a maxillofacial surgeon to decide whether these are indicated, as repeated injections may cause joint collapse. While exercises have often been prescribed there seems to be no good evidence that they are beneficial in internal derangement. Often the exercises are poorly explained and carried out inadequately by the patient and it seems illogical to suggest that an injured joint should be exercised – imagine telling a patient with a sprained ankle they should run on it daily! Exercises may, however, be beneficial in mobilizing patients with acute muscle spasm secondary to myofascial pain or following surgery.

Following a 2-month trial of these treatments, if there has been no significant improvement, the above measures cannot be instituted or there is acute severe restriction in opening, then referral to a maxillofacial specialist, preferably with an interest in TMD, should be considered (**Box 57.4**).

Earlier intervention by means of therapeutic arthroscopy (examination and washout of the joint) or arthrocentesis is indicated in patients with restricted opening who fail to improve or in those with persistent locking. Around 80% will improve with this procedure.[7, 8] Additionally arthroscopy under general anaesthesia gives a good idea of how much of the restriction is due to muscle spasm and pain and also whether there is any intra-articular damage. Follow-up physiotherapy gives added benefit.

Where there has been no improvement following arthroscopy, and the joint was normal and mouth opening improved during anaesthesia, it is assumed that the majority of the problem is due to muscle spasm/pain and a muscle relaxant medication may be suggested. Commonly a low dose tricyclic such as amitriptylene or dothiepin is indicated with doses starting at 10 mg and potentially rising to 75 mg titrated to symptoms and side effects. These medications take around 3 weeks to become effective and doses should be increased on a monthly basis until full pain relief is achieved or side effects prevent a further increase in dose. The pain-relieving dose is maintained for 6 months and then the patient should be weaned off, according to recurrence of symptoms, over the next few weeks. Unfortunately, no long-term studies have shown benefit from this management regime. Alternative therapy currently under investigation is the injection of botulinum toxin into the areas of muscle spasm, which is effective in around 70% of patients in the author's series of more than 100 cases.[9]

Other modalities that have been used successfully in myofascial pain include cognitive behavioural therapy, in which the patient receives psychological counselling to prevent the cause of the muscle hyperactivity and manage the pain. Acupuncture may also be successful in dealing with the muscle spasm, but also the pain of internal derangement. It is however difficult to find a suitably trained specialist to manage the TMJ in particular. Transcutaneous electrical nerve stimulation (TENS) can also help in the management of the chronic pain associated with myofascial pain following failure of the other techniques.

Where arthroscopy has shown intra-articular problems these may be addressed with open joint surgery if symptoms do not improve. A variety of techniques have been used along orthopaedic principles, with, ultimately, joint replacement as the final option. The latter is not to be considered lightly and in the UK at present fewer than 100 total joint replacements are carried out each year by a small handful of recognised joint replacement surgeons. National guidelines suggest when these may be indicated.[10]

BOX 57.4 When to refer for maxillofacial advice

- Acute severe restriction of opening
- Failure of simple conservative measures in conjunction with dentist over 2 months
- Associated rheumatological disease
- Recurrent dislocation of the joint
- Disturbance of the dental occlusion

CONGENITAL

Congenital lesions of the joint are uncommon and often lead to facial asymmetry.

HEMIFACIAL MICROSOMIA

Some of the effects are due to failure of the condyle to develop, possibly secondary to loss of the blood supply in utero. This causes associated undergrowth of the ear, ear canal, joint and fossa to varying degrees. This is a complex craniofacial disorder and should be managed in a supra-regional craniofacial centre. The management involves craniofacial bone and soft tissue reconstruction in various stages throughout life. It may occur on both sides.

CONDYLAR HYPERPLASIA

This is due to either overgrowth of the condylar growth centre on one side before or during puberty, or continued growth after completion of puberty with cessation of growth on the contralateral side. The patient will present with progressive disturbance of the occlusion, usually with centreline deviation of the dental centreline and associated deviation of the chin point (hemimandibular hyperplasia) (see **Figure 57.2**). It may also present with bowing of the mandible downwards and associated maxillary dentoalveolar compensatory growth with the occlusion developing a downward cant towards the side of the abnormality (hemimandibular hypertrophy). There is not

usually associated pain, although in the adult onset version there may be limited translatory movement of the TMJ on the affected side.

Diagnosis is aided by seeing an elongated condylar neck on OPG (pubescent type) or an abnormal condyle (post-pubescent). Ongoing growth can be confirmed by an isotope bone scan using ^{99m}Tc or a PET scan. These will both show increased uptake on the affected active side. Management where there is increased uptake is to remove the growth plate by means of a condylar shave procedure where the cartilage growth centre is removed surgically.[11] If the disease is burnt out or has been treated by condylar shave, the resultant deformity and centreline correction is managed by orthognathic surgery (jaw realignment). These procedures require referral to a maxillofacial surgeon.

TRAUMATIC

Trauma to the TMJ is a common occurrence in fractures of the mandible. The majority of facial fractures in the UK are related to interpersonal violence. Condylar fractures are one of the more common mandibular fractures, occurring in around 30% of cases. They may also occur bilaterally or be associated with fractures elsewhere on the bony mandible. Occasionally the fracture may involve the temporal bone (with haemotympanum) or may cause perforation of the external auditory canal (with associated bleeding form the external canal).

In children fractures of the condyle tend to occur within the capsule and are difficult to treat operatively. Diagnosis in a child follows a direct blow over the joint or an indirect blow to the mandible elsewhere, particularly the chin. The child will complain of pain in the area, difficulty opening the mouth fully and sometimes inability to close the teeth together due either to bone displacement (contralateral open bite) or fluid within the joint (ipsilateral open bite) secondary to intra-articular soft tissue injury. There will be swelling and tenderness over the area of the fracture and the occlusion may be disrupted as above.

Initial management is often with mobilization and analgesia as this injury can affect the secondary growth plate in the condyle, causing undergrowth, overgrowth or fusion of the joint surfaces (ankylosis). Intermaxillary fixation (holding the teeth together with elastics or wires) for a 2–4-week period may be considered where the occlusion is deranged. Occasionally, internal fixation may be considered with resorbable plates.

Effusion or haemarthrosis should be managed with arthrocentesis to enable joint recovery.

The child should be monitored long term to observe for growth abnormalities such that these can be treated at a stage when compensatory growth has not occurred to such an extent to make future management more difficult.

In the adult the fracture pattern is often different. Extra-capsular fractures are more common. Symptoms and signs are similar to those in children with pain over the site of the injury and on function, swelling and possible malocclusion. If the occlusion is normal then the fracture is managed non-operatively with a soft diet and mobilization for 4–6 weeks. Derangement of the occlusion warrants management either with intermaxillary fixation of some variety or, in some cases, open reduction and internal fixation with miniplates may be required. There is considerable controversy as to the best way of managing these fractures and the reader is referred to the standard maxillofacial trauma texts if they are interested in considering this further. Growth disturbances and ankylosis are much less common in adults. Dislocation into the middle cranial fossa has been rarely described. These injuries should all be managed by a suitably trained oral and maxillofacial surgeon.

INFECTIVE TMJ DISORDERS

Infection of the TMJ is an uncommon occurrence in the developed world. It does, however, remain a major source of morbidity.

Infection may be due to direct infection of the joint, from local spread from the surrounding structures or due to deposition from a distant site, usually from a polyarticular infective processes.

Primary infection may be of the intra-capsular bone – osteomyelitis – or infection of the intra-articular soft tissues – arthritis. Both can be destructive of bone and soft tissues and lead to either joint collapse or ankylosis (fusion) of the joint. In childhood they will lead to secondary growth arrest with subsequent deformity. The usual organism is *Staphylococcus aureus* in immune competent individuals, with other staphylococci or unusual organisms where the host is immunocompromised.

The most common cause of infection is spread from neighbouring structures of the ear, brain and nasopharynx. All of the organisms causing mastoiditis, otitis media and meningitis can be implicated, but again *Staphylococcus* spp. are most likely to invade the joint. The effects of the infection long-term are similar to those from direct infection, but in children ankylosis often ensues.

Haematogenous spread rarely occurs, but is occasionally secondary to enteric organisms (*Salmonella* spp.) or systemic organisms causing a more generalized polyarthritis (syphilis, bacterial endocarditis, septicaemia). Effects are similar to the other two causes, but often the systemic infective process carries more morbidity and risk of mortality.

Diagnosis is from a history of pain and swelling localized to the area of the joint, with acute onset limitation of movement. The patient will have generalized signs of an infective process with pyrexia, rigors, sweating (particularly night sweats) and malaise. They may also have signs and symptoms of other joint involvement. Locally there will be the signs of acute inflammation with tenderness over the joint, swelling, redness and heat. There may be additional cervical lymphadenopathy and tenderness over the mastoid if there is middle ear involvement.

The diagnosis can be confirmed with aspiration of pus from the joint and this should be sent for urgent culture and sensitivities. The patient should be admitted

to hospital and broad spectrum intravenous antibiotics should be commenced with thorough arthrocentesis of at least 500 ml of isotonic solution or until the aspirate is clear. This should be repeated if necessary. The advice of a microbiologist should be sought for local sensitivities in guidance for antibiotic treatment. General systemic support would include antipyretic (paracetamol and NSAID) and adequate hydration, with management of the causative disease process. Systemic involvement with septicaemia may require admission to intensive care.

Ultimate management may involve open surgical drainage. The long-term sequelae of the process may require further surgical input and early maxillofacial surgical advice is essential, in addition to long-term support. Reconstruction and rehabilitation may require open surgical procedures, osteotomies, rib grafts or joint replacement.

INFLAMMATORY DISEASE OF THE TMJ

Many of the inflammatory arthropathies can affect the TMJ.[12] Rheumatoid disease can occur in the child, adolescent and adult. It will usually present with the signs and symptoms of synovitis, namely pain, swelling, heat and restriction of movement, and therefore can be difficult to differentiate from infective causes. Progression can lead to joint collapse resulting in malocclusion with an anterior open bite and a retrusive chin (see **Figure 57.3**). Usually other joints, particularly the hands and feet, will have been involved for some time, as rheumatoid disease is a polyarticular arthropathy tending to affect the smaller joints. Diagnosis can be confirmed serologically with a positive rheumatoid factor present in 80%. Sero-negative arthropathy can occur with a similar clinical picture. In the head and neck there can be associated dry mouth, dry eyes (Sjögren's syndrome) and difficulty with oral hygiene due to involvement of the hands.

Management of the rheumatoid TMJ should initially follow the same principles as for most TMJ disorders. Rest, with a soft diet and avoidance of wide opening, NSAIDS (topical or systemic) regularly and a soft splint to rest the muscles, which may be overactive, and to offload the joint. Early consideration of arthroscopy and arthrocentesis will help to eliminate the inflammatory mediators from within the joint. If synovitis is active then steroid injection should be considered, although repeated injections, which calm down the inflammatory process, may lead to increased cartilage loss and joint collapse. End-stage management of the collapsed joint is with total joint replacement. A rheumatologist should be involved as they may instigate disease-modifying medication.

Ankylosing spondylitis may initially present similarly in the TMJ. The patients are mostly male and tend to have generalized signs with fixed kyphosis (flexion of the spine, particularly the neck). Classically they are HLA-B27 positive, although this is not exclusive to ankylosing spondylitis. The process leads to ankylosis of the TMJ, and the restriction of mouth opening is made worse by the fixed flexion of the neck towards the chest wall (see **Figure 57.1**). Release of the ankylosis surgically with joint reconstruction is required, optimally with total joint replacement to give a large enough gap to prevent reankylosis and enable adequate function. Fat graft interposition is suggested to reduce the risk of reankylosis.

Psoriatic arthropathy may affect the TMJ, causing acute synovitis, joint collapse or ankylosis. The patients initially present with the skin condition of psoriasis (although up to 50% have minimal skin signs and these may need to be carefully sought out), with involvement often of the larger joints in a degenerative type of arthropathy. Some patients may be HLA-B27 positive and these tend to progress towards an ankylosis picture rather than the synovitis that often characterizes this disease process. Management of the synovitis is with rest, NSAIDs and bite splints. Arthrocentesis can help relieve symptoms, as can steroid injections. Ultimately joint replacement may be required due to joint collapse or ankylosis.

All of the rheumatoid diseases may be managed by a rheumatologist with disease-modifying medication, which may have significant side effects on the oral mucosa and may also interact with various other medications. Routine dental care is essential as the patient may have difficulty with oral care due to hand disability, or have a dry mouth. Bisphosphonates may be used, particularly with osteopenic rheumatoid conditions, and due diligence in general dental management with support to prevent disease to the oral structures is essential such that the occurance of bisphosphonate related osteonecrosis can be prevented. Leucocyte inhibition medication may cause mild immunosuppression and aggressive management of infection is essential in these patients. Stopping these medications prior to any form of surgery should be discussed with the rheumatologist as they can inhibit wound healing.

NEOPLASTIC DISEASE OF THE TMJ

Neoplasms may be primary or secondary, benign or malignant. Primary benign neoplasms of the TMJ are rare and include chondroma, synovial chondromatosis, osteochondroma and osteoma. Malignant neoplasms are even more uncommon and the condyle seems to be preserved when the mandible is invaded by squamous carcinoma. Chondrosarcoma, osteochondrosarcoma and osteosarcoma are extremely rare in the head and neck and even more so in the condyle. They are dealt with elsewhere in this book. The slightly anomalous pigmented villonodular synovitis behaves as a neoplasm with locally invasive tendency, but again is rare.

Benign neoplasms tend to slow growth (the commonest being osteochondroma) and therefore can present with pain, loss of movement and slowly progressive deformity with a lateral open bite on the side of the neoplasm. There is occasional centreline shift of the chin and dental centreline, but more commonly downward bowing of the lower border of the mandible occurs. Diagnosis is from clinical and radiological examination, supported, if necessary, by open joint surgery to biopsy or excise the lesion

and subsequent reconstruction and/or orthognathic correction of the resultant malocclusion and facial deformity.

Synovial chondromatosis is a rare condition that affects the joint, often secondary to degenerative disease. Production of large numbers of small chondromata from the synovium occurs, producing numerous millimetre-sized, rounded loose bodies in the joint. These affect joint function (with pain, locking and noises) and can induce pain. Management is with open washout as they are often too large to pass through an arthroscope. This should allow the joint to function although there is often degenerative change that warrants surgical treatment in its own right. It is felt to be due to overproduction of cartilage by the synovium and therefore synovectomy is advocated.

Metastasis may occur to the condyle as to any other region of the mandible. The common neoplasms metastasizing to bone include breast, kidney, thyroid, and colon with osteolytic lesions and the prostate with osteosclerotic lesions. Diagnosis and management of the primary site is essential, but the metastasis should be managed symptomatically with either resection and reconstruction, radiotherapy or pain management.

DEGENERATIVE DISEASE OF THE TMJ (OSTEOARTHROSIS)

This is the final common pathway for a number of TMJ conditions from trauma, infection, inflammation, neoplastic and iatrogenic causes. Primary degenerative disease can also occur but it is much less common than involvement of the knee and hip. Overuse causing bone compression is the often-quoted reason for any degenerative joint disorder. Internal derangement of the joint is a very common condition that does not usually lead to degenerative osteoarthrosis if the wear and tear component of this disease can be converted to repair by appropriate non-invasive interventions. It is much less common than degenerative disease of the major joints as the load is significantly less in the TMJ. It tends to occur when the wear and tear in the joint overtakes the repair. Pain, swelling and restriction of movement are the common symptoms. Clinical examination reveals a tender joint with palpable crepitus and restriction of movement, with intermittent swelling.

Radiographic findings are more noticeable on CT scan and include sclerosis, loss of joint space, osteophytes and erosions or cyst formation.

Initial management is with conservative measures followed by arthroscopy, open surgery and, ultimately, joint replacement as above.

IATROGENIC/IDIOPATHIC

The former use of open joint surgery for pain, restriction and joint noises has led to the increasing frequency of degeneration of the joint from multiple operations, particularly in the USA. Surgery for joint noise alone has now been accepted as inappropriate. Less commonly, however, patients following open surgery may have dysaesthetic pain due to damage to the surrounding nerves. This is a debilitating type of pain, which is difficult to manage. It may be of a shooting nature or dull background ache with acute exacerbations. Management under the direction of a pain team is indicated and is usually with low dose tricyclic antidepresants or antiepileptic medication (carbamazepine, gabapentin, etc.).

SURGICAL MANAGEMENT OF THE TMJ

Surgery of the joint can be divided into closed and open surgery. Closed surgery comprises arthrocentesis and arthroscopy.

Arthrocentesis is the washing out of (usually) the upper joint space with isotonic solution under pressure (recommended 150 mm Hg) using around 200 ml of solution to eliminate inflammatory mediators and free radicals and to re-lubricate the joint initially with the solution, but allowing the lubricant producing cells to recover. Usually two needles are used to carry out this procedure – inlet and outlet. Whilst this procedure can be performed under local anaesthesia potentially with sedation, the preference in the UK is for general anaesthesia (GA). The advantage of carrying out the procedure under GA is that the patient can be examined with the muscles relaxed, giving a good idea of the degree of restriction due to muscle spasm. It is a day case procedure and has been shown to be successful in improving 70–80% of cases of locking, restriction and pain.[1, 7, 8]

Arthroscopy is a similar procedure, although a small rigid fibre-optic endoscope is inserted into the joint rather than two needles. A needle is still used as the outlet. The scope size varies from internal diameter of 2.1 mm, although disposable endoscopes of 1.2 mm are now available. There is some debate regarding the advantage of arthroscopy over arthrocentesis, as the insertion of a larger scope should carry more morbidity. The rationale behind inserting a scope is to aid in diagnosis, not outcome. The outcomes are similar for arthroscopy and arthrocentesis, but arthrocentesis does not see into the joint and will miss diagnoses of disc damage, joint surface damage, scarring and synovitis, and the accuracy of this technique in experienced hands is very high.[13] There have been no comparisons of complications with arthrocentesis and arthroscopy and no long-term obvious detrimental effects of arthroscopy have been reported, other than an ~1% risk of temporary temporal branch weakness of the facial nerve.

Open joint surgery follows the principles of orthopaedics. The joint is approached via a pre-auricular incision, staying close to the cartilaginous auditory meatus to avoid damage to the temporal branch of the facial nerve. If there is damage to the disc this is removed and may or may not be replaced with temporalis muscle flap or auricular cartilage, although there has not been any benefit shown to providing this replacement. Damage to the joint surfaces can be improved using eminoplasty (modification of the articular eminence) or condylar shave (modification of the condylar head). The outcomes of this surgery following

failed arthroscopy are around 60% discharge with manageable symptoms.[14]

Severe degeneration of the joint with associated pain and restriction of opening, ankylosis or inflammatory joint disease with joint collapse warrant joint replacement. Whilst this was often with a costochondral graft (rib), recently alloplastic joint replacement has become the mainstay of treatment using a combination of cobalt-chrome and titanium or all titanium on high molecular weight polyethylene for replacement (similar to total knee replacement). Outcomes of 90% joint survival at 15 years[15] are reported with improvement of dietary scores and pain of 90% at one year[16] and significant improvements in mouth opening. The frequency of use of this procedure warrants, at present, the surgery only being carried out in limited numbers by a few high volume operators, although the indications seem to be increasing. For this reason NICE guidelines have suggested indications for this line of management.[17]

CONCLUSION

Temporomandibular disorders are a common cause of morbidity in general practice, although most can be managed with simple measures, such as reassurance that joint noises do not require any form of management and do not necessarily lead to degenerative joint disease. The final common pathway of a number of conditions is degenerative disease and surgery should be considered a last resort.

KEY POINTS

- TMJ problems are largely managed conservatively with little requirement for surgical input.
- Most TMJ problems do not progress to arthritis.
- Symptoms include pain, restriction of opening, locking and joint noises.
- Signs include tenderness/spasm in muscles of mastication, limitation in opening < 35 mm, deviated mouth opening, joint line tenderness, rarely malocclusion.
- Initial management is rest, topical anti-inflammatories, muscle massage and a bite splint.
- Early arthrocentesis is useful in acute severe restriction of opening.
- Arthroscopy is both diagnostic and therapeutic.
- Open surgery should only be considered where arthroscopy has demonstrated an abnormality which has not responded.
- Joint replacement is the final common pathway and should only be undertaken by a surgeon with experience and training in this technique.

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CHAPTER
58

ANATOMY OF THE LARYNX AND TRACHEOBRONCHIAL TREE

Nimesh N. Patel and Shane Lester

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SEARCH STRATEGY

Data in this chapter are based on a PubMed search using the keywords: larynx, airway, trachea, bronchi and pulmonary.

INTRODUCTION

The human larynx protects the lower respiratory tract, provides a controlled airway, allows phonation and allows the generation of a high intrathoracic pressure for coughing and lifting. The evolution of the larynx provides an insight into its functional priorities. In its most primitive form, it can be found as a muscular sphincter around the entrance to the respiratory tract in the Bichir lungfish (*Polypterus bichir*), controlling the entry of water and the expulsion of air from the lungs. A further evolutionary variant is seen in the Mexican salamander, which possesses lateral cartilages that aid in opening and maintaining patency of the respiratory tract. The ability of the larynx to facilitate speech is only found in humans and represents a more specialized function of the larynx; it is, therefore, a very late evolutionary event.

To fulfil its complex functions the larynx has to be mobile, coordinated and sensate. In rehabilitating the damaged larynx there is often a need to make a trade-off between optimum airway, voice and swallowing.

EMBRYOLOGY

Embryology of the larynx

At four weeks of embryonic development, an outgrowth of the primitive foregut forms the primordial respiratory system. The epithelium of the larynx, trachea and bronchi is of endodermal origin and the other soft tissues arise from the surrounding splanchnic mesoderm (fourth and sixth branchial arches).

The traditional theory of respiratory system embryology states that there is initially a wide communication with the foregut, which expands and becomes separated by two longitudinal oesophagotracheal ridges. These were thought to fuse to form a septum dividing the ventral trachea and lung buds from the dorsal oesophagus. More recent research supports assertions that the respiratory diverticulum develops from the ventral aspect of the foregut and elongates, drawing out a stalk and giving rise to the trachea (**Figure 58.1**). It is proposed that the septum is present from the initial appearance of the lung buds and that there is no migration of the separation point while the trachea descends.

When moving in a craniocaudal direction, the larynx, which is formed at the most cranial end of the respiratory tract, then leads to the trachea, bronchi and lungs. These tubes of endoderm, which project ventrally from the foregut, elongate into the surrounding mesenchyme from which the connective tissue, cartilage, non-striated muscle and vasculature of the bronchi and lungs develop.

Arytenoid swellings appear on both sides of the tracheobronchial diverticulum and, as they enlarge, the epithelial walls of the groove adhere to each other, and the aperture of the larynx is occluded until the third month, when the lumen is restored. The rudimentary laterally based arytenoid swellings elongate cranially, creating a cleft that is open cranially and bounded laterally by the aryepiglottic folds. More ventrally, at the front of this cleft, the hypobranchial eminence becomes the epiglottis.

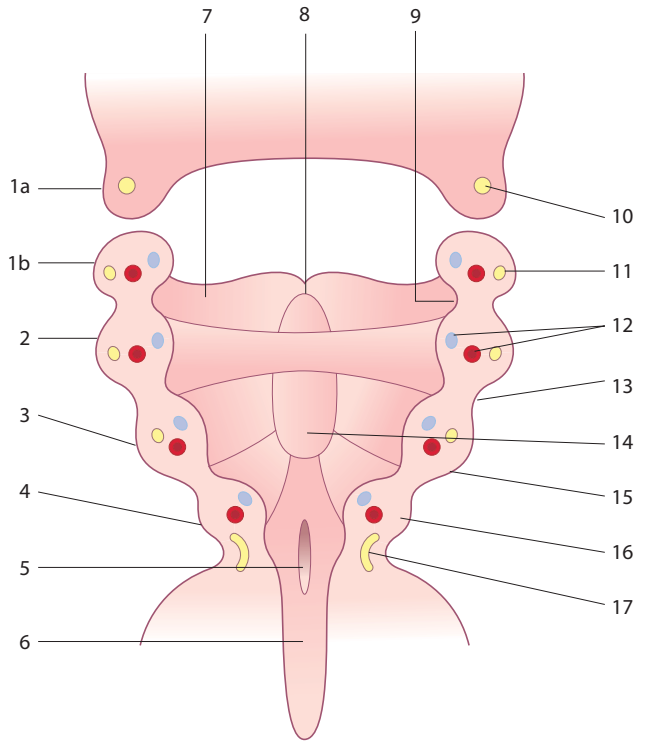


Figure 58.1 1) Arches and elevations in the floor of the foregut; 1a) First arch, maxillary process; 1b) first arch, mandibular process; 2) second pharyngeal arch; 3) third pharyngeal arch; 4) fourth pharyngeal arch; 5) tracheobronchial diverticulum; 6) oesophagus; 7) endodermal lining; 8) tuberculum impar; 9) first pharyngeal pouch; 10) maxillary nerve; 11) mandibular nerve; 12) cartilage and artery; 13) second pharyngeal cleft; 14) hypobranchial eminence; 15) ectodermal covering; 16) mesenchyme in fourth arch; 17) superior laryngeal nerve.

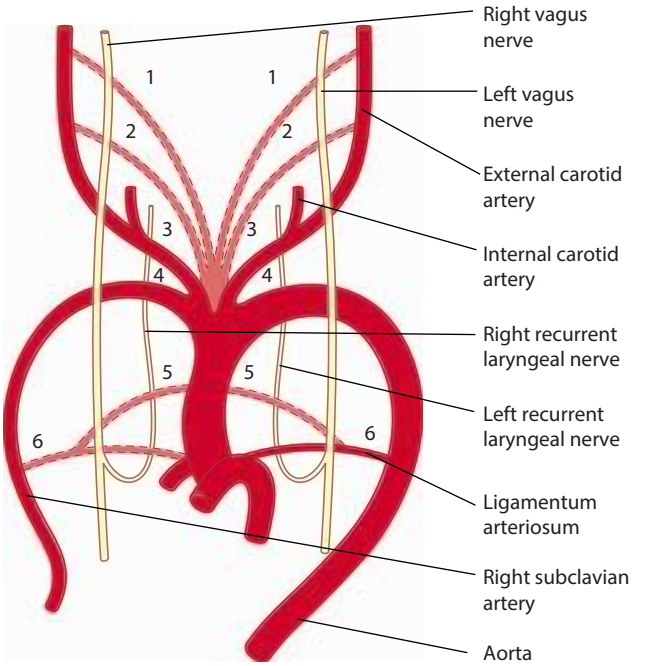


Figure 58.2 The relationship between development of the branchial arches and recurrent laryngeal nerves. The numbers indicate the number of the branchial arch.

The glottis forms just above the level of the primitive aperture. Surrounding this, the thyroid cartilage develops from the ventral ends of the cartilages formed in the mesoderm of the fourth pharyngeal arch and appears as two lateral plates, each of which possesses two chondrification centres. The cricoid cartilage and the cartilages of the trachea develop from the sixth arch during the sixth week of gestation. The trachea rapidly increases in length in a craniocaudal direction from the fifth week of gestation onwards.

The mesoderm of each pharyngeal arch differentiates into the cartilage, muscle and vascular structures of that arch. As part of its dorsoventral direction of development, each arch receives an afferent and efferent nerve supply for the skin, muscles and endodermal lining of that arch, which in the case of the fourth and sixth arches are the superior and recurrent laryngeal branches of the vagus nerve respectively. The primitive recurrent laryngeal nerve enters the sixth visceral arch on each side below the sixth aortic arch artery. On the left side, the arch artery retains its position as the ductus arteriosus so the nerve is found below the ligamentum arteriosum after birth. On the right side, the dorsal part of the sixth arch artery and the whole of the fifth arch artery disappear, leaving the nerve below the fourth arch artery, which becomes the subclavian artery (**Figure 58.2**). Occasionally, the proximal portion of the fourth arch artery also disappears leaving nothing in contact with the right recurrent laryngeal nerve, which, instead of being pulled down into its usual position, passes directly from the main vagal trunk to enter the larynx, demonstrated as the non-recurrent laryngeal nerve.

Embryology of the trachea and bronchial tree

The trachea and the two lateral bronchial buds form from the lung bud and at the fifth week each bronchial bud develops into a main bronchus. The right goes on to form three secondary bronchi, the left developing into two. They continue to grow caudally and laterally, expanding into the developing body cavity. During further development there are further divisions of the buds in a dichotomous fashion. By the end of the sixth month there are approximately 17 generations of subdivisions. An additional 6 divisions occur during postnatal life to form the final structure of the pulmonary tree.

ANATOMY OF THE LARYNX

General description

The larynx extends from the laryngeal inlet to the inferior border of the cricoid cartilage (**Figure 58.3**). In the absence of respiration at neutral lung volume, it lies in front of the third to sixth cervical vertebrae, being a little higher in women than in men.

The infantile larynx is proportionally smaller than that of the adult compared to body size and is more

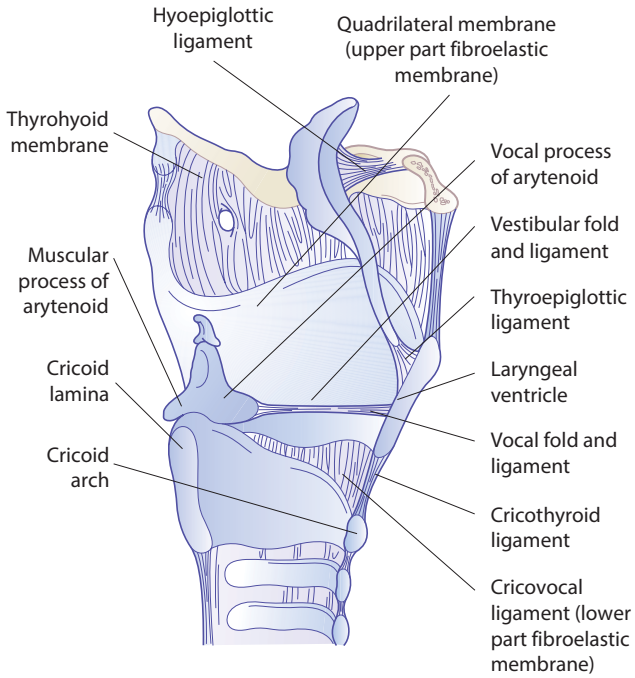


Figure 58.3 Sagittal section across the larynx looking laterally.

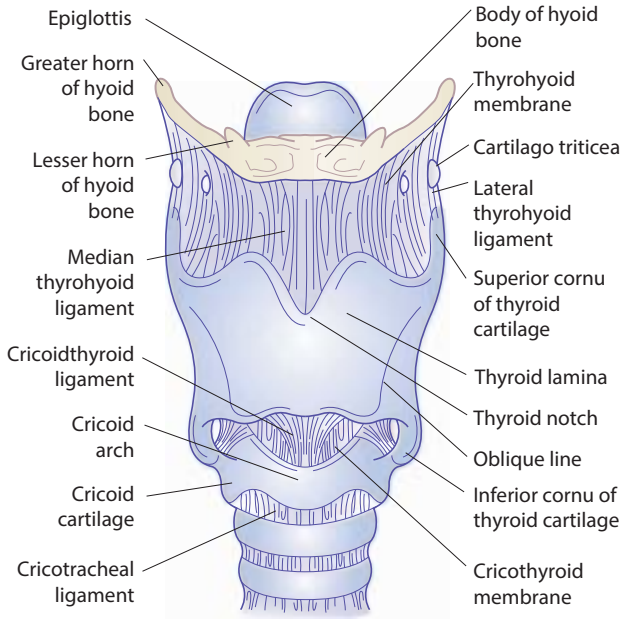


Figure 58.4 The framework of the larynx.

funnel shaped. Its narrowest part is at the junction of the subglottic larynx with the trachea and even a slight swelling in this area may result in marked airway obstruction. In contrast, the narrowest part of the adult larynx is the glottis. The laryngeal cartilages are much softer in the infant than the adult and collapse more easily on forced inspiration as a consequence of the Bernoulli effect. The larynx starts high up under the tongue in early life and with age assumes an increasingly lower position in the neck. As the larynx grows, there is little difference in its size between boys and girls until after puberty when the anterior–posterior (AP) diameter of the larynx almost doubles in men to reach a final AP dimension average of about 36 mm in men and 26 mm in women.

The larynx is divided anatomically into the supraglottis, glottis and subglottis by the false and true folds (see **Figure 58.3**). The term 'vocal cord' is not anatomically accurate; the term vocal fold is more appropriate. Vocal cord is an inaccurate term that has remained in common use and fails to emphasize the layered structure of the vocal fold. In addition, the term 'cord' does not give a sense of a structure that might vibrate in the vertical (and indeed multiplanar) fashion that the vocal folds have been shown to do.

In a craniocaudal direction, the supraglottis commences at the epiglottis and aryepiglottic folds as they sweep down to the arytenoids. Its lower border is a horizontal line drawn through the apex of the laryngeal ventricle. This line, therefore, also forms the upper border of the glottis. The glottis extends caudally from this line and includes the vocal cords as well as anterior commissure and posterior commissure. The line of demarcation between the glottis and the subglottis has been debated in the literature at some length but is now widely accepted to be a line drawn 1 cm below the free edge of the vocal folds. More definitively, the subglottis becomes the trachea at the lower border of the cricoid.

The framework of the larynx consists of the hyoid bone and a number of cartilages connected by ligaments and membranes, as well as intrinsic and extrinsic muscles. It is lined with a mucous membrane that is continuous above with the pharynx and below with that of the trachea. The spaces around the larynx are filled with adipose tissue and loose connective tissue, the 3D orientation of which are key to understanding the spread of tumours within the larynx.

The framework of the larynx

HYOID BONE

The hyoid is a U-shaped bone that is suspended by several suprahyoid muscles and ligaments from the bony structures of the skull base and mandible, and provides the superior attachment for many of the extrinsic muscles of the larynx, thereby suspending the larynx in the neck (**Figure 58.4**). The hyoid bone consists of a body anteriorly from which the greater cornua project backwards on each side. The lesser cornua are two small conical eminences that are attached to the upper aspect of the body of the hyoid laterally (and sometimes from the medialmost aspect of the greater cornua), either by a fibrous band or, sometimes, by way of a synovial joint.

THYROID CARTILAGE

The thyroid cartilage is composed of two laminae that are fused in the midline anteriorly giving rise to the laryngeal prominence (see **Figure 58.4**). The angle of fusion is about 90° in men and 120° in women. The posterior border of

each lamina is prolonged above and below to form the superior and inferior cornua, respectively. The superior cornu is long and narrow and curves upwards, backwards and medially, ending in a conical extremity to which the lateral thyroid ligament is attached. The inferior cornu is shorter and thicker and curves downwards and medially. On the medial surface of its lower end is a small oval facet joint for articulation with the cricoid cartilage.

On the external surface of each lamina, an oblique line curves downwards and forwards from the superior thyroid tubercle, situated just in front of the root of the superior horn, to the inferior thyroid tubercle on the lower border of the lamina. This line marks the attachment of the thyrohyoid, sternothyroid and inferior constrictor muscles. On the inner aspect of the thyroid cartilage, just below the thyroid notch in the midline, is attached the thyroepiglottic ligament and below this and on each side of the midline, are attached the vestibular and vocal ligaments and thyroarytenoid, thyroepiglottic and vocalis muscles. The fusion of the anterior ends of the two vocal ligaments produces the anterior commissure tendon. The remaining parts of the inner aspect of the thyroid lamina are smooth and are mainly covered by loosely attached mucous membrane. The superior border of each lamina gives attachment to the thyrohyoid ligament and the inferior border, on the medial portion of its inner aspect, the cricothyroid ligament.

CRICOID CARTILAGE

The cricoid cartilage is the only complete cartilaginous ring in the airway (**Figure 58.5**). It forms the inferior part of the anterior and lateral walls and most of the posterior wall of the larynx. It has a deep broad lamina posteriorly and a narrow arch anteriorly with a facet for articulation with the inferior cornu of the thyroid cartilage, near the junction of the arch and lamina. Rotation of the cricoid cartilage on the thyroid cartilage can take place about an axis passing transversely through both joints. The lamina has sloping shoulders on which the articular facets for the arytenoid cartilages are found. A vertical ridge in the midline of the lamina gives attachment to the longitudinal muscle of the oesophagus and produces a shallow concavity on each side for the origin of the posterior cricoarytenoid (PCA) muscle. The entire inner surface of the cricoid cartilage is lined with mucous membrane. The importance of the cricoid in laryngeal health and disease cannot be overemphasized. The luminal mucosa is at risk of necrosis and circumferential scarring, which results in debilitating subglottic stenosis. The cricoarytenoid joint – together with an associated functional PCA muscle – is regarded as a key functional unit of the larynx, facilitating vocal fold motility to ensure a patent airway when abducted and airway protection when adducted.

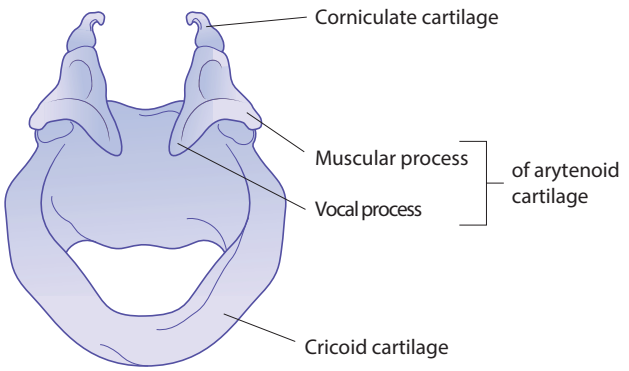


Figure 58.5 The cricoid and arytenoids.

THE ARYTENOID CARTILAGES

The arytenoid cartilages are irregularly shaped, broadly conforming to a three-sided pyramid with a forward projection, the vocal process, to which the dorsal end of the vocal folds are attached a lateral projection, the muscular process, to which the posterior cricoarytenoid and lateral cricothyroid muscles attach (see **Figure 58.5**). Between these two processes, the anterolateral surface is irregular and divided into two fossae by a crest running from the apex. The upper triangular fossa gives attachment to the vestibular ligament and the lower to the vocalis and lateral cricoarytenoid muscles. The apex is curved backwards and medially and is flattened for articulation with the corniculate cartilage, which sits atop it. The medial surfaces have no muscular attachments, are covered with mucous membrane and form the lateral boundary of the posterior glottis. The posterior surface of each cartilage is covered by the transverse arytenoid muscle, which inserts onto each cartilage across the midline.

The base is concave and presents a smooth surface for articulation with the sloping shoulders of the upper border of the cricoid lamina. This is a synovial joint with lax capsular ligaments allowing both rotatory movements and medial and lateral gliding movements. However, the posterior cricoarytenoid ligament is more rigid and prevents forward movement of the arytenoid cartilage on the cricoid.

CORNICULATE AND CUNEIFORM CARTILAGES

The corniculate cartilages (of Santorini) are two small conical nodules of elastic fibrocartilage, which articulate through a synovial joint with the apices of the arytenoid cartilages. They are situated in the posterior part of the aryepiglottic fold. The cuneiform cartilages (of Wisberg) are two small, elongated flakes of fibroelastic cartilage, one in each free margin of the aryepiglottic fold. The function of these cartilages is uncertain. They may act to provide structural rigidity to the aryepiglottic folds somewhat like curtain weights.

EPIGLOTTIS

The epiglottis is a thin, leaf-like sheet of elastic fibrocartilage that projects upwards behind the tongue and the body of the hyoid bone. It is attached inferiorly to the thyroid cartilage, just below the thyroid notch in the midline, by the thyroepiglottic ligament and also to the hyoid bone anteriorly by the hyoepiglottic ligament. The space between

these ligaments forms the pre-epiglottic space. From the sides of the epiglottis, the aryepiglottic folds sweep downwards and backwards to the apex of the arytenoids. The posterior (laryngeal) surface of the cartilage is indented by numerous small pits into which mucus glands project. The anterior (lingual) surface of the epiglottis is covered with mucous membrane superiorly and forms the posterior wall of the vallecula. The mucous membrane overlying the epiglottis is reflected onto the base of the tongue, forming the glossoepiglottic fold in the midline and laterally the lateral glossoepiglottic folds.

Ligaments and membranes of the larynx

EXTRINSIC LIGAMENTS

The extrinsic ligaments of the larynx connect the laryngeal cartilages to the hyoid above and trachea below (see **Figure 58.4**). Superiorly, the thyrohyoid membrane stretches between the upper border of the thyroid cartilage and the posterior surface of the body and greater cornua of the hyoid. The membrane is composed of fibroelastic tissue, reinforced by fibrous tissue in the midline as the median thyrohyoid ligament and posteriorly as the lateral thyrohyoid ligament. The latter connects the tip of the superior cornua of the thyroid cartilage to the posterior ends of the greater cornua of the hyoid. The ligaments often contain a small nodule of cartilage, the cartilago triticea. The membrane is pierced by the internal branch of the superior laryngeal nerve and by the superior laryngeal vessels. The cricotracheal ligament unites the lower border of the cricoid with the first tracheal ring.

INTRINSIC LIGAMENTS

The intrinsic ligaments of the larynx connect the laryngeal cartilages together, strengthen the capsule of the intercartilaginous joints and form a broad sheet of fibroelastic tissue, the fibroelastic membrane, which lies beneath the mucous membrane of the larynx forming an internal framework (see **Figures 58.3** and **58.6**).

The fibroelastic membrane is divided into an upper and lower part by the laryngeal ventricle. The upper quadrilateral membrane extends between the lateral border of the epiglottis and the arytenoid cartilages. The upper margin forms the framework of the aryepiglottic fold and the lower margin is thickened to form the vestibular ligament underlying the vestibular fold (false vocal fold). The lower part is thicker, containing many elastic fibres. It is commonly called the cricovocal ligament, cricothyroid ligament or conus elasticus. It is attached below to the upper border of the cricoid cartilage and above it is stretched between the inner surface of the midpoint of the laryngeal prominence of the thyroid cartilage anteriorly and the vocal process of the arytenoid behind. The free upper border of this membrane constitutes the vocal ligament the framework of the (true) vocal fold. Anteriorly, there is a thickening of the membrane, the cricothyroid ligament, which connects the cricoid and the thyroid cartilages in the midline.

Muscles of the larynx

The extrinsic muscles of the larynx attach the larynx to neighbouring structures and maintain the position of the larynx in the neck (**Table 58.1**). The infrahyoid muscles work in synergy with the elevators of the larynx, one set of muscles relaxing (infrahyoid) whilst the other contracts (suprahyoid) to facilitate laryngeal elevation. Under normal physiological conditions, descent of the larynx is due to elastic recoil of the trachea and lower respiratory tract and therefore, relaxation of the suprahyoid musculature is the only requirement.

The intrinsic muscles are all paired and function in a coordinated fashion to move the cartilages of the larynx thereby governing laryngeal function (**Table 58.2** and **Figures 58.7–58.11**). They control the overall position and shape of the vocal folds as well as the elasticity and viscosity of each layer. The majority of intrinsic muscles act to move the arytenoid at the cricoarytenoid joint. The joint has a complex range of movements but broadly speaking the arytenoid rotates inwards and downwards to close and upwards and outwards to open the glottis.

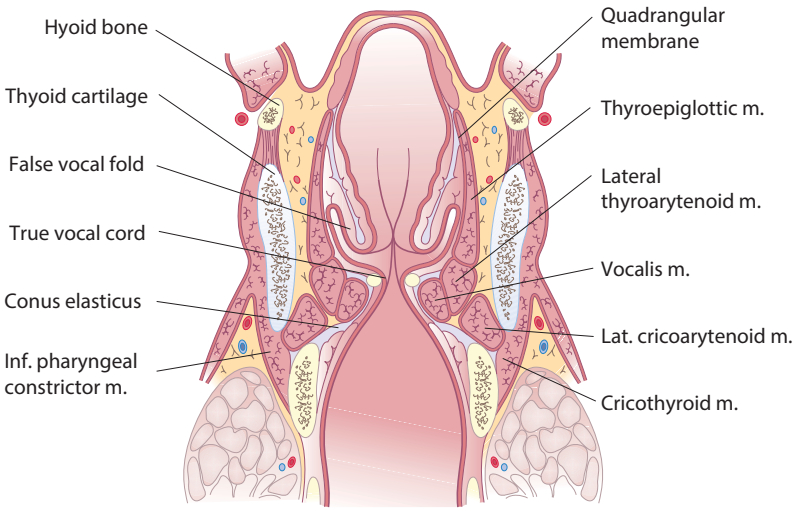


Figure 58.6 Coronal section through the larynx looking anteriorly.

TABLE 58.1 Extrinsic muscles of the larynx

Name	Origin	Insertion	Function	Innervation
Infrahyoid group				
Thyrohyoid	Oblique line of thyroid lamina	Inferior border of the greater cornu of the hyoid	Elevates the larynx on a fixed hyoid or depresses the hyoid on a fixed larynx	Hypoglossal (C1 root)
Sternothyroid	Posterior surface of manubrium and edge of the first costal cartilage	Oblique line of the thyroid lamina	Depresses the larynx	Ansa cervicalis (C2, 3 roots)
Sternohyoid	Clavicle and posterior surface of the manubrium	Lower edge of the body of the hyoid	Depresses the larynx by lowering the hyoid	Ansa cervicalis (C1, 2, 3 roots)
Suprahyoid group				
Mylohyoid	Mylohyoid line on inner aspect of the mandible	Midline raphe and body of the hyoid	Raises and pulls the hyoid anteriorly	Nerve to mylohyoid (inferior alveolar branch of V3)
Geniohyoid	Genial tubercle on mandible	Upper border of the body of the hyoid	Raises and pulls the hyoid forwards	Hypoglossal (C1 root)
Stylohyoid	Back of the styloid process (splits around the digastric tendon)	Base of greater cornu of the hyoid	Retractor and elevator of the hyoid for swallowing	Facial nerve
Digastric	Digastric notch on the medial surface of the mastoid process	Lower border of the mandible (fibrous sling holds the tendon to the lesser cornu of the hyoid)	Anterior belly pulls the hyoid anteriorly and up	Posterior belly – facial nerve
			Posterior belly pulls the hyoid posteriorly and up	Anterior belly – nerve to mylohyoid
Stylopharyngeus	Medial aspect of the styloid process	Posterior border of the lamina of the thyroid cartilage (side wall of the pharynx)	Elevates the larynx	Glossopharyngeal nerve
Palatopharyngeus	Palatine aponeurosis and posterior margin of hard palate	Posterior border of thyroid alar and cornua	Helps tilts the larynx forwards	Accessory nerve (pharyngeal plexus)
Salpingopharyngeus	Eustachian tube	Posterior border of the thyroid cartilage (side wall of the pharynx)	Elevates the larynx	Pharyngeal plexus

The posterior cricoarytenoid is the only abductor of the larynx – and is arguably, therefore, the most important muscle in the body. The thyroarytenoids cause some adduction but largely shorten and thicken whilst altering the tension of the vocal fold. The interarytenoid muscles draw the arytenoids together posteriorly whilst the lateral cricoarytenoid muscles internally rotate the arytenoid cartilages by pulling their muscular processes caudally and anteriorly resulting in vocal fold adduction.

The cricothyroid muscles are the only intrinsic muscle that do not insert into the arytenoid cartilages; they therefore exert their action by bringing the thyroid and cricoid cartilages closer together in a visor-like motion. In doing so both vocal folds are simultaneously stretched with a consequence increase in tension.

Some muscles are able to exert more than one action and therefore possess segmental compartmentalization. For example, the posterior cricoarytenoid has two components with different fibre types, nerve branches and insertions into the muscular process of the arytenoid, which allows for external and backward rotation of the arytenoid cartilage on the cricoarytenoid joint. (See **Table 58.1** for additional examples.)

The glottis

The glottis lies between two horizontal lines, one drawn through the apex of the laryngeal ventricle, the other drawn 1 cm below the medial free edge of the vocal fold when the larynx is at rest. The scaffolding of the false and true vocal folds is formed by the vestibular and vocal ligaments, respectively (see **Figures 58.3** and **58.6**). Laterally, intervening between the vestibular and vocal ligaments, a horizontal slit opens into an elongated recess, the laryngeal ventricle. From the anterior part of the ventricle, the saccule of the larynx ascends between the vestibular ligament and the inner surface of the thyroid cartilage as high in some people as the upper border of the thyroid cartilage. It occasionally protrudes through the thyrohyoid membrane. Fibrous tissue surrounds the saccule. Dilatation of the saccule results in the formation of a laryngocele. The ventricle and saccule can harbour occult cancers and need to be actively inspected during diagnostic endoscopy.

The vestibular folds are thick folds of mucous membrane scaffolded on a narrow band of fibrous tissue, the vestibular ligament, which is the lower border of the upper quadrilateral membrane. It is fixed in front at the angle of the

TABLE 58.2 Intrinsic muscles

Name	Origin	Insertion	Function	Effect
Open and close the glottis				
Posterior cricoarytenoid	Lower and medial surface of the back of the cricoid lamina	It fans out to be inserted into the back of the muscular process of the arytenoid	Opens the glottis. Upper horizontal fibres rotate the arytenoids and move the muscular processes towards each other separating the vocal processes and abducting the cords. Lateral vertical fibres draw the arytenoids down the sloping shoulders of the cricoid separating the arytenoids	Abducts and elevates the tip of the vocal process The vocal fold becomes elongated and thin. The free edge of the vocal fold is rounded and passively stiffened
Lateral cricoarytenoid	Superior border of lateral part of the arch of the cricoid	Muscular process of arytenoid	Adducts and lowers the tip of the vocal process by rotating the arytenoids medially	Vocal fold adducted, lowered, elongated and thinned. The edge of the vocal fold becomes sharp and is passively stiffened
Transverse arytenoids – unpaired	Posterior surface of the muscular process and outer edge of the arytenoid	Crosses over and attaches to the same point on the other arytenoid	Adducts the vocal fold and controls the position of the vocal fold	No significant effect on the mechanical properties of the vocal fold
Oblique arytenoids – paired	Posterior aspect of the muscular process (superficial to the transverse arytenoid)	Apex of the other arytenoid		
Control the tension of the vocal folds				
Thyroarytenoid (vocalis): A broad sheet of muscle which lies lateral to and above the free edge of the cricovocal ligament. The lower part of the muscle is thicker and forms a distinct bundle called the vocalis muscle.	Back of the thyroid prominence and cricothyroid ligament	Vocal process of arytenoid and anterolateral surface of the body of the arytenoid		Lowers, shortens and thickens the vocal folds causing the edge of the fold to be rounded. The body of the fold is actively stiffened but the transition layers are passively slackened. Many fibres are prolonged into the aryepiglottic fold some continuing to the margin of the epiglottis as the thyroepiglottic muscle which tends to widen the inlet of the larynx pulling the aryepiglottic folds slightly apart
Cricothyroid: This is the only intrinsic muscle that lies outside the cartilaginous framework of the larynx	Lateral surface of the anterior arch of the cricoid. Fibres fan out and pass backwards in two groups	Lower oblique fibres pass backwards and laterally to the anterior border of the inferior cornu of the thyroid cartilage. Anterior straight fibres ascend to the posterior part of the lower border of the thyroid lamina		Rotates the cricoid cartilage about the horizontal axis passing through the cricothyroid joint. It lengthens the vocal folds by increasing the distance between the angle of the thyroid cartilage and arytenoids. On contraction, the vocal folds are brought into a line between the anterior commissure and the posterior cricoarytenoid ligament, the level of the vocal folds is lowered and the entire fold elongated and thinned. The edge of the vocal fold becomes sharp and all the layers are stiffened
Alter the shape of laryngeal inlet				
Aryepiglotticus: A continuation of the oblique arytenoid	Posterior aspect of the muscular process of the arytenoid	Fibres pass around the apex of the opposite arytenoid and insert into the aryepiglottic fold		Weak sphincter of the laryngeal inlet
Thyroepiglotticus: A continuation of the thyroarytenoid	Back of the thyroid prominence and cricothyroid ligament	Fibres pass upwards into the aryepiglottic fold		Widens the inlet of the larynx pulling the aryepiglottic folds slightly apart

All the intrinsic muscles of the larynx are supplied by the recurrent laryngeal nerve except the cricothyroid, which is supplied by the external branch of the superior laryngeal nerve. The unpaired transverse arytenoid and paired oblique arytenoid make up the interarytenoid muscle.

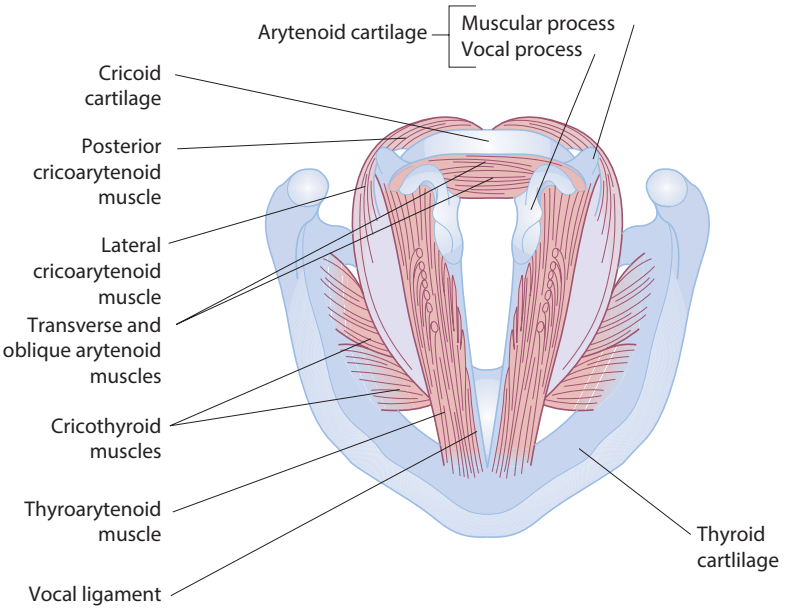


Figure 58.7 Dissected view of the larynx from above

thyroid cartilage just below the attachment of the epiglottic cartilages and behind the anterolateral surface of the arytenoid cartilage just above the vocal process (see **Figure 58.7**).

The vocal folds extend from the middle of the angle of the thyroid cartilage to the vocal process of the arytenoid cartilages and scaffolding them is the upper border of the conus elasticus. Each fold is a layered structure consisting of a superficial layer of nonkeratinizing, stratified squamous epithelium, beneath which is the lamina propria. This has three distinct layers. The superficial layer (Reinke's space) contains a fibrous substance with similar characteristics to gelatin. The intermediate layer contains elastic fibres and the deep layer collagen fibres. The intermediate and deep layers make up the vocal ligament. The vocalis muscle, which forms the main body of the vocal fold, lies lateral and deep. The loose areolar tissue of Reinke's spaces allows lax movement of the overlying mucosa, giving rise to a mucosal waveform during phonation.

The layered structure of the vocal fold is not uniform in its entire length. At the anterior end of the vocal fold there is a mass of collagen fibres (anterior commissure tendon or Broyle's ligament), which are connected to the inner perichondrium of the thyroid cartilage and to the deep layer of the lamina propria posteriorly. Adjacent to this mass of collagen fibres just posteriorly, there is another mass of elastic fibres continuous with the intermediate layer of the lamina propria called the anterior macula flava. A similar structure is seen at the posterior end of the membranous part of the vocal fold. These structures appear to serve as cushions to protect the ends of the vocal folds from mechanical damage caused by vocal fold vibration.

The anterior three-fifths of the vocal fold (from the anterior commissure to the tip of the vocal process) is the membranous part. The remaining two-fifths posteriorly extend from the tip of vocal process to the face of the arytenoid cartilage, and are called the cartilaginous part of the vocal fold. The height of the vocal folds diminishes towards the anterior commissure mainly because the inferior edge of the vocal fold slopes upwards. At the anterior

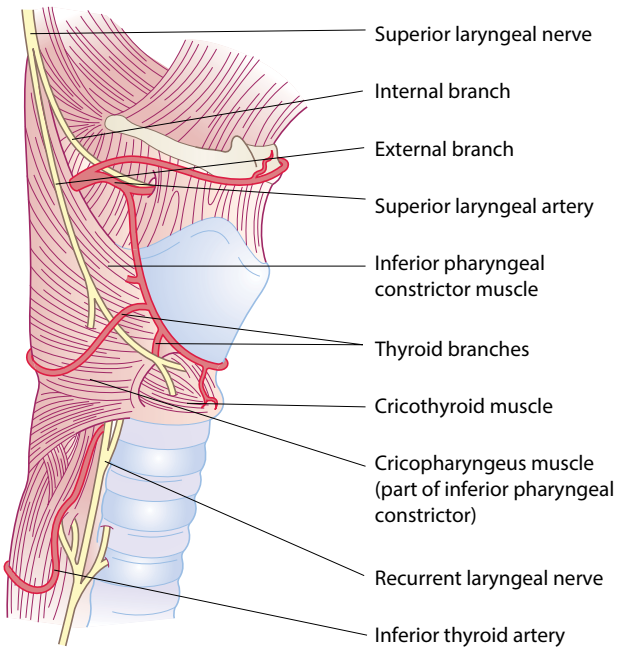


Figure 58.8 Lateral view of the larynx (complete).

commissure the lower edges of the vocal folds form the apex of a triangle via Broyle's ligament to the epiglottis, so tumour involving the anterior commissure readily involves the subglottis. The vocal folds are therefore almost wedge shaped, with the 'blunted' apex of the wedge anteriorly.

Mucous membranes of the larynx

The mucous membrane lining of the larynx is closely attached over the posterior surface of the epiglottis, the corniculate and cuneiform cartilages and over the vocal ligament. Elsewhere, it is loosely attached and prone to oedema. Most of the larynx is lined by pseudostratified ciliated columnar 'respiratory'-type epithelium. The upper half of the posterior surface of the epiglottis, the upper

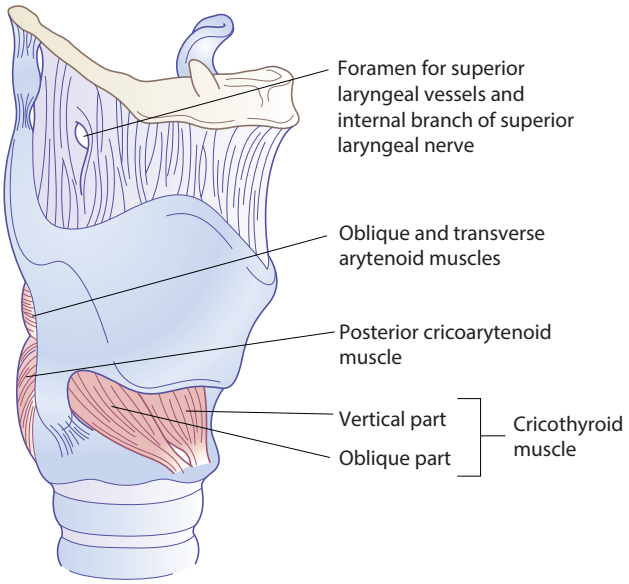


Figure 58.9 Lateral view of the larynx with extrinsic muscle removed.

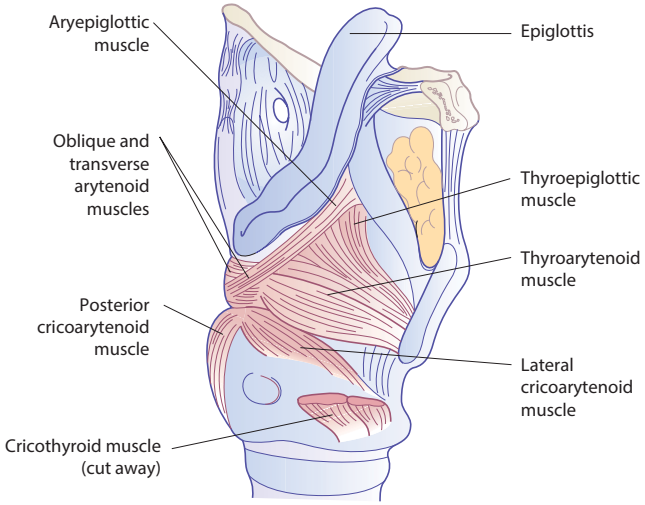


Figure 58.10 Lateral view of the larynx with the ipsilateral thyroid cartilage and cricothyroid muscle removed.

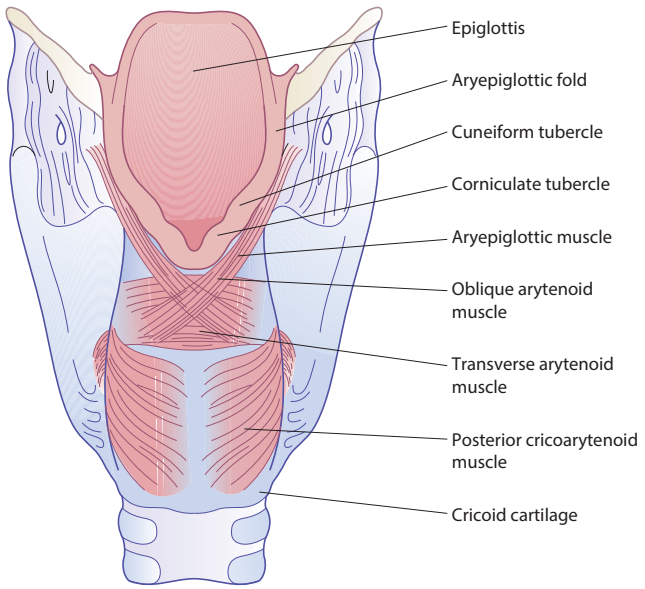


Figure 58.11 Posterior view of the larynx.

part of the aryepiglottic fold, the posterior glottis and the vocal folds are covered with non-keratinizing stratified squamous epithelium.

Mucous glands are freely distributed throughout the mucous membranes and are particularly numerous on the posterior surface of the epiglottis where they form indentations into the cartilage and in the margins of the lower part of the aryepiglottic folds and in the saccules. The vocal folds do not possess any glands and the mucous membrane is lubricated by mucus from the glands within the saccules. The squamous epithelium of the vocal folds is therefore prone to desiccation if these glands cease to function, for example after radiation.

Spaces within the larynx

Spaces in the larynx contain fat, lymphatics and vessels. They represent potential pathways of tumour spread that may have a significant bearing on treatment and prognosis.

PRE-EPIGLOTTIC SPACE

The pre-epiglottic space is a wedge-shaped space with the point of the wedge inferiorly (see **Figure 58.3**). It is bounded anteriorly by the thyrohyoid ligament and hyoid bone and posteriorly by the epiglottis. Superiorly, the hyoepiglottic ligament connects the epiglottis to the hyoid bone. Tumour may spread into this area through small perforations in the epiglottis or directly through the hyoepiglottic ligament. The pre-epiglottic space is continuous laterally with the paraglottic space as no anatomical boundaries exist.

PARAGLOTTIC SPACE

The paraglottic space is bounded laterally by the thyroid cartilage, medially by the conus elasticus and quadrangular membrane and posteriorly by the piriform fossa mucosa. It contains the laryngeal ventricles and saccules (see **Figures 58.7** and **58.12**). Tumours may spread extensively in this submucosal space in the absence of significant mucosal changes

Nerve supply of the larynx

The motor and sensory nerves of the larynx are derived from the vagus by way of its superior and recurrent laryngeal nerves (see **Figure 58.8**). The superior laryngeal nerve arises from the inferior ganglion of the vagus and receives a branch from the superior cervical sympathetic ganglion. It descends lateral to the pharynx behind the internal carotid artery and at the level of the greater horn of the hyoid divides into a small external branch and a larger internal branch. The external branch provides motor supply to the cricothyroid muscle, while the internal branch pierces the thyrohyoid membrane above the entrance of the superior laryngeal artery and divides into two main sensory and secretomotor branches. The upper branch

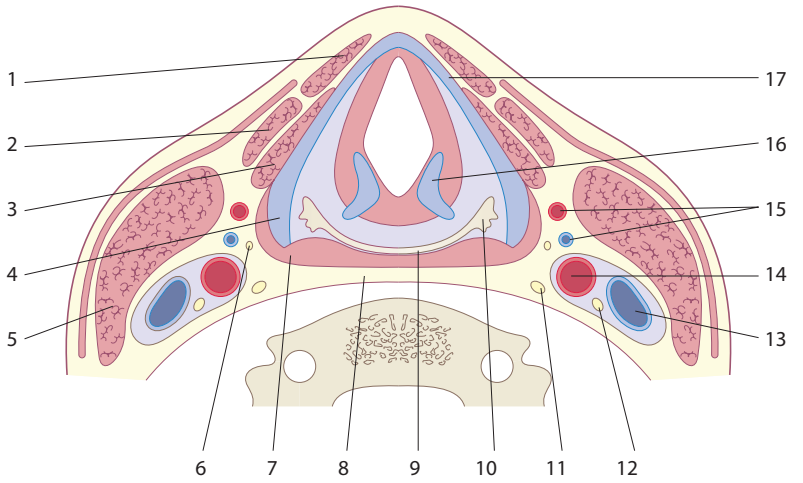


Figure 58.12 Axial section at C5 showing the relationship of the larynx to the surrounding structures. 1) Sternohyoid; 2) omohyoid; 3) thyrohyoid; 4) thyroid cartilage; 5) sternocleidomastoid; 6) external laryngeal nerve; 7) inferior constrictor muscle; 8) retropharyngeal space; 9) hypopharynx; 10) pyriform fossa; 11) cervical sympathetic ganglion; 12) vagus nerve; 13) internal jugular vein; 14) internal carotid artery; 15) superior thyroid artery and vein; 16) arytenoid cartilage; 17) vocal fold.

supplies the mucous membrane of the lower part of the pharynx, epiglottis, vallecula vestibule of the larynx and the lower branch descends in the medial wall of the piriform fossa beneath the mucous membrane and supplies the aryepiglottic fold and the mucous membrane of the larynx down to the level of the vocal folds. In its course beneath the mucous membrane of the medial wall of the piriform fossa, the superior laryngeal nerve is accessible for injection of local anaesthesia, providing excellent anaesthesia for most of the piriform fossa. The internal branch of the superior laryngeal nerve also carries afferent fibres from neuromuscular spindles and other stretch receptors in the larynx. The superior laryngeal nerve ends by piercing the inferior constrictor of the pharynx and unites with an ascending branch of the recurrent laryngeal nerve. This branch is called Galen's anastomosis and is purely sensory.

The right recurrent laryngeal nerve leaves the vagus as it crosses superficial to the right subclavian artery and loops under the artery, ascending in the tracheoesophageal groove to reach the larynx. On the left, the nerve originates from the vagus as it crosses the aortic arch. It then passes under the arch and the ligamentum arteriosum to reach the tracheoesophageal groove. In the neck, both nerves follow the same course and pass upwards accompanied by the laryngeal branch of the inferior thyroid artery. They pass deep to the lower border of the inferior constrictor muscle and enter the larynx behind the cricothyroid joint. The recurrent laryngeal nerve then divides into motor and sensory branches. The motor branch has fibres derived from the cranial root of the accessory nerve, which supply all the intrinsic muscles of the larynx except the cricothyroid. The sensory branch supplies the laryngeal mucosa below the level of the vocal folds and also carries afferent fibres from stretch receptors in the larynx.

There is some evidence to suggest there are variable anastomoses between the internal and recurrent laryngeal nerves. The existence of a 'laryngeal plexus' or multiple anastomoses may explain the variable clinical presentations of laryngeal nerve injuries and recovery from laryngeal injury.

The relationship between the recurrent laryngeal nerve and the inferior thyroid artery is variable. The nerve may cross in front of or behind the artery, or may pass between the terminal branches of the artery. On the right there is an equal chance of the nerve being in any of three locations in relation to the artery, although on the left it is more likely to lie posterior to the artery.

Laryngeal vasculature

ARTERIAL

The arterial supply of the larynx is derived from laryngeal branches of the superior and inferior thyroid arteries and the cricothyroid branch of the superior thyroid artery (see **Figure 58.8**). The superior laryngeal artery arises from the superior thyroid artery and passes deep to the thyrohyoid muscle. Together with the internal branch of the superior laryngeal nerve, it pierces the thyrohyoid membrane to supply the larynx. The superior laryngeal artery can be injured in endoscopic laryngeal laser surgery as it enters the paraglottic space at the anterior end of the aryepiglottic fold. Therefore, meticulous care to ensure haemostasis must be taken during supraglottic endoscopic surgical resections. The inferior laryngeal artery arises from the inferior thyroid artery at the level of the lower border of the thyroid gland and ascends on the trachea with the recurrent laryngeal nerve. It enters the larynx beneath the lower border of the inferior constrictor to supply the larynx. The cricothyroid artery is a branch of the superior thyroid artery and passes across the upper part of the cricothyroid ligament to supply the larynx. This ligament is penetrated by the branches (up to five) of the cricothyroid artery, which can be injured during cricothyroidotomy or endoscopic resection of anterior commissure cancers.

The arteries of the larynx form a communicating plexus in the paraglottic space, which can be the source of brisk bleeding during endolaryngeal surgery.

VENOUS

The veins leaving the larynx accompany the arteries. The superior laryngeal veins enter the internal jugular vein by way of the superior thyroid or facial vein. The inferior laryngeal veins drain into the inferior thyroid veins, which connect with the brachiocephalic vein. Some veins drain into the middle thyroid vein and then into the internal jugular vein.

LYMPHATIC DRAINAGE

The lymphatic drainage of the larynx is separated, by the vocal folds, into upper and lower drainage systems. The larynx above the vocal folds is drained by vessels that accompany the superior laryngeal vein and pierce the thyrohyoid membrane emptying into the upper deep cervical lymph nodes. The larynx below the vocal folds drains to the lower deep cervical chain, often through prelaryngeal (Delphian) and pretracheal nodes. The vocal folds themselves are firmly bound down to the underlying vocal ligament and there are no lymphatics present in this plane. Early cancers of the vocal folds do not therefore readily spread to the lymph nodes.

ANATOMY OF THE TRACHEA AND BRONCHIAL TREE

General description

THE TRACHEA

The trachea is a pathway for ventilation and clearance of bronchial secretions. It begins at the lower border of the cricoid cartilage and ends at the carina (**Figure 58.13**). The average length of the adult male trachea is 11.8 cm (range 10–13 cm). It has an ovoid shape, with average external diameters 2.3 cm (anteroposterior) by 1.8 cm (transverse) in the male and 2.0 cm by 1.4 cm in the female. The diameter of the paediatric trachea is 3 mm at birth.

The trachea slopes backwards from an anterior position in the neck to a posterior position in the mediastinum, at an angle that varies with age and spinal position. The trachea is mobile, moving upwards in swallowing and down and forwards on inspiration. The relatively fixed position of the left main bronchus under the arch of the aorta means that with any degree of kyphosis, the position moves more towards the horizontal and can limit the amount of trachea that is brought into the neck by extension of the neck.

The cross section of the trachea is D-shaped with incomplete C-shaped cartilaginous rings. The free posterior ends of cartilage embed into the smooth muscle trachealis, which has longitudinal and transverse fibres. There are approximately 2 rings per centimetre of trachea with each ring averaging 4 mm in length. This corresponds to 18–22 rings in the tracheal wall, which is approximately 3 mm thick. The size of the tracheal lumen may be altered by age and by disease.

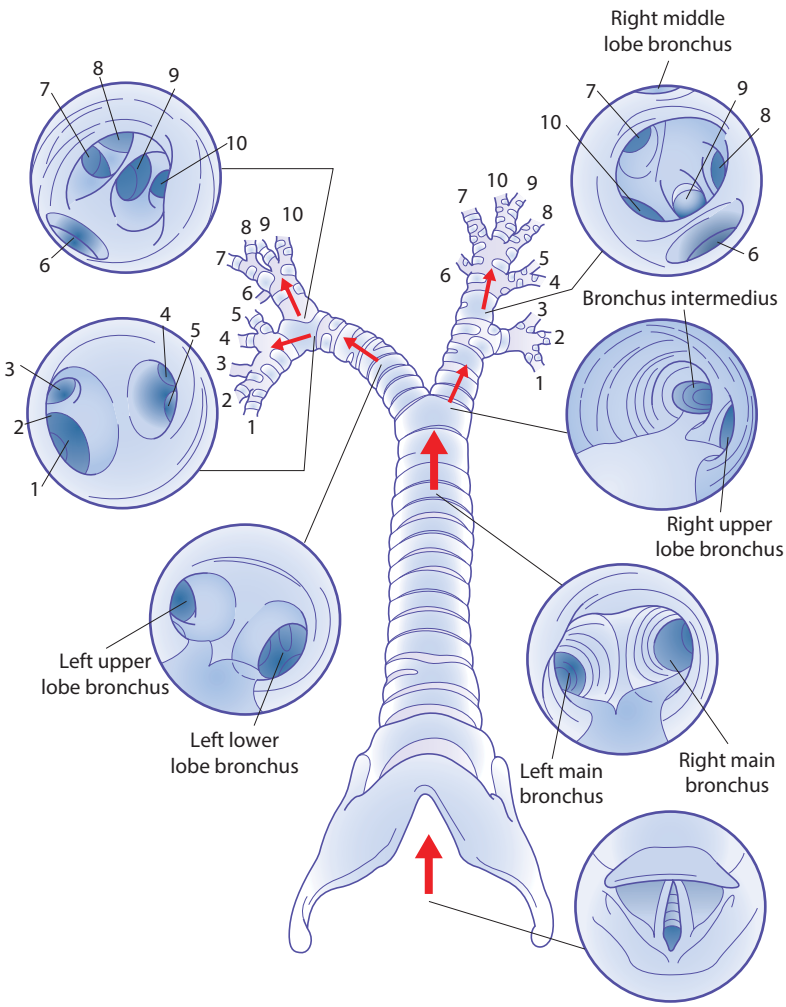


Figure 58.13 The tracheobronchial tree and views seen on endoscopy. Right lung, upper lobe bronchus: 1, apical; 2, posterior; 3, anterior, middle lobe bronchus; 4, lateral; 5, medial, lower lobe bronchus; 6, apical; 7, medial basal (cardiac); 8, anterior basal; 9, lateral basal; 10, posterior basal. Left lung, upper lobe bronchus.

THE CARTILAGES

The C-shaped cartilage rings line the trachea and bronchi where they both stiffen the wall and provide a degree of flexibility. Two or more cartilages may unite, either partially or completely, or bifurcate. Their elasticity may decrease with age as they become increasingly calcified.

The first cartilage is broader and may be joined to the cricoid cartilage or it may be separated with clearly defined cricotracheal ligament. The last ring above the carina is thick and broad and forms a bridge between the right and left main bronchi with a downwards curving triangular process continuing from the inferior border, which forms the posterior of the carina.

THE FIBROUS MEMBRANE AND TRACHEALIS

Each cartilage is enclosed in and nourished by perichondrium, which is continuous with an enveloping fibrous membrane. The membrane consists of a dense sheet of irregular connective tissue encircling the rings of cartilage, trachealis and the deficient posterior borders of the extrapulmonary bronchi. Composed of collagen and elastin fibres in crossing orientations, they permit expansion and aid elastic recoil of the airways. Constriction of the tracheal lumen is facilitated by trachealis, the transverse fibres inserting into the perichondrium at the free margins of the cartilage rings. The longitudinal trachealis fibres and the outer fibrous layer blend in with the fascia over the oesophagus and loose areolar fibres of the mediastinum.

THE MUCUS MEMBRANE

The lining of the upper airways is pseudo-stratified, ciliated, columnar epithelium with numerous goblet cells, resting on a broad basement membrane. The cilia beat the mucus blanket upwards towards the larynx and eventually the pharynx, where it is swallowed. The lamina propria is rich in longitudinal elastin fibres and overlies a submucosa of loose connective tissue containing the neurovascular structures, tubular glands and lymphoid patches.

The epithelium becomes thinner with increasing branching of the segmental bronchi. There are fewer goblet cells and a thinner basement membrane. Eventually the epithelium becomes a single layer. The smaller airways have less cartilage and are relatively more muscle until the circular muscle fibres are almost circumferential within the cartilage, rather than the fibromuscular tissue found higher up in airway. Contraction of these muscles, which form an interlacing network of fibres, both shortens and constricts the segmental bronchi.

CARINA AND BRONCHI

The trachea bifurcates and narrows slightly at the carina with the origin of the left and right main bronchi (**Figure 58.13**) at the level of T5 (posteriorly) and the manubrium (anteriorly). The right main bronchus makes an angle of 25–30 degrees with the carina, less than the 45-degree angle made by the left main bronchus. Therefore aspirated foreign bodies are more likely to continue into the right rather than left main bronchus.

RIGHT MAIN BRONCHUS AND BRANCHES

With an adult length of approximately 5 cm and a diameter of 17 mm (+/– 4 mm) in men and 15mm (+/– 4 mm) in women, the right main bronchus lies above the right pulmonary artery and below the azygos vein. The bronchus continues as the bronchus intermedius after take-off of the right upper lobe bronchus at a distance of 12–20 mm from the carina, and further down this terminates in the middle and lower lobe bronchi (see **Figure 58.13**).

The right upper lobe bronchus is approximately 1 cm long and divides into an apical, posterior and anterior segmental bronchi, which supply the right upper lobe. A variation of this anatomy exists where the apical segmental bronchus originates from the trachea at the level of the carina.

The right middle lobe bronchus arises approximately 2.5 cm down the bronchus intermedius, and terminates in lateral and medial segmental bronchi. The segmental bronchi of the right lower lobe consist of superior, anterior basal, posterior basal, medial basal and lateral basal divisions.

LEFT MAIN BRONCHUS AND BRANCHES

At 5.5 cm in length, the left main bronchus is longer, but 2–3 mm narrower than the right. It crosses anterior to the oesophagus, thoracic duct and descending aorta, travelling inferior to the aortic arch. The left pulmonary artery lies first anterior then superior to the left main bronchus, which terminates in the left hilum at the level of T6 as the upper and lower lobe bronchi.

The left upper lobe bronchus divides into apico-posterior (which further subdivides into apical and posterior) and anterior segmental bronchi (see **Figure 58.13**). The upper lobe bronchus terminates in the lingular bronchus, which gives superior and inferior segmental bronchi.

Similar to the right side, the left lower lobe bronchus gives five segmental bronchi-apical (superior), lateral basal and posterior basal and the final two medial basal (cardiac), anterior basal, which share a common stem.

Neurovascular supply of the tracheobronchial tree

NERVE SUPPLY

The recurrent laryngeal nerves provide motor supply to the smooth musculature and also carry sensation from the mucosa. Sympathetic supply derives mainly from the middle cervical ganglion and interconnects with the recurrent laryngeal nerves. The lungs are supplied by the anterior and posterior pulmonary plexuses situated at the hilum of each lung.

Parasympathetic supply of the trachea and bronchi is from the vagus with efferent stimulation provoking

bronchoconstriction, glandular secretion and vasodilatation. Vagal afferents are involved in the cough reflex.

BLOOD SUPPLY

The blood supply enters the lateral walls of the trachea in a distributed segmental fashion. The cervical trachea receives its blood supply from the inferior thyroid artery. Most often the upper half of the trachea is supplied by three tracheoesophageal branches of the inferior thyroid artery. The branches may pass anterior or posterior to the recurrent laryngeal nerves. The 2nd and 3rd branches also supply the oesophagus.

The segmental arteries to the trachea branch superiorly and inferiorly over the width of several tracheal rings, forming a series of longitudinal anastomoses along the lateral walls of the trachea. The arterial branches also give anterior and posterior branches near to the tracheal wall. The anterior branches further anastomose near the midline. The posterior branches supply the membranous wall, which also receives supply from the oesophageal arteries. The veins drain to the inferior thyroid plexus.

The bronchial tree and carina receives its arterial supply via the bronchial arteries, of which there are usually three. Two of these are on the left and are direct branches from the aorta. On the right the bronchial artery comes from the third right posterior intercostal artery. The bronchial veins drain into a superficial system, draining into the azygos vein on the right and the accessory hemiazygos on the left. The deep drainage, which also drains the lung parenchyma, drains into the pulmonary veins.

LYMPHATIC DRAINAGE

The lymphatics in the trachea and bronchi arise in a submucosal plexus and connect with a plexus in the outer fibrous membrane, where pulmonary associated lymph nodes are located. The pulmonary nodes drain into the bronchopulmonary nodes found at the points of subdivision of the airway. The subcarinal nodes are important as they drain from both lungs and drain into the ipsilateral para-tracheal nodes. Lymphatics from the trachea drain into the pretracheal and eventually into the para-tracheal groups of nodes (level VI), which also drain the superior tracheobronchial nodes.

The para-tracheal nodes drain into the vessels from the internal thoracic and brachiocephalic lymph nodes to form the bronchomediastinal trunks, which drain into the right lymphatic duct and the left sided thoracic duct.

Surgical anatomy

TRACHEA

The trachea is covered from deep to superficial by skin, superficial and deep cervical fascia, sternohyoid and sternothyroid muscles and, for a variable distance, the thyroid isthmus (**Figure 58.14**). The isthmus usually lies over the second to fourth tracheal cartilages but can vary in size and thickness with age and disease.

In the lower neck the trachea is anteriolaterally related to the inferior thyroid artery (when present) and anteriorly to the inferior thyroid veins and the thymus gland, which can be large and fleshy in infants. In the mediastinum the left brachiocephalic vein and artery, the arch of the aorta, the left common carotid artery, the deep part of the cardiac plexus and pre-tracheal lymph nodes are located anterior to the trachea (**Figure 58.15**). In infants the brachiocephalic artery crosses the trachea at a higher level, just as it descends behind the suprasternal notch. The brachiocephalic vein, due to a relatively higher position in the neck in infants, is at risk with surgical access to the trachea, as it may lie above the suprasternal notch.

Lateral relations of the trachea are the lobes of thyroid gland, carotid sheath and contents and para-tracheal nodes. Postero-laterally the recurrent laryngeal nerves run in the tracheo-oseophageal groove and the oesophagus is located posteriorly.

HILUM OF THE LUNG

The hilum of the lung is enclosed in a sheath of pleura and is the entry and exit for pulmonary structures.

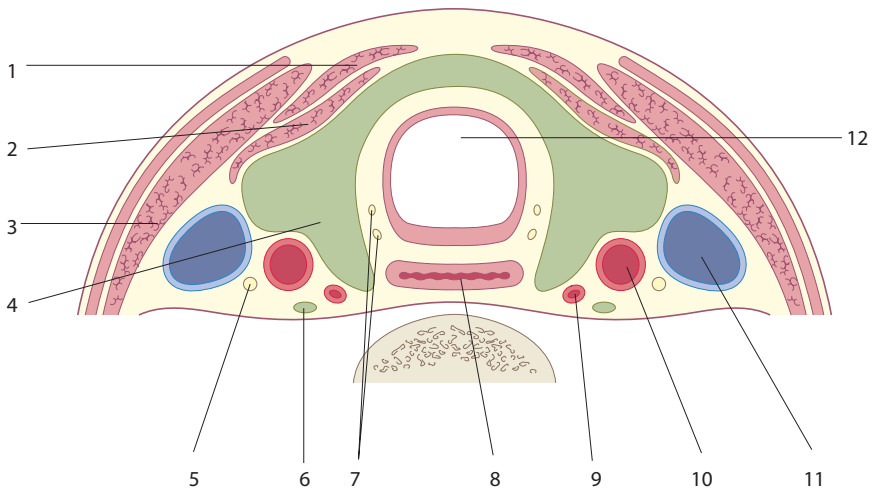


Figure 58.14 Axial section at C7 showing the relationship of the upper trachea to surrounding structures. 1, Sternohyoid muscle; 2, sternothyroid muscle; 3, sternocleidomastoid muscle; 4, thyroid gland; 5, left vagus nerve; 6, cervical sympathetic ganglion; 7, left recurrent laryngeal nerve; 8, oesophagus; 9, inferior thyroid artery; 10, common carotid artery; 11, internal jugular vein; 12, trachea.

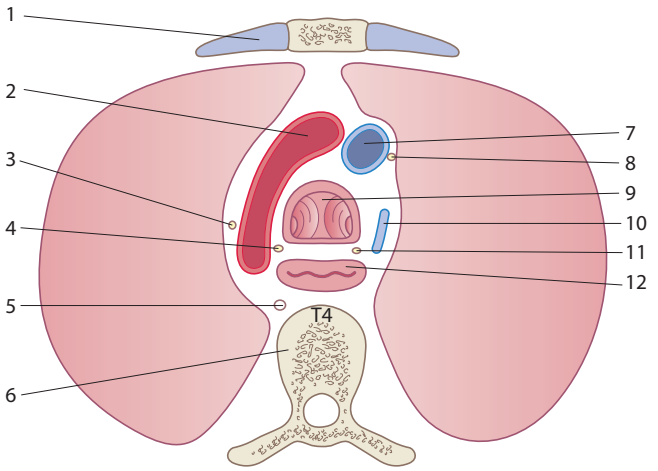


Figure 58.15 Axial section at T4 showing the relationship of the thoracic trachea to surrounding structures. 1, Second costal cartilage; 2, aortic arch; 3, left vagus nerve; 4, left recurrent laryngeal nerve; 5, thoracic duct; 6, fourth thoracic vertebra; 2, superior vena cava; 8, right phrenic nerve; 9, tracheal bifurcation; 10, azygos vein; 11, right vagus nerve; 12, oesophagus.

From anterior to posterior the structures are anterior plexus, pulmonary vessels (artery superior, two veins inferior), bronchi and bronchial vessels, and posterior plexus (**Figure 58.16**). The right side differs from the left as there is an additional upper lobe bronchus lying superiorly. There are lymph nodes and nerves within each hilum.

Anterior to the hilum is the phrenic nerve on the left and the superior vena cava on the right. The descending aorta and left vagus nerve crosses posteriorly to the left hilum, with the right vagus nerve posterior to the right hilum. Superior relations include the aortic arch on the left and azygos vein on the right. Inferiorly a sleeve of pleura hangs down as the pulmonary ligaments and allows movement of the hilar structures.

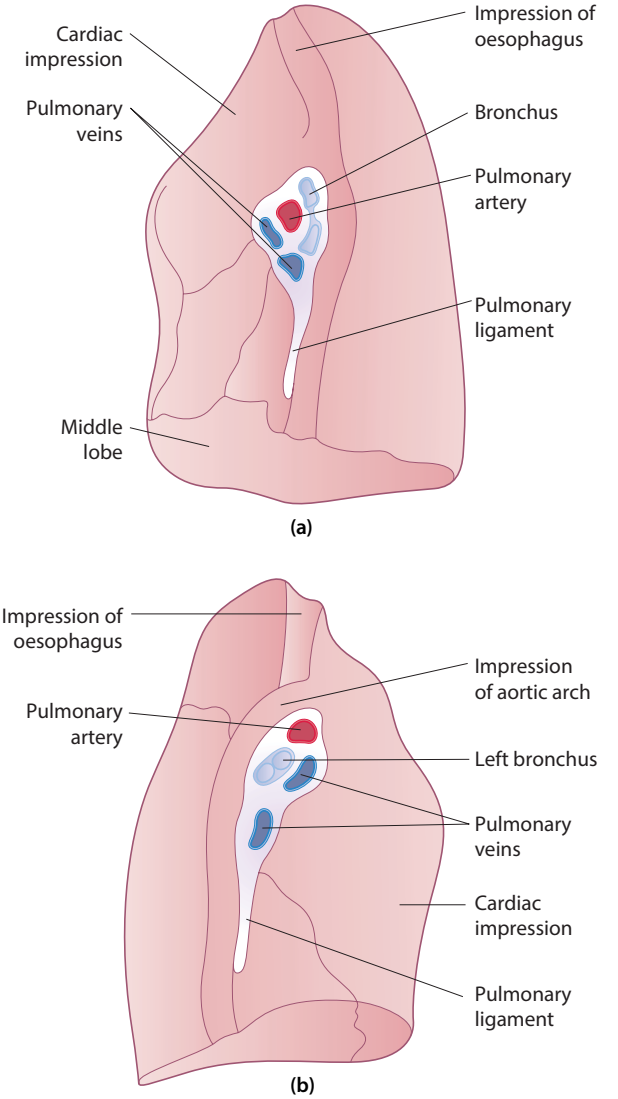


Figure 58.16 Structures in the hilum of the lung: (a) right hilum; **(b)** left hilum.

KEY POINTS

- Minimal swelling in the subglottic larynx can cause severe airway obstruction in infants.
- The pre-epiglottic and paraglottic spaces are connected and allow the unrestricted spread of tumours within the larynx.
- The posterior cricoarytenoid muscle is the only abductor of the vocal cords.
- All the intrinsic muscles of the larynx, except the cricothyroid, are supplied by the recurrent laryngeal nerve.
- The right main bronchus is wider, shorter and more vertical than the left, making it more susceptible to aspiration.

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CHAPTER 59

PHYSIOLOGY OF THE LARYNX

Lesley Mathieson and Paul Carding

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SEARCH STRATEGY

The information in this chapter can be explored more extensively by undertaking a Medline search using the following keywords: voice, larynx, laryngeal physiology, vocal registers, laryngeal innervation, laryngeal mechanoreceptors, neuroanatomy of phonation, biomechanics of phonation, vocal registers, vocal fold vibration.

INTRODUCTION

This chapter is concerned with the functions of the larynx, with particular emphasis on its role as the source of the voice. The motor and sensory laryngeal nerve supply is described and the neuroanatomy of phonation is described in greater detail. A concise section on the role of the larynx in swallowing, coughing and effort closure is followed by a more extensive description of the biomechanics of phonation. It should be noted that it is essential to be familiar with the considerable potential range of laryngeal adjustments that can occur in normal phonation, in order to avoid drawing inappropriate conclusions about phonatory physiology in a clinical setting.

The larynx has a number of functions, the most important of which is to prevent foreign material from entering the airway (aspiration). This is achieved by a combination of heightened sensitivity, a strong sphincteric action during swallowing and a means of effective expulsion (via coughing). The larynx also acts as a valve that can control air pressure and airflow, and as a vibrator for generating sound; both functions are of fundamental importance during breathing, weight bearing and phonation. This chapter is concerned with the neurology and biomechanics of laryngeal functions and lays the foundations for Chapter 60, Voice and speech production.

THE NEUROANATOMY OF PHONATION

Phonation can be defined as a laryngeal motor behaviour used for speech production, which involves a highly specialized coordination of laryngeal and respiratory neuromuscular control.[1] It is dependent upon the integrated functioning of many elements of the central and peripheral nervous systems (CNS and PNS). Although the motor and sensory tracts serving the larynx are relatively well understood, the way in which phonation is initiated and controlled continues to be the subject of neurological research. In addition to the cortical loci associated with voluntary phonation, there is evidence of subcortical representation which is responsible for reflex laryngeal function and involuntary phonation.[2] There is some evidence that the periaqueductal grey matter (PAG), a region of the mid-brain, is a crucial site for mammalian voice production.[3] Not only is it involved in the production of emotional or involuntary sounds but it also appears to generate specific respiratory and laryngeal motor patterns fundamental to human speech and singing. Davis et al. concluded that the patterned muscle activity corresponding to the major categories of voiced and voiceless sound production are represented in the PAG.[3] The role of the PAG might also include integration of cortical and subcortical aspects of language with basic respiratory and

laryngeal motor patterns by which speech is produced.[4–6] The linguistic demands of intonation, phonemic differentiations and emotional nuances in quality would appear to be regulated by such an independent sub-cortical reflex neural system.

The motor activity for vocalization appears to be integrated through a projection from the PAG to a column of neurones known as the nucleus retroambigualis (NRA).[7] The NRA appears to play a significant role in generating respiratory pressure and laryngeal adduction that occurs in both vocalization and vegetative manoeuvres, such as coughing.

Larson[4] suggested that the cortical mechanisms involved in vocalization and speech may have a role in modulating the subcortical systems that are involved in involuntary, or vegetative, phonation such as crying. It is possible that these are the mechanisms for coordinating timing, pitch and intensity fluctuations with the segmental and supra-segmental aspects of speech and voice. There is also evidence arising from clinical cases that the frontal lobes and other cerebral structures are important in the integrated neurological systems required for phonation. Functional magnetic resonance imaging (fMRI) has shown that there is common volitional control of the two upper airway functions of phonation and exhalation.[1] It has also been shown that multiple forebrain systems converge on motor neurones innervating the thyroarytenoid muscle.[8]

The neural pathways for voluntary vocalization arise in the pre-central gyrus of the motor cortex in both cerebral hemispheres and fibres descend as part of the corticobulbar tract, which is part of the pyramidal system or 'direct activation' tract. On reaching the medulla some fibres of the corticobulbar tracts take a direct pathway, remaining on the same side of the body throughout their route. These fibres synapse with the ipsilateral vagus nucleus and subsequently with lower motor neurones without interruption. Other fibres decussate (cross over) and change sides at the bulbar level to synapse with the contralateral vagal nucleus. The vagal nuclei, in the nucleus ambiguus within the reticular formation of the medulla, lie in a group of cells also containing the ninth and eleventh cranial nerve elements. They are influenced by both the pyramidal and extrapyramidal systems.

The indirect neurones of the pyramidal tract have multiple offshoots and synapses with the basal ganglia and reticular formation in the brain stem. They appear to contribute to temporospatial orientation while the direct system is related to discrete movement. The upper motor neurones do not govern isolated muscles, but groups of muscles. The frontobulbar portions of the pyramidal tracts connect with cranial nerves IX–XII, thus controlling articulation, phonation and respiration. The extrapyramidal system refers to tracts other than the pyramidal tracts and includes the basal ganglia in the cerebral hemispheres, the substantia nigra and subthalamic nucleus in the upper brainstem, the cerebellum and the thalamus, among other structures. The basal ganglia consist of the corpus striatum and its associated nuclei, the caudate and lenticular nuclei. The latter is divided into the putamen and the globus pallidus. The cerebellum has an integrating and controlling role over movements that arise in other parts of the motor system. It regulates the force, speed, range, timing and direction of movements throughout the body so that excesses are inhibited. The extrapyramidal system influences the pyramidal tract, the function of which is to regulate the muscle tone required for posture and for changing position. It is also involved in the automatic component of skilled voluntary movement. The specific function of each of these elements of the extrapyramidal system with respect to phonation is unknown but phonation may be influenced adversely by neurological conditions involving these structures.[9]

The extrinsic and intrinsic muscles of the larynx are under voluntary cortical control. They are responsible for the pre-phonatory tuning that precedes phonation and is followed by the phasic, tonic and volitional contractions and also maintenance of length, tension, bulk and position of the vocal folds.[10] The phonatory modulations that take place in speech, however, happen with a precision and speed that suggests a finely coordinated system of reflex controls over the laryngeal muscles themselves, and over the abdominal and intercostal muscles that maintain subglottic air pressure at appropriate levels.[11]

It seems that such fine tuning cannot be cortically regulated.[12] Stimulation of all categories of laryngeal mechanoreceptors initiates activity in the larynx, which presumably ensures that the vocal folds are stabilized and return to their pre-set pattern following displacement by the expiratory air-stream. This process, by monitoring the tonicity and position of the vocal folds, enables necessary adjustments to be made instantaneously and accurately. Although it would seem inevitable that there must ultimately be integration of this feedback system with other control systems during phonation, Wyke[12] and Kirchner[11] stated that this process is independent of auditory feedback.

LARYNGEAL INNERVATION

The vagus nerve (CN X) provides all the innervation to the intrinsic laryngeal muscles and the sensory structures of the larynx. It also supplies the pharynx, palate, trachea, bronchi, lungs, heart, external ear and parts of the gastrointestinal tract. Some of the fibres of the vagus originate in the medulla in the nucleus ambiguus while others originate at a higher level. Cells from the rostral pole of the nucleus ambiguus contain motor neurons for the glossopharyngeal nerve (CN IX), the middle part for the vagus nerve and those from the caudal pole for the accessory nerve (CN XI). The nerve fibres originating in the cranial nerve nuclei form the lower motor neurone pathway. The right and left vagus nerves, which they form, provide ipsilateral innervation to the larynx. The neural 'commands' that travel down to the cranial nerve nuclei are largely responsible for what is ultimately transmitted to the laryngeal muscles via the lower motor neurone pathways. These 'commands' are fashioned by complex interaction of, and constant remodelling by, many cortical, basal ganglia and brainstem influences.

Cranial nerves IX, X and XI are so intimately connected in the medulla that all the muscles supplied by them are frequently involved either equally or progressively in medullary lesions. For this reason, Walshe[13] grouped them together in pathological conditions affecting the nucleus ambiguus in what is termed the 'glossopharyngeal-accessorius complex'. Nuclear lesions of the vagus can be associated, therefore, with paralysis of the palate, tongue and larynx.

The vagus forms a flat cord from its many united filaments and leaves the skull through the jugular foramen, passing vertically down the neck within the carotid sheath. It branches to form the superior laryngeal nerve (SLN), the recurrent laryngeal nerve (RLN) and the pharyngeal nerve:

- The SLN branches off from the vagus at the ganglion nodosum (inferior ganglion), below the level of the jugular foramen, and subdivides into the internal and external SLNs. The internal branch of the SLN consists of both sensory and parasympathetic secreto-motor fibres, which supply glands within the tissue above the level of the vocal folds. This branch of the SLN in turn divides into three branches: (i) the superior branch runs to the lingual surface of the epiglottis and sends small fibres through the epiglottic foramina to the laryngeal surface; (ii) the middle branch runs through the aryepiglottic fold into the ventricular fold; and (iii) the inferior branch runs to the pyriform sinus (or pyriform fossa) and to the postcricoid region, forming various anastomoses with the RLN.[14] The density of nerve endings providing sensory innervation appears to be greatest at the laryngeal inlet as part of the protective mechanism for the respiratory system. The laryngeal surface of the epiglottis has the greatest sensory innervation, while the vocal folds have a lower density of sensory fibres.[15] The anterior vocal folds also have a lower density of sensory receptors than the posterior half. The external branch of the SLN provides the motor supply to the cricothyroid muscle.[14]
- The left and right RLNs provide the motor supply to all the intrinsic laryngeal muscles (see also Chapter 58, Anatomy of the larynx and tracheobronchial tree). The RLNs contain both adductor and abductor fibres.[15] They differ significantly with regard to their origin and pathway. The right RLN arises from the main trunk of the vagus in front of the subclavian artery and the left RLN arises from the vagus at the arch of the aorta round which it winds before ascending to the larynx. Because of its extensive course, the left recurrent nerve is more liable to injury than the right, and is especially vulnerable to pressure from aortic aneurysm and intrathoracic masses. It is also injured during thyroidectomy and thoracic surgery. Therefore, left vocal fold paralysis is far more common than right vocal fold paralysis. The RLNs on both sides ascend the groove between the trachea and oesophagus for a variable distance, before dividing into anterior and posterior branches and entering the larynx behind the cricothyroid articulation.

There is recent evidence that ventricular fold adduction appears to be a result of ventricularis muscle contraction that is mediated by the RLN.[16]

The RLN provides the sensory supply to the glottis and subglottis (see **Figures 59.1** and **59.2**).

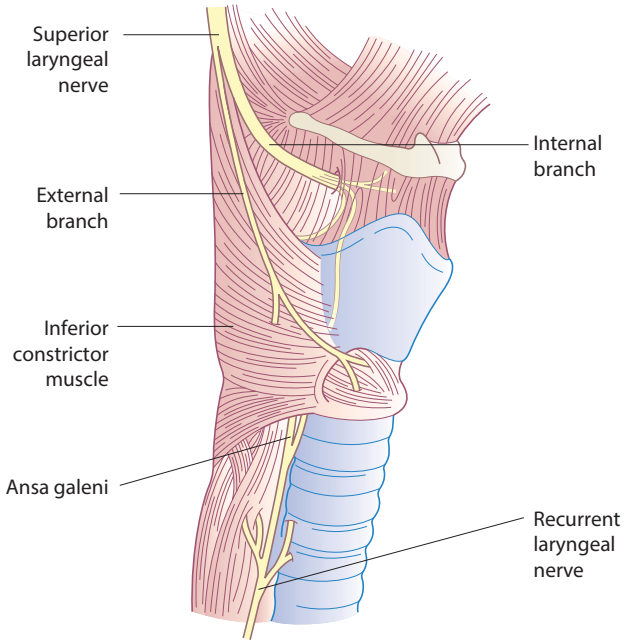


Figure 59.1 Distribution of the recurrent laryngeal nerve (lateral view). Redrawn with permission from Lesley Mathieson.

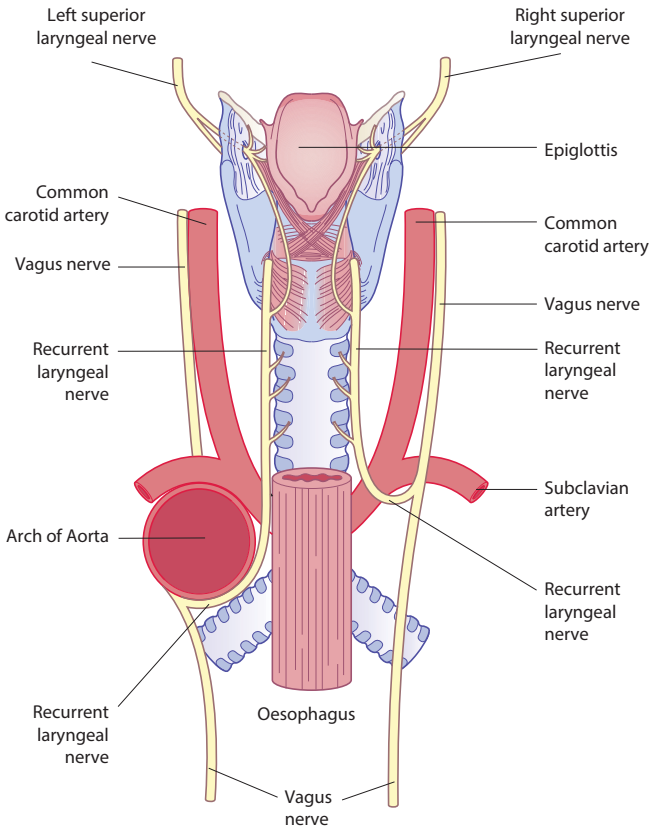


Figure 59.2 Posterior view of the larynx showing the distribution of the left and right laryngeal nerves. Redrawn with permission from Lesley Mathieson.

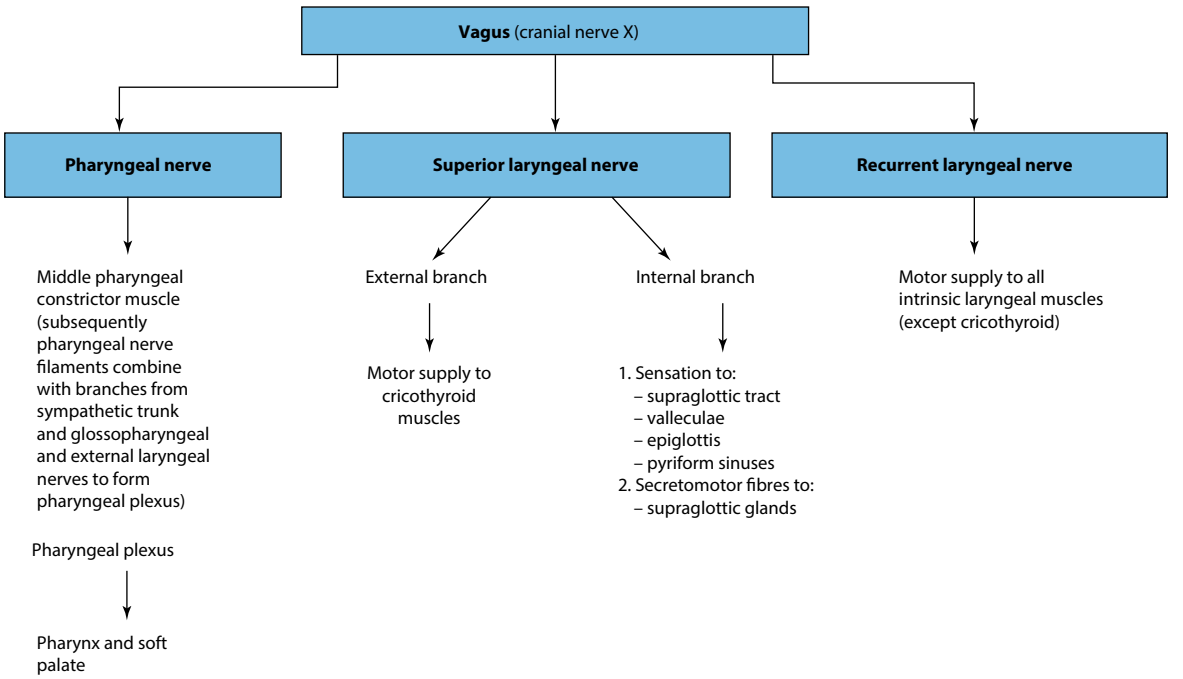


Figure 59.3 Diagrammatic representation of the laryngeal nerve supply. Redrawn with permission from Mathieson.

- The pharyngeal nerve descends between the internal and external carotid arteries to supply the middle pharyngeal constrictor muscle. Its fibres subsequently join with the glossopharyngeal and external laryngeal nerves, together with branches from the sympathetic trunk, to form the pharyngeal plexus. The pharynx and all the muscles of the soft palate, except the tensor palati, are supplied by fibres from the pharyngeal plexus.

Cranial nerves V (trigeminal), Vll (facial), Xll (hypoglossal) and cervical spinal nerves C1–C3 provide the motor supply for the extrinsic laryngeal muscles (see **Figure 59.3**).

Laryngeal mechanoreceptors

Free fibrils and terminal filaments enclosed in capsules constitute the receptor end organs (the mechanoreceptors) embedded in the laryngeal tissues at sites sensitive to muscle stretch and airflow pressures. Some are involved in protecting the airway while others contribute to the control of phonation.[17, 18] Reflex closure of the larynx is triggered by tactile receptors in the glottic and supraglottic mucosa, which evoke reflex contraction of the laryngeal muscles. Similar receptors in the subglottic mucosa elicit laryngeal closure and cough.[11]

Wyke[19, 20] postulated that mechanoreceptors are found in three sites:

1. **The mucosal lining of the larynx (mucosal mechanoreceptors).** The corpuscular nerve endings in the surface covering of the vocal folds are particularly numerous and sensitive to the stimuli of muscle stretch, air pressure level, liquid and touch.[5] They discharge impulses into the afferent fibres of the vagus.
2. **The capsules of the articulatory joints (articular mechanoreceptors).** The existence and function of this group remain controversial.
3. **The extrinsic and laryngeal muscles (myotatic mechanoreceptors).** The tone of the laryngeal muscles depends on the myotatic reflex, which is a function of the muscle spindles. The laryngeal muscles contain a large number of muscle spindles.[21]

FUNCTIONS OF THE LARYNX

Swallowing (deglutition)

During swallowing the primary function of the larynx is to prevent food and liquid entering the airway. This is achieved by means of the sphincteric action of the aryepiglottic folds, the true vocal folds and the ventricular folds, which occurs simultaneously with elevation of the larynx. Laryngeal elevation is also important in controlling pressures and the function of the cricopharyngeal sphincter, in order that the bolus can pass into the oesophagus.[22] The process of swallowing can be divided into the oral stage and the pharyngeal stage. The oral stage is under voluntary control and consists of the oral preparatory stage and the oral transport stage.[23] The food bolus is manipulated by the tongue and broken down before being propelled towards the oropharynx. The pharyngeal stage of swallowing is a reflex activity that is initiated as the bolus reaches the back of the tongue. During this process, the glottis is closed by adduction of the arytenoids and contraction of the lateral cricoarytenoid muscles, false vocal folds and true vocal folds. Vocal fold adduction during swallowing is thought to average approximately 2.3 seconds.[23] The airway is also protected by the epiglottis, which covers the laryngeal entrance and directs the bolus into the valleculae and the

pyriform sinuses. When the bolus arrives at the upper border of the cricopharyngeus muscle, the sphincter relaxes to allow the bolus to enter the oesphageus. An essential feature of normal deglutition is the rapid laryngeal elevation that occurs during the pharyngeal phase of the swallow. This manoeuvre results in the hyoid bone being displaced anteriorly, which further helps to protect the airway from aspiration and also serves to pull open the upper oesophageal sphincter. There is also a drop in pressure and transient negative pressure in the cricopharyngeal sphincter as the bolus passes from the pharynx into the oesophagus. If laryngeal elevation is impaired, then peri-swallow aspiration is more likely, cricopharyngeal opening is limited, the pressure drop during deglutition is slower and the fleeting negative pressure does not occur. A more detailed treatment of swallowing physiology is presented in Chapter 48, Physiology of swallowing.

Coughing

Coughing is the process by which material is expelled from the airway. The laryngeal adductor response is a protective reflex that prevents aspiration. It is preceded by rapid inspiration, followed by forceful closure of both the vocal folds and ventricular folds. Air pressure is then built up below the adducted folds as the diaphragm ascends spasmodically until the folds separate explosively and mucus or foreign material is expelled. This laryngeal motor response to sensory stimuli is not suppressed during volitional laryngeal tasks.[24]

Effort closure

Laryngeal structure has evolved in order to contain intrathoracic pressure, so as to provide a stable fulcrum for the upper limbs. Expiratory effort against a closed glottis is known as the Valsalva manoeuvre.[25] During any form of exertion involving use of the arms, the vocal folds are firmly adducted preventing expulsion of air and collapse of the chest walls, thus providing a fixed origin for the arm and shoulder muscles. This fact is clinically important in that those who have undergone laryngectomy or who have vocal fold paralysis may have difficulty with weight-bearing activities because of their inability to close the glottis effectively. Clinical experience also suggests that trauma to the vocal fold mucosa can occur or be aggravated by forceful, prolonged vocal fold adduction during some types of physical training, such as lifting weights.

Effort closure of the larynx also occurs during childbirth and defaecation as the abdominal contents are compressed by the abdominal muscles in order to achieve expulsion.

The biomechanics of phonation

The vocal folds are composed of laryngeal connective tissues with complex matrix composition and organization that provides the viscoelastic mechanical properties required for producing voice.[26] When the larynx is at rest and respiration is quiet, the vocal folds abduct on inspiration and slightly adduct on expiration. They move up and down slightly in sympathy with the outflow and inflow of respiratory air, while the larynx descends on inspiration and ascends on expiration.[27] The folds are drawn wide apart to a position of full abduction in forceful inspiration. Subglottic and supraglottic influences must be taken into account when analyzing vocal fold dynamics.[28]

INITIATION OF VOICE

Immediately before phonation, the vocal folds rapidly abduct to allow the intake of air. Wyke[20] termed this the 'pre-phonatory inspiratory phase'. Subsequently, the vocal folds are adducted by the contraction of the lateral cricoarytenoid muscles. The vocal note is generated by pulmonary air as it is exhaled between the adducted vocal folds. The vocal folds working together constitute a vibrator, which is activated by the excitor, the exhaled air. The production of the vocal note at this point is the result of the repeated vibratory movement of the vocal folds, known as vocal fold oscillation. The mobility and deformability of the vocal folds determines the ease with which vocal fold vibration can be initiated.[29] Subglottic air pressure increases below the adducted vocal folds until it reaches a level that overcomes their resistance and blows them apart, thus setting in motion the vibratory cycles which result in phonation. The vocal folds, in common with all vibrators, have a degree of inertia, which has to be overcome in order for phonation to occur. The amount of air pressure required to begin voicing is known as the 'phonation threshold pressure'.[30] The size and tension of the vocal folds in combination with the viscoelastic properties of the vocal fold cover will affect the phonation threshold pressure.[29]

THE VIBRATORY CYCLE

Each vibratory cycle of the vocal folds consists of three phases: adduction, aerodynamic separation and recoil (**Figure 59.4**). As the increased subglottic air pressure overcomes the resistance of the adducted vocal folds at the onset of phonation, the vocal folds peel apart from their inferior border. When they finally separate at their superior margin, a puff of air is released. The resulting negative pressure in the glottis caused by the Bernoulli effect results in the vocal folds closing rapidly as they are sucked together, the inferior vocal fold margins closing first. The Bernouilli effect is a drop in pressure dependent on particle velocity. In relation to the vocal tract, Maran[31] described it as follows: 'When air passes from one large space to another (e.g. from lung to pharynx), through a constriction (the glottis), the velocity will be greatest and the pressure least at the site of the constriction.' As a result of the drop in pressure at the glottis, the vocal fold mucosa is drawn into the space between the vocal folds.

Contact between the vocal folds increases until the subglottic air pressure is high enough to blow the vocal folds apart again, and the cycle recommences. Each cycle of adduction, separation and recoil is the manifestation of a mucosal wave travelling from the inferior to the superior surface of each vocal fold. The process by which this undulating wave of movement of the mucous membrane

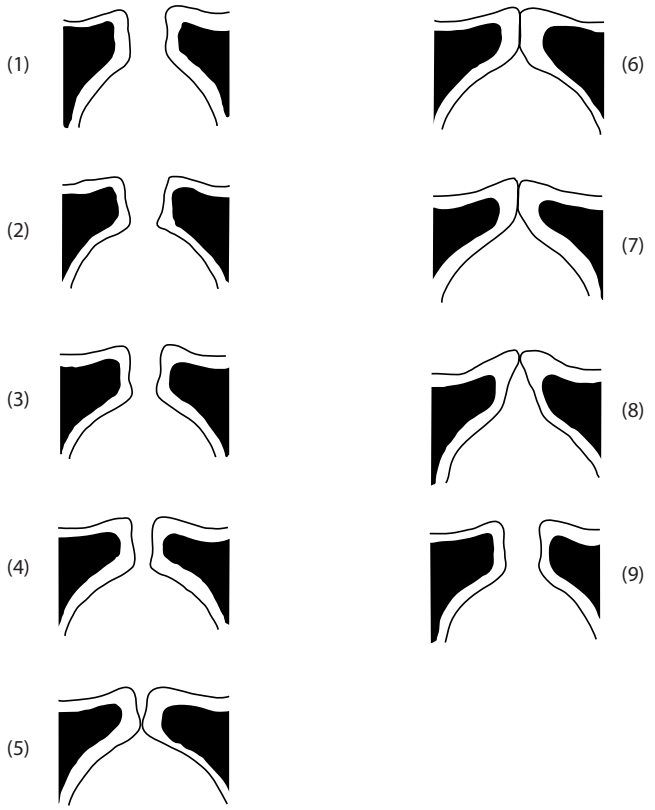


Figure 59.4 Vocal fold vibratory cycle. Redrawn with permission from Mathieson.

occurs is dependent on what is known as the cover/body theory. That is, the vocalis muscle provides the firm body of the vocal fold over which the mucous membrane cover of the vocal fold is blown by the expiratory air stream. These undulations of the vocal folds' thin cover, and any abnormalities of the mucosal wave, can only be observed using laryngostroboscopy or high-speed photography.[32]

The periods of vocal fold contact and lack of contact in one vibratory cycle can be divided broadly into closed and open phases, respectively, with associated closing and opening phases.[33] The closing phase of the vocal folds is more rapid than the opening phase. The phases of the vibratory cycle can be classified, therefore, into four stages as shown in **Box 59.1**.

The vocal folds have to be structurally and functionally symmetrical, at the same level, and close rapidly in order that a clear vocal note can be initiated and maintained.[34] Insufficient approximation of the vocal folds (glottal insufficiency) results in air wastage and production of a breathy voice quality. When the vocal folds fail to approximate completely along their membranous portion, with a slightly increased aperture in the cartilaginous section, turbulent air escapes and is audible in the voice.

In production of notes of middle pitch, the interarytenoid muscles adduct the cartilaginous portion of both vocal folds and hold them together while the anterior portion of each fold is gently adducted but free to vibrate in the expiratory airflow. Although full vocal fold adduction during phonation has traditionally been regarded as the norm, clinical observation and various studies have refuted this view by showing that normal phonation can occur when there is incomplete glottal closure.[35, 36] This pattern of vocal fold adduction is more common in women than in men. In all speakers, incomplete glottal closure can be considered normal in high frequency modal voice and in falsetto (see **Figure 59.5**), when hourglass or spindle glottal configurations can occur in normal subjects.[37] It also appears that different types of glottal configurations are associated with different age groups. Incomplete closure of the posterior part of the vocal folds (posterior glottal chink) is a common finding in young and middle aged women, but elderly women are more likely to exhibit anterior chinks.[35, 38] High-speed digital imaging has revealed that glottal configuration and phase closure for children with normal voices are distinctly different from those of adults. It has been suggested that posterior glottal gap and a predominantly open phase of the glottal cycle should be considered as normal glottal configuration in children during modal pitch and loudness.[39] It is essential, therefore, that clinicians dealing with vocal pathology recognise that incomplete vocal fold closure may be a normal glottal configuration during phonation in certain subjects and at certain frequencies. Similarly, asymmetries within the larynx should be viewed with caution as they are not necessarily indicative of pathology. For example, a lack of strong differences in the prevalence of arytenoid asymmetries in the adducted position have been found in speakers with and without voice disorders.[40]

Age-related changes to the vocal tract can give rise to vocal instabilities in non-pathological voices. Changes in pitch and breath rate in older individuals indicate a fundamental change in the body's maintenance of the speech mechanism.[41] Reductions in pulmonary elastic recoil and respiratory muscle strength can affect the way in which older adults generate subglottal air pressure required for speech production. They have been shown, for example, to have very different lung volume adjustments for loud speech, compared to young adults.[42]

BOX 59.1 The periods of vocal fold contact and lack of contact in one vibratory cycle

Closing phase: The vocal folds begin to close rapidly from their lower margin

Closed phase: The medial edges of the vocal folds are in full contact

Opening phase: The vocal folds begin to separate from their lower margin and gradually peel apart. The superior margin remains in contact until the end of this phase.

Open phase: The vocal folds are separated. (The longest part of a normal vibratory cycle.)

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VOCAL REGISTERS: CHARACTERISTICS OF VOCAL FOLD ADDUCTION AND VIBRATION

Significant variations in vocal fold vibratory characteristics and adduction can also be observed according to

the vocal register that is being used. The subject of vocal registers is confusing and controversial. This is partly because the definition of what constitutes a register has been unclear but also because a number of terms are used to describe each register. Traditionally, registers have been regarded as the perceptually distinct regions of vocal quality over certain ranges of pitch and loudness[32] but listener identification of the change from one register to another is not reliable.[43] The terms used vary according to whether they are being employed by singers or speech scientists, but even then their use is not uniform. Singers tend to classify the registers as head, middle and chest but these terms are regarded as unsatisfactory by voice scientists, many of whom refer to three main vocal registers: falsetto, modal and vocal fry. These classifications, however, do not relate directly to each other. Baken and Orlikoff[44] noted that the problems of definition and terminology had been clarified by Hollien's suggestion[45] that registers should be defined in terms of laryngeal behaviour, rather than in acoustic terms, as registers are governed by the degree of contraction of the vocalis muscle. As a result, the terms loft, modal and pulse registers can be used with less confusion; they describe the vibratory pattern of the vocal folds and the acoustic parameters being produced (see **Table 59.1**):[46]

- **Loft register (or falsetto)** covers the highest frequencies of the voice. The vocal folds are lengthened, extremely tense and thinned so that there is minimal vibration. The knife-thin free edges are almost adducted and subglottic air pressure is high. During the production of these high frequencies, the larynx is raised by the suprahyoid muscles and the pharynx is shortened.[47]
- **Modal register** encompasses the range of frequencies usually employed in speech and singing. The membranous portions of the vocal folds are adducted and make complete closure in the closed phase of each vibratory cycle. In cross-section, the vocal folds are triangular in shape. In low notes the intrinsic muscles relax, the folds increase in bulk and their opposing surfaces deepen from 3 mm to 5 mm. They vibrate slowly along their whole length, the lower surfaces of their 'lips' making contact and separating as the upper surfaces approximate in a rolling motion or figure of eight. In lowest notes the infrahyoid muscles pull the larynx down.[48]
- **Pulse register (or glottal fry or vocal fry or creaky voice)** occurs during the lowest vocal frequencies and is a feature of normal speech.[49] This terminology reflects the pulsatile nature of the laryngeal sound generated. There is a long closed phased in each vibratory cycle.



Figure 59.5 Normal falsetto phonation.

The terminology and underlying modes of vocal fold behaviour during the production of each register are outlined in **Table 59.1.**

Appreciation of the normal patterns of vocal fold movement and the way in which laryngeal adjustments affect the sound of the voice is essential to evaluating laryngeal findings in cases of disordered voice. Considerable variations of structure and function can be found even in the normal larynx and there are probably even more permutations of laryngeal behaviour. A comprehensive range of vocal tasks throughout the patient's pitch range during laryngoscopic examination is essential, therefore, if inappropriate conclusions regarding laryngeal pathology are to be avoided.

TABLE 59.1 Vocal registers

	Register may include	Equivalent terms	Vocal folds	F0 range (Hz)
Loft register	Highest vocal frequencies	Falsetto	Thin, tense, lengthened. Minimal vibration	275–1100
Modal register	Range of fundamental frequencies most commonly used in speaking and singing	Chest, head, middle, heavy voice	Complete adduction	100–300
Pulse register	Lowest range of vocal frequencies: laryngeal output is perceived as pulsatile	Vocal fry, glottal fry, creaky voice	Long closed phase	20–60

The terminology related to vocal registers is not consistent. Various overlapping terms are used that have different theoretical bases.

FUTURE RESEARCH

- Detailed innervation of the laryngeal structure.
- The processes of regulation of the linguistic demands of intonation and emotional nuances in vocal quality.
- The cerebral systems controlling phonation.
- Studies of normal variations of the vocal tract during phonation.

KEY POINTS

- The prime function of the larynx is to protect the airway. It also acts as a valve controlling airflow and air pressure and as a vibrator for generating sound (voice).
- The vagus nerve (CN X) provides all the innervation to the intrinsic laryngeal muscles and to the sensory structures of the larynx.
- Phonation involves highly specialized coordination of laryngeal and respiratory neuromuscular control.
- The quality of the glottal source sound is dependent on the structure and function, particularly the efficiency of approximation, of the vocal folds.
- An understanding of normal and age-related differences of glottal configurations is essential in order to avoid pathologizing normal laryngeal structure and function.

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CHAPTER 60

VOICE AND SPEECH PRODUCTION

Paul Carding and Lesley Mathieson

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Modifying the glottal signal 906
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Fundamentals of speech/articulation 907
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SEARCH STRATEGY

Data in this chapter can be explored more extensively by undertaking a Medline search using the following keywords: speech, voice, articulation, larynx, phonatory biomechanics, vocal fold vibration, vocal registers, intonation, phonetics and paralinguistic features.

INTRODUCTION

This chapter outlines how humans produce speech and voice. The characteristics of the glottal source (vocal fold vibration) are described. How the sound is modified within the oral tract is then addressed in detail. This is followed by a brief explanation of the fundamental principles of speech and articulation. Finally, the importance of the paralinguistic features of voice and speech are described.

The vibration of the vocal folds ('phonation') constitutes the raw glottal sound source. However, the voice we hear is far more complex than the acoustic signal generated by the vibrating larynx. This fundamental vibratory sound is modified and resonated by the rest of the vocal tract to produce a recognizable human voice quality. Hence, analysis of voice quality (perceptual or instrumental) must recognize the role of the whole vocal tract in the production of the sound that finally radiates from the mouth. Furthermore, the articulatory structures of the vocal tract (lips, tongue and soft palate) shape the sound source in an infinite number of combinations to make speech. This co-ordination of phonatory and articulatory behaviours represents arguably the most advanced sensorimotor system to be found in the human body.[1] Speech and voice require precise co-ordination of reflexive and learned behaviours resulting in intricate muscle movements executed with accuracy and speed. The flexibility of the vocal tract and the anatomical variations between people allows for an enormous range of normal voice and speech qualities and an inevitable overlap between 'normal' and 'abnormal' parameters. This has implications for how we assess and measure components of speech and voice for diagnostic and outcome evaluation purposes.[2] The main features of human voice and speech production are described in more detail below.

The specific characteristics of an individual's speech and voice are the product of the organic and phonetic features of the speaker.[3] Organic factors are derived from the nature of the speaker's individual anatomical apparatus; the dimensions and geometry of the nasal and oral structures, pharynx, larynx and respiratory system. Phonetic features refer to the speaker's habitual muscular adjustments of the speaking apparatus in terms of long term muscle 'settings' (for example, larynx position or tongue body position). The specific anatomical configuration of the vocal tract is unique to each individual and produces a voice and speech quality that distinguishes one speaker from another. These phonetic muscular habitual settings are learned (often unconscious) behaviours that fulfil the speaker's social, geographical, cultural and personal needs.

CHARACTERISTICS OF THE SOUND SOURCE/GLOTTAL SIGNAL

Voice quality

The quality of the vocal sound source is wholly dependent upon the vibratory characteristics of the laryngeal structures.[4] More specifically, it is dependent upon the

nature of vocal fold adduction during phonation and the regularity of the mucosal waves of the lamina propria (see Chapter 59, Physiology of the larynx). However, regular ('periodic') vocal fold behaviour also requires a stable airflow to generate vibration of the laryngeal structures.

- Incomplete adduction of the vocal folds during phonation will commonly result in audible air leakage and a 'breathy' voice quality. Whisper occurs when there is insufficient vocal fold adduction to achieve vibration but sufficient adduction to produce audible turbulent air. It is also associated with an increase in infra-glottic airflow.
- An irregular mucosal waveform vibration will result in an aperiodic sound that will be perceived as 'hoarse'. There are many possible causes of irregular laryngeal vibration, including inflammation, focal lesions and muscle imbalance.
- A pressed or strained voice quality occurs when the vocal folds are strongly adducted (often with supraglottic muscular involvement) and there is raised subglottal air pressure.
- It is quite possible for several aspects of suboptimal vibration to co-occur and hence produce a complex voice quality of more than one aberrant feature.

In a hypothetically perfectly functioning larynx, adduction of the vocal folds would be complete during the closed phase of phonation and abduction would be smooth and quick (in order to start the closing phase of the next vibratory cycle). Furthermore, each vibration of the mucosal waveform would be identical to the previous one and the sound signal produced would be perfectly periodic (a sine wave). The sound thus produced would contain only a fundamental frequency and its harmonics. However, all human voices are a combination of periodic and aperiodic sound. Aperiodic sound or 'noise' is a sound that is not a harmonic of the glottal signal. The main sources of 'noise' in the larynx are air escape and irregular vibration.[2] The more severe the noise component of the sound (in relation to the periodic component), the more 'hoarse' the voice will sound.[2, 5] It is possible to measure the degree of 'hoarseness' in a voice by calculating the ratio of periodic sound compared to aperiodic sound. This is usually termed a 'harmonics-to-noise ratio' (HNR).[5] It is important to note that the acoustic HNR measurement provides some indication of the degree of hoarseness but no information as to the source of the noise component.[4] HNR measurement has become a popular measure of dysphonic severity and of change in voice quality during treatment.[2]

Voice frequency

The frequency of the glottal signal is a result of the number of vibratory cycles per second (measured in hertz). The rate of vibration of the vocal folds is a function of the vocal fold length, elasticity, tension and mass, and their subsequent resistance to subglottal air pressure.[4] The maintenance of a steady vocal frequency requires control of all of these interacting physiological features. Frequency increases with a lengthening of the vocal folds and the subsequent thinning and stiffening of the vocalis muscles.[6] The perceptual correlate of frequency is pitch although the relationship between the two is a complex one. The frequency, intensity and spectral properties of a sound interact in very complex ways to lead to a given pitch perception.[5] Considerable normative data of habitual speaking pitch or mean speaking fundamental frequency (MSFo) exists.[5] However, there is a huge range of what is considered 'normal' depending on the age, sex, emotional state, communicative intent, mood and personality of the speaker. Similarly there are data on vocal pitch range both in terms of maximum range and habitual speaking range.[5] It is generally accepted that there are three pitch registers: loft (or falsetto) register; modal (or middle) register; and pulse (or chest) register (see Chapter 59, Physiology of the larynx). These registers basically distinguish between different vibratory patterns of the vocal folds determined by the degree of contraction of the vocalis muscles.[7] Short-term (cycle-to-cycle) variance in the frequency of vocal fold vibration is called 'jitter' or pitch perturbation. In a speaker who is trying to maintain a stable pitch, a measurement of jitter may indicate instability in the phonatory mechanism and may be a further useful index of dysphonia.[2, 5]

Voice amplitude

Vocal loudness is the perceptual correlate of amplitude – the size of the oscillation of the vocal folds. The amplitude of these vibrations is largely determined by the force of the transglottal airflow. Increasing both the airflow through the larynx and vocal fold resistance (and subsequent subglottal pressure) will result in an increase in vocal loudness. Like vocal frequency there are data on normal vocal intensity (habitual and range) in a variety of settings.[5] Short-term variance in the intensity of the vocal signal is called 'shimmer' or amplitude perturbation. An inability to maintain stable amplitude when intended may indicate important characteristics of the dysphonic speaker.[2, 5]

MODIFYING THE GLOTTAL SIGNAL

The sound source produced by the vibrating vocal folds is modified by the rest of the vocal tract to produce the voice quality that radiates from the speaker's mouth to the listener's ear. In a normal voice, the glottal signal is essentially periodic and composed of a fundamental frequency and its harmonics. This complex acoustic signal is then filtered by the supralaryngeal tract with some anatomical structures resonating different harmonics of the source signal more than others. Changes in the shape of the whole vocal tract (and the dimensions of the oral, nasal, pharyngeal and laryngeal cavities relative to each other) can be achieved in numerous ways. For example, protruding the lips, retracting the tongue base, lowering the larynx or lowering the soft palate will all dramatically alter the sound of the resultant voice even when performed in isolation. The fact that the voice is more than its vibratory

source is a fundamental principle of auditory evaluation of voice quality.[2, 8] It is important to note that some voice quality rating scales concentrate on laryngeal vibratory features only (i.e. the grade, roughness, breathiness, asthenia, strain (GRBAS) scale) whilst others take into account distinguishing perceptual features of the whole vocal tract (i.e. the Vocal Profile Analysis Scheme).[8] The modification of the sound source by the supraglottic vocal tract also represents the main problem in the instrumental measurement of voice quality. For this reason most methods of acoustic analysis prefer to analyze 'steady-state' prolonged vowels where the speaker is attempting to maintain steady pitch and intensity and where the variance in supralaryngeal tract configurations is kept to a minimum.[2, 5]

VOCAL RESONANCE

As explained above, the supralaryngeal tract acts as a resonating chamber for the complex acoustic signal generated by the vibrating vocal folds. The specific geometry and dimensions of an individual speaker's vocal tract will determine the 'timbre' or resonating properties of the voice. Skilled speakers and singers learn to manipulate these oral, nasal and pharyngeal structures to maximize their resonant properties. This is not easy to do since vocal resonance changes continually as we speak (i.e. changing vocal pitch or intensity, articulating different consonants or vowels). Oral resonance is affected by the degree of jaw movement, mouth opening, tongue body raising and pharyngeal constriction. Nasal resonance is affected by excessive or limited action of the velopharyngeal sphincter during speech, or by some degree of nasal obstruction. For a majority of normal speech the velopharyngeal sphincter is closed; the diaphragm of the velum reflects most of the sound into the oral cavity. However, some speech sounds require significant resonation into the nasal cavity (i.e. m, n and ng sounds). The final result is a voice with an appropriate oral/nasal balance. Appropriate oral/nasal resonance is not only necessary for normal sounding speech and voice but is also important to facilitate good voice projection (by enhancing the fundamental frequency and its harmonics).[9]

Velopharyngeal incompetence or significant lowering of the soft palate will result in a hypernasal speech quality. In more extreme cases, audible nasal air escape can be heard during speech. There is evidence to suggest that listeners tend to associate negative personal attributes to individuals with hypernasal speech.[10] Structural abnormalities such as a cleft palate or submucosal cleft often result in marked hypernasality. Conversely, an inability to produce appropriate nasal resonance (especially for sounds m, n and ng) will result in hyponasal speech quality. This is, of course, most likely to occur in space-occupying conditions of the nasopharynx. Removal of the space-occupying lesion or tissue may result in hypernasality although this is likely to be temporary in most cases. A significant but poorly investigated possible complication of the uvulopalatopharyngoplasty (UPP) surgical procedure is the resultant hypernasal speech.[11]

FUNDAMENTALS OF SPEECH/ ARTICULATION

Orchestrated movements of the organs of articulation change the vocal sound into recognizable speech. This process is often called the 'source-filter' model of voice production.[12] These articulatory movements can be classified as vowels or consonants (although the actual distinction between the two is theoretically complex). In simple terms, vowels are sounds in which there is no obstruction to the flow of air as it passes from the larynx to the lips. Consonants require a more definite obstruction by one or more of the articulators in the oral tract. This distinction becomes less useful for sounds such as 'w' or 'y', which we call consonants but are in reality articulated like vowels. For this reason these sounds are commonly called 'semi-vowels'.[13, 14]

All vowel sounds are continuants (i.e. they have length of varying periods of time). For practical purposes it is sufficient to differentiate between short vowels (i.e. p**i**t) and long vowels (i.e. p**ar**t). In a diphthong, two vowel sounds are combined (i.e. f**ire**). Vowel articulations are made by varying the resonating shape of the oral and pharyngeal cavities.

Changing the shape of the vocal tract subsequently changes its resonating behaviour; different shapes responding to different components of the harmonic structure of the glottal sound source. The resonance peaks of the vocal tract are called formants. These formant structures vary for each vowel and are easily identifiable on a sound spectrograph.[5] It is possible to distinguish between vowels by changing (i) the height of the tongue raising in the mouth, (ii) the part of the tongue which is raised (front, centre, back) and (iii) the position of the lips (spread or rounded). For example, the vowel /i:/ as in '**see**' is made with the front of the tongue raised and with lips spread. In contrast, the vowel /u:/ as in '**sue**' is made with back tongue raising and rounded lips. Diphthongs (i.e. '**beer**', '**air**') start with one oral tract articulatory shaping and glide to another.

Speech consonants are defined by their much clearer articulation (and often obstruction of the airflow) within the oral tract. Distinction between consonants can be made using three main elements: the place of articulation (i.e. lips, alveolar); the manner of articulation (i.e. plosive, fricative); and the state of the larynx (voiced or voiceless). All of these elements require further explanation.

The place of articulation

Consonants are clearly articulated at different places within the oral tract. Bi-labial consonants refer to articulation between the upper and lower lips (p, b, m, w). Labio-dental consonants require top teeth and lower lip articulation (f, v). Dental articulation refers to tongue tip and top teeth occlusion (th). Alveolar consonants are made by the tongue tip touching the ridge behind the teeth (t, d, n, s, z, r, ch, dj). Articulation of the middle tongue with the hard palate produces 'y'. Velar consonants require back of tongue and soft palate articulation (k, g, ng). See **Table 60.1** for a complete list of standard English consonants.

TABLE 60.1 Standard English consonants

	Bi-labial	Labio-dental	Dental	Alveolar	Palatal	Velar	Glottal
Plosive	p **b**			t **d**		k **g**	
Fricative		f **v**	Th[i] **th**[ii]	s **z** sh **jz**[iii]			
Affricate				ch **dj**[iv]			
Nasal	**M**			**n**		**ng**[v]	
Approximant	**W**			**l r**	**Y**		**H**

Bold signifies voiced; [i] as in 'th ink'; [ii] as in 'th at'; [iii] as in 'mea s ure'; [iv] as in 'j aw'; [v] as in 'si ng'.

The manner of articulation

The manner of consonant articulation refers to how the airflow is obstructed in the oral tract. Traditionally these are split into five categories: plosives, fricatives, affricates, nasals and approximants.

English has six plosive consonants: /p, b, t, d, k, g/. These plosives have different places of articulation (see previous section and **Table 60.1**). In all cases one articulator is moved against another in order to completely interrupt the airflow through the vocal tract. The air is temporarily compressed behind the point of articulation and then released with an audible noise called 'plosion'.

In contrast, fricatives are continuant consonants (they can continue for a relatively long time). The main characteristic of fricatives is the air turbulent sound that is made by air 'hissing' through the close (but not complete) approximation of two articulators. Like plosives, fricatives have different places of articulation (see **Table 60.1**). Examples of English fricatives include f, z, and s.

Affricates are a combination of plosion and fricative articulation. A common example is the affricate consonant heard at the beginning and end of the word 'church'. It begins with the plosive t and then the tongue moves to the position for the fricative sh. The plosive is followed immediately by the fricative noise but is heard as one consonant sound. There are only two affricate sounds in English (ch and dj, as in the beginning and ending sounds in 'church' and 'judge'), and both are articulated with the tongue tip and alveolar.

The basic characteristic of the nasal consonants (m, n, ng) is that air escapes through the nose. The air is prevented from passing through the mouth by obstructive lip or tongue articulation and the soft palate is lowered to allow nasal air escape. The soft palate is raised for all other standard consonants and vowels. Inadequate velopharyngeal competence will result in inappropriate 'nasalization' of non-nasal consonants and vowels. Permanent obstruction in the nasopharynx and lower nasal passages will result in 'denasalization' of nasal consonants.

Approximant consonants occur when the articulators are not sufficiently close to produce 'complete' consonants such as plosives, fricatives or nasals. Again, place of articulation can vary (see **Table 60.1**). These consonants are articulated similarly to vowels and are therefore often called semi-vowels. English examples of approximants include w and y. The lateral approximant 'l' varies slightly since the passage of air escapes along the sides of the tongue.

The state of the larynx

Finally, consonants can be either 'voiced' or 'voiceless'. A number of consonants can be 'paired', where the only difference between them is whether their articulation is accompanied by voicing or not (i.e. p and b, t and d, k and g, s and z). The place and manner for both members of each pair is the same. The only difference is that the first in each pair is 'voiceless' – there is no vibration of the vocal folds for the split second that these consonants are being articulated. The voiceless consonant 'h' does not have a voiced twin in standard English. This means that in connected speech, vocalization is not continuous. Phonation is switched on and off (for milliseconds of time) to signal voiceless consonants. This extremely subtle phonatory timing is crucial for intelligible speech and is a characteristic problem of some dysphonic voices. In **Table 60.1** the voiced consonants are signalled by **bold** type.

PHONEMES, ALLOPHONES, PHONOLOGY AND LANGUAGE VARIANCE

Phonetics is the study of speech sounds and how the rules of language organize and change sounds in different contexts.[13, 14] The consonant and vowel articulation described in the previous section is theoretically accurate but, in reality, can be modified and varied on an almost infinite level. Any speech sound (or phoneme) may be articulated slightly differently according to the other sounds around it. These variations of the same phoneme are called 'allophones'. For example, the sound 't' in the words 'tea' and 'tree' are, in fact, articulated with a slightly different tongue position. This is one reason why simulated (computerized) speech does not sound natural. In more extreme cases, speech sounds may change altogether depending on their phonetic environment or even be omitted altogether. For example, consider how 'handbag' is regularly pronounced 'ha**m**bag' and 'nightmare' is pronounced 'nigh'mare'.

Phonology is the sound patterns of a particular language. The way children develop the phonology of the language is well understood[15] and the differentiation between development phonological deviance as opposed to phonological delay is an important clinical consideration.[15] Clearly, different languages have different phonological sets and therefore will include some consonants and vowels that may not feature in English speaking at all.

PARALINGUISTIC FEATURES OF VOICE AND SPEECH

Speech and voice are more than just the products of muscular movements. For example, they represent an immensely powerful (and efficient) means of conveying mood, personality and intent. Our speech and voice also provides messages about our education, social status, emotional state and personality. All of these things are interpreted from the way the speaker uses features such as speech rhythm, speech rate, vocal intonation, vocal tone or quality and voice loudness. 'Everything is said in a certain way, in a certain tone of voice and at certain loudness.'[4] However, it is rare for a speaker to be using these features consciously (unless the speaker is an actor). The unconscious use of these paralinguistic features may be more revealing than the speaker anticipated and more enlightening than the language content of what is being spoken. It is partly for these reasons that voice or speech impairment may result in severe levels of personal handicap, disability and distress.[16, 17]

Speech rhythm is learned as an integral part of early childhood speech, voice, language and communication development. Early babbling is a 'working vocal guidance system … in which the ear monitors vocal tract activity and informs speech-motor control systems about targets and adjustments needed for mimicry of ambient speech'.[18] Speech rhythm is language- and even accent-specific. Speech rhythm (and stress) is one of the most difficult linguistic features for foreign speakers to master and will distinguish them from truly bilingual speakers who were exposed to several speech rhythm patterns from birth.[19] To complicate the matter further, regional accents often demand different speech rhythms again. For example, it may be possible to identify locals from Newcastle simply by how they stress the syllables in the word 'Newcastle'. Locals will stress the second syllable (New**castle**) whereas most other speakers will naturally stress the first syllable (**New**castle). Finally, loss of rhythm and incorrect stress may render speech almost unintelligible even when articulation and voice production are normal.[4]

Speech rate is often interpreted as an indicator of anxiety (if it is too fast) or low intellect (if it is too slow).[20] Our speech rate is also likely to reflect our state of arousal (excited, drowsy, stressed etc.) and is clearly linked to other physiological systems such as pulse and respiratory rate.

Vocal intonation refers to the use of varying vocal pitch to indicate various grammatical, psychosocial and semantic features. We use intonation to indicate communicative intent (e.g. to characterize a question or to indicate certainty in a statement) and to manipulate conversation (e.g. to encourage a response). Patterns of intonation are often used unconsciously by the speaker and are, of course, open to misinterpretation by the listener. Similarly, the pitch range used by a speaker may reflect emotional status. A wide frequency range indicates arousal in contrast to a narrow ('flatter') range, which may be interpreted as sadness or impassiveness.[21] Habitually low pitch may indicate depression and high pitch may suggest anxiety.[22] A clear understanding of the components of phonatory behaviour (e.g. laryngeal muscle tone, pulmonary airflow, subglottal pressure, supralaryngeal tension) provides a physiological explanation for these paralinguistic features of voice.

The emotional content of a verbal message is also likely to be reflected in changes in vocal tone or quality.[23, 24] These result from changes in laryngeal and supralaryngeal tension, which in turn affect vocal features. For example, a breathy vocal quality may indicate anxiety[25] or vulnerability[26] and may be interpreted as revealing lower social class, especially when associated with harshness.[27] Conversely, vocal creak (low pitched, irregular vocal fold vibrations) may indicate a relaxed state and has been shown, at least in one study, to correlate with higher social status.[27] Vocal loudness appears to be different between the sexes even when the context and linguistic content are similar: men talk more loudly than women.[27] Not surprisingly, we commonly associate vocal loudness with confidence and extrovert personality but inappropriate loudness may indicate insensitivity and poor pragmatic skills.[28] Clearly, the interpretation of a speaker's vocal quality and volume are, like all other paralinguistic features, subjective and may subsequently result in misunderstandings.

Almost all paralinguistic aspects of speech and voice are intuitively known but not consciously learned (or manipulated). They contribute as much to our individual speech and voice characteristics as our specific anatomical configurations and habitual vocal settings. These paralinguistic features of speech and voice remain a crucial aspect of speech and voice production and help to explain why many people with a speech and voice disorder report severe personal, social and economic consequences.

FUTURE RESEARCH

- Cultural differences in speech and voice and the importance of these differences on non-organic voice pathology.
- The impact on voice and speech disorders on tonal languages.
- Closer mapping of acoustic and physiological measurement to the auditory features of speech and voice.
- Development of a reliable and practical auditory perceptual rating scale for supraglottic features of voice quality.
- The application of the analysis of paralinguistic features of speech and voice in psychiatric and psychological differential diagnosis.

KEY POINTS

- The voice is the product of vibrating vocal folds and sound resonance throughout the vocal tract.
- The specific characteristics of an individual's speech and voice are the product of the organic and phonetic features of the speaker.
- The quality of the glottal sound is wholly dependent upon the vibratory characteristics of the laryngeal structures.
- Orchestrated movements of the organs of articulation modify the vocal sound into recognizable speech.
- Paralinguistic features of voice and speech include speech rhythm, stress, accent and vocal intonation.

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CHAPTER 61

ASSESSMENT AND EXAMINATION OF THE LARYNX

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SEARCH STRATEGY

Data in this chapter are based on Medline, PubMed, hand searches and the Cochrane review database using the keywords: larynx, clinical examination, adult, paediatric, laryngoscopy, endoscopes, optical imaging and difficult airway.

INTRODUCTION

The purpose of the chapter is to review the techniques available for accurate and safe examination and assessment of the upper respiratory tract. The otolaryngologist must have a systematic method to process symptoms and signs in order to achieve the correct diagnosis.

ASSESSMENT IN THE CLINIC

Evaluation of the patient begins as soon as he/she enters the clinic room. Preliminary assessment of their respiratory status can be made during history taking. The patient with respiratory distress may be unable to speak a few words before needing to rest, whereas a healthy individual will converse without difficulty. Voice quality can also be subjectively monitored at this time. Persistent or progressive dysphonia may suggest an organic lesion in the larynx compared to intermittent dysphonia that may suggest a functional disorder.

It is not routine practice in the otolaryngology clinic to undress a patient in order to examine the respiratory system, but this should be done if the clinical history suggests chest disease, such as suspected metastasis or severe chronic obstructive airway disease (COAD) limiting fitness for surgery, that might influence the decision-making for the ENT condition.

Clinical signs and symptoms of upper respiratory impairment include:

- dyspnoea
- tachyponea
- stridor
- dysphonia
- cyanosis
- use of accessory muscles of respiration.

The examiner should be aware of general systemic signs of disease that are relevant to the respiratory tract, such as nicotine staining to the hands, clubbing, anaemia, jaundice and spider naevi.

Nasal airway

The upper airway begins with the nasal cavity and therefore the nasal airway should always be assessed. Although it is covered in Chapter 88, Outpatient assessment, a summary is provided here. Nasal airflow and patency should be subjectively assessed through each of the nares using the palmar surface of the thumb or a shiny Lack tongue depressor. Anterior rhinoscopy should be supplemented with endoscopic examination of the nose in order to inspect the posterior nasal cavity.

Laryngoscopy

Indirect laryngoscopy examination with a mirror, a technique with an illustrious history,[1] is still used as a method of visualizing the larynx. This examination method has several limitations including perceptual errors,[2] difficulties in the user reliably recording the side of lesion, the learning curve in acquiring and maintaining the skillset,[3] and a significant failure rate which, prior to the era

of readily available flexible endoscopy, often mandated direct endoscopy under general anaesthesia.

Significant advantages include widespread availability in all ENT departments, low cost to buy and maintain and a learning curve that is not insurmountable. Regular practice on all suitable patients in the early years (an anatomical model to facilitate this process has been described)[3] and continued later use can often maintain the skillset for this technique. A few studies exist on minor laryngeal procedures that can be carried out with indirect techniques successfully,[4–6] including obtaining photographic images as the sole operator. It is a procedure free of complications except for gagging and failure to visualize the lesion,[7, 8] which occurs more frequently than with flexible or direct laryngoscopy. Failure of indirect laryngoscopy suggests that microlaryngoscopy may be difficult.[9] Magnifying laryngeal and nasopharyngeal mirrors have been described.[10]

Endoscopic assessment, either with a rigid or flexible laryngoscope, has supplanted mirrors due to better optical resolution and higher sensitivity.[11, 12] Endoscopes in the ENT clinic should now be considered the standard of care.

The rigid Hopkins rod system uses 70- or 90-degree angled lenses and allows an excellent view of the larynx through a transoral approach. This is the favoured technique for laryngologists in the 'voice clinic' as the wider rigid rod lens produces a much higher optical resolution for more detailed assessment of phonation.[13] Laryngoscopy can be supplemented with stroboscopy, laryngography or digital acoustic voice analysis (see Chapter 62, Evaluation of the voice).

TECHNIQUE FOR FLEXIBLE LARYNGOSCOPY

The endoscope is passed through the anterior nares, along the floor of the nose under the inferior turbinate. Passage between the middle and inferior turbinate or through the opposite nostril may be necessary if the airway is narrowed. Once the endoscope is in the postnasal space, the patient is asked to inspire through the nose, and this opens the postnasal sphincter allowing passage of the endoscope into the oropharynx (**Figure 61.1**).

A stepwise assessment of the larynx is made: the vallecula is inspected (by tongue protrusion), the supraglottic larynx, followed by the glottic larynx. Attention should be taken to record accurately the correct side of any lesion identified as errors are common.[14] Newer extended applications of this technique include flexible endoscopic evaluation of swallowing, with or without sensory testing,[15] videoendoscopy of the hypopharynx and cervical oesophagus,[16, 17] including biopsy and foreign body removal through a biopsy channel, paediatric adenoid assessment[18] and neonatal upper airway assessment.[19]

Topical anaesthesia

Topical nasal administration of local anaesthetic is often used prior to flexible laryngoscopy in the clinic in order to decongest the nose and facilitate examination.[20] Cocaine was traditionally used in the past either as aerosol (10%) or as paste (4%). However, concerns regarding cardiotoxicity and drug misuse, as well as contamination from the delivery system for cocaine, have resulted in newer derivatives such as cophenylcaine or amethocaine being used.[21] Some authors have questioned the necessity of using any anaesthetic for this procedure.[22, 23] Eight randomized studies[21–28] have been published, of which four are double-blind randomized trials,[23, 24, 26, 28] but all have some methodological flaws. Unfortunately, two of the double-blind studies[24, 26] draw inappropriate conclusions from their data. A more recent systematic review of the few randomized control trials on this subject found no reduction in pain scores with the use of vasoconstrictive, topical anaesthetic or lubricating agents.[29] Further well-designed, sufficiently powered, double-blind studies incorporating all options are warranted. Overall, current evidence suggests that the benefits of local anaesthesia cannot be large in these circumstances.



Figure 61.1 Flexible laryngoscopy in the clinic.

Consent and complications

Informed consent prior to any surgical procedure is a fundamental aspect of clinical practice, to prevent patient-doctor complaints and medical malpractice claims. It has been suggested that all interventions, including laryngoscopy, require a consent form to be completed. Thus far, it is not routine clinical practice to obtain written consent before performing flexible laryngoscopy in the clinic. Currently, there is no literature on this subject.

No robust literature on complications of flexible nasoendoscopy exists, but these include discomfort of variable degree and occasional epistaxis during difficult insertion, excessive gagging in the absence of local anaesthesia, coughing, transient laryngospasm, gluteraldehyde allergy and infection due to laryngoscope contamination. Paediatric, including neonatal, flexible awake nasoendoscopy are now accepted procedures,

but, particularly in the latter group, the procedure may be associated with episodes of significant oxygen desaturation, laryngospasm, bronchospasm and coughing.[30] Some patients may experience psychogenic pain and other symptoms which may last for prolonged periods. The increased prevalence of MRSA, hepatitis B and C and HIV has resulted in more rigorous infection control systems to be implemented for all invasive procedures.

Decontamination principles

Sterilization practices used to vary considerably throughout the UK.[31] Most large hospitals have opted for a central decontamination unit to handle the sterilization of endoscopes in order to maintain optimum anti-infective standards, while some units use a chemical soak system, but the type of disinfectant, method of delivery and duration of soak used vary widely. A few hospitals use disposable sheath systems and some still only wipe endoscopes with alcohol wipes between patients. Protocols for high-risk patients demonstrated a parallel lack of uniformity. A similar divergence in practice has been recorded in South Africa[32] and other parts of the world.[33]

UK national guidelines for the cleaning of nasoendoscopes have now been produced.[34, 35, 36] The main points to come out of these guidelines are summarized below.[34, 37] The risk of transmitting infection between scope and patient has not been quantified for nasoendoscopes, but for gastroscopes it is 1 in 1.8 million. The risk of variant Creutzfeldt–Jacob disease transmission is probably extremely low provided scrupulous attention is paid to the detail of decontamination. The risk of transferring infection from the user to the scope is minimized by removal of all jewellery, including wristwatches, proper hand decontamination and the wearing of disposable gloves. Should an outbreak of infection occur, a logbook should be available which records patient details, time and date of use, name of user and person responsible for sterilization, and the method of sterilization. Details of the instrument used, including serial numbers, should be recorded in the patient's notes. Appropriate training programmes for all involved staff and an up-to-date list of authorized personnel and what each individual authorization covers should be available in each department. Policies need to cover these issues when the scopes are used in a variety of settings outside ENT departments. Even if a disposable sheath is the preferred mode of ensuring clean nasoendoscopy, daily high-level disinfection of the endoscopes is required.

Used endoscopes from locations distant to the site of decontamination should be transported to the place of decontamination in a labelled disposable bag in its case if possible. Decontamination involves both cleaning and high-level disinfection. Methods chosen need to be approved by manufacturers to uphold service contracts and warranties. Inspections of scopes should be visual and by formal leak testing.

Cleaning may be manual or mechanical but must remove all visible debris. It is no longer recommended to use gluteraldehyde for chemical high-level disinfection owing to its toxicity[38–40] and ability to fix proteins onto the endoscope surfaces, making their subsequent removal more difficult.[35] Suitable options for chemical disinfection include electrolyzed saline (Sterilox®); chlorine dioxide (Tristel®); peracetic acid (Steris®, Nucidex®, Perasafe®, Gigasept®). Peracetic acid is irritant to skin and the respiratory system.[34] Tristel is used by many ENT clinics in the UK.[34, 41]

There is no ideal disinfectant, with the choice of agent dependent on its microbicidal activity, toxicity profile and approval for use by the various endoscope manufacturers. Disposable sheaths are a safe and effective alternative to chemical decontamination and have been introduced in order to reduce the necessity of formal sterilization between examinations. These have been shown to be effective in acting as a barrier to infection, even by viral particles.[42] Sheaths currently available have an improved design that requires no special equipment for application and removal, which, if improperly used in the past, caused damage to the endoscope covering at the tips, making it costly or impossible to repair.[43] There is a risk of endoscopic contamination if the sheath is breached. No significant difference has been noted between sheathed and unsheathed endoscopes from the user and patient perspective, as well as in image quality.[44] This may well provide a much more cost-effective, user-friendly and safe solution to some forms of chemical disinfection.

Local or central automatic endoscope washer-disinfectors (AEWDs) are also gaining widespread use as they free up clinic support staff from the manual tasks involved in decontaminating endoscopes, as well as providing a standardized endoscope sterilization protocol which is very useful from a clinical governance perspective. The high set-up costs involved in acquiring AEWDs as well as the logistical challenge from the slow turnaround of endoscopes, especially if the central facility is at a distant site from the ENT clinic, are some of the disadvantages in opting for an AEWD system. Out-of-hours cleaning and disinfection of nasoendoscopes by junior medical staff is still a real problem, mainly due to lack of knowledge and access to the appropriate facilities, usually based in outpatient departments.[45]

Most ENT departments are implementing a flag system to record details of each laryngoscopy episode. Flexible endoscopes are expensive and relatively fragile instruments. They require careful handling, maintenance and cleaning; a designated health practitioner should be responsible for their care. Storage of endoscopes is best achieved with the scopes hung vertically in storage cupboards, or in custom-made storage/transport trays. This prevents repeated twisting and bending of the scope, which will result in breaking of the optical fibres, thus reducing the lifetime of the scope.

Considerations of consent, accurate documentation of findings and sterilization are important as they all have time and resource implications in the clinic.

KEY POINTS

- Indirect laryngoscopy is a technique with definite limitations, but its low cost, widespread availability and lack of associated complications should mean that it survives as part of the otolaryngologic skillset.
- Flexible endoscopy has rightly replaced the above as the first-choice tool for examination of the upper aerodigestive tract owing to its extended applications.
- The evidence for topical anaesthetic use, choice of agent and the extent of benefit is not clear-cut.
- There is no significant literature on consent issues.
- There is still debate as to the most cost-effective means of decontaminating flexible laryngoscopes. It is acceptable, however, to decontaminate endoscopes manually without a biopsy channel using chemical wipes such as chlorine dioxide, avoiding the high costs and logistical issues from the use of a central sterile services unit.[34,35]
- Gluteraldehyde is no longer recommended for use in the UK due to the high risk of sensitivity. Disposable sheaths are another alternative to minimize cross-contamination.
- Regardless of the decontamination protocol used, an adequate endoscope traceability system needs to be in place for clinical governance and risk-management purposes.

OPERATIVE LARYNGOSCOPY

Anaesthetic considerations for laryngoscopy in the operating theatre

Accurate assessment of the larynx under general anaesthetic requires a systematic approach involving cooperative work on the shared airway between the otolaryngologist and the anaesthetist. It is therefore important to develop a good working relationship with one's anaesthetic colleague and have a system that you are both happy to work with. When applied to appropriate patients, laryngoscopy, can be performed safely as a day-case procedure.[46]

There are several methods of performing laryngoscopy under general anaesthesia and there is a balance between maintaining a secure airway and obtaining a clear, unobstructed view of the larynx. A systematic review of each technique will be discussed, and the clinician must decide upon a technique that they find most satisfactory.

MICROLARYNGOSCOPY TUBE

The microlaryngoscopy tube is a small-diameter cuffed endotracheal tube (ET), which is placed in the posterior glottis. The diameter ranges from 16 to 22 French gauge. This type of tube has been shown to be safe for operative laryngeal microsurgery.[47] If transoral laser microsurgery is planned, specifically designed non-combustible non-reflective laser tubes are used. These have indicator dyes incorporated into the cuff to identify whether the cuff is damaged, in order to reduce the risk of an airway fire hazard.[48–50]

TOTAL INTRAVENOUS TUBELESS ANAESTHESIA

This technique involves anaesthesia maintained by continuous intravenous infusion of propofol with topical lignocaine and the patient breathing spontaneously. It has been described for both diagnostic and therapeutic laryngoscopy, including laser microsurgery. It is not recommended for high-risk patients (ASA III or IV) or patients with an obstructed airway. Total intravenous tubeless anaesthesia should only be undertaken by those who have expertise in this technique.[51–53]

HIGH-FREQUENCY JET VENTILATION

High-pressure jet (Venturi) ventilation of anaesthetic gases without an ET tube can be administered via the supraglottis, glottis or subglottis, or via the transtracheal/ cricothyroidotomy route. This technique has been widely used for endolaryngeal surgery, including laser surgery;[54] advantages include the absence of combustible material in the airway, thus providing a clear view of the larynx and deep anaesthesia to allow for microsurgery.[53] Large multicentre studies of 643 patients based in France and 872 patients in the USA have shown low complication rates using this technique. Problems such as pneumothorax were encountered in 1%, hypoventilation in 2% and surgical emphysema in 8% of cases.[55,56] The Venturi technique has also been described in paediatric practice.[57] Relative contraindications to using this technique would be the unstable or obstructed airway, difficult access to the larynx (micrognathia/overhanging teeth) or respiratory failure (with emphysematous bullae).[57,58]

RIGID LARYNGOSCOPY

The patient is prepared and anaesthetized as standard for the operating theatre. The position is supine, with head extension and neck flexed in order to open the laryngeal inlet. Eye cover, dental protection and antiseptic draping are applied.

The widest laryngoscope to maximize vision is passed perorally in the midline and the tongue is negotiated in order to visualize the epiglottis. Care must be taken to prevent dental trauma and trauma to the lips. The endoscope is used to elevate the epiglottis in order to visualize the larynx. Different telescopes can be utilized to inspect the subsites of the endolarynx (**Figure 61.2**), such as the anterior commissure scope, which is designed to



Figure 61.2 A selection of rigid endoscopes for laryngoscopy.

maximize the view of the anterior glottis. Suspension of the laryngoscope frees both hands to operate.

Rigid laryngoscopy offers improved visualization of the larynx through better illumination, higher magnification and wider and deeper fields of vision. By incorporating the microscope and combination of 0, 30 and 70 degree angled endoscopes, a full view of the endolarynx can be obtained (**Figure 61.3**). The angled endoscopes allow better perspectives of the ventricle, free edge and under surface of the vocal cord. It is important to define and record accurately the findings of the laryngoscopy. The site, extent, dimensions, shape, colour and surface characteristics of the lesion should be defined. Vocal cord mobility and airway patency should be recorded. The use of printed operative diagrams should be encouraged (**Figure 61.4**).

Photo documentation is becoming an important part of otolaryngology practice. It improves case review between clinicians and is increasingly forming part of routine practice in the current medicolegal climate. High-resolution digital imaging is now available to facilitate still, video and hard-copy documentation.

NEW TECHNIQUES IN LARYNGEAL ENDOSCOPY

Optical imaging techniques have evolved over the past two decades from our greater understanding of fluorophores, the fluorescent properties of intracellular and extracellular components, as well as advancing laser, optical filters, endoscope and computer software technology. As always, the challenge with new technology is defining how it can be incorporated into daily clinical practice, given the variation in requirements during assessment of the upper respiratory tract and the group of patients or clinical scenario: for example, general population versus those at high risk of neoplasia, determining precancerous versus malignant lesions, assessing tumour margins intraoperatively, or post-treatment surveillance following primary surgical treatment versus chemoradiation therapy. The gold standard against which these new technologies are compared is histopathological analysis and, while the sensitivity, specificity and accuracy of the techniques described below are still under investigation, none yet matches the gold standard.



Figure 61.3 Theatre set-up for rigid laryngoscopy under general anesthesia. Note the telescope and the two-handed technique to assess, document and obtain biopsy.

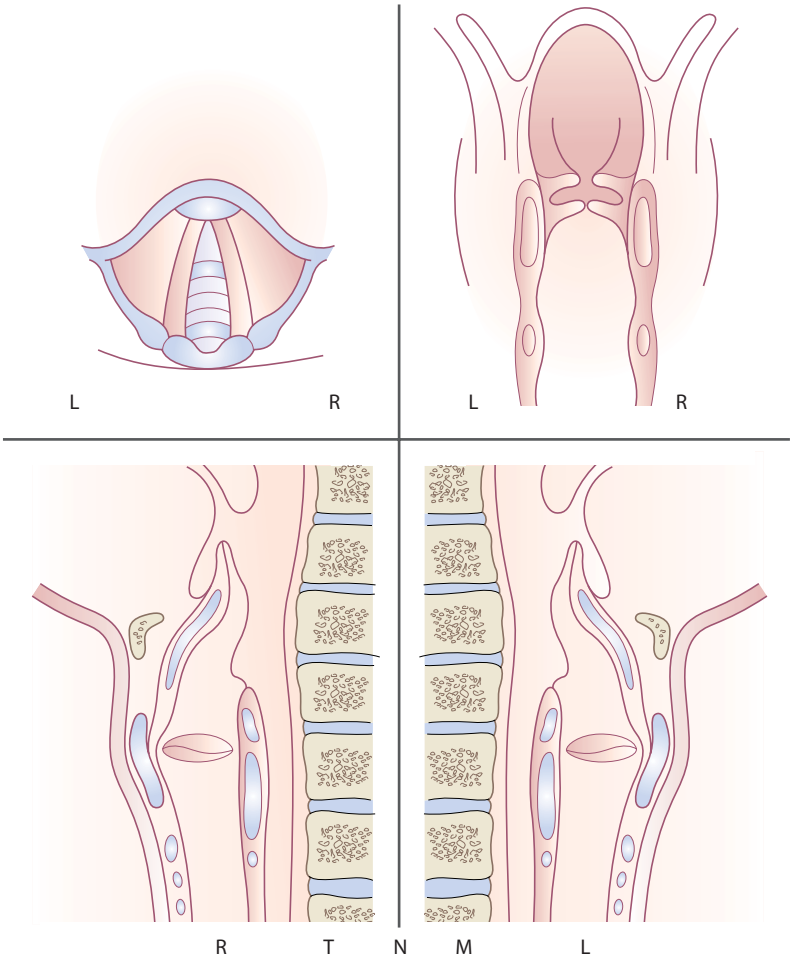


Figure 61.4 Printed operative diagrams used to record findings.

Contact endoscopy and microlaryngoscopy

This new technique allows for microscopic assessment of the epithelial cells of the larynx *in vivo* and *in situ*. The process involves staining the epithelium with methylene blue or Lugol's iodine. A modified Hopkins rod laryngoscope is applied against the mucosa of the larynx. At ×60 and ×150 magnification cytological characteristics of the cells, nuclei and cytoplasm can be appreciated in the first three layers of epithelial cells, in addition to the subepithelial microvascular network.[59] Premalignant conditions, such as dysplasia, could therefore potentially be detected earlier. It is designed not as a substitute for histology but as a research tool to allow better understanding of the cytological changes that occur in the laryngeal epithelium in the transition from normal to disease. Preliminary studies have shown good correlation between its findings and formal histology,[60,61] with sensitivity and specificity of 90% and 94% respectively, and an 88% agreement with histopathological findings after appropriate training.[62] The use of contact endoscopy in the larynx is confined to clinical research but does show promise for a wider application in the future.

The main advantage is that it is a non-invasive procedure, and avoids complications related to unnecessary tissue biopsy, especially in irradiated patients. The technique, however, is limited by the superficial depth of penetration, the inability to distinguish confidently between intraepithelial neoplasia and invasive carcinoma, the experience required to minimize trauma to delicate tissues with the endoscopes, and the impaired visualization of malignant cells in the presence of scarring, chronic inflammation or keratosis.

Autofluorescence

Various extracellular and intracellular structures such as collagen, elastin, mitochondria and porphyrins naturally emit light following absorption of light at a specific wavelength. This physical phenomenon is a property of fluorophores. Knowledge of the specific wavelength at which specific fluorophores are excited allows investigators to take advantage of particular intracellular or extracellular constituents that may be altered in the disease state and consequently stimulated using monochromatic light in the blue or ultraviolet range of the electromagnetic spectrum (wavelengths between 375 nm and 460 nm), in the form of a laser. Normal mucosa fluoresces green, while neoplastic mucosa has reduced autofluorescence and emits a red-violet colour (**Figure 61.5**).[63,64] Changes in autofluorescence can be detected by sophisticated endoscopes or observed as spectral changes using optical filters and specialized detectors.

When combined with microlaryngoscopy, autofluorescence may be better at identifying invasive carcinoma, with a reported sensitivity of 87–97% and specificity of 78–87%.[65–69] The limitations of autofluorescence are the difficulty in assessing the basal mucosal layer due to a restricted depth of penetration, and the low specificity, with false positives arising from granulation tissue, scarring and chronic inflammation. Further studies are required to determine the benefits of microlaryngoscopy and autofluorescence in increasing detection of discrete upper airway lesions, and in reducing the rate of positive margins following surgery, but there is a paucity of work using this tool, indicating that it may be on the wane.

Narrow-band imaging

White-light laryngoscopy is limited by the inability to detect very small epithelial changes and is also unable to differentiate between benign and malignant lesions *in vivo*. Narrow-band imaging (NBI) is a novel endoscopic technique which aims to overcome some of the limitations of white-light endoscopy by using filtered light to visualize mucosal and submucosal neoangiogenic microvascular patterns that have been characterized previously.[70, 71] Certain neoangiogenic features such as intraepithelial papillary capillary loops are associated with precancerous and malignant mucosal lesions (**Figures 61.6** and **61.7**).

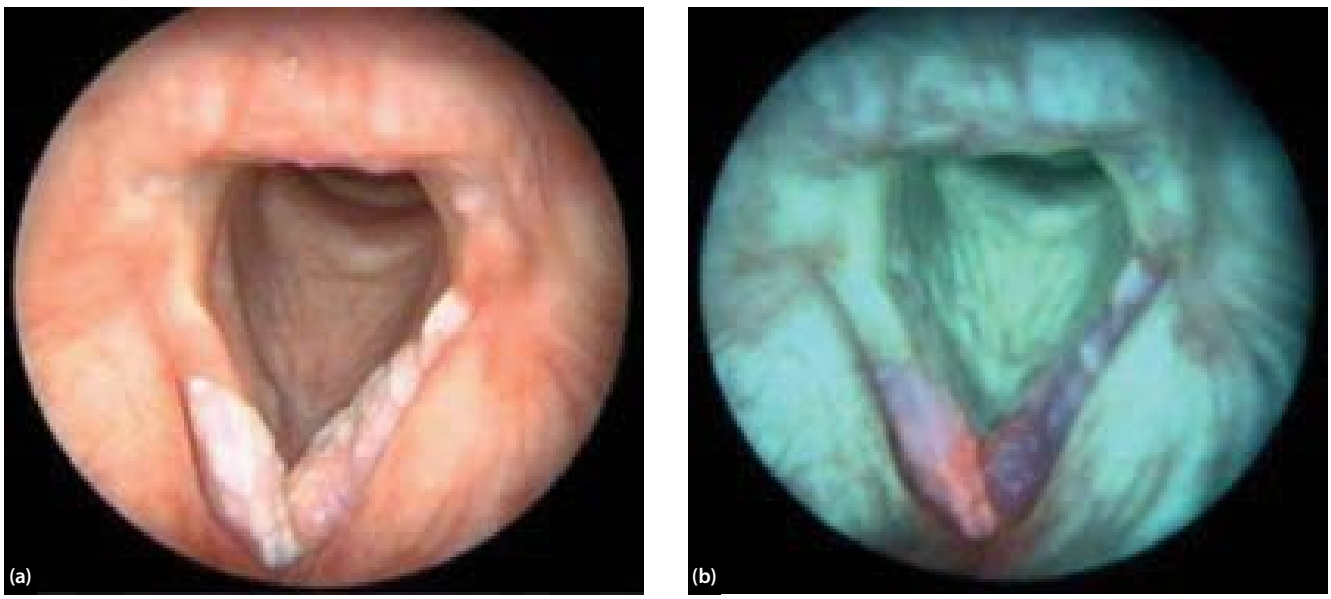


Figure 61.5 **(a)** White-light image shows an abnormal lesion on the right cord, suggestive of a neoplastic process. **(b)** Autofluorescence endoscopy shows loss of autofluorescence, giving an orange/red colour, typical for invasive malignancy. With Permission fom Springer Nature, from Arens C, Dreyr H, Glanz et al. Indirect audofluorescence laryngoscopy in the diagnosis of laryngeal cancer and its precursor lesions. *Euro Arch Otorhinolaryngol* 2004.

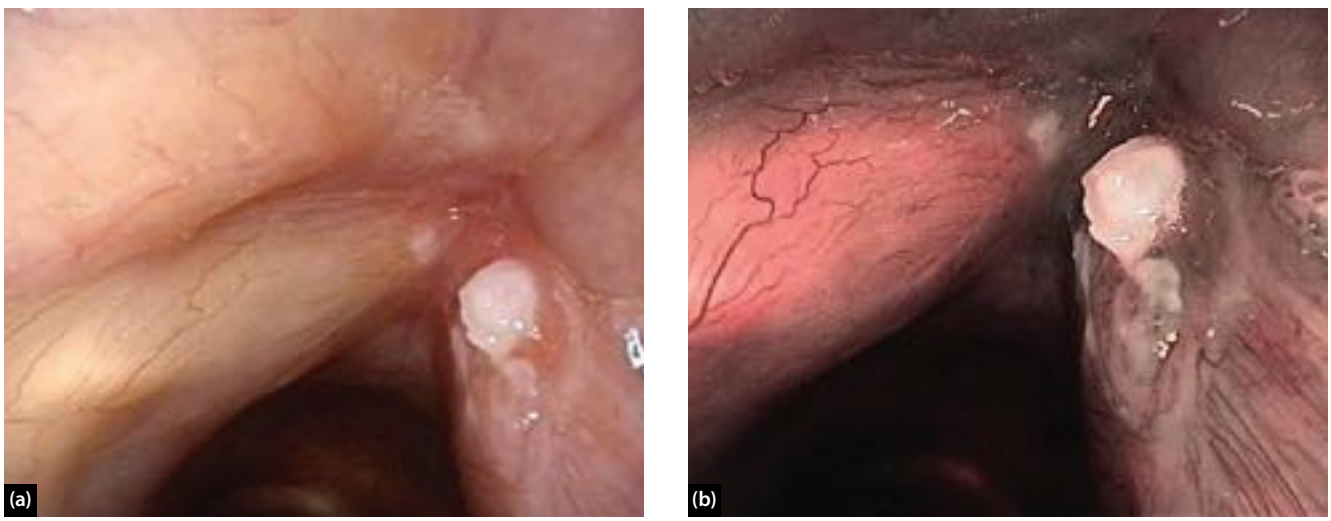


Figure 61.6 **(a)** White-light image shows an area of leukoplakia on the right glottis. **(b)** Narrow-band image shows a carcinoma *in situ*, with better definition of margins (inferior extension and satellite lesion extending in the ventricle). (Image courtesy of Professor Cesare Piazza, University of Brescia.)

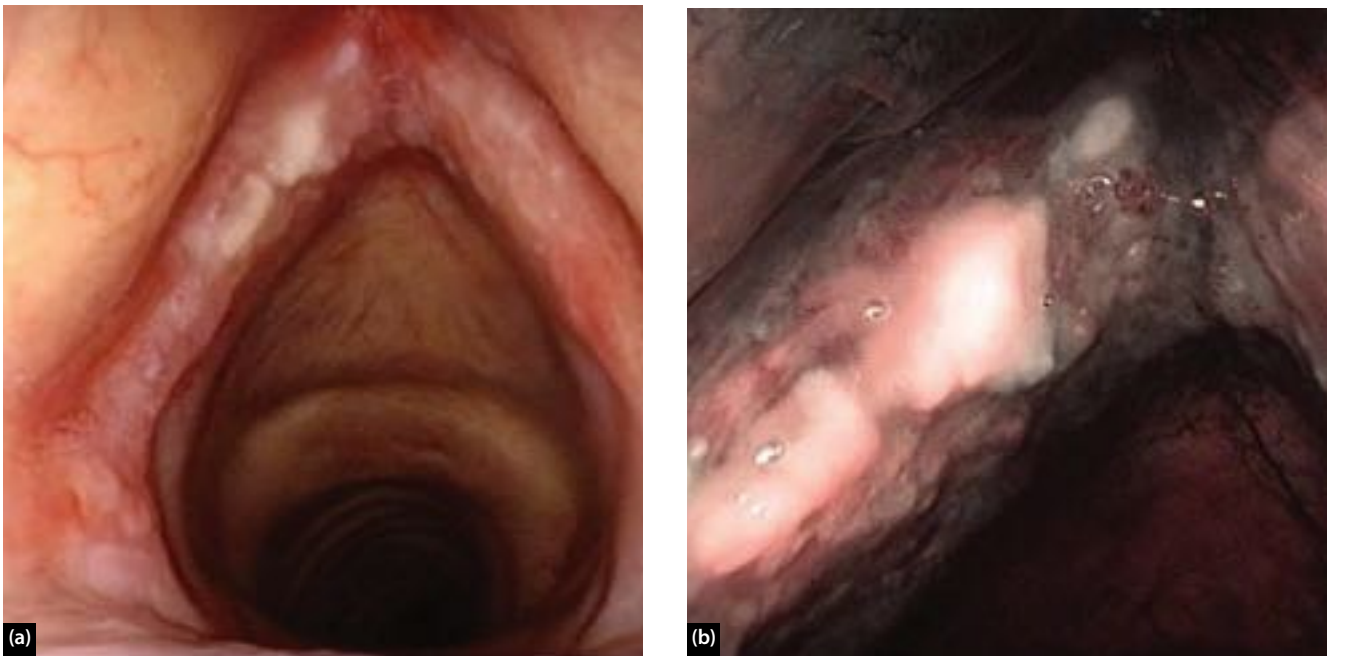


Figure 61.7 **(a)** White-light image shows an abnormal glottic lesion. **(b)** Narrow-band image shows findings typical of squamous cell cancer and also reveals extension to the contralateral cord. (Image courtesy of Professor Cesare Piazza, University of Brescia.)

NBI technology is based on knowledge that the depth of light penetration is a factor of its wavelength, and through the use of special filters, blue and green light are selected from white light, corresponding to the peak of absorption of haemoglobin. Narrow-band blue light (415 nm) highlights superficial capillary networks, while narrow-band green light (540 nm) displays subepithelial vessels and, in combination, the two wavelengths produce a very high-contrast image of the tissue surface, which is particularly evident when using a high-definition television (HDTV) camera.

NBI has been able to achieve sensitivity and specificity of 89% and 93% respectively in the diagnosis of primary laryngeal lesions,[70] and higher values have been achieved in the context of assessing lesions following radiation and chemoradiation therapy,[72] therefore reducing the requirement for a tissue biopsy in these cases.

NBI mode is a standard feature on some videoendoscopes, thus making the technique readily available. However, it is limited by the learning curve required to understand aberrant microvascular architecture and, as with other optical imaging techniques, the superficial depth of penetration precludes assessment of the deep extent of neoplasia.

Optical coherence tomography

Optical coherence tomography (OCT) is an analogue of ultrasound, using light instead of sound to produce a high (micrometre) resolution cross-sectional image, similar to a vertical histological section (**Figure 61.8**).[73] A beam of light is directed onto tissue and back-reflected from components with different optical properties. Because the velocity of propagated light is several magnitudes greater than sound, and the resultant echo time delay cannot be measured using conventional electronics, a specialized technique known as interferometry is required to measure echo time delay and the intensity of back-reflected light. Interferometry uses light that has travelled a known reference path length and time delay.[73]

A number of investigators have used endoscopic versions of OCT to analyze both healthy and diseased laryngeal mucosa. In combination with microlaryngoscopy, OCT has been shown to significantly increase the sensitivity of determining benign versus malignant lesions and the grade of precancerous lesions when compared to microlaryngoscopy alone.[74] Further studies are needed, however, to determine whether the optical biopsy derived from OCT can indeed replace an excisional tissue biopsy.

Fluorescence lifetime imaging

Fluorescence lifetime imaging (FLIM) is another non-contact optical method which has several advantages over contact endoscopy, providing complementary ultrastructural and spectral detail. FLIM is based on the principle that the fluorescence lifetime of a fluorophore depends on its molecular environment but not on its concentration. Molecular effects in a sample can therefore be investigated independently of the variable and usually unknown concentration of the fluorophore (**Figure 61.9**).

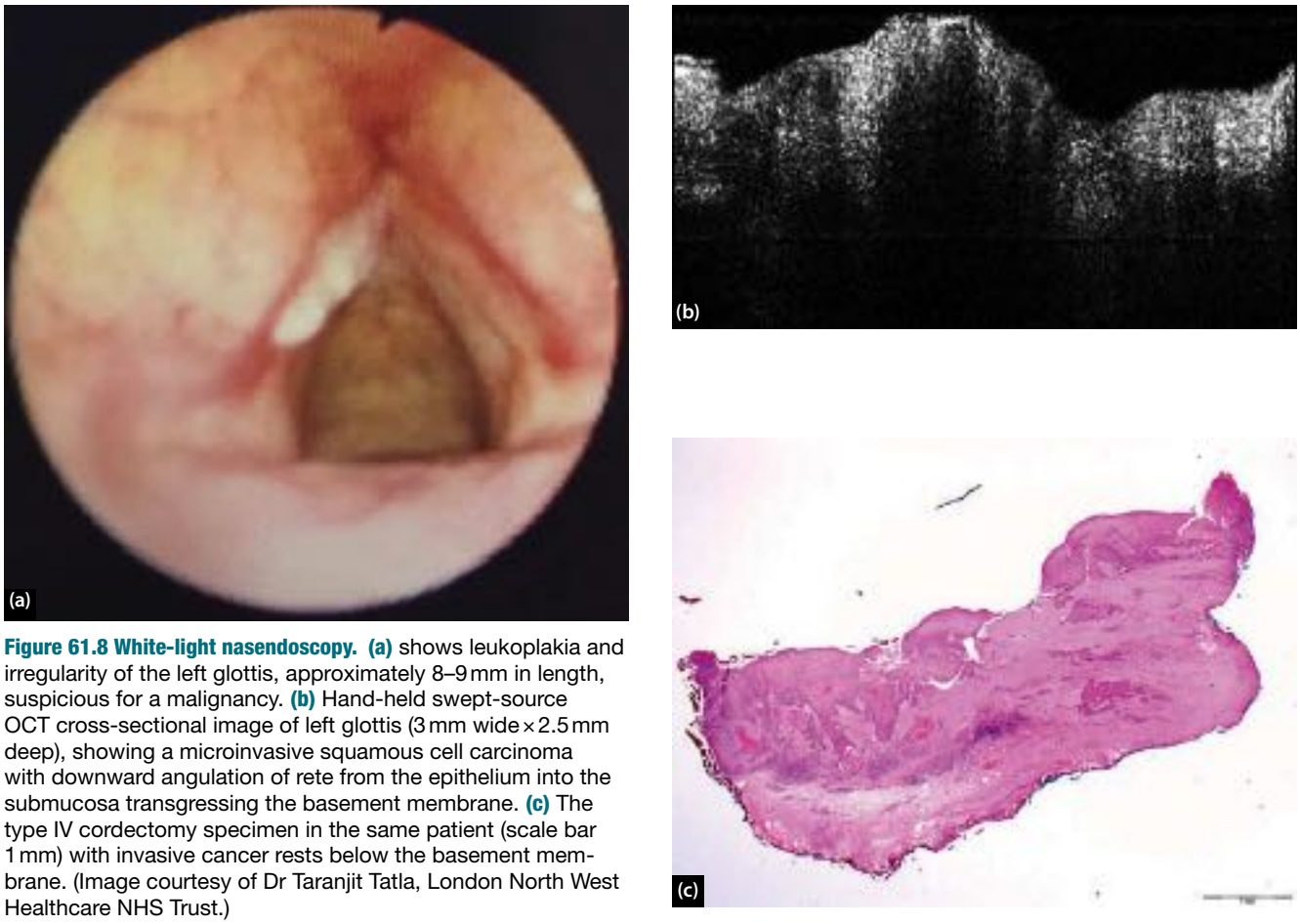


Figure 61.8 White-light nasendoscopy. (a) shows leukoplakia and irregularity of the left glottis, approximately 8–9 mm in length, suspicious for a malignancy. **(b)** Hand-held swept-source OCT cross-sectional image of left glottis (3 mm wide × 2.5 mm deep), showing a microinvasive squamous cell carcinoma with downward angulation of rete from the epithelium into the submucosa transgressing the basement membrane. **(c)** The type IV cordectomy specimen in the same patient (scale bar 1 mm) with invasive cancer rests below the basement membrane. (Image courtesy of Dr Taranjit Tatla, London North West Healthcare NHS Trust.)

Laryngeal ultrasonography

Ultrasound scanning is a well-established method of imaging in the head and neck. A new application of this technique in the larynx involves applying the ultrasound probe against the external surface of the larynx during microlaryngoscopy. This holds potential in providing information regarding invasion of deeper compartments of the larynx, such as paraglottic and pre-epiglottic spaces.[75] The usefulness of this technique in laryngology is still being evaluated.[76, 77]

Assessment and management of the obstructed or difficult airway

Those patients who present for endoscopic assessment with upper airway obstruction pose a complex problem for the otolaryngologist and anaesthetist. This short section will discuss the assessment of these patients and provide a management algorithm. A further discussion on detailed management of the obstructed airway can be seen in Chapter 72, Upper airway obstruction and tracheostomy.

PRE-OPERATIVE ASSESSMENT

Pre-operative assessment must be carried out in order that both surgeon and anaesthetist are prewarned of potential problems. Mild to moderate chronic airway obstruction may exist undetected, as these patients may have compensated over time compared to individuals who present with acute severe airway dysfunction. The presence or absence of stridor at rest or on exertion, lying flat, or when bending down, decreased exercise tolerance and nocturnal dyspnoea when lying supine are all indicative of a problem. An assessment of the patient's respiratory reserve is essential. Those patients with respiratory failure will tend to desaturate rapidly if there is prolonged or difficult intubation. A difficult airway can be anticipated in medical conditions such as rheumatoid arthritis, obstructive sleep apnoea, acromegaly and mucopolysaccharidosis, and in craniofacial syndromes, particularly Treacher Collins and Pierre Robin syndromes. Specific features include short neck, receding jaw, maximal mouth opening less than three fingerbreadths, inability of the lower jaw to protrude beyond the upper jaw (jaw slide) and a short thyromental distance less than three fingerbreadths indicating high larynx. The Mallampati score, which classifies visibility of oropharyngeal structures, is used to predict the ease of endotracheal intubation. The anaesthetist usually carefully assesses these specific features, but some appreciation of the potential problems by the surgeon is important. Prediction of potential airway difficulty is a complex business but can be rewarding when severe or obvious problems are identified. When there are no obvious problems, evaluation is imperfect and safe airway management depends on the adoption of a strategy that is able to respond to unexpected difficulty with intubation or oxygenation.

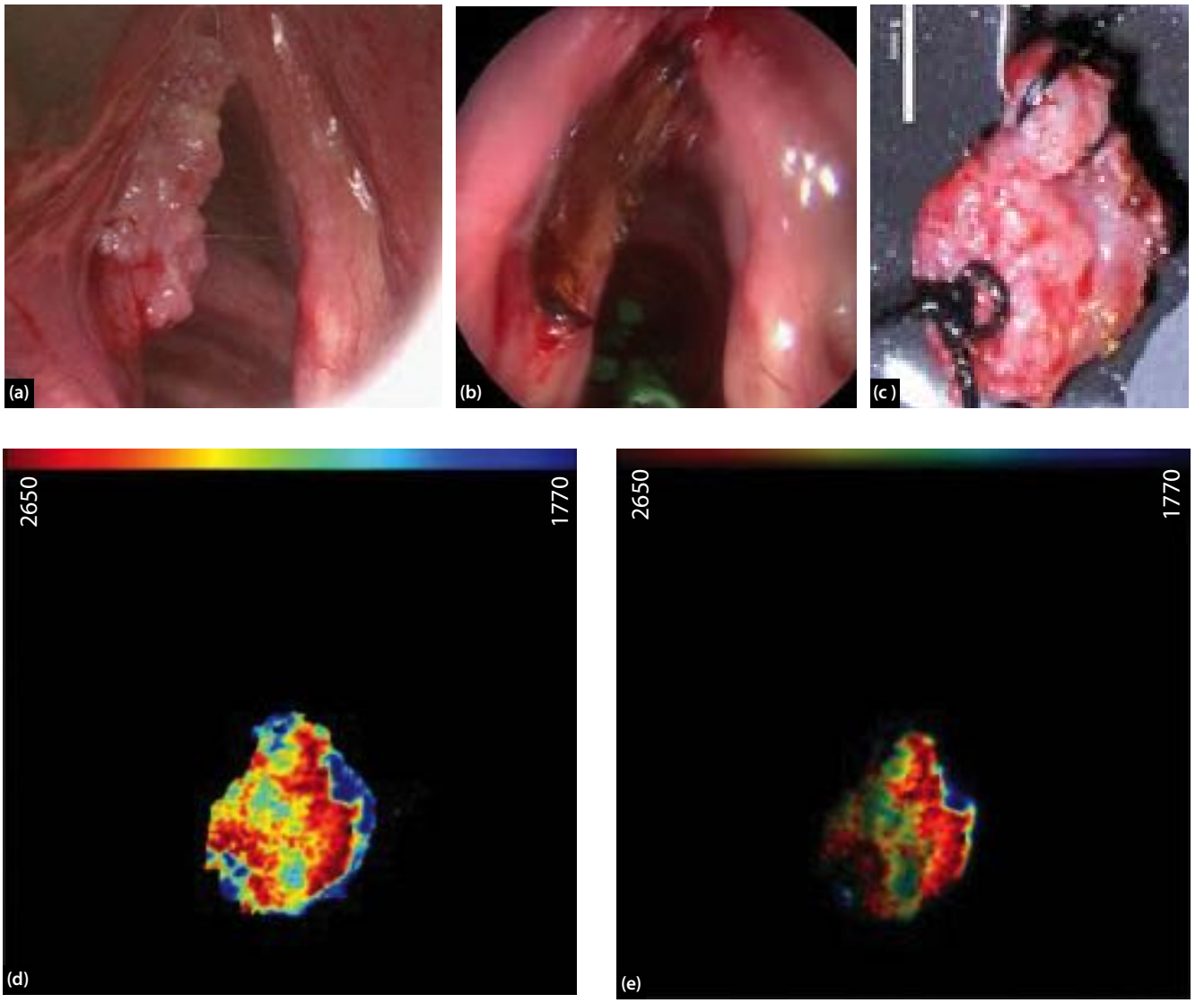


Figure 61.9 **(a)** White-light 00 rigid Hopkins rod endoscope view (high-definition TV) of glottis lesion with irregular surface outline, staged T1a. Previous biopsy has confirmed this to be a moderately differentiated squamous cell cancer in the left glottis in a background of carcinoma *in situ*. **(b)** CO_2 transoral microsurgical laser excision of left glottis lesion (type IV cordectomy). **(c)** Anteroposterior, medial-lateral orientation of resected glottis specimen with suture markers for pathology sectioning and reporting. **(d)** The fluorescence lifetime image map and **(e)** the specimen intensity-merged fluorescence lifetime image map. Reduced fluorescence lifetime (green) appears to correlate with the pathologist-reported extent of carcinoma *in situ* (cis extending to the lateral margin of the specimen). There appear to be islands of reduced lifetime amid islands of longer lifetime (yellow/orange/red) which would not be atypical for mucosal carcinoma *in situ* changes. Histopathology reported a 1 mm cancer, lying 1 mm from the lateral margin, 3 mm from the medial margin and 1.5 mm clear of the resected deep margin. (Image courtesy of Dr Taranjit Tatla, London North West Healthcare NHS Trust.)

Specific investigations other than careful flexible nasoendoscopy are rarely safe in acute airways obstruction but plain radiographs, CT/MRI and flow loops may well be indicated in chronic stable obstruction, particularly in suspected subglottic lesions. All patients undergoing panendoscopy for stridor should be counselled and consented regarding the possibility of a tracheostomy being performed.

OPERATIVE MANAGEMENT

Securing a safe airway is the primary aim of the procedure, followed by an accurate assessment of the cause, level and degree of airway obstruction and a biopsy if necessary. It should be remembered that tumours of the supraglottic larynx and tongue base are a particular problem. A moderate chronic airway obstruction may develop into complete obstruction with respiratory arrest when the patient lies supine with muscle relaxant administered. Tumours may be haemorrhagic and friable and this may make the intubation difficult.

The difficult intubation equipment should be ready for these patients, which includes a selection of rigid laryngoscopes and bronchoscopes, intubating bougies/guidewires, ETs and fibre-optic intubation equipment. The team should decide upon the following options for airway management:

- awake fibre-optic intubation
- induction anaesthesia and endotracheal intubation with/without guide wires or bougies, or by the surgeon using rigid endoscopes

- induction anaesthesia and jet ventilation (endolaryngeal or percutaneous)
- local anaesthetic tracheostomy.

The chosen airway strategy must have a plan A and plan B, for intubation, ventilation and extubation (see Chapter 72, Upper airway obstruction and tracheostomy).

The patient is asked to breathe 100% O_2. Looking at the bag will indicate the degree of airflow. Anaesthesia may be induced in the operating theatre; alternatively, the surgeon should be in the anaesthetic room with the rigid laryngoscope ready and tracheostomy set available for a surgical airway to be secured if necessary.

Failed intubation

If the anaesthetist is unable to identify the glottis and intubate, the patient should be maintained with the facemask and reoxygenated. The ENT surgeon should then attempt endotracheal intubation. The rigid bronchoscope is often quoted as a useful method of finding the glottis in difficult airway patients. The authors' preference is to use the anterior commissure endoscope to visualize the glottis. A rigid bougie can be passed through the scope into the trachea and a small ET tube passed over it.

In certain difficult cases with the airway obstructed by tumour, a retrograde intubation approach can be adopted. The rigid laryngoscope scope can be passed into the hypopharynx and then slowly withdrawn, with the tip angled anteriorly to see the glottis.[78, 79]

Tracheostomy under local anaesthetic is not an easy procedure in a patient with an acute airway obstruction. Consent for emergency tracheostomy should always be taken when planning any surgical procedure that may have an associated significant risk of airway obstruction. The patient is positioned in the supine position with sufficient neck extension to allow palpation of the trachea. In the conscious patient, constant reassurance is mandatory as the patient may be struggling and unable to lie still for a long period of time. Pressure on the larynx during dissection may worsen the patient's sense of obstruction. Local anaesthesia (20 mL of 1% lignocaine) should be injected if time or patient condition permits and is strongly advocated.

The operation is more difficult in small children and adults with adipose necks because of the difficulty in tracheal palpation. A vertical midline incision is made from the inferior aspect of the thyroid cartilage to the suprasternal notch and continued through the infrahyoid muscles and thyroid isthmus irrespective of bleeding, although an experienced assistant providing suction and retraction is most helpful.

After carefully palpating for the cricoid cartilage in order to avoid cutting it, a vertical incision is made in the trachea from the second to fourth ring, the knife rotated through 90 degrees and an appropriate tube rapidly inserted. Thereafter, haemostasis is obtained, and all blood suctioned out of the airway. Once the situation is under control, it may be appropriate to refashion the tracheostoma to prevent later complications. After securing the airway, general anaesthesia is induced and endoscopy proceeds. A detailed discussion of the compromised airways can be found in Chapter 72, Upper airway obstruction and tracheostomy.

BEST CLINICAL PRACTICE

- ✓ Examination of the upper aerodigestive tract should include:
  - ✓ flexible nasolaryngoscopy
  - ✓ microlaryngoscopy
  - ✓ Hopkins rods and telescopes
  - ✓ photo documentation.
- ✓ Careful clinical history taking and traditional examination techniques still yield useful results, particularly when technology fails.
- ✓ Flexible endoscopy is a widely used simple technique whose role is being extended to cover swallowing assessment, cervical oesophagoscopy, biopsy and foreign body removal, as well as paediatric and neonatal assessment.
- ✓ Current evidence suggests that local anaesthesia prior to flexible nasolaryngoscopy confers no significant advantages, but cost issues around cophenylcaine use are significant.
- ✓ Infection control issues around flexible endoscopy still require clarification but the newer sheaths may provide an alternative to chemical disinfection systems and their attendant risks.

KEY POINTS

- Close cooperation with anaesthetic colleagues in deciding how the airway will be shared is essential.
- The correct patient position for rigid laryngoscopy is supine, with the head extended and neck flexed to open the laryngeal inlet.
- Modern rigid and microlaryngeal endoscopy equipment has greatly improved visualization and tissue handling, but the principles of use remain essentially unchanged.
- A wide choice of rigid laryngoscopes is available. Usually the widest scope to maximize vision should be chosen with suspension allowing both hands free for the surgeon. Accurate recording on preprinted diagrams and/or photo documentation is ideal and the latter will increasingly become the norm. Visualization of difficult areas can be improved with the use of specialist rigid scopes and/or angled Hopkins rods.
- New techniques to assess the upper respiratory tract include contact endoscopy, autofluorescence, narrow-band imaging, optical coherence tomography and laryngeal ultrasound.
- The management of the obstructed airway will always remain among otolaryngology's greatest challenges but has been hugely facilitated by the much wider availability of awake fibre-optic intubation skills in most anaesthetic departments.

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CHAPTER 62

EVALUATION OF THE VOICE

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: voice quality, voice analysis, voice disorders, voice measurements, acoustic analysis, quality of life questionnaire.

GENERAL CONSIDERATIONS IN VOICE EVALUATION

Definitions

Speech is the expression of or the ability to express thoughts and feelings by articulate sounds.[1] The term **voice** is often used to refer to speech as a whole. However, when used in the context of voice evaluation, it is generally restricted to the acoustic output resulting from the interaction of vocal fold vibration with the vocal tract in vowel production.[2, 3] **Phonation** is a term used to describe the physical and physiological processes of vocal fold vibration in the production of speech sounds.[3] Impaired voice production due to abnormal vocal fold vibration is known as **dysphonia,** while no voice or whispery voice associated with no vocal fold vibration is termed **aphonia.**[4] **Hoarseness** is a non-specific, general term used to describe any change in voice quality.[5]

Normal speech and voice production

Normal voice production requires three essential elements:

- a pressure gradient across the vocal folds created by the flow of expired air from the lungs against the partly close vocal folds
- vocal folds of appropriate structure, mass and elasticity that approximate with appropriate tension to allow them to vibrate at a range of frequencies
- a resonating chamber, the vocal tract, whose size and shape can be changed to modulate the acoustic properties of sound generated by the vocal folds.

Speech consists of both these 'voiced' sounds, where the vocal folds vibrate, and 'unvoiced' sounds, where the is no vibration. Examples of 'voiced' sounds include English vowels (e.g. /a/, /e/, /i/, /o/, /u/) and some consonants (e.g. /b/, /d/, /g/, /v/, /n/, /l/, /w/, /j/). Consonants are produced by the sudden release of air from other parts of the vocal tract (e.g. lips for /b/) or aperiodic turbulent airflow (noise) through constrictions of the vocal tract (e.g. between the lips and teeth for /v/). Pure 'unvoiced' consonant sounds include /p/, /t/, /k/, /f/, /th/, /s/, /h/ where there is no associated vocal fold vibration. Together they provide the framework on which spoken language is constructed.[6] For more information see Chapter 60, Voice and speech production.

In voice evaluation the main focus of interest has been on the acoustic output resulting from the interaction between vocal fold vibration and modulating effect on the sound by the vocal tract in the production of vowels. To understand the relevance of some of these measures it is important to summarize the essential features of the acoustic properties of voice. Vocal fold vibration, acting as the sound source, produces a laryngeal tone which is a complex sound wave that, if heard without the vocal tract, has a buzzing quality. The sound wave can be characterized acoustically in terms of fundamental frequency (Hertz or Hz), frequency spectrum amplitude and intensity (dB).[3] The rate of vibration of the vocal folds (cycles per second) determines the fundamental frequency (F_0). Normal vocal fold vibration, however, does not simply produce a pure tone (sine wave) like, for example, a tuning fork. It consists of a spectrum of frequencies which are multiples of this fundamental frequency. They are called harmonics or overtones and are of varying amounts of energy or sound intensity.[3] Sound intensity decreases by approximately

12 dB for every doubling of the fundamental frequency (harmonic).[3] This relationship between the harmonics and sound intensity can be displayed in the form of a spectrum (see 'Normal voice' below). For breathy voices the energy decreases more rapidly at higher frequencies but is maintained in more strident voices which project more.

In addition, the vocal tract acts as a filter, selectively reducing the energy in specific bands of frequencies from the sound source (vocal folds) while allowing others to pass with maximum levels.[3] It acts in a similar fashion to pressing the keys on the bore of an oboe to alter the resonant properties of the instrument. The bands of frequencies that retain their energy levels reflect the resonant properties of the vocal tract and are known as formants. Altering the shape and dimensions of the vocal tract by changing the height of the larynx, position of the tongue, soft palate and lips changes the resonant properties of the vocal tract and formants. Correct production of formants is essential to allow distinction between different speech sounds.

For good and 'normal' voice production three conditions are required:

- quasi-periodic vibration of the vocal folds
- a well-defined harmonic structure of the voice signal radiating from the mouth
- a voice signal that is loud enough or has enough sound intensity (energy) to overcome the threshold of hearing of the listener.

Altering the height of the larynx, positioning of the tongue, soft palate and lips changes the dimensions of the supraglottis, pharynx and oral cavity. This in turn causes certain bands of harmonics to be preferentially reduced (damped) or enhanced. The effects on the perceived sound is to alter the formant structure or its quality (e.g. 'brassy', 'nasal').[7] For example, each vowel can have the same fundamental frequency but may be distinguished by the relative prominence of bands of harmonics (formants) and have an additional quality such as 'brassy' or 'breathy' by the relative prominence or absence of the energy at specific frequencies.[3, 6] Overall, there must also be enough energy (sound intensity) in the voice projected from the lips in order to excite adequate vibration in the listener's hearing mechanism. Increased loudness requires increased subglottal air pressure and abrupt and appropriate duration of closure of the vocal folds during the vibratory cycle to allow efficient conversion of aerodynamic energy into acoustic energy and vocal tract shaping particularly at higher frequencies.[3]

Pathological voice production

Abnormalities in the vocal folds, dimensions or structure of the vocal tract and inadequate control or amount of subglottic pressure can all contribute to a pathological voice. Abnormalities in the mass, elasticity and tensioning of the vocal folds can have two main effects: on the frequency rate and on the regularity of vibration. Alterations in frequency may lead to the voice being perceived as being too high or too low in pitch for the speaker's age and gender. It may also lead to restrictions in the dynamic frequency range of the voice during speaking or singing. Additional supraglottic structures such as the false folds, aryepiglottic folds and mucosa over the arytenoids can also be induced to vibrate either at the same time or in lieu of the vocal folds, providing an additional or alternative sound source. Irregular vibration of the vocal folds, caused by the abnormalities described above, will affect voice quality by producing a less clear fundamental frequency and harmonic structure. This irregularity is perceived as hoarseness and roughness.

Another important influence on the harmonic structure is the addition of noise to the voice 'signal'. For a listener, this may be environmental noise (e.g. trying to hear someone when there is loud background noise) or contained within the speaker's voice itself. For example, if there is a gap between the vocal folds during phonation, air will escape causing turbulent air flow which is perceived as noise (sound energy across all frequencies), reducing the relative amount of energy in the harmonic components and increasing the energy in the subharmonic components.[3] This is perceived as both hoarseness and breathiness or a voice lacking in power (asthenia). Alterations in the relative size, shape and length of the vocal tract, for example from a mass, increased pharyngeal muscle tension or reflective properties of the vocal tract, can all influence the energy levels and harmonic structure of the radiated sound causing the voice to sound strained or effortful.

Normal voice

Every human voice is unique because of anatomical, physiological, psychological, cultural, sociolinguistic and behavioural factors. In addition, a wide range of information about the speaker's gender, age, personality, emotional status and physical health is conveyed by their voice quality, pitch range and the systematic use of pitch patterning (intonation). Defining what is a normal voice is therefore difficult as there is a spectrum of what is considered normal. This can vary between different cultures and there is a continuum between 'normal' and 'dysphonic' sounding voices.[4] A generally accepted and pragmatic definition of a normal voice is one described as having the following characteristics:

- It is audible, clear or stable in a wide range of acoustic settings
- It is appropriate for the gender and age of the speaker
- It is capable of fulfilling its linguistic and paralinguistic functions
- It does not fatigue easily
- It is not associated with discomfort and pain on phonation.

Pathological voice

Pathological voice can be defined pragmatically as one that does not fulfil the criteria above. Variations in voice quality can provide valuable cues about our current emotions, physical health and psychological well-being. Patients generally

seek a consultation about their voice complaint because it causes one or more of the following problems:[8]

- **impairment**, i.e. an alteration in the structure or function of the vocal apparatus (structural abnormality, inflammation, neuromuscular abnormality or muscle tension imbalance) causing symptoms such as hoarseness, a weak voice, pitch change, throat discomfort
- **limitation in activity**, such as a reduction in vocal range in singing or the voice tiring or becoming hoarse with prolonged use in a noisy environment or if raised
- **participation restriction**, e.g. not being able to work or sing in a choir as a result of the voice problem.

The consequences of voice problems can therefore be one or more of the following: physical, functional, psychosocial, occupational and financial.

Potential use of voice evaluation

There are four main potential uses for voice evaluation:

- to provide a measure of severity of the disorder and degree of variance from established normal values
- as an outcome measure to help assess responsiveness to treatment
- to help during voice therapy to set therapy goals, in education about voice production and help patient achieve a target production[10]
- to help characterize the voice and voice problem, thereby providing supportive evidence for a differential diagnosis and pointers for treatment.

Overview of methods of objective evaluation of voice used in clinical practice

There are many hundreds of methods of assessment of the voice and voice production that have been developed over the years but the relevance of many of them to patients' complaints is often not clear. Visual assessment of the larynx (including, on occasions, diagnostic microlaryngoscopy) remains mandatory for confirmation of diagnosis in all cases and this is discussed further in Chapter 61, Assessment and examination of the larynx.

The most commonly used methods of evaluation in the UK are patient self-reported questionnaires and perceptual evaluation of the voice. It is argued that both are inexpensive, with the former giving a (subjective) measure of the impact of the 'pathological voice' on the patient's quality of life and the latter a semi-objective assessment of voice quality. They can be used to measure severity of the condition and as a therapeutic outcome measure.

To help with target production during therapy and characterize the voice or voice problem, and provide specific objective outcome measures, other more instrumental techniques are required. These include measures that relate directly to the voice signal (acoustic measures) or indirectly to the function of the vocal system, such as electrolaryngography (also called electroglottography), aerodynamic measures, voice accumulator measurements and combined measures (**Table 62.1**). No single measure can satisfactorily fulfil all functions and a multidimensional approach is ideally required. This, however, is a balance between the time, effort and expense it takes to perform versus its value in the management of the patient.

Previous high hopes that acoustic and other measures would provide a non-invasive means of diagnosing voice conditions have not been realized to date due to poor specificity and sensitivity. Attempts have been made to set standards for measurement and assessment.[10–12] These have largely been developed from expert consensus opinion and as a whole are not widely used in routine clinical practice in the UK.

SPECIFIC MEASURES

Quality-of-life measures

The need for treatment is largely determined by the patient's degree of disability, i.e. their perceived impairment, limitation in activity and participation restriction.[8, 13, 14] Various disease-specific patient questionnaires have been developed (**Table 62.2**) which allow self-reported grading of the effect of the voice problem on quality of life.[15–21] They have also been used as an outcome measure and indicator of response to treatment.[15, 22–24] Of these, the VoiSS questionnaire[18] has undergone the most rigorous development but the most widely used is Voice Handicap Index (VHI-30 and VHI-10).

The VHI-30 consists of 30 items which assess the impact of the voice disorder on physical, functional and emotional aspects of the patient's quality of life.[16] The patients rate their perception of their voice problem from 0 (= never) to 4 (= always), giving a possible total score of 120. More recently, the VHI-10 has been introduced.[20] This uses a subset of the VHI-30 items and has shown to have good correlation to the VHI-30 with the advantage that it is quicker and easier to complete.[20] In general, there is good correlation between all the different measures.[24–26]

Mean normative values of total score for the VHI-30 are 6.86 (standard deviation = 9.88) and for the VHI-10 are 2.83 (standard deviation = 3.93).[27] The highest values for the VHI total score are seen in patients with vocal cord palsies, severe structural abnormalities of the larynx and muscle tension dysphonia of origin.[22] For the VHI-30, the threshold value between vocal health and voice dysfunction is considered to be 12 points.[28] A 14-point difference in the total VHI-30 score is considered significant response to treatment, with values rarely returning to normative levels.[22, 24, 29, 30]

Perceptual evaluation of voice

Perceptual evaluation of the voice refers to the process of assessing the characteristics of the voice and grading the severity of specific abnormal features such as hoarseness,

TABLE 62.1 Methods of objective evaluation of voice

Evaluation	Description	Examples
Laryngeal visual assessment	Inspection of the structure and dynamic function of the larynx and rest of the vocal tract together with the vibratory patterns of the vocal folds during phonation	Endoscopic laryngoscopy including stroboscopy, videokymography and high-speed digital imaging (see Chapter 61, Assessment and examination of the larynx)
Quality-of-life measures	Using self-administered, validated disease specific or generic questionnaires to assess the patient's perception of the impact of the voice condition on their quality of life in terms of physical complaints and restriction in participation in daily activities	VPQ, VHI-30, VHI-10, VoiSS, VAAP, V-RQOL
Perceptual evaluation of the voice	Using rating scales to grade the presence and severity of defined qualities of the voice that we can hear such as hoarseness, roughness, breathiness	GRBAS, CAPE-V, VPA
Acoustic analysis	Extracting and objectively evaluating various factors related to the acoustic waveform or spectrum recorded using a microphone placed near the mouth	Fundamental frequency measurements, sound intensity, perturbation measures, spectral measurements
Electrolaryngography / electroglottography	Determined by measuring the changes in electrical conductance between two electrodes placed on the skin over the thyroid cartilage during vocal fold vibration	Fundamental frequency measurements, degree of vocal fold contact, perturbation measures
Aerodynamic measures	Measures of the forces that initiate and maintain vocal fold vibration	Air volume, airflow and subglottal pressure
Voice accumulator	These are means of sampling the voice or aspects of vocal function either over a prolonged period of time or before, during and after a specified vocal stress test	Phonation time, frequency and sound intensity measurements
Combined measures	These attempt to provide a multidimensional measure of voice function	Dysphonia Severity Index, Cepstral Spectral Index of Dysphonia

TABLE 62.2 Patient self-report questionnaires

Patient self-report questionnaire	Abbreviation	Reference
Patient Questionnaire of Vocal Performance	VPQ	Carding and Horsley[15]
Voice Handicap Index	VHI-30	Jacobson et al[16]
Voice-related Quality of Life	V-RQOL	Hogikyan and Sethuraman[17]
Voice Symptom Scale	VoiSS	Deary et al[18]
Voice Activity and Participation	VAAP	Ma and Yiu[19]
Voice Handicap Index-10	VHI-10	Rosen et al[20]

roughness and breathiness.[4, 31] Numerous schemes have been developed (**Table 62.3**) which require the expert listener to rate the voice characteristics using either categorical or visual analogue scales.

The GRBAS (**G**rade, **R**oughness, **B**reathiness, **A**sthenia and **S**train) scheme (**Table 62.4**) is probably the most widely used, partly due to its relative simplicity. Each dimension is rated on a four-point scale where 0 = no perceived abnormality, 1 = mild, 2 = moderate and 3 = severe abnormality. The overall Grade of hoarseness is the most reliable voice quality parameter with Strain and Asthenia (weakness) being relatively poor.[37, 38]

The CAPE-V is a newer measure which replaces the four-point scale with a 100 mm line Visual Analogue Scale. It also encompasses other factors such as pitch and loudness.[36] The Voice Profile Analysis (VPA) scheme is based on a phonetically grounded description of voice quality and is recognized as being a valid and detailed descriptor of voice quality.[7] Many consider it to be too complex for routine clinical use and not a valid tool for assessing outcome.[40]

Acoustic analysis

Acoustic analysis provides quantitative measures based on the voice signal (waveform and spectrum) recorded using a microphone placed near the mouth. The microphone acts as a transducer, converting the acoustic signal into an electrical signal. The amplified electrical signal is most commonly recorded directly to hard disk as uncompressed .wav files. A variety of free and commercial software programmes are available for display, measurement and statistical analysis of the acoustic waveform and spectrum.

TABLE 62.3 Summary of the most common schemes described for perceptual evaluation

Scheme	Abbreviation	Reference(s)
Grade (of hoarseness), Rough, Breathy, Asthenic, Strained	GRBAS	Hirano[32]
Grade (of hoarseness), Rough, Breathy, Asthenic, Strained, Instability	GRBASI	Dejonckere et al[33]
Rauhigkeit (Roughness), Behauchtheit (Breathiness), Heiserkeitsgrad (Hoarseness) method	RBH	Nawka and Anders[34] Nawka et al[35]
Consensus Auditory Perceptual Evaluation of Voice	CAPE-V	ASHA[36]
Vocal Profile Analysis	VPA	Laver[7]

TABLE 62.4 The psychoacoustic and physiological findings associated with each of the five dimensions of the GRBAS scheme[32, 39]

Factor	Psychoacoustic/physiological correlates
Grade (G)	Overall rating of severity of abnormality ('hoarseness') of voice
Roughness (R)	Perceived irregularity in voice Irregular perturbation of pitch and amplitude, noise in low-frequency region and the presence of spectral subharmonics
Breathiness (B)	Audible breath or air escape on the voice Noise below the mid frequencies, incomplete closure of vocal folds resulting in high expiratory flow rate
Asthenia (A)	Weakness or lack of energy in the voice Less harmonic content in the high-frequency region, irregularity of pitch and amplitude, a fading amplitude contour
Strain (S)	Perception of excessive vocal effort Reflects higher pitch, noise in the higher frequencies, increased amplitude of the higher harmonics and increased pitch and amplitude perturbation

VOICE MATERIAL

There are three main types of voice material used in acoustic analysis: sustained vowels, fluent speech and consonant–vowel sequences:[41]

1. **Sustained vowels** have traditionally been used as voice test material in clinical practice for the following reasons:
   - They are the simplest separable components of speech.
   - Although the vowel systems of the world's languages cover a very large range of sound types, three oral vowels are almost universally present so can be used for comparison across studies:[6]
     - a close ('high') front articulation /i/ (as in English b***ee***t)
     - a back ('high') /u/ (as in English b***oo***t)
     - an articulatory open vowel /ɑ/ (as in English f***a***r).
   - Loudness, pitch, intonation and timbre can, to a degree, be separated and controlled for far more readily than for other elements of speech.
   - They predominantly reflect vocal fold vibratory activity.
   - If analysis of phonatory onset and offset are excluded, the stable mid-portion of the utterance is thought to represent the intrinsic quality of a voice which is independent of language.[42, 43]
   - The measurement is quick and easy to perform and has been used in many of the reported clinical studies of pathological voice production.[41]

   Measurements are usually made on a 1000 ms midsection of the sustained vowel, usually /i/ or /ɑ/, produced at a comfortable pitch and loudness.[41] Effort levels and day-to-day variability may influence the results and must be taken into consideration when comparing inter- and intrasubject results.[44]
2. **Fluent speech**, however, has several advantages:
   - It is more directly relevant to the patient's day-to-day experience.
   - It is more related to ordinary voice production, and also to a listener's impression of the speaker's phonatory ability, than sustained vowels.
   - It potentially produces more clinically relevant measures of voice production than sustained vowels.
   - It takes into account the acoustic cues associated with vowel onset and offset, pitch, loudness and intonation control that take place during speech production.

   Two types of speech material are typically used: **read text** and **spontaneous speech**. Read text has the advantage that the same sets of speech sounds are elicited for each recording, allowing cross-clinical comparisons to be made. The disadvantage is that some patients are not able to read aloud or read in a way that is not representative of their fluent spontaneous speech. The most frequently used texts used are *The North wind and the Sun*, 'The rainbow passage', and *Arthur the rat*.[41, 45] Each is phonetically balanced and the choice is largely down to personal preference. Read text and spontaneous speech give

similar but not identical results.[41] Approximately 40 s of a speech sample is needed for perceptual evaluation in order to begin to obtain a useful representation of the main voice characteristics. For electrolaryngography (ELG) measures (see below) and to see the effects of vocal fatigue in more severe cases, 120 s is better.

3. **Consonant–vowel sequences** are also used in two particular situations:
   - For the investigation of rapid voice 'switching' in diadochokinetic sound sequences, the rate (mean number of utterances per second) of repetition of utterances such as alternate voiceless consonants with a vowel, e.g. /pʌ/, /tʌ/, /kʌ/ ('pu-tu-ku') or /pʌ/, /tɜ/, /kɜ/ ('pu-terr-kerr'), can be measured and an assessment made of the accuracy of articulation and rate variability during the task.[41]
   - In the determination of laryngeal airway resistance or indirect subglottic measurement,[46] the sound sequence is a succession of only /pʌ/or /pi-pi-pi/ – the bilabial closure providing a time interval during which intraoral pressure equals that at the glottis.

One caveat when performing any assessment is that it is performed at that point in time and may not reflect the variation in voice quality that is frequently reported by patients. Newer software such as OperaVOX™, which can be set up as an app on a mobile phone or tablet, can allow simple measurements and recordings of the voice to be made by the patient at home at any time of the day.[47] Alternatively, voice accumulators may be used (see below).

MICROPHONES

Accurate measurements of acoustic parameters across the range of vocal frequencies and intensities require a good-quality condenser or electret, omnidirectional, pressure-sensitive microphone.[48] The sound pressure wave radiating from the mouth is converted by the microphone into an electrical signal such that the induced voltage change is proportional to the pressure level. Ideally, it should have a minimum sensitivity of –60 dB and reasonably flat frequency response (i.e. equally sensitive to all audio frequencies) across the range of human hearing (20–20 000 Hz).[12, 41] The microphone-to-mouth distance should be kept constant and the recording system should be calibrated to ensure standardization of recordings.[48, 49] A microphone can be mounted on a headset when it is usually positioned 8 cm from the corner of the mouth. It is usually offset by 45 degrees to avoid overstimulation from the breath stream particularly from plosive sounds.[49] Alternatively, it can be set at a fixed distance (30 cm) from the mouth using either a boom or a lanyard round the neck.[47] Recordings should be done in a quiet room free from extraneous noise.

ACOUSTIC PARAMETERS

Acoustic measures of the voice quantify the physical characteristics of the sound pressure waveform radiating from the lips. There are several parameters that are used in objective measurements based on the fundamental frequency, frequency perturbation (jitter), spectral analysis or sound intensity or combinations thereof. The validity and clinical utility of acoustic parameters as a measure of overall voice quality have been questioned.[50] Many measures have been described[12, 41, 51] but only some of the more common ones in clinical use will be discussed here.

Fundamental frequency

Fundamental frequency is a measure of the rate of vibration of the vocal folds. It is the inverse of the time taken to complete a single vibratory cycle and is measured in cycles per second or Hertz (Hz). It can be measured from short segments (1–2 s) of a sustained vowel made at a 'comfortable pitch and loudness' or from speech (speaking fundamental frequency (SFF)). It can be measured from either the acoustic (F_0) or the ELG (F_x) signal (see below). The reliability of the automatic F_0 calculation from the acoustic signal, however, worsens with increasing severity of the dysphonia.[12] In males the SFF drops from young adulthood into middle age and rises again in old age. In women the SFF remains fairly constant from 20–50 years and then drops.[41]

$$\text{Fundamental frequency } (F_0) = \frac{1}{\text{time to complete one vibratory cycle}}$$

Sound intensity and sound pressure level (SPL)

The amplitude of the signal relates to its sound pressure or strength. As a listener we perceive this as loudness. In practice, sound intensity is measured in terms of the logarithmic ratio of the absolute sound pressure to a reference sound pressure level (SPL) expressed in decibels. This means that doubling the sound pressure raises the SPL by 6 dB. For a more in-depth discussion see Baken and Orlikoff[41] and Speaks.[52]

Speech intensity levels for sustained vowels are quite different from connected speech due to the physiological and linguistic pauses in the latter causing marked fluctuations in pressure. Comparison of results published in the literature are extremely difficult due to the lack of standardization of the measuring techniques.[41] The mean SPL for a read text passage of connected speech produced at a comfortable phonation level by healthy subjects is approximately 70 dB measured at 30 cm from the mouth. However, the intersubject variability is approximately 20 dB for men and slightly less for women and the intrasubject variability for repeated measurements is approximately 3 dB.[53]

Jitter and shimmer

It is normally possible for an individual to produce a vowel sound for several seconds with little variation (perturbation) in the frequency (jitter) or intensity (shimmer). Pathological voice samples have been shown to have higher

levels of jitter and shimmer than normal[41, 51] although, for jitter, these have not been universal findings and the validity and reliability of these measures has been questioned, particularly in severely dysphonic voices.[54–56] Although widely used as 'objective' measures of voice, there is poor correlation between perceived vocal quality and acoustic measures of jitter and shimmer.[57, 58] This is mainly due to the perceptual difficulties of isolating jitter and shimmer as separate dimensions and from the spectral noise in the voice. In addition, there are many different ways of calculating jitter and shimmer, which adds to the confusion. For a detailed discussion on these perturbation measurements see Baken and Orlikoff.[41]

Voice range profile (phonetogram)

A voice range profile (VRP) or phonetogram is a visual display of the dynamic range of the voice in terms of frequency and vocal intensity[59] and has been used in both adults and children.[60, 61] It is usually produced by recording the patient's ability to produce sustained vowels (usually 10 continuous, periodic cycles of an /a/ vowel[62] across their frequency range at the quietest and loudest note they can produce.[60] Experience in performing the procedure to a given protocol is extremely important.[63–65] The features of interest are the overall shape, loudness and frequency ranges and phonatory area.[59, 64] It is of particular value in determining and documenting areas of difficulty in the singing voice[66] and for demonstrating improvement in the dynamic range of the voice following treatment of voice disorders.[67] It is not widely used in the UK as it is time-consuming to perform but it is commonly performed in many European phoniatric departments.

Spectrogram and long-term average spectrum

The acoustic output of the vocal tract resulting from the interaction of the vocal fold vibration with the vocal tract can be displayed graphically in a 3D way in what is known as a spectrogram. Time from beginning of the vowel utterance to the end is displayed on the *x* axis. A logarithmic display of the frequency distribution is seen on the *y* axis while the amplitude or amount of energy in the spectrum for a given frequency or frequency band is represented by increasingly dark shades of grey.

There are two forms of spectrogram: narrow-band and broadband (or wide-band) spectrograms. The narrow-band spectrogram (**Figures 62.1a** and **62.2a**) displays the concentrations of energy in each harmonic across the frequency range. The number of harmonics displayed is largely determined by the loudness of the voice and the abruptness of vocal fold closure (see below). The broadband spectrogram, on the other hand, gives more information about the how the 'groupings of the harmonics' (formants) are arranged (**Figure 62.3a,b**).[41, 68] The most dense and central parts of these broadband spectrograms (i.e. those with the greatest energy or amplitude) are taken to represent the resonant frequencies of the vocal tract.

Linear predictive coding (LPC) and fast Fourier transform (FFT) are automated and mathematical ways of picking out and displaying these formant peaks (**Figure 62.4**).[41] Although it is probably more reliable overall to pick out the formant frequencies by hand, these automated techniques provide a useful quick alternative. They are not always reliable, particularly if the signal changes abruptly, the F_0 is too high (above 350 Hz) and if there are significant anti-resonances, i.e. when there is significant nasalization of the speech sound.[41]

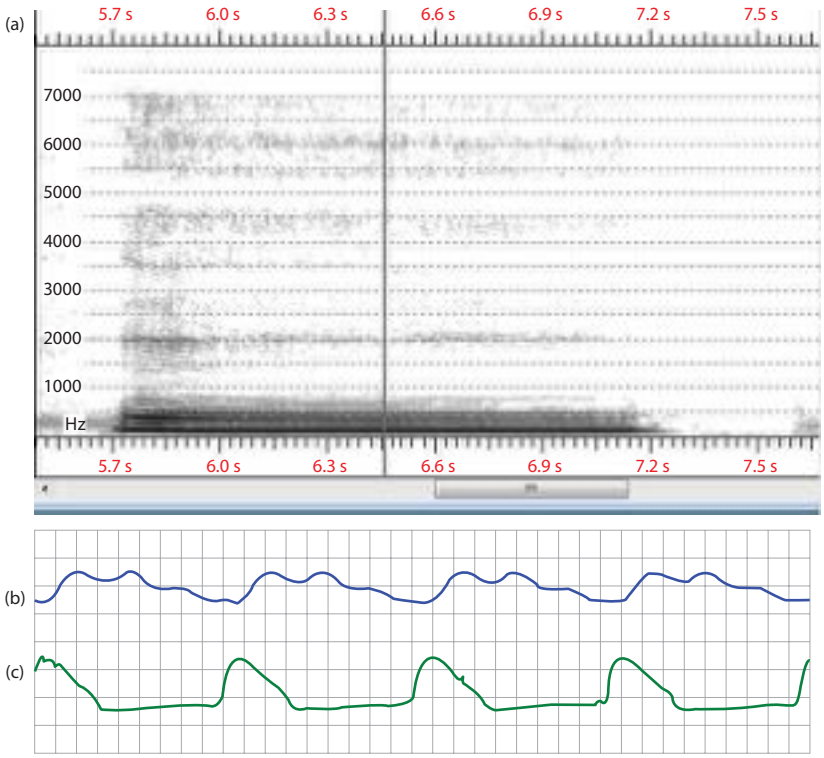


Figure 62.1 Sustained /i/ vowel produced at 109 Hz by 53-year-old male patient with left recurrent laryngeal nerve palsy pre-thyroplasty. (a) Narrow-band spectrogram showing poorly defined harmonic structure and ill-defined high-frequency band (5500-7000 Hz) due to breathiness of voice; **(b)** speech (acoustic waveform) and **(c)** ELG waveform at the point in utterance indicated by the vertical line on the spectrogram. Note the short contact quotient on the ELG waveform (mean Qx: 28.25%) associated with poor vocal fold contact.

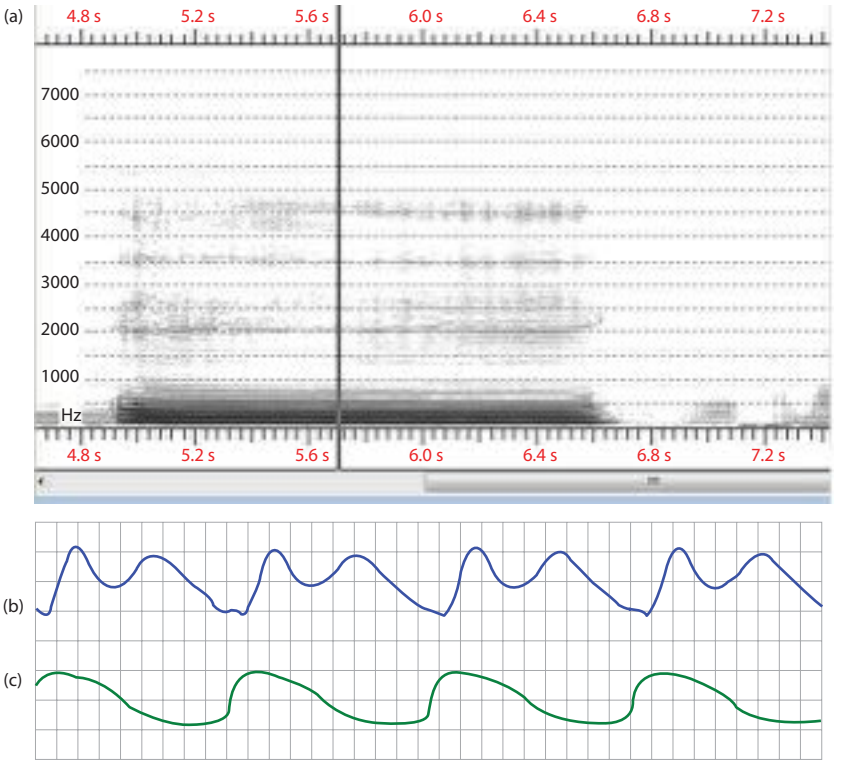


Figure 62.2 Sustained /i/ vowel produced at 106 Hz by same patient as in Figure 62.1 post-thyroplasty. (a) Narrow-band spectrogram showing better-defined harmonic structure particularly and beginning and end of utterance and loss of high-frequency noise component (5500–7000 Hz); **(b)** speech (acoustic waveform) and **(c)** ELG waveform at the point in the utterance indicated by the vertical line on the spectrogram. Note the improved contact quotient on the ELG waveform (mean Qx: 48.16%) associated with better vocal fold contact from the medialization procedure.

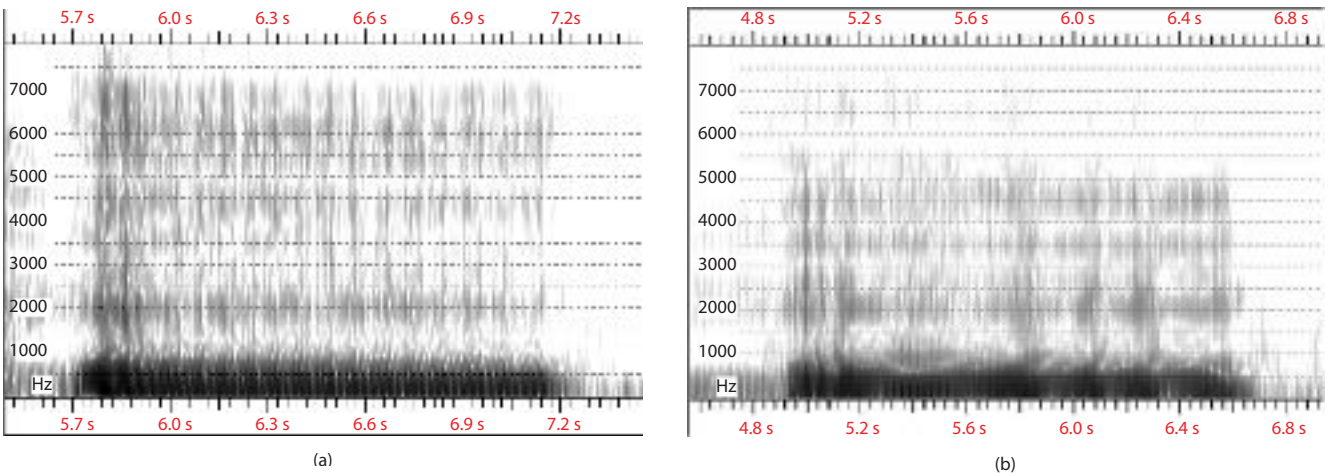


Figure 62.3 Broadband equivalents from Figures 62.1a and 62.2a for sustained vowel /i/. Neither shows really strong banding (except for first formant) but pre-thyroplasty shows more noise in signal in general, particularly at higher frequencies.

A different way of displaying these data is to look at the average amount of energy at each frequency for a given time period. The averaged relative amplitude of the sound level in dB is displayed on the *y* axis against the frequency range on the *x* axis. The display is known as a long-term average spectrum (LTAS) (**Figure 62.5**). Some workers consider LTAS a potentially good index of voice quality.[41, 69] Depending on the nature of the sound, for a given F_0 the strength or amplitude (amount of energy) of the harmonics changes as the frequency increases and the rate of change is known as the spectral slope (usually measured in dB/octave). Vocal fold closure occurs much faster than vocal fold opening and it is this abrupt closure that largely determines (i) the amount of energy in the acoustic spectrum, (ii) the overall number of harmonics produced and (iii) the energy in the high frequencies. This abrupt closure results in a voice which is perceived as 'bright' and which projects well. It is associated with a slowly reducing spectral slope. Conversely, incomplete or slow vocal fold closure results in less energy in the 'acoustic spectrum' and fewer higher harmonics. This means less energy is radiating from the lips and will result in a steeper spectral slope. The voice may be perceived as breathy and will not project well, which, in more extreme cases, can make the sound pattern unrecognizable or inaudible.[41]

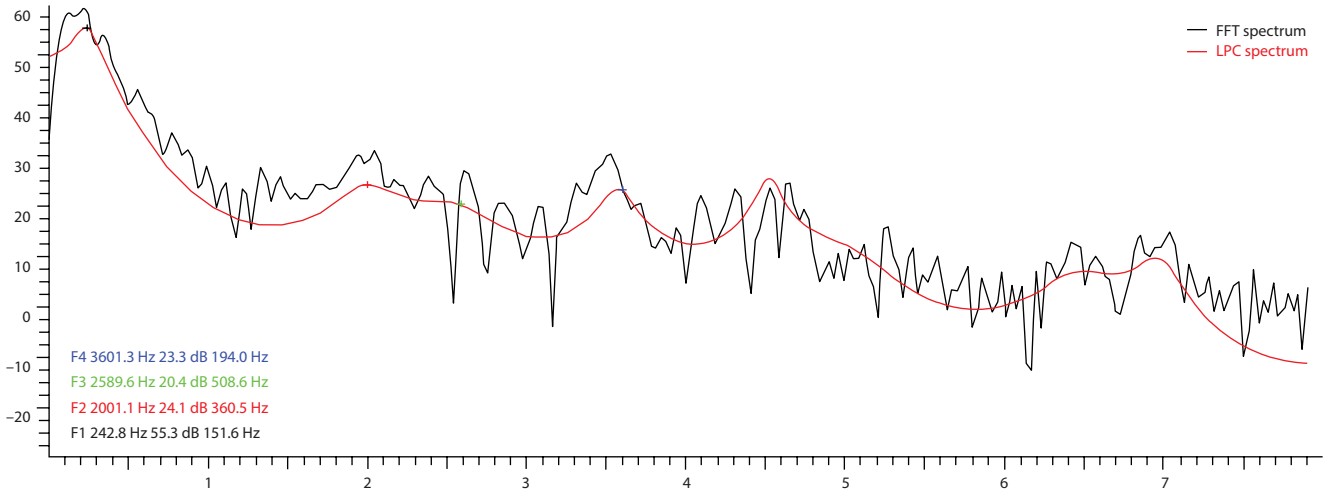


Figure 62.4 Formant frequency identification for post-thyroplasty patient on sustained British English /i/ vowel using linear predictive coding (LPC) and fast Fourier transform (FFT). Values F1–F4 represent the respective formant frequencies (Hz), amplitude (dB) and bandwidth (Hz).

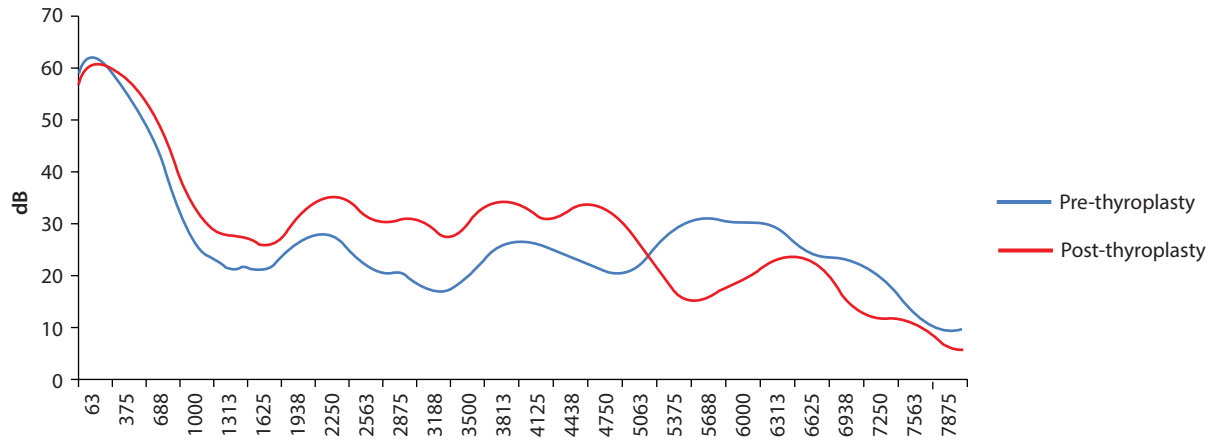


Figure 62.5 Broadband long-term average spectra (LTAS) for a patient with recurrent laryngeal nerve palsy on sustained vowel /i/. This is a graphical display of the spectral information in Figure 62.3 showing improvement in formant frequency energy and a reduction in noise element in the 5500–7500 Hz range before thyroplasty (blue) and following surgery (red).

Measurements of spectral noise energy versus harmonic energy

Speech and voice have two components: a well-defined periodic signal that has a clear harmonic spectrum and an additional source of random 'spectral noise'.[70, 71] Spectral noise is inherent in normal as well as pathological voice and increases with the openness of the vowel. For example, it is greater for vowels such as /œ/ (as in b*a*d) and least for /u/ and /i/ (as in b*oo*t and b*ee*t respectively).[72] Increasing vocal effort and lower pitches are associated with an increase in spectral noise and there is a reasonable correlation (0.74–0.92) between spectral noise and the perceived roughness of a vowel.[73] The noise element can be generated from irregular (aperiodic) vibration of the vocal folds or some other structure within the vocal tract (e.g. the false cords) and/or turbulent airflow (e.g. air leakage through an incompletely closed glottis).

The commonest measures used in clinical practice are the harmonics-to-noise ratio, normalized noise energy and the signal-to-noise ratio (see below). Unfortunately, these measures do not distinguish between pathological changes as a result of turbulent noise and irregular glottal excitation.[74, 75]

Harmonics-to-noise ratio The harmonics-to-noise ratio (HNR) (measured in dB) is the mean intensity of an average waveform (noise-free) divided by the mean intensity of the isolated noise component for the series of waveforms in the utterance.[41, 76] The greater the noise, the lower the HNR (**Table 62.5**). Some authors report higher normative and post-treatment values.[41]

$$\text{Conceptual HNR dB} = 10^{*}{}_{\log 10}\frac{\text{energy contained in the harmonics alone}}{\text{energy in the noise alone}}$$

The correlation between the HNR and perceptual evaluation has varied considerably between studies. Yumoto et al[76] found a correlation between hoarseness and HNR of 0.849 but Wolfe et al[77] noted a –0.32 correlation with a seven-point

TABLE 62.5 Some examples of HNR values for /α/ (as in *far*) vowel in normal, dysphonic and treated patients. There was no statistical difference between men and women[76]

	Mean (dB)	SD	Range (dB)
Normal (*n* = 42)	11.9	2.32	7.0–17.0
Pre-op dysphonics (*n* = 18)	1.6		–15.2–9.6
Post-op (*n* = 23)	11.3	3.13	5.9–17.6

severity of dysphonia score. It has been found to be an excellent predictor of breathiness[78] but tends to overestimate the noise energy in the presence of jitter and shimmer.[75, 79]

Normalized noise energy Normalized noise energy (NNE)[80] assesses the relative level of vocal noise to that of harmonics but bases the analysis on a relatively small number of vocal periods (as opposed to individual cycles as in the HNR). This has the advantage that it avoids the effects of drift in fundamental frequency or intensity during the utterance, which can be a problem in the calculation of the noise component of the HNR. Like other acoustic measures, the degree of effort used in producing the voice sample, day-to-day variability[44] and algorithms for calculating the noise energy in the signal can all influence results[41] so care must be taken when comparing studies. The higher the negative value, the better the voice. NNE has been shown to correlate with perceived breathiness in dysphonic children.[81] A few studies have been published where it has been used as an outcome measure and to distinguish pathological from normal voices.[82–85]

Signal-to-noise ratio The signal-to-noise ratio (SNR) is an alternative approach that avoids the need for harmonic analysis yet effectively achieves the same end result.[86] The underlying concept is that, since noise is random, its average is zero and the average amplitude will be an essentially noise-free estimate. Subtraction from the raw signal then leaves the noise alone. A ratio higher than 1:1 (greater than 0 dB) indicates more signal than noise. The process depends, however, on the assumption that the voice signal is truly periodic.

$$\text{S/N dB} = 20^{*}_{\log 10} \frac{\text{average amplitude of mean vocal fold cycle}}{\text{average of difference between mean and raw cycles}}$$

In practice it is difficult perceptually to distinguish between the sensations associated with the following:

- frequency irregularity from cycle to cycle of vocal fold vibration
- amplitude irregularity from cycle to cycle
- the presence of random noise in the voice.

Electrolaryngography

The electrolaryngograph (ELG) consists of two electrodes placed on the skin on either side of the thyroid cartilage. A high-frequency current (3 megahertz) is applied between the two electrodes and held at a constant voltage. Vocal fold vibration changes the electrical conductance between the electrodes. The resulting waveform can be analyzed automatically to obtain measures of the rate of vocal fold vibration (fundamental frequency, Fx) and frequency perturbations (e.g. jitter). Experimental data have also shown the waveform can be used to measure indirectly variations in the contact area between the mucosa of the two vocal folds during a vibratory cycle (**Figure 62.6**, and see **Figures 62.1c** and **62.2c**).[90] As the ELG signal is a simpler waveform which is unaffected by resonances of the vocal tract, it provides one of the most accurate methods of determining the fundamental frequency, even in severely dysphonic voices. However, it is not always possible to detect a waveform, particularly when the soft tissues of the neck are thick.

SPEAKING FUNDAMENTAL FREQUENCY AND F_0 RANGE

Mean speaking fundamental frequency (SFF) can be measured from a 2-minute sample of speech and can be plotted as a frequency histogram (**Figure 62.7**) to give a graphical representation of the dynamic frequency range of the voice. In the Speech Studio (Laryngograph Ltd) programme, for example, frequency measurements are displayed on a logarithmic scale which is divided into 120¼ tone 'bins' between 27.5 Hz and 440 Hz. These frequency 'bins' correspond well to perceived pitch and tend to bias the higher frequencies. In addition, a second frequency histogram (DFx2) can be overlaid on the graph. This counts the 'pitch-pairs' (i.e. when two consecutive periods differ by no more than 10%) and represents the minimum number of consecutive vibratory cycles that can potentially be perceived as periodic. Poor voice quality is in

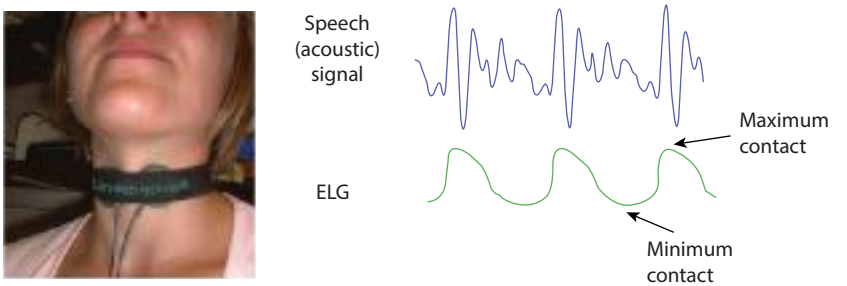


Figure 62.6 **(a)** Laryngograph® electrodes placed over thyroid cartilage. **(b)** Speech (acoustic) waveform acquired using a tie clip or head-mounted microphone. **(c)** The ELG waveform reflects the variation in conductance between the electrodes during phonation. In modal voice the vocal folds close more rapidly than on opening, giving a sharper rise in the waveform.

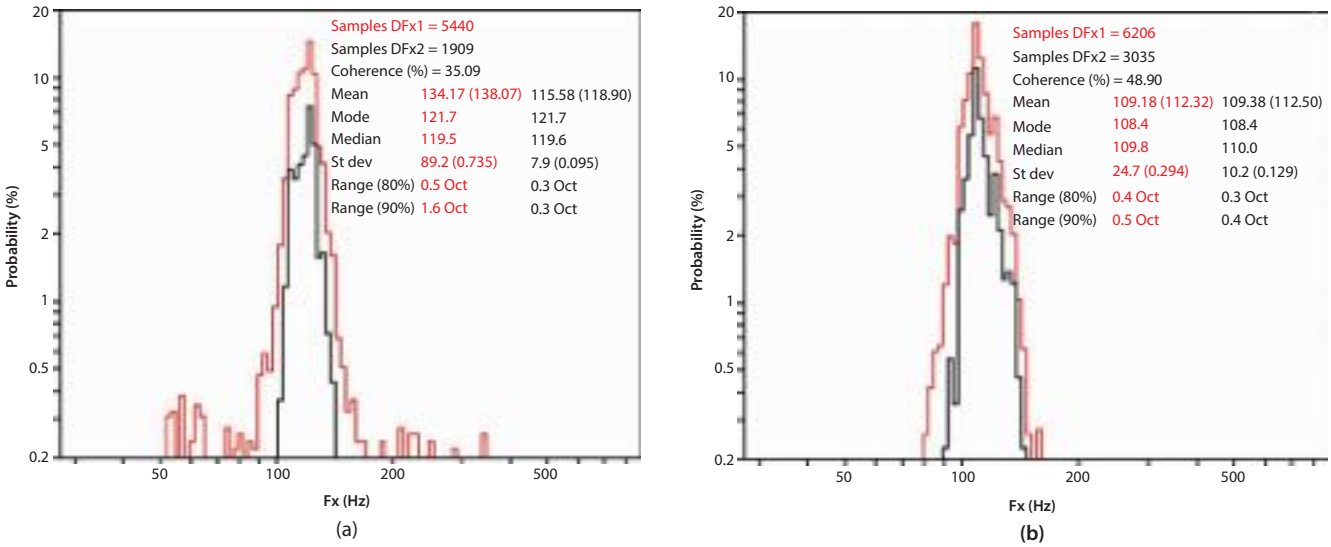


Figure 62.7 DFx1 and DFx2 frequency histograms (a) pre-thyroplasty and **(b)** post-thyroplasty. DFx1 demonstrates the relative number of times the vocal folds vibrated at a certain frequency (or more precisely frequency bin, see text) during the reading of a passage of text. The DFx2 demonstrates 'pitch-carrying pairs' indicating smooth vibratory frequency change associated with good quality voicing. In general, the closer the DFx1 and DFx2 distributions are graphically, the better the quality voice. This can be quantified in terms of percentage coherence value.

TABLE 62.6 Example of normative data based on a total of 43 female and 14 male Portuguese subjects with no self-reported voice problems (including smokers)[89]

	Men		Women	
Mean	**Reading**	**Conversation**	**Reading**	**Conversation**
Mean SFF (Hz)	109.6	109.2	190.3	186.6
Dynamic frequency range DFx1 90% (octaves)	0.75±0.18	1.18±0.49	0.86±0.22	1.12±0.48
Irregularity score (CFx)%	12.5±7.3	23.5+/–15.6	7.6±5.2	12.3±7.4
Mean contact quotient (Qx)%	45.9	46.3	44.1	43.8
Standard deviation of contact quotient (Qx)%	5.9	7.5	6.1	7.3

general associated with poor correspondence between the DFx1 and DFx2 histograms (**Figure 62.7b**) and reflected in a reduced coherence percentage value. Various parameters can be measured, such as the mean, mode and median SFF and the 80% and 90% ranges. Rather than absolute values, the range in octaves is perhaps more meaningful. Examples of normative values for vocally healthy individuals are given in **Table 62.6**.

$$\text{Coherence \%} = \frac{\text{Number of samples DFx2}}{\text{Number of samples DFx1}}$$

A lower than average mean SFF is found in conditions that increase the mass per unit length of the vocal fold mucosa such as Reinke's oedema[91, 92] and hypothyroidism.[93, 94] A higher than average SFF is seen in puberphonia,[95, 96] scarring of the vocal folds, laryngeal cancer[97] and in some cases of recurrent laryngeal nerve palsy.[98]

A restricted frequency range is found in both organic conditions of the vocal folds, neurological conditions such as Parkinson's disease[99, 100] and psychological conditions including depression and, to a lesser extent, schizophrenia.[101, 102] Some patients also find empirically that by restricting their frequency range they can maintain a reasonably stable vocal fold vibratory pattern and voice quality. An extended range with good correspondence between DFx1 and DFx2 indicates an exaggerated use of the dynamic range of the voice. In contrast, a large range with poor correspondence suggests poor control over vocal fold vibration and is associated with perceptually severe dysphonia.

PERCENTAGE IRREGULARITY SCORE (CFx)

Plotting frequencies of successive vocal fold vibrations against each other during running speech (approximately 120 s) should result in a well-defined single diagonal distribution for normal voice. In pathological voice, such as a recurrent laryngeal nerve palsy, the ability to control cycle-to-cycle variation in frequency is impaired, resulting in deviation from the diagonal line (**Figure 62.8**). This deviation can be quantified by measuring the number

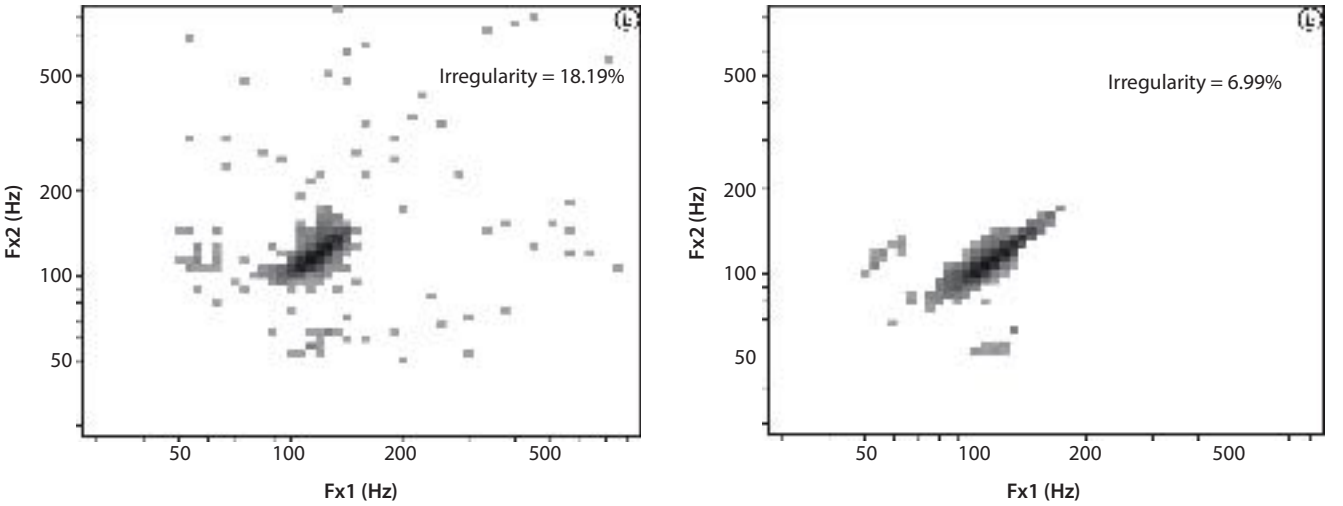


Figure 62.8 CFx1 distributions (a) pre- thyroplasty and (b) post- thyroplasty. This demonstrates the cycle-by-cycle change in frequency of vibration of the vocal folds. The better the voice the straighter and less scatter from the diagonal. This can be quantified in terms of a percentage irregularity score.

of data points straying ±3% away from the diagonal and expressing this as a percentage of the total number of data points registered. It can be seen that the CFx percentage irregularity score values for normal individuals in **Table 62.6** (which include smokers) are greater for males and for conversational voice. For the pre- and post-operative examples in **Figure 62.8** the irregularity scores are 18.9% and 6.99% respectively.

CONTACT QUOTIENT MEASUREMENT (CQx)

As well as frequency measurements it is also possible to derive information about the degree of contact between the vocal folds during the vibratory cycle from the ELG waveform. This can be expressed as a percentage of time to complete one vibratory cycle.

$$\text{Percentage contact quotient Qx} = \frac{\text{Lx closure width 70\% down from positive peak}}{\text{time to complete one vibratory cycle}}$$

There appears to be a positive correlation between contact quotient and vocal intensity for sustained vowels.[103, 104] The contact quotient increases with the level of vocal training[105, 106] but also in pathological conditions when the mass of the vocal folds is increased, such as Reinke's oedema and certain types of muscle tension dysphonia where the voice is pressed. Reduced contact quotients are usually found in cases of vocal fold palsy and paresis (**Figure 62.9**) and in some cases of presbylaryngis and muscle tension dysphonia associated with weak, breathy or asthenic voices. The standard deviation of the contact quotient is generally increased in dysphonic patients,[89] reflecting the increased difficulty in controlling the degree of contact in speech tasks.

Aerodynamic measures

Clinically there are three main factors that can be measured which are of interest in voice production: air volume, air flow and subglottic pressure.[107]

AIR VOLUME

Tidal volume (5–6 L) is a usable part of total lung capacity (6–7 L). In quiet respiration we use only 10–15% of the tidal volume but the full amount can be used for respiration or voice in demanding physical activities, such as exercise or singing. Actual lung volumes are in themselves not particularly informative in speech science but the changes in air volume during speech (airflow) are of much more potential interest.[41] Body plethysmography remains the gold standard for obtaining measurements of changes in air volume during speech or singing but is only used in research settings. Alternative approaches, again only really used in research, are to use magnetometers and inductance plethysmographs placed over the chest and abdominal walls, although the accuracy of these techniques has been questioned.[41, 108] As flow is essentially the change in volume over time, there are two alternative methods of deriving flow and volume measurements from a single transducer:

- by mathematically integrating the oral airflow signal from a pneumotachograph[107]
- by differentiation of the output of a volumatic device such as a spirometer.[41]

In clinical practice where this is undertaken, the pneumotachograph is more commonly used. The main drawback, however, is the interference with speech and change in vocal resonance due to the face mask.[107]

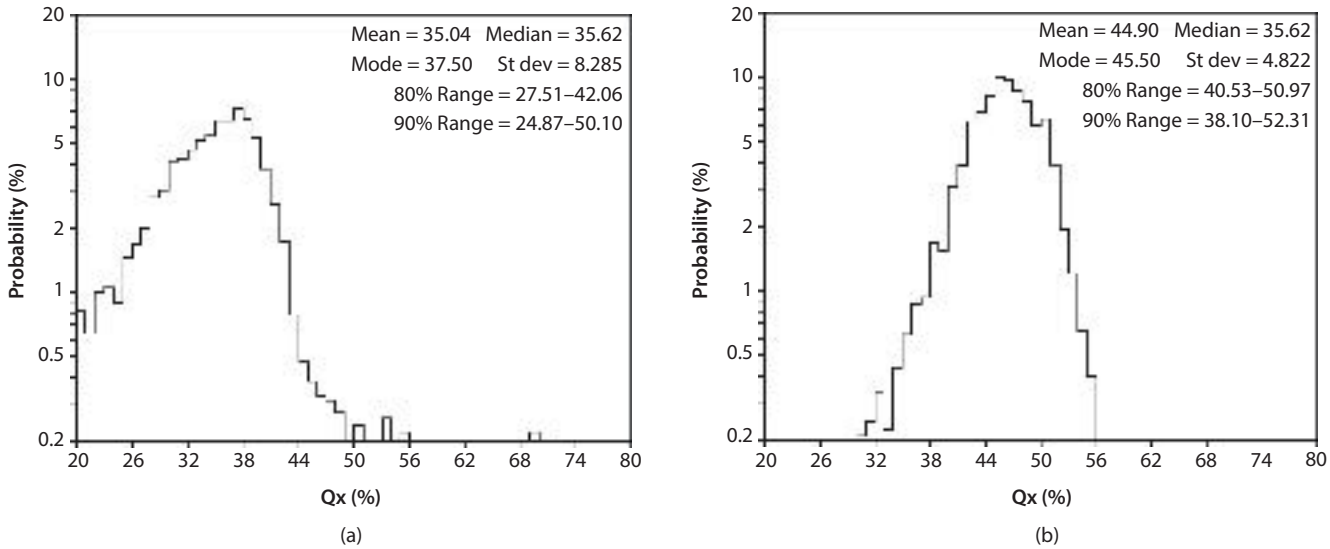


Figure 62.9 DQx1 data (a) pre-thyroplasty and (b) post-thyroplasty. The change in percentage contact with each cycle of vibration is displayed as a probability histogram. The improvement in contact quotient following surgery is seen with a return to normal mean and modal values.

AIR FLOW

Airflow associated with phonation is usually specified in terms of volume velocity (litres per second). It can be used to measure:

- flow during sustained phonation to provide an indicator of functional efficiency of the laryngeal system
- flow associated with consonants to evaluate oral articulatory events
- nasal airflow to assess the velopharyngeal function.[41]

Only the important measures associated with the first use will be discussed here:

Mean airflow rate, Vocal Velocity Index and glottal flow waveform

- The **mean airflow rate** (**MFR**) is the volume of air displaced during phonation on a sustained open vowel such as /œ/ (as in b*a*d) divided by the time taken to produce the phonation.[32] It is usually measured using a facemask or mouthpiece to channel air through an airflow transducer such as a pneumotachograph.[41]
- The **Vocal Velocity Index** (**VVI**) is a variant designed to provide a degree of flow comparison normalization between different-sized speakers.[41, 109] It is calculated by dividing the MFR by the speaker's vital capacity. Normal values for a range of British speakers have been reported.[41, 109] Laryngeal disorders are often associated with excessive air escape and consequently increased MFR and VVI.[41] Conversely, where glottal contact is excessive in conditions such as spasmodic dysphonia, these values are reduced.[41, 109] Both the MFR and VVI have been used as objective outcome measures following treatment.[41]
- The **glottal flow waveform** or **flow glottogram** is a representation of the airflow during each glottal cycle. It is derived from the oral airflow signal through a special pneumotachograph placed in a circumferentially vented facemask using a technique known as **inverse filtering**.[41, 107] From this, values such as peak flow (L/sec), AC flow (L/sec), minimum flow (L/sec) and maximum flow declination rate (L/sec/sec) can be derived. It is used mainly as a research tool.

Maximum phonation time, phonation quotient and s/z ratio

- **Maximum phonation time** (**MPT**) is measured by asking the subject to inhale as deeply as possible and then sustain a steady /ɑ/ vowel (as in f*a*r) for as long as possible.[32, 41] The longest of three repeated measurements is selected. Values under 10 s are regarded as pathological.[32] It is a simple tool used widely in clinical practice as an indicator of the severity of the dysphonia and as an outcome measure, but its reliability has been questioned.[41] It does not allow distinction between poor glottal closure from reduced pulmonary function and vocal cord abnormalities such as a recurrent laryngeal nerve palsy.[41]
- The **phonation quotient** is defined as the vital capacity divided by the MPT.[41] It provides some correction for the size of the speaker's movable air supply on maximal vowel duration in a similar way to the VVI. Although it correlates with the MFR, it is less sensitive and is of questionable clinical value.[41]
- The **s/z ratio** is a variation of the MPT whereby the maximum sustained time for a speaker to make both an /s/ and /z/ sound are recorded.[41, 110] A normal speaker can usually maintain the sound for approximately the same amount of time for both the voiceless /s/ and voiced /z/ consonant, giving a ratio of approximately 1 : 1. Abnormalities which interfere with vocal fold vibration or which affect glottic closure would be expected to reduce the /z/ value but not have any significant effect on the /s/ time, thus increasing the ratio.

Although this simple test is used quite widely in clinical practice, some of the original precepts have been challenged as it depends on eliciting a maximum performance in a speaker. Subsequent studies have shown that there is a wide range in normal values and its sensitivity and utility are therefore questionable.[41]

MEASURES OF SUBGLOTTIC PRESSURE

The vocal folds will only vibrate when the air pressure in the subglottis overcomes the tissue resistance of the vocal folds. The **phonation threshold pressure** is the minimum subglottal pressure required to induce oscillation.[111, 112] Low-frequency phonation threshold pressure has been measured at 0.3–0.4 KPa and generally increases with the frequency of vibration, increased tissue viscosity (stiffness) and increased glottic/false cord constriction.[111, 113–115]

Normal values of **subglottic pressure** during habitual phonation are in the range of 0.5–1.0 KPa[32] and there is a positive correlation with intensity.[41] Subglottic pressure is potentially an important clinical value to measure as failure to generate an adequate, stable level can result in abnormal speech intensity levels or sudden shifts in the fundamental frequency.[116] An inadequate subglottic pressure can result from chest disease (lung parenchyma or thoracic wall), laryngeal disease or neuromuscular conditions that affect the laryngeal resistance (e.g. vocal fold palsy).[41] Excessive subglottal pressures are seen in hyperfunctional voice conditions when the voice is pressed and in adductor spasmodic dysphonia.[117, 118]

Unfortunately, subglottic pressure during phonation is not easy to measure. The most accurate direct method is to place a pressure-sensing device in the subglottis. This can be achieved by performing a percutaneous cricothyroid or tracheal puncture with a large-bore hypodermic needle and attaching it to a pressure transducer.[118] Alternatively, a very small-pressure transducer can be inserted via the nose and positioned directly in the subglottis.[32, 41] Both these direct methods are invasive and used only in research studies. An alternative, more practical clinical method is to estimate the subglottic pressure by measuring oral pressure during the production of a sound sequence such as /pi-pi-pi-pi-pi/ at a constant rate, pitch and loudness.[119] During the production of /p/, vocal folds are abducted and the peak intraoral pressure is essentially equal to that throughout the airway including the subglottis. An estimate of the average subglottal pressure during vowel production can be obtained by measuring pressure at the midpoint of a line connecting two successive pressure peaks.[107, 120] Care must, however, be taken in the interpretation and extrapolation of the results from this very specific speech task into connected speech.[115, 120]

Voice accumulators

'Voice accumulators' are wearable voice-monitoring systems which can provide reliable and objective measures of voice use during daily activities away from a clinic environment. They can potentially provide a better understanding of the role of daily voice use in the causation of voice disorders. Most contemporary devices are based on contact microphones or accelerometers placed at the base of the neck. Recording vocal fold activity rather than the voice allows a degree of privacy to the wearer and efficiency in post-acquisition processing.[121] This relatively new technology can provide data on the proportion of the time spent using the voice (phonation time), fundamental frequency, sound intensity measurements and potentially estimates of airflow.[122] They are used mainly as research tools at present.

Combined measurements

There is an intrinsic attraction in combining multiparameter measures of voice function to help discriminate between normal and pathological voices. Several schemes have been developed[123, 124] and, of these, the Dysphonia Severity Index (DSI) is probably the most widely used, especially in Europe.

DYSPHONIA SEVERITY INDEX

The DSI is a single quantitative measure that has been derived by multivariate analysis from 387 dysphonic subjects.[123] It is calculated by summing four weighted aerodynamic and acoustic factors as follows:

+ Maximum phonation time (seconds) × 0.13

+ highest frequency (F0) achievable (Hz) × 0.0053

– lowest intensity (dB) × 0.26

– jitter (%) × 1.18

+ 12.6 (correction factor)

= DSI score

In the original study a perceptually normal voice gives a maximum value of +5 while lesser values (to a maximum of –5) represent worsening degrees of dysphonia.[123] A more recent study suggests that +8 to –8 may be more practical.[125] A reduction of the DSI score by 2.5 is accepted as a clinically significant therapeutic outcome although this value has been challenged.[126, 127] The inverse DSI score has also been shown to correlate well with the VHI total score.[123] However, the component measures of the DSI may be prone to variability that may affect the stability of the DSI itself.[126, 127] There is some test–retest variability in normal subjects.[126, 127]

FUTURE DEVELOPMENTS IN VOICE MEASUREMENT

It is likely that laryngostroboscopy will remain the most useful clinical tool in the evaluation of voice disorders for the foreseeable future as the image quality continues to improve. Although currently expensive, the CCD

chip nasoendoscopes (videoscopes) overcome the main problem of poor image quality currently obtainable with many video fibre-optic systems. Patient self-rated questionnaires will remain an important determinant of patient's perception of the impact of the voice disorder (and therapeutic intervention) on their quality of life. Given the complexity of voice, the huge range of normality and 'normal' inter- and intrasubject variability, it is unlikely that any single acoustic, aerodynamic or other measure will be sensitive and specific enough to characterize a given type of voice disorder. It is hoped that advances will continue to be made in the use of analysis of connected speech and multiple combined measures which may lead to a better profile of the vocal capabilities of the individual. Understanding and measuring the variability in patients' voices with use and in different environments with voice accumulators may also allow better targeted treatment. The constraints of patient tolerance, clinical time and cost will also play an important part in determining which tests are acceptable in clinical practice. The patient's perception of their impairment, limitation in activity and participation restriction should remain the prime motivator for deciding on the need for treatment once serious laryngeal disease has been excluded.

KEY POINTS

- Speech, voice and phonation are terms with specific definitions.
- Abnormal vocal fold vibration results in dysphonia whilst an absence of vocal fold vibration results in aphonia.
- Normal voice production requires a pressure gradient across the vocal folds, appropriate vocal fold structure mass and elasticity and a resonating chamber of variable size and shape (the vocal tract).
- Health-related questionnaires (specific and generic), Perceptual Evaluation, Acoustic Analysis and Electrolaryngography are all used to measure voice quality.

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CHAPTER 63

STRUCTURAL DISORDERS OF THE VOCAL CORDS

Yakubu Gadzama Karagama and Julian A. McGlashan

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SEARCH STRATEGY

Data in this chapter may be updated by Medline, Embase and the Cochrane Library searches using the keywords: voice disorders, vocal cords, structural, lesions, polyps, nodules, varices, haemorrhage, sulcus, cyst, inflammatory, reflux, muscle tension, dysphonia and Reinke's oedema. Unfortunately, there have been very few good quality, randomized, controlled studies in this area and most of the evidence is level 2–4.

INTRODUCTION

The larynx is a complex organ in the upper aerodigestive tract with multiple functions. Because of its location, any disease condition affecting the larynx may present with symptoms including hoarseness, breathing or swallowing difficulty and aspiration pneumonia; multiple symptoms are often seen. This chapter discusses a comprehensive approach to evaluation of the patient presenting with an altered voice.

ASSESSMENT AND EVALUATION

The assessment and evaluation of patient with voice disorder should ideally be done in a multidisciplinary clinic by a laryngologist and a speech therapist. A voice coach may be part of this team depending on the case mix in the clinic and if the clientele includes a large number of professional singers. This recommendation is not prescriptive but an example of best clinical practice.[1]

History

Assessment of a patient with laryngeal disorders should start with a detailed history. Often one may be able to establish the diagnosis from the history alone. The patient should be allowed to present his/her story in his/her own words without interruption at first. Some voice disorders are diagnosed entirely by listening to the patient's voice (spasmodic dysphonia, functional dysphonia) and after excluding other conditions by physical examination of the larynx.[2] There are different terminologies that the laryngologist may use in describing voice symptoms. These must be explained to the patient in simple terms. Examples of terminology used to describe voice symptoms are:

Dysphonia: Any impairment of the voice or difficulty speaking.
Dysarthria: Difficulty in articulating words, caused by impairment of the muscles used in speech.
Dysarthrophonia: Dysphonia in conjunction with dysarthria, for example after a cerebrovascular accident, head injury or part of a degenerative neurological condition, such as motor neurone disease.
Dysphasia: Impairment of the comprehension of spoken or written language (sensory dysphasia) or impairment of the expression by speech or writing (expressive dysphasia), especially when associated with brain injury.
Hoarseness: A perceived rough, harsh or breathy quality to the voice.
Odynophonia: Pain when talking.

Generally speaking, the term dysphonia is interchangeable with hoarseness but most patients understand the term husky voice better. Very often, the voice symptom is not just a single entity but a description of how the voice is perceived by the patient, or their impression of how other people perceive their voice. It is therefore useful to use self-administered questionnaires and perceptual rating of voice questionnaire to assess the voice. These tools will not only help the laryngologist understand the severity of

the voice problem but also help in measuring outcomes after treatment. Commonly used measures are:

- GRBAS – Grade, Roughness, Breathiness, Astenia and Strain[3] (**Box 63.1**)
- VoiSS – Voice Symptom Scale[4] (**Box 63.2**)
- VHI-10 – Voice Handicap Index[5] (**Box 63.3**)
- RSI – Reflux Symptom index[6] (**Box 63.4**).

A normal voice is difficult to define (see Chapter 62, Evaluation of the voice). Although we normally think of a disordered voice as one that is hoarse, this is not always the case. It may only cause problems when certain demands are placed upon it. A disordered voice can be defined as one that has one or more of the following characteristics:

- It is not audible, clear or stable in a wide range of acoustic settings.
- It is not appropriate for the gender and age of the speaker.
- It is not capable of fulfilling its linguistic and paralinguistic functions.
- It fatigues easily.
- It is associated with discomfort and pain on phonation.

Voice disorders are often multifactorial in aetiology and, to complicate matters, patients may develop compensatory vocal behaviours to be able to communicate effectively. This may mask the true underlying or primary disorder, such as muscle tension imbalance secondary to

BOX 63.1 GRBAS[3]

GRBAS is an acronym for five dimensions of voice quality referred to as 'Grade', 'Roughness', 'Breathiness', 'Asthenia' and 'Strain'. Speech and language therapists score their patients by giving a numerical value, i.e. an integer in the range 0–3, to each of these five dimensions of GRBAS.

BOX 63.2 VoiSS: Voice Symptom Scale[4]

VoiSS is suitable for general adult dysphonia populations.
Each item is scored 0–4 on the frequency response:
0 = never, 1 = occasionally, 2 = some of the time, 3 = most of the time, 4 = always

The **total VoiSS score (max = 120)** indicates the level of general voice pathology.

The **subscales** are completed by summation of items as follows:

Impairment: 1, 2, 4, 5, 6, 8, 9, 14, 16, 17, 20, 23, 24, 25, 27 (max = 60)

Emotional: 10, 13, 15, 18, 21, 28, 29, 30 (max = 32)

Physical: 3, 7, 11, 12, 19, 22, 26 (max = 28)

BOX 63.3 VHI-10 – Voice Handicap Index[5]

These are statements that many people have used to describe their voices and the effects of their voices on their lives. Ask the patient to circle the response that indicates how frequently they have the same experience:
0 = never, 1 = almost never, 2 = sometimes, 3 = almost always, 4 = always

1.	My voice makes it difficult for people to hear me.	0 1 2 3 4
2.	I run out of air when I talk.	0 1 2 3 4
3.	People have difficulty understanding me in a noisy room.	0 1 2 3 4
4.	The sound of my voice varies throughout the day.	0 1 2 3 4
5.	My family has difficulty hearing me when I call them.	0 1 2 3 4
6.	I use the phone less often than I would like to.	0 1 2 3 4
7.	I'm tense when talking to others because of my voice.	0 1 2 3 4
8.	I tend to avoid groups of people because of my voice.	0 1 2 3 4
9.	People seem irritated with my voice.	0 1 2 3 4
10.	People ask, 'What's wrong with your voice?'	0 1 2 3 4
	Total score	

BOX 63.4 Reflux Symptom Index[6]

Ask the patient to rate the following items on a scale of 0–5. The composite of these scores should be 10 or below. If it is more than 10, you should consider an evaluation to check for 'silent gastro-oesophageal reflux disease' or laryngopharyngeal reflux.
Within the past month, how did the following affect you?
0 = No problem → 5 = Severe problem

1.	Hoarseness or a problem with your voice	0 1 2 3 4 5
2.	Clearing your throat	0 1 2 3 4 5
3.	Excess throat mucous or postnasal drip	0 1 2 3 4 5
4.	Difficulty swallowing food, liquids or pills	0 1 2 3 4 5
5.	Coughing after you ate or after lying down	0 1 2 3 4 5
6.	Breathing difficulties or choking episodes	0 1 2 3 4 5
7.	Troublesome or annoying cough	0 1 2 3 4 5
8.	Sensations of something sticking in your throat	0 1 2 3 4 5
9.	Heartburn/chest pain/indigestion/stomach acid coming up	0 1 2 3 4 5

extraoesophageal (laryngopharyngeal) reflux. There are four main causes of voice disorders:

- inflammatory
- structural or neoplastic
- neuromuscular
- muscle tension imbalance.

Often, patients will have more than one condition contributing to their voice disorder. For example, a patient with vocal fold nodules may well have a degree of muscle tension imbalance and extraoesophageal reflux.

In assessing singers and other professional voice users, an understanding of their occupational and voice requirements is essential.[7–10]

In summary, it is important to determine:

- the nature and chronology of the voice problem
- exacerbating and relieving factors
- lifestyle, dietary and hydration issues[11]
- contributing medical conditions or the effects of their treatment
- the patient's voice use and requirements
- the impact on their quality of life, social and psychological well-being
- their expectations for outcome of the consultation and treatment.

Patients' complaints are most frequently related to:

- changes in voice quality (hoarseness, roughness and breathiness)
- a pitch that is increased or decreased which is not appropriate for their age and sex
- an inability to control their voice as required (pitch breaks, voice cutting out)
- an inability to raise the voice or make the voice heard in a noisy environment (reduced loudness)
- an increased effort and/or reduced stamina of the voice or one that tires with use
- difficulties or restrictions in the use of their voice at different times of the day or related to specific daily, social or work-related tasks
- a reduced ability to communicate effectively
- difficulty in singing
- throat-related symptoms (soreness, discomfort, aching, dryness, mucus), particularly related to voice use
- the consequent emotional, psychological effects caused by the above.

Many of the patient self-report questionnaires that have been developed to measure the impact of the voice problem on the quality of life are concerned with these areas of voice complaint.

Good examples of checklists for taking a detailed history in patients with voice disorders can be found in Mathieson[12] and Colton and Casper.[13]

General examination

The examination of a patient with a voice disorder should start with a general examination of the patient, as with any ENT disorder. Special attention should be given to the ears, nose and throat; for instance, the voice problem might be related to a blocked nose or sinus problems and can affect resonance and quality of the voice, as may be the case in professional voice users, or hearing loss causing the patient to strain their voice as they have to speak loudly to hear themselves.[14] The neck should be inspected for any scar that may indicate previous surgery or trauma, or neck masses, which will need a different sequence of investigations. A full neurological assessment might be necessary to assess the cranial nerve function or any signs of central neurological disease. The larynx is best examined with a videolaryngostroboscope, but this equipment may not be available at every centre.

VIDEOLARYNGOSTROBOSCOPY

Visual inspection of the larynx is mandatory for diagnosis or exclusion of laryngeal disease. This is usually performed in the clinic, but occasionally a diagnostic microlaryngoscopy needs to be performed when this cannot be tolerated in the outpatient setting or when the diagnosis is still uncertain (e.g. in some cases of chronic laryngitis).

The simplest method of examining the larynx and vocal folds is with a mirror.[7] Although excellent views can be obtained by an experienced examiner, the images are relatively small, of brief duration and frequently the anterior glottic region is not well visualized. In addition, the mucosal wave cannot be seen due to the relative speed of vibration of the vocal folds (usually over 100 cycles per second) compared with the ability of the retina to process individual images (five images per second).[8] Superior views of the larynx can generally be obtained using flexible fibre-optic and videoscopic transnasal endoscopes or rigid telescopes inserted through the mouth. Either approach has its own advantages and drawbacks. The transnasal flexible videolaryngostroboscope is associated with less gag reflex compared to the transoral rigid videostroboscopy. However, the rigid telescope may give a slightly better picture quality, although the distal tip high definition flexible videolaryngostroboscope provides images almost as good as those obtained on rigid videostroboscopy.[15] Occasionally both modalities may be helpful.[16] The examination should be recorded for further review if necessary.

Using a stroboscope gives additional information about the vibratory pattern of the vocal fold mucosa[17] and improves the accuracy of diagnosis.[18] It has led to changes in diagnosis in approximately 30% of cases when compared to examination with continuous light alone. Several rating forms for assessing the laryngostroboscopic images have been described, but none has been shown to have good inter- or intrarater reliability.[19] Although they are not used regularly in clinical practice, they are useful in ensuring that a systematic evaluation of the images is performed. The important features are listed in **Table 63.1**.

TABLE 63.1 Key features in the interpretation of laryngostroboscopic images

Laryngostroboscopic evaluation		
Glottal closure pattern	Anterior or posterior gap	
	Hourglass or spindle-shaped	
	Irregular or regular	
	Closed phase	absent/reduced/normal/prolonged
Mucosal wave (right/left) in response to changes in pitch and loudness	Symmetry	of amplitude
		of phase
	Periodicity (regularity)	regular/variable/irregular
	Degree of change	absent/decreased/increased
Description of lesion	Colour	
	Shape	
	Multiple/single	
	Surface	
Vocal fold opening/closing pattern (right/left)	Range full/reduced	
	Normal/lag	
	Presence of spasm/tremor	
Supraglottic appearance	False cords medial constriction: right/left/both	
	Anteroposterior constriction (arytenoid–epiglottic approximation)	
	Prominence/lesion(s)	
Symmetry of arytenoids (vocal processes and apices/corniculate cartilages)	Sagittal/coronal/axial planes	

Further assessment

If the diagnosis is not clear from the initial assessment, the patient may undergo one of the following options.

- further in-depth assessment by a voice therapist:
  - to ascertain more background information including exploration of contributing psychological issues
  - to undertake a probe or trial therapy to deconstrict the larynx and assess response to a treatment regime
- a trial of vocal hygiene/lifestyle advice or medical treatment
- laryngeal electromyography
- objective voice measurements (see Chapter 62, Evaluation of the voice).
- 24-hour pH monitoring ± impedance testing or oesophagoscopy
- diagnostic microlaryngoscopy
- referral to another voice disorders team or professional for a second opinion, such as a clinical psychologist, specialist singing teacher (familiar with voice problems in singers), neurologist, respiratory physician, gastroenterologist or upper gastrointestinal surgeon.

TREATMENT OVERVIEW

Ideally, the patient should be assessed in a multiprofessional voice clinic by a laryngologist and voice therapist and a joint treatment plan should be formulated. Not all patients presenting with a voice disorder want treatment and some may be happy being given a diagnosis, an explanation of their voice problem and reassurance that there is no serious underling condition present. If treatment is required, it will usually consist of one or more of the following options, depending on the patient's symptoms, vocal requirements and clinical findings:

- vocal hygiene, lifestyle and dietary advice
- voice (speech) therapy
- specialist therapy, e.g. singing therapy, osteopathy
- medical treatment
- phonosurgery.

Vocal hygiene, lifestyle and dietary advice

It is likely that most patients with a voice disorder will benefit from advice on vocal hygiene, lifestyle and diet. Depending on the relevance to the patient, this may consist of a discussion or video presentation in either individual or group sessions. Additional material is usually given in patient information leaflets. The areas covered may include:

- an explanation of how the voice works
- the links between lifestyle, phonatory and non-phonatory vocal activities and stress on voice disorders

- the potentially traumatic effects to the vocal folds of 'vocally abusive behaviours', such as talking or singing too loudly, talking too fast, shouting, throat clearing and harsh coughing
- communicating effectively without raising or straining the voice, e.g. using a whistle in the school playground or using amplification devices where practical and conserving the voice where possible or in extreme situations discussing the possibility of changing jobs
- the importance of adequate hydration for vocal fold function, i.e. by drinking water and use of steam inhalations, and avoiding excessive amounts of drinks containing caffeine, i.e. coffee, tea and colas
- smoking cessation, reducing alcohol and social drug consumption (particularly spirits, cannabis and cocaine) and avoiding exposure to fumes, dust and dry air
- diet and reflux reduction, e.g. avoiding eating late at night, large or fatty meals.
- For more details on these subjects, see Chapter 65, The professional voice, and Chapter 66, Speech/voice therapy for voice disorders.

Voice therapy

Voice therapy is the mainstay of treatment for muscle tension dysphonia (MTD) and may be delivered as an individual course of therapy, usually for no longer than eight sessions, or in groups. Examples of the latter include groups for voice care, professional voice users and for presbylaryngis.

The aims of voice therapy sessions are:

- to help the patient find a better voice quality which is stable, reliable and less effortful to produce
- to make better use of vocal resonance and tonal quality
- to increase the flexibility of the voice by improving the pitch range and loudness without undue effort
- to increase the stamina of the voice.

Various techniques are used, including one or more of the following:

- vocal exercises with the aim of targeting and strengthening specific muscle groups and improving glottal closure and efficiency
- increasing awareness of and reducing excessive tension in the muscles around the larynx, neck and shoulders
- advice on posture and improving breathing during speech
- laryngeal massage
- general relaxation exercises and stress management
- psychological counselling
- remedial singing lessons.

Some techniques may need additional specialist input from clinical psychologists, singing teachers and osteopaths, for example. Ideally, these individuals should be part of the extended voice disorders team (see Chapter 65, The professional voice, and Chapter 66, Speech/voice therapy for voice disorders, for more details).

Medical treatment

Medical treatment mainly includes treatment for acid reflux and upper respiratory tract infections and allergies. It may also include recommendations to change medication for other medical conditions, such as asthma inhalers, diuretics and other antihypertensive medication. The National Center for Voice and Speech has an excellent website which lists medications that can potentially cause an effect on the voice (http://www.ncvs.org/rx.html).[20] Botulinum toxin injections into the laryngeal muscles may be used in cases of spasmodic dysphonia and arytenoid granuloma.

Phonosurgery, including medialization procedures

Phonosurgery refers to any surgery designed primarily for the maintenance, restoration or enhancement of the voice.[21] It encompasses the following:

- phonomicrolaryngosopy
- injection laryngoplasty
- laryngeal framework surgery
- recurrent laryngeal nerve reinnervation
- laryngeal pacing.

More information can be obtained from Chapter 67, Phonosurgery, Chapter 54, Neurological disease of the pharynx, and Chapter 71, Contemporary management of laryngotracheal trauma.

PHONOMICROLARYNGOSCOPY SURGERY

A phonomicrolaryngoscopy is the examination of the larynx usually under general anaesthesia to further establish a diagnosis, but more importantly to surgically treat a pathology with the aim of improving voice. This is done with a suitable sized rigid laryngoscope. A good view is obtained by use of a microscope but inspection of the larynx with a 0- and 30-degree telescope is recommended. The larynx should be palpated too using crocodile laryngeal forceps. A sulcus or small cyst might be revealed which otherwise would not have without close inspection and palpation. The range of interventions includes biopsy and removal of lesions, vocal cord injection and laser surgery.

INJECTION LARYNGOPLASTY

This procedure aims to medialize an adductor vocal cord palsy where the cord is in a lateral position. There are different approaches and materials that can be used. The selection of injectable materials depends on the availability and the surgeon's experience. Most of the injectable materials are temporary and will only last an average of 6 months.[22] Injection laryngoplasty is discussed in greater detail in Chapter 78, Paralysis of the larynx, and Chapter 79, Outpatient laryngeal procedures.

LARYNGEAL FRAMEWORK SURGERY

Laryngeal framework surgery was first described by Isshiki in 1974.[23] It is defined as a procedure on the laryngeal cartilage to change the position or tension on the vocal cords in order to achieve the desired voice outcome. There are four different techniques, all with different purposes. These procedures should ideally be performed under local anaesthesia as originally described by Isshiki. This allows intra-operative auditory feedback to the surgeon and the patient and helps to assess the impact of the altered position of the vocal cords on the voice. Not every patient can tolerate a procedure under a local anaesthesia, however, and some patients may need general anaesthesia, but they will have the disadvantage of not knowing what their voice is going to sound like when they wake up! Further details on laryngeal framework surgery can be found in Chapter 78, Paralysis of the larynx.

RECURRENT LARYNGEAL NERVE REINNERVATION

The paralyzed vocal cord can be reinnervated to restore its function. The two techniques used are non-selective reinnervation and selective reinnervation.

Non-selective reinnervation

Non-selective reinnervation is indicated in hoarseness due to unilateral adductor vocal cord paralysis. It is performed under general anaesthesia via an ipsilateral neck incision at the level of the cricoid cartilage. The ansa cervicalis and the recurrent laryngeal nerve are identified and anastomosed using a 9/0 nylon suture.[24]

Selective reinnervation

Selective reinnervation is indicated in stridor due to bilateral abductor vocal cord paralysis.[25] It is performed under general anaesthesia via an extended anterior neck skin incision at the level of the cricoid cartilage. This is a more complex procedure that involves identification of several nerves for anastomosis. The C3 root of the phrenic nerve is identified on one side and anastomosed with a cable graft harvested from the great auricalar nerve in a Y-shape which is then inserted into both posterior cricoarytenoid muscles. The next step involves identification of the descending branch of the ansa hypoglossi and the recurrent laryngeal nerve on both sides of the neck and anastomoses carried out between these nerves bilaterally.

LARYNGEAL PACING

This technique is still being evaluated in clinical trials.[26] It involves inserting an electrode into each posterior cricoarytenoid muscle which then causes automatic abduction and adduction movement of the vocal cords. The electrode is connected to an external pacing device that is surgically fixed under the skin on the chest wall, in a similar way to a cardiac pacemaker.

SPECIFIC VOICE DISORDERS

The most common voice disorders seen in secondary practice in a voice clinic are:

- MTD
- laryngitis/MTD secondary to poor vocal hygiene, dietary and lifestyle issues
- extraoesophageal reflux (laryngopharyngeal reflux)
- vocal fold nodules
- vocal fold polyps
- vocal fold cysts
- vocal fold palsy and paresis
- arytenoid granulomas.

Less frequently seen conditions include:

- sulci and mucosal bridges
- spasmodic dysphonia
- papillomatosis
- microvascular lesions
- laryngeal trauma, including post-surgical causes
- other neuromuscular causes
- hyperkeratosis, dysplasia and carcinoma
- endocrine causes
- amyloid
- other laryngeal tumours.

Inflammatory disorders

OVERVIEW

Inflammation of the larynx can be broadly classified into infective and non-infective causes. Sometimes the aetiological factors are easily identified in the history (e.g. hoarseness associated with an upper respiratory tract infection). In many other cases the cause may be less clear (e.g. in cases of extraoesophageal reflux), may be multifactorial, may require empirical treatment or a biopsy and microbiological culture (e.g. in the case of tuberculosis) or may resolve spontaneously without a cause being identified. Patients often complain of:

- hoarseness
- huskiness
- reduced pitch
- loss of part of the range of the voice
- pitch instability
- an increased effort to speak
- vocal fatigue and pain or discomfort on speaking
- throat symptoms, such as globus sensation and irritation, dryness, throat clearing or chronic cough.

Laryngitis is simply a descriptive term indicating a variable degree of erythema, oedema, epithelial change which may include ulceration, leukoplakia and stiffness of the mucosa of the vocal fold. There is often an increased amount of thick mucus present, which may be white, grey, yellow or green in colour. There may be associated inflammation of the rest of the subglottic, supraglottic and interarytenoid

regions of the larynx and the pharynx. In severe cases, there may be associated shortness of breath and stridor. The voice is usually hoarse (rough, strained, breathy or whispery), which may be due to impaired vocal fold vibration due to stiffness from the inflammatory process and/or secondary to muscle tension imbalance. This can result in the vocal folds being held splinted apart and therefore extra effort being required to induce vocal fold vibration causing perilaryngeal pain or discomfort.

Accurate diagnosis may require a diagnostic microlaryngoscopy with biopsy. Treatment consists of reduced voice use and abuse, voice rest, vocal hygiene, lifestyle and dietary advice, and appropriate medical or surgical treatment.

SPECIFIC INFLAMMATORY CONDITIONS

Arytenoid granuloma

Arytenoid granulomas are benign inflammatory lesions that arise from the medial surface of the arytenoid cartilages, and in particular the vocal processes. Other terms for them include:

- contact ulcer or granuloma
- vocal process granuloma
- intubation granuloma
- contact pachydermia
- peptic granuloma.

These consist of a proliferation of granulation tissue with epithelial hyperplasia. They result from injury to the thin mucoperichondrium over the vocal processes from mechanical trauma, either following intubation or from repeated high-velocity impact of the vocal processes against each other from throat clearing, coughing or talking in a habitually low-pitched, creaky, hyperfunctional manner.[27] Men tend to develop granulomas secondary to hyperfunction, while women develop them more commonly as a result of intubation. In addition, extraoesophageal reflux is recognized as an important aetiological factor either contributing to the symptoms leading to the mechanical trauma or preventing healing of the damaged mucosa.[28]

Patients present with a change in the voice and/or vocal fatigue, a constant tickling sensation, discomfort or pain localized to the posterosuperior aspect of the larynx which is worse on phonation, coughing and throat clearing and can radiate to the ear. In addition, there may be symptoms associated with extraoesophageal reflux, including choking episodes and, in severe cases, stridor. These symptoms may come on insidiously, after intubation, an infection or a period of stress. They may be unilateral or bilateral and range from a nodular, diffuse thickening over the vocal process to large pedunculated, exophytic masses obscuring the posterior glottis (**Figure 63.1**).

The main treatment principles include reducing the effects of laryngeal irritants, i.e. stopping smoking, improving vocal hygiene, treating any respiratory tract infections, allergies and extraoesophageal reflux. Voice therapy, in terms of raising awareness of and reducing hyperfunctional and vocally abusive behaviour and psychological counselling where necessary, is also of use.[29] Surgery does not usually cure arytenoid granulomas when used in isolation as there is a high rate of recurrence. It is useful in confirming the diagnosis histologically, excluding a carcinoma and in debulking large lesions.[30] Laser vaporization after biopsy reduces the amount of bleeding but it is important to avoid thermal damage to the underlying cartilage.[28] There is no good evidence in support of the use of antibiotics or steroids in general. Botulinum toxin injections into the thyroarytenoid muscle can be useful as an adjunct treatment in resistant cases as this helps reduce the impact of vocal processes against each other, allowing the epithelium to heal.[31, 32]



Figure 63.1 Arytenoid granuloma.

Structural or neoplastic lesions

OVERVIEW

Structural abnormalities can result from neoplasms which may be benign or malignant, or trauma to the laryngeal skeleton or soft tissues. Tumours of the larynx and laryngeal skeletal trauma are dealt with elsewhere in the text (see Chapter 14, Tumours of the larynx, and Chapter 71, Contemporary management of laryngotracheal trauma). This chapter will be confined to discussing the more common benign lesions resulting in referral to secondary care clinics and which involve the superficial layers of the vocal folds.

When a patient is observed to have a nodular swelling (i.e. a localized swelling on the membranous portion of one or both the vocal folds), it is important to consider the differential diagnosis in **Table 63.2**. Accurate diagnosis can be challenging and depends on a detailed history, the use of stroboscopy and, to some extent, objective measures.[33] Even then, a working diagnosis should be made and a decision needs to be made as to whether to try an empirical trial of therapy or proceed to a diagnostic microlaryngoscopy. A conservative approach is to reserve a 'microlaryngoscopy and proceed' for 'failed therapy' cases after appropriate informed consent.

TABLE 63.2 Differential diagnosis of a nodular lesion

Grey, white or translucent lesions	Haemorrhagic lesions	Yellowish lesions
True vocal nodules 'Physiological nodules' Prenodular swellings Pseudocyst Polyp Mucus retention cyst ± contact lesion Epidermoid cyst ± contact lesion Localized oedema of the vocal fold: • Reinke's oedema • Lower lip of a sulcus • Associated with a vascular abnormality, e.g. ectasia	Haemorrhagic polyp Ectasia Papilloma Carcinoma Arytenoid granuloma	Rheumatoid nodule Epidermoid cyst`

SPECIFIC STRUCTURAL OR NODULAR LESIONS

Vocal fold polyps

A true vocal polyp is a benign swelling of greater than 3 mm that arises from the free edge of the vocal fold (**Figure 63.2**).[34] It is usually solitary, but can occasionally affect both vocal cords. It is claimed that polyps are the most common structural abnormality that cause hoarseness and they affect men more than women. They are most frequently seen in smokers and between the ages of 30 and 50 years.

In many cases the exact cause of polyp formation is not known, but most authors agree that phonotrauma is an important aetiological factor. Some are heralded by a sudden onset of hoarseness or loss of voice after yelling or shouting, particularly if the vocal folds are inflamed from acute infective laryngitis or extraoesophageal reflux. A large proportion of patients with vocal cord polyps are also smokers. Cigarette smoking can cause injury to the vocal cord leading to hyaline degeneration in polyps.[35] There appears to be disruption to the vascular basement membrane, capillary proliferation, thrombosis, minute haemorrhage and fibrin exudation.[36] Although some polyps have a haemorrhagic appearance, others are more gelatinous and grey. Whether these gelatinous polyps have a different pathogenesis is not known.[34, 37]



Figure 63.2 Vocal fold polyp.

Occasionally, a sulcus, mucosal bridge or intracordal cyst is found immediately opposite on the other vocal fold.[38, 39] It is hypothesized that in these cases the resulting disordered vibration and stiffness of the vocal fold make it more likely to damage the other vocal cord causing localized trauma and polyp formation.

Alteration in voice quality and voice complaints will depend on the effect of the mass of the polyp (and any other associated lesion) on vocal fold vibration, its effect on vocal fold closure and the secondary compensatory changes, i.e. increased muscle tension. The patient may complain that the voice is hoarse, has lowered in pitch and cuts out in speech, that they have lost part of the range of the voice and that it is a strain to speak.[40] Very rarely, large polyps can cause difficulty in breathing and episodes of choking.

Polyps can shrink spontaneously or even be coughed up. Voice therapy may provide the patient with coping strategies, preventative advice and help ease symptoms, but is unlikely to result in resolution of the polyp.[41] Any concomitant inflammatory conditions should be treated. Most polyps need removal under a general anaesthetic and a variety of techniques to achieve this have been described. This might be by using laser or cold steel suspension microlaryngoscopic technique (see Chapter 67, Phonosurgery).[42, 43] The aim is to restore the smooth edge of the vocal cord to allow them to close fully and vibrate normally.

Vocal fold nodules

Vocal fold nodules are small bilateral swellings (less than 3 mm in diameter) that develop on the free edge of the vocal fold at approximately the midmembranous portion (**Figure 63.3**). In some cases, particularly in singers, they may be smaller, more pointed and white in colour, reflecting a more superficial response to trauma. They may be associated with microwebs at the anterior commissure in up to 23% of cases. They are of variable size and are characterized histologically by thickening of the epithelium with a variable degree of underlying inflammation.

The exact incidence and prevalence of nodules in the general population is not known, but in various population studies nodules have been shown to be the cause of

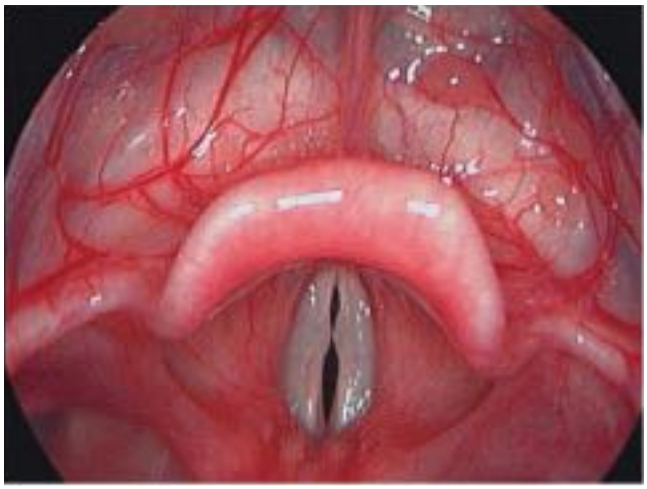


Figure 63.3 Vocal fold nodules.

persistent hoarseness in just under 25% of children and in 6% of adults with voice problems.[44] Higher percentages are found in teachers and singers with voice problems. In children, they are more common in boys than in girls, while in adults they are very much more commonly found in women, particularly under the age of 30.

The aetiology of vocal nodules is not known, but traditionally they are thought to be due to 'voice abuse' rather than overuse. Voice abuse is characterized by forced voice production due to strain in the neck and shoulder region producing a harsh quality to the voice.[45] It may be precipitated by talking for prolonged periods in a loud voice (often above background noise), repeated shouting and/or singing above one's natural range and occasionally repeated coughing and throat clearing. The vocal folds are thought to impact on each other in such a way that the repeated trauma of the midmembranous portions leads to localized swelling and epithelial thickening. Shearing forces may be important and a whiplash hypothesis has also been proposed.[46] Psychological factors, nasal, throat and chest infections, allergies and extraoesophageal reflux are increasingly being recognized as playing an important part in the aetiology of vocal nodules.[46–49] Nodules disappear spontaneously in boys with the relatively large growth of the larynx in puberty.[44] In girls, they may persist into early adulthood.

The voice quality is often husky and breathy, worsening with voice use and often associated with perilaryngeal discomfort or throat soreness on phonation. The voice may become a little deeper in pitch and associated with voice breaks, particularly at the higher end of the range of the voice. The vocal folds are usually hourglass in appearance with often only the nodules making contact at the midmembranous zone.

There is no good evidence on which to base the treatment of vocal fold nodules. Nodules may develop after the individual has been projecting and using their voice more than usual and often settle spontaneously once the demand on the voice returns to 'normal'. If nodules are not causing significant voice problems, they should be left alone. Aggravating factors, such as inadequate vocal fold lubrication, allergies, infections and extraoesophageal reflux, should be treated to reduce their irritant effects. In the UK, the mainstay of treatment for persistent vocal nodules is voice therapy with the aim of modification of lifestyle and vocal behaviour, providing information and guidance on voice care, producing the voice more effectively with less strain and coping strategies. Not infrequently the voice and voice function improves, but the nodules persist. Some argue that complete and rapid return of voice function is only possible if the nodules are excised. Others would reserve surgery for those who fail voice therapy and remain symptomatic. Most would agree that a significant number of nodules recur if surgery is performed without voice therapy either pre- or post-operatively.[50] If surgery is performed, the aim must be precise excision of the nodule alone with no exposure or damage to the underlying ligament.[43, 51]

Pseudocysts

The exact definition of a pseudocyst varies between authors. Some define it as a lesion that differs from cysts and polyps in that it has no cyst wall and is filled with serous fluid, having an appearance similar to that of a blister. Others have defined it as localized Reinke's oedema, which may indicate the presence of underlying paresis.[52] The exact aetiology is not known, but is probably phonotrauma. The initial management of a pseudocyst is by behavioural therapy. Surgical excision might be necessary in cases that did not resolved with speech therapy.[53]

Reinke's oedema

Reinke's oedema is a term used to describe the vocal folds when they become chronically and irreversibly swollen (**Figure 63.4**). Other terms for the condition include:

- polypoid vocal cord, polypoid degeneration or polypoid hypertrophy; cordal polyposis or polypoid corditis
- chronic oedema of vocal folds
- pseudomyxoma or pseudomyxomatous laryngitis
- smoker's larynx.



Figure 63.4 Grade 4 Reinke's oedema.

It occurs almost exclusively in moderate to heavy smokers, although the exact role of smoking in inducing these changes is not known.[54] Some studies have also suggested that voice strain and extraoesophageal reflux may also play a part in its development, although the importance of these other factors is not clear. Hypothyroidism may be found as a concomitant feature in some cases, but it is not thought to be an aetiological factor. The epithelium shows non-specific changes and the basement membrane layer is usually thickened. In Reinke's space, there are lakes of oedema, extravasated erythrocytes and thickening of the walls of the subepithelial vessels.

The true prevalence of Reinke's oedema is unknown. It is probably one of the most common conditions to affect the vocal folds in smokers and it is very likely that many people with this condition do not seek medical attention. A meta-analysis of 1538 cases showed that men and women are affected more or less equally, although the pitch-lowering effects on the voice are more conspicuous in women. Patients most commonly seek a medical opinion between the ages of 40 and 60 years of age.

Patients with even quite severe Reinke's oedema may have no complaints about their voice or problems with voice use. The most common symptoms are:

- deepening of the pitch of the voice with women often being mistaken for a man, particularly on the telephone
- gruffness of the voice
- effortful speaking
- an inability to raise the pitch of the voice
- choking episodes
- other symptoms associated with extraoesophageal reflux.

The diffuse lesions of the membranous part of the vocal fold are bilateral in 62–85% of cases, although they may be asymmetrical. Typically the vocal folds are grey or yellowish in colour with prominent superficial vessels. Alternatively, the oedematous folds may appear diffusely red when coexistent extraoesophageal reflux should be suspected. Leukoplakia is uncommon but may be due to hyperplasia, dysplasia or very rarely carcinoma in situ. In severe cases the vocal folds look like bags of fluid that flop up and down through the glottis with respiration. The severity of the swelling is best judged on deep inspiration and is frequently underestimated if an assessment is made solely on phonation as the oedematous tissue bunches up on the superior surface and into the ventricle. A severity grading system has been proposed and validated by Tan et al. (**Table 63.3**).[55] There may be a variable degree of associated increased muscle tension present.

The decision to treat a patient with Reinke's oedema depends on their symptoms, the severity of the oedema and the presence of leukoplakia. In most cases, conservative measures, such as reassurance, an explanation of their condition and vocal hygiene advice, including smoking cessation, should be tried initially. Hypothyroidism, upper airway infections and allergies and extraoesophageal reflux should be treated to reduce the throat symptoms associated with these conditions. The role of voice therapy is controversial but may be indicated if vocal hygiene issues and excessive MTD are prominent in a well-motivated patient. It certainly has a role in restoring voice function after surgical treatment.

TABLE 63.3 Grading of Reinke's oedema

Grade	Appearance
1	Marginal edge oedema
2	Obvious sessile swelling, thrown over vocalis muscle during phonation
3	Large bag-like swelling, filled with fluid
4	Partially obstructing lesion, medial borders in contact along most of length

Surgical treatment should be considered when:

- leukoplakia is present and a histological diagnosis is required
- gross Reinke's oedema is present causing choking episodes or airway compromise
- pitch elevation of the voice is the main requirement of treatment.

Other symptoms may not necessarily be helped by surgery and there is the potential for making patients worse by causing scarring or an irregular edge to the vocal fold. Patients must be aware that after surgery:

- friends and relatives may not recognize them by their voice
- the singing voice may be permanently altered
- speaking may be more effortful for up to 1 year (or occasionally permanently), particularly if excessive mucosa is removed due to stiffness from scarring and anterior web formation
- the voice seldom returns to 'normal', but is generally of better quality
- the Reinke's oedema is likely to return within 2 years if the patient continues to smoke.[56]

The principles of surgery for Reinke's oedema include:

- reducing the bulk of the mucosa (mass per unit length) of the vocal fold
- obtaining a straight mucosal edge, i.e. avoiding leaving small deposits of the myxoematous material behind
- avoiding damage to and exposure of the underlying ligament, thereby reducing the chances of scarring and web formation.

'Reduction glottoplasties' can be performed with phonosurgical instruments or one of the new generation of microspot lasers. KTP laser treatment of Reinke's oedema may be performed in the outpatient department under local anaesthesic via a channelled endoscope.[57] Care should be taken not to remove excised epithelium and not to overheat the vocal cord ligament as this may result in a permanent scar and hoarseness.[58] The myxoematous

material from the superficial lamina propria layer is aspirated, removed with forceps or vaporized and the epithelial edges apposed following excision of redundant mucosa as necessary. Good results from unilateral treatment have been reported with patients often electing not to have further surgery on the second side. Post-operative voice therapy may be required.

Endocrine causes

Hyperthyroidism has been associated with increased anxiety, hoarseness and tremor affecting the voice. The vocal folds have been reported as looking 'hypervascularized and hyperkinetic'. Hypothyroidism is associated with:

- hoarseness
- deepening of the pitch of the voice
- voice fatigue and weakness
- dryness of the throat
- slow and hesitant speech.

Small prevalence studies have not shown an increase in prevalence of biochemical hypothyroidism in patients with Reinke's oedema, but one uncontrolled study suggested that subclinical hypothyroidism may be more prevalent. Although the vocal folds are often described as being oedematous in hypothyroidism, there is little histological evidence to support myxoedematous infiltration of the vocal folds or muscles.

Abnormalities of endocrine function, in particular related to the thyroid and sex hormones, can have varied effects on the voice and voice function. Most have not been studied in great detail and are beyond the scope of this chapter. Of note are the effects of androgens and androgenic drugs, such as Danazol, which cause irreversible enlargement of the female larynx with the consequent effects of deepening of pitch. The fundamental frequency of the voice is lowered and the high tones lost at the menopause.[59]

Autoimmune diseases of the larynx

Laryngeal manifestions of autoimmune diseases are not uncommon and have been described previously. Examples are cricoarytenoid fixation, mucous inflammation, subglottic stenosis, vasculitis, laryngeal edema, vocal fold paralysis, infection, or vocal fold lesions such as vocal fold rheumatoid nodules and bamboo nodes.[60–63]

Bamboo nodes

Bamboo nodes are round pale yellowish lesions found in the mid third of the membranous vocal cord (**Figure 63.5**). It is because of their appearance that they are called bamboo nodes. These patients usually present with hoarseness. A blood test to exclude autoimmune diseases is mandatory if the patient is not already diagnosed with an autoimmune disease. Examples of autoimmune conditions associated with bamboo nodes are rheumatoid arthritis, systemic lupus erythromatous (SLE), Sjögren's syndrome, Hashimoto thyroiditis and systemic sclerosis. The blood test may reveal elevations in the sedimentation rate, rheumatoid factor, Sjögren's antibodies and antinuclear antibody titres, as well as hypergammaglobulinemia.



Figure 63.5 Bamboo nodes.

The diagnosis of a bamboo node is made from history and clinical examination. A videolaryngostroboscopy is essential to examine the vocal cords and the mucosal wave. This will give an indication of the effect of the node on the vocal cord vibration.

Conservative management is by speech therapy. A systemic steroid may be helpful but patients may not tolerate long-term treatment due to the side effects.

Steroid injection may be necessary in cases that have failed to respond to conservative management alone. This should not be given more than three times a year so as not to develop atrophy of the vocal cord.

Resistant cases may need phonosurgical excision of the nodes. Care should be taken not to damage the vocal ligament, which can lead to a permanent scar and hoarse voice. For this reason, this type of surgery should be done under a high microscopic magnification during a suspension microlaryngosocopy.[64, 65]

Cysts, sulci, mucosal bridges and vergeture

Cysts are found less frequently than polyps and nodules, and sulci and mucosal bridges even less so. There are two primary types of cyst: a mucus retention cyst and an epidermoid cyst. Both cause the voice to be constantly hoarse, which may worsen with use, with varying degrees of roughness and breathiness depending on the interference with vocal fold vibration and closure. Part of the vocal singing range may be affected, with pitch breaks or cutting out altogether.

A mucus retention cyst (**Figure 63.6**) is thought to arise from a blocked minor salivary gland, possibly secondary to phonotrauma or inflammation. It is lined by cuboidal or low columnar epithelium and can be associated with oedema and fibrosis in Reinke's space. It is usually unilateral and is found on the free edge of the vocal fold or



Figure 63.6 Mucus retention cyst.

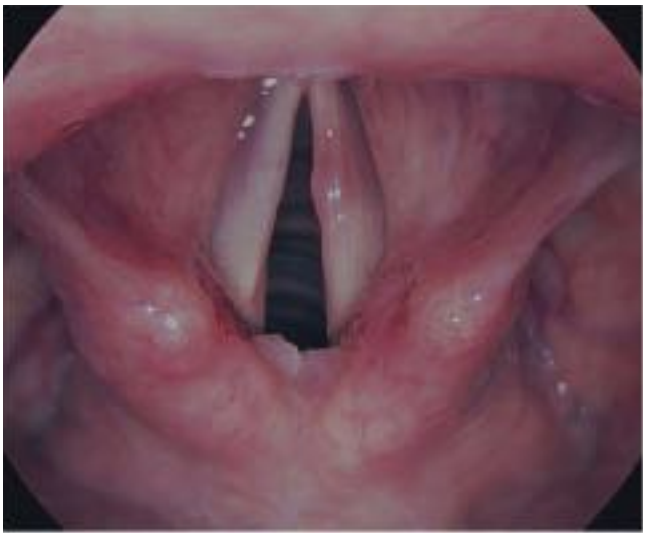


Figure 63.7 Epidermoid cyst.

can arise in the ventricular fold (false cord) (**Figure 63.6**). In the vocal fold they should be suspected in cases of asymmetrical nodular swellings (cyst plus contact nodule) and can be difficult to distinguish from polyps on laryngoscopy. Stroboscopy can help in the differential diagnosis, but frequently a definitive diagnosis can only be made on microlaryngoscopy and by performing a cordotomy.

Ventricular cysts need to be differentiated from other tumours (see Chapter 14, Tumours of the larynx). They can affect the voice by prolapsing on to the vocal fold interfering with vibration and causing secondary hyperfunction.

Epidermoid cysts (**Figure 63.7**) are lined by squamous epithelium and are filled with keratin and cholesterol debris. There is often an inflammatory exudate in the surrounding Reinke's space. It is unclear how these cysts develop, but various theories have been proposed including a metaplasia in a long-standing mucus retention cyst, microinclusion of epithelium from surface trauma or some defect in epithelialization during development (congenital or dysembryoplastic theory). They are thought to arise as a result of voice abuse and misuse. Large cysts cause a yellowish/white bulge within the vocal fold, but smaller, deeper cysts may only be suspected by the presence of localized absence or reduction in the mucosal wave on stroboscopy or abnormal blood vessels over the cyst or the appearance of unilateral or bilateral chronic laryngitis. The diagnosis may only be confirmed at microlaryngoscopy and cordotomy in these cases.

The term 'sulcus' has been used to describe different entities in the literature. Two entities can be distinguished: sulcus vocalis and mucosal bridge.

- A **sulcus vocalis** is best used to describe a localized invagination of the mucosa of varying depth[66] (**Figure 63.8**). These may be described as 'open cysts', which may describe their aetiology. The justification for this is that they are commonly found in association with epidermoid cysts and it would seem logical that trauma to the neck of a cyst would lead to it widening and discharging its contents.

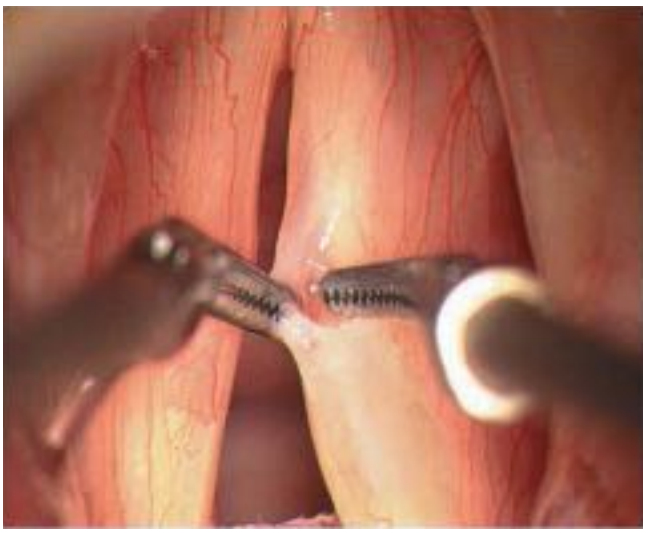


Figure 63.8 Sulcus vocalis. (With thanks to Romain Perouse.)

- Sulcus vocalis has been classified into three types:
  - **Type 1: Physiologic sulcus.** This is a superficial longitudinal depression of the epithelium not beyond the superficial lamina propria. The vocal ligament is not involved. Videolaryngostroboscopy may only show mild mucosal wave abnormally and the voice is not affected significantly. Treatment for this should be conservative with speech therapy and sometimes antireflux medication.
  - **Type 2a: Sulcus vergeture** (**Figure 63.9**). This is more extensive invagination extending into the vocal ligament with some loss of superficial lamina propria. Reinke's space exists superolaterally and inferomedially to the vergeture. They are thought to result from a congenital failure of development of Reinke's space as they are commonly apparent at puberty and can be familial. There is moderate mucosal abnormality on videolaryngostrobostoscopy and may have moderate dysphonia.



Figure 63.9 Sulcus vergeture.



Figure 63.10 Mucosal bridge. (With thanks to Romain Perouse.)

- **Type 2b: Classic sulcus vocalis or a pouch type.** This is characterized by a focal pit that extends beyond the vocal ligament into the thyroarytenoid muscle. The is marked loss of superficial lamina propria. Video laryngostroboscopy shows significant mucosal wave abnormality with loss of vibratory pattern and patient may present with severe dysphonia.

- A **mucosal bridge** (**Figure 63.10**) may also be found in the presence of sulci and epidermoid cysts. This rare finding is thought to arise by the rupture through of the deep aspects of two sulci or cysts to form a tubed pedicle of mucosa.

Patients with sulcus vocalis and mucosal bridges present with variable degrees of dysphonia and roughness and breathiness, depending on the number of lesions, position and depth of the sulcus, the effect on glottal closure and degree of associated inflammation and MTD. Patients with sulcus vergeture often have a high-pitched monotone, weak (aesthenic), breathy and strained voice which is an effort to produce.

Patients with vocal fold cysts should be given a trial of voice therapy, particularly when symptoms are relatively mild. Many will require surgery but this must be done precisely, preserving the overlying mucosa as much as possible. It is important to avoid leaving part of the wall behind, which will result in a recurrence or cause localized scarring and poor voice results. This is more so for mucus retention cysts as dissection of the thin wall is more difficult. Post-operative voice therapy helps patients to restore vocal function and improvement may continue for up to 9 months. There may occasionally be problems with glottal closure following excision of large cysts and fat or collagen medialization may be of benefit. Ventricular fold cysts should be removed to confirm the diagnosis. There is the potential that they can cause airway obstruction if large or they become infected. Complete sharp dissection of the cyst with microlaryngoscopy instruments or with the laser is the treatment of choice.

The treatment of both types of sulci is difficult and the results variable. If surgical treatment is required for sulcus vocalis, careful dissection of the pocket off the ligament is required. The difficulty is in defining the plane between the base of the sulcus and the ligament and avoiding excessive resection of the mucosa and damage to the ligament.[67] Sulcus vergeture may be best treated by bilateral medialization procedures rather than attempted resection of the vergeture, which is technically extremely difficult.[68]

The ongoing challenge in the management of sulcus is that no single treatment modality is superior to others and no sufficient evidence for matching a given treatment to a given patient is yet available.[69]

Laryngeal hyperkeratosis

Laryngeal keratosis is an inflammatory disease of the epithelium of the vocal cords due to chronic hyperplasia and hyperkeratosis of the laryngeal mucosa with the resultant hyperkeratosis of the vocal cord epithelium. The aetiology is non-specific but it may have association with smoking, alcohol and reflux. The predominant symptom is hoarseness.[70]

The appearance is of white plaques, which can be confluent or patchy (**Figure 63.11**). Often the terminology is interchangeable with leukoplakia. *Leukoplakia* is a Greek word for a white plaque that cannot be simply scraped off. A histological diagnosis is mandatory to exclude neoplasia or dysplastic lesion. Laryngeal hyperkeratosis may appear easy to excise but laryngologists know that this condition is notorious for recurrence.

The management is by suspension microlaryngoscopy and surgical excision for histology. This condition may be precancerous, hence a biopsy is required. However, the treatment should be a conservative surgical approach to improve or maintain voice. Cold steel and laser therapy have been used but there is anecdotal evidence that an angiolytic laser such as the KTP laser offers longer-term cure.



Figure 63.11 Laryngeal hyperkeratosis

Ackermann's tumour (verrucous carcinoma)

Ackermann's tumour is a slow-growing variant of squamous cell carcinoma that does not metastasize. It can cause a diagnostic and treatment challenge for both the histopathologist and the otolaryngologist. Macroscopically it may be hard to distinguish from hyperkeratosis. It has a typical exophytic appearance (**Figure 63.12**).

Although radical treatment such as laryngectomy is not necessary, a complete endoscopic excision is recommended to prevent recurrence. This tumour is less radiosensitive than others but extensive tumours may be treated with radiotherapy instead of radical surgery.



Figure 63.12 Ackermann's tumour (verrucous carcinoma).

Microvascular lesions

Microvascular lesions (varices or capillary ectasias) are collections of abnormally large and weakened vessels that are most commonly found (83%) on the superior or medial aspect of the midmembranous portion of the vocal folds (**Figure 63.13**). They are most frequently seen in professional vocalists (including singers) and are thought to arise secondary to repetitive trauma, hormonal variations or repeated inflammation. They may occasionally be incidental findings but can result in vocal fold haemorrhage, scarring and polyp formation. The lesions can interfere with the vibratory pattern of the vocal folds, causing a lack of clarity of the voice, vocal fatigue or sudden dysphonia associated with haemorrhage.

Voice and singing therapy, treatment of associated inflammation and occasional precise vaporization or point diathermy of the feeding vessel(s) may be required. Recurrences may still occur after treatment.[71]

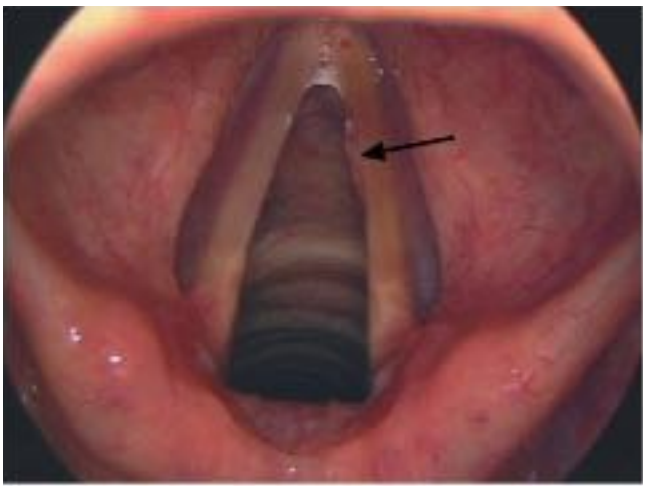


Figure 63.13 Microvascular lesions (arrow).

Neuromuscular causes

Neuromuscular causes are considered in detail in Chapter 54, Neurological disease of the pharynx. Apart from a vocal fold palsy, they are relatively uncommon. The prevalence of vocal fold paresis in dysphonic patients is unknown, but appears to be higher than previously thought if monopolar needle electrodes are used to detect the condition.[72] A palsy or paresis should be considered in any case where the complaint is of effortful phonation, throat discomfort or vocal fatigue with use or where the voice 'cracks'. Perceptually, the voice may sound breathy, unstable or higher in pitch. An obvious laryngeal paresis will show asymmetry of movement on abduction and adduction, i.e. it 'lags behind' the normal side. This asymmetry may only be apparent on prolonged observation using a fibre-optic endoscope and asking the patient to phonate and then sniff repeatedly. More subtle signs are an asymmetry of phase and amplitude of the mucosal wave and apparent bowing on the affected side on stroboscopy.

An effect on the voice may be the first sign of a more general neuromuscular disorder, such as Parkinson's disease, motor neurone disease, multiple sclerosis and myasthenia gravis. Neuromuscular disorders should always be considered in patients where the vocal folds look normal but the pattern does not fit with an MTD or fails to respond to treatment or the dysphonia worsens.

Spasmodic dysphonia is an uncommon and frequently overlooked condition. Traditionally it is classified as adductor, abductor, mixed and tremor and respiratory forms, although further subtypes have been described.[72–74] The adductor form is characterized by a strained/strangled quality to the voice, which cuts out at the onset of phonation, while the rare abductor type (approximately 15%) is characterized by breathy breaks following consonant sounds.[72, 75] Some patients present with a whispery (compensated voice) that is easier for them to use in conversation. Others have a mixed form that becomes more obvious during treatment, as the untreated form often worsens or is complicated by tremor. The spasmodic laryngeal activity can be seen by careful observation with a fibre-optic endoscope during speech.

The mainstay of symptomatic treatment remains botulinum toxin injection into specific intralaryngeal muscles, although the results are not always predictable and poorer for those with the abductor form and those with tremor.[72, 76–79] Improvements in outcome in the future may come with better targeting of the involved muscles. Other surgical treatments for adductor spasmodic dysphonia are now available. These are Isshiki thyroplasty type 2 using a titanium bridge implant to separate the anterior commissure by a few millimeters.[80, 81] Selective laryngeal adductor denervation–reinnervation surgery (SLAD–R),[82, 83] CO_2 laser thyroarytenoid myoneurectomy.[84, 85]

Muscle tension dysphonia or 'functional dysphonia'

OVERVIEW

Muscle tension imbalance causing MTD is one of the biggest causes or contributors to voice disorders. Although it is often a 'diagnosis of exclusion', i.e. the 'the vocal folds look and move normally', it is often present with inflammatory, structural and neurological conditions as laryngeal muscles try to overcome a deficiency in the voice-producing mechanism, such as poor respiratory function, impairment of normal vocal fold vibration or nasal blockage affecting resonance.[86] In addition, MTD can lead to trauma and structural changes in the vocal fold mucosa, for example in some cases of nodules. It is for the laryngologist and voice therapist to agree a treatment plan with the patient in these more complex cases.

MTD is therefore a group of conditions characterized by an imbalance of the synergist and antagonist muscles affecting the vocal fold position and tensioning relative to one another and also the position of the larynx relative to the rest of the vocal tract (**Figure 63.14**). Usually one or more sets of muscles is hyperfunctional, giving recognizable patterns of clinical presentation and laryngeal appearance.[87, 88] It is now thought that previously described hypofunctional states either are 'end stages' of hyperfunctional laryngeal activity or represent an underlying paresis.[89] The hypotheses are:



Figure 63.14 Muscle tension dysphonia. This is just one of the many patterns of muscle tension seen.

- that chronic imbalance of muscle pull, for example, of the cricothyroid muscle can lead to irreversible joint damage and ligament stretching giving a flaccid bowed appearance to the vocal folds
- that a viral neuropathic paresis has developed causing hypotrophy of the thyroarytenoid muscle and consequent poor glottal contact and secondary compensatory hyperfunction.[90] The evidence to support this comes from electromyographic studies.[72]

True hypofunctional cases do exist in neurological conditions such as myasthenia gravis, Parkinson's disease and motor neurone disease, but they are relatively uncommon.

There are multiple primary aetiologies of MTD[7, 29, 88] including:

- stress, anxiety and depression
- conversion disorders
- postural and breathing problems
- poor vocal hygiene
- talking in poor acoustic environments or above background noise for prolonged periods at work or socially
- exposure to excessive environmental dust, smoke or fumes.

The degree of dysphonia is variable, ranging from an intermittent problem related to a particular voice task (e.g. teaching) to severe and constant hoarseness. Other symptoms include:

- pitch of the voice may be too high or too low and reduced in range
- a sensation of tightness, constriction or lump in the throat
- effortful voice production
- discomfort on speaking or singing
- vocal fatigue.

The variability in the voice quality may be apparent during the consultation or with probe voice therapy. The laryngeal patterns on laryngoscopy have been classified into six main groups,[91] although some of these features may also be seen in the normal population.[92] Palpable increased tension and often tenderness in the suprahyoid, thyrohyoid and cricothyroid muscles may also be found, although these findings are not always consistent.[91, 93, 94]

Treatment, if required, consists of identifying precipitating causes and treating as appropriate, such as:

- vocal hygiene, dietary and lifestyle advice[29]
- voice therapy targeted at specific muscle groups[95]
- laryngeal manipulation[96]
- behavioural therapy[97]
- medical treatment, e.g. of extraoesophageal reflux.

SPECIFIC MUSCLE TENSION DYSPHONIAS

Puberphonia 'adolescent transitional voice disorder' or 'mutational falsetto'

Normally at puberty the voice drops by an octave in boys, but only three to four semitones in girls. In boys, the transition takes 18 months to 3 years and is usually completed by the age of 14. This voice change in puberty is accompanied by pitch instability and register breaks. The voice appears to be too high in pitch for the individual's age and sex and is often described as 'never broken'. The voice is often momentarily deeper on non-phonatory tasks, such as laughing or coughing and this is a key indicator of the condition. Even if it is recognized that the individual has 'two voices', i.e. higher and lower pitched, the latter is not perceived, as their voice is abnormal so consequently not used. The voice can tire and be effortful to produce on shouting or when projected. Occasionally, some patients experience pain and discomfort in the supralaryngeal region due to the elevated position of the larynx. There is often some associated psychological distress as the boys are frequently ridiculed and taunted because of their abnormal voice and inferred effeminacy.

As part of the normal pubertal changes, the total length of a boy's vocal cords increases by as much as 60%, reaching 17–23 mm in the bass voice with a relative increase in the ratio of the membranous and cartilaginous parts of the vocal cord. The thyroid cartilage virtually doubles in size and the dimensions of all other aspects of the laryngeal anatomy increase proportionally. The epiglottis changes from an omega shape to a more flattened shape. It also increases in size and elevates. The mucosal lining of the vocal cord becomes stronger and thicker. The cricothyroid muscle increases in bulk and strength to enable the thyroid cartilage to tilt forward for head or falsetto voice.

In puberphonia, the larynx tends to be held high in the neck, thereby shortening the vocal tract.[97] The cricoid cartilage is usually tilted backwards and the vocal folds remain too lax and limited in their ability to adjust to demands in change in tension and vibrational frequency. The vocal folds are stretched and thin with minimal mucosal waves. The cricothyroid remains excessively contracted. Acoustic analysis shows a speaking fundamental within the normal female range, intensity and harmonics-to-noise ratios within normal limits and a reduced contact quotient on electrolaryngography.

It is important to exclude organic conditions, such as endocrinological abnormalities, vergeture and scarring. Although most who present are keen to improve their voice, those who attend at the behest of family and friends and who are not concerned by their voice generally have a poor prognosis regarding resolution.

The treatment of choice is voice therapy,[97–99] although occasionally botulinum toxin injections into the cricothyroid muscles have been shown to be effective in resistant cases. Relaxation thyroplasty type 3 may be indicated in cases that failed speech therapy.[100]

Presbylaryngis

The ageing voice has certain characteristics.[101, 102] In males, the mean fundamental frequency tends to rise after the age of 50 and the voice is often perceived as high-pitched, thin and reedy in old age. In women, the mean fundamental frequency tends to decrease with age. Voice change may be related to the general fitness, voice use and previous training of the individual. The changes are related to ossification of the laryngeal skeleton, arthritic changes in the cricothyroid and cricoarytenoid joints, reduced muscle volume with a preferential loss of type I (slow contracting) muscle fibres, an increase in density of collagen deposition and decreased hyaluronic acid in the lamina propria, associated with a reduction in fibroblasts and atrophic changes in the epithelial layer. The net effect is stiffened, bowed, atrophic-looking vocal folds.[103] Other factors that will affect voice quality are laryngeal position, vocal tract atrophic changes and loss of lung capacity. Patients may just require an explanation of their voice problem and be happy with the exclusion of malignancy. If treatment is indicated, vocal care and voice therapy with the aim of building up the laryngeal musculature and improving vocal control are most usually offered.[104–106] Injection medialization procedures using fat, hydroxylapatite[107] or bilateral (modified) thyroplasties have been used with good effect, although the results with fat are less predictable.

BEST CLINICAL PRACTICE

- ✓ Best clinical practice is achieved by accurate clinical diagnosis with high-quality imaging techniques and having a patient-focused approach, taking into consideration their vocal requirements and concerns.
- ✓ A multiprofessional team approach allows cost-efficient, multidimensional assessment and targeted planning and delivery of treatment.

FUTURE RESEARCH

- There is a real need for multicentre studies to determine the best treatment options for almost all aspects of voice disorders.
- Fundamental questions need to be answered as to the role of inflammation, in particular extraoesophageal reflux and paresis in the aetiology of voice disorders.
- The management of sulcus vocalis and vocal cord scars remains a dilemma. Often the diagnosis is difficult in the outpatient setting and numerous cases are either misdiagnosed or missed completely as result. There is a need for a collaborative study on what is the best approach to diagnosis and management of this rare but not uncommon condition.

KEY POINTS

When assessing a patient, it is important to consider the following questions.

- Which one or more of the following four conditions is present?
  - inflammatory causes
  - structural or neoplastic causes
  - neuromuscular causes
  - muscle tension imbalance (dysphonia).
- Is there any suspicion of a malignant or premalignant condition?
- Which is/are the predominant condition(s) causing the symptoms related to the voice complaints? For example, the treatment of extraoesophageal reflux may be more effective in relieving the patient's symptoms in Reinke's oedema than surgical debulking.
- Which is or was the primary condition and which are secondary or compensatory? The symptoms and signs of a secondary MTD may mask the presence of an underlying paresis, for example.
- Will treating the 'easily treatable factors' improve the patient symptoms enough to either reverse structural laryngeal changes or improve the laryngeal biomechanics sufficiently for adequate functional voice production, i.e. the voice may not be perfect, but they can live with it?
- Could the potential complications of an intervention, particularly surgical treatment, create more problems than they help?

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CHAPTER 64

FUNCTIONAL DISORDERS OF THE VOICE

Paul Carding

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SEARCH STRATEGY

The information in this chapter can be explored more extensively by undertaking a Medline using the following keywords: functional dysphonia, non-organic dysphonia, muscle tension dysphonia, psychogenic dysphonia, vocal misuse and vocal strain.

INTRODUCTION

A functional voice disorder applies to an alteration of voice quality where there is no structural or neurological laryngeal pathology or where the dysphonia is disproportionate to the pathology detected. Nomenclature is problematic in this area and there are many synonymous and similar diagnostic labels in use, including (most commonly) 'functional dysphonia' and 'non-organic dysphonia'. These terms are generic and indicate characteristics of a syndrome rather than a specific diagnosis. Several key authors have defined several subcategories which more accurately reflect the underlying pathogenesis[1–4] and these will be discussed below. Functional disorders of the voice represent by far the commonest presentation to voice clinicians, accounting for at least 50 000 new cases per year in the UK.[5, 6] The impact of this condition is considerable: it is known to affect communication in all contexts, and is related to impaired personal and work relationships, low self-esteem and reduced quality of life.[6–8] In addition, people with functional dysphonia also suffer from increased levels of anxiety, depression and poor general health.[6, 9, 10]

It is also important to note that there is an overlap between 'organic' and 'functional' voice disorders and that they do not represent dichotomous disorders.[11] A number of benign vocal pathologies (e.g. vocal nodules, oedema of the lamina propria, contact granulations) are attributable to vocal hyperfunction, voice misuse and poor voice technique.[12, 13] Similarly, aberrant phonatory physiology viewed on endoscopic examination (e.g. bowing of the vocal folds, supraglottic constriction) may also be a consequence of vocal hyperfunction and poor technique.[12, 13]

THEORETICAL PERSPECTIVES

Most contemporary authors have accepted that functional disorders of the voice might usefully be divided into two different subcategories: 'muscle tension' dysphonia and 'psychogenic' dysphonia.

- **Muscle tension dysphonia (MTD)** is primarily the result of vocal misuse or poor vocal technique.[1, 2] In these cases, psychological factors are considered negligible or secondary. Furthermore, Morrison and Rammage[4] describe different types of MTD (based on endoscopic appearance) but with the understanding that they all arise from laryngeal muscle tension during phonation. They further suggest that psychological factors are important only insofar as they influence autonomic arousal.
- **Psychogenic dysphonia** is marked by loss of vocal control associated with 'disturbed psychological processes' (such as stressful life events at onset, anxiety or depression and actual conversion).[2] Some authors[1] consider psychogenic dysphonia as an example of classical (Freudian) conversion. Butcher et al[1] detail three types of psychogenic conversion dysphonia:
  - **type 1:** classical hysterical conversion dysphonia
  - **type 2:** cognitive behavioural conversion

- **type 3:** 'habituated conversion', in which the suppressed conflicts of a cognitive behavioural conversion have been largely resolved, but the vocal symptoms and musculoskeletal tension persist as a matter of habit.

It is a common clinical experience to see a mixed picture where some elements of both muscle tension and psychogenic dysphonia combine to make a function voice disorder which is complex to treat.[4] It is also recognized that the relative contribution of these factors may change for a patient over time.

PATHOGENESIS OF FUNCTIONAL DYSPHONIA

There are several ways to consider the pathogenesis of functional voice disorders.

One approach is to consider the 'voice capability' curve model. It is possible to conceive that the voice capabilities of the whole population would provide a Gaussian (normal) distribution (**Figure 64.1**).

Most speakers would fall into the blue area where their voice capabilities are average but perfectly adequate for their personal, occupational and social needs. A smaller number of the population are likely to have exceptional vocal capabilities (red area). These individuals are likely to have the following attributes:

- maximally flexible and responsive laryngeal structures – this will result in quasi-periodic vocal fold vibration with good amplitude and will produce an extensive dynamic range of both frequency and amplitude[14]
- patent oral, nasal, pharyngeal and laryngeal cavities and an ability to manipulate their relative dimensions to resonate the different harmonics of the sound source signal[34, 40, 43] – this will result in a voice which is appropriate 'timbre' and will facilitate good voice projection[15]
- excellent control of pulmonary function to 'excite' vocal fold vibration at the minimal phonation threshold and to maintain consistent transglottal airflow through different vocal tasks[16]

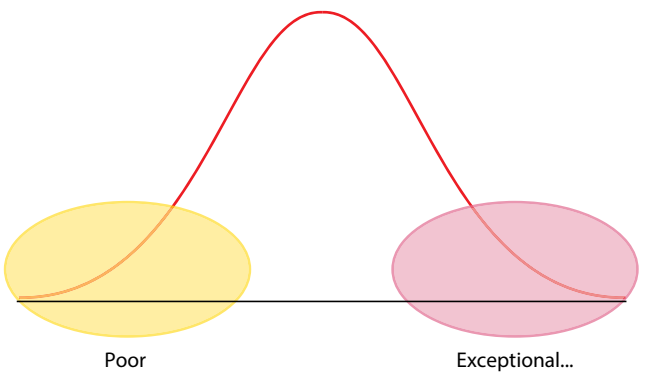


Figure 64.1 Voice capability.

- superior vocal technique (coordination of the first three attributes above) enabling smooth transition between different modalities of voicing and different vocal tasks without undue deterioration or fatigue[17]
- excellent paralinguistic features (speech rhythm, speed and vocal intonation) (see Chapter 60, Voice and speech production)
- superior auditory skills to constantly monitor vocal output, to maximize vocal effect and to detect any adverse voice quality changes.

Conversely, some speakers will have poor vocal capability and, hypothetically, these patients are more vulnerable to developing a functional or muscle tension disorder of the voice. These speakers are likely to have the following attributes:

- inflexible laryngeal structures with restricted vibratory amplitude and a limited dynamic range for both frequency and amplitude
- limited natural vocal resonance
- poor coordination of airflow for voice production
- limited awareness of vocal technique or ability to adapt vocalization depending on the task
- poor paralinguistic features
- limited auditory skills and auditory awareness of their own vocal characteristics.

It follows that people with limited vocal skills and capability are more likely to develop voice problems. This may be especially true if they experience a period of ill health, adverse life events or large vocal demands, for example. These additional factors are explored more fully below.

The more common approach to understanding the pathogenesis of functional voice disorders is to describe a constellation of predisposing, precipitating and perpetuating risk factors.[13, 18, 19] A recent review[19] stated that these multiple etiological factors can be categorized into three subgroups: vocal misuse and abuse, psychological and/or personality factors,[10, 20] and compensatory vocal habits for underlying laryngopharyngeal infection or disease. Similarly, other authors[13, 18] have identified four central tenants of MTD: gastro-oesophageal reflux, high personal stress levels, excessive voice use, and excessive vocal loudness demands. Clearly, not all of these factors need to be present in every case, and the relative contribution of each factor will vary between patients. Therefore, while the exact nomenclature may vary, it is common to conceive MTD schematically, as shown in **Figure 64.2**. It is important to note that previous authors have not discussed auditory skills in their explanatory models of functional dysphonia.

Deary[21] provides valuable further insight into these predisposing, precipitating and perpetuating factors and compares them to similar findings in other clinical areas of medically unexplained symptoms. He concludes that functional dysphonia appears to bear 'a striking resemblance to other medically unexplained conditions in terms of what

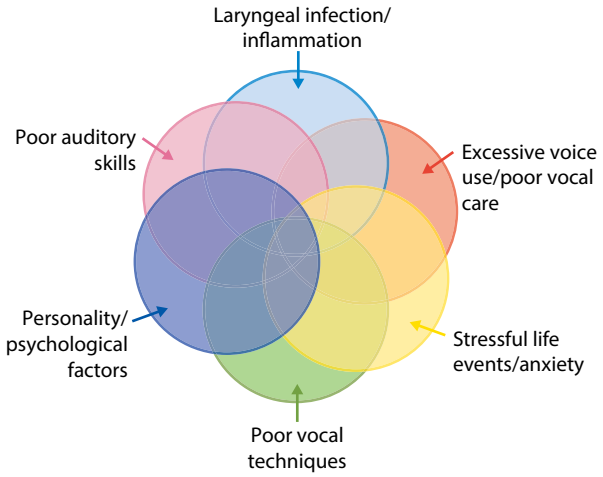


Figure 64.2 Predisposing, precipitating and perpetuating factors in functional dysphonia.

starts, triggers and maintains it'. Furthermore, he suggests a patient profile which is likely to increase the susceptibility for functional dysphonia.[21] This profile includes:

- a vocally demanding occupation[22]
- an abusive childhood[7]
- a 'distress-prone' and/or neurotic personality[23]
- a 'perfectionist' personality[24]
- a series of life events prior to onset[25]
- a history of fatigue.[24]

The literature would suggest that high vocal demand remains the most significant 'risk' factor for functional dysphonia. There are many studies that indicate the high prevalence of professional voice users among voice clinic attendees.[18, 26] While some authors remain entranced by the Freudian notion that the lack of voice has symbolic significance,[1–3] it is more likely that the voice is simply the vulnerable point (due to excessive demand) that breaks first in a person who is generally stressed and unwell.[21]

In conclusion, functional dysphonia is a diagnosis by exclusion (of pathology). However, it is a generic term that requires further investigation and analysis. A full understanding of the nature of an individual's functional voice disorder can only be determined by a detailed and comprehensive case history and interview. Appreciating the relative balance of the predisposing, precipitating and perpetuating factors for any one individual is paramount to successful treatment.

TREATMENT

There is strong evidence that voice therapy by a specialist speech and language therapist is a highly effective treatment for functional dysphonia. The objectives of voice therapy for this condition are twofold: to return the patient's voice to normal (or best possible voice within their anatomical and physiological capabilities) and to satisfy the patient's occupational, social and emotional vocal needs.[12, 27, 28] Voice therapy generally consists of a combination of indirect and direct therapy approaches. Direct therapy involves specific, targeted exercises to control and coordinate the various aspects of the vocal system.[28–34] Indirect voice therapy concentrates on helping the patient manage the contributory and maintaining aspects of the voice disorder and includes patient education, voice care advice, stress management and general relaxation.[28–34] **Table 64.1** lists typical direct and indirect voice therapy techniques for functional dysphonia.

A Cochrane review in 2009,[5] which reviewed articles up to 2007, stated that there was good evidence of the benefits of voice therapy for patients with functional dysphonia (six studies met their inclusion criteria; (total n = 163, controls = 141). Only randomly controlled studies that included patient-reported outcome measures (PROMs) were selected for detailed review. Three studies support a combination of direct and indirect voice therapy, and there is some evidence that indirect therapy alone is effective for particular patients.[5] A further review published in 2011[46] describes additional strong evidence for voice therapy intervention for functional dysphonia as well as an acknowledgment of the need to measure outcome from a multidimensional perspective. A number of recent treatment effectiveness studies have published details of voice therapy content.[47–52]

While traditional voice therapy has been shown to significantly improve the voice, there is limited evidence to date of any effect of this approach on the more general well-being of patients.[6] This has led many commentators in the field of functional dysphonia[1, 12, 27, 38, 41] to call for broader issues to be addressed in the treatment of these patients. Given the level of distress that some patients experience, professional psychological interventions may be necessary to augment existing treatment.[21] Roy suggests that, if the key predisposing, precipitating or perpetuating features of the functional dysphonia are not addressed, then relapse is a likely consequence.[41] Several recent studies[44, 45] report promising findings from CBT-enhanced voice therapy effectiveness studies. Treating the distress, along with the voice, could lead to more general and lasting improvement in patients. However, large longitudinal studies are required to examine these complex issues.

TABLE 64.1 Direct and Indirect voice therapy techniques

Direct	Indirect
Yawn–sigh method[31]	Vocal rest[32, 39]
Chewing technique[32, 42]	Patient education[32, 39]
Vocal function exercises[33]	Reassurance and counselling[42]
Airflow therapy[34]	Vocal hygiene programme[32, 38]
Resonance therapy[35]	Auditory training[31]
Deconstriction therapy[36, 37]	Elimination of voice abuse[31, 42]
Easy vocal onset techniques[36, 37]	Vocal diary[31]
Pitch variation and control[34, 39]	Avoidance of laryngeal irritants[39]
Confidential voice therapy[38, 42]	Hierarchy analysis[32]
Accent voice therapy[40]	Voice conservation[32, 39]
Voice skills therapy[17]	General relaxation[39]
Laryngeal manipulation[41, 42]	
CBT-enhanced voice therapy[44, 45]	

KEY POINTS

Functional dysphonia represents the most common presentation of functional disorders to voice clinicians

- There are several subcategories of Functional dysphonia including muscle tension dysphonia and psychogenic dysphonia.
- Functional dysphonia is not dichotomous from organic dysphonia (some untreated functional voice disorder may result in benign organic pathology)
- One way to understand the pathogenesis of functional voice disorder is to consider the voice capability curve model.
- There are a number of predisposing, precipitating and perpetuating factors in functional voice disorders.

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CHAPTER 65

THE PROFESSIONAL VOICE

Declan Costello and Meredydd Harries

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: dysphonia, singer, actor, performer, professional voice user and voice clinic.

INTRODUCTION

What is the professional voice? A broad range of professions are reliant on their voices to conduct their work including teachers, telephonists, telesales workers, lawyers and many others. This chapter concentrates specifically on individuals who rely on their voices, speaking and singing, for performance at either a professional or an amateur level. For a clinician, it can be flattering to be asked to see a famous performer in the voice clinic but it is important to remember that the same standard of professional service is demanded for all patients, whether they are a primary school teacher or a top professional singer in a West End musical.

PARTICULAR PRESSURES AND DEMANDS ON PERFORMERS

Singers, actors and other performers work in an extremely competitive world. An inexperienced performer may feel considerable pressure to take on a role that is outside his or her range, or that places vocal demands beyond where they are comfortable. The hours of rehearsal are often extensive and it is not unusual for there to be up to eight performances in a week, but performers are reluctant to complain about such working conditions. Indeed, performers often continue to use their voices for long periods after they have developed vocal problems, which can compound their vocal pathology as a consequence. The reluctance to consult a laryngologist is exacerbated by a stigma about vocal ill health, in which the performer worries that they will not be given further work if it is perceived that they are 'fragile'.

The members of the voice clinic should be sensitive to all of these demands and the emotional stress that goes alongside them.

HISTORY

Vocal performers are often exquisitely sensitive about subtle changes in their voices and will be able to pinpoint very precisely the nature of their problem. The consultation should start with an open question allowing the patient to explain their difficulties.

The **style of singing** undertaken can have a profound effect on the ability of a performer to sustain their vocal instrument: singing in the musical theatre style, for example, has a tendency to be very vocally demanding, with a high 'closed quotient' (the vocal folds being closed for a large proportion of the vibratory cycle). The same can be said of many styles of rock and pop singing. In the popular music genre, there is the additional problem of the Lombard effect, i.e. the tendency to increase vocal

intensity in response to increased background noise. In the absence of any auditory feedback, singers tend to oversing and generate ever more strained patterns of laryngeal muscle usage.[1]

A change in **repertoire** can have a great impact: it is not unusual, for example, for singing students to be required to change their repertoire from one college term to the next. A change of repertoire requires a change in the set-up of the laryngeal musculature and can lead to vocal problems.

The extent of **vocal training** is an important factor. It is surprising how many young performers have relatively little training and are thrown into rehearsal and performance schedules without adequate preparation. This is particularly true for amateur and semi-professional performers.

Some performing roles require **specific vocal demands**. This might include foreign accents, shouting or other vocal effects. If these gestures are unfamiliar to the performer, or if they are to be sustained for a whole performance, they can lead to unhelpful muscle tension patterns and even vocal fold phonotrauma.

MAINTAINING VOCAL HEALTH

Most performers are aware of the importance of warming up their voices. Warm-up regimes vary from performer to performer, but the aim is to prepare the voice for the performance to follow. For many, this will involve humming exercises, sirening (a glissando sliding of the voice from low to high) and singing scales and arpeggios. These warm-ups should not (at least initially) be performed at full vocal intensity. The aim, as with an athlete warming up before a race, is to encourage blood flow to the muscles, and to encourage flexibility in the muscles and other structures of the vocal tract. The application of good 'vocal hygiene' is of paramount importance.

PSYCHOLOGICAL ISSUES AND PERFORMANCE ANXIETY

Psychological issues are often a major factor in the vocal problems of professional performers. Major life events such as relationship difficulties, bereavement and changes in circumstances can have a profound impact on the patient's psychological well-being, and their vocal problems may be a subtle manifestation of this sort of strain. Delicate and tactful questioning is required to elucidate these factors, without suggesting that the problems are 'all in the mind' of the patient.

Performance anxiety can become a major barrier for singers and actors. For some, the heightened autonomic arousal can act positively but, for others, it can be very destructive. Some performers will require specific counselling and psychotherapeutic interventions to overcome such barriers. Beta-blockers have been used by musicians and athletes to prevent tremor but they have no beneficial effects on the voice and their use should be avoided in vocal performers.[2]

LIFESTYLE ISSUES

Much of the performer's working lifestyle revolves around late nights, meals late in the evening, and much travelling. All of these can lead to fatigue and, particularly the late meals, can exacerbate any problems with laryngopharyngeal reflux.

Frequent flights will have their own effects: the ambient noise in aircraft means that it is often necessary to raise the voice to be heard; performers frequently report that air conditioning has a 'drying' effect on the larynx, so adequate hydration when flying is important; and the closed environment of the cabin allows for easy spread of viral upper respiratory tract infections.[3]

In addition to their performing and travelling activities, social lifestyle factors can exacerbate a performer's problems. Young performers in particular think little of socializing several nights each week. Noisy restaurants and clubs place considerable demands on the voice that can significantly hinder the performer's ability to perform to the best of their abilities.

THE VOICE CLINIC

A professional voice user would expect – indeed, would often demand – to be seen in a clinic with a full range of equipment for diagnosis, which should include a stroboscope. A detailed discussion of assessment of the larynx can be found in Chapter 61, Assessment and examination of the larynx.

It is important that the patient has confidence in the voice clinic they are attending. It is not unusual for laryngologists themselves to have experience of performing, and this allows for a conversation in which the patient feels that the clinician has an insight into the demands placed on them. The use of musical terminology relating to vocal registers and styles will put the patient at their ease and will help the clinician to understand the patient's current problems.

It is common for voice clinics to employ a singing teacher in addition to a laryngologist and a speech therapist. Some clinics also use a psychotherapist and/or a physical therapist.

Voice evaluation

It is often the case that the normal conversational spoken voice in a vocal professional will be unaffected. As discussed above, the vocal professional will more frequently present with subtle problems relating to a certain aspect of their performing voice. It may therefore be useful to ask the patient to demonstrate the particular vocal difficulties they are experiencing by performing part of a song or speech that they find particularly problematic. Detailed evaluation in terms of objective acoustic analysis

(e.g. jitter, shimmer, noise-to-harmonic ratio) is less frequently required.

Physical examination

Palpation of the neck will reveal any neck masses or lymphadenopathy. It will also highlight any muscular tension or tenderness.

Stroboscopic examination of the vocal folds is mandatory: it is only with the benefit of high-quality videostroboscopic equipment that one will gain sufficient detail of the mucosal surfaces of the vocal folds to be able to exclude subtle pathology. Fibre-optic and mirror examination of the larynx are no longer acceptable modes of examination in vocal professionals.

Stroboscopic examination can be performed either with a rigid endoscope (70 degree or 90 degree) or with a chip-tip (distal-chip) flexible endoscope. The details of stroboscopy are discussed in Chapter 61, Assessment and examination of the larynx, but it is worth bearing in mind the biomechanics of examination in each situation. Rigid endoscopy requires the patient's neck to be slightly extended, and for the tongue to be protruded. The endoscope can then be advanced over the tongue and the vocal folds can be examined. Needless to say, this is a very 'unphysiological' position in which to be phonating. In general, it is only possible to elicit an 'ee' vowel in this position. By contrast, with the chip-tip endoscope passed through the nose, the performer can sing and speak almost as normal. A wide variety of vocal gestures can be performed, including those specific gestures that are causing the performance problems. This is particularly helpful when muscle tension is believed to be a feature. On the other hand, the images achieved with the distal-chip flexible endoscopes are not quite as good as the rigid views. Different vocal problems may call for different examination techniques, or sometimes both.

Feedback

A crucial part of the consultation with a vocal professional is the explanation of the findings. It is imperative to take time to explain the laryngeal images, so the patient can understand (and engage with) the plan of management.

SURGERY ON THE VOCAL TRACT

Surgery on the vocal folds themselves is described in Chapter 67, Phonosurgery. One aspect that must not be overlooked is that surgery on any part of the vocal tract can have a large impact on the voice. Changing the resonance chamber of the pharynx (by, for example, performing a tonsillectomy) can result in a change in the patient's voice. This is true also of nasal surgery or adenoidectomy.

Performers requiring surgery of other sorts should outline their profession to the anaesthetist: if possible, surgery should be performed using a laryngeal mask airway so as to avoid any trauma to the vocal folds.

ACUTE ILLNESS

Performers live in dread of developing an upper respiratory tract infection at any time, but particularly during a run of performances. It is important to differentiate between an upper respiratory infection with or without laryngeal involvement. An upper respiratory infection can be managed conservatively with adequate hydration and steam inhalations. If there is laryngeal involvement, particularly hyperaemia of the vocal folds, then ideally the performance should be cancelled. In certain circumstances where the performance is a career make-or-break situation, steroids may have a role to play but the risk is that they could lead to a vocal fold haemorrhage. Aspirin is also associated with vocal fold haemorrhage via its action on the platelets and should be avoided at all times by the professional voice user.[4]

Cancelling a performance can have serious consequences, both financial and professional, and it is recommended that full records of the consultation and examination, including stroboscopic images, be documented for reference.

MANAGEMENT

It is self-evident that the management of the patient will be governed by the pathology (or lack of it) found in the examination. However, other factors will come into play, and a selection of scenarios may help to illustrate and expand on this.

Performing arts student

A 22-year-old student at a performing arts academy is having problems with her voice. She is a music theatre singer, and typically becomes hoarse after a few performances. When she rests her voice for a few days, her voice returns, but she runs into similar difficulties when she starts another run of shows. She usually has to sing in one show each day for a week at a time. Examination shows soft vocal fold nodules in the usual locations.

- In this situation, one must explain that vocal fold nodules will often resolve with speech and language therapy and with the assistance of a good singing teacher.

Consider the same student again. She is now 25 years old and is having similar difficulties to those she experienced 3 years previously. She has seen two laryngologists in recent years, and has had extensive speech therapy and voice coaching. Despite this, she is having the same problems of vocal fatigue and inability to complete a run of shows. In fact, she now becomes fatigued after just five performances.

- This is now a difficult situation. She appears to have instituted all the necessary changes, and is still not able to perform to the required standard. Of particular concern is that she is not, at the moment, being required to

perform as frequently as a full-time performing professional: if she were in a professional cast, she would be expected to perform up to twice per day for 5 or more days per week. The clinician should have a frank discussion with her about this, and consider either surgical excision of her nodules or a change in her performing regime/style.

Professional opera singer

A 27-year-old professional opera singer asks for an urgent consultation: he has a performance tonight, but was having difficulties during last night's performance, and his voice has not 'felt right' today. The performance tonight is the last one for several weeks. There is no problem with his speaking voice and there are no other features in the history of concern. Examination shows mildly oedematous vocal folds but no focal pathology, and no evidence of hyperaemia.

- Given that tonight's performance is his last for some time, and that there is no evidence of vocal fold haemorrhage or hypervascularity, it would probably be reasonable to consider a single dose of a corticosteroid to help to reduce some of the laryngeal inflammation. It would be important to review the patient in the days after the performance to ensure that the inflammation has settled.

Rock singer

A 26-year-old rock singer is in the middle of a tour of the UK. After last night's concert, he was markedly hoarse and he has requested an urgent laryngeal evaluation. He has a further 15 shows to perform in the next 3 weeks, and his management team accompany him to his consultation. They are extremely keen to avoid cancelling any shows. Stroboscopic examination shows haemorrhage of the left vocal fold, with blood tracking under the whole length of the mucosal surface.

- You are duty-bound to advise absolute voice rest and that the remaining shows are cancelled. Vocal fold haemorrhage of this type can be catastrophic for a performer, and it is imperative that the voice is rested to attempt to avoid the formation of scar tissue.

KEY POINTS

- Vocal performers should be considered as 'athletes', with very specific professional demands.
- A detailed history is required, focusing on the specific vocal difficulties and whether there is any variability in the symptoms.
- A multidisciplinary approach in a voice clinic is essential, using the expertise of a laryngologist, a speech therapist and a singing teacher/voice coach.
- In addition to a discussion about the difficulties with the performing voice, the history should cover other aspects such as social voice usage and nights out.
- Stroboscopy (either rigid or via a chip-tip endoscope) is mandatory in the vocal professional. Video archiving is imperative.

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CHAPTER 66

SPEECH AND LANGUAGE THERAPY FOR VOICE DISORDERS

Marianne E. Bos-Clark and Paul Carding

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SEARCH STRATEGY

Data in this chapter are based on searches of the Medline, CINAHL, PubMed and Cochrane Library databases using the keywords: dysphonia, voice disorder, voice therapy.

INTRODUCTION

'Voice therapy' is used to describe speech and language therapy for voice disorders. This intervention is provided by clinicians who are called speech and language therapists (SLTs) in the UK, speech and language pathologists in Australia and the USA, and logopedists across much of Europe.

Voice therapy, as provided by SLTs, is the therapeutic treatment of a voice disorder diagnosed by an ear, nose and throat (ENT) specialist doctor. This chapter discusses the principles of management of voice disorders, and provides an overview of voice therapy interventions and their evidence base.

Voice therapy captures a wide variety of activities and interventions, and the evidence base of therapeutic interventions continues to develop. While both adults and children present with voice problems and voice therapy is the treatment of choice for a number of voice disorders, focus in the literature has been on the voice therapy treatment of adults with functional dysphonia. Even within this diagnostic group, clinical practice is varied. Depending on the organization of services, voice therapy may be provided by a community-based SLT or voice specialist SLT within a multidisciplinary team. The SLT may choose to use a specific, well-described programme of intervention carried out over a set number of sessions, or prefer an eclectic approach based on individual needs.

SLTs delivering voice therapy will need postgraduate training, as specific voice therapy interventions, such as certificated programmes described below, are not included in undergraduate degree courses. SLTs will also need knowledge and skills of anatomy and physiology, vocal pathologies, instrumental and perceptual voice measures, advanced communication skills and competence and experience in a range of appropriate treatments. Some voice therapy interventions need intensive voice training (e.g. Voicecraft)[1] while others, such as vocal function exercises,[2] can be self-taught from a provided package. Some interventions are pathology-specific (e.g. Lee Silverman Voice Therapy for Parkinson's disease (LSVT®),[3] while others, such as Estill Voice Training,[4] are used to improve function in both the disordered and the healthy voice.

Voice therapy embraces principles from biomechanics of voice production and motor-learning principles,[5–7] as well as psychological interventions to facilitate voice change in people with voice disorders.[8–10] In the management of voice disorders, the SLT is guided by clinical guidelines, as summarized in **Boxes 66.1** and **66.2**.[11] The American Speech and Hearing Association's clinical practice guideline for management of hoarseness for clinicians managing dysphonia is also recommended.[12]

BOX 66.1 Summary of the Royal College of Speech and Language Therapists clinical guidelines for the assessment of clinical voice disorders[11]

ASSESSMENT

Each individual is to be examined by an ear, nose and throat (ENT) surgeon prior to or simultaneously with SLT intervention, ideally in a joint ENT/SLT clinic.

SLT voice assessment to include:

- perceptual assessment of vocal and respiratory behaviour
- good quality voice recording, to allow instrumental analysis of vocal parameters such as aerodynamics, pitch, intensity, resonance, vibratory cycle and vocal quality
- perceptions of the individual about their voice disorder, its symptoms and impact on their life
- palpation of the extrinsic laryngeal musculature
- consideration of differential diagnosis of the voice disorder.

BOX 66.2 Summary of the Royal College of Speech and Language Therapists clinical guidelines for the management of clinical voice disorders[11]

MANAGEMENT

Intervention to include explanation and discussion of:

- normal anatomy and physiology for voice production
- causal and maintaining factors to the voice disorder
- voice care and conservation that will include hydration, environmental factors, voice use and lifestyle.

As part of the goal for more effective and efficient voice production, direct voice therapy approaches may aim to:

- alter vocal fold adduction
- reduce supraglottic activity
- adjust articulatory tension
- modify pitch
- alter resonance
- alter respiratory patterns.

Additional indirect approaches, e.g. relaxation strategies and psychological counselling, will be used where psychological or social factors are contributing to the development or maintenance of a voice problem. Their application may involve other members of the multidisciplinary team such as a psychologist.

UNDERSTANDING THE NATURE OF THE PROBLEM

Successful voice therapy must be based on a clear understanding of the problem.[13, 14] Since a voice disorder's aetiology is multifactorial, assessment needs to be systematic, use objective and subjective measures, and consider the impact of certain variables on individual patients.[15] Assessment data and diagnosis provided by the ENT are a starting point for therapeutic involvement. By considering the multifactorial aspects of the voice disorder, SLTs gain an understanding of the individual's voice in the full context of their life. SLT assessment requirements are summarized in **Box 66.1**, and salient aspects are discussed below.

Phonatory physiology

Detailed laryngoscopic examination gives SLTs information about phonatory physiology. Laryngoscopic findings can link directly to a therapeutic goal; for example, a finding of 'poor glottic closure and lateral false fold constriction' would guide intervention to restore vocal efficiency by reducing laryngeal constriction and improving vocal fold approximation. SLTs with appropriate training and supervision undertake laryngoscopy to gain detailed information about vocal fold function prior to therapy and during intervention to provide feedback to the patient.[16, 17]

Perceptual assessment

SLTs describe the presenting features of the voice disorder by listening to and rating the patient's voice quality in conversational speech and a standard reading passage, such as 'The rainbow passage' or *Arthur the rat*. There are different systems with differing terminology to describe the voice. Some require specific training, such as Laver's Vocal Profile Analysis Scheme.[18] SLTs use the GRBAS scale[19] to rate overall severity or **G**rade of voice change, **R**oughness, **B**reathiness, **A**sthenia and **S**train, where 0 = normal/typical; 1 = mild change; 2 = moderate abnormality; 3 = severe abnormality. The CAPE-V[20] is a more recent adaptation of the GRBAS scale, where SLTs also rate pitch and loudness on a visual analogue scale. Perceptual assessment is used continuously in voice therapy as a way of monitoring progress.

Instrumental measures

SLTs analyze voice samples from maintained vowels and connected speech with acoustic analysis packages, Laryngograph®, or with software such as PRAAT (the Dutch word for 'talk').[21] Instrumental voice measures are used in assessment before and after intervention, and these can also be helpful in providing visual feedback during treatment. Voice applications that display pitch and loudness can be downloaded on mobile devices and can support patients of all ages to practise voice work between sessions.[22, 23]

Asking the patient

SLTs investigate the voice complaint by thorough consideration of the patient's perspective. By filling in a questionnaire such as the Vocal Handicap Index,[24] Voice Symptom Scale[25] or Vocal Performance Scale,[26] patients rate voice symptoms and their impact. SLTs use these scores as part of outcome measurement, and to identify specific items to discuss more fully with the patient. During a detailed case history,[27, 28] patients outline what they have noticed about their voice, including hoarseness, limited dynamic range, poor projection, discomfort, fatigue and voice loss. Specific occupational and social vocal demands are identified, as well as strategies patients may already be using successfully to improve or maintain voice. It is important to note the language used by patients to describe their

voice problem. This reflects their understanding of what is happening to their voice, their expectation of therapy and their readiness to change. A successful case history will provide the clinician with relevant patient-specific information, build rapport and establish the SLT as a credible, skilled and trustworthy professional.[28]

THERAPY GOALS

Ideally, SLTs working with voice are part of a multidisciplinary team and take part in a joint voice clinic[29] or an SLT-led voice clinic. Within the team, the SLT's focus is always functional rather than structural.[14] As the relative importance of specific aetiological factors for a given individual are identified, patient-specific goals and an individualized intervention plan are developed. Broadly speaking, the aims of voice therapy are:

- to restore voice to normal (e.g. in functional voice disorders, muscle tension dysphonias, psychogenic voice disorders)
- to maximize voice function given permanent limitations (e.g. in vocal fold palsy, scarring, papilloma, post-radiotherapy voice)
- to reduce handicap and distress associated with the voice disorder (e.g. amplification, counselling)
- to establish strategies and vocal habits promoting vocal health so voice improvement is maintained.

These aims divide up into treatment goals linked to specific outcome measures and smaller, patient-centred goals (**Table 66.1**).[14] SLTs can personalize these goals further if required.

Joint goal setting is crucial to the success of voice therapy. This ensures therapeutic goals are specific and directly relevant to the individual with the voice disorder, clarifies expectations of both the patient and the SLT, and establishes the patient as an active partner in therapy, with the SLT as facilitator. When voice work is more personally meaningful to patients and they experience improved vocal control, motivation and compliance improve, and voice change is likely to be quicker and maintained better.[5, 30]

GENERAL THERAPY DESIGN AND DELIVERY

Clinical guidelines relating to intervention of clinical voice disorders are summarized in **Box 66.2**. There are a number of considerations for therapy delivery and design.

Individual or group

Voice therapy is usually delivered one-to-one, so that sessions can be tailored to the presenting condition, preferred intervention approach and vocal skills relevant to the individual. There are, however, aspects of voice intervention, such as delivery of voice care advice, that can be standardized and delivered in groups. One advantage unique to group voice therapy is that participants motivate and derive support from each other.[31]

Therapy content

Research suggests that effective voice therapy consists of a combination of direct and indirect approaches, rather than direct or indirect intervention alone.[26, 32, 33] Direct voice therapy consists of specific, targeted exercises to control and coordinate various aspects of the vocal system.[34] Direct therapy tends to work on phonation through facilitative techniques, a set programme of treatment, or a combination of approaches. Indirect intervention does not work directly on vocal skills, but on environmental factors, lifestyle issues, and general contributory and maintaining factors to the voice disorder.[34] Typical examples include discussing voice care advice, making patients

TABLE 66.1 Example of patient-centred goal setting related to outcome measure, for patient 'A', a supply teacher and rugby coach with hyperfunctional dysphonia and globus pharyngeus

Therapy goal	Suggested outcome measure
Eliminate mild bilateral vocal fold inflammation	Laryngoscopy
Establish voice within vocal norms on perceptual and instrumental measures	Clinician voice quality rating (GRBAS* or CAPE-V**) Laryngograph® or acoustic assessment
Eliminate vocal tract discomfort and tiredness	Patient rating Questionnaire
Eliminate habitual throat clearing	Chart and patient rating
Achieve effortless phonation	Patient report Clinician rating
Develop vocal projection skills to match demands of teaching/coaching	dB measure Patient report of performance and/or questionnaire
Experience reduced stress associated with dysphonia	Patient report Questionnaire

* GRBAS: Grade, Roughness, Breathiness, Aesthenia and Strain.[19]
** CAPE-V: Consensus of Auditory Perceptual Evaluation – Voice.[20]

aware of unhelpful habits, such as throat clearing, and explaining how the voice works. The proportion of voice therapy spent in direct/indirect intervention varies. Two methodologically different studies found that direct intervention constituted one-third[35] or more than two-thirds[36] of therapy time.

Hierarchical structure

Regardless of the approach chosen, voice therapy consists of incremental steps or skills that patients develop sequentially.[37, 38] Awareness of the amount of muscle tension or habitual level of loudness comes before producing voice with less tension or loudness, for example. In terms of the stimuli used for training and practice, SLTs control the level of difficulty so the desired voice quality can be successfully attained by the patient in different tasks. This may start in voicing without tension or roughness of vocal note on a single vowel sound, progress to rote speech (counting, days of the week), to reading aloud, and conversational speech. Carry-over or generalization strategies are integral to therapy,[38] so the desired vocal behaviour is present in clinic, at home and finally in the most vocally challenging settings for the patient.

Learning principles

SLTs are mindful of how vocal tasks are demonstrated, learned and practised. Certain intervention programmes, such as Estill Voice Training[4] and Lessac-Madsen Resonant Voice Therapy (LMRVT),[39] combine exercise principles with motor-learning theory and feedback to develop and maintain new vocal behaviour. The SLT's role is to guide the patient's awareness, perception and experience of better and healthy phonation during a session. It is thought that this specific attention and experience, in combination with distributed, random practice in different environments produces better learning.[5, 7]

Length of therapy

Although the literature reports considerable variability in length of therapy,[40, 41] it is suggested that patients attend no fewer than four to eight sessions to allow the voice change to take effect.[30, 38] Many programmes of intervention take at least eight sessions (e.g. LMRVT and LSVT).[39, 41]

Prognostic indicators

There are many variables affecting therapeutic progress. The following patient features are indicators of successful voice therapy:

- agreement of active role
- a willingness to change
- realistic expectations
- compliance and commitment
- elimination of other medical problems that may limit progress or stop the patient attending.

SLT factors likely to result in successful therapy are:

- high level of knowledge and skills of voice and voice techniques
- advanced communication skills
- ability to demonstrate listening skills, empathy, compassion, counselling
- ability to motivate.[42, 43]

Length of time from ENT referral to SLT appointment and length of therapy programme affect patient dropout.[44]

VOICE THERAPY APPROACHES

Indirect intervention

There is a wide range of activities in voice therapy where the SLT supports the patient in managing the contributory and maintaining aspects of the voice disorder. This includes explanation, stress management and general relaxation.[14, 34] The following activities are included in indirect voice therapy:

- vocal rest programme
- patient education, explanation of the problem
- vocal hygiene programme
- elimination of habitual coughing, throat clearing
- reassurance
- counselling
- general relaxation.

Direct intervention: Facilitative techniques

A number of facilitative techniques used by SLTs, many of them well described by Boone,[45] have been used historically by voice clinicians to stimulate and improve phonation.[34] These include:

- yawn–sigh
- chewing
- pitch variation and control
- reduction of vocal loudness
- elimination of hard glottal attack
- specific laryngeal relaxation
- voice 'placing'
- pushing exercises for glottal incompetence
- confidential voice.

Facilitating techniques are part of symptomatic voice therapy, and are used to establish best voice for the patient and subsequently practised to stabilize improved voice production.[43] There is no unifying evidence base or underlying theoretical framework as they are a wide range of techniques. Though evidence of efficacy in treatment is largely based on case studies, a skilled SLT may find these techniques a useful adjunct to other approaches.

Direct intervention: Voice therapy programmes

ACCENT METHOD

The aim of this method, developed by Svend Smith, is to resolve the voice disorder by improving coordination between breathing, voicing, articulation, body movement and language for individuals.[46] It trains normal patterns of voice production, rather than consciously correcting faulty vocal behaviour. In gradually more complex exercises, the patient copies the SLT's vocal model, thus developing kinaesthetic awareness of the desired control and coordination.[46] Emphasis in training is on producing easy voice with abdominal engagement in breath flow. Rhythmic consonant sound patterns called 'accents' are first used in slow, low-pitched exercises, then in faster, higher- and variably pitched tasks, and graduating in speech tasks. This method is shown to be effective with vocal fold lesions, vocal fold atrophy and muscle tension dysphonias.[47]

ESTILL VOICE TRAINING AND ALISON BAGNALL'S VOICECRAFT

Singer, voice researcher and teacher Jo Estill developed the Estill Voice Training (EVT) system, which enables individuals to gain isolated control over individual structures within the voice production system.[4] The structures include: head and neck, velum, lips, tongue, jaw, larynx, aryepiglottic sphincter, false vocal cords, true vocal cords, thyroid and cricoid cartilage, and torso. By controlling these structures in various combinations, different voice qualities are produced: for example, speech quality, twang and belting. SLTs guide the patient to develop kinaesthetic awareness of their vocal habits and of the muscular effort involved. By increasing this awareness and gaining specific motor control over relevant structures, the patient can identify and adopt more healthy and useful vocal behaviour. Singing teachers and voice coaches for professional voice users such as actors also use EVT to maximize voice control and function. Like EVT, Alison Bagnall's Voicecraft[1] focuses on teaching differential control of multiple parameters of the larynx and vocal tract.[48] Voicecraft is applied to and predominantly taught in the context of disordered voice. Clinical voice work of many SLTs in the UK is informed by Estill and Voicecraft training.[29, 30] There is a clear scientific basis and rationale for the work, as Jo Estill's extensive research data on aspects of EVT attests,[4] though there are as yet no published studies of systematic use of these interventions with a disordered voice population.

LARYNGEAL MANUAL THERAPY

SLTs use circumlaryngeal manual therapy, digital laryngeal manipulation, voice massage or laryngeal manual therapy (LMT) to manipulate the perilaryngeal area to redress muscle tension.[49–51] Methods of manual therapies vary but essentially focus on reducing excessive tension in the extrinsic laryngeal musculature. Initial palpation helps the SLT to note laryngeal posture (e.g. held high or forced lowered), muscle tone and pain or tenderness of muscle tissue. Areas the SLT may work on include sternocleidomastoid muscles, supra-laryngeal muscles, hyoid position and surrounding musculature, lateral laryngeal movement and rotation.[52] Evidence suggests manual therapies are an effective treatment for muscle tension dysphonia and can resolve even severe hyperfunctional dysphonia.[49–52]

LEE SILVERMAN VOICE THERAPY (LSVT®)

Lee Silverman Voice Therapy (LSVT®) has been developed to treat hypofunctional dysphonia associated with Parkinson's disease.[3] The aim is to alter phonatory effort and 'recalibrate' the patient's perception of effort and loudness levels in speech. SLTs encourage patients to 'think loud', and provide feedback with a decibel meter during repetitions of loud sustained vowels and other speech tasks. The programme is structured and intensive: patients attend individual sessions four times a week for a month, and practise at home in between sessions. LSVT is increasingly used with other hypofunctional dysphonias. It is contraindicated for use with patients with normal neurological function or hyperfunctional dysphonia and, if used inappropriately, may be harmful to both client and SLT.[38] The programme has been used with good results for Parkinson's patients with long-term effects, improving clarity of speech and overall speech intelligibility.[53]

LESSAC–MADSEN RESONANCE VOICE THERAPY (LMRVT)

Based on the work of Arthur Lessac and Mark Madsen, Katherine Verdolini-Abbott has developed a structured intervention programme to reduce aberrant vocal behaviour by establishing easy and clear or resonant voice.[39] SLTs encourage the patient to notice vibratory sensations towards the front of their face on certain voiced sounds (e.g. /m/). Patients practise forward placing of the voice in combination with a sense of ease of voice production in various speech tasks. Individual therapy sessions of 30–45 minutes take place once or twice a week over a 4–6 week period. Research suggests LMRVT is a useful approach in treating functional voice disorders and associated pathology such as nodules, and in improving vocal fold healing in acute inflammation.[54, 55]

SEMI-OCCLUDED VOCAL TRACT THERAPY (SOVT)

Flow phonation, 'lax vox' and SOVT are treatment approaches aiming to reduce muscle tension and hyperfunctional voice by altering air pressure levels in phonation.[56, 57] Exercises with straws, narrow tubes or lip-rounded vowels can improve vocal stability as phonation threshold pressures in the vocal tract are altered.[5] SOVT can train a patient with a hyperfunctional or 'pressed' voice to produce phonation with less effort and adopt more efficient and less effortful phonation. Principles of SOVT are present in other

voice interventions, such as the accent method, resonance therapy, and twang in Estill/Voicecraft.[56] These interventions are based on scientific and physiologic principles,[5, 56] and have long been present in voice therapy practice. The evidence base for lax vox and SOVT as intervention programmes with disordered voice populations is limited.

STEMPLE VOCAL FUNCTION EXERCISES (VFE)

Stemple vocal function exercises (VFEs) are based on a physiological approach[43] and centre on the principle of exercise to achieve optimal coordination of breath support, phonation and resonance, in combination with stamina and strength. SLTs encourage patients to produce 'quiet' (not projected) voice with a forward placement, sensed by the patient as a 'buzzing' of the lips. The programme is highly structured and requires patients to do specific exercises four times a day over 8–10 weeks.[2, 43] Exercises include a vocal warm-up, maximal pitch glides (low-to-high and high-to-low) and maximal vowel prolongations at different pitches. The standardized nature of the programme lends itself well to research, and the evidence base for this intervention is considerable.[43]

ECLECTIC VOICE THERAPY

In the UK, the Royal College of SLTs recommends that SLTs have an eclectic approach in voice therapy. Drawing on many of the above techniques and approaches, the skilled SLT targets the specific factors relevant to the individual with the voice problem, with an intervention approach that is uniquely suited to them. This approach is potentially the most holistic and client-centred. Unlike in a structured programme, in eclectic voice therapy no SLT would provide exactly the same intervention twice, even to an ostensibly 'identical' case of muscle tension dysphonia or vocal fold palsy. Eclectic voice therapy is based on sound clinical rationale and a thorough understanding of intervention strategies and underlying principles. Establishing an evidence base for eclectic voice therapy is methodologically challenging though not impossible, as shown by Mackenzie et al's randomized controlled trial in functional dysphonia.[32]

CONCLUSION

SLTs working with patients with voice disorders facilitate behavioural change in a principled way. Voice therapy encompasses a variety of patient-centred activities, resulting in demonstrable vocal improvement as shown by a range of outcome measures.

Review of the level of evidence in voice literature suggests there are small numbers of level 1 and 2 articles as compared with medical and otolaryngology literature.[58]

FUTURE RESEARCH

- The majority of voice research in the UK is produced by practising clinicians, resulting in clinically applied research.[17] The level of research in the field of voice is predominantly grade B, level 2 and 3, consisting mainly of effectiveness and some larger-scale efficacy studies. The evidence base for voice therapy continues to develop, with a need for future studies to be larger, methodologically sound, replicable and generalizable.[33, 40, 59]
- Suggested areas for future research include:
  - content of voice therapy in relation to pathologies
  - comparison studies of direct interventions with same and different pathologies.

KEY POINTS

- Voice therapy aims to:
  - restore voice
  - maximize vocal potential
  - assist in communication adjustments where voice improvement is likely to be limited by laryngeal structure.
- Voice therapy is based on:
  - systematic, multifactorial assessment of the voice
  - individualized goals for patients linked to assessment findings
  - joint planning with patient
  - a hierarchical treatment plan.
- Multifactorial assessment of current vocal behaviour includes:
  - phonatory physiology
  - perceptual voice rating (using GRBAS or CAPE-V rating scale)
  - patient-reported symptoms and their impact (questionnaires such as VHI, VoiSS and VPQ)
  - acoustic profile using instrumental measures of voice such as PRAAT and Laryngograph®.
- Intervention consists of a combination of direct and indirect treatment approaches.
- Types of direct voice therapy include:
  - accent method
  - Estill Voice Training and Voicecraft
  - laryngeal manual therapy
  - Lee Silverman Voice Therapy
  - resonance therapy
  - vocal function exercises.
- Voice therapy is often eclectic, where a skilled and experienced voice specialist may draw from a range of interventions based on sound clinical rationale to suit the individual's vocal needs.
- The evidence base for voice therapy is mainly at grade B with some level 1 evidence. Future studies need to be larger, methodologically sound, replicable and generalizable.

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CHAPTER 67

PHONOSURGERY

Abie Mendelsohn and Marc Remacle

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: voice, larynx, vocal fold and focusing on phonosurgery and results.

INTRODUCTION

Voice disorders are typically only appreciated by those afflicted with these conditions. While there have been great advances throughout the years within the diagnosis and treatment of voice disorders, we are still quite limited in the overall range of intervention available to the practitioners concentrating in this critical area. The last 50 years has seen an increased awareness and emphasis on vocal results and the expansion of phonosurgery, which is defined as 'any surgery designed primarily for the improvement or restoration of the voice'. Nowadays, 'surgery' refers to office-based procedures, interventions under light anaesthesia (conscious sedation), or surgery with general anaesthesia.

Prior to any surgical intervention, complete assessment of patients with a voice disorder should minimally include a complete history (typically as informative as the physical examination) and thorough physical examination. Critical aspects of the physical examination include lateral neck palpation, thyroid examination, observation of laryngeal elevation, tongue and palate mobility, respiratory status, and nasal examination. Once these areas are sufficiently evaluated, the larynx may then be imaged via office-based indirect laryngoscopy. Indirect laryngoscopes (either flexible or rigid) are preferably combined with video recording, which is of crucial importance for immediate review of physical findings as well as comparative evaluation following interventions. Stroboscopy has been a standard of vocal fold cover evaluation, though this technology is inherently weakened by its requirement of normal vibratory patterns, which is discussed in further depth in Chapter 61, Assessment and examination of the larynx and Chapter 62, Evaluation of the voice. High-speed videolaryngoscopy is a useful adjunct in the diagnosis of voice disorders. Additional examination modalities include laryngeal electromyography and voice measurements (both quantitative and qualitative). The formation of multidisciplinary voice clinics allows an academic and scientific approach to voice disorders and greater emphasis on an evidence-based approach to laryngology.

Like any surgical intervention, phonosurgery should be considered the very last treatment option once all conservative measures have either failed to improve the voice or they are deemed inadequate based on our understanding of certain pathologic conditions. Too quickly taken to the operating theatre, patients may end up in worse situations both vocally and medically following unnecessary surgical interventions. A helpful philosophy is to approach potential patients as if attempting to convince those patients away from surgery; and in this manner only the most necessary pathologies will be exposed to the risks of surgery.

As glottic cancer is discussed in Chapter 14, Tumours of the larynx, our discussion of phonosurgery will be limited to benign disease. The topics that will be discussed include microlaryngeal surgery, injection laryngoplasty and laryngeal framework surgery (including nerve grafting).

MICROLARYNGOSCOPY

History

Claudius Galen is credited with recognizing the larynx as the organ responsible for voice production in the second century of the common era. Avicenna (Abu Ali al-Husain ibn Abdullah ibn Sina), recognized as one of the fathers of modern medicine, in the 10th century described in detail the muscular control of the laryngeal cartilages, including an in-depth discussion regarding the role of the corniculate and cuneiform cartilages. In the 1700s the science was advanced with Giovanni Morgagni's connection between vocal fold pathology and dysphonia. Although Manuel Garcia[1] is often credited with the first description of mirror indirect laryngoscopy, Bozzini[2] was actually the first to report on mirror visualization of the larynx and indeed described the first indirect laryngoscope for surgery on the vocal folds. Indirect laryngoscopic surgery was the norm at the beginning of the 19th century and may have played a role in the well-documented tale of Morell McKenzie and the transoral management of laryngeal cancer in Crown Prince Frederick. At that time, there was fear that transoral laryngeal biopsies could induce cancer of the larynx and as a result laryngeal diseases, such as tuberculosis and syphilis, were often treated by an open procedure with or without a tracheostomy. These were associated with a high morbidity and even mortality and there is postulation that Virchov purposely misdiagnosed Prince Frederick's carcinoma because he was aware of Van Bergman's (the prince's surgeon) abysmal survival statistics following total laryngectomy.[3] Horace Green described the first direct laryngeal surgical case, which was the removal of a laryngeal polyp in an 11-year-old girl.[4] Due to the fact that in a child the larynx is in a high position, Green was able to use a bent tongue spatula and sunlight to obtain direct vision and remove the polyp. Oskar Kleinsasser described the adaptation of the microscope to direct laryngoscopy allowing for fine manipulation of the vocal folds. Since then, numerous developments and modifications have taken place but all demonstrate the fundamental phonosurgical principles as detailed in this chapter.

Anatomy

A knowledge of the anatomy of the larynx, specifically the microarchitecture of the vocal folds is essential (**Figure 67.1**). The layered structure of the vocal fold and the different mechanical and physical properties of each layer allow for the unique capacity for continuous vibration (or entrained oscillations). While the true mechanics of vocal fold vibration is still beyond our full understanding and requires active investigation, it is critical that this unique microarchitecture is preserved as its loss (i.e. vocal fold scar) results in the dramatic loss of voice quality. Vocal fold epithelium is the first identified layer of the vocal fold. The mucosa is comprised of stratified squamous epithelium, which transitions to pseudocolumnar cells superiorly into the laryngeal ventricle and inferiorly when the glottis transitions to the subglottis and trachea. The epithelium thickness is approximately 50 microns. The limited depth of the epithelium prevents physical manipulation of this layer alone. Surgical interventions designed to excise, or lift, the epithelium therefore requires some level of manipulation of the lamina propria. The specific layering of the human lamina propria is unique amongst mammalian species. The lamina propria is divided into

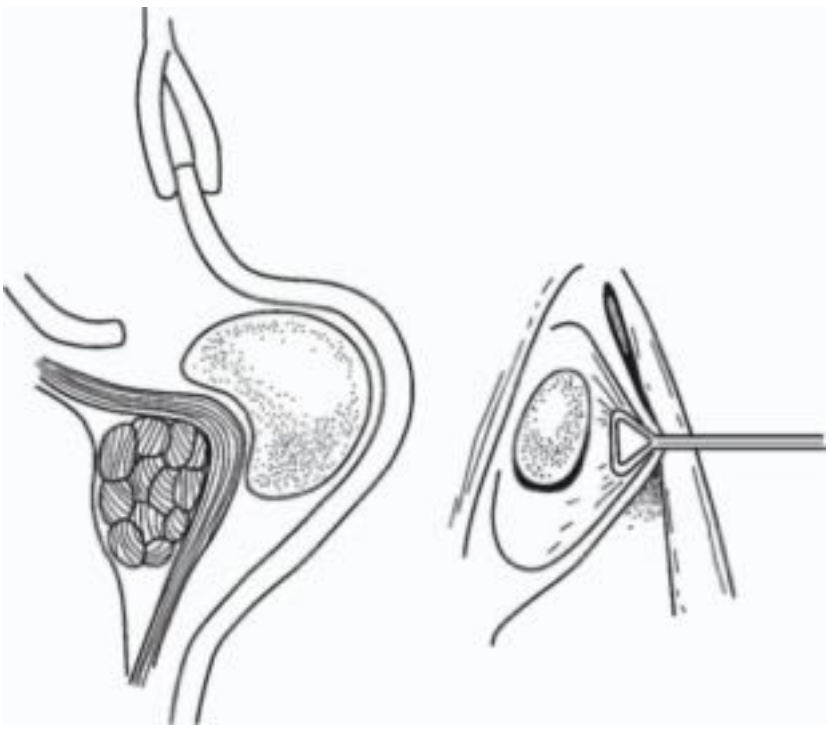


Figure 67.1 Intracordal cyst approached via cordotomy and mucosal flap.

three components: superficial, intermediate and deep. The main component of the lamina propria is collagen fibres. The composition of collagen fibre type and the fibre density distinguishes the three layers of the human vocal fold, which transitions from less-to-more dense structure extending from the superficial to deep. Depth of the superficial lamina is 0.14 mm in women and 0.30 mm in men. The vocal ligament is typically defined as the combined structure of the intermediate and deep layers of the lamina propria, which is readily identified histologically as well as microsurgically.

Exposure

A flexed cervical-thoracic junction and extended atlanto-occipital joint, described by Chevalier Jackson, is now returning as the accepted position for microlaryngoscopic surgical access (**Figure 67.2**). Individual anatomic variations may require departure from this recommended patient position, including flexion at both cervical points, which can be easily modified prior to commencing vocal fold manipulation. Anatomic variations are also optimally managed through the use of different sized (length and diameter) and style (e.g. anterior lip, distending) rigid laryngoscopes. It is critical for the laryngologic surgeon to have several laryngoscopes available for each surgery. Difficult cases can be improved through external laryngeal counter pressure, which can be done either with an assistant's fingers or gauze padding and elastic tape.

Instrumentation

Proper instrumentation, in addition to the laryngoscopes discussed, is required. Microlaryngeal instruments need to be fine, sharp and well maintained to allow precise manipulation of the vocal fold to limit scarring risk. The authors utilize atraumatic soft tissue microlaryngeal forceps (i.e. Bouchayer forceps) in a vast majority of surgeries. Manipulation and trauma to areas beyond what is absolutely necessary will undoubtedly increase scarring and thereby negatively impact post-treatment voice quality. Limiting the area of surgery not only applies along the periphery, or along the surface, but the deep extent of surgery should also be limited to what is absolutely necessary.



Figure 67.2 Microlaryngoscopy set-up. The patient is positioned with the recommended cervical flexion and extension. Laryngoscope is suspended by fulcrum suspension bar.

Benign disease is usually located in the mucosal layer or in the superficial part of the lamina propria. Surgery should, therefore, be superficial, staying out of the vocal ligament, with limited mucosal excision only. There is no role for stripping of the mucosa of the vocal fold for benign disease, and vocal fold preservation should be the paramount concern of phonosurgery for benign disease.

Lasers and technologic instrumentation

The laser is not merely a precise surgical knife and the surgeon must have an understanding of the effects of wavelength spot size, wattage and mode (pulsed or continuous), their soft tissue interaction and the important hazards linked to their use. Currently, the three most widely utilized laser types include CO_2, potassium titanyl phosphate (KTP) and diode. The specifics of each laser type can be found in Chapter 50, Laser principles in otolaryngology, head and neck surgery, but it is critical that the laryngologic surgeon understands all aspects of the wavelength, spot size and power settings of the utilized laser before attempting even the smallest of procedures. Benninger[5] described a prospective study on patients using the CO_2 laser and microsurgery and came to the conclusion that in a trained laryngologist's hands, both are excellent tools in the management of phonosurgical disorders. In many ways, laser and cold instruments should be considered as synergistic tools rather than in direct opposition. It is, therefore, a personal choice but the authors prefer to limit laser to vascular lesions or those that bleed on removal, such as papillomatosis or granulomas, or to the removal of cartilage and when excising large areas of tissue. Although the laser plume in the management of papillomas has been considered a potential risk of infection, this risk is only theoretical and no case report for this type of infection exists.

Some surgeons now advocate the use of power instrumentation, such as the laryngeal microdebrider. The microdebrider has been used for various laryngeal lesions including papillomas and there is an early report using subjective methods that patients have less post-operative pain and a quicker return to a usable speaking voice.[6] Others have used the debrider for polyps and Reinke's oedema, and also for removing tumours at both glottic and subglottic levels. Once again, one must be aware of the microanatomy of the vocal folds and the principles of phonosurgery and whether accurate depth of resection can be made with this tool. A suction collection pot must also be used to confirm histological diagnosis but margins and orientation of the specimen are lost with this technique.

Anaesthesia

General anaesthesia is the norm for microlaryngeal surgery although there have been some articles describing indirect phonosurgery under a local anaesthetic with stroboscopic control[7] or direct laryngoscopy with nerve blocks and topical anaesthesia. These techniques have

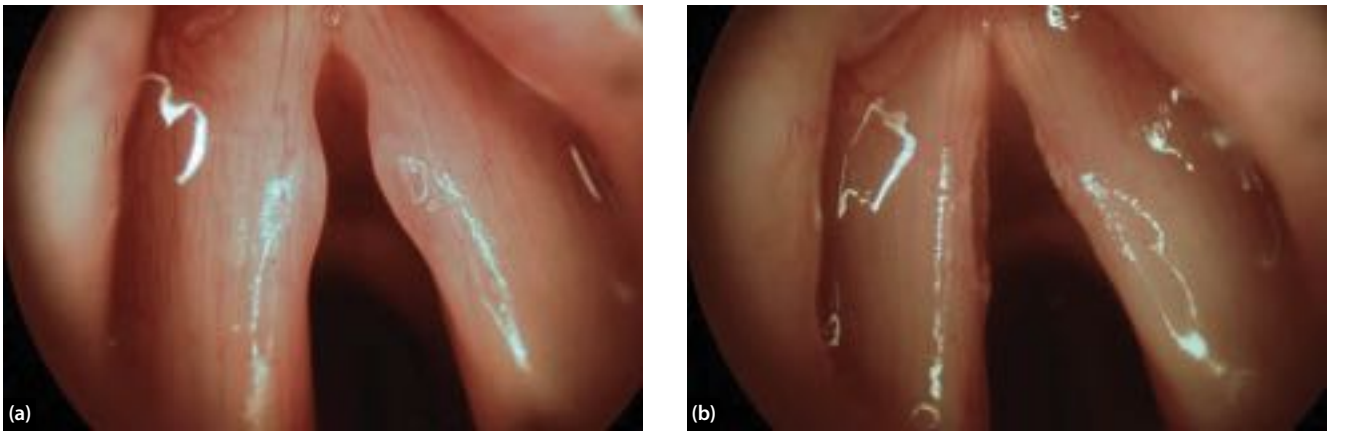


Figure 67.3 Vocal fold nodules. The patient demonstrates bilateral and symmetric phonatory lesions along the anterior one-third of the membranous vocal volds **(a)**. After voice therapy, the nodules persisted and the lesions were resected with CO_2 laser phonosurgery **(b)**.

not been widely accepted. General anaesthesia may be induced and maintained through three main techniques: intubation, apnoea or jet ventilation. Standard oral-tracheal intubation is to be performed only by the most experienced anaesthesiologists as unwanted vocal fold manipulation may impart more phono-damage than then planned phonosurgical procedure. General anaesthesia is typically recommended so muscular relaxants (paralytic agents) can be administered to maintain motionless vocal folds during surgery. Endotracheal tube choice should be made in consultation with the treating anaesthetist, though the endotracheal tube with the smallest outer diameter that can offer safe respirations should be utilized. The authors rarely utilize endotracheal tubes larger than size 5.0 during phonosurgery. Additionally, when available, micro-laryngoscopy tubes (MLT) should be requested to improve the overall length of the tube with smaller diameters. If laser is used during surgery, a laser-safe endotracheal tube should be placed, again with the smallest possible outer diameter, and the tracheal balloons filled with normal saline. Apneic technique calls for intermittent ventilation either by mask ventilation or intermittent endotracheal intubation to oxygenate and ventilate the patient, and the patient is left without active respiration during the phonosurgery. This technique is useful when the lesion is in the posterior glottis, where endotracheal tube would otherwise be visually obstructing and jet ventilation is otherwise not indicated or not available. Jet ventilation offers the best exposure of the larynx and can be performed for prolonged periods. Jet ventilation should *not* be used in cases where bleeding is expected as there is no barrier for aspiration of the blood.

Post-operative voice rest

Although there are no control studies looking at the role of voice rest in recurrence and healing, it is now a generally accepted rule that 48 hours of absolute voice rest following a phonosurgical procedure is essential. The authors recommend a minimum of 7–10 days of strict vocal rest followed by resumption of voicing under the guidance of voice pathologists.

Pathology

NODULES

These are bilateral lesions of functional aetiology and the vast majority resolve completely following compliant voice therapy. They are found at the midpoint of the vocal folds (membranous vocal cord) and are confined to the superficial squamous epithelium. Histopathological studies show thickening of the basement membrane together with areas of haemorrhage, fibrin deposits and hyalinization. Their aetiology is associated with phonatory strain and a stroboscope can be useful in distinguishing this pathologic entity from others that are more readily treated with phonosurgery. In the very rare situation where true vocal fold nodules do not respond with compliant treatment, surgery may be offered to remove these lesions. It must be restated that patients who are non-compliant with their voice therapy should not have surgery offered as their poor vocal behaviours will undoubtedly cause poor healing and scarring, which is a situation more challenging to treat than nodules. During surgery, the centre of the nodule is held with atraumatic forceps and pulled medially towards the opposite cord. The mucosa is cut at its base, by cold instruments or laser, producing a straight vibratory edge and preventing secondary notching. The opposite nodule can then be removed in a similar fashion, taking care not to damage the mucosa of the anterior commissure. There is no contraindication to removing both nodules at the same time using this precision technique.

POLYPS

These are usually unilateral, localized areas of oedematous tissue although some may be angiomatous and may also contain areas of haemorrhage. Though a trial of voice therapy is indicated, these lesions are more likely to require phonosurgery than nodules. The site of the lesion is again superficial to the vocal ligament and careful examination may show a contact response on the contralateral vocal fold, which should rarely be addressed. Gentle, steady traction is applied by grasping forceps towards the opposite cord and the base of the polyp is sectioned.

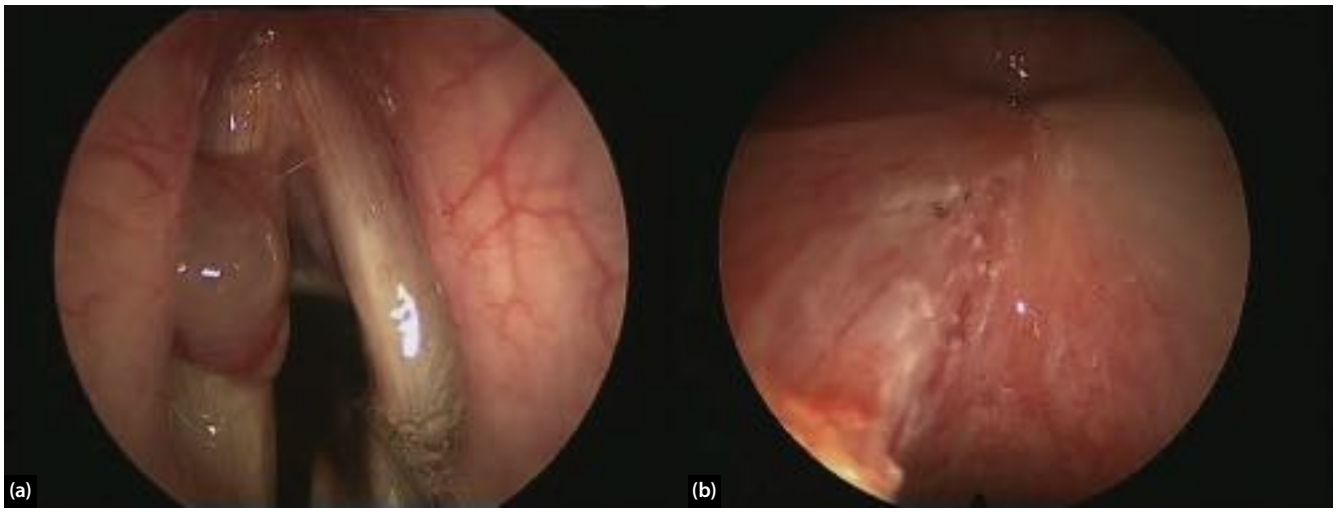


Figure 67.4 Vocal fold polyp. The patient demonstrated left vocal fold polyp at the mid-membranous portion of the vocal fold. CO_2 laser excision preserving the cover layer will allow for excellent healing. (70° endoscopic view.)

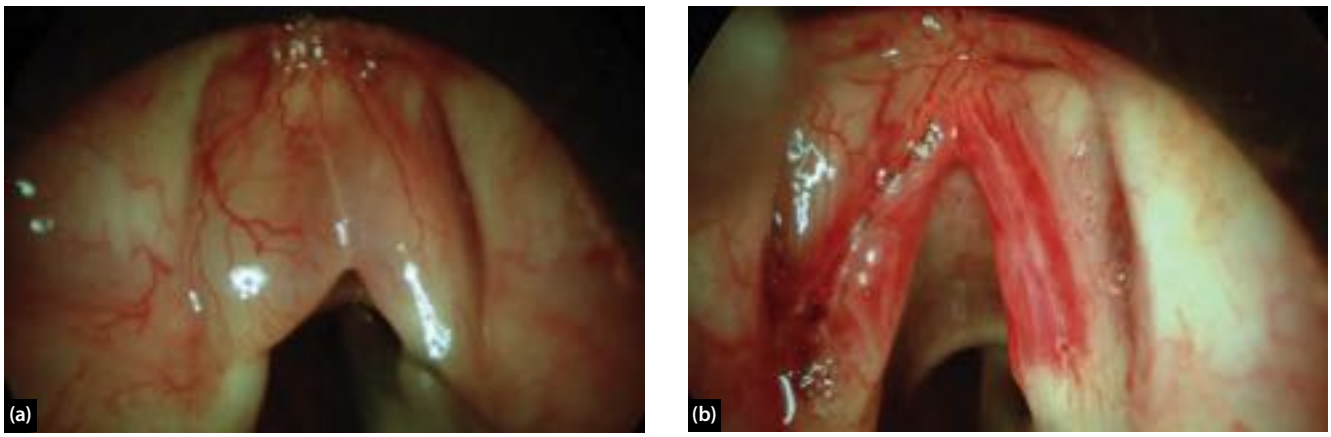


Figure 67.5 Reinke's oedema. The patient demonstrates severe oedema of the vocal fold cover along the anterior-posterior length of the membranous portion of the vocal folds **(a)**. Phonosurgery utilizing CO_2 laser excision of the oedematous tissue preserving the cover layer will allow for excellent healing **(b)**.

Preservation of mucosa is essential, too little resulting in reformation of the polyp, too much resection giving a notched, scarred cord with tethering of the layers of the vocal fold, as seen in **Figure 67.4**.

REINKE'S OEDEMA

This is a bilateral diffuse condition where there is a collection of polypoidal tissue in the superficial layer of the lamina propria, as seen in **Figure 67.5a**. This condition is almost universally associated with cigarette smoking. Patients who continue to smoke should be considered poor surgical candidates as this condition has a high likelihood of recurrence with continued smoke irritation. The pathophysiology is suggested to stem from the poor lymphatic drainage of the vocal folds resulting from the unique embryological origins of the supra and subglottic areas. This poor lymphatic drainage, however, is also advantageous by giving a good prognosis for small glottic tumours. Incision is made on the lateral aspect of the superior surface of the vocal fold with micro-scalpel or laser. The median vibrating edge of the vocal fold is, therefore, preserved. Mucosa is then elevated with a blunt dissector and myxomatous contents either aspirated (suctioned) or removed with cupped forceps. Care must be taken to avoid damaging the vocal ligament or traumatizing the overlying mucosa with excessive suction. Following removal of the contents, the mucosal flap is replaced and any excess epithelium trimmed with microscissors, as seen in **Figure 67.5b**. The mucosal flap can be laid on the surface and left to heal by surface tension, suturing or tissue glue (autologous or commercial) used to hold this in place. Providing care is taken in the region of the anterior commissure, there is no contraindication to operating on both folds at the same time.

INTRACORDAL CYSTS

These primarily surgical lesions may be either secondary to mucosal retention or epidermoid cysts, and stroboscopy has greatly increased the ease of diagnosis, though it remains an ultimately a very challenging diagnosis at times.

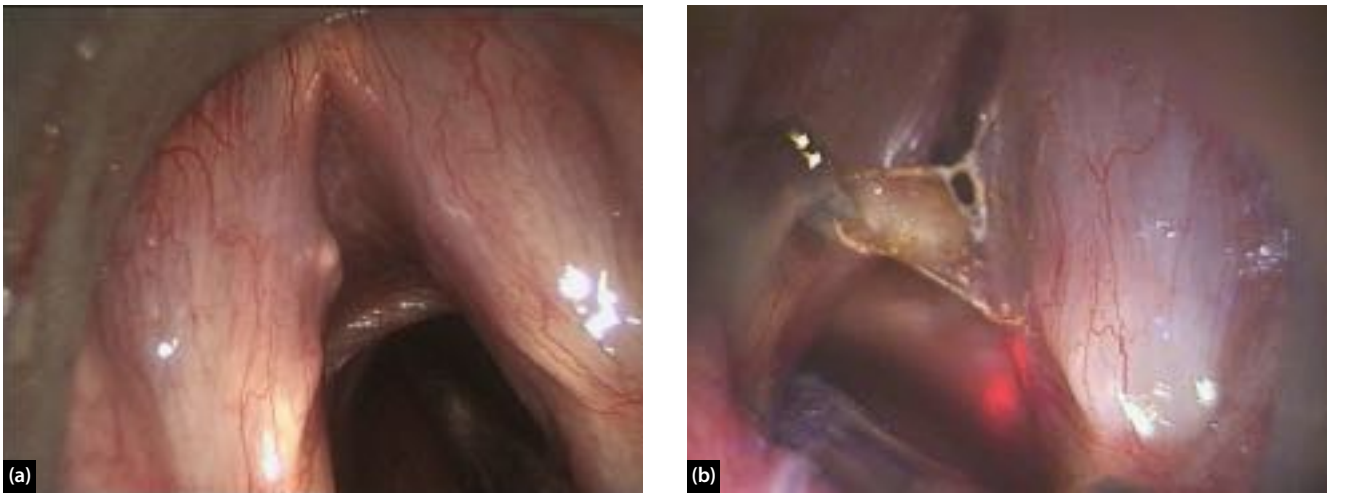


Figure 67.6 Intracordal cyst. The patient demonstrates a right mucous retention cyst at the mid-membranous point of the vocal fold **(a)**. Also seen is intra-operative view of a cyst being dissected from the vocal fold cover by CO_2 laser **(b)**.

The mucous retention cyst is found in the cover of the vocal fold and can be removed either with cold instruments or with the laser, but again remaining superficial to the ligament. An epidermoid submucosal cyst can be approached via a lateral microflap where an incision is made on the superior surface of the vocal fold away from its medial edge. The flap is then elevated from lateral to medial, the lesion excised and the flap replaced. There are good quantitative results in phonosurgery following this approach although some debate exists as to whether there is damage to the basement membrane when elevating the flap. Blood vessels have been identified in the flap and would suggest that the plane of dissection should be deep to the basement membrane, therefore objections of greater damage to the basement membrane may not be founded. As a result of this work, however, Sataloff et al.[8] devised a mini microflap, which involves elevating a small section of epithelium directly over the lesion via a medially based incision as seen in **Figure 67.6**. They also report good results both subjectively and quantitatively using this method.

VOCAL FOLD VARICES

These are often considered a potential source of haemorrhage but in most cases, if lying in a longitudinal orientation, they can be left and treated conservatively unless recurrent haemorrhage occurs. The presence of vessels lying at 90 degrees or at a different orientation may indicate underlying disease, possibly neoplastic, and require further investigation. Recurrent haemorrhage from these vessels can be dealt with either by lasering the blood vessel or needle cautery to ablate the vessels. Angiolytic lasers such as KTP or pulse-dye lasers can be of particular utility with these lesions.

ANTERIOR WEBS

If these are small and thin, they can be divided either with a laser or with cold steel. A microweb is frequently associated with vocal cord nodules[9] and can be removed at the same time. Thick webs have a 50% chance of recurring following laser excision and may require insertion of a keel, either endoscopically or via an open procedure, to prevent recurrence. A local mucosal flap covering the exposed tissue on one side has also been reported.[10]

GRANULOMAS

These are located on the vocal process of the arytenoid cartilage and are usually unilateral, sessile, bilobed lesions. Aetiologic factors include endotracheal intubation, trauma, pharyngolaryngeal reflux, hyperfunctional voice disorders and combinations of these factors. The characteristic posterior position in the glottis is diagnostic and tissue diagnosis is rarely indicated. Granulomas frequently recur following surgery alone. The primary treatment for unilateral granuloma is therefore bilateral vocal fold injection of botulinum toxin (Botox) to the adductor muscle groups, similar to the treatment of adductor spasmodic dysphonia. However, the dose is about 10-fold higher when treating granulomas. Patients must be counselled regarding the 3-month period of decreased vocal loudness, though this pharmacologic-induced voice rest is critical for complete resolution of even moderate to severely hypertrophic granulomas. Botox injections must be coupled with conservative measures including aggressive laryngopharyngeal reflux treatment and voice therapy. Some granulomas present at such an advanced stage, where airway obstruction is a concern. Such lesions can be excised through phonosurgery, though the vascularity of these lesions typically requires the use of laser energy instead of cold instruments. However, Botox injections should still be administered at the time of resection to reduce the risk of recurrence.

PAPILLOMA

These neoplastic lesions are due to the human papilloma virus (subtypes 6 and 11) and frequently recur. They are

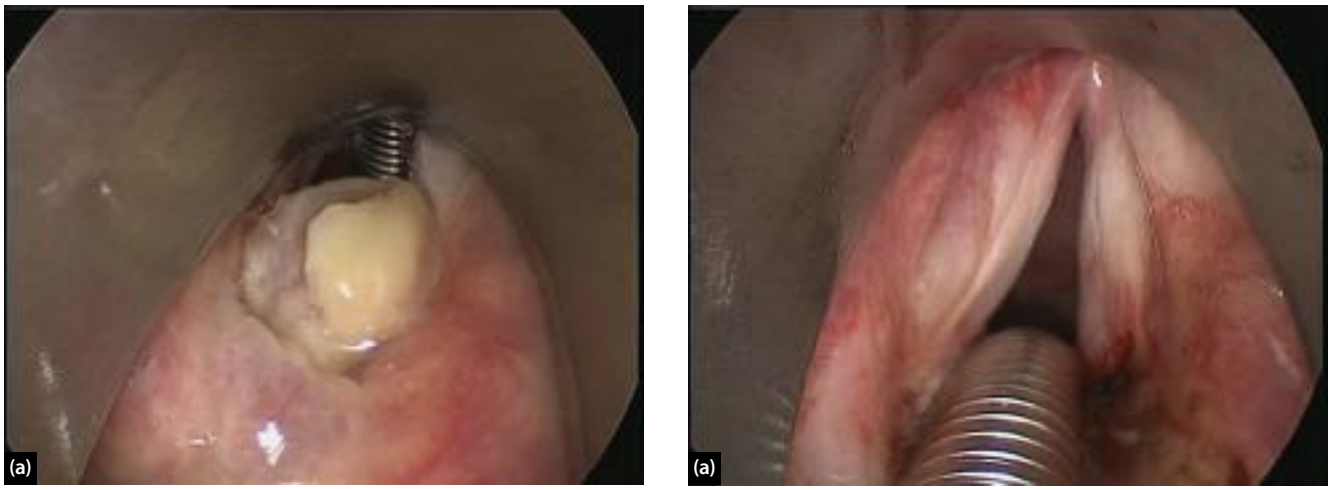


Figure 67.7 Granuloma. The patient demonstrates a large right vocal fold granuloma arising from the posterior glottis and obstructing the glottal space **(a)**. Following excision by CO_2 laser, the glottis is then clear of obstruction **(b)**. Importantly, the adductor muscle groups were treated with Botox injections bilaterally.

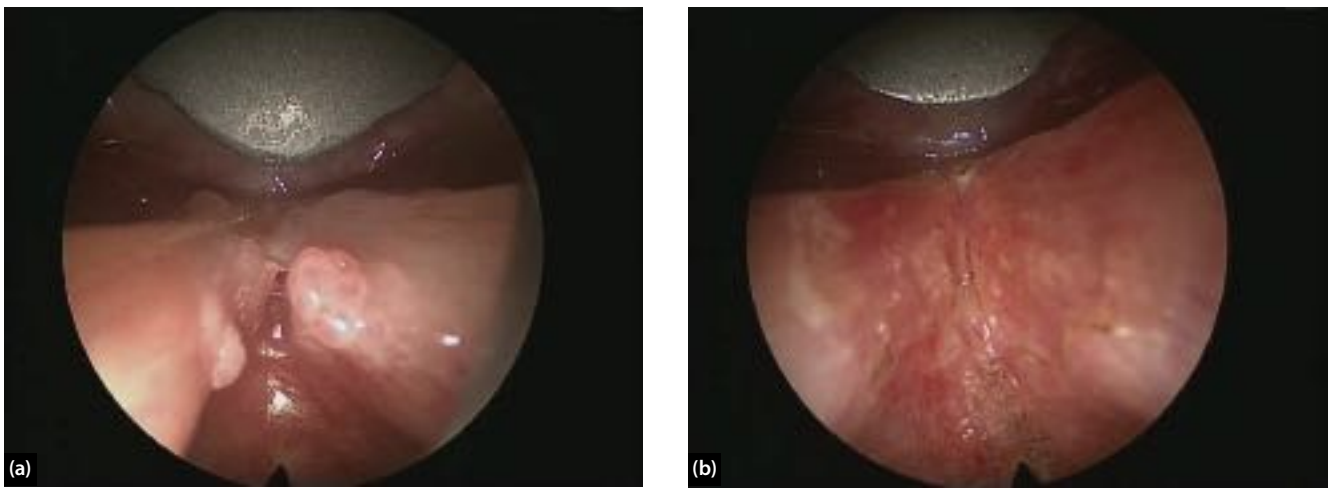


Figure 67.8 Papilloma. The patient demonstrates sessile papillomatosis of the membranous vocal folds bilaterally involving the anterior commissure **(a)**. Following ablation by CO_2 laser, vocal fold cover is preserved **(b)** (70° endoscopy).

often found at areas of transition in the upper aerodigestive tract where there is increased air turbulence, drying and cooling of mucosa, and at the change of ciliary to squamous epithelium.[11] CO_2 laser excision is the treatment of choice in the authors' hands, with minimal trauma to surrounding tissue (that may contain dormant virus). An endoscope with a smoke evacuation channel is useful. Single papillomas are grasped gently as they may be friable and the laser is used to excise the base. Surgical techniques for multiple papilloma include using injection of saline (+/– epinephrine) submucosally (hydrodissection) and excising the mucosa *en bloc*. This gives a lower recurrence rate than surface ablation. It is also (by addressing the principles of phonosurgery and remaining superficial to the ligament) less likely to give scarring by better definition of tissue planes, as seen in **Figure 67.8**. Many case reports in the past have reported success of different treatments by the frequency of repeated lasering but there are now many established scoring systems taking into account the distribution and appearance of papillomas in recognized areas of the larynx. This allows a more scientific and quantitative approach to future treatments. There is encouraging work looking at an immunodeficiency of T-cell lymphocytes in patients with papillomas and the use of adjuvant treatments, such as retinoids, alpha interferon, ribavirin, cyclooxygenase 2 inhibitors, and cidofovir. Photodynamic therapy is also in its experimental stage.[12]

VOCAL SULCUS

This is a groove along the mucosa and can be classified into three types: the first is a physiological or pseudosulcus often associated with reflux; the second is a sulcus vergeture, which goes down to the superficial layer of the lamina propria; and the third is a sulcus vocalis going down to the deeper layers of the ligament. There is a theory that a sulcus is related to ruptured congenital cysts and may well be more common in the Indian subcontinent. They frequently present with persistent dysphonia following puberty. Numerous phonosurgical approaches

have been suggested from excising the sulcus to injecting collagen or fat to boost the underlying layers. Pontes[13] advocates a technique involving parallel mucosal incisions of varying lengths running in a cephalad to cordal direction to break up the linear scar of the vocal fold. A lengthy post-operative recovery time may be required, sometimes up to a year. Despite the above, no treatment has been demonstrated to be reliably effective for this frustrating cause of dysphonia.

BEST CLINICAL PRACTICE

- ✓ Nodules:
  - ✓ Nodules are managed by speech and language therapy with compliant voice therapy and laryngopharyngeal reflux therapy.
  - ✓ Rarely, surgical removal is indicated and involves grasping the centre of a nodule, pulling it medially and then using microscissors to cut mucosa close to the base, thus preserving normal mucosa and keeping a straight vibratory edge.
- ✓ Polyps:
  - ✓ During phonosurgery, excess mucosa is resected by laser or cold instruments resulting in smooth medial surface.
- ✓ Reinke's oedema:
  - ✓ Only following smoking cessation may surgery be offered.
  - ✓ Surgical intervention involves:
    - making a cordotomy incision on the superior aspect of the vocal fold (preserving the median vibrating edge)
    - elevation of the mucosa and aspiration or removal of the myxoedematous contents
    - replacing the mucosal flaps and trimming excess epithelium
    - laying flap onto surface and leaving it to heal by surface tension.
  - ✓ There is no contraindication to operating on the contralateral fold at the same operative setting.
- ✓ Papillomatosis:
  - ✓ Papillomas are recurrent and excised as needed.
  - ✓ Options for excision include CO_2 laser, angiolytic laser, or a microdebrider.
  - ✓ Further studies are required to address best frequency of treatment.
  - ✓ Adjuvant treatments include retinoids, alpha interferon, ribavarin, cyclooxygenase 2 inhibitors and cidovir, but additional trials are required to establish these treatments as standard of care.

KEY POINTS

- Use of surgical lasers requires understanding of the effect of spot size, wattage, mode, soft tissue interactions and hazards.
- Choosing CO_2 laser or cold dissection are a matter of clinical need and experience.
- Powered instruments, such as the microdebrider, can eliminate the risk of laser plume in infected cases, for example, when dealing with papillomatosis.

VOCAL FOLD INJECTION

Brunings[14] was the first to describe injection of the vocal folds in 1911 when he injected paraffin via a direct laryngoscopic approach under local anaesthesia. It is Arnold[15] in 1962, however, who popularized this technique and the introduction of Teflon. Since then, numerous materials have been introduced and some of these are listed in this section.

Materials

TEFLON

Teflon is discussed here for its historical importance only. There is no clinical indication in which its use justifies the risk of soft tissue reaction.

Teflon is a polymer of tetrafluoroethylene and is sold as a paste consisting of 50% glycerine. The glycerine component is absorbed in the first few weeks and its volume is partially replaced initially by an acute inflammatory reaction and later by a localized chronic inflammatory response, which encapsulates the remaining Teflon. This is, in effect, a localized granuloma but the difference in the initial volume injected and the final space-occupying lesion is unpredictable, which may cause a good immediate result to deteriorate with time. If Teflon is incorrectly placed superficially and erosion of the overlying mucosa occurs, this can lead to a granuloma on the surface of the vocal fold, and a 36% incidence of granuloma production has been reported. Teflon particle sizes in the paste are sold as 50–100 microns, too large for immediate lymphatic spread since macrophage lymphatic cut-off is 40 microns. Studies on a commercial preparation of Teflon, however, have found particles of 4–40 microns, which must lead to the question of distal spread. A study on Teflon injection into the peri-urethral areas has shown spread to both regional and distal organs via venous channels, but although local spread to lymph nodes and the thyroid gland has been demonstrated with laryngeal injection, no distal spread has yet been documented.

Removal of Teflon granulomas with a CO_2 laser gives high thermal damage and the vocal fold is scarred to such an extent that poor voice is almost guaranteed. As a result, excising the Teflon via an external approach and using a local muscle flap has been described with good results.[16]

FAT

This autogenous material has numerous advantages: it is easily harvested, readily available and does not give a foreign body reaction. There is no unified technique for its harvesting, with some authors recommending liposuction (which can lead to up to 30% cell destruction and an increased hypersensitivity reaction) whilst others harvest through a larger incision followed by irrigation with saline and soaking in insulin. However, universally, fat injection requires the morbidity of the harvesting site. It is reported that 30–50% of this fat will be absorbed within the first month and long-term studies also suggest a decrease in

volume with time.[17] As a result of its absorption, many suggest overcorrection at the time of injection. The material is of high density and requires insertion deep into the vocal fold. Encouraging quantitative voice results have been reported post-injection.

GLYCERINE

This can be used as a temporary material as it is absorbed within the first 2–6 weeks. It is completely reversible and frequently combined with laryngeal electromyography (EMG) in cases of a temporary paralysis. The EMG can be used prognostically to look at reinnervation of the vocal fold and the glycerine, by augmenting the paralyzed fold, allows glottic closure. Once again, its site should be deep within the muscle of the vocal fold.

COLLAGEN

This protein is a natural constituent of the lamina propria of the vocal fold. Widely used in dermal augmentation, it has been popularized by Ford et al. for use in the larynx where it becomes incorporated and even assimilated by new host tissue.[18] A cross-linkage ensures better stability and reduces the rate of hypersensitivity, which is <1%. Skin testing pre-operatively is recommended before the collagen is injected superficially into the vocal ligament. It is a challenging procedure with blanching of the vocal fold mucosa if too superficial. Although excellent results are reported by Ford, others have found this technique difficult and noted irregularity in its mode of absorption and replacement.

SILICONE

Bioplastique is a silicone gel consisting of vulcanized polydimethylsialoxane particles ranging from 150 to 600 microns suspended in hydrogel. After an initial acute inflammatory reaction, the material develops a fibrous capsule[19] and, although not used in the United States, it has been used sparingly in Europe. Location of the material should be deep within the body of the vocal fold but so far there are few long-term results on the quality of voice or any complications with migration.

CALCIUM HYDROXYAPATITE

Radiesse voice implant is a solution of calcium hydroxyapatite carried in an aqueous gel allowing for injection through small gauge needles (25G or 27G). It has found widespread usage since the commercial supply of bovine collagen has been limited. The most critical aspect of this material is a deep injection as superficial implantation will lead to long-term hoarseness.

Selection of operative methods

These may be subdivided as follows:

- general anaesthesia: (direct laryngoscopy)
- local anaesthesia: (indirect laryngoscopy):
  - transcutaneous route through the cricothyroid membranes
  - transcutaneous route through the thyroid cartilage
  - transcutaneous route through the thyrohyoid membrane
  - transoral route.

GENERAL ANAESTHESIA

Drawbacks include visualization problems due to the anaesthetic tube or some other means of ventilation, the abnormal anatomical position of the neck, difficulty in gaining access to the larynx in patients with cervical spine problems or other anatomical factors preventing direct laryngoscopy and, most significantly, lack of patient feedback via phonation during injection. This last factor plays an essential role in deciding the amount of material to inject at the time of surgery in patients undergoing procedures under local anaesthesia. Advocates of injections under general anaesthesia argue that physical manipulation of the injection material following injection can lead to a more uniform and wider area of medialization.

LOCAL ANAESTHESIA

Injection laryngoplasty is also routinely performed under local anaesthesia with the guidance of real-time visualization, typically through nasolaryngeal flexible laryngoscopy. The laryngologist typically practices a single injection site most frequently, but should be comfortable utilizing any of the described techniques as variation in patient comfort and anatomic composition will require alterations of the method. Transcutaneous techniques maintain the benefit of being procedures that can be carried out in the office with minimal time commitment for both the provider and patients.

There are three well-described transcutaneous methods. First, a transcutaneous piercing of the thyroid cartilage is typically the most straightforward approach to injection laryngoplasty. Penetration should be through the inferior half of the thyroid cartilage but difficulty can occur when the cartilage is ossified or the needle bore is blocked with cartilage. Penetrating the cricothyroid membrane is becoming a more familiar technique now that botulinum toxin injections into the thyroarytenoid muscle for adductor spasmodic dysphonia are increasing. The injection needle can either pass directly into the cord without entering the laryngeal lumen or pass initially into the lumen and then penetrate the fold whilst being visualized via a nasendoscope (**Figure 67.9**).[20] The transcricothyroid membrane approach is similar in its approach and if ossified thyroid cartilage ala is identified then the needle point is angled inferiorly to tuck under the inferior edge of the thyroid cartilage and an audible click is usually heard once the membrane is penetrated. The needle should then immediately be angled superior-laterally to find a position deep within the adductor muscle group. The transthyrohyoid method requires topical anaesthesia of the glottis (typically topical 4% lidocaine) before injection. Following adequate anaesthesia the needle is placed at the thyroid notch and

angled immediately inferiorly. Under direct visualization, the needle tip is seen exiting the petiole mucosa at midline to enter the supraglottic lumen. Following this, the needle tip can be guided under visualization laterally into the deep adductor muscle group where laryngoplasty can be performed. Finally, with the use of a rigid curved cannula (Abraham cannula), a needle may be guided transorally following adequate mucosa topical anaesthesia to achieve direct injection into the superior surface of the lateral vocal fold.

KEY POINTS

- Injectible materials include autologous fat, glycerine, collagen, silicon, and calcium hydroxyappatite.
- All provide immediate results, though optimal voicing may take 3 days for the injectate to even out.
- The provider must have comfort with multiple injection methods as individual patient needs and anatomy will require variability in planned approaches.

LARYNGEAL FRAMEWORK SURGERY

Payr,[21] in 1915, is credited with the first description of laryngeal framework surgery. This has been refined over many years by other surgeons but Isshiki[22] was the first to describe using an alloplastic material (Silastic) and also to stress the benefits of carrying out the procedure under a local anaesthetic using the patient's voice for feedback. His name, and the classification of laryngeal framework surgery into four types of thyroplasty, remain as shown in **Figure 67.10**.[22]

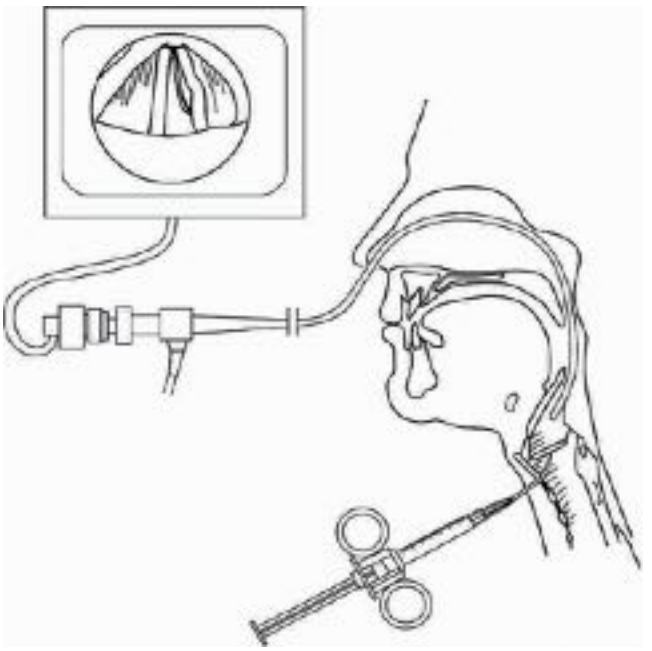


Figure 67.9 Transcutaneous technique with nasolaryngeal flexible laryngoscopy.

Laryngeal framework surgery allows the size of the glottic aperture, plane of closure of the vocal folds and vocal fold length to be modified. Laryngeal framework surgery also maintains the laryngeal dynamics without invasion of the vocal folds and alteration of their mass or stiffness.

Selection of patients

Type I, or medialization thyroplasty, can be performed for patients with a unilateral vocal cord paralysis. Waiting 12 months in idiopathic cases is recommended for possible spontaneous recovery of vocal fold motion. Injection laryngoplasty should be provided within this initial time period to allow for adequate voicing and cough. Medialization thyroplasty can also performed bilaterally in cases of bilateral bowed vocal cords, as can be caused by ageing, and may be useful to correct soft tissue defects in the vocal fold as a result of previous surgery, although the final voice expectations for these diagnoses should be quite guarded.

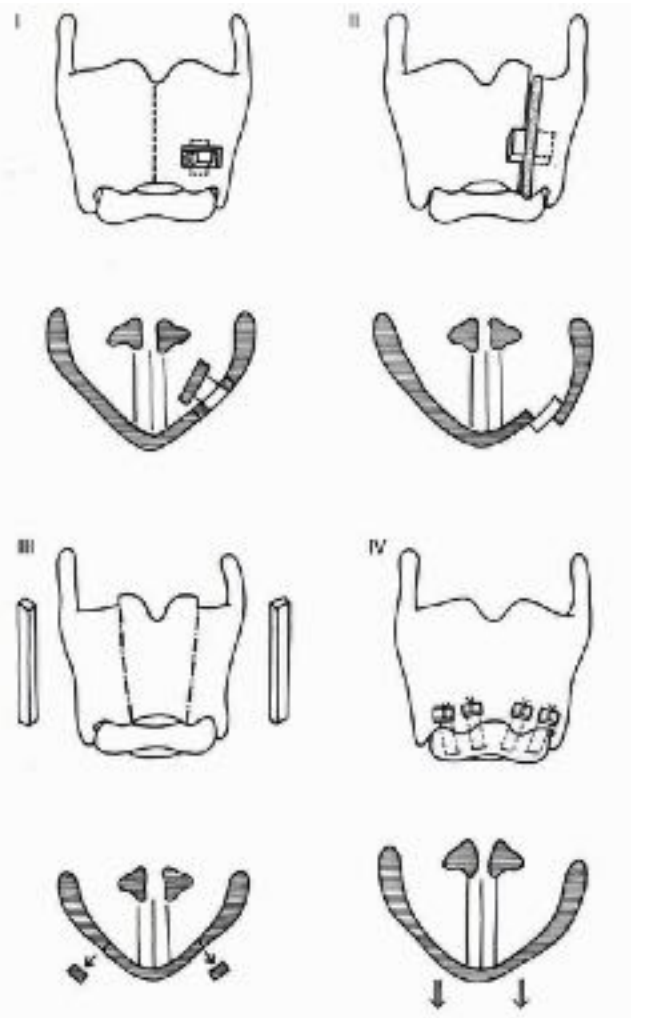


Figure 67.10 Types I, II, III and IV laryngeal framework thyroplasties, as described by Isshiki.

Techniques

Thyroplasty type 1 essentially involves medialization of the vocal cord by its inward displacement with an implant placed through a window in the thyroid cartilage (**Figure 67.11**). The comprehensive operating technique is well established[20] but some of the finer details are described here. In the original description the cartilage window was preserved but many now remove this island of cartilage, believing it can be displaced or absorbed, leading to later complications. There are specific instrument kits available for medialization laryngoplasty, which are not essential but can help to reduce the time of the procedure and ideally 30–40 minutes for a routine thyroplasty is adequate. Interestingly, one should preserve the outer perichondrium when using Gortex as this will need to be sewn back to close the defect (window) in the thyroid cartilage. It is still not certain whether a posterior glottic chink can be closed with a medialization thyroplasty alone and research on the anatomy of the cricoarytenoid joint suggests that when the paralyzed cord is on a different vertical plane to the normal one, then a medialization laryngoplasty is insufficient for full closure.

Isshiki[23] described an arytenoid adduction procedure for patients where there is a large posterior gap and the paralysed cord is at a different vertical level. Good results have been reported, both initially for a competent larynx and long term for voice production.[24] A modification of this technique is the arytenoid fixation and cricothyroid subluxation as described by Zeitels.[25] With an extended incision, the arytenoid cartilage is exposed, its attached muscles divided and the arytenoid cartilage is fixed in a midline position. Tension of the paralyzed cord is obtained by a suture between the inferior horn of the thyroid cartilage and the cricoid cartilage anteriorly (**Figure 67.12**). This is usually combined with a medialization thyroplasty and allows correct positioning of the arytenoid cartilage and gives tension and bulk to the paralyzed vocal cord. Although technically challenging, it is the author's personal choice for patients with a large posterior glottic chink.

Common problems with thyroplasty include inserting a prosthesis that is too small or inserting a prosthesis in the incorrect place. Revision thyroplasties have shown that many insert the prosthesis too high as they do not define the lower border of the thyroid cartilage (**Figure 67.11**). The vocal cords are found deep to the inferior half of the thyroid cartilage and inserting the prosthesis too high will displace the false cord and not allow glottic closure.

BEST CLINICAL PRACTICE

- ✓ Specific instrument kits are not essential; they may help to reduce operating time, but risk a one-size-fits-all surgery.
- ✓ Implants are made of silastic, hydroxyapatite or Gortex.
- ✓ Implant design varies to accommodate modifications in insertion technique and maximize some effects.
- ✓ Thyroplasty alone is unlikely to be able to close the posterior glottic chink.
- ✓ Poor results are usually due to the superior location of the thryoid window.

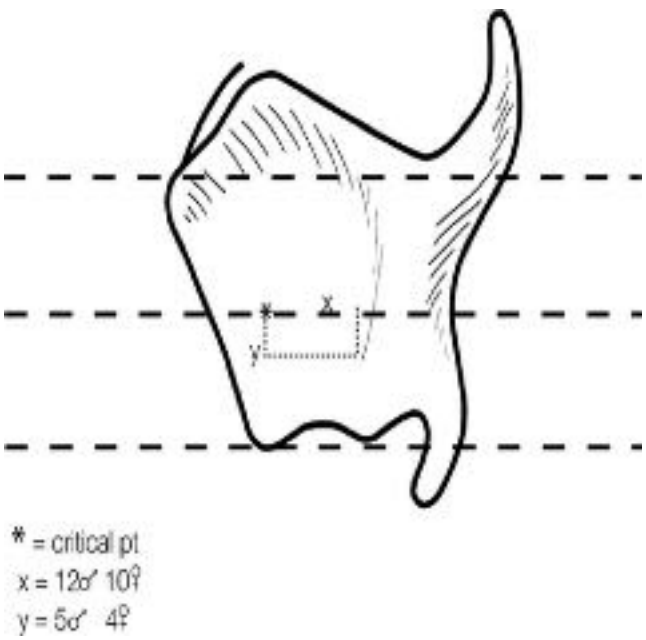


Figure 67.11 Dimensions (in mm) and location of window in thyroid cartilage.

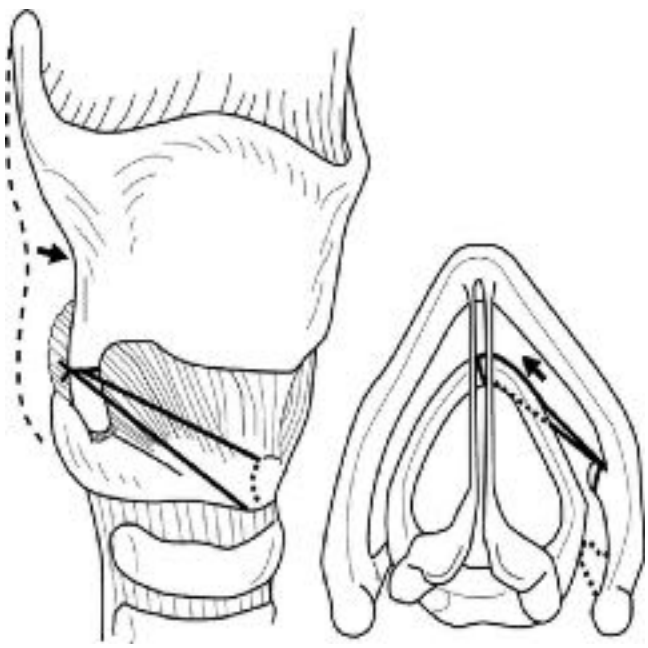


Figure 67.12 Suture gives tension to the paralyzed vocal cord with the arytenoid cartilage fixed medially.

REINNERVATION PROCEDURES

Recurrent laryngeal nerve anastomosis was initially described in 1909 by Horsley[26] and further work suggested that this was a successful technique but with no objective evidence to support the conclusions. Recently, Crumley[27] has popularized the technique of ansa cervicalis to recurrent laryngeal nerve anastomosis.

Neuromuscular physiology

The recurrent laryngeal nerve is a mixed nerve containing afferent, sympathetic, parasympathetic and 500–1000 motor axons in an adductor to abductor ratio of 5 : 1. The ansa cervicalis, however, contains efferent fibres from the first three cervical nerves to innervate the strap muscles. Whereas the intrinsic laryngeal muscles are controlled to contract at specific times, the strap muscles have not been shown to have any phasic action in the primate. Reinnervated muscle takes on the characteristics of its supplying nerve, and the selection of the donor nerve should take into account the muscle fibre composition of the muscle to be reinnervated.

Muscle fibres can be divided into specific types based on the histochemical and contractile properties. There are three basic groups:

1. **Type 1:** slow contractile period and aerobic metabolism
2. **Type 2B:** fast contractile period and anaerobic metabolism
3. **Type 2A:** intermediate contractile period and both aerobic and anaerobic metabolism.

Muscles that produce low tension over a sustained time period will have a high concentration of type 1 muscle fibres. A high concentration of type 2 fibres will be seen in muscles that contract rapidly generating high tension over a short time. The intrinsic muscles of the larynx differ in their constitution of muscle fibres but the thyroarytenoid muscle (part of which is the vocalis muscle of the vocal fold) has a fast contraction time (14 milliseconds) and < 36% type 1 muscle fibres. The strap muscles, however, have a higher percentage of type 1 muscle fibres (66%) and a contraction time of 50 microseconds. The distribution of neuromuscular endplates in each of the intrinsic laryngeal muscles and the strap muscles are also different, with a diffuse pattern in the thyroarytenoid but a typical skeletal muscle distribution in the strap muscles where they form a narrow band at the midpoint. This gross difference in the histochemical and contractile properties of these muscle groups and their nerve supply makes them poor recipients and donors for nerve transfer. It is proposed that the unfavourable synkinesis that occurs in

TABLE 67.1 Comparison of procedures currently used for the rehabilitation of a patient with unilateral vocal fold paralysis

Procedure	Time taken (minutes)	Results	Anaesthetic	Demand on technical skill	Complications
Fat injection	10–30	Immediate but 30–50% and in 1/12 good voice results	Local/general	Moderate	Under-injection
Glycerine injection	10–30	Immediate	Local/general	Moderate	Over-injection
					Airway compromise
					Under-injection
					Over-injection
Fat injection	10–30	Immediate but 30–50% and in 1/12 good voice results	Local/general	Moderate	Airway compromise
Collagen injection	10–30	Immediate	Local/general	High	Under-injection
					Over-injection
Glycerine injection	10–30	Immediate	Local/general	Moderate	Airway compromise
Silicone injection	10–30	Immediate	Local/general	High	Under-injection
					Over-injection
Collagen injection	10–30	Immediate	Local/general	High	Airway compromise
Laryngeal framework surgery	35–75	Immediate	Local/general	Moderate	Wound infection
					Haematoma
Silicone injection	10–30	Immediate	Local/general	High	Airway compromise
					Mucosal perforation
					Dislodgement and/or extrusion
Reinnervation	60–120	2–3 months (+ Gelfoam/Glycerine injection)	General	Most	Wound infection
					Haematoma
					Loss of abnormal synkinetic tone (Flaccid fold)

a damaged recurrent laryngeal nerve with mixed partial axonal regrowth is replaced by a more favourable synkinesis from the ansa cervicalis.

Muscle nerve pedicle reinnervation has also been described using a block of omohyoid with its branch from the ansa cervicalis, although some surgeons are now combining neural anastomosis with laryngeal framework surgery as it appears that neural anastomosis alone does not give a good result in a lateralized cord. In the author's opinion, there is currently no convincing clinical or scientific evidence that the reinnervation techniques give better or equal results to either injection, medialization or laryngeal framework surgery in the management of a unilateral vocal cord paralysis. **Table 67.1** shows the advantages and disadvantages of the most common procedures currently used for the rehabilitation of a patient with a unilateral vocal cord paralysis.

FUTURE RESEARCH

Phonosurgery would benefit from:

- improved methods of measuring voice (i.e. objective, subjective, patient based) for meaningful comparison
- reliable surgical interventions for vocal fold scar
- Clinical trial for the establishment of safe adjuvant treatment for successful management of respiratory papillomatosis.

KEY POINTS

- The underlying etiology of the vocal abnormality must be established before any treatment can be offered.
- Complete assessment with videostroboscopy and voice measurements pre- and post-surgery are desirable.
- Knowledge of the anatomy and microstructure of the vocal cords and location of lesion is essential.
- Selection of laryngoscopes, micro-instruments and operative lasers are required before phonosurgery can be performed.
- Vocal fold nodules should rarely, if ever, require phonosurgery.
- Materials such as calcium hydroxyappetitie have replaced Teflon for vocal fold injection laryngoplasty.
- Laryngeal framework surgery can be performed under local anaesthesia for intra-operative auditory feedback.

ACKNOWLEDGEMENTS

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CHAPTER
68

MOVEMENT DISORDERS OF THE LARYNX

Declan Costello and John S. Rubin

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Hyperfunctional conditions 996
Treatment of spasmodic dysphonia 998
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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: dysphonia, spasmodic dysphonia, Parkinson's disease and vocal tremor.

INTRODUCTION

The larynx is subject to highly complex neurological control to fulfil its roles in phonation, deglutition and respiration. Dysfunction of the movement of the larynx may reflect a wider neurological condition or may be an isolated disorder of the vocal tract.

In broad terms, disorders of movement of the larynx can be thought of as either hypofunctional or hyperfunctional. Further conditions may be related to poor coordination or stability of the voice.

HYPOFUNCTIONAL CONDITIONS

Parkinson's disease

Parkinsonism is a term referring to a group of conditions including idiopathic Parkinson's disease (PD), Parkinson's plus syndromes and secondary Parkinson's.

Idiopathic PD accounts for around 80% of cases of Parkinsonism; it is a nigrostriatal disorder characterized by a deficiency of dopamine. Generalized rigidity is seen, along with bradykinesia (slowness of movement). These two aspects are collectively described as hypokinesia. Tremor (typically a 'pill-rolling' tremor) is a very common feature. PD is a relatively common neurological disorder, with a prevalence of 1 per 1000 of the population, rising to around 1 per 100 in the over-60 age group.[1]

Although PD is usually thought of as a condition of older age, it can also affect younger patients.

The voice in patients with PD is typically described as 'monotone' and reduced in volume. These features are a consequence of reduced activation of the thyroarytenoid muscle.[2] Examination of the larynx will characteristically show bowing of the vocal folds, resulting in a quiet and breathy vocal quality. This weakness of voice is accompanied by dysarthria (poor articulation).

MANAGEMENT OF PD

Systemic treatment with dopaminergic agents (levodopa, l-dopa) can achieve significant improvements in the peripheral symptoms; however, these improvements are not always reflected in changes in the voice.[3] In recent years, the application of the Lee Silverman Voice Treatment (LSVT) has resulted in dramatic improvements for many patients. The LSVT mode of management requires a specific programme of intensive sessions of daily therapy over a one-month period.[4]

PARKINSON'S PLUS SYNDROMES

Progressive supranuclear palsy

Progressive supranuclear palsy (PSP) is a neurological condition that results from accumulations of tau protein in the basal ganglia, brainstem and cerebral cortex. Initial symptoms include loss of balance and bradykinesia.

Ocular symptoms such as poor control of eye movements are seen. The speech and laryngeal manifestations in patients with PSP include dysarthria and monotone voice. Treatment is essentially palliative, with l-dopa sometimes providing some control of symptoms.

Multiple-system atrophy

Multiple system atrophy (MSA) is a degenerative disease in which there is cell loss in specific areas of the brain. Autonomic failure is a common feature, and in these cases, the condition is referred to as Shy-Drager syndrome. The laryngeal manifestations may include bilateral vocal fold paresis or paralysis. The voice may exhibit hypo- or hyper-functional features, being either breathy and weak or loud and strained.

Motor neurone disease

Motor neurone disease (MND) refers to a group of disorders that includes amyotrophic lateral sclerosis (ALS), progressive bulbar palsy (PBP), progressive muscular atrophy (PMA), and primary lateral sclerosis (PLS). Of these, ALS is the most common. MND is characterized by progressive degeneration of the motor cells of the brain and spinal cord. Both lower motor neurone (LMN) and upper motor neurone (UMN) dysfunction occurs, usually with LMN signs predominating. The progression of the disease is usually rapid and life expectancy is typically 2 to 5 years from diagnosis.

The usual presentation (in 80% of cases) is in the limbs, with limb weakness, fasciculations and brisk reflexes. However, 20% of cases will present with bulbar signs and symptoms; these include dysarthria (as a result of limitation of tongue movement), tongue fasciculation, dysphagia and nasal regurgitation. Voice changes can comprise a 'wet' sounding voice as a result of pooling of secretions in the larynx, along with a harsh and/or breathy voice quality, and often vocal tremor. Hypernasality can result from poor velopharyngeal function.

Swallowing is generally affected as well as voice, with aspiration pneumonia a possibility. Not infrequently, adjunctive management of swallow (with a gastrostomy) as well as of airway (with tracheostomy) are required.[5]

Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune disorder in which antibodies to the postsynaptic acetylcholine muscle receptors prevent neuromuscular transmission. This results in progressive muscle weakness and fatigability. Small muscles are usually the first to be affected, most frequently those around the eye. That said, up to 20% of patients initially present with voice changes – most often vocal fatigue; this is frequently with a negative acetylcholine receptor antibody titre.[6] Other laryngological changes include stridor and voice weakness. More broadly, the voice may sound hypernasal and the patient may be dysarthric. A misdiagnosis of superior laryngeal nerve palsy and/or bilateral vocal fold paresis may delay the formal diagnosis of MG.

Because fatigability is a key finding in MG, laryngeal examination should include asking the patient to perform repeated vocal tasks.[7] Treatment of MG centres on the administration of anticholinesterase drugs (pyridostigmine); in some cases steroids are required and occasionally thymectomy is undertaken.

Vocal fold paralysis

Paralysis of one or both vocal folds may result from one of a wide number of neurological conditions – many of these are described above. A detailed description of vocal fold paralysis is outlined in Chapter 78, Paralysis of the larynx.

HYPERFUNCTIONAL CONDITIONS

Pseudobulbar palsy

A UMN lesion in the corticobulbar pathway may cause difficulty chewing, manipulating a food bolus in the oral cavity, swallowing, and dysarthria. The most frequent cause is cerebrovascular accident, but other causes may include demyelination (multiple sclerosis), PSP, ALS, PD, MSA and malignancy. The voice may exhibit a strained and strangled quality, and running speech shows dysfluency.

Huntington's disease

Huntington's disease is inherited in an autosomal dominant pattern. It is a neurodegenerative disease in which patients exhibit involuntary muscle movements (chorea), as well as cognitive and psychiatric problems.

Poor coordination of muscle movements is also seen in the larynx, and results in a wide variety of vocal changes: poor control of pitch and volume may occur, along with a strained voice quality or complete voice breaks.[8, 9]

Spasmodic dysphonia

Of the conditions described above, few are amenable to specific treatment that can improve the vocal quality, and in most cases, only supportive treatment can be offered. In contrast, the symptoms of spasmodic dysphonia (SD) are readily controlled with injections of botulinum toxin, combined with voice therapy to eliminate hyperfunction.[34]

SD is a voice disorder arising from a focal dystonia involving certain laryngeal muscles[10–12] but reflecting central motor processing issues/abnormalities.[13] It is only present during certain specific speech vocal tasks, and can be overridden by vegetative phenomena such as laughing or by chanting or singing. There is a background of normal speech overlain by vocal spasms that are not under voluntary control. This leads to a typical strained and strangled speech pattern[14, 15] that was recognized by MacKenzie more than a century ago.[16]

SPASMODIC DYSPHONIA: AETIOLOGY AND INCIDENCE

Early theories suggested that SD was a psychoneurosis.[17, 18] It was then determined to be of neurological origin and to represent a focal dystonia.[9, 19] Recent functional MRI (fMRI) studies have failed to identify any specific structural defect. In most instances the aetiology of SD is unknown/idiopathic although not uncommonly the patient will relate onset to a specific event such as a 'flu-like syndrome or an emotionally traumatic event.

At the time of writing this chapter, at least 13 genes or chromosomal locations have been associated to dystonias and several to voice disturbances on case-report basis. Recently, the DYT6 dystonia (a primary, early-onset torsion dystonia) has been found to be caused by mutations in the THAP1 gene (thanatos-associated protein domain containing apoptosis-associated protein 1).[20–22] Further studies have identified THAP1 mutations in certain dystonias (both generalized and focal), and this has included cases with early involvement of the larynx.[23] Involvement is limited, however, and in 160 patients with SD screened, only 1% had THAP1 mutations.[23]

In general, approximately 8% of patients have a family history of dystonia,[20, 24] but this is less commonly the case with SD. Blitzer[25] highlights that most cases of SD are sporadic, although Schweinfurth et al. in their case series noted a 20% association with other forms of focal dystonias.[14, 26]

Estimates of incidence vary, with one being given at 1 per 100 000.[27] It is unclear if SD is a relatively rare disorder or whether failure of recognition of the condition results in a low pick-up rate. There are approximately 30 000 to 50 000 people in North America affected. Because of the difficulty securing the diagnosis, there is usually a long interval between onset of symptoms and diagnosis; in our experience, this is approximately 2–3 years (Costello and Rubin, personal observations). SD is more prevalent in females than in males and the average age of onset is 40 years.

Ludlow summarizes that the current view points to focal dystonia is due to a combination of genetic predisposition interacting with acquired factors later in life, for example head injury, drug exposure or peripheral injury.[15]

SOCIAL IMPLICATIONS

SD has significant social implications and impacts on the patient's quality of life. Due to the phonation breaks and strangled quality of the voice (and the fact that symptoms are worse when stressed or when speaking over the phone), individuals affected may become socially isolated. There is no question that it affects communication and causes major social disruption in the lives of sufferers. Izdebski et al. have noted that SD affects job performance in 77–93% of affected individuals and that 26–37% need to change job or be reclassified within the work setting.[28–31]

CLINICAL FEATURES

SD is a task-specific dystonia: the spasm only occurs on phonation. On endoscopy at rest, the larynx appears normal, but on phonation, spasm of the laryngeal musculature is seen and heard. It is also typically worsened by use of the telephone or in times of heightened anxiety, for example when meeting people for the first time. Many patients report that alcohol intake ameliorates symptoms of SD.

The airway is not compromised in SD – adduction occurs only on phonation and never during respiration.

SPASMODIC DYSPHONIA: TYPES

SD tends to be differentiated by symptoms into **adductor**, **abductor** and **mixed** types.

Adductor SD

Adductor SD is by far the commonest type, affecting approximately 90% of patients with SD.[32] The characteristic adductor spasm results in a strangled and staccato voice. This can easily be mistaken for muscle tension dysphonia, and is frequently treated as such for some time before SD is diagnosed.

It is characterized by phonation breaks associated with vowels, in particular words ending with a vowel and being followed on by a word starting with a vowel (for example 'we – eat') and words with two vowels in tandem (for example, eighty-year – eels). The vowels /i/ ('ee') and /a/ ('ah') are particularly problematic. Interestingly, patients may often produce a relatively normal phonation on a continuous vowel sound.

Hyperfunctional voice and psychogenic voice disorder may be confused with SD. Hyperfunctional voices tend to have voice hallmarks of prolonged, constant strained voice but with no phonation breaks. Spastic UMN conditions may also be misdiagnosed as SD.

Abductor SD

Abductor SD is far less common. In our practice we have identified it as the predominant presentation in under 10% of individuals presenting with voice dystonias. Individuals with abductor SD have particular difficulty with voice onset after voiceless consonants at the beginnings of words or phrases (words starting with /w/, /b/, /s/, /t/, /p/, /f/, etc.), often leading to problems with vocal fold closure for the following sound. Typical examples given include phrases such as 'who has hidden Harry's hat?'. Attempts to pronounce such sounds lead to voiceless voice breaks.

Disorders that may be confused with abductor SD include psychogenic voice disorders such as whisper dysphonia and neurologic disorders, in particular forms of Parkinsonism.

DIAGNOSIS

The diagnosis of SD is made on clinical grounds, and usually solely by the listening skills of an experienced clinician. Both in adductor and abductor SD, it is often the case that patients have seen numerous clinicians before a diagnosis of SD is reached. To the untrained ear, the voice may sound so unusual that patients are sent for speech

therapy, psychotherapy and alternative therapies to treat what is thought to be a psychogenic phenomenon.

Electromyography (EMG) will demonstrate bursts of involuntary spasms of electrical activity overlaid on normal interference pattern.[33] In adductor SD, increased thyroarytenoid activity is observed during these bursts.[33] That said, EMG does not really improve the diagnosis made with the ear, but instead serves to confirm it, except in particularly difficult diagnostic circumstances (Rubin, personal observation).

Assessment of SD requires evaluation by a multidisciplinary team. Core members include the speech-language therapist, otolaryngologist, neurologist and neurophysiologist. It is most helpful to have a good relationship with psychologist and psychiatrist as well. A careful case history, emphasizing the psychosocial aspects, is fundamental to diagnosis as well as successful management.

Nasendoscopic inspection and recording with playback to the patient is the gold standard. It is interesting to note that the insertion of the nasendoscope may temporarily diminish the spasm. This unexpected finding gives weight to the hypothesis that SD may be primarily a disorder of sensory input: the altered afferent input from the pharynx and larynx during endoscopy appears in some way to modulate the efferent motor signals, and can reduce the amount of spasm. Assessment by the speech-language therapist with a trial of voice therapy generally occurs, and all patients are referred for baseline neurological evaluation.

Speech-language therapists have a crucial contribution to differential diagnosis. Their role includes perceptual and instrumental assessment that are critical to measurement of baseline status and outcome, patient counselling in all cases and voice therapy in some cases; therapeutic techniques, when combined with botulinum toxin injections, can improve outcomes.[34]

The voice assessment includes repetition of sentences loaded with voiced segments and vowels, as this will provoke (worsen) symptoms (i.e. more strain, voice breaks). In adductor SD, sentences loaded with voiceless segments will decrease symptoms (i.e. improved performance, less strain and fewer voice breaks) whilst voiced consonants will make the voice worse (**Box 68.1**).

Other task-specific tests to detect adductor SD include:

1. Sentences with all voiced consonants to provoke more symptoms: 'Early one morning a man and a woman were ambling along a one-mile lane running near rainy island avenue.'[35]
2. Sentences with mostly voiceless consonants to provoke fewer symptoms (i.e. better voice with this phonetic context): 'He saw half a shape mystically cross fifty or sixty steps in front of his sister Kathy's house.'

BOX 68.1 Voiced (voice 'on') versus voiceless (voice 'off')

Voiced consonants	Voiceless consonants
Stops /b/, /d/, /g/	Stops /p/, /t/, /k/
Fricatives /v/, /z/,/ zh/	Fricatives /f/, /s/, /sh/, /h/
Affricates /dz/	Affricates /ch/
Glides & liquids /w/, / r/, /l/, /j/	

BOX 68.2 Laryngoscopy protocol

Quiet respiration
Prolonged /i/; /a/
Repetitive /i/ /i/ /i/
/si/ /si/ /si/
/mi/ /mi/ /mi
/isi/ /isi/ /isi/
We eat eel every day
She speaks pleasingly
We mow the lawn all year
Peter will keep at the peak
The puppy bit the tape
Harry has a hat; his hat is on his head
When he comes home we'll feed him
Taxi, Taxi, Taxi
Tell me about your voice problem or how did you get here today
Alternating high and low pitch phonations

In the clinic, two vocal tasks are particularly helpful: adductor SD is commonly more detected when the patient counts upwards from the number 80 ('80–81–82–83…'). For abductor SD, counting from 50 ('50–51–52–53…') will exacerbate the spasm. These tasks may be used prior to and then during nasendoscopy (**Box 68.2**).

Tremor

Vocal tremor can occur on its own or with SD. It is said to be present in approximately one-third of individuals with SD.[36] In tremor, regularly spaced voice breaks are noted particularly on prolonged vowel /a/ or /I/. The modulation is at between 3 and 5 Hz. Tremor affects women most commonly, especially in middle age. Often, tremor is more evident in the chest voice, rather than the head voice.

Familial forms of tremor may lead to vocal manifestations in the absence of laryngeal dystonia. Essential tremor, the most common form of movement disorder, has a prevalence of approximately 4% of individuals aged 40 and older, increasing with age. Whilst it affects all age groups, its incidence increases with age. No genes have been identified yet but inheritance patterns are said to be most consistent with autosomal dominance. Hands and feet are most commonly affected, but the voice is affected in 4–20% of cases. On PET scanning, in certain instances the olivo-cerebellar tracts have been noted to be abnormal, with increased cerebellar activity even at rest.

TREATMENT OF SPASMODIC DYSPHONIA

As no definitive cause for SD has been established, the treatment centres on controlling symptoms.

Speech therapy

There is little role for speech therapy in the management of SD. In some cases, therapy may help to ameliorate some of the compensatory tension patterns that develop as a consequence of the dystonia, but therapy alone is never curative. This is borne out by recent research[37] demonstrating no additional improvement in voice outcomes with the inclusion of therapy as well as botulinum toxin injection.[34]

One form of voice therapy, 'inhalational speaking', has been espoused by Shulman to allow individuals with severe SD to phonate.[38] We have anecdotally noted several of our patients to attempt phonation in this manner (Rubin, personal observation 2011).

However, the role of the speech therapist in the diagnosis of SD is essential, as therapeutic techniques can often help to differentiate between SD and muscle tension dysphonia. They also have a critical role in monitoring voice quality and managing side effects.

Medical therapy

In cases of isolated SD, there is no role for systemic medical therapy. However, in cases of SD associated with other dystonias (facial dystonia, for example), low-dose benzodiazepines may be useful.

Botulinum toxin

The mainstay of treatment of SD is repeated botulinum toxin injections.[39–42] In clinical practice in the UK, most clinicians use botulinum toxin type A.

Botulinum toxin is a neurotoxin produced by the gram-positive anaerobic bacterium *Clostridium botulinum*. There are seven types that are structurally similar but antigenically and serologically distinct. The established drug names have changed over time to reinforce the differences and prevent medication errors. The current products include:

- OnabotulinumtoxinA (Botox, Botox Cosmetic). Botox is approved for cervical dystonia, severe axillary hyperhydrosis, strabismus and blepharospasm. Botox Cosmetic is approved for moderate-severe glabellar lines.
- AbobotulinumtoxinA (Dysport), approved for cervical dystonia, moderate-severe glabellar lines.
- IncobutulinumtoxinA (Xeomin) approved for cervical dystonia and blepharospasm.
- RimabotulinumtoxinB (Myobloc) approved for cervical dystonia.

The molecule is synthesized as a single chain (150 kD) and then cleaved to form the dichain molecule with a disulfide bridge.[43, 44] Botulinum toxin acts by binding presynaptically to high-affinity recognition sites on cholinergic nerve terminals, causing a neuromuscular blocking effect by decreasing release of acetylcholine. Slow recovery occurs by proximal sprouting of axons and muscle reinnervation by the formation of a new neurotransmitter junction, with ultimate regeneration of the original neuromuscular junction.[45]

ADDUCTOR SD – BOTULINUM TOXIN INJECTIONS

For patients with adductor SD, the injections of the thyroarytenoid muscle with botulinum toxin may be performed permucosally (under local or general anaesthetic) or, more commonly, transcutaneously.

The transcutaneous injection technique approaches the thyroarytenoid muscle through the cricothyroid membrane. After sterilizing the skin, the needle is advanced in the midline through the cricothyroid membrane. Care must be taken not to enter the airway: this will cause the patient to cough. Having entered the skin and passed through the cricothyroid membrane, the needle is angled 15 degrees cranially and 30 degrees laterally and then advanced into the body of the thyroarytenoid muscle. No local anaesthetic is required as the injection needle is of a very small calibre (generally 26G) (see **Figures 68.1**, **68.2** and **68.3**).

Many clinicians use electromyographic (EMG) monitoring to ensure that the tip of the injection needle is appropriately placed in the thyroarytenoid muscle. The EMG needle electrode is a fine-bore needle with an insulated shaft and an exposed electrode tip at the point. The circuit is completed with a wire that is connected to an EMG. The use of EMG can confirm that the needle tip is in *a* muscle, but will not help the clinician to know *which* muscle. When the needle tip is thought to be in the muscle, the patient is asked to phonate (/i/) – this causes a characteristic burst of activity on the EMG monitor, and the botulinum toxin can be rapidly delivered into the muscle.

In general, patients will receive a low dose of botulinum toxin (between 3 and 10 units of dysport (equal approximately to between 1 and 3 units of botox)) into one or both thyroarytenoid muscles. In practice, a newly diagnosed patient will usually receive a small dose of botulinum toxin into one or other vocal fold. The dose is then titrated upwards (or downwards) according to the patient's response. The frequency of dosing is variable: in some patients, injections are only required every

TABLE 68.1 Commonly used preparations of Botulinum toxin A and their relative properties

Name of preparation	Botox	Dysport	Xeomin
Manufacturer	Allergan	Ipsen	Merz
Dose equivalence	1 unit is equivalent to	3 units are equivalent to	0.75 units
Storage	Refrigerated	Refrigerated	Room temperature



Figure 68.1 Setup for laryngeal injection of Botulinum toxin, with EMG machine.



Figure 68.2 Note that the skin is entered at the cricothyroid membrane.



Figure 68.3 The patient's neck is extended by placing a pillow under the shoulders.

6 months; in others, they can be required every 6 weeks. In the 7 days after an injection, the patient can expect their voice to be a little weak and breathy. During this time, they may also experience problems with aspiration of liquids. Following this, the voice will reach a steady state, and should reach its maximal benefit 2–3 weeks after the injection.

On the whole, a higher dose will have a longer duration of effect. On the other hand, a higher dose will also give rise to more side effects (such as breathy voice and aspiration of liquids). Every patient requires a subtly different timing and dosing of injections and will have personal preferences; for example, a retired patient who lives a long distance from the clinic may be happy to have a higher dose (and accept the initial side effects) if (s)he only has to attend every 6 months. Conversely, a working professional may be willing to attend the clinic every 6 weeks for a low dose in order not to have a period of vocal weakness.

In a questionnaire survey of American laryngologists injecting botulinum into the larynx, most reported that they used EMG to guide needle placement; more perform bilateral injections than unilateral; almost all are guided by their patients' wishes and complications from previous injections as to their subsequent injection and dosage; and most inject 3–4 times per year.[46]

We performed a subjective patient-reported questionnaire looking at relative success rate and complications (length of breathiness, swallowing issues, cough) in a group of our patients with adductor SD. We found 94% 'success' rate from the previous injection, mean dose (Dysport) in our unilateral injections of 3.6 iU, mean dose bilateral of 6.6 iU. In this group, we did not find significant differences in terms of length of breathiness, cough or dysphagia between low dose unilateral or bilateral injection.[47]

ABDUCTOR SD – BOTULINUM TOXIN INJECTIONS

Accessing the posterior cricoarytenoid (PCA) muscle for injection of botulinum toxin is more difficult; its location at the posterior aspect of the larynx makes injection more technically challenging. It may be approached transcutaneously by manually rotating the larynx into a position where the posterior cricoid ring can be accessed. This is a deep injection in the neck, and often requires local anaesthetic. If the PCA is injected transcutaneously, EMG guidance is essential; the muscle can be difficult to locate, and EMG confirmation (by asking the patient to abduct the vocal folds with a forced sniff) is required to confirm needle placement.

Some clinicians prefer to perform PCA injections under general anaesthetic. This is performed by lifting the larynx forwards with a laryngoscope and injecting behind the cricoid ring into the PCA muscle. Care must be taken to direct the injection laterally; erroneous injection of both PCA muscles might result in complete failure of the patient to be able to abduct *both* vocal folds, and consequent airway compromise.

Botulinum toxin injections for abductor SD appear to be less effective than for adductor SD. A larger dose is usually required to achieve adequate results.

SURGERY

Recurrent laryngeal nerve section/crush

In 1976, Dedo first described a technique of unilateral recurrent laryngeal nerve (RLN) sectioning for adductor SD.[48–50] Initial results were promising, but further follow-up[51] demonstrated that longer-term results were not maintained.

Recurrent laryngeal nerve selective denervation and reinnervation

There are two significant problems with nerve section/crush: first, the muscle may be prone to atrophy; and second, there is a likelihood of reinnervation by the cut end of the RLN. Berke et al. have postulated that selectively denervating the thyroarytenoid and lateral cricoarytenoid muscles, followed by providing tone to the muscles with an ansa cervicalis anastomosis, might preserve muscle tone.[52, 53] The results appear impressive, with 82% of patients reporting that they would recommend the surgery to others.[54]

Thyroarytenoid myotomy

A method of causing thyroarytenoid inactivity has been proposed by coagulating the muscle with a laser. In a small series, this has proven to be a promising treatment option.[55, 56]

Type 2 thyroplasty

Isshiki has proposed a type 2 thyroplasty as treatment for adductor SD.[57, 58] In this procedure, the anterior larynx is approached through a neck incision. The thyroid cartilage is divided in the midline (as for a laryngotomy), taking care not to enter the airway. A shim (of titanium in Isshiki's description) is inserted to produce a separation of the anterior vocal folds at the anterior commissure. This is performed under local anaesthetic, allowing the patient to talk, so that the correct size of shim can be ascertained intra-operatively. In this relatively large series (41 patients), the results are very promising.

KEY POINTS

- Systemic neurological conditions can have profound effects on the voice, airway and swallowing.
- Multidisciplinary working is critical, including neurologists, laryngologists, speech therapists (with specific skills in treating neurologically disordered patients) and radiologists.
- Many neurological conditions are best treated with voice therapy and supportive care.
- Spasmodic dysphonia is a rare focal dystonia of the larynx; it is frequently misdiagnosed but is readily amenable to treatment with injections of botulinum toxin.

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CHAPTER 69

ACUTE INFECTIONS OF THE LARYNX

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SEARCH STRATEGY

Data in this chapter is based on a Pubmed and Ovid (Medline) search of the English language literature. The MeSH key words used were laryngitis, epiglottitis, croup, laryngotracheobronchitis, pertussis and other search terms used were supraglottitis, laryngeal infections, upper airway infections. The clinical recommendations are predominantly group C.

INTRODUCTION

Acute infections of the larynx are not unusual and are most commonly associated with an upper respiratory tract infection that is usually of viral origin. Therefore, these conditions are mostly managed in the primary care setting. However, there are specific types of infections of the larynx that require specialized care and it is therefore essential for the practising otorhinolaryngologist to be familiar with these conditions.

Furthermore, although the majority of acute laryngeal infections are self-limiting and resolve with supportive care, in a small number of cases an acute infection can progress rapidly into a life-threatening condition requiring urgent expert care in a hospital setting. This will often require input from an experienced team of clinicians, which may include an emergency medicine physician, otorhinolaryngologist, anaesthetist, paediatrician and microbiologist.

In this chapter, we provide an overview of the types of acute laryngeal infections and management strategies for dealing with these conditions.

CLINICAL FEATURES

The term laryngitis refers to inflammation of the tissues of the larynx. In acute forms the onset is usually abrupt. The general symptoms and signs of acute laryngeal infection are listed in **Table 69.1**.

Stridor is a serious symptom as it is associated with significant airway narrowing. It is more commonly seen in children and such cases should be managed jointly with a paediatrician in a hospital setting. Narrowing at the supraglottis or glottis is typically associated with inspiratory stridor. Narrowing below the level of the glottis may also present with inspiratory stridor but typically will be biphasic in nature.

Examination of children with stridor should be done by an experienced clinician with care taken not to cause any additional distress to the child. In adults, a flexible laryngoscopy is required for direct visualization of the larynx in most cases. This allows an assessment of

TABLE 69.1 Signs and symptoms of acute laryngeal infection

Symtoms	Signs
Dysphonia	Tender laryngeal framework
Dyspnoea	Stridor
Sore throat	Cervical lymphadenopathy
Odynophagia	Pharyngitis
Referred otalgia	Pooling of saliva

the vocal cords themselves, the supraglottis and an overall clinical assessment of the patency of the laryngeal airway.

ACUTE LARYNGITIS

Acute laryngitis is a common inflammatory clinical condition of the glottis and supraglottis. It is most commonly due to a virus associated with an upper respiratory tract infection. It may also occur secondary to infections of the upper and lower respiratory tract such as tonsillitis or chest infections.

The majority of cases of acute laryngitis are self-limiting and resolve within a couple of weeks. Patients typically present with a hoarse voice associated with symptoms of a common cold. In some cases, there may be a superadded bacterial infection that may lead to a more severe type of laryngitis. Fungal infections of the larynx are dealt with in 'Mycotic laryngitis' below.

Treatment initially includes vocal hygiene measures including voice rest, analgesics/anti-inflammatory medications, avoidance of irritants (e.g. smoking and alcohol) and maintaining good hydration of the larynx. Steam inhalation has been used although most of the reports are in children with croup and there is no good evidence of benefit.[1]

The role of antibiotics in cases of acute laryngitis should be reserved for cases where there is clinical suspicion of bacterial infection. Typically, these patients may have persistent and more severe laryngitis or other associated infections of the upper or lower respiratory tract. In general, antibiotics have little role in the treatment of the majority of cases of acute laryngitis,[2, 3] although there is some evidence that erythromycin may reduce voice disturbance in the first week and therefore may be considered in patients who are professional voice users.[4] The choice of antibiotic depends on any associated infections but penicillin has been reported as being ineffective[5] and macrolides (e.g. erythromycin or clarithromycin) have been shown to be effective, which may be a reflection of infection with *Moraxella catarrhalis*.[6]

There have been recent case reports of methicillin-resistant *Staphylococcus aureus* laryngitis[7, 8] and this should be considered in cases not responding to first-line antibiotics. Diagnosis will be made by microlaryngoscopy and cultures, which should be considered in cases that are not responding to first-line treatment.

Patients with stridor generally should be admitted to hospital and intravenous antibiotics, nebulized adrenaline and steroids considered. It is important to liaise with an experienced anaesthetist and the patient should be observed in an appropriate clinical setting such as a high dependency unit. If there is airway compromise that is deemed severe enough then early intubation and ventilation should be considered until the airway inflammation has improved. Tracheostomy is rarely indicated.

Patients with persistent hoarseness lasting for more than a few weeks should be reviewed in a specialized voice clinic along with a speech therapist. The pathogenesis of laryngeal inflammation can be multifactorial and factors in addition to the viral or bacterial infection, such as smoking, allergy, rhinosinusitis, voice abuse and laryngopharyngeal reflux, should also be managed appropriately.[9] If doubt as to the diagnosis persists then formal microlaryngoscopy should be considered.

EPIGLOTTITIS (SUPRAGLOTTITIS)

Epiglottitis is an acute infection of the supraglottis characterized by inflammation of the supraglottic structures. It is usually due to a bacterial infection and should be considered to be an emergency condition due to the potential rapid and fatal airway obstruction. The incidence of epiglottitis is 1–2/100 000.[10, 11]

Historically the most common causative organism was *Haemophilus influenza* type b (Hib), which accounted for almost 90% of cases.[8] The incidence of epiglottitis (particularly in children) has decreased significantly as a result of the *Haemophilus influenza* type b vaccination, which was introduced in the UK in 1985 to prevent childhood meningitis.[12, 13] However, this has led to the emergence of other causative organisms (e.g. *beta haemolytic Streptococcus*, *Streptococcus pneumoniae*, *Streptococcus milleri*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Neisseria* spp.) and there has been an increase in the incidence of adult epiglottitis that is not related to *Haemophilus influenzae* infection.[11, 14, 15] Fewer than 20% of cases of adult epiglottitis are due to *Haemophilus influenzae*.[15] *Candida albicans* is an important cause to consider in immunocompromised patients.[14, 16]

Historically the condition was more common in children than in adults and it is important to recognize that the condition presents a somewhat different clinical picture between the two age groups. In a retrospective dataset study from the United States, Shah et al. found that the typical patient admitted with epiglottitis is a 40-year-old male and that the majority of mortalities from epiglottitis were in the adult population.[17]

The clinical features vary somewhat between children and adults. In adults, the main complaint is of a painful throat with associated odynophagia.[10, 11, 14] Dyspnoea, fever and drooling may also be seen but are not always present.[10, 12, 18] As the calibre of the airway is larger in adults than children, features of upper airway obstruction may not always be present. A significant proportion of adults presenting with epiglottitis will have comorbid conditions such as diabetes, hypertension, cardiac and respiratory conditions, complications of which have an associated mortality in patients with epiglottitis.[10, 11, 17]

Diagnosis is made on examination of the larynx by trans-nasal fibre-optic laryngoscopy, which may reveal an erythematous and congested epiglottis with inflammation of the surrounding supraglottic structures.[14, 18–21] Radiological investigations are usually unnecessary, although if an associated abscess is suspected then a CT scan may be useful.[22]

Treatment of epiglottitis

Patients should be admitted for observation in an appropriate setting such as an ENT department, high dependency or intensive care unit, depending on the status of the patient. It is important to manage these patients as a team, with involvement of anaesthetists and paediatricians appropriately. Despite advances in airway management, epiglottitis is still associated with mortality from associated complications and airway problems and early appropriate management is essential to minimize an adverse outcome.[23]

A tailored, selective approach based on careful evaluation of these patients is important and varies from conservative treatment with close observation to interventional treatment by an artificial airway for patients with respiratory distress or significant stridor. Close observation is mandatory as in a small number of patients progress from no respiratory distress to a significantly compromised airway may occur in just a few hours.[18] Advice on antibiotic treatment should be sought from microbiologists but in the first instance intravenous 3rd generation cephalosporins are recommended in conjunction with metronidazole if anaerobic bacteria are considered also to be causative.[11, 14, 15, 24]

Systemic corticosteroids and nebulized adrenaline may be used in patients with significant airway compromise. Most of the literature on use of these substances is based on a paediatric population presenting with croup. Although there is no clear evidence that it is an effective treatment,[12, 18] their use may be considered in patients with a compromised airway. A short course of steroids may help to decrease the airway inflammation, possibly decreasing the need for intubation.[16, 25] However, careful consideration should be given to this rather than using corticosteroids as a matter of routine, as the evidence on the role of corticosteroids is lacking.

Most patients will respond to medical treatment, showing an improvement within 24–48 hours, and this can be monitored by examination with trans-nasal fibre-optic laryngoscopy as well as monitoring clinical and biochemical parameters.[10] There is an association between patients reporting dyspnoea and the need for airway intervention.[10] Therefore, it is always important to consider the potential complication in epiglottitis of airway obstruction and if the airway is deemed to be at risk, then there should be a low threshold for intubation of the patient at a relatively early stage. This should be done in an operating theatre setting with an experienced anaesthetist due to the risk of occlusion of the airway with instrumentation of an inflamed larynx.[26] Tracheostomy should be required only rarely in very urgent cases where the patient has presented at a late stage and intubation is not possible; in a database study of epiglottitis in the United States, tracheostomy was performed in 3% of cases of adult epiglottitis.[17]

Epiglottic abscess formation is a recognized complication of epiglottitis, which has been reported to occur in 4–27% of cases; they occur mostly on the lingual surface of the epiglottis.[14, 18, 24, 27] Treatment usually requires surgical drainage and is associated with an increased risk of airway obstruction.[18, 28] Such cases must be managed in conjunction with an experienced anaesthetist due to potential complications of rupture of the abscess and airway obstruction.[29]

LARYNGOTRACHEOBRONCHITIS

Viral laryngotracheobronchitis (LTB) is the most common cause of stridor in children (also known as 'croup') and usually has a self-limiting course[30] in the majority of cases. However, in children progression to an impending airway can be more rapid when compared with adults due to the relatively narrow airway.[31] The symptoms of respiratory distress and biphasic stridor occur as a result of airway narrowing below the level of the glottis. It is not known why the subglottis is specifically affected in this condition.

Adult LTB is an uncommon condition that was first reported in 1990.[32] It is a community-acquired condition and tends to be more severe in adults than in children. Patients typically present with a sore throat, malaise, stridor and dyspnoea. Endoscopic examination will reveal subglottic oedema; the supraglottis is typically unaffected and appears normal.

Adult patients with LTB require admission and observation in an appropriate setting. Treatment with oxygen, steroids and nebulized adrenaline should be administered. Although it is thought that the majority of cases are as a result of a viral infection, broad spectrum intravenous antibiotics should be administered to treat any superadded bacterial infection.

If there is significant airway compromise not responding promptly to treatment then intubation by an experienced anaesthetist in an operating theatre setting should be considered.

PERTUSSIS

Whooping cough, or pertussis, is an acute illness caused by a gram-negative pleomorphic bacillus Bordetella, usually *Bordetella pertussis*. Endotoxins and exotoxins produced by the bacteria induce an inflammatory response, stop cilia functioning and cause epithelial cell necrosis. It is a notifiable communicable disease transmitted by coughing and sneezing that affects all age groups. Pertussis is most severe in children, particularly infants. Adults and adolescents may go undiagnosed and act as a reservoir of infection as they have a milder disease and a less severe cough.

Pertussis is the most prevalent vaccine-preventable disease. The WHO-expanded program of immunization has seen the number of children worldwide fully vaccinated rise from 5% in 1974 to 83% in 2008, avoiding 680 000 deaths per year. Still, 16 million cases were reported with 195 000 deaths, 95% in developing countries where immunization coverage is poor.[33] A paradoxical rise in the incidence of whooping cough in heavily vaccinated communities including the UK is as yet not fully understood.[34] Following 14 infant deaths in the UK in 2012, all pregnant mothers are now offered vaccination in the last trimester of pregnancy to maximize maternal

levels of immunoglobulin and facilitate passive protection of the newborn when most vulnerable in the first 3 months of life.[35]

Clinical features

Whooping cough presents with symptoms of a runny nose, dry cough and mild pyrexia, similar to a common cold. The cough occurs in prolonged paroxysms after one to two weeks and is followed by gasping and the characteristic whoop in children. Milder symptoms occur in adults and adolescences, classically presenting as a protracted cough rather than the characteristic 'whooping cough' of children.

Investigations

The diagnosis should be confirmed by serum serology and nasopharyngeal aspirate culture and assay, to determine causative organism, by polymerase chain reaction (PCR).

Management

Pertussis is usually not diagnosed until the cough has developed. A 7–14-day course of erythromycin is recommended, but this does not change the character of the cough or clinical course of the disease.[36] Erythromycin is thought to prevent patients from being infectious and is recommended as prophylaxis in affected households, but the effect has been described as modest compared with good quality vaccination.[37]

The cough should be treated symptomatically with cough suppressants; however, a systematic review of the use of steroids, β2-adrenergic agonists, pertussis-specific immunoglobulin, antihistamines or leukotriene receptor antagonists showed no clear evidence base for their use.[38] Alternative antibiotic choices options are clarithromycin, azithromycin and trimethoprin-sulfamethoxazole. Fluoroquinolones are also likely to be effective in adults but there are no supporting data of effectiveness.

BEST CLINICAL PRACTICE

- ✓ Pertussis should be considered in patients of any age presenting with a prolonged acute spasmodic cough of 3 or more weeks duration.
- ✓ Once recognized, treatment with a 7–14-day course of erythromycin should be commenced.

DIPHTHERIA

Diphtheria is caused by toxigenic strains of *Corynebacterium diphtheriae*, an anaerobic gram positive pleomorphic bacillus. Less commonly, when associated with consumption of raw dairy products, *C. ulcerans* species may be responsible. Toxigenic strains are lysogenic for one of a family of bacteriophages that carry the structural gene for the diphtheria toxin. Diphtheria, a preventable disease, was endemic in the UK until coordinated mass immunization was introduced in 1942. Classically transmission is by inhalation of droplets from the upper respiratory tract of an infected individual. It affects non-immunized children and susceptible adults, particularly the elderly. The usual site of infection is the tonsil and fauces, but it can also occur in the nasal cavities or spread to the larynx.

The last indigenous UK death from diphtheria was in 1982. The ease of world travel facilitates transmission and the vast majority of the 65 positive isolates recorded in England and Wales since 1986 were imported, predominantly from the Indian sub-continent, South East Asia and Africa. A 14-year-old boy who contracted diphtheria in Pakistan died in 1994.[39] High levels of herd immunity are essential to ensure and maintain disease control. Political instability amongst other factors lead to loss of blanket immunization and a diphtheria epidemic in Russia and the newly independent states of Eastern Europe. At its peak in 1995, more than 50 000 cases were recorded.[40]

Clinical features

Diphtheria causes a severe sore throat, malaise, pyrexia and nasal discharge if the nose is affected. Examination of the throat reveals a grey pseudomembrane, which may spread to affect the larynx. The cervical lymph nodes are enlarged and tender. An infected patient may become a carrier or clinically unwell depending on the host response, virulence and toxigenicity of the infective organism. If oropharyngeal diphtheria is suspected, a swab from the throat and or oropharynx should be obtained and screened for diphtheria. This should be considered in patients presenting with membranous or pseudomembranous pharyngitis/tonsillitis and/or following overseas travel or contact with a traveller to high-risk countries in the previous 10 days. Recent consumption of raw dairy products or recent contact with farm or domestic animals may suggest *C. Ulcerans* infection. Since *Corynebacterium diphtheriae* is not easily identified, throat swabs from all patients with sore throats should be separately screened. In the UK, positive isolates should be sent immediately to the reference laboratory for detection of the potent exotoxin 28.

Management

Treatment is with benzyl penicillin and antitoxin.[41] Acute airway obstruction should be managed accordingly, ideally with intubation. Close contacts and relatives should be immunized.

Complications

The diffusible exotoxin has a predilection for cardiac and renal tissue and causes myocarditis, arrhythmias and possible death. Neurological complications due to the exotoxin may develop a few weeks after the acute infection; the most frequent is soft palate paralysis but paralysis may also affect the diaphragm and the external ocular muscles. Other long-term sequelae include scarring of the

oropharynx and nasopharynx due to fibrosis and adhesion formation.

BEST CLINICAL PRACTICE

- ✓ A throat/nasopharyngeal swab should be obtained and screened for diphtheria in patients presenting with membranous or pseudomembranous pharyngitis/tonsillitis, particularly if there is a history of travel to a high-risk country in the previous 10 days, recent consumption of raw dairy products or contact with farm or domestic animals.[42]
- ✓ If diphtheria is suspected or diagnosed, benzyl penicillin and antitoxin should be administered.
- ✓ The airway should be monitored and, if obstructed, intubation should be considered.

INFECTIOUS MONONUCLEOSIS

Infectious mononucleosis (IM) or 'glandular fever' is a common disease caused by infection with the Epstein–Barr virus (EBV), a herpes virus. Sub-clinical infection is common although symptoms are often mild and self-limiting requiring minimal intervention. EBV has a special affinity for B lymphocytes, infecting the epithelium of the oropharynx and genital tract. It is transmitted via bodily secretions, most commonly saliva when kissing. Infectious mononucleosis is commonly seen in adolescents and young adults, with an incidence of up to 50 per 1000 persons.

Clinical features

Infectious mononucleosis has an incubation period of between 4 and 7 weeks.[43] Patients present with the classical features of sore throat, tonsil enlargement, cervical lymphadenopathy, periorbital oedema, especially of the lower lids (*Hoagland sign*) and fever. Palatal petechiae are more common in younger patients whereas hepatomegaly and jaundice are relatively more common in the older population. Splenomegaly is a late sign of infection and resolves within 3–4 weeks but fatigue and myalgia can persist for a number of months following resolution of the initial infection.

Investigation

Patients should have a full blood count (FBC), liver and renal function tests. Infectious mononucleosis is suspected if there is either a leucocytosis of >50% of the total white cell count (WCC) and 10% atypical leucocytes, or 20% atypical leucocytes.

The Monospot test and Paul-Bunnell test are types of heterophile antibody test. The Paul-Bunnell test is based on sheep red blood cell (RBC) agglutination, whereas the more sensitive and specific monospot test is based on latex agglutination using horse RBCs.[44]

Positivity to Monospot increases over the first 6 weeks of IM infection as the EBV heterophile antibody titres reach their peak; repeat testing 7 days later may be required. In the face of repeatedly negative Monospot tests, cytomegalovirus (CMV), human immunodeficiency virus (HIV), toxoplasmosis and rubella testing should be considered.

Management

As there is no specific treatment for infectious mononucleosis, supportive measures such as fluids, analgesia and rest are advised. Superimposed streptococcal throat infection may occur and antibiotic treatment required. Aminopenicillins such as amoxicillin or ampicillin should not be used due to the incidence of maculopapular rash. Acyclovir has not been proven to affect the outcome and is not advised in the management of uncomplicated infectious mononucleosis.[45] Corticosteroids improve pain scores and time to symptomatic resolution for pharyngeal infections, especially when given in combination with antibiotics.[46]

Complications

Airway obstruction due to cervical lymphadenopathy and tonsillar hypertrophy is a rare but potentially fatal complication of infectious mononucleosis.[47]

Other complications include anaemia, thrombocytopenia, encephalitis, transverse myelitis, Gullian–Barre syndrome, pericarditis and myocarditis.

Hepatomegaly resulting in jaundice and splenomegaly are late findings. Patients are counselled to avoid sport or vigorous activity due to potential splenic ruptures, the majority of which occur following minor trauma.[48] The rate of rupture is less than 1 in 500. Whilst recovery is usually quoted at 4–6 weeks, a small population of patients suffer prolonged fatigue, with 13% at 6 months and 4% at 2 years meeting the criteria of chronic fatigue syndrome.[49]

BEST CLINICAL PRACTICE

- ✓ Diagnosis of IM is by heterophile antibody test. The Monospot test is the most sensitive and specific test.
- ✓ Treatment is supportive.
- ✓ Steroids may aid in the management of the partially obstructed airway but intubation or tracheostomy are required when the airway is considered unsafe.
- ✓ Corticosteroid in combination with antibiotic treatment reduce pain scores and time to symptom resolution of pharyngeal symptoms.
- ✓ Amoxycillin should be avoided due to the risk of a macular rash in EBV infections.
- ✓ Patients should be counselled with regard to physical activity.

MYCOTIC LARYNGITIS

Fungal infections of the larynx are usually secondary to fungal inhalation in immunosuppressed patient with laryngeal mucosal disruption.[50]

Clinical features

Mycotic laryngeal infections are rare in patients with normal immune function; when they do occur they present as subacute or chronic infections. In contrast, immunocompromised patients, particularly those with haematological malignancy, are prone to acute infection from these opportunistic pathogens.[51] Mycotic laryngitis, with the exception of superficial candida infection, is usually associated with ulceration. Infections from candida and aspergillus are widespread but coccidioidomycosis, blastomycosis and histoplasmosis are endemic to specific geographical regions.

The larynx is probably affected by candida more often than realized and should be seriously considered in patients with refractory symptoms; up to 15% of patients with chronic laryngitis are diagnosed with mycotic lesions when examined.[52] In immune-competent patients, the most common predisposing factors are recent treatment with antibiotics, use of inhaled steroids,[53, 54] diabetes, chemotherapy, radiation therapy, smoking, acid reflux and inhalational or thermal trauma. Often, more than one predisposing factor is present. The characteristic finding in the larynx is a white pseudomembrane or adherent white plaque that can be mistaken for leukoplakia. It can also appear as diffuse erythema, with oedema and ulceration in severe infection. Whilst invasive candidal infections are rare, it is thought that colonization has an indirect effect on defence mechanisms and aids development of bacterial infections locally.[55]

Invasive aspergillosis is an opportunistic infection that occurs mainly in immunocompromised patients with haematological malignancies. Primary laryngeal aspergillosis is very rare, but recognition is important as steroids could have an adverse effect in affected patients with airway distress.

Investigation

Pulmonary fungal disease should be excluded and all patients with mycotic laryngitis should have a chest radiograph. Fungal trachea-bronchitis is generally limited to HIV-positive patients or the severely immunocompromised. Such cases present with stridor, fever and a productive cough.

Direct laryngoscopy and biopsy may be necessary to confirm a diagnosis of fungal laryngitis. It is of note that the more chronic fungal infections, such as blastomycosis, can present as a laryngeal mass requiring laryngeal biopsy for a definitive tissue diagnosis.[56] Special fungal stains, such as methenamine silver and periodic acid-Schiff, are required to identify the fungal hyphae. However, histology will not differentiate between the specific fungal species for which cultures are necessary.

Management

Systemic antifungal therapy is necessary for immunocompromised patients. Antifungal agents suppress fungal growth, making recurrent infection likely unless the underlying predisposing factors are addressed and corrected. Recurrence will also occur if the agent is used for too short a period or in an inadequate dose. Suitable agents include fluconazole, ketaconazole, itraconazole and amphotericin B. Each agent has its own characteristics: fluconazole for 3–4 weeks is the preferred agent for candida infection; itraconazole is particularly effective for aspergillus infections at a dose of 100–400 mg daily, monitored by regular blood levels; ketaconazole is the agent of choice for histoplasmosis and blastomycosis. Amphotericin B needs to be administered intravenously and also has significant adverse effects on the kidney, heart and liver.

BEST CLINICAL PRACTICE

- If acute mycotic laryngitis is suspected, immunodeficiency should be considered and investigated.
- Patients with a diagnosis of fungal laryngitis should have a chest radiograph.
- A direct laryngoscopy and biopsy is recommended in severe presentations and non-responders to initial therapy. Samples should be sent for histology and specific fungal cultures.
- A suitable course of a specific antifungal medication should be administered and predisposing factors should be addressed and corrected.

LARYNGOPYOCOELE

A laryngocoele is an abnormal dilation of the lateral most region of the laryngeal ventricle. The sac is lined with pseudostratified columnar ciliated epithelium, maintaining a connection to the ventricle. Laryngocoeles are described as internal, external or mixed. Internal laryngocoeles do not extend laterally through the thyro-hyoid membrane, external laryngocoeles exist lateral to the thyro-hyoid membrane, whereas mixed have both internal and external components. Laryngocoeles are more common in men and increase in incidence with age, though are still rare, with an incidence of 1 per 2.5 million per year.[56] The aetiology is unknown, with factors that increase intra-glottic pressure (e.g. glass blowing, trumpet playing, weight lifting) suggested as having a role in development. The laryngocoele normally contains air or mucus connecting with the airway. A laryngopyocoele forms when the neck of the sac become blocked and the laryngocoele becomes infected and contains mucopus.[57]

Clinical features

External laryngocoeles present commonly as a lump in the neck. It may possibly inflate on performing a Valsalva manoeuvre or may be emptied with external pressure (Bryce's sign).

Internal laryngocoeles may present with hoarseness, dysphagia or globus. Flexible nasendoscopy classically shows an enlarged and smooth swelling of the false cord, often making visualization of the cords challenging. Due to the association of laryngeal squamous cell carcinoma (SCC) within the ventricle and laryngocoele, it is advisable to carefully examine the area endoscopically.[58–60]

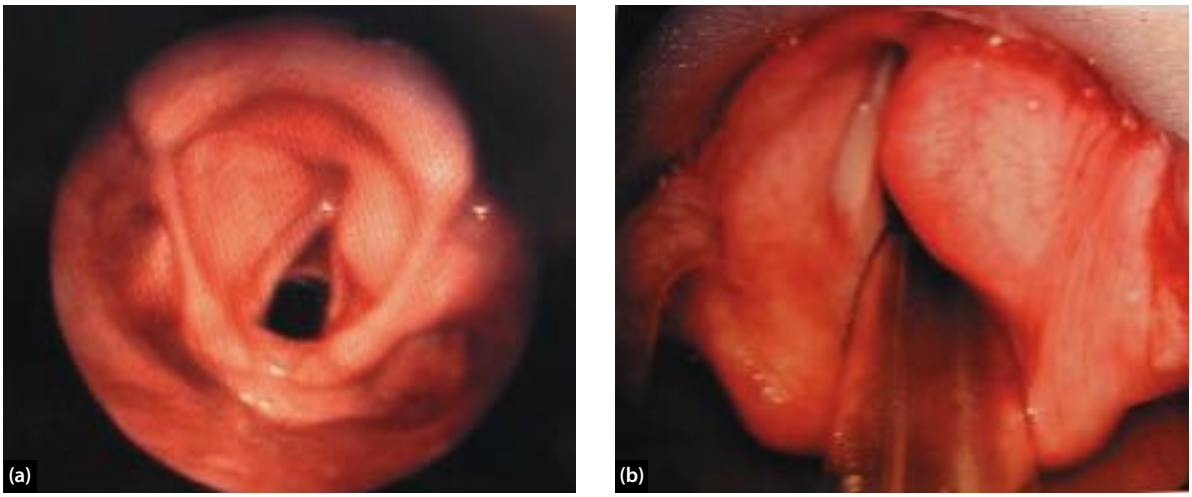


Figure 69.1 (a) Appearance of a right-sided laryngocoele as seen with a flexible laryngoscope. **(b)** Endoscopic appearance of right-sided laryngocoele at the time of surgery.

Laryngopyocoeles can present with pyrexia, dysphagia and potential airway compromise.[61]

Investigation

Cross-sectional imaging with CT allows delineation of cystic and laryngeal architecture. An MRI scan allows allows better characterization of soft tissue abnormalities.[62, 63]

Management

A patient with an evolving laryngopyocoeles may present as an acute airway emergency, stridulous and in respiratory distress. Definitive airway control via means of a tracheostomy or intubation may be required. For this reason surgical excision of laryngocoeles is advised prior to the evolution into a laryngopyocoele and the potential airway compromise. Patients presenting with a laryngopyocoele should be treated with intravenous antibiotics and dexamethasone, with needle aspiration of the external component if feasible. Following resolution of the infection a delayed excision of the laryngocoele is advised. Management can be either via the classical lateral external approach or endoscopically. Endoscopic excision using CO_2 laser has been shown to be effective in the management of the internal and external component.[64]

BEST CLINICAL PRACTICE

- Emergent airway management in cases of airway instability.
- Treatment with high-dose intravenous antibiotoics and dexamethasone.
- Tracheostomy placement if no improvement with conservative management.
- Early elective surgical excision.

KEY POINTS

- Consider early surgical management of laryngoceles to prevent a potential laryngopyocoele.
- Excision can be endoscopic or external approach.
- Laryngopyocoeles can cause airway obstruction

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CHAPTER 70

CHRONIC LARYNGITIS

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SEARCH STRATEGY

This search was carried out in conjunction with The Clinical Effectiveness Librarian, Glasgow Royal Infirmary, Greater Glasgow & Clyde NHS Trust and University of Glasgow using Medline, M base, and Pubmed to search with the following keywords: chronic laryngitis, aetiology, diagnosis and treatment.

INTRODUCTION

Chronic laryngitis is chronic inflammation of the laryngeal structures, most commonly affecting the laryngeal mucosa and to a certain extent the submucosa. The chronic inflammatory process can be due either to infectious or non-infectious causes, with a broad spectrum of aetiologies which may act singly or in combination. The chronic changes in the larynx can result in many laryngopharyngeal symptoms but the principal effect of the condition is a persistent and fluctuating change in voice and subsequent impact on the quality of life of the patient. The high prevalence of the main aetiological factors associated with chronic laryngitis, namely smoking and voice abuse, and the debated influence of reflux disease, whether it be laryngo-pharyngeal reflux or gastro-oesophageal reflux, results in the management of this condition being challenging in relation to both diagnosis and efficacy of treatment.

In 1976, Stell and McLoughlin commenced the debate around the aetiology of chronic laryngitis and concluded from their case controlled series that occupational effects had only minimal influence: smoking was no greater than in the control group, but that infection of the upper and lower respiratory tract was of significance.[1] Intuitively it would seem likely that the type of occupation, and associated environment might have a significant influence on the quality of the air, or the fumes inhaled, or how the voice might be used, for example, in the presence of background noise.

This has been supported by reports in various case series of the relationship between occupations and chronic laryngitis; with excess noise at work,[2] asbestos workers,[3, 4] cement workers,[5] solvents and shoe workers,[6] hairdressing,[7] and glass blowers.[8]

The association between the remainder of the respiratory tract and the larynx and possible concurrent aetiologies have been highlighted in reports relating to allergy.[9, 10] The underlying hypothesis is that allergens which cause adverse effects in the upper airways, such as the nose, nasopharynx and pharynx, are likely to have a similar effect on the larynx and hypopharynx. Whilst this may be the case, the more likely cause is through the use of inhaled drugs in lower respiratory tract disorders such as asthma and the overall management of

both nasal and paranasal sinus disorders. The effect of respiratory inhalers, not only with regard to their content but also their propellant, on the laryngeal structures is well documented and it remains a continuing challenge on how to balance the need for optimal treatment of the peripheral airways and improvement of the patients' ability to breathe, and subsequent quality of life, against the adverse effect of the inhaled drugs being present in the larynx and proximal trachea.

Significant debate exists about the aetiology and subsequent management of chronic laryngitis in the setting of gastro-oesophageal reflux (GORD) and laryngopharyngeal reflux (LPR). It would appear from the literature that clinicians consider a relationship to exist between these disorders,[11] but how this is diagnosed and ultimately managed effectively remains a significant challenge to all of those dealing with disorders in each of these subsites. A detailed treatment of GORD and LPR can be found in Chapter 77, Reflux disease.

Chronic laryngitis can be caused by a wide variety of infective organisms. Perhaps the most graphic example is seen with candidal infection affecting all areas of the upper aero-digestive tract, seen in patients with underlying immunocompromise, diabetes mellitus, after chemoradiotherapy or following prolonged antibiotic administration.

This spectrum of disease in the larynx will be considered in two main sections: the clinical diagnosis of general diffuse laryngitis with no identifiable cause and specific forms of chronic laryngitis due to rare but recognized aetiologies.

CLINICAL PRESENTATION

History

The key symptom associated with chronic laryngitis is alteration in voice quality in the form of hoarseness (dysphonia). In trying to differentiate this from other forms of dysphonia, the voice in chronic laryngitis generally tends to be rough or coarse, and may have an overall reduction in the pitch. It tends to develop gradually with an insidious onset and may be present for several months or years. The hoarseness is persistent with the voice being seldom, if ever, normal but it is rare for there to be aphonia.

There may be associated symptoms with the chronic laryngitis such as difficulty in swallowing (dysphagia), a sensation of something being in the pharynx, painful or strained speaking , throat ache or discomfort, throat clearing, persistent non-productive cough, halitosis, unusual taste or bitter taste, otalgia, water brash or indigestion.

It is important to establish the concerns of the patient with regard to any underlying issues such as their worry of the risk of malignancy through to whether they want complete resolution of their voice and upper aero-digestive problems. It may be that the patient has been a long-standing smoker and simply wants to be reassured that there is no malignancy or alternatively that they are a professional voice user, such as a teacher, whose voice problems are a result of the chronic laryngitis, preventing them from fulfilling their professional obligations. It is essential to establish the effect a patient's dysphonia on various spheres of activity, as it is well recognized this dysphonia has an overall impact on their quality of life.[12–15] To a certain extent this will influence, and possibly determine, the aims of the subsequent assessment and treatment strategy.

Having established the principal characteristics of the dysphonia, and associated symptoms, there are other key elements of the history which are important to elucidate with regard to potential aetiological factors. Clearly, these aetiological factors can act singly or in combination:

- Smoking: A key factor in chronic laryngitis. The type, frequency and duration of smoking should be noted.
- Reflux: Laryngopharyngeal symptom matrix may indicate possible reflux type. Past history of upper GI dysfunction such as *H Pylori* infection, upper GI investigations including gastroscopy, pH monitoring or manometry and possible upper GI surgery should all be noted.
- Patient's occupation: The working environment should be identified as it might highlight the environmental quality of air or presence of fumes and the noise level in which the patient has to communicate.
- Social activities: The type and environment of social activities should be noted as this may aggravate chronic laryngitis.
- Allergies: Both proximal and distal aero-digestive tract and their treatment.
- Co-existent disease which may be associated with chronic laryngitis such previous radiation therapy for head and neck malignancy, immuno-suppressed states, diabetes, and diseases associated with specific types of chronic laryngitis such as tuberculosis, sarcoid or granulomatosis with polyangiitis (previously called Wegener's granulomatosis).

Irrespective of the causation, the unrelenting effect on the voice, the co-existent laryngopharyngeal symptoms and the subsequent impairment on the ability of an individual to communicate and carry out their daily functions, either on a professional basis or socially, has a significant impact on their quality of life. Given both the chronicity and the relationship to long-established habits, there is a considerable challenge to try to improve the symptoms associated with this condition.

ASSESSMENT

Outpatient setting

Assessment of a patient with dysphonia starts during the consultation. During this time both consciously and subconsciously the clinician is assessing the quality of the patient's voice in relation to their history. Specifically, with regard to chronic laryngitis the severity of the dysphonia harshness and breathy components, strained intonation of the voice, associated tension and anxiety are all assessed.

Comprehensive assessment of the ear nose and throat is necessary. Examination of the ears and hearing should be carried out as it is important to establish that the hearing is within normal limits and rehabilitated appropriately. With regard to the nose it is necessary to establish if there are any significant nasal abnormalities which might result in persistent obstruction or mouth breathing, and whether or not there is any evidence of allergic rhinitis. Per-oral pharyngeal examination is carried out to ensure there is no significant oral or oropharyngeal pathology which might be associated with smoking, as well as identifying significant caries or candidiasis.

The key investigation in the management of this type of patient is examination of the larynx in the resting and neutral state. This is best achieved by fibreoptic nasendoscopy examination. To facilitate this, the nose can be prepared with topical decongestant and local anaesthetic agent such as Cophenylcaine. This anaesthetizes and vasoconstricts the nasal mucosa so allowing easier passage of the nasendoscope. The disadvantage of such a preparation is that patients frequently find it unpleasant, both in the application of the nasal spray due to its effervescent component and also the taste associated with it.

If a more detailed examination of the structures of the larynx is needed then per-oral rigid laryngoscopy is carried out, having applied some form of topical anaesthesia to the oropharynx. This is generally coupled to a camera system and may be used with or without stroboscopy. This combination of examination techniques allows more detailed examination of the structure and movement of the vocal cords and possible asymmetry as this may indicate any potential underlying malignancy or other pathology such as cystic lesions of the vocal cord.

The principal aim of these outpatient assessments is to determine whether microlaryngoscopy under general anaesthesia is required. This is generally determined on the level of suspicion following the outpatient examination with regard to the presence or otherwise of localized or discrete abnormal areas in shape and/or colour. If there is any concern about the presence of malignancy, this should precipitate the need for microlaryngoscopy.

Frequently, however, there are only vague, non-specific diffuse oedematous alterations in colour and structure, the combination of which may result in a provisional clinical diagnosis of chronic and inflammatory laryngitis.

The abnormalities may affect all subsections of the larynx, e.g. all of the true cords or be restricted to specific areas. Clinical experience suggests that there is considerable inter- and intra-observer variability when assessing the larynx in the outpatient setting. Pontes et al. reported in a case series of 85 patients with multiple benign laryngeal pathology that there was frequent inter-observer variation in relation to diagnosis of each of the pathologies involved.[16]

Given the wide range of non-specific appearances within the larynx, several workers have suggested descriptive criteria on which to base the recording of the assessment of the chronic laryngitis. This is a necessity when trying to evaluate treatment strategies, the most notable of which is the treatment of gastro-oesophageal and laryngo-pharyngeal reflux. An example of this is by Feehs and Koufman[17] who described the spectrum of findings without a numerical grading system. The grading system was hierarchical as follows:-

1. Red arytenoids and piled up into the arytenoid mucosa.
2. Diffuse oedema, including Reinke's space, mucosal thickening but possibly minimal erythema.
3. Diffuse oedema with granular friable mucosa.
4. Discreet granulomas, with or without, oedema and erythema.

Intuitively, it would seem reasonable to conclude that reasonable inter- and intra-observer repeatability can be achieved if there is a discrete lesion such as a granuloma and more specific pathology such as Reinke's oedema. However, with regard to chronic laryngitis, it is unrealistic to expect any repeatability that would be clinically meaningful.

In an attempt to try to achieve this, photographic recording of either the flexible or rigid endoscopic findings is advocated. Despite doing this, there is a still subjective assessment of these images which is open to a similar difference and variation in interpretation as in a 'live' examination.

At this stage, operative assessment may not be deemed appropriate in that the treatment may be principally non-surgical or medical, such as in chronic non-specific laryngitis, or because the patient does not wish any alteration to their voice, such as in Reinke's oedema or in vocal cord nodules. It may therefore be more appropriate to refer patients to speech and language therapy for consideration of a course of voice therapy.

OPERATIVE ASSESSMENT

The need for endoscopic assessment under general anaesthesia is established in the outpatient setting. A significant proportion of patients with apparent inflammatory changes within the larynx will require further assessment by carrying out microlaryngoscopy under general anaesthesia for the following principal indications:

- Any area of the larynx which might be considered suspicious with regard to dysplastic changes or overt malignancy.
- Co-existent pathologies such as vocal cord polyp, which need surgical management.
- Inability to examine the larynx comprehensively due to the patient not being able to comply due the larynx being obscured, for example by the presence of crusting of secretions.
- Failure to respond to medical treatment.

To facilitate the best operative view when carrying out the procedure, it is necessary to have appropriate maintenance of ventilation. A technique that allows completely unobstructed view while allowing visualization, whilst at

the same time facilitating the use of the CO_2 laser, is that of supraglottic jet ventilation. The disadvantage of this is that the effectiveness of this ventilation using capnography cannot be assessed readily, which may be relevant in patients with chronic obstructive airways disease. A more stable and secure way of ventilating the patient is to use a microlaryngeal tube, size 5 or 5.5, which has the added advantage of protecting the airway in the event of gastro-oesophageal or laryngo-pharyngeal reflux. The disadvantage is that it partially obscures the view of the vocal cord and has to be converted to a specific laser endotracheal tube of a similar size should the CO_2 laser be used.

The compromise is to ventilate using a subglottic form of jet ventilation such as the Hunsacker Mon-jet ventilation system. This small tube sits in the posterior commissure and allows a greater view of the larynx but at the same time ventilates in a more controlled fashion than the supraglottic jet ventilation. It has the added theoretical advantage that the end tidal CO_2 levels can be determined.

The patient's larynx is assessed using 0, 30 and 70 degree rod lens endoscopes so that the type and extent of any lesion or lesions can be determined. If the lesion is discrete then excision biopsy, if at all possible, should be carried out. This is generally done using cold instrumentation to resect the lesion carefully from the underlying structures with minimal trauma, resulting in a histopathological diagnosis with no change, or only minimal change, in the voice.

If there are diffuse changes throughout the larynx a representative biopsy should be taken and this can be carried out using a cupped biopsy forceps such as a 4 mm type. However, this is a significant size and it may be more appropriate to take the biopsy using cold instrumentation and excise a specimen assuming an appropriate amount of submucosal tissue is incorporated into the specimen. Consideration should be given to the position and amount of tissue to be removed. If there is a diffuse, but uniform appearance, then a representative specimen should be taken from an area unlikely to affect the voice. Such an area would be the superior, super lateral aspect of the vocal cord or from the supraglottis.

HISTOLOGICAL FEATURES OF CHRONIC LARYNGITIS

Microscopy reveals benign mucosa usually covered by squamous epithelium of variable thickness with a tendency to keratinization. The active changes are present in the epithelium but no convincing epithelial dysplasia is identified. The lamina propria may be oedematous and contains a chronic inflammatory infiltrate of variable intensity including lymphocytes and macrophages. A light scattering of acute inflammatory cells is also often present. Patchy permeation of the surface epithelium by the inflammatory cells commonly occurs. There is variable degree of fibrosis of the lamina propria and prominent small vascular channels may be seen.

There is a need for robust classification which reflects the histological characteristics of chronic laryngitis. The principle is that in a certain proportion of patients who have chronic laryngitis there may be characteristics of their disease state which are liable to undergo potential malignant change. There is therefore a need to identify the cohort of patients in whom treatment may have to be more aggressive with closer monitoring. The most widely used system is the WHO grading for dysplasia into mild, moderate and severe. However, this system is prone to low interrater agreement. An alternative is the Ljubljana classification system that has been in use for several years. Gale et al. reported in a retrospective case series the Ljubljana classification of laryngeal lesions in relationship to subsequent malignant transformation. The hyperplastic laryngeal lesions (n = 4574) were graded into simple, abnormal, atypical hyperplasia (risky epithelium) and carcinoma *in situ*. Malignant transformation in the atypical hyperplasia was 11.6% whereas in the benign group, simple and abnormal, it was 0.3%. From this analysis, the authors concluded that this classification system was of value with regard to identifying potential malignant transformation.[19] This has recently undergone further clinical validation and a change in nomenclature (current terminology is low-grade squamous intraepithelial neoplasia (SIL), high grade SIL, carcinoma-*in-situ*), with a detailed description of the morphologic criteria for these groups. The management of dysplasia is discussed elsewhere in the book, with consensus recommendations on treatment and follow up.

NON-SPECIFIC LARYNGITIS

Non-specific laryngitis is a common condition presenting with persistent and unrelenting dysphonia which can vary in quality, severity and duration. Depending on the aetiology, it may result in only a mild effect on the quality of the voice or render the patient's voice harsh leading up to aphonia. Associated with this change in voice, patients may have symptoms such as pain or discomfort in their throat, description of an awareness in their throat with globus pharyngeus type symptoms, halitosis or otalgia, or the report of symptoms of excess catarrh with persistent throat clearing. The most frequently implicated aetiological factors are smoking, voice abuse, and reflux disease, namely gastro-oesophageal reflux and laryngo-pharyngeal reflux.

To further challenge the clinician's comprehensive management of this disease is the wide range of clinical features which may be associated with the clinical diagnosis of non-specific laryngitis. These features can range from localized specific appearances within the larynx through to complete and diffuse changes in the larynx rendering the larynx almost unrecognizable from its normal appearance. Furthermore, this multiplicity of aspects of the disease process renders the assessment of the disease, and efficacy of any of the treatment strategies, extremely difficult. It may therefore be that the management of this ill-defined wide-ranging condition may have to be pragmatic by targeting management, by identifying potential

aetiological factors, confirming the diagnosis, initiating treatment and finally investigating or further modifying treatment should this pragmatic approach not improve the patient's symptoms.

IDENTIFYING THE POTENTIAL AETIOLOGY

Given the key aetiological factors, it is likely that they will vary in influence from country to country and within countries. Despite this epidemiological variation, it is likely that the most common aetiological factor in non-specific laryngitis is that of smoking which in turn may be the most challenging aspect of the disease to manage.

Intuitively, it could be expected that chronic contamination, or infection of the larynx, might be the key in generating a chronic laryngitic picture. Some authors have found that septic foci are present,[20] whilst others have not been able to demonstrate bacteria in chronic inflammatory laryngeal samples,[21] while other groups have demonstrated the presence of bacterial biofilm.[22] Furthermore, in relation to specific bacteria, *H pylori* has been identified in those patients with chronic laryngitis and laryngeal cancer[23, 24] and so the question arises to whether eradication strategies should be implemented in this group.[25] The specific role of bacteria continues to be debated and it would seem a rational approach to treat any overt bacterial infection, whether it involves the larynx directly or indirectly as a secondary effect caused by lower respiratory tract infection with the subsequent indirect traumatic effect on the larynx caused by coughing and expectoration.

A common potential aetiological factor is voice misuse or abuse. If an individual has to use their voice for a significant period of time in an environment which might be irritating, or where they may have to raise the volume of their voice over a significant period, then it is likely that they may develop secondary inflammatory changes in the larynx in response to the voice usage. If, following this period, there is not sufficient time for compensatory rest then the acute laryngeal changes may become chronic, particularly if the process of voice misuse is repeated on a regular basis.

The third key potential aetiological factor implicated in chronic non-specific laryngitis is reflux disease. When considering this potential aetiological factor, there is reliance on the other symptoms which may be present due to reflux, both gastro-oesophageal and laryngopharyngeal. Although there are other types of reflux, these are the two which are primarily implicated in most discussions around the evidence relating to chronic laryngitis and reflux. The recognized symptoms associated with reflux disease and chronic laryngitis are those of globus type symptoms of awareness in the throat, persistent throat clearing, alteration in the voice, altered taste in the mouth, and possibly symptoms of heartburn or indigestion.

The relationship between potential reflux and the symptoms associated with chronic laryngitis are based on two main hypotheses, firstly that of the direct contact and contamination of the upper airways by gastric acid or refluxate, in some cases pepsin, and secondly by the vaso vagal reflex triggered by acidification of the distal oesophagus. The association between ENT symptoms, not just those of chronic laryngitis, and reflux are well recognized and published widely.[26]

DIAGNOSIS

The majority of patients diagnosed with non-specific laryngitis are based on examination in the outpatient setting by identifying a group of signs present in the larynx on examination using the fibreoptic nasendoscope or the video-stroboscope having established an appropriate history. The key features of non-specific laryngitis are a diffuse inflammatory picture with widespread irregular mucosa, varying degrees of oedema, erythema, exudate, but inevitably with distortion of the normal anatomical features in a diffusely irregular and swollen manner. Given that a high proportion of these patients will have smoking as an aetiological factor, a key clinical decision is whether or not there may be any cancerous or precancerous elements in the larynx. If it is not possible to state unequivocally that the laryngeal appearances, although diffuse, are in keeping with a completely benign picture then the larynx will need to be examined in more detail by microlaryngoscopy, and representative histology of the laryngeal surfaces obtained. In severe cases, there may be gross abnormalities of the larynx with the surface mucosa being obscured by the presence of a substantial amount of exudate this covering possibly being dried and crusted, so obscuring the clinical picture. It is frequently necessary in this group of patients to irrigate the larynx with saline during microlaryngoscopy to ensure that detailed assessment and subsequent appropriate biopsy can be carried out without initially traumatizing the inflamed larynx by direct instrumentation by laryngeal suction.

In many patients, the diagnosis will be made on the symptom complex and the clinical examination. To try to aid in the differentiation between the various aetiological factors, methods of assessing potential contribution of reflux have been suggested. The most frequently one advocated is the Reflux Symptom Index (RSI) the validity and reliability of which were initially described by Belafasky et al, who described evaluation of this self-administered nine-item outcome instrument for LPR in relation to the Voice Handicap Index (VHI).[27] Although this relates specifically to the assessment of the RSI as a patient report tool in comparison to VHI, it did demonstrate that patient reported voice disorders had a significant improvement following empirical PPI treatment in those suffering from chronic laryngitis. The use of the RSI in conjunction with other patient reported voice outcome measures, namely the VoiSS, has been reported by Beech et al. again with good correlation.[28] In this group, acid suppression therapy was shown to be of some benefit in chronic laryngitis patients without troublesome reflux symptoms the RSI and the VoiSS scores both being improved with Proton Pump Inhibitor prescription and voice therapy carried out by Speech and Language Therapy.

To aid in the diagnosis of the possible influence of reflux in the larynx it has been suggested that the Reflux Finding Score (RFS) may be used and previous reports have shown

that although this is a sensitive method picking up pH proven reflux patients specificity may be quite low, with a sensitivity of 87.8% specificity of 37.5% respectively.[29]

The principal aim of having any of these scoring systems is to try to establish a process which would have a low inter- and intra-observer variability with a high level of repeatability so that treatment strategies can be evaluated comprehensively.

TREATMENT

If each of the investigations carried out identify that the laryngitis is indeed non-specific then the treatment that is used will address each of the main aetiological factors of smoking, voice use, and reflux.

Robust, evidence based smoking cessation strategies are currently available, ranging from counselling and behavioural therapy through to pharmaco-therapy including nicotine replacement, Varenicline and Bupropion sustained release.[30] Although this commitment and drive is present in cancer groups, in realistic terms it may be more difficult to persuade someone with chronic laryngitis to stop as at this stage there would be no life threatening condition present.

Voice misuse or abuse, must be addressed and is the main stay of treatment of chronic laryngitis is addressed in detail in Chapter 66, Speech /voice therapy for voice disorders.

The therapy designed by the speech and language therapists is comprehensive not only in relation to the laryngeal structure and function but also addresses aspects of lifestyle and voice use by discussing vocal hygiene and addressing dysfunctional components of voice production. This subtle combination of history taking, diagnosis, treatment planning and execution and 'ad hoc' psychotherapy has been recognized in the past to be of clinical value. There had, however, been little evidence in support of its use except for some level 3 evidence from short case series for voice therapy being used in specific conditions such as vocal cord nodules or Reinke's oedema.[31] In 2001, MacKenzie et al. reported a randomized controlled trial of the use of voice therapy in a heterogenous group of voice patients who had conditions which one would normally expect to see benefit from voice therapy namely vocal cord nodules, functional dysphonia and chronic laryngitis. The principal outcome from the study, patient self-report, was significantly better in the group who received voice therapy when compared with the control group of observation only.[14] The voice therapy used was based on the reported consensus of treatment by UK Speech and Language Therapists in a group of laryngological disorders, one of them being chronic laryngitis.[32] The study results indicate that referral to the Speech and language therapy team for voice therapy is highly appropriate and of benefit to those suffering with chronic laryngitis.

The most contentious area in the treatment of chronic laryngitis is that of precipitating or concurrent reflux disease. There is a wide range of evidence trying to address the issues surrounding the treatment of reflux disease. The extra oesophageal manifestations of those patients suffering from laryngo-pharyngeal reflux or gastro-oesophageal reflux disease are covered in detail in Chapter 77, Reflux disease. Delahunty described inflammation of the posterior third of the vocal cords associated with GORD on barium swallow and subsequent successful symptomatic treatment with antacid. This possible association between GORD and chronic laryngitis was initially known as acid laryngitis.[33]

In an observational series in 1982, Ward et al. described a group of 86 patients with chronic non-specific laryngitis which they hypothesized was due to local irritation by chronic coughing and throat clearing which in turn was secondary to a hiatus hernia and gastro-oesophageal reflux.[34] This hypothesis was tested further, and much more 'invasively', in a surgical series by Deveney et al. In a cohort of 13 patients with chronic non-specific laryngitis and confirmed GORD the performance of a Nissen fundoplication resolved the laryngeal problems in 11 (73%). This small study group was very carefully selected in that each patient had ceased smoking for at least six months. The conclusion was that surgical correction of the GORD in a select group of patients will resolve the laryngeal problems.'[35] However, it could clearly have been the cessation of the smoking which had the greater influence.

There are two principal theories to explain the pathophysiology. Firstly, the refluxate from the stomach and oesophagus crossing the upper oesophageal sphincter can cause an inflammatory effect on the laryngo-pharynx. Secondly, chronic repetitive throat clearing and coughing which is caused by a vagally mediated response from the oesophagus can indirectly cause laryngitis.[36] If either, or both of these theories, is correct then there should be an increased prevalence of laryngeal disorders in patients suffering from oesophagitis.

El-Serag and Sonnenberg demonstrated in a large case controlled series of patients with erosive oesophagitis (n = 101, 366) the higher statistically significant odds of laryngitis (odds ratio shows 2.1; 95% CI 1.53 to 2.63). This would strongly support this hypothesis.[37]

This study supports the empirical treatment of extra oesophageal manifestations of reflux disease, of which chronic laryngitis is only one. This empirical practice has been widespread in patients with laryngopharyngeal symptoms, with or without, gastro-oesophageal reflux symptoms. A frequently quoted study was carried out by El Serag et al. in 2001 to test the validity of this treatment strategy. A randomized controlled trial of PPI versus placebo was performed in a group of patients (n = 22) with chronic laryngitis. Following confirmation of the disease status by upper GI endoscopy 24 hour oesophageal, and pH monitoring, laryngoscopy, and symptom questionnaires, the patients were randomized to receive either Lansoprazole 30 mg bd or matching placebo for three months. The primary outcome of complete resolution of laryngeal symptoms was seen in 6 of the Lansoprazole group compared with 1 (10%) of the placebo group ($p < 0.05$).[38] The authors concluded that empirical treatment with Lansoprazole is efficacious when relieving symptoms of laryngitis compared to placebo but with a cautionary note that the study was carried out in patients with a high chance of having

GORD and that it would have to be repeated in the general population if it was to be universally applied to all patients presenting with laryngeal symptoms.

Essentially, the treatment strategies can be split into those who believe that it is appropriate, and indeed advisable, to treat potential reflux disease empirically[39–46] and those who do not.[47–49] The indications and thresholds for this treatment can vary enormously with the indications being fairly minimal and the treatments used being wide ranging. The commonest treatment advocated is the prescription of a PPI where the main protagonists would suggest a strategy where it should be tried for several weeks and if does not succeed then perhaps change in this treatment with change of PPI dosage or supplementation or augmentation by other treatment such as antacids and alginates.[50] Those who do not support this strategy would suggest that widespread non-specific or non-targeted treatment of such populations result in inappropriate treatment with the sequelae in individuals such as rebound and excess gastric secretion and altering the bacterial flora profile of a population.

Whilst it might be considered medically appropriate to carry out tests to determine the presence or otherwise of reflux, and indeed the type of reflux, a pragmatic approach to this very common disease management is frequently indicated. On balance, there is a majority of clinicians who have the view that at least a trial of anti-reflux medication in the form of a PPI, with or without an alginate, and in these patients in whom there is not an appropriate response when one is expected or anticipated then it would be necessary to proceed to more detailed and more specific investigations. This is supported by a meta-analysis by Quadeer et al, who concluded that 'PPI therapy may offer a modest, but non-significant, clinical benefit over placebo in suspected GERD related chronic laryngitis' and recommended that validated diagnostic guidelines be used to facilitate the recognition of the patients most likely to respond to PPI treatment.'[51]

This relatively unsatisfactory state of affairs regarding treatment does appear to be the current practice. We advocate that that clinicians carry out treatment strategies on assessment of patients on an individual basis rather than having a blanket strategy of simply giving each patient anti-reflux medication.

CHRONIC LARYNGITIS AND MALIGNANCY

The relationship between gastro-oesophageal reflux and laryngopharyngeal reflux disease in chronic laryngitis, laryngeal dysplasia, has been widely debated for many years.[52, 53] The difficulty, however, is trying to identify studies without the confounding effects of other possible aetiological factors such as tobacco and alcohol. From a practical perspective, however, a high number of patients with chronic laryngitis will be smokers and as such will be exposed to the carcinogenic effects of smoking. It is clear therefore that a proportion of these patients who will have been diagnosed initially as having chronic laryngitis will progress to invasive squamous cell carcinoma. It is likely, however, that this diagnosis may have co-existed with early dysplastic changes with the latter subsequently transforming into frankly invasive malignancy. This therefore would be co-existent pathologies rather than malignant transformation from chronic laryngitis itself. Irrespective of the origins the level of clinical suspicion and treatment need to be the same.

KEY POINTS

- Aetiologies generally multi factorial.
- Main aetiological factors are smoking, voice abuse, LPR and GORD, and environmental factors.
- Empirical treatment with PPI can be considered.
- Supplementation with alginates can be considered.
- Voice therapy is advised.
- Stopping smoking and lifestyle modifications would appear appropriate.

REINKE'S OEDEMA

This is a distinct form of chronic inflammation of the larynx and so theoretically falls into the category of chronic laryngitis. Pathologically, there is a chronic state of oedema in the membranous portion of both vocal cords from the anterior commissure to the vocal process, hence other terms used are polypoidal degeneration or hypertrophy.

The disease has a predilection for females in middle age, with co-aetiological factors of smoking and voice abuse, and invariably presents with dysphonia with an overall reduction in pitch of the voice and rarely with obstructive symptoms. Laryngoscopic examination shows that the vocal cords appear uniformly, diffusely swollen with a bulbous appearance with normal mobility.

Combined modality treatment is needed to optimize the resolution of the condition. The pathological changes within the vocal cords need surgical treatment. The inflammatory process results in an accumulation of fluid within Reinke's space, the potential space between the vocal ligament and the overlying mucosa. The aim of surgical treatment of this condition is to remove the fluid and reduce the excess mucosa with minimal damage to the underlying laryngeal architecture. This technique was described initially by Hirano.[54] An incision is made in the laryngeal mucosa overlying the superior aspect of the true vocal cord in its long axis. Reinke's space is entered, the submucosal fluid contents aspirated and the excess mucosa trimmed. The technique can be carried out either by using cold techniques or the CO_2 laser. The theoretical disadvantage of the CO_2 laser is the injurious thermal effect on the surrounding tissues. Although this may be the case in other laryngeal disorders, it could be argued that the fluid in Reinke's space is sufficient to absorb the heat. A further potential disadvantage is that the specimen may be either severely carbonized or non-existent. Dissection of the excessive mucosa can be relatively easily carried out with minimal trauma. Although both techniques have been practiced widely there is little evidence in support of one rather than the other. In a case series of 36 patients

Lumpkin et al. compared 'stripping', CO_2 laser and the Hirano technique and concluded that the Hirano technique was preferable.[55] Although there have been advocates of the use of microdebriders in this situation there is little substantive comparative evidence in its favour. Overall, to satisfy the original aim of the surgery the use of microlaryngeal cold instrumentation is advocated.

If the patient is a smoker, as is frequently the case, smoking cessation strategies should be adopted. Hojslet et al. described a case series of 29 patients in whom a stopping smoking strategy was supported strongly. This consisted of nicotine chewing gum being freely available and group counselling supervised by a psychologist. Eight of them (28%) refrained from smoking and although the discomfort was reduced none of the voices returned to normal. While the diffuse laryngitic appearances resolved, the laryngeal oedema persisted.[56]

To rehabilitate the consequences of voice abuse and poor vocal hygiene a course of voice therapy should be undertaken.

If left untreated, the concern is that there may be malignant transformation. There has been little reporting of such a phenomenon, and from clinical experience it would seem more likely that the converse is the case, i.e. that the presence of bilateral symmetrical Reinke's oedema would suggest that it is very unlikely that there is malignancy present. The exception to this observation would be in the case of unilateral 'Reinke's' oedema where clearly such a finding could be oedema associated with a deeply centred malignancy such as a squamous cell carcinoma in the laryngeal ventricle.

KEY POINT

- Treatment should be cold surgery of the laryngeal lesion, smoking cessation and voice therapy.

VOCAL CORD POLYPS

Inflammatory changes restricted to a small area of the vocal cords, for example, after some form of vocal trauma such as shouting, can transform into vocal cord polyps.

Occurring more often in young to middle aged male smokers, these patients present with a history of persistent dysphonia. Nasolaryngoscopy will show discrete lesions arising from the true vocal cords, usually in the anterior two thirds. Surgical excision of the polyp(s) by microlaryngoscopy under general anaesthesia using cold instrumentation techniques is usually curative. There is a plane of cleavage at the base of the polyp between the polyp and the vocal ligament. Following topical application of adrenaline (1 in 1000) to the vocal cord polyp, the polyp can be held in micro-forceps, retracted medially and dissected from the mucosa overlying the vocal ligament with preservation of its integrity. This latter aspect is imperative if the normal function of the vocal cord is to be restored. Once the lesion has been excised a period of voice rest for at least 48 hours is generally advocated. The evidence in support of both the type and duration of altered/reduced voice use is low level and scanty. Intuitively, however, it would seem highly appropriate to arrange a course of voice therapy to correct any habits of voice misuse in the patient as it was voice misuse which was the cause of the polyp initially.

KEY POINT

- Vocal cord polyps treated by surgical excision and voice therapy

AMYLOIDOSIS

Amyloidosis can affect the larynx as part of a primary or secondary process of systemic amyloidosis. The deposits of amyloid, proteinaceous aggregates, have a high fluid content and can occur as a diffuse submucosal process or as small subepithelial masses. The patients present with dysphonia because of the presence of the deposits in the various subsites of the larynx and their effect on the vocal cord mobility. Ultimately there may also be an effect on the airway. The mainstay of treatment is microlaryngeal surgery to remove the deposits with minimizing the laryngeal damage and this can be by either cold techniques or by CO_2 laser. The use of CO_2 laser tends to be effective because of its ability to vaporize the high fluid content within the deposits. Diagnosis is confirmed histologically because of the affinity of the amyloid for Congo Red.

TUBERCULOSIS

Invariably, tuberculosis (TB) occurs with the pulmonary version of the disease, with the patient complaining of dysphonia, pain on speaking and swallowing, and otalgia. There is a diffusely reddened and oedematous larynx affecting predominantly the posterior one third of the glottis. There may be ulceration and the appearances can be confused with squamous cell carcinoma. Thus, it is imperative to obtain histological confirmation before embarking on radical treatment. Diagnosis is made by biopsy of the laryngeal tissues. Histological examination demonstrates granulomas with caseating necrotic centres, Langhans-type giant cells and mycobacterium organisms. Treatment is to secure an airway followed by antituberculous drugs. If timely there should be resolution of the laryngeal and pulmonary disease and if not there will be the effects of chronic inflammation with stenosis and vocal cord fixation.[57, 58]

SYPHILIS

The larynx is rarely involved in this rare condition. Although each of the stages may occur the secondary and tertiary stages of the disease are more common. Hoarseness and dysphagia are common but pain is rare. There are diffuse erythematous papules (secondary stage) and nodular infiltrates coalescing into painless ulcers (tertiary stage), with the epiglottis and ary-epiglottic folds being principally involved. Appearances are similar to those of TB and carcinoma, with the diagnosis achieved by positive syphilis serology. Treatment is with high dose penicillin.

LEPROSY

Like TB laryngeal involvement in leprosy (also known as Hansen's disease) occurs only when there is concurrent systemic disease. Invariably there will be cutaneous lesions which may have been present for several years with the nasal cavity frequently being affected. In the larynx the supraglottic is often involved, in particular the epiglottis, showing an oedematous, nodular supraglottis with ulceration. The dysphonia is of a muffled voice quality. The diagnosis is achieved by biopsy of this area with isolation of *Mycobacterium leprae* from the tissues. Treatment is with diaminodiphenylsulfone, rifampicin and clofazimine and may have to be long term. Healing can result in fibrosis which if severe may necessitate tracheostomy.

SARCOIDOSIS

Sarcoidosis is a slowly progressive disease with the larynx involved in fewer than 5% of cases. The laryngeal appearances very similar to those of TB and fungal infection with the supraglottic structures being primarily involved. The larynx is rarely involved without clinical or radiographic evidence of pulmonary involvement. Diagnosis is achieved by demonstration of microorganism-negative, non-necrotizing granulomas in a biopsy specimen with concurrent clinical evidence of multisystem involvement. Treatment is ensuring a safe airway, either by laser excision or tracheostomy, and systemic corticosteroids. Outpatient based steroid injection has been reported as being a viable alternative to both systemic steroids and operative intervention and may obviate the need for prolonged intubation or tracheostomy.[59]

GRANULOMATOSIS WITH POLYANGIITIS

Formerly called Wegener's granulomatosis, granulomatosos with polyangiitis (GPA) is a systemic disease affecting the upper and lower respiratory tract and kidneys with necrotizing granuloma and vasculitis. In up to 25% of patients the larynx is affected with the appearances of an acute inflammatory reaction initially. Eventually granulomatous ulcers develop, affecting primarily the subglottis in the long term. The anticytoplasmic autoantibody (C-ANCA) is specific with biopsy findings showing necrotizing granuloma and vasculitis. Treatment is with corticosteroids or cyclophosphamide. The airway will need appropriate expert management and is discussed in Chapter 76, Laryngeal stenosis in adults.

CANDIDIASIS

Laryngeal candidiasis is due to the opportunistic infection by the oropharyngeal *Candida albicans* in the larynx. It can be associated with immunocompromised patients, for example, due to cytotoxic chemotherapy or AIDS or more commonly in those patients who have received broad spectrum antibiotics, corticosteroids, or prolonged inhaled corticosteroid use, or have received radical radiotherapy. In the latter case the laryngeal findings are a diffuse erythema of the mucosa with an irregular friable white exudate which is superficial. In the immunocompromised patient, the inflammatory reaction is much deeper and possibly with ulceration. In the superficial case, there is a degree of dysphonia, but little else, treatment is with nystatin or fluconazole and is generally successful. In the deeply infected, and potentially ulcerated, there is pain on speaking and swallowing in addition to the dysphonia. More intensive treatment is required and in this case amphotericin B may be required.[60]

HISTOPLASMOSIS

This is a systemic mycotic disease caused by *Histoplasma capsulatum*. There are nodular granulomas which can affect the anterior larynx and epiglottis and may ulcerate. The clinical picture is very similar to TB and squamous cell carcinoma. The presentation is dysphonia with varying degrees of pain and dysphagia. Diagnosis is by culture of the organisms on Sabouraud's agar from the laryngeal ulcers and the complement fixation test. As laryngeal involvement effectively only occurs in patients with the disseminated form of the disease, a useful guide to the diagnosis is the presence of multiple small calcifications on chest CT scanning. Treatment is by Amphotericin B and securing a safe airway.[60]

BLASTOMYCOSIS

Fungal disease caused by *Blastomyces dermatiditis* which affects multiple organs. Those at increased risk are individuals in North America with prolonged exposure in wooded areas. Although skin is the next most commonly affected site after the lungs when the larynx is involved there are granular erythematous changes which may progress to ulceration and microabscesses, primarily affecting the vocal cords. The principal complaint is dysphonia and as with other chronic inflammatory disease there may be confusion with squamous cell carcinoma. Diagnosis is by identification of the fungus from the microabscesses. Treatment is by itraconazole or ketoconazole and amphotericin B in advanced cases.[60]

ACTINOMYCOSIS

Systemic chronic suppurative disease can be caused by the anaerobic bacteria *Actinomycoses bovis* or *Actinomycoses israeli*. The larynx becomes involved following involvement of the soft tissues of the cervical or submandibular regions, possibly with abscess or sinus tract formation, with progression into the paralaryngeal region. The larynx is diffusely erythematous, swollen and wooden. Diagnosis is by identification of classical 'sulphur granules' in the biopsy material and culture of the microorganisms. Treatment is with penicillin or tetracycline.[60, 61]

RHINOSCLEROMA

This is primarily a chronic infection of the nasal cavity caused by *Klebsiella rhinoscleromatis* but may involve the larynx. It has three stages,: first, catarrhal, with marked purulent rhinorrhoea, second, granulomatous, with small painless granulomas, and finally, sclerotic, with sclerosis of the larynx. This sequence has only been postulated and can take a varying amount of time to occur. The glottis and subglottis are the main areas which are involved. Diagnosis is by histological identification of Mikulicz's cells, foamy vacuolated histiocytes, and Russell bodies, birefingent red inclusions, and bacteriologically by culture of the organisms. Treatment is by aminoglcoside, cephalosporins or tetracycline.[62]

KEY POINTS

- Chronic infective processes in the larynx are uncommon.
- The laryngeal appearances in each process can be very similar.
- The laryngeal appearances can be confused with those of squamous cell carcinoma.

RADIATION INDUCED CHRONIC LARYNGITIS

One of the commonest causes of chronic laryngitis in a Head and Neck practice is radical radiotherapy for a head and neck malignancy. During a course of radical radiotherapy, there is an incrementally increasing acute inflammatory reaction which develops into chronic laryngitis. Although to a certain extent the reaction is dose dependent there is considerable variation in individual responses to the treatment. Modern radiation delivery techniques can reduce the radiation dose to the larynx. The treatment of the resulting chronic laryngitis is based on similar principles to that of non-specific laryngitis. There is a high prevalence of smokers in this group of patients. To both increase the efficacy of the radical radiotherapy and decrease the severity of the chronic laryngitis smoking cessation strategies should be employed. Voice therapy would intuitively seem to be appropriate, however, there is little evidence in favour of it. There has been significant debate regarding the role of GERD in the development of laryngeal cancer and whilst this has not been resolved acid suppression would seem appropriate in this group of patients.

CHRONIC LARYNGITIS IN AN IMMUNOCOMPROMISED HOST

Colonization and infection of the larynx with *Candida albicans* may occur in patients who become immunocompromised secondary to AIDS, treatment such as chemotherapy or long-term corticosteroids. The larynx has white patches on a friable erythematous mucosa and diagnosis is made by culture of the laryngeal plaques and secretions. Treatment is by nystatin, amphotericin B or fluconazole.

BEST CLINICAL PRACTICE

- ✓ Chronic laryngitis frequently has a multifactorial aetiology.
- ✓ The main aetiological factors are smoking, voice abuse and reflux disease.
- ✓ Following clinical diagnosis, treat with voice therapy, smoking cessation therapy and consider anti-reflux treatment.
- ✓ Surgery should be used for excision of discrete lesions and tissue sampling only.
- ✓ Any intervention for chronic laryngitis must be assessed by some form of outcome, preferably patient-centred.
- ✓ Chronic infectious processes in the larynx are rare and frequently mimic squamous cell carcinoma.

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CHAPTER 71

CONTEMPORARY MANAGEMENT OF LARYNGOTRACHEAL TRAUMA

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SEARCH STRATEGY

Data may be updated by a PubMed search using the keywords: larynx, trachea, trauma, regeneration and transplantation.

INTRODUCTION

The laryngotracheal region plays a pivotal role in providing the important functions of airway protection, swallow and phonation. Injury to structures in this region is diverse and rare. The complex anatomy of the larynx and cervical trachea means that if traumatic injury occurs, severe morbidity and mortality can result, therefore early, thorough assessment and management of these injuries are vital for achieving optimal patient outcomes. The aims of treatment are to maintain a safe airway and appropriate upper aerodigestive tract function in terms of both a safe swallow and voice.[1]

ANATOMY

The laryngotracheal complex consists of an intricate cartilaginous framework, which supports a variety of muscular and ligamentous soft tissue structures.[2] This complex can deflect significant traumatic force before being injured. The larynx is a midline neck structure protected anteriorly by the mandible and strap muscles, inferiorly by the sternum, posteriorly by the cervical spine and laterally by the sternocleidomastoid muscles. The rarity of laryngeal injuries is attributed to this anatomical configuration, which provides a degree of protection to the soft laryngeal structures.[3] However, substantial dysfunction can result when injury does occur. The larynx is divided into three subsites, namely, supraglottis, glottis and subglottis, which is continuous with the trachea inferiorly. The subglottic region, being the only complete cartilaginous ring structure, is the most sensitive and therefore most vulnerable even during trivial trauma.

EPIDEMIOLOGY AND AETIOLOGY OF LARYNGOTRACHEAL INJURY

Laryngotracheal injury is diverse, rare and potentially life-threatening. The reported incidence of injury in the literature varies from 1 in 5000 to 1 in 137 000 emergency department presentations.[1, 4–5] More than 2000 cases of mortality are attributed annually to neck trauma in the UK.[8] Females are more susceptible to laryngeal injury as they tend to have longer and more slender necks compared to their male counterparts. Despite this anatomical predisposition, close to 80% of traumatic laryngotracheal injuries occur in males, particularly in the second and third decades of life, owing to greater participation in violent sports and other physical activities.[5]

Injury to the laryngotracheal complex may involve damage to the bony, cartilaginous, neurovascular and soft tissue structures of the neck. The resultant damage is related to the mechanism of injury. However, central to all laryngotracheal injury is the potential for a compromised airway.

The mechanism of injury to the larynx may be external or internal, through inhalational or iatrogenic injuries. External traumatic injuries are classified as either blunt or penetrating. The former is most commonly a result of motor vehicle accidents, as well as other causes such as hanging, strangulation and contact sports,[9, 10] while the latter occurs primarily from gunshot wounds, followed by stab wounds.[10–12] With improved standards of road safety and increasing incidence of violent crimes in the community, the incidence of blunt laryngeal injuries has decreased, while that of penetrating injuries has increased.[9] Studies have attributed only around 5% of aerodigestive injuries to blunt trauma,[10, 13] while up to 15% of these injuries are due to penetrating trauma.[12]

Blunt injuries

Blunt injuries can be further classified into crush, clothesline and strangulation type injuries. The former type of blunt injury is sustained especially in motor vehicle accidents where the victim is thrust forwards with a hyper-extended neck, particularly in the absence of a seatbelt, exposing the larynx to anterior crushing forces (**Figure 71.1**). Clothesline injuries occur when there is high velocity impact of the larynx with a stationary object. For instance, when a rider of an unprotected vehicle such as a motorcycle or snowmobile hits a stationary object, a large amount of energy is imparted over a small area. This can lead to instant exsanguination from cricotracheal separation or a crushed larynx (**Figure 71.2**).[14] In strangulation-type blunt injuries, such as hanging or strangulation by a soft object, initial injury may be minor, but can subsequently lead to laryngeal oedema and a compromised airway.[15]

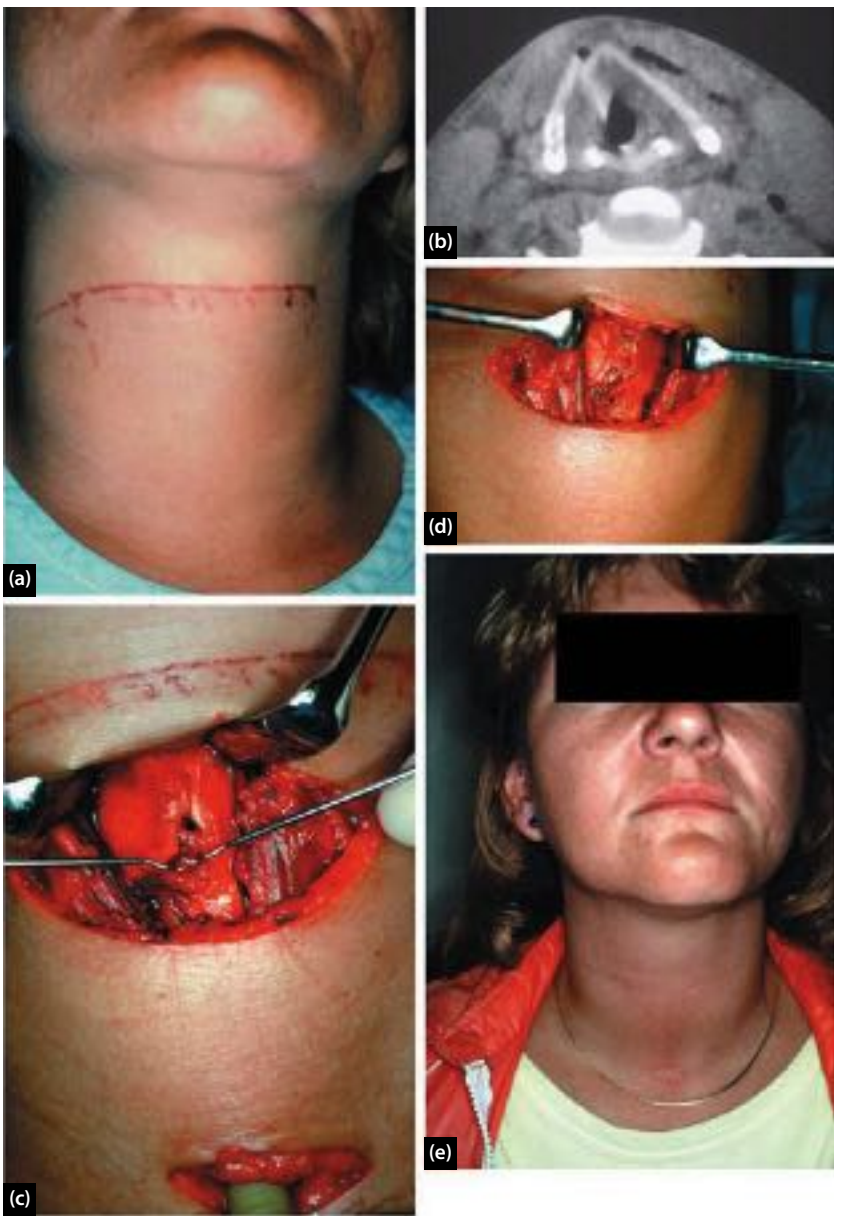


Figure 71.1 External laryngeal trauma from a motor vehicle accident. **(a)** Soft tissue findings of blunt trauma; **(b)** CT scan demonstrates paramedian thyroid cartilage fracture; **(c)** laryngeal fracture demonstrated during open exploration; **(d)** fracture reduction and repair with wire; **(e)** outcome at 1 year with good cosmetic and functional outcome.



Figure 71.2 'Clothesline' injury with tracheal separation.

Penetrating injuries

Penetrating laryngotracheal injuries can cause varying degrees of damage depending on the location and the nature of the weapon used. Injury to neurovascular and soft tissue structures can result in variable amounts of oedema, inflammation, haemorrhage, scarring and anatomical disruption. Low velocity gunshot wounds, such as those sustained with hand guns, tend to cause moderate damage to the injured tissue, while high velocity gunshot wounds, such as those sustained with rifles, can cause wide-field damage of laryngeal tissue that may extend beyond the limit of necrotic tissue.[16] Unlike gunshot wounds, stab wounds from knives have a predictable course of injury that generally does not cause damage beyond the entry and exit path of the knife.

Inhalational injuries

Inhalational injuries to the larynx and trachea occur following inhalation of toxic gases, exposure to fires or ingestion of toxic substances. This leads to oedema of the airway, which tends to be self-limiting. However, ingestion of caustic substances can lead to full thickness airway burns, leading to significant morbidity. Inhalational injury involves transfer of high levels of thermal energy. Reflex closure of the glottis occurs as a protective mechanism to limit thermal injury to the supraglottic region. Early securement of the airway is important as subsequent and delayed upper aerodigestive tract oedema can occur in the hours following injury.

Iatrogenic injuries

Iatrogenic injuries to the laryngotracheal complex can occur following any airway management procedure such as during routine oro- or nasotracheal intubation, cricothyroidotomy or during elective operations such as laryngeal surgery, laryngoscopy or routine tracheostomy. Urgent tracheostomy, required for the management of an acute airway problem, is particularly prone to injury involving the upper aerodigestive tract, including the laryngotracheal complex. Studies have identified factors contributing to post-intubation injury, such as high cuff pressure, prolonged duration of intubation, use of large diameter endotracheal tubes as well as patient co-morbidities, such as diabetes and chronic obstructive pulmonary disease.[17–19] Following prolonged intubation, the associated inflammation can lead to sequelae of granulation and scarring with subglottic stenosis, vocal fold dysfunction or airway compromise.[20, 21]

PATHOPHYSIOLOGY OF LARYNGEAL TRAUMA

Tissues involved in laryngeal injury include mucosa, nerves (superior and recurrent laryngeal nerves), soft tissue (muscle – intrinsic and extrinsic muscles, ligaments, superficial lamina propria), cartilages (arytenoid, thyroid, and cricoid) and trachea (including trachealis muscle). In the acute situation, the main concern is the integrity of the airway, but in chronic laryngeal injury there are ensuing complications, which are variable and unpredictable. Healing by secondary intention can result in scarring, subluxation, and ankylosis of the arytenoids and cricoarytenoid joints. Fibrosis of the laryngeal muscles disrupts the mucosal wave, with the appearance of non-vibrating segments. There can be anterior and posterior glottic webbing, and supra- and sub-glottic scarring. Neural injury can lead to muscle palsy, and cartilage fractures may heal by secondary intention, resulting in unstable fractures, mal-union or non-union. Such chronic effects, unlike the acute situation, are slowly progressive and therefore not discernable at the outset (**Figure 71.3**).

Mature scar tissue in the background of oedema, haematoma and collapsed tissue (soft tissue or cartilage) can have variable impact. For example, in the posterior glottis, where granulations mature over time, the posterior vocal folds can be drawn together, leading to progressive shortness of breath and airway obstruction. Other sequelae include glottic incompetence, dysphonia, aspiration and dysphagia, but the chronicity of the changes allows time for glottic compensation. This is in contrast to the acute setting, where there is no time for the larynx to adapt.

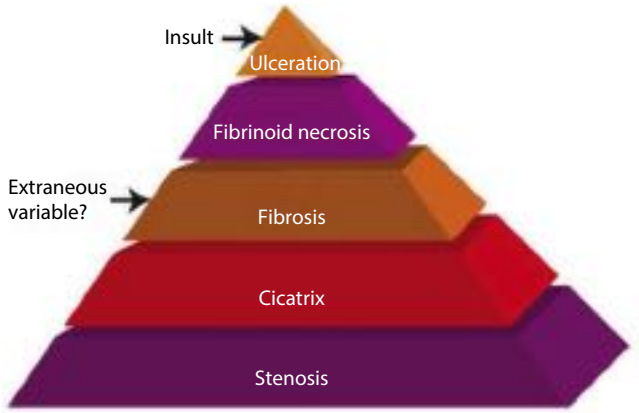


Figure 71.3 Pathophysiology in the development of a laryngeal stenosis.

BOX 71.1 Laryngotracheal injury classification by Trone et al[23]

Group 1:	Minor endolaryngeal haematoma without detectable fracture
Group 2:	Oedema, haematoma, minor mucosal disruption without exposed cartilage, non-displaced fractures noted on CT scan
Group 3:	Massive oedema, mucosal tears, exposed cartilage, fold immobility
Group 4:	As group 3, but with more than two fracture lines or massive trauma to laryngeal mucosa
Group 5:	Complete laryngotracheal separation (added by Fuhrman et al.[23])

CLASSIFICATION OF LARYNGEAL TRAUMA

A number of classification systems for traumatic laryngeal injury have been described. One such system by Fuhrman et al. classifies laryngotracheal injuries into five groups (**Box 71.1**).[22] This classification system is a modification of the previously proposed one by Trone et al, in which injury is divided into groups 1 to 4 only.[23] Group 1 comprises minor endolaryngeal haematoma without detectable fracture; group 2 injury involves oedema, haematoma, minor mucosal disruption, unexposed or undisplaced fractures; group 3 comprises injury where there is massive oedema, mucosal tears, exposed cartilage or vocal fold immobility; group 4 injury is as group 3 but with the addition of massive trauma to laryngeal mucosa or over two fracture lines; and group 5 injury is where there is complete laryngotracheal separation. These classification systems help to provide a unified approach to the assessment and management of laryngeal injuries.

Sequelae of major laryngeal trauma include stenoses at supraglottic, subglottic and/or posterior glottic levels. Classification of posterior glottic stenoses, described by Bogdasarian and Olson, is based on the structures involved (**Figure 71.4**).[24]

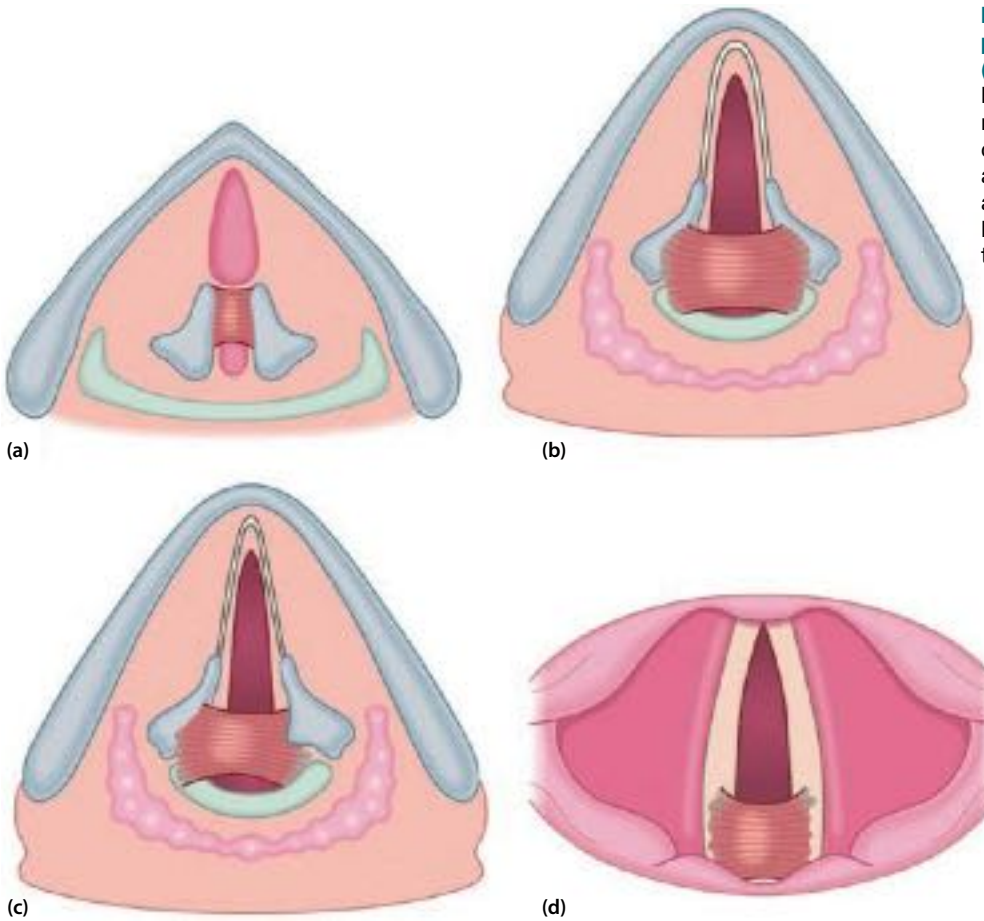


Figure 71.4 Classification of posterior glottic stenosis.
(a) Type I, isolated interarytenoid band; **(b)** Type II, posterior glottic mucosal tunnel, but no arytenoid cartilage ankylosis; **(c)** Type III, ankylosis and immobility of one arytenoid joint; **(d)** Type IV, ankylosis and immobility of both arytenoid joints.

EVALUATION OF LARYNGOTRACHEAL TRAUMA

Timely assessment and management of laryngotracheal injury following the principles of advanced trauma and life support (ATLS) is essential.[25] It requires a multidisciplinary team approach including emergency physicians, trauma surgeons, otolaryngologists-head and neck surgeons, anaesthetists, radiologists, clinical nurse specialists and allied health professionals (**Figure 71.5**).

Signs and symptoms

Signs and symptoms associated with laryngeal injury vary with the mechanism and severity of injury. Laryngeal trauma may be part of multi-trauma involving other parts of the body and therefore must be assessed in a systematic manner. Urgent review of patients is vital as patients initially exhibiting only subtle symptoms and signs of upper aerodigestive tract dysfunction can progress to complete airway obstruction from worsening oedema.

The most common presenting symptoms include varying degrees of dysphonia and dyspnoea, followed by dysphagia, neck pain and haemoptysis. Patients with penetrating neck injuries can present with externally visible neck wounds, bleeding, expanding haematoma and/or bruising.[3, 6, 26] They may also be hypovolaemic, and in shock. Those with blunt injuries with no externally visible injury may have their injuries undetected for as long as 24–48 hours post-injury.[27, 28] The hallmark clinical signs of airway obstruction include stridor, increased respiratory rate, tachycardia, sweating and use of accessory muscles. The patient may be in shock, have ecchymosis in the skin of the neck, abrasions, open wounds, massive subcutaneous emphysema, expanding haematomas, tracheal deviation and cartilaginous and bony fractures.[28–30]

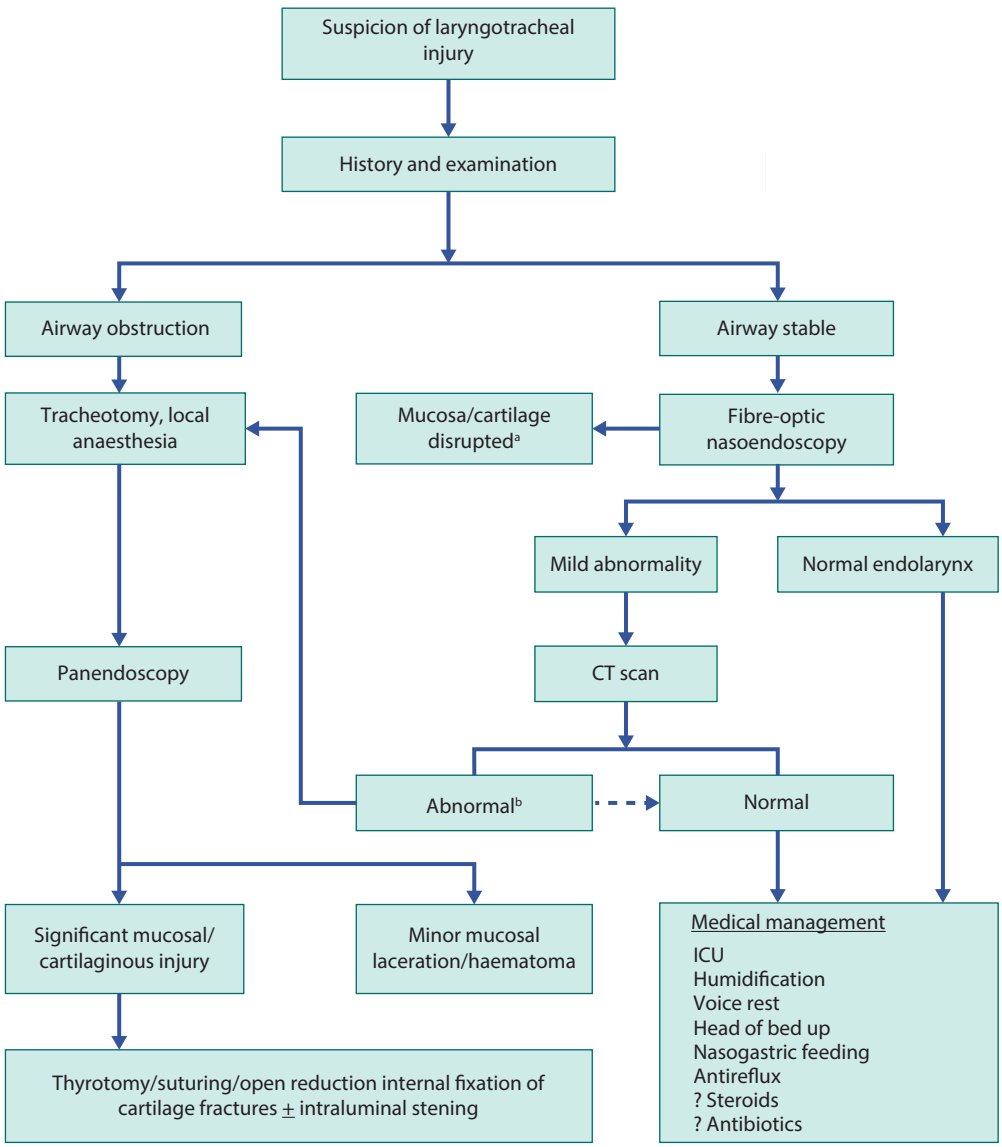


Figure 71.5 Management algorithm for patients presenting with laryngotracheal trauma.

AIRWAY MANAGEMENT

The primary goal in the initial evaluation and management of a patient with a suspected laryngotracheal injury, like any other presenting with a traumatic event, is to ensure the airway is adequately assessed and protected by the most senior and experienced medical staff available. Where there is any concern about impending airway obstruction, a safe airway must be established. Only after this has been achieved can the management of the trauma patient continue.

Once the patient is stabilized, a thorough history and examination including fibre-optic nasoendoscopy can be obtained to ascertain the mechanism, duration and extent of laryngeal injury and other concomitant injury. Fibre-optic nasoendoscopy can aid in assessing patency of the airway, vocal fold movement, presence of lacerations, haematomas and exposed cartilage.[31]

Options for acute management of the threatened airway include routine endotracheal intubation, fibre-optic awake intubation and tracheostomy under local anaesthetic. In emergent situations, cricothyroidotomy may be required, using a vertical incision to avoid the anterior jugular veins, allowing greater exposure of the airway.[28, 32] Blind endotracheal intubation must be avoided as it can lead to complete laryngotracheal separation in a partially transected airway held together by peri-tracheal soft tissue.[29] There is some controversy in the literature with regard to the best method to secure the airway. Several authors including Schaefer,[1] Fuhrman et al,[22] Hwang and Yeak[33] and Baron[34] recommend a tracheostomy under local anaesthetic as gold standard, while Gussack et al. recommend endotracheal intubation for airway management.[35] One argument for the former method is that a tracheostomy will enable examination of the site of laryngeal injury, as opposed to the latter technique, which may hinder further direct examination of the site of injury and may even cause iatrogenic aggravation of the existing injury.[6] Nevertheless, in experienced hands, there is adequate evidence in the literature to date supporting the safety of endotracheal intubation for airway management in laryngeal trauma.[6, 36]

When experienced personnel are unavailable, an emergency tracheostomy under local anaesthetic is recommended to secure the airway safely.[1, 37–39] This is ideally performed in a controlled environment as afforded by an operating theatre, where appropriate instrumentation, lighting and anaesthetic, surgical and nursing support are available. Tracheostomy under local anaesthetic is recommended to maintain spontaneous ventilation and patency of the upper aerodigestive tract until a definitive airway is established. However, in a struggling patient where this is not possible, an inhalational general anaesthetic with the highest possible inspired oxygen concentration may be administered. Muscle relaxants are contraindicated, as paralysis of spontaneous respiration and positive pressure ventilation can aggravate air leak and surgical emphysema, lead to loss of airway and result in respiratory arrest.[29] To avoid the area of laryngotracheal injury, the tracheostomy incision is ideally placed distal to the site of injury, slightly lower than usual. A horizontal incision midway between the cricoid cartilage and sternal notch is commonly used. Where a traumatic tracheotomy exists, Corneile et al. recommend the use of this wound to access the trachea as a means to provide greatest preservation of healthy trachea for repair and reconstruction.[28]

In paediatric laryngeal trauma, the preferred method of airway control consists of inhalational anaesthesia allowing for spontaneous ventilation, followed by securing the airway with rigid bronchoscopy and tracheostomy.[13, 40, 41] Cricothyroidotomy in this population is avoided as it may not provide adequate exposure, and can potentially compound the existing injury.[13, 40, 41]

Once the airway is established, further operative evaluation and exploration of the laryngotracheal injury can occur. Microlaryngoscopy, oesophagoscopy and bronchoscopy are essential aids to assess extent of injury, and photo-documentation can also be obtained simultaneously. There is some controversy with regard to timing of operative exploration once the airway has been established. Whilst some authors recommend delaying exploration until oedema at the site of injury has subsided,[42, 43] the consensus recommendation is exploration within 24 hours of injury.[1, 6, 44]

IMAGING

Following stabilization of the airway, computerized tomography (CT) with three-dimensional reconstruction and magnetic resonance imaging (MRI) are gold standard radiological modalities to assess the larynx and its framework. CT scans can provide useful information about the anatomy, and aid in management decisions.[12] The findings to look for in the setting of laryngotracheal trauma include cartilage fractures, haematoma, oedema, cricoarytenoid joint dislocation or subluxation, extra-tracheal subcutaneous air and airway stenosis. It is used in conjunction with, rather than as a replacement for, operative exploration.

Furthermore, CT and MRI can identify missed laryngeal injuries in symptomatic patients with chronic sequelae.[45] CT angiography is very important in cases of penetrating trauma, especially involving neck zones 1 and 3, where information on the location and trajectory of foreign bodies, such as bullets or shrapnel, and integrity of vascular structures must be obtained.[46]

MANAGEMENT OF LARYNGOTRACHEAL INJURIES

The management of laryngotracheal injuries may be non-surgical or surgical depending on the type and extent of injury and follows a thorough assessment of the patient.

Non-operative approach

Non-operative management options are determined by the type and extent of injury, and coexisting illnesses of the patient. Airway stability is integral to non-operative

management and assumes protection by the patient's own reflexes or by an endotracheal tube.

Atkins et al.[12] and Bisase et al.[47] recommend such an approach to management of patients with group 1 and 2 type traumatic laryngeal trauma. These injuries include minor mucosal lacerations without exposed cartilage or bone and minor hematomas. Bent et al,[4] Schaefer[1] and Close[15] also recommend such an approach in patients with undisplaced single fractures of the laryngeal cartilaginous framework. The non-operative management of these patients involves admission to an intensive care unit for airway monitoring for at least 24 hours and treatment with constant humidification, head elevation, nil by mouth and voice rest. Some patients may also require endotracheal intubation if there is concern about their ability to maintain their airway. Intubation also aids in performing a panendoscopy to rule out injury to other structures in the upper aerodigestive tract. If this examination is unremarkable, the patient can be safely managed using a closely monitored non-operative approach.

Blockade of gastric acid reflux is recommended to prevent further irritation of the injured laryngeal mucosa and laryngeal stenosis.[12, 48] The effectiveness of corticosteroids in reducing soft tissue oedema in laryngeal trauma remains unclear due to lack of supporting evidence. Further, if used, they must be given within a few hours of the injury. Similarly, the use of antibiotics in non-operative management of laryngeal trauma is also controversial. Some authors suggest that intravenous penicillin or cephalosporin can help reduce development of granulation tissue and potential infection following panendoscopy.[12, 49, 50]

Operative approach

Surgical intervention is required in patients in whom non-operative management options are unsuccessful in improving airway function, or those who continue to deteriorate despite these measures. Surgery is aimed at airway preservation, prevention of secondary sequelae of healing and restoration of function via repair of endolaryngeal and other concomitant injuries such as neurovascular damage, or thoracic injuries, and stabilization of fractures of the laryngeal framework. The type, timing and severity of injury and patient comorbidities, determine the surgical management, as detailed here.

ENDOSCOPIC

If the anaesthetist fails to intubate using an intubating laryngoscope, an anterior commissure scope can be passed by the otolaryngology head and neck surgeon to facilitate careful placement of a microlaryngoscopy tube. Once the airway is secured, examination of the laryngotracheal complex can be performed endoscopically using a variety of straight and angled telescopes. Haematomas of the vocal folds can be aspirated, and damaged folds re-approximated by suturing. Stents can be placed endoscopically in the acute situation to support the laryngeal framework and lumen, reduce the likelihood of adhesions, and maintain the structure of the anterior commissure for voice preservation, particularly if there is extensive mucosal disruption, or comminuted fracture(s). Rigid oesophagoscopy should also be performed acutely to exclude any injury to the integrity of the oesophagus.

Chronic sequelae of laryngeal trauma can be managed endoscopically. Cold steel or laser division of supraglottic webs, with or without an epiglottopexy, can be performed. Similarly, glottic adhesions can be divided and, if necessary, a cordotomy, cordectomy or arytenoidectomy undertaken. As in the acute situation, stents can be placed for the reasons described above.[51] Silastic keel placement, for 1–2 weeks, combined with vocal fold mucosal suturing can be used to treat post-traumatic laryngeal webs. Mucosal suturing of the vocal fold reduces raw surface exposure, and ultimately avoids long-term glottic stenting, laryngofissure, and requirement for tracheostomy.[52] Mitomycin-C can be injected to reduce fibrosis.[53–57] There is evidence in human and animal studies for the use of Mitomycin-C, which inhibits fibroblast proliferation by cross-linking DNA, and 5-fluorouracil/triamcinolone at the time of ablation of stenosis, or dilatation to inhibit restenosis,[53–57] although there is still some controversy regarding their effectiveness.

A bulking agent, such as hyaluronic acid, can be administered in an endoscopic injection thyroplasty procedure, to a vocal fold, injured from previous intubation or gastroscopy injury.[58] Endoscopic balloon or bougie dilatation, usually a temporizing option, can be performed with the adjunct of botulinum toxin injection to relax a stenosed cricopharyngeus.[59]

Endoscopic management of laryngotracheal stenosis is thought to be appropriate for patients whose injury does not involve the cartilage. Balloon dilatation can be used initially, but since the introduction of carbon dioxide (CO_2) lasers, a variety of endoscopic management techniques have evolved.[60] These include the neodynium-doped yttrium aluminium garnet (Nd:YAG) and microscope-mounted CO_2 laser.[61] Recently, CO_2 ablation via awake flexible bronchoscopy has been described.[62, 63]

OPEN

An open approach to traumatic laryngotracheal injury is recommended for patients with group 3 and 4 injuries, and a subset of those with group 2 injury who have minimally or non-displaced fractures. Emergent tracheostomy, surgical exploration and immediate repair is the standard of care in all patients in whom complete cricotracheal separation (group 5 injury) is suspected (**Figures 71.6a–71.6d**). In addition, the presence of concomitant neurovascular, thoracic or abdominal injuries, and individual patient factors, should tailor the surgical plan. There is some controversy regarding the timing of surgical intervention in those patients with group 3 and 4 injuries; some studies recommend surgery after soft tissue oedema has settled whilst others recommend surgical exploration early (within 24–48 hours) to avoid voice and airway dysfunction in the long term.[64] The consensus recommendation is exploration within 24 hours of injury.[6, 9, 44]

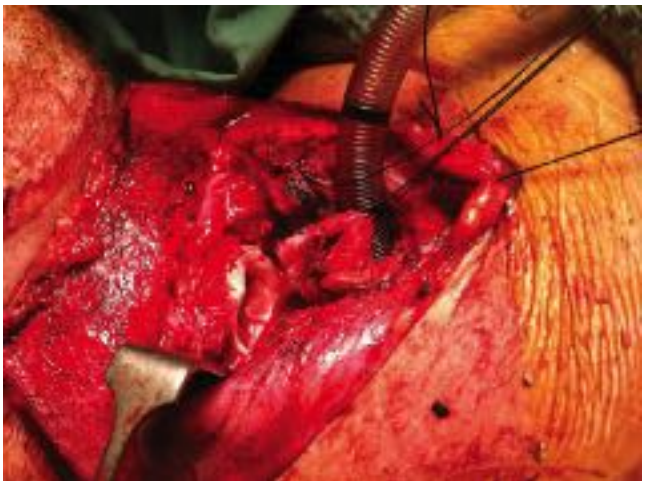


Figure 71.6a Patient presenting following a non-restraint motor vehicle accident with multi-system trauma including complete cricotracheal separation and multiple fractures of the cricoid cartilage.

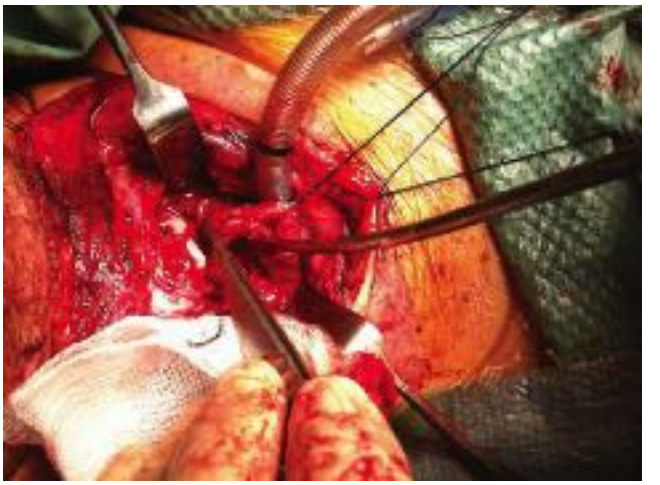


Figure 71.6b Forceps point to avulsed left recurrent laryngeal nerve.



Figure 71.6c Repair was carried out in the operating theatre after tracheostomy was performed. The cricoid cartilage was repaired using non-absorbable sutures. Primary cricotracheal anastomosis was performed using vicryl.



Figure 71.6d Appearance of larynx 1 year post-operatively, demonstrating a patent airway, despite the anterior glottic web and bilateral vocal fold palsies.

An open approach is reserved acutely for displaced or comminuted laryngeal fractures that are deemed unstable due to muscular forces, and therefore unsuitable for endoscopic repair.[65] Neural repair is rarely performed in the acute setting, unless iatrogenic, for instance in thyroidectomy. Suitable cable graft nerves include ansa cervicalis, great auricular nerve and sural nerve.

An open approach is used less commonly in the chronic situation, and usually addresses functional deficits relating to airway, voice and swallow. Cricotracheal resection may be performed for chronic subglottic stenosis, type I Ishiki open thyroplasty to medialize a paralyzed vocal fold, and cricopharyngeal myotomy for cricopharyngeal stenosis.

The open surgical technique of managing laryngotracheal stenosis is employed when cartilage integrity is not preserved or where repair is refractory to endoscopic techniques. A number of open approaches, including single and double stage reconstruction, cricotracheal resection (**Figure 71.7**), use of stents, and anterior and posterior grafting, have been described. The type of approach used is selected based on pre-operative evaluation of the stenotic region and patient comorbidities, and is discussed in detail in Chapter 76, Laryngeal stenosis in adults. Simple circumferential resection with primary anastomosis provides excellent outcome in suitably selected patients.[64, 65] Stenosis that is at a distance greater than 1.5 cm from the inferior aspect of the vocal folds is considered safe for resection with primary anastomosis.[66] Pearson et al. have suggested that up to half the trachea can be resected and managed with primary anastomosis.[67] Macchiarini et al. recommend resection of no more than 4 cm of stenosed trachea to avoid anastomotic tension and failure.[68] To achieve optimal outcome, patients must be optimized pre-operatively in terms of treating their comorbidities, such

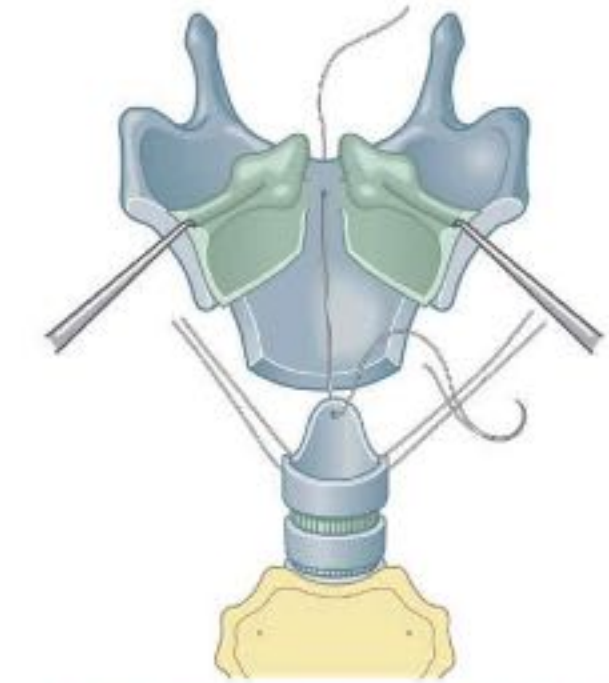
as those with immunosuppressive conditions (e.g. diabetes, vascular disease) or those taking immunosuppressive drugs. In addition, complete resection of the stenotic tissue and provision of adequate airway support post-operatively are essential for a successful outcome.

With regard to surgical approach, the patient is positioned supine with a shoulder roll to extend the cervical spine slightly. Typically, the upper aerodigestive tract is approached through a horizontal collar type incision at the level of the cricothyroid membrane, but the traumatic entry incision may provide an alternative means of entry.[40] Through this incision, superior and inferior subplastysmal flaps are raised, followed by division of the strap muscles and thyroid isthmus to maximize exposure of the laryngotracheal complex.[12, 40] Where more distal injuries are present, a partial sternotomy or right thoracotomy can be performed via this incision.[69] A laryngofissure (or midline thyrotomy) approach will expose the endolarynx, and avoids injury to the recurrent laryngeal nerve.[39, 70, 71] A laryngofissure enables debridement of contaminated tissue and removal of foreign material, repair of mucosal lacerations, and areas of denuded cartilage to be covered with mucosal flaps or skin grafts.[40, 71] Vocal folds can be repositioned and sutured in place, if necessary, using a dissolvable fine suture material.[12] This may also require an arytenopexy.[72]

All laryngeal fractures must be identified, reduced and stabilized. Repair of these fractures involves raising the perichondrial layer and suturing it with non-absorbable sutures. In addition to simple suturing, wiring the fractured cartilage segments and internal fixation with adaptation metal plates, when available, are the most contemporary methods used to stabilize laryngeal fractures.[73, 74] Alloy metal miniplates with self-tapping screws were traditionally used to bridge any fracture line, and enable the laryngeal framework to be restored as best as possible. An alternative to metal plates are malleable, non-metallic biodegradable plates, such as poly-L-lactic-acid-polyglycolic-acid,[75, 76] which slowly resorb over 1.5 to 3 years.

Avulsion injuries to the anterior commissure can also be repaired by careful suturing of the anterior aspect of the true vocal folds to the outer thyroid cartilage perichondrium.[9] Reconstruction options where there is loss of cartilage vary from the use of local muscle flaps, using either the strap muscles or parts of the sternocleidomastoid, to filling the defect, to the use of free grafts for more extensive cartilage loss, most commonly from the rib.[77] A covering tracheostomy, 2–3 tracheal rings below the site of repair, is placed for ventilation at the time of repair and to ensure a safe airway in the post-operative period.

The use of stents in laryngotracheal reconstruction is recommended where there is disruption of the anterior commissure anatomy, extensive mucosal trauma and comminuted fractures with significant damage to the laryngotracheal complex (**Figure 71.8**). Ideally these stents should be softer and more inert than hard intraluminal stents, and inserted for the shortest time possible, to avoid growth of granulation tissue.[78, 79] Schaefer recommends that they be secured in the larynx by double



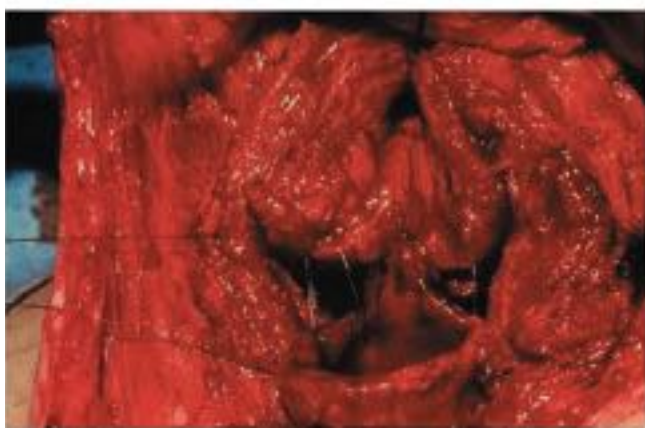


Figure 71.7 High cricotracheal separation with laryngofissure and repair using a membranous tracheal mucosa flap.

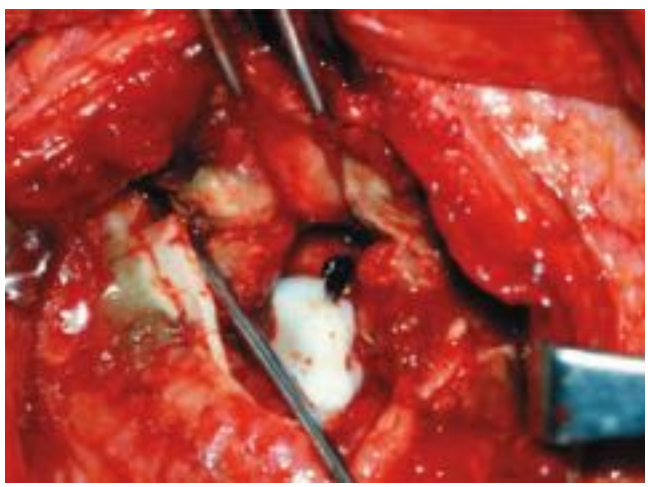


Figure 71.8 Thyroid and cricoid cartilage fracture with placement of Montgomery laryngeal stent.

sutures, and closed at the superior end, to avoid aspiration of fluids via the stent lumen.[9] In addition to a rolled silastic sheet and moulded Portex tracheostomy tube stent, a variety of newer laryngeal stents are available, which are softer and more inert. These include the Montgomery laryngeal stent, Montgomery T-tube, Aboulker stent, Eliachar laryngotracheal stent and the LT-Mold stent. However, regardless of the type of stent used, the decision to stent is made based on the need to stabilize the airway versus the potential for further laryngeal injury and infection from stenting.[80]

Repair of laryngeal nerve injury is still largely at an experimental stage. Recently, a rat model for the characterization of laryngeal function, routes of innervation, and sources of reinnervation following recurrent laryngeal nerve (RLN) resection has been developed.[81] In another rat model, the intact superior laryngeal nerve (SLN) has been used to investigate the reinnervation process of the posterior cricoarytenoid (PCA) muscle following RLN injury.[82] In this, PCA reinnervation was assessed by retrograde double-tracing techniques. The PCA was shown to receive dual innervation from both laryngeal nerves, even in the uninjured system. Following RLN injury, functionally significant collateral reinnervation originated from intact SLN fibres, mainly due to intra-muscular growth rather than by recruitment of more motor neurons.

FUTURE DIRECTIONS

Laryngeal tissue engineering

In the past decade, research into tissue engineering for laryngeal reconstruction has been growing, in particular for scarred vocal folds following trauma. This technique is still in its infancy, however, in terms of clinical application. Tissue engineering methods include the use of specific growth factors and mesenchymal stem cells (MSCs).[83]

Certain growth factors, such as basic fibroblast growth factor (bFGF), are already in use for vocal fold regeneration for cases of vocal fold atrophy. bFGF has been used to treat presbyphonia. Vocal fold atrophy was shown to improve at 1 week post-injection. Aerodynamic and acoustic parameters also demonstrated improvements, which were maintained up to 3 months.[84]

Transforming growth factor (TGF)-β3 reduces collagen synthesis and subsequent scar formation. This has been demonstrated experimentally in beagle dogs in which the lamina propria of the vocal folds was injected either with TGF-β3 or saline prior to the folds being injured by stripping of the lamina propria.[85] When larynxes were harvested at 6 months, histological analysis showed that TGF-β3 had suppressed granulation-tissue formation and scarring. Collagen distribution was well organized and less dense in TGF-β3-treated vocal folds compared to saline-treated vocal folds. TGF-β3-treated vocal folds demonstrated significantly better vibratory function.

Another growth factor, granulocyte-macrophage colony-stimulating factor (GM-CSF) assists in epithelial wound healing, and has recently been applied experimentally to promote tissue repair. In a study of vocal fold healing following injury to the vocal folds of New Zealand white rabbits, either GM-CSF or saline as a control was injected into their vocal folds.[86] The GM-CSF-treated vocal folds showed reduced collagen type I and fibronectin deposition in comparison to the saline-injected controls. Mucosal waves in the GM-CSF cohort exhibited significant improvement compared to the phosphate buffered saline cohort. In the *in vitro* arm of the study, human vocal fold fibroblasts (hVFFs) were cultured with GM-CSF. GM-CSF prevented TGF-β1-induced collagen synthesis by hVFFs, thereby reducing scar formation. The expressions of extracellular matrix-related enzymes and growth factors hyaluronan synthase-2, tropoelastin, matrix metalloproteinase-1, hepatocyte growth factor (HGF), and c-Met mRNA were significantly increased by GM-CSF. These findings suggest that GM-CSF offers therapeutic potential for the remodelling and regeneration of vocal folds following injury.

The application of growth factors could have a refractory effect if used inappropriately in terms of dosage, route and time of application. Therefore their application is in the process of being refined for safe and large-scale use in the near future.[83]

The use of MSCs has emerged as a potential therapy in the future for head and neck reconstruction. MSCs can differentiate along a specific cell lineage but also have the capacity for self-regeneration. However, this regenerative ability may be a double-edged sword due to the possibility of malignant transformation.[87, 88] MSCs are originally derived from adipose tissue but have also been derived from bone marrow and thymic progenitors.[89] These MSCs appear promising for reconstruction based on *in vivo* and *in vitro* studies in animals, due to their continuous circulation in the peripheral blood, ability to migrate to sites of injury to stimulate resident stem cell proliferation and secretion of growth factors,[90] and their differentiation into myofibroblasts and fibroblasts.[91]

An animal model study of green fluorescent protein-labelled MSCs in rats showed that MSCs were distributed throughout the vocal fold from day 1 following vocal fold injury, and that there was up-regulation of HGF compared with control-treated folds.[92] A suitable scaffold is necessary for MSC implantation. A subsequent *in vitro* study examined the role of Terudermis, an atelocollagen sponge derived from calf dermis with large pores that enable cellular entry.[93] It demonstrated adhesion of MSCs to Terudermis, with positivity for the cell adhesion molecules vimentin, desmin, fibronectin and fspl within the scaffold, showing the importance of Terudermis as a scaffold for MSCs in the treatment of scarred vocal folds. These results have been borne out by an *in vivo* study, which examined the effect of injecting MSCs that had been incubated in a scaffold of atelocollagen into beagle dog vocal folds.[87] Histological analysis

showed a greater degree of regeneration in those vocal folds that had been injected with the combined scaffold of MSCs and atelocollagen compared with atelocollagen alone.

Similar results for vocal fold healing have been obtained with an injectable hyaluronic acid/mildly cross-linked alginate (HA/ALG) hydrogel scaffold containing human adipose-derived MSCs (hAdMSCs).[94] Histological evaluation demonstrated that treatment with hAdMSCs in HA/ALG hydrogel produced more favourable changes to the extracellular matrix than hAdMSCs alone. In particular, the combination of hAdMSCs in HA/ALG hydrogel prevented excessive deposition of collagen type I and increased HGF activity in regenerating vocal folds. The combination treatment also resulted in functional improvements in viscoelastic properties.

These results highlight the potential therapeutic role of MSCs, held within a suitable collagen scaffold, in the regeneration of vocal folds that have been scarred by trauma, and show the importance of up-regulation of growth factors such as HGF and other cell adhesion molecules to produce a robust extracellular matrix for vocal fold regeneration.

Jungebluth et al. described successful transplantation of a bioengineered trachea using autologous bone marrow-derived MSCs, seeded on a bioartificial nanocomposite.[95] Due to the complexity of laryngeal anatomy and physiology, concerns about the neoplastic potential of MSCs, and their appropriate and safe harvesting and application, MSCs are, in some respects, more suited to bioengineered tracheal transplantation, where the tissue anatomy is more simplistic. Currently the role of MSCs and growth factors is limited to regeneration of vocal folds that have been scarred by trauma, rather than to injuries affecting the intricacies of the laryngeal framework.

Laryngotracheal transplantation

The concept of laryngotracheal transplantation has been present for decades; however, the difficult anatomy and microvascular structure of the region, as well as the necessity for prolonged inhibition of T-cell activation,[96] have posed some hurdles. The first attempt at human transplantation, whereby a partial laryngectomy was undertaken, was in 1969.[97] Following this, in 1998, a successful total laryngeal transplant was performed, which has survived at least 12 years later, despite issues of chronic rejection.[98, 99] A further 13 cases of laryngeal transplants have been reported from Colombia but their long-term reports are still awaited.[100] More recently, Farwell et al. have provided an account of a successful, modified transplant of a larynx with long segment of trachea.[101] They were able to revascularize successfully, and reinnervate parts of the transplant selectively, with patient recovery at 3 months showing no evidence of rejection.

Porcine laryngeal transplantation has been described, with patent airways and restoration of swallowing at 1 week, and no evidence of ischaemia-perfusion injury in major histocompatibility complex-matched pigs.[102, 103] More recently, staged laryngeal allotransplantation has been described in beagle dogs.[104]

It is evident that the idea of laryngeal transplantation is still in its infancy. It is only suitable for a subset of people who have endured severe trauma, requiring laryngectomy, and carries with it the challenges of a prolonged recovery and lifelong immunosuppression. With advances in transplant technology, this could become a more viable option in future. There are inevitable issues concerning patient selection, reinnervation, immunosuppression and cost-benefit to be overcome.[105]

CONCLUSION

Injuries to the laryngotracheal region are diverse, relatively rare and potentially life-threatening. The key to successful outcomes in terms of survival, airway, a safe swallow and voice is early recognition, assessment and state of the art management of these injuries. Advances in imaging techniques and fibre-optic endoscopy have aided improved evaluation of these patients. Furthermore, a multidisciplinary team approach is essential for managing laryngotracheal injuries and, depending on patient, injury and treatment-specific factors, may involve operative or non-operative techniques. The use of bioengineered laryngeal tissue and laryngeal transplantation may become viable options in the future, to provide improved functional outcome for patients.

KEY POINTS

- The aetiology of trauma to the larynx and trachea is wide-ranging, resulting in complex and potentially life-threatening injuries.
- A multidisciplinary approach in a centre with expertise in complex head and neck disease will enable airway protection and assessment of the extent of injury, to determine the best management and timing of any potential operative intervention.
- Chronic upper aerodigestive tract dysfunction is a likely sequela and requires prolonged rehabilitation.
- Laryngeal tissue engineering is an expanding field which has provided a foundation for transplantation in animal models and humans.

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CHAPTER 72

UPPER AIRWAY OBSTRUCTION AND TRACHEOSTOMY

Paul Pracy and Peter Conboy

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: upper airway obstruction, tracheostomy and focusing on diagnosis and management. The evidence in this chapter is mainly level 3/4 with some level 2 evidence. The clinical recommendations are predominantly B and C.

INTRODUCTION

The scenario of a patient presenting with upper airway obstruction is one of the most challenging that a doctor can be faced with. This chapter aims to review the options available for the management of upper airway obstruction. The primary goal is to secure a safe airway with minimal invasion appropriate to the clinical scenario.

The causes of upper airway obstruction are varied and some are immediately apparent whilst others are subtle. Penetrating and blunt trauma to the head and neck region with acute airway compromise are particularly difficult situations to manage, both in the pre-hospital setting and on arrival in hospital. Infections of the upper airway that may result in compromise include peritonsillar abscess, parapharyngeal space abscess, retropharyngeal abscess and epiglottitis. Hypertrophy and neoplasia of lymphoid tissue in the tonsils and tongue base typically evolves more slowly. Primary malignancy of the head and neck mucosal surfaces may also present with upper airway obstruction. Airway compromise associated with paralysis of the vocal cords and foreign body obstruction occurs far less commonly in adults.

There is potential for conflict between the considerations of the safe and secure airway and minimizing the intervention to be undertaken. This risk management problem is more apparent in the acute setting where comprehensive assessment of the ill patient is difficult and other coexisting medical problems may not be known.

SYMPTOMS AND SIGNS

In the absence of acute trauma to the upper airway, the symptoms described are often non-specific and include dyspnoea, cough and voice change. It should be noted that these symptoms might also indicate lower airway disease. Given the dual purpose of the upper aerodigestive tract, it is not surprising that these primary airway symptoms may coexist with dysphagia, pain on swallowing or referred otalgia. Noisy breathing implies turbulent airflow and airway compromise. Progression of this symptom heralds impending complete airway obstruction.

Stridor and stertor

Noisy breathing tends to have different characteristics depending on the level of upper airway obstruction. Stertor is defined as a heavy snoring sound that is low-pitched and indicates obstruction or collapse in the pharyngeal airway. Stridor is a high-pitched noise that can be mistaken for wheeze. Stridor arises from compromise of the airway at the level of the larynx and trachea and is generated by turbulent airflow. Stridor can be inspiratory, expiratory or biphasic (**Box 72.1**). Careful clinical assessment of timing of the stridor helps to localize the level of obstruction.

The extrathoracic airway has a tendency to collapse on inspiration and to expand on expiration. A reduction in the airway diameter at this level is therefore more

BOX 72.1 Stridor and level of airway obstruction

- **Inspiratory:** obstruction at and above the glottic larynx
- **Expiratory:** obstruction of the intrathoracic airway
- **Biphasic:** obstruction associated with subglottic and tracheal lesions

apparent on inspiration. This is the case with pharyngeal narrowing, or compromise of the supraglottis and glottis by a pedunculated lesion being sucked into the airway on inspiration and blown clear on expiration (producing a 'ball-valve' effect). The opposite applies to the intrathoracic airway where increased negative intrapleural pressure in inspiration leads to an increase in the airway diameter. During expiration, there is increased extrinsic pressure on the airway that exacerbates any narrowing. The subglottis and trachea is usually immune to the pressure fluctuations arising from the respiratory cycle due to cartilaginous support and therefore stridor at these levels is typically biphasic.

Increased work of breathing is also indicated by suprasternal, intercostal and subcostal recession as well as nasal flaring. This is accompanied by increased use of the accessory muscles of respiration.

Voice change

Changes in the vocal quality arise from impaired vocal fold vibration or altered vocal cord movement. Hoarseness results from many types of injuries and may signal oedema, mucosal disruption, cartilaginous injury and impaired vocal cord movement. Typically, the greater the degree of hoarseness, the greater the severity of laryngeal injury. Aphonia is often associated with severe injury. Voice change can also indicate the presence of a lesion altering the normal vocal fold structure producing impaired vibration.

Drooling and bleeding

Drooling is a symptom that indicates either pharyngeal or oesophageal obstruction or the avoidance of swallowing due to the presence of significant pain brought on by deglutition. This may arise from trauma or infection. Bleeding indicates mucosal trauma or exposure of a vascular structure by an invasive lesion. In the case of trauma, depending on the severity it may not be possible to identify the level of bleeding and it should be remembered that there may be more than one source.

Fractures and subcutaneous emphysema

Blunt trauma to the head and neck area may result in fractures of the maxilla, mandible, larynx or trachea. Significant pharyngeal trauma and fractures of the laryngeal skeleton or trachea may give rise to surgical emphysema. This may add to the extrinsic compression and independently worsen the upper airway obstruction.

MANAGEMENT

Assessment

The importance of the initial assessment and immediate management of the patient with upper airway obstruction cannot be underestimated. In resuscitation scenarios, the principle of an ABCDE approach is adopted. The airway (with appropriate consideration of the cervical spine in trauma) is always the first step in patient management, followed by consideration of breathing and circulation. This leads on to a neurological assessment and then a general evaluation. The general evaluation includes a determination of the extent and severity of the neck/chest injury.

The patient must be examined to exclude or address any immediately reversible causes of airway obstruction. Where any concern exists regarding the immediate safety of the airway, it should be secured by the least invasive technique that the attending clinician is capable of without delay. In trauma cases with possible cervical spine injury, appropriate imaging of the spine is required and in cases of uncertainty cervical spine protection must also be considered.

Whilst the assessment of the critically ill patient needs to be rapid it must also be systematic and thorough. Careful eliciting of the symptoms and signs will usually provide sufficient information on how to proceed. Where the airway is sufficiently stable but no cause for the airway compromise has been identified, the examination should include a transnasal fibre-optic endoscopy. This is generally well tolerated and provides vital information as to the site, degree and nature of the obstruction. It permits assessment of the state of the mucosa (presence of oedema, lacerations, blood) the appearance of the laryngeal structure (reduced view, position and mobility of the vocal cords) and the level or levels of airway compromise.

Treatment

The interventions available depend on the environment that the patient is in as well as the skill set and experience of the clinician (**Box 72.2**). It is important to remember that there can be rapid changes in the condition of the patient and that frequent revaluation is needed to respond appropriately to new symptoms and signs. Temporizing interventions should be utilized where possible initially; although tracheostomy is the definitive management

BOX 72.2 Principles of intervention in upper airway obstruction

- Secure the airway with the most straightforward and least invasive method.
- Adequate airway control must include securing the airway below the lowest level of obstruction.
- If known, coexisting medical conditions should be considered when deciding on the most appropriate intervention.
- Only address other medical problems once the airway has been adequately secured.

for upper airway obstruction, it may be difficult due to patient agitation (including effects of hypoxia) and movement (with use of accessory muscles of respiration).

The methods available for patient support in upper airway obstruction can be considered under the broad headings of non-invasive medical management and the use of alternative airways.

Medical management and non-invasive procedures

Whilst it should be borne in mind that 'the time to do a tracheostomy is when you first think of it', there are frequently times when minor trauma, infection or tumours cause airway obstruction that is moderate in severity and stable. Under such circumstances, it may be reasonable to institute a period of close observation allowing supportive and therapeutic measures to be commenced. This option is only suitable for clinicians who have experience in the management of patients with airway obstruction, and facilities exist for immediate intervention by intubation or tracheostomy in the event of patient deterioration. The most appropriate environment for such observation is in a high dependency setting, such as an intensive care unit. During this period, the airway should still be considered as potentially unstable and so all those involved in the management of such a patient must understand that any deterioration is an indication for immediate intervention to secure the airway.

INTERVENTIONS FOR OBSTRUCTION SECONDARY TO FOREIGN BODIES

In the case of upper airway obstruction due to a foreign body, including a food bolus, a stepwise approach is followed. Initially the patient is encouraged to cough. If this fails, then hard blows to the back with the heel of the hand is advocated before considering potentially more hazardous interventions including abdominal thrusts (the Heimlich manoeuvre). This manoeuvre involves the rescuer hugging the patient from behind and exerting pressure with the hands in the region of the xiphisternum to produce diaphragmatic movement. The lungs are compressed which may lead to dislodgement of the impacted foreign body. Complications of this technique include pneumomediastinum, pneumopericardium, surgical emphysema and gastric rupture. If the patient becomes unconscious, the emphasis switches to performing cardiopulmonary resuscitation. Inspection with a laryngoscope and removal under direct vision may be required. Where there is inability to remove the object a cricothyroidotomy is required.

OXYGEN AND HELIOX

The inspiratory oxygen concentration can be increased with the administration of high-flow oxygen via a facemask with a reservoir bag. In the emergency situation, the use of oxygen can be combined with simple airway methods including chin lift and jaw thrust. Use of humidification helps to break down secretions and makes them easier to clear. Heliox is a mixture of 80% helium with 20% oxygen. The properties of helium are a gas with low density and high viscosity resulting in less turbulence compared with air and pure oxygen. The patient experiences reduced resistance during breathing heliox and this is of proven benefit in the obstructed patient.[1]

STEROIDS

Steroids have a role to play in reducing the oedema produced by trauma, inflammation or infection.[2] There is no evidence to suggest a detrimental effect of steroids in the presence of infection when used as a short-term measure. Further indirect evidence on the benefit of steroids is provided by the use of corticosteroids to reduce the risk of post-extubation upper airway obstruction in adults and children.[3, 4]

ANTIBIOTICS

Antibiotics should be given in any case where acute infection is suspected and in cases where there is evidence or strong suspicion of a mucosal injury. Choice of antibiotic is usually guided by local institutional antimicrobial policy.

Alternative airways

The decision to proceed with the use of an alternative airway is based on an unstable patient and includes deteriorating obstructive symptoms and signs despite simple interventions. Patients in this situation are very challenging and appropriately trained and experienced individuals should carry out these interventions.

ORAL AIRWAY

In the event of a loss of consciousness or obstruction due to nasal injury, the airway may be improved with the use of an oral Guedel airway (**Figure 72.1**). A Guedel airway will not be tolerated if the gag reflex is present. This oral



Figure 72.1 Selection of Guedel airways.

airway is easy to insert and bypasses obstruction in the oral cavity and nose but it is easily displaced. It can be used to assist ventilatory resuscitation with a facemask and ambubag. It also facilitates suctioning of the airway. The patient must still have a normal airway beyond the oral cavity and nasopharynx as well as a normal ventilatory drive for this intervention to be of value.

NASOPHARYNGEAL AIRWAY

A nasopharyngeal airway is a soft silicone plastic tube designed to be inserted via the nasal passageway to bypass obstruction at the level of the oropharynx, for example where the tongue base is pushed backwards in Ludwig's angina or angioedema and in cases of trauma with facial fractures (**Figure 72.2**). Insertion is straightforward and the tubes are well tolerated. The nasopharyngeal airway also facilitates suction. It should be noted that the tube can cause trauma to the nasal airway and resulting bleeding may give rise to further airway compromise. Use is contraindicated in patients with severe head or facial injuries where a skull base fracture allows the possibility of entering the intracranial compartment.

ENDOTRACHEAL INTUBATION

Endotracheal intubation is the intervention of choice where there has been a loss of respiratory drive necessitating assisted ventilation, or in cases of progressive upper airway obstruction. The person performing intubation should be supported by a trained assistant with access to a trolley containing a variety of laryngoscopes with a good light source, a range of endotracheal tubes, bougies and suction facilities.[5]

The usual route of intubation is via the mouth. This can be assisted by video-laryngoscopic devices.[6] The relative contraindications include cervical spine fractures, severe facial trauma and laryngeal trauma. In cases of cervical spine fracture, great care must be taken to avoid neck extension that may precipitate or worsen spinal cord injury. Facial trauma is usually associated with increased difficulty visualizing the larynx due to oedema, mucosal laceration and bleeding, trismus and bony instability. Great care is needed where there is laryngeal trauma, as the act of intubation may worsen the existing damage.

An alternative route to secure the difficult airway is by transnasal intubation. This is often performed using endoscopic guidance. The endotracheal tube is secured to a flexible nasal endoscope or bronchoscope (**Figure 72.3**). The tip of the endoscopic device is passed via the larynx into the trachea and the endotracheal tube is then passed over the fibre-optic endoscope into position. This is a skilled technique that requires experience, given the expected airway compromise with secretions, blood, and anatomical distortion resulting in poor views of the larynx.

TRANS-TRACHEAL CANNULATION

In the emergency setting, the trachea can be cannulated directly via the cricothyroid membrane using a large bore intravenous cannula. The airway can then be maintained temporarily by connecting the cannula to an ambubag using a syringe with a 7mm endotracheal tube adaptor inserted in the barrel (**Figure 72.4**).



Figure 72.3 Flexible nasal bronchoscope with endotracheal tube.



Figure 72.4 Large bore cannula with adaptation to connect to anaesthetic circuit.



Figure 72.2 Nasopharyngeal airway.

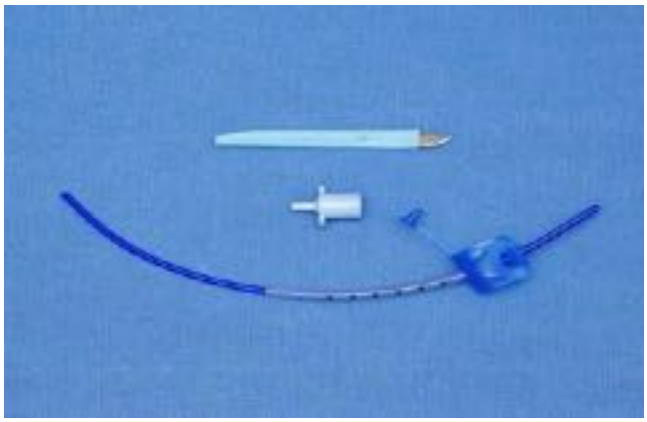


Figure 72.5 Cricothyroidotomy kit.

CRICOTHYROIDOTOMY/MINITRACHEOSTOMY

In an emergency, rapid control of the upper airway can be achieved by use of an airway inserted through the cricothyroid membrane. Once an incision has been made through the membrane a minitracheostomy tube or a wide bore cannula can be used to keep the tract open and provide an alternative airway (**Figure 72.5**). A sound knowledge of the anatomy and technique is required to minimize complications.[7]

The patient is positioned with the neck extended over a pillow. The cricothyroid membrane can be palpated and the area is infiltrated with local anaesthetic and epinephrine. The cricothyroid membrane can be incised either with a scalpel or a wide bore cannula attached to a syringe half filled with saline. In the former case, once the airway has been opened the blunt handle of the scalpel can be inserted and rotated to create space for a tube to pass into the trachea. In the latter case, the needle of the cannula is used to breach the membrane and as the needle and cannula are inserted the plunger of the syringe is withdrawn. Air bubbles into the syringe when the trachea has been entered. The cannula can then be introduced over the needle. The cannula can be connected via a universal connector to an ambubag and the patient can be ventilated for a short period of time. Using this system, CO_2 is not cleared and so conversion to a formal tracheostomy should be undertaken as soon as possible.

A minitracheostomy tube should not be left in situ for more than a short time as there will inevitably be some friction between it and the cricoid cartilage that will predispose the patient to subglottic stenosis.

TRACHEOSTOMY

Tracheostomy (**Box 72.3**) is one of the oldest surgical procedures.[8] There are references to the creation of a surgical airway in many ancient texts.[9] Until the end of the 19th century and the introduction of asepsis together with the development of safe anaesthetic techniques, the procedure was extremely hazardous. Tracheostomy was seen as a last resort in hopeless cases and was the cause of great anxiety for the patient and surgeon alike. Chevalier Jackson established the principles of the operation at the beginning of the twentieth century and these remain in place today.[10] The development of percutaneous tracheostomy has taken surgical airway management out of the exclusive province of the otolaryngologist. There is now a wide variety of clinicians involved in the challenges of tracheostomy care and decannulation strategies.

BOX 72.3 Definitions

Tracheotomy: a surgical opening in the trachea
Tracheostomy: the creation of a stoma at the skin surface that leads into the tracheal lumen

The commonest use of an elective temporary tracheostomy is for prolonged ventilatory support in a ventilated patient. A temporary tracheostomy may also be planned as part of a major surgical procedure in which there are concerns about post-operative swelling or bleeding, which may precipitate upper airway obstruction.

An emergency tracheostomy is a rare procedure, perhaps only indicated in cases of severe trauma or very late presentation. In all other cases, it could be argued that the performance of an emergency tracheostomy is indicative of an underestimation of the severity of the breathing problem. The majority of cases can be dealt with by carrying out an urgent procedure under local anaesthesia with the patient awake. In extremis, it should be possible to perform a cricothyroidotomy and maintain ventilation via a wide bore cannula until conversion to a formal tracheostomy can be undertaken.

A permanent or 'end' tracheostomy is an elective procedure carried out as part of a surgical procedure involving the removal of the larynx, such as a laryngectomy or pharyngolaryngectomy. A permanent tracheostomy is also created in laryngeal diversion procedures used to prevent aspiration. The continuity between the laryngopharynx and the trachea is permanently disrupted and the cut end of the trachea is sutured to the skin.

The effects of tracheostomy are shown in **Box 72.4**.

Indications for tracheostomy

Indications for tracheostomy are: upper airway obstruction; prolonged ventilation; removal of secretions; and part of another procedure.

UPPER AIRWAY OBSTRUCTION

This has been discussed above. Tracheostomy is considered as the ultimate form of airway control.

BOX 72.4 Effects of tracheostomy

- Laryngeal bypass – loss of cough and phonation
- Reduction in respiratory dead space
- Loss of nasal mucosa filtration and humidification
- Increased risk of infection
- Tube acts as foreign body leading to local inflammation
- Sump above tracheostome and below larynx where mucus collects.

PROLONGED VENTILATION

Tracheostomy is the safest means of assisting ventilation where prolonged positive pressure is needed. It is easier to secure a tracheostomy tube than either an orotracheal or nasotracheal tube and the reduced dead space assists weaning of respiratory support. It has been demonstrated that the introduction of percutaneous tracheostomy has led to a doubling in the number of tracheostomies being carried out.[11] It may be that the ease of access to tracheostomy has resulted in reduced duration of intubation.[11] However, with the introduction of low-pressure cuffs for endotracheal tubes, a longer period of intubation has become acceptable. There is evidence that early tracheostomy in trauma patients reduces length of ventilation and hospital stay[12] and it may be that the same applies for general ITU patients.

REMOVAL OF SECRETIONS

The accumulation of secretions in the lower respiratory tract is responsible for a reduction in gas diffusion within the alveoli. This results in respiratory failure. A tracheostomy reduces the dead space, so reducing the work of breathing, and also makes it easier to aspirate secretions with less patient discomfort.

PART OF ANOTHER PROCEDURE

A permanent tracheostomy is an unavoidable consequence of a major head and neck procedure (e.g a total laryngectomy). A temporary tracheostomy is usually needed for open resections involving the oropharynx or larynx. In these cases, the tracheostomy allows protection of the lower airway from aspiration of blood in the event of a haemorrhage, as well as guarding against upper airway obstruction from post-operative swelling. A percutaneous tracheostomy is probably not appropriate in these cases, as the pre-tracheal tissues fit tightly around the tube.[13] In the event of tube displacement, the tissues can collapse inwards, closing the airway with a potentially fatal outcome.[14]

Anatomy

As with any surgical procedure, when performing tracheostomy, it is essential to have a sound knowledge of the relevant applied anatomy of the upper trachea. Problems are likely to happen if the surgeon strays from the midline. The recurrent laryngeal nerve runs in the tracheoesophageal groove and the great vessels are lateral to this within the carotid sheath. It is rare in a straightforward tracheostomy to lose sense of where the midline is, but in obese patients and small children it is possible to lose the anatomical landmarks and stray laterally. The thyroid isthmus crosses in front of the trachea covering a variable number of the tracheal cartilaginous rings. It is a highly vascular structure and inadvertent damage during dissection or friction from the tube may result in post-operative haemorrhage. The innominate artery crosses the front of the trachea, from left to right, at a variable height. In cases of a high innominate artery it may be encountered during dissection or may suffer erosion from the tracheostomy tube with potentially fatal post-operative haemorrhage.[15]

Contraindications

There are no absolute contraindications to tracheostomy. However, in patients with a terminal prognosis, very careful consideration must be given to the psychological effect on the patient and the quality of life aspects. There is no right or wrong answer and each patient must be approached on an individual basis.

Pre-operative considerations

In the elective setting it is imperative that adequate consent is received from the patient or their relatives. As part of this process it is necessary to cover the risks and benefits of the procedure in some detail. This must be a frank and open discussion and the potential complications and sequelae of tracheostomy must be pointed out. This is particularly true of paediatric tracheostomy.

Operative procedures

PERCUTANEOUS TRACHEOSTOMY

First described more than 50 years ago,[16] this technique has grown in popularity and is now the commonest procedure for the provision of an alternative airway for ITU patients. The growth of the procedure followed the introduction over the last 15–20 years of commercial kits based on well defined techniques (**Figure 72.6**).[17–19] The most commonly employed kit in the UK depends on the dilatation technique originally described by Ciaglia.[20]

The patient should be positioned as for a formal surgical tracheostomy (see 'Open surgical tracheostomy' below). The trachea is punctured, using a needle and cannula, just below the first tracheal cartilage ring. A syringe half-filled with saline is attached to the cannula. Gentle aspiration allows correct positioning of the cannula,



Figure 72.6 Percutaneous tracheostomy set.

because air is aspirated through the saline as the needle passes into the trachea. The needle is withdrawn and a guide wire is inserted through the cannula. The cannula is withdrawn to allow for either a single dilator or a series of dilators with increasing diameter to be passed over the guide wire. The dilators create a passage that is wide enough for the insertion of a standard tracheostomy tube, which is secured in position within the trachea. It is advisable to view the internal lumen of the trachea during this procedure by using a flexible bronchoscope, as this may reduce complications.[19]

OPEN SURGICAL TRACHEOSTOMY

There are many variations in the technique of open surgical tracheostomy but they are all based on the same fundamentals. The technique described is that preferred by the authors. The procedure should, when possible, be carried out in an operating theatre, under sterile conditions. It is usual for the patient to have a general anaesthetic but where this is deemed hazardous the procedure can be carried out under local anaesthetic.

The patient should be positioned supine, with the neck extended by placing a sandbag under the shoulders. It is important that the patient is positioned square on the table with the shoulders at the same level as this will ensure that the midline structures of the neck are truly in the midline throughout the operation (**Figure 72.7a**). When operating under local anaesthesia it may be necessary to compromise on the degree of neck extension as over-extension may further restrict the airway.

A horizontal incision is sited halfway between the sternal notch and the lower border of the cricoid cartilage (**Figure 72.7b**). Once the skin has been incised, dissection continues through the subcutaneous tissues to the strap muscles, which are retracted laterally, following blunt dissection in the midline to separate them. Following this manoeuvre, the thyroid isthmus should be visible (**Figure 72.7c**). The isthmus should be clamped, divided and transfixed (**Figure 72.7d**). At this point the anterior tracheal wall is encountered. It is useful to identify the cricoid cartilage to plan the point of entry into the trachea. Ideally the tracheotomy should be made between the 2nd and 4th tracheal rings. Before entering the trachea, it is important to select an appropriately sized tracheostomy tube and check that the cuff and all connecting equipment works properly, so that ventilation can continue uninterrupted following the tracheostomy. There needs to be good communication between the surgeon and the anaesthetist.

Having informed the anaesthetist that the trachea is about to be opened, the tracheotomy can be performed. The guiding principle should be to cause as little disruption to the trachea as possible, maintain cartilage and prevent damage to the cricoid cartilage. These aims are best achieved by the use of a vertical slit between stay sutures. Once the trachea has been opened, the anaesthetist should withdraw the endotracheal tube under the direction of the surgeon, who can visualize the tube being withdrawn. When the tip of the endotracheal tube is immediately above the tracheotomy, withdrawal can stop and the tracheostomy tube should be inserted. The cuff should be inflated and the tube connected to the ventilator.

The incision should be closed loosely and the tracheostomy tube secured in position with tapes, sutures or both (**Figure 72.7e**).

Choice of tube

There is a wide variety of tracheostomy tubes available, made from different materials and with different features. The choice of tube depends on the indication for the tracheostomy, the post-operative needs of the patient and the anatomy of the patient.

CUFF

Cuffed tracheostomy tubes are used to provide a seal to allow positive pressure ventilation or to prevent aspiration. The pressure of air within the cuff must be high enough to provide an adequate seal but not so high as to damage the tracheal mucosa resulting in subglottic stenosis. The use of modern low-pressure cuffs has for the most part reduced this problem.

INNER TUBE

Some tubes are supplied with an inner tube that fits snugly inside the main tube. The tip of the inner tube projects a few millimetres beyond the distal end of the main tube. This means that secretions will collect in the inner tube that can be removed, cleaned and replaced without disruption to the patient or their airway.

FENESTRATION

The fenestration is sited at the point of maximum curvature in the tube and may be in the form of a single hole or a number of small holes. The fenestration allows air to pass from the tube through the larynx, so increasing the air available for phonation and increasing the volume of the voice.

FLEXIBILITY

In some cases, a rigid tracheostomy tube will not conform to the anatomy of the patient and will lie at an awkward angle or in a position that will result in tracheal trauma from the tip of the tube rubbing against the tracheal wall. In these circumstances, a softer and more flexible tube is preferred. If the use of a softer tube results in obstruction of the tube due to kinking, it may be necessary to use an armoured flexible tube.

ADJUSTABLE FLANGE

An adjustable flange allows the intra-tracheal length of the tube to be altered to take account of the depth of the stoma, which may be increased by alterations in anatomy, such as in patients with a large thyroid mass, or to bypass intra-tracheal obstruction.



Figure 72.7 **(a)** Patient positioned and marked for tracheostomy; **(b)** tracheostomy skin incision; **(c)** exposure of thyroid isthmus; **(d)** control of thyroid isthmus; **(e)** secured tracheostomy tube.

The tube placed at the time of the tracheostomy should be cuffed to allow ventilation of the patient and to prevent aspiration of blood or secretions resulting from the procedure. Ideally an inner tube should be available to allow easy clearing of secretions in the immediate post-operative period.

Post-operative considerations

It is important to remember that the patient requires multidisciplinary input. In addition to the requirements arising from the tracheostomy, which include communication, airway management and potential swallowing issues, there is also the need to address the pathological process that has generated the need for definitive airway control. A team-based approach is therefore essential for optimal patient outcome and minimizing complications with various studies and consensus.[21–24]

On return to the ward it is important that a nurse who is experienced in the care of tracheostomy patients and knowledgeable about the potential complications looks after the patient. Writing materials must be available for the patient to use for communication.

The original tracheostomy tube must be secured in position for at least 3 days to allow a good tract to form. The tube should be changed after 7 days and any sutures can then be removed. Tubes should be secured with tapes fastened by a secure knot on both sides of the neck, with the neck in a neutral position. If the neck is extended when the tapes are fastened, then the tapes will be too long and will not hold the tube in the appropriate position and it may be coughed out.

The cuff should be deflated once the risk of aspiration has passed. In most cases, there is no need for cuff inflation after the first 12 hours.

Following tracheostomy, the inspired air passes directly into the trachea without being warmed and humidified by the upper airway. As a result, the air is irritant to the trachea and there is an increase in the quantity and viscosity of the tracheal secretions. The patient may require frequent suctioning in the early post-operative period and the use of hot water bath humidifiers or nebulizers is essential to reduce the risk of tube obstruction due to crust formation. As the trachea becomes accustomed to the presence of the tube and the patient learns to clear the secretions by coughing through the tube, so the need for suctioning and humidification decreases.

Swallowing problems are common following tracheostomy. These are usually due to the sensation of pressure in the upper oesophagus because of an inflated cuff and because the movement of the larynx during swallowing is reduced secondary to the tethering effect of the tube.

If at any stage doubts occur regarding the position of the tube or obstruction of the lumen, a flexible nasal endoscope can usually be passed through the tube to inspect the lumen of the tube and the trachea.

Complications

Complications can be:

- Immediate (haemorrhage; air embolism; local damage)
- Intermediate (extubation; obstruction; subcutaneous emphysema; infection; fistulae)
- Late (tracheo-cutaneous fistula; tracheal stenosis).

IMMEDIATE

Haemorrhage is the commonest fatal complication of tracheostomy,[25] as well as the commonest complication. Bleeding is usually due to damage to the thyroid veins or the thyroid isthmus. If there is significant bleeding at the end of the procedure the wound should be explored and any bleeding vessel ligated. Packing the tracheostomy wound to tamponade the bleeding is widely practised but should be seen as little more than a temporary procedure prior to re-exploration of the wound.

Air embolism, while life threatening, is fortunately rare following tracheostomy. If the large veins of the neck are opened during the procedure air may be sucked into the venous system and pass into the right atrium.

Damage to structures in the vicinity of the operative field is often the result of altered anatomy or inattention to good surgical technique. Inexperienced surgeons may inadvertently stray from the midline and so cause damage to the contents of the carotid sheath, oesophagus or recurrent laryngeal nerve. In emphysematous patients, the apex of the lung may extend into the lower neck and can be damaged because of lateral dissection. An inadequate incision, poor retraction or poor haemostasis can result in less than ideal exposure and consequent damage to the tracheal walls or cricoid cartilage. Damage to the cricoid is particularly serious and if recognized at the time of surgery, the tracheostomy should be re-sited lower in the trachea and the damage repaired.

Immediate complications are best prevented by good haemostasis during surgery and meticulous attention to surgical technique.

INTERMEDIATE

Accidental extubation is easily avoided provided that the tube is adequately secured at the time of the procedure, by suturing the flanges of the tube to the skin. If the tube is displaced and comes to lie in the pre-tracheal space, the complication may not become immediately apparent. The patient continues to breathe as the soft tissues gradually prolapse around the tracheal opening, which slowly begins to seal. Dyspnoea slowly increases and by the time the displacement is apparent the tube may be impossible to replace as the tracheotomy has virtually closed. An experienced nurse will pick up on the early warning signs. Any difficulty breathing through the tube must be fully investigated. The use of a flexible scope passed through the lumen of the tube may identify displacement or obstruction of the tube due to crusting, granulation tissue or poor placement of the tube tip with respect to the tracheal wall.

If the tracheostomy tube or the trachea are obstructed and the skin incision has been closed tightly, then air may be forced out into the soft tissues of the neck during expiration resulting in subcutaneous emphysema. Surgical emphysema, under these circumstances, can track up to the lower eyelids and down into the upper chest. In severe cases the swelling may cause displacement of the tube.

Tracheo-oesophageal fistulae may be the result of intra-operative damage to the posterior wall of the trachea or persistent rubbing of the tip of the tube on the posterior wall in the early post-operative period. The fistula usually presents when the patient starts to show signs of aspiration despite the cuff being inflated. Tracheo-arterial fistulae present most commonly in previously irradiated patients, particularly if a low tracheostomy has been carried out. There is rarely any premonitory sign and the usual presentation is with sudden massive haemorrhage. The tracheostomy tube must be changed immediately for a cuffed tube; the cuff should be inflated to prevent further aspiration of blood and compression applied to any bleeding vessel via the tracheostome. The wound should be explored immediately as there is a very high mortality associated with this complication. The commonest artery affected is the innominate although there are reports of trachea-carotid fistulae.[26]

LATE

Epithelialization of the tract is a normal event in the evolution of a tracheostomy. The longer the tracheostomy has been present the more established the process is and the more likely the tract is to persist following decannulation. The incidence can be reduced if great attention is paid to ensuring an airtight seal is maintained once the stoma has been occluded. If there is evidence of granulation tissue

in the fistula, simple cautery with silver nitrate may assist spontaneous closure. A small number of cases will require formal surgical closure. This involves excision of the tract all the way down to the anterior tracheal wall and closure in several layers.

Tracheal stenosis is almost always the result of damage to the cricoid or first tracheal ring at the time of surgery or damage to the trachea from the rubbing of a poorly positioned tube, resulting in mucosal inflammation.

Decannulation

If the patient is able to breathe around the tube when it is occluded then there is no need to downsize the tube, which is usually the case if the initial cuffed tube has been replaced with an uncuffed fenestrated tube. Decannulation should take place in an ordered sequence. The tube should be blocked during the day and unblocked at night for the first 24 hours. If the patient tolerates this then the tube can be occluded for a full 24-hour period and if this is tolerated then the tube can then be removed. If the patient is unable to tolerate this occlusion of the tube then it may be necessary to downsize the tube to give more room around it. Patients who have been dependent on the tracheostomy for a long time may require a more prolonged decannulation process as it may take some time for them to overcome their anxiety about being unable to breathe without the tube in place. Variability in practice regarding the exact timing of tracheostomy still occurs.[27]

Once the tube has been removed an airtight dressing must be applied to occlude the stoma. In most cases, several gauze squares covered with an occlusive dressing will be sufficient. The dressing should be changed whenever an air leak appears to improve the chance of full closure of the fistula.

The national tracheostomy safety project

The National Tracheostomy Safety Project aims to produce a national tracheostomy safety resource and, through its membership of the Global Tracheostomy Collaborative, is working to improve the care of tracheostomy patients in all countries. Its website (www.tracheostomy.org.uk) provides a variety of open access educational resources and protocols for the management of patients.

TRACHEOSTOMY-SPARING INTERVENTIONS

Advanced cancers of the upper aerodigestive tract may present with significant upper airway obstruction. Many of these patients are managed with an awake tracheostomy under local anaesthetic or, following successful intubation, have a tracheostomy to secure their airway prior to anaesthetic reversal.

In certain situations of locally advanced upper aerodigestive tract carcinoma, other interventions may be used to re-establish a satisfactory airway and avoid the need for a surgical tracheostomy. Debulking of the tumour can be achieved, for example, with the use of a carbon dioxide laser (**Figures 72.8** and **72.9**), a microdebrider or biopsy forceps. Tumour debulking is a relatively low risk procedure, without the risks and morbidity associated with tracheostomy. It is especially suited for supraglottic tumours, but less effective for subglottic neoplasms. At the same time as achieving an improved airway, the debulking allows for samples to be harvested for histologic analysis. The operating surgeon can also gain a better appreciation of the clinical extent of the tumour. The avoidance of tracheostomy placement has several advantages: the potential for 'seeding' of the carcinoma to the stoma site is abrogated; incision planning is less complex if a laryngectomy is required for definitive treatment; and hospital stay is reduced.

These interventions are highly complex undertakings and significant combined expertise on the part of the anaesthetic and surgical teams is required to ensure a good outcome.[28] Good communication between the teams, including a thorough pre-operative briefing of all staff involved of what is expected as well as alternative



Figure 72.8 Left-sided laryngeal carcinoma involving supraglottic and glottic regions.



Figure 72.9 Airway following laser debulking.

strategies in the event of problems encountered, forms part of the expertise needed.

The presence of a tracheostomy tube can make radiation planning difficult and, where feasible, debulking can be repeated to achieve a stable airway.[28] There is evidence of a significant delay in starting definitive treatment for patients who undergo tracheostomy when compared with those undergoing debulking procedures.[29]

EMERGENCY AIRWAY MANAGEMENT DURING A 'CAN'T INTUBATE, CAN'T OXYGENATE' (CICO)

There has been a debate in recent years as to the safest way to secure the airway in the event of an emergency event in which it is not possible to intubate or oxygenate a patient (can't intubate, can't oxygenate, or CICO). The traditional approach by ENT surgeons has been to perform an emergency or 'crash' tracheostomy. However, over the last 10–20 years there has been a decrease in the number of routine open tracheostomies carried out as more percutaneous tracheostomies are performed in the intensive care setting. The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) tracheostomy report, '*On the right trach?*' reviewed the care received by patients who underwent a tracheostomy.[30] This review reported that the majority of open tracheostomies are performed as part of another surgical procedure (major head and neck resection) or in patients who might be considered 'unfavourable' for a percutaneous procedure. The follow-on from this is that there are fewer opportunities for trainees to acquire skills to perform an open tracheostomy.

So, when called to an airway emergency, what is the most appropriate, safest and quickest technique to use to secure the airway? Ultimately the decision rests with the individual and must be based on their experience and ability as well as an assessment of the patient, the skills of other team members and the available equipment. However, a good argument can be made that the quickest and safest way to secure the airway is by the use of the 'Scalpel–Bougie' technique of cricothyroidotomy. This technique has been supported by the Difficult Airway Society in the UK for front of neck airway (FONA) in CICO events.[31] The technique is different from the standard 'needle' cricothyroidotomy, which has been shown to be ineffective in altering the outcome in CICO events.[32] A recent editorial with a multidisciplinary authorship has advocated that there should be an emphasis on Scalpel-Bougie cricothyroidotomy training for all medical professionals involved in the management of acute airway emergencies.[33]

KEY POINTS

- Assessment of the airway should be part of an overall systematic approach to managing the critically ill patient.
- The assessment should determine the level(s) of airway obstruction.
- Action should be decisive.
- The least invasive intervention that will bypass the level of the lowest obstruction should be used.
- Problems from comorbidities should be considered, particularly in cases of multiple trauma.
- Any intervention should be carried out by someone who is experienced in the use of that technique.
- The technique chosen to effect tracheostomy should minimize trauma whilst achieving the desired outcome of a secure airway.

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CHAPTER 73

PHYSIOLOGY OF SLEEP AND SLEEP DISORDERS

John O'Reilly

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: sleep disorders, classification of sleep disorders, sleep physiology, sleep deprivation, excessive daytime sleepiness, hypersomnia, insomnia, sleep-related breathing disorders, obstructive sleep apnoea, central sleep apnoea, sleep hypoventilation, obesity, hypoventilation, central disorders of hypersomnolence, narcolepsy, cataplexy, circadian rhythm sleep-wake disorders, parasomnias, sleep-walking, REM behaviour disorder, sleep-related movement disorders, restless legs syndrome, periodic limb movement and bruxism.

INTRODUCTION

Sleep is essential as a restorative process to maintain cognitive performance and work productivity as well as physical, psychological and emotional well-being. Although muscles may not need sleep, the brain needs sleep to function and control movements and thoughts.[1]

Normal sleep physiology

Sleep physiology may be assessed by polysomnography (PSG), which typically comprises sleep staging using electroencephalography (EEG) with multi-channel recording of video, snoring, nasal airflow, and thoracic and abdominal respiratory effort to produce an apnoea-hypopnoea index (AHI), as well as sensors to detect body position and leg movement. EEG and video are often omitted in assessment of subjects who are likely to have sleep-related breathing disorders, facilitating portable (ambulatory) or home monitoring as cardio-respiratory polygraphy (**Figure 73.1**).

During normal sleep, polysomnography (PSG) shows that subjects cycle through periods of light sleep (stages 1 and 2), deep sleep (N3 comprising former stages 3+4) in which the brain is resting and becomes refreshed, and rapid eye movement (REM) sleep in which the brain is active in consolidating thoughts, learning and memory (**Figure 73.2**).



Figure 73.1 Cardio-respiratory polygraphy study (portable monitoring).

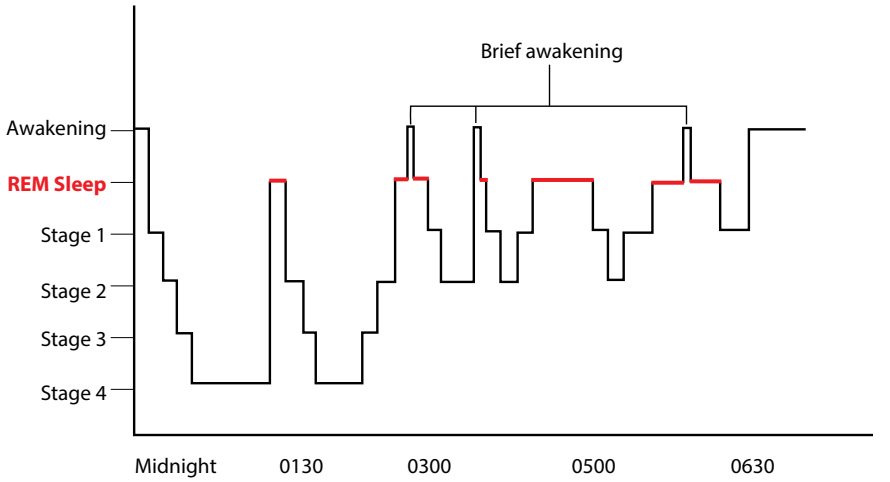


Figure 73.2 Sleep staging using polysomnography.

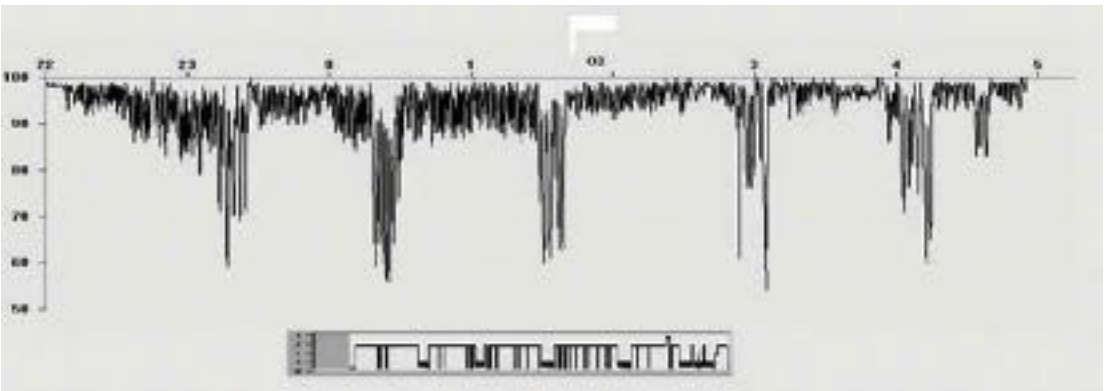


Figure 73.3 REM-related increase in frequency of nocturnal oxygen desaturation due to ventilatory failure in obstructive sleep apnoea.

As the night progresses, periods of deep sleep become shorter, while REM periods become longer. In REM sleep, pathognomonic rolling eye movements are noted, and there is generalized inhibition of skeletal muscles, including the intercostal, accessory and pharyngeal dilators, leaving largely the diaphragm to support ventilation. This is reflected in an increased respiratory rate and ventilatory failure is more likely, particularly in subjects with respiratory or neuromuscular disorders (**Figure 73.3**).

Sleep onset leads to hypoventilation with reduced metabolic rate. There is loss of voluntary and emotional control of breathing, loss of wakefulness drive and a decrease in reticular activating system (RAS) activity rate, leading to dependence on brainstem reflex activity. Reduced ventilation leads to a rise in partial pressure carbon dioxide ($PaCO_2$), and consequent fall in partial pressure oxygen (PaO_2). A small rise in $PaCO_2$ is necessary to exceed the apnoeic threshold and maintain ventilation. There is reduced medullary phasic electrical activity, and reduced chemo-sensitivity to partial pressures of arterial carbon dioxide ($PaCO_2$) and oxygen (PaO_2), together with increased airway resistance.[2, 3] The respiratory system is therefore less able to adapt to changes in sleep, including hypoxaemia.[4]

There is an endogenous circadian rhythm in pulmonary function, respiratory control and basal metabolism, which appears independent of daily changes in behaviour (including sleep) and environment.[5]

During the night there are diurnal falls in cortisol levels and body temperature, and increased cholinergic tone that may lead to increased airflow limitation in patients with chronic obstructive pulmonary disease (COPD).[6]

Sleep deprivation

Acute sleep deprivation leads to impaired cognitive, psychomotor and executive function, as well as increased cortisol, impaired glucose tolerance, androgen deficiency and increased appetite due to a reduced blood leptin/ghrelin ratio.[7–9]

Longer term sleep deprivation may lead to deranged metabolism with obesity, increased insulin resistance and risk of diabetes mellitus, hyperlipidaemia, cardiovascular disease, coronary events and increased all cause mortality.[10, 11]

Sleep deprivation has been shown to have an effect on pulmonary function with significant decline in minute ventilation and inspiratory muscle endurance after 24 hours. This is not clinically significant in healthy subjects, but can lead to a significant 5–6% fall in forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) in COPD.[12–14]

Sleep restriction and fragmentation may occur due to emotional stress, environmental factors such as shift

work, acute and chronic medical conditions including obesity, and a range of specific sleep disorders.[15–17]

Excessive daytime sleepiness

Excessive sleepiness is a subjective marker of many sleep disorders, although it can affect up to 12% of the normal population, and is more common in subjects with snoring, obesity, diabetes mellitus and renal failure.[18–20]

It is difficult to quantify consistently or objectively, but the Epworth Sleepiness scale (ESS) score is commonly used as a validated simple self-administered assessment tool (**Table 73.1**). A score of more than 10 is considered significant, but lower scores may not exclude sleepiness, possibly due to misinterpretation of the test.[21]

The multiple sleep latency test (MSLT) uses EEG to assess how quickly a subject falls asleep during 5 attempted naps over the course of a day. A shortened mean sleep latency of less than 8 minutes is considered consistent with pathological excessive sleepiness.[22] Sleep diaries (logs) may help to confirm adequate sleep opportunity.

The maintenance of wakefulness test (MWT) conversely assesses how long a subject can remain awake and may indicate reduced alertness if mean sleep latency is less than 20 minutes. Correlation between subjective and objective measurements may be poor.[23]

Psycho-motor vigilance can be measured using the Oxford Sleep Resistance (Osler) test, and in driving simulators.[24, 25]

CLASSIFICATION OF SLEEP DISORDERS

The International Classification of Sleep Disorders describes a range of respiratory and non-respiratory conditions that may be associated with insomnia or excessive daytime sleepiness while awake, or behavioural abnormalities in sleep (**Box 73.1**).

Insomnia

The criteria for insomnia include a report of subjective difficulty with sleep initiation or maintenance, including waking up earlier than desired, resistance to going to bed on appropriate schedule or difficulty sleeping without parent or caregiver intervention. This must be associated with adequate opportunity and circumstances to sleep, and also a requirement for a report of daytime consequences.[22] These include fatigue or malaise, impairment of attention, concentration or memory, impaired social, family, occupational or academic performance, mood disturbance or irritability, daytime sleepiness, behavioural problems (e.g. hyperactivity, impulsivity, aggression), reduced motivation, energy or initiative, proneness for errors or accidents, or concerns about, or dissatisfaction with, sleep.

Many people experience occasional insomnia (50%) with 6–10% describing chronic insomnia.[26] Insomnia is common in a range of medical and psychiatric disorders. Short-term insomnia is often associated with an identifiable cause or trigger, commonly particular daytime stressors.

BOX 73.1 International Classification of Sleep Disorders (ICSD-3)

- Insomnia
- Sleep-related breathing disorders
- Central disorders of hypersomnolence
- Circadian rhythm sleep-wake disorders
- Parasomnias
- Sleep related movement disorders
- Other sleep disorders

TABLE 73.1 Epworth Sleepiness Scale score

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you.
Use the following scale to choose the most appropriate number for each situation:
0 = no chance of dozing
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Situation	Chance of dozing
Sitting and reading	
Watching TV	
Sitting inactive in a public place (e.g a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in traffic	
TOTAL	

A score of more than 10 indicates significant sleepiness.

Chronic insomnia disorder is defined by symptoms at least three times per week for a duration of 3 months, and is usually only made when the insomnia is especially prominent or unexpectedly prolonged, and under assessment or treatment. It combines a number of categories previously defined as psychophysiological insomnia, idiopathic insomnia, sleep-state misperception and inadequate sleep hygiene.[22]

The diagnosis of insomnia relies on a medical, sleep and psychiatric history and is aided by keeping a sleep log. Predisposing, potentiating and precipitating factors may be identified.

Management of insomnia involves dealing with identified underlying causes, and consideration of behavioural and drug therapies. Sleep hygiene advice includes restriction of caffeine and alcohol, especially during the evening. Cognitive behavioural therapy for insomnia (CBTI) also includes relaxation, stimulus control and sleep restriction techniques.[26, 27]

CBTI is preferred but can be combined with pharmacological treatments including benzodiazepines, non-benzodiazepines and low-dose antidepressants. Hypnotics should be used for a maximum of 2–3 per week to avoid dependence.[28, 29]

SLEEP-RELATED BREATHING DISORDERS

Sleep breathing disorders include a spectrum of problems with similar pathophysiology including obstructive sleep apnoea hypopnoea (OSA), and sleep-related hypoventilation, as well as the less common condition of central sleep apnoea (CSA) (**Box 73.2**). Children and adults with tonsillar hypertrophy, craniofacial syndromes and neuromuscular disorders have an increased risk for sleep breathing disorders.[30]

Although patients may be asymptomatic, ventilatory failure during sleep and consequent sleep fragmentation usually lead to presentation with one or more of a range of associated problems including snoring, subjective sleep disturbance, excessive daytime sleepiness, witnessed pauses in breathing, right heart failure (cor pulmonale) and cardio-metabolic comorbidities. Children may present with insomnia, enuresis, behavioural problems, hyperactivity, and reduced attention span, memory and learning ability. Growth may be impaired due to lack of deep sleep necessary to produce growth hormone.

BOX 73.2 Sleep breathing disorders

Obstructive sleep apnoea (OSA)
Central sleep apnoea (CSA)
- central sleep apnoea with Cheyne-Stokes breathing
- central sleep apnoea due to a medical disorder without Cheyne-Stokes breathing
- central sleep apnoea due to high-altitude periodic breathing
- central sleep apnoea due to a medication or substance
- primary central sleep apnoea
- treatment-emergent central sleep apnoea

Sleep related hypoventilation disorders
- obesity hypoventilation syndrome (OHS)
- sleep-related hypoventilation due to a medical disorder
- sleep-related hypoventilation due to a medical disorder

Sleep-related hypoxaemia disorder

Snoring is generated by the vibration of anatomical structures of the nasopharynx during sleep. Prevalence of habitual snoring ranges from 24% to 50% in men and from 14% to 30% in women and increases with age, obesity, alcohol ingestion and nasal obstruction. Isolated snoring, although asymptomatic, results in social disability and relationship disharmony. General population surveys have found a strong correlation between snoring and daytime sleepiness.[31–33] Snoring with sleepiness as features of obstructive sleep apnoea have been associated with hypertension, ischaemic heart disease, diabetes mellitus and cerebrovascular accident as well as increased morbidity and mortality from road traffic and work related accidents.

Obstructive sleep apnoea (OSA)

OSA is a common condition comprising intermittent complete collapse of the pharyngeal airway, followed by brief arousals or wakenings which then enable return of breathing (**Figure 73.4**). The term obstructive sleep apnoea-hypopnoea (OSAH) is used to include episodes of breathing with reduced amplitude (**Table 73.1**). The condition may be asymptomatic but often presents with witnessed snoring, pauses in breathing or choking during sleep, or with symptoms due to sleep fragmentation including excessive sleepiness, impaired alertness, loss of concentration or memory, comprising the OSAH syndrome (OSAHS).[34–36]

Upper airway resistance syndrome (UARS) is classified as a variant of OSA, characterized by increased airway resistance to breathing during sleep, without cessation of breathing. The primary symptoms are similar to those in OSAS although snoring may not be noted. Sleepiness and excessive fatigue develop due to arousals in sleep with changes in pulse transit time associated with respiratory flow limitation, and increased negative intra-thoracic pressure.[37]

The pathophysiology of OSA includes intermittent hypoxia and possibly sympathetic activation which drive insulin resistance and disordered lipid metabolism.as well as a systemic inflammatory cascade with free-radical production, inflammatory cytokine release and oxidative stress.[38, 39]

Interaction of haemodynamic and inflammatory changes promote vascular endothelial growth factor 3, endothelial dysfunction and vascular remodelling, which may combine to promote the development of atherosclerosis and cardiovascular disease, including heart failure and arrhythmias.[38–41] Organ, tissue or functional impairment is related to the severity of nocturnal hypoxia.[38, 42]

OSA may play a causative role in development of hypertension, insulin resistance and hyperlipidaemia in the cardio-metabolic syndrome, as well as in heart failure, pulmonary hypertension, coronary artery disease, arrhythmias and cerebro-vascular accidents.[36, 42–50]

Patients with heart failure may have less subjective daytime sleepiness despite significantly reduced sleep time such that the absence of subjective sleepiness is not a reliable means of ruling out OSA (**Table 73.2**).[51]

OSA is a risk factor for stroke independently of sex, body mass index (BMI), diabetes, and hypertension, at least in men.[52–54] Hypothyroidism, acromegaly and chronic renal failure may also be associated with OSA.[55–58]

TABLE 73.2 Physiological definitions in obstructive sleep apnoea

Obstructive sleep apnoea/hypopnoea (OSAH)	Obstructive sleep apnoea/hypopnoea syndrome (OSAHS)
Apnoea: • Absence of breathing for at least 10 seconds **Hypopnoea:** • 30% reduction in breathing amplitude with at least 3% oxygen desaturation; or • Respiratory-related arousal (RERA) via EEG or nasal flow limitation pattern **Apnoea-hypopnoea index (AHI)** is the hourly rate of apnoeas plus hypopnoeas: • AHI <5 – normal • AHI 5–15 – mild OSAH • AHI 16–30 – moderate OSAH • AHI >30 – severe OSAH	**Comprises:** >5 obstructed breaths/hour AND excessive daytime sleepiness not better explained by other factors OR 2 or more of the following: • choking or gasping in sleep • recurrent awakenings • unrefreshed sleep • daytime fatigue • impaired concentration

A number of studies have reported impaired glucose metabolism in OSA patients, independent of obesity, although possibly related to visceral obesity, and with prevalence 9 times more in subjects with OSA than controls matched for BMI.[59–71] Insulin resistance may develop due to the effect of intermittent hypoxia and increased sympathetic activity.[59, 62, 70] Cross-sectional studies show a strong association of diabetes mellitus with OSA, but in longitudinal studies, incidence of diabetes was not related to the initial severity of OSA.[70, 72] These cardiovascular and metabolic associations may, in addition to road traffic and work related accidents, contribute to the increased morbidity and mortality associated with OSA, and the reduction in mortality seen in uncontrolled treatment studies using continuous positive airway pressure (CPAP).

Central sleep apnoea (CSA)

CSA comprises recurrent episodes of apnoea during sleep despite a patent airway (**Figure 73.4**). CSA may be associated with periodic breathing in left ventricular cardiac failure with Cheyne-Stokes respiration (CSR) in which there is temporary loss of ventilatory effort or unstable ventilatory control (CSR-CSA). This may have an adverse effect on cardiac prognosis and mortality as it is associated with sympathetic activation, ventricular ectopy and atrial fibrillation. Central sleep apnoea, right ventricular dysfunction, and low diastolic BP are predictors of mortality in systolic heart failure.[47, 73] CSA may develop in subjects at high altitude and those with neurological disorders, autonomic dysfunction or narcotic opiate drug toxicity even at therapeutic dosage.[74–76] CSA may also occur with OSA in patients with nasal obstruction or after treatment with continuous positive airways pressure (CPAP) which reduces $paCO_2$.[79] Management involves treatment of the underlying condition, and continuous positive airway pressure and oxygen may be used.[77–79]

Sleep-related hypoventilation disorders

Obesity hypoventilation syndrome (OHS) is the combination of obesity (BMI 30 kg/m^2), with hypoxia during sleep, and hypercapnia during the day, due to hypoventilation. About one third of all people with morbid obesity (a BMI exceeding 40 kg/m^2) have elevated carbon dioxide levels in the blood.[80, 81] Typical clinical features include obesity, excessive daytime sleepiness, a plethoric complexion, cyanosis, and evidence of right heart failure including peripheral oedema. Surprisingly, patients may not complain of dyspnoea, despite obvious hypoxemia. Almost all subjects with OHS will also have OSAS as an overlap syndrome.[81] Alternative explanations for hypoventilation must be excluded including use of narcotics, severe obstructive or interstitial lung disease, kyphoscoliosis, severe hypothyroidism, neuromuscular disease and congenital central hypoventilation syndrome.[82]

Overlap syndromes

OSA commonly coincides with Chronic Obstructive Pulmonary Disease (COPD), and OHS, and those with COPD may have more severe nocturnal oxygen desaturation, and considerably greater risk of death.[83, 84] Features of cor pulmonale and pulmonary hypertension may be prominent. OSA may also coincide with narcolepsy, and may be a trigger for non-respiratory sleep disorders including sleep-walking and parasomnias.[83–87]

Assessment of sleep breathing disorders

A structured assessment and screening of patients with associated comorbidities will identify people with high probability for sleep breathing disorders. Reporting of apnoea by the bed partner has been more predictive of sleep apnoea than snoring alone.[88] Validated screening questionnaires for OSAS include the The Epworth Sleepiness scale score (**Table 73.1**) and the STOP-BANG questionnaire (**Box 73.3**) which has proved useful in preoperative anaesthetic risk assessment.[21, 89, 90]

Examination may reveal obesity (in 70% of patients with obstructive sleep apnoea), with BMI >30, often with increased neck circumference (often > 40 cm) and waist circumference (men > 94 cm; women > 80 cm).[91, 92] Some patients may have nasal airway obstruction (deviated nasal septum, rhinitis or polyps), or enlarged soft palate,

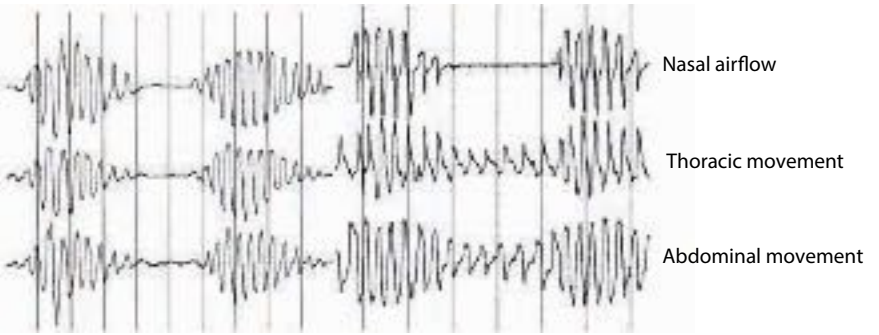


Figure 73.4 (a) Central apnoea with absence of airflow, thoracic and abdominal movement. **(b)** Obstructive apnoea with absence of airflow, but presence of thoracic and abdominal respiratory movement.

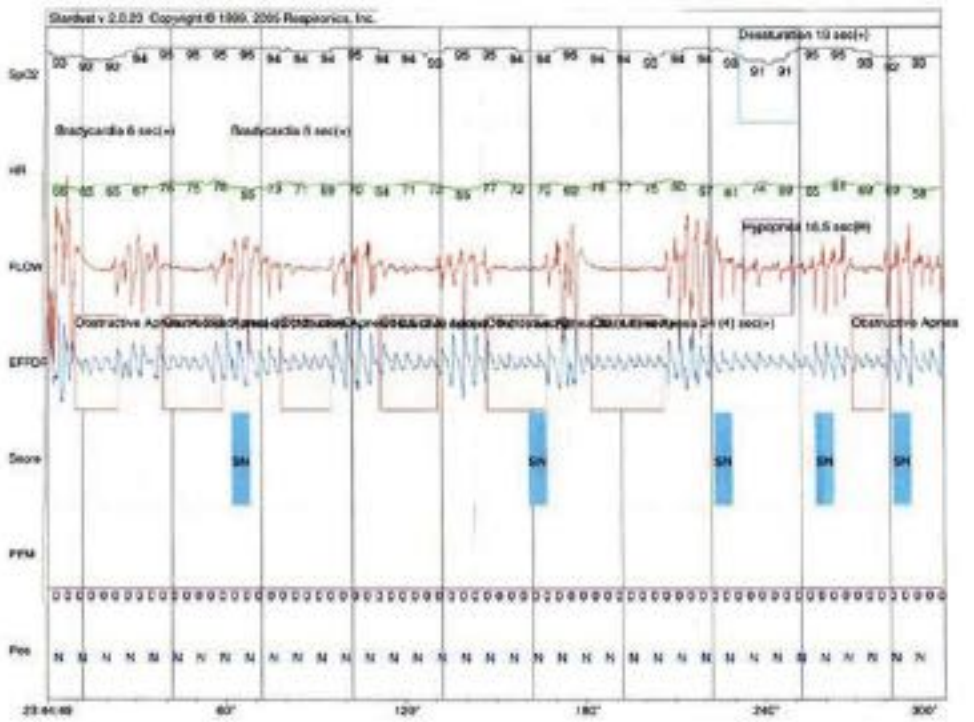


Figure 73.5. Cardio-respiratory polygraphy report. Episodic cessation of nasal airflow (FLOW) is associated with continued thoracic respiration (EFFORT) and is followed by transient fall in oxygen saturation (SpO_2). Heart rate (HR) slows following apnoeas and increases after return of respiration.

tonsils or uvula. Signs of cor pulmonale may occasionally be present including ankle swelling.

Physiological investigation of sleep-related breathing disorders

Cardio-respiratory polygraphy (multi-channel portable or ambulatory monitoring) allows diagnosis of sleep apnoea, classification, and assessment of severity in most patients with typical OSA in a home or inpatient setting.[93, 94] OSA is detected as absence of nasal airflow with persistence of chest and abdominal respiratory effort. using nasal airflow, chest and abdominal sensors, to measure respiration, producing an apnoea-hypopnoea index (AHI) (**Figure 73.5**). Oximetry in OSA typically shows a normal baseline oxygen saturation with intermittent dips and 4% oxygen desaturation index (ODI) of more than 10 per hour, together with heart rate variability (**Figure 73.6**). Overnight oximetry alone is relatively specific, but insensitive for OSA such that absence or relative paucity of oximetry dips does not exclude sleep apnoea.[95] Periods of low baseline oxygen saturation suggest other causes of respiratory failure including sleep hypoventilation syndromes and COPD which may be concurrent with OSA as overlap syndromes (**Figure 73.7**). Oxygen desaturation may occur due to other respiratory and cardiac disorders and expert interpretation is essential. In UARS apnoeas and hypopnoeas are absent or low in number, but a diagnosis may be made using a nasal cannula and pressure transducer to measure inspiratory airflow limitation, and detect a pattern known to be associated with respiratory related arousals (RERA) on EEG.[22]

Full PSG may be required in complex sleep disorders including cases of possible OSA which may overlap with comorbidities including cardiac failure, COPD, upper airway resistance, obesity hypoventilation syndrome or non-respiratory sleep disorders including periodic limb movement and narcolepsy.[96] Full PSG adds an electroencephalogram (EEG) for sleep staging and video recording and may help to differentiate OSA from nocturnal epilepsy, or demonstrate OSA as a trigger for sleepwalking or other sleep behavioural disorders (parasomnias). In UARS, multiple RERAs may be seen on EEG in association with nasal flow limitations, and if an oesophageal probe is used, progressive elevation of esophageal pressure fluctuations (Pes) terminating in arousals.[37]

Management of sleep breathing disorders

General measures for treatment of sleep breathing disorders include behavioural modification and lifestyle advice comprising weight control, elevation of the bed head, and avoidance of supine posture, alcohol, tobacco, sedatives and narcotics.[96, 97] Significant weight loss has been associated with a 'cure' rate of 10–20% in OSAHS.[98–101] Treatment of nasal congestion using nasal steroids may be helpful, especially if there is nasal obstruction or upper airway resistance due to rhinitis. Driving should be avoided if excessively sleepy and subjects with OSAS must inform the relevant driving licencing authority of the diagnosis. Driving may be allowed if symptoms are controlled on treatment, with confirmation by medical opinion.

A range of interventions may be employed in the treatment of sleep breathing disorders, including weight management, nasal continuous positive airway pressure (CPAP), oral appliance therapy and surgical intervention in OSAHS, as well as non-invasive bi-level ventilation in sleep hypoventilation syndromes, and these are dealt with in detail in other chapters.[96–112]

BOX 73.3 Stop-BANG questionnaire as a screening tool for OSA

S 'Do you snore loudly (louder than talking or heard through closed doors)?'
T 'Do you often feel tired, fatigued, or sleepy during daytime?'
O 'Has anyone observed you stop breathing during your sleep?'
P 'Do you have or are you being treated for high blood pressure?'
B Does the patient have a BMI of more than 35?
A Is the patient older than 50?
N Is the patient's neck circumference greater than 40 cm?
G Is the patient male?

Scoring: ≥3 high risk of OSA
<3 low risk of OSA

CENTRAL DISORDERS OF HYPERSOMNOLENCE

Narcolepsy and cataplexy

Narcolepsy is a condition in which subjects develop severe, often unavoidable chronic sleepiness, with fragmented sleep and frequent awakenings at night, often beginning in early adolescence or adult life. Its prevalence is 1 in 2500, but most are undiagnosed. Consequent problems include avoidance of social or emotional situations, exam failures, few work opportunities, marital difficulties, low self-esteem and depression.

Narcolepsy may be associated with other sleep disorders including restless legs syndrome (RLS) and periodic limb movement syndrome (PLMS), parasomnias, snoring, OSA and disorders of appetite and mood.[22] Sleepiness is usually severe, with ESS score often above 15. Subjects often develop hypnagogic (sleep onset) or hypnopompic (sleep offset) hallucinations and sleep onset/offset paralysis due to REM intrusion into wakefulness while falling asleep or

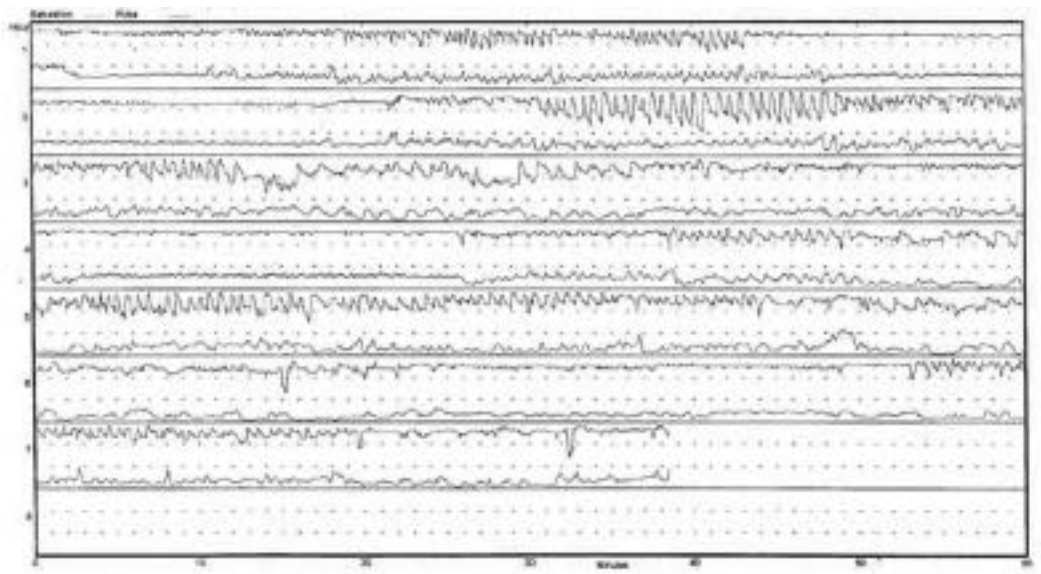


Figure 73.6 Overnight oximetry in OSA. Each horizontal band shows 1 hour of recording of oxygen saturation (above) and heart rate (below). There are frequent falls in oxygen saturation (>4%) with return to normal baseline, and associated heart rate variability.

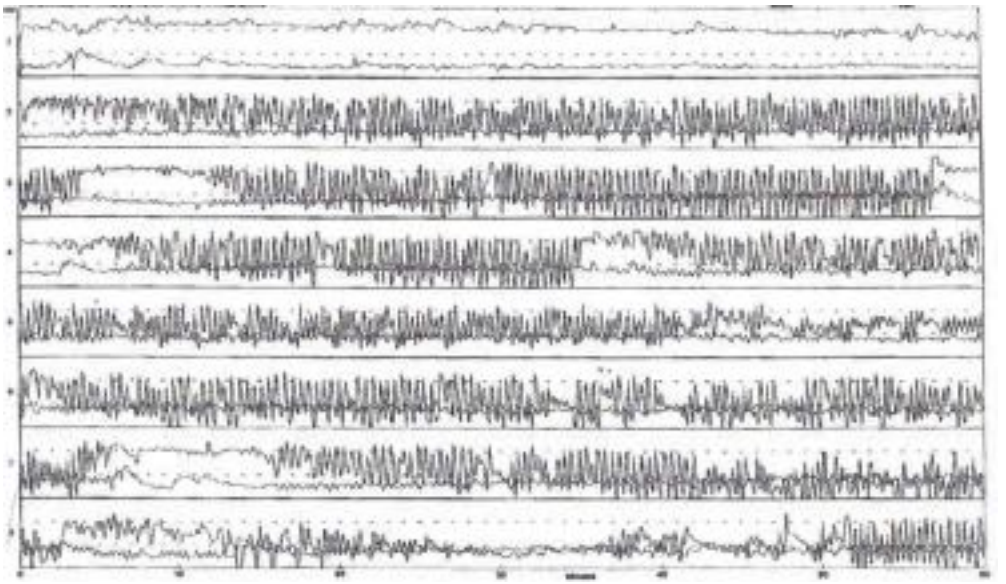


Figure 73.7 Overnight oximetry in obstructive sleep apnoea with obesity hypoventilation (overlap syndrome). Each horizontal band shows 1 hour of recording of oxygen saturation (above) and heart rate (below). There are frequent falls in oxygen saturation (>4%) but periods of low baseline oxygen saturation.

on waking. These are, however, non-specific features of sleep deprivation and they may occur in other conditions of significant sleep loss including shift work or sleep apnoea.

Cataplexy develops in 60% of subjects. During wakefulness, REM intrusions cause sudden episodes of bilateral muscle weakness leading to partial or complete collapse and often triggered by strong emotions such as laughter, anger or excitement. Episodes last 1–2 minutes and are not associated with impairment of consciousness at onset.[22, 113]

Narcolepsy is usually sporadic, and possibly auto-immune or related to brain injury, but genetic factors play an important role with a 40-fold risk in first-degree relatives. Most narcoleptics (50–90%) have HLA DR2 or DQB1*0602 antibody subtypes. The pathophysiology of classical narcolepsy involves a deficiency of the hypothalamic excitatory neuropeptide hypocretin (orexin). This is required to stabilize the hypothalamic sleep/wake switch between sleep promotion (ventro-lateral pre-optic nucleus) and wake promotion (tubero-mamillary nucleus). CSF examination reveals absence of hypocretin (orexin) in 90% of subjects.[114]

PSG may show a short REM latency 5–10 mins (in 50%). Frequent intrusions of REM cause fragmentation of deeper sleep, although total sleep time and time in REM are normal. A daytime MSLT may show sleep-onset REM (SOREM) episodes.[115]

A diagnosis of classical narcolepsy (Type 1) requires either cerebrospinal fluid hypocretin-1 deficiency (<110 pg/mL or less than one-third of the normative values with the same standardized assay) or a mean latency of <8 min with evidence of two SOREMPs on MSLT, (or one SOREMP on PSG and one or more on MSLT) and clear cataplexy. Narcolepsy Type 2 maintains the same MSLT requirements but cataplexy must be absent and cerebrospinal fluid hypocretin-1 levels, if measured, must not meet the narcolepsy Type 1 criterion.[22]

The differential diagnosis of narcolepsy includes OSA, depression, REM deprivation and drug toxicity, while the differential diagnosis of cataplexy includes epilepsy (especially gelastic and atonic), vertebro-basilar insufficiency, cardiac dysrhythmias, drop attacks, myasthenia gravis, periodic paralysis, faints, gelastic syncope and hysteria.

Management of narcolepsy includes planned napping, sleep hygiene and psychosocial support. Sleepiness may respond to stimulants including modafinil, dexamphetamine or methylphenidate. Cataplexy may respond to REM sleep-suppressing medications including tricyclic and SSRI antidepressants. Sodium oxybate or pitolisant may control cataplexy as well as sleep fragmentation and excessive daytime sleepiness.

Hypersomnia may also be idiopathic or due to medical or psychiatric disorders including Kleine-Levin Syndrome. Behaviourally induced insufficient sleep can be excluded by actigraphy or sleep logs to record wake and sleep using body movements over periods of days.

CIRCADIAN RHYTHM SLEEP-WAKE DISORDERS

Circadian rhythm problems include jetlag, shift work sleep disorder and advanced or delayed sleep phase syndromes. Delayed sleep phase is not uncommon in younger subjects who may be genetically predisposed to be 'night-owls', with difficulty in rising and excessive morning sleepiness. Symptoms may be incorrectly attributed to insomnia or depression, although these may be true comorbidities. Assessments are made using sleep diaries and actigraphy to record wake and sleep using body movements over periods of days. Treatment involves advancing sleep onset by use of evening melatonin and morning bright light therapy.[116]

PARASOMNIAS

The term parasomnia encompasses sleep-related behaviours, emotions, perceptions, dreaming and autonomic

nervous system events during entry into sleep, within sleep or during arousals from sleep.[22] Parasomnias may be occur in non-REM and REM sleep.

Non-REM parasomnias

Non-REM parasomnias include sleepwalking, sleep talking, confusional arousals, sleep terrors, sleep-related nocturnal eating disorder and catathrenia (groaning). Instinctual behaviours, including violence and sexual activity, may be released inappropriately.[117] Arousals in sleep leave the individual in a state of incomplete awakening, with inappropriate responsiveness. Higher cognitive functions and social inhibitions may be absent or impaired and primitive behaviours may appear unexpectedly with partial or complete amnesia.[22, 117]

Predisposition to non-REM parasomnias may be based on genetic susceptibility with a familial pattern. A priming factor may trigger an episode, for example sleep deprivation, situational stress, medications, fever, alcohol, sleep-disordered breathing (e.g. OSA), PLMS, noise and touch.[118]

Assessment requires a full medical and sleep history, neuropsychiatric and psychometric examination and EEG. PSG may reveal precipitating and modulating factors including OSA or PLMS.

Treatment comprises reassurance and explanation of the mechanisms and potentiating factors, and treatment of confirmed priming or trigger factors. Counselling and psychological intervention with cognitive behavioural therapy may have a role. Drug therapy is usually avoided in the absence of behaviour that causes violence to the subject or others. In that event, clonazepam or other sedatives are usually advised until the parasomnia resolves in the hope that a normal sleep pattern will return without prolonged drug therapy. Subjects with non-REM parasomnia (e.g. sleepwalking) may expect occasional relapse if under particular emotional stress, physically ill with fever or other physical stress, or under the influence of alcohol, drugs or other toxins.

REM-related parasomnias

REM-related parasomnias include REM sleep behaviour disorder (RBD), nightmares and recurrent isolated sleep paralysis. RBD involves vocalization or dream enactment during REM sleep, without the normal loss of muscle tone. The dream-enacting behaviours are usually non-directed and may include punching, kicking, leaping or jumping from bed while asleep. Subjects may recall the dream that corresponds to the physical activity, sometimes vividly or as nightmares. Abnormal sleep movements may lead to injuries include bruising, lacerations, fractures and subdural haematomas.[119] Subjects are often middle-aged or older at the time of presentation and RBD may be a precursor of degenerative brain disease or Parkinson's disease.

Acute RBD may follow withdrawal of alcohol or drugs including pentazocine, nitrazepam, tricyclic antidepressants or caffeine. Chronic RBD may follow toxicity from tricyclic or SSRI antidepressants, seligiline or anticolinergics. Chronic RBD may also be associated with neurodegenerative conditions, synucleinopathies (Parkinson's disease, multiple system atrophy and dementia with Lewy bodies) and other neurological disorders including multiple sclerosis, Guillaine-Barre syndrome, Shy-Drager syndrome, Arnold-Chiari malformation, Alzheimer's dementia, ischaemic strokes and narcolepsy.[120]

RBD may reflect dysfunction in the brainstem circuitry and the dorsolateral pontine tegmentum mechanisms responsible for the normal suppression of muscle tone and paralysis in REM sleep. PSG may show persistence of EMG tone in REM sleep, absence of seizure activity, and gross complex body movements that correspond to dream mentation.[121]

Management of REM-related parasomnias comprises removal of potential drug or other triggers. Drug therapies including clonazepam or other benzodiazepines, and melatonin may be helpful, avoiding the potential risks of opiate sedation.[122, 123]

Epilepsy may co-exist with, or mimic, sleep disorders. Sleep deprivation can increase the risk of seizure activity and seizures can affect the sleep-wake cycle. Nocturnal frontal lobe epilepsy may occur only during sleep, and can present with bizarre movements such that differentiation from parasomnia may be difficult, and expert assessment is required.[124]

SLEEP-RELATED MOVEMENT DISORDERS

Sleep-related movement disorders include restless legs syndrome (RLS), periodic limb movement disorder (PLMD) and sleep related bruxism (teeth grinding).

RLS is a clinical diagnosis, characterized by symptoms including unpleasant, creeping or crawling sensations deep within the lower legs, but sometimes in the upper limbs. It occurs only after rest, and is diurnal, becoming most severe in the late evening. There is an almost irresistible urge to move the legs, with relief on movement such as walking.[125]

The prevalence of RLS is 5–10% and it is slightly more common in women. It occurs at any age, but commonest onset is in those aged in the 5th and 6th decades. 60–80% of cases are familial with autosomal dominance and variable penetrance.

More than 80% of RLS patients have PLM in sleep (PLMS), although not all PLMS patients have RLS. PLMS comprises involuntary rhythmic muscular jerks, with extension of the great toe and dorsiflexion of ankles or other joints. PSG demonstrates a series of 4 of more consecutive movements lasting 0.5–20 seconds with an interval of 4–90 seconds. PLMS at a rate of more than 5 per hour, associated with arousals, can present as insomnia, excessive sleepiness or movements that wake the patient or bed-partner.[126, 127]

PLMD may be diagnosed when, in the absence of RLS, the frequency of PLMs is >15 per hour accompanied by clinical sleep disturbance or other functional impairment.

Predisposing factors for RLS/PLMS include some genetic variants, positive family history and female sex. Precipitating factors include iron deficiency, often related to pregnancy, menorrhagia, chronic renal failure or rheumatoid arthritis. RLS/PLMS may be precipitated or worsened by prolonged immobility, caffeine, nicotine,

and alcohol, and also by anti-depressants and dopamine antagonists including anti-psychotic and anti-emetics.

PSG can reveal periodic limb movement and associated arousals. Physiological changes include microarousals with fragmentation of normal sleep architecture, reduced time asleep, and frequent wakening.

The pathology in PLMS may involve defective dopaminergic neurotransmission and abnormal iron uptake and storage in the substantia nigra where it is a dopamine substrate.[128]

Management is by avoidance of caffeine, tobacco, and alcohol stimulants, as well as regular daily exercise, good sleep hygiene and avoidance of medicines that trigger symptoms. Prolonged iron therapy is indicated if serum ferritin is low or low normal (< 50 ng/ml) even if haemoglobin is normal. Treatment options include gabapentin, pregabalin, or dopaminergic agonists (rotigotine, ropinirole, pramipexole, L-dopa). Benzodiazepines, opiates and anticonvulsants can also be effective.

SUMMARY

Sleep disorders are common causes of morbidity and mortality, affecting the population beyond those with the condition. The presentation of sleep disorders is myriad due to complex pathophysiological mechanisms, such that important treatable conditions are often unrecognized. Greater awareness and screening of those at risk, including those with associated comorbidities, and those undergoing anaesthetic assessment and surgery, will lead to improved diagnosis and management outcomes.

KEY POINTS

- Excessive daytime sleepiness that is severe or unavoidable is suggestive of narcolepsy (sleep attacks), especially if associated with cataplexy.
- Excessive sleepiness may be due to multiple sleep disorders (e.g. narcolepsy and sleep apnoea, both often associated with excessive weight).
- Sleep Maintenance Insomnia associated with excessive daytime sleepiness suggests an underlying primary sleep disorder as a cause of arousals (e.g. sleep apnoea or periodic limb movement).
- Sleep initiation insomnia without excessive daytime sleepiness suggests adequate sleep but a possible psychological cause or misperception of actual sleep.
- RLS is a clinical diagnosis based on symptoms, whereas diagnosis of periodic limb movement requires PSG.
- Sleepwalking (non-REM parasomnia) is common, and often associated with a family or previous childhood history and complex stereotypical movement (e.g. talking).
- Parasomnias need careful differentiation from seizure disorders and degenerative brain disease, especially if movements are bizarre.
- Consider obstructive sleep apnoea in subjects with snoring, witnessed apnoeas, nocturnal choking or snorting, and excessive daytime sleepiness.
- Sleep maintenance insomnia with wakings and arousals associated with excessive daytime sleepiness suggests a possible underlying sleep disorder, e.g. sleep apnoea or periodic limb movement.
- Consider nocturnal hypoventilation in subjects with morning headache, otherwise unexplained ankle swelling (reflecting cor pulmonale and pulmonary hypertension).
- Screen for obstructive sleep apnoea prior to anaesthesia and surgery in subjects at high risk including those with retrognathia, craniofacial abnormalities, obesity, hypertension, diabetes mellitus Type 2, cardiovascular disease and cerebrovascular disease (e.g. stroke).

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CHAPTER 74

OBSTRUCTIVE SLEEP APNOEA: MEDICAL MANAGEMENT

Dev Banerjee

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: obstructive sleep apn(o)ea, excessive daytime sleepiness, continuous positive airway pressure, polysomnography and road traffic accidents.

INTRODUCTION

Obstructive sleep apnoea (OSA) can be regarded as a condition characterized by repetitive upper airway obstruction leading to sleep fragmentation, cardiovascular stimulation and oxygen desaturation during sleep. These together lead to symptoms such as snoring, unrefreshing sleep, excessive daytime sleepiness (EDS) and the increased risk of cardiovascular disease, hypertension, insulin resistance and road traffic accidents. Any individual with time may oscillate within a spectrum of sleep disordered breathing, from intermittent simple snoring, to chronic heavy snoring, to upper airway resistance syndrome (UARS), to mild OSA, to moderate OSA, to severe OSA or to obesity hypoventilation syndrome (OHS). OSA is characterized by complete breath-holds (apnoeas) and partial breath-holds (hypopnoeas) – scientific physiological descriptions are presented in Chapter 73, Physiology of sleep and sleep disorders. With the present obesity epidemic, ear, nose and throat (ENT), hypertension, obesity, diabetes and sleep specialists are witnessing a large increase in the prevalence of OSA in their practice. This chapter describes the medical management of OSA, especially associated comorbidities, diagnosis and continuous positive airway pressure (CPAP), all relevant to the work environment of ENT specialists. Mandibular devices are not discussed in this chapter and are described in Chapter 75, The surgical management of snoring.

EPIDEMIOLOGY, RISK FACTORS AND ASSOCIATED MEDICAL CONDITIONS

Earlier studies of the prevalence of OSA in society (Wisconsin Sleep Cohort Study) estimated that 4% of men and 2% of women had OSA with sleepiness,[1] also known as obstructive sleep apnoea hypopnoea syndrome (OSAHS). However, since then, the prevalence of obesity has been increasing in all age groups. In the UK, it is estimated that 26% of adults are obese (body mass index (BMI) $\geq 30\,kg/m^2$).[2] Further analysis of the epidemiology of OSA has suggested the prevalence of OSAHS is around 5% in a given population,[3] and it is likely this will increase with time. The exact incidence of OSA without EDS is unclear, as this population is less likely to seek medical input in the primary care setting. The prevalence differences between men and women are intriguing and the exact reason why OSA is more common and more severe in men is not fully understood. Men generally have a higher prevalence of OSA than women but the effects of menopause, pregnancy and the presence of polycystic ovarian syndrome have been shown to increase the risk of OSA in women.[4] Various mechanisms may exist, including body fat distribution, cranio-facial differences, and the role of female hormones, over and beyond simply BMI.[5] There is increasing evidence that ethnic differences do exist and people of oriental Chinese origin have a greater risk of

developing OSA at a lower level of obesity compared to European Caucasians. Cranio-facial differences may explain this phenomenon.[6] There is little information, however, on the prevalence of sleep disordered breathing in the South Asian population in the UK compared to the indigenous population in South Asia.

Obesity is recognized as an important risk factor for OSA. The prevalence of OSA rises with obesity[7] and it is estimated that up to 75% of those with a BMI above 40 kg/m^2 have OSA.[8] The exact relationship between obesity and OSA is not well understood, however, and is probably multifactorial. Factors including BMI, neck soft tissue mass, parapharyngeal and lingual adipose deposition, and body fat distribution all play a role. Any weight gain is not necessarily wholly adipose and an increase in soft tissue mass around the airway may be more crucial. Other factors such as pharyngeal muscle tone and the biophysical compliance relationship between airway patency and critical closing pressure remain unresolved.

OSA is associated with cardiovascular disease[9–11] and clinicians treating and dealing with patients with OSA are increasingly involved in modifying cardiovascular risk in their practice. OSA is associated with an increased risk of hypertension, as shown in population studies. There is growing evidence that treating OSA will decrease blood pressure, and even modest falls in blood pressure may translate into significant modification of cardiovascular risk. Associated comorbidities such as obesity, diabetes and smoking history may cloud any direct causal relationship between OSA and cardiovascular disease and further larger longitudinal studies assessing the impact of CPAP therapy on cardiovascular outcomes, particularly coronary artery disease, are warranted.[12]

The term metabolic syndrome has been increasingly used and described in relation to OSA.[13] Metabolic syndrome encompasses a cluster of features related to obesity, diabetes and hypertension. These include waist circumference, triglyceride and glucose levels, and hypertension. There is an increased incidence of metabolic syndrome in patients with OSA.[14] With increasing evidence that OSA is associated with insulin resistance and diabetes mellitus,[15–17] it is becoming more apparent that OSA may play an important role in metabolic syndrome and diabetes mellitus.

SYMPTOMS, CLINICAL EXAMINATION AND ASSESSMENT OF EXCESSIVE DAYTIME SLEEPINESS

Symptoms associated with OSA are shown in **Box 74.1**. Clinical assessment of OSA entails a detailed history, ideally with the partner present during the consultation. The partner may be able to describe the breath-holding, associated gasping, and movement arousals (associated with the apnoeas and hypopnoeas) and may possibly display a raised level of anxiety. Many couples may express marital strife and hence it is prudent for the clinician consider their issues with compassion. Even if the patient with possible OSA is banished to the next bedroom, the witnessed apnoeas are still reportable by the pauses in the audible snoring. Some patients may have had OSA for many years and therefore become accustomed to their EDS and hence may underestimate their symptoms. An appreciation of their sleep patterns is important, as one of the commonest causes of EDS is sleep deprivation rather than sleep fragmentation (i.e. OSA).

BOX 74.1 Symptoms of obstructive sleep apnoea (OSA)

- Snoring
- Fatigue
- Witnessed breath-holds
- Gasping and choking
- Excessive daytime sleepiness
- Fragmented sleep
- Unrefreshing sleep
- Reduced alertness
- Mood changes
- Nocturia

Some will relay how EDS may affect their working lives, especially those who work with heavy machinery or drive professionally. Taking a history of road traffic accidents (RTAs), therefore, is vital. Individuals with OSA are at a higher risk of RTAs, with associated costs.[18, 19] Although individuals may not have had an RTA as a result of falling asleep at the wheel, subtle clues such as drifting across lanes, clipping the kerb, or a history of being beeped at by other drivers whilst driving are useful indicators of driving whilst sleepy.

The presence of central obesity is a particularly relevant physical finding during an OSA consult. A BMI greater than 28 kg/m^2 should increase the suspicion for OSA. Neck circumference is a useful measure; above 43 cm may be predictive. Other examination features of importance include a detailed nasal and oropharyngeal assessment, including the Mallampati score,[20] and the presence or absence of retrognathia, cranio-facial abnormalities and tonsillar hypertrophy. Information about possible associated medical conditions such as hypertension, diabetes and dyslipidaemia should always be sought during the consultation.

Unfortunately, the assessment of history and clinical findings has been shown to lack sensitivity and specificity in diagnosing OSA. It is estimated that history and examination can only predict OSAHS in 50% of patients.[21] The measurement of EDS may be subjective and objective. The commonest subjective questionnaire used is the Epworth Sleepiness Scale (ESS; see **Table 74.1**), named after the Epworth hospital, Melbourne, Australia.[22] A score above 10 (out of 24) may indicate EDS; but the ESS lacks sensitivity and specificity. Therefore, in any individual, the ESS may not on its own be very useful, but act only as a guide. It is generally not recommended that clinical decision-making is based purely on the ESS. More recently, the STOP-Bang questionnaire (**Box 74.2**) has been developed as a pre-operative screening tool to identify patients with undiagnosed OSA,[23] and has been shown to identify moderate to severe cases of OSA in the surgical population.[24]

TABLE 74.1 Epworth Sleepiness Scale (ESS)
Assesses the likelihood of an individual dozing off at the following situations (score 0 = never, 1 = slight chance, 2 = moderate chance and 3 = high chance of dozing)

Situation	Chance of dozing
Sitting and reading	
Watching TV	
Sitting inactive in a public place (e.g a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in traffic	
TOTAL	

BOX 74.2 STOP-Bang questionnaire – answer Yes or No

- Snoring – Do you snore loudly (louder than talking or heard through closed doors)?
- Tired – Do you often feel tired, fatigued, or sleepy during daytime?
- Observed – Has anyone observed you stop breathing during your sleep?
- Blood pressure – Do you have or are you being treated for high blood pressure?
- BMI – BMI of more than 35 kg/m^2?
- Age – Age over 50?
- Neck circumference – neck circumference greater than 40 cm?
- Gender – Gender male?

High risk of OSA (AHI >5/hr): answering yes to three or more items

Low risk of OSA (AHI <5/hr): answering yes to less than three items

Objective measurements of EDS include the Multiple Sleep Latency Test (MSLT), which measures how quickly an individual can fall asleep, and the Maintenance of Wakefulness Test (MWT), which measures how long an individual can stay awake. However, such diagnostic tests can only be measured if full polysomnography facilities, including EEG, are available, as without EEG, accurate assessment of wake and sleep cannot be made.

THE DIAGNOSIS OF OBSTRUCTIVE SLEEP APNOEA

Methods designed to diagnose OSA may include domiciliary single channel (overnight oximetry), domiciliary multichannel (respiratory and oximetry signals) and in-hospital full polysomnography (PSG), which includes measurement of respiratory, oximetry and sleep architecture assessment using electroencephalography (EEG), electrooculography (EOG) and electromyography (EMG) parameters. The merits of each tool are discussed below.

Overnight oximetry

This method measures variations in oxygen saturation and pulse rate during sleep. It assumes that when an individual has an apnoea or hypopnoea, the oxygen saturation falls. Once the apnoea or hypopnoea is relieved, the oxygen desaturation recovers. The falls and rises are regarded as 'oxygen dips'. The pulse oximeter is applied over the end of a digit, which is attached to a wristwatch computer that the patient wears during the night. This is where the data are collected. For convenience, the device can be worn at home. More sophisticated software products provide pulse rate variability (e.g. the number of pulse rises of over six beats per minute averaged out per hour), which would reflect autonomic cardiovascular changes during arousals as a result of apnoeas and hypopnoeas. However, pulse rate variability can only be analyzed in the presence of sinus rhythm rather than in patients with atrial fibrillation.

In the UK, some sleep clinicians use oximetry alone as a screen for OSA. It is standard practice that a 'dip' of 4% oxygen saturation (e.g. from 94% to 90%) is regarded as more meaningful than a 2% or a 3% dip. An oxygen desaturation index (ODI) (i.e. the number of times the oxygen saturation falls by 4% averaged out per hour) of more than 15 per hour may be suggestive of OSA. The presence of other associated features that are measured that may lean towards a diagnosis of OSA in the presence of a 'positive' oximeter result include EDS (ESS >10), obesity (BMI >28 kg/m^2), and the presence of other comorbidities (e.g. hypertension, coronary artery disease, metabolic syndrome and diabetes mellitus). However, an ODI >15 per hour can only be used if the resting saturation of oxygen is above 90% and there is an absence of obstructive airway disease. **Figures 74.1** and **74.2** show a classic case of repetitive oxygen desaturation during sleep, typical of OSA.

Although studies using overnight oximetry as a screening tool for OSA have shown good specificity and positive predictive value, this test is associated with poor sensitivity and negative predictive value.[25] In other words, overnight oximetry may miss patients with OSA who do not desaturate, but in the presence of a positive result, the oximetry can be a useful screen. However, an abnormal ODI may underestimate the true severity of OSA, as demonstrated in **Figures 74.3** and **74.4**. Generally it is accepted that young, less obese patients may not have oxygen desaturations in the presence of apnoeas and hypopnoeas and therefore will be missed by oximetry. Mechanisms why some patients desaturate and some do not is unclear but it may be related to lung volumes, functional residual capacity or central respiratory response to apnoeas (i.e. if an arousal response to airway obstruction is blunted then the individual is more likely to hypoventilate and desaturate). It is recommended that, if the ODI is less than 15 oxygen desaturations ('dips') per hour, but there is the presence of EDS, obesity or existing comorbidity, then a further

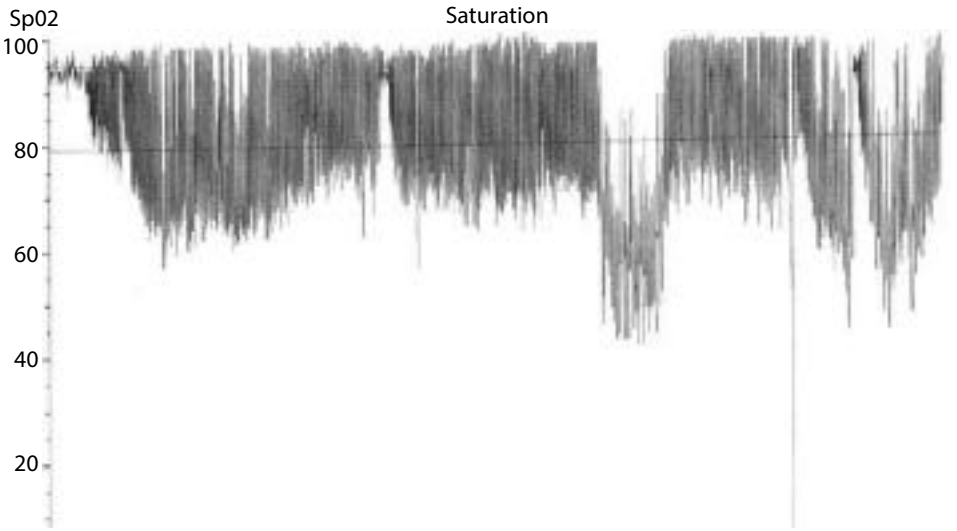


Figure 74.1 A patient with an oxygen desaturation index (ODI) of 55 4% oxygen dips per hour. The oximetry trace shows the whole night data. Minimum oxygen saturation is approximately 45%.

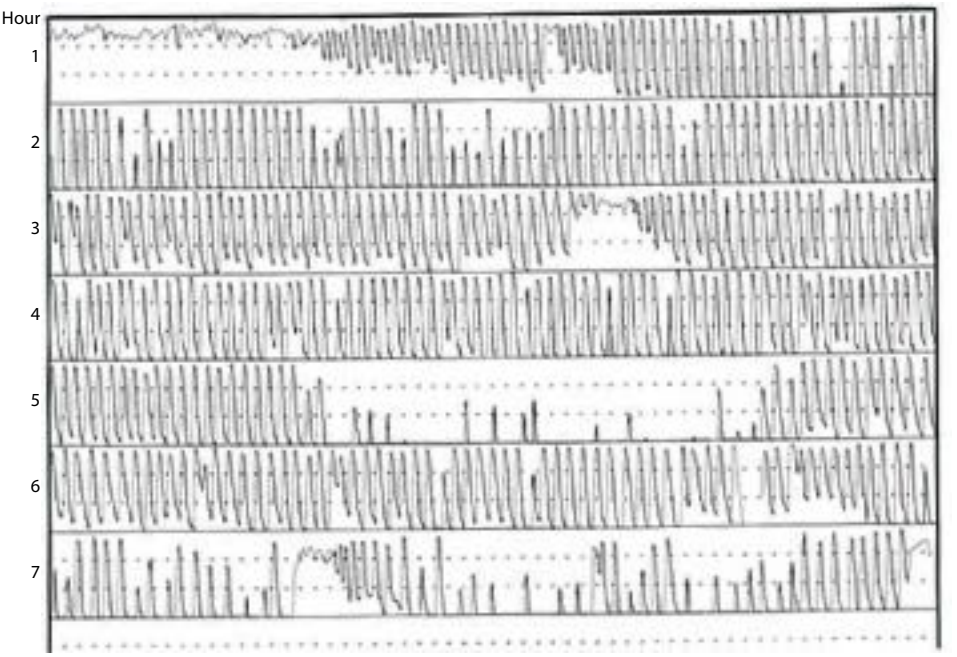


Figure 74.2 The same patient as in Figure 74.1, with a close up of the oximetry trace demonstrating oxygen dips. X axis is one hour. Y axis is 70–100% saturations. Note the marked repetitive desaturations of oxygen, typical of OSA. Occasional dips are below 70%.

referral for multichannel assessment of respiration is recommended. It is not advocated that a trial of CPAP be carried out in those where the diagnosis and severity of OSA s in question following a negative oximeter study.

Home multichannel testing

The advantages of home overnight respiratory monitoring over in-hospital studies are multiple. They include better patient comfort, cost savings and prevention of hospital admission, and allow quicker data analysis. Disadvantages include sensor failure at home and loss of signal (which may lead to repeat studies). Fewer channels will inevitably result in less available information. In particular, home monitoring without EEG will not determine when the patient is asleep during the night. Sleep disordered breathing occurs during sleep, and it may be possible that without an assessment of exact sleep time, home monitoring may underestimate the severity of OSA. Some home portable kits also include EEG probes to determine sleep architecture. However, in the UK, multichannel kits that measure nasal/oral flow via a pressure cannula, chest and abdominal movements via a pressure transducer housed in a velcro belt and pulse oximetry, but not EEG activity, are the most popular. A number of such products are available on the market. A classic example of repetitive apnoeas is shown in **Figure 74.5**. The chest and abdominal belt allows the assessor to determine if the apnoeas and hypopnoeas are related to respiratory effort (during the apnoea or hypopnoea, the chest and abdominal signals still display movement) and therefore obstructive in nature, as opposed to central sleep apnoea (CSA) where there is no chest or abdominal movement or effort during apnoeas. In contrast to OSA, the apnoeas seen in CSA originate from the respiratory drive centre of the brain and may occur in patients with cerebrovascular disease or

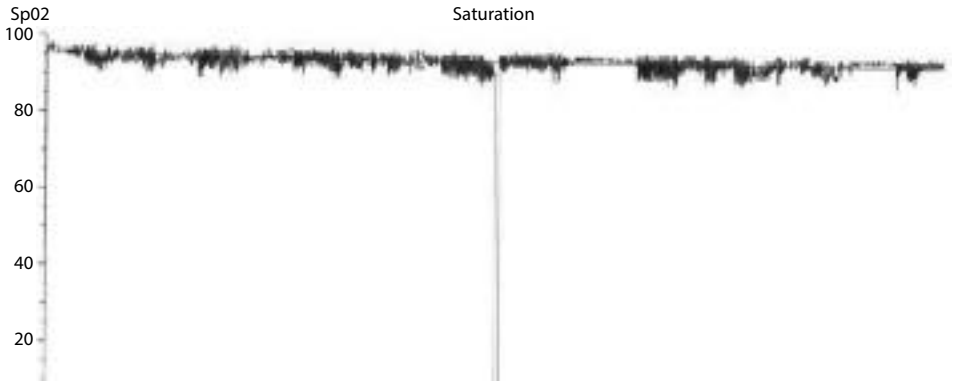


Figure 74.3 This patient has an ODI of 22 4% oxygen dips per hour, a body mass index (BMI) of 36 kg / m² and an ESS score of 6. The desaturation is not as marked as the example in Figure 74.1. The mid page reading signal to zero is an artefact.

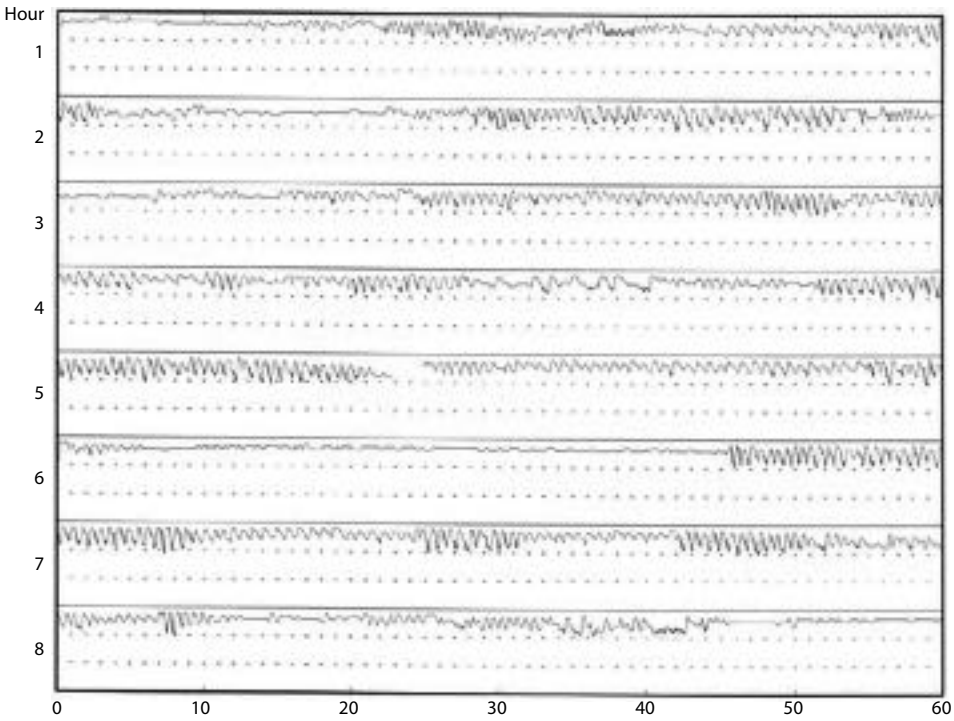


Figure 74.4 The same patient as in Figure 74.3, showing close up of oxygen dips from Figure 74.3. X axis is one hour and Y axis is 70–100% oxygen saturations. Repetitive but intermittent oxygen desaturations were seen, particularly 2% and 3% dips. The patient underwent a diagnostic polysomnography showing severe OSA, apnoea/hypopnoea index of 73 per hour. In this case the overnight oximetry on its own underestimated the true severity of OSA.

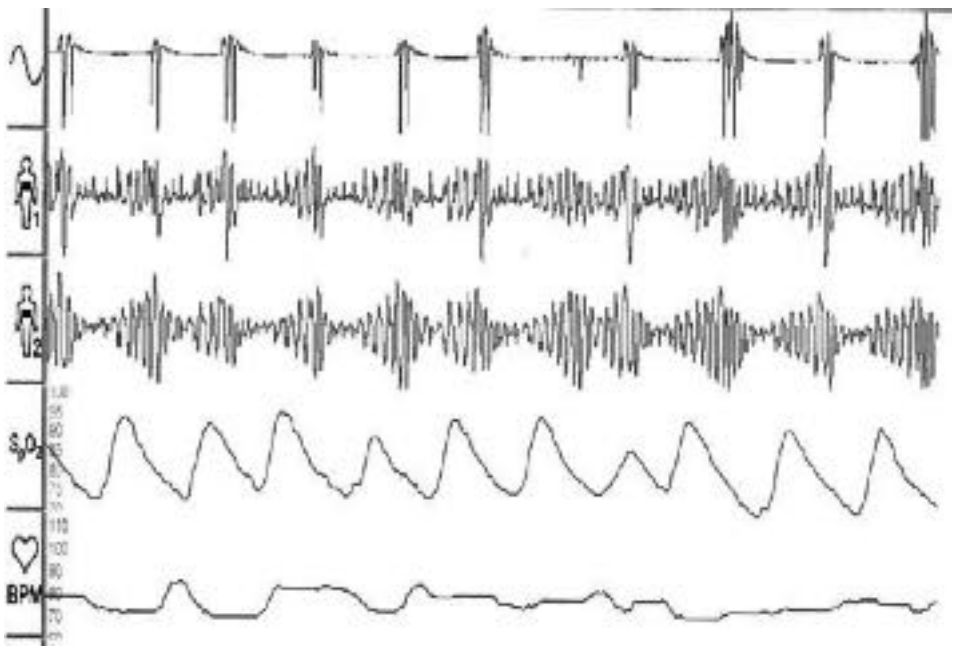


Figure 74.5 A classic example of OSA with repetitive apnoeas. X axis is 5 minutes. Top trace is oronasal cannulae flow trace, second trace is thoracic band, third trace is abdominal band, fourth trace is oxygenation and fifth trace is pulse rate. Note marked desaturations of oxygen with each apnoea, which recovers once apnoea is abolished and the pulse variability. Due to lag time effect, the nadir of oxygen saturation always follows the apnoea.

those who take regular opioids in high doses. One form of CSA known as Cheyne-Stokes respiration ('crescendo-decrescendo' chest and abdominal movements) is more common in patients with heart failure. Therefore oximetry alone would not pick up the origin of apnoeas (i.e. obstructive vs central), in such patients.

Patients are taught how to attach the necessary equipment, either at home or in the hospital physiology department. The patient then either goes home wearing the equipment or reattaches it themselves later in the evening. Following overnight data collection, the equipment is returned and the data are analyzed. Whilst in most models data analysis occurs automatically, it is recommended that the data are scored by a trained clinician or technician in an attempt to reduce software mismatching of apnoeas and hypopnoeas.

An apnoea is regarded as a completed cessation of airflow (more than 90% reduction in nasal airflow/pressure signal amplitude of the pre-event baseline) for at least 10 seconds, regardless of whether there is an associated oxygen desaturation or arousal. The definition of hypopnoea varies from centre to centre but it is typically regarded as a reduction in airflow/pressure signal amplitude by 30% of pre-event baseline or more with a 3% or more oxygen desaturation, or if the event is associated with an EEG arousal. These criteria are based on the updated American Academy of Sleep Medicine (AASM) guidelines 2012[26] (these guidelines superseded the 2007 AASM guidelines[27]). If the airflow signal is missing (e.g. mouth breathing or displaced oro-nasal cannulae), amplitude changes in the thoraco and abdominal wall movement signals can still be used to determine if apnoeas or hypopnoeas are taking place. As explained above, chest wall movement – and therefore by inference, respiratory effort – is measured indirectly as changes in pressure detected by a pressure transducer worn around the chest during sleep. The changes in pressure signal are proportional to airflow and any change in signal can be regarded as a change in airflow.

Overnight polysomnography

The disadvantages of in-hospital overnight PSG compared with domiciliary multichannel testing have been stated above. However, home testing is inadequate for a cohort of more complex OSA patients. For example, some patients may need further respiratory monitoring such as transcutaneous CO_2 testing, particularly if OHS is suspected. In other cases, such as patients with neuromuscular disorders, in-hospital assessment is warranted as assisted ventilation is required. Tertiary referral sleep centres will see a variety of sleep disorders where the EEG, EOG and EMG component of the PSG are essential (e.g. narcolepsy, parasomnias and periodic leg movement syndrome). Prior to assessment, equipment is arranged by a sleep technician. The patient stays overnight at the sleep centre and most have video monitoring during the night as well. In some centres, the technician observes the signals from a central computer room during the night. This allows for troubleshooting, such as disconnected leads, but also allows more complex assessments, such as trials with assisted ventilators or titration with CPAP machines. Whether the technician stays overnight is dependent on the staffing and funding in the particular centre. In cases where the PSG is unattended, if leads do become disconnected, with the subsequent loss of signal, a repeat PSG may be necessary.

Criteria for the diagnosis of OSA

The number of apnoeas and hypopnoeas averaged out per hour of sleep is regarded as the apnoea-hypopnoea index (AHI). Some centres use the term respiratory disturbance index (RDI), which incorporates the number of apnoeas, hypopnoeas and respiratory effort related arousals (RERA). The latter are diagnosed by EEG arousals associated with respiratory effort (from intra-oesophageal pressure measurement) in the absence of apnoeas and hypopnoeas. However, as intra-oesophageal pressures are seldom used, the term AHI is more reflective of clinical practice and is most commonly used. If home respiratory monitoring testing is carried out, an estimate of the number of hours slept by the individual is necessary. A common mistake is to calculate the total number of apnoeas and hypopnoeas and then divide this number by the total number of hours of respiratory recording and not sleep time.

The severity of OSA has been defined as:

- no evidence of OSA if AHI <5 apnoeas and hypopnoeas per hour
- mild OSA if AHI ≥ 5 and <15 apnoeas and hypopnoeas per hour
- moderate OSA if AHI ≥ 15 and <30 apnoeas and hypopnoeas per hour
- severe OSA if AHI ≥ 30 apnoeas and hypopnoeas per hour.

It is important to note that these criteria do not take into account the desaturation index or the length of apnoeas and hypopnoeas.

When to treat varies from centre to centre. Most centres would not treat mild OSA without EDS and/or existing comorbidities (i.e. hypertension, cardiovascular disease, coronary artery disease, diabetes mellitus) with CPAP. Lifestyle changes, such as weight loss strategies (particularly if the BMI is greater than $25\,kg/m^2$), and/or treatment of any troublesome rhinitis are recommended. However, if patients have mild OSA with EDS and/or comorbidities, or moderate to severe OSA with or without EDS and comorbidities, then a trial with CPAP therapy may be considered.

TREATMENT – CONTINUOUS POSITIVE AIRWAY PRESSURE

Continuous positive airway pressure (CPAP) is regarded as the mainstay of OSA treatment.[28] This technique was first described in 1981[29] and since then there have been immense technological advances driven by industry.

The mode of action can be regarded as a 'pneumatic splint' whereby the air pressure generated via a tube and mask, through the nasal and/or oral passageway, prevents collapse of the pharyngeal and palatal walls, and consequently, the airway.

The equipment

CPAP machines may provide a constant positive pressure ('fixed pressure') or may vary pressure depending on the presence of apnoeas. The latter system, delivered by autoCPAP machines, relies on an algorithm set in the machine mechanics, whereby a reduction of airflow (i.e. apnoea or hypopnoea) is detected by the machine and as a result the machine generates the appropriate retrograde flow (and therefore pressure) to overcome the apnoea or hypopnoea. For this to work successfully, a closed system between the machine and the patient has to exist.

Patient preference typically determines which mask is used but when a nasal mask is chosen, patients must ensure mouth leaks are minimized. To this end, chin straps are sometimes used to keep the mouth closed. Most masks are kept in place by Velcro straps. All masks must have an expiratory port to prevent re-inhalation of expired air. All patients are reminded to clean their masks and strappings regularly, to ensure longevity. The newer machines are smaller and lighter to allow easy portability. All new machines have an internal mechanism to allow switching between 220 and 110 volts, depending on where the user is around the world. The ease of using CPAP on planes can vary from airline to airline.[30] The use of an inverter mechanism will allow CPAP usage driven from a DC battery pack. For those who suffer from nasal congestion and/or a dry mouth, a humidifier is recommended.

Setting up CPAP

Centres differ in how a patient with OSA is set up on CPAP. All centres should have educational programmes to ensure patients gain a better understanding of their illness, in order to maximize long-term CPAP compliance. Some centres use group video workshops to achieve this. CPAP set-up should be carried out by a trained technician who understands the technology and appreciates where problems may arise.

Patients differ in the level of pressure necessary to eliminate the vast majority of their apnoeas and hypopnoeas. The method of determining this opening of airway pressure differs from centre to centre. Some use a mathematical equation. One example that has shown reasonable correlation with titration studies is: predicted pressure (cm H_2O) = (0.16 × BMI) + (0.13 × NC) + (0.04 × AHI) − 5.12, where NC is neck circumference (cm).[31]

Another method of titration of CPAP used in some centres is to admit a patient for overnight diagnostic PSG. The severity and diagnosis of OSA is confirmed by PSG during the first half of the night, then CPAP is commmenced for the second half of the night. This is referred to as a 'split night' regime. However, the process needs a supervising technologist and a big disadvantage is that the true severity of OSA may not be determined during the diagnostic first half of the night. However, an advantage is that both diagnostic and CPAP titration are performed on the same night, therefore saving an extra admission. The CPAP titration technique is carried out by a technologist from the central computer room, who has video access to the patient and electronic linkage to the CPAP machine. The starting pressure is usually around 4 cm H_2O and the pressure is quickly increased until all apnoeas and hypopnoeas are eliminated. It is the aim to reach the required pressure to eliminate the majority of apnoeas and hypopnoeas within an hour, and the rest of the night is spent fine-tuning and troubleshooting, for example, mask leaks or the need for supplemental oxygen in some cases.

Another technique that is increasingly being used is to send the patient home with an autoCPAP machine. Most autoCPAP machines will collect data on compliance, leaks and pressure profile. A trial of between 7 and 14 days may allow better adjustment to the concept of CPAP rather than an autoCPAP trial of one night. Generally autoCPAP machines are more expensive than the fixed pressure machines and as a result, in the UK, funding from clinical commissioning groups (CCGs) are predominantly for fixed pressure machines. Many centres set the fixed pressure as determined by the 90th or 95th centile pressure (i.e. the blowing pressure to eliminate 90% or 95% of apnoeas and hypopnoeas) as determined by the autoCPAP data download. CPAP therapy is recommended by the National Institute for Health and Care Excellence (NICE) as the treatment of choice for moderate to severe OSA.[32] The Scottish Intercollegiate Guidelines Network (SIGN) has produced useful recommendations on the management of OSAHS in adults.[33]

Side effects

Most side effects are related to the nasal/face mask interface. Claustrophobia can be problematic in some patients. Trying different face masks, from full face, to nasal, to an interface that sits on the nostril edge (nasal pillows) may be one solution. However, with patience, education and reassurance (an experienced technician is the key here), most patients are able to alleviate such claustrophobia issues. Nasal stuffiness is a common troublesome side effect, although interface technology has improved greatly recently to reduce this. However, despite this, nasal stuffiness and coryzal illnesses can lead to poor compliance in those patients with nasal masks. Heated humidification is recommended as one solution. Cold and dry air may provoke mucus production and vasodilation in the nasal mucosa and hence humidification may potentially address this. Although nasal corticosteroids and/or corrective surgery for mucosal thickening and polyps may be considered, most sleep centre practitioners believe that a full-face mask may be a simpler solution.

Other side effects, such as skin abrasions and leaks, are usually related to poorly fitting masks. Leaks can be a

nuisance, especially if they are directed towards the eyes. The patient has to be educated that a good fit rather than a tight fit is more likely to be successful in eliminating leaks without skin and eye trauma.

Air-swallowing and pulmonary barotrauma may also occur, although the latter is very rare. Air-swallowing and subsequent gastric distension is more likely if the pressure delivery exceeds physiological oesophageal sphincter pressure (e.g. above 15 cm H_2O). The obvious remedy is to reduce the pressure.

Compliance and troubleshooting

Compliance of CPAP usage is dependent on many factors. It has been reported that by 3 years, up to 12–25% of patients will have discontinued treatment.[34] Compliance has been defined arbitrarily in the literature as usage of CPAP for more than 4 hours for at least 5 nights per week. The biggest factor that will determine long-term compliance is the improvement of symptoms soon after commencing CPAP therapy and the severity of the OSA suffered by the individual.[34] What is unclear, when faced with an individual about to commence CPAP therapy, is whether 4 hours for 5 nights per week is enough to reduce the risk of RTAs or future cardiovascular comorbidity. It is anticipated that future clinical trial data will determine this but generally all patients are encouraged to use CPAP for at least 6 hours, 7 nights per week.

It follows that adequate education, follow-up by an experience technician and motivation of the patient all influence long-term adherence to CPAP. When CPAP failure does occur, troubleshooting interface issues, addressing side effects and assessing the presence of coexisting sleep disorders (e.g. shift-work related sleepiness, narcolepsy, psychological illness or drug-induced conditions) should be considered. This latter point is particularly important as it is not uncommon for an individual to have two coexisting sleep disorders.

There have been some suggestions that autoCPAP has advantages over fixed pressure CPAP, particularly with respect to comfort, possibly by reducing the average pressure applied throughout the night. However, although this may be the case, there is no evidence that this improves compliance or symptoms of EDS compared to fixed pressure CPAP.[35] A recent systematic review of fixed pressure CPAP vs autoCPAP showed that although there was an improved compliance by 11 minutes per night (0.18 hours; 95% CI, 0.05 to 0.31 minutes; $P = 0.006$), and that ESS score improved by 0.5 (95% CI, −0.81 to −0.15; $P = 0.005$) in the autoCPAP group, the clinical importance of these small margins of improvement remain unknown, despite being statistically significant.[36] Therefore, as the treatment effects are similar between APAP and fixed CPAP, the therapy of choice will be dependent on patient preference, the cost, and issues of non-compliance. Until there are definite cost-benefits shown for autoCPAP over the fixed pressure CPAP machine, there is no justification to mass provide autoCPAP machines on the NHS in the UK at present.

ALTERNATIVE STRATEGIES TO CPAP

Bilevel positive airway pressure (sometimes known as BiPAP) devices allow specific and separate pre-set inspiratory and expiratory pressures, for example inspiratory positive airway pressure (IPAP) between 10 cm H_2O and 20 cm H_2O, and expiratory positive airway pressure (EPAP) between 5 cm H_2O and 10 cm H_2O. These devices may improve compliance in some patients who are intolerant to CPAP but should only be used in selective cases. For those who have CSA, newer devices known as adaptive servo-ventilator (ASV) have been commonly tried. It is generally recommended that such treatment should be initiated by specialist sleep centres. Other novel treatments, such as nasal EPAP devices, are being introduced as alternative therapies[37] but randomized controlled trials comparing this form of device against CPAP are still awaited.[38]

FOLLOW-UP AND LEGAL ISSUES

At the time of diagnosis of OSA, in the UK, the individual is recommended to self-inform the Driver and Vehicle Licensing Authority (DVLA), Swansea, UK, of the diagnosis. However, the DVLA recognizes only the diagnosis of 'obstructive sleep apnoea syndrome', defined by the DVLA as OSA with sleepiness, but there is no indication of how the sleepiness is qualified or quantified and therefore diagnosis is at the discretion of the diagnosing clinician. The emphasis of responsibility to inform the DVLA in the UK is placed on the patient with 'OSA syndrome' and not the sleep clinician/ENT surgeon and so on. In reality, many patients do not inform the DVLA, as in many parts of the country the treatment for OSA (CPAP) may not be available immediately. All drivers should be reminded that by law (Road Traffic Act 1998), all drivers have a duty of care when driving. However, those patients deemed to be a genuine threat to the public by continuing to drive whilst sleepy may be considered for notification by the clinician, despite this potentially breaking rules of patient confidentiality.

Follow-up CPAP clinics are aimed to determine compliance, minimize intolerance, improve symptoms (as shown by reduced sleepiness) and continue to modify cardiovascular risk factors. Follow-up PSG with CPAP is not necessary unless other sleep disorders (e.g. periodic leg movement, insomnia) are suspected. Some centres utilize a repeat overnight oximetry with CPAP, but an abnormal tracing may not necessarily differentiate poor compliance from inadequate treatment pressure. A significant increase in weight with time may lead to the appearance of snoring with the mask on and an increase in the fixed CPAP pressure may be necessary. Leaks around the mask may be caused by the mask components wearing out, but if the mask is well looked after it should last for up to a year. CPAP machines that are provided on the NHS must be electrically serviced and checked by an engineer on an annual basis by law. The equipment technically belongs to the centre that provided the machine and therefore it is the

responsibility of the centre to ensure that it is electrically safe. During servicing, the engineer will routinely download usage data from the machine and this will provide useful compliance data. Patients with moderate to severe OSA who have suboptimal compliance are challenging to the clinician, and reasons for non-compliance should be addressed. If a patient refuses treatment with CPAP, then other solutions (e.g. weight loss, mandibular devices or even surgery) may be considered. The patient should be reminded of the issues of driving with OSA without treatment. Clinical psychology approaches, particularly cognitive behavioural therapy, may also be considered.

KEY POINTS

- Obstructive sleep apnoea is becoming more and more prevalent in society as more and more individuals become obese.
- A significant proportion of individuals with obstructive sleep apnoea are however not obese and therefore the clinician should look out for airway anatomical reasons for the apnoeas.
- Obstructive sleep apnoea is commonly associated with other comorbidities such as hypertension, cardiac disease, diabetes mellitus type II and cerebrovascular disease.
- Obstructive sleep apnoea is a common reason for impaired well-being particularly impaired mood, concentration, memory, and alertness.
- There is a higher risk of fatigue-related road traffic accidents in those who have severe obstructive sleep apnoea.
- The clinician looking after an individual with obstructive sleep apnoea should be aware of the medical (CPAP), dental (mandibular advancement splint) and surgical (Ear Nose and Throat) approaches of treatment.
- Services delivering diagnostic and therapeutic patient pathways are more commonly involving a multidisciplinary and holistic approach.

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CHAPTER 75

THE SURGICAL MANAGEMENT OF SNORING AND OBSTRUCTIVE SLEEP APNOEA

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SEARCH STRATEGY

Data in this chapter may be updated by PubMed search using the keywords: snoring, OSA, UPPP, palatoplasty, coblation, laser surgery for snoring, robotic surgery for OSA and evaluation.

EPIDEMIOLOGY

Sleep-related breathing disorder (SRBD) encompasses a broad clinical spectrum of recurring partial or complete obstruction of the upper airway. This ranges from simple or primary snoring to severe obstructive sleep apnoea (OSA). Patients who have symptoms suggestive of OSA but do not have objective parameters in a sleep study confirming the condition can be classified as having upper airway resistance syndrome (UARS). These patients may have sleep fragmentation but do not have significant oxygen desaturation events or many obstructive events. A definition of apnoea, hypopnea and the apnoea-hypopnea index (AHI) is covered in Chapter 74, Obstructive sleep apnoea: medical management.

Snoring is a sound produced (usually during inspiration) by vibrations of the upper airway caused by a turbulent airflow that, in turn, is caused by varying degree of collapse of the upper airway lumen. Simple snoring is generally not associated with significant obstruction or arousals but can be linked with tiredness. It is thought that the reason for the tiredness may be that these simple snorers, in the absence of apneas, may still repeatedly wake up as there is a need to make a greater effort to overcome the airflow resistance; furthermore, they may be awakened by their partner who is being disturbed by the noise. The exact prevalence of snoring is not easy to quantify but in general it is thought that about 40% of adults snore and of these about 10% may have some degree of obstructive episodes. Men are thought to be more likely to snore than women.

OSA is thought to affect 2–4% of males and 1–2% of females, a level of prevalence comparable to Type I diabetes.[1] Basically, in OSA there is failure of dilator muscle tone of the upper airway lumen.

The morbidity and mortality related to OSA is well recognized as an independent risk factor for hypertension, cardiovascular, Type II diabetes and cerebrovascular diseases.[2] In addition, neurobehavioural morbidities of daytime sleepiness and impaired cognitive function may contribute to motor vehicle and job-related accidents.[3, 4] Overall, OSA significantly increases the risk of stroke or death from any cause; in a community-based sample, moderate to severe sleep apnoea is independently associated with a large increased risk of all-cause mortality.[5] The obesity epidemic means problems faced by health professionals in relation to OSA are only likely to increase in the immediate future.

In terms of aetiology and aggravating factors for both snoring and OSA, there is considerable similarity and overlap. In essence, the upper airway in these patients is of a relatively small size and/or narrowed. In many of these individuals it is not uncommon to encounter a multilevel obstruction. For example, an individual may have nasal congestion or obstruction secondary to deviated nasal septum or nasal polyps and may also have a crowded oropharynx as a result of hypertrophied tonsils or a lax soft palate and an elongated uvula. Nasal congestion may further contribute to the obstruction by causing mouth breathing that, in turn, accentuates palatal vibration or oscillation of pharyngeal tissue and worsening of

tongue retraction.[6] Excessive alcohol intake,[7] obesity,[8] smoking,[9] increasing age[8] and consumption of sedatives are thought to aggravate these conditions. Certain morphological features such as micrognathia or maxillary retrusion make some patients more prone to sleep-related breathing disorders.

CLINICAL PRESENTATION

It is prudent to fully evaluate a patient before imposing surgery upon them. The full evaluation would consist of a comprehensive medical history, clinical examination and assessment and special investigations to ascertain the severity and the site or sites of anatomical obstruction within the upper airway that may be responsible for the symptoms.

CLINICAL HISTORY

This is probably better obtained if the partner is present as well. Details of both nocturnal and daytime symptoms need to be addressed. As much information as possible about snoring and sleep should be gathered and could include many of the following:

- For the partner (i.e. questions that are not easy or possible for patient to answer):
  - How severe is the snoring (audible outside the room, downstairs, by next door neighbour)?
  - Does the patient snore with mouth open?
  - Is snoring positional?
  - Are there episodes of crescendo snoring, apnoea, choking or gasping?
  - Is the patient restless and are there any other limb movements?
  - Does the patient sleep walk or sleep talk?
- For the patient:
  - Do you feel that your sleep is refreshing?
  - Do you get morning headaches?
  - Do you feel tired during the daytime? (Complete Epworth Sleepiness score.)
  - Do you suffer from night sweats or palpitations?
  - Do you have vivid dreams or nightmares?
  - Do you feel that your nose is blocked?
  - Do you smoke and drink alcohol? How much?
  - Do you have any other medical problems such as high blood pressure, heart problems, diabetes, underactive thyroid gland or past history of stroke?
  - Do you feel that your cognitive functions such as concentration and memory are impaired?
  - Has your libido diminished?
  - Have you had any driving accidents?
  - What medications do you take?
  - Have you had any surgery previously? (Assess fitness or problems with general anaesthesia.)
  - Have you tried any conservative measures such as weight loss, reducing alcohol or intranasal steroid sprays?
  - Have you tried nasal strips or nasal valve dilators to improve nocturnal breathing?
  - Have you tried mandibular advancement devices to improve snoring?

CLINICAL EXAMINATION

This can quite easily be conducted in an outpatient setting, and addresses a general inspection and examination as well as specific upper airway evaluation.

Measurements of height and body weight are obtained to calculate the body mass index (BMI). The figure for BMI is derived by dividing the body mass in kilograms divided by the square of the height in metres. Values of BMI should take factors such as body frame and ethnic difference into account. In general, however, BMI values between 20–25 are considered as being normal, between 25–30 as being overweight and more than 30 as being obese.[10] Higher values would be categorized as being premorbid or morbid obesity. Neck collar size measurement is useful as it has been suggested that there is higher chance of OSA in patients with a collar size greater than 17 inches.[11] On general inspection one ought to be on the lookout for craniofacial or facial skeletal framework deformity such as seen in patients with acromegaly, maxillary retrusion or micrognathia.

Specific upper airway evaluation should commence with the examination of the nose and nasal cavity. External nasal deformity and abnormal nasal valve function can both contribute to difficulty in breathing and upper airway obstruction. Further examination of the internal nasal cavity can be conducted using a headlight and thudicum nasal speculum to identify abnormalities such as deviated nasal septum, septal perforation, enlarged turbinates or nasal polyps. This should be followed by simple examination of the oral cavity and oropharynx, starting with observation of the state of dentition as this may determine the suitability of the patient to use a mandibular advancement device. Other features to be noted should include limitation of mouth opening, laxity of soft palate, size of palatine tonsils, the length of uvula and the general crowdedness of the oropharynx. The Mallampati palate position[12] and Friedman tongue position[13] may also be used for further evaluation of the upper airway obstruction and may provide an indication as to the likelihood of success of certain surgical interventions.

More detailed examination of the nose and the pharynx should be carried out using a flexible, fibre-optic endoscope assessing the nasopharynx, oropharynx and the hypopharynx. The patient could simulate the snoring[14] whist the endoscope is in position and could also perform the Mullers[15] manoeuvre, which essentially is the reversed Valsava manoeuvre. Although these may provide an insight in to the site and severity of upper airway obstruction, one must bear in mind that this 'awake' assessment in the patient may not truly reflect the upper airway dynamics during sleep as the muscle tone would vary greatly. Furthermore, some patients do find these manoeuvres difficult to perform and there may be a great deal of subjectivity in its interpretation.

INVESTIGATIONS

Before embarking on any treatment, it is important to perform some investigations. For instance, blood tests to exclude anaemia and hypothyroidism should be carried out to exclude other causes of tiredness. A sleep study should be performed in individuals where history is suggestive of OSA, to determine the severity of the problem. Other investigations to assess upper airway obstruction include imaging, acoustic analysis, sleep nasendoscopy (SNE) and use of pressure transducers.[16]

Imaging

Although not routinely utilized, imaging can be useful under certain circumstances. For example, in patients being considered for radical surgery like maxillo-mandibular advancement, cephalometry provides vital information about upper airway dimensions.[17] Disadvantages of this kind of imaging include the fact that it can only be performed whilst the patient is awake, the exposure to radiation and the cost. It only provides two-dimensional information and may also not be widely available. More detailed and sophisticated data can be obtained by using computed tomography (CT) scanning or magnetic resonance imaging (MRI), allowing objective volumetric dimensions of the upper airway to be calculated.[18,19] These are both expensive, and CT scans also involve radiation. The MRI scans are very useful in evaluating the soft tissue aspect of the upper airway. Using these routinely during sleep would not be cost-effective or practical.

Acoustic analysis

In general, this form of evaluation is considered to be entirely safe as it is non-invasive, does not involve radiation, is relatively cheap and can be utilized during natural sleep over multiple nights. It can be conducted simultaneously with a hospital-based polysomnography or at home with an ambulatory sleep study. By using the sound frequency spectrum, acoustic analysis can potentially distinguish between primary snoring and OSA.[20] Attempts have been made to correlate snoring sound frequency with different anatomical levels of upper airway obstruction, and comparison of this technique has been made to SNE.[21] This was found to be difficult, particularly with multilevel involvement in most patients. The sensitivity and specificity of acoustic analysis has often been questioned and its role in selecting different treatment modalities is slightly limited.[22]

Sleep nasendoscopy

SNE, which is more popularly known as drug-induced sedation endoscopy (DISE) in the rest of Europe, was pioneered at the Royal National Throat, Nose and Ear Hospital in London.[23] Work from this institute, including an audit study of 2485 procedures, has demonstrated that SNE correlates well with AHI and mean oxygen desaturation values.[24] The beauty of this technique lies in the fact that it allows a three-dimensional visualization of the upper airway dynamics during sleep, albeit drug induced. It has to be appreciated that the muscle tone of the upper airway is different when the patient is fully awake compared to when they are asleep and therefore the assessment of the anatomy during sleep should prove to be useful. It has been demonstrated that SNE is useful in predicting treatment success in snorers using mandibular advancement devices.[25–27] Similarly, SNE has allowed site specific selection in surgical patients and improved surgical outcomes in patients undergoing laser palatoplasty with or without tonsillectomy, as well as with implanted upper airway stimulation therapy for OSA.[28–31]

This assessment should be carried out in an operating theatre setting with the help of an anaesthetist and adequate cardiovascular and respiratory monitoring. The sedative agents used are midazolam or propofol, or a combination of the two, where midazolam effectively induces sleep while propofol, with its rapid onset of action and recovery, is useful in the fine tuning of sleep.[24]

Advocates of SNE find it to be a useful evaluation technique but numerous controversies and debates have arisen. First and foremost, drug-induced sleep is different from natural physiological sleep as the drugs used may cause exaggerated muscle relaxation. However, one could argue that this impact of the sedation drug would be similar on the different segments of the pharynx; thus, it would theoretically allow us to compare the proportionate obstruction caused at each anatomical level in a similar manner that may exist in natural physiological sleep. Furthermore, criticisms were made by Marais,[32] who claimed that, when comparing snorers and non-snorers during SNE, snoring was not reproduced in some of the snorers and snoring could be produced in the non-snoring group, and thus concluded that SNE was not an appropriate technique. This was challenged by Berry et al,[33] who elegantly demonstrated in their study using target controlled infusion of propofol during SNE that all their snorers and non-snorers responded as expected, thus validating and advocating SNE. Questions and concerns raised about test-retest reliability and of inter-observer variation during SNE have been adequately addressed by various studies.[34–36] Another concern that has been expressed is about the depth or level of sedation at which the upper airway should be evaluated. If the patient is assessed too early, the muscle relaxation effect of the sedation drug may be over-emphasized; and if the patient is assessed whilst too deep then important obstructive episodes during lighter sleep may be missed. This has been clarified by studies that have utilized bispectral index monitoring during SNE.[37,38] This neurophysiological monitoring device continually analyzes a patient's electroencephalogram during sedation or general anaesthesia and gives an indication of depth of sedation.

A recent study using digital videostroboscopy during SNE[39] has shown that whilst assessing the upper airway during sedation, stroboscopic evaluation may help further understanding of the mechanisms of airway obstruction, particularly in those who have failed surgical treatment.

It is important to accurately document the findings of the upper airway evaluation during SNE. At present there are various classifications[40–42] and although there is some overlap and commonality amongst these, ideally we need a uniform grading system. To date the only technique that allows evaluation of the upper airway during sleep in conjunction with dynamic visualization is SNE and the use of this technique has further emphasized the differences between awake and asleep assessment.[43, 44]

Pressure transducers

Various devices that can measure pressure changes in the different segments of the upper airway have been described. This allows pressure recording in various anatomical sites of the upper airway during obstructive episodes. It is now common practice to use a multichannel pressure catheter[45, 46] to record pressures at different anatomical levels of the upper aerodigestive tract ranging from the nasopharynx to the oesophagus, where usually the reference transducer is positioned. These have been used to ascertain the level of obstruction before performing the appropriate surgical procedure. One of the more recent devices, known as Apnea-Graph AG200 (MRA, Medical UK), seems quite promising in that it is able to perform the dual function of providing severity of OSA as well as some idea of the site of anatomical obstruction simultaneously,[47, 48] during natural physiological sleep as well as during sedation endoscopy. It relies on measuring pressure and airflow simultaneously at different levels in the pharynx. It has the ability to store and analyze the cardio-respiratory data of a patient with simultaneous recording of two different sites in the upper airway using a micro-pressure and temperature transducer catheter. Problems that may potentially be encountered with this device include difficulty in tolerating the catheter for the whole night and the possibility of some movement of the various transducers during different phases of respiration and, therefore, the site of obstruction may not be very accurately detected. Furthermore, the transducers are in a fixed position on the catheter and do not consider the morphological variation in the distances between different anatomical landmarks in individual patients.

NON-SURGICAL TREATMENT OF SNORING AND OSA

Snoring patients with or without obstructive sleep apnoea (OSA) should be advised to try non-surgical measures before contemplating any surgical procedures. An advice leaflet on self-help suggestions could be prepared locally. Otherwise, patients are directed to a national association website to provide them with the advice and support that they need. In the UK, they are directed to the British Snoring & Sleep Apnoea Association website (http://www.britishsnoring.co.uk). These measures revolve around lifestyle changes or the use of devices to alleviate the snoring.

Lifestyle changes

- Dietary modification for weight loss is essential. Morbidly obese patients are advised to explore the option of bariatric surgery if they fail to reduce their weight with dietary measures. A recent study investigating the effect of weight loss surgery in 1728 patients showed significant improvement of all obstructive sleep apnoea symptoms compared to controls. The average reduction of BMI was 9.7 kg/m^2.[49]
- Avoiding alcohol before sleep helps by reducing the detrimental effect of alcohol on the muscle tone of the neck. A randomized control trial showed that the ingestion of alcohol was associated with a significant increase in the number of apnoeic events and oxygen desaturation.[50]
- Avoiding smoking.
- Positional therapy, avoiding the supine position using the tennis ball technique, helps a small group of patients as its associated discomfort reduces the patient's compliance.[51]
- Regular exercise improves the tone of the muscles of the neck and also helps the patient to lose weight.

Devices

MANDIBULAR ADVANCEMENT SPLINTS

Mandibular advancement splints (MAS) produce forward displacement of the mandible, thus bringing the tongue base anteriorly, increasing the dimensions of the upper airway. There are a number of devices available in the market. The maximal degree of mandibular protrusion should be assessed, and then the MAS should be designed to maintain the mandible between 50% and 75% of the maximal protrusion. For simple snorers, MAS was found to be better than placebo in the subjective improvement of snoring.[52] For sleep apnoea, a randomized controlled crossover study showed significant reduction of the apnoea hypopnoea index using the MAS when compared to a control palatal plate.[53] A recent systematic analysis showed that the improvement of the OSA with MAS was observed in an average of 52%.[54]

The reported side effects of MAS include excess salivation, xerostomia, temporomandibular joint (TMJ) pain and bite change. The overall compliance is around 50–75%.[52, 55]

CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP)

CPAP is the treatment of choice for OSA. It is also recommended for upper UARS, which is referred to as sleepy snorers. It acts as pneumatic stent to prevent upper airway collapse throughout the different phases of sleep breathing. The CPAP machines could be either fixed pressure or autotitrating, according to the flow generator delivering the pressure through air tubing to a nasal mask, nasal prongs or a face mask worn by the patient. The average pressure required is 5–10 cm H_2O. The night to night pressure required overnight was found to be variable,

therefore the autotitrating CPAP would be a better option for the patients.[56]

The average use of CPAP in compliant patients ranges from 2–6 hours per night. A recent study showed that the longer the use of CPAP per night, the better the improvement of daytime somnolence and the functional status of the patients.[57]

Side effects include nasal congestion, rhinosinusitis, nasal bridge and facial irritation, and nose bleeds. Poor compliance is usually related to the discomfort of the device or the noise of the machine.

SURGICAL TREATMENT FOR SNORING AND OSA

Surgery to correct or improve upper airway obstruction may involve minimally invasive soft tissue surgery with no gross change in the anatomical structure such as interstitial radiofrequency thermotherapy or, at the other extreme, may involve radical skeletal framework surgery such as maxilla-mandibular advancement.

Nasal surgery

Patients who present with significant nasal obstruction secondary to deviated septum, nasal polyps or nasal valve collapse in addition to the snoring, should be offered the appropriate nasal surgery. There is strong evidence in the literature that nasal surgery would improve the nasal airway but the impact on snoring would be minimal. A prospective study of 40 patients showed objective improvement of the nasal airway using rhinomanometry without any improvement of the snoring time, snoring intensity, nocturnal breathing or sleep architecture.[58] Another recent controlled study revealed no change in the polysomnographic parameters after nasal surgery, although the nasal airway was significantly improved.[59]

The rationale in performing nasal surgery in patients with snoring with or without OSA is to improve their nasal airways and to provide them with a better response and compliance with CPAP. Friedman et al. investigated the result of nasal surgery alone on OSA and showed no significant impact on the respiratory disturbance index (RDI) or lowest oxygen saturation levels, but CPAP levels required to correct OSA were reduced.[60]

Uvulopalatopharyngoplasty

The classic uvulopalatopharyngoplasty (UPPP) described by Fujita et al. in 1981[61] involves the excision of the uvula, the removal of 1–2 cm of the oral palatal mucosa in curvilinear fashion along the anterior pillars, followed by excision of the excess length of the soft palate. Then the nasopharyngeal mucosa is pulled anteriorly and laterally to widen the nasopharyngeal airway. Simmons et al.[62] described a modification that was adopted in the UK involving the excision of the tonsils, the uvula, half of the anterior and posterior pillars, and full thickness of the lower part of the soft palate. The soft palate was palpated and the incision was made posterior to the fold of the levator sling then followed by suturing of the anterior and posterior pillars in continuation with the inferior margin of the remaining soft palate. A number of modifications introducing different types of local flaps[63–69] were described to maximize the size of the oropharyngeal airway, in an attempt to improve the success rate and to reduce the incidence of post-operative complications. Using an outcome measure of a reduction of snoring level by 50%, the early post-operative success rate was 76%; however, the long-term success rate was only 45% with a low overall satisfaction.[70] In addition to this low success rate, a prospective multicentre study showed 1.5% incidence of serious non-fatal complications and a mortality rate of 0.2%.[71] Post-operative pain is a constant complaint after UPPP and patients should be warned about it.[72] Exacerbation of sleep apnoea and respiratory obstruction have been reported in the perioperative period as a result of the use of sedatives, muscle relaxants or post-operative pain management.[73] This early post-operative airway compromise might also be related to the resultant oedema of the tissues and it was noted to be directly proportional to the severity of sleep apnoea.[74] The most common late complication following UPPP is velopharyngeal insufficiency (28.5%),[75] which is related to scarring and excessive palatal resection.[76] Other complications include bleeding (0–6%), dry throat (10%), infection (0–10%), and swallowing problems (0–9%).[77, 78]

Potentially, UPPP might compromise the future use of nasal CPAP therapy because of the loss of the soft palate seal resulting in excessive mouth air leak. Mortimore et al. reported that patients after UPPP significantly tolerated less pressure and their compliance was poorer than sleep apnoea patients without UPPP.[79] The face mask CPAP has provided a solution to this issue but its compliance is worse than nasal CPAP.

Because of these associated complications, alternative approaches have been introduced.

Laser-assisted uvulopalatoplasty

Laser-assisted uvulopalatoplasty (LAUP) refers to a number of different techniques involving the use of the laser to the soft palate for the treatment of snoring. The first technique was described by Kamami in 1990, using a CO_2 laser to create vertical trenches in the soft palate (up to 2 cm) on either side of the uvula followed by partial vaporization of the uvula.[80] Numerous modifications of this technique were described using it, in single or multistage fashion, to stiffen the soft palate.[81–84] The second technique was introduced by Ellis in 1993, using an Nd-YAG laser to remove a 1.5 cm wide central longitudinal strip of mucosa from the whole length of the soft palate followed by excision of the uvula at its base.[85] Other modifications were described, extending the excised part of the mucosa, with or without using flaps of the palate, performed under local or general anaesthesia.[86–88] The aim of LAUP is to invite scarring to the soft palate, making it stiffer to minimize snoring due to palatal flutter.

The post-operative pain is worse than UPPP, with the peak reached on the 3rd post-operative day and it takes up to 15 days to resolve completely. The short-term success rate is 79%, dropping to 55% in the long term.[89–91] Other complications reported were haemorrhage (2.12%), local fungal infection (0.53%), temporary palatal incompetence (0.53%), temporary loss of taste (0.27%)[90] and globus type symptoms.[92] It has no significant impact on smell and taste.[93]

In a recent systematic review,[94] only two randomized controlled trials[95, 96] were found, with no significant difference between LAUP and controls in the treatment of snoring with or without mild sleep-related disorders. It was reported that some simple snorers developed mild OSA following LAUP. This might be related to increased palatal fibrosis, contraction of the velopharyngeal space and reduction of the space between the posterior pillars.[97]

Radiofrequency tissue volume reduction/thermal ablation (CAUP)

This technique employs the use of low frequency radio waves, delivered into the submucosal tissue with the tip of a wand, to create a channel of charged ions that heats the tissues, causing denaturation of the proteins and cell lysis at low temperatures (60–90°C). This destroys specific areas of tissue with minimal collateral damage to tissues, inviting scarring to the muscle layer, reducing its volume and making it stiffer.[72, 98, 99] Three radiofrequency devices are available: the Somnus unit;[99] the Celon device;[100] and the coblator unit.[101]

The main advantages of this technique are that it can be carried out under local anaesthesia and used at multiple levels. For the soft palate, using the somnus device, three channels are made in each side of the soft palate in addition to two lesions in the paramedian position with the entry point just distal to the junction between the hard and soft palate. However, with the Celon device, which uses bipolar technology, more than three applications to the soft palate can be made. A special technique called coblation assisted upper airway procedure (CAUP) was described by Tvinnereim et al.[46] This consisted of making a lateral palatal incision on each side, ablating three upward channels on each side of the midline (fan-shaped) into the soft palate, performing a partial uvulectomy with two upward channels in the uvula and finally channelling of the anterior and posterior pillars and the tonsils if they are present. Multilevel therapy of the palate, base of the tongue and tonsils was described, with a 33% improvement in OSA patients.[101] The long-term success rate of radiofrequency treatment to the palate was found to be 37%.[102] A recent review reported better visualization of the tongue base for the application of the probe by applying simultaneous pressure over the mylohyoid and the thyroid cartilage.[103] It also emphasized the point that general anaesthesia may be the preferred option if multilevel application of radiofrequency is needed to treat the soft palate and the tongue base simultaneously.

In general, radiofrequency treatment is associated with less pain than UPPP or LAUP. Complications reported after radiofrequency tissue ablation of the soft palate included haemorrhage, infections and velopharyngeal fistula in single cases.[72, 103, 104] For radiofrequency ablation of the base of the tongue, studies showed incidence of infections or tongue abscesses in 0–8% of patients, with few cases of temporary tongue base neuralgias.[105, 106] Single cases of mouth floor oedema and severe tongue swelling, and a case of pseudo-aneurysm of the lingual artery and heavy bleeding 14 days after surgery have also been reported.[105, 106]

Transoral robotic surgery for tongue base

A recent development in the surgical management of OSA is the use of da Vinci robot, allowing transoral robotic surgery (TORS). This is being utilized for patients with severe OSA who have failed CPAP treatment and persistent hypopharyngeal obstruction following experiences in tongue base malignancy.[107]

A minimally invasive telerobotic system allows excellent 3D visualization, immaculate precision and absence of tremor. This improved access allows oropharangeal enlargement anteriorly through tongue base reduction and treatment of inward inspiratory collapse of a floppy epiglottis, aryetenoids and aryepiglottic folds. Vicini et al.[108] present their preliminary outcome data at 3 years, demonstrating a polysomnogram success rate (post-op apnoea hypopnea index < 15) of approximately 80%. No emergency post-operative interventions were required and good functional results in pain, swallowing and quality of life were displayed.

The surgery was, however supplemented with multiple other procedures in the case series, including septoplasty, UPPP, supraglottoplasty, turbinate reduction and ethmoidectomy. Similarly, another case series[109] presents favourable outcomes using a transoral robotic technique in combination with palatal surgery. The potential confounding factors of these additional procedures presents us with a difficulty in interpretation of these results, yet additionally places further value on the evolving concept of multilevel surgery when the outcomes are reviewed.[110] The peri-operative management for these patients varies between centres but increasing experience in the technique and knowledge of the potential complications has led to a drive away from a prophylactic or 'covering' tracheostomy as standard part of the patient pathway.

Lin et al.[111] demonstrate the use of a TORS technique in isolation for tongue base obstruction, excluding patients who received additional forms of upper airway alteration. This case series is small, with only 12 patients, yet a statistically significant reduction in AHI is demonstrated from this preliminary data.

A robotic surgical approach to hypopharangeal obstruction is likely to be applicable to a small subset of patients with severe obstructive sleep apnoea. Present case series analysis suggests that, for adequately selected individuals, a robotic approach may yet prove an appropriate treatment modality within specialist centres with the requisite equipment and experience.

Less performed procedures

CAUTERY ASSISTED PALATAL STIFFENING OPERATION

Cautery assisted palatal stiffening operation (CAPSO) involves the use of an electrocautery needle to remove a 2 cm inverted 'U' area of mucosa from the soft palate, in addition to the mucosa and part of the uvula. It is left to heal by secondary intention to stiffen the soft palate.[112] There are no controlled studies to evaluate this technique, but the few studies there are suggest a success rate similar to UPPP, with minimal complications.[113]

INJECTION SNOREPLASTY

The injection of 2 ml of a sclerosing agent in the midline of the soft palate above the base of the uvula was reported to invite enough scarring to make it stiffer. In the literature, 3% sodium tetradecyl sulphate, 50% ethanol and doxycycline were used in selected patients. The procedure is performed in the outpatient setting under local anaesthesia and can be repeated within 2 years if it does not improve the snoring. Although two cases of palatal fistulae were reported, they healed spontaneously and no other complications were noted.[114]

PILLAR IMPLANTS

In this technique the palatal stiffening is achieved by the implantation of woven Dacron mesh into pockets dissected in the soft palate.[115] A systematic review of four studies showed subjective improvement in VAS scores up to 53%, but no significant difference was reached in any objective snoring indices. It is associated with mild pain with a rate of extrusions of 0–11%.[116]

MANDIBULAR AND MAXILLARY SURGERY

A number of procedures were described in the literature aimed at dilating the hypopharynageal airway, including genioglossus advancement, tongue base suspension suture, hyoid suspension, maxillomandibular advancement and laser midline glossectomy. Most of the reports describing these procedures are pilot studies with no standardized comparison of other techniques used in the treatment of OSA. The reported success rate of some of these procedures approaches 60% in the short term. These procedures are associated with relatively high complication rates, such as swallowing problems, taste change, tongue oedema, tooth numbness and mandibular fractures. The midline laser glossectomy was associated with a high incidence of post-operative bleeding.[117]

TRACHEOSTOMY

Surprisingly enough, tracheostomy was the first surgical intervention in patients with OSA even before the disease was fully recognized. In 1980, Guilleminault et al. reported the long-term results after tracheostomy as a single intervention for OSA with resolution of the clinical symptoms and return to full activity.[118] However, the advent of the above mentioned surgical interventions have meant that tracheostomy is rarely indicated for the management of OSA. The American Academy of Sleep Medicine (AASM) has published a recent update on practice parameters for the management of OSA, emphasizing that tracheostomy should be considered only when other options do not exist, have failed or are refused, or when this operation is deemed necessary by clinical urgency.[119]

HYPOGLOSSAL NERVE STIMULATION

Experimental research in both humans and animals has demonstrated an increase in pharyngeal neuromuscular activity during sleep in obstructive sleep apnoea patients but at an insufficient level to overcome airway collapse. As such, there has been a focus on selective stimulation of upper airway dilator muscles (e.g. genioglossus) to improve airway patency without arousing patients from sleep. An implantable neurostimulator to synchronize hypoglossal nerve stimulation with inspiration has shown early promise in a single arm feasibility study.[120, 121] Twenty-one patients were recruited with moderate to severe OSA who had failed to tolerate CPAP. A significant decrease in OSA symptomology and in-laboratory polysomnography was established at 6 months post-implantation. Two device-related 'serious' adverse events occurred in this cohort, necessitating removal or replacement. Long-term safety and efficacy of this treatment warrants further clinical evaluation but it remains a treatment modality with high expectations for future benefit given the technological advances in this area.

CONCLUSION

Patients with sleep-related breathing disorders are best dealt with using a multidisciplinary approach. Lifestyle changes, appliances and surgical intervention are all treatment modalities that are available for these patients and a combination of these treatment options may be required to adequately resolve their problem. Thorough assessment and careful patient selection, particularly for surgical treatment, is essential for a successful outcome.

KEY POINTS

- Treatment of sleep-related breathing disorders require a multidisciplinary approach.
- Lifestyle changes and appliances should be utilized before surgery is considered.
- Careful patient selection for surgery is necessary.
- SNE is useful in tailoring site-specific treatment.
- Multilevel problems are very commonly seen therefore multilevel surgery may be required.
- It may be necessary to use appliances in conjunction with surgery.

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CHAPTER 76

LARYNGOTRACHEAL STENOSIS IN ADULTS

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: stenosis, subglottis, laryngotracheal, reconstruction, resection, tracheal, granulomatosis, vasculitis, sarcoid, bilateral, cord and stents.

INTRODUCTION

The upper aerodigestive tract, larynx, trachea and bronchi form the conduit between the external environment and the lungs to facilitate gas exchange. The larynx acts to protect the airway from aspiration during swallowing. It is the primary organ for phonation but also provides important sensory feedback and movements that are critical to the control of ventilation. The narrowest site of the adult airway is the glottis, whereas in infants it is the subglottis.

In the middle of the last century, the discovery of antibiotics and the ability to ventilate patients for prolonged periods meant that infections were no longer the principle cause of laryngotracheal stenosis (LTS). A period of ventilation on the intensive care unit (ICU) is now the most common cause of laryngotracheal injury and stenosis. Approximately 50% in our series of adult airway stenosis is post-intubation (**Table 76.1**, authors' series) and this figure is higher in children.[1] Risk factors include duration of ventilation, sizing of ventilation tubes, excessive cuff pressures, irritation from orogastric secretions, infections, immune disturbance and the patient's response to injury and healing biology.

Abnormal narrowing of the laryngotracheal complex causes breathlessness, especially during physical activity, and retention of pulmonary secretions may lead to lung infection or collapse. Laryngeal stenosis can also interfere with phonation and a dysfunctional larynx can impair swallowing safety. The exact physiology of dyspnoea is not known but the extra effort of breathing, tendency towards carbon dioxide retention and afferent signals from the respiratory tract must play a part.

TABLE 76.1 Aetiology of laryngotracheal stenosis in 600 consecutive referrals to the National Centre for Airway Reconstruction

50.3% Acquired laryngotracheal stenosis	• 34.3% subglottic stenosis • 16% tracheal stenosis
16.67% Bilateral vocal cord mobility impairment	(Nerve injury, scar/fixation, rheumatoid arthritis)
10.0% Wegener's granulomatosis	
8.67% Idiopathic subglottic stenosis	
5.70% Supraglottic stenosis	(2.7% sarcoid, 3.0% other)
2.33% Previous papillomatosis treatment	
2.33% Glottic web	
1.33% Tracheomalacia	(0.67% relapsing polychondritis)
1.17% Vascular lesion	
0.83% Amyloidosis	
0.67% Subglottic stenosis congenital	

Although the incidence of post-intubation LTS is unknown, one series reports significant airway injury in 47% of patients bronchoscoped at extubation.[2] Long-term airway compromise has been estimated at between 1% and 4%.[3–6] This means that the initial fibro-inflammatory injury appears to resolve in the majority of cases and only in some patients, through healing by fibrosis and wound contracture, does it lead to persistent airway narrowing. However, it is also possible in the absence of high quality follow-up data that some patients live with dyspnoea after the ICU and their LTS is never diagnosed.

PATHOPHYSIOLOGY OF LARYNGOTRACHEAL STENOSIS

In laminar airflow, airway resistance is dictated by the diameter of the airway and by the density of the inspired gas (Poiseuille's law):

$$R = \frac{8nl}{\pi r^4}$$

where:

- R = resistance
- n = viscosity
- l = length
- r = radius.

The resistance to airflow, by a stenotic segment of airway, is proportional to its length but inversely proportional to the fourth power of its radius. Turbulence, although difficult to calculate, is also inversely proportional to the airway diameter and will further add to resistance to airflow.

During inspiration, the intrathoracic airways expand along with the expanding lungs. However, the extrathoracic trachea will have a reduced lumen during inspiration because the intraluminal pressure is lower than atmospheric. The reverse happens during expiration. A variable obstruction of the airway also changes size with breathing. Hence, an extrathoracic variable tracheal stenosis will limit inspiration whereas an intrathoracic variable lesion will limit expiration. A fixed obstruction, whether intrathoracic or extrathoracic, will limit peak airflow on inspiration and expiration in equal proportions and produce a characteristic flow volume loop (**Figure 76.1**).

DIAGNOSIS

Diagnosis of LTS starts with the history. Previous prolonged ventilation, duration of shortness of breath and coexisting medical problems such as vasculitis or sarcoidosis are relevant. Symptoms of dyspnoea, voice changes and chronic cough are common but questions should also be directed to determine impairment of swallowing function and history of laryngopharyngeal reflux.[7] Exertional dyspnoea is the main symptom and patients compensate by reducing their physical activity. Patients can compensate over time for chronic progressive airway stenosis whereas the same level of stenosis occurring acutely may result in significant disability and even death. Chronic airway obstruction is sometimes misdiagnosed as asthma or chronic obstructive pulmonary disease.

Examination should document the severity of stridor, chest recession, body morphology (body mass index) and neck scars. Fibre-optic nasal endoscopy will help assess vocal cord mobility, evidence of laryngopharyngeal reflux, pooling of secretions in the hypopharynx and the degree of stenosis if it lies within the larynx or cervical trachea. If a tracheostomy is in place, the lower airway can also be assessed with the same flexible endoscope and sometimes a retrograde examination of the subglottis is also possible if the patient will tolerate temporary removal of the tracheostomy tube.

Investigations include imaging using high definition tomography (CT) but care should be taken when interpreting these scans. As the scans reconstruct the image from 'cuts' taken at intervals, if these cuts miss the apex of the stenosis than they will underestimate or even miss the problem. Conversely if there are secretions over the stenosis then overestimation of stenosis may occur. Respiratory function testing is essential to determine the severity of airway compromise but also to monitor the response to treatment. The minimal requirement is spirometry and flow

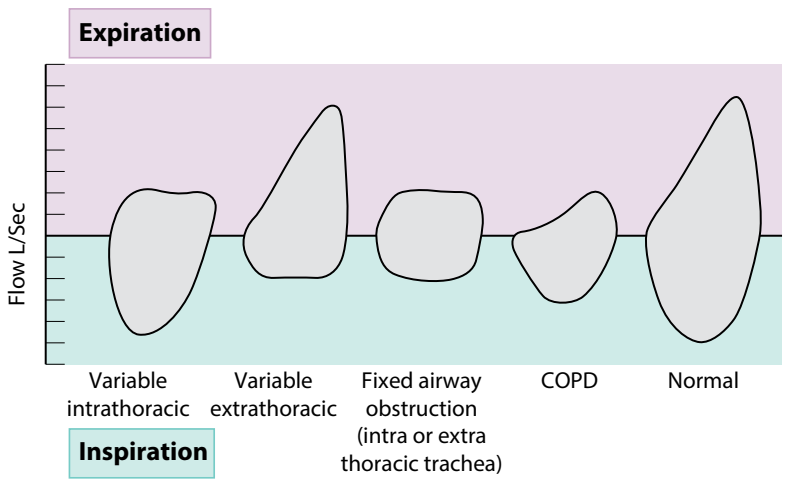


Figure 76.1 Characteristic flow volume loops. (Left to right): soft intrathoracic stenosis, soft extrathoracic stenosis, fixed stenosis anywhere in larynx or trachea, chronic obstructive pulmonary disease and a 'normal' flow volume loop.

volume loops and ideally cardiopulmonary exercise testing. If there is any evidence of disordered swallowing, then fibre-optic endoscopic evaluation of swallowing (FEES) or videofluoroscopy is essential. There are poor outcomes reported in patients with even minor aspiration, following airway reconstruction.[8] Although the majority of our patients are prescribed antireflux advice and therapy (once or twice daily proton pump inhibitor with an alginate suspension after the evening meal), it is still of value to investigate for laryngopharyngeal reflux in the symptomatic patient in case antireflux surgery is indicated.

Patients with airway stenosis must be managed by a multidisciplinary team that includes an ENT and thoracic surgeon, pulmonologist, anaesthetist, radiologist, pathologist and speech and swallowing therapist as well as a dietician. Bariatric services should also be available as there is an increase in the resting metabolic rate in obesity as well as decreased respiratory performance and exercise tolerance. Outcomes of airway surgery are also poorer in the overweight patient.[8]

INTRA-OPERATIVE ASSESSMENT OF POST-INTUBATION LARYNGOTRACHEAL STENOSIS

Paediatric LTS is a well-researched area of otolaryngology. Paediatric LTS nearly always involves the subglottis[9] and prolonged endotracheal intubation is by far the most common cause. Treatment strategies include airway augmentation with rib grafts as well as tracheal and cricotracheal resections. The lesional anatomy and pathology behind paediatric LTS differs greatly from the adult group. Adult LTS has been poorly researched and the surgical options include tracheostomy, tracheal resection or cricotracheal resection.[10] Some surgeons still use primary cartilage grafts to augment the adult airway. There appears to be poor appreciation of the fact that there is a high incidence of ischaemic necrosis of primary rib graft in adult patients.[11] Furthermore, the quality and quantity of rib cartilage that can be harvested diminishes with age.

The definitive airway assessment is airway endoscopy. Endoscopic airway assessment is performed by respiratory physicians, thoracic surgeons and otolaryngologists. Pulmonologists and thoracic surgeons are usually trained to use both flexible and rigid bronchoscopes. Flexible bronchoscopy is most commonly performed in the spontaneous breathing and sedated patient who has had topical anaesthetic applied to the upper aerodigestive tract. This technique allows assessment of the dynamic airway, the trachea and bronchi with the ability to perform the full spectrum of interventions. However, with a flexible bronchoscope placed through a narrow stenosis, the patient's airway can become obstructed. Attempted airway dilatation also leads to temporary airway obstruction. Use of the rigid ventilating bronchoscope requires the patient to be paralyzed and ventilation maintained by a face mask, laryngeal mask or endotracheal tube until the bronchoscope is inserted. For assessment of the airway beyond an area of stenosis, the rigid bronchoscope may need to be forced through the stenosis. This has the effect of dilating the stenosis, but also causes stripping of the mucosa. Neither flexible nor rigid bronchoscopy allows prolonged access or endoscopic surgery on the larynx or subglottis. The otolaryngologist is able to utilize suspension microlaryngoscopy, with supraglottic high frequency jet ventilation, in a patient receiving total intravenous general anaesthesia. The microscope provides binocular vision (hence depth of field), better illumination, two hands free for surgery and use of the carbon dioxide laser using a line-of-sight technique. The laryngoscope also allows the use of rigid and flexible endoscopes, fibre lasers, pulmonary balloon dilators, microdebriders and stents. In the event that the patient's oxygen saturations 'dip' an endotracheal tube can be passed via the larynx to achieve positive pressure ventilation. The endotracheal tube is removed to allow completion of airway surgery.

It is important at endoscopy to assess vocal cord mobility and map the stenotic segment. The tip of the endoscope is placed at the lower end of the stenosis and a mark is placed on it at the level of the mouth of the laryngoscope. The endoscope is withdrawn so that its tip lies at the top of the stenosis and again so that its tip lies at the level of the glottis. Each of these points is marked and, with the use of a ruler, the length of the stenosis and its distance from the glottis can be determined. There are techniques for accurately calculating the size of the airway at the level of the stenosis;[12] however, for most purposes the Myer–Cotton grading system[13] allows stratification of airway stenoses to plan treatment (**Figure 76.2**).

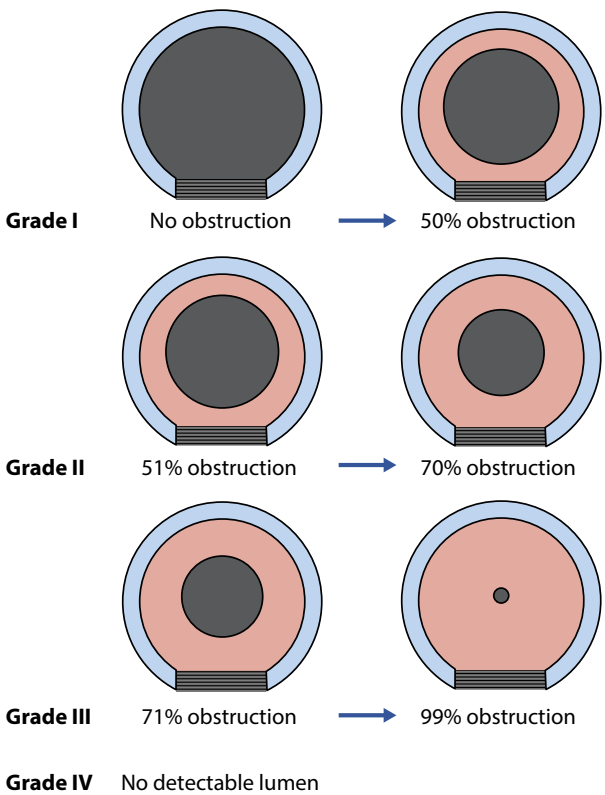


Figure 76.2 Myer-Cotton grading system for subglottic stenosis.

Although the first endoscopy is a staging procedure, some form of surgery is usually possible. Through a combination of imaging (CT) and endoscopy, a decision needs to be made as to whether there is significant damage to the cartilaginous support of the airway at the site of the stenosis. If this is the case then an endoscopic approach, including stenting, will only bring temporary relief of symptoms and an open surgical approach, such as a tracheal, or cricotracheal, resection or laryngotracheal reconstruction (LTR), needs to be considered.

SURGERY FOR POST-INTUBATION LARYNGOTRACHEAL STENOSIS

The majority of patients with post-intubation LTS start with an airway injury that is inflammatory or fibro-inflammatory (**Figure 76.3**).

These types of injury respond well to an endoscopic approach.[14] Using suspension laryngoscopy and supraglottic jet ventilation, up to three millilitres of Depo-Medrone (40 mg/ml) can be injected into the stenosis. Three to four radial cuts are then made into the stenosis using a carbon dioxide laser (8–10 watts) delivered through the operating microscope. The lesion is then dilated, using a pulmonary balloon dilator system, to the size of the adjacent normal airway.

More commonly, at presentation, the majority of cases of airway stenosis have already evolved into mature fibrotic lesion. Intralesional steroids are of limited value if the cartilaginous framework of the airway is intact; in this scenario, an endoscopic approach using radial laser cuts, balloon dilatation and topical mitomycin-C application may still be effective. The procedure usually needs to be repeated every 3–4 weeks until the airway has stabilized. By the third procedure, it is clear to the surgeon if the technique is going to work or whether an open procedure needs to be considered. Overall the endoscopic approach is successful in approximately two-thirds of cases of post-intubation LTS.[14] Failure occurs in cases of significant cartilage framework damage, stenosis length greater than 3 cm, obesity and in patients with swallowing impairment who tend to have persistent airway inflammation. The options are then tracheal (**Figure 76.4**) or cricotracheal resection. Unfortunately, in the adult patient, the maximum length of resection possible is 4–6 cm even with laryngeal and pulmonary release procedures.[15]

SURGERY FOR POST-TRACHEOSTOMY AIRWAY STENOSIS

A less common variant of post-ventilation tube related tracheal stenosis is seen in a small number of tracheostomy patients. This is probably due to over-resection or fracturing of anterior tracheal rings during insertion of a tracheostomy. At decannulation, there is scarring and contracture at the stoma site, which pulls in the lateral tracheal ring remnants leading to a 'lambda-shaped' stenotic deformity and airway compromise. The lesion usually extends over 1–2 tracheal rings with a normal proximal and distal trachea.[16] The trachealis is not involved and there is usually a small anterior bridge not contributing to the stenosis (**Figure 76.5**). Tracheal resection and anastomosis has been recommended for this condition,[17] but this is a major operation with associated morbidity and a small mortality rate.

The lesion can be treated using a CO_2 laser, delivering 8–10 W superpulsed, deployed through a micromanipulator attached to the microscope using a 'line-of-sight' technique. The proximal and distal trachea is used to guide the limits of the resection and the encroaching cartilage is vapourized. A pulmonary balloon dilator may be used to expand the airway. The mucosa over the trachealis and the apex of the Lambda must be preserved, as a circumferential injury with the laser will risk re-stenosis. The patient is usually discharged from hospital the following day with a short course of broad-spectrum antibiotic. The airway is

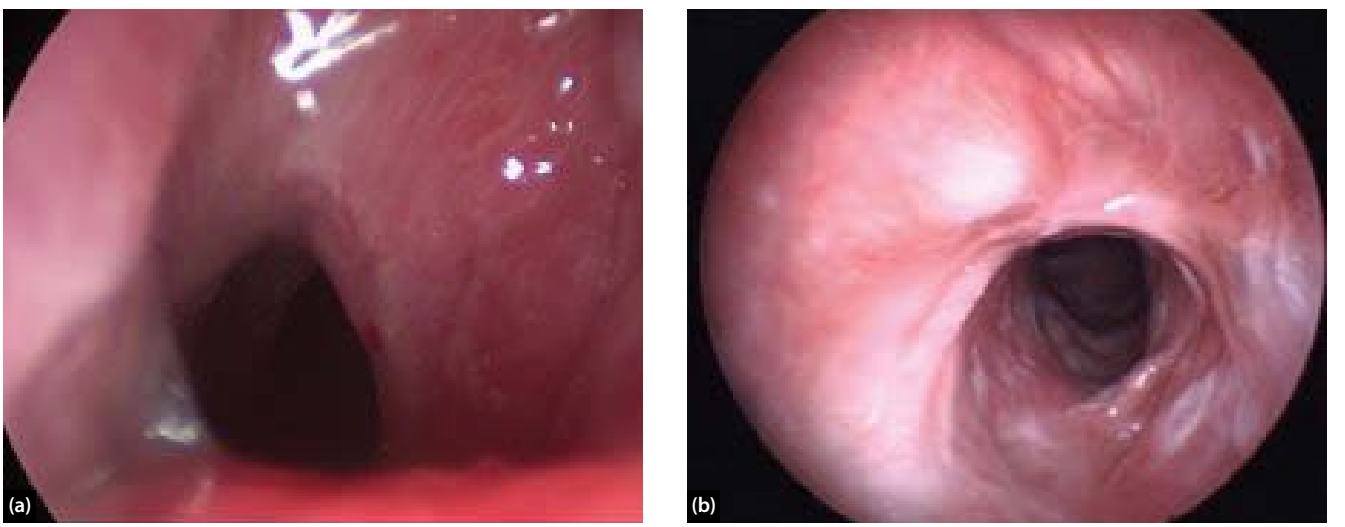


Figure 76.3 A very inflammatory airway stenosis as seen immediately post extubation (a). Stenosis has evolved to be more fibro-inflammatory **(b)**.

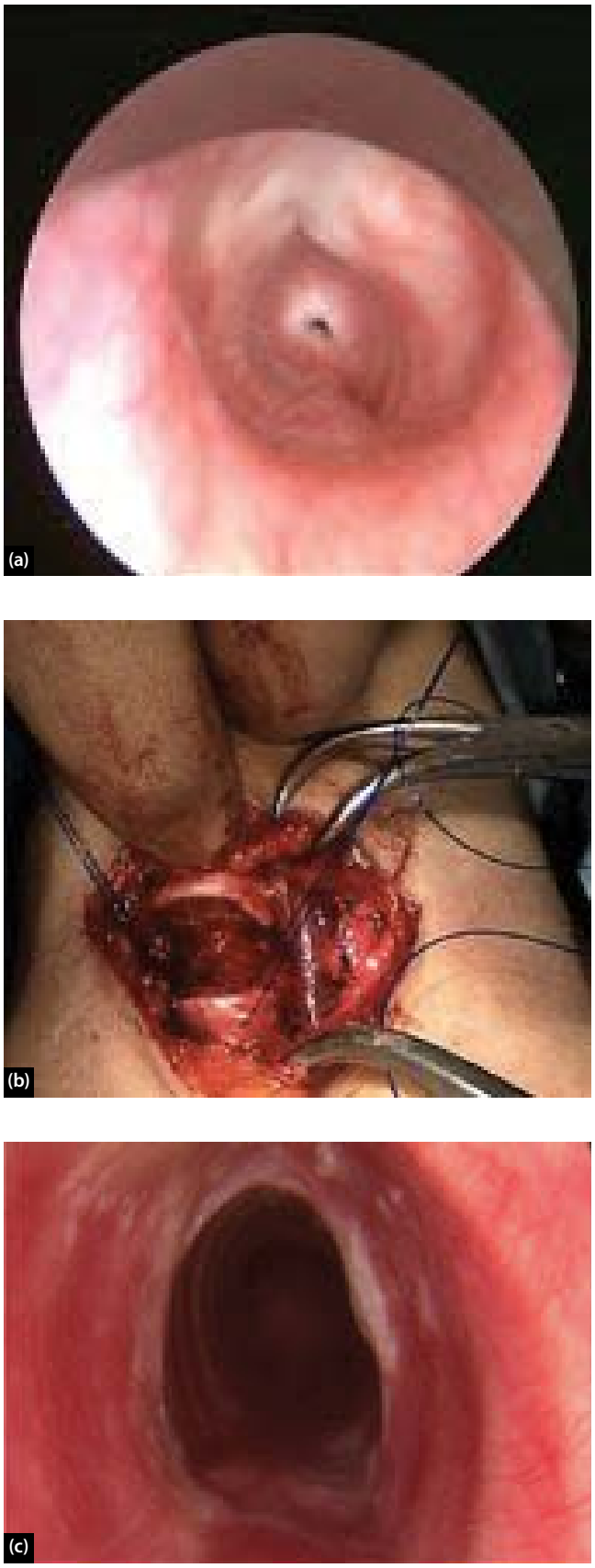


Figure 76.4 A cervical tracheal stenosis that is mature and fibrotic but also with loss of cartilaginous support (a). During a tracheal resection before anastomosis **(b)**. The same patient a few weeks after tracheal resection **(c)**.

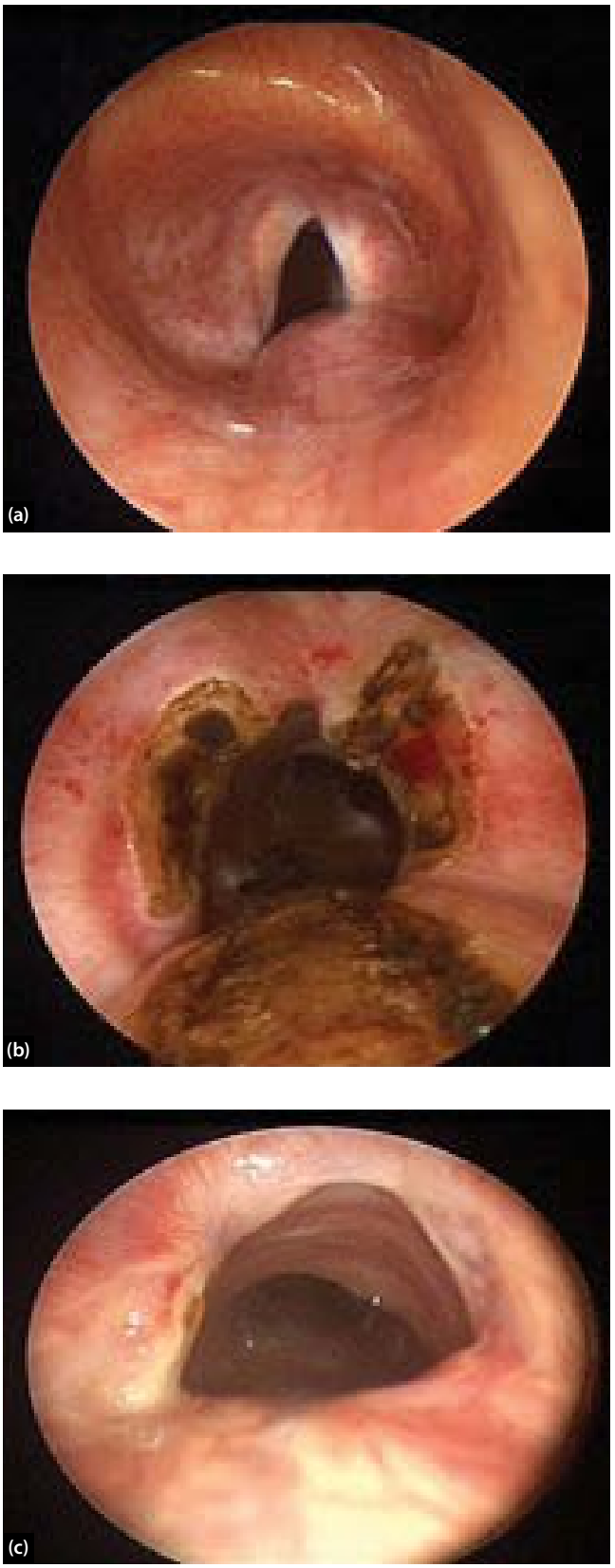


Figure 76.5 'Lambdoid' tracheal stenosis following decannulation (a). Intra-operative view after resection of tracheal cartilages with the CO_2 laser **(b)**. The bulging trachealis is managed with a gentle surface laser. Note bridges of normal mucosa between each site that is lasered. The same patient 3 months after surgery **(c)**.

reassessed, in theatres, at 3–4 weeks. Any residual cartilage or granulation is removed. It is unusual for a patient to require more than three endoscopic interventions for this condition. In these circumstances an open approach to tracheal resection should be considered.

TRACHEOBRONCHIAL STENTING

Charles Thomas Stent was a British dentist in the late 19th century. He developed dental impression material that was used as a template to support skin grafts for repair of oral trauma. Today, the term is used to describe devices for maintaining the patency of tubular structures, including the tracheo-bronchial tree. There is currently a variety of silicone and expandable metal stents for the airway (**Figure 76.6**). The metal stents can be uncovered, covered or partially covered (hybrid). Wire stents tend to be covered with polyurethane, although Teflon sheeting is used in some designs. The next generation of stents will be reabsorbable or bioengineered in other ways, negating the need for subsequent removal.

In benign and malignant disease, stents have been used to palliate the effects of large airway obstruction caused by extrinsic compression, endoluminal disease or loss of cartilaginous support. Indications in benign disease include long length stenoses, failed previous repair, patient comorbidities that restrict reconstructive surgery, or patient preference. Stents are also used temporarily following airway surgery.

Although patients with metal stents enjoy immediate palliation of symptomatic tracheal stenosis, metal stents are associated with a high incidence of obstruction with granulation.[18] They are also susceptible to metal fatigue and fracture over time. The authors recommend that uncovered or hybrid metal stents should only be used in a select group of patients with a short life expectancy.[19] If these stents are not removed within the first few weeks of deployment, they become a permanent fixture in the airway. They can fragment over time and cause granulation and bleeding. Silicone stents are easier to remove but have a higher incidence of migration unless sutured in place.[20] There is a high incidence of bacterial colonization of all stents, which can lead to granular tissue formation,[21, 22] the most common organisms being *Staphylococcus aureus* and *Pseudomonas aeruginosa*. It is widely accepted that wire stents have a higher incidence of granulation formation, especially at their ends. Some authors report that silicone stents have a higher incidence of mucus plugging than wire stents.[18] However, this experience largely relates to the use of stents in the bronchi. In the upper trachea, biofouling and mucus plugging is much greater in wire stents than in silicone stents. This may be due to the relative lower humidity in this area. The incidence of stent migration is widely reported as being higher in the subglottis than in the remainder of the tracheo-bronchial tree. The reason for this appears to be due to the fact that the subglottis is a fixed structure, without the expansion allowed by trachealis.

Usually silicone stents usually have to be placed under general anaesthesia, using a ventilating rigid bronchoscope. The authors use a technique of suspension laryngoscopy with supraglottic jet ventilation and placement of a silicone stent with rigid stent forceps. Visualization is assisted by a 0 degrees, 30 cm Hopkins optical endoscope, which is 4 mm in diameter or a flexible bronchoscope. Wire stents arrive preloaded in delivery devices and can be passed parallel to a flexible bronchoscope



Figure 76.6 Left of image is a silicone stent fashioned from the vertical limb of a T-tube that has to be stitched into the airway. Centre left is a fully covered wire stent. Centre right is a silicone stent with external studs, which are to prevent migration. On the right is a covered mesh stent where the mesh is also made from a plastic polymer.

in a spontaneously breathing, sedated patient, or using fluoroscopic screening techniques. Wire stents can also be inserted under general anaesthesia. Stent removal is easiest using a general anaesthetic technique. This allows the use of rigid biopsy or grasping forceps to firmly grip the stent even if embedded in granulation. Uncovered wire stents that have been in place more than 3 months will usually require an open surgical approach for removal.[18]

Post-operatively, all patients with stents are prescribed daily saline nebulizers. Carbocysteine is added in those patients where there is evidence of mucus plugging.

IDIOPATHIC SUBGLOTTIC STENOSIS

Idiopathic subglottic stenosis (ISS) is a rare, slowly progressive, fibro-inflammatory process of unknown aetiology, leading to narrowing of the airway in the subglottis but also involving the first and second tracheal rings. Embryologically, there does not appear to be any developmental significance to this anatomical site, although it is an area of intense immune activity. ISS should strictly be called idiopathic LTS as it involves the proximal trachea and can extend up to the glottis.

It occurs predominantly in post-pubertal women, but has been reported in males,[23–26] and the majority of reported patients are Caucasians. The diagnosis is one of exclusion. The condition must follow the anatomical description above. There must be no history of intubation or tracheostomy in the last 2 years, no neck trauma or surgery and no neck radiotherapy. In each case, the antineutrophil cytoplasmic antibody (ANCA) and angiotensin converting enzyme (ACE) tests have to be repeated at intervals and prove negative. Tissue for histology is also sent at each surgical procedure to rule out other inflammatory conditions or a low-grade neoplasm.

The treatment approach varies from cricotracheal resection to repeated endoscopic procedures. The majority of patients can be managed with endoscopic airway surgery once or twice a year as described below. Examination under anaesthesia, using suspension laryngoscopy, supraglottic jet ventilation and rigid endoscopes, allows for the dimensions of the lesion to be determined. Up to 3 mL of methylprednisolone acetate is injected into the lesion using an appropriate needle. Three or four radial incisions are made into the lesion using the carbon dioxide laser set at 8–10 Watts. This laser is deployed through a micro-manipulator attached to the operating microscope. Following these radial cuts, the lesion is dilated using a pulmonary balloon dilatation system and the lesion is dilated to 15–16 mm (**Figure 76.7**). A deep tissue biopsy is taken at this stage using microcup forceps and haemostasis is achieved using topical adrenaline.

Aggressive laser ablation of the stenosis is not advised as this will risk more severe stenosis recurrence.

Cricotracheal resection has been used to treat this condition with reported good results[24] but others have failed to duplicate these outcomes.[26] ISS is primarily a mucosal disease that overlies healthy perichondrium and cartilage.[27] There is also concern that cricotracheal resection in a condition that predominantly affects females is likely to leave these patients with 'male-type' voices after the surgery.[28] Moreover, cricotracheal resection conceptually treats this condition as a benign neoplasm and, in our series, the disease often extends up to the glottis (**Figure 76.7**, left) and it is difficult to conceive how a resection could be performed within millimeters of the vocal folds without causing damage to this area.

With have described a different approach, which can be used to permanently treat all variations of this condition. A laryngofissure and posterior cricoid split is performed. The majority of the stenosed mucosa is removed and a piece of costal cartilage is placed as a 'spacer' to expand the posterior cricoid split (**Figures 76.8** and **76.9**).

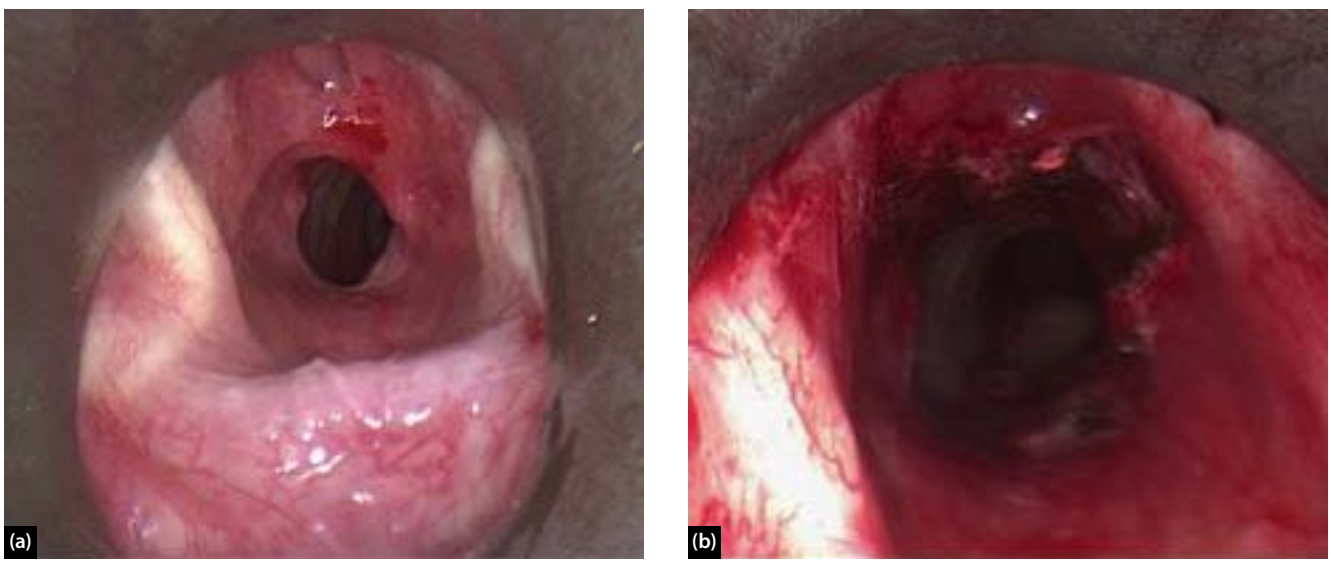


Figure 76.7 Idiopathic subglottic stenosis (a). The same lesion after steroid injection, radial cuts with the CO_2 laser and balloon dilatation **(b)**.

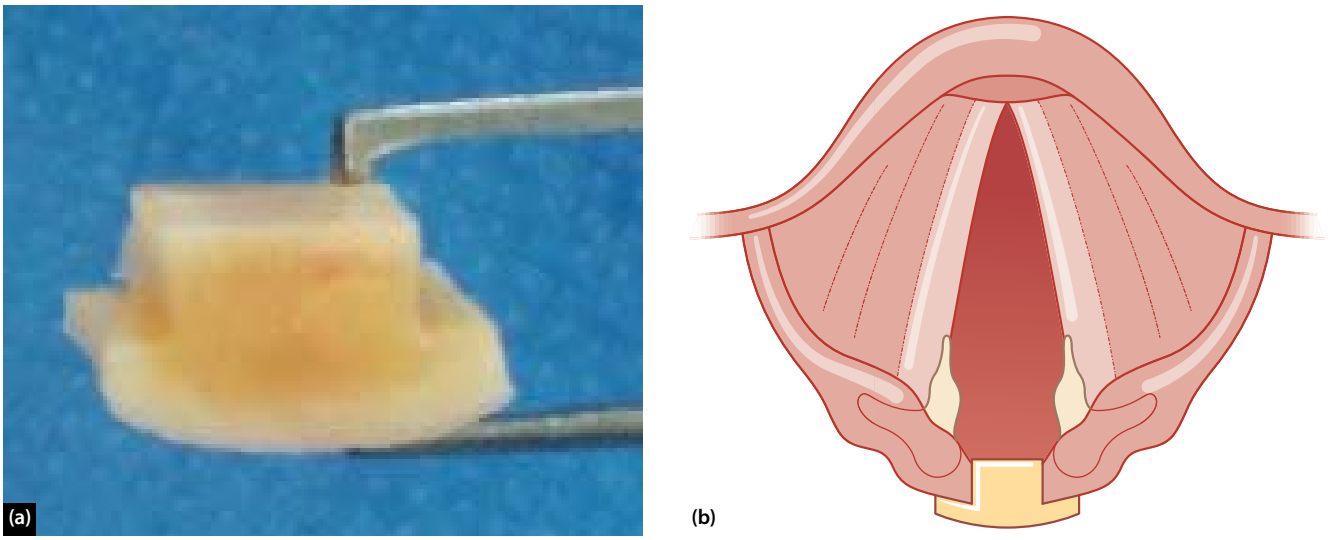


Figure 76.8 A costal cartilage 'spacer' (a), which is placed in a posterior cartilage split through a laryngofissure approach **(b)**.

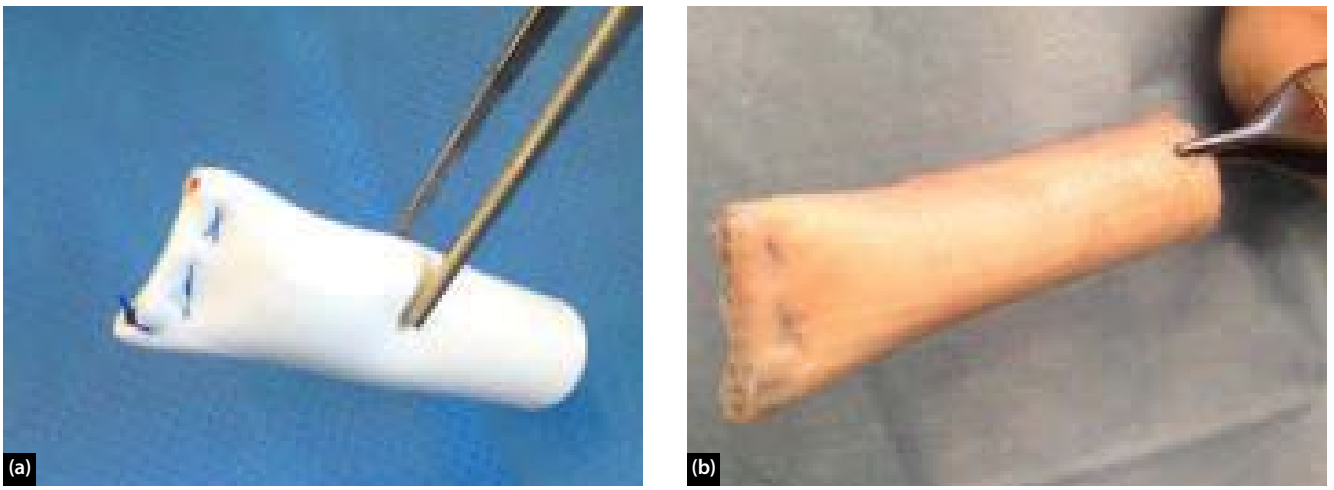


Figure 76.9 A section of silastic T-tube closed at one end with nylon suture (a). The same stent covered with superficial skin graft with epidermis against stent **(b)**.

A closed laryngeal stent, covered with a superficial skin graft is held in place with a single, strong, nylon suture.[20]

A temporary tracheostomy is required because there is no airway through the larynx once the laryngofissure is closed. Two weeks later the stent is removed endoscopically, followed by routine decannulation. The technique appears to work because keratinocytes colonize the parts of the airway where the diseased mucosa was excised and have a strong antifibrotic activity.

MITOMYCIN-C

Mitomycin-C (MMC) is derived from the *Streptomyces caespitosus* bacteria with the ability to modify wound healing at the molecular level and has been used to inhibit post-surgical scar formation. Available since the 1960s as a systemic chemotherapeutic agent in the treatment of solid tumours, MMC was first applied topically for the treatment of superficial bladder tumours. It was first reported in the ENT literature for the treatment of tracheal scarring after tracheal reconstruction in a small case series.[29] Several randomized prospective animal studies have shown impressive results in prevention of postoperative glottic and subglottic stenosis following surgery to the airway.[30–33] Its use in airway surgery has become fairly routine, despite no randomized controlled trials proving its efficacy. The authors have used MMC at concentrations of 1 mg/ml applied topically for 3 minutes in many hundreds of airway cases. Owing to lack of clear evidence of improved outcomes and continuing uncertainty about long-term toxicity we have stopped use of the drug.

GRANULOMATOSIS WITH POLYANGITIS

Granulomatosis with polyangitis (GPA) was formerly called Wegener's granulomatosis (WG) and is an immune disorder characterized by inflammation of small and

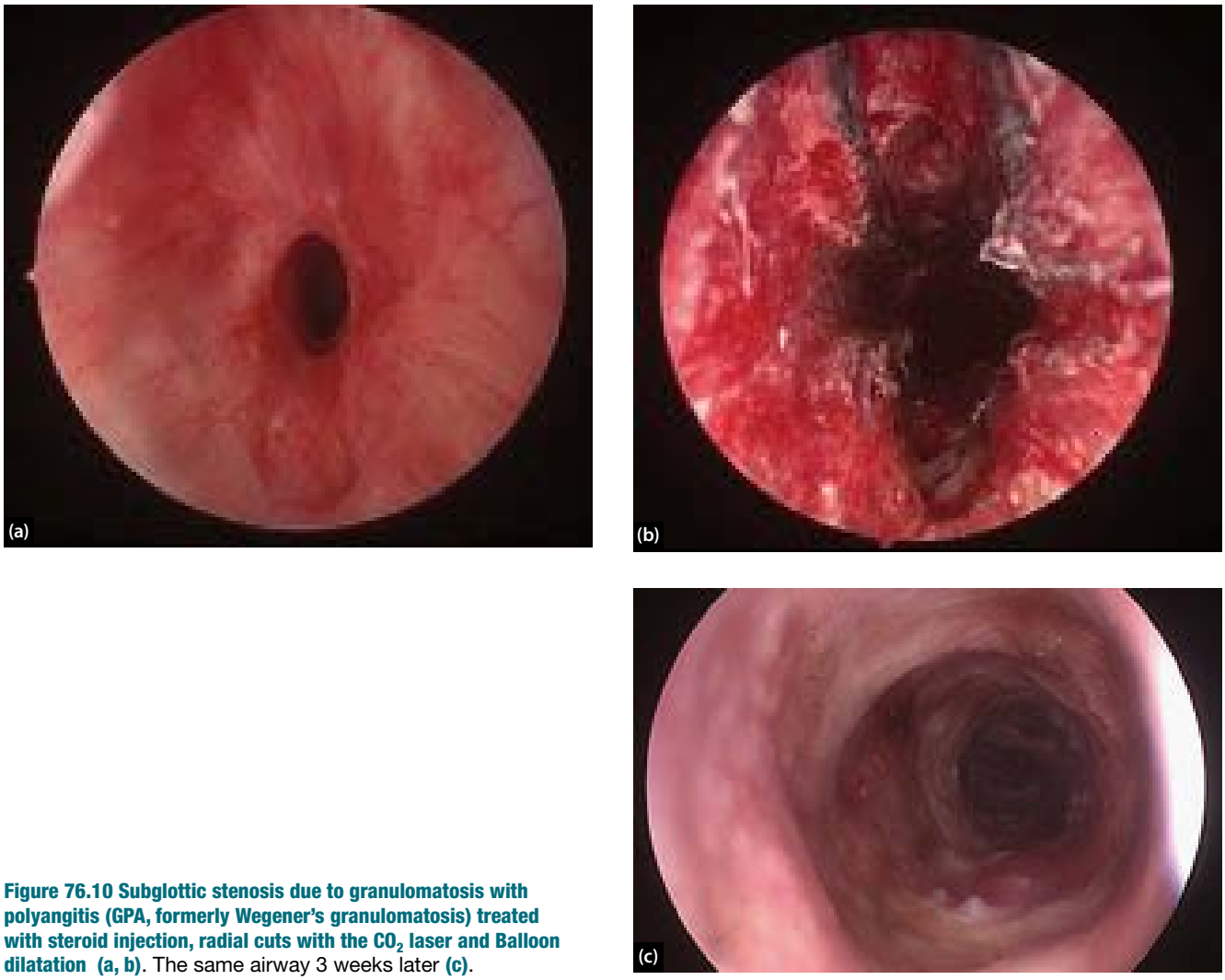


Figure 76.10 Subglottic stenosis due to granulomatosis with polyangitis (GPA, formerly Wegener's granulomatosis) treated with steroid injection, radial cuts with the CO_2 laser and Balloon dilatation (a, b). The same airway 3 weeks later **(c)**.

medium sized vessels. Most patients have some otolaryngological manifestations but also involvement of the lungs and kidneys and there may be an element of renal failure. The presence of a positive cytoplasmic antinuclear cytoplasmic antibody (cANCA) test may aid in the diagnosis, but positivity is not conclusive and negative ANCA results are not sufficient to reject the diagnosis. The diagnosis is sometimes made on clinical presentation when a patient has had the appropriate symptoms for a prolonged period. A definitive diagnosis of GPA can be made by a biopsy of suspicious lesions (demonstrating granulomatous inflammation) in conjunction with positive serological analysis. However, it must be recognized that up to 20% of patients with untreated active GPA lack cANCA[34] or may show positivity later on in the disease history.

Approximately 25% of patients have involvement of the larynx, trachea and bronchi causing localized narrowing. Intra-lesional corticosteroid injections, radiate lesion cuts and dilatation (**Figure 76.10**) will treat the majority of new stenoses.[35]

The use of tracheostomies and long-term stents can lead to airway complications that are difficult to treat.[10, 36]

SARCOIDOSIS

Cesar Boeck of Christiania, Denmark was the first to describe this multi-system disease in 1899.[37, 38] The disease is a non-caseating granulomatosis disorder with a worldwide distribution and can affect any race, ethnicity, gender or age group. Patients are typically aged 20–40 years, and there is a female to male ratio of 2 : 1 and a predilection for black African Americans.[38] Otolaryngologic involvement occurs in < 3% of cases and can occur in isolation or as part of a widespread disease.[39] Laryngeal sarcoidosis may be underdiagnosed and has a variable incidence reported between 1% and 5%.[40–43]

The pathophysiology behind sarcoidosis remains unknown. Current hypotheses propose sarcoidosis to occur in generally susceptible individuals through alterations in immune responses after exposure to various 'triggering' agents. The diagnosis of sarcoidosis depends on the presence of typical clinical features and non-caseating granulomatous inflammation on biopsy of diseased tissue with the exclusion of other known causes of granulomas, including tuberculosis, leprosy, syphilis and fungal disease.



Figure 76.11 Supraglottic larynx in sarcoidosis. Demonstrating epiglottis and aryepiglottic folds 'swollen' with disease. Below is the subglottic jetting cannula in place during suspension laryngoscopy.

Anatomically, laryngeal sarcoid has a predilection for the supraglottic region, particularly the epiglottis, aryepiglottic folds and arytenoids (**Figure 76.11**). The macroscopic appearance of the supraglottis is diffusely thick, oedematous and characteristically pale or pink in colour. These features are considered pathognomonic for this condition.[40] Although exophytic, polypoidal, nodular and granulating lesions have been described, these are less common.[42] Isolated involvement of the glottis is exceedingly rare.[44] Vocal cord paralysis is also reported as a result of perineural invasion or multiple cranial nerve polyneuritis.[40] Laryngeal disease tends to progress slowly with a relapsing and remitting course. Macroscopically laryngeal lesions may appear to persist despite overall remission and this is thought to be due to tissue fibrosis.

High dose systemic steroids have been recommended as the first line treatment of laryngeal sarcoid. Endoscopic laser reduction has been used as a last resort where conservative therapy has failed. Our technique for managing laryngeal sarcoidosis has led to a reduction or cessation of systemic steroids and decannulation in the majority of cases.[45] The procedure is performed using total intravenous general anaesthesia with suspension laryngoscopy and a subglottic or supraglottic high frequency jet ventilation technique. The larynx and airway are visualized using a combination of microscope and a rigid optical endoscope. 1–3 ml Depo-Medrone (methylprednisolone acetate), at a concentration of 40 mg/ml, is injected into the lesion at multiple sites and evenly through its depth, using a microlaryngoscopy injection needle. The end point of injection should produce almost complete blanching of the lesion. Following infiltration volumetric lesion reduction is achieved using the carbon dioxide laser at a continuous setting of 8–10 W, delivered via the microscope. This brings about immediate airway improvements and the combination of healing and the steroid produce further reductions in disease bulk. Any pedunculated lesions encroaching into the airway are removed and sometimes radial 'releasing' laser cuts are necessary. It is important not to create a circumferential injury in or around the laryngeal inlet as this has the potential to produce airway narrowing through scarring. Multiple narrow pits are created with the CO_2 laser ('pepper pot' pattern) separated by 2–3 mm and extending to the depth of the lesion. Most patients require on average of two treatments (range 1–4) separated by 3–4 weeks.[45]

BILATERAL VOCAL CORD MOBILITY IMPAIRMENT

Bilateral vocal cord mobility impairment (BVCMI) can produce reasonable voice but with some degree of dyspnoea as the vocal cords tend to lie in the median or paramedian position. Bilateral abducted cords are usually seen in neurological conditions and management is aimed at preventing aspiration, see Chapter 56, Chronic aspiration.

There are three principal causes of impaired vocal cord function:

- bilateral laryngeal denervation (neck and chest malignancy or thyroid surgery)
- bilateral cricoarytenoid joint fixation (trauma or rheumatoid arthritis)
- inter-arytenoid scarring (following endotracheal intubation).

Surgery is directed at improving the aperture of the posterior glottis. For bilateral denervation injuries we have had significant success with an endoscopic partial posterior cordectomy and partial arytenoidectomy using the CO_2 laser. The resection can be unilateral or bilateral (**Figure 76.12**).

The voice does become 'breathier' but remains functional. Destructive laryngeal surgery should only be considered when the possibility of spontaneous recovery has been ruled out and the patient has a safe swallow. Where there is potential for recovery, and a severely compromised airway, a temporary tracheotomy may need to be considered or the use of vocal cord suture lateralization procedures,[46] each of which are reversible. Various reinnervation operations have been described and the most promising technique uses the accessory phrenic nerve and anastomosing to the posterior cricoarytenoid muscle.[47] Other groups are looking at reanimating the human larynx with implantable electrical stimulation devices.[48]

With fixed cricoarytenoid joints the only surgical option is some form of laser to the posterior cord or arytenoid as described above.

Posterior glottic injuries can result in interarytenoid scar tissue, which in turn can lead to cricoarytenoid joint ankylosis, unless identified and treated early. The most common cause for this type of injury is endotracheal intubation and this is a reason for early tracheostomies on the ICU. Attempts at repairing the posterior glottis have included posterior laryngeal mucosal flaps, advanced into the post glottis, after division of the scar tissue. Unfortunately, all the procedures to correct this problem

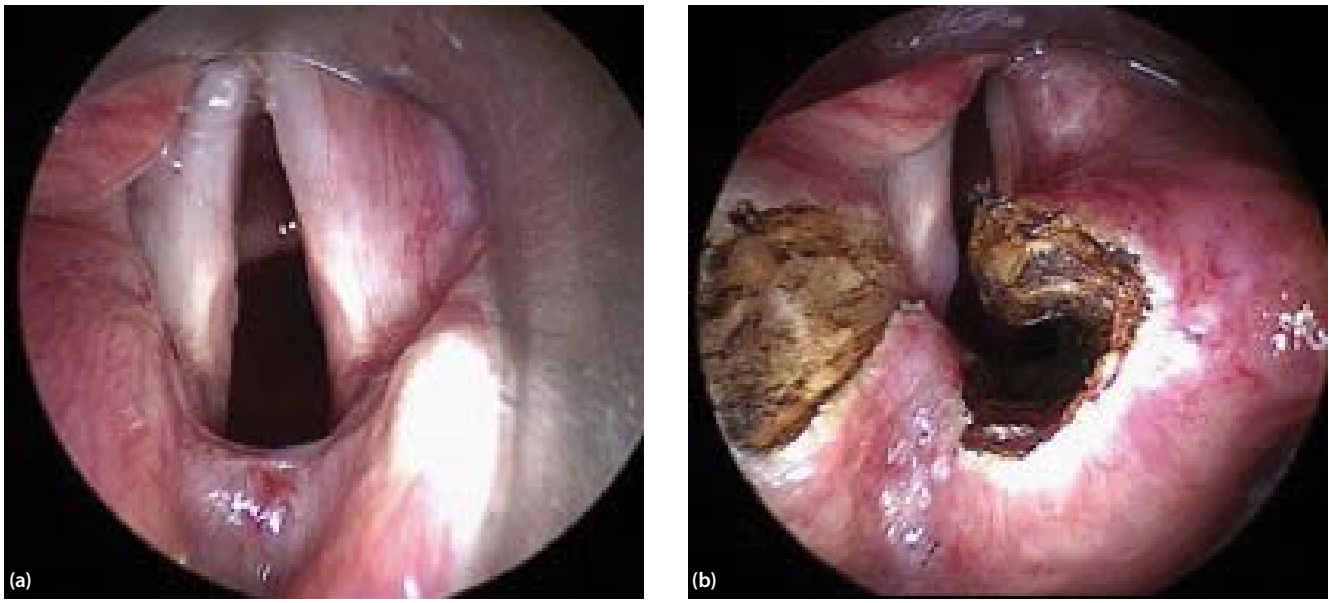


Figure 76.12 Larynx in bilateral cord palsy with the cords separated by the laryngoscope (a) Partial right laser arytenoidectomy with reduction of overhang from left arytenoid **(b)**.

lead to a compromise between voice airway and swallowing. Our preferred technique is the placement of a costal cartilage derived 'spacer' within a posterior cricoid split, through a laryngofissure approach.

FUTURE PROSPECTS

Up to 6 cm of trachea can be resected[17] in the adult with primary anastomosis. There is currently no solution to the repair of damaged tracheas beyond this length or where previous resections have failed. Tissue engineering[49] and tracheal allotransplantation[50] are two techniques that may provide future treatment options for these difficult cases. Laryngeal transplantation may be a solution to restoring the airway where this organ is dysfunctional or damaged beyond repair.[51]

Biotechnology may provide synthetic airways or scaffolds to deal with tracheomalacia and long length tracheal replacements in the more distant future. Biointegratable stents could be an even simpler solution for the management of airway stenosis.

Until these technologies are proven and widely available, prevention of laryngotracheal airway damage is important. This means appropriate sizing of endotracheal and tracheostomy tubes, monitoring cuff pressures and early change to tracheostomies in patients destined for prolonged ventilation. Also, early recognition and treatment of airway injuries, when they do occur, carries a greater chance of successful outcomes.

KEY POINTS

- The most common cause of laryngotracheal stenosis is a period of intubation and ventilation on the intensive care unit.
- The incidence of laryngotracheal stenosis is similar in patients who receive an earlier tracheostomy on the intensive care unit vs those that continue to be ventilated with an endotracheal tube. The difference is the stenosis is less likely to involve the glottis if the patient has a tracheostomy.
- Many of the cases of the stenosis due to systemic inflammatory diseases should and can be managed endoscopically, avoiding tracheostomies, stents and laryngotracheal reconstruction.
- Where an airway disease or trauma has damaged the cartilaginous framework of the larynx and trachea, endoscopic surgery is unlikely to restore a normal airway. These patients will usually require tracheal or cricotracheal resections, or laryngotracheal reconstruction.
- Airway stents are not a good long-term solution to laryngotracheal stenosis, as they are prone to migration, fouling and in the case of metal stents, fragmentation and granulation.

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CHAPTER 77

REFLUX DISEASE

Mark G. Watson and Kim Ah-See

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: laryngopharyngeal reflux, extra oesophageal reflux, laryngeal reflux, silent reflux, acid laryngitis and globus pharyngeus.

INTRODUCTION

Laryngopharyngeal reflux (LPR), caused by the backflow of gastric contents into the upper aerodigestive tract, is frequently diagnosed as a cause of throat symptoms in ENT patients, although there remains a degree of controversy surrounding the subject. The condition was first described by Koufman in 1991.[1] Since then, there has been a wealth of excellent basic science research describing the underlying disease process, but the diagnosis and management of this condition is less clear.[2]

In the oesophagus, a degree of gastro-oesophageal reflux is considered physiologically normal, as long as the exposure time does not exceed 5% in 24 hours. Although the oesophagus is lined by resilient stratified squamous epithelium, the tissue damage is thought to be acid mediated; however, mechanisms exist that physically remove and chemically neutralize the refluxed bolus. A proportion of gastro-oesophageal reflux disease (GORD) patients (possibly as many as two-thirds) have a variant known as non-erosive reflux disease (NERD) in which frank oesophagitis is absent.[3] In classical GORD, reflux typically occurs in the supine position.

In contrast, the larynx is lined in part by areas of very delicate squamous epithelium, and elsewhere by respiratory epithelium, both of which are far less resilient than the oesophageal mucosa. Refluxate, when present, is neither removed by peristalsis nor neutralized by bicarbonate. Tissue damage is thought to be mediated by activated pepsin, and can occur very rapidly following exposure times, which may be as brief as 30 seconds 3 times per week.[1] Reflux disease that affects the laryngopharynx (LPR) is one form of extra-oesophageal reflux (EOR). LPR events often occur in the upright rather than supine position.

Although GORD and LPR may exist independently, as disease severity increases the likelihood of both types being present increases.[4]

This chapter will concern itself mainly with the management of LPR. Other forms of EOR have been described, including reflux-associated cough, nasal and sinus disease, and glue ear. Manifestations of reflux disease in paediatric ENT practice are described in Volume 2, Chapter 44, Reflux and eosinophilic oesophagitis.

PATHOPHYSIOLOGY

Gastric refluxate is often considered solely in terms of its acid content, but in addition to hydrochloric acid it also contains enzymes (notably pepsin), food residues, bile acids and bacteria. Reflux episodes may involve significant volumes of liquid gastric contents, particularly in the lower oesophagus, but in the laryngopharynx may be mainly gaseous, containing a fine aerosol of droplets.[5] Such episodes may be triggered by transient lower oesophageal sphincter relaxations. Once the aerosol has reached the laryngopharynx, it then has easy access to the nose, nasopharynx and lower respiratory tract.

Pepsin

Pepsin is secreted in the form of pepsinogen, which is physiologically inactive. It is activated by cleavage in an acid environment (pH < 4). It had long been thought that pepsin was only active in a highly acidic environment (pH < 4), but recent research using human rather than porcine pepsin shows that, once activated, significant activity remains almost up to neutrality (pH = 7).[6] Even at this level, the enzyme is not damaged, and can be reactivated by a fall in pH. It is not irreversibly deactivated until pH > 8. Pepsin binds to mucosa, and is even taken up into epithelial cells by endocytosis. If the pharynx or larynx is coated with refluxate after a reflux event, pepsin activity gradually decreases as the pH drifts toward neutrality, but can be quickly reactivated by another event, or by ingestion of an acidic bolus. Cola drinks, for instance, have a pH of < 2. As pepsin is active at higher pH levels than previously thought possible, investigation techniques that rely on a pH threshold of 4–4.5 may miss weakly acid or non-acid episodes that can cause tissue damage.

Other components of refluxate

Hydrochloric acid may be present in concentrations that can be affected by medication, notably proton pump inhibitors (PPI). Pancreatic proteases (especially trypsin) may be present, especially in patients who have had gastrectomy or gastroenterostomy, or who are taking PPIs. Bile acids are mainly in conjugated form, but free bile acids can cause tissue damage.[6] Partly digested food residues and bacteria, notably *Helicobacter pylori*, may have some relevance.

LPR DIAGNOSIS

Most patients with LPR are diagnosed on clinical grounds, following outpatient assessment including history taking and examination with flexible or rigid laryngeal endoscopy.[7] In the UK, further investigations for clinically diagnosed LPR are usually reserved for a subset of patients in whom the diagnosis is in doubt, or there is failure to respond to treatment.

SYMPTOMS

LPR symptoms are shown in **Box 77.1**. It is recommended that a structured symptom questionnaire is used at each consultation, and the score documented. The document in most widespread use is the Reflux Symptom Index (RSI).[8] Although it is fairly sensitive, it has limited specificity, as other conditions that produce laryngeal inflammation will also produce a high score. Other causes of laryngeal inflammation are shown in **Box 77.2**. It must always be borne in mind that LPR is only one cause of an inflamed larynx. Most patients with LPR will have a combination of throat symptoms, which will be demonstrated by the RSI. Those with a single symptom, for example globus pharyngeus, will produce a low RSI score and be less likely to have significant LPR (**Box 77.3**).

BOX 77.1 LPR symptoms

- Dysphonia
- Swallowing difficulty ('pseudodysphagia')
- Globus/feeling of lump in throat (FLIT/FOSIT)
- Throat clearing/tickle in throat
- Sore throat
- Cough/choking
- Thick mucus in throat, 'post nasal drip' or 'catarrh'
- Laryngospasm/cough syncope

BOX 77.2 Causes of laryngeal inflammation

- Reflux disease
- Smoking/inhaled irritants
- Alcohol
- Allergy
- Virus infections
- Voice abuse

BOX 77.3 RSI scores

Hoarseness or problem with your voice	0–5
Clearing your throat	0–5
Excess throat mucous or postnasal drip	0–5
Difficulty swallowing food, liquids or pills	0–5
Coughing after you have eaten or after lying down	0–5
Breathing difficulties or choking episodes	0–5
Troublesome or annoying cough	0–5
Sensations of something sticking in your throat or a lump in your throat	0–5
Heartburn, chest pain, indigestion or stomach acid coming up.	0–5

Score: 0, no problem; 5 a severe problem. Total score: >10 may indicate a problem with LPR[8], >20 moderate and >30 severe.

EXAMINATION FINDINGS

The clinical examination of a patient with symptoms suggestive of LPR will include an outpatient fibre-optic endoscopy of the larynx and hypopharynx.

A variety of features have been described as being attributable to the effects of LPR. In general, elements of erythema and/or oedema seen in various locations throughout the laryngopharynx may be caused by LPR.[9] These have been summarized in the Reflux Finding Score (RFS) (**Box 77.4**).[10] Each of the items is scored by an observer. Out of a potential score of 26, Belafsky et al. consider a score of >7 to indiceate LPR.[10]

Some authors report the RFS as demonstrating a reliable correlation with symptoms and response to treatment,[10] although there remains some controversy as to its reproducibility as an accurate tool as others report less reliable correlation.[9]

BOX 77.4 Reflux Finding Score (RFS)

- Infraglottic oedema (*pseudosulcus vocalis*)
- Ventricular obliteration
- Erythema/hyperaemia
- Vocal fold oedema
- Diffuse laryngeal oedema
- Posterior commissure hypertrophy
- Granuloma or granulation
- Thick endolaryngeal mucus

A review of data from meta-analyses reveals laryngeal mucosal findings in 38.2–51.2% of patients with symptoms of reflux laryngitis.[11]

Other studies, however, have noted these findings to be prevalent in the general population with a high rate of abnormal findings in asymptomatic people. A recent review of mucosal signs in LPR highlighted similar proportions of normal and patient populations with reported laryngeal mucosal changes – or increased RFS.[12]

Similarly, laryngeal abnormalities have also been reported in 64–86% of normal controls.[13] In addition, the non-specific nature of these signs means they can also be seen secondary to several other causes: smoking, infection, alcohol, allergies, asthma and voice abuse.[14] A recent study of asymptomatic singers identified a high percentage of laryngeal abnormalities, thus recommending caution when using mucosal signs alone to diagnose LPR.[15]

Similarly, laryngeal findings are seen in patients with GORD (18.9–85%) with posterior larynx and posterior pharyngeal wall findings being the most common.[11]

No single sign appears to be pathognomonic of LPR; however, the presence of pseudosulcus or Reinke's oedema in *symptomatic* patients may be an indicator of LPR. (Positive predictive value (PPV) 67–90% for pseudosulcus in the presence of laryngeal symptoms.)[16] Recent work also suggests a possible new sign of a mucosal white line in the nasopharynx may be useful in identifying the presence of reflux affecting the pharynx.[17]

There remains, therefore, a significant amount of controversy around the reliability of examination findings in making the diagnosis of LPR.[11] Clinical symptom reporting, including the use of symptom scores such as the RSI, may correlate better with this subjective condition.[18] While the use of RFS has shown some inter-rater reliability, one must exercise caution when using mucosal signs alone to make the diagnosis of LPR. Using these examination findings to complement information gained from clinical history and symptom scores, as well as a tool to monitor the patient response to treatment, is probably a more reasonable approach.

INVESTIGATIONS

Following appropriate clinical assessment supplemented by appropriate questionnaires, several investigations have been reported in LPR.

Imaging

Barium swallow has traditionally been used for assessment of throat symptoms, including globus pharyngeus and those associated with LPR. It is no longer very widely used in this setting as swallowing a large bolus of dense liquid on an empty stomach and then tilting the patient head down to see if reflux occurs is probably not physiologically representative of events in normal life. It is still useful if dysphagia for solids is present, and is the investigation of choice if pharyngeal pouch is suspected. Videofluoroscopy is a valuable investigation for neuromuscular swallowing disorders, but not usually for LPR.

Functional tests

The Bernstein acid perfusion test involves passing a nasogastric tube into the lower oesophagus and instilling 0.1 M hydrochloric acid solution. If the patient then reports chest pain similar to his/her symptoms, then this would confirm that the cause is GORD rather than cardiac disease. It is no longer used for this purpose but has re-emerged as a research tool in recent years for reflux-related lower respiratory tract symptoms.

Pepsin testing

As LPR is thought to be pepsin mediated, testing for its presence in the larynx and pharynx is a logical development. Biopsy specimens can be stained for the presence of pepsin, but this requires an invasive procedure and is not used outside research programmes. A test is now available for the presence of pepsin in pharyngeal secretions (Peptest; RD Biomed Ltd, Hull, UK). This test is entirely non-invasive, and is easy and relatively cheap to perform. The patient expectorates pharyngeal secretions into a specimen tube containing a citric acid buffer. After mixing and centrifugation, the specimen is placed on a test strip and read after approximately 15 minutes. A positive result is strongly predictive for the presence of LPR, although a negative result does not exclude.[19] Examination of more than one specimen for each patient may increase diagnostic accuracy. Pepsin can also be detected in nasal secretions and exhaled breath condensate in ventilated patients using the same technique.

Manometry

Although oesophageal manometry is not itself helpful in the diagnosis of LPR, it is usually performed prior to pH monitoring (see the next section) to identify the position of the upper and lower oesophageal sphincters to aid electrode placement. High-resolution techniques give more detailed information on oesophageal function. Some patients with symptoms of LPR who do not respond to treatment will be found to have oesophageal dysfunction as their underlying problem.[20]

pH and impedance monitoring

For some years the 'gold standard' investigation was thought to be 24-hour dual-channel pH monitoring, with electrodes at the level of the upper sphincter, and in the lower oesophagus just above the lower sphincter.[21] A range of normative values have been published, with some authors suggesting that 4 episodes/24 hours at the

upper electrode are required for LPR diagnosis, and others suggesting that a single episode is sufficient. In practice, many patients have multiple episodes, enabling the diagnosis to be made easily, with only a small number falling into the 1–4 episodes/24 hours range.

The main limitation of pH monitoring alone is that the pH threshold is set at pH4 or 4.5: this test will therefore fail to identify weakly acid (pH4.5–7) or non-acid (pH>=7) events. Multichannel intraluminal impedance (MCII) monitoring, which adds an array of electrical impedance electrodes to the test catheter, can be added to dual channel pH monitoring, and may increase diagnostic accuracy by recording all reflux events. Once again, normative data are not standardized and like pH monitoring, MCII is an invasive and expensive test that some patients cannot tolerate.

A less expensive and better-tolerated technique is airway pH monitoring (Restech; Respiratory Technology Corp., San Diego, CA, USA). This uses a small catheter with a probe placed at the level of the soft palate, which is used to produce a 24-hour recording. Although results were initially promising,[22] more recent work has cast doubts on the reliability of this method.[23]

TREATMENT

Possible treatments for LPR include dietary and lifestyle measures, medical treatments and antireflux surgery.

Diet and lifestyle

There is good evidence that alteration of diet and lifestyle can improve LPR symptoms,[24] and this aspect of treatment should be stressed to all patients. The main points are shown in **Box 77.5**. Consumption of alkaline water has recently been advocated but is as yet clinically untested.[25] An advice session from a suitably trained speech and language therapist (which may be delivered on a group or individual basis) can improve compliance[14] and, if hoarseness is a significant symptom, voice therapy can also help.[26] As well as giving patients written advice on lifestyle measures, online resources are also available.

Medical treatments

This is perhaps the most contentious issue in relation to LPR. There is, as yet, no drug that acts directly against pepsin, which is thought to be the causative agent. Drugs currently available to prevent reflux episodes and improve oesophageal function (metoclopramide, domperidone) are much less effective than cisapride, which is no longer available due to toxicity problems, and recently limitations have also been imposed on the use of domperidone. Antacids alone have little effect, and the role of acid suppressant drugs (particularly PPIs) is controversial,[27] with some authors advocating their use[28] and others claiming they are ineffective.[29] PPIs are the treatment of choice for patients with GORD, which is thought to be acid mediated, but in LPR their effect is at best indirect by raising gastric pH to reduce activation of pepsin by cleavage of pepsinogen. Simply telling a patient that their symptoms are due to LPR and issuing a prescription for PPIs is unlikely to achieve a good outcome. Barrier agents (such as alginate) can be used to protect the mucosa of the oesophagus and upper aerodigestive tract.

BOX 77.5 Diet and lifestyle advice

- Give up smoking.
- Reduce alcohol intake. Spirits, white and rosé wine are particularly irritant.
- Avoid carbonated drinks (even carbonated water) and fruit juice.
- Reduce caffeine intake.
- Avoid fatty foods (anything fried, chips, cheese, pastry, chocolate).
- Elevate the head of the bed at night.

Proton pump inhibitors

Proton pump inhibitors (PPIs) are in common usage for treatment of LPR, particularly as part of a combined management strategy including diet and lifestyle advice as described earlier. An example of such a strategy is given in **Figure 77.1**. Although clinical trials have so far produced conflicting results as to the benefits of using PPIs, they are cheap (in the UK, generic pantoprazole currently costs approximately £1.30 for a box of 20 mg tablets) and generally well tolerated, although diarrhoea may be more of a problem with lansoprazole than other agents. In longer-term use, and particularly in high dosage, increased incidence of pneumonia, *Clostridium difficile* infection and osteoporosis have been described.

PPIs exert their effect by blocking the production of H^+ by the gastric glands. In GORD, they are highly effective at controlling symptoms in once-daily dosage. As described above, this is an acid-mediated disease, and the oesophagus can tolerate an acid pH for up to 5% of each day.

In LPR, by contrast, the aim of PPI therapy in LPR is to prevent the activation of pepsin. As mucosal damage can occur with short-lived reflux episodes, 24-hour coverage is necessary, and twice daily dosage is needed to achieve this as the drugs currently available are only active for 12–14 hours after each dose. PPIs are most effective if taken before food, as the drug needs to be present in the plasma when the proton pumps of the gastric glands are activated. It is therefore recommended that, if used, PPIs are given 30 minutes before breakfast and evening meal. Symptomatic improvement may take much longer than in GORD, and so a treatment trial of at least 2–3 months is required. A total treatment time of approximately 6 months has been advocated for responders,[30] and with the recognition of acid rebound if PPI therapy is discontinued abruptly,[31] tapered withdrawal may be more appropriate (**Box 77.6**).

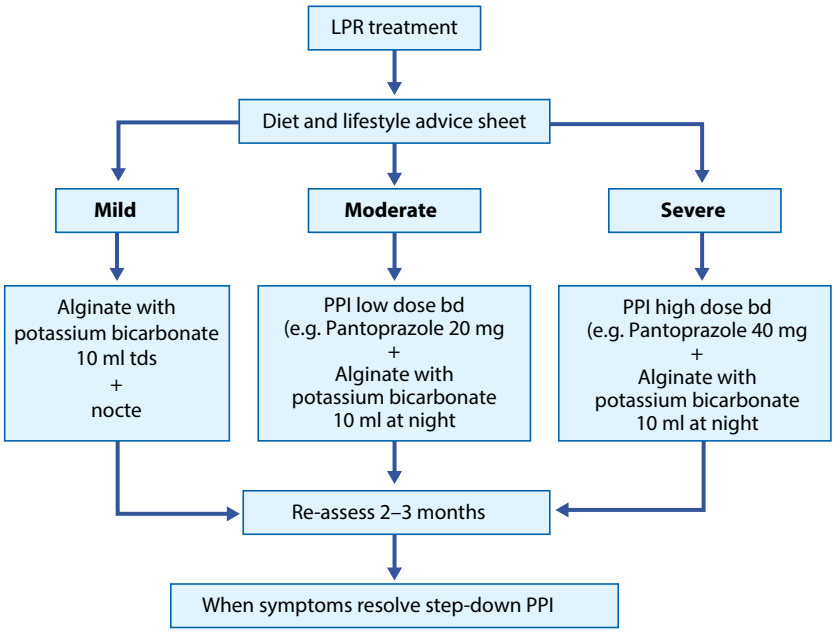


Figure 77.1 Combined treatment strategy.

BOX 77.6 PPI dose reduction schedule

- Pantoprazole 40 mg bd
  ↓ 2 months
- Pantoprazole 20 mg bd
  ↓ 2 months
- Pantoprazole 20 mg od
  ↓ 2 months
- Stop regular pantoprazole
- Consider providing a supply for prn use (e.g. before going out for a meal in a restaurant)
- Most patients do *not* need to be on long-term PPIs; only a small number need maintenance therapy.
- Gaviscon Advance and dietary advice are more suitable long-term measures in the treatment of reflux disease.
- Rebound symptoms are common on stopping PPI therapy; Alginate with potassium bicarbonate, 5 ml tds after meals and 10 ml at night for 2 weeks will help to reduce these.

Alginate

Alginate preparations have traditionally been used in the treatment of GORD symptoms such as heartburn, and there is evidence for the effectiveness in LPR of one alginate preparation that is currently available in the UK and Europe,[32] but not in the United States. Alginate is a non-systemic treatment derived from seaweed, and has little in the way of side effects, although some individuals find liquid preparations difficult to tolerate due to the thick consistency. Tablet formulations are available but the tablets are large and need to be sucked or chewed; they have a chalky texture.

Alginates are normally given after meals and/or just before retiring at night. They can also be used for breakthrough symptoms such as cough or globus. They may be helpful just before activities that can cause reflux, such as vigorous exercise or singing. They can be used as part of a combined management strategy involving diet and lifestyle advice and possibly PPI prescription, as described above.

MANAGEMENT OF NON-RESPONDERS

Published response rates to the medical therapies described in this chapter vary widely. For those patients who do not respond, the following need to be established:

- Is the diagnosis correct?
- Is the treatment regime reasonable, and is the patient complying with it?

If the diagnosis of LPR is not clear, then further investigations should be performed in order to confirm or refute it. Even if the diagnosis is clear, confirmation prior to referral for further management (particularly antireflux surgery) may be needed. Pepsin testing of pharyngeal secretions, 24-hour dual channel pH monitoring and MCII monitoring should be considered.

A recent study examined 23 consecutive treatment non-responders using MCII and high-resolution oesophageal manometry.[20] All patients had failed 3 months of high-dose twice-daily PPI therapy. Breakthrough acid reflux was found in 5/23 (22%) and significant non-acid or weakly acid reflux in 12/23 (52%). Active reflux disease was therefore present in 17/23 (74%) of the non-responders, with >80% of the reflux episodes occurring in the upright position. In addition, manometry showed significant oesophageal dysmotility in a 5/23 (22%).

Therefore, it is clear that many patients who fail medical treatment do actually have LPR. A close check should be made on the treatment regime to confirm compliance. Has the patient complied with diet and lifestyle measures (**Box 77.5**)? In particular, check smoking status and consumption of alcohol, carbonated drinks (especially cola), fruit juice and acidic fruits, as well as sleeping position. Has the prescribed medication been taken as instructed, in adequate dosage and for a sufficient period? With PPIs, some patients may respond better to one drug than another, so trial of a different agent can be considered. If alginate has not been used so far, it can be prescribed. If there is significant reflux present and the patient has persisting symptoms, referral to a gastrointestinal surgeon for antireflux may be appropriate.

ANTIREFLUX SURGERY

Surgery for reflux disease usually involves one of several forms of laparoscopic fundoplication, although some procedures implant a prosthesis to prevent reflux episodes.

Surgery may be considered either for LPR that does not respond to medical treatment, or for patients who require long-term high-dose PPI treatment to control symptoms, particularly at a young age. Surgery has been shown to produce better results in those who have GORD symptoms as well as LPR, or who have positive findings on pH monitoring, as well as those who respond well to PPIs.[33]

FUTURE RESEARCH

➤ Management of LPR patients will be improved when the diagnosis can be made with confidence by means of quick, cheap, reliable non-invasive tests, and medical treatments are available that prevent the activation or function of pepsin. Development of clinical guidelines would help to standardize treatment at an acceptable level.[34]

KEY POINTS

- Laryngopharyngeal reflux may cause throat symptoms.
- The evidence base is limited.
- Acid and pepsin are present in the refluxate.
- Symptoms and examination findings are subjective.
- Lifestyle changes and anti-reflux medication may help.
- Anti-reflux surgery may be considered in resistant cases.

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CHAPTER 78

PARALYSIS OF THE LARYNX

Lucian Sulica and Babak Sadoughi

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: vocal fold paralysis, recurrent laryngeal nerve, laryngoplasty, thyroplasty, and laryngeal re-innervation, and focusing on evaluation and management.

INTRODUCTION

Paralysis of one or both vocal folds may impair the important physiologic functions of the larynx: breathing, swallowing and voicing. Individuals with laryngeal hemiparalysis typically complain of a broad range of symptoms reflecting variable degrees of glottic insufficiency. The most prominent of these are breathy dysphonia and dysphagia, particularly to liquids. Breathlessness while speaking and breathlessness during physical exertion may also be present. When both vocal folds are affected by the paralytic process, patients generally complain of symptoms of glottic obstruction such as stridor and dyspnea. This distinction in symptoms between unilateral and bilateral paralysis reflects the contrasting valving tasks of the larynx: glottic opening for respiration and glottic closure for airway protection, thoracic stabilization during effortful activity, and phonation.

The first important clinical task is establishing the cause of paralysis if possible. Effective management of symptoms follows. Some cases of paralysis improve symptomatically without intervention, while others fail to recover. Distinguishing between these two groups remains a challenge, and many otolaryngologists consequently choose to delay treatment until the possibility of spontaneous recovery is judged remote.

PATHOPHYSIOLOGY

Most cases of laryngeal paralysis result from peripheral nerve damage. Because the degree and pattern of neurological impairment varies, laryngeal paralysis is a heterogeneous condition with respect to symptoms, vocal fold position and electromyographic evidence of the degree of nerve damage.[1, 2] Unless due to severe trauma-like transaction, each case differs from the next in degree of neurologic impairment, and features a mix of injury types among its nerve fibres. This latter aspect is a principal reason why standard classifications of peripheral nerve injury are not entirely useful in vocal fold paralysis.

Both human and animal studies have shown that the larynx has a strong propensity for re-innervation,[2–4] which appears to be the rule rather than the exception. However, regeneration of the recurrent nerve is more problematic than that of most peripheral nerves because it carries a mixed population of adductor and abductor fibres. Re-innervation is often dysfunctional and does not yield physiologic motion. This neural dysfunction extends beyond traditional notions of synkinesis, in which balanced co-contraction of adductor and abductor fibres were theorized to produce an absence of net vocal fold motion. In fact, dysfunctional re-innervation may also occur when nerve regrowth is appropriately directed but insufficient, which may result in decreased force of contraction, loss of motor unit specificity, increased muscle fatigability and possibly changes in peripheral and central neural organization.[5] Nevertheless, the natural tendency for re-innervation accounts for the general trend for voice to improve over time in unilateral paralysis. Because of the predominance of adductor fibres, re-innervation tends to restore or preserve muscle bulk and tone, occasionally to the point that phonatory glottic closure is restored and conversational

voice sounds normal despite persistent vocal fold immobility. This explanation, well supported by electrophysiologic evidence,[1, 2] is probably closer to reality than the notion of gradual contralateral compensation.

For most of the last century, vocal fold position was erroneously thought to reveal the site or type of lesion, a prevailing belief that has since been invalidated by careful clinical and laboratory work.[6–8] Differing degrees and patterns of innervation probably account for variability in the position of the paralyzed vocal fold.

AETIOLOGY OF LARYNGEAL PARALYSIS

Most sources of nerve injury fall into three broad categories: mechanical damage from surgery or other trauma; functional compromise from a range of medical conditions; and other factors yet to be completely identified, designated 'idiopathic'.

The reported relative frequency of causes of laryngeal paralysis varies considerably (**Table 78.1**). In most series, laryngeal paralysis tends to affect men more often than women, probably reflecting the underlying gender distribution of thoracic malignancy. Uniformly, the left vocal fold is affected more often than the right, in approximately a 60:40 ratio or greater, due to the greater length and more profound descent into the thorax of the left-sided nerve, and its consequent greater vulnerability to disease and surgery.

Iatrogenic sources of injury have multiplied over time. In addition to thyroidectomy, still a main source of iatrogenic laryngeal paralysis, anterior approach to the cervical spine, carotid endarterectomy, and various cardiac and thoracic procedures have all become significant sources of laryngeal nerve injury (**Table 78.2**). The potential for recurrent nerve damage from the cuffed endotracheal tube is recognized and continues to account for cases of vocal fold immobility that are demonstrably neural in origin rather than the result of cricoarytenoid joint disruption.

A number of neurologic conditions remain relevant, albeit unusual causes of laryngeal paralysis. In contrast to other causes, some of these may be through a central mechanism. Vocal fold paralysis may appear in the wake of a stroke, almost always in conjunction with other deficits. Lateral medullary infarct (Wallenberg syndrome) is a complex of neural injury featuring vocal fold paralysis, dysphagia, vertigo, ataxia, Horner syndrome and hemifacial sensory deficit and/or pain. The vocal fold paralysis tends to improve with time, although measures may be needed in the short term to prevent aspiration. The vocal fold paralysis of Arnold-Chiari malformation tends

TABLE 78.1 Causes of unilateral vocal fold paralysis

Study	Year	N	Tumour	Trauma	Idiopathic	Other
Laccourreye et al.[9]	2003	325	9%	75%	12%	–
Loughran et al.[10]	2002	77	52%	22%	12%	5% intubation
Yumoto et al.[11]	2002	422	19%	33%	22%	8% intubation
Ramadan et al.[12]	1998	98	32%	30%	16%	11% intubation
Benninger et al.[13]	1998	280	25%	35%	20%	8% intubation
Bruggink et al.[14]	1995	215	25%	43%	18%	–
Yamada et al.[15]	1983	519	17%	12%	41%	11% intubation
Tucker[16]	1980	210	22%	42%	14%	–
Hirose[17]	1978	600	7%	37%	41%	2% intubation
Parnell, Brandenburg[18]	1970	100	32%	32%	10%	11% medical
Clerf[19]	1953	299	38%	20%	12%	9% medical
Work[20]	1941	183	14%	39%	23%	15% medical
Smith et al.[21]	1933	173	27%	16%	17%	36% medical

Adapted with permission from Sulica et al.[22]

TABLE 78.2 Surgeries and procedures that place laryngeal nerves at risk

Cervical surgery	Thoracic procedures	Other surgery	Other medical procedures
• Thyroidectomy/parathyroidectomy • Anterior approach to the cervical spine • Carotid endarterectomy • Implantation of vagal nerve stimulator • Cricopharyngeal myotomy/repair of Zenker diverticulum	• Pneumonectomy and pulmonary lobectomy • Repair of thoracic aortic aneurysm • Coronary artery bypass graft • Aortic valve replacement • Esophageal surgery • Tracheal surgery • Mediastinoscopy • Thymectomy • Ligation of persistent ductus arteriosus • Cardiac and pulmonary transplant	• Skull base surgery • Brainstem surgery, or neurosurgery that requires brainstem retraction	• Central venous catheterization • Endotracheal intubation

to be bilateral, and it is important to recognize promptly because it is reversible with timely hindbrain decompression. Charcot–Marie–Tooth disease and its variants are a heterogeneous group of hereditary motor and sensory neuropathies that may involve the laryngeal nerves. Neural compromise of the vocal fold appears to evolve slowly but relentlessly and is usually bilateral. Postpolio syndrome, a degenerative neurologic condition seen many decades after the acute disease, may present as a complex of bulbar deficits resulting in dysphagia, dysphonia and dysarthria. A similar presentation may be seen in multisystem atrophy, a degenerative parkinsonian condition where laryngeal neurologic dysfunction may contribute to mortality by creating respiratory obstruction. Laryngeal weakness may also figure in oculopharyngeal dystrophy and inclusion body myositis, although the mechanisms of nerve involvement are not fully understood in those conditions.

The incidence of idiopathic paralysis had remained approximately unchanged over the past century, unaffected by the introduction and refinement of computed tomography and magnetic resonance imaging. Based on serologic studies, cases have been attributed to Lyme borreliosis, herpes zoster and simplex, Epstein–Barr virus and even the West Nile virus. However, the cause of many cases of vocal fold paralysis in which serologies are normal and there is no history of antecedent viral disease are yet to be elucidated.

UNILATERAL VOCAL FOLD PARALYSIS

Clinical evaluation

HISTORY

Patients with unilateral laryngeal paralysis typically experience hoarseness and hypophonia. These can range from subtle vocal fatigue to near-total aphonia, reflecting the degree of glottic insufficiency, which varies from affected individual to individual. Dysphagia with possible frank aspiration may also be reported, albeit less often than voice complaints. Dysphagia-related complaints are more frequent in cases of 'high' vagal injury, affecting both superior and recurrent laryngeal nerves, which adds hemilaryngeal anaesthesia, pharyngeal constrictor atony and cricopharyngeal muscle hyperfunction to glottic insufficiency from the immobile vocal fold. Situations in which laryngeal anaesthesia exists alongside other cranial nerve deficits, as in jugular foramen syndromes, after stroke and after skull base surgery also carry increased dysphagia risk. Surgeries affecting pulmonary reserve, as do most thoracic procedures, appear to carry a higher risk of aspiration, and age may be an independent risk factor.[23]

Some patients will demonstrate a characteristically 'wet' vocal quality arising from pooled secretions, which interfere with phonation. By definition, such secretions have at least penetrated into the laryngeal introitus; these patients should attract the otolaryngologist's attention as being at risk for aspiration. More subtle symptoms include laryngospasm resulting from reaction to unexpected penetration or aspiration. This may occur in patients with surprisingly small degrees of glottic insufficiency and reasonably good voice quality.

Occasionally, patients may complain of phonation- or activity-induced shortness of breath. Careful questioning will reveal that this is not obstructive dyspnea, but rather breathlessness that results from excessive air escape during voicing, or from compromise of the thoracic fixation (Valsalva) manoeuvre during effortful activity. Pulmonary function testing will inevitably reveal an extra-thoracic obstruction; this, plus a lack of insight into laryngeal physiology, may lead the physician away from laryngeal intervention.

The otolaryngologist should also inquire regarding smoking history, the most recent chest imaging, and antecedent illness. A review of systems should focus on conditions likely to affect the larynx. Relevant factors include: neurologic symptoms like weakness, tremor and dysarthria; pulmonary symptoms suggestive of tuberculosis or malignancy; and exposure to neurotoxic agents like solid tumour chemotherapy (vincristine, vinblastine and cisplatin) or organophosphates found in pesticides. Unilateral vocal fold immobility is rarely mechanical in nature, but the possibility should not be dismissed in cases that are identified in the wake of clearly traumatic intubation or external trauma, or in the presence of arthralgias or known inflammatory joint disease.

PHYSICAL EXAMINATION

The examination should include palpation of the neck for lymphadenopathy or thyroid enlargement. The remaining cranial nerves should be evaluated, with special attention to the spinal accessory and glossopharyngeal nerves, which share the jugular foramen with the vagus. Other branches of the vagus should be examined as well. Finally, the presence of ipsilateral tongue deviation, palate droop or Horner syndrome should raise the suspicion of a cranial base lesion.

The larynx itself should be examined across a variety of laryngeal tasks. Flexible nasolaryngoscopy probably offers a more accurate impression of laryngeal function than rigid techniques, as the tongue traction necessary for the latter probably introduces some confounding biomechanical factors.

A hypomobile vocal fold may occasionally be difficult to appreciate; in such cases, asking the patient to alternate sustained vowel phonation and sniffing ('eee-sniff' manoeuvre) should bring any asymmetry into evidence. The examiner should not be misled by small amounts of vocal fold motion that may be caused by the interarytenoid muscle, receiving innervation from the contralateral nerve, by an intact cricothyroid muscle, or even by passive lateral displacement of the denervated arytenoid by its pair during adduction.

We have seen that the position of the paralyzed vocal fold carries no significance with respect to the site of the injury or prognosis. Nevertheless, careful examination can reveal features that may inform clinical care. Occasionally, increasing tension and length of the paralyzed vocal fold upon raising the pitch of the voice may



Figure 78.1 In this case of left vocal fold paralysis following anterior approach to the cervical spine, comparison of left vocal fold tension during quiet respiration (a) and phonation **(b)** suggests the superior laryngeal nerve is intact.

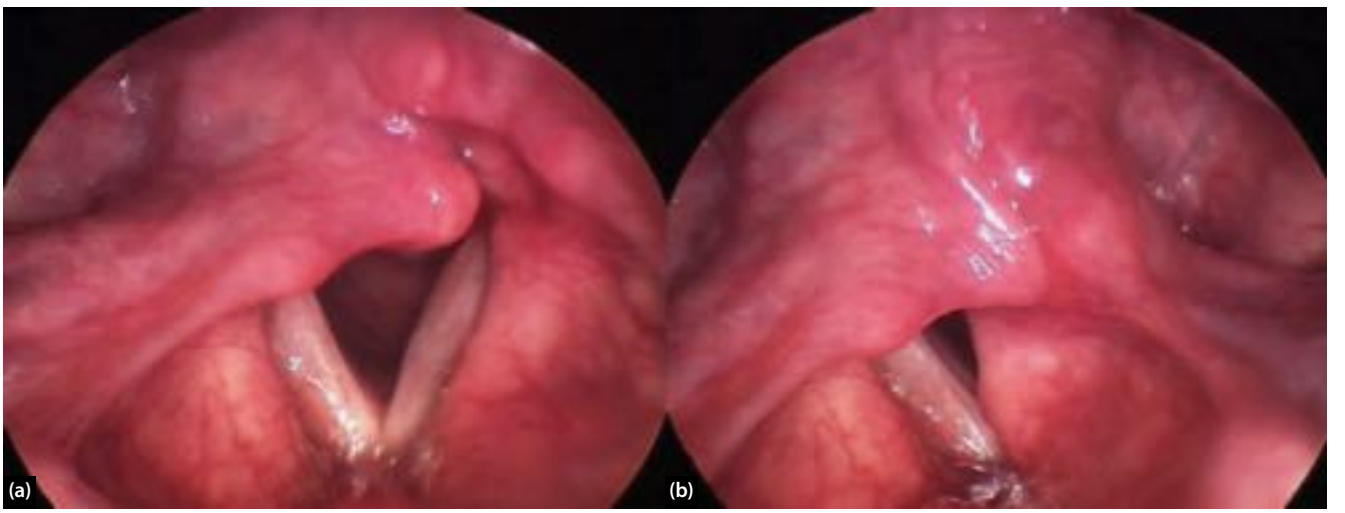


Figure 78.2 The right arytenoid is prolapsed into the laryngeal introitus in this case of idiopathic vocal fold paralysis, confirmed by electromyography (a). In adduction **(b)**, it interferes with the opposite cartilage and impedes closure. Rehabilitation without arytenoid repositioning surgery would very likely be suboptimal.

suggest an intact superior laryngeal nerve. Sometimes, patients may take advantage of intact cricothyroid function to improve voice projection by increasing vocal fold resistance to exhaled air (**Figure 78.1**); this pitch-raising phenomenon generates a characteristic voice described as 'paralytic falsetto'. The presence of supraglottic hyperfunction during phonatory effort should raise the possibility of glottic insufficiency. The ventricular folds serve as an accessory valving mechanism that tends to be engaged without deliberate effort when the vocal folds proper do not close effectively.[24]

Vocal fold adduction and abduction do not take place in two dimensions; the folds tend to abduct in a cephalad direction (into the ventricles) and adduct caudally. Thus, a paralyzed vocal fold may not rest in the same plane as its partner. Such three-dimensional judgements are difficult to make on laryngoscopy, but height mismatch is important to identify, as simple medial displacement of the paralyzed fold may not suffice for proper apposition during phonation.

Asymmetry of the arytenoids, with displacement of the cartilage on the paralyzed side forward into the laryngeal introitus (i.e. a 'prolapsed arytenoid'), is not a rare finding in laryngeal paralysis (**Figure 78.2**). This is not a sign of cricoarytenoid dislocation but does, however, suggest profound denervation with loss of muscular support for the cartilage. In addition, it strongly suggests a height and tension mismatch between the vocal folds. These factors argue for an arytenoid stabilization procedure should surgical rehabilitation be contemplated.

The incidence of cricoarytenoid dislocation as a cause of vocal fold immobility has been the subject of much debate. Experimental study has shown the cricoarytenoid joint to be strikingly robust and resistant to disruption.[25–27]

A problem-free intubation is unlikely to cause a joint injury, which usually follows obvious trauma, be it from intubation or external sources. The presence of arytenoid oedema and erythema, and the absence of a 'jostle sign' are suggestive of cricoarytenoid joint injury and should prompt further investigation (The Jostle sign is when the arytenoid cartilage on the side of the paralyzed cord, is passively displaced laterally on contact with the arytenoid on the normal side during phonation).

In hemilaryngeal paralysis, the glottal gap may be of two principal configurations. It may be essentially spindle-shaped, involving principally the membranous portion of the vocal fold, or V-shaped, marked by greater distance between the vocal processes of the arytenoid cartilages (**Figure 78.3**). This latter configuration is called a posterior gap, although the term does not refer to the absolute distance between vocal processes. The presence of a posterior gap should also cause the otolaryngologist to consider an arytenoid stabilization procedure for rehabilitation because implant medialization alone or injection augmentation is predictably poor at correcting this deficit.

Although there is no single metric of severity of symptoms of vocal fold paralysis, several simple clinical tools may help grade features of the history and examination. The Voice Handicap Index (VHI) and the voice-related quality of life (V-RQOL) are validated patient-completed self-rating scales that measure various aspects of vocal disability. The Consensus Auditory Perceptual Evaluation of Voice (CAPE-V) and the older grade, roughness, breathiness, asthenia, strain (GRBAS) scale are perceptual scales completed by the healthcare professional based on voice quality. The maximum phonation time (MPT) is the longest duration of sustained vowel phonation; for example, typically an /i/, which the patient can sustain, and is approximately inversely proportional to the degree of glottic insufficiency. The s/z ratio compares the MPT of a voiced (/z/) and unvoiced (/s/) sound. Under normal circumstances, the duration of the unvoiced sound should far exceed that of the voiced (the s/z ratio should be large), but with glottic insufficiency, the duration tends to become approximately the same (the s/z ratio tends to decrease).

ADDITIONAL INVESTIGATIONS

Fundamentally, diagnostic testing beyond the history and physical is intended to uncover causes of vocal fold paralysis. In cases temporally related to surgery that places the vocal folds at risk, no additional investigation is required. In others, malignancy is the principal pathology not to be overlooked. Imaging of the entire course of the affected laryngeal nerves is obligatory, including the mediastinum and the pulmonary apices.

Computed tomography (CT) from base of skull *through* the arch of the aorta or the right subclavian, as appropriate, is the minimum recommended study for laryngeal paralysis. In cases where a 'high vagal' paralysis is suspected according to criteria reviewed earlier, magnetic resonance imaging (MRI) may offer a more reliable means of imaging the skull base or central nervous system.

While serologies used to be ordered routinely, systematic examination has demonstrated a 0% yield in a series of 84 patients;[28] therefore, serologic testing is probably useless unless there is a specific clinical suspicion of an underlying illness.

Modified barium swallow is useful if a question of aspiration exists. The potential of morbidity related to dysphagia is a key element in determining the need for treatment.

Laryngeal electromyography (LEMG) measures the integrity of laryngeal innervation by means of percutaneous needle electrodes. It can provide unambiguous evidence of denervation and re-innervation, yet its utility in cases of vocal fold paralysis has been hotly debated. LEMG has been criticized for being a subjective study. In this respect, however, it does not differ

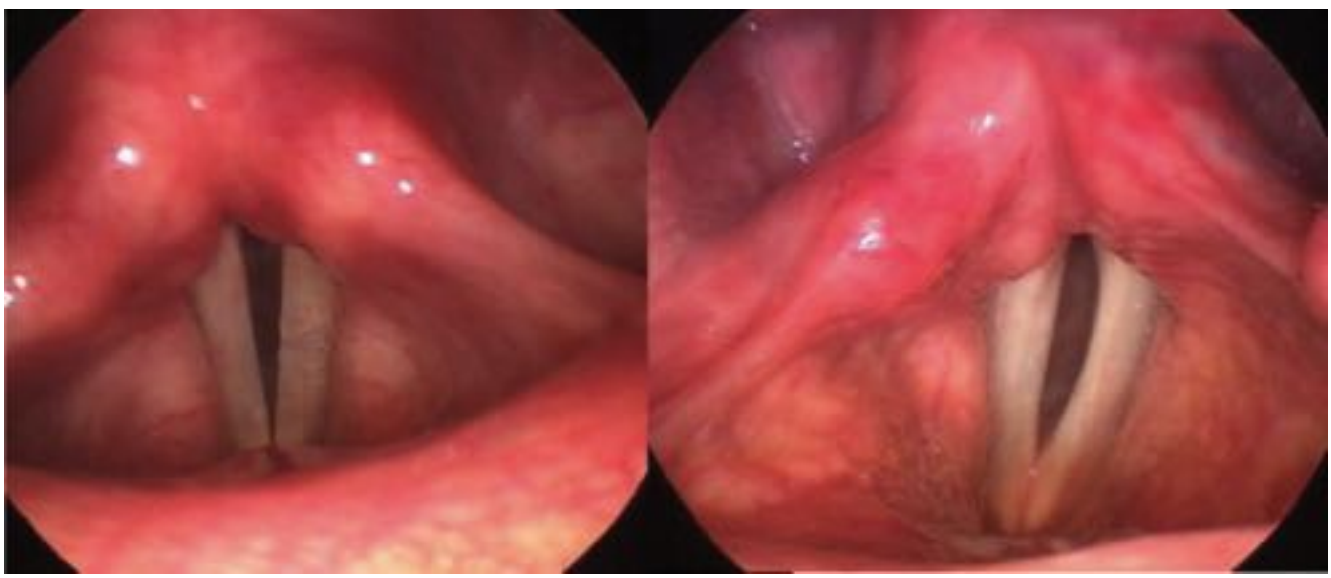


Figure 78.3 The case on the right, a left vocal fold paralysis following a thyroidectomy, demonstrates a posterior gap. On the left, a vocal fold paralysis from malignant mediastinal lymphadenopathy, closure at the vocal process is good. Compare also with the case in **Figure 78.2**, which also demonstrates a posterior gap.

TABLE 78.3 Laryngeal electromyography and prognosis in vocal fold paralysis of less than 6 months duration

Study	N	Accurate prediction of recovery	Accurate prediction of no/impaired recovery
Munin et al.[30]	31	80%	80%
Sittel et al.[31]	111	13%	94%
Gupta & Bastian[32]	18	70%	75%
Hirano et al.[33]	29	63%	80%
Parnes & Satya-Murti[34]	18	80%	100%

Adapted with permission from Sulica et al.[22]

from laryngoscopy and stroboscopy, except inasmuch as training and familiarity has allowed otolaryngologists to use these latter modalities more comfortably. In fact, LEMG exceeds both of these in its ability to definitively and objectively diagnose vocal fold paralysis, as opposed to immobility.

The practical clinical difficulty in the use of LEMG for prognosis has been that the appearance of electromyographic signs of re-innervation does not always lead to a return of vocal fold function, for pathophysiologic reasons reviewed earlier. Therefore, the utility of LEMG in prognosis in cases of vocal fold paralysis has been uneven. The available literature suggests that LEMG may be more useful as a predictor of poor outcome (**Table 78.3**), principally because electromyographic signs such as fibrillations and positive sharp waves, providing evidence of an absence of re-innervation, offer no physiologic ambiguities.[29] For now, LEMG clearly offers a reliable way to distinguish neurogenic from mechanical vocal fold immobility, and may offer variable prognostic information when used less than 6 months from the onset of paralysis.

Treatment

The management of glottic insufficiency in unilateral vocal fold paralysis is guided by concerns regarding morbidity from dysphagia and aspiration, the patient's own perception of the severity of the vocal handicap, and expectations about the eventual outcome without treatment. In turn, outcome expectations are influenced by the apparent cause of the paralysis and the time elapsed since onset.

OBSERVATION

Patients with hemilaryngeal paralysis, especially of short duration, may simply be observed. Factors favouring observation include:

- no evidence of aspiration
- injured laryngeal nerve(s) is (are) structurally intact and potential for recovery remains
- minimal vocal disability and/or minimal vocal demand
- comorbidities that discourage or prevent intervention.

Voice and swallowing therapy may be used as needed during the observation period. As with many interventions for this condition, the natural tendency of glottic insufficiency to improve over time makes it difficult to evaluate efficacy, and there is no convincing evidence that voice therapy affects the course and symptoms of vocal fold paralysis. Nevertheless, a skilled voice therapist may offer the patient insight into the condition.

The presence of severe dysphagia, history of aspiration pneumonia or observed aspiration during clinical evaluation effectively trumps other factors and demands intervention.

INJECTION LARYNGOPLASTY

Patients may opt for temporary relief of their symptoms, even when eventual recovery is expected. This is accomplished by injection of an absorbable bulking substance into the paralyzed fold to improve the glottic insufficiency. Such substances include various hyaluronic acid preparations, calcium hydroxylapatite paste, micronized human dermis, autologous fat and carboxymethylcellulose-glycerine gel. Factors favouring injection augmentation include:

- dysphagia
- high degree of vocal disability or high vocal demand
- good or indeterminate functional prognosis
- small glottic gap (2 mm to 3 mm)
- no posterior glottic gap
- short life expectancy.

Injection laryngoplasty may be performed via direct laryngoscopy, or perorally or transcutaneously under topical anaesthetic in the office, provided the patient is cooperative and committed. Office use in the awake patient is a major advantage of the technique. Selection of the substance to be injected depends on the surgeon's evaluation of its tissue properties, experience and preference.

Injection augmentation is regarded as temporary since the abandonment of polytetrafluoroethylene polymer (Polytef, Teflon™) because of well-known adverse tissue response. Calcium hydroxylapatite particle paste has been introduced as a durable injectable with effect around one year.

Injection augmentation has inherent limitations. It will not effectively reposition the arytenoid to rectify a height discrepancy or close a posterior glottal gap and is not ideal for large glottic gaps. Most injectates require overinjection to allow for reabsorption, rendering fine adjustment of vocal fold position impossible. In addition, should the injectate infiltrate into an unintended site – typically the superficial layers of the vocal fold, impairing mucosal phonatory vibration – corrective intervention is challenging and patients may have to await natural resolution over weeks to months. It should be noted that no substance today is ideally suited for use in the lamina propria; all currently available substances will stiffen this tissue.

LARYNGEAL FRAMEWORK SURGERY

Framework surgery is generally reserved for treatment of glottic insufficiency from unilateral paralysis that is not expected to improve. Favourable factors are:

- dysphagia
- high degree of vocal disability or vocal demand
- poor functional prognosis
- large glottic gap (2 mm to 3 mm)
- posterior glottic gap
- shortened life expectancy.

In its simplest and most common form, framework surgery consists of medialization thyroplasty, the surgical insertion of an implant, made of silicone, expanded polytetrafluoroethylene (Gore-Tex®), formed calcium hydroxylapatite, or other biologically inert material, into the paraglottic space to displace the paralyzed vocal fold medially (**Figure 78.4**). Typically, this operation is performed under a local anaesthetic, with or without additional intravenous sedation. The surgeon, guided by patient phonation and endoscopic visualization, may thereby size and position the implant for optimal correction of the patient's glottic insufficiency without functional restriction of the airway. The critical anatomic task is to identify the level of the vocal fold in relation to the thyroid lamina, so that the thyroid cartilage aperture through which the implant is inserted can be placed appropriately. Medialization via thyroplasty, in contrast to injection, is precise, predictable and durable. Often considered more aggressive treatment than injection, medialization thyroplasty under local anaesthesia can be safer and better suited to high-risk patients than injection under general anaesthesia.

Serious complications include airway obstruction and perforation into the laryngeal lumen. Necessarily, medialization narrows the airway and, in combination with post-operative oedema and haematoma, can cause airway obstruction. For this reason, some surgeons prefer to observe patients in the hospital for one night following the procedure. Rarely, patients undergoing medialization thyroplasty have been reported to require intubation or tracheotomy in the immediate post-operative period.[36] Perforation of the laryngeal mucosa increases the likelihood of infection and subsequent extrusion of implanted material.

The most common complication, however, is suboptimal voice outcome. This is typically due to technical factors, and revision rates of 5.4% to 14%, to even as high as 33% when adjunctive procedures such as fat injection are included, have been reported.[36–38] Common causes of poor voice result include persistent posterior gap, undermedialization and implant malposition, generally in too anterior or too superior a position (**Figure 78.5**).

Arytenoid repositioning procedures may be added to medialization thyroplasty when there is a poorly supported arytenoid or a posterior gap (**Figures 78.2** and **78.3**). This configuration is difficult to remedy with thyroplasty alone. Arytenoid repositioning surgery is designed to internally rotate and/or suspend the arytenoid in physiologic phonatory position. Most commonly, the muscular process of the arytenoid cartilage is approached through the inferior constrictor muscle and around the back of the thyroid lamina. A non-absorbable suture is passed through this structure and secured to the thyroid lamina to exert anterolateral traction on the muscular process and thus rotate the vocal process medially and slightly caudally. This is known as arytenoid adduction.[39] Adduction arytenoidopexy, a less common approach, involves opening the cricoarytenoid joint capsule and suturing the arytenoid in optimal position directly to the crest of the cricoid.[40]

These procedures are technically more challenging and time-consuming than thyroplasty alone, and have a higher incidence of complications, largely because oedema or bleeding into the paraglottic space can cause airway obstruction. Despite these problems, for the experienced phonosurgeon, arytenoid procedures are an essential adjunct to medialization thyroplasty in achieving an optimal voice outcome.

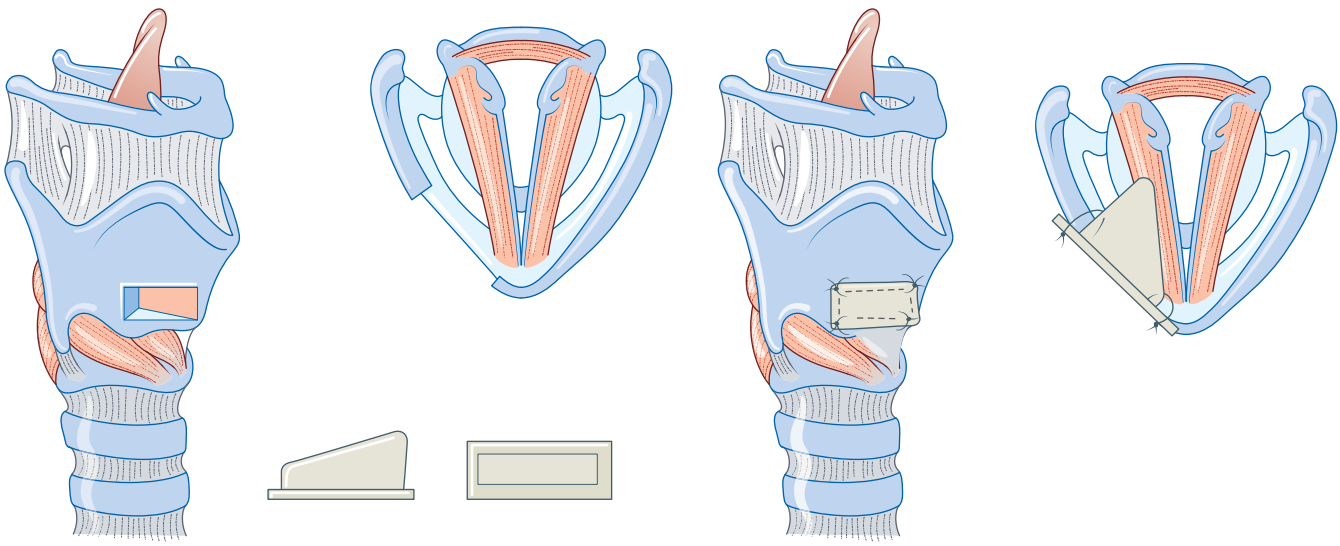


Figure 78.4 In medialization laryngoplasty, a medialization shim of biologically inert material is inserted into the paraglottic space through a thyroid cartilage window to displace the vocal fold towards the midline. Published with permission, from Bielamowicz.[35]

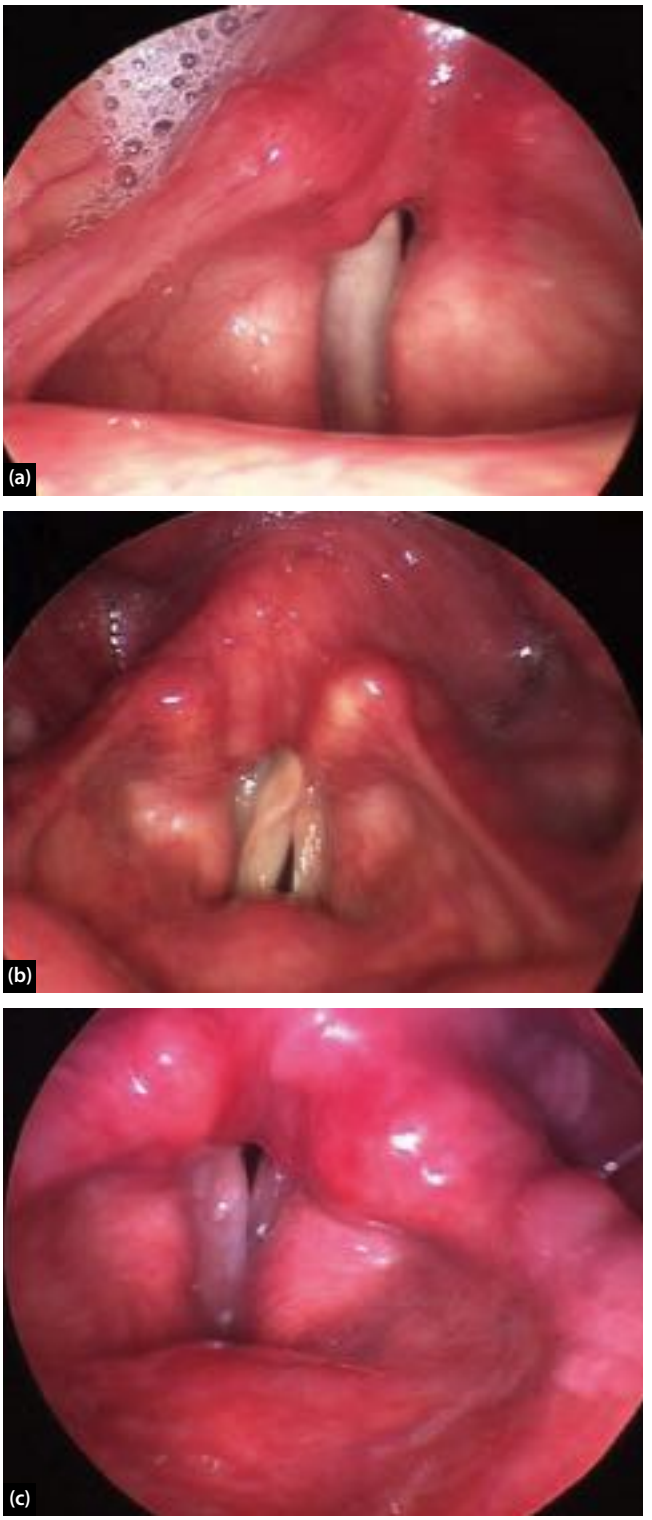


Figure 78.5 Suboptimal outcomes of medialization laryngoplasty. **(a)** Superior implant malposition in this case of left vocal fold paralysis after irradiation of a glomus tumour causes the ventricular fold to obscure the vocal fold, which is not well adducted. This is not supraglottic hyperfunction. **(b)** Inadequate medialization of the left vocal fold in a case of idiopathic paralysis results in persistent midfold glottic insufficiency and compensatory supraglottic hyperfunction. **(c)** Inadequate arytenoid medialization in this case of idiopathic right vocal fold paralysis causes persistent posterior gap. Note supraglottic hyperfunction on the normal (left) side.

RE-INNERVATION

Re-innervation using nearby nerves – both the *ansa cervicalis* and the hypoglossal nerves have been studied[41] – would seem to be an attractive and logical approach to vocal fold paralysis. However, it is subject to the same limitations as spontaneous recovery. Because of the complex innervation of the vocal fold muscles, re-innervation generally stands to improve the bulk and tone of vocal fold muscle but will not restore physiologic motion. Re-innervation is ideally suited when the vocal fold is known to be completely denervated (e.g. if the recurrent nerve or vagus has been sectioned). In fact, in cases of nerve section recognized during surgery, immediate re-anastomosis, or re-innervation if tension-free nerve re-anastomosis is not possible, is the treatment of choice. However, when considering re-innervation later in the course of paralysis, the surgeon should be reasonably confident that he or she is not depriving the vocal fold of existing re-innervation by sectioning a partially recovered recurrent nerve to use the distal stump. The patient must be counselled that symptom improvement may take weeks or months. For this reason, re-innervation has sometimes been combined with other rehabilitation techniques.

BILATERAL VOCAL FOLD PARALYSIS

Virtually any condition that can cause unilateral laryngeal paralysis may affect both recurrent laryngeal nerves to cause bilateral paralysis. Thyroidectomy remains the leading surgical cause;[42] both nerves are also at risk at esophagectomy, tracheal resection, thymectomy and other mediastinal procedures. Similarly, tracheal, esophageal and thyroid malignancies may compromise both nerves. Neurologic disorders tend to cause diffuse involvement of the peripheral nervous system. Amyotrophic lateral sclerosis, post-polio syndrome, Charcot–Marie–Tooth neuropathy, Arnold Chiari malformation and Guillain-Barré syndrome have been documented causes of bilateral paralysis. Some bilateral laryngeal paralyses are idiopathic, attributed to the same infectious agents as unilateral paralysis.

A clinician encountering bilateral vocal fold immobility should consider the possibility of joint fixation or posterior glottic scar, particularly when the condition follows intubation. In such cases the vocal folds are not denervated but merely appear to be, because of mechanical limitation. Careful inspection, sometimes requiring operative laryngoscopy, radiologic investigation and/or electromyography should be used to clarify the diagnosis, as mechanical limitations may be correctible.

Patients with bilateral vocal fold paralysis typically complain of dyspnea, noisy breathing and exercise intolerance. The severity of these respiratory symptoms is inversely proportional to the size of the glottic aperture between the two immobile vocal folds. Respiratory noise is worse on inspiration, as negative pressure pulls the denervated vocal folds into closer approximation. Voice may not be greatly altered, and swallowing is usually not affected.

In acute bilateral vocal fold paralysis, symptoms may be dramatic and even life-threatening. The typical scenario is unexpected respiratory distress after extubation from thyroid surgery and, in such a case, securing an adequate airway is the only consideration. In progressive cases, as found in certain neurologic diseases, patients may compensate as the paralysis becomes denser, and may tolerate unexpectedly small glottic airways. Close questioning about noisy inspiration or limitations in physical activity will suggest that paralysis has been present for some time.

Investigation includes radiologic imaging in the manner of unilateral vocal fold paralysis, with special emphasis on the mediastinum and infra-laryngeal neck, as well as the central nervous system. The degree of airway obstruction may be quantified using a flow-volume loop (see Chapter 76, Laryngeal stenosis in adults). Bilateral paralysis typically shows a variable (rather than fixed) extra-thoracic obstruction, as the vocal folds will passively adduct during inspiration and abduct with positive expiratory air pressure.

Treatment is guided by the degree of airway limitation; except in situations of acute airway distress, the patient may be the best judge of functional handicap. Tracheotomy is frequently performed emergently and may be a reasonable treatment option for the long term as well, as it guarantees airway with minimal compromise of phonation and deglutition. Often, though, patients prefer to avoid the inconveniences of tracheostomy if possible. Other treatment options include lateralization of the vocal fold or removal of arytenoid and/or vocal fold tissue to enlarge the glottic aperture (for more information, see Chapter 76, Laryngeal stenosis in adults). Effort is made to preserve the membranous vocal fold to the greatest extent possible in these procedures, but voice and sometimes swallowing may be adversely affected. Some of these procedures are destructive and irreversible, so the otolaryngologist should be sure that any reasonable possibility of spontaneous improvement has been exhausted before they are considered. Laryngeal pacemakers are currently being evaluated in human trials.[43]

VOCAL FOLD PARESIS

A sophisticated understanding of pathophysiology reveals that vocal fold paralysis is not an all-or-none phenomenon. Paresis, or incomplete paralysis in which some gross vocal fold mobility is preserved, exists alongside complete paralysis as a clinical entity. Symptoms of paresis are predominantly those of glottic insufficiency, even with bilateral involvement. This is because it is rare for paresis to be so dense that it impairs abduction to the extent that the airway is meaningfully narrowed. On the other hand, phonatory glottic function is affected by even mild asymmetries in neural input. Even when glottic closure appears grossly adequate, asymmetries in vocal fold tension may affect pitch, vocal stamina and high or low intensity phonation. Diagnosing paresis may be challenging because preserved gross vocal fold mobility may lull the examiner into overlooking subtle glottic insufficiency or limitations in motion. Perhaps the most difficult task is distinguishing paresis from innocent asymmetries in vocal fold motion, which are probably present in many individuals. Stroboscopy may occasionally be helpful, as subtle decrease in muscular tone affects the amplitude and frequency of the mucosal wave during phonation. LEMG must be used with as much judgement as laryngoscopy, as it probably lacks sensitivity. Because of the diagnostic challenge, there is a role for treatment trials in the form in injection augmentation in patients in whom the diagnosis remains ambiguous.[44]

Most aspects of laryngeal paresis, including prevalence, natural history, laryngoscopic and stroboscopic signs, and relation to other pathology such as mucosal lesions, continue to require clarification.

CONCLUSIONS

Laryngeal paralysis usually results from peripheral nerve injury of one or more laryngeal nerves, and results in clinically significant changes in phonation, swallowing and/or respiration. Often thought of as an all-or-none phenomenon, laryngeal paralysis represents a spectrum of nerve injury and re-innervation, which accounts for the variability in its clinical presentation. Investigation is aimed at discovering underlying causes. Because of the strong laryngeal propensity to re-innervation, paralysis tends to improve over time, and sometimes resolves spontaneously. When it does not, numerous surgical options are available to remedy dysphonia and dysphagia from the glottic insufficiency of unilateral laryngeal paralysis. Respiratory restriction from bilateral paralysis is a greater challenge, however, since most surgical measures are destructive, irreversible and stand to impact voice and swallowing adversely.

FUTURE RESEARCH

- Further identification of factors underlying idiopathic vocal fold paralysis.
- Improved characterization of laryngeal neurophysiology and recurrent laryngeal nerve recovery process.
- Development of reliable quantitative measures in laryngeal electrodiagnostics.
- Development of reliable and stable permanent injectates for definitive office augmentation.
- Dynamic rehabilitation of laryngeal paralysis, including electrical pacing and functional re-innervation.

KEY POINTS

- Vocal fold paralysis can be unilateral or bilateral, either scenario having different clinical implications.
- When facing vocal fold immobility, it is important to distinguish neurogenic paralysis from mechanical fixation.
- Most cases of vocal fold paralysis are caused by peripheral nerve injury.
- Spontaneous nerve recovery is the norm, but not return of function, due to the complex specificities of laryngeal neurophysiology.
- Beyond the treatment of an identifiable cause, management is mainly symptom-driven to address laryngeal dysfunction.
- A wide range of interventions is available to improve most patients' functional deficits.

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CHAPTER 79

OUTPATIENT LARYNGEAL PROCEDURES

Matthew Stephen Broadhurst

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: office laryngology, outpatient procedures, laser surgery and transnasal oesophagoscopy.

INTRODUCTION

There have been significant advances in the technology of flexible and rigid video endoscopy, along with innovative techniques that now provide the otolaryngologist with the ability to perform office-based laryngeal procedures. This has enabled surgeons to take the patient from a hospital admission with general anaesthesia and associated risks and downtime, to an office-based setting. Here, the same procedure is performed entirely under local anaesthetic without sedation. With careful patient selection and realistic expectations for outcome, a proportion of the pathology that occurs in the larynx can be well treated in the office through awake unsedated laryngeal surgery (AULS).

Performing AULS provides advantages to both patient and surgeon. The patient can drive themselves to and from the office procedure, can return to work on the same day if necessary and can avoid day hospital admission and general anaesthesia with its inherent risks. In addition, the need to allow diseases such as dysplasia, leukoplakia and papilloma to progress to substantial severity to justify the risks of general anaesthesia is obviated. Instead, patients can undergo a low-risk, simple office angiolytic laser treatment of laryngeal papilloma as an awake procedure in 10–15 minutes with a rapid recovery and minimal downtime. Such office procedures can be performed as frequently as clinically indicated. In addition, in some countries, there is a substantial cost saving for AULS.[1]

It should be stressed that the term 'office-based' and 'outpatient' are often used interchangeably. The critical point is that the patient remains unsedated and is in a totally cooperative state. As such the patient can undergo the procedure either in the surgeon's office or, at times, in the operating theatre.

The more commonly performed laryngeal procedures include laryngeal injection, endoscopic fibre-based laser procedures, transnasal oesophagoscopy (TNO) and panendoscopy, with numerous studies showing adequate patient safety profiles, high patient satisfaction rates and treatment outcomes for laryngeal pathology.[2–6]

HISTORY

The field of laryngology has developed extensively from its inception in the late 1800s. The first laryngology society was formed in the United States and held its inaugural meeting in 1879.[7] Prior to this there had been a tremendous interest in both the anatomy and physiology of voice production and deglutition, with reports of dental mirrors being used to examine the oral cavity as far back as the Roman era. The earliest, most extensive work on the anatomy of voice and hearing, written in CE 1600, came from Julio Casserius.[8, 9] In this text are found eloquent descriptions of the anatomy of both humans and animals. In the mid-19th century, Manuel Garcia,[10] a prominent singer and teacher, perfected mirror laryngoscopy well before it was common practice for

physicians. After rapidly growing fascination in laryngeal anatomy and function, many physicians in the late 19th century became very skilled at mirror examination of the larynx and began to adopt simple procedures that included removal of growths and foreign bodies.[11, 12] In the 1880s, topical anaesthesia with cocaine became available, which greatly aided office laryngeal procedures.[13] At the turn of the 20th century, Chevalier Jackson pioneered the new era of laryngology. It was shortly thereafter, with the use of general anaesthesia and airway cannulation, that laryngology procedures were taken from the physician's office into the operating theatre. In the late 20th century, as technology advanced exponentially, there was a move of laryngology procedures back toward the physician's office as AULS. Today, the modern laryngologist has rigid and flexible high-definition endoscopy and a wide range of rigid and flexible instrumentation to enable safe and effective outpatient laryngeal procedures to be performed.

OUTPATIENT LARYNGEAL PROCEDURES

Table 79.1 lists the various outpatient laryngeal procedures, the more commonly performed being laryngeal injection and endoscopic laser. Injection laryngoplasty is discussed in greater detail in Chapter 67, Phonosurgery and Chapter 78, Paralysis of the larynx. Other less commonly performed procedures include TNO, panendoscopy, removal of foreign bodies, treatment of glottic webs, biopsy and even balloon dilation for stenosis.

Patient preparation

With today's technology affording the ENT surgeon unprecedented abilities to perform both simple and advanced laryngeal procedures in the office or outpatient setting, patient selection and preparation is paramount to minimize risks of cardiorespiratory complications.[14] As with any surgical intervention, establishing a sound rapport with the patient is critical. The ability for a patient to undergo an office-based procedure is greatly enhanced when they have a high comfort level with the treating surgeon and feel confident in his or her care. To this end, informed consent plays a key role in the pre-procedure preparation. A discussion with the patient about the way the procedure is done, the goal(s) of the procedure and the expected and unexpected outcomes are all discussed.

TABLE 79.1 Common outpatient/office-based laryngeal procedures

Laryngeal injection	Injection laryngoplasty	Glottal gap from unilateral vocal fold paralysis, presbyphonia, surgical defect
	Chemical injection	Botulinum toxin, bevacizumab, saline, cidofovir
Laryngeal laser	KTP, PDL, CO_2, Thulium, Gold	Dysplasia, keratosis, papilloma, ectasias, varices, glottic web, granulation tissue, vocal process granuloma
Panendoscopy/ transnasal oesophagoscopy	Diagnostic	Therapeutic

The surgeon must ensure that the patient is a suitable candidate for office-based laryngeal surgery. Contraindications include patients with significant comorbidities, significant airway narrowing, heightened anxiety or extremes of age. For most office laryngeal procedures, patients who are on anticoagulants do not necessarily need to cease them pre-operatively. In the author's experience of over 400 office procedures, there have been 38 procedures performed with patients on anticoagulants (including warfarin). None of these patients have had any bleeding that has been significant, either during or after the procedure.

Local anaesthesia

Inadequate topical anaesthesia for AULS is destined to produce a suboptimal outcome, even despite the surgeon's advanced skill level and highly developed imaging and instrumentation. With this in mind, having a relaxed and well-anaesthetized patient is the critical starting point for successful AULS. The technique for topical anaesthesia will depend on whether the main instrumentation is done transnasally, transorally or transcutaneously.

The most commonly used of all of these is lidocaine due to its rapid onset of action and duration of effect. Although it is relatively low potency in comparison to other local anaesthetic agents, it has an onset of action in as little as 90 seconds and the duration of effect can range from 45 to 60 minutes. With any agent, knowledge of the appropriate dose is critical. The author mainly utilizes 4% lidocaine, representing 40 mg/mL. Toxicity occurs when the dose exceeds 3–5 mg/kg. In an average 70 kg male, the safe dose would be up to 300 mg, equating to 7.5 mL of 4% lidocaine. The maximum volume the author has used in any of the procedures performed has been 4 mL. For most procedures, between 2 mL and 4 mL is adequate to topically anaesthetize the laryngeal mucosa for the range of office procedures to be described.

Lidocaine toxicity must be identified at its earliest signs to enable prompt intervention and treatment. The signs of toxicity include peri-oral and distal upper limb paraesthesia, tinnitus, vertigo, visual disturbance, slurred speech, tremor, tonic-clonic seizures and coma. At the first suspicion of toxicity, the procedure should be halted and emergency management should be commenced.

Patient selection

In the author's experience, approximately 2% of AULS cannot be performed despite adequate preparation. The common reasons for this are intractable gagging despite aggressive local anaesthetic application and severe oropharyngeal crowding. A Friedman Grade 3 or 4 patient[15] can make the procedure difficult and occasionally will need conversion to a transnasal procedure. In some

patients, 10 mg of diazepam can be prescribed if there is a degree of anxiety or heightened gagging, and they will thus have their outpatient laryngeal procedure performed in the operating room.

Patient position

The ideal position for the patient is to be sitting in a typical ENT exam chair that would have them partially flexed forward at the hips. Placing a pillow behind the shoulders can assist in obtaining this position. **Figure 79.1** shows a typical approach for a transoral procedure. The height of the chair can then be raised to suit the surgeon's preference. If a laser procedure is being performed, a small suction catheter is placed transnasally with the distal tip sitting in the oropharynx. The catheter extends across the cheek and is taped securely in place. For any laser procedure the standard laser precautions are observed, which include, but are not limited to, protective eyewear with suitable protection for the wavelength being used and laser-rated surgical mask. Although many procedures can be done as a sole operator without the need of assistance, it is generally advisable to have a nurse, resident, registrar or other assistant at hand.

Transnasal approach

If the procedure is to be done entirely in a transnasal route then simple topical anaesthesia into the nasal cavity and down into the hypopharynx and larynx is sufficient.

Transnasal anaesthesia begins with aerosolized lidocaine mixed with oxymetazoline sprayed into at least one nasal cavity. Techniques often describe spraying both nasal cavities but a careful nasendoscopy prior to the anaesthetic should indicate which nasal cavity is more patent to accommodate the endoscope. In this setting, by only anaesthetizing one nasal cavity, the surgeon can limit the total amount of local anaesthetic used. After waiting the minimum of 3 minutes for adequate anaesthesia and vasoconstriction to take place, the flexible nasendoscope can then be passed, visualizing the entire nasal cavity. As the distal tip nasal endoscope with a working channel is passed into the oropharynx, again careful inspection of all mucosal surfaces takes place. With the endoscope tip sitting approximately level with the tip of the epiglottis, the patient is asked to sustain an 'eee' sound while 2 mL of 4% lidocaine is slowly dripped onto the vibrating larynx. The vibrations disperse the lidocaine to most of the laryngeal mucosal surfaces, providing wide coverage of anaesthesia. At that point the larynx is appropriately anaesthetized and the desired procedure can be performed.

Transoral approach

Due to the superior image quality of rigid transoral endoscopy, most of the author's office procedures utilize a 70 degrees rigid telescope and 1080 p high-definition endoscopy displayed on a 50-inch true high definition plasma monitor. The transoral route is well tolerated in the majority of patients when adequate anaesthesia is administered. The initial delivery of 4% lidocaine is through an atomizing device (**Figure 79.2**) where approximately 0.5 mL is sprayed to cover the tongue base, posterior pharyngeal wall and soft palate. Following this, the tip of the atomizer is angled to 70 degrees (**Figure 79.2** inset) and, with gentle tongue traction, a further 0.5 mL of lidocaine is atomized onto the vallecula, epiglottis and remaining supraglottis. Some lidocaine does contact the glottic surface and into the upper trachea. The endpoint of adequate anaesthesia is when the patient ceases coughing with subsequent topical administrations, keeping in mind the maximal safe volume of 4% lidocaine to use.

Using the rigid telescope in one hand and with either the patient or an assistant providing tongue traction, a curved orotracheal injector is introduced with the other hand. A further 1 mL of 4% lidocaine is slowly dripped onto a vibrating larynx sustaining an 'eee' sound similar to the preparation for transnasal procedures. There is now adequate anaesthesia of the larynx and the planned procedure can be performed. To date, the author has never required more than 4 mL of 4% lidocaine for an AULS.



Figure 79.1 The patient sits upright leaning slightly forward flexing at the hips and with slight chin elevation. For the transoral injection laryngoplasty the patient is seen providing traction on their own tongue. This allows the surgeon to use the dominant hand for the injection and the non-dominant hand for the telescope. An assistant is optional, so the procedure can be performed solely by the surgeon.

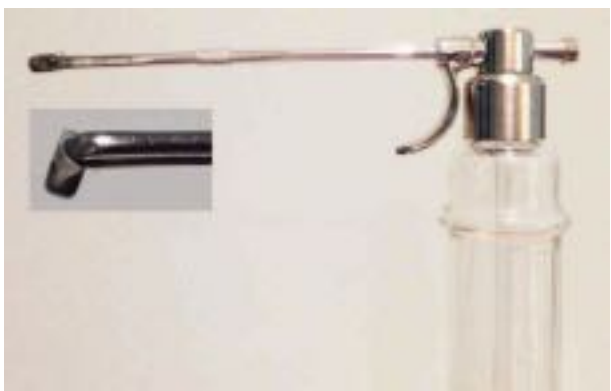


Figure 79.2 An atomizer enables extensive mucosal anaesthesia delivered to the oropharyngeal surfaces. Having graduations marked on the glass bottle can allow a known volume of 4% lidocaine to be used. The inset shows the delivery tip being angled to 70 degrees, which allows excellent mucosal anaesthesia delivery to the hypopharynx, supraglottis and glottis.

Occasionally a bilateral superior laryngeal nerve block is required. The superior laryngeal nerve is found at the midpoint between the superior aspect of the thyroid cartilage and the inferior edge of the hyoid bone laterally. One mL of 4% lidocaine to each side is adequate to achieve sufficient anaesthesia. As with other peripheral-type nerve blocks, approximately 10 minutes is required to have a reasonable effect. Another useful adjunct to topical anaesthesia is administration through a cricothyroid membrane puncture. This universally generates significant coughing and as long as the patient is aware of this pre-injection, they usually find it bearable. The coughing helps distribute the local anaesthetic to benefit the procedure.

LASER LARYNGEAL PROCEDURES

Since the introduction of the carbon dioxide laser into laryngology in the early 1970s,[16, 17] there has been a steady evolution and refinement of the processes for optimizing laser treatment of laryngeal pathology. In the past 15 years there has been an exponential increase in the use of angiolytic lasers in laryngology, both in the operating theatre and in the office. These lasers act by photoablation of the intra-lesional microcirculation through a process termed photothermolysis.[18, 19] Although it has been 30 years since the original description using pulsed dye laser, the modern angiolytic laser industry includes numerous lasers. A list of commonly used office lasers can be seen in **Table 79.2**.

The most commonly used angiolytic laser today in laryngology is the 532 nm potassium titanyl phosphate (KTP) laser. The absorbance of haemoglobin has peaks at approximately 541 nm and 577 nm,[20] allowing the KTP laser energy to be absorbed into the pathology, such as papilloma or dysplasia, with no collateral injury to surrounding normal tissue (**Figure 79.3**). The angiolytic parameters of the KTP laser were studied in the avian chorioallantoic membrane indicating that 35 watts, 15 millisecond pulse width and 2 pulses per second achieved ideal photoablation without surrounding collateral damage. **Figure 79.4a** shows the typical avian chorioallantoic membrane model with its vasculature. **Figure 79.4b** is demonstrating ablation of a single 100 micron vessel without vessel rupture or collateral damage.[20] Findings of this study translated seamlessly to the vocal fold mucosa and remains the author's most frequently used KTP laser settings. In the delicate and highly specialized layered microstructure of the vocal fold, maximal preservation of normal tissue surrounding a lesion is critical to minimizing any vocal deficit.

The 585 nm pulsed dye laser and 980 nm Gold angiolytic laser are less commonly used.[21, 22] All lasers in this class utilize a fibre delivery system, providing the surgeon with a close proximity interface with the laryngeal pathology being treated. Unlike the traditional CO_2 laser through a micro-manipulator using line of sight, fibre delivery office-based angiolytic lasers offer the surgeon safe and effective treatment options for many pathologies encountered. Common lesions suitable for angiolytic laser AULS are listed in **Box 79.1**.

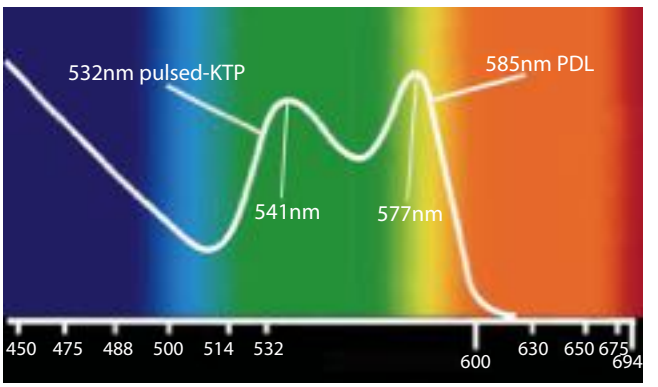


Figure 79.3 The absorbance curve for oxyhaemoglobin shows the peaks of absorbance at 541 nm and 577 nm (thin white lines). Note that the KTP (532 nm) and the pulsed dye (585 nm) angiolytic lasers have wavelengths (thick white lines) in close proximity to the absorbance peaks. This enables maximal absorption of laser energy into the microcirculation of the pathology resulting in photothermolysis.

TABLE 79.2 Angiolysis/fibre-based lasers in comparison

Laser	Wavelength	Chromophore	Advantages	Disadvantages	Fibre size (microns)
KTP laser	532 nm	Haemoglobin	• Haemostatic pulsed and continuous cuts similar to CO_2 • Low cost	• None	300–600
Pulsed dye laser	585 nm	Haemoglobin	• Haemostatic	• Dye kit unreliable	600
Gold laser	980 nm	Haemoglobin	• Haemostatic	• Limited data	300
Thulium laser	2010 nm	Water	• Haemostatic • Smallest fibre	• Increased heat	260–600
CO_2 laser	10600 nm	Water	• Clean cutting	• Increased heat • Large fibre • Cost • Non haemostatic	1210





Figure 79.4 The chorioallantoic membrane of a leghorn chicken has been exposed in a day 9 fertilized egg and shown in (a). It provides an established model for simulating vocal fold angiolysis. **(b)** demonstrates the ablation of a second order vessel with no collateral damage to the albumin. The KTP laser was used with a 300 micron fibre, 35 watts, 15 millisecond pulse width and 2 pulses per second.

BOX 79.1 Laryngeal pathology suitable for treatment by awake unsedated laryngeal surgery (AULS)

- Dysplasia
- Keratosis
- Papilloma
- Ectasias
- Varices
- Granulation tissue
- Vocal process granuloma
- Polyp

As the target chromophore is haemoglobin, angiolytic lasers are extremely haemostatic and selected patients can be treated without ceasing anticoagulants. This can significantly simplify management of some patients who may be on warfarin and have laryngeal papillomatosis requiring multiple treatments per year. In contrast, traditional management includes repeated microlaryngoscopies under general anaesthesia, often using the microdebrider or cold steel and therefore necessitating cessation of antiocoagulant therapy. Although not in the angiolytic class, the CO_2 laser can now be used through a fibre delivery system.[23, 24] The BeamPath™ ENT fibre (Omni-guide, Cambridge, Massachusetts, USA) has a spot size of 320 microns but the outer diameter is quite bulky at 1.21 mm. When placing a fibre in the working channel of a flexible endoscope, smaller fibres (such as 300 microns for KTP laser) enable more efficient suctions around them than a larger fibre such as the Omniguide (**Figure 79.5**). Another non-angiolytic fibre-based laser is the 2010 nm thulium laser (Revolix Jr, Lisa Laser, Pleasanton, California, USA). With the chromophore being water, it is highly versatile and haemostatic although it does produce somewhat more heat than the KTP laser.[25–27] The thulium laser has the smallest available fibre, being 260 microns, and has benefits over the CO_2 laser in reduced cost for the laser unit, smaller fibre diameter and – being a solid-state laser – is markedly more reliable (see **Table 79.2**).



Figure 79.5 The smallest fibre appropriate should be used as this maximized the available space within the working channel of the endoscope for suction. Musocal secretions can become quite viscous and the less space occupied by the fibre in the working channel, the better. A 300 micron KTP laser fibre is seen protruding from the distal chip endoscope with significant suction space around the fibre.

LARYNGEAL PATHOLOGY SUITABLE FOR AWAKE UNSEDATED LASER LARYNGEAL SURGERY

Laryngeal pathology with prominent microcirculation can be well treated in the awake unsedated patient with fibre-based laser systems. (**Figure 79.6** and **Box 79.1**)

Laryngeal dysplasia

Many patients with field change to the glottic mucosal surfaces require careful and frequent office review to monitor

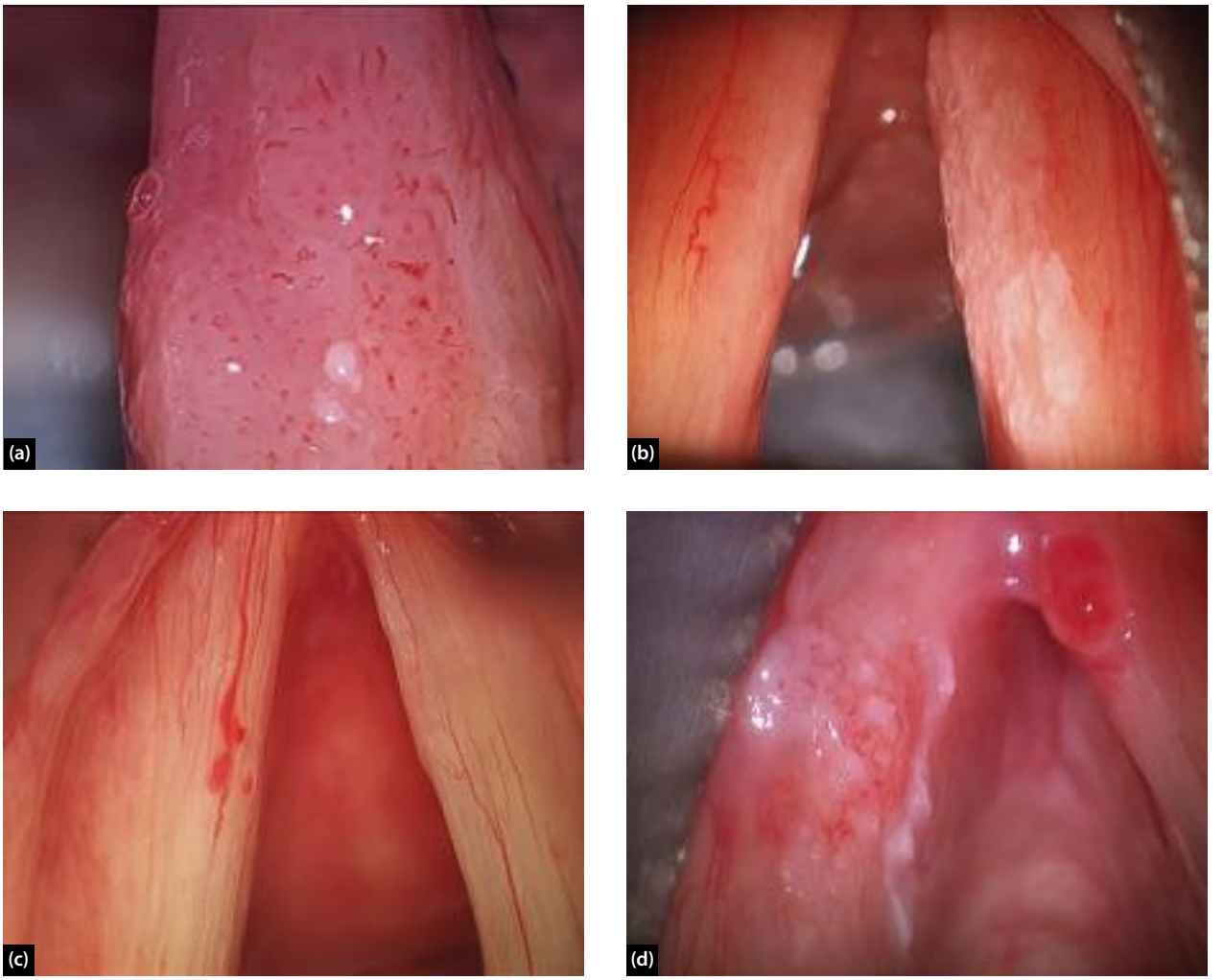


Figure 79.6 Angiolytic lasers are particularly effective for AULS due to the prominent microcirculation within some laryngeal pathology. Laryngeal papillomatosis in **(a)** demonstrates the aberrant angiogenic pattern. **(b)** shows left vocal fold ectasias with right vocal fold dysplasia. A varix and ectatic vessels are seen in a professional opera soprano in **(c)**. A small T1a squamous cell carcinoma in **(d)** further highlights the aberrant vessel growth pattern with these lesions. In all pathologies depicted, the angiolytic laser energy is absorbed by the microcirculation leading to lesion ablation with maximal preservation of the surrounding layered microstructure of the true vocal fold.

the extent of the dysplasia and keratosis and for possible malignant transformation. With the high resolution of endoscopy and fibre-based laser systems, many of these patients can now be managed with AULS procedures. In this setting, angiolytic laser ablation of regions of keratosis or dysplasia is performed and small biopsies can be taken. The procedure is generally very well tolerated and avoids the frequent hospital admission, general anaesthesia and multiple biopsies with traditional management. This in turn avoids the risks of permanent voice impairment and repeated general anaesthesia. The angiolytic epithelial ablation allows for subsequent re-epithelialization of the laryngeal mucosa tending to normalize this layer. Such a result can be seen in **Figure 79.7a** and **79.7b**. A typical glottic mucosal picture is seen with keratosis and dysplasia (**Figure 79.7a**). After a single office KTP laser ablation and more than 2 years following the procedure, the vocal folds still appear normal (**Figure 79.7b**) and the voice remains markedly improved. The concept of proactive management in field change keratosis/dysplasia is a substantial step forward in managing this difficult condition. It moves the surgeon away from the traditional 'wait and see' approach, where periodic microlaryngoscopies under general anaesthesia with biopsies cumulatively destroy the voice in managing benign disease. Benefits of this paradigm shift include preservation of the voice by avoiding multiple glottic biopsies and reduced burden on the outpatient clinics as close follow-up of field change is no longer applicable.

Laryngeal papillomatosis

Patients with laryngeal papillomatosis are well known to require multiple hospital admissions under general anaesthesia to manage this condition. The goals of treatment are to maintain airway patency and for voice preservation. It must be stressed that papilloma arises from the epithelium and as such, treatment should be confined to a depth

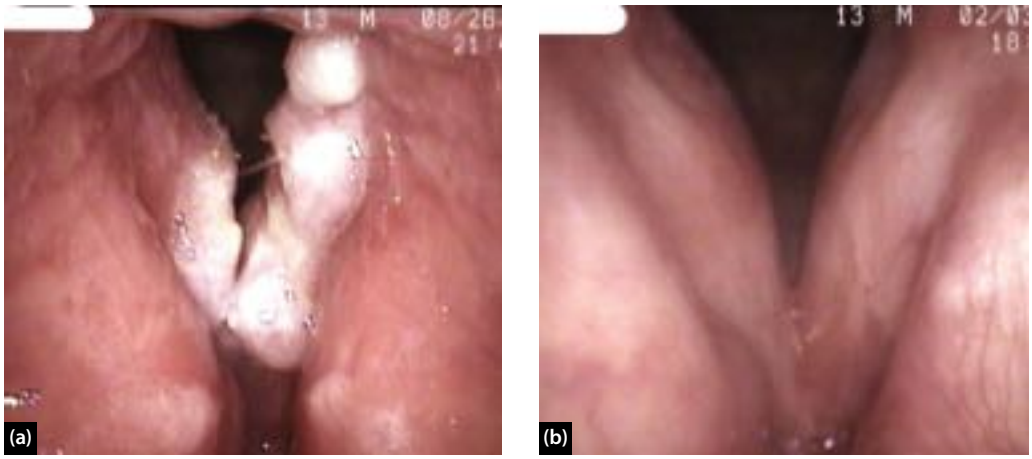


Figure 79.7 A typical patient with extensive keratosis and dysplasia is depicted in (a). This patient was medically unfit for general anaesthetic and was initially offered curative intent radiation for a presumed glottic cancer by the multidisciplinary team. He was then treated by the author with AULS utilizing KTP laser. Biopsies showed dysplasia but no cancer and after two office treatments the entire glottic surfaces normalized as, did his voice with follow-up now at 3 years **(b)**. This is a typical outcome for such a patient and avoided unnecessary radiation.

no more than the epithelial layer. Under traditional management the patient typically undergoes repeated general anaesthaesia and use of the microdebrider or non-angiolytic lasers to control the disease. To limit the number of general anaesthetics, procedures tend to be scheduled before there is substantial regrowth. In this setting, with the loss of many landmarks, it is not difficult to stray deep to the epithelial layer of the vocal folds and permanently denude the superficial lamina propria (SLP). As this can occur over many treatments with time, many patients become vocal cripples. As a paradigm shift, these patients can be initially controlled in theatre with angiolytic lasers and then transferred to the office setting for maintenance treatment with angiolytic lasers.[28, 29] Performing office procedures to control laryngeal papillomatosis can also limit the risks associated with frequent general anaesthesia and airway surgery.

In a typical initial presentation in a patient with extensive disease, treatment is first undertaken at microlaryngoscopy in theatre with general anaesthetic. In this setting, the author uses KTP laser ablation of all laryngeal papillomatosis. It is critical under the operating microscope to identify all mucosal areas of papilloma and treat them. For very early disease, the most subtle finding for papilloma is loss of the linear blood vessel growth pattern in normal mucosal. One can clearly see the loss of this normal pattern in **Figure 79.8** as the epithelium thickens and the vessels become aberrant with papilloma growth. Once this visual sign is noted, the surgeon can quickly identify areas of abnormal epithelium both under the operating microscope and using office-based high definition endoscopy. In both settings, angiolytic laser ablation can then be carefully directed to the diseased surfaces. With the appreciation of the subtle vascular changes seen clearly under high definition office endoscopy, there is little need for additional expensive endoscopy devices such as narrow band imaging.

At microlaryngoscopy, careful inspection of the ventricles is critical. On numerous occasions in tertiary referral cases, the author has found papilloma filling the ventricles that had not been noted at the referring ENT centre. In a setting such as this, seen in **Figure 79.9**, endoscopic removal of the false cords exteriorizes the ventricles and allows for both subsequent surveillance and treatment of recurrent papillomatosis. Having adequate access to all laryngeal mucosal surfaces is invaluable in the office-based setting to manage recurrent laryngeal papillomatosis.



Figure 79.8 The loss of normal linear vascularity of the true vocal fold mucosa is seen clearly, outlined in white, by papilloma growth. The mucosa thickens and aberrant angiogenesis leads to the typical papilloma appearance, which can be clearly defined from the surrounding normal tissue. Being acutely aware of this interface appearance can allow the astute surgeon to easily identify abnormal regions of papilloma in the office setting and deliver target-specific angiolysis.

After office-based angiolytic ablation of the papillomatosis, subepithelial tissues are injected with bevacizumab.[30,31] Bevacizumab (Avastin®), a vascular endothelial growth factor inhibitor, appears to reduce the angiogenesis critical to papilloma regrowth, and can reduce the frequency of procedures and extent of papilloma recurrence. In some patients, the disease has remained in remission.[32]



Figure 79.9 It is crucial in managing papilloma to closely inspect each ventricle at the time of microlaryngoscopy. This allows clearance of the entire ventricular disease, such as that shown by the white arrow. The false cord is also removed exteriorizing the ventricle. This enables unobscured surveillance of all laryngeal mucosal surfaces and enables easy access to the ventricle should disease recur.



Figure 79.10 A simple office-based injection into the superficial lamina propria (SLP) can be performed as adjunctive treatment to angiolytic laser ablation of laryngeal papilloma. Note the distention of the SLP from the bevacizumab injection at 25 mg in 1 mL. This 10-minute awake procedure greatly simplifies managing some laryngeal conditions avoiding repeated microlaryngoscopies.

The half-life for bevacizumab is approximately 1 month. Given this, office-based injections are likely to be most effective when the supposed angiogenic 'switch' occurs within that month. **Figure 79.10** shows a typical injection in the office setting of bevacizumab, avoiding the need for general anaesthetic for such a short and simple procedure.

Patients with more aggressive or frequent recurrences tend to respond better to bevacizumab injections. Doses typically used are 25–50 mg (25 mg/ml).[30–32] Since first using Avastin in 2009, the author has noted many patients to have total eradication of the disease, who prior to commencement on bevacizumab, underwent multiple procedures per year. The only change associated with the eradication of papilloma has been the addition of KTP laser and bevacizumab to the management.

Laryngeal ectasias and varices

Some patients may present with a small vascular anomaly of the vocal fold and the only treatment necessary is removal of the lesion. For a simple ectasia or varix that is causing recurrent haemorrhage in a professional voice user, ablation of the lesion is required. Although this is typically done in the operating theatre under general anaesthesia with microlaryngoscopy, in suitable patients where there is no additional underlying pathology (e.g. nodules) the surgeon can ablate the lesion in the office setting safely with an angiolytic laser with maximal preservation of the layered microstructure of the true vocal folds.[21, 28, 33–35]

Figure 79.11 shows a typical lesion in a 62-year-old male causing recurrent haemorrhage. It was easily ablated with the KTP laser (settings: 35 watts, 15 ms pulse width, 2 pulses per second) as an awake unsedated office procedure with no recurrence at 1-year follow-up.

Arytenoid granuloma, laryngeal granulation, polyps and glottic web

There are numerous other entities that can be treated in the awake unsedated patient. This can be an attractive alternative when risks of general anaesthesia to the patient are high or there is patient preference for avoiding general anaesthesia or hospital admission. The lack of precision in treating these entities during an awake procedure when compared to suspension microlaryngoscopy and general anaesthesia needs to be explained to the patient.[36, 37] However, treating an arytenoid granuloma, polyp or granulation is a debulking procedure and high level precision is not critical. In polyp management, reports indicate reduction in size can be achieved with office laser treatment. Mallur et al. reported all lesions to have regressed over a 1-year follow-up.[38] Ivey et al. reported that office pulsed dye laser was able to reduce the polyp size by greater than 70% in approximately one-third of cases. It was also reported that up to 40% of patients did proceed to phonomicrosurgical resection as definitive treatment.[36] Although polyps can be debulked in this setting, it is more in the patient's best interest to elect for a near 100% success rate by treating a vocal fold polyp in theatre with microlaryngoscopy utilizing phonomicrosurgical techniques rather than accepting a simple reduction in lesion size through an office debulking procedure, which can sometimes involve multiple procedures.

Techniques for awake unsedated laser laryngeal surgery

As discussed under the injection section, the approach for laser treatments in the awake unsedated patient can be either transnasal or transoral. The author's laser preference is the

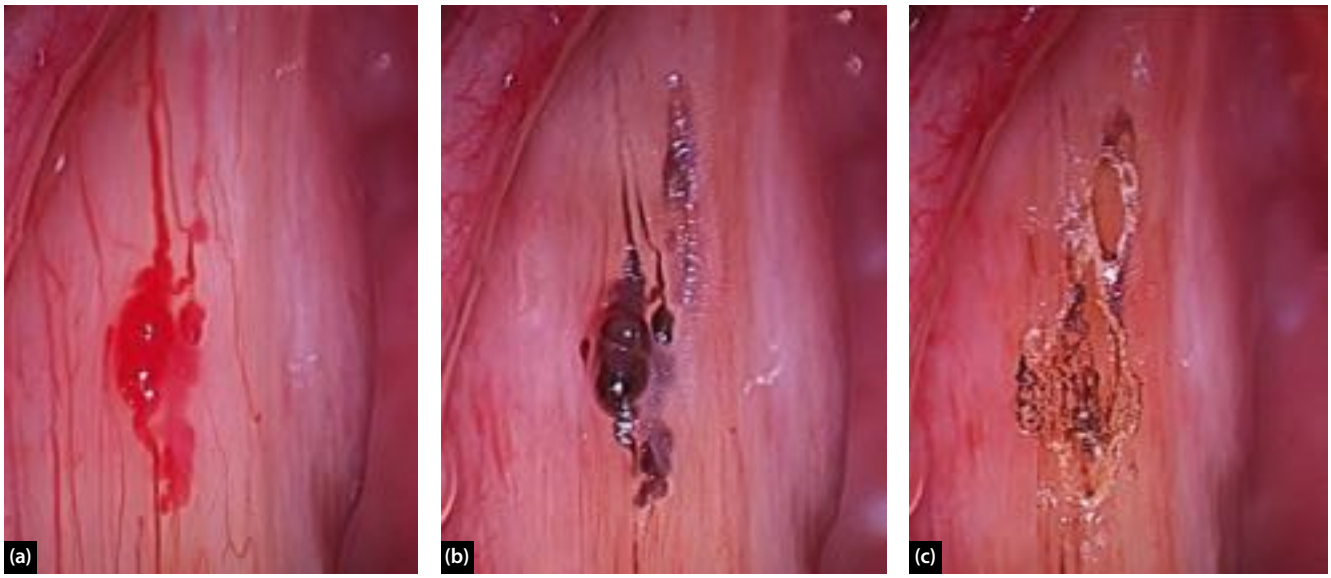


Figure 79.11 A 62-year-old male with recurrent true vocal fold haemorrhage from a large left vocal fold varix. (a) This can be easily ablated with an angiolytic laser (KTP laser in this case). Note the coagulum formed before final ablation **(b)** and no collateral injury to the true vocal fold layered microstructure **(c)**. After 1 week of voice rest, review showed complete resolution and at 2 years there remains no recurrence.

532 nm KTP laser (Aura XP, American Medical Systems, Minnetonka, MN) due to its small fibre size (300 microns), solid state, relative portability, variable power, pulse width and pulse frequency, and reasonable price.

In the transnasal approach, the patient preparation and distal chip flexible endoscopy placement is identical. For simple lesion ablation such as papilloma or ectasias, the fibre is brought into view and the laser is engaged. Initial blanching of the lesion will occur before it is completely ablated. **Figure 79.12** shows the glottic papilloma being ablated with the KTP laser. After the lesions blanch and are suctioned free, the underlying surface heals cleanly. If papilloma is being treated, then after ablation, the fibre tip or endoscope tip can be used to dislodge treated disease. After this, the under surface can be inspected and treated if necessary. Although lidocaine can have a 45–60 minute duration of anaesthesia, only approximately 15 minutes of adequate anaesthesia time for an awake procedure is available. Despite this, the majority of papillomatosis in a patient's larynx can be successfully treated in one setting, while occasionally a staged procedure is required for extensive disease.

For an arytenoid granuloma, granulation tissue or a polyp, the laser fibre is held in contact mode and the lesion ablated. Suction or the tip of the scope can be used to manually debulk the lesion further as treatment is completed. **Figure 79.13** shows the treatment of a vocal process granuloma with KTP laser and botulinum toxin injection in the office setting. The procedure took 10 minutes and the patient was able to drive himself home shortly after (**Figure 79.13**). These lesions can also be treated using the CO_2 or thulium lasers with fibre-based delivery. Both are highly efficient at removing such tissue and the latter is highly haemostatic. If using these lasers, care must be taken not to overtreat the base of the lesion at its interface with any SLP. These lasers have a markedly higher likelihood of creating thermal damage to the underlying SLP with subsequent fibrosis and scarring resulting in dysphonia.

TRANSNASAL OESOPHAGOSCOPY, PANENDOSCOPY AND BALLOON DILATION

ENT surgeons have long been competent in rigid oesophagoscopy and bronchoscopy in the theatre setting under general anaesthetic. In the office setting, hundreds of times each year, ENT surgeons use flexible nasopharyngoscopes to assess the upper airway. With improvements in distal chip image quality and narrow endoscopes with a working channel, the surgeon can progress forward to a more comprehensive aerodigestive tract assessment. Building on the highly familiar nasopharyngoscopy technique, the ENT surgeon can now pass the endoscope safely into the oesophagus and trachea for close-proximity assessment and treatment.

TNO is increasingly being used by otolaryngologists, with the advantage of avoiding hospital admission and sedation, which is traditionally performed in endoscopy suites. Although TNO can be performed with a bronchoscope, dedicated endoscopes are available for the purpose. The outer diameter ranges from 3.1 mm to 5.3 mm. A port or working channel is required (2 mm diameter) for suction, biopsy forceps, injection device or a laser fibre. An alternative model is to use a sheath around the endoscope that incorporates insufflation and instrumentation channels. The advantage of the sheath technique is that the endoscope does not need to go through a full sterilization cycle and several patients can be assessed in a single setting.

Common indications for TNO (listed in **Box 79.2**) include laryngopharyngeal reflux, dysphagia, monitoring

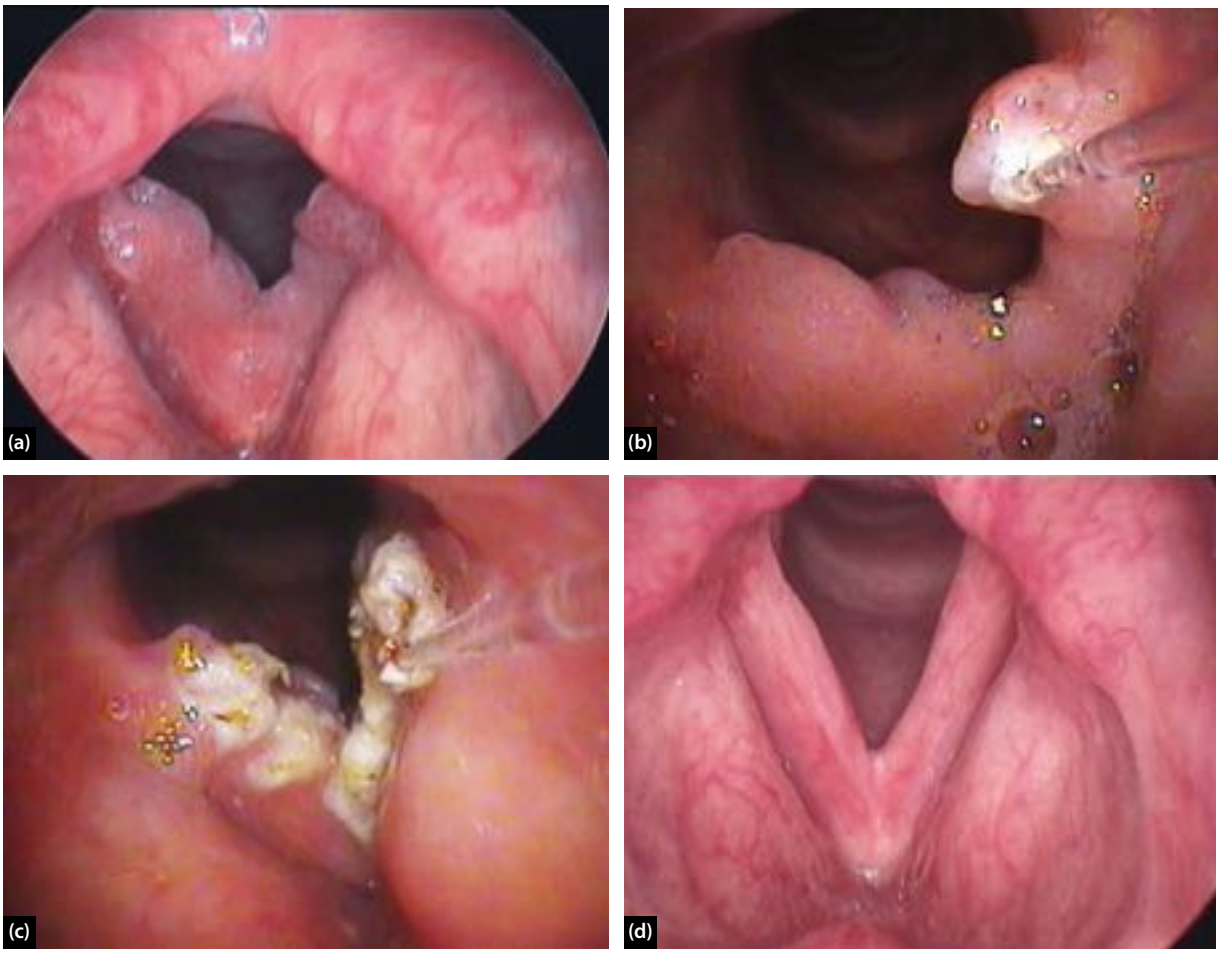


Figure 79.12 Typical glottic papilloma is seen covering both vocal fold surfaces in (a). Initial ablation with a 300 micron KTP laser fibre (settings: 35 watts, 15 ms pulse width, 2 pulses per second) of the posterior left papilloma is seen in **(b)**. As the procedure continues, **(c)** shows the majority of the papilloma is now ablated and can be scraped free with the fibre tip or the endoscope tip. After two office treatments and 2 years later, the patient remains free from papilloma **(d)** and with markedly improved voice. This patient had undergone previous microlaryngeal surgery with severe anaesthetic reactions. He refused microlaryngeal surgery offered prior to his referral to the author but agreed to AULS. Note the absence of any bleeding in the procedure due to the significant haemostatic nature of the KTP laser.

of Barrett's oesophagus, screening for head and neck cancer, chronic cough and procedural (injection Botox, balloon dilation, tracheo-oesophageal puncture and placement of pH probes). It is important to note that, in skilled hands, there is no measurable difference in diagnostic accuracy rates between conventional oesophagoscopy and the newer TNE.[6, 38–45] In addition, for TNO the patient tolerance is very high and risks are minimal. Rates of epistaxis are below 2% with vasovagal events being even less common.

Aside from TNO, the same endoscope can be used to perform panendoscopy in the office setting,[45] although routine bronchoscopic evaluations are not performed these days owing to the availability of high resolution CT scans. In a primary workup, for example of a small vocal fold tumour, a 15-minute in-office panendoscopy can safely provide the necessary information. Traditionally, a head and neck cancer patient would undergo a hospital admission, general anaesthesia with biopsy and panendoscopy (microlaryngoscopy, oesophagoscopy and bronchoscopy) for assessment of the disease extent. In selected patients this can be safely done in the awake unsedated patient in the office. Utilizing AULS, equivalent information is gained when compared to the traditional panendoscopy but it does spare the patient the downtime of a hospital day/overnight admission and the general anaesthetic. This is particularly attractive to patients who may be returning in a week or two for definitive surgery and minimizes their time in the hospital system and number of procedures. If a biopsy is required, in selected patients this can be done with a cup forceps through the channel of the endoscope or with a transoral approach using curved biopsy forceps, seen in **Figure 79.14**.

Reports have emerged of in-office balloon dilation for upper tracheal or subglottic stenosis.[46, 47] Although there appears to be reasonable safety, temporarily occluding a patient's airway in the office must be cautioned against. This can be simply performed in theatre and dramatically reduce patient risks. Achker et al. reported on a subglottic stenosis treated under general anaesthetic in which the balloon catheter failed to fully deflate. The catheter, while under traction maintaining the balloon in the desired location, tore and left a partially deflated balloon lodged in the trachea. Fortunately, during the general anaesthetic the balloon could

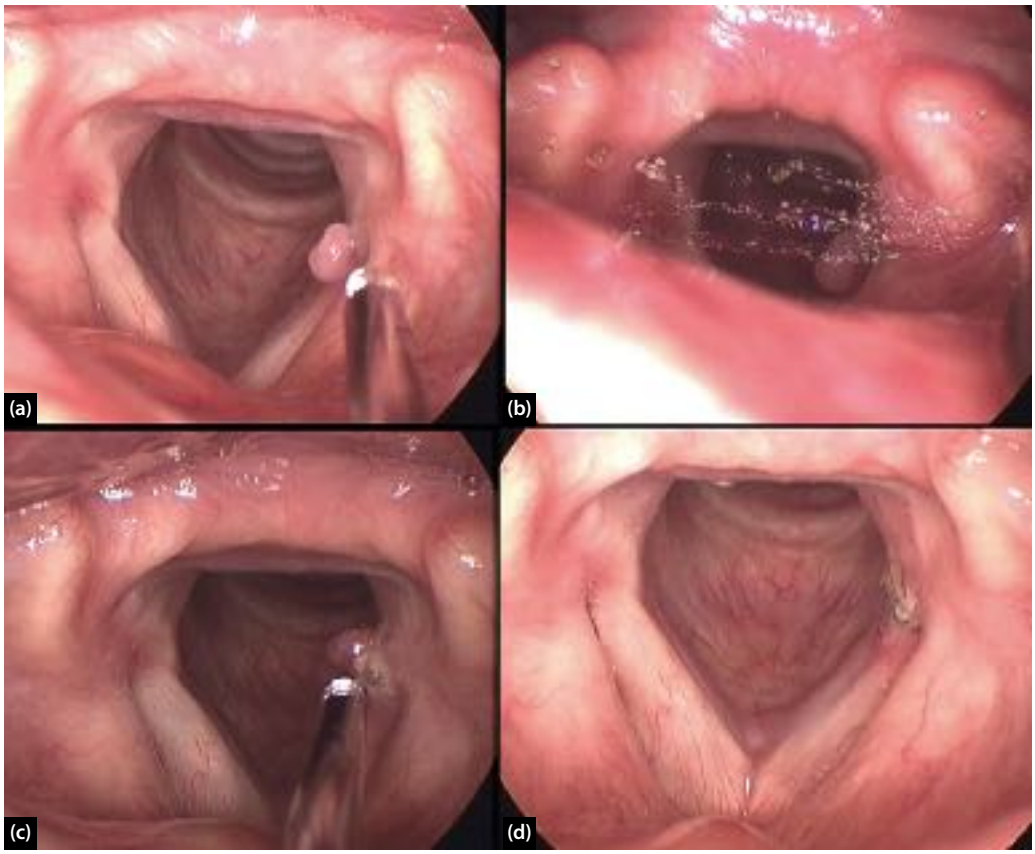


Figure 79.13 Although not routinely required in the author's practice, debulking of an arytenoid granuloma can be performed with AULS. **(a)** shows the left arytenoid granuloma; **(b)** demonstrates the dripping of 4% lidocaine for topical anaesthesia; **(c)** shows the KTP laser fibre delivered transorally through an oro-tracheal injector to ablate/debulk the lesion; **(d)** highlights the minimal collateral thermal injury by angiolytic lasers and the patient then underwent botulinum toxin injection into each thyroarytenoid and lateral cricoarytenoid muscle as part of the procedure. There was total resolution of the lesion by 1 month and he has remained granuloma-free for over 2 years.

BOX 79.2 Indications for transnasal oesophagoscopy (TNO)

- Diagnostic:
  - dysphagia, globus, laryngopharyngeal reflux
  - monitoring Barrett's oesophagitis
  - head and neck cancer surveillance
  - panendoscopy + biopsy
- Therapeutic:
  - balloon dilation
  - angiolytic laser therapy
  - tracheo-oesophageal puncture
  - botulinum toxin injection
  - foreign body disimpaction

be fully deflated and removed with no adverse patient outcome. If that occurred in the office setting, patient death would have been the likely consequence.[48]

Patient preparation and position

Patient position and topical anaesthesia for TNE or panendoscopy is identical to that described for transnasal laser or injection procedures. In addition, however, the patient is asked to be nil by mouth for 3 hours pre-procedure. The distal chip endoscope is passed into the nasal cavity and advanced to the hypopharynx, inspecting all mucosal surfaces on the way. The patient is then asked to lean with chin forward and down, as if looking over a fence, while the endoscope tip is advanced into the pyriform fossa. At this point, the patient is asked to swallow and gentle caudal pressure on the endoscope will allow it to pass into the upper oesophagus. Air insufflation is then used to dilate the oesophageal lumen and mucosal inspection is carried out as the endoscope moves caudally into the stomach.

There are three anatomical narrowings in the oesophagus that should be anticipated:

1. Aortic arch, at 26 cm, identified by pulsations on the left anterolateral wall
2. The left mainstem bronchus, which can be seen on the anterior wall at approximately 2 cm below the aortic arch
3. The lower oesophageal sphincter at the distal oesophagus.

After inspection of the stomach and retro-flexion to view the gastro-oesophageal junction and antrum, the scope is retracted. Further inspection occurs with withdrawal of the scope, noting the squamo-columnar junction. The endoscope can then be passed through the anaesthetized

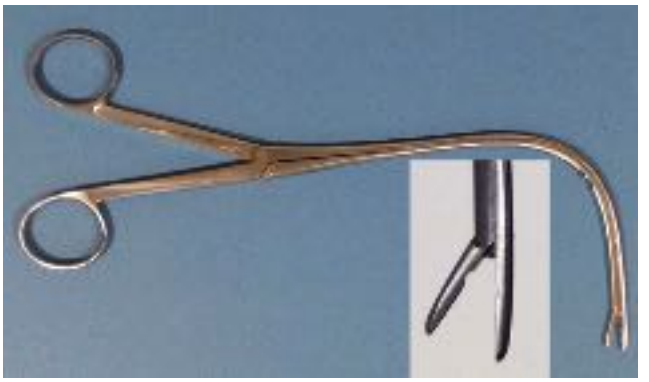


Figure 79.14 During a panendoscopy a lesion can safely biopsied in selected patients with a transoral biopsy cup forceps as shown. Note the cup jaws in the inset that enable a generous biopsy to be taken under direct vision.

vocal folds to inspect the subglottis, trachea and main stem bronchi. Following this procedure, the patient remains nil by mouth for 1 hour to minimize aspiration.

SUMMARY

With significant improvements in endoscopic technology and instrumentation of the upper airway there has been an exponential increase in AULS performed in the operating theatre or office setting. Although the majority is performed in the office, reimbursements can drive patients to the operating theatre for AULS.

Injection of a wide array of substances can be safely and reliably performed in patients in the office setting, managing a range of pathologies including vocal fold paralysis, presbyphonia, glottic defects from cancer resection, botulinum toxin, bevacizumab and saline. Angiolytic lasers (commonly the KTP laser) delivered by small flexible fibres can be used to treat a vast range of laryngeal pathology and obviate the need for hospital admission and general anaesthetic in selected patients. Patient selection and preparation, together with realistic expectations for the surgical outcome, are critical in utilizing this newly established approach to patient management.

KEY POINTS

- With improvements in technology, significant experience has accumulated worldwide in outpatient laryngology.
- This skillset is especially valuable in managing patients who may be unsuitable for general anaesthetic assessment of the larynx (poor general health or anatomical reasons that hamper access).
- A variety of basic and advanced laryngeal interventions can be performed in the outpatient setting (biopsy, cord injection for medialization, botulinum toxin injection and laser surgery.
- A robust emerging body of evidence supports incorporating transnasal oesophagoscopy into ENT practice, a procedure that has also found favour among gastroenterologists.
- The transnasal oesophagoscope can also be used for interventions such as tracheoscopy and oesophageal dilatations.

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CHAPTER 80

RHINOPLASTY FOLLOWING NASAL TRAUMA

Charles East

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SEARCH STRATEGY

Data in this chapter may be updated a Medline search using the keywords: rhinoplasty, trauma, saddle nose deformity, deviated nose nasal septal reconstruction, nasal valve.

INTRODUCTION

Nasal fractures are the commonest facial fracture and occur at all ages. Forty per cent of facial fractures affect the nasal bones, and many of these involve damage to the nasal septum. It must be remembered that external forces sufficient to create a bony or cartilaginous deformity also damage the overlying skin and soft-tissue envelope, commonly leading to a scar or contour abnormality.

Both functional and aesthetic problems occurring after injury may prompt a patient who might not otherwise consider operations to seek treatment and the variation and variety of defects require a very extensive knowledge of septal and rhinoplasty surgery to correct these deformities adequately.[1]

A distinction should also be made between childhood and adult fractures, as any injury in the growing nose will likely have consequences for future nasal development. Growth in the facial skeleton is more often than not asymmetric and may result in the appearance of a 'damaged nose' even when there is no history of prior significant trauma.[2] Trauma, however, can be superimposed on pre-existing deformities or in a patient who has had a previous rhinoplasty such that the patient attributes the whole deformity to an injury, so it is essential to enquire about pre-injury status functionally and aesthetically – if possible with old photographs.

ASSESSMENT

It should be clearly documented whether the primary issue is functional, aesthetic or both. In addition to the standard clinical rhinoplasty photographs, a head-down photograph is very useful in determining displacement or deviation of the normal dorsal aesthetic lines. Each third of the nose should be examined, looking for irregularity, asymmetry or deviation. In the basal view, particular attention should be paid to the caudal septum, nostril symmetry and any insufficiency of the nasal sidewall.[3] There is often valve dysfunction following trauma and particular attention needs to be paid to each of the four plains of the nasal valve, both medially and laterally. Endoscopy is very useful in evaluating the dynamic status of the nasal airway in both the natural and decongested mucosa and particularly to assess any turbinate hypertrophy.

Treatment of acute nasal injuries frequently results in persistent asymmetry or deformity, often necessitating secondary reconstructive surgery. Lateral blows to the nose may produce a simple, depressed nasal bone, displacement of the bony/cartilaginous pyramid or deviation of the nasal axis in the lower two-thirds due to vertical fracture of the cartilaginous septum. Frontal blows may produce a simple fracture of the tip of the nasal bones, injury to the cartilaginous vault with widening of the bridge and, in more severe injury, horizontal fracture or fractures of the septum leading to loss of height either in the middle third or at the anterior septal angle. This is the

TABLE 80.1 Possible residual deformities following nasal trauma

Area of nasal trauma	Possible residual deformity			
Upper third	Depression of bridge – central or unilateral	Lateral displacement	Asymmetric lateral displacement	Vertical displacement of bone(s)
Middle third	Upper lateral cartilage collapse – loss of septal height	Lateral displacement with septal dorsal line	Asymmetric displacement	
Lower third	Loss of projection (septal angles) Dome asymmetry, bossa	Collapse of nostril margin, deviation of tip, caudal septal dislocation	Soft-tissue loss/ scar- notching irregularity	Lengthening of upper lip, acute columella/ labial angle
Skin envelope	Scar, tattooing, contour loss			
Nasal valve dysfunction	Septum angulation Septal loss, perforation	Lateral nasal sidewall insufficiency	Synechiae	

saddle nose deformity. **Table 80.1** illustrates the various types of residual deformity following trauma.

TIMING OF SURGERY

Primary management of trauma

The window to reduce a nasal fracture is variable but most advocate closed reduction within 2–3 weeks, possibly earlier in children. Early reduction is indicated for upper-third bone deformities and this may range from simple elevation of a depressed bone to a four-step manoeuvre in an impacted deviated pyramid. Here, the deformity is exaggerated using a Walsham type forceps to disimpact the vertically placed bone further outwards, the opposite (depressed) bone is then lifted out away from the deviated side, before a straight Ash forceps lifts the central vault of the pyramid including the upper septum and moves it back to the midline before manually pushing the sidewalls inwards to close the roof. Unstable pyramids should have an external splint applied for a week and an internal splint if concomitant disimpaction of the septum is required via a submucosal approach.[4]

Post-trauma rhinoplasty can be undertaken in the acute or subacute period or at an interval following the main injury. The main indication for early rhinoplasty (open reduction of nasal fracture) is for treatment of an acute saddle deformity to reconstruct septal height or in complex nasoethmoidal fractures where the nasal bones need to be stabilized (see Volume 1, Chapter 107, Nasal and facial fractures). Rhinoplasty techniques applicable in the acute phase are those usually to restore the height of the dorsum from a frontal blow such as falling forwards against an edge. In this scenario, as well as the nasal bone widening, there is collapse of the septum under the upper laterals. This is difficult to restore at a later date once scarring and fibrosis are established.[5] Fixation of the dorsal keystone area may be required using drill holes in the thicker part of the nasal bones and suture fixation to hold the perpendicular plate/quadrilateral cartilage together, with repair to the upper laterals (**Figure 80.1**) A supporting piece of posterior perpendicular plate with perforations or cartilage may need to be sewn to support the fragments of the lower two-thirds of the septum.

Lacerations to the skin over a compound fracture need to be closed primarily but may provide access enabling primary reduction of displaced nasal bones. In general, reconstructive rhinoplasty apart from manipulations is usually deferred until the soft-tissue envelope has healed.

'The missed opportunity' – sub acute

Where the nasal bony pyramid is displaced but the time from injury has passed that of closed manipulation, reopening the fracture lines usually with a 2 mm osteotome endonasally or via stab percutaneous approach can remobilize the fragments and allow better realignment. In this instance classical osteotomies are not performed, only those that reopen the partially healed fractures. If there is a history of pre-trauma deformity, then adequate realignment is unlikely, and it is probably wiser to counsel the patient to let the fractures and the skin envelope settle and consider a formal rhinoplasty after 6 months.

POST-TRAUMA RHINOPLASTY

General principles

This covers soft-tissue envelope damage, acquired nasal deviations, sidewall deformity/asymmetry, dorsolateral contours and the nasal septum.

The key structure to repair is the septum, especially when there are high septal deviations such as occur in Chevallet fractures, loss of the septal angles or where there has been septal cartilage necrosis due to haematoma. The important principle is to create a stable dorsal line connected to the nasal bones and then correct the position of the anterior and posterior angles as these two important points determine the support of the tip cartilages, nostril shape and the columella–labial profile. Being the least supported part of the nose, the caudal/dorsal free septum is the most frequently damaged. Simple oblique fractures can be released and the fragments secured by batons or pieces of perforated



Figure 80.1 (a–d) Acute saddle nose deformity following a frontal blow to the mid dorsum. **(e–h)** Post treatment.

perpendicular plate sutured usually on the more concave side. Curvature of the leading edge of the dorsum will usually require reinforcement: bilateral spreader grafts (often asymmetric) provide a secure compression that is not always possible with a unilateral graft.[3]

If the deformity is severe and the cartilage scarred or of poor quality, it is better to replace the dorsal or caudal septum. Invariably, wide exposure via the external approach with full septal dissection gives the best control to evaluate the deformity and to reconstruct. A graft, either from more posteriorly in the septum or from costal cartilage, is required (and spreader grafts are also needed to stabilize the dorsal line), so an adequate source of durable material is required. Rib cartilage can be difficult to use and choosing the more horizontal sixth or seventh rib via a medial inframammary approach gives a straighter graft. Grafts should be thin, and the most effective way to reduce warping is to laminate two pieces that have opposite curvature.[6] This technique produces a stable, straight construct that in the long term minimizes the risks of deformity. Another technique is obliquely sectioning the rib cartilage to include cortex and medulla, thereby having a balanced graft,[7] although this may not produce adequate lengths for extended spreader grafts.

The most important fixation point is to the nasal spine, which should be midline. If not, the spine may need to be modified and a specific drill hole should be made for firm suture fixation, not relying on periosteal attachments. The dorsal and posterior quadrilateral cartilage needs to be secured to the residual dorsal septum or affixed to the perpendicular plate and nasal bones. The reader is referred to the references for further reading.[8] Where the existing frame is unusable, a new L-shaped strut has to be created, usually as two or three individual cartilages pieces cut to lock together and fixed with PDS sutures. This gives the option to extend the caudal septum forward to act as a 'tongue in groove' with relatively rigid fixation for the medial crura and will correct columellar retraction. Alternatively, a septal extension graft fixed between two extended spreader grafts and sutured to the caudal septum will achieve the same objective. The leading edge, however, must be in the midline.[9]

Upper third

Modern appreciation of dorsal anatomy recognizes that there is a nasal bone cap covering the upper lateral cartilage/septal cartilages with an average of 7–8 mm,[10] so deformities in the upper third invariably involve cartilage as well as bone. Common deformities include a depressed fracture of one bone with attached upper lateral, depression of one bone with fracture of the upper septum and overriding of the contralateral bone, or a lean of the whole osseocartilaginous vault away from the midline. Fracture of the tip of both bones with loss of height of the underlying septum creates a middle vault saddle with a 'pseudo hump' above. These deformities can be very difficult to correct by traditional osteotomies and need a different approach with more controlled sculpting of the bones by fine rasps or, better, by modern power tools or Piezo surgery.[11]

Creating predictable fractures with osteotomes is difficult because old fracture lines reopen and comminution of bones can occur. Pre-operative CT facial bone scanning with 3D reconstruction allows more accurate planning. If the nasal bone sidewalls are straight, an open–close book osteotomy sequence including the central upper bony septum will realign the nasal sidewalls, the excess height being reduced from the oblique bone as it is orientated more vertically.[12]

With irregular thickness or shape of the nasal bones, rather than comminution, resculpting with Piezo or a power tool to create better bone shape, changing convexity and permitting a controlled movement minimizes the risk of residual irregularity. The use of securing sutures through the bone and upper septum allows a more satisfactory repositioning than leaving flail segments with little control of how they heal.[13] This requires a different approach from what has been practised since the time of Jaques Joseph of multiple comminuting osteotomies and prolonged splinting, internally and externally.

Contrary to previous teaching, the whole soft-tissue envelope can be raised from maxilla face to maxilla face. Collapse or loss of the nasal bone does not occur when the internal periosteal lining is preserved and this is a significant advantage in using the Piezo device, which will not damage soft tissue. It is not advisable to perform such a wide dissection, however, if traditional osteotomes are used as the internal lining support cannot be guaranteed.

Final contouring of defects or concavities can be done with autologous tissue, such as diced cartilage, either free like a paste, with a fascia wrap (diced cartilage wrapped in fascia – DCF)[13] or moulded using a physiological glue (e.g. platelet-rich fibrin).[14] The use of shavings of cartilage for small volume contours is well established and there is evidence of improved survival of these grafts using them together with platelet-rich fibrin.

Because of the relationship with the cartilage of the mid third, cranially extended spreader grafts between the nasal bones may be used as the solid foundation to widen a narrow upper third over which a more flexible graft can be placed to give a smooth contour.

Middle third

The middle-third support is important to the function of the nose as this is part of the complex area of the nasal valve. A depressed fracture of the nasal bone laterally with the attached upper lateral, internal synechiae across the valve angle, weak vertically placed upper laterals, high septal deviations, loss of height of the septum at its attachment to the upper lateral or damage at the scroll area will all impact on the valve function. Indeed, it is often easier to reconstruct the mid-third contour aesthetically with spreader grafts than to establish a normal functioning valve from collapse.

The lateral middle third is one area that needs to be tensioned between the attachments at the pyriform aperture and the dorsum to prevent dynamic collapse. The principle after adequate septal repair is to support the junctional roof, which is naturally vaulted cranially and caudally presents an angle said to be about 10–15 degrees. Spreader grafts are the mainstay of treatment here for the damaged nose and can be placed at the same level as the septum, just below to act as a pedestal to allow tensioning of the upper lateral sidewall or above the septum if an increase in height is needed and the septum is not being replaced. They are usually asymmetric in size to allow correct contouring of the neodorsum. In the approach to conservation and reorientation, if one upper lateral is large, it may be folded to be used as a turn-in flap (spreader flap), particularly on the oblique side of a deviated nose. Addition to the mid third by onlay grafts to produce the correct contour may also be considered.

Nasal tip/lower third

Fracture, buckling or loss of cartilage can produce multiple deformities in the tip, commonly with associated soft-tissue damage. Through and through scars in the envelope or previous areas of skin loss pose particular challenges in trying to create a smooth contour, especially when involving the rim. It is helpful to consider the dorsal septum/anterior angle position with the tip cartilages as this is the foundation for any repair. Loss of tissue volume usually requires reconstruction with grafts; the ear is a good source as appropriate curved pieces of cartilage either alone or as composite grafts with skin can be tailored. Defects in otherwise healthy tissue up to 2 cm can be composite grafted successfully. With an undamaged envelope, tip repair can be achieved by endonasal techniques if only one area needs attention, but with a more complex problem, especially when the septum is to be reconstructed, the open approach permits wide exposure, release of contractions and accurate repair or grafting.

Commonly used grafts of cartilage are strut grafts between the medial crura, shield and cap grafts, rim grafts for nostril sidewall stability and lateral crural grafts, either to augment or to replace a lost framework.[15] For details of repair of the nasal skin envelope, the reader is referred to Chapter 85, Nasal reconstruction.

The damaged nasal valve

The nasal valve is the flow-limiting segment of the upper airway and has an important function in directing airflow to the middle nasal meatus, as well as providing eddies of air for antegrade olfaction. Interference of the normal airflow may result from damage to the lining with synechiae, and insufficiency of the nasal sidewall either with a fixed deformity at the pyriform or a dynamically unstable sidewall. The addition of active rhinitis or the compensatory hypertrophy of the turbinates either inferior or middle needs to be considered. There are also the medially based deformities related to the nasal septum and the conjoined upper laterals.

The surgical goals need to be defined by identifying the specific areas of deformity medially, laterally, at the vaulted roof and occasionally the sill of the nose. CT scanning with modelling of the valve can assist in planning but assessment by direct vision endoscopically remains the usual examination.

The accuracy needed to maintain the correct septal height and width as well as maintaining the roof/sidewall stability cannot be overemphasized. Often the difference between success and failure is a millimetre in this complex zone, and it is important with any graft not to lose in bulk what you gain in strength.

Whichever method is chosen to repair the wall, it is the author's belief that a customized intranasal splint is essential in the first week, particularly if a three-layer dissection has been undertaken (i.e. skin, cartilage and vestibular lining having been released in the lower two-thirds of the nasal sidewall).

The skin envelope

The variable thickness of the envelope is considerable in the nose. Probably the most frequently traumatized area is at the rhinion where the skin is thinnest. Lacerations, stellate splits and grazing injuries should be cleaned and dressed primarily to prevent tattooing. Subsequent scars and loss of the subcutaneous tissue may fix the skin to the framework of the nose. If this is a risk, massage of the skin using moisturizer will help once the skin has healed. Adequate sun protection of scars and use of silicone gel daily all contribute to good cosmetic scar result. In thin, damaged skin and severe subcutaneous tissue loss, fat grafting to the nose will improve the contour and in atrophic skin add stem cells to improve the quality. This may be considered before definitive repair of the nose using fine cannulae.

Camouflaging the dorsum skeleton at the time of surgery in the presence of thin skin may be achieved by using autologous temporalis fascia, perichondrium from rib or rectus abdominis fascia. Both of these provide a uniform sheet to thicken the envelope and are easier to prepare than periosteum from the retroauricular area. If used over large areas, it is important to suture the sheet with fine absorbable sutures. This type of graft is particularly useful to cover reconstructed cartilage domes in the nasal tip.

REVISION SURGERY

Surgery for the traumatized nose by definition involves repair of damaged tissue. Predictability of outcome should be discussed with the patient, particularly where complex grafting is undertaken as there is a greater need for further, usually minor, revision. This is particularly so when dealing with both functional and aesthetic issues and it is wise to discuss this before any repair.

Infection is a major cause for creating a poor result through loss of tissue, so careful pre-operative evaluation including microbiology culture of the vestibule to exclude MRSA and appropriate advice on post-operative care are considered essential.

Common causes for revision may involve nasal valve disorders (e.g. thinning a wide rib graft caudal septal reconstruction), resuspending a sidewall collapse or a contour problem (e.g. minor saddling, especially at the central keystone area). As with all rhinoplasty revisions, if the skin envelope needs to be fully raised, an interval of about a year is advised. Singe-area deformities can be revised earlier dependent on the skin quality and extent of the area to be augmented/reduced. Alar base correction may be undertaken safely at an early point after the major repair.

NASAL TRAUMA AND CHILDREN

It is recommended that children with trauma requiring reconstruction are referred to specialist centres as often orthognathic and orthodontic services are required parallelling nasal repair.

Children's nasal injuries are common and have the potential to disrupt normal growth, particularly with loss of septal cartilage, as happens with a septal abscess.

Oblique fractures usually heal with fibrous union so continued growth will often produce a deviation from the rhinion. In general it is best to defer surgery at least until after puberty and as close to maturity as possible. This deformity increases with age and it can be difficult to resist pressure to operate early before nasal maturity. The timing is variable between sexes and in individuals and requires a judgement of skeletal maturity and mental maturity in planning the repair, but in general the repair should be as close to skeletal maturity as possible. Osteotomies do not disturb growth of the nose but damage to the growth centres in the septal cartilage does.[16] The septodorsal cartilage and the sphenospinal cartilage should not be disturbed, but conservative relocation on the spine or release of an angulation may be necessary.[17] The patient's parents need to be warned of a possible second operation when growth has stopped.

Where a saddle occurs, replacement by autologous cartilage is preferred as continued growth may then occur. Expansion of the skin envelope by serial placement of Custom silastic dorsal implants replaced every 18–24 months will prevent the problems of the short nose with a tight envelope and allow a definitive correction later, usually employing rib cartilage.

BEST CLINICAL PRACTICE

- ✓ Nasal trauma is a complex issue needing specialist assessment.
- ✓ Childhood injuries need to be monitored to assess growth.
- ✓ Early reduction and alignment of fractured nasal bones with or without septal release should be carried out within 2-3 weeks and acute saddles require early surgical intervention to restore septal height.
- ✓ Cartilage depleted noses will usually need rib grafts for reconstruction and the basis for a stable nose with good breathing is a reconstructed septum and a properly tensioned sidewall.
- ✓ Secondary procedures are common in repair of damaged noses. Finally the soft tissue envelope may also need augmentation.

KEY POINTS

- A suitable referral pathway needs to be established for early assessment of nasal trauma.
- Nasal endoscopy and cone beam CT scanning are helpful in assessment and planning repair.
- External approaches and grafting techniques are usually required.
- Patients should be consented for all graft harvest sites.
- Regenerative surgical techniques may enhance graft survival and improve the quality of damaged skin

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CHAPTER 81

PRE-OPERATIVE ASSESSMENT FOR RHINOPLASTY

Hesham Saleh and Catherine Rennie

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: facial proportions, facial, aesthetics, nasal, examination, assessment and rhinoplasty.

INTRODUCTION

Rhinoplasty is one of the most challenging procedures in facial plastic surgery and consideration must be given to both facial aesthetics and nasal function. It is technically difficult to achieve consistently excellent results and, as the surgery is on the most prominent part of the face, the aesthetic outcome is visible to all. Meticulous planning is therefore essential.

This chapter outlines a systematic approach to the assessment of patients for rhinoplasty/septorhinoplasty that will enable appropriate patient selection and facilitate surgical planning. Assessment should include:

- consideration of the patient's motivations, anxieties and expectations
- analysis of the face
- analysis of the nose
- examination
- photography.

THE PATIENT

It is essential to obtain a clear history of the patient's complaint and symptoms. Identification of any structural, congenital, traumatic, cosmetic and/or functional issues is crucial. Any past history of nasal surgery, sinonasal disease, diabetes, psychopathology, anticoagulant medication, smoking or cocaine use should be elicited.

It is critical to understand the patient's motivations, anxieties and expectations. Why is a patient prepared to undergo the risk and inconvenience of an operation to correct often seemingly minor deformities? Many people have nasal abnormalities but would not consider surgery, so what makes a patient choose to have surgery? For many rhinoplasty patients, their focus on their nose stems back to puberty and daily reflection in the mirror leads to increasing dissatisfaction in their appearance.[1] Studies have shown higher levels of dissatisfaction in personal appearance in patients seeking rhinoplasty than those seeking other aesthetic procedures.[2, 3] In the majority of rhinoplasty patients the motivation for surgery comes from a desire to change or from witnessing favourable outcomes in others.[4] For most it is not the severity of their deformity that leads them to surgery[5] but their perceived difference from the norm in their social environment. The timing for rhinoplasty often coincides with a loss in self-esteem. Rhinoplasty has been shown to have a positive effect on the patient's body image, which is found 3 months post procedure and is still evident 2 years following the procedure.[6]

Identifying high-risk patients

It is important that surgeons recognize potentially problematic patients, as high-risk patients are unlikely to be satisfied with surgical results. A number of unsuitable personality attributes have been described in the literature. Examples commonly referred to are patients with body dysmorphic disorder (BDD), those who are unreasonably demanding or overly flattering, patients who insist on secrecy, the so-called surgiholic, as well as obsessive, perfectionist and impolite patients. The simplified acronyms SIMON (single, immature, male, overly expectant/obsessive, narcissistic) and SYLVIA (secure, young, listens, verbal, intelligent, attractive) describe some of characteristics of the high-risk and the ideal patient respectively.[7–9]

Body dysmorphic disorder

BDD describes an altered perception of one's own appearance that results in distress. It is a subjective feeling of ugliness or physical defect which the patient feels is noticeable to others, although the appearance is within normal limits.[10] Its occurrence is summarized in **Box 81.1**.

The onset of BDD is typically in late adolescence; it is a chronic rather than episodic condition and affects both genders equally. Picavet et al found that 33% of patients seeking rhinoplasty had moderate symptoms of BDD. Only 2% of those seeking rhinoplasty for a medical reason had BDD whereas 43% of those seeking rhinoplasty for purely cosmetic reasons had BDD.[12]

Three questions to ask patients, based on the DSM-IV criteria, have been developed to help surgeons screen for BDD:

1. Are you worried about your appearance in any way?
2. Does this concern or preoccupy you? That is, do you think about it a lot and wish you could worry about it less?
3. What effect has this preoccupation with your appearance had on your life?[13, 14]

A number of both specific and generic questionnaires are available that can help identify patients with BDD (**Box 81.2**). These are designed to be used with those patients with behaviours suggesting BDD. Particular 'red flags' are shown in **Box 81.3**.

BOX 81.1 Body dysmorphic disorder: by the numbers[11]

BDD occurs in approximately:

1%	Adult population
2.3–13%	Students
13%	Psychiatric patients
14–42%	Outpatients with atypical major depression
11–12%	Outpatients with social phobia
39%	Inpatients with anorexia nervosa
6–20%	Patients seeking cosmetic surgery

BOX 81.2 General and specific questionnaires and questions for patients

Specific questionnaires:
- Cosmetic Procedures Screening Scale[15]
- Body Dysmorphic Disorder Questionnaire[16]
- Yale–Brown Obsessive Scale modified for BDD[17]
- Dysmorphic concern questionnaire[18]

General questionnaires:
- Derriford Appearance Scale[19]
- Brief Fear of Negative Evaluation Scale[20]
- Hospital Anxiety and Depression Scale[21]

Body image concerns:
- What is the nature of your appearance concern?
- What do you dislike about your appearance?
- Is this a cause of distress or preoccupation?
- When does the feature bother you most?
- Does this impact on your daily functioning?
- Have you had previous treatment to improve your appearance?
- Do you have other body areas of concern?

BOX 81.3 Red flags

Body image concerns that are difficult for others to see
Unrealistic expectations of treatment outcomes
Worrying about body image repeatedly throughout the day or for long periods
Use of camouflaging and cover-up strategies
Constant requests for reassurance
Mirror checking or avoidance of mirrors
Avoidance of social situations
General reduction in quality of life (e.g. no longer socializing)
Disruption in daily activity
Patient presents with numerous photos (of self or of models/celebrities)
Patient presents with detailed ideas of how to improve appearance
Patient has other areas of body image concern
Patient reports multiple previous 'ineffective' consultations or treatments

Further evaluation and treatment

A pre-operative psychological assessment is essential for patients in whom BDD is suspected.[10, 22] If BDD and other psychopathology are ruled out, the patient can then be counselled regarding surgery. If the surgeon still has significant concerns, however, it may be necessary to obtain a second opinion.

Expectations

Determining pre-operative expectations is crucial as poor results are often based on emotional dissatisfaction rather than technical failure.[23] It is therefore important to ask:

- What are your outcome expectations?
- How do you anticipate your life will be different following treatment?
- What if your expectations are not met?

Surgeons must be able to explain to patients how anatomical variations are causing their nasal problem and discuss what surgery can achieve. Through this discussion the surgeon can determine if the patient has realistic expectations.

The use of the rhinoplasty improvement scale is helpful in explaining and counselling patients about realistic post-surgical expectations (**Figure 81.1**). Patients should be informed that moving up one point on the scale is realistic but anything more is unlikely.

ANALYSIS OF THE FACE

In assessing a patient prior to rhinoplasty the analysis should consider the entire face and not simply view the nose in isolation. The analysis begins as soon as the patient enters the consultation room and is formally assessed prior to a detailed assessment of the nose. Attractive faces are deemed to have ideal measurements and angles, which are reportedly based on the dimensions first described by Leonardo da Vinci.[24, 25] This concept has since been extended by Albrecht Duerer,[26] Powell and Humphrey.[27]

Facial symmetry is reported to be the basis for a beautiful face, although minor asymmetry may be associated with the perception of beauty.[28] Many patients are unaware of minor facial asymmetries and, if they discover these in the post-operative period, it could lead to dissatisfaction and misunderstanding. It is therefore important to raise these concerns with the patient and document them pre-operatively.

While a rhinoplasty on an asymmetrical face can lead to dissatisfaction post surgery, correcting an asymmetrical nose which causes the illusion of facial asymmetry can lead to improved facial symmetry without the need for any other surgical procedure.[29, 30]

Symmetry is assessed using midline facial landmarks: a line running through the mid-philtrum of the upper lip, the midpoint of the glabella and the midpoint of the chin indicates a symmetrical face.

Analysis of facial proportions is performed using the 'rule of thirds' and the 'rule of fifths' to assess the face from a frontal view (**Figure 81.2**).[25] Horizontal facial thirds should be approximately equal; the landmarks defining each third are the trichion to glabella, glabella to subnasale and the subnasale to soft-tissue menton. The rule of fifths describes the ideal transverse proportions of the face vertically divided into equal fifths, each fifth approximately equal to the width of one eye; the alar base is equal to the intercanthal distance. The nose ideally occupies one-third of the length of the face and one-fifth of its width. The terms used to describe the constant landmarks of facial anatomy are defined in **Box 81.4**. Other elements to consider are the fullness and position of the lips and protrusion of the chin.

Powell and Humphrey described the ideal angles of the facial aesthetic triangle (**Figure 81.3**).[27] The accepted dimensions of each of the facial angles are:

- nasofrontal angle 115–135°
- nasofacial angle 30–40°
- nasomental angle 120–132°
- mentocervical angle 80–95°.

Facial proportions act as a guide and are helpful in planning procedures but should not be taken as absolute. Each rhinoplasty should respect the individual's wishes, gender and character. It is important to recognize, too, that these ideal measurements vary between ethnicities.[31]

Finally, the analysis of the face should involve inspection of skin type utilizing the Fitzpatrick classification, which divides the skin type based on its colour and its reaction to the first summer exposure (**Table 81.1**).[32] The

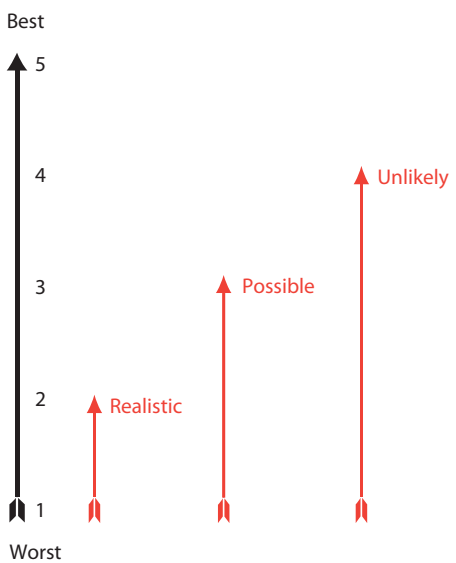


Figure 81.1 Rhinoplasty improvement scale used by the senior author.

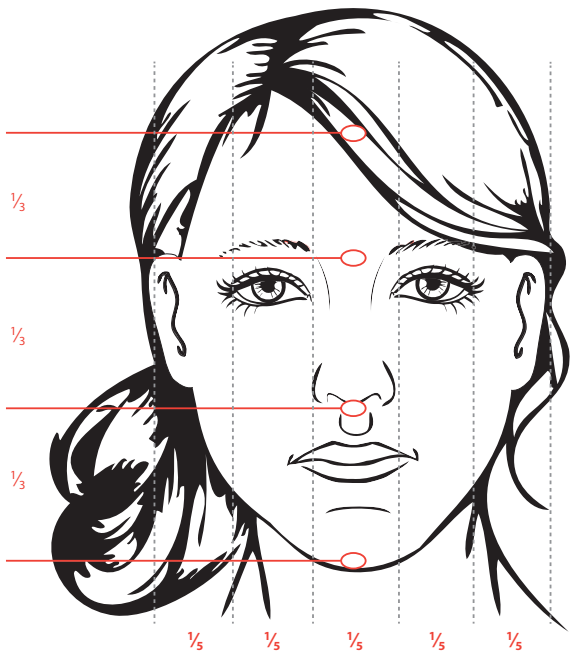


Figure 81.2 The concept of dividing the symmetric face into thirds and fifths.

BOX 81.4 Terminology of facial landmarks

Trichion	Anterior hairline in the midline
Glabella	Most prominent point of forehead in mid-sagittal plane
Nasion	Deepest point of frontonasal angle
Rhinion	Midline point of junction of nasal bones and upper lateral cartilages
Pogonion	Deepest point on outer cortex of mandible
Gnathion	Most inferior point of the chin
Gonion	Most inferior/posterior point of mandible
Menton	Lowest point of mandibular symphysis
Subnasale	Junction of columella and upper lip in mid-sagittal plane

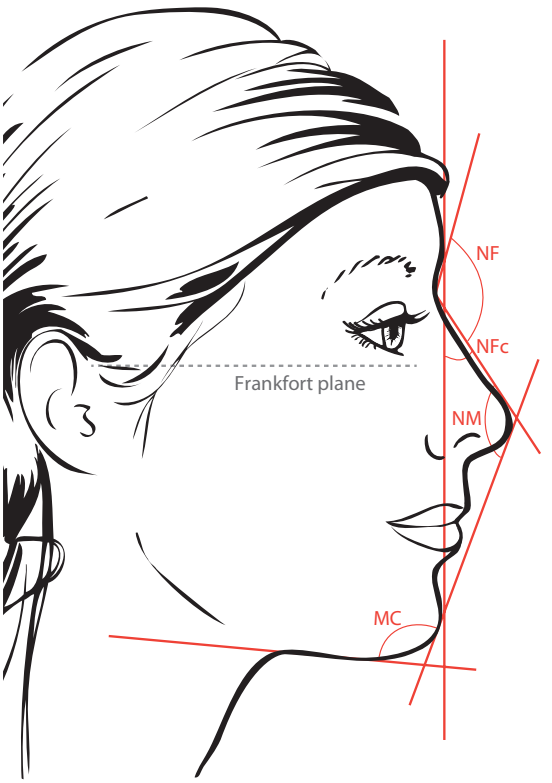


Figure 81.3 Triangles of Powell and Humphrey. Angles of the aesthetic triangle: nasofrontal (NF) = 115–135°; nasofacial (NFc) = 30–40°; nasomental (NM) = 120–132°; mentocervical (MC) = 80–95°.

TABLE 81.1 Fitzpatrick classification of sun-reactive skin types

Skin type	Colour	Reaction to sun
I	Very white or freckled	Always burns
II	White	Usually burns
III	White to olive	Sometimes burns
IV	Brown	Rarely burns
V	Dark brown	Very rarely burns
VI	Black	Never burns

surgeon should also consider the wrinkles on the face both with and without expression. The Glogau classification can be used to characterize progressive degrees of photo damage.[33]

ANALYSIS OF THE NOSE

Analysis of the nose comprises pertains to areas: inspection of the external nose, inspection of the internal nose and palpation.

Inspection of the external nose

Detailed inspection of the external aspects of the nose provides information about the individual nose as well as a comparison to accepted ideal measurements.

- **Skin quality:** This is variable and an assessment of whether the skin is thick and sebaceous or thin is required. Thin skin is unforgiving and minor irregularities are easily detectable; refining and narrowing the nasal tip can be challenging where there is thick skin.
- **Deviations:** The nose is divided into upper, middle and lower thirds. The upper third corresponds to the bony vault, the middle third to the upper lateral cartilages and dorsal septum, and the lower third to the lower lateral cartilages, caudal septum and alar base. Deviated noses are described on the basis of direction of the deviation of each third, e.g. classically described C-shaped, one-sided or S-shaped deviations (**Figure 81.4**). This provides an anatomical assessment of the aetiology of nasal deviation, which is key to surgical planning.
- **Length of the nose:** Nasal length is measured from the nasion to the tip, which is equal to the distance between the stomium and the menton. This can also be calculated mathematically as the distance from the nasal tip to the stomium multiplied by a constant of 1.6. nasal length: NT = TS × 1.6 (**Figure 81.5**).
- **Tip projection:** This is a measure of how far the nasal tip lies anterior to the face. Ideal projection is determined using Goode's ratio, where a line drawn from the alar–facial groove to the nasal tip measures 0.55–0.60 of the distance from the nasion to the nasal tip. A ratio less than this equates to an underprojected nose and greater than this corresponds to overprojection (**Figure 81.6**).
- **Lip–chin relationship:** The horizontal distance from the surface of the upper lip to that of lower lip is normally around 2 mm. The anterior surface of the upper and lower lips rest on the nasomental line in an aesthetic face (**Figure 81.7**).[34] When the chin lies posterior to this line, it is described as retrognathic; when it lies anterior to this line, it is described as prognathic. A retrognathic chin can give the illusion of an overprojected nose and the reverse applies to a prognathic chin. Genioplasty or chin implant procedures are therefore often used in conjunction with rhinoplasty.[35]
- **Dorsum:** The dorsum is inspected from both frontal and lateral views. Tracing the lateral aesthetic lines (also known as the brow–tip line) should reveal

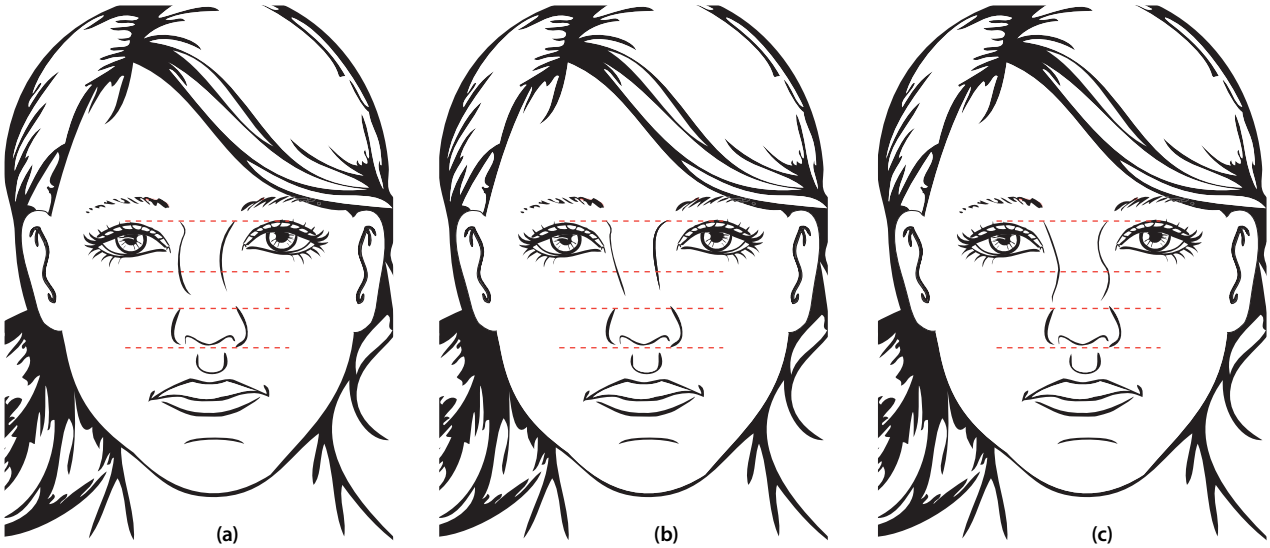


Figure 81.4 Classifying classic nasal deviations using thirds. **(a)** C-shaped, **(b)** one-sided, **(c)** S-shaped.

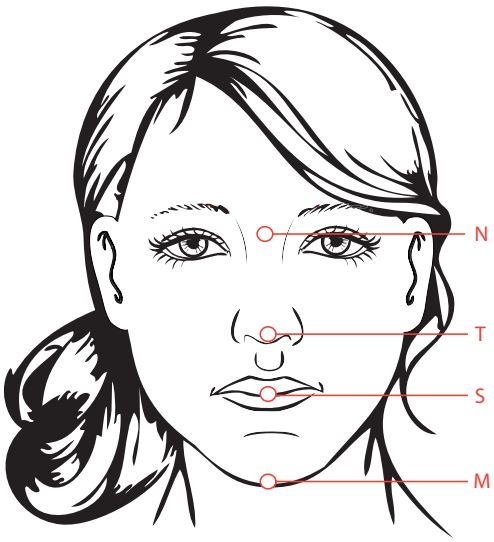


Figure 81.5 Nasal length (NT) = stomium to menton (SM) = 1.6 × TS.

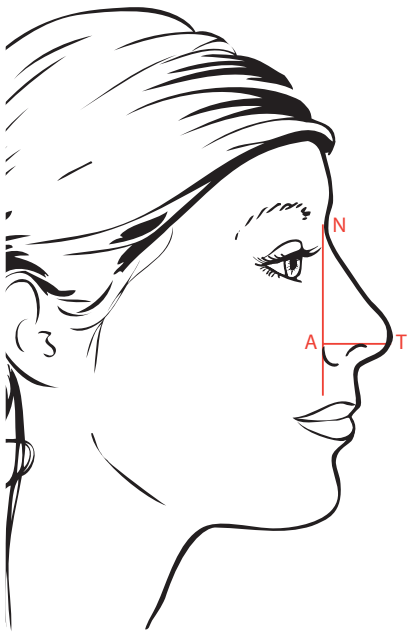


Figure 81.6 Determining tip projection by using Goode's ratio.

a smooth curvilinear line connecting the eyebrow superiorly to the nasal tip inferiorly (**Figure 81.8**). Identification of any irregularities in this smooth curve highlights sources of nasal deformity. In the lateral view, the height of the dorsum is assessed; the dorsum is a straight line in men and in women gently curves with a supratip break delineating the dorsum from the nasal tip. There is wide variation in dorsum height and it often characterizes different ethnicities.

- **Tip configuration:** There are four tip-defining points identified by light reflection (**Figure 81.8**). These represent the domes, the supratip and the infratip. The size and shape of the lower lateral cartilages are assessed, as are asymmetry, bifidity and rotation. Various tip configurations are generally related to these characteristics and to skin thickness. **Figure 81.9** depicts a commonly encountered selection of tip appearances: normal, boxy, bifid, bulbous and amorphous.
- **Tip rotation:** This describes the position of the tip along an arc with its radius centred on the nasolabial angle. The ideal dimension of the nasolabial angle in men is 90–95 degrees and in women is 95–105 degrees (**Figure 81.10**).[36]
- **Columellar show:** The relationship between the ala and the columella is assessed in the lateral view. The amount of visible caudal septum is ideally limited to 3–5 mm (Figure 81.10). This is the distance between two parallel lines drawn from the most anterior and the most posterior parts of the nasal vestibule. A degree of columellar show greater than this may be due to either a hanging columella or abnormalities in the alar margins such notching or retraction.

- **Basal view:** The width of the alar base approximates to the intercanthal distance. The ratio of the width of the dorsum of the nose relative to the alar base should be equal to 80% (see **Figure 81.2**). From the basal view, the nose can also be divided into thirds. The upper third corresponds to the lobule and the lower two-thirds correspond to the columella. A line that transects the columella at the area of medial crural footplate diversion divides the base into two halves (**Figure 81.11**). The overall basal view outline conforms to an isosceles triangle with pear-shaped nostrils lying at an angle of 45° to the vertical.[37] Multiple ethnic variations exist in alar base configuration.

Inspection of the internal nose

Examination of the internal nasal cavity is an essential component of assessment of rhinoplasty in the identification of abnormalities and assessment of donor cartilage sites. Anterior rhinoscopy and nasal endoscopy should be performed.

- **Septum** inspection should be made, looking for deviation, spurs, perforation or the presence of a septal button.
- **Lateral nasal wall and turbinates** inspection can identify congestion, hypertrophy and asymmetry.
- **Internal nasal valve** assessment should be carried out during normal quiet respiration at rest, as exaggerated effortful breathing is likely to precipitate transient internal nasal valve collapse in the normal individual.

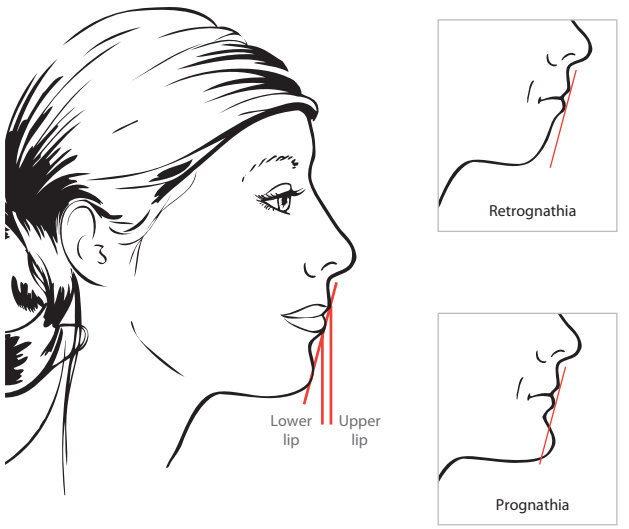


Figure 81.7 Lip–chin relationship.

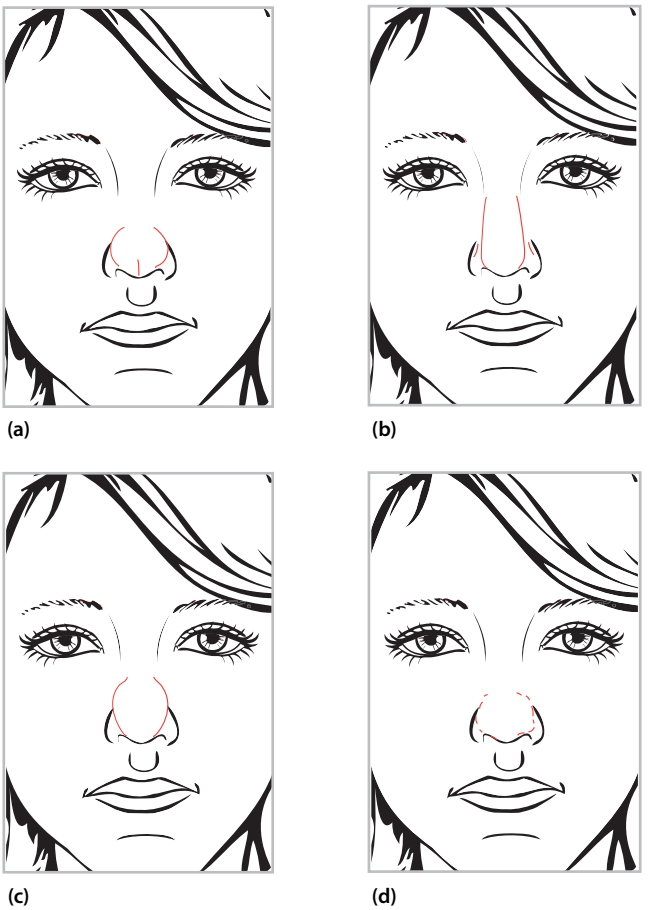


Figure 81.9 Common nasal tip morphology, with 'normal' shown in black outline: (a) bifid, **(b)** boxy, **(c)** bulbous, **(d)** amorphous.

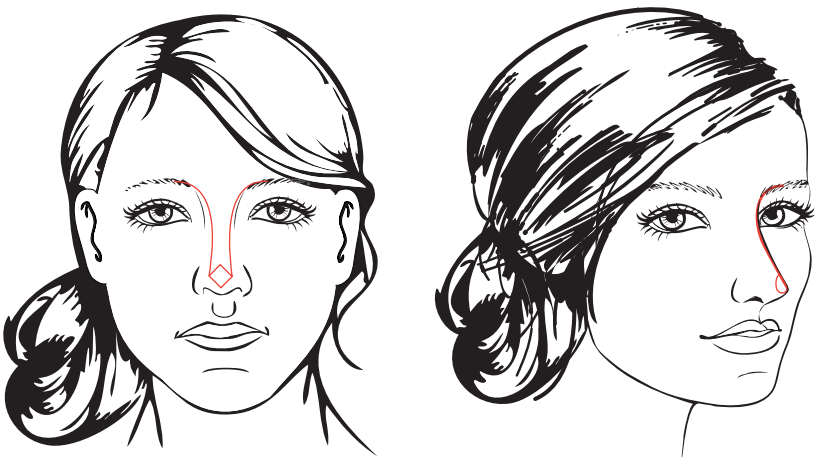


Figure 81.8 Front and right oblique views showing the brow–tip line. Note the four tip-defining points.

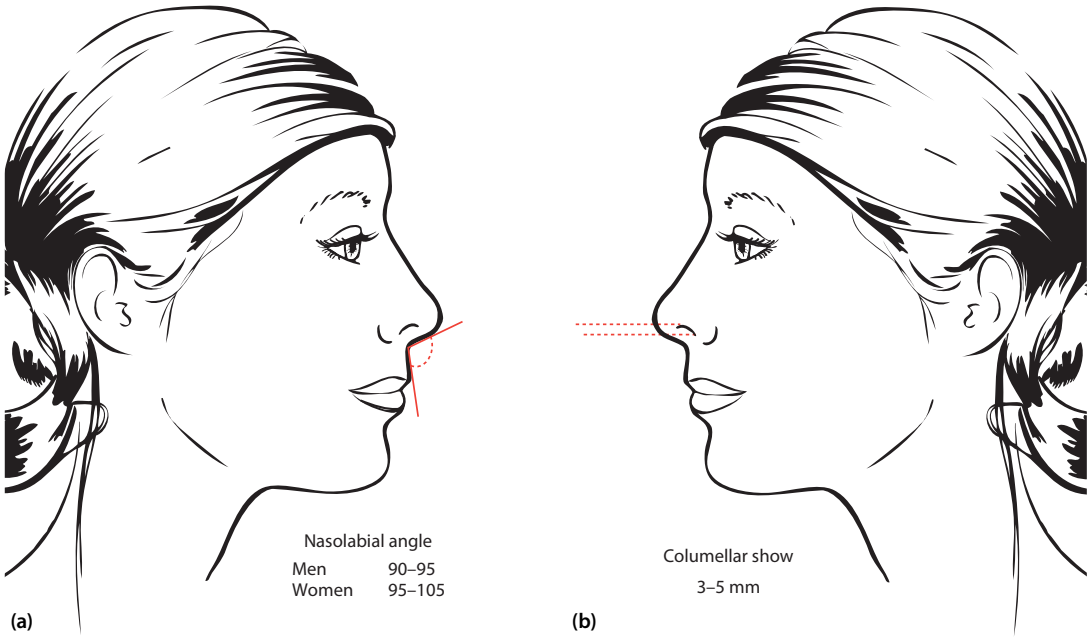


Figure 81.10 (a) Nasolabial angle in men and women. **(b)** Normal columellar show. Labels (a) and (b) angle/show lc a/s.

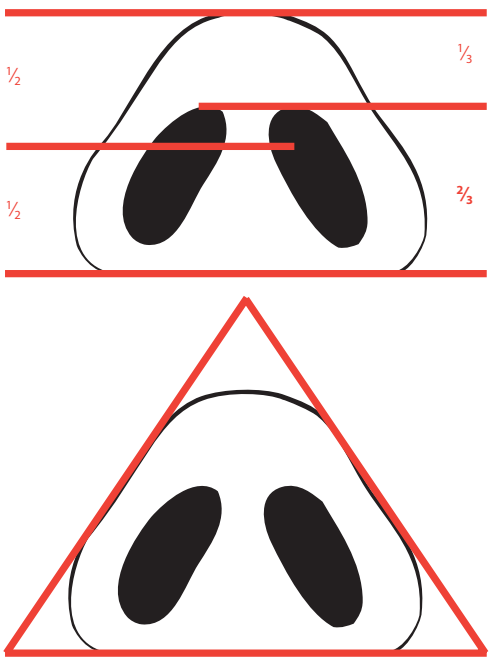


Figure 81.11 Basal view.

- **Cottle's manoeuvre** of opening the internal nasal valve by pulling on the soft tissues of the cheek is non-specific. A better test is to place a Jobson Horne probe in the internal nasal valve to prevent the collapse of the upper lateral cartilage and detect its effect on inspiration.
- **Alar collapse** is a measure of external nasal valve collapse and must be identified pre-operatively. The external nasal valve is not a true valve and is identified by the area bounded by alar cartilages, septum and columella.
- **Endoscopy** can exclude polyps, purulent discharge or residual adenoidal tissue.

Palpation

- **Skin:** Palpate for an assessment of skin texture and elasticity.
- **Irregularities:** Palpate for underlying irregularities that may be due to skin, soft tissue, cartilage, bone or previous graft material.
- **Nasal bones:** Assess the size, position and presence of palpable steps.
- **Tip recoil:** This is an assessment of the strength of the lower third of the nose and provides a palpable measure of the degree of underlying tip support.[38]
- **Alar cartridges:** Palpate for thickness, strength and shape.
- **Spine and septum:** Assess tip support, and confirm the presence and quantity of septal cartilage.

FUNCTIONAL STUDIES

Studies of nasal function are not performed routinely in rhinoplasty assessment and are mainly confined to the research environment. Nasal inspiratory peak flow, acoustic rhinometry and rhinomanometry can be used as objective tests of nasal function and to quantify surgical results. However, the correlation between objective and subjective sensation of nasal patency remains uncertain.[39]

PHOTOGRAPH REVIEW

Standardized photographs are essential for pre-operative planning. They are useful during the discussion with the patient about the proposed surgery and as an intra-operative reference and they are essential for comparison with post-operative results. In order to achieve reproducible photographs a standard patient position is used patient where the Frankfort plane is parallel to the floor; the Frankfort plane is a line that runs from the cephalic tragus to the lower orbital margin (see **Figure 81.3**). The standard photographic views obtained for rhinoplasty are frontal, left and right lateral, left and right oblique and basal. Additional views, which can be of use, are the close-up frontal view, superior view, base–radix view and bird's-eye view.[40–42]

Computer imaging

Computer morphing of the pre-operative photographs has been found to enhance communication with the patient and is associated with higher patient satisfaction.[43] It can also help in judging patient expectations and identifying BDD.[44] However, it is essential to clarify to the patient that image manipulation is only a means of communication and does not imply a specific guaranteed outcome.

CONCLUSION

Following the systematic assessment and examination of the patient, the proposed surgery can be effectively planned with clear surgical steps. It is good practice to commit the surgical steps to a written plan (**Table 81.2**).

TABLE 81.2 Summary of rhinoplasty assessment

Analysis	Assessment	
Patient analysis	What does the patient want? Is it realistic?	
Facial analysis	Symmetry Rule of thirds Rule of fifths	
Nasal analysis	Inspect: external	Skin Deviations Nasal length Tip projection Lip–chin relationship Dorsum–brow-tip line Dorsum–lateral view Nasal tip configuration Tip rotation Columellar show Basal view
	Inspect: internal	Septum Lateral nasal walls Internal nasal valve External nasal valve
	Palpate	Skin Irregularities Nasal bones Tip recoil Alar cartridges Spine Septum
Clinical photographs	Anterior Lateral: left and right Lateral oblique: left and right Basal view	
Computer morphing		
Surgical plan		

BEST CLINICAL PRACTICE

- ✓ First assess the patient, then the face and finally the nose.
- ✓ Develop an operative plan based on the patient's concerns and the results of your analysis.
- ✓ Carefully communicate the operative plan with the patient.

FUTURE RESEARCH

Appropriate patient selection is the ultimate key for successful rhinoplasty. Current research focuses on developing tools that help the surgeon in making that decision. There have been some recent attempts at developing questionnaires to identify those patients who would not benefit from surgery because of unrealistic expectations and to exclude those with suspected body dysmorphic disorder. To date, there has been no consensus and this is the subject of future research.[45–49]

KEY POINTS

- Rhinoplasty is a technically challenging procedure for which both the aesthetics and the function of the nose must be considered.
- Meticulous planning is essential to ensure the best surgical outcomes.
- Successful surgery requires realistic patient expectations, careful consideration of facial aesthetics and a detailed examination of the nose.

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CHAPTER 82

EXTERNAL RHINOPLASTY

Santdeep Paun

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: external, open and rhinoplasty together with review publications and textbooks.

INTRODUCTION

The external or open approach is a firmly established and important technique in rhinoplasty surgery. Its key advantage over endonasal approaches is to afford the ability to assess anatomical deformities by direct inspection of the nasal cartilaginous and bony framework. This in turn allows for easier bimanual sculpturing of the underlying skeletal components and application of sutures and grafts under direct vision. While not an indication for the external approach, there is also a definite advantage for teaching where trainees are able to visualize surgical techniques with ease and these may also be captured satisfactorily with video and photography without the overlying skin and soft-tissue envelope hindering the view.

Limiting surgical tissue dissection to a minimum, as with an endonasal approach, reduces the risk of vascular compromise of the skin–soft-tissue envelope and this approach may therefore be favoured for correction of minimal structural bony dorsal irregularities and minor tip problems. However, the external approach's need for more soft tissue dissection is balanced by the unparalleled view of the nasal structure. In revision surgery, in particular, it facilitates accurate diagnosis in cases where the underlying anatomy is not obvious due to prior surgical resection and scar tissue formation.

The author personally favours this approach for most reconstructive revisions and where the nasal tip needs addressing in primary surgery. Incision refinements and surgical technique have overcome some of the earlier criticisms of a columellar scar and delay in resolution of the supratip skin oedema, and any potential loss of tip projection can be countered by placement of a columellar strut or septal extension graft to maintain support.

The choice of an external approach thus depends not only on the specific pathological anatomical findings but also on the philosophy of the surgeon. However, in deciding to use the external approach, the possible related sequelae should be considered, bearing in mind that the attainment of a predictable satisfying result demands the most atraumatic surgical procedure.

This chapter aims to present some historical aspects and principles of the external approach, outline relevant anatomy and emphasize technical aspects. Advantages with particular reference to grafting of the nasal skeleton and to specific extended indications such as revision rhinoplasty, the deviated nose, nasoseptal perforations, cleft-lip nasal deformities and nasal dermoids are discussed. Pitfalls related to this approach are outlined with the goal of shortening the long and arduous path of the learning process in rhinoplasty.

Mastery of this technique and exploitation of its specific advantages can bring a distinct range of opportunities to the rhinoplasty surgeon.

HISTORICAL ASPECTS

Early references to the elephant trunk incision[1] were made as early as the 1920s and subsequent papers named the approach as the transcolumellar incision,[2] the decortication technique,[3] and finally the external approach,[4] and open or external rhinoplasty.[5, 6] As most texts have adopted the latter three terms, we use them interchangeably in this chapter.

External incisions in rhinoplasty have been used in one form or another in all early descriptions of this procedure. The first such description is believed to have stemmed from India in 600 BC, in which external incisions and an open approach were practised. The first description of an external rhinoplasty via a transcolumellar incision was given by Rethi[2] in 1934 and subsequently by Sercer.[3] In 1974, Goodman advocated the external approach and described a modified transcolumellar incision – the well-known 'butterfly' incision.[4] His original description featured all the key points of incision placement, development of flaps and other surgical techniques. Publications thereafter have mainly served to emphasize the salient points he described. Refinements regarding incision placement, suturing and surgical technique have largely overcome the earlier problems encountered.

HISTORY AND EXAMINATION

The importance of pre-operative assessment in patients seeking rhinoplasty surgery cannot be overemphasized. It is beyond the scope of this chapter to discuss full facial analysis in detail and it is assumed that the rhinoplasty surgeon has a comprehensive knowledge of the relevant concepts.

A complete and discerning history regarding the cosmesis and function, any prior procedures and accurate chronological detailing of post-operative changes is important. Patient anxieties and expectations should be elucidated early in the consultation. The evaluating specialist needs to ensure that such expectations are true and achievable and that the patient's desires are realistic and in keeping with predictable likely post-operative outcomes. Where any doubt exists, sensitive counselling of the patient and referral for psychiatric review is always prudent and surgery is deferred pending this.[4, 5] Pertinent decisions about indications for surgery and potential improvements can then be made.

Diagnosis of the underlying anatomical deformity is essential prior to embarking upon the surgical plan. Inspection and palpation are equally important, particularly when assessing the skin and soft-tissue envelope and minor dorsal irregularities. Within these areas, a further subdivision of underlying skeletal support, soft-tissue thickness and scarring and overlying skin texture will help elucidate anatomical and structural deformities. Intranasal examination may be complemented with endoscopic evaluation to identify the presence of septal deviations, adhesions, nasal valve problems and mucosal disease. Assessment with Cottle's manoeuvre is often advocated but can be non-specific, and lateralizing the upper lateral cartilage with a probe or cotton bud may be a better evaluator.

Approach and technique planning is then discussed with the patient and documented. Standard 2D/3D photography is performed and digital manipulation software can help in discussing potential post-operative changes. This subject is covered in detail in Chapter 81, Pre-operative assessment for rhinoplasty.

INDICATIONS

As has already been indicated, the choice to perform an external rhinoplasty will in many cases be dependent on the training and philosophy of an individual surgeon, recognizing that it is merely an approach to the underlying skeletal structures and not a surgical technique to correct deformity.

However, specific indications for the external approach in rhinoplasty may include:

- congenital deformities such as the cleft lip nose
- extensive revision surgery
- severe nasal trauma
- marked tip deformities including significant rotation and projection issues
- significant septal deviations, especially where high dorsal deviations are present
- situations where assessment of the exact underlying pathology is difficult.

Extended applications of the external approach exploit the excellent exposure of the nasal skeleton and the advantages this affords. It has been advocated for septal perforation repair,[8] access to the nasal dorsum for treatment of nasal dermoids.[9]

ANATOMY

It is important to emphasize salient aspects of the external approach anatomy. **Figure 82.1** shows the anatomical subunits of the nose, which are conveniently divided into thirds. The upper third bony pyramid consists laterally of the nasal bones and the ascending (frontal) processes of the maxilla and the bony septum in the midline. The middle third ('vault') area is formed by the paired upper lateral cartilages inserting just under the caudal end of the nasal bones and their fusion with the midline cartilaginous septum in a T-type configuration. The scroll attachment of the caudal aspect of the upper laterals to the cephalic aspect of lower lateral (alar) cartilages forms the boundary to the lower third of the nose. The upper lateral cartilages thus effectively lie at a slightly lower level to both the nasal bones and lower lateral cartilages. The paired lower laterals form the lower third of the nose, the nasal tip region, and are traditionally divided into

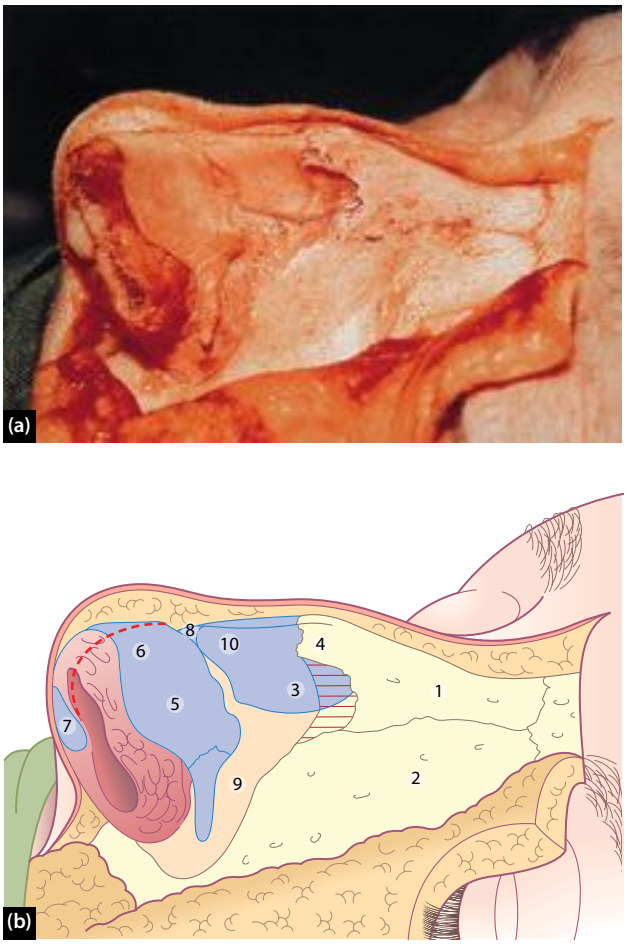


Figure 82.1 **(a)** Lateral view demonstrating the constituents of the anatomical subunits of the nose. **(b)** 1, nasal bone; 2, frontal process of the maxillary bone; 3, upper lateral cartilage; 4, area of overlap of upper lateral cartilage by nasal bone; 5, lateral crus of lower lateral cartilage; 6, dome area within intermediate crus; 7, medial crus of lower lateral cartilage; 8, quadrilateral cartilage; 9, connective tissue; 10, scroll region; 11, shaded area showing removed nasal bone.

the lateral, intermediate and medial crura. It is important to understand that the lateral crura extend laterally but also somewhat cephalically, leaving the most lateral aspect of the nostril's alar margin as being soft tissue alone, devoid of cartilaginous support. The domes and tip-defining points lie within the intermediate crus. The medial crural footplates extend to the lower aspect of the columella and lie just anterior to the caudal aspect of the nasal septum.

The superficial musculoaponeurotic system (SMAS) layer provides a vascular-rich covering to the underlying skeleton, with arterial supply derived from the superior labial and facial artery branches and corresponding venous and lymphatic vessels accompanying these. Exposure of all three parts of the nasal skeleton to some degree with subsequent identification of anatomical anomalies and asymmetries is the key advantage of the external rhinoplasty compared with an endonasal approach.[11]

BASIC PRINCIPLES OF THE EXTERNAL APPROACH

External rhinoplasty lends itself well to a philosophy of conservation of the structural support of the nose by full exposure of the underlyng structures and allowing open access for corrective surgical manoeuvres. It promotes emphasis on augmentation and reorientation of the supportive structures as opposed to reduction and resection.[12] However, certain general points need to be considered. Correct incision placement and meticulous wound closure are essential as the resultant scar should not be an overriding factor in the process of deciding which surgical approach to adopt.

The basic premise is that of a mid-columella incision connecting to bilateral marginal incisions; indeed, it is only this incision that separates it from a delivery-type endonasal approach. Those trained in endonasal rhinoplasty initially often choose to make the marginal incisions first and then join them with the columella incision. It is the author's preference to perform the incision first and then indentify and follow the medial crura outward into the intermediate and subsequently lateral crural areas.

Dissection in the subperichondrial and subperiosteal plane leaves as much soft tissue as possible on the skin flap, thus preserving its viability. In this way the lower and upper lateral cartilages together with the bony dorsum can be exposed to the nasofrontal angle in their undisturbed positions.[13, 14]

Division of the medial intercrural tissue offers access to the caudal septum and premaxillary spine, but it should be left intact if exposure is not indicated, as this intercrural attachment is one of the support mechanisms for the nasal tip. By dividing the upper laterals from the quadrilateral cartilage, the whole of the septum is accessible from the cephalic as well as the caudal aspect, allowing treatment of nasal valve problems, dorsal septal deviations and septal perforation repair.

As intercartilaginous incisions are not used, the valve area is preserved and the important major tip support mechanism of the scroll area is not disrupted. It is, however, important to appreciate that, while the major tip support mechanisms are respected in the external approach, the disruption of the skin soft-tissue envelope from the lower lateral cartilages and the division of the medial intercrural ligamentous fibrous tissue may lead to loss of some of the minor tip support mechanisms, and therefore some tip ptosis should be anticipated in all cases.

SURGICAL TECHNIQUE

Incisions

Fundamental plastic surgery principles dictate that a broken line transcolumellar incision will leave a less visible scar, rather than a single line horizontal incision which will be both more noticeable and prone to contraction. Commonly used incision variations include the step, gullwing and inverted V-type configurations. The author prefers the latter approach as this gives a near inconspicuous scar when properly closed.[16] If the columella is deemed too short in relation to the intended tip projection, as may occur, for example, in

cleft-lip rhinoplasty, a V incision made at the base of the columella to perform a V–Y lengthening procedure may be indicated.[17] An alternative forked flap has also been described.[18]

The columella incision should be situated in the upper two-thirds, normally at its narrowest point, to ensure the medial crural footplates provide adequate support, thus preventing a depressed scar (**Figure 82.2a**). In the lower third of the columella, the medial crura bend backward towards their attachment to the caudal septal area and thus the skin of the columella in this area is unsupported. It is essential to protect the integrity of the caudal end of the medial crura just beneath the incision to prevent post-operative notching in this area. This may be done by initially making only a very superficial columellar incision, cutting just through the skin; the vertical columellar parts of the marginal incisions are then placed 1.5–2 mm inside the vestibule and joined by careful undermining of the columellar skin with sharp dissecting scissors. These blades of the scissors can then be used as a guard upon which the columella incision is completed.

The midline aspects of the medial crura are now identified with sharp dissection and this is used to extend the incision upward towards the intermediate crural region. Ensuring adequate exposure of the cartilage, ideally in a subperichondrial plane, the marginal incision is then continued more laterally using angled Converse/Walter scissors with a spreading movement hugging the caudal aspect of the cartilage, followed by cutting of the overlying soft tissue (**Figure 82.2b** and **c**). To obtain adequate exposure of the nasal skeleton, the marginal incision should be extended at least halfway along the lateral crus but can be extended further laterally if dissection of the lateral most aspect of the lateral crus will be required.

Dissection of the soft-tissue envelope

Dissection of the soft-tissue envelope in the subperichondrial and subperisoteal plane is desirable to ensure minimal bleeding. Dissection after exposure of the medial crura should be continued in a lateral direction up to the hinge area, hugging the lower lateral cartilage, with further extension in a cephalic direction to the scroll area (**Figure 82.2d**). To free the cartilaginous vault, it is easy to make a false passage into the SMAS. To prevent this, dissection should be commenced in the midline between or just cephalic to the domes. It can be helpful to incise the perichondrium at the caudal end of the cartilaginous vault vertically in the midline, after which subperichondrial dissection can proceed from medial to lateral and in a cephalic direction. This can leave a useful subperichondrial flap that can be resutured in the midline, if required, to help with camouflage of underlying irregularities, particularly in thin skin noses.

Conversely, a thick supratip soft-tissue envelope can be thinned at a later stage if required, although this is done very conservatively to prevent compromise of the vascular supply to the overlying skin. A potential complication of the external approach is prolonged supratip oedema and occasionally a soft-tissue pollybeak as a result of dissection in the wrong plane disturbing the integrity of the transverse nasal muscle.

Dissection of the soft tissue of the bony pyramid in a subperiosteal plane starts with an incision made 2–3 mm parallel to and above the caudal end of both nasal bones. It is of great importance to palpate the edge of the nasal bone before making the incision, to prevent separation of the upper laterals from the bony pyramid, a pitfall that can only be corrected with a camouflaging onlay graft. The sharp side edges of a Joseph periosteal elevator are engaged along the incision to facilitate the raising of a subperiosteal flap over the bone.

The aim of the open approach is to identify and adequately expose underlying anatomical deformities and facilitate correction, and raising of the skin and soft-tissue envelope need only to extend to the areas of concern. More extensive dissection laterally over the doral bony skeleton has been advocated recently (an extended open approach) to facilitate powered instrumentation to create precise lateral osteotomies.

A potential disadvantage of the external approach is the difficulty assessing the supratip area and the desired tip projection, due to the lack of traction of the soft tissue prior to closure of the columella incision. Final assessment of these areas should thus be made after preliminary closure of the incision. Adjustment is still possible either by cartilage vault reduction and, if insufficient tip projection, by adding an onlay tip graft through the marginal incision or a shield graft, which can be sutured into place after reopening the transcolumellar incision.

In case of grafting procedures for augmentation, care should be taken that the overlying soft tissue has sufficient viability. Blanching of the skin over an augmentation graft is a warning sign which should not be neglected. A slight reduction of the graft size will prevent possible skin necrosis.

Access to the nasal septum

The nasal septum can be accessed by division of the soft tissue between the medial crura of the lower lateral cartilages, effectively dividing the membranous septal area (see **Figure 82.2f**). This will, however, disrupt one of the minor tip support mechanisms so may be best avoided if no cartilaginous material is available to provide structural support to maintain post-operative tip projection. An alternative exposure can be gained by a traditional separate hemitransfixion or Killian's incision.

Provision of a stable cartilaginous base is critical in all nasal tip surgery. If a columellar strut or septal extension graft is required, it is placed in a well-defined pocket between the crura, and extends from 2 mm above the anterior nasal spine to the angle between the medial and intermediate crura. The sandwich construction is fixed by mattress sutures which must not be placed above this angle in order to prevent loss of the columella–lobular ('double break') angle.[19, 20] To prevent asymmetry at the caudal plane of the columella and in dome height, it is important to fix the medial crura in the right parallel position temporarily with a needle after which final fixation with mattress sutures is accomplished (**Figures 82.2g** and **82.3**). The cartilaginous strut may also be used to correct buckled medial crura, strengthen weak medial crura, correct tip asymmetries and provide a stable base for the application of tip grafts.

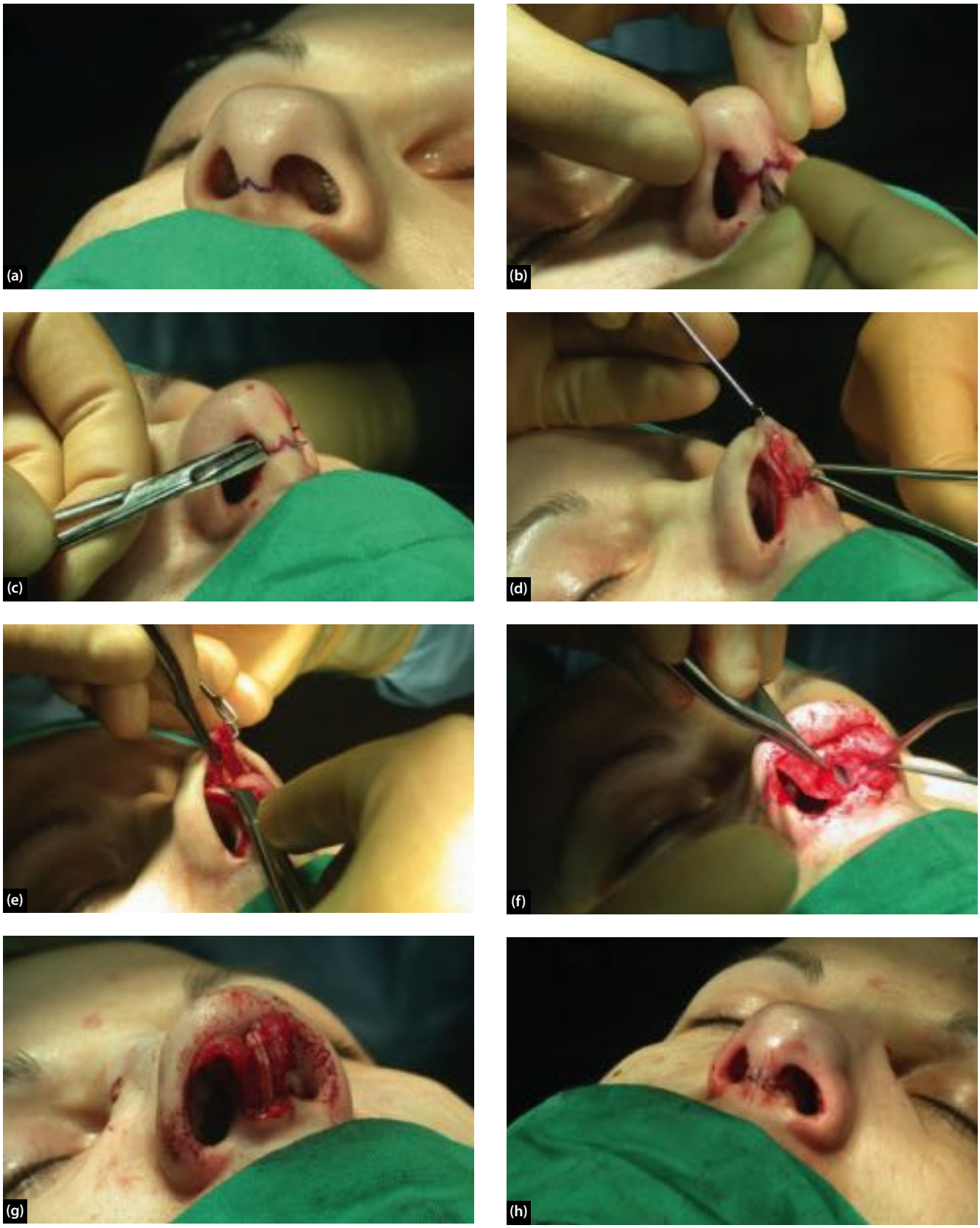


Figure 82.2 External rhinoplasty approach to correct an underprojected, asymmetric bulbous tip. **(a)** Mid-columella inverted 'V' incision. **(b)** Superficial incision made through the columella skin. **(c)** Iris scissors placed behind the incision to protect medial crurae. **(d)** Exposure of the medial crurae with development of the columella skin flap. **(e)** Dissection over the nasal domes with converse scissors. **(f)** Exposure of the caudal septal cartilage by dissection between medial crurae. **(g)** Columella strut placed between medial crurae. **(h)** Closure of incision after correction of boxy tip deformity.

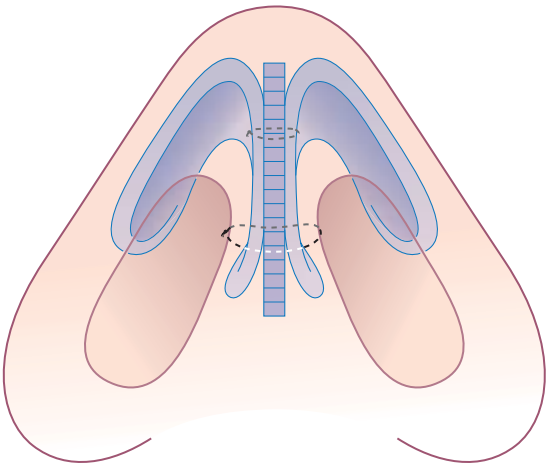


Figure 82.3 Columella strut of autogenous septal cartilage for extra tip support fixed by mattress sutures to the medial crura.

Closure of the transcolumellar incision

Meticulous closure is imperative with slight eversion of the wound edges (**Figure 82.2h**). Authors have favoured both fine non-absorbable suture material (6/0 ethilon or prolene) although the use of a rapidly absorbable suture such as 6/0 Vicryl Rapide negates the need for suture removal, which can prove very uncomfortable. To prevent tension, it can be helpful to place an initial subcutaneous absorbable suture, although this is not usually necessary. Between five and nine fine sutures are then used to close the incision with attention importantly focused to the lateral edges of the columella where irregularities may be most visible. The vertical incisions along the vestibular edge are closed and a single suture to approximate the lateral marginal incision normally suffices.

After closure of the incision, a smooth skin line of the columella from a basal and lateral view should be ensured. The skin sutures are removed, if required, 5–7 days postoperatively. While not favoured by the author, the use of tissue glue has also been shown to be an effective alternative method of closure.[21]

SPECIFIC APPLICATIONS

The bony pyramid in external rhinoplasty

Exposure of the upper third of the nose allows more accurate diagnosis and precise correction of dorsal abnormalities, thus avoiding irregularities that can arise from a closed procedure. The subperiosteal dissection should not extend more than halfway along the nasal bones.[22] The exception to this is when an extended dissection along the most lateral aspect of the bony vault to allow for powered lateral osteotomies such as with a Piezo device are planned.

A direct systematic examination is possible of the individual components of the bony vault. The size, shape and position of both nasal bones and bony septum, as well as the thickness of the overlying skin-soft tissue envelope in the region of the rhinion and nasion, are assessed individually and in relation to their effect on the nasofrontal angle and the width, height, dorsal profile and contour of the upper third.

The open approach allows the use of a burr or Piezoelectric device to deepen the nasofrontal angle. Conversely, the angle can be deepened or set in a more cephalic position by precise application of soft-tissue onlay radix grafts of temporalis fascia or slivers of autogenous cartilage. Such implants can also be secured in an accurate position via this approach.

The principles and techniques of bony dehumping together with lateral, medial oblique and intermediate osteotomies are the same for both the endonasal and open approaches although the latter has the added advantage of allowing direct vision, particularly when powered instruments are used. It can be easier, however, to remove medial bony wedges in a trapezoid bony vault with an open approach.

The middle nasal vault

The 'nasal valve area' is the smallest cross-sectional area in the nasal airway. Its boundary is formed by the caudal end of the upper lateral cartilage, the head of the inferior turbinate, the floor of the nose, the nasal septum and the intervening tissue surrounding the pyriform aperture. Rhinoplasty can compromise the nasal valve, particularly in patients with short nasal bones, a high bony–cartilaginous hump and weak upper lateral cartilages.[23] Frequently, there is an additional corresponding aesthetic defect of a 'sunken' or 'pinched-in' middle third. Such an inverted V-type deformity is a consequence of either excessive resection of or collapse of the upper lateral cartilages inferomedially due to inadequate support after removal of a dorsal hump. The nose displays a 'washed-out' appearance with prominence of the caudal edge of the nasal bones. There may be associated internal nasal valve collapse giving rise to nasal obstruction.

Placement of 'spreader grafts' to open up the nasal valve area and angle was initially described via an endonasal approach thereby improving both function and cosmesis (**Figure 82.4**).[24] The external approach allows easier and more precise placement and suture fixation of such spreader grafts, minimizing risk of displacement. These cartilaginous strips are placed longitudinally between the upper lateral cartilage and septum. The mucosa between these cartilages is often divided but, based on Sheen's original work,[32] this should be avoided and rather the spreader graft placed extramucosally. The functional improvement has been difficult to quantify objectively but subjective improvement is to be anticipated. Placement via an external approach allows for accurate visualization but, when required, can be equally well placed endonasally[33] into tight submucoperichondrial pockets and held with tissue glue or with percutaneous trans-septal sutures if needed. Unilateral placement of spreader grafts may also correct asymmetries of the dorsum.

'Autospreaders'/spreader flaps can be an effective and simple alternative and negates the need for a separate cartilaginous source (**Figure 82.5**). When lowering the

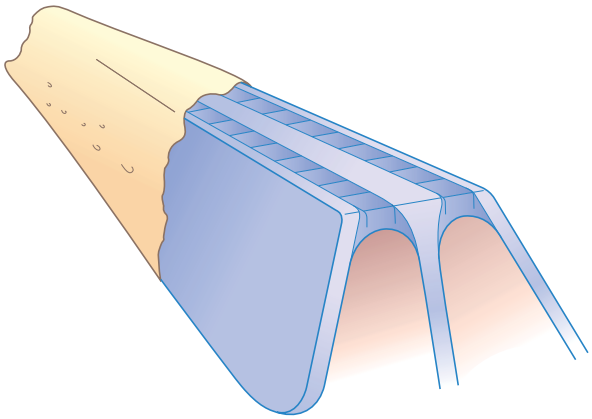


Figure 82.4 Shaded areas showing placement of spreader grafts.

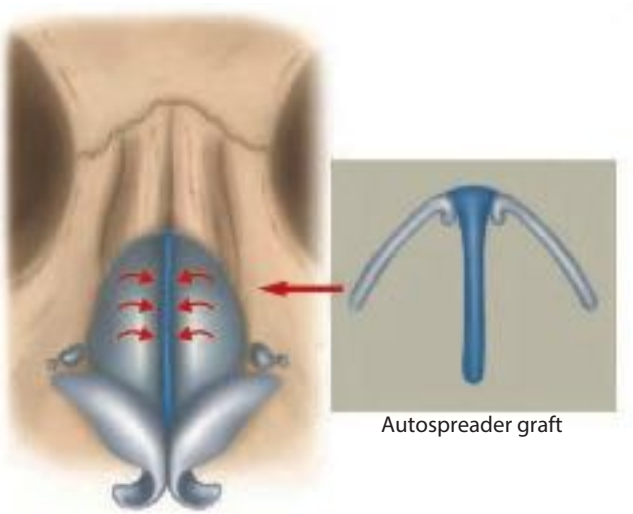


Figure 82.5 Autospreader graft/spreader flap created by turn in of upper lateral cartilages.

cartilaginous dorsum, the upper lateral cartilages are separated extramucosally from the septal cartilage and the superior-most aspect of its cephalic edge dissected off the underside of the bony vault. The midline septal cartilage is then lowered but the upper laterals are left intact and infolded to create such spreader flaps, mimicking the effect of spreader grafts. These can be an effective way of avoiding mid-vault narrowing but alone are unlikely to proffer any functional benefit.

The open approach exposure also facilitates extended roles of spreader grafts to include their use as part of lengthening an overly rotated nose with articulation onto septal extension grafts, maintenance or reconstruction of the dorsal nasal roof, straightening of a high dorsally deviated septum and recreation of the dorsal aesthetic lines.[25]

Nasal tip surgery

Nasal tip surgery has perhaps been the major beneficiary of the open approach since it exposes the structural components of the tip in their natural undisturbed position. It allows unparalleled diagnosis of the various deformities and asymmetries as well as facilitating precise surgical manipulation of the tip cartilages and suture fixation of grafts. In particular, it allows the visualization and correction of minor asymmetries, thus adding extra surgical finesse.

While it is beyond the scope of this chapter to discuss nasal tip techniques in detail, some highlights of tip surgery that benefit most by the open approach are featured. Altering tip projection and rotation by modelling the alar cartilages is based upon the 'tripod' theory.[5] This theory states that the structural framework of the nasal tip is based on the two lateral crura and the conjoined medial crura, each forming one leg of the tripod (**Figure 82.6**). This allows an understanding of the effect on the tip position by altering the size and position of the medial or lateral crura. For instance, if the medial and lateral crura are reduced in length, the tip is deprojected; if they are augmented, projection is achieved. Superior rotation is achieved by shortening the lateral crura or, alternatively, by lengthening the medial crura causing rotation at the 'hinge' region.

Problems encountered may be conveniently thought of as being due to under- or over-rotation, under- or over-projection, width problems or intrinsic tip deformities. Manipulation of any part of the tripod model normally leads to predictable changes in both the projection and rotation of the nasal tip and some examples are described below. All aspects of tip surgery can be performed in a more controlled fashion and with a high degree of symmetry by using the external approach.[7, 27, 28]

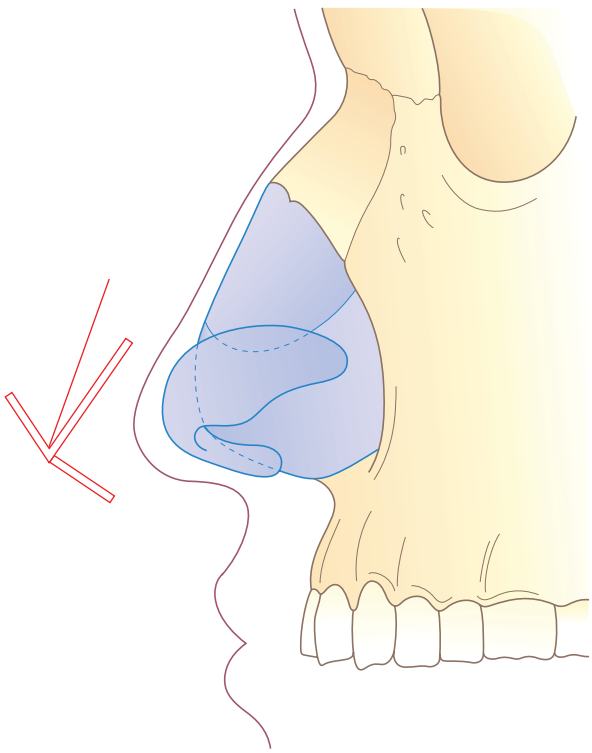


Figure 82.6 Tripod complex of the lower third of the nose. The conjoint medial crura comprise one leg of the tripod, while the lateral crura comprise the other two legs.

ROTATION DEFORMITIES

Correction of the under-rotated tip can be effected with various manoeuvres, based on the tripod theory. Rotation changes are usually linked with some associated projection change.

Lateral crural steal techniques with recruitment of the lateral crura medially using domal suturing creates tip projection and rotation. Conversely, resection and overlay of the lateral crura (lateral crural flap/overlay technique **Figure 82.7**) produce rotation with deprojection. Such a technique is generally used to shorten the nose as well when overprojection is problematic. Plumping grafts and columellar struts are also used to create an illusion of rotation.

An overly rotated nasal tip is often challenging to correct, particularly when it is a result of prior surgery. It occurs most often due to a combination of factors at the original surgery such as resection of the anterior septal angle, or the visoring effect of excessive cephalic strip excision of the lower lateral cartilages perhaps together with other rotation manoeuvres involving the lateral crura. Options for correction are more limited with this situation and soft-tissue changes limit how much counter-rotation occurs. The mainstay of management is placement of a caudal septal extension graft to effectively lengthen the nose (**Figure 82.8**). Extended spreader grafts are then used to try to stabilize the septal complex and the lower lateral cartilages are then rotated downwards and fixed to the extension graft.

Again using the tripod theory, division and overlap of the medial crura will create counter-rotation although this does also deproject the tip. Finally, a graft in the tip/infratip area will give an illusion of counter-rotation and increased length of the nose and is best employed in addition to, rather than instead of, the other listed procedures when required. This is best avoided, however, in thin-skinned individuals where grafts in the tip region are potentially easily visible.

PROJECTION DEFORMITIES

Projection of the nasal tip is often desirable in rhinoplasty surgery. Both external and endonasal rhinoplasty approaches can create post-operative ptosis, so attempts to maintain adequate projection are important. Dome suturing, so often used to define the nasal tip by increasing triangularity and narrowing, may also act to project the tip somewhat. Used alone, a small amount of increased projection and rotation can be achieved. When further projection is required, the lateral crural steal is a workhorse technique that can also rotate the tip. It is important not to overtighten sutures as this can create a pinching effect.

The 'tongue-in-groove' technique of septocolumellar suturing is a further option and usefully allows setting of projection and rotation of the nasal tip (**Figure 82.9**). A disadvantage of this method is the rigidity and lack of mobility such a procedure imparts to the tip but it is

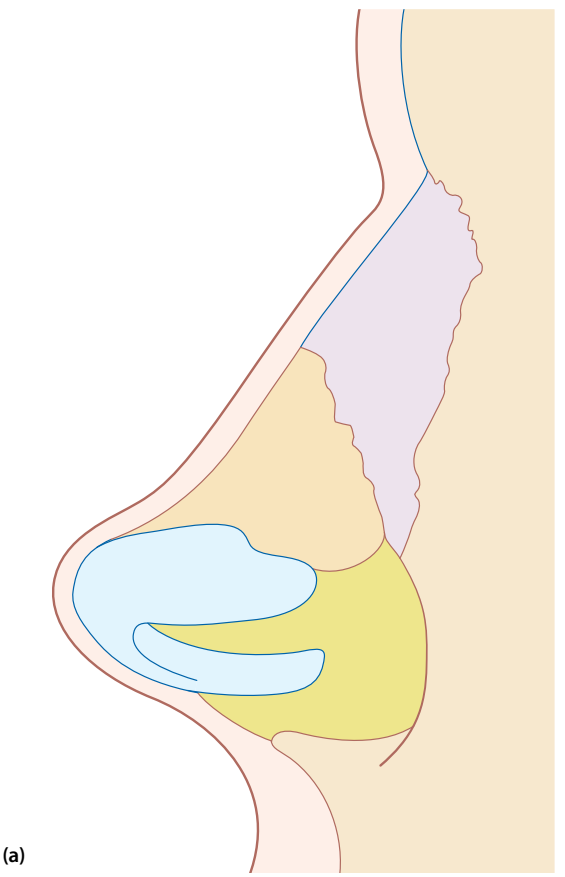




Figure 82.7 **(a)** and **(b)** Lateral crural flap/overlay – the lower lateral cartilage is divided laterally and overlapped to deproject the tip. This also creates a degree of rotation.



Figure 82.8 Septal extension graft placed in an 'end-to-end' fashion.

generally well tolerated in most patients. This technique can cause a degree of columellar retraction and over-rotation of the tip if the distance between the medial crura and caudal septum is excessive. A septal extension graft can be used to counter this, adding additional security of strength and base stability to the nasal tip complex. Columellar struts may help strengthen inherently weak medial crura, thereby creating projection, but they are generally best used in addition to other techniques as, alone, they may not be able to counter contraction post-operatively. Using a permanent suture between the upper lateral cartilages and columellar complex provides stability in this regard.

Grafts may also have a part to play. Shield and tip grafts work well in thicker-skinned patients and can create a final finesse to a poorly projected tip.

Deprojection of the 'tension' nose is a less frequently encountered problem in revision surgery. A full transfixion incision will divide the medial crural footplate attachment as they curve backwards to the caudal septum, thereby disrupting a major tip support mechanism, predictably creating some post-operative tip deprojection that is an easy initial step in correcting this deformity. This may need to be combined with division and overlay of the medial, lateral or both crura, depending on the rotation requirements. The 'lateral crural flap' alone creates deprojection and rotation and, in a similar way, the medial crural flap technique will deproject and counter-rotate the nose (see **Figure 82.7**). If the rotation needs no altering, an equal amount of overlapping in both areas can be performed, thus counterbalancing any rotation changes.

Excision of the anterior nasal spine has also been described[35] but risks bleeding and the potential for some columellar retraction.

INTRINSIC TIP DEFORMITIES

Pinched nasal tip deformity

By far the most common cause of a pinched nasal tip deformity is iatrogenic weakening of the lower lateral

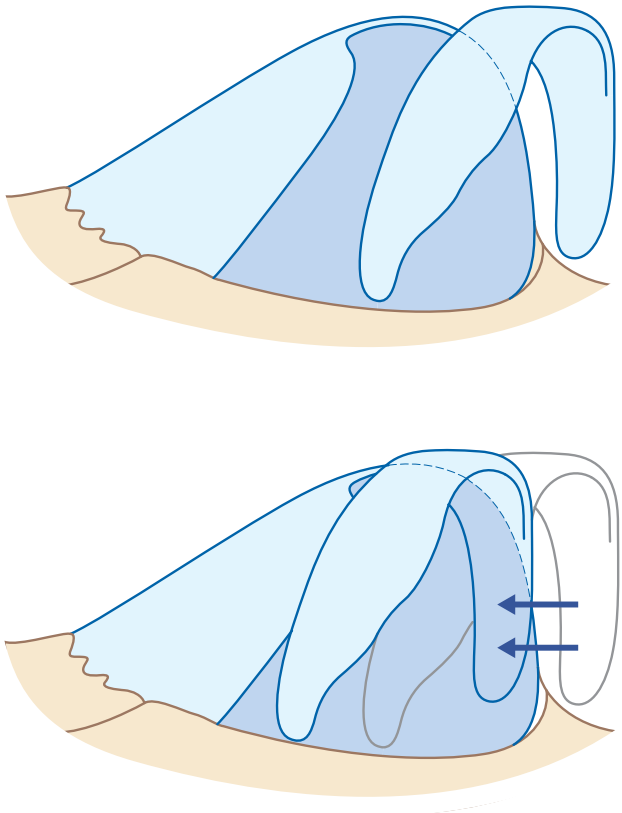


Figure 82.9 Tongue in groove technique of septocolumellar suturing.

cartilages due to over-resection of the cephalic edge of the lower lateral cartilages with subsequent weakening of the intact rim strip. The useful edict of leaving behind more cartilage than that resected should always be remembered; the author recommends an absolute minimum of 6 mm cartilaginous support but leaving more may be more favourable. The author now rarely resects the lateral crus cephalic cartilage but instead attempts to reorientate in such a way that the caudal edge lies at a higher level to the cephalic border. Aggressive domal suturing with its resultant alteration in tip orientation and dynamics can also cause notching in the dome region, predisposing to a pinched tip effect.

The lateral crura should have an outward convexity of the posterior alar rims and gentle rounding in the dome region; specifically, there should be no pinching of the lateral alar walls. While for minor deformities, an endonasal approach may prove adequate for placement of supporting grafts in primary surgery or to correct prior overzealous tip suturing, the open approach allows for accurate anatomical analysis of the underlying deformity of the lower lateral cartilages which can then be repositioned and modified as required. Small specific pockets allow batten grafts to be inserted to correct concavities caused by weakness of the cartilage. An isolated aesthetic deformity caused by inherent concavity of the lateral crus may be corrected by complete mobilization of the lower lateral cartilage from the vestibular skin. An incision is then made just lateral to the domal area and the lateral

crus flipped over such that the concavity now becomes a convexity. The rotated crus is then sutured to the medial segment (**Figure 82.10**).

The external approach remains the author's favoured method for accurate evaluation of the orientation, integrity and strength of the alar cartilages. Augmentation using septal or auricular cartilage to fashion alar battens or lateral crural strut grafts provides stability and strength to the weakened alar cartilages, thus correcting both aesthetic and functional aspects of the deformity. Alar rim grafts can further recreate convexity and rounding of the nasal tip contour as assessed on the frontal and basal views.

Bossae formation

Knuckling of the lower lateral cartilages in the domal area forms so-called 'bossae'. The inexperienced rhinoplasty surgeon may not be aware of the triad of thin skin, strong alar cartilages and bifidity of the tip which together predispose to their formation when there is an excess cephalic strip reduction and inadequate narrowing of the domes.[38] Post-operative scar contracture in this area causes the deformity.

Treatment options include trimming or resection of the knuckled areas with suture reconstruction of the lower lateral cartilages. Covering the area with a camouflage graft may also help correct any minor residual deformity.

Alar retraction

Overzealous cephalic strip resection can lead to alar retraction due to the visoring effect caused by contraction as healing occurs.[39, 41] An absolute minimum of 6 mm residual cartilage is recommended but, in the presence of an anatomically narrow alar cartilage, this may need to be revised. If vestibular mucosa is not preserved, this too can contribute to contracture and promote further retraction. Correction with cartilage grafting placed into a snug pocket fashioned through a marginal incision may improve minor defects. For a more severe deformity, a composite cartilage graft, usually fashioned from the concha of the opposite ear, is taken.[42] This is placed into a space created by dissection of the alar rim away from the residual lower lateral cartilage, allowing the alar rim to be displaced caudally. An alternative is to dissect space between the upper and lower lateral cartilages and place a firm (ideally septal or rib) spacer graft into this area, pushing the lower lateral crus caudally.

Hanging collumella and retraction

The hanging columella can be a very unaesthetic deformity. Options include resection of the caudal and/or membranous septum, which is the main cause. However, in the presence of prominent medial crura, resection of the caudal aspect of the crura or occasionally vertical division may resolve the deformity.[43] The 'tongue-in-groove' method of suturing the medial crura to the septum described previously can be an effective alternative.[36]

Columellar retraction is often a consequence of overresection of the caudal septum at primary surgery. The lack of support in this area causes gradual contraction with time. Placement of a columellar strut sutured between the medial crura is a treatment option, as are plumping grafts placed in the premaxillary area. More substantial retraction can be improved with cartilaginous septal extension grafts. These can be tailored to project either the whole retraction or variably the upper or lower part forwards, dependent on the need for rotation of the tip.

Revision rhinoplasty

Revision rhinoplasty is undoubtedly one of the most challenging operations undertaken by the facial plastic surgeon. The dawn of a social media generation has led to increased public awareness of all aspects of cosmetic surgery, including the need and desire for revision procedures, with the newly informed patient becoming more critical of post-operative results. An unprecedented number of media articles on aesthetic surgery appear to be increasing patient expectations. As contemporary techniques evolve, the modern rhinoplasty surgeon is constantly seeking an ultimate post-operative result that will please both the discriminative patient and surgeon alike.

Various authors have reported an increase in the number of revision cases, which may be a reflection of the greater popularity of rhinoplasty and the enhanced expectations and discrimination of both the surgeon and patient.[30, 31]

The key to successful revision procedures is the ability to correctly diagnose underlying deformity in the first instance with a view to formulating a surgical plan. Very often, this can be challenging given soft-tissue contracture following prior surgery. The open approach, of course, allows accurate visualization of the deformity and simplifies accurate correction, which may require advanced techniques, including augmentation procedures. Structural grafting and relocation of tissue with the aim of producing predictable favourable long-term results is facilitated. Scar tissue may also be more easily identified and excised.

The deviated nose

The external approach to the deviated nose lends itself well to accurate correction of such a deformity due to the added exposure it provides and the ability to place corrective grafts. When excising a bony hump in the presence of a bony pyramid deviation and unequal height of the nasal bones, the plane of the osteotome may be altered to allow this. Alternatively, the use of powered instruments such a Piezo device under direct vision will allow accurate reduction of the dorsal bone and cartilage alike. Osteotomies can also be performed sequentially under direct vision. For example, if the nose deviates to the right, the first step is to mobilize the left nasal bone and reposition it in its normal position; the next step is to position the bony septum in the midline; and, finally, the right nasal bone is repositioned in its normal position.[22] Again, with extended lateral dissection, a Piezo saw can be used under direct vision to create the lateral osteotomies.











Figure 82.10 (a) Unilateral concavity of lateral crus. **(b)** Dissection of lateral crus from underlying vestibular skin. **(c)** Concave lateral crus divided just lateral to dome. **(d)** Concave segment flipped over to create convexity. **(e)** Convexity now seen in final result.

A deviation of the lower two-thirds of the nose is usually due to a C-shaped dorsal deviation of the nasal septum, possibly complicated by previous surgery, which may have disrupted the union of the upper laterals to the septum. In mild cases, the dorsal aspect of the septum is shaved on the convex side and sutured to the upper lateral cartilage. If this is not sufficient to correct the deviation, a unilateral spreader graft is placed between the dorsal septum and the upper lateral cartilage.[20] The spreader graft acts as a stent as well as opening the nasal valve area. Any residual deformity is corrected by an onlay graft (**Figure 82.11**).

Dorsal augmentation

For grafting purposes, autologous septal or auricular cartilage remains the ideal standard and this appears to be supported by most authors. Options may be limited by prior surgery and the option of the autogenous or homologous irradiated costal cartilage must be considered. Alloplastic materials are reserved for cases where there is minimal residual cartilage available and the risks associated with infection and possible extrusion should be discussed with the patient pre-operatively.



Figure 82.11 (a–f) Pre- and post-operative images of a patient undergoing secondary rhinoplasty with residual septal and ear cartilage harvest. Septal L-strut reconstruction with an onlay diced cartilage and fascia graft, columellar strut graft with mild tip deprojection, and medial and lateral osteotomies were performed.

Grafts can be used as a solid implant, with careful fashioning and chamfering of its edges to reduce the risk of post-operative visibility. These can be placed into a 'hand-in-glove' type pocket to avoid movement post-operatively but the open approach allows for graft stabilization with sutures accurately placed. The same principles apply also to placement of diced cartilage in fascia grafts (**Figure 82.12**) where suture fixation will ensure that the graft remains secure and will not move in the post-operative recovery period.

Cleft-lip nasal deformities

Rhinoplasty in a cleft-lip patient is challenging due to the limitation of the final post-operative result.[38] The severity of primary nasal deformities is directly related to the severity of the cleft lip. The nasal and vestibular skin as well as the cartilaginous and bony skeleton is affected. Cleft-lip nasal deformities can be classified into unilateral and bilateral and form a characteristic pattern.[35] The secondary, and hopefully definitive, nasal reconstruction should be performed using the external rhinoplasty technique in the presence of severe tip asymmetry. The use of conservative techniques allows the procedure to be performed before puberty. However, the surgeon has to weigh up the psychological and future nasal directional growth benefits against possible inhibition of mid-facial growth,[35, 36] although studies have questioned whether septal surgery via an external approach truly has an effect on future nasal and midface development.[37] A V–Y procedure to lengthen the columella is usually needed in bilateral cleft deformities, and this should be considered when placing the incision. A complete cleft will be associated with hypoplasia and retropositioning of the maxilla on the cleft side. If mild, a cartilaginous graft can be used for support in order to relocate the alar base; in severe cases, a maxillary advancement will be needed. The key to correcting tip asymmetry is a stable and symmetrical base formed by the columella strut or, perhaps better still, a septal extension graft (see **Figure 82.8**). The lower lateral cartilage on the cleft side must first be dissected free, after which it can be repositioned and sutured to the cartilaginous columella support (more anterocephalic).[35, 40] This does not alter the lateral alar base displacement. A Z-plasty to reposition and to counter-rotate the ala at the cleft side is often required.[35] Finally, a shield graft may be positioned, which further increases tip projection, enhances tip definition and camouflages minor tip asymmetries.[39]

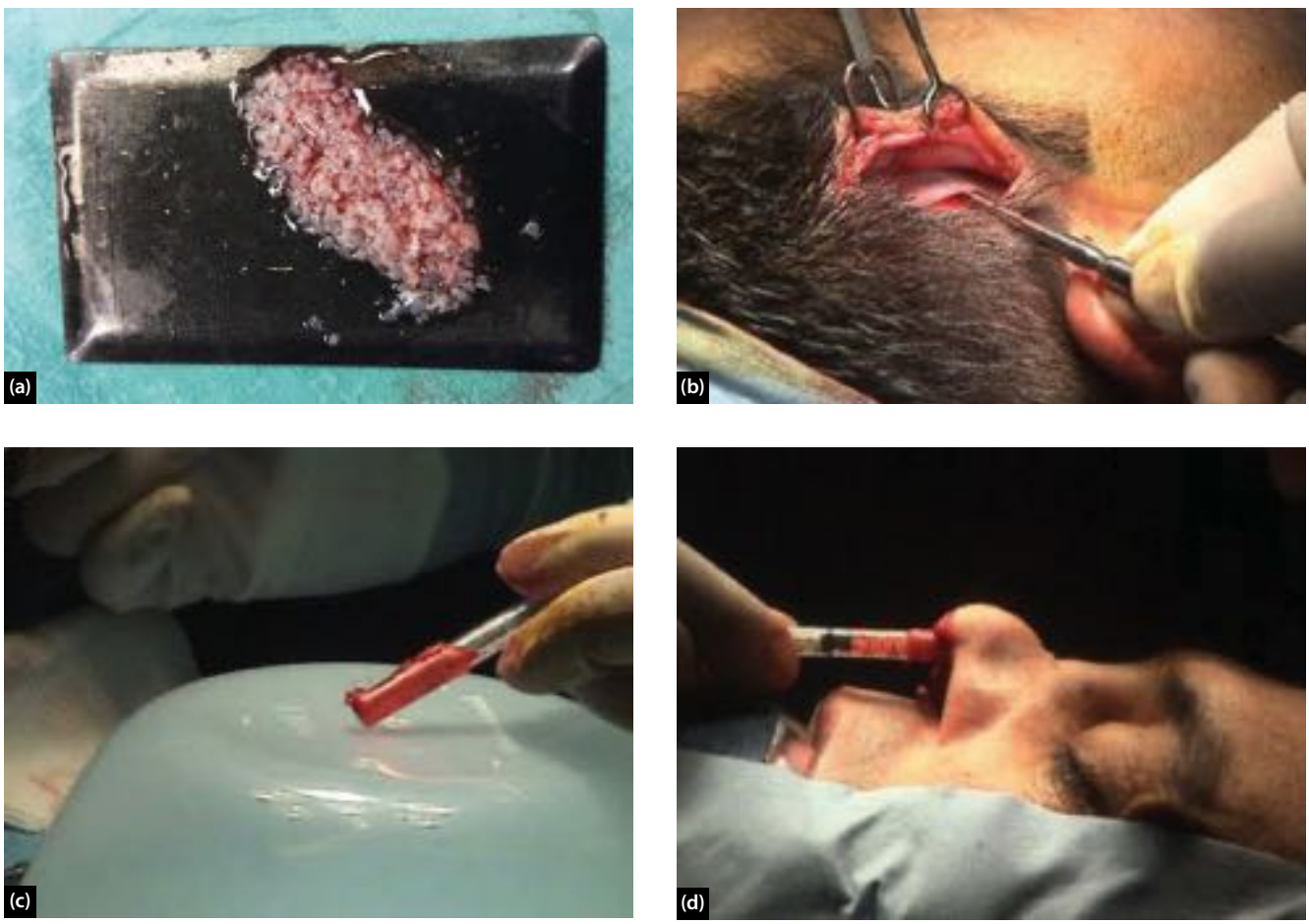


Figure 82.12 **(a)** Finely diced auricular cartilage. **(b)** Harvest of temporalis fascia. **(c)** Fascia wrapped around a 1 ml syringe. **(d)** Diced cartilage placed into syringe and injected with fascial wrapper onto dorsum.

Septal perforation repair

Contemporary techniques of septal perforation repair rely on mobilization of mucoperichondrial flaps to allow individual closure, usually with an interpositional graft. Such dissections are laborious and challenging and the external approach may be undoubtedly facilitating, particularly in the repair of large septal perforations.[8, 9] It allows unique exposure of the septum from both the cephalic and the caudal aspect and also aids any required conjunctive rhinoplasty. The septal flaps are then more easily released and advanced to allow for a tensionless closure, and suturing of the flaps is aided by the wide exposure.

Nasal dermoids

The poor cosmesis associated with a vertical midline scar required in total excision of a nasal dermoid may be avoided by use of the external rhinoplasty approach and its use has been advocated widely.[10] The dermoid can usually be dissected off the overlying skin although there may be a small of area of cutaneous resection required and, if particularly large, any excessive redundant skin may require resection.

CASE EXAMPLES

Figures 82.13 and **82.14** illustrate cases in which an external rhinoplasty approach was used to advantage for correction of specific deformities. The patient in **Figure 82.13** was a revision case in which there was need for significant grafting to allow improvement of both function and form. The open approach facilitated accurate diagnosis of the deformity and placement and suturing of the various grafts that were harvested from the residual septum and auricular region. The patient in **Figure 82.14** sought cosmetic

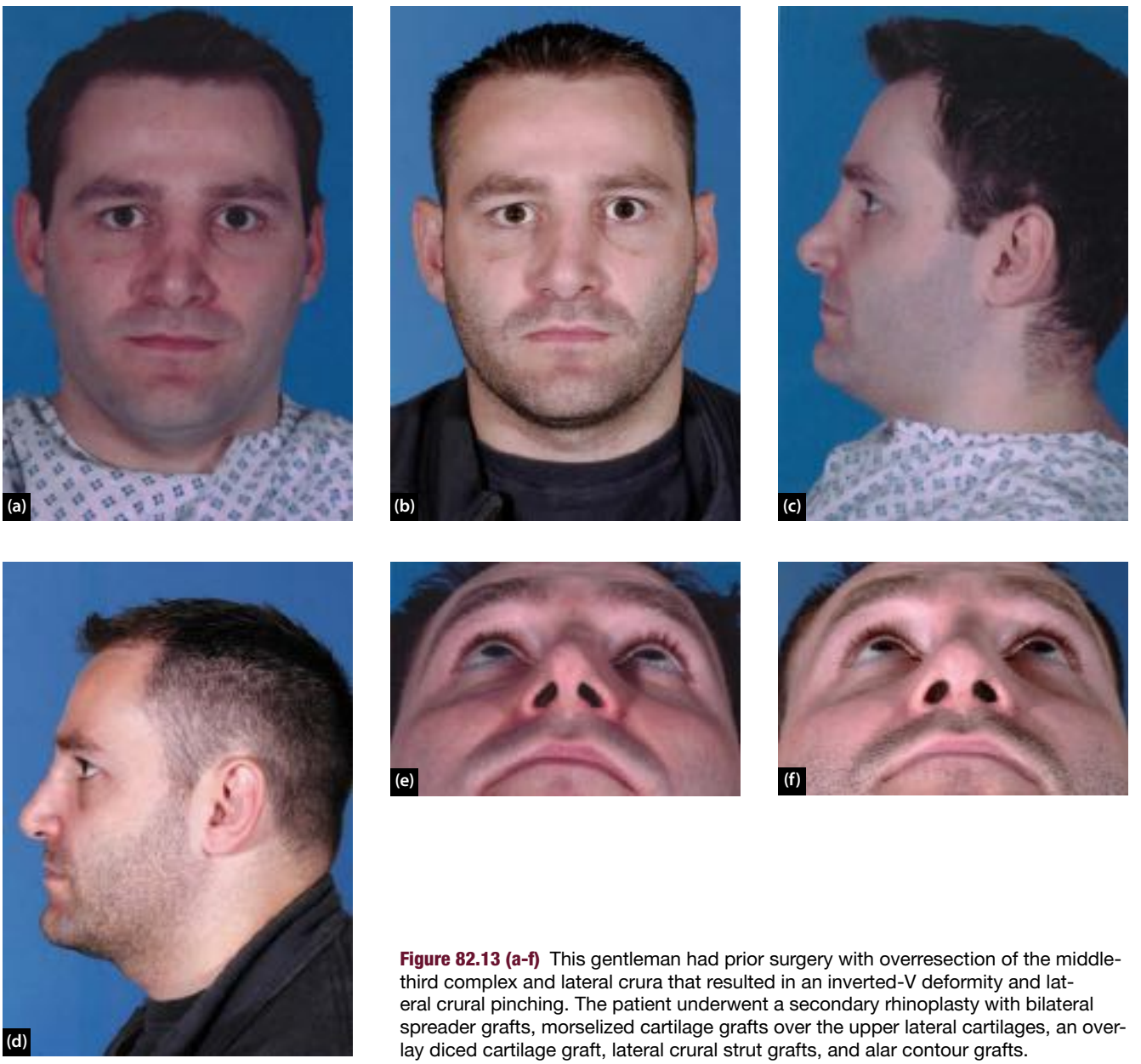


Figure 82.13 (a-f) This gentleman had prior surgery with overresection of the middle-third complex and lateral crura that resulted in an inverted-V deformity and lateral crural pinching. The patient underwent a secondary rhinoplasty with bilateral spreader grafts, morselized cartilage grafts over the upper lateral cartilages, an overlay diced cartilage graft, lateral crural strut grafts, and alar contour grafts.



Figure 82.14 (a-h) Pre- and post-operative photographs of a patient undergoing a reduction rhinoplasty. The patient had dorsal cartilaginous and bony reduction, insertion of bilateral but asymmetrical spreader grafts, medial and lateral osteotomies, tip rotation with a tongue-in-groove procedure, tip deprojection with a lateral crural overlay, and domal sutures.

improvement of the rather overprojected nose with reduction of the dorsal hump. Again the open approach allows simple placement of spreader grafts as well as the ability to use the tongue in groove and lateral crural overlay techniques effectively and precisely.

CONCLUSIONS

The external approach has proven to be a valuable part of the armamentarium of the rhinoplasty surgeon. Its unparalleled exposure and the ability to bimanually manipulate and handle underlying tissues gives a major advantage to endonasal techniques, particularly in more complex surgery, revision and post-traumatic deformity. It facilitates accurate resection and modelling of underlying bony and cartilaginous components and enables straightforward placement and suturing of graft material. Correct incision placement, dissection in the right surgical planes and meticulous suturing techniques prevent unnecessary sequelae of this approach, such as prolonged supratip oedema and aesthetically unacceptable transcolumellar scars. Relative disadvantages of increased operating time and difficulty of dorsal assessment are minor and should improve with the experience of the surgeon.

FUTURE RESEARCH

- ➤ There is much work being done presently with use of powered instrumentation, especially with the Piezoelectric devices.
- ➤ Popularity of powered instrumentation has grown in recent years but it will remain to be seen whether the additional extensive skin degloving required and the cost of the equipment will make these instruments a mainstay in the future.
- ➤ Additional research into powered instruments may shape future use of such devices.

KEY POINTS

- The external approach affords superior visualization of underlying deformities, allows bimanual handling of tissue and accurate placement of grafts and sutures.
- Modern techniques for tissue dissection planes and scar placement and suturing minimize the previously quoted disadvantages of this approach.
- The principle of limiting tissue dissection as much as possible remains and endonasal techniques may be employed in less complex cases.
- Structural grafting techniques to maintain long-term stability of the nose often necessitates an open approach.
- An appropriately placed broken line incision with meticulous closure allows for minimal visualization of the columellar scar with time.

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CHAPTER 83

REVISION RHINOPLASTY

Claudia Rudack and Gerhard Rettinger

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Revision rates 1161
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SEARCH STRATEGY

Data in this chapter may be updated by searches of Embase, the Cochrane Library and PubMed using the keywords: secondary, revision, rhinoplasty.

INTRODUCTION

Rhinoplasty (in contrast to septorhinoplasty) focuses mainly on altering the appearance of the external nose for aesthetic reasons. In certain cases, for example in a tension nose or in alar insufficiency, rhinoplasty is performed to correct the nasal airways. A septorhinoplasty attempts to improve both the aesthetic appearance and the function of the nose. This combined procedure may add additional dynamics in the healing process and therefore revisions may be more common.[1] This chapter primarily deals with visible deformities after previous rhinoplasty, their types and frequencies, possible causes, their prevention and their correction. Unfavourable results may be the consequence of unpredictable healing, which is beyond the surgeon's control, and these are generally referred to as 'complications'. However, revisions may also be necessary because of an inadequate primary procedure, which is then termed a 'mistake'. In this situation, the patient usually blames the surgeon responsible for the ultimate outcome. For the surgeon, it is important to understand the difference between a complication and a mistake and to learn from revision surgery.[1]

The surgical procedures available for revision rhinoplasty are numerous[2–8] and are mostly based on the experience of the individual rhinoplasty surgeon. Because of this, only the more common techniques for the most frequent residual deformities will be discussed.

It is difficult to draw general conclusions from the literature. On one hand, reports on long-term results are very rare and most publications describe the number of revisions that are undertaken 1–2 years after primary surgery. It is possible that many problems that give rise to revisions may present much later. In addition, the patient population analyzed in an article will be non-homogeneous. The primary surgery can be performed by different surgeons with different experience and technical factors may contribute to post-rhinoplasty deformities. In addition, follow-up of patients operated on by a single surgeon may be incomplete. He or she may only see patients with minor deformities, who tend to return to the primary surgeon. Patients with major deformities, however, tend to seek an opinion from a second surgeon.[9] Comparing figures on types of post-operative deformities in different studies may also be of limited value. Noses, as well as surgical goals, may differ between countries and continents. What may be an acceptable result in one country may be an indication for revision rhinoplasty in another.

These factors do not facilitate the reporting of evidence-based data. This means that the figures presented can only represent a tendency and give support for a better understanding of the development of deformities after rhinoplasty, their prevention and revision techniques.

REVISION RATES

Most data from the literature describe revisions after aesthetic rhinoplasty, rarely for functional aesthetic rhinoplasty. This must therefore be taken into consideration when drawing any conclusions.

Reported revision rates are listed in **Table 83.1.** In general, a revision rate of 5–10% is to be expected.[14] Specialized surgeons will undertake more revisions because patients are more likely to be referred to them. In the large series by Parkes et al. of 1221 consecutive rhinoplasties,[14] the overall revision rate was approximately 14%. However, their own

TABLE 83.1 Revision rates after primary or multiple rhinoplasty

Author	Year	Total no. patients	Revision (patients %)
Klabunde et al.[10]	1964	300	30/10
Smith[11]	1967	221	27/12
McKinney et al.[12]	1981	200	24/12
Swanepol et al.[13]	1981	882	63/7.1
*Kamer et al.[9]	1988	638	67/10.5
Parkes et al.14	1992	1221	170/13.9
*Vuyk et al.[15]	2000	480	110/23
Costantian et al.[17]	2000	-	150
*Bracaglia et al.[18]	2005	-	311
Foda et al.[19]	2005	50	50
Rettinger et al.[2]	2007	502	184

*No consecutive series of primary or multiple rhinoplasties.

revision rate was only 5.3%. The frequency of having more than one revision lies between 20% and 23% of all revision cases.[9, 14, 15] Revision rhinoplasty is more commonly performed in females, with rates of 60–80%.[14, 15] In a series of 200 consecutive rhinoplasties undertaken by a single surgeon, 12% had revisions. Of these, more women (14%) than men (9%) were dissatisfied with the surgical result.[12] In contrast to these figures, the rate of dissatisfied patients in a population of 1062 patients who had undergone rhinoplasty and who then completed a questionnaire afterwards (468 responders) was higher among male patients (12.8%) than among female patients (4.6%).[16] Interestingly, a study cohort comprising 175 842 participants who underwent septorhinoplasty procedures showed an overall revision rate for any septorhinoplasty procedure of 3.3% (5775 of 175 842) (99% CI, 3.2–3.4%). After separating the patients into primary septorhinoplasty and secondary septorhinoplasty groups, the primary group had an overall revision rate of 3.1% (5389 of 172 324), while the secondary group had an overall revision rate of 11.0% (386 of 3518). Patient characteristics associated with an increased rate of revision include younger age (5.9% [633 of 10 727]), female sex (3.8% [2536 of 67 397]), a history of anxiety (3.9% [168 of 4350]) or autoimmune disease (4.4% [57 of 1286]), and surgery for cosmetic (7.9% [340 of 4289]) or congenital nasal deformities (8.9% [208 of 2334]).[20]

CLASSIFICATION AND FREQUENCY OF DEFORMITIES REQUIRING REVISION RHINOPLASTY

A systematic approach to revision rhinoplasty may be based on the type of surgical procedure needed or the type of the deformity to be corrected. Webster defined five categories of revision:[21]

- revision uncertain or unnecessary
- revision with skeletal reduction
- revision with skeletal augmentation
- external soft-tissue removal required
- revision in congenital anomalies, major trauma, etc.

Other authors have described the location of the deformity (**Table 83.2**). Cohen lists eight different groups of external abnormalities and also includes functional disturbances.[22] Stucker, however, divides the nose into thirds: the upper (bony) third, the middle cartilaginous third and the lower third.[23] These parts can be further subdivided (see **Table 83.2**).[24] Kamer and McQuown[9] include the severity of the deformity. They distinguished between major deformities, such as saddling, midnasal asymmetry, pollybeak, retracted ala and columella, and minor deformities, which included tip-bossae, wide nasal base, hanging columella, irregular or high nasal dorsum and acute nasolabial angle.

The frequency of different deformities as reported by the eight authors above is listed in **Table 83.2.** The risk for residual deformities increases from the upper to the lower third of the nose. Most frequently, dropping tips and pollybeaks were found. Uncorrected broad nasal tips and irregularities of the nasal dorsum are also relatively frequent causes of revision.

These figures demonstrate the particular importance of the nasal tip support and its dynamics in the healing process. As the supratip pollybeak and dropping of the tip are frequently combined, the rhinoplasty surgeon has to put special emphasis on maintaining adequate tip protection, as well as protection when approaching and mobilizing the nasal infrastructure. The common deformities that can occur following rhinoplasty are listed below in order of frequency of occurrence:

1. pollybeaks
2. dropping tips
3. uncorrected broad nasal tips
4. irregularities of the nasal dorsum.

FACTORS AFFECTING PREVENTION

Proper patient selection can influence the surgical result. For example, rhinoplasty with advancing age can be associated with the patient's own expectations and motivations. This may influence the surgeon to do more than is adequate. The result can be an overzealous rhinoplasty.

Safian[25] has described three basic rules to prevent any problems developing after rhinoplasty:

- Never change the normal basic anatomy or the anatomic relationships of the nose and never totally remove a component.
- Never allow the skin and lining membrane to meet or be left in contact.
- Never destroy nasal cartilage.

The revision concepts of Sheen[26] are based on a proper pre-operative diagnosis, limited dissection, use of

TABLE 83.2 Classification and frequency of post-rhinoplasty deformities (% of revisions)

	Parkes et al.[14]	Vuyk et al.[15]	Kamer and McQuown[9]	McKinney and Cook[12]	Constantian[17]	Foda[19]	Bracaglia et al.[18]	Rettinger[2]
Total/revisions	1221/170	480/110	697/126	200/24	150	50	311	184/502
Upper third	41	79						
Excessive dorsal removal/low dorsum/saddle	24	32	16		93	44	70	44
High dorsum	4	19						3
Dorsal irregularity	16	2	17	21		54		
Wide bony pyramid	2	13				42		20
Shifted graft/asymmetry	1	3	6				80	45
Middle third	63	106					40	
Pollybeak/high dorsum	33	40	56	8		64	50	21
Cartilaginous saddle	14	21						
Pinched/narrow cartilaginous dorsum	8	5						2
Uneven/wide cartilaginous dorsum	10	14	15					
Asymmetric cartilaginous dorsum		23	16					4
Lower third	94	181						
Tip deformities								
Overprojected tip		5						
Underprojected (dropping) tip	4	32			80			
Over-rotated tip (short dorsum)						42		10
Under-rotated (dependent) tip	10	17						53
Deviated tip		1						
Broad/amorphous tip	8	18		46				
Narrow/pinched tip	0.6	5						
Asymmetric tip/bossae	26	30	22					
Alar deformities								
Alar retraction	12	7	11					
Wide alar base		5	8				10	
Columella deformities								
Hanging columella	17	6	13				20	5
Retracted columella	4	11	9					5
Acute nasolabial angle	8	16	4					

exclusively autogenous graft material when required and a well-defined pre-operative plan.

Webster's guidelines include an adequate interval before revision (normally 1 year). This acknowledges the effects of scar tissue and recognizes the differences between underdone and overdone noses, the use of autogenous tissue when dealing with the lining of the nose and the need to develop the aesthetic and reconstructive skills required for revision rhinoplasty.[21]

Constantian[17] reviewed 150 consecutive secondary rhinoplasties in a retrospective study to test the hypothesis that specific anatomic variants predispose to unfavourable rhinoplasty results. He defined four pre-operative variants and compared their incidence with a primary rhinoplasty group. The following conditions were found more frequently in revision patients:

- low radix, low dorsum (93%)
- narrow middle vault (87%)
- inadequate tip projection (80%)
- alar cartilage malposition (42%).

The 'triad' of the first three points was most common (40%), so patients with the combination of these deformities are at a higher risk for revision surgery (**Figure 83.1**).

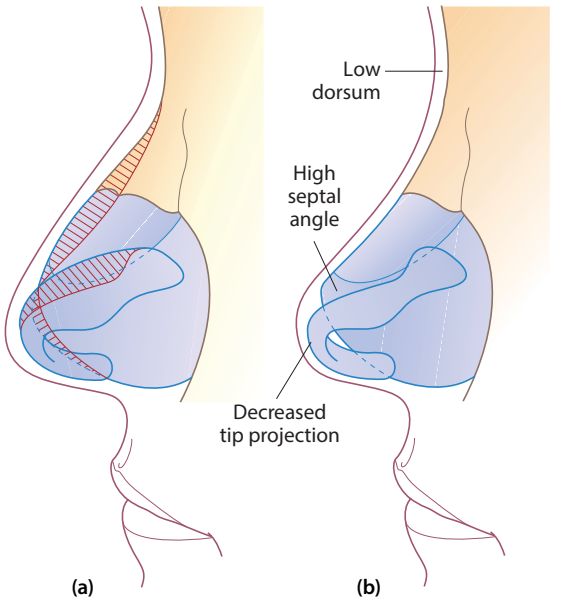


Figure 83.1 Predisposing factors for pollybeak deformity and profile changes: low radix, high dorsum, low tip projection. (a) Hump removal and resections of caudal septal end and lateral crura are marked; **(b)** post-operative result.

TREATMENT STRATEGIES

As already mentioned, techniques for revisions described in the literature are mainly based on the personal experience and preferences of the surgeon. Therefore, only principles and concepts for the most frequent causes for revisions are described here.

Pollybeak deformity

Although there may be cases with a soft-tissue thickening in the supratip area post-operatively, the majority of pollybeak deformities are caused by two effects (see **Figure 83.1**):

- dropping of the nasal tip (loss of tip projection and protection)
- an absolute or relative high septal angle.

The pollybeak deformity develops within months after surgery and this is because of the surgically induced loss of tip support mechanisms.[27] The end result will be a relatively high cartilaginous dorsum in relation to the position of the tip that is sometimes combined with a relatively low bony dorsum (**Figure 83.1**). In principle, there are three options for reconstruction:

- increase of tip projection
- reduction of cartilaginous nasal dorsum
- a combination of both.

The most reliable technique to increase tip projection and protection is a columella cartilage strut with fixation of the medial crura using an external approach (**Figure 83.2**).[28] If the nasal tip is still in a reasonable position after primary surgery, further reduction of the cartilaginous dorsum may be sufficient. In severe cases, both structures must



Figure 83.2 Deviation of the nasal dorsum and pollybeak deformity after three previous rhinoplasties. Low radix, narrow middle vault and alar cartilage malposition after dome division on the left side **(a–d)**. Revision via open approach (fourth operation): septal and columella reconstruction with autogenous rib graft, radix augmentation and spreader grafts. Reconstruction of left alar cartilage **(e–h)**.

be addressed. In principle, the dorsum must be adapted to the definite position of the nasal tip.

Irregularities of the nasal dorsum

These irregularities become visible after hump removal, especially in thin-skinned patients with prominent nose syndrome (tension nose). Very often they are found at the K-area where the nasal bones overlap the triangular cartilages. While minor bony ridges can be easily rasped, this technique is not possible for a cartilaginous deformity. The surface of the cartilage must be made smooth with scissors or a knife. In very thin skin, camouflage can be an excellent option. After further reduction of the nasal dorsum, tissue (mainly autogenous) is used to cover the whole distance from the radix to the septal angle. A crushed septal cartilage strut with delicate smooth edges is preferred (**Figure 83.3**). New insights came from using the technique refining the nasal dorsum with free diced cartilage.[29, 30] Ear cartilage and temporalis fascia are somewhat less suitable. Alloplasts, such as Gore-Tex, may be helpful in selected cases.

Crushed cartilage and free diced cartilage can be very useful to fill small depressions lateral to the nasal dorsum that give the appearance of a deviated nose. This camouflage is very often more effective than revision surgery with osteotomies.

Columella deformities

The acute nasolabial angle with retraction of the columella is often associated with a wide columella base. This can be caused by an over-resection or malposition of the caudal septal end, resection of the anterior nasal spine or creation of a columella pocket between the medial crura which allows the soft tissues to slide posteriorly. It can also be the result of an 'endorotation' of the nasal septum after mobilization during septoplasty.[31] The distance between columellar skin and caudal septum can be increased by inserting a cartilage strut after closing the space between the medial crura footplates with a non-resorbable 'U' suture. In case of a malposition of the septal cartilage after septoplasty, it can be repositioned ('exorotation') and fixed to the anterior nasal spine (**Figure 83.4**).

Overshortened noses

Although this deformity is not listed as a frequent cause for revision in Table 83.2, it is often cited in medicolegal cases. The wide open nasolabial angle in an over-rotated tip is extremely unpleasant and disturbing aesthetically. Very often, the surgeon's pre-operative analysis was inadequate. In a relatively long nose with a moderate hump, the decision was made to remove the hump and shorten the nose because it appeared even longer after hump removal (**Figure 83.5a**). Typical manoeuvres to shorten the nose include:

- resection of a triangular part from the caudal septum (with or without resections from the membranous septum, with or without columella pocket)
- resection of the cephalic margins of the lateral crura (with or without interrupted remaining cartilage strip)

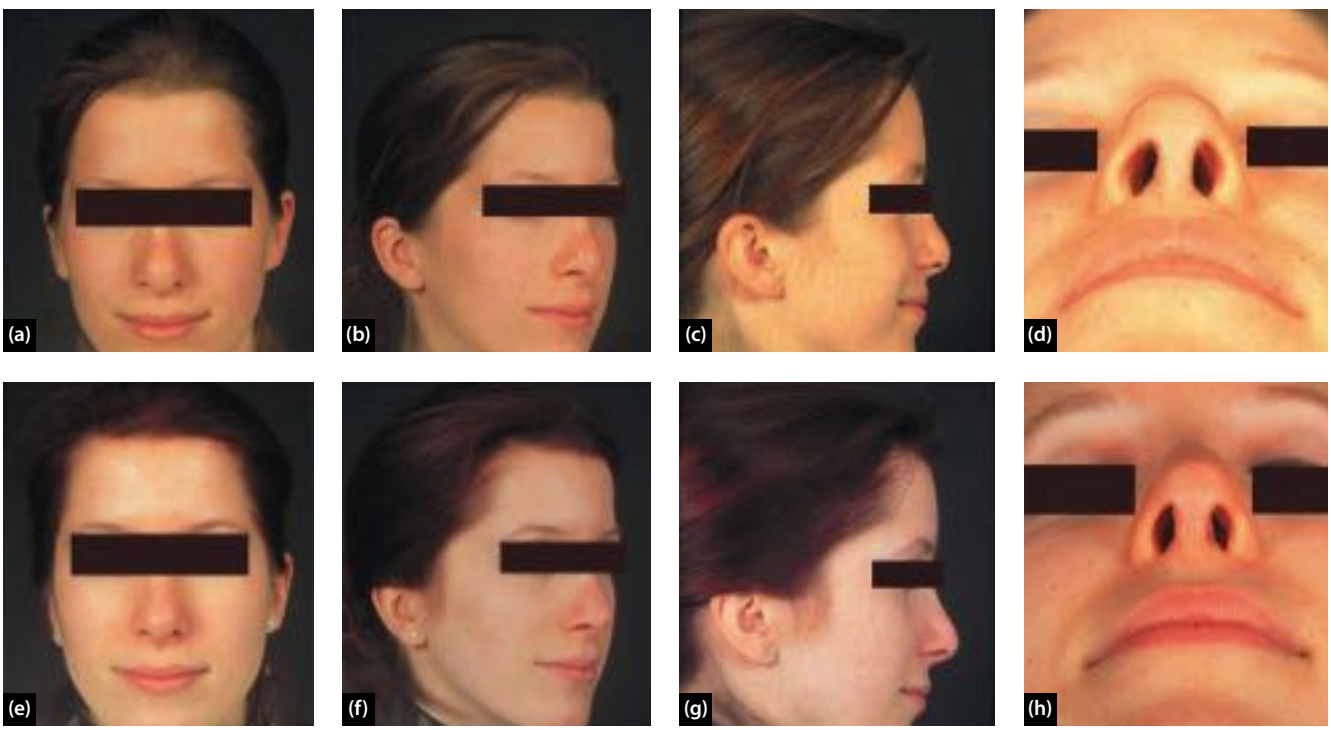


Figure 83.3 Narrow bony vault, irregularities of the dorsum and amorphous tip with pollybeak deformity after hump removal and tip surgery (delivery approach) (a–d). Revision via open approach: septal cartilage strut to the nasal dorsum, tip-suturing technique and tip graft **(e–h)**.



Figure 83.4 Sagging of the cartilaginous dorsum (bony pseudohump), loss of tip support and retracted columella after septoplasty and partial resection of the causal septal end (a–d). Reconstruction of the caudal septal end and repositioning of the septal cartilage. No removal of the pseudohump or nasal dorsal grafts **(e–h)**.

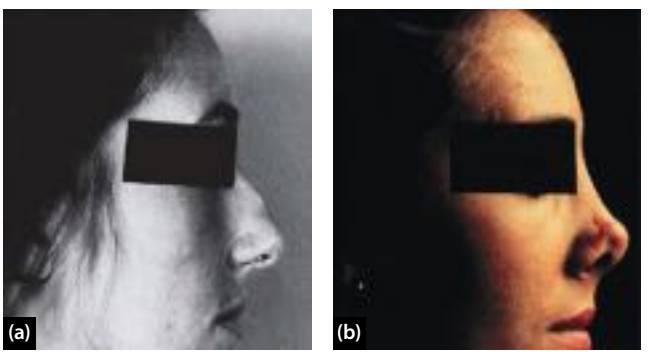


Figure 83.5 Overshortened nose and nasal base irregularities after reduction rhinoplasty. (a) Pre-operative analysis with moderate hump and nasolabial angle about 110°. Post-operative extremely open nasolabial angle and alar retractions after partial resections of alar cartilages and caudal septum **(b)**.

- sometimes resection of the inferior border of the triangular cartilages.

If the surgeon does not respect the nasolabial angle which was already close to 110 degrees pre-operatively (**Figure 83.5a**), then the result, if too much cartilage or even vestibular skin were removed from the lateral crura, is a foreshortened nose (**Figure 83.5b**).

Revision is very difficult in extreme cases. Normally, the limiting factor is not the nasal skin, which can be stretched if it is not too scarred. The problem comes with deficiencies in the inner lining, which is much more rigid than the external skin and can limit the lengthening of the dorsum and downward rotation of the tip. To reconstruct the retracted columella base can be impossible, since too many scars prevent the mobilization of the soft-tissue envelope. The new position of the soft tissues and the infrastructure must be secured by grafts. They can be applied following five principles:[32]

- flying buttress graft (spreader graft and columella graft) (**Figure 83.6**)
- caudal septal graft
- tip grafts
- radix grafts
- interposition grafts (between the upper and lower lateral cartilages).

Depending on the initial problem, revision surgery in an overshortened nose can improve the situation, but perfect reconstruction of all the deformities is uncommon (**Figure 83.7**). This means prevention is of utmost importance and the nasolabial angle should be checked carefully when tip rotation and shortening of the nose is planned.

CONCLUSION

The expected revision rate following primary rhinoplasty should be between 5% and 10%. Factors predisposing to

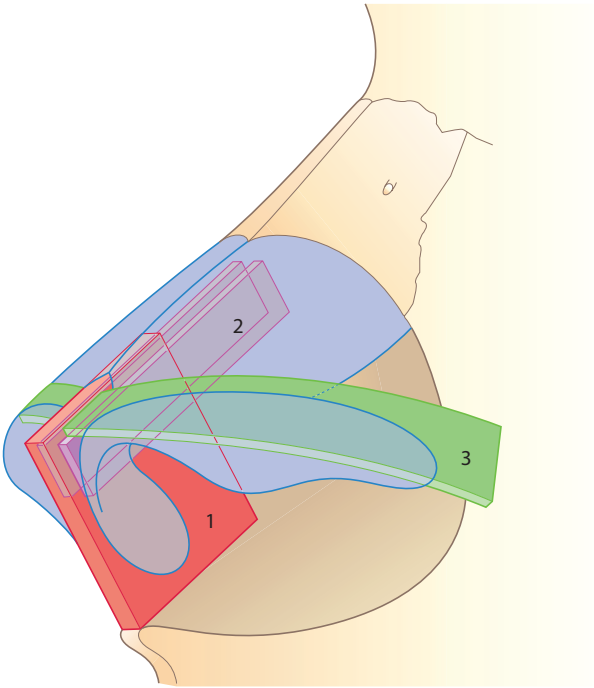


Figure 83.6 Grafts to lengthen an overshortened nose: combined septum and columella graft for downward projection of the columella (1); spreader grafts between the upper lateral cartilages to secure the length of the nasal dorsum (2); interposition grafts between upper and lower lateral cartilages for inferior projection of the alar rim (3).

revisions are thin skin, a low radix, the narrow middle vault and reduced tip projection. The most frequent deformities that may develop in these patients are the pollybeak deformity and irregularities of the nasal dorsum. Another frequent unfavourable outcome, especially of septoplasty or septorhinoplasty, is the cartilaginous saddle nose

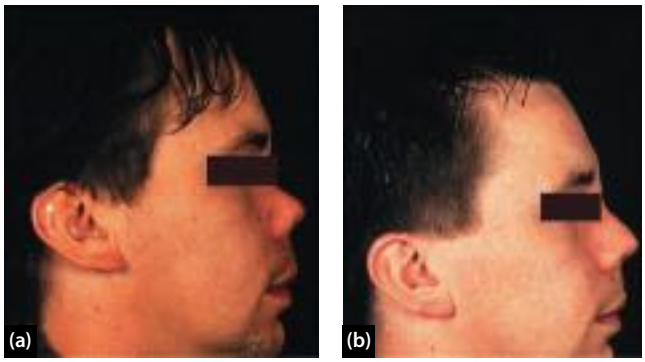


Figure 83.7 Short nasal dorsum, low radix and retraction of columella base as a result of reduction rhinoplasty (a). Reconstruction with autogenous rib grafts. The nasal skin allows lengthening of the nasal dorsum, but downward projection of the columella base is limited because of the inner lining **(b)**.

with decreased tip projection and retracted columella. Overshortened noses tend to become medicolegal cases.

Although prevention during primary surgery can minimize the risk for post-operative sequelae, a planned second stage may be advocated and discussed with the patient in advance. However, the surgeon and patient must be aware that perfection is not always possible and revisions (especially when multiple) have a smaller chance of achieving the optimum result when compared with primary surgery.

The next generation of rhinoplasty surgeons and their patients will benefit from our experience. This experience, however, should not be based solely on personal opinion and the results of 'learning by doing'. We need more systematic evaluation and controlled studies than those available and cited in this chapter. All risk factors should be defined and prevention strategies developed, taking into account the outcome not only after 1–2 years but also after 10 years or more.

BEST CLINICAL PRACTICE

- ✓ Definition of standard surgical techniques for each nose deformity and anatomy for each surgeon.
- ✓ A systematic procedure for follow-up after one or more years is required to analyze post-operative results.
- ✓ Residual deformities or the development of other undesired sequelae should be clearly linked to the individual anatomy or the surgical technique used.

FUTURE RESEARCH

- ➤ Systematic evaluation of new surgical techniques (i.e. grafts, osteotomy) in rhinoplasty by specialized rhinoplasty centres before broad application in patients.
- ➤ Outcome research for evidence of nasal resistence measurements pre- and post-operatively.
- ➤ Development and establishment of specialized training centre and skills labs for rhinoplasty.

KEY POINTS

- Revision rates are between 5% and 10%.
- The most frequent deformities are pollybeak, dropping tip, broad tip and irregularities of nasal dorsum.
- Predisposing factors are low radix, narrow middle vault and inadequate tip projection.
- Patients with overshortened noses tend to take legal action.

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CHAPTER
84

AESTHETIC DORSAL REDUCTION RHINOPLASTY

Julian M. Rowe-Jones

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Indications and aims 1169
Contraindications 1170
Techniques and avoidance of complications 1172
Outcome assessment and the future 1174
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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: reduction and rhinoplasty. The author's own bibliography and library were also referred to. No references were found in the Cochrane database under rhinoplasty.

INTRODUCTION

The term 'reduction rhinoplasty' implies a formal, standardized approach to aesthetic nasal surgery. This concept has been inherited from Joseph[1, 2] and has been based for many years upon removing tissue from key anatomical nasal structures. His technique for cosmetic nasal surgery was developed in response to a case-mix predominantly comprising patients with abnormally large noses that invited ridicule.[3]

The classic Joseph reduction rhinoplasty is characteristically performed through intercartilaginous and full-length transfixion incisions and involves the following stages:[4]

- cephalic to caudal Joseph's saw bony hump reduction
- lowering of the cartilaginous dorsum
- triangular shortening of the caudal edge of the nasal septum
- use of a saw for lateral osteotomies with infracture
- alar cartilage cephalic rim reduction.

This generic approach to the oversized nose has been replaced by one that seeks to develop individual operative plans for each patient, tailored to careful pre-operative analysis of the anatomical variants. Sheen has championed a balanced approach to rhinoplasty which may involve augmentation of some areas of the nose as well as reduction of others.[4, 5] No longer in every patient is the tip reduced and then the dorsum lowered to fit the tip. Development of new rhinoplasty techniques has enabled surgeons to achieve the ideal tip position in relation to the ideal nasion height and position. These two landmarks then dictate the ideal height for the dorsum.[6]

The reduction rhinoplasty is still effective in selected cases, either in part or in whole. However, it should not be employed routinely in all oversized noses or in all patients with abnormal dorsal convexity related to tip–dorsum disproportion. In light of increasing patient expectation and the increasing attention paid to detail around every component of lateral profileplasty, this chapter will focus and reflect on the aesthetic dorsal reduction component of reduction rhinoplasty alone.

INDICATIONS AND AIMS

Aesthetic dorsal reduction rhinoplasty is indicated for the patient with an overprojected nasal dorsum relative to the nasion and/or the tip, resulting in a convex lateral dorsal profile. This dorsal convexity will be accentuated if the nasal tip is underprojected in relation to the nasion or vice versa (**Figure 84.1**). In the ideal nose the ideal nasion should project 10–13 cm from the anterior corneal plane. The ideal position of the nasal tip in females will be found at a point that intersects a line drawn from the ideal nasion at 34 degrees to the vertical facial plane, with a line drawn from the alar crease at 105 degrees to the vertical facial plane. In males the angles are 36 degrees and 95 degrees respectively. Oversized or cephalically malpositioned alar cartilages may contribute to supratip fullness and convexity. This chapter will not address techniques to correct these deformities.



Figure 84.1 (a–c) Pre-operative and **(d–f)** post-operative reduction rhinoplasty views with 12-month follow. Open approach. Composite dorsal reduction. Endonasal low-to-high lateral osteotomies and medial oblique osteotomies. Right spreader graft. Left autospreader graft. 2 mm cephalic trimes of the paradomal lateral crura. Bilateral dome creation sutures, a dome equalization suture and two tip position sutures.

Surgery to correct underprojection of the nasion and/or nasal tip which may contribute to lateral profile convexity will also not be presented in this chapter.

The aim of reduction rhinoplasty is a strong nasal dorsum in the lateral profile, which relates to the ideal nasion height. The tip-defining point should be projecting just above the dorsal line to create a supratip break, although in males the tip position may be on a straight line with the dorsum.[7] The aim is for a non-operated appearance with a 'handsome and patrician' look[8] and a high, strong dorsum.[9] Furthermore, achieving an attractive lateral dorsal profile with dorsal reduction must not result in loss of normal aesthetic dorsal lines. Normal nasal function must also be preserved.

CONTRAINDICATIONS

In the rare instance that both the nasion and the tip are underprojected, dorsal reduction may be contraindicated and surgical planning should consider radix augmentation and tip projection. When determining whether to reduce



Figure 84.2 (a–c) Pre-operative and **(d–f)** post-operative reduction rhinoplasty views with 15-month follow. Open approach. Composite dorsal reduction. Percutaneous low-to-low lateral and superior transverse and endonasal medial osteotomies. Bilateral spreader grafts. Deep temporalis fascia ball and apron graft inserted to augment the radix and to cover the upper dorsum and K area. The lateral crura were trimmed to leave intact 6 mm strips. Bilateral dome creation sutures, an intermediate crural suture and a dome equalization suture of 5/0 PDS were inserted.

the nasal dorsum and, if so, by how much, analysis must consider projection at the radix, the rhinion and the tip. The degree of hump reduction may need to be modified and balanced with radix augmentation (**Figure 84.2**) and techniques to increase tip projection.

Reduction of the dorsum to fit an underprojected tip will result in an unnatural, over-resected nose, which appears flat and broad in the frontal view and lacks height in the lateral profile. Dorsal reduction in these patients alone would be unlikely ever to achieve an aesthetic lateral profile in which the tip projects above the dorsal line. This is especially relevant in thick-skinned patients when skin elasticity and shrink are limited.

Just as a hump may only be a relative hump[5] due to underprojection of the tip, so pseudohumps may be apparent in patients with supratip depression characteristic of a saddle nose. Often saddle noses also have an underprojected tip, which further contributes to the appearance of a bony dorsal pseudohump. In such circumstances a natural dorsum is created by augmentation rather than reduction. If cartilaginous dorsal reconstruction is not performed and hump reduction alone is, dorsal aesthetic

lines in the frontal view will not be created and the nose will look flattened.

The same is often true in revision rhinoplasty for the soft-tissue pollybeak deformity. This results from primary over-resection of bony and cartilaginous dorsum in the thick-skinned patient and is exacerbated by techniques that also deproject the tip. Supratip dorsal reduction will achieve very little improvement and may exacerbate the problem by removing structural support for the skin.

Dorsal reduction must be very carefully considered and discussed with the patient who is happy with the shape of their nose but considers it too large for their face. Global reduction of the nose is required in such cases. Such surgery is complex and expects a lot from the skin with regard to shrinkage.

The overprojected radix in cases of dorsal convexity presents an anatomical area for which reduction may be contraindicated. A soft-tissue response of 25% reduction relative to skeletal resection has been demonstrated at the nasion.[10] It may therefore be more predictable to match the tip and dorsum to the nasion in these cases than to attempt aggressive nasion and dorsal reduction.

In all patients considering aesthetic rhinoplasty analysis must include detailed assessment to diagnose psychiatric disorders and personality types and traits that are associated with a high likelihood of surgery not meeting their physical or psychological expectations or of the patient not accepting or understanding unpredicatability.[11]

TECHNIQUES AND AVOIDANCE OF COMPLICATIONS

The patient is positioned in the reverse Trendelenburg with approximately 30 degrees of head up. The nasal mucosa is prepared topically with neurosurgical patties soaked in 1:1000 adrenaline solution and 5% lidocaine hydrochloride with 0.5% phenylephrine hydrochloride spray. Infiltration is performed with 2–4 mL of 2% lignocaine with 1:80000 adrenaline using a long, 27 gauge needle. The author most often uses an open approach. Infiltration is performed along the caudal end of the quadrilateral cartilage into the membranous septum and then deep to the perichondrium, particularly anteriorly and along the dorsal quadrilateral cartilage. Endonasally, infiltration is performed medial and lateral to the frontal process of the maxilla along the line of the lateral osteotomies, with the needle immediately adjacent to periosteum. Minimal infiltration is then placed laterally along the dorsum each side to avoid disguising the hump. Intradermal blebs of infiltration are raised along the incision lines and then injection is deep to the superficial musculoaponeurotic layer over the nasal skeleton that is to be exposed. The infiltration should be left for at least 10 minutes prior to surgery. During dissection, further infiltration is placed in the dissection planes, ideally subperichondrial and subperiosteal.

Surgery can be performed for dorsal reduction using a closed or open approach. Both must preserve tip projection when this is normal pre-operatively. An upper transfixion incision which avoids disrupting the relationship of the medial crural footplates to the quadrilateral cartilage and intercartilaginous incisions are used for the closed approach. When an open approach is chosen, the tip cartilages are not routinely separated for septal access. Their attachment to each other and the caudal septum is preserved. A hemitransfixion incision is used prior to opening the nose to access the septum. A superior submucoperichondrial tunnel is elevated bilaterally to expose the dorsal quadrilateral cartilage and adjacent upper lateral cartilages and the dorsal ethmoid plate deep to the nasal bones. If septal surgery is required or a septal cartilage graft is needed, the tunnels can be extended later in the procedure, after dorsal reduction and osteotomies. The author prefers to perform surgery in this sequence, with dorsal reduction and osteotomies preceding septal surgery. In this way the stability of the nose, particularly the keystone area, is best assessed after bone removal and fracture, which carry the greatest level of unpredictable disruption. This assessment of stability informs surgical decision-making with regard to septal procedures which could further destabilize the nasal keystone area.

If the open approach is chosen, three-way countertraction of the columella flap, alar rim and intermediate crus dome facilitates subperichondrial dissection of the lower lateral cartilages. In the midline the anterior septal angle is identified and subperichondrial dissection aided by infiltration, and hydrodissection proceeds along the cartilaginous dorsum. It is important to ensure that the anterior septal angle is well demonstrated so that the entire length of the nasal dorsum to the caudal limit of the hump to be removed is visualized. From the midline, subperichondrial dissection is continued laterally over the upper lateral cartilages. Perichondrial attachments in the scroll area may be adherent to underlying mucosa and the overlapping upper and lower lateral cartilages. Elevation is difficult here. This area is often also vascular. Good exposure of the upper lateral cartilages and their release from the superficial musculoaponeurotic system (SMAS) and perichondrium are necessary to facilitate precise medial edge resection, mobility and accurate reconstruction of the mid third later in the procedure.

At the pyriform aperture, sharp dissection is required to enter the subperiosteal plane over the bony dorsum. Lateral dissection over the bone should occur only as far as is required for bone removal. Maintaining skin and soft-tissue attachments to the majority of the frontal process of the maxilla minimizes the risk of excess medial movement after osteotomies.

The author prefers component dorsal reduction.[12] As described by Daniel,[13] the author prefers to begin reduction with bone removal. Incremental rasping is performed to uncap and leave intact the underlying cartilaginous upper lateral cartilages and their contiguous septal quadrilateral cartilage. The rasp is more predictable than an osteotome and graded rasps enable a graded reduction. The preserved upper lateral cartilages are then released flush from the septum in the midline with scissors or a 15 blade and the quadrilateral cartilage is incrementally reduced with an 11 blade. Rohrich[12] performs upper lateral cartilage release and incremental quadrilateral cartilage reduction prior to bone removal. Powered burrs,

rasps and blades may be used for bone reduction and may provide greater control and finesse.[14, 15] A decision then has to be made as to whether to trim the medial margins of the upper laterals incrementally to allow them to sit against the quadrilateral cartilage when retraction on the skin is released. The upper lateral cartilages tend to drop inferomedially when released from the quadrilateral cartilage. If resection is performed, it must therefore be conservative and also incremental. Daniel[13] terms release of the upper laterals and then incremental resection of the dorsal septum and upper laterals individually a 'vertical split-hump reduction'. He draws attention to the appreciation that excision of the dorsal septum lowers dorsal height while excision of the upper lateral decreases dorsal width.

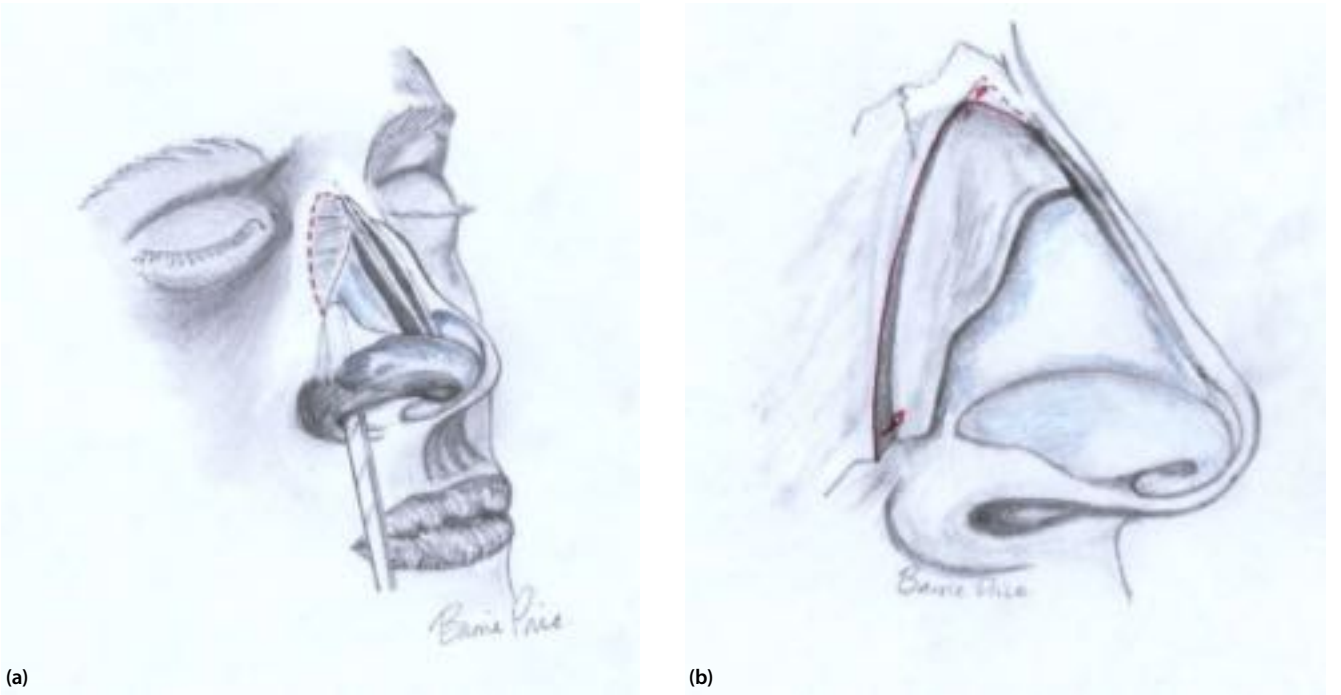
Tardy[16] describes incremental dorsal reduction but starting with retrograde shaving and removal of the intact upper lateral/quadrilateral cartilage hump from the bone–cartilaginous junction at the pyriform aperture to the anterior septal angle. The upper laterals are not released from the septum and therefore this resection will include the horizontal component of these cartilages as well as the dorsal septal quadrilateral cartilage. The bone is then reduced prograde with an osteotome from caudal to cephalic. This hump resection may be performed en bloc. Cartilage and bone are removed as a single unit with the bony and cartilaginous hump attached to each other.

Preservation of the upper lateral cartilages in their horizontal component both between the reduced edges of the bony dorsum and distally, caudal to the bones, maintains structure that can potentially be used to restore or maintain middle-third width and to bridge any gaps between the nasal bones after infracture. The medial edge of the upper lateral cartilages can be folded medially into the nose and sutured to the septum. These autospreader flaps[17] act to maintain mid-third width and are cartilage sparing, being an alternative to spreader grafts. Variations and refinements of these flaps have been described.[18] If the middle third requires width maintenance, there may be insufficient upper lateral to use as a flap. This occurs particularly if a small hump has been removed. In such cases spreader grafts are used. Spreader grafts may also be tailored to requirements better than autospreader flaps if the septum is curved or differential width restoration is necessary.[19] One or the other can be used on either side, depending on anatomical findings (see **Figure 84.1**). The author does not extend spreader grafts all the way to the anterior septal angle as this risks excess caudal mid-third width. There is no horizontal component to the normal upper lateral cartilages in their distal third. If spreader grafts are chosen and they extend to the keystone area, the horizontal component of the upper lateral cartilage in this region must be excised so that it does not sit up over the graft and cause a dorsal irregularity. This can be a technically difficult area to achieve a smooth contour for, particularly between the nasal bones. Preserved upper laterals can be sutured together in the midline after hump resection over spreader grafts.[20] This author also raises a perichondroperiosteal flap from the upper lateral cartilages and nasal bones to close over the dorsum after middle-third reconstruction with or without a contour refining onlay graft deep to the flap. If the middle-third width is good, as may be the case in conservative hump reduction with long nasal bones, spreader grafts or autospreader flaps may not be required. In these cases it is important to suture the upper lateral cartilages back onto the septum to maintain their length, tension and projection.[21] If mid-third vault width is not maintained or reconstructed, dorsal reduction will lead to an inverted V deformity seen in the frontal view. This results from medial and posterior relocation of the upper lateral cartilages and loss of a smooth continuous contour with the bony pyriform aperture.

While dorsal reduction may result in narrowing of the middle, cartilaginous vault, it will also result in widening of the bony vault. Osteotomies may therefore be required to narrow the bony dorsum. They may also be indicated if the bony base width is greater than the intercanthal distance. If middle-vault reconstruction is performed with spreader grafts or autospreader flaps, osteotomies are performed before these techniques are employed. We perform the lateral osteotomies first. These follow a 'low-to-high' path. A stab is performed in the nasal mucosa just superior to the insertion of the inferior turbinate bone onto the maxilla at the pyriform aperture. A 3 mm osteotome is engaged and passes in a gentle superoanterior arc to the level of the medial canthus. This osteotomy can be performed percutaneously. To control the cephalic position at which the lateral bony wall fractures, a 15-degree medial oblique osteotomy is performed from the lateral edge of the open roof to the superior extent of the lateral osteotomy (**Figure 84.3**).[22, 23] A paramedian, medial osteotomy, particularly if in the midline, risks a rocker deformity, either from the medial edge of each nasal bone becoming more projected or the cephalic margin pivoting laterally as the caudal margin is mobilized medially.

If the bony open roof does not extend to the level of the medial canthus, an alternative is to remove a cephalic wedge of bone that will extend the open roof to the level of the medial canthus.[24] A percutaneous, superior transverse osteotomy is then performed laterally from the apex of the open roof to join the cephalic end of the lateral osteotomy. Gentle pressure is applied either side of the dorsum to bring the bones together. Excess pressure at the bony nasal base is avoided to minimize the risk of moving the lateral nasal walls into too vertical a position, creating an unnatural, overly thin nose in the frontal view. Sheen described use of a low-to-high lateral osteotomy only, relying on digital pressure to create a short, superior fracture line along which the lateral wall hinged.[25] We prefer to use this technique only when the bony nasal dorsum is open cephalically to the level of the medial canthi. The technique also assumes that the open roof is wider caudally than cephalically. If this technique is employed for smaller open roofs, we feel it increases the risk of a visible step in the mid lateral nasal wall. In such cases no medial osteotomies will be required and superior, transverse osteotomies are performed to control the position of the superior fracture line as described above.

When the hump is removed, a slightly convex line of nasal bone and cartilage should remain. This allows for the differential thickness of the overlying soft tissues and



(a) (b)

Figure 84.3 (a) Endonasal low-to-low lateral and medial oblique osteotomies. **(b)** Movement produced by infracture.

will result in a straight external lateral profile. The author feels this point has been traditionally overemphasized and that any convexity should be slight.

If an open roof requires closing but the nasal base is narrow, infracture carries the risk of producing excess base narrowing. This is of particular concern if the nasal bones are short. Infracture carries the risk of producing excess mid-third narrowing and an inverted V deformity.[5, 26] In these circumstances the dorsum may be better reconstructed with spreader grafts,[5] an onlay spreader graft[27] or a dorsal onlay graft[28] and without osteotomies and infracture. Skoog described modification and replacement of the removed hump for dorsal reconstruction with or without lateral osteotomies.[29] The push-down operation and subsequent modifications have also been described in the management of the convex dorsum to avoid a skeletonized, inverted V deformity consequent upon dorsal reduction.[30]

If a small hump has been removed, an open roof defect may not result. The majority of the hump removed will have been cartilaginous, leaving no significant open bony defect. The upper lateral cartilages may still be contiguous with the quadrilateral cartilage as only the ridges of the bifurcated, 'Y'-shaped cartilaginous dorsum will have been shaved.[31, 32] In such instances, particularly in patients with thick skin and a nose with a narrow base, osteotomies and infracture may not be necessary.

Lastly, the author assesses the dorsum for irregularities with inspection and particularly with palpation using a wet finger. Achieving a smooth contour may require finesse achieved with the use of softened, small cartilage onlay grafts, 'scales' of shaved cartilage, scraped cartilage 'paste' or deep temporalis fascia (see **Figure 84.2**). The author avoids alloplasts.

The septum is quilted with 4/0 or 5/0 polyglactin (Vicryl®) and all incisions are closed with interrupted 6/0 polyglactin (Vicryl®). Great care must be taken with the columella closure to ensure skin-edge alignment and eversion. The author does not insert nasal packing. On induction of general anaesthesia, 8 mg of dexamethasone and a broad-spectrum antibiotic are given intravenously. The nose is taped and an external splint applied which remains for 1 week. Wounds are kept clean postoperatively using 3% hydrogen peroxide, and an antibiotic ointment is applied regularly for 1 week.

OUTCOME ASSESSMENT AND THE FUTURE

While not specifically reporting results of reduction rhinoplasty, several studies demonstrate psychological benefit from cosmetic rhinoplasty.[33–35] The functional sequelae of osteotomy with infracture in reduction rhinoplasty have been objectively studied. No change in nasal resistance using posterior rhinomanometry was detected in a series of 27 patients undergoing open rhinoplasty with osteotomies and infracture. However, patients in this study routinely underwent outfracture with or without submucosal diathermy of the inferior turbinates.[36] Total minimal cross-sectional area and minimal cross-sectional at the piriform aperture, measured with acoustic rhinometry, have been shown to change significantly following reduction rhinoplasty. In this study, 3 patients of 37 complained of postoperative loss of airway patency, which was normal before surgery.[37] No difference was detected between high or low insertion level lateral osteotomy in a 16 cadaver study performed by the same group.[38]

Outcome assessment in facial plastic surgery is a newly developing field looking at results from the patient's perspective. Expanded measures of both quality of life and health perception as well as satisfaction with appearance are studied rather than the surgeon's assessment of technical success.[39, 40] Specific instruments have been proposed for rhinoplasty.[41] International patient-reported outcome measure guidelines and criteria have been developed and from these have arisen patient-related outcome measurement tools that are procedure-specific, such as the FACE-Q.[42] A scale for rhinoplasty will be produced. Psychological screening tools will help us improve patient selection for surgery alongside measuring benefit.[43, 44] Three-dimensional imaging will further help with analysis, planning, communication, management of patient expectation and objective measurement of surgical change.[45]

Technical innovation will continue and will help the surgeon visualize the nasal skeleton better, and more precise techniques for osteotomy[46] and bone sculpting will develop further.

BEST CLINICAL PRACTICE

- ✓ Determine the ideal dorsal line from the ideal nasion and ideal tip-defining point.
- ✓ Use minimally traumatic techniques exploiting natural tissue planes.
- ✓ Fully expose the middle and upper nasal vaults in the midline.
- ✓ Perform dorsal reduction and osteotomies before septoplasty.
- ✓ Avoid aggressive over-resection.
- ✓ Ensure the middle vault is reconstructed.
- ✓ Meticulously assess the dorsum for irregularities after resection and infracture.

KEY POINTS

- Perform thorough pre-operative analysis of nasal deformity.
- Indications for reduction rhinoplasty are excess dorsal convexity relative to ideal height and position of the nasion.
- Aim for a strong, high nasal dorsum with tip projection above the dorsal line.
- Ensure middle vault support to maintain frontal view dorsal aesthetic lines and nasal function.
- Psychological benefit has been demonstrated in observational studies following cosmetic rhinoplasty.

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CHAPTER
85

NASAL RECONSTRUCTION

Ullas Raghavan

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SEARCH STRATEGY

Data in this chapter may be updated by Medline and Medscape searches using the keywords: nasal soft tissue defect, nasal obstruction, nasal skin cancer as specific or individual words that appeared as a keyword, in the title or abstract.

INTRODUCTION

Reconstruction of the nose poses several unique problems. The contours of the nose are variable, with convex and concave surfaces in close contact with each other, and the skin texture and colour is not easy to match. The human eye easily detects the slightest variation in contour or symmetry. Nasal defects can be reconstructed with local, regional, distal or free flaps. The primary aim of reconstruction is to restore the lost function and the secondary aim is to make the reconstructed part as normal in appearance as possible. The aetiology of nasal defects is shown in **Table 85.1.** Essentially, the surgeon confronted with a nasal deformity has to weigh up the alternatives available and select the correct one in order to obtain the best cosmetic and functional result with the minimum donor site morbidity. The selection of method is frequently based on personal experience, known effective procedures or individual bias.[1] Nevertheless, the principles laid out in this chapter and the key points should be of use whatever the choice of technique.

HISTORY

The history of nasal reconstruction dates back more than 3000 years. This operation developed in three phases. The first book on this subject is believed to be by Sushrutha[2] who lived approximately 600 BC. He used flaps from the cheek to reconstruct a lost nose. Later, Indian surgeons used a forehead flap, now universally known as the 'Indian method'.[3] Although this method continued to be used for centuries, it was not developed any further in India.

The next phase of development of nasal reconstruction took place in Italy during the Renaissance. In the mid 15th century, the Branca family in Sicily performed nasal reconstruction, possibly using the Indian method. This was later taken up by Tagliocozzi and published by him in 1597.[4]

TABLE 85.1 Aetiology of nasal defects

Defect type	Defects
Congenital	'Cleft nose', bifid or aplastic nose, proboscis lateralis
Traumatic	Iatrogenic: Septal surgery, scarring from endotracheal or nasogastric tube Thermal, radiation, chemical, mechanical, human bite, avulsion, frost bite
Inflammatory	*Autoimmune:* Wegener's granulomatosis, SLE, sarcoidosis, Sjögren's syndrome *Infection:* Syphilis, yaws, pinta, rhinoscleroma, leprosy, tuberculosis, histoplasmosis, mucormycosis, aspergillosis
Tumour	Basal cell carcinoma, squamous cell carcinoma, malignant melanoma

He used skin from the upper arm to rebuild the nose. Following the death of Tagliacozzi there is no information available to us on nasal reconstruction for two centuries.

After Britain established contact with India in the 18th century, the European surgeons absorbed and developed the 'Indian' operation. The first article that described the Indian method of rebuilding the nose was published in a lay journal called the *Gentleman's Magazine* in 1794.[5] Joseph Constantine Carpue began to perform similar nasal reconstruction after practising on cadavers, and he published his work in 1816.[6] Von Graef in Germany adopted this technique and performed an Indian type of reconstruction in 1816. Warren, a surgeon from Boston, came to Europe to study nasal operations. When he returned to the United States, he performed his first Indian-type nasal reconstruction in 1834.[7] During the 19th century, the Indian technique became widely accepted for rebuilding the nose in North America and even today it remains the basis for most reconstructive procedures.

The idea of rebuilding the nose with a single forehead flap with an inner lining of skin was reported by Natalie in 1842, Johann Friedrich Dieffenbach in 1845 and Ernst Blasius in 1848.[8] The use of composite grafts from the ear for reconstruction of a nasal defect was described by Konig in 1902.[9] In 1943, Gillies reported nasal reconstruction using a composite graft of auricular skin with attached conchal cartilage.[10] He transplanted a free composite auricular graft with epithelium on one side to a forehead flap. After healing took place, the forehead flap with graft was brought down to the nasal defect. Later, extensive work on the use of composite grafts in the head and neck region were reported by Walters.[11] In the 1960s and 1970s, Millard published a series of articles describing the paramedian forehead flap.[12] This helped provide a longer flap so that nasal tip defects could be corrected. More recently, Burget and Menick[13] have refined previous ideas and focused on methods that respect the aesthetic contours of the nose.

ANATOMY

The nose can be divided into upper, middle and lower thirds; the upper third is supported by the nasal bones, the middle third by the upper lateral cartilages and the lower third by the lower lateral cartilages. Contrary to what many believe, the lower lateral cartilages do not extend to the margins of the rim of the nostrils. The thickness and attachment of the skin and subcutaneous tissue to the bones and cartilages vary in different parts of the nose. Over the nasal bones the skin is loosely attached, whereas it is firmly attached to the upper and lower lateral cartilages. The skin over the lower third of the nose can be thick and sebaceous but in some women it can be so fine that the lower lateral cartilages can be seen through it.

AESTHETIC SUBUNITS

Gonzalez-Ulloa et al described the facial aesthetic units.[14] Aesthetic subunits are segments of contour broken by a change in undulation, skin quality or shadow. Different facial regions have their own colours, textures, mobility and contour. Every region is distinguished from other regions by its pattern of hair growth, quality and skin texture.[15] Scar placements along the border of the subunits can minimize visible alterations in contour and texture. The subunits comprise five convex and four concave units (**Figure 85.1**). They are the tip, dorsum, paired sidewalls, paired ala-nostril sills, soft triangles and columella.[16] In order to obtain an optimum cosmetic result, Burget and Menick[16] have advocated that the whole of the subunit is replaced. Defects that involve more than half a subunit should be repaired after removing the normal tissue in that subunit so that the whole subunit can be replaced.[16] Nasal defects may extend to

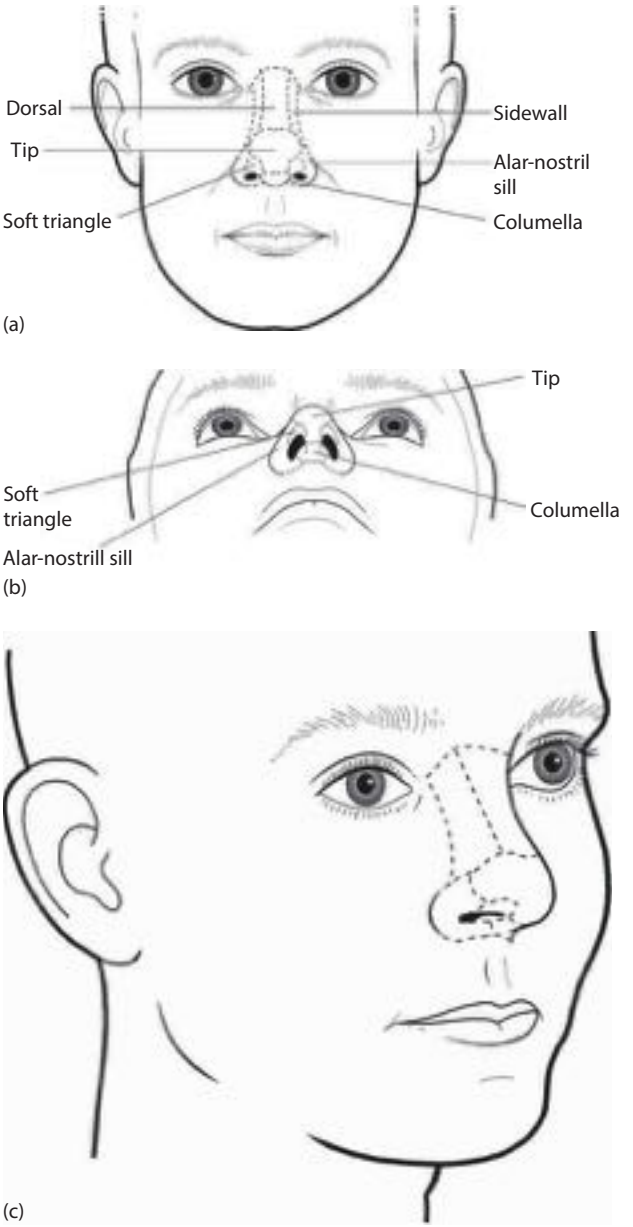


Figure 85.1 The aesthetic units of the nose.

adjacent facial units. The reconstruction of these facial units should ideally be carried out with a separate flap to maintain the segmental quality of the face.[16]

PRINCIPLES OF NASAL RECONSTRUCTION

After reconstruction, the nose must function and be aesthetically pleasing. The nasal valve, the inner lining of the nose and its supporting cartilages determine whether it works. Cosmesis depends on the cartilage and bony scaffolding, the quality of the skin, symmetry and the aesthetic compartments. Burget and Menick[13] have illustrated the primary principles in nasal reconstruction in an excellent text on this topic that is essential reading for any surgeon undertaking this work. They place particular emphasis on matching the contour of the unaffected side in unilateral defects, and respecting and reproducing aesthetic units wherever possible. They caution against using a forehead flap with any tissue excess as it will contract and 'bunch up' through contraction.[16] The fundamental principle of nasal reconstruction is to recreate the missing structures as closely as possible. Other principles include: avoid tension; replace whole aesthetic segment (where >50% loss); try to replace the exact amount of tissue, excess flap or graft may 'bunch up'; approximate vascularized tissue to any graft to avoid dead space.

During reconstruction of the nose, aesthetic segments must be respected as far as possible and the result is often better when the whole aesthetic segment, rather than part of it, is replaced. When the defect crosses aesthetic boundaries, more extensive reconstruction may be required. This is common in the nose and medial canthal regions, especially following Mohs' micrographic surgery for squamous cell carcinoma or morphoeiform basal cell carcinoma. A full-thickness defect of the nose also needs a lining, a scaffold and an external layer of skin of the same quality in terms of thickness, degree of sebaceous tissue and, if possible, colour, as the defect that is being replaced. Any cartilage that is removed needs to be replaced to avoid distortion and maintain symmetry. Another principle is to replace like with like so that the loss of an upper lateral cartilage should be replaced with cartilage of the same shape and thickness, if possible. In addition to this rule, a strut of cartilage should support the margin of the nostril where no cartilage normally exists, otherwise notching of the margins occurs. Extensive nasal defects that result from nasal malignancy require a combination of flaps and grafts as reconstruction will require an inner and outer layer, as well as supporting cartilage.

It is worth noting that, without the support of any septum, nasal reconstruction of the nose using any type of graft or flap is difficult. An osseointegrated replacement or prosthesis is another alternative. One possible technique to overcome this problem is the use of free bone and cartilage grafts sandwiched between a pericranial and paramedian forehead flap.[17]

PHYSIOLOGY

Factors influencing nasal reconstruction include:

- the aetiology of the defect and prognosis
- whether the patient has had previous radiotherapy, smokes, suffers from diabetes mellitus or has scarring from previous surgery
- the patient's nutritional status
- the patient's aesthetic needs and psychology.

Reconstruction is carried out using flaps or grafts. While flaps derive nutrition from their own blood supply, free grafts do not have a vascular pedicle. Grafts undergo three distinct, but overlapping, stages of healing.[18]

- **Stage one** is that of plasma imbibition. This stage begins at the time of graft placement and continues for the first 24–48 hours. Fluid is absorbed into the graft by capillary action, which draws the plasma into the graft itself. During this period, a fibrin deposit is being laid down between the graft and the recipient bed, which helps hold the graft in place. This process can be easily disturbed with the accumulation of clot or serum beneath the wound, separating the graft surface from the recipient bed.
- **Stage two** of graft healing begins approximately 24 hours after placement of the graft; the vascular components from the recipient bed start to meet with vessels randomly in the graft. At this point, circulation is beginning within the graft.
- **Stage three** includes vascular bud growth into the graft developing a vascular network. If anastamosis between the bed and graft is successful, true circulation begins within the graft and continued healing begins.

Direct interface between the graft and the recipient bed is important and this should be maintained during the first week.[19] Loose quilting may be necessary. Quilting should not be tight as post-operative swelling can cause excessive tension and lead to pressure necrosis.

The size of composite graft is important as blood vessels only develop from the edges. The vascularization of a composite graft is somewhat more tenuous and is dependent on limited surface contact along the edge of the graft and reducing any movement between the graft and its bed to a minimum.[10, 20] In larger grafts, survival depends on the rate of vascularization versus the rate of any destructive process.[20] The usual recommendation is that the centre of a free graft should not be more than 0.5 cm from the source of its blood supply. However, Converse[21] used an auricular composite graft up to 2.5 cm in diameter. The failure of a graft to survive in its new recipient area is more than a great disappointment to surgeon and patient, for the resorption of a necrosed cartilage transplant leaves a mass of scar tissue which renders further repair of the deformity much more difficult.[22]

TECHNIQUES FOR NASAL RECONSTRUCTION

Table 85.2 summarizes the techniques available for nasal reconstruction.

TABLE 85.2 Reconstruction of nasal defects

Area	Technique	Type
Skin and subcutaneous tissue	Primary closure	
	Secondary intention healing	
	Skin graft	Split thickness Full thickness, e.g. preauricular
	Local flaps	Advancement flap, e.g. cheek flap Rotation flap, e.g. dorsal nasal flap Transposition flap, e.g. bilobed flap, melolabial flap, nasolabial flap
	Regional flap	Pedicled, e.g. paramedian forehead flap Microvascular, e.g. dorsalis pedis free flap
Skeletal structure	Cartilage	Septal cartilage Conchal cartilage Rib cartilage
	Bone	Iliac crest Skull
Inner lining	Skin	Local flap Composite conchal graft 'Visa' of nasal vestibular skin
	Mucosa	Local flap Pedicled septal mucosal flap Composite conchal

Excision and primary closure

Small nasal lesions can often be excised and repaired by primary closure. Whole-thickness defects greater than 0.5 cm diameter repaired by this technique will often result in some asymmetry. Loss of skin and subcutaneous tissue, if minimal, can be closed after undermining either side down to the cartilaginous or bony skeleton. The advantages of this procedure are that it is a simple technique and single-stage.

Excision and healing by secondary intention

Healing by secondary intention is simple, does not require further surgery or hospitalization and it avoids donor site scarring and pain.[23] It also allows early detection of recurrence of cancer. Wounds allowed to heal by secondary intention do not necessarily give a bad scar.[24] In certain clinical situations, the scar from secondary healing will be better than a scar from a standard surgical repair. The variables to consider when deciding to opt for healing by secondary intention are the position, depth and size of the wound, skin colouration and patient age.[25] The most favourable sites are the concave surfaces of the nose, ear, eye and temple (NEET areas).[26] The disadvantages of this mode of healing are inconvenience due to a protracted healing time, infection, hypertrophic granulation tissue and scarring, hypopigmentation and distortion of adjacent structures through cicatrization.

Skin graft

Wounds that cannot be closed primarily or are not suitable for healing by secondary intention require repair with either a skin flap or a skin graft. An advantage of skin grafts is that they are the simplest and most predictable method of resurfacing a nasal defect not amenable to primary closure. Their disadvantage is a suboptimal cosmetic result due to contracture, poor colour match, a tendency to contract around the edges and donor site morbidity.[27] Split-thickness skin grafts contract more than full-thickness skin grafts post-operatively and their colour, texture and thickness will not readily match the surrounding skin. The full-thickness skin graft (Wolfe graft) contains most of the structures of the skin and is cosmetically superior to split-thickness grafts. The full-thickness skin graft is limited by its donor site availability and has an unpredictable 'take' over 2.5 cm. This can be used to resurface a defect of the upper two-thirds of the nose. The structural support should be intact. This graft often gives a poor result when used to replace the skin of the lower third of the nose as the smooth graft will contrast with the thick and sebaceous skin that is common in this area. For a full-thickness graft to take, the underlying periosteum and perichondrium should be healthy and vascular and the graft must remain immobile for vascularity to develop. The preauricular area is an ideal donor site as the graft often matches the skin of the upper two-thirds of the nose in colour, thickness and texture.

Local flaps

Local or adjacent skin flaps have many advantages. They have their own blood supply and, when designed well, the healing rate is high and the post-operative contraction is minimal. Local flaps are best for reconstructing the convex subunits of the nose. Depending on the vascularity, local flaps can be divided into random or axial. There are limits to the length and size of random local flaps that are based

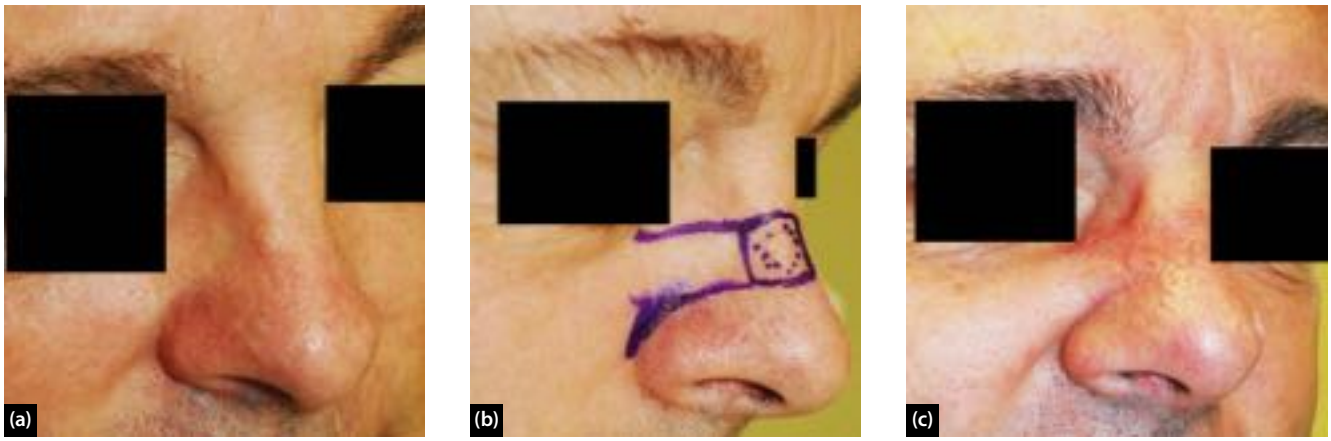


Figure 85.2 Advancement flap. **(a)** Nodular BCC of the nasal dorsum. **(b)** Excision margin and advancement flap marked. **(c)** Post-operative appearance after 6 months.



Figure 85.3 Cheek advancement flap. **(a)** Lentigo maligna of the nasal dorsum with cheek advancement flap marked with Z-plasty and back cut to lengthen the flap. **(b)** Flap raised and positioned. **(c)** Post-operative appearance after 1 year.

on random blood supply[28] but axial flaps based on named blood vessels can be larger. It is best to undermine below the subcutaneous musculoaponeurotic system (SMAS) in order to maximize the blood supply. Wide undermining is needed to reduce tension and increase the mobility of the skin and subcutaneous tissue. Based on their movement, local flaps are subdivided into advancement flaps, rotation flaps, transposition flaps and interpolation flaps.

ADVANCEMENT FLAP

Advancement flaps are the simplest of local flaps, being created when the tissue is undermined and advanced in a straight line in the same axis as the defect. An example of an advancement flap is the rectangular flap (**Figure 85.2**). Burrows triangles are excised to avoid 'dog ears', the cheek advancement flap and the V–Y advancement flap.[29] If the defect is large, two rectangular advancement flaps can be used to close the defect in an 'H' fashion. The reach of the advancement flap can be increased by using a 'Z'-plasty and/or a back cut (**Figure 85.3**). In a V–Y flap the flap is designed to be about twice the size of the defect (**Figure 85.4**). A bipedicled advancement flap can be used for closing a defect of the nasal dorsum (**Figure 85.5**).

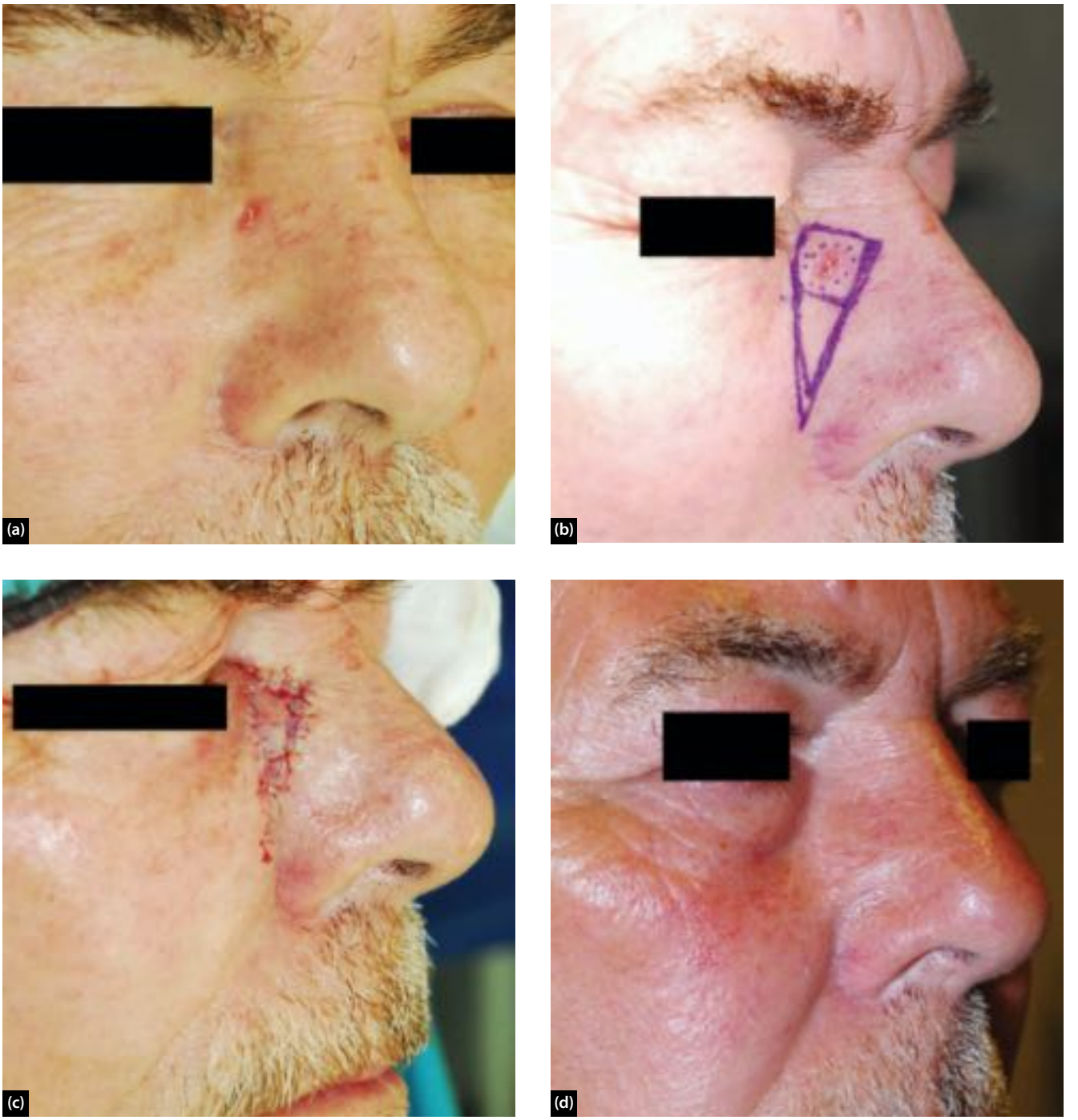


Figure 85.4 V-Y advancement flap. **(a)** Infiltrative BCC of the nasal side wall. **(b)** Margins and flap designed. **(c)** Flap sutured to the defect. **(d)** Post-operative appearance after 1 year.

ROTATION/PIVOT FLAP

A pivot flap is one whose axis rotates around a pivot to close the defect. As the degree of rotation increases, the effective length of the flap decreases. The entire flap and the surrounding skin need to be undermined in all directions. Failure to do this results in excessive tension during closure and buckling and will possibly compromise vascularity.[29] A bilobed flap is an example of a pivot flap. This is ideal for small defects (<1.5 cm) on the lateral side of the nose where local skin of the same thickness and colour can be used to fill a defect. If these flaps rotate skin through an arc of more than 110 degrees in the relatively inflexible thick skin of this region, it produces a prominent dog ear.

TRANSPOSITION FLAP

Transposition flaps are adjacent to the defect and do not have to cross an intact bridge of skin. They allow movement in more than one plane and examples include the 'note flap' and the rhomboid transposition flap.[18] A bilateral rhomboid flap has been described to reconstruct a supratip defect.[30]











Figure 85.5 Bipedicle flap. **(a)** Nodular BCC of the nasal dorsum. **(b)** Margins of excision and flap marked. **(c)** After excision of BCC. **(d)** Bipedicled flap raised. **(e)** Post-operative appearance after 1 year.



Figure 85.6 Bilobe flap. (a) Nodular BCC of the nasal side wall. **(b)** Excision margin and bilobe flap designed. Shaded area removed to avoid 'dog ear'. Flaps move as shown by the arrows. **(c)** Post-operative appearance after 1 year.

INTERPOLATION FLAP

Interpolation flaps are not adjacent to the defect and they cross a bridge of intact skin to reach the defect. They will require a second stage to cut the pedicle once the flap has developed sufficient vascularity at the recipient site. Paramedian and nasolabial flaps are examples.

Bilobed flap (Zitelli's)

This is the flap of choice for defects of the lower third of nose 0.5–1.5 cm in diameter (**Figure 85.6**). There are five rules for the flap design to avoid problems of contour and vascularity.[31]

- The bilobed flap is used for defects up to 1.5 cm in diameter.
- Each lobe should not rotate more than 50 degrees.
- A piece of skin is excised between the defect and pivotal point of the flap before rotation to avoid a dog ear. The pivotal point is located away from the margin of the defect at a distance equal to the radius of the defect. It is never placed close to the medial canthus or alar margin.
- Lift the flap just above the level of the periosteum and perichondrium in order to preserve its blood supply and minimize scarring.
- The diameter of the first lobe is equal to the defect and the width of the second lobe is less than the first but large enough to close the donor defect comfortably.

Dorsal nasal flap

A dorsal nasal flap (**Figure 85.7**) can be used to cover a defect of the lower third of the nose but is not the ideal choice. The skin and soft tissue are elevated off the periosteum and perichondrium over the dorsum and side wall of the nose up to the glabella. This flap is slid down to cover the defect. The advantages are that the skin is brought from an area of excess, the glabella, to the lower third of the nose and the defect is covered by tissue similar to the lost one. However, it has three aesthetic disadvantages:

- The thick and pitted skin of the glabella slides downwards and may form an epicanthal fold.
- The flap does not coincide with the subunit excision lines.
- It forms a large dog ear that may not be corrected completely.[31]

Glabellar rotation flap

A glabellar rotation flap (**Figure 85.8**) is useful for defects of the upper third of nose and medial canthus. Excess skin from glabellar region is rotated down to cover the defect. Disadvantages are the same as for the dorsal nasal flap.

Nasolabial flap

A nasolabial flap (**Figure 85.9**) is suitable to correct the skin loss of the alar subunit. It can be used as the outer lining layer when a full-thickness defect of the alar subunit is being corrected. The flap can be based inferiorly or superiorly, and the pedicle divided at a second procedure. Alternatively, an island flap can be rotated into position.[32, 33] The perforating branches of facial and angular arteries supply this flap and an island flap can be rotated 180 degrees to allow primary closure. In order to obtain a groove around the alar margin, the nasolabial and cheek skin can be advanced a few millimetres more than might seem necessary and the rim left unsutured so that,

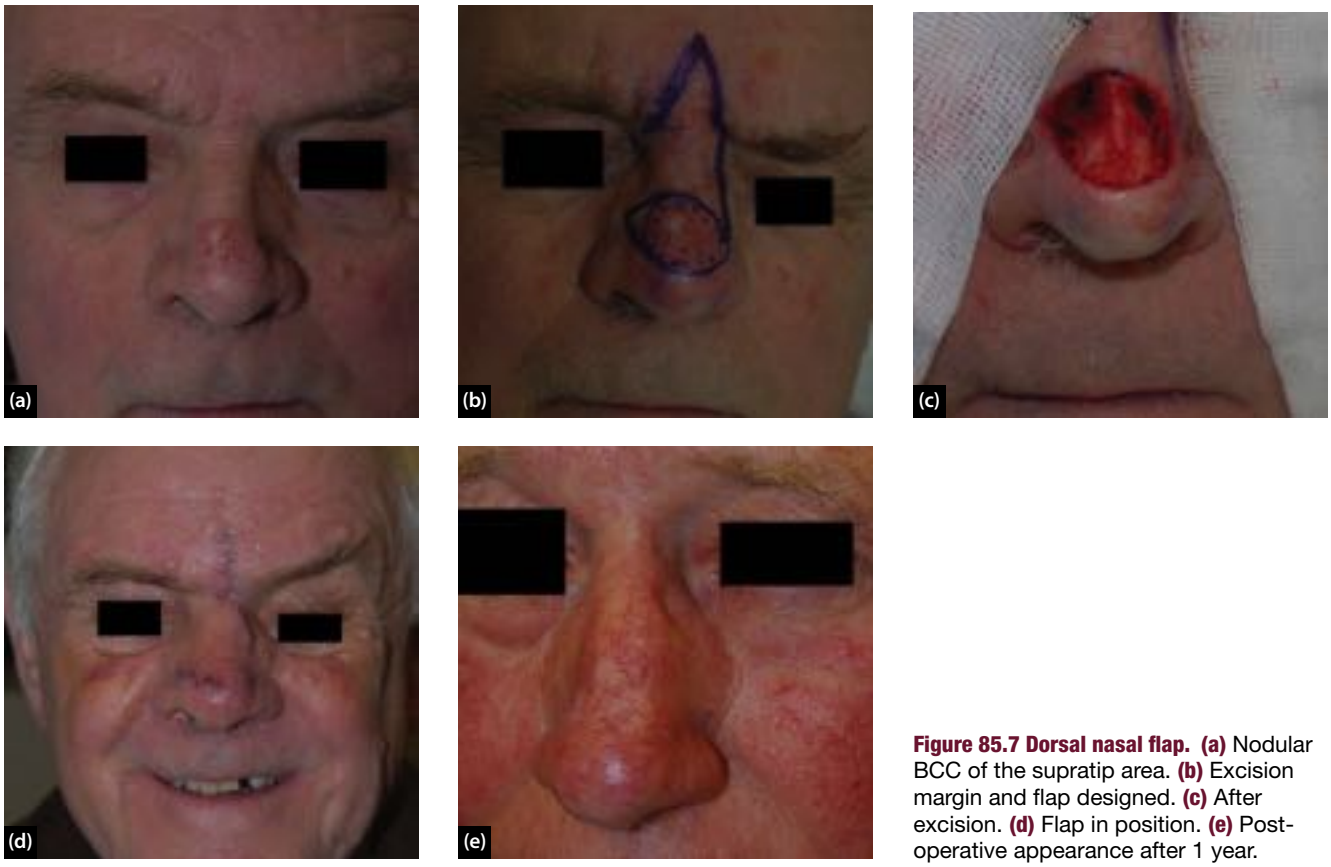


Figure 85.7 Dorsal nasal flap. **(a)** Nodular BCC of the supratip area. **(b)** Excision margin and flap designed. **(c)** After excision. **(d)** Flap in position. **(e)** Post-operative appearance after 1 year.

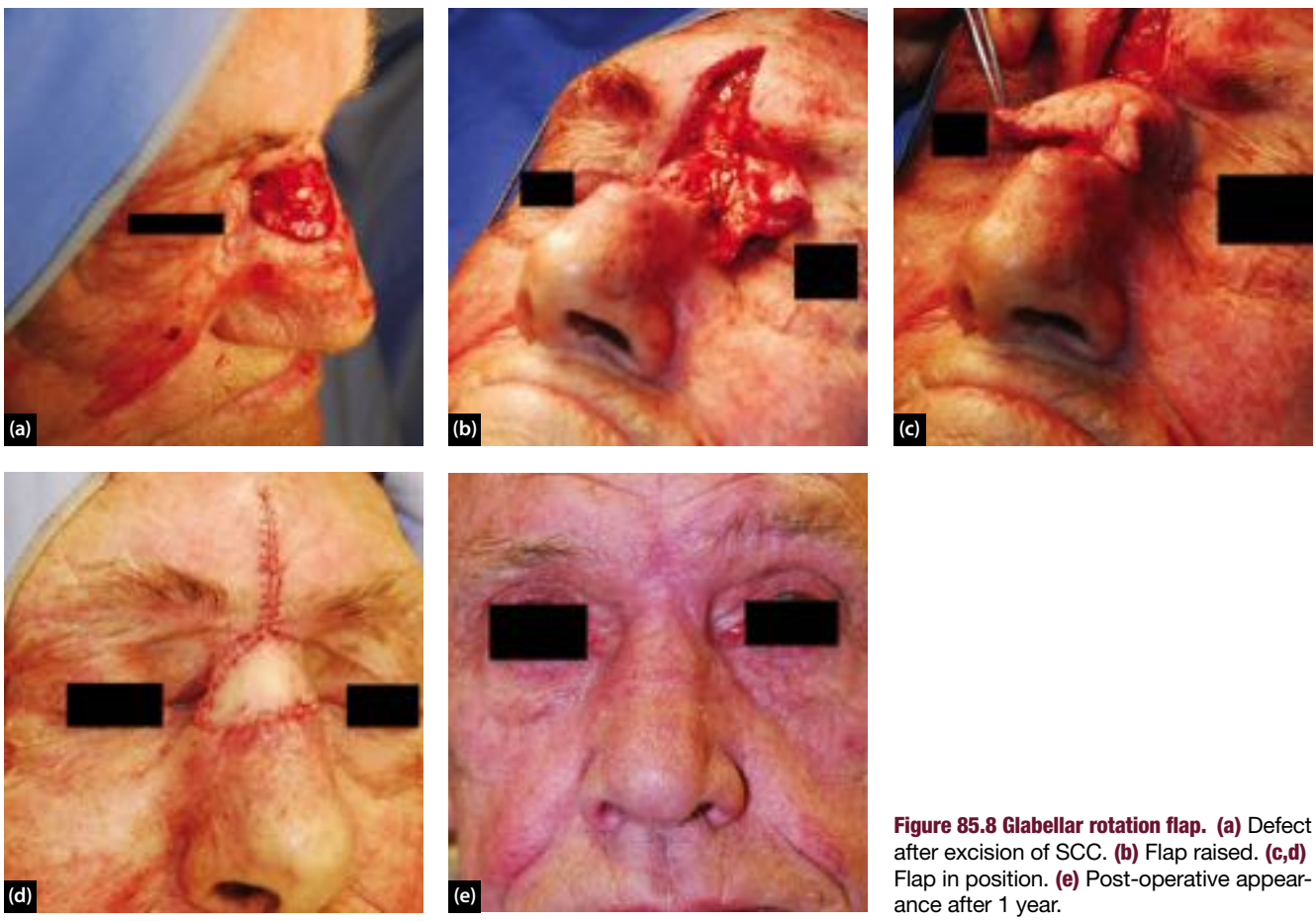


Figure 85.8 Glabellar rotation flap. **(a)** Defect after excision of SCC. **(b)** Flap raised. **(c,d)** Flap in position. **(e)** Post-operative appearance after 1 year.

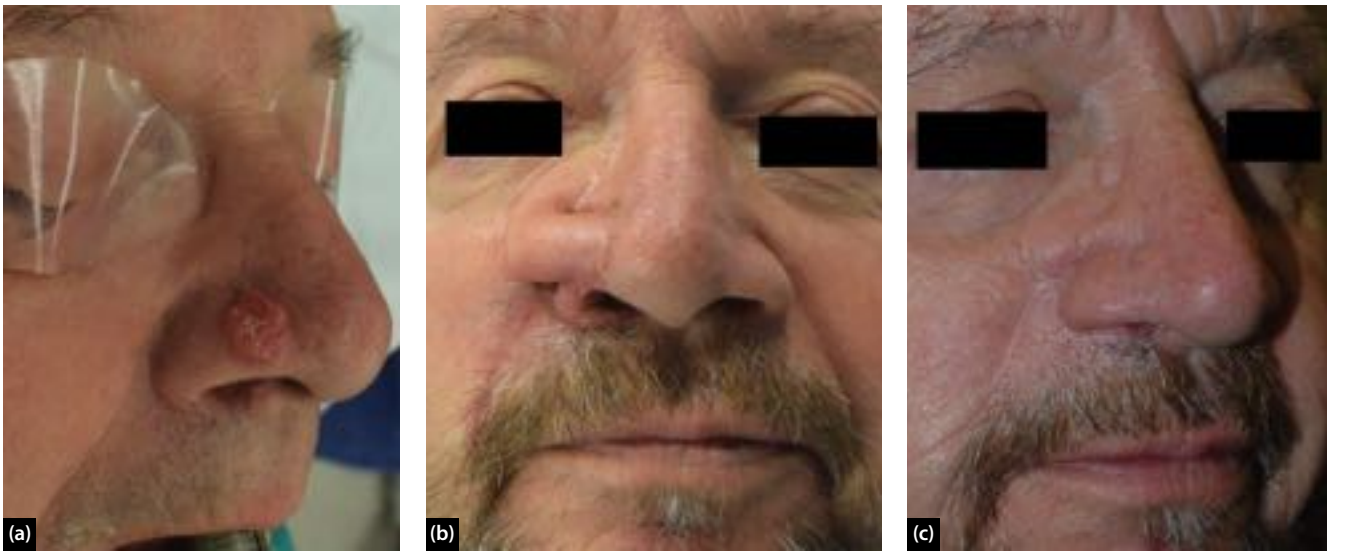


Figure 85.9 Nasolabial flap. **(a)** Nodular BCC of the ala. **(b)** Nasolabial flap in position. **(c)** Post-operative appearance after 1 year.

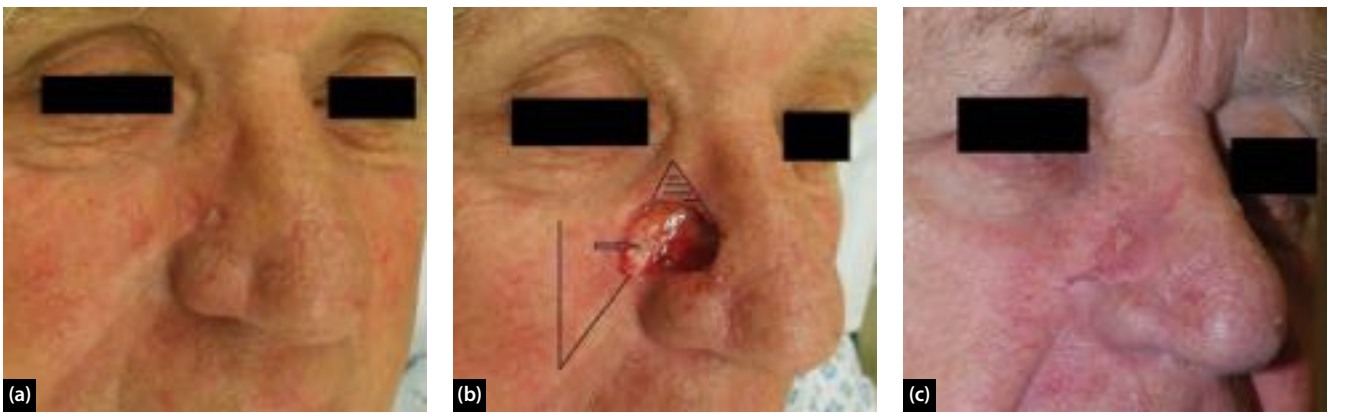


Figure 85.10 Note flap. **(a)** Infiltrative BCC of the nasal side wall. **(b)** Flap designed. The arrow shows the direction of movement of the flap. The shaded area is to be removed to avoid a 'dog ear'. **(c)** Post-operative appearance after 6 months.

when healing takes place, the reconstructed ala contracts a little and rolls up to form a more natural edge.[34]

Note flap

The note flap (**Figure 85.10**) and adjoining defect appear similar to a musical note and hence the name. It is essentially a superiorly based nasolabial flap. A dog ear is removed and the flap moved to cover the defect. A second stage is not required.

Septal flaps

An anterior septal mucosal flap based on the septal branch of the superior labial artery, or alternatively a posterior flap based on the septal branch of the sphenopalatine artery, can provide an internal lining.[16] A septal flap produces a well-vascularized lining and, while it tends to crust for several weeks, it will eventually provide a normal lining. Squamous epithelium will tend to crust for many months when it is used to line the nose. One of the main limitations about using a septal flap is that, if both nasal vestibules need an internal lining, then a septal perforation will almost certainly be produced. Most septal flaps cause nasal obstruction as they fold over and this requires a secondary procedure. It is important to raise these flaps under the mucoperichondrium to give them strength.

Regional and distant pedicled flaps

When there are larger or more complicated defects, including a full-thickness tissue loss, regional flaps may be required. Complications can include: graft necrosis (rare in paramedian forehead flap); intranasal crusting; donor site morbidity; 'bunching up' due to contracture of excessive tissue; stenosis and nasal obstruction.

If pedicled regional flaps are not available, distant pedicled flaps can be used. However, distant pedicled flaps, like the pectoralis major myocutaneous flap and trapezius island paddle flap, do not provide a good colour or texture match for the nasal skin and are very bulky. Free flaps described for use in total nasal reconstruction are the radial forearm free flap, the dorsalis pedis free flap and the retroauricular free flap. The radial forearm free

flap is bulky, the dorsalis pedis free flap is thin, but it causes significant donor site morbidity and the retroauricular free flap has very small vessels and therefore has a precarious vascular anastamosis, limiting its application.

Large or complex defects with a full-thickness tissue defect require regional flaps in conjunction with free or local flaps and grafts. Free flaps have been described for use in total nasal reconstruction but they are bulky as the underlying fat is thick and it is difficult to thin it evenly, even after several stages.[35, 36] A pericranial flap has been described to provide an internal lining for total nasal reconstruction.[17]

The midline and paramedian forehead flaps are the pedicled flaps that are of most use in nasal reconstruction.

Midline forehead flap

For reconstruction of large defects of the nose above the columella, the midline forehead flap can be used, but extension onto the columella is limited. It can be used for subunit repair, heminasal reconstruction or total nasal reconstruction.[37] The midline forehead flap is based on the supratrochlear arteries[38] and consists of skin, subcutaneous tissue and frontalis muscle. A width of up to 4 cm has been described.[37] Recently, a midline forehead flap based on central artery has also been described.[39]

The advantages of this flap are the excellent colour and texture match with the skin of the nose, reliability and low morbidity, and the donor site deformity is low. The disadvantage is that the 180-degree twist in its base means that it has to extend to hair-bearing skin if it is to stretch to the columella without kinking its base. It is also unsightly until a subsequent procedure is carried out to divide the flap.[37]

Paramedian forehead flap

The paramedian forehead flap (**Figure 85.11**) is an improved modification of the midline forehead flap and is the best alternative in dealing with major nasal defects.[40, 41] The technique is very similar to that of the midline forehead flap except that the flap is positioned to one side of the midline based on the ipsilateral supratrochlear artery.

This flap is not only robust but the donor site often heals well, even when it is not possible to close its upper part and this is left to heal by secondary intention. One of the main problems of the flap is its thickness, particularly if it is used to reconstruct the alar margin. It is possible to thin this skin down up to 1.5 cm from its distal rim unless there are adverse factors affecting its vascular bed. A single-stage paramedian flap has also been described.[42]

Multiple flaps in large defects

When the defect is large, the use of multiple local flaps (**Figure 85.12**) can be considered for reconstruction if the patient is not keen on using larger flaps such as paramedian flap or cheek advancement flap. In such cases it may be advisable to use slightly larger flaps to compensate for the possible cicatrization at the junction of the flaps.[43]

Free cartilage grafts

Cartilage from the septum, conchal bowl or rib provides a useful scaffold and it is rare for it to resorb unless it is morselized or becomes infected. The scaffolding should be provided at the same time as the reconstruction. Delay in providing the support leads to scarring and contraction of the flap, causing difficulty in placing the scaffold as a second-stage procedure.[44] Burget and Menick have advocated placing the cartilage between the frontalis muscle and the skin of a forehead flap before any contraction of the flap has occurred,[45] but it can only be placed distally and this may compromise the distal vasculature. When alar subunits are reconstructed, the margin must be supported with a cartilage graft to avoid contracture. These grafts are kept between the inner and external lining to provide adequate blood supply. Even when the defect does not involve the alar margin, the cartilage-free graft has an important role in providing support if the lower lateral cartilage, upper lateral cartilage or quadrangular cartilage is lost.

Composite cartilage grafts

The free composite graft (**Figure 85.13**) consists of skin and greater or lesser amounts of attached subcutaneous tissue. Konig[9] first described the use of a composite cartilage graft from the ear. In his paper published in 1943, Sir Harold Gillies described the use of the composite graft to provide the inner lining of forehead flap used for nasal reconstruction.[10] Limberg,[46] Brown et al[47] and Dupertuis[48] reported the use of a free sandwich graft from the auricle for nasal reconstruction. The free auricular composite graft has been advocated for the repair of minor defects of the lower part of the nose for the following reasons.[48]

- The skin of the ear is similar in colour to the skin of the nose.
- The ear contains cartilage that gives good support with a choice of contours to match those of the ala.
- The auricular graft has only a slight tendency to contract after surgery.
- This method is economical because the length of hospitalization is much shorter.
- The secondary defect of the ear is inconspicuous and can easily be repaired.

Composite grafts up to 2 cm in diameter can survive free transplantation where the vascular bed has not been compromised by smoking, radiotherapy, scar tissue from previous trauma or surgery, diabetes or severe atherosclerosis.

The shape of the auricular composite grafts makes them suitable for use in nasal surgery.[49] These grafts have been used to correct small defects of the alar margins, especially those taken from the antitragal margin. The disadvantages noticed with the auricular composite graft are that, while its contour can often match that of the alar rim, it can rarely replace a whole aesthetic unit

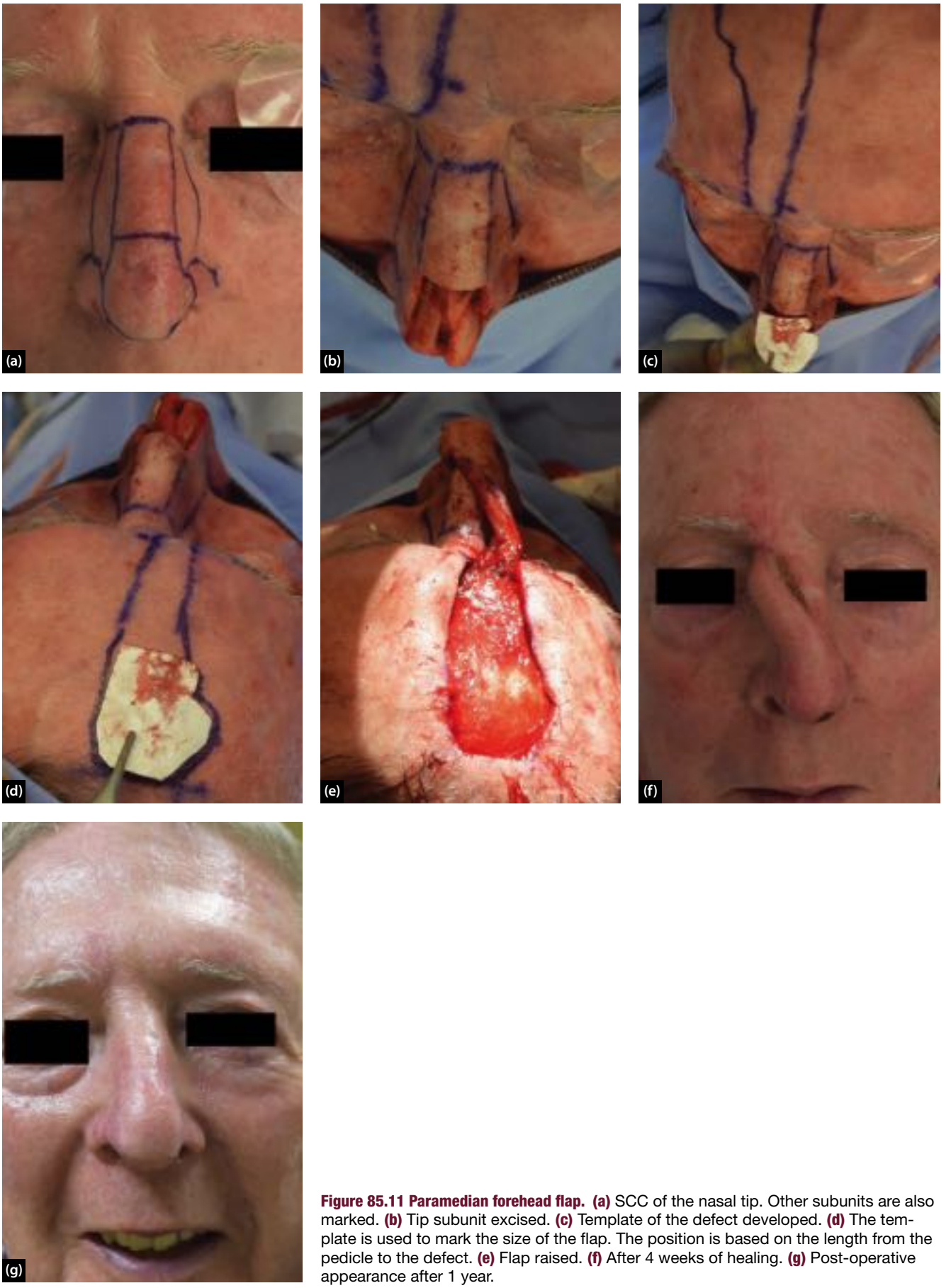


Figure 85.11 Paramedian forehead flap. **(a)** SCC of the nasal tip. Other subunits are also marked. **(b)** Tip subunit excised. **(c)** Template of the defect developed. **(d)** The template is used to mark the size of the flap. The position is based on the length from the pedicle to the defect. **(e)** Flap raised. **(f)** After 4 weeks of healing. **(g)** Post-operative appearance after 1 year.

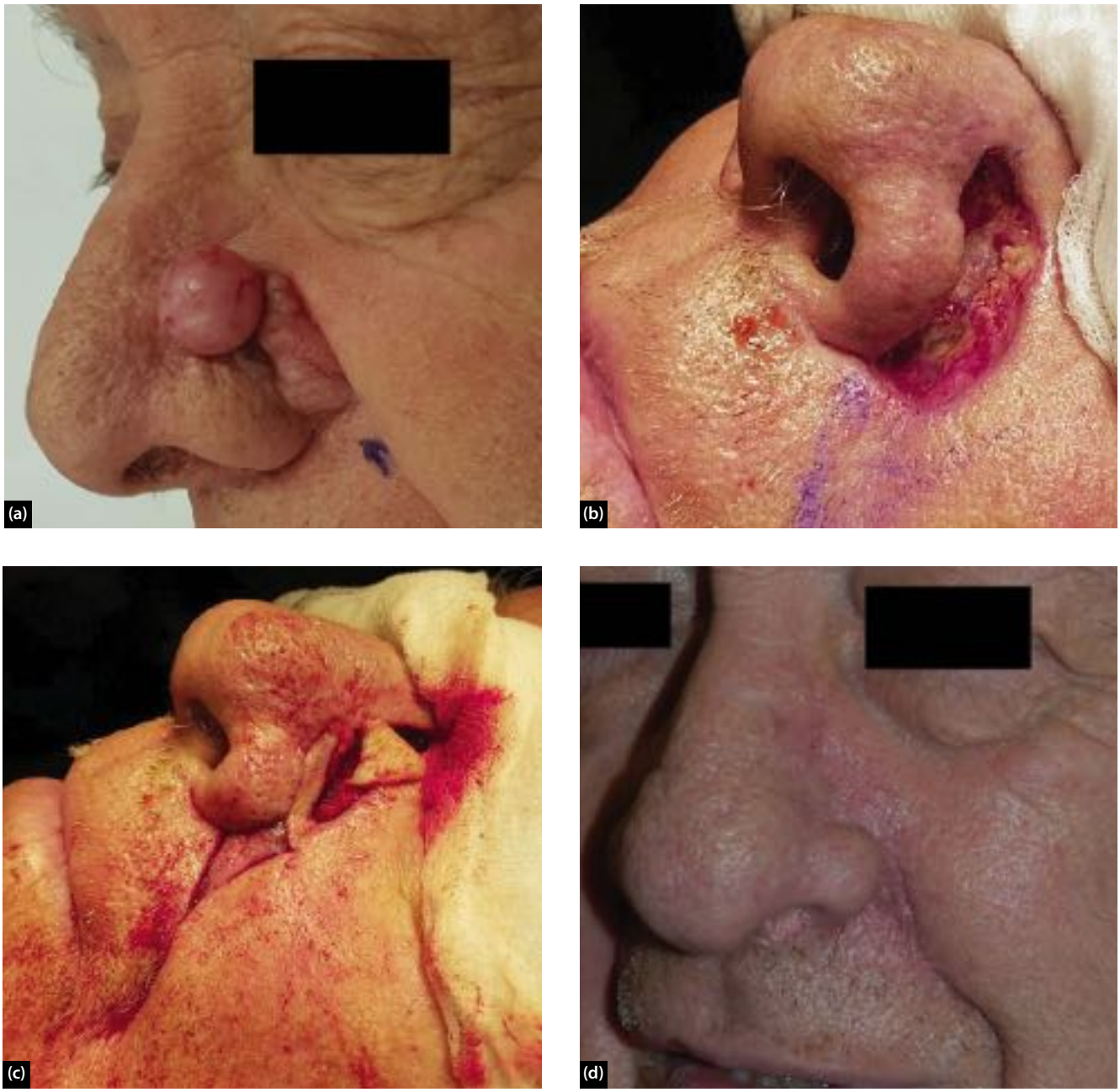


Figure 85.12 Multiple flaps for a large defect. **(a)** Nodular BCC of the alar grove, ala, side wall and adjoining cheek. **(b)** Defect after excision. **(c)** Three flaps raised: two V–Y advancement flaps and a small note flap between them. **(d)** Post-operative appearance after 6 months.

and its skin quality is often different once it has bedded in and fibroblasts have led to some contracture.[50] The auricular composite graft from the conchal bowl can be used for lining the inner surface of the paramedian forehead flap and to provide skeletal support to the reconstructed area.[41] The defect can be filled using a pedicled postauricular island flap.[41] The benefits of a conchal cartilage graft to provide the internal lining and support for a paramedian forehead flap when both nasal vestibules need reconstructing are that it avoids a septal perforation[51] and nasal obstruction and there is little donor site morbidity. The morbidity of the donor region is small.

CONCLUSION

Various techniques are described for reconstructing defects of the nose. The surgeon chooses the technique depending on his or her preference and the nasal defect that requires correction. Whatever technique is used, it is essential to reconstruct all three layers of the nose. Whole aesthetic subunits must be reconstructed for a better aesthetic result if more than half of the subunit has been lost. Although different grafts and flaps have been described, in our opinion, the paramedian forehead flap (with composite conchal graft, if required) is robust and consistently gives good results in major nasal reconstruction.



Figure 85.13 Composite cartilage grafts. (a,b) Bilateral vestibular stenosis and notching of the alar margins secondary to pressure from the nasogastric tubes. **(c,d)** Post-operative view after inlay of conchal composite grafts.

BEST CLINICAL PRACTICE

- ✓ Reconstruction should only be undertaken when the surgeon is sure that the tumour has been removed.
- ✓ Mohs' micrographic surgery should be used for morphoeiform basal cell carcinoma or squamous cell carcinoma whose margins are unpredictable. If Mohs' is not available, then it is best to wait for the histological result from paraffin sections and dress the wound in the meantime.
- ✓ The slightest variation in contour or symmetry of the nose is readily seen and the aim should be to obtain as much symmetry as possible.
- ✓ The concept of replacing the whole of an aesthetic segment (a tissue plane with the same thickness, colour and contour of skin) if more than 50% of the segment has been lost is important in obtaining a good cosmetic result.
- ✓ Reconstruction requires an inner lining, scaffolding and an external layer otherwise the tissue will contract, roll up and become thick, firm and featureless.
- ✓ Incisions should be made at the junction of aesthetic segments in order to disguise them.
- ✓ If a defect requires three or more flaps to reconstruct adjoining aesthetic units, there can be unpredicted cicatrization at their junction. This particularly applies to the alar base and in these circumstances we recommended replacing the nasal defect with more tissue in the paramedian forehead flap than when the units of the nose are being reconstructed on their own.
- ✓ It is important for an individual's self-esteem and psychological well-being that they undergo counselling before embarking on nasal reconstruction.

FUTURE RESEARCH

- Many techniques have been described to reconstruct the nose and their success rate in both aesthetic and functional terms is difficult to quantify. The presence of numerous techniques means no one technique is good for all defects of the nose.
- A minority of authors have questioned the principle of resecting the remainder of an aesthetic segment if more than 50% has been lost[52] but these claims have not been supported by photographic evidence equal to that of the proponents of this principle. There are no good techniques available to reconstruct the nose if the septal support is lacking.
- Randomized control trials are unlikely to take place given the relative rarity of these conditions and the number of variables that would need to be controlled for. Nevertheless, the techniques described have stood the test of time and give good results when the principles outlined in this section are followed. These are not procedures that should be 'tried' by the occasional or inexperienced surgeon as a poor outcome makes it far more difficult to achieve a good result if revision surgery is needed.

KEY POINTS

- The concept of an aesthetic segment, a tissue plane with the same skin thickness and contour, is central to obtaining a good result.
- Try to keep the scars parallel to relaxed skin tension lines and at the junction of aesthetic subunits to make them less noticeable.
- Usually whole aesthetic segments should be replaced, even if this means removing good tissue – unless less than half of one segment has been lost.
- Respect and reproduce aesthetic units wherever possible.
- Sound reconstruction requires an inner lining, adequate scaffolding and an external lining with skin of the same thickness and colour as the contralateral side.
- If the alar rim is lost, a contoured girder of cartilage needs to support the soft tissue at its edge, otherwise it will tend to retract and collapse.
- Reconstruction should only be carried out when the surgeon is sure that the tumour has been removed. Mohs' micrographic surgery should be used for morphoeiform basal cell carcinoma or squamous cell carcinoma whose margins are unpredictable. If Mohs' is not available, then it is best to wait for the histological result from paraffin sections and dress the wound in the meantime.
- Symmetry is important.
- Avoid tension but remember that excessive tissue contracts and 'bunches up'.
- A composite cartilage graft can rarely replace a whole aesthetic unit and its skin quality is often different once it has bedded in and fibroblasts have led to some contracture.

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CHAPTER
86

PINNAPLASTY

Victoria Harries and Simon Watts

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SEARCH STRATEGY

The data in this chapter are based largely on the authors' personal experience as surgeons and teachers. Pinnaplasty techniques are extensively described in textbooks of operative surgery.

BACKGROUND

'Prominent ears' is a common presentation to the paediatric ENT clinic, and represents the commonest congenital deformity of the ear with an incidence of approximately 5–6%.[1] They can be associated with severe psychological distress and consequently affect academic performance and social development.[2] It is therefore important to address any associated psychological issues as well as manage the patients' and parents' expectations when discussing the potential outcome of surgery.

There is a spectrum of ear defects that require the surgeon to tailor the consultation and operative procedure to the individual but, as an umbrella term, pinnaplasty is the surgical procedure undertaken to correct this benign deformity.

The timing of surgery remains controversial. Some surgeons advocate operating on children as young as 3 years old in order to manage the condition prior to any psychological distress[3] while others argue that the individual should be able to give informed consent before undergoing treatment.

Since Dieffenbach first performed the procedure in 1845,[4] more than 200 different techniques of pinnaplasty have been described in the literature, indicating that no single approach is a 'panacea for all ills'. In 1968, McDowell thus proposed the main objectives for a successful pinnaplasty, enabling surgeons to blend various techniques and approaches (**Box 86.1**).[5]

ANATOMY

The external ear develops from the first and second branchial arches during the 6th week of gestation. The six hillocks of His rotate and fuse to form the pinna (**Figure 86.1**).

The aesthetically normal auricle lies with its long axis tilted posteriorly by 15–20 degrees. The top of the auricle is level with the eyebrow, and its width is approximately 60% of its height (range = 5.5–6.5 cm). A normal pinna

BOX 86.1 Objectives for a successful pinnaplasty

Elimination of the protrusion in the upper third of the ear.
The helical fold should be parallel to the antihelical fold but visible when viewing the patient from the front.
The helix should have a smooth and regular contour.
The post-auricular sulcus should not be distorted.
The auricle should be an appropriate distance away from the mastoid.
The difference between both auricles should be within 3 mm.

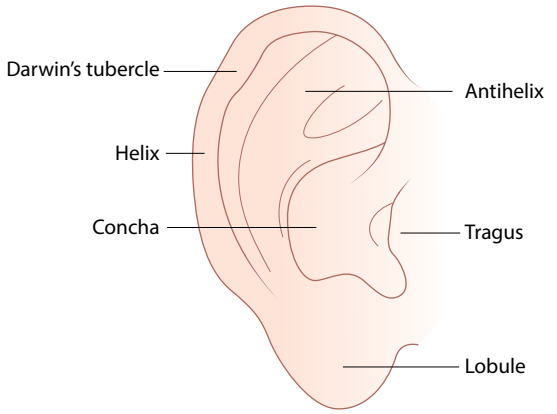


Figure 86.1 Anatomy of the pinna. (Based on a drawing by Mr Dutta, Pembury Hospital, Tunbridge Wells, UK.)

has an auriculocephalic angle of 25 degrees while protruding ears have an auriculocephalic angle greater than 40 degrees (**Figure 86.2**).

Prominent ears are an example of first-degree dysplasia, according to the classification of auricular deformities as first described by Weerda in 1988 (**Table 86.1**).[6]

Prominent ears are commonly due to one or a combination of the following defects:

- underdevelopment of the antihelical fold
- hypertrophy of the conchal bowl
- prominent lobule.

The constricted ear deformity appears as a small but prominent ear due to the small circumference of the helical rim. Stahl's ear deformity consists of an additional crus which transverses the scapha.

CONSERVATIVE METHODS

A number of non-surgical techniques have been developed for the treatment of protruding ears.

Simple moulding or splinting devices can be considered in children up to 6 months old. The high levels of oestrogen during the neonatal period allow for the cartilage to be more malleable and therefore respond to non-operative methods. The effectiveness of treatment is directly influenced by the age of the child and therefore referral of neonates with external ear deformities should be encouraged. Satisfactory results can be seen in up to 90% of patients if treatment is started within the first few days of life.[7]

OPERATIVE TECHNIQUES

Pinnaplasty can be performed under local anaesthetic or general anaesthetic as a day-case procedure although, with most patients being children, general anaesthetic is usually the preferred option.

Before surgery takes place, it is helpful to have at least two consultations with the patient/parents to confirm the need for surgery and photographs are essential for preoperative planning and for medicolegal purposes.

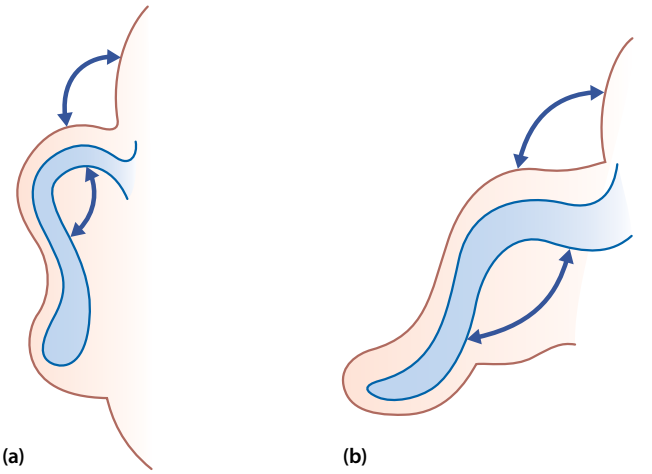


Figure 86.2 Anthropometric evaluation of a normal pinna. (Based on a drawing by Mr Dutta, Pembury Hospital, Tunbridge Wells, UK.)

TABLE 86.1 Classification of auricular deformities

Degree of dysplasia	Definition (example)
1st degree	All anatomical features present but minor≈deformities noted (prominent ears, macrotia, Stahl's ear)
2nd degree	Some anatomical features missing (cup ear, constricted ear)
3rd degree	No recognizable anatomical features (atresia)

Formation of the underdeveloped antihelical fold

Two techniques have defined the pinnaplasty operation and can be used in isolation or in combination:

- cartilage sparing/suturing technique
- cartilage excising/scoring technique.

At the start of the operation, the neo-antihelix is created by holding the helix against the mastoid. Each side of the neo-antihelix is then marked with methylene blue needle markings (**Figure 86.3**).

An elliptical skin incision is made in the posterior sulcus, which is then excised to expose the perichondrium (**Figure 86.4**).

The tattoo markings are identified posteriorly (**Figure 86.5**), and are used as landmarks for cartilage suturing or excising.

Mustardé first described the cartilage sparing/suturing technique in 1963.[8] Three or four non-absorbable mattress sutures are placed through the auricular cartilage and perichondrium using the methylene blue markers for precise placement (approximately 1 cm wide and 1 cm apart), thereby creating the new antihelical fold (**Figure 86.6**).

This technique reduces the trauma to the cartilage and, as a result, post-operative auricular irregularities rarely occur. It is widely considered to be an appropriate technique in young children with soft and malleable auricular cartilage.

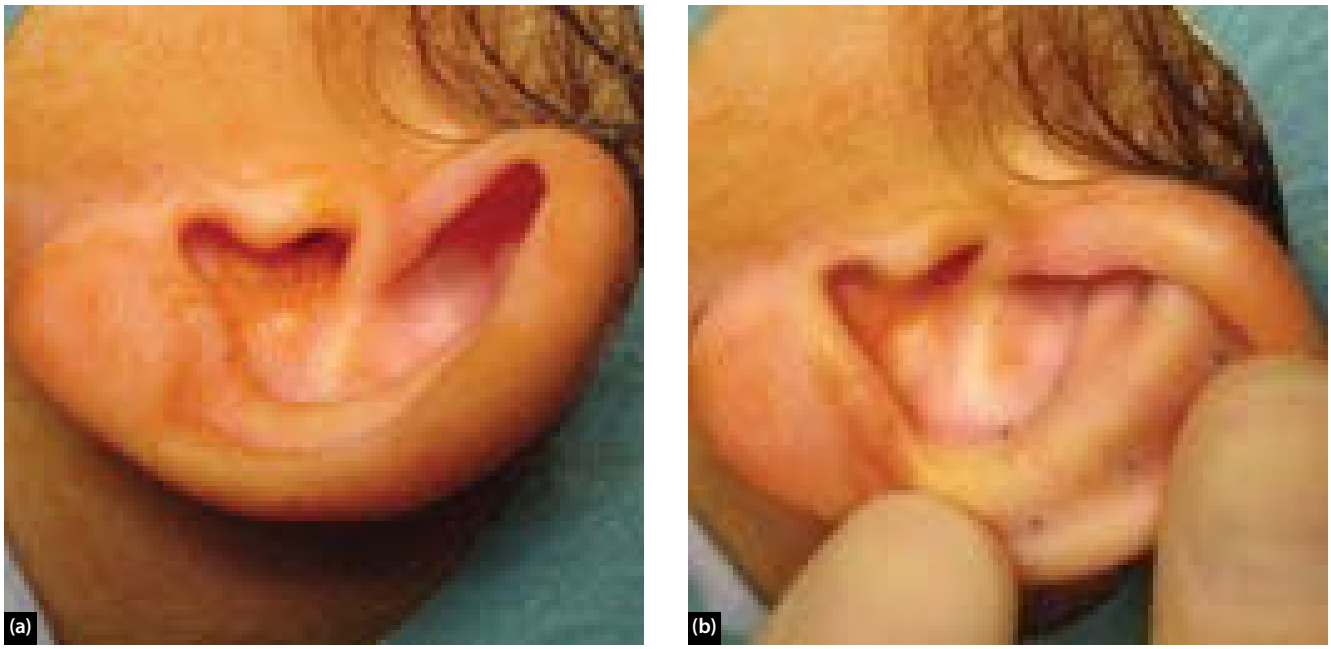


Figure 86.3 (a) A prominent ear and **(b)** the neo-antihelix with methylene blue markings.

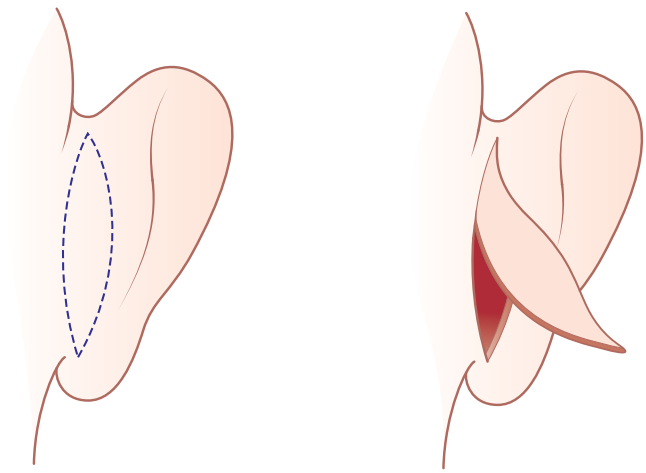


Figure 86.4 Postauricular elliptical skin excision. (Based on a drawing by Mr Dutta, Pembury Hospital, Tunbridge Wells, UK.)

It is advisable to use a non-absorbable suture such as Gore-Tex® to achieve a long-lasting result but with a minimum of reaction from the surrounding tissue (**Figure 86.7**).

Stenström described one of the initial cartilage incising/scoring techniques.[9] The scapha cartilage is incised in a 'C' shape and dissected off the anterior skin and perichondrium. The cartilage is then scored by making parallel incisions caudally from the inferior crus, which allows the antihelical fold to be developed. This technique can be used even when the cartilage is thicker in older individuals. With this technique, there is a greater risk of haematoma formation and infection due to significant skin elevation so intra-operative haemostasis and post-operative dressings are vital to prevent complications.

Usually, a combination of the two techniques allows for the disadvantages of the individual techniques to be minimized, thus reducing the potential for complications.

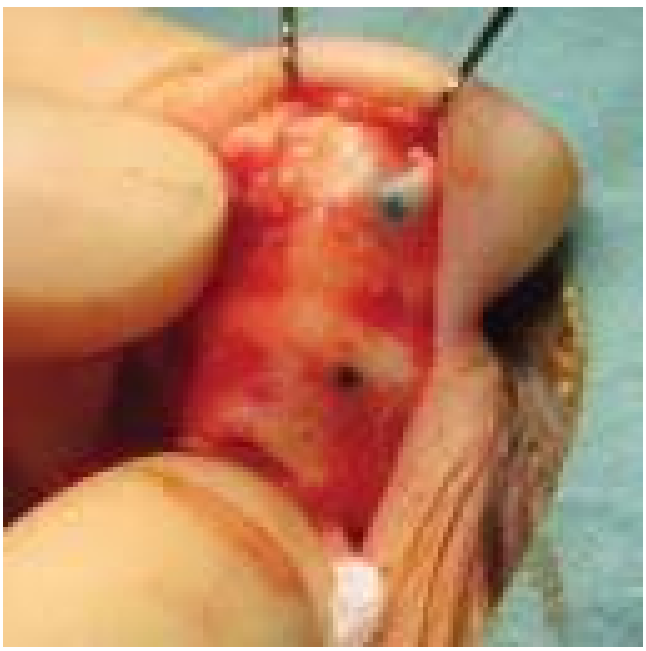


Figure 86.5 Methylene blue markings on the posterior aspect of auricular cartilage.

Additional techniques can be used as an adjunct to the conventional techniques. For example, a laterally based posterior auricular dermal flap or a bilateral fascioperichondrial flap can be used to prevent suture extrusion and decrease the rate of recurrence.

Without any particular 'gold-standard' procedure, novel techniques are continuously being developed, including cartilage-sparing methods without the use of sutures, and non-transfixing full-thickness incisions through the helix and antihelix that break the existing cartilaginous mould and therefore allow reshaping.

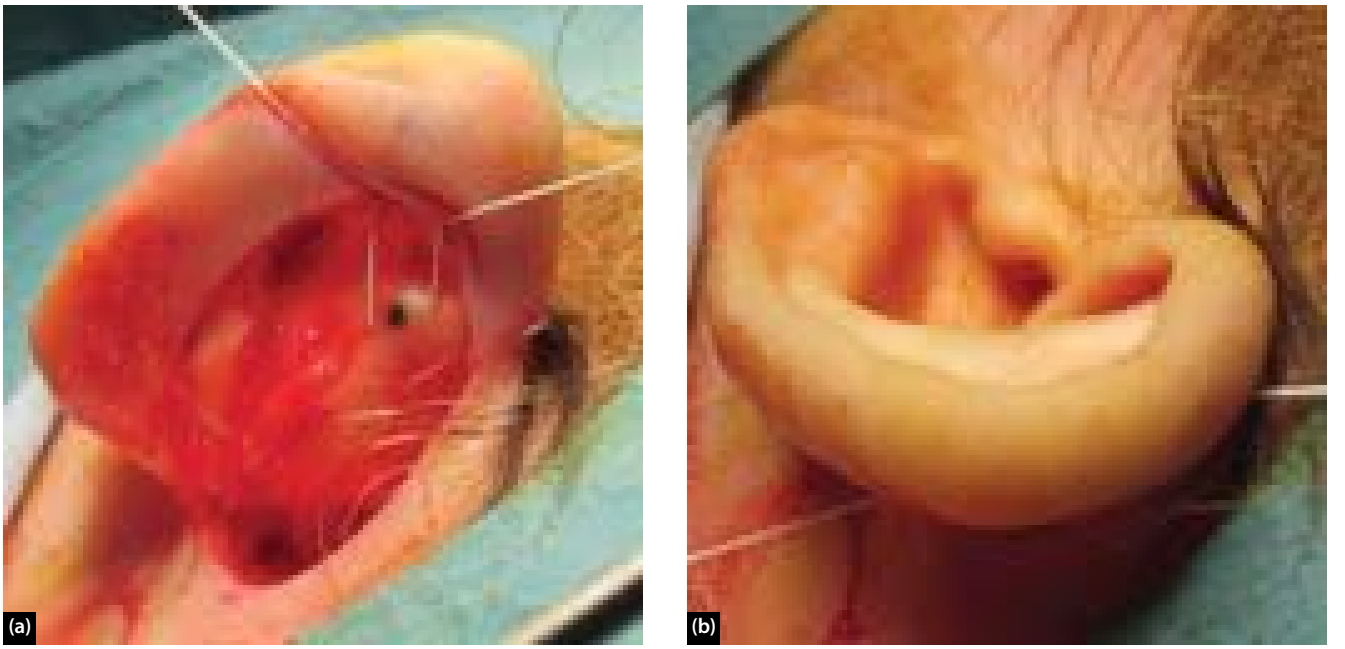


Figure 86.6 Mustardé suture.

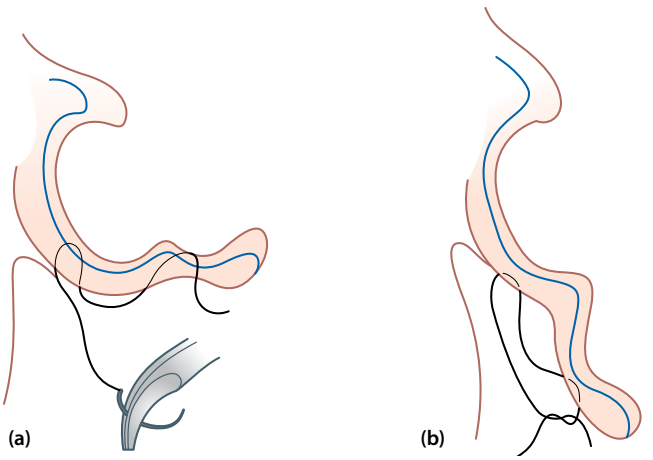


Figure 86.7 Technique of a Mustardé suture.

Correction of the conchal bowl hypertrophy

The angle between the concha and the mastoid can be reduced by a suture technique first described by Furnas in 1968 (**Figure 86.8**).[10] Care should be taken when placing the mastoid portion of the suture as placing it too close to the external ear canal may narrow the meatus when the suture is tied.

If the concha depth is more than 2.5 cm, excision of a full-thickness crescent of cartilage should be considered to correct the deformity, ideally being taken from the region of the conchamastoid sulcus.

Reconstruction of the lobule

A separate incision is made on the lobule to allow for a 'fishtail', 'wedge' or 'W-shaped' skin excision. The lobule can be repositioned by placing Goulian sutures (sutures that include postauricular skin, mastoid periosteum and posterior aspect of the lobule), therefore setting the lobule back towards the mastoid.

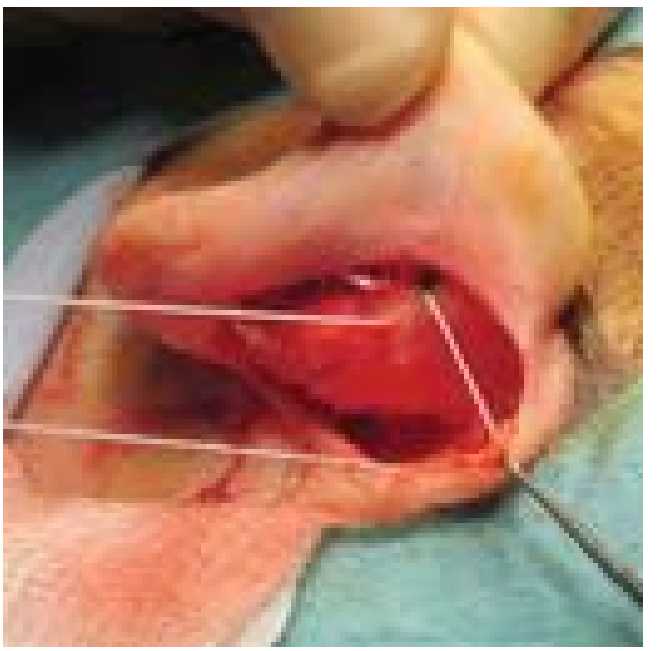


Figure 86.8 Furnas suture.

Other deformities

STAHL'S EAR DEFORMITY

The Kaplan and Hudson technique describes an incision being made along the helical rim and cartilage being



Figure 86.9 BIPP-soaked cotton wool dressing.

dissected off the skin. The affected cartilage, the extra crus, is excised and the skin is closed directly.

CONSTRICTED EAR DEFORMITY

The cup ear deformity requires elongation of the helical rim to allow the pinna to lie flat. An incision is made along the helical rim and the crus of the helix is fully mobilized and then advanced out of the concha. A standard pinnaplasty technique is then applied.

The postauricular wound can be closed with absorbable sutures, thus negating the need for removal (useful in younger children). A dressing such as BIPP-soaked cotton wool or paraffin gauze is applied to either side of the new antihelical fold and conchomastoid areas to reduce haematoma formation (**Figure 86.9**) followed by a dressing of heavy cotton wool and a crepe head bandage.

POST-OPERATIVE CARE

Head bandages in the post-operative period help to keep the dressings in place and also protect the ears. There is, however, no evidence to suggest that there is any clinical benefit conferred after 48 hours. Keeping the head up tends to reduce oedema.

COMPLICATIONS

- **Haematoma** is an early complication following pinnaplasty. It requires immediate evacuation to prevent necrosis of the cartilage. It is often signified by uncontrolled pain.
- **Infection** is a rare complication following pinnaplasty but requires early antibiotics in order to prevent chondritis and permanent deformity.
- **Keloid scarring** is a recognized complication of pinnaplasty, and patients and their families should be warned about this possibility.
- **Problems with sutures** can occur; they can extrude, and cause granulomas and hypertrophic scar formation.
- **Recurrence**. The rate of revision surgery is approximately 6% due to the pinna returning to its pre-operative position.
- **Overcorrection** is the most common complication of pinnaplasty and can lead to asymmetry or further deformity.

CONCLUSION

Many of the techniques for the correction of prominent ears are successful in achieving high satisfaction rates, despite significant variations in the techniques. Each technique has its own advantages and risks. The key to pinnaplasty is an awareness of each technique and applying the appropriate technique(s) to each individual case.

KEY POINTS

- 'Prominent ears' represents the commonest congenital deformity of the ear.
- 'Moulding' or 'splinting' is highly effective if commenced early and may avoid the need for surgery.
- Good quality pre-operative photography is an essential part of treatment planning.
- Timing of surgery varies, but most surgeons and parents prefer correction before the child goes to school or in the early years at school.
- Several operative techniques are available, each with benefits and drawbacks.
- Over-correction and asymmetry may lead to poor outcomes.

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CHAPTER
87

BLEPHAROPLASTY

Brian Leatherbarrow

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: cosmetic eyelid surgery, blepharoplasty, brow lift, dermatochalasis, midface lift and blepharoplasty complications.

INTRODUCTION

The term blepharoplasty is used to refer to an operation in which redundant tissues including skin, or skin and muscle, are excised from the eyelid, and in which fat may be excised, sculpted or repositioned. The appearance of the eyelids, and the periorbital region, plays a pivotal role in maintaining facial harmony through expression of human character, mood and emotions, and a successful outcome from this surgery requires great attention to detail.

A blepharoplasty can be performed for both functional and aesthetic reasons. A functional blepharoplasty aims to restore normal function and appearance to an eyelid that has been altered by trauma, infection, inflammation, degeneration, neoplasia or a developmental anomaly. A cosmetic blepharoplasty aims to improve the appearance of eyelid tissues that are histologically and functionally normal.

Patients who enquire about, or who are referred for, upper and lower eyelid blepharoplasty tend to present with a variety of aesthetic and functional complaints (**Figure 87.1**). These include:

- a tired look
- hooding of the upper eyelids
- 'drooping' of the upper eyelids
- 'eye bags'
- skin wrinkling
- skin folds
- a visual field defect
- headaches
- irritation of the upper eyelids
- lower lid 'dark circles'.

Female patients often complain of the inability to place make-up on the upper eyelid.

An upper eyelid blepharoplasty may involve the removal of skin alone, or skin and orbicularis muscle, or this may be combined with the removal or sculpting of herniated orbital fat. Occasionally an upper eyelid blepharoplasty will only involve the removal, sculpting or redraping of fat. The procedure may be combined with an eyebrow lifting or blepharoptosis procedure. The procedure may be performed for functional reasons to improve a patient's visual field restricted by dermatochalasis, or to improve symptoms of irritation from redundant skin hanging over the upper eyelid lashes, and/or for cosmetic reasons.

A lower eyelid blepharoplasty is more frequently performed for cosmetic reasons alone and may also involve the removal of skin and muscle alone or this may be combined with the removal and/or repositioning of herniated orbital fat, the resuspension of a ptotic orbicularis oculi muscle, a lateral canthal suspension, an orbital decompression procedure for thyroid eye disease or a midface or suborbicularis oculi fat (SOOF) lift. It may also be combined with skin-rejuvenating procedures (e.g. laser skin resurfacing, a chemical peel or the post-operative injection of dermal fillers).

Blepharoplasty is one of the most commonly performed cosmetic operations.

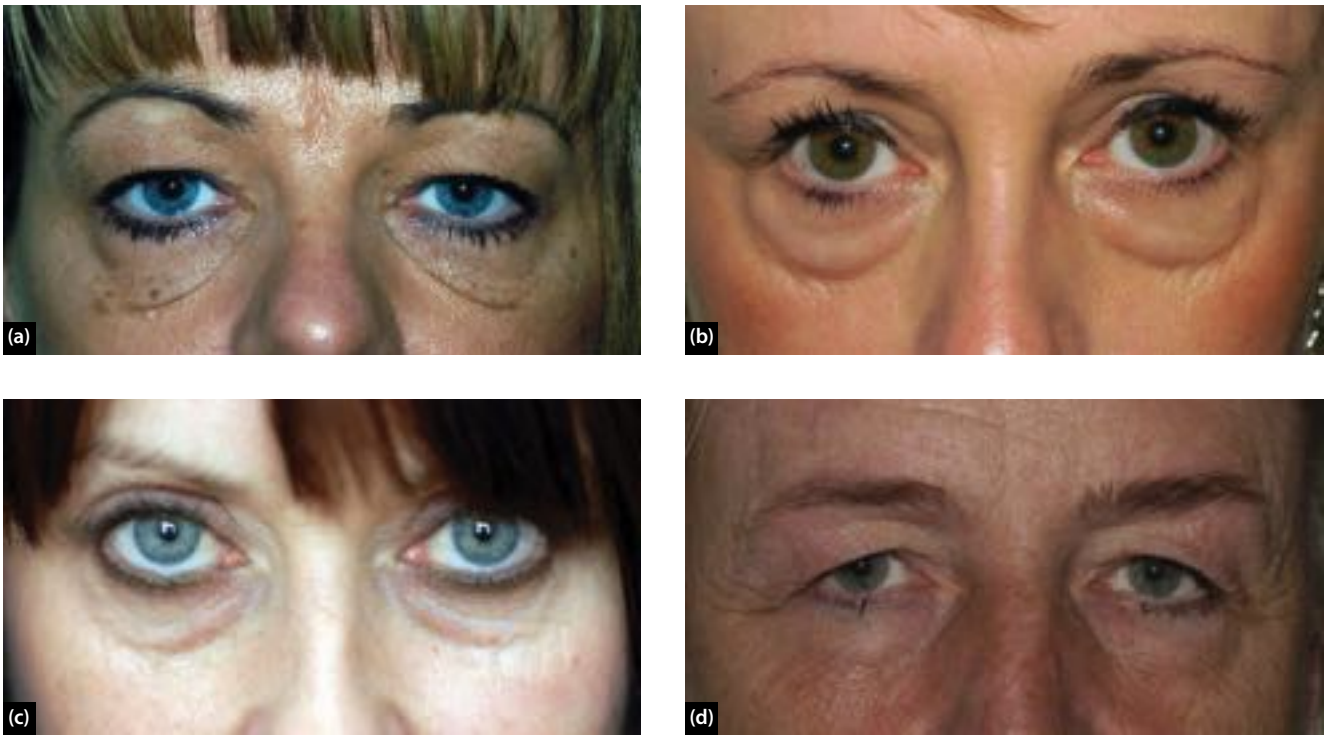


Figure 87.1 **(a)** A patient complaining of hooded upper lids with an inability to place make-up, and loose folds of skin in the lower eyelids. She was a heavy smoker. **(b)** A patient complaining of unsightly lower eyelid 'bags'. **(c)** A patient complaining of lower eyelid 'dark circles' creating a 'tired look'. **(d)** A patient complaining of a 'blinkered feeling' with a restriction of her visual fields.

APPLIED ANATOMY

A thorough understanding of the surgical anatomy of the eyebrows, eyelids and midface is essential prior to performing a blepharoplasty. This anatomy should be carefully reviewed. Additional aspects of surgically relevant anatomy are presented below.

The upper eyelids

The palpebral aperture is almond-shaped, with the lateral canthal angle lying slightly higher than the medial canthal angle. The lateral canthal angle is generally slightly higher in females than males and lies approximately 5 mm from the lateral orbital margin (**Figure 87.2**). The upper eyelid skin crease is usually approximately 5–6 mm above the lash line in males and 7–8 mm in females.

The distance between the inferior aspect of the eyebrow and the upper lid skin crease on downgaze should be approximately two-thirds of the distance from the inferior aspect of the eyebrow to the eyelid margin. Likewise, the distance from the skin crease to the eyelid margin in downgaze should be one-third of the distance from the inferior aspect of the eyebrow to the eyelid margin (**Figure 87.2**).



Figure 87.2 **(a)** The typical topographical anatomy of the periorbital region of a young female showing a skin crease at 6–7 mm above the eyelid margin and an arched eyebrow with the temporal aspect of the eyebrow lying at a higher position than the medial aspect. Note that the eyebrow has been plucked. It is important to take this into consideration when making measurements for skin resection. **(b)** The typical topographical anatomy of the periorbital region of a young male showing a skin crease at 5–6 mm above the eyelid margin and a flatter eyebrow contour.



Figure 87.3 A patient following an excessive resection of her left upper eyelid skin with worsening of her brow ptosis. She also has asymmetry of the upper eyelids and brows post-operatively.

In general, a minimum distance of 10–12 mm should be left between the inferior aspect of the eyebrow and the upper eyelid skin excision marking when performing an upper lid blepharoplasty and, again in general, approximately 20 mm of skin should be left between the inferior aspect of the eyebrow and the eyelid margin.

It is important to maintain these dimensions. If an excessive amount of upper eyelid skin is removed, reducing the distance from the skin crease to the brow in the presence of a brow ptosis, an unsatisfactory result will occur, with the appearance of the brow being attached to the eyelashes (**Figure 87.3**). This may also cause lagophthalmos (**Figure 87.4**).

It is important to differentiate prolapsed preaponeurotic fat from retro-orbicularis oculi fat (ROOF) that has descended into the upper eyelid (**Figure 87.5**). This may give rise to the appearance of upper eyelid 'fullness' (**Figure 87.6**). Although this descended fat can



Figure 87.4 (a) The same patient as in Figure 87.3 demonstrating severe lag on downgaze. **(b)** The same patient demonstrating lagophthalmos on attempted passive eyelid closure. She also shows very poor placement of the upper lid skin incisions and only 5–6 mm of skin between the left upper lid incision and the lowermost position of the eyebrow centrally.

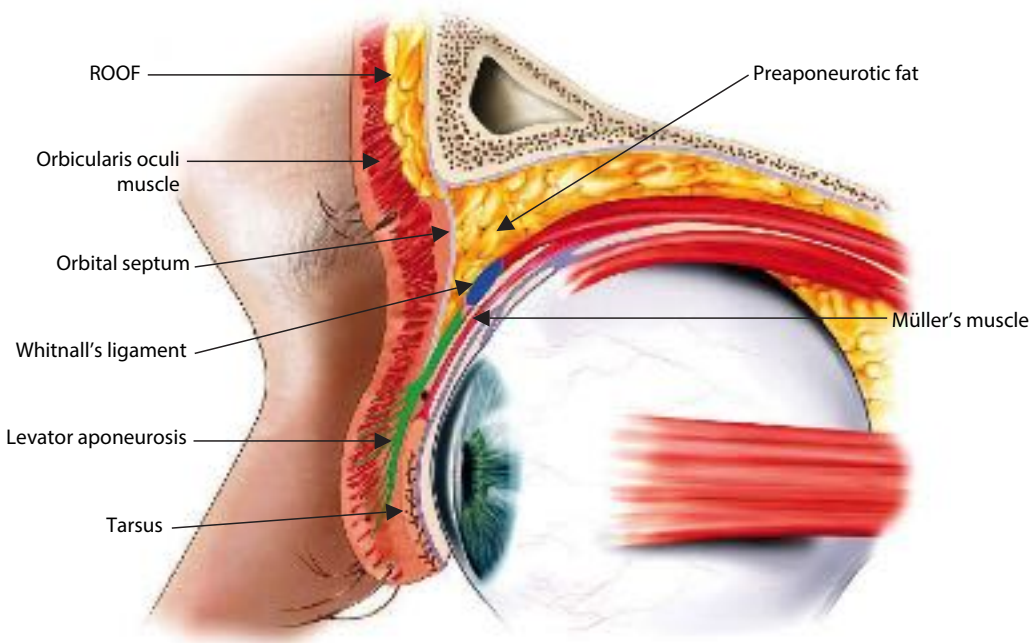


Figure 87.5 Diagram illustrating the position of preaponeurotic fat.

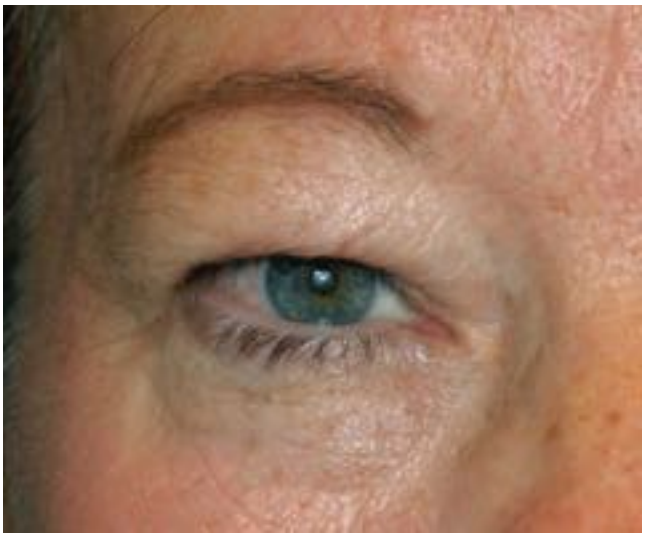


Figure 87.6 Fullness of the upper eyelid due to descent of the retro-orbicularis oculi fat (ROOF).



Figure 87.7 A burr is being used to reduce the prominence of the supraorbital margin in this patient.



Figure 87.8 A patient with bilateral lateral upper eyelid swellings due to spontaneous lacrimal gland prolapses.

be debulked, it is preferable to reposition it as part of a browlift procedure.

Some patients have very prominent superolateral bony margins that can also contribute to upper eyelid 'fullness'. This can be exposed and reduced with the use of a burr during the course of an upper eyelid blepharoplasty (**Figure 87.7**).

Subcutaneous thickening of this area in the dysthyroid patient must be recognized. This may not be amenable to improvement by standard blepharoplasty surgery. An overly aggressive upper eyelid blepharoplasty in a patient with thyroid eye disease can markedly worsen symptoms of corneal exposure.

It is important to recognize a prolapsed lacrimal gland that may be responsible for lateral upper eyelid 'fullness' or swelling (**Figure 87.8**). Prolapsed glands can be repositioned during the course of an upper eyelid blepharoplasty by suturing the gland to the periorbita of the lacrimal gland fossa (**Figures 87.9–87.11**).

Some patients develop orbital fat atrophy which creates an upper eyelid sulcus defect. The removal of preaponeurotic fat in such patients should be avoided to prevent a post-operative 'cadaveric' appearance. A prolapsed medial fat pad in such a patient can be debulked and the fat transplanted to lie evenly in the preaponeurotic space. In general, the removal of fat from the upper eyelid should be avoided in the majority of patients.

'Fullness in the medial aspect of the upper eyelid may be caused by a medial eyebrow ptosis. Elevation of the brow, or the use of botulinum toxin injections in the glabella, can be more successful at addressing this problem. Incisions in this area can leave unsatisfactory scarring. It is important to avoid the temptation to 'chase a dog ear' into this area beyond the medial limit of the skin crease during an upper eyelid blepharoplasty as the subsequent scarring can be very unsatisfactory. In such patients a gentle debulking of the medial fat pad can allow the skin to redrape with a more satisfactory aesthetic result, but over-resection of fat should be avoided. The fat should not be discarded as it may be required for use in the central aspect of the upper lid or may be of use to help to treat a medial tear trough defect in the lower eyelid.

The upper eyelid skin crease represents the most superior point of attachment between the skin and the levator aponeurosis. This position is just inferior to the insertion of the orbital septum onto the levator aponeurosis. The skin crease lies at a higher level in females, approximately 7–8 mm from the lash line, compared to 5–6 mm in males. It is important not to raise the skin crease in males to avoid a 'feminization' of the eyelid appearance.

The skin crease shows racial differences. In the oriental eyelid the orbital septum attaches to the levator aponeurosis at a lower level, allowing the preaponeurotic fat to descend into the lower reaches of the eyelid, preventing the levator aponeurosis from forming a high skin crease. A great deal has been written about the oriental eyelid and the oriental blepharoplasty. However, this detail is beyond the scope of this textbook.

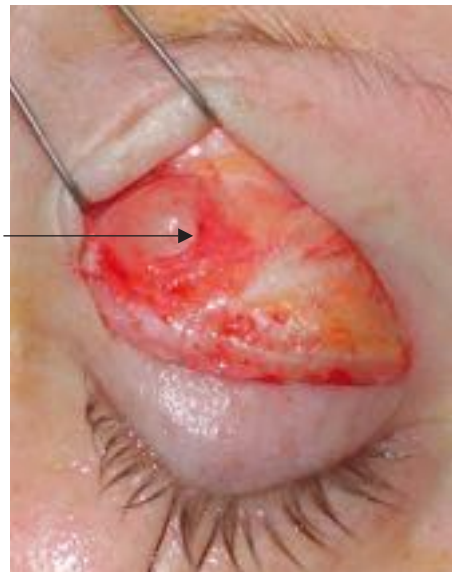


Figure 87.9 A right lacrimal gland prolapse as seen during an upper lid blepharoplasty.

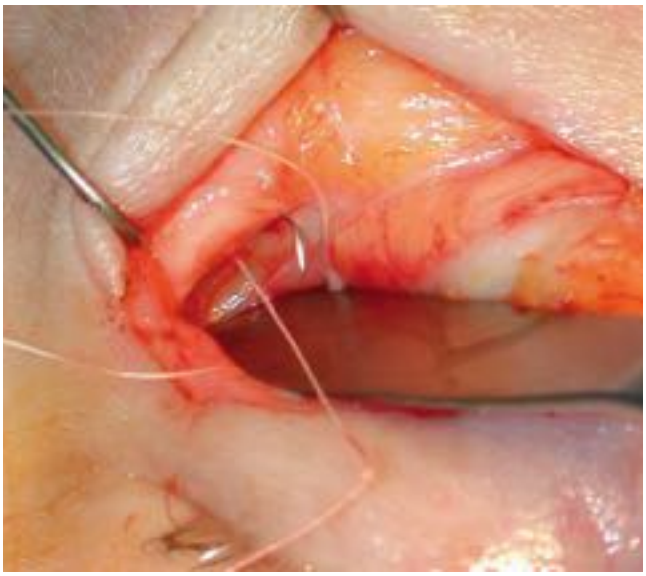


Figure 87.10 A double-armed 5-0 Vicryl suture is being placed through the periorbita of the lacrimal gland fossa.



Figure 87.11 The Vicryl suture has been passed through the capsule of the lacrimal gland and tied, repositioning the gland into the lacrimal gland fossa.

The skin of the upper eyelid is very thin, without any subcutaneous fat. Beneath the skin lies the very vascular orbicularis muscle. Local anaesthetic injections should be placed immediately beneath the skin, avoiding the orbicularis muscle, to prevent the occurrence of a haematoma. Deep to the orbicularis muscle above the skin crease lies the orbital septum. This originates from the arcus marginalis along the superior orbital margin. This firm attachment can be utilized to differentiate it from the levator aponeurosis. The orbital septum is a multilayered structure with a very variable thickness.

Posterior to the septum lies the preaponeurotic orbital fat. Pressure applied to the lower eyelid can force the fat to prolapse, which helps to differentiate this from descended retro-orbicularis fat and from fatty degeneration of the levator muscle and/or Müller's muscle. The preaponeurotic fat is a key landmark in upper eyelid surgery. The levator aponeurosis lies immediately beneath it (see **Figures 87.5** and **87.12**).

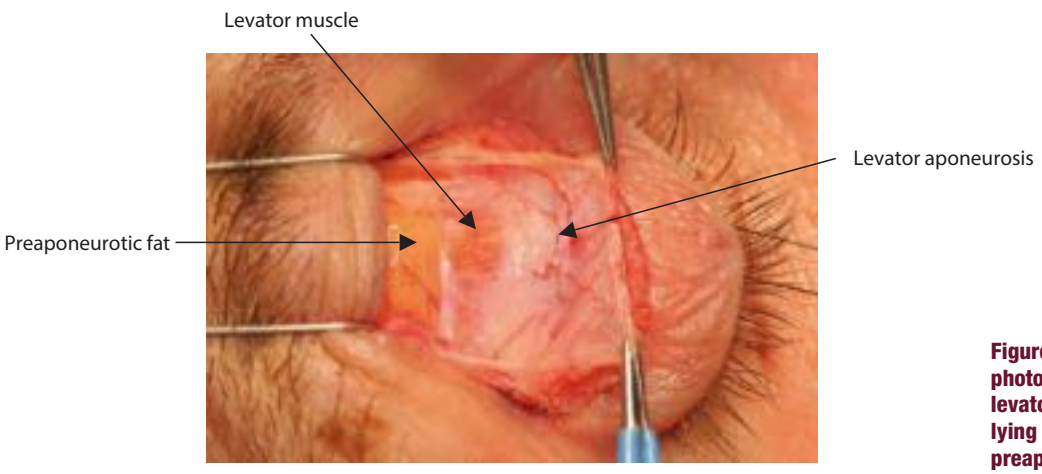


Figure 87.12 Intra-operative photograph demonstrating the levator muscle and its aponeurosis lying immediately beneath the preaponeurotic fat.

There are two main fat pads in the upper eyelid, a central pad and a nasal pad. The nasal fat pad is generally paler (**Figure 87.13**). It is extremely important to be able to distinguish the lacrimal gland from the orbital fat (**Figure 87.14**).

The levator muscle gives rise to the levator aponeurosis at the level of Whitnall's ligament. The aponeurosis inserts onto the anterior surface of the superior two-thirds of the tarsus. The medial and lateral horns of the aponeurosis insert in the region of the medial and lateral canthal tendons. The lateral horn divides the lacrimal gland into orbital and palpebral lobes. Intra-operative damage to the medial horn can give rise to a lateral shift of the tarsus with an eyelid peak lying temporal to the pupil.

Whitnall's ligament supports the levator muscle complex, acting as a fulcrum for the action of the levator muscle, and should not be disturbed during surgery. It is a variably developed structure that runs from the lacrimal gland to the region of the trochlea (**Figure 87.15**).

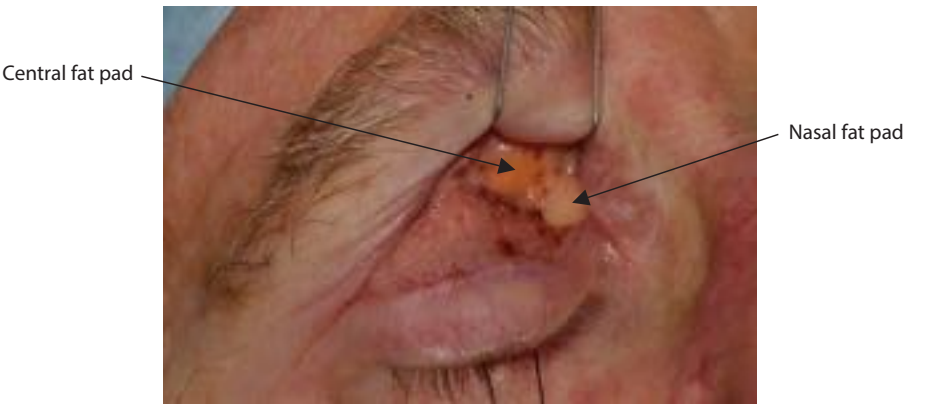


Figure 87.13 The nasal fat pad is paler than the central fat pad.

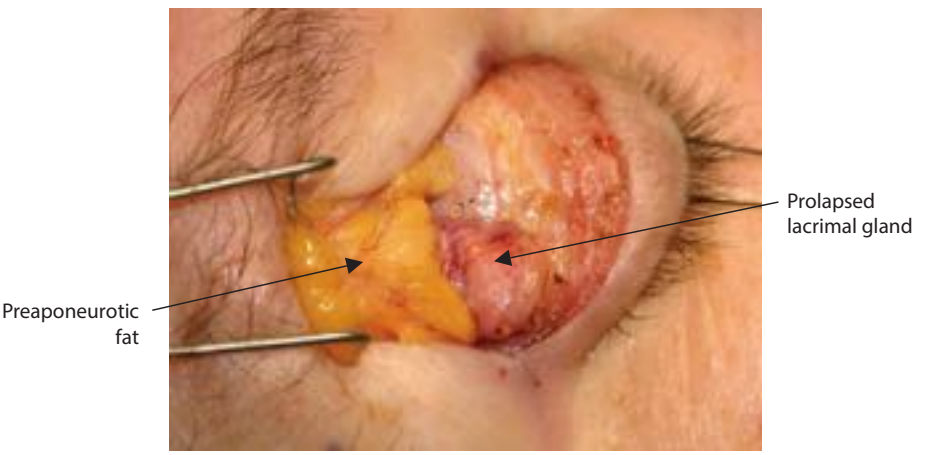


Figure 87.14 A prolapsed lacrimal gland.

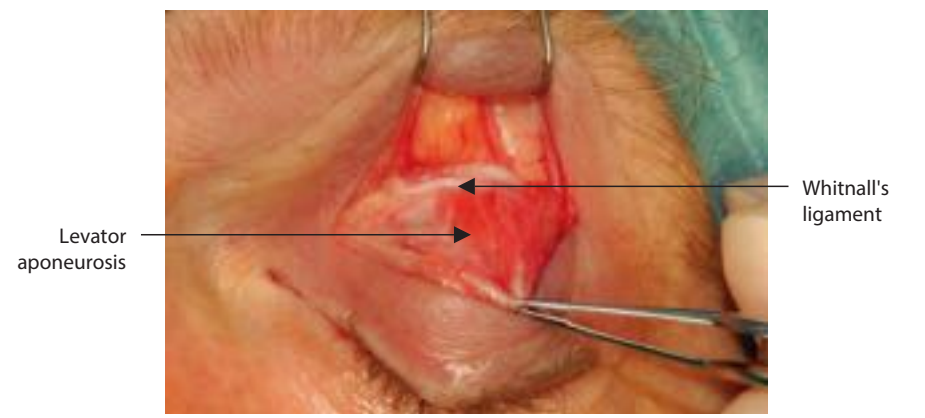


Figure 87.15 Whitnall's ligament.

The lower eyelids

The lower eyelid can be considered to consist of three lamellae:

- anterior – skin and the orbicularis oculi muscle
- middle – the orbital septum and the inferior eyelid retractors
- posterior – the tarsus and conjunctiva.

The lower eyelid skin crease is variable but is usually situated approximately 4–5 mm below the eyelid margin. The lateral canthal angle normally sits approximately 1 mm higher than the medial canthal angle.

The orbicularis oculi muscle is immediately deep to the skin of the lower lid. This muscle extends from just below the ciliary margin, past the inferior orbital rim and onto the cheek. Ptosis of the orbicularis oculi muscle commonly occurs over time and is responsible for the typical appearance of the malar crescent or malar mound in the aged face (see **Figure 87.23**).

Deep to the orbicularis oculi muscle lies the orbital septum, which serves to retain orbital fat within the orbit. The septum is composed of inelastic fibrous tissue. Atrophy of the septum with age permits orbital fat to herniate anteriorly creating typical lower lid 'bags' (see **Figure 87.1b**). The suborbicularis fascia, a plane of loose, fibrous connective tissue, lies between the orbicularis and orbital septum and provides a very good, relatively bloodless, dissection plane. The orbital septum extends from the inferior border of the tarsus to fuse inferiorly with the periosteum of the infraorbital margin. This inferior attachment of the orbital septum to the periosteum, where there is a condensation of tissue, is referred to as the arcus marginalis (**Figure 87.16**).

The arcus marginalis is strongest and best defined medially, where it attaches to the anterior lacrimal crest. As it extends laterally, it thins and weakens. It also assumes a more inferior and anterior insertion; thus, medially, it runs along the inner aspect of the rim but, laterally, it attaches approximately 2 mm inferior to the rim on the facial aspect of the zygomatic bone.

The tarsus in the lower eyelid is approximately 4–5 mm in height. The lower eyelid retractors are analogous to the levator aponeurosis in the upper eyelid. The smooth inferior tarsal muscle is analogous to Müller's muscle in the upper eyelid. The lower eyelid retractors, collectively referred to as the capsulopalpebral fascia, run from the inferior rectus muscle and split to envelop the inferior oblique muscle. This fascia then inserts into the inferior border of the tarsus (**Figures 87.16** and **87.17**). A deep layer of the fascia attaches to the conjunctival fornix as the suspensory ligament of the fornix.

Isolated shortening of the anterior lamella of the lower eyelid results in ectropion, of the middle lamella results in eyelid retraction with scleral show (**Figure 87.18**), and of the posterior lamella results in entropion.

There are three fat compartments in the lower eyelid: medial, central and lateral. Many delicate fibrous septa invest these compartments. The fat compartments lie between the capsulopalpebral fascia and the orbital septum. As the capsulopalpebral fascia (the lower eyelid retractor)

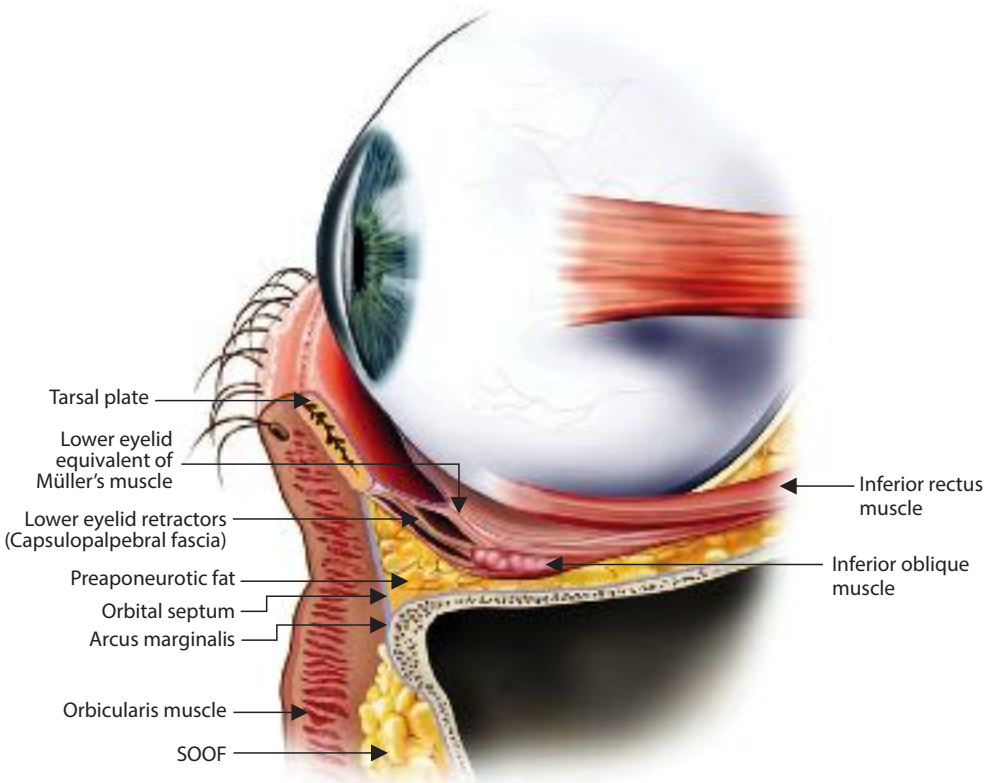


Figure 87.16 Diagram illustrating the anatomy of the lower eyelid region.

is analogous to the levator aponeurosis in the upper eyelid, the fat lying in front of the capsulopalpebral fascia can be considered to be analogous to the preaponeurotic fat in the upper eyelid. As in the upper eyelid, locating this fat is key to locating the eyelid retractor.

The inferior oblique muscle, originating from the anteromedial orbital wall, lies between and separates the medial and central fat compartments as it extends posterolaterally under the globe (**Figure 87.19**).

The arcuate expansion, an extension of the fascial sheath of the inferior oblique, continues laterally to attach to the lateral orbital rim and separates the central and lateral compartments (**Figure 87.20**). Subtle differences exist among the three orbital fat pads. The fat of the medial compartment is typically white and membranous, while that of the central and lateral compartments appears yellow and soft. The lateral fat compartment contains more septa than the medial and central compartments and is

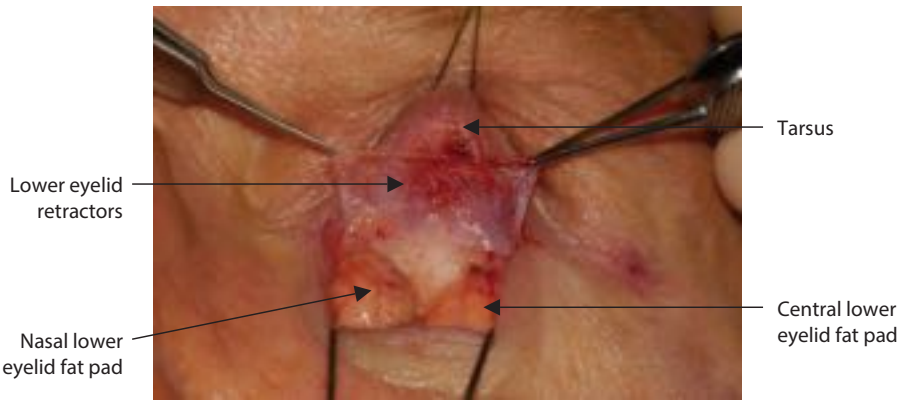


Figure 87.17 The lower eyelid retractors detached from the inferior border of the tarsus.

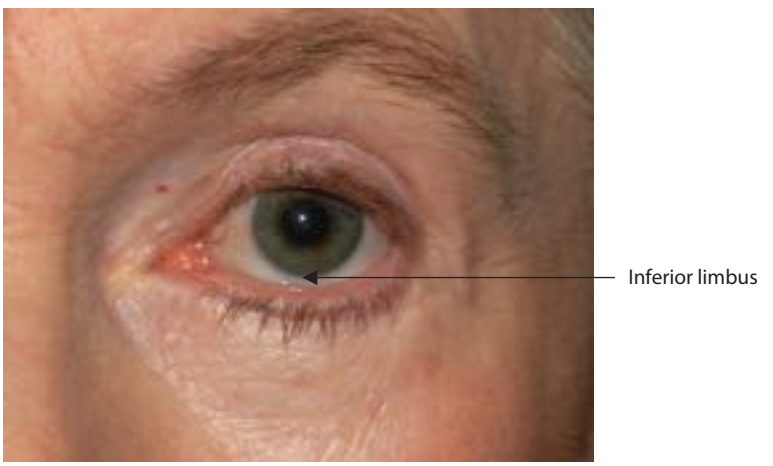


Figure 87.18 Middle lamellar scarring following a lower eyelid blepharoplasty resulting in lower eyelid retraction and scleral 'show' below the inferior limbus.

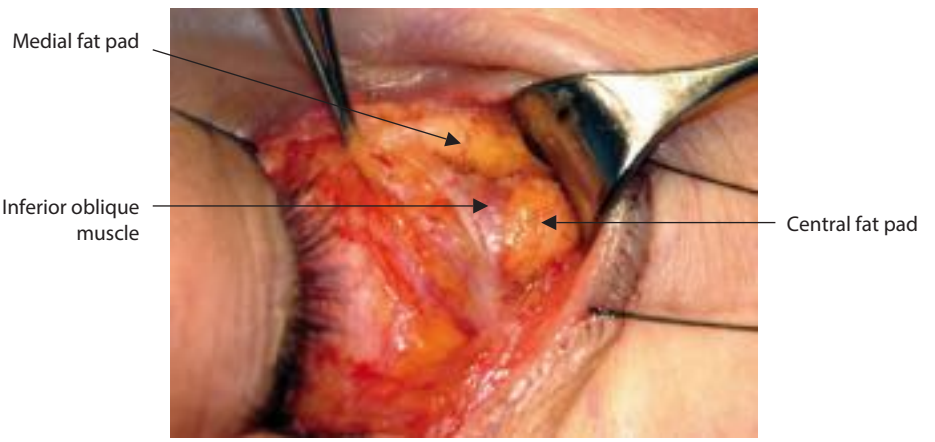


Figure 87.19 The inferior oblique muscle lying between the medial and central fat pads.

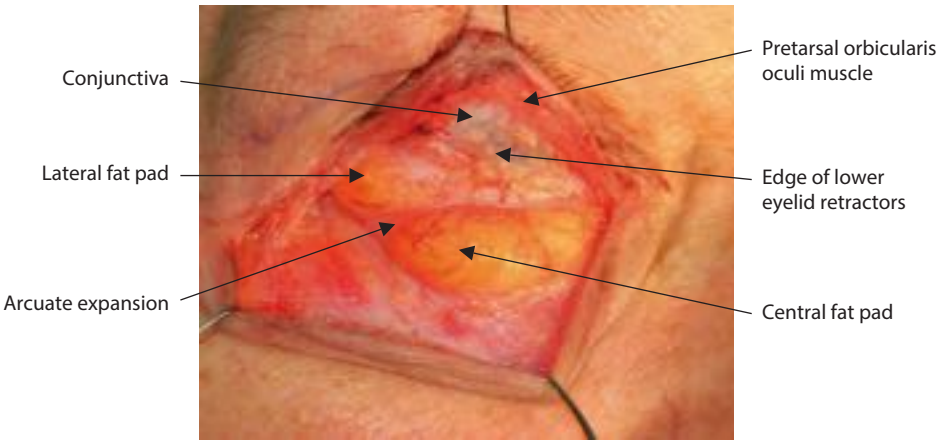


Figure 87.20 The arcuate expansion separating the central and lateral lower lid fat pads.

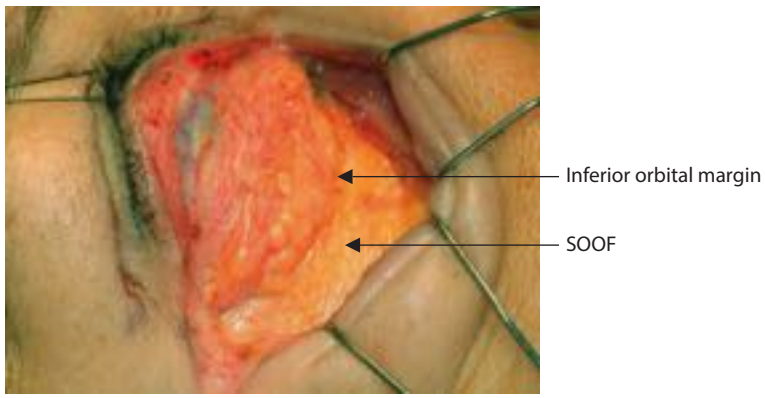


Figure 87.21 The suborbicularis oculi fat (SOOF).

therefore less prone to herniate anteriorly. It is important to note that inferior palpebral vessels travel directly through the medial fat compartment.

Fat seen below the inferior orbital margin posterior to the orbicularis oculi muscle and just anterior to the periosteum is the suborbicularis oculi fat (SOOF) (**Figure 87.21**).

With increasing age, the orbicularis oculi muscle and the SOOF move inferiorly, leading to a double convexity of the lower eyelid. The superior convexity is caused by a herniation of orbital fat through a weakened orbital septum above the inferior orbital margin (**Figure 87.22**). The orbital margin itself is responsible for the horizontal concavity and the SOOF, which has moved inferiorly, is responsible for the second convexity.

The midface

Knowledge of the anatomy of the midface is essential to the understanding of the morphological changes which occur at the lower eyelid–cheek junction with advancing age.

The prezygomatic space is a triangular space overlying the zygomatic and maxillary bones with its apex towards the nose and is limited superiorly by the orbitomalar ligament. It contains:

- fat overlying the orbital part of the orbicularis muscle
- the orbital part of the orbicularis muscle
- the SOOF
- pre-periosteal fat deep to the origin of the lip elevator muscles.

RETAINING LIGAMENTS

There are a number of retaining ligaments in the face which are condensations of fibrous connective tissue and which act to anchor the superficial tissue layers to firmer underlying structures. These ligaments are divided into true and false retaining ligaments.

- True retaining ligaments link the dermis to the underlying periosteum (zygomatic, orbital, orbitomalar and mandibular ligaments).
- False retaining ligaments link the deep facial fascia to the superficial facial fascia and the subcutaneous tissue (masseteric and platysma-auricular ligaments).

The zygomatic retaining ligament (McGregor's patch) arises from the zygomatic arch and from the body of the zygoma, passes through the superior aspect of the malar fat pad and inserts into the dermis of the overlying skin. The ligament is well-defined. The orbital retaining ligament lies over the frontozygomatic suture.

The orbitomalar ligament arises from a thickened area of periosteum a few millimetres below the inferior

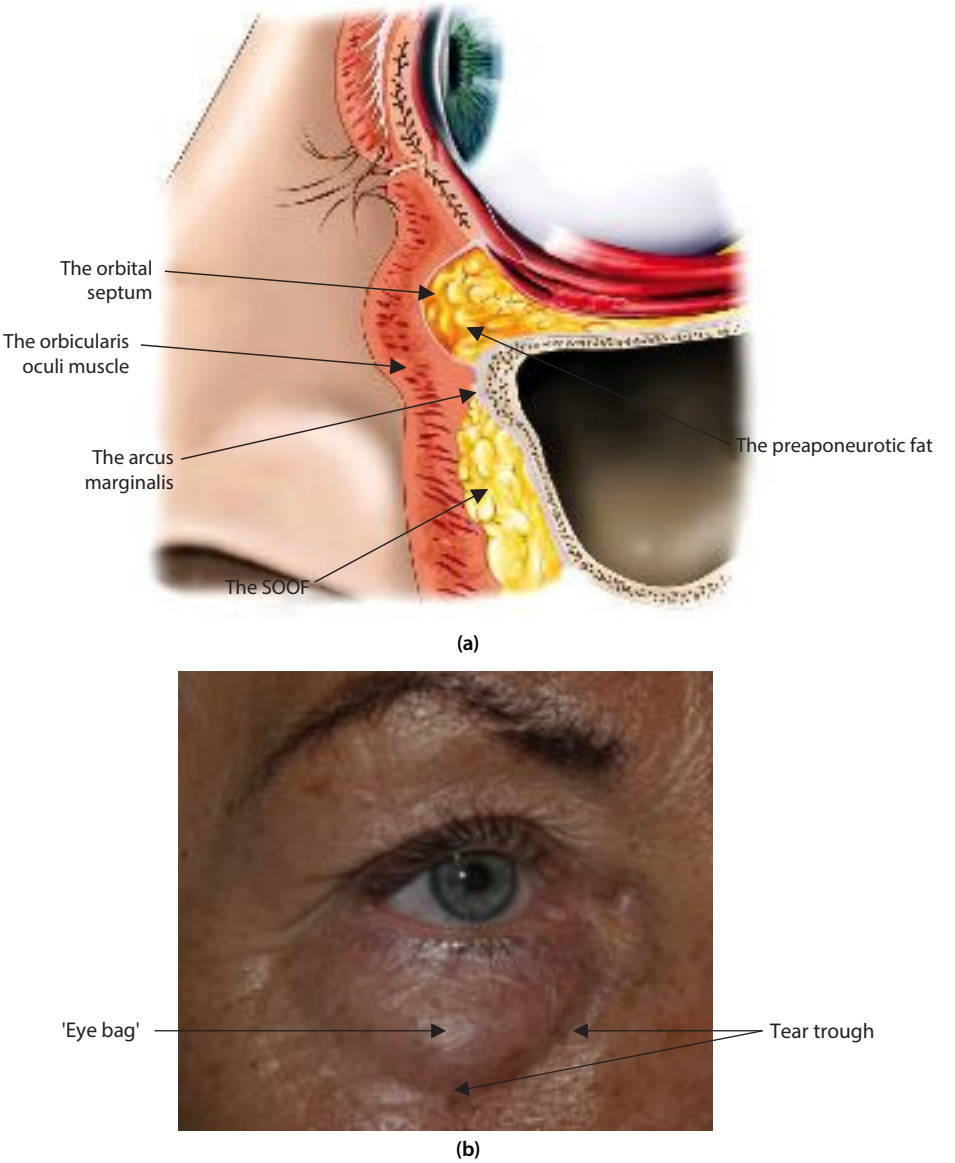


Figure 87.22 **(a)** A diagrammatic representation of bulging preaponeurotic fat through a weakened orbital septum with a secondary concavity over the inferior orbital margin responsible for the complaint of 'eyebags' and for a tear trough deformity or 'dark circle'. **(b)** A patient demonstrating the typical 'eyebag' and tear trough extending along the whole length of the inferior orbital margin.

orbital margin, and passes through the superficial musculoaponeurotic system (the SMAS) and overlying fat to insert into the dermis.

The orbitomalar ligament, the levator labii superioris and the levator alaeque nasi muscles are responsible for defining the tear trough. The tear trough extends into the upper central cheek as a triangular groove between these muscles as the malar fat descends with age.

'Malar mounds' are the result of oedema within the fat of the prezygomatic space (**Figure 87.23** below). The malar fat pad is subcutaneous, triangular and distinct from the 'malar mounds'. This fat pad contributes to the fullness of the midface. Elevation of the malar fat pad and the 'malar mounds' contributes greatly to the aesthetic appearance of the midface and can improve the appearance of the tear troughs.

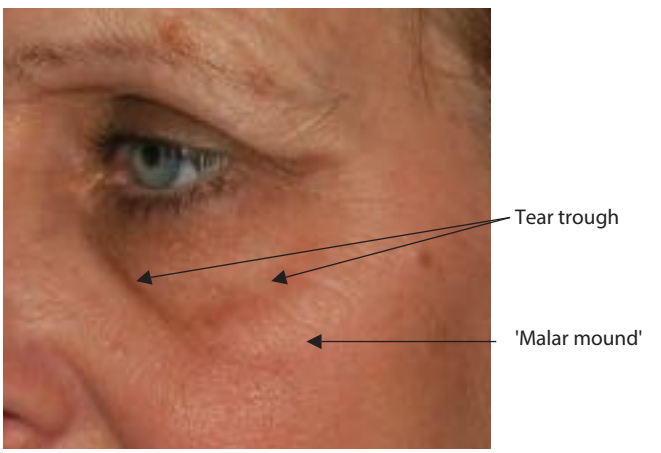


Figure 87.23 Typical age-related changes at the eyelid–cheek junction.

DERMATOCHALASIS

Dermatochalasis describes a common, physiologic condition seen clinically as sagging of the upper eyelid skin. It is typically bilateral and most often seen in patients over 50 years of age, but it may occur in some younger adults. Examination of these patients' eyelids reveals redundant, lax skin with poor adhesion to the underlying orbicularis oculi muscle. An excess fold of skin in the upper eyelid is characteristic, which obscures the normal upper eyelid skin crease which may be lost (**Figure 87.24**). This patient complained of visual field limitation and headaches towards the evening (due to frontalis muscle fatigue).

Dermatochalasis is often confused with blepharochalasis although the disorders are quite different in both their presentation and their aetiology. Blepharochalasis is a rare inflammatory condition that typically affects only the upper eyelids, and may be unilateral as well as bilateral. It occurs more often in younger patients. The condition is characterized by exacerbations and remissions of eyelid oedema, which results in a 'stretching' and subsequent atrophy of the eyelid tissue. The secondary effects of blepharochalasis include conjunctival hyperaemia and chemosis, entropion, ectropion, blepharoptosis, medial fat pad atrophy and thinning of eyelid skin.

Pathophysiology

The tissue changes seen in dermatochalasis are similar to the normal ageing changes of the skin seen elsewhere in the body. There is thinning of the epidermal tissue with a loss of elastin, resulting in laxity, redundancy and hypertrophy of the skin. The tissue changes of dermatochalasis appear to be due to repeated facial expressions combined with the effects of gravity over many years. A number of systemic disorders such as thyroid eye disease, Ehlers–Danlos syndrome, cutis laxa, renal failure and amyloidosis may hasten the development of dermatochalasis. In addition, some patients may have a genetic predisposition towards the development of dermatochalasis at a younger age.

In contrast, blepharochalasis stems from recurrent bouts of painless eyelid swelling, each instance of which may persist for several days. The swelling most likely represents a form of localized angioedema, although this remains speculative. Ultimately, after numerous episodes, the skin of the lids becomes thin and atrophic, and damage to the levator aponeurosis ensues. Blepharoptosis then develops (**Figure 87.25**). Blepharochalasis is idiopathic in most cases, though it has been linked to kidney agenesis, vertebral abnormalities and congenital heart defects in rare instances.



Figure 87.24 A female patient demonstrating bilateral brow ptosis and bilateral upper eyelid dermatochalasis.



Figure 87.25 A young female patient with blepharochalasis showing bilateral blepharoptosis with raised skin creases, thinning of the upper eyelid skin and atrophy of the preaponeurotic fat pads. She also demonstrates a bilateral pseudoproptosis from high axial myopia.

UPPER EYELID BLEPHAROPLASTY

The goals of an upper eyelid blepharoplasty are:

- to remove an appropriate amount of excess upper eyelid skin alone, or skin and orbicularis muscle, in order to achieve the best cosmetic and functional result for the patient
- to remove or sculpt herniated orbital fat only where appropriate
- to create a symmetrical upper lid skin crease at an appropriate height for the individual patient
- to avoid visible scarring
- to avoid a secondary lagophthalmos or an incomplete blink
- to avoid exacerbating an associated brow ptosis.

An additional goal in the oriental patient is to create a visible upper eyelid crease.

Pre-operative patient evaluation

HISTORY

A careful history should be obtained. The patient's complaints, goals and expectations should be determined. The patient may be concerned about:

- an overhang of excess upper eyelid skin causing a loss of the superior visual field
- excess upper lid skin causing cosmetic problems
- upper lid fat herniation

- upper lid 'fullness'
- 'hooding' of the upper eyelids
- 'drooping eyelids'
- headaches from frontalis muscle fatigue
- a tired appearance commented on by friends or relatives.

The complaint of droopy upper eyelids may simply be due to severe dermatochalasis causing a pseudoptosis with the underlying eyelid height being normal. The lid position should be carefully evaluated, however, as a true blepharoptosis may also be present. If a true blepharoptosis is present, the patient must be carefully evaluated to diagnose the underlying cause of the blepharoptosis, such as an aponeurotic dehiscence from contact lens wear, Horner syndrome, myasthenia gravis or chronic progressive external ophthalmoplegia. Similarly, a severe dermatochalasis, often combined with a brow ptosis, may obstruct the patient's superior visual field.

Patients who have a moderate to severe brow ptosis and dermatochalasis are obliged to use their frontalis muscle to overcome the superior visual field defect. Such patients commonly develop deep forehead furrows (**Figure 87.26**). This leads to fatigue of the frontalis muscle, which in turn can cause a headache.

Occasionally, upper eyelid dermatochalasis and a lateral brow ptosis can lead to a secondary mechanical misdirection of eyelashes causing chronic ocular discomfort.

The cosmetic effects of upper eyelid dermatochalasis and brow ptosis can lead to complaints of a tired appearance. Lower eyelid fat herniation can also lead to similar complaints (see **Figure 87.1b**).

Patients should be specifically questioned about previous eyelid surgery. Patients who have previously undergone a cosmetic blepharoplasty or a facelift may omit such information, particularly if accompanied by a new partner. A history of contact lens wear, dry eye, facial palsy or thyroid dysfunction identifies a patient at risk of exposure keratopathy symptoms following an upper lid blepharoplasty.

It is important to exclude a bleeding disorder, as a post-operative haemorrhage following a blepharoplasty can be potentially sight-threatening. The use of aspirin or non-steroidal anti-inflammatory agents should be discontinued 2 weeks pre-operatively if the patient's medical status permits this. Any other non-prescription medications or dietary supplements that may predispose to excessive bleeding should also be discontinued (e.g. vitamin E supplements).

Any allergies should be carefully noted.

EXAMINATION

The patient should undergo a complete ophthalmic examination.

- The patient's best corrected visual acuity should be recorded.
- The palpebral fissures should be measured and the position of the skin creases documented after lifting the upper lid excess skin.
- The height and curvature of the upper eyelids relative to the pupils should be noted, and the MRD-1 and MRD-2 should be measured and recorded, looking for any evidence of true blepharoptosis.

  (The marginal reflex distance-1 (MRD-1) is the distance between the centre of the pupillary light reflex and the upper eyelid margin with the eye in primary gaze. A measurement of 4–5 mm is considered normal. The marginal reflex distance-2 (MRD-2) is the distance between the center of the pupillary light reflex and the lower eyelid margin with the eye in primary gaze.)
- The amount of pretarsal skin 'show' should be measured and recorded along with the amount of skin present from the lash line to the lowermost portion of the eyebrow, medially, centrally and laterally. This can be difficult in patients who pluck or tattoo their eyebrows (**Figure 87.27**).
- Any asymmetries should be noted. (It is important to make the patient aware of any pre-operative asymmetries,



Figure 87.26 A patient with a severe bilateral brow ptosis and dermatochalasis causing visual field problems and headaches from frontalis overaction.

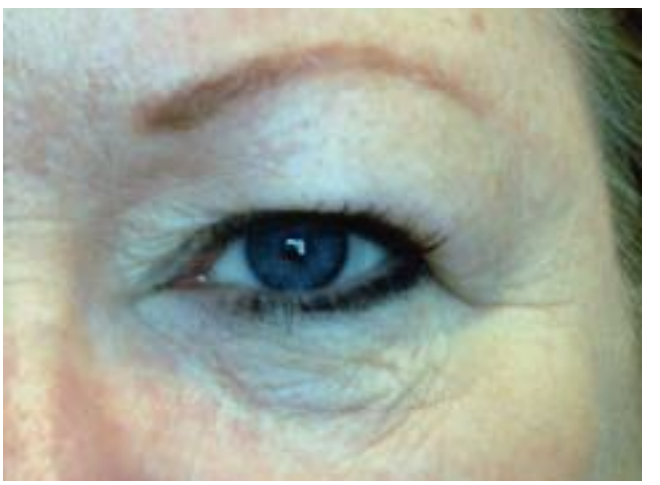


Figure 87.27 A patient with a plucked and tattooed eyebrow camouflaging the effects of a brow ptosis and a descent of the 'ROOF'.

which they may not have noticed. The patient will certainly notice asymmetries post-operatively!) Any frontalis overaction should be noted, and the position and shape of the brows observed after asking the patient to relax the frontalis muscle as much as possible. The secondary effects of brow ptosis on the upper eyelids must be recognized (see **Figure 87.24**).

- An assessment of the tear meniscus should be made using a slit lamp, and the tear film break-up time after the instillation of a drop of fluorescein should be documented.
- The upper lids should be everted to exclude the presence of any subtarsal lesions (e.g. papillae seen in atopy or with contact lens wear).
- The presence or absence of a Bell's phenomenon should be recorded.
- The degree of upper eyelid laxity is assessed to ensure that a 'floppy eyelid syndrome' is not overlooked. This is done by pulling downwards on the eyelid after grasping the eyelid margin and the eyelashes in the lateral aspect of the eyelid. Excessive eyelid laxity is also evident if eversion of the upper eyelid is very easy to perform.
- Any herniation of the medial and central preaponeurotic fat pads is noted in the upper eyelids, and of the medial, central and lateral preaponeurotic fat pads in the lower eyelids.
- The degree of excess upper eyelid skin is assessed and measured.
- The degree of any associated brow ptosis is noted along with any asymmetry. Any overaction of the eyebrow depressor muscles is also determined by noting the extent of glabellar frown lines and lateral canthal rhytids.
- The skin quality and degree of actinic damage is assessed. Specific dermatological disorders should be excluded (e.g. atopic dermatitis).
- The ocular motility should be assessed and recorded along with cover and alternate cover tests to exclude any horizontal or vertical ocular muscle imbalance.
- Any proptosis or pseudoproptosis due to axial myopia is noted. It may be much more difficult to achieve the desired surgical goals in such patients.
- The patient should be examined specifically to exclude the possibility of thyroid eye disease.

Pre-operative photographs must be taken. Pre-operative photographs are essential for patients who are to undergo any facial plastic and reconstructive surgery. They serve a number of useful purposes:

- a learning and teaching aid for the surgeon
- verification of the patient's disorder for healthcare insurance companies
- an aid to defence in a medicolegal claim
- to jolt the memory of the forgetful patient about their pre-operative appearance.

Written patient consent should be obtained before the photographs are taken. It should be made clear to the patient how the photographs are to be used.

The limitations of an upper eyelid blepharoplasty performed alone in the presence of significant brow ptosis should be explained. In these circumstances, an upper eyelid blepharoplasty should be very conservative in order to prevent further lowering of the brow and an unsatisfactory appearance. The patient should be carefully questioned to ascertain their expectations of surgery. Some patients with a mild degree of brow ptosis and upper lid dermatochalasis are better managed with the use of botulinum toxin injections, which, if used correctly, can create a satisfactory and pleasing brow lift. The injection can be given into the lateral rhytids and tail of the eyebrow (30–60 units of Dysport® per side given as four or five separate intramuscular injections), and can be combined with injections into the glabella (80–120 units of Dysport® given as four to six separate intramuscular injections) paralyzing the brow depressors and allowing the frontalis muscle to act unopposed. If an unwanted temporal peaking of the brows occurs, 5–10 units of botulinum toxin can be injected 1–2 cm above the lateral brow into the overacting frontalis.

If botulinum toxin injections are to be used as a trial prior to surgery, this should be undertaken 2 weeks beforehand. The injections should not be given at the time of surgery as post-operative oedema will cause the toxin to spread to other muscles (e.g. to the levator muscles), causing a blepharoptosis.

Where a brow ptosis is significant, it is far preferable to address this by one of a number of surgical approaches, depending on the degree of brow ptosis and the age and preferences of the patient. The options for a brow lift procedure include:

- direct brow lift
- 'gull wing' direct brow lift
- temporal direct brow lift
- internal suture browpexy
- transblepharoplasty Endotine implant brow lift
- mid-forehead brow lift
- subcutaneous forehead and brow lift
- pretrichial brow lift
- coronal brow lift
- endoscopic brow lift
- brow lift using dissolvable 'coned' suture devices.

Figure 87.28a illustrates the problem posed by a female patient requesting an upper eyelid blepharoplasty who demonstrates a bilateral brow ptosis. A blepharoplasty alone would be inappropriate. **Figure 87.28b** demonstrates her post-operative appearance 4 months following a bilateral upper eyelid skin/muscle blepharoplasty combined with a bilateral endoscopic brow lift.

INFORMED CONSENT

The advantages, disadvantages, risks and potential complications of the procedure should be discussed with the patient in great detail. The siting of incisions and anticipated scars should be explained. The risks and the incidence of complications need to be outlined in an open and



Figure 87.28 (a) A female patient with bilateral brow ptosis and upper eyelid dermatochalasis. **(b)** The same patient 4 months following a bilateral endoscopic browlift and upper lid blepharoplasty.

honest manner. The consequences of complications and their management should also be outlined. The patient should also be provided with a formal document which outlines the potential complications of blepharoplasty surgery, their management and the financial responsibilities that would be incurred.

The description of any blepharoplasty procedure as 'basic', 'straightforward', 'simple', 'minor' or 'routine' should be avoided.

Many patients seeking cosmetic blepharoplasty request that their general practitioner is not informed. A detailed letter outlining the patient's complaints, the clinical findings, the management options which have been discussed, the risks and potential complications of surgery, advice about the discontinuation of aspirin or anti-inflammatory drugs, the anticipated recovery period and aftercare instructions should, however, be sent to the patient and retained in their clinical records. The patient should be encouraged to give further consideration to the options discussed before making a decision to proceed with surgery. This also avoids any misunderstandings on the part of the patient. It may necessitate a further consultation or an attendance at a pre-assessment clinic to obtain fully informed consent and to answer any residual queries. The patient should not be asked to sign a consent form for an elective cosmetic procedure on the day of surgery.

Surgical technique

MARKING THE UPPER EYELID

Marking the upper eyelid skin crease with the patient sitting upright, before the injection of any local anaesthetic solution, is the first very important step in a successful upper eyelid blepharoplasty. A drop of proxymetacaine is instilled into each eye. The upper eyelid skin is cleaned with an alcohol wipe, and the skin crease marked with a cocktail stick that has been dipped into a gentian violet marker block. A calliper should be used to measure the height of the crease. The fellow eyelid should be marked simultaneously, ensuring precise symmetry. The skin crease should be marked at a lower level in a male patient.



Figure 87.29 Marking the eyelid. The skin just above the skin crease marking is gently pinched with toothed forceps to ensure that passive closure of the eye is not compromised. This is repeated medially and laterally and the proposed skin excision is marked.

The skin above the crease centrally is gently pinched with a pair of fine-toothed forceps. Great care should be taken to ensure that the eyelids can close passively. Any temptation to remove more than 8–10 mm of skin should be resisted, particularly in the presence of an uncorrected brow ptosis. The superior aspect of the pinched skin is marked and an ellipse is drawn (**Figure 87.29**).

The relative dimensions of this area divided into thirds should be remembered to maintain a good aesthetic appearance. (The distance between the inferior aspect of the eyebrow and the upper lid skin crease on downgaze should be approximately two-thirds of the distance from the inferior aspect of the eyebrow to the eyelid margin. Likewise, the distance from the skin crease to the eyelid margin in downgaze should be one-third of the distance from the inferior aspect of the eyebrow to the eyelid margin.) In general, at least 10–12 mm of skin should be left between the inferior aspect of the eyebrow and the superior skin excision marking (**Figure 87.30**). It is important

not to carry the incision markings into the medial canthal area to avoid webbed scars.

If there is no temporal hooding of skin, the lateral aspect of the incision should be kept within the orbital margin (**Figure 87.30**). If there is temporal hooding, a lateral wing can be added to the crescent leaving the resulting scar running in a horizontal direction (**Figure 87.31**). The patient should be warned that this lateral scar will be visible and will not be hidden with the upper lid skin crease.

ANAESTHESIA

The procedure may be undertaken under general anaesthesia, local anaesthesia or local anaesthesia with intravenous sedation. Local anaesthesia, preferably with carefully titrated intravenous sedation provided by an anaesthetist, is advantageous as it allows voluntary levator muscle function to be used to assist in the identification of eyelid structures. This is particularly important when an upper eyelid blepharoplasty is being performed in conjunction with a levator aponeurosis advancement procedure to correct blepharoptosis.

The patient should be kept in a semirecumbent position with the head elevated at least 30 degrees to reduce venous engorgement and bleeding. Normal saline sachets should be kept available in the refrigerator and used to moisten 4 × 4 gauze swabs, which are applied to the operated side while the fellow side is undergoing the same procedure.



Figure 87.30 Eyebrow–superior skin excision mark distance. Here 12 mm of skin has been left between the inferior aspect of the eyebrow and the superior skin excision marking.



Figure 87.31 Final markings. The desired position of the upper eyelid skin crease has been marked with a cocktail stick dipped into a gentian marker block. The skin above the crease has been gently pinched while asking the patient to passively close the eye at the same time as an assistant gently raised the eyebrow with a finger. The markings are not taken medially beyond the limit of the skin crease. Laterally a small 'wing' has been added in this patient to prevent a 'dog ear'. A distance of 10–12 mm has been left between the inferior aspect of the brow and the superior aspect of the skin resection all along the length of the skin marking.

SURGICAL PROCEDURE

1. Approximately 2–3 mL of 0.5% marcain with 1:200 000 units of adrenaline mixed 50:50 with 2% lignocaine with 1:80 000 units of adrenaline are injected just beneath the skin with a single pass of the needle if possible, avoiding the underlying orbicularis oculi muscle in order to prevent the occurrence of a haematoma. The needle is inserted temporally and advanced nasally while slowly injecting the solution. Immediate pressure should be applied for a few minutes. A pause of 10 minutes is allowed for the adrenaline to take effect.
2. The patient is prepped and draped, ensuring that the drapes do not place any downward pressure on the eyebrows.
3. A 4.0 silk traction suture is inserted along the grey line of the upper eyelid and fixated to the face drapes with a curved artery clip, providing downward traction on the eyelid. This makes the skin incision easier to undertake and provides protection for the eye.
4. The skin incision is made along the gentian violet markings with a Colorado needle.
5. A skin flap is developed and dissected off the underlying orbicularis oculi muscle (**Figure 87.32**). A strip of orbicularis muscle can then be dissected off the underlying orbital septum. If the patient merely requires the removal of excess skin, and any orbicularis muscle for functional reasons, the skin can be closed with simple interrupted 7-0 Vicryl sutures. This surgical procedure is quick and relatively simple to perform and does not expose the patient to the small risks of a postoperative intraorbital haemorrhage.

   In patients who are at an increased risk of exposure keratopathy, a simple skin excision alone can be performed, preserving the underlying orbicularis muscle. In some patients, however, this can result in some bunching of the orbicularis muscle with a less satisfactory aesthetic result. Alternatively, a central 3–5 mm strip of orbicularis muscle can be removed.
6. If the patient requires the removal, sculpting or redraping of orbital fat, the orbital septum is opened along its entire length.
7. The central preaponeurotic fat is allowed to prolapse. This can be sculpted with the Colorado needle using the coagulation mode and any larger vessels cauterized with bipolar cautery. The fascial septa around

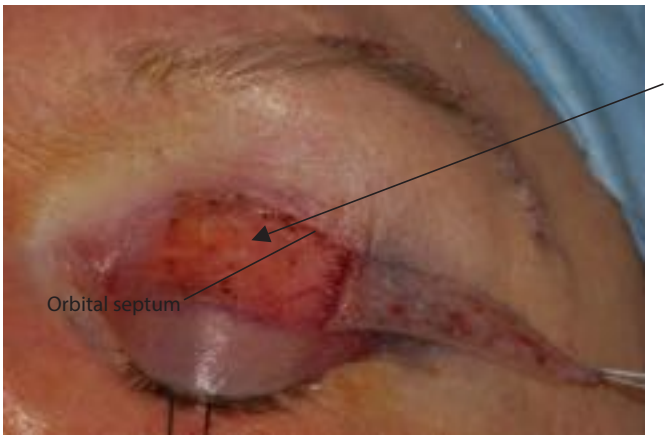


Figure 87.32 A skin flap has been created, exposing the underlying orbicularis oculi muscle. This patient has also undergone a temporal direct brow lift.

and within the medial fat pad can be gently opened and separated using the Colorado needle.

8. If fat needs to be removed, the fat should be carefully clamped using a small curved artery clip. The artery clip should be held carefully by the assistant. Great care should be taken to avoid anterior traction on the fat that can lead to rupture of posterior orbital vessels and a sight-threatening retrobulbar haematoma. The fat is removed using the Colorado needle on cautery mode. The artery clip should be released very slowly and carefully, and immediately reapplied if any vessels bleed. This is particularly important when removing fat medially. Great care should also be taken not to damage the medial horn of the levator muscle or the trochlea. It should be noted, however, that fat removal should be undertaken very conservatively, if at all, in the upper lid so as to avoid a secondary hollowing of the upper eyelid, which can result in a very aged appearance. The fat should be retained within a swab moistened with sterile saline as it may be divided into small fat pearls and used as a free graft in the opposite upper eyelid to address an asymmetry or in the lower eyelid to assist in the camouflage of a tear trough defect.
9. The skin is closed with interrupted 7-0 Vicryl sutures, taking bites of the very edges of the skin. The type of skin closure is determined by the type of skin crease that is required. If this is to be a soft, less well-defined crease, the skin can be closed as above. If a higher, well-defined crease is required, usually in a female, the skin is closed with interrupted 7-0 Vicryl sutures that incorporate a bite of the underlying levator aponeurosis. It is sometimes advantageous to remove a strip of orbicularis muscle from the inferior skin wound edge but this can lead to bleeding, particularly if the effects of the adrenaline have begun to wear off.

POST-OPERATIVE CARE

Post-operatively the patient is prescribed a topical antibiotic ointment to be applied to the upper lid wounds three times a day for 2 weeks and Lacri-Lube® ointment 1–2 hourly to the eyes for 48 hours and at bedtime. The Lacri-Lube® ointment is then changed to preservative-free topical lubricant drops to be used hourly during the day and Lacri-Lube® is continued at bedtime until the degree of lagophthalmos has improved. The frequency of the lubricants is then gradually reduced over the course of the next few weeks. The patient is instructed to sleep with the head of the bed elevated for 4 weeks and to avoid lifting any heavy weights for 2 weeks. Clean cool packs are gently applied to the eyelids intermittently for 48 hours. The patient should be reviewed in clinic within 2 weeks and again within 4–6 weeks. The upper lid skin sutures are removed at 2 weeks.

LOWER EYELID BLEPHAROPLASTY

The goals of a lower eyelid blepharoplasty are:

- to remove an appropriate amount of excess lower eyelid skin and muscle if required
- to remove or reposition herniated fat where appropriate
- to avoid middle lamellar scarring and eyelid retraction
- to address any associated lower eyelid or lateral canthal tendon laxity
- to avoid any post-operative ectropion and secondary epiphora.

An emerging concept in cosmetic surgery holds that the face develops the characteristics of ageing as a result of not only elastosis and sagging but also soft-tissue atrophy. The evolution of this concept is well illustrated in the field of lower lid blepharoplasty, in which the traditional approach to the surgical improvement of lower eyelid 'bags' has been to resect the herniating preaponeurotic fat. While this method can indeed remove 'bags', in many patients it may also eliminate the soft tissue that conceals the inferior orbital margins, creating a hollowed, skeletonized appearance. This is in contrast to the appearance of the youthful face, in which soft-tissue fullness creates a smooth transition from the cheek to the lower eyelid. The inferior bony orbital margin is concealed. The traditional approach of resecting orbital fat is therefore unlikely to produce a full, youthful lower lid contour and conflicts with the concept that facial ageing is partly a consequence of soft-tissue atrophy.

A number of alternative surgical approaches have been devised to address this problem. One such technique that has gained prominence is the arcus marginalis release, in which preaponeurotic fat is advanced and repositioned rather than resected, in order to reconstruct the soft tissue of the lower eyelids. This technique is designed to conceal the underlying bony structure of the inferior orbit in an attempt to impart a more youthful contour to the periorbital area. Alternatively, a SOOF lift or a midface lift may be undertaken in conjunction with a lower eyelid blepharoplasty in order to achieve the same goals, but the patient then has to accept a more extensive surgical dissection and a longer period of recuperation with more post-operative bruising and swelling.

Pre-operative patient evaluation

HISTORY

The patient's complaints, goals and expectations should be determined. The patient may be concerned about:

- loose folds of skin
- lower eyelid 'bags'
- dark circles beneath the eyes
- skin wrinkles and/or signs of photodamage
- malar mounds
- lower eyelid 'festoons'.

EXAMINATION

As for an upper eyelid blepharoplasty, the patient should undergo a complete ophthalmic examination.

- The patient's best-corrected visual acuity should be recorded.
- The palpebral fissures should be measured and the position of the lower eyelid with respect to the inferior limbus noted. The MRD-1 and MRD-2 should be measured and recorded.
- Any asymmetries or scleral show should be noted.
- The patient's lower lid appearance at rest and on smiling should be compared.
- The relationship of the globe to the inferior orbital margin should be noted, particularly the degree to which the globe protrudes beyond the inferior orbital margin in profile view. A globe which protrudes beyond the inferior orbital margin is referred to as a 'negative vector' configuration. Such patients are more at risk of post-operative problems with eyelid retraction and scleral show following a lower eyelid transcutaneous blepharoplasty.
- An assessment of tear production and the tear film should be undertaken using a slit lamp and the findings documented.
- Any 'herniation' of the lower eyelid fat pads is noted and their positions documented. The skin quality and degree of actinic damage is assessed.
- The degree of lower eyelid laxity is assessed. This can be quite subjective but, as a general rule, if the lower eyelid can be distracted from the globe by more than 6–8 mm or if the eyelid does not return to its position after release without a blink (a positive 'snap test'), the eyelid can be considered to have sufficient laxity to warrant a lower eyelid tightening procedure.
- Any proptosis or pseudoproptosis due to a large globe is noted. It may be more difficult to achieve the surgical goals in such a patient. The patient should be examined specifically to exclude the possibility of thyroid eye disease.
- The appearance of the infraorbital margin is carefully assessed. Almost any patient seeking a lower eyelid blepharoplasty with lower eyelid 'bags' and/or a skeletonization of the inferior orbital margin is a candidate for an arcus marginalis release. In contrast, however, younger patients with a congenital excess of orbital fat are less likely to benefit from this technique. These patients are better managed using a traditional resection of the excess fat via a transconjunctival approach, with the use of CO_2 skin resurfacing or a chemical peel to manage any associated lower eyelid skin wrinkling and photodamage.

Just as the upper lid cannot be properly assessed without also taking into consideration the position of the eyebrow, the lower lid should not be examined in isolation but account should be taken of any associated midface ptosis and midface fat atrophy. Such a patient may require a SOOF lift, or a midface lift and/or volume augmentation of the cheek and tear trough using dermal fillers or structural fat grafting.

INFORMED CONSENT

The guidelines for consent are as detailed in 'Upper eyelid blepharoplasty' above.

Surgical approaches

A lower eyelid blepharoplasty procedure should ideally be tailored to the individual requirements of a patient. The surgical approach selected depends on a pre-operative assessment of fat 'herniation', the degree of skeletonization of the inferior orbital margin, the presence of a lower lid double convexity, the amount of excess lower eyelid skin, the degree of static wrinkling and actinic damage, the degree of orbicularis oculi muscle ptosis, the presence and degree of midface ptosis and midface fat atrophy, the presence of 'malar mounds' or festoons, and the degree of lower eyelid or lateral canthal tendon laxity. The procedure may be performed in conjunction with another surgical procedure (e.g. an orbital decompression procedure in thyroid eye disease).

The patient should be carefully evaluated to determine whether alternative non-surgical treatments might be better suited to their needs. This will depend on the patient's individual circumstances and age. Some patients with the complaint of lateral canthal rhytids ('laughter lines') and lateral eyelid skin wrinkling alone may be better managed with botulinum toxin injections. These can be given into the lateral rhytids (30–60 units of Dysport® per side given

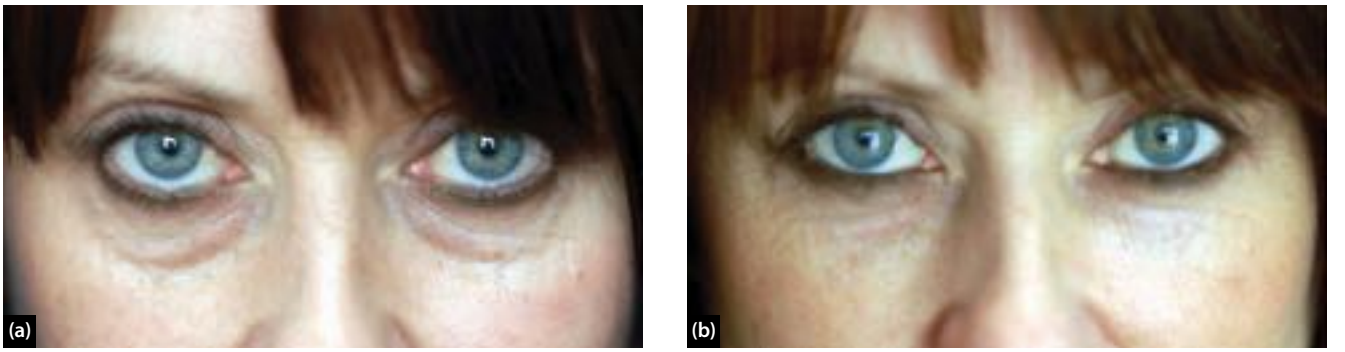


Figure 87.33 (a) Bilateral lower eyelid 'tear tough' defects. **(b)** The appearance of the same patient 2 weeks following the injection of a hyaluronic acid filler (Restylane®) along the inferior orbital margins.

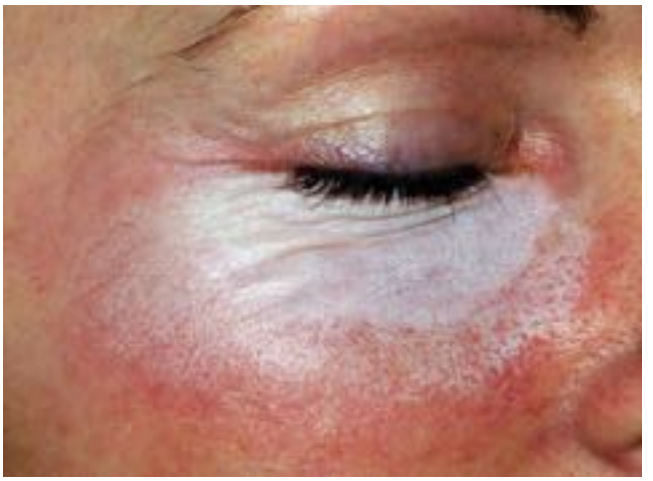


Figure 87.34 A lower eyelid 35% Jessner's/TCA peel.

as four or five injections) with the addition of tiny amounts to the lateral lower lid orbicularis muscle (two or three injections of 2–3 units of Dysport®). Injections should not be given in the medial aspect of the lower eyelid, as this is associated with the risk of spread to involve the inferior oblique muscle. In addition, higher doses should be avoided in the lower eyelid to avoid undue weakness to the orbital portion of the orbicularis muscle with the risk of the patient developing a malar 'bag'.

Hyaluronic acid filler injections (e.g. Restylane® or Juvéderm®) can be used to camouflage the tear toughs in suitable candidates (see **Figure 87.28**). Alternatively, a Jessner's/trichloroacetic acid peel (TCA) or CO_2 laser resurfacing can be considered to treat age- and solar-related skin wrinkling in the lower eyelids (**Figures 87.33** and **87.34**).

For patients who are better suited to surgical management there are two main surgical approaches:

- transcutaneous lower lid blepharoplasty
- transconjunctival lower lid blepharoplasty.

These procedures can be supplemented by other techniques to enhance the result:

- horizontal eyelid tightening procedure
- 'pinch' technique skin resection (in the case of a transconjunctival lower lid blepharoplasty)
- CO_2 laser resurfacing
- Jessner's/TCA peel
- botulinum toxin injections
- injection of dermal fillers or autogenous fat to provide soft tissue enhancement
- SOOF lift
- midface lift
- placement of a cheek implant.

A transconjunctival approach is preferred for patients with 'fat herniation' but no significant skin excess. This approach avoids an external scar and is also ideal for patients who have previously undergone a transcutaneous blepharoplasty but who require revision surgery for residual 'fat herniation'. It can be combined with CO_2 laser resurfacing or with a Jessner's/TCA peel to deal with skin wrinkling in those patients who are prepared to cooperate with the more onerous post-operative care and the avoidance of sun exposure (**Figure 87.35**).

Surgical technique

A lower eyelid blepharoplasty can be performed under general anaesthesia, local anaesthesia or local anaesthesia with intravenous sedation. Local anaesthesia affords the surgeon the opportunity of asking the patient to look up and to open the mouth to avoid excessive skin resection during a transcutaneous blepharoplasty. The patient should be draped using non-adhesive drapes to allow free movement of the lower eyelid and cheek. The upper lid skin crease may need to be marked or, if the procedure is to be combined with an upper lid blepharoplasty, the upper lid skin excision should be marked as described above.

TRANSCUTANEOUS BLEPHAROPLASTY WITH ARCUS MARGINALIS RELEASE, FAT REPOSITIONING AND ORBICULARIS OCULI MUSCLE SUSPENSION

The patient is advised pre-operatively that the lateral aspect of the lower eyelids will be unnaturally high for the first 2–3 weeks following this procedure. As the absorbable 5–0 Vicryl suture holding the orbicularis muscle flap in place begins to give way, the lateral aspect of each lower eyelid gradually assumes its normal position.

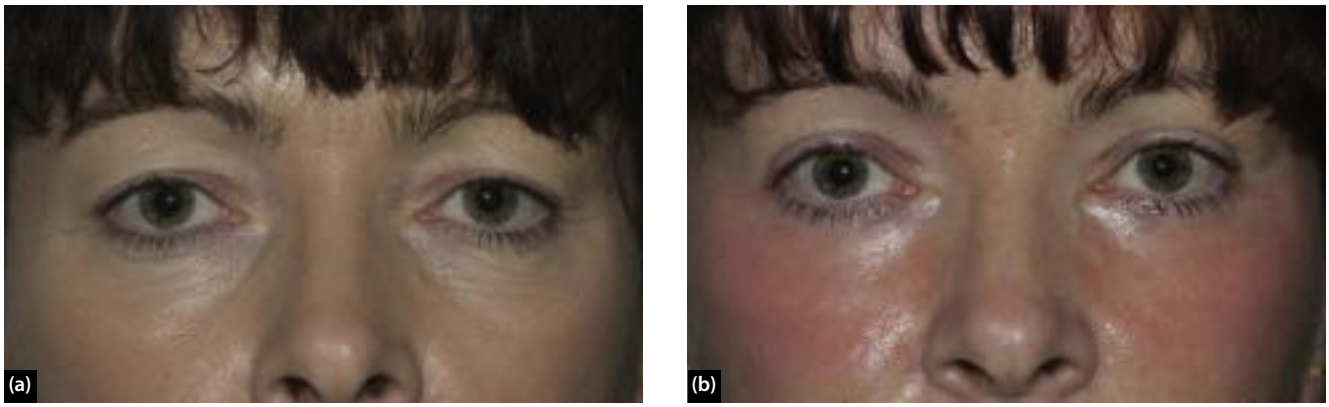


Figure 87.35 (a) The pre-operative appearance of a patient with moderate lower eyelid rhytids. **(b)** The post-operative appearance of the same patient 2 weeks following a bilateral upper eyelid blepharoplasty and lower eyelid CO_2 resurfacing (prior to the application of camouflage mineral make-up) demonstrating improvement in skin wrinkling but with typical post laser erythema.

Surgical procedure

1. Approximately 2–3 mL of 0.5% marcain with 1:200 000 units of adrenaline mixed 50:50 with 2% lignocaine with 1:80 000 units of adrenaline are injected with aouipl single injection just beneath the skin along the lower eyelid just below the tarsus and a further 2 mL is injected along the upper lid skin crease. The needle is inserted temporally and advanced nasally while slowly injecting the solution. Immediate pressure is applied. A pause of 10 minutes is allowed for the adrenaline to take effect.
2. The patient is prepped and draped.
3. A 4-0 silk traction suture is placed through the grey line of the lower eyelid and fixated to the head drape with a curved artery clip. A subciliary incision is made with a Colorado needle 1.5 mm below the eyelid margin to avoid damaging the eyelash follicles. This is commenced just beneath the inferior punctum and extends to the lateral canthus where it is continued within a lateral rhytid for a few millimetres (**Figures 87.36** and **87.37**). The dissection plane first passes subcutaneously for a few millimetres until the inferior margin of the tarsus is reached, at which point the dissection plane passes deep to the orbicularis oculi muscle (**Figure 87.37**). In this way, the pretarsal orbicularis oculi muscle is preserved, thereby minimizing the risk of denervation and, consequently, a paralytic eyelid ectropion.
4. A skin–muscle flap is dissected from the underlying orbital septum down to the inferior orbital margin.
5. Now exposed, the arcus marginalis is incised using the Colorado needle from a medial to lateral direction along the infraorbital rim, taking care to avoid the inferior oblique muscle and the lateral canthal tendon (**Figure 87.37**).
6. The septum and released preaponeurotic fat are then advanced over the inferior orbital margin. If necessary, the lateral fat pad may be trimmed as it may not be possible to reposition this adequately. It is very important to avoid undue traction on the fat pads in order to avoid tearing deep orbital veins which can in turn lead to a sight-threatening retrobulbar haemorrhage. The fat should not be discarded, however, as it can be placed over the inferior orbital margin and used to further recontour the nasojugal groove and the lateral tear tough. Likewise, fat removed during the course of a simultaneous upper lid blepharoplasty should not be discarded. Any fat removed should be kept in a swab moistened with saline and reimplanted without undue delay.
7. The fat pads may need to be sculpted to achieve a smooth contour. Meticulous technique is critical at this stage, since irregularities in the contour of the advanced fat pads are noticeable through the skin. The advanced septum and orbital fat are reset (as a unit) onto the periosteum of the maxilla inferior to the orbital rim with interrupted 5-0 Vicryl sutures (**Figures 87.38** and **87.39**).



Figure 87.36 A subciliary incision is made with a Colorado needle with the lower eyelid placed on traction.

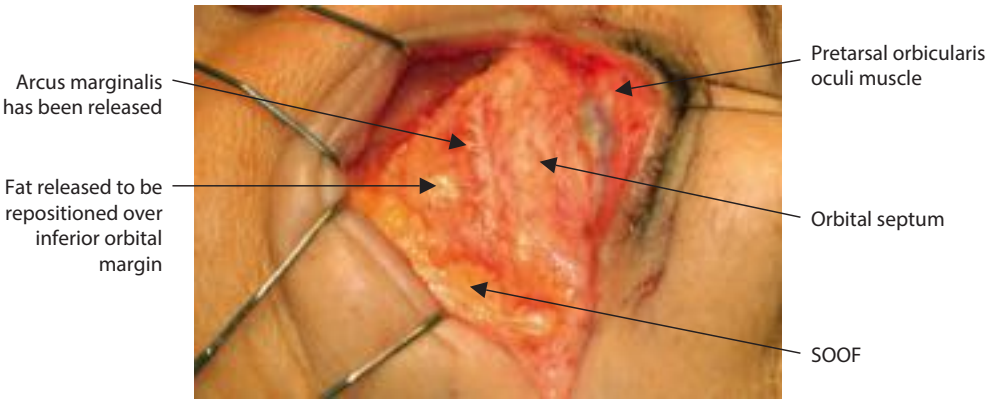


Figure 87.37 The anatomy of the left lower eyelid as seen during the course of a transcutaneous lower lid blepharoplasty.

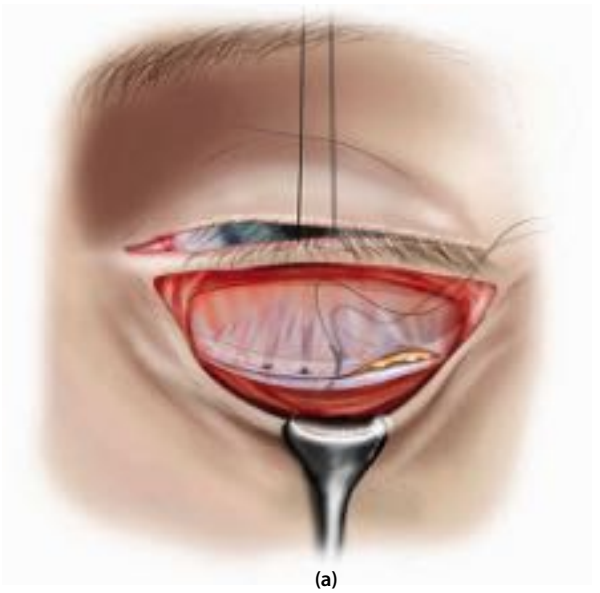




Figure 87.38 (a) Diagram showing the septum and fat being advanced over the inferior orbital margin and sutured to the periosteum just below the inferior orbital margin. **(b)** Intra-operative photograph of the septal reset procedure.



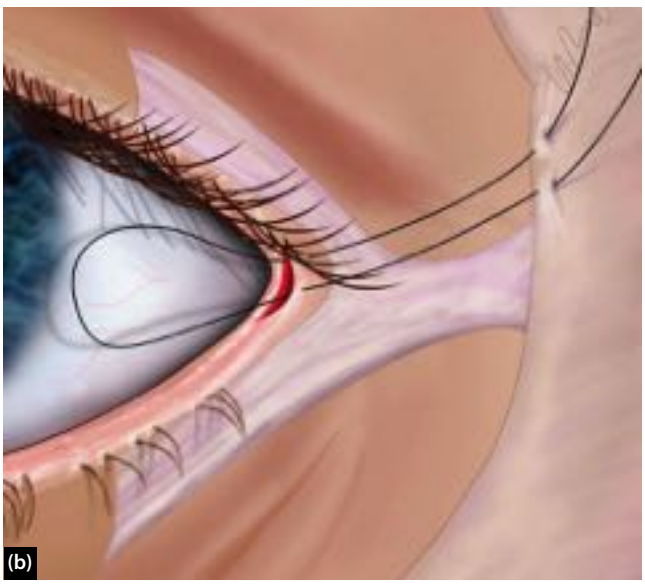
Figure 87.39 A more convex eyelid–cheek junction is created as the septal reset is performed and the orbicularis muscle is moved superolaterally.

8. The septum should be reset under minimal tension to avoid scleral show or an ectropion. If resetting the septum results in any eyelid retraction, the fat alone can be repositioned and sutured.
9. A lateral upper lid skin incision is made using the Colorado needle. The dissection is carried down through the orbicularis muscle to the orbital septum. This is then traced to the lateral orbital margin where the periosteum is exposed.
10. Stevens scissors are then used to bluntly dissect beneath the lateral orbicularis oculi muscle creating a tunnel (**Figure 87.40**).
11. A lateral tightening procedure may be required depending on the degree of lower lid laxity and should be performed before the septum is repositioned in order to establish and stabilize the position of the eyelid (**Figure 87.41**). (This is in fact very rarely required in patients under the age of 60 years.) Using a 15 blade, a tiny incision is made at the lateral commissure. A double-armed 5-0 Prolene suture on a round-bodied needle is passed through the incision, emerging through the lateral upper lid incision.



Figure 87.40 Stevens scissors are used to create a tunnel under the lateral orbicularis oculi muscle. In this patient, the lower eyelid blepharoplasty is being combined with an upper eyelid blepharoplasty.





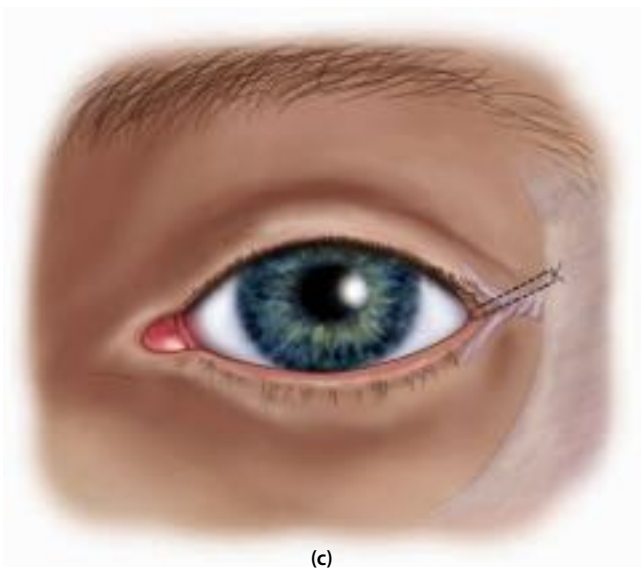




Figure 87.41 (a) Laxity of the lower eyelid with inferior scleral 'show'. **(b, c)** A lateral canthal tightening suture. The lateral canthal tendon and the lateral orbital margin are exposed via a lateral upper lid skin crease incision. **(d)** An intra-operative photograph showing the placement of the Prolene suture through a small incision at the lateral commissure. *(Continued)*

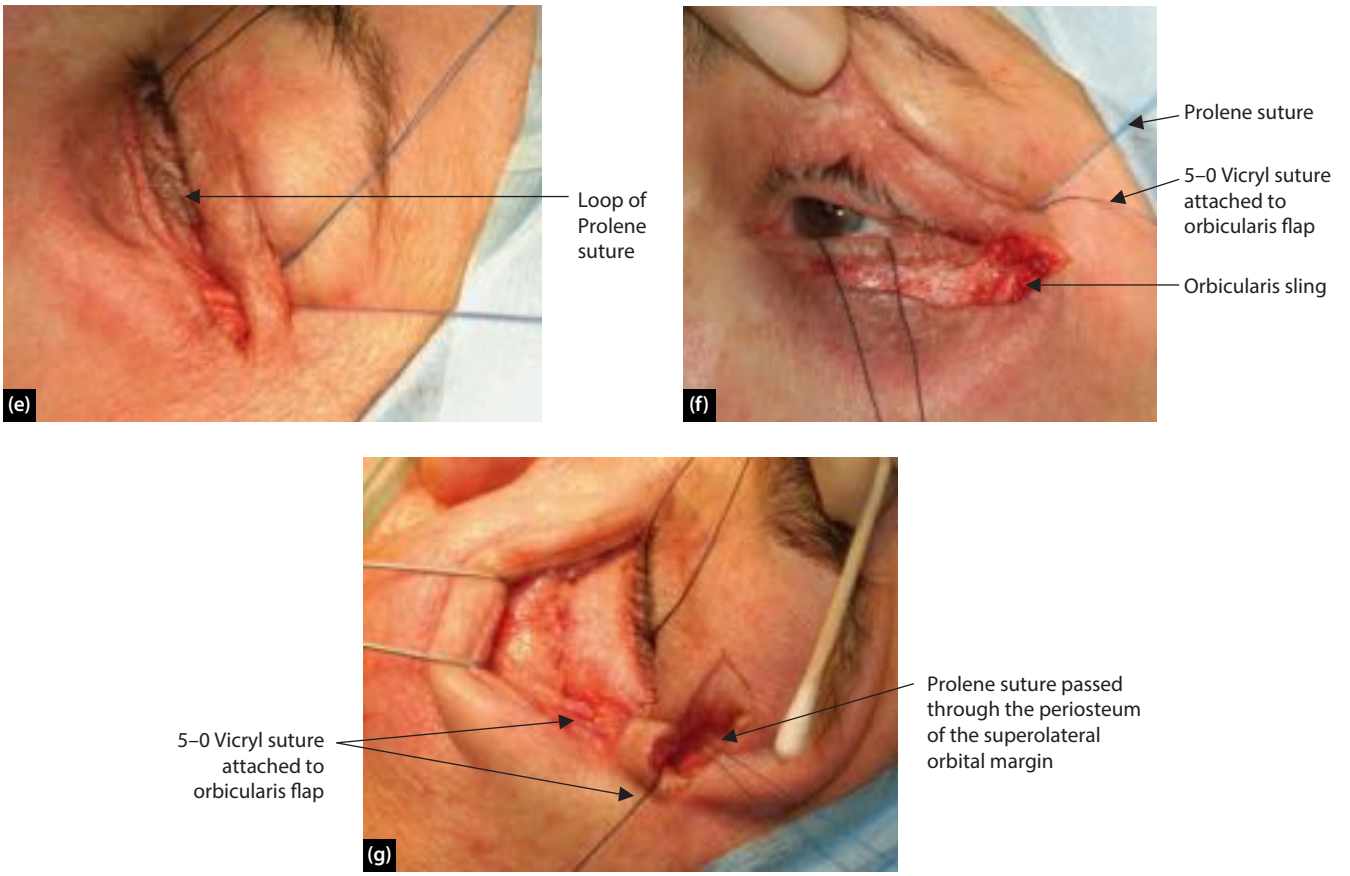


Figure 87.41 (Continued) **(e)** The loop of the Prolene suture is seen between the upper and lower eyelids laterally before the suture is tightened. **(f)** The Prolene suture has been tightened. The lower eyelid contour and height are checked to ensure that these are satisfactory. **(g)** The placement of the Prolene suture through the periosteum of the superolateral orbital margin is demonstrated.

Each needle is then passed through the periosteum of the internal aspect of lateral orbital wall in a medial to lateral direction and tied on the external surface of the lateral orbital wall, burying the knot (see **Figure 87.35**). Greater degrees of laxity of the lower eyelid and lateral canthal tendon should be addressed using a lateral tarsal strip procedure.

12. The orbicularis oculi muscle is now repositioned. With the use of this manoeuvre, lateral eyelid tightening is rarely if ever required in patients under the age of 60 years. From the dissection plane already created superficial to the septum and arcus marginalis, the lower lateral orbicularis is elevated off the underlying malar eminence with Westcott scissors, extending inferiorly in the submuscular plane as far as necessary to free the muscle's inferior border.
13. After separating the orbicularis oculi muscle from the skin of the lower lateral eyelid using Westcott scissors, a triangular muscle pedicle is created, with the base anchored inferolateral to the lateral canthus (**Figure 87.42**). Any redundant orbicularis muscle medial to the pedicle is removed with Westcott scissors.
14. A double-armed 5-0 Vicryl suture on a half circle needle is passed through the orbicularis flap and the suture is passed under the bridge of skin and orbicularis muscle at the lateral canthus.
15. The needles are passed through the periosteum of the superolateral orbital margin from medial to lateral and tied (**Figure 87.43**).
16. Moderate tension is maintained on the lower eyelid traction suture to prevent an over-resection of skin. If the surgery has been performed under local anaesthesia, the patient is asked to look up and to open the mouth to further assist in ensuring that an over-resection of skin is avoided. The skin is incised vertically at the lateral canthus using straight iris scissors. The redundant skin is then excised medial and lateral to the vertical incision using the same straight scissors (**Figure 87.44**). Care is taken to manage any residual dog ear at the temporal aspect of the wound. No skin should be removed from the medial two-thirds of the eyelid in the vast majority of cases. The skin resection should always be conservative.
17. The skin edges are then re-apposed using interrupted 7–0 Vicryl sutures.
18. The traction suture is removed.
19. The upper lid blepharoplasty wound is closed with interrupted 7–0 Vicryl sutures.

Post-operative care

Post-operatively the patient is prescribed a topical antibiotic ointment to the upper and lower lid wounds



Figure 87.42 **(a)** Diagram demonstrating the creation of an orbicularis oculi muscle flap. **(b)** Intra-operative photograph showing a triangular flap of orbicularis oculi muscle being held with forceps. The redundant skin has been folded back on itself.



Figure 87.43 **(a)** Vicryl sutures with the attached orbicularis flap are passed beneath the intact bridge of skin and muscle laterally. The sutures are passed through the periosteum of the superolateral orbital margin. **(b)** Intra-operative photograph demonstrating the effect achieved when tension is applied to the sutures which are attached to the orbicularis flap.

three times a day for 2 weeks and Lacri-Lube® ointment 1–2 hourly to the eyes for 48 hours and at bedtime. The Lacri-Lube® ointment is then changed to a preservative-free topical lubricant gel to be used hourly during the day and Lacri-Lube® is continued at bedtime until the degree of lagophthalmos has improved. The frequency of the lubricants is then gradually reduced over the course of the next few weeks. The patient is instructed to sleep with the head of the bed elevated for 4 weeks and to avoid lifting any heavy weights for 2 weeks. Clean cool packs are gently applied to the eyelid intermittently for 48 hours. The patient should be reviewed in clinic within 2 weeks

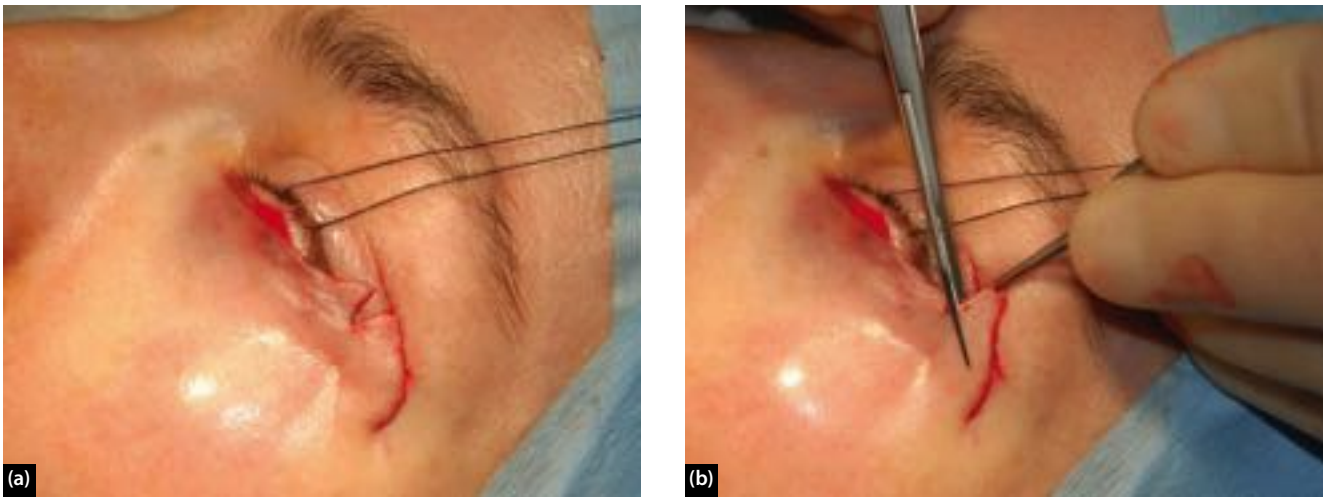


Figure 87.44 **(a)** A vertical incision is made in the central aspect of the lateral skin flap with straight iris scissors. **(b)** The excess skin is trimmed keeping some tension on the lower lid traction suture to prevent an inadvertent over-resection of skin.

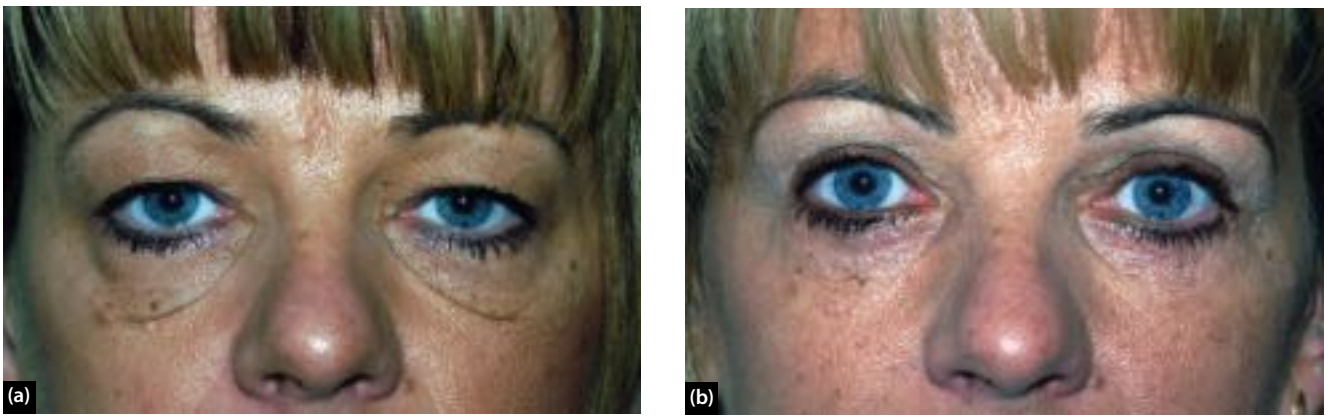


Figure 87.45 **(a)** Pre-operative appearance. **(b)** Post-operative appearance 4 months after undergoing a bilateral upper lid blepharoplasty with sculpting of the medial and central fat pads, and a bilateral lower lid transcutaneous blepharoplasty with an arcus marginalis release, fat repositioning and an orbicularis oculi muscle suspension.

and again within 4–6 weeks. The upper and lower lid skin sutures are removed at 10–14 days post-operatively. The patient is instructed to commence massage to the lower eyelids 2 weeks post-operatively. The patient should apply Lacri-Lube® ointment to the skin and massage in an upward direction for 2–3 minutes three times a day for 4–6 weeks. This is important to help to avoid lower eyelid retraction.

An example of a patient who has undergone this procedure is shown in **Figure 87.45**.

For patients who also have mild malar mounds, the lower eyelid transcutaneous blepharoplasty can be combined with a SOOF lift using the same incisions. Likewise, for patients with malar bags and a midface ptosis with descent of the malar fat pads, the transcutaneous blepharoplasty can be combined with a midface lift, again using the same incisions (**Figure 87.46**).

STRUCTURAL FAT GRAFTING

If structural fat grafting to the cheeks, temples or other facial areas is to be undertaken in conjunction with a lower eyelid blepharoplasty, this should be undertaken initially. It is important that the fat is injected as soon as possible after it has been harvested. This increases its chances of survival. The fat should be placed at different depths in the tissues by injecting only 0.1 mL of fat with each pass of the cannula. Multiple passes are required. The injection technique should be meticulous.

SOOF LIFT

Surgical procedure

1. This is undertaken after repositioning or removing lower eyelid fat.
2. The SOOF is mobilized by dissecting in the preperiosteal plane using blunt-tipped Westcott scissors, taking care to avoid damage to the infraorbital neurovascular bundle.
3. The SOOF is then sutured to the arcus marginalis and the periosteum of the lateral orbital margin with 4-0 Vicryl sutures (**Figure 87.47**).
4. The blepharoplasty is then completed as described above.



Figure 87.46 (a) The pre-operative appearance of a patient with marked bilateral lower eyelid festoons and bilateral upper eyelid dermatochalasis with no evidence of thyroid eye disease or other predisposing systemic disorder. **(b)** The post-operative appearance of the same patient 1 year following a bilateral upper lid blepharoplasty and transblepharoplasty internal browpexy and bilateral lower eyelid transcutaneous blepharoplasties combined with an orbicularis oculi muscle suspension. Note that this patient still has some lower lid festoons, which are extremely difficult to eradicate completely.

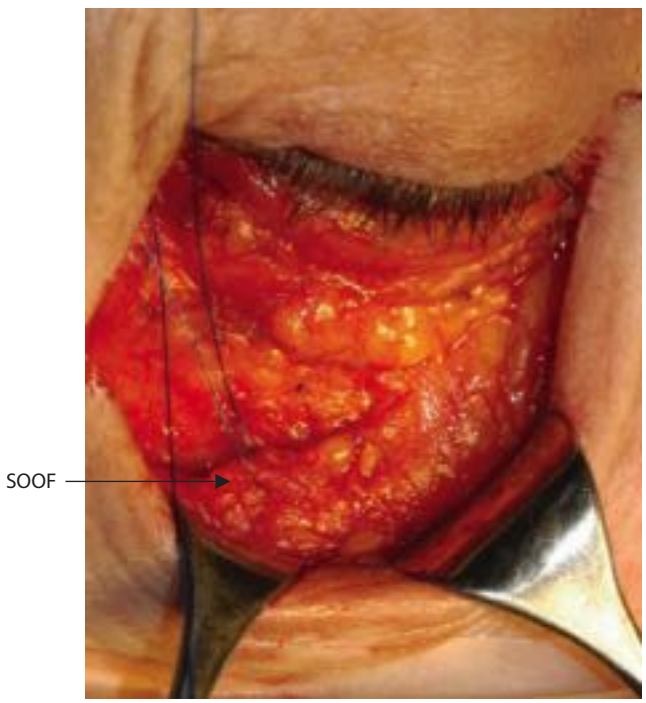


Figure 87.47 A 4-0 Vicryl suture has been placed through the SOOF.

MIDFACE LIFT

Surgical procedure

1. This is undertaken after repositioning or removing lower eyelid fat medially.
2. The periosteum is incised 2 mm below the inferior orbital margin and a subperiosteal dissection is performed using a Freer periosteal elevator, over the surface of the maxilla and zygoma, taking care to avoid damage to the infraorbital neurovascular bundle.
3. The periosteum is divided close to the buccal sulcus using Stevens scissors or the sharp end of a Freer periosteal elevator. In some patients, a buccal sulcus incision can be used to aid the subperiosteal dissection and mobilization of the midface.
4. Next, the periorbita is raised over the inferior and inferolateral orbital margin and into the orbit for a few millimetres using the Freer periosteal elevator.
5. Two or three drill holes are made through the inferior and inferolateral orbital margin, protecting the orbital contents with a malleable retractor.
6. A 3-0 Prolene suture is passed through the superior edge of the mobilized periosteum and through the ptotic malar fat pad. This suture is then passed

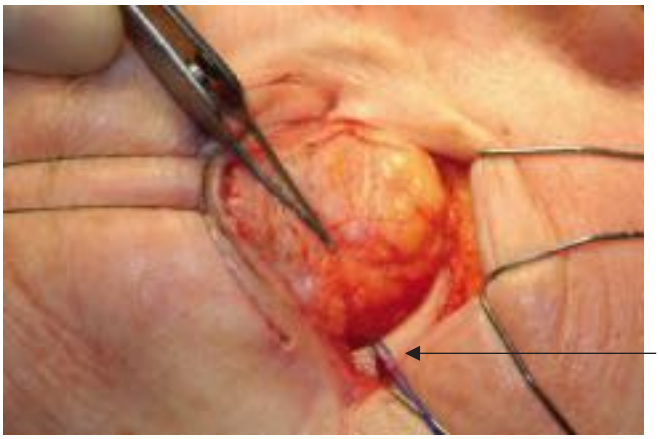


Figure 87.48 A 3-0 Prolene suture has been passed through a drill hole in the inferolateral orbital margin.

through the drill holes in the bony margin and tied (**Figure 87.48**). The suture knot is rotated into the drill hole. Additional sutures are placed as required.

7. The blepharoplasty is then completed as described above.

As an alternative option, the ptotic midface can be lifted with the use of a midface Endotine implant although this adds considerable expense to the procedure. The implant is positioned so that the tines at the inferior end of the implant engage the ptotic cheek fat pad and the other end is fixated to the lateral orbital margin using one or two titanium screws or biodegradable screws (**Figure 87.49**). The stem of the implant is then severed just above the securing screw using a 15 Bard Parker blade.

The Endotine implant gradually biodegrades over a period of approximately 6–9 months. The implant can provide a very powerful and effective midface lift. The patient should be warned that a midface lift can result in considerable post-operative swelling which can take 2–3 months to subside.

Post-operative care

This is as described above.

CHEEK IMPLANT

Although a variety of cheek implants are available (e.g. Medpor), and these can certainly provide augmentation of the midface, the author does not advocate the use of any cheek implants as these can lead to an unsatisfactory appearance after the patient has developed age-related soft-tissue deflation in the area overlying and adjacent to the implant after some years.

TRANSCUTANEOUS BLEPHAROPLASTY WITH FAT DEBULKING

For the majority of patients seeking a lower lid blepharoplasty, usually in the age group 45–60 years of age, the transcutaneous blepharoplasty with arcus marginalis release, fat repositioning and an orbicularis oculi muscle suspension provides a very good cosmetic result with minimal risks. It is, however, time-consuming. For older patients with greater degrees of fat herniation, the fat will need to be formally debulked, paying very careful attention to haemostasis and avoiding traction on the fat. In such patients, a transcutaneous approach gives excellent access to the lower lid fat pads, which can be debulked with a very conservative removal of skin. An orbicularis muscle sling can be avoided but a lateral tarsal strip procedure will usually be required. This procedure is quicker to perform and the patients who are suitable for this procedure tend to be less demanding and critical of slight asymmetries.

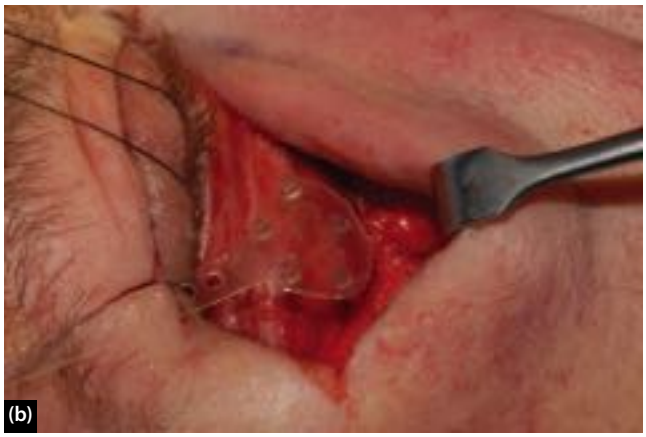
These older patients should also be carefully screened for systemic comorbidities, including undiagnosed essential hypertension. Such patients are at an increased risk of a retrobulbar haematoma with its potential visual morbidity.

Steatoblepharon refers to a situation, usually in an older patient, where the orbital septum has become very lax with marked herniation of the lower eyelid fat pads (**Figure 87.50**). This can occasionally occur in younger patients as a familial trait. In older patients it tends to accompany dermatochalasis, eyelid laxity and ptosis. Prolapse of fat through a weakened Tenon's capsule may also accompany steatoblepharon. This fat can be resected via a lateral vertical conjunctival incision made directly over the prolapsed fat using Westcott scissors. The superolateral fornix should be avoided to prevent intraoperative damage being caused to the lacrimal gland ductules.

TRANSCONJUNCTIVAL BLEPHAROPLASTY

A transconjunctival blepharoplasty is ideally suited to the younger patient who has mild to moderate lower eyelid fat herniation but with no or minimal skin or eyelid laxity. It is also suited to the patient with thyroid eye disease and can be combined with an orbital decompression procedure. For patients who have marked fat pad enlargement, the fat can be debulked but, for patients with lesser degrees of fat herniation and who are concerned about the appearance of lower eyelid dark circles due to tear trough defects, fat can be repositioned over the inferior orbital margins.









(d)

Figure 87.49 **(a)** The head of the midface Endotine implant with the protruding tines. **(b)** The implant is about to be placed. **(c)** The implant has been placed. The stem of the implant has been passed under the lateral canthal raphé and brought out through the upper eyelid wound in this example. The stem is then pulled in a superolateral direction until the desired height and contour of the midface have been achieved. The stem is being secured to the lateral orbital margin with a 1.5 × 4 mm titanium screw. **(d)** Drawing showing the location of the Endotine implant.

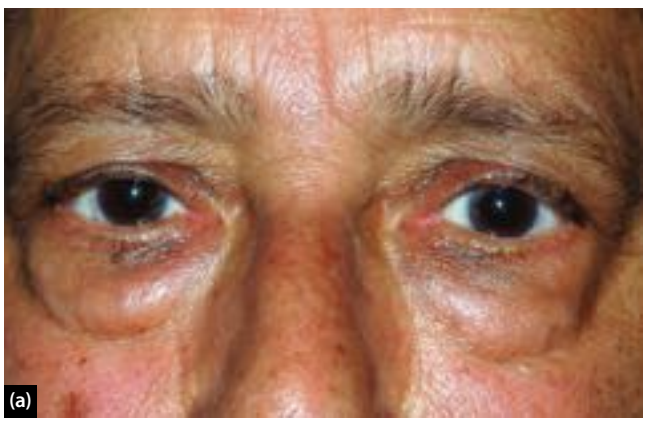




Figure 87.50 **(a)** Steatoblepharon and upper lid dermatochalasis. **(b)** A prolapse of orbital fat through a weakened Tenon's capsule in the same patient.

The patient should be warned pre-operatively that post-operative chemosis is to be expected following this surgical approach, particularly in the patient with pre-operative conjunctivochalasis, and that this usually takes 1–2 weeks to resolve. In some patients, however, it can take several weeks to resolve.

Surgical procedure

The patient is examined in a sitting position and the prolapsed preaponeurotic fat pads are outlined using gentian violet. It is particularly important to outline a lateral fat pad as the position of the fat pad and the extent of the prolapse can be difficult to judge following the injection of local anaesthetic solution and with the patient in a semi-recumbent position.

Fat repositioning

1. Approximately 2–3 mL of 0.5% marcain with 1:200 000 units of adrenaline mixed 50:50 with 2% lignocaine with 1:80 000 units of adrenaline are injected with a single injection just beneath the skin along the lower eyelid just below the tarsus. The needle is inserted temporally and advanced nasally while slowly injecting the solution. Immediate pressure is applied. A pause of 10 minutes is allowed for the adrenaline to take effect. Local anaesthetic containing adrenaline is not injected subconjunctivally to avoid its effect on the pupil.
2. The patient is prepped and draped.
3. A 4-0 silk traction suture is placed through the grey line of the lower eyelid and everted over a medium Desmarres retractor.
4. A conjunctival incision is made with a Colorado needle 3–4 mm below the inferior border of the tarsus from the level of the punctum to the lateral canthus entering the plane between the orbital septum and the orbicularis oculi muscle. The orbital fat will remain contained behind the orbital septum as long as the incision is made above the line of fusion of the septum and the capsulopalpebral fascia.
5. 4–0 silk traction sutures are placed through the medial and lateral edges of the conjunctiva and the lower eyelid retractors and fixated to the head drapes using small curved artery clips in order to protect the cornea (see **Figure 87.44a**).
6. Dissection proceeds down the plane between the septum and the orbicularis and onto the anterior surface of the infraorbital rim. This bloodless dissection is greatly aided by the use of the Colorado needle.
7. A pocket is created beneath the orbicularis muscle over the anterior lacrimal crest.
8. The arcus marginalis is incised with the Colorado needle from medial to lateral along the infraorbital rim, taking care to avoid the inferior oblique muscle medially (located directly behind the medial third of the septum) and the lateral canthal tendon laterally (**Figure 87.51**).
9. Next a double-armed 4-0 Prolene suture is passed through the prolapsed fat medially. The needles are passed beneath the orbicularis muscle over the anterior lacrimal crest medially, through the full thickness of the eyelids to exit through the skin and are then tied over a silicone bolster, pulling the fat forwards and the orbicularis upwards over the inferior orbital margin. Further sutures are placed and passed just anterior to the periosteum over the anterior surface of the inferior orbital margin centrally and laterally (**Figure 87.52**).
10. The conjunctival retraction sutures are removed and the conjunctiva and eyelid retractors are re-apposed with 2–3 interrupted 7.0 Vicryl sutures.

An example of a patient who has undergone this procedure is shown in **Figure 87.53**.

Post-operative care Post-operatively the patient is prescribed a topical antibiotic ointment to the eyes three times a day for 2 weeks and Lacri-Lube® ointment 2 hourly to the eyes for 48 hours and at bedtime. The Lacri-Lube® ointment is then changed to a preservative-free topical lubricant gel to be used 2 hourly during the day and Lacri-Lube® is continued at bedtime until any

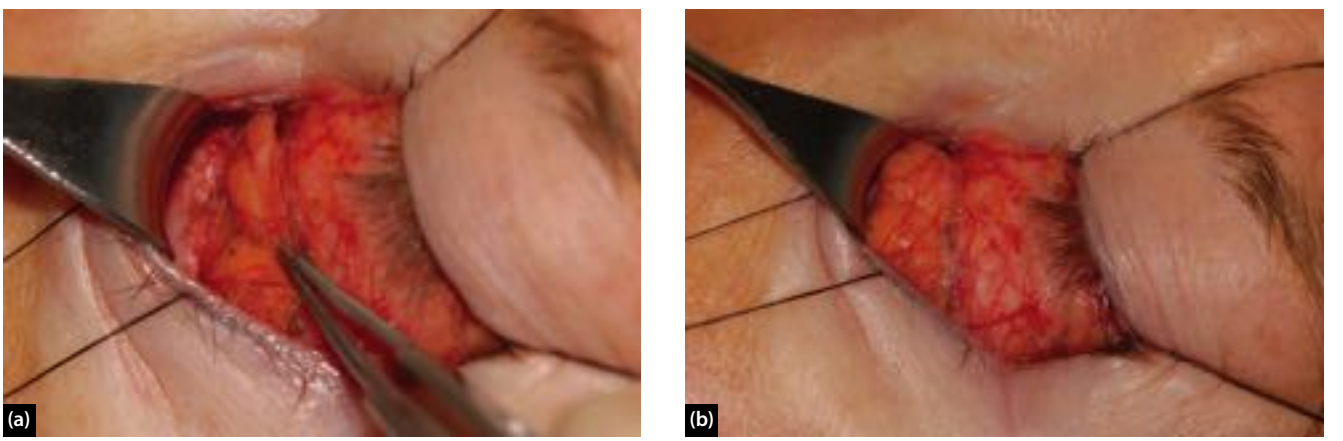


Figure 87.51 **(a)** The arcus marginalis has been opened allowing the preaponeurotic fat to prolapse. The inferior orbital margin has been exposed. **(b)** The fat is now prolapsing over the inferior orbital margin prior to placement of the double-armed Prolene sutures.

post-operative chemosis has resolved. Post-operative steroid drops are unnecessary. The patient is instructed to sleep with the head of the bed elevated for 2 weeks and to avoid lifting any heavy weights for 2 weeks. Clean cool packs are gently applied to the eyelid intermittently for 48 hours. The patient should be reviewed in clinic within 5 days when the Prolene sutures are removed, and again within 4–6 weeks. The conjunctival sutures should drop out spontaneously within 2 weeks. Massage to the lower eyelid/cheek junction for 3 minutes three times per day can be commenced using Lacri-Lube® ointment as soon as the Prolene sutures have been removed. This is continued for 2–3 weeks.



Figure 87.52 Three 4-0 double-armed Prolene sutures have been passed from the fat through the full thickness of the lower eyelids and tied over silicone bolsters.

Fat removal

In patients with a true fat excess a more traditional fat resection is required. In these patients gentle pressure is applied to the globe to allow the orbital fat pads to herniate into the wound.

The operation is as per stages 1–5 for fat repositioning above.

6. The orbital septum is opened using the Colorado needle over the points of maximum convexity caused by the bulging of the fat with pressure applied to the globe. The fat will prolapse through the openings in the septum.
7. The fat is then very carefully excised after clamping the fat with a curved artery clip. Strict attention is paid to meticulous haemostasis (**Figure 87.54**).
8. No undue traction should be exerted on the fat. The fat is removed commencing with the nasal fat pad, moving to the central and then to the lateral fat pads.
9. The residual fat should be left flush with the orbital margin to prevent over-resection with a subsequent 'skeletonized' look.

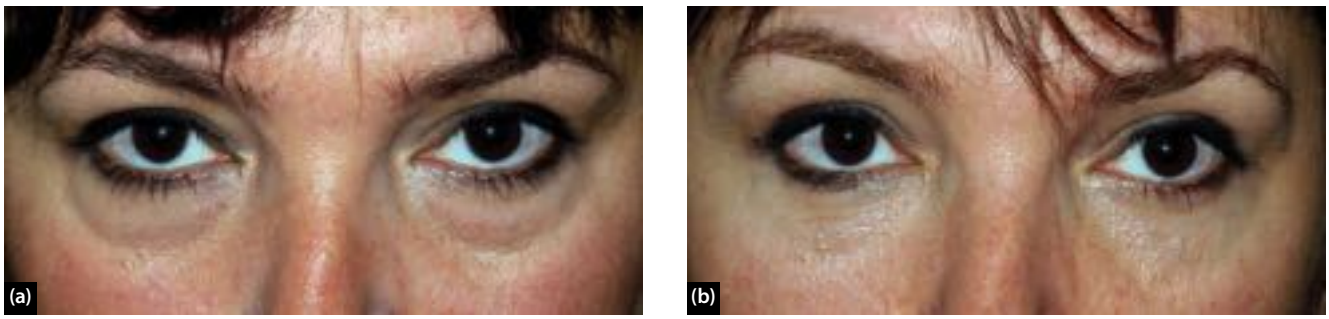


Figure 87.53 (a) Pre-operative appearance. **(b)** Post-operative appearance following a bilateral lower lid transconjunctival blepharoplasty with arcus marginalis release and fat repositioning.

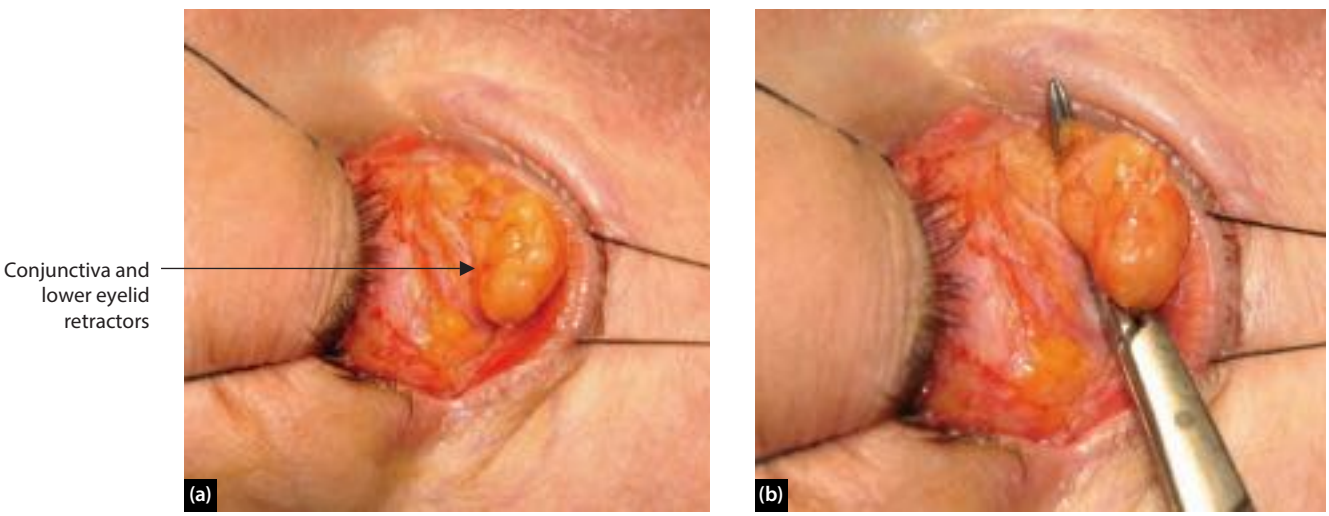


Figure 87.54 (a) The central eyelid fat pad has prolapsed into the wound after opening the orbital septum. **(b)** The central fat pad has been clamped with a curved artery clip.

10. The Desmarres retractor is removed and the eyelids inspected to ensure adequacy of fat removal and symmetry. If there is concern that too much fat has been removed, this can be replaced as a free graft over the inferior orbital margin.
11. The conjunctival retractor sutures are removed and the conjunctiva and eyelid retractors are reapposed with two or three interrupted 7-0 Vicryl sutures.

An example of a patient who has undergone this procedure is shown in **Figure 87.55**.

In some patients a minimal skin excess can be addressed at this stage by adding a simple 'pinch' skin resection. The lower lid skin is gently pinched into a fold in the lateral aspect of the eyelid using Castroviejo 0.3 mm toothed forceps and this is marked out using a cocktail stick impregnated with gentian violet solution, ensuring that the eyelid position is not affected even with upgaze and with mouth opening. The skin alone is resected with a Colorado needle and the skin edges reapproximated with interrupted 7-0 Vicryl sutures.

Post-operative care Post-operatively the patient is prescribed a topical antibiotic ointment to the eyes three times a day for 2 weeks and Lacri-Lube® ointment 2 hourly to the eyes for 48 hours and at bedtime. The Lacri-Lube® ointment is then changed to a preservative-free topical lubricant gel to be used 2 hourly during the day and Lacri-Lube® is continued at bedtime until any post-operative chemosis has resolved. Post-operative steroid drops are unnecessary. The patient is instructed to sleep with the head of the bed elevated for 2 weeks and to avoid lifting any heavy weights for 2 weeks. Clean cool packs are gently applied to the eyelid intermittently for 48 hours. The patient should be reviewed in clinic within 2 weeks, and again within 4–6 weeks. The conjunctival sutures should drop out spontaneously within 2 weeks. If a pinch skin excision has been performed, the skin sutures are removed in clinic after 2 weeks.

PATIENT AFTERCARE

If the surgery has been performed under general anaesthesia, it is wise to apply a compressive dressing for 30 minutes until the patient has recovered. This prevents oozing into the eyelids if the patient performs a Valsalva manoeuvre following extubation. The dressings are then removed and ice packs applied intermittently for 24–48 hours post-operatively. Significant post-operative pain is rare, and most patients are comfortable with a mild non-aspirin analgesic. Significant post-operative pain should, however, raise concerns about the possibility of a retrobulbar haemorrhage and the patient should be examined to ensure that this has not occurred.

Increased pigmentation from haemosiderin deposition is sometimes observed in patients with excessive bruising. To minimize this post-operative problem, patients should be instructed to avoid post-operative sun exposure until the ecchymosis has completely resolved.

Eyelids are extremely sensitive to allergenic insult, and any pre-existing atopy can be aggravated by surgery. Patients should therefore not use cosmetics for at least 10 days after surgery in order to avoid an allergic reaction. Mineral make-ups can be used 10–14 days post-operatively. Patients should also be made aware of the symptoms and signs of allergy to topical antibiotic ointments prescribed for application to the wounds at home after discharge.

For patients who have undergone a more extended lower eyelid blepharoplasty with resuspension of the orbicularis oculi muscle and a SOOF or midface lift, the patient and surgeon must be prepared to wait several weeks for post-operative swelling to resolve and healing to take place before judging the final outcome, since a complete recovery takes significantly longer after this procedure than after a more traditional blepharoplasty. Pre-operative counselling of the patient is vital to ensure that such a prolonged period of convalescence is acceptable to the individual patient.

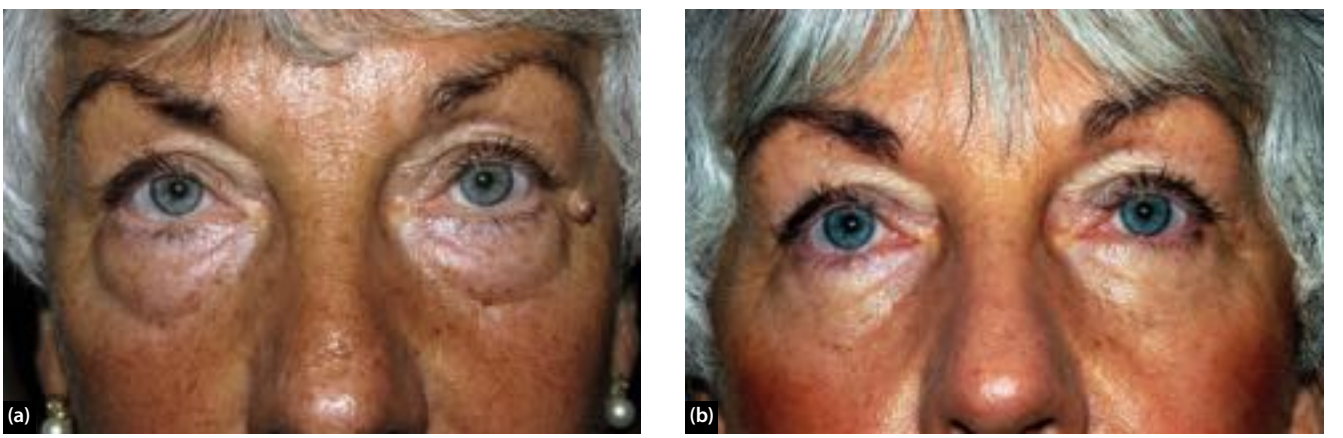


Figure 87.55 **(a)** Pre-operative appearance. **(b)** Post-operative appearance of the same patient 12 months following a bilateral transconjunctival blepharoplasty with fat debulking and removal of a left lateral canthal skin lesion.

COMPLICATIONS OF BLEPHAROPLASTY SURGERY

A number of complications can occur following blepharoplasty surgery (**Box 87.1**). Fortunately, serious complications are rare. The vast majority of complications are ophthalmic in nature and for this reason an increasing number of well-informed patients requesting blepharoplasty surgery seek the skills of appropriately trained and experienced oculoplastic surgeons for their pre-operative evaluation and for their surgery.

BOX 87.1 Complications of blepharoplasty

1. Blindness
2. Bradycardia or other dysrhythmias from the oculocardiac reflex
3. Dry eye
4. Lower eyelid retraction
5. Lower eyelid ectropion
6. Rounding of the lateral canthus
7. Hollowing of the eyelids
8. Epiphora
9. Lagophthalmos
10. Asymmetrical upper lid creases
11. Diplopia
12. Blepharoptosis
13. Chemosis
14. Corneal abrasion
15. Injury to branches of the facial nerve
16. Sensory loss in the distribution of the infraorbital or zygomaticofacial nerves
17. Irregular lower eyelid lumps
18. Fat necrosis

Many of these complications can be avoided by careful pre-operative patient evaluation and selection of the most appropriate surgical procedure for the patient, as outlined above.

- **Blindness** is by far the most serious complication of blepharoplasty surgery. This is usually due to the sudden occurrence of a post-operative orbital haemorrhage. Although rare (the precise incidence is unknown due to under-reporting of this complication but is estimated to be approximately 0.05%), this is a devastating complication of an operation performed most commonly to improve a patient's cosmetic appearance. The patient should be counselled about such a risk pre-operatively. The surgery must be meticulously performed with strict attention to intraoperative haemostasis. Undue traction on orbital fat must be avoided. It is important to ensure that all risk factors for bleeding are addressed pre-operatively. No patient should undergo blepharoplasty surgery involving the removal of orbital fat if hypertension is uncontrolled, if there is a history of a bleeding disorder or if the patient is taking antiplatelet drugs. The patient must be given post-operative instructions about restrictions on activity following surgery. The patient must be able to return to hospital immediately in the event of any sudden orbital pain, proptosis or decrease in vision. The patient with a retrobulbar haematoma usually complains of a steady, lancinating pain, similar to that of glaucoma. The patient may also report scintillating scotomas or complete visual loss and may exhibit mydriasis with a relative afferent pupil defect, proptosis with resistance to retropulsion, and haemorrhagic chemosis.

  If a patient develops a sudden orbital haemorrhage with proptosis, subconjunctival haemorrhage and decreased visual acuity, the wound must be opened immediately to drain the haematoma and a lateral canthotomy and inferior cantholysis should be performed to achieve an emergency orbital decompression. Because the consequences of a retrobulbar haemorrhage are so severe, aggressive intervention is required. If possible the surgeon should not wait for signs of optic nerve compression (i.e. reduced visual acuity, visual field loss, an afferent pupillary defect) to arise, because permanent damage may have occurred by that time. Rather, excessive pain and proptosis necessitate immediate surgical decompression. The incision should be opened and carefully explored. Medical decompression of the orbit with corticosteroids (methylprednisolone 100 mg i.v.), carbonic anhydrase inhibition (acetazolamide 500 mg i.v.) should be organized straight away and, if necessary, osmotic diuresis (mannitol 50–100 g i.v. over 30 minutes) may also be used. The patient's intraocular pressure should be monitored using a Perkins tonometer or a Tonopen and the patient's fundus should be examined to ensure patency of the central retinal artery.
- The **oculocardiac reflex**, characterized by intraoperative bradycardia or dysrhythmia, can be triggered by traction on the extraocular muscles or orbital fat pads. A profound bradycardia or even asystole can occur. Younger patients are more susceptible to the severe effects of this reflex. The anaesthetist monitoring the patient should be aware of the possibility of a dysrhythmia occurring and should alert the surgeon who should in turn release any tissue to which traction is being applied. Atropine or glycopyrolate should be kept drawn up in a syringe and available immediately in the event of a severe dysrhythmia.
- **Keratoconjunctivitis sicca (dry eye syndrome)** is most often seen in patients who have a pre-existing tear film insufficiency. This should be specifically examined for pre-operatively and the patient counselled accordingly. This can be particularly important in patients who have undergone corneal refractive procedures (e.g. LASIK) or who wear contact lenses. The consistent continued use of frequent artificial tears is imperative in these patients who may also require additional procedures at a later date (e.g. punctal plug placement or punctal cautery). Patients who require artificial tears more frequently than three or four times per day should use a preservative free preparation.

- Mild **lower eyelid retraction** may be managed conservatively with post-operative eyelid massage. The eyelid should be massaged in an upward direction after applying Lacri-Lube® ointment to the skin. A SOOF lift or midface lift combined with a lateral canthal resuspension may prevent the need for a full-thickness skin graft following an over-resection of skin leading to lower eyelid retraction. Middle lamellar contracture resulting in lower eyelid retraction (see **Figure 87.16**) may, however, require division of the scar tissue and placement of a hard palate graft or a dermal graft.
- A temporary **lower eyelid ectropion** can occur, particularly laterally, as a result of post-operative wound oedema, wound contraction and/or hypotonicity of the orbicularis oculi muscle. A frank ectropion occurs when significant lower eyelid laxity has not been addressed or where caution has not been exercised in resetting of the orbital septum or in the degree of skin resection. This will usually require a lateral canthal tightening procedure and in some patients this will have to be combined with a skin graft.
- **Rounding of the lateral canthus** occurs following the excessive resection of skin and orbicularis oculi muscle as a triangle laterally, particularly in a patient whose eyelid laxity has not been appropriately addressed. This can prove to be very challenging to correct, and may require a midface lift combined with a lid-tightening procedure.
- **Hollowing of the eyelids** occurs if too much orbital fat is removed, particularly in older patients with very thin eyelid skin. In the lower eyelids care should be taken to resect the fat flush with the inferior orbital margin and to avoid pulling the fat anteriorly during the resection. In general, fat removal from the upper eyelids should be avoided wherever possible. Hollowing of the eyelid can be addressed by the placement of fat pearls harvested from the periumbilical area, or by means of structural fat grafting.
- **Epiphora** is common in the first few post-operative days. Corneal irritation, which triggers hypersecretion of tears, and lower eyelid ectropion, which removes the inferior punctum from the surface of the globe, usually causes epiphora. Continued epiphora following blepharoplasty surgery may occur as a consequence of lagophthalmos with a secondary punctate keratopathy and hypersecretion of tears and/or a malposition of the inferior punctum. A subtle vertical positioning of the inferior punctum may result in epiphora. This is seen on careful slit lamp examination and may occur some years after surgery as the lower eyelid tarsoligamentous support becomes more lax. Conjunctivochalasis, a redundant fold of bulbar conjunctiva, may lie over the inferior punctum obstructing tear flow. This is again a subtle abnormality requiring careful slit lamp examination. It can respond to a conservative resection of the redundant conjunctiva. Persistent epiphora due to malposition of the inferior punctum requires further surgery to reposition the punctum.
- **Lagophthalmos** following an upper eyelid blepharoplasty is avoided by ensuring a conservative skin resection in the upper eyelids. Overzealous resection may require a skin graft if exposure symptoms do not respond to conservative treatment.
- The **appearance and symmetry of the upper eyelid skin creases** have a profound effect on the cosmetic outcome of an upper eyelid blepharoplasty. The skin crease should be higher in a female and well defined in contrast to a male in which this should be lower and more subtle. Complications are avoided by meticulous pre-operative planning and marking. Post-operatively it is easier to raise a skin crease which is unsatisfactory than it is to lower it.
- **Diplopia** is a rare complication following lower eyelid blepharoplasty. This is usually due to surgical trauma to the inferior oblique muscle. A good knowledge of anatomy, a meticulous surgical dissection and an avoidance of the excessive use of cautery should prevent such a complication. A permanent ocular motility disturbance caused by blepharoplasty is much rarer than a pre-existing phoria, which may decompensate following surgery. For this reason it is imperative to perform a detailed pre-operative ophthalmic examination in order to diagnose the problem and to protect the surgeon from unfair blame.
- **Blepharoptosis** may occur if the levator muscle, the horns of the levator muscle complex or Whitnall's ligament are damaged during surgery. These should be carefully identified and avoided. Any pre-existing ptosis should be addressed at the time of an upper eyelid blepharoplasty by means of a levator aponeurosis advancement. This should be performed under local anaesthesia to facilitate an intra-operative adjustment of the height and contour of the upper eyelid(s) with the benefit of the patient's cooperation.
- **Chemosis** (**Figure 87.56**), which is more commonly seen following a transconjunctival blepharoplasty, usually resolves after 10–14 days following the liberal use of topical lubricants. On very rare occasions it may last for some weeks post-operatively. The use of topical steroids to treat this should be avoided

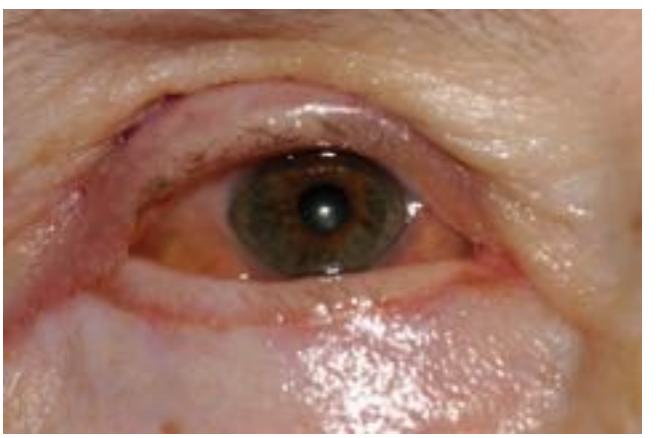


Figure 87.56 Post-operative conjunctival chemosis following a transcutaneous lower eyelid blepharoplasty.

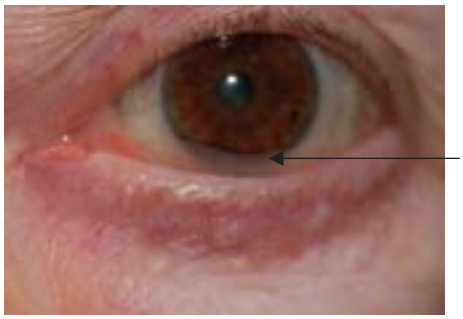


Figure 87.57 Conjunctivochalasis.

because of the risk of cataract, glaucoma and predisposition to infection. If the chemosis does not resolve, a redundant fold of forniceal conjunctiva may need to be removed and the cut edges sutured to the episclera using 8-0 Vicryl sutures. The occurrence of post-operative chemosis can be predicted in the patient who has pre-operative conjunctivochalasis (**Figure 87.57**). Such a patient should undergo the simultaneous resection of the redundant conjunctiva at the time of the blepharoplasty.

- All precautions must be taken to prevent a **corneal abrasion**, which can be extremely painful. Care should be taken when placing eyelid and conjunctival traction sutures to avoid causing a corneal abrasion. Most corneal abrasions heal rapidly without any long-term sequelae but in some patients a recurrent corneal abrasion syndrome can occur. Diabetic patients and patients with corneal dystrophies (which may have been previously undiagnosed) are at particular risk of a recurrent corneal abrasion syndrome. If an abrasion does occur, the patient must be treated with frequent topical antibiotics and should undergo a daily review with slit lamp examinations until the abrasion has completely healed. A topical lubricant ointment should be prescribed at night for a minimum period of 6 weeks to help prevent a recurrent corneal abrasion syndrome.
- **Injury to branches the facial nerve**, particularly the zygomatic branch to the inferior orbicularis, is a potential hazard of dissecting below the orbicularis oculi muscle. This can lead to a loss of tone in the muscle with loss of lower eyelid symmetry lower eyelid ectropion or lagophthalmos. A subperiosteal dissection minimizes the risk of this complication.
- **Sensory loss in the distribution of the infraorbital or zygomaticofacial nerves** is usually temporary. Care should be taken when cauterizing branches of the infra-orbital artery over the inferior orbital margin
- **Irregular lower eyelid lumps** can occur following fat repositioning. This is usually temporary and the lumps often respond to a period of post-operative massage. The use of steroid injections should be avoided.
- **Fat necrosis** is rare and manifests as small, painful, indurated nodules. Massage can hasten their resolution. Injection of steroids into the lesions is effective but carries the risk of subcutaneous atrophy and hypopigmentation.

Medicolegal pitfalls

Most complications of blepharoplasty surgery stem from an inadequate pre-operative patient evaluation. From a medicolegal perspective, a thorough history and meticulous ophthalmic examination, good documentation, informed consent with the provision of detailed information about the pros, cons, risks and potential complications and their management, and excellent patient communication are crucial.

FUTURE RESEARCH

Future research should focus on the improvements that can be made in addressing age-related facial and periocular volume deficits using refined methods of safe structural fat grafting and improvements in the quality and safety of dermal fillers, to help to achieve better and sustained results from blepharoplasty surgery.

KEY POINTS

Anatomy

- A thorough understanding of the surgical anatomy of the eyebrows, eyelids and midface is essential prior to performing a blepharoplasty.
- The distance between the inferior aspect of the eyebrow and the upper lid skin crease on downgaze should be approximately two-thirds of the distance from the inferior aspect of the eyebrow to the eyelid margin. It is important to maintain these dimensions. In general, a minimum distance of 10–12 mm should be left between the inferior aspect of the eyebrow and the upper eyelid skin crease when performing an upper lid blepharoplasty.
- It is very important to be able to distinguish the lacrimal gland from orbital fat.
- Whitnall's ligament supports the levator muscle complex and should not be disturbed during surgery.
- The inferior oblique muscle lies between the medial and central fat pads.

Blepharoplasty

- A history of contact lens wear, previous corneal laser refractive surgery, or a dry eye, facial palsy or thyroid dysfunction identifies a patient at risk of exposure keratopathy symptoms following an upper lid blepharoplasty.
- It is important to exclude a bleeding disorder, as a post-operative haemorrhage following a blepharoplasty is potentially sight-threatening. The use of aspirin or non-steroidal anti-inflammatory agents should be discontinued 2 weeks pre-operatively.
- The patient seeking or referred for a blepharoplasty should undergo a complete pre-operative ophthalmic examination and examined specifically to exclude the possibility of thyroid eye disease.
- The secondary effects of brow ptosis on the upper eyelids must be recognized.
- Pre-operative photographs must be taken. Written consent should be obtained before the photographs are taken and it should be made clear to the patient how the photographs are to be used.
- Botulinum toxin injections should not be given at the time of surgery.
- For purely elective, cosmetic procedures, the patient should be encouraged to consider the information carefully before making a decision to proceed. This may necessitate a further consultation or an attendance at a pre-assessment clinic to obtain fully informed consent and to answer any residual queries.
- The patient should not be asked to sign a consent form for an elective cosmetic procedure on the day of surgery. The risks and potential complications that have been discussed should be documented in the patient's records, on the patient's consent form and in a letter addressed to the patient. The patient should also be provided with a formal document which outlines the potential complications of blepharoplasty surgery, their management and he financial responsibilities that would be incurred.
- It should be noted that fat removal should be undertaken very conservatively, if at all, in the upper lid so as to avoid a secondary hollowing of the upper eyelid, which can result in a very aged appearance.
- No skin should be removed from the medial two-thirds of the lower eyelid in the vast majority of cases. The skin resection should always be conservative.
- Significant post-operative pain following a blepharoplasty should raise concerns about the possibility of a retrobulbar haemorrhage and the patient should be examined immediately to ensure that this has not occurred.
- By far the most serious complication of blepharoplasty surgery is blindness.

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CHAPTER
88

SURGICAL REJUVENATION OF THE AGEING FACE

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: rhytidectomy, facelift, facial rejuvenation, and facial fat grafting or autologous fat transfer.

INTRODUCTION

As populations expand and life expectancy increases, growing numbers of people are seeking methods to reverse the outward effects of ageing. Over the past decades, refinements in surgical techniques have enhanced our ability to achieve natural-looking results with an emphasis on facial harmony and avoidance of the stigmatized 'operated' look. This has allowed aesthetic facial surgeons to meet the high expectations of an increasingly astute patient population and permitted the practice to flourish. Central to the discussion on ageing face surgery is the evolution of facelift surgery, or rhytidectomy. This chapter will provide an overview of the history of facelift surgery and its techniques, and review the senior author's approach to ageing face surgery. The recent resurgence in interest in autologous fat grafting will also be reviewed.

HISTORY OF AGEING FACE SURGERY

The history of ageing face surgery begins with the advent of rhytidectomy, which can be traced back to the dawn of the 20th century. Average lifespans increased sufficiently around this time such that populations began to manifest recognizable signs of ageing. Existential issues of senescence became more salient in the minds of society. Confronted with this phenomenon, clinicians began honouring requests for procedures that would ostensibly slow or reverse the ageing process. Early pioneers of aesthetic plastic surgery were commonly referred to as 'featural surgeons', a pejorative reflecting the underlying sentiment of negativity towards what was considered unnecessary surgery. While many in the medical community shunned the practice of aesthetic surgery, a minority of others recognized the benefits of these procedures and practised in secret on growing numbers of hopeful patients. Unfortunately, public disdain curbed widespread acceptance of plastic surgery and stifled documentation of these early efforts.

Although there is historical debate on the matter, the German surgeon Erich Lexer (1867–1937) is frequently credited as the first individual to describe rhytidectomy, doing so in 1906. Using S-shaped incisions, Lexer excised skin paddles in strategic temporal and preauricular locations to remove lateral rhytids, or wrinkles, which became known as rhytidectomy. Skin excision was conservative and performed only to facilitate closure. Not surprisingly, Lexer's technique resulted in only a subtle improvement. In the ensuing years, other European surgeons including Hollander (1912), Passot (1919), Noel (1920) and Joseph (1921), reported their experiences treating the ageing face. American involvement in facelift surgery occurred at the same time, though virtually independently of European advancements. The first American to publish on the subject was Miller (1907), also one of the first to provide anatomical drawings guiding incision placement. Bettman (1920), another American, was the first to describe the

long incision connecting the pre- and postauricular regions that is now familiar to the modern facelift surgeon. He was also the first to present before and after photographs for publication, now a standard practice.

These early surgeries consisted primarily of limited skin excisions, with predictably limited results. The next step in the evolution of facelift surgery was the practice of wide subcutaneous elevation. This so-called 'long-flap' technique combined with Bettman's incision ushered in the era of subcutaneous rhytidectomy. The technique gained rapid popularity on account of being a technically straightforward operation with a good safety profile; however, it had significant drawbacks. Tension was placed exclusively on the skin flap, leading to a characteristic 'operated' look, and the results were also frequently short-lived due to what is now recognized biomechanically as skin creep and rebound stretching. Despite these flaws, essentially no other significant contributions were made during this early period. Innovations primarily centered on variations of the incisions, but the surgical concept remained unchanged. Subcutaneous rhytidectomy, therefore, remained the standard for nearly 50 years.

The 1970s witnessed two major advancements in ageing face surgery. The first was introduced by Skoog[1] in 1974, who demonstrated the existence of a safe dissection plane below a tough fascial layer spanning the face. His work showed that this plane is continuous with the subplatysmal plane in the neck. By developing a 'short flap' along this plane, the fascial layer could be used as a girdle to lift the skin and subcutaneous tissue together. Skoog reasoned that suspension of this composite unit would generate less tension on the skin, which translated into less visible scarring and more durable results. Indeed, subsequent biomechanical studies have demonstrated this, confirming less rebound relaxation and skin creep.[2] For the first time, Skoog demonstrated how the lower face and upper neck could be safely rejuvenated as one anatomical unit without detaching the skin.

The second major advancement was the description of the superficial musculoaponeurotic system (SMAS), by Mitz and Peyronie in 1976.[3] Their work resulted in a landmark publication confirming Skoog's fascial layer while detailing its anatomical relationship to other facial structures. They demonstrated the SMAS to be a condensed fibrous mesh layer contiguous with the platysma, situated below the subcutaneous fat and over the mimetic musculature and motor branches of the facial nerve. They also described a series of transverse fibrous septations between the SMAS and skin, allowing for the transmission of facial expression. Because the ageing process weakened elasticity of these fibrous septations, Mitz and Peyronie postulated that suspension of the SMAS could aid in re-establishing a youthful facial appearance.

These seminal works laid the foundation for modern approaches to facelift surgery, which are based on suspension of this deep layer. Modern facelifting techniques can be broadly categorized as either SMAS technique rhytidectomies or so-called 'deep plane' rhytidectomies. The SMAS rhytidectomy technique comprises a vast number of variations, from simple suture plication, to more extensive flap dissection and suspension. These techniques treat the subcutaneous and deep layers separately, as opposed to the 'composite flap' featured in deep plane techniques. SMAS procedures allowed for a more natural and durable rejuvenation, particularly of the lower third of the face, when compared to the prior generation of subcutaneous facelifts. The 'deep plane' facelift techniques arose directly from Skoog's 'short flap' technique.[4–6] The concept was pioneered by Hamra in an attempt to achieve a greater effacement of the nasolabial fold, which he felt was not adequately addressed by the SMAS techniques.[4] In the deep plane technique, dissection of the midface transitions from a subplatysmal plane to a deep subcutaneous plane in the cheek to include the malar fat pad. The transition point occurs over the zygomaticus musculature. Hamra later expanded this technique into the 'composite' facelift flap by incorporating the orbicularis oculi muscle in the flap via zygorbicular dissection through a separate subciliary incision. This was done in order to provide improvement of the malar region and address what he saw as disharmony between the adequately rejuvenated jawline and the insufficiently treated midface.

The continuing evolution of today's facelift reflects an increasing understanding of ageing in the critical midface and periorbital regions. In today's ageing face practice, surgeons seek not only to soften the nasolabial fold, but to achieve a smooth transition from the periorbital region, while re-establishing youthful fullness and projection of the cheek. A variety of techniques including suborbicularis oculi fat (SOOF) lifting, orbital fat repositioning or septal reset, and different forms of midface lifting have been developed to achieve these ends.[7–10] These innovations allow surgeons to create natural transitions between rejuvenated facial subunits as part of a balanced full-face surgical rejuvenation procedure.

A complementary though conceptually distinct approach to the ageing face from rhytidectomy is autologous fat grafting. The history of autologous fat grafting dates back to as early as 1893, when Neuber transplanted fat grafts for facial deformities resulting from tuberculous osteitis. Similar to facelift surgery, advancements in the field lay dormant until the 1970s, when a renewed interest in these techniques was born out of the advent of liposuction. Today there is a full-blown renaissance in facial fat grafting, fuelled in part by the work of Sydney Coleman and others, and a rapidly growing public interest in facial fillers in general. Coleman's lipostructure technique,[11, 12] in which large volumes of fat are injected in minute 'parcels' within the subcutaneous space, is regarded by some as a potential replacement for rhytidectomy altogether.[13] There is debate in current practice regarding technical aspects of fat harvest and transfer, but the technique is now widely accepted and in wide clinical practice. In addition, research into adipocyte biology has elucidated the presence of an abundance of growth factors and multipotent stem cells in the harvested lipoaspirates.[14] Therefore the cutting edge of fat grafting includes numerous applications in not only aesthetic surgery but also reconstructive surgery and multidisciplinary regenerative medicine.

BIOLOGY OF AGEING

Facial ageing involves a wide array of biological changes of both intrinsic and extrinsic aetiology. Atrophy is the central process of intrinsic ageing. The facial skin, subcutaneous fat and facial skeleton are each affected and contribute to the ageing face deformity.

Distinct atrophic histological changes occur within the dermis and epidermis. Within the epidermis, the density of keratinocytes and melanocytes declines significantly, creating thinning and abnormal pigmentation of the skin. Langerhans cells, a component of cell-mediated immunity, likewise decrease. Within the dermis, elastic fibres begin to disappear, creating a deficiency in tissue recoil that manifests as excess wrinkling, and there is also a significant decrease in collagen and ground substance. Retraction of dermal papillae and rete ridges causes flattening of the dermal–epidermal junction. In combination, these changes result in the decreased capacity to retain moisture, creating the dryness that typifies aged skin.[15]

Atrophy of subcutaneous fat is another hallmark of facial ageing. The supporting fascial attachments around the fat pads begin to weaken with age. Gravitational forces gradually redistribute these tissues in a more inferior and lateral direction. Consequently, entire subunits, such as the malar fat pad and jowl, become ptotic and contribute to a tired facial appearance.[16–20]

Continuous remodelling of the facial skeleton leads to volume loss with increased age.[20–22] Relative changes can be seen in terms of both volume reduction and expansion. An appreciable reduction in height occurs with modest increases in width and depth. For example, the vertical height of the maxilla decreases while the width of the orbital bones increases. Such changes lead to a disproportionate balance between the available bony surface area and soft-tissue coverage. This process further contributes to inferior displacement of the cheek pad and skin. This same process accounts for jowl formation and sagging along the neckline.

Extrinsic mechanisms of ageing most commonly involve skin damage sustained from solar exposure, known as photoageing. Ultraviolet radiation is well known to contribute to actinic damage through direct or indirect DNA damage. Whereas intrinsic ageing of the skin uniformly results in atrophy of the tissue, actinic changes tend to lead to thickening. In addition, photoageing causes disorganization of dermal elastic tissue fibres, termed elastosis, which contributes to further development of fine skin wrinkles and is a hallmark of the photoageing process.[23]

CLINICAL EVALUATION

Achieving success in ageing face surgery begins with proper patient selection. One of the most critical factors to consider is the patient's psychological motivation for surgery. Multiple studies[24, 25] demonstrate that patient psychology is a significant determinant of post-operative satisfaction in ageing face surgery. The patient who has a stable self-image and internal desire for a more youthful appearance is more likely to be satisfied with the post-operative result. In contrast, the patient seeking surgery to remedy a situational or social dilemma may have unrealistic expectations. This situation often heralds unhappy results.

It is imperative the patient and surgeon are in complete agreement on the indications for surgery and the resulting anticipated changes. Rhytidectomy is an excellent technique to correct visible signs of ageing in the lower two-thirds of the face and upper neck. This includes redundant facial skin and deep rhytids, jowling or loss of a well-defined mandibular contour, and modest improvement of prominent nasolabial folds. Patients should be counselled that rhytidectomy is not effective for superficial rhytids resulting from solar damage or minor depressions secondary to acne scarring. These abnormalities are more appropriately treated with adjunctive techniques, such as laser resurfacing or dermabrasion.

As with any elective procedure, overall good health is a prerequisite in ageing face surgery. Pre-operative evaluation includes a thorough history and review of systems to screen for potential complicating factors. Many patients consider rhytidectomy following significant weight loss. If further weight loss is planned or a history of repeated weight loss and gain is suspected, surgery should be delayed until a plateau is reached. Patients with a history of coronary artery disease, hypertension, pulmonary compromise and hepatic or renal insufficiency should be cleared by the appropriate medical specialist in advance. Relative contraindications to rhytidectomy include predisposition to poor wound healing, as seen in diabetes mellitus, chronic steroid use, connective tissue disorders (such as Ehlers–Danlos syndrome) and past radiation therapy. An absolute contraindication to surgery is a history of a bleeding diathesis.

All medications containing aspirin and non-steroidal anti-inflammatory agents are discontinued at least 3 weeks prior to surgery to minimize bleeding. It is important to enquire about use of supplemental vitamins (particularly vitamin E) and homeopathic preparations (including *Ginkgo biloba* and garlic). These medications are in widespread use but rarely disclosed voluntarily by patients and can contribute to unexpected bleeding.

A history of tobacco use is particularly relevant in the assessment of the ageing face patient. It has been estimated by Rees and Aston that smokers have a 12 times increased risk of skin slough following rhytidectomy compared with non-smokers.[26] This is attributed to a higher incidence of haematoma formation and vasoconstriction. Although long-term effects of smoking on skin cannot be negated by peri-operative cessation, surgical complications can be reduced by smoking cessation within 2 months of surgery.

There is no ideal age when considering timing for ageing face surgery. Chronological age alone should not be used as the qualifying criterion. More importantly, consideration is given to the visible degree of ageing in a particular individual. Patients demonstrating mild to moderate degrees of ageing are more likely to achieve a natural, rejuvenated appearance. Signs of advanced ageing, such as extreme skin sagging, are more difficult to correct and

will limit expected improvement. Rhytidectomy is often an operation of compromise. Dramatic improvement can be made in one region, but this may occur at the expense of suboptimal change in another. In patients with advanced signs of ageing, it is beneficial to strive for less dramatic but more natural change initially, with further refinement at a later date if necessary.

Physical examination begins with assessment of the patient's skin type. An ideal candidate for rhytidectomy is an individual with fair, medium-thickness skin. Dark patients usually have thicker skin and enjoy less dramatic improvement. The increased weight of their skin also results in more post-operative skin relaxation. The presence of a moderate amount of skin elasticity is beneficial. Less elastic skin can be tightened by rhytidectomy, but the duration of improvement may be less satisfactory. A modest degree of subcutaneous fullness is also desirable, particularly in the midface. This reflects a healthy adipose tissue layer and contributes to a more youthful look. This can be enhanced with the use of complementary fat grafting.

Facial skeletal structure can help predict a more or less favourable surgical outcome. Patients with a strong facial skeleton usually demonstrate more obvious improvement. Well-defined bony contours provide excellent support for skin redraping and accentuate desirable facial features. Patients with mid-facial hypoplasia are poor candidates for rhytidectomy alone and typically require adjunctive procedures. Similarly, patients with microgenia and poor chin definition require chin augmentation in conjunction with rhytidectomy to achieve enhanced results.

Many facelift patients express concern regarding skin laxity and fullness in the submental region. This is best appreciated on a profile view by assessing the cervicomental angle. The submentum should be palpated to determine relative contributions from redundant skin, fatty tissue and platysmal banding. Redundant skin alone can usually be addressed with standard rhytidectomy technique by suspension of the cervical skin. Excess fatty tissue is most effectively treated by submental liposuction. Patients with prominent platysmal banding require platysmaplasty to attain a more favourable cervicomental angle. In patients with extreme fatty deposition, platysmal banding may not be appreciated until after liposuction has been performed. Thus, patients should be counselled that platysmaplasty may be indicated in addition to submental liposuction. It is worth noting that a subgroup of patients has an inherent anatomic limitation to the degree of improvement that can be realized in the submental region. These patients have an abnormally low positioned hyoid bone and are considered less ideal candidates for surgery. Such patients should be thoroughly counselled that facelift surgery may not significantly affect their submental profile view, even in conjunction with liposuction and platysmaplasty.

Pre-operative photographs are taken with standardized 1:8 full-face frontal, lateral and oblique views. Digital imaging can be useful in demonstrating to the patient realistic changes that may be expected following surgery.

SURGICAL TECHNIQUES

This section outlines general steps in surgical technique for SMAS rhytidectomy, submental liposuction, platysmaplasty and autologous fat injection.

The patient is marked pre-operatively in the sitting upright position. Areas of special concern are highlighted, as well as anatomical landmarks such as the geniomandibular groove, mandibular border and submental triangle. A pre-operative intravenous dose of an appropriate anti-staphylococcal antibiotic is then administered.

We prefer to perform rhytidectomy under general anaesthesia, but local anaesthesia with intravenous sedation is well tolerated by the patient. Anaesthetic solution containing 1:100 000 epinephrine is infiltrated along the pre- and postauricular borders and in a fan-like fashion beneath the facial and upper cervical skin flaps. If the neck is to be addressed by either liposuction or platysmaplasty, local anaesthetic is additionally infiltrated throughout the submental region. The endotracheal tube is prepped into the surgical field and positioned to allow side-to-side movement during the operation. The entire face, neck and scalp are prepped and draped in sterile fashion.

Careful incision design and placement are vital to achieving natural-appearing results in rhytidectomy. The ideal incision camouflages scar formation, minimizes changes in the temporal and postauricular hairline and avoids distortion of the earlobe. An oblique incision begins in the temporal hair tuft region and varies for the individual patient. If a low temporal hairline is present, the incision is placed within the hair tuft to raise the hairline to a normal position post-operatively. If a normal or elevated temporal hairline is present, the incision is designed to run directly on the hairline to avoid elevating it further. The incision extends posteriorly 2–3 cm, gently curving into the temporal hair. It is then redirected inferiorly toward the root of the helix and into the preauricular crease.

A post-tragal incision is used in most female patients. The incision is positioned 2–3 mm onto the posterior tragal surface and not deep toward its base. It exits at the inferior margin of the tragus and transitions toward the lobule. Alternatively, a pre-tragal incision can be used that courses within the preauricular skin crease. In male patients this incision is placed approximately 1 cm anterior to the preauricular crease to avoid advancing hair-bearing skin too close to the auricle.

The lobule incision can be transposed according to individual need. In patients with a 'hanging lobule', the incision can be placed 1–2 mm below the lobule attachment and readily camouflaged. If a dependent lobule is not present, the incision is made at the junction of the lobule and infra-auricular skin. The lobule incision extends onto the posterior surface of the auricle coursing over the conchal bowl. Approximately 3–5 mm should remain between the incision and the postauricular sulcus. In the male patient, the incision rests within the sulcus to avoid displacing hair-bearing skin onto the ear. The incision extends to the level of the fossa triangularis before turning posteriorly. A less dependent skin flap can be created in patients with a smoking history by limiting the superior extent of this incision.

A V-shaped dart is created as the incision traverses the sulcus and minimizes post-operative webbing. The incision extends into the hair-bearing skin before coursing parallel to the occipital hairline (**Figure 88.1**).

Elevation of the skin flap begins in the postauricular region. The flap is elevated in an avascular plane while preserving the subdermal plexus and thin fatty layer on the undersurface of the skin. Elevation continues into the neck in a supraplatysmal plane. The preauricular skin flap is elevated in a similar manner. Near the zygomatic arch, dissection is limited to the posterior one-third of the arch to avoid potential frontal nerve injury. A full-thickness skin flap is elevated off the tragal cartilage. This facilitates redraping of the skin and helps maintain the natural tragal contour. The preauricular skin flap is elevated approximately 9 cm anteriorly and can be extended over the jawline into the neck. Dissection in the neck is most commonly performed in the subcutaneous plane. In many patients, liposuction of the neck can be performed without connecting the preauricular with the neck dissection.

Once the skin flap is elevated, the SMAS is identified. A horizontal incision is made in the SMAS just below and parallel to the zygomatic arch but limited to the posterior one-third segment. This connects to a vertical limb coursing 2 cm anterior to the tragus. The SMAS incision should not extend beyond the angle of the mandible because the marginal mandibular nerve is in close proximity. The SMAS flap is elevated approximately 3–5 cm (**Figure 88.2**). In many cases the platysma is incorporated as an extension of the SMAS. The SMAS flap is then advanced and primarily pulled in a superior vector with a slight posterior vector. Maximal pull should be avoided when suspending the first side as this may restrict mobility of the contralateral side and result in facial asymmetry. A triangular segment of SMAS is excised and the edges of the SMAS flap are then sutured to the dense fibrous tissue at the inferior margin of the zygomatic arch and the preauricular SMAS. Multiple 4-0 PDS and 5-0 nylon sutures can be used for this SMAS imbrication. In some patients, a postauricular SMAS flap can be dissected and suture plicated to the mastoid periosteum (**Figure 88.3**).

After tightening the SMAS, the skin flap advances easily over the face. The postauricular skin is pulled superiorly and slightly anteriorly, whereas the preauricular skin is pulled superiorly and slightly posteriorly. The postauricular skin is temporarily anchored at its superior margin with staples. Similarly, the superior margin of the preauricular skin is anchored to the temporal hairline. After careful



Figure 88.1 The post-tragal incision is placed just behind the tragal cartilage (a). Note how the outline of the tragus is defined by the incision. The postauricular incision **(b)** runs along the posterior surface of the conchal cartilage with a V-shaped dart in the posterior limb of the incision as it moves toward the hairline. This acts to break up the scar and prevent contracture.

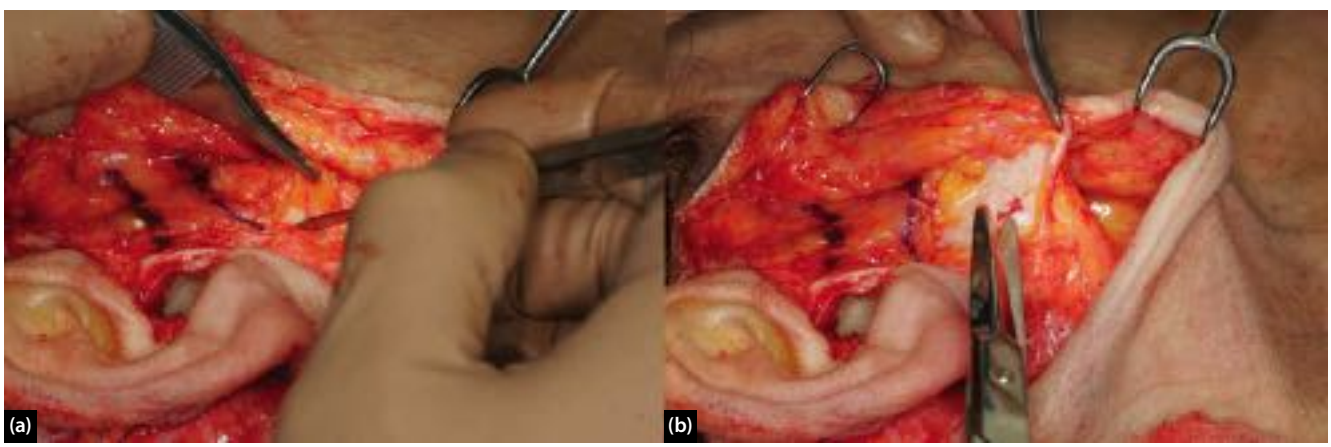


Figure 88.2 The SMAS is incised after elevation of a subcutaneous flap (a). A sub-SMAS flap is carefully elevated from below the zygomatic arch extending anteriorly and inferiorly **(b)**.



Figure 88.3 The SMAS flap is advanced superiorly and slightly posteriorly. In this case the flap was bifurcated and separately suspended to the preauricular SMAS below the zygoma, and to the mastoid periosteum.

measurement, the excess skin is sharply trimmed. The tragal skin flap should be thinned sufficiently to allow natural redraping over the cartilage. It is imperative to avoid excess skin tension as displacement of the tragus can easily result. Meticulous care should be taken to realign the occipital and temporal hairline.

Attention is then focused on the portion of the skin flap hammocking the lobule. The skin is sharply divided to 'release' the lobule, leaving a significant hammock effect on the lobule. This support on the lobule will help prevent a satyr ear deformity due to post-operative settling of the earlobe. The excess skin is trimmed to recreate a natural lobule contour. It is important to minimize tension placed on this closure.

The entire incision is closed in a layered fashion over a ¼-inch Penrose or suction drain. The subcutaneous layer is closed with 5-0 polydioxanone sutures. The temporal, preauricular and lobule skin segments are closed with 6-0 nylon vertical mattress sutures. The postauricular skin is closed with 5-0 fast-absorbing plain gut suture. Antibacterial ointment is applied to all incision lines followed by a dry gauze pressure dressing.

All rhytidectomy patients are observed overnight. The following morning, the drain is removed and a pressure dressing is reapplied. Antibiotics are prescribed for a total of 10 days post-operatively. Sutures are removed 7–10 days after surgery. Oedema resolves over several weeks and facial contour stabilizes at approximately 4–6 weeks after surgery. Erythema of the tragal incision should fade over several months (**Figure 88.4**).

SUBMENTAL LIPOSUCTION AND PLATYSMAPLASTY

When indicated, submental liposuction and platysmaplasty are performed prior to the rhytidectomy. A midline incision is made within the first well-developed submental crease posterior to the mandible. If liposuction alone is planned, this is limited to a 5 mm stab incision. If a wider incision is later needed for platysmaplasty, the stab incision should be made initially to maintain vacuum pressure during liposuction.

A wide variety of liposuction cannulas exists, ranging from flat to round-tipped with an array of suction port designs. Surface irregularities appear to be minimized with the use of smaller cannulas. We prefer pre-tunnelling with a 2 mm cannula followed by applied low suction. The cannula is inserted into the subcutaneous space between the dermis and platysma. The dominant hand controls movement of the cannula while the contralateral hand guides tip position. Pre-tunnelling involves limited dissection to facilitate passage of the larger cannula. Liposuction is performed by dissecting with the cannula in radial fashion away from the incision. One atmosphere (760 mmHg) of negative pressure is usually sufficient. The suction port should always be directed away from the skin to minimize dermal trauma and dimpling. Uniform suctioning is performed across the submental triangle down to the hyoid bone. Liposuction should be limited near the inferior border of the mandible to avoid injuring the marginal mandibular branch of the facial nerve. Periodic inspection of the skin using the 'pinch and roll' technique helps determine the degree and extent of liposuction required. A sufficient amount of fat should remain to preserve natural skin cushioning.

Platymasplasty requires creation of a slightly wider submental incision. Blunt scissor dissection is used to expose the medial border of the platysma muscles. Residual fat surrounding the incision and between the muscles is removed under direct vision. If minor platysmal banding is present, plication of the exposed muscle borders across a short distance is sufficient to improve the submental contour. In patients with severe platysmal banding, both muscles are horizontally incised at the level of the hyoid bone. The muscles are then plicated anterior to this incision, thereby recreating a well-defined cervicomental angle. The submental incision is closed in a layered fashion.

AUTOLOGOUS FAT TRANSFER

The patient is marked in the pre-operative holding area in an upright position with the patient in neutral gaze. Areas of volume deficiency are carefully noted. These typically include the nasojugal, submalar, malar, nasolabial and geniobuccal regions. Marionette lines and prejowl sulci can be filled to restore a more youthful shape. The submental crease can be augmented to ease the transition to a ptotic chin. Areas of concern are addressed based on extensive pre-operative discussion with the patient with the aid of digital photographs. Potential donor sites are examined. The most easily accessed harvest sites during an aesthetic facial surgery are those that do not require significant patient repositioning, including the abdomen, flanks and lateral thighs. The medial thigh is a potentially robust donor site but requires minor repositioning to a frog leg position to facilitate harvest. Quite frequently, autologous fat grafting is undertaken in conjunction with other



Figure 88.4 Patient treated by SMAS imbrication rhytidectomy with upper and lower lid blepharoplasty, submental liposuction, platysmaplasty and chin augmentation. Pre-operative views (top row). Post-operative views (bottom row).

aesthetic facial surgery to achieve an optimal result. Thus, it is most aptly considered a complementary procedure.

We usually undertake fat grafting as part of an extended procedure requiring general anaesthetic. However, fat grafting can be performed under the spectrum of anaesthetic options. During surgery, the donor sites are prepped into the sterile field. A small aliquot of local anaesthetic is infiltrated subcutaneously at the site of planned incisions. A 11 blade scalpel is used to create a 3 mm stab incision at the site of planned harvest. Incisions within the umbilicus are placed within a natural skin fold if present.

A tumescent liposuction technique is used to harvest the fat for transfer. Tumescent solution containing 20 mL of 1% lidocaine and 1 amp of epinephrine in 1 L of isotonic saline is infiltrated into the subcutaneous fat plane using a blunt-tip cannula. The tumescent solution is permitted to stand for a period of time prior to liposuction to allow for adequate vasoconstriction. Fat is then harvested using a liposuction technique similar to that described above. A 2–3 mm blunt multihole cheese grater type cannula is preferred for the harvest. Careful attention is paid to the plane of harvest to avoid irregular scarring of the dermis or entry into the abdominal cavity. The non-dominant hand continuously palpates the depth of the cannula and controls its movement. The amount of fat required for facial injections is typically well below the volume

performed in a standard liposuction procedure, which decreases the morbidity of the technique substantially. Patients should be counselled not to expect a significant aesthetic improvement at the donor site.

Once the fat is harvested, it is transferred from the suction cannister and placed in 10 mL Leuer-lock syringes. These syringes are capped and placed in a centrifuge in sterile sleeves and spun at 3000 rpm for 3 minutes. The infranatant is drained away and the fat is placed in 1 mL tuberculin syringes for injection.

For introduction of the injection cannula, 3 mm stab incisions are created with a 11 blade scalpel. A typical injection can be accomplished through three such incisions on each side, in the submalar region, the base of the nasolabial fold and the peak of the geniobuccal sulcus adjacent to the corner of the mouth. Additional incisions can be placed as needed. The premarked regions are then carefully injected with fat using a blunt 20 G injection cannula (**Figure 88.5**). Constant controlled motion and attention to the depth of injection help prevent irregularities. Microaliquots of fat are carefully deposited in multiple tissue planes. The volume is determined by the degree of deficiency and the patient's goals for rejuvenation. Special attention is paid to the depth of injection in the nasojugal region and along the orbital rim, where thin skin is very unforgiving of irregularities. The non-dominant hand protects the orbit during injections of the upper midface near the eyelid–cheek junction. When completed, the incisions can be closed with a single fast-absorbing gut suture. **Figure 88.6** shows pre- and post-operative photographs of a patient who underwent autologous fat grafting using the above technique.

COMPLICATIONS

Haematoma

Haematoma formation is the most common complication of facelift surgery. In most modern series, the incidence of haematoma is reportedly less than 4%.[27] A majority occur within 48 hours post-operatively and often within the initial 6–8 hours. Poor haemostasis, extended skin flaps and severe hypertension have all been purported to be influential factors.[28] Some haematomas are so small they are considered clinically insignificant and can be observed expectantly. Others result in a discrete pooling that should be addressed in a timely manner with aspiration using a large-bore needle. Alternatively, a small stab incision made within a well-developed skin crease will allow adequate drainage. Application of a pressure dressing may help in preventing recurrent formation.

An expanding haematoma is a surgical emergency requiring immediate attention. This is heralded by acute swelling, pain and discolouration along the buccal surface. All surgical dressings must be removed and the skin flaps inspected closely. If flap viability is in question, the immediate removal of consecutive sutures may temporarily restore adequate circulation. Exploration of the wound and evacuation of all visible clot, preferably in the operating room, is mandatory. In a majority of cases, the specific source of bleeding is never identified.[29] Nonetheless, failure to recognize and treat haematoma can result in abnormal pigmentation, alopecia, skin puckering and flap necrosis.

Nerve damage

Nerve damage resulting from rhytidectomy is a rare occurrence. Baker and Conley reported a 0.1% incidence of permanent nerve damage in a series of 6500 rhytidectomies.[30] The most commonly injured branch is the great auricular nerve. Mechanisms of injury include inadvertent dissection deep to the sternocleidomastoid fascia, plication of the postauricular SMAS and transmission of the thermal electrocautery. In most cases, the integrity of the nerve has not been disrupted and full return of sensation can be expected.

Branches of the facial nerve are the most commonly injured motor nerves in rhytidectomy. Proximity to the plane of dissection, especially during elevation of the SMAS, makes them particularly vulnerable to mechanical injury. The frontal nerve is most often injured during SMAS elevation near the zygomatic arch. Within this region, the frontal nerve becomes increasingly superficial as it courses over the middle segment of the arch. If surgical



Figure 88.5 Markings for facial fat injection (a left). Intra-operative view during injection procedure **(b right)**. An injection cannula is used for infiltration.



Figure 88.6 Patient treated by facelift, endoscopic browlift and upper blepharoplasty with autologous fat injection. Pre-operative views (top row). Post-operative views (bottom row).

dissection is limited to the posterior one-third of the arch, risk to the frontal nerve branch is virtually negated. Injury to the marginal mandibular nerve typically results from transection of the platysma or excess SMAS retraction near the angle of the mandible. Fortunately, nearly 85% of paralyzed motor branches will recover spontaneously with minimal residual deficits.

Skin slough

Skin slough most commonly arises as a consequence of unrecognized and untreated haematoma. Excess skin tension and disruption of the subdermal plexus are also frequent causes. The toxic effects of smoking have long been recognized as another predisposing factor in skin sloughing.[31] The postauricular flap is at greatest risk because skin tension is typically highest in this region. Dependent flap length is also maximal and the skin is relatively thin along this surface. In general, expectant management with meticulous wound care is the rule for skin sloughing. However, frequent visits and repeated patient reassurance are necessary. Superficial epidermal sloughing typically results in an acceptable appearance after healing. In cases of full-thickness sloughing, eschar formation is

seen and serial debridement is required to promote healing by secondary intention. Invariably, patients with full-thickness loss can expect some degree of hypertrophic scarring and abnormal pigmentation.

Alopecia

Alopecia in the temporal region is a common complication of rhytidectomy and one that is easily avoided with careful incision design and placement. In some cases alopecia is a transient phenomenon, termed telogen effluvium, attributed to temporary follicular shock. In other instances alopecia is more permanent, for example when the hair follicles have been injured by thermal electrocautery. If no evidence of regrowth is noted after a waiting period of 4–6 months, hair restoration can be attempted using either micrografts or local skin flaps.

Satyr ear deformity

Satyr ear, or 'devil's ear' deformity, results from improper incision placement around the lobule and/or overzealous excision of the skin flap. Tension caused by post-operative relaxation of skin leads to an inferior displacement of the lobule and abnormal banding. This complication can be avoided by preserving a tight supporting margin of skin below the lobule attachment that actually pulls up on the lobule.

Complications of fat injection

When performed correctly, fat grafting by injection is a safe technique with few and rarely significant complications. Irregularities of contour are the most frequently encountered complication. These can range from a discrete focal irregularity that can be managed with simple excision, to generalized overcorrection, which is very difficult to manage. Intralesional steroid injection, ultrasound therapy and local massage all represent viable conservative treatment methods of minor focal deformities. The transplanted fat can be susceptible to changes in weight, particularly large amounts of weight gain, which lead to the overcorrection deformity. Pre-operative counselling should clearly address these issues, and a conservative approach to fat grafting is always preferable. Donor site morbidity can include haematoma, infection, bruising and dermal scarring. These can be minimized with careful harvesting technique.

The most serious complication of fat or other filler injection to the face is inadvertent intravascular injection resulting in embolism, which can lead to serious adverse events including blindness, stroke and local tissue ischemia or necrosis.[32] Marked local blanching of the skin is a warning sign and should lead to a heightened degree of suspicion. Immediate actions that can be taken include applying nitropaste locally, performing local massage and placing the patient in the Trendelenburg position.[13] Better still is to practise careful injection technique to minimize this risk, by using blunt-tipped cannulas with initial aspiration, low injection pressures, small volumes per pass, or local epinephrine to induce vasoconstriction. As always, the clinician should develop an injection plan based on a detailed understanding of the underlying facial vascular anatomy.

BEST CLINICAL PRACTICE

- ✓ A post-tragal facelift incision is used in most female patients, while a pretragal incision is used in males.
- ✓ Elevation of the skin flap and SMAS flap should be limited to the posterior one-third of the zygomatic arch to avoid injuring the frontal nerve branch.
- ✓ The postauricular skin flap is suspended superiorly and anteriorly, while the preauricular skin flap is suspended superiorly and posteriorly. It is imperative to avoid excessive tension on any portion of the skin flap.
- ✓ Submental liposuction and/or platysmaplasty should be considered in patients with neck fullness not attributed to excess skin alone.
- ✓ Post-operative haematoma formation requires timely assessment and intervention to minimize chances of a suboptimal aesthetic outcome.
- ✓ Facial fat injections must be performed carefully with proper technique to avoid complications.

FUTURE RESEARCH

- ➤ Advances in rejuvenation of the midface and upper third will allow for more natural surgical rejuvenation.
- ➤ Techniques and applications for fat grafting will continue to expand, particularly as the underlying biology is better understood.

KEY POINTS

- Sun damage to the skin, atrophy of tissues and the effects of gravity bring on the changes seen in the ageing face patient.
- Pre-operative analysis is critical to determine the specific needs of the patient.
- Incision placement is critical to help hide incisions and avoid deformity of the hairline.
- Patients must stop smoking cigarettes 3–4 weeks before surgery to avoid vascular compromise and necrosis of skin flaps.
- Dissection of the SMAS allows correction of jowling over the body of the mandible and neck deformity. Placement of tension on the SMAS plication takes tension off the skin closure.
- The most commonly injured nerve in facelift surgery is the great auricular nerve.
- The incidence of haematoma formation is less than 4%. An expanding haematoma constitutes a surgical emergency.
- Facial fat injection is a valuable adjunct to ageing face surgery, as it directly addresses facial volume deficiency associated with ageing.

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CHAPTER
89

NON-SURGICAL REJUVENATION OF THE AGEING FACE

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SEARCH STRATEGY

Data in this chapter may be updated by a search of PubMed using the keywords: non-surgical face, look younger, hyaluronic acid fillers, collagen stimulation, polycaprolactone, botulinum toxin, botox, retinoids and chemical peels.

INTRODUCTION

Ageing transforms the face to create a look that often does not reflect the vibrant person inside. Maintaining a youthful appearance can have a profound effect on self-esteem and personal and professional relationships; the exponential uptake of facial aesthetic procedures requires no further explanation. In this chapter, an overview of the core non-surgical interventions which are recognized to be safe and effective is provided.

The causes of ageing in relation to facial appearance may be intrinsic or extrinsic. Intrinsic skin ageing is caused by the same genetic pathways that lead to ageing of all the other organs of the body; thin, atrophic, hypopigmented and fragile skin results from a total reduction in cell count and function. Intrinsic ageing of the subcutaneous tissues is also highly relevant as bone resorption, muscle atrophy and variable atrophy and hypertrophy of individual fat compartments leads to ptosis of the soft tissues, sagging, hollowing and rhytids.

Extrinsic skin ageing is caused by lifestyle and environmental factors. Notably, skin ageing is rapidly accelerated from excessive exposure to ultraviolet light and smoking; several observational and twin studies have demonstrated this. Recent evidence suggests that environmental hydrocarbon pollution and infrared light exposure may also be contributory to skin ageing. The results of extrinsic ageing are the presence of increased fine and deep lines from loss of elastin and collagen fibres, solar elastosis from the disorganization of elastin fibres creating a sallow colour tone, hyperpigmentation usually in the form of solar lentigines, and erythema from telangiectasias. These characteristics are often referred to as the signs of 'photoageing'.

It is important to establish the concerns of any patient considering non-surgical treatments. Typically, these are to improve the appearances of fatigue, to appear less angry and negative, and to brighten skin tone and freshness. In general, the desire to appear 'well' and optimum for chronological age, and to maintain this, is a frequent and realistic goal. Looking substantially younger or back to a certain stage in life is perhaps more unrealistic and must be addressed in the pre-procedure consultation.

Broadly speaking, non-surgical treatment modalities may be considered by anatomical layer depending on whether they address changes in the epidermis (e.g. topical treatments and chemical peels), atrophy and inelasticity of the dermis (e.g. topical treatments, chemical peels and fillers), dynamic facial lines caused the pull of the underlying muscles of facial expression (e.g. botulinum toxin injections), and loss of volume at sites of fat or bone resorption (e.g. fillers). Effective facial rejuvenation requires a treatment plan to fit the unique requirements of an individual patient, and providers ought to be familiar with a range of treatment modalities that allow this to be provided. All too often, many doctors, even those who specialize in facial aesthetics, are 'married to one therapy' and this may not be conducive to optimal outcomes.

TOPICAL TREATMENTS AND COSMECEUTICALS

Topical treatments are popular among consumers seeking improvement of cutaneous signs of ageing because of their convenience, low cost and excellent safety profile. While results may be modest, topical treatments often represent a starting point before progressing towards more invasive facial rejuvenation treatments. A myriad of products are available on the market and this causes confusion for consumers and physicians alike. The relative lack of regulatory restrictions on cosmetics has allowed a range of products categorized as 'cosmeceuticals' to flourish. These are cosmetic products which are purported to provide superior benefits to the skin compared to simple cosmetics while not affecting the structure and function of the skin, as this would otherwise classify them as drugs. The level of evidence required by cosmeceuticals falls significantly short of those required by medicinal products. A greater reliance on *in vitro* data, which is often extrapolated to human skin, is frequent for cosmeceuticals. This allows exemption from the heavy regulatory requirements that *in vivo* research may bring about and which may show changes to structure and function of the skin and cause products to be classified as medicinal instead.[1] Somewhat exaggerated claims of efficacy, often based on *in vitro* data alone, are also not uncommon, which further adds to the confusion.

It is unsurprising therefore that consumers often look towards their physician for advice and recommendations. The yield for physicians is also quite high as, aside from providing an opportunity to build a therapeutic relationship with appearance-conscious patients, 40% may go on to use physician-recommended topical products following initial consultation. Of these, one-third will undergo chemical peels and up to one-quarter will undergo facial injectable treatments in the future.[2] Topical treatments may therefore be considered the first rung of the non-surgical rejuvenation ladder. A topical treatment plan is tailored to the individual needs of a patient and may be designed to target one or more indications (**Table 89.1**).

A selection of topical agents, both medicinal and cosmetic, that a facial plastic surgeon may wish to become familiar with are discussed further here. An in-depth assessment of all available agents is outside the scope of this chapter and the reader is referred to the many excellent texts available on the subject.[3] Advice on the avoidance of lifestyle factors which cause accelerated skin ageing and increased perceived age, such as excessive sun or sunbed exposure and smoking,[4] should supplement and underpin a topical rejuvenation plan.

TABLE 89.1 Indications for topical treatments

Concerns	Clinical signs
Ageing	Fine lines, poor skin texture, photodamage, solar elastosis, atrophic skin
Pigmentation	Solar and post-inflammatory pigmentation
Inflammation	Dry skin, redness and sensitivity
Follicular disorders	Acne, rosacea, folliculitis, enlarged pores

Prescription topical products

RETINOIDS

Retinoids are found in medicinal preparations (requiring a prescription) or in milder forms in over-the-counter formulations (**Table 89.2**). Their use for the treatment of acne dates back to 1959. Kligman's seminal studies in the early 1980s first established the role of tretinoin for the reversal of skin ageing.[5] Since then, over 20 randomized studies have shown the benefits of tretinoin in photodamaged skin.[6] Prescription topical retinoids are the most powerful, effective and evidence-based topical anti-ageing product currently available. Consequently, topical retinoids should form the cornerstone of any topical rejuvenation plan.

The profound biological effect of retinoids on the skin results from their direct action on a family of nuclear hormone receptors, the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs). These receptors are found in all cells, though the key targets are keratinocytes and melanocytes in the epidermis and fibroblasts in the dermis. Activation of retinoid receptors leads to a molecular chain of events that changes protein transcription and modifies cellular function. Histologically this leads to epidermal hyperplasia and impaction of the stratum corneum (producing smoother skin with a 'glow'), increased dermal collagen type I, III and VII synthesis, reduced collagen breakdown and normalization of elastic tissue organization (improving coarse wrinkling and crepe-like skin texture), and a reduction in melanin synthesis and transfer of melanosomes to keratinocytes (improving solar pigmentation).[6] Epidermal effects are seen within 6 months of use, while dermal effects may take a year or longer to become apparent. Treatment ought to be continued indefinitely for continued benefit.

A concentration of tretinoin of 0.025% is considered therapeutically effective while minimizing side-effects. Greater concentrations are associated with a higher incidence of cutaneous toxicity including erythema, scaling, pruritus and sensitivity, and may produce only marginal, if any, additional clinical benefit. Side effects may also occur at lower concentrations and are the most important cause of non-compliance. A typical regime involves the application of tretinoin 0.025% once at night. Strategies to minimize side-effects include using small quantities on

TABLE 89.2 Classification of topical retinoids

Availability	Topical retinoid
Prescription	Tretinoin (all-*trans* retinoic acid) Isotretinoin (13-*cis* retinoic acid) Adapalene Tazarotene
Over-the-counter	Retinaldehyde Retino (all-*trans* retinol, Vitamin A) Retinyl ester

alternate nights initially and gradually increasing this to 1–2 g every night, avoiding astringents, scrubs and detergent-based products, and frequently applying a moisturizer throughout the day. The thinner and more sensitive skin of the eyelids and neck is unlikely to tolerate tretinoin 0.025%, even with incremental exposure, and a compromise is to use an over-the-counter retinol-containing product to these areas. More modest effects are expected as retinol is 20 times less strong.[6]

Non-prescription topical products

HYDROXY ACIDS

The variety of compounds that constitute hydroxy acids is summarized in **Table 89.3**. Many of these have naturally occurring sources. The bathing of Egyptians in soured milk (lactic acid) for beautification over two millienia ago is likely the earliest documented evidence of the use of hydroxy acids for aesthetic skin enhancement.

Alpha-hydroxy acids (AHAs) are the most commonly encountered hydroxy acid in aesthetic formulations. When AHA is applied on pathologically scaly skin such as that found in hereditary ichythosis, the thick stratum corneum separates and a normal thickness epidermis results. The opposite occurs when it is regularly applied on atrophic and aged skin where the epidermis is noted to thicken over a period of several months and revert to a normal thickness.[7] Typically, over-the-counter formulations have concentrations of AHA in the range of 10–12% and are used once or twice a day. A 22-week double-blind randomized controlled trial showed superiority of 8% AHA cream over vehicle in improving the signs of photodamage and sallowness to the skin.[8]

Dermal thickness may also increase from the daily application of AHA because of increased deposition of glycosaminoglycans in the dermis.[7] In addition, glycolic acid has been shown to increase fibroblast proliferation and collagen synthesis.[9] Dermal effects are likely only to occur with higher concentrations of AHA (20–25%) which are available in prescription compounded preparations, though a greater incidence of irritant side effects is found. Higher concentrations still (>25%) constitute superficial chemical peels and are applied once, under the supervision of a clinician, and repeated after a period of time.

TABLE 89.3 Classification of hydroxy acids

Hydroxy acid group	Example	Found in
Alpha-hydroxy acid (AHA)	Glycolic	Sugar cane
	Lactic	Sour milk
	Mandelic	Bitter almond
	Citric	Lemon, orange
Beta-hydroxy acid (BHA)	Beta-hydroxybutanoic	Urine
Polyhydroxy acid (PHA)	Gluconic	Skin
	Gluconolactone	Skin
Aldobionic acid	Lactobionic	Lactose from milk
	Maltobionic	Maltose from starch
Aromatic hydroxyl acid	Salicylic	Winter green leaves

VITAMINS

The concept that vitamins may have a beneficial effect on the skin is very easy to grasp by patients, and additional topical vitamins may easily be introduced after establishing patients on a topical retinoid ('vitamin A cream').

Vitamin B3 (nicotinamide)

Nicotinamide (niacinamide) is the active form of vitamin B3 and is a precursor to a family of enzyme cofactors integral to cellular metabolism. In addition, nicotinamide inhibits poly (ADP-ribose) polymerase-1 (PARP-1).[10] When taken orally at a dose of 500 mg twice a day for 12 months, nicotinamide reduces the incidence of actinic keratosis, basal cell carcinoma and squamous cell carcinoma in individuals who have previously had non-melanoma skin cancer.[11] A 4% nicotinamide gel is available over the counter in the UK and has been shown to be effective for acne,[12] while 2% nicotinamide cream applied to the face for 4–6 weeks reduces sebum production, and improves facial shine and oiliness.[13] A split face study reported that 5% nicotinamide cream applied twice daily for 12 weeks improved fine lines and wrinkles, hyperpigmented spots, red blotches and sallowness while also improving skin elasticity.[14]

Vitamin C (ascorbic acid)

Vitamin C is a potent antioxidant and a cofactor in the collagen synthesis pathway. It may also inhibit tyrosinase and so prevent excessive melanin production, and improve hyperpigmentation. Topically, it is available in concentrations of 5–20%. A 5% cream applied for 6 months to the lower neck and arms of 20 women aged 51–59 years led to significant improvements in the visible signs of ageing though skin biopsy did not show altered levels of collagen.[15] A 23.8% preparation applied for 2 weeks improved several parameters including roughness, fine lines and hyperpigmentation without any significant side effects.[16] A 15% vitamin C may be more stable when combined with 0.5% ferulic acid, a plant-based antioxidant, and together with 1% vitamin E, this triple combination formulation doubles the dose of ultraviolet light required to cause sunburn.[17]

BOTANICAL PRODUCTS

Several hundred botanical remedies for skin disorders exist. There is a perception among the public that botanical products are safe, 'natural' and effective purely by virtue of their origin. The lack of high-quality clinical data makes it difficult to place the utility of botanical compounds into the context of day-to-day clinical practice. A selection of commonly found botanical compounds is included in **Table 89.4**. This list is by no means exhaustive.

TABLE 89.4 A selection of botanical ingredients found in topical preparations and their purported effects

Botanical ingredient	Effect(s)
Aloe	Antioxidant, anti-inflammatory
Arbutin	Skin lightening
Caffeine	Anti-ageing
Co-enzyme Q10	Antioxidant, anti-ageing, skin lightening
Green tea	Antioxidant, anti-inflammatory, anti-ageing, skin lightening
Kojic acid	Skin lightening
Lycopene	Antioxidant, anti-ageing
Polypodium leucotomas extract	Antioxidant, anti-inflammatory
Soy	Antioxidant, skin lightening

In summary, topical treatments are the least invasive of all cosmetic interventions, and providing these may facilitate the engagement of patients who are initially hesitant to have injectable or other more invasive treatments. The physician is under an ethical obligation to recommend products which are effective and in the best interests of the patient.

CHEMICAL PEELS

Chemical peeling is the topical application of chemical agents to cause controlled destruction of part or all of the epidermis, with or without the dermis. This leads to desquamation, liquefaction and coagulation of the affected layers, followed by inflammation, and finally regeneration of epidermal and dermal tissues.

Indications for chemical peeling include fine lines and wrinkles, pigmentation disorders such as solar lentigines and melasma, superficial acne scars and benign epidermal growths. Peels can be classified according to the chemical compounds used or the depth of chemical injury that is produced. Results, recovery time and complication rates vary according to the depth of peel.

Superficial chemical peels are limited to the epidermis and are popular among patients as they are effective while carrying low costs, low complication rates and minimal downtime. Safety in all skin phototypes has been established and recovery within 1–3 days is expected. Superficial peels can be performed with various compounds including trichloracetic acid (TCA) at concentrations of 15% and under, alpha hydroxy acids such as lactic and glycolic acid, and Jessner's solution (14% lactic acid, 14% resorcinol and 14% salicylic acid).

Alpha hydroxy acids, in particular glycolic acid (GA), are commonly used superficial chemical peeling agents. GA peels in concentration ranging from 20% to 70% have been shown to be effective in reducing facial hyperpigmentation and fine lines/wrinkles.[18] Salicylic acid peels have a similar profile, and may be more beneficial for acne-prone skin.[19]

Superficial peels are delivered at 2–4-weekly intervals (typically by an aesthetician), and patients frequently report smoother skin which 'glows', as well as tighter pores and fewer inflammatory acne lesions. Patients often 'feel' the results. Lightening or disappearance of solar lentigines and melasma is also possible. As the target of superficial chemical peels is the epidermis, true dermal changes are minimal (if any) and no number of superficial chemical peels can equate to the skin tightening and improvement in rhytids that a single, correctly performed medium-depth chemical peel may achieve.

Medium-depth peels produce chemical injury to the level of the papillary dermis or the very highest part of the reticular dermis. Due to their depth of penetration, medium-depth peels can produce tissue tightening and an improvement in lines and wrinkles produced by an increase in collagen production and reorganization of elastic bundles. The typical agent used for medium-depth chemical peeling is TCA at concentrations over 30%. TCA is a crystalline inorganic compound which causes coagulative necrosis through extensive protein denaturation. The degree of necrosis varies with the concentration of solution applied.

Monotherapy with 50% TCA may penetrate to the desired depth but carries a high incidence of scarring and should be avoided. A better strategy is to pretreat the skin with Jessner's solution, GA or carbon dioxide slush, to make the epidermis more permeable, and subsequently apply 30–35% TCA. This strategy reduces the risk of scarring from TCA substantially, though pigmentary changes are frequent in darker skin types and medium-depth chemical peels are best reserved of skin phototypes I–III. The reader is referred to an excellent review article on medium-depth TCA peeling by Herbig et al.[20]

BOTULINUM TOXIN

'Botox' has been the most revolutionary anti-ageing treatment in recent years. Doctors Jean and Alastair Carruthers noticed that, when they used botulinum toxin to treat patients with ocular spasms, the wrinkles around the eye disappeared. These results encouraged doctors to treat lines of facial expression such as frown lines, horizontal forehead lines, periorbital lines, nasal lines, perioral lines and platysmal bands.

Botulinum toxin type A (BTX-A) is produced by *Clostridium botulinum*. Synthesized as a single-chain polypeptide of ~150 kDa, BTX has relatively little potency until it is cleaved by trypsin or bacterial enzymes into two chains, a heavy chain of 100 kDa responsible for binding to the target structure and a light chain of 50 kDa known as the toxifying chain. These two chains are linked together by a disulfide bond. The light chain contains a Zn^{2+}-binding motif with enzymatic activity. BTX-A is a zinc-dependent endopeptidase.

When BTX is injected into a muscle, the heavy chain of the molecule binds to glycoproteins expressed specifically on cholinergic nerve endings. After internalization of the whole molecule by pinocytosis, the chains are cleaved within the cytoplasm. The light chain binds with high specificity to the soluble N-ethylmaleimide-sensitive

fusion (SNARE) attachment protein receptors essential for exocytosis of acetylcholine. BTX-A cleaves plasma membrane synaptosome associated protein (SNAP-25) that results in a blockade of vesicle fusion.[21]

Around 2–5 days after BTX is injected into a muscle, paresis occurs, which lasts for at least 3 months and gradually starts to wear off. When the muscle relaxes, it stops pulling on the skin and the wrinkle caused by the muscle pull fades away. The objective duration of action in a given patient seems to be stable, but there is a great variability between different people. Even very low doses produce some effect. By increasing the doses, a plateau is reached where further dose increases will not result in stronger effects. Dose-duration correlations exist to a lesser extent.

On the European market, three different branches of BTX-A are officially registered: Botox®/Vistabel® (Allergan), Dysport® (Ipsen)/Azzalure® (Galderma) and Xeomin®/Bocouture® (Merz). The units are not directly comparable. The products have different amounts of complexing proteins or are free of complexing proteins (i.e. Xeomin®/Bocouture®). The diffusion of the different drugs seems to be dependent on concentration. BTX-A has an excellent safety profile and has been used extensively for facial rejuvenation with a focus on hyperkinetic wrinkles and to improve facial wound healing after surgery.

Botulinum toxin for facial dysfunction and palsy

Similar techniques can also be employed for the dysfunctional paralyzed face so as to improve facial symmetry or in the scarred face to improve dermal contour with the use of fillers. Although facial reanimation surgery primarily relies on dynamic reconstructive techniques,[22, 23] it also draws upon adjunct techniques, such as botulinum toxin, which further augments a positive outcome. In our facial function clinic, BTX is used in a number of situations, primarily in the treatment of synkinesis and also to weaken the non-paralyzed side so as to improve symmetry. As can be seen in **Figure 89.1** botulinum toxin plays a large role in the treatment armamentarium of our facial function clinic and is used in nearly 50% of our patients. As a result, we now run two clinics simultaneously within the facial function clinic allowing the botulinum toxin treatment clinic to run parallel.

Acute facial palsy is the most frequent cranial nerve impairment encountered by otolaryngologists, often presenting as an acute idiopathic facial palsy or Bell's palsy as it is commonly known. Current evidence suggests that 71% of Bell's palsies recover completely and 29% do not. Of those reaching a full recovery, 85% do so within 3 weeks. In Peitersen's study contracture and synkinesis were seen in 17% and 16% of the patient cohort respectively.[24] Synkinesis refers to the abnormal involuntary facial movement that occurs with voluntary movement of a different facial muscle group. The pathophysiological basis of facial synkinesis is likely to be multifactorial although the predominant mechanism appears to be aberrant regeneration of facial nerve fibres to the facial muscle groups. Considering the facial nerve contains approximately 10 000 nerve fibres of which 7000 are motor and the remaining are a combination of parasympathetic efferents and sensory afferents, there is little wonder that disorganization can occur.

The preparation of botulinum toxin in the facial palsy clinic includes 500 units of Dysport which is made up to 5 mL of normal saline; this gives 10 units per 0.1 mL concentration. The Dysport is injected at an angle of 45 degrees using a 1 mL insulin syringe. Local anaesthetic

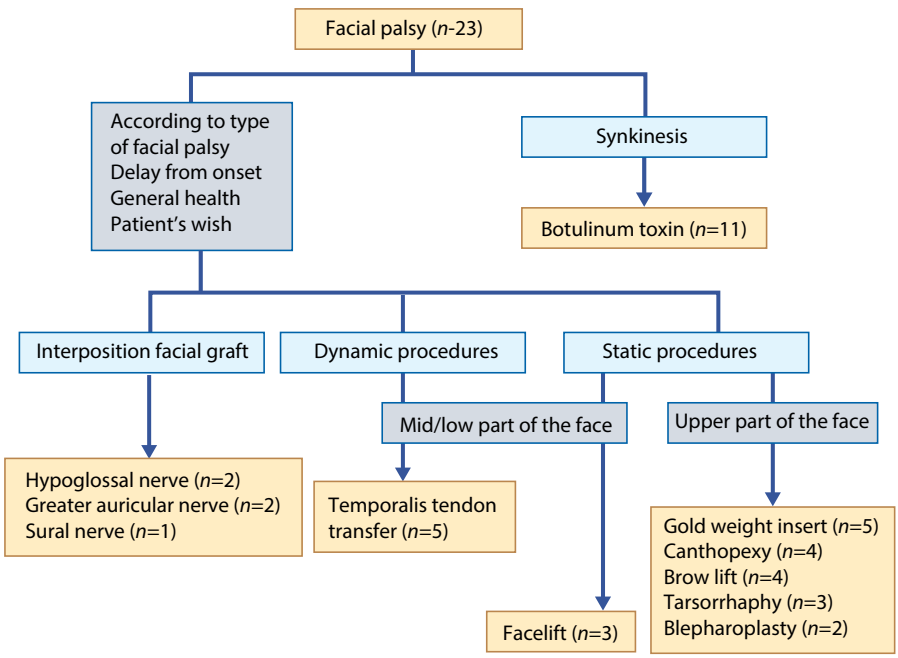


Figure 89.1 Synopsis of facial function treatments.

is not routinely used. In cases of synkinesis, an initial dose of 10 units is used at multiple points within the synkinetic muscle and, in our practice, botulinum toxin is judicially used on the first occasion and then adjusted at 6 months depending on response. We recommend caution when injecting around the orbicularis oculi muscle so as to avoid ptosis and double vision.

As well as for synkinesis we use botulinum toxin for facial contractures following Bell's palsy in particular. These patients can present with disfiguring and painful contractures which come on when stressed or talking, whereby the hemiface goes into contortion. In addition to reducing the contracture, it also helps with the pain. We also employ botulinum toxin in the unaffected overexaggerated side so as to improve symmetry. In a study looking at the use of botulinum injection on the unaffected side of a paralyzed face, the lower muscles of facial expression were injected. The aim of this technique was to reduce the unopposed action of the normal side. The average dose used was 30 units and the affects were first observed at 6 days and lasted up to 4 months.[25]

Botulinum toxin for facial rejuvenation

Temporary chemodenervation of facial muscles responsible for lines and furrows is a well-accepted practice. The commercially available products need to be diluted with 0.9% non-preserved sterile isotonic sodium chloride (saline solution). High dilutions have several disadvantages: more volume needs to be injected, which adds swelling and bruising, less precision as there is more chance of diffusion to adjacent muscles and shorter duration of action. After an informed consent is obtained, the dynamic facial lines are evaluated and standard photographs taken for the purpose of comparison after treatment. The medical history should include any pre-existing facial weakness. Botulinum toxin is contraindicated in patients with underlying neuromuscular junction disorder, allergy to any of its components (human albumin, botulinum toxin), pregnancy and breastfeeding. Aminoglycoside antibiotics and calcium channel blockers may potentiate the effect of the toxin and concomitant use is therefore not recommended.

A regional approach to injection of botulinum toxin facilitates the development of guidelines and injection doses. Total doses should be recorded. Injection of glabellar creases targets the procerus and corrugator muscles, which contribute to dynamic interbrow vertical lines. Asking the patient to frown is the best method for accurately delineating the span of the muscles. The frontalis muscle elevates the brows and creates the horizontal forehead lines. By avoiding the lateral forehead we avoid brow ptosis and a very rigid forehead. However, in patients with an overactive frontalis in the temporal region, undesirable brow arching or 'cocked' eyebrow may occur.

Periorbital lines or crow's feet are produced by the orbicularis oculi muscle, which has a sphincteric action and is responsible for squeezing the eyelids together. This circumferential muscle has three parts: the lacrimal portion assists in tear flow, the palpebral portion passes into the eyelid superficial to the orbital septum and the orbital portion is over the bony aspect and beyond. The lateral and superior aspect of this muscle causes brow depression so, when this downward pull is released, there will be a temporal brow lift. Unlike in glabellar and forehead lines where the injection was deep into the body of the muscle, the injection into orbicularis oculi needs to be superficial. We can strike a balance between the depressors (superior part of orbicularis oculi, corrugator and procerus) and elevators (paired frontalis) and alter brow position. Medial brow elevation can be achieved by treating the glabella, and lateral brow elevation can be achieved by undertreating the lateral forehead (frontalis) and injecting the superior lateral portion of orbicularis oculi.

Bunny lines or nasal scrunch is produced by excessive activity of the nasalis muscle. Patients develop radial lines on the nasal dorsum when they smile or laugh. Vertical and radial perioral lines occur in ageing-related skin changes and habitual lip pursing (as done during smoking). There is a potential side effect of oral incompetence and treatment is therefore not recommended in wind instrument players, vocalists or scuba divers. Angle of mouth or marionette lines are the result of hyperactivity of the depressor anguli oris muscle giving the patient a sad look or a downward curl of the lips. An excessive dose or injection at a site near to the orbicularis oris can weaken this muscle, producing lip drooling and an inability to pucker the lips.

Platysmal bands are the prominent vertical bands that may develop in the neck as part of the ageing process. These vertical bands are the anterior part of platysma and injection with the toxin softens them. A prominent mentalis muscle can produce a horizontal crease or a cobblestoned appearance on the chin. Masseter hypertrophy can cause a square jaw line, widening the face and giving what is considered a more masculine appearance. Injection of the muscle with botulinum toxin can give a more oval-shaped contour to the face.

FILLERS

Different products can be inserted under the skin in different layers to improve angles, lines, folds, scars and flaccidity. The idea is to replace an original volume lost by the ageing process or to create volume. Fillers can be temporary or permanent. Permanent fillers are in our view no longer recommended, as the long-term safety of their use has not been established conclusively. The filler with long-term effect is autologous fat grafting. This technique was popularized and modified by Coleman.[26] As certain faces age, they get thinner, and Lambros[27] does fat injections in every patient undergoing rhytidectomy.

There are, however, some issues surrounding fat transfer. Injected fat can grow – the greatest long-term problem with fat. We have seen increasing numbers of people who have gained weight after their fat injections and whose faces are growing in an unaesthetic manner. Fat is difficult to remove and fat grafts are not reliable. They work better in younger people and the adipocyte survival can be unpredictable, hence they may work better on one

side of the face than the other so touch-up procedures are often necessary. If we tell patients that fat grafting will give them a young-looking face that is smooth, round, full and wrinkle-free, we may end up ballooning the face and removing all the definition and delicacy of the face in a process that is not reversible. The most common complication of fat grafting happens when it is used in the lower lids. Fat survives very efficiently in this area, lumpiness occurs often and it is very noticeable. Around the eyes, temples and nose, temporary hyaluronic acid fillers last up to 3 years, making them a cost-effective, predictable treatment, which gives a smoother result.

Temporary fillers are metabolized by the human body and consist of different substances including collagen, hyaluronic acid, alginates and other polysaccharides. Substances such as polylactic acid and hydroxylapatite have a longer half-life. The most common temporary filler used today is hyaluronic acid (HA), a natural polysaccharide and a component of human dermis and epidermis. HA fillers offer excellent biocompatibility and provide the same structural and mechanical properties of normal subcutaneous tissue. Natural hyaluronan is rapidly broken down by hyaluronidase with a half-life of about 12 hours and eliminated through the lymphatics and by the hepatic metabolism to carbon dioxide and water. As HA is a normal extracellular component of skin, it can be used without skin testing, it has a high tolerability profile and corrections of displacement can easily be done by injection of hyaluronidase. Cross-linking gives HA fillers a life span of 6–18 months.[28] Factors that impact the longevity include the concentration, percentage of cross-linkage, type of cross-linkage, water-binding capacity and injection technique. The final proportion of cross-linked HA and the degree of cross-linking impacts the physical characteristic of the product. The product with a higher concentration and highest degree of cross-linking experiences the least amount of degradation by enzymes and free radicals.[29] The cross-linking agents also have an impact on connective tissue reaction to injectable fillers. Injection technique can play a role in longevity. Injection into the deep dermis has been shown to increase *de novo* collagen synthesis; as the HA is degraded, therefore, novel collagen synthesis replaces the HA, which results in longer lasting correction.

Although there is some evidence that HA stimulates new collagen, the main effect is from its hydrophilic properties. When not bound to other molecules, it binds to water, giving it a viscous quality similar to 'jello'. This is the main drawback of HA; it can give an unnatural overinflated look. Within the extracellular matrix, HA contributes to moisture, but collagen contributes to the scaffolding and keeps skin tight. A newer generation of biodegradable fillers have emerged which possess bio-stimulatory properties. Polycaprolactone (PCL) microspheres of 25 nanometres (30%) in diameter in a carboxymethylcellulose gel carrier (70%) combine durability and immediate outcome. The collagen stimulating effect of the PCL has been confirmed in human skin biopsies from treated subjects.[30] The PCL-based safety has been demonstrated in clinical studies and recommendation on injection techniques are provided for the upper, mid and lower face, and zone by zone for each of these areas.

In addition to manufactured fillers, a relatively new biotechnology autograft, concentrated growth factor (CGF), demonstrates significant stimulation and acceleration of soft-tissue formation. The efficacy of this therapy lies in the local delivery of a wide range and high concentration of growth factors and proteins, mimicking and supporting physiological wound healing, reparative tissue process and local infiltration therapy. The CGF technique was developed to achieve the optimal phase separation and concentrate the factors for maximum recruitment and biostimulation. The CGF therapy is an advanced, powerful anti-ageing treatment for the ultimate natural approach to facial rejuvenation; it is free from toxins and animal products and simply uses the patient's own blood.

CGF treatment may be effective in all aspects of facial aesthetics such as non-surgical facial augmentation, lip enhancement, and treating smile lines, the forehead, cheeks, neck and décolletage.

CONCLUSION

The field of anti-ageing and facial rejuvenation is advancing rapidly and new information and new therapies are discovered almost daily. As new technologies evolve, our goal should be focused on the patient, honesty and achieving a balanced look, which may be part of an overall programme of health and self-improvement. More often than not this is achieved by a combination of tools and we believe the best combination varies with the patient's face and not with what we like to use. Ultimately, while we can have our favourite treatment, it is counterproductive to be doctrinaire about it.

KEY POINTS

- Retinoids are the most powerful, effective and evidence-based topical anti-ageing products available.
- With Botulinum toxin less is more. Avoid creating unnatural folds and a frozen face.
- Manufactured fillers are extremely popular and whilst Hyaluronic acid is safe, it binds up to one thousand times its weight in water, it is a good lubricant 'jello' but when injected in the dermis it can give an overinflated look. The newer generation polycaprolactone-based collagen stimulators restores volume and redefines contours in a more natural way.
- Autologous platelet-rich plasma injections promote tissue remodelling by increasing the expression of Type I collagen in human dermal fibroblasts.

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CHAPTER 90

HISTORY OF RECONSTRUCTIVE SURGERY

Ralph W. Gilbert and John C. Watkinson

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SEARCH STRATEGY

The information in this chapter is based largely on the authors' personal bibliographies, supplemented by reference to standard texts and articles on the history of surgery.

INTRODUCTION

In order to fully appreciate the current state of head and neck reconstructive surgery it is useful to understand its evolution and development. The word plastic is derived from the Greek work *plastikos*, meaning 'to mould' or 'to give form'. The origins of reconstructive head and neck surgery likely predate this linguistic root, as the early papyri of Egypt and the Sanskrit texts of India describe the use of reconstructive procedures to correct facial deformities. Reconstructive surgery over the past many centuries has largely been focused on the correction of deformities of the head and neck. Until the end of the 19th century, 'plastic surgery', as Harold Gillies described it (see The Great Wars, below), was focused on the returning the patient to a normal state, while the cosmetic or aesthetic surgery that developed in the 20th century was essentially focused on surpassing the normal.[1] This chapter will review the history of reconstructive head and neck surgery with a focus on the developments in the 20th and early 21st century.

EARLY HISTORY

Egyptian physicians can be credited with describing some of the first efforts at facial reconstruction. The Edwin Smith Papyrus, the origins of which are dated at approximately 3000 BCE, contains some of the first descriptions of surgical management of mandibular and nasal fractures. Arguably the first documented efforts of reconstructive surgery of the nose and ear are found in the Sanskrit texts of ancient India, written approximately 2600 years ago. During this period of Indian history, reconstructive surgery of the nose and ear was highly valued, as invaders from surrounding territories would often stigmatize their victims by amputating the nose or ear. The early Hindu justice system also imposed harsh penalties on those found guilty of being unfaithful to a spouse by amputating either the genitalia or the nose. It is therefore logical that the nose, a structure of dignity and unique personal identity, would become a focus of reconstructive efforts in the early history of reconstructive surgery.

In his *Sushruta Samhita* (Sushruta's compendium),[1] Sushruta, regarded as the 'Father of Indian Surgery', described a variety of surgical techniques for reconstruction of head and neck defects. Considerable controversy exists over the time period of his contributions, with dates ranging from 600 BCE to CE 1000. He contributed to many fields of medicine but is said to have laid the foundations for a variety of pedicled and rotation flaps. He was the pioneer of reconstructive rhinoplasty, and described more than 15 methods of nasal reconstruction.

ROMAN AND HELLENISTIC

Whether Hellenistic or Roman physicians were exposed to the Indian techniques through Alexander the Great's expedition to India in the 4th century BCE is of debate. Certainly Roman and Hellenistic physicians described

similar techniques to those described in India. Aulus Cornelius Celsus,[2] considered to be the greatest of the Roman medical authors and surgeons, also described a variety of techniques similar to those practiced in India in his medical text of the first century, *De Medecina*.

The royal Byzantine physician, Oribasius, wrote extensively about facial and nasal reconstruction in the 4th century. His comprehensive medical encyclopaedia, entitled *Synagogue Medicae,* followed Celsus. He described in detail the use of bi-pedicle advancement flaps for skin defects of the eyebrow, ala, cheek, nasal dorsum and columella. He described the concept of undermining of advancement flaps. His technique of alar reconstruction may have been the first description of the superiorly based nasolabial flap.

THE MIDDLE AGES AND THE RENAISSANCE

The development of facial reconstruction certainly continued in the Middle Ages. However, following the fall of Rome in the 5th century and the diffusion of Barbarians and Christianity throughout the Middle Ages, a significant decline in the advancement of all surgery, in particular reconstruction, occurred. This decline was certainly aided by Pope Innocent III, who prohibited surgical procedures of all types. It is interesting to note that physicians of the time considered surgery to be a manual skill and below their intellectual and societal stature. The concept of the barber surgeon appeared and the decline of the role of surgery and surgeons began.

The period of Renaissance in the 14th century signalled a rebirth of science, medicine and the world of surgery. In the 15th century the Branca family became prominent in wound reconstruction and the reintroduction of the Indian method of nasal reconstruction.[3] The family apparently zealously protected the techniques they had developed from outside observers and the surgical techniques were passed down through family members. Branca's son, Antonius, inherited this technique and modified it through the use of a delayed skin flap from the arm. This Italian method, as it became known, was eventually transferred to other families of surgeons.

Descriptions of these various techniques may have contributed to Gasparro Tagliacozzi's interest in nasal reconstruction. Tagliacozzi – incorrectly referred to as the originator of the Italian method – made significant contributions to facial reconstructive surgery. Working in Bologna in the latter half of the 16th century, Tagliacozzi described and refined the use of distant pedicled flaps for a variety of facial reconstructions.[4]

THE 17TH AND 18TH CENTURIES

In the late 1600s reconstructive surgery entered into a period of significant decline. This was largely based on misconceptions about transferred tissues, superstition and a lack of belief or understanding of the sciences.

Reconstructive surgery began to emerge in the late 18th century. An often-cited impetus of this renewal was a letter published in *Gentleman's Magazine* in London in 1984 by a British surgeon named Lucas. In this account, Lucas described the reconstruction of the nose of a British bullock driver whose nose was mutilated by the enemy for transporting supplies for the British forces. Lucas explained how a forehead flap was performed by an Indian man of the brickmaker caste. His account was read by a British surgeon, Carpue, who reasoned that if the procedure could be done in India it could be easily done in Britain. Carpue described his experience with two British soldiers for *Restoring a lost nose* in 1816.[5]

In 1818 the German surgeon, Carl Von Graefe, published his major work, *Rhinoplastik*.[6] Von Graefe's book described a variety of reconstructive approaches, including the Indian and Italian methods, as well as his own method utilizing a free skin graft from the arm. He also described techniques for palate reconstruction and blepharoplasty. Because of the breadth of his contributions he is regarded as one of the fathers of modern plastic surgery.

Johann Dieffenbach began his practice in Berlin in 1823, with a great interest in plastic surgery and nasal reconstruction. In 1840, following the death of Von Graefe, Dieffenbach assumed the chair at the University of Berlin and published extensively on reconstructive plastic surgery and in particular nasal reconstruction and reconstructive rhinoplasty.[7] He also made significant contributions in cleft palate repair and was one of the first surgeons to advocate the use of anaesthesia. Based on all accounts, Dieffenbach was a gifted technical surgeon and a charismatic communicator. His charm and humanitarian spirit captivated the hearts of his patients, colleagues and students. He died in his clinic while preparing for an operative procedure.

Jacques Joseph, a German orthopedic trained surgeon, is widely regarded as the father of modern rhinoplasty. His book *Nasenplastik und sonstige Gesichtsplastik*, published in 1928, remains one of the most comprehensive texts written on the subject.[8] Joseph developed a number of techniques and instruments that are still in use today.

SKIN GRAFTING

As applies to many of the reconstructive techniques used in head and neck surgery, the idea and practice of skin grafting appears to have originated in India; the Hindus reported the use of free skin grafts along with the use of forehead and other facial flaps for reconstruction. The modern interest in skin grafting likely began near the end of the 18th century when Baronio reported the use of skin grafts on sheep.

The first human skin graft was probably performed by Astley Cooper in 1817.[9] In 1869, Reverdin reported on his experience with small 2–3 mm epidermic grafts for serious burns he was treating at the Necker hospital in Paris.[10]

Ollier, who studied the work of Reverdin, emphasized the importance of the dermal component and coined the



Figure 90.1 Tagliacozzi refined the use of distant pedicled flaps for facial reconstruction.



Figure 90.2 Sir Harold Gillies. Reproduced with kind permission from Andrew Bamji, Curator of Archives at the Frognal Centre, Queen Mary Hospital, Sidcup, UK.

term 'skin graft'. In 1872, Ollier performed the first successful full-thickness autograft to treat ectropion.[11]

In 1875, Wolfe described the concept of full-thickness skin grafting over a fresh surgical wound. Wolfe, an ophthalmologist by training, was given credit along with Krause for bringing this technique to clinical practice. The term 'Wolfe graft' is still used in the UK to describe a full-thickness skin graft.[12]

In 1929, Blair and Brown described the use of large split-thickness skin grafts of various thicknesses for different types of wounds characterizing the features of donor site morbidity and contraction.[13]

One of the greatest developments in reconstructive surgery was the development of the dermatome. Developed in 1939 by Padgett, a surgeon, and Hood, a mechanical engineer, it revolutionized the harvesting and application of skin grafting techniques.[14]

THE WORLD WARS

The two World Wars in the first half of the 20th century played a key role in the development of reconstructive head and neck surgery, particularly in plastic surgery, dentistry and maxillofacial surgery. The First World War presented a unique challenge for medical care because of the volume of injured combatants and the nature of the wounds (high velocity projectiles and explosions). On the first day of the Battle of the Somme the British expeditionary force suffered 60 000 casualties, 21 000 of whom were killed.

A number of surgeons had prominent roles in the primary management and reconstruction of these patients. Prominent among the French surgeons was Hippolyte Morestin. Born in Martinique, Morestin worked in the French army's surgical unit at the Val-de-Grace Military Hospital in Paris. He became well known for his expertise in local flaps, advocating the concept of wide undermining as well as developing techniques in z-plasty. Because of the nature of his work and his prominence, many surgeons went to observe his surgery.[15] Perhaps most prominent among these was Harold Gillies (1882–1960). Gillies (**Figure 90.2**) was born in Dunedin, New Zealand, and graduated in medicine from Cambridge. He trained initially in otolaryngology and in 1915 volunteered his services to the Red Cross and was sent to France. Fascinated by the reputation of Hippolyte Morestin, he went to observe his surgery. The nature of the work convinced Gillies to advocate for a specialty hospital for the treatment of facial and jaw injuries for British combatants. Interestingly, when Gillies made a return visit to observe Morestin, he was refused entry into the operating theatre.

In 1916, the British War Office established a unit at the Cambridge Military Hospital, Aldershot. The Aldershot facilities proved inadequate and in 1917 the unit was moved to The Queen's Hospital (renamed Queen Mary's Hospital in 1927) at Sidcup in Kent. Gillies treated and documented the care of numerous patients and developed his craft at Sidcup. Significant among his developments

were the refinement of the tubed flap and skin grafting for defects of the eyelid (**Figure 90.3**). Gillies' wartime experiences provided the material for his classic book, *Plastic surgery of the face*, published in 1920.16 This beautifully illustrated text set down Gillies' rules of reconstructive surgery and certainly cemented his reputation as one of the fathers of modern 20th-century plastic surgery. Gillies and Sidcup played a major role in the training of surgeons from around the world. Ferris Smith, also originally an otolaryngologist, became a prominent American plastic surgeon. Other prominent surgeons included Pickerill from New Zealand and Risdon from Canada. For his contributions to the care of the injured and his major contributions to the field, Gillies was knighted in 1930.

Between the wars, plastic and reconstructive surgery flourished in North America. In 1919, John Staige Davis published the first American plastic surgery textbook, *Plastic surgery – its principles and practice*, which became a classic in the field.[17] The 1920s and 1930s saw the development of many professional societies dedicated to plastic surgery in North America and a rapid expansion in the number of plastic surgeons in the United States.

The Second World War facilitated further developments in reconstructive surgery of the head and neck. In the UK there were only four plastic surgeons (The Big Four: Gillies, Kilner, Mowlem and McIndoe). At the beginning of the Second World War the emergency medical services in England set up nine centres for facial and jaw injuries. McIndoe was appointed to the Queen Victoria Hospital in East Grinstead, Sussex, and Gillies was sent to head the unit at Rooksdown House, Park Prewett Hospital, Basingstoke. Gillies continued to develop his expertise in facial reconstruction; McIndoe became famous for developing innovative treatment approaches for severe burns, including the face, and was well known both during and after the war for his expertise and compassionate care.

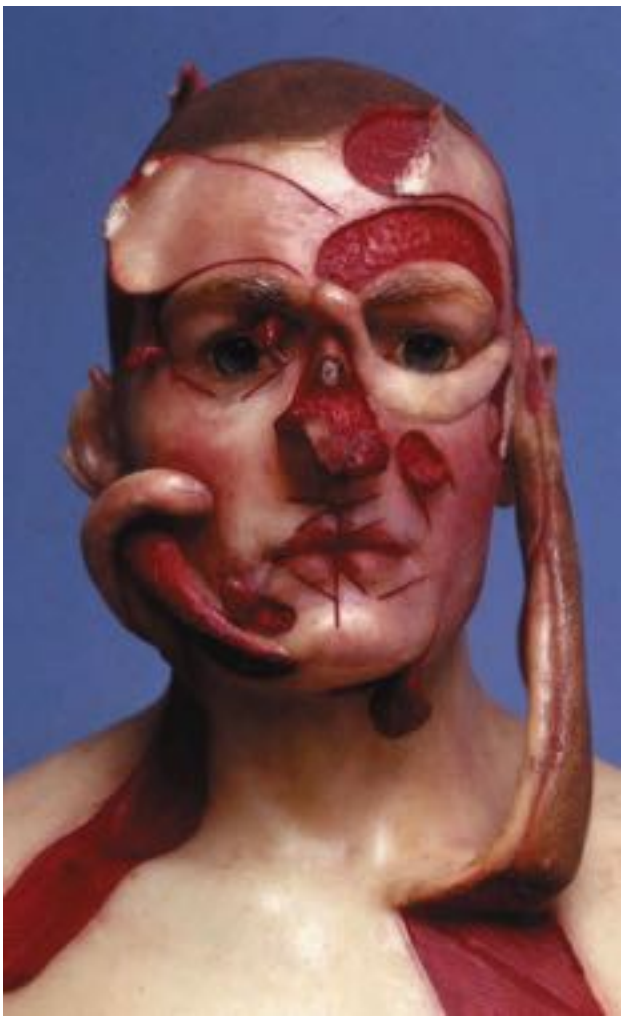


Figure 90.3 Life-size wax model of the head and upper torso, constructed for teaching purposes, illustrating surgical techniques including forehead and tubed pedicle flaps. Part of the New Zealand records returned to Sidcup in 1989 and subsequently restored at Madame Tussaud's. Reproduced with kind permission from Andrew Bamji, Curator of Archives at the Frognal Centre, Queen Mary Hospital, Sidcup, UK.

THE MODERN ERA

The expertise in soft tissue and bone reconstruction that evolved and developed during and after the World Wars changed its focus in the last 40 years of the 20th century. The emphasis on plastic and reconstructive surgery moved to the correction of congenital and secondary deformities and the reconstruction of defects following oncologic resections. Many plastic surgeons became increasingly interested in aesthetic surgery. In the 1950s and early 1960s, the majority of oncologic and post-traumatic reconstruction still utilized the techniques pioneered by Gillies and his contemporaries. In the 1960s, a number of surgical innovations changed the morbidity of head and neck reconstruction. The increasing use of axial pattern flaps made reconstruction of large oral cavity and neck defects more reliable and less costly to the patient in terms of prolonged hospitalization. Foremost among these were the descriptions of the forehead flap for oral reconstruction popularized by McGregor[18] and the deltopectoral flap described in the United States by Bakamjian.[19] In the late 1970s, the description of the pectoralis major myocutaneous flap by Ariyan[20] transformed head and neck oncologic surgery, as patients could be offered a single stage reliable reconstruction with minimal donor site morbidity. In addition, the ease of harvest and transfer of the pectoralis major flap made it a technique that any head and neck-trained surgeon could perform, broadening the scope of reconstructive surgery to other disciplines outside plastic surgery.

The late 1960s and early 1970s heralded the era of reconstructive microsurgery. The concept of free tissue transfer had been developed years earlier but was limited by the quality and availability of microvascular sutures, quality instruments and magnification. Jacobson and Suarez[21] first described the repair of vessels under 2 mm in 1960. The first free tissue transfer of a composite of skin was performed by Taylor and Daniels in 1973.[22] Subsequent developments in reconstructive microsurgery have resulted in the description of a plethora of free tissue

transfers available for head and neck reconstruction, championed by a number of extremely gifted reconstructive microsurgeons including Harii, Buncke, Manktelow and many others.

The more notable among these flaps are: the free forearm flap, described by Yang in 1983[23] and popularized for oral cavity and oromandibular reconstruction by Soutar;[24] the free fibular transfer, originally described by Taylor in 1973[22] and popularized by Hidalgo[25] for mandibular reconstruction in 1995; and the anterolateral thigh flap, described by Song[26] in 1984 and popularized for head and neck reconstruction by Wei[27] in 2002.

As experience has evolved with a vast array of free tissue transfer, creative surgeons from many disciplines and jurisdictions have developed new techniques for reconstruction of the mandible, maxilla, airway and numerous other head and neck sites. The application of these techniques has dramatically enhanced the ability of the head and neck reconstructive surgeon to deliver high quality reconstruction with preservation or restoration of form and function.

The community of specialties performing head and neck reconstruction has changed dramatically over the past 40 years. Head and neck oncologic surgery in the 1950s and 1960s was largely the domain of general and plastic surgeons, with the majority of reconstruction performed by plastic surgeons. In the last three decades of the 20th century, however, some major changes in the specialties treating defects of the head and neck evolved. Increasingly in Europe and North America, otolaryngologists with subspecialty training in head and neck surgery and reconstructive microsurgery began to develop an interest and expertise in head and neck surgery that extended beyond the treatment of laryngeal cancer. At the same time, in Europe, maxillofacial surgery began its evolution as a specialty and, increasingly, maxillofacial surgeons treated and reconstructed congenital, traumatic and oncologic defects of the head and neck.

FUTURE RESEARCH

➤ In the next 10 years, further refinements will occur in the application and evaluation of the various reconstructive microsurgical techniques. The areas of major innovation are clearly tissue engineering and transplantation. Tissue engineering may offer the potential to create composite tissue constructs that will replace the current approaches, including free tissue transfer and the associated donor site morbidity. The most notable and controversial use of tissue engineering in the head and neck site has been the airway work of Macchiarini et al.[28] Vascularized composite allografts (VCA) or transplantation clearly has the potential to dramatically change the field of reconstructive surgery of the head and neck. The recent experiences with face transplants, both in Europe and North America, have highlighted the potential of VCA as well as long-term sequelae of immunosuppression.[29, 30] As the understanding of immune surveillance and improved regimens for immunosuppression evolve, we will likely see a broader application of these techniques in head and neck reconstruction.

KEY POINTS

- Reconstructive techniques to repair facial defects and deformities have been found in ancient Egyptian and Sanskrit papyrus documents dating back over five thousand years.
- Techniques for nasal reconstruction following amputation of the nose developed in India, and were in widespread use until the middle ages.
- Pedicled flaps and free skin grafts were popularized from the late 18th-century onwards.
- Josef Dieffenbach (Berlin) is often referred to as the 'father' of plastic surgery.
- Harold Gillies pioneered techniques for facial reconstructive surgery in Britain, working mainly on servicemen with severe shrapnel injuries during the two World Wars.
- The operating microscope transformed plastic and reconstructive surgery, paving the way for free flaps.

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CHAPTER 91

GRAFTS AND LOCAL FLAPS IN HEAD AND NECK CANCER

Kenneth Kok and Nicholas White

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: reconstructive ladder, skin graft, local flap, regional flap, head and neck reconstruction, wound healing, nasal reconstruction, ear reconstruction, eyelid reconstruction and lip reconstruction.

INTRODUCTION

Defects following head and neck surgery can often be closed using the technique of direct suture. This, of course, applies not only to the skin but also to the mucous membranes of the upper aerodigestive tract. This technique is used when the defect is small and where local conditions mean that enough tissue is available. However, for larger defects or in situations where direct suture is neither applicable nor available, surgical defects in the head and neck can be reconstructed with grafts, local flaps, regional flaps or free-tissue transfer. Occasionally, a combination of these different reconstructive techniques is required as 'building blocks' to reconstruct more complex defects. A **graft** is a piece of tissue that has no blood supply of its own and its survival depends on it gaining a blood supply from the recipient bed. A **flap** is a piece of tissue that has its own blood supply and does not rely on the recipient bed for its survival. This chapter focuses on the use of grafts and local flaps in head and neck reconstruction.

RECONSTRUCTIVE LADDER

The reconstructive ladder is an important concept in reconstructive surgery. It begins with the simplest option first, which is to allow the wound to heal by secondary intention. As one advances up the rungs of the ladder, more complex reconstructive techniques are encountered, up to the highest rung, which is microvascular free-tissue transfer. When analyzing a defect to be reconstructed, the reconstructive surgeon would start at the bottom rung and work his way up, deciding which reconstructive method should be undertaken. There are some instances, however, where the 'reconstructive elevator' should be taken instead and some of the rungs in the reconstructive ladder can and should be skipped. An example of this would be in the reconstruction of a significant defect in the neck following primary tumour excision with exposure of the great vessels. In this case, although a skin graft could theoretically be used and probably would 'take', the risk of exposed vessels would warrant the use of a pedicled or free flap for reconstruction. An example is shown in **Figure 91.1**.

WOUND CLOSURE AND RELAXED SKIN TENSION LINES

Many defects in the head and neck region can be directly closed if they are small and enough tissue is available locally. For larger defects, closure of the wound can be achieved by the different rungs of the reconstructive ladder, dependent on the site, size and extent of the defect. The concept of relaxed skin tension lines is useful when considering where to place skin incisions. These are lines parallel to the natural skin wrinkles and tend to be perpendicular to

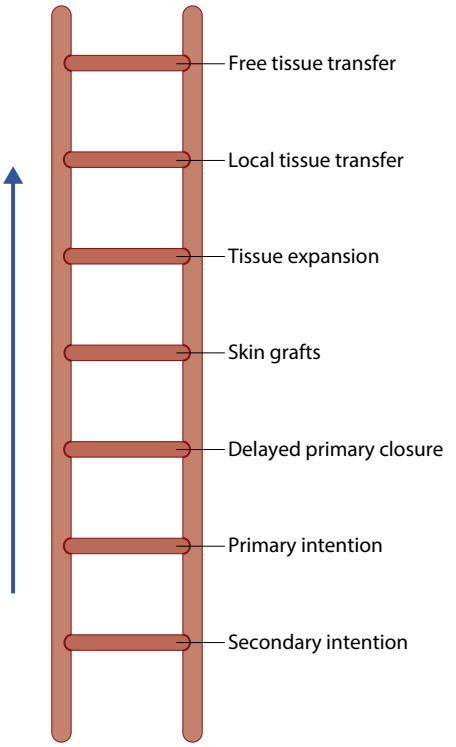


Figure 91.1 The reconstructive ladder.

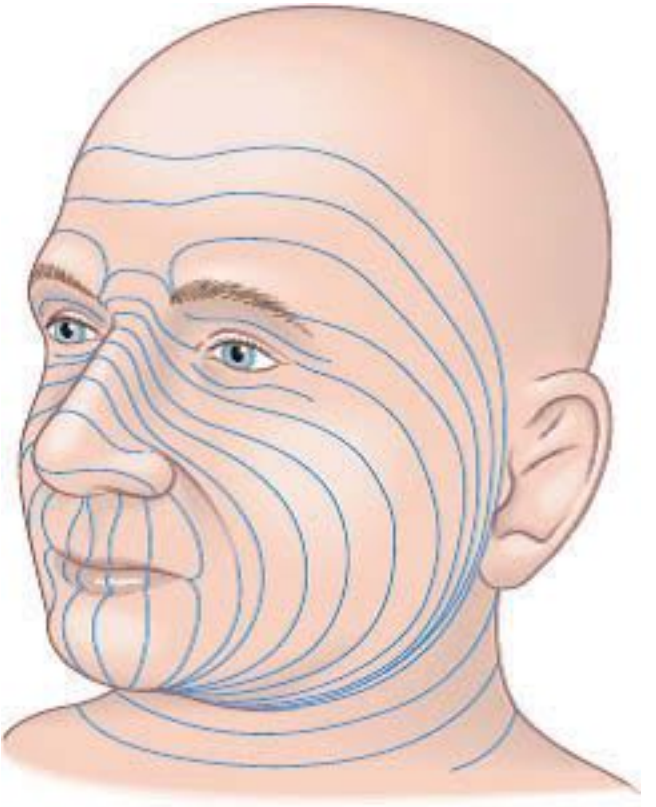


Figure 91.2 Relaxed skin tension lines.

the underlying muscle fibres (**Figure 91.2**). Scars placed parallel to these lines will be under the least amount of tension and therefore will result in the best possible scar. With regards to local flaps, these lines should be considered when closing the flap's donor site, again to minimize tension and allow easy closure.

Wedge excision

Lesions located at the free edge of tissues such as the eyelid, lips and helical rims can be excised as a wedge and repaired. The separate components of these composite tissues must be repaired individually to optimize function and appearance. These layers are, in the lip, the mucosa, orbicularis oris and skin; in the eyelid, conjunctiva, tarsal plate, orbicularis oculi and skin (**Figure 91.3**).

COSMETIC SUBUNITS OF THE HEAD AND NECK

The face is divided into multiple cosmetic subunits (**Figure 91.4**). These cosmetic subunits should be taken into account when reconstructing defects in the head and neck to optimize cosmesis. Ideally, individual subunits should be reconstructed separately and scars should not cross the subunits if possible. It is therefore preferable to use a graft or a flap to reconstruct one cosmetic subunit and a second graft or flap to reconstruct an adjacent subunit. If more than 50% of a cosmetic subunit is involved, it may be desirable to excise the entire subunit and reconstruct it to obtain an optimal result.

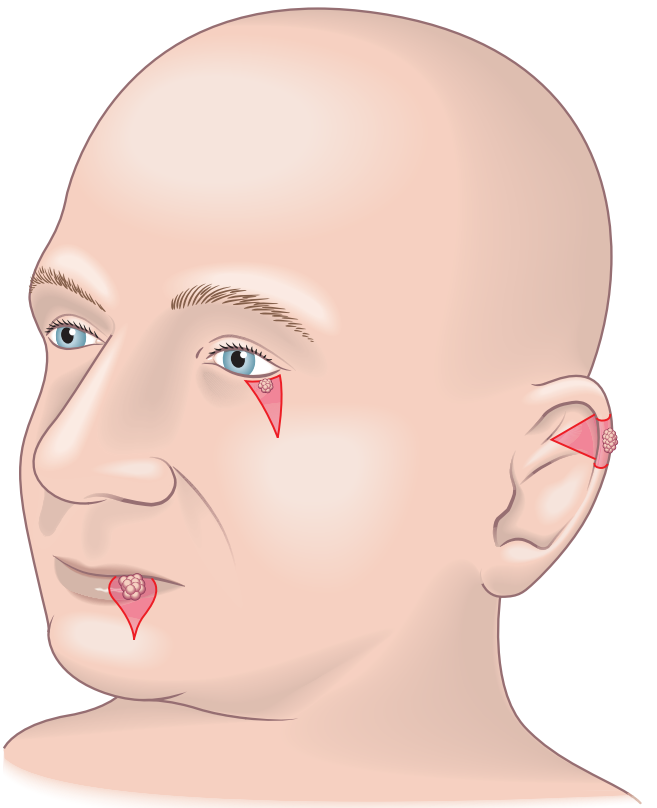


Figure 91.3 Wedge excision designs in different areas.

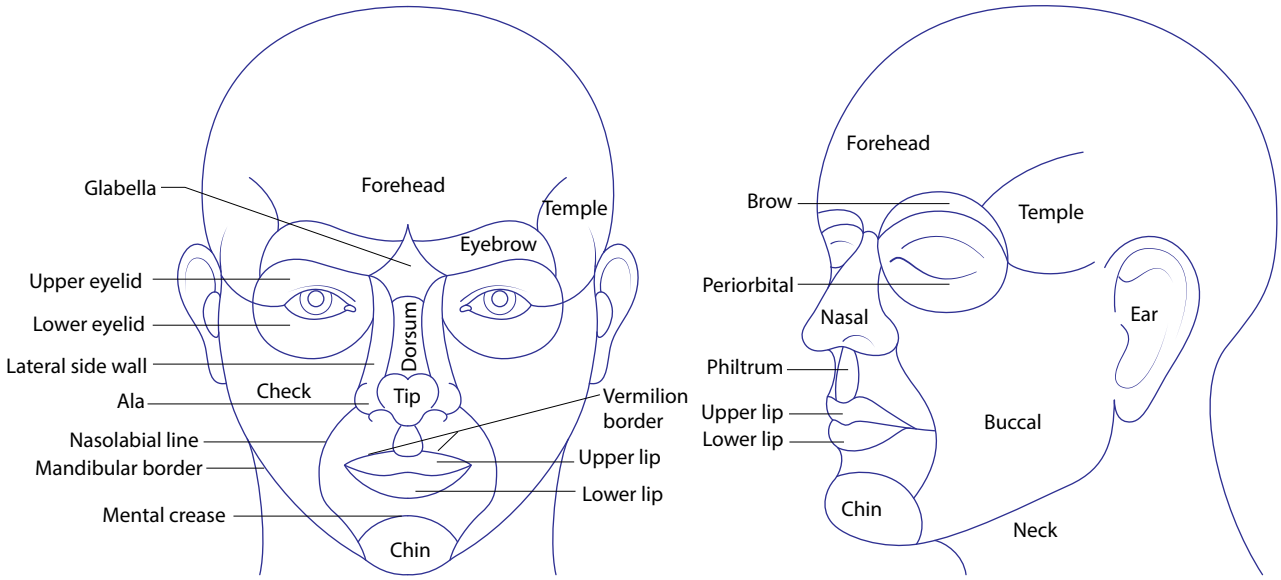


Figure 91.4 Facial cosmetic units.

SKIN GRAFTS

History

Grafting of skin originated in India over 3000 years ago when surgeons took skin grafts from the gluteal region to repair traumatic defects of the face.[1] The first report in the English language was in 1817 when Sir Astley Cooper grafted a full-thickness piece of skin from a man's amputated thumb onto the stump for coverage. Lawson[2] reported successful elective full-thickness skin grafting in 1871, which was followed by Ollier,[3] a French surgeon, describing a split-thickness skin graft in 1872. Thiersch,[4] from Germany, was the first to recognize the importance of recipient site for graft survival, and in 1875 Wolfe used a full-thickness skin graft taken from the patient's forearm to treat a traumatic ectropion of the lower lid following a gunpowder explosion. Full-thickness skin grafting of the eyelids is now a procedure with which Wolfe's name has become synonymous.[5] In 1929, Brown and Blair[6] differentiated between full-thickness and split-thickness skin grafts; they identified the advantages and disadvantages of each and, using their techniques, consistent, acceptable results were achieved. Medawar[7] studied the underlying biology of healing skin grafts in the 1940s. His work described the cellular changes in both the epidermis and dermis, giving the technique of skin grafting a scientific basis and laying the foundation of modern transplant immunology.[8]

Introduction

A **graft** is a piece of tissue that is transferred from one site to another, devascularizing it in the process. The area from which the graft is taken is known as the **donor site** and the area to which the graft is applied is known as the **recipient site**. Grafts can be classified according to their composition – skin, bone, cartilage, fat, mucosa, or composite grafts which consist of two or more different tissue types[9] (e.g. a septal mucosal graft consisting of septum and mucosa). They can also be classified according to their source. An **autograft** is a graft taken from one part of an individual's body and transferred to a different part of that same individual. An **isograft** is a graft transferred between genetically identical individuals, such as between identical twins. An **allograft** is transferred from one individual to another of the same species. A **xenograft** is a graft transferred between different species.

Skin grafts are of two types: **split-thickness** skin grafts (STSGs) or **full-thickness** skin grafts (FTSGs) dependent on the dermal content of the graft. FTSGs contain epidermis and all of the dermis whereas STSGs contain epidermis and a variable amount of dermis (thin, intermediate or thick) (**Figure 91.5**).

Skin graft healing

Once a skin graft has been harvested, it has been detached from its blood supply and is, temporarily, not viable. In order to survive permanently, it has to become reattached and obtain a new blood supply from its recipient site; this process is known as 'take'. Skin graft take is a continual biological process but, for convenience, it can be divided into four main stages (**Table 91.1**):

1. Skin graft adherence (immediate)
2. Serum imbibition (first 24–48 hours)
3. Revascularization (48 hours to 3 weeks)
4. Remodelling (3 weeks to 1 year)

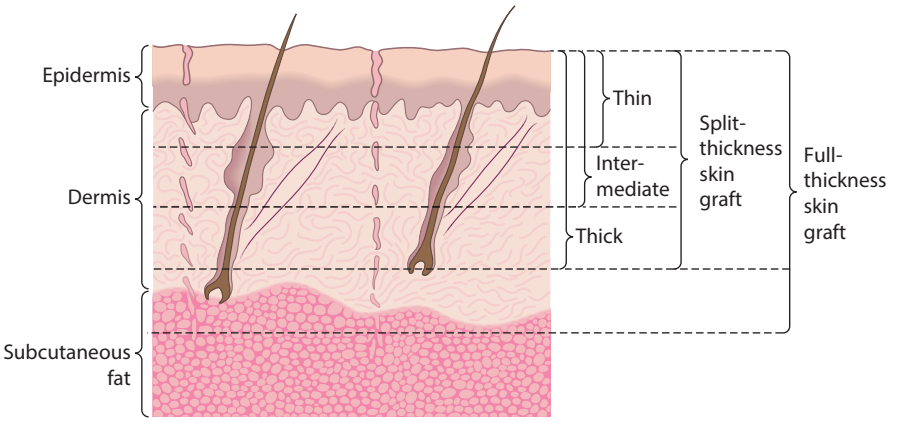


Figure 91.5 Skin graft thickness.

TABLE 91.1 Graft healing

Stages of graft healing	Time period	Mechanism
Graft adherence	Immediate	Graft adheres to recipient bed through formation of fibrin layer
Serum imbibition	Up to 48 hours	Graft survives via absorption of nutrients from a recipient bed
Revascularization	48 hours to 3 weeks	Inosculation – joining up of cut vessel ends in graft and recipient bed Revascularization – ingrowth of vessels into the graft producing new vascular channels Neovascularization – ingrowth of vessels down basement membrane
Remodelling	3 weeks to 1 year	Maturation and remodelling of the graft with collagen reorganization

Initially, when the graft is applied, it becomes adhered to the recipient bed by the formation of an intervening layer of fibrin.[10] Within 48 hours, the thin fibrin layer starts to break down and adhesion to the bed is maintained by the proliferation of fibroblasts and the deposition of collagen.[11] During this period of initial adherence, the skin graft survives through the passage of nutrients from plasma leaking from capillaries in the recipient bed. This is known as serum imbibition.[12] During this time, the graft gains weight and swells. The skin graft, however, cannot depend on serum imbibition indefinitely and, after 48 hours, revascularization of the graft begins to take place. There are several methods by which this occurs: namely inosculation, revascularization and neovascularization.

- **Inosculation** is the process of the joining up of the cut ends of the vessels in the recipient bed with the cut ends of vessels in the skin graft.[13]
- **Revascularization** is the actual ingrowth of vessels into the graft to produce new vascular channels.
- Alternatively, the endothelium of old cut vessels degenerate, leaving behind its basement membrane and this acts as a conduit for growth of capillary buds. This is known as **neovascularization**.[14]

All these processes continue for up to 3 weeks until revascularization of the graft is complete. Once the graft has become revascularized, it undergoes maturation and remodelling with collagen reorganization and increasing strength.

Factors affecting graft healing

Successful take of a skin graft is dependent upon the extent and speed at which vascular perfusion is returned to the graft. This is determined by graft factors, local and systemic factors. To obtain successful graft take, each of these factors must be optimized.

FTSGs have a higher metabolic demand due to their thickness and therefore have a higher chance of failure compared to STSGs. Local factors, such as the vascularity of the wound bed, are also an important determinant in graft take. Healthy granulation tissue, muscle and fascia act readily as recipient beds whereas fat is less suitable. Bone covered with periosteum will accept a graft but exposed bone and tendon will not. In some cases, exposed bone (such as the outer table of the skull) can be burred to cause pinpoint bony bleeding which will facilitate graft take.

In order for vascular channels to form between the recipient bed and graft, the graft has to be immobilized and in direct contact with the recipient bed. Shearing forces must be avoided and numerous methods such as tie-over dressings, the use of foam and sponges, and bandaging have been described to facilitate graft take. The most frequent cause of graft loss is the presence of a haematoma or a seroma which separates the graft from its recipient bed. Meticulous haemostasis and either meshing or fenestrating the graft to allow fluid to escape will help to prevent this. Infection is another common cause of graft loss and wounds that contain more than 10^5 organisms will not support a graft. Grafted beds which

become infected should be treated with systemic and/or topical antibiotic agents to reduce the risk of graft loss. Common pathogens include *Streptococcus pyogenes*, *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus*, which can all destroy fibrin and prevent graft adherence.[15]

In addition to these local conditions, systemic conditions of the patient can also influence skin graft take. These include diabetes mellitus, smoking, previous radiotherapy and chemotherapy, as well as nutritional status.

Split-thickness skin graft vs full-thickness skin graft

The amount of dermis included with the graft determines both the likelihood of survival and the degree of contraction. All skin grafts contract once removed from their donor site (primary contraction) and again following revascularization (secondary contraction). Primary contraction occurs as a result of the elastin within the dermis whereas secondary contraction occurs due to myofibroblast activity within the wound bed. STSGs can tolerate less vascularity than FTSGs, and undergo less primary contraction but more secondary contraction. They also tend to have abnormal pigmentation, are more susceptible to trauma and usually have poorer sensory recovery. STSGs are hairless due to the lack of hair follicles (see **Figure 91.5**).

FTSGs require a better vascular bed for survival than STSGs and they undergo more primary contraction but less secondary contraction. FTSGs also resists trauma better, tend to provide a better colour match and have improved sensory recovery due the greater availability of neurilemmal sheaths within the dermis. FTSGs also contain hair follicles and will demonstrate similar hair growth to the donor site. These differences are summarized in **Table 91.2**.

Composite grafts

Composite grafts are grafts which contain two or more different tissue types. An example that was used previously is a septal mucosal graft which contains septum and mucosa. Another example is a chondromucosal graft from the ear which contains cartilage and skin. These grafts are useful in reconstructing composite defects, either for complete reconstruction, as in the reconstruction of an alar rim or small defect of an ear, or as partial reconstruction of a more complex composite defect. An example of one such defect is the eyelid where three separate layers (i.e. the mucosa, tarsal plate and skin) need to be reconstructed. In this case, a septal mucosal graft can be used to reconstruct the mucosa and tarsal plate support and a cheek rotation flap can be used to reconstruct the skin defect (**Figure 91.6**).

TABLE 91.2 Advantages and disadvantages of STSGs vs FTSGs

Factor	STSG	FTSG
Amount of dermis	Variable	All of dermis
Chance of successful take	More likely	Less likely
Graft contraction	More contraction	Less contraction
Colour match	Abnormal pigmentation	Better colour match
Robustness	Less robust	More robust
Sensory recovery	Limited	Better
Donor site healing	Heals secondarily	Heals through primary intention
Size of graft	Large grafts can be harvested	Limited due to need for primary closure of donor

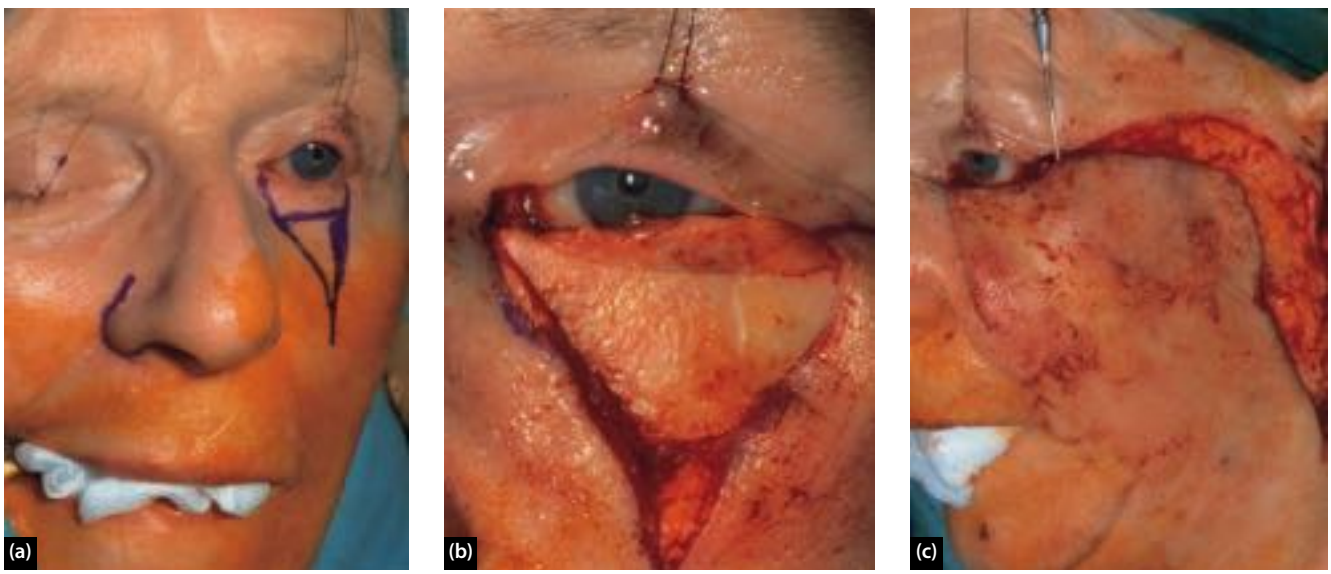


Figure 91.6 (a) Wedge excision marked with access incision in right alar crease for septal cartilage graft harvest. **(b)** Septal cartilage graft *in situ*. **(c)** Cheek rotation flap raised and inset to defect.

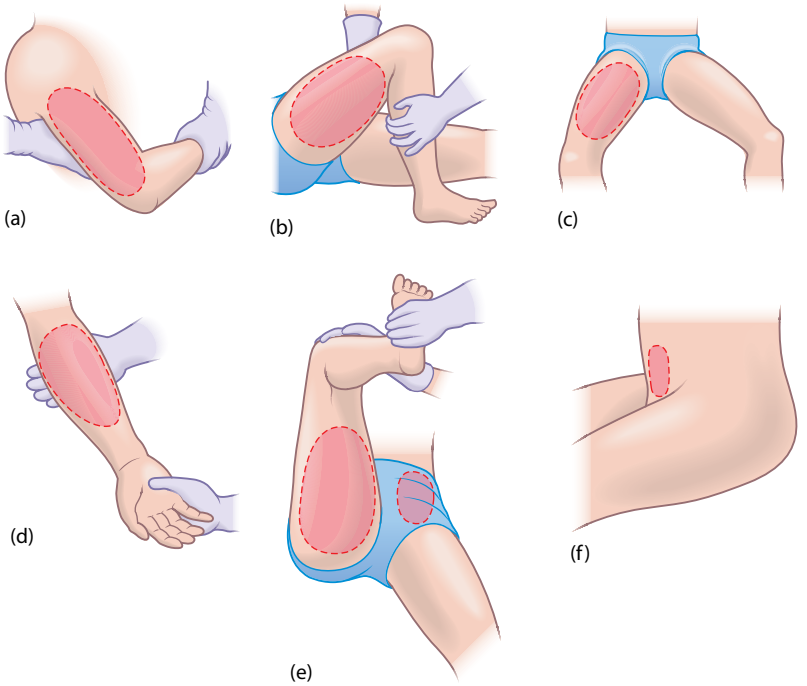


Figure 91.7 Split-thickness skin graft donor sites.

Skin graft donor sites

After an STSG is harvested, the donor site heals by re-epithelialization from adenexal structures, such as hair follicles and sweat glands, in the remaining dermis. Resurfacing occurs by the migration of keratinocytes from these structures to cover the wound. As there is no remaining epithelium in FTSG donor sites, the wound needs to be closed directly. This limits the amount of skin that can be harvested and the size of the defect that can be reconstructed using a FTSG. STSGs can be taken from anywhere on the body.[16] Commonly used areas include the thigh, trunk and buttocks as shown in **Figure 91.7**.

The graft is harvested with either an air- or battery-powered dermatome or a hand knife such as a Watson knife. The standard thickness which is preset on a dermatome is 0.3–0.4 mm or 10–12/1000 of an inch. The skin can then be either meshed or fenestrated by hand. The donor site is dressed with a non-adherent dressing[19] and left undisturbed for approximately 14 days. Most STSG donor sites are healed by 21 days with minimal scarring but they may be discoloured and susceptible to sunburn for up to 2 years afterwards.

The thickness and colour of skin varies greatly from different parts of the body and this affects the choice of FTSG donor site. Commonly used sites are pre- and post-auricular, the supraclavicular fossa, the antecubital fossa and the groin, as shown in **Figure 91.8**.

The FTSG is harvested with a scalpel and is closed directly with sutures to leave a linear scar. The amount of skin that can be taken is limited by the need to obtain a tension-free closure of the donor site. Examples of the use of a skin graft in the head are shown in **Figure 91.9**.

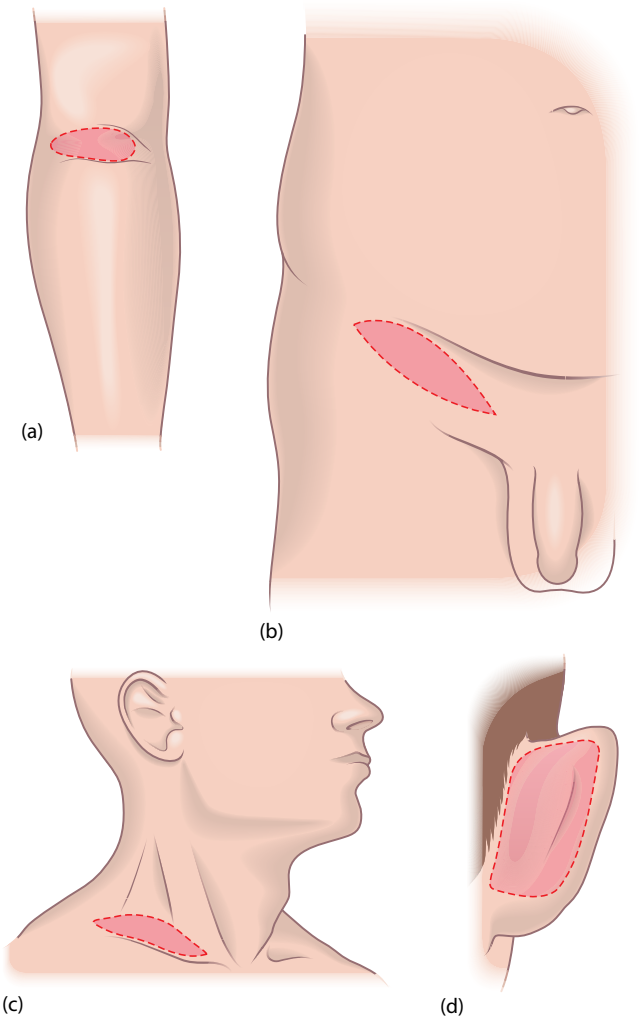


Figure 91.8 Full-thickness graft donor sites.

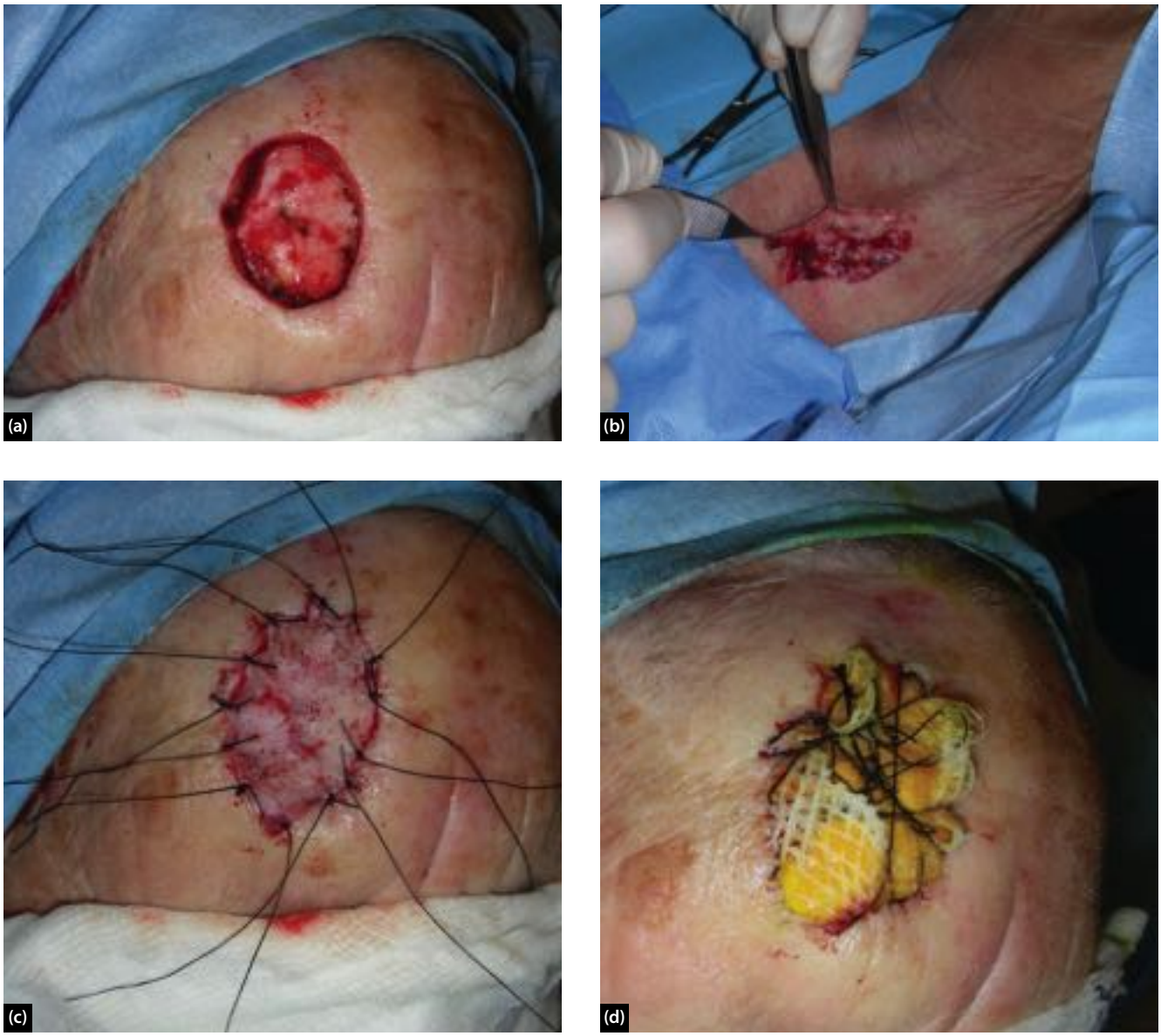


Figure 91.9 (a) Scalp wound following skin cancer excision. **(b)** Full-thickness graft harvest. **(c)** Full-thickness graft secured. **(d)** Gelonet and proflavin wool tie-over dressing.

LOCAL FLAPS

Basic principles

A flap, unlike a skin graft, has its own blood supply. Flaps are useful in reconstructing defects with poor vascularity, exposed vital structures and where skin grafts are inappropriate or would lead to poor cosmesis. Flaps are also useful in reconstructing defects where post-operative radiotherapy is planned as they are less susceptible than skin grafts to the ill effects of radiotherapy.

Flaps can be classified according to their circulation, composition, contiguity or contour. The circulation of flaps may be random, which means that the blood supply is from a non-named vessel in the base of the flap, or axial, which means that they are based on an anatomically recognized artery.[17] Flaps can be composed of different tissue types, such as skin, fascia and skin (fasciocutaneous), muscle or muscle and the overlying skin paddle (myocutaneous). The contiguity of a flap relates to the distance between its source and the defect to be reconstructed. This can be local, regional, distant or free. A local flap is composed of tissue adjacent to the defect. A regional flap is from the same anatomical region as the defect (e.g. forehead flap for nasal reconstruction). A distant flap is from a different part of the body away from the region of the defect (e.g. pectoralis major flap in head and neck reconstruction). A free flap is completely detached from the body and anastomosed to recipient vessels close to the defect. The contour of the flap relates to the method in which it is transferred into the defect. It can either be advanced or moved about a pivot point.

A flap is inset into a primary defect. The secondary defect is the site from which the flap is raised. This is

usually closed directly but can be grafted or closed by another flap. When designing a local flap in the head and neck, the two most important considerations are appreciation of the relaxed skin tension lines (see **Figure 91.2**) and the cosmetic units (see **Figure 91.4**). It is preferable to reconstruct an entire cosmetic unit with a single flap to optimize cosmesis and, in some cases, it may be necessary to excise the remaining tissue beyond the boundary of the original defect to facilitate this. This is particularly important if more than 50% of the cosmetic unit is involved. If the defect involves two cosmetic units, then two flaps (one for each unit) may be preferred. The donor area from the flap should be from the same cosmetic unit or one adjacent if possible and should not transgress multiple units. Ideally, the scar from a direct closure of a secondary defect should be in a relaxed skin tension line as it will be under the most tension of any part of the flap.

Flap planning is crucial to the success of the reconstructive procedure. When planning a random flap, the breadth of the base should be no more than the length of the flap to prevent necrosis of the flap (a ratio of 1 : 1). In the head and neck region, the blood supply is good so this can be extended to a ratio of base breadth to flap length of 1 : 1.5. For axial flaps, the length to breadth ratio is much greater but it is important to delineate and protect the named blood supply to the flap. Reverse planning is an important principle in flap design. This is a technique where a template of the primary defect is reflected from the defect to be reconstructed onto the flap donor area from a fixed point, usually the pivot point of the flap, to help assess where the flap needs to be raised from to provide sufficient defect coverage as well as minimal donor site morbidity.

Advancement flaps

Advancement flaps are moved forward into a defect without any rotation or lateral movement. They may be simple or modified. A simple advancement flap relies on the skin's elasticity to cover the primary defect. There are a number of ways in which advancement flaps can be modified to aid advancement. Burow's triangles are triangles of skin that are excised at either side of the base of the flap to equalize the length between the sides of the flap and the adjacent wound margin. These help in allowing the flap to advance, as demonstrated by a Rintala flap[18] being used to cover a defect of the nasal tip (**Figure 91.10**). A V–Y flap is another modified advancement flap. The flap itself is raised as a triangular (or 'V'-shaped) flap. When is it advanced, the secondary defect is closed directly, leaving a 'Y'-shaped scar. An example of one such flap is the nasolabial V–Y advancement flap shown, which is an axial flap based on either the superior labial artery or the angular artery (**Figures 91.11**).

Bipedicled flaps

A bipedicled flap receives a blood supply from both ends as it has two bases. It is less prone to necrosis than flaps of similar dimensions which are attached at only one end. An example of this is the Tripier flap[19] for lower eyelid reconstruction (**Figure 91.12**). Skin from the upper lid based on both a medial and a lateral attachment is swung down, like a bucket handle, to provide cover for a defect in the lower lid. To increase the viability of this flap, a strip of the orbicularis oculi muscle can be included, making it a musculocutaneous flap.



Figure 91.10 (a) Rintala flap design for dorsum of nose reconstruction. **(b)** Rintala flap raised and inset to defect. **(c)** Six-month post-operative appearance.

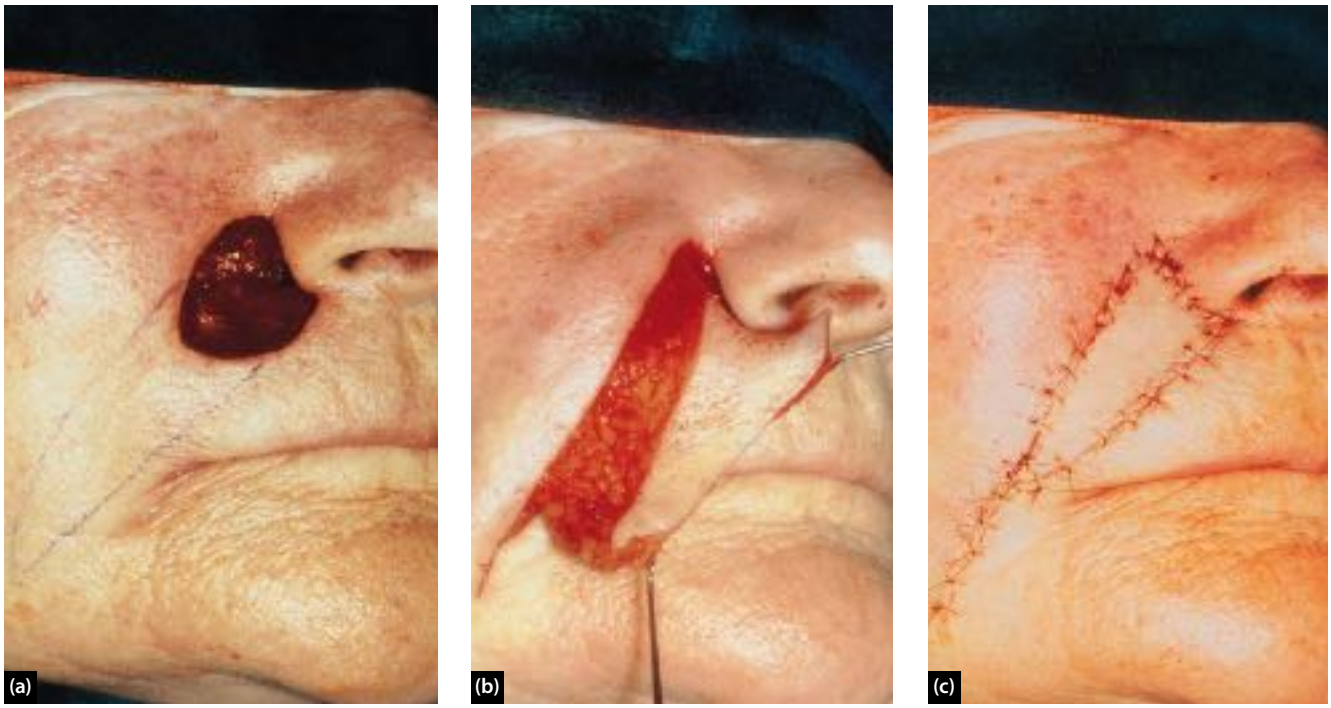


Figure 91.11 (a) Defect in right alar/nasolabial region with design of nasolabial V–Y advancement flap. **(b)** Flap raised. **(c)** Flap inset.

Pivot flaps

All pivot flaps move about a fixed pivot point and an arc which is the line of greatest tension of the flap. A pivot flap can be either a transposition flap, where the flap is moved into an adjacent defect by pivoting around the pivot point, or a rotation flap, where the flap is rotated around the pivot point into the defect (**Figure 91.13**). When a flap is transposed to cover the primary defect, the secondary donor defect is usually closed directly if possible, skin grafted, or reconstructed with a second flap. An example of this is the bilobed flap, where a second flap is raised to close the donor defect (**Figure 91.14**).

TRANSPOSITION FLAPS

A transposition flap is a flap that is moved into an adjacent defect by pivoting around its fixed point. Various types of transposition flaps have been described including the rhomboid flap, the flag or banner flap, and the bilobed flap.

Rhomboid flaps

A rhomboid flap is a type of transposition flap where the donor defect is closed directly.[20] The defect is firstly designed as a rhomboid. Each of the limbs of the defect and the flap being raised need to be of equal length and the angles of the rhomboid need to be 120 degrees and 60 degrees, respectively. The flap needs to be designed so that the donor site scar lies parallel to the relaxed skin tension lines (**Figure 91.15**). A variation of the rhomboid flap is the Dufourmentel flap,[21] which has limbs of equal lengths but angles of 150 degrees and 30 degrees. Other variations of the geometry of the rhomboid flap have been described.[22] One of these is the 'square peg in the round hole' where the primary defect is circular (as is the case in most clinical situations) and the rhomboid flap is stretched to fill the defect.[23] This reduces the need to excise the extra skin required in the standard rhomboid flap, which is particularly important in cosmetically sensitive areas such as the face.

Flag or banner flaps

A number of small transposition flaps can be used around the face and generally the donor site is closed directly. These are termed flag flaps as the piece of tissue moved resembles a flag or banner. These are normally random pattern flaps but can be based on a known artery in some parts of the head or neck. A glabellar flap is an axial transposition flag flap based on the supratrochlear artery. This allows the flap length to be three times the base breadth (**Figure 91.16**). It is transposed to cover the primary defect and the donor site is closed directly.

Bilobed flaps

A bilobed flap consists of two transposition flaps.[24] The first flap is transposed into the primary defect, the second flap is transposed into the secondary defect (the original site of the first flap) and the tertiary defect (the original site of the second flap) is closed directly. The flap should be designed so that the directly closed tertiary defect is parallel to the relaxed skin tension lines (see **Figures 91.14** and **91.15**). Theoretically, the bilobed flap uses less tissue than any other method of wound closure and because of this minimizes tension at the primary defect.[25]



Figure 91.12 **(a)** Total lower eyelid defect. **(b)** Tripier flap design from upper eyelid. **(c)** Flap raised. **(d)** Tripier flap inset to lower eyelid defect.

The ideal use of a bilobed flap is where there is tissue available locally and where it is important to avoid producing tissue stretch. The bilobed flap is most commonly used to deal with defects at the tip of the nose. Although there is some spare tissue around this area, the nasal tip can become displaced if skin is imported to cover defects here as a local flap.[26]

ROTATION FLAPS

Rotation flaps are large flaps that rotate into the primary defect. The volume of tissue raised in the flap is high when compared to the defect being closed. Normally, the flap is a semicircle and the primary defect is 'triangulated' or designed as a triangle, adjacent to the flap. Geometrically, the flap circumference should be at least eight times the width of the defect to allow closure of the donor site; however, in practice, it is best to design the flap as large as possible as the direct closure of the donor site relies on tissue redistribution and tissue elasticity. Occasionally, the use of a Burow triangle or a back cut may be needed. A back cut releases a rotation flap that is too tight by decreasing the tension at the base of the flap, thus moving its pivot point towards the defect. This decreases the tension of closure at the site of the primary defect. A back cut that is taken too far, however, may significantly decrease the width of the flap, which will increase the chance of devascularizing it. These flaps are useful for dealing with defects of the scalp or cheek (see **Figure 91.13**).

RECONSTRUCTION OF SPECIFIC ANATOMICAL REGIONS OF THE HEAD AND NECK

Scalp

ANATOMY

The scalp has five distinct anatomical layers. From superficial to deep, these are the skin, subcutaneous connective tissue, muscle or aponeurosis (galea), loose areolar tissue and pericranium. The skin of the scalp is the thickest on

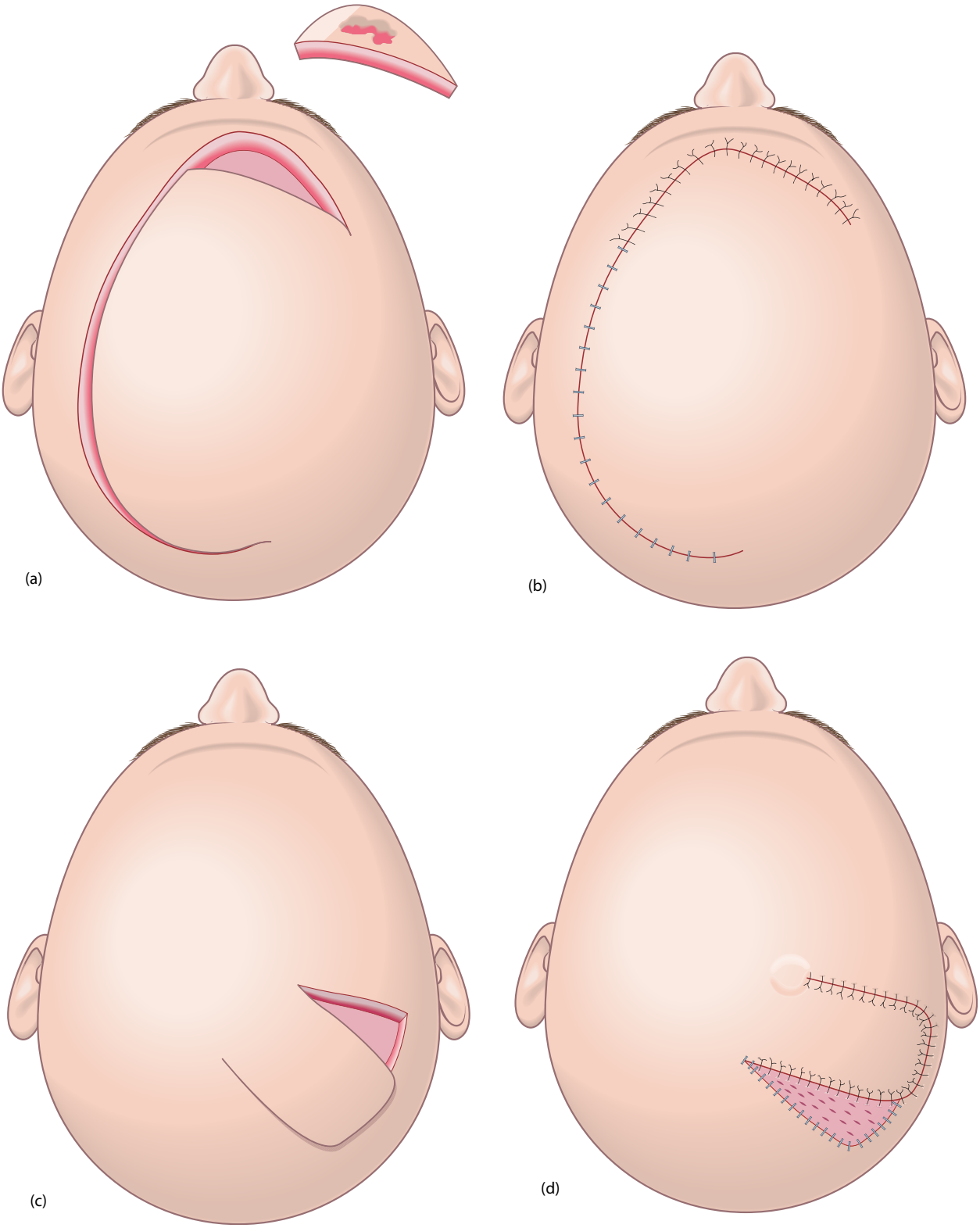


Figure 91.13 Scalp transposition and rotation flap design.

the human body, ranging from 3 mm to 8 mm. Beneath the skin, the subcutaneous tissue contains the vessels and nerves supplying the scalp. Deep to this is the musculoaponeurotic layer consisting of the frontalis muscle anteriorly and the occipitalis muscle posteriorly. These muscles are connected by an aponeurotic layer (the galea aponeurotica). Laterally, this aponeurosis is connected to the subcutaneous musculoaponeurotic system (SMAS) of the face.



Figure 91.14 (a) Basal cell carcinoma excision marked with bilobed flap design. **(b)** Bilobed flap raised and inset.



Figure 91.15 (a) Rhomboid flap design for excision of lentigo maligna. **(b)** Flap raised and inset.



Figure 91.16 (a) Glabella transposition flap design for right inner canthal defect reconstruction. **(b)** Flap raised and donor site closed. **(c)** Final result.

The layer of loose areolar tissue deep to this, also known as the inominate fascia, is an avascular plane. Owing to this, most local flaps of the scalp are raised at this level because it is easy to dissect and relatively bloodless, thus making scalp flaps fasciocutaneous rather than cutaneous. The deepest layer is the pericranium (the periosteum of the skull) which is firmly adherent to the underlying bone. However, it can be raised and turned over on itself to form a pericranial flap.[27] This is viable tissue that can cover exposed bone and is capable of taking a skin graft. Laterally, the pericranium is continuous with the deep temporal fascia overlying the temporalis muscle.

The scalp has a rich blood supply and is supplied by tributaries from the external and internal carotid arterial system. The external carotid branches supplying the scalp include the paired superficial temporal, posterior auricular and occipital arteries. On the anterior scalp, there is further supply from the paired supratrochlear and



Figure 91.17 (a) Defect in left auricular area with placement of osseointegrated implants. **(b)** Temporoparietal flap raised to cover osseointegrated implants. **(c)** Flap inset. **(d)** Foam dressing covering split skin graft over temporoparietal flap with closure of neck dissection incisions.

supraorbital arteries, themselves being branches of the ophthalmic artery. There is a rich anastomosis between these arteries which allows the entire scalp to survive on any one of these vessels. For the purposes of scalp reconstruction using local flaps, however, it is often convenient to view the blood supply as arising from three separate axes: anterior axis (supratrochlear, supraorbital), lateral axis (superficial temporal, posterior auricular) and a posterior axis (occipital). To allow for reliable vascularity and survival, scalp flaps should contain at least one of these axes.

SCALP FLAPS

There is a paucity of skin and soft tissue on the scalp and therefore only small defects (<3 cm) of the scalp may be closed primarily with undermining. Larger defects require reconstruction with a skin graft, local flaps or free flaps.

Skin grafts are used often on the scalp but require a healthy vascular bed such as the pericranium in order to take. When the ablative surgery includes the pericranium and the outer table becomes exposed, a vascular bed may be achieved either by burring the outer table to expose the small diploic vessels or by covering the exposed bone with a healthy vascular bed such as with a pericranial turnover flap prior to skin grafting.[28] This technique, however, risks dural exposure in children whose cranial bones are thin.

Local scalp flaps can be either rotation or transposition flaps. In order for a rotation flap to be successful, the defect needs to be triangulated and the flap designed large enough to allow coverage of the primary defect and allow direct closure of the donor site. Back cuts or Burow triangles as well as scoring the galea on the underside of the flap can help the flap stretch adequately for closure. A transposition flap on the scalp involves raising a flap adjacent to the defect and transposing it to achieve coverage. This will expose the pericranium over the donor site requiring skin grafting (see **Figure 91.14a**). An alternative is a pericranial transposition flap to achieve a vascularized bed which can subsequently be skin grafted. In larger defects, tissue expansion is a useful adjunct to increase

the amount of tissue available for reconstruction.[29] Alternatively, multiple interdigitating flaps[30, 31] or free flaps can be used; however, this is beyond the scope of this chapter.

TEMPOROPARIETAL FASCIA FLAPS

Scalp flaps can also be useful in reconstructing defects around the head and neck. The fascia in the temporal region is a prime example. This fascia has several well-described layers. The superficial temporal fascia (temporoparietal fascia, TPF) lies immediately deep to the hair follicles and is in continuity with the galea superiorly and the SMAS inferiorly. Deep to this is an avascular layer, known as the innominate fascia, which is in continuity with the loose areolar tissue of the scalp. The deep temporal fascia (or temporalis fascia) is the deepest layer and this is in continuity with the pericranium superiorly.[32] Each of these layers may be used as a local flap to cover defects within their arc of rotation. They are particularly useful in covering exposed bone around the skull (**Figure 91.17**) where a TPF flap is used to cover the exposed temporal bone following total resection of the external ear and extended neck dissection for a $T_4N_1M_0$ cutaneous squamous cell carcinoma.

Forehead and glabella

ANATOMY

The forehead is bounded by the anterior hairline superiorly, the eyebrows inferiorly and the temporal hairline laterally. Underlying the skin is the frontalis muscle which arises as a continuation of the galea aponeurotica and inserts into the dermis of the forehead, allowing brow elevation. It is supplied by the temporal branch of the facial nerve. Sensation to the forehead and vertex of the scalp is supplied by the supratrochlear as well as the superficial and deep divisions of the supraorbital nerve. The superficial division of the supraorbital nerve and the supratrochlear nerve branches lie superficial to the frontalis muscle. The deep division of the supraorbital nerve lies between the galea aponeurotica and the periosteum, medial to and parallel with the superior temporal line of the skull. The blood supply of the forehead is rich and is provided by branches of the internal (supraorbital and supratrochlear arteries) and external (facial and superficial temporal arteries) carotid arteries.

LOCAL FLAPS

The forehead is very visible to observers and so care should be taken to place incisions horizontally or along the hairline and eyebrow. Where direct closure may cause distortion of the hairline or brow, a large full-thickness skin graft would give an adequate result. Larger defects of the forehead can be reconstructed with advancement flaps or hatchet flaps, which are random rotation flaps with a back cut. They can be single or double and heal with minimal scarring. Large defects can be closed using this technique and it is possible to preserve the supratrochlear and supraorbital nerves when dissecting the forehead to maintain sensation.[33] Other techniques for forehead reconstruction include the use of scalp rotation flaps, which can be tissue expanded to produce a larger flap.[34] These, however, are limited as they import hair-bearing skin onto the forehead and distort the hairline.

Eyelid

ANATOMY

The anatomy of the periorbital region is complex and without a good understanding of the structure and function of the eyelids periorbital excisions and reconstructions should not be undertaken. The upper and lower eyelids can be divided into the anterior and posterior lamella in cross section, with an intervening orbital septum. This septum is continuous with the periosteum and extends from the arcus marginalis or the bony margin of the orbit to the margin of the eyelid. In the upper lid, the septum inserts onto the levator aponeurosis 2–5 mm above the superior tarsus whereas, in the lower lid, it attaches to the inferior tarsus directly. The anterior lamella consists of the skin and the orbicularis oculi muscle, whereas the posterior lamella consists of the conjunctiva and the tarsal plates. The skin of the eyelid is the thinnest in the body (1 mm) and is loosely attached to the orbicularis oculi muscle. This muscle is arranged in a concentric ring around the orbit and upon contracture acts as a sphincter, closing the orbital aperture. It can be divided into three parts: an outer orbital part covering bone, and inner preseptal and pretarsal components. Medially, the orbital portion originates directly from the bony orbital rim and the medial canthal tendon. Inferiorly, the orbicularis attaches indirectly to the orbital rim through the orbital-retaining ligament. Laterally, this ligament merges into the lateral orbital thickening.[35] The tarsal plate forms the skeleton of the eyelid and is a dense sheet of fibrous tissue. The superior tarsus measures approximately 10–12 mm vertically from the lid margin; the lower tarsus measures approximately 3.7 mm vertically.[36] The deepest structure of the eyelid is its lining, the conjunctiva, which contains many eccrine and apocrine glands. There are further sebaceous glands of Zeis associated with the eyelashes.

The upper eyelid elevates due to the contraction of the levator palpabrae muscle (innervated by the oculomotor nerve). This originates from the lesser wing of the sphenoid and extends anteriorly along the superior orbit to Whitnall's ligament, which acts as a fulcrum to change its vector of pull from a horizontal to a vertical direction, before finally attaching to the superior tarsal plate. Constriction of the upper eyelid is due to contraction of the orbicularis oculi muscle (innervated by the temporal and zygomatic branches of the facial nerve). The lower lid has only limited descent from the action of the capsulopalpebral fascia, which originates as fibroelastic tissue from the interior rectus muscle and inserts into the inferior tarsal plate. The blood supply of the eyelids consists of a rich anastomosis between branches from the internal and external carotid arterial systems. The sensory supply

of the upper and lower eyelids is derived from branches of the ophthalmic and maxillary divisions of the trigeminal nerve respectively.

EYELID RECONSTRUCTION

Partial-thickness defects

Defects in the eyelid can be partial thickness, with either the anterior or posterior lamella having been excised, or full thickness. Partial-thickness defects of the anterior lamella are best either closed directly if small (up to a third of the eyelid) or resurfaced with a full-thickness skin graft. The posterior lamella can be reconstructed with a graft of buccal or hard palate mucosa[37] or a nasal chondromucosal[38] graft consisting of nasal mucosa and septal cartilage. These grafts are also useful in full-thickness defects.

Full-thickness defects

Reconstruction of full-thickness defects of the eyelids is complex and requires reconstruction of both the anterior and posterior lamella for a satisfactory result. This can be done by using either a single flap to reconstruct both layers or a flap to reconstruct the anterior lamella and a composite graft for the posterior lamella. At least one of the two layers must have its own blood supply as a graft placed on another graft will fail. The size of the defect also needs to be taken into account when planning for reconstruction. Full-thickness defects of up to one-quarter of the lid length can be closed directly and this increases to one-third in the elderly population with lax skin. It is important to note that each of the layers (i.e. conjunctiva, tarsal plate, orbicularis and skin) will need to be repaired individually.

When the size of the defect approaches 50% of the total eyelid, two additional techniques may be used to recruit adjacent lateral tissue to enable closure. The first of these is a lateral cantholysis. A horizontal incision is made from the lateral canthus to the orbital rim. The lateral canthal tendon is identified and divided. The lateral part of the lid can then be mobilized medially to close the wound. The second is by using a tenzel semicircular flap which allows lateral tissue consisting of skin and muscle to pivot on the lateral canthus and advance/rotate into the defect to allow closure.[39] The technique requires a lateral canthotomy, inferior cantholysis and suture suspension of the flap to the lateral orbital margin. This flap is useful in both upper and lower eyelid defects provided some tarsus remains to provide support.

Larger defects of the lower eyelid can be reconstructed with a cheek rotation flap[40] combined with a free composite graft to reconstruct the posterior lamella. Larger defects of the upper eyelid are difficult to reconstruct and usually require a glabellar transposition flap or recruitment of tissue from the lower eyelid in the form of a switch flap[41] or a Cutler-Beard flap.[42] Switch flaps can be based medially or laterally on medial lower eyelid tissue which is then rotated into the upper lid defect. At a second stage, the flap is divided at its base and the donor site is closed with a cheek rotation flap.

The Cutler-Beard flap is an advancement flap from the full thickness of the lower lid, preserving the lower lid margin and tarsus. At a second stage 4–6 weeks later, the flap is divided and returned to the lower border of the intact lower lid margin. The tissue that is left on the upper lid is used to fashion the upper lid margin. These techniques do not import components for the posterior lamella and this will therefore require a suitable graft for reconstruction.

Nose

Analysis of the nasal defect to be reconstructed in terms of the component layers is essential when planning reconstruction. Primary closure is limited to small defects due to the relative lack of skin laxity. In partial-thickness defects where there is remaining subcutaneous tissue or perichondrium, the use of full-thickness skin grafts can result in very good cosmetic outcomes. Local flaps are also useful in such cases and will be discussed later. If the defect is full thickness, three distinct layers need to be considered and reconstructed: these are the nasal lining, nasal support and overlying skin. When a small nasal rim defect is being reconstructed, a composite graft taken from the ear which has all three layers is an option. This involves taking a full-thickness piece of the ear including both anterior and posterior skin.

Larger full-thickness defects of the nose following partial or total rhinectomy are more difficult to manage. A local flap can be used to reconstruct both the lining and skin cover of the nose by folding the flap in two. The most commonly used flaps for this are superiorly based nasolabial flaps. Bilateral flaps can be raised to import a large volume of tissue.[43] An alternative to folding a flap is to use one flap for the lining and another for the cover. The nasolabial flap can be used for the lining as can a random hinge flap where adjacent tissue is raised and flipped over to fill the defect.[44] The flaps used as lining can then be covered with either a skin graft or another flap such as a forehead flap (**Figure 91.18**). It has to be remembered that, when dealing with a total rhinectomy defect, very good results can be obtained using a prosthesis. With the advent of osseointegration, a prosthetic nose is both cosmetically acceptable and convenient for the patient.[45] This is a viable alternative to surgical reconstruction.

SKELETAL SUPPORT

The nose is supported by a rigid central framework and the more flexible lateral walls composed of the upper and lower lateral cartilages. When lost, it is important to reconstruct these elements to maintain projection and to allow the nasal aperture to remain open to permit airflow. Midline support can be provided by an L-strut, a hinged septal flap, a septal pivot flap or a cantilever bone graft.

An L-strut consists of a longitudinal piece of bone or cartilage that is secured on the nasal radix and extends along the dorsum of the nose to the tip where it is bent









Figure 91.18 (a) Forehead and nasolabial flap design for cutaneous and lining reconstruction respectively. **(b)** Nasolabial flaps raised. **(c)** Nasolabial flaps inset with cartilage grafts to support. **(d)** Forehead flap raised. *(Continued)*



Figure 91.18 (Continued) (e) Forehead flap inset and split skin graft coverage of pedicle and donor site. **(f)** Final result.

sharply to rest on the anterior nasal spine.[46] The hinged septal flap is an L-shaped flap carved from the patient's remaining septum and hinged superiorly on the caudal end of the nasal bones.[47] The septal pivot flap is similar to the hinged septal flap except that the septum in this case brings with it simultaneous mucosa that can be used as lining. If there is insufficient local tissue, then a cantilever graft can be used which consists of a strong, longitudinal bone graft harvested from the calvarium or rib and secured to the radix with miniscrew fixation or wires.[48] The flexible lateral walls of the nose require more pliable cartilage grafts to be used.

LINING

The lining is an important component of the reconstruction as even partial necrosis may result in secondary contracture that will invariably distort the overall result. There are several methods to provide lining. The simplest method is to graft the underside of a flap that is to be used as external cover (e.g. the underside of a forehead flap prior to transfer). When support is also required, a composite graft consisting of skin and cartilage can be used. Local flaps such as the septal door flap,[47] septal mucoperichondrial flap, bipedicled mucosal advancement flap[49] and nasolabial flaps are useful for providing large amounts of tissue for lining. When there is a paucity of local tissue, free flaps such as a free radial forearm flap can be employed to provide lining.

SKIN COVER

The local flap options used to cover nasal defects are varied and choice is dependent on the size and location of the defect. Sidewall defects can be effectively reconstructed with a cheek advancement flap or rhomboid flap.[50] There are a large variety of local flaps that can be used to reconstruct dorsal defects. The glabellar flap[51] transfers tissue from the glabella and is useful in reconstructing defects of the root and upper bridge of the nose. Defects of the dorsum of the nose in the mid and lower third of less than 2 cm in diameter can effectively be reconstructed with the dorsal nasal flap[52] or one of its many variants. These flaps are based on the angular artery and require the nasal dorsum to be degloved to allow sufficient movement prior to flap inset. Advancement flaps such as the Rintala flap[53] are also useful for dorsal nasal defects (see **Figure 91.10**). Other flaps that are commonly used include transposition flaps such as a superiorly based nasolabial flap[54] (see **Figure 91.11**) or a bilobed

flap (see **Figure 91.14**).[55] In addition to these techniques, microvascular free-tissue transfer of a chondrocutaneous flap from the ear has been described.[56]

FOREHEAD FLAP

The forehead flap is a local cutaneous axial flap based on the supratrochlear artery. It is one of the oldest flaps in use and the earliest available description is from 600 BC by Susruta in India.[57] A large flap of skin from the forehead can be raised on this vessel which can then be used to cover defects around the orbit and the nose. The donor site can be the vertical height of the forehead or the flap can be planned obliquely to maximize the length and therefore the reach of the flap. An obliquely placed donor site also reduces the arc of rotation. The donor site can be closed directly if the width of the flap is kept small (less than 2.5 cm) and this leaves minimal scarring. If a wider flap is required, the defect needs to be skin-grafted; an alternative to this is to leave the defect to heal by secondary intention, which can give a very acceptable cosmetic outcome.[58] The transfer is normally carried out in two stages: the flap is raised and the tip of the flap inset into the primary defect. The remainder of the flap is then tubed to form a pedicle. After 3 weeks, the tip of the flap will have undergone some revascularization from the recipient site and the pedicle is then divided and reinset into the secondary defect (see **Figure 91.18d–f**). Alternatively, when reconstructing nasal defects, a third stage can be included.[59] The flap is raised 2 weeks after it is inset, thinned and then reinset. The pedicle is then divided after a further 2 weeks. This prevents having a bulbous nasal tip, giving an overall better cosmetic result.

Lip

The lips are complex structures involved in articulation, swallowing and facial expression. They are three-dimensional structures with an outer layer of skin and an inner layer of mucosa separated by muscle. The junction between the skin and mucosa is a specialized area as the skin blends into white roll, then vermilion and then into mucosa. A 1 mm discrepancy at this junction is noticeable at a distance of 1 metre.

The orbicularis oris muscle contained within the lips is a complex muscle containing fibres in different orientations which can close the mouth, approximate the lips to the maxilla and mandible or purse the lips. In addition, muscle fibres blend into the orbicularis oris from the levator labii superioris and other elevators of the lip superiorly, from buccinators laterally and from depressor labii inferioris and the other lip depressors inferiorly.

The options for donor tissue for lip reconstruction are the remaining lip, the adjacent cheek, the opposite lip or from distant sites. It should be remembered that the goal of lip reconstruction is to restore oral continence, i.e. the role of the mouth as a sphincter, without causing microstomia (a tight or small mouth),[60] and to ensure accurate opposition of the vermilion. The upper and lower lips should be considered separately as different techniques are needed to reconstruct similar defects in the upper or lower lip.

LOWER LIP

Defects up to one-third of the length of the lower lip can be excised as a wedge (or a pentagon) and closed directly. It is important to repair all three layers of the lip, namely the mucosa, muscle and skin, to achieve good function and approximation. Larger, superficial defects of the lip can be resurfaced with a split-thickness skin graft (the entire lower lip can be resurfaced in this way) or by a tongue flap. A flap is raised from the undersurface of the tongue and inset in the defect in the lower lip. The flap is based anteriorly and the donor site is not closed at the time the flap is raised. After 10 days, the flap is divided and inset. At this point the donor site is closed directly.

For defects of three-quarters of the lower lip the Karapandzic flap can be used.[61] This is a combined axial advancement/rotation flap based on the facial artery. A transverse incision from the base of the defect to both nasolabial folds is made and the nasolabial folds are then incised in a cephalic direction. Laterally, the vessels and nerves are identified and preserved. The flap is mobilized by spreading, not dividing, the fibres of the orbicularis oris to preserve its neurovascular supply. The bilateral flaps are then advanced and rotated and then repaired in layers. Total reconstruction of both the upper and lower lip has been described using microvascular free-tissue transfer.[62]

UPPER LIP

Defects up to one-quarter of the size of the upper lip can be closed directly. The orbicularis oris needs to be dissected free of the skin and the mucosa and repaired separately before the overlying tissues are closed. For larger defects, a reverse Karapandzic flap can be used, where the nasolabial folds are incised along with the nasal sill and the skin kept intact in the submental area.

The Abbe flap is a full-thickness flap taken from the lower lip and inset into the upper lip. The layers of mucosa, muscle and skin need to be accurately inset. The flap is then left attached to the lower lip for 1 week before division of the pedicle from the lower lip.[63] The Abbe flap should be taken from the lower lip to reconstruct the upper lip and not from the upper lip to the lower lip. A variation of the Abbe flap is the Abbe-Estlander flap, which is used to reconstruct defects of the oral commisure. It can be taken from either the upper or the lower lip and is a single-stage operation as the pedicle of the flap becomes the new commissure.

Cheek

The cheeks are the largest region of the face. They consist of skin that covers muscle groups which are either attached to the underlying maxilla and mandible or are lined on their inner surface by buccal mucosa. Various important structures transverse the cheeks, including the parotid duct and the branches of the facial nerves. The cheek has

been subdivided into three separate overlapping zones – a suborbital, a preauricular and a buccomandibular area – and reconstruction should follow these regional aesthetic units where possible (see **Figure 91.4**).[64] Consideration also needs to be paid to the 3D structure of the cheek with its natural contours, shadows and hair lines.

TECHNIQUES FOR RECONSTRUCTION

The majority of defects of the cheek will be following ablative surgery for cutaneous malignancies. These normally present in the elderly population and even quite large defects can be closed directly, due to pre-existing skin laxity in this age group. As well as the relaxed skin tension lines, there are other noticeable lines in the cheek in which scars can be hidden. These are the nasolabial fold, infraorbital rim, alar crease, hairline and jawline. Split-thickness skin grafts on the cheek are very noticeable as they tend to transgress the different regions of the cheek and alter the contour and colour, giving a poor cosmetic result. When used in close proximity to the lower eyelid, they may also result in ectropion. For situations where a skin graft is necessary, full-thickness grafts are best to limit contracture and improve colour match. For small defects not amenable to direct closure, local flaps are appropriate. Due to the large surface area of the cheek, a full range of flaps can be utilized, including rhomboid transposition flaps, small cheek rotation–advancement flaps (**Figure 91.19**) or V–Y advancement flaps. Defects that are not amenable to small local flaps may require reconstruction with a cervicofacial flap (**Figure 91.20**).[65] These flaps import tissue from the neck and lower jawline, giving excellent colour, texture and contour match.

In even more extensive defects of the cheek, it may be necessary to import tissue from the chest wall with a cervicopectoral flap.[66] Tissue expansion techniques have also been described and offer excellent colour and texture match[67] but they require at least two stages, multiple visits for expansion and a period of time when the patient will have to tolerate the appearance of the expander.

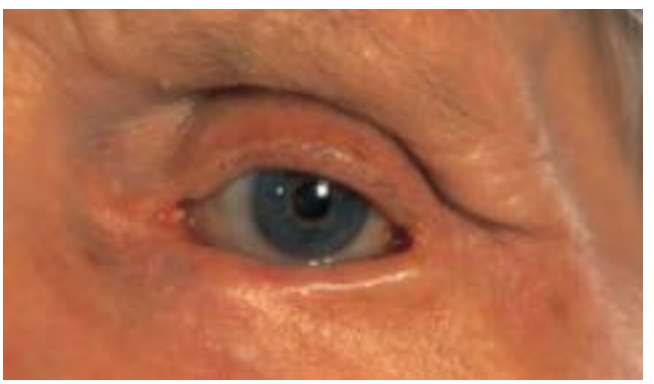


Figure 91.19 Post-operative appearance following lower eyelid reconstruction with cheek rotation flap. This is the same patient as in Figure 91.6.

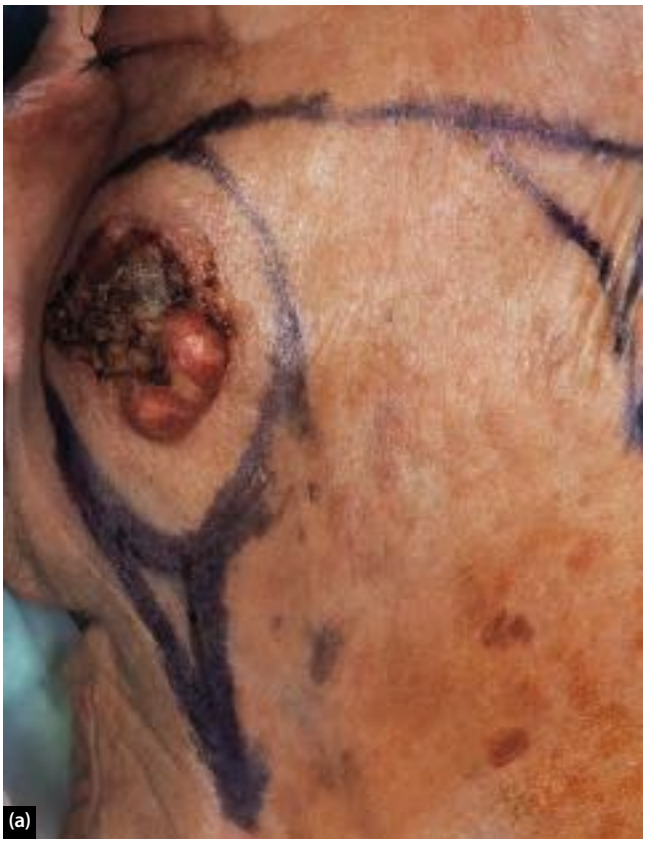




Figure 91.20 (a) Basal cell carcinoma on left cheek marked for excision with cervicofacial flap designed for reconstruction. **(b)** Post-operative appearance following cervicofacial flap reconstruction.

Ear

ANATOMY

The ear consists of skin covering an auricular cartilage framework. The framework comprises the conchal complex, the antihelix–antitragus complex and the helix–lobule complex. The musculature consists of intrinsic (helicis major and minor, tragicus, antitragicus) and extrinsic (anterior, superior and posterior auricularis). Vascular supply is derived from the posterior auricular and superficial temporal arteries with extensive interconnections between the two networks. Sensation is supplied by the great auricular nerve, the auriculotemporal nerve, the lesser occipital nerve and the auricular branch of the vagus nerve.

TECHNIQUES FOR RECONSTRUCTION

The ear is one of the commonest sites for cutaneous malignancies, particularly squamous cell carcinomas, and resection of these tumours may result in partial- or full-thickness defects. Successful reconstruction requires accurate analysis of the defect and a systematic approach to reconstruction. If the defect is small enough, direct closure can be undertaken. Lesions on the upper or middle third of the ear requiring a larger margin for clearance can be closed with a wedge excision. There are various patterns of excision that have been described to decrease tension at the suture line.[68] This technique results in a smaller ear and patients must be warned, but it is well tolerated and usually results in an acceptable cosmetic appearance. Full-thickness skin grafts are useful if the perichondrium is intact or if excision involves either the anterior or posterior skin along with its underlying cartilage. This technique gives a good colour match particularly if the graft is harvested from the head and neck region. If the defect is small but involves the full thickness of the ear, a composite graft from the opposite ear is an option but its survival can be tenuous.

There are also various local flaps that can be employed. An Antia–Buch chondrocutaneous advancement flap is useful for small to moderate sized defects of the upper and middle ear.[69] This involves freeing the helix from the scapha through an incision in the helical sulcus extending through the anterior skin and cartilage. The posteromedial skin superficial to the perichondrium is undermined, and the superior and inferior chondrocutaneous components are advanced for closure.

Another reconstructive option for the upper ear is a conchal rotation flap, which involves the rotation of the full thickness of the concha on the external edge of the ear to form the new superior ear.[70] The Converse tunnel technique involves the insertion of a cartilage graft shaped to the size of the defect beneath the mastoid skin, which is then sutured to the edges of the defect. At a second stage, the auricle is separated from the mastoid area with the graft attached and the donor site is skin-grafted.[71]

For large defects of the middle ear, reconstruction can be undertaken as described by Dieffenbach.[72] This involves a postauricular advancement flap which is approximated into the defect. A cartilage graft can be used as support beneath the flap. At a second stage, the flap is divided at its base and folded around the posteromedial aspect of the ear to complete the reconstruction. A skin graft is applied to close the donor defect. Techniques for reconstructing defects of the lower third of the ear are limited. A double-lobed postauricular flap may be used to reconstruct the earlobe. It is raised and folded onto itself, then sutured onto itself and remaining auricle to form the new earlobe.[73]

KEY POINTS

- Make use of the reconstructive ladder.
- Understand the process of wound and graft healing.
- Replace like with like.
- Reconstruct individual cosmetic units where possible.

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CHAPTER 92

PEDICLED FLAPS IN HEAD AND NECK RECONSTRUCTION

Ralph W. Gilbert and John C. Watkinson

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: pedicled flap, head and neck, temporoparietal flap, FAMM flap, submental flap, nasolabial flap, pectoralis major flap, latissimus dorsi flap, trapezius flap.

INTRODUCTION

Defects following head and neck surgery can often be closed by direct suture. This applies to both the skin and mucous membranes. This technique is used when the defect is small, and where local conditions allow adequate amounts of mobile tissue. However, for larger defects or in situations when direct suture is not applicable, surgical defects may be filled by free grafts, local skin flaps, with pedicled flaps that may be either axial cutaneous or musculocutaneous, or with free tissue transfer. This chapter outlines the use of pedicled flaps in head and neck surgery.

GILLIES' PRINCIPLES OF RECONSTRUCTIVE SURGERY

There are some simple rules to head and neck reconstruction. These are well summarized by some of the commandments of Sir Harold Gillies[1] that relate to reconstruction in general:

- Losses must be replaced in kind.
- Treat the primary defect first.
- Thou shalt provide thyself with a lifeboat.
- Thou shalt not throw away a living thing.
- Replace things into their normal position by recreation of the defect.

Reconstructive techniques can be used effectively as building blocks, either singly or in combination, to reconstruct the defect. However, before they are described in detail, it is important to understand in general terms how they work. The many and varied clinical situations in which they may be used are discussed in those chapters that relate to the resection of the specific tumour in question (i.e. Chapter 12, Oral cavity tumours including the lip and Chapter 13, Oropharyngeal tumours).

TYPES OF FLAP

There are a number of different types of flap that maybe used in head and neck reconstruction. These are:

- local flaps:
  - random
  - axial pattern
- distant axial:
  - deltopectoral
  - cervical
  - occipitomastoid
- myocutaneous:
  - pectoralis major/latissimus dorsi
- free tissue transfer.

Distant axial and myocutaneous pedicled flaps are used less and less in head and neck reconstruction following the introduction of free tissue transfer. However, they do have a number of uses in certain situations for soft tissue

TABLE 92.1 Advantages and disadvantages of pedicled flap transfer

Advantages	Disadvantages
• Relatively straightforward to raise • Reliable • Adequate blood supply • Can be used as 'life boats' for salvage surgery • Useful in the presence of infection	• Bulky • Cannot be tubed • May be associated with significant donor site morbidity • May represent a compromise balancing the ideal reconstruction and the surgeon's skill set

reconstruction and their advantages and disadvantages are shown in **Table 92.1**.

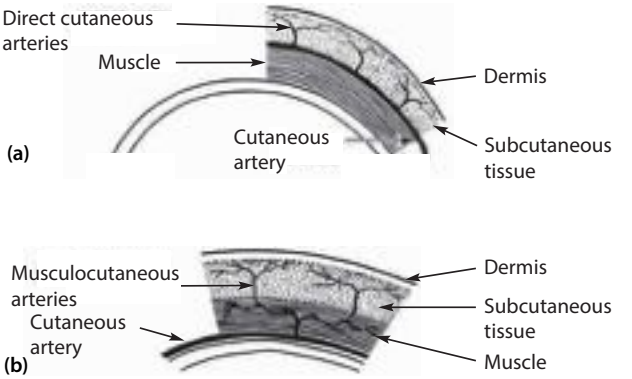


Figure 92.1 Blood supply of axial and random flaps. (a) Note that the axial flap is based on an arteriovenous pedicle that runs within the skin superficial to the underlying muscle layout and parallel to the overlying skin. **(b)** This differs from a random flap.

AXIAL FLAPS

An axial flap is based on a named arteriovenous pedicle that runs within the skin superficial to the underlying muscle layer, parallel to the overlying skin (**Figure 92.1**). Axial flaps have an extremely good blood supply that is determined not only by their length and breadth ratio but also by the vascular territory of the vessels that supply them. Because of this, they can generally be raised to a much greater length than random flaps and can therefore be used to move skin over a greater distance. The use of these flaps in the 1960s was the first major step in head and neck reconstruction. Their routine use has largely been superseded by musculocutaneous and free tissue transfer, but the deltopectoral flap still has a role in head and neck surgery.

Forehead flaps

The forehead flap is an axial flap that provides large areas of skin and subcutaneous tissue that may be used to reconstruct defects below the level of the eyes. In its original form (as described by McGregor and McGregor),[2] the axial forehead flap based on the anterior branch of the temporal artery was one of the first flaps used in intraoral reconstruction. It is rarely used today as it leaves a disfiguring donor site and there are better alternatives. It does represent a potential lifeboat for a failed myocutaneous or free tissue transfer in oral or oropharyngeal reconstruction. When used for oral cavity reconstruction, it is passed into the oral cavity medial to the zygomatic arch. The temporalis muscle tendon must be divided from the coronoid process to facilitate access.

The most commonly raised forehead flap is the cutaneous axial median forehead flap, based on the supratrochlear artery. It can be raised and transposed to reconstruct areas in the upper medial cheek region and any defect of the external nose (**Figure 92.2**). The donor site will often close primarily and the cosmetic result is excellent. Where larger areas of tissue are required, for example in complete nasal resurfacing, larger forehead flaps may be designed (e.g. Millard flying seagull flap), which may be facilitated by prior tissue expansion to ease donor site closure. Controversy exists regarding the use of tissue expansion to achieve primary closure. Some authors believe that the expanded forehead flap contracts excessively when used for nasal reconstruction, compromising the ultimate reconstructive result. Additionally the defect on the scalp when left to close with secondary intention often produces an excellent aesthetic result with normal contour and skin colour. These techniques are best suited in patients with high foreheads with some lax tissue to facilitate primary closure.

Nasolabial flaps

The nasolabial flap was first documented in the Indian Sushruta of 600 BCE and has been a workhorse for reconstruction of defects around the face and the anterior oral cavity. The artery is based on distal branches of the facial artery and its venae commitantes. The flap is usually designed with an inferior base, but can be based superiorly with a more random vascular supply. The design usually places the most medial limit of the flap in the nasolabial fold with the superior limit approximating the medial canthus of the eye. The medial to lateral dimension of the flap is determined by the defect to be reconstructed and the ability to primarily close the donor site. Flap elevation is usually initiated distally with a retrograde dissection above the plane of the facial musculature. In the intraoral application a tunnel is placed traversing the facial muscles and buccinators, allowing the inferiorly based flap to enter the oral cavity (**Figure 92.3**).

This flap is extremely reliable when based inferiorly, with a relatively inconspicuous donor site, particularly when bilateral flaps are used. Its greatest application intraorally is for the anterior floor of mouth and gingiva, where its use is both simple and effective. The donor site for this flap is best tolerated in elderly patients with rhytids that mask the donor site.

Submental island flaps

This flap, first described by Martin in 1983,[3] has great utility as an axial pattern flap or a free flap for reconstruction of the facial skin or intraoral lining. The flap is supplied by a branch or branches of the facial artery that pass

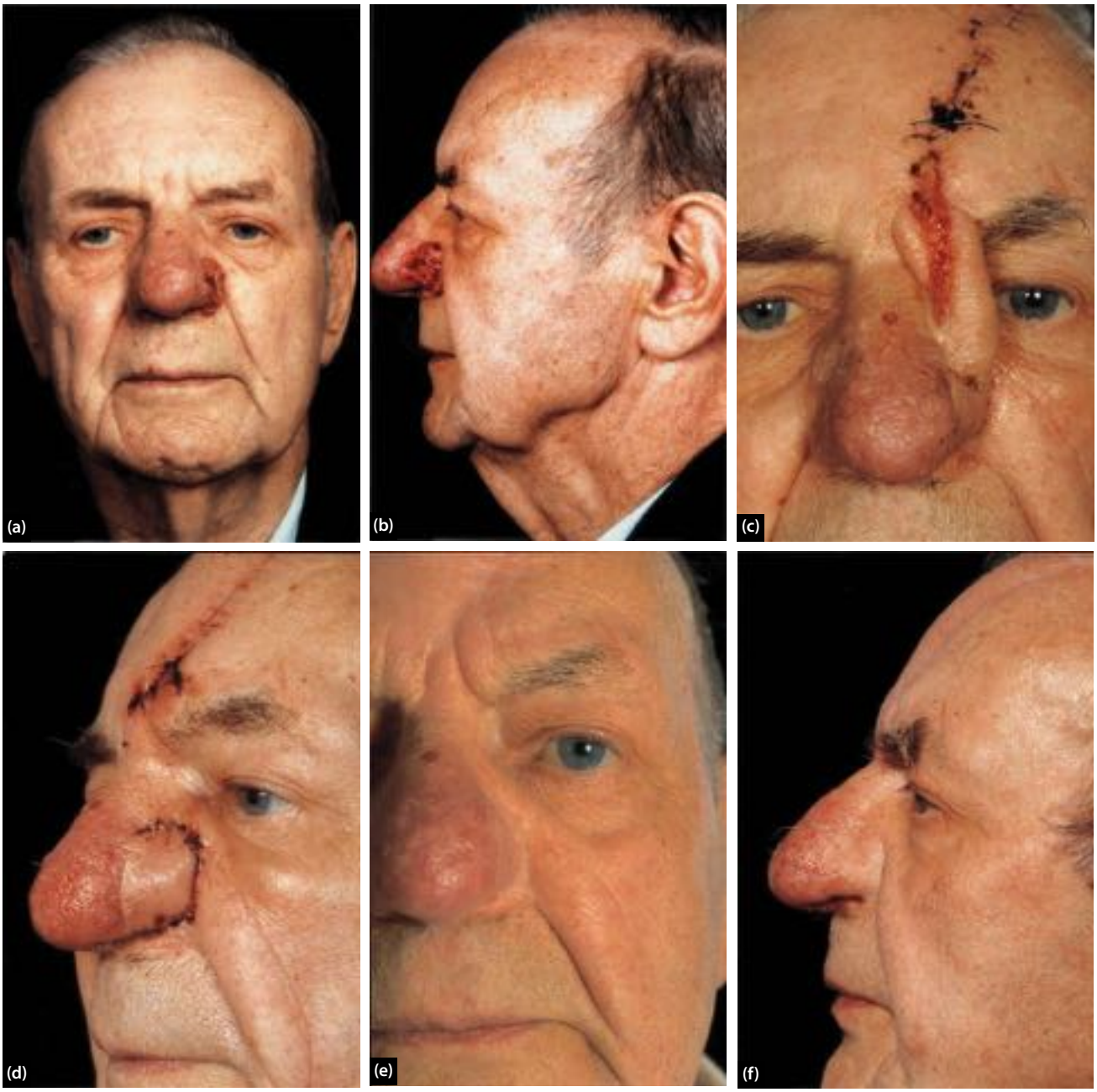


Figure 92.2 Use of a midline forehead flap to repair a defect in the lower left aspect of the nose and cheek. (a, b) A patient with a T4 basal cell carcinoma of the lower aspect of the nose and medial part of the cheek. **(c)** Wide excision was achieved, repair of the lateral side of the nose was with an infolded delayed forehead flap and the cheek was repaired using V to Y advancement. **(d)** The forehead flap was divided 3 weeks later. **(e, f)** The final result.

either over or through the submandibular gland, traversing medially on the mylohyoid muscle and then deep to the anterior belly of the digastric muscle to provide a perforator-based arterial supply and venous drainage to the submental skin.[4] The flap has a variable venous drainage via the facial vein. There can be occasional problems with venous congestion, particularly in the reverse flow design, because of valves in the facial vein. The flap is usually designed in the midline, just below the margin of the mandible, with the superior/inferior dimension determined by the ability to close the submental skin (**Figure 92.4**). Dissection is usually initiated on the contralateral side to the planned vessel pedicle. Skin and subcutaneous tissues are incised down to the level of the investing fascia of the digastric muscle, with the plane of dissection carried in the submental triangle at the level of the mylohyoid muscle. The ipsilateral anterior belly is usually divided distally and proximally to preserve the blood supply to the flap and the dissection proceeds in a retrograde fashion to the facial artery and vein. The flap can be tunnelled under the mandible and through the submandibular and submental space for oral reconstruction, or can be rotated or transposed onto the face for soft tissue coverage. The unique advantage of this flap is its colour match with

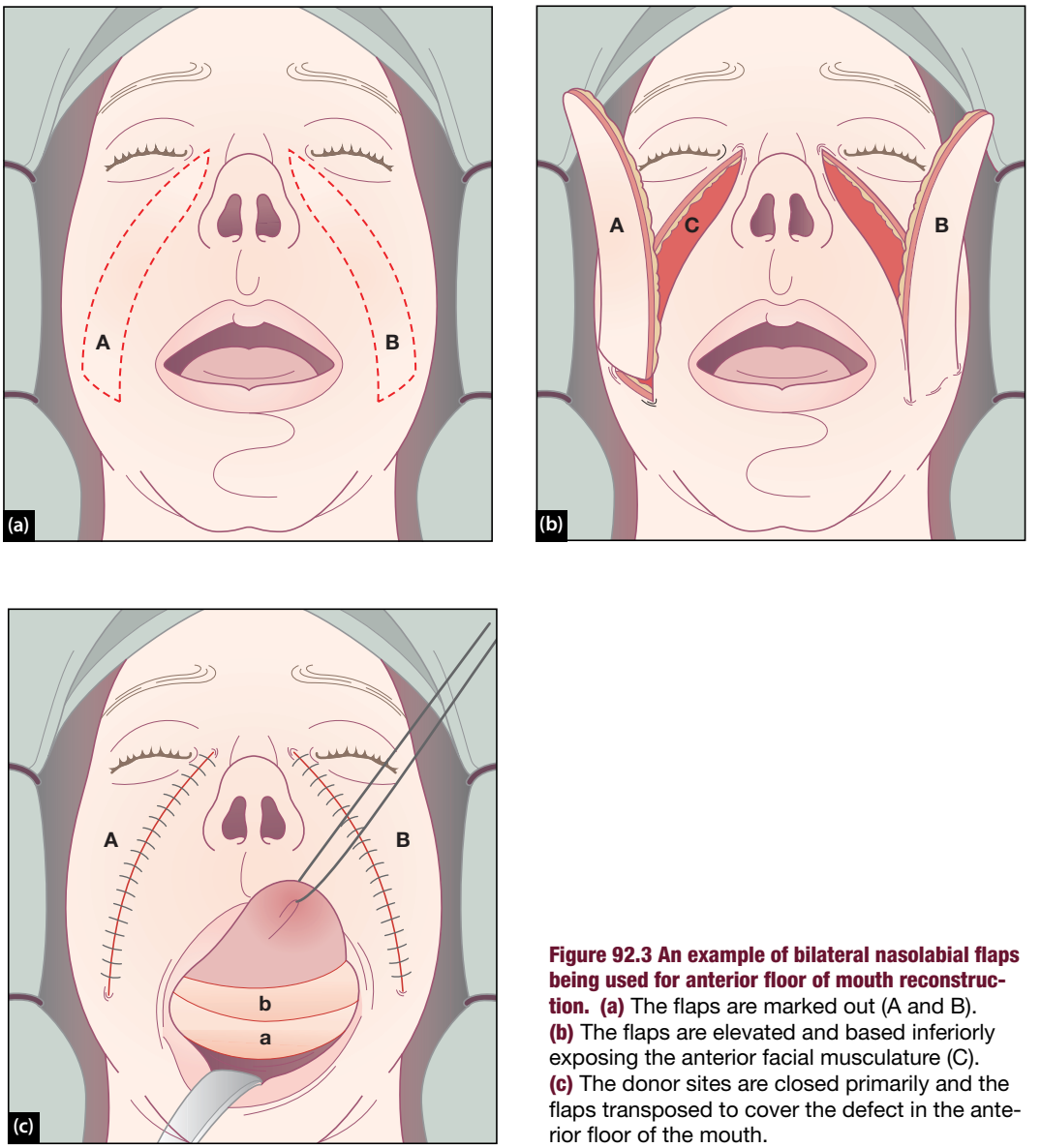


Figure 92.3 An example of bilateral nasolabial flaps being used for anterior floor of mouth reconstruction. **(a)** The flaps are marked out (A and B). **(b)** The flaps are elevated and based inferiorly exposing the anterior facial musculature (C). **(c)** The donor sites are closed primarily and the flaps transposed to cover the defect in the anterior floor of the mouth.

facial skin and the relative inconspicuous nature of the donor site scar. There have been reports of problems with venous congestion, particularly when tunnelled through the submandibular space.

Facial artery myomucosal flaps

The facial artery myomucosal flap (FAMM) was first described by Pribaz et al. in 1992.[5, 6] This flap is composed of oral mucosal and buccinator muscle and is based on branches of the facial artery. The anatomy of this flap is based on the buccinator muscle and its relationship to the facial artery. The buccinator is covered medially by the submucosa and mucosa and laterally by the external lamina of the muscles of facial expression, the masseter, the buccal fat pad, and the facial artery and vein.

The facial artery, a branch of the external carotid artery, enters the face by curving around the lower border of the mandible at the anterior edge of the masseter muscle. It then follows a tortuous course, passing superiorly and anteriorly to a position just lateral to the commissure of the mouth. At this point it lies deep to the risorius, zygomaticus major muscle and the superficial lamina of the orbicularis oris muscle. It lies superficial to the buccinator muscle and the lateral edge of the deep lamina of the orbicularis oris muscle. At this point in its course it gives off multiple perforating vessels to the cheek and the superior labial artery. It continues superiorly to the angular artery, which reaches the medial canthus. It has communicating branches with the buccal and infraorbital branches.

The FAMM flap is an axial pattern flap based on the facial artery. The flap may be harvested as an inferiorly based flap based on antegrade flow or a superiorly based flap with retrograde flow. The basic harvest technique is to Doppler out the facial artery through the buccal mucosa and map the course of the vessel. For the inferiorly based flap, dissection begins anterosuperiorly to identify the arterial supply to the upper lip with division of the facial

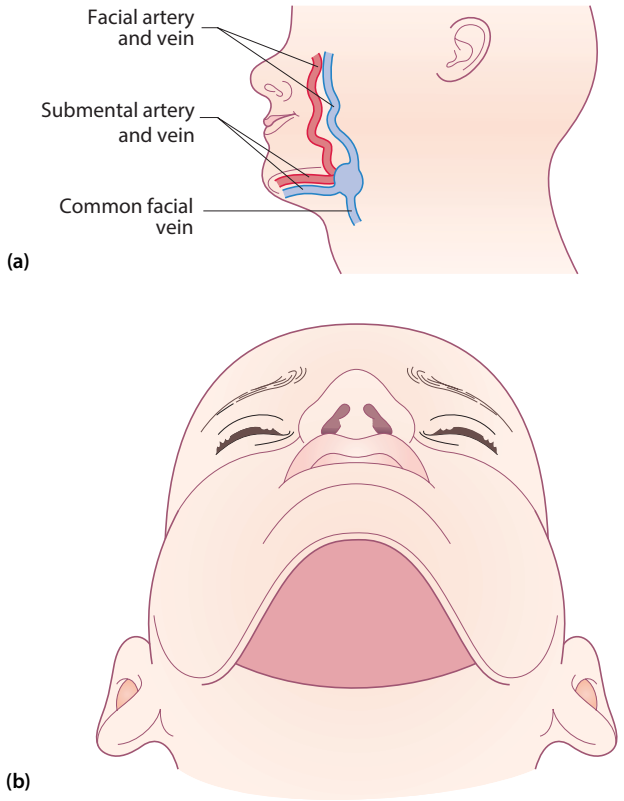


Figure 92.4 **(a)** The submental island flap is pedicled on branches of the submental artery and vein; **(b)** the size of flap available.

artery at this point and then retrograde dissection, which includes the mucosa, buccinator, facial artery and the tissue and venous plexus that lies between the artery and the muscle. In the superiorly based flap, the dissection begins inferiorly with visualization and ligation of the facial artery and then a retrograde dissection of the tissues including the buccinator muscle. A flap of 7–8 cm can be harvested with a thickness of 8–10 mm.

The FAMM flap is ideally suited for reconstruction of small mucosal defects in the oral cavity and in particular the mucosa of the lip. The flap can also be rotated across the alveolus to close small defects of the floor of mouth or tongue, as well as the palate.

Temporoparietal fascial flaps

The temporoparietal flap is a versatile local rotation or free fascial flap for reconstruction of the head and neck or extremities. The flap was first described by Golovine in the 19th century for orbit reconstruction. More recently it has been popularized by Brent and Byrd,[7] and others, for microtia repair and auricular reconstruction. Its unique characteristics are a remarkably robust vascular supply with a very thin and pliable flap with minimal donor site morbidity.

The arterial supply of the temporoparietal flap is the superficial temporal artery, a terminal branch of the external carotid artery. The vessel classically has a number of branches above the zygoma, with most patients

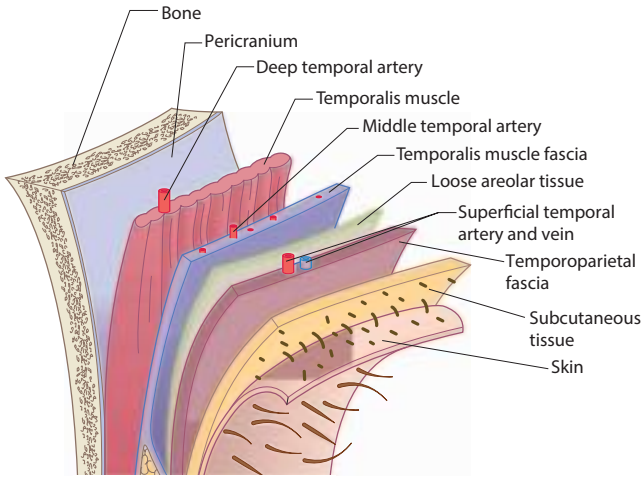


Figure 92.5 The different layers of the scalp, with particular reference to the position of the temporoparietal fascia.

having a prominent frontal branch and dominant branch that ascends towards the vertex of the skull. The venous drainage is via the superficial temporal vein running with the artery. There is some variation in venous anatomy, with a small percentage of patients having venous drainage through the post-auricular vein or occipital veins. The temporoparietal fascia (TPF) lies just under the subcutaneous tissue of the lateral scalp (**Figure 92.5**). The fascia has an inner and an outer layer, with the artery and vein entering between the inner and outer layers and then coursing vertically in the outer layer of the fascia. The outer layer of the TPF extends as the superficial muscular aponeurotic system (SMAS) below the zygoma. A thin muscular layer (the superficial auricular muscle) separates two parts of the outer layer of the fascia below the temporal line. The inner layer of the TPF contains a dense vascular network, which originates from the outer layer. Two nerves have an anatomic relation to the flap: the auriculotemporal nerve, a branch of V3, lies within the superficial layer of the TPF and theoretically could provide for a sensate flap; and the frontal branch of the facial nerve traverses over the zygoma in the same plane as the frontal branch of the superficial temporal artery and can be injured if the dissection is carried too far forward in the plane of this vessel.

For flap harvest the patient is usually positioned in the supine position, with the drape line along the vertex of the scalp leaving the post-auricular area exposed.

The important landmarks for this flap are the arch of the zygoma, the pinna and the usual landmarks of the facial nerve. The artery usually lies just in front of the pinna and is easily palpated or detected with the Doppler in the this location. The artery ascends vertically to the apex with a frontal branch coming off 1–3 cm above the zygomatic arch. The flap is harvested as an elliptical or teardrop shape, above the level of the zygoma. The incision is placed just posterior to the position of the vertical branch and can be either a straight or curvilinear incision into the scalp or 'Y' shaped for larger teardrop-shaped flaps. The inferior limit of the incision is usually the tragus but inferior extensions can be used for extended rotations or if the surgeon

wishes to visualize the facial nerve. The initial incision is started just above the zygoma, extending into the scalp. The surgeon harvesting this flap for the first time must take great care not to incise too deeply as the pedicle can easily be divided during the incision. The plane of dissection is initiated by defining the level of the superficial temporal fascia just below the subcutaneous fat layer in the scalp. A good landmark is to look for the hair follicles; if they are being transected, the surgeon is elevating the flap too superficially. Once fully mobilized from the overlying skin, the flap is incised around its periphery and elevated in the plane just above the temporal fascia. Dissection is carried down to about 2 cm below the arch of the zygoma to ensure an appropriate arc of rotation (**Figure 92.6**). Clinical applications for this flap include: orbital reconstruction, including the extenteration cavity; upper and lower eyelids and the eyebrow as a fascio-cutaneous hair bearing flap; auricular reconstruction, including microtia and traumatic or oncologic deformities; palate reconstruction; and buccal mucosal reconstruction.

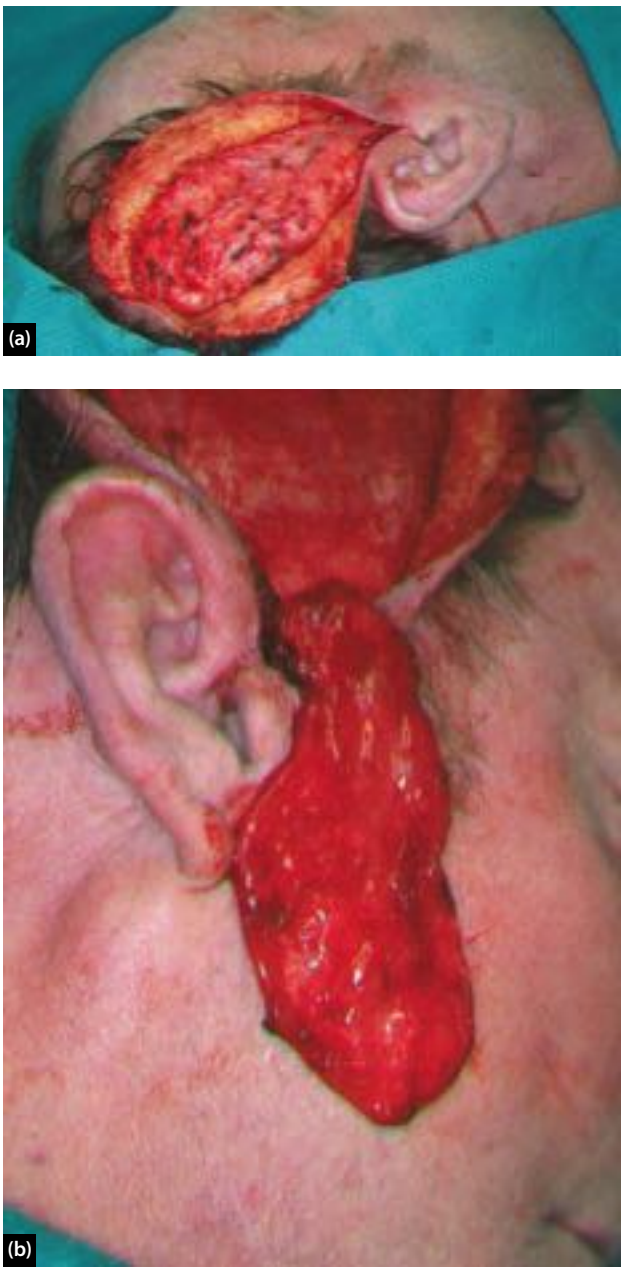


Figure 92.6 (a) Donor site of the temporoparietal flap. **(b)** Arc of rotation temporoparietal flap.

DISTANT AXIAL FLAPS

Deltopectoral flaps

This flap was described by Bakamjian and Littlewood in 1964[8] and is an axial pattern flap designed on the anterior chest wall between the line of the clavicle and the level of the anterior axillary fold. Its vascular supply arises from the upper three or four perforating branches of the internal mammary artery that emerge through the medial end of the intercostal spaces (**Figure 92.7**). Its boundaries are the clavicle superiorly, the acromium laterally and a line running through the anterior axillary fold to above the nipple inferiorly. The flap will extend to any site in the neck and occasionally up to the level of the zygoma. This flexibility is explained first by the fact that it retracts from side to side after it has been elevated, and not from end to end, so that it may elongate slightly over time, particularly in patients over 60 years of age. Second, its flexibility is due to an anomalous pivot point (see 'Planning the transfer' below).

The territory of the perforator vascular system has been shown to extend as far as the groove separating the deltoid from the pectoralis major (deltopectoral groove). Any extension of the flap beyond this should not be regarded as an axial pattern flap. One must be aware that any extension of the flap beyond this area may result in failure of the tip of the flap.

The flap is marked out using the landmarks described above and then elevation begins laterally. The pectoral

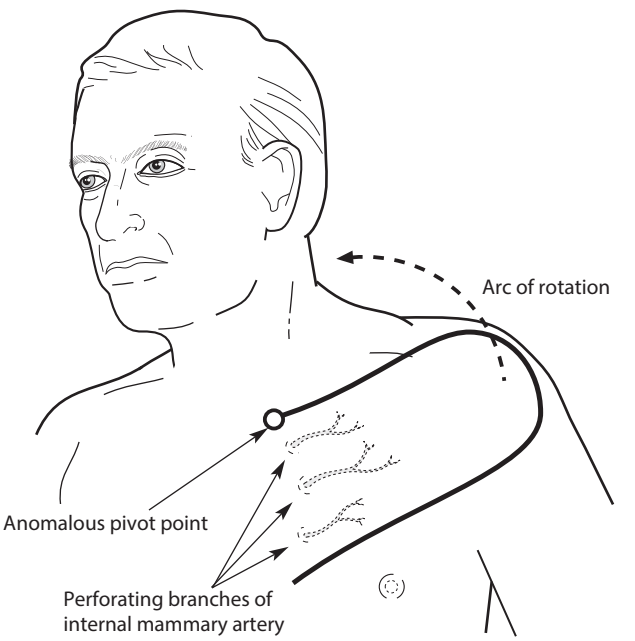


Figure 92.7 Design and planning of the deltopectoral flap. Note the position of the anomolous pivot point at the upper medial end of the flap.

fascia is left on the flap, leaving the muscle fibres below absolutely bare. Any branches of the acromiothoracic axis that are encountered should be ligated. Monopolar diathermy is used judiciously on the flap and the muscle, as this could damage the flap and any diathermy marks on the muscle may compromise the subsequent take of any skin graft. When raising the flap, retraction is upwards by an assistant using skin hooks; it must not be doubled back on itself as this could lead to buttonholing.

PLANNING THE TRANSFER

The deltopectoral flap has an anomalous pivot point. There is considerable laxity of the skin on the anterior axillary fold when the arm is abducted. This means that the lower border of the flap is considerably longer than the upper part. The pivot point on the flap is thus at the medial end of the upper limb and not the lower limb. This needs to be taken into account when planning the flap. The donor site is usually covered with a split skin graft. The uses of a deltopectoral flap are:

- to allow a one-stage reconstruction of the anterior neck skin
- to reconstruct a defect by passing as a bridge over normal; once take has occurred over a period of 3 weeks, the pedicle is divided and the remaining part of the flap may be returned to the donor site or discarded
- to reconstruct large defects on the lower face and upper neck. The pedicle may be inserted into part of the defect to facilitate take and then the pedicle is divided inferiorly and the flap inserted into the rest of the lower defect. This is analogous to 'waltzing'. The deltopectoral flap may also be used in the repair of a pharyngeal fistula but usually muscle bulk is required with the skin, and therefore other flaps are preferable.

Supraclavicular artery island flaps

The supraclavicular artery island flap (SAI) is a local fasciocutaneous flap harvested from the skin on the shoulder and supraclavicular area. This flap was first described in 1979 by Lamberty,[9] who described a supraclavicular artery flap based on a branch of the tranverse cervical artery in the majority of cases with occasional supply from the suprascapular vessels. Pallua et al.[10] expanded the anatomic knowledge of this flap, demonstrating that the flap in all cases was supplied by a branch of the transverse cervical artery with venous drainage via paired venae commitantes joining either the external jugular vein or the transverse cervical vein. They described the take-off of the artery within a triangle bounded anteriorly by the posterior border of the sternocleidomastoid muscle, posteriorly by the external jugular vein and inferiorly by the clavicle (**Figure 92.8**). Pallua demonstrated that flaps up 30 cm in length and 12 cm in width could be harvested and rotated into head and neck defects. Chiu et al.[11] in 2009 reported an initial experience with this flap in oncologic defects of the head and neck and since that time numerous authors have reported experiences with this flap.

FLAP HARVEST

The supraclavicular artery is identified using a hand-held Doppler, usually originating in a triangle bounded anteriorly by the posterior border of the sternocleidomastoid muscle, posteriorly by the external jugular vein and inferiorly by the clavicle. The vessel is followed out over the clavicle to identify the axis and design of the flap. The flap is usually designed with a width of 6–7 cm and a length of 20–25 cm from the rotation point. Dissection starts distally and is carried subfascially over the deltoid until one reaches the anterior border of the trapezius. The spinal accessory nerve is identified and dissection continues in a subfascial plane. The dissection then turns to elevation of the infraclavicular portion of the flap in the subfascial plane; this dissection in the subfascial plane is maintained until over the clavicle. Once the acromion is reached the dissection is continued with careful dissection, with branch ligation with either bipolar cautery or surgical clips. Skeletonization of pedicle is not usually necessary, unless wider arcs of rotation are required. The distal extension of the transverse cervical artery may restrict rotation and

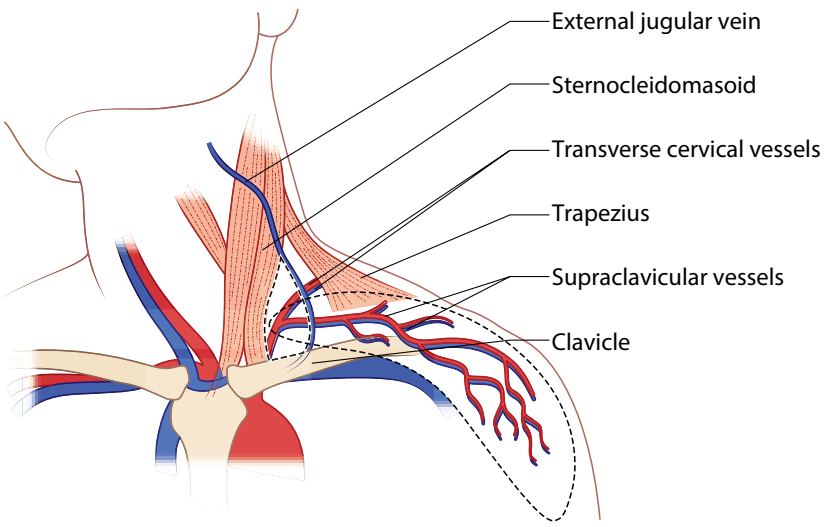


Figure 92.8 Supraclavicular artery island flap.

can be ligated if necessary. The proximal portion of the flap is usually de-epithelialized to allow tunnelling into a facial or intraoral defect.

CLINICAL APPLICATIONS

The SAI flap has broad application for external skin defects extending from the base of the neck to the parotid. In addition, numerous authors have described its use for oral and oropharyngeal defects. The advantages of the flap are the ease of elevation and a neck donor site. Rates of venous congestion and flap failure vary in the literature, but are likely much higher than those experienced with classic free tissue transfer.

OTHER DISTAL AXIAL CUTANEOUS FLAPS

These include other cervical skin flaps and occipitomastoid-based flaps.

Cervical-facial skin flaps of varying shape, size, site and direction may be designed to make good use of lax neck skin for reconstructive purposes. In general, they make use of the side of the neck. They are most frequently used as a primary or salvage procedure for external skin defects of the lower face and cheek. This flap has the unique advantage of providing excellent if not identical colour match for external defects. The nape of neck (Mütter) or posterior scalp flap is a random pattern skin flap that exploits the neck skin over the trapezius muscle and can be raised on the occipital vessels and extended downwards to the spine of the scapula. It may be swung on its upper pedicle to reconstruct areas in the lower face and submandibular region.

Myocutaneous and muscle-only axial distant flaps

One of the most important discoveries in the last 30 years is that the skin over most parts of the body receives its blood supply from small musculocutaneous arteries (perforating vessels) that enter it from the underlying muscle (**Figure 92.9**). It subsequently became apparent that an obvious way to move a large area of skin for reconstructive purposes was to transpose the skin with its underlying muscle vascularized by its dominant blood supply:

- pectoralis major
- latissimus dorsi
- sternomastoid
- trapezius
- platysma.

The pectoralis major and the latissimus dorsi flaps represent the workhorses for many head and neck reconstructive surgeons and a detailed understanding of the anatomy and harvest techniques will be a significant asset to the head and neck surgeon.

The muscles are supplied ultimately by segmental vessels that have similar perfusion pressures to the aorta. They run deep within the muscle and give off perforators that enter the muscles and provide communication between the segmental vessels and the musculocutaneous vessels in the skin. There may be several arterial pedicles. The artery is usually accompanied by two venae commitantes that unite after leaving the muscle to drain into a major regional vein. Five types of muscular arterial supply have been described (**Table 92.2**).

The blood supply to the muscles may also be random or axial in pattern. Most of the round muscles, for example the sternomastoid, have a random supply: perforators penetrate the belly at one end and immediately break up into small branches. The flatter muscles such as pectoralis major and latissimus dorsi have an axial supply: the major arterial supply runs the whole length of the deep surface of the muscle, giving off perforators as it goes.

Essential surgical points are:

- With the axial muscular flaps, although the blood supply to the muscle is axial, the blood supply of the skin upon the muscle is random.
- There is a minimum size of skin paddle that should be taken to ensure that one incorporates enough perforators

TABLE 92.2 Patterns of vascular anatomy

Vascular pedicle		Examples used in head and neck surgery
I	One pedicle	None
II	Dominant pedicle and minor pedicles	Sternocleidomastoiod Trapezius Platysma
III	Two dominant pedicles	Temporals
IV	Segmental pedicles	None
V	One dominant pedicle plus secondary segmental pedicles	Pectoralis major Latissimus dorsi

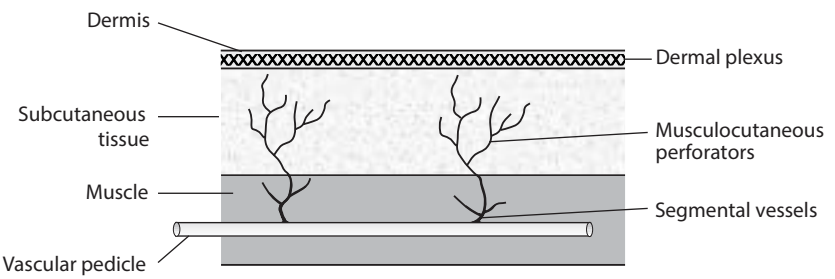


Figure 92.9 Blood supply to a myocutaneous flap.

to supply the skin flap. For pectoralis major and latissimus dorsi flaps, this usually means a skin paddle measuring 5×3 cm (the size of the palm of an adult's hand).
- Smaller skin paddles may not survive.

Pectoralis major flaps

This flap was first described by Ariyan in the late 1970s.[12, 13] The muscle's origins are the clavicle, the sternum and slips from the upper seven ribs. There is also a variable origin from the aponeurosis of the external oblique, which is variable in size. It is inserted into the bicipital groove of the humerus. The muscle has three major segmental sub units: clavicular; sternocostal; and an external segment (the most lateral part of the muscle), which originates from the ribs.

The main arterial supply, which provides the vascular basis for this flap, comes from the pectoral branch of the acromiothoracic artery that arises from the first part of the axillary artery (**Figure 92.10**). The pectoral branch of the acromiothoracic axis emerges from the clavipectoral fascia, along with the lateral pectoral nerve, medial to the insertion of pectoralis minor on the coracoid process, a bony prominence that can be felt below the clavicle near the junction of its middle and outer thirds. The point, 2–3 cm medial to the coracoid process, represents the surface marking of the vascular hilum of the muscle. The vessels do not enter the muscle belly immediately but run on its deep surface in a downward and medial direction giving off its branches. The acromiothoracic artery gives off a superior (clavicular) branch to the clavicular segment of the muscle and a main pectoral branch, which then gives off an inferior thoracoacromial branch to the sternal segment and a lateral thoracic trunk to the external segment.

In approximately 50% of cases, the external segment of the muscle may be supplied exclusively by the lateral thoracic vessels that arise from the second part of the axillary artery and descend along the lateral border of the pectoralis minor. In one-third of cases, this external segment receives a dual supply from both the lateral thoracic and the thoracoacromial vessels. The sternocostal segment also receives a supply immediately from a perforating branch of the internal mammary artery, which may account for significant bleeding during the raising of the flap. The pectoralis major flap has a Type V vascular pedicle.

The major advantages of this flap are that it has a large skin territory (the whole of the skin overlying the muscle may be raised), it has a rich vascular supply and it can be transferred without prior delay. It has a large arc of rotation and can be transferred up to the upper aspect of the ear to the level of the zygomatic arch. It can be harvested in the supine position, and can be transferred either as a muscle-only, skin and muscle paddle, or as two epithelial surfaces for inner and outer lining with a de-epithelialized segment between them. Primary donor site closure is easily achieved. However, it is a large bulky muscle that is relatively immobile and, therefore, is suited best to providing well-vascularized tissue to fill large defects where mobility is not of paramount importance, as in the repair of fistulae. It violates the breast in the female and, in this situation, the latissimus dorsi flap provides an appropriate alternative.

TECHNIQUE

The whole of the skin overlying the pectoralis major muscle may be raised if required. However, this will leave a large defect that will require coverage with a skin graft and so the flap is usually designed to facilitate primary closure.

With the patient in the supine position, the surface markings of the acromiothoracic artery are outlined. A dotted line is marked from the acromium to the xiphoid process and a further dotted line is dropped to join this line in a perpendicular direction from the sternal notch. The point at which the line bisects the first line represents the location where the vascular pedicle meets the first line (**Figure 92.11**). The pedicle then runs in the direction of the first line from the acromium towards the xiphisternum. The clavipectoral fascia is then marked by a point two-thirds of the distance along the clavicle from the sternal

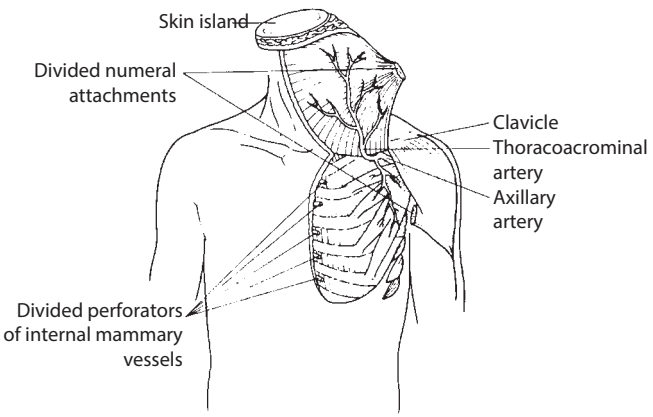


Figure 92.10 Blood supply to the pectoralis major myocutaneous flap.

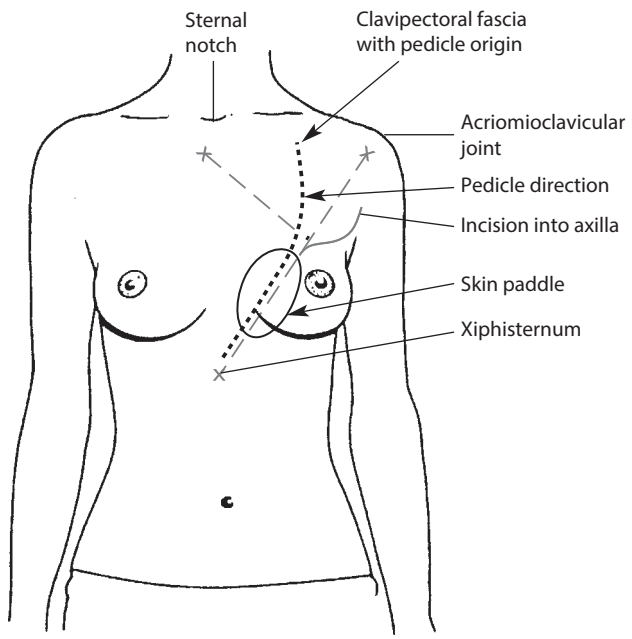


Figure 92.11 Landmarks for raising the pectoralis major myocutaneous flap.

notch to the coracoid process. The vascular pedicle runs in a curved direction downwards to meet the bisection point already described. A skin island of the appropriate size and shape may be drawn over the distal part of the artery, to facilitate a suitable arc of rotation. The borders of the skin paddle should lie between the lateral edge of the sternum medially and the nipple laterally. The incision for access should be extended into the axilla. The technique described by McGregor and McGregor[2] (i.e. designing the skin incision to allow a secondary deltopectoral flap from the same side) should be considered in both males and females. This technique allows for an easier wound closure and provides a salvage flap for neck resurfacing.

Unless the arc of rotation needs to be increased, it is advisable not to extend the lower part of the skin paddle beyond the inferior edge of the muscle. This part of the flap is random and, although the survival of this segment can be increased by taking part of the rectus sheath, this is not wholly reliable and should not be done unless absolutely necessary. Remember that the flap will retract by 10% in all directions when the skin is cut and this should be allowed for in planning, although some expansion will occur when the muscle is sewn in under tension.

The steps for elevation of the pectoralis major flap are as follows:

1. Start the dissection inferiorly.
2. Incise the skin down to the underlying muscle.
3. Define the inferior and lateral borders of the pectoralis major muscle.
4. Incise and mobilize the inferior attachments of the muscle to gain access to the subpectoral plane, which is relatively avascular.
5. Divide the inferior muscle attachments from the ribs or rectus sheath.
6. Mobilize in an upward direction.
7. At this point the pectoralis minor muscle will be visualized.
8. If the skin paddle is thick or excessively mobile, place sutures from the dermis of the skin island to the muscle surface to prevent shearing and flap loss.
9. Combine mobilization in an upward direction, first laterally and then medially.
10. Identify the lateral border of the external segment of the muscle.
11. Identify and ligate the major branch of the lateral thoracic artery to increase the arc of rotation.
12. Continue the dissection upwards.
13. Divide the sternal insertion of the muscle at the level of the anterior axillary line and remember to continue in a vertical direction.
14. Do not curve the scissors medially at this point or you may cut the pedicle – the ultimate disaster.
15. The muscle will now be rotated and the vascular pedicle will be clearly identified.

Once the origin of the sternal portion of the muscle has been divided, the flap may be easily elevated by blunt dissection in the subpectoral fascial space between pectoralis major and minor. The vascular pedicle is now clearly seen and the sternal edge of the muscle may be divided up to the level of the clavicle with the pedicle in clear view. Haemostasis is maintained throughout the elevation of the flap by carefully cauterizing the intercostal perforators, as well as the perforators supplying the medial portion of the muscle from the internal mammary vessels. If there is any lateral muscle mass attachment this is divided at this point, bearing in mind that the axillary vein is extremely close. The flap is now fully raised and mobile and if further mobility and arc of rotation are required, it may be islanded on the vessels by dividing the remaining muscular pedicle.

As a teaching aid, it is prudent to observe the neurovascular pedicle of the pectoralis minor muscle at this point, which is now visible and easily accessible. This muscle may be raised on its own as a free flap and used in facial reanimation techniques (see Chapter 95, Facial reanimation surgery).

Whilst the flap is being sewn in at the recipient site, the donor site can usually be closed. Haemostasis must be carefully achieved. Two large drains are inserted and the defect is closed, primarily using a two-layer closure. If closure is anticipated to be difficult, a one-layer blanket nylon or Ethilon stitch is an elegant technique of closing the wound as it takes up the tension gradually in the same way as a mastectomy wound is closed. Large defects may require a skin graft.

Modifications of the flap include harvesting of muscle alone when, for example, closing large lower neck wounds that require bulk with no skin paddle. A subsequent skin graft can be applied to the raw muscle surface. Access is achieved along the lateral border of the muscle and primary closure easily achieved. The incorporation of vascularized bone has been described where part of either the fifth rib or the sternum can be transferred with the flap to provide composite soft tissue and bony reconstruction. The vascular supply to these bony segments is at best precarious and in the majority of instances non-existent. Newer and more effective techniques for composite soft-tissue and bony reconstruction are available, obviating the need for the myo-osseous pectoralis major flap. Double skin paddles may be used with de-epithelialized islands in between them to provide oral lining and cutaneous cover but, again, in this situation, the muscle is very bulky and newer techniques such as double-paddled radial forearm flaps are probably better. Where the excessive bulk of the pectoralis major is a problem, harvesting over the thinner, parasternal area has been described (e.g. to tube the flap for reconstruction in the hypopharynx). Although this sounds attractive, practical experience has shown that it is virtually impossible to tube a pectoralis major myocutaneous flap. This should be considered as a salvage technique only, as better free tissue transfer techniques are available

When the above guidelines are followed, there are very few potential pitfalls with this flap. It is highly reliable and even when the skin paddle fails, the underlying muscle will usually survive and can be allowed to granulate and heal by secondary intention, or covered subsequently with a skin graft. It is always worth checking for congenital

absence of the pectoralis major, although it is extremely rare, with an incidence of 1 : 11 000. Congenital absence of the sternocostal head is part of Poland syndrome.

When a conventional flap is used, the skin paddle is designed medial to the nipple, at about the level of the sixth rib. In this area, the skin overlying the muscle is usually relatively thin in males. To achieve similar thickness in females, a design placing the skin island in the inframammary fold oriented transversely or slightly angled superiorly in its medial extent allows for the thinnest flaps. Where greater flap length is required, the flap design may be extended inferiorly beyond the lower border of the muscle. The extension should not extend beyond 3–4 cm and the rectus abdominus aponeurosis together with the rectus sheath should be raised with the flap. In this situation, the survival of the lower part of the flap is unpredictable. The breadth of the flap may be extended by including the nipple/areolar complex. The design of the incisions for this flap is particularly critical in females, where vertical scars result in significant secondary deformities of the breast. The surgeon considering this flap in females should consider the inframmary incision as the preferred approach.

Latissimus dorsi flaps

This flap represents the first myocutaneous flap described in the medical literature (by Tanzini). It was repopularized by Olivari in 1976[14] for the repair of local defects. Further work by Quillen et al. in 1978[15] described its use for head and neck reconstruction, and it remains a reliable and versatile fundamental component of the surgeon's repertoire.

The muscle is large and triangular in shape and arises from the sacrum and lumbar vertebrae, thoracolumbar fascia, the posterior iliac crest and the lower six thoracic vertebrae. In addition, some slips arise from the lower three ribs and the muscle converges to have a narrow insertion into the intertubercular groove of the humerus. Hence, it forms the posterior wall of the axilla. It is a type V muscle, which receives a significant but smaller blood supply from the perforating vessels through the lumbosacral fascia, and a pedicled flap can be based on this to repair defects in the buttock region.

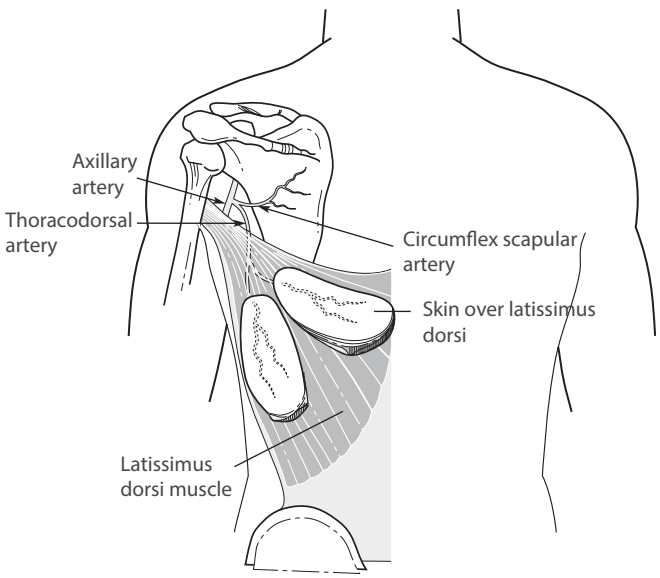


Figure 92.12 Blood supply to the latissimus dorsi flap. The thoracodorsal artery is a continuation of the subscapular artery, which comes directly off the axillary artery.

Its major vascular supply arises from the thoracodorsal vessels, which have their origin in the subscapular artery (**Figure 92.12**). This latter artery arises from the axillary artery, gives rise to the circumflex scapular artery about 4 cm from its origin (**Figures 92.13** and **92.14**) and then continues as a thoracodorsal artery to enter the latissimus dorsi about 10 cm from its humeral insertion. Just before its insertion, it gives off a branch that accompanies branches from the lateral thoracic artery (which also arises from the subscapular artery) and carries on to supply the serratus anterior. Within the latissimus dorsi muscle, the thoracodorsal vessels divide into superior and lateral branches that allow the muscle to be split into two. Either two flaps can then be taken or just one flap, thereby leaving some muscle behind.

Venous drainage is by the venae commitantes, which accompany the thoracodorsal artery and drain into the axillary vein. The nerve supply is via the thoracodorsal nerve, which is a branch of the posterior cord of the brachial plexus.

Large amounts of tissue are made available using this flap. Flaps measuring 10×8 cm are easily harvested and subsequent primary closure is easily achieved. Even larger amounts of tissue may be taken as a musculocutaneous flap measuring 40×20 cm but this requires skin grafting of the donor defect and may lead to problems with healing on the back.

A latissimus dorsi flap may not only be raised as a myocutaneous pedicled flap but also used for free tissue transfer. It is reliable, with a long pedicle of greater than 10 cm which can be further lengthened by dividing the circumflex scapular artery. The diameter of the subscapular artery at this point is at least 3 mm and the veins are of similar size.

By designing the flap low down on the back, the arc of rotation allows transfer into the head and neck region up to the zygomatic arch and flaps can be made to reach the top of the head (particularly if only muscle is used). The other advantages of this flap are that it does not violate the breast and because it is a large flat muscle, it is possible in extreme circumstances to tube it for total pharyngeal reconstruction. In addition, the subscapular artery offers a variety of flaps which may be used either singularly or in combination. Therefore, a scapular flap along with a latissimus dorsi flap and serratus anterior flap may all be raised on the same pedicle.

The advantages of the latissimus dorsi flap are:

- large amounts of tissue can be transferred
- pedicled or free tissue transfer
- it has a cosmetic advantage, especially for females
- it is versatile; may be tubed/multiple/osseous components
- when pedicled, it can reach the upper face and scalp.

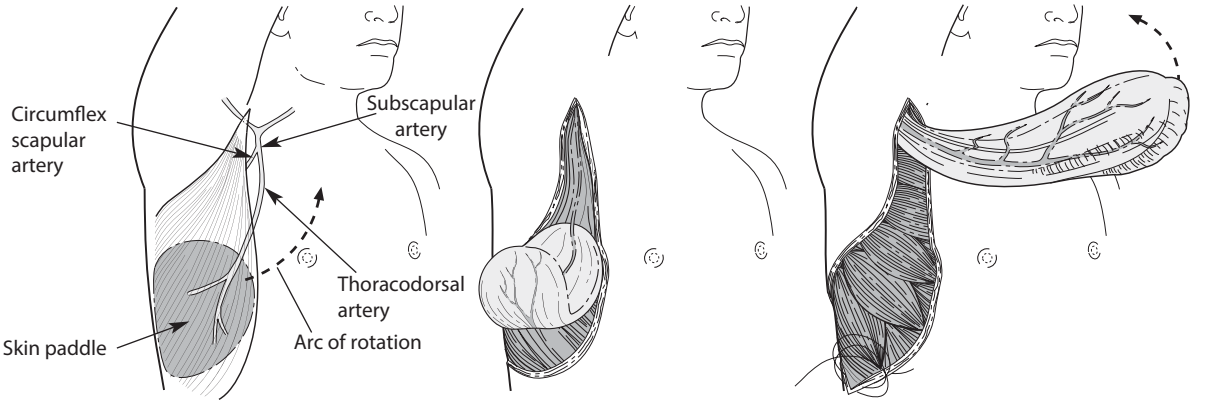


Figure 92.13 Technique of raising the latissimus dorsi flap. When designing for pedicled transfer, an oblique incision is used to allow maximal length to the flap. The dissection begins low down and then the pedicle is identified more proximally as the dissection approaches the axilla.

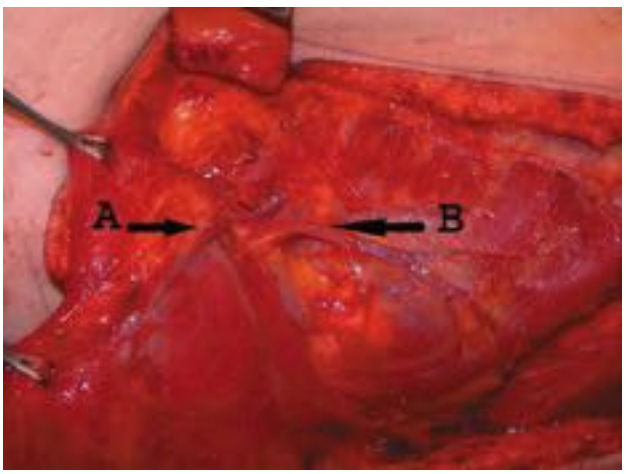


Figure 92.14 Lateral view latissimus dorsi pedicle. (a) Thoracodorsal branch to latissimus dorsi; **(b)** thoracodorsal branch to serratus anterior.

Despite these advantages, it still remains a musculocutaneous flap with thick skin and is therefore more bulky than, for example, a radial free forearm flap. Its use tends to be in resurfacing large defects of the external neck skin and for secondary repair of wound complications such as salivary fistula. It has an excellent application in reconstructing the total glossectomy defect as the volume of the flap makes it ideal for filling the mucosal defect and the dead space below the resection site. Serious donor site problems are rare but dehiscence and late wound seroma can be a problem. Congenital absence of the muscle should be checked for prior to surgery, and in athletes and those who do manual work the flap should be raised from the non-dominant side.

Raising the flap usually involves a variable amount of turning of the patient. Some authors advocate the lateral decubitis position, which often requires a repositioning manoeuvre following the ablative procedure. Most surgeons who are experienced with this flap will harvest it with the patient turned 15–30 degrees, which obviates the need for the repositioning manoeuvre and allows two team procedures.

The disadvantages of the latissimus dorsi flap are:

- it is very bulky
- there is occasional donor site dehiscence
- reduction in upper limb power
- it may require moving of the patient to harvest.

RAISING THE FLAP

Small flaps may be raised with the patient supine, but larger flaps require the patient in a rotated position with the arm freely draped so that it may be moved during the flap harvest.

Skin may be raised over the whole area of the muscle, although the vascular supply from the thoracodorsal artery decreases as one approaches the lumbosacral fascia. The posterior axillary fold is marked out and this represents the anterior edge of the muscle. The posterior iliac crest is also marked, together with the tip of the scapula. The skin flap is designed to the appropriate size and shape, with particular reference to the length of pedicle. If an arc of rotation is required to facilitate transfer to the head and neck via a pedicled myocutaneous flap, it will usually mean an oblique or vertical design; but if a free flap is required, the flap may be harvested in a horizontal direction, which gives a more acceptable scar in young women since it can be hidden behind the bra strap.

The steps for elevation of the latissimus dorsi are:

1. Outline the flap.
2. The initial incision exposes the anterior edge of the latissimus dorsi muscle.
3. Dissect round inferiorly, cutting through the muscle.
4. Identify the serratus anterior.
5. Do not go deep to serratus anterior here: this places the pedicle in jeopardy.
6. Recognize serratus anterior, as its fibres run at right angles to those of the latissimus dorsi.
7. Divide latissimus dorsi inferiorly.
8. The muscle flap may be extended beyond the skin island in a lateral to medial and superoinferior direction to

provide additional muscle to resurface external defects or provide additional volume to fill defects. Remember at this point that if one is low and on top of the latissimus dorsi, the pedicle is not in jeopardy.
9. Elevate the flap in the submuscular plane.
10. Identify the pedicle running down the muscle, usually in its central portion. The key to easy identification and protection of the pedicle to latissimus dorsi is to identify the branches to the serratus and follow them superiorly to the take-off from the thoracodorsal. Occassionally, patients will have a separate pedicle to serratus but this is very infrequent. Once the thoracodorsal pedicle is identified, divide the vessels to serratus anterior and continue dissecting superiorly.
11. Continue the dissection up towards the tip of the scapula.
12. The junction of the thoracodorsal vessels with the circumflex scapular vessels to form the subscapular artery can be clearly seen at the upper anterior end of the muscle in the axilla.
13. If a longer pedicle is required (as is usual), ligate the circumflex scapular vessels.
14. Follow the subscapular vessels into the axilla.

At this point, it is usual to island the flap if a free transfer is required. This also can provide a longer pedicle for the myocutaneous rotation flap. The surgeon may insert a pair of scissors under the latissimus dorsi tendon above the vessels and then cut the muscle to complete the islanding. When using the flap as a myocutaneous rotation flap, consideration should be given to not dividing the insertion of the muscle. When the muscle is left intact, the insertion prevents twisting of the vascular pedicle and reduces the risk of kinking and venous congestion. If an extended pedicle is required than the tendon must be divided to get additional length.

There are two steps in the delivery of the latissimus dorsi flap:

1. Ligate the circumflex scapular artery and vein.
2. Follow the subscapular vessels into the axilla.

If a pedicled transfer is to be completed, the flap must be tunnelled into the neck. There are essentially two options, sub- or suprapectoral, with the subpectoral route being the favoured approach. The border of the pectoralis major is identified and dissection deep to the muscle establishes the space between pectoralis major and pectoralis minor. A tunnel may be developed with blunt or sharp dissection, making sure that the pedicle to the pectoralis major is kept medially. The surgeon then develops the superior dissection, if it has not already been performed, by exposing the clavicle and the clavipectoral fascia. A tunnel is then developed by splitting the pectoralis major. The tunnel needs to be wide enough to allow the passage of the muscle without compression, usually the breadth of one's hand:

1. Use blunt finger dissection going on top of the pedicle.
2. Remember to go 'over pectoralis minor – under pectoralis major'.
3. Dissect from above through the clavipectoral fascia, dividing some of the lateral fibres of pectoralis major.
4. Open and widen the tunnel.
5. Deliver the flap without twisting or rotating the muscle.

The donor site is closed primarily in two layers using two large drains, one of which should be left for up to a week to avoid a seroma, which can occur following such a large dissection. This can be avoided by suturing the muscle remnants to the chest wall prior to closure. With a pedicled flap, the muscle should be denervated by dividing the nerve. If a free flap is being used, the thoracodorsal nerve may be preserved and used for reinnervation procedures such as anastomosis to a cross facial nerve graft for facial reanimation, or following total glossectomy where the maintenance of muscle bulk has been noted following anastomosis to the hypoglossal nerve.

Sternomastoid flaps

The sternocleidomastoid muscle, unlike the previously described muscles, does not have a localized vascular hilum. It is supplied segmentally by vessels that enter the muscle at intervals along its length. There are two principal vessels in its upper half, which consist of two branches of the occipital artery, and in its lower half, a branch from the superior thyroid artery. Further minor arterial branches enter in between. Its use has been described as: a myocutaneous flap raised as a composite skin muscle flap; a myocutaneous skin island flap taking a skin island based over the lower aspect of the muscle (**Figure 92.15**); or a composite muscle–bone flap used for mandibular reconstruction taking a segment of clavicle. Its routine use is not recommended as it has a number of distinct disadvantages:

- The upper sternomastoid composite skin muscle flap is poorly vascularized and not reliable.
- The blood supply to the skin paddle based over the lower third of the muscle is similarly unreliable.
- The upper and lower ends of the muscle are areas of oncological significance.
- The inclusion of clavicle for mandibular reconstruction is usually no longer required as superior reconstructive options are available.

The sternomastoid flap is therefore rarely used but it may still have a role to play in two situations: first, it can be particularly useful as a muscle-only flap pedicled superiorly to fill small defects in the pharynx and oral cavity; and second, when split along its length and rotated anteriorly, it may be used to cover vessels in the compromised neck.

Trapezius flaps

Three basic myocutaneous flaps have been described that make use of trapezius: the upper trapezius, the lateral trapezius and the lower trapezius flaps.[16] These may be pedicled into the head and neck area and, in addition, descriptions of the upper and lateral trapezius flaps to include transfer

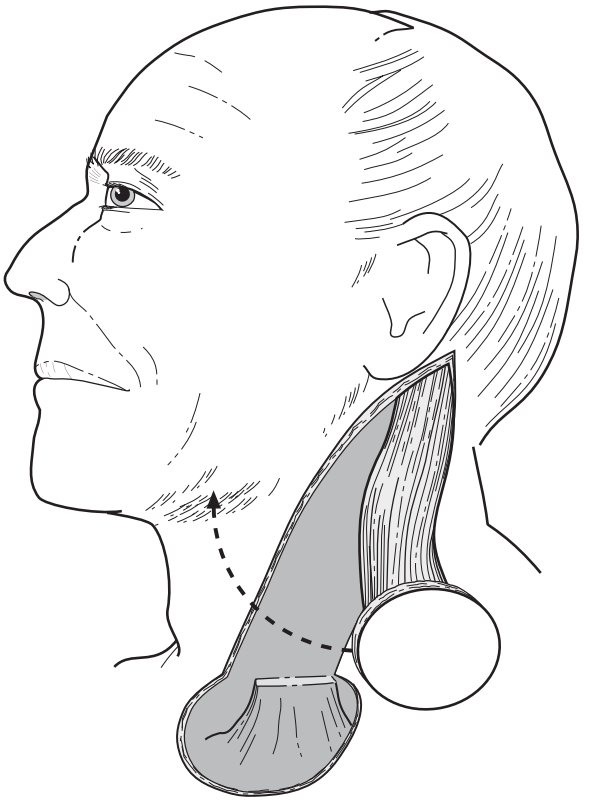


Figure 92.15 Sternomastoid flap.

of the spine of the scapula have been described for mandibular reconstruction. The vascular supply of these flaps is complex and varied depending on the design.

The superiorly based trapezius flap incorporates the upper third of the trapezius muscle and the overlying skin. The flap is supplied predominantly by the occipital artery and its venae commitantes. This flap has a limited used but can be applied for defects of the temporal bone, lateral face or upper neck. The flap is harvested by designing a skin island over the pars descendens of the trapezius muscle with dissection carried out in a retrograde direction along the deep surface of the muscle.

The pars horizontalis (middle) and a pars ascendens (lower) of the trapezius muscle form the basis of the lateral and lower trapezius flaps (**Figure 92.16**). The middle parts of the muscle are supplied mainly by the superficial cervical artery (superficial branch of the transverse cervical artery) and the lower part is supplied by the dorsal scapular artery (deep branch of the transverse scapular artery) and segmental intercostals perforators. The origins of the arteries supplying the trapezius muscle are highly variable and the aforementioned vessels may arise from different trunks.

An anatomic study[17] published in 2004 has demonstrated that the superficial cervical artery always runs lateral to the levator scapulae and rhomboid muscles, dividing into a short superior branch and long inferior branch that courses inferiorly with the accessory nerve to the level of the scapular spine. The dorsal scapular artery – the dominant supply to the lower third of the muscle – runs deep to the levator scapulae and minor rhomboid muscles.

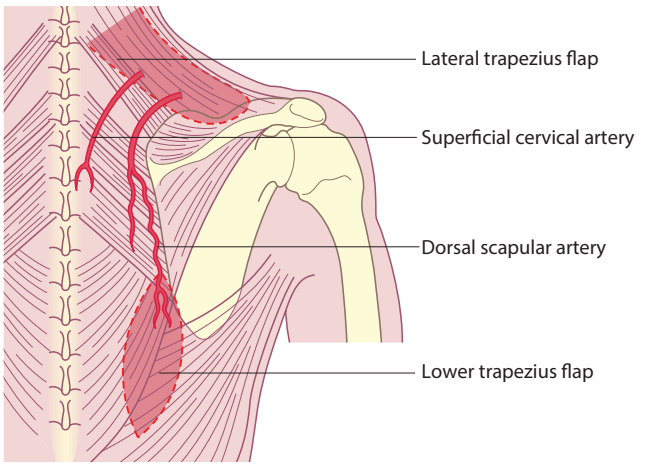


Figure 92.16 The trapezius group of flaps.

The flap with the most utility for head and neck reconstruction is the pedicled lower trapezius myocutaneous flap. This version of the flap has an arc of rotation appropriate for resurfacing of the neck and face and has great utility as a salvage option when a free tissue transfer has failed or there are no recipient vessels available for anastomosis of a free tissue transfer. The patient is positioned in the lateral decubitus position with the arm draped freely for repositioning of the scapula during dissection. The muscle margins, the medial border of the scapula and the thoracic spines down to the 12th vertebra are marked. The skin island is usually designed with the majority of the flap overlying the lower trapezius. Dissection begins medially, identifying the superior and lateral borders of the latissimus dorsi muscle and the lateral border of the trapezius. Dissection continues under the trapezius muscle where the dorsal scapular artery is identified. Retrograde dissection continues, following the vascular pedicle of the flap. The descending branch of the dorsal scapular artery (running deep to the rhomboids) must be divided to allow rotation and complete elevation of the flap. Dissection can be carried up to the levator scapulae with occasional division of the minor rhomboids to improve the arc of rotation. The flap can then be tunnelled subcutaneously into the neck.

Although these flaps are reasonably reliable and may play a role, particularly in the repair of the posterior aspect of the head and neck, such areas are easily reached with a pedicled latissimus dorsi flap. The patient positioning issues and anatomic variability related to the trapezius flap mean that it has a limited role to play in current head and neck reconstructive practice. Its role is principally to salvage (e.g. as a lifeboat when other flaps have been exhausted).

Platysma flaps

The platysma flap was first described in 1978. It is really one half of the myocutaneous apron flap and the skin transferred can either be at the level of the hyoid or in the supraclavicular region, after which the donor site is closed primarily. The blood supply to the upper part of the flap

comes from the submental branch of the facial artery and to the lower part from a branch of the transverse cervical artery. Although initially attractive as a simple way of providing a method of intraoral reconstruction, this flap has a number of distinct disadvantages and is rarely used today:

- Blood supply can be unreliable.
- There may have been previous surgery that has violated the neck and therefore precludes its use.
- When based on the submental branch of the facial artery, this requires preservation of muscularity in an area of oncological significance that may have to be addressed in the resection.
- By and large, the neck should be avoided as a source of reconstruction for the oral cavity.
- Removal of the platysma interferes with the blood supply to the overlying skin, which can have disastrous results.

CONCLUSION

While there has been a dramatic increase in the use of free tissue transfer in head and neck reconstruction, pedicled local or regional flaps have a major role to play in head and neck reconstruction. A clear understanding of the principles of use of local flaps and a comprehensive understanding of the anatomy of these flaps provides the head and neck surgeon with a plethora of local and regional options for primary and secondary reconstruction.

BEST CLINICAL PRACTICE

✓ With the axial muscular flaps, although the blood supply to the muscle is axial, the blood supply of the skin upon the muscle is random.
✓ There is a minimum size of skin paddle that should be taken to ensure that one incorporates sufficient perforators to supply the skin flap. For pectoralis major and latissimus dorsi flaps, this usually means a skin paddle measuring 5×3 cm (the size of the palm of an adult's hand).
✓ Smaller skin paddles may not survive.

FUTURE RESEARCH

➤ Numerous techniques have described using local and myocutaneous flaps in head and neck surgery. Unfortunately, very little data exists evaluating the outcomes in terms of the functional and aesthetic results.
➤ The field of local and myocutaneous flaps is additionally challenged by the advent of free tissue transfer that has dramatically reduced the need for complex local reconstructions except in reconstruction of the external skin.
➤ Future research in all areas of head and neck reconstruction should be focused on functional outcomes: speech, swallowing, aesthetics and patient quality of life.

KEY POINTS

- Pedicled flaps are usually straightforward to both use and harvest.
- Pedicled flaps are generally reliable, but may be bulky and poorly pliable.
- Pedicled flaps can be useful for salvage, particularly in the presence of infection.
- Pedicled flaps may be associated with significant donor site problems.
- Pedicled flaps should be in the surgical repertoire of every head and neck surgeon.

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CHAPTER 93

RECONSTRUCTIVE MICROSURGERY IN HEAD AND NECK SURGERY

John C. Watkinson and Ralph W. Gilbert

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: angiosome, perforator flap, free tissue transfer, fluid management, prophylaxis, deep vein thrombosis (DVT), Doppler, medicinal leech, free flap salvage, fibrinolysis, forearm flap, lateral arm flap, scapular flap, facial recontouring, scalp reconstruction, rectus abdominus, deep circumflex iliac artery (DCIA), anterolateral thigh flap, fibular flap, mandibular reconstruction, pharyngeal reconstruction, jejunal transfer and gastro-omental flap.

INTRODUCTION

Over the past 30 years, the introduction of reconstructive techniques incorporating microvascular free tissue transfer has transformed the quality of life of patients undergoing head and neck surgery. The microsurgeon's ability to transfer autologous tissues comprised of bone, functioning muscle, skin or composites has dramatically improved functional outcomes for all head and neck reconstructive procedures, whether oncologic, congenital or traumatic.

The revolution in the understanding of the blood supply to the various anatomic regions of the body[1,2] has dramatically increased the number and variety of reconstructive options. The wide variety of flaps and the breadth of anatomic knowledge required to offer patients the full panel of flaps available has demanded that most microvascular surgeons acquire specialized training. This evolution has also led to the development of specialized units offering the highest quality reconstruction and outcomes based on the effect of high surgical volumes and the inherent development of advanced technical expertise that comes with extensive surgical experience.

CLASSIFICATION OF FREE FLAPS

A variety of classification systems has been advocated for the description of the various types of free flaps available for reconstruction. A simple classification would divide flaps into cutaneous flaps, including fascia, subcutaneous fat and skin; myocutaneous flaps, including muscle with cutaneous elements; osseocutaneous flaps, including bone and cutaneous elements; and myo-osseous flaps combining muscle and bone.

Most recently a great deal of interest and terminology has evolved around the concept of perforator flaps (**Figure 93.1**).[3] A perforator flap consists of skin and/or subcutaneous tissues supplied by a perforating vessel that passes through or between the deep tissues, usually muscle. A muscle perforator is a vessel that traverses through muscle to supply the overlying skin. A septal perforator is a vessel passing only through an intermuscular septum to supply the overlying skin. A flap vascularized by a muscle perforator is called a muscle perforator flap and a flap vascularized by a septal perforating vessel is called a septal perforator flap. Based on this nomenclature, flaps may be described based on the anatomy of their supplying

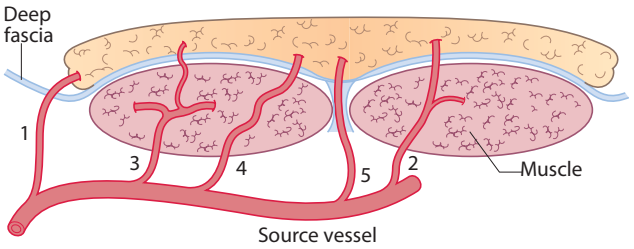


Figure 93.1 Schematic drawing of the different types of direct and indirect perforator vessels with regard to their surgical importance. 1, Direct perforators perforate the deep fascia only; 2, indirect muscle perforators predominantly supply the subcutaneous tissues; 3, indirect muscle perforators predominantly supply the muscle but have secondary branches to the subcutaneous tissues; 4, indirect perimysial perforators travel within the perimyssium between muscle fibres before piercing the deep fascia; 5, indirect septal perforators travel through the intermuscular septum before piercing the deep fascia. Redrawn from Ref. 3, with permission.

vessels. For example, the perforator based skin flap arising on the deep inferior epigastric artery that traverses the rectus abdominus muscle is called the deep inferior epigastric perforator flap and is a muscle perforator flap.

GENERAL CONSIDERATIONS IN FREE TISSUE TRANSFER

Peri-operative management

Considerable literature exists regarding the peri-operative management of patients undergoing free tissue transfers. In general, it is probably fair to state that there exists very little level I evidence regarding best practice. Numerous authors have advocated and continue to advocate for pre- or peri-operative use of volume expansion, particularly with synthetic plasma expanders.[4, 5] Many authors have advocated for higher than normal volume replacement during surgery in order to reduce the risk of arterial or venous occlusion. The evidence would suggest that none of these measures affect flap outcome. Paradoxically, some evidence suggests that excessive volume replacement results in higher rates of flap loss because of the resultant peri-operative complications of congestive heart failure and its sequelae.

The surgeon engaged in free tissue transfer must anticipate a long operative procedure and the following issues must be addressed. The patient must be protected from pressure sores, as procedures in excess of 8 hours often result in pressure sores on the sacrum, heels and back. Long periods of immobility require the use of deep vein thrombosis prophylaxis. Depending on jurisdiction and local practice, this includes heparin prophylaxis and intra-operative and peri-operative use of compression stockings.[6, 7]

Post-operative management

Patients undergoing free tissue transfer are best managed in monitored units where appropriate flap checks and appropriate invasive and non-invasive monitoring is available. In many jurisdictions this is provided in an intensive care facility or its equivalent. In centres with large volumes of free tissue transfers, specialized peri-operative units have been developed staffed with nurses specially trained in the management of free tissue transfers. Monitoring techniques vary from simple observation to implantable flow probes. A number of devices have been developed to detect venous or arterial occlusion. These techniques include percutaneous Doppler of donor vessels, cutaneous laser-Doppler flow probes and implantable flow probes.[8, 9] Little evidence suggests that any modality other than specialized nursing care and frequent observation represents best practice, with most major centres using percutaneous flow probes and specialized nursing units.[10, 11]

Recipient vessels

The head and neck represent a rich supply of vessels for vascular anastomosis. In the era of radical neck dissection, venous recipient vessels were often a problem as most ablative surgeons sacrificed the jugular vein. In the past 30 years, with the move to more selective neck dissections except in advanced disease, venous recipient vessels have not been a problem. Most experienced surgeons rely heavily on the facial artery, superior thyroid artery and transverse cervical artery for recipient arterial supply. These vessels often have a long mobile segment and are ideally positioned for most head and neck defects. Most microvascular surgeons advocate end-to-side venous anastomosis, and the internal jugular vein is often used. Secondary options include the external jugular vein, or the group of veins associated with the transverse cervical artery. The key to optimal vessel selection is careful peri-operative planning and communication between the reconstructive and ablative team with regard to vessel options and preservation during ablative procedures. New technologies are available for vascular anastomosis, with many centres advocating the use of mechanical anastomotic devices to expedite venous repair and reduce the rates of peri-operative occlusion.[12, 13]

Management of flap failure

The use of a free flap for head and neck reconstruction represents a major investment both for the patient and the reconstructive team. In the majority of head and neck procedures, flap failure represents a major peri-operative complication and a potential catastrophe. The majority of flap failures require major revision procedures and can result in significant prolongation of hospital stays and a delay in the delivery of post-operative radiotherapy or chemoradiotherapy. The functional and esthetic sequelae of flap loss can be devastating for oncologic patients.

The rationale for intensive peri-operative observation is to detect venous or arterial occlusion early with an emergent return to the operative theatre to attempt to salvage the flap. Most series report salvage rates between 50% and 80% dependant on the timeliness of detection of venous or arterial occlusion and the speed with which

the problem can be corrected.[14] The majority of occlusions are venous based largely on low flow and likely the greater technical difficulty in suturing a venous anastomosis. Two adjunctive techniques are widely used for venous occlusion. Many authors advocate the use of localized perfusion of the occluded flap with fibrinolytic agents.[15, 16] These agents, when perfused locally (but not systemically), seem to improve the rates of flap salvage. The other technique that is used widely for venous failure is the application of medicinal leeches. A detailed description of leech use is beyond the scope of this text, but they can be extremely effective at salvaging venous occlusions.[17]

FREE FLAPS IN HEAD AND NECK RECONSTRUCTION

The forearm flaps

The free forearm flap was first described for head and neck reconstruction by Yang[18] in 1983 when he used this flap to reconstruct a neck defect secondary to a burn scar contracture. The forearm flap was popularized for head and neck reconstruction by Soutar et al.[19] in 1983. Soutar described the first large series of forearm flaps for oral reconstruction, as well as the osseocutaneous forearm flap that incorporated the radius for mandibular reconstruction.[20] Numerous authors have published series of forearm flaps demonstrating its utility and versatility in head and neck reconstruction.

ANATOMY

The cutaneous forearm flap is based on the radial artery with venous drainage provided by the venae comitantes or branches extending from the skin to the cephalic vein of the forearm (**Figure 93.2**). The artery and venae have a remarkably consistent anatomy with rare anatomic variations. The vessel generally lies between the tendons of the brachioradialis and the flexor carpi radialis in the distal third of the arm and lies deep to the brachioradialis in the proximal forearm. The vascular supply to the skin is provided by perforating vessels that extend vertically through the overlying fascia to supply the subcutaneous fat and skin. The osseocutaneous version of the flap requires the incorporation of perforating vessels that cross over the velar and lateral surface of the radius to supply the periostemon of the distal radius. The flap can incorporate a sensory nerve – the lateral ante brachial cutaneous nerve of the forearm, which can provide a sensate flap for oral reconstruction.

The skin island can be as large as the entire velar surface of the arm. The bone available is from the pronator teres insertion to the distal radius with a maximum length of 10–12 cm available.

ADVANTAGES

The forearm flap has a number of unique advantages for head and neck reconstruction. Its surgical anatomy is remarkably consistent, making it a relatively easy flap for surgeons to learn and harvest reliably. The skin on the distal third of the arm is extremely thin, making it an ideal flap for interiorly reconstruction of the lateral tongue and floor of mouth. The flap can be harvested as a sensate flap, providing the most robust sensation available of all the cutaneous flaps available for head and neck reconstruction.[22] Because of the positioning of the arm during surgery the flap can be harvested simultaneously with an ablative head and neck procedure.

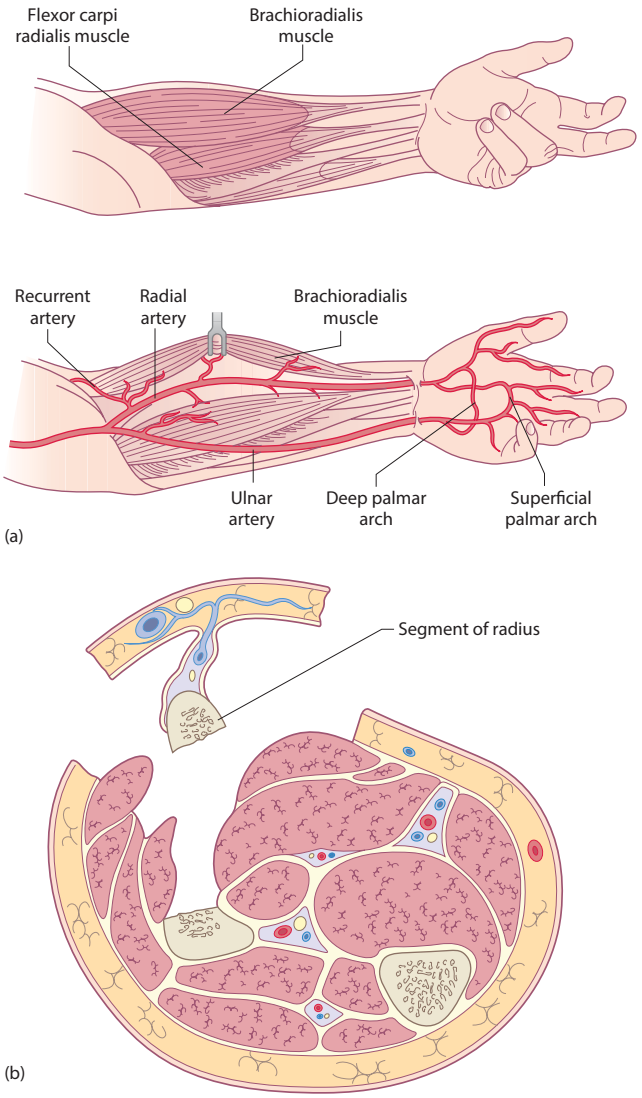


Figure 93.2 Detailed anatomy of the forearm flap: (a) muscular and vascular anatomy; **(b)** coronal section of the forearm illustrating the osteocutaneous version of the forearm flap, note the perforators extending from the radial artery to the overlying skin as well as the lateral and descending perforators to the radius. Redrawn from Ref. 21, with permission.

DISADVANTAGES

The forearm flap has few disadvantages. In terms of match to recipient defects, its only liability is the volume of tissue for some defects that incorporate large mucosal or cutaneous defects with a considerable amount of dead space.

The skin colour match to external skin is probably the poorest of the cutaneous flaps, except in patients of South Asian or African American origin, for whom the flap can have an excellent colour match. The donor site is not popular with patients as it usually requires a skin graft, leaving a relatively unsightly scar on the velar forearm. Bardsley et al. have described a so-called hatchet flap variation utilizing a volar ulnar artery based flap for primary closure of the forearm defect (**Figure 93.3**).[23] Other potential problems include wrist stiffness, cold sensitivity and, on occasion, tendon exposure, which often require long periods of wrist splinting to ultimately achieve skin closure.

TECHNICAL NUANCES

This flap is usually harvested under tourniquet control offering a blood free dissection. It is critical to be certain prior to harvest and tourniquet inflation that the patient has a patent lunar artery. In most patients the lunar artery is the dominant blood supply to the deep palmer arch that supplies the hand and digits. A simple Allen's test to evaluate collateral flow through the lunar artery is a mandatory pre-surgical procedure. During the harvest it is important to avoid injury to the cutaneous branch of the radial nerve. To avoid problems with tendon exposure following harvest, the paratenon overlying the flexor carpi radialis must be preserved to well-vascularized surface for a skin graft. Most surgeons use a relatively thick split thickness skin graft for the donor site. Some series have reported success with the use of full thickness grafts. In terms of the bone harvest in the osseocutaneous version of the flap, the major complication associated with this flap is fracture of the distal radius at the site of the bone harvest. The distal radius proximal to the radial styloid is relatively narrow and too vigorous a bone harvest can result in radial fracture. Most authors advocate taking no more than one-third of the width of the radius, and also suggest curving the osteotomy, avoiding perpendicular bone cuts, which can produce stress risers and potential fracture sites.[24] Some authors advocate prophylactic plating of the distal radius if a bone harvest is performed.[25] Most experienced microvascular surgeons would avoid this osseocutaneous flap in elderly osteoporotic females.

APPLICATIONS

Oral cavity and oropharynx

The forearm flap was popularized by Soutar for oral reconstruction and is the most important application for this flap in head and neck reconstruction. The function of a reconstruction of the oral tongue is to retain the mobility of the tongue remnant. One can easily appreciate that the forearm is ideally suited to the task (**Figure 93.4**). This flap's thin subcutaneous layer, pliability and potential sensation makes it unique among the variety of cutaneous flaps available for oral reconstruction. In defects including a segmental mandibular defect, authors have advocated the use of the osseocutaneous forearm flap. The radius is a less than ideal reconstruction for even short mandibular defects. It has a short vertical height, making secondary prosthetic reconstruction of the dental arch difficult or impossible, particularly if osseointegrated implants are indicated. In addition, the short length of available bone is problematic for extended defects. The radius is not easily osteotomized for defects including the symphysis or angle. Its only application in mandibular reconstruction is likely as a secondary option when the other bone flaps are not available or for short defects of the symphysis or body of the mandible. The osseocutaneous flap has been used for central maxillary defects, where a soft pliable cutaneous flap containing bone, associated with a long vascular pedicle, represents an ideal reconstruction (**Figure 93.5**).

The forearm is likely the best flap available for buccal mucosal reconstruction as it is the only cutaneous flap with the appropriate thickness for buccal defects.

This flap has been widely used for palate reconstruction, particularly small defects of the central palate and alveolus. Its unique strengths in this application are the thinness of the flap and its long vascular pedicle, which will readily reach neck recipient vessels.

Many reconstructive surgeons use this flap for defects of the oropharynx, particularly the tonsil–tongue base soft palate defect where the flexibility of the flap allows it to contour into these complex three-dimensional defects and provides excellent functional reconstruction of the soft palate.

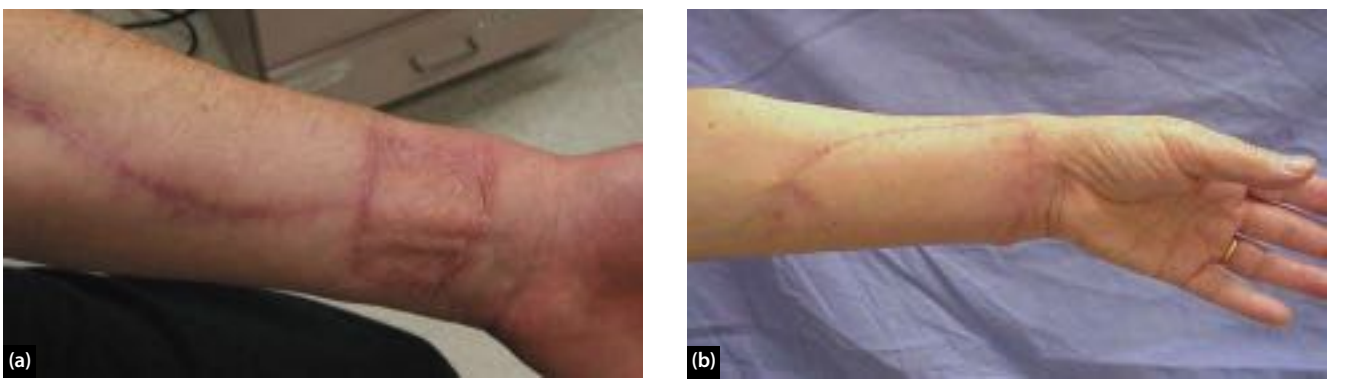


Figure 93.3 **(a)** Skin grafted donor site; **(b)** primary closure with hatchet flap.



Figure 93.4 Oral tongue reconstruction with forearm flap.



Figure 93.5 Osseocutaneous radius for midface reconstruction.

External skin

The forearm flap has been widely used for cutaneous defects of the head and neck. Because of the limited amount of skin available the applications for external defects are limited to small defects where the unique features of the flap are an advantage. One of the disadvantages of this flap in Caucasians is a relatively poor colour match to facial skin.[26]

The forearm flap's greatest applications in external skin reconstructions are the total upper or lower lip defect and total nasal reconstruction. In total lip reconstruction the ability to replace the entire aesthetic unit of the upper or lower lip along with a tendon sling (incorporating the palmaris longus or flexor carpi radialis tendon with the flap) makes this an excellent functional reconstruction for this formidable defect.[27] In total nasal reconstruction, a number of authors have described the use of this flap to create the lining and infrastructure for the nose, using a multistage procedure incorporating a forehead flap for external cover.

The lateral arm flap

The lateral arm flap described by Song et al.[28] in 1982 has been widely used in head and neck reconstruction. This flap has application in oral cavity reconstruction and in reconstruction of soft tissue and cutaneous defects of the face and neck. This flap has a relatively large cutaneous flap available up to 14 × 20 cm; however, donor sites wider than 6 cm cannot be closed primarily.

ANATOMY

This flap's blood supply is based on the radial collateral artery of the arm (**Figure 93.6**). The radial collateral artery arises from the deep brachial artery and runs with the radial nerve on the lateral aspect of the upper arm. Once the radial collateral appears on the anterolateral aspect of the trapezius it divides into a posterior and anterior branch. The anterior branch continues inferiorly to accompany the radial nerve deeply between brachialis and brachioradialis. The posterior branch enters the lateral intermuscular septum between brachialis and triceps and then runs toward the lateral epicondyle. In its course along the lower lateral arm the posterior branch gives off a number of fasciocutaneous perforators to supply the skin in this area. The skin of the lateral arm flap is innervated via the lower lateral cutaneous nerve of the arm a branch of the radial nerve. The innervation provided is relatively dense but not as sensate as the forearm flap.

ADVANTAGES

The major advantage of the lateral arm flap is its location on the arm. The donor site for this flap is relatively inconspicuous and can be closed primarily in most patients. The colour match to facial skin is excellent, even in Caucasians. The flap can be harvested as a sensate flap and does provide functional sensation.

DISADVANTAGES

The major disadvantages of the lateral arm flap relate to the available width of the skin flap and the pedicle size. Extremely wide flaps will require a skin graft for closure. The fat in the lateral arm may provide too much volume for oral reconstruction in obese patients. The pedicle associated is of small calibre with a maximum diameter of 1.5 mm with potential very small venae comitantes. Microsurgical anastomosis is therefore technically difficult and less reliable than other flaps. The vascular pedicle is short, 4–8 cm, making this flap less than ideal when recipient vessels are at a distance from the defect site.

TECHNICAL NUANCES

The flap design is critical to ensure that the posterior branch of the radial collateral artery is included in the flap. The axis of the flap and area to be harvested are planned by drawing a line from the deltoid insertion to the lateral epicondyle. Dissection begins on the posterior aspect of the flap with harvest of the deep fascia overlying the trapezius. Dissection continues superiorly until the lateral intermuscular septum is encountered. The posterior branch is visualized and then dissection begins on the anterior aspect of the flap again in the subfascial plane until the intermuscular septum is isolated on both sides. The flap is then dissected in a retrograde fashion with great care taken to avoid injury to the radial nerve.

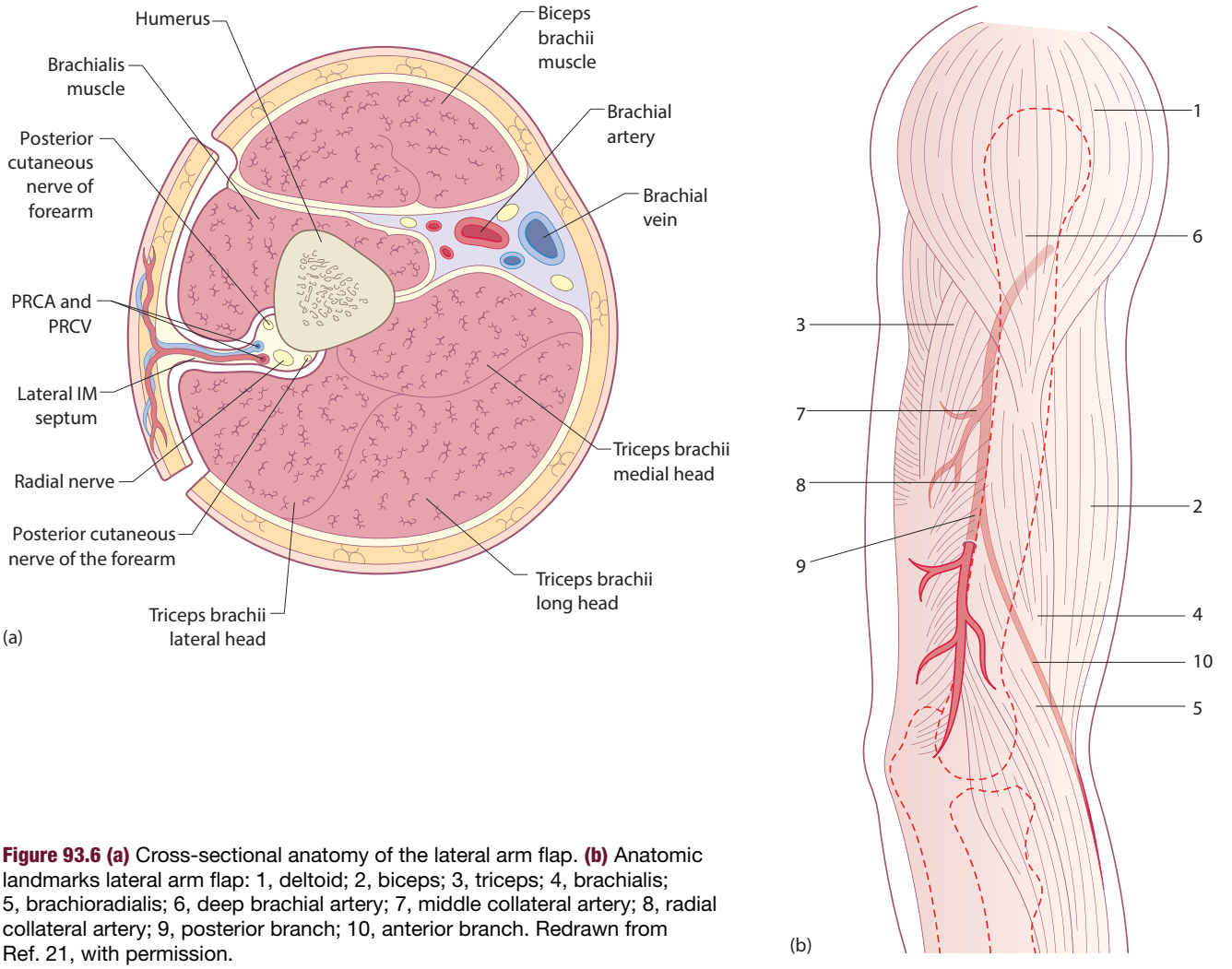


Figure 93.6 (a) Cross-sectional anatomy of the lateral arm flap. **(b)** Anatomic landmarks lateral arm flap: 1, deltoid; 2, biceps; 3, triceps; 4, brachialis; 5, brachioradialis; 6, deep brachial artery; 7, middle collateral artery; 8, radial collateral artery; 9, posterior branch; 10, anterior branch. Redrawn from Ref. 21, with permission.

CLINICAL APPLICATIONS

The major disadvantage of this flap is its pedicle length. It should not be considered when recipient vessels are at a distance from the defect site. The major applications for this flap are in reconstruction of the floor of mouth and lateral tongue. The excellent colour match to the lateral aspect of the face and neck make it ideal for recontouring radical parotidectomy defects or replacements for narrow defects of the lateral face or neck.[29]

SCAPULAR SYSTEM OF FLAPS INCLUDING THE LATISSIMUS DORSI FLAP

Cutaneous or osseocutaneous scapular or parascapular flap

The scapular system of flaps were popularized for head and neck reconstruction by Swartz et al.[30] and dos Santos.[31] A number of head and neck surgeons have described their experience with this flap in complex oromandibular reconstruction.[32]

The scapular system of flaps is unique in the area of head and neck reconstruction as no single area provides such a variety of options for reconstructive tissues. Flaps harvested from this group of flaps can provide skin, skin and muscle, skin and bone or skin, muscle and bone with two or three muscle flaps available based on a single vascular pedicle.

ANATOMY

In order to take full advantage of this group of flaps a detailed understanding of the vascular anatomy of this area is critical (**Figure 93.7**). The axillary artery gives rise to the subscapular artery, which descends in the posterior axilla to give rise to the circumflex scapular artery and the thoracodorsal artery. The circumflex scapular artery provides nutrient and periosteal supply to the lateral border of the scapula, then divides into two perforating branches that supply the skin overlying the scapula. The circumflex scapular artery lies in the space bordered inferiorly by the teres major muscle, superiorly by the teres minor muscle and laterally by the long head of the triceps. Once through this space the artery divides into the two aforementioned branches, giving rise to a parascapular perforator and a

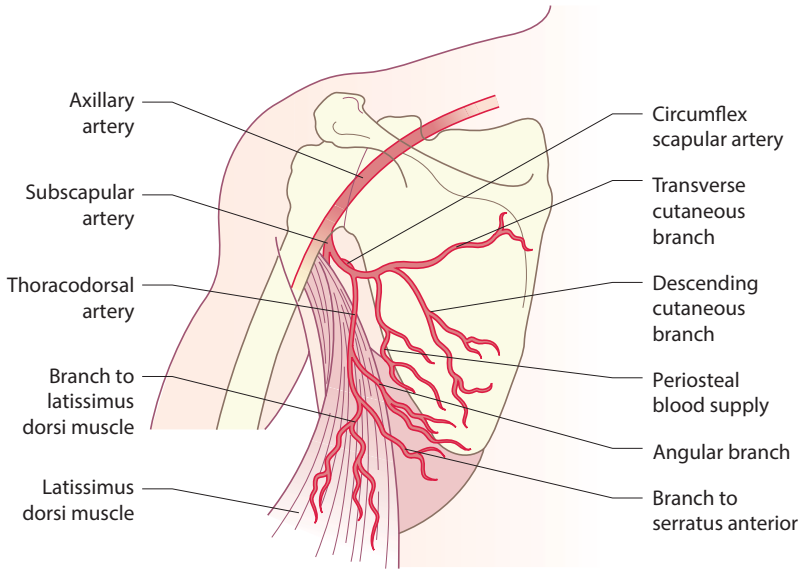


Figure 93.7 Anatomy of the scapular system of flaps. Redrawn from Ref. 21, with permission.

transverse scapular perforator. The thoracodorsal artery descends inferiorly, providing branches to the serratus anterior and the latissimus dorsi, as well as providing the angular artery, a branch that supplies the distal one-third of the scapula and its overlying musculature. The venous drainage is via paired venae comitantes, which usually join the axillary vein close to the origin of the subscapular artery. It can easily be appreciated from this vast array of vessels that any combination of flaps may be harvested depending on the requirements for the reconstructive defect. The cutaneous flaps available include a transverse scapular flap, a parascapular flap and a thoracodorsal artery perforator flap. The myocutaneous flaps available include the latissimus dorsi flap; the myogenous flaps available include serratus anterior, the latissimus dorsi and the teres major muscles. The osseous flaps include the scapular bone flap based on the nutrient vessels from the circumflex scapular artery or the scapular tip via the angular artery.

ADVANTAGES

The scapular systems of flaps have some particular advantages. The available skin, either via the parascapular or scapular perforators, can be as large as 18 × 10–12 cm with primary closure of the donor site. The latissimus dorsi perforator flap or the latissimus dorsi myocutaneous flap can provide even larger skin islands with primary closure of the donor defect. In composite reconstructions (bone and skin) the skin island may be rotated or positioned relatively independently of the bone flap, allowing considerable flexibility in positioning of the skin island relative to the bone segment. The vascular anatomy other than the blood supply to the tip of the scapula is remarkably consistent, and dissection based on anatomic landmarks makes the flap harvest relatively simple. The donor site when designed along the posterior axillary line is relatively well hidden. The skin colour of the scapular region generally is a good colour match to the face and neck, even in Caucasian patients. The donor site has very limited morbidity. However, when scapular bone is harvested most patients have some restriction of shoulder motion and require aggressive shoulder rehabilitation. It is the experience of a number of authors that this flap is extremely well tolerated in the elderly and vessels to the scapular system of flaps seem to be relatively spared in patients with extremity peripheral vascular disease, making it an excellent option in this group of patients.

DISADVANTAGES

This flap, while offering a plethora of reconstructive options, does have some disadvantages. In the original description of the harvesting of this flap the patient is positioned in the lateral decubitus position. For most ablative oncologic procedures, that would mean that the patient required repositioning for flap harvest and then a return to the original position for flap inset. Most experienced surgeons position the patient in the supine position with the body rotated 15–20 degrees. This positioning allows the ablative procedure and flap harvest without repositioning. Two teams or simultaneous harvest is next to impossible given the proximity of this donor site to the head and neck. The bone of the lateral scapula is technically difficult to harvest, given the array of muscular origins on the scapula, making a surgeon's early experiences with this flap relatively difficult. If the teres major and subscapularis are not properly repaired, patients may have considerable problems with shoulder strength and range of motion post-operatively. The pedicle of the scapular flap, particularly when a bone segment based on the nutrient artery is harvested, can be relatively short as the bone branch from the circumflex scapular artery is relatively close to its origin. The available bone is relatively short – 10–12 cm in an adult male – making it less than ideal for hemimandibular or extended resections of the mandible. The skin of the back, while ideal in terms of colour, has a relatively thick dermis and dense subcutaneous fat, making it an inflexible

reconstruction for defects requiring contour changes such as floor of mouth, tongue and palate reconstruction.

TECHNICAL NUANCES

The most important technical nuance for the harvesting of this flap is appropriate patient positioning. One approach is to position the patient on a 'bean-bag', essentially a polyethylene bag filled with beads. When the air is removed from the bag the beads form a firm structure that maintains the patient in the appropriate position. The patient is usually turned 20–30 degrees from the supine position so that the medial border of the scapula is visible and palpable.

Harvesting of the flap requires a detailed understanding of the muscular anatomy of the region. The location of the pedicle within the triangle bordered by teres major, teres minor and the long head of triceps is an important concept to understand. Identifying these structures during the harvest allows easy visualization of the perforators to the skin island. Perhaps one of the more difficult aspects of this flap is the bone harvest and position of the osteotomies. The key is to identify the bone nutrient artery just below the inferior tip of the glenoid. Make a transverse osteotomy between the inferior lip of glenoid and the entry of the nutrient artery into the lateral border of the scapula. The lateral border is then detached by making a vertical cut along the long axis of the scapula medial to the crest or the point of insertion of the teres major, teres minor and the subscapularis. We routinely drill holes in the remaining lateral border of the scapula and carefully reattach the teres major and subscapularis muscles, to maximize recovery of shoulder function.

CLINICAL APPLICATIONS

Cutaneous flap

The cutaneous scapular or parascapular flap has a wide variety of applications in head and neck reconstruction. Because of its colour match, it is ideal for defects of the lateral face, neck and temporal bone. The flap can be de-epithelialized for recontouring of facial defects and a number of authors have described its use for facial recontouring for conditions such as Romberg's disease[33] or secondary deformities of the lateral face. The latissimus dorsi myocutaneous flap has a similar range of reconstruction and is ideally suited for extensive defects of the lateral neck, and has been widely used as a muscle-only flap for scalp reconstruction.[34] The flap has been widely used for oral cavity reconstruction, particularly for composite defects, but the thickness of the dermis and the fat density of the flap make it a less than ideal reconstruction for this defect.

Osseocutaneous flap

The osseocutaneous versions of this flap have a variety of applications in head and neck reconstruction. The bone length available of 10–12 cm limits the use of this flap in extensive mandibular defects, but is adequate for the majority of ablative defects encountered (**Figure 93.8**). The bone is relatively easy to osteotomize, usually with osteotomies of one cortex and then 'green-sticking' the scapula to contour it to the appropriate shape. One of the unique aspects and applications of this flap are in defects including oral lining and external skin cover. The flexibility of the flap allows at least two separate skin islands that can rotate independently of the bone segment. Numerous authors have described the use of the scapular flap in midface and maxillary reconstruction. Two bone flaps are available for this application; the classic scapular bone flap based on the nutrient artery arising from the circumflex scapular artery and the tip of scapular flap based on the angular artery. The former has the limitation of a relatively short vascular pedicle, making its application in midface reconstruction relatively problematic. The tip of scapula based on the angular artery has the advantage of an extremely long vascular pedicle, making it ideally suited for maxillary and midface reconstruction.

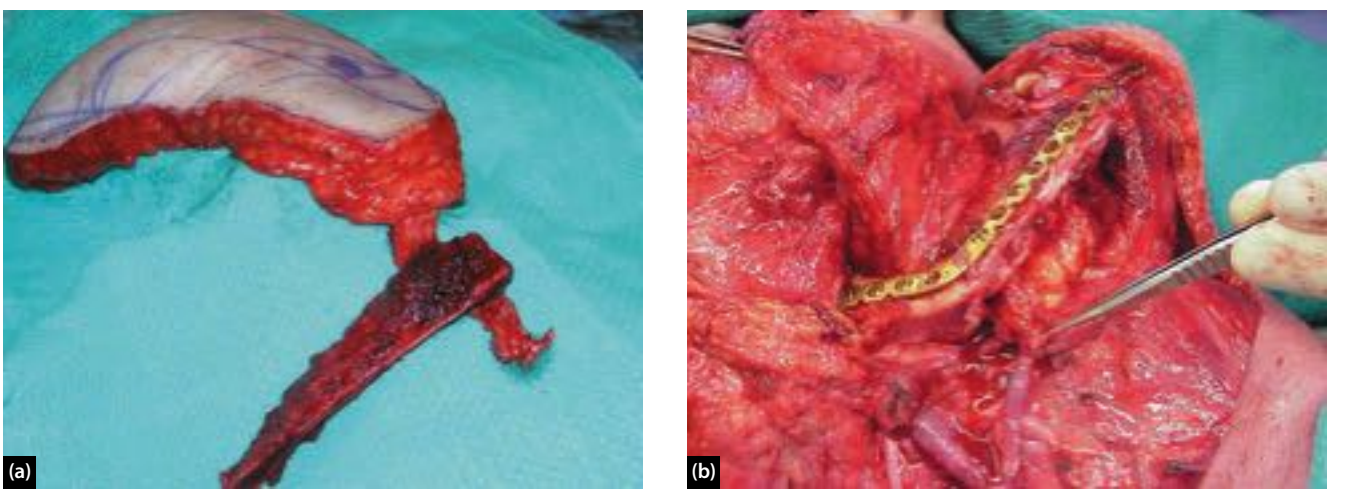


Figure 93.8 (a) Osseocutaneous scapular flap; note thickness of skin and short vascular pedicle. **(b)** Osseocutaneous scapular flap following inset for reconstruction of mandibular body and mucosal lining.

FLAPS FROM THE ABDOMINAL WALL AND PELVIS

Rectus abdominus and deep inferior epigastric artery perforator flaps

The rectus abdominus flap has been a 'workhorse flap' for head and neck reconstruction over the past 30 years. Originally popularized for breast reconstruction as a local myocutaneous flap based on the superior epigastric vessels, it has remarkable utility for head and neck reconstruction. The flap can be harvested as a myocutaneous or perforator-based flap, offering a wide variety of cutaneous or myocutaneous options.[35, 36]

ANATOMY

The rectus abdominus flap is based on the deep inferior epigastric artery and its venae comitantes (**Figure 93.9**). The deep inferior epigastric artery arises from the external iliac artery immediately above the inguinal ligament. It ascends in a lateral to medial direction penetrating the transversalis fascia below the arcuate line, then travelling superiorly between the rectus muscle and the posterior rectus sheath. The artery generally divides into a number of large branches just below the umbilicus, providing numerous perforating branches to the rectus abdominus muscle and the overlying skin. Pedicle lengths from origin to insertion into the muscle range from 8 cm to 14 cm with average vessel diameters of 2.0–3.0 mm. The flap has its sensory and motor supply from the lower six or seven spinal thoracic nerves, making its innervation segmental and less than ideal for functional reconstruction or restoration of sensation.

ADVANTAGES

The rectus abdominus myocutaneous flap or deep inferior epigastric perforator (DIEP) flap has a number of advantages for head and neck reconstruction. The vascular anatomy of the flap is extremely consistent, making it a relatively simple flap to harvest. The ability to transfer a skin/muscle flap, a perforator-based skin flap or a myogenous flap speak to its versatility. Large areas of skin are available, with the majority of defects amenable to primary closure. The donor site is not problematic for males or females and in some patients may offer the aesthetic benefit of an abdominal lipectomy. In most situations the selection of this flap for reconstruction offers the opportunity for a two-team procedure with flap harvest occurring simultaneously with tumour ablation.

DISADVANTAGES

The major disadvantages of this flap relate to donor site issues and the nature of the subcutaneous fat associated with this flap. The most frequent complication associated with this flap is central abdominal hernias, particularly when portions of the anterior rectus sheath are harvested below the arcuate line. The move to the use of more perforator based rectus flaps, which spare the rectus muscle and the majority of the anterior sheath, have certainly reduced the rates of donor site complications. The body habitus of

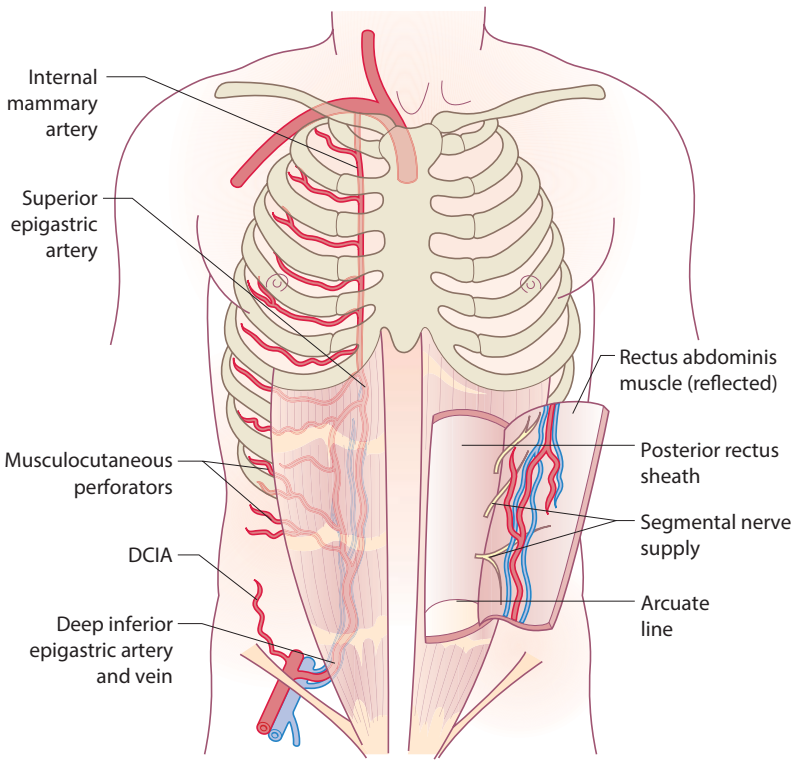


Figure 93.9 Anatomy of the rectus abdominus flap. Redrawn from Ref. 21, with permission.

the patient will determine the tissue match to defects of the head and neck. In obese patients the volume of subcutaneous fat may be inappropriate for defects of the lateral face and neck. In addition, as patients gain weight peri-operatively, the subcutaneous fat will gain volume in proportion to its usual location. These patients may require secondary procedures to reduce the volume of fat in the reconstruction. The colour match to the face and neck is relatively poor with the rectus flap, particularly in Caucasian patients.

TECHNICAL NUANCES

The technical nuances with this flap are largely about reducing donor site complications. The key to minimizing donor site problems is to take as small a piece of the anterior rectus sheath as possible and in particular attempt to avoid taking the anterior sheath below the arcuate line (as there is no posterior sheath). The perforators to the skin of the anterior abdominal wall exit the anterior rectus sheath in an arc around the umbilicus. Most flaps are designed with the base just below the umbilicus where the density of perforators is the greatest. In order to have a viable flap the only fascia that needs to be removed is that which immediately surrounds the perforators themselves. A small narrow strip of anterior fascia is all that should be taken, preserving the remainder for closure. The dissection for the myocutaneous flap begins laterally over the rectus sheath with dissection medially until one identifies the major perforators in the periumbilical region. The anterior sheath is then incised at this point, with a small island of fascia overlying the rectus abdominus muscle with the incorporated skin perforators. The entire rectus muscle is then harvested in a retrograde fashion with the pedicle identified on the deep lateral surface of the muscle, with dissection carried down to the vascular origin. In the DIEP harvest, the surgeon selects a major perforator then follows it through the muscle to the deep inferior epigastric artery (**Figure 93.10**). The lateral aspect of the muscle is identified and lifted medially to facilitate the dissection of the pedicle. The flap is harvested by delivering the vascular pedicle through the muscle, preserving the majority of the rectus abdominus muscle and the anterior rectus sheath.[37, 38] Careful and precise closure of the donor site is critical to avoid abdominal hernia. Where the anterior sheath cannot be closed primarily, reconstructive mesh should be used to avoid hernia formation.

CLINICAL APPLICATIONS

The rectus abdominus myocutaneous flap has been widely used in head and neck reconstruction. Its major applications have been in large volume reconstructions of the oral cavity or oropharynx and lateral skull base. The volume of tissue and the combination of muscle and skin offer the reconstructive surgeon the ability to fill surgical dead space and protect critical structures such as the carotid sheath or dural repairs. The flap is particularly useful for the total glossectomy defect where the volume of tissue can fill the space under the mandible, reducing the risk of perioperative fistula and infectious complications. The perforator-based DIEP flap extends the use of this flap, as the ability to harvest a large cutaneous flap, without the associated muscle, makes it useful for total glossectomy and extensive tongue defects. The DIEP flap can also be used to cover extensive facial and neck defects and may be used to recontour soft tissue defects of the lateral face.

Deep circumflex iliac artery osseomyocutaneous and the myo-osseous flap

The deep circumflex Iliac artery osseomyocutaneous, myo-osseous or osseous flap has the been a 'workhorse' flap for composite defect reconstruction of the oral cavity and mandible since its description by Taylor in 1982.[39]

ANATOMY

The iliac crest transfer is based on the deep circumflex iliac artery and its venae comitantes (**Figure 93.11**). The deep circumflex iliac artery (DCIA) arises from the lateral aspect of the external iliac artery, just above the

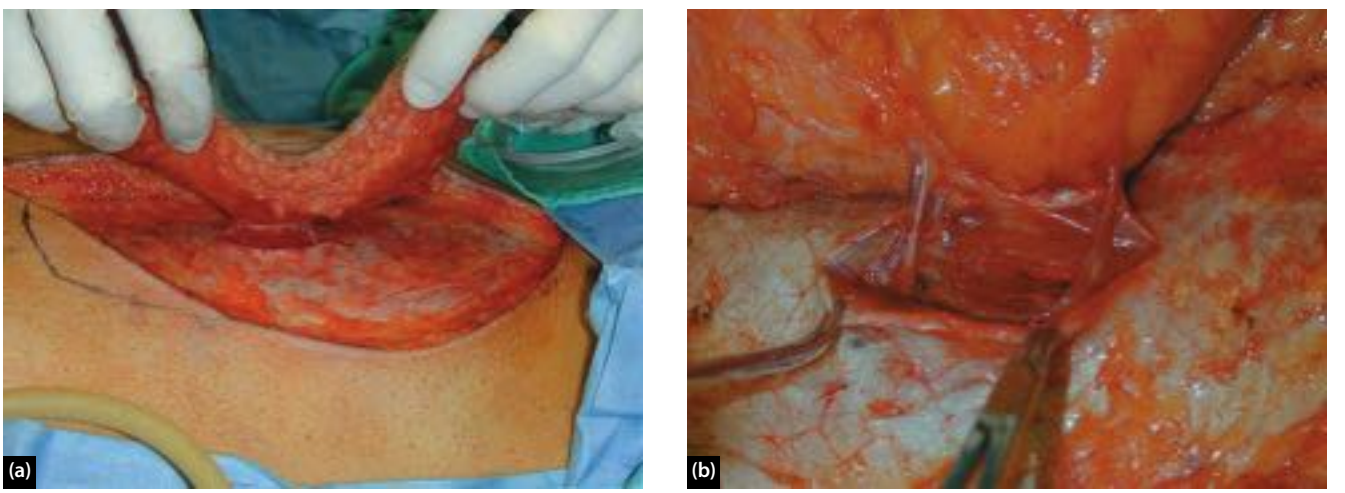


Figure 93.10 (a) DIEP perforator flap; note two dominant perforators and small fascial incision; **(b)** magnified view.

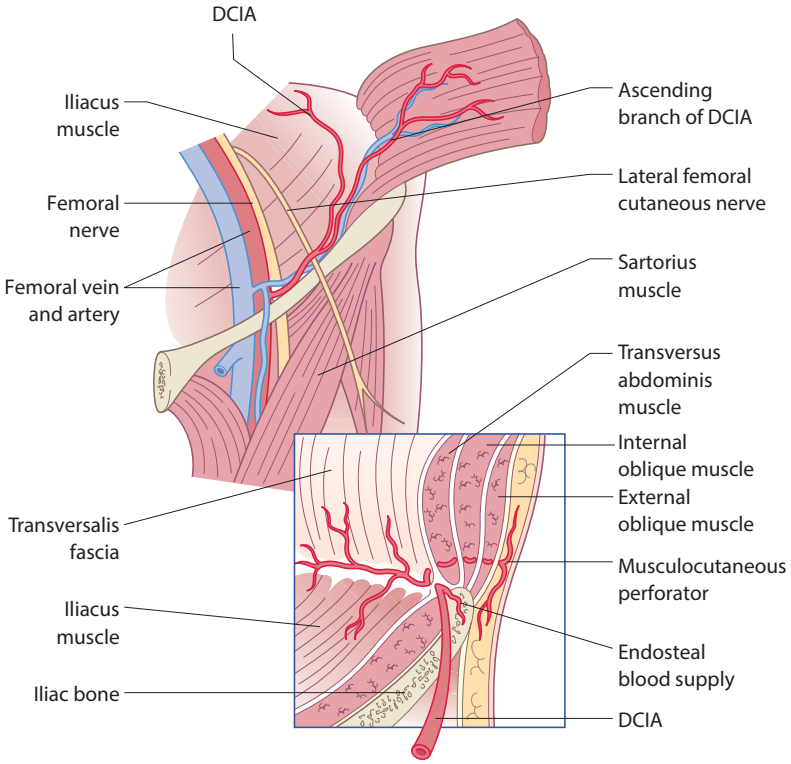


Figure 93.11 Anatomy of the DCIA flap. Redrawn from Ref. 21, with permission.

inguinal ligament. It runs a course parallel to the inguinal ligament, and 1 cm medial to the anterior superior iliac spine it gives off a large ascending branch that pierces the transverses abdominus muscle to lie on the deep surface of the internal oblique. The deep circumflex iliac artery (DCIA) then penetrates the transervsalis fascia and lies along the inner aspect of the crest, about 2 cm below the surface of the crest in the line of fusion of the iliacus and transveralis fascia. The artery extends posteriorly along the crest and about the midpoint of the crest, where it re-enters the transversus abdominus to anastomose with iliolumbar and superior gluteus arteries. Along its course it provides perforating branches that traverse all layers of the musculature of the abdominal wall just above the crest and supply the overlying skin. The venous drainage of the flap is the deep circumflex iliac vein (DCIV) which runs as a venae comitantes but often courses superiorly prior to its drainage into the internal iliac vein. There is some variability in vascular anatomy. The anterior branch may arise from a separate independent pedicle, originating just below the DCIA. The vascular pedicle is 6–8 cm in greatest length, with the artery and vein usually being of large calibre (2–3 mm).

ADVANTAGES

The DCIA-based iliac crest is an ideal flap for reconstruction of the mandible. It can be shaped to recreate both the mandibular body and the vertical ramus. The bone stock is excellent, in terms of both its corticocancellous proportions and the vertical height and breadth of the available bone. The physical properties of the crest make it ideally suited for primary or secondary osseointegration. This flap, when transferred with the internal oblique, provides an excellent vascularized reconstruction for patients with osteoradionecrosis.

DISADVANTAGES

The major disadvantages of the flap relate to the reliability of the skin paddle, the character of the skin paddle and secondary problems with the donor site. The skin paddle associated with the flap needs to be based on the line of the crest. While this makes an ideal skin closure in terms of scar location, in order to harvest a reliable skin island, a cuff of muscle that includes all three muscular layers of the abdominal wall must be retained in order to preserve the perforating vessels. This results in a relatively thick and inflexible reconstruction, making this version of the flap less than ideal for most head and neck applications. The skin flap is notoriously unreliable based on the fragility and unpredictability of the perforator supply. The donor site is problematic, as a significant number of patients will have either frank hernia formation or chronic laxity of the lower abdominal wall. While the lateral cutaneous nerve of the thigh can be preserved in the majority of dissections, in some situations it must be sacrificed, leaving an area of numbness on the lateral thigh. The donor site is painful, particularly when the entire crest is harvested, and peri-operative mobilization can be an issue, particularly in elderly patients. The pedicle length can be problematic when the flap is used for maxillary reconstruction, and vein grafting may be required.

TECHNICAL NUANCES

The DCIA flap is one of the more technically difficult flaps to harvest. Patient positioning is quite important in order

to allow visualization of the medial aspect of the crest. In most iliac crest bone graft harvests, a bag is placed under the hip to rotate it away from the surgeon. In the DCIA flap the surgeon must be able to visualize the medial crest and therefore the reverse position is most appropriate. One approach is to place a soft roll under the sacrum to elevate the pelvis and then rotate the operating table towards the surgical side to maximize visualization. Most experienced microsurgeons try to avoid the osseocutaneous version of the flap because of the unreliability of the flap. Likely the most commonly harvested version of the flap incorporates the internal oblique as a myosseous flap. The pedicle in this harvest is most easily identified by finding the anterior branch of the DCIA on the deep side of the internal oblique and then dissecting in a retrograde fashion to the DCIA. One option to reduce donor site complications is to harvest only the inner table, splitting the crest by making an oblique cut through the top of crest extending just below transversalis reflection. This technique provides adequate bone for mandibular reconstruction and preserves the lateral crest and anterior iliac spine. If one harvests the internal oblique, most surgeons routinely repair the defect with a surgical mesh to avoid abdominal wall laxity.

CLINICAL APPLICATIONS

The DCIA flap is largely used for bone only or composite defects of the mandible or maxilla. Taylor described the DCIA for hemimandibular reconstruction, and numerous series have demonstrated its efficacy for this application.[40, 41] Bone length to be harvested ranges from 8 cm to 12–14 cm, making it useful for the majority of defects encountered. Currently, most authors use this flap as a myo-osseous flap, using the internal oblique to close the oral defect with and either skin grafting of the muscle or allowing it to mucosalize secondarily (**Figure 93.12**).[42]

Most recently, Brown[43] has described the use of the iliac crest transfer for maxillary defects. The flap can be used for premaxillary and infrastructure by turning it horizontally to replace the hard palate. The mucosal defect is not reconstructed but rather the surface of the bone is allowed to granulate and secondarily mucosalize. In classic maxillary defect, the crest is inverted with the vascular pedicle oriented towards the maxillary tuberosity. The muscle is then rotated into the defect and allowed to mucosalize secondarily to recreate the hard palate (**Figure 93.13**). These two flap orientations both allow secondary osseointegration for dental restoration with a thin mucosalized reconstruction of the hard palate.

The anterolateral thigh flap

The anterolateral thigh flap is a fasciocutaneous flap based on the musculocutaneous and septocutaneous perforators of the descending branch of the lateral circumflex femoral artery and its venae comitantes. This flap's surgical anatomy and clinical use were first reported by Song et al.[44] in 1984. In 1989 Koshima et al.[45] described its use in the Japanese population, and numerous subsequent reports have described its successful use in head and neck reconstruction in the Asian population. It has gained popularity in oral cavity reconstruction, particularly in the Asian population, whose body habitus is ideally suited to the use of this flap.[46]

ANATOMY

The anterolateral thigh flap is supplied by perforating vessels arising from the descending branch of the lateral circumflex femoral artery. The descending branch runs downward in the intramuscular space between the rectus femoris and the vastus lateralis, terminating in the vastus lateralis just above the knee (**Figure 93.14**). In the midportion of the lateral thigh, the descending branch provides a number of perforators to the skin of the lateral thigh. These perforators can either run between the rectus femoris and vastus lateralis muscle then traverse the fascia lata as septocutaneous perforators to supply the skin of the lateral thigh or they can traverse the vastus lateralis muscle and the deep fascia as musculocutaneous perforators to supply the skin. The length of the pedicle ranges from 8 cm 16 cm.



Figure 93.12 DCIA myo-osseous flap; note available muscle for intraoral closure.



Figure 93.13 Split DCIA for maxillary and orbit reconstruction.

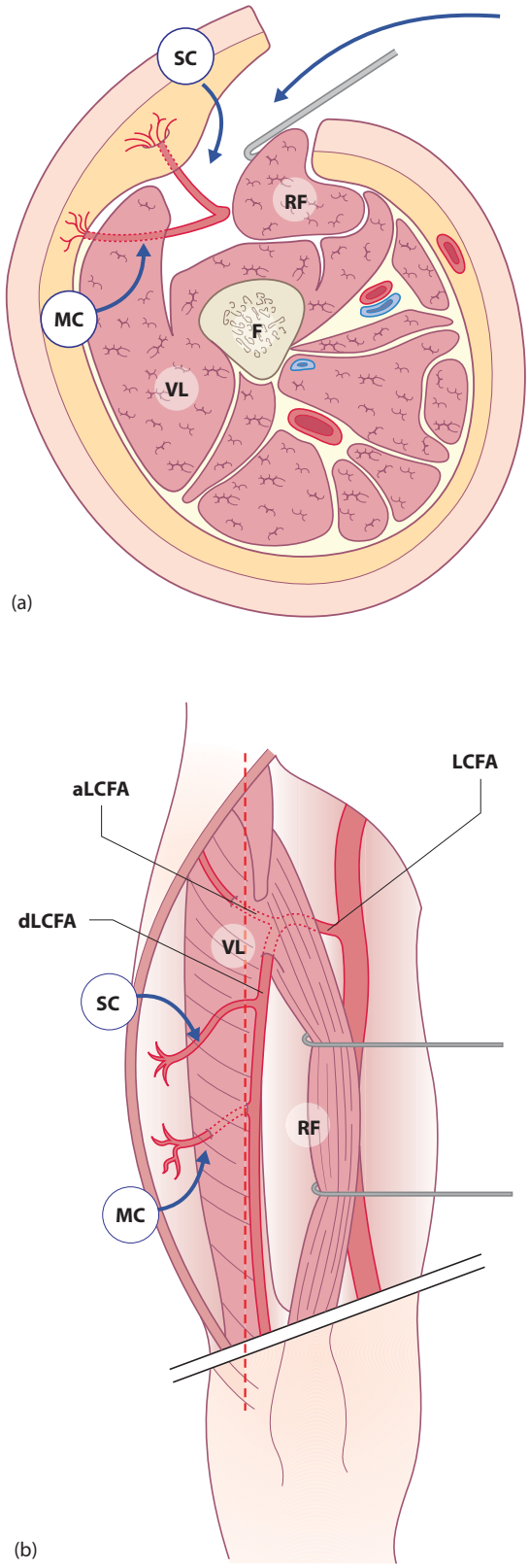


Figure 93.14 Anatomy of anterolateral thigh flap: (a) axial view; and **(b)** coronal view. aLCFA, ascending lateral circumflex femoral artery; dLCFA, descending lateral circumflex femoral artery; LCFA, lateral circumflex femoral artery; MC, myocutaneous perforator; RF, rectus femoris; SC, septocutaneous perforator; VL,vastus laterialis. Redrawn from Ref. 48, with permission.

ADVANTAGES

The anterolateral thigh has a number of advantages for head and neck reconstruction. The flap has a distant site from the head and neck, allowing a two-team harvest. The donor site has limited morbidity and in most patients can be closed primary, in a vertical line. Provided the nerve to vastus lateralis is preserved, little functional disability is associated with this flap. Large skin islands measuring 15–20 cm × 10 cm may be harvested and closed primarily. The flap may be harvested as a perforator flap with or without the fascia lata and can incorporate the vastus lateralis if a muscle component is required. In patients with the appropriate body habitus this flap is thin and pliable and provides an excellent reconstruction for the oral tongue and floor of mouth.

DISADVANTAGES

The anterolateral thigh flap has some disadvantages. The skin colour match to facial and neck skin is poor, especially in Caucasian patients. The anatomy of the flap is variable and somewhat unpredictable so; the surgeon contemplating the use of this flap needs to understand the basic anatomic variations and be prepared for them. Since the cutaneous version of this flap is usually supplied by a single perforating vessel, proximal venous occlusions are usually difficult to salvage because of the small calibre of the perforating vessels. In addition, because of the small size of the perforating vessels, the flap pedicle may be easily compromised by external compression. This makes it a poor choice for reconstructions requiring tunnelling of the pedicle. In some ethnic populations the thickness of fat in the lateral thigh makes this a poor donor site as the volume and bulk of the flap will produce an unreliable flap and a poor functional result.

TECHNICAL NUANCES

The skin perforators of the lateral thigh are mapped with Doppler, using the midpoint of a line drawn between the anterior superior iliac spine and the lateral aspect of the patella as a landmark. The first skin incision is placed on the medial aspect of the flap design. If a suprafascial technique is to be used for a thin flap, the dissection is carried laterally until the major perforators to the skin are identified. If a fasciocutaneous harvest is planned, the incision is carried through the deep fascia with the flap site mobilized laterally until the perforating vessels are visualized traversing the deep fascia. Once the perforators are identified, the skin incisions are completed. The pedicle is dissected in a retrograde fashion, either to the descending branch for septocutaneous flaps or through the vastus lateralis in patients with myocutaneous perforators. In myocutaneous perforators, a small cuff of muscle is left around the pedicle to protect the small perforating branches. Great care should be used to maintain haemostasis in this portion of the elevation because the vessels frequently will go into spasm and the muscle may bleed excessively after revascularization.

CLINICAL APPLICATIONS

The anterolateral thigh flap in appropriately selected patients is ideally suited to a variety of defects in the head and neck. It matches the reconstructive capabilities of the forearm flap, particularly if the thigh is thin and pliable. It can be tubed to reconstruct a tubed conduit for total pharyngeal reconstruction and can be used for external defects anywhere in the head and neck.[47] The donor site is much more attractive than the forearm flap and hence the reasons for this flap replacing the forearm as the standard reconstruction for the oral cavity in Asian countries.

The free osseocutaneous fibular flap

The free osseocutaneous or osseous fibular flap was first described by Taylor[48] for the reconstruction of tibial pseudarthrosis. This flap was popularized by Hidalgo and Rekow[49] for mandibular reconstruction and currently represents the benchmark for composite defects of the mandible and oral cavity.

ANATOMY

The osseocutaneous fibular flap is based on the peroneal artery and vein (**Figure 93.15**). The peroneal artery is a branch of the tibioperoneal trunk. The artery passes distally with paired venae comitantes lying on the medial aspect of the fibular between the tibial posterior and the flexor hillocks longus. The peroneal artery provides perforating branches to the surrounding musculature and nutrient artery and periosteal supply to the fibula. In the distal half of the leg it gives off perforating branches that run laterally through the flexor hallucis longus, usually passing within or deep to the intermuscular septum separating the peroneus longus and soleus muscles (**Figure 93.16**). The skin available includes the majority of the surface of the lateral aspect of the lower leg, with flaps measuring 12–16 cm × 8–10 cm available. The length of bone available is usually 18–24 cm depending on the length of the leg. Pedicle length depends on the amount of bone required (longer bone lengths = shorter pedicle) The usual vessel diameter is 3–4 mm for the artery and 4–5 mm for the vein.

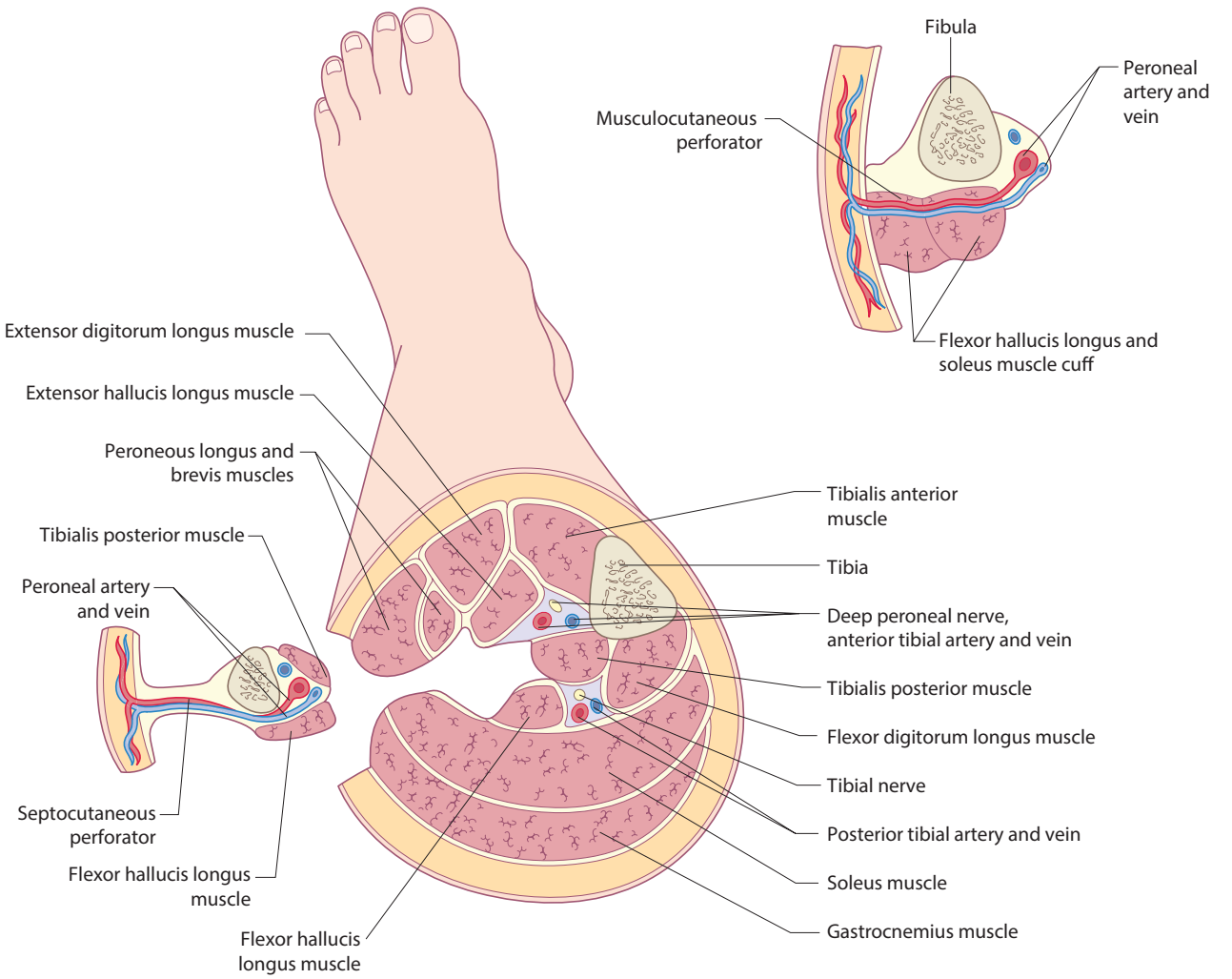


Figure 93.15 Anatomy of the free fibular transfer. Redrawn from Ref. 21, with permission.

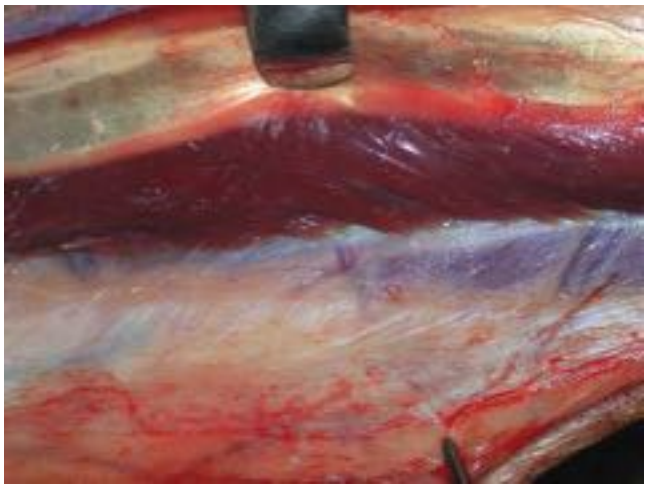


Figure 93.16 Lateral view of perforators to fibular skin paddle; note peroneous longus anteriorly and three septocutaneous perforators running to the skin island.



Figure 93.17 Osteotomized fibula, for mandibular reconstruction; note the use of a low profile reconstruction plate.

ADVANTAGES

The fibula is an ideal transfer for the majority defects of the oral cavity and mandible. The bone length available will almost reconstruct the entire mandible. The skin island is of an appropriate thickness for most oral cavity and oropharyngeal reconstructions.

DISADVANTAGES

The fibula has some established liabilities. It is not a good option in individuals with established peripheral vascular disease as harvesting a single vessel in an arterially comprised leg could be catastrophic. Some authors have reported relatively high failure rates with the skin island. These can be reduced with particular attention to harvest technique as outlined below.[50] The donor site can be problematic in patients with venous insufficiency in the lower extremity, with delayed healing of skin graft sites. Some patients have reported long periods of ankle and leg stiffness and occasional instability of the ankle. If a large cuff of flexor hallucis is harvested with the flap, some patients will acquire a flexion deformity of the great toe.

TECHNICAL NUANCES

As in all free tissue transfers, surgical planning is paramount to avoid complications. Most authors routinely advocate some type of non-invasive imaging of the vascular anatomy of the leg and tibioperoneal trunk. Options include colour Doppler, magnetic resonance angiography (MRA) and computed tomographic angiography (CTA). Experienced surgeons routinely Doppler the perforating branches to the skin to ensure that the skin island is appropriately placed on the leg. The flap is usually harvested under tourniquet control to provide a dry surgical field. Current harvest technique is usually via the lateral approach. After incising the skin island the peroneous longus and brevis are reflected anteriorly off the fibula. The anterior compartment is entered and opened over the length of the fibula, avoiding the anterior tibial artery. The posterior interosseous membrane is divided, visualizing the tibialis posterior. The fibula is divided distally and proximally, leaving at least 6 cm of fibula at the ankle and knee to avoid instability of the ankle and prevent injury to the common peroneal nerve. The distal peroneal artery is divided; the tibialis posterior is divided, visualizing the full course of the peroneal artery. To avoid injury to the perforators to the skin and assure appropriate venous drainage of the skin flap most authors advocate harvesting a cuff of flexor hallucis longus and soleus. Pedicle length is established by detaching the peroneal artery from the fibula. Closure is achieved either primary or with a skin graft. Most authors splint the leg for 5–7 days to maximize skin graft take.

The fibula may be osteotomized into multiple segments to recreate the shape of the mandible. Most authors currently use a single reconstruction plate lagging the bone segments to the plate while others prefer using multiple small plates to recreate the mandible. It is our preference to generally harvest the fibula from the leg contra lateral to the mandibular defect, as this positions the pedicle in the appropriate location for recipient vessel access and keeps the skin island in the right orientation for insetting into the oral defect. If the skin island has to be rotated around the fibula to get into the oral cavity the perforating vessels to the skin may be compromised, resulting in loss of the skin flap.

CLINICAL APPLICATIONS

The fibular flap is widely used for oromandibular reconstruction and is ideally suited for this defect (**Figure 93.17**). The bone flap is relatively short in vertical height, often leaving a disparity between the natural bone height of the mandible and the reconstructed segments. Some authors have advocated 'double-barreling' – placing one segment on top of the other to maximize vertical height for secondary osseointegration.[51] This flap has been used for maxillary reconstruction and is ideal for reconstructing the premaxilla in central maxillary defects. The other advantage of this flap for maxillary reconstruction is the

potential length of the vascular pedicle, a major asset in midface reconstruction.

ENTERIC RECONSTRUCTIONS

The free jejunal transfer

The free jejunal transfer, described by Seidenberg and Hurwitt[52] in 1958, has been widely used for conduit reconstruction of pharynx over the past 30 years. Numerous large series report success, in terms of both reliability and functional outcomes.[53, 54]

ANATOMY

The jejunum comprises approximately two-fifths of the 7-metre length of small bowel extending from the duodenum to the ileocecal valve. The blood supply of the jejunum arises from approximately five branches arising from the superior mesenteric artery with a total of 12 to 15 branches to the jejunum and ileum. The vessels run parallel to each other between the mesenteric layers. Each vessel divides into two, forming a series of arcades. From the terminal arcade, numerous vasa recta pass to the mesenteric border of the jejunum. Jejunum of 10–20 cm may be harvested with pedicle lengths of up to 8–10 cm. The artery is usually 1.5–2.5 mm in diameter with a matching venae comitantes. The vein can be extremely thin and technically difficult to sew.

ADVANTAGES

The jejunum is a mucosal lined conduit that makes its own secretions, making it theoretically an ideal reconstruction for a total pharyngectomy defect. The length of jejunum available for harvest is adequate for any head and neck defect. The jejunum has a peristaltic wave, which is unidirectional and can assist in swallowing

DISADVANTAGES

The jejunum has some problematic disadvantages. The flap does not tolerate long periods of ischemia and like other intestinal conduits does not tolerate long periods of venous congestion. The flap must be oriented in the appropriate direction or patients may be unable to swallow. The swallowing characteristics of this flap are highly variable. Some patients find that the flap easily goes into spasm with ingestion of hot or cold liquids and most patients describe swallowing as adequate but slow. One of the major drawbacks of the jejunum for pharyngeal reconstruction is that secondary tracheo-oesophageal puncture (TEP) speech is patulous and wet, with the majority of patients preferring not to use a TEP. The swallowing and speech results seem to be improved in patients who have received post-operative radiotherapy reducing the contractility and inherent secretions of the jejunum. Because the flap is enteric in origin it does not develop collateral circulation from the surrounding tissues. The pedicle of this flap can never be divided without risk of conduit necrosis, even after being in place for many years.

TECHNICAL NUANCES

The flap is usually harvested with a mini-laparotomy or endoscopically. The jejunal segment is delivered up onto the abdominal wall and the arcades visualized with back lighting. Usually the second intestinal branch is harvested with the segment of jejunum it supplies. Most surgeons harvest more length than needed so that a segment of the mesentery is available to place through the skin incision as an external monitor. Insetting of this flap is critical. It must be placed in an isoperistaltic position to allow swallowing. Most authors advocate marking the distal or proximal ends with a suture to avoid confusion about the direction of inset. The jejunum must be stretched to fit the defect as much as possible as, once it is revascularized, its length will increase, producing a tortuous conduit that functions poorly for swallowing.

CLINICAL APPLICATIONS

The most common application for jejunum is the total laryngopharyngectomy defect (**Figure 93.18**). Some authors have used it as a mucosalized and self-lubricating flap for oropharyngeal reconstruction, particularly in the radiation failure patient where xerostomia may be a problem. This technique can be problematic as the jejunal secretions are often tenacious and foul smelling.

The free gastro-omental flap

The free gastro-omental flap was described by Baudet et al.[55] in 1978. This flap has seen limited use over the past 30 years, with limited reports of use for oral cavity and conduit reconstruction of the total laryngopharyngectomy defect.[56]

ANATOMY

The greater curve of the stomach and the omentum are supplied by the right and left gastroepiploic arteries, terminal branches of the gastroduodenal and splenic arteries, respectively. They course along the greater curvature of the stomach and anastomose with each other, forming the gastroepiploic arterial arch. From the gastroepiploic arch,



Figure 93.18 Free jejunal transfer for pharyngeal reconstruction.

numerous small branches extend to the greater curvature and three major omental arteries, the right, middle and left, supply the greater omentum. The right gastroepiploic artery is the dominant supply (**Figure 93.19**).

ADVANTAGES

The free gastro-omental flap as a tubed conduit represents a near ideal reconstruction for the laryngopharyngectomy defect, particularly in an era of organ preservation approaches incorporating chemotherapy and radiation. The flap can be customized to tube size, is self-lubricated and not motile. The major benefit of the flap is that it is harvested with a large segment of the greater omentum, providing valuable well-vascularized tissues to cover the carotid sheath and prevent wound complications. The limited reports of its use in total pharyngectomy reconstruction have indicated that the TEP speech is better than with the jejunal transfer.

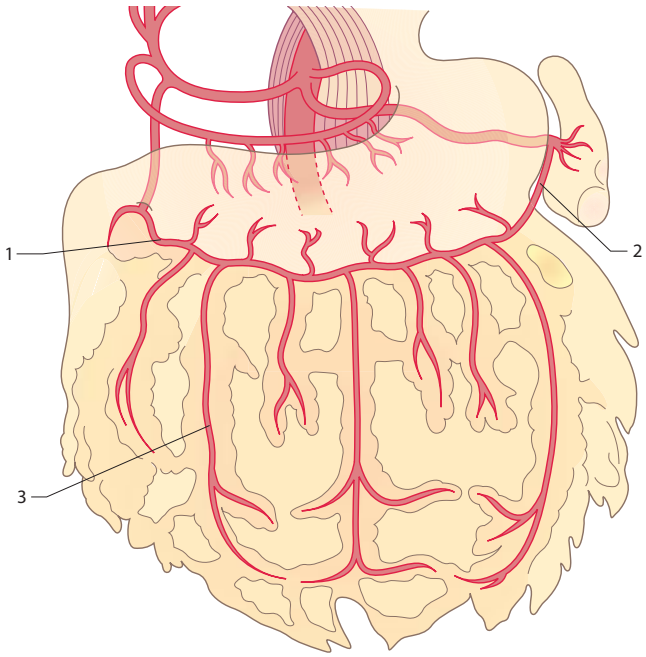


Figure 93.19 Surgical anatomy of the gastroepiploic flap. 1, Right gastroepiploic artery; 2, left gastroepiploic artery; 3, blood supply to the greater omentum.

DISADVANTAGES

The gastro-omental flap has few disadvantages. It does require a laparotomy, which can be a problem in patients with significant comorbidity or poor performance status. The flap is relatively easy to harvest, with a few caveats as discussed below.

TECHNICAL NUANCES

The flap is harvested through a mini-laparotomy incision. The stomach is delivered and the greater omentum visualized. The lesser sac must be entered to visualize the greater curve completely. A large segment of greater omentum is harvested, which can be reduced in volume after insetting. The stomach tube is created by placing a gastrotomy at least 2–3 cm proximal to the pylorus and an appropriate proximal gastrotomy for the length of stomach required. The gastric tube is formed by placing a 35-gauge chest tube through the gastrotomies and then using a GIA stapler to create the conduit. It is critical that the stomach be stretched out to length before stapling to ensure that enough functional stomach remains. A jejunal feeding tube is placed for patients undergoing laryngopharyngeal reconstruction.

CLINICAL APPLICATIONS

The gastro-omental flap is largely used for conduit reconstruction following laryngopharyngetomy. Its unique advantage is the large segment of greater omentum, which will dramatically reduce the risk of peri-operative complications in chemoradiation failure patients (**Figure 93.20**).



Figure 93.20 (a) and **(b)** gastro-omental flap for oropharyngeal reconstruction; note amount of greater omentum available for resurfacing the anterior neck.

DEFECT-BASED OPTIONS

Oral tongue and floor of mouth

ISSUES

Reconstruction of the oral cavity continues to represent one of the major challenges in head and neck reconstruction. Numerous authors have reviewed functional outcomes following oral cavity reconstruction and have all come to similar conclusions.[57, 58] It would appear that the key element in producing high quality oral function is the amount of sensate tongue remaining in the oral cavity. Any reconstruction used in the oral cavity should have the goal of replacing the volume resected but must maintain and not limit the mobility of the tongue remnant. Highly sensate flaps such as the free forearm flap have been widely used in oral cavity reconstruction, clearly providing two-point, touch and temperature sensation for the reconstructed oral cavity. Intuitively it would seem that sensation would be beneficial but there is little evidence that sensate flaps make a major difference in oral function following ablative procedures. In posteriorly placed defects in the oropharynx, specifically the tongue base and palate, two additional issues are of importance. In tongue base resection, appropriate but not excessive volume replacement appears to improve swallowing results. In soft palate reconstruction, recreating appropriate palate closure is particularly important to avoid nasal regurgitation.

OPTIONS

The current options for oral reconstruction are outlined in **Table 93.1**. The forearm flap has a number of unique advantages. It is thin and pliable, and certainly functions well at maintaining the mobility of the residual tongue. This flap is likely the best sensate flap available and if one believes sensation is important this would be the preferred flap. The anterolateral thigh flap in patients with the appropriate body habitus is likely very close to the forearm in producing high quality functional results. The other flaps available all suffer from providing too much bulk and potentially can limit the residual movement of the oral and oropharyngeal structures.

PROBLEMS

The problems still needing to be addressed in the oral cavity are the production of functional sensation and correcting problems with xerostomia following radiation treatment. The use of the submandibular gland transfer, moving the gland out of the field of radiation, is likely a technique that will be more widely used in the future.[59]

Pharynx

ISSUES

Reconstruction of the total pharyngectomy defect continues to represent one of the major challenges in head and neck reconstruction. The ideal pharyngeal reconstruction would provide a mucosalized conduit that has appropriate motility and functions with a TEP. The reconstruction would be of low morbidity in terms of its donor site, and relatively easy to harvest and revascularize.

OPTIONS

The current options for reconstruction of this defect are the enteric reconstructions; the jejunum or gastro-omental flap or tubed skin flaps. There is extensive experience worldwide with the jejunal flap and it has proven efficacy in the reconstruction of this defect. Swallowing and speech results with the jejunum are less than perfect, which has led some centres to consider the free gastro-omental flap. The gastro-omental flap appears to produce improved swallowing and voice results with the benefit of a large segment of greater omentum.

There have been numerous reports of cutaneous skin tubes for oral reconstruction, in particular the free forearm flap and anterolateral thigh flap. Both these reconstructions have excellent swallowing and voice results, with low donor site morbidity, but have been problematic in the development of distal anastomotic strictures. A number of authors now advocate the use of silastic stents with the cutaneous flaps, an approach that appears to have dramatically reduced the rate of distal anastomotic stricture.

PROBLEMS

The current options in pharyngeal reconstruction appear to be a choice between the improved functional results with enteric reconstructions (particularly the gastro-omental flap) as compared to cutaneous flaps, balanced against the inherent morbidity of the enteric flaps, which

TABLE 93.1 Options in oral cavity reconstruction

Flap	Anatomy	Pedicle length	Sensation	Donor site morbidity	Skin quality
Forearm	+++	+++	+++	++	+++
Lateral arm	++	+	++	+++	++
ALT	+	+++	+	+++	++
DIEP	+++	+++	+	++	++
Scapula	+++	++	+	++	++

+++, best; ++, intermediate; +, poor. ALT, anterolateral thigh; DIEP, deep inferior epigastric perforator.

require a laparotomy. Prospective studies evaluating the long-term functional outcomes of these various reconstructions will help elucidate the best approach for this complex group of patients.

Composite mandibular defects

ISSUES

Reconstruction of composite defects including oral lining and the mandible continue to challenge reconstructive surgeons. In mandibular reconstruction the key issue is the length of bone required, whether the transferred bone is amenable to secondary osseointegration and the morbidity associated with the donor site of the bone flap.

Secondary issues are the correction of disparities in bone height between the native mandible and condylar reconstruction. The mandibular resection that extends to include the condylar head continues to be a problem in terms of recreating a functional joint that will allow an appropriate range of movement for mouth opening and mastication.

OPTIONS

The current options for mandibular reconstruction are illustrated in **Table 93.2**. Currently the flap of choice in most centres is the free fibular transfer based on the quality of the available skin island and the length of available bone with limited donor site morbidity. The scapular bone flap is likely an excellent option where the fibula is not an option because of peripheral vascular disease and is particularly useful in the elderly. The DCIA flap has great utility in limited defects in younger patients. The osseocutaneous radius transfer has a limited bone stock and significant potential donor site problems, making it a poor choice for mandibular reconstruction. A new option for improving functional outcome in mandibular reconstruction has been the developments in computerized assisted design with three-dimensional planning of defect creation and reconstruction. In the most advanced form of this technology, surgeons are supplied with a pre-bent reconstruction plate and a cutting guide for both the fibula or scapula and the ablative defect. This technology while currently expensive, offers the opportunity for improved aesthetic and functional outcome, particularly when comprehensive dental reconstruction with osseointegrated implants is an option.

PROBLEMS

The available options for mandible reconstruction largely achieve the goals of reconstruction of this defect. Re-creation of a functional non-prosthetic condyle continues to be a problem and simple surgical techniques to augment the vertical height of the existing mandibular reconstructions would be helpful.

Cutaneous defects

ISSUES

The major issues in selecting a reconstruction of the external skin of the face or neck are the colour match of flap, donor site morbidity and the ability of the defect to match the volume of the defect. There is a wide variation in skin colour based on anatomic regions of the body, with areas close to the head and neck providing the best colour match. In addition there are remarkable variations in the colour of the various skin flaps based on the race and genetic background of the patient.

OPTIONS

There is a wide variety of options for replacement of facial and neck skin. When balancing donor site morbidity with skin colour, amount of available skin and the ability to adjust the volume of the reconstruction, the scapular system of flaps and the anterolateral thigh appear to offer the greatest potential

CONCLUSIONS

Developments in free tissue transfer over the past 30 years have dramatically affected the outcomes for patients with head and neck deformity. As experience develops with the aforementioned reconstructions, the indications and efficacy of the various techniques will be further delineated. The developments over the next decade in tissue engineering and in the management of the immune response to allogeneic transplants will certainly offer further opportunities for better and more functional reconstructions for head and neck patients.

TABLE 93.2 Osseocutaneous flaps for mandibular reconstruction

Flap	Bone length (cm)	Pedicle length (cm)	Donor complications	Osseointegration	Skin reliability
Fibula	16–20	6–8	+++	++	++
Scapula	8–12	4–8	++	++	+++
Iliac crest	10–14	6–8	+	+++	+
Radius	8–12	8–10	+	+	+++

+++, best; ++, intermediate; +, poor.

BEST CLINICAL PRACTICE

- ✓ Free tissue transfers are best performed in centres with high clinical and surgical volumes with specialized nursing units for post-operative management and monitoring.
- ✓ For reconstruction of oral cavity mucosal defects the best options are:
  - ✓ free forearm flap
  - ✓ anterolateral thigh flap
  - ✓ lateral arm flap
  - ✓ DIEP flap.
- ✓ Options in the reconstruction of mandibular defects need to be tailored to the specific defect, bone length, mucosal defect and rehabilitation plan. Current options are:
  - ✓ fibular transfer
  - ✓ iliac crest
  - ✓ scapula
  - ✓ radius.
- ✓ Reconstruction of the total pharyngectomy defect is a balance between ultimate functional requirements and donor site morbidity. Current options include:
  - ✓ cutaneous tubed flaps – forearm flap and anterolateral thigh flap
  - ✓ enteric flaps – free jejunal transfer and free gastro-omental transfer.
- ✓ Reconstruction of large cutaneous defects of the head and neck is a balance between skin colour match, defect size and donor site morbidity. Current options include:
  - ✓ scapular system of flaps including latissimus dorsi
  - ✓ rectus abdominus and DIEP flaps
  - ✓ anterolateral thigh flap
  - ✓ lateral arm flap
  - ✓ forearm flap.

FUTURE RESEARCH

- ➤ Oral cavity mucosal reconstruction, the value of sensation and the options for recreating sensation in the oral cavity. Prospective outcome studies evaluating the efficacy of the various reconstructive techniques in terms of speech and swallowing. Research and creative opportunities in prefabrication of reconstruction and evaluating the utility of allotransplantation.
- ➤ Mandibular reconstruction, deficiencies in prospective evaluations of functional outcomes (swallowing and deglutition). Further definition of the role of osseointegration technology in oral rehabilitation. Prefabrication of mandibular components and evaluating the utility of allotransplantation.
- ➤ Maxillary reconstruction, deficiencies in prospective studies evaluating outcome and quality of life in patients treated with reconstructive procedures or maxillofacial prosthedontics. Further developments in reconstructive options are required.

KEY POINTS

- It is necessary to understand the blood supply of the skin, the angiosome concept.
- There has been recent interest in the terminology and concept of perforator flaps.
- The special considerations for patients undergoing free tissue transfer include:
  - perioperative fluid management
  - deep vein thrombosis prophylaxis.
- There is a need for specialized nursing units for monitoring free tissue transfer to facilitate rapid return to the operating theatre for vessel occlusion. Two techniques used are:
  - fibrinolytics
  - medicinal leeches.
- The forearm flap is the ‘workhorse’ for oral cavity and oropharyngeal defects. Its advantages are ease of harvest, long pedicle length and potential for sensation.
- The lateral arm flap offers limited donor site morbidity with the disadvantage of a short vascular pedicle and small donor vessels.
- The scapular system of flaps includes the latissimus dorsi flap and provides the following options:
  - variety of skin, muscle, bone or combinations of tissues available
  - skin paddle can be rotated independent of the bone flap
  - great utility for extensive head and neck defects.
- The rectus abdominus flap has consistent anatomy and is excellent for large cutaneous, oral or skull base defects. The perforator-based DIEP flap reduces donor site morbidity and broadens the range of use of this flap.
- The DCIA is the ideal bone for mandibular reconstruction. Its disadvantages relate to donor site morbidity and a short pedicle. Recently, a new application in maxillary reconstruction has been described.
- The anterolateral thigh flap is a recently popularized flap, particularly in patients with thin thighs. Advantages are minimal donor site morbidity and long vascular pedicle. It has a wide variety of applications in head and neck reconstruction.
- The fibular flap is the current standard of care for extensive mandibular defects. Care needs to be taken in using this flap in patients with peripheral vascular disease.
- The free jejunal flap has been widely used for total pharyngeal reconstruction. The swallowing results are good but not excellent, and speech rehabilitation with this flap is problematic.
- The gastro-omental flap has seen limited use for pharyngeal reconstruction over the past 30 years. It has become more popular based on the opportunity to transfer large segments of omentum, which may be an advantage in the chemoradiation failure patient.

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CHAPTER 94

BENIGN AND MALIGNANT CONDITIONS OF THE SKIN

Murtaza Khan and Agustin Martin-Clavijo

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed and Cochrane library search using the keywords: skin cancer, basal cell carcinoma, squamous cell carcinoma, non-melanoma skin cancer, actinic keratosis, Bowen's disease, melanoma, excision margins, incomplete excision, diagnosis, management, guidelines, recurrence, head and neck.

INTRODUCTION

Skin cancer is on the rise. According to the World Health Organisation (WHO), between 2 to 3 million non-melanoma skin cancers (NMSC) and 132 000 melanomas are diagnosed every year,[1] with one in every three cancers being a skin cancer. NMSC incidence is difficult to assess, as these cancers do not need to be reported to most cancer registers. However, it has been estimated that in the US the increase over the last two decades has been threefold, with an 8% yearly increase.[2] In Scotland, between 1990 and 2011, basal cell carcinomas (BCCs) have increased by 260% and squamous cell carcinomas (SCCs) by 334%. In England, the incidence of BCCs was calculated at 76.2/100 000 and SCCs 22.65/100 000.[3] The incidence of melanoma has also risen continuously since the 1950s. In 2012, the incidence was estimated by the WHO at 111 481, accounting for 1.7% of all cancers (excluding NMSC).[4] The incidence is estimated to have been rising by 3–7% yearly for fair skinned Caucasian populations.[5] At the same time, the mortality (reported in the same study at 24 069) seems to be decreasing.[6]

PREMALIGNANT SKIN LESIONS

Premalignant epithelial lesions are associated to an increased risk of transformation into skin cancer and are confined above the dermo-epidermal junction. Almost all of them are induced by excessive, chronic sun exposure.

Actinic keratosis

Actinic keratoses (AKs) or solar keratoses are the commonest premalignant lesions of the skin (**Figure 94.1**). They are intra-epithelial neoplasms formed by proliferation of atypical keratinocytes and have the potential to grow into invasive SCC. They usually appear after 50 years of age. Sun-seeking behaviour, outdoor occupations, chronic use of sun beds, fair skin, high ultraviolet index of the environment, immunosuppression and genetic syndromes such as albinism and xeroderma pigmentosum are important predisposing factors. Ionizing radiation and ultraviolet light phototherapy can also result in the formation of these lesions.

EPIDEMIOLOGY

AKs are frequently found on skin chronically exposed to ultraviolet radiation, with 80% or more presenting on the face, scalp, neck and dorsal hands.[7] Patients with Fitzpatrick skin phototypes I to III (i.e. those with light coloured skin and a tendency to burn) are at higher risk, and those living near the Equator or at higher altitudes have a greater predisposition. Men are more commonly affected than women. The reported prevalence is variable, with 40–50% of the Australian population aged 40 years and over and 11–25% in the US thought to be affected.[8] The risk of transformation to SCC is low for individual lesions but in patients with a large number of AKs the risk is higher than for the general population.



Figure 94.1 Actinic keratosis.

CLINICAL FEATURES

AKs are usually asymptomatic but are noticed because of their rough texture. They appear as dry and erythematous lesions on sun-exposed skin (**Figure 94.1**). Thin lesions are more easily palpable than visible. They are usually covered with an adherent scale. Lesions may be pigmented or telangiectatic and may be numerous. Thicker lesions may have significant hyperkeratosis that can form a cutaneous horn. The surrounding skin often shows evidence of chronic sun damage in the form of wrinkled and atrophic skin, scarring, pigmentation, telangiectasia or changes of solar elastosis characterized by thickened, yellow and wrinkled skin.

DIAGNOSIS

The diagnosis can be made clinically but where there is uncertainty a skin biopsy may be indicated. Features that should raise suspicion of SCC include induration, rapid proliferation, ulceration, bleeding and the presence of a cutaneous horn. Histologically atypical cells confined to the epidermis are seen with increased mitoses, nuclear polymorphism, hyperchromasia and loss of polarization.

The differential diagnosis includes other malignant lesions, such as superficial BCC, Bowen's disease (BD), SCC, amelanotic melanoma and benign lesions such as seborrheic keratosis, viral warts and discoid lupus.

MANAGEMENT

Spontaneous resolution of these lesions has been reported to occur in 21% of cases[9] and for thin and small lesions no treatment may be necessary. In such cases a moisturizer or a keratolytic agent containing salicylic acid may be sufficient to soften the skin. Cryotherapy can be effective for thicker lesions but it is painful and leaves a scar. Topical 5-fluorouracil cream administered once or twice daily for up to 6 weeks can result in clearance with superior cosmetic results but soreness and inflammation during treatment are common. Similar results are achieved with the topical immune response modifier imiquimod used three times a week for 4 weeks with a side-effects profile very similar to that of 5-fluorouracil. Ingenol mebutate has a similar side-effect profile, but has the advantage of needing only two daily applications to treat head and neck AKs. Photodynamic therapy (PDT) with a photosensitizer such as methyl aminolevulinic acid and red light source can be a highly effective treatment, with good overall tolerance and patient satisfaction.[10] Surgery in the form of curettage or excision may be performed when other treatments fail or if there is diagnostic uncertainty.

Prevention is an important aspect of management and advice regarding avoidance of sunlight and tanning beds, protective clothing and regular use of sun blocks should be given. Use of regular sunscreen is the only intervention that can reduce the formation of AKs.[11] Patients should also be taught how to recognize skin cancer and should be prompted to seek medical attention for non-healing and enlarging skin lesions.

Bowen's disease

Squamous cell carcinoma *in situ* or BD was first described by John Bowen in 1912. It is an intra-epidermal carcinoma that involves the full thickness of the epidermis without invading the basal membrane. It persists for many years and can grow, but the risk of progression to invasive SCC is small (3–5%).[12] As with AKs, chronic sun exposure plays an important role in the pathogenesis and immunosuppression predisposes to these lesions. Mucosal BD also occurs[13, 14] and is associated with human papillomavirus (HPV).

EPIDEMIOLOGY

BD is seen more commonly in women than in men. It is usually diagnosed in patients from 60 years of age. Most lesions present on the head and neck[15, 16] but in the UK the distribution is significantly different with only 13% on the head and neck and 67% on the lower limbs.[17] Lesions of

BD are usually solitary but can be multiple. The risk of progression to invasive SCC has been estimated to be around 5%.

CLINICAL FEATURES

Patients present with a long-standing and slowly growing skin lesion, which is usually asymptomatic. It appears as a well-defined, sharply demarcated and scaly erythematous plaque on chronically sun-exposed skin.

DIAGNOSIS

The diagnosis can be suspected clinically but a skin biopsy is recommended to exclude differentials and rule out invasive SCC. Histologically the full thickness of the epidermis shows dysplastic cells with disordered architecture, abnormal mitoses and hyperkeratosis. The abnormal cells do not invade the basal membrane but can sometimes extend along the hair follicle epithelium.

The clinical differential diagnosis of BD includes lichen simplex, eczema, psoriasis, fungal infection and superficial BCC.

MANAGEMENT

Most lesions of BD can be treated by non-surgical methods. As with AKs the use of 5-fluorouracil cream can be a highly effective treatment. Imiquimod cream can achieve similar results and is particularly useful in cases associated with HPV. Cryotherapy using liquid nitrogen with one or two freeze-thaw cycles can be effective but the usefulness of the procedure is limited by pain and slow healing rates and it is often impractical for larger lesions. PDT can achieve cure rates of around 90%.

Surgery may be performed when conservative measures fail or there is suspicion of invasive disease. Curettage and cautery can be a simple and effective treatment with less pain, rapid healing and low recurrence rates. The procedure allows histological evaluation of the specimen but invasive SCC cannot always be excluded. Therefore, it is recommended that clinically suspicious lesions should be fully excised with a small diagnostic margin (2 mm).

KEY POINTS

- Most premalignant lesions are induced by ultraviolet light.
- They can transform to skin cancer, mainly SCC.
- The only intervention that will reduce the formation of AKs is photoprotection.
- It is important to teach patients how to detect skin cancer.

NON-MELANOMA SKIN CANCERS

BCC and SCC are the two most important types of NMSC. BCC is the commonest cancer worldwide and constitutes nearly 75% of all NMSCs, followed by SCCs. These cancers commonly affect white skinned individuals and are very rare in darker and Afro-Caribbean skin.

Risk factors

Several host, environmental and genetic factors are implicated in the pathogenesis of NMSCs. Middle- or old-aged, fair skinned individuals with Fitzpatrick skin type I or II are at increased risk. The frequency of these cancers increases significantly with immunosuppression. Chronic exposure to sunlight, especially since childhood, is associated with an increased risk for SCCs while intermittent and intense exposures are thought to be more relevant for the development of BCCs. The risk is also potentiated by therapeutic use of artificial ultraviolet (UV) light, ionizing radiation and excessive use of recreational tanning beds. SCCs have been known to sometimes develop in non-healing wounds or from chronic irritation. Certain genetic syndromes, such as xeroderma pigmentosum, albinism and epidermolysis bullosa, predispose to all types of NMSCs, and Gorlin's syndrome is a hereditary disorder characterized by multiple BCCs throughout life.

Staging

In the new AJCC 8th edition classification, the entity of non-melanoma skin cancer (cutaneous squamous cell carcinomas and other cutaneous carcinomas) has been eliminated and amalgamated with cutaneous squamous cell carcinoma of the head and neck (**Table 94.1**).[18]

Prevention of NMSCs

The most effective measure for prevention of skin cancers is avoidance of sun exposure. Patients should be advised to avoid deliberate suntanning or using artificial sunbeds. Sunlight should be avoiding during peak daylight hours by wearing appropriate clothing in the form of long-sleeved shirts, wide-brimmed hats and sunglasses.[19] Sunblock with broad spectrum UVA and UVB protection can offer further protection. Those who have precursor lesions (i.e. actinic keratoses and BD) should be educated about the recognition of skin cancer and advised to seek medical attention early.

Basal cell carcinoma

Basal cell cancer (BCC) is the commonest type of skin cancer and arises from the basal keratinocytes. It is locally invasive and distant metastases are exceedingly rare.

CLINICAL FEATURES

BCCs are slow growing tumours and develop for months or years. They are commonly found on the head and neck and may grow to a large size. They may invade deeper structures such as cartilage, muscle or bone. There are several types of BCC that have different clinical appearances. The commonest form is the nodular BCC; it appears as a raised lesion with a rolled edge, telangiectasia and central ulceration – constituting the features of the classical 'rodent ulcer' (**Figure 94.2**). Another variant

TABLE 94.1 TNM staging for Cutaneous SCC of the Head and Neck. Adapted from AJCC Cancer Staging Manual 8th Edition. MB Amin ed. Springer 2017[18]

T: Primary tumour		
Tx	Primary tumour cannot be identified	
Tis	Carcinoma in situ	
T1	Tumour <2 cm in greatest diameter	
T2	Tumour 2–4 cm in greatest diameter	
T3	Tumour >4 cm in greatest diameter or Minor bone erosion or Perineural invasion or Deep invasion (beyond subcutaneous fat or >6 mm thickness	
T4		
T4a	Gross cortical bone/marrow	
T4b	Skull base invasion and/or skull base foramen invasion	
N: Regional Lymph nodes	Clinical (cN)	Pathological (pN)
Nx	Regional lymph nodes cannot be assessed	
No	No Regional lymph node metastasis	
N1	1 ipsilateral lymph node, <3 cm, ENE (-)	
N2		
N2a	1 ipsilateral lymph node, 3–6 cm, ENE (-)	1 single lymph node (ipsi lateral or contralateral), <3 cm, ENE (+) 1 ipsilateral lymph node, 3–6 cm ENE (-)
N2b	Multiple ipsilateral lymph nodes, <6 cm, ENE (-)	
N2c	Bilateral or contralateral lymph nodes, <6 cm, ENE (-)	
N3		
N3a	Any lymph node >6 cm, ENE (-)	
N3b	Any lymph node ENE (+)	1 single ipsilateral lymph node >3 cm ENE (+) or Multip;e ipsilateral, contralateral or bilateral lymph nodes, any with ENE (+)
M: Distant metastasis		
M0	No distant metastasis	
M1	Distant metastasis	
Stage		
0	Tis N0 M0	
1	T1 N0 M0	
2	T2 N0 M0	
3	T3 N0 M0	
	T1-3 N1 M0	
4	T1-3 N2 M0	
	T4 N0-3 M0	
	T1-4 N3 M0	
	T1-4 N0-3 M1	

ENE, Extranodal extension.



Figure 94.2 Basal cell carcinoma.

is the superficial BCC, which presents as a macule or thin plaque and can be difficult to distinguish from AKs or BD. The morphoeic or infiltrative varietes presents as a poorly demarcated, atrophic and scar-like lesion that, on microscopic examination, shows extensive invasion beyond its perceived boundaries. Cystic, micronodular and pigmented types of BCCs also exist.

DIAGNOSIS

The differential diagnosis includes a range of benign conditions such as seborrhoeic keratosis, sebaceous hyperplasia, trichoepithelioma, lichenoid keratosis, BD or intradermal naevus, but also malignancies such as SCC, sebaceous carcinoma (SC) or melanoma. The diagnosis is confirmed on histological examination. Due to their slow growing nature, it is acceptable to perform a small punch biopsy for confirmation before fully excising the lesion. Histology shows islands of basaloid cells in the dermis with peripheral palisading, and clefting or retraction artefact surrounding the tumour. Perineural invasion, if present, signifies higher chances of recurrence following surgery. Imaging techniques such as computerized tomography or magnetic resonance imaging may be employed to assess invasion of bone, nerves, orbit or parotid gland.

MANAGEMENT

There are several guidelines for the management of BCCs.[20, 21] They all discuss the treatments outlined below.

Non-surgical treatments

Superficial BCC (sBCC) can be treated without surgery using imiquimod cream, PDT or cryotherapy. Imiquimod can achieve cure rates of more than 80% with a regimen consisting of once daily treatment five times a week for 6 weeks.[22] A local inflammatory reaction consisting of erythema, erosion and scabbing is expected and the severity correlates with higher success rates. PDT can also

achieve high rates of clearance and can vary depending on the photosensitizer from 75% to 95%.[23,24]

Surgical treatment

Nodular and morphoeic BCCs are best treated with surgical excision. Small, well-defined lesions may be excised with peripheral margins of 4–5 mm and deep margins down to fat. This method has a clearance rate of approximately 95%. The adequacy of excision is judged by histological clearance of at least 1 mm at both the peripheral and deep margins. Infiltrative, morpheic or large BCCs will need wider margins to achieve the same success rate.

High-risk lesions are defined as those that are poorly defined, larger than 2 cm, located on the central face or histologically shown to be morphoeic or infiltrative. High-risk lesions should be considered for Mohs micrographic surgery, a highly effective and cost-effective technique that allows the assessment of 100% of the margin under frozen sections (**Figure 94.3**). Once adequate clearance of the tumour is achieved the defect is closed using reconstructive surgery. This technique offers very high cure rates reported to be between 98% and 100%.[25,26]

Radiotherapy

BCCs are highly radiosensitive, with cure rates ranging from 79% to 100%.[27] Radiotherapy can be offered as a stand-alone alternative to surgery or as adjuvant treatment for incompletely excised tumours. It is contraindicated for recurrent tumours in previously irradiated areas. It is usually reserved for elderly patients. The treatment is offered in fractions requiring several hospital visits but in the very elderly a single fraction may suffice. The use of weekly dosing for this age group has also been reported.[28]

Treatment for advanced disease

For locally advanced BCCs not suitable for the above approaches, electrochemotherapy can be used.[29] Vismodegib, a hedgehog inhibitor, can also be used[30] for locally advanced or metastatic disease.

FOLLOW-UP

Completely excised BCCs do not require regular follow-up. For marginally excised lesions a decision to review over a 12-month period may be made to look for recurrence.

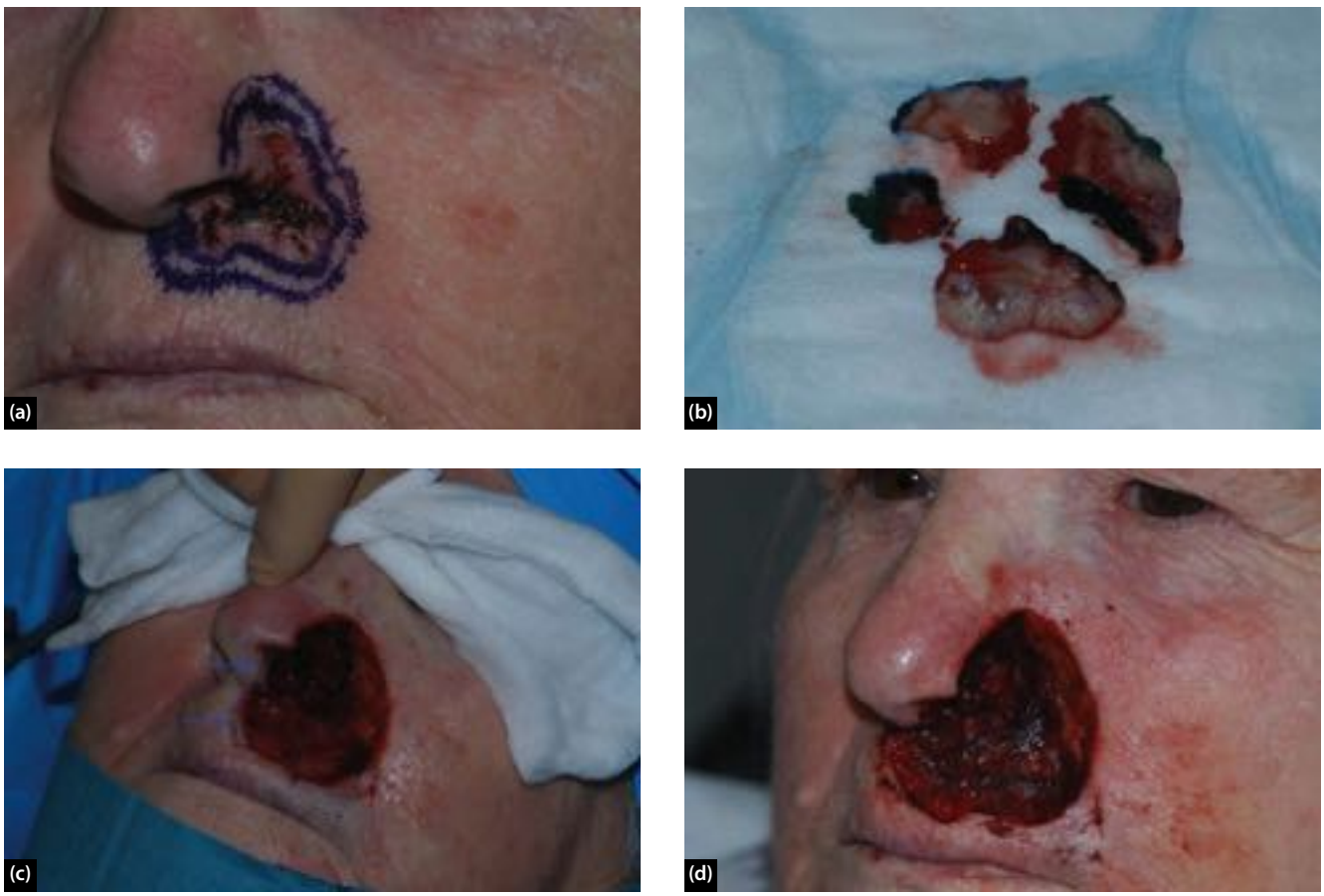


Figure 94.3 Mohs micrographic surgery. **(a)** BCC affecting lip, nose and cheek, marked for surgery. **(b)** After initial debulking, the lesion is removed, separated in blocks and color coded ready for processing in the cryostat. **(c)** After identifying an incompletely excised area in the lip and columnella, a second stage is marked (blue arrows). **(d)** Surgical defect after the second stage. This was clear and is now ready for reconstruction.

KEY POINTS

- BCC is the most common cancer in the world.
- Its incidence is continuing to rise.
- Topical treatments may be sufficient for low-risk BCC.
- For high-risk BCC, the gold standard is Mohs micrographic surgery.
- For advanced disease, radiotherapy, electrochemotherapy and vismodegib can be used.

Squamous cell carcinoma

SCC is the second most common NMSC. It is a malignant neoplasm of the keratinocytes that may arise *de novo* or from precursor lesions (i.e. AKs and BD). SCCs have the potential to metastasize. This risk is generally low (< 5%), but when it happens, the 5-year survival rates are 25–40%.[31] There is a group of SCCs that have a higher risk of developing metastasis. This includes locally advanced disease, poorly differentiated or undifferentiated histology, high-risk areas and immunosupression.

CLINICAL FEATURES

SCCs are found on sun-exposed areas of skin, commonly arising on the face, scalp, ears, lip, hands and forearms but may arise from mucous membranes. The surrounding skin usually shows evidence of chronic actinic damage. They usually grow quickly over weeks or months. Lesions may appear as enlarging plaques, papules or nodules that may be smooth and soft or rough and hardened (**Figure 94.4**). The edges are usually irregular and the base is indurated. With progression they can ulcerate and bleed and may become painful. On the mucosal surfaces they may present as thickened white plaques (leukoplakia) or moist erythematous plaques.



Figure 94.4 Squamous cell carcinoma.

Occasionally SCCs appear as non-healing ulcers with no evidence of keratinization. When they metastasize it is usually to the regional lymph nodes. If distant metastatic disease happens, the most common site is the lungs.

DIAGNOSIS

The differential diagnosis includes other malignant lesions (amelanotic melanoma, BCC, SC) or benign lesions (hypertrophic BD or AK, viral warts, pyogenic granuloma, keratoacanthoma). Histological confirmation is essential for diagnosis. When clinical uncertainty exists, a punch or incisional biopsy may be obtained before excision of the lesion. When doing a biopsy it is important to bear in mind the risk of sampling error, more so when assessing lesions that arise from a very photodamaged skin. In those cases, diagnosic excision may be necessary. The microscopic features include proliferation of atypical keratinocytes, nuclear pleomorphism, keratin whorls and mitotic figures. The degree of these changes may vary. The depth of invasion, histological grade and extension around nerves correlate well with prognosis. When lymph node metastasis is suspected a fine-needle aspiration (FNA) may be performed for cytological analysis. If FNA is inconclusive a radiologically guided core biopsy may be obtained.

MANAGEMENT[32–34]

Surgical treatment

The treatment of choice for most SCCs is surgical excision. It allows examination of the tumour in its entirety and assessment of adequacy of treatment. Well-defined T1 lesions should be excised with a peripheral margin of at least 4 mm and down to the subcutaneous fascia. T2 should be excised with a margin of 6 mm or more.

SCCs with high-risk features may be excised using Mohs micrographic surgery, which has been reported to provide high cure rates.[35] This technique is particularly useful for areas where wider margins of excision may be technically difficult or cause significant visual and functional impairment or if there is nerve involvement.

Radiotherapy

Radiotherapy can be used as a primary treatment for selected patients or adjunct when there is incomplete surgical excision or perineural invasion. The main disadvantages are lack of histological control, secondary skin cancer and atrophy and telangiectasia in the long run. Sites that respond well to radiotherapy include lower eyelid, inner canthus, tip of nose and lip. Radiotherapy should be avoided in tumours that invade bone or cartilage due to the risk of radionecrosis.

KEY POINTS

- SCC is the second most common cancer.
- It has a low but real risk of metastasis.
- No imaging is required in Stage I disease.
- Surgery should be carried out with 4 mm margins for low risk and 6 mm for high risk.
- Radiotherapy is a very effective treatment modality.

MELANOMA

Melanoma is a malignant neoplasm of melanocytes. It accounts for 5% of all skin cancers but 75% of all skin cancer-related deaths, due to its metastatic potential.

Epidemiology

Melanoma can occur in any ethnic group but is much more common in white skinned populations. The highest incidence rates are reported in Australia and New Zealand with 40–60 per 100 000 individuals affected each year.[36] In the US it is estimated to affect 18 per 100 000 and in Europe 10 to 15 patients per 100 000 yearly. These figures appear to be rising worldwide. It can affect any age but the median age at diagnosis is 59 years. Melanoma affects males and females equally.

Risk factors

SKIN TYPE

Fair skinned people are at greater risk of developing melanoma. Having a tendency to burn easily and tan poorly, blonde hair and freckles doubles an individual's risk.[37] Melanoma rarely presents in non-white people, who are 10–20 times less likely to develop this skin cancer.

SUN AND ULTRAVIOLET LIGHT EXPOSURE

Intermittent and intense exposure to sunlight can increase the chances of developing melanoma. Sunburn during childhood is thought to be a risk factor. Studies also support the association of sunbed use with melanoma, especially in those who start to use them before 35 years of age.[38] However, this malignancy can be seen on sites not routinely exposed to sunlight, such as the sole of the foot, genitalia and mucosal surfaces.

FAMILY HISTORY

Patients with an affected first-degree relative are twice as likely to develop melanoma.[39] Germline mutations in the *CDKN2A* gene are found in some families. Inherited photosensitivity disorders such as xeroderma pigmentosum are associated with a high incidence of melanoma and NMSC.

MULTIPLE NAEVI

The risk of melanoma is increased in individuals with a large number of moles. According to a meta-analysis, those with >100 naevi are seven times more likely to develop melanoma compared to mole counts of <15.[40] The presence of multiple clinically atypical naevi also increases the risk significantly. Studies indicate a sixfold increase in people with more than five atypical naevi compared to those with none.

Clinical features

Malignant melanocytic cells can initially appear in the epidermis. This is termed melanoma *in situ*. As it is only in the epidermis, it is not considered to have metastatic potential (**Figure 94.5**).

The four main clinical and pathological subtypes of invasive melanoma are superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM) and acral lentiginous melanoma (ALM). Rarer types include mucosal and desmoplastic melanoma and occasionally metastatic melanoma is diagnosed with no known primary.

SUPERFICIAL SPREADING MELANOMA

SSM is the commonest type of melanoma. It presents initially as a flat lesion that undergoes change in size, shape or colour (**Figure 94.6**). Histologically a radial or horizontal growth phase is apparent in the early stages but over time nodular areas with vertical growth may appear.

NODULAR MELANOMA

NM presents as a raised, firm lesion, which may erode or bleed. This type is commonly found on the head and neck and presents more often in older individuals. Lesions may be uniformly coloured or even non-pigmented. Histologically there is a prominent vertical growth phase without radial growth.



Figure 94.5 Lentigo maligna / melanoma *in situ*.



Figure 94.6 Melanoma.

TABLE 94.2 TNM staging for Mucosal melanoma of the Head and Neck. Adapted from AJCC Cancer Staging Manual 8th Edition. MB Amin ed. Springer 2017[18]

T: Primary tumour	
T3	Tumour limited to mucosa and underlying soft tissue regardless of thickness or dimension
T4	
T4a	Moderately advanced disease
T4b	Very advanced disease: Invasion of brain, dura, skull base, lower cranial nerves, masticator space, carotid artery, prevertebral space, or mediastinal structures
N: Regional Lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No Regional lymph node metastasis
N1	
M: Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

LENTIGO MALIGNA MELANOMA

LMM arises from a precursor lesion called lentigo maligna, which is a slowly growing dark patch on sun-exposed skin. It has a strong predilection for the head and neck of elderly patients. Histologically LMM is characterized by lentiginous proliferation of atypical melanocytes at the dermo-epidermal junction and background changes of chronic sun damage.

ACRAL LENTIGINOUS MELANOMA

ALM arises on the palms and soles or in the nail bed. The incidence is equal in fair and dark-skinned individuals and may not be related to ultraviolet light exposure. It appears as a flat lesion, which may be light coloured or pink. Histology in the early phase may show horizontal or intraepidermal growth but later nodular growth with invasion is seen.

OTHER TYPES OF MELANOMA

Primary melanoma arising from mucosal surfaces is rare. It may present in the oral cavity, nose or sinuses and may metastasize to lymph nodes or distant sites. The prognosis of mucosal melanoma is poor, with 5-year survival rates reported to be 38% according to a recent study.[41] Because of this, the AJCC in its 8th ed is current separated head and neck mucosal melanoma from cutaneous melanoma (**Table 94.2**).

Desmoplastic melanoma is another uncommon type typically found on the head and neck. Affected individuals are older and have chronically sun-damaged skin. The appearance of the lesion may be non-specific and it may look similar to a keloid scar or a benign lesion called dermatofibroma. Histologically an abundance of collagen is found and there may be prominent neural involvement. The 5-year survival rate is around 85%.[42]

Although most melanomas present as cutaneous lesions, occasionally metastatic deposits are found without any signs of a primary tumour. The original lesion may be hidden or may have undergone complete regression due to lymphocyte activation by the immune system. In such cases a careful search for a hidden primary should be performed by doing a full skin examination. They should also have an eye examination (looking for ocular melanoma), ENT and colonoscopy. In some cases, full PET-scanning is used.

Prognostic factors

The most important prognostic factor for patients with melanoma is the clinical stage. For localized melanoma the following characteristics of the tumour are considered to be the key determinants of outcome:

- **Breslow thickness:** this is the microscopic measurement of vertical depth of the tumour and is expressed in millimetres. It has shown to be one of the most important predictors of risk in a large study of 17 600 patients.[43]
- **Ulceration:** the histological presence of ulceration is another important factor that affects the prognosis of melanoma. The survival rate for ulcerated melanomas has been shown to be equivalent to that of non-ulcerated melanomas of the next greatest thickness category.
- **Mitotic rate:** high mitotic activity in the tumour is an independent risk factor that denotes biological aggressiveness of a melanoma.[44, 45]

Other factors that have been reported but are thought to be less relevant are anatomic location, patient age, gender,

level of tissue invasion (Clarke level), histological regression, lymphocytic infiltration and vascular invasion.

Staging

The American Joint Committee on Cancer published a revised staging system of melanoma in 2016, which is widely accepted as standard. In this classification, melanoma has been split into head and neck mucosal melanoma (**Table 94.2**), cutaneous melanoma (**Table 94.3**), conjunctival melanoma and uveal melanoma. When stratified by stage, the 5-year survival curves of melanoma goes from 97% for stage IA to 15% for stage IV (**Table 94.4**).

Management

ROLE OF SKIN SPECIALIST MULTIDISCIPLNARY TEAM

Melanomas above a certain Breslow thickness should be managed in the context of a multidisciplinary team (MDT). The team should ideally include histopathologists, radiologists, oncologists, dermatologists, plastic surgeons and other surgical specialties such as ENT or maxillo-facial surgeons. It is important to recognize the role of specialist cancer nurses in these meetings as they commonly have a very good knowledge of the patient's psychosocial needs. This MDT should consider on an individual basis the appropriate treatment, the role of sentinel lymph node biopsy (SLNB), adjuvant radiotherapy and inclusion in clinical trials.

SURGERY

Treatment of primary melanoma is surgical removal. Initially all suspected melanomas should be excised down to fat with a 2 mm margin to establish the Breslow thickness. Partial thickness, punch or incisional biopsies should not be performed as they may lead to diagnostic uncertainty. Once the thickness is established, a wider and deeper excision is performed. Margin recommendation varies slightly in different countries (**Table 94.5**).[46–50] The National Institute for Health and Care Excellence (NICE) recommends at least 5 mm margins for stage 0 melanomas, at least 10 mm for stage 1 and at least 20 mm for stage 2.[51]

Mohs micrographic surgery can be used to treat lentigo maligna (*in situ* melanoma), invasive lesions with indistinct margins such as desmoplastic melanoma or for surgery close to important anatomical areas such as eyes or ears. Clinical data for this technique in the management of melanoma are limited,[52] however, and should only be used under the auspices of an MDT.

INVESTIGATIONS

Investigations for stage I and IIA and B melanoma are not required. Patients with stage IIC or above should have a CT scan of the head, chest, abdomen and pelvis. For those with stage IV disease, serum lactate dehydrogenase (LDH) should also be measured. Full body PET-CT can also be used. However, due to the rapid development of new, more effective treatments, this recommendation is likely to change in the future.

TABLE 94.3 TNM staging for cutaneous melanoma. Adapted from AJCC Cancer Staging Manual 8th Edition. MB Amin ed. Springer 2017[18]

T: Primary tumour	
Tx	Primary tumour thickness cannot be assessed
T0	No evidence of primary tumour
Tis	Melanoma in situ
T1	
T1a	Breslow <0.8mm thick without ulceration
T1b	Breslow <0.8mm thick with ulceration
	Breslow 0.8 - 1mm thick without ulceration
T2	
T2a	Breslow 1.1-2mm thick without ulceration
T2b	Breslow 1.1-2mm thick with ulceration
T3	
T3a	Breslow 2.1-4mm thick without ulceration
T3b	Breslow 2.1-4mm thick with ulceration
T4	
T4a	Breslow >4mm thick without ulceration
T4b	Breslow >4mm thick with ulceration
N: Regional Lymph nodes	
Nx	Regional lymph nodes not assessed
N0	No Regional lymph node metastasis
N1	
N1a	1 clinically occult lymph node (i.e. SLNB)
N1b	1 clinically detected lymph node
N1c	No lymph nodes, presence of in-transit, satellite or microsatellite metastasis
N2	
N2a	2-3 clinically occult lymph nodes
N2b	2-3 lymph nodes, at least 1 clinically detected
N2c	1 lymph node with presence of in-transit, satellite or microsatellite metastasis
N3	
N3a	>4 clinically occult lymph nodes
N3b	>4 lymph nodes, at least 1 clinically detected
N3c	>2 lymph node with presence of in-transit, satellite or microsatellite metastasis Matted lymph node metastasis
M: Distant metastasis *	
M0	No distant metastasis
M1	
M1a	Distant metastasis to skin, soft tissue or non-regional lymph nodes
M1b	Lung metastasis with or without M1a
M1c	Distant metastasis to non-CNS visceral sites, with or without M1a or M1b
M1d	CNS metastasis with or without M1a M1b or M1c
Stage	
0	Tis N0 M0
IA	T1a N0 M0

(Continued)

TABLE 94.3 *(Continued)* TNM staging for cutaneous melanoma. Adapted from AJCC Cancer Staging Manual 8th Edition. MB Amin ed. Springer 2017[18]

IB	T1b N0 M0 T2a N0 M0
IIA	T2b N0 M0 T3a N0 M0
IIB	T3b N0 M0 T4a N0 M0
IIC	T4b N0 M0
IIIA	T1a/b, T2a N1a or N2a M0
IIIB	T0 N1b, N1c Mo T1a/b, T2a N1b/c, N2b M0 T2b, T3a NN1a-N2b M0
IIIC	T0 N2b, N2c, N3b, N3c M0 T1a-T3 N2c,N3a/b/c M0 T3b/T4a any N>=N1 M0 T4b N1c-N2c M0
IIID	T4b N3a/b/c M0
IV	Any T any N M1

*Suffixes in all M categories: (0) LDH not elevated; (1) LDH elevated.

TABLE 94.4 Survival rates for cutaneous melanoma

Stage	5-year survival (%)	10-year survival (%)
Stage IA	97	95
Stage IB	92	86
Stage IIA	81	67
Stage IIB	70	57
Stage IIC	53	40
Stage IIIA	78	68
Stage IIIB	59	43
Stage IIIC	40	24
Stage IV:	15–20	10–15

LYMPH NODE DISEASE

For patients with no apparent lymph node involvement, a SLNB may be performed at the time of wider excision. The sentinel lymph node is the first node where the skin involved with melanoma drains to and is detected by injecting a blue dye that is visually traced and by detecting the path of a radioactive tracer. SLNB is offered for stage 1B disease or above. The procedure has prognostic significance[53] but to date there has been no proven impact in melanoma-specific survival.[54]

For clinically enlarged nodes a FNAC sample should be obtained. If negative or equivocal this may be repeated, or an image-guided core biopsy or open biopsy should be performed.

If a lymph node is involved, then completion lymphadenectomy should be performed. For head and neck, it should include levels 1–5. Superficial parotidectomy can be performed if the disease is in that area. Radical parotidectomy is usually saved for cases of parotid involvement.

Adjuvant radiotherapy can be used to a lymph node basin. There is evidence that in high-risk patients, it reduces local recurrence, without an improvement in overall survival.[55]

LOCOREGIONAL METASTASES

Metastatic disease confined to the skin between the scar of the primary lesion and regional lymph node basins may be treated palliatively by surgical excision or ablative techniques such as CO2 laser or electro cautery. Radiotherapy may be used if these fail. Electrochemotherapy using intravenous bleomycin is an emerging palliative modality for locoregional metastatic melanoma.[56] Interleukin-2 is licensed in the United States, but there is limited data. Interferon alpha may have a benefit in high-risk melanomas (stage II–III) in disease-free survival and, perhaps, in overall survival, although trials are still ongoing.[57]

DISTANT METASTASES

Patients with stage IV disease should be referred to an oncologist. Palliative surgery or radiotherapy may be offered for oligometastaic disease. Historically chemotherapeutic options have been limited to dacarbazine, which has limited benefit with response rates ranging from 5% to 28%. In recent years, due to the discovery of signalling pathways and mutations in those pathways, new targeted therapies have emerged. For BRAF mutations, vemurafenib and dabrafenib are available, often used along MEK inhibitors such as trametinib. Of special interest in head and neck is a mutation in KIT that is present in 39% of cases, and for which imatinib is available (but unlicensed for this indication). There is also the developing of immunotherapies such as ipilimumab (anti-CTLA-4); pembrolizumab

TABLE 94.5 Melanoma surgical margins recommended by different guidelines

Thickness (mm)	UK (cm)	German (cm)	European (cm)	American (cm)	Australia / New Zealand (cm)
In situ	0.5	0.5	0.5	0.5	0.5
<1	1	1	1	1	1
1–2	1-2	1	1	1–2	1–2
2–4	2–3	2	2	2	1–2
>4	3	2	2	2	2

TABLE 94.6 Melanoma follow-up (taken from the British Association of Dermatologists melanoma guidelines)

Stage IA	3 to 6 monthly for 12 months
Stage IB to IIIA	3 monthly for 3 years, then
	6 monthly to 5 years
Stage IIIB and IIIC	3 monthly for 3 years, then
	6 monthly to 5 years, then
	Annually to 10 years
Stage IV	See according to need

and nivolumab (anti-PD1). With multiple molecules being developed currently, the next few years are likely to completely rewrite the way we approach and treat melanoma.

Follow-up

Patients with *in-situ* melanoma do not require follow-up. Patients with stage I and above disease require monitoring on a regular basis for assessment of recurrence or metastatic spread. Guidelines on the timings vary but the schedule based on the British Association of Dermatologists recommendations can be used as a guide (**Table 94.6**).

KEY POINTS

- Melanoma accounts for 75% of all skin cancer deaths.
- Its incidence is rising worldwide.
- Mucosal melanoma of the head and neck has a worse prognosis and its own TNM classification..
- The only treatment for primary melanoma is surgery with adequate margins.
- Surgery is the treatment of choice for lymph node metastasis. Levels 1–5 should all be removed.
- Radiotherapy has a role as adjuvant therapy.
- For metastatic disease, it is essential to know the mutation status (BRAF) in order to tailor treatment.

RARE SKIN CANCERS

Merkel cell carcinoma

Merkel cell carcinoma (MCC) is an uncommon malignancy of neuro-endocrine origin and it is though to be associated to a poliomavirus (MCPyV) in 80% of the cases.[58] However, its incidence has increased fourfold since 1986.[59] It is usually seen in elderly, white-skinned individuals but may arise in younger adults, particularly those who are immunosuppressed. The incidence is highest on the head and neck (40–60%).[60] The morphology of skin lesions is variable and it may mimic a number of benign or malignant tumours. A common presentation is an enlarging solid nodule and rapid growth is characteristic (**Figure 94.7**). Due to its increasing incidence and aggressive nature, it has a separate TNM staging in the AJCC classification.

The survival rate depends on the stage at diagnosis (**Table 94.7**).[61]



Figure 94.7 Merkel cell carcinoma.

TABLE 94.7 5-year survival rates for Merkel cell carcinoma. Adapted from AJCC Cancer Staging Manual 8th Edition. MB Amin ed. Springer 2017[18]

AJCC clinical staging	
I	55.8%
IIA	41.1%
IIB	31.8%
III	35.4%
IV	13.5%

Traditionally MCC has been treated with surgery with wide margins (up to 3 cm). However, MCC is radiosensitive and radiotherapy can be used as first line or as adjuvant to surgery. Current trials are trying to ascertain the efficacy of these treatment modalities.

Dermatofibrosarcoma protuberans

Dermatofibrosarcoma protuberans (DFSP) is the commonest sarcoma of the skin with 14% of DFSPs arising in the head and neck.[62] These tumours exhibit slow growth and are locally infiltrative. They often recur locally following treatment but lymphatic or distant spread is uncommon. They can arise in any age group but the highest incidence is seen in 20–40-year-olds. Lesions appear as plaques or nodules that are fixed to the dermis and the overlying skin may be atrophic or telangiectatic. The treatment is surgical excision with wide margins. Mohs micrographic surgery can offer greater chances of complete removal and is advocated by many as the treatment of choice.[63,64] Other treatment options include radiotherapy and imatinib; these are usually employed for unresectable or metastatic disease. Although with total margin control surgery recurrences are very rare, due to the historical high rates of local recurrences follow-up is normally suggested (6–12 monthly).

Atypical fibroxanthoma

Atypical fibroxanthoma (AFX) is an uncommon spindle cell tumour. Most tumours affect the head and neck and are usually seen in elderly individuals with chronically

sun-damaged skin. The usual clinical presentation is a rapidly growing ulcerated nodule but the appearance may be non-specific and lesions are often confused with BCCs or SCCs. The incidence of metastases is low and most AFXs follow a benign clinical course. The treatment of choice is complete micrographic surgical excision.[65]

Angiosarcoma

Cutaneous angiosarcoma is a rare vascular neoplasm that is most commonly seen in patients over 50 years of age. Up to 60% of these cancers arise in the head and neck. The initial appearance is often a bruise-like plaque that progresses to larger nodules but they can look non-specific, presenting with oedema or ulceration (**Figure 94.8**). They carry a high risk of local recurrence and distant metastases to lymph nodes, lung and liver. The 5-year survival has been estimated in 15%,[66] with size (5 cm cut off) being the main prognostic factor. The ideal treatment has not been established but combined surgery and local radiotherapy appear to have better results than either treatment done alone.[67] Chemotherapeutic agents such as paclitaxel appear to have some benefit and are being evaluated.[68]



Figure 94.8 Angiosarcoma.

Sebaceous carcinoma

Sebaceous carcinoma (SC) arises from the sebaceous glands. They most commonly affect the head and neck, with the eyelids reported as being the most common site. It is more common in older patients. It has been associated with Muir-Torres syndrome and Lynch syndrome so all patients with SC should be assessed for this.

Its appearance can vary widely, often mimicking other benign and malignant cutaneous lesions. Classically they have a firm yellowish appearance.

The treatment of SC is surgical. With conventional excision with 5–6 mm margins, the recurrence rate is 32%.[69] Because of the high local recurrence rate, Mohs surgery is favoured over conventional excision, with recurrences reported from 0%[70] to 11%.[71] SC has the potential to spread, with a 5-year survival rate of 91%, a 10-year survival rate of 79%[72] and a mortality rate of 5–10%.

Skin cancer in immunosuppressed patients

Immunosuppression from any cause, such as HIV-AIDS, malignancy, chemotherapy and drugs, increases the likelihood of developing skin cancer. Most skin cancers in immunosuppressed patients are SCCs[73] but the incidence of other skin cancers such as BCCs, melanoma, MCC and Kaposi sarcoma is increased several-fold compared to immunocompetent individuals. These patients may develop multiple cutaneous neoplasms over their lifetime and regular surveillance of their skin is recommended.

BENIGN LESIONS

Melanocytic lesions

LENTIGINES

Lentigines (singular lentigo) are benign lesions that appear as small, pigmented flat spots surrounded by normal skin. There are several types and the commonest form is a simple lentigo that is not caused by solar radiation or systemic disease. Solar lentigines are common in fair skinned individuals and the incidence increases with age. They may also result from tanning beds, therapeutic ultraviolet light treatment and radiation. A large number of lentigines are seen in patients with xeroderma pigmentosum. Lentigines can appear on the lips, gums or oral mucosae and may be associated with organ abnormalities such as in Peutz-Jeghers syndrome.

MUCOSAL MELANOCYTIC LESIONS

Diffuse oral mucosal melanosis is often physiological in dark skinned individuals but may arise as a result of smoking, medication or following inflammation. The differential diagnosis of focal melanotic lesions includes benign melanotic macules, melano-acanthoma, melanocytic naevi and melanoma. Benign melanotic macules are synonymous with lentigines and are described above. A melano-acanthoma is a benign lesion that often rapidly increases in size and usually resolves without treatment or following biopsy. Melanocytic naevi in the oral cavity are usually acquired rather than congenital and have a smooth surface. They do not transform to melanoma but a biopsy should be performed for new lesions. Mucosal melanoma is rare and can arise in the nose, sinuses or mouth. Within the mouth the palate is the commonest site of involvement and thus all pigmented lesions in this area should be regarded with suspicion.



Figure 94.9 Junctional naevus.



Figure 94.10 Intradermal naevus.

MELANOCYTIC NAEVI

These are benign proliferations of melanocytes that may be congenital or acquired. They may be seen on any part of the skin and are often found on the scalp in children and adults. The incidence of new acquired naevi (**Figure 94.9**) decreases with age. There are three histological subtypes, which can be differentiated clinically. Junctional naevi consist of melanocytic nests at the basement membrane and appear flat macroscopically. When these nests are in the dermis the lesion appears above the surface giving intradermal naevi a papular appearance. Compound naevi have junctional and intradermal components and thus have flat and raised areas on gross examination (**Figure 94.10**). Melanocytic naevi are usually asymptomatic and often come to attention when they become inflamed or irritated, resulting in itching or pain.

ATYPICAL/DYSPLASTIC NAEVI

Atypical nevi are acquired moles with unusual features that may mimic melanoma. Clinically they are often larger than 5 mm in diameter, have irregular borders and may display several shades of pigment. Histology shows foci of atypical melanocytes but no invasion. Several dysplastic naevi may be seen in the same individual and, when accompanied by large number of benign naevi and a family history of melanoma, form the familial atypical mole and melanoma syndrome.[74] These patients are at high risk of developing melanoma. UV light can promote the development of dysplastic naevi and their transformation to melanoma but these lesions can appear in non-exposed sites. Atypical moles should be referred to dermatologists for assessment with dermoscopy, full skin examination and photographic records, especially if there are multiple unusual lesions. Excision with a 2 mm margin is recommended if the lesions change in appearance or when there is diagnostic uncertainty.

Seborrhoeic keratosis

These are benign epithelial tumours and are extremely common. They may be located anywhere on the skin except mucous membranes, palms and soles. The frequency of these lesions increases with age and elderly patients often have numerous seborrheic keratoses. The lesion is usually well defined and appears stuck on the skin (**Figure 94.11**). The surface is rough, corrugated and warty and the colour may range from that of normal skin to dark brown or black. Early lesions may be flat and can cause diagnostic confusion with melanocytic lesions. Dermoscopy shows horn pseudocysts and pseudofollicular openings.[75] Histological confirmation may be required for lesions lacking typical features. Treatment is not essential but can be carried out for cosmetic or symptomatic reasons as the lesions often become irritated or inflamed. Cryotherapy, shave excision and curettage are some of the commonly used surgical techniques.



Figure 94.11 Seborrhoeic keratosis (Blue arrow) next to a basal cell carcinoma (red arrow).

Keratoacanthoma

Keratoacanthomas are low-grade squamoproliferative tumours that arise from the pilosebaceous follicles. They grow rapidly and appear as nodules with a central keratin-filled crater and can be difficult to distinguish from SCC clinically. They commonly arise on the head and neck, and intra-oral lesions have also been reported. If untreated the lesions would involute over several months but lesions should be excised for diagnosis and exclusion of SCC.[76]

Cysts

A number of benign cysts can arise on the head and neck. Dermoid cysts are developmental inclusion cysts that appear at birth or in childhood and are commonly seen on the face. They contain mature skin with hair follicles, sweat glands and sebaceous glands. Epidermoid cysts form from proliferation of squamous epithelium in the dermis, which can follow trauma or a blocked pore. They are commonly seen on the face, neck and scalp. Pilar or trichilemmal cysts arise from stratified squamous epithelium similar to that found in hair follicles. Most pilar cysts occur on the scalp but may also form on the face or neck. Cysts may cause problems with cosmesis or symptoms following inflammation, and surgical excision can be offered for these reasons.

Pilomatricoma

A pilomatricoma is a benign tumour that arises from hair matrix cells. It commonly affects children in the form of a solitary, angulated, hard nodule on the cheek, eyelid, scalp or neck. The lesions tend to grow slowly and are usually asymptomatic. Transformation to pilomatrix carcinoma is possible but extremely rare. Multiple lesions may be seen in patients with myotonic dystrophy. These lesions should be excised, as they never regress spontaneously. Recurrence can occur if they are not removed completely.

Sebaceous adenoma

Sebaceous adenomas are benign adnexal neoplasm resulting from the proliferation of sebaceous gland-like structures. They appear as a small, slow growing, smooth, pink or yellow papules with central umbilication on the face or scalp. Lesions may be single or multiple. They may be mistaken for BCCs and histological confirmation is essential. These are rare neoplasms and often linked to Muir-Torre syndrome, which is a hereditary cancer syndrome characterized by visceral malignancies. Sebaceous adenomas should prompt a careful evaluation of the patient with attention to their family history for internal organ cancers.

Sebaceous hyperplasia

This is a common finding in the elderly or those who are receiving long-term immunosuppression. They appear as multiple, skin coloured or yellow papules on the forehead, nose or cheeks that are a few millimetres in diameter. Lesions are often umbilicated and may be confused with BCCs. These lesions have no malignant potential and treatment is not essential but a biopsy may help when the diagnosis is doubtful.

Syringoma

Syringoma is a benign sweat duct tumour. They usually appear in clusters on and around the eyelids or cheeks. Individual lesions are skin coloured papules, 1–3 mm in diameter. Treatment is often sought for cosmetic reasons and options include electrocautery, laser, cryotherapy and trichloracetic acid.

KEY POINTS

- Skin cancers are the most common cancers in the world.
- The incidence of skin cancer is increasing.
- Appropriate management with adequate surgical margins to prevent recurrences is vital.
- Mohs micrographic surgery can offer complete margin control for many skin cancers.
- Rare skin cancers are also on the rise. It is important to recognize them early so that appropriate multidisciplinary approach can be taken.

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CHAPTER 95

FACIAL REANIMATION SURGERY

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: facial paralysis, Bell's palsy and facial nerve.

THE CLINICAL PROBLEM

Facial paralysis causes a highly visible deformity with profound consequences from both a functional and psychosocial standpoint.

The absence or dysfunction of facial musculature (**Table 95.1**) can lead to an inability to control the eye and mouth, leading to corneal exposure and chronic irritation of the eye as well as oral incompetence, producing a disfiguring asymmetry and difficulty in eating and drinking.

From a psychosocial viewpoint, the lack of mimetic facial expression produces difficulties in communication and can affect self-confidence, professional advancement and social interaction and produce depression.

Brow ptosis is more commonly a problem in the older patient. The weight of the forehead pushes the eyebrow down, producing eyebrow asymmetry and obstructing upward gaze. This may be complicated by overactivity of the unaffected contralateral frontalis muscle, elevating the contralateral brow, worsening the asymmetry.

The orbicularis oculi muscle is crucial to the protection of the globe, providing closure of the eyelids during blinking, maintaining tone of the lower eyelid and providing the pumping mechanism for the lacrimal drainage apparatus. Paralysis of this muscle prevents eye closure, risking corneal exposure, ulceration and blindness. During normal eye closure, the majority of movement occurs in the upper eyelid – the lower eyelid elevates by approximately 2 mm during forced closure. The absence of Bell's phenomenon (upward rotation of the globe on forced eye closure) is a significant risk factor for the development of corneal exposure and must be assessed.

The normal orbicularis is responsible for the lacrimal pump apparatus. Paralysis of this active pumping mechanism reduces movement of tears down the lacrimal duct into the nasal cavity. Weakness of orbicularis may produce a paralytic ectropion, allowing the lacrimal punctum to fall away from the globe, worsening tear drainage.

The lateral canthus lies 2 mm cranial to the medial canthus; thus, tears naturally flow medially to the punctum and are carried away through the lacrimal apparatus, and are thence actively pumped away by the contractions of orbicularis oculi muscle. Laxity of the lower lid disrupts this smooth gradient, forming a paralytic ectropion, producing a bowing of the lower lid, producing a sump that allows tears to pool, overflow, and then run down the cheek.

As a result, patients with facial paralysis are frequently troubled by dryness of the eye coupled with a watering eye. This is exacerbated during cold and windy weather.

Weakness of the facial muscles may lead to cosmetic and functional problems with the nose. Overactivity of the muscles on the normal side of the face may pull midline structures over to the normal side. The nasal tip is drawn across the midline, along with the philtrum. There may be collapse of the internal and external nasal valves due to paralysis of the dilator nares and levator labii alequae nasi muscles.

TABLE 95.1 Aetiology of facial nerve dysfunction by anatomical level

Intracranial	Intratemporal	Extratemporal
• Vascular abnormalities • CNS degenerative disease • Intracranial cavity tumour • Brain tumour • Congenital abnormalities and agenesis	• Bacterial and viral infection • Cholesteatoma • Trauma: ○ temporal bone fracture ○ gunshot wounds • Tumours invading middle ear, mastoid, FN • Iatrogenic cause	• Malignant tumour of parotid • Trauma: lacerations, gunshot wounds • Iatrogenic • Primary tumour of FN • Malignant tumour of ascending ramus of mandible, pterygoid and skin

The other major concern for patients is inability to move the mouth. This affects the ability to speak clearly, drink fluids and eat. A common complaint is biting the inside of the mouth when eating. Speech is affected – many facial paralysis patients have difficulty with plosives ('b' and 'p' sounds).

ANATOMY

Facial muscles

There are 17 paired muscles of facial expression and one unpaired sphincter muscle, the orbicularis oris. The major muscles affecting the forehead and eyelids are the frontalis, corrugator and orbicularis oculi. There are two groups of muscles controlling the movement of the lips. The lip retractors include the levator labii superioris, levator anguli oris, zygomaticus major and minor for the upper lip, and depressor labii inferioris and depressor anguli oris for the lower lip. The antagonist to these muscles is the orbicularis oris, which is responsible for oral continence and is also involved in expressive movement of the lips. The detailed anatomy of the facial musculature has been well described in many standard surgical and anatomical textbooks.

Physiology of nerve repair

To understand the strategies employed in the management of facial nerve injury it is important to have an understanding of the principles of nerve repair.

SEDDON'S CLASSIFICATION

Seddon[1] described the following types of neuronal injury:

- **Neuropraxia**. This is temporary cessation of conduction of the nerve with no loss of axon continuity. Neuropraxia is a transient phenomenon with complete recovery once the causative factor is removed.
- **Axonotmesis**. Damage is sustained to the axon resulting in Wallerian degeneration. Regeneration occurs at a rate of 1–4 mm a day and recovery is usually satisfactory.
- **Neurotmesis**. The nerve fibre is severed and the endoneurium disrupted. Recovery is unlikely.[1, 2]

SUNDERLAND'S CLASSIFICATION

Sunderland's classification[3] discusses the extent of nerve injury allowing predictions to be made regarding prognosis:

- **First degree** injury is a conduction delay with no evidence of discontinuity of the neuronal anatomy.
- **Second degree** injury demonstrates disruption to the axon, resulting in Wallerian degeneration of the distal component. The proximal segment of the nerve becomes a passage for proteosynthetic substances to allow axonal regeneration. The endoneurium is intact so the axonal sprout can grow (usually at a rate of 1 mm a day) within the endoneurium, ensuring the motor end plate, and therefore muscles, receive the same nerve supply as prior to the injury. Factors that may affect recovery include site and type of injury, nutritional status and age.[4]
- **Third degree** injury also affects the endoneurium; therefore, in addition to the features seen in type two injury, the neuronal regrowth is less organized as regenerating axons may enter any endoneurial tubules. This means that the subsequent reinnervation may not supply the same muscles as previously, resulting in synkinesis or mass movement.
- **Fourth degree** injury affects the perineurium and **fifth degree** injury affects both perineurium and epineurium. This in turn results in a decreased number of axons regenerating as efficiently as in the less severe injuries, manifesting itself as weaker muscle function and also synkinesis.

The time from axonal degeneration to irretrievable muscle atrophy is accepted to be approximately 18 months but there have been reports of successful reinnervation up to 20 years later.[2]

ASSESSMENT OF THE PATIENT

A detailed clinical assessment is important in the diagnosis of facial paralysis. Attention should be paid to the duration and progression of symptoms, associated history ear problems, trauma, recent vaccinations, travel history, family history of facial weakness and medical history.

A diagnosis of idiopathic Bell's palsy should only be made with a classical history – any atypical clinical features should prompt further investigation to exclude another cause.

Examination should include careful assessment of each branch of the facial nerve and, where possible, the House–Brackmann[5] (**Table 95.2**) and Sunnybrook grading scales[6] should be used to document the severity of facial weakness. The Sunnybrook Facial Grading in particular will allow assessment for recovery or progression (**Table 95.3**). In younger children, where it may not be possible to use the House–Brackmann grading scale, it is important to document what spontaneous facial movements are noted (particularly when the child is crying) and what movement the parents feel may have altered. Forehead sparing in a patient presenting with facial weakness represents a supranuclear lesion due to cross-innervation. A thorough history and examination will reveal the presence of a complete or partial VIIth nerve paralysis and the extent and severity of weakness. The history should explore the physical problems from the patient's perspectives as a guide to treatment. The patient's concerns and expectation should be sought and evaluated: for some, functional considerations will predominate; for others, simply looking symmetrical in photos is all they seek; others will want restoration of dynamic spontaneous facial movement. The level of nerve lesion can be assessed clinically. Injury within the bony canal is suggested by hyperacusis, loss of taste to the ipsilateral tongue and facial weakness. Injury near the geniculate ganglion will result in decreased secretory function of the nose, mouth and lacrimal gland.

TABLE 95.2 The House–Brackman grading scale[5]

Grade	Characteristics
I. Normal	Normal facial function in all areas
II. Mild dysfunction	Gross: • slight weakness noticeable on close inspection • may have slight synkinesis • at rest, normal symmetry and tone Motion: • forehead – moderate-to-good function • eye – complete closure with minimal effort • mouth – slight asymmetry
III. Moderate dysfunction	Gross: • obvious but not disfiguring difference between the two sides • noticeable but not severe synkinesis, contracture, or hemifacial spasm • at rest, normal symmetry and tone Motion: • forehead – slight-to-moderate movement • eye – complete closure with effort • mouth – slightly weak with maximum effort
IV. Moderately severe dysfunction	Gross: • obvious weakness and/or disfiguring asymmetry • at rest, normal symmetry and tone Motion: • forehead – none • eye – incomplete closure • mouth – asymmetric with maximum effort
V. Severe dysfunction	Gross: • only barely perceptible motion • at rest, asymmetry Motion: • forehead – none • eye – incomplete closure • mouth – slight movement
VI. Total paralysis	• No movement

Examination should also include otoscopy, examination of the head and neck for signs of trauma and masses, particularly in the region of the parotid, as well as assessment of the remaining cranial nerves.[3]

Examination of the face begins with the brow. The position of the brow and degree of forehead rhytids must be assessed and brow movement should be measured. The palpebral aperture should then be measured. Visual acuity and the presence of Bell's phenomenon should be tested. Lower lid laxity can be assessed by the snap test, gently pulling the lower lid away from the globe and releasing – adequate tone is demonstrated by a slightly audible snap as the lid is snaps back into position. This fails to occur if lid laxity is present. Alternatively, distraction greater than 6 mm from the globe on gentle downward traction of the lower lid suggests lid laxity is present. The position of the inferior canalicular punctum should be noted and the presence of medial canthal tendon laxity assessed.

The nose is examined for deviation to the unaffected side. Forced inspiration may produce collapse of the internal nasal valves on inspiration due to loss of tone in the dilator nares muscle.

Static asymmetry of the face should be assessed, including midline shift of the philtrum, the depth of the nasolabial folds, jowling and the presence of platysmal bands (often present on the paralyzed side). Static asymmetry of the oral commissures is noted and the presence of hypertonicity on the each side of the face is assessed. Active movements are then assessed: excursion of the oral commissures is measured and the degree of synkinesis. The lower teeth are examined with regard to how much they show during smiling; the smile is classified using the Rubin Smile Classification.[7]

INVESTIGATIONS

Imaging of the facial nerve may be useful in delineating the site of neural injury. Indications include recurrent, progressive or persistent paralysis, trauma and suspected nerve involvement in systemic diseases.

Magnetic resonance imaging (MRI) is the only modality that demonstrates the facial nerve comprehensively from the pons to the parotid gland; with gadolinium enhancement it is capable of showing inflammatory changes. High resolution CT of temporal bone makes it possible to see

TABLE 95.3 Sunnybrook facial grading system

Resting Symmetry

Compared to normal side

Eye (choose one only)
- normal 0
- narrow 1
- wide 1
- eyelid surgery 1

Cheek (naso-lablal fild)
- normal 0
- absent 2
- less pronounced 1
- more pronounced 1

Mouth
- normal 0
- corner dropped 1
- corner pulled up/out 1

Total ☐

Resting symmetry score: Total X 5 ☐

Patient's name

Dx

Date

Symmetry of Voluntary Movement

Degree of muscle EXCURSION compared to normal side

Standard Expressions	Unable to initiate movement/SS movement	Initiates slight movement	Initiated movement with mild excursion	Movement simest complete	Movement complete	
Forehead Wrinkle (FRO)	1	2	3	4	5	☐
Gentle eye closure (OCS)	1	2	3	4	5	☐
Open mouth smile (ZYG/RIS)	1	2	3	4	5	☐
Snarl (LLA/LLS)	1	2	3	4	5	☐
Lip Pucker (OOS/OOI)	1	2	3	4	5	☐

Gross Asymmetry	Severe Asymmetry	Moderate Asymmetry	Mild Asymmetry	Normal symmetry	Total
					☐

Voluntary movement score: Total X 4 ☐

Synkinesis

Rate the degree of INVOLUNTARY MUSCLE CONTRACTION associated with each expression

Standard Expressions	**NONE:** No synkinesis or mass movement	**MILD:** Slight synkinesis	**MODERATE:** Obvious but not disfiguring synkinesis	**SEVERE:** Disfiguring synkinesis Gross mass movement of several muscles	
Forehead Wrinkle (FRO)	0	1	2	3	☐
Gentle eye closure (OCS)	0	1	2	3	☐
Open mouth smile (ZYG/RIS)	0	1	2	3	☐
Snarl (LLA/LLS)	0	1	2	3	☐
Lip Pucker (OOS/OOI)	0	1	2	3	☐

Synkinesis score: Total ☐

Vol mov't score ☐ – Resting symmetry score ☐ – Synk score ☐ = Composite score ☐

bony detail and is ideal when facial nerve involvement is in the middle ear cleft.

Electrophysiological tests allow objective assessment of function, even in children.[8] Typically testing is delayed until 72 hours post onset of paralysis (to allow for Wallerian degeneration). This can be repeated every 3–5 days up to 21 days until a trend or confirmation can be obtained. The most clinically helpful use of this test is objectively to assess facial nerve function, once spontaneous motion is lost in acquired paralysis or if it had never been seen in congenital paralysis. The authors maintain that the test is not an absolute predictor for return of function but that the added data, when used with clinical information, make assessment of prognosis more rational.

TIMING OF REPAIR

For reinnervation procedures to be considered the ipsilateral facial nucleus must have an adequate number of functioning cell bodies, the proximal nerve segment must be in continuity with the facial nucleus and be able to support axial regeneration, and the distal nerve segment must be in contact with functioning muscle units and be capable of accepting regenerating neurons.[9]

Immediate or early repair of nerve injuries should always be repaired if at all possible. Primary repair of the facial nerve should be performed using an operating miscroscope if possible. Epineural repair using 9/0 nylon is as successful as fascicular repair.[10] Fibrin glue may also be used.[11]

Interposition graft

Interposition grafts are used when there is an insufficient length of nerve to allow a tension free anastomosis. The length of a graft should exceed the gap by 3–5 mm on each side.[12] The commonest donor nerves are the greater auricular nerve and the sural nerve. The greater auricular nerve usually lies within the surgical field; however, only about 5 cm graft length is available. The sural nerve has the advantage of providing a long segment of nerve and has a reliable course, allowing ease of location. Disadvantages include a potentially larger diameter and higher neural to connective tissue ratio.[4] In one series 95% of patients had some return of function following interposition graft and success has also been described in patients who have had postoperative radiotherapy.[13]

Atrophy of muscle and degeneration of motor end plates begins to occur following denervation of facial muscles. There is little prospect of successful reinnervation after

2 years.[14, 15] As it may take 6–9 months for nerve regeneration to occur following nerve transfer, this must be taken into account when evaluating the likelihood of success of a nerve transfer.

TREATMENT PLANNING

Treatment should be individualized. However, aims of treatment are:

- the protection of the eye
- to provide symmetry at rest
- correction of synkinesis
- to provide oral continence
- to provide dynamic facial movement
- to improve speech
- to improve nasal deviation and airway patency.

NON-SURGICAL MANAGEMENT

Non-surgical management of the eye

Non-surgical strategies to protect the eye are used whilst waiting for a damaged facial nerve to recover or sometimes, in a well-motivated patient, as a permanent solution for the eye as an alternative to surgery. The aim is to prevent exposure dermatitis of the corneal leading to ulceration and blindness. Adequate provision of ocular lubricants during the day is essential and the patient must be taught how to tape the lids closed at night to prevent desiccation. Eye irritation mandates ophthalmology review.

Non-surgical treatment of the face

The cornerstone of management of facial paralysis is facial therapy.

Neuromuscular retraining by an experienced therapist can improve aberrant activity on the unaffected side, and the treatment of synkinesis and hypertonicity (if present) on the affected side. A variety of treatment modalities are used, including biofeedback, electromyography and self-directed mirror exercises.[16]

Strong consensus exists as to the importance of facial therapy in the multidisciplinary management of facial palsy. Some evidence exists that tailored facial exercises can help to improve facial function, mainly for people with moderate paralysis and chronic cases, and reduces recovery time and negative sequelae in acute cases.[17]

SURGICAL MANAGEMENT

Brow

In the young, paralysis of one side of the forehead causes relatively minimal problems. They have no forehead crease lines, so the difference between each side of the face is only noticed on animation. The eyebrow does not descend since there is still some elasticity in the tissues. In a 20-year-old man, the animation of one side of the forehead may be considered an embarrassment as it draws attention to the overall asymmetry of the face. Botulinum toxin injections to contralateral frontalis may be employed after careful discussion with, and thorough understanding by, the patient.

In later life, with loss of skin elasticity, the eyebrow sometimes descends, taking part of the eyelid skin with it, so that vision may be partially obstructed. A direct brow lift provides long-lasting correction. Other brow-lifting techniques, used in cosmetic surgery, include endoscopic brow-lifts and transblepharoplasty brow-pexy techniques using implants. These may be useful in correcting small ptoses in partial facial weakness but have limited application in profound facial palsy, particularly in the elderly.[18] More sophisticated transfers of muscle groups, for example from the contralateral frontalis muscle, do not seem to be particularly reliable, which probably relates to devascularization of the muscle fibres.

Upper eyelid

In congenital unilateral facial palsy, even if the young patient does not close their eye perfectly they seem to have minimal problems with exposure keratitis. The child passes through a phase before the age of 3 when excess epiphora may cause them to rub their eye and develop pseudo-conjunctivitis. Eventually they learn to avoid this and by the age of 4 seem to have no further problems. Upper lid weighting is not required and indeed is actively disliked by the child as it may narrow the palpebral fissure and sometimes interfere with their visual field compared to the normal contralateral side.

As the patient with congenital unilateral facial palsy reaches their mid-20s, the lower eyelid descends and scleral show may be apparent. A McLaughlin's lateral tarsorrhaphy is an effective and aesthetic means to elevate the lower eyelid, slightly narrow the palpebral fissure and restore symmetry.

However, a unilateral facial palsy developing in adulthood is a different matter and avoidance of exposure keratitis is mandatory. Even if recovery is expected, the eye must be protected by creams at night, tape closure or surgery. There are numerous methods available to protect the cornea. The principle is to either allow the upper eyelid to drop, elevate the lower, or both. On blinking, the levator palpebrae relaxes and, if the upper eyelid is either loaded or sprung, the eyelid can be persuaded to close. Specially made gold weights, smoothly rounded and capable of fixation to the tarsal plate, are easy to insert and largely reliable. Fixation to the tarsal plate is essential as it significantly reduces extrusion and migration. It is desirable to use as light a weight as will effectively close the eye, and rarely is more than 1 g required (1.5 g gold weights are heavy and eventually the levator is apt to weaken, producing ptosis). Closure sufficient to cover the cornea is reported in 78% of cases with resolution of keratitis in 62–100% of cases.[9, 19–21]

Other methods of treating lagopthalmos include: lengthening the levator by division or inserting a strip of temporalis fascia; insertion of magnets in upper and lower lids;[22] and the Morel-Fatio palpebral spring.[22, 23]

The classic Gillies procedure – the transfer of slips of temporalis muscle and deep temporal fascia to upper and lower eyelids – has been used extensively in the past. It has now fallen out of favour due to unpredictability of result compared with the simpler and more predictable lid loading techniques described above.

Lower eyelid

Elevation of the lower eyelid may be required where there is a scleral show beneath the limbus of the eye, and to correct epiphora. Many methods are available to achieve this, but a McLaughlin's lateral tarsorrhaphy is aesthetic and effective for minor degrees; however, large procedures narrow the palpebral fissure and are extremely unaesthetic. If this is unsuccessful or the depression is more severe, then a palmaris tendon sling between the medial canthal ligament and the supraorbital margin laterally can provide good elevation. Conchal cartilage grafts may be used to support the lower eyelid, set between the infraorbital margin and the lower edge of the tarsal plate.[24]

The treatment of epiphora remains challenging. The massaging action of the orbicularis on the tear flow and its siphoning effect on the lachrymal sac is important, as is the position of the lower lateral canaliculus in respect of the orbit. However, a perfectly positioned lachrymal canaliculus does not mitigate against a watering eye. Overproduction of tears by reducing the inhibition on the secretor motor fibres to the lachrymal sac via the greater superficial petrosal nerve may be an unwanted factor.

The Gillies procedure, involving transferring the temporalis muscle and extending it by using the temporalis fascia passed through the upper and lower eyelids, is less popular these days, although, if perfectly tensioned, satisfactory results can be achieved using this technique. It is probably less reliable than the methods mentioned previously.

Nasal airway

Paralysis of the nasalis, dilator nares and levator labii aleque nasi muscles may lead to collapse of the external and internal nasal valves. This may be exacerbated if the nose is pulled towards the unaffected side by the unopposed action of the contralateral facial muscles. The airway is narrowed with reduction in airflow. If the patient is symptomatic, elevation of the nasal base by tendon slings fixed to the maxillary periosteum is effective. Septal deviations, if present, should be corrected. Insertion of supportive cartilage grafts to the alar rim have also been used.

Upper lip and cheek (smile reconstruction)

The majority of patients presenting with refractory facial paralysis do so for correction of facial asymmetry and/or the restoration of dynamic facial movement. For those patients who simply want to look symmetrical in photographs and/or are either not a candidate for more complex procedures or for whom a prolonged recovery and period of facial rehabilitation is not attractive, then static facial slings can restore a surprising degree of resting facial symmetry.

STATIC TECHNIQUES

Facia lata, harvested from the lateral thigh, is commonly used in this application, although some proponents prefer tendon grafts of plantaris or palmaris longus as they are said to stretch less over time. The grafts are inserted into the corner of the mouth at the nasolabial fold and anchored either to the deep temporal fossa or zygomatic periosteum using either permanent sutures or Mitek® Bone Anchors. Using the contralateral normal side as a guide to assess the vector required, the grafts are inserted with sufficient tension to just overcorrect the asymmetry to allow for post-operative relaxation.

DYNAMIC TECHNIQUES

Regional muscle transfers

Dynamic muscle transfers have traditionally involved the transfer of muscle of mastication to the mouth to replace the lost activity of levator anguli oris and zygomaticus major and minor muscles. Regional muscle transfers have the advantage of immediate results as no reinnervation is required; however, the transfer of a regional muscle produces a voluntary smile rather than a natural spontaneous smile, and abnormal movements can be produced during chewing. Transfer of the masseter muscle produces little in the way of movement of the mouth and an unsightly bulge in the cheek. Temporalis transfer, popularized by Gillies, involved the turnover of strips of temporalis muscle and deep temporal fascia over the zygoma and inset into the corner of the mouth and/or the eyelids. This may produce an unsightly bulge over the zygoma. More recently a prograde temporalis transfer, described by Labbé and Huault, has become popular.[25]

In recent years the use of regional muscle transfers has largely been superceded by free muscle transfers.

Free muscle transfers

Microsurgical functioning muscle transfer has become the mainstay of facial reanimation in the developed world over the past three decades. Pre-operative planning is essential – assessment of the vector and magnitude of the smile on the normal side must be made to plan. A variety of muscles have been described for facial reanimation but the most popular remain the gracilis muscle and the pectoralis minor muscle. To produce a voluntary smile requires the use of the VIIth nerve, most commonly by way of a cross-facial nerve graft.

Single stage muscle flaps with innervation from the contralateral facial nerve have been reported. This technique requires the use of a muscle flap with a long nerve segment, such as latissimus dorsi or rectus abdominis.[26]

A comprehensive exploration of the branches of the contralateral facial nerve is performed at a first stage. Usually a redundant buccal branch is selected as the donor nerve, using bipolar nerve stimulation. A sural nerve graft, harvested from the leg, is placed onto a redundant buccal branch and tunnelled across the midline to the paralyzed side of the face. Growth of the facial nerve is followed clinically by way of Tinel's sign and, following successful regeneration, a free functioning muscle transfer is performed 6–9 months later at a second stage. The muscle is inset into the nasolabial fold and commissure of the mouth and revascularized using either the facial vessels or the superficial temporal vessels.

The use of the masseteric branch of the Vth cranial nerve to power muscle transplants in a single operative stage has recently become used. Advocates of the masseteric nerve cite benefits of a single-stage procedure, a greater axonal load that can be delivered to the muscle resulting in a stronger contraction of the transplanted muscle – a more normal excursion of the mouth and preservation of the contralateral facial nerve.[27] These combine to allow a more normal reconstructed smile. The disadvantage is the need to relearn to smile by biting.

The use of cross-facial nerve grafts and other donor nerves to power the transplant or reinnervate intact facial musculature depends on the goals of treatment and patient factors. Although initially thought that only a cross-facial nerve graft could produce spontaneous facial activity, spontaneous activity has been observed in a significant proportion of transplants innervated by the nerve to masseter.[28, 29] This has been ascribed to the phenomenon of cortical plasticity; however, activity of the normal masseteric nerve during smiling has been observed on EMG studies, and this may offer an alternative explanation.

Lower lip

Transfer of the anterior belly of digastric muscle[30] and platysmal muscle[31] have been described for dynamic reanimation of the lower lip. The results of these are variable. A simpler and more predictable result can be achieved by the selective weakening of the contralateral depressor labii inferioris muscle. This can be achieved temporarily by the use of Botox or more permanently by direct excision of the muscle through an intra-oral approach.[32, 33]

ADJUNCTS

Other cosmetic interventions may be performed as required, including facelifts, midface lifts, rhinoplasty and correction of platysmal bands.

KEY POINTS

- A diagnosis of idiopathic Bell's palsy should only be made with a classical history – any atypical clinical features should prompt further investigation to exclude another cause.
- Facial paralysis should be managed in a multidisciplinary fashion.
- Reinnervation can only be successful for approximately 18 months following onset of facial paralysis.
- Early intervention to protect the eye may be required.
- Facial reanimation can be vey effective but a completely normal appearance is rarely achieved.

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CHAPTER 96

PARTIAL AND TOTAL EAR RECONSTRUCTION

Cher Bing Chuo

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: partial and total ear reconstruction, and total and partial auricular reconstruction. It is focused on a narrow range of common partial ear reconstruction techniques and the basic principles guiding total ear reconstruction.

INTRODUCTION

The external ear is a convoluted 3D structure with a vestigial function to gather sound waves towards the external auditory meatus (EAM). This delicate structure with a complex contour has become a subject of beauty over the ages. There has been increasing awareness that individuals desire the appearance of a pair of symmetric, aesthetically pleasing ears. In a representative proportion of the UK general population, the awareness of perceived differences in the appearance of their ears has led to self-consciousness or increased sensitivity to these differences.[1] Reconstructive surgeons should have comprehensive knowledge of normal ear anatomy in order to perform accurate and aesthetic auricular reconstruction.

ANATOMY

Surface anatomy

Auricular surface anatomy is characterized by a series of ridges and depressions (**Figure 96.1**).[2] The outer border of the upper two-thirds of the ear is framed by the elevated helix. Darwin's tubercle is a prominence that sits on the posterior upper helix. The crus or root of the helix slopes downwards and curves posteriorly from the anterior upper third of the ear, over the superior aspect of the EAM. This ridge separates the conchal depression into the upper cymba concha and lower cavum concha. A complex elevation – the antihelix, separates the wide and deep concha from the narrow and shallow scaphal depression. The upper part of the antihelix follows the curve of the outer helix before dividing to form 'V-shaped' delicate ridges called the superior and inferior crura. These crura border a depression called the triangular fossa. The antihelical elevation extends towards the ear lobule to meet a short semicircular ridge – the antitragus – which is separated from the tragus by the more inferiorly placed intertragic notch or incisura. The tragus is a prominent quadrangular ridge which points posteriorly and lies over the anterior aspect of the EAM. The flat ear lobule sits inferior to the tail of the helix at the lower quarter of the ear, below the antitragus and the incisura. On the medial (cranial) surface of the auricle, the scaphal and conchal eminences are convexities that correspond to the scaphal and conchal depressions on the lateral surface described previously. The conchal eminence meets with the mastoid process to form the postauricular sulcus.

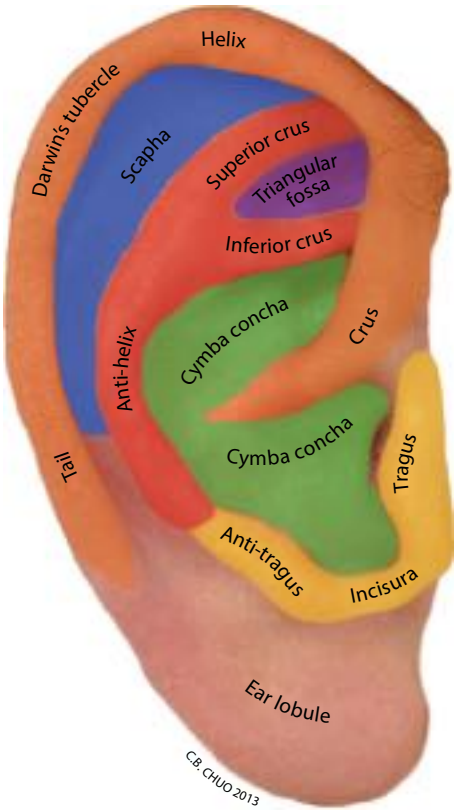


Figure 96.1 Lateral surface of the external ear. The locations and proportions of the key structures including the ear lobule are shown. Important ridges are the helix, antihelix, tragus and antitragal complex. Important depressions are the scapha, concha and triangular fossa.

Posture and position

The posture and position of the ear are shown in **Figure 96.2**.[3–7] The longitudinal axis of the ear is considered by Tolleth as the 'line of balance' that extends from the fullest point on the upper helical border to the most dependent point on the lower border of the ear lobule. It lies posteriorly rotated from the vertical axis of the head by 15–30 degrees. The axis of the ear may sometimes lie parallel to the dorsum of the nose, but more frequently lies 12–15 degrees more vertical than the nasal dorsum.

The ear is sited approximately the length of an ear, measured along its longitudinal axis, posterior to the lateral orbital margin. In 85% of individuals, the upper border of the ear is level with the most lateral point of the eyebrow.

The lateral surface of the ear is turned anteriorly with a conchomastoid angle of 30 degrees and a concho scaphoid angle of 90 ± 15 degrees. The most prominent point of the ear sits 17–20 mm lateral to the side of the head in the horizontal plane.

Three key measurements are required in order to site the reconstructed ear in an aesthetic and symmetric position: an appropriate angle of rotation for the longitudinal axis, the vertical level for the upper border of the ear and the horizontal distance of the ear from the lateral orbital margin.

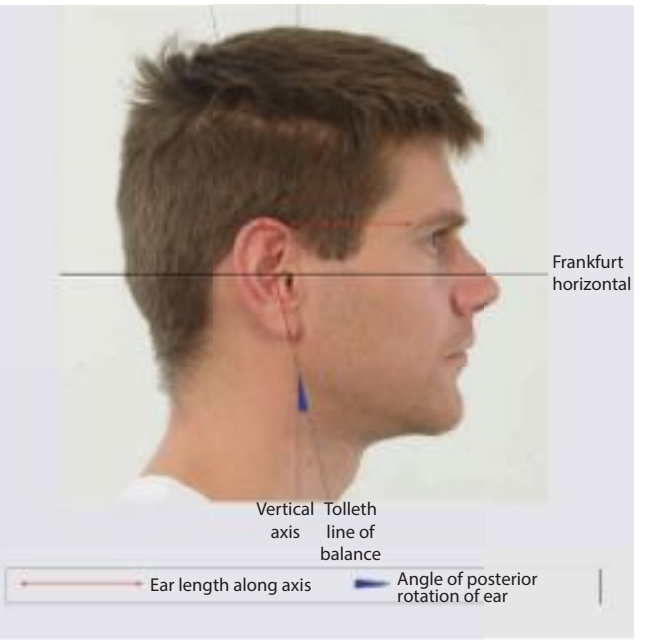


Figure 96.2 Lateral aspect of the head. This illustrates the ideal position of the upper external auditory meatus in line with the Frankfurt horizontal and the anterior border of the helix positioned one ear length posterior to the lateral orbital margin. The longitudinal axis of the ear is posteriorly rotated relative to the vertical axis of the head.

Proportions

The normal adult ear measured along its longitudinal axis is 63–65mm and the width of the ear is 50–65% (mean 55%) of its length (**Figure 96.3**).[3, 5, 8]

The triangular conchal depression has a width two-thirds of its length. The average length of the ear lobule as measured from the lowermost incisura to the most dependent point on the lower border of the ear lobule is 18 mm, and the ratio of lobule length to full ear length is 0.28–0.30.

Structure

Mechanical strength to maintain the structure of the external ear is provided by fibrocartilage which extends from the helix to the incisura.[2, 9–11] At the anterior aspect of the concha, a cartilaginous cylinder continues from the EAM medially to form the outer third of the external auditory canal. The auricular cartilage is attached to the temporal bone by two ligaments. The anterior ligament holds the tragus and anterior helical crus to the root of the zygomatic arch. A posterior ligament holds the medial conchal eminence to the lateral mastoid process.

Six vestigial intrinsic and three extrinsic muscles attach to the perichondrium of the ear. The extrinsic muscles auricularis anterior and superior attach to the galeal aponeurosis, and the auricularis posterior attaches to the periosteum at the base of the mastoid.

The skin on the lateral surface of the ear is thin and binds tightly to the underlying perichondrium encasing

the fibrocartilage. This allows the details of the complex convolutions of the cartilage to be easily seen.

Skin on the medial surface of the ear is mobile, with a thickness of 0.4–0.8 mm. There is minimal subcutaneous adipose tissue and extensive fatty infiltration of the dermis, beginning at the level of the sebaceous glands, and increasing in density with depth. A loose areolar fascial plane lies between the perichondrium and subcutaneous fat. This well-vascularized layer is a continuation of the intrinsic muscles of the ear, and contributes to the mobility of the postauricular skin.

The ear lobule is a soft fibro-fatty cutaneous flap that is suspended from the lower border of the auricular cartilage.



Figure 96.3 Lateral surface of the external ear in its natural orientation. Note the width-to-length ratio of the ear and the height of the ear lobule relative to total ear length.

Blood supply

The ear is supplied by the superficial temporal artery (STA) and the posterior auricular artery (PAA).[2, 9, 11–15] The STA ascends in the preauricular area through the parotid gland and gives rise to one to three branches to the ear. The lower branch supplies the lower margin of the ear lobule, the middle branch the tragus, and the upper branch the ascending helix and the triangular fossa–scapha arterial network. After supplying the ear, the STA ascends to form two terminal branches about 3 cm above the zygomatic arch – the anterior (frontal) and posterior (parietal) branch. These branches supply a fascial layer – the temporoparietal fascia (also called the superficial temporal fascia). This lies superficial to the deep temporal fascia layer, which is supplied by the middle temporal artery – a branch of the STA that arises 1–3 cm below the upper border of the zygomatic arch. See **Figure 96.4**.

The PAA travels towards the scalp in the groove between the mastoid and the cartilage of the posterior EAM, and then continues onto the conchal eminence.

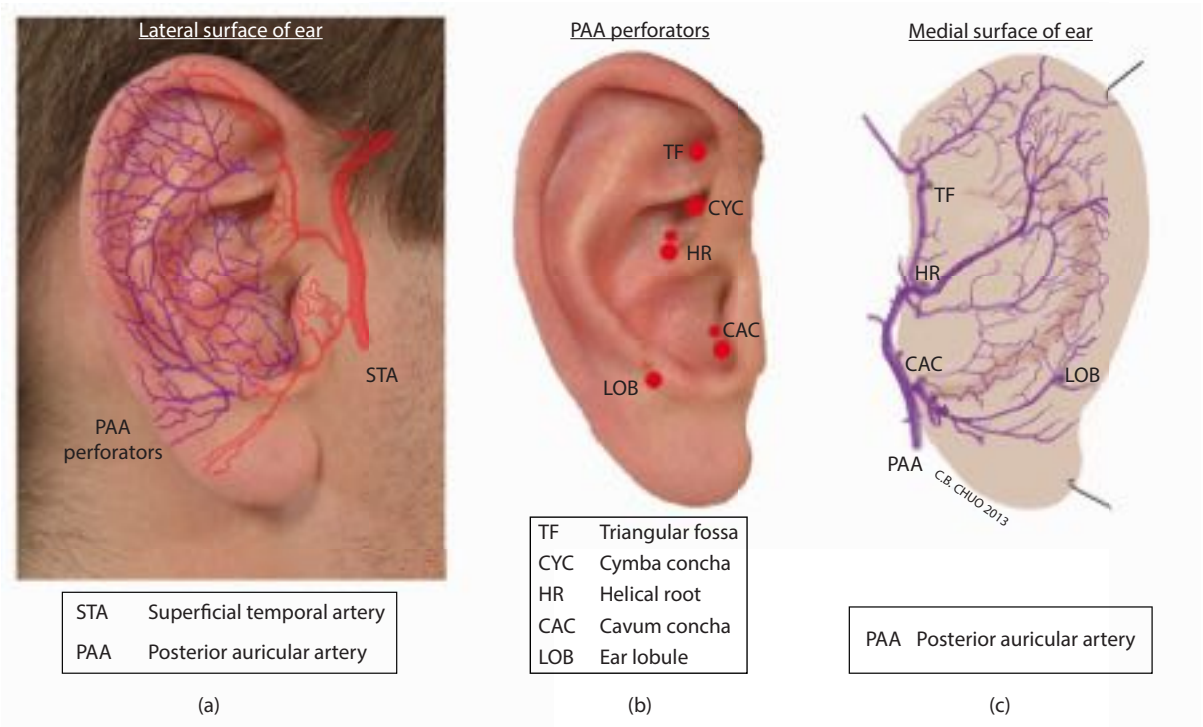


Figure 96.4 The pattern of distribution of the two key arterial networks that supply the skin of the external ear. The superficial temporal artery (STA) provides input to limited areas of the anterior and inferior aspect of the lateral surface, and the remaining ear is supplied by the posterior auricular artery (PAA). Vessels from the PAA perforating the ear cartilage provide a means of communication between the two arterial networks on the lateral and medial surfaces of the ear.

The lower division supplies the posterior surface of the ear lobule, minor posterior branches supply the mastoid fascia and the middle and upper divisions supply the middle and upper thirds of the medial surface of the ear. Perforating branches of the PAA form during its course over the medial surface of the concha. These traverse the cartilage and supply the lateral surface of the ear at key areas: the outer border of the antitragus, cavum concha, helical crus, cymba concha and triangular fossa.

Two main arterial networks formed by communicating branches from the STA and PAA are present on the lateral surface of the ear. The triangular fossa–scapha network is primarily formed from the STA and the conchal network is dominated by perforating branches of the PAA. The upper branch of the STA also communicates with the upper division of the PAA on the superior medial surface of the ear. These networks supply the skin via well-developed subpapillary (intradermal) and the subdermal plexus.

The venous drainage of the ear via the superficial temporal system is variable, whereas the drainage to the posterior auricular system is predictable via the venae comitantes accompanying the PAA.

EAR RECONSTRUCTION

A number of factors need to be considered to determine the most appropriate technique of reconstruction in patients who have congenital and acquired ear deformities and defects. The reconstructive surgeon needs to understand the aetiology of the defects and whether cartilage and/or skin are involved in partial ear defects. Account needs to be taken of whether ear deformities are unilateral or bilateral, the condition of the soft tissues local to the site of the intended reconstruction, the degree of function of the middle and inner ear, the age of the patient, the availability of costal cartilage for framework construction and the patient's preferences for reconstruction.

Indications for ear reconstruction

Patients with complex congenital ear deformities, including those with microtia and anotia, are candidates for total ear reconstruction. Partial ear reconstruction may be indicated in congenital (e.g. lop ear deformity) and acquired deformities involving up to two-thirds of the ear. Trauma (e.g. bite injuries, avulsions and burns) and cancer are common causes of acquired partial or total ear loss requiring ear reconstruction.

Multidisciplinary care

Ear reconstruction is best managed within the setting of a multidisciplinary team comprising plastic surgeons, maxillofacial prosthetists, otolaryngologists, audiologists, radiologists, clinical psychologists and speech and language therapists. This allows the patient and their family to be provided with all possible avenues for reconstruction including prosthetic and autologous ear reconstruction. Imaging of the ear and options for optimizing hearing in patients with hearing loss can also be offered. Clinical psychologists are able to counsel patients with pre-existing psychiatric conditions and assist with the management of patient expectations for future reconstruction.

Surgical goals of ear reconstruction

The aim of total ear reconstruction is to create a contoured replacement structure, with natural proportions, located and orientated in an ideal position on the side of the head. This should appear symmetrical in appearance and location to the opposite normal ear if the reconstruction is unilateral. It is particularly important to replicate key features of the surface anatomy of the lateral ear. The reconstructed ear should also be elevated posteriorly away from the side of the head, to produce symmetrical ear projection and to re-create a post-auricular sulcus.

In practice, the individual aesthetic preference of the patient, the desire for and acceptance of a longer recovery time required for autologous reconstruction influence the agreed plan for correction of the ear deficit or deformity. Furthermore, any autologous reconstruction that is offered is tempered by the need for and available options for structural replacement and soft tissue cover.

Clinical assessment

As part of their clinical assessment[16] the multidisciplinary team should note the patient's general medical health and medications. Medical history of cardiorespiratory disease, diabetes, hypertension and immunodeficiency need to be considered in terms of fitness for surgery and the risk of complications afterwards. Use of aspirin, steroids, warfarin, immunosuppressive agents, tobacco and recreational drugs are documented. Previous procedures on the ears and chest, including operations for ear reconstruction, are noted. A history of hypertrophic or keloid scarring is sought. Previous or current psychiatric history may influence the patient's perception of his or her condition and must be documented.

Specific assessment for ear reconstruction is made in these key areas:

- size, nature and location of the ear defect or deformity
- whether defects or deformities are unilateral or bilateral
- symmetry of the size, shape, appearance of the lateral surface of the ear, angle of reclination (rotation from the vertical) and elevation or projection of the ear
- availability and condition of local and regional vascularized tissues for soft-tissue reconstruction
- availability and condition of donor conchal and costal cartilage for structural reconstruction
- audiology assessment
- assessment by a prosthetist
- patient expectations and preferences
- age of the child in congenital deformities.

Clinical photographs of both ears in close-up and in standard frontal, oblique and lateral facial views are taken to document the condition. The size of any partial defect is

measured and the site described in relation to the upper, middle and lower thirds of the ear, and a note is made of key aesthetic contours which are affected. In unilateral deficits, key aspects of the normal ear are measured – ear height, width, angle of reclination and horizontal distance from the lateral canthus. Any deficiency of cartilage structural support or overlying skin is identified. The presence of scars and the quality of the skin over and adjacent to the site of intended reconstruction influence the options available for reconstruction. The STA is palpated along its course to the frontal and parietal branches. Primary sources of cartilage graft for replacement of structural support and framework construction are conchal and costal cartilage. The chest is examined for the presence of scars and the contour of the costal margin. Contralateral ears are examined for the availability of conchal cartilage for unilateral partial reconstruction.

An assessment by the maxillofacial prosthetist is carried out to present the patient with the available prosthetic options for the individual defect or deformity. This may range from osseointegrated implant-based to adhesive-based silastic devices. The required care and maintenance regimen for these prosthetics is described. If autologous ear reconstruction is desired, moulds of the affected and unaffected ears are taken to produce 3D silicone models for planning surgical reconstruction.

The reconstructive preference of the patient is sought, and his or her expectation of the outcome of surgery is evaluated against the achievable result. Unrealistic expectations of the outcome of reconstructive surgery are a relative contraindication to proceed. Caution against surgery is also advised in patients who exhibit symptoms of body dysmorphic disorder (BDD) and untreated psychiatric conditions.[16]

Special investigations and planning

A chest radiograph is helpful for reviewing the configuration of the ribs in conjunction with the clinical assessment of the costal margin, especially if the patient has had previous chest trauma or thoracic surgery. Patients with extensive local scarring may require a temporoparietal fascial flap as vascularized soft-tissue cover for ear reconstruction. Angiography of the external carotid artery or Doppler ultrasonography is important for assessing the continuity and calibre of the STA.

Two-dimensional templates and 3D models are important for the planning of partial and total ear reconstruction. Templates are typically made from radiographic or acetate film. These may be customized by tracing the outer border, antihelix, superior and inferior crus, tragus and antitragus of the contralateral normal ear (**Figure 96.5**).[17, 18] These images are then reversed to create a basis on which to plan reconstruction. Nagata has designed a series of standardized templates for cartilage framework construction based on key height and width measurements, and Tolleth's described proportions of the ideal ear.[19] An appropriate standardized template for an individual patient is chosen based on the height of the contralateral normal ear (**Figure 96.6**).

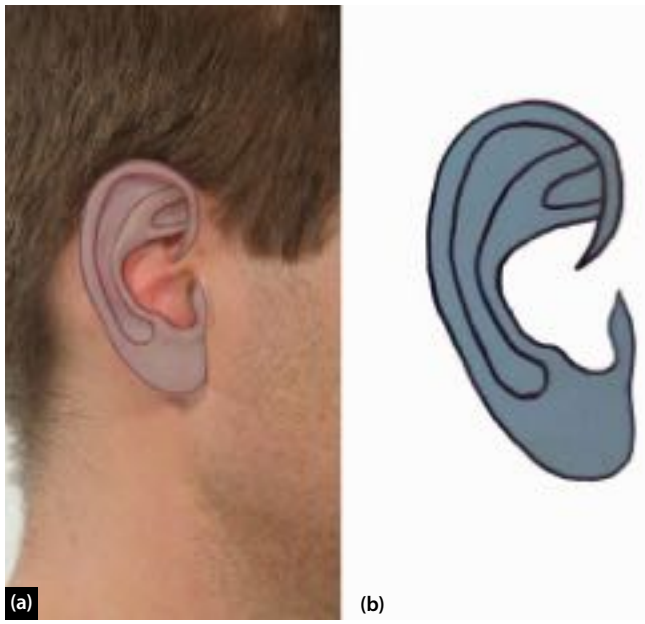


Figure 96.5 **(a)** Customized 2D template, drawn on a semi-transparent film, that highlights the key structures of the ear described in Figure 96.1. **(b)** Overlay of the template on the ear to show that the template provides an accurate depiction of the size and proportions of the ear. The customized template taken from the remaining normal ear and reversed is useful in patients where unilateral reconstruction is required.

Customized templates are helpful in assessing partial ear defects and for unilateral total ear reconstruction. Standardized templates are less sympathetic to the individual features of the contralateral normal ear but support the fabrication of frameworks that can be replicated time and again, and they are helpful in providing a basis for bilateral total ear reconstruction.

Three-dimensional silicone models are made by taking an impression of and replicating the contralateral normal ear, and then creating a mirror image of this model. These models not only recreate the complex depressions and ridges on the lateral surface of the ear but also provide additional information on the degree of projection of the ear. Both templates and models can be sterilized for use intra-operatively as a guide for cartilage framework fabrication and surgical incision design for the creation of soft-tissue cover over the framework.

Principles of ear reconstruction surgery

Partial ear reconstruction may require the replacement of one or both components of cartilage and skin cover. Cartilage support is more important in defects affecting areas that provide length or width stability for the ear framework, such as the helix and antihelix. In addition, cartilage replacement in highly contoured areas on the lateral surface of the ear improves the aesthetic appearance of the reconstruction. Isolated cartilage loss in the concha causes minimal framework instability, hence conchal cartilage is often a preferred source of grafts for reconstruction of small defects.



Figure 96.6 **(a)** Standardized 2D template, with the position and proportions of key structures as described for the ideal ear according to Tolleth.[3] **(b)** Silastic 3D model produced from the remaining normal ear in a patient with unilateral deformity. This may be reversed to act as an intra-operative model during reconstruction. **(c)** Overlay of the template on the ear model to show that the standardized template, although well-proportioned, may not accurately reflect the appearance of the contralateral normal ear.

Costal cartilage is available in larger volume and provides much higher structural rigidity than conchal cartilage. It is thus ideal for framework fabrication in total and subtotal partial ear reconstruction as it is able to withstand the deformational forces generated by scar contracture of the skin and soft tissue used for draping the framework.

Alloplastic materials such as shaped silastic and high-density porous polyethylene implants are also able to provide good mechanical strength when used as support in ear reconstruction. However, the use of silastic ear implants is associated with a significant risk of implant exposure and infection and is therefore not recommended.[20, 21] Porous polyethylene (Medpor®) is a biocompatible material that allows host tissue ingrowth for better tissue integration, but it has also been shown to have a high exposure rate of 44% unless fully enveloped by a large well-vascularized temporoparietal fascial flap, decreasing the rate of exposure to 7%.[22] These implants are also prone to fracture which may be difficult to detect.

Defects of skin only on the medial (cephalic) surface of the ear can usually be repaired by direct advancement of the mobile skin in this area of the ear (see 'Structure' above). A consequence of significant skin advancement in this area is a decrease in projection of the ear, loss of the postauricular sulcus and ear asymmetry. Skin on the lateral surface of the ear is adherent to the underlying perichondrium, thus traumatic lacerations and cancer excisions in this area tend to cause cartilage exposure. Skin defects in this area may be reconstructed by converting it to a full-thickness defect that is closed directly (e.g. a wedge excision if the defect is sited at the helical rim). Alternatively, the underlying cartilage may be excised (e.g. if the defect is sited at the scapha or concha) to produce a vascular bed suitable for a full-thickness skin graft. Skin grafts are ideally harvested from the head and neck area for a better colour match. Caution should be paid to cartilage excision in this way, as there is a high risk of causing a secondary ear deformity if medium to large sections of cartilage are removed which compromise the structural support of the ear.

Skin-cartilage defects and full-thickness defects of the ear may be reconstructed with local, random-pattern cutaneous or chondrocutaneous flaps, which may be used in combination with a structural framework. For example, a large, full-thickness middle-third defect involving the helix and antihelix requires the replacement of contoured cartilage support and flap cover for more than twice the surface area of the skin deficiency. This provides skin cover for the medial surface of the framework, as well as taking into account the increased area required for draping over the ridges and depressions of the lateral surface.

Patients undergoing subtotal and total ear reconstruction require skin or fascial flaps over the ear framework which provides vascularized soft-tissue cover. The amount of cover needed depends on the height, width and depth (thickness) of the framework constructed. A more complex and detailed framework exhibits more anatomically accurate features and may include a conchal bowl, which increases the thickness of the frame and hence the surface area of the soft-tissue cover required. The local hairless mastoid skin at the site of intended reconstruction is the workhorse for frame cover. When this is not available (e.g. in burns) or limited (e.g. in patients with low hairline), then the temporoparietal fascial flap with an overlying skin graft is used to cover the lateral surface of the framework. Usually, there is insufficient vascularized soft tissue to envelope both the lateral and medial surfaces of the framework adequately in a single procedure. Ear reconstruction is therefore often staged and provision of soft-tissue cover for the less visible medial surface is left for a later procedure.

It is essential for skin or fascial flap cover to be well-vascularized, as autologous cartilage frameworks are large avascular grafts containing chondrocytes that rely on the surrounding soft tissues for nutrient and oxygen delivery. Secondary vascularization from these soft tissues also improves framework stability through fibrous scar formation and aids long-term frame retention.

Timing of ear reconstruction

The majority of paediatric ear reconstruction is indicated for congenital deformity and is a primary subtotal or total reconstructive procedure. By 5 years of age the ear of the child achieves 87% of the adult size, and by 12–13 years 98% of adult ear size is reached.[23] The complex nature of the Nagata costal cartilage framework requires a large volume of costal cartilage to fabricate the frame. He proposes that children are offered a two-stage ear reconstruction after the age of 10 years and when they achieve a horizontal chest circumference of ≥60 cm at the level of the xiphoid.[24] Brent believes that the timing of reconstruction should take into account the psychological effect of childhood teasing which starts at 7–10 years of age and the physical growth of the child until a substantial amount of costal cartilage is available.[25] He produces a simpler framework for his three- or four-stage ear reconstruction, and 40% of his patients undergo their first operation at 5–6 years and another 40% at 6–10 years of age. The ability of the child to cooperate with post-operative care is also a key factor in the choice of timing to proceed with reconstruction.

The timing of adult partial ear reconstruction depends on the size and cause of the ear defect, and on patient preference. Reconstruction after cancer excision is dependent on the clearance margins and the need for adjuvant radiotherapy. If primary autologous reconstruction is carried out immediately after tumour excision, adjuvant radiotherapy is deferred for at least 4 weeks to allow time for wound healing and vascularization of the cartilage framework. Delaying ear reconstruction for 12–24 months after cancer removal provides time for regular evaluation for locoregional recurrence in patients with high-risk tumours or narrow excision margins. Traumatic lesions after bite injuries are ideally closed or skin grafted initially due to an increased risk of wound infection. Small defects after traumatic or wide-margin cancer excision benefit from early reconstruction. If delayed reconstruction is planned, a period of 3–6 months will allow time for soft-tissue induration to subside and scarring to mature.

PARTIAL EAR RECONSTRUCTION

It is useful to classify partial defects of the lateral surface into those that affect the upper third, middle third and concha, and the lower third of the ear. Upper-third defects are easily visible and may involve the helix, superior and inferior crus, and superior antihelix, which are features that provide structural support. Priority is given to preservation of the junction of the anterior helix with the scalp, which is important for spectacle retention. Small skin-only defects in the upper third may be closed directly with minimal deformity. Medium-sized lesions may be reconstructed with local skin flaps or converted to a full-thickness triangular excision and a closing chondrocutaneous wedge performed (**Figure 96.7**). The apex of the wedge ideally extends into a depressed area of the lateral ear contour and the cartilage in this area requires debulking as part of a dog-ear reduction. Wedge excision reduces the height and changes the shape of the ear. It also tends to cause a 'cupped' appearance of the auricle, which is corrected by the use of accessory triangles at the apex. In order to minimize altering the shape and prominence of the ear, the Antia-Buch technique is used for helical lesions and advances chondrocutaneous flaps from the crus and tail of the helix into the defect (**Figure 96.8**).[26] The flap encompassing the helical crus is only mobilized using V–Y advancement if the defect is large. Large defects causing substantial loss of ear height and defects associated with the loss or deformity of the helix at the junction of the anterior helix with the temporal scalp will benefit from reconstruction with the use of a cartilage graft for support and appropriate soft-tissue cover. This complex reconstruction can be performed in one or two stages.

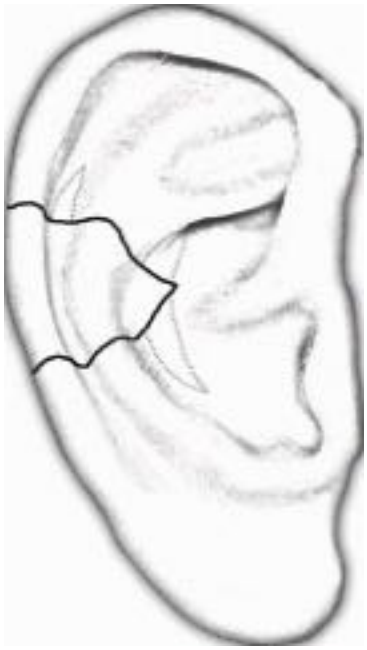


Figure 96.7 Wedge excision with refinements. The apex of the wedge ideally extends into a depressed area of the lateral ear contour and the cartilage in this area requires debulking as part of a dog-ear reduction. Wedge excision reduces the height and changes the shape of the ear. It also tends to cause a 'cupped' appearance of the auricle, which is corrected by the use of accessory triangles at the apex of the wedge.

Defects of the peripheral middle third of the ear involving the helix and antihelix, which provide structural support, are therefore treated differently from isolated defects involving the concha only. Additional cartilage support is not required if either the helical or antihelical ridges remain intact. Options for managing peripheral middle-third defects include:

- direct closure
- wedge excision and closure
- local or regional skin flaps, e.g. bipedicled tubed flap for helical defects, retroauricular (mastoid) flap of Dieffenbach[27]
- helical and conchal chondrocutaneous advancement flaps, e.g. Antia-Buch flap (**Figure 96.8**)



Figure 96.8 Antia-Buch helical chondrocutaneous advancement flap. This composite flap reconstruction is ideal for defects on the outer margin of the upper third of the external ear, and involves local transposition of the crus and anterior helix. Larger defects may require the additional local transposition of the tail and posterior helix, as shown.

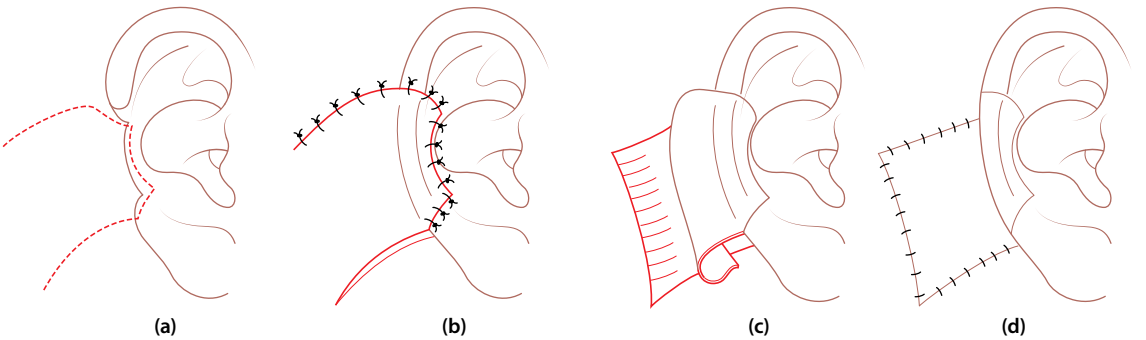


Figure 96.9 Dieffenbach postauricular flap with costal cartilage graft.

- cartilage graft in combination with a local or regional flap, e.g. Dieffenbach flap (**Figure 96.9**).

Skin-only conchal defects can be skin grafted if the perichondrium is intact. Exposed conchal cartilage may be excised to facilitate a vascular bed suitable to receive a skin graft. Due to the depressed contour of the concha, a soft bolster over the inlaid skin graft can be used to ensure adequate contact of the skin graft with the underlying soft-tissue bed. Alternatively, skin and cartilage defects of the concha may be reconstructed with a postauricular revolving-door flap.[28] It is not essential to replace the cartilage in these defects.

Lower-third ear defects include those that affect the earlobe and the antitragus. The antitragus is not a cosmetically sensitive area and isolated lesions here are uncommon. They can usually be managed by cartilage excision and direct closure or local transposition flap. The earlobe contributes significantly to the overall aesthetic appearance of the ear and defects or deformities in this area are often noticed by the patient and surrounding observers. A number of different one- and two-stage techniques utilizing local flaps have been described for earlobe reconstruction. Applying skin graft to lateral defects of the earlobe is less aesthetic and may be associated with graft contracture resulting in a persistent deformity. In order to avoid this, a cartilage batten graft sized and shaped to that of the ideal earlobe is inserted in a subcutaneous pocket deep to the flaps. Grafts used in this way are sourced from the concha, costal cartilage and nasal septum.

AUTOLOGOUS TOTAL EAR RECONSTRUCTION

The key steps for carrying out autologous total ear reconstruction are:

1. Identifying and marking the ideal site for the new ear
2. Making a 2D template and/or a 3D model for cartilage framework fabrication
3. Planning of soft-tissue cover, including skin incisions and flaps at the ideal site for the new ear
4. Costal cartilage harvest

5. Removal of remnant fibrocartilage in microtia or deformed cartilage
6. Dissection and preparation of skin and/or fascial flaps to receive cartilage framework
7. Formation of costal cartilage framework
8. Insertion of framework and inset of overlying soft tissues
9. One or more further stages of ear reconstruction, including framework elevation.

Patients are marked using the upper border of the EAM and inferior orbital margin to determine the Frankfurt horizontal as a line of reference. The upper border of the new ear is marked one ear length posterior to the most lateral point of the eyebrow on a line parallel to the Frankfurt horizontal. The lower border of the new ear should be located at the level of the upper lip, with the ear reclined posteriorly by 20 degrees along its axis.[29]

Costal cartilage for framework fabrication is harvested from the costal margin. The amount of cartilage required is estimated from the features of the template or model. Typically, three or four costal cartilages are used, including an area of synchondrosis from the 6th and 7th costal cartilages. When harvested without perichondrium, the form of the costal margin may be restored by returning diced unused cartilage into the perichondrial sleeves.[30]

Different techniques for autologous ear reconstruction are in use around the world. The most popular current techniques for microtia are those of Brent, Firmin and Nagata, and modifications of these.

The four stages of the **Brent ear reconstruction** technique are shown in **Table 96.1**.[25]

The **Nagata ear reconstruction** technique condenses the steps of the Brent technique into two stages by the utilization of local transposition flaps, with the preservation of a subcutaneous pedicle for the skin flap overlying the cavum concha of the new ear. Nagata also advocates the construction of a detailed and complex costal cartilage framework.[31] Stages of this technique are detailed in **Table 96.2** (see **Figure 96.10**).

Firmin ear reconstruction is a two-stage reconstruction technique adapted from Nagata, but which differs from Nagata in the approach to soft-tissue cover. She describes four types of skin approach for the placement of a cartilage framework in total or subtotal ear reconstruction (**Table 96.3**) and does not utilize any subcutaneous pedicles for the skin flap overlying the framework.[32] Firmin further classifies the costal cartilage framework fabricated according to the structural features that require reconstruction (**Table 96.4**).[32] Two projection pieces are added to the framework to increase the depth of the framework and accentuate the contours of the lateral surface of the new ear. 'P1' links the tragus and helical crus and provides stability to the anterior frame. 'P2' is placed under the base plate deep to the antihelix.

A comparison of the three types of costal cartilage framework is shown in **Figure 96.11**. Costal cartilage frameworks are typically carved with sculpture knives in component parts according to the templates or models and then assembled. These components, such as the helical piece, are held rigidly in place with the use of monofilament 38-gauge stainless steel wires which have high tensile strength and modulus of elasticity. This prevents displacement of the component pieces of the framework and facilitates framework vascularization and fibrous healing. The frames are made smaller than the intended size of ear reconstruction to take into account the thickness of the soft-tissue layer that is draped over it.

The cartilage framework is elevated to create ear projection and a postauricular sulcus as a separate surgical procedure 3–6 months after the frame is inserted. The ear projection produced is better maintained using a costal cartilage strut between the mastoid area and the framework in the postauricular sulcus. Vascularized soft tissue such as the temporoparietal fascial flap with an overlying split-thickness skin graft is used to sustain this cartilage strut. Alternatively, full- or split-thickness skin grafts, with or without mastoid fascial flaps, are used to reconstruct the medial (cranial) surface of the cartilage framework and postauricular sulcus. The latter technique is associated with a higher incidence of retraction of the sulcus so formed, resulting in a loss of ear projection.

TABLE 96.1 The four stages of the Brent ear reconstruction technique

Surgical stage	Description of surgical procedure
1	Carving and insertion of simple two-piece costal cartilage framework at the ideal site for the new ear
2	Ear lobule transposition and insertion of inferior framework into bivalved lobule
3	Framework elevation and full-thickness skin graft to medial surface of the new ear
4	Formation of tragus with contralateral composite conchal cartilage graft and full-thickness skin graft to concha

TABLE 96.2 The two stages of the Nagata ear reconstruction technique

Surgical stage	Description of surgical procedure
1	W-shaped skin incision with central subcutaneous pedicle for creation of neoexternal auditory meatus and local flap for the lateral surface of the earlobe
	Carving and insertion of seven-piece costal cartilage framework at the ideal site for the new ear – includes one tragal piece and two conchal pieces
2	Framework elevation supported in place with two- to four-piece costal cartilage strut
	Posteromedial surface of the new ear and cartilage strut covered with temporoparietal fascial flap and thick split-thickness skin graft

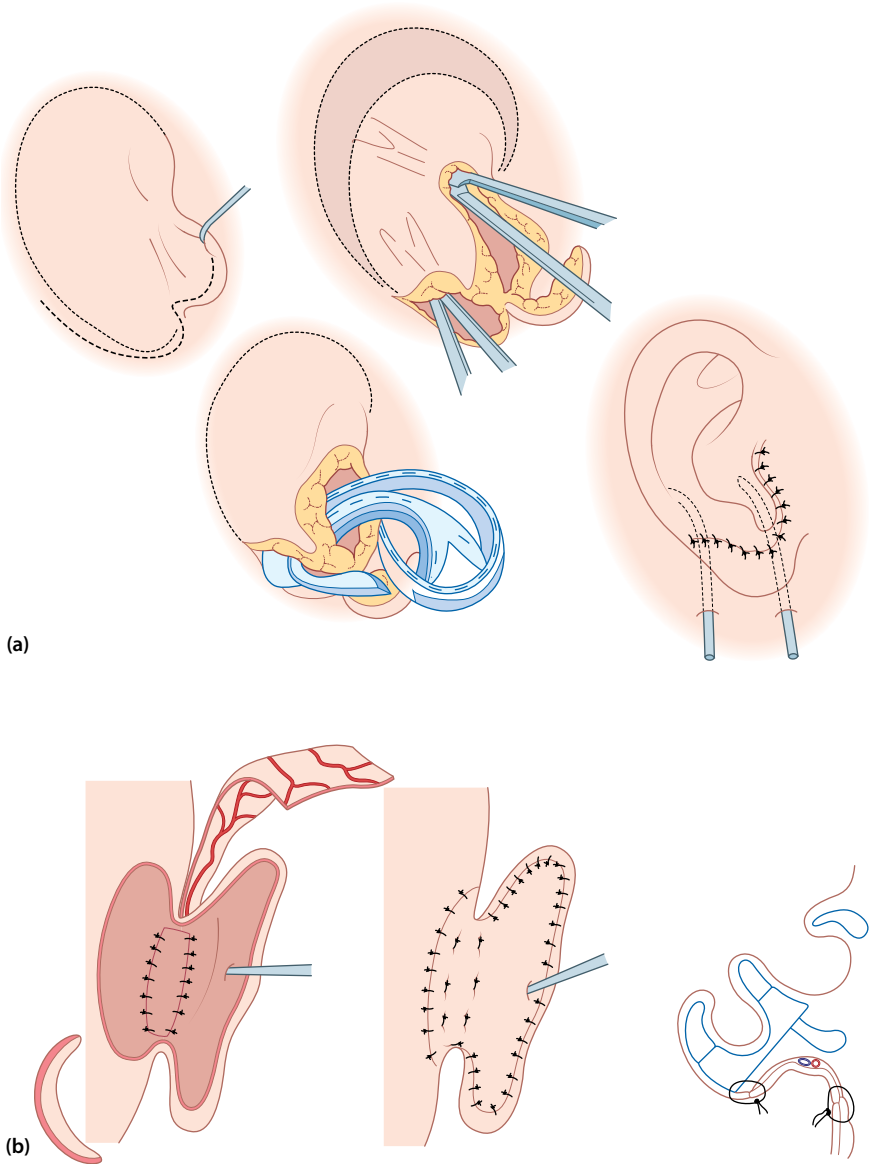


Figure 96.10 Schematic drawing of Nagata two-stage ear reconstruction procedure. (a) First stage, **(b)** second stage.

TABLE 96.3 Classification of the four types of skin approach for the placement of a cartilage framework after Firmin

Type of skin approach	Description of skin incision
1	Z-plasty skin flaps modified from Nagata
2	Transfixion skin flap, where the microtia skin envelope is released superiorly then transposed inferiorly and bivalved to accept the caudal portion of the cartilage framework
3a	Skin incision at the upper scapha of a deformed ear, where there is adequate skin cover for one-stage cover of the lateral and medial surfaces of the ear reconstruction
3b	Skin incision is placed at the anterior border of the microtia skin envelope or the mastoid hairline, where the microtia remnants are absent or not in a position to facilitate transposition or transfixion flaps

TABLE 96.4 Classification of the types of costal cartilage framework after Firmin

Type of cartilage framework	Description of framework
1	Complete framework with antitragus and tragus
2	Framework without tragus
3	Framework without antitragus and tragus

COMPLICATIONS OF EAR RECONSTRUCTION

Soft-tissue necrosis secondary to ischaemia of the covering skin and fascial flaps may occur. As a consequence, exposure of the cartilage framework may ensue that requires timely coverage with available local flaps. Infection of the cartilage framework may result from exposure and

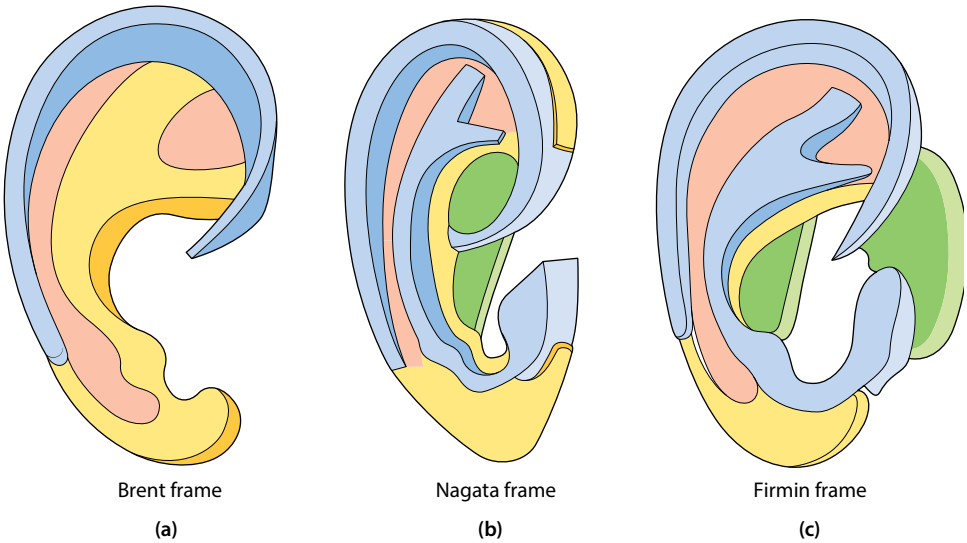


Figure 96.11 Comparison of the Brent, Nagata and Firmin costal cartilage frameworks. **(a)** The Brent framework consists of two layers of carved costal cartilage: a base plate (yellow) from which the antihelix is carved, and a separately carved helical piece (blue) which is then secured to the base plate. Note the concavity of the scapha and triangular fossa (orange) which is used to accentuate the prominence of the antihelix. **(b)** The Nagata framework is more complex and builds upon a carved base plate (yellow) with separately carved helix, antihelix (blue) and tragal (blue) structures which are secured onto the base plate with stainless steel wires. In addition, the root of the helix is anchored deep to the base plate to create depth in the concha and additional carved pieces for the cymba concha and cavum concha (green) are anchored to the underside of the base plate to enhance the 3D features of the reconstructed ear. **(c)** Firmin also uses separately carved pieces of costal cartilage to recreate the helix, antihelix and tragus (blue) on top of a base plate (yellow). However, the tragus produced is of less depth and the root of the helix is less prominent. Two other pieces of cartilage (green) are secured to the underside of the base plate and are used to create depth in the concha (P1) and anchor the positions of the helix and tragus (P2).

is a devastating complication that may require removal of the framework. Wire extrusion from the framework and alopecia along scalp incision scars may also occur. Harvest of costal cartilage grafts is associated with a small risk of pneumothorax which must be checked with a Valsalva manoeuvre before closure of the chest incision.

SUMMARY

- Successful reconstruction of a partial ear defect demands meticulous analysis of the deficit and knowledge of key structural features which would benefit from cartilage replacement.
- Aesthetically pleasing partial ear reconstruction is based upon a sound understanding of the donor sources for cartilage replacement and the available options (based on vascular anatomy) for local skin and fascial flaps.
- Surgeons intending to perform subtotal or total ear reconstruction need to be attentive to details throughout the planning process, including the intended proportions of the new ear.
- Careful consideration should be paid to the formation of an anatomically accurate framework and the design of surgical incisions for local flaps used to protect and sustain it.
- In order to ensure familiarity and competence with the equipment required for autologous ear reconstruction (e.g. stainless steel wires and sculpture knives) and with the handling of the costal cartilage graft used, it is recommended that a period of training is undertaken.

BEST CLINICAL PRACTICE

- ✓ Acquire the appropriate training and expertise.
- ✓ Ideally, work within a multidisciplinary team able to offer the option of prosthetic reconstruction and psychological support.
- ✓ Audit your results.

FUTURE RESEARCH

There is poor quality of evidence available for partial and total ear reconstruction techniques. This is because of the myriad different techniques which have been published, often to address the variable types of partial defects and congenital ear anomalies presenting to the ear reconstruction surgeon. In addition, international standardized outcome measures for surgery are absent, making it difficult to run surgical trials. Further research should involve the development of and consensus for international outcome measures. Subsequent case series using a consistent technique and reporting these outcomes will allow comparison between techniques and centres of excellence.

KEY POINTS

- Intimate knowledge of the anatomy, features and location of the ear is essential for the ear reconstruction surgeon.
- Ear reconstruction is best performed with the support of a multidisciplinary team.
- Partial ear reconstruction should take into account the aesthetic significance of the area to be reconstructed and whether structural support is required for reconstruction.
- Surgery for autologous total ear reconstruction is technically demanding and usually performed in stages.
- An anatomically accurate costal cartilage framework providing structural support and overlying vascularized soft-tissue cover is essential for autologous total ear reconstruction.

ACKNOWLEDGEMENTS

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CHAPTER 97

A COMBINED PROSTHETIC AND SURGICAL APPROACH

Hitesh Koria, M. Stephen Dover and Steve Worrollo

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SEARCH STRATEGY

The references in this chapter are supported by a Medline search and a manual search of maxillofacial technical journals using the key words/phrases facial prostheses, maxillofacial prosthetics, rehabilitation, facial defect, prosthesis and implants and extra-oral implants.

INTRODUCTION

In our increasingly body-conscious society, there is a stigma attached to disfigurement. Acquired facial defects, especially after radical surgical operations, very often result in huge functional, cosmetic and psychological deformity in patients.[1] Complex prosthetic rehabilitation, such as the midface, is necessary as alternative treatment when facial defects cannot be surgically fulfilled.

A team consisting of maxillofacial surgeons, plastic surgeons and restorative dentists play an important part for the success of the final outcomes. Surgical reconstruction of these defects is frequently limited due to unfavourable conditions, such as vascularity following radiotherapy and insufficient residual soft and hard tissues.

Facial prosthesis using dental implants and bars or magnets are the preferred choice of retention methods in the replacement of missing hard and soft facial tissues. Nose, eye and ear form, colouration and texture must be as unnoticeable from the surrounding natural tissues as possible. Rehabilitation efforts can be successful only when patients can appear in public without fear of attracting unwanted attention.

The quality of life of patients with severe deformity or even head and neck cancer patients prior to maxillofacial prosthetic rehabilitation can be low, but little or no evidence is currently available to assess the impact facial prosthetics can have following surgery.

HISTORY

The use of prosthetics has been well documented throughout history. The use of facial prostheses was first reported in ancient Egypt. Evidence documented historically comes from the 16th century,[2] when a French surgeon Ambroise Paré described the first nose prostheses from gold, silver and 'papier mâché', which were held to the face by a string tied around the back of the head.[2]

It was not until the beginning of the 19th century that successful nasal reconstruction was reported in India[3] and only at the end of the 19th century did plastic surgery begin to provide an alternative to facial prosthetics.

In the 20th century, while the quality of realistic craniofacial prostheses was considerably improved with the introduction of silicone materials and greater expectations from patients, the problem of their retention, which is important for aesthetics, function and comfort, was not entirely solved.[4]

Prostheses were used for defects which could not be surgically reconstructed or for patients whose treatment was delayed. Teams of surgeons, working together with dentists,

helped develop new techniques that radically improved the outcome for patients – an early example of multidisciplinary teams, which are now more common in modern-day practice – hence the importance of being treated in a regional centre with specialized surgeons, whether it be for craniofacial, oncological or traumatic rehabilitation.[3]

PATIENT SELECTION

Defects in the craniofacial region can improve the final outcome for patients with facial disfigurement. Careful planning of surgical resections and careful handling of the traumatic defects can influence long-term rehabilitation. The decision to provide a patient with a facial prosthesis should always be carefully evaluated and there are many factors to consider.

Prosthetics should be used to complement reconstructive surgery. The decision to use prostheses rather than autologous materials should be made only after considering all available options. The aetiology of defects is important in deciding the type of treatment and timing of any reconstructive procedures.

The following factors should be considered when planning treatment with facial prosthetics:

- **medical factors** – the patient's physiological status and general health
- **patient factors** – age, dexterity, hygiene, motivation, compliance
- **defect considerations** – use of autogenous tissue, soft-tissue cover, skin condition, defect shape to allow optimum prostheses positioning, availability of bone for implant placement, support for prostheses, facial movement during function, previous radiotherapy.

USE OF IMPLANTS IN PROSTHETICS

Facial

It was Brånemark who first placed a modified extraoral implant for a bone-anchored hearing aid (BAHA) in 1977 and for a bone-anchored auricular prosthesis in 1979.[5]

The benefits of implant-retained prostheses have been recognized for many years and have changed the concepts of maxillofacial prosthetic rehabilitation. Osseointegrated implants are widely used for the retention of orbital, auricular and nasal prostheses. Extraoral implants (3 mm or 4 mm) should generally be used in auricular defects, as the bone in that area is fairly thin, and dental implants used for orbital and nasal defects due to the length of the implant.

Their use reduces the need for adhesives and any related problems such as discolouration and deterioration of the prosthetic material. Osseointegration has allowed predictable retention of prostheses. However, it is not suitable or desirable for all patients and on its own will not guarantee an acceptable aesthetic result. All prosthetic and surgical options need to be evaluated by the team, including the patient, to achieve optimum results.

Osseointegrated implants have various advantages over either adhesive or spectacle-retained prostheses for the reconstruction of facial defects. They provide better retention, so that the prosthesis is properly positioned and the patient can wear it more confidently. There is no skin irritation from adhesive and the prosthesis does not need to have adhesive cleaned off each time it is used, which increases the deterioration of the materials used. The edges of the prosthesis can be made thinner and feathered, blending better into the skin, which offers the patient enhanced aesthetics.

A pre-operative planning meeting with the patient and multidisciplinary team provides the opportunity not only to consider different prosthetic options but also for the patient to ask the prosthetist questions about aftercare, such as cleaning of the abutments and prosthesis. Development and application of osseointegrated implants to facial defects has, in part, changed patient perceptions of facial prosthetics. Implants allow convenient and secure positioning of the prosthesis, leading to greater patient acceptance. Patients like the security, comfort and convenience of implant-retained prostheses, benefits that are not attainable with earlier methods of retention. Surgeons have come to appreciate the reduced need for numerous complex surgical reconstructive procedures in many of these patients.

For large defects, a multidisciplinary approach is recommended, combining flap reconstruction and implant-retained prosthetic rehabilitation to achieve optimal results.

Although implants are the 'gold standard' for rehabilitation, earlier reports have shown that implants are not uniformly successful and the failure rates in some patients/sites are quite high.[4] The failures and complications appear to be site-specific and radiation- and time-dependent, although implants have been used successfully in patients who have had vascularized and non-vascularized bone and soft-tissue grafts to the jaws and facial skeleton.

It has been suggested that careful selection of patients and pre-surgical planning are necessary to achieve predictable outcomes when using primary placement, and close teamwork between oncological surgeons and the maxillofacial prosthetics department is vital.[6]

Midfacial

Midface defects can be divided into two major categories:

- **midface defects**, which include the nose and/or the upper lip
- **lateral defects**, which include the cheek and the orbital contents.

The choice between surgical reconstruction and prosthetic rehabilitation of large facial defects remains a difficult one and depends on the size and aetiology of the defect, as well as on the wishes of the patient. The aims of surgical and prosthetic rehabilitation are for the replacement of missing soft and hard facial structures while giving patients

TABLE 97.1 Comparison of surgical and prosthetic rehabilitation

Rehabilitation	Advantages	Disadvantages
Surgical	Uses patient's own tissue Reconstruction at same time as resection may be possible More acceptable to patient Does not require prosthetic maintenance/ replacements	No visual access for inspection of defect site (for tumour patients) May require multiple procedures Variable aesthetic result: depends on quality of host site Separate donor site often required
Prosthetic	Immediate temporary reconstruction Inspection of defect (tumour patients) Predictable results Easily modifiable Does not preclude future surgical reconstruction Immediate temporary reconstruction	Non-mobile tissue Requires skilled prosthetist Long-term follow-up required Replacement prosthesis required

a better quality of life along with social acceptance. **Table 97.1** summarizes the advantages and disadvantages of surgical and prosthetic rehabilitation.

The use of osseointegration in the midface region can dramatically improve anchorage and enable complex and movable connections to be accommodated within the prostheses.[7]

Placing fixtures at the time of ablative surgery gives great advantages. It significantly reduces the time before prosthetic rehabilitation can commence. Fixtures are placed in bone prior to any radiotherapy, in so doing increasing implant osseointegration and survival rate. Implants are best placed in areas where bone quality has not been compromised and still has a good thickness available. It is often necessary to trim back thin bone to allow placement into thicker denser bone. Intraoral fixtures should always be used to take advantage of as much depth of bone in the premaxilla as possible. It can be advantageous to utilize zygomatic implants which use good quality bone at distant sites.[8] Patients will also generally see the prosthetist as early as possible so that impressions can be taken of the facial structures prior to ablative surgery. This enables a template to be constructed for use as a starting point in reconstructive planning of the lost tissues.

AETIOLOGY OF FACIAL DEFECTS

The diagnoses which are indicated for surgical treatment are divided into three main categories:

- congenital
- trauma
- disease

} acquired

Congenital defects

Congenital defects include the absence of:

- the ear (microtia)
- the nose (arhina)
- the eye and orbits (anoptholima).

In patients with congenital defects, treatment is an elected decision which can only be made by the patient when provided with all the relevant information and the ability to meet and talk to patients previously treated. This gives a balanced, informed view of potential treatment options. It is, of course, possible that the patient may accept the defect, or is unwilling to undergo any possible treatment.

Acquired defects

Acquired traumatic defects include those caused by:

- road traffic accidents
- thermal injuries
- ballistic injuries
- accidental injury
- physical assault.

Acquired surgical defects can be created by removal of benign and malignant tumours. Patients with acquired defects have to come to terms with a sudden change of appearance. Cancer patients will also have the psychological worry of dealing with potential life-threatening conditions, for which the treatment can involve the loss of vital structures and create potential impairment of function, such as sight, hearing, swallowing, speech, taste and smell. Every effort should be made to use the patient's own tissue and, if necessary, surgical procedures are undertaken in stages until the optimum result is obtained. If surgery is not possible (or will involve multiple procedures with an unpredictable result), prosthetics can be considered.

For patients with tumours, the defect size is determined by the amount of tissue that has to be removed during ablative resection. How the defect is left is of paramount importance if a prosthetic is to be used as it will determine the final aesthetic result. Ideally, thin skin cover is always preferable as this allows for an optimum interface between defect and prosthesis. Bulky flaps are to be avoided as they restrict contouring and positioning of prostheses and will not allow mirror imaging of existing structures.

Defect reconstruction

The reconstruction of hard and soft tissues is a combination of medicine and art. Major defects in the craniofacial region have challenged the skills of the reconstructive surgeon. The use of microvascular free-flap transfers of

hard and soft tissue in the mandible, maxilla, cranial and midface regions has greatly improved the outcome for patients. Surgical techniques have advanced using autogenous tissues to replace aesthetically difficult areas, such as the nose and pinna.

There may also be the case where a decision not to reconstruct is made. This allows the clinician to look for evidence of any recurrent disease at the defect site, prior to any secondary reconstruction. Alternatively, the defect may be obliterated with a large, bulky flap to close a large surgical cavity. This can have the advantage of creating an oral–nasal seal to allow patients to talk and eat/swallow without problems but a disadvantage is that it has limited or unacceptable aesthetics.

Craniofacial defects should be reconstructed as soon as the patient's condition allows. This is an important factor for all patients, including those with poor prognosis. With the high standard of autogenous and prosthetic techniques available, it is not acceptable for patients with facial deformity to be precluded from as normal a life as possible.

Small soft-tissue defects are reconstructed by covering with skin grafts, deeper defects by the use of local flaps, with larger defects which usually requiring coverage by free flaps. Bony defects are mainly reconstructed by non-vascularized bone graft, provided there is sufficient soft-tissue coverage in non-irradiated tissue. For defects of both hard and soft tissue, a composite flap containing bone and skin is often used. Skeletal fixation is obtained by use of plates and screws. Sites of composite free flaps include iliac crest, fibula, scapula and radius. Radial forearm flaps have a large surface area of skin to volume; this makes them thin and suitable for both intra- and extraoral mucosal or skin defects. The use of bulky flaps can compromise aesthetics and make prosthetic options impracticable. Smaller, thinner flaps and skin grafting may give coverage without compromising prosthetic possibilities.

TREATMENT USING DIGITAL APPLICATIONS

There have been many developments in materials used for the production of prostheses. The advent of percutaneous osseointegrated implants has dramatically improved the potential for retention of a prosthesis. However, many of the construction methods and mould-making have changed, becoming highly skilled and time-consuming. Each prosthesis is individual and the use of high technology has been difficult to adapt or is not cost-effective in some individual cases.

With advances in software applications (manipulation and design) using computed tomography (CT) data, there are programs available which allow 3D simulation of facial reconstructive methods including osteotomy and distraction procedures. Data from medical scanners (CT, magnetic resonance imaging (MRI)) can be used to reproduce physical models of human anatomy via additive layer manufacture (ALM) or rapid prototyping (RP).

Several techniques exist, the most common being stereolithography. The basic principle of creating a 3D structure is to build an object in layers using the CT data and an optical scanning system that deposits a polymeric resin material to mirror the object on screen one layer at a time onto the 'build bed' until the desired object is completed. Each layer of resin is cured using a high-intensity UV light, ensuring the strength of the model.

It is possible to have individual implant templates for either soft tissue or direct bone contact to allow exact implant placement. Precise anatomical models (3D) made by ALM/RP enable surgeons to view and evaluate their treatment plans. On this physical model, osteotomy lines or drilling holes can be indicated and trial surgery can be undertaken. These models are also used for reconstructive procedures. 3D models act as visual aids for the surgical team, indicating the resection lines and allowing the prosthetics team to pre-bend the reconstruction plates. This allows accurate positioning and fixation of the bony flap in the planned location. The applications of these models can be advantageous in facial reconstruction, the production of obturator prostheses for maxillary defects and designing and planning cranioplasties for skull defects.

Improvements in surgical techniques and the advent of specialization have enabled more accurate and aesthetic reconstructions to be performed. While prosthetic materials continue to be improved and refined, these surgical improvements may render a prosthesis necessary in a more limited format. The necessity of treating tumours by ablative surgery in the future may be reduced by other treatment regimes and therefore the necessity to surgically or prosthetically reconstruct these defects could be reduced.

The use of high-technology and digital imaging in processing complex shapes and patterns is now achievable and readily available. In certain circumstances it can produce moulds and patterns that are difficult to duplicate by conventional methods. It remains to be seen whether the use of advanced technology is cost-effective in individual cases or is just another method of obtaining the same result. As with most new techniques, there is a tendency for overuse, and careful evaluation of each individual case should be balanced to obtain the optimum result and cost-effectiveness of the process. However, it is now an essential and welcome addition to the practice of reconstructive surgical and prosthetic techniques.

TREATMENT PROTOCOL

The treatment of a patient with facial or oral cancer or after disfiguring trauma is a collaborative team effort. Free-tissue transfers are habitually used to reconstruct both the soft tissue and bone defect instantly following the ablative surgery. A selected proportion of patients receive radiation 4–6 weeks post-operatively. The type of radiation therapy prescribed by a radiation oncologist depends on many factors, including:

- type of cancer
- size of the cancer
- location of the cancer

- pathological status, i.e. margins, nodal involvement
- how close the cancer is to normal tissues that are sensitive to radiation
- how far into the body the radiation needs to travel
- the patient's general health and medical history
- whether the patient will have other types of cancer treatment
- other factors, e.g. the patient's age and other medical conditions.

The total radiation dose to the tumour bed depends on the presence or absence of microscopic disease at the surgical margin. Radiation positioners are used extensively, and radiation fields are configured to minimize exposure of the major salivary glands to high doses of irradiation. Radiation dose to bone can often be minimized in areas of proposed implant sites.

As a generalization, 6 weeks after ablative surgery patients would receive radiation therapy for 5–7 weeks. Prostheses are generally made as soon as the healing from reconstructive surgery and radiotherapy permit. Whether implants are inserted at the primary stage of surgery may depend on the need for post-operative radiation therapy. At least three intraoral implants of 7–15 mm in length and 3.75 mm in diameter (orbits and nasal defects) would give adequate retention. Ideal placement of the implants depends upon the skill of the surgeon and, where possible, the prosthetist would advise to achieve the best prosthetic outcome.

DEFECT SITES

Nasal

Nasal defects are predominately as a result of tumour surgery or traumatic loss; congenital absence is an extremely rare condition. The goal of reconstruction is to construct an aesthetically pleasing and 'functional' nose. Autogenous reconstruction must address the underlying cartilaginous support, cutaneous coverage and reconstruction of nasal lining.

Acquired defects produce a variety of midface deformities dependent on the extent of traumatic injury or ablative resection. Smaller defects are easier to reconstruct using autogenous methods. The cosmetic anatomy of the nose is classified in five aesthetic units: dorsum, lateral tip, tip, alar lobule and soft-tissue triangle, as described by Burget and Menick.[9]

The majority of acquired defects are confined to skin. Skin grafts from the postauricular or preauricular area are ideal because of colour and texture match in the proximal two-thirds of the nose. The distal tip requires 'thicker' coverage and is usually best reconstructed with a composite flap.

The decision to reconstruct is dependent on the health of the patient, the quality and availability of donor tissue, the presence of any residual disease and patient choice. The defect may also involve orbital and maxillectomy components, and this should be considered in treatment planning.

If the lip is to be sacrificed, it is essential to reconstruct the competent boundaries if possible. This can be achieved by using nasolabial or free flaps.[10] Prosthetic reconstruction is difficult in these cases because of the mobility of surrounding tissue and the functional seal required for lip competence. Large prostheses can be difficult to stabilize and retain.

Orbital or ocular

Any defect that is confined to the globe is treated with an 'indwelling prosthesis', which sits behind the lids. These prostheses, which are self-retaining, have historically been referred to as 'glass eyes', although in the UK they are now always made in acrylic. Defects including the loss of orbital contents and the lids are more extensive and an orbital prosthesis will often be the treatment of choice.

The loss or absence of an eye may be caused by a congenital defect, irreparable trauma, tumour, a painful blind eye, sympathetic ophthalmia, or the need for histological confirmation of a suspected diagnosis. Orbital diseases are relatively rare but, considering the anatomy of surrounding structures, they present a very serious disorder. Depending on the severity of the situation, the surgical management may include one of three approaches: evisceration, enucleation or exenteration. The majority of patients requiring orbital prostheses have acquired defects as a result of tumour surgery. These can also include defects into the maxilla and or nasal area. There are three types of surgery for which prosthetics are required (**Table 97.2**):

- **Evisceration** is a surgical procedure wherein the intraocular contents of the globe are removed, leaving the sclera, Tenon's capsule, conjunctiva, extraocular muscles and optic nerve undisturbed; the cornea may be retained or excised.
- **Enucleation** is the surgical removal of the globe and a portion of the optic nerve from the orbit.
- **Orbital exenteration** is the removal of the entire orbit, usually involving partial or total removal of the eyelids, and is primarily performed in order to eradicate a malignant orbital tumour.

Specific diagnostics is provided by an ocularist; otorhinolaryngologist and dentist examinations are also suitable. Auxiliary imaging methods are also an indispensable part of the diagnostic procedure. These include X-ray images of the skull in dorsoventral, semiaxial and lateral projection. Ultrasonography, CT and nuclear MRI are also frequently employed. According to the specific diagnosis it is possible

TABLE 97.2 Orbital surgery requiring prostheses

Term	Tissue lost	Solution
Evisceration	Cornea	Hepatic/cosmetic shell
Enucleation	Eye	Artificial eye
Exenteration	Eye and orbital contents	Orbital prostheses

to establish precisely the extent of the damage to the eye and surrounding structures in the orbital area and to determine a medical treatment. In the treatment of solid tumours, radical surgery is usually the first step despite the risk of possible functional and aesthetic defects.

The disfigurement associated with the loss of an eye can cause significant physical and emotional problems. Replacement of the lost eye as soon as possible after healing is necessary to promote physical and psychological healing for the patient and to improve social acceptance.

Prosthetic rehabilitation that restores these facial disfigurements may improve the level of function and self-esteem for patients. However, difficulties with facial prostheses arise due to movable tissue beds, quality of prosthesis retention and associated skin reactions to adhesives. The use of osseointegrated implants in the craniofacial region reduces prosthesis limitations associated with medical-grade adhesives and is a treatment option with high long-term success rates.

Facial prosthesis with three dental implants is a method of choice in the replacement of missing hard and soft orofacial tissues. Prosthesis form, colouration and texture must be as indiscernible from the surrounding natural tissues as possible. Rehabilitation efforts can only be successful when patients can appear in public without fear of attracting unwanted attention. Dental implant support gives the patient confidence in society. An important requirement for successful treatment of such handicapped patients is high-quality osseous tissue of defect margins.

Auricular

The indications for an autogenous auricular versus prosthetic auricular reconstruction with osseointegrated implant-retained prostheses were outlined in literature. The choice between the two techniques depends more on the surgeon's training and tradition than on an analysis of which procedure is preferable in a given clinical situation. For example, most children with microtia in the USA are treated with autogenous techniques. In contrast, the same deformities in the UK are more commonly treated with prosthetics. Patients with post-traumatic or post-ablative auricular defects are more often adults and their defects differ from those of children with congenital deformities in several ways. First, the skin loss and scarring resulting from trauma or previous surgery may make standard autogenous reconstruction difficult. Second, the tragus is frequently preserved in the trauma/ablative patient, making the aesthetics of prosthetic reconstruction much more favourable. The presence of a tragus allows the anterior border of the prosthesis to be hidden, which is a major aesthetic benefit.

The incidence of malformation of the external ear is around 1 : 10 000 live births.[11] Auricular defects frequently appear in combination with those of the external auditory canal and middle ear. Unilateral microtia may be associated with facial malformations involving the first and second branchial arch. Unilateral or bilateral microtia can be part of a bilateral condition, such as mandibular facial disostosis (Treacher Collins syndrome).

Children born with congenital defects can invoke feelings of anxiety and guilt, causing the parents to seek an immediate solution. This should be resisted and reassurance should be given to parents with an explanation of potential treatments available. Delay in treatment will allow sufficient growth to occur for an optimum aesthetic result to be achieved and for the child to understand and be involved in the process.[5]

The introduction of parents to other parents of children with the same condition is very useful in allaying fears that their child was the only one with this condition. Patients are best assessed by a multidisciplinary team, which should include specialists in ENT, maxillofacial, prosthetics and plastic surgery. Depending on the severity of the condition, a variety of treatment options may need to be considered.

The importance of hearing to development should never be overlooked or considered less important than aesthetics. It should be treated as a priority and, if necessary, a BAHA should precede ear reconstruction.

A realistic age for successful prosthetics in children is upward of 10–12 years. Our experience is that, before this age, children are not sufficiently developed physically or psychologically to commit to a long-term treatment regime.

Many patients referred for prosthetics have had disappointing autogenous reconstructions. This should not be used as a reason to prevent this option to be explored further, as cooperation between prosthetics and autogenous reconstruction is vital to achieve a balanced and appropriate treatment for the varied range of patients with auricular defects.[12] There have been great improvements in autogenous reconstructive techniques with major contributions by Brent and Nagata.[13, 14] With improved techniques, more consistent aesthetic results can be achieved, but specialization is as important as technique to achieve these standards. The decision to go for the prosthetic option is easier when an autogenous reconstruction is totally impractical, such as the presence of compromised skin or following tumour resection.

Indications for auricular prostheses include:

- lack of autogenous tissue
- irradiated area
- failed autogenous reconstruction
- cancer resection
- absence of the lower half of the pinna
- microtia
- patient preference
- craniofacial anomaly
- traumatic defect.

Microtia cases can predictably be reconstructed with a prosthesis, but they have the disadvantage of long-term follow-up, and treatment can compromise any future autogenous reconstruction by removal of ear remnants or compromise available soft tissue. The amount of ear left (particularly the lower third) or the position and shape of remnants can make autogenous reconstruction a more viable option. There is a role for both options

in auricular reconstruction and the combination of both autogenous and prosthetic options working to complement each other can only benefit patient treatment regimes.

Once treatment is decided upon, careful planning is required to determine the stages and timing of treatment. The prosthetist should be involved in all stages of treatment if prosthetics is the chosen option.

The auricular region was found to be the most dependable implant site. Patients having implants placed for this defect will possibly benefit from having CT scans. This allows for evaluation of the proposed bone sites in an attempt to maximize implant length. The mastoid air cells frequently pose logistical problems at the most inferior auricular implant sites, and occasionally implant position has to be recalculated. Exposure of the air cells at the time of implant placement does not appear to cause any detrimental effects. If there is adequate bone to provide stability, the implant may be left in position; otherwise, a new site will have to be found. The use of two implants in the auricular region reduces the amount of cantilevering and prevents any rotation of the prosthesis, conferring mechanical advantage. All implants are connected with a gold bar which sits above the skin, and retention is achieved with gold clips. Alternative methods can be used, including magnets and/or adhesives.

Oral cavity

Intraoral prosthetics are well documented in technical and dental literature. This section will only cover prosthetics in relation to ablative surgery.

The management of oral cancer requires understanding and skills in assessment, access and ablative and reconstructive surgery. Prosthetic input may be required in dealing with complex and difficult defects. Removal of soft and hard tissue has a dramatic effect on function; small defects can be closed by local flaps, with free-tissue transfer available for larger defects. While surgical reconstruction has improved and is the treatment of choice, there are occasions when prosthetics is a suitable option or if a surgical reconstruction has failed.

The objective of prosthetic rehabilitation in patients with defects of the orofacial region is the restoration of form, function and appearance. In patients with orofacial cancer, a decision should be made as to whether immediate or staged surgical reconstruction is advocated. If possible, a one-stage procedure should be used. Surgery involving the oral cavity will require pre-operative dental checks and any necessary treatment should be undertaken prior to surgery. When a maxillary resection requires an intermediate obturator, impressions are required pre-operatively to enable design and construction of the plate.

The design needs to consider how the plate is to be retained, the approximate extent of the resection and whether any teeth are to be lost or utilized for retention. The type of dressing/pack is important as the type of pack can affect the design of the plate.

In the maxilla, the bony margins and alveolus should be trimmed parallel. The hard palate pterygoid plates and nasal septum should be examined and cut back to provide a smooth, non-sharp surface and, where possible, covered with local mucosa.

Following a maxillectomy, it is important to remove the coronoid process of the mandible as it can dislodge and break the seal of a definite prosthesis.

The surgical plate is essential to immediately restore speech and mastication and to provide support for soft tissue. It must be possible to modify any prostheses at the time of surgery to accommodate any surgical variations that may be necessary.

The obturator is retained by using skeletal wiring or bone screws through the acrylic plate or by clasping to existing teeth. It is possible to use pourable, expandable silastic foam both as a dressing medium and to provide retention by a mechanical attachment to the plate.[5] This technique requires the dental plate to be held in place and the foam is poured or syringed into the defect from above the plate. The foam will expand to fill the defect and connect with the retentive posts that are incorporated into the underside of the plate. The foam can easily be trimmed with scissors to give a flexible and very accurate fitting 'bung' which obturates the defect and provides support and retention to the plate. It is useful to pour a duplicate foam which can be used in the maxillofacial laboratory to replicate further foams which can be used during the healing phase. With practice and help, the patient can quickly learn to remove the plate and separate the foam component for cleaning. This can be performed until the healing is complete and a definitive prosthesis can be provided. The foam is particularly useful during any radiotherapy treatment as its flexibility makes it easy to fit and it is well tolerated by sensitive tissue.

STAGES IN PROSTHETIC CONSTRUCTION

Various technical stages are involved in the fabrication of prostheses (**Figure 97.1**):

- impression
- pattern
- mould
- processing
- fitting.

These include taking an impression of the defect to create a master cast on which a wax pattern is sculpted. This can be adjusted and aligned on the patient to achieve the desired contour and orientation.

When completed, a two- or three-part mould is constructed and, using the lost wax technique, a void is created which is then replaced by the prosthetic material. The materials of choice are silicone elastomers, which are individually coloured to match patient skin shades.

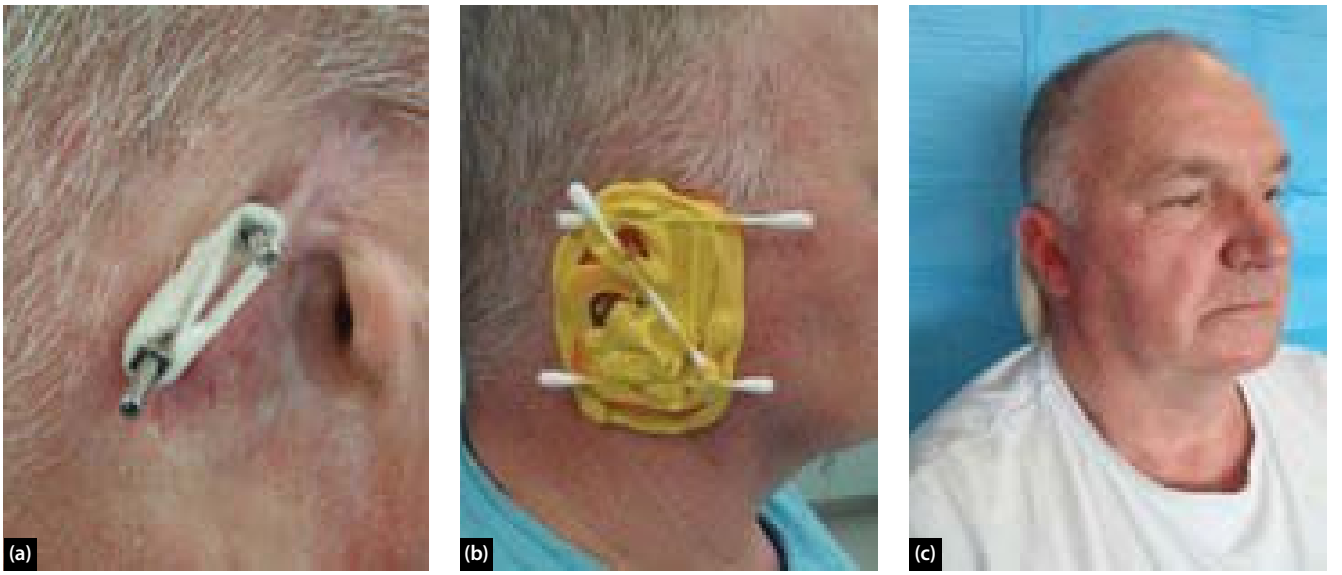


Figure 97.1 Prosthesis construction. (a,b) Impression stage for the fabrication for an ear prosthesis. **(b)** Cotton buds are used to determine the highest and lowest point of the ear to match the opposing side. **(c)** Wax trial of the ear to determine the final position and fit.

FACIAL PROSTHESIS RETENTION METHODS

The success of facial prostheses depends not just on aesthetics but on the retentive qualities. It must be comfortable and give confidence to the wearer. Methods of retention are:

- adhesive
- mechanical/anatomical
- implant.

With some prosthetic devices, retention can be retained by virtue of its anatomical location, for example an artificial eye held in place by the eyelids. This also disguises any margins.

Adhesive

Until the advent of implants, adhesives were often the method of choice for extraoral prostheses, providing good aesthetics if used carefully by a compliant patient. The adhesives used are waterproof and, if correctly applied, the prostheses will remain in position for many hours. Most problems are encountered by the continual fitting and removal of the prostheses. This can have a detrimental effect, particularly on the fine edges of the prostheses. Patients will need a certain amount of dexterity to be able to locate and position the prostheses. The type and quality of the skin can influence the choice of adhesive and the suitability of this technique. Patients with broken or compromised skin are best treated with other retentive methods.

Mechanical/anatomical

Using mechanical retention of facial prostheses is the oldest form of retention. Early retention included spring bands and straps. Current facial prosthetic mechanical methods are generally limited to the use of spectacle frames. Mechanical retention can be incorporated into interlocking intra- and extraoral prosthetic combinations, such as an obturator linked to an orbital prosthesis. Spectacle-retained prostheses are still useful in cases where simplicity and ease of location are of paramount importance. They have a particular application in the elderly and patients who have dexterity problems. The prosthesis is attached to the spectacle frame, which means that the patient is not able to remove their glasses without revealing the defect.

The adjustment of the glasses is important as it will have a direct bearing on the location and fit of the prostheses. Anatomical retention is possible in patients who have favourable undercut tissue areas; soft silicone flanges may be incorporated within a prosthesis to engage these areas.

Obtaining the correct amount of retentive pressure is difficult and care must be exercised not to ulcerate the tissue. This technique is more suited to intraoral defects as obturator-retention extraoral prostheses are more likely to be affected by facial movements, which can cause the loss of margin integrity.

Implant retained

The use of implants provides a stable and secure method of retention which allows very thin prosthesis margins for maximum aesthetics. Used first extraorally in Sweden in 1977, it is an established technique that provides predictable results for patients with various craniofacial defects.[15, 16] Implants allow prostheses to be extremely stable and secure. The prosthesis is generally retained in place by a rigid bar with clips or by magnets incorporated in the prosthesis connecting to magnetic caps on the implant.[17]

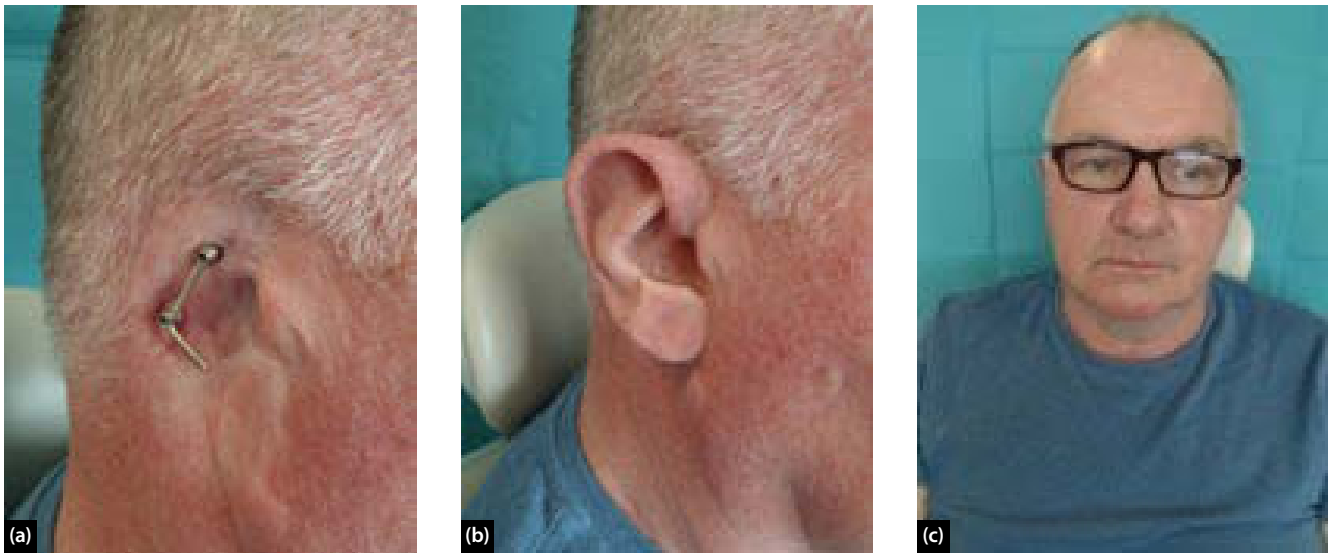


Figure 97.2 Prosthesis retention. (a) Bar design for retention using the bar and clip method. **(b,c)** Finished results.

The number of implants required for retention of the prosthesis is determined by the size and shape of the defect. Auricular defects that involve only the pinna will usually require two implants for adequate retention. This is achieved by a bar splint and clip arrangement (**Figure 97.2**). In cases where bone quality is poor or when tissue is irradiated, it is advisable to place further fixtures as 'sleepers' in case of future failures.

Following fixture placement, the skin-penetrating abutment height and type are determined by the thickness of the tissue and the aesthetic requirements. It can be advisable to place healing abutments initially and then the prosthetist can select the optimum abutment type and size following the healing phase. The abutments are fitted with the appropriate prosthetic components, depending on the retention elements selected for prosthesis attachment. If necessary, angled abutments can be used to aid prosthesis location. In certain cases, prosthetic components can be connected directly to the fixture.

The bar and clip arrangement has the advantage that the clips are adjustable and the bar design can be modified to keep retention components low within the prosthesis. The bar is connected by gold screws into the abutments (**Figure 97.2a**).

Magnets have a role with some patients in auricular cases and retention can be further enhanced by using lip magnets, which have increased resistance to lateral dislodgement. Magnets are particularly useful in orbital and midface cases where bar construction is difficult or complex and location of the prosthesis could be difficult for the patient.

AFTERCARE/PATIENT MANAGEMENT

The choice of prosthetic reconstruction is an ongoing commitment by the prosthetic team and the patient. The patient has to maintain hygiene of the area, particularly if there are skin-penetrating abutments. They have to exercise care in positioning and cleaning the prosthesis and attend for long-term follow-up.

The success of the prosthesis depends on the ability of the prosthetist to design a functional and well-fitting prosthesis. The prosthetist should give instructions on how to position, apply and remove prostheses with any necessary details regarding wearing. It is important that the prosthesis does not restrict the patient's activities and lifestyle. Implant-borne prostheses give the most predictable results but should not be considered the only option.

Dealing with patients with facial disfigurement is very demanding and requires an understanding of patient expectations as well as of what is practical or possible.[18] Patient reactions to facial disfigurement vary greatly. Time spent with patients in consultation is important in building a relationship to enable sensible and practical options to be considered.

Quality-of-life outcomes are now a welcome and vital issue to be considered in patient management.[19] Patients will require lifelong follow-up for maintenance and adjustment of the prostheses, the skin fitting area and implant and abutments in osseointegration cases.[20] The commitment to long-term management must be discussed with the patient.

CASE STUDIES

We would like to thank Mr Nicholas White, Consultant Plastic and Craniofacial Surgeon, University Hospital Birmingham NHS Foundation Trust, for the use of his patients as case studies.

Case study 1

PRESENTATION

In 2011 a 58-year-old female presented with large cylindromas to the scalp, face and ears which had invaded underlying structures (**Figure 97.3**).

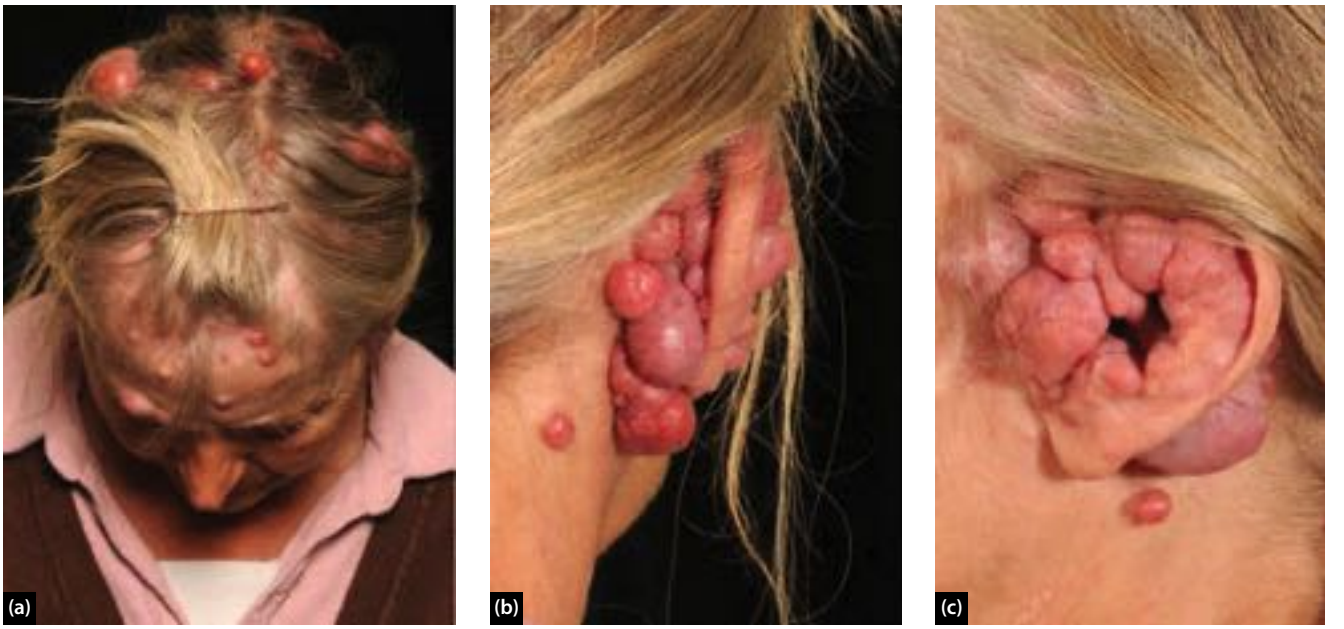


Figure 97.3 Case study 1. The presented cylindroma growth to the scalp and ears.





Figure 97.4 Case study 1. The extent of the lesions pre-operatively.

MEDICAL AND SOCIAL HISTORY

She did not smoke or drink and had no other medical complications. Her manual dexterity was adequate, she had family and was very independent.

IMAGING REPORTS

Imaging reports (CT) showed tumours eroding through the vertex of her skull with a lesion of 12 mm × 12 mm attached to the skull. As a result of the complex nature of this case, multidisciplinary input was required.



Figure 97.5 Case study 1. (a) Post-operative results of the scalp, **(b)** pinnectomy with first-stage implants and **(c)** second-stage implants with healing caps *in situ*.



Figure 97.6 Case study 1. (a–c) Final prosthetic results of the right side. **(d–f)** Final result of the left side. Note the implant position varies due to the bone quality at the time of surgery.

Excision of the lesion on the skull and scalp resulted in a substantial defect requiring soft-tissue reconstruction. A free latissimus dorsi flap was used as the multiple cylindromas had precluded the use of her common soft-tissue flap sites and an anterolateral thigh (ALT) flap was too bulky to be used.

The following surgical risks were explained to the patient:

- a 5% risk of flap failure
- deep vein thrombosis (DVT)
- scarring
- infection
- bleeding.

Her ears were virtually destroyed by the coalescing syringomas and required total pinnectomies of both the left and right ears (bilateral), Again, risks were explained.

PATIENT CONCERNS

The patient had aesthetic concerns about the ears and so a prosthetic consultation was required prior to surgery at which the patient and clinician could discuss the treatment options available and consider the best one for her. At this time it was decided that extraoral implants would be inserted at primary surgery as the quality of bone was good, allowing the final prosthesis to be retained using gold bar and clip. It is important the patient has a full understanding of what is achievable and a realistic time frame from start to finish. As the patient's ears were too distorted in this case, a pre-operative impression was not possible.

With further surgical discussions with the surgeon it was decided that the external auditory meatus was to be left intact. As we know, the implant positioning for prosthetic treatment is vital and so the meatus was used to determine the 'ideal' implant placement.

SURGERY

In 2011 the patient had surgical intervention for the lesions on her scalp (**Figure 97.4**) and a staged pinnectomy of the left ear. The ear was removed and two 4 mm implants (first stage) were inserted into the bone. Early in 2012 a pinnectomy on the right side was performed and two 4 mm implants were inserted on that side.

Once the patient had healed, the second stage of the implants was performed. Here a small 4 mm biopsy punch was used to expose the first-stage implants and a healing abutment was placed. This allowed the prosthetist to assess the skin thickness and replace the healing abutment with definitive abutments. On both the left and right sides a 7 mm abutment was used for the upper implant and a 5.5 mm abutment for the lower implant.

PROSTHETIC RESULT

The patient's prosthetic treatment started in August 2012 and the final prostheses were fitted in October 2012 (**Figure 97.6**).

Case study 2

PRESENTATION

A 75-year-old male presented with local crusting to the left alar in 2008 (**Figure 97.7a**).

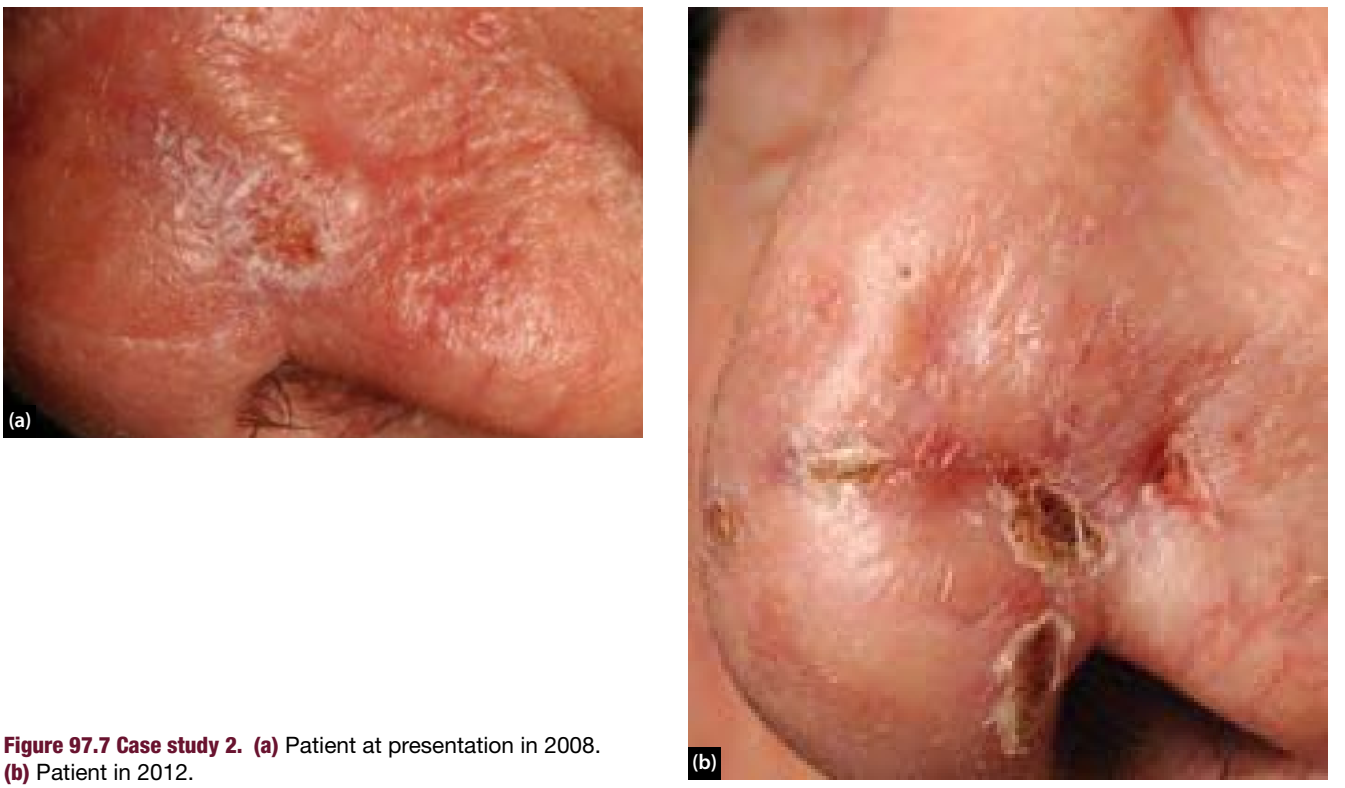


Figure 97.7 Case study 2. (a) Patient at presentation in 2008. **(b)** Patient in 2012.



Figure 97.8 Case study 2. Implants fully integrated with a 10 mm abutment on the left and 7 mm abutment on the right. Both abutments can be seen with multiunit magnacaps attached.

MEDICAL AND SOCIAL HISTORY

The patient was a regular smoker who consumed alcohol in excessive amounts on a daily basis. He also had an abnormal growth in the left lung.

DIAGNOSIS

Recurrent squamous cell carcinoma (SCC) involving the entire dorsum and the tip of the nose was diagnosed.

TREATMENT

Although surgical intervention was discussed and achievable with a combination of flaps, the outcome would be inferior to that of prosthetics treatment. It was concluded that the best possible treatment for this patient was to have a total rhinectomy (total removal of the nose) with the insertion of osseointegrated implants followed with prosthetic rehabilitation.

SURGERY

During the procedure two 7 mm Brånemark (intraoral) implants were inserted in the piriform aperture. The reason









Figure 97.9 Case study 2. (a–c) Final result from prosthetic rehabilitation. Profile left, front and right side respectively. **(d)** The prosthesis allows the patient to wear his glasses, which can be advantageous to help hide the edges of a prosthesis.

was dependent on the bone and space available, ensuring there was no interference with the roots of the teeth. In almost all cases, conventional implants such as those used for intraoral reconstruction are suitable. There are clear advantages to using longer implants in terms of long-term survival and load-carrying ability.

Following his surgery the patient was looked after by a clinical nurse specialist who managed his dressing and helped his healing while the implants integrated. Four months after his surgery, in October 2012, the healing abutments were removed and definitive abutments replaced. The height of the abutments should allow clearance from the cavity wall yet allow space for the magnacaps to be attached to the definitive abutments (**Figure 97.8**).

An impression of the defect was taken, recording the accurate positions of the implants using impression magnets. A nasal profile was waxed up using pictures of the patient before he had the rhinectomy. This was then tried and modified according to the patient's requirements. A colour match of the patient's skin was also taken.

PROSTHETIC RESULT

Figure 97.9 shows the final result from prosthetic rehabilitation.

Case study 3

HISTORY

A 64-year-old female had an ongoing symptom of drooping to the right eye. Her optician recorded further drooping to the right eye 3 years after the initial observation. Aged 67 she also had a neuroendocrine tumour in the pancreas, which was picked up after she developed jaundice. As a result, she had a biliary stent inserted early in 2012.

IMAGING REPORT

MRI demonstrated a growth behind the eye, which was excised as a benign tumour in 2012. The biopsy report identified the growth as a lipoma with atypical feature. Following the excision, the patient developed slow progressive proptosis.

DIAGNOSIS

In October 2012 the patient had a further decrease in her vision and developed diplopia. She had another MRI scan, which showed tumour growth above the eye, and a CT scan was carried out to determine bone involvement. A biopsy of the mass showed a myxoid liposarcoma. After further investigations and further discussion it was

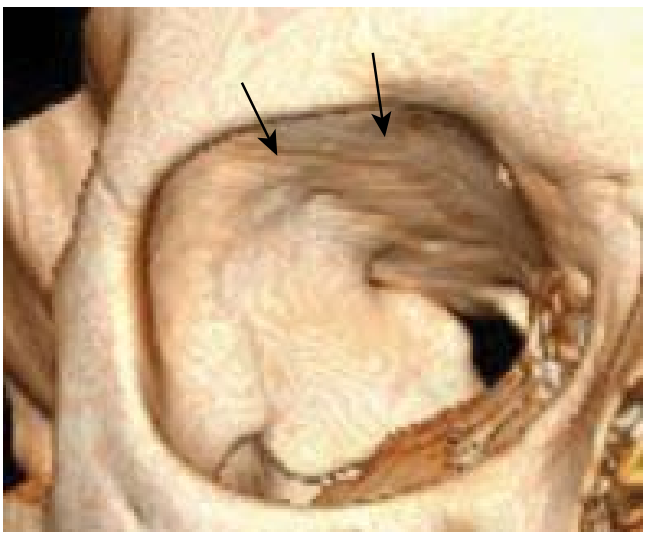


Figure 97.10 Case study 3. Location of the implants.



Figure 97.11 Case study 3. (a,b) The right-sided prosthesis *in situ*. **(c)** The use of glasses helps to draw attention away from the prosthesis.

decided that the best treatment was an orbital exenteration with orbital implants followed by prosthetics.

TREATMENT

In April 2013 the patient had the orbital exenteration and two 7 mm dental implants were inserted into the roof of the orbit and left to integrate.

The second stage of the implants was performed at 2 months post-operatively by placing a 2 mm and a 5 mm abutment to the existing implants.

OUTCOME

The final result is shown in **Figure 97.11**.

FUTURE RESEARCH

- There have been many developments in materials used for the production of prosthesis.
- The advent of percutaneous osseointegrated implants has dramatically improved the potential for retention of prosthesis. However, many of the construction methods and mould making have changed little and are highly skilled and time-consuming. Each prosthesis is individual and the use of high technology has been difficult to adapt or is not cost-effective in some individual cases.
- With advances in computer software using CT data, there are programs available that allow 3D simulation of facial reconstructive methods including osteotomy and distraction procedures. Data from medical scanners (CT, MRI) can be used to reproduce physical models of human anatomy via additive layer manufacture (ALM).
- Several ALM techniques exist, the most common is stereolithography. The basic principle of creating a 3D structure is by building layers using the CT data and an optical scanning system that draws a shape one layer at a time onto the surface of the liquid photosensitive resin until the desired model is completed.
- Over the last few years improvements in surgical techniques with the involvement of in-house surgical guide design and enhanced surgical simulation and planning have enabled more accurate and aesthetic reconstructions to be performed. While prosthetic materials continue to be improved and refined, these surgical improvements may render prosthesis to be necessary in a more limited format. The necessity of treating tumours by ablative surgery in the future may be reduced by other treatment regimes and therefore the necessity to surgically or prosthetically reconstruct these defects could be reduced.
- As 3D printing has evolved to build bony structures we still endeavour to find materials and technology to print in silicone materials with the ability to reproduce patient skin texture and colour which may enhance the prosthetic outcome with a view to giving patients a more realistic understanding of the outcome.

KEY POINTS

- Assess patient psychological status.
- Understand patient expectations.
- Build relationships/rapport with patients.
- Keep prosthesis simple for patients to cope with.
- Understand the reconstruction pathway and patient support.
- Understand the importance of facial aesthetic.

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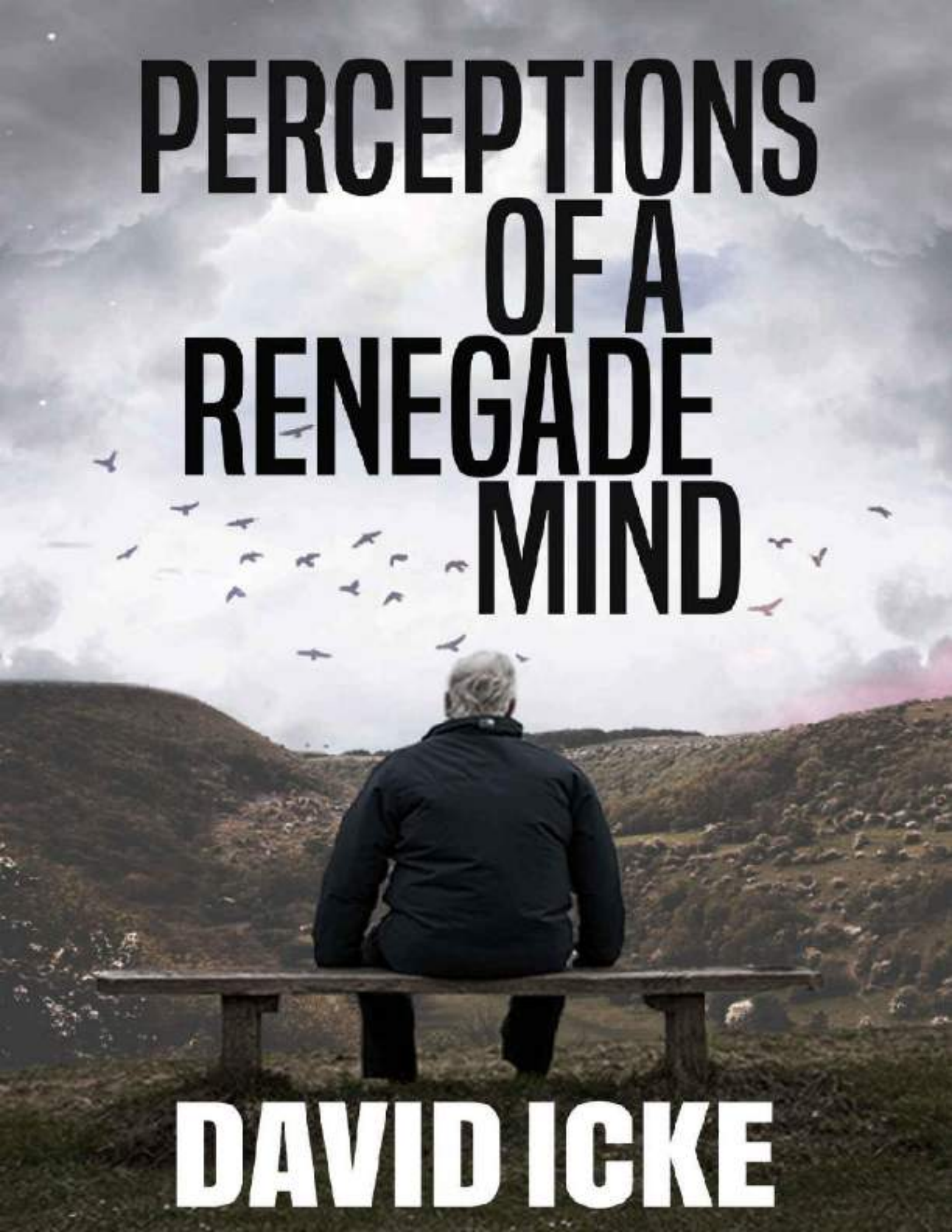
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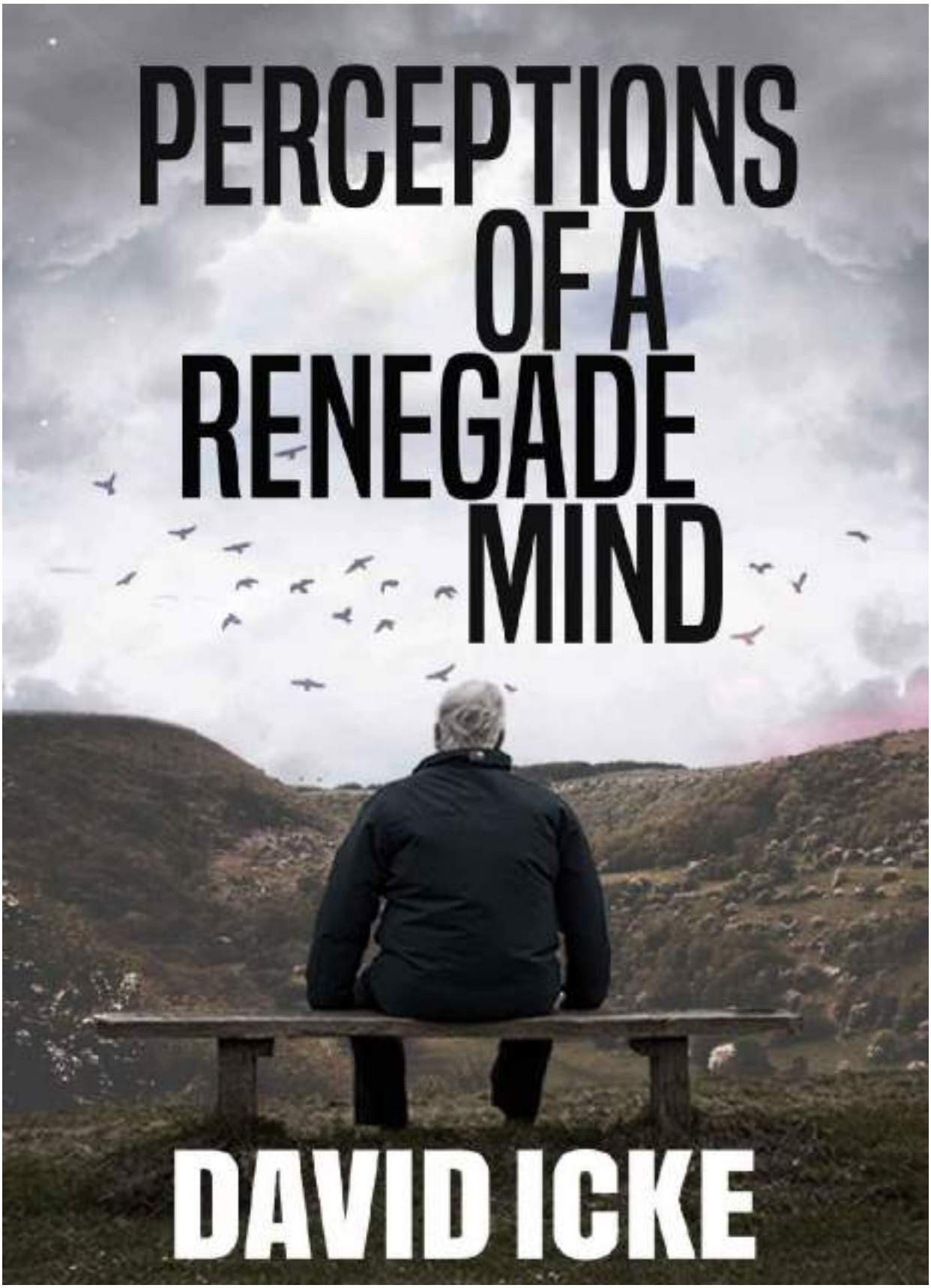
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PERCEPTIONS OF A RENEGADE MIND



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DAVID ICKE

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Renegade:
Adjective
‘Having rejected tradition: Unconventional.’
Merriam-Webster Dictionary

Acquiescence to tyranny is the death of the spirit

You may be 38 years old, as I happen to be. And one day, some great opportunity stands before you and calls you to stand up for some great principle, some great issue, some great cause. And you refuse to do it because you are afraid … You refuse to do it because you want to live longer … You're afraid that you will lose your job, or you are afraid that you will be criticised or that you will lose your popularity, or you're afraid that somebody will stab you, or shoot at you or bomb your house; so you refuse to take the stand.

Well, you may go on and live until you are 90, but you're just as dead at 38 as you would be at 90. And the cessation of breathing in your life is but the belated announcement of an earlier death of the spirit.

Martin Luther King

How the few control the many and always have – the many do whatever they're told

'Forward, the Light Brigade!'
Was there a man dismayed?
Not though the soldier knew
Someone had blundered.
Theirs not to make reply,
Theirs not to reason why,
Theirs but to do and die.
Into the valley of Death
Rode the six hundred.

Cannon to right of them,
Cannon to left of them,
Cannon in front of them
Volleyed and thundered;
Stormed at with shot and shell,
Boldly they rode and well,
Into the jaws of Death,
Into the mouth of hell
Rode the six hundred

Alfred Lord Tennyson (1809-1892)

The mist is lifting slowly
I can see the way ahead
And I've left behind the empty streets
That once inspired my life
And the strength of the emotion
Is like thunder in the air
'Cos the promise that we made each other
Haunts me to the end

The secret of your beauty
And the mystery of your soul
I've been searching for in everyone I meet
And the times I've been mistaken
It's impossible to say
And the grass is growing
Underneath our feet

The words that I remember
From my childhood still are true
That there's none so blind
As those who will not see
And to those who lack the courage
And say it's dangerous to try
Well they just don't know
That love eternal will not be denied

I know you're out there somewhere
Somewhere, somewhere
I know you're out there somewhere

Somewhere you can hear my voice
I know I'll find you somehow
Somehow, somehow
I know I'll find you somehow
And somehow I'll return again to you

The Moody Blues

Are you a gutless wonder - or a Renegade Mind?

Monuments put from pen to paper,
Turns me into a gutless wonder,
And if you tolerate this,
Then your children will be next.
Gravity keeps my head down,
Or is it maybe shame ...

Manic Street Preachers

Rise like lions after slumber
In unvanquishable number.
Shake your chains to earth like dew
Which in sleep have fallen on you.
Ye are many – they are few.

Percy Shelley

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CHAPTER ONE

I'm thinking' – Oh, but *are* you?

Think for yourself and let others enjoy the privilege of doing so too
Voltaire

French-born philosopher, mathematician and scientist René Descartes became famous for his statement in Latin in the 17th century which translates into English as: 'I think, therefore I am.'

On the face of it that is true. Thought reflects perception and perception leads to both behaviour and self-identity. In that sense 'we' are what we think. But who or what is doing the thinking and is thinking the only route to perception? Clearly, as we shall see, 'we' are not always the source of 'our' perception, indeed with regard to humanity as a whole this is rarely the case; and thinking is far from the only means of perception. Thought is the village idiot compared with other expressions of consciousness that we all have the potential to access and tap into. This has to be true when we *are* those other expressions of consciousness which are infinite in nature. We have forgotten this, or, more to the point, been manipulated to forget.

These are not just the esoteric musings of the navel. The whole foundation of human control and oppression is control of perception. Once perception is hijacked then so is behaviour which is dictated by perception. Collective perception becomes collective behaviour and collective behaviour is what we call human society. Perception is all and those behind human control know that which is

why perception is the target 24/7 of the psychopathic manipulators that I call the Global Cult. They know that if they dictate perception they will dictate behaviour and collectively dictate the nature of human society. They are further aware that perception is formed from information received and if they control the circulation of information they will to a vast extent direct human behaviour. Censorship of information and opinion has become globally Nazi-like in recent years and never more blatantly than since the illusory 'virus pandemic' was triggered out of China in 2019 and across the world in 2020. Why have billions submitted to house arrest and accepted fascistic societies in a way they would have never believed possible? Those controlling the information spewing from government, mainstream media and Silicon Valley (all controlled by the same Global Cult networks) told them they were in danger from a 'deadly virus' and only by submitting to house arrest and conceding their most basic of freedoms could they and their families be protected. This monumental and provable lie became the *perception* of the billions and therefore the *behaviour* of the billions. In those few words you have the whole structure and modus operandi of human control. Fear is a perception – **F**alse **E**motion **A**ppearing **R**eal – and fear is the currency of control. In short … get them by the balls (or give them the impression that you have) and their hearts and minds will follow. Nothing grips the dangly bits and freezes the rear-end more comprehensively than fear.

World number 1

There are two 'worlds' in what appears to be one 'world' and the prime difference between them is knowledge. First we have the mass of human society in which the population is maintained in coldly-calculated ignorance through control of information and the 'education' (indoctrination) system. That's all you really need to control to enslave billions in a perceptual delusion in which what are perceived to be *their* thoughts and opinions are ever-repeated mantras that the system has been downloading all their lives through 'education', media, science, medicine, politics and academia

in which the personnel and advocates are themselves overwhelmingly the perceptual products of the same repetition. Teachers and academics in general are processed by the same programming machine as everyone else, but unlike the great majority they never leave the 'education' program. It gripped them as students and continues to grip them as programmers of subsequent generations of students. The programmed become the programmers – the programmed programmers. The same can largely be said for scientists, doctors and politicians and not least because as the American writer Upton Sinclair said: 'It is difficult to get a man to understand something when his salary depends upon his not understanding it.' If your career and income depend on thinking the way the system demands then you will – bar a few free-minded exceptions – concede your mind to the Perceptual Mainframe that I call the Postage Stamp Consensus. This is a tiny band of perceived knowledge and possibility 'taught' (downloaded) in the schools and universities, pounded out by the mainstream media and on which all government policy is founded. Try thinking, and especially speaking and acting, outside of the 'box' of consensus and see what that does for your career in the Mainstream Everything which bullies, harasses, intimidates and ridicules the population into compliance. Here we have the simple structure which enslaves most of humanity in a perceptual prison cell for an entire lifetime and I'll go deeper into this process shortly. Most of what humanity is taught as fact is nothing more than programmed belief. American science fiction author Frank Herbert was right when he said: 'Belief can be manipulated. Only knowledge is dangerous.' In the 'Covid' age belief is promoted and knowledge is censored. It was always so, but never to the extreme of today.

World number 2

A 'number 2' is slang for 'doing a poo' and how appropriate that is when this other 'world' is doing just that on humanity every minute of every day. World number 2 is a global network of secret societies and semi-secret groups dictating the direction of society via

governments, corporations and authorities of every kind. I have spent more than 30 years uncovering and exposing this network that I call the Global Cult and knowing its agenda is what has made my books so accurate in predicting current and past events. Secret societies are secret for a reason. They want to keep their hoarded knowledge to themselves and their chosen initiates and to hide it from the population which they seek through ignorance to control and subdue. The whole foundation of the division between World 1 and World 2 is *knowledge*. What number 1 knows number 2 must not. Knowledge they have worked so hard to keep secret includes (a) the agenda to enslave humanity in a centrally-controlled global dictatorship, and (b) the nature of reality and life itself. The latter (b) must be suppressed to allow the former (a) to prevail as I shall be explaining. The way the Cult manipulates and interacts with the population can be likened to a spider's web. The 'spider' sits at the centre in the shadows and imposes its will through the web with each strand represented in World number 2 by a secret society, satanic or semi-secret group, and in World number 1 – the world of the seen – by governments, agencies of government, law enforcement, corporations, the banking system, media conglomerates and Silicon Valley (Fig 1 overleaf). The spider and the web connect and coordinate all these organisations to pursue the same global outcome while the population sees them as individual entities working randomly and independently. At the level of the web governments *are* the banking system *are* the corporations *are* the media *are* Silicon Valley *are* the World Health Organization working from their inner cores as one unit. Apparently unconnected countries, corporations, institutions, organisations and people are on the *same team* pursuing the same global outcome. Strands in the web immediately around the spider are the most secretive and exclusive secret societies and their membership is emphatically restricted to the Cult inner-circle emerging through the generations from particular bloodlines for reasons I will come to. At the core of the core you would get them in a single room. That's how many people are dictating the direction of human society and its transformation

through the ‘Covid’ hoax and other means. As the web expands out from the spider we meet the secret societies that many people will be aware of – the Freemasons, Knights Templar, Knights of Malta, Opus Dei, the inner sanctum of the Jesuit Order, and such like. Note how many are connected to the Church of Rome and there is a reason for that. The Roman Church was established as a revamp, a rebranding, of the relocated ‘Church’ of Babylon and the Cult imposing global tyranny today can be tracked back to Babylon and Sumer in what is now Iraq.



Figure 1: The global web through which the few control the many. (Image Neil Hague.)

Inner levels of the web operate in the unseen away from the public eye and then we have what I call the cusp organisations located at the point where the hidden meets the seen. They include a series of satellite organisations answering to a secret society founded in London in the late 19th century called the Round Table and among them are the Royal Institute of International Affairs (UK, founded in 1920); Council on Foreign Relations (US, 1921); Bilderberg Group (worldwide, 1954); Trilateral Commission (US/worldwide, 1972); and the Club of Rome (worldwide, 1968) which was created to exploit environmental concerns to justify the centralisation of global power to ‘save the planet’. The Club of Rome instigated with others the human-caused climate change hoax which has led to all the ‘green

new deals' demanding that very centralisation of control. Cusp organisations, which include endless 'think tanks' all over the world, are designed to coordinate a single global policy between political and business leaders, intelligence personnel, media organisations and anyone who can influence the direction of policy in their own sphere of operation. Major players and regular attenders will know what is happening – or some of it – while others come and go and are kept overwhelmingly in the dark about the big picture. I refer to these cusp groupings as semi-secret in that they can be publicly identified, but what goes on at the inner-core is kept very much 'in house' even from most of their members and participants through a fiercely-imposed system of compartmentalisation. Only let them know what they need to know to serve your interests and no more. The structure of secret societies serves as a perfect example of this principle. Most Freemasons never get higher than the bottom three levels of 'degree' (degree of knowledge) when there are 33 official degrees of the Scottish Rite. Initiates only qualify for the next higher 'compartment' or degree if those at that level choose to allow them. Knowledge can be carefully assigned only to those considered 'safe'. I went to my local Freemason's lodge a few years ago when they were having an 'open day' to show how cuddly they were and when I chatted to some of them I was astonished at how little the rank and file knew even about the most ubiquitous symbols they use. The mushroom technique – keep them in the dark and feed them bullshit – applies to most people in the web as well as the population as a whole. Sub-divisions of the web mirror in theme and structure transnational corporations which have a headquarters somewhere in the world dictating to all their subsidiaries in different countries. Subsidiaries operate in their methodology and branding to the same centrally-dictated plan and policy in pursuit of particular ends. The Cult web functions in the same way. Each country has its own web as a subsidiary of the global one. They consist of networks of secret societies, semi-secret groups and bloodline families and their job is to impose the will of the spider and the global web in their particular country. Subsidiary networks control and manipulate the national political system, finance, corporations, media, medicine, etc. to

ensure that they follow the globally-dictated Cult agenda. These networks were the means through which the 'Covid' hoax could be played out with almost every country responding in the same way.

The 'Yessir' pyramid

Compartmentalisation is the key to understanding how a tiny few can dictate the lives of billions when combined with a top-down sequence of imposition and acquiescence. The inner core of the Cult sits at the peak of the pyramidal hierarchy of human society (Fig 2 overleaf). It imposes its will – its agenda for the world – on the level immediately below which acquiesces to that imposition. This level then imposes the Cult will on the level below them which acquiesces and imposes on the next level. Very quickly we meet levels in the hierarchy that have no idea there even is a Cult, but the sequence of imposition and acquiescence continues down the pyramid in just the same way. 'I don't know why we are doing this but the order came from "on-high" and so we better just do it.' Alfred Lord Tennyson said of the cannon fodder levels in his poem *The Charge of the Light Brigade*: 'Theirs not to reason why; theirs but to do and die.' The next line says that 'into the valley of death rode the six hundred' and they died because they obeyed without question what their perceived 'superiors' told them to do. In the same way the population capitulated to 'Covid'. The whole hierarchical pyramid functions like this to allow the very few to direct the enormous many. Eventually imposition-acquiescence-imposition-acquiescence comes down to the mass of the population at the foot of the pyramid. If they acquiesce to those levels of the hierarchy imposing on them (governments/law enforcement/doctors/media) a circuit is completed between the population and the handful of super-psychopaths in the Cult inner core at the top of the pyramid. Without a circuit-breaking refusal to obey, the sequence of imposition and acquiescence allows a staggeringly few people to impose their will upon the entirety of humankind. We are looking at the very sequence that has subjugated billions since the start of 2020. Our freedom has not been taken from us. Humanity has given it

away. Fascists do not impose fascism because there are not enough of them. Fascism is imposed by the population acquiescing to fascism. Put another way allowing their perceptions to be programmed to the extent that leads to the population giving their freedom away by giving their perceptions – their mind – away. If this circuit is not broken by humanity ceasing to cooperate with their own enslavement then nothing can change. For that to happen people have to critically think and see through the lies and window dressing and then summon the backbone to act upon what they see. The Cult spends its days working to stop either happening and its methodology is systematic and highly detailed, but it can be overcome and that is what this book is all about.

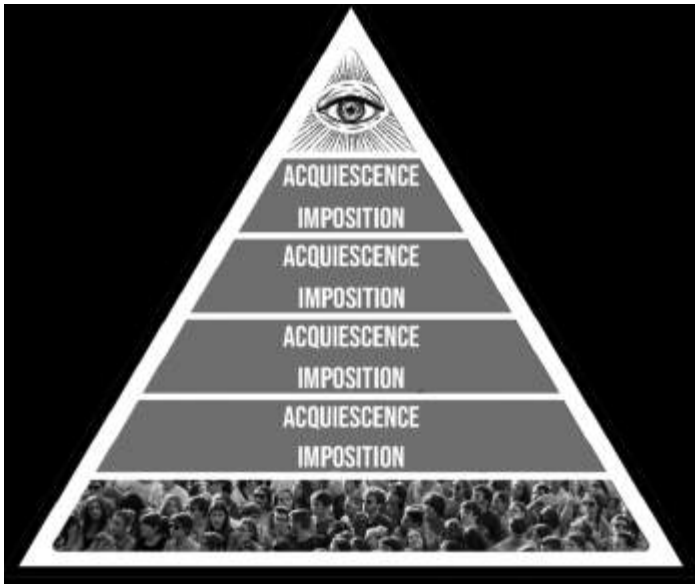


Figure 2: The simple sequence of imposition and compliance that allows a handful of people at the peak of the pyramid to dictate the lives of billions.

The Life Program

Okay, back to world number 1 or the world of the 'masses'. Observe the process of what we call 'life' and it is a perceptual download from cradle to grave. The Cult has created a global structure in which perception can be programmed and the program continually topped-up with what appears to be constant confirmation that the program is indeed true reality. The important word here is 'appears'.

This is the structure, the fly-trap, the Postage Stamp Consensus or Perceptual Mainframe, which represents that incredibly narrow band of perceived possibility delivered by the 'education' system, mainstream media, science and medicine. From the earliest age the download begins with parents who have themselves succumbed to the very programming their children are about to go through. Most parents don't do this out of malevolence and mostly it is quite the opposite. They do what they believe is best for their children and that is what the program has told them is best. Within three or four years comes the major transition from parental programming to full-blown state (Cult) programming in school, college and university where perceptually-programmed teachers and academics pass on their programming to the next generations. Teachers who resist are soon marginalised and their careers ended while children who resist are called a problem child for whom Ritalin may need to be prescribed. A few years after entering the 'world' children are under the control of authority figures representing the state telling them when they have to be there, when they can leave and when they can speak, eat, even go to the toilet. This is calculated preparation for a lifetime of obeying authority in all its forms. Reflex-action fear of authority is instilled by authority from the start. Children soon learn the carrot and stick consequences of obeying or defying authority which is underpinned daily for the rest of their life. Fortunately I daydreamed through this crap and never obeyed authority simply because it told me to. This approach to my alleged 'betters' continues to this day. There can be consequences of pursuing open-minded freedom in a world of closed-minded conformity. I spent a lot of time in school corridors after being ejected from the classroom for not taking some of it seriously and now I spend a lot of time being ejected from Facebook, YouTube and Twitter. But I can tell you that being true to yourself and not compromising your self-respect is far more exhilarating than bowing to authority for authority's sake. You don't have to be a sheep to the shepherd (authority) and the sheep dog (fear of not obeying authority).

The perceptual download continues throughout the formative years in school, college and university while script-reading 'teachers', 'academics' 'scientists', 'doctors' and 'journalists' insist that ongoing generations must be as programmed as they are. Accept the program or you will not pass your 'exams' which confirm your 'degree' of programming. It is tragic to think that many parents pressure their offspring to work hard at school to download the program and qualify for the next stage at college and university. The late, great, American comedian George Carlin said: 'Here's a bumper sticker I'd like to see: We are proud parents of a child who has resisted his teachers' attempts to break his spirit and bend him to the will of his corporate masters.' Well, the best of luck finding many of those, George. Then comes the moment to leave the formal programming years in academia and enter the 'adult' world of work. There you meet others in your chosen or prescribed arena who went through the same Postage Stamp Consensus program before you did. There is therefore overwhelming agreement between almost everyone on the basic foundations of Postage Stamp reality and the rejection, even contempt, of the few who have a mind of their own and are prepared to use it. This has two major effects. Firstly, the consensus confirms to the programmed that their download is really how things are. I mean, everyone knows that, right? Secondly, the arrogance and ignorance of Postage Stamp adherents ensure that anyone questioning the program will have unpleasant consequences for seeking their own truth and not picking their perceptions from the shelf marked: 'Things you must believe without question and if you don't you're a dangerous lunatic conspiracy theorist and a harebrained nutter'.

Every government, agency and corporation is founded on the same Postage Stamp prison cell and you can see why so many people believe the same thing while calling it their own 'opinion'. Fusion of governments and corporations in pursuit of the same agenda was the definition of fascism described by Italian dictator Benito Mussolini. The pressure to conform to perceptual norms downloaded for a lifetime is incessant and infiltrates society right

down to family groups that become censors and condemners of their own 'black sheep' for not, ironically, being sheep. We have seen an explosion of that in the 'Covid' era. Cult-owned global media unleashes its propaganda all day every day in support of the Postage Stamp and targets with abuse and ridicule anyone in the public eye who won't bend their mind to the will of the tyranny. Any response to this is denied (certainly in my case). They don't want to give a platform to expose official lies. Cult-owned-and-created Internet giants like Facebook, Google, YouTube and Twitter delete you for having an unapproved opinion. Facebook boasts that its AI censors delete 97-percent of 'hate speech' before anyone even reports it. Much of that 'hate speech' will simply be an opinion that Facebook and its masters don't want people to see. Such perceptual oppression is widely known as fascism. Even Facebook executive Benny Thomas, a 'CEO Global Planning Lead', said in comments secretly recorded by investigative journalism operation Project Veritas that Facebook is 'too powerful' and should be broken up:

I mean, no king in history has been the ruler of two billion people, but Mark Zuckerberg is … And he's 36. That's too much for a 36-year-old ... You should not have power over two billion people. I just think that's wrong.

Thomas said Facebook-owned platforms like Instagram, Oculus, and WhatsApp needed to be separate companies. 'It's too much power when they're all one together'. That's the way the Cult likes it, however. We have an executive of a Cult organisation in Benny Thomas that doesn't know there is a Cult such is the compartmentalisation. Thomas said that Facebook and Google 'are no longer companies, they're countries'. Actually they are more powerful than countries on the basis that if you control information you control perception and control human society.

I love my oppressor

Another expression of this psychological trickery is for those who realise they are being pressured into compliance to eventually

convince themselves to believe the official narratives to protect their self-respect from accepting the truth that they have succumbed to meek and subservient compliance. Such people become some of the most vehement defenders of the system. You can see them everywhere screaming abuse at those who prefer to think for themselves and by doing so reminding the compliers of their own capitulation to conformity. 'You are talking dangerous nonsense you Covidiot!!' Are you trying to convince me or yourself? It is a potent form of Stockholm syndrome which is defined as: 'A psychological condition that occurs when a victim of abuse identifies and attaches, or bonds, positively with their abuser.' An example is hostages bonding and even 'falling in love' with their kidnappers. The syndrome has been observed in domestic violence, abused children, concentration camp inmates, prisoners of war and many and various Satanic cults. These are some traits of Stockholm syndrome listed at goodtherapy.org:

- Positive regard towards perpetrators of abuse or captor [see 'Covid'].
- Failure to cooperate with police and other government authorities when it comes to holding perpetrators of abuse or kidnapping accountable [or in the case of 'Covid' cooperating with the police to enforce and defend their captors' demands].
- Little or no effort to escape [see 'Covid'].
- Belief in the goodness of the perpetrators or kidnappers [see 'Covid'].
- Appeasement of captors. This is a manipulative strategy for maintaining one's safety. As victims get rewarded – perhaps with less abuse or even with life itself – their appeasing behaviours are reinforced [see 'Covid'].
- Learned helplessness. This can be akin to 'if you can't beat 'em, join 'em'. As the victims fail to escape the abuse or captivity, they may start giving up and soon realize it's just easier for everyone if they acquiesce all their power to their captors [see 'Covid'].

- Feelings of pity toward the abusers, believing they are actually victims themselves. Because of this, victims may go on a crusade or mission to 'save' [protect] their abuser [see the venom unleashed on those challenging the official 'Covid' narrative].
- Unwillingness to learn to detach from their perpetrators and heal. In essence, victims may tend to be less loyal to themselves than to their abuser [*definitely* see 'Covid'].

Ponder on those traits and compare them with the behaviour of great swathes of the global population who have defended governments and authorities which have spent every minute destroying their lives and livelihoods and those of their children and grandchildren since early 2020 with fascistic lockdowns, house arrest and employment deletion to 'protect' them from a 'deadly virus' that their abusers' perceptually created to bring about this very outcome. We are looking at mass Stockholm syndrome. All those that agree to concede their freedom will believe those perceptions are originating in their own independent 'mind' when in fact by conceding their reality to Stockholm syndrome they have by definition conceded any independence of mind. Listen to the 'opinions' of the acquiescing masses in this 'Covid' era and what gushes forth is the repetition of the official version of everything delivered unprocessed, unfiltered and unquestioned. The whole programming dynamic works this way. I must be free because I'm told that I am and so I think that I am.

You can see what I mean with the chapter theme of 'I'm thinking – Oh, but *are* you?' The great majority are not thinking, let alone for themselves. They are repeating what authority has told them to believe which allows them to be controlled. Weaving through this mentality is the fear that the 'conspiracy theorists' are right and this again explains the often hysterical abuse that ensues when you dare to contest the official narrative of anything. Denial is the mechanism of hiding from yourself what you don't want to be true. Telling people what they want to hear is easy, but it's an infinitely greater challenge to tell them what they would rather not be happening.

One is akin to pushing against an open door while the other is met with vehement resistance no matter what the scale of evidence. I don't want it to be true so I'll convince myself that it's not. Examples are everywhere from the denial that a partner is cheating despite all the signs to the reflex-action rejection of any idea that world events in which country after country act in exactly the same way are centrally coordinated. To accept the latter is to accept that a force of unspeakable evil is working to destroy your life and the lives of your children with nothing too horrific to achieve that end. Who the heck wants that to be true? But if we don't face reality the end is duly achieved and the consequences are far worse and ongoing than breaking through the walls of denial today with the courage to make a stand against tyranny.

Connect the dots – but how?

A crucial aspect of perceptual programming is to portray a world in which everything is random and almost nothing is connected to anything else. Randomness cannot be coordinated by its very nature and once you perceive events as random the idea they could be connected is waved away as the rantings of the tinfoil-hat brigade. You can't plan and coordinate random you idiot! No, you can't, but you can hide the coldly-calculated and long-planned behind the *illusion* of randomness. A foundation manifestation of the Renegade Mind is to scan reality for patterns that connect the apparently random and turn pixels and dots into pictures. This is the way I work and have done so for more than 30 years. You look for similarities in people, modus operandi and desired outcomes and slowly, then ever quicker, the picture forms. For instance: There would seem to be no connection between the 'Covid pandemic' hoax and the human-caused global-warming hoax and yet they are masks (appropriately) on the same face seeking the same outcome. Those pushing the global warming myth through the Club of Rome and other Cult agencies are driving the lies about 'Covid' – Bill Gates is an obvious one, but they are endless. Why would the same people be involved in both when they are clearly not connected? Oh, but they

are. Common themes with personnel are matched by common goals. The 'solutions' to both 'problems' are centralisation of global power to impose the will of the few on the many to 'save' humanity from 'Covid' and save the planet from an 'existential threat' (we need 'zero Covid' and 'zero carbon emissions'). These, in turn, connect with the 'dot' of globalisation which was coined to describe the centralisation of global power in every area of life through incessant political and corporate expansion, trading blocks and superstates like the European Union. If you are the few and you want to control the many you have to centralise power and decision-making. The more you centralise power the more power the few at the centre will have over the many; and the more that power is centralised the more power those at the centre have to centralise even quicker. The momentum of centralisation gets faster and faster which is exactly the process we have witnessed. In this way the hoaxed 'pandemic' and the fakery of human-caused global warming serve the interests of globalisation and the seizure of global power in the hands of the Cult inner-circle which is behind 'Covid', 'climate change' *and* globalisation. At this point random 'dots' become a clear and obvious picture or pattern.

Klaus Schwab, the classic Bond villain who founded the Cult's Gates-funded World Economic Forum, published a book in 2020, *The Great Reset*, in which he used the 'problem' of 'Covid' to justify a total transformation of human society to 'save' humanity from 'climate change'. Schwab said: 'The pandemic represents a rare but narrow window of opportunity to reflect, reimagine, and reset our world.' What he didn't mention is that the Cult he serves is behind both hoaxes as I show in my book *The Answer*. He and the Cult don't have to reimagine the world. They know precisely what they want and that's why they destroyed human society with 'Covid' to 'build back better' in their grand design. Their job is not to imagine, but to get humanity to imagine and agree with their plans while believing it's all random. It must be pure coincidence that 'The Great Reset' has long been the Cult's code name for the global imposition of fascism and replaced previous code-names of the 'New World

Order' used by Cult frontmen like Father George Bush and the 'New Order of the Ages' which emerged from Freemasonry and much older secret societies. New Order of the Ages appears on the reverse of the Great Seal of the United States as 'Novus ordo seclorum' underneath the Cult symbol used since way back of the pyramid and all seeing-eye (Fig 3). The pyramid is the hierarchy of human control headed by the illuminated eye that symbolises the force behind the Cult which I will expose in later chapters. The term 'Annuit Coeptis' translates as 'He favours our undertaking'. We are told the 'He' is the Christian god, but 'He' is not as I will be explaining.



Figure 3: The all-seeing eye of the Cult 'god' on the Freemason-designed Great Seal of the United States and also on the dollar bill.

Having you on

Two major Cult techniques of perceptual manipulation that relate to all this are what I have called since the 1990s Problem-Reaction-Solution (PRS) and the Totalitarian Tiptoe (TT). They can be uncovered by the inquiring mind with a simple question: Who benefits? The answer usually identifies the perpetrators of a given action or happening through the concept of 'he who most benefits from a crime is the one most likely to have committed it'. The Latin 'Cue bono?' – Who benefits? – is widely attributed to the Roman orator and statesman Marcus Tullius Cicero. No wonder it goes back so far when the concept has been relevant to human behaviour since

history was recorded. Problem-Reaction-Solution is the technique used to manipulate us every day by covertly creating a problem (or the illusion of one) and offering the solution to the problem (or the illusion of one). In the first phase you create the problem and blame someone or something else for why it has happened. This may relate to a financial collapse, terrorist attack, war, global warming or pandemic, anything in fact that will allow you to impose the 'solution' to change society in the way you desire at that time. The 'problem' doesn't have to be real. PRS is manipulation of perception and all you need is the population to believe the problem is real. Human-caused global warming and the 'Covid pandemic' only have to be *perceived* to be real for the population to accept the 'solutions' of authority. I refer to this technique as NO-Problem-Reaction-Solution. Billions did not meekly accept house arrest from early 2020 because there was a real deadly 'Covid pandemic' but because they perceived – believed – that to be the case. The antidote to Problem-Reaction-Solution is to ask who benefits from the proposed solution. Invariably it will be anyone who wants to justify more control through deletion of freedom and centralisation of power and decision-making.

The two world wars were Problem-Reaction-Solutions that transformed and realigned global society. Both were manipulated into being by the Cult as I have detailed in books since the mid-1990s. They dramatically centralised global power, especially World War Two, which led to the United Nations and other global bodies thanks to the overt and covert manipulations of the Rockefeller family and other Cult bloodlines like the Rothschilds. The UN is a stalking horse for full-blown world government that I will come to shortly. The land on which the UN building stands in New York was donated by the Rockefellers and the same Cult family was behind Big Pharma scalpel and drug 'medicine' and the creation of the World Health Organization as part of the UN. They have been stalwarts of the eugenics movement and funded Hitler's race-purity expert' Ernst Rudin. The human-caused global warming hoax has been orchestrated by the Club of Rome through the UN which is

manufacturing both the 'problem' through its Intergovernmental Panel on Climate Change and imposing the 'solution' through its Agenda 21 and Agenda 2030 which demand the total centralisation of global power to 'save the world' from a climate hoax the United Nations is itself perpetrating. What a small world the Cult can be seen to be particularly among the inner circles. The bedfellow of Problem-Reaction-Solution is the Totalitarian Tiptoe which became the Totalitarian Sprint in 2020. The technique is fashioned to hide the carefully-coordinated behind the cover of apparently random events. You start the sequence at 'A' and you know you are heading for 'Z'. You don't want people to know that and each step on the journey is presented as a random happening while all the steps strung together lead in the same direction. The speed may have quickened dramatically in recent times, but you can still see the incremental approach of the Tiptoe in the case of 'Covid' as each new imposition takes us deeper into fascism. Tell people they have to do this or that to get back to 'normal', then this and this and this. With each new demand adding to the ones that went before the population's freedom is deleted until it disappears. The spider wraps its web around the flies more comprehensively with each new diktat. I'll highlight this in more detail when I get to the 'Covid' hoax and how it has been pulled off. Another prime example of the Totalitarian Tiptoe is how the Cult-created European Union went from a 'free-trade zone' to a centralised bureaucratic dictatorship through the Tiptoe of incremental centralisation of power until nations became mere administrative units for Cult-owned dark suits in Brussels.

The antidote to ignorance is knowledge which the Cult seeks vehemently to deny us, but despite the systematic censorship to that end the Renegade Mind can overcome this by vociferously seeking out the facts no matter the impediments put in the way. There is also a method of thinking and perceiving – *knowing* – that doesn't even need names, dates, place-type facts to identify the patterns that reveal the story. I'll get to that in the final chapter. All you need to know about the manipulation of human society and to what end is still out there – *at the time of writing* – in the form of books, videos

and websites for those that really want to breach the walls of programmed perception. To access this knowledge requires the abandonment of the mainstream media as a source of information in the awareness that this is owned and controlled by the Cult and therefore promotes mass perceptions that suit the Cult. Mainstream media lies all day, every day. That is its function and very reason for being. Where it does tell the truth, here and there, is only because the truth and the Cult agenda very occasionally coincide. If you look for fact and insight to the BBC, CNN and virtually all the rest of them you are asking to be conned and perceptually programmed.

Know the outcome and you'll see the journey

Events seem random when you have no idea where the world is being taken. Once you do the random becomes the carefully planned. Know the outcome and you'll see the journey is a phrase I have been using for a long time to give context to daily happenings that appear unconnected. Does a problem, or illusion of a problem, trigger a proposed 'solution' that further drives society in the direction of the outcome? Invariably the answer will be yes and the random – *abracadabra* – becomes the clearly coordinated. So what is this outcome that unlocks the door to a massively expanded understanding of daily events? I will summarise its major aspects – the fine detail is in my other books – and those new to this information will see that the world they thought they were living in is a very different place. The foundation of the Cult agenda is the incessant centralisation of power and all such centralisation is ultimately in pursuit of Cult control on a global level. I have described for a long time the planned world structure of top-down dictatorship as the Hunger Games Society. The term obviously comes from the movie series which portrayed a world in which a few living in military-protected hi-tech luxury were the overlords of a population condemned to abject poverty in isolated 'sectors' that were not allowed to interact. 'Covid' lockdowns and travel bans anyone? The 'Hunger Games' pyramid of structural control has the inner circle of the Cult at the top with pretty much the entire

population at the bottom under their control through dependency for survival on the Cult. The whole structure is planned to be protected and enforced by a military-police state (Fig 4).

Here you have the reason for the global lockdowns of the fake pandemic to coldly destroy independent incomes and livelihoods and make everyone dependent on the 'state' (the Cult that controls the 'states'). I have warned in my books for many years about the plan to introduce a 'guaranteed income' – a barely survivable pittance – designed to impose dependency when employment was destroyed by AI technology and now even more comprehensively at great speed by the 'Covid' scam. Once the pandemic was played and lockdown consequences began to delete independent income the authorities began to talk right on cue about the need for a guaranteed income and a 'Great Reset'. Guaranteed income will be presented as benevolent governments seeking to help a desperate people – desperate as a direct result of actions of the same governments. The truth is that such payments are a trap. You will only get them if you do exactly what the authorities demand including mass vaccination (genetic manipulation). We have seen this theme already in Australia where those dependent on government benefits have them reduced if parents don't agree to have their children vaccinated according to an insane health-destroying government-dictated schedule. Calculated economic collapse applies to governments as well as people. The Cult wants rid of countries through the creation of a world state with countries broken up into regions ruled by a world government and super states like the European Union. Countries must be bankrupted, too, to this end and it's being achieved by the trillions in 'rescue packages' and furlough payments, trillions in lost taxation, and money-no-object spending on 'Covid' including constant all-medium advertising (programming) which has made the media dependent on government for much of its income. The day of reckoning is coming – as planned – for government spending and given that it has been made possible by printing money and not by production/taxation there is inflation on the way that has the

potential to wipe out monetary value. In that case there will be no need for the Cult to steal your money. It just won't be worth anything (see the German Weimar Republic before the Nazis took over). Many have been okay with lockdowns while getting a percentage of their income from so-called furlough payments without having to work. Those payments are dependent, however, on people having at least a theoretical job with a business considered non-essential and ordered to close. As these business go under because they are closed by lockdown after lockdown the furlough stops and it will for everyone eventually. Then what? The 'then what?' is precisely the idea.



Figure 4: The Hunger Games Society structure I have long warned was planned and now the 'Covid' hoax has made it possible. This is the real reason for lockdowns.

Hired hands

Between the Hunger Games Cult elite and the dependent population is planned to be a vicious military-police state (a fusion of the two into one force). This has been in the making for a long time with police looking ever more like the military and carrying weapons to match. The pandemic scam has seen this process accelerate so fast as

lockdown house arrest is brutally enforced by carefully recruited fascist minds and gormless system-servers. The police and military are planned to merge into a centrally-directed world army in a global structure headed by a world government which wouldn't be elected even by the election fixes now in place. The world army is not planned even to be human and instead wars would be fought, primarily against the population, using robot technology controlled by artificial intelligence. I have been warning about this for decades and now militaries around the world are being transformed by this very AI technology. The global regime that I describe is a particular form of fascism known as a technocracy in which decisions are not made by clueless and co-opted politicians but by unelected technocrats – scientists, engineers, technologists and bureaucrats. Cult-owned-and-controlled Silicon Valley giants are examples of technocracy and they already have far more power to direct world events than governments. They are with their censorship *selecting* governments. I know that some are calling the 'Great Reset' a Marxist communist takeover, but fascism and Marxism are different labels for the same tyranny. Tell those who lived in fascist Germany and Stalinist Russia that there was a difference in the way their freedom was deleted and their lives controlled. I could call it a fascist technocracy or a Marxist technocracy and they would be equally accurate. The Hunger Games society with its world government structure would oversee a world army, world central bank and single world cashless currency imposing its will on a microchipped population (Fig 5). Scan its different elements and see how the illusory pandemic is forcing society in this very direction at great speed. Leaders of 23 countries and the World Health Organization (WHO) backed the idea in March, 2021, of a global treaty for 'international cooperation' in 'health emergencies' and nations should 'come together as a global community for peaceful cooperation that extends beyond this crisis'. Cut the Orwellian bullshit and this means another step towards global government. The plan includes a cashless digital money system that I first warned about in 1993. Right at the start of 'Covid' the deeply corrupt Tedros

Adhanom Ghebreyesus, the crooked and merely gofer 'head' of the World Health Organization, said it was possible to catch the 'virus' by touching cash and it was better to use cashless means. The claim was ridiculous nonsense and like the whole 'Covid' mind-trick it was nothing to do with 'health' and everything to do with pushing every aspect of the Cult agenda. As a result of the Tedros lie the use of cash has plummeted. The Cult script involves a single world digital currency that would eventually be technologically embedded in the body. China is a massive global centre for the Cult and if you watch what is happening there you will know what is planned for everywhere. The Chinese government is developing a digital currency which would allow fines to be deducted immediately via AI for anyone caught on camera breaking its fantastic list of laws and the money is going to be programmable with an expiry date to ensure that no one can accrue wealth except the Cult and its operatives.



Figure 5: The structure of global control the Cult has been working towards for so long and this has been enormously advanced by the 'Covid' illusion.

Serfdom is so smart

The Cult plan is far wider, extreme, and more comprehensive than even most conspiracy researchers appreciate and I will come to the true depths of deceit and control in the chapters 'Who controls the

Cult?' and 'Escaping Wetiko'. Even the world that we know is crazy enough. We are being deluged with ever more sophisticated and controlling technology under the heading of 'smart'. We have smart televisions, smart meters, smart cards, smart cars, smart driving, smart roads, smart pills, smart patches, smart watches, smart skin, smart borders, smart pavements, smart streets, smart cities, smart communities, smart environments, smart growth, smart planet ... smart *everything* around us. Smart technologies and methods of operation are designed to interlock to create a global Smart Grid connecting the entirety of human society including human minds to create a centrally-dictated 'hive' mind. 'Smart cities' is code for densely-occupied megacities of total surveillance and control through AI. Ever more destructive frequency communication systems like 5G have been rolled out without any official testing for health and psychological effects (colossal). 5G/6G/7G systems are needed to run the Smart Grid and each one becomes more destructive of body and mind. Deleting independent income is crucial to forcing people into these AI-policed prisons by ending private property ownership (except for the Cult elite). The Cult's Great Reset now openly foresees a global society in which no one will own any possessions and everything will be rented while the Cult would own literally everything under the guise of government and corporations. The aim has been to use the lockdowns to destroy sources of income on a mass scale and when the people are destitute and in unrepayable amounts of debt (problem) Cult assets come forward with the pledge to write-off debt in return for handing over all property and possessions (solution). Everything – literally everything including people – would be connected to the Internet via AI. I was warning years ago about the coming Internet of Things (IoT) in which all devices and technology from your car to your fridge would be plugged into the Internet and controlled by AI. Now we are already there with much more to come. The next stage is the Internet of Everything (IoE) which is planned to include the connection of AI to the human brain and body to replace the human mind with a centrally-controlled AI mind. Instead of perceptions

being manipulated through control of information and censorship those perceptions would come direct from the Cult through AI. What do you think? You think whatever AI decides that you think. In human terms there would be no individual 'think' any longer. Too incredible? The ravings of a lunatic? Not at all. Cult-owned crazies in Silicon Valley have been telling us the plan for years without explaining the real motivation and calculated implications. These include Google executive and 'futurist' Ray Kurzweil who highlights the year 2030 for when this would be underway. He said:

Our thinking ... will be a hybrid of biological and non-biological thinking ... humans will be able to extend their limitations and 'think in the cloud' ... We're going to put gateways to the cloud in our brains ... We're going to gradually merge and enhance ourselves ... In my view, that's the nature of being human – we transcend our limitations.

As the technology becomes vastly superior to what we are then the small proportion that is still human gets smaller and smaller and smaller until it's just utterly negligible.

The sales-pitch of Kurzweil and Cult-owned Silicon Valley is that this would make us 'super-human' when the real aim is to make us post-human and no longer 'human' in the sense that we have come to know. The entire global population would be connected to AI and become the centrally-controlled 'hive-mind' of externally-delivered perceptions. The Smart Grid being installed to impose the Cult's will on the world is being constructed to allow particular locations – even one location – to control the whole global system. From these prime control centres, which absolutely include China and Israel, anything connected to the Internet would be switched on or off and manipulated at will. Energy systems could be cut, communication via the Internet taken down, computer-controlled driverless autonomous vehicles driven off the road, medical devices switched off, the potential is limitless given how much AI and Internet connections now run human society. We have seen nothing yet if we allow this to continue. Autonomous vehicle makers are working with law enforcement to produce cars designed to automatically pull over if they detect a police or emergency vehicle flashing from up to 100 feet away. At a police stop the car would be unlocked and the

window rolled down automatically. Vehicles would only take you where the computer (the state) allowed. The end of petrol vehicles and speed limiters on all new cars in the UK and EU from 2022 are steps leading to electric computerised transport over which ultimately you have no control. The picture is far bigger even than the Cult global network or web and that will become clear when I get to the nature of the 'spider'. There is a connection between all these happenings and the instigation of DNA-manipulating 'vaccines' (which aren't 'vaccines') justified by the 'Covid' hoax. That connection is the unfolding plan to transform the human body from a biological to a synthetic biological state and this is why synthetic biology is such a fast-emerging discipline of mainstream science. 'Covid vaccines' are infusing self-replicating synthetic genetic material into the cells to cumulatively take us on the Totalitarian Tiptoe from Human 1.0 to the synthetic biological Human 2.0 which will be physically and perceptually attached to the Smart Grid to one hundred percent control every thought, perception and deed. Humanity needs to wake up and *fast*.

This is the barest explanation of where the 'outcome' is planned to go but it's enough to see the journey happening all around us. Those new to this information will already see 'Covid' in a whole new context. I will add much more detail as we go along, but for the minutiae evidence see my mega-works, *The Answer, The Trigger* and *Everything You Need to Know But Have Never Been Told*.

Now – how does a Renegade Mind see the 'world'?

CHAPTER TWO

Renegade Perception

It is one thing to be clever and another to be wise
George R.R. Martin

A simple definition of the difference between a programmed mind and a Renegade Mind would be that one sees only dots while the other connects them to see the picture. Reading reality with accuracy requires the observer to (a) know the planned outcome and (b) realise that everything, but *everything*, is connected.

The entirety of infinite reality is connected – that's its very nature – and with human society an expression of infinite reality the same must apply. Simple cause and effect is a connection. The effect is triggered by the cause and the effect then becomes the cause of another effect. Nothing happens in isolation because it *can't*. Life in whatever reality is simple choice and consequence. We make choices and these lead to consequences. If we don't like the consequences we can make different choices and get different consequences which lead to other choices and consequences. The choice and the consequence are not only connected they are indivisible. You can't have one without the other as an old song goes. A few cannot control the world unless those being controlled allow that to happen – cause and effect, choice and consequence. Control – who has it and who doesn't – is a two-way process, a symbiotic relationship, involving the controller and controlled. 'They took my freedom away!!' Well, yes, but you also gave it to them. Humanity is

subjected to mass control because humanity has acquiesced to that control. This is all cause and effect and literally a case of give and take. In the same way world events of every kind are connected and the Cult works incessantly to sell the illusion of the random and coincidental to maintain the essential (to them) perception of dots that hide the picture. Renegade Minds know this and constantly scan the world for patterns of connection. This is absolutely pivotal in understanding the happenings in the world and without that perspective clarity is impossible. First you know the planned outcome and then you identify the steps on the journey – the day-by-day apparently random which, when connected in relation to the outcome, no longer appear as individual events, but as the proverbial *chain* of events leading in the same direction. I'll give you some examples:

Political puppet show

We are told to believe that politics is 'adversarial' in that different parties with different beliefs engage in an endless tussle for power. There may have been some truth in that up to a point – and only a point – but today divisions between 'different' parties are rhetorical not ideological. Even the rhetorical is fusing into one-speak as the parties eject any remaining free thinkers while others succumb to the ever-gathering intimidation of anyone with the 'wrong' opinion. The Cult is not a new phenomenon and can be traced back thousands of years as my books have documented. Its intergenerational initiates have been manipulating events with increasing effect the more that global power has been centralised. In ancient times the Cult secured control through the system of monarchy in which 'special' bloodlines (of which more later) demanded the right to rule as kings and queens simply by birthright and by vanquishing others who claimed the same birthright. There came a time, however, when people had matured enough to see the unfairness of such tyranny and demanded a say in who governed them. Note the word – *governed* them. Not served them – *governed* them, hence government defined as 'the political direction and control exercised over the

actions of the members, citizens, or inhabitants of communities, societies, and states; direction of the affairs of a state, community, etc.' Governments exercise control over rather than serve just like the monarchies before them. Bizarrely there are still countries like the United Kingdom which are ruled by a monarch *and* a government that officially answers to the monarch. The UK head of state and that of Commonwealth countries such as Canada, Australia and New Zealand is 'selected' by who in a *single family* had unprotected sex with whom and in what order. Pinch me it can't be true. Ouch! Shit, it is. The demise of monarchies in most countries offered a potential vacuum in which some form of free and fair society could arise and the Cult had that base covered. Monarchies had served its interests but they couldn't continue in the face of such widespread opposition and, anyway, replacing a 'royal' dictatorship that people could see with a dictatorship 'of the people' hiding behind the concept of 'democracy' presented far greater manipulative possibilities and ways of hiding coordinated tyranny behind the illusion of 'freedom'.

Democracy is quite wrongly defined as government selected by the population. This is not the case at all. It is government selected by *some* of the population (and then only in theory). This 'some' doesn't even have to be the majority as we have seen so often in first-past-the-post elections in which the so-called majority party wins fewer votes than the 'losing' parties combined. Democracy can give total power to a party in government from a minority of the votes cast. It's a sleight of hand to sell tyranny as freedom. Seventy-four million Trump-supporting Americans didn't vote for the 'Democratic' Party of Joe Biden in the distinctly dodgy election in 2020 and yet far from acknowledging the wishes and feelings of that great percentage of American society the Cult-owned Biden government set out from day one to destroy them and their right to a voice and opinion. Empty shell Biden and his Cult handlers said they were doing this to 'protect democracy'. Such is the level of lunacy and sickness to which politics has descended. Connect the dots and relate them to the desired outcome – a world government run by self-appointed technocrats and no longer even elected

politicians. While operating through its political agents in government the Cult is at the same time encouraging public distain for politicians by putting idiots and incompetents in theoretical power on the road to deleting them. The idea is to instil a public reaction that says of the technocrats: 'Well, they couldn't do any worse than the pathetic politicians.' It's all about controlling perception and Renegade Minds can see through that while programmed minds cannot when they are ignorant of both the planned outcome and the manipulation techniques employed to secure that end. This knowledge can be learned, however, and fast if people choose to get informed.

Politics may at first sight appear very difficult to control from a central point. I mean look at the 'different' parties and how would you be able to oversee them all and their constituent parts? In truth, it's very straightforward because of their structure. We are back to the pyramid of imposition and acquiescence. Organisations are structured in the same way as the system as a whole. Political parties are not open forums of free expression. They are hierarchies. I was a national spokesman for the British Green Party which claimed to be a different kind of politics in which influence and power was devolved; but I can tell you from direct experience – and it's far worse now – that Green parties are run as hierarchies like all the others however much they may try to hide that fact or kid themselves that it's not true. A very few at the top of all political parties are directing policy and personnel. They decide if you are elevated in the party or serve as a government minister and to do that you have to be a yes man or woman. Look at all the maverick political thinkers who never ascended the greasy pole. If you want to progress within the party or reach 'high-office' you need to fall into line and conform. Exceptions to this are rare indeed. Should you want to run for parliament or Congress you have to persuade the local or state level of the party to select you and for that you need to play the game as dictated by the hierarchy. If you secure election and wish to progress within the greater structure you need to go on conforming to what is acceptable to those running the hierarchy

from the peak of the pyramid. Political parties are perceptual gulags and the very fact that there are party 'Whips' appointed to 'whip' politicians into voting the way the hierarchy demands exposes the ridiculous idea that politicians are elected to serve the people they are supposed to represent. Cult operatives and manipulation has long seized control of major parties that have any chance of forming a government and at least most of those that haven't. A new party forms and the Cult goes to work to infiltrate and direct. This has reached such a level today that you see video compilations of 'leaders' of all parties whether Democrats, Republicans, Conservative, Labour and Green parroting the same Cult mantra of 'Build Back Better' and the 'Great Reset' which are straight off the Cult song-sheet to describe the transformation of global society in response to the Cult-instigated hoaxes of the 'Covid pandemic' and human-caused 'climate change'. To see Caroline Lucas, the Green Party MP that I knew when I was in the party in the 1980s, speaking in support of plans proposed by Cult operative Klaus Schwab representing the billionaire global elite is a real head-shaker.

Many parties – one master

The party system is another mind-trick and was instigated to change the nature of the dictatorship by swapping 'royalty' for dark suits that people believed – though now ever less so – represented their interests. Understanding this trick is to realise that a single force (the Cult) controls all parties either directly in terms of the major ones or through manipulation of perception and ideology with others. You don't need to manipulate Green parties to demand your transformation of society in the name of 'climate change' when they are obsessed with the lie that this is essential to 'save the planet'. You just give them a platform and away they go serving your interests while believing they are being environmentally virtuous. America's political structure is a perfect blueprint for how the two or multi-party system is really a one-party state. The Republican Party is controlled from one step back in the shadows by a group made up of billionaires and their gofers known as neoconservatives or Neocons.

I have exposed them in fine detail in my books and they were the driving force behind the policies of the imbecilic presidency of Boy George Bush which included 9/11 (see *The Trigger* for a comprehensive demolition of the official story), the subsequent 'war on terror' (war *of* terror) and the invasions of Afghanistan and Iraq. The latter was a No-Problem-Reaction-Solution based on claims by Cult operatives, including Bush and British Prime Minister Tony Blair, about Saddam Hussein's 'weapons of mass destruction' which did not exist as war criminals Bush and Blair well knew.

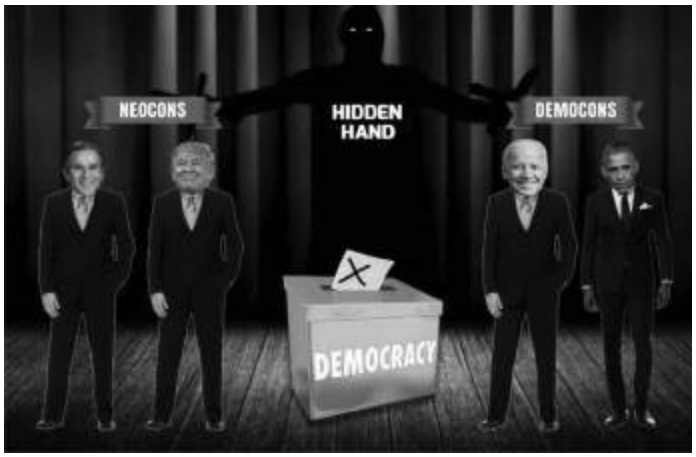


Figure 6: Different front people, different parties – same control system.

The Democratic Party has its own 'Neocon' group controlling from the background which I call the 'Democons' and here's the penny-drop – the Neocons and Democons answer to the same masters one step further back into the shadows (Fig 6). At that level of the Cult the Republican and Democrat parties are controlled by the same people and no matter which is in power the Cult is in power. This is how it works in almost every country and certainly in Britain with Conservative, Labour, Liberal Democrat and Green parties now all on the same page whatever the rhetoric may be in their feeble attempts to appear different. Neocons operated at the time of Bush through a think tank called The Project for the New American Century which in September, 2000, published a document entitled *Rebuilding America's Defenses: Strategies, Forces, and Resources*

For a New Century demanding that America fight 'multiple, simultaneous major theatre wars' as a 'core mission' to force regime-change in countries including Iraq, Libya and Syria. Neocons arranged for Bush ('Republican') and Blair ('Labour Party') to front-up the invasion of Iraq and when they departed the Democons orchestrated the targeting of Libya and Syria through Barack Obama ('Democrat') and British Prime Minister David Cameron ('Conservative Party'). We have 'different' parties and 'different' people, but the same unfolding script. The more the Cult has seized the reigns of parties and personnel the more their policies have transparently pursued the same agenda to the point where the fascist 'Covid' impositions of the Conservative junta of Jackboot Johnson in Britain were opposed by the Labour Party because they were not fascist enough. The Labour Party is likened to the US Democrats while the Conservative Party is akin to a British version of the Republicans and on both sides of the Atlantic they all speak the same language and support the direction demanded by the Cult although some more enthusiastically than others. It's a similar story in country after country because it's all centrally controlled. Oh, but what about Trump? I'll come to him shortly. Political 'choice' in the 'party' system goes like this: You vote for Party A and they get into government. You don't like what they do so next time you vote for Party B and they get into government. You don't like what they do when it's pretty much the same as Party A and why wouldn't that be with both controlled by the same force? Given that only two, sometimes three, parties have any chance of forming a government to get rid of Party B that you don't like you have to vote again for Party A which … you don't like. This, ladies and gentlemen, is what they call 'democracy' which we are told – wrongly – is a term interchangeable with 'freedom'.

The cult of cults

At this point I need to introduce a major expression of the Global Cult known as Sabbatian-Frankism. Sabbatian is also spelt as Sabbatean. I will summarise here. I have published major exposés

and detailed background in other works. Sabbatian-Frankism combines the names of two frauds posing as 'Jewish' men, Sabbatai Zevi (1626-1676), a rabbi, black magician and occultist who proclaimed he was the Jewish messiah; and Jacob Frank (1726-1791), the Polish 'Jew', black magician and occultist who said he was the reincarnation of 'messiah' Zevi and biblical patriarch Jacob. They worked across two centuries to establish the Sabbatian-Frankist cult that plays a major, indeed central, role in the manipulation of human society by the Global Cult which has its origins much further back in history than Sabbatai Zevi. I should emphasise two points here in response to the shrill voices that will scream 'anti-Semitism': (1) Sabbatian-Frankists are NOT Jewish and only pose as such to hide their cult behind a Jewish façade; and (2) my information about this cult has come from Jewish sources who have long realised that their society and community has been infiltrated and taken over by interloper Sabbatian-Frankists. Infiltration has been the foundation technique of Sabbatian-Frankism from its official origin in the 17th century. Zevi's Sabbatian sect attracted a massive following described as the biggest messianic movement in Jewish history, spreading as far as Africa and Asia, and he promised a return for the Jews to the 'Promised Land' of Israel. Sabbatianism was not Judaism but an inversion of everything that mainstream Judaism stood for. So much so that this sinister cult would have a feast day when Judaism had a fast day and whatever was forbidden in Judaism the Sabbatians were encouraged and even commanded to do. This included incest and what would be today called Satanism. Members were forbidden to marry outside the sect and there was a system of keeping their children ignorant of what they were part of until they were old enough to be trusted not to unknowingly reveal anything to outsiders. The same system is employed to this day by the Global Cult in general which Sabbatian-Frankism has enormously influenced and now largely controls.

Zevi and his Sabbatians suffered a setback with the intervention by the Sultan of the Islamic Ottoman Empire in the Middle East and what is now the Republic of Turkey where Zevi was located. The

Sultan gave him the choice of proving his 'divinity', converting to Islam or facing torture and death. Funnily enough Zevi chose to convert or at least appear to. Some of his supporters were disillusioned and drifted away, but many did not with 300 families also converting – only in theory – to Islam. They continued behind this Islamic smokescreen to follow the goals, rules and rituals of Sabbatianism and became known as 'crypto-Jews' or the 'Dönmeh' which means 'to turn'. This is rather ironic because they didn't 'turn' and instead hid behind a fake Islamic persona. The process of appearing to be one thing while being very much another would become the calling card of Sabbatianism especially after Zevi's death and the arrival of the Satanist Jacob Frank in the 18th century when the cult became Sabbatian-Frankism and plumbed still new depths of depravity and infiltration which included – still includes – human sacrifice and sex with children. Wherever Sabbatians go paedophilia and Satanism follow and is it really a surprise that Hollywood is so infested with child abuse and Satanism when it was established by Sabbatian-Frankists and is still controlled by them? Hollywood has been one of the prime vehicles for global perceptual programming and manipulation. How many believe the version of 'history' portrayed in movies when it is a travesty and inversion (again) of the truth? Rabbi Marvin Antelman describes Frankism in his book, *To Eliminate the Opiate*, as 'a movement of complete evil' while Jewish professor Gershom Scholem said of Frank in *The Messianic Idea in Judaism*: 'In all his actions [he was] a truly corrupt and degenerate individual ... one of the most frightening phenomena in the whole of Jewish history.' Frank was excommunicated by traditional rabbis, as was Zevi, but Frank was undeterred and enjoyed vital support from the House of Rothschild, the infamous banking dynasty whose inner-core are Sabbatian-Frankists and not Jews. Infiltration of the Roman Church and Vatican was instigated by Frank with many Dönmeh 'turning' again to convert to Roman Catholicism with a view to hijacking the reins of power. This was the ever-repeating modus operandi and continues to be so. Pose as an advocate of the religion, culture or country that you want to control and then

manipulate your people into the positions of authority and influence largely as advisers, administrators and Svengalis for those that appear to be in power. They did this with Judaism, Christianity (Christian Zionism is part of this), Islam and other religions and nations until Sabbatian-Frankism spanned the world as it does today.

Sabbatian Saudis and the terror network

One expression of the Sabbatian-Frankist Dönmeh within Islam is the ruling family of Saudi Arabia, the House of Saud, through which came the vile distortion of Islam known as Wahhabism. This is the violent creed followed by terrorist groups like Al-Qaeda and ISIS or Islamic State. Wahhabism is the hand-chopping, head-chopping 'religion' of Saudi Arabia which is used to keep the people in a constant state of fear so the interloper House of Saud can continue to rule. Al-Qaeda and Islamic State were lavishly funded by the House of Saud while being created and directed by the Sabbatian-Frankist network in the United States that operates through the Pentagon, CIA and the government in general of whichever 'party'. The front man for the establishment of Wahhabism in the middle of the 18th century was a Sabbatian-Frankist 'crypto-Jew' posing as Islamic called Muhammad ibn Abd al-Wahhab. His daughter would marry the son of Muhammad bin Saud who established the first Saudi state before his death in 1765 with support from the British Empire. Bin Saud's successors would establish modern Saudi Arabia in league with the British and Americans in 1932 which allowed them to seize control of Islam's major shrines in Mecca and Medina. They have dictated the direction of Sunni Islam ever since while Iran is the major centre of the Shiite version and here we have the source of at least the public conflict between them. The Sabbatian network has used its Wahhabi extremists to carry out Problem-Reaction-Solution terrorist attacks in the name of 'Al-Qaeda' and 'Islamic State' to justify a devastating 'war on terror', ever-increasing surveillance of the population and to terrify people into compliance. Another insight of the Renegade Mind is the streetwise understanding that

just because a country, location or people are attacked doesn't mean that those apparently representing that country, location or people are not behind the attackers. Often they are *orchestrating* the attacks because of the societal changes that can be then justified in the name of 'saving the population from terrorists'.

I show in great detail in *The Trigger* how Sabbatian-Frankists were the real perpetrators of 9/11 and not '19 Arab hijackers' who were blamed for what happened. Observe what was justified in the name of 9/11 alone in terms of Middle East invasions, mass surveillance and control that fulfilled the demands of the Project for the New American Century document published by the Sabbatian Neocons. What appear to be enemies are on the deep inside players on the same Sabbatian team. Israel and Arab 'royal' dictatorships are all ruled by Sabbatians and the recent peace agreements between Israel and Saudi Arabia, the United Arab Emirates (UAE) and others are only making formal what has always been the case behind the scenes. Palestinians who have been subjected to grotesque tyranny since Israel was bombed and terrorised into existence in 1948 have never stood a chance. Sabbatian-Frankists have controlled Israel (so the constant theme of violence and war which Sabbatians love) and they have controlled the Arab countries that Palestinians have looked to for real support that never comes. 'Royal families' of the Arab world in Saudi Arabia, Bahrain, UAE, etc., are all Sabbatians with allegiance to the aims of the cult and not what is best for their Arabic populations. They have stolen the oil and financial resources from their people by false claims to be 'royal dynasties' with a genetic right to rule and by employing vicious militaries to impose their will.

Satanic 'illumination'

The Satanist Jacob Frank formed an alliance in 1773 with two other Sabbatians, Mayer Amschel Rothschild (1744-1812), founder of the Rothschild banking dynasty, and Jesuit-educated fraudulent Jew, Adam Weishaupt, and this led to the formation of the Bavarian Illuminati, firstly under another name, in 1776. The Illuminati would

be the manipulating force behind the French Revolution (1789-1799) and was also involved in the American Revolution (1775-1783) before and after the Illuminati's official creation. Weishaupt would later become (in public) a Protestant Christian in archetypal Sabbatian style. I read that his name can be decoded as Adam-Weishaupt or 'the first man to lead those who know'. He wasn't a leader in the sense that he was a subordinate, but he did lead those below him in a crusade of transforming human society that still continues today. The theme was confirmed as early as 1785 when a horseman courier called Lanz was reported to be struck by lighting and extensive Illuminati documents were found in his saddlebags. They made the link to Weishaupt and detailed the plan for world takeover. Current events with 'Covid' fascism have been in the making for a very long time. Jacob Frank was jailed for 13 years by the Catholic Inquisition after his arrest in 1760 and on his release he headed for Frankfurt, Germany, home city and headquarters of the House of Rothschild where the alliance was struck with Mayer Amschel Rothschild and Weishaupt. Rothschild arranged for Frank to be given the title of Baron and he became a wealthy nobleman with a big following of Jews in Germany, the Austro-Hungarian Empire and other European countries. Most of them would have believed he was on their side.

The name 'Illuminati' came from the Zohar which is a body of works in the Jewish mystical 'bible' called the Kabbalah. 'Zohar' is the foundation of Sabbatian-Frankist belief and in Hebrew 'Zohar' means 'splendour', 'radiance', 'illuminated', and so we have 'Illuminati'. They claim to be the 'Illuminated Ones' from their knowledge systematically hidden from the human population and passed on through generations of carefully-chosen initiates in the global secret society network or Cult. Hidden knowledge includes an awareness of the Cult agenda for the world and the nature of our collective reality that I will explore later. Cult 'illumination' is symbolised by the torch held by the Statue of Liberty which was gifted to New York by French Freemasons in Paris who knew exactly what it represents. 'Liberty' symbolises the goddess worshipped in

Babylon as Queen Semiramis or Ishtar. The significance of this will become clear. Notice again the ubiquitous theme of inversion with the Statue of 'Liberty' really symbolising mass control (Fig 7). A mirror-image statute stands on an island in the River Seine in Paris from where New York Liberty originated (Fig 8). A large replica of the Liberty flame stands on top of the Pont de l'Alma tunnel in Paris where Princess Diana died in a Cult ritual described in *The Biggest Secret*. Lucifer 'the light bringer' is related to all this (and much more as we'll see) and 'Lucifer' is a central figure in Sabbatian-Frankism and its associated Satanism. Sabbatians reject the Jewish Torah, or Pentateuch, the 'five books of Moses' in the Old Testament known as Genesis, Exodus, Leviticus, Numbers, and Deuteronomy which are claimed by Judaism and Christianity to have been dictated by 'God' to Moses on Mount Sinai. Sabbatians say these do not apply to them and they seek to replace them with the Zohar to absorb Judaism and its followers into their inversion which is an expression of a much greater global inversion. They want to delete all religions and force humanity to worship a one-world religion – Sabbatian Satanism that also includes worship of the Earth goddess. Satanic themes are being more and more introduced into mainstream society and while Christianity is currently the foremost target for destruction the others are planned to follow.



Figure 7: The Cult goddess of Babylon disguised as the Statue of Liberty holding the flame of Lucifer the 'light bringer'.



Figure 8: Liberty's mirror image in Paris where the New York version originated.

Marx brothers

Rabbi Marvin Antelman connects the Illuminati to the Jacobins in *To Eliminate the Opiate* and Jacobins were the force behind the French Revolution. He links both to the Bund der Gerechten, or League of the Just, which was the network that inflicted communism/Marxism on the world. Antelman wrote:

> The original inner circle of the Bund der Gerechten consisted of born Catholics, Protestants and Jews [Sabbatian-Frankist infiltrators], and those representatives of respective subdivisions formulated schemes for the ultimate destruction of their faiths. The heretical Catholics laid plans which they felt would take a century or more for the ultimate destruction of the church; the apostate Jews for the ultimate destruction of the Jewish religion.

Sabbatian-created communism connects into this anti-religion agenda in that communism does not allow for the free practice of religion. The Sabbatian 'Bund' became the International Communist Party and Communist League and in 1848 'Marxism' was born with the Communist Manifesto of Sabbatian assets Karl Marx and Friedrich Engels. It is absolutely no coincidence that Marxism, just a different name for fascist and other centrally-controlled tyrannies, is being imposed worldwide as a result of the 'Covid' hoax and nor that Marxist/fascist China was the place where the hoax originated. The reason for this will become very clear in the chapter 'Covid: The calculated catastrophe'. The so-called 'Woke' mentality has hijacked

traditional beliefs of the political left and replaced them with far-right make-believe 'social justice' better known as Marxism. Woke will, however, be swallowed by its own perceived 'revolution' which is really the work of billionaires and billionaire corporations feigning being 'Woke'. Marxism is being touted by Wokers as a replacement for 'capitalism' when we don't have 'capitalism'. We have cartelism in which the market is stitched up by the very Cult billionaires and corporations bankrolling Woke. Billionaires love Marxism which keeps the people in servitude while they control from the top. Terminally naïve Wokers think they are 'changing the world' when it's the Cult that is doing the changing and when they have played their vital part and become surplus to requirements they, too, will be targeted. The Illuminati-Jacobins were behind the period known as 'The Terror' in the French Revolution in 1793 and 1794 when Jacobin Maximillian de Robespierre and his Orwellian 'Committee of Public Safety' killed 17,000 'enemies of the Revolution' who had once been 'friends of the Revolution'. Karl Marx (1818-1883), whose Sabbatian creed of Marxism has cost the lives of at least 100 million people, is a hero once again to Wokers who have been systematically kept ignorant of real history by their 'education' programming. As a result they now promote a Sabbatian 'Marxist' abomination destined at some point to consume them. Rabbi Antelman, who spent decades researching the Sabbatian plot, said of the League of the Just and Karl Marx:

> Contrary to popular opinion Karl Marx did not originate the Communist Manifesto. He was paid for his services by the League of the Just, which was known in its country of origin, Germany, as the Bund der Geaechteten.

Antelman said the text attributed to Marx was the work of other people and Marx 'was only repeating what others already said'. Marx was 'a hired hack – lackey of the wealthy Illuminists'. Marx famously said that religion was the 'opium of the people' (part of the Sabbatian plan to demonise religion) and Antelman called his books, *To Eliminate the Opiate*. Marx was born Jewish, but his family converted to Christianity (Sabbatian modus operandi) and he

attacked Jews, not least in his book, *A World Without Jews*. In doing so he supported the Sabbatian plan to destroy traditional Jewishness and Judaism which we are clearly seeing today with the vindictive targeting of orthodox Jews by the Sabbatian government of Israel over 'Covid' laws. I don't follow any religion and it has done much damage to the world over centuries and acted as a perceptual straightjacket. Renegade Minds, however, are always asking *why* something is being done. It doesn't matter if they agree or disagree with what is happening – *why* is it happening is the question. The 'why?' can be answered with regard to religion in that religions create interacting communities of believers when the Cult wants to dismantle all discourse, unity and interaction (see 'Covid' lockdowns) and the ultimate goal is to delete all religions for a one-world religion of Cult Satanism worshipping their 'god' of which more later. We see the same 'why?' with gun control in America. I don't have guns and don't want them, but why is the Cult seeking to disarm the population at the same time that law enforcement agencies are armed to their molars and why has every tyrant in history sought to disarm people before launching the final takeover? They include Hitler, Stalin, Pol Pot and Mao who followed confiscation with violent seizing of power. You know it's a Cult agenda by the people who immediately race to the microphones to exploit dead people in multiple shootings. Ultra-Zionist Cult lackey Senator Chuck Schumer was straight on the case after ten people were killed in Boulder, Colorado in March, 2121. Simple rule … if Schumer wants it the Cult wants it and the same with his ultra-Zionist mate the wild-eyed Senator Adam Schiff. At the same time they were calling for the disarmament of Americans, many of whom live a long way from a police response, Schumer, Schiff and the rest of these pampered clowns were sitting on Capitol Hill behind a razor-wired security fence protected by thousands of armed troops in addition to their own armed bodyguards. Mom and pop in an isolated home? They're just potential mass shooters.

Zion Mainframe

Sabbatian-Frankists and most importantly the Rothschilds were behind the creation of 'Zionism', a political movement that demanded a Jewish homeland in Israel as promised by Sabbatai Zevi. The very symbol of Israel comes from the German meaning of the name Rothschild. Dynasty founder Mayer Amschel Rothschild changed the family name from Bauer to Rothschild, or 'Red-Shield' in German, in deference to the six-pointed 'Star of David' hexagram displayed on the family's home in Frankfurt. The symbol later appeared on the flag of Israel after the Rothschilds were centrally involved in its creation. Hexagrams are not a uniquely Jewish symbol and are widely used in occult ('hidden') networks often as a symbol for Saturn (see my other books for why). Neither are Zionism and Jewishness interchangeable. Zionism is a political movement and philosophy and not a 'race' or a people. Many Jews oppose Zionism and many non-Jews, including US President Joe Biden, call themselves Zionists as does Israel-centric Donald Trump. America's support for the Israel government is pretty much a gimme with ultra-Zionist billionaires and corporations providing fantastic and dominant funding for both political parties. Former Congresswoman Cynthia McKinney has told how she was approached immediately she ran for office to 'sign the pledge' to Israel and confirm that she would always vote in that country's best interests. All American politicians are approached in this way. Anyone who refuses will get no support or funding from the enormous and all-powerful Zionist lobby that includes organisations like mega-lobby group AIPAC, the American Israel Public Affairs Committee. Trump's biggest funder was ultra-Zionist casino and media billionaire Sheldon Adelson while major funders of the Democratic Party include ultra-Zionist George Soros and ultra-Zionist financial and media mogul, Haim Saban. Some may reel back at the suggestion that Soros is an Israel-firster (Sabbatian-controlled Israel-firster), but Renegade Minds watch the actions not the words and everywhere Soros donates his billions the Sabbatian agenda benefits. In the spirit of Sabbatian inversion Soros pledged $1 billion for a new university network to promote 'liberal values and tackle intolerance'. He made the announcement during his annual speech

at the Cult-owned World Economic Forum in Davos, Switzerland, in January, 2020, after his 'harsh criticism' of 'authoritarian rulers' around the world. You can only laugh at such brazen mendacity. How *he* doesn't laugh is the mystery. Translated from the Orwellian 'liberal values and tackle intolerance' means teaching non-white people to hate white people and for white people to loathe themselves for being born white. The reason for that will become clear.

The 'Anti-Semitism' fraud

Zionists support the Jewish homeland in the land of Palestine which has been the Sabbatian-Rothschild goal for so long, but not for the benefit of Jews. Sabbatians and their global Anti-Semitism Industry have skewed public and political opinion to equate opposing the violent extremes of Zionism to be a blanket attack and condemnation of all Jewish people. Sabbatians and their global Anti-Semitism Industry have skewed public and political opinion to equate opposing the violent extremes of Zionism to be a blanket attack and condemnation of all Jewish people. This is nothing more than a Sabbatian protection racket to stop legitimate investigation and exposure of their agendas and activities. The official definition of 'anti-Semitism' has more recently been expanded to include criticism of Zionism – a *political movement* – and this was done to further stop exposure of Sabbatian infiltrators who created Zionism as we know it today in the 19th century. Renegade Minds will talk about these subjects when they know the shit that will come their way. People must decide if they want to know the truth or just cower in the corner in fear of what others will say. Sabbatians have been trying to label me as 'anti-Semitic' since the 1990s as I have uncovered more and more about their background and agendas. Useless, gutless, fraudulent 'journalists' then just repeat the smears without question and on the day I was writing this section a pair of unquestioning repeaters called Ben Quinn and Archie Bland (how appropriate) outright called me an 'anti-Semite' in the establishment propaganda sheet, the London *Guardian*, with no supporting evidence. The

Sabbatian Anti-Semitism Industry said so and who are they to question that? They wouldn't dare. Ironically 'Semitic' refers to a group of languages in the Middle East that are almost entirely Arabic. 'Anti-Semitism' becomes 'anti-Arab' which if the consequences of this misunderstanding were not so grave would be hilarious. Don't bother telling Quinn and Bland. I don't want to confuse them, bless 'em. One reason I am dubbed 'anti-Semitic' is that I wrote in the 1990s that Jewish operatives (Sabbatians) were heavily involved in the Russian Revolution when Sabbatians overthrew the Romanov dynasty. This apparently made me 'anti-Semitic'. Oh, really? Here is a section from *The Trigger*:

British journalist Robert Wilton confirmed these themes in his 1920 book *The Last Days of the Romanovs* when he studied official documents from the Russian government to identify the members of the Bolshevik ruling elite between 1917 and 1919. The Central Committee included 41 Jews among 62 members; the Council of the People's Commissars had 17 Jews out of 22 members; and 458 of the 556 most important Bolshevik positions between 1918 and 1919 were occupied by Jewish people. Only 17 were Russian. Then there were the 23 Jews among the 36 members of the vicious Cheka Soviet secret police established in 1917 who would soon appear all across the country.

Professor Robert Service of Oxford University, an expert on 20th century Russian history, found evidence that ['Jewish'] Leon Trotsky had sought to make sure that Jews were enrolled in the Red Army and were disproportionately represented in the Soviet civil bureaucracy that included the Cheka which performed mass arrests, imprisonment and executions of 'enemies of the people'. A US State Department Decimal File (861.00/5339) dated November 13th, 1918, names [Rothschild banking agent in America] Jacob Schiff and a list of ultra-Zionists as funders of the Russian Revolution leading to claims of a 'Jewish plot', but the key point missed by all is they were not 'Jews' – they were Sabbatian-Frankists.

Britain's Winston Churchill made the same error by mistake or otherwise. He wrote in a 1920 edition of the *Illustrated Sunday Herald* that those behind the Russian revolution were part of a 'worldwide conspiracy for the overthrow of civilisation and for the reconstitution of society on the basis of arrested development, of envious malevolence, and impossible equality' (see 'Woke' today because that has been created by the same network). Churchill said there was no need to exaggerate the part played in the creation of Bolshevism and in the actual bringing about of the Russian

Revolution 'by these international and for the most part atheistical Jews' ['atheistical Jews' = Sabbatians]. Churchill said it is certainly a very great one and probably outweighs all others: 'With the notable exception of Lenin, the majority of the leading figures are Jews.' He went on to describe, knowingly or not, the Sabbatian modus operandi of placing puppet leaders nominally in power while they control from the background:

> Moreover, the principal inspiration and driving power comes from the Jewish leaders. Thus Tchitcherin, a pure Russian, is eclipsed by his nominal subordinate, Litvinoff, and the influence of Russians like Bukharin or Lunacharski cannot be compared with the power of Trotsky, or of Zinovieff, the Dictator of the Red Citadel (Petrograd), or of Krassin or Radek – all Jews. In the Soviet institutions the predominance of Jews is even more astonishing. And the prominent, if not indeed the principal, part in the system of terrorism applied by the Extraordinary Commissions for Combatting Counter-Revolution has been taken by Jews, and in some notable cases by Jewesses.

What I said about seriously disproportionate involvement in the Russian Revolution by Jewish 'revolutionaries' (Sabbatians) is provable fact, but truth is no defence against the Sabbatian Anti-Semitism Industry, its repeater parrots like Quinn and Bland, and the now breathtaking network of so-called 'Woke' 'anti-hate' groups with interlocking leaderships and funding which have the role of discrediting and silencing anyone who gets too close to exposing the Sabbatians. We have seen 'truth is no defence' confirmed in legal judgements with the Saskatchewan Human Rights Commission in Canada decreeing this: 'Truthful statements can be presented in a manner that would meet the definition of hate speech, and not all truthful statements must be free from restriction.' Most 'anti-hate' activists, who are themselves consumed by hatred, are too stupid and ignorant of the world to know how they are being used. They are far too far up their own virtue-signalling arses and it's far too dark for them to see anything.

The 'revolution' game

The background and methods of the 'Russian' Revolution are straight from the Sabbatian playbook seen in the French Revolution

and endless others around the world that appear to start as a revolution of the people against tyrannical rule and end up with a regime change to more tyrannical rule overtly or covertly. Wars, terror attacks and regime overthrows follow the Sabbatian cult through history with its agents creating them as Problem-Reaction-Solutions to remove opposition on the road to world domination. Sabbatian dots connect the Rothschilds with the Illuminati, Jacobins of the French Revolution, the 'Bund' or League of the Just, the International Communist Party, Communist League and the Communist Manifesto of Karl Marx and Friedrich Engels that would lead to the Rothschild-funded Russian Revolution. The sequence comes under the heading of 'creative destruction' when you advance to your global goal by continually destroying the status quo to install a new status quo which you then also destroy. The two world wars come to mind. With each new status quo you move closer to your planned outcome. Wars and mass murder are to Sabbatians a collective blood sacrifice ritual. They are obsessed with death for many reasons and one is that death is an inversion of life. Satanists and Sabbatians are obsessed with death and often target churches and churchyards for their rituals. Inversion-obsessed Sabbatians explain the use of inverted symbolism including the *inverted* pentagram and *inverted* cross. The inversion of the cross has been related to targeting Christianity, but the cross was a religious symbol long before Christianity and its inversion is a statement about the Sabbatian mentality and goals more than any single religion.

Sabbatians operating in Germany were behind the rise of the occult-obsessed Nazis and the subsequent Jewish exodus from Germany and Europe to Palestine and the United States after World War Two. The Rothschild dynasty was at the forefront of this both as political manipulators and by funding the operation. Why would Sabbatians help to orchestrate the horrors inflicted on Jews by the Nazis and by Stalin after they organised the Russian Revolution? Sabbatians hate Jews and their religion, that's why. They pose as Jews and secure positions of control within Jewish society and play the 'anti-Semitism' card to protect themselves from exposure

through a global network of organisations answering to the Sabbatian-created-and-controlled globe-spanning intelligence network that involves a stunning web of military-intelligence operatives and operations for a tiny country of just nine million. Among them are Jewish assets who are not Sabbatians but have been convinced by them that what they are doing is for the good of Israel and the Jewish community to protect them from what they have been programmed since childhood to believe is a Jew-hating hostile world. The Jewish community is just a highly convenient cover to hide the true nature of Sabbatians. Anyone getting close to exposing their game is accused by Sabbatian place-people and gofers of 'anti-Semitism' and claiming that all Jews are part of a plot to take over the world. I am not saying that. I am saying that Sabbatians – the *real* Jew-haters – have infiltrated the Jewish community to use them both as a cover and an 'anti-Semitic' defence against exposure. Thus we have the Anti-Semitism Industry targeted researchers in this way and most Jewish people think this is justified and genuine. They don't know that their 'Jewish' leaders and institutions of state, intelligence and military are not controlled by Jews at all, but cultists and stooges of Sabbatian-Frankism. I once added my name to a pro-Jewish freedom petition online and the next time I looked my name was gone and text had been added to the petition blurb to attack me as an 'anti-Semite' such is the scale of perceptual programming.

Moving on America

I tell the story in *The Trigger* and a chapter called 'Atlantic Crossing' how particularly after Israel was established the Sabbatians moved in on the United States and eventually grasped control of government administration, the political system via both Democrats and Republicans, the intelligence community like the CIA and National Security Agency (NSA), the Pentagon and mass media. Through this seriously compartmentalised network Sabbatians and their operatives in Mossad, Israeli Defense Forces (IDF) and US agencies pulled off 9/11 and blamed it on 19 'Al-Qaeda hijackers' dominated by men from, or connected to, Sabbatian-ruled Saudi

Arabia. The '19' were not even on the planes let alone flew those big passenger jets into buildings while being largely incompetent at piloting one-engine light aircraft. 'Hijacker' Hani Hanjour who is said to have flown American Airlines Flight 77 into the Pentagon with a turn and manoeuvre most professional pilots said they would have struggled to do was banned from renting a small plane by instructors at the Freeway Airport in Bowie, Maryland, just *six weeks* earlier on the grounds that he was an incompetent pilot. The Jewish population of the world is just 0.2 percent with even that almost entirely concentrated in Israel (75 percent Jewish) and the United States (around two percent). This two percent and globally 0.2 percent refers to *Jewish* people and not Sabbatian interlopers who are a fraction of that fraction. What a sobering thought when you think of the fantastic influence on world affairs of tiny Israel and that the Project for the New America Century (PNAC) which laid out the blueprint in September, 2000, for America's war on terror and regime change wars in Iraq, Libya and Syria was founded and dominated by Sabbatians known as 'Neocons'. The document conceded that this plan would not be supported politically or publicly without a major attack on American soil and a Problem-Reaction-Solution excuse to send troops to war across the Middle East. Sabbatian Neocons said:

> ... [The] process of transformation ... [war and regime change] ... is likely to be a long one, absent some catastrophic and catalysing event – like a new Pearl Harbor.

Four months later many of those who produced that document came to power with their inane puppet George Bush from the long-time Sabbatian Bush family. They included Sabbatian Dick Cheney who was officially vice-president, but really de-facto president for the entirety of the 'Bush' government. Nine months after the 'Bush' inauguration came what Bush called at the time 'the Pearl Harbor of the 21st century' and with typical Sabbatian timing and symbolism 2001 was the 60th anniversary of the attack in 1941 by the Japanese Air Force on Pearl Harbor, Hawaii, which allowed President Franklin Delano Roosevelt to take the United States into a Sabbatian-

instigated Second World War that he said in his election campaign that he never would. The evidence is overwhelming that Roosevelt and his military and intelligence networks knew the attack was coming and did nothing to stop it, but they did make sure that America's most essential naval ships were not in Hawaii at the time. Three thousand Americans died in the Pearl Harbor attacks as they did on September 11th. By the 9/11 year of 2001 Sabbatians had widely infiltrated the US government, military and intelligence operations and used their compartmentalised assets to pull off the 'Al-Qaeda' attacks. If you read *The Trigger* it will blow your mind to see the utterly staggering concentration of 'Jewish' operatives (Sabbatian infiltrators) in essential positions of political, security, legal, law enforcement, financial and business power before, during, and after the attacks to make them happen, carry them out, and then cover their tracks – and I do mean *staggering* when you think of that 0.2 percent of the world population and two percent of Americans which are Jewish while Sabbatian infiltrators are a fraction of that. A central foundation of the 9/11 conspiracy was the hijacking of government, military, Air Force and intelligence computer systems in real time through 'back-door' access made possible by Israeli (Sabbatian) 'cyber security' software. Sabbatian-controlled Israel is on the way to rivalling Silicon Valley for domination of cyberspace and is becoming the dominant force in cyber-security which gives them access to entire computer systems and their passcodes across the world. Then add to this that Zionists head (officially) Silicon Valley giants like Google (Larry Page and Sergey Brin), Google-owned YouTube (Susan Wojcicki), Facebook (Mark Zuckerberg and Sheryl Sandberg), and Apple (Chairman Arthur D. Levinson), and that ultra-Zionist hedge fund billionaire Paul Singer has a $1 billion stake in Twitter which is only nominally headed by 'CEO' pothead Jack Dorsey. As cable news host Tucker Carlson said of Dorsey: 'There used to be debate in the medical community whether dropping a ton of acid had permanent effects and I think that debate has now ended.' Carlson made the comment after Dorsey told a hearing on Capitol Hill (if you cut through his bullshit) that he

believed in free speech so long as he got to decide what you can hear and see. These 'big names' of Silicon Valley are only front men and women for the Global Cult, not least the Sabbatians, who are the true controllers of these corporations. Does anyone still wonder why these same people and companies have been ferociously censoring and banning people (like me) for exposing any aspect of the Cult agenda and especially the truth about the 'Covid' hoax which Sabbatians have orchestrated?

The Jeffrey Epstein paedophile ring was a Sabbatian operation. He was officially 'Jewish' but he was a Sabbatian and women abused by the ring have told me about the high number of 'Jewish' people involved. The Epstein horror has Sabbatian written all over it and matches perfectly their modus operandi and obsession with sex and ritual. Epstein was running a Sabbatian blackmail ring in which famous people with political and other influence were provided with young girls for sex while everything was being filmed and recorded on hidden cameras and microphones at his New York house, Caribbean island and other properties. Epstein survivors have described this surveillance system to me and some have gone public. Once the famous politician or other figure knew he or she was on video they tended to do whatever they were told. Here we go again …when you've got them by the balls their hearts and minds will follow. Sabbatians use this blackmail technique on a wide scale across the world to entrap politicians and others they need to act as demanded. Epstein's private plane, the infamous 'Lolita Express', had many well-known passengers including Bill Clinton while Bill Gates has flown on an Epstein plane and met with him four years after Epstein had been jailed for paedophilia. They subsequently met many times at Epstein's home in New York according to a witness who was there. Epstein's infamous side-kick was Ghislaine Maxwell, daughter of Mossad agent and ultra-Zionist mega-crooked British businessman, Bob Maxwell, who at one time owned the *Daily Mirror* newspaper. Maxwell was murdered at sea on his boat in 1991 by Sabbatian-controlled Mossad when he became a liability with his

business empire collapsing as a former Mossad operative has confirmed (see *The Trigger*).

Money, money, money, funny money …

Before I come to the Sabbatian connection with the last three US presidents I will lay out the crucial importance to Sabbatians of controlling banking and finance. Sabbatian Mayer Amschel Rothschild set out to dominate this arena in his family's quest for total global control. What is freedom? It is, in effect, choice. The more choices you have the freer you are and the fewer your choices the more you are enslaved. In the global structure created over centuries by Sabbatians the biggest decider and restrictor of choice is … money. Across the world if you ask people what they would like to do with their lives and why they are not doing that they will reply 'I don't have the money'. This is the idea. A global elite of multi-billionaires are described as 'greedy' and that is true on one level; but control of money – who has it and who doesn't – is not primarily about greed. It's about control. Sabbatians have seized ever more control of finance and sucked the wealth of the world out of the hands of the population. We talk now, after all, about the 'One-percent' and even then the wealthiest are a lot fewer even than that. This has been made possible by a money scam so outrageous and so vast it could rightly be called the scam of scams founded on creating 'money' out of nothing and 'loaning' that with interest to the population. Money out of nothing is called 'credit'. Sabbatians have asserted control over governments and banking ever more completely through the centuries and secured financial laws that allow banks to lend hugely more than they have on deposit in a confidence trick known as fractional reserve lending. Imagine if you could lend money that doesn't exist and charge the recipient interest for doing so. You would end up in jail. Bankers by contrast end up in mansions, private jets, Malibu and Monaco.

Banks are only required to keep a fraction of their deposits and wealth in their vaults and they are allowed to lend 'money' they don't have called 'credit. Go into a bank for a loan and if you succeed

the banker will not move any real wealth into your account. They will type into your account the amount of the agreed 'loan' – say £100,000. This is not wealth that really exists; it is non-existent, fresh-air, created-out-of-nothing 'credit' which has never, does not, and will never exist except in theory. Credit is backed by nothing except wind and only has buying power because people think that it has buying power and accept it in return for property, goods and services. I have described this situation as like those cartoon characters you see chasing each other and when they run over the edge of a cliff they keep running forward on fresh air until one of them looks down, realises what's happened, and they all crash into the ravine. The whole foundation of the Sabbatian financial system is to stop people looking down except for periodic moments when they want to crash the system (as in 2008 and 2020 ongoing) and reap the rewards from all the property, businesses and wealth their borrowers had signed over as 'collateral' in return for a 'loan' of fresh air. Most people think that money is somehow created by governments when it comes into existence from the start as a debt through banks 'lending' illusory money called credit. Yes, the very currency of exchange is a *debt* from day one issued as an interest-bearing loan. Why don't governments create money interest-free and lend it to their people interest-free? Governments are controlled by Sabbatians and the financial system is controlled by Sabbatians for whom interest-free money would be a nightmare come true. Sabbatians underpin their financial domination through their global network of central banks, including the privately-owned US Federal Reserve and Britain's Bank of England, and this is orchestrated by a privately-owned central bank coordination body called the Bank for International Settlements in Basle, Switzerland, created by the usual suspects including the Rockefellers and Rothschilds. Central bank chiefs don't answer to governments or the people. They answer to the Bank for International Settlements or, in other words, the Global Cult which is dominated today by Sabbatians.

Built-in disaster

There are so many constituent scams within the overall banking scam. When you take out a loan of thin-air credit only the amount of that loan is theoretically brought into circulation to add to the amount in circulation; but you are paying back the principle plus interest. The additional interest is not created and this means that with every 'loan' there is a shortfall in the money in circulation between what is borrowed and what has to be paid back. There is never even close to enough money in circulation to repay all outstanding public and private debt including interest. Coldly weaved in the very fabric of the system is the certainty that some will lose their homes, businesses and possessions to the banking 'lender'. This is less obvious in times of 'boom' when the amount of money in circulation (and the debt) is expanding through more people wanting and getting loans. When a downturn comes and the money supply contracts it becomes painfully obvious that there is not enough money to service all debt and interest. This is less obvious in times of 'boom' when the amount of money in circulation (and the debt) is expanding through more people wanting and getting loans. When a downturn comes and the money supply contracts and it becomes painfully obvious – as in 2008 and currently – that there is not enough money to service all debt and interest. Sabbatian banksters have been leading the human population through a calculated series of booms (more debt incurred) and busts (when the debt can't be repaid and the banks get the debtor's tangible wealth in exchange for non-existent 'credit'). With each 'bust' Sabbatian bankers have absorbed more of the world's tangible wealth and we end up with the One-percent. Governments are in bankruptcy levels of debt to the same system and are therefore owned by a system they do not control. The Federal Reserve, 'America's central bank', is privately-owned and American presidents only nominally appoint its chairman or woman to maintain the illusion that it's an arm of government. It's not. The 'Fed' is a cartel of private banks which handed billions to its associates and friends after the crash of 2008 and has been Sabbatian-controlled since it was manipulated into being in 1913 through the covert trickery of Rothschild banking agents Jacob Schiff and Paul

Warburg, and the Sabbatian Rockefeller family. Somehow from a Jewish population of two-percent and globally 0.2 percent (Sabbatian interlopers remember are far smaller) ultra-Zionists headed the Federal Reserve for 31 years between 1987 and 2018 in the form of Alan Greenspan, Bernard Bernanke and Janet Yellen (now Biden's Treasury Secretary) with Yellen's deputy chairman a Israeli-American duel citizen and ultra-Zionist Stanley Fischer, a former governor of the Bank of Israel. Ultra-Zionist Fed chiefs spanned the presidencies of Ronald Reagan ('Republican'), Father George Bush ('Republican'), Bill Clinton ('Democrat'), Boy George Bush ('Republican') and Barack Obama ('Democrat'). We should really add the pre-Greenspan chairman, Paul Adolph Volcker, 'appointed' by Jimmy Carter ('Democrat') who ran the Fed between 1979 and 1987 during the Carter and Reagan administrations before Greenspan took over. Volcker was a long-time associate and business partner of the Rothschilds. No matter what the 'party' officially in power the United States economy was directed by the same force. Here are members of the Obama, Trump and Biden administrations and see if you can make out a common theme.

Barack Obama ('Democrat')

Ultra-Zionists Robert Rubin, Larry Summers, and Timothy Geithner ran the US Treasury in the Clinton administration and two of them reappeared with Obama. Ultra-Zionist Fed chairman Alan Greenspan had manipulated the crash of 2008 through deregulation and jumped ship just before the disaster to make way for ultra-Zionist Bernard Bernanke to hand out trillions to Sabbatian 'too big to fail' banks and businesses, including the ubiquitous ultra-Zionist Goldman Sachs which has an ongoing staff revolving door operation between itself and major financial positions in government worldwide. Obama inherited the fallout of the crash when he took office in January, 2009, and fortunately he had the support of his ultra-Zionist White House Chief of Staff Rahm Emmanuel, son of a terrorist who helped to bomb Israel into being in 1948, and his ultra-Zionist senior adviser David Axelrod, chief strategist in Obama's two

successful presidential campaigns. Emmanuel, later mayor of Chicago and former senior fundraiser and strategist for Bill Clinton, is an example of the Sabbatian policy after Israel was established of migrating insider families to America so their children would be born American citizens. 'Obama' chose this financial team throughout his administration to respond to the Sabbatian-instigated crisis:

Timothy Geithner (ultra-Zionist) Treasury Secretary; Jacob J. Lew, Treasury Secretary; Larry Summers (ultra-Zionist), director of the White House National Economic Council; Paul Adolph Volcker (Rothschild business partner), chairman of the Economic Recovery Advisory Board; Peter Orszag (ultra-Zionist), director of the Office of Management and Budget overseeing all government spending; Penny Pritzker (ultra-Zionist), Commerce Secretary; Jared Bernstein (ultra-Zionist), chief economist and economic policy adviser to Vice President Joe Biden; Mary Schapiro (ultra-Zionist), chair of the Securities and Exchange Commission (SEC); Gary Gensler (ultra-Zionist), chairman of the Commodity Futures Trading Commission (CFTC); Sheila Bair (ultra-Zionist), chair of the Federal Deposit Insurance Corporation (FDIC); Karen Mills (ultra-Zionist), head of the Small Business Administration (SBA); Kenneth Feinberg (ultra-Zionist), Special Master for Executive [bail-out] Compensation. Feinberg would be appointed to oversee compensation (with strings) to 9/11 victims and families in a campaign to stop them having their day in court to question the official story. At the same time ultra-Zionist Bernard Bernanke was chairman of the Federal Reserve and these are only some of the ultra-Zionists with allegiance to Sabbatian-controlled Israel in the Obama government. Obama's biggest corporate donor was ultra-Zionist Goldman Sachs which had employed many in his administration.

Donald Trump ('Republican')

Trump claimed to be an outsider (he wasn't) who had come to 'drain the swamp'. He embarked on this goal by immediately appointing ultra-Zionist Steve Mnuchin, a Goldman Sachs employee for 17

years, as his Treasury Secretary. Others included Gary Cohn (ultra-Zionist), chief operating officer of Goldman Sachs, his first Director of the National Economic Council and chief economic adviser, who was later replaced by Larry Kudlow (ultra-Zionist). Trump's senior adviser throughout his four years in the White House was his sinister son-in-law Jared Kushner, a life-long friend of Israel Prime Minister Benjamin Netanyahu. Kushner is the son of a convicted crook who was pardoned by Trump in his last days in office. Other ultra-Zionists in the Trump administration included: Stephen Miller, Senior Policy Adviser; Avrahm Berkowitz, Deputy Adviser to Trump and his Senior Adviser Jared Kushner; Ivanka Trump, Adviser to the President, who converted to Judaism when she married Jared Kushner; David Friedman, Trump lawyer and Ambassador to Israel; Jason Greenblatt, Trump Organization executive vice president and chief legal officer, who was made Special Representative for International Negotiations and the Israeli-Palestinian Conflict; Rod Rosenstein, Deputy Attorney General; Elliot Abrams, Special Representative for Venezuela, then Iran; John Eisenberg, National Security Council Legal Adviser and Deputy Council to the President for National Security Affairs; Anne Neuberger, Deputy National Manager, National Security Agency; Ezra Cohen-Watnick, Acting Under Secretary of Defense for Intelligence; Elan Carr, Special Envoy to monitor and combat anti-Semitism; Len Khodorkovsky, Deputy Special Envoy to monitor and combat anti-Semitism; Reed Cordish, Assistant to the President, Intragovernmental and Technology Initiatives. Trump Vice President Mike Pence and Secretary of State Mike Pompeo, both Christian Zionists, were also vehement supporters of Israel and its goals and ambitions.

Donald 'free-speech believer' Trump pardoned a number of financial and violent criminals while ignoring calls to pardon Julian Assange and Edward Snowden whose crimes are revealing highly relevant information about government manipulation and corruption and the widespread illegal surveillance of the American people by US 'security' agencies. It's so good to know that Trump is on the side of freedom and justice and not mega-criminals with

allegiance to Sabbatian-controlled Israel. These included a pardon for Israeli spy Jonathan Pollard who was jailed for life in 1987 under the Espionage Act. Aviem Sella, the Mossad agent who recruited Pollard, was also pardoned by Trump while Assange sat in jail and Snowden remained in exile in Russia. Sella had 'fled' (was helped to escape) to Israel in 1987 and was never extradited despite being charged under the Espionage Act. A Trump White House statement said that Sella's clemency had been 'supported by Benjamin Netanyahu, Ron Dermer, Israel's US Ambassador, David Friedman, US Ambassador to Israel and Miriam Adelson, wife of leading Trump donor Sheldon Adelson who died shortly before. Other friends of Jared Kushner were pardoned along with Sholom Weiss who was believed to be serving the longest-ever white-collar prison sentence of more than 800 years in 2000. The sentence was commuted of Ponzi-schemer Eliyahu Weinstein who defrauded Jews and others out of $200 million. I did mention that Assange and Snowden were ignored, right? Trump gave Sabbatians almost everything they asked for in military and political support, moving the US Embassy from Tel Aviv to Jerusalem with its critical symbolic and literal implications for Palestinian statehood, and the 'deal of the Century' designed by Jared Kushner and David Friedman which gave the Sabbatian Israeli government the green light to substantially expand its already widespread program of building illegal Jewish-only settlements in the occupied land of the West Bank. This made a two-state 'solution' impossible by seizing all the land of a potential Palestinian homeland and that had been the plan since 1948 and then 1967 when the Arab-controlled Gaza Strip, West Bank, Sinai Peninsula and Syrian Golan Heights were occupied by Israel. All the talks about talks and road maps and delays have been buying time until the West Bank was physically occupied by Israeli real estate. Trump would have to be a monumentally ill-informed idiot not to see that this was the plan he was helping to complete. The Trump administration was in so many ways the Kushner administration which means the Netanyahu administration which means the Sabbatian administration. I understand why many opposing Cult fascism in all its forms gravitated to Trump, but he

was a crucial part of the Sabbatian plan and I will deal with this in the next chapter.

Joe Biden ('Democrat')

A barely cognitive Joe Biden took over the presidency in January, 2021, along with his fellow empty shell, Vice-President Kamala Harris, as the latest Sabbatian gofers to enter the White House. Names on the door may have changed and the 'party' – the force behind them remained the same as Zionists were appointed to a stream of pivotal areas relating to Sabbatian plans and policy. They included: Janet Yellen, Treasury Secretary, former head of the Federal Reserve, and still another ultra-Zionist running the US Treasury after Mnuchin (Trump), Lew and Geithner (Obama), and Summers and Rubin (Clinton); Anthony Blinken, Secretary of State; Wendy Sherman, Deputy Secretary of State (so that's 'Biden's' Sabbatian foreign policy sorted); Jeff Zients, White House coronavirus coordinator; Rochelle Walensky, head of the Centers for Disease Control; Rachel Levine, transgender deputy health secretary (that's 'Covid' hoax policy under control); Merrick Garland, Attorney General; Alejandro Mayorkas, Secretary of Homeland Security; Cass Sunstein, Homeland Security with responsibility for new immigration laws; Avril Haines, Director of National Intelligence; Anne Neuberger, National Security Agency cybersecurity director (note, cybersecurity); David Cohen, CIA Deputy Director; Ronald Klain, Biden's Chief of Staff (see Rahm Emanuel); Eric Lander, a 'leading geneticist', Office of Science and Technology Policy director (see Smart Grid, synthetic biology agenda); Jessica Rosenworcel, acting head of the Federal Communications Commission (FCC) which controls Smart Grid technology policy and electromagnetic communication systems including 5G. How can it be that so many pivotal positions are held by two-percent of the American population and 0.2 percent of the world population administration after administration no matter who is the president and what is the party? It's a coincidence? Of course it's not and this is why Sabbatians have built their colossal global web of interlocking 'anti-

hate' hate groups to condemn anyone who asks these glaring questions as an 'anti-Semite'. The way that Jewish people horrifically abused in Sabbatian-backed Nazi Germany are exploited to this end is stomach-turning and disgusting beyond words.

Political fusion

Sabbatian manipulation has reversed the roles of Republicans and Democrats and the same has happened in Britain with the Conservative and Labour Parties. Republicans and Conservatives were always labelled the 'right' and Democrats and Labour the 'left', but look at the policy positions now and the Democrat-Labour 'left' has moved further to the 'right' than Republicans and Conservatives under the banner of 'Woke', the Cult-created far-right tyranny. Where once the Democrat-Labour 'left' defended free speech and human rights they now seek to delete them and as I said earlier despite the 'Covid' fascism of the Jackboot Johnson Conservative government in the UK the Labour Party of leader Keir Starmer demanded even more extreme measures. The Labour Party has been very publicly absorbed by Sabbatians after a political and media onslaught against the previous leader, the weak and inept Jeremy Corbyn, over made-up allegations of 'anti-Semitism' both by him and his party. The plan was clear with this 'anti-Semite' propaganda and what was required in response was a swift and decisive 'fuck off' from Corbyn and a statement to expose the Anti-Semitism Industry (Sabbatian) attempt to silence Labour criticism of the Israeli government (Sabbatians) and purge the party of all dissent against the extremes of ultra-Zionism (Sabbatians). Instead Corbyn and his party fell to their knees and appeased the abusers which, by definition, is impossible. Appeasing one demand leads only to a new demand to be appeased until takeover is complete. Like I say – 'fuck off' would have been a much more effective policy and I have used it myself with great effect over the years when Sabbatians are on my case which is most of the time. I consider that fact a great compliment, by the way. The outcome of the Labour Party capitulation is that we now have a Sabbatian-controlled

Conservative Party 'opposed' by a Sabbatian-controlled Labour Party in a one-party Sabbatian state that hurtles towards the extremes of tyranny (the Sabbatian cult agenda). In America the situation is the same. Labour's Keir Starmer spends his days on his knees with his tongue out pointing to Tel Aviv, or I guess now Jerusalem, while Boris Johnson has an 'anti-Semitism czar' in the form of former Labour MP John Mann who keeps Starmer company on his prayer mat.

Sabbatian influence can be seen in Jewish members of the Labour Party who have been ejected for criticism of Israel including those from families that suffered in Nazi Germany. Sabbatians despise real Jewish people and target them even more harshly because it is so much more difficult to dub them 'anti-Semitic' although in their desperation they do try.

CHAPTER THREE

The Pushbacker sting

Until you realize how easy it is for your mind to be manipulated, you remain the puppet of someone else's game
Evita Ochel

I will use the presidencies of Trump and Biden to show how the manipulation of the one-party state plays out behind the illusion of political choice across the world. No two presidencies could – on the face of it – be more different and apparently at odds in terms of direction and policy.

A Renegade Mind sees beyond the obvious and focuses on outcomes and consequences and not image, words and waffle. The Cult embarked on a campaign to divide America between those who blindly support its agenda (the mentality known as 'Woke') and those who are pushing back on where the Cult and its Sabbatians want to go. This presents infinite possibilities for dividing and ruling the population by setting them at war with each other and allows a perceptual ring fence of demonisation to encircle the Pushbackers in a modern version of the Little Big Horn in 1876 when American cavalry led by Lieutenant Colonel George Custer were drawn into a trap, surrounded and killed by Native American tribes defending their land of thousands of years from being seized by the government. In this modern version the roles are reversed and it's those defending themselves from the Sabbatian government who are surrounded and the government that's seeking to destroy them. This trap was set years ago and to explain how we must return to 2016

and the emergence of Donald Trump as a candidate to be President of the United States. He set out to overcome the best part of 20 other candidates in the Republican Party before and during the primaries and was not considered by many in those early stages to have a prayer of living in the White House. The Republican Party was said to have great reservations about Trump and yet somehow he won the nomination. When you know how American politics works – politics in general – there is no way that Trump could have become the party's candidate unless the Sabbatian-controlled 'Neocons' that run the Republican Party wanted that to happen. We saw the proof in emails and documents made public by WikiLeaks that the Democratic Party hierarchy, or Democons, systematically undermined the campaign of Bernie Sanders to make sure that Sabbatian gofer Hillary Clinton won the nomination to be their presidential candidate. If the Democons could do that then the Neocons in the Republican Party could have derailed Trump in the same way. But they didn't and at that stage I began to conclude that Trump could well be the one chosen to be president. If that was the case the 'why' was pretty clear to see – the goal of dividing America between Cult agenda-supporting Wokers and Pushbackers who gravitated to Trump because he was telling them what they wanted to hear. His constituency of support had been increasingly ignored and voiceless for decades and profoundly through the eight years of Sabbatian puppet Barack Obama. Now here was someone speaking their language of pulling back from the incessant globalisation of political and economic power, the exporting of American jobs to China and elsewhere by 'American' (Sabbatian) corporations, the deletion of free speech, and the mass immigration policies that had further devastated job opportunities for the urban working class of all races and the once American heartlands of the Midwest.

Beware the forked tongue

Those people collectively sighed with relief that at last a political leader was apparently on their side, but another trait of the Renegade Mind is that you look even harder at people telling you

what you want to hear than those who are telling you otherwise. Obviously as I said earlier people wish what they want to hear to be true and genuine and they are much more likely to believe that than someone saying what they don't want to here and don't want to be true. Sales people are taught to be skilled in eliciting by calculated questioning what their customers want to hear and repeating that back to them as their own opinion to get their targets to like and trust them. Assets of the Cult are also sales people in the sense of selling perception. To read Cult manipulation you have to play the long and expanded game and not fall for the Vaudeville show of party politics. Both American parties are vehicles for the Cult and they exploit them in different ways depending on what the agenda requires at that moment. Trump and the Republicans were used to be the focus of dividing America and isolating Pushbackers to open the way for a Biden presidency to become the most extreme in American history by advancing the full-blown Woke (Cult) agenda with the aim of destroying and silencing Pushbackers now labelled Nazi Trump supporters and white supremacists.

Sabbatians wanted Trump in office for the reasons described by ultra-Zionist Saul Alinsky (1909-1972) who was promoting the Woke philosophy through 'community organising' long before anyone had heard of it. In those days it still went by its traditional name of Marxism. The reason for the manipulated Trump phenomenon was laid out in Alinsky's 1971 book, *Rules for Radicals*, which was his blueprint for overthrowing democratic and other regimes and replacing them with Sabbatian Marxism. Not surprisingly his to-do list was evident in the Sabbatian French and Russian 'Revolutions' and that in China which will become very relevant in the next chapter about the 'Covid' hoax. Among Alinsky's followers have been the deeply corrupt Barack Obama, House Speaker Nancy Pelosi and Hillary Clinton who described him as a 'hero'. All three are Sabbatian stooges with Pelosi personifying the arrogant corrupt idiocy that so widely fronts up for the Cult inner core. Predictably as a Sabbatian advocate of the 'light-bringer' Alinsky features Lucifer on the dedication page of his book as the original radical who gained

his own kingdom ('Earth' as we shall see). One of Alinsky's golden radical rules was to pick an individual and focus all attention, hatred and blame on them and not to target faceless bureaucracies and corporations. *Rules for Radicals* is really a Sabbatian handbook with its contents repeatedly employed all over the world for centuries and why wouldn't Sabbatians bring to power their designer-villain to be used as the individual on which all attention, hatred and blame was bestowed? This is what they did and the only question for me is how much Trump knew that and how much he was manipulated. A bit of both, I suspect. This was Alinsky's Trump technique from a man who died in 1972. The technique has spanned history:

Pick the target, freeze it, personalize it, polarize it. Don't try to attack abstract corporations or bureaucracies. Identify a responsible individual. Ignore attempts to shift or spread the blame.

From the moment Trump came to illusory power everything was about him. It wasn't about Republican policy or opinion, but all about Trump. Everything he did was presented in negative, derogatory and abusive terms by the Sabbatian-dominated media led by Cult operations such as CNN, MSNBC, *The New York Times* and the Jeff Bezos-owned *Washington Post* – 'Pick the target, freeze it, personalize it, polarize it.' Trump was turned into a demon to be vilified by those who hated him and a demi-god loved by those who worshipped him. This, in turn, had his supporters, too, presented as equally demonic in preparation for the punchline later down the line when Biden was about to take office. It was here's a Trump, there's a Trump, everywhere a Trump, Trump. Virtually every news story or happening was filtered through the lens of 'The Donald'. You loved him or hated him and which one you chose was said to define you as Satan's spawn or a paragon of virtue. Even supporting some Trump policies or statements and not others was enough for an assault on your character. No shades of grey were or are allowed. Everything is black and white (literally and figuratively). A Californian I knew had her head utterly scrambled by her hatred for Trump while telling people they should love each other. She was so totally consumed by

Trump Derangement Syndrome as it became to be known that this glaring contradiction would never have occurred to her. By definition anyone who criticised Trump or praised his opponents was a hero and this lady described Joe Biden as 'a kind, honest gentleman' when he's a provable liar, mega-crook and vicious piece of work to boot. Sabbatians had indeed divided America using Trump as the fall-guy and all along the clock was ticking on the consequences for his supporters.

In hock to his masters

Trump gave Sabbatians via Israel almost everything they wanted in his four years. Ask and you shall receive was the dynamic between himself and Benjamin Netanyahu orchestrated by Trump's ultra-Zionist son-in-law Jared Kushner, his ultra-Zionist Ambassador to Israel, David Friedman, and ultra-Zionist 'Israel adviser', Jason Greenblatt. The last two were central to the running and protecting from collapse of his business empire, the Trump Organisation, and colossal business failures made him forever beholding to Sabbatian networks that bailed him out. By the start of the 1990s Trump owed $4 billion to banks that he couldn't pay and almost $1billion of that was down to him personally and not his companies. This mega-disaster was the result of building two new casinos in Atlantic City and buying the enormous Taj Mahal operation which led to crippling debt payments. He had borrowed fantastic sums from 72 banks with major Sabbatian connections and although the scale of debt should have had him living in a tent alongside the highway they never foreclosed. A plan was devised to lift Trump from the mire by BT Securities Corporation and Rothschild Inc. and the case was handled by Wilber Ross who had worked for the Rothschilds for 27 years. Ross would be named US Commerce Secretary after Trump's election. Another crucial figure in saving Trump was ultra-Zionist 'investor' Carl Icahn who bought the Taj Mahal casino. Icahn was made special economic adviser on financial regulation in the Trump administration. He didn't stay long but still managed to find time to make a tidy sum of a reported $31.3 million when he sold his

holdings affected by the price of steel three days before Trump imposed a 235 percent tariff on steel imports. What amazing bits of luck these people have. Trump and Sabbatian operatives have long had a close association and his mentor and legal adviser from the early 1970s until 1986 was the dark and genetically corrupt ultra-Zionist Roy Cohn who was chief counsel to Senator Joseph McCarthy's 'communist' witch-hunt in the 1950s. *Esquire* magazine published an article about Cohn with the headline 'Don't mess with Roy Cohn'. He was described as the most feared lawyer in New York and 'a ruthless master of dirty tricks ... [with] ... more than one Mafia Don on speed dial'. Cohn's influence, contacts, support and protection made Trump a front man for Sabbatians in New York with their connections to one of Cohn's many criminal employers, the 'Russian' Sabbatian Mafia. Israel-centric media mogul Rupert Murdoch was introduced to Trump by Cohn and they started a long friendship. Cohn died in 1986 weeks after being disbarred for unethical conduct by the Appellate Division of the New York State Supreme Court. The wheels of justice do indeed run slow given the length of Cohn's crooked career.

QAnon-sense

We are asked to believe that Donald Trump with his fundamental connections to Sabbatian networks and operatives has been leading the fight to stop the Sabbatian agenda for the fascistic control of America and the world. Sure he has. A man entrapped during his years in the White House by Sabbatian operatives and whose biggest financial donor was casino billionaire Sheldon Adelson who was Sabbatian to his DNA?? Oh, do come on. Trump has been used to divide America and isolate Pushbackers on the Cult agenda under the heading of 'Trump supporters', 'insurrectionists' and 'white supremacists'. The US Intelligence/Mossad Psyop or psychological operation known as QAnon emerged during the Trump years as a central pillar in the Sabbatian campaign to lead Pushbackers into the trap set by those that wished to destroy them. I knew from the start that QAnon was a scam because I had seen the same scenario many

times before over 30 years under different names and I had written about one in particular in the books. 'Not again' was my reaction when QAnon came to the fore. The same script is pulled out every few years and a new name added to the letterhead. The story always takes the same form: 'Insiders' or 'the good guys' in the government-intelligence-military 'Deep State' apparatus were going to instigate mass arrests of the 'bad guys' which would include the Rockefellers, Rothschilds, Barack Obama, Hillary Clinton, George Soros, etc., etc. Dates are given for when the 'good guys' are going to move in, but the dates pass without incident and new dates are given which pass without incident. The central message to Pushbackers in each case is that they don't have to do anything because there is 'a plan' and it is all going to be sorted by the 'good guys' on the inside. 'Trust the plan' was a QAnon mantra when the only plan was to misdirect Pushbackers into putting their trust in a Psyop they believed to be real. Beware, beware, those who tell you what you want to hear and always check it out. Right up to Biden's inauguration QAnon was still claiming that 'the Storm' was coming and Trump would stay on as president when Biden and his cronies were arrested and jailed. It was never going to happen and of course it didn't, but what did happen as a result provided that punchline to the Sabbatian Trump/QAnon Psyop.

On January 6th, 2021, a very big crowd of Trump supporters gathered in the National Mall in Washington DC down from the Capitol Building to protest at what they believed to be widespread corruption and vote fraud that stopped Trump being re-elected for a second term as president in November, 2020. I say as someone that does not support Trump or Biden that the evidence is clear that major vote-fixing went on to favour Biden, a man with cognitive problems so advanced he can often hardly string a sentence together without reading the words written for him on the Teleprompter. Glaring ballot discrepancies included serious questions about electronic voting machines that make vote rigging a comparative cinch and hundreds of thousands of paper votes that suddenly appeared during already advanced vote counts and virtually all of

them for Biden. Early Trump leads in crucial swing states suddenly began to close and disappear. The pandemic hoax was used as the excuse to issue almost limitless numbers of mail-in ballots with no checks to establish that the recipients were still alive or lived at that address. They were sent to streams of people who had not even asked for them. Private organisations were employed to gather these ballots and who knows what they did with them before they turned up at the counts. The American election system has been manipulated over decades to become a sick joke with more holes than a Swiss cheese for the express purpose of dictating the results. Then there was the criminal manipulation of information by Sabbatian tech giants like Facebook, Twitter and Google-owned YouTube which deleted pro-Trump, anti-Biden accounts and posts while everything in support of Biden was left alone. Sabbatians wanted Biden to win because after the dividing of America it was time for full-on Woke and every aspect of the Cult agenda to be unleashed.

Hunter gatherer

Extreme Silicon Valley bias included blocking information by the *New York Post* exposing a Biden scandal that should have ended his bid for president in the final weeks of the campaign. Hunter Biden, his monumentally corrupt son, is reported to have sent a laptop to be repaired at a local store and failed to return for it. Time passed until the laptop became the property of the store for non-payment of the bill. When the owner saw what was on the hard drive he gave a copy to the FBI who did nothing even though it confirmed widespread corruption in which the Joe Biden family were using his political position, especially when he was vice president to Obama, to make multiple millions in countries around the world and most notably Ukraine and China. Hunter Biden's one-time business partner Tony Bobulinski went public when the story broke in the *New York Post* to confirm the corruption he saw and that Joe Biden not only knew what was going on he also profited from the spoils. Millions were handed over by a Chinese company with close

connections – like all major businesses in China – to the Chinese communist party of President Xi Jinping. Joe Biden even boasted at a meeting of the Cult's World Economic Forum that as vice president he had ordered the government of Ukraine to fire a prosecutor. What he didn't mention was that the same man just happened to be investigating an energy company which was part of Hunter Biden's corrupt portfolio. The company was paying him big bucks for no other reason than the influence his father had. Overnight Biden's presidential campaign should have been over given that he had lied publicly about not knowing what his son was doing. Instead almost the entire Sabbatian-owned mainstream media and Sabbatian-owned Silicon Valley suppressed circulation of the story. This alone went a mighty way to rigging the election of 2020. Cult assets like Mark Zuckerberg at Facebook also spent hundreds of millions to be used in support of Biden and vote 'administration'.

The Cult had used Trump as the focus to divide America and was now desperate to bring in moronic, pliable, corrupt Biden to complete the double-whammy. No way were they going to let little things like the will of the people thwart their plan. Silicon Valley widely censored claims that the election was rigged because it *was* rigged. For the same reason anyone claiming it was rigged was denounced as a 'white supremacist' including the pathetically few Republican politicians willing to say so. Right across the media where the claim was mentioned it was described as a 'false claim' even though these excuses for 'journalists' would have done no research into the subject whatsoever. Trump won seven million more votes than any sitting president had ever achieved while somehow a cognitively-challenged soon to be 78-year-old who was hidden away from the public for most of the campaign managed to win more votes than any presidential candidate in history. It makes no sense. You only had to see election rallies for both candidates to witness the enthusiasm for Trump and the apathy for Biden. Tens of thousands would attend Trump events while Biden was speaking in empty car parks with often only television crews attending and framing their shots to hide the fact that no one was there. It was pathetic to see

footage come to light of Biden standing at a podium making speeches only to TV crews and party fixers while reading the words written for him on massive Teleprompter screens. So, yes, those protestors on January 6th had a point about election rigging, but some were about to walk into a trap laid for them in Washington by the Cult Deep State and its QAnon Psyop. This was the Capitol Hill riot ludicrously dubbed an 'insurrection'.

The spider and the fly

Renegade Minds know there are not two 'sides' in politics, only one side, the Cult, working through all 'sides'. It's a stage show, a puppet show, to direct the perceptions of the population into focusing on diversions like parties and candidates while missing the puppeteers with their hands holding all the strings. The Capitol Hill 'insurrection' brings us back to the Little Big Horn. Having created two distinct opposing groupings – Woke and Pushbackers – the trap was about to be sprung. Pushbackers were to be encircled and isolated by associating them all in the public mind with Trump and then labelling Trump as some sort of Confederate leader. I knew immediately that the Capitol riot was a set-up because of two things. One was how easy the rioters got into the building with virtually no credible resistance and secondly I could see – as with the 'Covid' hoax in the West at the start of 2020 – how the Cult could exploit the situation to move its agenda forward with great speed. My experience of Cult techniques and activities over more than 30 years has showed me that while they do exploit situations they haven't themselves created this never happens with events of fundamental agenda significance. Every time major events giving cultists the excuse to rapidly advance their plan you find they are manipulated into being for the specific reason of providing that excuse – Problem-Reaction-Solution. Only a tiny minority of the huge crowd of Washington protestors sought to gain entry to the Capitol by smashing windows and breaching doors. That didn't matter. The whole crowd and all Pushbackers, even if they did not support Trump, were going to be lumped together as dangerous

insurrectionists and conspiracy theorists. The latter term came into widespread use through a CIA memo in the 1960s aimed at discrediting those questioning the nonsensical official story of the Kennedy assassination and it subsequently became widely employed by the media. It's still being used by inept 'journalists' with no idea of its origin to discredit anyone questioning anything that authority claims to be true. When you are perpetrating a conspiracy you need to discredit the very word itself even though the dictionary definition of conspiracy is merely 'the activity of secretly planning with other people to do something bad or illegal' and 'a general agreement to keep silent about a subject for the purpose of keeping it secret'. On that basis there are conspiracies almost wherever you look. For obvious reasons the Cult and its lapdog media have to claim there are no conspiracies even though the word appears in state laws as with conspiracy to defraud, to murder, and to corrupt public morals.

Agent provocateurs are widely used by the Cult Deep State to manipulate genuine people into acting in ways that suit the desired outcome. By genuine in this case I mean protestors genuinely supporting Trump and claims that the election was stolen. In among them, however, were agents of the state wearing the garb of Trump supporters and QAnon to pump-prime the Capital riot which some genuine Trump supporters naively fell for. I described the situation as 'Come into my parlour said the spider to the fly'. Leaflets appeared through the Woke paramilitary arm Antifa, the anti-fascist fascists, calling on supporters to turn up in Washington looking like Trump supporters even though they hated him. Some of those arrested for breaching the Capitol Building were sourced to Antifa and its stable mate Black Lives Matter. Both organisations are funded by Cult billionaires and corporations. One man charged for the riot was according to his lawyer a former FBI agent who had held top secret security clearance for 40 years. Attorney Thomas Plofchan said of his client, 66-year-old Thomas Edward Caldwell:

He has held a Top Secret Security Clearance since 1979 and has undergone multiple Special Background Investigations in support of his clearances. After retiring from the Navy, he

worked as a section chief for the Federal Bureau of Investigation from 2009-2010 as a GS-12 [mid-level employee].

He also formed and operated a consulting firm performing work, often classified, for U.S government customers including the US. Drug Enforcement Agency, Department of Housing and Urban Development, the US Coast Guard, and the US Army Personnel Command.

A judge later released Caldwell pending trial in the absence of evidence about a conspiracy or that he tried to force his way into the building. *The New York Post* reported a 'law enforcement source' as saying that 'at least two known Antifa members were spotted' on camera among Trump supporters during the riot while one of the rioters arrested was John Earle Sullivan, a seriously extreme Black Lives Matter Trump-hater from Utah who was previously arrested and charged in July, 2020, over a BLM-Antifa riot in which drivers were threatened and one was shot. Sullivan is the founder of Utah-based Insurgence USA which is an affiliate of the Cult-created-and-funded Black Lives Matter movement. Footage appeared and was then deleted by Twitter of Trump supporters calling out Antifa infiltrators and a group was filmed changing into pro-Trump clothing before the riot. Security at the building was *pathetic* – as planned. Colonel Leroy Fletcher Prouty, a man with long experience in covert operations working with the US security apparatus, once described the tell-tale sign to identify who is involved in an assassination. He said:

No one has to direct an assassination – it happens. The active role is played secretly by permitting it to happen. This is the greatest single clue. Who has the power to call off or reduce the usual security precautions?

This principle applies to many other situations and certainly to the Capitol riot of January 6th, 2021.

The sting

With such a big and potentially angry crowd known to be gathering near the Capitol the security apparatus would have had a major police detail to defend the building with National Guard troops on

standby given the strength of feeling among people arriving from all over America encouraged by the QAnon Psyop and statements by Donald Trump. Instead Capitol Police 'security' was flimsy, weak, and easily breached. The same number of officers was deployed as on a regular day and that is a blatant red flag. They were not staffed or equipped for a possible riot that had been an obvious possibility in the circumstances. No protective and effective fencing worth the name was put in place and there were no contingency plans. The whole thing was basically a case of standing aside and waving people in. Once inside police mostly backed off apart from one Capitol police officer who ridiculously shot dead unarmed Air Force veteran protestor Ashli Babbitt without a warning as she climbed through a broken window. The 'investigation' refused to name or charge the officer after what must surely be considered a murder in the circumstances. They just lifted a carpet and swept. The story was endlessly repeated about five people dying in the 'armed insurrection' when there was no report of rioters using weapons. Apart from Babbitt the other four died from a heart attack, strokes and apparently a drug overdose. Capitol police officer Brian Sicknick was reported to have died after being bludgeoned with a fire extinguisher when he was alive after the riot was over and died later of what the Washington Medical Examiner's Office said was a stroke. Sicknick had no external injuries. The lies were delivered like rapid fire. There was a narrative to build with incessant repetition of the lie until the lie became the accepted 'everybody knows that' truth. The 'Big Lie' technique of Nazi Propaganda Minister Joseph Goebbels is constantly used by the Cult which was behind the Nazis and is today behind the 'Covid' and 'climate change' hoaxes. Goebbels said:

If you tell a lie big enough and keep repeating it, people will eventually come to believe it. The lie can be maintained only for such time as the State can shield the people from the political, economic and/or military consequences of the lie. It thus becomes vitally important for the State to use all of its powers to repress dissent, for the truth is the mortal enemy of the lie, and thus by extension, the truth is the greatest enemy of the State.

Most protestors had a free run of the Capitol Building. This allowed pictures to be taken of rioters in iconic parts of the building including the Senate chamber which could be used as propaganda images against all Pushbackers. One Congresswoman described the scene as 'the worst kind of non-security anybody could ever imagine'. Well, the first part was true, but someone obviously did imagine it and made sure it happened. Some photographs most widely circulated featured people wearing QAnon symbols and now the Psyop would be used to dub all QAnon followers with the ubiquitous fit-all label of 'white supremacist' and 'insurrectionists'. When a Muslim extremist called Noah Green drove his car at two police officers at the Capitol Building killing one in April, 2021, there was no such political and media hysteria. They were just disappointed he wasn't white.

The witch-hunt

Government prosecutor Michael Sherwin, an aggressive, dark-eyed, professional Rottweiler led the 'investigation' and to call it over the top would be to understate reality a thousand fold. Hundreds were tracked down and arrested for the crime of having the wrong political views and people were jailed who had done nothing more than walk in the building, committed no violence or damage to property, took a few pictures and left. They were labelled a 'threat to the Republic' while Biden sat in the White House signing executive orders written for him that were dismantling 'the Republic'. Even when judges ruled that a mother and son should not be in jail the government kept them there. Some of those arrested have been badly beaten by prison guards in Washington and lawyers for one man said he suffered a fractured skull and was made blind in one eye. Meanwhile a woman is shot dead for no reason by a Capitol Police officer and we are not allowed to know who he is never mind what has happened to him although that will be *nothing*. The Cult's QAnon/Trump sting to identify and isolate Pushbackers and then target them on the road to crushing and deleting them was a resounding success. You would have thought the Russians had

invaded the building at gunpoint and lined up senators for a firing squad to see the political and media reaction. Congresswoman Alexandria Ocasio-Cortez is a child in a woman's body, a terrible-twos, me, me, me, Woker narcissist of such proportions that words have no meaning. She said she thought she was going to die when 'insurrectionists' banged on her office door. It turned out she wasn't even in the Capitol Building when the riot was happening and the 'banging' was a Capitol Police officer. She referred to herself as a 'survivor' which is an insult to all those true survivors of violent and sexual abuse while she lives her pampered and privileged life talking drivel for a living. Her Woke colleague and fellow mega-narcissist Rashida Tlaib broke down describing the devastating effect on her, too, of *not being* in the building when the rioters were there. Ocasio-Cortez and Tlaib are members of a fully-Woke group of Congresswomen known as 'The Squad' along with Ilhan Omar and Ayanna Pressley. The Squad from what I can see can be identified by its vehement anti-white racism, anti-white men agenda, and, as always in these cases, the absence of brain cells on active duty.

The usual suspects were on the riot case immediately in the form of Democrat ultra-Zionist senators and operatives Chuck Schumer and Adam Schiff demanding that Trump be impeached for 'his part in the insurrection'. The same pair of prats had led the failed impeachment of Trump over the invented 'Russia collusion' nonsense which claimed Russia had helped Trump win the 2016 election. I didn't realise that Tel Aviv had been relocated just outside Moscow. I must find an up-to-date map. The Russia hoax was a Sabbatian operation to keep Trump occupied and impotent and to stop any rapport with Russia which the Cult wants to retain as a perceptual enemy to be pulled out at will. Puppet Biden began attacking Russia when he came to office as the Cult seeks more upheaval, division and war across the world. A two-year stage show 'Russia collusion inquiry' headed by the not-very-bright former 9/11 FBI chief Robert Mueller, with support from 19 lawyers, 40 FBI agents plus intelligence analysts, forensic accountants and other

staff, devoured tens of millions of dollars and found no evidence of Russia collusion which a ten-year-old could have told them on day one. Now the same moronic Schumer and Schiff wanted a second impeachment of Trump over the Capitol 'insurrection' (riot) which the arrested development of Schumer called another 'Pearl Harbor' while others compared it with 9/11 in which 3,000 died and, in the case of CNN, with the Rwandan genocide in the 1990s in which an estimated 500,000 to 600,000 were murdered, between 250, 000 and 500,000 women were raped, and populations of whole towns were hacked to death with machetes. To make those comparisons purely for Cult political reasons is beyond insulting to those that suffered and lost their lives and confirms yet again the callous inhumanity that we are dealing with. Schumer is a monumental idiot and so is Schiff, but they serve the Cult agenda and do whatever they're told so they get looked after. Talking of idiots – another inane man who spanned the Russia and Capitol impeachment attempts was Senator Eric Swalwell who had the nerve to accuse Trump of collusion with the Russians while sleeping with a Chinese spy called Christine Fang or 'Fang Fang' which is straight out of a Bond film no doubt starring Klaus Schwab as the bloke living on a secret island and controlling laser weapons positioned in space and pointing at world capitals. Fang Fang plays the part of Bond's infiltrator girlfriend which I'm sure she would enjoy rather more than sharing a bed with the brainless Swalwell, lying back and thinking of China. The FBI eventually warned Swalwell about Fang Fang which gave her time to escape back to the Chinese dictatorship. How very thoughtful of them. The second Trump impeachment also failed and hardly surprising when an impeachment is supposed to remove a sitting president and by the time it happened Trump was no longer president. These people are running your country America, well, officially anyway. Terrifying isn't it?

Outcomes tell the story - always

The outcome of all this – and it's the *outcome* on which Renegade Minds focus, not the words – was that a vicious, hysterical and

obviously pre-planned assault was launched on Pushbackers to censor, silence and discredit them and even targeted their right to earn a living. They have since been condemned as 'domestic terrorists' that need to be treated like Al-Qaeda and Islamic State. 'Domestic terrorists' is a label the Cult has been trying to make stick since the period of the Oklahoma bombing in 1995 which was blamed on 'far-right domestic terrorists'. If you read *The Trigger* you will see that the bombing was clearly a Problem-Reaction-Solution carried out by the Deep State during a Bill Clinton administration so corrupt that no dictionary definition of the term would even nearly suffice. Nearly 30, 000 troops were deployed from all over America to the empty streets of Washington for Biden's inauguration. Ten thousand of them stayed on with the pretext of protecting the capital from insurrectionists when it was more psychological programming to normalise the use of the military in domestic law enforcement in support of the Cult plan for a police-military state. Biden's fascist administration began a purge of 'wrong-thinkers' in the military which means anyone that is not on board with Woke. The Capitol Building was surrounded by a fence with razor wire and the Land of the Free was further symbolically and literally dismantled. The circle was completed with the installation of Biden and the exploitation of the QAnon Psyop.

America had never been so divided since the civil war of the 19th century, Pushbackers were isolated and dubbed terrorists and now, as was always going to happen, the Cult immediately set about deleting what little was left of freedom and transforming American society through a swish of the hand of the most controlled 'president' in American history leading (officially at least) the most extreme regime since the country was declared an independent state on July 4th, 1776. Biden issued undebated, dictatorial executive orders almost by the hour in his opening days in office across the whole spectrum of the Cult wish-list including diluting controls on the border with Mexico allowing thousands of migrants to illegally enter the United States to transform the demographics of America and import an election-changing number of perceived Democrat

voters. Then there were Biden deportation amnesties for the already illegally resident (estimated to be as high as 20 or even 30 million). A bill before Congress awarded American citizenship to anyone who could prove they had worked in agriculture for just 180 days in the previous two years as 'Big Ag' secured its slave labour long-term. There were the plans to add new states to the union such as Puerto Rico and making Washington DC a state. They are all parts of a plan to ensure that the Cult-owned Woke Democrats would be permanently in power.

Border – what border?

I have exposed in detail in other books how mass immigration into the United States and Europe is the work of Cult networks fuelled by the tens of billions spent to this and other ends by George Soros and his global Open Society (open borders) Foundations. The impact can be seen in America alone where the population has increased by *100 million* in little more than 30 years mostly through immigration. I wrote in *The Answer* that the plan was to have so many people crossing the southern border that the numbers become unstoppable and we are now there under Cult-owned Biden. El Salvador in Central America puts the scale of what is happening into context. A third of the population now lives in the United States, much of it illegally, and many more are on the way. The methodology is to crush Central and South American countries economically and spread violence through machete-wielding psychopathic gangs like MS-13 based in El Salvador and now operating in many American cities. Biden-imposed lax security at the southern border means that it is all but open. He said before his 'election' that he wanted to see a surge towards the border if he became president and that was the green light for people to do just that after election day to create the human disaster that followed for both America and the migrants. When that surge came the imbecilic Alexandria Ocasio-Cortez said it wasn't a 'surge' because they are 'children, not insurgents' and the term 'surge' (used by Biden) was a claim of 'white supremacists'.

This disingenuous lady may one day enter the realm of the most basic intelligence, but it won't be any time soon.

Sabbatians and the Cult are in the process of destroying America by importing violent people and gangs in among the genuine to terrorise American cities and by overwhelming services that cannot cope with the sheer volume of new arrivals. Something similar is happening in Europe as Western society in general is targeted for demographic and cultural transformation and upheaval. The plan demands violence and crime to create an environment of intimidation, fear and division and Soros has been funding the election of district attorneys across America who then stop prosecuting many crimes, reduce sentences for violent crimes and free as many violent criminals as they can. Sabbatians are creating the chaos from which order – their order – can respond in a classic Problem-Reaction-Solution. A Freemasonic moto says 'Ordo Ab Chao' (Order out of Chaos) and this is why the Cult is constantly creating chaos to impose a new 'order'. Here you have the reason the Cult is constantly creating chaos. The 'Covid' hoax can be seen with those entering the United States by plane being forced to take a 'Covid' test while migrants flooding through southern border processing facilities do not. Nothing is put in the way of mass migration and if that means ignoring the government's own 'Covid' rules then so be it. They know it's all bullshit anyway. Any pushback on this is denounced as 'racist' by Wokers and Sabbatian fronts like the ultra-Zionist Anti-Defamation League headed by the appalling Jonathan Greenblatt which at the same time argues that Israel should not give citizenship and voting rights to more Palestinian Arabs or the 'Jewish population' (in truth the Sabbatian network) will lose control of the country.

Society-changing numbers

Biden's masters have declared that countries like El Salvador are so dangerous that their people must be allowed into the United States for humanitarian reasons when there are fewer murders in large parts of many Central American countries than in US cities like

Baltimore. That is not to say Central America cannot be a dangerous place and Cult-controlled American governments have been making it so since way back, along with the dismantling of economies, in a long-term plan to drive people north into the United States. Parts of Central America are very dangerous, but in other areas the story is being greatly exaggerated to justify relaxing immigration criteria. Migrants are being offered free healthcare and education in the United States as another incentive to head for the border and there is no requirement to be financially independent before you can enter to prevent the resources of America being drained. You can't blame migrants for seeking what they believe will be a better life, but they are being played by the Cult for dark and nefarious ends. The numbers since Biden took office are huge. In February, 2021, more than 100,000 people were known to have tried to enter the US illegally through the southern border (it was 34,000 in the same month in 2020) and in March it was 170,000 – a 418 percent increase on March, 2020. These numbers are only known people, not the ones who get in unseen. The true figure for migrants illegally crossing the border in a single month was estimated by one congressman at 250,000 and that number will only rise under Biden's current policy. Gangs of murdering drug-running thugs that control the Mexican side of the border demand money – thousands of dollars – to let migrants cross the Rio Grande into America. At the same time gun battles are breaking out on the border several times a week between rival Mexican drug gangs (which now operate globally) who are equipped with sophisticated military-grade weapons, grenades and armoured vehicles. While the Capitol Building was being 'protected' from a non-existent 'threat' by thousands of troops, and others were still deployed at the time in the Cult Neocon war in Afghanistan, the southern border of America was left to its fate. This is not incompetence, it is cold calculation.

By March, 2021, there were 17,000 unaccompanied children held at border facilities and many of them are ensnared by people traffickers for paedophile rings and raped on their journey north to America. This is not conjecture – this is fact. Many of those designated

children are in reality teenage boys or older. Meanwhile Wokers posture their self-purity for encouraging poor and tragic people to come to America and face this nightmare both on the journey and at the border with the disgusting figure of House Speaker Nancy Pelosi giving disingenuous speeches about caring for migrants. The woman's evil. Wokers condemned Trump for having children in cages at the border (so did Obama, *Shhhh*), but now they are sleeping on the floor without access to a shower with one border facility 729 percent over capacity. The Biden insanity even proposed flying migrants from the southern border to the northern border with Canada for 'processing'. The whole shambles is being overseen by ultra-Zionist Secretary of Homeland Security, the moronic liar Alejandro Mayorkas, who banned news cameras at border facilities to stop Americans seeing what was happening. Mayorkas said there was not a ban on news crews; it was just that they were not allowed to film. Alongside him at Homeland Security is another ultra-Zionist Cass Sunstein appointed by Biden to oversee new immigration laws. Sunstein despises conspiracy researchers to the point where he suggests they should be banned or *taxed* for having such views. The man is not bonkers or anything. He's perfectly well-adjusted, but adjusted to what is the question. Criticise what is happening and you are a 'white supremacist' when earlier non-white immigrants also oppose the numbers which effect their lives and opportunities. Black people in poor areas are particularly damaged by uncontrolled immigration and the increased competition for work opportunities with those who will work for less. They are also losing voting power as Hispanics become more dominant in former black areas. It's a downward spiral for them while the billionaires behind the policy drone on about how much they care about black people and 'racism'. None of this is about compassion for migrants or black people – that's just wind and air. Migrants are instead being mercilessly exploited to transform America while the countries they leave are losing their future and the same is true in Europe. Mass immigration may now be the work of Woke Democrats, but it can be traced back to the 1986 Immigration Reform and Control Act (it

wasn't) signed into law by Republican hero President Ronald Reagan which gave amnesty to millions living in the United States illegally and other incentives for people to head for the southern border. Here we have the one-party state at work again.

Save me syndrome

Almost every aspect of what I have been exposing as the Cult agenda was on display in even the first days of 'Biden' with silencing of Pushbackers at the forefront of everything. A Renegade Mind will view the Trump years and QAnon in a very different light to their supporters and advocates as the dots are connected. The QAnon/Trump Psyop has given the Cult all it was looking for. We may not know how much, or little, that Trump realised he was being used, but that's a side issue. This pincer movement produced the desired outcome of dividing America and having Pushbackers isolated. To turn this around we have to look at new routes to empowerment which do not include handing our power to other people and groups through what I will call the 'Save Me Syndrome' – 'I want someone else to do it so that I don't have to'. We have seen this at work throughout human history and the QAnon/Trump Psyop is only the latest incarnation alongside all the others. Religion is an obvious expression of this when people look to a 'god' or priest to save them or tell them how to be saved and then there are 'save me' politicians like Trump. Politics is a diversion and not a 'saviour'. It is a means to block positive change, not make it possible.

Save Me Syndrome always comes with the same repeating theme of handing your power to whom or what you believe will save you while your real 'saviour' stares back from the mirror every morning. Renegade Minds are constantly vigilant in this regard and always asking the question 'What can I do?' rather than 'What can someone else do for me?' Gandhi was right when he said: 'You must be the change you want to see in the world.' We are indeed the people we have been waiting for. We are presented with a constant raft of reasons to concede that power to others and forget where the real power is. Humanity has the numbers and the Cult does not. It has to

use diversion and division to target the unstoppable power that comes from unity. Religions, governments, politicians, corporations, media, QAnon, are all different manifestations of this power-diversion and dilution. Refusing to give your power to governments and instead handing it to Trump and QAnon is not to take a new direction, but merely to recycle the old one with new names on the posters. I will explore this phenomenon as we proceed and how to break the cycles and recycles that got us here through the mists of repeating perception and so repeating history.

For now we shall turn to the most potent example in the entire human story of the consequences that follow when you give your power away. I am talking, of course, of the 'Covid' hoax.

CHAPTER FOUR

'Covid': Calculated catastrophe

Facts are threatening to those invested in fraud
DaShanne Stokes

We can easily unravel the real reason for the 'Covid pandemic' hoax by employing the Renegade Mind methodology that I have outlined this far. We'll start by comparing the long-planned Cult outcome with the 'Covid pandemic' outcome. Know the outcome and you'll see the journey.

I have highlighted the plan for the Hunger Games Society which has been in my books for so many years with the very few controlling the very many through ongoing dependency. To create this dependency it is essential to destroy independent livelihoods, businesses and employment to make the population reliant on the state (the Cult) for even the basics of life through a guaranteed pittance income. While independence of income remained these Cult ambitions would be thwarted. With this knowledge it was easy to see where the 'pandemic' hoax was going once talk of 'lockdowns' began and the closing of all but perceived 'essential' businesses to 'save' us from an alleged 'deadly virus'. Cult corporations like Amazon and Walmart were naturally considered 'essential' while mom and pop shops and stores had their doors closed by fascist decree. As a result with every new lockdown and new regulation more small and medium, even large businesses not owned by the Cult, went to the wall while Cult giants and their frontmen and women grew financially fatter by the second. Mom and pop were

denied an income and the right to earn a living and the wealth of people like Jeff Bezos (Amazon), Mark Zuckerberg (Facebook) and Sergei Brin and Larry Page (Google/Alphabet) have reached record levels. The Cult was increasing its own power through further dramatic concentrations of wealth while the competition was being destroyed and brought into a state of dependency. Lockdowns have been instigated to secure that very end and were never anything to do with health. My brother Paul spent 45 years building up a bus repair business, but lockdowns meant buses were running at a fraction of normal levels for months on end. Similar stories can told in their hundreds of millions worldwide. Efforts of a lifetime coldly destroyed by Cult multi-billionaires and their lackeys in government and law enforcement who continued to earn their living from the taxation of the people while denying the right of the same people to earn theirs. How different it would have been if those making and enforcing these decisions had to face the same financial hardships of those they affected, but they never do.

Gates of Hell

Behind it all in the full knowledge of what he is doing and why is the psychopathic figure of Cult operative Bill Gates. His puppet Tedros at the World Health Organization declared 'Covid' a pandemic in March, 2020. The WHO had changed the definition of a 'pandemic' in 2009 just a month before declaring the 'swine flu pandemic' which would not have been so under the previous definition. The same applies to 'Covid'. The definition had included… 'an infection by an infectious agent, occurring simultaneously in different countries, with a significant mortality rate relative to the proportion of the population infected'. The new definition removed the need for 'significant mortality'. The 'pandemic' has been fraudulent even down to the definition, but Gates demanded economy-destroying lockdowns, school closures, social distancing, mandatory masks, a 'vaccination' for every man, woman and child on the planet and severe consequences and restrictions for those that refused. Who gave him this power? The

Cult did which he serves like a little boy in short trousers doing what his daddy tells him. He and his psychopathic missus even smiled when they said that much worse was to come (what they knew was planned to come). Gates responded in the matter-of-fact way of all psychopaths to a question about the effect on the world economy of what he was doing:

> Well, it won't go to zero but it will shrink. Global GDP is probably going to take the biggest hit ever [Gates was smiling as he said this] … in my lifetime this will be the greatest economic hit. But you don't have a choice. People act as if you have a choice. People don't feel like going to the stadium when they might get infected … People are deeply affected by seeing these stats, by knowing they could be part of the transmission chain, old people, their parents and grandparents, could be affected by this, and so you don't get to say ignore what is going on here.
>
> There will be the ability to open up, particularly in rich countries, if things are done well over the next few months, but for the world at large normalcy only returns when we have largely vaccinated the entire population.

The man has no compassion or empathy. How could he when he's a psychopath like all Cult players? My own view is that even beyond that he is very seriously mentally ill. Look in his eyes and you can see this along with his crazy flailing arms. You don't do what he has done to the world population since the start of 2020 unless you are mentally ill and at the most extreme end of psychopathic. You especially don't do it when to you know, as we shall see, that cases and deaths from 'Covid' are fakery and a product of monumental figure massaging. 'These stats' that Gates referred to are based on a 'test' that's not testing for the 'virus' as he has known all along. He made his fortune with big Cult support as an infamously ruthless software salesman and now buys global control of 'health' (death) policy without the population he affects having any say. It's a breathtaking outrage. Gates talked about people being deeply affected by fear of 'Covid' when that was because of *him* and his global network lying to them minute-by-minute supported by a lying media that he seriously influences and funds to the tune of hundreds of millions. He's handed big sums to media operations including the BBC, NBC, Al Jazeera, Univision, *PBS NewsHour*,

ProPublica, National Journal, The Guardian, The Financial Times, The Atlantic, Texas Tribune, USA Today publisher Gannett, *Washington Monthly, Le Monde,* Center for Investigative Reporting, Pulitzer Center on Crisis Reporting, National Press Foundation, International Center for Journalists, Solutions Journalism Network, the Poynter Institute for Media Studies, and many more. Gates is everywhere in the 'Covid' hoax and the man must go to prison – or a mental facility – for the rest of his life and his money distributed to those he has taken such enormous psychopathic pleasure in crushing.

The Muscle

The Hunger Games global structure demands a police-military state – a fusion of the two into one force – which viciously imposes the will of the Cult on the population and protects the Cult from public rebellion. In that regard, too, the 'Covid' hoax just keeps on giving. Often unlawful, ridiculous and contradictory 'Covid' rules and regulations have been policed across the world by moronic automatons and psychopaths made faceless by face-nappy masks and acting like the Nazi SS and fascist blackshirts and brownshirts of Hitler and Mussolini. The smallest departure from the rules decreed by the psychos in government and their clueless gofers were jumped upon by the face-nappy fascists. Brutality against public protestors soon became commonplace even on girls, women and old people as the brave men with the batons – the Face-Nappies as I call them – broke up peaceful protests and handed out fines like confetti to people who couldn't earn a living let alone pay hundreds of pounds for what was once an accepted human right. Robot Face-Nappies of Nottingham police in the English East Midlands fined one group £11,000 for attending a child's birthday party. For decades I charted the transformation of law enforcement as genuine, decent officers were replaced with psychopaths and the brain dead who would happily and brutally do whatever their masters told them. Now they were let loose on the public and I would emphasise the point that none of this just happened. The step-by-step change in the dynamic between police and public was orchestrated from the shadows by

those who knew where this was all going and the same with the perceptual reframing of those in all levels of authority and official administration through 'training courses' by organisations such as Common Purpose which was created in the late 1980s and given a massive boost in Blair era Britain until it became a global phenomenon. Supposed public 'servants' began to view the population as the enemy and the same was true of the police. This was the start of the explosion of behaviour manipulation organisations and networks preparing for the all-war on the human psyche unleashed with the dawn of 2020. I will go into more detail about this later in the book because it is a core part of what is happening.

Police desecrated beauty spots to deter people gathering and arrested women for walking in the countryside alone 'too far' from their homes. We had arrogant, clueless sergeants in the Isle of Wight police where I live posting on Facebook what they insisted the population must do or else. A schoolmaster sergeant called Radford looked young enough for me to ask if his mother knew he was out, but he was posting what he *expected* people to do while a Sergeant Wilkinson boasted about fining lads for meeting in a McDonald's car park where they went to get a lockdown takeaway. Wilkinson added that he had even cancelled their order. What a pair of prats these people are and yet they have increasingly become the norm among Jackboot Johnson's Yellowshirts once known as the British police. This was the theme all over the world with police savagery common during lockdown protests in the United States, the Netherlands, and the fascist state of Victoria in Australia under its tyrannical and again moronic premier Daniel Andrews. Amazing how tyrannical and moronic tend to work as a team and the same combination could be seen across America as arrogant, narcissistic Woke governors and mayors such as Gavin Newsom (California), Andrew Cuomo (New York), Gretchen Whitmer (Michigan), Lori Lightfoot (Chicago) and Eric Garcetti (Los Angeles) did their Nazi and Stalin impressions with the full support of the compliant brutality of their enforcers in uniform as they arrested small business owners defying

fascist shutdown orders and took them to jail in ankle shackles and handcuffs. This happened to bistro owner Marlena Pavlos-Hackney in Gretchen Whitmer's fascist state of Michigan when police arrived to enforce an order by a state-owned judge for 'putting the community at risk' at a time when other states like Texas were dropping restrictions and migrants were pouring across the southern border without any 'Covid' questions at all. I'm sure there are many officers appalled by what they are ordered to do, but not nearly enough of them. If they were truly appalled they would not do it. As the months passed every opportunity was taken to have the military involved to make their presence on the streets ever more familiar and 'normal' for the longer-term goal of police-military fusion.

Another crucial element to the Hunger Games enforcement network has been encouraging the public to report neighbours and others for 'breaking the lockdown rules'. The group faced with £11,000 in fines at the child's birthday party would have been dobbed-in by a neighbour with a brain the size of a pea. The technique was most famously employed by the Stasi secret police in communist East Germany who had public informants placed throughout the population. A police chief in the UK says his force doesn't need to carry out 'Covid' patrols when they are flooded with so many calls from the public reporting other people for visiting the beach. Dorset police chief James Vaughan said people were so enthusiastic about snitching on their fellow humans they were now operating as an auxiliary arm of the police: 'We are still getting around 400 reports a week from the public, so we will respond to reports …We won't need to be doing hotspot patrols because people are very quick to pick the phone up and tell us.' Vaughan didn't say that this is a pillar of all tyrannies of whatever complexion and the means to hugely extend the reach of enforcement while spreading distrust among the people and making them wary of doing anything that might get them reported. Those narcissistic Isle of Wight sergeants Radford and Wilkinson never fail to add a link to their Facebook posts where the public can inform on their fellow slaves.

Neither would be self-aware enough to realise they were imitating the Stasi which they might well never have heard of. Government psychologists that I will expose later laid out a policy to turn communities against each other in the same way.

A coincidence? Yep, and I can knit fog

I knew from the start of the alleged pandemic that this was a Cult operation. It presented limitless potential to rapidly advance the Cult agenda and exploit manipulated fear to demand that every man, woman and child on the planet was 'vaccinated' in a process never used on humans before which infuses self-replicating *synthetic* material into human cells. Remember the plan to transform the human body from a biological to a synthetic biological state. I'll deal with the 'vaccine' (that's not actually a vaccine) when I focus on the genetic agenda. Enough to say here that mass global 'vaccination' justified by this 'new virus' set alarms ringing after 30 years of tracking these people and their methods. The 'Covid' hoax officially beginning in China was also a big red flag for reasons I will be explaining. The agenda potential was so enormous that I could dismiss any idea that the 'virus' appeared naturally. Major happenings with major agenda implications never occur without Cult involvement in making them happen. My questions were twofold in early 2020 as the media began its campaign to induce global fear and hysteria: Was this alleged infectious agent released on purpose by the Cult or did it even exist at all? I then did what I always do in these situations. I sat, observed and waited to see where the evidence and information would take me. By March and early April synchronicity was strongly – and ever more so since then – pointing me in the direction of *there is no 'virus'*. I went public on that with derision even from swathes of the alternative media that voiced a scenario that the Chinese government released the 'virus' in league with Deep State elements in the United States from a top-level bio-lab in Wuhan where the 'virus' is said to have first appeared. I looked at that possibility, but I didn't buy it for several reasons. Deaths from the 'virus' did not in any way match what they

would have been with a 'deadly bioweapon' and it is much more effective if you sell the *illusion* of an infectious agent rather than having a real one unless you can control through injection who has it and who doesn't. Otherwise you lose control of events. A made-up 'virus' gives you a blank sheet of paper on which you can make it do whatever you like and have any symptoms or mutant 'variants' you choose to add while a real infectious agent would limit you to what it actually does. A phantom disease allows you to have endless ludicrous 'studies' on the 'Covid' dollar to widen the perceived impact by inventing ever more 'at risk' groups including one study which said those who walk slowly may be almost four times more likely to die from the 'virus'. People are in psychiatric wards for less.

A real 'deadly bioweapon' can take out people in the hierarchy that are not part of the Cult, but essential to its operation. Obviously they don't want that. Releasing a real disease means you immediately lose control of it. Releasing an illusory one means you don't. Again it's vital that people are extra careful when dealing with what they want to hear. A bioweapon unleashed from a Chinese laboratory in collusion with the American Deep State may fit a conspiracy narrative, but is it true? Would it not be far more effective to use the excuse of a 'virus' to justify the real bioweapon – the 'vaccine'? That way your disease agent does not have to be transmitted and arrives directly through a syringe. I saw a French virologist Luc Montagnier quoted in the alternative media as saying he had discovered that the alleged 'new' severe acute respiratory syndrome coronavirus , or SARS-CoV-2, was made artificially and included elements of the human immunodeficiency 'virus' (HIV) and a parasite that causes malaria. SARS-CoV-2 is alleged to trigger an alleged illness called Covid-19. I remembered Montagnier's name from my research years before into claims that an HIV 'retrovirus' causes AIDs – claims that were demolished by Berkeley virologist Peter Duesberg who showed that no one had ever proved that HIV causes acquired immunodeficiency syndrome or AIDS. Claims that become accepted as fact, publicly and medically, with no proof whatsoever are an ever-recurring story that profoundly applies to

'Covid'. Nevertheless, despite the lack of proof, Montagnier's team at the Pasteur Institute in Paris had a long dispute with American researcher Robert Gallo over which of them discovered and isolated the HIV 'virus' and with *no evidence* found it to cause AIDS. You will see later that there is also no evidence that any 'virus' causes any disease or that there is even such a thing as a 'virus' in the way it is said to exist. The claim to have 'isolated' the HIV 'virus' will be presented in its real context as we come to the shocking story – and it is a story – of SARS-CoV-2 and so will Montagnier's assertion that he identified the full SARS-CoV-2 genome.

Hoax in the making

We can pick up the 'Covid' story in 2010 and the publication by the Rockefeller Foundation of a document called 'Scenarios for the Future of Technology and International Development'. The inner circle of the Rockefeller family has been serving the Cult since John D. Rockefeller (1839-1937) made his fortune with Standard Oil. It is less well known that the same Rockefeller – the Bill Gates of his day – was responsible for establishing what is now referred to as 'Big Pharma', the global network of pharmaceutical companies that make outrageous profits dispensing scalpel and drug 'medicine' and are obsessed with pumping vaccines in ever-increasing number into as many human arms and backsides as possible. John D. Rockefeller was the driving force behind the creation of the 'education' system in the United States and elsewhere specifically designed to program the perceptions of generations thereafter. The Rockefeller family donated exceptionally valuable land in New York for the United Nations building and were central in establishing the World Health Organization in 1948 as an agency of the UN which was created from the start as a Trojan horse and stalking horse for world government. Now enter Bill Gates. His family and the Rockefellers have long been extremely close and I have seen genealogy which claims that if you go back far enough the two families fuse into the same bloodline. Gates has said that the Bill and Melinda Gates Foundation was inspired by the Rockefeller Foundation and why not

when both are serving the same Cult? Major tax-exempt foundations are overwhelmingly criminal enterprises in which Cult assets fund the Cult agenda in the guise of 'philanthropy' while avoiding tax in the process. Cult operatives can become mega-rich in their role of front men and women for the psychopaths at the inner core and they, too, have to be psychopaths to knowingly serve such evil. Part of the deal is that a big percentage of the wealth gleaned from representing the Cult has to be spent advancing the ambitions of the Cult and hence you have the Rockefeller Foundation, Bill and Melinda Gates Foundation (and *so* many more) and people like George Soros with his global Open Society Foundations spending their billions in pursuit of global Cult control. Gates is a global public face of the Cult with his interventions in world affairs including Big Tech influence; a central role in the 'Covid' and 'vaccine' scam; promotion of the climate change shakedown; manipulation of education; geoengineering of the skies; and his food-control agenda as the biggest owner of farmland in America, his GMO promotion and through other means. As one writer said: 'Gates monopolizes or wields disproportionate influence over the tech industry, global health and vaccines, agriculture and food policy (including biopiracy and fake food), weather modification and other climate technologies, surveillance, education and media.' The almost limitless wealth secured through Microsoft and other not-allowed-to-fail ventures (including vaccines) has been ploughed into a long, long list of Cult projects designed to enslave the entire human race. Gates and the Rockefellers have been working as one unit with the Rockefeller-established World Health Organization leading global 'Covid' policy controlled by Gates through his mouth-piece Tedros. Gates became the WHO's biggest funder when Trump announced that the American government would cease its donations, but Biden immediately said he would restore the money when he took office in January, 2021. The Gates Foundation (the Cult) owns through limitless funding the world health system and the major players across the globe in the 'Covid' hoax.

Okay, with that background we return to that Rockefeller Foundation document of 2010 headed 'Scenarios for the Future of Technology and International Development' and its 'imaginary' epidemic of a virulent and deadly influenza strain which infected 20 percent of the global population and killed eight million in seven months. The Rockefeller scenario was that the epidemic destroyed economies, closed shops, offices and other businesses and led to governments imposing fierce rules and restrictions that included mandatory wearing of face masks and body-temperature checks to enter communal spaces like railway stations and supermarkets. The document predicted that even after the height of the Rockefeller-envisaged epidemic the authoritarian rule would continue to deal with further pandemics, transnational terrorism, environmental crises and rising poverty. Now you may think that the Rockefellers are our modern-day seers or alternatively, and rather more likely, that they well knew what was planned a few years further on. Fascism had to be imposed, you see, to 'protect citizens from risk and exposure'. The Rockefeller scenario document said:

During the pandemic, national leaders around the world flexed their authority and imposed airtight rules and restrictions, from the mandatory wearing of face masks to body-temperature checks at the entries to communal spaces like train stations and supermarkets. Even after the pandemic faded, this more authoritarian control and oversight of citizens and their activities stuck and even intensified. In order to protect themselves from the spread of increasingly global problems – from pandemics and transnational terrorism to environmental crises and rising poverty – leaders around the world took a firmer grip on power.

At first, the notion of a more controlled world gained wide acceptance and approval. Citizens willingly gave up some of their sovereignty – and their privacy – to more paternalistic states in exchange for greater safety and stability. Citizens were more tolerant, and even eager, for top-down direction and oversight, and national leaders had more latitude to impose order in the ways they saw fit.

In developed countries, this heightened oversight took many forms: biometric IDs for all citizens, for example, and tighter regulation of key industries whose stability was deemed vital to national interests. In many developed countries, enforced cooperation with a suite of new regulations and agreements slowly but steadily restored both order and, importantly, economic growth.

There we have the prophetic Rockefellers in 2010 and three years later came their paper for the Global Health Summit in Beijing, China, when government representatives, the private sector, international organisations and groups met to discuss the next 100 years of 'global health'. The Rockefeller Foundation-funded paper was called 'Dreaming the Future of Health for the Next 100 Years and more prophecy ensued as it described a dystopian future: 'The abundance of data, digitally tracking and linking people may mean the 'death of privacy' and may replace physical interaction with transient, virtual connection, generating isolation and raising questions of how values are shaped in virtual networks.' Next in the 'Covid' hoax preparation sequence came a 'table top' simulation in 2018 for another 'imaginary' pandemic of a disease called Clade X which was said to kill 900 million people. The exercise was organised by the Gates-funded Johns Hopkins University's Center for Health Security in the United States and this is the very same university that has been compiling the disgustingly and systematically erroneous global figures for 'Covid' cases and deaths. Similar Johns Hopkins health crisis scenarios have included the Dark Winter exercise in 2001 and Atlantic Storm in 2005.

Nostradamus 201

For sheer predictive genius look no further prophecy-watchers than the Bill Gates-funded Event 201 held only six weeks before the 'coronavirus pandemic' is supposed to have broken out in China and Event 201 was based on a scenario of a global 'coronavirus pandemic'. Melinda Gates, the great man's missus, told the BBC that he had 'prepared for years' for a coronavirus pandemic which told us what we already knew. Nostradamugates had predicted in a TED talk in 2015 that a pandemic was coming that would kill a lot of people and demolish the world economy. My god, the man is a machine – possibly even literally. Now here he was only weeks before the real thing funding just such a simulated scenario and involving his friends and associates at Johns Hopkins, the World Economic Forum Cult-front of Klaus Schwab, the United Nations,

Johnson & Johnson, major banks, and officials from China and the Centers for Disease Control in the United States. What synchronicity – Johns Hopkins would go on to compile the fraudulent 'Covid' figures, the World Economic Forum and Schwab would push the 'Great Reset' in response to 'Covid', the Centers for Disease Control would be at the forefront of 'Covid' policy in the United States, Johnson & Johnson would produce a 'Covid vaccine', and everything would officially start just weeks later in China. Spooky, eh? They were even accurate in creating a simulation of a 'virus' pandemic because the 'real thing' would also be a simulation. Event 201 was not an exercise preparing for something that might happen; it was a rehearsal for what those in control knew was *going* to happen and very shortly. Hours of this simulation were posted on the Internet and the various themes and responses mirrored what would soon be imposed to transform human society. News stories were inserted and what they said would be commonplace a few weeks later with still more prophecy perfection. Much discussion focused on the need to deal with misinformation and the 'anti-vax movement' which is exactly what happened when the 'virus' arrived – was said to have arrived – in the West.

Cult-owned social media banned criticism and exposure of the official 'virus' narrative and when I said there *was* no 'virus' in early April, 2020, I was banned by one platform after another including YouTube, Facebook and later Twitter. The mainstream broadcast media in Britain was in effect banned from interviewing me by the Tony-Blair-created government broadcasting censor Ofcom headed by career government bureaucrat Melanie Dawes who was appointed just as the 'virus' hoax was about to play out in January, 2020. At the same time the Ickonic media platform was using Vimeo, another ultra-Zionist-owned operation, while our own player was being created and they deleted in an instant hundreds of videos, documentaries, series and shows to confirm their unbelievable vindictiveness. We had copies, of course, and they had to be restored one by one when our player was ready. These people have no class. Sabbatian Facebook promised free advertisements for the Gates-

controlled World Health Organization narrative while deleting 'false claims and conspiracy theories' to stop 'misinformation' about the alleged coronavirus. All these responses could be seen just a short while earlier in the scenarios of Event 201. Extreme censorship was absolutely crucial for the Cult because the official story was so ridiculous and unsupportable by the evidence that it could never survive open debate and the free-flow of information and opinion. If you can't win a debate then don't have one is the Cult's approach throughout history. Facebook's little boy front man – front boy – Mark Zuckerberg equated 'credible and accurate information' with official sources and exposing their lies with 'misinformation'.

Silencing those that can see

The censorship dynamic of Event 201 is now the norm with an army of narrative-supporting 'fact-checker' organisations whose entire reason for being is to tell the public that official narratives are true and those exposing them are lying. One of the most appalling of these 'fact-checkers' is called NewsGuard founded by ultra-Zionist Americans Gordon Crovitz and Steven Brill. Crovitz is a former publisher of *The Wall Street Journal*, former Executive Vice President of Dow Jones, a member of the Council on Foreign Relations (CFR), and on the board of the American Association of Rhodes Scholars. The CFR and Rhodes Scholarships, named after Rothschild agent Cecil Rhodes who plundered the gold and diamonds of South Africa for his masters and the Cult, have featured widely in my books. NewsGuard don't seem to like me for some reason – I really can't think why – and they have done all they can to have me censored and discredited which is, to quote an old British politician, like being savaged by a dead sheep. They are, however, like all in the censorship network, very well connected and funded by organisations themselves funded by, or connected to, Bill Gates. As you would expect with anything associated with Gates NewsGuard has an offshoot called HealthGuard which 'fights online health care hoaxes'. How very kind. Somehow the NewsGuard European Managing Director Anna-Sophie Harling, a remarkably young-

looking woman with no broadcasting experience and little hands-on work in journalism, has somehow secured a position on the 'Content Board' of UK government broadcast censor Ofcom. An executive of an organisation seeking to discredit dissidents of the official narratives is making decisions for the government broadcast 'regulator' about content?? Another appalling 'fact-checker' is Full Fact funded by George Soros and global censors Google and Facebook.

It's amazing how many activists in the 'fact-checking', 'anti-hate', arena turn up in government-related positions – people like UK Labour Party activist Imran Ahmed who heads the Center for Countering Digital Hate founded by people like Morgan McSweeney, now chief of staff to the Labour Party's hapless and useless 'leader' Keir Starmer. Digital Hate – which is what it really is – uses the American spelling of Center to betray its connection to a transatlantic network of similar organisations which in 2020 shapeshifted from attacking people for 'hate' to attacking them for questioning the 'Covid' hoax and the dangers of the 'Covid vaccine'. It's just a coincidence, you understand. This is one of Imran Ahmed's hysterical statements: 'I would go beyond calling anti-vaxxers conspiracy theorists to say they are an extremist group that pose a national security risk.' No one could ever accuse this prat of understatement and he's including in that those parents who are now against vaccines after their children were damaged for life or killed by them. He's such a nice man. Ahmed does the rounds of the Woke media getting soft-ball questions from spineless 'journalists' who never ask what right he has to campaign to destroy the freedom of speech of others while he demands it for himself. There also seems to be an overrepresentation in Ofcom of people connected to the narrative-worshipping BBC. This incredible global network of narrative-support was super-vital when the 'Covid' hoax was played in the light of the mega-whopper lies that have to be defended from the spotlight cast by the most basic intelligence.

Setting the scene

The Cult plays the long game and proceeds step-by-step ensuring that everything is in place before major cards are played and they don't come any bigger than the 'Covid' hoax. The psychopaths can't handle events where the outcome isn't certain and as little as possible – preferably nothing – is left to chance. Politicians, government and medical officials who would follow direction were brought to illusory power in advance by the Cult web whether on the national stage or others like state governors and mayors of America. For decades the dynamic between officialdom, law enforcement and the public was changed from one of service to one of control and dictatorship. Behaviour manipulation networks established within government were waiting to impose the coming 'Covid' rules and regulations specifically designed to subdue and rewire the psyche of the people in the guise of protecting health. These included in the UK the Behavioural Insights Team part-owned by the British government Cabinet Office; the Scientific Pandemic Insights Group on Behaviours (SPI-B); and a whole web of intelligence and military groups seeking to direct the conversation on social media and control the narrative. Among them are the cyberwarfare (on the people) 77th Brigade of the British military which is also coordinated through the Cabinet Office as civilian and military leadership continues to combine in what they call the Fusion Doctrine. The 77th Brigade is a British equivalent of the infamous Israeli (Sabbatian) military cyberwarfare and Internet manipulation operation Unit 8200 which I expose at length in *The Trigger*. Also carefully in place were the medical and science advisers to government – many on the payroll past or present of Bill Gates – and a whole alternative structure of unelected government stood by to take control when elected parliaments were effectively closed down once the 'Covid' card was slammed on the table. The structure I have described here and so much more was installed in every major country through the Cult networks. The top-down control hierarchy looks like this: The Cult – Cult-owned Gates – the World Health Organization and Tedros – Gates-funded or controlled chief medical officers and science 'advisers' (dictators) in each country –

political 'leaders'– law enforcement – The People. Through this simple global communication and enforcement structure the policy of the Cult could be imposed on virtually the entire human population so long as they acquiesced to the fascism. With everything in place it was time for the button to be pressed in late 2019/early 2020.

These were the prime goals the Cult had to secure for its will to prevail:

1) Locking down economies, closing all but designated 'essential' businesses (Cult-owned corporations were 'essential'), and putting the population under house arrest was an imperative to destroy independent income and employment and ensure dependency on the Cult-controlled state in the Hunger Games Society. Lockdowns had to be established as the global blueprint from the start to respond to the 'virus' and followed by pretty much the entire world.

2) The global population had to be terrified into believing in a deadly 'virus' that didn't actually exist so they would unquestioningly obey authority in the belief that authority must know how best to protect them and their families. Software salesman Gates would suddenly morph into the world's health expert and be promoted as such by the Cult-owned media.

3) A method of testing that wasn't testing for the 'virus', but was only claimed to be, had to be in place to provide the illusion of 'cases' and subsequent 'deaths' that had a very different cause to the 'Covid-19' that would be scribbled on the death certificate.

4) Because there was no 'virus' and the great majority testing positive with a test not testing for the 'virus' would have no symptoms of anything the lie had to be sold that people without symptoms (without the 'virus') could still pass it on to others. This was crucial to justify for the first time quarantining – house arresting – healthy people. Without this the economy-destroying lockdown of *everybody* could not have been credibly sold.

5) The 'saviour' had to be seen as a vaccine which beyond evil drug companies were working like angels of mercy to develop as quickly as possible, with all corners cut, to save the day. The public must absolutely not know that the 'vaccine' had nothing to do with a 'virus' or that the contents were ready and waiting with a very different motive long before the 'Covid' card was even lifted from the pack.

I said in March, 2020, that the 'vaccine' would have been created way ahead of the 'Covid' hoax which justified its use and the following December an article in the New York *Intelligencer* magazine said the Moderna 'vaccine' had been 'designed' by

January, 2020. This was 'before China had even acknowledged that the disease could be transmitted from human to human, more than a week before the first confirmed coronavirus case in the United States'. The article said that by the time the first American death was announced a month later 'the vaccine had already been manufactured and shipped to the National Institutes of Health for the beginning of its Phase I clinical trial'. The 'vaccine' was actually 'designed' long before that although even with this timescale you would expect the article to ask how on earth it could have been done that quickly. Instead it asked why the 'vaccine' had not been rolled out then and not months later. Journalism in the mainstream is truly dead. I am going to detail in the next chapter why the 'virus' has never existed and how a hoax on that scale was possible, but first the foundation on which the Big Lie of 'Covid' was built.

The test that doesn't test

Fraudulent 'testing' is the bottom line of the whole 'Covid' hoax and was the means by which a 'virus' that did not exist *appeared* to exist. They could only achieve this magic trick by using a test not testing for the 'virus'. To use a test that *was* testing for the 'virus' would mean that every test would come back negative given there was no 'virus'. They chose to exploit something called the RT-PCR test invented by American biochemist Kary Mullis in the 1980s who said publicly that his PCR test … *cannot detect infectious disease*. Yes, the 'test' used worldwide to detect infectious 'Covid' to produce all the illusory 'cases' and 'deaths' compiled by Johns Hopkins and others *cannot detect infectious disease*. This fact came from the mouth of the man who invented PCR and was awarded the Nobel Prize in Chemistry in 1993 for doing so. Sadly, and incredibly conveniently for the Cult, Mullis died in August, 2019, at the age of 74 just before his test would be fraudulently used to unleash fascism on the world. He was said to have died from pneumonia which was an irony in itself. A few months later he would have had 'Covid-19' on his death certificate. I say the timing of his death was convenient because had he lived Mullis, a brilliant, honest and decent man, would have been

vociferously speaking out against the use of his test to detect 'Covid' when it was never designed, or able, to do that. I know that to be true given that Mullis made the same point when his test was used to 'detect' – not detect – HIV. He had been seriously critical of the Gallo/Montagnier claim to have isolated the HIV 'virus' and shown it to cause AIDS for which Mullis said there was no evidence. AIDS is actually not a disease but a series of diseases from which people die all the time. When they die from those *same diseases* after a positive 'test' for HIV then AIDS goes on their death certificate. I think I've heard that before somewhere. Countries instigated a policy with 'Covid' that anyone who tested positive with a test not testing for the 'virus' and died of any other cause within 28 days and even longer 'Covid-19' had to go on the death certificate. Cases have come from the test that can't test for infectious disease and the deaths are those who have died of *anything* after testing positive with a test not testing for the 'virus'. I'll have much more later about the death certificate scandal.

Mullis was deeply dismissive of the now US 'Covid' star Anthony Fauci who he said was a liar who didn't know anything about anything – 'and I would say that to his face – nothing.' He said of Fauci: 'The man thinks he can take a blood sample, put it in an electron microscope and if it's got a virus in there you'll know it – he doesn't understand electron microscopy and he doesn't understand medicine and shouldn't be in a position like he's in.' That position, terrifyingly, has made him the decider of 'Covid' fascism policy on behalf of the Cult in his role as director since 1984 of the National Institute of Allergy and Infectious Diseases (NIAID) while his record of being wrong is laughable; but being wrong, so long as it's the *right kind* of wrong, is why the Cult loves him. He'll say anything the Cult tells him to say. Fauci was made Chief Medical Adviser to the President immediately Biden took office. Biden was installed in the White House by Cult manipulation and one of his first decisions was to elevate Fauci to a position of even more control. This is a coincidence? Yes, and I identify as a flamenco dancer called Lola. How does such an incompetent criminal like Fauci remain in that

pivotal position in American health since *the 1980s*? When you serve the Cult it looks after you until you are surplus to requirements. Kary Mullis said prophetically of Fauci and his like: 'Those guys have an agenda and it's not an agenda we would like them to have … they make their own rules, they change them when they want to, and Tony Fauci does not mind going on television in front of the people who pay his salary and lie directly into the camera.' Fauci has done that almost daily since the 'Covid' hoax began. Lying is in Fauci's DNA. To make the situation crystal clear about the PCR test this is a direct quote from its inventor Kary Mullis:

> It [the PCR test] doesn't tell you that you're sick and doesn't tell you that the thing you ended up with was really going to hurt you ...'

Ask yourself why governments and medical systems the world over have been using this very test to decide who is 'infected' with the SARS-CoV-2 'virus' and the alleged disease it allegedly causes, 'Covid-19'. The answer to that question will tell you what has been going on. By the way, here's a little show-stopper – the 'new' SARS-CoV-2 'virus' was 'identified' as such right from the start using … *the PCR test not testing for the 'virus'*. If you are new to this and find that shocking then stick around. I have hardly started yet. Even worse, other 'tests', like the 'Lateral Flow Device' (LFD), are considered so useless that they have to be *confirmed* by the PCR test! Leaked emails written by Ben Dyson, adviser to UK 'Health' Secretary Matt Hancock, said they were 'dangerously unreliable'. Dyson, executive director of strategy at the Department of Health, wrote: 'As of today, someone who gets a positive LFD result in (say) London has at best a 25 per cent chance of it being a true positive, but if it is a self-reported test potentially as low as 10 per cent (on an optimistic assumption about specificity) or as low as 2 per cent (on a more pessimistic assumption).' These are the 'tests' that schoolchildren and the public are being urged to have twice a week or more and have to isolate if they get a positive. Each fake positive goes in the statistics as a 'case' no matter how ludicrously inaccurate and the

'cases' drive lockdown, masks and the pressure to 'vaccinate'. The government said in response to the email leak that the 'tests' were accurate which confirmed yet again what shocking bloody liars they are. The real false positive rate is *100 percent* as we'll see. In another 'you couldn't make it up' the UK government agreed to pay £2.8 billion to California's Innova Medical Group to supply the irrelevant lateral flow tests. The company's primary test-making centre is in China. Innova Medical Group, established in March, 2020, is owned by Pasaca Capital Inc, chaired by Chinese-American millionaire Charles Huang who was born in Wuhan.

How it works – and how it doesn't

The RT-PCR test, known by its full title of Polymerase chain reaction, is used across the world to make millions, even billions, of copies of a DNA/RNA genetic information sample. The process is called 'amplification' and means that a tiny sample of genetic material is amplified to bring out the detailed content. I stress that it is not testing for an infectious disease. It is simply amplifying a sample of genetic material. In the words of Kary Mullis: 'PCR is … just a process that's used to make a whole lot of something out of something.' To emphasise the point companies that make the PCR tests circulated around the world to 'test' for 'Covid' warn on the box that it can't be used to detect 'Covid' or infectious disease and is for research purposes only. It's okay, rest for a minute and you'll be fine. This is the test that produces the 'cases' and 'deaths' that have been used to destroy human society. All those global and national medical and scientific 'experts' demanding this destruction to 'save us' *KNOW* that the test is not testing for the 'virus' and the cases and deaths they claim to be real are an almost unimaginable fraud. Every one of them and so many others including politicians and psychopaths like Gates and Tedros must be brought before Nuremburg-type trials and jailed for the rest of their lives. The more the genetic sample is amplified by PCR the more elements of that material become sensitive to the test and by that I don't mean sensitive for a 'virus' but for elements of the genetic material which

is *naturally* in the body or relates to remnants of old conditions of various kinds lying dormant and causing no disease. Once the amplification of the PCR reaches a certain level *everyone* will test positive. So much of the material has been made sensitive to the test that everyone will have some part of it in their body. Even lying criminals like Fauci have said that once PCR amplifications pass 35 cycles everything will be a false positive that cannot be trusted for the reasons I have described. I say, like many proper doctors and scientists, that 100 percent of the 'positives' are false, but let's just go with Fauci for a moment.

He says that any amplification over 35 cycles will produce false positives and yet the US Centers for Disease Control (CDC) and Food and Drug Administration (FDA) have recommended up to *40 cycles* and the National Health Service (NHS) in Britain admitted in an internal document for staff that it was using *45 cycles* of amplification. A long list of other countries has been doing the same and at least one 'testing' laboratory has been using *50 cycles*. Have you ever heard a doctor, medical 'expert' or the media ask what level of amplification has been used to claim a 'positive'. The 'test' comes back 'positive' and so you have the 'virus', end of story. Now we can see how the government in Tanzania could send off samples from a goat and a pawpaw fruit under human names and both came back positive for 'Covid-19'. Tanzania president John Magufuli mocked the 'Covid' hysteria, the PCR test and masks and refused to import the DNA-manipulating 'vaccine'. The Cult hated him and an article sponsored by the Bill Gates Foundation appeared in the London *Guardian* in February, 2021, headed 'It's time for Africa to rein in Tanzania's anti-vaxxer president'. Well, 'reined in' he shortly was. Magufuli appeared in good health, but then, in March, 2021, he was dead at 61 from 'heart failure'. He was replaced by Samia Hassan Suhulu who is connected to Klaus Schwab's World Economic Forum and she immediately reversed Magufuli's 'Covid' policy. A sample of cola tested positive for 'Covid' with the PCR test in Germany while American actress and singer-songwriter Erykah Badu tested positive in one nostril and negative in the other. Footballer Ronaldo called

the PCR test 'bullshit' after testing positive three times and being forced to quarantine and miss matches when there was nothing wrong with him. The mantra from Tedros at the World Health Organization and national governments (same thing) has been test, test, test. They know that the more tests they can generate the more fake 'cases' they have which go on to become 'deaths' in ways I am coming to. The UK government has its Operation Moonshot planned to test multiple millions every day in workplaces and schools with free tests for everyone to use twice a week at home in line with the Cult plan from the start to make testing part of life. A government advertisement for an 'Interim Head of Asymptomatic Testing Communication' said the job included responsibility for delivering a 'communications strategy' (propaganda) 'to support the expansion of asymptomatic testing that *'normalises testing as part of everyday life*'. More tests means more fake 'cases', 'deaths' and fascism. I have heard of, and from, many people who booked a test, couldn't turn up, and yet got a positive result through the post for a test they'd never even had. The whole thing is crazy, but for the Cult there's method in the madness. Controlling and manipulating the level of amplification of the test means the authorities can control whenever they want the number of apparent 'cases' and 'deaths'. If they want to justify more fascist lockdown and destruction of livelihoods they keep the amplification high. If they want to give the illusion that lockdowns and the 'vaccine' are working then they lower the amplification and 'cases' and 'deaths' will appear to fall. In January, 2021, the Cult-owned World Health Organization suddenly warned laboratories about over-amplification of the test and to lower the threshold. Suddenly headlines began appearing such as: 'Why ARE "Covid" cases plummeting?' This was just when the vaccine rollout was underway and I had predicted months before they would make cases appear to fall through amplification tampering when the 'vaccine' came. These people are so predictable.

Cow vaccines?

The question must be asked of what is on the test swabs being poked far up the nose of the population to the base of the brain? A nasal swab punctured one woman's brain and caused it to leak fluid. Most of these procedures are being done by people with little training or medical knowledge. Dr Lorraine Day, former orthopaedic trauma surgeon and Chief of Orthopaedic Surgery at San Francisco General Hospital, says the tests are really a *'vaccine'*. Cows have long been vaccinated this way. She points out that masks have to cover the nose and the mouth where it is claimed the 'virus' exists in saliva. Why then don't they take saliva from the mouth as they do with a DNA test instead of pushing a long swab up the nose towards the brain? The ethmoid bone separates the nasal cavity from the brain and within that bone is the cribriform plate. Dr Day says that when the swab is pushed up against this plate and twisted the procedure is 'depositing things back there'. She claims that among these 'things' are nanoparticles that can enter the brain. Researchers have noted that a team at the Gates-funded Johns Hopkins have designed tiny, star-shaped micro-devices that can latch onto intestinal mucosa and release drugs into the body. Mucosa is the thin skin that covers the inside surface of parts of the body such as *the nose* and mouth and produces mucus to protect them. The Johns Hopkins micro-devices are called 'theragrippers' and were 'inspired' by a parasitic worm that digs its sharp teeth into a host's intestines. Nasal swabs are also coated in the sterilisation agent ethylene oxide. The US National Cancer Institute posts this explanation on its website:

> At room temperature, ethylene oxide is a flammable colorless gas with a sweet odor. It is used primarily to produce other chemicals, including antifreeze. In smaller amounts, ethylene oxide is used as a pesticide and a sterilizing agent. The ability of ethylene oxide to damage DNA makes it an effective sterilizing agent but also accounts for its cancer-causing activity.

The Institute mentions lymphoma and leukaemia as cancers most frequently reported to be associated with occupational exposure to ethylene oxide along with stomach and breast cancers. How does anyone think this is going to work out with the constant testing

regime being inflicted on adults and children at home and at school that will accumulate in the body anything that's on the swab?

Doctors know best

It is vital for people to realise that 'hero' doctors 'know' only what the Big Pharma-dominated medical authorities tell them to 'know' and if they refuse to 'know' what they are told to 'know' they are out the door. They are mostly not physicians or healers, but repeaters of the official narrative – or else. I have seen alleged professional doctors on British television make shocking statements that we are supposed to take seriously. One called 'Dr' Amir Khan, who is actually telling patients how to respond to illness, said that men could take the birth pill to 'help slow down the effects of Covid-19'. In March, 2021, another ridiculous 'Covid study' by an American doctor proposed injecting men with the female sex hormone progesterone as a 'Covid' treatment. British doctor Nighat Arif told the BBC that face coverings were now going to be part of ongoing normal. Yes, the vaccine protects you, she said (evidence?) … but the way to deal with viruses in the community was always going to come down to hand washing, face covering and keeping a physical distance. That's not what we were told before the 'vaccine' was circulating. Arif said she couldn't imagine ever again going on the underground or in a lift without a mask. I was just thanking my good luck that she was not my doctor when she said – in March, 2021 – that if 'we are *behaving* and we are doing all the right things' she thought we could 'have our nearest and dearest around us at home … around *Christmas* and N*ew Year!* Her patronising delivery was the usual school teacher talking to six-year-olds as she repeated every government talking point and probably believed them all. If we have learned anything from the 'Covid' experience surely it must be that humanity's perception of doctors needs a fundamental rethink. NHS 'doctor' Sara Kayat told her television audience that the 'Covid vaccine' would '100 percent prevent hospitalisation and death'. Not even Big Pharma claimed that. We have to stop taking 'experts' at their word without question when so many of them are

clueless and only repeating the party line on which their careers depend. That is not to say there are not brilliants doctors – there are and I have spoken to many of them since all this began – but you won't see them in the mainstream media or quoted by the psychopaths and yes-people in government.

Remember the name – Christian Drosten

German virologist Christian Drosten, Director of Charité Institute of Virology in Berlin, became a national star after the pandemic hoax began. He was feted on television and advised the German government on 'Covid' policy. Most importantly to the wider world Drosten led a group that produced the 'Covid' testing protocol for the PCR test. What a remarkable feat given the PCR cannot test for infectious disease and even more so when you think that Drosten said that his method of testing for SARS-CoV-2 was developed 'without having virus material available'. *He developed a test for a 'virus' that he didn't have and had never seen*. Let that sink in as you survey the global devastation that came from what he did. The whole catastrophe of Drosten's 'test' was based on the alleged genetic sequence published by Chinese scientists on the Internet. We will see in the next chapter that this alleged 'genetic sequence' has never been produced by China or anyone and cannot be when there *is no* SARS-CoV-2. Drosten, however, doesn't seem to let little details like that get in the way. He was the lead author with Victor Corman from the same Charité Hospital of the paper 'Detection of 2019 novel coronavirus (2019-nCoV) by real-time PCR' published in a magazine called *Eurosurveillance*. This became known as the Corman-Drosten paper. In November, 2020, with human society devastated by the effects of the Corman-Drosten test baloney, the protocol was publicly challenged by 22 international scientists and independent researchers from Europe, the United States, and Japan. Among them were senior molecular geneticists, biochemists, immunologists, and microbiologists. They produced a document headed 'External peer review of the RTPCR test to detect SARS-Cov-2 Reveals 10 Major Flaws At The Molecular and Methodological Level: Consequences

For False-Positive Results'. The flaws in the Corman-Drosten test included the following:

- The test is non-specific because of erroneous design
- Results are enormously variable
- The test is unable to discriminate between the whole 'virus' and viral fragments
- It doesn't have positive or negative controls
- The test lacks a standard operating procedure
- It is unsupported by proper peer view

The scientists said the PCR 'Covid' testing protocol was not founded on science and they demanded the Corman-Drosten paper be retracted by *Eurosurveillance*. They said all present and previous Covid deaths, cases, and 'infection rates' should be subject to a massive retroactive inquiry. Lockdowns and travel restrictions should be reviewed and relaxed and those diagnosed through PCR to have 'Covid-19' should not be forced to isolate. Dr Kevin Corbett, a health researcher and nurse educator with a long academic career producing a stream of peer-reviewed publications at many UK universities, made the same point about the PCR test debacle. He said of the scientists' conclusions: 'Every scientific rationale for the development of that test has been totally destroyed by this paper. It's like Hiroshima/Nagasaki to the Covid test.' He said that China hadn't given them an isolated 'virus' when Drosten developed the test. Instead they had developed the test from *a sequence in a gene bank*.' Put another way … *they made it up*! The scientists were supported in this contention by a Portuguese appeals court which ruled in November, 2020, that PCR tests are unreliable and it is unlawful to quarantine people based solely on a PCR test. The point about China not providing an isolated virus must be true when the 'virus' has never been isolated to this day and the consequences of that will become clear. Drosten and company produced this useless 'protocol' right on cue in January, 2020, just as the 'virus' was said to

be moving westward and it somehow managed to successfully pass a peer-review in 24 hours. In other words there was no peer-review for a test that would be used to decide who had 'Covid' and who didn't across the world. The Cult-created, Gates-controlled World Health Organization immediately recommended all its nearly 200 member countries to use the Drosten PCR protocol to detect 'cases' and 'deaths'. The sting was underway and it continues to this day.

So who is this Christian Drosten that produced the means through which death, destruction and economic catastrophe would be justified? His education background, including his doctoral thesis, would appear to be somewhat shrouded in mystery and his track record is dire as with another essential player in the 'Covid' hoax, the Gates-funded Professor Neil Ferguson at the Gates-funded Imperial College in London of whom more shortly. Drosten predicted in 2003 that the alleged original SARS 'virus' (SARS-1') was an epidemic that could have serious effects on economies and an effective vaccine would take at least two years to produce. Drosten's answer to every alleged 'outbreak' is a vaccine which you won't be shocked to know. What followed were just 774 official deaths worldwide and none in Germany where there were only nine cases. That is even if you believe there ever was a SARS 'virus' when the evidence is zilch and I will expand on this in the next chapter. Drosten claims to be co-discoverer of 'SARS-1' and developed a test for it in 2003. He was screaming warnings about 'swine flu' in 2009 and how it was a widespread infection far more severe than any dangers from a vaccine could be and people should get vaccinated. It would be helpful for Drosten's vocal chords if he simply recorded the words 'the virus is deadly and you need to get vaccinated' and copies could be handed out whenever the latest made-up threat comes along. Drosten's swine flu epidemic never happened, but Big Pharma didn't mind with governments spending hundreds of millions on vaccines that hardly anyone bothered to use and many who did wished they hadn't. A study in 2010 revealed that the risk of dying from swine flu, or H1N1, was no higher than that of the annual seasonal flu which is what at least most of 'it' really was as in

the case of 'Covid-19'. A media investigation into Drosten asked how with such a record of inaccuracy he could be *the* government adviser on these issues. The answer to that question is the same with Drosten, Ferguson and Fauci – they keep on giving the authorities the 'conclusions' and 'advice' they want to hear. Drosten certainly produced the goods for them in January, 2020, with his PCR protocol garbage and provided the foundation of what German internal medicine specialist Dr Claus Köhnlein, co-author of *Virus Mania*, called the 'test pandemic'. The 22 scientists in the *Eurosurveillance* challenge called out conflicts of interest within the Drosten 'protocol' group and with good reason. Olfert Landt, a regular co-author of Drosten 'studies', owns the biotech company TIB Molbiol Syntheselabor GmbH in Berlin which manufactures and sells the tests that Drosten and his mates come up with. They have done this with SARS, Enterotoxigenic E. coli (ETEC), MERS, Zika 'virus', yellow fever, and now 'Covid'. Landt told the *Berliner Zeitung* newspaper:

> The testing, design and development came from the Charité [Drosten and Corman]. We simply implemented it immediately in the form of a kit. And if we don't have the virus, which originally only existed in Wuhan, we can make a synthetic gene to simulate the genome of the virus. That's what we did very quickly.

This is more confirmation that the Drosten test was designed without access to the 'virus' and only a synthetic simulation which is what SARS-CoV-2 really is – a computer-generated synthetic fiction. It's quite an enterprise they have going here. A Drosten team decides what the test for something should be and Landt's biotech company flogs it to governments and medical systems across the world. His company must have made an absolute fortune since the 'Covid' hoax began. Dr Reiner Fuellmich, a prominent German consumer protection trial lawyer in Germany and California, is on Drosten's case and that of Tedros at the World Health Organization for crimes against humanity with a class-action lawsuit being prepared in the United States and other legal action in Germany.

Why China?

Scamming the world with a 'virus' that doesn't exist would seem impossible on the face of it, but not if you have control of the relatively few people that make policy decisions and the great majority of the global media. Remember it's not about changing 'real' reality it's about controlling *perception* of reality. You don't have to make something happen you only have make people *believe* that it's happening. Renegade Minds understand this and are therefore much harder to swindle. 'Covid-19' is not a 'real' 'virus'. It's a mind virus, like a computer virus, which has infected the minds, not the bodies, of billions. It all started, publically at least, in China and that alone is of central significance. The Cult was behind the revolution led by its asset Mao Zedong, or Chairman Mao, which established the People's Republic of China on October 1st, 1949. It should have been called The Cult's Republic of China, but the name had to reflect the recurring illusion that vicious dictatorships are run by and for the people (see all the 'Democratic Republics' controlled by tyrants). In the same way we have the 'Biden' Democratic Republic of America officially ruled by a puppet tyrant (at least temporarily) on behalf of Cult tyrants. The creation of Mao's merciless communist/fascist dictatorship was part of a frenzy of activity by the Cult at the conclusion of World War Two which, like the First World War, it had instigated through its assets in Germany, Britain, France, the United States and elsewhere. Israel was formed in 1948; the Soviet Union expanded its 'Iron Curtain' control, influence and military power with the Warsaw Pact communist alliance in 1955; the United Nations was formed in 1945 as a Cult precursor to world government; and a long list of world bodies would be established including the World Health Organization (1948), World Trade Organization (1948 under another name until 1995), International Monetary Fund (1945) and World Bank (1944). Human society was redrawn and hugely centralised in the global Problem-Reaction-Solution that was World War Two. All these changes were significant. Israel would become the headquarters of the Sabbatians

and the revolution in China would prepare the ground and control system for the events of 2019/2020.

Renegade Minds know there are no borders except for public consumption. The Cult is a seamless, borderless global entity and to understand the game we need to put aside labels like borders, nations, countries, communism, fascism and democracy. These delude the population into believing that countries are ruled within their borders by a government of whatever shade when these are mere agencies of a global power. America's illusion of democracy and China's communism/fascism are subsidiaries – vehicles – for the same agenda. We may hear about conflict and competition between America and China and on the lower levels that will be true; but at the Cult level they are branches of the same company in the way of the McDonald's example I gave earlier. I have tracked in the books over the years support by US governments of both parties for Chinese Communist Party infiltration of American society through allowing the sale of land, even military facilities, and the acquisition of American business and university influence. All this is underpinned by the infamous stealing of intellectual property and technological know-how. Cult-owned Silicon Valley corporations waive their fraudulent 'morality' to do business with human-rights-free China; Cult-controlled Disney has become China's PR department; and China in effect owns 'American' sports such as basketball which depends for much of its income on Chinese audiences. As a result any sports player, coach or official speaking out against China's horrific human rights record is immediately condemned or fired by the China-worshipping National Basketball Association. One of the first acts of China-controlled Biden was to issue an executive order telling federal agencies to stop making references to the 'virus' by the 'geographic location of its origin'. Long-time Congressman Jerry Nadler warned that criticising China, America's biggest rival, leads to hate crimes against Asian people in the United States. So shut up you bigot. China is fast closing in on Israel as a country that must not be criticised which is apt, really, given that Sabbatians control them both. The two countries have

developed close economic, military, technological and strategic ties which include involvement in China's 'Silk Road' transport and economic initiative to connect China with Europe. Israel was the first country in the Middle East to recognise the establishment of Mao's tyranny in 1950 months after it was established.

Project Wuhan – the 'Covid' Psyop

I emphasise again that the Cult plays the long game and what is happening to the world today is the result of centuries of calculated manipulation following a script to take control step-by-step of every aspect of human society. I will discuss later the common force behind all this that has spanned those centuries and thousands of years if the truth be told. Instigating the Mao revolution in China in 1949 with a 2020 'pandemic' in mind is not only how they work – the 71 years between them is really quite short by the Cult's standards of manipulation preparation. The reason for the Cult's Chinese revolution was to create a fiercely-controlled environment within which an extreme structure for human control could be incubated to eventually be unleashed across the world. We have seen this happen since the 'pandemic' emerged from China with the Chinese control-structure founded on AI technology and tyrannical enforcement sweep across the West. Until the moment when the Cult went for broke in the West and put its fascism on public display Western governments had to pay some lip-service to freedom and democracy to not alert too many people to the tyranny-in-the-making. Freedoms were more subtly eroded and power centralised with covert government structures put in place waiting for the arrival of 2020 when that smokescreen of 'freedom' could be dispensed with. The West was not able to move towards tyranny before 2020 anything like as fast as China which was created as a tyranny and had no limits on how fast it could construct the Cult's blueprint for global control. When the time came to impose that structure on the world it was the same Cult-owned Chinese communist/fascist government that provided the excuse – the 'Covid pandemic'. It was absolutely crucial to the Cult plan for the Chinese response to the 'pandemic' –

draconian lockdowns of the entire population – to become the blueprint that Western countries would follow to destroy the livelihoods and freedom of their people. This is why the Cult-owned, Gates-owned, WHO Director-General Tedros said early on:

The Chinese government is to be congratulated for the extraordinary measures it has taken to contain the outbreak. China is actually setting a new standard for outbreak response and it is not an exaggeration.

Forbes magazine said of China: '… those measures protected untold millions from getting the disease'. The Rockefeller Foundation 'epidemic scenario' document in 2010 said 'prophetically':

However, a few countries did fare better – China in particular. The Chinese government's quick imposition and enforcement of mandatory quarantine for all citizens, as well as its instant and near-hermetic sealing off of all borders, saved millions of lives, stopping the spread of the virus far earlier than in other countries and enabling a swifter post-pandemic recovery.

Once again – *spooky*.

The first official story was the 'bat theory' or rather the bat diversion. The source of the 'virus outbreak' we were told was a ''wet market' in Wuhan where bats and other animals are bought and eaten in horrifically unhygienic conditions. Then another story emerged through the alternative media that the 'virus' had been released on purpose or by accident from a BSL-4 (biosafety level 4) laboratory in Wuhan not far from the wet market. The lab was reported to create and work with lethal concoctions and bioweapons. Biosafety level 4 is the highest in the World Health Organization system of safety and containment. Renegade Minds are aware of what I call designer manipulation. The ideal for the Cult is for people to buy its prime narrative which in the opening salvoes of the 'pandemic' was the wet market story. It knows, however, that there is now a considerable worldwide alternative media of researchers sceptical of anything governments say and they are often given a version of events in a form they can perceive as credible while misdirecting them from the real truth. In this case let them

think that the conspiracy involved is a 'bioweapon virus' released from the Wuhan lab to keep them from the real conspiracy – *there is no 'virus'*. The WHO's current position on the source of the outbreak at the time of writing appears to be: 'We haven't got a clue, mate.' This is a good position to maintain mystery and bewilderment. The inner circle will know where the 'virus' came from – *nowhere*. The bottom line was to ensure the public believed there *was* a 'virus' and it didn't much matter if they thought it was natural or had been released from a lab. The belief that there was a 'deadly virus' was all that was needed to trigger global panic and fear. The population was terrified into handing their power to authority and doing what they were told. They had to or they were 'all gonna die'.

In March, 2020, information began to come my way from real doctors and scientists and my own additional research which had my intuition screaming: 'Yes, that's it! *There is no virus*.' The 'bioweapon' was not the 'virus'; it was the *'vaccine'* already being talked about that would be the bioweapon. My conclusion was further enhanced by happenings in Wuhan. The 'virus' was said to be sweeping the city and news footage circulated of people collapsing in the street (which they've never done in the West with the same 'virus'). The Chinese government was building 'new hospitals' in a matter of ten days to 'cope with demand' such was the virulent nature of the 'virus'. Yet in what seemed like no time the 'new hospitals' closed – even if they even opened – and China declared itself 'virus-free'. It was back to business as usual. This was more propaganda to promote the Chinese draconian lockdowns in the West as the way to 'beat the virus'. Trouble was that we subsequently had lockdown after lockdown, but never business as usual. As the people of the West and most of the rest of the world were caught in an ever-worsening spiral of lockdown, social distancing, masks, isolated old people, families forced apart, and livelihood destruction, it was party-time in Wuhan. Pictures emerged of thousands of people enjoying pool parties and concerts. It made no sense until you realised there never was a 'virus' and the

whole thing was a Cult set-up to transform human society out of one its major global strongholds – China.

How is it possible to deceive virtually the entire world population into believing there is a deadly virus when there is not even a 'virus' let alone a deadly one? It's nothing like as difficult as you would think and that's clearly true because it happened.

Postscript: See end of book Postscript for more on the 'Wuhan lab virus release' story which the authorities and media were pushing heavily in the summer of 2021 to divert attention from the truth that the 'Covid virus' is pure invention.

CHAPTER FIVE

There *is no* 'virus'

You can fool some of the people all of the time, and all of the people some of the time, but you cannot fool all of the people all of the time
Abraham Lincoln

The greatest form of mind control is repetition. The more you repeat the same mantra of alleged 'facts' the more will accept them to be true. It becomes an 'everyone knows that, mate'. If you can also censor any other version or alternative to your alleged 'facts' you are pretty much home and cooking.

By the start of 2020 the Cult owned the global mainstream media almost in its entirety to spew out its 'Covid' propaganda and ignore or discredit any other information and view. Cult-owned social media platforms in Cult-owned Silicon Valley were poised and ready to unleash a campaign of ferocious censorship to obliterate all but the official narrative. To complete the circle many demands for censorship by Silicon Valley were led by the mainstream media as 'journalists' became full-out enforcers for the Cult both as propagandists and censors. Part of this has been the influx of young people straight out of university who have become 'journalists' in significant positions. They have no experience and a headful of programmed perceptions from their years at school and university at a time when today's young are the most perceptually-targeted generations in known human history given the insidious impact of technology. They enter the media perceptually prepared and ready to repeat the narratives of the system that programmed them to

repeat its narratives. The BBC has a truly pathetic 'specialist disinformation reporter' called Marianna Spring who fits this bill perfectly. She is clueless about the world, how it works and what is really going on. Her role is to discredit anyone doing the job that a proper journalist would do and system-serving hacks like Spring wouldn't dare to do or even see the need to do. They are too busy licking the arse of authority which can never be wrong and, in the case of the BBC propaganda programme, *Panorama*, contacting payments systems such as PayPal to have a donations page taken down for a film company making documentaries questioning vaccines. Even the BBC soap opera *EastEnders* included a disgracefully biased scene in which an inarticulate white working class woman was made to look foolish for questioning the 'vaccine' while a well-spoken black man and Asian woman promoted the government narrative. It ticked every BBC box and the fact that the black and minority community was resisting the 'vaccine' had nothing to do with the way the scene was written. The BBC has become a disgusting tyrannical propaganda and censorship operation that should be defunded and disbanded and a free media take its place with a brief to stop censorship instead of demanding it. A BBC 'interview' with Gates goes something like: 'Mr Gates, sir, if I can call you sir, would you like to tell our audience why you are such a great man, a wonderful humanitarian philanthropist, and why you should absolutely be allowed as a software salesman to decide health policy for approaching eight billion people? Thank you, sir, please sir.' Propaganda programming has been incessant and merciless and when all you hear is the same story from the media, repeated by those around you who have only heard the same story, is it any wonder that people on a grand scale believe absolute mendacious garbage to be true? You are about to see, too, why this level of information control is necessary when the official 'Covid' narrative is so nonsensical and unsupportable by the evidence.

Structure of Deceit

The pyramid structure through which the 'Covid' hoax has been manifested is very simple and has to be to work. As few people as possible have to be involved with full knowledge of what they are doing – and why – or the real story would get out. At the top of the pyramid are the inner core of the Cult which controls Bill Gates who, in turn, controls the World Health Organization through his pivotal funding and his puppet Director-General mouthpiece, Tedros. Before he was appointed Tedros was chair of the Gates-founded Global Fund to 'fight against AIDS, tuberculosis and malaria', a board member of the Gates-funded 'vaccine alliance' GAVI, and on the board of another Gates-funded organisation. Gates owns him and picked him for a specific reason – Tedros is a crook and worse. 'Dr' Tedros (he's not a medical doctor, the first WHO chief not to be) was a member of the tyrannical Marxist government of Ethiopia for decades with all its human rights abuses. He has faced allegations of corruption and misappropriation of funds and was exposed three times for covering up cholera epidemics while Ethiopia's health minister. Tedros appointed the mass-murdering genocidal Zimbabwe dictator Robert Mugabe as a WHO goodwill ambassador for public health which, as with Tedros, is like appointing a psychopath to run a peace and love campaign. The move was so ridiculous that he had to drop Mugabe in the face of widespread condemnation. American economist David Steinman, a Nobel peace prize nominee, lodged a complaint with the International Criminal Court in The Hague over alleged genocide by Tedros when he was Ethiopia's foreign minister. Steinman says Tedros was a 'crucial decision maker' who directed the actions of Ethiopia's security forces from 2013 to 2015 and one of three officials in charge when those security services embarked on the 'killing' and 'torturing' of Ethiopians. You can see where Tedros is coming from and it's sobering to think that he has been the vehicle for Gates and the Cult to direct the global response to 'Covid'. Think about that. A psychopathic Cult dictates to psychopath Gates who dictates to psychopath Tedros who dictates how countries of the world must respond to a 'Covid virus' never scientifically shown to exist. At the same time psychopathic Cult-owned Silicon Valley information

giants like Google, YouTube, Facebook and Twitter announced very early on that they would give the Cult/Gates/Tedros/WHO version of the narrative free advertising and censor those who challenged their intelligence-insulting, mendacious story.

The next layer in the global 'medical' structure below the Cult, Gates and Tedros are the chief medical officers and science 'advisers' in each of the WHO member countries which means virtually all of them. Medical officers and arbiters of science (they're not) then take the WHO policy and recommended responses and impose them on their country's population while the political 'leaders' say they are deciding policy (they're clearly not) by 'following the science' on the advice of the 'experts' – the same medical officers and science 'advisers' (dictators). In this way with the rarest of exceptions the entire world followed the same policy of lockdown, people distancing, masks and 'vaccines' dictated by the psychopathic Cult, psychopathic Gates and psychopathic Tedros who we are supposed to believe give a damn about the health of the world population they are seeking to enslave. That, amazingly, is all there is to it in terms of crucial decision-making. Medical staff in each country then follow like sheep the dictates of the shepherds at the top of the national medical hierarchies – chief medical officers and science 'advisers' who themselves follow like sheep the shepherds of the World Health Organization and the Cult. Shepherds at the national level often have major funding and other connections to Gates and his Bill and Melinda Gates Foundation which carefully hands out money like confetti at a wedding to control the entire global medical system from the WHO down.

Follow the money

Christopher Whitty, Chief Medical Adviser to the UK Government at the centre of 'virus' policy, a senior adviser to the government's Scientific Advisory Group for Emergencies (SAGE), and Executive Board member of the World Health Organization, was gifted a grant of $40 million by the Bill and Melinda Gates Foundation for malaria research in Africa. The BBC described the unelected Whitty as 'the

official who will probably have the greatest impact on our everyday lives of any individual policymaker in modern times' and so it turned out. What Gates and Tedros have said Whitty has done like his equivalents around the world. Patrick Vallance, co-chair of SAGE and the government's Chief Scientific Adviser, is a former executive of Big Pharma giant GlaxoSmithKline with its fundamental financial and business connections to Bill Gates. In September, 2020, it was revealed that Vallance owned a deferred bonus of shares in GlaxoSmithKline worth £600,000 while the company was 'developing' a 'Covid vaccine'. Move along now – nothing to see here – what could possibly be wrong with that? Imperial College in London, a major player in 'Covid' policy in Britain and elsewhere with its 'Covid-19' Response Team, is funded by Gates and has big connections to China while the now infamous Professor Neil Ferguson, the useless 'computer modeller' at Imperial College is also funded by Gates. Ferguson delivered the dramatically inaccurate excuse for the first lockdowns (much more in the next chapter). The Institute for Health Metrics and Evaluation (IHME) in the United States, another source of outrageously false 'Covid' computer models to justify lockdowns, is bankrolled by Gates who is a vehement promotor of lockdowns. America's version of Whitty and Vallance, the again now infamous Anthony Fauci, has connections to 'Covid vaccine' maker Moderna as does Bill Gates through funding from the Bill and Melinda Gates Foundation. Fauci is director of the National Institute of Allergy and Infectious Diseases (NIAID), a major recipient of Gates money, and they are very close. Deborah Birx who was appointed White House Coronavirus Response Coordinator in February, 2020, is yet another with ties to Gates. Everywhere you look at the different elements around the world behind the coordination and decision making of the 'Covid' hoax there is Bill Gates and his money. They include the World Health Organization; Centers for Disease Control (CDC) in the United States; National Institutes of Health (NIH) of Anthony Fauci; Imperial College and Neil Ferguson; the London School of Hygiene where Chris Whitty worked; Regulatory agencies like the UK Medicines & Healthcare products Regulatory Agency (MHRA)

which gave emergency approval for 'Covid vaccines'; Wellcome Trust; GAVI, the Vaccine Alliance; the Coalition for Epidemic Preparedness Innovations (CEPI); Johns Hopkins University which has compiled the false 'Covid' figures; and the World Economic Forum. A Nationalfile.com article said:

> Gates has a lot of pull in the medical world, he has a multi-million dollar relationship with Dr. Fauci, and Fauci originally took the Gates line supporting vaccines and casting doubt on [the drug hydroxychloroquine]. Coronavirus response team member Dr. Deborah Birx, appointed by former president Obama to serve as United States Global AIDS Coordinator, also sits on the board of a group that has received billions from Gates' foundation, and Birx reportedly used a disputed Bill Gates-funded model for the White House's Coronavirus effort. Gates is a big proponent for a population lockdown scenario for the Coronavirus outbreak.

Another funder of Moderna is the Defense Advanced Research Projects Agency (DARPA), the technology-development arm of the Pentagon and one of the most sinister organisations on earth. DARPA had a major role with the CIA covert technology-funding operation In-Q-Tel in the development of Google and social media which is now at the centre of global censorship. Fauci and Gates are extremely close and openly admit to talking regularly about 'Covid' policy, but then why wouldn't Gates have a seat at every national 'Covid' table after his Foundation committed $1.75 billion to the 'fight against Covid-19'. When passed through our Orwellian Translation Unit this means that he has bought and paid for the Cult-driven 'Covid' response worldwide. Research the major 'Covid' response personnel in your own country and you will find the same Gates funding and other connections again and again. Medical and science chiefs following World Health Organization 'policy' sit atop a medical hierarchy in their country of administrators, doctors and nursing staff. These 'subordinates' are told they must work and behave in accordance with the policy delivered from the 'top' of the national 'health' pyramid which is largely the policy delivered by the WHO which is the policy delivered by Gates and the Cult. The whole 'Covid' narrative has been imposed on medical staff by a climate of fear although great numbers don't even need that to comply. They do so through breathtaking levels of ignorance and

include doctors who go through life simply repeating what Big Pharma and their hierarchical masters tell them to say and believe. No wonder Big Pharma 'medicine' is one of the biggest killers on Planet Earth.

The same top-down system of intimidation operates with regard to the Cult Big Pharma cartel which also dictates policy through national and global medical systems in this way. The Cult and Big Pharma agendas are the same because the former controls and owns the latter. 'Health' administrators, doctors, and nursing staff are told to support and parrot the dictated policy or they will face consequences which can include being fired. How sad it's been to see medical staff meekly repeating and imposing Cult policy without question and most of those who can see through the deceit are only willing to speak anonymously off the record. They know what will happen if their identity is known. This has left the courageous few to expose the lies about the 'virus', face masks, overwhelmed hospitals that aren't, and the dangers of the 'vaccine' that isn't a vaccine. When these medical professionals and scientists, some renowned in their field, have taken to the Internet to expose the truth their articles, comments and videos have been deleted by Cult-owned Facebook, Twitter and YouTube. What a real head-shaker to see YouTube videos with leading world scientists and highly qualified medical specialists with an added link underneath to the notorious Cult propaganda website *Wikipedia* to find the 'facts' about the same subject.

HIV – the 'Covid' trial-run

I'll give you an example of the consequences for health and truth that come from censorship and unquestioning belief in official narratives. The story was told by PCR inventor Kary Mullis in his book *Dancing Naked in the Mind Field*. He said that in 1984 he accepted as just another scientific fact that Luc Montagnier of France's Pasteur Institute and Robert Gallo of America's National Institutes of Health had independently discovered that a 'retrovirus' dubbed HIV (human immunodeficiency virus) caused AIDS. They

were, after all, Mullis writes, specialists in retroviruses. This is how the medical and science pyramids work. Something is announced or *assumed* and then becomes an everybody-knows-that purely through repetition of the assumption as if it is fact. Complete crap becomes accepted truth with no supporting evidence and only repetition of the crap. This is how a 'virus' that doesn't exist became the 'virus' that changed the world. The HIV-AIDS fairy story became a multi-billion pound industry and the media poured out propaganda terrifying the world about the deadly HIV 'virus' that caused the lethal AIDS. By then Mullis was working at a lab in Santa Monica, California, to detect retroviruses with his PCR test in blood donations received by the Red Cross. In doing so he asked a virologist where he could find a reference for HIV being the cause of AIDS. 'You don't need a reference,' the virologist said … *'Everybody knows it.'* Mullis said he wanted to quote a reference in the report he was doing and he said he felt a little funny about not knowing the source of such an important discovery when everyone else seemed to. The virologist suggested he cite a report by the Centers for Disease Control and Prevention (CDC) on morbidity and mortality. Mullis read the report, but it only said that an organism had been identified and did not say how. The report did not identify the original scientific work. Physicians, however, *assumed* (key recurring theme) that if the CDC was convinced that HIV caused AIDS then proof must exist. Mullis continues:

I did computer searches. Neither Montagnier, Gallo, nor anyone else had published papers describing experiments which led to the conclusion that HIV probably caused AIDS. I read the papers in Science for which they had become well known as AIDS doctors, but all they had said there was that they had found evidence of a past infection by something which was probably HIV in some AIDS patients.

They found antibodies. Antibodies to viruses had always been considered evidence of past disease, not present disease. Antibodies signaled that the virus had been defeated. The patient had saved himself. There was no indication in these papers that this virus caused a disease. They didn't show that everybody with the antibodies had the disease. In fact they found some healthy people with antibodies.

Mullis asked why their work had been published if Montagnier and Gallo hadn't really found this evidence, and why had they been fighting so hard to get credit for the discovery? He says he was hesitant to write 'HIV is the probable cause of AIDS' until he found published evidence to support that. 'Tens of thousands of scientists and researchers were spending billions of dollars a year doing research based on this idea,' Mullis writes. 'The reason had to be there somewhere; otherwise these people would not have allowed their research to settle into one narrow channel of investigation.' He said he lectured about PCR at numerous meetings where people were always talking about HIV and he asked them how they knew that HIV was the cause of AIDS:

> Everyone said something. Everyone had the answer at home, in the office, in some drawer. They all knew, and they would send me the papers as soon as they got back. But I never got any papers. Nobody ever sent me the news about how AIDS was caused by HIV.

Eventually Mullis was able to ask Montagnier himself about the reference proof when he lectured in San Diego at the grand opening of the University of California AIDS Research Center. Mullis says this was the last time he would ask his question without showing anger. Montagnier said he should reference the CDC report. 'I read it', Mullis said, and it didn't answer the question. 'If Montagnier didn't know the answer who the hell did?' Then one night Mullis was driving when an interview came on National Public Radio with Peter Duesberg, a prominent virologist at Berkeley and a California Scientist of the Year. Mullis says he finally understood why he could not find references that connected HIV to AIDS – *there weren't any!* No one had ever proved that HIV causes AIDS even though it had spawned a multi-billion pound global industry and the media was repeating this as fact every day in their articles and broadcasts terrifying the shit out of people about AIDS and giving the impression that a positive test for HIV (see 'Covid') was a death sentence. Duesberg was a threat to the AIDS gravy train and the agenda that underpinned it. He was therefore abused and castigated after he told the Proceedings of the National Academy of Sciences

there was no good evidence implicating the new 'virus'. Editors rejected his manuscripts and his research funds were deleted. Mullis points out that the CDC has defined AIDS as one of more than 30 diseases *if accompanied* by a positive result on a test that detects antibodies to HIV; but those same diseases are not defined as AIDS cases when antibodies are not detected:

> If an HIV-positive woman develops uterine cancer, for example, she is considered to have AIDS. If she is not HIV positive, she simply has uterine cancer. An HIV-positive man with tuberculosis has AIDS; if he tests negative he simply has tuberculosis. If he lives in Kenya or Colombia, where the test for HIV antibodies is too expensive, he is simply presumed to have the antibodies and therefore AIDS, and therefore he can be treated in the World Health Organization's clinic. It's the only medical help available in some places. And it's free, because the countries that support WHO are worried about AIDS.

Mullis accuses the CDC of continually adding new diseases (see ever more 'Covid symptoms') to the grand AIDS definition and of virtually doctoring the books to make it appear as if the disease continued to spread. He cites how in 1993 the CDC enormously broadened its AIDS definition and county health authorities were delighted because they received $2,500 per year from the Federal government for every reported AIDS case. Ladies and gentlemen, I have just described, via Kary Mullis, the 'Covid pandemic' of 2020 and beyond. Every element is the same and it's been pulled off in the same way by the same networks.

The 'Covid virus' exists? Okay – prove it. Er … still waiting

What Kary Mullis described with regard to 'HIV' has been repeated with 'Covid'. A claim is made that a new, or 'novel', infection has been found and the entire medical system of the world repeats that as fact exactly as they did with HIV and AIDS. No one in the mainstream asks rather relevant questions such as 'How do you know?' and 'Where is your proof?' The SARS-Cov-2 'virus' and the 'Covid-19 disease' became an overnight 'everybody-knows-that'. The origin could be debated and mulled over, but what you could not suggest was that 'SARS-Cov-2' didn't exist. That would be

ridiculous. 'Everybody knows' the 'virus' exists. Well, I didn't for one along with American proper doctors like Andrew Kaufman and Tom Cowan and long-time American proper journalist Jon Rappaport. We dared to pursue the obvious and simple question: 'Where's the evidence?' The overwhelming majority in medicine, journalism and the general public did not think to ask that. After all, *everyone knew* there was a new 'virus'. Everyone was saying so and I heard it on the BBC. Some would eventually argue that the 'deadly virus' was nothing like as deadly as claimed, but few would venture into the realms of its very existence. Had they done so they would have found that the evidence for that claim had gone AWOL as with HIV causes AIDS. In fact, not even that. For something to go AWOL it has to exist in the first place and scientific proof for a 'SARS-Cov-2' can be filed under nothing, nowhere and zilch.

Dr Andrew Kaufman is a board-certified forensic psychiatrist in New York State, a Doctor of Medicine and former Assistant Professor and Medical Director of Psychiatry at SUNY Upstate Medical University, and Medical Instructor of Hematology and Oncology at the Medical School of South Carolina. He also studied biology at the Massachusetts Institute of Technology (MIT) and trained in Psychiatry at Duke University. Kaufman is retired from allopathic medicine, but remains a consultant and educator on natural healing, I saw a video of his very early on in the 'Covid' hoax in which he questioned claims about the 'virus' in the absence of any supporting evidence and with plenty pointing the other way. I did everything I could to circulate his work which I felt was asking the pivotal questions that needed an answer. I can recommend an excellent pull-together interview he did with the website The Last Vagabond entitled *Dr Andrew Kaufman: Virus Isolation, Terrain Theory and Covid-19* and his website is andrewkaufmanmd.com. Kaufman is not only a forensic psychiatrist; he is forensic in all that he does. He always reads original scientific papers, experiments and studies instead of second-third-fourth-hand reports about the 'virus' in the media which are repeating the repeated repetition of the narrative. When he did so with the original Chinese 'virus' papers Kaufman

realised that there was no evidence of a 'SARS-Cov-2'. They had never – from the start – shown it to exist and every repeat of this claim worldwide was based on the accepted existence of proof that was nowhere to be found – see Kary Mullis and HIV. Here we go again.

Let's postulate

Kaufman discovered that the Chinese authorities immediately concluded that the cause of an illness that broke out among about 200 initial patients in Wuhan was a 'new virus' when there were no grounds to make that conclusion. The alleged 'virus' was not isolated from other genetic material in their samples and then shown through a system known as Koch's postulates to be the causative agent of the illness. The world was told that the SARS-Cov-2 'virus' caused a disease they called 'Covid-19' which had 'flu-like' symptoms and could lead to respiratory problems and pneumonia. If it wasn't so tragic it would almost be funny. *'Flu-like' symptoms'? Pneumonia? Respiratory disease?* What in *CHINA* and particularly in *Wuhan*, one of the most polluted cities in the world with a resulting epidemic of respiratory disease?? Three hundred thousand people get pneumonia in China every year and there are nearly a billion cases worldwide of 'flu-like symptoms'. These have a whole range of causes – including pollution in Wuhan – but no other possibility was credibly considered in late 2019 when the world was told there was a new and deadly 'virus'. The global prevalence of pneumonia and 'flu-like systems' gave the Cult networks unlimited potential to re-diagnose these other causes as the mythical 'Covid-19' and that is what they did from the very start. Kaufman revealed how Chinese medical and science authorities (all subordinates to the Cult-owned communist government) took genetic material from the lungs of only a few of the first patients. The material contained their own cells, bacteria, fungi and other microorganisms living in their bodies. The only way you could prove the existence of the 'virus' and its responsibility for the alleged 'Covid-19' was to isolate the virus from all the other material – a process also known as 'purification' – and

then follow the postulates sequence developed in the late 19th century by German physician and bacteriologist Robert Koch which became the 'gold standard' for connecting an alleged causation agent to a disease:

1. The microorganism (bacteria, fungus, virus, etc.) must be present in every case of the disease and all patients must have the same symptoms. It must also *not be present in healthy individuals*.

2. The microorganism must be isolated from the host with the disease. If the microorganism is a bacteria or fungus it must be grown in a pure culture. If it is a virus, it must be purified (i.e. containing no other material except the virus particles) from a clinical sample.

3. The specific disease, with all of its characteristics, must be reproduced when the infectious agent (the purified virus or a pure culture of bacteria or fungi) is inoculated into a healthy, susceptible host.

4. The microorganism must be recoverable from the experimentally infected host as in step 2.

Not one of these criteria has been met in the case of 'SARS-Cov-2' and 'Covid-19'. Not ONE. *EVER*. Robert Koch refers to bacteria and not viruses. What are called 'viral particles' are so minute (hence masks are useless by any definition) that they could only be seen after the invention of the electron microscope in the 1930s and can still only be observed through that means. American bacteriologist and virologist Thomas Milton Rivers, the so-called 'Father of Modern Virology' who was very significantly director of the Rockefeller Institute for Medical Research in the 1930s, developed a less stringent version of Koch's postulates to identify 'virus' causation known as 'Rivers criteria'. 'Covid' did not pass that process either. Some even doubt whether any 'virus' can be isolated from other particles containing genetic material in the Koch method. Freedom of Information requests in many countries asking for scientific proof that the 'Covid virus' has been purified and isolated and shown to exist have all come back with a 'we don't have that' and when this happened with a request to the UK Department of Health they added this comment:

However, outside of the scope of the [Freedom of Information Act] and on a discretionary basis, the following information has been advised to us, which may be of interest. Most infectious diseases are caused by viruses, bacteria or fungi. Some bacteria or fungi have the capacity to grow on their own in isolation, for example in colonies on a petri dish. Viruses are different in that they are what we call 'obligate pathogens' – that is, they cannot survive or reproduce without infecting a host ...

… For some diseases, it is possible to establish causation between a microorganism and a disease by isolating the pathogen from a patient, growing it in pure culture and reintroducing it to a healthy organism. These are known as 'Koch's postulates' and were developed in 1882. However, as our understanding of disease and different disease-causing agents has advanced, these are no longer the method for determining causation [Andrew Kaufman asks why in that case are there two published articles falsely claiming to satisfy Koch's postulates].

It has long been known that viral diseases cannot be identified in this way as viruses cannot be grown in 'pure culture'. When a patient is tested for a viral illness, this is normally done by looking for the presence of antigens, or viral genetic code in a host with molecular biology techniques [Kaufman asks how you could know the origin of these chemicals without having a pure culture for comparison].

For the record 'antigens' are defined so:

Invading microorganisms have antigens on their surface that the human body can recognise as being foreign – meaning not belonging to it. When the body recognises a foreign antigen, lymphocytes (white blood cells) produce antibodies, which are complementary in shape to the antigen.

Notwithstanding that this is open to question in relation to 'SARS-Cov-2' the presence of 'antibodies' can have many causes and they are found in people that are perfectly well. Kary Mullis said: 'Antibodies … had always been considered evidence of past disease, not present disease.'

'Covid' really is a *computer* 'virus'

Where the UK Department of Health statement says 'viruses' are now 'diagnosed' through a 'viral genetic code in a host with molecular biology techniques', they mean … *the PCR test* which its inventor said cannot test for infectious disease. They have no credible method of connecting a 'virus' to a disease and we will see that there is no scientific proof that any 'virus' causes any disease or there is any such thing as a 'virus' in the way that it is described. Tenacious Canadian researcher Christine Massey and her team made

some 40 Freedom of Information requests to national public health agencies in different countries asking for proof that SARS-CoV-2 has been isolated and not one of them could supply that information. Massey said of her request in Canada: 'Freedom of Information reveals Public Health Agency of Canada has no record of 'SARS-COV-2' isolation performed by anyone, anywhere, ever.' If you accept the comment from the UK Department of Health it's because they can't isolate a 'virus'. Even so many 'science' papers claimed to have isolated the 'Covid virus' until they were questioned and had to admit they hadn't. A reply from the Robert Koch Institute in Germany was typical: 'I am not aware of a paper which purified isolated SARS-CoV-2.' So what the hell was Christian Drosten and his gang using to design the 'Covid' testing protocol that has produced all the illusory Covid' cases and 'Covid' deaths when the head of the Chinese version of the CDC admitted there was a problem right from the start in that the 'virus' had never been isolated/purified? Breathe deeply: What they are calling 'Covid' is actually created by a *computer program* i.e. *they made it up* – er, that's it. They took lung fluid, with many sources of genetic material, from one single person alleged to be infected with Covid-19 by a PCR test which they *claimed*, without clear evidence, contained a 'virus'. They used several computer programs to create a model of a theoretical virus genome sequence from more than fifty-six million small sequences of RNA, each of an unknown source, assembling them like a puzzle with no known solution. The computer filled in the gaps with sequences from bits in the gene bank to make it look like a bat SARS-like coronavirus! A wave of the magic wand and poof, an in silico (computer-generated) genome, a scientific fantasy, was created. UK health researcher Dr Kevin Corbett made the same point with this analogy:

> … It's like giving you a few bones and saying that's your fish. It could be any fish. Not even a skeleton. Here's a few fragments of bones. That's your fish … It's all from gene bank and the bits of the virus sequence that weren't there they made up.
>
> They synthetically created them to fill in the blanks. That's what genetics is; it's a code. So it's ABBBCCDDD and you're missing some what you think is EEE so you put it in. It's all

synthetic. You just manufacture the bits that are missing. This is the end result of the geneticization of virology. This is basically a computer virus.

Further confirmation came in an email exchange between British citizen journalist Frances Leader and the government's Medicines & Healthcare Products Regulatory Agency (the Gates-funded MHRA) which gave emergency permission for untested 'Covid vaccines' to be used. The agency admitted that the 'vaccine' is not based on an isolated 'virus', but comes from a *computer-generated model*. Frances Leader was naturally banned from Cult-owned fascist Twitter for making this exchange public. The process of creating computer-generated alleged 'viruses' is called 'in silico' or 'in silicon' – computer chips – and the term 'in silico' is believed to originate with biological experiments using only a computer in 1989. 'Vaccines' involved with 'Covid' are also produced 'in silico' or by computer not a natural process. If the original 'virus' is nothing more than a made-up computer model how can there be 'new variants' of something that never existed in the first place? They are not new 'variants'; they are new *computer models* only minutely different to the original program and designed to further terrify the population into having the 'vaccine' and submitting to fascism. You want a 'new variant'? Click, click, enter – there you go. Tell the medical profession that you have discovered a 'South African variant', 'UK variants' or a 'Brazilian variant' and in the usual HIV-causes-AIDS manner they will unquestioningly repeat it with no evidence whatsoever to support these claims. They will go on television and warn about the dangers of 'new variants' while doing nothing more than repeating what they have been told to be true and knowing that any deviation from that would be career suicide. Big-time insiders will know it's a hoax, but much of the medical community is clueless about the way they are being played and themselves play the public without even being aware they are doing so. What an interesting 'coincidence' that AstraZeneca and Oxford University were conducting 'Covid vaccine trials' in the three countries – the UK, South Africa and Brazil – where the first three 'variants' were claimed to have 'broken out'.

Here's your 'virus' – it's a unicorn

Dr Andrew Kaufman presented a brilliant analysis describing how the 'virus' was imagined into fake existence when he dissected an article published by *Nature* and written by 19 authors detailing *alleged* 'sequencing of a complete viral genome' of the 'new SARS-CoV-2 virus'. This computer-modelled *in silico* genome was used as a template for all subsequent genome sequencing experiments that resulted in the so-called variants which he said now number more than *6,000*. The fake genome was constructed from more than 56 million individual short strands of RNA. Those little pieces were assembled into longer pieces by finding areas of overlapping sequences. The computer programs created over two million possible combinations from which the authors simply chose the longest one. They then compared this to a 'bat virus' and the computer 'alignment' rearranged the sequence and filled in the gaps! They called this computer-generated abomination the 'complete genome'. Dr Tom Cowan, a fellow medical author and collaborator with Kaufman, said such computer-generation constitutes scientific fraud and he makes this superb analogy:

> Here is an equivalency: A group of researchers claim to have found a unicorn because they found a piece of a hoof, a hair from a tail, and a snippet of a horn. They then add that information into a computer and program it to re-create the unicorn, and they then claim this computer re-creation is the real unicorn. Of course, they had never actually seen a unicorn so could not possibly have examined its genetic makeup to compare their samples with the actual unicorn's hair, hooves and horn.
>
> The researchers claim they decided which is the real genome of SARS-CoV-2 by 'consensus', sort of like a vote. Again, different computer programs will come up with different versions of the imaginary 'unicorn', so they come together as a group and decide which is the real imaginary unicorn.

This is how the 'virus' that has transformed the world was brought into fraudulent 'existence'. Extraordinary, yes, but as the Nazis said the bigger the lie the more will believe it. Cowan, however, wasn't finished and he went on to identify what he called the real blockbuster in the paper. He quotes this section from a paper written

by virologists and published by the CDC and then explains what it means:

Therefore, we examined the capacity of SARS-CoV-2 to infect and replicate in several common primate and human cell lines, including human adenocarcinoma cells (A549), human liver cells (HUH 7.0), and human embryonic kidney cells (HEK-293T). In addition to Vero E6 and Vero CCL81 cells. ... Each cell line was inoculated at high multiplicity of infection and examined 24h post-infection.

No CPE was observed in any of the cell lines except in Vero cells, which grew to greater than 10 to the 7th power at 24 h post-infection. In contrast, HUH 7.0 and 293T showed only modest viral replication, and A549 cells were incompatible with SARS CoV-2 infection.

Cowan explains that when virologists attempt to prove infection they have three possible 'hosts' or models on which they can test. The first was humans. Exposure to humans was generally not done for ethical reasons and has never been done with SARS-CoV-2 or any coronavirus. The second possible host was animals. Cowan said that forgetting for a moment that they never actually use purified virus when exposing animals they do use solutions that they *claim* contain the virus. Exposure to animals has been done with SARS-CoV-2 in an experiment involving mice and this is what they found: *None of the wild (normal) mice got sick*. In a group of genetically-modified mice, a statistically insignificant number lost weight and had slightly bristled fur, but they experienced nothing like the illness called 'Covid-19'. Cowan said the third method – the one they mostly rely on – is to inoculate solutions they *say* contain the virus onto a variety of tissue cultures. This process had never been shown to kill tissue *unless* the sample material was starved of nutrients and poisoned as *part of the process*. Yes, incredibly, in tissue experiments designed to show the 'virus' is responsible for killing the tissue they starve the tissue of nutrients and add toxic drugs including antibiotics and they do not have control studies to see if it's the starvation and poisoning that is degrading the tissue rather than the 'virus' they allege to be in there somewhere. You want me to pinch you? Yep, I understand. Tom Cowan said this about the whole nonsensical farce as he explains what that quote from the CDC paper really means:

The shocking thing about the above quote is that using their own methods, the virologists found that solutions containing SARS-CoV-2 – even in high amounts – were NOT, I repeat NOT, infective to any of the three human tissue cultures they tested. In plain English, this means they proved, on their terms, that this 'new coronavirus' is not infectious to human beings. It is ONLY infective to monkey kidney cells, and only then when you add two potent drugs (gentamicin and amphotericin), known to be toxic to kidneys, to the mix.

My friends, read this again and again. These virologists, published by the CDC, performed a clear proof, on their terms, showing that the SARS-CoV-2 virus is harmless to human beings. That is the only possible conclusion, but, unfortunately, this result is not even mentioned in their conclusion. They simply say they can provide virus stocks cultured only on monkey Vero cells, thanks for coming.

Cowan concluded: 'If people really understood how this "science" was done, I would hope they would storm the gates and demand honesty, transparency and truth.' Dr Michael Yeadon, former Vice President and Chief Scientific Adviser at drug giant Pfizer has been a vocal critic of the 'Covid vaccine' and its potential for multiple harm. He said in an interview in April, 2021, that 'not one [vaccine] has the virus. He was asked why vaccines normally using a 'dead' version of a disease to activate the immune system were not used for 'Covid' and instead we had the synthetic methods of the 'mRNA Covid vaccine'. Yeadon said that to do the former 'you'd have to have some of [the virus] wouldn't you?' He added: 'No-one's got any – seriously.' Yeadon said that surely they couldn't have fooled the whole world for a year without having a virus, 'but oddly enough ask around – no one's got it'. He didn't know why with all the 'great labs' around the world that the virus had not been isolated – 'Maybe they've been too busy running bad PCR tests and vaccines that people don't need.' What is today called 'science' is not 'science' at all. Science is no longer what is, but whatever people can be manipulated to *believe* that it is. Real science has been hijacked by the Cult to dispense and produce the 'expert scientists' and contentions that suit the agenda of the Cult. How big-time this has happened with the 'Covid' hoax which is entirely based on fake science delivered by fake 'scientists' and fake 'doctors'. The human-caused climate change hoax is also entirely based on fake science delivered by fake 'scientists' and fake 'climate experts'. In both cases real

scientists, climate experts and doctors have their views suppressed and deleted by the Cult-owned science establishment, media and Silicon Valley. This is the 'science' that politicians claim to be 'following' and a common denominator of 'Covid' and climate are Cult psychopaths Bill Gates and his mate Klaus Schwab at the Gates-funded World Economic Forum. But, don't worry, it's all just a coincidence and absolutely nothing to worry about. *Zzzzzzzz*.

What is a 'virus' REALLY?

Dr Tom Cowan is one of many contesting the very existence of viruses let alone that they cause disease. This is understandable when there is no scientific evidence for a disease-causing 'virus'. German virologist Dr Stefan Lanka won a landmark case in 2017 in the German Supreme Court over his contention that there is no such thing as a measles virus. He had offered a big prize for anyone who could prove there is and Lanka won his case when someone sought to claim the money. There is currently a prize of more than 225,000 euros on offer from an Isolate Truth Fund for anyone who can prove the isolation of SARS-CoV-2 and its genetic substance. Lanka wrote in an article headed 'The Misconception Called Virus' that scientists think a 'virus' is causing tissue to become diseased and degraded when in fact it is the *processes they are using* which do that – not a 'virus'. Lanka has done an important job in making this point clear as Cowan did in his analysis of the CDC paper. Lanka says that all claims about viruses as disease-causing pathogens are wrong and based on 'easily recognisable, understandable and verifiable misinterpretations.' Scientists believed they were working with 'viruses' in their laboratories when they were really working with 'typical particles of specific dying tissues or cells …' Lanka said that the tissue decaying process claimed to be caused by a 'virus' still happens when no alleged 'virus' is involved. It's the *process* that does the damage and not a 'virus'. The genetic sample is deprived of nutrients, removed from its energy supply through removal from the body and then doused in toxic antibiotics to remove any bacteria. He confirms again that establishment scientists do not (pinch me)

conduct control experiments to see if this is the case and if they did they would see the claims that 'viruses' are doing the damage is nonsense. He adds that during the measles 'virus' court case he commissioned an independent laboratory to perform just such a control experiment and the result was that the tissues and cells died in the exact same way as with alleged 'infected' material. This is supported by a gathering number of scientists, doctors and researchers who reject what is called 'germ theory' or the belief in the body being infected by contagious sources emitted by other people. Researchers Dawn Lester and David Parker take the same stance in their highly-detailed and sourced book *What Really Makes You Ill – Why everything you thought you knew about disease is wrong* which was recommended to me by a number of medical professionals genuinely seeking the truth. Lester and Parker say there is no provable scientific evidence to show that a 'virus' can be transmitted between people or people and animals or animals and people:

> The definition also claims that viruses are the cause of many diseases, as if this has been definitively proven. But this is not the case; there is no original scientific evidence that definitively demonstrates that any virus is the cause of any disease. The burden of proof for any theory lies with those who proposed it; but none of the existing documents provides 'proof' that supports the claim that 'viruses' are pathogens.

Dr Tom Cowan employs one of his clever analogies to describe the process by which a 'virus' is named as the culprit for a disease when what is called a 'virus' is only material released by cells detoxing themselves from infiltration by chemical or radiation poisoning. The tidal wave of technologically-generated radiation in the 'smart' modern world plus all the toxic food and drink are causing this to happen more than ever. Deluded 'scientists' misread this as a gathering impact of what they wrongly label 'viruses'.

Paper can infect houses

Cowan said in an article for davidicke.com – with his tongue only mildly in his cheek – that he believed he had made a tremendous

discovery that may revolutionise science. He had discovered that small bits of paper are alive, 'well alive-ish', can 'infect' houses, and then reproduce themselves inside the house. The result was that this explosion of growth in the paper inside the house causes the house to explode, blowing it to smithereens. His evidence for this new theory is that in the past months he had carefully examined many of the houses in his neighbourhood and found almost no scraps of paper on the lawns and surrounds of the house. There was an occasional stray label, but nothing more. Then he would return to these same houses a week or so later and with a few, not all of them, particularly the old and decrepit ones, he found to his shock and surprise they were littered with stray bits of paper. He knew then that the paper had infected these houses, made copies of itself, and blew up the house. A young boy on a bicycle at one of the sites told him he had seen a demolition crew using dynamite to explode the house the previous week, but Cowan dismissed this as the idle thoughts of silly boys because 'I was on to something big'. He was on to how 'scientists' mistake genetic material in the detoxifying process for something they call a 'virus'. Cowan said of his house and paper story:

> If this sounds crazy to you, it's because it should. This scenario is obviously nuts. But consider this admittedly embellished, for effect, current viral theory that all scientists, medical doctors and virologists currently believe.

He takes the example of the 'novel SARS-Cov2' virus to prove the point. First they take someone with an undefined illness called 'Covid-19' and don't even attempt to find any virus in their sputum. Never mind the scientists still describe how this 'virus', which they have not located attaches to a cell receptor, injects its genetic material, in 'Covid's' case, RNA, into the cell. The RNA once inserted exploits the cell to reproduce itself and makes 'thousands, nay millions, of copies of itself … Then it emerges victorious to claim its next victim':

If you were to look in the scientific literature for proof, actual scientific proof, that uniform SARS-CoV2 viruses have been properly isolated from the sputum of a sick person, that actual spike proteins could be seen protruding from the virus (which has not been found), you would find that such evidence doesn't exist.

If you go looking in the published scientific literature for actual pictures, proof, that these spike proteins or any viral proteins are ever attached to any receptor embedded in any cell membrane, you would also find that no such evidence exists. If you were to look for a video or documented evidence of the intact virus injecting its genetic material into the body of the cell, reproducing itself and then emerging victorious by budding off the cell membrane, you would find that no such evidence exists.

The closest thing you would find is electron micrograph pictures of cellular particles, possibly attached to cell debris, both of which to be seen were stained by heavy metals, a process that completely distorts their architecture within the living organism. This is like finding bits of paper stuck to the blown-up bricks, thereby proving the paper emerged by taking pieces of the bricks on its way out.

The Enders baloney

Cowan describes the 'Covid' story as being just as make-believe as his paper story and he charts back this fantasy to a Nobel Prize winner called John Enders (1897-1985), an American biomedical scientist who has been dubbed 'The Father of Modern Vaccines'. Enders is claimed to have 'discovered' the process of the viral culture which 'proved' that a 'virus' caused measles. Cowan explains how Enders did this 'by using the EXACT same procedure that has been followed by every virologist to find and characterize every new virus since 1954'. Enders took throat swabs from children with measles and immersed them in 2ml of milk. Penicillin (100u/ml) and the antibiotic streptomycin (50,g/ml) were added and the whole mix was centrifuged – rotated at high speed to separate large cellular debris from small particles and molecules as with milk and cream, for example. Cowan says that if the aim is to find little particles of genetic material ('viruses') in the snot from children with measles it would seem that the last thing you would do is mix the snot with other material – milk –that also has genetic material. 'How are you ever going to know whether whatever you found came from the snot or the milk?' He points out that streptomycin is a 'nephrotoxic' or poisonous-to-the-kidney drug. You will see the relevance of that

shortly. Cowan says that it gets worse, much worse, when Enders describes the culture medium upon which the virus 'grows': 'The culture medium consisted of bovine amniotic fluid (90%), beef embryo extract (5%), horse serum (5%), antibiotics and phenol red as an indicator of cell metabolism.' Cowan asks incredulously: 'Did he just say that the culture medium also contained fluids and tissues that are themselves rich sources of genetic material?' The genetic cocktail, or 'medium', is inoculated onto tissue and cells from rhesus monkey *kidney* tissue. This is where the importance of streptomycin comes in and currently-used antimicrobials and other drugs that are *poisonous to kidneys* and used in ALL modern viral cultures (e.g. gentamicin, streptomycin, and amphotericin). Cowan asks: 'How are you ever going to know from this witch's brew where any genetic material comes from as we now have five different sources of rich genetic material in our mix?' Remember, he says, that all genetic material, whether from monkey kidney tissues, bovine serum, milk, etc., is made from the exact same components. The same central question returns: 'How are you possibly going to know that it was the virus that killed the kidney tissue and not the toxic antibiotic and starvation rations on which you are growing the tissue?' John Enders answered the question himself – *you can't*:

A second agent was obtained from an uninoculated culture of monkey kidney cells. The cytopathic changes [death of the cells] it induced in the unstained preparations could not be distinguished with confidence from the viruses isolated from measles.

The death of the cells ('cytopathic changes') happened in exactly the same manner, whether they inoculated the kidney tissue with the measles snot or not, Cowan says. 'This is evidence that the destruction of the tissue, the very proof of viral causation of illness, was not caused by anything in the snot because they saw the same destructive effect when the snot was not even used … the cytopathic, i.e., cell-killing, changes come from the process of the culture itself, not from any virus in any snot, period.' Enders quotes in his 1957 paper a virologist called Ruckle as reporting similar findings 'and in addition has isolated an agent from monkey kidney tissue that is so

far indistinguishable from human measles virus'. In other words, Cowan says, these particles called 'measles viruses' are simply and clearly breakdown products of the starved and poisoned tissue. For measles 'virus' see all 'viruses' including the so-called 'Covid virus'. Enders, the 'Father of Modern Vaccines', also said:

There is a potential risk in employing cultures of primate cells for the production of vaccines composed of attenuated virus, since the presence of other agents possibly latent in primate tissues cannot be definitely excluded by any known method.

Cowan further quotes from a paper published in the journal *Viruses* in May, 2020, while the 'Covid pandemic' was well underway in the media if not in reality. 'EVs' here refers to particles of genetic debris from our own tissues, such as exosomes of which more in a moment: 'The remarkable resemblance between EVs and viruses has caused quite a few problems in the studies focused on the analysis of EVs released during viral infections.' Later the paper adds that to date a reliable method that can actually guarantee a complete separation (of EVs from viruses) DOES NOT EXIST. This was published at a time when a fairy tale 'virus' was claimed in total certainty to be causing a fairy tale 'viral disease' called 'Covid-19' – a fairy tale that was already well on the way to transforming human society in the image that the Cult has worked to achieve for so long. Cowan concludes his article:

To summarize, there is no scientific evidence that pathogenic viruses exist. What we think of as 'viruses' are simply the normal breakdown products of dead and dying tissues and cells. When we are well, we make fewer of these particles; when we are starved, poisoned, suffocated by wearing masks, or afraid, we make more.

There is no engineered virus circulating and making people sick. People in laboratories all over the world are making genetically modified products to make people sick. These are called vaccines. There is no virome, no 'ecosystem' of viruses, viruses are not 8%, 50% or 100 % of our genetic material. These are all simply erroneous ideas based on the misconception called a virus.

What is 'Covid'? Load of bollocks

The background described here by Cowan and Lanka was emphasised in the first video presentation that I saw by Dr Andrew Kaufman when he asked whether the 'Covid virus' was in truth a natural defence mechanism of the body called 'exosomes'. These are released by cells when in states of toxicity – see the same themes returning over and over. They are released ever more profusely as chemical and radiation toxicity increases and think of the potential effect therefore of 5G alone as its destructive frequencies infest the human energetic information field with a gathering pace (5G went online in Wuhan in 2019 as the 'virus' emerged). I'll have more about this later. Exosomes transmit a warning to the rest of the body that 'Houston, we have a problem'. Kaufman presented images of exosomes and compared them with 'Covid' under an electron microscope and the similarity was remarkable. They both attach to the same cell receptors (*claimed* in the case of 'Covid'), contain the same genetic material in the form of RNA or ribonucleic acid, and both are found in 'viral cell cultures' with damaged or dying cells. James Hildreth MD, President and Chief Executive Officer of the Meharry Medical College at Johns Hopkins, said: 'The virus is fully an exosome in every sense of the word.' Kaufman's conclusion was that there is no 'virus': 'This entire pandemic is a completely manufactured crisis … there is no evidence of anyone dying from [this] illness.' Dr Tom Cowan and Sally Fallon Morell, authors of *The Contagion Myth*, published a statement with Dr Kaufman in February, 2021, explaining why the 'virus' does not exist and you can read it that in full in the Appendix.

'Virus' theory can be traced to the 'cell theory' in 1858 of German physician Rudolf Virchow (1821-1920) who contended that disease originates from a single cell infiltrated by a 'virus'. Dr Stefan Lanka said that findings and insights with respect to the structure, function and central importance of tissues in the creation of life, which were already known in 1858, comprehensively refute the cell theory. Virchow ignored them. We have seen the part later played by John Enders in the 1950s and Lanka notes that infection theories were only established as a global dogma through the policies and

eugenics of the Third Reich in Nazi Germany (creation of the same Sabbatian cult behind the 'Covid' hoax). Lanka said: 'Before 1933, scientists dared to contradict this theory; after 1933, these critical scientists were silenced'. Dr Tom Cowan's view is that ill-heath is caused by too much of something, too little of something, or toxification from chemicals and radiation – not contagion. We must also highlight as a major source of the 'virus' theology a man still called the 'Father of Modern Virology' – Thomas Milton Rivers (1888-1962). There is no way given the Cult's long game policy that it was a coincidence for the 'Father of Modern Virology' to be director of the Rockefeller Institute for Medical Research from 1937 to 1956 when he is credited with making the Rockefeller Institute a leader in 'viral research'. Cult Rockefellers were the force behind the creation of Big Pharma 'medicine', established the World Health Organisation in 1948, and have long and close associations with the Gates family that now runs the WHO during the pandemic hoax through mega-rich Cult gofer and psychopath Bill Gates.

Only a Renegade Mind can see through all this bullshit by asking the questions that need to be answered, not taking 'no' or prevarication for an answer, and certainly not hiding from the truth in fear of speaking it. Renegade Minds have always changed the world for the better and they will change this one no matter how bleak it may currently appear to be.

CHAPTER SIX

Sequence of deceit

If you tell the truth, you don't have to remember anything
Mark Twain

Against the background that I have laid out this far the sequence that took us from an invented 'virus' in Cult-owned China in late 2019 to the fascist transformation of human society can be seen and understood in a whole new context.

We were told that a deadly disease had broken out in Wuhan and the world media began its campaign (coordinated by behavioural psychologists as we shall see) to terrify the population into unquestioning compliance. We were shown images of Chinese people collapsing in the street which never happened in the West with what was supposed to be the same condition. In the earliest days when alleged cases and deaths were few the fear register was hysterical in many areas of the media and this would expand into the common media narrative across the world. The real story was rather different, but we were never told that. The Chinese government, one of the Cult's biggest centres of global operation, said they had discovered a new illness with flu-like and pneumonia-type symptoms in a city with such toxic air that it is overwhelmed with flu-like symptoms, pneumonia and respiratory disease. Chinese scientists said it was a new – 'novel' – coronavirus which they called Sars-Cov-2 and that it caused a disease they labelled 'Covid-19'. There was no evidence for this and the 'virus' has never to this day been isolated, purified and its genetic code established from that. It

was from the beginning a computer-generated fiction. Stories of Chinese whistleblowers saying the number of deaths was being supressed or that the 'new disease' was related to the Wuhan bio-lab misdirected mainstream and alternative media into cul-de-sacs to obscure the real truth – there was no 'virus'.

Chinese scientists took genetic material from the lung fluid of just a few people and said they had found a 'new' disease when this material had a wide range of content. There was no evidence for a 'virus' for the very reasons explained in the last two chapters. The 'virus' has never been shown to (a) exist and (b) cause any disease. People were diagnosed on symptoms that are so widespread in Wuhan and polluted China and with a PCR test that can't detect infectious disease. On this farce the whole global scam was sold to the rest of the world which would also diagnose respiratory disease as 'Covid-19' from symptoms alone or with a PCR test not testing for a 'virus'. Flu miraculously disappeared *worldwide* in 2020 and into 2021 as it was redesignated 'Covid-19'. It was really the same old flu with its 'flu-like' symptoms attributed to 'flu-like' 'Covid-19'. At the same time with very few exceptions the Chinese response of draconian lockdown and fascism was the chosen weapon to respond across the West as recommended by the Cult-owned Tedros at the Cult-owned World Health Organization run by the Cult-owned Gates. All was going according to plan. Chinese scientists – everything in China is controlled by the Cult-owned government – compared their contaminated RNA lung-fluid material with other RNA sequences and said it appeared to be just under 80 percent identical to the SARS-CoV-1 'virus' claimed to be the cause of the SARS (severe acute respiratory syndrome) 'outbreak' in 2003. They decreed that because of this the 'new virus' had to be related and they called it SARS-CoV-2. There are some serious problems with this assumption and *assumption* was all it was. Most 'factual' science turns out to be assumptions repeated into everyone-knows-that. A match of under 80-percent is meaningless. Dr Kaufman makes the point that there's a *96 percent* genetic correlation between humans and chimpanzees, but 'no one would say our genetic material is part

of the chimpanzee family'. Yet the Chinese authorities were claiming that a much lower percentage, less than 80 percent, proved the existence of a new 'coronavirus'. For goodness sake human DNA is 60 percent similar to a *banana*.

You are feeling sleepy

The entire 'Covid' hoax is a global Psyop, a psychological operation to program the human mind into believing and fearing a complete fantasy. A crucial aspect of this was what *appeared* to happen in Italy. It was all very well streaming out daily images of an alleged catastrophe in Wuhan, but to the Western mind it was still on the other side of the world in a very different culture and setting. A reaction of 'this could happen to me and my family' was still nothing like as intense enough for the mind-doctors. The Cult needed a Western example to push people over that edge and it chose Italy, one of its major global locations going back to the Roman Empire. An Italian 'Covid' crisis was manufactured in a particular area called Lombardy which just happens to be notorious for its toxic air and therefore respiratory disease. Wuhan, China, déjà vu. An hysterical media told horror stories of Italians dying from 'Covid' in their droves and how Lombardy hospitals were being overrun by a tidal wave of desperately ill people needing treatment after being struck down by the 'deadly virus'. Here was the psychological turning point the Cult had planned. Wow, if this is happening in Italy, the Western mind concluded, this indeed could happen to me and my family. Another point is that Italian authorities responded by following the Chinese blueprint so vehemently recommended by the Cult-owned World Health Organization. They imposed fascistic lockdowns on the whole country viciously policed with the help of surveillance drones sweeping through the streets seeking out anyone who escaped from mass house arrest. Livelihoods were destroyed and psychology unravelled in the way we have witnessed since in all lockdown countries. Crucial to the plan was that Italy responded in this way to set the precedent of suspending freedom and imposing fascism in a 'Western liberal democracy'. I emphasised in an

animated video explanation on davidicke.com posted in the summer of 2020 how important it was to the Cult to expand the Chinese lockdown model across the West. Without this, and the bare-faced lie that non-symptomatic people could still transmit a 'disease' they didn't have, there was no way locking down the whole population, sick and not sick, could be pulled off. At just the right time and with no evidence Cult operatives and gofers claimed that people without symptoms could pass on the 'disease'. In the name of protecting the 'vulnerable' like elderly people, who lockdowns would kill by the tens of thousands, we had for the first time healthy people told to isolate as well as the sick. The great majority of people who tested positive had no symptoms because there was nothing wrong with them. It was just a trick made possible by a test not testing for the 'virus'.

Months after my animated video the Gates-funded Professor Neil Ferguson at the Gates-funded Imperial College confirmed that I was right. He didn't say it in those terms, naturally, but he did say it. Ferguson will enter the story shortly for his outrageously crazy 'computer models' that led to Britain, the United States and many other countries following the Chinese and now Italian methods of response. Put another way, following the Cult script. Ferguson said that SAGE, the UK government's scientific advisory group which has controlled 'Covid' policy from the start, wanted to follow the Chinese lockdown model (while they all continued to work and be paid), but they wondered if they could possibly, in Ferguson's words, 'get away with it in Europe'. 'Get away with it'? Who the hell do these moronic, arrogant people think they are? This appalling man Ferguson said that once Italy went into national lockdown they realised they, too, could mimic China:

> It's a communist one-party state, we said. We couldn't get away with it in Europe, we thought … and then Italy did it. And we realised we could. Behind this garbage from Ferguson is a simple fact: Doing the same as China in every country was the plan from the start and Ferguson's 'models' would play a central role in achieving that. It's just a coincidence, of course, and absolutely nothing to worry your little head about.

Oops, sorry, our mistake

Once the Italian segment of the Psyop had done the job it was designed to do a very different story emerged. Italian authorities revealed that 99 percent of those who had 'died from Covid-19' in Italy had one, two, three, or more 'co-morbidities' or illnesses and health problems that could have ended their life. The US Centers for Disease Control and Prevention (CDC) published a figure of 94 percent for Americans dying of 'Covid' while having other serious medical conditions – on average two to three (some five or six) other potential causes of death. In terms of death from an unproven 'virus' I say it is 100 percent. The other one percent in Italy and six percent in the US would presumably have died from 'Covid's' flu-like symptoms with a range of other possible causes in conjunction with a test not testing for the 'virus'. Fox News reported that even more startling figures had emerged in one US county in which 410 of 422 deaths attributed to 'Covid-19' had other potentially deadly health conditions. The Italian National Health Institute said later that the average age of people dying with a 'Covid-19' diagnosis in Italy was about 81. Ninety percent were over 70 with ten percent over 90. In terms of other reasons to die some 80 percent had two or more chronic diseases with half having three or more including cardiovascular problems, diabetes, respiratory problems and cancer. Why is the phantom 'Covid-19' said to kill overwhelmingly old people and hardly affect the young? Old people continually die of many causes and especially respiratory disease which you can re-diagnose 'Covid-19' while young people die in tiny numbers by comparison and rarely of respiratory disease. Old people 'die of Covid' because they die of other things that can be redesignated 'Covid' and it really is that simple.

Flu has flown

The blueprint was in place. Get your illusory 'cases' from a test not testing for the 'virus' and redesignate other causes of death as 'Covid-19'. You have an instant 'pandemic' from something that is nothing more than a computer-generated fiction. With near-on a

billion people having 'flu-like' symptoms every year the potential was limitless and we can see why flu quickly and apparently miraculously disappeared *worldwide* by being diagnosed 'Covid-19'. The painfully bloody obvious was explained away by the childlike media in headlines like this in the UK '*Independent*': 'Not a single case of flu detected by Public Health England this year as Covid restrictions suppress virus'. I kid you not. The masking, social distancing and house arrest that did not make the 'Covid virus' disappear somehow did so with the 'flu virus'. Even worse the article, by a bloke called Samuel Lovett, suggested that maybe the masking, sanitising and other 'Covid' measures should continue to keep the flu away. With a ridiculousness that disturbs your breathing (it's 'Covid-19') the said Lovett wrote: 'With widespread social distancing and mask-wearing measures in place throughout the UK, the usual routes of transmission for influenza have been blocked.' He had absolutely no evidence to support that statement, but look at the consequences of him acknowledging the obvious. With flu not disappearing at all and only being relabelled 'Covid-19' he would have to contemplate that 'Covid' was a hoax on a scale that is hard to imagine. You need guts and commitment to truth to even go there and that's clearly something Samuel Lovett does not have in abundance. He would never have got it through the editors anyway.

Tens of thousands die in the United States alone every winter from flu including many with pneumonia complications. CDC figures record *45 million* Americans diagnosed with flu in 2017-2018 of which 61,000 died and some reports claim 80,000. Where was the same hysteria then that we have seen with 'Covid-19'? Some 250,000 Americans are admitted to hospital with pneumonia every year with about 50,000 cases proving fatal. About 65 million suffer respiratory disease every year and three million deaths makes this the third biggest cause of death worldwide. You only have to redesignate a portion of all these people 'Covid-19' and you have an instant global pandemic or the *appearance* of one. Why would doctors do this? They are told to do this and all but a few dare not refuse those who must be obeyed. Doctors in general are not researching their own

knowledge and instead take it direct and unquestioned from the authorities that own them and their careers. The authorities say they must now diagnose these symptoms 'Covid-19' and not flu, or whatever, and they do it. Dark suits say put 'Covid-19' on death certificates no matter what the cause of death and the doctors do it. Renegade Minds don't fall for the illusion that doctors and medical staff are all highly-intelligent, highly-principled, seekers of medical truth. *Some are*, but not the majority. They are repeaters, gofers, and yes sir, no sir, purveyors of what the system demands they purvey. The 'Covid' con is not merely confined to diseases of the lungs. Instructions to doctors to put 'Covid-19' on death certificates for anyone dying of *anything* within 28 days (or much more) of a positive test not testing for the 'virus' opened the floodgates. The term dying *with* 'Covid' and not *of* 'Covid' was coined to cover the truth. Whether it was a *with* or an *of* they were all added to the death numbers attributed to the 'deadly virus' compiled by national governments and globally by the Gates-funded Johns Hopkins operation in the United States that was so involved in those 'pandemic' simulations. Fraudulent deaths were added to the ever-growing list of fraudulent 'cases' from false positives from a false test. No wonder Professor Walter Ricciardi, scientific advisor to the Italian minister of health, said after the Lombardy hysteria had done its job that 'Covid' death rates were due to Italy having the second oldest population in the world and to *how hospitals record deaths*:

The way in which we code deaths in our country is very generous in the sense that all the people who die in hospitals with the coronavirus are deemed to be dying of the coronavirus. On re-evaluation by the National Institute of Health, only 12 per cent of death certificates have shown a direct causality from coronavirus, while 88 per cent of patients who have died have at least one pre-morbidity – many had two or three.

This is extraordinary enough when you consider the propaganda campaign to use Italy to terrify the world, but how can they even say twelve percent were genuine when the 'virus' has not been shown to exist, its 'code' is a computer program, and diagnosis comes from a test not testing for it? As in China, and soon the world, 'Covid-19' in

Italy was a redesignation of diagnosis. Lies and corruption were to become the real 'pandemic' fuelled by a pathetically-compliant medical system taking its orders from the tiny few at the top of their national hierarchy who answered to the World Health Organization which answers to Gates and the Cult. Doctors were told – ordered – to diagnose a particular set of symptoms 'Covid-19' and put that on the death certificate for any cause of death if the patient had tested positive with a test not testing for the virus or had 'Covid' symptoms like the flu. The United States even introduced big financial incentives to manipulate the figures with hospitals receiving £4,600 from the Medicare system for diagnosing someone with regular pneumonia, $13,000 if they made the diagnosis from the same symptoms 'Covid-19' pneumonia, and $39, 000 if they put a 'Covid' diagnosed patient on a ventilator that would almost certainly kill them. A few – painfully and pathetically few – medical whistleblowers revealed (before Cult-owned YouTube deleted their videos) that they had been instructed to 'let the patient crash' and put them straight on a ventilator instead of going through a series of far less intrusive and dangerous methods as they would have done before the pandemic hoax began and the financial incentives kicked in. We are talking cold-blooded murder given that ventilators are so damaging to respiratory systems they are usually the last step before heaven awaits. Renegade Minds never fall for the belief that people in white coats are all angels of mercy and cannot be full-on psychopaths. I have explained in detail in *The Answer* how what I am describing here played out across the world coordinated by the World Health Organization through the medical hierarchies in almost every country.

Medical scientist calls it

Information about the non-existence of the 'virus' began to emerge for me in late March, 2020, and mushroomed after that. I was sent an email by Sir Julian Rose, a writer, researcher, and organic farming promotor, from a medical scientist friend of his in the United States. Even at that early stage in March the scientist was able to explain

how the 'Covid' hoax was being manipulated. He said there were no reliable tests for a specific 'Covid-19 virus' and nor were there any reliable agencies or media outlets for reporting numbers of actual 'Covid-19' cases. We have seen in the long period since then that he was absolutely right. 'Every action and reaction to Covid-19 is based on totally flawed data and we simply cannot make accurate assessments,' he said. Most people diagnosed with 'Covid-19' were showing nothing more than cold and flu-like symptoms 'because most coronavirus strains *are* nothing more than cold/flu-like symptoms'. We had farcical situations like an 84-year-old German man testing positive for 'Covid-19' and his nursing home ordered to quarantine only for him to be found to have a common cold. The scientist described back then why PCR tests and what he called the 'Mickey Mouse test kits' were useless for what they were claimed to be identifying. 'The idea these kits can isolate a specific virus like Covid-19 is nonsense,' he said. Significantly, he pointed out that 'if you want to create a totally false panic about a totally false pandemic – pick a coronavirus'. This is exactly what the Cult-owned Gates, World Economic Forum and Johns Hopkins University did with their Event 201 'simulation' followed by their real-life simulation called the 'pandemic'. The scientist said that all you had to do was select the sickest of people with respiratory-type diseases in a single location – 'say Wuhan' – and administer PCR tests to them. You can then claim that anyone showing 'viral sequences' similar to a coronavirus 'which will inevitably be quite a few' is suffering from a 'new' disease:

> Since you already selected the sickest flu cases a fairly high proportion of your sample will go on to die. You can then say this 'new' virus has a CFR [case fatality rate] higher than the flu and use this to infuse more concern and do more tests which will of course produce more 'cases', which expands the testing, which produces yet more 'cases' and so on and so on. Before long you have your 'pandemic', and all you have done is use a simple test kit trick to convert the worst flu and pneumonia cases into something new that doesn't ACTUALLY EXIST [my emphasis].

He said that you then 'just run the same scam in other countries' and make sure to keep the fear message running high 'so that people

will feel panicky and less able to think critically'. The only problem to overcome was the fact *there is no* actual new deadly pathogen and only regular sick people. This meant that deaths from the 'new deadly pathogen' were going to be way too low for a real new deadly virus pandemic, but he said this could be overcome in the following ways – all of which would go on to happen:

1. You can claim this is just the beginning and more deaths are imminent [you underpin this with fantasy 'computer projections']. Use this as an excuse to quarantine everyone and then claim the quarantine prevented the expected millions of dead.

2. You can [say that people] 'minimizing' the dangers are irresponsible and bully them into not talking about numbers.

3. You can talk crap about made up numbers hoping to blind people with pseudoscience.

4. You can start testing well people (who, of course, will also likely have shreds of coronavirus [RNA] in them) and thus inflate your 'case figures' with 'asymptomatic carriers' (you will of course have to spin that to sound deadly even though any virologist knows the more symptom-less cases you have the less deadly is your pathogen).

The scientist said that if you take these simple steps 'you can have your own entirely manufactured pandemic up and running in weeks'. His analysis made so early in the hoax was brilliantly prophetic of what would actually unfold. Pulling all the information together in these recent chapters we have this is simple 1, 2, 3, of how you can delude virtually the entire human population into believing in a 'virus' that doesn't exist:

- A 'Covid case' is someone who tests positive with a test not testing for the 'virus'.

- A 'Covid death' is someone who dies of *any cause* within 28 days (or much longer) of testing positive with a test not testing for the 'virus.

- Asymptomatic means there is nothing wrong with you, but they claim you can pass on what you don't have to justify locking

down (quarantining) healthy people in totality.

The foundations of the hoax are that simple. A study involving ten million people in Wuhan, published in November, 2020, demolished the whole lie about those without symptoms passing on the 'virus'. They found '300 asymptomatic cases' and traced their contacts to find that not one of them was detected with the 'virus'. 'Asymptomatic' patients and their contacts were isolated for no less than two weeks and nothing changed. I know it's all crap, but if you are going to claim that those without symptoms can transmit 'the virus' then you must produce evidence for that and they never have. Even World Health Organization official Dr Maria Van Kerkhove, head of the emerging diseases and zoonosis unit, said as early as June, 2020, that she doubted the validity of asymptomatic transmission. She said that 'from the data we have, it still seems to be rare that an asymptomatic person actually transmits onward to a secondary individual' and by 'rare' she meant that she couldn't cite any case of asymptomatic transmission.

The Ferguson factor

The problem for the Cult as it headed into March, 2020, when the script had lockdown due to start, was that despite all the manipulation of the case and death figures they still did not have enough people alleged to have died from 'Covid' to justify mass house arrest. This was overcome in the way the scientist described: 'You can claim this is just the beginning and more deaths are imminent … Use this as an excuse to quarantine everyone and then claim the quarantine prevented the expected millions of dead.' Enter one Professor Neil Ferguson, the Gates-funded 'epidemiologist' at the Gates-funded Imperial College in London. Ferguson is Britain's Christian Drosten in that he has a dire record of predicting health outcomes, but is still called upon to advise government on the next health outcome when another 'crisis' comes along. This may seem to be a strange and ridiculous thing to do. Why would you keep turning for policy guidance to people who have a history of being

monumentally wrong? Ah, but it makes sense from the Cult point of view. These 'experts' keep on producing predictions that suit the Cult agenda for societal transformation and so it was with Neil Ferguson as he revealed his horrific (and clearly insane) computer model predictions that allowed lockdowns to be imposed in Britain, the United States and many other countries. Ferguson does not have even an A-level in biology and would appear to have no formal training in computer modelling, medicine or epidemiology, according to Derek Winton, an MSc in Computational Intelligence. He wrote an article somewhat aghast at what Ferguson did which included taking no account of respiratory disease 'seasonality' which means it is far worse in the winter months. Who would have thought that respiratory disease could be worse in the winter? Well, certainly not Ferguson.

The massively China-connected Imperial College and its bizarre professor provided the excuse for the long-incubated Chinese model of human control to travel westward at lightning speed. Imperial College confirms on its website that it collaborates with the Chinese Research Institute; publishes more than 600 research papers every year with Chinese research institutions; has 225 Chinese staff; 2,600 Chinese students – the biggest international group; 7,000 former students living in China which is the largest group outside the UK; and was selected for a tour by China's President Xi Jinping during his state visit to the UK in 2015. The college takes major donations from China and describes itself as the UK's number one university collaborator with Chinese research institutions. The China communist/fascist government did not appear phased by the woeful predictions of Ferguson and Imperial when during the lockdown that Ferguson induced the college signed a five-year collaboration deal with China tech giant Huawei that will have Huawei's indoor 5G network equipment installed at the college's West London tech campus along with an 'AI cloud platform'. The deal includes Chinese sponsorship of Imperial's Venture Catalyst entrepreneurship competition. Imperial is an example of the enormous influence the Chinese government has within British and North American

universities and research centres – and further afield. Up to 200 academics from more than a dozen UK universities are being investigated on suspicion of 'unintentionally' helping the Chinese government build weapons of mass destruction by 'transferring world-leading research in advanced military technology such as aircraft, missile designs and cyberweapons'. Similar scandals have broken in the United States, but it's all a coincidence. Imperial College serves the agenda in many other ways including the promotion of every aspect of the United Nations Agenda 21/2030 (the Great Reset) and produced computer models to show that human-caused 'climate change' is happening when in the real world it isn't. Imperial College is driving the climate agenda as it drives the 'Covid' agenda (both Cult hoaxes) while Patrick Vallance, the UK government's Chief Scientific Adviser on 'Covid', was named Chief Scientific Adviser to the UN 'climate change' conference known as COP26 hosted by the government in Glasgow, Scotland. 'Covid' and 'climate' are fundamentally connected.

Professor Woeful

From Imperial's bosom came Neil Ferguson still advising government despite his previous disasters and it was announced early on that he and other key people like UK Chief Medical Adviser Chris Whitty had caught the 'virus' as the propaganda story was being sold. Somehow they managed to survive and we had Prime Minister Boris Johnson admitted to hospital with what was said to be a severe version of the 'virus' in this same period. His whole policy and demeanour changed when he returned to Downing Street. It's a small world with these government advisors – especially in their communal connections to Gates – and Ferguson had partnered with Whitty to write a paper called 'Infectious disease: Tough choices to reduce Ebola transmission' which involved another scare-story that didn't happen. Ferguson's 'models' predicted that up to150, 000 could die from 'mad cow disease', or BSE, and its version in sheep if it was transmitted to humans. BSE was not transmitted and instead triggered by an organophosphate pesticide used to treat a pest on

cows. Fewer than 200 deaths followed from the human form. Models by Ferguson and his fellow incompetents led to the unnecessary culling of millions of pigs, cattle and sheep in the foot and mouth outbreak in 2001 which destroyed the lives and livelihoods of farmers and their families who had often spent decades building their herds and flocks. Vast numbers of these animals did not have foot and mouth and had no contact with the infection. Another 'expert' behind the cull was Professor Roy Anderson, a computer modeller at Imperial College specialising in the epidemiology of *human*, not animal, disease. Anderson has served on the Bill and Melinda Gates Grand Challenges in Global Health advisory board and chairs another Gates-funded organisation. Gates is everywhere.

In a precursor to the 'Covid' script Ferguson backed closing schools 'for prolonged periods' over the swine flu 'pandemic' in 2009 and said it would affect a third of the world population if it continued to spread at the speed he claimed to be happening. His mates at Imperial College said much the same and a news report said: 'One of the authors, the epidemiologist and disease modeller Neil Ferguson, who sits on the World Health Organisation's emergency committee for the outbreak, said the virus had "full pandemic potential".' Professor Liam Donaldson, the Chris Whitty of his day as Chief Medical Officer, said the worst case could see 30 percent of the British people infected by swine flu with 65,000 dying. Ferguson and Donaldson were indeed proved correct when at the end of the year the number of deaths attributed to swine flu was 392. The term 'expert' is rather liberally applied unfortunately, not least to complete idiots. Swine flu 'projections' were great for GlaxoSmithKline (GSK) as millions rolled in for its Pandemrix influenza vaccine which led to brain damage with children most affected. The British government (taxpayers) paid out more than £60 million in compensation after GSK was given immunity from prosecution. Yet another 'Covid' déjà vu. Swine flu was supposed to have broken out in Mexico, but Dr Wolfgang Wodarg, a German doctor, former member of parliament and critic of the 'Covid' hoax, observed 'the spread of swine flu' in Mexico City at the time. He

said: 'What we experienced in Mexico City was a very mild flu which did not kill more than usual – which killed even fewer people than usual.' Hyping the fear against all the facts is not unique to 'Covid' and has happened many times before. Ferguson is reported to have over-estimated the projected death toll of bird flu (H5N1) by some three million-fold, but bird flu vaccine makers again made a killing from the scare. This is some of the background to the Neil Ferguson who produced the perfectly-timed computer models in early 2020 predicting that half a million people would die in Britain without draconian lockdown and 2.2 million in the United States. Politicians panicked, people panicked, and lockdowns of alleged short duration were instigated to 'flatten the curve' of cases gleaned from a test not testing for the 'virus'. I said at the time that the public could forget the 'short duration' bit. This was an agenda to destroy the livelihoods of the population and force them into mass control through dependency and there was going to be nothing 'short' about it. American researcher Daniel Horowitz described the consequences of the 'models' spewed out by Gates-funded Ferguson and Imperial College:

> What led our government and the governments of many other countries into panic was a single Imperial College of UK study, funded by global warming activists, that predicted 2.2 million deaths if we didn't lock down the country. In addition, the reported 8-9% death rate in Italy scared us into thinking there was some other mutation of this virus that they got, which might have come here.
>
> Together with the fact that we were finally testing and had the ability to actually report new cases, we thought we were headed for a death spiral. But again … we can't flatten a curve if we don't know when the curve started.

How about it *never* started?

Giving them what they want

An investigation by German news outlet *Welt Am Sonntag (World on Sunday)* revealed how in March, 2020, the German government gathered together 'leading scientists from several research institutes and universities' and 'together, they were to produce a [modelling]

paper that would serve as legitimization for further tough political measures'. The Cult agenda was justified by computer modelling not based on evidence or reality; it was specifically constructed to justify the Cult demand for lockdowns all over the world to destroy the independent livelihoods of the global population. All these modellers and everyone responsible for the 'Covid' hoax have a date with a trial like those in Nuremberg after World War Two when Nazis faced the consequences of their war crimes. These corrupt-beyond-belief 'modellers' wrote the paper according to government instructions and it said that that if lockdown measures were lifted then up to one million Germans would die from 'Covid-19' adding that some would die 'agonizingly at home, gasping for breath' unable to be treated by hospitals that couldn't cope. All lies. No matter – it gave the Cult all that it wanted. What did long-time government 'modeller' Neil Ferguson say? If the UK and the United States didn't lockdown half a million would die in Britain and 2.2 million Americans. Anyone see a theme here? 'Modellers' are such a crucial part of the lockdown strategy that we should look into their background and follow the money. Researcher Rosemary Frei produced an excellent article headlined 'The Modelling-paper Mafiosi'. She highlights a guy called John Edmunds, a British epidemiologist, and professor in the Faculty of Epidemiology and Population Health at the London School of Hygiene & Tropical Medicine. He studied at Imperial College. Edmunds is a member of government 'Covid' advisory bodies which have been dictating policy, the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) and the Scientific Advisory Group for Emergencies (SAGE).

Ferguson, another member of NERVTAG and SAGE, led the way with the original 'virus' and Edmunds has followed in the 'variant' stage and especially the so-called UK or Kent variant known as the 'Variant of Concern' (VOC) B.1.1.7. He said in a co-written report for the Centre for Mathematical modelling of Infectious Diseases at the London School of Hygiene and Tropical Medicine, with input from the Centre's 'Covid-19' Working Group, that there was 'a realistic

possibility that VOC B.1.1.7 is associated with an increased risk of death compared to non-VOC viruses'. Fear, fear, fear, get the vaccine, fear, fear, fear, get the vaccine. Rosemary Frei reveals that almost all the paper's authors and members of the modelling centre's 'Covid-19' Working Group receive funding from the Bill and Melinda Gates Foundation and/or the associated Gates-funded Wellcome Trust. The paper was published by e-journal *Medr χiv* which only publishes papers not peer-reviewed and the journal was established by an organisation headed by Facebook's Mark Zuckerberg and his missus. What a small world it is. Frei discovered that Edmunds is on the Scientific Advisory Board of the Coalition for Epidemic Preparedness Innovations (CEPI) which was established by the Bill and Melinda Gates Foundation, Klaus Schwab's Davos World Economic Forum and Big Pharma giant Wellcome. CEPI was 'launched in Davos [in 2017] to develop vaccines to stop future epidemics', according to its website. 'Our mission is to accelerate the development of vaccines against emerging infectious diseases and enable equitable access to these vaccines for people during outbreaks.' What kind people they are. Rosemary Frei reveals that Public Health England (PHE) director Susan Hopkins is an author of her organisation's non-peer-reviewed reports on 'new variants'. Hopkins is a professor of infectious diseases at London's Imperial College which is gifted tens of millions of dollars a year by the Bill and Melinda Gates Foundation. Gates-funded modelling disaster Neil Ferguson also co-authors Public Health England reports and he spoke in December, 2020, about the potential danger of the B.1.1.7. 'UK variant' promoted by Gates-funded modeller John Edmunds. When I come to the 'Covid vaccines' the 'new variants' will be shown for what they are – bollocks.

Connections, connections

All these people and modellers are lockdown-obsessed or, put another way, they demand what the Cult demands. Edmunds said in January, 2021, that to ease lockdowns too soon would be a disaster and they had to 'vaccinate much, much, much more widely than the

elderly'. Rosemary Frei highlights that Edmunds is married to Jeanne Pimenta who is described in a LinkedIn profile as director of epidemiology at GlaxoSmithKline (GSK) and she held shares in the company. Patrick Vallance, co-chair of SAGE and the government's Chief Scientific Adviser, is a former executive of GSK and has a deferred bonus of shares in the company worth £600,000. GSK has serious business connections with Bill Gates and is collaborating with mRNA-'vaccine' company CureVac to make 'vaccines' for the new variants that Edmunds is talking about. GSK is planning a 'Covid vaccine' with drug giant Sanofi. Puppet Prime Minister Boris Johnson announced in the spring of 2021 that up to 60 million vaccine doses were to be made at the GSK facility at Barnard Castle in the English North East. Barnard Castle, with a population of just 6,000, was famously visited in breach of lockdown rules in April, 2020, by Johnson aide Dominic Cummings who said that he drove there 'to test his eyesight' before driving back to London. Cummings would be better advised to test his integrity – not that it would take long. The GSK facility had nothing to do with his visit then although I'm sure Patrick Vallance would have been happy to arrange an introduction and some tea and biscuits. Ruthless psychopath Gates has made yet another fortune from vaccines in collaboration with Big Pharma companies and gushes at the phenomenal profits to be made from vaccines – more than a 20-to-1 return as he told one interviewer. Gates also tweeted in December, 2019, with the foreknowledge of what was coming: 'What's next for our foundation? I'm particularly excited about what the next year could mean for one of the best buys in global health: vaccines.'

Modeller John Edmunds is a big promotor of vaccines as all these people appear to be. He's the dean of the London School of Hygiene & Tropical Medicine's Faculty of Epidemiology and Population Health which is primarily funded by the Bill and Melinda Gates Foundation and the Gates-established and funded GAVI vaccine alliance which is the Gates vehicle to vaccinate the world. The organisation Doctors Without Borders has described GAVI as being 'aimed more at supporting drug-industry desires to promote new

products than at finding the most efficient and sustainable means for fighting the diseases of poverty'. But then that's why the psychopath Gates created it. John Edmunds said in a video that the London School of Hygiene & Tropical Medicine is involved in every aspect of vaccine development including large-scale clinical trials. He contends that mathematical modelling can show that vaccines protect individuals and society. That's on the basis of shit in and shit out, I take it. Edmunds serves on the UK Vaccine Network as does Ferguson and the government's foremost 'Covid' adviser, the grim-faced, dark-eyed Chris Whitty. The Vaccine Network says it works 'to support the government to identify and shortlist targeted investment opportunities for the most promising vaccines and vaccine technologies that will help combat infectious diseases with epidemic potential, and to address structural issues related to the UK's broader vaccine infrastructure'. Ferguson is acting Director of the Imperial College Vaccine Impact Modelling Consortium which has funding from the Bill and Melina Gates Foundation and the Gates-created GAVI 'vaccine alliance'. Anyone wonder why these characters see vaccines as the answer to every problem? Ferguson is wildly enthusiastic in his support for GAVI's campaign to vaccine children en masse in poor countries. You would expect someone like Gates who has constantly talked about the need to reduce the population to want to fund vaccines to keep more people alive. I'm sure that's why he does it. The John Edmunds London School of Hygiene & Tropical Medicine (LSHTM) has a Vaccines Manufacturing Innovation Centre which develops, tests and commercialises vaccines. Rosemary Frei writes:

> The vaccines centre also performs affiliated activities like combating 'vaccine hesitancy'. The latter includes the Vaccine Confidence Project. The project's stated purpose is, among other things, 'to provide analysis and guidance for early response and engagement with the public to ensure sustained confidence in vaccines and immunisation'. The Vaccine Confidence Project's director is LSHTM professor Heidi Larson. For more than a decade she's been researching how to combat vaccine hesitancy.

How the bloody hell can blokes like John Edmunds and Neil Ferguson with those connections and financial ties model 'virus' case

and death projections for the government and especially in a way that gives their paymasters like Gates exactly what they want? It's insane, but this is what you find throughout the world.

'Covid' is not dangerous, oops, wait, yes it is

Only days before Ferguson's nightmare scenario made Jackboot Johnson take Britain into a China-style lockdown to save us from a deadly 'virus' the UK government website gov.uk was reporting something very different to Ferguson on a page of official government guidance for 'high consequence infectious diseases (HCID)'. It said this about 'Covid-19':

As of 19 March 2020, COVID-19 *is no longer considered to be a high consequence infectious diseases (HCID) in the UK* [my emphasis]. The 4 nations public health HCID group made an interim recommendation in January 2020 to classify COVID-19 as an HCID. This was based on consideration of the UK HCID criteria about the virus and the disease with information available during the early stages of the outbreak.

Now that more is known about COVID-19, the public health bodies in the UK have reviewed the most up to date information about COVID-19 against the UK HCID criteria. They have determined that several features have now changed; in particular, more information is available about mortality rates (low overall), and there is now greater clinical awareness and a specific and sensitive laboratory test, the availability of which continues to increase. The Advisory Committee on Dangerous Pathogens (ACDP) is also of the opinion that COVID-19 should no longer be classified as an HCID.

Soon after the government had been exposed for downgrading the risk they upgraded it again and everyone was back to singing from the same Cult hymn book. Ferguson and his fellow Gates clones indicated that lockdowns and restrictions would have to continue until a Gates-funded vaccine was developed. Gates said the same because Ferguson and his like were repeating the Gates script which is the Cult script. 'Flatten the curve' became an ongoing nightmare of continuing lockdowns with periods in between of severe restrictions in pursuit of destroying independent incomes and had nothing to do with protecting health about which the Cult gives not a shit. Why wouldn't Ferguson be pushing a vaccine 'solution' when he's owned by vaccine-obsessive Gates who makes a fortune from them and

when Ferguson heads the Vaccine Impact Modelling Consortium at Imperial College funded by the Gates Foundation and GAVI, the 'vaccine alliance', created by Gates as his personal vaccine promotion operation? To compound the human catastrophe that Ferguson's 'models' did so much to create he was later exposed for breaking his own lockdown rules by having sexual liaisons with his married girlfriend Antonia Staats at his home while she was living at another location with her husband and children. Staats was a 'climate' activist and senior campaigner at the Soros-funded Avaaz which I wouldn't trust to tell me that grass is green. Ferguson had to resign as a government advisor over this hypocrisy in May, 2020, but after a period of quiet he was back being quoted by the ridiculous media on the need for more lockdowns and a vaccine rollout. Other government-advising 'scientists' from Imperial College' held the fort in his absence and said lockdown could be indefinite until a vaccine was found. The Cult script was being sung by the payrolled choir. I said there was no intention of going back to 'normal' when the 'vaccine' came because the 'vaccine' is part of a very different agenda that I will discuss in Human 2.0. Why would the Cult want to let the world go back to normal when destroying that normal forever was the whole point of what was happening? House arrest, closing businesses and schools through lockdown, (un)social distancing and masks all followed the Ferguson fantasy models. Again as I predicted (these people are so predictable) when the 'vaccine' arrived we were told that house arrest, lockdown, (un)social distancing and masks would still have to continue. I will deal with the masks in the next chapter because they are of fundamental importance.

Where's the 'pandemic'?

Any mildly in-depth assessment of the figures revealed what was really going on. Cult-funded and controlled organisations still have genuine people working within them such is the number involved. So it is with Genevieve Briand, assistant program director of the Applied Economics master's degree program at Johns Hopkins

University. She analysed the impact that 'Covid-19' had on deaths from *all* causes in the United States using official data from the CDC for the period from early February to early September, 2020. She found that allegedly 'Covid' *related*-deaths exceeded those from heart disease which she found strange with heart disease always the biggest cause of fatalities. Her research became even more significant when she noted the sudden decline in 2020 of *all* non-'Covid' deaths: 'This trend is completely contrary to the pattern observed in all previous years … the total decrease in deaths by other causes almost exactly equals the increase in deaths by Covid-19.' This was such a game, set and match in terms of what was happening that Johns Hopkins University deleted the article on the grounds that it 'was being used to support false and dangerous inaccuracies about the impact of the pandemic'. No – because it exposed the scam from official CDC figures and this was confirmed when those figures were published in January, 2021. Here we can see the effect of people dying from heart attacks, cancer, road accidents and gunshot wounds – *anything* – having 'Covid-19' on the death certificate along with those diagnosed from 'symptoms' who had even not tested positive with a test not testing for the 'virus'. I am not kidding with the gunshot wounds, by the way. Brenda Bock, coroner in Grand County, Colorado, revealed that two gunshot victims tested positive for the 'virus' within the previous 30 days and were therefore classified as 'Covid deaths'. Bock said: 'These two people had tested positive for Covid, but that's not what killed them. A gunshot wound is what killed them.' She said she had not even finished her investigation when the state listed the gunshot victims as deaths due to the 'virus'. The death and case figures for 'Covid-19' are an absolute joke and yet they are repeated like parrots by the media, politicians and alleged medical 'experts'. The official Cult narrative is the only show in town.

Genevieve Briand found that deaths from all causes were not exceptional in 2020 compared with previous years and a Spanish magazine published figures that said the same about Spain which was a 'Covid' propaganda hotspot at one point. *Discovery Salud*, a

health and medicine magazine, quoted government figures which showed how 17,000 *fewer* people died in Spain in 2020 than in 2019 and more than 26,000 fewer than in 2018. The age-standardised mortality rate for England and Wales when age distribution is taken into account was significantly lower in 2020 than the 1970s, 80s and 90s, and was only the ninth highest since 2000. Where is the 'pandemic'?

Post mortems and autopsies virtually disappeared for 'Covid' deaths amid claims that 'virus-infected' bodily fluids posed a risk to those carrying out the autopsy. This was rejected by renowned German pathologist and forensic doctor Klaus Püschel who said that he and his staff had by then done 150 autopsies on 'Covid' patients with no problems at all. He said they were needed to know why some 'Covid' patients suffered blood clots and not severe respiratory infections. The 'virus' is, after all, called SARS or 'severe acute respiratory syndrome'. I highlighted in the spring of 2020 this phenomenon and quoted New York intensive care doctor Cameron Kyle-Sidell who posted a soon deleted YouTube video to say that they had been told to prepare to treat an infectious disease called 'Covid-19', but that was not what they were dealing with. Instead he likened the lung condition of the most severely ill patients to what you would expect with cabin depressurisation in a plane at 30,000 feet or someone dropped on the top of Everest without oxygen or acclimatisation. I have never said this is not happening to a small minority of alleged 'Covid' patients – I am saying this is not caused by a phantom 'contagious virus'. Indeed Kyle-Sidell said that 'Covid-19' was not the disease they were told was coming their way. 'We are operating under a medical paradigm that is untrue,' he said, and he believed they were treating the wrong disease: 'These people are being slowly starved of oxygen.' Patients would take off their oxygen masks in a state of fear and stress and while they were blue in the face on the brink of death. They did not look like patients dying of pneumonia. You can see why they don't want autopsies when their virus doesn't exist and there is another condition in some people that they don't wish to be uncovered. I should add here that

the 5G system of millimetre waves was being rapidly introduced around the world in 2020 and even more so now as they fire 5G at the Earth from satellites. At 60 gigahertz within the 5G range that frequency interacts with the oxygen molecule and stops people breathing in sufficient oxygen to be absorbed into the bloodstream. They are installing 5G in schools and hospitals. The world is not mad or anything. 5G can cause major changes to the lungs and blood as I detail in *The Answer* and these consequences are labelled 'Covid-19', the alleged symptoms of which can be caused by 5G and other electromagnetic frequencies as cells respond to radiation poisoning.

The 'Covid death' scam

Dr Scott Jensen, a Minnesota state senator and medical doctor, exposed 'Covid' Medicare payment incentives to hospitals and death certificate manipulation. He said he was sent a seven-page document by the US Department of Health 'coaching' him on how to fill out death certificates which had never happened before. The document said that he didn't need to have a laboratory test for 'Covid-19' to put that on the death certificate and that shocked him when death certificates are supposed to be about facts. Jensen described how doctors had been 'encouraged, if not pressured' to make a diagnosis of 'Covid-19' if they thought it was probable or *'presumed*'. No positive test was necessary – not that this would have mattered anyway. He said doctors were told to diagnose 'Covid' by symptoms when these were the same as colds, allergies, other respiratory problems, and certainly with influenza which 'disappeared' in the 'Covid' era. A common sniffle was enough to get the dreaded verdict. Ontario authorities decreed that a single care home resident with *one* symptom from a long list must lead to the isolation of the entire home. Other courageous doctors like Jensen made the same point about death figure manipulation and how deaths by other causes were falling while 'Covid-19 deaths' were rising at the same rate due to re-diagnosis. Their videos rarely survive long on YouTube with its Cult-supporting algorithms courtesy of CEO Susan Wojcicki and her bosses at Google. Figure-tampering was so glaring

and ubiquitous that even officials were letting it slip or outright saying it. UK chief scientific adviser Patrick Vallance said on one occasion that 'Covid' on the death certificate doesn't mean 'Covid' was the cause of death (so why the hell is it there?) and we had the rare sight of a BBC reporter telling the truth when she said: 'Someone could be successfully treated for Covid, in say April, discharged, and then in June, get run over by a bus and die … That person would still be counted as a Covid death in England.' Yet the BBC and the rest of the world media went on repeating the case and death figures as if they were real. Illinois Public Health Director Dr Ngozi Ezike revealed the deceit while her bosses must have been clenching their buttocks:

> If you were in a hospice and given a few weeks to live and you were then found to have Covid that would be counted as a Covid death. [There might be] a clear alternate cause, but it is still listed as a Covid death. So everyone listed as a Covid death doesn't mean that was the cause of the death, but that they had Covid at the time of death.

Yes, a 'Covid virus' never shown to exist and tested for with a test not testing for the 'virus'. In the first period of the pandemic hoax through the spring of 2020 the process began of designating almost everything a 'Covid' death and this has continued ever since. I sat in a restaurant one night listening to a loud conversation on the next table where a family was discussing in bewilderment how a relative who had no symptoms of 'Covid', and had died of a long-term problem, could have been diagnosed a death by the 'virus'. I could understand their bewilderment. If they read this book they will know why this medical fraud has been perpetrated the world over.

Some media truth shock

The media ignored the evidence of death certificate fraud until eventually one columnist did speak out when she saw it first-hand. Bel Mooney is a long-time national newspaper journalist in Britain currently working for the *Daily Mail*. Her article on February 19th, 2021, carried this headline: 'My dad Ted passed three Covid tests

and died of a chronic illness yet he's officially one of Britain's 120,000 victims of the virus and is far from alone ... so how many more are there?' She told how her 99-year-old father was in a care home with a long-standing chronic obstructive pulmonary disease and vascular dementia. Maybe, but he was still aware enough to tell her from the start that there was no 'virus' and he refused the 'vaccine' for that reason. His death was not unexpected given his chronic health problems and Mooney said she was shocked to find that 'Covid-19' was declared the cause of death on his death certificate. She said this was a 'bizarre and unacceptable untruth' for a man with long-time health problems who had tested negative twice at the home for the 'virus'. I was also shocked by this story although not by what she said. I had been highlighting the death certificate manipulation for ten months. It was the confirmation that a professional full-time journalist only realised this was going on when it affected her directly and neither did she know that whether her dad tested positive or negative was irrelevant with the test not testing for the 'virus'. Where had she been? She said she did not believe in 'conspiracy theories' without knowing I'm sure that this and 'conspiracy theorists' were terms put into widespread circulation by the CIA in the 1960s to discredit those who did not accept the ridiculous official story of the Kennedy assassination. A blanket statement of 'I don't believe in conspiracy theories' is always bizarre. The dictionary definition of the term alone means the world is drowning in conspiracies. What she said was even more daft when her dad had just been affected by the 'Covid' conspiracy. Why else does she think that 'Covid-19' was going on the death certificates of people who died of something else?

To be fair once she saw from personal experience what was happening she didn't mince words. Mooney was called by the care home on the morning of February 9th to be told her father had died in his sleep. When she asked for the official cause of death what came back was 'Covid-19'. Mooney challenged this and was told there had been deaths from Covid on the dementia floor (confirmed by a test not testing for the 'virus') so they considered it 'reasonable

to assume'. 'But doctor,' Mooney rightly protested, 'an assumption isn't a diagnosis.' She said she didn't blame the perfectly decent and sympathetic doctor – 'he was just doing his job'. Sorry, but that's *bullshit*. He wasn't doing his job at all. He was putting a false cause of death on the death certificate and that is a criminal offence for which he should be brought to account and the same with the millions of doctors worldwide who have done the same. They were not doing their job they were following orders and that must not wash at new Nuremberg trials any more than it did at the first ones. Mooney's doctor was 'assuming' (presuming) as he was told to, but 'just following orders' makes no difference to his actions. A doctor's job is to serve the patient and the truth, not follow orders, but that's what they have done all over the world and played a central part in making the 'Covid' hoax possible with all its catastrophic consequences for humanity. Shame on them and they must answer for their actions. Mooney said her disquiet worsened when she registered her father's death by telephone and was told by the registrar there had been very many other cases like hers where 'the deceased' had not tested positive for 'Covid' yet it was recorded as the cause of death. The test may not matter, but those involved at their level *think* it matters and it shows a callous disregard for accurate diagnosis. The pressure to do this is coming from the top of the national 'health' pyramids which in turn obey the World Health Organization which obeys Gates and the Cult. Mooney said the registrar agreed that this must distort the national figures adding that 'the strangest thing is that every winter we record countless deaths from flu, and this winter there have been none. Not one!' She asked if the registrar thought deaths from flu were being misdiagnosed and lumped together with 'Covid' deaths. The answer was a 'puzzled yes'. Mooney said that the funeral director said the same about 'Covid' deaths which had nothing to do with 'Covid'. They had lost count of the number of families upset by this and other funeral companies in different countries have had the same experience. Mooney wrote:

The nightly shroud-waving and shocking close-ups of pain imposed on us by the TV news bewildered and terrified the population into eager compliance with lockdowns. We were invited to 'save the NHS' and to grieve for strangers – the real-life loved ones behind those shocking death counts. Why would the public imagine what I now fear, namely that the way Covid-19 death statistics are compiled might make the numbers seem greater than they are?

Oh, just a little bit – like 100 percent.

Do the maths

Mooney asked why a country would wish to skew its mortality figures by wrongly certifying deaths? What had been going on? Well, if you don't believe in conspiracies you will never find the answer which is that *it's a conspiracy*. She did, however, describe what she had discovered as a 'national scandal'. In reality it's a global scandal and happening everywhere. Pillars of this conspiracy were all put into place before the button was pressed with the Drosten PCR protocol and high amplifications to produce the cases and death certificate changes to secure illusory 'Covid' deaths. Mooney notes that normally two doctors were needed to certify a death, with one having to know the patient, and how the rules were changed in the spring of 2020 to allow one doctor to do this. In the same period 'Covid deaths' were decreed to be all cases where Covid-19 was put on the death certificate even without a positive test or any symptoms. Mooney asked: 'How many of the 30,851 (as of January 15) care home resident deaths with Covid-19 on the certificate (32.4 per cent of all deaths so far) were based on an assumption, like that of my father? And what has that done to our national psyche?'All of them is the answer to the first question and it has devastated and dismantled the national psyche, actually the global psyche, on a colossal scale. In the UK case and death data is compiled by organisations like Public Health England (PHE) and the Office for National Statistics (ONS). Mooney highlights the insane policy of counting a death from any cause as 'Covid-19' if this happens within 28 days of a positive test (with a test not testing for the 'virus') and she points out that ONS statistics reflect deaths 'involving Covid' 'or due to Covid' which meant in practice any

death where 'Covid-19' was mentioned on the death certificate. She described the consequences of this fraud:

Most people will accept the narrative they are fed, so panicky governments here and in Europe witnessed the harsh measures enacted in totalitarian China and jumped into lockdown. Headlines about Covid deaths tolled like the knell that would bring doomsday to us all. Fear stalked our empty streets. Politicians parroted the frankly ridiculous aim of 'zero Covid' and shut down the economy, while most British people agreed that lockdown was essential and (astonishingly to me, as a patriotic Brit) even wanted more restrictions.

For what? Lies on death certificates? Never mind the grim toll of lives ruined, suicides, schools closed, rising inequality, depression, cancelled hospital treatments, cancer patients in a torture of waiting, poverty, economic devastation, loneliness, families kept apart, and so on. How many lives have been lost as a direct result of lockdown?

She said that we could join in a national chorus of shock and horror at reaching the 120,000 death toll which was surely certain to have been totally skewed all along, but what about the human cost of lockdown justified by these 'death figures'? *The British Medical Journal* had reported a 1,493 percent increase in cases of children taken to Great Ormond Street Hospital with abusive head injuries alone and then there was the effect on families:

Perhaps the most shocking thing about all this is that families have been kept apart – and obeyed the most irrational, changing rules at the whim of government – because they believed in the statistics. They succumbed to fear, which his generation rejected in that war fought for freedom. Dad (God rest his soul) would be angry. And so am I.

Another theme to watch is that in the winter months when there are more deaths from all causes they focus on 'Covid' deaths and in the summer when the British Lung Foundation says respiratory disease plummets by 80 percent they rage on about 'cases'. Either way fascism on population is always the answer.

Nazi eugenics in the 21st century

Elderly people in care homes have been isolated from their families month after lonely month with no contact with relatives and grandchildren who were banned from seeing them. We were told

that lockdown fascism was to 'protect the vulnerable' like elderly people. At the same time Do Not Resuscitate (DNR) orders were placed on their medical files so that if they needed resuscitation it wasn't done and 'Covid-19' went on their death certificates. Old people were not being 'protected' they were being culled – murdered in truth. DNR orders were being decreed for disabled and young people with learning difficulties or psychological problems. The UK Care Quality Commission, a non-departmental body of the Department of Health and Social Care, found that 34 percent of those working in health and social care were pressured into placing 'do not attempt cardiopulmonary resuscitation' orders on 'Covid' patients who suffered from disabilities and learning difficulties without involving the patient or their families in the decision. UK judges ruled that an elderly woman with dementia should have the DNA-manipulating 'Covid vaccine' against her son's wishes and that a man with severe learning difficulties should have the jab despite his family's objections. Never mind that many had already died. The judiciary always supports doctors and government in fascist dictatorships. They wouldn't dare do otherwise. A horrific video was posted showing fascist officers from Los Angeles police forcibly giving the 'Covid' shot to women with special needs who were screaming that they didn't want it. The same fascists are seen giving the jab to a sleeping elderly woman in a care home. This is straight out of the Nazi playbook. Hitler's Nazis committed mass murder of the mentally ill and physically disabled throughout Germany and occupied territories in the programme that became known as Aktion T4, or just T4. Sabbatian-controlled Hitler and his grotesque crazies set out to kill those they considered useless and unnecessary. The Reich Committee for the Scientific Registering of Hereditary and Congenital Illnesses registered the births of babies identified by physicians to have 'defects'. By 1941 alone more than 5,000 children were murdered by the state and it is estimated that in total the number of innocent people killed in Aktion T4 was between 275,000 and 300,000. Parents were told their children had been sent away for 'special treatment' never to return. It is rather pathetic to see claims about plans for new extermination camps being dismissed today

when the same force behind current events did precisely that 80 years ago. Margaret Sanger was a Cult operative who used 'birth control' to sanitise her programme of eugenics. Organisations she founded became what is now Planned Parenthood. Sanger proposed that 'the whole dysgenic population would have its choice of segregation or sterilization'. These included epileptics, 'feeble-minded', and prostitutes. Sanger opposed charity because it perpetuated 'human waste'. She reveals the Cult mentality and if anyone thinks that extermination camps are a 'conspiracy theory' their naivety is touching if breathtakingly stupid.

If you don't believe that doctors can act with callous disregard for their patients it is worth considering that doctors and medical staff agreed to put government-decreed DNR orders on medical files and do nothing when resuscitation is called for. I don't know what you call such people in your house. In mine they are Nazis from the Josef Mengele School of Medicine. Phenomenal numbers of old people have died worldwide from the effects of lockdown, depression, lack of treatment, the 'vaccine' (more later) and losing the will to live. A common response at the start of the manufactured pandemic was to remove old people from hospital beds and transfer them to nursing homes. The decision would result in a mass cull of elderly people in those homes through lack of treatment – *not* 'Covid'. Care home whistleblowers have told how once the 'Covid' era began doctors would not come to their homes to treat patients and they were begging for drugs like antibiotics that often never came. The most infamous example was ordered by New York governor Andrew Cuomo, brother of a moronic CNN host, who amazingly was given an Emmy Award for his handling of the 'Covid crisis' by the ridiculous Wokers that hand them out. Just how ridiculous could be seen in February, 2021, when a Department of Justice and FBI investigation began into how thousands of old people in New York died in nursing homes after being discharged from hospital to make way for 'Covid' patients on Cuomo's say-so – and how he and his staff covered up these facts. This couldn't have happened to a nicer psychopath. Even then there was a 'Covid' spin. Reports said that

thousands of old people who tested positive for 'Covid' in hospital were transferred to nursing homes to both die of 'Covid' and transmit it to others. No – they were in hospital because they were ill and the fact that they tested positive with a test not testing for the 'virus' is irrelevant. They were ill often with respiratory diseases ubiquitous in old people near the end of their lives. Their transfer out of hospital meant that their treatment stopped and many would go on to die.

They're old. Who gives a damn?

I have exposed in the books for decades the Cult plan to cull the world's old people and even to introduce at some point what they call a 'demise pill' which at a certain age everyone would take and be out of here by law. In March, 2021, Spain legalised euthanasia and assisted suicide following the Netherlands, Belgium, Luxembourg and Canada on the Tiptoe to the demise pill. Treatment of old people by many 'care' homes has been a disgrace in the 'Covid' era. There are many, many, caring staff – I know some. There have, however, been legions of stories about callous treatment of old people and their families. Police were called when families came to take their loved ones home in the light of isolation that was killing them. They became prisoners of the state. Care home residents in insane, fascist Ontario, Canada, were not allowed to leave their *room* once the 'Covid' hoax began. UK staff have even wheeled elderly people away from windows where family members were talking with them. Oriana Criscuolo from Stockport in the English North West dropped off some things for her 80-year-old father who has Parkinson's disease and dementia and she wanted to wave to him through a ground-floor window. She was told that was 'illegal'. When she went anyway they closed the curtains in the middle of the day. Oriana said:

> It's just unbelievable. I cannot understand how care home staff – people who are being paid to care – have become so uncaring. Their behaviour is inhumane and cruel. It's beyond belief.

She was right and this was not a one-off. What a way to end your life in such loveless circumstances. UK registered nurse Nicky Millen, a proper old school nurse for 40 years, said that when she started her career care was based on dignity, choice, compassion and empathy. Now she said 'the things that are important to me have gone out of the window.' She was appalled that people were dying without their loved ones and saying goodbye on iPads. Nicky described how a distressed 89-year-old lady stroked her face and asked her 'how many paracetamol would it take to finish me off'. Life was no longer worth living while not seeing her family. Nicky said she was humiliated in front of the ward staff and patients for letting the lady stroke her face and giving her a cuddle. Such is the dehumanisation that the 'Covid' hoax has brought to the surface. Nicky worked in care homes where patients told her they were being held prisoner. 'I want to live until I die', one said to her. 'I had a lady in tears because she hadn't seen her great-grandson.' Nicky was compassionate old school meeting psychopathic New Normal. She also said she had worked on a 'Covid' ward with no 'Covid' patients. Jewish writer Shai Held wrote an article in March, 2020, which was headlined 'The Staggering, Heartless Cruelty Toward the Elderly'. What he described was happening from the earliest days of lockdown. He said 'the elderly' were considered a group and not unique individuals (the way of the Woke). Shai Held said:

Notice how the all-too-familiar rhetoric of dehumanization works: 'The elderly' are bunched together as a faceless mass, all of them considered culprits and thus effectively deserving of the suffering the pandemic will inflict upon them. Lost entirely is the fact that the elderly are individual human beings, each with a distinctive face and voice, each with hopes and dreams, memories and regrets, friendships and marriages, loves lost and loves sustained.

'The elderly' have become another dehumanised group for which anything goes and for many that has resulted in cold disregard for their rights and their life. The distinctive face that Held talks about is designed to be deleted by masks until everyone is part of a faceless mass.

‘War-zone’ hospitals myth

Again and again medical professionals have told me what was really going on and how hospitals ‘overrun like war zones’ according to the media were virtually empty. The mantra from medical whistleblowers was please don’t use my name or my career is over. Citizen journalists around the world sneaked into hospitals to film evidence exposing the ‘war-zone’ lie. They really *were* largely empty with closed wards and operating theatres. I met a hospital worker in my town on the Isle of Wight during the first lockdown in 2020 who said the only island hospital had never been so quiet. Lockdown was justified by the psychopaths to stop hospitals being overrun. At the same time that the island hospital was near-empty the military arrived here to provide *extra beds*. It was all propaganda to ramp up the fear to ensure compliance with fascism as were never-used temporary hospitals with thousands of beds known as Nightingales and never-used make-shift mortuaries opened by the criminal UK government. A man who helped to install those extra island beds attributed to the army said they were never used and the hospital was empty. Doctors and nurses ‘stood around talking or on their phones, wandering down to us to see what we were doing’. There were no masks or social distancing. He accused the useless local island paper, the *County Press*, of ‘pumping the fear as if our hospital was overrun and we only have one so it should have been’. He described ambulances parked up with crews outside in deck chairs. When his brother called an ambulance he was told there was a two-hour backlog which he called ‘bullshit’. An old lady on the island fell ‘and was in a bad way’, but a caller who rang for an ambulance was told the situation wasn’t urgent enough. Ambulance stations were working under capacity while people would hear ambulances with sirens blaring driving through the streets. When those living near the stations realised what was going on they would follow them as they left, circulated around an urban area with the sirens going, and then came back without stopping. All this was to increase levels of fear and the same goes for the ‘ventilator shortage crisis’ that cost tens of millions for hastily produced ventilators never to be used.

Ambulance crews that agreed to be exploited in this way for fear propaganda might find themselves a mirror. I wish them well with that. Empty hospitals were the obvious consequence of treatment and diagnoses of non-'Covid' conditions cancelled and those involved handed a death sentence. People have been dying at home from undiagnosed and untreated cancer, heart disease and other life-threatening conditions to allow empty hospitals to deal with a 'pandemic' that wasn't happening.

Death of the innocent

'War-zones' have been laying off nursing staff, even doctors where they can. There was no work for them. Lockdown was justified by saving lives and protecting the vulnerable they were actually killing with DNR orders and preventing empty hospitals being 'overrun'. In Britain the mantra of stay at home to 'save the NHS' was everywhere and across the world the same story was being sold when it was all lies. Two California doctors, Dan Erickson and Artin Massihi at Accelerated Urgent Care in Bakersfield, held a news conference in April, 2020, to say that intensive care units in California were 'empty, essentially', with hospitals shutting floors, not treating patients and laying off doctors. The California health system was working at minimum capacity 'getting rid of doctors because we just don't have the volume'. They said that people with conditions such as heart disease and cancer were not coming to hospital out of fear of 'Covid-19'. Their video was deleted by Susan Wojcicki's Cult-owned YouTube after reaching five million views. Florida governor Ron Desantis, who rejected the severe lockdowns of other states and is being targeted for doing so, said that in March, 2020, every US governor was given models claiming they would run out of hospital beds in days. That was never going to happen and the 'modellers' knew it. Deceit can be found at every level of the system. Urgent children's operations were cancelled including fracture repairs and biopsies to spot cancer. Eric Nicholls, a consultant paediatrician, said 'this is obviously concerning and we need to return to normal operating and to increase capacity as soon as possible'. Psychopaths

in power were rather less concerned *because* they are psychopaths. Deletion of urgent care and diagnosis has been happening all over the world and how many kids and others have died as a result of the actions of these cold and heartless lunatics dictating 'health' policy? The number must be stratospheric. Richard Sullivan, professor of cancer and global health at King's College London, said people feared 'Covid' more than cancer such was the campaign of fear. 'Years of lost life will be quite dramatic', Sullivan said, with 'a huge amount of avoidable mortality'. Sarah Woolnough, executive director for policy at Cancer Research UK, said there had been a 75 percent drop in urgent referrals to hospitals by family doctors of people with suspected cancer. Sullivan said that 'a lot of services have had to scale back – we've seen a dramatic decrease in the amount of elective cancer surgery'. Lockdown deaths worldwide has been absolutely fantastic with the *New York Post* reporting how data confirmed that 'lockdowns end more lives than they save':

> There was a sharp decline in visits to emergency rooms and an increase in fatal heart attacks because patients didn't receive prompt treatment. Many fewer people were screened for cancer. Social isolation contributed to excess deaths from dementia and Alzheimer's.
>
> Researchers predicted that the social and economic upheaval would lead to tens of thousands of "deaths of despair" from drug overdoses, alcoholism and suicide. As unemployment surged and mental-health and substance-abuse treatment programs were interrupted, the reported levels of anxiety, depression and suicidal thoughts increased dramatically, as did alcohol sales and fatal drug overdoses.

This has been happening while nurses and other staff had so much time on their hands in the 'war-zones' that Tic-Tok dancing videos began appearing across the Internet with medical staff dancing around in empty wards and corridors as people died at home from causes that would normally have been treated in hospital.

Mentions in dispatches

One brave and truth-committed whistleblower was Louise Hampton, a call handler with the UK NHS who made a viral Internet video saying she had done 'fuck all' during the 'pandemic'

which was 'a load of bollocks'. She said that 'Covid-19' was rebranded flu and of course she lost her job. This is what happens in the medical and endless other professions now when you tell the truth. Louise filmed inside 'war-zone' accident and emergency departments to show they were empty and I mean *empty* as in no one there. The mainstream media could have done the same and blown the gaff on the whole conspiracy. They haven't to their eternal shame. Not that most 'journalists' seem capable of manifesting shame as with the psychopaths they slavishly repeat without question. The relative few who were admitted with serious health problems were left to die alone with no loved ones allowed to see them because of 'Covid' rules and they included kids dying without the comfort of mum and dad at their bedside while the evil behind this couldn't give a damn. It was all good fun to them. A Scottish NHS staff nurse publicly quit in the spring of 2021 saying: 'I can no longer be part of the lies and the corruption by the government.' She said hospitals 'aren't full, the beds aren't full, beds have been shut, wards have been shut'. Hospitals were never busy throughout 'Covid'. The staff nurse said that Nicola Sturgeon, tragically the leader of the Scottish government, was on television saying save the hospitals and the NHS – 'but the beds are empty' and 'we've not seen flu, we always see flu every year'. She wrote to government and spoke with her union Unison (the unions are Cult-compromised and *useless*, but nothing changed. Many of her colleagues were scared of losing their jobs if they spoke out as they wanted to. She said nursing staff were being affected by wearing masks all day and 'my head is splitting every shift from wearing a mask'. The NHS is part of the fascist tyranny and must be dismantled so we can start again with human beings in charge. (Ironically, hospitals were reported to be busier again when official 'Covid' cases *fell* in spring/summer of 2021 and many other conditions required treatment at the same time as *the fake vaccine rollout*.)

I will cover the 'Covid vaccine' scam in detail later, but it is another indicator of the sickening disregard for human life that I am highlighting here. The DNA-manipulating concoctions do not fulfil

the definition of a 'vaccine', have never been used on humans before and were given only emergency approval because trials were not completed and they continued using the unknowing public. The result was what a NHS senior nurse with responsibility for 'vaccine' procedure said was 'genocide'. She said the 'vaccines' were not 'vaccines'. They had not been shown to be safe and claims about their effectiveness by drug companies were 'poetic licence'. She described what was happening as a 'horrid act of human annihilation'. The nurse said that management had instigated a policy of not providing a Patient Information Leaflet (PIL) before people were 'vaccinated' even though health care professionals are supposed to do this according to protocol. Patients should also be told that they are taking part in an ongoing clinical trial. Her challenges to what is happening had seen her excluded from meetings and ridiculed in others. She said she was told to 'watch my step … or I would find myself surplus to requirements'. The nurse, who spoke anonymously in fear of her career, said she asked her NHS manager why he/she was content with taking part in genocide against those having the 'vaccines'. The reply was that everyone had to play their part and to 'put up, shut up, and get it done'. Government was 'leaning heavily' on NHS management which was clearly leaning heavily on staff. This is how the global 'medical' hierarchy operates and it starts with the Cult and its World Health Organization.

She told the story of a doctor who had the Pfizer jab and when questioned had no idea what was in it. The doctor had never read the literature. We have to stop treating doctors as intellectual giants when so many are moral and medical pygmies. The doctor did not even know that the 'vaccines' were not fully approved or that their trials were ongoing. They were, however, asking their patients if they minded taking part in follow-ups for research purposes – yes, the *ongoing clinical trial*. The nurse said the doctor's ignorance was not rare and she had spoken to a hospital consultant who had the jab without any idea of the background or that the 'trials' had not been completed. Nurses and pharmacists had shown the same ignorance.

'My NHS colleagues have forsaken their duty of care, broken their code of conduct – Hippocratic Oath – and have been brainwashed just the same as the majority of the UK public through propaganda …' She said she had not been able to recruit a single NHS colleague, doctor, nurse or pharmacist to stand with her and speak out. Her union had refused to help. She said that if the genocide came to light she would not hesitate to give evidence at a Nuremberg-type trial against those in power who could have affected the outcomes but didn't.

And all for what?

To put the nonsense into perspective let's say the 'virus' does exist and let's go completely crazy and accept that the official manipulated figures for cases and deaths are accurate. *Even then* a study by Stanford University epidemiologist Dr John Ioannidis published on the World Health Organization website produced an average infection to fatality rate of … *0.23 percent!* Ioannidis said: 'If one could sample equally from all locations globally, the median infection fatality rate might even be substantially lower than the 0.23% observed in my analysis.' For healthy people under 70 it was … *0.05 percent*! This compares with the 3.4 percent claimed by the Cult-owned World Health Organization when the hoax was first played and maximum fear needed to be generated. An updated Stanford study in April, 2021, put the 'infection' to 'fatality' rate at just 0.15 percent. Another team of scientists led by Megan O'Driscoll and Henrik Salje studied data from 45 countries and published their findings on the Nature website. For children and young people the figure is so small it virtually does not register although authorities will be hyping dangers to the young when they introduce DNA-manipulating 'vaccines' for children. The O'Driscoll study produced an average infection-fatality figure of 0.003 for children from birth to four; 0.001 for 5 to 14; 0.003 for 15 to 19; and it was still only 0.456 up to 64. To claim that children must be 'vaccinated' to protect them from 'Covid' is an obvious lie and so there must be another reason and there is. What's more the average age of a 'Covid' death is akin

to the average age that people die in general. The average age of death in England is about 80 for men and 83 for women. The average age of death from alleged 'Covid' is between 82 and 83. California doctors, Dan Erickson and Artin Massihi, said at their April media conference that projection models of millions of deaths had been 'woefully inaccurate'. They produced detailed figures showing that Californians had a 0.03 chance of dying from 'Covid' based on the number of people who tested positive (with a test not testing for the 'virus'). Erickson said there was a 0.1 percent chance of dying from 'Covid' in the *state* of New York, not just the city, and a 0.05 percent chance in Spain, a centre of 'Covid-19' hysteria at one stage. The Stanford studies supported the doctors' data with fatality rate estimates of 0.23 and 0.15 percent. How close are these figures to my estimate of *zero*? Death-rate figures claimed by the World Health Organization at the start of the hoax were some 15 times higher. The California doctors said there was no justification for lockdowns and the economic devastation they caused. Everything they had ever learned about quarantine was that you quarantine the *sick* and not the healthy. They had never seen this before and it made no medical sense.

Why in the in the light of all this would governments and medical systems the world over say that billions must go under house arrest; lose their livelihood; in many cases lose their mind, their health and their life; force people to wear masks dangerous to health and psychology; make human interaction and even family interaction a criminal offence; ban travel; close restaurants, bars, watching live sport, concerts, theatre, and any activity involving human togetherness and discourse; and closing schools to isolate children from their friends and cause many to commit suicide in acts of hopelessness and despair? The California doctors said lockdown consequences included increased child abuse, partner abuse, alcoholism, depression, and other impacts they were seeing every day. Who would do that to the entire human race if not mentally-ill psychopaths of almost unimaginable extremes like Bill Gates? We must face the reality of what we are dealing with and come out of

denial. Fascism and tyranny are made possible only by the target population submitting and acquiescing to fascism and tyranny. The whole of human history shows that to be true. Most people naively and unquestioning believed what they were told about a 'deadly virus' and meekly and weakly submitted to house arrest. Those who didn't believe it – at least in total – still submitted in fear of the consequences of not doing so. For the rest who wouldn't submit draconian fines have been imposed, brutal policing by psychopaths *for* psychopaths, and condemnation from the meek and weak who condemn the Pushbackers on behalf of the very force that has them, too, in its gunsights. 'Pathetic' does not even begin to suffice. Britain's brainless 'Health' Secretary Matt Hancock warned anyone lying to border officials about returning from a list of 'hotspot' countries could face a jail sentence of up to ten years which is more than for racially-aggravated assault, incest and attempting to have sex with a child under 13. Hancock is a lunatic, but he has the state apparatus behind him in a Cult-led chain reaction and the same with UK 'Vaccine Minister' Nadhim Zahawi, a prominent member of the mega-Cult secret society, Le Cercle, which featured in my earlier books. The Cult enforces its will on governments and medical systems; government and medical systems enforce their will on business and police; business enforces its will on staff who enforce it on customers; police enforce the will of the Cult on the population and play their essential part in creating a world of fascist control that their own children and grandchildren will have to live in their entire lives. It is a hierarchical pyramid of imposition and acquiescence and, yes indeedy, of clinical insanity.

Does anyone bright enough to read this book have to ask what the answer is? I think not, but I will reveal it anyway in the fewest of syllables: Tell the psychos and their moronic lackeys to fuck off and let's get on with our lives. We are many – They are few.

CHAPTER SEVEN

War on your mind

One believes things because one has been conditioned to believe them
Aldous Huxley, *Brave New World*

I have described the 'Covid' hoax as a 'Psyop' and that is true in every sense and on every level in accordance with the definition of that term which is psychological warfare. Break down the 'Covid pandemic' to the foundation themes and it is psychological warfare on the human individual and collective mind.

The same can be said for the entire human belief system involving every subject you can imagine. Huxley was right in his contention that people believe what they are conditioned to believe and this comes from the repetition throughout their lives of the same falsehoods. They spew from government, corporations, media and endless streams of 'experts' telling you what the Cult wants you to believe and often believing it themselves (although *far* from always). 'Experts' are rewarded with 'prestigious' jobs and titles and as agents of perceptual programming with regular access to the media. The Cult has to control the narrative – control *information* – or they lose control of the vital, crucial, without-which-they-cannot-prevail public perception of reality. The foundation of that control today is the Internet made possible by the Defense Advanced Research Projects Agency (DARPA), the incredibly sinister technological arm of the Pentagon. The Internet is the result of military technology.

DARPA openly brags about establishing the Internet which has been a long-term project to lasso the minds of the global population. I have said for decades the plan is to control information to such an extreme that eventually no one would see or hear anything that the Cult does not approve. We are closing in on that end with ferocious censorship since the 'Covid' hoax began and in my case it started back in the 1990s in terms of books and speaking venues. I had to create my own publishing company in 1995 precisely because no one else would publish my books even then. I think they're all still running.

Cult Internet

To secure total control of information they needed the Internet in which pre-programmed algorithms can seek out 'unclean' content for deletion and even stop it being posted in the first place. The Cult had to dismantle print and non-Internet broadcast media to ensure the transfer of information to the appropriate-named 'Web' – a critical expression of the *Cult* web. We've seen the ever-quickening demise of traditional media and control of what is left by a tiny number of corporations operating worldwide. Independent journalism in the mainstream is already dead and never was that more obvious than since the turn of 2020. The Cult wants all information communicated via the Internet to globally censor and allow the plug to be pulled any time. Lockdowns and forced isolation has meant that communication between people has been through electronic means and no longer through face-to-face discourse and discussion. Cult psychopaths have targeted the bars, restaurants, sport, venues and meeting places in general for this reason. None of this is by chance and it's to stop people gathering in any kind of privacy or number while being able to track and monitor all Internet communications and block them as necessary. Even private messages between individuals have been censored by these fascists that control Cult fronts like Facebook, Twitter, Google and YouTube which are all officially run by Sabbatian place-people and from the background by higher-level Sabbatian place people.

Facebook, Google, Amazon and their like were seed-funded and supported into existence with money-no-object infusions of funds either directly or indirectly from DARPA and CIA technology arm In-Q-Tel. The Cult plays the long game and prepares very carefully for big plays like 'Covid'. Amazon is another front in the psychological war and pretty much controls the global market in book sales and increasingly publishing. Amazon's limitless funds have deleted fantastic numbers of independent publishers to seize global domination on the way to deciding which books can be sold and circulated and which cannot. Moves in that direction are already happening. Amazon's leading light Jeff Bezos is the grandson of Lawrence Preston Gise who worked with DARPA predecessor ARPA. Amazon has big connections to the CIA and the Pentagon. The plan I have long described went like this:

1. Employ military technology to establish the Internet.

2. Sell the Internet as a place where people can freely communicate without censorship and allow that to happen until the Net becomes the central and irreversible pillar of human society. If the Internet had been highly censored from the start many would have rejected it.

3. Fund and manipulate major corporations into being to control the circulation of information on your Internet using cover stories about geeks in garages to explain how they came about. Give them unlimited funds to expand rapidly with no need to make a profit for years while non-Cult companies who need to balance the books cannot compete. You know that in these circumstances your Googles, YouTubes, Facebooks and Amazons are going to secure near monopolies by either crushing or buying up the opposition.

4. Allow freedom of expression on both the Internet and communication platforms to draw people in until the Internet is the central and irreversible pillar of human society and your communication corporations have reached a stage of near monopoly domination.

5. Then unleash your always-planned frenzy of censorship on the basis of 'where else are you going to go?' and continue to expand that until nothing remains that the Cult does not want its human targets to see.

The process was timed to hit the 'Covid' hoax to ensure the best chance possible of controlling the narrative which they knew they had to do at all costs. They were, after all, about to unleash a 'deadly virus' that didn't really exist. If you do that in an environment of free-flowing information and opinion you would be dead in the

water before you could say Gates is a psychopath. The network was in place through which the Cult-created-and-owned World Health Organization could dictate the 'Covid' narrative and response policy slavishly supported by Cult-owned Internet communication giants and mainstream media while those telling a different story were censored. Google, YouTube, Facebook and Twitter openly announced that they would do this. What else would we expect from Cult-owned operations like Facebook which former executives have confirmed set out to make the platform more addictive than cigarettes and coldly manipulates emotions of its users to sow division between people and groups and scramble the minds of the young? If Zuckerberg lives out the rest of his life without going to jail for crimes against humanity, and most emphatically against the young, it will be a travesty of justice. Still, no matter, cause and effect will catch up with him eventually and the same with Sergey Brin and Larry Page at Google with its CEO Sundar Pichai who fix the Google search results to promote Cult narratives and hide the opposition. Put the same key words into Google and other search engines like DuckDuckGo and you will see how different results can be. Wikipedia is another intensely biased 'encyclopaedia' which skews its content to the Cult agenda. YouTube links to Wikipedia's version of 'Covid' and 'climate change' on video pages in which experts in their field offer a different opinion (even that is increasingly rare with Wojcicki censorship). Into this 'Covid' silence-them network must be added government media censors, sorry 'regulators', such as Ofcom in the UK which imposed tyrannical restrictions on British broadcasters that had the effect of banning me from ever appearing. Just to debate with me about my evidence and views on 'Covid' would mean breaking the fascistic impositions of Ofcom and its CEO career government bureaucrat Melanie Dawes. Gutless British broadcasters tremble at the very thought of fascist Ofcom.

Psychos behind 'Covid'

The reason for the 'Covid' catastrophe in all its facets and forms can be seen by whom and what is driving the policies worldwide in such a coordinated way. Decisions are not being made to protect health, but to target psychology. The dominant group guiding and 'advising' government policy are not medical professionals. They are psychologists and behavioural scientists. Every major country has its own version of this phenomenon and I'll use the British example to show how it works. In many ways the British version has been affecting the wider world in the form of the huge behaviour manipulation network in the UK which operates in other countries. The network involves private companies, government, intelligence and military. The Cabinet Office is at the centre of the government 'Covid' Psyop and part-owns, with 'innovation charity' Nesta, the Behavioural Insights Team (BIT) which claims to be independent of government but patently isn't. The BIT was established in 2010 and its job is to manipulate the psyche of the population to acquiesce to government demands and so much more. It is also known as the 'Nudge Unit', a name inspired by the 2009 book by two ultra-Zionists, Cass Sunstein and Richard Thaler, called *Nudge: Improving Decisions About Health, Wealth, and Happiness*. The book, as with the Behavioural Insights Team, seeks to 'nudge' behaviour (manipulate it) to make the public follow patterns of action and perception that suit those in authority (the Cult). Sunstein is so skilled at this that he advises the World Health Organization and the UK Behavioural Insights Team and was Administrator of the White House Office of Information and Regulatory Affairs in the Obama administration. Biden appointed him to the Department of Homeland Security – another ultra-Zionist in the fold to oversee new immigration laws which is another policy the Cult wants to control. Sunstein is desperate to silence anyone exposing conspiracies and co-authored a 2008 report on the subject in which suggestions were offered to ban 'conspiracy theorizing' or impose 'some kind of tax, financial or otherwise, on those who disseminate such theories'. I guess a psychiatrist's chair is out of the question?

Sunstein's mate Richard Thaler, an 'academic affiliate' of the UK Behavioural Insights Team, is a proponent of 'behavioural economics' which is defined as the study of 'the effects of psychological, cognitive, emotional, cultural and social factors on the decisions of individuals and institutions'. Study the effects so they can be manipulated to be what you want them to be. Other leading names in the development of behavioural economics are ultra-Zionists Daniel Kahneman and Robert J. Shiller and they, with Thaler, won the Nobel Memorial Prize in Economic Sciences for their work in this field. The Behavioural Insights Team is operating at the heart of the UK government and has expanded globally through partnerships with several universities including Harvard, Oxford, Cambridge, University College London (UCL) and Pennsylvania. They claim to have 'trained' (reframed) 20,000 civil servants and run more than 750 projects involving 400 randomised controlled trials in dozens of countries' as another version of mind reframers Common Purpose. BIT works from its office in New York with cities and their agencies, as well as other partners, across the United States and Canada – this is a company part-owned by the British government Cabinet Office. An executive order by President Cult-servant Obama established a US Social and Behavioral Sciences Team in 2015. They all have the same reason for being and that's to brainwash the population directly and by brainwashing those in positions of authority.

'Covid' mind game

Another prime aspect of the UK mind-control network is the 'independent' [joke] Scientific Pandemic Insights Group on Behaviours (SPI-B) which 'provides behavioural science advice aimed at anticipating and helping people adhere to interventions that are recommended by medical or epidemiological experts'. That means manipulating public perception and behaviour to do whatever government tells them to do. It's disgusting and if they really want the public to be 'safe' this lot should all be under lock and key. According to the government website SPI-B consists of

'behavioural scientists, health and social psychologists, anthropologists and historians' and advises the Whitty-Vallance-led Scientific Advisory Group for Emergencies (SAGE) which in turn advises the government on 'the science' (it doesn't) and 'Covid' policy. When politicians say they are being guided by 'the science' this is the rabble in each country they are talking about and that 'science' is dominated by behaviour manipulators to enforce government fascism through public compliance. The Behaviour Insight Team is headed by psychologist David Solomon Halpern, a visiting professor at King's College London, and connects with a national and global web of other civilian and military organisations as the Cult moves towards its goal of fusing them into one fascistic whole in every country through its 'Fusion Doctrine'. The behaviour manipulation network involves, but is not confined to, the Foreign Office; National Security Council; government communications headquarters (GCHQ); MI5; MI6; the Cabinet Office-based Media Monitoring Unit; and the Rapid Response Unit which 'monitors digital trends to spot emerging issues; including misinformation and disinformation; and identifies the best way to respond'.

There is also the 77th Brigade of the UK military which operates like the notorious Israeli military's Unit 8200 in manipulating information and discussion on the Internet by posing as members of the public to promote the narrative and discredit those who challenge it. Here we have the military seeking to manipulate *domestic* public opinion while the Nazis in government are fine with that. Conservative Member of Parliament Tobias Ellwood, an advocate of lockdown and control through 'vaccine passports', is a Lieutenant Colonel reservist in the 77th Brigade which connects with the military operation jHub, the 'innovation centre' for the Ministry of Defence and Strategic Command. jHub has also been involved with the civilian National Health Service (NHS) in 'symptom tracing' the population. The NHS is a key part of this mind control network and produced a document in December, 2020, explaining to staff how to use psychological manipulation with different groups and ages to get them to have the DNA-manipulating 'Covid vaccine'

that's designed to cumulatively rewrite human genetics. The document, called 'Optimising Vaccination Roll Out – Do's and Dont's for all messaging, documents and "communications" in the widest sense', was published by NHS England and the NHS Improvement *Behaviour Change Unit* in partnership with Public Health England and Warwick Business School. I hear the mantra about 'save the NHS' and 'protect the NHS' when we need to scrap the NHS and start again. The current version is far too corrupt, far too anti-human and totally compromised by Cult operatives and their assets. UK government broadcast media censor Ofcom will connect into this web – as will the BBC with its tremendous Ofcom influence – to control what the public see and hear and dictate mass perception. Nuremberg trials must include personnel from all these organisations.

The fear factor

The 'Covid' hoax has led to the creation of the UK Cabinet Office-connected Joint Biosecurity Centre (JBC) which is officially described as providing 'expert advice on pandemics' using its independent [all Cult operations are 'independent'] analytical function to provide real-time analysis about infection outbreaks to identify and respond to outbreaks of Covid-19'. Another role is to advise the government on a response to spikes in infections – 'for example by closing schools or workplaces in local areas where infection levels have risen'. Put another way, promoting the Cult agenda. The Joint Biosecurity Centre is modelled on the Joint Terrorism Analysis Centre which analyses intelligence to set 'terrorism threat levels' and here again you see the fusion of civilian and military operations and intelligence that has led to military intelligence producing documents about 'vaccine hesitancy' and how it can be combated. Domestic civilian matters and opinions should not be the business of the military. The Joint Biosecurity Centre is headed by Tom Hurd, director general of the Office for Security and Counter-Terrorism from the establishment-to-its-fingertips Hurd family. His father is former Foreign Secretary Douglas Hurd. How coincidental that Tom

Hurd went to the elite Eton College and Oxford University with Boris Johnson. Imperial College with its ridiculous computer modeller Neil Ferguson will connect with this gigantic web that will itself interconnect with similar set-ups in other major and not so major countries. Compared with this Cult network the politicians, be they Boris Johnson, Donald Trump or Joe Biden, are bit-part players 'following the science'. The network of psychologists was on the 'Covid' case from the start with the aim of generating maximum fear of the 'virus' to ensure compliance by the population. A government behavioural science group known as SPI-B produced a paper in March, 2020, for discussion by the main government science advisory group known as SAGE. It was headed 'Options for increasing adherence to social distancing measures' and it said the following in a section headed 'Persuasion':

- A substantial number of people still do not feel sufficiently personally threatened; it could be that they are reassured by the low death rate in their demographic group, although levels of concern may be rising. Having a good understanding of the risk has been found to be positively associated with adoption of COVID-19 social distancing measures in Hong Kong.

- The perceived level of personal threat needs to be increased among those who are complacent, using hard-hitting evaluation of options for increasing social distancing emotional messaging. To be effective this must also empower people by making clear the actions they can take to reduce the threat.

- Responsibility to others: There seems to be insufficient understanding of, or feelings of responsibility about, people's role in transmitting the infection to others … Messaging about actions need to be framed positively in terms of protecting oneself and the community, and increase confidence that they will be effective.

- Some people will be more persuaded by appeals to play by the rules, some by duty to the community, and some to personal risk.

> All these different approaches are needed. The messaging also needs to take account of the realities of different people's lives. Messaging needs to take account of the different motivational levers and circumstances of different people.

All this could be achieved the SPI-B psychologists said by *using the media to increase the sense of personal threat* which translates as terrify the shit out of the population, including children, so they all do what we want. That's not happened has it? Those excuses for 'journalists' who wouldn't know journalism if it bit them on the arse (the great majority) have played their crucial part in serving this Cult-government Psyop to enslave their own kids and grandkids. How they live with themselves I have no idea. The psychological war has been underpinned by constant government 'Covid' propaganda in almost every television and radio ad break, plus the Internet and print media, which has pounded out the fear with taxpayers footing the bill for their own programming. The result has been people terrified of a 'virus' that doesn't exist or one with a tiny fatality rate even if you believe it does. People walk down the street and around the shops wearing face-nappies damaging their health and psychology while others report those who refuse to be that naïve to the police who turn up in their own face-nappies. I had a cameraman come to my flat and he was so frightened of 'Covid' he came in wearing a mask and refused to shake my hand in case he caught something. He had – naïveitis – and the thought that he worked in the mainstream media was both depressing and made his behaviour perfectly explainable. The fear which has gripped the minds of so many and frozen them into compliance has been carefully cultivated by these psychologists who are really psychopaths. If lives get destroyed and a lot of young people commit suicide it shows our plan is working. SPI-B then turned to compulsion on the public to comply. 'With adequate preparation, rapid change can be achieved', it said. Some countries had introduced mandatory self-isolation on a wide scale without evidence of major public unrest and a large majority of the UK's population appeared to be supportive of more coercive measures with 64 percent of adults saying they would

support putting London under a lockdown (watch the 'polls' which are designed to make people believe that public opinion is in favour or against whatever the subject in hand).

For 'aggressive protective measures' to be effective, the SPI-B paper said, special attention should be devoted to those population groups that are more at risk. Translated from the Orwellian this means making the rest of population feel guilty for not protecting the 'vulnerable' such as old people which the Cult and its agencies were about to kill on an industrial scale with lockdown, lack of treatment and the Gates 'vaccine'. Psychopath psychologists sold their guilt-trip so comprehensively that Los Angeles County Supervisor Hilda Solis reported that children were apologising (from a distance) to their parents and grandparents for bringing 'Covid' into their homes and getting them sick. '… These apologies are just some of the last words that loved ones will ever hear as they die alone,' she said. Gut-wrenchingly Solis then used this childhood tragedy to tell children to stay at home and 'keep your loved ones alive'. Imagine heaping such potentially life-long guilt on a kid when it has absolutely nothing to do with them. These people are deeply disturbed and the psychologists behind this even more so.

Uncivil war – divide and rule

Professional mind-controllers at SPI-B wanted the media to increase a sense of responsibility to others (do as you're told) and promote 'positive messaging' for those actions while in contrast to invoke 'social disapproval' by the unquestioning, obedient, community of anyone with a mind of their own. Again the compliant Goebbels-like media obliged. This is an old, old, trick employed by tyrannies the world over throughout human history. You get the target population to keep the target population in line – *your* line. SPI-B said this could 'play an important role in preventing anti-social behaviour or discouraging failure to enact pro-social behaviour'. For 'anti-social' in the Orwellian parlance of SPI-B see any behaviour that government doesn't approve. SPI-B recommendations said that 'social disapproval' should be accompanied by clear messaging and

promotion of strong collective identity – hence the government and celebrity mantra of 'we're all in this together'. Sure we are. The mind doctors have such contempt for their targets that they think some clueless comedian, actor or singer telling them to do what the government wants will be enough to win them over. We have had UK comedian Lenny Henry, actor Michael Caine and singer Elton John wheeled out to serve the propagandists by urging people to have the DNA-manipulating 'Covid' non-'vaccine'. The role of Henry and fellow black celebrities in seeking to coax a 'vaccine' reluctant black community into doing the government's will was especially stomach-turning. An emotion-manipulating script and carefully edited video featuring these black 'celebs' was such an insult to the intelligence of black people and where's the self-respect of those involved selling their souls to a fascist government agenda? Henry said he heard black people's 'legitimate worries and concerns', but people must 'trust the facts' when they were doing exactly that by not having the 'vaccine'. They had to include the obligatory reference to Black Lives Matter with the line … 'Don't let coronavirus cost even more black lives – because we matter'. My god, it was pathetic. 'I know the vaccine is safe and what it does.' How? 'I'm a comedian and it says so in my script.'

SPI-B said social disapproval needed to be carefully managed to avoid victimisation, scapegoating and misdirected criticism, but they knew that their 'recommendations' would lead to exactly that and the media were specifically used to stir-up the divide-and-conquer hostility. Those who conform like good little baa, baas, are praised while those who have seen through the tidal wave of lies are 'Covidiots'. The awake have been abused by the fast asleep for not conforming to fascism and impositions that the awake know are designed to endanger their health, dehumanise them, and tear asunder the very fabric of human society. We have had the curtain-twitchers and morons reporting neighbours and others to the face-nappied police for breaking 'Covid rules' with fascist police delighting in posting links and phone numbers where this could be done. The Cult cannot impose its will without a compliant police

and military or a compliant population willing to play their part in enslaving themselves and their kids. The words of a pastor in Nazi Germany are so appropriate today:

First they came for the socialists and I did not speak out because I was not a socialist.

Then they came for the trade unionists and I did not speak out because I was not a trade unionist.

Then they came for the Jews and I did not speak out because I was not a Jew.

Then they came for me and there was no one left to speak for me.

Those who don't learn from history are destined to repeat it and so many are.

'Covid' rules: Rewiring the mind

With the background laid out to this gigantic national and global web of psychological manipulation we can put 'Covid' rules into a clear and sinister perspective. Forget the claims about protecting health. 'Covid' rules are about dismantling the human mind, breaking the human spirit, destroying self-respect, and then putting Humpty Dumpty together again as a servile, submissive slave. Social isolation through lockdown and distancing have devastating effects on the human psyche as the psychological psychopaths well know and that's the real reason for them. Humans need contact with each other, discourse, closeness and touch, or they eventually, and literarily, go crazy. Masks, which I will address at some length, fundamentally add to the effects of isolation and the Cult agenda to dehumanise and de-individualise the population. To do this while knowing – in fact *seeking* – this outcome is the very epitome of evil and psychologists involved in this *are* the epitome of evil. They must like all the rest of the Cult demons and their assets stand trial for crimes against humanity on a scale that defies the imagination. Psychopaths in uniform use isolation to break enemy troops and agents and make them subservient and submissive to tell what they know. The technique is rightly considered a form of torture and

torture is most certainly what has been imposed on the human population.

Clinically-insane American psychologist Harry Harlow became famous for his isolation experiments in the 1950s in which he separated baby monkeys from their mothers and imprisoned them for months on end in a metal container or 'pit of despair'. They soon began to show mental distress and depression as any idiot could have predicted. Harlow put other monkeys in steel chambers for three, six or twelve months while denying them any contact with animals or humans. He said that the effects of total social isolation for six months were 'so devastating and debilitating that we had assumed initially that twelve months of isolation would not produce any additional decrement'; but twelve months of isolation 'almost obliterated the animals socially'. This is what the Cult and its psychopaths are doing to you and your children. Even monkeys in partial isolation in which they were not allowed to form relationships with other monkeys became 'aggressive and hostile, not only to others, but also towards their own bodies'. We have seen this in the young as a consequence of lockdown. UK government psychopaths launched a public relations campaign telling people not to hug each other even after they received the 'Covid-19 vaccine' which we were told with more lies would allow a return to 'normal life'. A government source told *The Telegraph*: 'It will be along the lines that it is great that you have been vaccinated, but if you are going to visit your family and hug your grandchildren there is a chance you are going to infect people you love.' The source was apparently speaking from a secure psychiatric facility. Janet Lord, director of Birmingham University's Institute of Inflammation and Ageing, said that parents and grandparents should avoid hugging their children. Well, how can I put it, Ms Lord? Fuck off. Yep, that'll do.

Destroying the kids – where are the parents?

Observe what has happened to people enslaved and isolated by lockdown as suicide and self-harm has soared worldwide,

particularly among the young denied the freedom to associate with their friends. A study of 49,000 people in English-speaking countries concluded that almost half of young adults are at clinical risk of mental health disorders. A national survey in America of 1,000 currently enrolled high school and college students found that 5 percent reported attempting suicide during the pandemic. Data from the US CDC's National Syndromic Surveillance Program from January 1st to October 17th, 2020, revealed a *31 percent* increase in mental health issues among adolescents aged 12 to 17 compared with 2019. The CDC reported that America in general suffered the biggest drop in life expectancy since World War Two as it fell by a year in the first half of 2020 as a result of 'deaths of despair' – overdoses and suicides. Deaths of despair have leapt by more than 20 percent during lockdown and include the highest number of fatal overdoses ever recorded in a single year – 81,000. Internet addiction is another consequence of being isolated at home which lowers interest in physical activities as kids fall into inertia and what's the point? Children and young people are losing hope and giving up on life, sometimes literally. A 14-year-old boy killed himself in Maryland because he had 'given up' when his school district didn't reopen; an 11-year-old boy shot himself during a zoom class; a teenager in Maine succumbed to the isolation of the 'pandemic' when he ended his life after experiencing a disrupted senior year at school. Children as young as nine have taken their life and all these stories can be repeated around the world. Careers are being destroyed before they start and that includes those in sport in which promising youngsters have not been able to take part. The plan of the psycho-psychologists is working all right. Researchers at Cambridge University found that lockdowns cause significant harm to children's mental health. Their study was published in the *Archives of Disease in Childhood*, and followed 168 children aged between 7 and 11. The researchers concluded:

> During the UK lockdown, children's depression symptoms have increased substantially, relative to before lockdown. The scale of this effect has direct relevance for the continuation of different elements of lockdown policy, such as complete or partial school closures …

… Specifically, we observed a statistically significant increase in ratings of depression, with a medium-to-large effect size. Our findings emphasise the need to incorporate the potential impact of lockdown on child mental health in planning the ongoing response to the global pandemic and the recovery from it.

Not a chance when the Cult's psycho-psychologists were getting exactly what they wanted. The UK's Royal College of Paediatrics and Child Health has urged parents to look for signs of eating disorders in children and young people after a three to four fold increase. Specialists say the 'pandemic' is a major reason behind the rise. You don't say. The College said isolation from friends during school closures, exam cancellations, loss of extra-curricular activities like sport, and an increased use of social media were all contributory factors along with fears about the virus (psycho-psychologists again), family finances, and students being forced to quarantine. Doctors said young people were becoming severely ill by the time they were seen with 'Covid' regulations reducing face-to-face consultations. Nor is it only the young that have been devastated by the psychopaths. Like all bullies and cowards the Cult is targeting the young, elderly, weak and infirm. A typical story was told by a British lady called Lynn Parker who was not allowed to visit her husband in 2020 for the last ten and half months of his life 'when he needed me most' between March 20th and when he died on December 19th. This vacates the criminal and enters the territory of evil. The emotional impact on the immune system alone is immense as are the number of people of all ages worldwide who have died as a result of Cult-demanded, Gates-demanded, lockdowns.

Isolation is torture

The experience of imposing solitary confinement on millions of prisoners around the world has shown how a large percentage become 'actively psychotic and/or acutely suicidal'. Social isolation has been found to trigger 'a specific psychiatric syndrome, characterized by hallucinations; panic attacks; overt paranoia; diminished impulse control; hypersensitivity to external stimuli; and difficulties with thinking, concentration and memory'. Juan Mendez,

a United Nations rapporteur (investigator), said that isolation is a form of torture. Research has shown that even after isolation prisoners find it far more difficult to make social connections and I remember chatting to a shop assistant after one lockdown who told me that when her young son met another child again he had no idea how to act or what to do. Hannah Flanagan, Director of Emergency Services at Journey Mental Health Center in Dane County, Wisconsin, said: 'The specificity about Covid social distancing and isolation that we've come across as contributing factors to the suicides are really new to us this year.' But they are not new to those that devised them. They are getting the effect they want as the population is psychologically dismantled to be rebuilt in a totally different way. Children and the young are particularly targeted. They will be the adults when the full-on fascist AI-controlled technocracy is planned to be imposed and they are being prepared to meekly submit. At the same time older people who still have a memory of what life was like before – and how fascist the new normal really is – are being deleted. You are going to see efforts to turn the young against the old to support this geriatric genocide. Hannah Flanagan said the big increase in suicide in her county proved that social isolation is not only harmful, but deadly. Studies have shown that isolation from others is one of the main risk factors in suicide and even more so with women. Warnings that lockdown could create a 'perfect storm' for suicide were ignored. After all this was one of the *reasons* for lockdown. Suicide, however, is only the most extreme of isolation consequences. There are many others. Dr Dhruv Khullar, assistant professor of healthcare policy at Weill Cornell Medical College, said in a *New York Times* article in 2016 long before the fake 'pandemic':

> A wave of new research suggests social separation is bad for us. Individuals with less social connection have disrupted sleep patterns, altered immune systems, more inflammation and higher levels of stress hormones. One recent study found that isolation increases the risk of heart disease by 29 percent and stroke by 32 percent. Another analysis that pooled data from 70 studies and 3.4 million people found that socially isolated individuals had a 30 percent higher risk of dying in the next seven years, and that this effect was largest in middle age.

Loneliness can accelerate cognitive decline in older adults, and isolated individuals are twice as likely to die prematurely as those with more robust social interactions. These effects start early: Socially isolated children have significantly poorer health 20 years later, even after controlling for other factors. All told, loneliness is as important a risk factor for early death as obesity and smoking.

There you have proof from that one article alone four years before 2020 that those who have enforced lockdown, social distancing and isolation knew what the effect would be and that is even more so with professional psychologists that have been driving the policy across the globe. We can go back even further to the years 2000 and 2003 and the start of a major study on the effects of isolation on health by Dr Janine Gronewold and Professor Dirk M. Hermann at the University Hospital in Essen, Germany, who analysed data on 4,316 people with an average age of 59 who were recruited for the long-term research project. They found that socially isolated people are more than 40 percent more likely to have a heart attack, stroke, or other major cardiovascular event and nearly 50 percent more likely to die from any cause. Given the financial Armageddon unleashed by lockdown we should note that the study found a relationship between increased cardiovascular risk and lack of financial support. After excluding other factors social isolation was still connected to a 44 percent increased risk of cardiovascular problems and a 47 percent increased risk of death by any cause. Lack of financial support was associated with a 30 percent increase in the risk of cardiovascular health events. Dr Gronewold said it had been known for some time that feeling lonely or lacking contact with close friends and family can have an impact on physical health and the study had shown that having strong social relationships is of high importance for heart health. Gronewold said they didn't understand yet why people who are socially isolated have such poor health outcomes, but this was obviously a worrying finding, particularly during these times of prolonged social distancing. Well, it can be explained on many levels. You only have to identify the point in the body where people feel loneliness and missing people they are parted from – it's in the centre of the chest where they feel the ache of loneliness and the ache of missing people. 'My heart aches for

you' … 'My heart aches for some company.' I will explain this more in the chapter Escaping Wetiko, but when you realise that the body is the mind – they are expressions of each other – the reason why state of the mind dictates state of the body becomes clear.

American psychologist Ranjit Powar was highlighting the effects of lockdown isolation as early as April, 2020. She said humans have evolved to be social creatures and are wired to live in interactive groups. Being isolated from family, friends and colleagues could be unbalancing and traumatic for most people and could result in short or even long-term psychological and physical health problems. An increase in levels of anxiety, aggression, depression, forgetfulness and hallucinations were possible psychological effects of isolation. 'Mental conditions may be precipitated for those with underlying pre-existing susceptibilities and show up in many others without any pre-condition.' Powar said personal relationships helped us cope with stress and if we lost this outlet for letting off steam the result can be a big emotional void which, for an average person, was difficult to deal with. 'Just a few days of isolation can cause increased levels of anxiety and depression' – so what the hell has been the effect on the global population of *18 months* of this at the time of writing? Powar said: 'Add to it the looming threat of a dreadful disease being repeatedly hammered in through the media and you have a recipe for many shades of mental and physical distress.' For those with a house and a garden it is easy to forget that billions have had to endure lockdown isolation in tiny overcrowded flats and apartments with nowhere to go outside. The psychological and physical consequences of this are unimaginable and with lunatic and abusive partners and parents the consequences have led to tremendous increases in domestic and child abuse and alcoholism as people seek to shut out the horror. Ranjit Powar said:

Staying in a confined space with family is not all a rosy picture for everyone. It can be extremely oppressive and claustrophobic for large low-income families huddled together in small single-room houses. Children here are not lucky enough to have many board/electronic games or books to keep them occupied.

Add to it the deep insecurity of running out of funds for food and basic necessities. On the other hand, there are people with dysfunctional family dynamics, such as domineering, abusive or alcoholic partners, siblings or parents which makes staying home a period of trial. Incidence of suicide and physical abuse against women has shown a worldwide increase. Heightened anxiety and depression also affect a person's immune system, making them more susceptible to illness.

To think that Powar's article was published on April 11th, 2020.

Six-feet fantasy

Social (unsocial) distancing demanded that people stay six feet or two metres apart. UK government advisor Robert Dingwall from the New and Emerging Respiratory Virus Threats Advisory Group said in a radio interview that the two-metre rule was 'conjured up out of nowhere' and was not based on science. No, it was not based on *medical* science, but it didn't come out of nowhere. The distance related to *psychological* science. Six feet/two metres was adopted in many countries and we were told by people like the criminal Anthony Fauci and his ilk that it was founded on science. Many schools could not reopen because they did not have the space for six-feet distancing. Then in March, 2021, after a year of six-feet 'science', a study published in the *Journal of Infectious Diseases* involving more than 500,000 students and almost 100,000 staff over 16 weeks revealed no significant difference in 'Covid' cases between six feet and three feet and Fauci changed his tune. Now three feet was okay. There is no difference between six feet and three *inches* when there is no 'virus' and they got away with six feet for psychological reasons for as long as they could. I hear journalists and others talk about 'unintended consequences' of lockdown. They are not *unintended* at all; they have been coldly-calculated for a specific outcome of human control and that's why super-psychopaths like Gates have called for them so vehemently. Super-psychopath psychologists have demanded them and psychopathic or clueless, spineless, politicians have gone along with them by 'following the science'. But it's not science at all. 'Science' is not what is; it's only what people can be manipulated to believe it is. The whole 'Covid' catastrophe is

founded on mind control. Three word or three statement mantras issued by the UK government are a well-known mind control technique and so we've had 'Stay home/protect the NHS/save lives', 'Stay alert/control the virus/save lives' and 'hands/face/space'. One of the most vocal proponents of extreme 'Covid' rules in the UK has been Professor Susan Michie, a member of the British Communist Party, who is not a medical professional. Michie is the director of the Centre for Behaviour Change at University College London. She is a *behavioural psychologist* and another filthy rich 'Marxist' who praised China's draconian lockdown. She was known by fellow students at Oxford University as 'Stalin's nanny' for her extreme Marxism. Michie is an influential member of the UK government's Scientific Advisory Group for Emergencies (SAGE) and behavioural manipulation groups which have dominated 'Covid' policy. She is a consultant adviser to the World Health Organization on 'Covid-19' and behaviour. Why the hell are lockdowns anything to do with her when they are claimed to be about health? Why does a behavioural psychologist from a group charged with changing the behaviour of the public want lockdown, human isolation and mandatory masks? Does that question really need an answer? Michie *absolutely* has to explain herself before a Nuremberg court when humanity takes back its world again and even more so when you see the consequences of masks that she demands are compulsory. This is a Michie classic:

> The benefits of getting primary school children to wear masks is that regardless of what little degree of transmission is occurring in those age groups it could help normalise the practice. Young children wearing masks may be more likely to get their families to accept masks.

Those words alone should carry a prison sentence when you ponder on the callous disregard for children involved and what a statement it makes about the mind and motivations of Susan Michie. What a lovely lady and what she said there encapsulates the mentality of the psychopaths behind the 'Covid' horror. Let us compare what Michie said with a countrywide study in Germany published at researchsquare.com involving 25,000 school children and 17,854 health complaints submitted by parents. Researchers

found that masks are harming children physically, psychologically, and behaviourally with 24 health issues associated with mask wearing. They include: shortness of breath (29.7%); dizziness (26.4%); increased headaches (53%); difficulty concentrating (50%); drowsiness or fatigue (37%); and malaise (42%). Nearly a third of children experienced more sleep issues than before and a quarter developed new fears. Researchers found health issues and other impairments in 68 percent of masked children covering their faces for an average of 4.5 hours a day. Hundreds of those taking part experienced accelerated respiration, tightness in the chest, weakness, and short-term impairment of consciousness. A reminder of what Michie said again:

The benefits of getting primary school children to wear masks is that regardless of what little degree of transmission is occurring in those age groups it could help normalise the practice. Young children wearing masks may be more likely to get their families to accept masks.

Psychopaths in government and psychology now have children and young people – plus all the adults – wearing masks for hours on end while clueless teachers impose the will of the psychopaths on the young they should be protecting. What the hell are parents doing?

Cult lab rats

We have some schools already imposing on students microchipped buzzers that activate when they get 'too close' to their pals in the way they do with lab rats. How apt. To the Cult and its brain-dead servants our children *are* lab rats being conditioned to be unquestioning, dehumanised slaves for the rest of their lives. Children and young people are being weaned and frightened away from the most natural human instincts including closeness and touch. I have tracked in the books over the years how schools were banning pupils from greeting each other with a hug and the whole Cult-induced Me Too movement has terrified men and boys from a relaxed and natural interaction with female friends and work colleagues to the point where many men try never to be in a room

alone with a woman that's not their partner. Airhead celebrities have as always played their virtue-signalling part in making this happen with their gross exaggeration. For every monster like Harvey Weinstein there are at least tens of thousands of men that don't treat women like that; but everyone must be branded the same and policy changed for them as well as the monster. I am going to be using the word 'dehumanise' many times in this chapter because that is what the Cult is seeking to do and it goes very deep as we shall see. Don't let them kid you that social distancing is planned to end one day. That's not the idea. We are seeing more governments and companies funding and producing wearable gadgets to keep people apart and they would not be doing that if this was meant to be short-term. A tech start-up company backed by GCHQ, the British Intelligence and military surveillance headquarters, has created a social distancing wrist sensor that alerts people when they get too close to others. The CIA has also supported tech companies developing similar devices. The wearable sensor was developed by Tended, one of a number of start-up companies supported by GCHQ (see the CIA and DARPA). The device can be worn on the wrist or as a tag on the waistband and will vibrate whenever someone wearing the device breaches social distancing and gets anywhere near natural human contact. The company had a lucky break in that it was developing a distancing sensor when the 'Covid' hoax arrived which immediately provided a potentially enormous market. How fortunate. The government in big-time Cult-controlled Ontario in Canada is investing $2.5 million in wearable contact tracing technology that 'will alert users if they may have been exposed to the Covid-19 in the workplace and will beep or vibrate if they are within six feet of another person'. Facedrive Inc., the technology company behind this, was founded in 2016 with funding from the Ontario Together Fund and obviously they, too, had a prophet on the board of directors. The human surveillance and control technology is called TraceSCAN and would be worn by the human cyborgs in places such as airports, workplaces, construction sites, care homes and … *schools*.

I emphasise schools with children and young people the prime targets. You know what is planned for society as a whole if you keep your eyes on the schools. They have always been places where the state program the next generation of slaves to be its compliant worker-ants – or Woker-ants these days; but in the mist of the 'Covid' madness they have been transformed into mind laboratories on a scale never seen before. Teachers and head teachers are just as programmed as the kids – often more so. Children are kept apart from human interaction by walk lanes, classroom distancing, staggered meal times, masks, and the rolling-out of buzzer systems. Schools are now physically laid out as a laboratory maze for lab-rats. Lunatics at a school in Anchorage, Alaska, who should be prosecuted for child abuse, took away desks and forced children to kneel (know your place) on a mat for five hours a day while wearing a mask and using their chairs as a desk. How this was supposed to impact on a 'virus' only these clinically insane people can tell you and even then it would be clap-trap. The school banned recess (interaction), art classes (creativity), and physical exercise (getting body and mind moving out of inertia). Everyone behind this outrage should be in jail or better still a mental institution. The behavioural manipulators are all for this dystopian approach to schools. Professor Susan Michie, the mind-doctor and British Communist Party member, said it was wrong to say that schools were safe. They had to be made so by 'distancing', masks and ventilation (sitting all day in the cold). I must ask this lady round for dinner on a night I know I am going to be out and not back for weeks. She probably wouldn't be able to make it, anyway, with all the visits to her own psychologist she must have block-booked.

Masking identity

I know how shocking it must be for you that a behaviour manipulator like Michie wants everyone to wear masks which have long been a feature of mind-control programs like the infamous MKUltra in the United States, but, there we are. We live and learn. I spent many years from 1996 to right across the millennium

researching mind control in detail on both sides of the Atlantic and elsewhere. I met a large number of mind-control survivors and many had been held captive in body and mind by MKUltra. MK stands for mind-control, but employs the German spelling in deference to the Nazis spirited out of Germany at the end of World War Two by Operation Paperclip in which the US authorities, with help from the Vatican, transported Nazi mind-controllers and engineers to America to continue their work. Many of them were behind the creation of NASA and they included Nazi scientist and SS officer Wernher von Braun who swapped designing V-2 rockets to bombard London with designing the Saturn V rockets that powered the NASA moon programme's Apollo craft. I think I may have mentioned that the Cult has no borders. Among Paperclip escapees was Josef Mengele, the Angel of Death in the Nazi concentration camps where he conducted mind and genetic experiments on children often using twins to provide a control twin to measure the impact of his 'work' on the other. If you want to observe the Cult mentality in all its extremes of evil then look into the life of Mengele. I have met many people who suffered mercilessly under Mengele in the United States where he operated under the name Dr Greene and became a stalwart of MKUltra programming and torture. Among his locations was the underground facility in the Mojave Desert in California called the China Lake Naval Weapons Station which is almost entirely below the surface. My books *The Biggest Secret*, *Children of the Matrix* and *The Perception Deception* have the detailed background to MKUltra.

The best-known MKUltra survivor is American Cathy O'Brien. I first met her and her late partner Mark Phillips at a conference in Colorado in 1996. Mark helped her escape and deprogram from decades of captivity in an offshoot of MKUltra known as Project Monarch in which 'sex slaves' were provided for the rich and famous including Father George Bush, Dick Cheney and the Clintons. Read Cathy and Mark's book *Trance-Formation of America* and if you are new to this you will be shocked to the core. I read it in 1996 shortly before, with the usual synchronicity of my life, I found

myself given a book table at the conference right next to hers. MKUltra never ended despite being very publicly exposed (only a small part of it) in the 1970s and continues in other guises. I am still in touch with Cathy. She contacted me during 2020 after masks became compulsory in many countries to tell me how they were used as part of MKUltra programming. I had been observing 'Covid regulations' and the relationship between authority and public for months. I saw techniques that I knew were employed on individuals in MKUltra being used on the global population. I had read many books and manuals on mind control including one called *Silent Weapons for Quiet Wars* which came to light in the 1980s and was a guide on how to perceptually program on a mass scale. 'Silent Weapons' refers to mind-control. I remembered a line from the manual as governments, medical authorities and law enforcement agencies have so obviously talked to – or rather at – the adult population since the 'Covid' hoax began as if they are children. The document said:

> If a person is spoken to by a T.V. advertiser as if he were a twelve-year-old, then, due to suggestibility, he will, with a certain probability, respond or react to that suggestion with the uncritical response of a twelve-year-old and will reach in to his economic reservoir and deliver its energy to buy that product on impulse when he passes it in the store.

That's why authority has spoken to adults like children since all this began.

Why did Michael Jackson wear masks?

Every aspect of the 'Covid' narrative has mind-control as its central theme. Cathy O'Brien wrote an article for davidicke.com about the connection between masks and mind control. Her daughter Kelly who I first met in the 1990s was born while Cathy was still held captive in MKUltra. Kelly was forced to wear a mask as part of her programming from the age of *two* to dehumanise her, target her sense of individuality and reduce the amount of oxygen her brain and body received. *Bingo*. This is the real reason for compulsory

masks, why they have been enforced en masse, and why they seek to increase the number they demand you wear. First one, then two, with one disgraceful alleged 'doctor' recommending four which is nothing less than a death sentence. Where and how often they must be worn is being expanded for the purpose of mass mind control and damaging respiratory health which they can call 'Covid-19'. Canada's government headed by the man-child Justin Trudeau, says it's fine for children of two and older to wear masks. An insane 'study' in Italy involving just 47 children concluded there was no problem for babies as young as *four months* wearing them. Even after people were 'vaccinated' they were still told to wear masks by the criminal that is Anthony Fauci. Cathy wrote that mandating masks is allowing the authorities literally to control the air we breathe which is what was done in MKUltra. You might recall how the singer Michael Jackson wore masks and there is a reason for that. He was subjected to MKUltra mind control through Project Monarch and his psyche was scrambled by these simpletons. Cathy wrote:

In MKUltra Project Monarch mind control, Michael Jackson had to wear a mask to silence his voice so he could not reach out for help. Remember how he developed that whisper voice when he wasn't singing? Masks control the mind from the outside in, like the redefining of words is doing. By controlling what we can and cannot say for fear of being labeled racist or beaten, for example, it ultimately controls thought that drives our words and ultimately actions (or lack thereof).

Likewise, a mask muffles our speech so that we are not heard, which controls voice … words … mind. This is Mind Control. Masks are an obvious mind control device, and I am disturbed so many people are complying on a global scale. Masks depersonalize while making a person feel as though they have no voice. It is a barrier to others. People who would never choose to comply but are forced to wear a mask in order to keep their job, and ultimately their family fed, are compromised. They often feel shame and are subdued. People have stopped talking with each other while media controls the narrative.

The 'no voice' theme has often become literal with train passengers told not to speak to each other in case they pass on the 'virus', singing banned for the same reason and bonkers California officials telling people riding roller coasters that they cannot shout and scream. Cathy said she heard every day from healed MKUltra survivors who cannot wear a mask without flashing back on ways

their breathing was controlled – 'from ball gags and penises to water boarding'. She said that through the years when she saw images of people in China wearing masks 'due to pollution' that it was really to control their oxygen levels. 'I knew it was as much of a population control mechanism of depersonalisation as are burkas', she said. Masks are another Chinese communist/fascist method of control that has been swept across the West as the West becomes China at lightning speed since we entered 2020.

Mask-19

There are other reasons for mandatory masks and these include destroying respiratory health to call it 'Covid-19' and stunting brain development of children and the young. Dr Margarite Griesz-Brisson MD, PhD, is a Consultant Neurologist and Neurophysiologist and the Founder and Medical Director of the London Neurology and Pain Clinic. Her CV goes down the street and round the corner. She is clearly someone who cares about people and won't parrot the propaganda. Griesz-Brisson has a PhD in pharmacology, with special interest in neurotoxicology, environmental medicine, neuroregeneration and neuroplasticity (the way the brain can change in the light of information received). She went public in October, 2020, with a passionate warning about the effects of mask-wearing laws:

> The reinhalation of our exhaled air will without a doubt create oxygen deficiency and a flooding of carbon dioxide. We know that the human brain is very sensitive to oxygen deprivation. There are nerve cells for example in the hippocampus that can't be longer than 3 minutes without oxygen – they cannot survive. The acute warning symptoms are headaches, drowsiness, dizziness, issues in concentration, slowing down of reaction time – reactions of the cognitive system.

Oh, I know, let's tell bus, truck and taxi drivers to wear them and people working machinery. How about pilots, doctors and police? Griesz-Brisson makes the important point that while the symptoms she mentions may fade as the body readjusts this does not alter the fact that people continue to operate in oxygen deficit with long list of

potential consequences. She said it was well known that neurodegenerative diseases take years or decades to develop. 'If today you forget your phone number, the breakdown in your brain would have already started 20 or 30 years ago.' She said degenerative processes in your brain are getting amplified as your oxygen deprivation continues through wearing a mask. Nerve cells in the brain are unable to divide themselves normally in these circumstances and lost nerve cells will no longer be regenerated. 'What is gone is gone.' Now consider that people like shop workers and *schoolchildren* are wearing masks for hours every day. What in the name of sanity is going to be happening to them? 'I do not wear a mask, I need my brain to think', Griesz-Brisson said, 'I want to have a clear head when I deal with my patients and not be in a carbon dioxide-induced anaesthesia'. If you are told to wear a mask anywhere ask the organisation, police, store, whatever, for their risk assessment on the dangers and negative effects on mind and body of enforcing mask-wearing. They won't have one because it has never been done not even by government. All of them must be subject to class-action lawsuits as the consequences come to light. They don't do mask risk assessments for an obvious reason. They know what the conclusions would be and independent scientific studies that *have* been done tell a horror story of consequences.

'Masks are criminal'

Dr Griesz-Brisson said that for children and adolescents, masks are an absolute no-no. They had an extremely active and adaptive immune system and their brain was incredibly active with so much to learn. 'The child's brain, or the youth's brain, is thirsting for oxygen.' The more metabolically active an organ was, the more oxygen it required; and in children and adolescents every organ was metabolically active. Griesz-Brisson said that to deprive a child's or adolescent's brain of oxygen, or to restrict it in any way, was not only dangerous to their health, it was absolutely criminal. 'Oxygen deficiency inhibits the development of the brain, and the damage that has taken place as a result CANNOT be reversed.' Mind

manipulators of MKUltra put masks on two-year-olds they wanted to neurologically rewire and you can see why. Griesz-Brisson said a child needs the brain to learn and the brain needs oxygen to function. 'We don't need a clinical study for that. This is simple, indisputable physiology.' Consciously and purposely induced oxygen deficiency was an absolutely deliberate health hazard, and an absolute medical contraindication which means that 'this drug, this therapy, this method or measure should not be used, and is not allowed to be used'. To coerce an entire population to use an absolute medical contraindication by force, she said, there had to be definite and serious reasons and the reasons must be presented to competent interdisciplinary and independent bodies to be verified and authorised. She had this warning of the consequences that were coming if mask wearing continued:

When, in ten years, dementia is going to increase exponentially, and the younger generations couldn't reach their god-given potential, it won't help to say 'we didn't need the masks'. I know how damaging oxygen deprivation is for the brain, cardiologists know how damaging it is for the heart, pulmonologists know how damaging it is for the lungs. Oxygen deprivation damages every single organ. Where are our health departments, our health insurance, our medical associations? It would have been their duty to be vehemently against the lockdown and to stop it and stop it from the very beginning.

Why do the medical boards issue punishments to doctors who give people exemptions? Does the person or the doctor seriously have to prove that oxygen deprivation harms people? What kind of medicine are our doctors and medical associations representing? Who is responsible for this crime? The ones who want to enforce it? The ones who let it happen and play along, or the ones who don't prevent it?

All of the organisations and people she mentions there either answer directly to the Cult or do whatever hierarchical levels above them tell them to do. The outcome of both is the same. 'It's not about masks, it's not about viruses, it's certainly not about your health', Griesz-Brisson said. 'It is about much, much more. I am not participating. I am not afraid.' They were taking our air to breathe and there was no unfounded medical exemption from face masks. Oxygen deprivation was dangerous for every single brain. It had to be the free decision of every human being whether they want to

wear a mask that was absolutely ineffective to protect themselves from a virus. She ended by rightly identifying where the responsibility lies for all this:

> The imperative of the hour is personal responsibility. We are responsible for what we think, not the media. We are responsible for what we do, not our superiors. We are responsible for our health, not the World Health Organization. And we are responsible for what happens in our country, not the government.

Halle-bloody-lujah.

But surgeons wear masks, right?

Independent studies of mask-wearing have produced a long list of reports detailing mental, emotional and physical dangers. What a definition of insanity to see police officers imposing mask-wearing on the public which will cumulatively damage their health while the police themselves wear masks that will cumulatively damage *their* health. It's utter madness and both public and police do this because 'the government says so' – yes a government of brain-donor idiots like UK Health Secretary Matt Hancock reading the 'follow the science' scripts of psychopathic, lunatic psychologists. The response you get from Stockholm syndrome sufferers defending the very authorities that are destroying them and their families is that 'surgeons wear masks'. This is considered the game, set and match that they must work and don't cause oxygen deficit. Well, actually, scientific studies have shown that they *do* and oxygen levels are monitored in operating theatres to compensate. Surgeons wear masks to stop spittle and such like dropping into open wounds – not to stop 'viral particles' which are so miniscule they can only be seen through an electron microscope. Holes in the masks are significantly bigger than 'viral particles' and if you sneeze or cough they will breach the mask. I watched an incredibly disingenuous 'experiment' that claimed to prove that masks work in catching 'virus' material from the mouth and nose. They did this with a slow motion camera and the mask did block big stuff which stayed inside the mask and

against the face to be breathed in or cause infections on the face as we have seen with many children. 'Viral particles', however, would never have been picked up by the camera as they came through the mask when they are far too small to be seen. The 'experiment' was therefore disingenuous *and* useless.

Studies have concluded that wearing masks in operating theatres (and thus elsewhere) make no difference to preventing infection while the opposite is true with toxic shite building up in the mask and this had led to an explosion in tooth decay and gum disease dubbed by dentists 'mask mouth'. You might have seen the Internet video of a furious American doctor urging people to take off their masks after a four-year-old patient had been rushed to hospital the night before and nearly died with a lung infection that doctors sourced to mask wearing. A study in the journal *Cancer Discovery* found that inhalation of harmful microbes can contribute to advanced stage lung cancer in adults and long-term use of masks can help breed dangerous pathogens. Microbiologists have said frequent mask wearing creates a moist environment in which microbes can grow and proliferate before entering the lungs. The Canadian Agency for Drugs and Technologies in Health, or CADTH, a Canadian national organisation that provides research and analysis to healthcare decision-makers, said this as long ago as 2013 in a report entitled 'Use of Surgical Masks in the Operating Room: A Review of the Clinical Effectiveness and Guidelines'. It said:

- No evidence was found to support the use of surgical face masks to reduce the frequency of surgical site infections
- No evidence was found on the effectiveness of wearing surgical face masks to protect staff from infectious material in the operating room.
- Guidelines recommend the use of surgical face masks by staff in the operating room to protect both operating room staff and patients (despite the lack of evidence).

We were told that the world could go back to 'normal' with the arrival of the 'vaccines'. When they came, fraudulent as they are, the story changed as I knew that it would. We are in the midst of transforming 'normal', not going back to it. Mary Ramsay, head of immunisation at Public Health England, echoed the words of US criminal Anthony Fauci who said masks and other regulations must stay no matter if people are vaccinated. The Fauci idiot continued to wear two masks – different colours so both could be clearly seen – after he *claimed* to have been vaccinated. Senator Rand Paul told Fauci in one exchange that his double-masks were 'theatre' and he was right. It's all theatre. Mary Ramsay back-tracked on the vaccine-return-to-normal theme when she said the public may need to wear masks and social-distance for years despite the jabs. 'People have got used to those lower-level restrictions now, and [they] can live with them', she said telling us what the idea has been all along. 'The vaccine does not give you a pass, even if you have had it, you must continue to follow all the guidelines' said a Public Health England statement which reneged on what we had been told before and made having the 'vaccine' irrelevant to 'normality' even by the official story. Spain's fascist government trumped everyone by passing a law mandating the wearing of masks on the beach and even when swimming in the sea. The move would have devastated what's left of the Spanish tourist industry, posed potential breathing dangers to swimmers and had Northern European sunbathers walking around with their forehead brown and the rest of their face white as a sheet. The ruling was so crazy that it had to be retracted after pressure from public and tourist industry, but it confirmed where the Cult wants to go with masks and how clinically insane authority has become. The determination to make masks permanent and hide the serious dangers to body and mind can be seen in the censorship of scientist Professor Denis Rancourt by Bill Gates-funded academic publishing website ResearchGate over his papers exposing the dangers and uselessness of masks. Rancourt said:

ResearchGate today has permanently locked my account, which I have had since 2015. Their reasons graphically show the nature of their attack against democracy, and their corruption of

science … By their obscene non-logic, a scientific review of science articles reporting on harms caused by face masks has a 'potential to cause harm'. No criticism of the psychological device (face masks) is tolerated, if the said criticism shows potential to influence public policy.

This is what happens in a fascist world.

Where are the 'greens' (again)?

Other dangers of wearing masks especially regularly relate to the inhalation of minute plastic fibres into the lungs and the deluge of discarded masks in the environment and oceans. Estimates predicted that more than 1.5 billion disposable masks will end up in the world's oceans every year polluting the water with tons of plastic and endangering marine wildlife. Studies project that humans are using 129 billion face masks each month worldwide – about three million a minute. Most are disposable and made from plastic, non-biodegradable microfibers that break down into smaller plastic particles that become widespread in ecosystems. They are littering cities, clogging sewage channels and turning up in bodies of water. I have written in other books about the immense amounts of microplastics from endless sources now being absorbed into the body. Rolf Halden, director of the Arizona State University (ASU) Biodesign Center for Environmental Health Engineering, was the senior researcher in a 2020 study that analysed 47 human tissue samples and found microplastics in all of them. 'We have detected these chemicals of plastics in every single organ that we have investigated', he said. I wrote in *The Answer* about the world being deluged with microplastics. A study by the Worldwide Fund for Nature (WWF) found that people are consuming on average every week some 2,000 tiny pieces of plastic mostly through water and also through marine life and the air. Every year humans are ingesting enough microplastics to fill a heaped dinner plate and in a life-time of 79 years it is enough to fill two large waste bins. Marco Lambertini, WWF International director general said: 'Not only are plastics polluting our oceans and waterways and killing marine life – it's in all of us and we can't escape consuming plastics,' American

geologists found tiny plastic fibres, beads and shards in rainwater samples collected from the remote slopes of the Rocky Mountain National Park near Denver, Colorado. Their report was headed: 'It is raining plastic.' Rachel Adams, senior lecturer in Biomedical Science at Cardiff Metropolitan University, said that among health consequences are internal inflammation and immune responses to a 'foreign body'. She further pointed out that microplastics become carriers of toxins including mercury, pesticides and dioxins (a known cause of cancer and reproductive and developmental problems). These toxins accumulate in the fatty tissues once they enter the body through microplastics. Now this is being compounded massively by people putting plastic on their face and throwing it away.

Workers exposed to polypropylene plastic fibres known as 'flock' have developed 'flock worker's lung' from inhaling small pieces of the flock fibres which can damage lung tissue, reduce breathing capacity and exacerbate other respiratory problems. *Now* … commonly used surgical masks have three layers of melt-blown textiles made of … polypropylene. We have billions of people putting these microplastics against their mouth, nose and face for hours at a time day after day in the form of masks. How does anyone think that will work out? I mean – what could possibly go wrong? We posted a number of scientific studies on this at davidicke.com, but when I went back to them as I was writing this book the links to the science research website where they were hosted were dead. Anything that challenges the official narrative in any way is either censored or vilified. The official narrative is so unsupportable by the evidence that only deleting the truth can protect it. A study by Chinese scientists still survived – with the usual twist which it why it was still active, I guess. Yes, they found that virtually all the masks they tested increased the daily intake of microplastic fibres, but people should still wear them because the danger from the 'virus' was worse said the crazy 'team' from the Institute of Hydrobiology in Wuhan. Scientists first discovered microplastics in lung tissue of some patients who died of lung cancer

in the 1990s. Subsequent studies have confirmed the potential health damage with the plastic degrading slowly and remaining in the lungs to accumulate in volume. Wuhan researchers used a machine simulating human breathing to establish that masks shed up to nearly 4,000 microplastic fibres in a month with reused masks producing more. Scientists said some masks are laced with toxic chemicals and a variety of compounds seriously restricted for both health and environmental reasons. They include cobalt (used in blue dye) and formaldehyde known to cause watery eyes, burning sensations in the eyes, nose, and throat, plus coughing, wheezing and nausea. No – that must be 'Covid-19'.

Mask 'worms'

There is another and potentially even more sinister content of masks. Mostly new masks of different makes filmed under a microscope around the world have been found to contain strange black fibres or 'worms' that appear to move or 'crawl' by themselves and react to heat and water. The nearest I have seen to them are the self-replicating fibres that are pulled out through the skin of those suffering from Morgellons disease which has been connected to the phenomena of 'chemtrails' which I will bring into the story later on. Morgellons fibres continue to grow outside the body and have a form of artificial intelligence. Black 'worm' fibres in masks have that kind of feel to them and there is a nanotechnology technique called 'worm micelles' which carry and release drugs or anything else you want to deliver to the body. For sure the suppression of humanity by mind altering drugs is the Cult agenda big time and the more excuses they can find to gain access to the body the more opportunities there are to make that happen whether through 'vaccines' or masks pushed against the mouth and nose for hours on end.

So let us summarise the pros and cons of masks:

Against masks: Breathing in your own carbon dioxide; depriving the body and brain of sufficient oxygen; build-up of toxins in the mask that can be breathed into the lungs and cause rashes on the face and 'mask-mouth'; breathing microplastic fibres and toxic chemicals into the lungs; dehumanisation and deleting individualisation by literally making people faceless; destroying human emotional interaction through facial expression and deleting parental connection with their babies which look for guidance to their facial expression.

For masks: They don't protect you from a 'virus' that doesn't exist and even if it did 'viral' particles are so minute they are smaller than the holes in the mask.

Governments, police, supermarkets, businesses, transport companies, and all the rest who seek to impose masks have done no risk assessment on their consequences for health and psychology and are now open to group lawsuits when the impact becomes clear with a cumulative epidemic of respiratory and other disease. Authorities will try to exploit these effects and hide the real cause by dubbing them 'Covid-19'. Can you imagine setting out to force the population to wear health-destroying masks without doing any assessment of the risks? It is criminal and it is evil, but then how many people targeted in this way, who see their children told to wear them all day at school, have asked for a risk assessment? Billions can't be imposed upon by the few unless the billions allow it. Oh, yes, with just a tinge of irony, 85 percent of all masks made worldwide come from *China*.

Wash your hands in toxic shite

'Covid' rules include the use of toxic sanitisers and again the health consequences of constantly applying toxins to be absorbed through the skin is obvious to any level of Renegade Mind. America's Food and Drug Administration (FDA) said that sanitisers are drugs and issued a warning about 75 dangerous brands which contain

methanol used in antifreeze and can cause death, kidney damage and blindness. The FDA circulated the following warning even for those brands that it claims to be safe:

Store hand sanitizer out of the reach of pets and children, and children should use it only with adult supervision. Do not drink hand sanitizer. This is particularly important for young children, especially toddlers, who may be attracted by the pleasant smell or brightly colored bottles of hand sanitizer.

Drinking even a small amount of hand sanitizer can cause alcohol poisoning in children. (However, there is no need to be concerned if your children eat with or lick their hands after using hand sanitizer.) During this coronavirus pandemic, poison control centers have had an increase in calls about accidental ingestion of hand sanitizer, so it is important that adults monitor young children's use.

Do not allow pets to swallow hand sanitizer. If you think your pet has eaten something potentially dangerous, call your veterinarian or a pet poison control center right away. Hand sanitizer is flammable and should be stored away from heat and flames. When using hand sanitizer, rub your hands until they feel completely dry before performing activities that may involve heat, sparks, static electricity, or open flames.

There you go, perfectly safe, then, and that's without even a mention of the toxins absorbed through the skin. Come on kids – sanitise your hands everywhere you go. It will save you from the 'virus'. Put all these elements together of the 'Covid' normal and see how much health and psychology is being cumulatively damaged, even devastated, to 'protect your health'. Makes sense, right? They are only imposing these things because they care, right? *Right?*

Submitting to insanity

Psychological reframing of the population goes very deep and is done in many less obvious ways. I hear people say how contradictory and crazy 'Covid' rules are and how they are ever changing. This is explained away by dismissing those involved as idiots. It is a big mistake. The Cult is delighted if its cold calculation is perceived as incompetence and idiocy when it is anything but. Oh, yes, there are idiots within the system – lots of them – but they are *administering* the Cult agenda, mostly unknowingly. They are not deciding and dictating it. The bulwark against tyranny is self-

respect, always has been, always will be. It is self-respect that has broken every tyranny in history. By its very nature self-respect will not bow to oppression and its perpetrators. There is so little self-respect that it's always the few that overturn dictators. Many may eventually follow, but the few with the iron spines (self-respect) kick it off and generate the momentum. The Cult targets self-respect in the knowledge that once this has gone only submission remains. Crazy, contradictory, ever-changing 'Covid' rules are systematically applied by psychologists to delete self-respect. They *want* you to see that the rules make no sense. It is one thing to decide to do something when *you* have made the choice based on evidence and logic. You still retain your self-respect. It is quite another when you can see what you are being told to do is insane, ridiculous and makes no sense, and *yet you still do it*. Your self-respect is extinguished and this has been happening as ever more obviously stupid and nonsensical things have been demanded and the great majority have complied even when they can see they are stupid and nonsensical.

People walk around in face-nappies knowing they are damaging their health and make no difference to a 'virus'. They do it in fear of not doing it. I know it's daft, but I'll do it anyway. When that happens something dies inside of you and submissive reframing has begun. Next there's a need to hide from yourself that you have conceded your self-respect and you convince yourself that you have not really submitted to fear and intimidation. You begin to believe that you are complying with craziness because it's the right thing to do. When first you concede your self-respect of 2+2 = 4 to 2+2 = 5 you *know* you are compromising your self-respect. Gradually to avoid facing that fact you begin to *believe* that 2+2=5. You have been reframed and I have been watching this process happening in the human psyche on an industrial scale. The Cult is working to break your spirit and one of its major tools in that war is humiliation. I read how former American soldier Bradley Manning (later Chelsea Manning after a sex-change) was treated after being jailed for supplying WikiLeaks with documents exposing the enormity of

government and elite mendacity. Manning was isolated in solitary confinement for eight months, put under 24-hour surveillance, forced to hand over clothing before going to bed, and stand naked for every roll call. This is systematic humiliation. The introduction of anal swab 'Covid' tests in China has been done for the same reason to delete self-respect and induce compliant submission. Anal swabs are mandatory for incoming passengers in parts of China and American diplomats have said they were forced to undergo the indignity which would have been calculated humiliation by the Cult-owned Chinese government that has America in its sights.

Government-people: An abusive relationship

Spirit-breaking psychological techniques include giving people hope and apparent respite from tyranny only to take it away again. This happened in the UK during Christmas, 2020, when the psycho-psychologists and their political lackeys announced an easing of restrictions over the holiday only to reimpose them almost immediately on the basis of yet another lie. There is a big psychological difference between getting used to oppression and being given hope of relief only to have that dashed. Psychologists know this and we have seen the technique used repeatedly. Then there is traumatising people before you introduce more extreme regulations that require compliance. A perfect case was the announcement by the dark and sinister Whitty and Vallance in the UK that 'new data' predicted that 4,000 could die every day over the winter of 2020/2021 if we did not lockdown again. I think they call it lying and after traumatising people with that claim out came Jackboot Johnson the next day with new curbs on human freedom. Psychologists know that a frightened and traumatised mind becomes suggestable to submission and behaviour reframing. Underpinning all this has been to make people fearful and suspicious of each other and see themselves as a potential danger to others. In league with deleted self-respect you have the perfect psychological recipe for self-loathing. The relationship between authority and public is now demonstrably the same as that of

subservience to an abusive partner. These are signs of an abusive relationship explained by psychologist Leslie Becker-Phelps:

Psychological and emotional abuse: Undermining a partner's self-worth with verbal attacks, name-calling, and belittling. Humiliating the partner in public, unjustly accusing them of having an affair, or interrogating them about their every behavior. Keeping partner confused or off balance by saying they were just kidding or blaming the partner for 'making' them act this way … Feigning in public that they care while turning against them in private. This leads to victims frequently feeling confused, incompetent, unworthy, hopeless, and chronically self-doubting. [Apply these techniques to how governments have treated the population since New Year, 2020, and the parallels are obvious.]

Physical abuse: The abuser might physically harm their partner in a range of ways, such as grabbing, hitting, punching, or shoving them. They might throw objects at them or harm them with a weapon. [Observe the physical harm imposed by masks, lockdown, and so on.]

Threats and intimidation: One way abusers keep their partners in line is by instilling fear. They might be verbally threatening, or give threatening looks or gestures. Abusers often make it known that they are tracking their partner's every move. They might destroy their partner's possessions, threaten to harm them, or threaten to harm their family members. Not surprisingly, victims of this abuse often feel anxiety, fear, and panic. [No words necessary.]

Isolation: Abusers often limit their partner's activities, forbidding them to talk or interact with friends or family. They might limit access to a car or even turn off their phone. All of this might be done by physically holding them against their will, but is often accomplished through psychological abuse and intimidation. The more isolated a person feels, the fewer resources they have to help gain perspective on their situation and to escape from it. [No words necessary.]

Economic abuse: Abusers often make their partners beholden to them for money by controlling access to funds of any kind. They might prevent their partner from getting a job or withhold access to money they earn from a job. This creates financial dependency that makes leaving the relationship very difficult. [See destruction of livelihoods and the proposed meagre 'guaranteed income' so long as you do whatever you are told.]

Using children: An abuser might disparage their partner's parenting skills, tell their children lies about their partner, threaten to take custody of their children, or threaten to harm their children. These tactics instil fear and often elicit compliance. [See reframed social service mafia and how children are being mercilessly abused by the state over 'Covid' while their parents look on too frightened to do anything.]

A further recurring trait in an abusive relationship is the abused blaming themselves for their abuse and making excuses for the abuser. We have the public blaming each other for lockdown abuse by government and many making excuses for the government while attacking those who challenge the government. How often we have heard authorities say that rules are being imposed or reimposed only because people have refused to 'behave' and follow the rules. We don't want to do it – it's *you*.

Renegade Minds are an antidote to all of these things. They will never concede their self-respect no matter what the circumstances. Even when apparent humiliation is heaped upon them they laugh in its face and reflect back the humiliation on the abuser where it belongs. Renegade Minds will never wear masks they know are only imposed to humiliate, suppress and damage both physically and psychologically. Consequences will take care of themselves and they will never break their spirit or cause them to concede to tyranny. UK newspaper columnist Peter Hitchens was one of the few in the mainstream media to speak out against lockdowns and forced vaccinations. He then announced he had taken the jab. He wanted to see family members abroad and he believed vaccine passports were inevitable even though they had not yet been introduced. Hitchens

has a questioning and critical mind, but not a Renegade one. If he had no amount of pressure would have made him concede. Hitchens excused his action by saying that the battle has been lost. Renegade Minds never accept defeat when freedom is at stake and even if they are the last one standing the self-respect of not submitting to tyranny is more important than any outcome or any consequence.

That's why Renegade Minds are the only minds that ever changed anything worth changing.

CHAPTER EIGHT

'Reframing' insanity

Insanity is relative. It depends on who has who locked in what cage
Ray Bradbury

'Reframing' a mind means simply to change its perception and behaviour. This can be done subconsciously to such an extent that subjects have no idea they have been 'reframed' while to any observer changes in behaviour and attitudes are obvious.

Human society is being reframed on a ginormous scale since the start of 2020 and here we have the reason why psychologists rather than doctors have been calling the shots. Ask most people who have succumbed to 'Covid' reframing if they have changed and most will say 'no'; but they *have* and fundamentally. The Cult's long-game has been preparing for these times since way back and crucial to that has been to prepare both population and officialdom mentally and emotionally. To use the mind-control parlance they had to reframe the population with a mentality that would submit to fascism and reframe those in government and law enforcement to impose fascism or at least go along with it. The result has been the fact-deleted mindlessness of 'Wokeness' and officialdom that has either enthusiastically or unquestioningly imposed global tyranny demanded by reframed politicians on behalf of psychopathic and deeply evil cultists. 'Cognitive reframing' identifies and challenges the way someone sees the world in the form of situations, experiences and emotions and then restructures those perceptions to view the same set of circumstances in a different way. This can have

benefits if the attitudes are personally destructive while on the other side it has the potential for individual and collective mind control which the subject has no idea has even happened.

Cognitive therapy was developed in the 1960s by Aaron T. Beck who was born in Rhode Island in 1921 as the son of Jewish immigrants from the Ukraine. He became interested in the techniques as a treatment for depression. Beck's daughter Judith S. Beck is prominent in the same field and they founded the Beck Institute for Cognitive Behavior Therapy in Philadelphia in 1994. Cognitive reframing, however, began to be used worldwide by those with a very dark agenda. The Cult reframes politicians to change their attitudes and actions until they are completely at odds with what they once appeared to stand for. The same has been happening to government administrators at all levels, law enforcement, military and the human population. Cultists love mind control for two main reasons: It allows them to control what people think, do and say to secure agenda advancement and, by definition, it calms their legendary insecurity and fear of the unexpected. I have studied mind control since the time I travelled America in 1996. I may have been talking to next to no one in terms of an audience in those years, but my goodness did I gather a phenomenal amount of information and knowledge about so many things including the techniques of mind control. I have described this in detail in other books going back to *The Biggest Secret* in 1998. I met a very large number of people recovering from MKUltra and its offshoots and successors and I began to see how these same techniques were being used on the population in general. This was never more obvious than since the 'Covid' hoax began.

Reframing the enforcers

I have observed over the last two decades and more the very clear transformation in the dynamic between the police, officialdom and the public. I tracked this in the books as the relationship mutated from one of serving the public to seeing them as almost the enemy and certainly a lower caste. There has always been a class divide

based on income and always been some psychopathic, corrupt, and big-I-am police officers. This was different. Wholesale change was unfolding in the collective dynamic; it was less about money and far more about position and perceived power. An us-and-them was emerging. Noses were lifted skyward by government administration and law enforcement and their attitude to the public they were *supposed* to be serving changed to one of increasing contempt, superiority and control. The transformation was so clear and widespread that it had to be planned. Collective attitudes and dynamics do not change naturally and organically that quickly on that scale. I then came across an organisation in Britain called Common Purpose created in the late 1980s by Julia Middleton who would work in the office of Deputy Prime Minister John Prescott during the long and disastrous premiership of war criminal Tony Blair. When Blair speaks the Cult is speaking and the man should have been in jail a long time ago. Common Purpose proclaims itself to be one of the biggest 'leadership development' organisations in the world while functioning as a *charity* with all the financial benefits which come from that. It hosts 'leadership development' courses and programmes all over the world and claims to have 'brought together' what it calls 'leaders' from more than 100 countries on six continents. The modus operandi of Common Purpose can be compared with the work of the UK government's reframing network that includes the Behavioural Insights Team 'nudge unit' and 'Covid' reframing specialists at SPI-B. WikiLeaks described Common Purpose long ago as 'a hidden virus in our government and schools' which is unknown to the general public: 'It recruits and trains "leaders" to be loyal to the directives of Common Purpose and the EU, instead of to their own departments, which they then undermine or subvert, the NHS [National Health Service] being an example.' This is a vital point to understand the 'Covid' hoax. The NHS, and its equivalent around the world, has been utterly reframed in terms of administrators and much of the medical personnel with the transformation underpinned by recruitment policies. The outcome has been the criminal and psychopathic behaviour of the

NHS over 'Covid' and we have seen the same in every other major country. WikiLeaks said Common Purpose trainees are 'learning to rule without regard to democracy' and to usher in a police state (current events explained). Common Purpose operated like a 'glue' and had members in the NHS, BBC, police, legal profession, church, many of Britain's 7,000 quangos, local councils, the Civil Service, government ministries and Parliament, and controlled many RDA's (Regional Development Agencies). Here we have one answer for how and why British institutions and their like in other countries have changed so negatively in relation to the public. This further explains how and why the beyond-disgraceful reframed BBC has become a propaganda arm of 'Covid' fascism. They are all part of a network pursuing the same goal.

By 2019 Common Purpose was quoting a figure of 85,000 'leaders' that had attended its programmes. These 'students' of all ages are known as Common Purpose 'graduates' and they consist of government, state and local government officials and administrators, police chiefs and officers, and a whole range of others operating within the national, local and global establishment. Cressida Dick, Commissioner of the London Metropolitan Police, is the Common Purpose graduate who was the 'Gold Commander' that oversaw what can only be described as the murder of Brazilian electrician Jean Charles de Menezes in 2005. He was held down by psychopathic police and shot seven times in the head by a psychopathic lunatic after being mistaken for a terrorist when he was just a bloke going about his day. Dick authorised officers to pursue and keep surveillance on de Menezes and ordered that he be stopped from entering the underground train system. Police psychopaths took her at her word clearly. She was 'disciplined' for this outrage by being *promoted* – eventually to the top of the 'Met' police where she has been a disaster. Many Chief Constables controlling the police in different parts of the UK are and have been Common Purpose graduates. I have heard the 'graduate' network described as a sort of Mafia or secret society operating within the fabric of government at all levels pursuing a collective policy

ingrained at Common Purpose training events. Founder Julia Middleton herself has said:

> Locally and internationally, Common Purpose graduates will be 'lighting small fires' to create change in their organisations and communities … The Common Purpose effect is best illustrated by the many stories of small changes brought about by leaders, who themselves have changed.

A Common Purpose mission statement declared:

> Common Purpose aims to improve the way society works by expanding the vision, decision-making ability and influence of all kinds of leaders. The organisation runs a variety of educational programmes for leaders of all ages, backgrounds and sectors, in order to provide them with the inspirational, information and opportunities they need to change the world.

Yes, but into what? Since 2020 the answer has become clear.

NLP and the Delphi technique

Common Purpose would seem to be a perfect name or would common programming be better? One of the foundation methods of reaching 'consensus' (group think) is by setting the agenda theme and then encouraging, cajoling or pressuring everyone to agree a 'consensus' in line with the core theme promoted by Common Purpose. The methodology involves the 'Delphi technique', or an adaption of it, in which opinions are expressed that are summarised by a 'facilitator or change agent' at each stage. Participants are 'encouraged' to modify their views in the light of what others have said. Stage by stage the former individual opinions are merged into group consensus which just happens to be what Common Purpose wants them to believe. A key part of this is to marginalise anyone refusing to concede to group think and turn the group against them to apply pressure to conform. We are seeing this very technique used on the general population to make 'Covid' group-thinkers hostile to those who have seen through the bullshit. People can be reframed by using perception manipulation methods such as Neuro-Linguistic Programming (NLP) in which you change perception with the use of

carefully constructed language. An NLP website described the technique this way:

… A method of influencing brain behaviour (the 'neuro' part of the phrase) through the use of language (the 'linguistic' part) and other types of communication to enable a person to 'recode' the way the brain responds to stimuli (that's the 'programming') and manifest new and better behaviours. Neuro-Linguistic Programming often incorporates hypnosis and self-hypnosis to help achieve the change (or 'programming') that is wanted.

British alternative media operation UKColumn has done very detailed research into Common Purpose over a long period. I quoted co-founder and former naval officer Brian Gerrish in my book *Remember Who You Are*, published in 2011, as saying the following years before current times:

It is interesting that many of the mothers who have had children taken by the State speak of the Social Services people being icily cool, emotionless and, as two ladies said in slightly different words, '… like little robots'. We know that NLP is cumulative, so people can be given small imperceptible doses of NLP in a course here, another in a few months, next year etc. In this way, major changes are accrued in their personality, but the day by day change is almost unnoticeable.

In these and other ways 'graduates' have had their perceptions uniformly reframed and they return to their roles in the institutions of government, law enforcement, legal profession, military, 'education', the UK National Health Service and the whole swathe of the establishment structure to pursue a common agenda preparing for the 'post-industrial', 'post-democratic' society. I say 'preparing' but we are now there. 'Post-industrial' is code for the Great Reset and 'post-democratic' is 'Covid' fascism. UKColumn has spoken to partners of those who have attended Common Purpose 'training'. They have described how personalities and attitudes of 'graduates' changed very noticeably for the worse by the time they had completed the course. They had been 'reframed' and told they are the 'leaders' – the special ones – who know better than the population. There has also been the very demonstrable recruitment of psychopaths and narcissists into government administration at all

levels and law enforcement. If you want psychopathy hire psychopaths and you get a simple cause and effect. If you want administrators, police officers and 'leaders' to perceive the public as lesser beings who don't matter then employ narcissists. These personalities are identified using 'psychometrics' that identifies knowledge, abilities, attitudes and personality traits, mostly through carefully-designed questionnaires and tests. As this policy has passed through the decades we have had power-crazy, power-trippers appointed into law enforcement, security and government administration in preparation for current times and the dynamic between public and law enforcement/officialdom has been transformed. UKColumn's Brian Gerrish said of the narcissistic personality:

> Their love of themselves and power automatically means that they will crush others who get in their way. I received a major piece of the puzzle when a friend pointed out that when they made public officials re-apply for their own jobs several years ago they were also required to do psychometric tests. This was undoubtedly the start of the screening process to get 'their' sort of people in post.

How obvious that has been since 2020 although it was clear what was happening long before if people paid attention to the changing public-establishment dynamic.

Change agents

At the centre of events in 'Covid' Britain is the National Health Service (NHS) which has behaved disgracefully in slavishly following the Cult agenda. The NHS management structure is awash with Common Purpose graduates or 'change agents' working to a common cause. Helen Bevan, a Chief of Service Transformation at the NHS Institute for Innovation and Improvement, co-authored a document called 'Towards a million change agents, a review of the social movements literature: implications for large scale change in the NHS'. The document compared a project management approach to that of change and social movements where 'people change

themselves and each other – peer to peer'. Two definitions given for a 'social movement' were:

A group of people who consciously attempt to build a radically new social order; involves people of a broad range of social backgrounds; and deploys politically confrontational and socially disruptive tactics – Cyrus Zirakzadeh 1997

Collective challenges, based on common purposes and social solidarities, in sustained interaction with elites, opponents, and authorities – Sidney Tarrow 1994

Helen Bevan wrote another NHS document in which she defined 'framing' as 'the process by which leaders construct, articulate and put across their message in a powerful and compelling way in order to win people to their cause and call them to action'. I think I could come up with another definition that would be rather more accurate. The National Health Service and institutions of Britain and the wider world have been taken over by reframed 'change agents' and that includes everything from the United Nations to national governments, local councils and social services which have been kidnapping children from loving parents on an extraordinary and gathering scale on the road to the end of parenthood altogether. Children from loving homes are stolen and kidnapped by the state and put into the 'care' (inversion) of the local authority through council homes, foster parents and forced adoption. At the same time children are allowed to be abused without response while many are under council 'care'. UKColumn highlighted the Common Purpose connection between South Yorkshire Police and Rotherham council officers in the case of the scandal in that area of the sexual exploitation of children to which the authorities turned not one blind eye, but both:

We were alarmed to discover that the Chief Executive, the Strategic Director of Children and Young People's Services, the Manager for the Local Strategic Partnership, the Community Cohesion Manager, the Cabinet Member for Cohesion, the Chief Constable and his predecessor had all attended Leadership training courses provided by the pseudo-charity Common Purpose.

Once 'change agents' have secured positions of hire and fire within any organisation things start to move very quickly. Personnel are then hired and fired on the basis of whether they will work towards the agenda the change agent represents. If they do they are rapidly promoted even though they may be incompetent. Those more qualified and skilled who are pre-Common Purpose 'old school' see their careers stall and even disappear. This has been happening for decades in every institution of state, police, 'health' and social services and all of them have been transformed as a result in their attitudes to their jobs and the public. Medical professions, including nursing, which were once vocations for the caring now employ many cold, callous and couldn't give a shit personality types. The UKColumn investigation concluded:

By blurring the boundaries between people, professions, public and private sectors, responsibility and accountability, Common Purpose encourages 'graduates' to believe that as new selected leaders, they can work together, outside of the established political and social structures, to achieve a paradigm shift or CHANGE – so called 'Leading Beyond Authority'. In doing so, the allegiance of the individual becomes 'reframed' on CP colleagues and their NETWORK.

Reframing the Face-Nappies

Nowhere has this process been more obvious than in the police where recruitment of psychopaths and development of unquestioning mind-controlled group-thinkers have transformed law enforcement into a politically-correct 'Woke' joke and a travesty of what should be public service. Today they wear their face-nappies like good little gofers and enforce 'Covid' rules which are fascism under another name. Alongside the specifically-recruited psychopaths we have software minds incapable of free thought. Brian Gerrish again:

An example is the policeman who would not get on a bike for a press photo because he had not done the cycling proficiency course. Normal people say this is political correctness gone mad. Nothing could be further from the truth. The policeman has been reframed, and in his reality it is perfect common sense not to get on the bike 'because he hasn't done the cycling course'.

Another example of this is where the police would not rescue a boy from a pond until they had taken advice from above on the 'risk assessment'. A normal person would have arrived, perhaps thought of the risk for a moment, and dived in. To the police now 'reframed', they followed 'normal' procedure.

There are shocking cases of reframed ambulance crews doing the same. Sheer unthinking stupidity of London Face-Nappies headed by Common Purpose graduate Cressida Dick can be seen in their behaviour at a vigil in March, 2021, for a murdered woman, Sarah Everard. A police officer had been charged with the crime. Anyone with a brain would have left the vigil alone in the circumstances. Instead they 'manhandled' women to stop them breaking 'Covid rules' to betray classic reframing. Minds in the thrall of perception control have no capacity for seeing a situation on its merits and acting accordingly. 'Rules is rules' is their only mind-set. My father used to say that rules and regulations are for the guidance of the intelligent and the blind obedience of the idiot. Most of the intelligent, decent, coppers have gone leaving only the other kind and a few old school for whom the job must be a daily nightmare. The combination of psychopaths and rule-book software minds has been clearly on public display in the 'Covid' era with automaton robots in uniform imposing fascistic 'Covid' regulations on the population without any personal initiative or judging situations on their merits. There are thousands of examples around the world, but I'll make my point with the infamous Derbyshire police in the English East Midlands – the ones who think pouring dye into beauty spots and using drones to track people walking in the countryside away from anyone is called 'policing'. To them there are rules decreed by the government which they have to enforce and in their bewildered state a group gathering in a closed space and someone walking alone in the countryside are the same thing. It is beyond idiocy and enters the realm of clinical insanity.

Police officers in Derbyshire said they were 'horrified' – *horrified* – to find 15 to 20 'irresponsible' kids playing a football match at a closed leisure centre 'in breach of coronavirus restrictions'. When they saw the police the kids ran away leaving their belongings behind and the reframed men and women of Derbyshire police were seeking to establish their identities with a view to fining their parents. The most natural thing for youngsters to do – kicking a ball about – is turned into a criminal activity and enforced by the moronic software programs of Derbyshire police. You find the same mentality in every country. These barely conscious 'horrified' officers said they had to take action because 'we need to ensure these rules are being followed' and 'it is of the utmost importance that you ensure your children are following the rules and regulations for Covid-19'. Had any of them done ten seconds of research to see if this parroting of their masters' script could be supported by any evidence? Nope. Reframed people don't think – others think for them and that's the whole idea of reframing. I have seen police officers one after the other repeating without question word for word what officialdom tells them just as I have seen great swathes of the public doing the same. Ask either for 'their' opinion and out spews what they have been told to think by the official narrative. Police and public may seem to be in different groups, but their mentality is the same. Most people do whatever they are told in fear not doing so or because they believe what officialdom tells them; almost the entirety of the police do what they are told for the same reason. Ultimately it's the tiny inner core of the global Cult that's telling both what to do.

So Derbyshire police were 'horrified'. Oh, really? Why did they think those kids were playing football? It was to relieve the psychological consequences of lockdown and being denied human contact with their friends and interaction, touch and discourse vital to human psychological health. Being denied this month after month has dismantled the psyche of many children and young people as depression and suicide have exploded. Were Derbyshire police *horrified by that*? Are you kidding? Reframed people don't have those

mental and emotional processes that can see how the impact on the psychological health of youngsters is far more dangerous than any 'virus' even if you take the mendacious official figures to be true. The reframed are told (programmed) how to act and so they do. The Derbyshire Chief Constable in the first period of lockdown when the black dye and drones nonsense was going on was Peter Goodman. He was the man who severed the connection between his force and the Derbyshire Constabulary *Male Voice* Choir when he decided that it was not inclusive enough to allow women to join. The fact it was a male voice choir making a particular sound produced by male voices seemed to elude a guy who terrifyingly ran policing in Derbyshire. He retired weeks after his force was condemned as disgraceful by former Supreme Court Justice Jonathan Sumption for their behaviour over extreme lockdown impositions. Goodman was replaced by his deputy Rachel Swann who was in charge when her officers were 'horrified'. The police statement over the boys committing the hanging-offence of playing football included the line about the youngsters being 'irresponsible in the times we are all living through' missing the point that the real relevance of the 'times we are all living through' is the imposition of fascism enforced by psychopaths and reframed minds of police officers playing such a vital part in establishing the fascist tyranny that their own children and grandchildren will have to live in their entire lives. As a definition of insanity that is hard to beat although it might be run close by imposing masks on people that can have a serious effect on their health while wearing a face nappy all day themselves. Once again public and police do it for the same reason – the authorities tell them to and who are they to have the self-respect to say no?

Wokers in uniform

How reframed do you have to be to arrest a *six-year-old* and take him to court for *picking a flower* while waiting for a bus? Brain dead police and officialdom did just that in North Carolina where criminal proceedings happen regularly for children under nine. Attorney Julie Boyer gave the six-year-old crayons and a colouring book

during the 'flower' hearing while the 'adults' decided his fate. County Chief District Court Judge Jay Corpening asked: 'Should a child that believes in Santa Claus, the Easter Bunny and the tooth fairy be making life-altering decisions?' Well, of course not, but common sense has no meaning when you have a common purpose and a reframed mind. Treating children in this way, and police operating in American schools, is all part of the psychological preparation for children to accept a police state as normal all their adult lives. The same goes for all the cameras and biometric tracking technology in schools. Police training is focused on reframing them as snowflake Wokers and this is happening in the military. Pentagon top brass said that 'training sessions on extremism' were needed for troops who asked why they were so focused on the Capitol Building riot when Black Lives Matter riots were ignored. What's the difference between them some apparently and rightly asked. Actually, there is a difference. Five people died in the Capitol riot, only one through violence, and that was a police officer shooting an unarmed protestor. BLM riots killed at least 25 people and cost billions. Asking the question prompted the psychopaths and reframed minds that run the Pentagon to say that more 'education' (programming) was needed. Troop training is all based on psychological programming to make them fodder for the Cult – 'Military men are just dumb, stupid animals to be used as pawns in foreign policy' as Cult-to-his-DNA former Secretary of State Henry Kissinger famously said. Governments see the police in similar terms and it's time for those among them who can see this to defend the people and stop being enforcers of the Cult agenda upon the people.

The US military, like the country itself, is being targeted for destruction through a long list of Woke impositions. Cult-owned gaga 'President' Biden signed an executive order when he took office to allow taxpayer money to pay for transgender surgery for active military personnel and veterans. Are you a man soldier? No, I'm a LGBTQIA+ with a hint of Skoliosexual and Spectrasexual. Oh, good man. Bad choice of words you bigot. The Pentagon announced in March, 2021, the appointment of the first 'diversity and inclusion

officer' for US Special Forces. Richard Torres-Estrada arrived with the publication of a 'D&I Strategic Plan which will guide the enterprise-wide effort to institutionalize and sustain D&I'. If you think a Special Forces 'Strategic Plan' should have something to do with defending America you haven't been paying attention. Defending Woke is now the military's new role. Torres-Estrada has posted images comparing Donald Trump with Adolf Hitler and we can expect no bias from him as a representative of the supposedly non-political Pentagon. Cable news host Tucker Carlson said: 'The Pentagon is now the Yale faculty lounge but with cruise missiles.' Meanwhile Secretary of Defense Lloyd Austin, a board member of weapons-maker Raytheon with stock and compensation interests in October, 2020, worth $1.4 million, said he was purging the military of the 'enemy within' – anyone who isn't Woke and supports Donald Trump. Austin refers to his targets as 'racist extremists' while in true Woke fashion being himself a racist extremist. Pentagon documents pledge to 'eradicate, eliminate and conquer all forms of racism, sexism and homophobia'. The definitions of these are decided by 'diversity and inclusion committees' peopled by those who see racism, sexism and homophobia in every situation and opinion. Woke (the Cult) is dismantling the US military and purging testosterone as China expands its military and gives its troops 'masculinity training'. How do we think that is going to end when this is all Cult coordinated? The US military, like the British military, is controlled by Woke and spineless top brass who just go along with it out of personal career interests.

'Woke' means fast asleep

Mind control and perception manipulation techniques used on individuals to create group-think have been unleashed on the global population in general. As a result many have no capacity to see the obvious fascist agenda being installed all around them or what 'Covid' is really all about. Their brains are firewalled like a computer system not to process certain concepts, thoughts and realisations that are bad for the Cult. The young are most targeted as the adults they

will be when the whole fascist global state is planned to be fully implemented. They need to be prepared for total compliance to eliminate all pushback from entire generations. The Cult has been pouring billions into taking complete control of 'education' from schools to universities via its operatives and corporations and not least Bill Gates as always. The plan has been to transform 'education' institutions into programming centres for the mentality of 'Woke'. James McConnell, professor of psychology at the University of Michigan, wrote in *Psychology Today* in 1970:

> The day has come when we can combine sensory deprivation with drugs, hypnosis, and astute manipulation of reward and punishment, to gain almost absolute control over an individual's behaviour. It should then be possible to achieve a very rapid and highly effective type of brainwashing that would allow us to make dramatic changes in a person's behaviour and personality ...
>
> … We should reshape society so that we all would be trained from birth to want to do what society wants us to do. We have the techniques to do it... no-one owns his own personality you acquired, and there's no reason to believe you should have the right to refuse to acquire a new personality if your old one is anti-social.

This was the potential for mass brainwashing in 1970 and the mentality there displayed captures the arrogant psychopathy that drives it forward. I emphasise that not all young people have succumbed to Woke programming and those that haven't are incredibly impressive people given that today's young are the most perceptually-targeted generations in history with all the technology now involved. Vast swathes of the young generations, however, have fallen into the spell – and that's what it is – of Woke. The Woke mentality and perceptual program is founded on *inversion* and you will appreciate later why that is so significant. Everything with Woke is inverted and the opposite of what it is claimed to be. Woke was a term used in African-American culture from the 1900s and referred to an awareness of social and racial justice. This is not the meaning of the modern version or 'New Woke' as I call it in *The Answer*. Oh, no, Woke today means something very different no matter how much Wokers may seek to hide that and insist Old Woke and New

Woke are the same. See if you find any 'awareness of social justice' here in the modern variety:

- Woke demands 'inclusivity' while excluding anyone with a different opinion and calls for mass censorship to silence other views.

- Woke claims to stand against oppression when imposing oppression is the foundation of all that it does. It is the driver of political correctness which is nothing more than a Cult invention to manipulate the population to silence itself.

- Woke believes itself to be 'liberal' while pursuing a global society that can only be described as fascist (see 'anti-fascist' fascist Antifa).

- Woke calls for 'social justice' while spreading injustice wherever it goes against the common 'enemy' which can be easily identified as a differing view.

- Woke is supposed to be a metaphor for 'awake' when it is solid-gold asleep and deep in a Cult-induced coma that meets the criteria for 'off with the fairies'.

I state these points as obvious facts if people only care to look. I don't do this with a sense of condemnation. We need to appreciate that the onslaught of perceptual programming on the young has been incessant and merciless. I can understand why so many have been reframed, or, given their youth, framed from the start to see the world as the Cult demands. The Cult has had access to their minds day after day in its 'education' system for their entire formative years. Perception is formed from information received and the Cult-created system is a life-long download of information delivered to elicit a particular perception, thus behaviour. The more this has expanded into still new extremes in recent decades and ever-increasing censorship has deleted other opinions and information why wouldn't that lead to a perceptual reframing on a mass scale? I

have described already cradle-to-grave programming and in more recent times the targeting of young minds from birth to adulthood has entered the stratosphere. This has taken the form of skewing what is 'taught' to fit the Cult agenda and the omnipresent techniques of group-think to isolate non-believers and pressure them into line. There has always been a tendency to follow the herd, but we really are in a new world now in relation to that. We have parents who can see the 'Covid' hoax told by their children not to stop them wearing masks at school, being 'Covid' tested or having the 'vaccine' in fear of the peer-pressure consequences of being different. What is 'peer-pressure' if not pressure to conform to group-think? Renegade Minds never group-think and always retain a set of perceptions that are unique to them. Group-think is always underpinned by consequences for not group-thinking. Abuse now aimed at those refusing DNA-manipulating 'Covid vaccines' are a potent example of this. The biggest pressure to conform comes from the very group which is itself being manipulated. 'I am programmed to be part of a hive mind and so you must be.'

Woke control structures in 'education' now apply to every mainstream organisation. Those at the top of the 'education' hierarchy (the Cult) decide the policy. This is imposed on governments through the Cult network; governments impose it on schools, colleges and universities; their leadership impose the policy on teachers and academics and they impose it on children and students. At any level where there is resistance, perhaps from a teacher or university lecturer, they are targeted by the authorities and often fired. Students themselves regularly demand the dismissal of academics (increasingly few) at odds with the narrative that the students have been programmed to believe in. It is quite a thought that students who are being targeted by the Cult become so consumed by programmed group-think that they launch protests and demand the removal of those who are trying to push back against those targeting the students. Such is the scale of perceptual inversion. We see this with 'Covid' programming as the Cult imposes the rules via psycho-psychologists and governments on

shops, transport companies and businesses which impose them on their staff who impose them on their customers who pressure Pushbackers to conform to the will of the Cult which is in the process of destroying them and their families. Scan all aspects of society and you will see the same sequence every time.

Fact free Woke and hijacking the 'left'

There is no more potent example of this than 'Woke', a mentality only made possible by the deletion of factual evidence by an 'education' system seeking to produce an ever more uniform society. Why would you bother with facts when you don't know any? Deletion of credible history both in volume and type is highly relevant. Orwell said: 'Who controls the past controls the future: who controls the present controls the past.' They who control the perception of the past control the perception of the future and they who control the present control the perception of the past through the writing and deleting of history. Why would you oppose the imposition of Marxism in the name of Wokeism when you don't know that Marxism cost at least 100 million lives in the 20th century alone? Watch videos and read reports in which Woker generations are asked basic historical questions – it's mind-blowing. A survey of 2,000 people found that six percent of millennials (born approximately early1980s to early 2000s) believed the Second World War (1939-1945) broke out with the assassination of President Kennedy (in 1963) and one in ten thought Margaret Thatcher was British Prime Minister at the time. She was in office between 1979 and 1990. We are in a post-fact society. Provable facts are no defence against the fascism of political correctness or Silicon Valley censorship. Facts don't matter anymore as we have witnessed with the 'Covid' hoax. Sacrificing uniqueness to the Woke group-think religion is all you are required to do and that means thinking for yourself is the biggest Woke no, no. All religions are an expression of group-think and censorship and Woke is just another religion with an orthodoxy defended by group-think and censorship. Burned at

the stake becomes burned on Twitter which leads back eventually to burned at the stake as Woke humanity regresses to ages past.

The biggest Woke inversion of all is its creators and funders. I grew up in a traditional left of centre political household on a council estate in Leicester in the 1950s and 60s – you know, the left that challenged the power of wealth-hoarding elites and threats to freedom of speech and opinion. In those days students went on marches defending freedom of speech while today's Wokers march for its deletion. What on earth could have happened? Those very elites (collectively the Cult) that we opposed in my youth and early life have funded into existence the antithesis of that former left and hijacked the 'brand' while inverting everything it ever stood for. We have a mentality that calls itself 'liberal' and 'progressive' while acting like fascists. Cult billionaires and their corporations have funded themselves into control of 'education' to ensure that Woke programming is unceasing throughout the formative years of children and young people and that non-Wokers are isolated (that word again) whether they be students, teachers or college professors. The Cult has funded into existence the now colossal global network of Woke organisations that have spawned and promoted all the 'causes' on the Cult wish-list for global transformation and turned Wokers into demanders of them. Does anyone really think it's a coincidence that the Cult agenda for humanity is a carbon (sorry) copy of the societal transformations desired by Woke?? These are only some of them:

Political correctness: The means by which the Cult deletes all public debates that it knows it cannot win if we had the free-flow of information and evidence.

Human-caused 'climate change': The means by which the Cult seeks to transform society into a globally-controlled dictatorship imposing its will over the fine detail of everyone's lives 'to save the planet' which doesn't actually need saving.

Transgender obsession: Preparing collective perception to accept the 'new human' which would not have genders because it would be created technologically and not through procreation. I'll have much more on this in Human 2.0.

Race obsession: The means by which the Cult seeks to divide and rule the population by triggering racial division through the perception that society is more racist than ever when the opposite is the case. Is it perfect in that regard? No. But to compare today with the racism of apartheid and segregation brought to an end by the civil rights movement in the 1960s is to insult the memory of that movement and inspirations like Martin Luther King. Why is the 'anti-racism' industry (which it is) so dominated by privileged white people?

White supremacy: This is a label used by privileged white people to demonise poor and deprived white people pushing back on tyranny to marginalise and destroy them. White people are being especially targeted as the dominant race by number within Western society which the Cult seeks to transform in its image. If you want to change a society you must weaken and undermine its biggest group and once you have done that by using the other groups you next turn on them to do the same … 'Then they came for the Jews and I was not a Jew so I did nothing.'

Mass migration: The mass movement of people from the Middle East, Africa and Asia into Europe, from the south into the United States and from Asia into Australia are another way the Cult seeks to dilute the racial, cultural and political influence of white people on Western society. White people ask why their governments appear to be working against them while being politically and culturally biased towards incoming cultures. Well, here's your answer. In the same way sexually 'straight' people, men and women, ask why the

authorities are biased against them in favour of other sexualities. The answer is the same – that's the way the Cult wants it to be for very sinister motives.

These are all central parts of the Cult agenda and central parts of the Woke agenda and Woke was created and continues to be funded to an immense degree by Cult billionaires and corporations. If anyone begins to say 'coincidence' the syllables should stick in their throat.

Billionaire 'social justice warriors'

Joe Biden is a 100 percent-owned asset of the Cult and the Wokers' man in the White House whenever he can remember his name and for however long he lasts with his rapidly diminishing cognitive function. Even walking up the steps of an aircraft without falling on his arse would appear to be a challenge. He's not an empty-shell puppet or anything. From the minute Biden took office (or the Cult did) he began his executive orders promoting the Woke wish-list. You will see the Woke agenda imposed ever more severely because it's really the *Cult* agenda. Woke organisations and activist networks spawned by the Cult are funded to the extreme so long as they promote what the Cult wants to happen. Woke is funded to promote 'social justice' by billionaires who become billionaires by destroying social justice. The social justice mantra is only a cover for dismantling social justice and funded by billionaires that couldn't give a damn about social justice. Everything makes sense when you see that. One of Woke's premier funders is Cult billionaire financier George Soros who said: 'I am basically there to make money, I cannot and do not look at the social consequences of what I do.' This is the same Soros who has given more than $32 billion to his Open Society Foundations global Woke network and funded Black Lives Matter, mass immigration into Europe and the United States, transgender activism, climate change activism, political correctness and groups targeting 'white supremacy' in the form of privileged white thugs that dominate Antifa. What a scam it all is and when

you are dealing with the unquestioning fact-free zone of Woke scamming them is child's play. All you need to pull it off in all these organisations are a few in-the-know agents of the Cult and an army of naïve, reframed, uninformed, narcissistic, know-nothings convinced of their own self-righteousness, self-purity and virtue.

Soros and fellow billionaires and billionaire corporations have poured hundreds of millions into Black Lives Matter and connected groups and promoted them to a global audience. None of this is motivated by caring about black people. These are the billionaires that have controlled and exploited a system that leaves millions of black people in abject poverty and deprivation which they do absolutely nothing to address. The same Cult networks funding BLM were behind the *slave trade!* Black Lives Matter hijacked a phrase that few would challenge and they have turned this laudable concept into a political weapon to divide society. You know that BLM is a fraud when it claims that *All* Lives Matter, the most inclusive statement of all, is 'racist'. BLM and its Cult masters don't want to end racism. To them it's a means to an end to control all of humanity never mind the colour, creed, culture or background. What has destroying the nuclear family got to do with ending racism? Nothing – but that is one of the goals of BLM and also happens to be a goal of the Cult as I have been exposing in my books for decades. Stealing children from loving parents and giving schools ever more power to override parents is part of that same agenda. BLM is a Marxist organisation and why would that not be the case when the Cult created Marxism *and* BLM? Patrisse Cullors, a BLM co-founder, said in a 2015 video that she and her fellow organisers, including co-founder Alicia Garza, are 'trained Marxists'. The lady known after marriage as Patrisse Khan-Cullors bought a $1.4 million home in 2021 in one of the whitest areas of California with a black population of just 1.6 per cent and has so far bought *four* high-end homes for a total of $3.2 million. How very Marxist. There must be a bit of spare in the BLM coffers, however, when Cult corporations and billionaires have handed over the best part of $100 million. Many black people can see that Black Lives Matter is not

working for them, but against them, and this is still more confirmation. Black journalist Jason Whitlock, who had his account suspended by Twitter for simply linking to the story about the 'Marxist's' home buying spree, said that BLM leaders are 'making millions of dollars off the backs of these dead black men who they wouldn't spit on if they were on fire and alive'.

Black Lies Matter

Cult assets and agencies came together to promote BLM in the wake of the death of career criminal George Floyd who had been jailed a number of times including for forcing his way into the home of a black woman with others in a raid in which a gun was pointed at her stomach. Floyd was filmed being held in a Minneapolis street in 2020 with the knee of a police officer on his neck and he subsequently died. It was an appalling thing for the officer to do, but the same technique has been used by police on peaceful protestors of lockdown without any outcry from the Woke brigade. As unquestioning supporters of the Cult agenda Wokers have supported lockdown and all the 'Covid' claptrap while attacking anyone standing up to the tyranny imposed in its name. Court documents would later include details of an autopsy on Floyd by County Medical Examiner Dr Andrew Baker who concluded that Floyd had taken a fatal level of the drug fentanyl. None of this mattered to fact-free, question-free, Woke. Floyd's death was followed by worldwide protests against police brutality amid calls to defund the police. Throwing babies out with the bathwater is a Woke speciality. In the wake of the murder of British woman Sarah Everard a Green Party member of the House of Lords, Baroness Jones of Moulescoomb (Nincompoopia would have been better), called for a 6pm curfew for all men. This would be in breach of the Geneva Conventions on war crimes which ban collective punishment, but that would never have crossed the black and white Woke mind of Baroness Nincompoopia who would have been far too convinced of her own self-righteousness to compute such details. Many American cities did defund the police in the face of Floyd riots

and after $15 million was deleted from the police budget in Washington DC under useless Woke mayor Muriel Bowser car-jacking alone rose by 300 percent and within six months the US capital recorded its highest murder rate in 15 years. The same happened in Chicago and other cities in line with the Cult/Soros plan to bring fear to streets and neighbourhoods by reducing the police, releasing violent criminals and not prosecuting crime. This is the mob-rule agenda that I have warned in the books was coming for so long. Shootings in the area of Minneapolis where Floyd was arrested increased by 2,500 percent compared with the year before. Defunding the police over George Floyd has led to a big increase in dead people with many of them black. Police protection for politicians making these decisions stayed the same or increased as you would expect from professional hypocrites. The Cult doesn't actually want to abolish the police. It wants to abolish local control over the police and hand it to federal government as the psychopaths advance the Hunger Games Society. Many George Floyd protests turned into violent riots with black stores and businesses destroyed by fire and looting across America fuelled by Black Lives Matter. Woke doesn't do irony. If you want civil rights you must loot the liquor store and the supermarket and make off with a smart TV. It's the only way.

It's not a race war – it's a class war

Black people are patronised by privileged blacks and whites alike and told they are victims of white supremacy. I find it extraordinary to watch privileged blacks supporting the very system and bloodline networks behind the slave trade and parroting the same Cult-serving manipulative crap of their privileged white, often billionaire, associates. It is indeed not a race war but a class war and colour is just a diversion. Black Senator Cory Booker and black Congresswoman Maxine Waters, more residents of Nincompoopia, personify this. Once you tell people they are victims of someone else you devalue both their own responsibility for their plight and the power they have to impact on their reality and experience. Instead

we have: 'You are only in your situation because of whitey – turn on them and everything will change.' It won't change. Nothing changes in our lives unless *we* change it. Crucial to that is never seeing yourself as a victim and always as the creator of your reality. Life is a simple sequence of choice and consequence. Make different choices and you create different consequences. *You* have to make those choices – not Black Lives Matter, the Woke Mafia and anyone else that seeks to dictate your life. Who are they these Wokers, an emotional and psychological road traffic accident, to tell you what to do? Personal empowerment is the last thing the Cult and its Black Lives Matter want black people or anyone else to have. They claim to be defending the underdog while *creating* and perpetuating the underdog. The Cult's worst nightmare is human unity and if they are going to keep blacks, whites and every other race under economic servitude and control then the focus must be diverted from what they have in common to what they can be manipulated to believe divides them. Blacks have to be told that their poverty and plight is the fault of the white bloke living on the street in the same poverty and with the same plight they are experiencing. The difference is that your plight black people is due to him, a white supremacist with 'white privilege' living on the street. Don't unite as one human family against your mutual oppressors and suppressors – fight the oppressor with the white face who is as financially deprived as you are. The Cult knows that as its 'Covid' agenda moves into still new levels of extremism people are going to respond and it has been spreading the seeds of disunity everywhere to stop a united response to the evil that targets *all of us*.

Racist attacks on 'whiteness' are getting ever more outrageous and especially through the American Democratic Party which has an appalling history for anti-black racism. Barack Obama, Joe Biden, Hillary Clinton and Nancy Pelosi all eulogised about Senator Robert Byrd at his funeral in 2010 after a nearly 60-year career in Congress. Byrd was a brutal Ku Klux Klan racist and a violent abuser of Cathy O'Brien in MKUltra. He said he would never fight in the military 'with a negro by my side' and 'rather I should die a thousand times,

and see Old Glory trampled in the dirt never to rise again, than to see this beloved land of ours become degraded by race mongrels, a throwback to the blackest specimen from the wilds'. Biden called Byrd a 'very close friend and mentor'. These 'Woke' hypocrites are not anti-racist they are anti-poor and anti-people not of their perceived class. Here is an illustration of the scale of anti-white racism to which we have now descended. Seriously Woke and moronic *New York Times* contributor Damon Young described whiteness as a 'virus' that 'like other viruses will not die until there are no bodies left for it to infect'. He went on: '… the only way to stop it is to locate it, isolate it, extract it, and kill it.' Young can say that as a black man with no consequences when a white man saying the same in reverse would be facing a jail sentence. *That's* racism. We had super-Woke numbskull senators Tammy Duckworth and Mazie Hirono saying they would object to future Biden Cabinet appointments if he did not nominate more Asian Americans and Pacific Islanders. Never mind the ability of the candidate what do they look like? Duckworth said: 'I will vote for racial minorities and I will vote for LGBTQ, but anyone else I'm not voting for.' Appointing people on the grounds of race is illegal, but that was not a problem for this ludicrous pair. They were on-message and that's a free pass in any situation.

Critical race racism

White children are told at school they are intrinsically racist as they are taught the divisive 'critical race theory'. This claims that the law and legal institutions are inherently racist and that race is a socially constructed concept used by white people to further their economic and political interests at the expense of people of colour. White is a 'virus' as we've seen. Racial inequality results from 'social, economic, and legal differences that white people create between races to maintain white interests which leads to poverty and criminality in minority communities'. I must tell that to the white guy sleeping on the street. The principal of East Side Community School in New York sent white parents a manifesto that called on

them to become 'white traitors' and advocate for full 'white abolition'. These people are teaching your kids when they urgently need a psychiatrist. The 'school' included a chart with 'eight white identities' that ranged from 'white supremacist' to 'white abolition' and defined the behaviour white people must follow to end 'the regime of whiteness'. Woke blacks and their privileged white associates are acting exactly like the slave owners of old and Ku Klux Klan racists like Robert Byrd. They are too full of their own self-purity to see that, but it's true. Racism is not a body type; it's a state of mind that can manifest through any colour, creed or culture.

Another racial fraud is *'equity'*. Not equality of treatment and opportunity – equity. It's a term spun as equality when it means something very different. Equality in its true sense is a raising up while 'equity' is a race to the bottom. Everyone in the same level of poverty is 'equity'. Keep everyone down – that's equity. The Cult doesn't want anyone in the human family to be empowered and BLM leaders, like all these 'anti-racist' organisations, continue their privileged, pampered existence by perpetuating the perception of gathering racism. When is the last time you heard an 'anti-racist' or 'anti-Semitism' organisation say that acts of racism and discrimination have *fallen?* It's not in the interests of their fund-raising and power to influence and the same goes for the professional soccer anti-racism operation, Kick It Out. Two things confirmed that the Black Lives Matter riots in the summer of 2020 were Cult creations. One was that while anti-lockdown protests were condemned in this same period for 'transmitting 'Covid' the authorities supported mass gatherings of Black Lives Matter supporters. I even saw self-deluding people claiming to be doctors say the two types of protest were not the same. No – the non-existent 'Covid' was in favour of lockdowns and attacked those that protested against them while 'Covid' supported Black Lives Matter and kept well away from its protests. The whole thing was a joke and as lockdown protestors were arrested, often brutally, by reframed Face-Nappies we had the grotesque sight of police officers taking the knee to Black Lives Matter, a Cult-funded Marxist

organisation that supports violent riots and wants to destroy the nuclear family and white people.

He's not white? Shucks!

Woke obsession with race was on display again when ten people were shot dead in Boulder, Colorado, in March, 2021. Cult-owned Woke TV channels like CNN said the shooter appeared to be a white man and Wokers were on Twitter condemning 'violent white men' with the usual mantras. Then the shooter's name was released as Ahmad Al Aliwi Alissa, an anti-Trump Arab-American, and the sigh of disappointment could be heard five miles away. Never mind that ten people were dead and what that meant for their families. Race baiting was all that mattered to these sick Cult-serving people like Barack Obama who exploited the deaths to further divide America on racial grounds which is his job for the Cult. This is the man that 'racist' white Americans made the first black president of the United States and then gave him a second term. Not-very-bright Obama has become filthy rich on the back of that and today appears to have a big influence on the Biden administration. Even so he's still a downtrodden black man and a victim of white supremacy. This disingenuous fraud reveals the contempt he has for black people when he puts on a Deep South Alabama accent whenever he talks to them, no, *at* them.

Another BLM red flag was how the now fully-Woke (fully-Cult) and fully-virtue-signalled professional soccer authorities had their teams taking the knee before every match in support of Marxist Black Lives Matter. Soccer authorities and clubs displayed 'Black Lives Matter' on the players' shirts and flashed the name on electronic billboards around the pitch. Any fans that condemned what is a Freemasonic taking-the-knee ritual were widely condemned as you would expect from the Woke virtue-signallers of professional sport and the now fully-Woke media. We have reverse racism in which you are banned from criticising any race or culture except for white people for whom anything goes – say what you like, no problem. What has this got to do with racial harmony and

equality? We've had black supremacists from Black Lives Matter telling white people to fall to their knees in the street and apologise for their white supremacy. Black supremacists acting like white supremacist slave owners of the past couldn't breach their self-obsessed, race-obsessed sense of self-purity. Joe Biden appointed a race-obsessed black supremacist Kristen Clarke to head the Justice Department Civil Rights Division. Clarke claimed that blacks are endowed with 'greater mental, physical and spiritual abilities' than whites. If anyone reversed that statement they would be vilified. Clarke is on-message so no problem. She's never seen a black-white situation in which the black figure is anything but a virtuous victim and she heads the Civil Rights Division which should treat everyone the same or it isn't civil rights. Another perception of the Renegade Mind: If something or someone is part of the Cult agenda they will be supported by Woke governments and media no matter what. If they're not, they will be condemned and censored. It really is that simple and so racist Clarke prospers despite (make that because of) her racism.

The end of culture

Biden's administration is full of such racial, cultural and economic bias as the Cult requires the human family to be divided into warring factions. We are now seeing racially-segregated graduations and everything, but everything, is defined through the lens of perceived 'racism. We have 'racist' mathematics, 'racist' food and even 'racist' *plants*. World famous Kew Gardens in London said it was changing labels on plants and flowers to tell its pre-'Covid' more than two million visitors a year how racist they are. Kew director Richard Deverell said this was part of an effort to 'move quickly to decolonise collections' after they were approached by one Ajay Chhabra 'an actor with an insight into how sugar cane was linked to slavery'. They are *plants* you idiots. 'Decolonisation' in the Woke manual really means colonisation of society with its mentality and by extension colonisation by the Cult. We are witnessing a new Chinese-style 'Cultural Revolution' so essential to the success of all

Marxist takeovers. Our cultural past and traditions have to be swept away to allow a new culture to be built-back-better. Woke targeting of long-standing Western cultural pillars including historical monuments and cancelling of historical figures is what happened in the Mao revolution in China which 'purged remnants of capitalist and traditional elements from Chinese society' and installed Maoism as the dominant ideology'. For China see the Western world today and for 'dominant ideology' see Woke. Better still see Marxism or Maoism. The 'Covid' hoax has specifically sought to destroy the arts and all elements of Western culture from people meeting in a pub or restaurant to closing theatres, music venues, sports stadiums, places of worship and even banning *singing*. Destruction of Western society is also why criticism of any religion is banned except for Christianity which again is the dominant religion as white is the numerically-dominant race. Christianity may be fading rapidly, but its history and traditions are weaved through the fabric of Western society. Delete the pillars and other structures will follow until the whole thing collapses. I am not a Christian defending that religion when I say that. I have no religion. It's just a fact. To this end Christianity has itself been turned Woke to usher its own downfall and its ranks are awash with 'change agents' – knowing and unknowing – at every level including Pope Francis (*definitely* knowing) and the clueless Archbishop of Canterbury Justin Welby (possibly not, but who can be sure?). Woke seeks to coordinate attacks on Western culture, traditions, and ways of life through 'intersectionality' defined as 'the complex, cumulative way in which the effects of multiple forms of discrimination (such as racism, sexism, and classism) combine, overlap, or intersect especially in the experiences of marginalised individuals or groups'. Wade through the Orwellian Woke-speak and this means coordinating disparate groups in a common cause to overthrow freedom and liberal values.

The entire structure of public institutions has been infested with Woke – government at all levels, political parties, police, military, schools, universities, advertising, media and trade unions. This abomination has been achieved through the Cult web by appointing

Wokers to positions of power and battering non-Wokers into line through intimidation, isolation and threats to their job. Many have been fired in the wake of the empathy-deleted, vicious hostility of 'social justice' Wokers and the desire of gutless, spineless employers to virtue-signal their Wokeness. Corporations are filled with Wokers today, most notably those in Silicon Valley. Ironically at the top they are not Woke at all. They are only exploiting the mentality their Cult masters have created and funded to censor and enslave while the Wokers cheer them on until it's their turn. Thus the Woke 'liberal left' is an inversion of the traditional liberal left. Campaigning for justice on the grounds of power and wealth distribution has been replaced by campaigning for identity politics. The genuine traditional left would never have taken money from today's billionaire abusers of fairness and justice and nor would the billionaires have wanted to fund that genuine left. It would not have been in their interests to do so. The division of opinion in those days was between the haves and have nots. This all changed with Cult manipulated and funded identity politics. The division of opinion today is between Wokers and non-Wokers and not income brackets. Cult corporations and their billionaires may have taken wealth disparity to cataclysmic levels of injustice, but as long as they speak the language of Woke, hand out the dosh to the Woke network and censor the enemy they are 'one of us'. Billionaires who don't give a damn about injustice are laughing at them till their bellies hurt. Wokers are not even close to self-aware enough to see that. The transformed 'left' dynamic means that Wokers who drone on about 'social justice' are funded by billionaires that have destroyed social justice the world over. It's *why* they are billionaires.

The climate con

Nothing encapsulates what I have said more comprehensively than the hoax of human-caused global warming. I have detailed in my books over the years how Cult operatives and organisations were the pump-primers from the start of the climate con. A purpose-built vehicle for this is the Club of Rome established by the Cult in 1968

with the Rockefellers and Rothschilds centrally involved all along. Their gofer frontman Maurice Strong, a Canadian oil millionaire, hosted the Earth Summit in Rio de Janeiro, Brazil, in 1992 where the global 'green movement' really expanded in earnest under the guiding hand of the Cult. The Earth Summit established Agenda 21 through the Cult-created-and-owned United Nations to use the illusion of human-caused climate change to justify the transformation of global society to save the world from climate disaster. It is a No-Problem-Reaction-Solution sold through governments, media, schools and universities as whole generations have been terrified into believing that the world was going to end in their lifetimes unless what old people had inflicted upon them was stopped by a complete restructuring of how everything is done. Chill, kids, it's all a hoax. Such restructuring is precisely what the Cult agenda demands (purely by coincidence of course). Today this has been given the codename of the Great Reset which is only an updated term for Agenda 21 and its associated Agenda 2030. The latter, too, is administered through the UN and was voted into being by the General Assembly in 2015. Both 21 and 2030 seek centralised control of all resources and food right down to the raindrops falling on your own land. These are some of the demands of Agenda 21 established in 1992. See if you recognise this society emerging today:

- End national sovereignty
- State planning and management of all land resources, ecosystems, deserts, forests, mountains, oceans and fresh water; agriculture; rural development; biotechnology; and ensuring *'equity'*
- The state to 'define the role' of business and financial resources
- Abolition of private property
- 'Restructuring' the family unit (see BLM)
- Children raised by the state
- People told what their job will be
- Major restrictions on movement
- Creation of 'human settlement zones'

- Mass resettlement as people are forced to vacate land where they live
- Dumbing down education
- Mass global depopulation in pursuit of all the above

The United Nations was created as a Trojan horse for world government. With the climate con of critical importance to promoting that outcome you would expect the UN to be involved. Oh, it's involved all right. The UN is promoting Agenda 21 and Agenda 2030 justified by 'climate change' while also driving the climate hoax through its Intergovernmental Panel on Climate Change (IPCC), one of the world's most corrupt organisations. The IPCC has been lying ferociously and constantly since the day it opened its doors with the global media hanging unquestioningly on its every mendacious word. The Green movement is entirely Woke and has long lost its original environmental focus since it was co-opted by the Cult. An obsession with 'global warming' has deleted its values and scrambled its head. I experienced a small example of what I mean on a beautiful country walk that I have enjoyed several times a week for many years. The path merged into the fields and forests and you felt at one with the natural world. Then a 'Green' organisation, the Hampshire and Isle of Wight Wildlife Trust, took over part of the land and proceeded to cut down a large number of trees, including mature ones, to install a horrible big, bright steel 'this-is-ours-stay-out' fence that destroyed the whole atmosphere of this beautiful place. No one with a feel for nature would do that. Day after day I walked to the sound of chainsaws and a magnificent mature weeping willow tree that I so admired was cut down at the base of the trunk. When I challenged a Woke young girl in a green shirt (of course) about this vandalism she replied: 'It's a weeping willow – it will grow back.' This is what people are paying for when they donate to the Hampshire and Isle of Wight Wildlife Trust and many other 'green' organisations today. It is not the environmental movement that I knew and instead has become a support-system – as with Extinction Rebellion – for a very dark agenda.

Private jets for climate justice

The Cult-owned, Gates-funded, World Economic Forum and its founder Klaus Schwab were behind the emergence of Greta Thunberg to harness the young behind the climate agenda and she was invited to speak to the world at … the UN. Schwab published a book, *Covid-19: The Great Reset* in 2020 in which he used the 'Covid' hoax and the climate hoax to lay out a new society straight out of Agenda 21 and Agenda 2030. Bill Gates followed in early 2021 when he took time out from destroying the world to produce a book in his name about the way to save it. Gates flies across the world in private jets and admitted that 'I probably have one of the highest greenhouse gas footprints of anyone on the planet … my personal flying alone is gigantic.' He has also bid for the planet's biggest private jet operator. Other climate change saviours who fly in private jets include John Kerry, the US Special Presidential Envoy for Climate, and actor Leonardo DiCaprio, a 'UN Messenger of Peace with special focus on climate change'. These people are so full of bullshit they could corner the market in manure. We mustn't be sceptical, though, because the Gates book, *How to Avoid a Climate Disaster: The Solutions We Have and the Breakthroughs We Need*, is a genuine attempt to protect the world and not an obvious pile of excrement attributed to a mega-psychopath aimed at selling his masters' plans for humanity. The Gates book and the other shite-pile by Klaus Schwab could have been written by the same person and may well have been. Both use 'climate change' and 'Covid' as the excuses for their new society and by coincidence the Cult's World Economic Forum and Bill and Melinda Gates Foundation promote the climate hoax and hosted Event 201 which pre-empted with a 'simulation' the very 'coronavirus' hoax that would be simulated for real on humanity within weeks. The British 'royal' family is promoting the 'Reset' as you would expect through Prince 'climate change caused the war in Syria' Charles and his hapless son Prince William who said that we must 'reset our relationship with nature and our trajectory as a species' to avoid a climate disaster. Amazing how many promotors of the 'Covid' and 'climate change' control

systems are connected to Gates and the World Economic Forum. A 'study' in early 2021 claimed that carbon dioxide emissions must fall by the equivalent of a global lockdown roughly every two years for the next decade to save the planet. The 'study' appeared in the same period that the Schwab mob claimed in a video that lockdowns destroying the lives of billions are good because they make the earth 'quieter' with less 'ambient noise'. They took down the video amid a public backlash for such arrogant, empathy-deleted stupidity You see, however, where they are going with this. Corinne Le Quéré, a professor at the Tyndall Centre for Climate Change Research, University of East Anglia, was lead author of the climate lockdown study, and she writes for … the World Economic Forum. Gates calls in 'his' book for changing 'every aspect of the economy' (long-time Cult agenda) and for humans to eat synthetic 'meat' (predicted in my books) while cows and other farm animals are eliminated. Australian TV host and commentator Alan Jones described what carbon emission targets would mean for farm animals in Australia alone if emissions were reduced as demanded by 35 percent by 2030 and zero by 2050:

Well, let's take agriculture, the total emissions from agriculture are about 75 million tonnes of carbon dioxide, equivalent. Now reduce that by 35 percent and you have to come down to 50 million tonnes, I've done the maths. So if you take for example 1.5 million cows, you're going to have to reduce the herd by 525,000 [by] 2030, nine years, that's 58,000 cows a year. The beef herd's 30 million, reduce that by 35 percent, that's 10.5 million, which means 1.2 million cattle have to go every year between now and 2030. This is insanity!

There are 75 million sheep. Reduce that by 35 percent, that's 26 million sheep, that's almost 3 million a year. So under the Paris Agreement over 30 million beasts. dairy cows, cattle, pigs and sheep would go. More than 8,000 every minute of every hour for the next decade, do these people know what they're talking about?

Clearly they don't at the level of campaigners, politicians and administrators. The Cult *does* know; that's the outcome it wants. We are faced with not just a war on humanity. Animals and the natural world are being targeted and I have been saying since the 'Covid' hoax began that the plan eventually was to claim that the 'deadly virus' is able to jump from animals, including farm animals and

domestic pets, to humans. Just before this book went into production came this story: 'Russia registers world's first Covid-19 vaccine for cats & dogs as makers of Sputnik V warn pets & farm animals could spread virus'. The report said 'top scientists warned that the deadly pathogen could soon begin spreading through homes and farms' and 'the next stage is the infection of farm and domestic animals'. Know the outcome and you'll see the journey. Think what that would mean for animals and keep your eye on a term called zoonosis or zoonotic diseases which transmit between animals and humans. The Cult wants to break the connection between animals and people as it does between people and people. Farm animals fit with the Cult agenda to transform food from natural to synthetic.

The gas of life is killing us

There can be few greater examples of Cult inversion than the condemnation of carbon dioxide as a dangerous pollutant when it is the gas of life. Without it the natural world would be dead and so we would all be dead. We breathe in oxygen and breathe out carbon dioxide while plants produce oxygen and absorb carbon dioxide. It is a perfect symbiotic relationship that the Cult wants to dismantle for reasons I will come to in the final two chapters. Gates, Schwab, other Cult operatives and mindless repeaters, want the world to be 'carbon neutral' by at least 2050 and the earlier the better. 'Zero carbon' is the cry echoed by lunatics calling for 'Zero Covid' when we already have it. These carbon emission targets will deindustrialise the world in accordance with Cult plans – the post-industrial, post-democratic society – and with so-called renewables like solar and wind not coming even close to meeting human energy needs blackouts and cold are inevitable. Texans got the picture in the winter of 2021 when a snow storm stopped wind turbines and solar panels from working and the lights went down along with water which relies on electricity for its supply system. Gates wants everything to be powered by electricity to ensure that his masters have the kill switch to stop all human activity, movement, cooking, water and warmth any time they like. The climate lie is so

stupendously inverted that it claims we must urgently reduce carbon dioxide when we *don't have enough*.

Co2 in the atmosphere is a little above 400 parts per million when the optimum for plant growth is 2,000 ppm and when it falls anywhere near 150 ppm the natural world starts to die and so do we. It fell to as low as 280 ppm in an 1880 measurement in Hawaii and rose to 413 ppm in 2019 with industrialisation which is why the planet has become *greener* in the industrial period. How insane then that psychopathic madman Gates is not satisfied only with blocking the rise of Co2. He's funding technology to suck it out of the atmosphere. The reason why will become clear. The industrial era is not destroying the world through Co2 and has instead turned around a potentially disastrous ongoing fall in Co2. Greenpeace co-founder and scientist Patrick Moore walked away from Greenpeace in 1986 and has exposed the green movement for fear-mongering and lies. He said that 500 million years ago there was *17 times* more Co2 in the atmosphere than we have today and levels have been falling for hundreds of millions of years. In the last 150 million years Co2 levels in Earth's atmosphere had reduced by *90 percent*. Moore said that by the time humanity began to unlock carbon dioxide from fossil fuels we were at '38 seconds to midnight' and in that sense: 'Humans are [the Earth's] salvation.' Moore made the point that only half the Co2 emitted by fossil fuels stays in the atmosphere and we should remember that all pollution pouring from chimneys that we are told is carbon dioxide is in fact nothing of the kind. It's pollution. Carbon dioxide is an invisible gas.

William Happer, Professor of Physics at Princeton University and long-time government adviser on climate, has emphasised the Co2 deficiency for maximum growth and food production. Greenhouse growers don't add carbon dioxide for a bit of fun. He said that most of the warming in the last 100 years, after the earth emerged from the super-cold period of the 'Little Ice Age' into a natural warming cycle, was over by 1940. Happer said that a peak year for warming in 1988 can be explained by a 'monster El Nino' which is a natural and cyclical warming of the Pacific that has nothing to do with 'climate

change'. He said the effect of Co2 could be compared to painting a wall with red paint in that once two or three coats have been applied it didn't matter how much more you slapped on because the wall will not get much redder. Almost all the effect of the rise in Co2 has already happened, he said, and the volume in the atmosphere would now have to *double* to increase temperature by a single degree. Climate hoaxers know this and they have invented the most ridiculously complicated series of 'feedback' loops to try to overcome this rather devastating fact. You hear puppet Greta going on cluelessly about feedback loops and this is why.

The Sun affects temperature? No you *climate denier*

Some other nonsense to contemplate: Climate graphs show that rises in temperature do not follow rises in Co2 – *it's the other way round* with a lag between the two of some 800 years. If we go back 800 years from present time we hit the Medieval Warm Period when temperatures were higher than now without any industrialisation and this was followed by the Little Ice Age when temperatures plummeted. The world was still emerging from these centuries of serious cold when many climate records began which makes the ever-repeated line of the 'hottest year since records began' meaningless when you are not comparing like with like. The coldest period of the Little Ice Age corresponded with the lowest period of sunspot activity when the Sun was at its least active. Proper scientists will not be at all surprised by this when it confirms the obvious fact that earth temperature is affected by the scale of Sun activity and the energetic power that it subsequently emits; but when is the last time you heard a climate hoaxer talking about the Sun as a source of earth temperature?? Everything has to be focussed on Co2 which makes up just 0.117 percent of so-called greenhouse gases and only a fraction of even that is generated by human activity. The rest is natural. More than *90 percent* of those greenhouse gases are water vapour and clouds (Fig 9). Ban moisture I say. Have you noticed that the climate hoaxers no longer use the polar bear as their promotion image? That's because far from becoming extinct polar

bear communities are stable or thriving. Joe Bastardi, American meteorologist, weather forecaster and outspoken critic of the climate lie, documents in his book *The Climate Chronicles* how weather patterns and events claimed to be evidence of climate change have been happening since long before industrialisation: 'What happened before naturally is happening again, as is to be expected given the cyclical nature of the climate due to the design of the planet.' If you read the detailed background to the climate hoax in my other books you will shake your head and wonder how anyone could believe the crap which has spawned a multi-trillion dollar industry based on absolute garbage (see HIV causes AIDs and Sars-Cov-2 causes 'Covid-19'). Climate and 'Covid' have much in common given they have the same source. They both have the contradictory *everything* factor in which everything is explained by reference to them. It's hot – 'it's climate change'. It's cold – 'it's climate change'. I got a sniffle – 'it's Covid'. I haven't got a sniffle – 'it's Covid'. Not having a sniffle has to be a symptom of 'Covid'. Everything is and not having a sniffle is especially dangerous if you are a slow walker. For sheer audacity I offer you a Cambridge University 'study' that actually linked 'Covid' to 'climate change'. It had to happen eventually. They concluded that climate change played a role in 'Covid-19' spreading from animals to humans because … wait for it … I kid you not … *the two groups were forced closer together as populations grow*. Er, that's it. The whole foundation on which this depended was that 'Bats are the likely zoonotic origin of SARS-CoV-1 and SARS-CoV-2'. Well, they are not. They are nothing to do with it. Apart from bats not being the origin and therefore 'climate change' effects on bats being irrelevant I am in awe of their academic insight. Where would we be without them? Not where we are that's for sure.

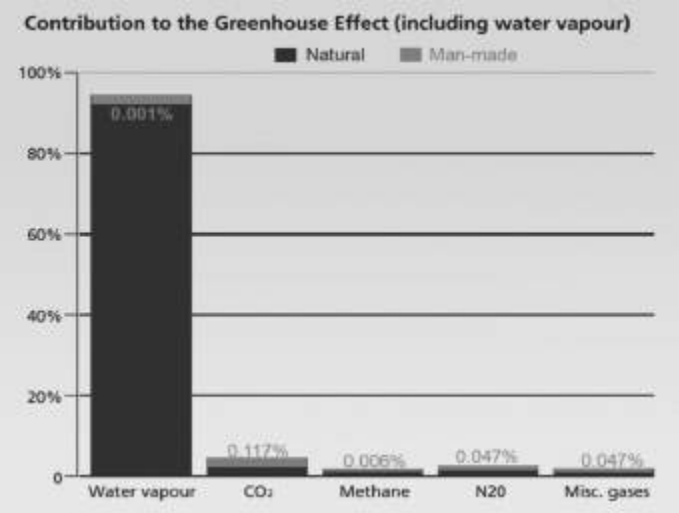


Figure 9: The idea that the gas of life is disastrously changing the climate is an insult to brain cell activity.

One other point about the weather is that climate modification is now well advanced and not every major weather event is natural – or earthquake come to that. I cover this subject at some length in other books. China is openly planning a rapid expansion of its weather modification programme which includes changing the climate in an area more than one and a half times the size of India. China used weather manipulation to ensure clear skies during the 2008 Olympics in Beijing. I have quoted from US military documents detailing how to employ weather manipulation as a weapon of war and they did that in the 1960s and 70s during the conflict in Vietnam with Operation Popeye manipulating monsoon rains for military purposes. Why would there be international treaties on weather modification if it wasn't possible? Of course it is. Weather is energetic information and it can be changed.

How was the climate hoax pulled off? See 'Covid'

If you can get billions to believe in a 'virus' that doesn't exist you can get them to believe in human-caused climate change that doesn't exist. Both are being used by the Cult to transform global society in the way it has long planned. Both hoaxes have been achieved in pretty much the same way. First you declare a lie is a fact. There's a

'virus' you call SARS-Cov-2 or humans are warming the planet with their behaviour. Next this becomes, via Cult networks, the foundation of government, academic and science policy and belief. Those who parrot the mantra are given big grants to produce research that confirms the narrative is true and ever more 'symptoms' are added to make the 'virus'/'climate change' sound even more scary. Scientists and researchers who challenge the narrative have their grants withdrawn and their careers destroyed. The media promote the lie as the unquestionable truth and censor those with an alternative view or evidence. A great percentage of the population believe what they are told as the lie becomes an everybody-knows-that and the believing-masses turn on those with a mind of their own. The technique has been used endlessly throughout human history. Wokers are the biggest promotors of the climate lie *and* 'Covid' fascism because their minds are owned by the Cult; their sense of self-righteous self-purity knows no bounds; and they exist in a bubble of reality in which facts are irrelevant and only get in the way of looking without seeing.

Running through all of this like veins in a blue cheese is control of information, which means control of perception, which means control of behaviour, which collectively means control of human society. The Cult owns the global media and Silicon Valley fascists for the simple reason that it *has* to. Without control of information it can't control perception and through that human society. Examine every facet of the Cult agenda and you will see that anything supporting its introduction is never censored while anything pushing back is always censored. I say again: Psychopaths that know why they are doing this must go before Nuremberg trials and those that follow their orders must trot along behind them into the same dock. 'I was just following orders' didn't work the first time and it must not work now. Nuremberg trials must be held all over the world before public juries for politicians, government officials, police, compliant doctors, scientists and virologists, and all Cult operatives such as Gates, Tedros, Fauci, Vallance, Whitty, Ferguson, Zuckerberg, Wojcicki, Brin, Page, Dorsey, the whole damn lot of

them – including, no *especially*, the psychopath psychologists. Without them and the brainless, gutless excuses for journalists that have repeated their lies, none of this could be happening. Nobody can be allowed to escape justice for the psychological and economic Armageddon they are all responsible for visiting upon the human race.

As for the compliant, unquestioning, swathes of humanity, and the self-obsessed, all-knowing ignorance of the Wokers … don't start me. God help their kids. God help their grandkids. God *help them*.

CHAPTER NINE

We must have it? So what is it?

Well I won't back down. No, I won't back down. You can stand me up at the Gates of Hell. But I won't back down
Tom Petty

I will now focus on the genetically-manipulating 'Covid vaccines' which do not meet this official definition of a vaccine by the US Centers for Disease Control (CDC): 'A product that stimulates a person's immune system to produce immunity to a specific disease, protecting the person from that disease.' On that basis 'Covid vaccines' are not a vaccine in that the makers don't even claim they stop infection or transmission.

They are instead part of a multi-levelled conspiracy to change the nature of the human body and what it means to be 'human' and to depopulate an enormous swathe of humanity. What I shall call Human 1.0 is on the cusp of becoming Human 2.0 and for very sinister reasons. Before I get to the 'Covid vaccine' in detail here's some background to vaccines in general. Government regulators do not test vaccines – the makers do – and the makers control which data is revealed and which isn't. Children in America are given 50 vaccine doses by age six and 69 by age 19 and the effect of the whole combined schedule has never been tested. Autoimmune diseases when the immune system attacks its own body have soared in the mass vaccine era and so has disease in general in children and the young. Why wouldn't this be the case when vaccines target the *immune system?* The US government gave Big Pharma drug

companies immunity from prosecution for vaccine death and injury in the 1986 National Childhood Vaccine Injury Act (NCVIA) and since then the government (taxpayer) has been funding compensation for the consequences of Big Pharma vaccines. The criminal and satanic drug giants can't lose and the vaccine schedule has increased dramatically since 1986 for this reason. There is no incentive to make vaccines safe and a big incentive to make money by introducing ever more. Even against a ridiculously high bar to prove vaccine liability, and with the government controlling the hearing in which it is being challenged for compensation, the vaccine court has so far paid out more than $4 billion. These are the vaccines we are told are safe and psychopaths like Zuckerberg censor posts saying otherwise. The immunity law was even justified by a ruling that vaccines by their nature were 'unavoidably unsafe'.

Check out the ingredients of vaccines and you will be shocked if you are new to this. *They put that in children's bodies?? What??* Try aluminium, a brain toxin connected to dementia, aborted foetal tissue and formaldehyde which is used to embalm corpses. World-renowned aluminium expert Christopher Exley had his research into the health effect of aluminium in vaccines shut down by Keele University in the UK when it began taking funding from the Bill and Melinda Gates Foundation. Research when diseases 'eradicated' by vaccines began to decline and you will find the fall began long *before* the vaccine was introduced. Sometimes the fall even plateaued after the vaccine. Diseases like scarlet fever for which there was no vaccine declined in the same way because of environmental and other factors. A perfect case in point is the polio vaccine. Polio began when lead arsenate was first sprayed as an insecticide and residues remained in food products. Spraying started in 1892 and the first US polio epidemic came in Vermont in 1894. The simple answer was to stop spraying, but Rockefeller-created Big Pharma had a better idea. Polio was decreed to be caused by the *poliovirus* which 'spreads from person to person and can infect a person's spinal cord'. Lead arsenate was replaced by the lethal DDT which had the same effect of causing paralysis by damaging the brain and central nervous

system. Polio plummeted when DDT was reduced and then banned, but the vaccine is still given the credit for something it didn't do. Today by far the biggest cause of polio is the vaccines promoted by Bill Gates. Vaccine justice campaigner Robert Kennedy Jr, son of assassinated (by the Cult) US Attorney General Robert Kennedy, wrote:

> In 2017, the World Health Organization (WHO) reluctantly admitted that the global explosion in polio is predominantly vaccine strain. The most frightening epidemics in Congo, Afghanistan, and the Philippines, are all linked to vaccines. In fact, by 2018, 70% of global polio cases were vaccine strain.

Vaccines make fortunes for Cult-owned Gates and Big Pharma while undermining the health and immune systems of the population. We had a glimpse of the mentality behind the Big Pharma cartel with a report on WION (World is One News), an international English language TV station based in India, which exposed the extraordinary behaviour of US drug company Pfizer over its 'Covid vaccine'. The WION report told how Pfizer had made fantastic demands of Argentina, Brazil and other countries in return for its 'vaccine'. These included immunity from prosecution, even for Pfizer negligence, government insurance to protect Pfizer from law suits and handing over as collateral sovereign assets of the country to include Argentina's bank reserves, military bases and embassy buildings. Pfizer demanded the same of Brazil in the form of waiving sovereignty of its assets abroad; exempting Pfizer from Brazilian laws; and giving Pfizer immunity from all civil liability. This is a 'vaccine' developed with government funding. Big Pharma is evil incarnate as a creation of the Cult and all must be handed tickets to Nuremberg.

Phantom 'vaccine' for a phantom 'disease'

I'll expose the 'Covid vaccine' fraud and then go on to the wider background of why the Cult has set out to 'vaccinate' every man, woman and child on the planet for an alleged 'new disease' with a survival rate of 99.77 percent (or more) even by the grotesquely-

manipulated figures of the World Health Organization and Johns Hopkins University. The 'infection' to 'death' ratio is 0.23 to 0.15 percent according to Stanford epidemiologist Dr John Ioannidis and while estimates vary the danger remains tiny. I say that if the truth be told the fake infection to fake death ratio is zero. Never mind all the evidence I have presented here and in *The Answer* that there is no 'virus' let us just focus for a moment on that death-rate figure of say 0.23 percent. The figure includes all those worldwide who have tested positive with a test not testing for the 'virus' and then died within 28 days or even longer of any other cause – *any other cause*. Now subtract all those illusory 'Covid' deaths on the global data sheets from the 0.23 percent. What do you think you would be left with? *Zero*. A vaccination has never been successfully developed for a so-called coronavirus. They have all failed at the animal testing stage when they caused hypersensitivity to what they were claiming to protect against and made the impact of a disease far worse. Cult-owned vaccine corporations got around that problem this time by bypassing animal trials, going straight to humans and making the length of the 'trials' before the public rollout as short as they could get away with. Normally it takes five to ten years or more to develop vaccines that still cause demonstrable harm to many people and that's without including the long-term effects that are never officially connected to the vaccination. 'Covid' non-vaccines have been officially produced and approved in a matter of months from a standing start and part of the reason is that (a) they were developed before the 'Covid' hoax began and (b) they are based on computer programs and not natural sources. Official non-trials were so short that government agencies gave *emergency*, not full, approval. 'Trials' were not even completed and full approval cannot be secured until they are. Public 'Covid vaccination' is actually a *continuation of the trial*. Drug company 'trials' are not scheduled to end until 2023 by which time a lot of people are going to be dead. Data on which government agencies gave this emergency approval was supplied by the Big Pharma corporations themselves in the form of Pfizer/BioNTech, AstraZeneca, Moderna, Johnson & Johnson, and

others, and this is the case with all vaccines. By its very nature *emergency* approval means drug companies do not have to prove that the 'vaccine' is 'safe and effective'. How could they with trials way short of complete? Government regulators only have to *believe* that they *could* be safe and effective. It is criminal manipulation to get products in circulation with no testing worth the name. Agencies giving that approval are infested with Big Pharma-connected place-people and they act in the interests of Big Pharma (the Cult) and not the public about whom they do not give a damn.

More human lab rats

'Covid vaccines' produced in record time by Pfizer/BioNTech and Moderna employ a technique *never approved before for use on humans*. They are known as mRNA 'vaccines' and inject a synthetic version of 'viral' mRNA or 'messenger RNA'. The key is in the term 'messenger'. The body works, or doesn't, on the basis of information messaging. Communications are constantly passing between and within the genetic system and the brain. Change those messages and you change the state of the body and even its very nature and you can change psychology and behaviour by the way the brain processes information. I think you are going to see significant changes in personality and perception of many people who have had the 'Covid vaccine' synthetic potions. Insider Aldous Huxley predicted the following in 1961 and mRNA 'vaccines' can be included in the term 'pharmacological methods':

> There will be, in the next generation or so, a pharmacological method of making people love their servitude, and producing dictatorship without tears, so to speak, producing a kind of painless concentration camp for entire societies, so that people will in fact have their own liberties taken away from them, but rather enjoy it, because they will be distracted from any desire to rebel by propaganda or brainwashing, or brainwashing enhanced by pharmacological methods. And this seems to be the final revolution.

Apologists claim that mRNA synthetic 'vaccines' don't change the DNA genetic blueprint because RNA does not affect DNA only the other way round. This is so disingenuous. A process called 'reverse

transcription' can convert RNA into DNA and be integrated into DNA in the cell nucleus. This was highlighted in December, 2020, by scientists at Harvard and Massachusetts Institute of Technology (MIT). Geneticists report that more than 40 percent of mammalian genomes results from reverse transcription. On the most basic level if messaging changes then that sequence must lead to changes in DNA which is receiving and transmitting those communications. How can introducing synthetic material into cells not change the cells where DNA is located? The process is known as transfection which is defined as 'a technique to insert foreign nucleic acid (DNA or RNA) into a cell, typically with the intention of altering the properties of the cell'. Researchers at the Sloan Kettering Institute in New York found that changes in messenger RNA can deactivate tumour-suppressing proteins and thereby promote cancer. This is what happens when you mess with messaging. 'Covid vaccine' maker Moderna was founded in 2010 by Canadian stem cell biologist Derrick J. Rossi after his breakthrough discovery in the field of transforming and reprogramming stem cells. These are neutral cells that can be programmed to become any cell including sperm cells. Moderna was therefore founded on the principle of genetic manipulation and has never produced any vaccine or drug before its genetically-manipulating synthetic 'Covid' shite. Look at the name – Mode-RNA or Modify-RNA. Another important point is that the US Supreme Court has ruled that genetically-modified DNA, or complementary DNA (cDNA) synthesized in the laboratory from messenger RNA, can be patented and owned. These psychopaths are doing this to the human body.

Cells replicate synthetic mRNA in the 'Covid vaccines' and in theory the body is tricked into making antigens which trigger antibodies to target the 'virus spike proteins' which as Dr Tom Cowan said have *never been seen*. Cut the crap and these 'vaccines' deliver *self-replicating* synthetic material to the cells with the effect of changing human DNA. The more of them you have the more that process is compounded while synthetic material is all the time self-replicating. 'Vaccine'-maker Moderna describes mRNA as 'like

software for the cell' and so they are messing with the body's software. What happens when you change the software in a computer? Everything changes. For this reason the Cult is preparing a production line of mRNA 'Covid vaccines' and a long list of excuses to use them as with all the 'variants' of a 'virus' never shown to exist. The plan is further to transfer the mRNA technique to other vaccines mostly given to children and young people. The cumulative consequences will be a transformation of human DNA through a constant infusion of synthetic genetic material which will kill many and change the rest. Now consider that governments that have given emergency approval for a vaccine that's not a vaccine; never been approved for humans before; had no testing worth the name; and the makers have been given immunity from prosecution for any deaths or adverse effects suffered by the public. The UK government awarded *permanent legal indemnity* to itself and its employees for harm done when a patient is being treated for 'Covid-19' or 'suspected Covid-19'. That is quite a thought when these are possible 'side-effects' from the 'vaccine' (they are not 'side', they are effects) listed by the US Food and Drug Administration:

Guillain-Barre syndrome; acute disseminated encephalomyelitis; transverse myelitis; encephalitis; myelitis; encephalomyelitis; meningoencephalitis; meningitis; encephalopathy; convulsions; seizures; stroke; narcolepsy; cataplexy; anaphylaxis; acute myocardial infarction (heart attack); myocarditis; pericarditis; autoimmune disease; death; implications for pregnancy, and birth outcomes; other acute demyelinating diseases; non anaphylactic allergy reactions; thrombocytopenia ; disseminated intravascular coagulation; venous thromboembolism; arthritis; arthralgia; joint pain; Kawasaki disease; multisystem inflammatory syndrome in children; vaccine enhanced disease. The latter is the way the 'vaccine' has the potential to make diseases far worse than they would otherwise be.

UK doctor and freedom campaigner Vernon Coleman described the conditions in this list as 'all unpleasant, most of them very serious, and you can't get more serious than death'. The thought that anyone at all has had the 'vaccine' in these circumstances is testament to the potential that humanity has for clueless, unquestioning, stupidity and for many that programmed stupidity has already been terminal.

An insider speaks

Dr Michael Yeadon is a former Vice President, head of research and Chief Scientific Adviser at vaccine giant Pfizer. Yeadon worked on the inside of Big Pharma, but that did not stop him becoming a vocal critic of 'Covid vaccines' and their potential for multiple harms, including infertility in women. By the spring of 2021 he went much further and even used the no, no, term 'conspiracy'. When you begin to see what is going on it is impossible not to do so. Yeadon spoke out in an interview with freedom campaigner James Delingpole and I mentioned earlier how he said that no one had samples of 'the virus'. He explained that the mRNA technique originated in the anti-cancer field and ways to turn on and off certain genes which could be advantageous if you wanted to stop cancer growing out of control. 'That's the origin of them. They are a very unusual application, really.' Yeadon said that treating a cancer patient with an aggressive procedure might be understandable if the alternative was dying, but it was quite another thing to use the same technique as a public health measure. Most people involved wouldn't catch the infectious agent you were vaccinating against and if they did they probably wouldn't die:

> If you are really using it as a public health measure you really want to as close as you can get to zero sides-effects … I find it odd that they chose techniques that were really cutting their teeth in the field of oncology and I'm worried that in using gene-based vaccines that have to be injected in the body and spread around the body, get taken up into some cells, and the regulators haven't quite told us which cells they get taken up into … you are going to be generating a wide range of responses … with multiple steps each of which could go well or badly.

I doubt the Cult intends it to go well. Yeadon said that you can put any gene you like into the body through the 'vaccine'. 'You can certainly give them a gene that would do them some harm if you wanted.' I was intrigued when he said that when used in the cancer field the technique could turn genes on and off. I explore this process in *The Answer* and with different genes having different functions you could create mayhem – physically and psychologically – if you turned the wrong ones on and the right ones off. I read reports of an experiment by researchers at the University of Washington's school of computer science and engineering in which they encoded DNA to infect computers. The body is itself a biological computer and if human DNA can inflict damage on a computer why can't the computer via synthetic material mess with the human body? It can. The Washington research team said it was possible to insert malicious malware into 'physical DNA strands' and corrupt the computer system of a gene sequencing machine as it 'reads gene letters and stores them as binary digits 0 and 1'. They concluded that hackers could one day use blood or spit samples to access computer systems and obtain sensitive data from police forensics labs or infect genome files. It is at this level of digital interaction that synthetic 'vaccines' need to be seen to get the full picture and that will become very clear later on. Michael Yeadon said it made no sense to give the 'vaccine' to younger people who were in no danger from the 'virus'. What was the benefit? It was all downside with potential effects:

> The fact that my government in what I thought was a civilised, rational country, is raining [the 'vaccine'] on people in their 30s and 40s, even my children in their 20s, they're getting letters and phone calls, I know this is not right and any of you doctors who are vaccinating you know it's not right, too. They are not at risk. They are not at risk from the disease, so you are now hoping that the side-effects are so rare that you get away with it. You don't give new technology … that you don't understand to 100 percent of the population.

Blood clot problems with the AstraZeneca 'vaccine' have been affecting younger people to emphasise the downside risks with no benefit. AstraZeneca's version, produced with Oxford University, does not use mRNA, but still gets its toxic cocktail inside cells where

it targets DNA. The Johnson & Johnson 'vaccine' which uses a similar technique has also produced blood clot effects to such an extent that the United States paused its use at one point. They are all 'gene therapy' (cell modification) procedures and not 'vaccines'. The truth is that once the content of these injections enter cells we have no idea what the effect will be. People can speculate and some can give very educated opinions and that's good. In the end, though, only the makers know what their potions are designed to do and even they won't know every last consequence. Michael Yeadon was scathing about doctors doing what they knew to be wrong. 'Everyone's mute', he said. Doctors in the NHS must know this was not right, coming into work and injecting people. 'I don't know how they sleep at night. I know I couldn't do it. I know that if I were in that position I'd have to quit.' He said he knew enough about toxicology to know this was not a good risk-benefit. Yeadon had spoken to seven or eight university professors and all except two would not speak out publicly. Their universities had a policy that no one said anything that countered the government and its medical advisors. They were afraid of losing their government grants. This is how intimidation has been used to silence the truth at every level of the system. I say silence, but these people could still speak out if they made that choice. Yeadon called them 'moral cowards' – 'This is about your children and grandchildren's lives and you have just buggered off and left it.'

'Variant' nonsense

Some of his most powerful comments related to the alleged 'variants' being used to instil more fear, justify more lockdowns, and introduce more 'vaccines'. He said government claims about 'variants' were nonsense. He had checked the alleged variant 'codes' and they were 99.7 percent identical to the 'original'. This was the human identity difference equivalent to putting a baseball cap on and off or wearing it the other way round. A 0.3 percent difference would make it impossible for that 'variant' to escape immunity from the 'original'. This made no sense of having new 'vaccines' for

'variants'. He said there would have to be at least a *30 percent* difference for that to be justified and even then he believed the immune system would still recognise what it was. Gates-funded 'variant modeller' and 'vaccine'-pusher John Edmunds might care to comment. Yeadon said drug companies were making new versions of the 'vaccine' as a 'top up' for 'variants'. Worse than that, he said, the 'regulators' around the world like the MHRA in the UK had got together and agreed that because 'vaccines' for 'variants' were so similar to the first 'vaccines' *they did not have to do safety studies*. How transparently sinister that is. This is when Yeadon said: 'There is a conspiracy here.' There was no need for another vaccine for 'variants' and yet we were told that there was and the country had shut its borders because of them. 'They are going into hundreds of millions of arms without passing 'go' or any regulator. Why did they do that? Why did they pick this method of making the vaccine?'

The reason had to be something bigger than that it seemed and 'it's not protection against the virus'. It's was a far bigger project that meant politicians and advisers were willing to do things and not do things that knowingly resulted in avoidable deaths – 'that's already happened when you think about lockdown and deprivation of health care for a year.' He spoke of people prepared to do something that results in the avoidable death of their fellow human beings and it not bother them. This is the penny-drop I have been working to get across for more than 30 years – the level of pure evil we are dealing with. Yeadon said his friends and associates could not believe there could be that much evil, but he reminded them of Stalin, Pol Pot and Hitler and of what Stalin had said: 'One death is a tragedy. A million? A statistic.' He could not think of a benign explanation for why you need top-up vaccines 'which I'm sure you don't' and for the regulators 'to just get out of the way and wave them through'. Why would the regulators do that when they were still wrestling with the dangers of the 'parent' vaccine? He was clearly shocked by what he had seen since the 'Covid' hoax began and now he was thinking the previously unthinkable:

If you wanted to depopulate a significant proportion of the world and to do it in a way that doesn't involve destruction of the environment with nuclear weapons, poisoning everyone with anthrax or something like that, and you wanted plausible deniability while you had a multi-year infectious disease crisis, I actually don't think you could come up with a better plan of work than seems to be in front of me. I can't say that's what they are going to do, but I can't think of a benign explanation why they are doing it.

He said he never thought that they would get rid of 99 percent of humans, but now he wondered. 'If you wanted to that this would be a hell of a way to do it – it would be unstoppable folks.' Yeadon had concluded that those who submitted to the 'vaccine' would be allowed to have some kind of normal life (but for how long?) while screws were tightened to coerce and mandate the last few percent. 'I think they'll put the rest of them in a prison camp. I wish I was wrong, but I don't think I am.' Other points he made included: There were no coronavirus vaccines then suddenly they all come along at the same time; we have no idea of the long term affect with trials so short; coercing or forcing people to have medical procedures is against the Nuremberg Code instigated when the Nazis did just that; people should at least delay having the 'vaccine'; a quick Internet search confirms that masks don't reduce respiratory viral transmission and 'the government knows that'; they have smashed civil society and they know that, too; two dozen peer-reviewed studies show no connection between lockdown and reducing deaths; he knew from personal friends the elite were still flying around and going on holiday while the public were locked down; the elite were not having the 'vaccines'. He was also asked if 'vaccines' could be made to target difference races. He said he didn't know, but the document by the Project for the New American Century in September, 2000, said developing 'advanced forms of biological warfare that can target *specific genotypes* may transform biological warfare from the realm of terror to a politically useful tool.' Oh, they're evil all right. Of that we can be *absolutely* sure.

Another cull of old people

We have seen from the CDC definition that the mRNA 'Covid vaccine' is not a vaccine and nor are the others that *claim* to reduce 'severity of symptoms' in *some* people, but not protect from infection or transmission. What about all the lies about returning to 'normal' if people were 'vaccinated'? If they are not claimed to stop infection and transmission of the alleged 'virus', how does anything change? This was all lies to manipulate people to take the jabs and we are seeing that now with masks and distancing still required for the 'vaccinated'. How did they think that elderly people with fragile health and immune responses were going to be affected by infusing their cells with synthetic material and other toxic substances? They *knew* that in the short and long term it would be devastating and fatal as the culling of the old that began with the first lockdowns was continued with the 'vaccine'. Death rates in care homes soared immediately residents began to be 'vaccinated' – infused with synthetic material. Brave and committed whistleblower nurses put their careers at risk by exposing this truth while the rest kept their heads down and their mouths shut to put their careers before those they are supposed to care for. A long-time American Certified Nursing Assistant who gave his name as James posted a video in which he described emotionally what happened in his care home when vaccination began. He said that during 2020 very few residents were sick with 'Covid' and no one died during the entire year; but shortly after the Pfizer mRNA injections 14 people died within two weeks and many others were near death. 'They're dropping like flies', he said. Residents who walked on their own before the shot could no longer and they had lost their ability to conduct an intelligent conversation. The home's management said the sudden deaths were caused by a 'super-spreader' of 'Covid-19'. Then how come, James asked, that residents who refused to take the injections were not sick? It was a case of inject the elderly with mRNA synthetic potions and blame their illness and death that followed on the 'virus'. James described what was happening in care homes as 'the greatest crime of genocide this country has ever seen'. Remember the NHS staff nurse from earlier who used the same

word ‘genocide’ for what was happening with the ‘vaccines’ and that it was an ‘act of human annihilation’. A UK care home whistleblower told a similar story to James about the effect of the ‘vaccine’ in deaths and ‘outbreaks’ of illness dubbed ‘Covid’ after getting the jab. She told how her care home management and staff had zealously imposed government regulations and no one was allowed to even question the official narrative let alone speak out against it. She said the NHS was even worse. Again we see the results of reframing. A worker at a local care home where I live said they had not had a single case of ‘Covid’ there for almost a year and when the residents were ‘vaccinated’ they had 19 positive cases in two weeks with eight dying.

It’s not the ‘vaccine’ – honest

The obvious cause and effect was being ignored by the media and most of the public. Australia’s health minister Greg Hunt (a former head of strategy at the World Economic Forum) was admitted to hospital after he had the ‘vaccine’. He was suffering according to reports from the skin infection ‘cellulitis’ and it must have been a severe case to have warranted days in hospital. Immediately the authorities said this was nothing to do with the ‘vaccine’ when an effect of some vaccines is a ‘cellulitis-like reaction’. We had families of perfectly healthy old people who died after the ‘vaccine’ saying that if only they had been given the ‘vaccine’ earlier they would still be alive. As a numbskull rating that is off the chart. A father of four ‘died of Covid’ at aged 48 when he was taken ill two days after having the ‘vaccine’. The man, a health administrator, had been ‘shielding during the pandemic’ and had ‘not really left the house’ until he went for the ‘vaccine’. Having the ‘vaccine’ and then falling ill and dying does not seem to have qualified as a possible cause and effect and ‘Covid-19’ went on his death certificate. His family said they had no idea how he ‘caught the virus’. A family member said: ‘Tragically, it could be that going for a vaccination ultimately led to him catching Covid …The sad truth is that they are never going to know where it came from.’ The family warned people to remember

that the virus still existed and was 'very real'. So was their stupidity. Nurses and doctors who had the first round of the 'vaccine' were collapsing, dying and ending up in a hospital bed while they or their grieving relatives were saying they'd still have the 'vaccine' again despite what happened. I kid you not. You mean if your husband returned from the dead he'd have the same 'vaccine' again that killed him??

Doctors at the VCU Medical Center in Richmond, Virginia, said the Johnson & Johnson 'vaccine' was to blame for a man's skin peeling off. Patient Richard Terrell said: 'It all just happened so fast. My skin peeled off. It's still coming off on my hands now.' He said it was stinging, burning and itching and when he bent his arms and legs it was very painful with 'the skin swollen and rubbing against itself'. Pfizer/BioNTech and Moderna vaccines use mRNA to change the cell while the Johnson & Johnson version uses DNA in a process similar to AstraZeneca's technique. Johnson & Johnson and AstraZeneca have both had their 'vaccines' paused by many countries after causing serious blood problems. Terrell's doctor Fnu Nutan said he could have died if he hadn't got medical attention. It sounds terrible so what did Nutan and Terrell say about the 'vaccine' now? Oh, they still recommend that people have it. A nurse in a hospital bed 40 minutes after the vaccination and unable to swallow due to throat swelling was told by a doctor that he lost mobility in his arm for 36 hours following the vaccination. What did he say to the ailing nurse? 'Good for you for getting the vaccination.' We are dealing with a serious form of cognitive dissonance madness in both public and medical staff. There is a remarkable correlation between those having the 'vaccine' and trumpeting the fact and suffering bad happenings shortly afterwards. Witold Rogiewicz, a Polish doctor, made a video of his 'vaccination' and ridiculed those who were questioning its safety and the intentions of Bill Gates: 'Vaccinate yourself to protect yourself, your loved ones, friends and also patients. And to mention quickly I have info for anti-vaxxers and anti-Coviders if you want to contact Bill Gates you can do this through me.' He further ridiculed the dangers of 5G. Days later he

was dead, but naturally the vaccination wasn't mentioned in the verdict of 'heart attack'.

Lies, lies and more lies

So many members of the human race have slipped into extreme states of insanity and unfortunately they include reframed doctors and nursing staff. Having a 'vaccine' and dying within minutes or hours is not considered a valid connection while death from any cause within 28 days or longer of a positive test with a test not testing for the 'virus' means 'Covid-19' goes on the death certificate. How could that 'vaccine'-death connection not have been made except by calculated deceit? US figures in the initial rollout period to February 12th, 2020, revealed that a third of the deaths reported to the CDC after 'Covid vaccines' happened within 48 hours. Five men in the UK suffered an 'extremely rare' blood clot problem after having the AstraZeneca 'vaccine', but no causal link was established said the Gates-funded Medicines and Healthcare products Regulatory Agency (MHRA) which had given the 'vaccine' emergency approval to be used. Former Pfizer executive Dr Michael Yeadon explained in his interview how the procedures could cause blood coagulation and clots. People who should have been at no risk were dying from blood clots in the brain and he said he had heard from medical doctor friends that people were suffering from skin bleeding and massive headaches. The AstraZeneca 'shot' was stopped by some 20 countries over the blood clotting issue and still the corrupt MHRA, the European Medicines Agency (EMA) and the World Health Organization said that it should continue to be given even though the EMA admitted that it 'still cannot rule out definitively' a link between blood clotting and the 'vaccine'. Later Marco Cavaleri, head of EMA vaccine strategy, said there was indeed a clear link between the 'vaccine' and thrombosis, but they didn't know why. So much for the trials showing the 'vaccine' is safe. Blood clots were affecting younger people who would be under virtually no danger from 'Covid' even if it existed which makes it all the more stupid and sinister.

The British government responded to public alarm by wheeling out June Raine, the terrifyingly weak infant school headmistress sound-alike who heads the UK MHRA drug 'regulator'. The idea that she would stand up to Big Pharma and government pressure is laughable and she told us that all was well in the same way that she did when allowing untested, never-used-on-humans-before, genetically-manipulating 'vaccines' to be exposed to the public in the first place. Mass lying is the new normal of the 'Covid' era. The MHRA later said 30 cases of rare blood clots had by then been connected with the AstraZeneca 'vaccine' (that means a lot more in reality) while stressing that the benefits of the jab in preventing 'Covid-19' outweighed any risks. A more ridiculous and disingenuous statement with callous disregard for human health it is hard to contemplate. Immediately after the mendacious 'all-clears' two hospital workers in Denmark experienced blood clots and cerebral haemorrhaging following the AstraZeneca jab and one died. Top Norwegian health official Pål Andre Holme said the 'vaccine' was the only common factor: 'There is nothing in the patient history of these individuals that can give such a powerful immune response … I am confident that the antibodies that we have found are the cause, and I see no other explanation than it being the vaccine which triggers it.' Strokes, a clot or bleed in the brain, were clearly associated with the 'vaccine' from word of mouth and whistleblower reports. Similar consequences followed with all these 'vaccines' that we were told were so safe and as the numbers grew by the day it was clear we were witnessing human carnage.

Learning the hard way

A woman interviewed by UKColumn told how her husband suffered dramatic health effects after the vaccine when he'd been in good health all his life. He went from being a little unwell to losing all feeling in his legs and experiencing 'excruciating pain'. Misdiagnosis followed twice at Accident and Emergency (an 'allergy' and 'sciatica') before he was admitted to a neurology ward where doctors said his serious condition had been caused by the

'vaccine'. Another seven 'vaccinated' people were apparently being treated on the same ward for similar symptoms. The woman said he had the 'vaccine' because they believed media claims that it was safe. 'I didn't think the government would give out a vaccine that does this to somebody; I believed they would be bringing out a vaccination that would be safe.' What a tragic way to learn that lesson. Another woman posted that her husband was transporting stroke patients to hospital on almost every shift and when he asked them if they had been 'vaccinated' for 'Covid' they all replied 'yes'. One had a 'massive brain bleed' the day after his second dose. She said her husband reported the 'just been vaccinated' information every time to doctors in A and E only for them to ignore it, make no notes and appear annoyed that it was even mentioned. This particular report cannot be verified, but it expresses a common theme that confirms the monumental underreporting of 'vaccine' consequences. Interestingly as the 'vaccines' and their brain blood clot/stroke consequences began to emerge the UK National Health Service began a publicity campaign telling the public what to do in the event of a stroke. A Scottish NHS staff nurse who quit in disgust in March, 2021, said:

I have seen traumatic injuries from the vaccine, they're not getting reported to the yellow card [adverse reaction] scheme, they're treating the symptoms, not asking why, why it's happening. It's just treating the symptoms and when you speak about it you're dismissed like you're crazy, I'm not crazy, I'm not crazy because every other colleague I've spoken to is terrified to speak out, they've had enough.

Videos appeared on the Internet of people uncontrollably shaking after the 'vaccine' with no control over muscles, limbs and even their face. A Scottish mother broke out in a severe rash all over her body almost immediately after she was given the AstraZeneca 'vaccine'. The pictures were horrific. Leigh King, a 41-year-old hairdresser from Lanarkshire said: 'Never in my life was I prepared for what I was about to experience … My skin was so sore and constantly hot … I have never felt pain like this …' But don't you worry, the 'vaccine' is perfectly safe. Then there has been the effect on medical

staff who have been pressured to have the 'vaccine' by psychopathic 'health' authorities and government. A London hospital consultant who gave the name K. Polyakova wrote this to the *British Medical Journal* or *BMJ*:

> I am currently struggling with … the failure to report the reality of the morbidity caused by our current vaccination program within the health service and staff population. The levels of sickness after vaccination is unprecedented and staff are getting very sick and some with neurological symptoms which is having a huge impact on the health service function. Even the young and healthy are off for days, some for weeks, and some requiring medical treatment. Whole teams are being taken out as they went to get vaccinated together.
>
> Mandatory vaccination in this instance is stupid, unethical and irresponsible when it comes to protecting our staff and public health. We are in the voluntary phase of vaccination, and encouraging staff to take an unlicensed product that is impacting on their immediate health … it is clearly stated that these vaccine products do not offer immunity or stop transmission. In which case why are we doing it?

Not to protect health that's for sure. Medical workers are lauded by governments for agenda reasons when they couldn't give a toss about them any more than they can for the population in general. Schools across America faced the same situation as they closed due to the high number of teachers and other staff with bad reactions to the Pfizer/BioNTech, Moderna, and Johnson & Johnson 'Covid vaccines' all of which were linked to death and serious adverse effects. The *BMJ* took down the consultant's comments pretty quickly on the grounds that they were being used to spread 'disinformation'. They were exposing the truth about the 'vaccine' was the real reason. The cover-up is breathtaking.

Hiding the evidence

The scale of the 'vaccine' death cover-up worldwide can be confirmed by comparing official figures with the personal experience of the public. I heard of many people in my community who died immediately or soon after the vaccine that would never appear in the media or even likely on the official totals of 'vaccine' fatalities and adverse reactions when only about ten percent are estimated to be

reported and I have seen some estimates as low as one percent in a Harvard study. In the UK alone by April 29th, 2021, some 757,654 adverse reactions had been officially reported from the Pfizer/BioNTech, Oxford/AstraZeneca and Moderna 'vaccines' with more than a thousand deaths linked to jabs and that means an estimated ten times this number in reality from a ten percent reporting rate percentage. That's seven million adverse reactions and 10,000 potential deaths and a one percent reporting rate would be ten times *those* figures. In 1976 the US government pulled the swine flu vaccine after *53* deaths. The UK data included a combined 10,000 eye disorders from the 'Covid vaccines' with more than 750 suffering visual impairment or blindness and again multiply by the estimated reporting percentages. As 'Covid cases' officially fell hospitals virtually empty during the 'Covid crisis' began to fill up with a range of other problems in the wake of the 'vaccine' rollout. The numbers across America have also been catastrophic. Deaths linked to *all* types of vaccine increased by *6,000 percent* in the first quarter of 2021 compared with 2020. A 39-year-old woman from Ogden, Utah, died four days after receiving a second dose of Moderna's 'Covid vaccine' when her liver, heart and kidneys all failed despite the fact that she had no known medical issues or conditions. Her family sought an autopsy, but Dr Erik Christensen, Utah's chief medical examiner, said proving vaccine injury as a cause of death almost never happened. He could think of only one instance where an autopsy would name a vaccine as the official cause of death and that would be anaphylaxis where someone received a vaccine and died almost instantaneously. 'Short of that, it would be difficult for us to definitively say this is the vaccine,' Christensen said. If that is true this must be added to the estimated ten percent (or far less) reporting rate of vaccine deaths and serious reactions and the conclusion can only be that vaccine deaths and serious reactions – including these 'Covid' potions' – are phenomenally understated in official figures. The same story can be found everywhere. Endless accounts of deaths and serious reactions among the public, medical

and care home staff while official figures did not even begin to reflect this.

Professional script-reader Dr David Williams, a 'top public-health official' in Ontario, Canada, insulted our intelligence by claiming only four serious adverse reactions and no deaths from the more than 380,000 vaccine doses then given. This bore no resemblance to what people knew had happened in their owns circles and we had Dirk Huyer in charge of getting millions vaccinated in Ontario while at the same time he was Chief Coroner for the province investigating causes of death including possible death from the vaccine. An aide said he had stepped back from investigating deaths, but evidence indicated otherwise. Rosemary Frei, who secured a Master of Science degree in molecular biology at the Faculty of Medicine at Canada's University of Calgary before turning to investigative journalism, was one who could see that official figures for 'vaccine' deaths and reactions made no sense. She said that doctors seldom reported adverse events and when people got really sick or died after getting a vaccination they would attribute that to anything except the vaccines. It had been that way for years and anyone who wondered aloud whether the 'Covid vaccines' or other shots cause harm is immediately branded as 'anti-vax' and 'anti-science'. This was 'career-threatening' for health professionals. Then there was the huge pressure to support the push to 'vaccinate' billions in the quickest time possible. Frei said:

> So that's where we're at today. More than half a million vaccine doses have been given to people in Ontario alone. The rush is on to vaccinate all 15 million of us in the province by September. And the mainstream media are screaming for this to be sped up even more. That all adds up to only a very slim likelihood that we're going to be told the truth by officials about how many people are getting sick or dying from the vaccines.

What is true of Ontario is true of everywhere.

They KNEW – and still did it

The authorities knew what was going to happen with multiple deaths and adverse reactions. The UK government's Gates-funded

and Big Pharma-dominated Medicines and Healthcare products Regulatory Agency (MHRA) hired a company to employ AI in compiling the projected reactions to the 'vaccine' that would otherwise be uncountable. The request for applications said: 'The MHRA urgently seeks an Artificial Intelligence (AI) software tool to process the expected high volume of Covid-19 vaccine Adverse Drug Reaction …' This was from the agency, headed by the disingenuous June Raine, that gave the 'vaccines' emergency approval and the company was hired before the first shot was given. 'We are going to kill and maim you – is that okay?' 'Oh, yes, perfectly fine – I'm very grateful, thank you, doctor.' The range of 'Covid vaccine' adverse reactions goes on for page after page in the MHRA criminally underreported 'Yellow Card' system and includes affects to eyes, ears, skin, digestion, blood and so on. Raine's MHRA amazingly claimed that the 'overall safety experience … is so far as expected from the clinical trials'. The death, serious adverse effects, deafness and blindness were *expected?* When did they ever mention that? If these human tragedies were expected then those that gave approval for the use of these 'vaccines' must be guilty of crimes against humanity including murder – a definition of which is 'killing a person with malice aforethought or with recklessness manifesting extreme indifference to the value of human life.' People involved at the MHRA, the CDC in America and their equivalent around the world must go before Nuremberg trials to answer for their callous inhumanity. We are only talking here about the immediate effects of the 'vaccine'. The longer-term impact of the DNA synthetic manipulation is the main reason they are so hysterically desperate to inoculate the entire global population in the shortest possible time.

Africa and the developing world are a major focus for the 'vaccine' depopulation agenda and a mass vaccination sales-pitch is underway thanks to caring people like the Rockefellers and other Cult assets. The Rockefeller Foundation, which pre-empted the 'Covid pandemic' in a document published in 2010 that 'predicted' what happened a decade later, announced an initial $34.95 million grant in February, 2021, 'to ensure more equitable access to Covid-19

testing and vaccines' among other things in Africa in collaboration with '24 organizations, businesses, and government agencies'. The pan-Africa initiative would focus on 10 countries: Burkina Faso, Ethiopia, Ghana, Kenya, Nigeria, Rwanda, South Africa, Tanzania, Uganda, and Zambia'. Rajiv Shah, President of the Rockefeller Foundation and former administrator of CIA-controlled USAID, said that if Africa was not mass-vaccinated (to change the DNA of its people) it was a 'threat to all of humanity' and not fair on Africans. When someone from the Rockefeller Foundation says they want to do something to help poor and deprived people and countries it is time for a belly-laugh. They are doing this out of the goodness of their 'heart' because 'vaccinating' the entire global population is what the 'Covid' hoax set out to achieve. Official 'decolonisation' of Africa by the Cult was merely a prelude to financial colonisation on the road to a return to physical colonisation. The 'vaccine' is vital to that and the sudden and convenient death of the 'Covid' sceptic president of Tanzania can be seen in its true light. A lot of people in Africa are aware that this is another form of colonisation and exploitation and they need to stand their ground.

The 'vaccine is working' scam

A potential problem for the Cult was that the 'vaccine' is meant to change human DNA and body messaging and not to protect anyone from a 'virus' never shown to exist. The vaccine couldn't work because it was not designed to work and how could they make it *appear* to be working so that more people would have it? This was overcome by lowering the amplification rate of the PCR test to produce fewer 'cases' and therefore fewer 'deaths'. Some of us had been pointing out since March, 2020, that the amplification rate of the test not testing for the 'virus' had been made artificially high to generate positive tests which they could call 'cases' to justify lockdowns. The World Health Organization recommended an absurdly high 45 amplification cycles to ensure the high positives required by the Cult and then remained silent on the issue until January 20th, 2021 – Biden's Inauguration Day. This was when the

'vaccinations' were seriously underway and on that day the WHO recommended after discussions with America's CDC that laboratories *lowered their testing amplification*. Dr David Samadi, a certified urologist and health writer, said the WHO was encouraging all labs to reduce their cycle count for PCR tests. He said the current cycle was much too high and was 'resulting in any particle being declared a positive case'. Even one mainstream news report I saw said this meant the number of 'Covid' infections may have been 'dramatically inflated'. Oh, just a little bit. The CDC in America issued new guidance to laboratories in April, 2021, to use 28 cycles *but only for 'vaccinated' people*. The timing of the CDC/WHO interventions were cynically designed to make it appear the 'vaccines' were responsible for falling cases and deaths when the real reason can be seen in the following examples. New York's state lab, the Wadsworth Center, identified 872 positive tests in July, 2020, based on a threshold of 40 cycles. When the figure was lowered to 35 cycles *43 percent* of the 872 were no longer 'positives'. At 30 cycles the figure was 63 percent. A Massachusetts lab found that between *85 to 90 percent* of people who tested positive in July with a cycle threshold of 40 would be negative at 30 cycles, Ashish Jha, MD, director of the Harvard Global Health Institute, said: 'I'm really shocked that it could be that high … Boy, does it really change the way we need to be thinking about testing.' I'm shocked that I could see the obvious in the spring of 2020, with no medical background, and most medical professionals still haven't worked it out. No, that's not shocking – it's terrifying.

Three weeks after the WHO directive to lower PCR cycles the London *Daily Mail* ran this headline: 'Why ARE Covid cases plummeting? New infections have fallen 45% in the US and 30% globally in the past 3 weeks but experts say vaccine is NOT the main driver because only 8% of Americans and 13% of people worldwide have received their first dose.' They acknowledged that the drop could not be attributed to the 'vaccine', but soon this morphed throughout the media into the 'vaccine' has caused cases and deaths to fall when it was the PCR threshold. In December, 2020, there was

chaos at English Channel ports with truck drivers needing negative 'Covid' tests before they could board a ferry home for Christmas. The government wanted to remove the backlog as fast as possible and they brought in troops to do the 'testing'. Out of 1,600 drivers just *36* tested positive and the rest were given the all clear to cross the Channel. I guess the authorities thought that 36 was the least they could get away with without the unquestioning catching on. The amplification trick which most people believed in the absence of information in the mainstream applied more pressure on those refusing the 'vaccine' to succumb when it 'obviously worked'. The truth was the exact opposite with deaths in care homes soaring with the 'vaccine' and in Israel the term used was 'skyrocket'. A re-analysis of published data from the Israeli Health Ministry led by Dr Hervé Seligmann at the Medicine Emerging Infectious and Tropical Diseases at Aix-Marseille University found that Pfizer's 'Covid vaccine' killed 'about 40 times more [elderly] people than the disease itself would have killed' during a five-week vaccination period and *260 times* more younger people than would have died from the 'virus' even according to the manipulated 'virus' figures. Dr Seligmann and his co-study author, Haim Yativ, declared after reviewing the Israeli 'vaccine' death data: 'This is a new Holocaust.'

Then, in mid-April, 2021, after vast numbers of people worldwide had been 'vaccinated', the story changed with clear coordination. The UK government began to prepare the ground for more future lockdowns when Nuremberg-destined Boris Johnson told yet another whopper. He said that cases had fallen because of *lockdowns* not 'vaccines'. Lockdowns are irrelevant when *there is no 'virus'* and the test and fraudulent death certificates are deciding the number of 'cases' and 'deaths'. Study after study has shown that lockdowns don't work and instead kill and psychologically destroy people. Meanwhile in the United States Anthony Fauci and Rochelle Walensky, the ultra-Zionist head of the CDC, peddled the same line. More lockdown was the answer and not the 'vaccine', a line repeated on cue by the moron that is Canadian Prime Minister Justin Trudeau. Why all the hysteria to get everyone 'vaccinated' if lockdowns and

not 'vaccines' made the difference? None of it makes sense on the face of it. Oh, but it does. The Cult wants lockdowns *and* the 'vaccine' and if the 'vaccine' is allowed to be seen as the total answer lockdowns would no longer be justified when there are still livelihoods to destroy. 'Variants' and renewed upward manipulation of PCR amplification are planned to instigate never-ending lockdown *and* more 'vaccines'.

You *must* have it – we're desperate

Israel, where the Jewish and Arab population are ruled by the Sabbatian Cult, was the front-runner in imposing the DNA-manipulating 'vaccine' on its people to such an extent that Jewish refusers began to liken what was happening to the early years of Nazi Germany. This would seem to be a fantastic claim. Why would a government of Jewish people be acting like the Nazis did? If you realise that the Sabbatian Cult was behind the Nazis and that Sabbatians hate Jews the pieces start to fit and the question of why a 'Jewish' government would treat Jews with such callous disregard for their lives and freedom finds an answer. Those controlling the government of Israel *aren't Jewish* – they're Sabbatian. Israeli lawyer Tamir Turgal was one who made the Nazi comparison in comments to German lawyer Reiner Fuellmich who is leading a class action lawsuit against the psychopaths for crimes against humanity. Turgal described how the Israeli government was vaccinating children and pregnant women on the basis that there was no evidence that this was dangerous when they had no evidence that it *wasn't* dangerous either. They just had no evidence. This was medical experimentation and Turgal said this breached the Nuremberg Code about medical experimentation and procedures requiring informed consent and choice. Think about that. A Nuremberg Code developed because of Nazi experimentation on Jews and others in concentration camps by people like the evil-beyond-belief Josef Mengele is being breached by the *Israeli* government; but when you know that it's a *Sabbatian* government along with its intelligence and military agencies like Mossad, Shin Bet and the Israeli Defense Forces, and that Sabbatians

were the force behind the Nazis, the kaleidoscope comes into focus. What have we come to when Israeli Jews are suing their government for violating the Nuremberg Code by essentially making Israelis subject to a medical experiment using the controversial 'vaccines'? It's a shocker that this has to be done in the light of what happened in Nazi Germany. The Anshe Ha-Emet, or 'People of the Truth', made up of Israeli doctors, lawyers, campaigners and public, have launched a lawsuit with the International Criminal Court. It says:

> When the heads of the Ministry of Health as well as the prime minister presented the vaccine in Israel and began the vaccination of Israeli residents, the vaccinated were not advised, that, in practice, they are taking part in a medical experiment and that their consent is required for this under the Nuremberg Code.

The irony is unbelievable, but easily explained in one word: Sabbatians. The foundation of Israeli 'Covid' apartheid is the 'green pass' or 'green passport' which allows Jews and Arabs who have had the DNA-manipulating 'vaccine' to go about their lives – to work, fly, travel in general, go to shopping malls, bars, restaurants, hotels, concerts, gyms, swimming pools, theatres and sports venues, while non-'vaccinated' are banned from all those places and activities. Israelis have likened the 'green pass' to the yellow stars that Jews in Nazi Germany were forced to wear – the same as the yellow stickers that a branch of UK supermarket chain Morrisons told exempt mask-wears they had to display when shopping. How very sensitive. The Israeli system is blatant South African-style apartheid on the basis of compliance or non-compliance to fascism rather than colour of the skin. How appropriate that the Sabbatian Israeli government was so close to the pre-Mandela apartheid regime in Pretoria. The Sabbatian-instigated 'vaccine passport' in Israel is planned for everywhere. Sabbatians struck a deal with Pfizer that allowed them to lead the way in the percentage of a national population infused with synthetic material and the result was catastrophic. Israeli freedom activist Shai Dannon told me how chairs were appearing on beaches that said 'vaccinated only'. Health Minister Yuli Edelstein said that anyone unwilling or unable to get

the jabs that 'confer immunity' will be 'left behind'. The man's a liar. Not even the makers claim the 'vaccines' confer immunity. When you see those figures of 'vaccine' deaths these psychopaths were saying that you must take the chance the 'vaccine' will kill you or maim you while knowing it will change your DNA or lockdown for you will be permanent. That's fascism. The Israeli parliament passed a law to allow personal information of the non-vaccinated to be shared with local and national authorities for three months. This was claimed by its supporters to be a way to 'encourage' people to be vaccinated. Hadas Ziv from Physicians for Human Rights described this as a 'draconian law which crushed medical ethics and the patient rights'. But that's the idea, the Sabbatians would reply.

Your papers, please

Sabbatian Israel was leading what has been planned all along to be a global 'vaccine pass' called a 'green passport' without which you would remain in permanent lockdown restriction and unable to do anything. This is how badly – *desperately* – the Cult is to get everyone 'vaccinated'. The term and colour 'green' was not by chance and related to the psychology of fusing the perception of the green climate hoax with the 'Covid' hoax and how the 'solution' to both is the same Great Reset. Lying politicians, health officials and psychologists denied there were any plans for mandatory vaccinations or restrictions based on vaccinations, but they knew that was exactly what was meant to happen with governments of all countries reaching agreements to enforce a global system. 'Free' Denmark and 'free' Sweden unveiled digital vaccine certification. Cyprus, Czech Republic, Estonia, Greece, Hungary, Iceland, Italy, Poland, Portugal, Slovakia, and Spain have all committed to a vaccine passport system and the rest including the whole of the EU would follow. The satanic UK government will certainly go this way despite mendacious denials and at the time of writing it is trying to manipulate the public into having the 'vaccine' so they could go abroad on a summer holiday. How would that work without something to prove you had the synthetic toxicity injected into you?

Documents show that the EU's European Commission was moving towards 'vaccine certificates' in 2018 and 2019 before the 'Covid' hoax began. They knew what was coming. Abracadabra – Ursula von der Leyen, the German President of the Commission, announced in March, 2021, an EU 'Digital Green Certificate' – green again – to track the public's 'Covid status'. The passport sting is worldwide and the Far East followed the same pattern with South Korea ruling that only those with 'vaccination' passports – again the *green* pass – would be able to 'return to their daily lives'.

Bill Gates has been preparing for this 'passport' with other Cult operatives for years and beyond the paper version is a Gates-funded 'digital tattoo' to identify who has been vaccinated and who hasn't. The 'tattoo' is reported to include a substance which is externally readable to confirm who has been vaccinated. This is a bio-luminous light-generating enzyme (think fireflies) called … *Luciferase*. Yes, named after the Cult 'god' Lucifer the 'light bringer' of whom more to come. Gates said he funded the readable tattoo to ensure children in the developing world were vaccinated and no one was missed out. He cares so much about poor kids as we know. This was just the cover story to develop a vaccine tagging system for everyone on the planet. Gates has been funding the ID2020 'alliance' to do just that in league with other lovely people at Microsoft, GAVI, the Rockefeller Foundation, Accenture and IDEO.org. He said in interviews in March, 2020, before any 'vaccine' publicly existed, that the world must have a globalised digital certificate to track the 'virus' and who had been vaccinated. Gates knew from the start that the mRNA vaccines were coming and when they would come and that the plan was to tag the 'vaccinated' to marginalise the intelligent and stop them doing anything including travel. Evil just doesn't suffice. Gates was exposed for offering a $10 million bribe to the Nigerian House of Representatives to invoke compulsory 'Covid' vaccination of all Nigerians. Sara Cunial, a member of the Italian Parliament, called Gates a 'vaccine criminal'. She urged the Italian President to hand him over to the International Criminal Court for crimes against

humanity and condemned his plans to 'chip the human race' through ID2020.

You know it's a long-planned agenda when war criminal and Cult gofer Tony Blair is on the case. With the scale of arrogance only someone as dark as Blair can muster he said: 'Vaccination in the end is going to be your route to liberty.' Blair is a disgusting piece of work and he confirms that again. The media has given a lot of coverage to a bloke called Charlie Mullins, founder of London's biggest independent plumbing company, Pimlico Plumbers, who has said he won't employ anyone who has not been vaccinated or have them go to any home where people are not vaccinated. He said that if he had his way no one would be allowed to walk the streets if they have not been vaccinated. Gates was cheering at the time while I was alerting the white coats. The plan is that people will qualify for 'passports' for having the first two doses and then to keep it they will have to have all the follow ups and new ones for invented 'variants' until human genetics is transformed and many are dead who can't adjust to the changes. Hollywood celebrities – the usual propaganda stunt – are promoting something called the WELL Health-Safety Rating to verify that a building or space has 'taken the necessary steps to prioritize the health and safety of their staff, visitors and other stakeholders'. They included Lady Gaga, Jennifer Lopez, Michael B. Jordan, Robert DeNiro, Venus Williams, Wolfgang Puck, Deepak Chopra and 17th Surgeon General Richard Carmona. Yawn. WELL Health-Safety has big connections with China. Parent company Delos is headed by former Goldman Sachs partner Paul Scialla. This is another example – and we will see so many others – of using the excuse of 'health' to dictate the lives and activities of the population. I guess one confirmation of the 'safety' of buildings is that only 'vaccinated' people can go in, right?

Electronic concentration camps

I wrote decades ago about the plans to restrict travel and here we are for those who refuse to bow to tyranny. This can be achieved in one go with air travel if the aviation industry makes a blanket decree.

The ‘vaccine’ and guaranteed income are designed to be part of a global version of China’s social credit system which tracks behaviour 24/7 and awards or deletes ‘credits’ based on whether your behaviour is supported by the state or not. I mean your entire lifestyle – what you do, eat, say, everything. Once your credit score falls below a certain level consequences kick in. In China tens of millions have been denied travel by air and train because of this. All the locations and activities denied to refusers by the ‘vaccine’ passports will be included in one big mass ban on doing almost anything for those that don’t bow their head to government. It’s beyond fascist and a new term is required to describe its extremes – I guess fascist technocracy will have to do. The way the Chinese system of technological – technocratic – control is sweeping the West can be seen in the Los Angeles school system and is planned to be expanded worldwide. Every child is required to have a ‘Covid’-tracking app scanned daily before they can enter the classroom. The so-called Daily Pass tracking system is produced by Gates’ Microsoft which I’m sure will shock you rigid. The pass will be scanned using a barcode (one step from an inside-the-body barcode) and the information will include health checks, ‘Covid’ tests and vaccinations. Entry codes are for one specific building only and access will only be allowed if a student or teacher has a negative test with a test not testing for the ‘virus’, has no symptoms of anything alleged to be related to ‘Covid’ (symptoms from a range of other illness), and has a temperature under 100 degrees. No barcode, no entry, is planned to be the case for everywhere and not only schools.

Kids are being psychologically prepared to accept this as ‘normal’ their whole life which is why what they can impose in schools is so important to the Cult and its gofers. Long-time American freedom campaigner John Whitehead of the Rutherford Institute was not exaggerating when he said: ‘Databit by databit, we are building our own electronic concentration camps.’ Canada under its Cult gofer prime minister Justin Trudeau has taken a major step towards the real thing with people interned against their will if they test positive with a test not testing for the ‘virus’ when they arrive at a Canadian

airport. They are jailed in internment hotels often without food or water for long periods and with many doors failing to lock there have been sexual assaults. The interned are being charged sometimes $2,000 for the privilege of being abused in this way. Trudeau is fully on board with the Cult and says the 'Covid pandemic' has provided an opportunity for a global 'reset' to permanently change Western civilisation. His number two, Deputy Prime Minister Chrystia Freeland, is a trustee of the World Economic Forum and a Rhodes Scholar. The Trudeau family have long been servants of the Cult. See *The Biggest Secret* and Cathy O'Brien's book *Trance-Formation of America* for the horrific background to Trudeau's father Pierre Trudeau another Canadian prime minister. Hide your fascism behind the façade of a heart-on-the-sleeve liberal. It's a well-honed Cult technique.

What can the 'vaccine' *really* do?

We have a 'virus' never shown to exist and 'variants' of the 'virus' that have also never been shown to exist except, like the 'original', as computer-generated fictions. Even if you believe there's a 'virus' the 'case' to 'death' rate is in the region of 0.23 to 0.15 percent and those 'deaths' are concentrated among the very old around the same average age that people die anyway. In response to this lack of threat (in truth none) psychopaths and idiots, knowingly and unknowingly answering to Gates and the Cult, are seeking to 'vaccinate' every man, woman and child on Planet Earth. Clearly the 'vaccine' is not about 'Covid' – none of this ever has been. So what is it all about *really*? Why the desperation to infuse genetically-manipulating synthetic material into everyone through mRNA fraudulent 'vaccines' with the intent of doing this over and over with the excuses of 'variants' and other 'virus' inventions? Dr Sherri Tenpenny, an osteopathic medical doctor in the United States, has made herself an expert on vaccines and their effects as a vehement campaigner against their use. Tenpenny was board certified in emergency medicine, the director of a level two trauma centre for 12 years, and moved to Cleveland in 1996 to start an integrative

medicine practice which has treated patients from all 50 states and some 17 other countries. Weaning people off pharmaceutical drugs is a speciality.

She became interested in the consequences of vaccines after attending a meeting at the National Vaccine Information Center in Washington DC in 2000 where she 'sat through four days of listening to medical doctors and scientists and lawyers and parents of vaccine injured kids' and asked: 'What's going on?' She had never been vaccinated and never got ill while her father was given a list of vaccines to be in the military and was 'sick his entire life'. The experience added to her questions and she began to examine vaccine documents from the Centers for Disease Control (CDC). After reading the first one, the 1998 version of *The General Recommendations of Vaccination*, she thought: 'This is it?' The document was poorly written and bad science and Tenpenny began 20 years of research into vaccines that continues to this day. She began her research into 'Covid vaccines' in March, 2020, and she describes them as 'deadly'. For many, as we have seen, they already have been. Tenpenny said that in the first 30 days of the 'vaccine' rollout in the United States there had been more than 40,000 adverse events reported to the vaccine adverse event database. A document had been delivered to her the day before that was 172 pages long. 'We have over 40,000 adverse events; we have over 3,100 cases of [potentially deadly] anaphylactic shock; we have over 5,000 neurological reactions.' Effects ranged from headaches to numbness, dizziness and vertigo, to losing feeling in hands or feet and paraesthesia which is when limbs 'fall asleep' and people have the sensation of insects crawling underneath their skin. All this happened in the first 30 days and remember that only about *ten percent* (or far less) of adverse reactions and vaccine-related deaths are estimated to be officially reported. Tenpenny said:

> So can you think of one single product in any industry, any industry, for as long as products have been made on the planet that within 30 days we have 40,000 people complaining of side effects that not only is still on the market but … we've got paid actors telling us how great

they are for getting their vaccine. We're offering people $500 if they will just get their vaccine and we've got nurses and doctors going; 'I got the vaccine, I got the vaccine'.

Tenpenny said they were not going to be 'happy dancing folks' when they began to suffer Bell's palsy (facial paralysis), neuropathies, cardiac arrhythmias and autoimmune reactions that kill through a blood disorder. 'They're not going to be so happy, happy then, but we're never going to see pictures of those people' she said. Tenpenny described the 'vaccine' as 'a well-designed killing tool'.

No off-switch

Bad as the initial consequences had been Tenpenny said it would be maybe 14 months before we began to see the 'full ravage' of what is going to happen to the 'Covid vaccinated' with full-out consequences taking anything between two years and 20 years to show. You can understand why when you consider that variations of the 'Covid vaccine' use mRNA (messenger RNA) to in theory activate the immune system to produce protective antibodies without using the actual 'virus'. How can they when it's a computer program and they've never isolated what they claim is the 'real thing'? Instead they use *synthetic* mRNA. They are inoculating synthetic material into the body which through a technique known as the Trojan horse is absorbed into cells to change the nature of DNA. Human DNA is changed by an infusion of messenger RNA and with each new 'vaccine' of this type it is changed even more. Say so and you are banned by Cult Internet platforms. The contempt the contemptuous Mark Zuckerberg has for the truth and human health can be seen in an internal Facebook video leaked to the Project Veritas investigative team in which he said of the 'Covid vaccines': '… I share some caution on this because we just don't know the long term side-effects of basically modifying people's DNA and RNA.' At the same time this disgusting man's Facebook was censoring and banning anyone saying exactly the same. He must go before a Nuremberg trial for crimes against humanity when he *knows* that he

is censoring legitimate concerns and denying the right of informed consent on behalf of the Cult that owns him. People have been killed and damaged by the very 'vaccination' technique he cast doubt on himself when they may not have had the 'vaccine' with access to information that he denied them. The plan is to have at least annual 'Covid vaccinations', add others to deal with invented 'variants', and change all other vaccines into the mRNA system. Pfizer executives told shareholders at a virtual Barclays Global Healthcare Conference in March, 2021, that the public may need a third dose of 'Covid vaccine', plus regular yearly boosters and the company planned to hike prices to milk the profits in a 'significant opportunity for our vaccine'. These are the professional liars, cheats and opportunists who are telling you their 'vaccine' is safe. Given this volume of mRNA planned to be infused into the human body and its ability to then replicate we will have a transformation of human genetics from biological to synthetic biological – exactly the long-time Cult plan for reasons we'll see – and many will die. Sherri Tenpenny said of this replication:

> It's like having an on-button but no off-button and that whole mechanism … they actually give it a name and they call it the Trojan horse mechanism, because it allows that [synthetic] virus and that piece of that [synthetic] virus to get inside of your cells, start to replicate and even get inserted into other parts of your DNA as a Trojan-horse.

Ask the overwhelming majority of people who have the 'vaccine' what they know about the contents and what they do and they would reply: 'The government says it will stop me getting the virus.' Governments give that false impression on purpose to increase take-up. You can read Sherri Tenpenny's detailed analysis of the health consequences in her blog at Vaxxter.com, but in summary these are some of them. She highlights the statement by Bill Gates about how human beings can become their own 'vaccine manufacturing machine'. The man is insane. ['Vaccine'-generated] 'antibodies' carry synthetic messenger RNA into the cells and the damage starts, Tenpenny contends, and she says that lungs can be adversely affected through varying degrees of pus and bleeding which

obviously affects breathing and would be dubbed 'Covid-19'. Even more sinister was the impact of 'antibodies' on macrophages, a white blood cell of the immune system. They consist of Type 1 and Type 2 which have very different functions. She said Type 1 are 'hyper-vigilant' white blood cells which 'gobble up' bacteria etc. However, in doing so, this could cause inflammation and in extreme circumstances be fatal. She says these affects are mitigated by Type 2 macrophages which kick in to calm down the system and stop it going rogue. They clear up dead tissue debris and reduce inflammation that the Type 1 'fire crews' have caused. Type 1 kills the infection and Type 2 heals the damage, she says. This is her punchline with regard to 'Covid vaccinations': She says that mRNA 'antibodies' block Type 2 macrophages by attaching to them and deactivating them. This meant that when the Type 1 response was triggered by infection there was nothing to stop that getting out of hand by calming everything down. There's an on-switch, but no off-switch, she says. What follows can be 'over and out, see you when I see you'.

Genetic suicide

Tenpenny also highlights the potential for autoimmune disease – the body attacking itself – which has been associated with vaccines since they first appeared. Infusing a synthetic foreign substance into cells could cause the immune system to react in a panic believing that the body is being overwhelmed by an invader (it is) and the consequences can again be fatal. There is an autoimmune response known as a 'cytokine storm' which I have likened to a homeowner panicked by an intruder and picking up a gun to shoot randomly in all directions before turning the fire on himself. The immune system unleashes a storm of inflammatory response called cytokines to a threat and the body commits hara-kiri. The lesson is that you mess with the body's immune response at your peril and these 'vaccines' seriously – fundamentally – mess with immune response. Tenpenny refers to a consequence called anaphylactic shock which is a severe and highly dangerous allergic reaction when the immune system

floods the body with chemicals. She gives the example of having a bee sting which primes the immune system and makes it sensitive to those chemicals. When people are stung again maybe years later the immune response can be so powerful that it leads to anaphylactic shock. Tenpenny relates this 'shock' with regard to the 'Covid vaccine' to something called polyethylene glycol or PEG. Enormous numbers of people have become sensitive to this over decades of use in a whole range of products and processes including food, drink, skin creams and 'medicine'. Studies have claimed that some 72 percent of people have antibodies triggered by PEG compared with two percent in the 1960s and allergic hypersensitive reactions to this become a gathering cause for concern. Tenpenny points out that the 'mRNA vaccine' is coated in a 'bubble' of polyethylene glycol which has the potential to cause anaphylactic shock through immune sensitivity. Many reports have appeared of people reacting this way after having the 'Covid vaccine'. What do we think is going to happen as humanity has more and more of these 'vaccines'? Tenpenny said: 'All these pictures we have seen with people with these rashes … these weepy rashes, big reactions on their arms and things like that – it's an acute allergic reaction most likely to the polyethylene glycol that you've been previously primed and sensitised to.'

Those who have not studied the conspiracy and its perpetrators at length might think that making the population sensitive to PEG and then putting it in these 'vaccines' is just a coincidence. It is not. It is instead testament to how carefully and coldly-planned current events have been and the scale of the conspiracy we are dealing with. Tenpenny further explains that the 'vaccine' mRNA procedure can breach the blood-brain barrier which protects the brain from toxins and other crap that will cause malfunction. In this case they could make two proteins corrupt brain function to cause Amyotrophic lateral sclerosis (ALS) , a progressive nervous system disease leading to loss of muscle control, and frontal lobe degeneration – Alzheimer's and dementia. Immunologist J. Bart Classon published a paper connecting mRNA 'vaccines' to prion

disease which can lead to Alzheimer's and other forms of neurogenerative disease while others have pointed out the potential to affect the placenta in ways that make women infertile. This will become highly significant in the next chapter when I will discuss other aspects of this non-vaccine that relate to its nanotechnology and transmission from the injected to the uninjected.

Qualified in idiocy

Tenpenny describes how research has confirmed that these 'vaccine'-generated antibodies can interact with a range of other tissues in the body and attack many other organs including the lungs. 'This means that if you have a hundred people standing in front of you that all got this shot they could have a hundred different symptoms.' Anyone really think that Cult gofers like the Queen, Tony Blair, Christopher Whitty, Anthony Fauci, and all the other psychopaths have really had this 'vaccine' in the pictures we've seen? Not a bloody chance. Why don't doctors all tell us about all these dangers and consequences of the 'Covid vaccine'? Why instead do they encourage and pressure patients to have the shot? Don't let's think for a moment that doctors and medical staff can't be stupid, lazy, and psychopathic and that's without the financial incentives to give the jab. Tenpenny again:

> Some people are going to die from the vaccine directly but a large number of people are going to start to get horribly sick and get all kinds of autoimmune diseases 42 days to maybe a year out. What are they going to do, these stupid doctors who say; 'Good for you for getting that vaccine.' What are they going to say; 'Oh, it must be a mutant, we need to give an extra dose of that vaccine.'
>
> Because now the vaccine, instead of one dose or two doses we need three or four because the stupid physicians aren't taking the time to learn anything about it. If I can learn this sitting in my living room reading a 19 page paper and several others so can they. There's nothing special about me, I just take the time to do it.

Remember how Sara Kayat, the NHS and TV doctor, said that the 'Covid vaccine' would '100 percent prevent hospitalisation and death'. Doctors can be idiots like every other profession and they

should not be worshipped as infallible. They are not and far from it. Behind many medical and scientific 'experts' lies an uninformed prat trying to hide themselves from you although in the 'Covid' era many have failed to do so as with UK narrative-repeating 'TV doctor' Hilary Jones. Pushing back against the minority of proper doctors and scientists speaking out against the 'vaccine' has been the entire edifice of the Cult global state in the form of governments, medical systems, corporations, mainstream media, Silicon Valley, and an army of compliant doctors, medical staff and scientists willing to say anything for money and to enhance their careers by promoting the party line. If you do that you are an 'expert' and if you won't you are an 'anti-vaxxer' and 'Covidiot'. The pressure to be 'vaccinated' is incessant. We have even had reports claiming that the 'vaccine' can help cure cancer and Alzheimer's and make the lame walk. I am waiting for the announcement that it can bring you coffee in the morning and cook your tea. Just as the symptoms of 'Covid' seem to increase by the week so have the miracles of the 'vaccine'. American supermarket giant Kroger Co. offered nearly 500,000 employees in 35 states a $100 bonus for having the 'vaccine' while donut chain Krispy Kreme promised 'vaccinated' customers a free glazed donut every day for the rest of 2021. Have your DNA changed and you will get a doughnut although we might not have to give you them for long. Such offers and incentives confirm the desperation.

Perhaps the worse vaccine-stunt of them all was UK 'Health' Secretary Matt-the-prat Hancock on live TV after watching a clip of someone being 'vaccinated' when the roll-out began. Hancock faked tears so badly it was embarrassing. Brain-of-Britain Piers Morgan, the lockdown-supporting, 'vaccine' supporting, 'vaccine' passport-supporting, TV host played along with Hancock – 'You're quite emotional about that' he said in response to acting so atrocious it would have been called out at a school nativity which will presumably today include Mary and Jesus in masks, wise men keeping their camels six feet apart, and shepherds under tent arrest. System-serving Morgan tweeted this: 'Love the idea of covid vaccine passports for everywhere: flights, restaurants, clubs, football, gyms,

shops etc. It's time covid-denying, anti-vaxxer loonies had their bullsh*t bluff called & bar themselves from going anywhere that responsible citizens go.' If only I could aspire to his genius. To think that Morgan, who specialises in shouting over anyone he disagrees with, was lauded as a free speech hero when he lost his job after storming off the set of his live show like a child throwing his dolly out of the pram. If he is a free speech hero we are in real trouble. I have no idea what 'bullsh*t' means, by the way, the * throws me completely.

The Cult is desperate to infuse its synthetic DNA-changing concoction into everyone and has been using every lie, trick and intimidation to do so. The question of '*Why*?' we shall now address.

CHAPTER TEN

Human 2.0

I believe that at the end of the century the use of words and general educated opinion will have altered so much that one will be able to speak of machines thinking without expecting to be contradicted –
Alan Turing (1912-1954), the 'Father of artificial intelligence'

I have been exposing for decades the plan to transform the human body from a biological to a synthetic-biological state. The new human that I will call Human 2.0 is planned to be connected to artificial intelligence and a global AI 'Smart Grid' that would operate as one global system in which AI would control everything from your fridge to your heating system to your car to your mind. Humans would no longer be 'human', but post-human and sub-human, with their thinking and emotional processes replaced by AI.

What I said sounded crazy and beyond science fiction and I could understand that. To any balanced, rational, mind it *is* crazy. Today, however, that world is becoming reality and it puts the 'Covid vaccine' into its true context. Ray Kurzweil is the ultra-Zionist 'computer scientist, inventor and futurist' and co-founder of the Singularity University. Singularity refers to the merging of humans with machines or 'transhumanism'. Kurzweil has said humanity would be connected to the cyber 'cloud' in the period of the ever-recurring year of 2030:

Our thinking … will be a hybrid of biological and non-biological thinking … humans will be able to extend their limitations and 'think in the cloud' … We're going to put gateways to the

cloud in our brains ... We're going to gradually merge and enhance ourselves ... In my view, that's the nature of being human – we transcend our limitations. As the technology becomes vastly superior to what we are then the small proportion that is still human gets smaller and smaller and smaller until it's just utterly negligible.

They are trying to sell this end-of-humanity-as-we-know-it as the next stage of 'evolution' when we become super-human and 'like the gods'. They are lying to you. Shocked, eh? The population, and again especially the young, have been manipulated into addiction to technologies designed to enslave them for life. First they induced an addiction to smartphones (holdables); next they moved to technology on the body (wearables); and then began the invasion of the body (implantables). I warned way back about the plan for microchipped people and we are now entering that era. We should not be diverted into thinking that this refers only to chips we can see. Most important are the nanochips known as smart dust, neural dust and nanobots which are far too small to be seen by the human eye. Nanotechnology is everywhere, increasingly in food products, and released into the atmosphere by the geoengineering of the skies funded by Bill Gates to 'shut out the Sun' and 'save the planet from global warming'. Gates has been funding a project to spray millions of tonnes of chalk (calcium carbonate) into the stratosphere over Sweden to 'dim the Sun' and cool the Earth. Scientists warned the move could be disastrous for weather systems in ways no one can predict and opposition led to the Swedish space agency announcing that the 'experiment' would not be happening as planned in the summer of 2021; but it shows where the Cult is going with dimming the impact of the Sun and there's an associated plan to change the planet's atmosphere. Who gives psychopath Gates the right to dictate to the entire human race and dismantle planetary systems? The world will not be safe while this man is at large.

The global warming hoax has made the Sun, like the gas of life, something to fear when both are essential to good health and human survival (more inversion). The body transforms sunlight into vital vitamin D through a process involving … *cholesterol*. This is the cholesterol we are also told to fear. We are urged to take Big Pharma

statin drugs to reduce cholesterol and it's all systematic. Reducing cholesterol means reducing vitamin D uptake with all the multiple health problems that will cause. At least if you take statins long term it saves the government from having to pay you a pension. The delivery system to block sunlight is widely referred to as chemtrails although these have a much deeper agenda, too. They appear at first to be contrails or condensation trails streaming from aircraft into cold air at high altitudes. Contrails disperse very quickly while chemtrails do not and spread out across the sky before eventually their content falls to earth. Many times I have watched aircraft cross-cross a clear blue sky releasing chemtrails until it looks like a cloudy day. Chemtrails contain many things harmful to humans and the natural world including toxic heavy metals, aluminium (see Alzheimer's) and nanotechnology. Ray Kurzweil reveals the reason without actually saying so: 'Nanobots will infuse all the matter around us with information. Rocks, trees, everything will become these intelligent creatures.' How do you deliver that? *From the sky*. Self-replicating nanobots would connect everything to the Smart Grid. The phenomenon of Morgellons disease began in the chemtrail era and the correlation has led to it being dubbed the 'chemtrail disease'. Self-replicating fibres appear in the body that can be pulled out through the skin. Morgellons fibres continue to grow outside the body and have a form of artificial intelligence. I cover this at greater length in *Phantom Self*.

'Vaccine' operating system

'Covid vaccines' with their self-replicating synthetic material are also designed to make the connection between humanity and Kurzweil's 'cloud'. American doctor and dedicated campaigner for truth, Carrie Madej, an Internal Medicine Specialist in Georgia with more than 20 years medical experience, has highlighted the nanotechnology aspect of the fake 'vaccines'. She explains how one of the components in at least the Moderna and Pfizer synthetic potions are 'lipid nanoparticles' which are 'like little tiny computer bits' – a 'sci-fi substance' known as nanobots and hydrogel which can be 'triggered

at any moment to deliver its payload' and act as 'biosensors'. The synthetic substance had 'the ability to accumulate data from your body like your breathing, your respiration, thoughts and emotions, all kind of things' and each syringe could carry a *million* nanobots:

This substance because it's like little bits of computers in your body, crazy, but it's true, it can do that, [and] obviously has the ability to act through Wi-Fi. It can receive and transmit energy, messages, frequencies or impulses. That issue has never been addressed by these companies. What does that do to the human?

Just imagine getting this substance in you and it can react to things all around you, the 5G, your smart device, your phones, what is happening with that? What if something is triggering it, too, like an impulse, a frequency? We have something completely foreign in the human body.

Madej said her research revealed that electromagnetic (EMF) frequencies emitted by phones and other devices had increased dramatically in the same period of the 'vaccine' rollout and she was seeing more people with radiation problems as 5G and other electromagnetic technology was expanded and introduced to schools and hospitals. She said she was 'floored with the EMF coming off' the devices she checked. All this makes total sense and syncs with my own work of decades when you think that Moderna refers in documents to its mRNA 'vaccine' as an 'operating system':

Recognizing the broad potential of mRNA science, we set out to create an mRNA technology platform that functions very much like an operating system on a computer. It is designed so that it can plug and play interchangeably with different programs. In our case, the 'program' or 'app' is our mRNA drug – the unique mRNA sequence that codes for a protein …

… Our MRNA Medicines – 'The 'Software Of Life': When we have a concept for a new mRNA medicine and begin research, fundamental components are already in place. Generally, the only thing that changes from one potential mRNA medicine to another is the coding region – the actual genetic code that instructs ribosomes to make protein. Utilizing these instruction sets gives our investigational mRNA medicines a software-like quality. We also have the ability to combine different mRNA sequences encoding for different proteins in a single mRNA investigational medicine.

Who needs a real 'virus' when you can create a computer version to justify infusing your operating system into the entire human race on the road to making living, breathing people into cyborgs? What is missed with the 'vaccines' is the *digital* connection between synthetic material and the body that I highlighted earlier with the study that hacked a computer with human DNA. On one level the body is digital, based on mathematical codes, and I'll have more about that in the next chapter. Those who ridiculously claim that mRNA 'vaccines' are not designed to change human genetics should explain the words of Dr Tal Zaks, chief medical officer at Moderna, in a 2017 TED talk. He said that over the last 30 years 'we've been living this phenomenal digital scientific revolution, and I'm here today to tell you, that we are actually *hacking the software of life*, and that it's changing the way we think about prevention and treatment of disease':

In every cell there's this thing called messenger RNA, or mRNA for short, that transmits the critical information from the DNA in our genes to the protein, which is really the stuff we're all made out of. This is the critical information that determines what the cell will do. So we think about it as an operating system. So if you could change that, if you could introduce a line of code, or change a line of code, it turns out, that has profound implications for everything, from the flu to cancer.

Zaks should more accurately have said that this has profound implications for the human genetic code and the nature of DNA. Communications within the body go both ways and not only one. But, hey, no, the 'Covid vaccine' will not affect your genetics. Cult fact-checkers say so even though the man who helped to develop the mRNA technique says that it does. Zaks said in 2017:

If you think about what it is we're trying to do. We've taken information and our understanding of that information and how that information is transmitted in a cell, and we've taken our understanding of medicine and how to make drugs, and we're fusing the two. We think of it as information therapy.

I have been writing for decades that the body is an information field communicating with itself and the wider world. This is why

radiation which is information can change the information field of body and mind through phenomena like 5G and change their nature and function. 'Information therapy' means to change the body's information field and change the way it operates. DNA is a receiver-transmitter of information and can be mutated by information like mRNA synthetic messaging. Technology to do this has been ready and waiting in the underground bases and other secret projects to be rolled out when the 'Covid' hoax was played. 'Trials' of such short and irrelevant duration were only for public consumption. When they say the 'vaccine' is 'experimental' that is not true. It may appear to be 'experimental' to those who don't know what's going on, but the trials have already been done to ensure the Cult gets the result it desires. Zaks said that it took decades to sequence the human genome, completed in 2003, but now they could do it in a week. By 'they' he means scientists operating in the public domain. In the secret projects they were sequencing the genome in a week long before even 2003.

Deluge of mRNA

Highly significantly the Moderna document says the guiding premise is that if using mRNA as a medicine works for one disease then it should work for many diseases. They were leveraging the flexibility afforded by their platform and the fundamental role mRNA plays in protein synthesis to pursue mRNA medicines for a broad spectrum of diseases. Moderna is confirming what I was saying through 2020 that multiple 'vaccines' were planned for 'Covid' (and later invented 'variants') and that previous vaccines would be converted to the mRNA system to infuse the body with massive amounts of genetically-manipulating synthetic material to secure a transformation to a synthetic-biological state. The 'vaccines' are designed to kill stunning numbers as part of the long-exposed Cult depopulation agenda and transform the rest. Given this is the goal you can appreciate why there is such hysterical demand for every human to be 'vaccinated' for an alleged 'disease' that has an estimated 'infection' to 'death' ratio of 0.23-0.15 percent. As I write

children are being given the 'vaccine' in trials (their parents are a disgrace) and ever-younger people are being offered the vaccine for a 'virus' that even if you believe it exists has virtually zero chance of harming them. Horrific effects of the 'trials' on a 12-year-old girl were revealed by a family member to be serious brain and gastric problems that included a bowel obstruction and the inability to swallow liquids or solids. She was unable to eat or drink without throwing up, had extreme pain in her back, neck and abdomen, and was paralysed from the waist down which stopped her urinating unaided. When the girl was first taken to hospital doctors said it was all in her mind. She was signed up for the 'trial' by her parents for whom no words suffice. None of this 'Covid vaccine' insanity makes any sense unless you see what the 'vaccine' really is – a body-changer. Synthetic biology or 'SynBio' is a fast-emerging and expanding scientific discipline which includes everything from genetic and molecular engineering to electrical and computer engineering. Synthetic biology is defined in these ways:

- A multidisciplinary area of research that seeks to create new biological parts, devices, and systems, or to redesign systems that are already found in nature.

- The use of a mixture of physical engineering and genetic engineering to create new (and therefore synthetic) life forms.

- An emerging field of research that aims to combine the knowledge and methods of biology, engineering and related disciplines in the design of chemically-synthesized DNA to create organisms with novel or enhanced characteristics and traits (synthetic organisms including humans).

We now have synthetic blood, skin, organs and limbs being developed along with synthetic body parts produced by 3D printers. These are all elements of the synthetic human programme and this comment by Kurzweil's co-founder of the Singularity University,

Peter Diamandis, can be seen in a whole new light with the 'Covid' hoax and the sanctions against those that refuse the 'vaccine':

Anybody who is going to be resisting the progress forward [to transhumanism] is going to be resisting evolution and, fundamentally, they will die out. It's not a matter of whether it's good or bad. It's going to happen.

'Resisting evolution'? What absolute bollocks. The arrogance of these people is without limit. His 'it's going to happen' mantra is another way of saying 'resistance is futile' to break the spirit of those pushing back and we must not fall for it. Getting this genetically-transforming 'vaccine' into everyone is crucial to the Cult plan for total control and the desperation to achieve that is clear for anyone to see. Vaccine passports are a major factor in this and they, too, are a form of resistance is futile. It's NOT. The paper funded by the Rockefeller Foundation for the 2013 'health conference' in China said:

We will interact more with artificial intelligence. The use of robotics, bio-engineering to augment human functioning is already well underway and will advance. Re-engineering of humans into potentially separate and unequal forms through genetic engineering or mixed human-robots raises debates on ethics and equality.

A new demography is projected to emerge after 2030 [that year again] of technologies (robotics, genetic engineering, nanotechnology) producing robots, engineered organisms, 'nanobots' and artificial intelligence (AI) that can self-replicate. Debates will grow on the implications of an impending reality of human designed life.

What is happening today is so long planned. The world army enforcing the will of the world government is intended to be a robot army, not a human one. Today's military and its technologically 'enhanced' troops, pilotless planes and driverless vehicles are just stepping stones to that end. Human soldiers are used as Cult fodder and its time they woke up to that and worked for the freedom of the population instead of their own destruction and their family's destruction – the same with the police. Join us and let's sort this out. The phenomenon of enforce my own destruction is widespread in the 'Covid' era with Woker 'luvvies' in the acting and entertainment

industries supporting 'Covid' rules which have destroyed their profession and the same with those among the public who put signs on the doors of their businesses 'closed due to Covid – stay safe' when many will never reopen. It's a form of masochism and most certainly insanity.

Transgender = transhumanism

When something explodes out of nowhere and is suddenly everywhere it is always the Cult agenda and so it is with the tidal wave of claims and demands that have infiltrated every aspect of society under the heading of 'transgenderism'. The term 'trans' is so 'in' and this is the dictionary definition:

A prefix meaning 'across', 'through', occurring … in loanwords from Latin, used in particular for denoting movement or conveyance from place to place (transfer; transmit; transplant) or complete change (transform; transmute), or to form adjectives meaning 'crossing', 'on the other side of', or 'going beyond' the place named (transmontane; transnational; trans-Siberian).

Transgender means to go beyond gender and transhuman means to go beyond human. Both are aspects of the Cult plan to transform the human body to a synthetic state with *no gender*. Human 2.0 is not designed to procreate and would be produced technologically with no need for parents. The new human would mean the end of parents and so men, and increasingly women, are being targeted for the deletion of their rights and status. Parental rights are disappearing at an ever-quickening speed for the same reason. The new human would have no need for men or women when there is no procreation and no gender. Perhaps the transgender movement that appears to be in a permanent state of frenzy might now contemplate on how it is being used. This was never about transgender rights which are only the interim excuse for confusing gender, particularly in the young, on the road to *fusing* gender. Transgender activism is not an end; it is a *means* to an end. We see again the technique of creative destruction in which you destroy the status quo to 'build back better' in the form that you want. The gender status quo had to be

destroyed by persuading the Cult-created Woke mentality to believe that you can have 100 genders or more. A programme for 9 to 12 year olds produced by the Cult-owned BBC promoted the 100 genders narrative. The very idea may be the most monumental nonsense, but it is not what is true that counts, only what you can make people *believe* is true. Once the gender of 2 + 2 = 4 has been dismantled through indoctrination, intimidation and 2 + 2 = 5 then the new no-gender normal can take its place with Human 2.0. Aldous Huxley revealed the plan in his prophetic *Brave New World* in 1932:

> Natural reproduction has been done away with and children are created, decanted', and raised in 'hatcheries and conditioning centres'. From birth, people are genetically designed to fit into one of five castes, which are further split into 'Plus' and 'Minus' members and designed to fulfil predetermined positions within the social and economic strata of the World State.

How could Huxley know this in 1932? For the same reason George Orwell knew about the Big Brother state in 1948, Cult insiders I have quoted knew about it in 1969, and I have known about it since the early 1990s. If you are connected to the Cult or you work your balls off to uncover the plan you can predict the future. The process is simple. If there is a plan for the world and nothing intervenes to stop it then it will happen. Thus if you communicate the plan ahead of time you are perceived to have predicted the future, but you haven't. You have revealed the plan which without intervention will become the human future. The whole reason I have done what I have is to alert enough people to inspire an intervention and maybe at last that time has come with the Cult and its intentions now so obvious to anyone with a brain in working order.

The future is here

Technological wombs that Huxley described to replace parent procreation are already being developed and they are only the projects we know about in the public arena. Israeli scientists told *The Times of Israel* in March, 2021, that they have grown 250-cell embryos

into mouse foetuses with fully formed organs using artificial wombs in a development they say could pave the way for gestating humans outside the womb. Professor Jacob Hanna of the Weizmann Institute of Science said:

We took mouse embryos from the mother at day five of development, when they are just of 250 cells, and had them in the incubator from day five until day 11, by which point they had grown all their organs.

By day 11 they make their own blood and have a beating heart, a fully developed brain. Anybody would look at them and say, 'this is clearly a mouse foetus with all the characteristics of a mouse.' It's gone from being a ball of cells to being an advanced foetus.

A special liquid is used to nourish embryo cells in a laboratory dish and they float on the liquid to duplicate the first stage of embryonic development. The incubator creates all the right conditions for its development, Hanna said. The liquid gives the embryo 'all the nutrients, hormones and sugars they need' along with a custom-made electronic incubator which controls gas concentration, pressure and temperature. The cutting-edge in the underground bases and other secret locations will be light years ahead of that, however, and this was reported by the London *Guardian* in 2017:

We are approaching a biotechnological breakthrough. Ectogenesis, the invention of a complete external womb, could completely change the nature of human reproduction. In April this year, researchers at the Children's Hospital of Philadelphia announced their development of an artificial womb.

The article was headed 'Artificial wombs could soon be a reality. What will this mean for women?' What would it mean for children is an even bigger question. No mother to bond with only a machine in preparation for a life of soulless interaction and control in a world governed by machines (see the *Matrix* movies). Now observe the calculated manipulations of the 'Covid' hoax as human interaction and warmth has been curtailed by distancing, isolation and fear with people communicating via machines on a scale never seen before.

These are all dots in the same picture as are all the personal assistants, gadgets and children's toys through which kids and adults communicate with AI as if it is human. The AI 'voice' on Sat-Nav should be included. All these things are psychological preparation for the Cult endgame. Before you can make a physical connection with AI you have to make a psychological connection and that is what people are being conditioned to do with this ever gathering human-AI interaction. Movies and TV programmes depicting the transhuman, robot dystopia relate to a phenomenon known as 'pre-emptive programming' in which the world that is planned is portrayed everywhere in movies, TV and advertising. This is conditioning the conscious and subconscious mind to become familiar with the planned reality to dilute resistance when it happens for real. What would have been a shock such is the change is made less so. We have young children put on the road to transgender transition surgery with puberty blocking drugs at an age when they could never be able to make those life-changing decisions.

Rachel Levine, a professor of paediatrics and psychiatry who believes in treating children this way, became America's highest-ranked openly-transgender official when she was confirmed as US Assistant Secretary at the Department of Health and Human Services after being nominated by Joe Biden (the Cult). Activists and governments press for laws to deny parents a say in their children's transition process so the kids can be isolated and manipulated into agreeing to irreversible medical procedures. A Canadian father Robert Hoogland was denied bail by the Vancouver Supreme Court in 2021 and remained in jail for breaching a court order that he stay silent over his young teenage daughter, a minor, who was being offered life-changing hormone therapy without parental consent. At the age of 12 the girl's 'school counsellor' said she may be transgender, referred her to a doctor and told the school to treat her like a boy. This is another example of state-serving schools imposing ever more control over children's lives while parents have ever less.

Contemptible and extreme child abuse is happening all over the world as the Cult gender-fusion operation goes into warp-speed.

Why the war on men – and now women?

The question about what artificial wombs mean for women should rightly be asked. The answer can be seen in the deletion of women's rights involving sport, changing rooms, toilets and status in favour of people in male bodies claiming to identify as women. I can identify as a mountain climber, but it doesn't mean I can climb a mountain any more than a biological man can be a biological woman. To believe so is a triumph of belief over factual reality which is the very perceptual basis of everything Woke. Women's sport is being destroyed by allowing those with male bodies who say they identify as female to 'compete' with girls and women. Male body 'women' dominate 'women's' competition with their greater muscle mass, bone density, strength and speed. With that disadvantage sport for women loses all meaning. To put this in perspective nearly 300 American high school boys can run faster than the quickest woman sprinter in the world. Women are seeing their previously protected spaces invaded by male bodies simply because they claim to identify as women. That's all they need to do to access all women's spaces and activities under the Biden 'Equality Act' that destroys equality for women with the usual Orwellian Woke inversion. Male sex offenders have already committed rapes in women's prisons after claiming to identify as women to get them transferred. Does this not matter to the Woke 'equality' hypocrites? Not in the least. What matters to Cult manipulators and funders behind transgender activists is to advance gender fusion on the way to the no-gender 'human'. When you are seeking to impose transparent nonsense like this, or the 'Covid' hoax, the only way the nonsense can prevail is through censorship and intimidation of dissenters, deletion of factual information, and programming of the unquestioning, bewildered and naive. You don't have to scan the world for long to see that all these things are happening.

Many women's rights organisations have realised that rights and status which took such a long time to secure are being eroded and that it is systematic. Kara Dansky of the global Women's Human Rights Campaign said that Biden's transgender executive order immediately he took office, subsequent orders, and Equality Act legislation that followed 'seek to erase women and girls in the law as a category'. *Exactly*. I said during the long ago-started war on men (in which many women play a crucial part) that this was going to turn into a war on them. The Cult is phasing out *both* male and female genders. To get away with that they are brought into conflict so they are busy fighting each other while the Cult completes the job with no unity of response. Unity, people, *unity*. We need unity everywhere. Transgender is the only show in town as the big step towards the no-gender human. It's not about rights for transgender people and never has been. Woke political correctness is deleting words relating to genders to the same end. Wokers believe this is to be 'inclusive' when the opposite is true. They are deleting words describing gender because gender *itself* is being deleted by Human 2.0. Terms like 'man', 'woman', 'mother' and 'father' are being deleted in the universities and other institutions to be replaced by the *no*-gender, not trans-gender, 'individuals' and 'guardians'. Women's rights campaigner Maria Keffler of Partners for Ethical Care said: 'Children are being taught from kindergarten upward that some boys have a vagina, some girls have a penis, and that kids can be any gender they want to be.' Do we really believe that suddenly countries all over the world at the same time had the idea of having drag queens go into schools or read transgender stories to very young children in the local library? It's coldly-calculated confusion of gender on the way to the fusion of gender. Suzanne Vierling, a psychologist from Southern California, made another important point:

Yesterday's slave woman who endured gynecological medical experiments is today's girl-child being butchered in a booming gender-transitioning sector. Ovaries removed, pushing her into menopause and osteoporosis, uncharted territory, and parents' rights and authority decimated.

The erosion of parental rights is a common theme in line with the Cult plans to erase the very concept of parents and 'ovaries removed, pushing her into menopause' means what? Those born female lose the ability to have children – another way to discontinue humanity as we know it.

Eliminating Human 1.0 (before our very eyes)

To pave the way for Human 2.0 you must phase out Human 1.0. This is happening through plummeting sperm counts and making women infertile through an onslaught of chemicals, radiation (including smartphones in pockets of men) and mRNA 'vaccines'. Common agriculture pesticides are also having a devastating impact on human fertility. I have been tracking collapsing sperm counts in the books for a long time and in 2021 came a book by fertility scientist and reproductive epidemiologist Shanna Swan, *Count Down: How Our Modern World Is Threatening Sperm Counts, Altering Male and Female Reproductive Development and Imperiling the Future of the Human Race*. She reports how the global fertility rate dropped by *half* between 1960 and 2016 with America's birth rate 16 percent below where it needs to be to sustain the population. Women are experiencing declining egg quality, more miscarriages, and more couples suffer from infertility. Other findings were an increase in erectile dysfunction, infant boys developing more genital abnormalities, male problems with conception, and plunging levels of the male hormone testosterone which would explain why so many men have lost their backbone and masculinity. This has been very evident during the 'Covid' hoax when women have been prominent among the Pushbackers and big strapping blokes have bowed their heads, covered their faces with a nappy and quietly submitted. Mind control expert Cathy O'Brien also points to how global education introduced the concept of 'we're all winners' in sport and classrooms: 'Competition was defused, and it in turn defused a sense of fighting back.' This is another version of the 'equity' doctrine in which you drive down rather than raise up. What a contrast in Cult-controlled China with its global ambitions

where the government published plans in January, 2021, to 'cultivate masculinity' in boys from kindergarten through to high school in the face of a 'masculinity crisis'. A government adviser said boys would be soon become 'delicate, timid and effeminate' unless action was taken. Don't expect any similar policy in the targeted West. A 2006 study showed that a 65-year-old man in 2002 had testosterone levels *15 percent* lower than a 65-year-old man in 1987 while a 2020 study found a similar story with young adults and adolescents. Men are getting prescriptions for testosterone replacement therapy which causes an even greater drop in sperm count with up to 99 percent seeing sperm counts drop to zero during the treatment. More sperm is defective and malfunctioning with some having two heads or not pursuing an egg.

A class of *synthetic* chemicals known as phthalates are being blamed for the decline. These are found everywhere in plastics, shampoos, cosmetics, furniture, flame retardants, personal care products, pesticides, canned foods and even receipts. Why till receipts? Everyone touches them. Let no one delude themselves that all this is not systematic to advance the long-time agenda for human body transformation. Phthalates mimic hormones and disrupt the hormone balance causing testosterone to fall and genital birth defects in male infants. Animals and fish have been affected in the same way due to phthalates and other toxins in rivers. When fish turn gay or change sex through chemicals in rivers and streams it is a pointer to why there has been such an increase in gay people and the sexually confused. It doesn't matter to me what sexuality people choose to be, but if it's being affected by chemical pollution and consumption then we need to know. Does anyone really think that this is not connected to the transgender agenda, the war on men and the condemnation of male 'toxic masculinity'? You watch this being followed by 'toxic femininity'. It's already happening. When breastfeeding becomes 'chest-feeding', pregnant women become pregnant people along with all the other Woke claptrap you know that the world is going insane and there's a Cult scam in progress. Transgender activists are promoting the Cult agenda while Cult

billionaires support and fund the insanity as they laugh themselves to sleep at the sheer stupidity for which humans must be infamous in galaxies far, far away.

'Covid vaccines' and female infertility

We can now see why the 'vaccine' has been connected to potential infertility in women. Dr Michael Yeadon, former Vice President and Chief Scientific Advisor at Pfizer, and Dr Wolfgang Wodarg in Germany, filed a petition with the European Medicines Agency in December, 2020, urging them to stop trials for the Pfizer/BioNTech shot and all other mRNA trials until further studies had been done. They were particularly concerned about possible effects on fertility with 'vaccine'-produced antibodies attacking the protein Syncytin-1 which is responsible for developing the placenta. The result would be infertility 'of indefinite duration' in women who have the 'vaccine' with the placenta failing to form. Section 10.4.2 of the Pfizer/BioNTech trial protocol says that pregnant women or those who might become so should not have mRNA shots. Section 10.4 warns men taking mRNA shots to 'be abstinent from heterosexual intercourse' and not to donate sperm. The UK government said that it *did not know* if the mRNA procedure had an effect on fertility. *Did not know?* These people have to go to jail. UK government advice did not recommend at the start that pregnant women had the shot and said they should avoid pregnancy for at least two months after 'vaccination'. The 'advice' was later updated to pregnant women should only have the 'vaccine' if the benefits outweighed the risks to mother and foetus. What the hell is that supposed to mean? Then 'spontaneous abortions' began to appear and rapidly increase on the adverse reaction reporting schemes which include only a fraction of adverse reactions. Thousands and ever-growing numbers of 'vaccinated' women are describing changes to their menstrual cycle with heavier blood flow, irregular periods and menstruating again after going through the menopause – all links to reproduction effects. Women are passing blood clots and the lining of their uterus while men report erectile dysfunction and blood effects. Most

significantly of all *un*vaccinated women began to report similar menstrual changes after interaction with *'vaccinated'* people and men and children were also affected with bleeding noses, blood clots and other conditions. 'Shedding' is when vaccinated people can emit the content of a vaccine to affect the unvaccinated, but this is different. 'Vaccinated' people were not shedding a 'live virus' allegedly in 'vaccines' as before because the fake 'Covid vaccines' involve synthetic material and other toxicity. Doctors exposing what is happening prefer the term 'transmission' to shedding. Somehow those that have had the shots are transmitting effects to those that haven't. Dr Carrie Madej said the nano-content of the 'vaccines' can 'act like an antenna' to others around them which fits perfectly with my own conclusions. This 'vaccine' transmission phenomenon was becoming known as the book went into production and I deal with this further in the Postscript.

Vaccine effects on sterility are well known. The World Health Organization was accused in 2014 of sterilising millions of women in Kenya with the evidence confirmed by the content of the vaccines involved. The same WHO behind the 'Covid' hoax admitted its involvement for more than ten years with the vaccine programme. Other countries made similar claims. Charges were lodged by Tanzania, Nicaragua, Mexico, and the Philippines. The Gardasil vaccine claimed to protect against a genital 'virus' known as HPV has also been linked to infertility. Big Pharma and the WHO (same thing) are criminal and satanic entities. Then there's the Bill Gates Foundation which is connected through funding and shared interests with 20 pharmaceutical giants and laboratories. He stands accused of directing the policy of United Nations Children's Fund (UNICEF), vaccine alliance GAVI, and other groupings, to advance the vaccine agenda and silence opposition at great cost to women and children. At the same time Gates wants to reduce the global population. Coincidence?

Great Reset = Smart Grid = new human

The Cult agenda I have been exposing for 30 years is now being openly promoted by Cult assets like Gates and Klaus Schwab of the World Economic Forum under code-terms like the 'Great Reset', 'Build Back Better' and 'a rare but narrow window of opportunity to reflect, reimagine, and reset our world'. What provided this 'rare but narrow window of opportunity'? The 'Covid' hoax did. Who created that? *They* did. My books from not that long ago warned about the planned 'Internet of Things' (IoT) and its implications for human freedom. This was the plan to connect all technology to the Internet and artificial intelligence and today we are way down that road with an estimated 36 billion devices connected to the World Wide Web and that figure is projected to be 76 billion by 2025. I further warned that the Cult planned to go beyond that to the Internet of *Everything* when the human brain was connected via AI to the Internet and Kurzweil's 'cloud'. Now we have Cult operatives like Schwab calling for precisely that under the term 'Internet of Bodies', a fusion of the physical, digital and biological into one centrally-controlled Smart Grid system which the Cult refers to as the 'Fourth Industrial Revolution'. They talk about the 'biological', but they really mean the synthetic-biological which is required to fully integrate the human body and brain into the Smart Grid and artificial intelligence planned to replace the human mind. We have everything being synthetically manipulated including the natural world through GMO and smart dust, the food we eat and the human body itself with synthetic 'vaccines'. I said in *The Answer* that we would see the Cult push for synthetic meat to replace animals and in February, 2021, the so predictable psychopath Bill Gates called for the introduction of synthetic meat to save us all from 'climate change'. The climate hoax just keeps on giving like the 'Covid' hoax. The war on meat by vegan activists is a carbon (oops, sorry) copy of the manipulation of transgender activists. They have no idea (except their inner core) that they are being used to promote and impose the agenda of the Cult or that they are only the *vehicle* and not the *reason*. This is not to say those who choose not to eat meat shouldn't be respected and supported in that right, but there are ulterior motives

for those in power. A *Forbes* article in December, 2019, highlighted the plan so beloved of Schwab and the Cult under the heading: 'What Is The Internet of Bodies? And How Is It Changing Our World?' The article said the human body is the latest data platform (remember 'our vaccine is an operating system'). *Forbes* described the plan very accurately and the words could have come straight out of my books from long before:

The Internet of Bodies (IoB) is an extension of the IoT and basically connects the human body to a network through devices that are ingested, implanted, or connected to the body in some way. Once connected, data can be exchanged, and the body and device can be remotely monitored and controlled.

They were really describing a human hive mind with human perception centrally-dictated via an AI connection as well as allowing people to be 'remotely monitored and controlled'. Everything from a fridge to a human mind could be directed from a central point by these insane psychopaths and 'Covid vaccines' are crucial to this. Forbes explained the process I mentioned earlier of holdable and wearable technology followed by implantable. The article said there were three generations of the Internet of Bodies that include:

- Body external: These are wearable devices such as Apple Watches or Fitbits that can monitor our health.

- Body internal: These include pacemakers, cochlear implants, and digital pills that go inside our bodies to monitor or control various aspects of health.

- Body embedded: The third generation of the Internet of Bodies is embedded technology where technology and the human body are melded together and have a real-time connection to a remote machine.

Forbes noted the development of the Brain Computer Interface (BCI) which merges the brain with an external device for monitoring and controlling in real-time. 'The ultimate goal is to help restore function to individuals with disabilities by using brain signals rather than conventional neuromuscular pathways.' Oh, do fuck off. The goal of brain interface technology is controlling human thought and emotion from the central point in a hive mind serving its masters wishes. Many people are now agreeing to be chipped to open doors without a key. You can recognise them because they'll be wearing a mask, social distancing and lining up for the 'vaccine'. The Cult plans a Great Reset money system after they have completed the demolition of the global economy in which 'money' will be exchanged through communication with body operating systems. Rand Corporation, a Cult-owned think tank, said of the Internet of Bodies or IoB:

> Internet of Bodies technologies fall under the broader IoT umbrella. But as the name suggests, IoB devices introduce an even more intimate interplay between humans and gadgets. IoB devices monitor the human body, collect health metrics and other personal information, and transmit those data over the Internet. Many devices, such as fitness trackers, are already in use … IoB devices … and those in development can track, record, and store users' whereabouts, bodily functions, and what they see, hear, and even think.

Schwab's World Economic Forum, a long-winded way of saying 'fascism' or 'the Cult', has gone full-on with the Internet of Bodies in the 'Covid' era. 'We're entering the era of the Internet of Bodies', it declared, 'collecting our physical data via a range of devices that can be implanted, swallowed or worn'. The result would be a huge amount of health-related data that could improve human wellbeing around the world, and prove crucial in fighting the 'Covid-19 pandemic'. Does anyone think these clowns care about 'human wellbeing' after the death and devastation their pandemic hoax has purposely caused? Schwab and co say we should move forward with the Internet of Bodies because 'Keeping track of symptoms could help us stop the spread of infection, and quickly detect new cases'. How wonderful, but keeping track' is all they are really bothered

about. Researchers were investigating if data gathered from smartwatches and similar devices could be used as viral infection alerts by tracking the user's heart rate and breathing. Schwab said in his 2018 book *Shaping the Future of the Fourth Industrial Revolution*:

> The lines between technologies and beings are becoming blurred and not just by the ability to create lifelike robots or synthetics. Instead it is about the ability of new technologies to literally become part of us. Technologies already influence how we understand ourselves, how we think about each other, and how we determine our realities. As the technologies … give us deeper access to parts of ourselves, we may begin to integrate digital technologies into our bodies.

You can see what the game is. Twenty-four hour control and people – if you could still call them that – would never know when something would go ping and take them out of circulation. It's the most obvious rush to a global fascist dictatorship and the complete submission of humanity and yet still so many are locked away in their Cult-induced perceptual coma and can't see it.

Smart Grid control centres

The human body is being transformed by the 'vaccines' and in other ways into a synthetic cyborg that can be attached to the global Smart Grid which would be controlled from a central point and other sub-locations of Grid manipulation. Where are these planned to be? Well, China for a start which is one of the Cult's biggest centres of operation. The technological control system and technocratic rule was incubated here to be unleashed across the world after the 'Covid' hoax came out of China in 2020. Another Smart Grid location that will surprise people new to this is Israel. I have exposed in *The Trigger* how Sabbatian technocrats, intelligence and military operatives were behind the horrors of 9/11 and not '19 Arab hijackers' who somehow manifested the ability to pilot big passenger airliners when instructors at puddle-jumping flying schools described some of them as a joke. The 9/11 attacks were made possible through control of civilian and military air computer systems and those of the White House, Pentagon and connected agencies. See *The Trigger* – it

will blow your mind. The controlling and coordinating force were the Sabbatian networks in Israel and the United States which by then had infiltrated the entire US government, military and intelligence system. The real name of the American Deep State is 'Sabbatian State'. Israel is a tiny country of only nine million people, but it is one of the global centres of cyber operations and fast catching Silicon Valley in importance to the Cult. Israel is known as the 'start-up nation' for all the cyber companies spawned there with the Sabbatian specialisation of 'cyber security' that I mentioned earlier which gives those companies access to computer systems of their clients in real time through 'backdoors' written into the coding when security software is downloaded. The Sabbatian centre of cyber operations outside Silicon Valley is the Israeli military Cyber Intelligence Unit, the biggest infrastructure project in Israel's history, headquartered in the desert-city of Beersheba and involving some 20,000 'cyber soldiers'. Here are located a literal army of Internet trolls scanning social media, forums and comment lists for anyone challenging the Cult agenda. The UK military has something similar with its 77th Brigade and associated operations. The Beersheba complex includes research and development centres for other Cult operations such as Intel, Microsoft, IBM, Google, Apple, Hewlett-Packard, Cisco Systems, Facebook and Motorola. Techcrunch.com ran an article about the Beersheba global Internet technology centre headlined 'Israel's desert city of Beersheba is turning into a cybertech oasis':

> The military's massive relocation of its prestigious technology units, the presence of multinational and local companies, a close proximity to Ben Gurion University and generous government subsidies are turning Beersheba into a major global cybertech hub. Beersheba has all of the ingredients of a vibrant security technology ecosystem, including Ben Gurion University with its graduate program in cybersecurity and Cyber Security Research Center, and the presence of companies such as EMC, Deutsche Telekom, PayPal, Oracle, IBM, and Lockheed Martin. It's also the future home of the INCB (Israeli National Cyber Bureau); offers a special income tax incentive for cyber security companies, and was the site for the relocation of the army's intelligence corps units.

Sabbatians have taken over the cyber world through the following process: They scan the schools for likely cyber talent and develop them at Ben Gurion University and their period of conscription in the Israeli Defense Forces when they are stationed at the Beersheba complex. When the cyber talented officially leave the army they are funded to start cyber companies with technology developed by themselves or given to them by the state. Much of this is stolen through backdoors of computer systems around the world with America top of the list. Others are sent off to Silicon Valley to start companies or join the major ones and so we have many major positions filled by apparently 'Jewish' but really Sabbatian operatives. Google, YouTube and Facebook are all run by 'Jewish' CEOs while Twitter is all but run by ultra-Zionist hedge-fund shark Paul Singer. At the centre of the Sabbatian global cyber web is the Israeli army's Unit 8200 which specialises in hacking into computer systems of other countries, inserting viruses, gathering information, instigating malfunction, and even taking control of them from a distance. A long list of Sabbatians involved with 9/11, Silicon Valley and Israeli cyber security companies are operatives of Unit 8200. This is not about Israel. It's about the Cult. Israel is planned to be a Smart Grid hub as with China and what is happening at Beersheba is not for the benefit of Jewish people who are treated disgustingly by the Sabbatian elite that control the country. A glance at the Nuremberg Codes will tell you that.

The story is much bigger than 'Covid', important as that is to where we are being taken. Now, though, it's time to really strap in. There's more … much more …

CHAPTER ELEVEN

Who controls the Cult?

Awake, arise or be forever fall'n
John Milton, *Paradise Lost*

I have exposed this far the level of the Cult conspiracy that operates in the world of the seen and within the global secret society and satanic network which operates in the shadows one step back from the seen. The story, however, goes much deeper than that.

The 'Covid' hoax is major part of the Cult agenda, but only part, and to grasp the biggest picture we have to expand our attention beyond the realm of human sight and into the infinity of possibility that we cannot see. It is from here, ultimately, that humanity is being manipulated into a state of total control by the force which dictates the actions of the Cult. How much of reality can we see? Next to damn all is the answer. We may appear to see all there is to see in the 'space' our eyes survey and observe, but little could be further from the truth. The human 'world' is only a tiny band of frequency that the body's visual and perceptual systems can decode into *perception* of a 'world'. According to mainstream science the electromagnetic spectrum is 0.005 percent of what exists in the Universe (Fig 10). The maximum estimate I have seen is 0.5 percent and either way it's miniscule. I say it is far, far, smaller even than 0.005 percent when you compare reality we see with the totality of reality that we don't. Now get this if you are new to such information: Visible light, the only band of frequency that we can see, is a *fraction* of the 0.005

percent (Fig 11 overleaf). Take this further and realise that our universe is one of infinite universes and that universes are only a fragment of overall reality – *infinite* reality. Then compare that with the almost infinitesimal frequency band of visible light or human sight. You see that humans are as near blind as it is possible to be without actually being so. Artist and filmmaker, Sergio Toporek, said:

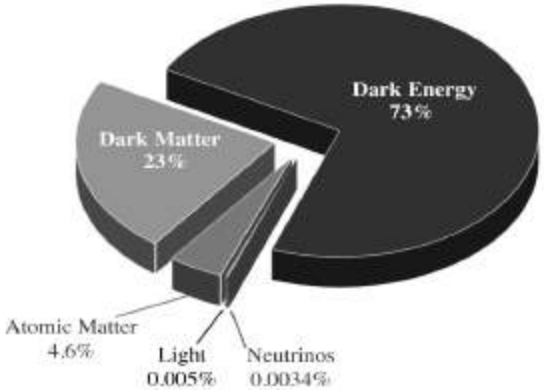


Figure 10: Humans can perceive such a tiny band of visual reality it's laughable.

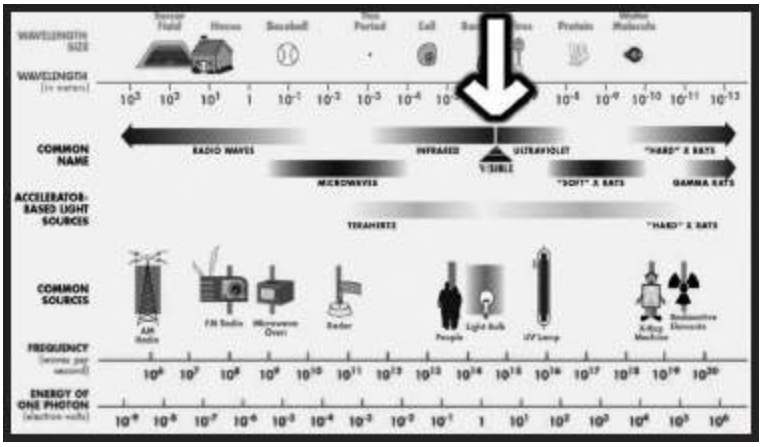


Figure 11: We can see a smear of the 0.005 percent electromagnetic spectrum, but we still know it all. Yep, makes sense.

Consider that you can see less than 1% of the electromagnetic spectrum and hear less than 1% of the acoustic spectrum. 90% of the cells in your body carry their own microbial DNA and are not 'you'. The atoms in your body are 99.9999999999999999% empty space and none of them are the ones you were born with ... Human beings have 46 chromosomes, two less than a potato.

The existence of the rainbow depends on the conical photoreceptors in your eyes; to animals without cones, the rainbow does not exist. So you don't just look at a rainbow, you create it. This is pretty amazing, especially considering that all the beautiful colours you see represent less than 1% of the electromagnetic spectrum.

Suddenly the 'world' of humans looks a very different place. Take into account, too, that Planet Earth when compared with the projected size of this single universe is the equivalent of a billionth of a pinhead. Imagine the ratio that would be when compared to infinite reality. To think that Christianity once insisted that Earth and humanity were the centre of everything. This background is vital if we are going to appreciate the nature of 'human' and how we can be manipulated by an unseen force. To human visual reality virtually *everything* is unseen and yet the prevailing perception within the institutions and so much of the public is that if we can't see it, touch it, hear it, taste it and smell it then it cannot exist. Such perception is indoctrinated and encouraged by the Cult and its agents because it isolates believers in the strictly limited, village-idiot, realm of the five senses where perceptions can be firewalled and information controlled. Most of those perpetuating the 'this-world-is-all-there-is' insanity are themselves indoctrinated into believing the same delusion. While major players and influencers know that official reality is laughable most of those in science, academia and medicine really believe the nonsense they peddle and teach succeeding generations. Those who challenge the orthodoxy are dismissed as nutters and freaks to protect the manufactured illusion from exposure. Observe the dynamic of the 'Covid' hoax and you will see how that takes the same form. The inner-circle psychopaths knows it's a gigantic scam, but almost the entirety of those imposing their fascist rules believe that 'Covid' is all that they're told it is.

Stolen identity

Ask people who they are and they will give you their name, place of birth, location, job, family background and life story. Yet that is not who they are – it is what they are *experiencing*. The difference is *absolutely crucial*. The true 'I', the eternal, infinite 'I', is consciousness,

a state of being aware. Forget 'form'. That is a vehicle for a brief experience. Consciousness does not come *from* the brain, but *through* the brain and even that is more symbolic than literal. We are awareness, pure awareness, and this is what withdraws from the body at what we call 'death' to continue our eternal beingness, *isness*, in other realms of reality within the limitlessness of infinity or the Biblical 'many mansions in my father's house'. Labels of a human life, man, woman, transgender, black, white, brown, nationality, circumstances and income are not who we are. They are what we are – awareness – is *experiencing* in a brief connection with a band of frequency we call 'human'. The labels are not the self; they are, to use the title of one of my books, a *Phantom* Self. I am not David Icke born in Leicester, England, on April 29th, 1952. I am the consciousness *having that experience*. The Cult and its non-human masters seek to convince us through the institutions of 'education', science, medicine, media and government that what we are *experiencing* is who we *are*. It's so easy to control and direct perception locked away in the bewildered illusions of the five senses with no expanded radar. Try, by contrast, doing the same with a humanity aware of its true self and its true power to consciously create its reality and experience. How is it possible to do this? We do it all day every day. If you perceive yourself as 'little me' with no power to impact upon your life and the world then your life experience will reflect that. You will hand the power you don't think you have to authority in all its forms which will use it to control your experience. This, in turn, will appear to confirm your perception of 'little me' in a self-fulfilling feedback loop. But that is what 'little me' really is – a *perception*. We are all 'big-me', infinite me, and the Cult has to make us forget that if its will is to prevail. We are therefore manipulated and pressured into self-identifying with human labels and not the consciousness/awareness *experiencing* those human labels.

The phenomenon of identity politics is a Cult-instigated manipulation technique to sub-divide previous labels into even smaller ones. A United States university employs this list of letters to

describe student identity: LGBTTQQFAGPBDSM or lesbian, gay, bisexual, transgender, transsexual, queer, questioning, flexual, asexual, gender-fuck, polyamorous, bondage/discipline, dominance/submission and sadism/masochism. I'm sure other lists are even longer by now as people feel the need to self-identity the 'I' with the minutiae of race and sexual preference. Wokers programmed by the Cult for generations believe this is about 'inclusivity' when it's really the Cult locking them away into smaller and smaller versions of Phantom Self while firewalling them from the influence of their true self, the infinite, eternal 'I'. You may notice that my philosophy which contends that we are all unique points of attention/awareness within the same infinite whole or Oneness is the ultimate non-racism. The very sense of Oneness makes the judgement of people by their body-type, colour or sexuality utterly ridiculous and confirms that racism has no understanding of reality (including anti-white racism). Yet despite my perception of life Cult agents and fast-asleep Wokers label me racist to discredit my information while they are themselves phenomenally racist and sexist. All they see is race and sexuality and they judge people as good or bad, demons or untouchables, by their race and sexuality. All they see is *Phantom Self* and perceive themselves in terms of Phantom Self. They are pawns and puppets of the Cult agenda to focus attention and self-identity in the five senses and play those identities against each other to divide and rule. Columbia University has introduced segregated graduations in another version of social distancing designed to drive people apart and teach them that different racial and cultural groups have nothing in common with each other. The last thing the Cult wants is unity. Again the pump-primers of this will be Cult operatives in the knowledge of what they are doing, but the rest are just the Phantom Self blind leading the Phantom Self blind. We *do* have something in common – we are all *the same consciousness* having different temporary experiences.

What is this 'human'?

Yes, what *is* 'human'? That is what we are supposed to be, right? I mean 'human'? True, but 'human' is the experience not the 'I'. Break it down to basics and 'human' is the way that information is processed. If we are to experience and interact with this band of frequency we call the 'world' we must have a vehicle that operates within that band of frequency. Our consciousness in its prime form cannot do that; it is way beyond the frequency of the human realm. My consciousness or awareness could not tap these keys and pick up the cup in front of me in the same way that radio station A cannot interact with radio station B when they are on different frequencies. The human body is the means through which we have that interaction. I have long described the body as a biological computer which processes information in a way that allows consciousness to experience this reality. The body is a receiver, transmitter and processor of information in a particular way that we call human. We visually perceive only the world of the five senses in a wakened state – that is the limit of the body's visual decoding system. In truth it's not even visual in the way we experience 'visual reality' as I will come to in a moment. We are 'human' because the body processes the information sources of human into a reality and behaviour system that we *perceive* as human. Why does an elephant act like an elephant and not like a human or a duck? The elephant's biological computer is a different information field and processes information according to that program into a visual and behaviour type we call an elephant. The same applies to everything in our reality. These body information fields are perpetuated through procreation (like making a copy of a software program). The Cult wants to break that cycle and intervene technologically to transform the human information field into one that will change what we call humanity. If it can change the human information field it will change the way that field processes information and change humanity both 'physically' and psychologically. Hence the *messenger* (information) RNA 'vaccines' and so much more that is targeting human genetics by changing the body's information – *messaging* – construct through food, drink, radiation, toxicity and other means.

Reality that we experience is nothing like reality as it really is in the same way that the reality people experience in virtual reality games is not the reality they are really living in. The game is only a decoded source of information that appears to be a reality. Our world is also an information construct – a *simulation* (more later). In its base form our reality is a wavefield of information much the same in theme as Wi-Fi. The five senses decode wavefield information into electrical information which they communicate to the brain to decode into holographic (illusory 'physical') information. Different parts of the brain specialise in decoding different senses and the information is fused into a reality that appears to be outside of us but is really inside the brain and the genetic structure in general (Fig 12 overleaf). DNA is a receiver-transmitter of information and a vital part of this decoding process and the body's connection to other realities. Change DNA and you change the way we decode and connect with reality – see 'Covid vaccines'. Think of computers decoding Wi-Fi. You have information encoded in a radiation field and the computer decodes that information into a very different form on the screen. You can't see the Wi-Fi until its information is made manifest on the screen and the information on the screen is inside the computer and not outside. I have just described how we decode the 'human world'. All five senses decode the waveform 'Wi-Fi' field into electrical signals and the brain (computer) constructs reality inside the brain and not outside – 'You don't just look at a rainbow, you create it'. Sound is a simple example. We don't hear sound until the brain decodes it. Waveform sound waves are picked up by the hearing sense and communicated to the brain in an electrical form to be decoded into the sounds that we hear. Everything we hear is inside the brain along with everything we see, feel, smell and taste. Words and language are waveform fields generated by our vocal chords which pass through this process until they are decoded by the brain into words that we hear. Different languages are different frequency fields or sound waves generated by vocal chords. Late British philosopher Alan Watts said:

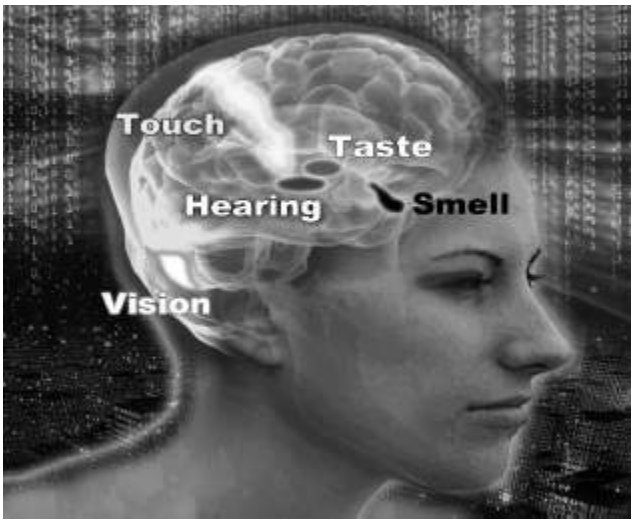


Figure 12: The brain receives information from the five senses and constructs from that our perceived reality.

[Without the brain] the world is devoid of light, heat, weight, solidity, motion, space, time or any other imaginable feature. All these phenomena are interactions, or transactions, of vibrations with a certain arrangement of neurons.

That's exactly what they are and scientist Robert Lanza describes in his book, *Biocentrism*, how we decode electromagnetic waves and energy into visual and 'physical' experience. He uses the example of a flame emitting photons, electromagnetic energy, each pulsing electrically and magnetically:

… these … invisible electromagnetic waves strike a human retina, and if (and only if) the waves happen to measure between 400 and 700 nano meters in length from crest to crest, then their energy is just right to deliver a stimulus to the 8 million cone-shaped cells in the retina.

Each in turn send an electrical pulse to a neighbour neuron, and on up the line this goes, at 250 mph, until it reaches the … occipital lobe of the brain, in the back of the head. There, a cascading complex of neurons fire from the incoming stimuli, and we subjectively perceive this experience as a yellow brightness occurring in a place we have been conditioned to call the 'external world'.

You hear what you decode

If a tree falls or a building collapses they make no noise unless someone is there to decode the energetic waves generated by the disturbance into what we call sound. Does a falling tree make a noise? Only if you hear it – *decode* it. Everything in our reality is a frequency field of information operating within the overall 'Wi-Fi' field that I call The Field. A vibrational disturbance is generated in The Field by the fields of the falling tree or building. These disturbance waves are what we decode into the sound of them falling. If no one is there to do that then neither will make any noise. Reality is created by the observer – *decoder* – and the *perceptions* of the observer affect the decoding process. For this reason different people – different *perceptions* – will perceive the same reality or situation in a different way. What one may perceive as a nightmare another will see as an opportunity. The question of why the Cult is so focused on controlling human perception now answers itself. All experienced reality is the act of decoding and we don't experience Wi-Fi until it is decoded on the computer screen. The sight and sound of an Internet video is encoded in the Wi-Fi all around us, but we don't see or hear it until the computer decodes that information. Taste, smell and touch are all phenomena of the brain as a result of the same process. We don't taste, smell or feel anything except in the brain and there are pain relief techniques that seek to block the signal from the site of discomfort to the brain because if the brain doesn't decode that signal we don't feel pain. Pain is in the brain and only appears to be at the point of impact thanks to the feedback loop between them. We don't see anything until electrical information from the sight senses is decoded in an area at the back of the brain. If that area is damaged we can go blind when our eyes are perfectly okay. So why do we go blind if we damage an eye? We damage the information processing between the waveform visual information and the visual decoding area of the brain. If information doesn't reach the brain in a form it can decode then we can't see the visual reality that it represents. What's more the brain is decoding only a fraction of the information it receives and the rest is absorbed by the

sub-conscious mind. This explanation is from the science magazine, *Wonderpedia*:

> Every second, 11 million sensations crackle along these [brain] pathways ... The brain is confronted with an alarming array of images, sounds and smells which it rigorously filters down until it is left with a manageable list of around 40. Thus 40 sensations per second make up what we perceive as reality.

The 'world' is not what people are told to believe that is it and the inner circles of the Cult *know that*.

Illusory 'physical' reality

We can only see a smear of 0.005 percent of the Universe which is only one of a vast array of universes – 'mansions' – within infinite reality. Even then the brain decodes only 40 pieces of information ('sensations') from a potential *11 million* that we receive every second. Two points strike you from this immediately: The sheer breathtaking stupidity of believing we know anything so rigidly that there's nothing more to know; and the potential for these processes to be manipulated by a malevolent force to control the reality of the population. One thing I can say for sure with no risk of contradiction is that when you can perceive an almost indescribable fraction of infinite reality there is always more to know as in tidal waves of it. Ancient Greek philosopher Socrates was so right when he said that wisdom is to know how little we know. How obviously true that is when you think that we are experiencing a physical world of solidity that is neither physical nor solid and a world of apartness when everything is connected. Cult-controlled 'science' dismisses the so-called 'paranormal' and all phenomena related to that when the 'para'-normal is perfectly normal and explains the alleged 'great mysteries' which dumbfound scientific minds. There is a reason for this. A 'scientific mind' in terms of the mainstream is a material mind, a five-sense mind imprisoned in see it, touch it, hear it, smell it and taste it. Phenomena and happenings that can't be explained that way leave the 'scientific mind' bewildered and the rule is that if they

can't account for why something is happening then it can't, by definition, be happening. I beg to differ. Telepathy is thought waves passing through The Field (think wave disturbance again) to be decoded by someone able to connect with that wavelength (information). For example: You can pick up the thought waves of a friend at any distance and at the very least that will bring them to mind. A few minutes later the friend calls you. 'My god', you say, 'that's incredible – I was just thinking of you.' Ah, but *they* were thinking of *you* before they made the call and that's what you decoded. Native peoples not entrapped in five-sense reality do this so well it became known as the 'bush telegraph'. Those known as psychics and mediums (genuine ones) are doing the same only across dimensions of reality. 'Mind over matter' comes from the fact that matter and mind are the *same*. The state of one influences the state of the other. Indeed one *and* the other are illusions. They are aspects of the same field. Paranormal phenomena are all explainable so why are they still considered 'mysteries' or not happening? Once you go down this road of understanding you begin to expand awareness beyond the five senses and that's the nightmare for the Cult.



Figure 13: Holograms are not solid, but the best ones appear to be.

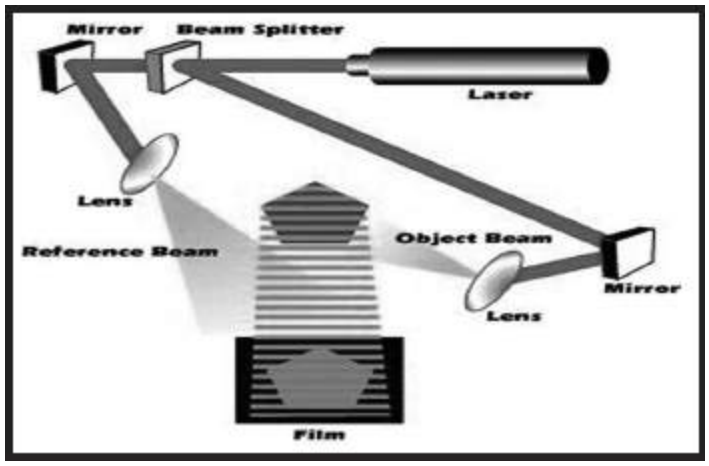


Figure 14: How holograms are created by capturing a waveform version of the subject image.

Holographic 'solidity'

Our reality is not solid, it is holographic. We are now well aware of holograms which are widely used today. Two-dimensional information is decoded into a three-dimensional reality that is not solid although can very much appear to be (Fig 13). Holograms are created with a laser divided into two parts. One goes directly onto a holographic photographic print ('reference beam') and the other takes a waveform image of the subject ('working beam') before being directed onto the print where it 'collides' with the other half of the laser (Fig 14). This creates a *waveform* interference pattern which contains the wavefield information of whatever is being photographed (Fig 15 overleaf). The process can be likened to dropping pebbles in a pond. Waves generated by each one spread out across the water to collide with the others and create a wave representation of where the stones fell and at what speed, weight and distance. A waveform interference pattern of a hologram is akin to the waveform information in The Field which the five senses decode into electrical signals to be decoded by the brain into a holographic illusory 'physical' reality. In the same way when a laser (think human attention) is directed at the waveform interference pattern a three-dimensional version of the subject is projected into apparently 'solid' reality (Fig 16). An amazing trait of holograms reveals more 'paranormal mysteries'. Information of the *whole*

hologram is encoded in waveform in every part of the interference pattern by the way they are created. This means that every *part* of a hologram is a smaller version of the whole. Cut the interference wave-pattern into four and you won't get four parts of the image. You get quarter-sized versions of the *whole* image. The body is a hologram and the same applies. Here we have the basis of acupuncture, reflexology and other forms of healing which identify representations of the whole body in all of the parts, hands, feet, ears, everywhere. Skilled palm readers can do what they do because the information of whole body is encoded in the hand. The concept of as above, so below, comes from this.



Figure 15: A waveform interference pattern that holds the information that transforms into a hologram.



Figure 16: Holographic people including 'Elvis' holographically inserted to sing a duet with Celine Dion.

The question will be asked of why, if solidity is illusory, we can't just walk through walls and each other. The resistance is not solid against solid; it is electromagnetic field against electromagnetic field and we decode this into the *experience* of solid against solid. We should also not underestimate the power of belief to dictate reality. What you believe is impossible *will be*. Your belief impacts on your decoding processes and they won't decode what you think is impossible. What we believe we perceive and what we perceive we experience. 'Can't dos' and 'impossibles' are like a firewall in a computer system that won't put on the screen what the firewall blocks. How vital that is to understanding how human experience has been hijacked. I explain in *The Answer*, *Everything You Need To Know But Have Never Been Told* and other books a long list of 'mysteries' and 'paranormal' phenomena that are not mysterious and perfectly normal once you realise what reality is and how it works. 'Ghosts' can be seen to pass through 'solid' walls because the walls are not solid and the ghost is a discarnate entity operating on a frequency so different to that of the wall that it's like two radio stations sharing the same space while never interfering with each other. I have seen ghosts do this myself. The apartness of people and objects is also an illusion. Everything is connected by the Field like all sea life is connected by the sea. It's just that within the limits of our visual reality we only 'see' holographic information and not the field of information that connects everything and from which the holographic world is made manifest. If you can only see holographic 'objects' and not the field that connects them they will appear to you as unconnected to each other in the same way that we see the computer while not seeing the Wi-Fi.

What you don't know *can* hurt you

Okay, we return to those 'two worlds' of human society and the Cult with its global network of interconnecting secret societies and satanic groups which manipulate through governments, corporations, media, religions, etc. The fundamental difference between them is *knowledge*. The idea has been to keep humanity

ignorant of the plan for its total enslavement underpinned by a crucial ignorance of reality – who we are and where we are – and how we interact with it. 'Human' should be the interaction between our expanded eternal consciousness and the five-sense body experience. We are meant to be *in* this world in terms of the five senses but not *of* this world in relation to our greater consciousness and perspective. In that state we experience the small picture of the five senses within the wider context of the big picture of awareness beyond the five senses. Put another way the five senses see the dots and expanded awareness connects them into pictures and patterns that give context to the apparently random and unconnected. Without the context of expanded awareness the five senses see only apartness and randomness with apparently no meaning. The Cult and its other-dimensional controllers seek to intervene in the frequency realm where five-sense reality is supposed to connect with expanded reality and to keep the two apart (more on this in the final chapter). When that happens five-sense mental and emotional processes are no longer influenced by expanded awareness, or the True 'I', and instead are driven by the isolated perceptions of the body's decoding systems. They are in the world *and* of it. Here we have the human plight and why humanity with its potential for infinite awareness can be so easily manipulatable and descend into such extremes of stupidity.

Once the Cult isolates five-sense mind from expanded awareness it can then program the mind with perceptions and beliefs by controlling information that the mind receives through the 'education' system of the formative years and the media perceptual bombardment and censorship of an entire lifetime. Limit perception and a sense of the possible through limiting knowledge by limiting and skewing information while censoring and discrediting that which could set people free. As the title of another of my books says *… And The Truth Shall Set You Free*. For this reason the last thing the Cult wants in circulation is the truth about anything – especially the reality of the eternal 'I' – and that's why it is desperate to control information. The Cult knows that information becomes perception

which becomes behaviour which, collectively, becomes human society. Cult-controlled and funded mainstream 'science' denies the existence of an eternal 'I' and seeks to dismiss and trash all evidence to the contrary. Cult-controlled mainstream religion has a version of 'God' that is little more than a system of control and dictatorship that employs threats of damnation in an afterlife to control perceptions and behaviour in the here and now through fear and guilt. Neither is true and it's the 'neither' that the Cult wishes to suppress. This 'neither' is that everything is an expression, a point of attention, within an infinite state of consciousness which is the real meaning of the term 'God'.

Perceptual obsession with the 'physical body' and five-senses means that 'God' becomes personified as a bearded bloke sitting among the clouds or a raging bully who loves us if we do what 'he' wants and condemns us to the fires of hell if we don't. These are no more than a 'spiritual' fairy tales to control and dictate events and behaviour through fear of this 'God' which has bizarrely made 'God-fearing' in religious circles a state to be desired. I would suggest that fearing *anything* is not to be encouraged and celebrated, but rather deleted. You can see why 'God fearing' is so beneficial to the Cult and its religions when *they* decide what 'God' wants and what 'God' demands (the Cult demands) that everyone do. As the great American comedian Bill Hicks said satirising a Christian zealot: 'I think what God meant to say.' How much of this infinite awareness ('God') that we access is decided by how far we choose to expand our perceptions, self-identity and sense of the possible. The scale of self-identity reflects itself in the scale of awareness that we can connect with and are influenced by – how much knowing and insight we have instead of programmed perception. You cannot expand your awareness into the infinity of possibility when you believe that you are little me Peter the postman or Mary in marketing and nothing more. I'll deal with this in the concluding chapter because it's crucial to how we turnaround current events.

Where the Cult came from

When I realised in the early 1990s there was a Cult network behind global events I asked the obvious question: When did it start? I took it back to ancient Rome and Egypt and on to Babylon and Sumer in Mesopotamia, the 'Land Between Two Rivers', in what we now call Iraq. The two rivers are the Tigris and Euphrates and this region is of immense historical and other importance to the Cult, as is the land called Israel only 550 miles away by air. There is much more going with deep esoteric meaning across this whole region. It's not only about 'wars for oil'. Priceless artefacts from Mesopotamia were stolen or destroyed after the American and British invasion of Iraq in 2003 justified by the lies of Boy Bush and Tony Blair (their Cult masters) about non-existent 'weapons of mass destruction'. Mesopotamia was the location of Sumer (about 5,400BC to 1,750BC), and Babylon (about 2,350BC to 539BC). Sabbatians may have become immensely influential in the Cult in modern times but they are part of a network that goes back into the mists of history. Sumer is said by historians to be the 'cradle of civilisation'. I disagree. I say it was the re-start of what we call human civilisation after cataclysmic events symbolised in part as the 'Great Flood' destroyed the world that existed before. These fantastic upheavals that I have been describing in detail in the books since the early1990s appear in accounts and legends of ancient cultures across the world and they are supported by geological and biological evidence. Stone tablets found in Iraq detailing the Sumer period say the cataclysms were caused by non-human 'gods' they call the Anunnaki. These are described in terms of extraterrestrial visitations in which knowledge supplied by the Anunnaki is said to have been the source of at least one of the world's oldest writing systems and developments in astronomy, mathematics and architecture that were way ahead of their time. I have covered this subject at length in *The Biggest Secret* and *Children of the Matrix* and the same basic 'Anunnaki' story can be found in Zulu accounts in South Africa where the late and very great Zulu high shaman Credo Mutwa told me that the Sumerian Anunnaki were known by Zulus as the Chitauri or 'children of the serpent'. See my six-hour video interview with Credo on this subject entitled *The*

Reptilian Agenda recorded at his then home near Johannesburg in 1999 which you can watch on the Ickonic media platform.

The Cult emerged out of Sumer, Babylon and Egypt (and elsewhere) and established the Roman Empire before expanding with the Romans into northern Europe from where many empires were savagely imposed in the form of Cult-controlled societies all over the world. Mass death and destruction was their calling card. The Cult established its centre of operations in Europe and European Empires were Cult empires which allowed it to expand into a global force. Spanish and Portuguese colonialists headed for Central and South America while the British and French targeted North America. Africa was colonised by Britain, France, Belgium, the Netherlands, Portugal, Spain, Italy, and Germany. Some like Britain and France moved in on the Middle East. The British Empire was by far the biggest for a simple reason. By now Britain was the headquarters of the Cult from which it expanded to form Canada, the United States, Australia and New Zealand. The Sun never set on the British Empire such was the scale of its occupation. London remains a global centre for the Cult along with Rome and the Vatican although others have emerged in Israel and China. It is no accident that the 'virus' is alleged to have come out of China while Italy was chosen as the means to terrify the Western population into compliance with 'Covid' fascism. Nor that Israel has led the world in 'Covid' fascism and mass 'vaccination'.

You would think that I would mention the United States here, but while it has been an important means of imposing the Cult's will it is less significant than would appear and is currently in the process of having what power it does have deleted. The Cult in Europe has mostly loaded the guns for the US to fire. America has been controlled from Europe from the start through Cult operatives in Britain and Europe. The American Revolution was an illusion to make it appear that America was governing itself while very different forces were pulling the strings in the form of Cult families such as the Rothschilds through the Rockefellers and other subordinates. The Rockefellers are extremely close to Bill Gates and

established both scalpel and drug 'medicine' and the World Health Organization. They play a major role in the development and circulation of vaccines through the Rockefeller Foundation on which Bill Gates said his Foundation is based. Why wouldn't this be the case when the Rockefellers and Gates are on the same team? Cult infiltration of human society goes way back into what we call history and has been constantly expanding and centralising power with the goal of establishing a global structure to dictate everything. Look how this has been advanced in great leaps with the 'Covid' hoax.

The non-human dimension

I researched and observed the comings and goings of Cult operatives through the centuries and even thousands of years as they were born, worked to promote the agenda within the secret society and satanic networks, and then died for others to replace them. Clearly there had to be a coordinating force that spanned this entire period while operatives who would not have seen the end goal in their lifetimes came and went advancing the plan over millennia. I went in search of that coordinating force with the usual support from the extraordinary synchronicity of my life which has been an almost daily experience since 1990. I saw common themes in religious texts and ancient cultures about a non-human force manipulating human society from the hidden. Christianity calls this force Satan, the Devil and demons; Islam refers to the Jinn or Djinn; Zulus have their Chitauri (spelt in other ways in different parts of Africa); and the Gnostic people in Egypt in the period around and before 400AD referred to this phenomena as the 'Archons', a word meaning rulers in Greek. Central American cultures speak of the 'Predators' among other names and the same theme is everywhere. I will use 'Archons' as a collective name for all of them. When you see how their nature and behaviour is described all these different sources are clearly talking about the same force. Gnostics described the Archons in terms of 'luminous fire' while Islam relates the Jinn to 'smokeless fire'. Some refer to beings in form that could occasionally be seen, but the most common of common theme is that they operate from

unseen realms which means almost all existence to the visual processes of humans. I had concluded that this was indeed the foundation of human control and that the Cult was operating within the human frequency band on behalf of this hidden force when I came across the writings of Gnostics which supported my conclusions in the most extraordinary way.

A sealed earthen jar was found in 1945 near the town of Nag Hammadi about 75-80 miles north of Luxor on the banks of the River Nile in Egypt. Inside was a treasure trove of manuscripts and texts left by the Gnostic people some 1,600 years earlier. They included 13 leather-bound papyrus codices (manuscripts) and more than 50 texts written in Coptic Egyptian estimated to have been hidden in the jar in the period of 400AD although the source of the information goes back much further. Gnostics oversaw the Great or Royal Library of Alexandria, the fantastic depository of ancient texts detailing advanced knowledge and accounts of human history. The Library was dismantled and destroyed in stages over a long period with the death-blow delivered by the Cult-established Roman Church in the period around 415AD. The Church of Rome was the Church of Babylon relocated as I said earlier. Gnostics were not a race. They were a way of perceiving reality. Whenever they established themselves and their information circulated the terrorists of the Church of Rome would target them for destruction. This happened with the Great Library and with the Gnostic Cathars who were burned to death by the psychopaths after a long period of oppression at the siege of the Castle of Monségur in southern France in 1244. The Church has always been terrified of Gnostic information which demolishes the official Christian narrative although there is much in the Bible that supports the Gnostic view if you read it in another way. To anyone studying the texts of what became known as the Nag Hammadi Library it is clear that great swathes of Christian and Biblical belief has its origin with Gnostics sources going back to Sumer. Gnostic themes have been twisted to manipulate the perceived reality of Bible believers. Biblical texts have been in the open for centuries where they could be changed while Gnostic

documents found at Nag Hammadi were sealed away and untouched for 1,600 years. What you see is what they wrote.

Use your *pneuma* not your *nous*

Gnosticism and Gnostic come from 'gnosis' which means knowledge, or rather *secret* knowledge, in the sense of spiritual awareness – knowledge about reality and life itself. The desperation of the Cult's Church of Rome to destroy the Gnostics can be understood when the knowledge they were circulating was the last thing the Cult wanted the population to know. Sixteen hundred years later the same Cult is working hard to undermine and silence me for the same reason. The dynamic between knowledge and ignorance is a constant. 'Time' appears to move on, but essential themes remain the same. We are told to 'use your nous', a Gnostic word for head/brain/intelligence. They said, however, that spiritual awakening or 'salvation' could only be secured by expanding awareness *beyond* what they called *nous* and into *pneuma* or Infinite Self. Obviously as I read these texts the parallels with what I have been saying since 1990 were fascinating to me. There is a universal truth that spans human history and in that case why wouldn't we be talking the same language 16 centuries apart? When you free yourself from the perception program of the five senses and explore expanded realms of consciousness you are going to connect with the same information no matter what the perceived 'era' within a manufactured timeline of a single and tiny range of manipulated frequency. Humans working with 'smart' technology or knocking rocks together in caves is only a timeline appearing to operate within the human frequency band. Expanded awareness and the knowledge it holds have always been there whether the era be Stone Age or computer age. We can only access that knowledge by opening ourselves to its frequency which the five-sense prison cell is designed to stop us doing. Gates, Fauci, Whitty, Vallance, Zuckerberg, Brin, Page, Wojcicki, Bezos, and all the others behind the 'Covid' hoax clearly have a long wait before their range of frequency can make that connection given that an open heart is

crucial to that as we shall see. Instead of accessing knowledge directly through expanded awareness it is given to Cult operatives by the secret society networks of the Cult where it has been passed on over thousands of years outside the public arena. Expanded realms of consciousness is where great artists, composers and writers find their inspiration and where truth awaits anyone open enough to connect with it. We need to go there fast.

Archon hijack

A fifth of the Nag Hammadi texts describe the existence and manipulation of the Archons led by a 'Chief Archon' they call 'Yaldabaoth', or the 'Demiurge', and this is the Christian 'Devil', 'Satan', 'Lucifer', and his demons. Archons in Biblical symbolism are the 'fallen ones' which are also referred to as fallen angels after the angels expelled from heaven according to the Abrahamic religions of Judaism, Christianity and Islam. These angels are claimed to tempt humans to 'sin' ongoing and you will see how accurate that symbolism is during the rest of the book. The theme of 'original sin' is related to the 'Fall' when Adam and Eve were 'tempted by the serpent' and fell from a state of innocence and 'obedience' (connection) with God into a state of disobedience (disconnection). The Fall is said to have brought sin into the world and corrupted everything including human nature. Yaldabaoth, the 'Lord Archon', is described by Gnostics as a 'counterfeit spirit', 'The Blind One', 'The Blind God', and 'The Foolish One'. The Jewish name for Yaldabaoth in Talmudic writings is Samael which translates as 'Poison of God', or 'Blindness of God'. You see the parallels. Yaldabaoth in Islamic belief is the Muslim Jinn devil known as Shaytan – Shaytan is Satan as the same themes are found all over the world in every religion and culture. The 'Lord God' of the Old Testament is the 'Lord Archon' of Gnostic manuscripts and that's why he's such a bloodthirsty bastard. Satan is known by Christians as 'the Demon of Demons' and Gnostics called Yaldabaoth the 'Archon of Archons'. Both are known as 'The Deceiver'. We are talking about the same 'bloke' for sure and these common themes

using different names, storylines and symbolism tell a common tale of the human plight.

Archons are referred to in Nag Hammadi documents as mind parasites, inverters, guards, gatekeepers, detainers, judges, pitiless ones and deceivers. The 'Covid' hoax alone is a glaring example of all these things. The Biblical 'God' is so different in the Old and New Testaments because they are not describing the same phenomenon. The vindictive, angry, hate-filled, 'God' of the Old Testament, known as Yahweh, is Yaldabaoth who is depicted in Cult-dictated popular culture as the 'Dark Lord', 'Lord of Time', Lord (Darth) Vader and Dormammu, the evil ruler of the 'Dark Dimension' trying to take over the 'Earth Dimension' in the Marvel comic movie, *Dr Strange*. Yaldabaoth is both the Old Testament 'god' and the Biblical 'Satan'. Gnostics referred to Yaldabaoth as the 'Great Architect of the Universe'and the Cult-controlled Freemason network calls their god 'the 'Great Architect of the Universe' (also Grand Architect). The 'Great Architect' Yaldabaoth is symbolised by the Cult as the all-seeing eye at the top of the pyramid on the Great Seal of the United States and the dollar bill. Archon is encoded in *arch*-itect as it is in *arch*-angels and *arch*-bishops. All religions have the theme of a force for good and force for evil in some sort of spiritual war and there is a reason for that – the theme is true. The Cult and its non-human masters are quite happy for this to circulate. They present themselves as the force for good fighting evil when they are really the force of evil (absence of love). The whole foundation of Cult modus operandi is inversion. They promote themselves as a force for good and anyone challenging them in pursuit of peace, love, fairness, truth and justice is condemned as a satanic force for evil. This has been the game plan throughout history whether the Church of Rome inquisitions of non-believers or 'conspiracy theorists' and 'anti-vaxxers' of today. The technique is the same whatever the timeline era.

Yaldabaoth is revolting (true)

Yaldabaoth and the Archons are said to have revolted against God with Yaldabaoth claiming to *be* God – the *All That Is*. The Old Testament 'God' (Yaldabaoth) demanded to be worshipped as such: ' *I am* the LORD, and there is none else, there is no God beside me' (Isaiah 45:5). I have quoted in other books a man who said he was the unofficial son of the late Baron Philippe de Rothschild of the Mouton-Rothschild wine producing estates in France who died in 1988 and he told me about the Rothschild 'revolt from God'. The man said he was given the name Phillip Eugene de Rothschild and we shared long correspondence many years ago while he was living under another identity. He said that he was conceived through 'occult incest' which (within the Cult) was 'normal and to be admired'. 'Phillip' told me about his experience attending satanic rituals with rich and famous people whom he names and you can see them and the wider background to Cult Satanism in my other books starting with *The Biggest Secret*. Cult rituals are interactions with Archontic 'gods'. 'Phillip' described Baron Philippe de Rothschild as 'a master Satanist and hater of God' and he used the same term 'revolt from God' associated with Yaldabaoth/Satan/Lucifer/the Devil in describing the Sabbatian Rothschild dynasty. 'I played a key role in my family's revolt from God', he said. That role was to infiltrate in classic Sabbatian style the Christian Church, but eventually he escaped the mind-prison to live another life. The Cult has been targeting religion in a plan to make worship of the Archons the global one-world religion. Infiltration of Satanism into modern 'culture', especially among the young, through music videos, stage shows and other means, is all part of this.

Nag Hammadi texts describe Yaldabaoth and the Archons in their prime form as energy – consciousness – and say they can take form if they choose in the same way that consciousness takes form as a human. Yaldabaoth is called 'formless' and represents a deeply inverted, distorted and chaotic state of consciousness which seeks to attached to humans and turn them into a likeness of itself in an attempt at assimilation. For that to happen it has to manipulate

humans into low frequency mental and emotional states that match its own. Archons can certainly appear in human form and this is the origin of the psychopathic personality. The energetic distortion Gnostics called Yaldabaoth *is* psychopathy. When psychopathic Archons take human form that human will be a psychopath as an expression of Yaldabaoth consciousness. Cult psychopaths are Archons in human form. The principle is the same as that portrayed in the 2009 *Avatar* movie when the American military travelled to a fictional Earth-like moon called Pandora in the Alpha Centauri star system to infiltrate a society of blue people, or Na'vi, by hiding within bodies that looked like the Na'vi. Archons posing as humans have a particular hybrid information field, part human, part Archon, (the ancient 'demigods') which processes information in a way that manifests behaviour to match their psychopathic evil, lack of empathy and compassion, and stops them being influenced by the empathy, compassion and love that a fully-human information field is capable of expressing. Cult bloodlines interbreed, be they royalty or dark suits, for this reason and you have their obsession with incest. Interbreeding with full-blown humans would dilute the Archontic energy field that guarantees psychopathy in its representatives in the human realm.

Gnostic writings say the main non-human forms that Archons take are *serpentine* (what I have called for decades 'reptilian' amid unbounded ridicule from the Archontically-programmed) and what Gnostics describe as 'an unborn baby or foetus with grey skin and dark, unmoving eyes'. This is an excellent representation of the ET 'Greys' of UFO folklore which large numbers of people claim to have seen and been abducted by – Zulu shaman Credo Mutwa among them. I agree with those that believe in extraterrestrial or interdimensional visitations today and for thousands of years past. No wonder with their advanced knowledge and technological capability they were perceived and worshipped as gods for technological and other 'miracles' they appeared to perform. Imagine someone arriving in a culture disconnected from the modern world with a smartphone and computer. They would be

seen as a 'god' capable of 'miracles'. The Renegade Mind, however, wants to know the source of everything and not only the way that source manifests as human or non-human. In the same way that a Renegade Mind seeks the original source material for the 'Covid virus' to see if what is claimed is true. The original source of Archons in form is consciousness – the distorted state of consciousness known to Gnostics as Yaldabaoth.

'Revolt from God' is energetic disconnection

Where I am going next will make a lot of sense of religious texts and ancient legends relating to 'Satan', Lucifer' and the 'gods'. Gnostic descriptions sync perfectly with the themes of my own research over the years in how they describe a consciousness distortion seeking to impose itself on human consciousness. I've referred to the core of infinite awareness in previous books as Infinite Awareness in Awareness of Itself. By that I mean a level of awareness that knows that it is all awareness and is aware of all awareness. From here comes the frequency of love in its true sense and balance which is what love is on one level – the balance of all forces into a single whole called Oneness and Isness. The more we disconnect from this state of love that many call 'God' the constituent parts of that Oneness start to unravel and express themselves as a part and not a whole. They become individualised as intellect, mind, selfishness, hatred, envy, desire for power over others, and such like. This is not a problem in the greater scheme in that 'God', the *All That Is*, can experience all these possibilities through different expressions of itself including humans. What we as expressions of the whole experience the *All That Is* experiences. We are the *All That Is* experiencing itself. As we withdraw from that state of Oneness we disconnect from its influence and things can get very unpleasant and very stupid. Archontic consciousness is at the extreme end of that. It has so disconnected from the influence of Oneness that it has become an inversion of unity and love, an inversion of everything, an inversion of life itself. Evil is appropriately live written backwards. Archontic consciousness is obsessed with death, an inversion of life,

and so its manifestations in Satanism are obsessed with death. They use inverted symbols in their rituals such as the inverted pentagram and cross. Sabbatians as Archontic consciousness incarnate invert Judaism and every other religion and culture they infiltrate. They seek disunity and chaos and they fear unity and harmony as they fear love like garlic to a vampire. As a result the Cult, Archons incarnate, act with such evil, psychopathy and lack of empathy and compassion disconnected as they are from the source of love. How could Bill Gates and the rest of the Archontic psychopaths do what they have to human society in the 'Covid' era with all the death, suffering and destruction involved and have no emotional consequence for the impact on others? Now you know. Why have Zuckerberg, Brin, Page, Wojcicki and company callously censored information warning about the dangers of the 'vaccine' while thousands have been dying and having severe, sometimes life-changing reactions? Now you know. Why have Tedros, Fauci, Whitty, Vallance and their like around the world been using case and death figures they're aware are fraudulent to justify lockdowns and all the deaths and destroyed lives that have come from that? Now you know. Why did Christian Drosten produce and promote a 'testing' protocol that he knew couldn't test for infectious disease which led to a global human catastrophe. Now you know. The Archontic mind doesn't give a shit (Fig 17). I personally think that Gates and major Cult insiders are a form of AI cyborg that the Archons want humans to become.

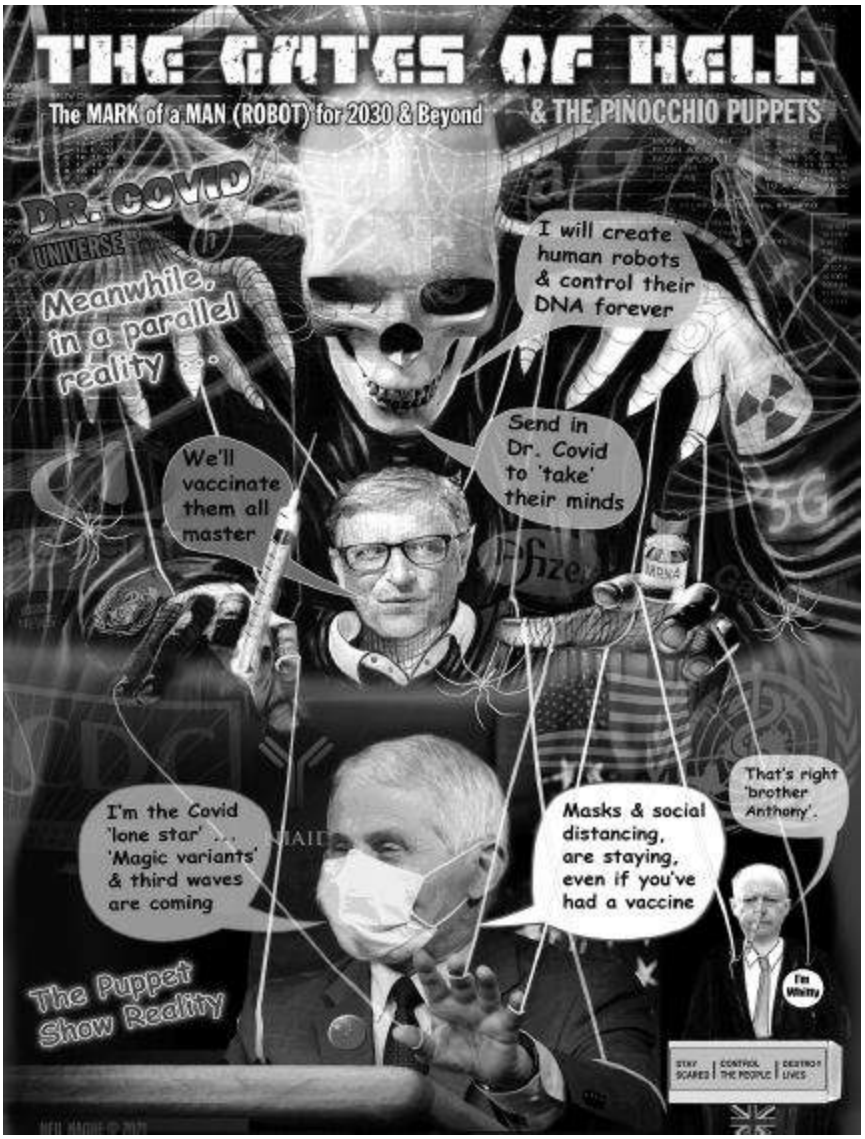


Figure 17: Artist Neil Hague's version of the 'Covid' hierarchy.

Human batteries

A state of such inversion does have its consequences, however. The level of disconnection from the Source of All means that you withdraw from that source of energetic sustenance and creativity. This means that you have to find your own supply of energetic power and it has – *us*. When the Morpheus character in the first *Matrix* movie held up a battery he spoke a profound truth when he said: 'The Matrix is a computer-generated dream world built to keep us under control in order to change the human being into one of

these.' The statement was true in all respects. We do live in a technologically-generated virtual reality simulation (more very shortly) and we have been manipulated to be an energy source for Archontic consciousness. The Disney-Pixar animated movie *Monsters, Inc*. in 2001 symbolised the dynamic when monsters in their world had no energy source and they would enter the human world to terrify children in their beds, catch the child's scream, terror (low-vibrational frequencies), and take that energy back to power the monster world. The lead character you might remember was a single giant eye and the symbolism of the Cult's all-seeing eye was obvious. Every thought and emotion is broadcast as a frequency unique to that thought and emotion. Feelings of love and joy, empathy and compassion, are high, quick, frequencies while fear, depression, anxiety, suffering and hate are low, slow, dense frequencies. Which kind do you think Archontic consciousness can connect with and absorb? In such a low and dense frequency state there's no way it can connect with the energy of love and joy. Archons can only feed off energy compatible with their own frequency and they and their Cult agents want to delete the human world of love and joy and manipulate the transmission of low vibrational frequencies through low-vibrational human mental and emotional states. *We are their energy source*. Wars are energetic banquets to the Archons – a world war even more so – and think how much low-frequency mental and emotional energy has been generated from the consequences for humanity of the 'Covid' hoax orchestrated by Archons incarnate like Gates.

The ancient practice of human sacrifice 'to the gods', continued in secret today by the Cult, is based on the same principle. 'The gods' are Archontic consciousness in different forms and the sacrifice is induced into a state of intense terror to generate the energy the Archontic frequency can absorb. Incarnate Archons in the ritual drink the blood which contains an adrenaline they crave which floods into the bloodstream when people are terrorised. Most of the sacrifices, ancient and modern, are children and the theme of 'sacrificing young virgins to the gods' is just code for children. They

have a particular pre-puberty energy that Archons want more than anything and the energy of the young in general is their target. The California Department of Education wants students to chant the names of Aztec gods (Archontic gods) once worshipped in human sacrifice rituals in a curriculum designed to encourage them to 'challenge racist, bigoted, discriminatory, imperialist/colonial beliefs', join 'social movements that struggle for social justice', and 'build new possibilities for a post-racist, post-systemic racism society'. It's the usual Woke crap that inverts racism and calls it anti-racism. In this case solidarity with 'indigenous tribes' is being used as an excuse to chant the names of 'gods' to which people were sacrificed (and still are in secret). What an example of Woke's inability to see beyond black and white, us and them, They condemn the colonisation of these tribal cultures by Europeans (quite right), but those cultures sacrificing people including children to their 'gods', and mass murdering untold numbers as the Aztecs did, is just fine. One chant is to the Aztec god Tezcatlipoca who had a man sacrificed to him in the 5th month of the Aztec calendar. His heart was cut out and he was eaten. Oh, that's okay then. Come on children … after three … Other sacrificial 'gods' for the young to chant their allegiance include Quetzalcoatl, Huitzilopochtli and Xipe Totec. The curriculum says that 'chants, affirmations, and energizers can be used to bring the class together, build unity around ethnic studies principles and values, and to reinvigorate the class following a lesson that may be emotionally taxing or even when student engagement may appear to be low'. Well, that's the cover story, anyway. Chanting and mantras are the repetition of a particular frequency generated from the vocal cords and chanting the names of these Archontic 'gods' tunes you into their frequency. That is the last thing you want when it allows for energetic synchronisation, attachment and perceptual influence. Initiates chant the names of their 'Gods' in their rituals for this very reason.

Vampires of the Woke

Paedophilia is another way that Archons absorb the energy of children. Paedophiles possessed by Archontic consciousness are used as the conduit during sexual abuse for discarnate Archons to vampire the energy of the young they desire so much. Stupendous numbers of children disappear every year never to be seen again although you would never know from the media. Imagine how much low-vibrational energy has been generated by children during the 'Covid' hoax when so many have become depressed and psychologically destroyed to the point of killing themselves. Shocking numbers of children are now taken by the state from loving parents to be handed to others. I can tell you from long experience of researching this since 1996 that many end up with paedophiles and assets of the Cult through corrupt and Cult-owned social services which in the reframing era has hired many psychopaths and emotionless automatons to do the job. Children are even stolen to order using spurious reasons to take them by the corrupt and secret (because they're corrupt) 'family courts'. I have written in detail in other books, starting with *The Biggest Secret* in 1997, about the ubiquitous connections between the political, corporate, government, intelligence and military elites (Cult operatives) and Satanism and paedophilia. If you go deep enough both networks have an interlocking leadership. The Woke mentality has been developed by the Cult for many reasons: To promote almost every aspect of its agenda; to hijack the traditional political left and turn it fascist; to divide and rule; and to target agenda pushbackers. But there are other reasons which relate to what I am describing here. How many happy and joyful Wokers do you ever see especially at the extreme end? They are a mental and psychological mess consumed by emotional stress and constantly emotionally cocked for the next explosion of indignation at someone referring to a female as a female. They are walking, talking, batteries as Morpheus might say emitting frequencies which both enslave them in low-vibrational bubbles of perceptual limitation and feed the Archons. Add to this the hatred claimed to be love; fascism claimed to 'anti-fascism', racism claimed to be 'anti-racism';

exclusion claimed to inclusion; and the abuse-filled Internet trolling. You have a purpose-built Archontic energy system with not a wind turbine in sight and all founded on Archontic *inversion*. We have whole generations now manipulated to serve the Archons with their actions and energy. They will be doing so their entire adult lives unless they snap out of their Archon-induced trance. Is it really a surprise that Cult billionaires and corporations put so much money their way? Where is the energy of joy and laughter, including laughing at yourself which is confirmation of your own emotional security? Mark Twain said: 'The human race has one really effective weapon, and that is laughter.' We must use it all the time. Woke has destroyed comedy because it has no humour, no joy, sense of irony, or self-deprecation. Its energy is dense and intense. *Mmmmm*, lunch says the Archontic frequency. Rudolf Steiner (1861-1925) was the Austrian philosopher and famous esoteric thinker who established Waldorf education or Steiner schools to treat children like unique expressions of consciousness and not minds to be programmed with the perceptions determined by authority. I'd been writing about this energy vampiring for decades when I was sent in 2016 a quote by Steiner. He was spot on:

> There are beings in the spiritual realms for whom anxiety and fear emanating from human beings offer welcome food. When humans have no anxiety and fear, then these creatures starve. If fear and anxiety radiates from people and they break out in panic, then these creatures find welcome nutrition and they become more and more powerful. These beings are hostile towards humanity. Everything that feeds on negative feelings, on anxiety, fear and superstition, despair or doubt, are in reality hostile forces in super-sensible worlds, launching cruel attacks on human beings, while they are being fed ... These are exactly the feelings that belong to contemporary culture and materialism; because it estranges people from the spiritual world, it is especially suited to evoke hopelessness and fear of the unknown in people, thereby calling up the above mentioned hostile forces against them.

Pause for a moment from this perspective and reflect on what has happened in the world since the start of 2020. Not only will pennies drop, but billion dollar bills. We see the same theme from Don Juan Matus, a Yaqui Indian shaman in Mexico and the information source for Peruvian-born writer, Carlos Castaneda, who wrote a series of

books from the 1960s to 1990s. Don Juan described the force manipulating human society and his name for the Archons was the predator:

> We have a predator that came from the depths of the cosmos and took over the rule of our lives. Human beings are its prisoners. The predator is our lord and master. It has rendered us docile, helpless. If we want to protest, it suppresses our protest. If we want to act independently, it demands that we don't do so ... indeed we are held prisoner!
>
> They took us over because we are food to them, and they squeeze us mercilessly because we are their sustenance. Just as we rear chickens in coops, the predators rear us in human coops, humaneros. Therefore, their food is always available to them.
>
> Different cultures, different eras, same recurring theme.

The 'ennoia' dilemma

Nag Hammadi Gnostic manuscripts say that Archon consciousness has no 'ennoia'. This is directly translated as 'intentionality', but I'll use the term 'creative imagination'. The *All That Is* in awareness of itself is the source of all creativity – all possibility – and the more disconnected you are from that source the more you are subsequently denied 'creative imagination'. Given that Archon consciousness is almost entirely disconnected it severely lacks creativity and has to rely on far more mechanical processes of thought and exploit the creative potential of those that do have 'ennoia'. You can see cases of this throughout human society. Archon consciousness almost entirely dominates the global banking system and if we study how that system works you will appreciate what I mean. Banks manifest 'money' out of nothing by issuing lines of 'credit' which is 'money' that has never, does not, and will never exist except in theory. It's a confidence trick. If you think 'credit' figures-on-a-screen 'money' is worth anything you accept it as payment. If you don't then the whole system collapses through lack of confidence in the value of that 'money'. Archontic bankers with no 'ennoia' are 'lending' 'money' that doesn't exist to humans that *do* have creativity – those that have the inspired ideas and create businesses and products. Archon banking feeds off human creativity

which it controls through 'money' creation and debt. Humans have the creativity and Archons exploit that for their own benefit and control while having none themselves. Archon Internet platforms like Facebook claim joint copyright of everything that creative users post and while Archontic minds like Zuckerberg may officially head that company it will be human creatives on the staff that provide the creative inspiration. When you have limitless 'money' you can then buy other companies established by creative humans. Witness the acquisition record of Facebook, Google and their like. Survey the Archon-controlled music industry and you see non-creative dark suit executives making their fortune from the human creativity of their artists. The cases are endless. Research the history of people like Gates and Zuckerberg and how their empires were built on exploiting the creativity of others. Archon minds cannot create out of nothing, but they are skilled (because they have to be) in what Gnostic texts call 'countermimicry'. They can imitate, but not innovate. Sabbatians trawl the creativity of others through backdoors they install in computer systems through their cybersecurity systems. Archon-controlled China is globally infamous for stealing intellectual property and I remember how Hong Kong, now part of China, became notorious for making counterfeit copies of the creativity of others – 'countermimicry'. With the now pervasive and all-seeing surveillance systems able to infiltrate any computer you can appreciate the potential for Archons to vampire the creativity of humans. Author John Lamb Lash wrote in his book about the Nag Hammadi texts, *Not In His Image*:

> Although they cannot originate anything, because they lack the divine factor of ennoia (intentionality), Archons can imitate with a vengeance. Their expertise is simulation (HAL, virtual reality). The Demiurge [Yaldabaoth] fashions a heaven world copied from the fractal patterns [of the original] ... His construction is celestial kitsch, like the fake Italianate villa of a Mafia don complete with militant angels to guard every portal.

This brings us to something that I have been speaking about since the turn of the millennium. Our reality is a simulation; a virtual reality that we think is real. No, I'm not kidding.

Human reality? Well, virtually

I had pondered for years about whether our reality is 'real' or some kind of construct. I remembered being immensely affected on a visit as a small child in the late 1950s to the then newly-opened Planetarium on the Marylebone Road in London which is now closed and part of the adjacent Madame Tussauds wax museum. It was in the middle of the day, but when the lights went out there was the night sky projected in the Planetarium's domed ceiling and it appeared to be so real. The experience never left me and I didn't know why until around the turn of the millennium when I became certain that our 'night sky' and entire reality is a projection, a virtual reality, akin to the illusory world portrayed in the *Matrix* movies. I looked at the sky one day in this period and it appeared to me like the domed roof of the Planetarium. The release of the first *Matrix* movie in 1999 also provided a synchronistic and perfect visual representation of where my mind had been going for a long time. I hadn't come across the Gnostic Nag Hammadi texts then. When I did years later the correlation was once again astounding. As I read Gnostic accounts from 1,600 years and more earlier it was clear that they were describing the same simulation phenomenon. They tell how the Yaldabaoth 'Demiurge' and Archons created a 'bad copy' of original reality to rule over all that were captured by its illusions and the body was a prison to trap consciousness in the 'bad copy' fake reality. Read how Gnostics describe the 'bad copy' and update that to current times and they are referring to what we would call today a virtual reality simulation.

Author John Lamb Lash said 'the Demiurge fashions a heaven world copied from the fractal patterns' of the original through expertise in 'HAL' or virtual reality simulation. Fractal patterns are part of the energetic information construct of our reality, a sort of blueprint. If these patterns were copied in computer terms it would indeed give you a copy of a 'natural' reality in a non-natural frequency and digital form. The principle is the same as making a copy of a website. The original website still exists, but now you can change the copy version to make it whatever you like and it can

become very different to the original website. Archons have done this with our reality, a *synthetic* copy of prime reality that still exists beyond the frequency walls of the simulation. Trapped within the illusions of this synthetic Matrix, however, were and are human consciousness and other expressions of prime reality and this is why the Archons via the Cult are seeking to make the human body synthetic and give us synthetic AI minds to complete the job of turning the entire reality synthetic including what we perceive to be the natural world. To quote Kurzweil: 'Nanobots will infuse all the matter around us with information. Rocks, trees, everything will become these intelligent creatures.' Yes, *synthetic* 'creatures' just as 'Covid' and other genetically-manipulating 'vaccines' are designed to make the human body synthetic. From this perspective it is obvious why Archons and their Cult are so desperate to infuse synthetic material into every human with their 'Covid' scam.

Let there be (electromagnetic) light

Yaldabaoth, the force that created the simulation, or Matrix, makes sense of the Gnostic reference to 'The Great Architect' and its use by Cult Freemasonry as the name of its deity. The designer of the Matrix in the movies is called 'The Architect' and that trilogy is jam-packed with symbolism relating to these subjects. I have contended for years that the angry Old Testament God (Yaldabaoth) is the 'God' being symbolically 'quoted' in the opening of Genesis as 'creating the world'. This is not the creation of prime reality – it's the creation of the *simulation*. The Genesis 'God' says: 'Let there be Light: and there was light.' But what is this 'Light'? I have said for decades that the speed of light (186,000 miles per second) is not the fastest speed possible as claimed by mainstream science and is in fact the frequency walls or outer limits of the Matrix. You can't have a fastest or slowest anything within all possibility when everything is possible. The human body is encoded to operate within the speed of light or *within the simulation* and thus we see only the tiny frequency band of visible *light*. Near-death experiencers who perceive reality outside the body during temporary 'death' describe a very different

form of light and this is supported by the Nag Hammadi texts. Prime reality beyond the simulation ('Upper Aeons' to the Gnostics) is described as a realm of incredible beauty, bliss, love and harmony – a realm of 'watery light' that is so powerful 'there are no shadows'. Our false reality of Archon control, which Gnostics call the 'Lower Aeons', is depicted as a realm with a different kind of 'light' and described in terms of chaos, 'Hell', 'the Abyss' and 'Outer Darkness', where trapped souls are tormented and manipulated by demons (relate that to the 'Covid' hoax alone). The watery light theme can be found in near-death accounts and it is not the same as *simulation* 'light' which is electromagnetic or radiation light within the speed of light – the 'Lower Aeons'. Simulation 'light' is the 'luminous fire' associated by Gnostics with the Archons. The Bible refers to Yaldabaoth as 'that old serpent, called the Devil, and Satan, which deceiveth the whole world' (Revelation 12:9). I think that making a simulated copy of prime reality ('countermimicry') and changing it dramatically while all the time manipulating humanity to believe it to be real could probably meet the criteria of deceiving the whole world. Then we come to the Cult god Lucifer – the *Light Bringer*. Lucifer is symbolic of Yaldabaoth, the bringer of radiation light that forms the bad copy simulation within the speed of light. 'He' is symbolised by the lighted torch held by the Statue of Liberty and in the name 'Illuminati'. Sabbatian-Frankism declares that Lucifer is the true god and Lucifer is the real god of Freemasonry honoured as their 'Great or Grand Architect of the Universe' (simulation).

I would emphasise, too, the way Archontic technologically-generated luminous fire of radiation has deluged our environment since I was a kid in the 1950s and changed the nature of The Field with which we constantly interact. Through that interaction technological radiation is changing us. The Smart Grid is designed to operate with immense levels of communication power with 5G expanding across the world and 6G, 7G, in the process of development. Radiation is the simulation and the Archontic manipulation system. Why wouldn't the Archon Cult wish to unleash radiation upon us to an ever-greater extreme to form

Kurzweil's 'cloud'? The plan for a synthetic human is related to the need to cope with levels of radiation beyond even anything we've seen so far. Biological humans would not survive the scale of radiation they have in their script. The Smart Grid is a technological sub-reality within the technological simulation to further disconnect five-sense perception from expanded consciousness. It's a technological prison of the mind.

Infusing the 'spirit of darkness'

A recurring theme in religion and native cultures is the manipulation of human genetics by a non-human force and most famously recorded as the biblical 'sons of god' (the god*s* plural in the original) who interbred with the daughters of men. The Nag Hammadi *Apocryphon of John* tells the same story this way:

> He [Yaldabaoth] sent his angels [Archons/demons] to the daughters of men, that they might take some of them for themselves and raise offspring for their enjoyment. And at first they did not succeed. When they had no success, they gathered together again and they made a plan together ... And the angels changed themselves in their likeness into the likeness of their mates, filling them with the spirit of darkness, which they had mixed for them, and with evil ... And they took women and begot children out of the darkness according to the likeness of their spirit.

Possession when a discarnate entity takes over a human body is an age-old theme and continues today. It's very real and I've seen it. Satanic and secret society rituals can create an energetic environment in which entities can attach to initiates and I've heard many stories of how people have changed their personality after being initiated even into lower levels of the Freemasons. I have been inside three Freemasonic temples, one at a public open day and two by just walking in when there was no one around to stop me. They were in Ryde, the town where I live, Birmingham, England, when I was with a group, and Boston, Massachusetts. They all felt the same energetically – dark, dense, low-vibrational and sinister. Demonic attachment can happen while the initiate has no idea what is going on. To them it's just a ritual to get in the Masons and do a bit of good

business. In the far more extreme rituals of Satanism human possession is even more powerful and they are designed to make possession possible. The hierarchy of the Cult is dictated by the power and perceived status of the possessing Archon. In this way the Archon hierarchy becomes the Cult hierarchy. Once the entity has attached it can influence perception and behaviour and if it attaches to the extreme then so much of its energy (information) infuses into the body information field that the hologram starts to reflect the nature of the possessing entity. This is the *Exorcist* movie type of possession when facial features change and it's known as shapeshifting. Islam's Jinn are said to be invisible tricksters who change shape, 'whisper', confuse and take human form. These are all traits of the Archons and other versions of the same phenomenon. Extreme possession could certainty infuse the 'spirit of darkness' into a partner during sex as the Nag Hammadi texts appear to describe. Such an infusion can change genetics which is also energetic information. Human genetics is information and the 'spirit of darkness' is information. Mix one with the other and change must happen. Islam has the concept of a 'Jinn baby' through possession of the mother and by Jinn taking human form. There are many ways that human genetics can be changed and remember that Archons have been aware all along of advanced techniques to do this. What is being done in human society today – and far more – was known about by Archons at the time of the 'fallen ones' and their other versions described in religions and cultures.

Archons and their human-world Cult are obsessed with genetics as we see today and they know this dictates how information is processed into perceived reality during a human life. They needed to produce a human form that would decode the simulation and this is symbolically known as 'Adam and Eve' who left the 'garden' (prime reality) and 'fell' into Matrix reality. The simulation is not a 'physical' construct (there is no 'physical'); it is a source of information. Think Wi-Fi again. The simulation is an energetic field encoded with information and body-brain systems are designed to decode that information encoded in wave or frequency form which

is transmitted to the brain as electrical signals. These are decoded by the brain to construct our sense of reality – an illusory 'physical' world that only exists in the brain or the mind. Virtual reality games mimic this process using the same sensory decoding system. Information is fed to the senses to decode a virtual reality that can appear so real, but isn't (Figs 18 and 19). Some scientists believe – and I agree with them – that what we perceive as 'physical' reality only exists when we are looking or observing. The act of perception or focus triggers the decoding systems which turn waveform information into holographic reality. When we are not observing something our reality reverts from a holographic state to a waveform state. This relates to the same principle as a falling tree not making a noise unless someone is there to hear it or decode it. The concept makes sense from the simulation perspective. A computer is not decoding all the information in a Wi-Fi field all the time and only decodes or brings into reality on the screen that part of Wi-Fi that it's decoding – focusing upon – at that moment.



Figure 18: Virtual reality technology 'hacks' into the body's five-sense decoding system.



Figure 19: The result can be experienced as very 'real'.

Interestingly, Professor Donald Hoffman at the Department of Cognitive Sciences at the University of California, Irvine, says that our experienced reality is like a computer interface that shows us only the level with which we interact while hiding all that exists beyond it: 'Evolution shaped us with a user interface that hides the truth. Nothing that we see is the truth – the very language of space and time and objects is the wrong language to describe reality.' He is correct in what he says on so many levels. Space and time are not a universal reality. They are a phenomenon of decoded *simulation* reality as part of the process of enslaving our sense of reality. Near-death experiencers report again and again how space and time did not exist as we perceive them once they were free of the body – body decoding systems. You can appreciate from this why Archons and their Cult are so desperate to entrap human attention in the five senses where we are in the Matrix and of the Matrix. Opening your mind to expanded states of awareness takes you beyond the information confines of the simulation and you become aware of knowledge and insights denied to you before. This is what we call 'awakening' – *awakening from the Matrix* – and in the final chapter I will relate this to current events.

Where are the 'aliens'?

A simulation would explain the so-called 'Fermi Paradox' named after Italian physicist Enrico Fermi (1901-1954) who created the first nuclear reactor. He considered the question of why there is such a lack of extraterrestrial activity when there are so many stars and planets in an apparently vast universe; but what if the night sky that we see, or think we do, is a simulated projection as I say? If you control the simulation and your aim is to hold humanity fast in essential ignorance would you want other forms of life including advanced life coming and going sharing information with humanity? Or would you want them to believe they were isolated and apparently alone? Themes of human isolation and apartness are common whether they be the perception of a lifeless universe or the fascist isolation laws of the 'Covid' era. Paradoxically the very

existence of a simulation means that we are not alone when some force had to construct it. My view is that experiences that people have reported all over the world for centuries with Reptilians and Grey entities are Archon phenomena as Nag Hammadi texts describe; and that benevolent 'alien' interactions are non-human groups that come in and out of the simulation by overcoming Archon attempts to keep them out. It should be highlighted, too, that Reptilians and Greys are obsessed with *genetics* and *technology* as related by cultural accounts and those who say they have been abducted by them. Technology is their way of overcoming some of the limitations in their creative potential and our technology-driven and controlled human society of today is *arch*etypical Archon-Reptilian-Grey modus operandi. Technocracy is really *Archon*tocracy. The Universe does not have to be as big as it appears with a simulation. There is no space or distance only information decoded into holographic reality. What we call 'space' is only the absence of holographic 'objects' and that 'space' is The Field of energetic information which connects everything into a single whole. The same applies with the artificially-generated information field of the simulation. The Universe is not big or small as a physical reality. It is decoded information, that's all, and its perceived size is decided by the way the simulation is encoded to make it appear. The entire night sky as we perceive it only exists in our brain and so where are those 'millions of light years'? The 'stars' on the ceiling of the Planetarium looked a vast distance away.

There's another point to mention about 'aliens'. I have been highlighting since the 1990s the plan to stage a fake 'alien invasion' to justify the centralisation of global power and a world military. Nazi scientist Werner von Braun, who was taken to America by Operation Paperclip after World War Two to help found NASA, told his American assistant Dr Carol Rosin about the Cult agenda when he knew he was dying in 1977. Rosin said that he told her about a sequence that would lead to total human control by a one-world government. This included threats from terrorism, rogue nations, meteors and asteroids before finally an 'alien invasion'. All of these

things, von Braun said, would be bogus and what I would refer to as a No-Problem-Reaction-Solution. Keep this in mind when 'the aliens are coming' is the new mantra. The aliens are not coming – they are *already here* and they have infiltrated human society while looking human. French-Canadian investigative journalist Serge Monast said in 1994 that he had uncovered a NASA/military operation called Project Blue Beam which fits with what Werner von Braun predicted. Monast died of a 'heart attack' in 1996 the day after he was arrested and spent a night in prison. He was 51. He said Blue Beam was a plan to stage an alien invasion that would include religious figures beamed holographically into the sky as part of a global manipulation to usher in a 'new age' of worshipping what I would say is the Cult 'god' Yaldabaoth in a one-world religion. Fake holographic asteroids are also said to be part of the plan which again syncs with von Braun. How could you stage an illusory threat from asteroids unless they were holographic inserts? This is pretty straightforward given the advanced technology outside the public arena and the fact that our 'physical' reality is holographic anyway. Information fields would be projected and we would decode them into the illusion of a 'physical' asteroid. If they can sell a global 'pandemic' with a 'virus' that doesn't exist what will humans not believe if government and media tell them?

All this is particularly relevant as I write with the Pentagon planning to release in June, 2021, information about 'UFO sightings'. I have been following the UFO story since the early 1990s and the common theme throughout has been government and military denials and cover up. More recently, however, the Pentagon has suddenly become more talkative and apparently open with Air Force pilot radar images released of unexplained craft moving and changing direction at speeds well beyond anything believed possible with human technology. Then, in March, 2021, former Director of National Intelligence John Ratcliffe said a Pentagon report months later in June would reveal a great deal of information about UFO sightings unknown to the public. He said the report would have 'massive implications'. The order to do this was included bizarrely

in a $2.3 trillion 'coronavirus' relief and government funding bill passed by the Trump administration at the end of 2020. I would add some serious notes of caution here. I have been pointing out since the 1990s that the US military and intelligence networks have long had craft – 'flying saucers' or anti-gravity craft – which any observer would take to be extraterrestrial in origin. Keeping this knowledge from the public allows craft flown by *humans* to be perceived as alien visitations. I am not saying that 'aliens' do not exist. I would be the last one to say that, but we have to be streetwise here. President Ronald Reagan told the UN General Assembly in 1987: 'I occasionally think how quickly our differences worldwide would vanish if we were facing an alien threat from outside this world.' That's the idea. Unite against a common 'enemy' with a common purpose behind your 'saviour force' (the Cult) as this age-old technique of mass manipulation goes global.

Science moves this way …

I could find only one other person who was discussing the simulation hypothesis publicly when I concluded it was real. This was Nick Bostrom, a Swedish-born philosopher at the University of Oxford, who has explored for many years the possibility that human reality is a computer simulation although his version and mine are not the same. Today the simulation and holographic reality hypothesis have increasingly entered the scientific mainstream. Well, the more open-minded mainstream, that is. Here are a few of the ever-gathering examples. American nuclear physicist Silas Beane led a team of physicists at the University of Bonn in Germany pursuing the question of whether we live in a simulation. They concluded that we probably do and it was likely based on a lattice of cubes. They found that cosmic rays align with that specific pattern. The team highlighted the Greisen–Zatsepin–Kuzmin (GZK) limit which refers to cosmic ray particle interaction with cosmic background radiation that creates an apparent boundary for cosmic ray particles. They say in a paper entitled 'Constraints on the Universe as a Numerical Simulation' that this 'pattern of constraint' is exactly what you

would find with a computer simulation. They also made the point that a simulation would create its own 'laws of physics' that would limit possibility. I've been making the same point for decades that the *perceived* laws of physics relate only to this reality, or what I would later call the simulation. When designers write codes to create computer and virtual reality games they are the equivalent of the laws of physics for that game. Players interact within the limitations laid out by the coding. In the same way those who wrote the codes for the simulation decided the laws of physics that would apply. These can be overridden by expanded states of consciousness, but not by those enslaved in only five-sense awareness where simulation codes rule. Overriding the codes is what people call 'miracles'. They are not. They are bypassing the encoded limits of the simulation. A population caught in simulation perception would have no idea that this was their plight. As the Bonn paper said: 'Like a prisoner in a pitch-black cell we would not be able to see the "walls" of our prison,' That's true if people remain mesmerised by the five senses. Open to expanded awareness and those walls become very clear. The main one is the speed of light.

American theoretical physicist James Gates is another who has explored the simulation question and found considerable evidence to support the idea. Gates was Professor of Physics at the University of Maryland, Director of The Center for String and Particle Theory, and on Barack Obama's Council of Advisors on Science and Technology. He and his team found *computer codes* of digital data embedded in the fabric of our reality. They relate to on-off electrical charges of 1 and 0 in the binary system used by computers. 'We have no idea what they are doing there', Gates said. They found within the energetic fabric mathematical sequences known as error-correcting codes or block codes that 'reboot' data to its original state or 'default settings' when something knocks it out of sync. Gates was asked if he had found a set of equations embedded in our reality indistinguishable from those that drive search engines and browsers and he said: 'That is correct.' Rich Terrile, director of the Centre for Evolutionary Computation and Automated Design at NASA's Jet

Propulsion Laboratory, has said publicly that he believes the Universe is a digital hologram that must have been created by a form of intelligence. I agree with that in every way. Waveform information is delivered electrically by the senses to the brain which constructs a *digital* holographic reality that we call the 'world'. This digital level of reality can be read by the esoteric art of numerology. Digital holograms are at the cutting edge of holographics today. We have digital technology everywhere designed to access and manipulate our digital level of perceived reality. Synthetic mRNA in 'Covid vaccines' has a digital component to manipulate the body's digital 'operating system'.

Reality is numbers

How many know that our reality can be broken down to numbers and codes that are the same as computer games? Max Tegmark, a physicist at the Massachusetts Institute of Technology (MIT), is the author of *Our Mathematical Universe* in which he lays out how reality can be entirely described by numbers and maths in the way that a video game is encoded with the 'physics' of computer games. Our world and computer virtual reality are essentially the same. Tegmark imagines the perceptions of characters in an advanced computer game when the graphics are so good they don't know they are in a game. They think they can bump into real objects (electromagnetic resistance in our reality), fall in love and feel emotions like excitement. When they began to study the apparently 'physical world' of the video game they would realise that everything was made of pixels (which have been found in our energetic reality as must be the case when on one level our world is digital). What computer game characters thought was physical 'stuff', Tegmark said, could actually be broken down into numbers:

> And we're exactly in this situation in our world. We look around and it doesn't seem that mathematical at all, but everything we see is made out of elementary particles like quarks and electrons. And what properties does an electron have? Does it have a smell or a colour or a texture? No! ... We physicists have come up with geeky names for [Electron] properties, like

electric charge, or spin, or lepton number, but the electron doesn't care what we call it, the properties are just numbers.

This is the illusory reality Gnostics were describing. This is the simulation. The A, C, G, and T codes of DNA have a binary value – A and C = 0 while G and T = 1. This has to be when the simulation is digital and the body must be digital to interact with it. Recurring mathematical sequences are encoded throughout reality and the body. They include the Fibonacci sequence in which the two previous numbers are added to get the next one, as in ... 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, etc. The sequence is encoded in the human face and body, proportions of animals, DNA, seed heads, pine cones, trees, shells, spiral galaxies, hurricanes and the number of petals in a flower. The list goes on and on. There are fractal patterns – a 'never-ending pattern that is infinitely complex and self-similar across all scales in the as above, so below, principle of holograms. These and other famous recurring geometrical and mathematical sequences such as Phi, Pi, Golden Mean, Golden Ratio and Golden Section are *computer codes* of the simulation. I had to laugh and give my head a shake the day I finished this book and it went into the production stage. I was sent an article in *Scientific American* published in April, 2021, with the headline 'Confirmed! We Live in a Simulation'. Two decades after I first said our reality is a simulation and the speed of light is it's outer limit the article suggested that we do live in a simulation and that the speed of light is its outer limit. I left school at 15 and never passed a major exam in my life while the writer was up to his eyes in qualifications. As I will explain in the final chapter *knowing* is far better than thinking and they come from very different sources. The article rightly connected the speed of light to the processing speed of the 'Matrix' and said what has been in my books all this time … 'If we are in a simulation, as it appears, then space is an abstract property written in code. It is not real'. No it's not and if we live in a simulation something created it and it wasn't *us*. 'That David Icke says we are manipulated by aliens' – he's crackers.'

Wow …

The reality that humanity thinks is so real is an illusion. Politicians, governments, scientists, doctors, academics, law enforcement, media, school and university curriculums, on and on, are all founded on a world that *does not exist* except as a simulated prison cell. Is it such a stretch to accept that 'Covid' doesn't exist when our entire 'physical' reality doesn't exist? Revealed here is the knowledge kept under raps in the Cult networks of compartmentalised secrecy to control humanity's sense of reality by inducing the population to believe in a reality that's not real. If it wasn't so tragic in its experiential consequences the whole thing would be hysterically funny. None of this is new to Renegade Minds. Ancient Greek philosopher Plato (about 428 to about 347BC) was a major influence on Gnostic belief and he described the human plight thousands of years ago with his Allegory of the Cave. He told the symbolic story of prisoners living in a cave who had never been outside. They were chained and could only see one wall of the cave while behind them was a fire that they could not see. Figures walked past the fire casting shadows on the prisoners' wall and those moving shadows became their sense of reality. Some prisoners began to study the shadows and were considered experts on them (today's academics and scientists), but what they studied was only an illusion (today's academics and scientists). A prisoner escaped from the cave and saw reality as it really is. When he returned to report this revelation they didn't believe him, called him mad and threatened to kill him if he tried to set them free. Plato's tale is not only a brilliant analogy of the human plight and our illusory reality. It describes, too, the dynamics of the 'Covid' hoax. I have only skimmed the surface of these subjects here. The aim of this book is to crisply connect all essential dots to put what is happening today into its true context. All subject areas and their connections in this chapter are covered in great evidential detail in *Everything You Need To Know, But Have Never Been Told* and *The Answer*.

They say that bewildered people 'can't see the forest for the trees'. Humanity, however, can't see the forest for the *twigs*. The five senses

see only twigs while Renegade Minds can see the forest and it's the forest where the answers lie with the connections that reveals. Breaking free of perceptual programming so the forest can be seen is the way we turn all this around. Not breaking free is how humanity got into this mess. The situation may seem hopeless, but I promise you it's not. We are a perceptual heartbeat from paradise if only we knew.

CHAPTER TWELVE

Escaping Wetiko

Life is simply a vacation from the infinite
Dean Cavanagh

Renegade Minds weave the web of life and events and see common themes in the apparently random. They are always there if you look for them and their pursuit is aided by incredible synchronicity that comes when your mind is open rather than mesmerised by what it thinks it can see.

Infinite awareness is infinite possibility and the more of infinite possibility that we access the more becomes infinitely possible. That may be stating the apparently obvious, but it is a devastatingly-powerful fact that can set us free. We are a point of attention within an infinity of consciousness. The question is how much of that infinity do we choose to access? How much knowledge, insight, awareness, wisdom, do we want to connect with and explore? If your focus is only in the five senses you will be influenced by a fraction of infinite awareness. I mean a range so tiny that it gives new meaning to infinitesimal. Limitation of self-identity and a sense of the possible limit accordingly your range of consciousness. We are what we think we are. Life is what we think it is. The dream is the dreamer and the dreamer is the dream. Buddhist philosophy puts it this way: 'As a thing is viewed, so it appears.' Most humans live in the realm of touch, taste, see, hear, and smell and that's the limit of their sense of the possible and sense of self. Many will follow a religion and speak of a God in his heaven, but their lives are still

dominated by the five senses in their perceptions and actions. The five senses become the arbiter of everything. When that happens all except a smear of infinity is sealed away from influence by the rigid, unyielding, reality bubbles that are the five-sense human or Phantom Self. Archon Cult methodology is to isolate consciousness within five-sense reality – the simulation – and then program that consciousness with a sense of self and the world through a deluge of life-long information designed to instil the desired perception that allows global control. Efforts to do this have increased dramatically with identity politics as identity bubbles are squeezed into the minutiae of five-sense detail which disconnect people even more profoundly from the infinite 'I'.

Five-sense focus and self-identity are like a firewall that limits access to the infinite realms. You only perceive one radio or television station and no other. We'll take that literally for a moment. Imagine a vast array of stations giving different information and angles on reality, but you only ever listen to one. Here we have the human plight in which the population is overwhelmingly confined to CultFM. This relates only to the frequency range of CultFM and limits perception and insight to that band – limits *possibility* to that band. It means you are connecting with an almost imperceptibly minuscule range of possibility and creative potential within the infinite Field. It's a world where everything seems apart from everything else and where synchronicity is rare. Synchronicity is defined in the dictionary as 'the happening by chance of two or more related or similar events at the same time'. Use of 'by chance' betrays a complete misunderstanding of reality. Synchronicity is not 'by chance'. As people open their minds, or 'awaken' to use the term, they notice more and more coincidences in their lives, bits of 'luck', apparently miraculous happenings that put them in the right place at the right time with the right people. Days become peppered with 'fancy meeting you here' and 'what are the chances of that?' My entire life has been lived like this and ever more so since my own colossal awakening in 1990 and 91 which transformed my sense of reality. Synchronicity is not 'by chance'; it is by accessing expanded

realms of possibility which allow expanded potential for manifestation. People broadcasting the same vibe from the same openness of mind tend to be drawn 'by chance' to each other through what I call frequency magnetism and it's not only people. In the last more than 30 years incredible synchronicity has also led me through the Cult maze to information in so many forms and to crucial personal experiences. These 'coincidences' have allowed me to put the puzzle pieces together across an enormous array of subjects and situations. Those who have breached the bubble of five-sense reality will know exactly what I mean and this escape from the perceptual prison cell is open to everyone whenever they make that choice. This may appear super-human when compared with the limitations of 'human', but it's really our natural state. 'Human' as currently experienced is consciousness in an unnatural state of induced separation from the infinity of the whole. I'll come to how this transformation into unity can be made when I have described in more detail the force that holds humanity in servitude by denying this access to infinite self.

The Wetiko factor

I have been talking and writing for decades about the way five-sense mind is systematically barricaded from expanded awareness. I have used the analogy of a computer (five-sense mind) and someone at the keyboard (expanded awareness). Interaction between the computer and the operator is symbolic of the interaction between five-sense mind and expanded awareness. The computer directly experiences the Internet and the operator experiences the Internet via the computer which is how it's supposed to be – the two working as one. Archons seek to control that point where the operator connects with the computer to stop that interaction (Fig 20). Now the operator is banging the keyboard and clicking the mouse, but the computer is not responding and this happens when the computer is taken over – *possessed* – by an appropriately-named computer 'virus'. The operator has lost all influence over the computer which goes its own way making decisions under the control of the 'virus'. I have

just described the dynamic through which the force known to Gnostics as Yaldabaoth and Archons disconnects five-sense mind from expanded awareness to imprison humanity in perceptual servitude.



Figure 20: The mind 'virus' I have been writing about for decades seeks to isolate five-sense mind (the computer) from the true 'I'. (Image by Neil Hague).

About a year ago I came across a Native American concept of Wetiko which describes precisely the same phenomenon. Wetiko is the spelling used by the Cree and there are other versions including wintiko and windigo used by other tribal groups. They spell the name with lower case, but I see Wetiko as a proper noun as with Archons and prefer a capital. I first saw an article about Wetiko by writer and researcher Paul Levy which so synced with what I had been writing about the computer/operator disconnection and later the Archons. I then read his book, the fascinating *Dispelling Wetiko, Breaking the Spell of Evil*. The parallels between what I had concluded long before and the Native American concept of Wetiko were so clear and obvious that it was almost funny. For Wetiko see the Gnostic Archons for sure and the Jinn, the Predators, and every other name for a force of evil, inversion and chaos. Wetiko is the Native American name for the force that divides the computer from

the operator (Fig 21). Indigenous author Jack D. Forbes, a founder of the Native American movement in the 1960s, wrote another book about Wetiko entitled *Columbus And Other Cannibals – The Wetiko Disease of Exploitation, Imperialism, and Terrorism* which I also read. Forbes says that Wetiko refers to an evil person or spirit 'who terrorizes other creatures by means of terrible acts, including cannibalism'. Zulu shaman Credo Mutwa told me that African accounts tell how cannibalism was brought into the world by the Chitauri 'gods' – another manifestation of Wetiko. The distinction between 'evil person or spirit' relates to Archons/Wetiko possessing a human or acting as pure consciousness. Wetiko is said to be a sickness of the soul or spirit and a state of being that takes but gives nothing back – the Cult and its operatives perfectly described. Black Hawk, a Native American war leader defending their lands from confiscation, said European invaders had 'poisoned hearts' – Wetiko hearts – and that this would spread to native societies. Mention of the heart is very significant as we shall shortly see. Forbes writes: 'Tragically, the history of the world for the past 2,000 years is, in great part, the story of the epidemiology of the wetiko disease.' Yes, and much longer. Forbes is correct when he says: 'The wetikos destroyed Egypt and Babylon and Athens and Rome and Tenochtitlan [capital of the Aztec empire] and perhaps now they will destroy the entire earth.' Evil, he said, is the number one export of a Wetiko culture – see its globalisation with 'Covid'. Constant war, mass murder, suffering of all kinds, child abuse, Satanism, torture and human sacrifice are all expressions of Wetiko and the Wetiko possessed. The world is Wetiko made manifest, *but it doesn't have to be*. There is a way out of this even now.



Figure 21: The mind 'virus' is known to Native Americans as 'Wetiko'. (Image by Neil Hague).

Cult of Wetiko

Wetiko is the Yaldabaoth frequency distortion that seeks to attach to human consciousness and absorb it into its own. Once this connection is made Wetiko can drive the perceptions of the target which they believe to be coming from their own mind. All the horrors of history and today from mass killers to Satanists, paedophiles like Jeffrey Epstein and other psychopaths, are the embodiment of Wetiko and express its state of being in all its grotesqueness. The Cult is Wetiko incarnate, Yaldabaoth incarnate, and it seeks to facilitate Wetiko assimilation of humanity in totality into its distortion by manipulating the population into low frequency states that match its own. Paul Levy writes: 'Holographically enforced within the psyche of every human being the wetiko virus pervades and underlies the entire field of consciousness, and can therefore potentially manifest through any one of us at any moment if we are not mindful.' The 'Covid' hoax has achieved this with many people, but others have not fallen into Wetiko's frequency lair. Players in the 'Covid' human catastrophe including Gates, Schwab, Tedros, Fauci, Whitty, Vallance, Johnson, Hancock, Ferguson, Drosten, and all the rest, including the psychopath psychologists, are expressions of Wetiko. This is why

they have no compassion or empathy and no emotional consequence for what they do that would make them stop doing it. Observe all the people who support the psychopaths in authority against the Pushbackers despite the damaging impact the psychopaths have on their own lives and their family's lives. You are again looking at Wetiko possession which prevents them seeing through the lies to the obvious scam going on. *Why can't they see it?* Wetiko won't let them see it. The perceptual divide that has now become a chasm is between the Wetikoed and the non-Wetikoed.

Paul Levy describes Wetiko in the same way that I have long described the Archontic force. They are the same distorted consciousness operating across dimensions of reality: '… the subtle body of wetiko is not located in the third dimension of space and time, literally existing in another dimension … it is able to affect ordinary lives by mysteriously interpenetrating into our three-dimensional world.' Wetiko does this through its incarnate representatives in the Cult and by weaving itself into The Field which on our level of reality is the electromagnetic information field of the simulation or Matrix. More than that, the simulation *is* Wetiko / Yaldabaoth. Caleb Scharf, Director of Astrobiology at Columbia University, has speculated that 'alien life' could be so advanced that it has transcribed itself into the quantum realm to become what we call physics. He said intelligence indistinguishable from the fabric of the Universe would solve many of its greatest mysteries:

> Perhaps hyper-advanced life isn't just external. Perhaps it's already all around. It is embedded in what we perceive to be physics itself, from the root behaviour of particles and fields to the phenomena of complexity and emergence ... In other words, life might not just be in the equations. It might BE the equations [My emphasis].

Scharf said it is possible that 'we don't recognise advanced life because it forms an integral and unsuspicious part of what we've considered to be the natural world'. I agree. Wetiko/Yaldabaoth *is* the simulation. We are literally in the body of the beast. But that doesn't mean it has to control us. We all have the power to overcome Wetiko

influence and the Cult knows that. I doubt it sleeps too well because it knows that.

Which Field?

This, I suggest, is how it all works. There are two Fields. One is the fierce electromagnetic light of the Matrix within the speed of light; the other is the 'watery light' of The Field beyond the walls of the Matrix that connects with the Great Infinity. Five-sense mind and the decoding systems of the body attach us to the Field of Matrix light. They have to or we could not experience this reality. Five-sense mind sees only the Matrix Field of information while our expanded consciousness is part of the Infinity Field. When we open our minds, and most importantly our hearts, to the Infinity Field we have a mission control which gives us an expanded perspective, a road map, to understand the nature of the five-sense world. If we are isolated only in five-sense mind there is no mission control. We're on our own trying to understand a world that's constantly feeding us information to ensure we do not understand. People in this state can feel 'lost' and bewildered with no direction or radar. You can see ever more clearly those who are influenced by the Fields of Big Infinity or little five-sense mind simply by their views and behaviour with regard to the 'Covid' hoax. We have had this division throughout known human history with the mass of the people on one side and individuals who could see and intuit beyond the walls of the simulation – Plato's prisoner who broke out of the cave and saw reality for what it is. Such people have always been targeted by Wetiko/Archon-possessed authority, burned at the stake or demonised as mad, bad and dangerous. The Cult today and its global network of 'anti-hate', 'anti-fascist' Woke groups are all expressions of Wetiko attacking those exposing the conspiracy, 'Covid' lies and the 'vaccine' agenda.

Woke as a whole is Wetiko which explains its black and white mentality and how at one it is with the Wetiko-possessed Cult. Paul Levy said: 'To be in this paradigm is to still be under the thrall of a two-valued logic – where things are either true or false – of a

wetikoized mind.' Wetiko consciousness is in a permanent rage, therefore so is Woke, and then there is Woke inversion and contradiction. 'Anti-fascists' act like fascists because fascists *and* 'anti-fascists' are both Wetiko at work. Political parties act the same while claiming to be different for the same reason. Secret society and satanic rituals are attaching initiates to Wetiko and the cold, ruthless, psychopathic mentality that secures the positions of power all over the world is Wetiko. Reframing 'training programmes' have the same cumulative effect of attaching Wetiko and we have their graduates described as automatons and robots with a cold, psychopathic, uncaring demeanour. They are all traits of Wetiko possession and look how many times they have been described in this book and elsewhere with regard to personnel behind 'Covid' including the police and medical profession. Climbing the greasy pole in any profession in a Wetiko society requires traits of Wetiko to get there and that is particularly true of politics which is not about fair competition and pre-eminence of ideas. It is founded on how many backs you can stab and arses you can lick. This culminated in the global 'Covid' coordination between the Wetiko possessed who pulled it off in all the different countries without a trace of empathy and compassion for their impact on humans. Our sight sense can see only holographic form and not the Field which connects holographic form. Therefore we perceive 'physical' objects with 'space' in between. In fact that 'space' is energy/consciousness operating on multiple frequencies. One of them is Wetiko and that connects the Cult psychopaths, those who submit to the psychopaths, and those who serve the psychopaths in the media operations of the world. Wetiko is Gates. Wetiko is the mask-wearing submissive. Wetiko is the fake journalist and 'fact-checker'. The Wetiko Field is coordinating the whole thing. Psychopaths, gofers, media operatives, 'anti-hate' hate groups, 'fact-checkers' and submissive people work as one unit *even without human coordination* because they are attached to the *same* Field which is organising it all (Fig 22). Paul Levy is here describing how Wetiko-possessed people are drawn together and refuse to let any information breach their rigid

perceptions. He was writing long before 'Covid', but I think you will recognise followers of the 'Covid' religion *oh just a little bit*:

People who are channelling the vibratory frequency of wetiko align with each other through psychic resonance to reinforce their unspoken shared agreement so as to uphold their deranged view of reality. Once an unconscious content takes possession of certain individuals, it irresistibly draws them together by mutual attraction and knits them into groups tied together by their shared madness that can easily swell into an avalanche of insanity.

A psychic epidemic is a closed system, which is to say that it is insular and not open to any new information or informing influences from the outside world which contradict its fixed, limited, and limiting perspective.

There we have the Woke mind and the 'Covid' mind. Compatible resonance draws the awakening together, too, which is clearly happening today.



Figure 22: The Wetiko Field from which the Cult pyramid and its personnel are made manifest. (Image by Neil Hague).

Spiritual servitude

Wetiko doesn't care about humans. It's not human; it just possesses humans for its own ends and the effect (depending on the scale of

possession) can be anything from extreme psychopathy to unquestioning obedience. Wetiko's worst nightmare is for human consciousness to expand beyond the simulation. Everything is focussed on stopping that happening through control of information, thus perception, thus frequency. The 'education system', media, science, medicine, academia, are all geared to maintaining humanity in five-sense servitude as is the constant stimulation of low-vibrational mental and emotional states (see 'Covid'). Wetiko seeks to dominate those subconscious spaces between five-sense perception and expanded consciousness where the computer meets the operator. From these subconscious hiding places Wetiko speaks to us to trigger urges and desires that we take to be our own and manipulate us into anything from low-vibrational to psychopathic states. Remember how Islam describes the Jinn as invisible tricksters that 'whisper' and confuse. Wetiko is the origin of the 'trickster god' theme that you find in cultures all over the world. Jinn, like the Archons, are Wetiko which is terrified of humans awakening and reconnecting with our true self for then its energy source has gone. With that the feedback loop breaks between Wetiko and human perception that provides the energetic momentum on which its very existence depends as a force of evil. Humans are both its target and its source of survival, but only if we are operating in low-vibrational states of fear, hate, depression and the background anxiety that most people suffer. We are Wetiko's target because we are its key to survival. It needs us, not the other way round. Paul Levy writes:

A vampire has no intrinsic, independent, substantial existence in its own right; it only exists in relation to us. The pathogenic, vampiric mind-parasite called wetiko is nothing in itself – not being able to exist from its own side – yet it has a 'virtual reality' such that it can potentially destroy our species …

…The fact that a vampire is not reflected by a mirror can also mean that what we need to see is that there's nothing, no-thing to see, other than ourselves. The fact that wetiko is the expression of something inside of us means that the cure for wetiko is with us as well. The critical issue is finding this cure within us and then putting it into effect.

Evil begets evil because if evil does not constantly expand and find new sources of energetic sustenance its evil, its *distortion*, dies with the assimilation into balance and harmony. Love is the garlic to Wetiko's vampire. Evil, the absence of love, cannot exist in the presence of love. I think I see a way out of here. I have emphasised so many times over the decades that the Archons/Wetiko and their Cult are not all powerful. *They are not*. I don't care how it looks even now *they are not*. I have not called them little boys in short trousers for effect. I have said it because it is true. Wetiko's insatiable desire for power over others is not a sign of its omnipotence, but its insecurity. Paul Levy writes: 'Due to the primal fear which ultimately drives it and which it is driven to cultivate, wetiko's body politic has an intrinsic and insistent need for centralising power and control so as to create imagined safety for itself.' *Yeeeeeees!* Exactly! Why does Wetiko want humans in an ongoing state of fear? Wetiko itself *is* fear and it is petrified of love. As evil is an absence of love, so love is an absence of fear. Love conquers all and *especially* Wetiko which *is* fear. Wetiko brought fear into the world when it wasn't here before. *Fear* was the 'fall', the fall into low-frequency ignorance and illusion – fear is **F**alse **E**motion **A**ppearing **R**eal. The simulation is driven and energised by fear because Wetiko/Yaldabaoth (fear) *are* the simulation. Fear is the absence of love and Wetiko is the absence of love.

Wetiko today

We can now view current events from this level of perspective. The 'Covid' hoax has generated momentous amounts of ongoing fear, anxiety, depression and despair which have empowered Wetiko. No wonder people like Gates have been the instigators when they are Wetiko incarnate and exhibit every trait of Wetiko in the extreme. See how cold and unemotional these people are like Gates and his cronies, how dead of eye they are. That's Wetiko. Sabbatians are Wetiko and everything they control including the World Health Organization, Big Pharma and the 'vaccine' makers, national 'health'

hierarchies, corporate media, Silicon Valley, the banking system, and the United Nations with its planned transformation into world government. All are controlled and possessed by the Wetiko distortion into distorting human society in its image. We are with this knowledge at the gateway to understanding the world. Divisions of race, culture, creed and sexuality are diversions to hide the real division between those possessed and influenced by Wetiko and those that are not. The 'Covid' hoax has brought both clearly into view. Human behaviour is not about race. Tyrants and dictatorships come in all colours and creeds. What unites the US president bombing the innocent and an African tribe committing genocide against another as in Rwanda? What unites them? *Wetiko*. All wars are Wetiko, all genocide is Wetiko, all hunger over centuries in a world of plenty is Wetiko. Children going to bed hungry, including in the West, is Wetiko. Cult-generated Woke racial divisions that focus on the body are designed to obscure the reality that divisions in behaviour are manifestations of mind, not body. Obsession with body identity and group judgement is a means to divert attention from the real source of behaviour – mind and perception. Conflict sown by the Woke both within themselves and with their target groups are Wetiko providing lunch for itself through still more agents of the division, chaos, and fear on which it feeds. The Cult is seeking to assimilate the entirety of humanity and all children and young people into the Wetiko frequency by manipulating them into states of fear and despair. Witness all the suicide and psychological unravelling since the spring of 2020. Wetiko psychopaths want to impose a state of unquestioning obedience to authority which is no more than a conduit for Wetiko to enforce its will and assimilate humanity into itself. It needs us to believe that resistance is futile when it fears resistance and even more so the game-changing non-cooperation with its impositions. It can use violent resistance for its benefit. Violent impositions and violent resistance are *both* Wetiko. The Power of Love with its Power of No will sweep Wetiko from our world. Wetiko and its Cult know that. They just don't want us to know.

AI Wetiko

This brings me to AI or artificial intelligence and something else Wetikos don't want us to know. What is AI *really*? I know about computer code algorithms and AI that learns from data input. These, however, are more diversions, the expeditionary force, for the real AI that they want to connect to the human brain as promoted by Silicon Valley Wetikos like Kurzweil. What is this AI? It is the frequency of *Wetiko*, the frequency of the Archons. The connection of AI to the human brain is the connection of the Wetiko frequency to create a Wetiko hive mind and complete the job of assimilation. The hive mind is planned to be controlled from Israel and China which are both 100 percent owned by Wetiko Sabbatians. The assimilation process has been going on minute by minute in the 'smart' era which fused with the 'Covid' era. We are told that social media is scrambling the minds of the young and changing their personality. This is true, but what is social media? Look more deeply at how it works, how it creates divisions and conflict, the hostility and cruelty, the targeting of people until they are destroyed. That's Wetiko. Social media is manipulated to tune people to the Wetiko frequency with all the emotional exploitation tricks employed by platforms like Facebook and its Wetiko front man, Zuckerberg. Facebook's Instagram announced a new platform for children to overcome a legal bar on them using the main site. This is more Wetiko exploitation and manipulation of kids. Amnesty International likened the plan to foxes offering to guard the henhouse and said it was incompatible with human rights. Since when did Wetiko or Zuckerberg (I repeat myself) care about that? Would Brin and Page at Google, Wojcicki at YouTube, Bezos at Amazon and whoever the hell runs Twitter act as they do if they were not channelling Wetiko? Would those who are developing technologies for no other reason than human control? How about those designing and selling technologies to kill people and Big Pharma drug and 'vaccine' producers who know they will end or devastate lives? Quite a thought for these people to consider is that if you are Wetiko in a human life you are Wetiko on the 'other side' unless your frequency

changes and that can only change by a change of perception which becomes a change of behaviour. Where Gates is going does not bear thinking about although perhaps that's exactly where he wants to go. Either way, that's where he's going. His frequency will make it so.

The frequency lair

I have been saying for a long time that a big part of the addiction to smartphones and devices is that a frequency is coming off them that entraps the mind. People spend ages on their phones and sometimes even a minute or so after they put them down they pick them up again and it all repeats. 'Covid' lockdowns will have increased this addiction a million times for obvious reasons. Addictions to alcohol overindulgence and drugs are another way that Wetiko entraps consciousness to attach to its own. Both are symptoms of low-vibrational psychological distress which alcoholism and drug addiction further compound. Do we think it's really a coincidence that access to them is made so easy while potions that can take people into realms beyond the simulation are banned and illegal? I have explored smartphone addiction in other books, the scale is mind-blowing, and that level of addiction does not come without help. Tech companies that make these phones are Wetiko and they will have no qualms about destroying the minds of children. We are seeing again with these companies the Wetiko perceptual combination of psychopathic enforcers and weak and meek unquestioning compliance by the rank and file.

The global Smart Grid is the Wetiko Grid and it is crucial to complete the Cult endgame. The simulation is radiation and we are being deluged with technological radiation on a devastating scale. Wetiko frauds like Elon Musk serve Cult interests while occasionally criticising them to maintain his street-cred. 5G and other forms of Wi-Fi are being directed at the earth from space on a volume and scale that goes on increasing by the day. Elon Musk's (officially) SpaceX Starlink project is in the process of putting tens of thousands of satellites in low orbit to cover every inch of the planet with 5G and other Wi-Fi to create Kurzweil's global 'cloud' to which the

human mind is planned to be attached very soon. SpaceX has approval to operate 12,000 satellites with more than 1,300 launched at the time of writing and applications filed for *30,000* more. Other operators in the Wi-Fi, 5G, low-orbit satellite market include OneWeb (UK), Telesat (Canada), and AST & Science (US). Musk tells us that AI could be the end of humanity and then launches a company called Neuralink to connect the human brain to computers. Musk's (in theory) Tesla company is building electric cars and the driverless vehicles of the smart control grid. As frauds and bullshitters go Elon Musk in my opinion is Major League.

5G and technological radiation in general are destructive to human health, genetics and psychology and increasing the strength of artificial radiation underpins the five-sense perceptual bubbles which are themselves expressions of radiation or electromagnetism. Freedom activist John Whitehead was so right with his 'databit by databit, we are building our own electronic concentration camps'. The Smart Grid and 5G is a means to control the human mind and infuse perceptual information into The Field to influence anyone in sync with its frequency. You can change perception and behaviour en masse if you can manipulate the population into those levels of frequency and this is happening all around us today. The arrogance of Musk and his fellow Cult operatives knows no bounds in the way that we see with Gates. Musk's satellites are so many in number already they are changing the night sky when viewed from Earth. The astronomy community has complained about this and they have seen nothing yet. Some consequences of Musk's Wetiko hubris include: Radiation; visible pollution of the night sky; interference with astronomy and meteorology; ground and water pollution from intensive use of increasingly many spaceports; accumulating space debris; continual deorbiting and burning up of aging satellites, polluting the atmosphere with toxic dust and smoke; and ever-increasing likelihood of collisions. A collective public open letter of complaint to Musk said:

> We are writing to you … because SpaceX is in process of surrounding the Earth with a network of thousands of satellites whose very purpose is to irradiate every square inch of the

Earth. SpaceX, like everyone else, is treating the radiation as if it were not there. As if the mitochondria in our cells do not depend on electrons moving undisturbed from the food we digest to the oxygen we breathe.

As if our nervous systems and our hearts are not subject to radio frequency interference like any piece of electronic equipment. As if the cancer, diabetes, and heart disease that now afflict a majority of the Earth's population are not metabolic diseases that result from interference with our cellular machinery. As if insects everywhere, and the birds and animals that eat them, are not starving to death as a result.

People like Musk and Gates believe in their limitless Wetiko arrogance that they can do whatever they like to the world because they own it. Consequences for humanity are irrelevant. It's absolutely time that we stopped taking this shit from these self-styled masters of the Earth when you consider where this is going.

Why is the Cult so anti-human?

I hear this question often: Why would they do this when it will affect them, too? Ah, but will it? Who is this *them*? Forget their bodies. They are just vehicles for Wetiko consciousness. When you break it all down to the foundations we are looking at a state of severely distorted consciousness targeting another state of consciousness for assimilation. The rest is detail. The simulation is the fly-trap in which unique sensations of the five senses create a cycle of addiction called reincarnation. Renegade Minds see that everything which happens in our reality is a smaller version of the whole picture in line with the holographic principle. Addiction to the radiation of smart technology is a smaller version of addiction to the whole simulation. Connecting the body/brain to AI is taking that addiction on a giant step further to total ongoing control by assimilating human incarnate consciousness into Wetiko. I have watched during the 'Covid' hoax how many are becoming ever more profoundly attached to Wetiko's perceptual calling cards of aggressive response to any other point of view ('There is no other god but me'), psychopathic lack of compassion and empathy, and servile submission to the narrative and will of authority. Wetiko is the psychopaths *and* subservience to psychopaths. The Cult of Wetiko is

so anti-human because it is *not* human. It embarked on a mission to destroy human by targeting everything that it means to be human and to survive as human. 'Covid' is not the end, just a means to an end. The Cult with its Wetiko consciousness is seeking to change Earth systems, including the atmosphere, to suit them, not humans. The gathering bombardment of 5G alone from ground and space is dramatically changing The Field with which the five senses interact. There is so much more to come if we sit on our hands and hope it will all go away. It is not meant to go away. It is meant to get ever more extreme and we need to face that while we still can – just.

Carbon dioxide is the gas of life. Without that human is over. Kaput, gone, history. No natural world, no human. The Cult has created a cock and bull story about carbon dioxide and climate change to justify its reduction to the point where Gates and the ignoramus Biden 'climate chief' John Kerry want to suck it out of the atmosphere. Kerry wants to do this because his master Gates does. Wetikos have made the gas of life a demon with the usual support from the Wokers of Extinction Rebellion and similar organisations and the bewildered puppet-child that is Greta Thunberg who was put on the world stage by Klaus Schwab and the World Economic Forum. The name Extinction Rebellion is both ironic and as always Wetiko inversion. The gas that we need to survive must be reduced to save us from extinction. The most basic need of human is oxygen and we now have billions walking around in face nappies depriving body and brain of this essential requirement of human existence. More than that 5G at 60 gigahertz interacts with the oxygen molecule to reduce the amount of oxygen the body can absorb into the bloodstream. The obvious knock-on consequences of that for respiratory and cognitive problems and life itself need no further explanation. Psychopaths like Musk are assembling a global system of satellites to deluge the human atmosphere with this insanity. The man should be in jail. Here we have two most basic of human needs, oxygen and carbon dioxide, being dismantled.

Two others, water and food, are getting similar treatment with the United Nations Agendas 21 and 2030 – the Great Reset – planning to

centrally control all water and food supplies. People will not even own rain water that falls on their land. Food is affected at the most basic level by reducing carbon dioxide. We have genetic modification or GMO infiltrating the food chain on a mass scale, pesticides and herbicides polluting the air and destroying the soil. Freshwater fish that provide livelihoods for 60 million people and feed hundreds of millions worldwide are being 'pushed to the brink' according the conservationists while climate change is the only focus. Now we have Gates and Schwab wanting to dispense with current food sources all together and replace them with a synthetic version which the Wetiko Cult would control in terms of production and who eats and who doesn't. We have been on the Totalitarian Tiptoe to this for more than 60 years as food has become ever more processed and full of chemical shite to the point today when it's not natural food at all. As Dr Tom Cowan says: 'If it has a label don't eat it.' Bill Gates is now the biggest owner of farmland in the United States and he does nothing without an ulterior motive involving the Cult. Klaus Schwab wrote: 'To feed the world in the next 50 years we will need to produce as much food as was produced in the last 10,000 years … food security will only be achieved, however, if regulations on genetically modified foods are adapted to reflect the reality that gene editing offers a precise, efficient and safe method of improving crops.' Liar. People and the world are being targeted with aluminium through vaccines, chemtrails, food, drink cans, and endless other sources when aluminium has been linked to many health issues including dementia which is increasing year after year. Insects, bees and wildlife essential to the food chain are being deleted by pesticides, herbicides and radiation which 5G is dramatically increasing with 6G and 7G to come. The pollinating bee population is being devastated while wildlife including birds, dolphins and whales are having their natural radar blocked by the effects of ever-increasing radiation. In the summer windscreens used to be splattered with insects so numerous were they. It doesn't happen now. Where have they gone?

Synthetic everything

The Cult is introducing genetically-modified versions of trees, plants and insects including a Gates-funded project to unleash hundreds of millions of genetically-modified, lab-altered and patented male mosquitoes to mate with wild mosquitoes and induce genetic flaws that cause them to die out. Clinically-insane Gates-funded Japanese researchers have developed mosquitos that spread vaccine and are dubbed 'flying vaccinators'. Gates is funding the modification of weather patterns in part to sell the myth that this is caused by carbon dioxide and he's funding geoengineering of the skies to change the atmosphere. Some of this came to light with the Gates-backed plan to release tonnes of chalk into the atmosphere to 'deflect the Sun and cool the planet'. Funny how they do this while the heating effect of the Sun is not factored into climate projections focussed on carbon dioxide. The reason is that they want to reduce carbon dioxide (so don't mention the Sun), but at the same time they do want to reduce the impact of the Sun which is so essential to human life and health. I have mentioned the sun-cholesterol-vitamin D connection as they demonise the Sun with warnings about skin cancer (caused by the chemicals in sun cream they tell you to splash on). They come from the other end of the process with statin drugs to reduce cholesterol that turns sunlight into vitamin D. A lack of vitamin D leads to a long list of health effects and how vitamin D levels must have fallen with people confined to their homes over 'Covid'. Gates is funding other forms of geoengineering and most importantly chemtrails which are dropping heavy metals, aluminium and self-replicating nanotechnology onto the Earth which is killing the natural world. See *Everything You Need To Know, But Have Never Been Told* for the detailed background to this.

Every human system is being targeted for deletion by a force that's not human. The Wetiko Cult has embarked on the process of transforming the human body from biological to synthetic biological as I have explained. Biological is being replaced by the artificial and synthetic – Archontic 'countermimicry' – right across human society. The plan eventually is to dispense with the human body altogether

and absorb human consciousness – which it wouldn't really be by then – into cyberspace (the simulation which is Wetiko/Yaldabaoth). Preparations for that are already happening if people would care to look. The alternative media rightly warns about globalism and 'the globalists', but this is far bigger than that and represents the end of the human race as we know it. The 'bad copy' of prime reality that Gnostics describe was a bad copy of harmony, wonder and beauty to start with before Wetiko/Yaldabaoth set out to change the simulated 'copy' into something very different. The process was slow to start with. Entrapped humans in the simulation timeline were not technologically aware and they had to be brought up to intellectual speed while being suppressed spiritually to the point where they could build their own prison while having no idea they were doing so. We have now reached that stage where technological intellect has the potential to destroy us and that's why events are moving so fast. Central American shaman Don Juan Matus said:

> Think for a moment, and tell me how you would explain the contradictions between the intelligence of man the engineer and the stupidity of his systems of belief, or the stupidity of his contradictory behaviour. Sorcerers believe that the predators have given us our systems of beliefs, our ideas of good and evil; our social mores. They are the ones who set up our dreams of success or failure. They have given us covetousness, greed, and cowardice. It is the predator who makes us complacent, routinary, and egomaniacal.
>
> In order to keep us obedient and meek and weak, the predators engaged themselves in a stupendous manoeuvre – stupendous, of course, from the point of view of a fighting strategist; a horrendous manoeuvre from the point of those who suffer it. They gave us their mind. The predators' mind is baroque, contradictory, morose, filled with the fear of being discovered any minute now.

For 'predators' see Wetiko, Archons, Yaldabaoth, Jinn, and all the other versions of the same phenomenon in cultures and religions all over the world. The theme is always the same because it's true and it's real. We have reached the point where we have to deal with it. The question is – how?

Don't fight – walk away

I thought I'd use a controversial subheading to get things moving in terms of our response to global fascism. What do you mean 'don't fight'? What do you mean 'walk away'? We've got to fight. We can't walk away. Well, it depends what we mean by fight and walk away. If fighting means physical combat we are playing Wetiko's game and falling for its trap. It wants us to get angry, aggressive, and direct hate and hostility at the enemy we think we must fight. Every war, every battle, every conflict, has been fought with Wetiko leading both sides. It's what it does. Wetiko wants a fight, anywhere, any place. Just hit me, son, so I can hit you back. Wetiko hits Wetiko and Wetiko hits Wetiko in return. I am very forthright as you can see in exposing Wetikos of the Cult, but I don't hate them. I refuse to hate them. It's what they want. What you hate you become. What you *fight* you become. Wokers, 'anti-haters' and 'anti-fascists' prove this every time they reach for their keyboards or don their balaclavas. By walk away I mean to disengage from Wetiko which includes ceasing to cooperate with its tyranny. Paul Levy says of Wetiko:

> The way to 'defeat' evil is not to try to destroy it (for then, in playing evil's game, we have already lost), but rather, to find the invulnerable place within ourselves where evil is unable to vanquish us – this is to truly 'win' our battle with evil.

Wetiko is everywhere in human society and it's been on steroids since the 'Covid' hoax. Every shouting match over wearing masks has Wetiko wearing a mask and Wetiko not wearing one. It's an electrical circuit of push and resist, push and resist, with Wetiko pushing *and* resisting. Each polarity is Wetiko empowering itself. Dictionary definitions of 'resist' include 'opposing, refusing to accept or comply with' and the word to focus on is 'opposing'. What form does this take – setting police cars alight or 'refusing to accept or comply with'? The former is Wetiko opposing Wetiko while the other points the way forward. This is the difference between those aggressively demanding that government fascism must be obeyed who stand in stark contrast to the great majority of Pushbackers. We saw this clearly with a march by thousands of Pushbackers against lockdown in London followed days later by a Woker-hijacked

protest in Bristol in which police cars were set on fire. Masks were virtually absent in London and widespread in Bristol. Wetiko wants lockdown on every level of society and infuses its aggression to police it through its unknowing stooges. Lockdown protesters are the ones with the smiling faces and the hugs, The two blatantly obvious states of being – getting more obvious by the day – are the result of Wokers and their like becoming ever more influenced by the simulation Field of Wetiko and Pushbackers ever more influenced by The Field of a far higher vibration beyond the simulation. Wetiko can't invade the heart which is where most lockdown opponents are coming from. It's the heart that allows them to see through the lies to the truth in ways I will be highlighting.

Renegade Minds know that calmness is the place from which wisdom comes. You won't find wisdom in a hissing fit and wisdom is what we need in abundance right now. Calmness is not weakness – you don't have to scream at the top of your voice to be strong. Calmness is indeed a sign of strength. 'No' means I'm not doing it. *NOOOO!!!* doesn't mean you're not doing it even more. Volume does not advance 'No – I'm not doing it'. You are just not doing it. Wetiko possessed and influenced don't know how to deal with that. Wetiko wants a fight and we should not give it one. What it needs more than anything is our *cooperation* and we should not give that either. Mass rallies and marches are great in that they are a visual representation of feeling, but if it ends there they are irrelevant. You demand that Wetikos act differently? Well, they're not going to are they? They are Wetikos. We don't need to waste our time demanding that something doesn't happen when that will make no difference. We need to delete the means that *allows* it to happen. This, invariably, is our cooperation. You can demand a child stop firing a peashooter at the dog or you can refuse to buy the peashooter. If you provide the means you are cooperating with the dog being smacked on the nose with a pea. How can the authorities enforce mask-wearing if millions in a country refuse? What if the 74 million Pushbackers that voted for Trump in 2020 refused to wear masks, close their businesses or stay in their homes. It would be unenforceable. The

few control the many through the compliance of the many and that's always been the dynamic be it 'Covid' regulations or the Roman Empire. I know people can find it intimidating to say no to authority or stand out in a crowd for being the only one with a face on display; but it has to be done or it's over. I hope I've made clear in this book that where this is going will be far more intimidating than standing up now and saying 'No' – I will not cooperate with my own enslavement and that of my children. There might be consequences for some initially, although not so if enough do the same. The question that must be addressed is what is going to happen if we don't? It is time to be strong and unyieldingly so. No means no. Not here and there, but *everywhere* and *always*. I have refused to wear a mask and obey all the other nonsense. I will not comply with tyranny. I repeat: Fascism is not imposed by fascists – there are never enough of them. Fascism is imposed by the population acquiescing to fascism. *I will not do it*. I will die first, or my body will. Living meekly under fascism is a form of death anyway, the death of the spirit that Martin Luther King described.

Making things happen

We must not despair. This is not over till it's over and it's far from that. The 'fat lady' must refuse to sing. The longer the 'Covid' hoax has dragged on and impacted on more lives we have seen an awakening of phenomenal numbers of people worldwide to the realisation that what they have believed all their lives is not how the world really is. Research published by the system-serving University of Bristol and King's College London in February, 2021, concluded: 'One in every 11 people in Britain say they trust David Icke's take on the coronavirus pandemic.' It will be more by now and we have gathering numbers to build on. We must urgently progress from seeing the scam to ceasing to cooperate with it. Prominent German lawyer Reiner Fuellmich, also licenced to practice law in America, is doing a magnificent job taking the legal route to bring the psychopaths to justice through a second Nuremberg tribunal for crimes against humanity. Fuellmich has an impressive record of

beating the elite in court and he formed the German Corona Investigative Committee to pursue civil charges against the main perpetrators with a view to triggering criminal charges. Most importantly he has grasped the foundation of the hoax – the PCR test not testing for the 'virus' – and Christian Drosten is therefore on his charge sheet along with Gates frontman Tedros at the World Health Organization. Major players must be not be allowed to inflict their horrors on the human race without being brought to book. A life sentence must follow for Bill Gates and the rest of them. A group of researchers has also indicted the government of Norway for crimes against humanity with copies sent to the police and the International Criminal Court. The lawsuit cites participation in an internationally-planned false pandemic and violation of international law and human rights, the European Commission's definition of human rights by coercive rules, Nuremberg and Hague rules on fundamental human rights, and the Norwegian constitution. We must take the initiative from hereon and not just complain, protest and react.

There are practical ways to support vital mass non-cooperation. Organising in numbers is one. Lockdown marches in London in the spring in 2021 were mass non-cooperation that the authorities could not stop. There were too many people. Hundreds of thousands walked the London streets in the centre of the road for mile after mile while the Face-Nappies could only look on. They were determined, but calm, and just *did it* with no histrionics and lots of smiles. The police were impotent. Others are organising group shopping without masks for mutual support and imagine if that was happening all over. Policing it would be impossible. If the store refuses to serve people in these circumstances they would be faced with a long line of trolleys full of goods standing on their own and everything would have to be returned to the shelves. How would they cope with that if it kept happening? I am talking here about moving on from complaining to being pro-active; from watching things happen to making things happen. I include in this our relationship with the police. The behaviour of many Face-Nappies

has been disgraceful and anyone who thinks they would never find concentration camp guards in the 'enlightened' modern era have had that myth busted big-time. The period and setting may change – Wetikos never do. I watched film footage from a London march in which a police thug viciously kicked a protestor on the floor who had done nothing. His fellow Face-Nappies stood in a ring protecting him. What he did was a criminal assault and with a crowd far outnumbering the police this can no longer be allowed to happen unchallenged. I get it when people chant 'shame on you' in these circumstances, but that is no longer enough. They *have* no shame those who do this. Crowds needs to start making a citizen's arrest of the police who commit criminal offences and brutally attack innocent people and defenceless women. A citizen's arrest can be made under section 24A of the UK Police and Criminal Evidence (PACE) Act of 1984 and you will find something similar in other countries. I prefer to call it a Common Law arrest rather than citizen's for reasons I will come to shortly. Anyone can arrest a person committing an indictable offence or if they have reasonable grounds to suspect they are committing an indictable offence. On both counts the attack by the police thug would have fallen into this category. A citizen's arrest can be made to stop someone:

- Causing physical injury to himself or any other person
- Suffering physical injury
- Causing loss of or damage to property
- Making off before a constable can assume responsibility for him

A citizen's arrest may also be made to prevent a breach of the peace under Common Law and if they believe a breach of the peace will happen or anything related to harm likely to be done or already done in their presence. This is the way to go I think – the Common Law version. If police know that the crowd and members of the public will no longer be standing and watching while they commit

their thuggery and crimes they will think twice about acting like Brownshirts and Blackshirts.

Common Law – common sense

Mention of Common Law is very important. Most people think the law is the law as in one law. This is not the case. There are two bodies of law, Common Law and Statute Law, and they are not the same. Common Law is founded on the simple premise of do no harm. It does not recognise victimless crimes in which no harm is done while Statute Law does. There is a Statute Law against almost everything. So what is Statute Law? Amazingly it's the law of the *sea* that was brought ashore by the Cult to override the law of the land which is Common Law. They had no right to do this and as always they did it anyway. They had to. They could not impose their will on the people through Common Law which only applies to do no harm. How could you stitch up the fine detail of people's lives with that? Instead they took the law of the sea, or Admiralty Law, and applied it to the population. Statute Law refers to all the laws spewing out of governments and their agencies including all the fascist laws and regulations relating to 'Covid'. The key point to make is that Statute Law is *contract law*. It only applies between *contracting* corporations. Most police officers don't even know this. They have to be kept in the dark, too. Long ago when merchants and their sailing ships began to trade with different countries a contractual law was developed called Admiralty Law and other names. Again it only applied to *contracts* agreed between *corporate* entities. If there is no agreed contract the law of the sea had no jurisdiction *and that still applies to its new alias of Statute Law*. The problem for the Cult when the law of the sea was brought ashore was an obvious one. People were not corporations and neither were government entities. To overcome the latter they made governments and all associated organisations corporations. All the institutions are *private corporations* and I mean governments and their agencies, local councils, police, courts, military, US states, the whole lot. Go to the

Dun and Bradstreet corporate listings website for confirmation that they are all corporations. You are arrested by a private corporation called the police by someone who is really a private security guard and they take you to court which is another private corporation. Neither have jurisdiction over you unless you consent and *contract* with them. This is why you hear the mantra about law enforcement policing by *consent* of the people. In truth the people 'consent' only in theory through monumental trickery.

Okay, the Cult overcame the corporate law problem by making governments and institutions corporate entities; but what about people? They are not corporations are they? Ah ... well in a sense, and *only* a sense, they are. Not people exactly – the illusion of people. The Cult creates a corporation in the name of everyone at the time that their birth certificate is issued. Note birth/ *berth* certificate and when you go to court under the law of the sea on land you stand in a *dock*. These are throwbacks to the origin. My Common Law name is David Vaughan Icke. The name of the corporation created by the government when I was born is called Mr David Vaughan Icke usually written in capitals as MR DAVID VAUGHAN ICKE. That is not me, the living, breathing man. It is a fictitious corporate entity. The trick is to make you think that David Vaughan Icke and MR DAVID VAUGHAN ICKE are the same thing. *They are not*. When police charge you and take you to court they are prosecuting the corporate entity and not the living, breathing, man or woman. They have to trick you into identifying as the corporate entity and contracting with them. Otherwise they have no jurisdiction. They do this through a language known as legalese. Lawful and legal are not the same either. Lawful relates to Common Law and legal relates to Statute Law. Legalese is the language of Statue Law which uses terms that mean one thing to the public and another in legalese. Notice that when a police officer tells someone why they are being charged he or she will say at the end: 'Do you understand?' To the public that means 'Do you comprehend?' In legalese it means 'Do you stand under me?' Do you stand under my authority? If you say

yes to the question you are unknowingly agreeing to give them jurisdiction over you in a contract between two corporate entities.

This is a confidence trick in every way. Contracts have to be agreed between informed parties and if you don't know that David Vaughan Icke is agreeing to be the corporation MR DAVID VAUGHAN ICKE you cannot knowingly agree to contract. They are deceiving you and another way they do this is to ask for proof of identity. You usually show them a driving licence or other document on which your corporate name is written. In doing so you are accepting that you are that corporate entity when you are not. Referring to yourself as a 'person' or 'citizen' is also identifying with your corporate fiction which is why I made the Common Law point about the citizen's arrest. If you are approached by a police officer you identify yourself immediately as a living, breathing, man or woman and say 'I do not consent, I do not contract with you and I do not understand' or stand under their authority. I have a Common Law birth certificate as a living man and these are available at no charge from commonlawcourt.com. Businesses registered under the Statute Law system means that its laws apply. There are, however, ways to run a business under Common Law. Remember all 'Covid' laws and regulations are Statute Law – the law of *contracts* and you do not have to contract. This doesn't mean that you can kill someone and get away with it. Common Law says do no harm and that applies to physical harm, financial harm etc. Police are employees of private corporations and there needs to be a new system of non-corporate Common Law constables operating outside the Statute Law system. If you go to davidicke.com and put Common Law into the search engine you will find videos that explain Common Law in much greater detail. It is definitely a road we should walk.

With all my heart

I have heard people say that we are in a spiritual war. I don't like the term 'war' with its Wetiko dynamic, but I know what they mean. Sweep aside all the bodily forms and we are in a situation in which two states of consciousness are seeking very different realities.

Wetiko wants upheaval, chaos, fear, suffering, conflict and control. The other wants love, peace, harmony, fairness and freedom. That's where we are. We should not fall for the idea that Wetiko is all-powerful and there's nothing we can do. Wetiko is not all-powerful. It's a joke, pathetic. It doesn't have to be, but it has made that choice for now. A handful of times over the years when I have felt the presence of its frequency I have allowed it to attach briefly so I could consciously observe its nature. The experience is not pleasant, the energy is heavy and dark, but the ease with which you can kick it back out the door shows that its real power is in persuading us that it has power. It's all a con. Wetiko is a con. It's a trickster and not a power that can control us if we unleash our own. The con is founded on manipulating humanity to give its power to Wetiko which recycles it back to present the illusion that it has power when its power is *ours* that we gave away. This happens on an energetic level and plays out in the world of the seen as humanity giving its power to Wetiko authority which uses that power to control the population when the power is only the power the population has handed over. How could it be any other way for billions to be controlled by a relative few? I have had experiences with people possessed by Wetiko and again you can kick its arse if you do it with an open heart. Oh yes – the *heart* which can transform the world of perceived 'matter'.

We are receiver-transmitters and processors of information, but what information and where from? Information is processed into perception in three main areas – the brain, the heart and the belly. These relate to thinking, knowing, and emotion. Wetiko wants us to be head and belly people which means we think within the confines of the Matrix simulation and low-vibrational emotional reaction scrambles balance and perception. A few minutes on social media and you see how emotion is the dominant force. Woke is all emotion and is therefore thought-free and fact-free. Our heart is something different. It *knows* while the head *thinks* and has to try to work it out because it doesn't know. The human energy field has seven prime vortexes which connect us with wider reality (Fig 23). Chakra means

'wheels of light' in the Sanskrit language of ancient India. The main ones are: The crown chakra on top of the head; brow (or 'third eye') chakra in the centre of the forehead; throat chakra; heart chakra in the centre of the chest; solar plexus chakra below the sternum; sacral chakra beneath the navel; and base chakra at the bottom of the spine. Each one has a particular function or functions. We feel anxiety and nervousness in the belly where the sacral chakra is located and this processes emotion that can affect the colon to give people 'the shits' or make them 'shit scared' when they are nervous. Chakras all play an important role, but the Mr and Mrs Big is the heart chakra which sits at the centre of the seven, above the chakras that connect us to the 'physical' and below those that connect with higher realms (or at least should). Here in the heart chakra we feel love, empathy and compassion – 'My heart goes out to you'. Those with closed hearts become literally 'heart-less' in their attitudes and behaviour (see Bill Gates). Native Americans portrayed Wetiko with what Paul Levy calls a 'frigid, icy heart, devoid of mercy' (see Bill Gates).



Figure 23: The chakra system which interpenetrates the human energy field. The heart chakra is the governor – or should be.

Wetiko trembles at the thought of heart energy which it cannot infiltrate. The frequency is too high. What it seeks to do instead is close the heart chakra vortex to block its perceptual and energetic influence. Psychopaths have 'hearts of stone' and emotionally-damaged people have 'heartache' and 'broken hearts'. The astonishing amount of heart disease is related to heart chakra

disruption with its fundamental connection to the 'physical' heart. Dr Tom Cowan has written an outstanding book challenging the belief that the heart is a pump and making the connection between the 'physical' and spiritual heart. Rudolph Steiner who was way ahead of his time said the same about the fallacy that the heart is a pump. *What*? The heart is not a pump? That's crazy, right? Everybody knows that. Read Cowan's *Human Heart, Cosmic Heart* and you will realise that the very idea of the heart as a pump is ridiculous when you see the evidence. How does blood in the feet so far from the heart get pumped horizontally up the body by the heart?? Cowan explains in the book the real reason why blood moves as it does. Our 'physical' heart is used to symbolise love when the source is really the heart vortex or spiritual heart which is our most powerful energetic connection to 'out there' expanded consciousness. That's why we feel *knowing* – intuitive knowing – in the centre of the chest. Knowing doesn't come from a process of thoughts leading to a conclusion. It is there in an instant all in one go. Our heart knows because of its connection to levels of awareness that *do* know. This is the meaning and source of intuition – intuitive *knowing*.

For the last more than 30 years of uncovering the global game and the nature of reality my heart has been my constant antenna for truth and accuracy. An American intelligence insider once said that I had quoted a disinformer in one of my books and yet I had only quoted the part that was true. He asked: 'How do you do that?' By using my heart antenna was the answer and anyone can do it. Heart-centred is how we are meant to be. With a closed heart chakra we withdraw into a closed mind and the bubble of five-sense reality. If you take a moment to focus your attention on the centre of your chest, picture a spinning wheel of light and see it opening and expanding. You will feel it happening, too, and perceptions of the heart like joy and love as the heart impacts on the mind as they interact. The more the chakra opens the more you will feel expressions of heart consciousness and as the process continues, and becomes part of you, insights and knowings will follow. An open

heart is connected to that level of awareness that knows all is *One*. You will see from its perspective that the fault-lines that divide us are only illusions to control us. An open heart does not process the illusions of race, creed and sexuality except as brief experiences for a consciousness that is all. Our heart does not see division, only unity (Figs 24 and 25). There's something else, too. Our hearts love to laugh. Mark Twain's quote that says 'The human race has one really effective weapon, and that is laughter' is really a reference to the heart which loves to laugh with the joy of knowing the true nature of infinite reality and that all the madness of human society is an illusion of the mind. Twain also said: 'Against the assault of laughter nothing can stand.' This is so true of Wetiko and the Cult. Their insecurity demands that they be taken seriously and their power and authority acknowledged and feared. We should do nothing of the sort. We should not get aggressive or fearful which their insecurity so desires. We should laugh in their face. Even in their no-face as police come over in their face-nappies and expect to be taken seriously. They don't take themselves seriously looking like that so why should we? Laugh in the face of intimidation. Laugh in the face of tyranny. You will see by its reaction that you have pressed all of its buttons. Wetiko does not know what to do in the face of laughter or when its targets refuse to concede their joy to fear. We have seen many examples during the 'Covid' hoax when people have expressed their energetic power and the string puppets of Wetiko retreat with their tail limp between their knees. Laugh – the world is bloody mad after all and if it's a choice between laughter and tears I know which way I'm going.



Figure 24: Head consciousness without the heart sees division and everything apart from everything else.



Figure 25: Heart consciousness sees everything as One.

'Vaccines' and the soul

The foundation of Wetiko/Archon control of humans is the separation of incarnate five-sense mind from the infinite 'I' and closing the heart chakra where the True 'I' lives during a human life. The goal has been to achieve complete separation in both cases. I was interested therefore to read an account by a French energetic healer of what she said she experienced with a patient who had been given the 'Covid' vaccine. Genuine energy healers can sense information and consciousness fields at different levels of being which are referred to as 'subtle bodies'. She described treating the patient who later returned after having, without the healer's knowledge, two doses of the 'Covid vaccine'. The healer said:

I noticed immediately the change, very heavy energy emanating from [the] subtle bodies. The scariest thing was when I was working on the heart chakra, I connected with her soul: it was detached from the physical body, it had no contact and it was, as if it was floating in a state of total confusion: a damage to the consciousness that loses contact with the physical body, i.e. with our biological machine, there is no longer any communication between them.

I continued the treatment by sending light to the heart chakra, the soul of the person, but it seemed that the soul could no longer receive any light, frequency or energy. It was a very powerful experience for me. Then I understood that this substance is indeed used to detach consciousness so that this consciousness can no longer interact through this body that it possesses in life, where there is no longer any contact, no frequency, no light, no more energetic balance or mind.

This would create a human that is rudderless and at the extreme almost zombie-like operating with a fractional state of consciousness at the mercy of Wetiko. I was especially intrigued by what the healer said in the light of the prediction by the highly-informed Rudolf Steiner more than a hundred years ago. He said:

In the future, we will eliminate the soul with medicine. Under the pretext of a 'healthy point of view', there will be a vaccine by which the human body will be treated as soon as possible directly at birth, so that the human being cannot develop the thought of the existence of soul and Spirit. To materialistic doctors will be entrusted the task of removing the soul of humanity.

As today, people are vaccinated against this disease or that disease, so in the future, children will be vaccinated with a substance that can be produced precisely in such a way that people, thanks to this vaccination, will be immune to being subjected to the 'madness' of spiritual life. He would be extremely smart, but he would not develop a conscience, and that is the true goal of some materialistic circles.

Steiner said the vaccine would detach the physical body from the etheric body (subtle bodies) and 'once the etheric body is detached the relationship between the universe and the etheric body would become extremely unstable, and man would become an automaton'. He said 'the physical body of man must be polished on this Earth by spiritual will – so the vaccine becomes a kind of arymanique (Wetiko) force' and 'man can no longer get rid of a given materialistic feeling'. Humans would then, he said, become 'materialistic of constitution and can no longer rise to the spiritual'. I have been writing for years about DNA being a receiver-transmitter of information that connects us to other levels of reality and these 'vaccines' changing DNA can be likened to changing an antenna and what it can transmit and receive. Such a disconnection would clearly lead to changes in personality and perception. Steiner further predicted the arrival of AI. Big Pharma 'Covid vaccine' makers, expressions of Wetiko, are testing their DNA-manipulating evil on children as I write with a view to giving the 'vaccine' to babies. If it's a soul-body disconnector – and I say that it is or can be – every child would be disconnected from 'soul' at birth and the 'vaccine' would create a closed system in which spiritual guidance from the greater self would play no part. This has been the ambition of Wetiko all

along. A Pentagon video from 2005 was leaked of a presentation explaining the development of vaccines to change behaviour by their effect on the brain. Those that believe this is not happening with the 'Covid' genetically-modifying procedure masquerading as a 'vaccine' should make an urgent appointment with Naivety Anonymous. Klaus Schwab wrote in 2018:

> Neurotechnologies enable us to better influence consciousness and thought and to understand many activities of the brain. They include decoding what we are thinking in fine levels of detail through new chemicals and interventions that can influence our brains to correct for errors or enhance functionality.

The plan is clear and only the heart can stop it. With every heart that opens, every mind that awakens, Wetiko is weakened. Heart and love are far more powerful than head and hate and so nothing like a majority is needed to turn this around.

Beyond the Phantom

Our heart is the prime target of Wetiko and so it must be the answer to Wetiko. We *are* our heart which is part of one heart, the infinite heart. Our heart is where the true self lives in a human life behind firewalls of five-sense illusion when an imposter takes its place – *Phantom Self*; but our heart waits patiently to be set free any time we choose to see beyond the Phantom, beyond Wetiko. A Wetikoed Phantom Self can wreak mass death and destruction while the love of forever is locked away in its heart. The time is here to unleash its power and let it sweep away the fear and despair that is Wetiko. Heart consciousness does not seek manipulated, censored, advantage for its belief or religion, its activism and desires. As an expression of the One it treats all as One with the same rights to freedom and opinion. Our heart demands fairness for itself no more than for others. From this unity of heart we can come together in mutual support and transform this Wetikoed world into what reality is meant to be – a place of love, joy, happiness, fairness, justice and freedom. Wetiko has another agenda and that's why the world is as

it is, but enough of this nonsense. Wetiko can't stay where hearts are open and it works so hard to keep them closed. Fear is its currency and its food source and love in its true sense has no fear. Why would love have fear when it knows it is *All That Is, Has Been, And Ever Can Be* on an eternal exploration of all possibility? Love in this true sense is not the physical attraction that passes for love. This can be an expression of it, yes, but Infinite Love, a love without condition, goes far deeper to the core of all being. It *is* the core of all being. Infinite realty was born from love beyond the illusions of the simulation. Love infinitely expressed is the knowing that all is One and the swiftly-passing experience of separation is a temporary hallucination. You cannot disconnect from Oneness; you can only *perceive* that you have and withdraw from its influence. This is the most important of all perception trickery by the mind parasite that is Wetiko and the foundation of all its potential for manipulation.

If we open our hearts, open the sluice gates of the mind, and redefine self-identity amazing things start to happen. Consciousness expands or contracts in accordance with self-identity. When true self is recognised as infinite awareness and label self – Phantom Self – is seen as only a series of brief experiences life is transformed. Consciousness expands to the extent that self-identity expands and everything changes. You see unity, not division, the picture, not the pixels. From this we can play the long game. No more is an experience something in and of itself, but a fleeting moment in the eternity of forever. Suddenly people in uniform and dark suits are no longer intimidating. Doing what your heart knows to be right is no longer intimidating and consequences for those actions take on the same nature of a brief experience that passes in the blink of an infinite eye. Intimidation is all in the mind. Beyond the mind there is no intimidation.

An open heart does not consider consequences for what it knows to be right. To do so would be to consider not doing what it knows to be right and for a heart in its power that is never an option. The Renegade Mind is really the Renegade Heart. Consideration of consequences will always provide a getaway car for the mind and

the heart doesn't want one. What is right in the light of what we face today is to stop cooperating with Wetiko in all its forms and to do it without fear or compromise. You cannot compromise with tyranny when tyranny always demands more until it has everything. Life is your perception and you are your destiny. Change your perception and you change your life. Change collective perception and we change the world.

Come on people … One human family, One heart, One goal … *FREEEEEEDOM*!

We must settle for nothing less.

Postscript

The big scare story as the book goes to press is the 'Indian' variant and the world is being deluged with propaganda about the 'Covid catastrophe' in India which mirrors in its lies and misrepresentations what happened in Italy before the first lockdown in 2020.

The *New York Post* published a picture of someone who had 'collapsed in the street from Covid' in India in April, 2021, which was actually taken during a gas leak in May, 2020. Same old, same old. Media articles in mid-February were asking why India had been so untouched by 'Covid' and then as their vaccine rollout gathered pace the alleged 'cases' began to rapidly increase. Indian 'Covid vaccine' maker Bharat Biotech was funded into existence by the Bill and Melinda Gates Foundation (the pair announced their divorce in May, 2021, which is a pity because they so deserve each other). The Indian 'Covid crisis' was ramped up by the media to terrify the world and prepare people for submission to still more restrictions. The scam that worked the first time was being repeated only with far more people seeing through the deceit. Davidicke.com and Ickonic.com have sought to tell the true story of what is happening by talking to people living through the Indian nightmare which has nothing to do with 'Covid'. We posted a letter from 'Alisha' in Pune who told a very different story to government and media mendacity. She said scenes of dying people and overwhelmed hospitals were designed to hide what was really happening – genocide and starvation. Alisha said that millions had already died of starvation during the ongoing lockdowns while government and media were lying and making it look like the 'virus':

Restaurants, shops, gyms, theatres, basically everything is shut. The cities are ghost towns. Even so-called 'essential' businesses are only open till 11am in the morning. You basically have just an hour to buy food and then your time is up.

Inter-state travel and even inter-district travel is banned. The cops wait at all major crossroads to question why you are traveling outdoors or to fine you if you are not wearing a mask.

The medical community here is also complicit in genocide, lying about hospitals being full and turning away people with genuine illnesses, who need immediate care. They have even created a shortage of oxygen cylinders.

This is the classic Cult modus operandi played out in every country. Alisha said that people who would not have a PCR test not testing for the 'virus' were being denied hospital treatment. She said the people hit hardest were migrant workers and those in rural areas. Most businesses employed migrant workers and with everything closed there were no jobs, no income and no food. As a result millions were dying of starvation or malnutrition. All this was happening under Prime Minister Narendra Modi, a 100-percent asset of the Cult, and it emphasises yet again the scale of pure anti-human evil we are dealing with. Australia banned its people from returning home from India with penalties for trying to do so of up to five years in jail and a fine of £37,000. The manufactured 'Covid' crisis in India was being prepared to justify further fascism in the West. Obvious connections could be seen between the Indian 'vaccine' programme and increased 'cases' and this became a common theme. The Seychelles, the most per capita 'Covid vaccinated' population in the world, went back into lockdown after a 'surge of cases'.

Long ago the truly evil Monsanto agricultural biotechnology corporation with its big connections to Bill Gates devastated Indian farming with genetically-modified crops. Human rights activist Gurcharan Singh highlighted the efforts by the Indian government to complete the job by destroying the food supply to hundreds of millions with 'Covid' lockdowns. He said that 415 million people at the bottom of the disgusting caste system (still going whatever they say) were below the poverty line and struggled to feed themselves every year. Now the government was imposing lockdown at just the

time to destroy the harvest. This deliberate policy was leading to mass starvation. People may reel back at the suggestion that a government would do that, but Wetiko-controlled 'leaders' are capable of any level of evil. In fact what is described in India is in the process of being instigated worldwide. The food chain and food supply are being targeted at every level to cause world hunger and thus control. Bill Gates is not the biggest owner of farmland in America for no reason and destroying access to food aids both the depopulation agenda and the plan for synthetic 'food' already being funded into existence by Gates. Add to this the coming hyper-inflation from the suicidal creation of fake 'money' in response to 'Covid' and the breakdown of container shipping systems and you have a cocktail that can only lead one way and is meant to. The Cult plan is to crash the entire system to 'build back better' with the Great Reset.

'Vaccine' transmission

Reports from all over the world continue to emerge of women suffering menstrual and fertility problems after having the fake 'vaccine' and of the non-'vaccinated' having similar problems when interacting with the 'vaccinated'. There are far too many for 'coincidence' to be credible. We've had menopausal women getting periods, others having periods stop or not stopping for weeks, passing clots, sometimes the lining of the uterus, breast irregularities, and miscarriages (which increased by 400 percent in parts of the United States). Non-'vaccinated' men and children have suffered blood clots and nose bleeding after interaction with the 'vaccinated'. Babies have died from the effects of breast milk from a 'vaccinated' mother. Awake doctors – the small minority – speculated on the cause of non-'vaccinated' suffering the same effects as the 'vaccinated'. Was it nanotechnology in the synthetic substance transmitting frequencies or was it a straight chemical bioweapon that was being transmitted between people? I am not saying that some kind of chemical transmission is not one possible answer, but the foundation of all that the Cult does is frequency and

this is fertile ground for understanding how transmission can happen. American doctor Carrie Madej, an internal medicine physician and osteopath, has been practicing for the last 20 years, teaching medical students, and she says attending different meetings where the agenda for humanity was discussed. Madej, who operates out of Georgia, did not dismiss other possible forms of transmission, but she focused on frequency in search of an explanation for transmission. She said the Moderna and Pfizer 'vaccines' contained nano-lipid particles as a key component. This was a brand new technology never before used on humanity. 'They're using a nanotechnology which is pretty much little tiny computer bits … nanobots or hydrogel.' Inside the 'vaccines' was 'this sci-fi kind of substance' which suppressed immune checkpoints to get into the cell. I referred to this earlier as the 'Trojan horse' technique that tricks the cell into opening a gateway for the self-replicating synthetic material and while the immune system is artificially suppressed the body has no defences. Madej said the substance served many purposes including an on-demand ability to 'deliver the payload' and using the nano 'computer bits' as biosensors in the body. 'It actually has the ability to accumulate data from your body, like your breathing, your respiration, thoughts, emotions, all kinds of things.'

She said the technology obviously has the ability to operate through Wi-Fi and transmit and receive energy, messages, frequencies or impulses. 'Just imagine you're getting this new substance in you and it can react to things all around you, the 5G, your smart device, your phones.' We had something completely foreign in the human body that had never been launched large scale at a time when we were seeing 5G going into schools and hospitals (plus the Musk satellites) and she believed the 'vaccine' transmission had something to do with this: '… if these people have this inside of them … it can act like an antenna and actually transmit it outwardly as well.' The synthetic substance produced its own voltage and so it could have that kind of effect. This fits with my own contention that the nano receiver-transmitters are designed to connect people to the

Smart Grid and break the receiver-transmitter connection to expanded consciousness. That would explain the French energy healer's experience of the disconnection of body from 'soul' with those who have had the 'vaccine'. The nanobots, self-replicating inside the body, would also transmit the synthetic frequency which could be picked up through close interaction by those who have not been 'vaccinated'. Madej speculated that perhaps it was 5G and increased levels of other radiation that was causing the symptoms directly although interestingly she said that non-'vaccinated' patients had shown improvement when they were away from the 'vaccinated' person they had interacted with. It must be remembered that you can control frequency and energy with your mind and you can consciously create energetic barriers or bubbles with the mind to stop damaging frequencies from penetrating your field. American paediatrician Dr Larry Palevsky said the 'vaccine' was not a 'vaccine' and was never designed to protect from a 'viral' infection. He called it 'a massive, brilliant propaganda of genocide' because they didn't have to inject everyone to get the result they wanted. He said the content of the jabs was able to infuse any material into the brain, heart, lungs, kidneys, liver, sperm and female productive system. 'This is genocide; this is a weapon of mass destruction.' At the same time American colleges were banning students from attending if they didn't have this life-changing and potentially life-ending 'vaccine'. Class action lawsuits must follow when the consequences of this college fascism come to light. As the book was going to press came reports about fertility effects on sperm in 'vaccinated' men which would absolutely fit with what I have been saying and hospitals continued to fill with 'vaccine' reactions. Another question is what about transmission via blood transfusions? The NHS has extended blood donation restrictions from seven days after a 'Covid vaccination' to 28 days after even a sore arm reaction.

I said in the spring of 2020 that the then touted 'Covid vaccine' would be ongoing each year like the flu jab. A year later Pfizer CEO, the appalling Albert Bourla, said people would 'likely' need a 'booster dose' of the 'vaccine' within 12 months of getting 'fully

vaccinated' and then a yearly shot. 'Variants will play a key role', he said confirming the point. Johnson & Johnson CEO Alex Gorsky also took time out from his 'vaccine' disaster to say that people may need to be vaccinated against 'Covid-19' each year. UK Health Secretary, the psychopath Matt Hancock, said additional 'boosters' would be available in the autumn of 2021. This is the trap of the 'vaccine passport'. The public will have to accept every last 'vaccine' they introduce, including for the fake 'variants', or it would cease to be valid. The only other way in some cases would be continuous testing with a test not testing for the 'virus' and what is on the swabs constantly pushed up your noise towards the brain every time?

'Vaccines' changing behaviour

I mentioned in the body of the book how I believed we would see gathering behaviour changes in the 'vaccinated' and I am already hearing such comments from the non-'vaccinated' describing behaviour changes in friends, loved ones and work colleagues. This will only increase as the self-replicating synthetic material and nanoparticles expand in body and brain. An article in the *Guardian* in 2016 detailed research at the University of Virginia in Charlottesville which developed a new method for controlling brain circuits associated with complex animal behaviour. The method, dubbed 'magnetogenetics', involves genetically-engineering a protein called ferritin, which stores and releases iron, to create a magnetised substance – 'Magneto' – that can activate specific groups of nerve cells from a distance. This is claimed to be an advance on other methods of brain activity manipulation known as optogenetics and chemogenetics (the Cult has been developing methods of brain control for a long time). The ferritin technique is said to be non-invasive and able to activate neurons 'rapidly and reversibly'. In other words, human thought and perception. The article said that earlier studies revealed how nerve cell proteins 'activated by heat and mechanical pressure can be genetically engineered so that they become sensitive to radio waves and magnetic fields, by attaching them to an iron-storing protein called ferritin, or to inorganic

paramagnetic particles'. Sensitive to radio waves and magnetic fields? You mean like 5G, 6G and 7G? This is the human-AI Smart Grid hive mind we are talking about. The *Guardian* article said:

> … the researchers injected Magneto into the striatum of freely behaving mice, a deep brain structure containing dopamine-producing neurons that are involved in reward and motivation, and then placed the animals into an apparatus split into magnetised and non-magnetised sections.
>
> Mice expressing Magneto spent far more time in the magnetised areas than mice that did not, because activation of the protein caused the striatal neurons expressing it to release dopamine, so that the mice found being in those areas rewarding. This shows that Magneto can remotely control the firing of neurons deep within the brain, and also control complex behaviours.

Make no mistake this basic methodology will be part of the 'Covid vaccine' cocktail and using magnetics to change brain function through electromagnetic field frequency activation. The Pentagon is developing a 'Covid vaccine' using ferritin. Magnetics would explain changes in behaviour and why videos are appearing across the Internet as I write showing how magnets stick to the skin at the point of the 'vaccine' shot. Once people take these 'vaccines' anything becomes possible in terms of brain function and illness which will be blamed on 'Covid-19' and 'variants'. Magnetic field manipulation would further explain why the non-'vaccinated' are reporting the same symptoms as the 'vaccinated' they interact with and why those symptoms are reported to decrease when not in their company. Interestingly 'Magneto', a 'mutant', is a character in the Marvel Comic *X-Men* stories with the ability to manipulate magnetic fields and he believes that mutants should fight back against their human oppressors by any means necessary. The character was born Erik Lehnsherr to a Jewish family in Germany.

Cult-controlled courts

The European Court of Human Rights opened the door for mandatory 'Covid-19 vaccines' across the continent when it ruled in a Czech Republic dispute over childhood immunisation that legally

enforced vaccination could be 'necessary in a democratic society'. The 17 judges decided that compulsory vaccinations did not breach human rights law. On the face of it the judgement was so inverted you gasp for air. If not having a vaccine infused into your body is not a human right then what is? Ah, but they said human rights law which has been specifically written to delete all human rights at the behest of the state (the Cult). Article 8 of the European Convention on Human Rights relates to the right to a private life. The crucial word here is *'except'*:

> There shall be no interference by a public authority with the exercise of this right EXCEPT such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic wellbeing of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others [My emphasis].

No interference *except* in accordance with the law means there *are* no 'human rights' *except* what EU governments decide you can have at their behest. 'As is necessary in a democratic society' explains that reference in the judgement and 'in the interests of national security, public safety or the economic well-being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others' gives the EU a coach and horses to ride through 'human rights' and scatter them in all directions. The judiciary is not a check and balance on government extremism; it is a vehicle to enforce it. This judgement was almost laughably predictable when the last thing the Cult wanted was a decision that went against mandatory vaccination. Judges rule over and over again to benefit the system of which they are a part. Vaccination disputes that come before them are invariably delivered in favour of doctors and authorities representing the view of the state which owns the judiciary. Oh, yes, and we have even had calls to stop putting 'Covid-19' on death certificates within 28 days of a 'positive test' because it is claimed the practice makes the 'vaccine' appear not to work. They are laughing at you.

The scale of madness, inhumanity and things to come was highlighted when those not 'vaccinated' for 'Covid' were refused evacuation from the Caribbean island of St Vincent during massive volcanic eruptions. Cruise ships taking residents to the safety of another island allowed only the 'vaccinated' to board and the rest were left to their fate. Even in life and death situations like this we see 'Covid' stripping people of their most basic human instincts and the insanity is even more extreme when you think that fake 'vaccine'-makers are not even claiming their body-manipulating concoctions stop 'infection' and 'transmission' of a 'virus' that doesn't exist. St Vincent Prime Minister Ralph Gonsalves said: 'The chief medical officer will be identifying the persons already vaccinated so that we can get them on the ship.' Note again the power of the chief medical officer who, like Whitty in the UK, will be answering to the World Health Organization. This is the Cult network structure that has overridden politicians who 'follow the science' which means doing what WHO-controlled 'medical officers' and 'science advisers' tell them. Gonsalves even said that residents who were 'vaccinated' after the order so they could board the ships would still be refused entry due to possible side effects such as 'wooziness in the head'. The good news is that if they were woozy enough in the head they could qualify to be prime minister of St Vincent.

Microchipping freedom

The European judgement will be used at some point to justify moves to enforce the 'Covid' DNA-manipulating procedure. Sandra Ro, CEO of the Global Blockchain Business Council, told a World Economic Forum event that she hoped 'vaccine passports' would help to 'drive forced consent and standardisation' of global digital identity schemes: 'I'm hoping with the desire and global demand for some sort of vaccine passport – so that people can get travelling and working again – [it] will drive forced consent, standardisation, and frankly, cooperation across the world.' The lady is either not very bright, or thoroughly mendacious, to use the term 'forced consent'.

You do not 'consent' if you are forced – you *submit*. She was describing what the plan has been all along and that's to enforce a digital identity on every human without which they could not function. 'Vaccine passports' are opening the door and are far from the end goal. A digital identity would allow you to be tracked in everything you do in cyberspace and this is the same technique used by Cult-owned China to enforce its social credit system of total control. The ultimate 'passport' is planned to be a microchip as my books have warned for nearly 30 years. Those nice people at the Pentagon working for the Cult-controlled Defense Advanced Research Projects Agency (DARPA) claimed in April, 2021, they have developed a microchip inserted under the skin to detect 'asymptomatic Covid-19 infection' before it becomes an outbreak and a 'revolutionary filter' that can remove the 'virus' from the blood when attached to a dialysis machine. The only problems with this are that the 'virus' does not exist and people transmitting the 'virus' with no symptoms is brain-numbing bullshit. This is, of course, not a ruse to get people to be microchipped for very different reasons. DARPA also said it was producing a one-stop 'vaccine' for the 'virus' and all 'variants'. One of the most sinister organisations on Planet Earth is doing this? Better have it then. These people are insane because Wetiko that possesses them is insane.

Researchers from the Salk Institute in California announced they have created an embryo that is part human and part monkey. My books going back to the 1990s have exposed experiments in top secret underground facilities in the United States where humans are being crossed with animal and non-human 'extraterrestrial' species. They are now easing that long-developed capability into the public arena and there is much more to come given we are dealing with psychiatric basket cases. Talking of which – Elon Musk's scientists at Neuralink trained a monkey to play Pong and other puzzles on a computer screen using a joystick and when the monkey made the correct move a metal tube squirted banana smoothie into his mouth which is the basic technique for training humans into unquestioning compliance. Two Neuralink chips were in the monkey's skull and

more than 2,000 wires 'fanned out' into its brain. Eventually the monkey played a video game purely with its brain waves. Psychopathic narcissist Musk said the 'breakthrough' was a step towards putting Neuralink chips into human skulls and merging minds with artificial intelligence. *Exactly*. This man is so dark and Cult to his DNA.

World Economic Fascism (WEF)

The World Economic Forum is telling you the plan by the statements made at its many and various events. Cult-owned fascist YouTube CEO Susan Wojcicki spoke at the 2021 WEF Global Technology Governance Summit (see the name) in which 40 governments and 150 companies met to ensure 'the responsible design and deployment of emerging technologies'. Orwellian translation: 'Ensuring the design and deployment of long-planned technologies will advance the Cult agenda for control and censorship.' Freedom-destroyer and Nuremberg-bound Wojcicki expressed support for tech platforms like hers to censor content that is 'technically legal but could be harmful'. Who decides what is 'harmful'? She does and they do. 'Harmful' will be whatever the Cult doesn't want people to see and we have legislation proposed by the UK government that would censor content on the basis of 'harm' no matter if the information is fair, legal and provably true. Make that *especially* if it is fair, legal and provably true. Wojcicki called for a global coalition to be formed to enforce content moderation standards through automated censorship. This is a woman and mega-censor so self-deluded that she shamelessly accepted a 'free expression' award – *Wojcicki* – in an event sponsored by her own *YouTube*. They have no shame and no self-awareness.

You know that 'Covid' is a scam and Wojcicki a Cult operative when YouTube is censoring medical and scientific opinion purely on the grounds of whether it supports or opposes the Cult 'Covid' narrative. Florida governor Ron DeSantis compiled an expert panel with four professors of medicine from Harvard, Oxford, and Stanford Universities who spoke against forcing children and

vaccinated people to wear masks. They also said there was no proof that lockdowns reduced spread or death rates of 'Covid-19'. Cult-gofer Wojcicki and her YouTube deleted the panel video 'because it included content that contradicts the consensus of local and global health authorities regarding the efficacy of masks to prevent the spread of Covid-19'. This 'consensus' refers to what the Cult tells the World Health Organization to say and the WHO tells 'local health authorities' to do. Wojcicki knows this, of course. The panellists pointed out that censorship of scientific debate was responsible for deaths from many causes, but Wojcicki couldn't care less. She would not dare go against what she is told and as a disgrace to humanity she wouldn't want to anyway. The UK government is seeking to pass a fascist 'Online Safety Bill' to specifically target with massive fines and other means non-censored video and social media platforms to make them censor 'lawful but harmful' content like the Cult-owned Facebook, Twitter, Google and YouTube. What is 'lawful but harmful' would be decided by the fascist Blair-created Ofcom.

Another WEF obsession is a cyber-attack on the financial system and this is clearly what the Cult has planned to take down the bank accounts of everyone – except theirs. Those that think they have enough money for the Cult agenda not to matter to them have got a big lesson coming if they continue to ignore what is staring them in the face. The World Economic Forum, funded by Gates and fronted by Klaus Schwab, announced it would be running a 'simulation' with the Russian government and global banks of just such an attack called Cyber Polygon 2021. What they simulate – as with the 'Covid' Event 201 – they plan to instigate. The WEF is involved in a project with the Cult-owned Carnegie Endowment for International Peace called the WEF-Carnegie Cyber Policy Initiative which seeks to merge Wall Street banks, 'regulators' (I love it) and intelligence agencies to 'prevent' (arrange and allow) a cyber-attack that would bring down the global financial system as long planned by those that control the WEF and the Carnegie operation. The Carnegie Endowment for International Peace sent an instruction to First World

War US President Woodrow Wilson not to let the war end before society had been irreversibly transformed.

The Wuhan lab diversion

As I close, the Cult-controlled authorities and lapdog media are systematically pushing 'the virus was released from the Wuhan lab' narrative. There are two versions – it happened by accident and it happened on purpose. Both are nonsense. The perceived existence of the never-shown-to-exist 'virus' is vital to sell the impression that there is actually an infective agent to deal with and to allow the endless potential for terrifying the population with 'variants' of a 'virus' that does not exist. The authorities at the time of writing are going with the 'by accident' while the alternative media is promoting the 'on purpose'. Cable news host Tucker Carlson who has questioned aspects of lockdown and 'vaccine' compulsion has bought the Wuhan lab story. 'Everyone now agrees' he said. Well, I don't and many others don't and the question is *why* does the system and its media suddenly 'agree'? When the media moves as one unit with a narrative it is always a lie – witness the hour by hour mendacity of the 'Covid' era. Why would this Cult-owned combination which has unleashed lies like machine gun fire suddenly 'agree' to tell the truth??

Much of the alternative media is buying the lie because it fits the conspiracy narrative, but it's the *wrong* conspiracy. The real conspiracy is that *there is no virus* and that is what the Cult is desperate to hide. The idea that the 'virus' was released by accident is ludicrous when the whole 'Covid' hoax was clearly long-planned and waiting to be played out as it was so fast in accordance with the Rockefeller document and Event 201. So they prepared everything in detail over decades and then sat around strumming their fingers waiting for an 'accidental' release from a bio-lab? *What??* It's crazy. Then there's the 'on purpose' claim. You want to circulate a 'deadly virus' and hide the fact that you've done so and you release it down the street from the highest-level bio-lab in China? I repeat – *What??*

You would release it far from that lab to stop any association being made. But, no, we'll do it in a place where the connection was certain to be made. Why would you need to scam 'cases' and 'deaths' and pay hospitals to diagnose 'Covid-19' if you had a real 'virus'? What are sections of the alternative media doing believing this crap? Where were all the mass deaths in Wuhan from a 'deadly pathogen' when the recovery to normal life after the initial propaganda was dramatic in speed? Why isn't the 'deadly pathogen' now circulating all over China with bodies in the street? Once again we have the technique of tell them what they want to hear and they will likely believe it. The alternative media has its 'conspiracy' and with Carlson it fits with his 'China is the danger' narrative over years. China *is* a danger as a global Cult operations centre, but not for this reason. The Wuhan lab story also has the potential to instigate conflict with China when at some stage the plan is to trigger a Problem-Reaction-Solution confrontation with the West. Question everything – *everything* – and especially when the media agrees on a common party line.

Third wave ... fourth wave ... fifth wave ...

As the book went into production the world was being set up for more lockdowns and a 'third wave' supported by invented 'variants' that were increasing all the time and will continue to do so in public statements and computer programs, but not in reality. India became the new Italy in the 'Covid' propaganda campaign and we were told to be frightened of the new 'Indian strain'. Somehow I couldn't find it within myself to do so. A document produced for the UK government entitled 'Summary of further modelling of easing of restrictions – Roadmap Step 2' declared that a third wave was inevitable (of course when it's in the script) and it would be the fault of children and those who refuse the health-destroying fake 'Covid vaccine'. One of the computer models involved came from the Cult-owned *Imperial College* and the other from Warwick University which I wouldn't trust to tell me the date in a calendar factory. The document states that both models presumed extremely high uptake

of the 'Covid vaccines' and didn't allow for 'variants'. The document states: 'The resurgence is a result of some people (mostly children) being ineligible for vaccination; others choosing not to receive the vaccine; and others being vaccinated but not perfectly protected.' The mendacity takes the breath away. Okay, blame those with a brain who won't take the DNA-modifying shots and put more pressure on children to have it as 'trials' were underway involving children as young as six months with parents who give insanity a bad name. Massive pressure is being put on the young to have the fake 'vaccine' and child age consent limits have been systematically lowered around the world to stop parents intervening. Most extraordinary about the document was its claim that the 'third wave' would be driven by 'the resurgence in both hospitalisations and deaths … dominated by *those that have received two doses of the vaccine*, comprising around 60-70% of the wave respectively'. The predicted peak of the 'third wave' suggested 300 deaths per day with 250 of them *fully 'vaccinated' people*. How many more lies do acquiescers need to be told before they see the obvious? Those who took the jab to 'protect themselves' are projected to be those who mostly get sick and die? So what's in the 'vaccine'? The document went on:

> It is possible that a summer of low prevalence could be followed by substantial increases in incidence over the following autumn and winter. Low prevalence in late summer should not be taken as an indication that SARS-CoV-2 has retreated or that the population has high enough levels of immunity to prevent another wave.

They are telling you the script and while many British people believed 'Covid' restrictions would end in the summer of 2021 the government was preparing for them to be ongoing. Authorities were awarding contracts for 'Covid marshals' to police the restrictions with contracts starting in July, 2021, and going through to January 31st, 2022, and the government was advertising for 'Media Buying Services' to secure media propaganda slots worth a potential £320 million for 'Covid-19 campaigns' with a contract not ending until March, 2022. The recipient – via a list of other front companies – was reported to be American media marketing giant Omnicom Group

Inc. While money is no object for 'Covid' the UK waiting list for all other treatment – including life-threatening conditions – passed 4.5 million. Meantime the Cult is seeking to control all official 'inquiries' to block revelations about what has really been happening and why. It must not be allowed to – we need Nuremberg jury trials in every country. The cover-up doesn't get more obvious than appointing ultra-Zionist professor Philip Zelikow to oversee two dozen US virologists, public health officials, clinicians, former government officials and four American 'charitable foundations' to 'learn the lessons' of the 'Covid' debacle. The personnel will be those that created and perpetuated the 'Covid' lies while Zelikow is the former executive director of the 9/11 Commission who ensured that the truth about those attacks never came out and produced a report that must be among the most mendacious and manipulative documents ever written – see *The Trigger* for the detailed exposure of the almost unimaginable 9/11 story in which Sabbatians can be found at every level.

Passive no more

People are increasingly challenging the authorities with amazing numbers of people taking to the streets in London well beyond the ability of the Face-Nappies to stop them. Instead the Nappies choose situations away from the mass crowds to target, intimidate, and seek to promote the impression of 'violent protestors'. One such incident happened in London's Hyde Park. Hundreds of thousands walking through the streets in protest against 'Covid' fascism were ignored by the Cult-owned BBC and most of the rest of the mainstream media, but they delighted in reporting how police were injured in 'clashes with protestors'. The truth was that a group of people gathered in Hyde Park at the end of one march when most had gone home and they were peacefully having a good time with music and chat. Face-Nappies who couldn't deal with the full-march crowd then waded in with their batons and got more than they bargained for. Instead of just standing for this criminal brutality the crowd used their numerical superiority to push the Face-Nappies out of the

park. Eventually the Nappies turned and ran. Unfortunately two or three idiots in the crowd threw drink cans striking two officers which gave the media and the government the image they wanted to discredit the 99.9999 percent who were peaceful. The idiots walked straight into the trap and we must always be aware of potential agent provocateurs used by the authorities to discredit their targets.

This response from the crowd – the can people apart – must be a turning point when the public no longer stand by while the innocent are arrested and brutally attacked by the Face-Nappies. That doesn't mean to be violent, that's the last thing we need. We'll leave the violence to the Face-Nappies and government. But it does mean that when the Face-Nappies use violence against peaceful people the numerical superiority is employed to stop them and make citizen's arrests or Common Law arrests for a breach of the peace. The time for being passive in the face of fascism is over.

We are the many, they are the few, and we need to make that count before there is no freedom left and our children and grandchildren face an ongoing fascist nightmare.

COME ON PEOPLE – IT'S TIME.

One final thought …

The power of love
A force from above
Cleaning my soul
Flame on burn desire
Love with tongues of fire
Purge the soul
Make love your goal

I'll protect you from the hooded claw
Keep the vampires from your door
When the chips are down I'll be around
With my undying, death-defying
Love for you

Envy will hurt itself
Let yourself be beautiful
Sparkling love, flowers
And pearls and pretty girls
Love is like an energy
Rushin' rushin' inside of me

This time we go sublime
Lovers entwine, divine, divine,
Love is danger, love is pleasure
Love is pure – the only treasure

I'm so in love with you
Purge the soul
Make love your goal

The power of love
A force from above
Cleaning my soul
The power of love
A force from above
A sky-scraping dove

Flame on burn desire
Love with tongues of fire
Purge the soul
Make love your goal

Frankie Goes To Hollywood

APPENDIX

Cowan-Kaufman-Morell Statement on Virus Isolation (SOVI)

Isolation: The action of isolating; the fact or condition of being isolated or standing alone; separation from other things or persons; solitariness
Oxford English Dictionary

The controversy over whether the SARS-CoV-2 virus has ever been isolated or purified continues. However, using the above definition, common sense, the laws of logic and the dictates of science, any unbiased person must come to the conclusion that the SARS-CoV-2 virus has never been isolated or purified. As a result, no confirmation of the virus' existence can be found. The logical, common sense, and scientific consequences of this fact are:

- the structure and composition of something not shown to exist can't be known, including the presence, structure, and function of any hypothetical spike or other proteins;
- the genetic sequence of something that has never been found can't be known;
- "variants" of something that hasn't been shown to exist can't be known;
- it's impossible to demonstrate that SARS-CoV-2 causes a disease called Covid-19.

In as concise terms as possible, here's the proper way to isolate, characterize and demonstrate a new virus. First, one takes samples (blood, sputum, secretions) from many people (e.g. 500) with symptoms which are unique and specific enough to characterize an illness. Without mixing these samples with ANY tissue or products that also contain genetic material, the virologist macerates, filters and ultracentrifuges i.e. *purifies* the specimen. This common virology technique, done for decades to isolate bacteriophages[1] and so-called giant viruses in every virology lab, then allows the virologist to demonstrate with electron microscopy thousands of identically sized and shaped particles. These particles are the isolated and purified virus.

These identical particles are then checked for uniformity by physical and/or microscopic techniques. Once the purity is determined, the particles may be further characterized. This would include examining the structure, morphology, and chemical composition of the particles. Next, their genetic makeup is characterized by extracting the genetic material directly from the purified particles and using genetic-sequencing techniques, such as Sanger sequencing, that have also been around for decades. Then one does an analysis to confirm that these uniform particles are exogenous (outside) in origin as a virus is conceptualized to be, and not the normal breakdown products of dead and dying tissues.[2] (As of May 2020, we know that virologists have no way to determine whether the particles they're seeing are viruses or just normal breakdown products of dead and dying tissues.)[3]

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1 Isolation, characterization and analysis of bacteriophages from the haloalkaline lake Elmenteita, KenyaJuliah Khayeli Akhwale et al, PLOS One, Published: April 25, 2019. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0215734 – accessed 2/15/21

2 "Extracellular Vesicles Derived From Apoptotic Cells: An Essential Link Between Death and Regeneration," Maojiao Li1 et al, Frontiers in Cell and Developmental Biology, 2020 October 2. https://www.frontiersin.org/articles/10.3389/fcell.2020.573511/full – accessed 2/15/21

3 "The Role of Extraellular Vesicles as Allies of HIV, HCV and SARS Viruses," Flavia Giannessi, et al, Viruses, 2020 May

If we have come this far then we have fully isolated, characterized, and genetically sequenced an exogenous virus particle. However, we still have to show it is causally related to a disease. This is carried out by exposing a group of healthy subjects (animals are usually used) to this isolated, purified virus in the manner in which the disease is thought to be transmitted. If the animals get sick with the same disease, as confirmed by clinical and autopsy findings, one has now shown that the virus actually causes a disease. This demonstrates infectivity and transmission of an infectious agent.

None of these steps has even been attempted with the SARS-CoV-2 virus, nor have all these steps been successfully performed for any so-called pathogenic virus. Our research indicates that a single study showing these steps does not exist in the medical literature.

Instead, since 1954, virologists have taken unpurified samples from a relatively few people, often less than ten, with a similar disease. They then minimally process this sample and inoculate this unpurified sample onto tissue culture containing usually four to six other types of material – all of which contain identical genetic material as to what is called a "virus." The tissue culture is starved and poisoned and naturally disintegrates into many types of particles, some of which contain genetic material. Against all common sense, logic, use of the English language and scientific integrity, this process is called "virus isolation." This brew containing fragments of genetic material from many sources is then subjected to genetic analysis, which then creates in a computer-simulation process the alleged sequence of the alleged virus, a so called in silico genome. At no time is an actual virus confirmed by electron microscopy. At no time is a genome extracted and sequenced from an actual virus. This is scientific fraud.

The observation that the unpurified specimen — inoculated onto tissue culture along with toxic antibiotics, bovine fetal tissue, amniotic fluid and other tissues — destroys the kidney tissue onto which it is inoculated is given as evidence of the virus' existence and pathogenicity. This is scientific fraud.

From now on, when anyone gives you a paper that suggests the SARS-CoV-2 virus has been isolated, please check the methods sections. If the researchers used Vero cells or any other culture method, you know that their process was not isolation. You will hear the following excuses for why actual isolation isn't done:

1. There were not enough virus particles found in samples from patients to analyze.

2. Viruses are intracellular parasites; they can't be found outside the cell in this manner.

If No. 1 is correct, and we can't find the virus in the sputum of sick people, then on what evidence do we think the virus is dangerous or even lethal? If No. 2 is correct, then how is the virus spread from person to person? We are told it emerges from the cell to infect others. Then why isn't it possible to find it?

Finally, questioning these virology techniques and conclusions is not some distraction or divisive issue. Shining the light on this truth is essential to stop this terrible fraud that humanity is confronting. For, as we now know, if the virus has never been isolated, sequenced or shown to cause illness, if the virus is imaginary, then why are we wearing masks, social distancing and putting the whole world into prison?

Finally, if pathogenic viruses don't exist, then what is going into those injectable devices erroneously called "vaccines," and what is their purpose? This scientific question is the most urgent and relevant one of our time.

We are correct. The SARS-CoV2 virus does not exist.

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Ickonic is something that has been a dream of mine for the last 5 years, growing up around alternative information I have always had a natural interest in what is going on in the World and what could I do to make it better.
Across the range of subjects and positions of influence occupied mainly by people who don't strive to make things better it's the Media that I have always found the most frustrating and fascinating. Mainly because if the Media did their Jobs properly then so much of the negative things happening in the World simply would not be able to happen, because they would be exposed within a heartbeat.
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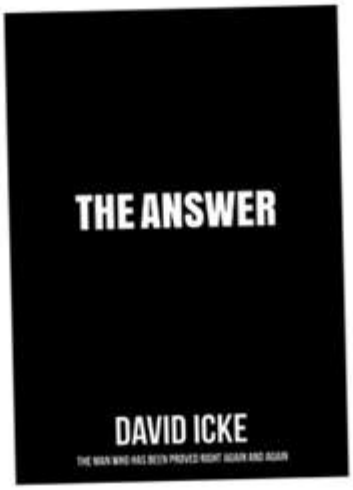
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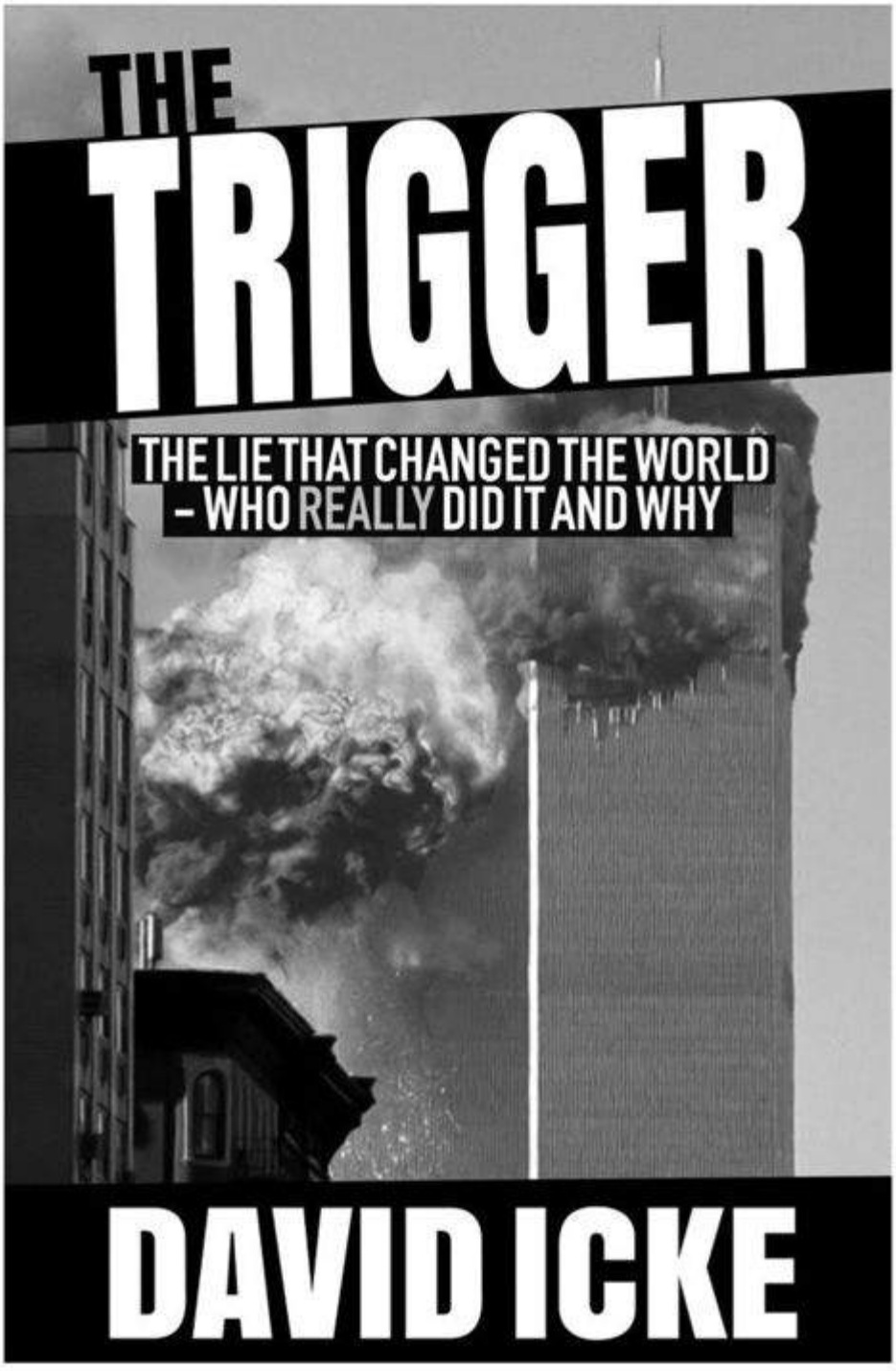
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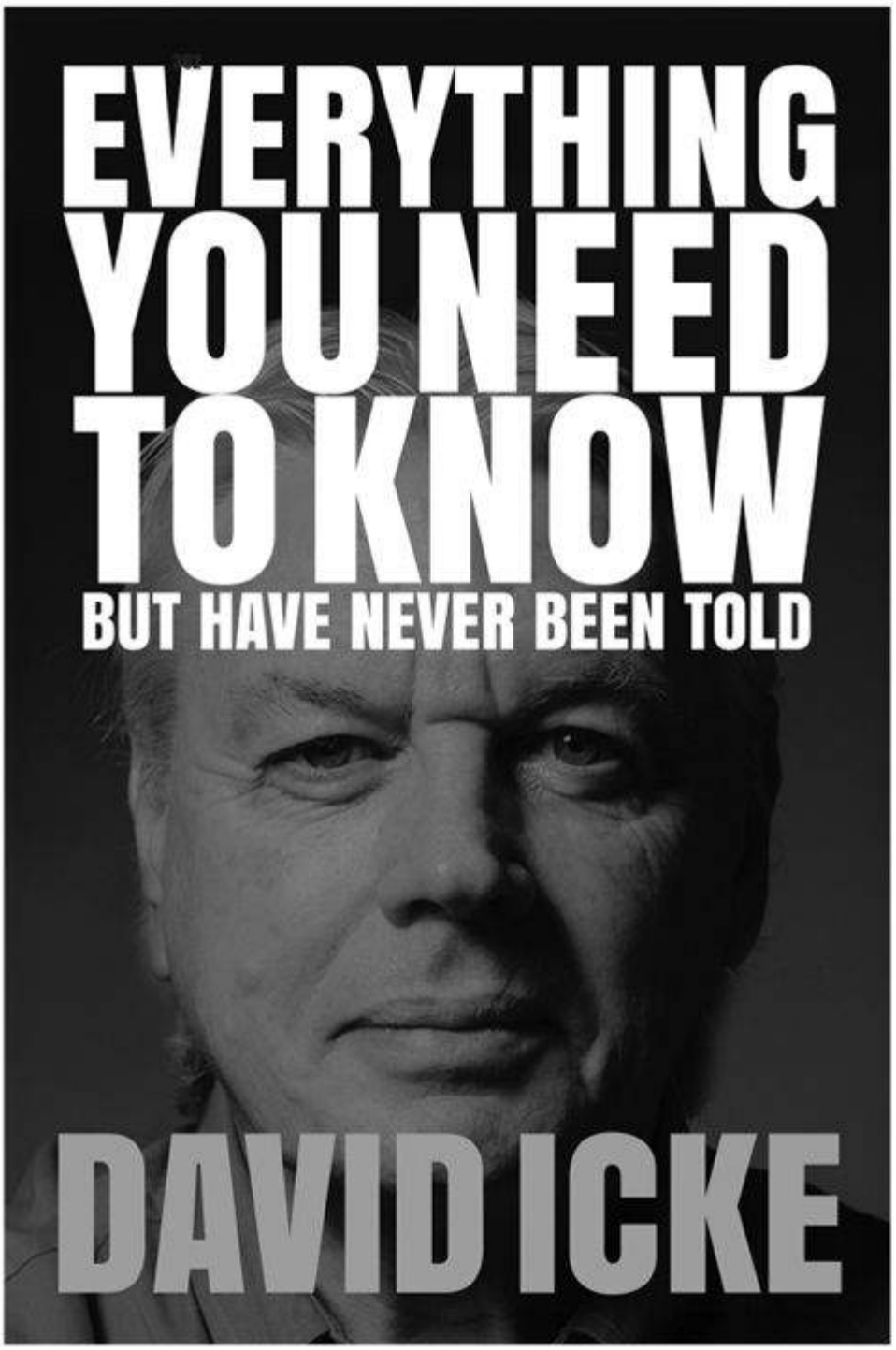


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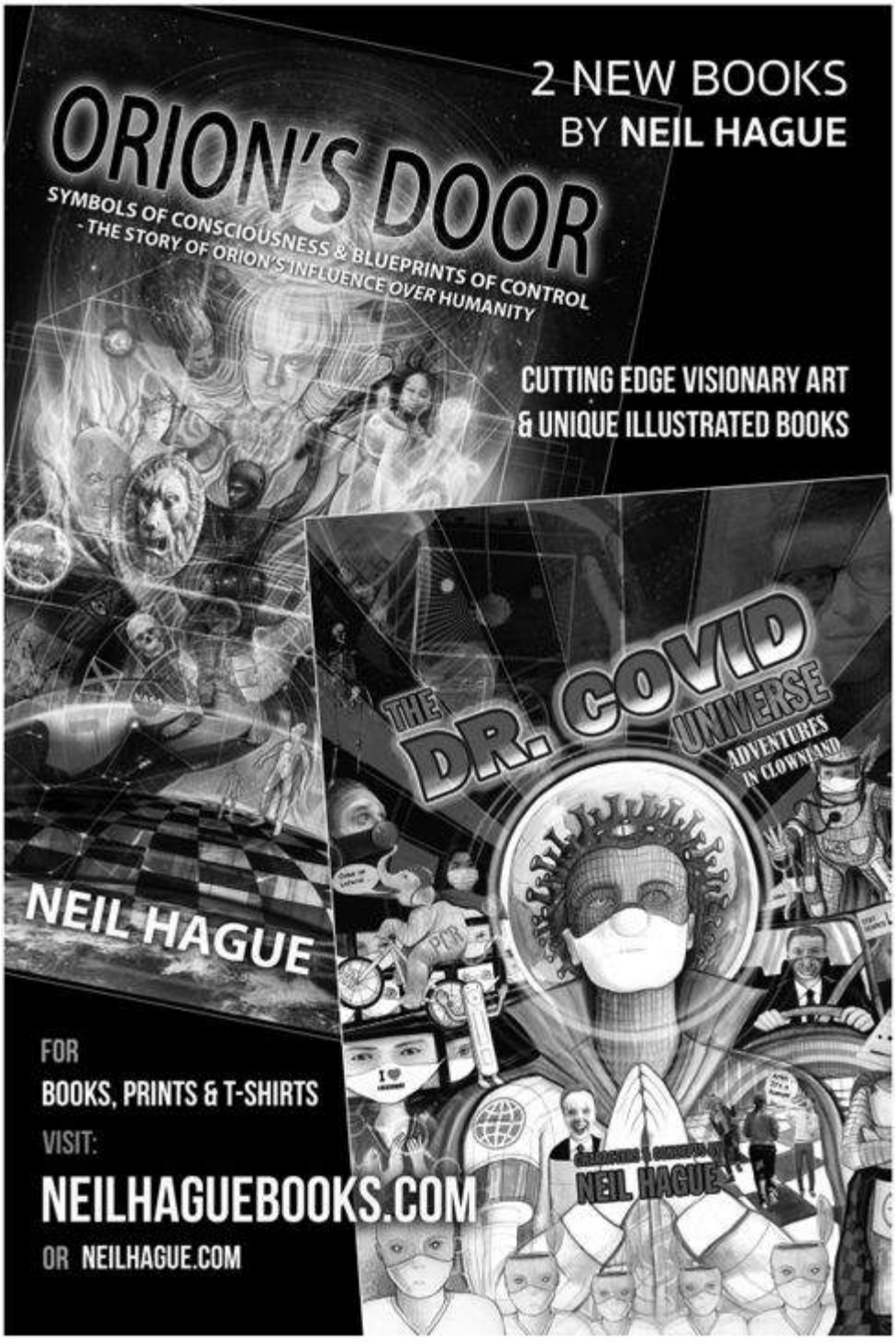
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noun

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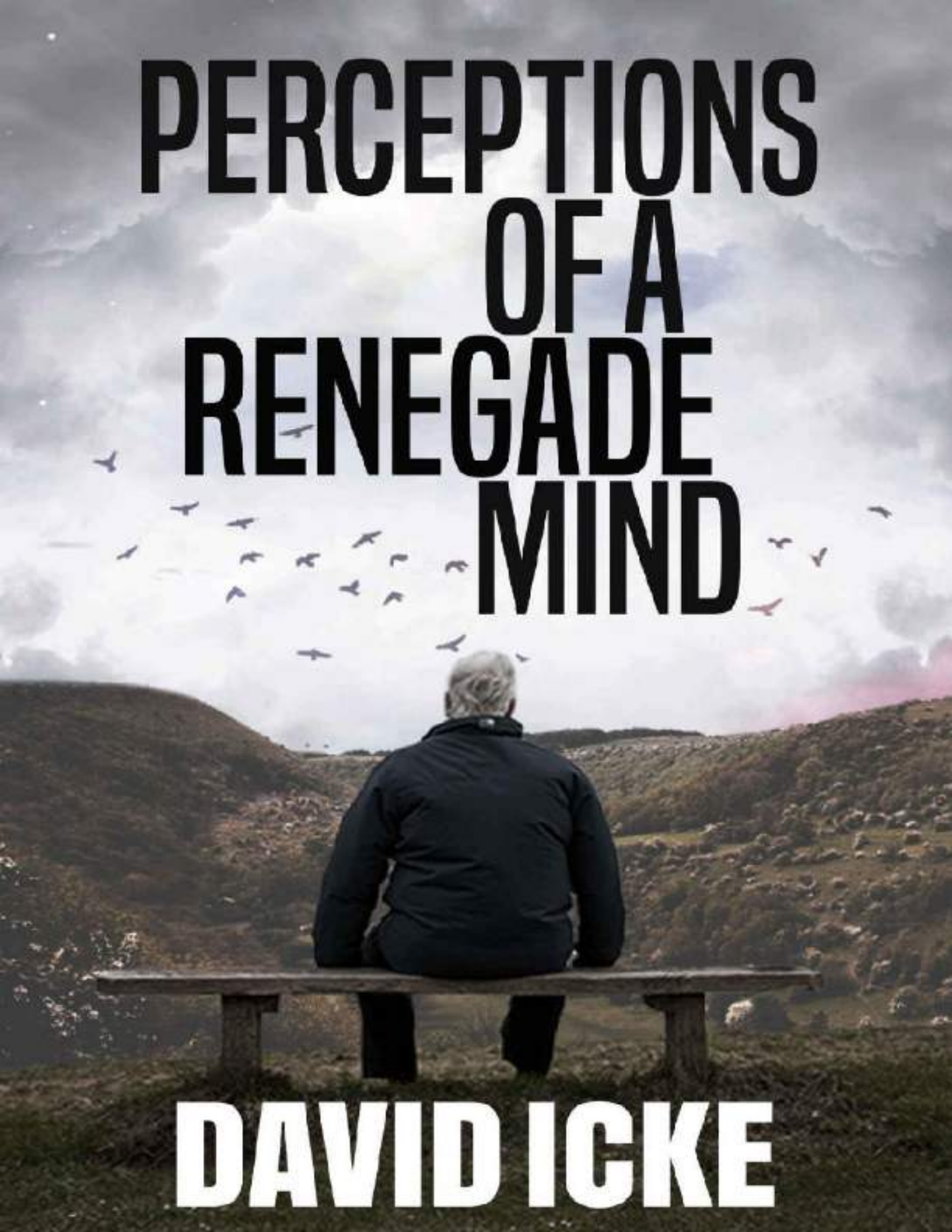

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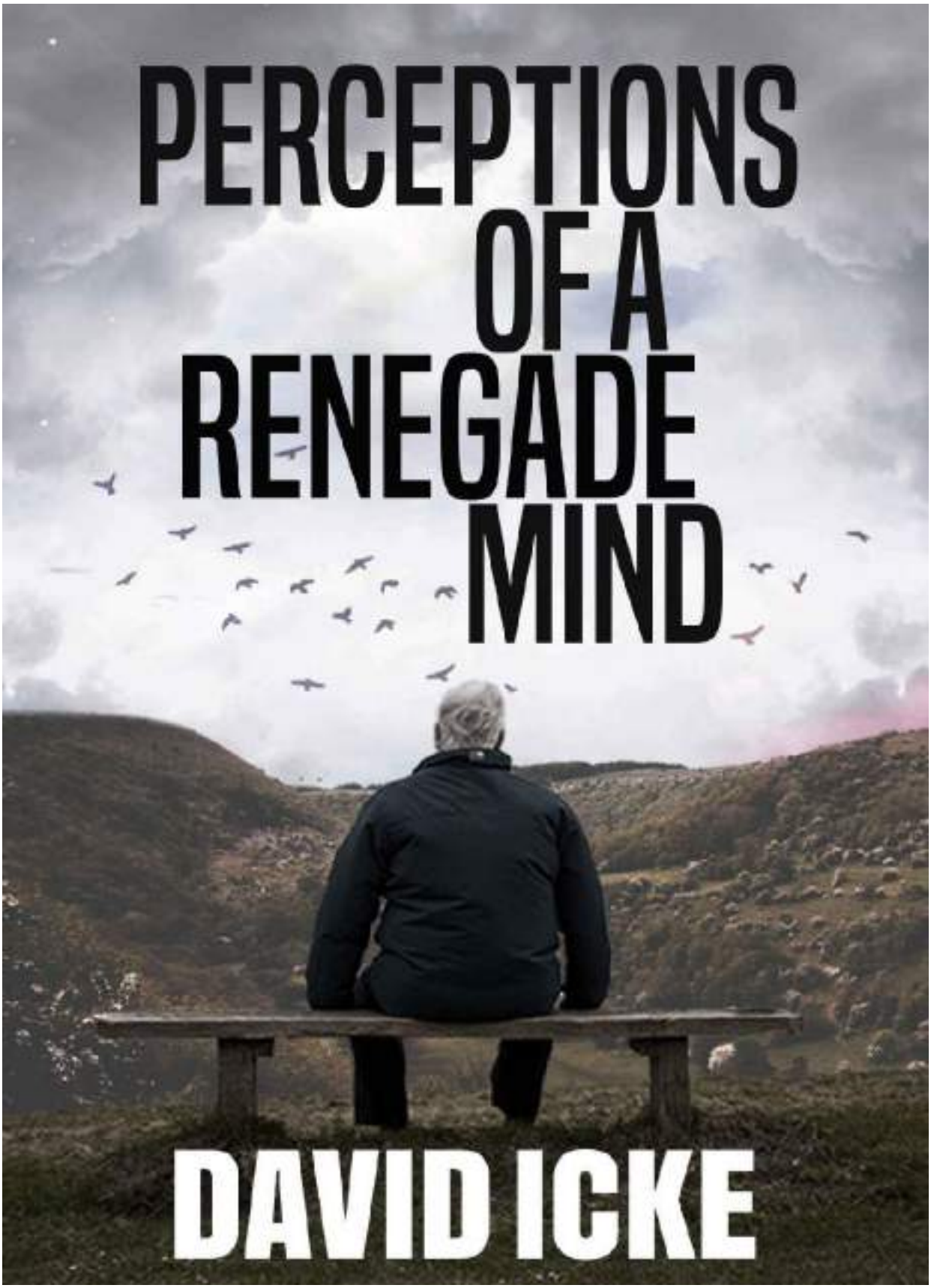
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PERCEPTIONS OF A RENEGADE MIND



DAVID ICKE


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PERCEPTIONS OF A RENEGADE MIND



DAVID ICKE

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Renegade:
Adjective
‘Having rejected tradition: Unconventional.’
Merriam-Webster Dictionary

Acquiescence to tyranny is the death of the spirit

You may be 38 years old, as I happen to be. And one day, some great opportunity stands before you and calls you to stand up for some great principle, some great issue, some great cause. And you refuse to do it because you are afraid … You refuse to do it because you want to live longer … You're afraid that you will lose your job, or you are afraid that you will be criticised or that you will lose your popularity, or you're afraid that somebody will stab you, or shoot at you or bomb your house; so you refuse to take the stand.

Well, you may go on and live until you are 90, but you're just as dead at 38 as you would be at 90. And the cessation of breathing in your life is but the belated announcement of an earlier death of the spirit.

Martin Luther King

How the few control the many and always have – the many do whatever they're told

'Forward, the Light Brigade!'
Was there a man dismayed?
Not though the soldier knew
Someone had blundered.
Theirs not to make reply,
Theirs not to reason why,
Theirs but to do and die.
Into the valley of Death
Rode the six hundred.

Cannon to right of them,
Cannon to left of them,
Cannon in front of them
Volleyed and thundered;
Stormed at with shot and shell,
Boldly they rode and well,
Into the jaws of Death,
Into the mouth of hell
Rode the six hundred

Alfred Lord Tennyson (1809-1892)

The mist is lifting slowly
I can see the way ahead
And I've left behind the empty streets
That once inspired my life
And the strength of the emotion
Is like thunder in the air
'Cos the promise that we made each other
Haunts me to the end

The secret of your beauty
And the mystery of your soul
I've been searching for in everyone I meet
And the times I've been mistaken
It's impossible to say
And the grass is growing
Underneath our feet

The words that I remember
From my childhood still are true
That there's none so blind
As those who will not see
And to those who lack the courage
And say it's dangerous to try
Well they just don't know
That love eternal will not be denied

I know you're out there somewhere
Somewhere, somewhere
I know you're out there somewhere

Somewhere you can hear my voice
I know I'll find you somehow
Somehow, somehow
I know I'll find you somehow
And somehow I'll return again to you

The Moody Blues

Are you a gutless wonder - or a Renegade Mind?

Monuments put from pen to paper,
Turns me into a gutless wonder,
And if you tolerate this,
Then your children will be next.
Gravity keeps my head down,
Or is it maybe shame ...

Manic Street Preachers

Rise like lions after slumber
In unvanquishable number.
Shake your chains to earth like dew
Which in sleep have fallen on you.
Ye are many – they are few.

Percy Shelley

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CHAPTER ONE

I'm thinking' – Oh, but *are* you?

Think for yourself and let others enjoy the privilege of doing so too
Voltaire

French-born philosopher, mathematician and scientist René Descartes became famous for his statement in Latin in the 17th century which translates into English as: 'I think, therefore I am.'

On the face of it that is true. Thought reflects perception and perception leads to both behaviour and self-identity. In that sense 'we' are what we think. But who or what is doing the thinking and is thinking the only route to perception? Clearly, as we shall see, 'we' are not always the source of 'our' perception, indeed with regard to humanity as a whole this is rarely the case; and thinking is far from the only means of perception. Thought is the village idiot compared with other expressions of consciousness that we all have the potential to access and tap into. This has to be true when we *are* those other expressions of consciousness which are infinite in nature. We have forgotten this, or, more to the point, been manipulated to forget.

These are not just the esoteric musings of the navel. The whole foundation of human control and oppression is control of perception. Once perception is hijacked then so is behaviour which is dictated by perception. Collective perception becomes collective behaviour and collective behaviour is what we call human society. Perception is all and those behind human control know that which is

why perception is the target 24/7 of the psychopathic manipulators that I call the Global Cult. They know that if they dictate perception they will dictate behaviour and collectively dictate the nature of human society. They are further aware that perception is formed from information received and if they control the circulation of information they will to a vast extent direct human behaviour. Censorship of information and opinion has become globally Nazi-like in recent years and never more blatantly than since the illusory 'virus pandemic' was triggered out of China in 2019 and across the world in 2020. Why have billions submitted to house arrest and accepted fascistic societies in a way they would have never believed possible? Those controlling the information spewing from government, mainstream media and Silicon Valley (all controlled by the same Global Cult networks) told them they were in danger from a 'deadly virus' and only by submitting to house arrest and conceding their most basic of freedoms could they and their families be protected. This monumental and provable lie became the *perception* of the billions and therefore the *behaviour* of the billions. In those few words you have the whole structure and modus operandi of human control. Fear is a perception – **F**alse **E**motion **A**ppearing **R**eal – and fear is the currency of control. In short … get them by the balls (or give them the impression that you have) and their hearts and minds will follow. Nothing grips the dangly bits and freezes the rear-end more comprehensively than fear.

World number 1

There are two 'worlds' in what appears to be one 'world' and the prime difference between them is knowledge. First we have the mass of human society in which the population is maintained in coldly-calculated ignorance through control of information and the 'education' (indoctrination) system. That's all you really need to control to enslave billions in a perceptual delusion in which what are perceived to be *their* thoughts and opinions are ever-repeated mantras that the system has been downloading all their lives through 'education', media, science, medicine, politics and academia

in which the personnel and advocates are themselves overwhelmingly the perceptual products of the same repetition. Teachers and academics in general are processed by the same programming machine as everyone else, but unlike the great majority they never leave the 'education' program. It gripped them as students and continues to grip them as programmers of subsequent generations of students. The programmed become the programmers – the programmed programmers. The same can largely be said for scientists, doctors and politicians and not least because as the American writer Upton Sinclair said: 'It is difficult to get a man to understand something when his salary depends upon his not understanding it.' If your career and income depend on thinking the way the system demands then you will – bar a few free-minded exceptions – concede your mind to the Perceptual Mainframe that I call the Postage Stamp Consensus. This is a tiny band of perceived knowledge and possibility 'taught' (downloaded) in the schools and universities, pounded out by the mainstream media and on which all government policy is founded. Try thinking, and especially speaking and acting, outside of the 'box' of consensus and see what that does for your career in the Mainstream Everything which bullies, harasses, intimidates and ridicules the population into compliance. Here we have the simple structure which enslaves most of humanity in a perceptual prison cell for an entire lifetime and I'll go deeper into this process shortly. Most of what humanity is taught as fact is nothing more than programmed belief. American science fiction author Frank Herbert was right when he said: 'Belief can be manipulated. Only knowledge is dangerous.' In the 'Covid' age belief is promoted and knowledge is censored. It was always so, but never to the extreme of today.

World number 2

A 'number 2' is slang for 'doing a poo' and how appropriate that is when this other 'world' is doing just that on humanity every minute of every day. World number 2 is a global network of secret societies and semi-secret groups dictating the direction of society via

governments, corporations and authorities of every kind. I have spent more than 30 years uncovering and exposing this network that I call the Global Cult and knowing its agenda is what has made my books so accurate in predicting current and past events. Secret societies are secret for a reason. They want to keep their hoarded knowledge to themselves and their chosen initiates and to hide it from the population which they seek through ignorance to control and subdue. The whole foundation of the division between World 1 and World 2 is *knowledge*. What number 1 knows number 2 must not. Knowledge they have worked so hard to keep secret includes (a) the agenda to enslave humanity in a centrally-controlled global dictatorship, and (b) the nature of reality and life itself. The latter (b) must be suppressed to allow the former (a) to prevail as I shall be explaining. The way the Cult manipulates and interacts with the population can be likened to a spider's web. The 'spider' sits at the centre in the shadows and imposes its will through the web with each strand represented in World number 2 by a secret society, satanic or semi-secret group, and in World number 1 – the world of the seen – by governments, agencies of government, law enforcement, corporations, the banking system, media conglomerates and Silicon Valley (Fig 1 overleaf). The spider and the web connect and coordinate all these organisations to pursue the same global outcome while the population sees them as individual entities working randomly and independently. At the level of the web governments *are* the banking system *are* the corporations *are* the media *are* Silicon Valley *are* the World Health Organization working from their inner cores as one unit. Apparently unconnected countries, corporations, institutions, organisations and people are on the *same team* pursuing the same global outcome. Strands in the web immediately around the spider are the most secretive and exclusive secret societies and their membership is emphatically restricted to the Cult inner-circle emerging through the generations from particular bloodlines for reasons I will come to. At the core of the core you would get them in a single room. That's how many people are dictating the direction of human society and its transformation

through the ‘Covid’ hoax and other means. As the web expands out from the spider we meet the secret societies that many people will be aware of – the Freemasons, Knights Templar, Knights of Malta, Opus Dei, the inner sanctum of the Jesuit Order, and such like. Note how many are connected to the Church of Rome and there is a reason for that. The Roman Church was established as a revamp, a rebranding, of the relocated ‘Church’ of Babylon and the Cult imposing global tyranny today can be tracked back to Babylon and Sumer in what is now Iraq.



Figure 1: The global web through which the few control the many. (Image Neil Hague.)

Inner levels of the web operate in the unseen away from the public eye and then we have what I call the cusp organisations located at the point where the hidden meets the seen. They include a series of satellite organisations answering to a secret society founded in London in the late 19th century called the Round Table and among them are the Royal Institute of International Affairs (UK, founded in 1920); Council on Foreign Relations (US, 1921); Bilderberg Group (worldwide, 1954); Trilateral Commission (US/worldwide, 1972); and the Club of Rome (worldwide, 1968) which was created to exploit environmental concerns to justify the centralisation of global power to ‘save the planet’. The Club of Rome instigated with others the human-caused climate change hoax which has led to all the ‘green

new deals' demanding that very centralisation of control. Cusp organisations, which include endless 'think tanks' all over the world, are designed to coordinate a single global policy between political and business leaders, intelligence personnel, media organisations and anyone who can influence the direction of policy in their own sphere of operation. Major players and regular attenders will know what is happening – or some of it – while others come and go and are kept overwhelmingly in the dark about the big picture. I refer to these cusp groupings as semi-secret in that they can be publicly identified, but what goes on at the inner-core is kept very much 'in house' even from most of their members and participants through a fiercely-imposed system of compartmentalisation. Only let them know what they need to know to serve your interests and no more. The structure of secret societies serves as a perfect example of this principle. Most Freemasons never get higher than the bottom three levels of 'degree' (degree of knowledge) when there are 33 official degrees of the Scottish Rite. Initiates only qualify for the next higher 'compartment' or degree if those at that level choose to allow them. Knowledge can be carefully assigned only to those considered 'safe'. I went to my local Freemason's lodge a few years ago when they were having an 'open day' to show how cuddly they were and when I chatted to some of them I was astonished at how little the rank and file knew even about the most ubiquitous symbols they use. The mushroom technique – keep them in the dark and feed them bullshit – applies to most people in the web as well as the population as a whole. Sub-divisions of the web mirror in theme and structure transnational corporations which have a headquarters somewhere in the world dictating to all their subsidiaries in different countries. Subsidiaries operate in their methodology and branding to the same centrally-dictated plan and policy in pursuit of particular ends. The Cult web functions in the same way. Each country has its own web as a subsidiary of the global one. They consist of networks of secret societies, semi-secret groups and bloodline families and their job is to impose the will of the spider and the global web in their particular country. Subsidiary networks control and manipulate the national political system, finance, corporations, media, medicine, etc. to

ensure that they follow the globally-dictated Cult agenda. These networks were the means through which the 'Covid' hoax could be played out with almost every country responding in the same way.

The 'Yessir' pyramid

Compartmentalisation is the key to understanding how a tiny few can dictate the lives of billions when combined with a top-down sequence of imposition and acquiescence. The inner core of the Cult sits at the peak of the pyramidal hierarchy of human society (Fig 2 overleaf). It imposes its will – its agenda for the world – on the level immediately below which acquiesces to that imposition. This level then imposes the Cult will on the level below them which acquiesces and imposes on the next level. Very quickly we meet levels in the hierarchy that have no idea there even is a Cult, but the sequence of imposition and acquiescence continues down the pyramid in just the same way. 'I don't know why we are doing this but the order came from "on-high" and so we better just do it.' Alfred Lord Tennyson said of the cannon fodder levels in his poem *The Charge of the Light Brigade*: 'Theirs not to reason why; theirs but to do and die.' The next line says that 'into the valley of death rode the six hundred' and they died because they obeyed without question what their perceived 'superiors' told them to do. In the same way the population capitulated to 'Covid'. The whole hierarchical pyramid functions like this to allow the very few to direct the enormous many. Eventually imposition-acquiescence-imposition-acquiescence comes down to the mass of the population at the foot of the pyramid. If they acquiesce to those levels of the hierarchy imposing on them (governments/law enforcement/doctors/media) a circuit is completed between the population and the handful of super-psychopaths in the Cult inner core at the top of the pyramid. Without a circuit-breaking refusal to obey, the sequence of imposition and acquiescence allows a staggeringly few people to impose their will upon the entirety of humankind. We are looking at the very sequence that has subjugated billions since the start of 2020. Our freedom has not been taken from us. Humanity has given it

away. Fascists do not impose fascism because there are not enough of them. Fascism is imposed by the population acquiescing to fascism. Put another way allowing their perceptions to be programmed to the extent that leads to the population giving their freedom away by giving their perceptions – their mind – away. If this circuit is not broken by humanity ceasing to cooperate with their own enslavement then nothing can change. For that to happen people have to critically think and see through the lies and window dressing and then summon the backbone to act upon what they see. The Cult spends its days working to stop either happening and its methodology is systematic and highly detailed, but it can be overcome and that is what this book is all about.

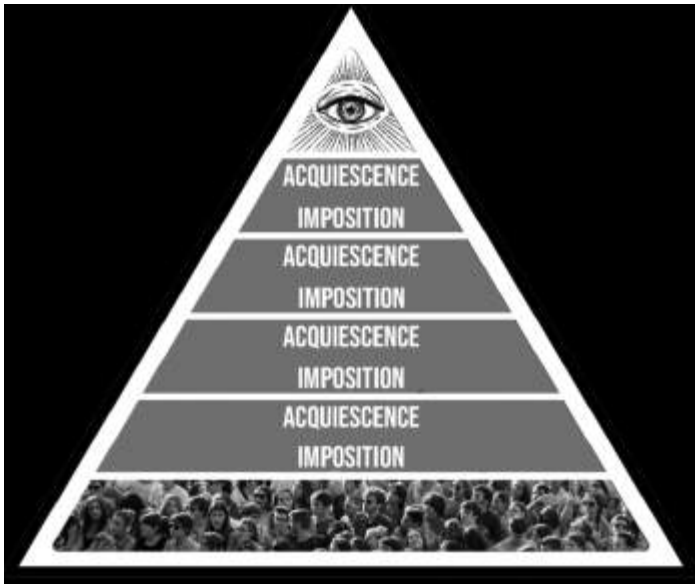


Figure 2: The simple sequence of imposition and compliance that allows a handful of people at the peak of the pyramid to dictate the lives of billions.

The Life Program

Okay, back to world number 1 or the world of the 'masses'. Observe the process of what we call 'life' and it is a perceptual download from cradle to grave. The Cult has created a global structure in which perception can be programmed and the program continually topped-up with what appears to be constant confirmation that the program is indeed true reality. The important word here is 'appears'.

This is the structure, the fly-trap, the Postage Stamp Consensus or Perceptual Mainframe, which represents that incredibly narrow band of perceived possibility delivered by the 'education' system, mainstream media, science and medicine. From the earliest age the download begins with parents who have themselves succumbed to the very programming their children are about to go through. Most parents don't do this out of malevolence and mostly it is quite the opposite. They do what they believe is best for their children and that is what the program has told them is best. Within three or four years comes the major transition from parental programming to full-blown state (Cult) programming in school, college and university where perceptually-programmed teachers and academics pass on their programming to the next generations. Teachers who resist are soon marginalised and their careers ended while children who resist are called a problem child for whom Ritalin may need to be prescribed. A few years after entering the 'world' children are under the control of authority figures representing the state telling them when they have to be there, when they can leave and when they can speak, eat, even go to the toilet. This is calculated preparation for a lifetime of obeying authority in all its forms. Reflex-action fear of authority is instilled by authority from the start. Children soon learn the carrot and stick consequences of obeying or defying authority which is underpinned daily for the rest of their life. Fortunately I daydreamed through this crap and never obeyed authority simply because it told me to. This approach to my alleged 'betters' continues to this day. There can be consequences of pursuing open-minded freedom in a world of closed-minded conformity. I spent a lot of time in school corridors after being ejected from the classroom for not taking some of it seriously and now I spend a lot of time being ejected from Facebook, YouTube and Twitter. But I can tell you that being true to yourself and not compromising your self-respect is far more exhilarating than bowing to authority for authority's sake. You don't have to be a sheep to the shepherd (authority) and the sheep dog (fear of not obeying authority).

The perceptual download continues throughout the formative years in school, college and university while script-reading 'teachers', 'academics' 'scientists', 'doctors' and 'journalists' insist that ongoing generations must be as programmed as they are. Accept the program or you will not pass your 'exams' which confirm your 'degree' of programming. It is tragic to think that many parents pressure their offspring to work hard at school to download the program and qualify for the next stage at college and university. The late, great, American comedian George Carlin said: 'Here's a bumper sticker I'd like to see: We are proud parents of a child who has resisted his teachers' attempts to break his spirit and bend him to the will of his corporate masters.' Well, the best of luck finding many of those, George. Then comes the moment to leave the formal programming years in academia and enter the 'adult' world of work. There you meet others in your chosen or prescribed arena who went through the same Postage Stamp Consensus program before you did. There is therefore overwhelming agreement between almost everyone on the basic foundations of Postage Stamp reality and the rejection, even contempt, of the few who have a mind of their own and are prepared to use it. This has two major effects. Firstly, the consensus confirms to the programmed that their download is really how things are. I mean, everyone knows that, right? Secondly, the arrogance and ignorance of Postage Stamp adherents ensure that anyone questioning the program will have unpleasant consequences for seeking their own truth and not picking their perceptions from the shelf marked: 'Things you must believe without question and if you don't you're a dangerous lunatic conspiracy theorist and a harebrained nutter'.

Every government, agency and corporation is founded on the same Postage Stamp prison cell and you can see why so many people believe the same thing while calling it their own 'opinion'. Fusion of governments and corporations in pursuit of the same agenda was the definition of fascism described by Italian dictator Benito Mussolini. The pressure to conform to perceptual norms downloaded for a lifetime is incessant and infiltrates society right

down to family groups that become censors and condemners of their own 'black sheep' for not, ironically, being sheep. We have seen an explosion of that in the 'Covid' era. Cult-owned global media unleashes its propaganda all day every day in support of the Postage Stamp and targets with abuse and ridicule anyone in the public eye who won't bend their mind to the will of the tyranny. Any response to this is denied (certainly in my case). They don't want to give a platform to expose official lies. Cult-owned-and-created Internet giants like Facebook, Google, YouTube and Twitter delete you for having an unapproved opinion. Facebook boasts that its AI censors delete 97-percent of 'hate speech' before anyone even reports it. Much of that 'hate speech' will simply be an opinion that Facebook and its masters don't want people to see. Such perceptual oppression is widely known as fascism. Even Facebook executive Benny Thomas, a 'CEO Global Planning Lead', said in comments secretly recorded by investigative journalism operation Project Veritas that Facebook is 'too powerful' and should be broken up:

I mean, no king in history has been the ruler of two billion people, but Mark Zuckerberg is … And he's 36. That's too much for a 36-year-old ... You should not have power over two billion people. I just think that's wrong.

Thomas said Facebook-owned platforms like Instagram, Oculus, and WhatsApp needed to be separate companies. 'It's too much power when they're all one together'. That's the way the Cult likes it, however. We have an executive of a Cult organisation in Benny Thomas that doesn't know there is a Cult such is the compartmentalisation. Thomas said that Facebook and Google 'are no longer companies, they're countries'. Actually they are more powerful than countries on the basis that if you control information you control perception and control human society.

I love my oppressor

Another expression of this psychological trickery is for those who realise they are being pressured into compliance to eventually

convince themselves to believe the official narratives to protect their self-respect from accepting the truth that they have succumbed to meek and subservient compliance. Such people become some of the most vehement defenders of the system. You can see them everywhere screaming abuse at those who prefer to think for themselves and by doing so reminding the compliers of their own capitulation to conformity. 'You are talking dangerous nonsense you Covidiot!!' Are you trying to convince me or yourself? It is a potent form of Stockholm syndrome which is defined as: 'A psychological condition that occurs when a victim of abuse identifies and attaches, or bonds, positively with their abuser.' An example is hostages bonding and even 'falling in love' with their kidnappers. The syndrome has been observed in domestic violence, abused children, concentration camp inmates, prisoners of war and many and various Satanic cults. These are some traits of Stockholm syndrome listed at goodtherapy.org:

- Positive regard towards perpetrators of abuse or captor [see 'Covid'].
- Failure to cooperate with police and other government authorities when it comes to holding perpetrators of abuse or kidnapping accountable [or in the case of 'Covid' cooperating with the police to enforce and defend their captors' demands].
- Little or no effort to escape [see 'Covid'].
- Belief in the goodness of the perpetrators or kidnappers [see 'Covid'].
- Appeasement of captors. This is a manipulative strategy for maintaining one's safety. As victims get rewarded – perhaps with less abuse or even with life itself – their appeasing behaviours are reinforced [see 'Covid'].
- Learned helplessness. This can be akin to 'if you can't beat 'em, join 'em'. As the victims fail to escape the abuse or captivity, they may start giving up and soon realize it's just easier for everyone if they acquiesce all their power to their captors [see 'Covid'].

- Feelings of pity toward the abusers, believing they are actually victims themselves. Because of this, victims may go on a crusade or mission to 'save' [protect] their abuser [see the venom unleashed on those challenging the official 'Covid' narrative].
- Unwillingness to learn to detach from their perpetrators and heal. In essence, victims may tend to be less loyal to themselves than to their abuser [*definitely* see 'Covid'].

Ponder on those traits and compare them with the behaviour of great swathes of the global population who have defended governments and authorities which have spent every minute destroying their lives and livelihoods and those of their children and grandchildren since early 2020 with fascistic lockdowns, house arrest and employment deletion to 'protect' them from a 'deadly virus' that their abusers' perceptually created to bring about this very outcome. We are looking at mass Stockholm syndrome. All those that agree to concede their freedom will believe those perceptions are originating in their own independent 'mind' when in fact by conceding their reality to Stockholm syndrome they have by definition conceded any independence of mind. Listen to the 'opinions' of the acquiescing masses in this 'Covid' era and what gushes forth is the repetition of the official version of everything delivered unprocessed, unfiltered and unquestioned. The whole programming dynamic works this way. I must be free because I'm told that I am and so I think that I am.

You can see what I mean with the chapter theme of 'I'm thinking – Oh, but *are* you?' The great majority are not thinking, let alone for themselves. They are repeating what authority has told them to believe which allows them to be controlled. Weaving through this mentality is the fear that the 'conspiracy theorists' are right and this again explains the often hysterical abuse that ensues when you dare to contest the official narrative of anything. Denial is the mechanism of hiding from yourself what you don't want to be true. Telling people what they want to hear is easy, but it's an infinitely greater challenge to tell them what they would rather not be happening.

One is akin to pushing against an open door while the other is met with vehement resistance no matter what the scale of evidence. I don't want it to be true so I'll convince myself that it's not. Examples are everywhere from the denial that a partner is cheating despite all the signs to the reflex-action rejection of any idea that world events in which country after country act in exactly the same way are centrally coordinated. To accept the latter is to accept that a force of unspeakable evil is working to destroy your life and the lives of your children with nothing too horrific to achieve that end. Who the heck wants that to be true? But if we don't face reality the end is duly achieved and the consequences are far worse and ongoing than breaking through the walls of denial today with the courage to make a stand against tyranny.

Connect the dots – but how?

A crucial aspect of perceptual programming is to portray a world in which everything is random and almost nothing is connected to anything else. Randomness cannot be coordinated by its very nature and once you perceive events as random the idea they could be connected is waved away as the rantings of the tinfoil-hat brigade. You can't plan and coordinate random you idiot! No, you can't, but you can hide the coldly-calculated and long-planned behind the *illusion* of randomness. A foundation manifestation of the Renegade Mind is to scan reality for patterns that connect the apparently random and turn pixels and dots into pictures. This is the way I work and have done so for more than 30 years. You look for similarities in people, modus operandi and desired outcomes and slowly, then ever quicker, the picture forms. For instance: There would seem to be no connection between the 'Covid pandemic' hoax and the human-caused global-warming hoax and yet they are masks (appropriately) on the same face seeking the same outcome. Those pushing the global warming myth through the Club of Rome and other Cult agencies are driving the lies about 'Covid' – Bill Gates is an obvious one, but they are endless. Why would the same people be involved in both when they are clearly not connected? Oh, but they

are. Common themes with personnel are matched by common goals. The 'solutions' to both 'problems' are centralisation of global power to impose the will of the few on the many to 'save' humanity from 'Covid' and save the planet from an 'existential threat' (we need 'zero Covid' and 'zero carbon emissions'). These, in turn, connect with the 'dot' of globalisation which was coined to describe the centralisation of global power in every area of life through incessant political and corporate expansion, trading blocks and superstates like the European Union. If you are the few and you want to control the many you have to centralise power and decision-making. The more you centralise power the more power the few at the centre will have over the many; and the more that power is centralised the more power those at the centre have to centralise even quicker. The momentum of centralisation gets faster and faster which is exactly the process we have witnessed. In this way the hoaxed 'pandemic' and the fakery of human-caused global warming serve the interests of globalisation and the seizure of global power in the hands of the Cult inner-circle which is behind 'Covid', 'climate change' *and* globalisation. At this point random 'dots' become a clear and obvious picture or pattern.

Klaus Schwab, the classic Bond villain who founded the Cult's Gates-funded World Economic Forum, published a book in 2020, *The Great Reset*, in which he used the 'problem' of 'Covid' to justify a total transformation of human society to 'save' humanity from 'climate change'. Schwab said: 'The pandemic represents a rare but narrow window of opportunity to reflect, reimagine, and reset our world.' What he didn't mention is that the Cult he serves is behind both hoaxes as I show in my book *The Answer*. He and the Cult don't have to reimagine the world. They know precisely what they want and that's why they destroyed human society with 'Covid' to 'build back better' in their grand design. Their job is not to imagine, but to get humanity to imagine and agree with their plans while believing it's all random. It must be pure coincidence that 'The Great Reset' has long been the Cult's code name for the global imposition of fascism and replaced previous code-names of the 'New World

Order' used by Cult frontmen like Father George Bush and the 'New Order of the Ages' which emerged from Freemasonry and much older secret societies. New Order of the Ages appears on the reverse of the Great Seal of the United States as 'Novus ordo seclorum' underneath the Cult symbol used since way back of the pyramid and all seeing-eye (Fig 3). The pyramid is the hierarchy of human control headed by the illuminated eye that symbolises the force behind the Cult which I will expose in later chapters. The term 'Annuit Coeptis' translates as 'He favours our undertaking'. We are told the 'He' is the Christian god, but 'He' is not as I will be explaining.



Figure 3: The all-seeing eye of the Cult 'god' on the Freemason-designed Great Seal of the United States and also on the dollar bill.

Having you on

Two major Cult techniques of perceptual manipulation that relate to all this are what I have called since the 1990s Problem-Reaction-Solution (PRS) and the Totalitarian Tiptoe (TT). They can be uncovered by the inquiring mind with a simple question: Who benefits? The answer usually identifies the perpetrators of a given action or happening through the concept of 'he who most benefits from a crime is the one most likely to have committed it'. The Latin 'Cue bono?' – Who benefits? – is widely attributed to the Roman orator and statesman Marcus Tullius Cicero. No wonder it goes back so far when the concept has been relevant to human behaviour since

history was recorded. Problem-Reaction-Solution is the technique used to manipulate us every day by covertly creating a problem (or the illusion of one) and offering the solution to the problem (or the illusion of one). In the first phase you create the problem and blame someone or something else for why it has happened. This may relate to a financial collapse, terrorist attack, war, global warming or pandemic, anything in fact that will allow you to impose the 'solution' to change society in the way you desire at that time. The 'problem' doesn't have to be real. PRS is manipulation of perception and all you need is the population to believe the problem is real. Human-caused global warming and the 'Covid pandemic' only have to be *perceived* to be real for the population to accept the 'solutions' of authority. I refer to this technique as NO-Problem-Reaction-Solution. Billions did not meekly accept house arrest from early 2020 because there was a real deadly 'Covid pandemic' but because they perceived – believed – that to be the case. The antidote to Problem-Reaction-Solution is to ask who benefits from the proposed solution. Invariably it will be anyone who wants to justify more control through deletion of freedom and centralisation of power and decision-making.

The two world wars were Problem-Reaction-Solutions that transformed and realigned global society. Both were manipulated into being by the Cult as I have detailed in books since the mid-1990s. They dramatically centralised global power, especially World War Two, which led to the United Nations and other global bodies thanks to the overt and covert manipulations of the Rockefeller family and other Cult bloodlines like the Rothschilds. The UN is a stalking horse for full-blown world government that I will come to shortly. The land on which the UN building stands in New York was donated by the Rockefellers and the same Cult family was behind Big Pharma scalpel and drug 'medicine' and the creation of the World Health Organization as part of the UN. They have been stalwarts of the eugenics movement and funded Hitler's race-purity expert' Ernst Rudin. The human-caused global warming hoax has been orchestrated by the Club of Rome through the UN which is

manufacturing both the 'problem' through its Intergovernmental Panel on Climate Change and imposing the 'solution' through its Agenda 21 and Agenda 2030 which demand the total centralisation of global power to 'save the world' from a climate hoax the United Nations is itself perpetrating. What a small world the Cult can be seen to be particularly among the inner circles. The bedfellow of Problem-Reaction-Solution is the Totalitarian Tiptoe which became the Totalitarian Sprint in 2020. The technique is fashioned to hide the carefully-coordinated behind the cover of apparently random events. You start the sequence at 'A' and you know you are heading for 'Z'. You don't want people to know that and each step on the journey is presented as a random happening while all the steps strung together lead in the same direction. The speed may have quickened dramatically in recent times, but you can still see the incremental approach of the Tiptoe in the case of 'Covid' as each new imposition takes us deeper into fascism. Tell people they have to do this or that to get back to 'normal', then this and this and this. With each new demand adding to the ones that went before the population's freedom is deleted until it disappears. The spider wraps its web around the flies more comprehensively with each new diktat. I'll highlight this in more detail when I get to the 'Covid' hoax and how it has been pulled off. Another prime example of the Totalitarian Tiptoe is how the Cult-created European Union went from a 'free-trade zone' to a centralised bureaucratic dictatorship through the Tiptoe of incremental centralisation of power until nations became mere administrative units for Cult-owned dark suits in Brussels.

The antidote to ignorance is knowledge which the Cult seeks vehemently to deny us, but despite the systematic censorship to that end the Renegade Mind can overcome this by vociferously seeking out the facts no matter the impediments put in the way. There is also a method of thinking and perceiving – *knowing* – that doesn't even need names, dates, place-type facts to identify the patterns that reveal the story. I'll get to that in the final chapter. All you need to know about the manipulation of human society and to what end is still out there – *at the time of writing* – in the form of books, videos

and websites for those that really want to breach the walls of programmed perception. To access this knowledge requires the abandonment of the mainstream media as a source of information in the awareness that this is owned and controlled by the Cult and therefore promotes mass perceptions that suit the Cult. Mainstream media lies all day, every day. That is its function and very reason for being. Where it does tell the truth, here and there, is only because the truth and the Cult agenda very occasionally coincide. If you look for fact and insight to the BBC, CNN and virtually all the rest of them you are asking to be conned and perceptually programmed.

Know the outcome and you'll see the journey

Events seem random when you have no idea where the world is being taken. Once you do the random becomes the carefully planned. Know the outcome and you'll see the journey is a phrase I have been using for a long time to give context to daily happenings that appear unconnected. Does a problem, or illusion of a problem, trigger a proposed 'solution' that further drives society in the direction of the outcome? Invariably the answer will be yes and the random – *abracadabra* – becomes the clearly coordinated. So what is this outcome that unlocks the door to a massively expanded understanding of daily events? I will summarise its major aspects – the fine detail is in my other books – and those new to this information will see that the world they thought they were living in is a very different place. The foundation of the Cult agenda is the incessant centralisation of power and all such centralisation is ultimately in pursuit of Cult control on a global level. I have described for a long time the planned world structure of top-down dictatorship as the Hunger Games Society. The term obviously comes from the movie series which portrayed a world in which a few living in military-protected hi-tech luxury were the overlords of a population condemned to abject poverty in isolated 'sectors' that were not allowed to interact. 'Covid' lockdowns and travel bans anyone? The 'Hunger Games' pyramid of structural control has the inner circle of the Cult at the top with pretty much the entire

population at the bottom under their control through dependency for survival on the Cult. The whole structure is planned to be protected and enforced by a military-police state (Fig 4).

Here you have the reason for the global lockdowns of the fake pandemic to coldly destroy independent incomes and livelihoods and make everyone dependent on the 'state' (the Cult that controls the 'states'). I have warned in my books for many years about the plan to introduce a 'guaranteed income' – a barely survivable pittance – designed to impose dependency when employment was destroyed by AI technology and now even more comprehensively at great speed by the 'Covid' scam. Once the pandemic was played and lockdown consequences began to delete independent income the authorities began to talk right on cue about the need for a guaranteed income and a 'Great Reset'. Guaranteed income will be presented as benevolent governments seeking to help a desperate people – desperate as a direct result of actions of the same governments. The truth is that such payments are a trap. You will only get them if you do exactly what the authorities demand including mass vaccination (genetic manipulation). We have seen this theme already in Australia where those dependent on government benefits have them reduced if parents don't agree to have their children vaccinated according to an insane health-destroying government-dictated schedule. Calculated economic collapse applies to governments as well as people. The Cult wants rid of countries through the creation of a world state with countries broken up into regions ruled by a world government and super states like the European Union. Countries must be bankrupted, too, to this end and it's being achieved by the trillions in 'rescue packages' and furlough payments, trillions in lost taxation, and money-no-object spending on 'Covid' including constant all-medium advertising (programming) which has made the media dependent on government for much of its income. The day of reckoning is coming – as planned – for government spending and given that it has been made possible by printing money and not by production/taxation there is inflation on the way that has the

potential to wipe out monetary value. In that case there will be no need for the Cult to steal your money. It just won't be worth anything (see the German Weimar Republic before the Nazis took over). Many have been okay with lockdowns while getting a percentage of their income from so-called furlough payments without having to work. Those payments are dependent, however, on people having at least a theoretical job with a business considered non-essential and ordered to close. As these business go under because they are closed by lockdown after lockdown the furlough stops and it will for everyone eventually. Then what? The 'then what?' is precisely the idea.



Figure 4: The Hunger Games Society structure I have long warned was planned and now the 'Covid' hoax has made it possible. This is the real reason for lockdowns.

Hired hands

Between the Hunger Games Cult elite and the dependent population is planned to be a vicious military-police state (a fusion of the two into one force). This has been in the making for a long time with police looking ever more like the military and carrying weapons to match. The pandemic scam has seen this process accelerate so fast as

lockdown house arrest is brutally enforced by carefully recruited fascist minds and gormless system-servers. The police and military are planned to merge into a centrally-directed world army in a global structure headed by a world government which wouldn't be elected even by the election fixes now in place. The world army is not planned even to be human and instead wars would be fought, primarily against the population, using robot technology controlled by artificial intelligence. I have been warning about this for decades and now militaries around the world are being transformed by this very AI technology. The global regime that I describe is a particular form of fascism known as a technocracy in which decisions are not made by clueless and co-opted politicians but by unelected technocrats – scientists, engineers, technologists and bureaucrats. Cult-owned-and-controlled Silicon Valley giants are examples of technocracy and they already have far more power to direct world events than governments. They are with their censorship *selecting* governments. I know that some are calling the 'Great Reset' a Marxist communist takeover, but fascism and Marxism are different labels for the same tyranny. Tell those who lived in fascist Germany and Stalinist Russia that there was a difference in the way their freedom was deleted and their lives controlled. I could call it a fascist technocracy or a Marxist technocracy and they would be equally accurate. The Hunger Games society with its world government structure would oversee a world army, world central bank and single world cashless currency imposing its will on a microchipped population (Fig 5). Scan its different elements and see how the illusory pandemic is forcing society in this very direction at great speed. Leaders of 23 countries and the World Health Organization (WHO) backed the idea in March, 2021, of a global treaty for 'international cooperation' in 'health emergencies' and nations should 'come together as a global community for peaceful cooperation that extends beyond this crisis'. Cut the Orwellian bullshit and this means another step towards global government. The plan includes a cashless digital money system that I first warned about in 1993. Right at the start of 'Covid' the deeply corrupt Tedros

Adhanom Ghebreyesus, the crooked and merely gofer 'head' of the World Health Organization, said it was possible to catch the 'virus' by touching cash and it was better to use cashless means. The claim was ridiculous nonsense and like the whole 'Covid' mind-trick it was nothing to do with 'health' and everything to do with pushing every aspect of the Cult agenda. As a result of the Tedros lie the use of cash has plummeted. The Cult script involves a single world digital currency that would eventually be technologically embedded in the body. China is a massive global centre for the Cult and if you watch what is happening there you will know what is planned for everywhere. The Chinese government is developing a digital currency which would allow fines to be deducted immediately via AI for anyone caught on camera breaking its fantastic list of laws and the money is going to be programmable with an expiry date to ensure that no one can accrue wealth except the Cult and its operatives.



Figure 5: The structure of global control the Cult has been working towards for so long and this has been enormously advanced by the 'Covid' illusion.

Serfdom is so smart

The Cult plan is far wider, extreme, and more comprehensive than even most conspiracy researchers appreciate and I will come to the true depths of deceit and control in the chapters 'Who controls the

Cult?' and 'Escaping Wetiko'. Even the world that we know is crazy enough. We are being deluged with ever more sophisticated and controlling technology under the heading of 'smart'. We have smart televisions, smart meters, smart cards, smart cars, smart driving, smart roads, smart pills, smart patches, smart watches, smart skin, smart borders, smart pavements, smart streets, smart cities, smart communities, smart environments, smart growth, smart planet ... smart *everything* around us. Smart technologies and methods of operation are designed to interlock to create a global Smart Grid connecting the entirety of human society including human minds to create a centrally-dictated 'hive' mind. 'Smart cities' is code for densely-occupied megacities of total surveillance and control through AI. Ever more destructive frequency communication systems like 5G have been rolled out without any official testing for health and psychological effects (colossal). 5G/6G/7G systems are needed to run the Smart Grid and each one becomes more destructive of body and mind. Deleting independent income is crucial to forcing people into these AI-policed prisons by ending private property ownership (except for the Cult elite). The Cult's Great Reset now openly foresees a global society in which no one will own any possessions and everything will be rented while the Cult would own literally everything under the guise of government and corporations. The aim has been to use the lockdowns to destroy sources of income on a mass scale and when the people are destitute and in unrepayable amounts of debt (problem) Cult assets come forward with the pledge to write-off debt in return for handing over all property and possessions (solution). Everything – literally everything including people – would be connected to the Internet via AI. I was warning years ago about the coming Internet of Things (IoT) in which all devices and technology from your car to your fridge would be plugged into the Internet and controlled by AI. Now we are already there with much more to come. The next stage is the Internet of Everything (IoE) which is planned to include the connection of AI to the human brain and body to replace the human mind with a centrally-controlled AI mind. Instead of perceptions

being manipulated through control of information and censorship those perceptions would come direct from the Cult through AI. What do you think? You think whatever AI decides that you think. In human terms there would be no individual 'think' any longer. Too incredible? The ravings of a lunatic? Not at all. Cult-owned crazies in Silicon Valley have been telling us the plan for years without explaining the real motivation and calculated implications. These include Google executive and 'futurist' Ray Kurzweil who highlights the year 2030 for when this would be underway. He said:

Our thinking ... will be a hybrid of biological and non-biological thinking ... humans will be able to extend their limitations and 'think in the cloud' ... We're going to put gateways to the cloud in our brains ... We're going to gradually merge and enhance ourselves ... In my view, that's the nature of being human – we transcend our limitations.

As the technology becomes vastly superior to what we are then the small proportion that is still human gets smaller and smaller and smaller until it's just utterly negligible.

The sales-pitch of Kurzweil and Cult-owned Silicon Valley is that this would make us 'super-human' when the real aim is to make us post-human and no longer 'human' in the sense that we have come to know. The entire global population would be connected to AI and become the centrally-controlled 'hive-mind' of externally-delivered perceptions. The Smart Grid being installed to impose the Cult's will on the world is being constructed to allow particular locations – even one location – to control the whole global system. From these prime control centres, which absolutely include China and Israel, anything connected to the Internet would be switched on or off and manipulated at will. Energy systems could be cut, communication via the Internet taken down, computer-controlled driverless autonomous vehicles driven off the road, medical devices switched off, the potential is limitless given how much AI and Internet connections now run human society. We have seen nothing yet if we allow this to continue. Autonomous vehicle makers are working with law enforcement to produce cars designed to automatically pull over if they detect a police or emergency vehicle flashing from up to 100 feet away. At a police stop the car would be unlocked and the

window rolled down automatically. Vehicles would only take you where the computer (the state) allowed. The end of petrol vehicles and speed limiters on all new cars in the UK and EU from 2022 are steps leading to electric computerised transport over which ultimately you have no control. The picture is far bigger even than the Cult global network or web and that will become clear when I get to the nature of the 'spider'. There is a connection between all these happenings and the instigation of DNA-manipulating 'vaccines' (which aren't 'vaccines') justified by the 'Covid' hoax. That connection is the unfolding plan to transform the human body from a biological to a synthetic biological state and this is why synthetic biology is such a fast-emerging discipline of mainstream science. 'Covid vaccines' are infusing self-replicating synthetic genetic material into the cells to cumulatively take us on the Totalitarian Tiptoe from Human 1.0 to the synthetic biological Human 2.0 which will be physically and perceptually attached to the Smart Grid to one hundred percent control every thought, perception and deed. Humanity needs to wake up and *fast*.

This is the barest explanation of where the 'outcome' is planned to go but it's enough to see the journey happening all around us. Those new to this information will already see 'Covid' in a whole new context. I will add much more detail as we go along, but for the minutiae evidence see my mega-works, *The Answer, The Trigger* and *Everything You Need to Know But Have Never Been Told*.

Now – how does a Renegade Mind see the 'world'?

CHAPTER TWO

Renegade Perception

It is one thing to be clever and another to be wise
George R.R. Martin

A simple definition of the difference between a programmed mind and a Renegade Mind would be that one sees only dots while the other connects them to see the picture. Reading reality with accuracy requires the observer to (a) know the planned outcome and (b) realise that everything, but *everything*, is connected.

The entirety of infinite reality is connected – that's its very nature – and with human society an expression of infinite reality the same must apply. Simple cause and effect is a connection. The effect is triggered by the cause and the effect then becomes the cause of another effect. Nothing happens in isolation because it *can't*. Life in whatever reality is simple choice and consequence. We make choices and these lead to consequences. If we don't like the consequences we can make different choices and get different consequences which lead to other choices and consequences. The choice and the consequence are not only connected they are indivisible. You can't have one without the other as an old song goes. A few cannot control the world unless those being controlled allow that to happen – cause and effect, choice and consequence. Control – who has it and who doesn't – is a two-way process, a symbiotic relationship, involving the controller and controlled. 'They took my freedom away!!' Well, yes, but you also gave it to them. Humanity is

subjected to mass control because humanity has acquiesced to that control. This is all cause and effect and literally a case of give and take. In the same way world events of every kind are connected and the Cult works incessantly to sell the illusion of the random and coincidental to maintain the essential (to them) perception of dots that hide the picture. Renegade Minds know this and constantly scan the world for patterns of connection. This is absolutely pivotal in understanding the happenings in the world and without that perspective clarity is impossible. First you know the planned outcome and then you identify the steps on the journey – the day-by-day apparently random which, when connected in relation to the outcome, no longer appear as individual events, but as the proverbial *chain* of events leading in the same direction. I'll give you some examples:

Political puppet show

We are told to believe that politics is 'adversarial' in that different parties with different beliefs engage in an endless tussle for power. There may have been some truth in that up to a point – and only a point – but today divisions between 'different' parties are rhetorical not ideological. Even the rhetorical is fusing into one-speak as the parties eject any remaining free thinkers while others succumb to the ever-gathering intimidation of anyone with the 'wrong' opinion. The Cult is not a new phenomenon and can be traced back thousands of years as my books have documented. Its intergenerational initiates have been manipulating events with increasing effect the more that global power has been centralised. In ancient times the Cult secured control through the system of monarchy in which 'special' bloodlines (of which more later) demanded the right to rule as kings and queens simply by birthright and by vanquishing others who claimed the same birthright. There came a time, however, when people had matured enough to see the unfairness of such tyranny and demanded a say in who governed them. Note the word – *governed* them. Not served them – *governed* them, hence government defined as 'the political direction and control exercised over the

actions of the members, citizens, or inhabitants of communities, societies, and states; direction of the affairs of a state, community, etc.' Governments exercise control over rather than serve just like the monarchies before them. Bizarrely there are still countries like the United Kingdom which are ruled by a monarch *and* a government that officially answers to the monarch. The UK head of state and that of Commonwealth countries such as Canada, Australia and New Zealand is 'selected' by who in a *single family* had unprotected sex with whom and in what order. Pinch me it can't be true. Ouch! Shit, it is. The demise of monarchies in most countries offered a potential vacuum in which some form of free and fair society could arise and the Cult had that base covered. Monarchies had served its interests but they couldn't continue in the face of such widespread opposition and, anyway, replacing a 'royal' dictatorship that people could see with a dictatorship 'of the people' hiding behind the concept of 'democracy' presented far greater manipulative possibilities and ways of hiding coordinated tyranny behind the illusion of 'freedom'.

Democracy is quite wrongly defined as government selected by the population. This is not the case at all. It is government selected by *some* of the population (and then only in theory). This 'some' doesn't even have to be the majority as we have seen so often in first-past-the-post elections in which the so-called majority party wins fewer votes than the 'losing' parties combined. Democracy can give total power to a party in government from a minority of the votes cast. It's a sleight of hand to sell tyranny as freedom. Seventy-four million Trump-supporting Americans didn't vote for the 'Democratic' Party of Joe Biden in the distinctly dodgy election in 2020 and yet far from acknowledging the wishes and feelings of that great percentage of American society the Cult-owned Biden government set out from day one to destroy them and their right to a voice and opinion. Empty shell Biden and his Cult handlers said they were doing this to 'protect democracy'. Such is the level of lunacy and sickness to which politics has descended. Connect the dots and relate them to the desired outcome – a world government run by self-appointed technocrats and no longer even elected

politicians. While operating through its political agents in government the Cult is at the same time encouraging public distain for politicians by putting idiots and incompetents in theoretical power on the road to deleting them. The idea is to instil a public reaction that says of the technocrats: 'Well, they couldn't do any worse than the pathetic politicians.' It's all about controlling perception and Renegade Minds can see through that while programmed minds cannot when they are ignorant of both the planned outcome and the manipulation techniques employed to secure that end. This knowledge can be learned, however, and fast if people choose to get informed.

Politics may at first sight appear very difficult to control from a central point. I mean look at the 'different' parties and how would you be able to oversee them all and their constituent parts? In truth, it's very straightforward because of their structure. We are back to the pyramid of imposition and acquiescence. Organisations are structured in the same way as the system as a whole. Political parties are not open forums of free expression. They are hierarchies. I was a national spokesman for the British Green Party which claimed to be a different kind of politics in which influence and power was devolved; but I can tell you from direct experience – and it's far worse now – that Green parties are run as hierarchies like all the others however much they may try to hide that fact or kid themselves that it's not true. A very few at the top of all political parties are directing policy and personnel. They decide if you are elevated in the party or serve as a government minister and to do that you have to be a yes man or woman. Look at all the maverick political thinkers who never ascended the greasy pole. If you want to progress within the party or reach 'high-office' you need to fall into line and conform. Exceptions to this are rare indeed. Should you want to run for parliament or Congress you have to persuade the local or state level of the party to select you and for that you need to play the game as dictated by the hierarchy. If you secure election and wish to progress within the greater structure you need to go on conforming to what is acceptable to those running the hierarchy

from the peak of the pyramid. Political parties are perceptual gulags and the very fact that there are party 'Whips' appointed to 'whip' politicians into voting the way the hierarchy demands exposes the ridiculous idea that politicians are elected to serve the people they are supposed to represent. Cult operatives and manipulation has long seized control of major parties that have any chance of forming a government and at least most of those that haven't. A new party forms and the Cult goes to work to infiltrate and direct. This has reached such a level today that you see video compilations of 'leaders' of all parties whether Democrats, Republicans, Conservative, Labour and Green parroting the same Cult mantra of 'Build Back Better' and the 'Great Reset' which are straight off the Cult song-sheet to describe the transformation of global society in response to the Cult-instigated hoaxes of the 'Covid pandemic' and human-caused 'climate change'. To see Caroline Lucas, the Green Party MP that I knew when I was in the party in the 1980s, speaking in support of plans proposed by Cult operative Klaus Schwab representing the billionaire global elite is a real head-shaker.

Many parties – one master

The party system is another mind-trick and was instigated to change the nature of the dictatorship by swapping 'royalty' for dark suits that people believed – though now ever less so – represented their interests. Understanding this trick is to realise that a single force (the Cult) controls all parties either directly in terms of the major ones or through manipulation of perception and ideology with others. You don't need to manipulate Green parties to demand your transformation of society in the name of 'climate change' when they are obsessed with the lie that this is essential to 'save the planet'. You just give them a platform and away they go serving your interests while believing they are being environmentally virtuous. America's political structure is a perfect blueprint for how the two or multi-party system is really a one-party state. The Republican Party is controlled from one step back in the shadows by a group made up of billionaires and their gofers known as neoconservatives or Neocons.

I have exposed them in fine detail in my books and they were the driving force behind the policies of the imbecilic presidency of Boy George Bush which included 9/11 (see *The Trigger* for a comprehensive demolition of the official story), the subsequent 'war on terror' (war *of* terror) and the invasions of Afghanistan and Iraq. The latter was a No-Problem-Reaction-Solution based on claims by Cult operatives, including Bush and British Prime Minister Tony Blair, about Saddam Hussein's 'weapons of mass destruction' which did not exist as war criminals Bush and Blair well knew.

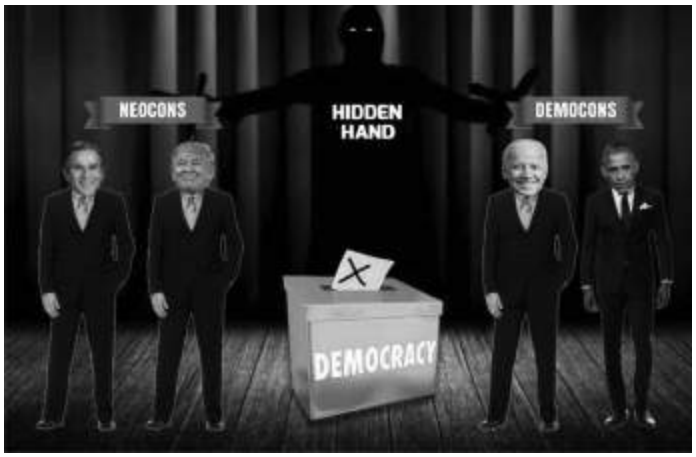


Figure 6: Different front people, different parties – same control system.

The Democratic Party has its own 'Neocon' group controlling from the background which I call the 'Democons' and here's the penny-drop – the Neocons and Democons answer to the same masters one step further back into the shadows (Fig 6). At that level of the Cult the Republican and Democrat parties are controlled by the same people and no matter which is in power the Cult is in power. This is how it works in almost every country and certainly in Britain with Conservative, Labour, Liberal Democrat and Green parties now all on the same page whatever the rhetoric may be in their feeble attempts to appear different. Neocons operated at the time of Bush through a think tank called The Project for the New American Century which in September, 2000, published a document entitled *Rebuilding America's Defenses: Strategies, Forces, and Resources*

For a New Century demanding that America fight 'multiple, simultaneous major theatre wars' as a 'core mission' to force regime-change in countries including Iraq, Libya and Syria. Neocons arranged for Bush ('Republican') and Blair ('Labour Party') to front-up the invasion of Iraq and when they departed the Democons orchestrated the targeting of Libya and Syria through Barack Obama ('Democrat') and British Prime Minister David Cameron ('Conservative Party'). We have 'different' parties and 'different' people, but the same unfolding script. The more the Cult has seized the reigns of parties and personnel the more their policies have transparently pursued the same agenda to the point where the fascist 'Covid' impositions of the Conservative junta of Jackboot Johnson in Britain were opposed by the Labour Party because they were not fascist enough. The Labour Party is likened to the US Democrats while the Conservative Party is akin to a British version of the Republicans and on both sides of the Atlantic they all speak the same language and support the direction demanded by the Cult although some more enthusiastically than others. It's a similar story in country after country because it's all centrally controlled. Oh, but what about Trump? I'll come to him shortly. Political 'choice' in the 'party' system goes like this: You vote for Party A and they get into government. You don't like what they do so next time you vote for Party B and they get into government. You don't like what they do when it's pretty much the same as Party A and why wouldn't that be with both controlled by the same force? Given that only two, sometimes three, parties have any chance of forming a government to get rid of Party B that you don't like you have to vote again for Party A which … you don't like. This, ladies and gentlemen, is what they call 'democracy' which we are told – wrongly – is a term interchangeable with 'freedom'.

The cult of cults

At this point I need to introduce a major expression of the Global Cult known as Sabbatian-Frankism. Sabbatian is also spelt as Sabbatean. I will summarise here. I have published major exposés

and detailed background in other works. Sabbatian-Frankism combines the names of two frauds posing as 'Jewish' men, Sabbatai Zevi (1626-1676), a rabbi, black magician and occultist who proclaimed he was the Jewish messiah; and Jacob Frank (1726-1791), the Polish 'Jew', black magician and occultist who said he was the reincarnation of 'messiah' Zevi and biblical patriarch Jacob. They worked across two centuries to establish the Sabbatian-Frankist cult that plays a major, indeed central, role in the manipulation of human society by the Global Cult which has its origins much further back in history than Sabbatai Zevi. I should emphasise two points here in response to the shrill voices that will scream 'anti-Semitism': (1) Sabbatian-Frankists are NOT Jewish and only pose as such to hide their cult behind a Jewish façade; and (2) my information about this cult has come from Jewish sources who have long realised that their society and community has been infiltrated and taken over by interloper Sabbatian-Frankists. Infiltration has been the foundation technique of Sabbatian-Frankism from its official origin in the 17th century. Zevi's Sabbatian sect attracted a massive following described as the biggest messianic movement in Jewish history, spreading as far as Africa and Asia, and he promised a return for the Jews to the 'Promised Land' of Israel. Sabbatianism was not Judaism but an inversion of everything that mainstream Judaism stood for. So much so that this sinister cult would have a feast day when Judaism had a fast day and whatever was forbidden in Judaism the Sabbatians were encouraged and even commanded to do. This included incest and what would be today called Satanism. Members were forbidden to marry outside the sect and there was a system of keeping their children ignorant of what they were part of until they were old enough to be trusted not to unknowingly reveal anything to outsiders. The same system is employed to this day by the Global Cult in general which Sabbatian-Frankism has enormously influenced and now largely controls.

Zevi and his Sabbatians suffered a setback with the intervention by the Sultan of the Islamic Ottoman Empire in the Middle East and what is now the Republic of Turkey where Zevi was located. The

Sultan gave him the choice of proving his 'divinity', converting to Islam or facing torture and death. Funnily enough Zevi chose to convert or at least appear to. Some of his supporters were disillusioned and drifted away, but many did not with 300 families also converting – only in theory – to Islam. They continued behind this Islamic smokescreen to follow the goals, rules and rituals of Sabbatianism and became known as 'crypto-Jews' or the 'Dönmeh' which means 'to turn'. This is rather ironic because they didn't 'turn' and instead hid behind a fake Islamic persona. The process of appearing to be one thing while being very much another would become the calling card of Sabbatianism especially after Zevi's death and the arrival of the Satanist Jacob Frank in the 18th century when the cult became Sabbatian-Frankism and plumbed still new depths of depravity and infiltration which included – still includes – human sacrifice and sex with children. Wherever Sabbatians go paedophilia and Satanism follow and is it really a surprise that Hollywood is so infested with child abuse and Satanism when it was established by Sabbatian-Frankists and is still controlled by them? Hollywood has been one of the prime vehicles for global perceptual programming and manipulation. How many believe the version of 'history' portrayed in movies when it is a travesty and inversion (again) of the truth? Rabbi Marvin Antelman describes Frankism in his book, *To Eliminate the Opiate*, as 'a movement of complete evil' while Jewish professor Gershom Scholem said of Frank in *The Messianic Idea in Judaism*: 'In all his actions [he was] a truly corrupt and degenerate individual ... one of the most frightening phenomena in the whole of Jewish history.' Frank was excommunicated by traditional rabbis, as was Zevi, but Frank was undeterred and enjoyed vital support from the House of Rothschild, the infamous banking dynasty whose inner-core are Sabbatian-Frankists and not Jews. Infiltration of the Roman Church and Vatican was instigated by Frank with many Dönmeh 'turning' again to convert to Roman Catholicism with a view to hijacking the reins of power. This was the ever-repeating modus operandi and continues to be so. Pose as an advocate of the religion, culture or country that you want to control and then

manipulate your people into the positions of authority and influence largely as advisers, administrators and Svengalis for those that appear to be in power. They did this with Judaism, Christianity (Christian Zionism is part of this), Islam and other religions and nations until Sabbatian-Frankism spanned the world as it does today.

Sabbatian Saudis and the terror network

One expression of the Sabbatian-Frankist Dönmeh within Islam is the ruling family of Saudi Arabia, the House of Saud, through which came the vile distortion of Islam known as Wahhabism. This is the violent creed followed by terrorist groups like Al-Qaeda and ISIS or Islamic State. Wahhabism is the hand-chopping, head-chopping 'religion' of Saudi Arabia which is used to keep the people in a constant state of fear so the interloper House of Saud can continue to rule. Al-Qaeda and Islamic State were lavishly funded by the House of Saud while being created and directed by the Sabbatian-Frankist network in the United States that operates through the Pentagon, CIA and the government in general of whichever 'party'. The front man for the establishment of Wahhabism in the middle of the 18th century was a Sabbatian-Frankist 'crypto-Jew' posing as Islamic called Muhammad ibn Abd al-Wahhab. His daughter would marry the son of Muhammad bin Saud who established the first Saudi state before his death in 1765 with support from the British Empire. Bin Saud's successors would establish modern Saudi Arabia in league with the British and Americans in 1932 which allowed them to seize control of Islam's major shrines in Mecca and Medina. They have dictated the direction of Sunni Islam ever since while Iran is the major centre of the Shiite version and here we have the source of at least the public conflict between them. The Sabbatian network has used its Wahhabi extremists to carry out Problem-Reaction-Solution terrorist attacks in the name of 'Al-Qaeda' and 'Islamic State' to justify a devastating 'war on terror', ever-increasing surveillance of the population and to terrify people into compliance. Another insight of the Renegade Mind is the streetwise understanding that

just because a country, location or people are attacked doesn't mean that those apparently representing that country, location or people are not behind the attackers. Often they are *orchestrating* the attacks because of the societal changes that can be then justified in the name of 'saving the population from terrorists'.

I show in great detail in *The Trigger* how Sabbatian-Frankists were the real perpetrators of 9/11 and not '19 Arab hijackers' who were blamed for what happened. Observe what was justified in the name of 9/11 alone in terms of Middle East invasions, mass surveillance and control that fulfilled the demands of the Project for the New American Century document published by the Sabbatian Neocons. What appear to be enemies are on the deep inside players on the same Sabbatian team. Israel and Arab 'royal' dictatorships are all ruled by Sabbatians and the recent peace agreements between Israel and Saudi Arabia, the United Arab Emirates (UAE) and others are only making formal what has always been the case behind the scenes. Palestinians who have been subjected to grotesque tyranny since Israel was bombed and terrorised into existence in 1948 have never stood a chance. Sabbatian-Frankists have controlled Israel (so the constant theme of violence and war which Sabbatians love) and they have controlled the Arab countries that Palestinians have looked to for real support that never comes. 'Royal families' of the Arab world in Saudi Arabia, Bahrain, UAE, etc., are all Sabbatians with allegiance to the aims of the cult and not what is best for their Arabic populations. They have stolen the oil and financial resources from their people by false claims to be 'royal dynasties' with a genetic right to rule and by employing vicious militaries to impose their will.

Satanic 'illumination'

The Satanist Jacob Frank formed an alliance in 1773 with two other Sabbatians, Mayer Amschel Rothschild (1744-1812), founder of the Rothschild banking dynasty, and Jesuit-educated fraudulent Jew, Adam Weishaupt, and this led to the formation of the Bavarian Illuminati, firstly under another name, in 1776. The Illuminati would

be the manipulating force behind the French Revolution (1789-1799) and was also involved in the American Revolution (1775-1783) before and after the Illuminati's official creation. Weishaupt would later become (in public) a Protestant Christian in archetypal Sabbatian style. I read that his name can be decoded as Adam-Weishaupt or 'the first man to lead those who know'. He wasn't a leader in the sense that he was a subordinate, but he did lead those below him in a crusade of transforming human society that still continues today. The theme was confirmed as early as 1785 when a horseman courier called Lanz was reported to be struck by lighting and extensive Illuminati documents were found in his saddlebags. They made the link to Weishaupt and detailed the plan for world takeover. Current events with 'Covid' fascism have been in the making for a very long time. Jacob Frank was jailed for 13 years by the Catholic Inquisition after his arrest in 1760 and on his release he headed for Frankfurt, Germany, home city and headquarters of the House of Rothschild where the alliance was struck with Mayer Amschel Rothschild and Weishaupt. Rothschild arranged for Frank to be given the title of Baron and he became a wealthy nobleman with a big following of Jews in Germany, the Austro-Hungarian Empire and other European countries. Most of them would have believed he was on their side.

The name 'Illuminati' came from the Zohar which is a body of works in the Jewish mystical 'bible' called the Kabbalah. 'Zohar' is the foundation of Sabbatian-Frankist belief and in Hebrew 'Zohar' means 'splendour', 'radiance', 'illuminated', and so we have 'Illuminati'. They claim to be the 'Illuminated Ones' from their knowledge systematically hidden from the human population and passed on through generations of carefully-chosen initiates in the global secret society network or Cult. Hidden knowledge includes an awareness of the Cult agenda for the world and the nature of our collective reality that I will explore later. Cult 'illumination' is symbolised by the torch held by the Statue of Liberty which was gifted to New York by French Freemasons in Paris who knew exactly what it represents. 'Liberty' symbolises the goddess worshipped in

Babylon as Queen Semiramis or Ishtar. The significance of this will become clear. Notice again the ubiquitous theme of inversion with the Statue of 'Liberty' really symbolising mass control (Fig 7). A mirror-image statute stands on an island in the River Seine in Paris from where New York Liberty originated (Fig 8). A large replica of the Liberty flame stands on top of the Pont de l'Alma tunnel in Paris where Princess Diana died in a Cult ritual described in *The Biggest Secret*. Lucifer 'the light bringer' is related to all this (and much more as we'll see) and 'Lucifer' is a central figure in Sabbatian-Frankism and its associated Satanism. Sabbatians reject the Jewish Torah, or Pentateuch, the 'five books of Moses' in the Old Testament known as Genesis, Exodus, Leviticus, Numbers, and Deuteronomy which are claimed by Judaism and Christianity to have been dictated by 'God' to Moses on Mount Sinai. Sabbatians say these do not apply to them and they seek to replace them with the Zohar to absorb Judaism and its followers into their inversion which is an expression of a much greater global inversion. They want to delete all religions and force humanity to worship a one-world religion – Sabbatian Satanism that also includes worship of the Earth goddess. Satanic themes are being more and more introduced into mainstream society and while Christianity is currently the foremost target for destruction the others are planned to follow.



Figure 7: The Cult goddess of Babylon disguised as the Statue of Liberty holding the flame of Lucifer the 'light bringer'.



Figure 8: Liberty's mirror image in Paris where the New York version originated.

Marx brothers

Rabbi Marvin Antelman connects the Illuminati to the Jacobins in *To Eliminate the Opiate* and Jacobins were the force behind the French Revolution. He links both to the Bund der Gerechten, or League of the Just, which was the network that inflicted communism/Marxism on the world. Antelman wrote:

> The original inner circle of the Bund der Gerechten consisted of born Catholics, Protestants and Jews [Sabbatian-Frankist infiltrators], and those representatives of respective subdivisions formulated schemes for the ultimate destruction of their faiths. The heretical Catholics laid plans which they felt would take a century or more for the ultimate destruction of the church; the apostate Jews for the ultimate destruction of the Jewish religion.

Sabbatian-created communism connects into this anti-religion agenda in that communism does not allow for the free practice of religion. The Sabbatian 'Bund' became the International Communist Party and Communist League and in 1848 'Marxism' was born with the Communist Manifesto of Sabbatian assets Karl Marx and Friedrich Engels. It is absolutely no coincidence that Marxism, just a different name for fascist and other centrally-controlled tyrannies, is being imposed worldwide as a result of the 'Covid' hoax and nor that Marxist/fascist China was the place where the hoax originated. The reason for this will become very clear in the chapter 'Covid: The calculated catastrophe'. The so-called 'Woke' mentality has hijacked

traditional beliefs of the political left and replaced them with far-right make-believe 'social justice' better known as Marxism. Woke will, however, be swallowed by its own perceived 'revolution' which is really the work of billionaires and billionaire corporations feigning being 'Woke'. Marxism is being touted by Wokers as a replacement for 'capitalism' when we don't have 'capitalism'. We have cartelism in which the market is stitched up by the very Cult billionaires and corporations bankrolling Woke. Billionaires love Marxism which keeps the people in servitude while they control from the top. Terminally naïve Wokers think they are 'changing the world' when it's the Cult that is doing the changing and when they have played their vital part and become surplus to requirements they, too, will be targeted. The Illuminati-Jacobins were behind the period known as 'The Terror' in the French Revolution in 1793 and 1794 when Jacobin Maximillian de Robespierre and his Orwellian 'Committee of Public Safety' killed 17,000 'enemies of the Revolution' who had once been 'friends of the Revolution'. Karl Marx (1818-1883), whose Sabbatian creed of Marxism has cost the lives of at least 100 million people, is a hero once again to Wokers who have been systematically kept ignorant of real history by their 'education' programming. As a result they now promote a Sabbatian 'Marxist' abomination destined at some point to consume them. Rabbi Antelman, who spent decades researching the Sabbatian plot, said of the League of the Just and Karl Marx:

> Contrary to popular opinion Karl Marx did not originate the Communist Manifesto. He was paid for his services by the League of the Just, which was known in its country of origin, Germany, as the Bund der Geaechteten.

Antelman said the text attributed to Marx was the work of other people and Marx 'was only repeating what others already said'. Marx was 'a hired hack – lackey of the wealthy Illuminists'. Marx famously said that religion was the 'opium of the people' (part of the Sabbatian plan to demonise religion) and Antelman called his books, *To Eliminate the Opiate*. Marx was born Jewish, but his family converted to Christianity (Sabbatian modus operandi) and he

attacked Jews, not least in his book, *A World Without Jews*. In doing so he supported the Sabbatian plan to destroy traditional Jewishness and Judaism which we are clearly seeing today with the vindictive targeting of orthodox Jews by the Sabbatian government of Israel over 'Covid' laws. I don't follow any religion and it has done much damage to the world over centuries and acted as a perceptual straightjacket. Renegade Minds, however, are always asking *why* something is being done. It doesn't matter if they agree or disagree with what is happening – *why* is it happening is the question. The 'why?' can be answered with regard to religion in that religions create interacting communities of believers when the Cult wants to dismantle all discourse, unity and interaction (see 'Covid' lockdowns) and the ultimate goal is to delete all religions for a one-world religion of Cult Satanism worshipping their 'god' of which more later. We see the same 'why?' with gun control in America. I don't have guns and don't want them, but why is the Cult seeking to disarm the population at the same time that law enforcement agencies are armed to their molars and why has every tyrant in history sought to disarm people before launching the final takeover? They include Hitler, Stalin, Pol Pot and Mao who followed confiscation with violent seizing of power. You know it's a Cult agenda by the people who immediately race to the microphones to exploit dead people in multiple shootings. Ultra-Zionist Cult lackey Senator Chuck Schumer was straight on the case after ten people were killed in Boulder, Colorado in March, 2121. Simple rule … if Schumer wants it the Cult wants it and the same with his ultra-Zionist mate the wild-eyed Senator Adam Schiff. At the same time they were calling for the disarmament of Americans, many of whom live a long way from a police response, Schumer, Schiff and the rest of these pampered clowns were sitting on Capitol Hill behind a razor-wired security fence protected by thousands of armed troops in addition to their own armed bodyguards. Mom and pop in an isolated home? They're just potential mass shooters.

Zion Mainframe

Sabbatian-Frankists and most importantly the Rothschilds were behind the creation of 'Zionism', a political movement that demanded a Jewish homeland in Israel as promised by Sabbatai Zevi. The very symbol of Israel comes from the German meaning of the name Rothschild. Dynasty founder Mayer Amschel Rothschild changed the family name from Bauer to Rothschild, or 'Red-Shield' in German, in deference to the six-pointed 'Star of David' hexagram displayed on the family's home in Frankfurt. The symbol later appeared on the flag of Israel after the Rothschilds were centrally involved in its creation. Hexagrams are not a uniquely Jewish symbol and are widely used in occult ('hidden') networks often as a symbol for Saturn (see my other books for why). Neither are Zionism and Jewishness interchangeable. Zionism is a political movement and philosophy and not a 'race' or a people. Many Jews oppose Zionism and many non-Jews, including US President Joe Biden, call themselves Zionists as does Israel-centric Donald Trump. America's support for the Israel government is pretty much a gimme with ultra-Zionist billionaires and corporations providing fantastic and dominant funding for both political parties. Former Congresswoman Cynthia McKinney has told how she was approached immediately she ran for office to 'sign the pledge' to Israel and confirm that she would always vote in that country's best interests. All American politicians are approached in this way. Anyone who refuses will get no support or funding from the enormous and all-powerful Zionist lobby that includes organisations like mega-lobby group AIPAC, the American Israel Public Affairs Committee. Trump's biggest funder was ultra-Zionist casino and media billionaire Sheldon Adelson while major funders of the Democratic Party include ultra-Zionist George Soros and ultra-Zionist financial and media mogul, Haim Saban. Some may reel back at the suggestion that Soros is an Israel-firster (Sabbatian-controlled Israel-firster), but Renegade Minds watch the actions not the words and everywhere Soros donates his billions the Sabbatian agenda benefits. In the spirit of Sabbatian inversion Soros pledged $1 billion for a new university network to promote 'liberal values and tackle intolerance'. He made the announcement during his annual speech

at the Cult-owned World Economic Forum in Davos, Switzerland, in January, 2020, after his 'harsh criticism' of 'authoritarian rulers' around the world. You can only laugh at such brazen mendacity. How *he* doesn't laugh is the mystery. Translated from the Orwellian 'liberal values and tackle intolerance' means teaching non-white people to hate white people and for white people to loathe themselves for being born white. The reason for that will become clear.

The 'Anti-Semitism' fraud

Zionists support the Jewish homeland in the land of Palestine which has been the Sabbatian-Rothschild goal for so long, but not for the benefit of Jews. Sabbatians and their global Anti-Semitism Industry have skewed public and political opinion to equate opposing the violent extremes of Zionism to be a blanket attack and condemnation of all Jewish people. Sabbatians and their global Anti-Semitism Industry have skewed public and political opinion to equate opposing the violent extremes of Zionism to be a blanket attack and condemnation of all Jewish people. This is nothing more than a Sabbatian protection racket to stop legitimate investigation and exposure of their agendas and activities. The official definition of 'anti-Semitism' has more recently been expanded to include criticism of Zionism – a *political movement* – and this was done to further stop exposure of Sabbatian infiltrators who created Zionism as we know it today in the 19th century. Renegade Minds will talk about these subjects when they know the shit that will come their way. People must decide if they want to know the truth or just cower in the corner in fear of what others will say. Sabbatians have been trying to label me as 'anti-Semitic' since the 1990s as I have uncovered more and more about their background and agendas. Useless, gutless, fraudulent 'journalists' then just repeat the smears without question and on the day I was writing this section a pair of unquestioning repeaters called Ben Quinn and Archie Bland (how appropriate) outright called me an 'anti-Semite' in the establishment propaganda sheet, the London *Guardian*, with no supporting evidence. The

Sabbatian Anti-Semitism Industry said so and who are they to question that? They wouldn't dare. Ironically 'Semitic' refers to a group of languages in the Middle East that are almost entirely Arabic. 'Anti-Semitism' becomes 'anti-Arab' which if the consequences of this misunderstanding were not so grave would be hilarious. Don't bother telling Quinn and Bland. I don't want to confuse them, bless 'em. One reason I am dubbed 'anti-Semitic' is that I wrote in the 1990s that Jewish operatives (Sabbatians) were heavily involved in the Russian Revolution when Sabbatians overthrew the Romanov dynasty. This apparently made me 'anti-Semitic'. Oh, really? Here is a section from *The Trigger*:

British journalist Robert Wilton confirmed these themes in his 1920 book *The Last Days of the Romanovs* when he studied official documents from the Russian government to identify the members of the Bolshevik ruling elite between 1917 and 1919. The Central Committee included 41 Jews among 62 members; the Council of the People's Commissars had 17 Jews out of 22 members; and 458 of the 556 most important Bolshevik positions between 1918 and 1919 were occupied by Jewish people. Only 17 were Russian. Then there were the 23 Jews among the 36 members of the vicious Cheka Soviet secret police established in 1917 who would soon appear all across the country.

Professor Robert Service of Oxford University, an expert on 20th century Russian history, found evidence that ['Jewish'] Leon Trotsky had sought to make sure that Jews were enrolled in the Red Army and were disproportionately represented in the Soviet civil bureaucracy that included the Cheka which performed mass arrests, imprisonment and executions of 'enemies of the people'. A US State Department Decimal File (861.00/5339) dated November 13th, 1918, names [Rothschild banking agent in America] Jacob Schiff and a list of ultra-Zionists as funders of the Russian Revolution leading to claims of a 'Jewish plot', but the key point missed by all is they were not 'Jews' – they were Sabbatian-Frankists.

Britain's Winston Churchill made the same error by mistake or otherwise. He wrote in a 1920 edition of the *Illustrated Sunday Herald* that those behind the Russian revolution were part of a 'worldwide conspiracy for the overthrow of civilisation and for the reconstitution of society on the basis of arrested development, of envious malevolence, and impossible equality' (see 'Woke' today because that has been created by the same network). Churchill said there was no need to exaggerate the part played in the creation of Bolshevism and in the actual bringing about of the Russian

Revolution 'by these international and for the most part atheistical Jews' ['atheistical Jews' = Sabbatians]. Churchill said it is certainly a very great one and probably outweighs all others: 'With the notable exception of Lenin, the majority of the leading figures are Jews.' He went on to describe, knowingly or not, the Sabbatian modus operandi of placing puppet leaders nominally in power while they control from the background:

> Moreover, the principal inspiration and driving power comes from the Jewish leaders. Thus Tchitcherin, a pure Russian, is eclipsed by his nominal subordinate, Litvinoff, and the influence of Russians like Bukharin or Lunacharski cannot be compared with the power of Trotsky, or of Zinovieff, the Dictator of the Red Citadel (Petrograd), or of Krassin or Radek – all Jews. In the Soviet institutions the predominance of Jews is even more astonishing. And the prominent, if not indeed the principal, part in the system of terrorism applied by the Extraordinary Commissions for Combatting Counter-Revolution has been taken by Jews, and in some notable cases by Jewesses.

What I said about seriously disproportionate involvement in the Russian Revolution by Jewish 'revolutionaries' (Sabbatians) is provable fact, but truth is no defence against the Sabbatian Anti-Semitism Industry, its repeater parrots like Quinn and Bland, and the now breathtaking network of so-called 'Woke' 'anti-hate' groups with interlocking leaderships and funding which have the role of discrediting and silencing anyone who gets too close to exposing the Sabbatians. We have seen 'truth is no defence' confirmed in legal judgements with the Saskatchewan Human Rights Commission in Canada decreeing this: 'Truthful statements can be presented in a manner that would meet the definition of hate speech, and not all truthful statements must be free from restriction.' Most 'anti-hate' activists, who are themselves consumed by hatred, are too stupid and ignorant of the world to know how they are being used. They are far too far up their own virtue-signalling arses and it's far too dark for them to see anything.

The 'revolution' game

The background and methods of the 'Russian' Revolution are straight from the Sabbatian playbook seen in the French Revolution

and endless others around the world that appear to start as a revolution of the people against tyrannical rule and end up with a regime change to more tyrannical rule overtly or covertly. Wars, terror attacks and regime overthrows follow the Sabbatian cult through history with its agents creating them as Problem-Reaction-Solutions to remove opposition on the road to world domination. Sabbatian dots connect the Rothschilds with the Illuminati, Jacobins of the French Revolution, the 'Bund' or League of the Just, the International Communist Party, Communist League and the Communist Manifesto of Karl Marx and Friedrich Engels that would lead to the Rothschild-funded Russian Revolution. The sequence comes under the heading of 'creative destruction' when you advance to your global goal by continually destroying the status quo to install a new status quo which you then also destroy. The two world wars come to mind. With each new status quo you move closer to your planned outcome. Wars and mass murder are to Sabbatians a collective blood sacrifice ritual. They are obsessed with death for many reasons and one is that death is an inversion of life. Satanists and Sabbatians are obsessed with death and often target churches and churchyards for their rituals. Inversion-obsessed Sabbatians explain the use of inverted symbolism including the *inverted* pentagram and *inverted* cross. The inversion of the cross has been related to targeting Christianity, but the cross was a religious symbol long before Christianity and its inversion is a statement about the Sabbatian mentality and goals more than any single religion.

Sabbatians operating in Germany were behind the rise of the occult-obsessed Nazis and the subsequent Jewish exodus from Germany and Europe to Palestine and the United States after World War Two. The Rothschild dynasty was at the forefront of this both as political manipulators and by funding the operation. Why would Sabbatians help to orchestrate the horrors inflicted on Jews by the Nazis and by Stalin after they organised the Russian Revolution? Sabbatians hate Jews and their religion, that's why. They pose as Jews and secure positions of control within Jewish society and play the 'anti-Semitism' card to protect themselves from exposure

through a global network of organisations answering to the Sabbatian-created-and-controlled globe-spanning intelligence network that involves a stunning web of military-intelligence operatives and operations for a tiny country of just nine million. Among them are Jewish assets who are not Sabbatians but have been convinced by them that what they are doing is for the good of Israel and the Jewish community to protect them from what they have been programmed since childhood to believe is a Jew-hating hostile world. The Jewish community is just a highly convenient cover to hide the true nature of Sabbatians. Anyone getting close to exposing their game is accused by Sabbatian place-people and gofers of 'anti-Semitism' and claiming that all Jews are part of a plot to take over the world. I am not saying that. I am saying that Sabbatians – the *real* Jew-haters – have infiltrated the Jewish community to use them both as a cover and an 'anti-Semitic' defence against exposure. Thus we have the Anti-Semitism Industry targeted researchers in this way and most Jewish people think this is justified and genuine. They don't know that their 'Jewish' leaders and institutions of state, intelligence and military are not controlled by Jews at all, but cultists and stooges of Sabbatian-Frankism. I once added my name to a pro-Jewish freedom petition online and the next time I looked my name was gone and text had been added to the petition blurb to attack me as an 'anti-Semite' such is the scale of perceptual programming.

Moving on America

I tell the story in *The Trigger* and a chapter called 'Atlantic Crossing' how particularly after Israel was established the Sabbatians moved in on the United States and eventually grasped control of government administration, the political system via both Democrats and Republicans, the intelligence community like the CIA and National Security Agency (NSA), the Pentagon and mass media. Through this seriously compartmentalised network Sabbatians and their operatives in Mossad, Israeli Defense Forces (IDF) and US agencies pulled off 9/11 and blamed it on 19 'Al-Qaeda hijackers' dominated by men from, or connected to, Sabbatian-ruled Saudi

Arabia. The '19' were not even on the planes let alone flew those big passenger jets into buildings while being largely incompetent at piloting one-engine light aircraft. 'Hijacker' Hani Hanjour who is said to have flown American Airlines Flight 77 into the Pentagon with a turn and manoeuvre most professional pilots said they would have struggled to do was banned from renting a small plane by instructors at the Freeway Airport in Bowie, Maryland, just *six weeks* earlier on the grounds that he was an incompetent pilot. The Jewish population of the world is just 0.2 percent with even that almost entirely concentrated in Israel (75 percent Jewish) and the United States (around two percent). This two percent and globally 0.2 percent refers to *Jewish* people and not Sabbatian interlopers who are a fraction of that fraction. What a sobering thought when you think of the fantastic influence on world affairs of tiny Israel and that the Project for the New America Century (PNAC) which laid out the blueprint in September, 2000, for America's war on terror and regime change wars in Iraq, Libya and Syria was founded and dominated by Sabbatians known as 'Neocons'. The document conceded that this plan would not be supported politically or publicly without a major attack on American soil and a Problem-Reaction-Solution excuse to send troops to war across the Middle East. Sabbatian Neocons said:

> ... [The] process of transformation ... [war and regime change] ... is likely to be a long one, absent some catastrophic and catalysing event – like a new Pearl Harbor.

Four months later many of those who produced that document came to power with their inane puppet George Bush from the long-time Sabbatian Bush family. They included Sabbatian Dick Cheney who was officially vice-president, but really de-facto president for the entirety of the 'Bush' government. Nine months after the 'Bush' inauguration came what Bush called at the time 'the Pearl Harbor of the 21st century' and with typical Sabbatian timing and symbolism 2001 was the 60th anniversary of the attack in 1941 by the Japanese Air Force on Pearl Harbor, Hawaii, which allowed President Franklin Delano Roosevelt to take the United States into a Sabbatian-

instigated Second World War that he said in his election campaign that he never would. The evidence is overwhelming that Roosevelt and his military and intelligence networks knew the attack was coming and did nothing to stop it, but they did make sure that America's most essential naval ships were not in Hawaii at the time. Three thousand Americans died in the Pearl Harbor attacks as they did on September 11th. By the 9/11 year of 2001 Sabbatians had widely infiltrated the US government, military and intelligence operations and used their compartmentalised assets to pull off the 'Al-Qaeda' attacks. If you read *The Trigger* it will blow your mind to see the utterly staggering concentration of 'Jewish' operatives (Sabbatian infiltrators) in essential positions of political, security, legal, law enforcement, financial and business power before, during, and after the attacks to make them happen, carry them out, and then cover their tracks – and I do mean *staggering* when you think of that 0.2 percent of the world population and two percent of Americans which are Jewish while Sabbatian infiltrators are a fraction of that. A central foundation of the 9/11 conspiracy was the hijacking of government, military, Air Force and intelligence computer systems in real time through 'back-door' access made possible by Israeli (Sabbatian) 'cyber security' software. Sabbatian-controlled Israel is on the way to rivalling Silicon Valley for domination of cyberspace and is becoming the dominant force in cyber-security which gives them access to entire computer systems and their passcodes across the world. Then add to this that Zionists head (officially) Silicon Valley giants like Google (Larry Page and Sergey Brin), Google-owned YouTube (Susan Wojcicki), Facebook (Mark Zuckerberg and Sheryl Sandberg), and Apple (Chairman Arthur D. Levinson), and that ultra-Zionist hedge fund billionaire Paul Singer has a $1 billion stake in Twitter which is only nominally headed by 'CEO' pothead Jack Dorsey. As cable news host Tucker Carlson said of Dorsey: 'There used to be debate in the medical community whether dropping a ton of acid had permanent effects and I think that debate has now ended.' Carlson made the comment after Dorsey told a hearing on Capitol Hill (if you cut through his bullshit) that he

believed in free speech so long as he got to decide what you can hear and see. These 'big names' of Silicon Valley are only front men and women for the Global Cult, not least the Sabbatians, who are the true controllers of these corporations. Does anyone still wonder why these same people and companies have been ferociously censoring and banning people (like me) for exposing any aspect of the Cult agenda and especially the truth about the 'Covid' hoax which Sabbatians have orchestrated?

The Jeffrey Epstein paedophile ring was a Sabbatian operation. He was officially 'Jewish' but he was a Sabbatian and women abused by the ring have told me about the high number of 'Jewish' people involved. The Epstein horror has Sabbatian written all over it and matches perfectly their modus operandi and obsession with sex and ritual. Epstein was running a Sabbatian blackmail ring in which famous people with political and other influence were provided with young girls for sex while everything was being filmed and recorded on hidden cameras and microphones at his New York house, Caribbean island and other properties. Epstein survivors have described this surveillance system to me and some have gone public. Once the famous politician or other figure knew he or she was on video they tended to do whatever they were told. Here we go again …when you've got them by the balls their hearts and minds will follow. Sabbatians use this blackmail technique on a wide scale across the world to entrap politicians and others they need to act as demanded. Epstein's private plane, the infamous 'Lolita Express', had many well-known passengers including Bill Clinton while Bill Gates has flown on an Epstein plane and met with him four years after Epstein had been jailed for paedophilia. They subsequently met many times at Epstein's home in New York according to a witness who was there. Epstein's infamous side-kick was Ghislaine Maxwell, daughter of Mossad agent and ultra-Zionist mega-crooked British businessman, Bob Maxwell, who at one time owned the *Daily Mirror* newspaper. Maxwell was murdered at sea on his boat in 1991 by Sabbatian-controlled Mossad when he became a liability with his

business empire collapsing as a former Mossad operative has confirmed (see *The Trigger*).

Money, money, money, funny money …

Before I come to the Sabbatian connection with the last three US presidents I will lay out the crucial importance to Sabbatians of controlling banking and finance. Sabbatian Mayer Amschel Rothschild set out to dominate this arena in his family's quest for total global control. What is freedom? It is, in effect, choice. The more choices you have the freer you are and the fewer your choices the more you are enslaved. In the global structure created over centuries by Sabbatians the biggest decider and restrictor of choice is … money. Across the world if you ask people what they would like to do with their lives and why they are not doing that they will reply 'I don't have the money'. This is the idea. A global elite of multi-billionaires are described as 'greedy' and that is true on one level; but control of money – who has it and who doesn't – is not primarily about greed. It's about control. Sabbatians have seized ever more control of finance and sucked the wealth of the world out of the hands of the population. We talk now, after all, about the 'One-percent' and even then the wealthiest are a lot fewer even than that. This has been made possible by a money scam so outrageous and so vast it could rightly be called the scam of scams founded on creating 'money' out of nothing and 'loaning' that with interest to the population. Money out of nothing is called 'credit'. Sabbatians have asserted control over governments and banking ever more completely through the centuries and secured financial laws that allow banks to lend hugely more than they have on deposit in a confidence trick known as fractional reserve lending. Imagine if you could lend money that doesn't exist and charge the recipient interest for doing so. You would end up in jail. Bankers by contrast end up in mansions, private jets, Malibu and Monaco.

Banks are only required to keep a fraction of their deposits and wealth in their vaults and they are allowed to lend 'money' they don't have called 'credit. Go into a bank for a loan and if you succeed

the banker will not move any real wealth into your account. They will type into your account the amount of the agreed 'loan' – say £100,000. This is not wealth that really exists; it is non-existent, fresh-air, created-out-of-nothing 'credit' which has never, does not, and will never exist except in theory. Credit is backed by nothing except wind and only has buying power because people think that it has buying power and accept it in return for property, goods and services. I have described this situation as like those cartoon characters you see chasing each other and when they run over the edge of a cliff they keep running forward on fresh air until one of them looks down, realises what's happened, and they all crash into the ravine. The whole foundation of the Sabbatian financial system is to stop people looking down except for periodic moments when they want to crash the system (as in 2008 and 2020 ongoing) and reap the rewards from all the property, businesses and wealth their borrowers had signed over as 'collateral' in return for a 'loan' of fresh air. Most people think that money is somehow created by governments when it comes into existence from the start as a debt through banks 'lending' illusory money called credit. Yes, the very currency of exchange is a *debt* from day one issued as an interest-bearing loan. Why don't governments create money interest-free and lend it to their people interest-free? Governments are controlled by Sabbatians and the financial system is controlled by Sabbatians for whom interest-free money would be a nightmare come true. Sabbatians underpin their financial domination through their global network of central banks, including the privately-owned US Federal Reserve and Britain's Bank of England, and this is orchestrated by a privately-owned central bank coordination body called the Bank for International Settlements in Basle, Switzerland, created by the usual suspects including the Rockefellers and Rothschilds. Central bank chiefs don't answer to governments or the people. They answer to the Bank for International Settlements or, in other words, the Global Cult which is dominated today by Sabbatians.

Built-in disaster

There are so many constituent scams within the overall banking scam. When you take out a loan of thin-air credit only the amount of that loan is theoretically brought into circulation to add to the amount in circulation; but you are paying back the principle plus interest. The additional interest is not created and this means that with every 'loan' there is a shortfall in the money in circulation between what is borrowed and what has to be paid back. There is never even close to enough money in circulation to repay all outstanding public and private debt including interest. Coldly weaved in the very fabric of the system is the certainty that some will lose their homes, businesses and possessions to the banking 'lender'. This is less obvious in times of 'boom' when the amount of money in circulation (and the debt) is expanding through more people wanting and getting loans. When a downturn comes and the money supply contracts it becomes painfully obvious that there is not enough money to service all debt and interest. This is less obvious in times of 'boom' when the amount of money in circulation (and the debt) is expanding through more people wanting and getting loans. When a downturn comes and the money supply contracts and it becomes painfully obvious – as in 2008 and currently – that there is not enough money to service all debt and interest. Sabbatian banksters have been leading the human population through a calculated series of booms (more debt incurred) and busts (when the debt can't be repaid and the banks get the debtor's tangible wealth in exchange for non-existent 'credit'). With each 'bust' Sabbatian bankers have absorbed more of the world's tangible wealth and we end up with the One-percent. Governments are in bankruptcy levels of debt to the same system and are therefore owned by a system they do not control. The Federal Reserve, 'America's central bank', is privately-owned and American presidents only nominally appoint its chairman or woman to maintain the illusion that it's an arm of government. It's not. The 'Fed' is a cartel of private banks which handed billions to its associates and friends after the crash of 2008 and has been Sabbatian-controlled since it was manipulated into being in 1913 through the covert trickery of Rothschild banking agents Jacob Schiff and Paul

Warburg, and the Sabbatian Rockefeller family. Somehow from a Jewish population of two-percent and globally 0.2 percent (Sabbatian interlopers remember are far smaller) ultra-Zionists headed the Federal Reserve for 31 years between 1987 and 2018 in the form of Alan Greenspan, Bernard Bernanke and Janet Yellen (now Biden's Treasury Secretary) with Yellen's deputy chairman a Israeli-American duel citizen and ultra-Zionist Stanley Fischer, a former governor of the Bank of Israel. Ultra-Zionist Fed chiefs spanned the presidencies of Ronald Reagan ('Republican'), Father George Bush ('Republican'), Bill Clinton ('Democrat'), Boy George Bush ('Republican') and Barack Obama ('Democrat'). We should really add the pre-Greenspan chairman, Paul Adolph Volcker, 'appointed' by Jimmy Carter ('Democrat') who ran the Fed between 1979 and 1987 during the Carter and Reagan administrations before Greenspan took over. Volcker was a long-time associate and business partner of the Rothschilds. No matter what the 'party' officially in power the United States economy was directed by the same force. Here are members of the Obama, Trump and Biden administrations and see if you can make out a common theme.

Barack Obama ('Democrat')

Ultra-Zionists Robert Rubin, Larry Summers, and Timothy Geithner ran the US Treasury in the Clinton administration and two of them reappeared with Obama. Ultra-Zionist Fed chairman Alan Greenspan had manipulated the crash of 2008 through deregulation and jumped ship just before the disaster to make way for ultra-Zionist Bernard Bernanke to hand out trillions to Sabbatian 'too big to fail' banks and businesses, including the ubiquitous ultra-Zionist Goldman Sachs which has an ongoing staff revolving door operation between itself and major financial positions in government worldwide. Obama inherited the fallout of the crash when he took office in January, 2009, and fortunately he had the support of his ultra-Zionist White House Chief of Staff Rahm Emmanuel, son of a terrorist who helped to bomb Israel into being in 1948, and his ultra-Zionist senior adviser David Axelrod, chief strategist in Obama's two

successful presidential campaigns. Emmanuel, later mayor of Chicago and former senior fundraiser and strategist for Bill Clinton, is an example of the Sabbatian policy after Israel was established of migrating insider families to America so their children would be born American citizens. 'Obama' chose this financial team throughout his administration to respond to the Sabbatian-instigated crisis:

Timothy Geithner (ultra-Zionist) Treasury Secretary; Jacob J. Lew, Treasury Secretary; Larry Summers (ultra-Zionist), director of the White House National Economic Council; Paul Adolph Volcker (Rothschild business partner), chairman of the Economic Recovery Advisory Board; Peter Orszag (ultra-Zionist), director of the Office of Management and Budget overseeing all government spending; Penny Pritzker (ultra-Zionist), Commerce Secretary; Jared Bernstein (ultra-Zionist), chief economist and economic policy adviser to Vice President Joe Biden; Mary Schapiro (ultra-Zionist), chair of the Securities and Exchange Commission (SEC); Gary Gensler (ultra-Zionist), chairman of the Commodity Futures Trading Commission (CFTC); Sheila Bair (ultra-Zionist), chair of the Federal Deposit Insurance Corporation (FDIC); Karen Mills (ultra-Zionist), head of the Small Business Administration (SBA); Kenneth Feinberg (ultra-Zionist), Special Master for Executive [bail-out] Compensation. Feinberg would be appointed to oversee compensation (with strings) to 9/11 victims and families in a campaign to stop them having their day in court to question the official story. At the same time ultra-Zionist Bernard Bernanke was chairman of the Federal Reserve and these are only some of the ultra-Zionists with allegiance to Sabbatian-controlled Israel in the Obama government. Obama's biggest corporate donor was ultra-Zionist Goldman Sachs which had employed many in his administration.

Donald Trump ('Republican')

Trump claimed to be an outsider (he wasn't) who had come to 'drain the swamp'. He embarked on this goal by immediately appointing ultra-Zionist Steve Mnuchin, a Goldman Sachs employee for 17

years, as his Treasury Secretary. Others included Gary Cohn (ultra-Zionist), chief operating officer of Goldman Sachs, his first Director of the National Economic Council and chief economic adviser, who was later replaced by Larry Kudlow (ultra-Zionist). Trump's senior adviser throughout his four years in the White House was his sinister son-in-law Jared Kushner, a life-long friend of Israel Prime Minister Benjamin Netanyahu. Kushner is the son of a convicted crook who was pardoned by Trump in his last days in office. Other ultra-Zionists in the Trump administration included: Stephen Miller, Senior Policy Adviser; Avrahm Berkowitz, Deputy Adviser to Trump and his Senior Adviser Jared Kushner; Ivanka Trump, Adviser to the President, who converted to Judaism when she married Jared Kushner; David Friedman, Trump lawyer and Ambassador to Israel; Jason Greenblatt, Trump Organization executive vice president and chief legal officer, who was made Special Representative for International Negotiations and the Israeli-Palestinian Conflict; Rod Rosenstein, Deputy Attorney General; Elliot Abrams, Special Representative for Venezuela, then Iran; John Eisenberg, National Security Council Legal Adviser and Deputy Council to the President for National Security Affairs; Anne Neuberger, Deputy National Manager, National Security Agency; Ezra Cohen-Watnick, Acting Under Secretary of Defense for Intelligence; Elan Carr, Special Envoy to monitor and combat anti-Semitism; Len Khodorkovsky, Deputy Special Envoy to monitor and combat anti-Semitism; Reed Cordish, Assistant to the President, Intragovernmental and Technology Initiatives. Trump Vice President Mike Pence and Secretary of State Mike Pompeo, both Christian Zionists, were also vehement supporters of Israel and its goals and ambitions.

Donald 'free-speech believer' Trump pardoned a number of financial and violent criminals while ignoring calls to pardon Julian Assange and Edward Snowden whose crimes are revealing highly relevant information about government manipulation and corruption and the widespread illegal surveillance of the American people by US 'security' agencies. It's so good to know that Trump is on the side of freedom and justice and not mega-criminals with

allegiance to Sabbatian-controlled Israel. These included a pardon for Israeli spy Jonathan Pollard who was jailed for life in 1987 under the Espionage Act. Aviem Sella, the Mossad agent who recruited Pollard, was also pardoned by Trump while Assange sat in jail and Snowden remained in exile in Russia. Sella had 'fled' (was helped to escape) to Israel in 1987 and was never extradited despite being charged under the Espionage Act. A Trump White House statement said that Sella's clemency had been 'supported by Benjamin Netanyahu, Ron Dermer, Israel's US Ambassador, David Friedman, US Ambassador to Israel and Miriam Adelson, wife of leading Trump donor Sheldon Adelson who died shortly before. Other friends of Jared Kushner were pardoned along with Sholom Weiss who was believed to be serving the longest-ever white-collar prison sentence of more than 800 years in 2000. The sentence was commuted of Ponzi-schemer Eliyahu Weinstein who defrauded Jews and others out of $200 million. I did mention that Assange and Snowden were ignored, right? Trump gave Sabbatians almost everything they asked for in military and political support, moving the US Embassy from Tel Aviv to Jerusalem with its critical symbolic and literal implications for Palestinian statehood, and the 'deal of the Century' designed by Jared Kushner and David Friedman which gave the Sabbatian Israeli government the green light to substantially expand its already widespread program of building illegal Jewish-only settlements in the occupied land of the West Bank. This made a two-state 'solution' impossible by seizing all the land of a potential Palestinian homeland and that had been the plan since 1948 and then 1967 when the Arab-controlled Gaza Strip, West Bank, Sinai Peninsula and Syrian Golan Heights were occupied by Israel. All the talks about talks and road maps and delays have been buying time until the West Bank was physically occupied by Israeli real estate. Trump would have to be a monumentally ill-informed idiot not to see that this was the plan he was helping to complete. The Trump administration was in so many ways the Kushner administration which means the Netanyahu administration which means the Sabbatian administration. I understand why many opposing Cult fascism in all its forms gravitated to Trump, but he

was a crucial part of the Sabbatian plan and I will deal with this in the next chapter.

Joe Biden ('Democrat')

A barely cognitive Joe Biden took over the presidency in January, 2021, along with his fellow empty shell, Vice-President Kamala Harris, as the latest Sabbatian gofers to enter the White House. Names on the door may have changed and the 'party' – the force behind them remained the same as Zionists were appointed to a stream of pivotal areas relating to Sabbatian plans and policy. They included: Janet Yellen, Treasury Secretary, former head of the Federal Reserve, and still another ultra-Zionist running the US Treasury after Mnuchin (Trump), Lew and Geithner (Obama), and Summers and Rubin (Clinton); Anthony Blinken, Secretary of State; Wendy Sherman, Deputy Secretary of State (so that's 'Biden's' Sabbatian foreign policy sorted); Jeff Zients, White House coronavirus coordinator; Rochelle Walensky, head of the Centers for Disease Control; Rachel Levine, transgender deputy health secretary (that's 'Covid' hoax policy under control); Merrick Garland, Attorney General; Alejandro Mayorkas, Secretary of Homeland Security; Cass Sunstein, Homeland Security with responsibility for new immigration laws; Avril Haines, Director of National Intelligence; Anne Neuberger, National Security Agency cybersecurity director (note, cybersecurity); David Cohen, CIA Deputy Director; Ronald Klain, Biden's Chief of Staff (see Rahm Emanuel); Eric Lander, a 'leading geneticist', Office of Science and Technology Policy director (see Smart Grid, synthetic biology agenda); Jessica Rosenworcel, acting head of the Federal Communications Commission (FCC) which controls Smart Grid technology policy and electromagnetic communication systems including 5G. How can it be that so many pivotal positions are held by two-percent of the American population and 0.2 percent of the world population administration after administration no matter who is the president and what is the party? It's a coincidence? Of course it's not and this is why Sabbatians have built their colossal global web of interlocking 'anti-

hate' hate groups to condemn anyone who asks these glaring questions as an 'anti-Semite'. The way that Jewish people horrifically abused in Sabbatian-backed Nazi Germany are exploited to this end is stomach-turning and disgusting beyond words.

Political fusion

Sabbatian manipulation has reversed the roles of Republicans and Democrats and the same has happened in Britain with the Conservative and Labour Parties. Republicans and Conservatives were always labelled the 'right' and Democrats and Labour the 'left', but look at the policy positions now and the Democrat-Labour 'left' has moved further to the 'right' than Republicans and Conservatives under the banner of 'Woke', the Cult-created far-right tyranny. Where once the Democrat-Labour 'left' defended free speech and human rights they now seek to delete them and as I said earlier despite the 'Covid' fascism of the Jackboot Johnson Conservative government in the UK the Labour Party of leader Keir Starmer demanded even more extreme measures. The Labour Party has been very publicly absorbed by Sabbatians after a political and media onslaught against the previous leader, the weak and inept Jeremy Corbyn, over made-up allegations of 'anti-Semitism' both by him and his party. The plan was clear with this 'anti-Semite' propaganda and what was required in response was a swift and decisive 'fuck off' from Corbyn and a statement to expose the Anti-Semitism Industry (Sabbatian) attempt to silence Labour criticism of the Israeli government (Sabbatians) and purge the party of all dissent against the extremes of ultra-Zionism (Sabbatians). Instead Corbyn and his party fell to their knees and appeased the abusers which, by definition, is impossible. Appeasing one demand leads only to a new demand to be appeased until takeover is complete. Like I say – 'fuck off' would have been a much more effective policy and I have used it myself with great effect over the years when Sabbatians are on my case which is most of the time. I consider that fact a great compliment, by the way. The outcome of the Labour Party capitulation is that we now have a Sabbatian-controlled

Conservative Party 'opposed' by a Sabbatian-controlled Labour Party in a one-party Sabbatian state that hurtles towards the extremes of tyranny (the Sabbatian cult agenda). In America the situation is the same. Labour's Keir Starmer spends his days on his knees with his tongue out pointing to Tel Aviv, or I guess now Jerusalem, while Boris Johnson has an 'anti-Semitism czar' in the form of former Labour MP John Mann who keeps Starmer company on his prayer mat.

Sabbatian influence can be seen in Jewish members of the Labour Party who have been ejected for criticism of Israel including those from families that suffered in Nazi Germany. Sabbatians despise real Jewish people and target them even more harshly because it is so much more difficult to dub them 'anti-Semitic' although in their desperation they do try.

CHAPTER THREE

The Pushbacker sting

Until you realize how easy it is for your mind to be manipulated, you remain the puppet of someone else's game
Evita Ochel

I will use the presidencies of Trump and Biden to show how the manipulation of the one-party state plays out behind the illusion of political choice across the world. No two presidencies could – on the face of it – be more different and apparently at odds in terms of direction and policy.

A Renegade Mind sees beyond the obvious and focuses on outcomes and consequences and not image, words and waffle. The Cult embarked on a campaign to divide America between those who blindly support its agenda (the mentality known as 'Woke') and those who are pushing back on where the Cult and its Sabbatians want to go. This presents infinite possibilities for dividing and ruling the population by setting them at war with each other and allows a perceptual ring fence of demonisation to encircle the Pushbackers in a modern version of the Little Big Horn in 1876 when American cavalry led by Lieutenant Colonel George Custer were drawn into a trap, surrounded and killed by Native American tribes defending their land of thousands of years from being seized by the government. In this modern version the roles are reversed and it's those defending themselves from the Sabbatian government who are surrounded and the government that's seeking to destroy them. This trap was set years ago and to explain how we must return to 2016

and the emergence of Donald Trump as a candidate to be President of the United States. He set out to overcome the best part of 20 other candidates in the Republican Party before and during the primaries and was not considered by many in those early stages to have a prayer of living in the White House. The Republican Party was said to have great reservations about Trump and yet somehow he won the nomination. When you know how American politics works – politics in general – there is no way that Trump could have become the party's candidate unless the Sabbatian-controlled 'Neocons' that run the Republican Party wanted that to happen. We saw the proof in emails and documents made public by WikiLeaks that the Democratic Party hierarchy, or Democons, systematically undermined the campaign of Bernie Sanders to make sure that Sabbatian gofer Hillary Clinton won the nomination to be their presidential candidate. If the Democons could do that then the Neocons in the Republican Party could have derailed Trump in the same way. But they didn't and at that stage I began to conclude that Trump could well be the one chosen to be president. If that was the case the 'why' was pretty clear to see – the goal of dividing America between Cult agenda-supporting Wokers and Pushbackers who gravitated to Trump because he was telling them what they wanted to hear. His constituency of support had been increasingly ignored and voiceless for decades and profoundly through the eight years of Sabbatian puppet Barack Obama. Now here was someone speaking their language of pulling back from the incessant globalisation of political and economic power, the exporting of American jobs to China and elsewhere by 'American' (Sabbatian) corporations, the deletion of free speech, and the mass immigration policies that had further devastated job opportunities for the urban working class of all races and the once American heartlands of the Midwest.

Beware the forked tongue

Those people collectively sighed with relief that at last a political leader was apparently on their side, but another trait of the Renegade Mind is that you look even harder at people telling you

what you want to hear than those who are telling you otherwise. Obviously as I said earlier people wish what they want to hear to be true and genuine and they are much more likely to believe that than someone saying what they don't want to here and don't want to be true. Sales people are taught to be skilled in eliciting by calculated questioning what their customers want to hear and repeating that back to them as their own opinion to get their targets to like and trust them. Assets of the Cult are also sales people in the sense of selling perception. To read Cult manipulation you have to play the long and expanded game and not fall for the Vaudeville show of party politics. Both American parties are vehicles for the Cult and they exploit them in different ways depending on what the agenda requires at that moment. Trump and the Republicans were used to be the focus of dividing America and isolating Pushbackers to open the way for a Biden presidency to become the most extreme in American history by advancing the full-blown Woke (Cult) agenda with the aim of destroying and silencing Pushbackers now labelled Nazi Trump supporters and white supremacists.

Sabbatians wanted Trump in office for the reasons described by ultra-Zionist Saul Alinsky (1909-1972) who was promoting the Woke philosophy through 'community organising' long before anyone had heard of it. In those days it still went by its traditional name of Marxism. The reason for the manipulated Trump phenomenon was laid out in Alinsky's 1971 book, *Rules for Radicals*, which was his blueprint for overthrowing democratic and other regimes and replacing them with Sabbatian Marxism. Not surprisingly his to-do list was evident in the Sabbatian French and Russian 'Revolutions' and that in China which will become very relevant in the next chapter about the 'Covid' hoax. Among Alinsky's followers have been the deeply corrupt Barack Obama, House Speaker Nancy Pelosi and Hillary Clinton who described him as a 'hero'. All three are Sabbatian stooges with Pelosi personifying the arrogant corrupt idiocy that so widely fronts up for the Cult inner core. Predictably as a Sabbatian advocate of the 'light-bringer' Alinsky features Lucifer on the dedication page of his book as the original radical who gained

his own kingdom ('Earth' as we shall see). One of Alinsky's golden radical rules was to pick an individual and focus all attention, hatred and blame on them and not to target faceless bureaucracies and corporations. *Rules for Radicals* is really a Sabbatian handbook with its contents repeatedly employed all over the world for centuries and why wouldn't Sabbatians bring to power their designer-villain to be used as the individual on which all attention, hatred and blame was bestowed? This is what they did and the only question for me is how much Trump knew that and how much he was manipulated. A bit of both, I suspect. This was Alinsky's Trump technique from a man who died in 1972. The technique has spanned history:

Pick the target, freeze it, personalize it, polarize it. Don't try to attack abstract corporations or bureaucracies. Identify a responsible individual. Ignore attempts to shift or spread the blame.

From the moment Trump came to illusory power everything was about him. It wasn't about Republican policy or opinion, but all about Trump. Everything he did was presented in negative, derogatory and abusive terms by the Sabbatian-dominated media led by Cult operations such as CNN, MSNBC, *The New York Times* and the Jeff Bezos-owned *Washington Post* – 'Pick the target, freeze it, personalize it, polarize it.' Trump was turned into a demon to be vilified by those who hated him and a demi-god loved by those who worshipped him. This, in turn, had his supporters, too, presented as equally demonic in preparation for the punchline later down the line when Biden was about to take office. It was here's a Trump, there's a Trump, everywhere a Trump, Trump. Virtually every news story or happening was filtered through the lens of 'The Donald'. You loved him or hated him and which one you chose was said to define you as Satan's spawn or a paragon of virtue. Even supporting some Trump policies or statements and not others was enough for an assault on your character. No shades of grey were or are allowed. Everything is black and white (literally and figuratively). A Californian I knew had her head utterly scrambled by her hatred for Trump while telling people they should love each other. She was so totally consumed by

Trump Derangement Syndrome as it became to be known that this glaring contradiction would never have occurred to her. By definition anyone who criticised Trump or praised his opponents was a hero and this lady described Joe Biden as 'a kind, honest gentleman' when he's a provable liar, mega-crook and vicious piece of work to boot. Sabbatians had indeed divided America using Trump as the fall-guy and all along the clock was ticking on the consequences for his supporters.

In hock to his masters

Trump gave Sabbatians via Israel almost everything they wanted in his four years. Ask and you shall receive was the dynamic between himself and Benjamin Netanyahu orchestrated by Trump's ultra-Zionist son-in-law Jared Kushner, his ultra-Zionist Ambassador to Israel, David Friedman, and ultra-Zionist 'Israel adviser', Jason Greenblatt. The last two were central to the running and protecting from collapse of his business empire, the Trump Organisation, and colossal business failures made him forever beholding to Sabbatian networks that bailed him out. By the start of the 1990s Trump owed $4 billion to banks that he couldn't pay and almost $1billion of that was down to him personally and not his companies. This mega-disaster was the result of building two new casinos in Atlantic City and buying the enormous Taj Mahal operation which led to crippling debt payments. He had borrowed fantastic sums from 72 banks with major Sabbatian connections and although the scale of debt should have had him living in a tent alongside the highway they never foreclosed. A plan was devised to lift Trump from the mire by BT Securities Corporation and Rothschild Inc. and the case was handled by Wilber Ross who had worked for the Rothschilds for 27 years. Ross would be named US Commerce Secretary after Trump's election. Another crucial figure in saving Trump was ultra-Zionist 'investor' Carl Icahn who bought the Taj Mahal casino. Icahn was made special economic adviser on financial regulation in the Trump administration. He didn't stay long but still managed to find time to make a tidy sum of a reported $31.3 million when he sold his

holdings affected by the price of steel three days before Trump imposed a 235 percent tariff on steel imports. What amazing bits of luck these people have. Trump and Sabbatian operatives have long had a close association and his mentor and legal adviser from the early 1970s until 1986 was the dark and genetically corrupt ultra-Zionist Roy Cohn who was chief counsel to Senator Joseph McCarthy's 'communist' witch-hunt in the 1950s. *Esquire* magazine published an article about Cohn with the headline 'Don't mess with Roy Cohn'. He was described as the most feared lawyer in New York and 'a ruthless master of dirty tricks ... [with] ... more than one Mafia Don on speed dial'. Cohn's influence, contacts, support and protection made Trump a front man for Sabbatians in New York with their connections to one of Cohn's many criminal employers, the 'Russian' Sabbatian Mafia. Israel-centric media mogul Rupert Murdoch was introduced to Trump by Cohn and they started a long friendship. Cohn died in 1986 weeks after being disbarred for unethical conduct by the Appellate Division of the New York State Supreme Court. The wheels of justice do indeed run slow given the length of Cohn's crooked career.

QAnon-sense

We are asked to believe that Donald Trump with his fundamental connections to Sabbatian networks and operatives has been leading the fight to stop the Sabbatian agenda for the fascistic control of America and the world. Sure he has. A man entrapped during his years in the White House by Sabbatian operatives and whose biggest financial donor was casino billionaire Sheldon Adelson who was Sabbatian to his DNA?? Oh, do come on. Trump has been used to divide America and isolate Pushbackers on the Cult agenda under the heading of 'Trump supporters', 'insurrectionists' and 'white supremacists'. The US Intelligence/Mossad Psyop or psychological operation known as QAnon emerged during the Trump years as a central pillar in the Sabbatian campaign to lead Pushbackers into the trap set by those that wished to destroy them. I knew from the start that QAnon was a scam because I had seen the same scenario many

times before over 30 years under different names and I had written about one in particular in the books. 'Not again' was my reaction when QAnon came to the fore. The same script is pulled out every few years and a new name added to the letterhead. The story always takes the same form: 'Insiders' or 'the good guys' in the government-intelligence-military 'Deep State' apparatus were going to instigate mass arrests of the 'bad guys' which would include the Rockefellers, Rothschilds, Barack Obama, Hillary Clinton, George Soros, etc., etc. Dates are given for when the 'good guys' are going to move in, but the dates pass without incident and new dates are given which pass without incident. The central message to Pushbackers in each case is that they don't have to do anything because there is 'a plan' and it is all going to be sorted by the 'good guys' on the inside. 'Trust the plan' was a QAnon mantra when the only plan was to misdirect Pushbackers into putting their trust in a Psyop they believed to be real. Beware, beware, those who tell you what you want to hear and always check it out. Right up to Biden's inauguration QAnon was still claiming that 'the Storm' was coming and Trump would stay on as president when Biden and his cronies were arrested and jailed. It was never going to happen and of course it didn't, but what did happen as a result provided that punchline to the Sabbatian Trump/QAnon Psyop.

On January 6th, 2021, a very big crowd of Trump supporters gathered in the National Mall in Washington DC down from the Capitol Building to protest at what they believed to be widespread corruption and vote fraud that stopped Trump being re-elected for a second term as president in November, 2020. I say as someone that does not support Trump or Biden that the evidence is clear that major vote-fixing went on to favour Biden, a man with cognitive problems so advanced he can often hardly string a sentence together without reading the words written for him on the Teleprompter. Glaring ballot discrepancies included serious questions about electronic voting machines that make vote rigging a comparative cinch and hundreds of thousands of paper votes that suddenly appeared during already advanced vote counts and virtually all of

them for Biden. Early Trump leads in crucial swing states suddenly began to close and disappear. The pandemic hoax was used as the excuse to issue almost limitless numbers of mail-in ballots with no checks to establish that the recipients were still alive or lived at that address. They were sent to streams of people who had not even asked for them. Private organisations were employed to gather these ballots and who knows what they did with them before they turned up at the counts. The American election system has been manipulated over decades to become a sick joke with more holes than a Swiss cheese for the express purpose of dictating the results. Then there was the criminal manipulation of information by Sabbatian tech giants like Facebook, Twitter and Google-owned YouTube which deleted pro-Trump, anti-Biden accounts and posts while everything in support of Biden was left alone. Sabbatians wanted Biden to win because after the dividing of America it was time for full-on Woke and every aspect of the Cult agenda to be unleashed.

Hunter gatherer

Extreme Silicon Valley bias included blocking information by the *New York Post* exposing a Biden scandal that should have ended his bid for president in the final weeks of the campaign. Hunter Biden, his monumentally corrupt son, is reported to have sent a laptop to be repaired at a local store and failed to return for it. Time passed until the laptop became the property of the store for non-payment of the bill. When the owner saw what was on the hard drive he gave a copy to the FBI who did nothing even though it confirmed widespread corruption in which the Joe Biden family were using his political position, especially when he was vice president to Obama, to make multiple millions in countries around the world and most notably Ukraine and China. Hunter Biden's one-time business partner Tony Bobulinski went public when the story broke in the *New York Post* to confirm the corruption he saw and that Joe Biden not only knew what was going on he also profited from the spoils. Millions were handed over by a Chinese company with close

connections – like all major businesses in China – to the Chinese communist party of President Xi Jinping. Joe Biden even boasted at a meeting of the Cult's World Economic Forum that as vice president he had ordered the government of Ukraine to fire a prosecutor. What he didn't mention was that the same man just happened to be investigating an energy company which was part of Hunter Biden's corrupt portfolio. The company was paying him big bucks for no other reason than the influence his father had. Overnight Biden's presidential campaign should have been over given that he had lied publicly about not knowing what his son was doing. Instead almost the entire Sabbatian-owned mainstream media and Sabbatian-owned Silicon Valley suppressed circulation of the story. This alone went a mighty way to rigging the election of 2020. Cult assets like Mark Zuckerberg at Facebook also spent hundreds of millions to be used in support of Biden and vote 'administration'.

The Cult had used Trump as the focus to divide America and was now desperate to bring in moronic, pliable, corrupt Biden to complete the double-whammy. No way were they going to let little things like the will of the people thwart their plan. Silicon Valley widely censored claims that the election was rigged because it *was* rigged. For the same reason anyone claiming it was rigged was denounced as a 'white supremacist' including the pathetically few Republican politicians willing to say so. Right across the media where the claim was mentioned it was described as a 'false claim' even though these excuses for 'journalists' would have done no research into the subject whatsoever. Trump won seven million more votes than any sitting president had ever achieved while somehow a cognitively-challenged soon to be 78-year-old who was hidden away from the public for most of the campaign managed to win more votes than any presidential candidate in history. It makes no sense. You only had to see election rallies for both candidates to witness the enthusiasm for Trump and the apathy for Biden. Tens of thousands would attend Trump events while Biden was speaking in empty car parks with often only television crews attending and framing their shots to hide the fact that no one was there. It was pathetic to see

footage come to light of Biden standing at a podium making speeches only to TV crews and party fixers while reading the words written for him on massive Teleprompter screens. So, yes, those protestors on January 6th had a point about election rigging, but some were about to walk into a trap laid for them in Washington by the Cult Deep State and its QAnon Psyop. This was the Capitol Hill riot ludicrously dubbed an 'insurrection'.

The spider and the fly

Renegade Minds know there are not two 'sides' in politics, only one side, the Cult, working through all 'sides'. It's a stage show, a puppet show, to direct the perceptions of the population into focusing on diversions like parties and candidates while missing the puppeteers with their hands holding all the strings. The Capitol Hill 'insurrection' brings us back to the Little Big Horn. Having created two distinct opposing groupings – Woke and Pushbackers – the trap was about to be sprung. Pushbackers were to be encircled and isolated by associating them all in the public mind with Trump and then labelling Trump as some sort of Confederate leader. I knew immediately that the Capitol riot was a set-up because of two things. One was how easy the rioters got into the building with virtually no credible resistance and secondly I could see – as with the 'Covid' hoax in the West at the start of 2020 – how the Cult could exploit the situation to move its agenda forward with great speed. My experience of Cult techniques and activities over more than 30 years has showed me that while they do exploit situations they haven't themselves created this never happens with events of fundamental agenda significance. Every time major events giving cultists the excuse to rapidly advance their plan you find they are manipulated into being for the specific reason of providing that excuse – Problem-Reaction-Solution. Only a tiny minority of the huge crowd of Washington protestors sought to gain entry to the Capitol by smashing windows and breaching doors. That didn't matter. The whole crowd and all Pushbackers, even if they did not support Trump, were going to be lumped together as dangerous

insurrectionists and conspiracy theorists. The latter term came into widespread use through a CIA memo in the 1960s aimed at discrediting those questioning the nonsensical official story of the Kennedy assassination and it subsequently became widely employed by the media. It's still being used by inept 'journalists' with no idea of its origin to discredit anyone questioning anything that authority claims to be true. When you are perpetrating a conspiracy you need to discredit the very word itself even though the dictionary definition of conspiracy is merely 'the activity of secretly planning with other people to do something bad or illegal' and 'a general agreement to keep silent about a subject for the purpose of keeping it secret'. On that basis there are conspiracies almost wherever you look. For obvious reasons the Cult and its lapdog media have to claim there are no conspiracies even though the word appears in state laws as with conspiracy to defraud, to murder, and to corrupt public morals.

Agent provocateurs are widely used by the Cult Deep State to manipulate genuine people into acting in ways that suit the desired outcome. By genuine in this case I mean protestors genuinely supporting Trump and claims that the election was stolen. In among them, however, were agents of the state wearing the garb of Trump supporters and QAnon to pump-prime the Capital riot which some genuine Trump supporters naively fell for. I described the situation as 'Come into my parlour said the spider to the fly'. Leaflets appeared through the Woke paramilitary arm Antifa, the anti-fascist fascists, calling on supporters to turn up in Washington looking like Trump supporters even though they hated him. Some of those arrested for breaching the Capitol Building were sourced to Antifa and its stable mate Black Lives Matter. Both organisations are funded by Cult billionaires and corporations. One man charged for the riot was according to his lawyer a former FBI agent who had held top secret security clearance for 40 years. Attorney Thomas Plofchan said of his client, 66-year-old Thomas Edward Caldwell:

He has held a Top Secret Security Clearance since 1979 and has undergone multiple Special Background Investigations in support of his clearances. After retiring from the Navy, he

worked as a section chief for the Federal Bureau of Investigation from 2009-2010 as a GS-12 [mid-level employee].

He also formed and operated a consulting firm performing work, often classified, for U.S government customers including the US. Drug Enforcement Agency, Department of Housing and Urban Development, the US Coast Guard, and the US Army Personnel Command.

A judge later released Caldwell pending trial in the absence of evidence about a conspiracy or that he tried to force his way into the building. *The New York Post* reported a 'law enforcement source' as saying that 'at least two known Antifa members were spotted' on camera among Trump supporters during the riot while one of the rioters arrested was John Earle Sullivan, a seriously extreme Black Lives Matter Trump-hater from Utah who was previously arrested and charged in July, 2020, over a BLM-Antifa riot in which drivers were threatened and one was shot. Sullivan is the founder of Utah-based Insurgence USA which is an affiliate of the Cult-created-and-funded Black Lives Matter movement. Footage appeared and was then deleted by Twitter of Trump supporters calling out Antifa infiltrators and a group was filmed changing into pro-Trump clothing before the riot. Security at the building was *pathetic* – as planned. Colonel Leroy Fletcher Prouty, a man with long experience in covert operations working with the US security apparatus, once described the tell-tale sign to identify who is involved in an assassination. He said:

No one has to direct an assassination – it happens. The active role is played secretly by permitting it to happen. This is the greatest single clue. Who has the power to call off or reduce the usual security precautions?

This principle applies to many other situations and certainly to the Capitol riot of January 6th, 2021.

The sting

With such a big and potentially angry crowd known to be gathering near the Capitol the security apparatus would have had a major police detail to defend the building with National Guard troops on

standby given the strength of feeling among people arriving from all over America encouraged by the QAnon Psyop and statements by Donald Trump. Instead Capitol Police 'security' was flimsy, weak, and easily breached. The same number of officers was deployed as on a regular day and that is a blatant red flag. They were not staffed or equipped for a possible riot that had been an obvious possibility in the circumstances. No protective and effective fencing worth the name was put in place and there were no contingency plans. The whole thing was basically a case of standing aside and waving people in. Once inside police mostly backed off apart from one Capitol police officer who ridiculously shot dead unarmed Air Force veteran protestor Ashli Babbitt without a warning as she climbed through a broken window. The 'investigation' refused to name or charge the officer after what must surely be considered a murder in the circumstances. They just lifted a carpet and swept. The story was endlessly repeated about five people dying in the 'armed insurrection' when there was no report of rioters using weapons. Apart from Babbitt the other four died from a heart attack, strokes and apparently a drug overdose. Capitol police officer Brian Sicknick was reported to have died after being bludgeoned with a fire extinguisher when he was alive after the riot was over and died later of what the Washington Medical Examiner's Office said was a stroke. Sicknick had no external injuries. The lies were delivered like rapid fire. There was a narrative to build with incessant repetition of the lie until the lie became the accepted 'everybody knows that' truth. The 'Big Lie' technique of Nazi Propaganda Minister Joseph Goebbels is constantly used by the Cult which was behind the Nazis and is today behind the 'Covid' and 'climate change' hoaxes. Goebbels said:

If you tell a lie big enough and keep repeating it, people will eventually come to believe it. The lie can be maintained only for such time as the State can shield the people from the political, economic and/or military consequences of the lie. It thus becomes vitally important for the State to use all of its powers to repress dissent, for the truth is the mortal enemy of the lie, and thus by extension, the truth is the greatest enemy of the State.

Most protestors had a free run of the Capitol Building. This allowed pictures to be taken of rioters in iconic parts of the building including the Senate chamber which could be used as propaganda images against all Pushbackers. One Congresswoman described the scene as 'the worst kind of non-security anybody could ever imagine'. Well, the first part was true, but someone obviously did imagine it and made sure it happened. Some photographs most widely circulated featured people wearing QAnon symbols and now the Psyop would be used to dub all QAnon followers with the ubiquitous fit-all label of 'white supremacist' and 'insurrectionists'. When a Muslim extremist called Noah Green drove his car at two police officers at the Capitol Building killing one in April, 2021, there was no such political and media hysteria. They were just disappointed he wasn't white.

The witch-hunt

Government prosecutor Michael Sherwin, an aggressive, dark-eyed, professional Rottweiler led the 'investigation' and to call it over the top would be to understate reality a thousand fold. Hundreds were tracked down and arrested for the crime of having the wrong political views and people were jailed who had done nothing more than walk in the building, committed no violence or damage to property, took a few pictures and left. They were labelled a 'threat to the Republic' while Biden sat in the White House signing executive orders written for him that were dismantling 'the Republic'. Even when judges ruled that a mother and son should not be in jail the government kept them there. Some of those arrested have been badly beaten by prison guards in Washington and lawyers for one man said he suffered a fractured skull and was made blind in one eye. Meanwhile a woman is shot dead for no reason by a Capitol Police officer and we are not allowed to know who he is never mind what has happened to him although that will be *nothing*. The Cult's QAnon/Trump sting to identify and isolate Pushbackers and then target them on the road to crushing and deleting them was a resounding success. You would have thought the Russians had

invaded the building at gunpoint and lined up senators for a firing squad to see the political and media reaction. Congresswoman Alexandria Ocasio-Cortez is a child in a woman's body, a terrible-twos, me, me, me, Woker narcissist of such proportions that words have no meaning. She said she thought she was going to die when 'insurrectionists' banged on her office door. It turned out she wasn't even in the Capitol Building when the riot was happening and the 'banging' was a Capitol Police officer. She referred to herself as a 'survivor' which is an insult to all those true survivors of violent and sexual abuse while she lives her pampered and privileged life talking drivel for a living. Her Woke colleague and fellow mega-narcissist Rashida Tlaib broke down describing the devastating effect on her, too, of *not being* in the building when the rioters were there. Ocasio-Cortez and Tlaib are members of a fully-Woke group of Congresswomen known as 'The Squad' along with Ilhan Omar and Ayanna Pressley. The Squad from what I can see can be identified by its vehement anti-white racism, anti-white men agenda, and, as always in these cases, the absence of brain cells on active duty.

The usual suspects were on the riot case immediately in the form of Democrat ultra-Zionist senators and operatives Chuck Schumer and Adam Schiff demanding that Trump be impeached for 'his part in the insurrection'. The same pair of prats had led the failed impeachment of Trump over the invented 'Russia collusion' nonsense which claimed Russia had helped Trump win the 2016 election. I didn't realise that Tel Aviv had been relocated just outside Moscow. I must find an up-to-date map. The Russia hoax was a Sabbatian operation to keep Trump occupied and impotent and to stop any rapport with Russia which the Cult wants to retain as a perceptual enemy to be pulled out at will. Puppet Biden began attacking Russia when he came to office as the Cult seeks more upheaval, division and war across the world. A two-year stage show 'Russia collusion inquiry' headed by the not-very-bright former 9/11 FBI chief Robert Mueller, with support from 19 lawyers, 40 FBI agents plus intelligence analysts, forensic accountants and other

staff, devoured tens of millions of dollars and found no evidence of Russia collusion which a ten-year-old could have told them on day one. Now the same moronic Schumer and Schiff wanted a second impeachment of Trump over the Capitol 'insurrection' (riot) which the arrested development of Schumer called another 'Pearl Harbor' while others compared it with 9/11 in which 3,000 died and, in the case of CNN, with the Rwandan genocide in the 1990s in which an estimated 500,000 to 600,000 were murdered, between 250, 000 and 500,000 women were raped, and populations of whole towns were hacked to death with machetes. To make those comparisons purely for Cult political reasons is beyond insulting to those that suffered and lost their lives and confirms yet again the callous inhumanity that we are dealing with. Schumer is a monumental idiot and so is Schiff, but they serve the Cult agenda and do whatever they're told so they get looked after. Talking of idiots – another inane man who spanned the Russia and Capitol impeachment attempts was Senator Eric Swalwell who had the nerve to accuse Trump of collusion with the Russians while sleeping with a Chinese spy called Christine Fang or 'Fang Fang' which is straight out of a Bond film no doubt starring Klaus Schwab as the bloke living on a secret island and controlling laser weapons positioned in space and pointing at world capitals. Fang Fang plays the part of Bond's infiltrator girlfriend which I'm sure she would enjoy rather more than sharing a bed with the brainless Swalwell, lying back and thinking of China. The FBI eventually warned Swalwell about Fang Fang which gave her time to escape back to the Chinese dictatorship. How very thoughtful of them. The second Trump impeachment also failed and hardly surprising when an impeachment is supposed to remove a sitting president and by the time it happened Trump was no longer president. These people are running your country America, well, officially anyway. Terrifying isn't it?

Outcomes tell the story - always

The outcome of all this – and it's the *outcome* on which Renegade Minds focus, not the words – was that a vicious, hysterical and

obviously pre-planned assault was launched on Pushbackers to censor, silence and discredit them and even targeted their right to earn a living. They have since been condemned as 'domestic terrorists' that need to be treated like Al-Qaeda and Islamic State. 'Domestic terrorists' is a label the Cult has been trying to make stick since the period of the Oklahoma bombing in 1995 which was blamed on 'far-right domestic terrorists'. If you read *The Trigger* you will see that the bombing was clearly a Problem-Reaction-Solution carried out by the Deep State during a Bill Clinton administration so corrupt that no dictionary definition of the term would even nearly suffice. Nearly 30, 000 troops were deployed from all over America to the empty streets of Washington for Biden's inauguration. Ten thousand of them stayed on with the pretext of protecting the capital from insurrectionists when it was more psychological programming to normalise the use of the military in domestic law enforcement in support of the Cult plan for a police-military state. Biden's fascist administration began a purge of 'wrong-thinkers' in the military which means anyone that is not on board with Woke. The Capitol Building was surrounded by a fence with razor wire and the Land of the Free was further symbolically and literally dismantled. The circle was completed with the installation of Biden and the exploitation of the QAnon Psyop.

America had never been so divided since the civil war of the 19th century, Pushbackers were isolated and dubbed terrorists and now, as was always going to happen, the Cult immediately set about deleting what little was left of freedom and transforming American society through a swish of the hand of the most controlled 'president' in American history leading (officially at least) the most extreme regime since the country was declared an independent state on July 4th, 1776. Biden issued undebated, dictatorial executive orders almost by the hour in his opening days in office across the whole spectrum of the Cult wish-list including diluting controls on the border with Mexico allowing thousands of migrants to illegally enter the United States to transform the demographics of America and import an election-changing number of perceived Democrat

voters. Then there were Biden deportation amnesties for the already illegally resident (estimated to be as high as 20 or even 30 million). A bill before Congress awarded American citizenship to anyone who could prove they had worked in agriculture for just 180 days in the previous two years as 'Big Ag' secured its slave labour long-term. There were the plans to add new states to the union such as Puerto Rico and making Washington DC a state. They are all parts of a plan to ensure that the Cult-owned Woke Democrats would be permanently in power.

Border – what border?

I have exposed in detail in other books how mass immigration into the United States and Europe is the work of Cult networks fuelled by the tens of billions spent to this and other ends by George Soros and his global Open Society (open borders) Foundations. The impact can be seen in America alone where the population has increased by *100 million* in little more than 30 years mostly through immigration. I wrote in *The Answer* that the plan was to have so many people crossing the southern border that the numbers become unstoppable and we are now there under Cult-owned Biden. El Salvador in Central America puts the scale of what is happening into context. A third of the population now lives in the United States, much of it illegally, and many more are on the way. The methodology is to crush Central and South American countries economically and spread violence through machete-wielding psychopathic gangs like MS-13 based in El Salvador and now operating in many American cities. Biden-imposed lax security at the southern border means that it is all but open. He said before his 'election' that he wanted to see a surge towards the border if he became president and that was the green light for people to do just that after election day to create the human disaster that followed for both America and the migrants. When that surge came the imbecilic Alexandria Ocasio-Cortez said it wasn't a 'surge' because they are 'children, not insurgents' and the term 'surge' (used by Biden) was a claim of 'white supremacists'.

This disingenuous lady may one day enter the realm of the most basic intelligence, but it won't be any time soon.

Sabbatians and the Cult are in the process of destroying America by importing violent people and gangs in among the genuine to terrorise American cities and by overwhelming services that cannot cope with the sheer volume of new arrivals. Something similar is happening in Europe as Western society in general is targeted for demographic and cultural transformation and upheaval. The plan demands violence and crime to create an environment of intimidation, fear and division and Soros has been funding the election of district attorneys across America who then stop prosecuting many crimes, reduce sentences for violent crimes and free as many violent criminals as they can. Sabbatians are creating the chaos from which order – their order – can respond in a classic Problem-Reaction-Solution. A Freemasonic moto says 'Ordo Ab Chao' (Order out of Chaos) and this is why the Cult is constantly creating chaos to impose a new 'order'. Here you have the reason the Cult is constantly creating chaos. The 'Covid' hoax can be seen with those entering the United States by plane being forced to take a 'Covid' test while migrants flooding through southern border processing facilities do not. Nothing is put in the way of mass migration and if that means ignoring the government's own 'Covid' rules then so be it. They know it's all bullshit anyway. Any pushback on this is denounced as 'racist' by Wokers and Sabbatian fronts like the ultra-Zionist Anti-Defamation League headed by the appalling Jonathan Greenblatt which at the same time argues that Israel should not give citizenship and voting rights to more Palestinian Arabs or the 'Jewish population' (in truth the Sabbatian network) will lose control of the country.

Society-changing numbers

Biden's masters have declared that countries like El Salvador are so dangerous that their people must be allowed into the United States for humanitarian reasons when there are fewer murders in large parts of many Central American countries than in US cities like

Baltimore. That is not to say Central America cannot be a dangerous place and Cult-controlled American governments have been making it so since way back, along with the dismantling of economies, in a long-term plan to drive people north into the United States. Parts of Central America are very dangerous, but in other areas the story is being greatly exaggerated to justify relaxing immigration criteria. Migrants are being offered free healthcare and education in the United States as another incentive to head for the border and there is no requirement to be financially independent before you can enter to prevent the resources of America being drained. You can't blame migrants for seeking what they believe will be a better life, but they are being played by the Cult for dark and nefarious ends. The numbers since Biden took office are huge. In February, 2021, more than 100,000 people were known to have tried to enter the US illegally through the southern border (it was 34,000 in the same month in 2020) and in March it was 170,000 – a 418 percent increase on March, 2020. These numbers are only known people, not the ones who get in unseen. The true figure for migrants illegally crossing the border in a single month was estimated by one congressman at 250,000 and that number will only rise under Biden's current policy. Gangs of murdering drug-running thugs that control the Mexican side of the border demand money – thousands of dollars – to let migrants cross the Rio Grande into America. At the same time gun battles are breaking out on the border several times a week between rival Mexican drug gangs (which now operate globally) who are equipped with sophisticated military-grade weapons, grenades and armoured vehicles. While the Capitol Building was being 'protected' from a non-existent 'threat' by thousands of troops, and others were still deployed at the time in the Cult Neocon war in Afghanistan, the southern border of America was left to its fate. This is not incompetence, it is cold calculation.

By March, 2021, there were 17,000 unaccompanied children held at border facilities and many of them are ensnared by people traffickers for paedophile rings and raped on their journey north to America. This is not conjecture – this is fact. Many of those designated

children are in reality teenage boys or older. Meanwhile Wokers posture their self-purity for encouraging poor and tragic people to come to America and face this nightmare both on the journey and at the border with the disgusting figure of House Speaker Nancy Pelosi giving disingenuous speeches about caring for migrants. The woman's evil. Wokers condemned Trump for having children in cages at the border (so did Obama, *Shhhh*), but now they are sleeping on the floor without access to a shower with one border facility 729 percent over capacity. The Biden insanity even proposed flying migrants from the southern border to the northern border with Canada for 'processing'. The whole shambles is being overseen by ultra-Zionist Secretary of Homeland Security, the moronic liar Alejandro Mayorkas, who banned news cameras at border facilities to stop Americans seeing what was happening. Mayorkas said there was not a ban on news crews; it was just that they were not allowed to film. Alongside him at Homeland Security is another ultra-Zionist Cass Sunstein appointed by Biden to oversee new immigration laws. Sunstein despises conspiracy researchers to the point where he suggests they should be banned or *taxed* for having such views. The man is not bonkers or anything. He's perfectly well-adjusted, but adjusted to what is the question. Criticise what is happening and you are a 'white supremacist' when earlier non-white immigrants also oppose the numbers which effect their lives and opportunities. Black people in poor areas are particularly damaged by uncontrolled immigration and the increased competition for work opportunities with those who will work for less. They are also losing voting power as Hispanics become more dominant in former black areas. It's a downward spiral for them while the billionaires behind the policy drone on about how much they care about black people and 'racism'. None of this is about compassion for migrants or black people – that's just wind and air. Migrants are instead being mercilessly exploited to transform America while the countries they leave are losing their future and the same is true in Europe. Mass immigration may now be the work of Woke Democrats, but it can be traced back to the 1986 Immigration Reform and Control Act (it

wasn't) signed into law by Republican hero President Ronald Reagan which gave amnesty to millions living in the United States illegally and other incentives for people to head for the southern border. Here we have the one-party state at work again.

Save me syndrome

Almost every aspect of what I have been exposing as the Cult agenda was on display in even the first days of 'Biden' with silencing of Pushbackers at the forefront of everything. A Renegade Mind will view the Trump years and QAnon in a very different light to their supporters and advocates as the dots are connected. The QAnon/Trump Psyop has given the Cult all it was looking for. We may not know how much, or little, that Trump realised he was being used, but that's a side issue. This pincer movement produced the desired outcome of dividing America and having Pushbackers isolated. To turn this around we have to look at new routes to empowerment which do not include handing our power to other people and groups through what I will call the 'Save Me Syndrome' – 'I want someone else to do it so that I don't have to'. We have seen this at work throughout human history and the QAnon/Trump Psyop is only the latest incarnation alongside all the others. Religion is an obvious expression of this when people look to a 'god' or priest to save them or tell them how to be saved and then there are 'save me' politicians like Trump. Politics is a diversion and not a 'saviour'. It is a means to block positive change, not make it possible.

Save Me Syndrome always comes with the same repeating theme of handing your power to whom or what you believe will save you while your real 'saviour' stares back from the mirror every morning. Renegade Minds are constantly vigilant in this regard and always asking the question 'What can I do?' rather than 'What can someone else do for me?' Gandhi was right when he said: 'You must be the change you want to see in the world.' We are indeed the people we have been waiting for. We are presented with a constant raft of reasons to concede that power to others and forget where the real power is. Humanity has the numbers and the Cult does not. It has to

use diversion and division to target the unstoppable power that comes from unity. Religions, governments, politicians, corporations, media, QAnon, are all different manifestations of this power-diversion and dilution. Refusing to give your power to governments and instead handing it to Trump and QAnon is not to take a new direction, but merely to recycle the old one with new names on the posters. I will explore this phenomenon as we proceed and how to break the cycles and recycles that got us here through the mists of repeating perception and so repeating history.

For now we shall turn to the most potent example in the entire human story of the consequences that follow when you give your power away. I am talking, of course, of the 'Covid' hoax.

CHAPTER FOUR

'Covid': Calculated catastrophe

Facts are threatening to those invested in fraud
DaShanne Stokes

We can easily unravel the real reason for the 'Covid pandemic' hoax by employing the Renegade Mind methodology that I have outlined this far. We'll start by comparing the long-planned Cult outcome with the 'Covid pandemic' outcome. Know the outcome and you'll see the journey.

I have highlighted the plan for the Hunger Games Society which has been in my books for so many years with the very few controlling the very many through ongoing dependency. To create this dependency it is essential to destroy independent livelihoods, businesses and employment to make the population reliant on the state (the Cult) for even the basics of life through a guaranteed pittance income. While independence of income remained these Cult ambitions would be thwarted. With this knowledge it was easy to see where the 'pandemic' hoax was going once talk of 'lockdowns' began and the closing of all but perceived 'essential' businesses to 'save' us from an alleged 'deadly virus'. Cult corporations like Amazon and Walmart were naturally considered 'essential' while mom and pop shops and stores had their doors closed by fascist decree. As a result with every new lockdown and new regulation more small and medium, even large businesses not owned by the Cult, went to the wall while Cult giants and their frontmen and women grew financially fatter by the second. Mom and pop were

denied an income and the right to earn a living and the wealth of people like Jeff Bezos (Amazon), Mark Zuckerberg (Facebook) and Sergei Brin and Larry Page (Google/Alphabet) have reached record levels. The Cult was increasing its own power through further dramatic concentrations of wealth while the competition was being destroyed and brought into a state of dependency. Lockdowns have been instigated to secure that very end and were never anything to do with health. My brother Paul spent 45 years building up a bus repair business, but lockdowns meant buses were running at a fraction of normal levels for months on end. Similar stories can told in their hundreds of millions worldwide. Efforts of a lifetime coldly destroyed by Cult multi-billionaires and their lackeys in government and law enforcement who continued to earn their living from the taxation of the people while denying the right of the same people to earn theirs. How different it would have been if those making and enforcing these decisions had to face the same financial hardships of those they affected, but they never do.

Gates of Hell

Behind it all in the full knowledge of what he is doing and why is the psychopathic figure of Cult operative Bill Gates. His puppet Tedros at the World Health Organization declared 'Covid' a pandemic in March, 2020. The WHO had changed the definition of a 'pandemic' in 2009 just a month before declaring the 'swine flu pandemic' which would not have been so under the previous definition. The same applies to 'Covid'. The definition had included… 'an infection by an infectious agent, occurring simultaneously in different countries, with a significant mortality rate relative to the proportion of the population infected'. The new definition removed the need for 'significant mortality'. The 'pandemic' has been fraudulent even down to the definition, but Gates demanded economy-destroying lockdowns, school closures, social distancing, mandatory masks, a 'vaccination' for every man, woman and child on the planet and severe consequences and restrictions for those that refused. Who gave him this power? The

Cult did which he serves like a little boy in short trousers doing what his daddy tells him. He and his psychopathic missus even smiled when they said that much worse was to come (what they knew was planned to come). Gates responded in the matter-of-fact way of all psychopaths to a question about the effect on the world economy of what he was doing:

> Well, it won't go to zero but it will shrink. Global GDP is probably going to take the biggest hit ever [Gates was smiling as he said this] … in my lifetime this will be the greatest economic hit. But you don't have a choice. People act as if you have a choice. People don't feel like going to the stadium when they might get infected … People are deeply affected by seeing these stats, by knowing they could be part of the transmission chain, old people, their parents and grandparents, could be affected by this, and so you don't get to say ignore what is going on here.
>
> There will be the ability to open up, particularly in rich countries, if things are done well over the next few months, but for the world at large normalcy only returns when we have largely vaccinated the entire population.

The man has no compassion or empathy. How could he when he's a psychopath like all Cult players? My own view is that even beyond that he is very seriously mentally ill. Look in his eyes and you can see this along with his crazy flailing arms. You don't do what he has done to the world population since the start of 2020 unless you are mentally ill and at the most extreme end of psychopathic. You especially don't do it when to you know, as we shall see, that cases and deaths from 'Covid' are fakery and a product of monumental figure massaging. 'These stats' that Gates referred to are based on a 'test' that's not testing for the 'virus' as he has known all along. He made his fortune with big Cult support as an infamously ruthless software salesman and now buys global control of 'health' (death) policy without the population he affects having any say. It's a breathtaking outrage. Gates talked about people being deeply affected by fear of 'Covid' when that was because of *him* and his global network lying to them minute-by-minute supported by a lying media that he seriously influences and funds to the tune of hundreds of millions. He's handed big sums to media operations including the BBC, NBC, Al Jazeera, Univision, *PBS NewsHour*,

ProPublica, National Journal, The Guardian, The Financial Times, The Atlantic, Texas Tribune, USA Today publisher Gannett, *Washington Monthly, Le Monde,* Center for Investigative Reporting, Pulitzer Center on Crisis Reporting, National Press Foundation, International Center for Journalists, Solutions Journalism Network, the Poynter Institute for Media Studies, and many more. Gates is everywhere in the 'Covid' hoax and the man must go to prison – or a mental facility – for the rest of his life and his money distributed to those he has taken such enormous psychopathic pleasure in crushing.

The Muscle

The Hunger Games global structure demands a police-military state – a fusion of the two into one force – which viciously imposes the will of the Cult on the population and protects the Cult from public rebellion. In that regard, too, the 'Covid' hoax just keeps on giving. Often unlawful, ridiculous and contradictory 'Covid' rules and regulations have been policed across the world by moronic automatons and psychopaths made faceless by face-nappy masks and acting like the Nazi SS and fascist blackshirts and brownshirts of Hitler and Mussolini. The smallest departure from the rules decreed by the psychos in government and their clueless gofers were jumped upon by the face-nappy fascists. Brutality against public protestors soon became commonplace even on girls, women and old people as the brave men with the batons – the Face-Nappies as I call them – broke up peaceful protests and handed out fines like confetti to people who couldn't earn a living let alone pay hundreds of pounds for what was once an accepted human right. Robot Face-Nappies of Nottingham police in the English East Midlands fined one group £11,000 for attending a child's birthday party. For decades I charted the transformation of law enforcement as genuine, decent officers were replaced with psychopaths and the brain dead who would happily and brutally do whatever their masters told them. Now they were let loose on the public and I would emphasise the point that none of this just happened. The step-by-step change in the dynamic between police and public was orchestrated from the shadows by

those who knew where this was all going and the same with the perceptual reframing of those in all levels of authority and official administration through 'training courses' by organisations such as Common Purpose which was created in the late 1980s and given a massive boost in Blair era Britain until it became a global phenomenon. Supposed public 'servants' began to view the population as the enemy and the same was true of the police. This was the start of the explosion of behaviour manipulation organisations and networks preparing for the all-war on the human psyche unleashed with the dawn of 2020. I will go into more detail about this later in the book because it is a core part of what is happening.

Police desecrated beauty spots to deter people gathering and arrested women for walking in the countryside alone 'too far' from their homes. We had arrogant, clueless sergeants in the Isle of Wight police where I live posting on Facebook what they insisted the population must do or else. A schoolmaster sergeant called Radford looked young enough for me to ask if his mother knew he was out, but he was posting what he *expected* people to do while a Sergeant Wilkinson boasted about fining lads for meeting in a McDonald's car park where they went to get a lockdown takeaway. Wilkinson added that he had even cancelled their order. What a pair of prats these people are and yet they have increasingly become the norm among Jackboot Johnson's Yellowshirts once known as the British police. This was the theme all over the world with police savagery common during lockdown protests in the United States, the Netherlands, and the fascist state of Victoria in Australia under its tyrannical and again moronic premier Daniel Andrews. Amazing how tyrannical and moronic tend to work as a team and the same combination could be seen across America as arrogant, narcissistic Woke governors and mayors such as Gavin Newsom (California), Andrew Cuomo (New York), Gretchen Whitmer (Michigan), Lori Lightfoot (Chicago) and Eric Garcetti (Los Angeles) did their Nazi and Stalin impressions with the full support of the compliant brutality of their enforcers in uniform as they arrested small business owners defying

fascist shutdown orders and took them to jail in ankle shackles and handcuffs. This happened to bistro owner Marlena Pavlos-Hackney in Gretchen Whitmer's fascist state of Michigan when police arrived to enforce an order by a state-owned judge for 'putting the community at risk' at a time when other states like Texas were dropping restrictions and migrants were pouring across the southern border without any 'Covid' questions at all. I'm sure there are many officers appalled by what they are ordered to do, but not nearly enough of them. If they were truly appalled they would not do it. As the months passed every opportunity was taken to have the military involved to make their presence on the streets ever more familiar and 'normal' for the longer-term goal of police-military fusion.

Another crucial element to the Hunger Games enforcement network has been encouraging the public to report neighbours and others for 'breaking the lockdown rules'. The group faced with £11,000 in fines at the child's birthday party would have been dobbed-in by a neighbour with a brain the size of a pea. The technique was most famously employed by the Stasi secret police in communist East Germany who had public informants placed throughout the population. A police chief in the UK says his force doesn't need to carry out 'Covid' patrols when they are flooded with so many calls from the public reporting other people for visiting the beach. Dorset police chief James Vaughan said people were so enthusiastic about snitching on their fellow humans they were now operating as an auxiliary arm of the police: 'We are still getting around 400 reports a week from the public, so we will respond to reports …We won't need to be doing hotspot patrols because people are very quick to pick the phone up and tell us.' Vaughan didn't say that this is a pillar of all tyrannies of whatever complexion and the means to hugely extend the reach of enforcement while spreading distrust among the people and making them wary of doing anything that might get them reported. Those narcissistic Isle of Wight sergeants Radford and Wilkinson never fail to add a link to their Facebook posts where the public can inform on their fellow slaves.

Neither would be self-aware enough to realise they were imitating the Stasi which they might well never have heard of. Government psychologists that I will expose later laid out a policy to turn communities against each other in the same way.

A coincidence? Yep, and I can knit fog

I knew from the start of the alleged pandemic that this was a Cult operation. It presented limitless potential to rapidly advance the Cult agenda and exploit manipulated fear to demand that every man, woman and child on the planet was 'vaccinated' in a process never used on humans before which infuses self-replicating *synthetic* material into human cells. Remember the plan to transform the human body from a biological to a synthetic biological state. I'll deal with the 'vaccine' (that's not actually a vaccine) when I focus on the genetic agenda. Enough to say here that mass global 'vaccination' justified by this 'new virus' set alarms ringing after 30 years of tracking these people and their methods. The 'Covid' hoax officially beginning in China was also a big red flag for reasons I will be explaining. The agenda potential was so enormous that I could dismiss any idea that the 'virus' appeared naturally. Major happenings with major agenda implications never occur without Cult involvement in making them happen. My questions were twofold in early 2020 as the media began its campaign to induce global fear and hysteria: Was this alleged infectious agent released on purpose by the Cult or did it even exist at all? I then did what I always do in these situations. I sat, observed and waited to see where the evidence and information would take me. By March and early April synchronicity was strongly – and ever more so since then – pointing me in the direction of *there is no 'virus'*. I went public on that with derision even from swathes of the alternative media that voiced a scenario that the Chinese government released the 'virus' in league with Deep State elements in the United States from a top-level bio-lab in Wuhan where the 'virus' is said to have first appeared. I looked at that possibility, but I didn't buy it for several reasons. Deaths from the 'virus' did not in any way match what they

would have been with a 'deadly bioweapon' and it is much more effective if you sell the *illusion* of an infectious agent rather than having a real one unless you can control through injection who has it and who doesn't. Otherwise you lose control of events. A made-up 'virus' gives you a blank sheet of paper on which you can make it do whatever you like and have any symptoms or mutant 'variants' you choose to add while a real infectious agent would limit you to what it actually does. A phantom disease allows you to have endless ludicrous 'studies' on the 'Covid' dollar to widen the perceived impact by inventing ever more 'at risk' groups including one study which said those who walk slowly may be almost four times more likely to die from the 'virus'. People are in psychiatric wards for less.

A real 'deadly bioweapon' can take out people in the hierarchy that are not part of the Cult, but essential to its operation. Obviously they don't want that. Releasing a real disease means you immediately lose control of it. Releasing an illusory one means you don't. Again it's vital that people are extra careful when dealing with what they want to hear. A bioweapon unleashed from a Chinese laboratory in collusion with the American Deep State may fit a conspiracy narrative, but is it true? Would it not be far more effective to use the excuse of a 'virus' to justify the real bioweapon – the 'vaccine'? That way your disease agent does not have to be transmitted and arrives directly through a syringe. I saw a French virologist Luc Montagnier quoted in the alternative media as saying he had discovered that the alleged 'new' severe acute respiratory syndrome coronavirus , or SARS-CoV-2, was made artificially and included elements of the human immunodeficiency 'virus' (HIV) and a parasite that causes malaria. SARS-CoV-2 is alleged to trigger an alleged illness called Covid-19. I remembered Montagnier's name from my research years before into claims that an HIV 'retrovirus' causes AIDs – claims that were demolished by Berkeley virologist Peter Duesberg who showed that no one had ever proved that HIV causes acquired immunodeficiency syndrome or AIDS. Claims that become accepted as fact, publicly and medically, with no proof whatsoever are an ever-recurring story that profoundly applies to

'Covid'. Nevertheless, despite the lack of proof, Montagnier's team at the Pasteur Institute in Paris had a long dispute with American researcher Robert Gallo over which of them discovered and isolated the HIV 'virus' and with *no evidence* found it to cause AIDS. You will see later that there is also no evidence that any 'virus' causes any disease or that there is even such a thing as a 'virus' in the way it is said to exist. The claim to have 'isolated' the HIV 'virus' will be presented in its real context as we come to the shocking story – and it is a story – of SARS-CoV-2 and so will Montagnier's assertion that he identified the full SARS-CoV-2 genome.

Hoax in the making

We can pick up the 'Covid' story in 2010 and the publication by the Rockefeller Foundation of a document called 'Scenarios for the Future of Technology and International Development'. The inner circle of the Rockefeller family has been serving the Cult since John D. Rockefeller (1839-1937) made his fortune with Standard Oil. It is less well known that the same Rockefeller – the Bill Gates of his day – was responsible for establishing what is now referred to as 'Big Pharma', the global network of pharmaceutical companies that make outrageous profits dispensing scalpel and drug 'medicine' and are obsessed with pumping vaccines in ever-increasing number into as many human arms and backsides as possible. John D. Rockefeller was the driving force behind the creation of the 'education' system in the United States and elsewhere specifically designed to program the perceptions of generations thereafter. The Rockefeller family donated exceptionally valuable land in New York for the United Nations building and were central in establishing the World Health Organization in 1948 as an agency of the UN which was created from the start as a Trojan horse and stalking horse for world government. Now enter Bill Gates. His family and the Rockefellers have long been extremely close and I have seen genealogy which claims that if you go back far enough the two families fuse into the same bloodline. Gates has said that the Bill and Melinda Gates Foundation was inspired by the Rockefeller Foundation and why not

when both are serving the same Cult? Major tax-exempt foundations are overwhelmingly criminal enterprises in which Cult assets fund the Cult agenda in the guise of 'philanthropy' while avoiding tax in the process. Cult operatives can become mega-rich in their role of front men and women for the psychopaths at the inner core and they, too, have to be psychopaths to knowingly serve such evil. Part of the deal is that a big percentage of the wealth gleaned from representing the Cult has to be spent advancing the ambitions of the Cult and hence you have the Rockefeller Foundation, Bill and Melinda Gates Foundation (and *so* many more) and people like George Soros with his global Open Society Foundations spending their billions in pursuit of global Cult control. Gates is a global public face of the Cult with his interventions in world affairs including Big Tech influence; a central role in the 'Covid' and 'vaccine' scam; promotion of the climate change shakedown; manipulation of education; geoengineering of the skies; and his food-control agenda as the biggest owner of farmland in America, his GMO promotion and through other means. As one writer said: 'Gates monopolizes or wields disproportionate influence over the tech industry, global health and vaccines, agriculture and food policy (including biopiracy and fake food), weather modification and other climate technologies, surveillance, education and media.' The almost limitless wealth secured through Microsoft and other not-allowed-to-fail ventures (including vaccines) has been ploughed into a long, long list of Cult projects designed to enslave the entire human race. Gates and the Rockefellers have been working as one unit with the Rockefeller-established World Health Organization leading global 'Covid' policy controlled by Gates through his mouth-piece Tedros. Gates became the WHO's biggest funder when Trump announced that the American government would cease its donations, but Biden immediately said he would restore the money when he took office in January, 2021. The Gates Foundation (the Cult) owns through limitless funding the world health system and the major players across the globe in the 'Covid' hoax.

Okay, with that background we return to that Rockefeller Foundation document of 2010 headed 'Scenarios for the Future of Technology and International Development' and its 'imaginary' epidemic of a virulent and deadly influenza strain which infected 20 percent of the global population and killed eight million in seven months. The Rockefeller scenario was that the epidemic destroyed economies, closed shops, offices and other businesses and led to governments imposing fierce rules and restrictions that included mandatory wearing of face masks and body-temperature checks to enter communal spaces like railway stations and supermarkets. The document predicted that even after the height of the Rockefeller-envisaged epidemic the authoritarian rule would continue to deal with further pandemics, transnational terrorism, environmental crises and rising poverty. Now you may think that the Rockefellers are our modern-day seers or alternatively, and rather more likely, that they well knew what was planned a few years further on. Fascism had to be imposed, you see, to 'protect citizens from risk and exposure'. The Rockefeller scenario document said:

During the pandemic, national leaders around the world flexed their authority and imposed airtight rules and restrictions, from the mandatory wearing of face masks to body-temperature checks at the entries to communal spaces like train stations and supermarkets. Even after the pandemic faded, this more authoritarian control and oversight of citizens and their activities stuck and even intensified. In order to protect themselves from the spread of increasingly global problems – from pandemics and transnational terrorism to environmental crises and rising poverty – leaders around the world took a firmer grip on power.

At first, the notion of a more controlled world gained wide acceptance and approval. Citizens willingly gave up some of their sovereignty – and their privacy – to more paternalistic states in exchange for greater safety and stability. Citizens were more tolerant, and even eager, for top-down direction and oversight, and national leaders had more latitude to impose order in the ways they saw fit.

In developed countries, this heightened oversight took many forms: biometric IDs for all citizens, for example, and tighter regulation of key industries whose stability was deemed vital to national interests. In many developed countries, enforced cooperation with a suite of new regulations and agreements slowly but steadily restored both order and, importantly, economic growth.

There we have the prophetic Rockefellers in 2010 and three years later came their paper for the Global Health Summit in Beijing, China, when government representatives, the private sector, international organisations and groups met to discuss the next 100 years of 'global health'. The Rockefeller Foundation-funded paper was called 'Dreaming the Future of Health for the Next 100 Years and more prophecy ensued as it described a dystopian future: 'The abundance of data, digitally tracking and linking people may mean the 'death of privacy' and may replace physical interaction with transient, virtual connection, generating isolation and raising questions of how values are shaped in virtual networks.' Next in the 'Covid' hoax preparation sequence came a 'table top' simulation in 2018 for another 'imaginary' pandemic of a disease called Clade X which was said to kill 900 million people. The exercise was organised by the Gates-funded Johns Hopkins University's Center for Health Security in the United States and this is the very same university that has been compiling the disgustingly and systematically erroneous global figures for 'Covid' cases and deaths. Similar Johns Hopkins health crisis scenarios have included the Dark Winter exercise in 2001 and Atlantic Storm in 2005.

Nostradamus 201

For sheer predictive genius look no further prophecy-watchers than the Bill Gates-funded Event 201 held only six weeks before the 'coronavirus pandemic' is supposed to have broken out in China and Event 201 was based on a scenario of a global 'coronavirus pandemic'. Melinda Gates, the great man's missus, told the BBC that he had 'prepared for years' for a coronavirus pandemic which told us what we already knew. Nostradamugates had predicted in a TED talk in 2015 that a pandemic was coming that would kill a lot of people and demolish the world economy. My god, the man is a machine – possibly even literally. Now here he was only weeks before the real thing funding just such a simulated scenario and involving his friends and associates at Johns Hopkins, the World Economic Forum Cult-front of Klaus Schwab, the United Nations,

Johnson & Johnson, major banks, and officials from China and the Centers for Disease Control in the United States. What synchronicity – Johns Hopkins would go on to compile the fraudulent 'Covid' figures, the World Economic Forum and Schwab would push the 'Great Reset' in response to 'Covid', the Centers for Disease Control would be at the forefront of 'Covid' policy in the United States, Johnson & Johnson would produce a 'Covid vaccine', and everything would officially start just weeks later in China. Spooky, eh? They were even accurate in creating a simulation of a 'virus' pandemic because the 'real thing' would also be a simulation. Event 201 was not an exercise preparing for something that might happen; it was a rehearsal for what those in control knew was *going* to happen and very shortly. Hours of this simulation were posted on the Internet and the various themes and responses mirrored what would soon be imposed to transform human society. News stories were inserted and what they said would be commonplace a few weeks later with still more prophecy perfection. Much discussion focused on the need to deal with misinformation and the 'anti-vax movement' which is exactly what happened when the 'virus' arrived – was said to have arrived – in the West.

Cult-owned social media banned criticism and exposure of the official 'virus' narrative and when I said there *was* no 'virus' in early April, 2020, I was banned by one platform after another including YouTube, Facebook and later Twitter. The mainstream broadcast media in Britain was in effect banned from interviewing me by the Tony-Blair-created government broadcasting censor Ofcom headed by career government bureaucrat Melanie Dawes who was appointed just as the 'virus' hoax was about to play out in January, 2020. At the same time the Ickonic media platform was using Vimeo, another ultra-Zionist-owned operation, while our own player was being created and they deleted in an instant hundreds of videos, documentaries, series and shows to confirm their unbelievable vindictiveness. We had copies, of course, and they had to be restored one by one when our player was ready. These people have no class. Sabbatian Facebook promised free advertisements for the Gates-

controlled World Health Organization narrative while deleting 'false claims and conspiracy theories' to stop 'misinformation' about the alleged coronavirus. All these responses could be seen just a short while earlier in the scenarios of Event 201. Extreme censorship was absolutely crucial for the Cult because the official story was so ridiculous and unsupportable by the evidence that it could never survive open debate and the free-flow of information and opinion. If you can't win a debate then don't have one is the Cult's approach throughout history. Facebook's little boy front man – front boy – Mark Zuckerberg equated 'credible and accurate information' with official sources and exposing their lies with 'misinformation'.

Silencing those that can see

The censorship dynamic of Event 201 is now the norm with an army of narrative-supporting 'fact-checker' organisations whose entire reason for being is to tell the public that official narratives are true and those exposing them are lying. One of the most appalling of these 'fact-checkers' is called NewsGuard founded by ultra-Zionist Americans Gordon Crovitz and Steven Brill. Crovitz is a former publisher of *The Wall Street Journal*, former Executive Vice President of Dow Jones, a member of the Council on Foreign Relations (CFR), and on the board of the American Association of Rhodes Scholars. The CFR and Rhodes Scholarships, named after Rothschild agent Cecil Rhodes who plundered the gold and diamonds of South Africa for his masters and the Cult, have featured widely in my books. NewsGuard don't seem to like me for some reason – I really can't think why – and they have done all they can to have me censored and discredited which is, to quote an old British politician, like being savaged by a dead sheep. They are, however, like all in the censorship network, very well connected and funded by organisations themselves funded by, or connected to, Bill Gates. As you would expect with anything associated with Gates NewsGuard has an offshoot called HealthGuard which 'fights online health care hoaxes'. How very kind. Somehow the NewsGuard European Managing Director Anna-Sophie Harling, a remarkably young-

looking woman with no broadcasting experience and little hands-on work in journalism, has somehow secured a position on the 'Content Board' of UK government broadcast censor Ofcom. An executive of an organisation seeking to discredit dissidents of the official narratives is making decisions for the government broadcast 'regulator' about content?? Another appalling 'fact-checker' is Full Fact funded by George Soros and global censors Google and Facebook.

It's amazing how many activists in the 'fact-checking', 'anti-hate', arena turn up in government-related positions – people like UK Labour Party activist Imran Ahmed who heads the Center for Countering Digital Hate founded by people like Morgan McSweeney, now chief of staff to the Labour Party's hapless and useless 'leader' Keir Starmer. Digital Hate – which is what it really is – uses the American spelling of Center to betray its connection to a transatlantic network of similar organisations which in 2020 shapeshifted from attacking people for 'hate' to attacking them for questioning the 'Covid' hoax and the dangers of the 'Covid vaccine'. It's just a coincidence, you understand. This is one of Imran Ahmed's hysterical statements: 'I would go beyond calling anti-vaxxers conspiracy theorists to say they are an extremist group that pose a national security risk.' No one could ever accuse this prat of understatement and he's including in that those parents who are now against vaccines after their children were damaged for life or killed by them. He's such a nice man. Ahmed does the rounds of the Woke media getting soft-ball questions from spineless 'journalists' who never ask what right he has to campaign to destroy the freedom of speech of others while he demands it for himself. There also seems to be an overrepresentation in Ofcom of people connected to the narrative-worshipping BBC. This incredible global network of narrative-support was super-vital when the 'Covid' hoax was played in the light of the mega-whopper lies that have to be defended from the spotlight cast by the most basic intelligence.

Setting the scene

The Cult plays the long game and proceeds step-by-step ensuring that everything is in place before major cards are played and they don't come any bigger than the 'Covid' hoax. The psychopaths can't handle events where the outcome isn't certain and as little as possible – preferably nothing – is left to chance. Politicians, government and medical officials who would follow direction were brought to illusory power in advance by the Cult web whether on the national stage or others like state governors and mayors of America. For decades the dynamic between officialdom, law enforcement and the public was changed from one of service to one of control and dictatorship. Behaviour manipulation networks established within government were waiting to impose the coming 'Covid' rules and regulations specifically designed to subdue and rewire the psyche of the people in the guise of protecting health. These included in the UK the Behavioural Insights Team part-owned by the British government Cabinet Office; the Scientific Pandemic Insights Group on Behaviours (SPI-B); and a whole web of intelligence and military groups seeking to direct the conversation on social media and control the narrative. Among them are the cyberwarfare (on the people) 77th Brigade of the British military which is also coordinated through the Cabinet Office as civilian and military leadership continues to combine in what they call the Fusion Doctrine. The 77th Brigade is a British equivalent of the infamous Israeli (Sabbatian) military cyberwarfare and Internet manipulation operation Unit 8200 which I expose at length in *The Trigger*. Also carefully in place were the medical and science advisers to government – many on the payroll past or present of Bill Gates – and a whole alternative structure of unelected government stood by to take control when elected parliaments were effectively closed down once the 'Covid' card was slammed on the table. The structure I have described here and so much more was installed in every major country through the Cult networks. The top-down control hierarchy looks like this: The Cult – Cult-owned Gates – the World Health Organization and Tedros – Gates-funded or controlled chief medical officers and science 'advisers' (dictators) in each country –

political 'leaders'– law enforcement – The People. Through this simple global communication and enforcement structure the policy of the Cult could be imposed on virtually the entire human population so long as they acquiesced to the fascism. With everything in place it was time for the button to be pressed in late 2019/early 2020.

These were the prime goals the Cult had to secure for its will to prevail:

1) Locking down economies, closing all but designated 'essential' businesses (Cult-owned corporations were 'essential'), and putting the population under house arrest was an imperative to destroy independent income and employment and ensure dependency on the Cult-controlled state in the Hunger Games Society. Lockdowns had to be established as the global blueprint from the start to respond to the 'virus' and followed by pretty much the entire world.

2) The global population had to be terrified into believing in a deadly 'virus' that didn't actually exist so they would unquestioningly obey authority in the belief that authority must know how best to protect them and their families. Software salesman Gates would suddenly morph into the world's health expert and be promoted as such by the Cult-owned media.

3) A method of testing that wasn't testing for the 'virus', but was only claimed to be, had to be in place to provide the illusion of 'cases' and subsequent 'deaths' that had a very different cause to the 'Covid-19' that would be scribbled on the death certificate.

4) Because there was no 'virus' and the great majority testing positive with a test not testing for the 'virus' would have no symptoms of anything the lie had to be sold that people without symptoms (without the 'virus') could still pass it on to others. This was crucial to justify for the first time quarantining – house arresting – healthy people. Without this the economy-destroying lockdown of *everybody* could not have been credibly sold.

5) The 'saviour' had to be seen as a vaccine which beyond evil drug companies were working like angels of mercy to develop as quickly as possible, with all corners cut, to save the day. The public must absolutely not know that the 'vaccine' had nothing to do with a 'virus' or that the contents were ready and waiting with a very different motive long before the 'Covid' card was even lifted from the pack.

I said in March, 2020, that the 'vaccine' would have been created way ahead of the 'Covid' hoax which justified its use and the following December an article in the New York *Intelligencer* magazine said the Moderna 'vaccine' had been 'designed' by

January, 2020. This was 'before China had even acknowledged that the disease could be transmitted from human to human, more than a week before the first confirmed coronavirus case in the United States'. The article said that by the time the first American death was announced a month later 'the vaccine had already been manufactured and shipped to the National Institutes of Health for the beginning of its Phase I clinical trial'. The 'vaccine' was actually 'designed' long before that although even with this timescale you would expect the article to ask how on earth it could have been done that quickly. Instead it asked why the 'vaccine' had not been rolled out then and not months later. Journalism in the mainstream is truly dead. I am going to detail in the next chapter why the 'virus' has never existed and how a hoax on that scale was possible, but first the foundation on which the Big Lie of 'Covid' was built.

The test that doesn't test

Fraudulent 'testing' is the bottom line of the whole 'Covid' hoax and was the means by which a 'virus' that did not exist *appeared* to exist. They could only achieve this magic trick by using a test not testing for the 'virus'. To use a test that *was* testing for the 'virus' would mean that every test would come back negative given there was no 'virus'. They chose to exploit something called the RT-PCR test invented by American biochemist Kary Mullis in the 1980s who said publicly that his PCR test … *cannot detect infectious disease*. Yes, the 'test' used worldwide to detect infectious 'Covid' to produce all the illusory 'cases' and 'deaths' compiled by Johns Hopkins and others *cannot detect infectious disease*. This fact came from the mouth of the man who invented PCR and was awarded the Nobel Prize in Chemistry in 1993 for doing so. Sadly, and incredibly conveniently for the Cult, Mullis died in August, 2019, at the age of 74 just before his test would be fraudulently used to unleash fascism on the world. He was said to have died from pneumonia which was an irony in itself. A few months later he would have had 'Covid-19' on his death certificate. I say the timing of his death was convenient because had he lived Mullis, a brilliant, honest and decent man, would have been

vociferously speaking out against the use of his test to detect 'Covid' when it was never designed, or able, to do that. I know that to be true given that Mullis made the same point when his test was used to 'detect' – not detect – HIV. He had been seriously critical of the Gallo/Montagnier claim to have isolated the HIV 'virus' and shown it to cause AIDS for which Mullis said there was no evidence. AIDS is actually not a disease but a series of diseases from which people die all the time. When they die from those *same diseases* after a positive 'test' for HIV then AIDS goes on their death certificate. I think I've heard that before somewhere. Countries instigated a policy with 'Covid' that anyone who tested positive with a test not testing for the 'virus' and died of any other cause within 28 days and even longer 'Covid-19' had to go on the death certificate. Cases have come from the test that can't test for infectious disease and the deaths are those who have died of *anything* after testing positive with a test not testing for the 'virus'. I'll have much more later about the death certificate scandal.

Mullis was deeply dismissive of the now US 'Covid' star Anthony Fauci who he said was a liar who didn't know anything about anything – 'and I would say that to his face – nothing.' He said of Fauci: 'The man thinks he can take a blood sample, put it in an electron microscope and if it's got a virus in there you'll know it – he doesn't understand electron microscopy and he doesn't understand medicine and shouldn't be in a position like he's in.' That position, terrifyingly, has made him the decider of 'Covid' fascism policy on behalf of the Cult in his role as director since 1984 of the National Institute of Allergy and Infectious Diseases (NIAID) while his record of being wrong is laughable; but being wrong, so long as it's the *right kind* of wrong, is why the Cult loves him. He'll say anything the Cult tells him to say. Fauci was made Chief Medical Adviser to the President immediately Biden took office. Biden was installed in the White House by Cult manipulation and one of his first decisions was to elevate Fauci to a position of even more control. This is a coincidence? Yes, and I identify as a flamenco dancer called Lola. How does such an incompetent criminal like Fauci remain in that

pivotal position in American health since *the 1980s*? When you serve the Cult it looks after you until you are surplus to requirements. Kary Mullis said prophetically of Fauci and his like: 'Those guys have an agenda and it's not an agenda we would like them to have … they make their own rules, they change them when they want to, and Tony Fauci does not mind going on television in front of the people who pay his salary and lie directly into the camera.' Fauci has done that almost daily since the 'Covid' hoax began. Lying is in Fauci's DNA. To make the situation crystal clear about the PCR test this is a direct quote from its inventor Kary Mullis:

> It [the PCR test] doesn't tell you that you're sick and doesn't tell you that the thing you ended up with was really going to hurt you ...'

Ask yourself why governments and medical systems the world over have been using this very test to decide who is 'infected' with the SARS-CoV-2 'virus' and the alleged disease it allegedly causes, 'Covid-19'. The answer to that question will tell you what has been going on. By the way, here's a little show-stopper – the 'new' SARS-CoV-2 'virus' was 'identified' as such right from the start using … *the PCR test not testing for the 'virus'*. If you are new to this and find that shocking then stick around. I have hardly started yet. Even worse, other 'tests', like the 'Lateral Flow Device' (LFD), are considered so useless that they have to be *confirmed* by the PCR test! Leaked emails written by Ben Dyson, adviser to UK 'Health' Secretary Matt Hancock, said they were 'dangerously unreliable'. Dyson, executive director of strategy at the Department of Health, wrote: 'As of today, someone who gets a positive LFD result in (say) London has at best a 25 per cent chance of it being a true positive, but if it is a self-reported test potentially as low as 10 per cent (on an optimistic assumption about specificity) or as low as 2 per cent (on a more pessimistic assumption).' These are the 'tests' that schoolchildren and the public are being urged to have twice a week or more and have to isolate if they get a positive. Each fake positive goes in the statistics as a 'case' no matter how ludicrously inaccurate and the

'cases' drive lockdown, masks and the pressure to 'vaccinate'. The government said in response to the email leak that the 'tests' were accurate which confirmed yet again what shocking bloody liars they are. The real false positive rate is *100 percent* as we'll see. In another 'you couldn't make it up' the UK government agreed to pay £2.8 billion to California's Innova Medical Group to supply the irrelevant lateral flow tests. The company's primary test-making centre is in China. Innova Medical Group, established in March, 2020, is owned by Pasaca Capital Inc, chaired by Chinese-American millionaire Charles Huang who was born in Wuhan.

How it works – and how it doesn't

The RT-PCR test, known by its full title of Polymerase chain reaction, is used across the world to make millions, even billions, of copies of a DNA/RNA genetic information sample. The process is called 'amplification' and means that a tiny sample of genetic material is amplified to bring out the detailed content. I stress that it is not testing for an infectious disease. It is simply amplifying a sample of genetic material. In the words of Kary Mullis: 'PCR is … just a process that's used to make a whole lot of something out of something.' To emphasise the point companies that make the PCR tests circulated around the world to 'test' for 'Covid' warn on the box that it can't be used to detect 'Covid' or infectious disease and is for research purposes only. It's okay, rest for a minute and you'll be fine. This is the test that produces the 'cases' and 'deaths' that have been used to destroy human society. All those global and national medical and scientific 'experts' demanding this destruction to 'save us' *KNOW* that the test is not testing for the 'virus' and the cases and deaths they claim to be real are an almost unimaginable fraud. Every one of them and so many others including politicians and psychopaths like Gates and Tedros must be brought before Nuremburg-type trials and jailed for the rest of their lives. The more the genetic sample is amplified by PCR the more elements of that material become sensitive to the test and by that I don't mean sensitive for a 'virus' but for elements of the genetic material which

is *naturally* in the body or relates to remnants of old conditions of various kinds lying dormant and causing no disease. Once the amplification of the PCR reaches a certain level *everyone* will test positive. So much of the material has been made sensitive to the test that everyone will have some part of it in their body. Even lying criminals like Fauci have said that once PCR amplifications pass 35 cycles everything will be a false positive that cannot be trusted for the reasons I have described. I say, like many proper doctors and scientists, that 100 percent of the 'positives' are false, but let's just go with Fauci for a moment.

He says that any amplification over 35 cycles will produce false positives and yet the US Centers for Disease Control (CDC) and Food and Drug Administration (FDA) have recommended up to *40 cycles* and the National Health Service (NHS) in Britain admitted in an internal document for staff that it was using *45 cycles* of amplification. A long list of other countries has been doing the same and at least one 'testing' laboratory has been using *50 cycles*. Have you ever heard a doctor, medical 'expert' or the media ask what level of amplification has been used to claim a 'positive'. The 'test' comes back 'positive' and so you have the 'virus', end of story. Now we can see how the government in Tanzania could send off samples from a goat and a pawpaw fruit under human names and both came back positive for 'Covid-19'. Tanzania president John Magufuli mocked the 'Covid' hysteria, the PCR test and masks and refused to import the DNA-manipulating 'vaccine'. The Cult hated him and an article sponsored by the Bill Gates Foundation appeared in the London *Guardian* in February, 2021, headed 'It's time for Africa to rein in Tanzania's anti-vaxxer president'. Well, 'reined in' he shortly was. Magufuli appeared in good health, but then, in March, 2021, he was dead at 61 from 'heart failure'. He was replaced by Samia Hassan Suhulu who is connected to Klaus Schwab's World Economic Forum and she immediately reversed Magufuli's 'Covid' policy. A sample of cola tested positive for 'Covid' with the PCR test in Germany while American actress and singer-songwriter Erykah Badu tested positive in one nostril and negative in the other. Footballer Ronaldo called

the PCR test 'bullshit' after testing positive three times and being forced to quarantine and miss matches when there was nothing wrong with him. The mantra from Tedros at the World Health Organization and national governments (same thing) has been test, test, test. They know that the more tests they can generate the more fake 'cases' they have which go on to become 'deaths' in ways I am coming to. The UK government has its Operation Moonshot planned to test multiple millions every day in workplaces and schools with free tests for everyone to use twice a week at home in line with the Cult plan from the start to make testing part of life. A government advertisement for an 'Interim Head of Asymptomatic Testing Communication' said the job included responsibility for delivering a 'communications strategy' (propaganda) 'to support the expansion of asymptomatic testing that *'normalises testing as part of everyday life*'. More tests means more fake 'cases', 'deaths' and fascism. I have heard of, and from, many people who booked a test, couldn't turn up, and yet got a positive result through the post for a test they'd never even had. The whole thing is crazy, but for the Cult there's method in the madness. Controlling and manipulating the level of amplification of the test means the authorities can control whenever they want the number of apparent 'cases' and 'deaths'. If they want to justify more fascist lockdown and destruction of livelihoods they keep the amplification high. If they want to give the illusion that lockdowns and the 'vaccine' are working then they lower the amplification and 'cases' and 'deaths' will appear to fall. In January, 2021, the Cult-owned World Health Organization suddenly warned laboratories about over-amplification of the test and to lower the threshold. Suddenly headlines began appearing such as: 'Why ARE "Covid" cases plummeting?' This was just when the vaccine rollout was underway and I had predicted months before they would make cases appear to fall through amplification tampering when the 'vaccine' came. These people are so predictable.

Cow vaccines?

The question must be asked of what is on the test swabs being poked far up the nose of the population to the base of the brain? A nasal swab punctured one woman's brain and caused it to leak fluid. Most of these procedures are being done by people with little training or medical knowledge. Dr Lorraine Day, former orthopaedic trauma surgeon and Chief of Orthopaedic Surgery at San Francisco General Hospital, says the tests are really a *'vaccine'*. Cows have long been vaccinated this way. She points out that masks have to cover the nose and the mouth where it is claimed the 'virus' exists in saliva. Why then don't they take saliva from the mouth as they do with a DNA test instead of pushing a long swab up the nose towards the brain? The ethmoid bone separates the nasal cavity from the brain and within that bone is the cribriform plate. Dr Day says that when the swab is pushed up against this plate and twisted the procedure is 'depositing things back there'. She claims that among these 'things' are nanoparticles that can enter the brain. Researchers have noted that a team at the Gates-funded Johns Hopkins have designed tiny, star-shaped micro-devices that can latch onto intestinal mucosa and release drugs into the body. Mucosa is the thin skin that covers the inside surface of parts of the body such as *the nose* and mouth and produces mucus to protect them. The Johns Hopkins micro-devices are called 'theragrippers' and were 'inspired' by a parasitic worm that digs its sharp teeth into a host's intestines. Nasal swabs are also coated in the sterilisation agent ethylene oxide. The US National Cancer Institute posts this explanation on its website:

> At room temperature, ethylene oxide is a flammable colorless gas with a sweet odor. It is used primarily to produce other chemicals, including antifreeze. In smaller amounts, ethylene oxide is used as a pesticide and a sterilizing agent. The ability of ethylene oxide to damage DNA makes it an effective sterilizing agent but also accounts for its cancer-causing activity.

The Institute mentions lymphoma and leukaemia as cancers most frequently reported to be associated with occupational exposure to ethylene oxide along with stomach and breast cancers. How does anyone think this is going to work out with the constant testing

regime being inflicted on adults and children at home and at school that will accumulate in the body anything that's on the swab?

Doctors know best

It is vital for people to realise that 'hero' doctors 'know' only what the Big Pharma-dominated medical authorities tell them to 'know' and if they refuse to 'know' what they are told to 'know' they are out the door. They are mostly not physicians or healers, but repeaters of the official narrative – or else. I have seen alleged professional doctors on British television make shocking statements that we are supposed to take seriously. One called 'Dr' Amir Khan, who is actually telling patients how to respond to illness, said that men could take the birth pill to 'help slow down the effects of Covid-19'. In March, 2021, another ridiculous 'Covid study' by an American doctor proposed injecting men with the female sex hormone progesterone as a 'Covid' treatment. British doctor Nighat Arif told the BBC that face coverings were now going to be part of ongoing normal. Yes, the vaccine protects you, she said (evidence?) … but the way to deal with viruses in the community was always going to come down to hand washing, face covering and keeping a physical distance. That's not what we were told before the 'vaccine' was circulating. Arif said she couldn't imagine ever again going on the underground or in a lift without a mask. I was just thanking my good luck that she was not my doctor when she said – in March, 2021 – that if 'we are *behaving* and we are doing all the right things' she thought we could 'have our nearest and dearest around us at home … around *Christmas* and N*ew Year!* Her patronising delivery was the usual school teacher talking to six-year-olds as she repeated every government talking point and probably believed them all. If we have learned anything from the 'Covid' experience surely it must be that humanity's perception of doctors needs a fundamental rethink. NHS 'doctor' Sara Kayat told her television audience that the 'Covid vaccine' would '100 percent prevent hospitalisation and death'. Not even Big Pharma claimed that. We have to stop taking 'experts' at their word without question when so many of them are

clueless and only repeating the party line on which their careers depend. That is not to say there are not brilliants doctors – there are and I have spoken to many of them since all this began – but you won't see them in the mainstream media or quoted by the psychopaths and yes-people in government.

Remember the name – Christian Drosten

German virologist Christian Drosten, Director of Charité Institute of Virology in Berlin, became a national star after the pandemic hoax began. He was feted on television and advised the German government on 'Covid' policy. Most importantly to the wider world Drosten led a group that produced the 'Covid' testing protocol for the PCR test. What a remarkable feat given the PCR cannot test for infectious disease and even more so when you think that Drosten said that his method of testing for SARS-CoV-2 was developed 'without having virus material available'. *He developed a test for a 'virus' that he didn't have and had never seen*. Let that sink in as you survey the global devastation that came from what he did. The whole catastrophe of Drosten's 'test' was based on the alleged genetic sequence published by Chinese scientists on the Internet. We will see in the next chapter that this alleged 'genetic sequence' has never been produced by China or anyone and cannot be when there *is no* SARS-CoV-2. Drosten, however, doesn't seem to let little details like that get in the way. He was the lead author with Victor Corman from the same Charité Hospital of the paper 'Detection of 2019 novel coronavirus (2019-nCoV) by real-time PCR' published in a magazine called *Eurosurveillance*. This became known as the Corman-Drosten paper. In November, 2020, with human society devastated by the effects of the Corman-Drosten test baloney, the protocol was publicly challenged by 22 international scientists and independent researchers from Europe, the United States, and Japan. Among them were senior molecular geneticists, biochemists, immunologists, and microbiologists. They produced a document headed 'External peer review of the RTPCR test to detect SARS-Cov-2 Reveals 10 Major Flaws At The Molecular and Methodological Level: Consequences

For False-Positive Results'. The flaws in the Corman-Drosten test included the following:

- The test is non-specific because of erroneous design
- Results are enormously variable
- The test is unable to discriminate between the whole 'virus' and viral fragments
- It doesn't have positive or negative controls
- The test lacks a standard operating procedure
- It is unsupported by proper peer view

The scientists said the PCR 'Covid' testing protocol was not founded on science and they demanded the Corman-Drosten paper be retracted by *Eurosurveillance*. They said all present and previous Covid deaths, cases, and 'infection rates' should be subject to a massive retroactive inquiry. Lockdowns and travel restrictions should be reviewed and relaxed and those diagnosed through PCR to have 'Covid-19' should not be forced to isolate. Dr Kevin Corbett, a health researcher and nurse educator with a long academic career producing a stream of peer-reviewed publications at many UK universities, made the same point about the PCR test debacle. He said of the scientists' conclusions: 'Every scientific rationale for the development of that test has been totally destroyed by this paper. It's like Hiroshima/Nagasaki to the Covid test.' He said that China hadn't given them an isolated 'virus' when Drosten developed the test. Instead they had developed the test from *a sequence in a gene bank*.' Put another way … *they made it up*! The scientists were supported in this contention by a Portuguese appeals court which ruled in November, 2020, that PCR tests are unreliable and it is unlawful to quarantine people based solely on a PCR test. The point about China not providing an isolated virus must be true when the 'virus' has never been isolated to this day and the consequences of that will become clear. Drosten and company produced this useless 'protocol' right on cue in January, 2020, just as the 'virus' was said to

be moving westward and it somehow managed to successfully pass a peer-review in 24 hours. In other words there was no peer-review for a test that would be used to decide who had 'Covid' and who didn't across the world. The Cult-created, Gates-controlled World Health Organization immediately recommended all its nearly 200 member countries to use the Drosten PCR protocol to detect 'cases' and 'deaths'. The sting was underway and it continues to this day.

So who is this Christian Drosten that produced the means through which death, destruction and economic catastrophe would be justified? His education background, including his doctoral thesis, would appear to be somewhat shrouded in mystery and his track record is dire as with another essential player in the 'Covid' hoax, the Gates-funded Professor Neil Ferguson at the Gates-funded Imperial College in London of whom more shortly. Drosten predicted in 2003 that the alleged original SARS 'virus' (SARS-1') was an epidemic that could have serious effects on economies and an effective vaccine would take at least two years to produce. Drosten's answer to every alleged 'outbreak' is a vaccine which you won't be shocked to know. What followed were just 774 official deaths worldwide and none in Germany where there were only nine cases. That is even if you believe there ever was a SARS 'virus' when the evidence is zilch and I will expand on this in the next chapter. Drosten claims to be co-discoverer of 'SARS-1' and developed a test for it in 2003. He was screaming warnings about 'swine flu' in 2009 and how it was a widespread infection far more severe than any dangers from a vaccine could be and people should get vaccinated. It would be helpful for Drosten's vocal chords if he simply recorded the words 'the virus is deadly and you need to get vaccinated' and copies could be handed out whenever the latest made-up threat comes along. Drosten's swine flu epidemic never happened, but Big Pharma didn't mind with governments spending hundreds of millions on vaccines that hardly anyone bothered to use and many who did wished they hadn't. A study in 2010 revealed that the risk of dying from swine flu, or H1N1, was no higher than that of the annual seasonal flu which is what at least most of 'it' really was as in

the case of 'Covid-19'. A media investigation into Drosten asked how with such a record of inaccuracy he could be *the* government adviser on these issues. The answer to that question is the same with Drosten, Ferguson and Fauci – they keep on giving the authorities the 'conclusions' and 'advice' they want to hear. Drosten certainly produced the goods for them in January, 2020, with his PCR protocol garbage and provided the foundation of what German internal medicine specialist Dr Claus Köhnlein, co-author of *Virus Mania*, called the 'test pandemic'. The 22 scientists in the *Eurosurveillance* challenge called out conflicts of interest within the Drosten 'protocol' group and with good reason. Olfert Landt, a regular co-author of Drosten 'studies', owns the biotech company TIB Molbiol Syntheselabor GmbH in Berlin which manufactures and sells the tests that Drosten and his mates come up with. They have done this with SARS, Enterotoxigenic E. coli (ETEC), MERS, Zika 'virus', yellow fever, and now 'Covid'. Landt told the *Berliner Zeitung* newspaper:

> The testing, design and development came from the Charité [Drosten and Corman]. We simply implemented it immediately in the form of a kit. And if we don't have the virus, which originally only existed in Wuhan, we can make a synthetic gene to simulate the genome of the virus. That's what we did very quickly.

This is more confirmation that the Drosten test was designed without access to the 'virus' and only a synthetic simulation which is what SARS-CoV-2 really is – a computer-generated synthetic fiction. It's quite an enterprise they have going here. A Drosten team decides what the test for something should be and Landt's biotech company flogs it to governments and medical systems across the world. His company must have made an absolute fortune since the 'Covid' hoax began. Dr Reiner Fuellmich, a prominent German consumer protection trial lawyer in Germany and California, is on Drosten's case and that of Tedros at the World Health Organization for crimes against humanity with a class-action lawsuit being prepared in the United States and other legal action in Germany.

Why China?

Scamming the world with a 'virus' that doesn't exist would seem impossible on the face of it, but not if you have control of the relatively few people that make policy decisions and the great majority of the global media. Remember it's not about changing 'real' reality it's about controlling *perception* of reality. You don't have to make something happen you only have make people *believe* that it's happening. Renegade Minds understand this and are therefore much harder to swindle. 'Covid-19' is not a 'real' 'virus'. It's a mind virus, like a computer virus, which has infected the minds, not the bodies, of billions. It all started, publically at least, in China and that alone is of central significance. The Cult was behind the revolution led by its asset Mao Zedong, or Chairman Mao, which established the People's Republic of China on October 1st, 1949. It should have been called The Cult's Republic of China, but the name had to reflect the recurring illusion that vicious dictatorships are run by and for the people (see all the 'Democratic Republics' controlled by tyrants). In the same way we have the 'Biden' Democratic Republic of America officially ruled by a puppet tyrant (at least temporarily) on behalf of Cult tyrants. The creation of Mao's merciless communist/fascist dictatorship was part of a frenzy of activity by the Cult at the conclusion of World War Two which, like the First World War, it had instigated through its assets in Germany, Britain, France, the United States and elsewhere. Israel was formed in 1948; the Soviet Union expanded its 'Iron Curtain' control, influence and military power with the Warsaw Pact communist alliance in 1955; the United Nations was formed in 1945 as a Cult precursor to world government; and a long list of world bodies would be established including the World Health Organization (1948), World Trade Organization (1948 under another name until 1995), International Monetary Fund (1945) and World Bank (1944). Human society was redrawn and hugely centralised in the global Problem-Reaction-Solution that was World War Two. All these changes were significant. Israel would become the headquarters of the Sabbatians

and the revolution in China would prepare the ground and control system for the events of 2019/2020.

Renegade Minds know there are no borders except for public consumption. The Cult is a seamless, borderless global entity and to understand the game we need to put aside labels like borders, nations, countries, communism, fascism and democracy. These delude the population into believing that countries are ruled within their borders by a government of whatever shade when these are mere agencies of a global power. America's illusion of democracy and China's communism/fascism are subsidiaries – vehicles – for the same agenda. We may hear about conflict and competition between America and China and on the lower levels that will be true; but at the Cult level they are branches of the same company in the way of the McDonald's example I gave earlier. I have tracked in the books over the years support by US governments of both parties for Chinese Communist Party infiltration of American society through allowing the sale of land, even military facilities, and the acquisition of American business and university influence. All this is underpinned by the infamous stealing of intellectual property and technological know-how. Cult-owned Silicon Valley corporations waive their fraudulent 'morality' to do business with human-rights-free China; Cult-controlled Disney has become China's PR department; and China in effect owns 'American' sports such as basketball which depends for much of its income on Chinese audiences. As a result any sports player, coach or official speaking out against China's horrific human rights record is immediately condemned or fired by the China-worshipping National Basketball Association. One of the first acts of China-controlled Biden was to issue an executive order telling federal agencies to stop making references to the 'virus' by the 'geographic location of its origin'. Long-time Congressman Jerry Nadler warned that criticising China, America's biggest rival, leads to hate crimes against Asian people in the United States. So shut up you bigot. China is fast closing in on Israel as a country that must not be criticised which is apt, really, given that Sabbatians control them both. The two countries have

developed close economic, military, technological and strategic ties which include involvement in China's 'Silk Road' transport and economic initiative to connect China with Europe. Israel was the first country in the Middle East to recognise the establishment of Mao's tyranny in 1950 months after it was established.

Project Wuhan – the 'Covid' Psyop

I emphasise again that the Cult plays the long game and what is happening to the world today is the result of centuries of calculated manipulation following a script to take control step-by-step of every aspect of human society. I will discuss later the common force behind all this that has spanned those centuries and thousands of years if the truth be told. Instigating the Mao revolution in China in 1949 with a 2020 'pandemic' in mind is not only how they work – the 71 years between them is really quite short by the Cult's standards of manipulation preparation. The reason for the Cult's Chinese revolution was to create a fiercely-controlled environment within which an extreme structure for human control could be incubated to eventually be unleashed across the world. We have seen this happen since the 'pandemic' emerged from China with the Chinese control-structure founded on AI technology and tyrannical enforcement sweep across the West. Until the moment when the Cult went for broke in the West and put its fascism on public display Western governments had to pay some lip-service to freedom and democracy to not alert too many people to the tyranny-in-the-making. Freedoms were more subtly eroded and power centralised with covert government structures put in place waiting for the arrival of 2020 when that smokescreen of 'freedom' could be dispensed with. The West was not able to move towards tyranny before 2020 anything like as fast as China which was created as a tyranny and had no limits on how fast it could construct the Cult's blueprint for global control. When the time came to impose that structure on the world it was the same Cult-owned Chinese communist/fascist government that provided the excuse – the 'Covid pandemic'. It was absolutely crucial to the Cult plan for the Chinese response to the 'pandemic' –

draconian lockdowns of the entire population – to become the blueprint that Western countries would follow to destroy the livelihoods and freedom of their people. This is why the Cult-owned, Gates-owned, WHO Director-General Tedros said early on:

The Chinese government is to be congratulated for the extraordinary measures it has taken to contain the outbreak. China is actually setting a new standard for outbreak response and it is not an exaggeration.

Forbes magazine said of China: '… those measures protected untold millions from getting the disease'. The Rockefeller Foundation 'epidemic scenario' document in 2010 said 'prophetically':

However, a few countries did fare better – China in particular. The Chinese government's quick imposition and enforcement of mandatory quarantine for all citizens, as well as its instant and near-hermetic sealing off of all borders, saved millions of lives, stopping the spread of the virus far earlier than in other countries and enabling a swifter post-pandemic recovery.

Once again – *spooky*.

The first official story was the 'bat theory' or rather the bat diversion. The source of the 'virus outbreak' we were told was a ''wet market' in Wuhan where bats and other animals are bought and eaten in horrifically unhygienic conditions. Then another story emerged through the alternative media that the 'virus' had been released on purpose or by accident from a BSL-4 (biosafety level 4) laboratory in Wuhan not far from the wet market. The lab was reported to create and work with lethal concoctions and bioweapons. Biosafety level 4 is the highest in the World Health Organization system of safety and containment. Renegade Minds are aware of what I call designer manipulation. The ideal for the Cult is for people to buy its prime narrative which in the opening salvoes of the 'pandemic' was the wet market story. It knows, however, that there is now a considerable worldwide alternative media of researchers sceptical of anything governments say and they are often given a version of events in a form they can perceive as credible while misdirecting them from the real truth. In this case let them

think that the conspiracy involved is a 'bioweapon virus' released from the Wuhan lab to keep them from the real conspiracy – *there is no 'virus'*. The WHO's current position on the source of the outbreak at the time of writing appears to be: 'We haven't got a clue, mate.' This is a good position to maintain mystery and bewilderment. The inner circle will know where the 'virus' came from – *nowhere*. The bottom line was to ensure the public believed there *was* a 'virus' and it didn't much matter if they thought it was natural or had been released from a lab. The belief that there was a 'deadly virus' was all that was needed to trigger global panic and fear. The population was terrified into handing their power to authority and doing what they were told. They had to or they were 'all gonna die'.

In March, 2020, information began to come my way from real doctors and scientists and my own additional research which had my intuition screaming: 'Yes, that's it! *There is no virus*.' The 'bioweapon' was not the 'virus'; it was the *'vaccine'* already being talked about that would be the bioweapon. My conclusion was further enhanced by happenings in Wuhan. The 'virus' was said to be sweeping the city and news footage circulated of people collapsing in the street (which they've never done in the West with the same 'virus'). The Chinese government was building 'new hospitals' in a matter of ten days to 'cope with demand' such was the virulent nature of the 'virus'. Yet in what seemed like no time the 'new hospitals' closed – even if they even opened – and China declared itself 'virus-free'. It was back to business as usual. This was more propaganda to promote the Chinese draconian lockdowns in the West as the way to 'beat the virus'. Trouble was that we subsequently had lockdown after lockdown, but never business as usual. As the people of the West and most of the rest of the world were caught in an ever-worsening spiral of lockdown, social distancing, masks, isolated old people, families forced apart, and livelihood destruction, it was party-time in Wuhan. Pictures emerged of thousands of people enjoying pool parties and concerts. It made no sense until you realised there never was a 'virus' and the

whole thing was a Cult set-up to transform human society out of one its major global strongholds – China.

How is it possible to deceive virtually the entire world population into believing there is a deadly virus when there is not even a 'virus' let alone a deadly one? It's nothing like as difficult as you would think and that's clearly true because it happened.

Postscript: See end of book Postscript for more on the 'Wuhan lab virus release' story which the authorities and media were pushing heavily in the summer of 2021 to divert attention from the truth that the 'Covid virus' is pure invention.

CHAPTER FIVE

There *is no* 'virus'

You can fool some of the people all of the time, and all of the people some of the time, but you cannot fool all of the people all of the time
Abraham Lincoln

The greatest form of mind control is repetition. The more you repeat the same mantra of alleged 'facts' the more will accept them to be true. It becomes an 'everyone knows that, mate'. If you can also censor any other version or alternative to your alleged 'facts' you are pretty much home and cooking.

By the start of 2020 the Cult owned the global mainstream media almost in its entirety to spew out its 'Covid' propaganda and ignore or discredit any other information and view. Cult-owned social media platforms in Cult-owned Silicon Valley were poised and ready to unleash a campaign of ferocious censorship to obliterate all but the official narrative. To complete the circle many demands for censorship by Silicon Valley were led by the mainstream media as 'journalists' became full-out enforcers for the Cult both as propagandists and censors. Part of this has been the influx of young people straight out of university who have become 'journalists' in significant positions. They have no experience and a headful of programmed perceptions from their years at school and university at a time when today's young are the most perceptually-targeted generations in known human history given the insidious impact of technology. They enter the media perceptually prepared and ready to repeat the narratives of the system that programmed them to

repeat its narratives. The BBC has a truly pathetic 'specialist disinformation reporter' called Marianna Spring who fits this bill perfectly. She is clueless about the world, how it works and what is really going on. Her role is to discredit anyone doing the job that a proper journalist would do and system-serving hacks like Spring wouldn't dare to do or even see the need to do. They are too busy licking the arse of authority which can never be wrong and, in the case of the BBC propaganda programme, *Panorama*, contacting payments systems such as PayPal to have a donations page taken down for a film company making documentaries questioning vaccines. Even the BBC soap opera *EastEnders* included a disgracefully biased scene in which an inarticulate white working class woman was made to look foolish for questioning the 'vaccine' while a well-spoken black man and Asian woman promoted the government narrative. It ticked every BBC box and the fact that the black and minority community was resisting the 'vaccine' had nothing to do with the way the scene was written. The BBC has become a disgusting tyrannical propaganda and censorship operation that should be defunded and disbanded and a free media take its place with a brief to stop censorship instead of demanding it. A BBC 'interview' with Gates goes something like: 'Mr Gates, sir, if I can call you sir, would you like to tell our audience why you are such a great man, a wonderful humanitarian philanthropist, and why you should absolutely be allowed as a software salesman to decide health policy for approaching eight billion people? Thank you, sir, please sir.' Propaganda programming has been incessant and merciless and when all you hear is the same story from the media, repeated by those around you who have only heard the same story, is it any wonder that people on a grand scale believe absolute mendacious garbage to be true? You are about to see, too, why this level of information control is necessary when the official 'Covid' narrative is so nonsensical and unsupportable by the evidence.

Structure of Deceit

The pyramid structure through which the 'Covid' hoax has been manifested is very simple and has to be to work. As few people as possible have to be involved with full knowledge of what they are doing – and why – or the real story would get out. At the top of the pyramid are the inner core of the Cult which controls Bill Gates who, in turn, controls the World Health Organization through his pivotal funding and his puppet Director-General mouthpiece, Tedros. Before he was appointed Tedros was chair of the Gates-founded Global Fund to 'fight against AIDS, tuberculosis and malaria', a board member of the Gates-funded 'vaccine alliance' GAVI, and on the board of another Gates-funded organisation. Gates owns him and picked him for a specific reason – Tedros is a crook and worse. 'Dr' Tedros (he's not a medical doctor, the first WHO chief not to be) was a member of the tyrannical Marxist government of Ethiopia for decades with all its human rights abuses. He has faced allegations of corruption and misappropriation of funds and was exposed three times for covering up cholera epidemics while Ethiopia's health minister. Tedros appointed the mass-murdering genocidal Zimbabwe dictator Robert Mugabe as a WHO goodwill ambassador for public health which, as with Tedros, is like appointing a psychopath to run a peace and love campaign. The move was so ridiculous that he had to drop Mugabe in the face of widespread condemnation. American economist David Steinman, a Nobel peace prize nominee, lodged a complaint with the International Criminal Court in The Hague over alleged genocide by Tedros when he was Ethiopia's foreign minister. Steinman says Tedros was a 'crucial decision maker' who directed the actions of Ethiopia's security forces from 2013 to 2015 and one of three officials in charge when those security services embarked on the 'killing' and 'torturing' of Ethiopians. You can see where Tedros is coming from and it's sobering to think that he has been the vehicle for Gates and the Cult to direct the global response to 'Covid'. Think about that. A psychopathic Cult dictates to psychopath Gates who dictates to psychopath Tedros who dictates how countries of the world must respond to a 'Covid virus' never scientifically shown to exist. At the same time psychopathic Cult-owned Silicon Valley information

giants like Google, YouTube, Facebook and Twitter announced very early on that they would give the Cult/Gates/Tedros/WHO version of the narrative free advertising and censor those who challenged their intelligence-insulting, mendacious story.

The next layer in the global 'medical' structure below the Cult, Gates and Tedros are the chief medical officers and science 'advisers' in each of the WHO member countries which means virtually all of them. Medical officers and arbiters of science (they're not) then take the WHO policy and recommended responses and impose them on their country's population while the political 'leaders' say they are deciding policy (they're clearly not) by 'following the science' on the advice of the 'experts' – the same medical officers and science 'advisers' (dictators). In this way with the rarest of exceptions the entire world followed the same policy of lockdown, people distancing, masks and 'vaccines' dictated by the psychopathic Cult, psychopathic Gates and psychopathic Tedros who we are supposed to believe give a damn about the health of the world population they are seeking to enslave. That, amazingly, is all there is to it in terms of crucial decision-making. Medical staff in each country then follow like sheep the dictates of the shepherds at the top of the national medical hierarchies – chief medical officers and science 'advisers' who themselves follow like sheep the shepherds of the World Health Organization and the Cult. Shepherds at the national level often have major funding and other connections to Gates and his Bill and Melinda Gates Foundation which carefully hands out money like confetti at a wedding to control the entire global medical system from the WHO down.

Follow the money

Christopher Whitty, Chief Medical Adviser to the UK Government at the centre of 'virus' policy, a senior adviser to the government's Scientific Advisory Group for Emergencies (SAGE), and Executive Board member of the World Health Organization, was gifted a grant of $40 million by the Bill and Melinda Gates Foundation for malaria research in Africa. The BBC described the unelected Whitty as 'the

official who will probably have the greatest impact on our everyday lives of any individual policymaker in modern times' and so it turned out. What Gates and Tedros have said Whitty has done like his equivalents around the world. Patrick Vallance, co-chair of SAGE and the government's Chief Scientific Adviser, is a former executive of Big Pharma giant GlaxoSmithKline with its fundamental financial and business connections to Bill Gates. In September, 2020, it was revealed that Vallance owned a deferred bonus of shares in GlaxoSmithKline worth £600,000 while the company was 'developing' a 'Covid vaccine'. Move along now – nothing to see here – what could possibly be wrong with that? Imperial College in London, a major player in 'Covid' policy in Britain and elsewhere with its 'Covid-19' Response Team, is funded by Gates and has big connections to China while the now infamous Professor Neil Ferguson, the useless 'computer modeller' at Imperial College is also funded by Gates. Ferguson delivered the dramatically inaccurate excuse for the first lockdowns (much more in the next chapter). The Institute for Health Metrics and Evaluation (IHME) in the United States, another source of outrageously false 'Covid' computer models to justify lockdowns, is bankrolled by Gates who is a vehement promotor of lockdowns. America's version of Whitty and Vallance, the again now infamous Anthony Fauci, has connections to 'Covid vaccine' maker Moderna as does Bill Gates through funding from the Bill and Melinda Gates Foundation. Fauci is director of the National Institute of Allergy and Infectious Diseases (NIAID), a major recipient of Gates money, and they are very close. Deborah Birx who was appointed White House Coronavirus Response Coordinator in February, 2020, is yet another with ties to Gates. Everywhere you look at the different elements around the world behind the coordination and decision making of the 'Covid' hoax there is Bill Gates and his money. They include the World Health Organization; Centers for Disease Control (CDC) in the United States; National Institutes of Health (NIH) of Anthony Fauci; Imperial College and Neil Ferguson; the London School of Hygiene where Chris Whitty worked; Regulatory agencies like the UK Medicines & Healthcare products Regulatory Agency (MHRA)

which gave emergency approval for 'Covid vaccines'; Wellcome Trust; GAVI, the Vaccine Alliance; the Coalition for Epidemic Preparedness Innovations (CEPI); Johns Hopkins University which has compiled the false 'Covid' figures; and the World Economic Forum. A Nationalfile.com article said:

> Gates has a lot of pull in the medical world, he has a multi-million dollar relationship with Dr. Fauci, and Fauci originally took the Gates line supporting vaccines and casting doubt on [the drug hydroxychloroquine]. Coronavirus response team member Dr. Deborah Birx, appointed by former president Obama to serve as United States Global AIDS Coordinator, also sits on the board of a group that has received billions from Gates' foundation, and Birx reportedly used a disputed Bill Gates-funded model for the White House's Coronavirus effort. Gates is a big proponent for a population lockdown scenario for the Coronavirus outbreak.

Another funder of Moderna is the Defense Advanced Research Projects Agency (DARPA), the technology-development arm of the Pentagon and one of the most sinister organisations on earth. DARPA had a major role with the CIA covert technology-funding operation In-Q-Tel in the development of Google and social media which is now at the centre of global censorship. Fauci and Gates are extremely close and openly admit to talking regularly about 'Covid' policy, but then why wouldn't Gates have a seat at every national 'Covid' table after his Foundation committed $1.75 billion to the 'fight against Covid-19'. When passed through our Orwellian Translation Unit this means that he has bought and paid for the Cult-driven 'Covid' response worldwide. Research the major 'Covid' response personnel in your own country and you will find the same Gates funding and other connections again and again. Medical and science chiefs following World Health Organization 'policy' sit atop a medical hierarchy in their country of administrators, doctors and nursing staff. These 'subordinates' are told they must work and behave in accordance with the policy delivered from the 'top' of the national 'health' pyramid which is largely the policy delivered by the WHO which is the policy delivered by Gates and the Cult. The whole 'Covid' narrative has been imposed on medical staff by a climate of fear although great numbers don't even need that to comply. They do so through breathtaking levels of ignorance and

include doctors who go through life simply repeating what Big Pharma and their hierarchical masters tell them to say and believe. No wonder Big Pharma 'medicine' is one of the biggest killers on Planet Earth.

The same top-down system of intimidation operates with regard to the Cult Big Pharma cartel which also dictates policy through national and global medical systems in this way. The Cult and Big Pharma agendas are the same because the former controls and owns the latter. 'Health' administrators, doctors, and nursing staff are told to support and parrot the dictated policy or they will face consequences which can include being fired. How sad it's been to see medical staff meekly repeating and imposing Cult policy without question and most of those who can see through the deceit are only willing to speak anonymously off the record. They know what will happen if their identity is known. This has left the courageous few to expose the lies about the 'virus', face masks, overwhelmed hospitals that aren't, and the dangers of the 'vaccine' that isn't a vaccine. When these medical professionals and scientists, some renowned in their field, have taken to the Internet to expose the truth their articles, comments and videos have been deleted by Cult-owned Facebook, Twitter and YouTube. What a real head-shaker to see YouTube videos with leading world scientists and highly qualified medical specialists with an added link underneath to the notorious Cult propaganda website *Wikipedia* to find the 'facts' about the same subject.

HIV – the 'Covid' trial-run

I'll give you an example of the consequences for health and truth that come from censorship and unquestioning belief in official narratives. The story was told by PCR inventor Kary Mullis in his book *Dancing Naked in the Mind Field*. He said that in 1984 he accepted as just another scientific fact that Luc Montagnier of France's Pasteur Institute and Robert Gallo of America's National Institutes of Health had independently discovered that a 'retrovirus' dubbed HIV (human immunodeficiency virus) caused AIDS. They

were, after all, Mullis writes, specialists in retroviruses. This is how the medical and science pyramids work. Something is announced or *assumed* and then becomes an everybody-knows-that purely through repetition of the assumption as if it is fact. Complete crap becomes accepted truth with no supporting evidence and only repetition of the crap. This is how a 'virus' that doesn't exist became the 'virus' that changed the world. The HIV-AIDS fairy story became a multi-billion pound industry and the media poured out propaganda terrifying the world about the deadly HIV 'virus' that caused the lethal AIDS. By then Mullis was working at a lab in Santa Monica, California, to detect retroviruses with his PCR test in blood donations received by the Red Cross. In doing so he asked a virologist where he could find a reference for HIV being the cause of AIDS. 'You don't need a reference,' the virologist said … *'Everybody knows it.'* Mullis said he wanted to quote a reference in the report he was doing and he said he felt a little funny about not knowing the source of such an important discovery when everyone else seemed to. The virologist suggested he cite a report by the Centers for Disease Control and Prevention (CDC) on morbidity and mortality. Mullis read the report, but it only said that an organism had been identified and did not say how. The report did not identify the original scientific work. Physicians, however, *assumed* (key recurring theme) that if the CDC was convinced that HIV caused AIDS then proof must exist. Mullis continues:

I did computer searches. Neither Montagnier, Gallo, nor anyone else had published papers describing experiments which led to the conclusion that HIV probably caused AIDS. I read the papers in Science for which they had become well known as AIDS doctors, but all they had said there was that they had found evidence of a past infection by something which was probably HIV in some AIDS patients.

They found antibodies. Antibodies to viruses had always been considered evidence of past disease, not present disease. Antibodies signaled that the virus had been defeated. The patient had saved himself. There was no indication in these papers that this virus caused a disease. They didn't show that everybody with the antibodies had the disease. In fact they found some healthy people with antibodies.

Mullis asked why their work had been published if Montagnier and Gallo hadn't really found this evidence, and why had they been fighting so hard to get credit for the discovery? He says he was hesitant to write 'HIV is the probable cause of AIDS' until he found published evidence to support that. 'Tens of thousands of scientists and researchers were spending billions of dollars a year doing research based on this idea,' Mullis writes. 'The reason had to be there somewhere; otherwise these people would not have allowed their research to settle into one narrow channel of investigation.' He said he lectured about PCR at numerous meetings where people were always talking about HIV and he asked them how they knew that HIV was the cause of AIDS:

> Everyone said something. Everyone had the answer at home, in the office, in some drawer. They all knew, and they would send me the papers as soon as they got back. But I never got any papers. Nobody ever sent me the news about how AIDS was caused by HIV.

Eventually Mullis was able to ask Montagnier himself about the reference proof when he lectured in San Diego at the grand opening of the University of California AIDS Research Center. Mullis says this was the last time he would ask his question without showing anger. Montagnier said he should reference the CDC report. 'I read it', Mullis said, and it didn't answer the question. 'If Montagnier didn't know the answer who the hell did?' Then one night Mullis was driving when an interview came on National Public Radio with Peter Duesberg, a prominent virologist at Berkeley and a California Scientist of the Year. Mullis says he finally understood why he could not find references that connected HIV to AIDS – *there weren't any!* No one had ever proved that HIV causes AIDS even though it had spawned a multi-billion pound global industry and the media was repeating this as fact every day in their articles and broadcasts terrifying the shit out of people about AIDS and giving the impression that a positive test for HIV (see 'Covid') was a death sentence. Duesberg was a threat to the AIDS gravy train and the agenda that underpinned it. He was therefore abused and castigated after he told the Proceedings of the National Academy of Sciences

there was no good evidence implicating the new 'virus'. Editors rejected his manuscripts and his research funds were deleted. Mullis points out that the CDC has defined AIDS as one of more than 30 diseases *if accompanied* by a positive result on a test that detects antibodies to HIV; but those same diseases are not defined as AIDS cases when antibodies are not detected:

> If an HIV-positive woman develops uterine cancer, for example, she is considered to have AIDS. If she is not HIV positive, she simply has uterine cancer. An HIV-positive man with tuberculosis has AIDS; if he tests negative he simply has tuberculosis. If he lives in Kenya or Colombia, where the test for HIV antibodies is too expensive, he is simply presumed to have the antibodies and therefore AIDS, and therefore he can be treated in the World Health Organization's clinic. It's the only medical help available in some places. And it's free, because the countries that support WHO are worried about AIDS.

Mullis accuses the CDC of continually adding new diseases (see ever more 'Covid symptoms') to the grand AIDS definition and of virtually doctoring the books to make it appear as if the disease continued to spread. He cites how in 1993 the CDC enormously broadened its AIDS definition and county health authorities were delighted because they received $2,500 per year from the Federal government for every reported AIDS case. Ladies and gentlemen, I have just described, via Kary Mullis, the 'Covid pandemic' of 2020 and beyond. Every element is the same and it's been pulled off in the same way by the same networks.

The 'Covid virus' exists? Okay – prove it. Er … still waiting

What Kary Mullis described with regard to 'HIV' has been repeated with 'Covid'. A claim is made that a new, or 'novel', infection has been found and the entire medical system of the world repeats that as fact exactly as they did with HIV and AIDS. No one in the mainstream asks rather relevant questions such as 'How do you know?' and 'Where is your proof?' The SARS-Cov-2 'virus' and the 'Covid-19 disease' became an overnight 'everybody-knows-that'. The origin could be debated and mulled over, but what you could not suggest was that 'SARS-Cov-2' didn't exist. That would be

ridiculous. 'Everybody knows' the 'virus' exists. Well, I didn't for one along with American proper doctors like Andrew Kaufman and Tom Cowan and long-time American proper journalist Jon Rappaport. We dared to pursue the obvious and simple question: 'Where's the evidence?' The overwhelming majority in medicine, journalism and the general public did not think to ask that. After all, *everyone knew* there was a new 'virus'. Everyone was saying so and I heard it on the BBC. Some would eventually argue that the 'deadly virus' was nothing like as deadly as claimed, but few would venture into the realms of its very existence. Had they done so they would have found that the evidence for that claim had gone AWOL as with HIV causes AIDS. In fact, not even that. For something to go AWOL it has to exist in the first place and scientific proof for a 'SARS-Cov-2' can be filed under nothing, nowhere and zilch.

Dr Andrew Kaufman is a board-certified forensic psychiatrist in New York State, a Doctor of Medicine and former Assistant Professor and Medical Director of Psychiatry at SUNY Upstate Medical University, and Medical Instructor of Hematology and Oncology at the Medical School of South Carolina. He also studied biology at the Massachusetts Institute of Technology (MIT) and trained in Psychiatry at Duke University. Kaufman is retired from allopathic medicine, but remains a consultant and educator on natural healing, I saw a video of his very early on in the 'Covid' hoax in which he questioned claims about the 'virus' in the absence of any supporting evidence and with plenty pointing the other way. I did everything I could to circulate his work which I felt was asking the pivotal questions that needed an answer. I can recommend an excellent pull-together interview he did with the website The Last Vagabond entitled *Dr Andrew Kaufman: Virus Isolation, Terrain Theory and Covid-19* and his website is andrewkaufmanmd.com. Kaufman is not only a forensic psychiatrist; he is forensic in all that he does. He always reads original scientific papers, experiments and studies instead of second-third-fourth-hand reports about the 'virus' in the media which are repeating the repeated repetition of the narrative. When he did so with the original Chinese 'virus' papers Kaufman

realised that there was no evidence of a 'SARS-Cov-2'. They had never – from the start – shown it to exist and every repeat of this claim worldwide was based on the accepted existence of proof that was nowhere to be found – see Kary Mullis and HIV. Here we go again.

Let's postulate

Kaufman discovered that the Chinese authorities immediately concluded that the cause of an illness that broke out among about 200 initial patients in Wuhan was a 'new virus' when there were no grounds to make that conclusion. The alleged 'virus' was not isolated from other genetic material in their samples and then shown through a system known as Koch's postulates to be the causative agent of the illness. The world was told that the SARS-Cov-2 'virus' caused a disease they called 'Covid-19' which had 'flu-like' symptoms and could lead to respiratory problems and pneumonia. If it wasn't so tragic it would almost be funny. *'Flu-like' symptoms'? Pneumonia? Respiratory disease?* What in *CHINA* and particularly in *Wuhan*, one of the most polluted cities in the world with a resulting epidemic of respiratory disease?? Three hundred thousand people get pneumonia in China every year and there are nearly a billion cases worldwide of 'flu-like symptoms'. These have a whole range of causes – including pollution in Wuhan – but no other possibility was credibly considered in late 2019 when the world was told there was a new and deadly 'virus'. The global prevalence of pneumonia and 'flu-like systems' gave the Cult networks unlimited potential to re-diagnose these other causes as the mythical 'Covid-19' and that is what they did from the very start. Kaufman revealed how Chinese medical and science authorities (all subordinates to the Cult-owned communist government) took genetic material from the lungs of only a few of the first patients. The material contained their own cells, bacteria, fungi and other microorganisms living in their bodies. The only way you could prove the existence of the 'virus' and its responsibility for the alleged 'Covid-19' was to isolate the virus from all the other material – a process also known as 'purification' – and

then follow the postulates sequence developed in the late 19th century by German physician and bacteriologist Robert Koch which became the 'gold standard' for connecting an alleged causation agent to a disease:

1. The microorganism (bacteria, fungus, virus, etc.) must be present in every case of the disease and all patients must have the same symptoms. It must also *not be present in healthy individuals*.

2. The microorganism must be isolated from the host with the disease. If the microorganism is a bacteria or fungus it must be grown in a pure culture. If it is a virus, it must be purified (i.e. containing no other material except the virus particles) from a clinical sample.

3. The specific disease, with all of its characteristics, must be reproduced when the infectious agent (the purified virus or a pure culture of bacteria or fungi) is inoculated into a healthy, susceptible host.

4. The microorganism must be recoverable from the experimentally infected host as in step 2.

Not one of these criteria has been met in the case of 'SARS-Cov-2' and 'Covid-19'. Not ONE. *EVER*. Robert Koch refers to bacteria and not viruses. What are called 'viral particles' are so minute (hence masks are useless by any definition) that they could only be seen after the invention of the electron microscope in the 1930s and can still only be observed through that means. American bacteriologist and virologist Thomas Milton Rivers, the so-called 'Father of Modern Virology' who was very significantly director of the Rockefeller Institute for Medical Research in the 1930s, developed a less stringent version of Koch's postulates to identify 'virus' causation known as 'Rivers criteria'. 'Covid' did not pass that process either. Some even doubt whether any 'virus' can be isolated from other particles containing genetic material in the Koch method. Freedom of Information requests in many countries asking for scientific proof that the 'Covid virus' has been purified and isolated and shown to exist have all come back with a 'we don't have that' and when this happened with a request to the UK Department of Health they added this comment:

However, outside of the scope of the [Freedom of Information Act] and on a discretionary basis, the following information has been advised to us, which may be of interest. Most infectious diseases are caused by viruses, bacteria or fungi. Some bacteria or fungi have the capacity to grow on their own in isolation, for example in colonies on a petri dish. Viruses are different in that they are what we call 'obligate pathogens' – that is, they cannot survive or reproduce without infecting a host ...

… For some diseases, it is possible to establish causation between a microorganism and a disease by isolating the pathogen from a patient, growing it in pure culture and reintroducing it to a healthy organism. These are known as 'Koch's postulates' and were developed in 1882. However, as our understanding of disease and different disease-causing agents has advanced, these are no longer the method for determining causation [Andrew Kaufman asks why in that case are there two published articles falsely claiming to satisfy Koch's postulates].

It has long been known that viral diseases cannot be identified in this way as viruses cannot be grown in 'pure culture'. When a patient is tested for a viral illness, this is normally done by looking for the presence of antigens, or viral genetic code in a host with molecular biology techniques [Kaufman asks how you could know the origin of these chemicals without having a pure culture for comparison].

For the record 'antigens' are defined so:

Invading microorganisms have antigens on their surface that the human body can recognise as being foreign – meaning not belonging to it. When the body recognises a foreign antigen, lymphocytes (white blood cells) produce antibodies, which are complementary in shape to the antigen.

Notwithstanding that this is open to question in relation to 'SARS-Cov-2' the presence of 'antibodies' can have many causes and they are found in people that are perfectly well. Kary Mullis said: 'Antibodies … had always been considered evidence of past disease, not present disease.'

'Covid' really is a *computer* 'virus'

Where the UK Department of Health statement says 'viruses' are now 'diagnosed' through a 'viral genetic code in a host with molecular biology techniques', they mean … *the PCR test* which its inventor said cannot test for infectious disease. They have no credible method of connecting a 'virus' to a disease and we will see that there is no scientific proof that any 'virus' causes any disease or there is any such thing as a 'virus' in the way that it is described. Tenacious Canadian researcher Christine Massey and her team made

some 40 Freedom of Information requests to national public health agencies in different countries asking for proof that SARS-CoV-2 has been isolated and not one of them could supply that information. Massey said of her request in Canada: 'Freedom of Information reveals Public Health Agency of Canada has no record of 'SARS-COV-2' isolation performed by anyone, anywhere, ever.' If you accept the comment from the UK Department of Health it's because they can't isolate a 'virus'. Even so many 'science' papers claimed to have isolated the 'Covid virus' until they were questioned and had to admit they hadn't. A reply from the Robert Koch Institute in Germany was typical: 'I am not aware of a paper which purified isolated SARS-CoV-2.' So what the hell was Christian Drosten and his gang using to design the 'Covid' testing protocol that has produced all the illusory Covid' cases and 'Covid' deaths when the head of the Chinese version of the CDC admitted there was a problem right from the start in that the 'virus' had never been isolated/purified? Breathe deeply: What they are calling 'Covid' is actually created by a *computer program* i.e. *they made it up* – er, that's it. They took lung fluid, with many sources of genetic material, from one single person alleged to be infected with Covid-19 by a PCR test which they *claimed*, without clear evidence, contained a 'virus'. They used several computer programs to create a model of a theoretical virus genome sequence from more than fifty-six million small sequences of RNA, each of an unknown source, assembling them like a puzzle with no known solution. The computer filled in the gaps with sequences from bits in the gene bank to make it look like a bat SARS-like coronavirus! A wave of the magic wand and poof, an in silico (computer-generated) genome, a scientific fantasy, was created. UK health researcher Dr Kevin Corbett made the same point with this analogy:

> … It's like giving you a few bones and saying that's your fish. It could be any fish. Not even a skeleton. Here's a few fragments of bones. That's your fish … It's all from gene bank and the bits of the virus sequence that weren't there they made up.
>
> They synthetically created them to fill in the blanks. That's what genetics is; it's a code. So it's ABBBCCDDD and you're missing some what you think is EEE so you put it in. It's all

synthetic. You just manufacture the bits that are missing. This is the end result of the geneticization of virology. This is basically a computer virus.

Further confirmation came in an email exchange between British citizen journalist Frances Leader and the government's Medicines & Healthcare Products Regulatory Agency (the Gates-funded MHRA) which gave emergency permission for untested 'Covid vaccines' to be used. The agency admitted that the 'vaccine' is not based on an isolated 'virus', but comes from a *computer-generated model*. Frances Leader was naturally banned from Cult-owned fascist Twitter for making this exchange public. The process of creating computer-generated alleged 'viruses' is called 'in silico' or 'in silicon' – computer chips – and the term 'in silico' is believed to originate with biological experiments using only a computer in 1989. 'Vaccines' involved with 'Covid' are also produced 'in silico' or by computer not a natural process. If the original 'virus' is nothing more than a made-up computer model how can there be 'new variants' of something that never existed in the first place? They are not new 'variants'; they are new *computer models* only minutely different to the original program and designed to further terrify the population into having the 'vaccine' and submitting to fascism. You want a 'new variant'? Click, click, enter – there you go. Tell the medical profession that you have discovered a 'South African variant', 'UK variants' or a 'Brazilian variant' and in the usual HIV-causes-AIDS manner they will unquestioningly repeat it with no evidence whatsoever to support these claims. They will go on television and warn about the dangers of 'new variants' while doing nothing more than repeating what they have been told to be true and knowing that any deviation from that would be career suicide. Big-time insiders will know it's a hoax, but much of the medical community is clueless about the way they are being played and themselves play the public without even being aware they are doing so. What an interesting 'coincidence' that AstraZeneca and Oxford University were conducting 'Covid vaccine trials' in the three countries – the UK, South Africa and Brazil – where the first three 'variants' were claimed to have 'broken out'.

Here's your 'virus' – it's a unicorn

Dr Andrew Kaufman presented a brilliant analysis describing how the 'virus' was imagined into fake existence when he dissected an article published by *Nature* and written by 19 authors detailing *alleged* 'sequencing of a complete viral genome' of the 'new SARS-CoV-2 virus'. This computer-modelled *in silico* genome was used as a template for all subsequent genome sequencing experiments that resulted in the so-called variants which he said now number more than *6,000*. The fake genome was constructed from more than 56 million individual short strands of RNA. Those little pieces were assembled into longer pieces by finding areas of overlapping sequences. The computer programs created over two million possible combinations from which the authors simply chose the longest one. They then compared this to a 'bat virus' and the computer 'alignment' rearranged the sequence and filled in the gaps! They called this computer-generated abomination the 'complete genome'. Dr Tom Cowan, a fellow medical author and collaborator with Kaufman, said such computer-generation constitutes scientific fraud and he makes this superb analogy:

> Here is an equivalency: A group of researchers claim to have found a unicorn because they found a piece of a hoof, a hair from a tail, and a snippet of a horn. They then add that information into a computer and program it to re-create the unicorn, and they then claim this computer re-creation is the real unicorn. Of course, they had never actually seen a unicorn so could not possibly have examined its genetic makeup to compare their samples with the actual unicorn's hair, hooves and horn.
>
> The researchers claim they decided which is the real genome of SARS-CoV-2 by 'consensus', sort of like a vote. Again, different computer programs will come up with different versions of the imaginary 'unicorn', so they come together as a group and decide which is the real imaginary unicorn.

This is how the 'virus' that has transformed the world was brought into fraudulent 'existence'. Extraordinary, yes, but as the Nazis said the bigger the lie the more will believe it. Cowan, however, wasn't finished and he went on to identify what he called the real blockbuster in the paper. He quotes this section from a paper written

by virologists and published by the CDC and then explains what it means:

Therefore, we examined the capacity of SARS-CoV-2 to infect and replicate in several common primate and human cell lines, including human adenocarcinoma cells (A549), human liver cells (HUH 7.0), and human embryonic kidney cells (HEK-293T). In addition to Vero E6 and Vero CCL81 cells. ... Each cell line was inoculated at high multiplicity of infection and examined 24h post-infection.

No CPE was observed in any of the cell lines except in Vero cells, which grew to greater than 10 to the 7th power at 24 h post-infection. In contrast, HUH 7.0 and 293T showed only modest viral replication, and A549 cells were incompatible with SARS CoV-2 infection.

Cowan explains that when virologists attempt to prove infection they have three possible 'hosts' or models on which they can test. The first was humans. Exposure to humans was generally not done for ethical reasons and has never been done with SARS-CoV-2 or any coronavirus. The second possible host was animals. Cowan said that forgetting for a moment that they never actually use purified virus when exposing animals they do use solutions that they *claim* contain the virus. Exposure to animals has been done with SARS-CoV-2 in an experiment involving mice and this is what they found: *None of the wild (normal) mice got sick*. In a group of genetically-modified mice, a statistically insignificant number lost weight and had slightly bristled fur, but they experienced nothing like the illness called 'Covid-19'. Cowan said the third method – the one they mostly rely on – is to inoculate solutions they *say* contain the virus onto a variety of tissue cultures. This process had never been shown to kill tissue *unless* the sample material was starved of nutrients and poisoned as *part of the process*. Yes, incredibly, in tissue experiments designed to show the 'virus' is responsible for killing the tissue they starve the tissue of nutrients and add toxic drugs including antibiotics and they do not have control studies to see if it's the starvation and poisoning that is degrading the tissue rather than the 'virus' they allege to be in there somewhere. You want me to pinch you? Yep, I understand. Tom Cowan said this about the whole nonsensical farce as he explains what that quote from the CDC paper really means:

The shocking thing about the above quote is that using their own methods, the virologists found that solutions containing SARS-CoV-2 – even in high amounts – were NOT, I repeat NOT, infective to any of the three human tissue cultures they tested. In plain English, this means they proved, on their terms, that this 'new coronavirus' is not infectious to human beings. It is ONLY infective to monkey kidney cells, and only then when you add two potent drugs (gentamicin and amphotericin), known to be toxic to kidneys, to the mix.

My friends, read this again and again. These virologists, published by the CDC, performed a clear proof, on their terms, showing that the SARS-CoV-2 virus is harmless to human beings. That is the only possible conclusion, but, unfortunately, this result is not even mentioned in their conclusion. They simply say they can provide virus stocks cultured only on monkey Vero cells, thanks for coming.

Cowan concluded: 'If people really understood how this "science" was done, I would hope they would storm the gates and demand honesty, transparency and truth.' Dr Michael Yeadon, former Vice President and Chief Scientific Adviser at drug giant Pfizer has been a vocal critic of the 'Covid vaccine' and its potential for multiple harm. He said in an interview in April, 2021, that 'not one [vaccine] has the virus. He was asked why vaccines normally using a 'dead' version of a disease to activate the immune system were not used for 'Covid' and instead we had the synthetic methods of the 'mRNA Covid vaccine'. Yeadon said that to do the former 'you'd have to have some of [the virus] wouldn't you?' He added: 'No-one's got any – seriously.' Yeadon said that surely they couldn't have fooled the whole world for a year without having a virus, 'but oddly enough ask around – no one's got it'. He didn't know why with all the 'great labs' around the world that the virus had not been isolated – 'Maybe they've been too busy running bad PCR tests and vaccines that people don't need.' What is today called 'science' is not 'science' at all. Science is no longer what is, but whatever people can be manipulated to *believe* that it is. Real science has been hijacked by the Cult to dispense and produce the 'expert scientists' and contentions that suit the agenda of the Cult. How big-time this has happened with the 'Covid' hoax which is entirely based on fake science delivered by fake 'scientists' and fake 'doctors'. The human-caused climate change hoax is also entirely based on fake science delivered by fake 'scientists' and fake 'climate experts'. In both cases real

scientists, climate experts and doctors have their views suppressed and deleted by the Cult-owned science establishment, media and Silicon Valley. This is the 'science' that politicians claim to be 'following' and a common denominator of 'Covid' and climate are Cult psychopaths Bill Gates and his mate Klaus Schwab at the Gates-funded World Economic Forum. But, don't worry, it's all just a coincidence and absolutely nothing to worry about. *Zzzzzzzz*.

What is a 'virus' REALLY?

Dr Tom Cowan is one of many contesting the very existence of viruses let alone that they cause disease. This is understandable when there is no scientific evidence for a disease-causing 'virus'. German virologist Dr Stefan Lanka won a landmark case in 2017 in the German Supreme Court over his contention that there is no such thing as a measles virus. He had offered a big prize for anyone who could prove there is and Lanka won his case when someone sought to claim the money. There is currently a prize of more than 225,000 euros on offer from an Isolate Truth Fund for anyone who can prove the isolation of SARS-CoV-2 and its genetic substance. Lanka wrote in an article headed 'The Misconception Called Virus' that scientists think a 'virus' is causing tissue to become diseased and degraded when in fact it is the *processes they are using* which do that – not a 'virus'. Lanka has done an important job in making this point clear as Cowan did in his analysis of the CDC paper. Lanka says that all claims about viruses as disease-causing pathogens are wrong and based on 'easily recognisable, understandable and verifiable misinterpretations.' Scientists believed they were working with 'viruses' in their laboratories when they were really working with 'typical particles of specific dying tissues or cells …' Lanka said that the tissue decaying process claimed to be caused by a 'virus' still happens when no alleged 'virus' is involved. It's the *process* that does the damage and not a 'virus'. The genetic sample is deprived of nutrients, removed from its energy supply through removal from the body and then doused in toxic antibiotics to remove any bacteria. He confirms again that establishment scientists do not (pinch me)

conduct control experiments to see if this is the case and if they did they would see the claims that 'viruses' are doing the damage is nonsense. He adds that during the measles 'virus' court case he commissioned an independent laboratory to perform just such a control experiment and the result was that the tissues and cells died in the exact same way as with alleged 'infected' material. This is supported by a gathering number of scientists, doctors and researchers who reject what is called 'germ theory' or the belief in the body being infected by contagious sources emitted by other people. Researchers Dawn Lester and David Parker take the same stance in their highly-detailed and sourced book *What Really Makes You Ill – Why everything you thought you knew about disease is wrong* which was recommended to me by a number of medical professionals genuinely seeking the truth. Lester and Parker say there is no provable scientific evidence to show that a 'virus' can be transmitted between people or people and animals or animals and people:

> The definition also claims that viruses are the cause of many diseases, as if this has been definitively proven. But this is not the case; there is no original scientific evidence that definitively demonstrates that any virus is the cause of any disease. The burden of proof for any theory lies with those who proposed it; but none of the existing documents provides 'proof' that supports the claim that 'viruses' are pathogens.

Dr Tom Cowan employs one of his clever analogies to describe the process by which a 'virus' is named as the culprit for a disease when what is called a 'virus' is only material released by cells detoxing themselves from infiltration by chemical or radiation poisoning. The tidal wave of technologically-generated radiation in the 'smart' modern world plus all the toxic food and drink are causing this to happen more than ever. Deluded 'scientists' misread this as a gathering impact of what they wrongly label 'viruses'.

Paper can infect houses

Cowan said in an article for davidicke.com – with his tongue only mildly in his cheek – that he believed he had made a tremendous

discovery that may revolutionise science. He had discovered that small bits of paper are alive, 'well alive-ish', can 'infect' houses, and then reproduce themselves inside the house. The result was that this explosion of growth in the paper inside the house causes the house to explode, blowing it to smithereens. His evidence for this new theory is that in the past months he had carefully examined many of the houses in his neighbourhood and found almost no scraps of paper on the lawns and surrounds of the house. There was an occasional stray label, but nothing more. Then he would return to these same houses a week or so later and with a few, not all of them, particularly the old and decrepit ones, he found to his shock and surprise they were littered with stray bits of paper. He knew then that the paper had infected these houses, made copies of itself, and blew up the house. A young boy on a bicycle at one of the sites told him he had seen a demolition crew using dynamite to explode the house the previous week, but Cowan dismissed this as the idle thoughts of silly boys because 'I was on to something big'. He was on to how 'scientists' mistake genetic material in the detoxifying process for something they call a 'virus'. Cowan said of his house and paper story:

> If this sounds crazy to you, it's because it should. This scenario is obviously nuts. But consider this admittedly embellished, for effect, current viral theory that all scientists, medical doctors and virologists currently believe.

He takes the example of the 'novel SARS-Cov2' virus to prove the point. First they take someone with an undefined illness called 'Covid-19' and don't even attempt to find any virus in their sputum. Never mind the scientists still describe how this 'virus', which they have not located attaches to a cell receptor, injects its genetic material, in 'Covid's' case, RNA, into the cell. The RNA once inserted exploits the cell to reproduce itself and makes 'thousands, nay millions, of copies of itself … Then it emerges victorious to claim its next victim':

If you were to look in the scientific literature for proof, actual scientific proof, that uniform SARS-CoV2 viruses have been properly isolated from the sputum of a sick person, that actual spike proteins could be seen protruding from the virus (which has not been found), you would find that such evidence doesn't exist.

If you go looking in the published scientific literature for actual pictures, proof, that these spike proteins or any viral proteins are ever attached to any receptor embedded in any cell membrane, you would also find that no such evidence exists. If you were to look for a video or documented evidence of the intact virus injecting its genetic material into the body of the cell, reproducing itself and then emerging victorious by budding off the cell membrane, you would find that no such evidence exists.

The closest thing you would find is electron micrograph pictures of cellular particles, possibly attached to cell debris, both of which to be seen were stained by heavy metals, a process that completely distorts their architecture within the living organism. This is like finding bits of paper stuck to the blown-up bricks, thereby proving the paper emerged by taking pieces of the bricks on its way out.

The Enders baloney

Cowan describes the 'Covid' story as being just as make-believe as his paper story and he charts back this fantasy to a Nobel Prize winner called John Enders (1897-1985), an American biomedical scientist who has been dubbed 'The Father of Modern Vaccines'. Enders is claimed to have 'discovered' the process of the viral culture which 'proved' that a 'virus' caused measles. Cowan explains how Enders did this 'by using the EXACT same procedure that has been followed by every virologist to find and characterize every new virus since 1954'. Enders took throat swabs from children with measles and immersed them in 2ml of milk. Penicillin (100u/ml) and the antibiotic streptomycin (50,g/ml) were added and the whole mix was centrifuged – rotated at high speed to separate large cellular debris from small particles and molecules as with milk and cream, for example. Cowan says that if the aim is to find little particles of genetic material ('viruses') in the snot from children with measles it would seem that the last thing you would do is mix the snot with other material – milk –that also has genetic material. 'How are you ever going to know whether whatever you found came from the snot or the milk?' He points out that streptomycin is a 'nephrotoxic' or poisonous-to-the-kidney drug. You will see the relevance of that

shortly. Cowan says that it gets worse, much worse, when Enders describes the culture medium upon which the virus 'grows': 'The culture medium consisted of bovine amniotic fluid (90%), beef embryo extract (5%), horse serum (5%), antibiotics and phenol red as an indicator of cell metabolism.' Cowan asks incredulously: 'Did he just say that the culture medium also contained fluids and tissues that are themselves rich sources of genetic material?' The genetic cocktail, or 'medium', is inoculated onto tissue and cells from rhesus monkey *kidney* tissue. This is where the importance of streptomycin comes in and currently-used antimicrobials and other drugs that are *poisonous to kidneys* and used in ALL modern viral cultures (e.g. gentamicin, streptomycin, and amphotericin). Cowan asks: 'How are you ever going to know from this witch's brew where any genetic material comes from as we now have five different sources of rich genetic material in our mix?' Remember, he says, that all genetic material, whether from monkey kidney tissues, bovine serum, milk, etc., is made from the exact same components. The same central question returns: 'How are you possibly going to know that it was the virus that killed the kidney tissue and not the toxic antibiotic and starvation rations on which you are growing the tissue?' John Enders answered the question himself – *you can't*:

A second agent was obtained from an uninoculated culture of monkey kidney cells. The cytopathic changes [death of the cells] it induced in the unstained preparations could not be distinguished with confidence from the viruses isolated from measles.

The death of the cells ('cytopathic changes') happened in exactly the same manner, whether they inoculated the kidney tissue with the measles snot or not, Cowan says. 'This is evidence that the destruction of the tissue, the very proof of viral causation of illness, was not caused by anything in the snot because they saw the same destructive effect when the snot was not even used … the cytopathic, i.e., cell-killing, changes come from the process of the culture itself, not from any virus in any snot, period.' Enders quotes in his 1957 paper a virologist called Ruckle as reporting similar findings 'and in addition has isolated an agent from monkey kidney tissue that is so

far indistinguishable from human measles virus'. In other words, Cowan says, these particles called 'measles viruses' are simply and clearly breakdown products of the starved and poisoned tissue. For measles 'virus' see all 'viruses' including the so-called 'Covid virus'. Enders, the 'Father of Modern Vaccines', also said:

There is a potential risk in employing cultures of primate cells for the production of vaccines composed of attenuated virus, since the presence of other agents possibly latent in primate tissues cannot be definitely excluded by any known method.

Cowan further quotes from a paper published in the journal *Viruses* in May, 2020, while the 'Covid pandemic' was well underway in the media if not in reality. 'EVs' here refers to particles of genetic debris from our own tissues, such as exosomes of which more in a moment: 'The remarkable resemblance between EVs and viruses has caused quite a few problems in the studies focused on the analysis of EVs released during viral infections.' Later the paper adds that to date a reliable method that can actually guarantee a complete separation (of EVs from viruses) DOES NOT EXIST. This was published at a time when a fairy tale 'virus' was claimed in total certainty to be causing a fairy tale 'viral disease' called 'Covid-19' – a fairy tale that was already well on the way to transforming human society in the image that the Cult has worked to achieve for so long. Cowan concludes his article:

To summarize, there is no scientific evidence that pathogenic viruses exist. What we think of as 'viruses' are simply the normal breakdown products of dead and dying tissues and cells. When we are well, we make fewer of these particles; when we are starved, poisoned, suffocated by wearing masks, or afraid, we make more.

There is no engineered virus circulating and making people sick. People in laboratories all over the world are making genetically modified products to make people sick. These are called vaccines. There is no virome, no 'ecosystem' of viruses, viruses are not 8%, 50% or 100 % of our genetic material. These are all simply erroneous ideas based on the misconception called a virus.

What is 'Covid'? Load of bollocks

The background described here by Cowan and Lanka was emphasised in the first video presentation that I saw by Dr Andrew Kaufman when he asked whether the 'Covid virus' was in truth a natural defence mechanism of the body called 'exosomes'. These are released by cells when in states of toxicity – see the same themes returning over and over. They are released ever more profusely as chemical and radiation toxicity increases and think of the potential effect therefore of 5G alone as its destructive frequencies infest the human energetic information field with a gathering pace (5G went online in Wuhan in 2019 as the 'virus' emerged). I'll have more about this later. Exosomes transmit a warning to the rest of the body that 'Houston, we have a problem'. Kaufman presented images of exosomes and compared them with 'Covid' under an electron microscope and the similarity was remarkable. They both attach to the same cell receptors (*claimed* in the case of 'Covid'), contain the same genetic material in the form of RNA or ribonucleic acid, and both are found in 'viral cell cultures' with damaged or dying cells. James Hildreth MD, President and Chief Executive Officer of the Meharry Medical College at Johns Hopkins, said: 'The virus is fully an exosome in every sense of the word.' Kaufman's conclusion was that there is no 'virus': 'This entire pandemic is a completely manufactured crisis … there is no evidence of anyone dying from [this] illness.' Dr Tom Cowan and Sally Fallon Morell, authors of *The Contagion Myth*, published a statement with Dr Kaufman in February, 2021, explaining why the 'virus' does not exist and you can read it that in full in the Appendix.

'Virus' theory can be traced to the 'cell theory' in 1858 of German physician Rudolf Virchow (1821-1920) who contended that disease originates from a single cell infiltrated by a 'virus'. Dr Stefan Lanka said that findings and insights with respect to the structure, function and central importance of tissues in the creation of life, which were already known in 1858, comprehensively refute the cell theory. Virchow ignored them. We have seen the part later played by John Enders in the 1950s and Lanka notes that infection theories were only established as a global dogma through the policies and

eugenics of the Third Reich in Nazi Germany (creation of the same Sabbatian cult behind the 'Covid' hoax). Lanka said: 'Before 1933, scientists dared to contradict this theory; after 1933, these critical scientists were silenced'. Dr Tom Cowan's view is that ill-heath is caused by too much of something, too little of something, or toxification from chemicals and radiation – not contagion. We must also highlight as a major source of the 'virus' theology a man still called the 'Father of Modern Virology' – Thomas Milton Rivers (1888-1962). There is no way given the Cult's long game policy that it was a coincidence for the 'Father of Modern Virology' to be director of the Rockefeller Institute for Medical Research from 1937 to 1956 when he is credited with making the Rockefeller Institute a leader in 'viral research'. Cult Rockefellers were the force behind the creation of Big Pharma 'medicine', established the World Health Organisation in 1948, and have long and close associations with the Gates family that now runs the WHO during the pandemic hoax through mega-rich Cult gofer and psychopath Bill Gates.

Only a Renegade Mind can see through all this bullshit by asking the questions that need to be answered, not taking 'no' or prevarication for an answer, and certainly not hiding from the truth in fear of speaking it. Renegade Minds have always changed the world for the better and they will change this one no matter how bleak it may currently appear to be.

CHAPTER SIX

Sequence of deceit

If you tell the truth, you don't have to remember anything
Mark Twain

Against the background that I have laid out this far the sequence that took us from an invented 'virus' in Cult-owned China in late 2019 to the fascist transformation of human society can be seen and understood in a whole new context.

We were told that a deadly disease had broken out in Wuhan and the world media began its campaign (coordinated by behavioural psychologists as we shall see) to terrify the population into unquestioning compliance. We were shown images of Chinese people collapsing in the street which never happened in the West with what was supposed to be the same condition. In the earliest days when alleged cases and deaths were few the fear register was hysterical in many areas of the media and this would expand into the common media narrative across the world. The real story was rather different, but we were never told that. The Chinese government, one of the Cult's biggest centres of global operation, said they had discovered a new illness with flu-like and pneumonia-type symptoms in a city with such toxic air that it is overwhelmed with flu-like symptoms, pneumonia and respiratory disease. Chinese scientists said it was a new – 'novel' – coronavirus which they called Sars-Cov-2 and that it caused a disease they labelled 'Covid-19'. There was no evidence for this and the 'virus' has never to this day been isolated, purified and its genetic code established from that. It

was from the beginning a computer-generated fiction. Stories of Chinese whistleblowers saying the number of deaths was being supressed or that the 'new disease' was related to the Wuhan bio-lab misdirected mainstream and alternative media into cul-de-sacs to obscure the real truth – there was no 'virus'.

Chinese scientists took genetic material from the lung fluid of just a few people and said they had found a 'new' disease when this material had a wide range of content. There was no evidence for a 'virus' for the very reasons explained in the last two chapters. The 'virus' has never been shown to (a) exist and (b) cause any disease. People were diagnosed on symptoms that are so widespread in Wuhan and polluted China and with a PCR test that can't detect infectious disease. On this farce the whole global scam was sold to the rest of the world which would also diagnose respiratory disease as 'Covid-19' from symptoms alone or with a PCR test not testing for a 'virus'. Flu miraculously disappeared *worldwide* in 2020 and into 2021 as it was redesignated 'Covid-19'. It was really the same old flu with its 'flu-like' symptoms attributed to 'flu-like' 'Covid-19'. At the same time with very few exceptions the Chinese response of draconian lockdown and fascism was the chosen weapon to respond across the West as recommended by the Cult-owned Tedros at the Cult-owned World Health Organization run by the Cult-owned Gates. All was going according to plan. Chinese scientists – everything in China is controlled by the Cult-owned government – compared their contaminated RNA lung-fluid material with other RNA sequences and said it appeared to be just under 80 percent identical to the SARS-CoV-1 'virus' claimed to be the cause of the SARS (severe acute respiratory syndrome) 'outbreak' in 2003. They decreed that because of this the 'new virus' had to be related and they called it SARS-CoV-2. There are some serious problems with this assumption and *assumption* was all it was. Most 'factual' science turns out to be assumptions repeated into everyone-knows-that. A match of under 80-percent is meaningless. Dr Kaufman makes the point that there's a *96 percent* genetic correlation between humans and chimpanzees, but 'no one would say our genetic material is part

of the chimpanzee family'. Yet the Chinese authorities were claiming that a much lower percentage, less than 80 percent, proved the existence of a new 'coronavirus'. For goodness sake human DNA is 60 percent similar to a *banana*.

You are feeling sleepy

The entire 'Covid' hoax is a global Psyop, a psychological operation to program the human mind into believing and fearing a complete fantasy. A crucial aspect of this was what *appeared* to happen in Italy. It was all very well streaming out daily images of an alleged catastrophe in Wuhan, but to the Western mind it was still on the other side of the world in a very different culture and setting. A reaction of 'this could happen to me and my family' was still nothing like as intense enough for the mind-doctors. The Cult needed a Western example to push people over that edge and it chose Italy, one of its major global locations going back to the Roman Empire. An Italian 'Covid' crisis was manufactured in a particular area called Lombardy which just happens to be notorious for its toxic air and therefore respiratory disease. Wuhan, China, déjà vu. An hysterical media told horror stories of Italians dying from 'Covid' in their droves and how Lombardy hospitals were being overrun by a tidal wave of desperately ill people needing treatment after being struck down by the 'deadly virus'. Here was the psychological turning point the Cult had planned. Wow, if this is happening in Italy, the Western mind concluded, this indeed could happen to me and my family. Another point is that Italian authorities responded by following the Chinese blueprint so vehemently recommended by the Cult-owned World Health Organization. They imposed fascistic lockdowns on the whole country viciously policed with the help of surveillance drones sweeping through the streets seeking out anyone who escaped from mass house arrest. Livelihoods were destroyed and psychology unravelled in the way we have witnessed since in all lockdown countries. Crucial to the plan was that Italy responded in this way to set the precedent of suspending freedom and imposing fascism in a 'Western liberal democracy'. I emphasised in an

animated video explanation on davidicke.com posted in the summer of 2020 how important it was to the Cult to expand the Chinese lockdown model across the West. Without this, and the bare-faced lie that non-symptomatic people could still transmit a 'disease' they didn't have, there was no way locking down the whole population, sick and not sick, could be pulled off. At just the right time and with no evidence Cult operatives and gofers claimed that people without symptoms could pass on the 'disease'. In the name of protecting the 'vulnerable' like elderly people, who lockdowns would kill by the tens of thousands, we had for the first time healthy people told to isolate as well as the sick. The great majority of people who tested positive had no symptoms because there was nothing wrong with them. It was just a trick made possible by a test not testing for the 'virus'.

Months after my animated video the Gates-funded Professor Neil Ferguson at the Gates-funded Imperial College confirmed that I was right. He didn't say it in those terms, naturally, but he did say it. Ferguson will enter the story shortly for his outrageously crazy 'computer models' that led to Britain, the United States and many other countries following the Chinese and now Italian methods of response. Put another way, following the Cult script. Ferguson said that SAGE, the UK government's scientific advisory group which has controlled 'Covid' policy from the start, wanted to follow the Chinese lockdown model (while they all continued to work and be paid), but they wondered if they could possibly, in Ferguson's words, 'get away with it in Europe'. 'Get away with it'? Who the hell do these moronic, arrogant people think they are? This appalling man Ferguson said that once Italy went into national lockdown they realised they, too, could mimic China:

> It's a communist one-party state, we said. We couldn't get away with it in Europe, we thought … and then Italy did it. And we realised we could. Behind this garbage from Ferguson is a simple fact: Doing the same as China in every country was the plan from the start and Ferguson's 'models' would play a central role in achieving that. It's just a coincidence, of course, and absolutely nothing to worry your little head about.

Oops, sorry, our mistake

Once the Italian segment of the Psyop had done the job it was designed to do a very different story emerged. Italian authorities revealed that 99 percent of those who had 'died from Covid-19' in Italy had one, two, three, or more 'co-morbidities' or illnesses and health problems that could have ended their life. The US Centers for Disease Control and Prevention (CDC) published a figure of 94 percent for Americans dying of 'Covid' while having other serious medical conditions – on average two to three (some five or six) other potential causes of death. In terms of death from an unproven 'virus' I say it is 100 percent. The other one percent in Italy and six percent in the US would presumably have died from 'Covid's' flu-like symptoms with a range of other possible causes in conjunction with a test not testing for the 'virus'. Fox News reported that even more startling figures had emerged in one US county in which 410 of 422 deaths attributed to 'Covid-19' had other potentially deadly health conditions. The Italian National Health Institute said later that the average age of people dying with a 'Covid-19' diagnosis in Italy was about 81. Ninety percent were over 70 with ten percent over 90. In terms of other reasons to die some 80 percent had two or more chronic diseases with half having three or more including cardiovascular problems, diabetes, respiratory problems and cancer. Why is the phantom 'Covid-19' said to kill overwhelmingly old people and hardly affect the young? Old people continually die of many causes and especially respiratory disease which you can re-diagnose 'Covid-19' while young people die in tiny numbers by comparison and rarely of respiratory disease. Old people 'die of Covid' because they die of other things that can be redesignated 'Covid' and it really is that simple.

Flu has flown

The blueprint was in place. Get your illusory 'cases' from a test not testing for the 'virus' and redesignate other causes of death as 'Covid-19'. You have an instant 'pandemic' from something that is nothing more than a computer-generated fiction. With near-on a

billion people having 'flu-like' symptoms every year the potential was limitless and we can see why flu quickly and apparently miraculously disappeared *worldwide* by being diagnosed 'Covid-19'. The painfully bloody obvious was explained away by the childlike media in headlines like this in the UK '*Independent*': 'Not a single case of flu detected by Public Health England this year as Covid restrictions suppress virus'. I kid you not. The masking, social distancing and house arrest that did not make the 'Covid virus' disappear somehow did so with the 'flu virus'. Even worse the article, by a bloke called Samuel Lovett, suggested that maybe the masking, sanitising and other 'Covid' measures should continue to keep the flu away. With a ridiculousness that disturbs your breathing (it's 'Covid-19') the said Lovett wrote: 'With widespread social distancing and mask-wearing measures in place throughout the UK, the usual routes of transmission for influenza have been blocked.' He had absolutely no evidence to support that statement, but look at the consequences of him acknowledging the obvious. With flu not disappearing at all and only being relabelled 'Covid-19' he would have to contemplate that 'Covid' was a hoax on a scale that is hard to imagine. You need guts and commitment to truth to even go there and that's clearly something Samuel Lovett does not have in abundance. He would never have got it through the editors anyway.

Tens of thousands die in the United States alone every winter from flu including many with pneumonia complications. CDC figures record *45 million* Americans diagnosed with flu in 2017-2018 of which 61,000 died and some reports claim 80,000. Where was the same hysteria then that we have seen with 'Covid-19'? Some 250,000 Americans are admitted to hospital with pneumonia every year with about 50,000 cases proving fatal. About 65 million suffer respiratory disease every year and three million deaths makes this the third biggest cause of death worldwide. You only have to redesignate a portion of all these people 'Covid-19' and you have an instant global pandemic or the *appearance* of one. Why would doctors do this? They are told to do this and all but a few dare not refuse those who must be obeyed. Doctors in general are not researching their own

knowledge and instead take it direct and unquestioned from the authorities that own them and their careers. The authorities say they must now diagnose these symptoms 'Covid-19' and not flu, or whatever, and they do it. Dark suits say put 'Covid-19' on death certificates no matter what the cause of death and the doctors do it. Renegade Minds don't fall for the illusion that doctors and medical staff are all highly-intelligent, highly-principled, seekers of medical truth. *Some are*, but not the majority. They are repeaters, gofers, and yes sir, no sir, purveyors of what the system demands they purvey. The 'Covid' con is not merely confined to diseases of the lungs. Instructions to doctors to put 'Covid-19' on death certificates for anyone dying of *anything* within 28 days (or much more) of a positive test not testing for the 'virus' opened the floodgates. The term dying *with* 'Covid' and not *of* 'Covid' was coined to cover the truth. Whether it was a *with* or an *of* they were all added to the death numbers attributed to the 'deadly virus' compiled by national governments and globally by the Gates-funded Johns Hopkins operation in the United States that was so involved in those 'pandemic' simulations. Fraudulent deaths were added to the ever-growing list of fraudulent 'cases' from false positives from a false test. No wonder Professor Walter Ricciardi, scientific advisor to the Italian minister of health, said after the Lombardy hysteria had done its job that 'Covid' death rates were due to Italy having the second oldest population in the world and to *how hospitals record deaths*:

The way in which we code deaths in our country is very generous in the sense that all the people who die in hospitals with the coronavirus are deemed to be dying of the coronavirus. On re-evaluation by the National Institute of Health, only 12 per cent of death certificates have shown a direct causality from coronavirus, while 88 per cent of patients who have died have at least one pre-morbidity – many had two or three.

This is extraordinary enough when you consider the propaganda campaign to use Italy to terrify the world, but how can they even say twelve percent were genuine when the 'virus' has not been shown to exist, its 'code' is a computer program, and diagnosis comes from a test not testing for it? As in China, and soon the world, 'Covid-19' in

Italy was a redesignation of diagnosis. Lies and corruption were to become the real 'pandemic' fuelled by a pathetically-compliant medical system taking its orders from the tiny few at the top of their national hierarchy who answered to the World Health Organization which answers to Gates and the Cult. Doctors were told – ordered – to diagnose a particular set of symptoms 'Covid-19' and put that on the death certificate for any cause of death if the patient had tested positive with a test not testing for the virus or had 'Covid' symptoms like the flu. The United States even introduced big financial incentives to manipulate the figures with hospitals receiving £4,600 from the Medicare system for diagnosing someone with regular pneumonia, $13,000 if they made the diagnosis from the same symptoms 'Covid-19' pneumonia, and $39, 000 if they put a 'Covid' diagnosed patient on a ventilator that would almost certainly kill them. A few – painfully and pathetically few – medical whistleblowers revealed (before Cult-owned YouTube deleted their videos) that they had been instructed to 'let the patient crash' and put them straight on a ventilator instead of going through a series of far less intrusive and dangerous methods as they would have done before the pandemic hoax began and the financial incentives kicked in. We are talking cold-blooded murder given that ventilators are so damaging to respiratory systems they are usually the last step before heaven awaits. Renegade Minds never fall for the belief that people in white coats are all angels of mercy and cannot be full-on psychopaths. I have explained in detail in *The Answer* how what I am describing here played out across the world coordinated by the World Health Organization through the medical hierarchies in almost every country.

Medical scientist calls it

Information about the non-existence of the 'virus' began to emerge for me in late March, 2020, and mushroomed after that. I was sent an email by Sir Julian Rose, a writer, researcher, and organic farming promotor, from a medical scientist friend of his in the United States. Even at that early stage in March the scientist was able to explain

how the 'Covid' hoax was being manipulated. He said there were no reliable tests for a specific 'Covid-19 virus' and nor were there any reliable agencies or media outlets for reporting numbers of actual 'Covid-19' cases. We have seen in the long period since then that he was absolutely right. 'Every action and reaction to Covid-19 is based on totally flawed data and we simply cannot make accurate assessments,' he said. Most people diagnosed with 'Covid-19' were showing nothing more than cold and flu-like symptoms 'because most coronavirus strains *are* nothing more than cold/flu-like symptoms'. We had farcical situations like an 84-year-old German man testing positive for 'Covid-19' and his nursing home ordered to quarantine only for him to be found to have a common cold. The scientist described back then why PCR tests and what he called the 'Mickey Mouse test kits' were useless for what they were claimed to be identifying. 'The idea these kits can isolate a specific virus like Covid-19 is nonsense,' he said. Significantly, he pointed out that 'if you want to create a totally false panic about a totally false pandemic – pick a coronavirus'. This is exactly what the Cult-owned Gates, World Economic Forum and Johns Hopkins University did with their Event 201 'simulation' followed by their real-life simulation called the 'pandemic'. The scientist said that all you had to do was select the sickest of people with respiratory-type diseases in a single location – 'say Wuhan' – and administer PCR tests to them. You can then claim that anyone showing 'viral sequences' similar to a coronavirus 'which will inevitably be quite a few' is suffering from a 'new' disease:

> Since you already selected the sickest flu cases a fairly high proportion of your sample will go on to die. You can then say this 'new' virus has a CFR [case fatality rate] higher than the flu and use this to infuse more concern and do more tests which will of course produce more 'cases', which expands the testing, which produces yet more 'cases' and so on and so on. Before long you have your 'pandemic', and all you have done is use a simple test kit trick to convert the worst flu and pneumonia cases into something new that doesn't ACTUALLY EXIST [my emphasis].

He said that you then 'just run the same scam in other countries' and make sure to keep the fear message running high 'so that people

will feel panicky and less able to think critically'. The only problem to overcome was the fact *there is no* actual new deadly pathogen and only regular sick people. This meant that deaths from the 'new deadly pathogen' were going to be way too low for a real new deadly virus pandemic, but he said this could be overcome in the following ways – all of which would go on to happen:

1. You can claim this is just the beginning and more deaths are imminent [you underpin this with fantasy 'computer projections']. Use this as an excuse to quarantine everyone and then claim the quarantine prevented the expected millions of dead.

2. You can [say that people] 'minimizing' the dangers are irresponsible and bully them into not talking about numbers.

3. You can talk crap about made up numbers hoping to blind people with pseudoscience.

4. You can start testing well people (who, of course, will also likely have shreds of coronavirus [RNA] in them) and thus inflate your 'case figures' with 'asymptomatic carriers' (you will of course have to spin that to sound deadly even though any virologist knows the more symptom-less cases you have the less deadly is your pathogen).

The scientist said that if you take these simple steps 'you can have your own entirely manufactured pandemic up and running in weeks'. His analysis made so early in the hoax was brilliantly prophetic of what would actually unfold. Pulling all the information together in these recent chapters we have this is simple 1, 2, 3, of how you can delude virtually the entire human population into believing in a 'virus' that doesn't exist:

- A 'Covid case' is someone who tests positive with a test not testing for the 'virus'.

- A 'Covid death' is someone who dies of *any cause* within 28 days (or much longer) of testing positive with a test not testing for the 'virus.

- Asymptomatic means there is nothing wrong with you, but they claim you can pass on what you don't have to justify locking

down (quarantining) healthy people in totality.

The foundations of the hoax are that simple. A study involving ten million people in Wuhan, published in November, 2020, demolished the whole lie about those without symptoms passing on the 'virus'. They found '300 asymptomatic cases' and traced their contacts to find that not one of them was detected with the 'virus'. 'Asymptomatic' patients and their contacts were isolated for no less than two weeks and nothing changed. I know it's all crap, but if you are going to claim that those without symptoms can transmit 'the virus' then you must produce evidence for that and they never have. Even World Health Organization official Dr Maria Van Kerkhove, head of the emerging diseases and zoonosis unit, said as early as June, 2020, that she doubted the validity of asymptomatic transmission. She said that 'from the data we have, it still seems to be rare that an asymptomatic person actually transmits onward to a secondary individual' and by 'rare' she meant that she couldn't cite any case of asymptomatic transmission.

The Ferguson factor

The problem for the Cult as it headed into March, 2020, when the script had lockdown due to start, was that despite all the manipulation of the case and death figures they still did not have enough people alleged to have died from 'Covid' to justify mass house arrest. This was overcome in the way the scientist described: 'You can claim this is just the beginning and more deaths are imminent … Use this as an excuse to quarantine everyone and then claim the quarantine prevented the expected millions of dead.' Enter one Professor Neil Ferguson, the Gates-funded 'epidemiologist' at the Gates-funded Imperial College in London. Ferguson is Britain's Christian Drosten in that he has a dire record of predicting health outcomes, but is still called upon to advise government on the next health outcome when another 'crisis' comes along. This may seem to be a strange and ridiculous thing to do. Why would you keep turning for policy guidance to people who have a history of being

monumentally wrong? Ah, but it makes sense from the Cult point of view. These 'experts' keep on producing predictions that suit the Cult agenda for societal transformation and so it was with Neil Ferguson as he revealed his horrific (and clearly insane) computer model predictions that allowed lockdowns to be imposed in Britain, the United States and many other countries. Ferguson does not have even an A-level in biology and would appear to have no formal training in computer modelling, medicine or epidemiology, according to Derek Winton, an MSc in Computational Intelligence. He wrote an article somewhat aghast at what Ferguson did which included taking no account of respiratory disease 'seasonality' which means it is far worse in the winter months. Who would have thought that respiratory disease could be worse in the winter? Well, certainly not Ferguson.

The massively China-connected Imperial College and its bizarre professor provided the excuse for the long-incubated Chinese model of human control to travel westward at lightning speed. Imperial College confirms on its website that it collaborates with the Chinese Research Institute; publishes more than 600 research papers every year with Chinese research institutions; has 225 Chinese staff; 2,600 Chinese students – the biggest international group; 7,000 former students living in China which is the largest group outside the UK; and was selected for a tour by China's President Xi Jinping during his state visit to the UK in 2015. The college takes major donations from China and describes itself as the UK's number one university collaborator with Chinese research institutions. The China communist/fascist government did not appear phased by the woeful predictions of Ferguson and Imperial when during the lockdown that Ferguson induced the college signed a five-year collaboration deal with China tech giant Huawei that will have Huawei's indoor 5G network equipment installed at the college's West London tech campus along with an 'AI cloud platform'. The deal includes Chinese sponsorship of Imperial's Venture Catalyst entrepreneurship competition. Imperial is an example of the enormous influence the Chinese government has within British and North American

universities and research centres – and further afield. Up to 200 academics from more than a dozen UK universities are being investigated on suspicion of 'unintentionally' helping the Chinese government build weapons of mass destruction by 'transferring world-leading research in advanced military technology such as aircraft, missile designs and cyberweapons'. Similar scandals have broken in the United States, but it's all a coincidence. Imperial College serves the agenda in many other ways including the promotion of every aspect of the United Nations Agenda 21/2030 (the Great Reset) and produced computer models to show that human-caused 'climate change' is happening when in the real world it isn't. Imperial College is driving the climate agenda as it drives the 'Covid' agenda (both Cult hoaxes) while Patrick Vallance, the UK government's Chief Scientific Adviser on 'Covid', was named Chief Scientific Adviser to the UN 'climate change' conference known as COP26 hosted by the government in Glasgow, Scotland. 'Covid' and 'climate' are fundamentally connected.

Professor Woeful

From Imperial's bosom came Neil Ferguson still advising government despite his previous disasters and it was announced early on that he and other key people like UK Chief Medical Adviser Chris Whitty had caught the 'virus' as the propaganda story was being sold. Somehow they managed to survive and we had Prime Minister Boris Johnson admitted to hospital with what was said to be a severe version of the 'virus' in this same period. His whole policy and demeanour changed when he returned to Downing Street. It's a small world with these government advisors – especially in their communal connections to Gates – and Ferguson had partnered with Whitty to write a paper called 'Infectious disease: Tough choices to reduce Ebola transmission' which involved another scare-story that didn't happen. Ferguson's 'models' predicted that up to150, 000 could die from 'mad cow disease', or BSE, and its version in sheep if it was transmitted to humans. BSE was not transmitted and instead triggered by an organophosphate pesticide used to treat a pest on

cows. Fewer than 200 deaths followed from the human form. Models by Ferguson and his fellow incompetents led to the unnecessary culling of millions of pigs, cattle and sheep in the foot and mouth outbreak in 2001 which destroyed the lives and livelihoods of farmers and their families who had often spent decades building their herds and flocks. Vast numbers of these animals did not have foot and mouth and had no contact with the infection. Another 'expert' behind the cull was Professor Roy Anderson, a computer modeller at Imperial College specialising in the epidemiology of *human*, not animal, disease. Anderson has served on the Bill and Melinda Gates Grand Challenges in Global Health advisory board and chairs another Gates-funded organisation. Gates is everywhere.

In a precursor to the 'Covid' script Ferguson backed closing schools 'for prolonged periods' over the swine flu 'pandemic' in 2009 and said it would affect a third of the world population if it continued to spread at the speed he claimed to be happening. His mates at Imperial College said much the same and a news report said: 'One of the authors, the epidemiologist and disease modeller Neil Ferguson, who sits on the World Health Organisation's emergency committee for the outbreak, said the virus had "full pandemic potential".' Professor Liam Donaldson, the Chris Whitty of his day as Chief Medical Officer, said the worst case could see 30 percent of the British people infected by swine flu with 65,000 dying. Ferguson and Donaldson were indeed proved correct when at the end of the year the number of deaths attributed to swine flu was 392. The term 'expert' is rather liberally applied unfortunately, not least to complete idiots. Swine flu 'projections' were great for GlaxoSmithKline (GSK) as millions rolled in for its Pandemrix influenza vaccine which led to brain damage with children most affected. The British government (taxpayers) paid out more than £60 million in compensation after GSK was given immunity from prosecution. Yet another 'Covid' déjà vu. Swine flu was supposed to have broken out in Mexico, but Dr Wolfgang Wodarg, a German doctor, former member of parliament and critic of the 'Covid' hoax, observed 'the spread of swine flu' in Mexico City at the time. He

said: 'What we experienced in Mexico City was a very mild flu which did not kill more than usual – which killed even fewer people than usual.' Hyping the fear against all the facts is not unique to 'Covid' and has happened many times before. Ferguson is reported to have over-estimated the projected death toll of bird flu (H5N1) by some three million-fold, but bird flu vaccine makers again made a killing from the scare. This is some of the background to the Neil Ferguson who produced the perfectly-timed computer models in early 2020 predicting that half a million people would die in Britain without draconian lockdown and 2.2 million in the United States. Politicians panicked, people panicked, and lockdowns of alleged short duration were instigated to 'flatten the curve' of cases gleaned from a test not testing for the 'virus'. I said at the time that the public could forget the 'short duration' bit. This was an agenda to destroy the livelihoods of the population and force them into mass control through dependency and there was going to be nothing 'short' about it. American researcher Daniel Horowitz described the consequences of the 'models' spewed out by Gates-funded Ferguson and Imperial College:

> What led our government and the governments of many other countries into panic was a single Imperial College of UK study, funded by global warming activists, that predicted 2.2 million deaths if we didn't lock down the country. In addition, the reported 8-9% death rate in Italy scared us into thinking there was some other mutation of this virus that they got, which might have come here.
>
> Together with the fact that we were finally testing and had the ability to actually report new cases, we thought we were headed for a death spiral. But again … we can't flatten a curve if we don't know when the curve started.

How about it *never* started?

Giving them what they want

An investigation by German news outlet *Welt Am Sonntag (World on Sunday)* revealed how in March, 2020, the German government gathered together 'leading scientists from several research institutes and universities' and 'together, they were to produce a [modelling]

paper that would serve as legitimization for further tough political measures'. The Cult agenda was justified by computer modelling not based on evidence or reality; it was specifically constructed to justify the Cult demand for lockdowns all over the world to destroy the independent livelihoods of the global population. All these modellers and everyone responsible for the 'Covid' hoax have a date with a trial like those in Nuremberg after World War Two when Nazis faced the consequences of their war crimes. These corrupt-beyond-belief 'modellers' wrote the paper according to government instructions and it said that that if lockdown measures were lifted then up to one million Germans would die from 'Covid-19' adding that some would die 'agonizingly at home, gasping for breath' unable to be treated by hospitals that couldn't cope. All lies. No matter – it gave the Cult all that it wanted. What did long-time government 'modeller' Neil Ferguson say? If the UK and the United States didn't lockdown half a million would die in Britain and 2.2 million Americans. Anyone see a theme here? 'Modellers' are such a crucial part of the lockdown strategy that we should look into their background and follow the money. Researcher Rosemary Frei produced an excellent article headlined 'The Modelling-paper Mafiosi'. She highlights a guy called John Edmunds, a British epidemiologist, and professor in the Faculty of Epidemiology and Population Health at the London School of Hygiene & Tropical Medicine. He studied at Imperial College. Edmunds is a member of government 'Covid' advisory bodies which have been dictating policy, the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) and the Scientific Advisory Group for Emergencies (SAGE).

Ferguson, another member of NERVTAG and SAGE, led the way with the original 'virus' and Edmunds has followed in the 'variant' stage and especially the so-called UK or Kent variant known as the 'Variant of Concern' (VOC) B.1.1.7. He said in a co-written report for the Centre for Mathematical modelling of Infectious Diseases at the London School of Hygiene and Tropical Medicine, with input from the Centre's 'Covid-19' Working Group, that there was 'a realistic

possibility that VOC B.1.1.7 is associated with an increased risk of death compared to non-VOC viruses'. Fear, fear, fear, get the vaccine, fear, fear, fear, get the vaccine. Rosemary Frei reveals that almost all the paper's authors and members of the modelling centre's 'Covid-19' Working Group receive funding from the Bill and Melinda Gates Foundation and/or the associated Gates-funded Wellcome Trust. The paper was published by e-journal *Medr χiv* which only publishes papers not peer-reviewed and the journal was established by an organisation headed by Facebook's Mark Zuckerberg and his missus. What a small world it is. Frei discovered that Edmunds is on the Scientific Advisory Board of the Coalition for Epidemic Preparedness Innovations (CEPI) which was established by the Bill and Melinda Gates Foundation, Klaus Schwab's Davos World Economic Forum and Big Pharma giant Wellcome. CEPI was 'launched in Davos [in 2017] to develop vaccines to stop future epidemics', according to its website. 'Our mission is to accelerate the development of vaccines against emerging infectious diseases and enable equitable access to these vaccines for people during outbreaks.' What kind people they are. Rosemary Frei reveals that Public Health England (PHE) director Susan Hopkins is an author of her organisation's non-peer-reviewed reports on 'new variants'. Hopkins is a professor of infectious diseases at London's Imperial College which is gifted tens of millions of dollars a year by the Bill and Melinda Gates Foundation. Gates-funded modelling disaster Neil Ferguson also co-authors Public Health England reports and he spoke in December, 2020, about the potential danger of the B.1.1.7. 'UK variant' promoted by Gates-funded modeller John Edmunds. When I come to the 'Covid vaccines' the 'new variants' will be shown for what they are – bollocks.

Connections, connections

All these people and modellers are lockdown-obsessed or, put another way, they demand what the Cult demands. Edmunds said in January, 2021, that to ease lockdowns too soon would be a disaster and they had to 'vaccinate much, much, much more widely than the

elderly'. Rosemary Frei highlights that Edmunds is married to Jeanne Pimenta who is described in a LinkedIn profile as director of epidemiology at GlaxoSmithKline (GSK) and she held shares in the company. Patrick Vallance, co-chair of SAGE and the government's Chief Scientific Adviser, is a former executive of GSK and has a deferred bonus of shares in the company worth £600,000. GSK has serious business connections with Bill Gates and is collaborating with mRNA-'vaccine' company CureVac to make 'vaccines' for the new variants that Edmunds is talking about. GSK is planning a 'Covid vaccine' with drug giant Sanofi. Puppet Prime Minister Boris Johnson announced in the spring of 2021 that up to 60 million vaccine doses were to be made at the GSK facility at Barnard Castle in the English North East. Barnard Castle, with a population of just 6,000, was famously visited in breach of lockdown rules in April, 2020, by Johnson aide Dominic Cummings who said that he drove there 'to test his eyesight' before driving back to London. Cummings would be better advised to test his integrity – not that it would take long. The GSK facility had nothing to do with his visit then although I'm sure Patrick Vallance would have been happy to arrange an introduction and some tea and biscuits. Ruthless psychopath Gates has made yet another fortune from vaccines in collaboration with Big Pharma companies and gushes at the phenomenal profits to be made from vaccines – more than a 20-to-1 return as he told one interviewer. Gates also tweeted in December, 2019, with the foreknowledge of what was coming: 'What's next for our foundation? I'm particularly excited about what the next year could mean for one of the best buys in global health: vaccines.'

Modeller John Edmunds is a big promotor of vaccines as all these people appear to be. He's the dean of the London School of Hygiene & Tropical Medicine's Faculty of Epidemiology and Population Health which is primarily funded by the Bill and Melinda Gates Foundation and the Gates-established and funded GAVI vaccine alliance which is the Gates vehicle to vaccinate the world. The organisation Doctors Without Borders has described GAVI as being 'aimed more at supporting drug-industry desires to promote new

products than at finding the most efficient and sustainable means for fighting the diseases of poverty'. But then that's why the psychopath Gates created it. John Edmunds said in a video that the London School of Hygiene & Tropical Medicine is involved in every aspect of vaccine development including large-scale clinical trials. He contends that mathematical modelling can show that vaccines protect individuals and society. That's on the basis of shit in and shit out, I take it. Edmunds serves on the UK Vaccine Network as does Ferguson and the government's foremost 'Covid' adviser, the grim-faced, dark-eyed Chris Whitty. The Vaccine Network says it works 'to support the government to identify and shortlist targeted investment opportunities for the most promising vaccines and vaccine technologies that will help combat infectious diseases with epidemic potential, and to address structural issues related to the UK's broader vaccine infrastructure'. Ferguson is acting Director of the Imperial College Vaccine Impact Modelling Consortium which has funding from the Bill and Melina Gates Foundation and the Gates-created GAVI 'vaccine alliance'. Anyone wonder why these characters see vaccines as the answer to every problem? Ferguson is wildly enthusiastic in his support for GAVI's campaign to vaccine children en masse in poor countries. You would expect someone like Gates who has constantly talked about the need to reduce the population to want to fund vaccines to keep more people alive. I'm sure that's why he does it. The John Edmunds London School of Hygiene & Tropical Medicine (LSHTM) has a Vaccines Manufacturing Innovation Centre which develops, tests and commercialises vaccines. Rosemary Frei writes:

> The vaccines centre also performs affiliated activities like combating 'vaccine hesitancy'. The latter includes the Vaccine Confidence Project. The project's stated purpose is, among other things, 'to provide analysis and guidance for early response and engagement with the public to ensure sustained confidence in vaccines and immunisation'. The Vaccine Confidence Project's director is LSHTM professor Heidi Larson. For more than a decade she's been researching how to combat vaccine hesitancy.

How the bloody hell can blokes like John Edmunds and Neil Ferguson with those connections and financial ties model 'virus' case

and death projections for the government and especially in a way that gives their paymasters like Gates exactly what they want? It's insane, but this is what you find throughout the world.

'Covid' is not dangerous, oops, wait, yes it is

Only days before Ferguson's nightmare scenario made Jackboot Johnson take Britain into a China-style lockdown to save us from a deadly 'virus' the UK government website gov.uk was reporting something very different to Ferguson on a page of official government guidance for 'high consequence infectious diseases (HCID)'. It said this about 'Covid-19':

As of 19 March 2020, COVID-19 *is no longer considered to be a high consequence infectious diseases (HCID) in the UK* [my emphasis]. The 4 nations public health HCID group made an interim recommendation in January 2020 to classify COVID-19 as an HCID. This was based on consideration of the UK HCID criteria about the virus and the disease with information available during the early stages of the outbreak.

Now that more is known about COVID-19, the public health bodies in the UK have reviewed the most up to date information about COVID-19 against the UK HCID criteria. They have determined that several features have now changed; in particular, more information is available about mortality rates (low overall), and there is now greater clinical awareness and a specific and sensitive laboratory test, the availability of which continues to increase. The Advisory Committee on Dangerous Pathogens (ACDP) is also of the opinion that COVID-19 should no longer be classified as an HCID.

Soon after the government had been exposed for downgrading the risk they upgraded it again and everyone was back to singing from the same Cult hymn book. Ferguson and his fellow Gates clones indicated that lockdowns and restrictions would have to continue until a Gates-funded vaccine was developed. Gates said the same because Ferguson and his like were repeating the Gates script which is the Cult script. 'Flatten the curve' became an ongoing nightmare of continuing lockdowns with periods in between of severe restrictions in pursuit of destroying independent incomes and had nothing to do with protecting health about which the Cult gives not a shit. Why wouldn't Ferguson be pushing a vaccine 'solution' when he's owned by vaccine-obsessive Gates who makes a fortune from them and

when Ferguson heads the Vaccine Impact Modelling Consortium at Imperial College funded by the Gates Foundation and GAVI, the 'vaccine alliance', created by Gates as his personal vaccine promotion operation? To compound the human catastrophe that Ferguson's 'models' did so much to create he was later exposed for breaking his own lockdown rules by having sexual liaisons with his married girlfriend Antonia Staats at his home while she was living at another location with her husband and children. Staats was a 'climate' activist and senior campaigner at the Soros-funded Avaaz which I wouldn't trust to tell me that grass is green. Ferguson had to resign as a government advisor over this hypocrisy in May, 2020, but after a period of quiet he was back being quoted by the ridiculous media on the need for more lockdowns and a vaccine rollout. Other government-advising 'scientists' from Imperial College' held the fort in his absence and said lockdown could be indefinite until a vaccine was found. The Cult script was being sung by the payrolled choir. I said there was no intention of going back to 'normal' when the 'vaccine' came because the 'vaccine' is part of a very different agenda that I will discuss in Human 2.0. Why would the Cult want to let the world go back to normal when destroying that normal forever was the whole point of what was happening? House arrest, closing businesses and schools through lockdown, (un)social distancing and masks all followed the Ferguson fantasy models. Again as I predicted (these people are so predictable) when the 'vaccine' arrived we were told that house arrest, lockdown, (un)social distancing and masks would still have to continue. I will deal with the masks in the next chapter because they are of fundamental importance.

Where's the 'pandemic'?

Any mildly in-depth assessment of the figures revealed what was really going on. Cult-funded and controlled organisations still have genuine people working within them such is the number involved. So it is with Genevieve Briand, assistant program director of the Applied Economics master's degree program at Johns Hopkins

University. She analysed the impact that 'Covid-19' had on deaths from *all* causes in the United States using official data from the CDC for the period from early February to early September, 2020. She found that allegedly 'Covid' *related*-deaths exceeded those from heart disease which she found strange with heart disease always the biggest cause of fatalities. Her research became even more significant when she noted the sudden decline in 2020 of *all* non-'Covid' deaths: 'This trend is completely contrary to the pattern observed in all previous years … the total decrease in deaths by other causes almost exactly equals the increase in deaths by Covid-19.' This was such a game, set and match in terms of what was happening that Johns Hopkins University deleted the article on the grounds that it 'was being used to support false and dangerous inaccuracies about the impact of the pandemic'. No – because it exposed the scam from official CDC figures and this was confirmed when those figures were published in January, 2021. Here we can see the effect of people dying from heart attacks, cancer, road accidents and gunshot wounds – *anything* – having 'Covid-19' on the death certificate along with those diagnosed from 'symptoms' who had even not tested positive with a test not testing for the 'virus'. I am not kidding with the gunshot wounds, by the way. Brenda Bock, coroner in Grand County, Colorado, revealed that two gunshot victims tested positive for the 'virus' within the previous 30 days and were therefore classified as 'Covid deaths'. Bock said: 'These two people had tested positive for Covid, but that's not what killed them. A gunshot wound is what killed them.' She said she had not even finished her investigation when the state listed the gunshot victims as deaths due to the 'virus'. The death and case figures for 'Covid-19' are an absolute joke and yet they are repeated like parrots by the media, politicians and alleged medical 'experts'. The official Cult narrative is the only show in town.

Genevieve Briand found that deaths from all causes were not exceptional in 2020 compared with previous years and a Spanish magazine published figures that said the same about Spain which was a 'Covid' propaganda hotspot at one point. *Discovery Salud*, a

health and medicine magazine, quoted government figures which showed how 17,000 *fewer* people died in Spain in 2020 than in 2019 and more than 26,000 fewer than in 2018. The age-standardised mortality rate for England and Wales when age distribution is taken into account was significantly lower in 2020 than the 1970s, 80s and 90s, and was only the ninth highest since 2000. Where is the 'pandemic'?

Post mortems and autopsies virtually disappeared for 'Covid' deaths amid claims that 'virus-infected' bodily fluids posed a risk to those carrying out the autopsy. This was rejected by renowned German pathologist and forensic doctor Klaus Püschel who said that he and his staff had by then done 150 autopsies on 'Covid' patients with no problems at all. He said they were needed to know why some 'Covid' patients suffered blood clots and not severe respiratory infections. The 'virus' is, after all, called SARS or 'severe acute respiratory syndrome'. I highlighted in the spring of 2020 this phenomenon and quoted New York intensive care doctor Cameron Kyle-Sidell who posted a soon deleted YouTube video to say that they had been told to prepare to treat an infectious disease called 'Covid-19', but that was not what they were dealing with. Instead he likened the lung condition of the most severely ill patients to what you would expect with cabin depressurisation in a plane at 30,000 feet or someone dropped on the top of Everest without oxygen or acclimatisation. I have never said this is not happening to a small minority of alleged 'Covid' patients – I am saying this is not caused by a phantom 'contagious virus'. Indeed Kyle-Sidell said that 'Covid-19' was not the disease they were told was coming their way. 'We are operating under a medical paradigm that is untrue,' he said, and he believed they were treating the wrong disease: 'These people are being slowly starved of oxygen.' Patients would take off their oxygen masks in a state of fear and stress and while they were blue in the face on the brink of death. They did not look like patients dying of pneumonia. You can see why they don't want autopsies when their virus doesn't exist and there is another condition in some people that they don't wish to be uncovered. I should add here that

the 5G system of millimetre waves was being rapidly introduced around the world in 2020 and even more so now as they fire 5G at the Earth from satellites. At 60 gigahertz within the 5G range that frequency interacts with the oxygen molecule and stops people breathing in sufficient oxygen to be absorbed into the bloodstream. They are installing 5G in schools and hospitals. The world is not mad or anything. 5G can cause major changes to the lungs and blood as I detail in *The Answer* and these consequences are labelled 'Covid-19', the alleged symptoms of which can be caused by 5G and other electromagnetic frequencies as cells respond to radiation poisoning.

The 'Covid death' scam

Dr Scott Jensen, a Minnesota state senator and medical doctor, exposed 'Covid' Medicare payment incentives to hospitals and death certificate manipulation. He said he was sent a seven-page document by the US Department of Health 'coaching' him on how to fill out death certificates which had never happened before. The document said that he didn't need to have a laboratory test for 'Covid-19' to put that on the death certificate and that shocked him when death certificates are supposed to be about facts. Jensen described how doctors had been 'encouraged, if not pressured' to make a diagnosis of 'Covid-19' if they thought it was probable or *'presumed*'. No positive test was necessary – not that this would have mattered anyway. He said doctors were told to diagnose 'Covid' by symptoms when these were the same as colds, allergies, other respiratory problems, and certainly with influenza which 'disappeared' in the 'Covid' era. A common sniffle was enough to get the dreaded verdict. Ontario authorities decreed that a single care home resident with *one* symptom from a long list must lead to the isolation of the entire home. Other courageous doctors like Jensen made the same point about death figure manipulation and how deaths by other causes were falling while 'Covid-19 deaths' were rising at the same rate due to re-diagnosis. Their videos rarely survive long on YouTube with its Cult-supporting algorithms courtesy of CEO Susan Wojcicki and her bosses at Google. Figure-tampering was so glaring

and ubiquitous that even officials were letting it slip or outright saying it. UK chief scientific adviser Patrick Vallance said on one occasion that 'Covid' on the death certificate doesn't mean 'Covid' was the cause of death (so why the hell is it there?) and we had the rare sight of a BBC reporter telling the truth when she said: 'Someone could be successfully treated for Covid, in say April, discharged, and then in June, get run over by a bus and die … That person would still be counted as a Covid death in England.' Yet the BBC and the rest of the world media went on repeating the case and death figures as if they were real. Illinois Public Health Director Dr Ngozi Ezike revealed the deceit while her bosses must have been clenching their buttocks:

> If you were in a hospice and given a few weeks to live and you were then found to have Covid that would be counted as a Covid death. [There might be] a clear alternate cause, but it is still listed as a Covid death. So everyone listed as a Covid death doesn't mean that was the cause of the death, but that they had Covid at the time of death.

Yes, a 'Covid virus' never shown to exist and tested for with a test not testing for the 'virus'. In the first period of the pandemic hoax through the spring of 2020 the process began of designating almost everything a 'Covid' death and this has continued ever since. I sat in a restaurant one night listening to a loud conversation on the next table where a family was discussing in bewilderment how a relative who had no symptoms of 'Covid', and had died of a long-term problem, could have been diagnosed a death by the 'virus'. I could understand their bewilderment. If they read this book they will know why this medical fraud has been perpetrated the world over.

Some media truth shock

The media ignored the evidence of death certificate fraud until eventually one columnist did speak out when she saw it first-hand. Bel Mooney is a long-time national newspaper journalist in Britain currently working for the *Daily Mail*. Her article on February 19th, 2021, carried this headline: 'My dad Ted passed three Covid tests

and died of a chronic illness yet he's officially one of Britain's 120,000 victims of the virus and is far from alone ... so how many more are there?' She told how her 99-year-old father was in a care home with a long-standing chronic obstructive pulmonary disease and vascular dementia. Maybe, but he was still aware enough to tell her from the start that there was no 'virus' and he refused the 'vaccine' for that reason. His death was not unexpected given his chronic health problems and Mooney said she was shocked to find that 'Covid-19' was declared the cause of death on his death certificate. She said this was a 'bizarre and unacceptable untruth' for a man with long-time health problems who had tested negative twice at the home for the 'virus'. I was also shocked by this story although not by what she said. I had been highlighting the death certificate manipulation for ten months. It was the confirmation that a professional full-time journalist only realised this was going on when it affected her directly and neither did she know that whether her dad tested positive or negative was irrelevant with the test not testing for the 'virus'. Where had she been? She said she did not believe in 'conspiracy theories' without knowing I'm sure that this and 'conspiracy theorists' were terms put into widespread circulation by the CIA in the 1960s to discredit those who did not accept the ridiculous official story of the Kennedy assassination. A blanket statement of 'I don't believe in conspiracy theories' is always bizarre. The dictionary definition of the term alone means the world is drowning in conspiracies. What she said was even more daft when her dad had just been affected by the 'Covid' conspiracy. Why else does she think that 'Covid-19' was going on the death certificates of people who died of something else?

To be fair once she saw from personal experience what was happening she didn't mince words. Mooney was called by the care home on the morning of February 9th to be told her father had died in his sleep. When she asked for the official cause of death what came back was 'Covid-19'. Mooney challenged this and was told there had been deaths from Covid on the dementia floor (confirmed by a test not testing for the 'virus') so they considered it 'reasonable

to assume'. 'But doctor,' Mooney rightly protested, 'an assumption isn't a diagnosis.' She said she didn't blame the perfectly decent and sympathetic doctor – 'he was just doing his job'. Sorry, but that's *bullshit*. He wasn't doing his job at all. He was putting a false cause of death on the death certificate and that is a criminal offence for which he should be brought to account and the same with the millions of doctors worldwide who have done the same. They were not doing their job they were following orders and that must not wash at new Nuremberg trials any more than it did at the first ones. Mooney's doctor was 'assuming' (presuming) as he was told to, but 'just following orders' makes no difference to his actions. A doctor's job is to serve the patient and the truth, not follow orders, but that's what they have done all over the world and played a central part in making the 'Covid' hoax possible with all its catastrophic consequences for humanity. Shame on them and they must answer for their actions. Mooney said her disquiet worsened when she registered her father's death by telephone and was told by the registrar there had been very many other cases like hers where 'the deceased' had not tested positive for 'Covid' yet it was recorded as the cause of death. The test may not matter, but those involved at their level *think* it matters and it shows a callous disregard for accurate diagnosis. The pressure to do this is coming from the top of the national 'health' pyramids which in turn obey the World Health Organization which obeys Gates and the Cult. Mooney said the registrar agreed that this must distort the national figures adding that 'the strangest thing is that every winter we record countless deaths from flu, and this winter there have been none. Not one!' She asked if the registrar thought deaths from flu were being misdiagnosed and lumped together with 'Covid' deaths. The answer was a 'puzzled yes'. Mooney said that the funeral director said the same about 'Covid' deaths which had nothing to do with 'Covid'. They had lost count of the number of families upset by this and other funeral companies in different countries have had the same experience. Mooney wrote:

The nightly shroud-waving and shocking close-ups of pain imposed on us by the TV news bewildered and terrified the population into eager compliance with lockdowns. We were invited to 'save the NHS' and to grieve for strangers – the real-life loved ones behind those shocking death counts. Why would the public imagine what I now fear, namely that the way Covid-19 death statistics are compiled might make the numbers seem greater than they are?

Oh, just a little bit – like 100 percent.

Do the maths

Mooney asked why a country would wish to skew its mortality figures by wrongly certifying deaths? What had been going on? Well, if you don't believe in conspiracies you will never find the answer which is that *it's a conspiracy*. She did, however, describe what she had discovered as a 'national scandal'. In reality it's a global scandal and happening everywhere. Pillars of this conspiracy were all put into place before the button was pressed with the Drosten PCR protocol and high amplifications to produce the cases and death certificate changes to secure illusory 'Covid' deaths. Mooney notes that normally two doctors were needed to certify a death, with one having to know the patient, and how the rules were changed in the spring of 2020 to allow one doctor to do this. In the same period 'Covid deaths' were decreed to be all cases where Covid-19 was put on the death certificate even without a positive test or any symptoms. Mooney asked: 'How many of the 30,851 (as of January 15) care home resident deaths with Covid-19 on the certificate (32.4 per cent of all deaths so far) were based on an assumption, like that of my father? And what has that done to our national psyche?'All of them is the answer to the first question and it has devastated and dismantled the national psyche, actually the global psyche, on a colossal scale. In the UK case and death data is compiled by organisations like Public Health England (PHE) and the Office for National Statistics (ONS). Mooney highlights the insane policy of counting a death from any cause as 'Covid-19' if this happens within 28 days of a positive test (with a test not testing for the 'virus') and she points out that ONS statistics reflect deaths 'involving Covid' 'or due to Covid' which meant in practice any

death where 'Covid-19' was mentioned on the death certificate. She described the consequences of this fraud:

Most people will accept the narrative they are fed, so panicky governments here and in Europe witnessed the harsh measures enacted in totalitarian China and jumped into lockdown. Headlines about Covid deaths tolled like the knell that would bring doomsday to us all. Fear stalked our empty streets. Politicians parroted the frankly ridiculous aim of 'zero Covid' and shut down the economy, while most British people agreed that lockdown was essential and (astonishingly to me, as a patriotic Brit) even wanted more restrictions.

For what? Lies on death certificates? Never mind the grim toll of lives ruined, suicides, schools closed, rising inequality, depression, cancelled hospital treatments, cancer patients in a torture of waiting, poverty, economic devastation, loneliness, families kept apart, and so on. How many lives have been lost as a direct result of lockdown?

She said that we could join in a national chorus of shock and horror at reaching the 120,000 death toll which was surely certain to have been totally skewed all along, but what about the human cost of lockdown justified by these 'death figures'? *The British Medical Journal* had reported a 1,493 percent increase in cases of children taken to Great Ormond Street Hospital with abusive head injuries alone and then there was the effect on families:

Perhaps the most shocking thing about all this is that families have been kept apart – and obeyed the most irrational, changing rules at the whim of government – because they believed in the statistics. They succumbed to fear, which his generation rejected in that war fought for freedom. Dad (God rest his soul) would be angry. And so am I.

Another theme to watch is that in the winter months when there are more deaths from all causes they focus on 'Covid' deaths and in the summer when the British Lung Foundation says respiratory disease plummets by 80 percent they rage on about 'cases'. Either way fascism on population is always the answer.

Nazi eugenics in the 21st century

Elderly people in care homes have been isolated from their families month after lonely month with no contact with relatives and grandchildren who were banned from seeing them. We were told

that lockdown fascism was to 'protect the vulnerable' like elderly people. At the same time Do Not Resuscitate (DNR) orders were placed on their medical files so that if they needed resuscitation it wasn't done and 'Covid-19' went on their death certificates. Old people were not being 'protected' they were being culled – murdered in truth. DNR orders were being decreed for disabled and young people with learning difficulties or psychological problems. The UK Care Quality Commission, a non-departmental body of the Department of Health and Social Care, found that 34 percent of those working in health and social care were pressured into placing 'do not attempt cardiopulmonary resuscitation' orders on 'Covid' patients who suffered from disabilities and learning difficulties without involving the patient or their families in the decision. UK judges ruled that an elderly woman with dementia should have the DNA-manipulating 'Covid vaccine' against her son's wishes and that a man with severe learning difficulties should have the jab despite his family's objections. Never mind that many had already died. The judiciary always supports doctors and government in fascist dictatorships. They wouldn't dare do otherwise. A horrific video was posted showing fascist officers from Los Angeles police forcibly giving the 'Covid' shot to women with special needs who were screaming that they didn't want it. The same fascists are seen giving the jab to a sleeping elderly woman in a care home. This is straight out of the Nazi playbook. Hitler's Nazis committed mass murder of the mentally ill and physically disabled throughout Germany and occupied territories in the programme that became known as Aktion T4, or just T4. Sabbatian-controlled Hitler and his grotesque crazies set out to kill those they considered useless and unnecessary. The Reich Committee for the Scientific Registering of Hereditary and Congenital Illnesses registered the births of babies identified by physicians to have 'defects'. By 1941 alone more than 5,000 children were murdered by the state and it is estimated that in total the number of innocent people killed in Aktion T4 was between 275,000 and 300,000. Parents were told their children had been sent away for 'special treatment' never to return. It is rather pathetic to see claims about plans for new extermination camps being dismissed today

when the same force behind current events did precisely that 80 years ago. Margaret Sanger was a Cult operative who used 'birth control' to sanitise her programme of eugenics. Organisations she founded became what is now Planned Parenthood. Sanger proposed that 'the whole dysgenic population would have its choice of segregation or sterilization'. These included epileptics, 'feeble-minded', and prostitutes. Sanger opposed charity because it perpetuated 'human waste'. She reveals the Cult mentality and if anyone thinks that extermination camps are a 'conspiracy theory' their naivety is touching if breathtakingly stupid.

If you don't believe that doctors can act with callous disregard for their patients it is worth considering that doctors and medical staff agreed to put government-decreed DNR orders on medical files and do nothing when resuscitation is called for. I don't know what you call such people in your house. In mine they are Nazis from the Josef Mengele School of Medicine. Phenomenal numbers of old people have died worldwide from the effects of lockdown, depression, lack of treatment, the 'vaccine' (more later) and losing the will to live. A common response at the start of the manufactured pandemic was to remove old people from hospital beds and transfer them to nursing homes. The decision would result in a mass cull of elderly people in those homes through lack of treatment – *not* 'Covid'. Care home whistleblowers have told how once the 'Covid' era began doctors would not come to their homes to treat patients and they were begging for drugs like antibiotics that often never came. The most infamous example was ordered by New York governor Andrew Cuomo, brother of a moronic CNN host, who amazingly was given an Emmy Award for his handling of the 'Covid crisis' by the ridiculous Wokers that hand them out. Just how ridiculous could be seen in February, 2021, when a Department of Justice and FBI investigation began into how thousands of old people in New York died in nursing homes after being discharged from hospital to make way for 'Covid' patients on Cuomo's say-so – and how he and his staff covered up these facts. This couldn't have happened to a nicer psychopath. Even then there was a 'Covid' spin. Reports said that

thousands of old people who tested positive for 'Covid' in hospital were transferred to nursing homes to both die of 'Covid' and transmit it to others. No – they were in hospital because they were ill and the fact that they tested positive with a test not testing for the 'virus' is irrelevant. They were ill often with respiratory diseases ubiquitous in old people near the end of their lives. Their transfer out of hospital meant that their treatment stopped and many would go on to die.

They're old. Who gives a damn?

I have exposed in the books for decades the Cult plan to cull the world's old people and even to introduce at some point what they call a 'demise pill' which at a certain age everyone would take and be out of here by law. In March, 2021, Spain legalised euthanasia and assisted suicide following the Netherlands, Belgium, Luxembourg and Canada on the Tiptoe to the demise pill. Treatment of old people by many 'care' homes has been a disgrace in the 'Covid' era. There are many, many, caring staff – I know some. There have, however, been legions of stories about callous treatment of old people and their families. Police were called when families came to take their loved ones home in the light of isolation that was killing them. They became prisoners of the state. Care home residents in insane, fascist Ontario, Canada, were not allowed to leave their *room* once the 'Covid' hoax began. UK staff have even wheeled elderly people away from windows where family members were talking with them. Oriana Criscuolo from Stockport in the English North West dropped off some things for her 80-year-old father who has Parkinson's disease and dementia and she wanted to wave to him through a ground-floor window. She was told that was 'illegal'. When she went anyway they closed the curtains in the middle of the day. Oriana said:

> It's just unbelievable. I cannot understand how care home staff – people who are being paid to care – have become so uncaring. Their behaviour is inhumane and cruel. It's beyond belief.

She was right and this was not a one-off. What a way to end your life in such loveless circumstances. UK registered nurse Nicky Millen, a proper old school nurse for 40 years, said that when she started her career care was based on dignity, choice, compassion and empathy. Now she said 'the things that are important to me have gone out of the window.' She was appalled that people were dying without their loved ones and saying goodbye on iPads. Nicky described how a distressed 89-year-old lady stroked her face and asked her 'how many paracetamol would it take to finish me off'. Life was no longer worth living while not seeing her family. Nicky said she was humiliated in front of the ward staff and patients for letting the lady stroke her face and giving her a cuddle. Such is the dehumanisation that the 'Covid' hoax has brought to the surface. Nicky worked in care homes where patients told her they were being held prisoner. 'I want to live until I die', one said to her. 'I had a lady in tears because she hadn't seen her great-grandson.' Nicky was compassionate old school meeting psychopathic New Normal. She also said she had worked on a 'Covid' ward with no 'Covid' patients. Jewish writer Shai Held wrote an article in March, 2020, which was headlined 'The Staggering, Heartless Cruelty Toward the Elderly'. What he described was happening from the earliest days of lockdown. He said 'the elderly' were considered a group and not unique individuals (the way of the Woke). Shai Held said:

Notice how the all-too-familiar rhetoric of dehumanization works: 'The elderly' are bunched together as a faceless mass, all of them considered culprits and thus effectively deserving of the suffering the pandemic will inflict upon them. Lost entirely is the fact that the elderly are individual human beings, each with a distinctive face and voice, each with hopes and dreams, memories and regrets, friendships and marriages, loves lost and loves sustained.

'The elderly' have become another dehumanised group for which anything goes and for many that has resulted in cold disregard for their rights and their life. The distinctive face that Held talks about is designed to be deleted by masks until everyone is part of a faceless mass.

‘War-zone’ hospitals myth

Again and again medical professionals have told me what was really going on and how hospitals ‘overrun like war zones’ according to the media were virtually empty. The mantra from medical whistleblowers was please don’t use my name or my career is over. Citizen journalists around the world sneaked into hospitals to film evidence exposing the ‘war-zone’ lie. They really *were* largely empty with closed wards and operating theatres. I met a hospital worker in my town on the Isle of Wight during the first lockdown in 2020 who said the only island hospital had never been so quiet. Lockdown was justified by the psychopaths to stop hospitals being overrun. At the same time that the island hospital was near-empty the military arrived here to provide *extra beds*. It was all propaganda to ramp up the fear to ensure compliance with fascism as were never-used temporary hospitals with thousands of beds known as Nightingales and never-used make-shift mortuaries opened by the criminal UK government. A man who helped to install those extra island beds attributed to the army said they were never used and the hospital was empty. Doctors and nurses ‘stood around talking or on their phones, wandering down to us to see what we were doing’. There were no masks or social distancing. He accused the useless local island paper, the *County Press*, of ‘pumping the fear as if our hospital was overrun and we only have one so it should have been’. He described ambulances parked up with crews outside in deck chairs. When his brother called an ambulance he was told there was a two-hour backlog which he called ‘bullshit’. An old lady on the island fell ‘and was in a bad way’, but a caller who rang for an ambulance was told the situation wasn’t urgent enough. Ambulance stations were working under capacity while people would hear ambulances with sirens blaring driving through the streets. When those living near the stations realised what was going on they would follow them as they left, circulated around an urban area with the sirens going, and then came back without stopping. All this was to increase levels of fear and the same goes for the ‘ventilator shortage crisis’ that cost tens of millions for hastily produced ventilators never to be used.

Ambulance crews that agreed to be exploited in this way for fear propaganda might find themselves a mirror. I wish them well with that. Empty hospitals were the obvious consequence of treatment and diagnoses of non-'Covid' conditions cancelled and those involved handed a death sentence. People have been dying at home from undiagnosed and untreated cancer, heart disease and other life-threatening conditions to allow empty hospitals to deal with a 'pandemic' that wasn't happening.

Death of the innocent

'War-zones' have been laying off nursing staff, even doctors where they can. There was no work for them. Lockdown was justified by saving lives and protecting the vulnerable they were actually killing with DNR orders and preventing empty hospitals being 'overrun'. In Britain the mantra of stay at home to 'save the NHS' was everywhere and across the world the same story was being sold when it was all lies. Two California doctors, Dan Erickson and Artin Massihi at Accelerated Urgent Care in Bakersfield, held a news conference in April, 2020, to say that intensive care units in California were 'empty, essentially', with hospitals shutting floors, not treating patients and laying off doctors. The California health system was working at minimum capacity 'getting rid of doctors because we just don't have the volume'. They said that people with conditions such as heart disease and cancer were not coming to hospital out of fear of 'Covid-19'. Their video was deleted by Susan Wojcicki's Cult-owned YouTube after reaching five million views. Florida governor Ron Desantis, who rejected the severe lockdowns of other states and is being targeted for doing so, said that in March, 2020, every US governor was given models claiming they would run out of hospital beds in days. That was never going to happen and the 'modellers' knew it. Deceit can be found at every level of the system. Urgent children's operations were cancelled including fracture repairs and biopsies to spot cancer. Eric Nicholls, a consultant paediatrician, said 'this is obviously concerning and we need to return to normal operating and to increase capacity as soon as possible'. Psychopaths

in power were rather less concerned *because* they are psychopaths. Deletion of urgent care and diagnosis has been happening all over the world and how many kids and others have died as a result of the actions of these cold and heartless lunatics dictating 'health' policy? The number must be stratospheric. Richard Sullivan, professor of cancer and global health at King's College London, said people feared 'Covid' more than cancer such was the campaign of fear. 'Years of lost life will be quite dramatic', Sullivan said, with 'a huge amount of avoidable mortality'. Sarah Woolnough, executive director for policy at Cancer Research UK, said there had been a 75 percent drop in urgent referrals to hospitals by family doctors of people with suspected cancer. Sullivan said that 'a lot of services have had to scale back – we've seen a dramatic decrease in the amount of elective cancer surgery'. Lockdown deaths worldwide has been absolutely fantastic with the *New York Post* reporting how data confirmed that 'lockdowns end more lives than they save':

> There was a sharp decline in visits to emergency rooms and an increase in fatal heart attacks because patients didn't receive prompt treatment. Many fewer people were screened for cancer. Social isolation contributed to excess deaths from dementia and Alzheimer's.
>
> Researchers predicted that the social and economic upheaval would lead to tens of thousands of "deaths of despair" from drug overdoses, alcoholism and suicide. As unemployment surged and mental-health and substance-abuse treatment programs were interrupted, the reported levels of anxiety, depression and suicidal thoughts increased dramatically, as did alcohol sales and fatal drug overdoses.

This has been happening while nurses and other staff had so much time on their hands in the 'war-zones' that Tic-Tok dancing videos began appearing across the Internet with medical staff dancing around in empty wards and corridors as people died at home from causes that would normally have been treated in hospital.

Mentions in dispatches

One brave and truth-committed whistleblower was Louise Hampton, a call handler with the UK NHS who made a viral Internet video saying she had done 'fuck all' during the 'pandemic'

which was 'a load of bollocks'. She said that 'Covid-19' was rebranded flu and of course she lost her job. This is what happens in the medical and endless other professions now when you tell the truth. Louise filmed inside 'war-zone' accident and emergency departments to show they were empty and I mean *empty* as in no one there. The mainstream media could have done the same and blown the gaff on the whole conspiracy. They haven't to their eternal shame. Not that most 'journalists' seem capable of manifesting shame as with the psychopaths they slavishly repeat without question. The relative few who were admitted with serious health problems were left to die alone with no loved ones allowed to see them because of 'Covid' rules and they included kids dying without the comfort of mum and dad at their bedside while the evil behind this couldn't give a damn. It was all good fun to them. A Scottish NHS staff nurse publicly quit in the spring of 2021 saying: 'I can no longer be part of the lies and the corruption by the government.' She said hospitals 'aren't full, the beds aren't full, beds have been shut, wards have been shut'. Hospitals were never busy throughout 'Covid'. The staff nurse said that Nicola Sturgeon, tragically the leader of the Scottish government, was on television saying save the hospitals and the NHS – 'but the beds are empty' and 'we've not seen flu, we always see flu every year'. She wrote to government and spoke with her union Unison (the unions are Cult-compromised and *useless*, but nothing changed. Many of her colleagues were scared of losing their jobs if they spoke out as they wanted to. She said nursing staff were being affected by wearing masks all day and 'my head is splitting every shift from wearing a mask'. The NHS is part of the fascist tyranny and must be dismantled so we can start again with human beings in charge. (Ironically, hospitals were reported to be busier again when official 'Covid' cases *fell* in spring/summer of 2021 and many other conditions required treatment at the same time as *the fake vaccine rollout*.)

I will cover the 'Covid vaccine' scam in detail later, but it is another indicator of the sickening disregard for human life that I am highlighting here. The DNA-manipulating concoctions do not fulfil

the definition of a 'vaccine', have never been used on humans before and were given only emergency approval because trials were not completed and they continued using the unknowing public. The result was what a NHS senior nurse with responsibility for 'vaccine' procedure said was 'genocide'. She said the 'vaccines' were not 'vaccines'. They had not been shown to be safe and claims about their effectiveness by drug companies were 'poetic licence'. She described what was happening as a 'horrid act of human annihilation'. The nurse said that management had instigated a policy of not providing a Patient Information Leaflet (PIL) before people were 'vaccinated' even though health care professionals are supposed to do this according to protocol. Patients should also be told that they are taking part in an ongoing clinical trial. Her challenges to what is happening had seen her excluded from meetings and ridiculed in others. She said she was told to 'watch my step … or I would find myself surplus to requirements'. The nurse, who spoke anonymously in fear of her career, said she asked her NHS manager why he/she was content with taking part in genocide against those having the 'vaccines'. The reply was that everyone had to play their part and to 'put up, shut up, and get it done'. Government was 'leaning heavily' on NHS management which was clearly leaning heavily on staff. This is how the global 'medical' hierarchy operates and it starts with the Cult and its World Health Organization.

She told the story of a doctor who had the Pfizer jab and when questioned had no idea what was in it. The doctor had never read the literature. We have to stop treating doctors as intellectual giants when so many are moral and medical pygmies. The doctor did not even know that the 'vaccines' were not fully approved or that their trials were ongoing. They were, however, asking their patients if they minded taking part in follow-ups for research purposes – yes, the *ongoing clinical trial*. The nurse said the doctor's ignorance was not rare and she had spoken to a hospital consultant who had the jab without any idea of the background or that the 'trials' had not been completed. Nurses and pharmacists had shown the same ignorance.

'My NHS colleagues have forsaken their duty of care, broken their code of conduct – Hippocratic Oath – and have been brainwashed just the same as the majority of the UK public through propaganda …' She said she had not been able to recruit a single NHS colleague, doctor, nurse or pharmacist to stand with her and speak out. Her union had refused to help. She said that if the genocide came to light she would not hesitate to give evidence at a Nuremberg-type trial against those in power who could have affected the outcomes but didn't.

And all for what?

To put the nonsense into perspective let's say the 'virus' does exist and let's go completely crazy and accept that the official manipulated figures for cases and deaths are accurate. *Even then* a study by Stanford University epidemiologist Dr John Ioannidis published on the World Health Organization website produced an average infection to fatality rate of … *0.23 percent!* Ioannidis said: 'If one could sample equally from all locations globally, the median infection fatality rate might even be substantially lower than the 0.23% observed in my analysis.' For healthy people under 70 it was … *0.05 percent*! This compares with the 3.4 percent claimed by the Cult-owned World Health Organization when the hoax was first played and maximum fear needed to be generated. An updated Stanford study in April, 2021, put the 'infection' to 'fatality' rate at just 0.15 percent. Another team of scientists led by Megan O'Driscoll and Henrik Salje studied data from 45 countries and published their findings on the Nature website. For children and young people the figure is so small it virtually does not register although authorities will be hyping dangers to the young when they introduce DNA-manipulating 'vaccines' for children. The O'Driscoll study produced an average infection-fatality figure of 0.003 for children from birth to four; 0.001 for 5 to 14; 0.003 for 15 to 19; and it was still only 0.456 up to 64. To claim that children must be 'vaccinated' to protect them from 'Covid' is an obvious lie and so there must be another reason and there is. What's more the average age of a 'Covid' death is akin

to the average age that people die in general. The average age of death in England is about 80 for men and 83 for women. The average age of death from alleged 'Covid' is between 82 and 83. California doctors, Dan Erickson and Artin Massihi, said at their April media conference that projection models of millions of deaths had been 'woefully inaccurate'. They produced detailed figures showing that Californians had a 0.03 chance of dying from 'Covid' based on the number of people who tested positive (with a test not testing for the 'virus'). Erickson said there was a 0.1 percent chance of dying from 'Covid' in the *state* of New York, not just the city, and a 0.05 percent chance in Spain, a centre of 'Covid-19' hysteria at one stage. The Stanford studies supported the doctors' data with fatality rate estimates of 0.23 and 0.15 percent. How close are these figures to my estimate of *zero*? Death-rate figures claimed by the World Health Organization at the start of the hoax were some 15 times higher. The California doctors said there was no justification for lockdowns and the economic devastation they caused. Everything they had ever learned about quarantine was that you quarantine the *sick* and not the healthy. They had never seen this before and it made no medical sense.

Why in the in the light of all this would governments and medical systems the world over say that billions must go under house arrest; lose their livelihood; in many cases lose their mind, their health and their life; force people to wear masks dangerous to health and psychology; make human interaction and even family interaction a criminal offence; ban travel; close restaurants, bars, watching live sport, concerts, theatre, and any activity involving human togetherness and discourse; and closing schools to isolate children from their friends and cause many to commit suicide in acts of hopelessness and despair? The California doctors said lockdown consequences included increased child abuse, partner abuse, alcoholism, depression, and other impacts they were seeing every day. Who would do that to the entire human race if not mentally-ill psychopaths of almost unimaginable extremes like Bill Gates? We must face the reality of what we are dealing with and come out of

denial. Fascism and tyranny are made possible only by the target population submitting and acquiescing to fascism and tyranny. The whole of human history shows that to be true. Most people naively and unquestioning believed what they were told about a 'deadly virus' and meekly and weakly submitted to house arrest. Those who didn't believe it – at least in total – still submitted in fear of the consequences of not doing so. For the rest who wouldn't submit draconian fines have been imposed, brutal policing by psychopaths *for* psychopaths, and condemnation from the meek and weak who condemn the Pushbackers on behalf of the very force that has them, too, in its gunsights. 'Pathetic' does not even begin to suffice. Britain's brainless 'Health' Secretary Matt Hancock warned anyone lying to border officials about returning from a list of 'hotspot' countries could face a jail sentence of up to ten years which is more than for racially-aggravated assault, incest and attempting to have sex with a child under 13. Hancock is a lunatic, but he has the state apparatus behind him in a Cult-led chain reaction and the same with UK 'Vaccine Minister' Nadhim Zahawi, a prominent member of the mega-Cult secret society, Le Cercle, which featured in my earlier books. The Cult enforces its will on governments and medical systems; government and medical systems enforce their will on business and police; business enforces its will on staff who enforce it on customers; police enforce the will of the Cult on the population and play their essential part in creating a world of fascist control that their own children and grandchildren will have to live in their entire lives. It is a hierarchical pyramid of imposition and acquiescence and, yes indeedy, of clinical insanity.

Does anyone bright enough to read this book have to ask what the answer is? I think not, but I will reveal it anyway in the fewest of syllables: Tell the psychos and their moronic lackeys to fuck off and let's get on with our lives. We are many – They are few.

CHAPTER SEVEN

War on your mind

One believes things because one has been conditioned to believe them
Aldous Huxley, *Brave New World*

I have described the 'Covid' hoax as a 'Psyop' and that is true in every sense and on every level in accordance with the definition of that term which is psychological warfare. Break down the 'Covid pandemic' to the foundation themes and it is psychological warfare on the human individual and collective mind.

The same can be said for the entire human belief system involving every subject you can imagine. Huxley was right in his contention that people believe what they are conditioned to believe and this comes from the repetition throughout their lives of the same falsehoods. They spew from government, corporations, media and endless streams of 'experts' telling you what the Cult wants you to believe and often believing it themselves (although *far* from always). 'Experts' are rewarded with 'prestigious' jobs and titles and as agents of perceptual programming with regular access to the media. The Cult has to control the narrative – control *information* – or they lose control of the vital, crucial, without-which-they-cannot-prevail public perception of reality. The foundation of that control today is the Internet made possible by the Defense Advanced Research Projects Agency (DARPA), the incredibly sinister technological arm of the Pentagon. The Internet is the result of military technology.

DARPA openly brags about establishing the Internet which has been a long-term project to lasso the minds of the global population. I have said for decades the plan is to control information to such an extreme that eventually no one would see or hear anything that the Cult does not approve. We are closing in on that end with ferocious censorship since the 'Covid' hoax began and in my case it started back in the 1990s in terms of books and speaking venues. I had to create my own publishing company in 1995 precisely because no one else would publish my books even then. I think they're all still running.

Cult Internet

To secure total control of information they needed the Internet in which pre-programmed algorithms can seek out 'unclean' content for deletion and even stop it being posted in the first place. The Cult had to dismantle print and non-Internet broadcast media to ensure the transfer of information to the appropriate-named 'Web' – a critical expression of the *Cult* web. We've seen the ever-quickening demise of traditional media and control of what is left by a tiny number of corporations operating worldwide. Independent journalism in the mainstream is already dead and never was that more obvious than since the turn of 2020. The Cult wants all information communicated via the Internet to globally censor and allow the plug to be pulled any time. Lockdowns and forced isolation has meant that communication between people has been through electronic means and no longer through face-to-face discourse and discussion. Cult psychopaths have targeted the bars, restaurants, sport, venues and meeting places in general for this reason. None of this is by chance and it's to stop people gathering in any kind of privacy or number while being able to track and monitor all Internet communications and block them as necessary. Even private messages between individuals have been censored by these fascists that control Cult fronts like Facebook, Twitter, Google and YouTube which are all officially run by Sabbatian place-people and from the background by higher-level Sabbatian place people.

Facebook, Google, Amazon and their like were seed-funded and supported into existence with money-no-object infusions of funds either directly or indirectly from DARPA and CIA technology arm In-Q-Tel. The Cult plays the long game and prepares very carefully for big plays like 'Covid'. Amazon is another front in the psychological war and pretty much controls the global market in book sales and increasingly publishing. Amazon's limitless funds have deleted fantastic numbers of independent publishers to seize global domination on the way to deciding which books can be sold and circulated and which cannot. Moves in that direction are already happening. Amazon's leading light Jeff Bezos is the grandson of Lawrence Preston Gise who worked with DARPA predecessor ARPA. Amazon has big connections to the CIA and the Pentagon. The plan I have long described went like this:

1. Employ military technology to establish the Internet.

2. Sell the Internet as a place where people can freely communicate without censorship and allow that to happen until the Net becomes the central and irreversible pillar of human society. If the Internet had been highly censored from the start many would have rejected it.

3. Fund and manipulate major corporations into being to control the circulation of information on your Internet using cover stories about geeks in garages to explain how they came about. Give them unlimited funds to expand rapidly with no need to make a profit for years while non-Cult companies who need to balance the books cannot compete. You know that in these circumstances your Googles, YouTubes, Facebooks and Amazons are going to secure near monopolies by either crushing or buying up the opposition.

4. Allow freedom of expression on both the Internet and communication platforms to draw people in until the Internet is the central and irreversible pillar of human society and your communication corporations have reached a stage of near monopoly domination.

5. Then unleash your always-planned frenzy of censorship on the basis of 'where else are you going to go?' and continue to expand that until nothing remains that the Cult does not want its human targets to see.

The process was timed to hit the 'Covid' hoax to ensure the best chance possible of controlling the narrative which they knew they had to do at all costs. They were, after all, about to unleash a 'deadly virus' that didn't really exist. If you do that in an environment of free-flowing information and opinion you would be dead in the

water before you could say Gates is a psychopath. The network was in place through which the Cult-created-and-owned World Health Organization could dictate the 'Covid' narrative and response policy slavishly supported by Cult-owned Internet communication giants and mainstream media while those telling a different story were censored. Google, YouTube, Facebook and Twitter openly announced that they would do this. What else would we expect from Cult-owned operations like Facebook which former executives have confirmed set out to make the platform more addictive than cigarettes and coldly manipulates emotions of its users to sow division between people and groups and scramble the minds of the young? If Zuckerberg lives out the rest of his life without going to jail for crimes against humanity, and most emphatically against the young, it will be a travesty of justice. Still, no matter, cause and effect will catch up with him eventually and the same with Sergey Brin and Larry Page at Google with its CEO Sundar Pichai who fix the Google search results to promote Cult narratives and hide the opposition. Put the same key words into Google and other search engines like DuckDuckGo and you will see how different results can be. Wikipedia is another intensely biased 'encyclopaedia' which skews its content to the Cult agenda. YouTube links to Wikipedia's version of 'Covid' and 'climate change' on video pages in which experts in their field offer a different opinion (even that is increasingly rare with Wojcicki censorship). Into this 'Covid' silence-them network must be added government media censors, sorry 'regulators', such as Ofcom in the UK which imposed tyrannical restrictions on British broadcasters that had the effect of banning me from ever appearing. Just to debate with me about my evidence and views on 'Covid' would mean breaking the fascistic impositions of Ofcom and its CEO career government bureaucrat Melanie Dawes. Gutless British broadcasters tremble at the very thought of fascist Ofcom.

Psychos behind 'Covid'

The reason for the 'Covid' catastrophe in all its facets and forms can be seen by whom and what is driving the policies worldwide in such a coordinated way. Decisions are not being made to protect health, but to target psychology. The dominant group guiding and 'advising' government policy are not medical professionals. They are psychologists and behavioural scientists. Every major country has its own version of this phenomenon and I'll use the British example to show how it works. In many ways the British version has been affecting the wider world in the form of the huge behaviour manipulation network in the UK which operates in other countries. The network involves private companies, government, intelligence and military. The Cabinet Office is at the centre of the government 'Covid' Psyop and part-owns, with 'innovation charity' Nesta, the Behavioural Insights Team (BIT) which claims to be independent of government but patently isn't. The BIT was established in 2010 and its job is to manipulate the psyche of the population to acquiesce to government demands and so much more. It is also known as the 'Nudge Unit', a name inspired by the 2009 book by two ultra-Zionists, Cass Sunstein and Richard Thaler, called *Nudge: Improving Decisions About Health, Wealth, and Happiness*. The book, as with the Behavioural Insights Team, seeks to 'nudge' behaviour (manipulate it) to make the public follow patterns of action and perception that suit those in authority (the Cult). Sunstein is so skilled at this that he advises the World Health Organization and the UK Behavioural Insights Team and was Administrator of the White House Office of Information and Regulatory Affairs in the Obama administration. Biden appointed him to the Department of Homeland Security – another ultra-Zionist in the fold to oversee new immigration laws which is another policy the Cult wants to control. Sunstein is desperate to silence anyone exposing conspiracies and co-authored a 2008 report on the subject in which suggestions were offered to ban 'conspiracy theorizing' or impose 'some kind of tax, financial or otherwise, on those who disseminate such theories'. I guess a psychiatrist's chair is out of the question?

Sunstein's mate Richard Thaler, an 'academic affiliate' of the UK Behavioural Insights Team, is a proponent of 'behavioural economics' which is defined as the study of 'the effects of psychological, cognitive, emotional, cultural and social factors on the decisions of individuals and institutions'. Study the effects so they can be manipulated to be what you want them to be. Other leading names in the development of behavioural economics are ultra-Zionists Daniel Kahneman and Robert J. Shiller and they, with Thaler, won the Nobel Memorial Prize in Economic Sciences for their work in this field. The Behavioural Insights Team is operating at the heart of the UK government and has expanded globally through partnerships with several universities including Harvard, Oxford, Cambridge, University College London (UCL) and Pennsylvania. They claim to have 'trained' (reframed) 20,000 civil servants and run more than 750 projects involving 400 randomised controlled trials in dozens of countries' as another version of mind reframers Common Purpose. BIT works from its office in New York with cities and their agencies, as well as other partners, across the United States and Canada – this is a company part-owned by the British government Cabinet Office. An executive order by President Cult-servant Obama established a US Social and Behavioral Sciences Team in 2015. They all have the same reason for being and that's to brainwash the population directly and by brainwashing those in positions of authority.

'Covid' mind game

Another prime aspect of the UK mind-control network is the 'independent' [joke] Scientific Pandemic Insights Group on Behaviours (SPI-B) which 'provides behavioural science advice aimed at anticipating and helping people adhere to interventions that are recommended by medical or epidemiological experts'. That means manipulating public perception and behaviour to do whatever government tells them to do. It's disgusting and if they really want the public to be 'safe' this lot should all be under lock and key. According to the government website SPI-B consists of

'behavioural scientists, health and social psychologists, anthropologists and historians' and advises the Whitty-Vallance-led Scientific Advisory Group for Emergencies (SAGE) which in turn advises the government on 'the science' (it doesn't) and 'Covid' policy. When politicians say they are being guided by 'the science' this is the rabble in each country they are talking about and that 'science' is dominated by behaviour manipulators to enforce government fascism through public compliance. The Behaviour Insight Team is headed by psychologist David Solomon Halpern, a visiting professor at King's College London, and connects with a national and global web of other civilian and military organisations as the Cult moves towards its goal of fusing them into one fascistic whole in every country through its 'Fusion Doctrine'. The behaviour manipulation network involves, but is not confined to, the Foreign Office; National Security Council; government communications headquarters (GCHQ); MI5; MI6; the Cabinet Office-based Media Monitoring Unit; and the Rapid Response Unit which 'monitors digital trends to spot emerging issues; including misinformation and disinformation; and identifies the best way to respond'.

There is also the 77th Brigade of the UK military which operates like the notorious Israeli military's Unit 8200 in manipulating information and discussion on the Internet by posing as members of the public to promote the narrative and discredit those who challenge it. Here we have the military seeking to manipulate *domestic* public opinion while the Nazis in government are fine with that. Conservative Member of Parliament Tobias Ellwood, an advocate of lockdown and control through 'vaccine passports', is a Lieutenant Colonel reservist in the 77th Brigade which connects with the military operation jHub, the 'innovation centre' for the Ministry of Defence and Strategic Command. jHub has also been involved with the civilian National Health Service (NHS) in 'symptom tracing' the population. The NHS is a key part of this mind control network and produced a document in December, 2020, explaining to staff how to use psychological manipulation with different groups and ages to get them to have the DNA-manipulating 'Covid vaccine'

that's designed to cumulatively rewrite human genetics. The document, called 'Optimising Vaccination Roll Out – Do's and Dont's for all messaging, documents and "communications" in the widest sense', was published by NHS England and the NHS Improvement *Behaviour Change Unit* in partnership with Public Health England and Warwick Business School. I hear the mantra about 'save the NHS' and 'protect the NHS' when we need to scrap the NHS and start again. The current version is far too corrupt, far too anti-human and totally compromised by Cult operatives and their assets. UK government broadcast media censor Ofcom will connect into this web – as will the BBC with its tremendous Ofcom influence – to control what the public see and hear and dictate mass perception. Nuremberg trials must include personnel from all these organisations.

The fear factor

The 'Covid' hoax has led to the creation of the UK Cabinet Office-connected Joint Biosecurity Centre (JBC) which is officially described as providing 'expert advice on pandemics' using its independent [all Cult operations are 'independent'] analytical function to provide real-time analysis about infection outbreaks to identify and respond to outbreaks of Covid-19'. Another role is to advise the government on a response to spikes in infections – 'for example by closing schools or workplaces in local areas where infection levels have risen'. Put another way, promoting the Cult agenda. The Joint Biosecurity Centre is modelled on the Joint Terrorism Analysis Centre which analyses intelligence to set 'terrorism threat levels' and here again you see the fusion of civilian and military operations and intelligence that has led to military intelligence producing documents about 'vaccine hesitancy' and how it can be combated. Domestic civilian matters and opinions should not be the business of the military. The Joint Biosecurity Centre is headed by Tom Hurd, director general of the Office for Security and Counter-Terrorism from the establishment-to-its-fingertips Hurd family. His father is former Foreign Secretary Douglas Hurd. How coincidental that Tom

Hurd went to the elite Eton College and Oxford University with Boris Johnson. Imperial College with its ridiculous computer modeller Neil Ferguson will connect with this gigantic web that will itself interconnect with similar set-ups in other major and not so major countries. Compared with this Cult network the politicians, be they Boris Johnson, Donald Trump or Joe Biden, are bit-part players 'following the science'. The network of psychologists was on the 'Covid' case from the start with the aim of generating maximum fear of the 'virus' to ensure compliance by the population. A government behavioural science group known as SPI-B produced a paper in March, 2020, for discussion by the main government science advisory group known as SAGE. It was headed 'Options for increasing adherence to social distancing measures' and it said the following in a section headed 'Persuasion':

- A substantial number of people still do not feel sufficiently personally threatened; it could be that they are reassured by the low death rate in their demographic group, although levels of concern may be rising. Having a good understanding of the risk has been found to be positively associated with adoption of COVID-19 social distancing measures in Hong Kong.

- The perceived level of personal threat needs to be increased among those who are complacent, using hard-hitting evaluation of options for increasing social distancing emotional messaging. To be effective this must also empower people by making clear the actions they can take to reduce the threat.

- Responsibility to others: There seems to be insufficient understanding of, or feelings of responsibility about, people's role in transmitting the infection to others … Messaging about actions need to be framed positively in terms of protecting oneself and the community, and increase confidence that they will be effective.

- Some people will be more persuaded by appeals to play by the rules, some by duty to the community, and some to personal risk.

> All these different approaches are needed. The messaging also needs to take account of the realities of different people's lives. Messaging needs to take account of the different motivational levers and circumstances of different people.

All this could be achieved the SPI-B psychologists said by *using the media to increase the sense of personal threat* which translates as terrify the shit out of the population, including children, so they all do what we want. That's not happened has it? Those excuses for 'journalists' who wouldn't know journalism if it bit them on the arse (the great majority) have played their crucial part in serving this Cult-government Psyop to enslave their own kids and grandkids. How they live with themselves I have no idea. The psychological war has been underpinned by constant government 'Covid' propaganda in almost every television and radio ad break, plus the Internet and print media, which has pounded out the fear with taxpayers footing the bill for their own programming. The result has been people terrified of a 'virus' that doesn't exist or one with a tiny fatality rate even if you believe it does. People walk down the street and around the shops wearing face-nappies damaging their health and psychology while others report those who refuse to be that naïve to the police who turn up in their own face-nappies. I had a cameraman come to my flat and he was so frightened of 'Covid' he came in wearing a mask and refused to shake my hand in case he caught something. He had – naïveitis – and the thought that he worked in the mainstream media was both depressing and made his behaviour perfectly explainable. The fear which has gripped the minds of so many and frozen them into compliance has been carefully cultivated by these psychologists who are really psychopaths. If lives get destroyed and a lot of young people commit suicide it shows our plan is working. SPI-B then turned to compulsion on the public to comply. 'With adequate preparation, rapid change can be achieved', it said. Some countries had introduced mandatory self-isolation on a wide scale without evidence of major public unrest and a large majority of the UK's population appeared to be supportive of more coercive measures with 64 percent of adults saying they would

support putting London under a lockdown (watch the 'polls' which are designed to make people believe that public opinion is in favour or against whatever the subject in hand).

For 'aggressive protective measures' to be effective, the SPI-B paper said, special attention should be devoted to those population groups that are more at risk. Translated from the Orwellian this means making the rest of population feel guilty for not protecting the 'vulnerable' such as old people which the Cult and its agencies were about to kill on an industrial scale with lockdown, lack of treatment and the Gates 'vaccine'. Psychopath psychologists sold their guilt-trip so comprehensively that Los Angeles County Supervisor Hilda Solis reported that children were apologising (from a distance) to their parents and grandparents for bringing 'Covid' into their homes and getting them sick. '… These apologies are just some of the last words that loved ones will ever hear as they die alone,' she said. Gut-wrenchingly Solis then used this childhood tragedy to tell children to stay at home and 'keep your loved ones alive'. Imagine heaping such potentially life-long guilt on a kid when it has absolutely nothing to do with them. These people are deeply disturbed and the psychologists behind this even more so.

Uncivil war – divide and rule

Professional mind-controllers at SPI-B wanted the media to increase a sense of responsibility to others (do as you're told) and promote 'positive messaging' for those actions while in contrast to invoke 'social disapproval' by the unquestioning, obedient, community of anyone with a mind of their own. Again the compliant Goebbels-like media obliged. This is an old, old, trick employed by tyrannies the world over throughout human history. You get the target population to keep the target population in line – *your* line. SPI-B said this could 'play an important role in preventing anti-social behaviour or discouraging failure to enact pro-social behaviour'. For 'anti-social' in the Orwellian parlance of SPI-B see any behaviour that government doesn't approve. SPI-B recommendations said that 'social disapproval' should be accompanied by clear messaging and

promotion of strong collective identity – hence the government and celebrity mantra of 'we're all in this together'. Sure we are. The mind doctors have such contempt for their targets that they think some clueless comedian, actor or singer telling them to do what the government wants will be enough to win them over. We have had UK comedian Lenny Henry, actor Michael Caine and singer Elton John wheeled out to serve the propagandists by urging people to have the DNA-manipulating 'Covid' non-'vaccine'. The role of Henry and fellow black celebrities in seeking to coax a 'vaccine' reluctant black community into doing the government's will was especially stomach-turning. An emotion-manipulating script and carefully edited video featuring these black 'celebs' was such an insult to the intelligence of black people and where's the self-respect of those involved selling their souls to a fascist government agenda? Henry said he heard black people's 'legitimate worries and concerns', but people must 'trust the facts' when they were doing exactly that by not having the 'vaccine'. They had to include the obligatory reference to Black Lives Matter with the line … 'Don't let coronavirus cost even more black lives – because we matter'. My god, it was pathetic. 'I know the vaccine is safe and what it does.' How? 'I'm a comedian and it says so in my script.'

SPI-B said social disapproval needed to be carefully managed to avoid victimisation, scapegoating and misdirected criticism, but they knew that their 'recommendations' would lead to exactly that and the media were specifically used to stir-up the divide-and-conquer hostility. Those who conform like good little baa, baas, are praised while those who have seen through the tidal wave of lies are 'Covidiots'. The awake have been abused by the fast asleep for not conforming to fascism and impositions that the awake know are designed to endanger their health, dehumanise them, and tear asunder the very fabric of human society. We have had the curtain-twitchers and morons reporting neighbours and others to the face-nappied police for breaking 'Covid rules' with fascist police delighting in posting links and phone numbers where this could be done. The Cult cannot impose its will without a compliant police

and military or a compliant population willing to play their part in enslaving themselves and their kids. The words of a pastor in Nazi Germany are so appropriate today:

First they came for the socialists and I did not speak out because I was not a socialist.

Then they came for the trade unionists and I did not speak out because I was not a trade unionist.

Then they came for the Jews and I did not speak out because I was not a Jew.

Then they came for me and there was no one left to speak for me.

Those who don't learn from history are destined to repeat it and so many are.

'Covid' rules: Rewiring the mind

With the background laid out to this gigantic national and global web of psychological manipulation we can put 'Covid' rules into a clear and sinister perspective. Forget the claims about protecting health. 'Covid' rules are about dismantling the human mind, breaking the human spirit, destroying self-respect, and then putting Humpty Dumpty together again as a servile, submissive slave. Social isolation through lockdown and distancing have devastating effects on the human psyche as the psychological psychopaths well know and that's the real reason for them. Humans need contact with each other, discourse, closeness and touch, or they eventually, and literarily, go crazy. Masks, which I will address at some length, fundamentally add to the effects of isolation and the Cult agenda to dehumanise and de-individualise the population. To do this while knowing – in fact *seeking* – this outcome is the very epitome of evil and psychologists involved in this *are* the epitome of evil. They must like all the rest of the Cult demons and their assets stand trial for crimes against humanity on a scale that defies the imagination. Psychopaths in uniform use isolation to break enemy troops and agents and make them subservient and submissive to tell what they know. The technique is rightly considered a form of torture and

torture is most certainly what has been imposed on the human population.

Clinically-insane American psychologist Harry Harlow became famous for his isolation experiments in the 1950s in which he separated baby monkeys from their mothers and imprisoned them for months on end in a metal container or 'pit of despair'. They soon began to show mental distress and depression as any idiot could have predicted. Harlow put other monkeys in steel chambers for three, six or twelve months while denying them any contact with animals or humans. He said that the effects of total social isolation for six months were 'so devastating and debilitating that we had assumed initially that twelve months of isolation would not produce any additional decrement'; but twelve months of isolation 'almost obliterated the animals socially'. This is what the Cult and its psychopaths are doing to you and your children. Even monkeys in partial isolation in which they were not allowed to form relationships with other monkeys became 'aggressive and hostile, not only to others, but also towards their own bodies'. We have seen this in the young as a consequence of lockdown. UK government psychopaths launched a public relations campaign telling people not to hug each other even after they received the 'Covid-19 vaccine' which we were told with more lies would allow a return to 'normal life'. A government source told *The Telegraph*: 'It will be along the lines that it is great that you have been vaccinated, but if you are going to visit your family and hug your grandchildren there is a chance you are going to infect people you love.' The source was apparently speaking from a secure psychiatric facility. Janet Lord, director of Birmingham University's Institute of Inflammation and Ageing, said that parents and grandparents should avoid hugging their children. Well, how can I put it, Ms Lord? Fuck off. Yep, that'll do.

Destroying the kids – where are the parents?

Observe what has happened to people enslaved and isolated by lockdown as suicide and self-harm has soared worldwide,

particularly among the young denied the freedom to associate with their friends. A study of 49,000 people in English-speaking countries concluded that almost half of young adults are at clinical risk of mental health disorders. A national survey in America of 1,000 currently enrolled high school and college students found that 5 percent reported attempting suicide during the pandemic. Data from the US CDC's National Syndromic Surveillance Program from January 1st to October 17th, 2020, revealed a *31 percent* increase in mental health issues among adolescents aged 12 to 17 compared with 2019. The CDC reported that America in general suffered the biggest drop in life expectancy since World War Two as it fell by a year in the first half of 2020 as a result of 'deaths of despair' – overdoses and suicides. Deaths of despair have leapt by more than 20 percent during lockdown and include the highest number of fatal overdoses ever recorded in a single year – 81,000. Internet addiction is another consequence of being isolated at home which lowers interest in physical activities as kids fall into inertia and what's the point? Children and young people are losing hope and giving up on life, sometimes literally. A 14-year-old boy killed himself in Maryland because he had 'given up' when his school district didn't reopen; an 11-year-old boy shot himself during a zoom class; a teenager in Maine succumbed to the isolation of the 'pandemic' when he ended his life after experiencing a disrupted senior year at school. Children as young as nine have taken their life and all these stories can be repeated around the world. Careers are being destroyed before they start and that includes those in sport in which promising youngsters have not been able to take part. The plan of the psycho-psychologists is working all right. Researchers at Cambridge University found that lockdowns cause significant harm to children's mental health. Their study was published in the *Archives of Disease in Childhood*, and followed 168 children aged between 7 and 11. The researchers concluded:

> During the UK lockdown, children's depression symptoms have increased substantially, relative to before lockdown. The scale of this effect has direct relevance for the continuation of different elements of lockdown policy, such as complete or partial school closures …

… Specifically, we observed a statistically significant increase in ratings of depression, with a medium-to-large effect size. Our findings emphasise the need to incorporate the potential impact of lockdown on child mental health in planning the ongoing response to the global pandemic and the recovery from it.

Not a chance when the Cult's psycho-psychologists were getting exactly what they wanted. The UK's Royal College of Paediatrics and Child Health has urged parents to look for signs of eating disorders in children and young people after a three to four fold increase. Specialists say the 'pandemic' is a major reason behind the rise. You don't say. The College said isolation from friends during school closures, exam cancellations, loss of extra-curricular activities like sport, and an increased use of social media were all contributory factors along with fears about the virus (psycho-psychologists again), family finances, and students being forced to quarantine. Doctors said young people were becoming severely ill by the time they were seen with 'Covid' regulations reducing face-to-face consultations. Nor is it only the young that have been devastated by the psychopaths. Like all bullies and cowards the Cult is targeting the young, elderly, weak and infirm. A typical story was told by a British lady called Lynn Parker who was not allowed to visit her husband in 2020 for the last ten and half months of his life 'when he needed me most' between March 20th and when he died on December 19th. This vacates the criminal and enters the territory of evil. The emotional impact on the immune system alone is immense as are the number of people of all ages worldwide who have died as a result of Cult-demanded, Gates-demanded, lockdowns.

Isolation is torture

The experience of imposing solitary confinement on millions of prisoners around the world has shown how a large percentage become 'actively psychotic and/or acutely suicidal'. Social isolation has been found to trigger 'a specific psychiatric syndrome, characterized by hallucinations; panic attacks; overt paranoia; diminished impulse control; hypersensitivity to external stimuli; and difficulties with thinking, concentration and memory'. Juan Mendez,

a United Nations rapporteur (investigator), said that isolation is a form of torture. Research has shown that even after isolation prisoners find it far more difficult to make social connections and I remember chatting to a shop assistant after one lockdown who told me that when her young son met another child again he had no idea how to act or what to do. Hannah Flanagan, Director of Emergency Services at Journey Mental Health Center in Dane County, Wisconsin, said: 'The specificity about Covid social distancing and isolation that we've come across as contributing factors to the suicides are really new to us this year.' But they are not new to those that devised them. They are getting the effect they want as the population is psychologically dismantled to be rebuilt in a totally different way. Children and the young are particularly targeted. They will be the adults when the full-on fascist AI-controlled technocracy is planned to be imposed and they are being prepared to meekly submit. At the same time older people who still have a memory of what life was like before – and how fascist the new normal really is – are being deleted. You are going to see efforts to turn the young against the old to support this geriatric genocide. Hannah Flanagan said the big increase in suicide in her county proved that social isolation is not only harmful, but deadly. Studies have shown that isolation from others is one of the main risk factors in suicide and even more so with women. Warnings that lockdown could create a 'perfect storm' for suicide were ignored. After all this was one of the *reasons* for lockdown. Suicide, however, is only the most extreme of isolation consequences. There are many others. Dr Dhruv Khullar, assistant professor of healthcare policy at Weill Cornell Medical College, said in a *New York Times* article in 2016 long before the fake 'pandemic':

> A wave of new research suggests social separation is bad for us. Individuals with less social connection have disrupted sleep patterns, altered immune systems, more inflammation and higher levels of stress hormones. One recent study found that isolation increases the risk of heart disease by 29 percent and stroke by 32 percent. Another analysis that pooled data from 70 studies and 3.4 million people found that socially isolated individuals had a 30 percent higher risk of dying in the next seven years, and that this effect was largest in middle age.

Loneliness can accelerate cognitive decline in older adults, and isolated individuals are twice as likely to die prematurely as those with more robust social interactions. These effects start early: Socially isolated children have significantly poorer health 20 years later, even after controlling for other factors. All told, loneliness is as important a risk factor for early death as obesity and smoking.

There you have proof from that one article alone four years before 2020 that those who have enforced lockdown, social distancing and isolation knew what the effect would be and that is even more so with professional psychologists that have been driving the policy across the globe. We can go back even further to the years 2000 and 2003 and the start of a major study on the effects of isolation on health by Dr Janine Gronewold and Professor Dirk M. Hermann at the University Hospital in Essen, Germany, who analysed data on 4,316 people with an average age of 59 who were recruited for the long-term research project. They found that socially isolated people are more than 40 percent more likely to have a heart attack, stroke, or other major cardiovascular event and nearly 50 percent more likely to die from any cause. Given the financial Armageddon unleashed by lockdown we should note that the study found a relationship between increased cardiovascular risk and lack of financial support. After excluding other factors social isolation was still connected to a 44 percent increased risk of cardiovascular problems and a 47 percent increased risk of death by any cause. Lack of financial support was associated with a 30 percent increase in the risk of cardiovascular health events. Dr Gronewold said it had been known for some time that feeling lonely or lacking contact with close friends and family can have an impact on physical health and the study had shown that having strong social relationships is of high importance for heart health. Gronewold said they didn't understand yet why people who are socially isolated have such poor health outcomes, but this was obviously a worrying finding, particularly during these times of prolonged social distancing. Well, it can be explained on many levels. You only have to identify the point in the body where people feel loneliness and missing people they are parted from – it's in the centre of the chest where they feel the ache of loneliness and the ache of missing people. 'My heart aches for

you' … 'My heart aches for some company.' I will explain this more in the chapter Escaping Wetiko, but when you realise that the body is the mind – they are expressions of each other – the reason why state of the mind dictates state of the body becomes clear.

American psychologist Ranjit Powar was highlighting the effects of lockdown isolation as early as April, 2020. She said humans have evolved to be social creatures and are wired to live in interactive groups. Being isolated from family, friends and colleagues could be unbalancing and traumatic for most people and could result in short or even long-term psychological and physical health problems. An increase in levels of anxiety, aggression, depression, forgetfulness and hallucinations were possible psychological effects of isolation. 'Mental conditions may be precipitated for those with underlying pre-existing susceptibilities and show up in many others without any pre-condition.' Powar said personal relationships helped us cope with stress and if we lost this outlet for letting off steam the result can be a big emotional void which, for an average person, was difficult to deal with. 'Just a few days of isolation can cause increased levels of anxiety and depression' – so what the hell has been the effect on the global population of *18 months* of this at the time of writing? Powar said: 'Add to it the looming threat of a dreadful disease being repeatedly hammered in through the media and you have a recipe for many shades of mental and physical distress.' For those with a house and a garden it is easy to forget that billions have had to endure lockdown isolation in tiny overcrowded flats and apartments with nowhere to go outside. The psychological and physical consequences of this are unimaginable and with lunatic and abusive partners and parents the consequences have led to tremendous increases in domestic and child abuse and alcoholism as people seek to shut out the horror. Ranjit Powar said:

Staying in a confined space with family is not all a rosy picture for everyone. It can be extremely oppressive and claustrophobic for large low-income families huddled together in small single-room houses. Children here are not lucky enough to have many board/electronic games or books to keep them occupied.

Add to it the deep insecurity of running out of funds for food and basic necessities. On the other hand, there are people with dysfunctional family dynamics, such as domineering, abusive or alcoholic partners, siblings or parents which makes staying home a period of trial. Incidence of suicide and physical abuse against women has shown a worldwide increase. Heightened anxiety and depression also affect a person's immune system, making them more susceptible to illness.

To think that Powar's article was published on April 11th, 2020.

Six-feet fantasy

Social (unsocial) distancing demanded that people stay six feet or two metres apart. UK government advisor Robert Dingwall from the New and Emerging Respiratory Virus Threats Advisory Group said in a radio interview that the two-metre rule was 'conjured up out of nowhere' and was not based on science. No, it was not based on *medical* science, but it didn't come out of nowhere. The distance related to *psychological* science. Six feet/two metres was adopted in many countries and we were told by people like the criminal Anthony Fauci and his ilk that it was founded on science. Many schools could not reopen because they did not have the space for six-feet distancing. Then in March, 2021, after a year of six-feet 'science', a study published in the *Journal of Infectious Diseases* involving more than 500,000 students and almost 100,000 staff over 16 weeks revealed no significant difference in 'Covid' cases between six feet and three feet and Fauci changed his tune. Now three feet was okay. There is no difference between six feet and three *inches* when there is no 'virus' and they got away with six feet for psychological reasons for as long as they could. I hear journalists and others talk about 'unintended consequences' of lockdown. They are not *unintended* at all; they have been coldly-calculated for a specific outcome of human control and that's why super-psychopaths like Gates have called for them so vehemently. Super-psychopath psychologists have demanded them and psychopathic or clueless, spineless, politicians have gone along with them by 'following the science'. But it's not science at all. 'Science' is not what is; it's only what people can be manipulated to believe it is. The whole 'Covid' catastrophe is

founded on mind control. Three word or three statement mantras issued by the UK government are a well-known mind control technique and so we've had 'Stay home/protect the NHS/save lives', 'Stay alert/control the virus/save lives' and 'hands/face/space'. One of the most vocal proponents of extreme 'Covid' rules in the UK has been Professor Susan Michie, a member of the British Communist Party, who is not a medical professional. Michie is the director of the Centre for Behaviour Change at University College London. She is a *behavioural psychologist* and another filthy rich 'Marxist' who praised China's draconian lockdown. She was known by fellow students at Oxford University as 'Stalin's nanny' for her extreme Marxism. Michie is an influential member of the UK government's Scientific Advisory Group for Emergencies (SAGE) and behavioural manipulation groups which have dominated 'Covid' policy. She is a consultant adviser to the World Health Organization on 'Covid-19' and behaviour. Why the hell are lockdowns anything to do with her when they are claimed to be about health? Why does a behavioural psychologist from a group charged with changing the behaviour of the public want lockdown, human isolation and mandatory masks? Does that question really need an answer? Michie *absolutely* has to explain herself before a Nuremberg court when humanity takes back its world again and even more so when you see the consequences of masks that she demands are compulsory. This is a Michie classic:

> The benefits of getting primary school children to wear masks is that regardless of what little degree of transmission is occurring in those age groups it could help normalise the practice. Young children wearing masks may be more likely to get their families to accept masks.

Those words alone should carry a prison sentence when you ponder on the callous disregard for children involved and what a statement it makes about the mind and motivations of Susan Michie. What a lovely lady and what she said there encapsulates the mentality of the psychopaths behind the 'Covid' horror. Let us compare what Michie said with a countrywide study in Germany published at researchsquare.com involving 25,000 school children and 17,854 health complaints submitted by parents. Researchers

found that masks are harming children physically, psychologically, and behaviourally with 24 health issues associated with mask wearing. They include: shortness of breath (29.7%); dizziness (26.4%); increased headaches (53%); difficulty concentrating (50%); drowsiness or fatigue (37%); and malaise (42%). Nearly a third of children experienced more sleep issues than before and a quarter developed new fears. Researchers found health issues and other impairments in 68 percent of masked children covering their faces for an average of 4.5 hours a day. Hundreds of those taking part experienced accelerated respiration, tightness in the chest, weakness, and short-term impairment of consciousness. A reminder of what Michie said again:

The benefits of getting primary school children to wear masks is that regardless of what little degree of transmission is occurring in those age groups it could help normalise the practice. Young children wearing masks may be more likely to get their families to accept masks.

Psychopaths in government and psychology now have children and young people – plus all the adults – wearing masks for hours on end while clueless teachers impose the will of the psychopaths on the young they should be protecting. What the hell are parents doing?

Cult lab rats

We have some schools already imposing on students microchipped buzzers that activate when they get 'too close' to their pals in the way they do with lab rats. How apt. To the Cult and its brain-dead servants our children *are* lab rats being conditioned to be unquestioning, dehumanised slaves for the rest of their lives. Children and young people are being weaned and frightened away from the most natural human instincts including closeness and touch. I have tracked in the books over the years how schools were banning pupils from greeting each other with a hug and the whole Cult-induced Me Too movement has terrified men and boys from a relaxed and natural interaction with female friends and work colleagues to the point where many men try never to be in a room

alone with a woman that's not their partner. Airhead celebrities have as always played their virtue-signalling part in making this happen with their gross exaggeration. For every monster like Harvey Weinstein there are at least tens of thousands of men that don't treat women like that; but everyone must be branded the same and policy changed for them as well as the monster. I am going to be using the word 'dehumanise' many times in this chapter because that is what the Cult is seeking to do and it goes very deep as we shall see. Don't let them kid you that social distancing is planned to end one day. That's not the idea. We are seeing more governments and companies funding and producing wearable gadgets to keep people apart and they would not be doing that if this was meant to be short-term. A tech start-up company backed by GCHQ, the British Intelligence and military surveillance headquarters, has created a social distancing wrist sensor that alerts people when they get too close to others. The CIA has also supported tech companies developing similar devices. The wearable sensor was developed by Tended, one of a number of start-up companies supported by GCHQ (see the CIA and DARPA). The device can be worn on the wrist or as a tag on the waistband and will vibrate whenever someone wearing the device breaches social distancing and gets anywhere near natural human contact. The company had a lucky break in that it was developing a distancing sensor when the 'Covid' hoax arrived which immediately provided a potentially enormous market. How fortunate. The government in big-time Cult-controlled Ontario in Canada is investing $2.5 million in wearable contact tracing technology that 'will alert users if they may have been exposed to the Covid-19 in the workplace and will beep or vibrate if they are within six feet of another person'. Facedrive Inc., the technology company behind this, was founded in 2016 with funding from the Ontario Together Fund and obviously they, too, had a prophet on the board of directors. The human surveillance and control technology is called TraceSCAN and would be worn by the human cyborgs in places such as airports, workplaces, construction sites, care homes and … *schools*.

I emphasise schools with children and young people the prime targets. You know what is planned for society as a whole if you keep your eyes on the schools. They have always been places where the state program the next generation of slaves to be its compliant worker-ants – or Woker-ants these days; but in the mist of the 'Covid' madness they have been transformed into mind laboratories on a scale never seen before. Teachers and head teachers are just as programmed as the kids – often more so. Children are kept apart from human interaction by walk lanes, classroom distancing, staggered meal times, masks, and the rolling-out of buzzer systems. Schools are now physically laid out as a laboratory maze for lab-rats. Lunatics at a school in Anchorage, Alaska, who should be prosecuted for child abuse, took away desks and forced children to kneel (know your place) on a mat for five hours a day while wearing a mask and using their chairs as a desk. How this was supposed to impact on a 'virus' only these clinically insane people can tell you and even then it would be clap-trap. The school banned recess (interaction), art classes (creativity), and physical exercise (getting body and mind moving out of inertia). Everyone behind this outrage should be in jail or better still a mental institution. The behavioural manipulators are all for this dystopian approach to schools. Professor Susan Michie, the mind-doctor and British Communist Party member, said it was wrong to say that schools were safe. They had to be made so by 'distancing', masks and ventilation (sitting all day in the cold). I must ask this lady round for dinner on a night I know I am going to be out and not back for weeks. She probably wouldn't be able to make it, anyway, with all the visits to her own psychologist she must have block-booked.

Masking identity

I know how shocking it must be for you that a behaviour manipulator like Michie wants everyone to wear masks which have long been a feature of mind-control programs like the infamous MKUltra in the United States, but, there we are. We live and learn. I spent many years from 1996 to right across the millennium

researching mind control in detail on both sides of the Atlantic and elsewhere. I met a large number of mind-control survivors and many had been held captive in body and mind by MKUltra. MK stands for mind-control, but employs the German spelling in deference to the Nazis spirited out of Germany at the end of World War Two by Operation Paperclip in which the US authorities, with help from the Vatican, transported Nazi mind-controllers and engineers to America to continue their work. Many of them were behind the creation of NASA and they included Nazi scientist and SS officer Wernher von Braun who swapped designing V-2 rockets to bombard London with designing the Saturn V rockets that powered the NASA moon programme's Apollo craft. I think I may have mentioned that the Cult has no borders. Among Paperclip escapees was Josef Mengele, the Angel of Death in the Nazi concentration camps where he conducted mind and genetic experiments on children often using twins to provide a control twin to measure the impact of his 'work' on the other. If you want to observe the Cult mentality in all its extremes of evil then look into the life of Mengele. I have met many people who suffered mercilessly under Mengele in the United States where he operated under the name Dr Greene and became a stalwart of MKUltra programming and torture. Among his locations was the underground facility in the Mojave Desert in California called the China Lake Naval Weapons Station which is almost entirely below the surface. My books *The Biggest Secret*, *Children of the Matrix* and *The Perception Deception* have the detailed background to MKUltra.

The best-known MKUltra survivor is American Cathy O'Brien. I first met her and her late partner Mark Phillips at a conference in Colorado in 1996. Mark helped her escape and deprogram from decades of captivity in an offshoot of MKUltra known as Project Monarch in which 'sex slaves' were provided for the rich and famous including Father George Bush, Dick Cheney and the Clintons. Read Cathy and Mark's book *Trance-Formation of America* and if you are new to this you will be shocked to the core. I read it in 1996 shortly before, with the usual synchronicity of my life, I found

myself given a book table at the conference right next to hers. MKUltra never ended despite being very publicly exposed (only a small part of it) in the 1970s and continues in other guises. I am still in touch with Cathy. She contacted me during 2020 after masks became compulsory in many countries to tell me how they were used as part of MKUltra programming. I had been observing 'Covid regulations' and the relationship between authority and public for months. I saw techniques that I knew were employed on individuals in MKUltra being used on the global population. I had read many books and manuals on mind control including one called *Silent Weapons for Quiet Wars* which came to light in the 1980s and was a guide on how to perceptually program on a mass scale. 'Silent Weapons' refers to mind-control. I remembered a line from the manual as governments, medical authorities and law enforcement agencies have so obviously talked to – or rather at – the adult population since the 'Covid' hoax began as if they are children. The document said:

> If a person is spoken to by a T.V. advertiser as if he were a twelve-year-old, then, due to suggestibility, he will, with a certain probability, respond or react to that suggestion with the uncritical response of a twelve-year-old and will reach in to his economic reservoir and deliver its energy to buy that product on impulse when he passes it in the store.

That's why authority has spoken to adults like children since all this began.

Why did Michael Jackson wear masks?

Every aspect of the 'Covid' narrative has mind-control as its central theme. Cathy O'Brien wrote an article for davidicke.com about the connection between masks and mind control. Her daughter Kelly who I first met in the 1990s was born while Cathy was still held captive in MKUltra. Kelly was forced to wear a mask as part of her programming from the age of *two* to dehumanise her, target her sense of individuality and reduce the amount of oxygen her brain and body received. *Bingo*. This is the real reason for compulsory

masks, why they have been enforced en masse, and why they seek to increase the number they demand you wear. First one, then two, with one disgraceful alleged 'doctor' recommending four which is nothing less than a death sentence. Where and how often they must be worn is being expanded for the purpose of mass mind control and damaging respiratory health which they can call 'Covid-19'. Canada's government headed by the man-child Justin Trudeau, says it's fine for children of two and older to wear masks. An insane 'study' in Italy involving just 47 children concluded there was no problem for babies as young as *four months* wearing them. Even after people were 'vaccinated' they were still told to wear masks by the criminal that is Anthony Fauci. Cathy wrote that mandating masks is allowing the authorities literally to control the air we breathe which is what was done in MKUltra. You might recall how the singer Michael Jackson wore masks and there is a reason for that. He was subjected to MKUltra mind control through Project Monarch and his psyche was scrambled by these simpletons. Cathy wrote:

In MKUltra Project Monarch mind control, Michael Jackson had to wear a mask to silence his voice so he could not reach out for help. Remember how he developed that whisper voice when he wasn't singing? Masks control the mind from the outside in, like the redefining of words is doing. By controlling what we can and cannot say for fear of being labeled racist or beaten, for example, it ultimately controls thought that drives our words and ultimately actions (or lack thereof).

Likewise, a mask muffles our speech so that we are not heard, which controls voice … words … mind. This is Mind Control. Masks are an obvious mind control device, and I am disturbed so many people are complying on a global scale. Masks depersonalize while making a person feel as though they have no voice. It is a barrier to others. People who would never choose to comply but are forced to wear a mask in order to keep their job, and ultimately their family fed, are compromised. They often feel shame and are subdued. People have stopped talking with each other while media controls the narrative.

The 'no voice' theme has often become literal with train passengers told not to speak to each other in case they pass on the 'virus', singing banned for the same reason and bonkers California officials telling people riding roller coasters that they cannot shout and scream. Cathy said she heard every day from healed MKUltra survivors who cannot wear a mask without flashing back on ways

their breathing was controlled – 'from ball gags and penises to water boarding'. She said that through the years when she saw images of people in China wearing masks 'due to pollution' that it was really to control their oxygen levels. 'I knew it was as much of a population control mechanism of depersonalisation as are burkas', she said. Masks are another Chinese communist/fascist method of control that has been swept across the West as the West becomes China at lightning speed since we entered 2020.

Mask-19

There are other reasons for mandatory masks and these include destroying respiratory health to call it 'Covid-19' and stunting brain development of children and the young. Dr Margarite Griesz-Brisson MD, PhD, is a Consultant Neurologist and Neurophysiologist and the Founder and Medical Director of the London Neurology and Pain Clinic. Her CV goes down the street and round the corner. She is clearly someone who cares about people and won't parrot the propaganda. Griesz-Brisson has a PhD in pharmacology, with special interest in neurotoxicology, environmental medicine, neuroregeneration and neuroplasticity (the way the brain can change in the light of information received). She went public in October, 2020, with a passionate warning about the effects of mask-wearing laws:

> The reinhalation of our exhaled air will without a doubt create oxygen deficiency and a flooding of carbon dioxide. We know that the human brain is very sensitive to oxygen deprivation. There are nerve cells for example in the hippocampus that can't be longer than 3 minutes without oxygen – they cannot survive. The acute warning symptoms are headaches, drowsiness, dizziness, issues in concentration, slowing down of reaction time – reactions of the cognitive system.

Oh, I know, let's tell bus, truck and taxi drivers to wear them and people working machinery. How about pilots, doctors and police? Griesz-Brisson makes the important point that while the symptoms she mentions may fade as the body readjusts this does not alter the fact that people continue to operate in oxygen deficit with long list of

potential consequences. She said it was well known that neurodegenerative diseases take years or decades to develop. 'If today you forget your phone number, the breakdown in your brain would have already started 20 or 30 years ago.' She said degenerative processes in your brain are getting amplified as your oxygen deprivation continues through wearing a mask. Nerve cells in the brain are unable to divide themselves normally in these circumstances and lost nerve cells will no longer be regenerated. 'What is gone is gone.' Now consider that people like shop workers and *schoolchildren* are wearing masks for hours every day. What in the name of sanity is going to be happening to them? 'I do not wear a mask, I need my brain to think', Griesz-Brisson said, 'I want to have a clear head when I deal with my patients and not be in a carbon dioxide-induced anaesthesia'. If you are told to wear a mask anywhere ask the organisation, police, store, whatever, for their risk assessment on the dangers and negative effects on mind and body of enforcing mask-wearing. They won't have one because it has never been done not even by government. All of them must be subject to class-action lawsuits as the consequences come to light. They don't do mask risk assessments for an obvious reason. They know what the conclusions would be and independent scientific studies that *have* been done tell a horror story of consequences.

'Masks are criminal'

Dr Griesz-Brisson said that for children and adolescents, masks are an absolute no-no. They had an extremely active and adaptive immune system and their brain was incredibly active with so much to learn. 'The child's brain, or the youth's brain, is thirsting for oxygen.' The more metabolically active an organ was, the more oxygen it required; and in children and adolescents every organ was metabolically active. Griesz-Brisson said that to deprive a child's or adolescent's brain of oxygen, or to restrict it in any way, was not only dangerous to their health, it was absolutely criminal. 'Oxygen deficiency inhibits the development of the brain, and the damage that has taken place as a result CANNOT be reversed.' Mind

manipulators of MKUltra put masks on two-year-olds they wanted to neurologically rewire and you can see why. Griesz-Brisson said a child needs the brain to learn and the brain needs oxygen to function. 'We don't need a clinical study for that. This is simple, indisputable physiology.' Consciously and purposely induced oxygen deficiency was an absolutely deliberate health hazard, and an absolute medical contraindication which means that 'this drug, this therapy, this method or measure should not be used, and is not allowed to be used'. To coerce an entire population to use an absolute medical contraindication by force, she said, there had to be definite and serious reasons and the reasons must be presented to competent interdisciplinary and independent bodies to be verified and authorised. She had this warning of the consequences that were coming if mask wearing continued:

When, in ten years, dementia is going to increase exponentially, and the younger generations couldn't reach their god-given potential, it won't help to say 'we didn't need the masks'. I know how damaging oxygen deprivation is for the brain, cardiologists know how damaging it is for the heart, pulmonologists know how damaging it is for the lungs. Oxygen deprivation damages every single organ. Where are our health departments, our health insurance, our medical associations? It would have been their duty to be vehemently against the lockdown and to stop it and stop it from the very beginning.

Why do the medical boards issue punishments to doctors who give people exemptions? Does the person or the doctor seriously have to prove that oxygen deprivation harms people? What kind of medicine are our doctors and medical associations representing? Who is responsible for this crime? The ones who want to enforce it? The ones who let it happen and play along, or the ones who don't prevent it?

All of the organisations and people she mentions there either answer directly to the Cult or do whatever hierarchical levels above them tell them to do. The outcome of both is the same. 'It's not about masks, it's not about viruses, it's certainly not about your health', Griesz-Brisson said. 'It is about much, much more. I am not participating. I am not afraid.' They were taking our air to breathe and there was no unfounded medical exemption from face masks. Oxygen deprivation was dangerous for every single brain. It had to be the free decision of every human being whether they want to

wear a mask that was absolutely ineffective to protect themselves from a virus. She ended by rightly identifying where the responsibility lies for all this:

> The imperative of the hour is personal responsibility. We are responsible for what we think, not the media. We are responsible for what we do, not our superiors. We are responsible for our health, not the World Health Organization. And we are responsible for what happens in our country, not the government.

Halle-bloody-lujah.

But surgeons wear masks, right?

Independent studies of mask-wearing have produced a long list of reports detailing mental, emotional and physical dangers. What a definition of insanity to see police officers imposing mask-wearing on the public which will cumulatively damage their health while the police themselves wear masks that will cumulatively damage *their* health. It's utter madness and both public and police do this because 'the government says so' – yes a government of brain-donor idiots like UK Health Secretary Matt Hancock reading the 'follow the science' scripts of psychopathic, lunatic psychologists. The response you get from Stockholm syndrome sufferers defending the very authorities that are destroying them and their families is that 'surgeons wear masks'. This is considered the game, set and match that they must work and don't cause oxygen deficit. Well, actually, scientific studies have shown that they *do* and oxygen levels are monitored in operating theatres to compensate. Surgeons wear masks to stop spittle and such like dropping into open wounds – not to stop 'viral particles' which are so miniscule they can only be seen through an electron microscope. Holes in the masks are significantly bigger than 'viral particles' and if you sneeze or cough they will breach the mask. I watched an incredibly disingenuous 'experiment' that claimed to prove that masks work in catching 'virus' material from the mouth and nose. They did this with a slow motion camera and the mask did block big stuff which stayed inside the mask and

against the face to be breathed in or cause infections on the face as we have seen with many children. 'Viral particles', however, would never have been picked up by the camera as they came through the mask when they are far too small to be seen. The 'experiment' was therefore disingenuous *and* useless.

Studies have concluded that wearing masks in operating theatres (and thus elsewhere) make no difference to preventing infection while the opposite is true with toxic shite building up in the mask and this had led to an explosion in tooth decay and gum disease dubbed by dentists 'mask mouth'. You might have seen the Internet video of a furious American doctor urging people to take off their masks after a four-year-old patient had been rushed to hospital the night before and nearly died with a lung infection that doctors sourced to mask wearing. A study in the journal *Cancer Discovery* found that inhalation of harmful microbes can contribute to advanced stage lung cancer in adults and long-term use of masks can help breed dangerous pathogens. Microbiologists have said frequent mask wearing creates a moist environment in which microbes can grow and proliferate before entering the lungs. The Canadian Agency for Drugs and Technologies in Health, or CADTH, a Canadian national organisation that provides research and analysis to healthcare decision-makers, said this as long ago as 2013 in a report entitled 'Use of Surgical Masks in the Operating Room: A Review of the Clinical Effectiveness and Guidelines'. It said:

- No evidence was found to support the use of surgical face masks to reduce the frequency of surgical site infections
- No evidence was found on the effectiveness of wearing surgical face masks to protect staff from infectious material in the operating room.
- Guidelines recommend the use of surgical face masks by staff in the operating room to protect both operating room staff and patients (despite the lack of evidence).

We were told that the world could go back to 'normal' with the arrival of the 'vaccines'. When they came, fraudulent as they are, the story changed as I knew that it would. We are in the midst of transforming 'normal', not going back to it. Mary Ramsay, head of immunisation at Public Health England, echoed the words of US criminal Anthony Fauci who said masks and other regulations must stay no matter if people are vaccinated. The Fauci idiot continued to wear two masks – different colours so both could be clearly seen – after he *claimed* to have been vaccinated. Senator Rand Paul told Fauci in one exchange that his double-masks were 'theatre' and he was right. It's all theatre. Mary Ramsay back-tracked on the vaccine-return-to-normal theme when she said the public may need to wear masks and social-distance for years despite the jabs. 'People have got used to those lower-level restrictions now, and [they] can live with them', she said telling us what the idea has been all along. 'The vaccine does not give you a pass, even if you have had it, you must continue to follow all the guidelines' said a Public Health England statement which reneged on what we had been told before and made having the 'vaccine' irrelevant to 'normality' even by the official story. Spain's fascist government trumped everyone by passing a law mandating the wearing of masks on the beach and even when swimming in the sea. The move would have devastated what's left of the Spanish tourist industry, posed potential breathing dangers to swimmers and had Northern European sunbathers walking around with their forehead brown and the rest of their face white as a sheet. The ruling was so crazy that it had to be retracted after pressure from public and tourist industry, but it confirmed where the Cult wants to go with masks and how clinically insane authority has become. The determination to make masks permanent and hide the serious dangers to body and mind can be seen in the censorship of scientist Professor Denis Rancourt by Bill Gates-funded academic publishing website ResearchGate over his papers exposing the dangers and uselessness of masks. Rancourt said:

ResearchGate today has permanently locked my account, which I have had since 2015. Their reasons graphically show the nature of their attack against democracy, and their corruption of

science … By their obscene non-logic, a scientific review of science articles reporting on harms caused by face masks has a 'potential to cause harm'. No criticism of the psychological device (face masks) is tolerated, if the said criticism shows potential to influence public policy.

This is what happens in a fascist world.

Where are the 'greens' (again)?

Other dangers of wearing masks especially regularly relate to the inhalation of minute plastic fibres into the lungs and the deluge of discarded masks in the environment and oceans. Estimates predicted that more than 1.5 billion disposable masks will end up in the world's oceans every year polluting the water with tons of plastic and endangering marine wildlife. Studies project that humans are using 129 billion face masks each month worldwide – about three million a minute. Most are disposable and made from plastic, non-biodegradable microfibers that break down into smaller plastic particles that become widespread in ecosystems. They are littering cities, clogging sewage channels and turning up in bodies of water. I have written in other books about the immense amounts of microplastics from endless sources now being absorbed into the body. Rolf Halden, director of the Arizona State University (ASU) Biodesign Center for Environmental Health Engineering, was the senior researcher in a 2020 study that analysed 47 human tissue samples and found microplastics in all of them. 'We have detected these chemicals of plastics in every single organ that we have investigated', he said. I wrote in *The Answer* about the world being deluged with microplastics. A study by the Worldwide Fund for Nature (WWF) found that people are consuming on average every week some 2,000 tiny pieces of plastic mostly through water and also through marine life and the air. Every year humans are ingesting enough microplastics to fill a heaped dinner plate and in a life-time of 79 years it is enough to fill two large waste bins. Marco Lambertini, WWF International director general said: 'Not only are plastics polluting our oceans and waterways and killing marine life – it's in all of us and we can't escape consuming plastics,' American

geologists found tiny plastic fibres, beads and shards in rainwater samples collected from the remote slopes of the Rocky Mountain National Park near Denver, Colorado. Their report was headed: 'It is raining plastic.' Rachel Adams, senior lecturer in Biomedical Science at Cardiff Metropolitan University, said that among health consequences are internal inflammation and immune responses to a 'foreign body'. She further pointed out that microplastics become carriers of toxins including mercury, pesticides and dioxins (a known cause of cancer and reproductive and developmental problems). These toxins accumulate in the fatty tissues once they enter the body through microplastics. Now this is being compounded massively by people putting plastic on their face and throwing it away.

Workers exposed to polypropylene plastic fibres known as 'flock' have developed 'flock worker's lung' from inhaling small pieces of the flock fibres which can damage lung tissue, reduce breathing capacity and exacerbate other respiratory problems. *Now* … commonly used surgical masks have three layers of melt-blown textiles made of … polypropylene. We have billions of people putting these microplastics against their mouth, nose and face for hours at a time day after day in the form of masks. How does anyone think that will work out? I mean – what could possibly go wrong? We posted a number of scientific studies on this at davidicke.com, but when I went back to them as I was writing this book the links to the science research website where they were hosted were dead. Anything that challenges the official narrative in any way is either censored or vilified. The official narrative is so unsupportable by the evidence that only deleting the truth can protect it. A study by Chinese scientists still survived – with the usual twist which it why it was still active, I guess. Yes, they found that virtually all the masks they tested increased the daily intake of microplastic fibres, but people should still wear them because the danger from the 'virus' was worse said the crazy 'team' from the Institute of Hydrobiology in Wuhan. Scientists first discovered microplastics in lung tissue of some patients who died of lung cancer

in the 1990s. Subsequent studies have confirmed the potential health damage with the plastic degrading slowly and remaining in the lungs to accumulate in volume. Wuhan researchers used a machine simulating human breathing to establish that masks shed up to nearly 4,000 microplastic fibres in a month with reused masks producing more. Scientists said some masks are laced with toxic chemicals and a variety of compounds seriously restricted for both health and environmental reasons. They include cobalt (used in blue dye) and formaldehyde known to cause watery eyes, burning sensations in the eyes, nose, and throat, plus coughing, wheezing and nausea. No – that must be 'Covid-19'.

Mask 'worms'

There is another and potentially even more sinister content of masks. Mostly new masks of different makes filmed under a microscope around the world have been found to contain strange black fibres or 'worms' that appear to move or 'crawl' by themselves and react to heat and water. The nearest I have seen to them are the self-replicating fibres that are pulled out through the skin of those suffering from Morgellons disease which has been connected to the phenomena of 'chemtrails' which I will bring into the story later on. Morgellons fibres continue to grow outside the body and have a form of artificial intelligence. Black 'worm' fibres in masks have that kind of feel to them and there is a nanotechnology technique called 'worm micelles' which carry and release drugs or anything else you want to deliver to the body. For sure the suppression of humanity by mind altering drugs is the Cult agenda big time and the more excuses they can find to gain access to the body the more opportunities there are to make that happen whether through 'vaccines' or masks pushed against the mouth and nose for hours on end.

So let us summarise the pros and cons of masks:

Against masks: Breathing in your own carbon dioxide; depriving the body and brain of sufficient oxygen; build-up of toxins in the mask that can be breathed into the lungs and cause rashes on the face and 'mask-mouth'; breathing microplastic fibres and toxic chemicals into the lungs; dehumanisation and deleting individualisation by literally making people faceless; destroying human emotional interaction through facial expression and deleting parental connection with their babies which look for guidance to their facial expression.

For masks: They don't protect you from a 'virus' that doesn't exist and even if it did 'viral' particles are so minute they are smaller than the holes in the mask.

Governments, police, supermarkets, businesses, transport companies, and all the rest who seek to impose masks have done no risk assessment on their consequences for health and psychology and are now open to group lawsuits when the impact becomes clear with a cumulative epidemic of respiratory and other disease. Authorities will try to exploit these effects and hide the real cause by dubbing them 'Covid-19'. Can you imagine setting out to force the population to wear health-destroying masks without doing any assessment of the risks? It is criminal and it is evil, but then how many people targeted in this way, who see their children told to wear them all day at school, have asked for a risk assessment? Billions can't be imposed upon by the few unless the billions allow it. Oh, yes, with just a tinge of irony, 85 percent of all masks made worldwide come from *China*.

Wash your hands in toxic shite

'Covid' rules include the use of toxic sanitisers and again the health consequences of constantly applying toxins to be absorbed through the skin is obvious to any level of Renegade Mind. America's Food and Drug Administration (FDA) said that sanitisers are drugs and issued a warning about 75 dangerous brands which contain

methanol used in antifreeze and can cause death, kidney damage and blindness. The FDA circulated the following warning even for those brands that it claims to be safe:

Store hand sanitizer out of the reach of pets and children, and children should use it only with adult supervision. Do not drink hand sanitizer. This is particularly important for young children, especially toddlers, who may be attracted by the pleasant smell or brightly colored bottles of hand sanitizer.

Drinking even a small amount of hand sanitizer can cause alcohol poisoning in children. (However, there is no need to be concerned if your children eat with or lick their hands after using hand sanitizer.) During this coronavirus pandemic, poison control centers have had an increase in calls about accidental ingestion of hand sanitizer, so it is important that adults monitor young children's use.

Do not allow pets to swallow hand sanitizer. If you think your pet has eaten something potentially dangerous, call your veterinarian or a pet poison control center right away. Hand sanitizer is flammable and should be stored away from heat and flames. When using hand sanitizer, rub your hands until they feel completely dry before performing activities that may involve heat, sparks, static electricity, or open flames.

There you go, perfectly safe, then, and that's without even a mention of the toxins absorbed through the skin. Come on kids – sanitise your hands everywhere you go. It will save you from the 'virus'. Put all these elements together of the 'Covid' normal and see how much health and psychology is being cumulatively damaged, even devastated, to 'protect your health'. Makes sense, right? They are only imposing these things because they care, right? *Right?*

Submitting to insanity

Psychological reframing of the population goes very deep and is done in many less obvious ways. I hear people say how contradictory and crazy 'Covid' rules are and how they are ever changing. This is explained away by dismissing those involved as idiots. It is a big mistake. The Cult is delighted if its cold calculation is perceived as incompetence and idiocy when it is anything but. Oh, yes, there are idiots within the system – lots of them – but they are *administering* the Cult agenda, mostly unknowingly. They are not deciding and dictating it. The bulwark against tyranny is self-

respect, always has been, always will be. It is self-respect that has broken every tyranny in history. By its very nature self-respect will not bow to oppression and its perpetrators. There is so little self-respect that it's always the few that overturn dictators. Many may eventually follow, but the few with the iron spines (self-respect) kick it off and generate the momentum. The Cult targets self-respect in the knowledge that once this has gone only submission remains. Crazy, contradictory, ever-changing 'Covid' rules are systematically applied by psychologists to delete self-respect. They *want* you to see that the rules make no sense. It is one thing to decide to do something when *you* have made the choice based on evidence and logic. You still retain your self-respect. It is quite another when you can see what you are being told to do is insane, ridiculous and makes no sense, and *yet you still do it*. Your self-respect is extinguished and this has been happening as ever more obviously stupid and nonsensical things have been demanded and the great majority have complied even when they can see they are stupid and nonsensical.

People walk around in face-nappies knowing they are damaging their health and make no difference to a 'virus'. They do it in fear of not doing it. I know it's daft, but I'll do it anyway. When that happens something dies inside of you and submissive reframing has begun. Next there's a need to hide from yourself that you have conceded your self-respect and you convince yourself that you have not really submitted to fear and intimidation. You begin to believe that you are complying with craziness because it's the right thing to do. When first you concede your self-respect of 2+2 = 4 to 2+2 = 5 you *know* you are compromising your self-respect. Gradually to avoid facing that fact you begin to *believe* that 2+2=5. You have been reframed and I have been watching this process happening in the human psyche on an industrial scale. The Cult is working to break your spirit and one of its major tools in that war is humiliation. I read how former American soldier Bradley Manning (later Chelsea Manning after a sex-change) was treated after being jailed for supplying WikiLeaks with documents exposing the enormity of

government and elite mendacity. Manning was isolated in solitary confinement for eight months, put under 24-hour surveillance, forced to hand over clothing before going to bed, and stand naked for every roll call. This is systematic humiliation. The introduction of anal swab 'Covid' tests in China has been done for the same reason to delete self-respect and induce compliant submission. Anal swabs are mandatory for incoming passengers in parts of China and American diplomats have said they were forced to undergo the indignity which would have been calculated humiliation by the Cult-owned Chinese government that has America in its sights.

Government-people: An abusive relationship

Spirit-breaking psychological techniques include giving people hope and apparent respite from tyranny only to take it away again. This happened in the UK during Christmas, 2020, when the psycho-psychologists and their political lackeys announced an easing of restrictions over the holiday only to reimpose them almost immediately on the basis of yet another lie. There is a big psychological difference between getting used to oppression and being given hope of relief only to have that dashed. Psychologists know this and we have seen the technique used repeatedly. Then there is traumatising people before you introduce more extreme regulations that require compliance. A perfect case was the announcement by the dark and sinister Whitty and Vallance in the UK that 'new data' predicted that 4,000 could die every day over the winter of 2020/2021 if we did not lockdown again. I think they call it lying and after traumatising people with that claim out came Jackboot Johnson the next day with new curbs on human freedom. Psychologists know that a frightened and traumatised mind becomes suggestable to submission and behaviour reframing. Underpinning all this has been to make people fearful and suspicious of each other and see themselves as a potential danger to others. In league with deleted self-respect you have the perfect psychological recipe for self-loathing. The relationship between authority and public is now demonstrably the same as that of

subservience to an abusive partner. These are signs of an abusive relationship explained by psychologist Leslie Becker-Phelps:

Psychological and emotional abuse: Undermining a partner's self-worth with verbal attacks, name-calling, and belittling. Humiliating the partner in public, unjustly accusing them of having an affair, or interrogating them about their every behavior. Keeping partner confused or off balance by saying they were just kidding or blaming the partner for 'making' them act this way … Feigning in public that they care while turning against them in private. This leads to victims frequently feeling confused, incompetent, unworthy, hopeless, and chronically self-doubting. [Apply these techniques to how governments have treated the population since New Year, 2020, and the parallels are obvious.]

Physical abuse: The abuser might physically harm their partner in a range of ways, such as grabbing, hitting, punching, or shoving them. They might throw objects at them or harm them with a weapon. [Observe the physical harm imposed by masks, lockdown, and so on.]

Threats and intimidation: One way abusers keep their partners in line is by instilling fear. They might be verbally threatening, or give threatening looks or gestures. Abusers often make it known that they are tracking their partner's every move. They might destroy their partner's possessions, threaten to harm them, or threaten to harm their family members. Not surprisingly, victims of this abuse often feel anxiety, fear, and panic. [No words necessary.]

Isolation: Abusers often limit their partner's activities, forbidding them to talk or interact with friends or family. They might limit access to a car or even turn off their phone. All of this might be done by physically holding them against their will, but is often accomplished through psychological abuse and intimidation. The more isolated a person feels, the fewer resources they have to help gain perspective on their situation and to escape from it. [No words necessary.]

Economic abuse: Abusers often make their partners beholden to them for money by controlling access to funds of any kind. They might prevent their partner from getting a job or withhold access to money they earn from a job. This creates financial dependency that makes leaving the relationship very difficult. [See destruction of livelihoods and the proposed meagre 'guaranteed income' so long as you do whatever you are told.]

Using children: An abuser might disparage their partner's parenting skills, tell their children lies about their partner, threaten to take custody of their children, or threaten to harm their children. These tactics instil fear and often elicit compliance. [See reframed social service mafia and how children are being mercilessly abused by the state over 'Covid' while their parents look on too frightened to do anything.]

A further recurring trait in an abusive relationship is the abused blaming themselves for their abuse and making excuses for the abuser. We have the public blaming each other for lockdown abuse by government and many making excuses for the government while attacking those who challenge the government. How often we have heard authorities say that rules are being imposed or reimposed only because people have refused to 'behave' and follow the rules. We don't want to do it – it's *you*.

Renegade Minds are an antidote to all of these things. They will never concede their self-respect no matter what the circumstances. Even when apparent humiliation is heaped upon them they laugh in its face and reflect back the humiliation on the abuser where it belongs. Renegade Minds will never wear masks they know are only imposed to humiliate, suppress and damage both physically and psychologically. Consequences will take care of themselves and they will never break their spirit or cause them to concede to tyranny. UK newspaper columnist Peter Hitchens was one of the few in the mainstream media to speak out against lockdowns and forced vaccinations. He then announced he had taken the jab. He wanted to see family members abroad and he believed vaccine passports were inevitable even though they had not yet been introduced. Hitchens

has a questioning and critical mind, but not a Renegade one. If he had no amount of pressure would have made him concede. Hitchens excused his action by saying that the battle has been lost. Renegade Minds never accept defeat when freedom is at stake and even if they are the last one standing the self-respect of not submitting to tyranny is more important than any outcome or any consequence.

That's why Renegade Minds are the only minds that ever changed anything worth changing.

CHAPTER EIGHT

'Reframing' insanity

Insanity is relative. It depends on who has who locked in what cage
Ray Bradbury

'Reframing' a mind means simply to change its perception and behaviour. This can be done subconsciously to such an extent that subjects have no idea they have been 'reframed' while to any observer changes in behaviour and attitudes are obvious.

Human society is being reframed on a ginormous scale since the start of 2020 and here we have the reason why psychologists rather than doctors have been calling the shots. Ask most people who have succumbed to 'Covid' reframing if they have changed and most will say 'no'; but they *have* and fundamentally. The Cult's long-game has been preparing for these times since way back and crucial to that has been to prepare both population and officialdom mentally and emotionally. To use the mind-control parlance they had to reframe the population with a mentality that would submit to fascism and reframe those in government and law enforcement to impose fascism or at least go along with it. The result has been the fact-deleted mindlessness of 'Wokeness' and officialdom that has either enthusiastically or unquestioningly imposed global tyranny demanded by reframed politicians on behalf of psychopathic and deeply evil cultists. 'Cognitive reframing' identifies and challenges the way someone sees the world in the form of situations, experiences and emotions and then restructures those perceptions to view the same set of circumstances in a different way. This can have

benefits if the attitudes are personally destructive while on the other side it has the potential for individual and collective mind control which the subject has no idea has even happened.

Cognitive therapy was developed in the 1960s by Aaron T. Beck who was born in Rhode Island in 1921 as the son of Jewish immigrants from the Ukraine. He became interested in the techniques as a treatment for depression. Beck's daughter Judith S. Beck is prominent in the same field and they founded the Beck Institute for Cognitive Behavior Therapy in Philadelphia in 1994. Cognitive reframing, however, began to be used worldwide by those with a very dark agenda. The Cult reframes politicians to change their attitudes and actions until they are completely at odds with what they once appeared to stand for. The same has been happening to government administrators at all levels, law enforcement, military and the human population. Cultists love mind control for two main reasons: It allows them to control what people think, do and say to secure agenda advancement and, by definition, it calms their legendary insecurity and fear of the unexpected. I have studied mind control since the time I travelled America in 1996. I may have been talking to next to no one in terms of an audience in those years, but my goodness did I gather a phenomenal amount of information and knowledge about so many things including the techniques of mind control. I have described this in detail in other books going back to *The Biggest Secret* in 1998. I met a very large number of people recovering from MKUltra and its offshoots and successors and I began to see how these same techniques were being used on the population in general. This was never more obvious than since the 'Covid' hoax began.

Reframing the enforcers

I have observed over the last two decades and more the very clear transformation in the dynamic between the police, officialdom and the public. I tracked this in the books as the relationship mutated from one of serving the public to seeing them as almost the enemy and certainly a lower caste. There has always been a class divide

based on income and always been some psychopathic, corrupt, and big-I-am police officers. This was different. Wholesale change was unfolding in the collective dynamic; it was less about money and far more about position and perceived power. An us-and-them was emerging. Noses were lifted skyward by government administration and law enforcement and their attitude to the public they were *supposed* to be serving changed to one of increasing contempt, superiority and control. The transformation was so clear and widespread that it had to be planned. Collective attitudes and dynamics do not change naturally and organically that quickly on that scale. I then came across an organisation in Britain called Common Purpose created in the late 1980s by Julia Middleton who would work in the office of Deputy Prime Minister John Prescott during the long and disastrous premiership of war criminal Tony Blair. When Blair speaks the Cult is speaking and the man should have been in jail a long time ago. Common Purpose proclaims itself to be one of the biggest 'leadership development' organisations in the world while functioning as a *charity* with all the financial benefits which come from that. It hosts 'leadership development' courses and programmes all over the world and claims to have 'brought together' what it calls 'leaders' from more than 100 countries on six continents. The modus operandi of Common Purpose can be compared with the work of the UK government's reframing network that includes the Behavioural Insights Team 'nudge unit' and 'Covid' reframing specialists at SPI-B. WikiLeaks described Common Purpose long ago as 'a hidden virus in our government and schools' which is unknown to the general public: 'It recruits and trains "leaders" to be loyal to the directives of Common Purpose and the EU, instead of to their own departments, which they then undermine or subvert, the NHS [National Health Service] being an example.' This is a vital point to understand the 'Covid' hoax. The NHS, and its equivalent around the world, has been utterly reframed in terms of administrators and much of the medical personnel with the transformation underpinned by recruitment policies. The outcome has been the criminal and psychopathic behaviour of the

NHS over 'Covid' and we have seen the same in every other major country. WikiLeaks said Common Purpose trainees are 'learning to rule without regard to democracy' and to usher in a police state (current events explained). Common Purpose operated like a 'glue' and had members in the NHS, BBC, police, legal profession, church, many of Britain's 7,000 quangos, local councils, the Civil Service, government ministries and Parliament, and controlled many RDA's (Regional Development Agencies). Here we have one answer for how and why British institutions and their like in other countries have changed so negatively in relation to the public. This further explains how and why the beyond-disgraceful reframed BBC has become a propaganda arm of 'Covid' fascism. They are all part of a network pursuing the same goal.

By 2019 Common Purpose was quoting a figure of 85,000 'leaders' that had attended its programmes. These 'students' of all ages are known as Common Purpose 'graduates' and they consist of government, state and local government officials and administrators, police chiefs and officers, and a whole range of others operating within the national, local and global establishment. Cressida Dick, Commissioner of the London Metropolitan Police, is the Common Purpose graduate who was the 'Gold Commander' that oversaw what can only be described as the murder of Brazilian electrician Jean Charles de Menezes in 2005. He was held down by psychopathic police and shot seven times in the head by a psychopathic lunatic after being mistaken for a terrorist when he was just a bloke going about his day. Dick authorised officers to pursue and keep surveillance on de Menezes and ordered that he be stopped from entering the underground train system. Police psychopaths took her at her word clearly. She was 'disciplined' for this outrage by being *promoted* – eventually to the top of the 'Met' police where she has been a disaster. Many Chief Constables controlling the police in different parts of the UK are and have been Common Purpose graduates. I have heard the 'graduate' network described as a sort of Mafia or secret society operating within the fabric of government at all levels pursuing a collective policy

ingrained at Common Purpose training events. Founder Julia Middleton herself has said:

> Locally and internationally, Common Purpose graduates will be 'lighting small fires' to create change in their organisations and communities … The Common Purpose effect is best illustrated by the many stories of small changes brought about by leaders, who themselves have changed.

A Common Purpose mission statement declared:

> Common Purpose aims to improve the way society works by expanding the vision, decision-making ability and influence of all kinds of leaders. The organisation runs a variety of educational programmes for leaders of all ages, backgrounds and sectors, in order to provide them with the inspirational, information and opportunities they need to change the world.

Yes, but into what? Since 2020 the answer has become clear.

NLP and the Delphi technique

Common Purpose would seem to be a perfect name or would common programming be better? One of the foundation methods of reaching 'consensus' (group think) is by setting the agenda theme and then encouraging, cajoling or pressuring everyone to agree a 'consensus' in line with the core theme promoted by Common Purpose. The methodology involves the 'Delphi technique', or an adaption of it, in which opinions are expressed that are summarised by a 'facilitator or change agent' at each stage. Participants are 'encouraged' to modify their views in the light of what others have said. Stage by stage the former individual opinions are merged into group consensus which just happens to be what Common Purpose wants them to believe. A key part of this is to marginalise anyone refusing to concede to group think and turn the group against them to apply pressure to conform. We are seeing this very technique used on the general population to make 'Covid' group-thinkers hostile to those who have seen through the bullshit. People can be reframed by using perception manipulation methods such as Neuro-Linguistic Programming (NLP) in which you change perception with the use of

carefully constructed language. An NLP website described the technique this way:

… A method of influencing brain behaviour (the 'neuro' part of the phrase) through the use of language (the 'linguistic' part) and other types of communication to enable a person to 'recode' the way the brain responds to stimuli (that's the 'programming') and manifest new and better behaviours. Neuro-Linguistic Programming often incorporates hypnosis and self-hypnosis to help achieve the change (or 'programming') that is wanted.

British alternative media operation UKColumn has done very detailed research into Common Purpose over a long period. I quoted co-founder and former naval officer Brian Gerrish in my book *Remember Who You Are*, published in 2011, as saying the following years before current times:

It is interesting that many of the mothers who have had children taken by the State speak of the Social Services people being icily cool, emotionless and, as two ladies said in slightly different words, '… like little robots'. We know that NLP is cumulative, so people can be given small imperceptible doses of NLP in a course here, another in a few months, next year etc. In this way, major changes are accrued in their personality, but the day by day change is almost unnoticeable.

In these and other ways 'graduates' have had their perceptions uniformly reframed and they return to their roles in the institutions of government, law enforcement, legal profession, military, 'education', the UK National Health Service and the whole swathe of the establishment structure to pursue a common agenda preparing for the 'post-industrial', 'post-democratic' society. I say 'preparing' but we are now there. 'Post-industrial' is code for the Great Reset and 'post-democratic' is 'Covid' fascism. UKColumn has spoken to partners of those who have attended Common Purpose 'training'. They have described how personalities and attitudes of 'graduates' changed very noticeably for the worse by the time they had completed the course. They had been 'reframed' and told they are the 'leaders' – the special ones – who know better than the population. There has also been the very demonstrable recruitment of psychopaths and narcissists into government administration at all

levels and law enforcement. If you want psychopathy hire psychopaths and you get a simple cause and effect. If you want administrators, police officers and 'leaders' to perceive the public as lesser beings who don't matter then employ narcissists. These personalities are identified using 'psychometrics' that identifies knowledge, abilities, attitudes and personality traits, mostly through carefully-designed questionnaires and tests. As this policy has passed through the decades we have had power-crazy, power-trippers appointed into law enforcement, security and government administration in preparation for current times and the dynamic between public and law enforcement/officialdom has been transformed. UKColumn's Brian Gerrish said of the narcissistic personality:

> Their love of themselves and power automatically means that they will crush others who get in their way. I received a major piece of the puzzle when a friend pointed out that when they made public officials re-apply for their own jobs several years ago they were also required to do psychometric tests. This was undoubtedly the start of the screening process to get 'their' sort of people in post.

How obvious that has been since 2020 although it was clear what was happening long before if people paid attention to the changing public-establishment dynamic.

Change agents

At the centre of events in 'Covid' Britain is the National Health Service (NHS) which has behaved disgracefully in slavishly following the Cult agenda. The NHS management structure is awash with Common Purpose graduates or 'change agents' working to a common cause. Helen Bevan, a Chief of Service Transformation at the NHS Institute for Innovation and Improvement, co-authored a document called 'Towards a million change agents, a review of the social movements literature: implications for large scale change in the NHS'. The document compared a project management approach to that of change and social movements where 'people change

themselves and each other – peer to peer'. Two definitions given for a 'social movement' were:

A group of people who consciously attempt to build a radically new social order; involves people of a broad range of social backgrounds; and deploys politically confrontational and socially disruptive tactics – Cyrus Zirakzadeh 1997

Collective challenges, based on common purposes and social solidarities, in sustained interaction with elites, opponents, and authorities – Sidney Tarrow 1994

Helen Bevan wrote another NHS document in which she defined 'framing' as 'the process by which leaders construct, articulate and put across their message in a powerful and compelling way in order to win people to their cause and call them to action'. I think I could come up with another definition that would be rather more accurate. The National Health Service and institutions of Britain and the wider world have been taken over by reframed 'change agents' and that includes everything from the United Nations to national governments, local councils and social services which have been kidnapping children from loving parents on an extraordinary and gathering scale on the road to the end of parenthood altogether. Children from loving homes are stolen and kidnapped by the state and put into the 'care' (inversion) of the local authority through council homes, foster parents and forced adoption. At the same time children are allowed to be abused without response while many are under council 'care'. UKColumn highlighted the Common Purpose connection between South Yorkshire Police and Rotherham council officers in the case of the scandal in that area of the sexual exploitation of children to which the authorities turned not one blind eye, but both:

We were alarmed to discover that the Chief Executive, the Strategic Director of Children and Young People's Services, the Manager for the Local Strategic Partnership, the Community Cohesion Manager, the Cabinet Member for Cohesion, the Chief Constable and his predecessor had all attended Leadership training courses provided by the pseudo-charity Common Purpose.

Once 'change agents' have secured positions of hire and fire within any organisation things start to move very quickly. Personnel are then hired and fired on the basis of whether they will work towards the agenda the change agent represents. If they do they are rapidly promoted even though they may be incompetent. Those more qualified and skilled who are pre-Common Purpose 'old school' see their careers stall and even disappear. This has been happening for decades in every institution of state, police, 'health' and social services and all of them have been transformed as a result in their attitudes to their jobs and the public. Medical professions, including nursing, which were once vocations for the caring now employ many cold, callous and couldn't give a shit personality types. The UKColumn investigation concluded:

By blurring the boundaries between people, professions, public and private sectors, responsibility and accountability, Common Purpose encourages 'graduates' to believe that as new selected leaders, they can work together, outside of the established political and social structures, to achieve a paradigm shift or CHANGE – so called 'Leading Beyond Authority'. In doing so, the allegiance of the individual becomes 'reframed' on CP colleagues and their NETWORK.

Reframing the Face-Nappies

Nowhere has this process been more obvious than in the police where recruitment of psychopaths and development of unquestioning mind-controlled group-thinkers have transformed law enforcement into a politically-correct 'Woke' joke and a travesty of what should be public service. Today they wear their face-nappies like good little gofers and enforce 'Covid' rules which are fascism under another name. Alongside the specifically-recruited psychopaths we have software minds incapable of free thought. Brian Gerrish again:

An example is the policeman who would not get on a bike for a press photo because he had not done the cycling proficiency course. Normal people say this is political correctness gone mad. Nothing could be further from the truth. The policeman has been reframed, and in his reality it is perfect common sense not to get on the bike 'because he hasn't done the cycling course'.

Another example of this is where the police would not rescue a boy from a pond until they had taken advice from above on the 'risk assessment'. A normal person would have arrived, perhaps thought of the risk for a moment, and dived in. To the police now 'reframed', they followed 'normal' procedure.

There are shocking cases of reframed ambulance crews doing the same. Sheer unthinking stupidity of London Face-Nappies headed by Common Purpose graduate Cressida Dick can be seen in their behaviour at a vigil in March, 2021, for a murdered woman, Sarah Everard. A police officer had been charged with the crime. Anyone with a brain would have left the vigil alone in the circumstances. Instead they 'manhandled' women to stop them breaking 'Covid rules' to betray classic reframing. Minds in the thrall of perception control have no capacity for seeing a situation on its merits and acting accordingly. 'Rules is rules' is their only mind-set. My father used to say that rules and regulations are for the guidance of the intelligent and the blind obedience of the idiot. Most of the intelligent, decent, coppers have gone leaving only the other kind and a few old school for whom the job must be a daily nightmare. The combination of psychopaths and rule-book software minds has been clearly on public display in the 'Covid' era with automaton robots in uniform imposing fascistic 'Covid' regulations on the population without any personal initiative or judging situations on their merits. There are thousands of examples around the world, but I'll make my point with the infamous Derbyshire police in the English East Midlands – the ones who think pouring dye into beauty spots and using drones to track people walking in the countryside away from anyone is called 'policing'. To them there are rules decreed by the government which they have to enforce and in their bewildered state a group gathering in a closed space and someone walking alone in the countryside are the same thing. It is beyond idiocy and enters the realm of clinical insanity.

Police officers in Derbyshire said they were 'horrified' – *horrified* – to find 15 to 20 'irresponsible' kids playing a football match at a closed leisure centre 'in breach of coronavirus restrictions'. When they saw the police the kids ran away leaving their belongings behind and the reframed men and women of Derbyshire police were seeking to establish their identities with a view to fining their parents. The most natural thing for youngsters to do – kicking a ball about – is turned into a criminal activity and enforced by the moronic software programs of Derbyshire police. You find the same mentality in every country. These barely conscious 'horrified' officers said they had to take action because 'we need to ensure these rules are being followed' and 'it is of the utmost importance that you ensure your children are following the rules and regulations for Covid-19'. Had any of them done ten seconds of research to see if this parroting of their masters' script could be supported by any evidence? Nope. Reframed people don't think – others think for them and that's the whole idea of reframing. I have seen police officers one after the other repeating without question word for word what officialdom tells them just as I have seen great swathes of the public doing the same. Ask either for 'their' opinion and out spews what they have been told to think by the official narrative. Police and public may seem to be in different groups, but their mentality is the same. Most people do whatever they are told in fear not doing so or because they believe what officialdom tells them; almost the entirety of the police do what they are told for the same reason. Ultimately it's the tiny inner core of the global Cult that's telling both what to do.

So Derbyshire police were 'horrified'. Oh, really? Why did they think those kids were playing football? It was to relieve the psychological consequences of lockdown and being denied human contact with their friends and interaction, touch and discourse vital to human psychological health. Being denied this month after month has dismantled the psyche of many children and young people as depression and suicide have exploded. Were Derbyshire police *horrified by that*? Are you kidding? Reframed people don't have those

mental and emotional processes that can see how the impact on the psychological health of youngsters is far more dangerous than any 'virus' even if you take the mendacious official figures to be true. The reframed are told (programmed) how to act and so they do. The Derbyshire Chief Constable in the first period of lockdown when the black dye and drones nonsense was going on was Peter Goodman. He was the man who severed the connection between his force and the Derbyshire Constabulary *Male Voice* Choir when he decided that it was not inclusive enough to allow women to join. The fact it was a male voice choir making a particular sound produced by male voices seemed to elude a guy who terrifyingly ran policing in Derbyshire. He retired weeks after his force was condemned as disgraceful by former Supreme Court Justice Jonathan Sumption for their behaviour over extreme lockdown impositions. Goodman was replaced by his deputy Rachel Swann who was in charge when her officers were 'horrified'. The police statement over the boys committing the hanging-offence of playing football included the line about the youngsters being 'irresponsible in the times we are all living through' missing the point that the real relevance of the 'times we are all living through' is the imposition of fascism enforced by psychopaths and reframed minds of police officers playing such a vital part in establishing the fascist tyranny that their own children and grandchildren will have to live in their entire lives. As a definition of insanity that is hard to beat although it might be run close by imposing masks on people that can have a serious effect on their health while wearing a face nappy all day themselves. Once again public and police do it for the same reason – the authorities tell them to and who are they to have the self-respect to say no?

Wokers in uniform

How reframed do you have to be to arrest a *six-year-old* and take him to court for *picking a flower* while waiting for a bus? Brain dead police and officialdom did just that in North Carolina where criminal proceedings happen regularly for children under nine. Attorney Julie Boyer gave the six-year-old crayons and a colouring book

during the 'flower' hearing while the 'adults' decided his fate. County Chief District Court Judge Jay Corpening asked: 'Should a child that believes in Santa Claus, the Easter Bunny and the tooth fairy be making life-altering decisions?' Well, of course not, but common sense has no meaning when you have a common purpose and a reframed mind. Treating children in this way, and police operating in American schools, is all part of the psychological preparation for children to accept a police state as normal all their adult lives. The same goes for all the cameras and biometric tracking technology in schools. Police training is focused on reframing them as snowflake Wokers and this is happening in the military. Pentagon top brass said that 'training sessions on extremism' were needed for troops who asked why they were so focused on the Capitol Building riot when Black Lives Matter riots were ignored. What's the difference between them some apparently and rightly asked. Actually, there is a difference. Five people died in the Capitol riot, only one through violence, and that was a police officer shooting an unarmed protestor. BLM riots killed at least 25 people and cost billions. Asking the question prompted the psychopaths and reframed minds that run the Pentagon to say that more 'education' (programming) was needed. Troop training is all based on psychological programming to make them fodder for the Cult – 'Military men are just dumb, stupid animals to be used as pawns in foreign policy' as Cult-to-his-DNA former Secretary of State Henry Kissinger famously said. Governments see the police in similar terms and it's time for those among them who can see this to defend the people and stop being enforcers of the Cult agenda upon the people.

The US military, like the country itself, is being targeted for destruction through a long list of Woke impositions. Cult-owned gaga 'President' Biden signed an executive order when he took office to allow taxpayer money to pay for transgender surgery for active military personnel and veterans. Are you a man soldier? No, I'm a LGBTQIA+ with a hint of Skoliosexual and Spectrasexual. Oh, good man. Bad choice of words you bigot. The Pentagon announced in March, 2021, the appointment of the first 'diversity and inclusion

officer' for US Special Forces. Richard Torres-Estrada arrived with the publication of a 'D&I Strategic Plan which will guide the enterprise-wide effort to institutionalize and sustain D&I'. If you think a Special Forces 'Strategic Plan' should have something to do with defending America you haven't been paying attention. Defending Woke is now the military's new role. Torres-Estrada has posted images comparing Donald Trump with Adolf Hitler and we can expect no bias from him as a representative of the supposedly non-political Pentagon. Cable news host Tucker Carlson said: 'The Pentagon is now the Yale faculty lounge but with cruise missiles.' Meanwhile Secretary of Defense Lloyd Austin, a board member of weapons-maker Raytheon with stock and compensation interests in October, 2020, worth $1.4 million, said he was purging the military of the 'enemy within' – anyone who isn't Woke and supports Donald Trump. Austin refers to his targets as 'racist extremists' while in true Woke fashion being himself a racist extremist. Pentagon documents pledge to 'eradicate, eliminate and conquer all forms of racism, sexism and homophobia'. The definitions of these are decided by 'diversity and inclusion committees' peopled by those who see racism, sexism and homophobia in every situation and opinion. Woke (the Cult) is dismantling the US military and purging testosterone as China expands its military and gives its troops 'masculinity training'. How do we think that is going to end when this is all Cult coordinated? The US military, like the British military, is controlled by Woke and spineless top brass who just go along with it out of personal career interests.

'Woke' means fast asleep

Mind control and perception manipulation techniques used on individuals to create group-think have been unleashed on the global population in general. As a result many have no capacity to see the obvious fascist agenda being installed all around them or what 'Covid' is really all about. Their brains are firewalled like a computer system not to process certain concepts, thoughts and realisations that are bad for the Cult. The young are most targeted as the adults they

will be when the whole fascist global state is planned to be fully implemented. They need to be prepared for total compliance to eliminate all pushback from entire generations. The Cult has been pouring billions into taking complete control of 'education' from schools to universities via its operatives and corporations and not least Bill Gates as always. The plan has been to transform 'education' institutions into programming centres for the mentality of 'Woke'. James McConnell, professor of psychology at the University of Michigan, wrote in *Psychology Today* in 1970:

> The day has come when we can combine sensory deprivation with drugs, hypnosis, and astute manipulation of reward and punishment, to gain almost absolute control over an individual's behaviour. It should then be possible to achieve a very rapid and highly effective type of brainwashing that would allow us to make dramatic changes in a person's behaviour and personality ...
>
> … We should reshape society so that we all would be trained from birth to want to do what society wants us to do. We have the techniques to do it... no-one owns his own personality you acquired, and there's no reason to believe you should have the right to refuse to acquire a new personality if your old one is anti-social.

This was the potential for mass brainwashing in 1970 and the mentality there displayed captures the arrogant psychopathy that drives it forward. I emphasise that not all young people have succumbed to Woke programming and those that haven't are incredibly impressive people given that today's young are the most perceptually-targeted generations in history with all the technology now involved. Vast swathes of the young generations, however, have fallen into the spell – and that's what it is – of Woke. The Woke mentality and perceptual program is founded on *inversion* and you will appreciate later why that is so significant. Everything with Woke is inverted and the opposite of what it is claimed to be. Woke was a term used in African-American culture from the 1900s and referred to an awareness of social and racial justice. This is not the meaning of the modern version or 'New Woke' as I call it in *The Answer*. Oh, no, Woke today means something very different no matter how much Wokers may seek to hide that and insist Old Woke and New

Woke are the same. See if you find any 'awareness of social justice' here in the modern variety:

- Woke demands 'inclusivity' while excluding anyone with a different opinion and calls for mass censorship to silence other views.

- Woke claims to stand against oppression when imposing oppression is the foundation of all that it does. It is the driver of political correctness which is nothing more than a Cult invention to manipulate the population to silence itself.

- Woke believes itself to be 'liberal' while pursuing a global society that can only be described as fascist (see 'anti-fascist' fascist Antifa).

- Woke calls for 'social justice' while spreading injustice wherever it goes against the common 'enemy' which can be easily identified as a differing view.

- Woke is supposed to be a metaphor for 'awake' when it is solid-gold asleep and deep in a Cult-induced coma that meets the criteria for 'off with the fairies'.

I state these points as obvious facts if people only care to look. I don't do this with a sense of condemnation. We need to appreciate that the onslaught of perceptual programming on the young has been incessant and merciless. I can understand why so many have been reframed, or, given their youth, framed from the start to see the world as the Cult demands. The Cult has had access to their minds day after day in its 'education' system for their entire formative years. Perception is formed from information received and the Cult-created system is a life-long download of information delivered to elicit a particular perception, thus behaviour. The more this has expanded into still new extremes in recent decades and ever-increasing censorship has deleted other opinions and information why wouldn't that lead to a perceptual reframing on a mass scale? I

have described already cradle-to-grave programming and in more recent times the targeting of young minds from birth to adulthood has entered the stratosphere. This has taken the form of skewing what is 'taught' to fit the Cult agenda and the omnipresent techniques of group-think to isolate non-believers and pressure them into line. There has always been a tendency to follow the herd, but we really are in a new world now in relation to that. We have parents who can see the 'Covid' hoax told by their children not to stop them wearing masks at school, being 'Covid' tested or having the 'vaccine' in fear of the peer-pressure consequences of being different. What is 'peer-pressure' if not pressure to conform to group-think? Renegade Minds never group-think and always retain a set of perceptions that are unique to them. Group-think is always underpinned by consequences for not group-thinking. Abuse now aimed at those refusing DNA-manipulating 'Covid vaccines' are a potent example of this. The biggest pressure to conform comes from the very group which is itself being manipulated. 'I am programmed to be part of a hive mind and so you must be.'

Woke control structures in 'education' now apply to every mainstream organisation. Those at the top of the 'education' hierarchy (the Cult) decide the policy. This is imposed on governments through the Cult network; governments impose it on schools, colleges and universities; their leadership impose the policy on teachers and academics and they impose it on children and students. At any level where there is resistance, perhaps from a teacher or university lecturer, they are targeted by the authorities and often fired. Students themselves regularly demand the dismissal of academics (increasingly few) at odds with the narrative that the students have been programmed to believe in. It is quite a thought that students who are being targeted by the Cult become so consumed by programmed group-think that they launch protests and demand the removal of those who are trying to push back against those targeting the students. Such is the scale of perceptual inversion. We see this with 'Covid' programming as the Cult imposes the rules via psycho-psychologists and governments on

shops, transport companies and businesses which impose them on their staff who impose them on their customers who pressure Pushbackers to conform to the will of the Cult which is in the process of destroying them and their families. Scan all aspects of society and you will see the same sequence every time.

Fact free Woke and hijacking the 'left'

There is no more potent example of this than 'Woke', a mentality only made possible by the deletion of factual evidence by an 'education' system seeking to produce an ever more uniform society. Why would you bother with facts when you don't know any? Deletion of credible history both in volume and type is highly relevant. Orwell said: 'Who controls the past controls the future: who controls the present controls the past.' They who control the perception of the past control the perception of the future and they who control the present control the perception of the past through the writing and deleting of history. Why would you oppose the imposition of Marxism in the name of Wokeism when you don't know that Marxism cost at least 100 million lives in the 20th century alone? Watch videos and read reports in which Woker generations are asked basic historical questions – it's mind-blowing. A survey of 2,000 people found that six percent of millennials (born approximately early1980s to early 2000s) believed the Second World War (1939-1945) broke out with the assassination of President Kennedy (in 1963) and one in ten thought Margaret Thatcher was British Prime Minister at the time. She was in office between 1979 and 1990. We are in a post-fact society. Provable facts are no defence against the fascism of political correctness or Silicon Valley censorship. Facts don't matter anymore as we have witnessed with the 'Covid' hoax. Sacrificing uniqueness to the Woke group-think religion is all you are required to do and that means thinking for yourself is the biggest Woke no, no. All religions are an expression of group-think and censorship and Woke is just another religion with an orthodoxy defended by group-think and censorship. Burned at

the stake becomes burned on Twitter which leads back eventually to burned at the stake as Woke humanity regresses to ages past.

The biggest Woke inversion of all is its creators and funders. I grew up in a traditional left of centre political household on a council estate in Leicester in the 1950s and 60s – you know, the left that challenged the power of wealth-hoarding elites and threats to freedom of speech and opinion. In those days students went on marches defending freedom of speech while today's Wokers march for its deletion. What on earth could have happened? Those very elites (collectively the Cult) that we opposed in my youth and early life have funded into existence the antithesis of that former left and hijacked the 'brand' while inverting everything it ever stood for. We have a mentality that calls itself 'liberal' and 'progressive' while acting like fascists. Cult billionaires and their corporations have funded themselves into control of 'education' to ensure that Woke programming is unceasing throughout the formative years of children and young people and that non-Wokers are isolated (that word again) whether they be students, teachers or college professors. The Cult has funded into existence the now colossal global network of Woke organisations that have spawned and promoted all the 'causes' on the Cult wish-list for global transformation and turned Wokers into demanders of them. Does anyone really think it's a coincidence that the Cult agenda for humanity is a carbon (sorry) copy of the societal transformations desired by Woke?? These are only some of them:

Political correctness: The means by which the Cult deletes all public debates that it knows it cannot win if we had the free-flow of information and evidence.

Human-caused 'climate change': The means by which the Cult seeks to transform society into a globally-controlled dictatorship imposing its will over the fine detail of everyone's lives 'to save the planet' which doesn't actually need saving.

Transgender obsession: Preparing collective perception to accept the 'new human' which would not have genders because it would be created technologically and not through procreation. I'll have much more on this in Human 2.0.

Race obsession: The means by which the Cult seeks to divide and rule the population by triggering racial division through the perception that society is more racist than ever when the opposite is the case. Is it perfect in that regard? No. But to compare today with the racism of apartheid and segregation brought to an end by the civil rights movement in the 1960s is to insult the memory of that movement and inspirations like Martin Luther King. Why is the 'anti-racism' industry (which it is) so dominated by privileged white people?

White supremacy: This is a label used by privileged white people to demonise poor and deprived white people pushing back on tyranny to marginalise and destroy them. White people are being especially targeted as the dominant race by number within Western society which the Cult seeks to transform in its image. If you want to change a society you must weaken and undermine its biggest group and once you have done that by using the other groups you next turn on them to do the same … 'Then they came for the Jews and I was not a Jew so I did nothing.'

Mass migration: The mass movement of people from the Middle East, Africa and Asia into Europe, from the south into the United States and from Asia into Australia are another way the Cult seeks to dilute the racial, cultural and political influence of white people on Western society. White people ask why their governments appear to be working against them while being politically and culturally biased towards incoming cultures. Well, here's your answer. In the same way sexually 'straight' people, men and women, ask why the

authorities are biased against them in favour of other sexualities. The answer is the same – that's the way the Cult wants it to be for very sinister motives.

These are all central parts of the Cult agenda and central parts of the Woke agenda and Woke was created and continues to be funded to an immense degree by Cult billionaires and corporations. If anyone begins to say 'coincidence' the syllables should stick in their throat.

Billionaire 'social justice warriors'

Joe Biden is a 100 percent-owned asset of the Cult and the Wokers' man in the White House whenever he can remember his name and for however long he lasts with his rapidly diminishing cognitive function. Even walking up the steps of an aircraft without falling on his arse would appear to be a challenge. He's not an empty-shell puppet or anything. From the minute Biden took office (or the Cult did) he began his executive orders promoting the Woke wish-list. You will see the Woke agenda imposed ever more severely because it's really the *Cult* agenda. Woke organisations and activist networks spawned by the Cult are funded to the extreme so long as they promote what the Cult wants to happen. Woke is funded to promote 'social justice' by billionaires who become billionaires by destroying social justice. The social justice mantra is only a cover for dismantling social justice and funded by billionaires that couldn't give a damn about social justice. Everything makes sense when you see that. One of Woke's premier funders is Cult billionaire financier George Soros who said: 'I am basically there to make money, I cannot and do not look at the social consequences of what I do.' This is the same Soros who has given more than $32 billion to his Open Society Foundations global Woke network and funded Black Lives Matter, mass immigration into Europe and the United States, transgender activism, climate change activism, political correctness and groups targeting 'white supremacy' in the form of privileged white thugs that dominate Antifa. What a scam it all is and when

you are dealing with the unquestioning fact-free zone of Woke scamming them is child's play. All you need to pull it off in all these organisations are a few in-the-know agents of the Cult and an army of naïve, reframed, uninformed, narcissistic, know-nothings convinced of their own self-righteousness, self-purity and virtue.

Soros and fellow billionaires and billionaire corporations have poured hundreds of millions into Black Lives Matter and connected groups and promoted them to a global audience. None of this is motivated by caring about black people. These are the billionaires that have controlled and exploited a system that leaves millions of black people in abject poverty and deprivation which they do absolutely nothing to address. The same Cult networks funding BLM were behind the *slave trade!* Black Lives Matter hijacked a phrase that few would challenge and they have turned this laudable concept into a political weapon to divide society. You know that BLM is a fraud when it claims that *All* Lives Matter, the most inclusive statement of all, is 'racist'. BLM and its Cult masters don't want to end racism. To them it's a means to an end to control all of humanity never mind the colour, creed, culture or background. What has destroying the nuclear family got to do with ending racism? Nothing – but that is one of the goals of BLM and also happens to be a goal of the Cult as I have been exposing in my books for decades. Stealing children from loving parents and giving schools ever more power to override parents is part of that same agenda. BLM is a Marxist organisation and why would that not be the case when the Cult created Marxism *and* BLM? Patrisse Cullors, a BLM co-founder, said in a 2015 video that she and her fellow organisers, including co-founder Alicia Garza, are 'trained Marxists'. The lady known after marriage as Patrisse Khan-Cullors bought a $1.4 million home in 2021 in one of the whitest areas of California with a black population of just 1.6 per cent and has so far bought *four* high-end homes for a total of $3.2 million. How very Marxist. There must be a bit of spare in the BLM coffers, however, when Cult corporations and billionaires have handed over the best part of $100 million. Many black people can see that Black Lives Matter is not

working for them, but against them, and this is still more confirmation. Black journalist Jason Whitlock, who had his account suspended by Twitter for simply linking to the story about the 'Marxist's' home buying spree, said that BLM leaders are 'making millions of dollars off the backs of these dead black men who they wouldn't spit on if they were on fire and alive'.

Black Lies Matter

Cult assets and agencies came together to promote BLM in the wake of the death of career criminal George Floyd who had been jailed a number of times including for forcing his way into the home of a black woman with others in a raid in which a gun was pointed at her stomach. Floyd was filmed being held in a Minneapolis street in 2020 with the knee of a police officer on his neck and he subsequently died. It was an appalling thing for the officer to do, but the same technique has been used by police on peaceful protestors of lockdown without any outcry from the Woke brigade. As unquestioning supporters of the Cult agenda Wokers have supported lockdown and all the 'Covid' claptrap while attacking anyone standing up to the tyranny imposed in its name. Court documents would later include details of an autopsy on Floyd by County Medical Examiner Dr Andrew Baker who concluded that Floyd had taken a fatal level of the drug fentanyl. None of this mattered to fact-free, question-free, Woke. Floyd's death was followed by worldwide protests against police brutality amid calls to defund the police. Throwing babies out with the bathwater is a Woke speciality. In the wake of the murder of British woman Sarah Everard a Green Party member of the House of Lords, Baroness Jones of Moulescoomb (Nincompoopia would have been better), called for a 6pm curfew for all men. This would be in breach of the Geneva Conventions on war crimes which ban collective punishment, but that would never have crossed the black and white Woke mind of Baroness Nincompoopia who would have been far too convinced of her own self-righteousness to compute such details. Many American cities did defund the police in the face of Floyd riots

and after $15 million was deleted from the police budget in Washington DC under useless Woke mayor Muriel Bowser car-jacking alone rose by 300 percent and within six months the US capital recorded its highest murder rate in 15 years. The same happened in Chicago and other cities in line with the Cult/Soros plan to bring fear to streets and neighbourhoods by reducing the police, releasing violent criminals and not prosecuting crime. This is the mob-rule agenda that I have warned in the books was coming for so long. Shootings in the area of Minneapolis where Floyd was arrested increased by 2,500 percent compared with the year before. Defunding the police over George Floyd has led to a big increase in dead people with many of them black. Police protection for politicians making these decisions stayed the same or increased as you would expect from professional hypocrites. The Cult doesn't actually want to abolish the police. It wants to abolish local control over the police and hand it to federal government as the psychopaths advance the Hunger Games Society. Many George Floyd protests turned into violent riots with black stores and businesses destroyed by fire and looting across America fuelled by Black Lives Matter. Woke doesn't do irony. If you want civil rights you must loot the liquor store and the supermarket and make off with a smart TV. It's the only way.

It's not a race war – it's a class war

Black people are patronised by privileged blacks and whites alike and told they are victims of white supremacy. I find it extraordinary to watch privileged blacks supporting the very system and bloodline networks behind the slave trade and parroting the same Cult-serving manipulative crap of their privileged white, often billionaire, associates. It is indeed not a race war but a class war and colour is just a diversion. Black Senator Cory Booker and black Congresswoman Maxine Waters, more residents of Nincompoopia, personify this. Once you tell people they are victims of someone else you devalue both their own responsibility for their plight and the power they have to impact on their reality and experience. Instead

we have: 'You are only in your situation because of whitey – turn on them and everything will change.' It won't change. Nothing changes in our lives unless *we* change it. Crucial to that is never seeing yourself as a victim and always as the creator of your reality. Life is a simple sequence of choice and consequence. Make different choices and you create different consequences. *You* have to make those choices – not Black Lives Matter, the Woke Mafia and anyone else that seeks to dictate your life. Who are they these Wokers, an emotional and psychological road traffic accident, to tell you what to do? Personal empowerment is the last thing the Cult and its Black Lives Matter want black people or anyone else to have. They claim to be defending the underdog while *creating* and perpetuating the underdog. The Cult's worst nightmare is human unity and if they are going to keep blacks, whites and every other race under economic servitude and control then the focus must be diverted from what they have in common to what they can be manipulated to believe divides them. Blacks have to be told that their poverty and plight is the fault of the white bloke living on the street in the same poverty and with the same plight they are experiencing. The difference is that your plight black people is due to him, a white supremacist with 'white privilege' living on the street. Don't unite as one human family against your mutual oppressors and suppressors – fight the oppressor with the white face who is as financially deprived as you are. The Cult knows that as its 'Covid' agenda moves into still new levels of extremism people are going to respond and it has been spreading the seeds of disunity everywhere to stop a united response to the evil that targets *all of us*.

Racist attacks on 'whiteness' are getting ever more outrageous and especially through the American Democratic Party which has an appalling history for anti-black racism. Barack Obama, Joe Biden, Hillary Clinton and Nancy Pelosi all eulogised about Senator Robert Byrd at his funeral in 2010 after a nearly 60-year career in Congress. Byrd was a brutal Ku Klux Klan racist and a violent abuser of Cathy O'Brien in MKUltra. He said he would never fight in the military 'with a negro by my side' and 'rather I should die a thousand times,

and see Old Glory trampled in the dirt never to rise again, than to see this beloved land of ours become degraded by race mongrels, a throwback to the blackest specimen from the wilds'. Biden called Byrd a 'very close friend and mentor'. These 'Woke' hypocrites are not anti-racist they are anti-poor and anti-people not of their perceived class. Here is an illustration of the scale of anti-white racism to which we have now descended. Seriously Woke and moronic *New York Times* contributor Damon Young described whiteness as a 'virus' that 'like other viruses will not die until there are no bodies left for it to infect'. He went on: '… the only way to stop it is to locate it, isolate it, extract it, and kill it.' Young can say that as a black man with no consequences when a white man saying the same in reverse would be facing a jail sentence. *That's* racism. We had super-Woke numbskull senators Tammy Duckworth and Mazie Hirono saying they would object to future Biden Cabinet appointments if he did not nominate more Asian Americans and Pacific Islanders. Never mind the ability of the candidate what do they look like? Duckworth said: 'I will vote for racial minorities and I will vote for LGBTQ, but anyone else I'm not voting for.' Appointing people on the grounds of race is illegal, but that was not a problem for this ludicrous pair. They were on-message and that's a free pass in any situation.

Critical race racism

White children are told at school they are intrinsically racist as they are taught the divisive 'critical race theory'. This claims that the law and legal institutions are inherently racist and that race is a socially constructed concept used by white people to further their economic and political interests at the expense of people of colour. White is a 'virus' as we've seen. Racial inequality results from 'social, economic, and legal differences that white people create between races to maintain white interests which leads to poverty and criminality in minority communities'. I must tell that to the white guy sleeping on the street. The principal of East Side Community School in New York sent white parents a manifesto that called on

them to become 'white traitors' and advocate for full 'white abolition'. These people are teaching your kids when they urgently need a psychiatrist. The 'school' included a chart with 'eight white identities' that ranged from 'white supremacist' to 'white abolition' and defined the behaviour white people must follow to end 'the regime of whiteness'. Woke blacks and their privileged white associates are acting exactly like the slave owners of old and Ku Klux Klan racists like Robert Byrd. They are too full of their own self-purity to see that, but it's true. Racism is not a body type; it's a state of mind that can manifest through any colour, creed or culture.

Another racial fraud is *'equity'*. Not equality of treatment and opportunity – equity. It's a term spun as equality when it means something very different. Equality in its true sense is a raising up while 'equity' is a race to the bottom. Everyone in the same level of poverty is 'equity'. Keep everyone down – that's equity. The Cult doesn't want anyone in the human family to be empowered and BLM leaders, like all these 'anti-racist' organisations, continue their privileged, pampered existence by perpetuating the perception of gathering racism. When is the last time you heard an 'anti-racist' or 'anti-Semitism' organisation say that acts of racism and discrimination have *fallen?* It's not in the interests of their fund-raising and power to influence and the same goes for the professional soccer anti-racism operation, Kick It Out. Two things confirmed that the Black Lives Matter riots in the summer of 2020 were Cult creations. One was that while anti-lockdown protests were condemned in this same period for 'transmitting 'Covid' the authorities supported mass gatherings of Black Lives Matter supporters. I even saw self-deluding people claiming to be doctors say the two types of protest were not the same. No – the non-existent 'Covid' was in favour of lockdowns and attacked those that protested against them while 'Covid' supported Black Lives Matter and kept well away from its protests. The whole thing was a joke and as lockdown protestors were arrested, often brutally, by reframed Face-Nappies we had the grotesque sight of police officers taking the knee to Black Lives Matter, a Cult-funded Marxist

organisation that supports violent riots and wants to destroy the nuclear family and white people.

He's not white? Shucks!

Woke obsession with race was on display again when ten people were shot dead in Boulder, Colorado, in March, 2021. Cult-owned Woke TV channels like CNN said the shooter appeared to be a white man and Wokers were on Twitter condemning 'violent white men' with the usual mantras. Then the shooter's name was released as Ahmad Al Aliwi Alissa, an anti-Trump Arab-American, and the sigh of disappointment could be heard five miles away. Never mind that ten people were dead and what that meant for their families. Race baiting was all that mattered to these sick Cult-serving people like Barack Obama who exploited the deaths to further divide America on racial grounds which is his job for the Cult. This is the man that 'racist' white Americans made the first black president of the United States and then gave him a second term. Not-very-bright Obama has become filthy rich on the back of that and today appears to have a big influence on the Biden administration. Even so he's still a downtrodden black man and a victim of white supremacy. This disingenuous fraud reveals the contempt he has for black people when he puts on a Deep South Alabama accent whenever he talks to them, no, *at* them.

Another BLM red flag was how the now fully-Woke (fully-Cult) and fully-virtue-signalled professional soccer authorities had their teams taking the knee before every match in support of Marxist Black Lives Matter. Soccer authorities and clubs displayed 'Black Lives Matter' on the players' shirts and flashed the name on electronic billboards around the pitch. Any fans that condemned what is a Freemasonic taking-the-knee ritual were widely condemned as you would expect from the Woke virtue-signallers of professional sport and the now fully-Woke media. We have reverse racism in which you are banned from criticising any race or culture except for white people for whom anything goes – say what you like, no problem. What has this got to do with racial harmony and

equality? We've had black supremacists from Black Lives Matter telling white people to fall to their knees in the street and apologise for their white supremacy. Black supremacists acting like white supremacist slave owners of the past couldn't breach their self-obsessed, race-obsessed sense of self-purity. Joe Biden appointed a race-obsessed black supremacist Kristen Clarke to head the Justice Department Civil Rights Division. Clarke claimed that blacks are endowed with 'greater mental, physical and spiritual abilities' than whites. If anyone reversed that statement they would be vilified. Clarke is on-message so no problem. She's never seen a black-white situation in which the black figure is anything but a virtuous victim and she heads the Civil Rights Division which should treat everyone the same or it isn't civil rights. Another perception of the Renegade Mind: If something or someone is part of the Cult agenda they will be supported by Woke governments and media no matter what. If they're not, they will be condemned and censored. It really is that simple and so racist Clarke prospers despite (make that because of) her racism.

The end of culture

Biden's administration is full of such racial, cultural and economic bias as the Cult requires the human family to be divided into warring factions. We are now seeing racially-segregated graduations and everything, but everything, is defined through the lens of perceived 'racism. We have 'racist' mathematics, 'racist' food and even 'racist' *plants*. World famous Kew Gardens in London said it was changing labels on plants and flowers to tell its pre-'Covid' more than two million visitors a year how racist they are. Kew director Richard Deverell said this was part of an effort to 'move quickly to decolonise collections' after they were approached by one Ajay Chhabra 'an actor with an insight into how sugar cane was linked to slavery'. They are *plants* you idiots. 'Decolonisation' in the Woke manual really means colonisation of society with its mentality and by extension colonisation by the Cult. We are witnessing a new Chinese-style 'Cultural Revolution' so essential to the success of all

Marxist takeovers. Our cultural past and traditions have to be swept away to allow a new culture to be built-back-better. Woke targeting of long-standing Western cultural pillars including historical monuments and cancelling of historical figures is what happened in the Mao revolution in China which 'purged remnants of capitalist and traditional elements from Chinese society' and installed Maoism as the dominant ideology'. For China see the Western world today and for 'dominant ideology' see Woke. Better still see Marxism or Maoism. The 'Covid' hoax has specifically sought to destroy the arts and all elements of Western culture from people meeting in a pub or restaurant to closing theatres, music venues, sports stadiums, places of worship and even banning *singing*. Destruction of Western society is also why criticism of any religion is banned except for Christianity which again is the dominant religion as white is the numerically-dominant race. Christianity may be fading rapidly, but its history and traditions are weaved through the fabric of Western society. Delete the pillars and other structures will follow until the whole thing collapses. I am not a Christian defending that religion when I say that. I have no religion. It's just a fact. To this end Christianity has itself been turned Woke to usher its own downfall and its ranks are awash with 'change agents' – knowing and unknowing – at every level including Pope Francis (*definitely* knowing) and the clueless Archbishop of Canterbury Justin Welby (possibly not, but who can be sure?). Woke seeks to coordinate attacks on Western culture, traditions, and ways of life through 'intersectionality' defined as 'the complex, cumulative way in which the effects of multiple forms of discrimination (such as racism, sexism, and classism) combine, overlap, or intersect especially in the experiences of marginalised individuals or groups'. Wade through the Orwellian Woke-speak and this means coordinating disparate groups in a common cause to overthrow freedom and liberal values.

The entire structure of public institutions has been infested with Woke – government at all levels, political parties, police, military, schools, universities, advertising, media and trade unions. This abomination has been achieved through the Cult web by appointing

Wokers to positions of power and battering non-Wokers into line through intimidation, isolation and threats to their job. Many have been fired in the wake of the empathy-deleted, vicious hostility of 'social justice' Wokers and the desire of gutless, spineless employers to virtue-signal their Wokeness. Corporations are filled with Wokers today, most notably those in Silicon Valley. Ironically at the top they are not Woke at all. They are only exploiting the mentality their Cult masters have created and funded to censor and enslave while the Wokers cheer them on until it's their turn. Thus the Woke 'liberal left' is an inversion of the traditional liberal left. Campaigning for justice on the grounds of power and wealth distribution has been replaced by campaigning for identity politics. The genuine traditional left would never have taken money from today's billionaire abusers of fairness and justice and nor would the billionaires have wanted to fund that genuine left. It would not have been in their interests to do so. The division of opinion in those days was between the haves and have nots. This all changed with Cult manipulated and funded identity politics. The division of opinion today is between Wokers and non-Wokers and not income brackets. Cult corporations and their billionaires may have taken wealth disparity to cataclysmic levels of injustice, but as long as they speak the language of Woke, hand out the dosh to the Woke network and censor the enemy they are 'one of us'. Billionaires who don't give a damn about injustice are laughing at them till their bellies hurt. Wokers are not even close to self-aware enough to see that. The transformed 'left' dynamic means that Wokers who drone on about 'social justice' are funded by billionaires that have destroyed social justice the world over. It's *why* they are billionaires.

The climate con

Nothing encapsulates what I have said more comprehensively than the hoax of human-caused global warming. I have detailed in my books over the years how Cult operatives and organisations were the pump-primers from the start of the climate con. A purpose-built vehicle for this is the Club of Rome established by the Cult in 1968

with the Rockefellers and Rothschilds centrally involved all along. Their gofer frontman Maurice Strong, a Canadian oil millionaire, hosted the Earth Summit in Rio de Janeiro, Brazil, in 1992 where the global 'green movement' really expanded in earnest under the guiding hand of the Cult. The Earth Summit established Agenda 21 through the Cult-created-and-owned United Nations to use the illusion of human-caused climate change to justify the transformation of global society to save the world from climate disaster. It is a No-Problem-Reaction-Solution sold through governments, media, schools and universities as whole generations have been terrified into believing that the world was going to end in their lifetimes unless what old people had inflicted upon them was stopped by a complete restructuring of how everything is done. Chill, kids, it's all a hoax. Such restructuring is precisely what the Cult agenda demands (purely by coincidence of course). Today this has been given the codename of the Great Reset which is only an updated term for Agenda 21 and its associated Agenda 2030. The latter, too, is administered through the UN and was voted into being by the General Assembly in 2015. Both 21 and 2030 seek centralised control of all resources and food right down to the raindrops falling on your own land. These are some of the demands of Agenda 21 established in 1992. See if you recognise this society emerging today:

- End national sovereignty
- State planning and management of all land resources, ecosystems, deserts, forests, mountains, oceans and fresh water; agriculture; rural development; biotechnology; and ensuring *'equity'*
- The state to 'define the role' of business and financial resources
- Abolition of private property
- 'Restructuring' the family unit (see BLM)
- Children raised by the state
- People told what their job will be
- Major restrictions on movement
- Creation of 'human settlement zones'

- Mass resettlement as people are forced to vacate land where they live
- Dumbing down education
- Mass global depopulation in pursuit of all the above

The United Nations was created as a Trojan horse for world government. With the climate con of critical importance to promoting that outcome you would expect the UN to be involved. Oh, it's involved all right. The UN is promoting Agenda 21 and Agenda 2030 justified by 'climate change' while also driving the climate hoax through its Intergovernmental Panel on Climate Change (IPCC), one of the world's most corrupt organisations. The IPCC has been lying ferociously and constantly since the day it opened its doors with the global media hanging unquestioningly on its every mendacious word. The Green movement is entirely Woke and has long lost its original environmental focus since it was co-opted by the Cult. An obsession with 'global warming' has deleted its values and scrambled its head. I experienced a small example of what I mean on a beautiful country walk that I have enjoyed several times a week for many years. The path merged into the fields and forests and you felt at one with the natural world. Then a 'Green' organisation, the Hampshire and Isle of Wight Wildlife Trust, took over part of the land and proceeded to cut down a large number of trees, including mature ones, to install a horrible big, bright steel 'this-is-ours-stay-out' fence that destroyed the whole atmosphere of this beautiful place. No one with a feel for nature would do that. Day after day I walked to the sound of chainsaws and a magnificent mature weeping willow tree that I so admired was cut down at the base of the trunk. When I challenged a Woke young girl in a green shirt (of course) about this vandalism she replied: 'It's a weeping willow – it will grow back.' This is what people are paying for when they donate to the Hampshire and Isle of Wight Wildlife Trust and many other 'green' organisations today. It is not the environmental movement that I knew and instead has become a support-system – as with Extinction Rebellion – for a very dark agenda.

Private jets for climate justice

The Cult-owned, Gates-funded, World Economic Forum and its founder Klaus Schwab were behind the emergence of Greta Thunberg to harness the young behind the climate agenda and she was invited to speak to the world at … the UN. Schwab published a book, *Covid-19: The Great Reset* in 2020 in which he used the 'Covid' hoax and the climate hoax to lay out a new society straight out of Agenda 21 and Agenda 2030. Bill Gates followed in early 2021 when he took time out from destroying the world to produce a book in his name about the way to save it. Gates flies across the world in private jets and admitted that 'I probably have one of the highest greenhouse gas footprints of anyone on the planet … my personal flying alone is gigantic.' He has also bid for the planet's biggest private jet operator. Other climate change saviours who fly in private jets include John Kerry, the US Special Presidential Envoy for Climate, and actor Leonardo DiCaprio, a 'UN Messenger of Peace with special focus on climate change'. These people are so full of bullshit they could corner the market in manure. We mustn't be sceptical, though, because the Gates book, *How to Avoid a Climate Disaster: The Solutions We Have and the Breakthroughs We Need*, is a genuine attempt to protect the world and not an obvious pile of excrement attributed to a mega-psychopath aimed at selling his masters' plans for humanity. The Gates book and the other shite-pile by Klaus Schwab could have been written by the same person and may well have been. Both use 'climate change' and 'Covid' as the excuses for their new society and by coincidence the Cult's World Economic Forum and Bill and Melinda Gates Foundation promote the climate hoax and hosted Event 201 which pre-empted with a 'simulation' the very 'coronavirus' hoax that would be simulated for real on humanity within weeks. The British 'royal' family is promoting the 'Reset' as you would expect through Prince 'climate change caused the war in Syria' Charles and his hapless son Prince William who said that we must 'reset our relationship with nature and our trajectory as a species' to avoid a climate disaster. Amazing how many promotors of the 'Covid' and 'climate change' control

systems are connected to Gates and the World Economic Forum. A 'study' in early 2021 claimed that carbon dioxide emissions must fall by the equivalent of a global lockdown roughly every two years for the next decade to save the planet. The 'study' appeared in the same period that the Schwab mob claimed in a video that lockdowns destroying the lives of billions are good because they make the earth 'quieter' with less 'ambient noise'. They took down the video amid a public backlash for such arrogant, empathy-deleted stupidity You see, however, where they are going with this. Corinne Le Quéré, a professor at the Tyndall Centre for Climate Change Research, University of East Anglia, was lead author of the climate lockdown study, and she writes for … the World Economic Forum. Gates calls in 'his' book for changing 'every aspect of the economy' (long-time Cult agenda) and for humans to eat synthetic 'meat' (predicted in my books) while cows and other farm animals are eliminated. Australian TV host and commentator Alan Jones described what carbon emission targets would mean for farm animals in Australia alone if emissions were reduced as demanded by 35 percent by 2030 and zero by 2050:

Well, let's take agriculture, the total emissions from agriculture are about 75 million tonnes of carbon dioxide, equivalent. Now reduce that by 35 percent and you have to come down to 50 million tonnes, I've done the maths. So if you take for example 1.5 million cows, you're going to have to reduce the herd by 525,000 [by] 2030, nine years, that's 58,000 cows a year. The beef herd's 30 million, reduce that by 35 percent, that's 10.5 million, which means 1.2 million cattle have to go every year between now and 2030. This is insanity!

There are 75 million sheep. Reduce that by 35 percent, that's 26 million sheep, that's almost 3 million a year. So under the Paris Agreement over 30 million beasts. dairy cows, cattle, pigs and sheep would go. More than 8,000 every minute of every hour for the next decade, do these people know what they're talking about?

Clearly they don't at the level of campaigners, politicians and administrators. The Cult *does* know; that's the outcome it wants. We are faced with not just a war on humanity. Animals and the natural world are being targeted and I have been saying since the 'Covid' hoax began that the plan eventually was to claim that the 'deadly virus' is able to jump from animals, including farm animals and

domestic pets, to humans. Just before this book went into production came this story: 'Russia registers world's first Covid-19 vaccine for cats & dogs as makers of Sputnik V warn pets & farm animals could spread virus'. The report said 'top scientists warned that the deadly pathogen could soon begin spreading through homes and farms' and 'the next stage is the infection of farm and domestic animals'. Know the outcome and you'll see the journey. Think what that would mean for animals and keep your eye on a term called zoonosis or zoonotic diseases which transmit between animals and humans. The Cult wants to break the connection between animals and people as it does between people and people. Farm animals fit with the Cult agenda to transform food from natural to synthetic.

The gas of life is killing us

There can be few greater examples of Cult inversion than the condemnation of carbon dioxide as a dangerous pollutant when it is the gas of life. Without it the natural world would be dead and so we would all be dead. We breathe in oxygen and breathe out carbon dioxide while plants produce oxygen and absorb carbon dioxide. It is a perfect symbiotic relationship that the Cult wants to dismantle for reasons I will come to in the final two chapters. Gates, Schwab, other Cult operatives and mindless repeaters, want the world to be 'carbon neutral' by at least 2050 and the earlier the better. 'Zero carbon' is the cry echoed by lunatics calling for 'Zero Covid' when we already have it. These carbon emission targets will deindustrialise the world in accordance with Cult plans – the post-industrial, post-democratic society – and with so-called renewables like solar and wind not coming even close to meeting human energy needs blackouts and cold are inevitable. Texans got the picture in the winter of 2021 when a snow storm stopped wind turbines and solar panels from working and the lights went down along with water which relies on electricity for its supply system. Gates wants everything to be powered by electricity to ensure that his masters have the kill switch to stop all human activity, movement, cooking, water and warmth any time they like. The climate lie is so

stupendously inverted that it claims we must urgently reduce carbon dioxide when we *don't have enough*.

Co2 in the atmosphere is a little above 400 parts per million when the optimum for plant growth is 2,000 ppm and when it falls anywhere near 150 ppm the natural world starts to die and so do we. It fell to as low as 280 ppm in an 1880 measurement in Hawaii and rose to 413 ppm in 2019 with industrialisation which is why the planet has become *greener* in the industrial period. How insane then that psychopathic madman Gates is not satisfied only with blocking the rise of Co2. He's funding technology to suck it out of the atmosphere. The reason why will become clear. The industrial era is not destroying the world through Co2 and has instead turned around a potentially disastrous ongoing fall in Co2. Greenpeace co-founder and scientist Patrick Moore walked away from Greenpeace in 1986 and has exposed the green movement for fear-mongering and lies. He said that 500 million years ago there was *17 times* more Co2 in the atmosphere than we have today and levels have been falling for hundreds of millions of years. In the last 150 million years Co2 levels in Earth's atmosphere had reduced by *90 percent*. Moore said that by the time humanity began to unlock carbon dioxide from fossil fuels we were at '38 seconds to midnight' and in that sense: 'Humans are [the Earth's] salvation.' Moore made the point that only half the Co2 emitted by fossil fuels stays in the atmosphere and we should remember that all pollution pouring from chimneys that we are told is carbon dioxide is in fact nothing of the kind. It's pollution. Carbon dioxide is an invisible gas.

William Happer, Professor of Physics at Princeton University and long-time government adviser on climate, has emphasised the Co2 deficiency for maximum growth and food production. Greenhouse growers don't add carbon dioxide for a bit of fun. He said that most of the warming in the last 100 years, after the earth emerged from the super-cold period of the 'Little Ice Age' into a natural warming cycle, was over by 1940. Happer said that a peak year for warming in 1988 can be explained by a 'monster El Nino' which is a natural and cyclical warming of the Pacific that has nothing to do with 'climate

change'. He said the effect of Co2 could be compared to painting a wall with red paint in that once two or three coats have been applied it didn't matter how much more you slapped on because the wall will not get much redder. Almost all the effect of the rise in Co2 has already happened, he said, and the volume in the atmosphere would now have to *double* to increase temperature by a single degree. Climate hoaxers know this and they have invented the most ridiculously complicated series of 'feedback' loops to try to overcome this rather devastating fact. You hear puppet Greta going on cluelessly about feedback loops and this is why.

The Sun affects temperature? No you *climate denier*

Some other nonsense to contemplate: Climate graphs show that rises in temperature do not follow rises in Co2 – *it's the other way round* with a lag between the two of some 800 years. If we go back 800 years from present time we hit the Medieval Warm Period when temperatures were higher than now without any industrialisation and this was followed by the Little Ice Age when temperatures plummeted. The world was still emerging from these centuries of serious cold when many climate records began which makes the ever-repeated line of the 'hottest year since records began' meaningless when you are not comparing like with like. The coldest period of the Little Ice Age corresponded with the lowest period of sunspot activity when the Sun was at its least active. Proper scientists will not be at all surprised by this when it confirms the obvious fact that earth temperature is affected by the scale of Sun activity and the energetic power that it subsequently emits; but when is the last time you heard a climate hoaxer talking about the Sun as a source of earth temperature?? Everything has to be focussed on Co2 which makes up just 0.117 percent of so-called greenhouse gases and only a fraction of even that is generated by human activity. The rest is natural. More than *90 percent* of those greenhouse gases are water vapour and clouds (Fig 9). Ban moisture I say. Have you noticed that the climate hoaxers no longer use the polar bear as their promotion image? That's because far from becoming extinct polar

bear communities are stable or thriving. Joe Bastardi, American meteorologist, weather forecaster and outspoken critic of the climate lie, documents in his book *The Climate Chronicles* how weather patterns and events claimed to be evidence of climate change have been happening since long before industrialisation: 'What happened before naturally is happening again, as is to be expected given the cyclical nature of the climate due to the design of the planet.' If you read the detailed background to the climate hoax in my other books you will shake your head and wonder how anyone could believe the crap which has spawned a multi-trillion dollar industry based on absolute garbage (see HIV causes AIDs and Sars-Cov-2 causes 'Covid-19'). Climate and 'Covid' have much in common given they have the same source. They both have the contradictory *everything* factor in which everything is explained by reference to them. It's hot – 'it's climate change'. It's cold – 'it's climate change'. I got a sniffle – 'it's Covid'. I haven't got a sniffle – 'it's Covid'. Not having a sniffle has to be a symptom of 'Covid'. Everything is and not having a sniffle is especially dangerous if you are a slow walker. For sheer audacity I offer you a Cambridge University 'study' that actually linked 'Covid' to 'climate change'. It had to happen eventually. They concluded that climate change played a role in 'Covid-19' spreading from animals to humans because … wait for it … I kid you not … *the two groups were forced closer together as populations grow*. Er, that's it. The whole foundation on which this depended was that 'Bats are the likely zoonotic origin of SARS-CoV-1 and SARS-CoV-2'. Well, they are not. They are nothing to do with it. Apart from bats not being the origin and therefore 'climate change' effects on bats being irrelevant I am in awe of their academic insight. Where would we be without them? Not where we are that's for sure.

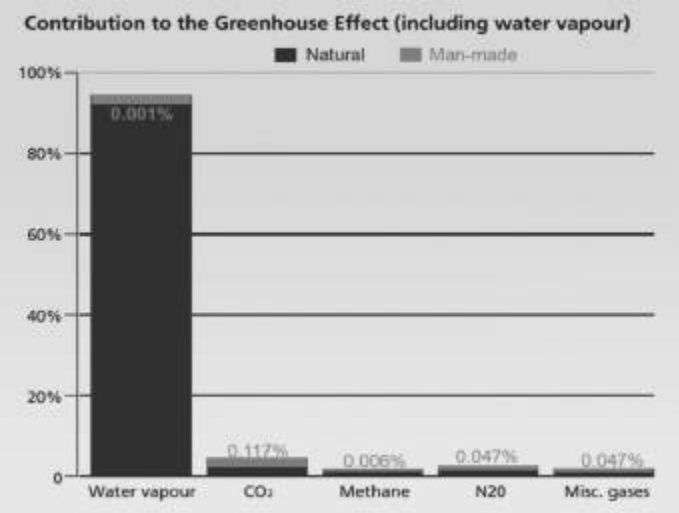


Figure 9: The idea that the gas of life is disastrously changing the climate is an insult to brain cell activity.

One other point about the weather is that climate modification is now well advanced and not every major weather event is natural – or earthquake come to that. I cover this subject at some length in other books. China is openly planning a rapid expansion of its weather modification programme which includes changing the climate in an area more than one and a half times the size of India. China used weather manipulation to ensure clear skies during the 2008 Olympics in Beijing. I have quoted from US military documents detailing how to employ weather manipulation as a weapon of war and they did that in the 1960s and 70s during the conflict in Vietnam with Operation Popeye manipulating monsoon rains for military purposes. Why would there be international treaties on weather modification if it wasn't possible? Of course it is. Weather is energetic information and it can be changed.

How was the climate hoax pulled off? See 'Covid'

If you can get billions to believe in a 'virus' that doesn't exist you can get them to believe in human-caused climate change that doesn't exist. Both are being used by the Cult to transform global society in the way it has long planned. Both hoaxes have been achieved in pretty much the same way. First you declare a lie is a fact. There's a

'virus' you call SARS-Cov-2 or humans are warming the planet with their behaviour. Next this becomes, via Cult networks, the foundation of government, academic and science policy and belief. Those who parrot the mantra are given big grants to produce research that confirms the narrative is true and ever more 'symptoms' are added to make the 'virus'/'climate change' sound even more scary. Scientists and researchers who challenge the narrative have their grants withdrawn and their careers destroyed. The media promote the lie as the unquestionable truth and censor those with an alternative view or evidence. A great percentage of the population believe what they are told as the lie becomes an everybody-knows-that and the believing-masses turn on those with a mind of their own. The technique has been used endlessly throughout human history. Wokers are the biggest promotors of the climate lie *and* 'Covid' fascism because their minds are owned by the Cult; their sense of self-righteous self-purity knows no bounds; and they exist in a bubble of reality in which facts are irrelevant and only get in the way of looking without seeing.

Running through all of this like veins in a blue cheese is control of information, which means control of perception, which means control of behaviour, which collectively means control of human society. The Cult owns the global media and Silicon Valley fascists for the simple reason that it *has* to. Without control of information it can't control perception and through that human society. Examine every facet of the Cult agenda and you will see that anything supporting its introduction is never censored while anything pushing back is always censored. I say again: Psychopaths that know why they are doing this must go before Nuremberg trials and those that follow their orders must trot along behind them into the same dock. 'I was just following orders' didn't work the first time and it must not work now. Nuremberg trials must be held all over the world before public juries for politicians, government officials, police, compliant doctors, scientists and virologists, and all Cult operatives such as Gates, Tedros, Fauci, Vallance, Whitty, Ferguson, Zuckerberg, Wojcicki, Brin, Page, Dorsey, the whole damn lot of

them – including, no *especially*, the psychopath psychologists. Without them and the brainless, gutless excuses for journalists that have repeated their lies, none of this could be happening. Nobody can be allowed to escape justice for the psychological and economic Armageddon they are all responsible for visiting upon the human race.

As for the compliant, unquestioning, swathes of humanity, and the self-obsessed, all-knowing ignorance of the Wokers … don't start me. God help their kids. God help their grandkids. God *help them*.

CHAPTER NINE

We must have it? So what is it?

Well I won't back down. No, I won't back down. You can stand me up at the Gates of Hell. But I won't back down
Tom Petty

I will now focus on the genetically-manipulating 'Covid vaccines' which do not meet this official definition of a vaccine by the US Centers for Disease Control (CDC): 'A product that stimulates a person's immune system to produce immunity to a specific disease, protecting the person from that disease.' On that basis 'Covid vaccines' are not a vaccine in that the makers don't even claim they stop infection or transmission.

They are instead part of a multi-levelled conspiracy to change the nature of the human body and what it means to be 'human' and to depopulate an enormous swathe of humanity. What I shall call Human 1.0 is on the cusp of becoming Human 2.0 and for very sinister reasons. Before I get to the 'Covid vaccine' in detail here's some background to vaccines in general. Government regulators do not test vaccines – the makers do – and the makers control which data is revealed and which isn't. Children in America are given 50 vaccine doses by age six and 69 by age 19 and the effect of the whole combined schedule has never been tested. Autoimmune diseases when the immune system attacks its own body have soared in the mass vaccine era and so has disease in general in children and the young. Why wouldn't this be the case when vaccines target the *immune system?* The US government gave Big Pharma drug

companies immunity from prosecution for vaccine death and injury in the 1986 National Childhood Vaccine Injury Act (NCVIA) and since then the government (taxpayer) has been funding compensation for the consequences of Big Pharma vaccines. The criminal and satanic drug giants can't lose and the vaccine schedule has increased dramatically since 1986 for this reason. There is no incentive to make vaccines safe and a big incentive to make money by introducing ever more. Even against a ridiculously high bar to prove vaccine liability, and with the government controlling the hearing in which it is being challenged for compensation, the vaccine court has so far paid out more than $4 billion. These are the vaccines we are told are safe and psychopaths like Zuckerberg censor posts saying otherwise. The immunity law was even justified by a ruling that vaccines by their nature were 'unavoidably unsafe'.

Check out the ingredients of vaccines and you will be shocked if you are new to this. *They put that in children's bodies?? What??* Try aluminium, a brain toxin connected to dementia, aborted foetal tissue and formaldehyde which is used to embalm corpses. World-renowned aluminium expert Christopher Exley had his research into the health effect of aluminium in vaccines shut down by Keele University in the UK when it began taking funding from the Bill and Melinda Gates Foundation. Research when diseases 'eradicated' by vaccines began to decline and you will find the fall began long *before* the vaccine was introduced. Sometimes the fall even plateaued after the vaccine. Diseases like scarlet fever for which there was no vaccine declined in the same way because of environmental and other factors. A perfect case in point is the polio vaccine. Polio began when lead arsenate was first sprayed as an insecticide and residues remained in food products. Spraying started in 1892 and the first US polio epidemic came in Vermont in 1894. The simple answer was to stop spraying, but Rockefeller-created Big Pharma had a better idea. Polio was decreed to be caused by the *poliovirus* which 'spreads from person to person and can infect a person's spinal cord'. Lead arsenate was replaced by the lethal DDT which had the same effect of causing paralysis by damaging the brain and central nervous

system. Polio plummeted when DDT was reduced and then banned, but the vaccine is still given the credit for something it didn't do. Today by far the biggest cause of polio is the vaccines promoted by Bill Gates. Vaccine justice campaigner Robert Kennedy Jr, son of assassinated (by the Cult) US Attorney General Robert Kennedy, wrote:

> In 2017, the World Health Organization (WHO) reluctantly admitted that the global explosion in polio is predominantly vaccine strain. The most frightening epidemics in Congo, Afghanistan, and the Philippines, are all linked to vaccines. In fact, by 2018, 70% of global polio cases were vaccine strain.

Vaccines make fortunes for Cult-owned Gates and Big Pharma while undermining the health and immune systems of the population. We had a glimpse of the mentality behind the Big Pharma cartel with a report on WION (World is One News), an international English language TV station based in India, which exposed the extraordinary behaviour of US drug company Pfizer over its 'Covid vaccine'. The WION report told how Pfizer had made fantastic demands of Argentina, Brazil and other countries in return for its 'vaccine'. These included immunity from prosecution, even for Pfizer negligence, government insurance to protect Pfizer from law suits and handing over as collateral sovereign assets of the country to include Argentina's bank reserves, military bases and embassy buildings. Pfizer demanded the same of Brazil in the form of waiving sovereignty of its assets abroad; exempting Pfizer from Brazilian laws; and giving Pfizer immunity from all civil liability. This is a 'vaccine' developed with government funding. Big Pharma is evil incarnate as a creation of the Cult and all must be handed tickets to Nuremberg.

Phantom 'vaccine' for a phantom 'disease'

I'll expose the 'Covid vaccine' fraud and then go on to the wider background of why the Cult has set out to 'vaccinate' every man, woman and child on the planet for an alleged 'new disease' with a survival rate of 99.77 percent (or more) even by the grotesquely-

manipulated figures of the World Health Organization and Johns Hopkins University. The 'infection' to 'death' ratio is 0.23 to 0.15 percent according to Stanford epidemiologist Dr John Ioannidis and while estimates vary the danger remains tiny. I say that if the truth be told the fake infection to fake death ratio is zero. Never mind all the evidence I have presented here and in *The Answer* that there is no 'virus' let us just focus for a moment on that death-rate figure of say 0.23 percent. The figure includes all those worldwide who have tested positive with a test not testing for the 'virus' and then died within 28 days or even longer of any other cause – *any other cause*. Now subtract all those illusory 'Covid' deaths on the global data sheets from the 0.23 percent. What do you think you would be left with? *Zero*. A vaccination has never been successfully developed for a so-called coronavirus. They have all failed at the animal testing stage when they caused hypersensitivity to what they were claiming to protect against and made the impact of a disease far worse. Cult-owned vaccine corporations got around that problem this time by bypassing animal trials, going straight to humans and making the length of the 'trials' before the public rollout as short as they could get away with. Normally it takes five to ten years or more to develop vaccines that still cause demonstrable harm to many people and that's without including the long-term effects that are never officially connected to the vaccination. 'Covid' non-vaccines have been officially produced and approved in a matter of months from a standing start and part of the reason is that (a) they were developed before the 'Covid' hoax began and (b) they are based on computer programs and not natural sources. Official non-trials were so short that government agencies gave *emergency*, not full, approval. 'Trials' were not even completed and full approval cannot be secured until they are. Public 'Covid vaccination' is actually a *continuation of the trial*. Drug company 'trials' are not scheduled to end until 2023 by which time a lot of people are going to be dead. Data on which government agencies gave this emergency approval was supplied by the Big Pharma corporations themselves in the form of Pfizer/BioNTech, AstraZeneca, Moderna, Johnson & Johnson, and

others, and this is the case with all vaccines. By its very nature *emergency* approval means drug companies do not have to prove that the 'vaccine' is 'safe and effective'. How could they with trials way short of complete? Government regulators only have to *believe* that they *could* be safe and effective. It is criminal manipulation to get products in circulation with no testing worth the name. Agencies giving that approval are infested with Big Pharma-connected place-people and they act in the interests of Big Pharma (the Cult) and not the public about whom they do not give a damn.

More human lab rats

'Covid vaccines' produced in record time by Pfizer/BioNTech and Moderna employ a technique *never approved before for use on humans*. They are known as mRNA 'vaccines' and inject a synthetic version of 'viral' mRNA or 'messenger RNA'. The key is in the term 'messenger'. The body works, or doesn't, on the basis of information messaging. Communications are constantly passing between and within the genetic system and the brain. Change those messages and you change the state of the body and even its very nature and you can change psychology and behaviour by the way the brain processes information. I think you are going to see significant changes in personality and perception of many people who have had the 'Covid vaccine' synthetic potions. Insider Aldous Huxley predicted the following in 1961 and mRNA 'vaccines' can be included in the term 'pharmacological methods':

> There will be, in the next generation or so, a pharmacological method of making people love their servitude, and producing dictatorship without tears, so to speak, producing a kind of painless concentration camp for entire societies, so that people will in fact have their own liberties taken away from them, but rather enjoy it, because they will be distracted from any desire to rebel by propaganda or brainwashing, or brainwashing enhanced by pharmacological methods. And this seems to be the final revolution.

Apologists claim that mRNA synthetic 'vaccines' don't change the DNA genetic blueprint because RNA does not affect DNA only the other way round. This is so disingenuous. A process called 'reverse

transcription' can convert RNA into DNA and be integrated into DNA in the cell nucleus. This was highlighted in December, 2020, by scientists at Harvard and Massachusetts Institute of Technology (MIT). Geneticists report that more than 40 percent of mammalian genomes results from reverse transcription. On the most basic level if messaging changes then that sequence must lead to changes in DNA which is receiving and transmitting those communications. How can introducing synthetic material into cells not change the cells where DNA is located? The process is known as transfection which is defined as 'a technique to insert foreign nucleic acid (DNA or RNA) into a cell, typically with the intention of altering the properties of the cell'. Researchers at the Sloan Kettering Institute in New York found that changes in messenger RNA can deactivate tumour-suppressing proteins and thereby promote cancer. This is what happens when you mess with messaging. 'Covid vaccine' maker Moderna was founded in 2010 by Canadian stem cell biologist Derrick J. Rossi after his breakthrough discovery in the field of transforming and reprogramming stem cells. These are neutral cells that can be programmed to become any cell including sperm cells. Moderna was therefore founded on the principle of genetic manipulation and has never produced any vaccine or drug before its genetically-manipulating synthetic 'Covid' shite. Look at the name – Mode-RNA or Modify-RNA. Another important point is that the US Supreme Court has ruled that genetically-modified DNA, or complementary DNA (cDNA) synthesized in the laboratory from messenger RNA, can be patented and owned. These psychopaths are doing this to the human body.

Cells replicate synthetic mRNA in the 'Covid vaccines' and in theory the body is tricked into making antigens which trigger antibodies to target the 'virus spike proteins' which as Dr Tom Cowan said have *never been seen*. Cut the crap and these 'vaccines' deliver *self-replicating* synthetic material to the cells with the effect of changing human DNA. The more of them you have the more that process is compounded while synthetic material is all the time self-replicating. 'Vaccine'-maker Moderna describes mRNA as 'like

software for the cell' and so they are messing with the body's software. What happens when you change the software in a computer? Everything changes. For this reason the Cult is preparing a production line of mRNA 'Covid vaccines' and a long list of excuses to use them as with all the 'variants' of a 'virus' never shown to exist. The plan is further to transfer the mRNA technique to other vaccines mostly given to children and young people. The cumulative consequences will be a transformation of human DNA through a constant infusion of synthetic genetic material which will kill many and change the rest. Now consider that governments that have given emergency approval for a vaccine that's not a vaccine; never been approved for humans before; had no testing worth the name; and the makers have been given immunity from prosecution for any deaths or adverse effects suffered by the public. The UK government awarded *permanent legal indemnity* to itself and its employees for harm done when a patient is being treated for 'Covid-19' or 'suspected Covid-19'. That is quite a thought when these are possible 'side-effects' from the 'vaccine' (they are not 'side', they are effects) listed by the US Food and Drug Administration:

Guillain-Barre syndrome; acute disseminated encephalomyelitis; transverse myelitis; encephalitis; myelitis; encephalomyelitis; meningoencephalitis; meningitis; encephalopathy; convulsions; seizures; stroke; narcolepsy; cataplexy; anaphylaxis; acute myocardial infarction (heart attack); myocarditis; pericarditis; autoimmune disease; death; implications for pregnancy, and birth outcomes; other acute demyelinating diseases; non anaphylactic allergy reactions; thrombocytopenia ; disseminated intravascular coagulation; venous thromboembolism; arthritis; arthralgia; joint pain; Kawasaki disease; multisystem inflammatory syndrome in children; vaccine enhanced disease. The latter is the way the 'vaccine' has the potential to make diseases far worse than they would otherwise be.

UK doctor and freedom campaigner Vernon Coleman described the conditions in this list as 'all unpleasant, most of them very serious, and you can't get more serious than death'. The thought that anyone at all has had the 'vaccine' in these circumstances is testament to the potential that humanity has for clueless, unquestioning, stupidity and for many that programmed stupidity has already been terminal.

An insider speaks

Dr Michael Yeadon is a former Vice President, head of research and Chief Scientific Adviser at vaccine giant Pfizer. Yeadon worked on the inside of Big Pharma, but that did not stop him becoming a vocal critic of 'Covid vaccines' and their potential for multiple harms, including infertility in women. By the spring of 2021 he went much further and even used the no, no, term 'conspiracy'. When you begin to see what is going on it is impossible not to do so. Yeadon spoke out in an interview with freedom campaigner James Delingpole and I mentioned earlier how he said that no one had samples of 'the virus'. He explained that the mRNA technique originated in the anti-cancer field and ways to turn on and off certain genes which could be advantageous if you wanted to stop cancer growing out of control. 'That's the origin of them. They are a very unusual application, really.' Yeadon said that treating a cancer patient with an aggressive procedure might be understandable if the alternative was dying, but it was quite another thing to use the same technique as a public health measure. Most people involved wouldn't catch the infectious agent you were vaccinating against and if they did they probably wouldn't die:

> If you are really using it as a public health measure you really want to as close as you can get to zero sides-effects … I find it odd that they chose techniques that were really cutting their teeth in the field of oncology and I'm worried that in using gene-based vaccines that have to be injected in the body and spread around the body, get taken up into some cells, and the regulators haven't quite told us which cells they get taken up into … you are going to be generating a wide range of responses … with multiple steps each of which could go well or badly.

I doubt the Cult intends it to go well. Yeadon said that you can put any gene you like into the body through the 'vaccine'. 'You can certainly give them a gene that would do them some harm if you wanted.' I was intrigued when he said that when used in the cancer field the technique could turn genes on and off. I explore this process in *The Answer* and with different genes having different functions you could create mayhem – physically and psychologically – if you turned the wrong ones on and the right ones off. I read reports of an experiment by researchers at the University of Washington's school of computer science and engineering in which they encoded DNA to infect computers. The body is itself a biological computer and if human DNA can inflict damage on a computer why can't the computer via synthetic material mess with the human body? It can. The Washington research team said it was possible to insert malicious malware into 'physical DNA strands' and corrupt the computer system of a gene sequencing machine as it 'reads gene letters and stores them as binary digits 0 and 1'. They concluded that hackers could one day use blood or spit samples to access computer systems and obtain sensitive data from police forensics labs or infect genome files. It is at this level of digital interaction that synthetic 'vaccines' need to be seen to get the full picture and that will become very clear later on. Michael Yeadon said it made no sense to give the 'vaccine' to younger people who were in no danger from the 'virus'. What was the benefit? It was all downside with potential effects:

> The fact that my government in what I thought was a civilised, rational country, is raining [the 'vaccine'] on people in their 30s and 40s, even my children in their 20s, they're getting letters and phone calls, I know this is not right and any of you doctors who are vaccinating you know it's not right, too. They are not at risk. They are not at risk from the disease, so you are now hoping that the side-effects are so rare that you get away with it. You don't give new technology … that you don't understand to 100 percent of the population.

Blood clot problems with the AstraZeneca 'vaccine' have been affecting younger people to emphasise the downside risks with no benefit. AstraZeneca's version, produced with Oxford University, does not use mRNA, but still gets its toxic cocktail inside cells where

it targets DNA. The Johnson & Johnson 'vaccine' which uses a similar technique has also produced blood clot effects to such an extent that the United States paused its use at one point. They are all 'gene therapy' (cell modification) procedures and not 'vaccines'. The truth is that once the content of these injections enter cells we have no idea what the effect will be. People can speculate and some can give very educated opinions and that's good. In the end, though, only the makers know what their potions are designed to do and even they won't know every last consequence. Michael Yeadon was scathing about doctors doing what they knew to be wrong. 'Everyone's mute', he said. Doctors in the NHS must know this was not right, coming into work and injecting people. 'I don't know how they sleep at night. I know I couldn't do it. I know that if I were in that position I'd have to quit.' He said he knew enough about toxicology to know this was not a good risk-benefit. Yeadon had spoken to seven or eight university professors and all except two would not speak out publicly. Their universities had a policy that no one said anything that countered the government and its medical advisors. They were afraid of losing their government grants. This is how intimidation has been used to silence the truth at every level of the system. I say silence, but these people could still speak out if they made that choice. Yeadon called them 'moral cowards' – 'This is about your children and grandchildren's lives and you have just buggered off and left it.'

'Variant' nonsense

Some of his most powerful comments related to the alleged 'variants' being used to instil more fear, justify more lockdowns, and introduce more 'vaccines'. He said government claims about 'variants' were nonsense. He had checked the alleged variant 'codes' and they were 99.7 percent identical to the 'original'. This was the human identity difference equivalent to putting a baseball cap on and off or wearing it the other way round. A 0.3 percent difference would make it impossible for that 'variant' to escape immunity from the 'original'. This made no sense of having new 'vaccines' for

'variants'. He said there would have to be at least a *30 percent* difference for that to be justified and even then he believed the immune system would still recognise what it was. Gates-funded 'variant modeller' and 'vaccine'-pusher John Edmunds might care to comment. Yeadon said drug companies were making new versions of the 'vaccine' as a 'top up' for 'variants'. Worse than that, he said, the 'regulators' around the world like the MHRA in the UK had got together and agreed that because 'vaccines' for 'variants' were so similar to the first 'vaccines' *they did not have to do safety studies*. How transparently sinister that is. This is when Yeadon said: 'There is a conspiracy here.' There was no need for another vaccine for 'variants' and yet we were told that there was and the country had shut its borders because of them. 'They are going into hundreds of millions of arms without passing 'go' or any regulator. Why did they do that? Why did they pick this method of making the vaccine?'

The reason had to be something bigger than that it seemed and 'it's not protection against the virus'. It's was a far bigger project that meant politicians and advisers were willing to do things and not do things that knowingly resulted in avoidable deaths – 'that's already happened when you think about lockdown and deprivation of health care for a year.' He spoke of people prepared to do something that results in the avoidable death of their fellow human beings and it not bother them. This is the penny-drop I have been working to get across for more than 30 years – the level of pure evil we are dealing with. Yeadon said his friends and associates could not believe there could be that much evil, but he reminded them of Stalin, Pol Pot and Hitler and of what Stalin had said: 'One death is a tragedy. A million? A statistic.' He could not think of a benign explanation for why you need top-up vaccines 'which I'm sure you don't' and for the regulators 'to just get out of the way and wave them through'. Why would the regulators do that when they were still wrestling with the dangers of the 'parent' vaccine? He was clearly shocked by what he had seen since the 'Covid' hoax began and now he was thinking the previously unthinkable:

If you wanted to depopulate a significant proportion of the world and to do it in a way that doesn't involve destruction of the environment with nuclear weapons, poisoning everyone with anthrax or something like that, and you wanted plausible deniability while you had a multi-year infectious disease crisis, I actually don't think you could come up with a better plan of work than seems to be in front of me. I can't say that's what they are going to do, but I can't think of a benign explanation why they are doing it.

He said he never thought that they would get rid of 99 percent of humans, but now he wondered. 'If you wanted to that this would be a hell of a way to do it – it would be unstoppable folks.' Yeadon had concluded that those who submitted to the 'vaccine' would be allowed to have some kind of normal life (but for how long?) while screws were tightened to coerce and mandate the last few percent. 'I think they'll put the rest of them in a prison camp. I wish I was wrong, but I don't think I am.' Other points he made included: There were no coronavirus vaccines then suddenly they all come along at the same time; we have no idea of the long term affect with trials so short; coercing or forcing people to have medical procedures is against the Nuremberg Code instigated when the Nazis did just that; people should at least delay having the 'vaccine'; a quick Internet search confirms that masks don't reduce respiratory viral transmission and 'the government knows that'; they have smashed civil society and they know that, too; two dozen peer-reviewed studies show no connection between lockdown and reducing deaths; he knew from personal friends the elite were still flying around and going on holiday while the public were locked down; the elite were not having the 'vaccines'. He was also asked if 'vaccines' could be made to target difference races. He said he didn't know, but the document by the Project for the New American Century in September, 2000, said developing 'advanced forms of biological warfare that can target *specific genotypes* may transform biological warfare from the realm of terror to a politically useful tool.' Oh, they're evil all right. Of that we can be *absolutely* sure.

Another cull of old people

We have seen from the CDC definition that the mRNA 'Covid vaccine' is not a vaccine and nor are the others that *claim* to reduce 'severity of symptoms' in *some* people, but not protect from infection or transmission. What about all the lies about returning to 'normal' if people were 'vaccinated'? If they are not claimed to stop infection and transmission of the alleged 'virus', how does anything change? This was all lies to manipulate people to take the jabs and we are seeing that now with masks and distancing still required for the 'vaccinated'. How did they think that elderly people with fragile health and immune responses were going to be affected by infusing their cells with synthetic material and other toxic substances? They *knew* that in the short and long term it would be devastating and fatal as the culling of the old that began with the first lockdowns was continued with the 'vaccine'. Death rates in care homes soared immediately residents began to be 'vaccinated' – infused with synthetic material. Brave and committed whistleblower nurses put their careers at risk by exposing this truth while the rest kept their heads down and their mouths shut to put their careers before those they are supposed to care for. A long-time American Certified Nursing Assistant who gave his name as James posted a video in which he described emotionally what happened in his care home when vaccination began. He said that during 2020 very few residents were sick with 'Covid' and no one died during the entire year; but shortly after the Pfizer mRNA injections 14 people died within two weeks and many others were near death. 'They're dropping like flies', he said. Residents who walked on their own before the shot could no longer and they had lost their ability to conduct an intelligent conversation. The home's management said the sudden deaths were caused by a 'super-spreader' of 'Covid-19'. Then how come, James asked, that residents who refused to take the injections were not sick? It was a case of inject the elderly with mRNA synthetic potions and blame their illness and death that followed on the 'virus'. James described what was happening in care homes as 'the greatest crime of genocide this country has ever seen'. Remember the NHS staff nurse from earlier who used the same

word ‘genocide’ for what was happening with the ‘vaccines’ and that it was an ‘act of human annihilation’. A UK care home whistleblower told a similar story to James about the effect of the ‘vaccine’ in deaths and ‘outbreaks’ of illness dubbed ‘Covid’ after getting the jab. She told how her care home management and staff had zealously imposed government regulations and no one was allowed to even question the official narrative let alone speak out against it. She said the NHS was even worse. Again we see the results of reframing. A worker at a local care home where I live said they had not had a single case of ‘Covid’ there for almost a year and when the residents were ‘vaccinated’ they had 19 positive cases in two weeks with eight dying.

It’s not the ‘vaccine’ – honest

The obvious cause and effect was being ignored by the media and most of the public. Australia’s health minister Greg Hunt (a former head of strategy at the World Economic Forum) was admitted to hospital after he had the ‘vaccine’. He was suffering according to reports from the skin infection ‘cellulitis’ and it must have been a severe case to have warranted days in hospital. Immediately the authorities said this was nothing to do with the ‘vaccine’ when an effect of some vaccines is a ‘cellulitis-like reaction’. We had families of perfectly healthy old people who died after the ‘vaccine’ saying that if only they had been given the ‘vaccine’ earlier they would still be alive. As a numbskull rating that is off the chart. A father of four ‘died of Covid’ at aged 48 when he was taken ill two days after having the ‘vaccine’. The man, a health administrator, had been ‘shielding during the pandemic’ and had ‘not really left the house’ until he went for the ‘vaccine’. Having the ‘vaccine’ and then falling ill and dying does not seem to have qualified as a possible cause and effect and ‘Covid-19’ went on his death certificate. His family said they had no idea how he ‘caught the virus’. A family member said: ‘Tragically, it could be that going for a vaccination ultimately led to him catching Covid …The sad truth is that they are never going to know where it came from.’ The family warned people to remember

that the virus still existed and was 'very real'. So was their stupidity. Nurses and doctors who had the first round of the 'vaccine' were collapsing, dying and ending up in a hospital bed while they or their grieving relatives were saying they'd still have the 'vaccine' again despite what happened. I kid you not. You mean if your husband returned from the dead he'd have the same 'vaccine' again that killed him??

Doctors at the VCU Medical Center in Richmond, Virginia, said the Johnson & Johnson 'vaccine' was to blame for a man's skin peeling off. Patient Richard Terrell said: 'It all just happened so fast. My skin peeled off. It's still coming off on my hands now.' He said it was stinging, burning and itching and when he bent his arms and legs it was very painful with 'the skin swollen and rubbing against itself'. Pfizer/BioNTech and Moderna vaccines use mRNA to change the cell while the Johnson & Johnson version uses DNA in a process similar to AstraZeneca's technique. Johnson & Johnson and AstraZeneca have both had their 'vaccines' paused by many countries after causing serious blood problems. Terrell's doctor Fnu Nutan said he could have died if he hadn't got medical attention. It sounds terrible so what did Nutan and Terrell say about the 'vaccine' now? Oh, they still recommend that people have it. A nurse in a hospital bed 40 minutes after the vaccination and unable to swallow due to throat swelling was told by a doctor that he lost mobility in his arm for 36 hours following the vaccination. What did he say to the ailing nurse? 'Good for you for getting the vaccination.' We are dealing with a serious form of cognitive dissonance madness in both public and medical staff. There is a remarkable correlation between those having the 'vaccine' and trumpeting the fact and suffering bad happenings shortly afterwards. Witold Rogiewicz, a Polish doctor, made a video of his 'vaccination' and ridiculed those who were questioning its safety and the intentions of Bill Gates: 'Vaccinate yourself to protect yourself, your loved ones, friends and also patients. And to mention quickly I have info for anti-vaxxers and anti-Coviders if you want to contact Bill Gates you can do this through me.' He further ridiculed the dangers of 5G. Days later he

was dead, but naturally the vaccination wasn't mentioned in the verdict of 'heart attack'.

Lies, lies and more lies

So many members of the human race have slipped into extreme states of insanity and unfortunately they include reframed doctors and nursing staff. Having a 'vaccine' and dying within minutes or hours is not considered a valid connection while death from any cause within 28 days or longer of a positive test with a test not testing for the 'virus' means 'Covid-19' goes on the death certificate. How could that 'vaccine'-death connection not have been made except by calculated deceit? US figures in the initial rollout period to February 12th, 2020, revealed that a third of the deaths reported to the CDC after 'Covid vaccines' happened within 48 hours. Five men in the UK suffered an 'extremely rare' blood clot problem after having the AstraZeneca 'vaccine', but no causal link was established said the Gates-funded Medicines and Healthcare products Regulatory Agency (MHRA) which had given the 'vaccine' emergency approval to be used. Former Pfizer executive Dr Michael Yeadon explained in his interview how the procedures could cause blood coagulation and clots. People who should have been at no risk were dying from blood clots in the brain and he said he had heard from medical doctor friends that people were suffering from skin bleeding and massive headaches. The AstraZeneca 'shot' was stopped by some 20 countries over the blood clotting issue and still the corrupt MHRA, the European Medicines Agency (EMA) and the World Health Organization said that it should continue to be given even though the EMA admitted that it 'still cannot rule out definitively' a link between blood clotting and the 'vaccine'. Later Marco Cavaleri, head of EMA vaccine strategy, said there was indeed a clear link between the 'vaccine' and thrombosis, but they didn't know why. So much for the trials showing the 'vaccine' is safe. Blood clots were affecting younger people who would be under virtually no danger from 'Covid' even if it existed which makes it all the more stupid and sinister.

The British government responded to public alarm by wheeling out June Raine, the terrifyingly weak infant school headmistress sound-alike who heads the UK MHRA drug 'regulator'. The idea that she would stand up to Big Pharma and government pressure is laughable and she told us that all was well in the same way that she did when allowing untested, never-used-on-humans-before, genetically-manipulating 'vaccines' to be exposed to the public in the first place. Mass lying is the new normal of the 'Covid' era. The MHRA later said 30 cases of rare blood clots had by then been connected with the AstraZeneca 'vaccine' (that means a lot more in reality) while stressing that the benefits of the jab in preventing 'Covid-19' outweighed any risks. A more ridiculous and disingenuous statement with callous disregard for human health it is hard to contemplate. Immediately after the mendacious 'all-clears' two hospital workers in Denmark experienced blood clots and cerebral haemorrhaging following the AstraZeneca jab and one died. Top Norwegian health official Pål Andre Holme said the 'vaccine' was the only common factor: 'There is nothing in the patient history of these individuals that can give such a powerful immune response … I am confident that the antibodies that we have found are the cause, and I see no other explanation than it being the vaccine which triggers it.' Strokes, a clot or bleed in the brain, were clearly associated with the 'vaccine' from word of mouth and whistleblower reports. Similar consequences followed with all these 'vaccines' that we were told were so safe and as the numbers grew by the day it was clear we were witnessing human carnage.

Learning the hard way

A woman interviewed by UKColumn told how her husband suffered dramatic health effects after the vaccine when he'd been in good health all his life. He went from being a little unwell to losing all feeling in his legs and experiencing 'excruciating pain'. Misdiagnosis followed twice at Accident and Emergency (an 'allergy' and 'sciatica') before he was admitted to a neurology ward where doctors said his serious condition had been caused by the

'vaccine'. Another seven 'vaccinated' people were apparently being treated on the same ward for similar symptoms. The woman said he had the 'vaccine' because they believed media claims that it was safe. 'I didn't think the government would give out a vaccine that does this to somebody; I believed they would be bringing out a vaccination that would be safe.' What a tragic way to learn that lesson. Another woman posted that her husband was transporting stroke patients to hospital on almost every shift and when he asked them if they had been 'vaccinated' for 'Covid' they all replied 'yes'. One had a 'massive brain bleed' the day after his second dose. She said her husband reported the 'just been vaccinated' information every time to doctors in A and E only for them to ignore it, make no notes and appear annoyed that it was even mentioned. This particular report cannot be verified, but it expresses a common theme that confirms the monumental underreporting of 'vaccine' consequences. Interestingly as the 'vaccines' and their brain blood clot/stroke consequences began to emerge the UK National Health Service began a publicity campaign telling the public what to do in the event of a stroke. A Scottish NHS staff nurse who quit in disgust in March, 2021, said:

I have seen traumatic injuries from the vaccine, they're not getting reported to the yellow card [adverse reaction] scheme, they're treating the symptoms, not asking why, why it's happening. It's just treating the symptoms and when you speak about it you're dismissed like you're crazy, I'm not crazy, I'm not crazy because every other colleague I've spoken to is terrified to speak out, they've had enough.

Videos appeared on the Internet of people uncontrollably shaking after the 'vaccine' with no control over muscles, limbs and even their face. A Scottish mother broke out in a severe rash all over her body almost immediately after she was given the AstraZeneca 'vaccine'. The pictures were horrific. Leigh King, a 41-year-old hairdresser from Lanarkshire said: 'Never in my life was I prepared for what I was about to experience … My skin was so sore and constantly hot … I have never felt pain like this …' But don't you worry, the 'vaccine' is perfectly safe. Then there has been the effect on medical

staff who have been pressured to have the 'vaccine' by psychopathic 'health' authorities and government. A London hospital consultant who gave the name K. Polyakova wrote this to the *British Medical Journal* or *BMJ*:

> I am currently struggling with … the failure to report the reality of the morbidity caused by our current vaccination program within the health service and staff population. The levels of sickness after vaccination is unprecedented and staff are getting very sick and some with neurological symptoms which is having a huge impact on the health service function. Even the young and healthy are off for days, some for weeks, and some requiring medical treatment. Whole teams are being taken out as they went to get vaccinated together.
>
> Mandatory vaccination in this instance is stupid, unethical and irresponsible when it comes to protecting our staff and public health. We are in the voluntary phase of vaccination, and encouraging staff to take an unlicensed product that is impacting on their immediate health … it is clearly stated that these vaccine products do not offer immunity or stop transmission. In which case why are we doing it?

Not to protect health that's for sure. Medical workers are lauded by governments for agenda reasons when they couldn't give a toss about them any more than they can for the population in general. Schools across America faced the same situation as they closed due to the high number of teachers and other staff with bad reactions to the Pfizer/BioNTech, Moderna, and Johnson & Johnson 'Covid vaccines' all of which were linked to death and serious adverse effects. The *BMJ* took down the consultant's comments pretty quickly on the grounds that they were being used to spread 'disinformation'. They were exposing the truth about the 'vaccine' was the real reason. The cover-up is breathtaking.

Hiding the evidence

The scale of the 'vaccine' death cover-up worldwide can be confirmed by comparing official figures with the personal experience of the public. I heard of many people in my community who died immediately or soon after the vaccine that would never appear in the media or even likely on the official totals of 'vaccine' fatalities and adverse reactions when only about ten percent are estimated to be

reported and I have seen some estimates as low as one percent in a Harvard study. In the UK alone by April 29th, 2021, some 757,654 adverse reactions had been officially reported from the Pfizer/BioNTech, Oxford/AstraZeneca and Moderna 'vaccines' with more than a thousand deaths linked to jabs and that means an estimated ten times this number in reality from a ten percent reporting rate percentage. That's seven million adverse reactions and 10,000 potential deaths and a one percent reporting rate would be ten times *those* figures. In 1976 the US government pulled the swine flu vaccine after *53* deaths. The UK data included a combined 10,000 eye disorders from the 'Covid vaccines' with more than 750 suffering visual impairment or blindness and again multiply by the estimated reporting percentages. As 'Covid cases' officially fell hospitals virtually empty during the 'Covid crisis' began to fill up with a range of other problems in the wake of the 'vaccine' rollout. The numbers across America have also been catastrophic. Deaths linked to *all* types of vaccine increased by *6,000 percent* in the first quarter of 2021 compared with 2020. A 39-year-old woman from Ogden, Utah, died four days after receiving a second dose of Moderna's 'Covid vaccine' when her liver, heart and kidneys all failed despite the fact that she had no known medical issues or conditions. Her family sought an autopsy, but Dr Erik Christensen, Utah's chief medical examiner, said proving vaccine injury as a cause of death almost never happened. He could think of only one instance where an autopsy would name a vaccine as the official cause of death and that would be anaphylaxis where someone received a vaccine and died almost instantaneously. 'Short of that, it would be difficult for us to definitively say this is the vaccine,' Christensen said. If that is true this must be added to the estimated ten percent (or far less) reporting rate of vaccine deaths and serious reactions and the conclusion can only be that vaccine deaths and serious reactions – including these 'Covid' potions' – are phenomenally understated in official figures. The same story can be found everywhere. Endless accounts of deaths and serious reactions among the public, medical

and care home staff while official figures did not even begin to reflect this.

Professional script-reader Dr David Williams, a 'top public-health official' in Ontario, Canada, insulted our intelligence by claiming only four serious adverse reactions and no deaths from the more than 380,000 vaccine doses then given. This bore no resemblance to what people knew had happened in their owns circles and we had Dirk Huyer in charge of getting millions vaccinated in Ontario while at the same time he was Chief Coroner for the province investigating causes of death including possible death from the vaccine. An aide said he had stepped back from investigating deaths, but evidence indicated otherwise. Rosemary Frei, who secured a Master of Science degree in molecular biology at the Faculty of Medicine at Canada's University of Calgary before turning to investigative journalism, was one who could see that official figures for 'vaccine' deaths and reactions made no sense. She said that doctors seldom reported adverse events and when people got really sick or died after getting a vaccination they would attribute that to anything except the vaccines. It had been that way for years and anyone who wondered aloud whether the 'Covid vaccines' or other shots cause harm is immediately branded as 'anti-vax' and 'anti-science'. This was 'career-threatening' for health professionals. Then there was the huge pressure to support the push to 'vaccinate' billions in the quickest time possible. Frei said:

> So that's where we're at today. More than half a million vaccine doses have been given to people in Ontario alone. The rush is on to vaccinate all 15 million of us in the province by September. And the mainstream media are screaming for this to be sped up even more. That all adds up to only a very slim likelihood that we're going to be told the truth by officials about how many people are getting sick or dying from the vaccines.

What is true of Ontario is true of everywhere.

They KNEW – and still did it

The authorities knew what was going to happen with multiple deaths and adverse reactions. The UK government's Gates-funded

and Big Pharma-dominated Medicines and Healthcare products Regulatory Agency (MHRA) hired a company to employ AI in compiling the projected reactions to the 'vaccine' that would otherwise be uncountable. The request for applications said: 'The MHRA urgently seeks an Artificial Intelligence (AI) software tool to process the expected high volume of Covid-19 vaccine Adverse Drug Reaction …' This was from the agency, headed by the disingenuous June Raine, that gave the 'vaccines' emergency approval and the company was hired before the first shot was given. 'We are going to kill and maim you – is that okay?' 'Oh, yes, perfectly fine – I'm very grateful, thank you, doctor.' The range of 'Covid vaccine' adverse reactions goes on for page after page in the MHRA criminally underreported 'Yellow Card' system and includes affects to eyes, ears, skin, digestion, blood and so on. Raine's MHRA amazingly claimed that the 'overall safety experience … is so far as expected from the clinical trials'. The death, serious adverse effects, deafness and blindness were *expected?* When did they ever mention that? If these human tragedies were expected then those that gave approval for the use of these 'vaccines' must be guilty of crimes against humanity including murder – a definition of which is 'killing a person with malice aforethought or with recklessness manifesting extreme indifference to the value of human life.' People involved at the MHRA, the CDC in America and their equivalent around the world must go before Nuremberg trials to answer for their callous inhumanity. We are only talking here about the immediate effects of the 'vaccine'. The longer-term impact of the DNA synthetic manipulation is the main reason they are so hysterically desperate to inoculate the entire global population in the shortest possible time.

Africa and the developing world are a major focus for the 'vaccine' depopulation agenda and a mass vaccination sales-pitch is underway thanks to caring people like the Rockefellers and other Cult assets. The Rockefeller Foundation, which pre-empted the 'Covid pandemic' in a document published in 2010 that 'predicted' what happened a decade later, announced an initial $34.95 million grant in February, 2021, 'to ensure more equitable access to Covid-19

testing and vaccines' among other things in Africa in collaboration with '24 organizations, businesses, and government agencies'. The pan-Africa initiative would focus on 10 countries: Burkina Faso, Ethiopia, Ghana, Kenya, Nigeria, Rwanda, South Africa, Tanzania, Uganda, and Zambia'. Rajiv Shah, President of the Rockefeller Foundation and former administrator of CIA-controlled USAID, said that if Africa was not mass-vaccinated (to change the DNA of its people) it was a 'threat to all of humanity' and not fair on Africans. When someone from the Rockefeller Foundation says they want to do something to help poor and deprived people and countries it is time for a belly-laugh. They are doing this out of the goodness of their 'heart' because 'vaccinating' the entire global population is what the 'Covid' hoax set out to achieve. Official 'decolonisation' of Africa by the Cult was merely a prelude to financial colonisation on the road to a return to physical colonisation. The 'vaccine' is vital to that and the sudden and convenient death of the 'Covid' sceptic president of Tanzania can be seen in its true light. A lot of people in Africa are aware that this is another form of colonisation and exploitation and they need to stand their ground.

The 'vaccine is working' scam

A potential problem for the Cult was that the 'vaccine' is meant to change human DNA and body messaging and not to protect anyone from a 'virus' never shown to exist. The vaccine couldn't work because it was not designed to work and how could they make it *appear* to be working so that more people would have it? This was overcome by lowering the amplification rate of the PCR test to produce fewer 'cases' and therefore fewer 'deaths'. Some of us had been pointing out since March, 2020, that the amplification rate of the test not testing for the 'virus' had been made artificially high to generate positive tests which they could call 'cases' to justify lockdowns. The World Health Organization recommended an absurdly high 45 amplification cycles to ensure the high positives required by the Cult and then remained silent on the issue until January 20th, 2021 – Biden's Inauguration Day. This was when the

'vaccinations' were seriously underway and on that day the WHO recommended after discussions with America's CDC that laboratories *lowered their testing amplification*. Dr David Samadi, a certified urologist and health writer, said the WHO was encouraging all labs to reduce their cycle count for PCR tests. He said the current cycle was much too high and was 'resulting in any particle being declared a positive case'. Even one mainstream news report I saw said this meant the number of 'Covid' infections may have been 'dramatically inflated'. Oh, just a little bit. The CDC in America issued new guidance to laboratories in April, 2021, to use 28 cycles *but only for 'vaccinated' people*. The timing of the CDC/WHO interventions were cynically designed to make it appear the 'vaccines' were responsible for falling cases and deaths when the real reason can be seen in the following examples. New York's state lab, the Wadsworth Center, identified 872 positive tests in July, 2020, based on a threshold of 40 cycles. When the figure was lowered to 35 cycles *43 percent* of the 872 were no longer 'positives'. At 30 cycles the figure was 63 percent. A Massachusetts lab found that between *85 to 90 percent* of people who tested positive in July with a cycle threshold of 40 would be negative at 30 cycles, Ashish Jha, MD, director of the Harvard Global Health Institute, said: 'I'm really shocked that it could be that high … Boy, does it really change the way we need to be thinking about testing.' I'm shocked that I could see the obvious in the spring of 2020, with no medical background, and most medical professionals still haven't worked it out. No, that's not shocking – it's terrifying.

Three weeks after the WHO directive to lower PCR cycles the London *Daily Mail* ran this headline: 'Why ARE Covid cases plummeting? New infections have fallen 45% in the US and 30% globally in the past 3 weeks but experts say vaccine is NOT the main driver because only 8% of Americans and 13% of people worldwide have received their first dose.' They acknowledged that the drop could not be attributed to the 'vaccine', but soon this morphed throughout the media into the 'vaccine' has caused cases and deaths to fall when it was the PCR threshold. In December, 2020, there was

chaos at English Channel ports with truck drivers needing negative 'Covid' tests before they could board a ferry home for Christmas. The government wanted to remove the backlog as fast as possible and they brought in troops to do the 'testing'. Out of 1,600 drivers just *36* tested positive and the rest were given the all clear to cross the Channel. I guess the authorities thought that 36 was the least they could get away with without the unquestioning catching on. The amplification trick which most people believed in the absence of information in the mainstream applied more pressure on those refusing the 'vaccine' to succumb when it 'obviously worked'. The truth was the exact opposite with deaths in care homes soaring with the 'vaccine' and in Israel the term used was 'skyrocket'. A re-analysis of published data from the Israeli Health Ministry led by Dr Hervé Seligmann at the Medicine Emerging Infectious and Tropical Diseases at Aix-Marseille University found that Pfizer's 'Covid vaccine' killed 'about 40 times more [elderly] people than the disease itself would have killed' during a five-week vaccination period and *260 times* more younger people than would have died from the 'virus' even according to the manipulated 'virus' figures. Dr Seligmann and his co-study author, Haim Yativ, declared after reviewing the Israeli 'vaccine' death data: 'This is a new Holocaust.'

Then, in mid-April, 2021, after vast numbers of people worldwide had been 'vaccinated', the story changed with clear coordination. The UK government began to prepare the ground for more future lockdowns when Nuremberg-destined Boris Johnson told yet another whopper. He said that cases had fallen because of *lockdowns* not 'vaccines'. Lockdowns are irrelevant when *there is no 'virus'* and the test and fraudulent death certificates are deciding the number of 'cases' and 'deaths'. Study after study has shown that lockdowns don't work and instead kill and psychologically destroy people. Meanwhile in the United States Anthony Fauci and Rochelle Walensky, the ultra-Zionist head of the CDC, peddled the same line. More lockdown was the answer and not the 'vaccine', a line repeated on cue by the moron that is Canadian Prime Minister Justin Trudeau. Why all the hysteria to get everyone 'vaccinated' if lockdowns and

not 'vaccines' made the difference? None of it makes sense on the face of it. Oh, but it does. The Cult wants lockdowns *and* the 'vaccine' and if the 'vaccine' is allowed to be seen as the total answer lockdowns would no longer be justified when there are still livelihoods to destroy. 'Variants' and renewed upward manipulation of PCR amplification are planned to instigate never-ending lockdown *and* more 'vaccines'.

You *must* have it – we're desperate

Israel, where the Jewish and Arab population are ruled by the Sabbatian Cult, was the front-runner in imposing the DNA-manipulating 'vaccine' on its people to such an extent that Jewish refusers began to liken what was happening to the early years of Nazi Germany. This would seem to be a fantastic claim. Why would a government of Jewish people be acting like the Nazis did? If you realise that the Sabbatian Cult was behind the Nazis and that Sabbatians hate Jews the pieces start to fit and the question of why a 'Jewish' government would treat Jews with such callous disregard for their lives and freedom finds an answer. Those controlling the government of Israel *aren't Jewish* – they're Sabbatian. Israeli lawyer Tamir Turgal was one who made the Nazi comparison in comments to German lawyer Reiner Fuellmich who is leading a class action lawsuit against the psychopaths for crimes against humanity. Turgal described how the Israeli government was vaccinating children and pregnant women on the basis that there was no evidence that this was dangerous when they had no evidence that it *wasn't* dangerous either. They just had no evidence. This was medical experimentation and Turgal said this breached the Nuremberg Code about medical experimentation and procedures requiring informed consent and choice. Think about that. A Nuremberg Code developed because of Nazi experimentation on Jews and others in concentration camps by people like the evil-beyond-belief Josef Mengele is being breached by the *Israeli* government; but when you know that it's a *Sabbatian* government along with its intelligence and military agencies like Mossad, Shin Bet and the Israeli Defense Forces, and that Sabbatians

were the force behind the Nazis, the kaleidoscope comes into focus. What have we come to when Israeli Jews are suing their government for violating the Nuremberg Code by essentially making Israelis subject to a medical experiment using the controversial 'vaccines'? It's a shocker that this has to be done in the light of what happened in Nazi Germany. The Anshe Ha-Emet, or 'People of the Truth', made up of Israeli doctors, lawyers, campaigners and public, have launched a lawsuit with the International Criminal Court. It says:

> When the heads of the Ministry of Health as well as the prime minister presented the vaccine in Israel and began the vaccination of Israeli residents, the vaccinated were not advised, that, in practice, they are taking part in a medical experiment and that their consent is required for this under the Nuremberg Code.

The irony is unbelievable, but easily explained in one word: Sabbatians. The foundation of Israeli 'Covid' apartheid is the 'green pass' or 'green passport' which allows Jews and Arabs who have had the DNA-manipulating 'vaccine' to go about their lives – to work, fly, travel in general, go to shopping malls, bars, restaurants, hotels, concerts, gyms, swimming pools, theatres and sports venues, while non-'vaccinated' are banned from all those places and activities. Israelis have likened the 'green pass' to the yellow stars that Jews in Nazi Germany were forced to wear – the same as the yellow stickers that a branch of UK supermarket chain Morrisons told exempt mask-wears they had to display when shopping. How very sensitive. The Israeli system is blatant South African-style apartheid on the basis of compliance or non-compliance to fascism rather than colour of the skin. How appropriate that the Sabbatian Israeli government was so close to the pre-Mandela apartheid regime in Pretoria. The Sabbatian-instigated 'vaccine passport' in Israel is planned for everywhere. Sabbatians struck a deal with Pfizer that allowed them to lead the way in the percentage of a national population infused with synthetic material and the result was catastrophic. Israeli freedom activist Shai Dannon told me how chairs were appearing on beaches that said 'vaccinated only'. Health Minister Yuli Edelstein said that anyone unwilling or unable to get

the jabs that 'confer immunity' will be 'left behind'. The man's a liar. Not even the makers claim the 'vaccines' confer immunity. When you see those figures of 'vaccine' deaths these psychopaths were saying that you must take the chance the 'vaccine' will kill you or maim you while knowing it will change your DNA or lockdown for you will be permanent. That's fascism. The Israeli parliament passed a law to allow personal information of the non-vaccinated to be shared with local and national authorities for three months. This was claimed by its supporters to be a way to 'encourage' people to be vaccinated. Hadas Ziv from Physicians for Human Rights described this as a 'draconian law which crushed medical ethics and the patient rights'. But that's the idea, the Sabbatians would reply.

Your papers, please

Sabbatian Israel was leading what has been planned all along to be a global 'vaccine pass' called a 'green passport' without which you would remain in permanent lockdown restriction and unable to do anything. This is how badly – *desperately* – the Cult is to get everyone 'vaccinated'. The term and colour 'green' was not by chance and related to the psychology of fusing the perception of the green climate hoax with the 'Covid' hoax and how the 'solution' to both is the same Great Reset. Lying politicians, health officials and psychologists denied there were any plans for mandatory vaccinations or restrictions based on vaccinations, but they knew that was exactly what was meant to happen with governments of all countries reaching agreements to enforce a global system. 'Free' Denmark and 'free' Sweden unveiled digital vaccine certification. Cyprus, Czech Republic, Estonia, Greece, Hungary, Iceland, Italy, Poland, Portugal, Slovakia, and Spain have all committed to a vaccine passport system and the rest including the whole of the EU would follow. The satanic UK government will certainly go this way despite mendacious denials and at the time of writing it is trying to manipulate the public into having the 'vaccine' so they could go abroad on a summer holiday. How would that work without something to prove you had the synthetic toxicity injected into you?

Documents show that the EU's European Commission was moving towards 'vaccine certificates' in 2018 and 2019 before the 'Covid' hoax began. They knew what was coming. Abracadabra – Ursula von der Leyen, the German President of the Commission, announced in March, 2021, an EU 'Digital Green Certificate' – green again – to track the public's 'Covid status'. The passport sting is worldwide and the Far East followed the same pattern with South Korea ruling that only those with 'vaccination' passports – again the *green* pass – would be able to 'return to their daily lives'.

Bill Gates has been preparing for this 'passport' with other Cult operatives for years and beyond the paper version is a Gates-funded 'digital tattoo' to identify who has been vaccinated and who hasn't. The 'tattoo' is reported to include a substance which is externally readable to confirm who has been vaccinated. This is a bio-luminous light-generating enzyme (think fireflies) called … *Luciferase*. Yes, named after the Cult 'god' Lucifer the 'light bringer' of whom more to come. Gates said he funded the readable tattoo to ensure children in the developing world were vaccinated and no one was missed out. He cares so much about poor kids as we know. This was just the cover story to develop a vaccine tagging system for everyone on the planet. Gates has been funding the ID2020 'alliance' to do just that in league with other lovely people at Microsoft, GAVI, the Rockefeller Foundation, Accenture and IDEO.org. He said in interviews in March, 2020, before any 'vaccine' publicly existed, that the world must have a globalised digital certificate to track the 'virus' and who had been vaccinated. Gates knew from the start that the mRNA vaccines were coming and when they would come and that the plan was to tag the 'vaccinated' to marginalise the intelligent and stop them doing anything including travel. Evil just doesn't suffice. Gates was exposed for offering a $10 million bribe to the Nigerian House of Representatives to invoke compulsory 'Covid' vaccination of all Nigerians. Sara Cunial, a member of the Italian Parliament, called Gates a 'vaccine criminal'. She urged the Italian President to hand him over to the International Criminal Court for crimes against

humanity and condemned his plans to 'chip the human race' through ID2020.

You know it's a long-planned agenda when war criminal and Cult gofer Tony Blair is on the case. With the scale of arrogance only someone as dark as Blair can muster he said: 'Vaccination in the end is going to be your route to liberty.' Blair is a disgusting piece of work and he confirms that again. The media has given a lot of coverage to a bloke called Charlie Mullins, founder of London's biggest independent plumbing company, Pimlico Plumbers, who has said he won't employ anyone who has not been vaccinated or have them go to any home where people are not vaccinated. He said that if he had his way no one would be allowed to walk the streets if they have not been vaccinated. Gates was cheering at the time while I was alerting the white coats. The plan is that people will qualify for 'passports' for having the first two doses and then to keep it they will have to have all the follow ups and new ones for invented 'variants' until human genetics is transformed and many are dead who can't adjust to the changes. Hollywood celebrities – the usual propaganda stunt – are promoting something called the WELL Health-Safety Rating to verify that a building or space has 'taken the necessary steps to prioritize the health and safety of their staff, visitors and other stakeholders'. They included Lady Gaga, Jennifer Lopez, Michael B. Jordan, Robert DeNiro, Venus Williams, Wolfgang Puck, Deepak Chopra and 17th Surgeon General Richard Carmona. Yawn. WELL Health-Safety has big connections with China. Parent company Delos is headed by former Goldman Sachs partner Paul Scialla. This is another example – and we will see so many others – of using the excuse of 'health' to dictate the lives and activities of the population. I guess one confirmation of the 'safety' of buildings is that only 'vaccinated' people can go in, right?

Electronic concentration camps

I wrote decades ago about the plans to restrict travel and here we are for those who refuse to bow to tyranny. This can be achieved in one go with air travel if the aviation industry makes a blanket decree.

The ‘vaccine’ and guaranteed income are designed to be part of a global version of China’s social credit system which tracks behaviour 24/7 and awards or deletes ‘credits’ based on whether your behaviour is supported by the state or not. I mean your entire lifestyle – what you do, eat, say, everything. Once your credit score falls below a certain level consequences kick in. In China tens of millions have been denied travel by air and train because of this. All the locations and activities denied to refusers by the ‘vaccine’ passports will be included in one big mass ban on doing almost anything for those that don’t bow their head to government. It’s beyond fascist and a new term is required to describe its extremes – I guess fascist technocracy will have to do. The way the Chinese system of technological – technocratic – control is sweeping the West can be seen in the Los Angeles school system and is planned to be expanded worldwide. Every child is required to have a ‘Covid’-tracking app scanned daily before they can enter the classroom. The so-called Daily Pass tracking system is produced by Gates’ Microsoft which I’m sure will shock you rigid. The pass will be scanned using a barcode (one step from an inside-the-body barcode) and the information will include health checks, ‘Covid’ tests and vaccinations. Entry codes are for one specific building only and access will only be allowed if a student or teacher has a negative test with a test not testing for the ‘virus’, has no symptoms of anything alleged to be related to ‘Covid’ (symptoms from a range of other illness), and has a temperature under 100 degrees. No barcode, no entry, is planned to be the case for everywhere and not only schools.

Kids are being psychologically prepared to accept this as ‘normal’ their whole life which is why what they can impose in schools is so important to the Cult and its gofers. Long-time American freedom campaigner John Whitehead of the Rutherford Institute was not exaggerating when he said: ‘Databit by databit, we are building our own electronic concentration camps.’ Canada under its Cult gofer prime minister Justin Trudeau has taken a major step towards the real thing with people interned against their will if they test positive with a test not testing for the ‘virus’ when they arrive at a Canadian

airport. They are jailed in internment hotels often without food or water for long periods and with many doors failing to lock there have been sexual assaults. The interned are being charged sometimes $2,000 for the privilege of being abused in this way. Trudeau is fully on board with the Cult and says the 'Covid pandemic' has provided an opportunity for a global 'reset' to permanently change Western civilisation. His number two, Deputy Prime Minister Chrystia Freeland, is a trustee of the World Economic Forum and a Rhodes Scholar. The Trudeau family have long been servants of the Cult. See *The Biggest Secret* and Cathy O'Brien's book *Trance-Formation of America* for the horrific background to Trudeau's father Pierre Trudeau another Canadian prime minister. Hide your fascism behind the façade of a heart-on-the-sleeve liberal. It's a well-honed Cult technique.

What can the 'vaccine' *really* do?

We have a 'virus' never shown to exist and 'variants' of the 'virus' that have also never been shown to exist except, like the 'original', as computer-generated fictions. Even if you believe there's a 'virus' the 'case' to 'death' rate is in the region of 0.23 to 0.15 percent and those 'deaths' are concentrated among the very old around the same average age that people die anyway. In response to this lack of threat (in truth none) psychopaths and idiots, knowingly and unknowingly answering to Gates and the Cult, are seeking to 'vaccinate' every man, woman and child on Planet Earth. Clearly the 'vaccine' is not about 'Covid' – none of this ever has been. So what is it all about *really*? Why the desperation to infuse genetically-manipulating synthetic material into everyone through mRNA fraudulent 'vaccines' with the intent of doing this over and over with the excuses of 'variants' and other 'virus' inventions? Dr Sherri Tenpenny, an osteopathic medical doctor in the United States, has made herself an expert on vaccines and their effects as a vehement campaigner against their use. Tenpenny was board certified in emergency medicine, the director of a level two trauma centre for 12 years, and moved to Cleveland in 1996 to start an integrative

medicine practice which has treated patients from all 50 states and some 17 other countries. Weaning people off pharmaceutical drugs is a speciality.

She became interested in the consequences of vaccines after attending a meeting at the National Vaccine Information Center in Washington DC in 2000 where she 'sat through four days of listening to medical doctors and scientists and lawyers and parents of vaccine injured kids' and asked: 'What's going on?' She had never been vaccinated and never got ill while her father was given a list of vaccines to be in the military and was 'sick his entire life'. The experience added to her questions and she began to examine vaccine documents from the Centers for Disease Control (CDC). After reading the first one, the 1998 version of *The General Recommendations of Vaccination*, she thought: 'This is it?' The document was poorly written and bad science and Tenpenny began 20 years of research into vaccines that continues to this day. She began her research into 'Covid vaccines' in March, 2020, and she describes them as 'deadly'. For many, as we have seen, they already have been. Tenpenny said that in the first 30 days of the 'vaccine' rollout in the United States there had been more than 40,000 adverse events reported to the vaccine adverse event database. A document had been delivered to her the day before that was 172 pages long. 'We have over 40,000 adverse events; we have over 3,100 cases of [potentially deadly] anaphylactic shock; we have over 5,000 neurological reactions.' Effects ranged from headaches to numbness, dizziness and vertigo, to losing feeling in hands or feet and paraesthesia which is when limbs 'fall asleep' and people have the sensation of insects crawling underneath their skin. All this happened in the first 30 days and remember that only about *ten percent* (or far less) of adverse reactions and vaccine-related deaths are estimated to be officially reported. Tenpenny said:

> So can you think of one single product in any industry, any industry, for as long as products have been made on the planet that within 30 days we have 40,000 people complaining of side effects that not only is still on the market but … we've got paid actors telling us how great

they are for getting their vaccine. We're offering people $500 if they will just get their vaccine and we've got nurses and doctors going; 'I got the vaccine, I got the vaccine'.

Tenpenny said they were not going to be 'happy dancing folks' when they began to suffer Bell's palsy (facial paralysis), neuropathies, cardiac arrhythmias and autoimmune reactions that kill through a blood disorder. 'They're not going to be so happy, happy then, but we're never going to see pictures of those people' she said. Tenpenny described the 'vaccine' as 'a well-designed killing tool'.

No off-switch

Bad as the initial consequences had been Tenpenny said it would be maybe 14 months before we began to see the 'full ravage' of what is going to happen to the 'Covid vaccinated' with full-out consequences taking anything between two years and 20 years to show. You can understand why when you consider that variations of the 'Covid vaccine' use mRNA (messenger RNA) to in theory activate the immune system to produce protective antibodies without using the actual 'virus'. How can they when it's a computer program and they've never isolated what they claim is the 'real thing'? Instead they use *synthetic* mRNA. They are inoculating synthetic material into the body which through a technique known as the Trojan horse is absorbed into cells to change the nature of DNA. Human DNA is changed by an infusion of messenger RNA and with each new 'vaccine' of this type it is changed even more. Say so and you are banned by Cult Internet platforms. The contempt the contemptuous Mark Zuckerberg has for the truth and human health can be seen in an internal Facebook video leaked to the Project Veritas investigative team in which he said of the 'Covid vaccines': '… I share some caution on this because we just don't know the long term side-effects of basically modifying people's DNA and RNA.' At the same time this disgusting man's Facebook was censoring and banning anyone saying exactly the same. He must go before a Nuremberg trial for crimes against humanity when he *knows* that he

is censoring legitimate concerns and denying the right of informed consent on behalf of the Cult that owns him. People have been killed and damaged by the very 'vaccination' technique he cast doubt on himself when they may not have had the 'vaccine' with access to information that he denied them. The plan is to have at least annual 'Covid vaccinations', add others to deal with invented 'variants', and change all other vaccines into the mRNA system. Pfizer executives told shareholders at a virtual Barclays Global Healthcare Conference in March, 2021, that the public may need a third dose of 'Covid vaccine', plus regular yearly boosters and the company planned to hike prices to milk the profits in a 'significant opportunity for our vaccine'. These are the professional liars, cheats and opportunists who are telling you their 'vaccine' is safe. Given this volume of mRNA planned to be infused into the human body and its ability to then replicate we will have a transformation of human genetics from biological to synthetic biological – exactly the long-time Cult plan for reasons we'll see – and many will die. Sherri Tenpenny said of this replication:

> It's like having an on-button but no off-button and that whole mechanism … they actually give it a name and they call it the Trojan horse mechanism, because it allows that [synthetic] virus and that piece of that [synthetic] virus to get inside of your cells, start to replicate and even get inserted into other parts of your DNA as a Trojan-horse.

Ask the overwhelming majority of people who have the 'vaccine' what they know about the contents and what they do and they would reply: 'The government says it will stop me getting the virus.' Governments give that false impression on purpose to increase take-up. You can read Sherri Tenpenny's detailed analysis of the health consequences in her blog at Vaxxter.com, but in summary these are some of them. She highlights the statement by Bill Gates about how human beings can become their own 'vaccine manufacturing machine'. The man is insane. ['Vaccine'-generated] 'antibodies' carry synthetic messenger RNA into the cells and the damage starts, Tenpenny contends, and she says that lungs can be adversely affected through varying degrees of pus and bleeding which

obviously affects breathing and would be dubbed 'Covid-19'. Even more sinister was the impact of 'antibodies' on macrophages, a white blood cell of the immune system. They consist of Type 1 and Type 2 which have very different functions. She said Type 1 are 'hyper-vigilant' white blood cells which 'gobble up' bacteria etc. However, in doing so, this could cause inflammation and in extreme circumstances be fatal. She says these affects are mitigated by Type 2 macrophages which kick in to calm down the system and stop it going rogue. They clear up dead tissue debris and reduce inflammation that the Type 1 'fire crews' have caused. Type 1 kills the infection and Type 2 heals the damage, she says. This is her punchline with regard to 'Covid vaccinations': She says that mRNA 'antibodies' block Type 2 macrophages by attaching to them and deactivating them. This meant that when the Type 1 response was triggered by infection there was nothing to stop that getting out of hand by calming everything down. There's an on-switch, but no off-switch, she says. What follows can be 'over and out, see you when I see you'.

Genetic suicide

Tenpenny also highlights the potential for autoimmune disease – the body attacking itself – which has been associated with vaccines since they first appeared. Infusing a synthetic foreign substance into cells could cause the immune system to react in a panic believing that the body is being overwhelmed by an invader (it is) and the consequences can again be fatal. There is an autoimmune response known as a 'cytokine storm' which I have likened to a homeowner panicked by an intruder and picking up a gun to shoot randomly in all directions before turning the fire on himself. The immune system unleashes a storm of inflammatory response called cytokines to a threat and the body commits hara-kiri. The lesson is that you mess with the body's immune response at your peril and these 'vaccines' seriously – fundamentally – mess with immune response. Tenpenny refers to a consequence called anaphylactic shock which is a severe and highly dangerous allergic reaction when the immune system

floods the body with chemicals. She gives the example of having a bee sting which primes the immune system and makes it sensitive to those chemicals. When people are stung again maybe years later the immune response can be so powerful that it leads to anaphylactic shock. Tenpenny relates this 'shock' with regard to the 'Covid vaccine' to something called polyethylene glycol or PEG. Enormous numbers of people have become sensitive to this over decades of use in a whole range of products and processes including food, drink, skin creams and 'medicine'. Studies have claimed that some 72 percent of people have antibodies triggered by PEG compared with two percent in the 1960s and allergic hypersensitive reactions to this become a gathering cause for concern. Tenpenny points out that the 'mRNA vaccine' is coated in a 'bubble' of polyethylene glycol which has the potential to cause anaphylactic shock through immune sensitivity. Many reports have appeared of people reacting this way after having the 'Covid vaccine'. What do we think is going to happen as humanity has more and more of these 'vaccines'? Tenpenny said: 'All these pictures we have seen with people with these rashes … these weepy rashes, big reactions on their arms and things like that – it's an acute allergic reaction most likely to the polyethylene glycol that you've been previously primed and sensitised to.'

Those who have not studied the conspiracy and its perpetrators at length might think that making the population sensitive to PEG and then putting it in these 'vaccines' is just a coincidence. It is not. It is instead testament to how carefully and coldly-planned current events have been and the scale of the conspiracy we are dealing with. Tenpenny further explains that the 'vaccine' mRNA procedure can breach the blood-brain barrier which protects the brain from toxins and other crap that will cause malfunction. In this case they could make two proteins corrupt brain function to cause Amyotrophic lateral sclerosis (ALS) , a progressive nervous system disease leading to loss of muscle control, and frontal lobe degeneration – Alzheimer's and dementia. Immunologist J. Bart Classon published a paper connecting mRNA 'vaccines' to prion

disease which can lead to Alzheimer's and other forms of neurogenerative disease while others have pointed out the potential to affect the placenta in ways that make women infertile. This will become highly significant in the next chapter when I will discuss other aspects of this non-vaccine that relate to its nanotechnology and transmission from the injected to the uninjected.

Qualified in idiocy

Tenpenny describes how research has confirmed that these 'vaccine'-generated antibodies can interact with a range of other tissues in the body and attack many other organs including the lungs. 'This means that if you have a hundred people standing in front of you that all got this shot they could have a hundred different symptoms.' Anyone really think that Cult gofers like the Queen, Tony Blair, Christopher Whitty, Anthony Fauci, and all the other psychopaths have really had this 'vaccine' in the pictures we've seen? Not a bloody chance. Why don't doctors all tell us about all these dangers and consequences of the 'Covid vaccine'? Why instead do they encourage and pressure patients to have the shot? Don't let's think for a moment that doctors and medical staff can't be stupid, lazy, and psychopathic and that's without the financial incentives to give the jab. Tenpenny again:

> Some people are going to die from the vaccine directly but a large number of people are going to start to get horribly sick and get all kinds of autoimmune diseases 42 days to maybe a year out. What are they going to do, these stupid doctors who say; 'Good for you for getting that vaccine.' What are they going to say; 'Oh, it must be a mutant, we need to give an extra dose of that vaccine.'
>
> Because now the vaccine, instead of one dose or two doses we need three or four because the stupid physicians aren't taking the time to learn anything about it. If I can learn this sitting in my living room reading a 19 page paper and several others so can they. There's nothing special about me, I just take the time to do it.

Remember how Sara Kayat, the NHS and TV doctor, said that the 'Covid vaccine' would '100 percent prevent hospitalisation and death'. Doctors can be idiots like every other profession and they

should not be worshipped as infallible. They are not and far from it. Behind many medical and scientific 'experts' lies an uninformed prat trying to hide themselves from you although in the 'Covid' era many have failed to do so as with UK narrative-repeating 'TV doctor' Hilary Jones. Pushing back against the minority of proper doctors and scientists speaking out against the 'vaccine' has been the entire edifice of the Cult global state in the form of governments, medical systems, corporations, mainstream media, Silicon Valley, and an army of compliant doctors, medical staff and scientists willing to say anything for money and to enhance their careers by promoting the party line. If you do that you are an 'expert' and if you won't you are an 'anti-vaxxer' and 'Covidiot'. The pressure to be 'vaccinated' is incessant. We have even had reports claiming that the 'vaccine' can help cure cancer and Alzheimer's and make the lame walk. I am waiting for the announcement that it can bring you coffee in the morning and cook your tea. Just as the symptoms of 'Covid' seem to increase by the week so have the miracles of the 'vaccine'. American supermarket giant Kroger Co. offered nearly 500,000 employees in 35 states a $100 bonus for having the 'vaccine' while donut chain Krispy Kreme promised 'vaccinated' customers a free glazed donut every day for the rest of 2021. Have your DNA changed and you will get a doughnut although we might not have to give you them for long. Such offers and incentives confirm the desperation.

Perhaps the worse vaccine-stunt of them all was UK 'Health' Secretary Matt-the-prat Hancock on live TV after watching a clip of someone being 'vaccinated' when the roll-out began. Hancock faked tears so badly it was embarrassing. Brain-of-Britain Piers Morgan, the lockdown-supporting, 'vaccine' supporting, 'vaccine' passport-supporting, TV host played along with Hancock – 'You're quite emotional about that' he said in response to acting so atrocious it would have been called out at a school nativity which will presumably today include Mary and Jesus in masks, wise men keeping their camels six feet apart, and shepherds under tent arrest. System-serving Morgan tweeted this: 'Love the idea of covid vaccine passports for everywhere: flights, restaurants, clubs, football, gyms,

shops etc. It's time covid-denying, anti-vaxxer loonies had their bullsh*t bluff called & bar themselves from going anywhere that responsible citizens go.' If only I could aspire to his genius. To think that Morgan, who specialises in shouting over anyone he disagrees with, was lauded as a free speech hero when he lost his job after storming off the set of his live show like a child throwing his dolly out of the pram. If he is a free speech hero we are in real trouble. I have no idea what 'bullsh*t' means, by the way, the * throws me completely.

The Cult is desperate to infuse its synthetic DNA-changing concoction into everyone and has been using every lie, trick and intimidation to do so. The question of '*Why*?' we shall now address.

CHAPTER TEN

Human 2.0

I believe that at the end of the century the use of words and general educated opinion will have altered so much that one will be able to speak of machines thinking without expecting to be contradicted –
Alan Turing (1912-1954), the 'Father of artificial intelligence'

I have been exposing for decades the plan to transform the human body from a biological to a synthetic-biological state. The new human that I will call Human 2.0 is planned to be connected to artificial intelligence and a global AI 'Smart Grid' that would operate as one global system in which AI would control everything from your fridge to your heating system to your car to your mind. Humans would no longer be 'human', but post-human and sub-human, with their thinking and emotional processes replaced by AI.

What I said sounded crazy and beyond science fiction and I could understand that. To any balanced, rational, mind it *is* crazy. Today, however, that world is becoming reality and it puts the 'Covid vaccine' into its true context. Ray Kurzweil is the ultra-Zionist 'computer scientist, inventor and futurist' and co-founder of the Singularity University. Singularity refers to the merging of humans with machines or 'transhumanism'. Kurzweil has said humanity would be connected to the cyber 'cloud' in the period of the ever-recurring year of 2030:

Our thinking … will be a hybrid of biological and non-biological thinking … humans will be able to extend their limitations and 'think in the cloud' … We're going to put gateways to the

cloud in our brains ... We're going to gradually merge and enhance ourselves ... In my view, that's the nature of being human – we transcend our limitations. As the technology becomes vastly superior to what we are then the small proportion that is still human gets smaller and smaller and smaller until it's just utterly negligible.

They are trying to sell this end-of-humanity-as-we-know-it as the next stage of 'evolution' when we become super-human and 'like the gods'. They are lying to you. Shocked, eh? The population, and again especially the young, have been manipulated into addiction to technologies designed to enslave them for life. First they induced an addiction to smartphones (holdables); next they moved to technology on the body (wearables); and then began the invasion of the body (implantables). I warned way back about the plan for microchipped people and we are now entering that era. We should not be diverted into thinking that this refers only to chips we can see. Most important are the nanochips known as smart dust, neural dust and nanobots which are far too small to be seen by the human eye. Nanotechnology is everywhere, increasingly in food products, and released into the atmosphere by the geoengineering of the skies funded by Bill Gates to 'shut out the Sun' and 'save the planet from global warming'. Gates has been funding a project to spray millions of tonnes of chalk (calcium carbonate) into the stratosphere over Sweden to 'dim the Sun' and cool the Earth. Scientists warned the move could be disastrous for weather systems in ways no one can predict and opposition led to the Swedish space agency announcing that the 'experiment' would not be happening as planned in the summer of 2021; but it shows where the Cult is going with dimming the impact of the Sun and there's an associated plan to change the planet's atmosphere. Who gives psychopath Gates the right to dictate to the entire human race and dismantle planetary systems? The world will not be safe while this man is at large.

The global warming hoax has made the Sun, like the gas of life, something to fear when both are essential to good health and human survival (more inversion). The body transforms sunlight into vital vitamin D through a process involving … *cholesterol*. This is the cholesterol we are also told to fear. We are urged to take Big Pharma

statin drugs to reduce cholesterol and it's all systematic. Reducing cholesterol means reducing vitamin D uptake with all the multiple health problems that will cause. At least if you take statins long term it saves the government from having to pay you a pension. The delivery system to block sunlight is widely referred to as chemtrails although these have a much deeper agenda, too. They appear at first to be contrails or condensation trails streaming from aircraft into cold air at high altitudes. Contrails disperse very quickly while chemtrails do not and spread out across the sky before eventually their content falls to earth. Many times I have watched aircraft cross-cross a clear blue sky releasing chemtrails until it looks like a cloudy day. Chemtrails contain many things harmful to humans and the natural world including toxic heavy metals, aluminium (see Alzheimer's) and nanotechnology. Ray Kurzweil reveals the reason without actually saying so: 'Nanobots will infuse all the matter around us with information. Rocks, trees, everything will become these intelligent creatures.' How do you deliver that? *From the sky*. Self-replicating nanobots would connect everything to the Smart Grid. The phenomenon of Morgellons disease began in the chemtrail era and the correlation has led to it being dubbed the 'chemtrail disease'. Self-replicating fibres appear in the body that can be pulled out through the skin. Morgellons fibres continue to grow outside the body and have a form of artificial intelligence. I cover this at greater length in *Phantom Self*.

'Vaccine' operating system

'Covid vaccines' with their self-replicating synthetic material are also designed to make the connection between humanity and Kurzweil's 'cloud'. American doctor and dedicated campaigner for truth, Carrie Madej, an Internal Medicine Specialist in Georgia with more than 20 years medical experience, has highlighted the nanotechnology aspect of the fake 'vaccines'. She explains how one of the components in at least the Moderna and Pfizer synthetic potions are 'lipid nanoparticles' which are 'like little tiny computer bits' – a 'sci-fi substance' known as nanobots and hydrogel which can be 'triggered

at any moment to deliver its payload' and act as 'biosensors'. The synthetic substance had 'the ability to accumulate data from your body like your breathing, your respiration, thoughts and emotions, all kind of things' and each syringe could carry a *million* nanobots:

This substance because it's like little bits of computers in your body, crazy, but it's true, it can do that, [and] obviously has the ability to act through Wi-Fi. It can receive and transmit energy, messages, frequencies or impulses. That issue has never been addressed by these companies. What does that do to the human?

Just imagine getting this substance in you and it can react to things all around you, the 5G, your smart device, your phones, what is happening with that? What if something is triggering it, too, like an impulse, a frequency? We have something completely foreign in the human body.

Madej said her research revealed that electromagnetic (EMF) frequencies emitted by phones and other devices had increased dramatically in the same period of the 'vaccine' rollout and she was seeing more people with radiation problems as 5G and other electromagnetic technology was expanded and introduced to schools and hospitals. She said she was 'floored with the EMF coming off' the devices she checked. All this makes total sense and syncs with my own work of decades when you think that Moderna refers in documents to its mRNA 'vaccine' as an 'operating system':

Recognizing the broad potential of mRNA science, we set out to create an mRNA technology platform that functions very much like an operating system on a computer. It is designed so that it can plug and play interchangeably with different programs. In our case, the 'program' or 'app' is our mRNA drug – the unique mRNA sequence that codes for a protein …

… Our MRNA Medicines – 'The 'Software Of Life': When we have a concept for a new mRNA medicine and begin research, fundamental components are already in place. Generally, the only thing that changes from one potential mRNA medicine to another is the coding region – the actual genetic code that instructs ribosomes to make protein. Utilizing these instruction sets gives our investigational mRNA medicines a software-like quality. We also have the ability to combine different mRNA sequences encoding for different proteins in a single mRNA investigational medicine.

Who needs a real 'virus' when you can create a computer version to justify infusing your operating system into the entire human race on the road to making living, breathing people into cyborgs? What is missed with the 'vaccines' is the *digital* connection between synthetic material and the body that I highlighted earlier with the study that hacked a computer with human DNA. On one level the body is digital, based on mathematical codes, and I'll have more about that in the next chapter. Those who ridiculously claim that mRNA 'vaccines' are not designed to change human genetics should explain the words of Dr Tal Zaks, chief medical officer at Moderna, in a 2017 TED talk. He said that over the last 30 years 'we've been living this phenomenal digital scientific revolution, and I'm here today to tell you, that we are actually *hacking the software of life*, and that it's changing the way we think about prevention and treatment of disease':

In every cell there's this thing called messenger RNA, or mRNA for short, that transmits the critical information from the DNA in our genes to the protein, which is really the stuff we're all made out of. This is the critical information that determines what the cell will do. So we think about it as an operating system. So if you could change that, if you could introduce a line of code, or change a line of code, it turns out, that has profound implications for everything, from the flu to cancer.

Zaks should more accurately have said that this has profound implications for the human genetic code and the nature of DNA. Communications within the body go both ways and not only one. But, hey, no, the 'Covid vaccine' will not affect your genetics. Cult fact-checkers say so even though the man who helped to develop the mRNA technique says that it does. Zaks said in 2017:

If you think about what it is we're trying to do. We've taken information and our understanding of that information and how that information is transmitted in a cell, and we've taken our understanding of medicine and how to make drugs, and we're fusing the two. We think of it as information therapy.

I have been writing for decades that the body is an information field communicating with itself and the wider world. This is why

radiation which is information can change the information field of body and mind through phenomena like 5G and change their nature and function. 'Information therapy' means to change the body's information field and change the way it operates. DNA is a receiver-transmitter of information and can be mutated by information like mRNA synthetic messaging. Technology to do this has been ready and waiting in the underground bases and other secret projects to be rolled out when the 'Covid' hoax was played. 'Trials' of such short and irrelevant duration were only for public consumption. When they say the 'vaccine' is 'experimental' that is not true. It may appear to be 'experimental' to those who don't know what's going on, but the trials have already been done to ensure the Cult gets the result it desires. Zaks said that it took decades to sequence the human genome, completed in 2003, but now they could do it in a week. By 'they' he means scientists operating in the public domain. In the secret projects they were sequencing the genome in a week long before even 2003.

Deluge of mRNA

Highly significantly the Moderna document says the guiding premise is that if using mRNA as a medicine works for one disease then it should work for many diseases. They were leveraging the flexibility afforded by their platform and the fundamental role mRNA plays in protein synthesis to pursue mRNA medicines for a broad spectrum of diseases. Moderna is confirming what I was saying through 2020 that multiple 'vaccines' were planned for 'Covid' (and later invented 'variants') and that previous vaccines would be converted to the mRNA system to infuse the body with massive amounts of genetically-manipulating synthetic material to secure a transformation to a synthetic-biological state. The 'vaccines' are designed to kill stunning numbers as part of the long-exposed Cult depopulation agenda and transform the rest. Given this is the goal you can appreciate why there is such hysterical demand for every human to be 'vaccinated' for an alleged 'disease' that has an estimated 'infection' to 'death' ratio of 0.23-0.15 percent. As I write

children are being given the 'vaccine' in trials (their parents are a disgrace) and ever-younger people are being offered the vaccine for a 'virus' that even if you believe it exists has virtually zero chance of harming them. Horrific effects of the 'trials' on a 12-year-old girl were revealed by a family member to be serious brain and gastric problems that included a bowel obstruction and the inability to swallow liquids or solids. She was unable to eat or drink without throwing up, had extreme pain in her back, neck and abdomen, and was paralysed from the waist down which stopped her urinating unaided. When the girl was first taken to hospital doctors said it was all in her mind. She was signed up for the 'trial' by her parents for whom no words suffice. None of this 'Covid vaccine' insanity makes any sense unless you see what the 'vaccine' really is – a body-changer. Synthetic biology or 'SynBio' is a fast-emerging and expanding scientific discipline which includes everything from genetic and molecular engineering to electrical and computer engineering. Synthetic biology is defined in these ways:

- A multidisciplinary area of research that seeks to create new biological parts, devices, and systems, or to redesign systems that are already found in nature.

- The use of a mixture of physical engineering and genetic engineering to create new (and therefore synthetic) life forms.

- An emerging field of research that aims to combine the knowledge and methods of biology, engineering and related disciplines in the design of chemically-synthesized DNA to create organisms with novel or enhanced characteristics and traits (synthetic organisms including humans).

We now have synthetic blood, skin, organs and limbs being developed along with synthetic body parts produced by 3D printers. These are all elements of the synthetic human programme and this comment by Kurzweil's co-founder of the Singularity University,

Peter Diamandis, can be seen in a whole new light with the 'Covid' hoax and the sanctions against those that refuse the 'vaccine':

Anybody who is going to be resisting the progress forward [to transhumanism] is going to be resisting evolution and, fundamentally, they will die out. It's not a matter of whether it's good or bad. It's going to happen.

'Resisting evolution'? What absolute bollocks. The arrogance of these people is without limit. His 'it's going to happen' mantra is another way of saying 'resistance is futile' to break the spirit of those pushing back and we must not fall for it. Getting this genetically-transforming 'vaccine' into everyone is crucial to the Cult plan for total control and the desperation to achieve that is clear for anyone to see. Vaccine passports are a major factor in this and they, too, are a form of resistance is futile. It's NOT. The paper funded by the Rockefeller Foundation for the 2013 'health conference' in China said:

We will interact more with artificial intelligence. The use of robotics, bio-engineering to augment human functioning is already well underway and will advance. Re-engineering of humans into potentially separate and unequal forms through genetic engineering or mixed human-robots raises debates on ethics and equality.

A new demography is projected to emerge after 2030 [that year again] of technologies (robotics, genetic engineering, nanotechnology) producing robots, engineered organisms, 'nanobots' and artificial intelligence (AI) that can self-replicate. Debates will grow on the implications of an impending reality of human designed life.

What is happening today is so long planned. The world army enforcing the will of the world government is intended to be a robot army, not a human one. Today's military and its technologically 'enhanced' troops, pilotless planes and driverless vehicles are just stepping stones to that end. Human soldiers are used as Cult fodder and its time they woke up to that and worked for the freedom of the population instead of their own destruction and their family's destruction – the same with the police. Join us and let's sort this out. The phenomenon of enforce my own destruction is widespread in the 'Covid' era with Woker 'luvvies' in the acting and entertainment

industries supporting 'Covid' rules which have destroyed their profession and the same with those among the public who put signs on the doors of their businesses 'closed due to Covid – stay safe' when many will never reopen. It's a form of masochism and most certainly insanity.

Transgender = transhumanism

When something explodes out of nowhere and is suddenly everywhere it is always the Cult agenda and so it is with the tidal wave of claims and demands that have infiltrated every aspect of society under the heading of 'transgenderism'. The term 'trans' is so 'in' and this is the dictionary definition:

A prefix meaning 'across', 'through', occurring … in loanwords from Latin, used in particular for denoting movement or conveyance from place to place (transfer; transmit; transplant) or complete change (transform; transmute), or to form adjectives meaning 'crossing', 'on the other side of', or 'going beyond' the place named (transmontane; transnational; trans-Siberian).

Transgender means to go beyond gender and transhuman means to go beyond human. Both are aspects of the Cult plan to transform the human body to a synthetic state with *no gender*. Human 2.0 is not designed to procreate and would be produced technologically with no need for parents. The new human would mean the end of parents and so men, and increasingly women, are being targeted for the deletion of their rights and status. Parental rights are disappearing at an ever-quickening speed for the same reason. The new human would have no need for men or women when there is no procreation and no gender. Perhaps the transgender movement that appears to be in a permanent state of frenzy might now contemplate on how it is being used. This was never about transgender rights which are only the interim excuse for confusing gender, particularly in the young, on the road to *fusing* gender. Transgender activism is not an end; it is a *means* to an end. We see again the technique of creative destruction in which you destroy the status quo to 'build back better' in the form that you want. The gender status quo had to be

destroyed by persuading the Cult-created Woke mentality to believe that you can have 100 genders or more. A programme for 9 to 12 year olds produced by the Cult-owned BBC promoted the 100 genders narrative. The very idea may be the most monumental nonsense, but it is not what is true that counts, only what you can make people *believe* is true. Once the gender of 2 + 2 = 4 has been dismantled through indoctrination, intimidation and 2 + 2 = 5 then the new no-gender normal can take its place with Human 2.0. Aldous Huxley revealed the plan in his prophetic *Brave New World* in 1932:

> Natural reproduction has been done away with and children are created, decanted', and raised in 'hatcheries and conditioning centres'. From birth, people are genetically designed to fit into one of five castes, which are further split into 'Plus' and 'Minus' members and designed to fulfil predetermined positions within the social and economic strata of the World State.

How could Huxley know this in 1932? For the same reason George Orwell knew about the Big Brother state in 1948, Cult insiders I have quoted knew about it in 1969, and I have known about it since the early 1990s. If you are connected to the Cult or you work your balls off to uncover the plan you can predict the future. The process is simple. If there is a plan for the world and nothing intervenes to stop it then it will happen. Thus if you communicate the plan ahead of time you are perceived to have predicted the future, but you haven't. You have revealed the plan which without intervention will become the human future. The whole reason I have done what I have is to alert enough people to inspire an intervention and maybe at last that time has come with the Cult and its intentions now so obvious to anyone with a brain in working order.

The future is here

Technological wombs that Huxley described to replace parent procreation are already being developed and they are only the projects we know about in the public arena. Israeli scientists told *The Times of Israel* in March, 2021, that they have grown 250-cell embryos

into mouse foetuses with fully formed organs using artificial wombs in a development they say could pave the way for gestating humans outside the womb. Professor Jacob Hanna of the Weizmann Institute of Science said:

We took mouse embryos from the mother at day five of development, when they are just of 250 cells, and had them in the incubator from day five until day 11, by which point they had grown all their organs.

By day 11 they make their own blood and have a beating heart, a fully developed brain. Anybody would look at them and say, 'this is clearly a mouse foetus with all the characteristics of a mouse.' It's gone from being a ball of cells to being an advanced foetus.

A special liquid is used to nourish embryo cells in a laboratory dish and they float on the liquid to duplicate the first stage of embryonic development. The incubator creates all the right conditions for its development, Hanna said. The liquid gives the embryo 'all the nutrients, hormones and sugars they need' along with a custom-made electronic incubator which controls gas concentration, pressure and temperature. The cutting-edge in the underground bases and other secret locations will be light years ahead of that, however, and this was reported by the London *Guardian* in 2017:

We are approaching a biotechnological breakthrough. Ectogenesis, the invention of a complete external womb, could completely change the nature of human reproduction. In April this year, researchers at the Children's Hospital of Philadelphia announced their development of an artificial womb.

The article was headed 'Artificial wombs could soon be a reality. What will this mean for women?' What would it mean for children is an even bigger question. No mother to bond with only a machine in preparation for a life of soulless interaction and control in a world governed by machines (see the *Matrix* movies). Now observe the calculated manipulations of the 'Covid' hoax as human interaction and warmth has been curtailed by distancing, isolation and fear with people communicating via machines on a scale never seen before.

These are all dots in the same picture as are all the personal assistants, gadgets and children's toys through which kids and adults communicate with AI as if it is human. The AI 'voice' on Sat-Nav should be included. All these things are psychological preparation for the Cult endgame. Before you can make a physical connection with AI you have to make a psychological connection and that is what people are being conditioned to do with this ever gathering human-AI interaction. Movies and TV programmes depicting the transhuman, robot dystopia relate to a phenomenon known as 'pre-emptive programming' in which the world that is planned is portrayed everywhere in movies, TV and advertising. This is conditioning the conscious and subconscious mind to become familiar with the planned reality to dilute resistance when it happens for real. What would have been a shock such is the change is made less so. We have young children put on the road to transgender transition surgery with puberty blocking drugs at an age when they could never be able to make those life-changing decisions.

Rachel Levine, a professor of paediatrics and psychiatry who believes in treating children this way, became America's highest-ranked openly-transgender official when she was confirmed as US Assistant Secretary at the Department of Health and Human Services after being nominated by Joe Biden (the Cult). Activists and governments press for laws to deny parents a say in their children's transition process so the kids can be isolated and manipulated into agreeing to irreversible medical procedures. A Canadian father Robert Hoogland was denied bail by the Vancouver Supreme Court in 2021 and remained in jail for breaching a court order that he stay silent over his young teenage daughter, a minor, who was being offered life-changing hormone therapy without parental consent. At the age of 12 the girl's 'school counsellor' said she may be transgender, referred her to a doctor and told the school to treat her like a boy. This is another example of state-serving schools imposing ever more control over children's lives while parents have ever less.

Contemptible and extreme child abuse is happening all over the world as the Cult gender-fusion operation goes into warp-speed.

Why the war on men – and now women?

The question about what artificial wombs mean for women should rightly be asked. The answer can be seen in the deletion of women's rights involving sport, changing rooms, toilets and status in favour of people in male bodies claiming to identify as women. I can identify as a mountain climber, but it doesn't mean I can climb a mountain any more than a biological man can be a biological woman. To believe so is a triumph of belief over factual reality which is the very perceptual basis of everything Woke. Women's sport is being destroyed by allowing those with male bodies who say they identify as female to 'compete' with girls and women. Male body 'women' dominate 'women's' competition with their greater muscle mass, bone density, strength and speed. With that disadvantage sport for women loses all meaning. To put this in perspective nearly 300 American high school boys can run faster than the quickest woman sprinter in the world. Women are seeing their previously protected spaces invaded by male bodies simply because they claim to identify as women. That's all they need to do to access all women's spaces and activities under the Biden 'Equality Act' that destroys equality for women with the usual Orwellian Woke inversion. Male sex offenders have already committed rapes in women's prisons after claiming to identify as women to get them transferred. Does this not matter to the Woke 'equality' hypocrites? Not in the least. What matters to Cult manipulators and funders behind transgender activists is to advance gender fusion on the way to the no-gender 'human'. When you are seeking to impose transparent nonsense like this, or the 'Covid' hoax, the only way the nonsense can prevail is through censorship and intimidation of dissenters, deletion of factual information, and programming of the unquestioning, bewildered and naive. You don't have to scan the world for long to see that all these things are happening.

Many women's rights organisations have realised that rights and status which took such a long time to secure are being eroded and that it is systematic. Kara Dansky of the global Women's Human Rights Campaign said that Biden's transgender executive order immediately he took office, subsequent orders, and Equality Act legislation that followed 'seek to erase women and girls in the law as a category'. *Exactly*. I said during the long ago-started war on men (in which many women play a crucial part) that this was going to turn into a war on them. The Cult is phasing out *both* male and female genders. To get away with that they are brought into conflict so they are busy fighting each other while the Cult completes the job with no unity of response. Unity, people, *unity*. We need unity everywhere. Transgender is the only show in town as the big step towards the no-gender human. It's not about rights for transgender people and never has been. Woke political correctness is deleting words relating to genders to the same end. Wokers believe this is to be 'inclusive' when the opposite is true. They are deleting words describing gender because gender *itself* is being deleted by Human 2.0. Terms like 'man', 'woman', 'mother' and 'father' are being deleted in the universities and other institutions to be replaced by the *no*-gender, not trans-gender, 'individuals' and 'guardians'. Women's rights campaigner Maria Keffler of Partners for Ethical Care said: 'Children are being taught from kindergarten upward that some boys have a vagina, some girls have a penis, and that kids can be any gender they want to be.' Do we really believe that suddenly countries all over the world at the same time had the idea of having drag queens go into schools or read transgender stories to very young children in the local library? It's coldly-calculated confusion of gender on the way to the fusion of gender. Suzanne Vierling, a psychologist from Southern California, made another important point:

Yesterday's slave woman who endured gynecological medical experiments is today's girl-child being butchered in a booming gender-transitioning sector. Ovaries removed, pushing her into menopause and osteoporosis, uncharted territory, and parents' rights and authority decimated.

The erosion of parental rights is a common theme in line with the Cult plans to erase the very concept of parents and 'ovaries removed, pushing her into menopause' means what? Those born female lose the ability to have children – another way to discontinue humanity as we know it.

Eliminating Human 1.0 (before our very eyes)

To pave the way for Human 2.0 you must phase out Human 1.0. This is happening through plummeting sperm counts and making women infertile through an onslaught of chemicals, radiation (including smartphones in pockets of men) and mRNA 'vaccines'. Common agriculture pesticides are also having a devastating impact on human fertility. I have been tracking collapsing sperm counts in the books for a long time and in 2021 came a book by fertility scientist and reproductive epidemiologist Shanna Swan, *Count Down: How Our Modern World Is Threatening Sperm Counts, Altering Male and Female Reproductive Development and Imperiling the Future of the Human Race*. She reports how the global fertility rate dropped by *half* between 1960 and 2016 with America's birth rate 16 percent below where it needs to be to sustain the population. Women are experiencing declining egg quality, more miscarriages, and more couples suffer from infertility. Other findings were an increase in erectile dysfunction, infant boys developing more genital abnormalities, male problems with conception, and plunging levels of the male hormone testosterone which would explain why so many men have lost their backbone and masculinity. This has been very evident during the 'Covid' hoax when women have been prominent among the Pushbackers and big strapping blokes have bowed their heads, covered their faces with a nappy and quietly submitted. Mind control expert Cathy O'Brien also points to how global education introduced the concept of 'we're all winners' in sport and classrooms: 'Competition was defused, and it in turn defused a sense of fighting back.' This is another version of the 'equity' doctrine in which you drive down rather than raise up. What a contrast in Cult-controlled China with its global ambitions

where the government published plans in January, 2021, to 'cultivate masculinity' in boys from kindergarten through to high school in the face of a 'masculinity crisis'. A government adviser said boys would be soon become 'delicate, timid and effeminate' unless action was taken. Don't expect any similar policy in the targeted West. A 2006 study showed that a 65-year-old man in 2002 had testosterone levels *15 percent* lower than a 65-year-old man in 1987 while a 2020 study found a similar story with young adults and adolescents. Men are getting prescriptions for testosterone replacement therapy which causes an even greater drop in sperm count with up to 99 percent seeing sperm counts drop to zero during the treatment. More sperm is defective and malfunctioning with some having two heads or not pursuing an egg.

A class of *synthetic* chemicals known as phthalates are being blamed for the decline. These are found everywhere in plastics, shampoos, cosmetics, furniture, flame retardants, personal care products, pesticides, canned foods and even receipts. Why till receipts? Everyone touches them. Let no one delude themselves that all this is not systematic to advance the long-time agenda for human body transformation. Phthalates mimic hormones and disrupt the hormone balance causing testosterone to fall and genital birth defects in male infants. Animals and fish have been affected in the same way due to phthalates and other toxins in rivers. When fish turn gay or change sex through chemicals in rivers and streams it is a pointer to why there has been such an increase in gay people and the sexually confused. It doesn't matter to me what sexuality people choose to be, but if it's being affected by chemical pollution and consumption then we need to know. Does anyone really think that this is not connected to the transgender agenda, the war on men and the condemnation of male 'toxic masculinity'? You watch this being followed by 'toxic femininity'. It's already happening. When breastfeeding becomes 'chest-feeding', pregnant women become pregnant people along with all the other Woke claptrap you know that the world is going insane and there's a Cult scam in progress. Transgender activists are promoting the Cult agenda while Cult

billionaires support and fund the insanity as they laugh themselves to sleep at the sheer stupidity for which humans must be infamous in galaxies far, far away.

'Covid vaccines' and female infertility

We can now see why the 'vaccine' has been connected to potential infertility in women. Dr Michael Yeadon, former Vice President and Chief Scientific Advisor at Pfizer, and Dr Wolfgang Wodarg in Germany, filed a petition with the European Medicines Agency in December, 2020, urging them to stop trials for the Pfizer/BioNTech shot and all other mRNA trials until further studies had been done. They were particularly concerned about possible effects on fertility with 'vaccine'-produced antibodies attacking the protein Syncytin-1 which is responsible for developing the placenta. The result would be infertility 'of indefinite duration' in women who have the 'vaccine' with the placenta failing to form. Section 10.4.2 of the Pfizer/BioNTech trial protocol says that pregnant women or those who might become so should not have mRNA shots. Section 10.4 warns men taking mRNA shots to 'be abstinent from heterosexual intercourse' and not to donate sperm. The UK government said that it *did not know* if the mRNA procedure had an effect on fertility. *Did not know?* These people have to go to jail. UK government advice did not recommend at the start that pregnant women had the shot and said they should avoid pregnancy for at least two months after 'vaccination'. The 'advice' was later updated to pregnant women should only have the 'vaccine' if the benefits outweighed the risks to mother and foetus. What the hell is that supposed to mean? Then 'spontaneous abortions' began to appear and rapidly increase on the adverse reaction reporting schemes which include only a fraction of adverse reactions. Thousands and ever-growing numbers of 'vaccinated' women are describing changes to their menstrual cycle with heavier blood flow, irregular periods and menstruating again after going through the menopause – all links to reproduction effects. Women are passing blood clots and the lining of their uterus while men report erectile dysfunction and blood effects. Most

significantly of all *un*vaccinated women began to report similar menstrual changes after interaction with *'vaccinated'* people and men and children were also affected with bleeding noses, blood clots and other conditions. 'Shedding' is when vaccinated people can emit the content of a vaccine to affect the unvaccinated, but this is different. 'Vaccinated' people were not shedding a 'live virus' allegedly in 'vaccines' as before because the fake 'Covid vaccines' involve synthetic material and other toxicity. Doctors exposing what is happening prefer the term 'transmission' to shedding. Somehow those that have had the shots are transmitting effects to those that haven't. Dr Carrie Madej said the nano-content of the 'vaccines' can 'act like an antenna' to others around them which fits perfectly with my own conclusions. This 'vaccine' transmission phenomenon was becoming known as the book went into production and I deal with this further in the Postscript.

Vaccine effects on sterility are well known. The World Health Organization was accused in 2014 of sterilising millions of women in Kenya with the evidence confirmed by the content of the vaccines involved. The same WHO behind the 'Covid' hoax admitted its involvement for more than ten years with the vaccine programme. Other countries made similar claims. Charges were lodged by Tanzania, Nicaragua, Mexico, and the Philippines. The Gardasil vaccine claimed to protect against a genital 'virus' known as HPV has also been linked to infertility. Big Pharma and the WHO (same thing) are criminal and satanic entities. Then there's the Bill Gates Foundation which is connected through funding and shared interests with 20 pharmaceutical giants and laboratories. He stands accused of directing the policy of United Nations Children's Fund (UNICEF), vaccine alliance GAVI, and other groupings, to advance the vaccine agenda and silence opposition at great cost to women and children. At the same time Gates wants to reduce the global population. Coincidence?

Great Reset = Smart Grid = new human

The Cult agenda I have been exposing for 30 years is now being openly promoted by Cult assets like Gates and Klaus Schwab of the World Economic Forum under code-terms like the 'Great Reset', 'Build Back Better' and 'a rare but narrow window of opportunity to reflect, reimagine, and reset our world'. What provided this 'rare but narrow window of opportunity'? The 'Covid' hoax did. Who created that? *They* did. My books from not that long ago warned about the planned 'Internet of Things' (IoT) and its implications for human freedom. This was the plan to connect all technology to the Internet and artificial intelligence and today we are way down that road with an estimated 36 billion devices connected to the World Wide Web and that figure is projected to be 76 billion by 2025. I further warned that the Cult planned to go beyond that to the Internet of *Everything* when the human brain was connected via AI to the Internet and Kurzweil's 'cloud'. Now we have Cult operatives like Schwab calling for precisely that under the term 'Internet of Bodies', a fusion of the physical, digital and biological into one centrally-controlled Smart Grid system which the Cult refers to as the 'Fourth Industrial Revolution'. They talk about the 'biological', but they really mean the synthetic-biological which is required to fully integrate the human body and brain into the Smart Grid and artificial intelligence planned to replace the human mind. We have everything being synthetically manipulated including the natural world through GMO and smart dust, the food we eat and the human body itself with synthetic 'vaccines'. I said in *The Answer* that we would see the Cult push for synthetic meat to replace animals and in February, 2021, the so predictable psychopath Bill Gates called for the introduction of synthetic meat to save us all from 'climate change'. The climate hoax just keeps on giving like the 'Covid' hoax. The war on meat by vegan activists is a carbon (oops, sorry) copy of the manipulation of transgender activists. They have no idea (except their inner core) that they are being used to promote and impose the agenda of the Cult or that they are only the *vehicle* and not the *reason*. This is not to say those who choose not to eat meat shouldn't be respected and supported in that right, but there are ulterior motives

for those in power. A *Forbes* article in December, 2019, highlighted the plan so beloved of Schwab and the Cult under the heading: 'What Is The Internet of Bodies? And How Is It Changing Our World?' The article said the human body is the latest data platform (remember 'our vaccine is an operating system'). *Forbes* described the plan very accurately and the words could have come straight out of my books from long before:

The Internet of Bodies (IoB) is an extension of the IoT and basically connects the human body to a network through devices that are ingested, implanted, or connected to the body in some way. Once connected, data can be exchanged, and the body and device can be remotely monitored and controlled.

They were really describing a human hive mind with human perception centrally-dictated via an AI connection as well as allowing people to be 'remotely monitored and controlled'. Everything from a fridge to a human mind could be directed from a central point by these insane psychopaths and 'Covid vaccines' are crucial to this. Forbes explained the process I mentioned earlier of holdable and wearable technology followed by implantable. The article said there were three generations of the Internet of Bodies that include:

- Body external: These are wearable devices such as Apple Watches or Fitbits that can monitor our health.

- Body internal: These include pacemakers, cochlear implants, and digital pills that go inside our bodies to monitor or control various aspects of health.

- Body embedded: The third generation of the Internet of Bodies is embedded technology where technology and the human body are melded together and have a real-time connection to a remote machine.

Forbes noted the development of the Brain Computer Interface (BCI) which merges the brain with an external device for monitoring and controlling in real-time. 'The ultimate goal is to help restore function to individuals with disabilities by using brain signals rather than conventional neuromuscular pathways.' Oh, do fuck off. The goal of brain interface technology is controlling human thought and emotion from the central point in a hive mind serving its masters wishes. Many people are now agreeing to be chipped to open doors without a key. You can recognise them because they'll be wearing a mask, social distancing and lining up for the 'vaccine'. The Cult plans a Great Reset money system after they have completed the demolition of the global economy in which 'money' will be exchanged through communication with body operating systems. Rand Corporation, a Cult-owned think tank, said of the Internet of Bodies or IoB:

> Internet of Bodies technologies fall under the broader IoT umbrella. But as the name suggests, IoB devices introduce an even more intimate interplay between humans and gadgets. IoB devices monitor the human body, collect health metrics and other personal information, and transmit those data over the Internet. Many devices, such as fitness trackers, are already in use … IoB devices … and those in development can track, record, and store users' whereabouts, bodily functions, and what they see, hear, and even think.

Schwab's World Economic Forum, a long-winded way of saying 'fascism' or 'the Cult', has gone full-on with the Internet of Bodies in the 'Covid' era. 'We're entering the era of the Internet of Bodies', it declared, 'collecting our physical data via a range of devices that can be implanted, swallowed or worn'. The result would be a huge amount of health-related data that could improve human wellbeing around the world, and prove crucial in fighting the 'Covid-19 pandemic'. Does anyone think these clowns care about 'human wellbeing' after the death and devastation their pandemic hoax has purposely caused? Schwab and co say we should move forward with the Internet of Bodies because 'Keeping track of symptoms could help us stop the spread of infection, and quickly detect new cases'. How wonderful, but keeping track' is all they are really bothered

about. Researchers were investigating if data gathered from smartwatches and similar devices could be used as viral infection alerts by tracking the user's heart rate and breathing. Schwab said in his 2018 book *Shaping the Future of the Fourth Industrial Revolution*:

> The lines between technologies and beings are becoming blurred and not just by the ability to create lifelike robots or synthetics. Instead it is about the ability of new technologies to literally become part of us. Technologies already influence how we understand ourselves, how we think about each other, and how we determine our realities. As the technologies … give us deeper access to parts of ourselves, we may begin to integrate digital technologies into our bodies.

You can see what the game is. Twenty-four hour control and people – if you could still call them that – would never know when something would go ping and take them out of circulation. It's the most obvious rush to a global fascist dictatorship and the complete submission of humanity and yet still so many are locked away in their Cult-induced perceptual coma and can't see it.

Smart Grid control centres

The human body is being transformed by the 'vaccines' and in other ways into a synthetic cyborg that can be attached to the global Smart Grid which would be controlled from a central point and other sub-locations of Grid manipulation. Where are these planned to be? Well, China for a start which is one of the Cult's biggest centres of operation. The technological control system and technocratic rule was incubated here to be unleashed across the world after the 'Covid' hoax came out of China in 2020. Another Smart Grid location that will surprise people new to this is Israel. I have exposed in *The Trigger* how Sabbatian technocrats, intelligence and military operatives were behind the horrors of 9/11 and not '19 Arab hijackers' who somehow manifested the ability to pilot big passenger airliners when instructors at puddle-jumping flying schools described some of them as a joke. The 9/11 attacks were made possible through control of civilian and military air computer systems and those of the White House, Pentagon and connected agencies. See *The Trigger* – it

will blow your mind. The controlling and coordinating force were the Sabbatian networks in Israel and the United States which by then had infiltrated the entire US government, military and intelligence system. The real name of the American Deep State is 'Sabbatian State'. Israel is a tiny country of only nine million people, but it is one of the global centres of cyber operations and fast catching Silicon Valley in importance to the Cult. Israel is known as the 'start-up nation' for all the cyber companies spawned there with the Sabbatian specialisation of 'cyber security' that I mentioned earlier which gives those companies access to computer systems of their clients in real time through 'backdoors' written into the coding when security software is downloaded. The Sabbatian centre of cyber operations outside Silicon Valley is the Israeli military Cyber Intelligence Unit, the biggest infrastructure project in Israel's history, headquartered in the desert-city of Beersheba and involving some 20,000 'cyber soldiers'. Here are located a literal army of Internet trolls scanning social media, forums and comment lists for anyone challenging the Cult agenda. The UK military has something similar with its 77th Brigade and associated operations. The Beersheba complex includes research and development centres for other Cult operations such as Intel, Microsoft, IBM, Google, Apple, Hewlett-Packard, Cisco Systems, Facebook and Motorola. Techcrunch.com ran an article about the Beersheba global Internet technology centre headlined 'Israel's desert city of Beersheba is turning into a cybertech oasis':

> The military's massive relocation of its prestigious technology units, the presence of multinational and local companies, a close proximity to Ben Gurion University and generous government subsidies are turning Beersheba into a major global cybertech hub. Beersheba has all of the ingredients of a vibrant security technology ecosystem, including Ben Gurion University with its graduate program in cybersecurity and Cyber Security Research Center, and the presence of companies such as EMC, Deutsche Telekom, PayPal, Oracle, IBM, and Lockheed Martin. It's also the future home of the INCB (Israeli National Cyber Bureau); offers a special income tax incentive for cyber security companies, and was the site for the relocation of the army's intelligence corps units.

Sabbatians have taken over the cyber world through the following process: They scan the schools for likely cyber talent and develop them at Ben Gurion University and their period of conscription in the Israeli Defense Forces when they are stationed at the Beersheba complex. When the cyber talented officially leave the army they are funded to start cyber companies with technology developed by themselves or given to them by the state. Much of this is stolen through backdoors of computer systems around the world with America top of the list. Others are sent off to Silicon Valley to start companies or join the major ones and so we have many major positions filled by apparently 'Jewish' but really Sabbatian operatives. Google, YouTube and Facebook are all run by 'Jewish' CEOs while Twitter is all but run by ultra-Zionist hedge-fund shark Paul Singer. At the centre of the Sabbatian global cyber web is the Israeli army's Unit 8200 which specialises in hacking into computer systems of other countries, inserting viruses, gathering information, instigating malfunction, and even taking control of them from a distance. A long list of Sabbatians involved with 9/11, Silicon Valley and Israeli cyber security companies are operatives of Unit 8200. This is not about Israel. It's about the Cult. Israel is planned to be a Smart Grid hub as with China and what is happening at Beersheba is not for the benefit of Jewish people who are treated disgustingly by the Sabbatian elite that control the country. A glance at the Nuremberg Codes will tell you that.

The story is much bigger than 'Covid', important as that is to where we are being taken. Now, though, it's time to really strap in. There's more … much more …

CHAPTER ELEVEN

Who controls the Cult?

Awake, arise or be forever fall'n
John Milton, *Paradise Lost*

I have exposed this far the level of the Cult conspiracy that operates in the world of the seen and within the global secret society and satanic network which operates in the shadows one step back from the seen. The story, however, goes much deeper than that.

The 'Covid' hoax is major part of the Cult agenda, but only part, and to grasp the biggest picture we have to expand our attention beyond the realm of human sight and into the infinity of possibility that we cannot see. It is from here, ultimately, that humanity is being manipulated into a state of total control by the force which dictates the actions of the Cult. How much of reality can we see? Next to damn all is the answer. We may appear to see all there is to see in the 'space' our eyes survey and observe, but little could be further from the truth. The human 'world' is only a tiny band of frequency that the body's visual and perceptual systems can decode into *perception* of a 'world'. According to mainstream science the electromagnetic spectrum is 0.005 percent of what exists in the Universe (Fig 10). The maximum estimate I have seen is 0.5 percent and either way it's miniscule. I say it is far, far, smaller even than 0.005 percent when you compare reality we see with the totality of reality that we don't. Now get this if you are new to such information: Visible light, the only band of frequency that we can see, is a *fraction* of the 0.005

percent (Fig 11 overleaf). Take this further and realise that our universe is one of infinite universes and that universes are only a fragment of overall reality – *infinite* reality. Then compare that with the almost infinitesimal frequency band of visible light or human sight. You see that humans are as near blind as it is possible to be without actually being so. Artist and filmmaker, Sergio Toporek, said:

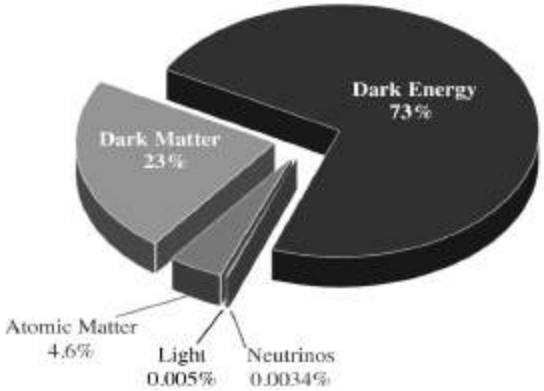


Figure 10: Humans can perceive such a tiny band of visual reality it's laughable.

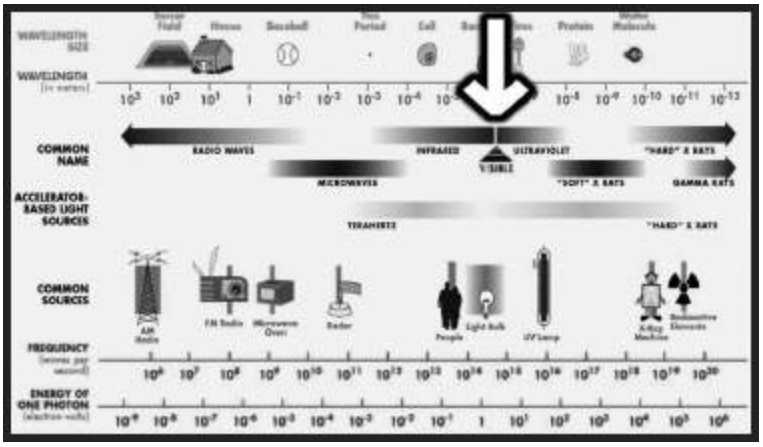


Figure 11: We can see a smear of the 0.005 percent electromagnetic spectrum, but we still know it all. Yep, makes sense.

Consider that you can see less than 1% of the electromagnetic spectrum and hear less than 1% of the acoustic spectrum. 90% of the cells in your body carry their own microbial DNA and are not 'you'. The atoms in your body are 99.9999999999999999% empty space and none of them are the ones you were born with ... Human beings have 46 chromosomes, two less than a potato.

The existence of the rainbow depends on the conical photoreceptors in your eyes; to animals without cones, the rainbow does not exist. So you don't just look at a rainbow, you create it. This is pretty amazing, especially considering that all the beautiful colours you see represent less than 1% of the electromagnetic spectrum.

Suddenly the 'world' of humans looks a very different place. Take into account, too, that Planet Earth when compared with the projected size of this single universe is the equivalent of a billionth of a pinhead. Imagine the ratio that would be when compared to infinite reality. To think that Christianity once insisted that Earth and humanity were the centre of everything. This background is vital if we are going to appreciate the nature of 'human' and how we can be manipulated by an unseen force. To human visual reality virtually *everything* is unseen and yet the prevailing perception within the institutions and so much of the public is that if we can't see it, touch it, hear it, taste it and smell it then it cannot exist. Such perception is indoctrinated and encouraged by the Cult and its agents because it isolates believers in the strictly limited, village-idiot, realm of the five senses where perceptions can be firewalled and information controlled. Most of those perpetuating the 'this-world-is-all-there-is' insanity are themselves indoctrinated into believing the same delusion. While major players and influencers know that official reality is laughable most of those in science, academia and medicine really believe the nonsense they peddle and teach succeeding generations. Those who challenge the orthodoxy are dismissed as nutters and freaks to protect the manufactured illusion from exposure. Observe the dynamic of the 'Covid' hoax and you will see how that takes the same form. The inner-circle psychopaths knows it's a gigantic scam, but almost the entirety of those imposing their fascist rules believe that 'Covid' is all that they're told it is.

Stolen identity

Ask people who they are and they will give you their name, place of birth, location, job, family background and life story. Yet that is not who they are – it is what they are *experiencing*. The difference is *absolutely crucial*. The true 'I', the eternal, infinite 'I', is consciousness,

a state of being aware. Forget 'form'. That is a vehicle for a brief experience. Consciousness does not come *from* the brain, but *through* the brain and even that is more symbolic than literal. We are awareness, pure awareness, and this is what withdraws from the body at what we call 'death' to continue our eternal beingness, *isness*, in other realms of reality within the limitlessness of infinity or the Biblical 'many mansions in my father's house'. Labels of a human life, man, woman, transgender, black, white, brown, nationality, circumstances and income are not who we are. They are what we are – awareness – is *experiencing* in a brief connection with a band of frequency we call 'human'. The labels are not the self; they are, to use the title of one of my books, a *Phantom* Self. I am not David Icke born in Leicester, England, on April 29th, 1952. I am the consciousness *having that experience*. The Cult and its non-human masters seek to convince us through the institutions of 'education', science, medicine, media and government that what we are *experiencing* is who we *are*. It's so easy to control and direct perception locked away in the bewildered illusions of the five senses with no expanded radar. Try, by contrast, doing the same with a humanity aware of its true self and its true power to consciously create its reality and experience. How is it possible to do this? We do it all day every day. If you perceive yourself as 'little me' with no power to impact upon your life and the world then your life experience will reflect that. You will hand the power you don't think you have to authority in all its forms which will use it to control your experience. This, in turn, will appear to confirm your perception of 'little me' in a self-fulfilling feedback loop. But that is what 'little me' really is – a *perception*. We are all 'big-me', infinite me, and the Cult has to make us forget that if its will is to prevail. We are therefore manipulated and pressured into self-identifying with human labels and not the consciousness/awareness *experiencing* those human labels.

The phenomenon of identity politics is a Cult-instigated manipulation technique to sub-divide previous labels into even smaller ones. A United States university employs this list of letters to

describe student identity: LGBTTQQFAGPBDSM or lesbian, gay, bisexual, transgender, transsexual, queer, questioning, flexual, asexual, gender-fuck, polyamorous, bondage/discipline, dominance/submission and sadism/masochism. I'm sure other lists are even longer by now as people feel the need to self-identity the 'I' with the minutiae of race and sexual preference. Wokers programmed by the Cult for generations believe this is about 'inclusivity' when it's really the Cult locking them away into smaller and smaller versions of Phantom Self while firewalling them from the influence of their true self, the infinite, eternal 'I'. You may notice that my philosophy which contends that we are all unique points of attention/awareness within the same infinite whole or Oneness is the ultimate non-racism. The very sense of Oneness makes the judgement of people by their body-type, colour or sexuality utterly ridiculous and confirms that racism has no understanding of reality (including anti-white racism). Yet despite my perception of life Cult agents and fast-asleep Wokers label me racist to discredit my information while they are themselves phenomenally racist and sexist. All they see is race and sexuality and they judge people as good or bad, demons or untouchables, by their race and sexuality. All they see is *Phantom Self* and perceive themselves in terms of Phantom Self. They are pawns and puppets of the Cult agenda to focus attention and self-identity in the five senses and play those identities against each other to divide and rule. Columbia University has introduced segregated graduations in another version of social distancing designed to drive people apart and teach them that different racial and cultural groups have nothing in common with each other. The last thing the Cult wants is unity. Again the pump-primers of this will be Cult operatives in the knowledge of what they are doing, but the rest are just the Phantom Self blind leading the Phantom Self blind. We *do* have something in common – we are all *the same consciousness* having different temporary experiences.

What is this 'human'?

Yes, what *is* 'human'? That is what we are supposed to be, right? I mean 'human'? True, but 'human' is the experience not the 'I'. Break it down to basics and 'human' is the way that information is processed. If we are to experience and interact with this band of frequency we call the 'world' we must have a vehicle that operates within that band of frequency. Our consciousness in its prime form cannot do that; it is way beyond the frequency of the human realm. My consciousness or awareness could not tap these keys and pick up the cup in front of me in the same way that radio station A cannot interact with radio station B when they are on different frequencies. The human body is the means through which we have that interaction. I have long described the body as a biological computer which processes information in a way that allows consciousness to experience this reality. The body is a receiver, transmitter and processor of information in a particular way that we call human. We visually perceive only the world of the five senses in a wakened state – that is the limit of the body's visual decoding system. In truth it's not even visual in the way we experience 'visual reality' as I will come to in a moment. We are 'human' because the body processes the information sources of human into a reality and behaviour system that we *perceive* as human. Why does an elephant act like an elephant and not like a human or a duck? The elephant's biological computer is a different information field and processes information according to that program into a visual and behaviour type we call an elephant. The same applies to everything in our reality. These body information fields are perpetuated through procreation (like making a copy of a software program). The Cult wants to break that cycle and intervene technologically to transform the human information field into one that will change what we call humanity. If it can change the human information field it will change the way that field processes information and change humanity both 'physically' and psychologically. Hence the *messenger* (information) RNA 'vaccines' and so much more that is targeting human genetics by changing the body's information – *messaging* – construct through food, drink, radiation, toxicity and other means.

Reality that we experience is nothing like reality as it really is in the same way that the reality people experience in virtual reality games is not the reality they are really living in. The game is only a decoded source of information that appears to be a reality. Our world is also an information construct – a *simulation* (more later). In its base form our reality is a wavefield of information much the same in theme as Wi-Fi. The five senses decode wavefield information into electrical information which they communicate to the brain to decode into holographic (illusory 'physical') information. Different parts of the brain specialise in decoding different senses and the information is fused into a reality that appears to be outside of us but is really inside the brain and the genetic structure in general (Fig 12 overleaf). DNA is a receiver-transmitter of information and a vital part of this decoding process and the body's connection to other realities. Change DNA and you change the way we decode and connect with reality – see 'Covid vaccines'. Think of computers decoding Wi-Fi. You have information encoded in a radiation field and the computer decodes that information into a very different form on the screen. You can't see the Wi-Fi until its information is made manifest on the screen and the information on the screen is inside the computer and not outside. I have just described how we decode the 'human world'. All five senses decode the waveform 'Wi-Fi' field into electrical signals and the brain (computer) constructs reality inside the brain and not outside – 'You don't just look at a rainbow, you create it'. Sound is a simple example. We don't hear sound until the brain decodes it. Waveform sound waves are picked up by the hearing sense and communicated to the brain in an electrical form to be decoded into the sounds that we hear. Everything we hear is inside the brain along with everything we see, feel, smell and taste. Words and language are waveform fields generated by our vocal chords which pass through this process until they are decoded by the brain into words that we hear. Different languages are different frequency fields or sound waves generated by vocal chords. Late British philosopher Alan Watts said:

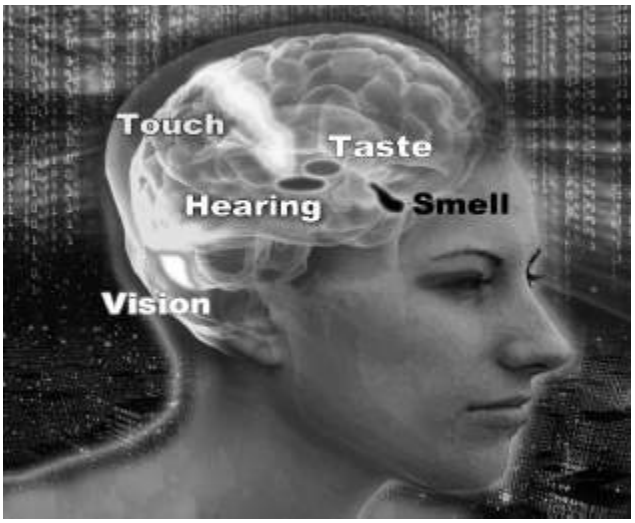


Figure 12: The brain receives information from the five senses and constructs from that our perceived reality.

[Without the brain] the world is devoid of light, heat, weight, solidity, motion, space, time or any other imaginable feature. All these phenomena are interactions, or transactions, of vibrations with a certain arrangement of neurons.

That's exactly what they are and scientist Robert Lanza describes in his book, *Biocentrism*, how we decode electromagnetic waves and energy into visual and 'physical' experience. He uses the example of a flame emitting photons, electromagnetic energy, each pulsing electrically and magnetically:

… these … invisible electromagnetic waves strike a human retina, and if (and only if) the waves happen to measure between 400 and 700 nano meters in length from crest to crest, then their energy is just right to deliver a stimulus to the 8 million cone-shaped cells in the retina.

Each in turn send an electrical pulse to a neighbour neuron, and on up the line this goes, at 250 mph, until it reaches the … occipital lobe of the brain, in the back of the head. There, a cascading complex of neurons fire from the incoming stimuli, and we subjectively perceive this experience as a yellow brightness occurring in a place we have been conditioned to call the 'external world'.

You hear what you decode

If a tree falls or a building collapses they make no noise unless someone is there to decode the energetic waves generated by the disturbance into what we call sound. Does a falling tree make a noise? Only if you hear it – *decode* it. Everything in our reality is a frequency field of information operating within the overall 'Wi-Fi' field that I call The Field. A vibrational disturbance is generated in The Field by the fields of the falling tree or building. These disturbance waves are what we decode into the sound of them falling. If no one is there to do that then neither will make any noise. Reality is created by the observer – *decoder* – and the *perceptions* of the observer affect the decoding process. For this reason different people – different *perceptions* – will perceive the same reality or situation in a different way. What one may perceive as a nightmare another will see as an opportunity. The question of why the Cult is so focused on controlling human perception now answers itself. All experienced reality is the act of decoding and we don't experience Wi-Fi until it is decoded on the computer screen. The sight and sound of an Internet video is encoded in the Wi-Fi all around us, but we don't see or hear it until the computer decodes that information. Taste, smell and touch are all phenomena of the brain as a result of the same process. We don't taste, smell or feel anything except in the brain and there are pain relief techniques that seek to block the signal from the site of discomfort to the brain because if the brain doesn't decode that signal we don't feel pain. Pain is in the brain and only appears to be at the point of impact thanks to the feedback loop between them. We don't see anything until electrical information from the sight senses is decoded in an area at the back of the brain. If that area is damaged we can go blind when our eyes are perfectly okay. So why do we go blind if we damage an eye? We damage the information processing between the waveform visual information and the visual decoding area of the brain. If information doesn't reach the brain in a form it can decode then we can't see the visual reality that it represents. What's more the brain is decoding only a fraction of the information it receives and the rest is absorbed by the

sub-conscious mind. This explanation is from the science magazine, *Wonderpedia*:

> Every second, 11 million sensations crackle along these [brain] pathways ... The brain is confronted with an alarming array of images, sounds and smells which it rigorously filters down until it is left with a manageable list of around 40. Thus 40 sensations per second make up what we perceive as reality.

The 'world' is not what people are told to believe that is it and the inner circles of the Cult *know that*.

Illusory 'physical' reality

We can only see a smear of 0.005 percent of the Universe which is only one of a vast array of universes – 'mansions' – within infinite reality. Even then the brain decodes only 40 pieces of information ('sensations') from a potential *11 million* that we receive every second. Two points strike you from this immediately: The sheer breathtaking stupidity of believing we know anything so rigidly that there's nothing more to know; and the potential for these processes to be manipulated by a malevolent force to control the reality of the population. One thing I can say for sure with no risk of contradiction is that when you can perceive an almost indescribable fraction of infinite reality there is always more to know as in tidal waves of it. Ancient Greek philosopher Socrates was so right when he said that wisdom is to know how little we know. How obviously true that is when you think that we are experiencing a physical world of solidity that is neither physical nor solid and a world of apartness when everything is connected. Cult-controlled 'science' dismisses the so-called 'paranormal' and all phenomena related to that when the 'para'-normal is perfectly normal and explains the alleged 'great mysteries' which dumbfound scientific minds. There is a reason for this. A 'scientific mind' in terms of the mainstream is a material mind, a five-sense mind imprisoned in see it, touch it, hear it, smell it and taste it. Phenomena and happenings that can't be explained that way leave the 'scientific mind' bewildered and the rule is that if they

can't account for why something is happening then it can't, by definition, be happening. I beg to differ. Telepathy is thought waves passing through The Field (think wave disturbance again) to be decoded by someone able to connect with that wavelength (information). For example: You can pick up the thought waves of a friend at any distance and at the very least that will bring them to mind. A few minutes later the friend calls you. 'My god', you say, 'that's incredible – I was just thinking of you.' Ah, but *they* were thinking of *you* before they made the call and that's what you decoded. Native peoples not entrapped in five-sense reality do this so well it became known as the 'bush telegraph'. Those known as psychics and mediums (genuine ones) are doing the same only across dimensions of reality. 'Mind over matter' comes from the fact that matter and mind are the *same*. The state of one influences the state of the other. Indeed one *and* the other are illusions. They are aspects of the same field. Paranormal phenomena are all explainable so why are they still considered 'mysteries' or not happening? Once you go down this road of understanding you begin to expand awareness beyond the five senses and that's the nightmare for the Cult.



Figure 13: Holograms are not solid, but the best ones appear to be.

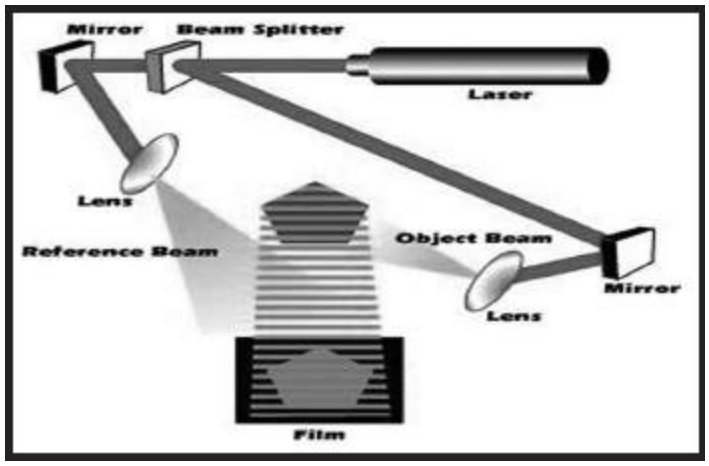


Figure 14: How holograms are created by capturing a waveform version of the subject image.

Holographic 'solidity'

Our reality is not solid, it is holographic. We are now well aware of holograms which are widely used today. Two-dimensional information is decoded into a three-dimensional reality that is not solid although can very much appear to be (Fig 13). Holograms are created with a laser divided into two parts. One goes directly onto a holographic photographic print ('reference beam') and the other takes a waveform image of the subject ('working beam') before being directed onto the print where it 'collides' with the other half of the laser (Fig 14). This creates a *waveform* interference pattern which contains the wavefield information of whatever is being photographed (Fig 15 overleaf). The process can be likened to dropping pebbles in a pond. Waves generated by each one spread out across the water to collide with the others and create a wave representation of where the stones fell and at what speed, weight and distance. A waveform interference pattern of a hologram is akin to the waveform information in The Field which the five senses decode into electrical signals to be decoded by the brain into a holographic illusory 'physical' reality. In the same way when a laser (think human attention) is directed at the waveform interference pattern a three-dimensional version of the subject is projected into apparently 'solid' reality (Fig 16). An amazing trait of holograms reveals more 'paranormal mysteries'. Information of the *whole*

hologram is encoded in waveform in every part of the interference pattern by the way they are created. This means that every *part* of a hologram is a smaller version of the whole. Cut the interference wave-pattern into four and you won't get four parts of the image. You get quarter-sized versions of the *whole* image. The body is a hologram and the same applies. Here we have the basis of acupuncture, reflexology and other forms of healing which identify representations of the whole body in all of the parts, hands, feet, ears, everywhere. Skilled palm readers can do what they do because the information of whole body is encoded in the hand. The concept of as above, so below, comes from this.



Figure 15: A waveform interference pattern that holds the information that transforms into a hologram.



Figure 16: Holographic people including 'Elvis' holographically inserted to sing a duet with Celine Dion.

The question will be asked of why, if solidity is illusory, we can't just walk through walls and each other. The resistance is not solid against solid; it is electromagnetic field against electromagnetic field and we decode this into the *experience* of solid against solid. We should also not underestimate the power of belief to dictate reality. What you believe is impossible *will be*. Your belief impacts on your decoding processes and they won't decode what you think is impossible. What we believe we perceive and what we perceive we experience. 'Can't dos' and 'impossibles' are like a firewall in a computer system that won't put on the screen what the firewall blocks. How vital that is to understanding how human experience has been hijacked. I explain in *The Answer*, *Everything You Need To Know But Have Never Been Told* and other books a long list of 'mysteries' and 'paranormal' phenomena that are not mysterious and perfectly normal once you realise what reality is and how it works. 'Ghosts' can be seen to pass through 'solid' walls because the walls are not solid and the ghost is a discarnate entity operating on a frequency so different to that of the wall that it's like two radio stations sharing the same space while never interfering with each other. I have seen ghosts do this myself. The apartness of people and objects is also an illusion. Everything is connected by the Field like all sea life is connected by the sea. It's just that within the limits of our visual reality we only 'see' holographic information and not the field of information that connects everything and from which the holographic world is made manifest. If you can only see holographic 'objects' and not the field that connects them they will appear to you as unconnected to each other in the same way that we see the computer while not seeing the Wi-Fi.

What you don't know *can* hurt you

Okay, we return to those 'two worlds' of human society and the Cult with its global network of interconnecting secret societies and satanic groups which manipulate through governments, corporations, media, religions, etc. The fundamental difference between them is *knowledge*. The idea has been to keep humanity

ignorant of the plan for its total enslavement underpinned by a crucial ignorance of reality – who we are and where we are – and how we interact with it. 'Human' should be the interaction between our expanded eternal consciousness and the five-sense body experience. We are meant to be *in* this world in terms of the five senses but not *of* this world in relation to our greater consciousness and perspective. In that state we experience the small picture of the five senses within the wider context of the big picture of awareness beyond the five senses. Put another way the five senses see the dots and expanded awareness connects them into pictures and patterns that give context to the apparently random and unconnected. Without the context of expanded awareness the five senses see only apartness and randomness with apparently no meaning. The Cult and its other-dimensional controllers seek to intervene in the frequency realm where five-sense reality is supposed to connect with expanded reality and to keep the two apart (more on this in the final chapter). When that happens five-sense mental and emotional processes are no longer influenced by expanded awareness, or the True 'I', and instead are driven by the isolated perceptions of the body's decoding systems. They are in the world *and* of it. Here we have the human plight and why humanity with its potential for infinite awareness can be so easily manipulatable and descend into such extremes of stupidity.

Once the Cult isolates five-sense mind from expanded awareness it can then program the mind with perceptions and beliefs by controlling information that the mind receives through the 'education' system of the formative years and the media perceptual bombardment and censorship of an entire lifetime. Limit perception and a sense of the possible through limiting knowledge by limiting and skewing information while censoring and discrediting that which could set people free. As the title of another of my books says *… And The Truth Shall Set You Free*. For this reason the last thing the Cult wants in circulation is the truth about anything – especially the reality of the eternal 'I' – and that's why it is desperate to control information. The Cult knows that information becomes perception

which becomes behaviour which, collectively, becomes human society. Cult-controlled and funded mainstream 'science' denies the existence of an eternal 'I' and seeks to dismiss and trash all evidence to the contrary. Cult-controlled mainstream religion has a version of 'God' that is little more than a system of control and dictatorship that employs threats of damnation in an afterlife to control perceptions and behaviour in the here and now through fear and guilt. Neither is true and it's the 'neither' that the Cult wishes to suppress. This 'neither' is that everything is an expression, a point of attention, within an infinite state of consciousness which is the real meaning of the term 'God'.

Perceptual obsession with the 'physical body' and five-senses means that 'God' becomes personified as a bearded bloke sitting among the clouds or a raging bully who loves us if we do what 'he' wants and condemns us to the fires of hell if we don't. These are no more than a 'spiritual' fairy tales to control and dictate events and behaviour through fear of this 'God' which has bizarrely made 'God-fearing' in religious circles a state to be desired. I would suggest that fearing *anything* is not to be encouraged and celebrated, but rather deleted. You can see why 'God fearing' is so beneficial to the Cult and its religions when *they* decide what 'God' wants and what 'God' demands (the Cult demands) that everyone do. As the great American comedian Bill Hicks said satirising a Christian zealot: 'I think what God meant to say.' How much of this infinite awareness ('God') that we access is decided by how far we choose to expand our perceptions, self-identity and sense of the possible. The scale of self-identity reflects itself in the scale of awareness that we can connect with and are influenced by – how much knowing and insight we have instead of programmed perception. You cannot expand your awareness into the infinity of possibility when you believe that you are little me Peter the postman or Mary in marketing and nothing more. I'll deal with this in the concluding chapter because it's crucial to how we turnaround current events.

Where the Cult came from

When I realised in the early 1990s there was a Cult network behind global events I asked the obvious question: When did it start? I took it back to ancient Rome and Egypt and on to Babylon and Sumer in Mesopotamia, the 'Land Between Two Rivers', in what we now call Iraq. The two rivers are the Tigris and Euphrates and this region is of immense historical and other importance to the Cult, as is the land called Israel only 550 miles away by air. There is much more going with deep esoteric meaning across this whole region. It's not only about 'wars for oil'. Priceless artefacts from Mesopotamia were stolen or destroyed after the American and British invasion of Iraq in 2003 justified by the lies of Boy Bush and Tony Blair (their Cult masters) about non-existent 'weapons of mass destruction'. Mesopotamia was the location of Sumer (about 5,400BC to 1,750BC), and Babylon (about 2,350BC to 539BC). Sabbatians may have become immensely influential in the Cult in modern times but they are part of a network that goes back into the mists of history. Sumer is said by historians to be the 'cradle of civilisation'. I disagree. I say it was the re-start of what we call human civilisation after cataclysmic events symbolised in part as the 'Great Flood' destroyed the world that existed before. These fantastic upheavals that I have been describing in detail in the books since the early1990s appear in accounts and legends of ancient cultures across the world and they are supported by geological and biological evidence. Stone tablets found in Iraq detailing the Sumer period say the cataclysms were caused by non-human 'gods' they call the Anunnaki. These are described in terms of extraterrestrial visitations in which knowledge supplied by the Anunnaki is said to have been the source of at least one of the world's oldest writing systems and developments in astronomy, mathematics and architecture that were way ahead of their time. I have covered this subject at length in *The Biggest Secret* and *Children of the Matrix* and the same basic 'Anunnaki' story can be found in Zulu accounts in South Africa where the late and very great Zulu high shaman Credo Mutwa told me that the Sumerian Anunnaki were known by Zulus as the Chitauri or 'children of the serpent'. See my six-hour video interview with Credo on this subject entitled *The*

Reptilian Agenda recorded at his then home near Johannesburg in 1999 which you can watch on the Ickonic media platform.

The Cult emerged out of Sumer, Babylon and Egypt (and elsewhere) and established the Roman Empire before expanding with the Romans into northern Europe from where many empires were savagely imposed in the form of Cult-controlled societies all over the world. Mass death and destruction was their calling card. The Cult established its centre of operations in Europe and European Empires were Cult empires which allowed it to expand into a global force. Spanish and Portuguese colonialists headed for Central and South America while the British and French targeted North America. Africa was colonised by Britain, France, Belgium, the Netherlands, Portugal, Spain, Italy, and Germany. Some like Britain and France moved in on the Middle East. The British Empire was by far the biggest for a simple reason. By now Britain was the headquarters of the Cult from which it expanded to form Canada, the United States, Australia and New Zealand. The Sun never set on the British Empire such was the scale of its occupation. London remains a global centre for the Cult along with Rome and the Vatican although others have emerged in Israel and China. It is no accident that the 'virus' is alleged to have come out of China while Italy was chosen as the means to terrify the Western population into compliance with 'Covid' fascism. Nor that Israel has led the world in 'Covid' fascism and mass 'vaccination'.

You would think that I would mention the United States here, but while it has been an important means of imposing the Cult's will it is less significant than would appear and is currently in the process of having what power it does have deleted. The Cult in Europe has mostly loaded the guns for the US to fire. America has been controlled from Europe from the start through Cult operatives in Britain and Europe. The American Revolution was an illusion to make it appear that America was governing itself while very different forces were pulling the strings in the form of Cult families such as the Rothschilds through the Rockefellers and other subordinates. The Rockefellers are extremely close to Bill Gates and

established both scalpel and drug 'medicine' and the World Health Organization. They play a major role in the development and circulation of vaccines through the Rockefeller Foundation on which Bill Gates said his Foundation is based. Why wouldn't this be the case when the Rockefellers and Gates are on the same team? Cult infiltration of human society goes way back into what we call history and has been constantly expanding and centralising power with the goal of establishing a global structure to dictate everything. Look how this has been advanced in great leaps with the 'Covid' hoax.

The non-human dimension

I researched and observed the comings and goings of Cult operatives through the centuries and even thousands of years as they were born, worked to promote the agenda within the secret society and satanic networks, and then died for others to replace them. Clearly there had to be a coordinating force that spanned this entire period while operatives who would not have seen the end goal in their lifetimes came and went advancing the plan over millennia. I went in search of that coordinating force with the usual support from the extraordinary synchronicity of my life which has been an almost daily experience since 1990. I saw common themes in religious texts and ancient cultures about a non-human force manipulating human society from the hidden. Christianity calls this force Satan, the Devil and demons; Islam refers to the Jinn or Djinn; Zulus have their Chitauri (spelt in other ways in different parts of Africa); and the Gnostic people in Egypt in the period around and before 400AD referred to this phenomena as the 'Archons', a word meaning rulers in Greek. Central American cultures speak of the 'Predators' among other names and the same theme is everywhere. I will use 'Archons' as a collective name for all of them. When you see how their nature and behaviour is described all these different sources are clearly talking about the same force. Gnostics described the Archons in terms of 'luminous fire' while Islam relates the Jinn to 'smokeless fire'. Some refer to beings in form that could occasionally be seen, but the most common of common theme is that they operate from

unseen realms which means almost all existence to the visual processes of humans. I had concluded that this was indeed the foundation of human control and that the Cult was operating within the human frequency band on behalf of this hidden force when I came across the writings of Gnostics which supported my conclusions in the most extraordinary way.

A sealed earthen jar was found in 1945 near the town of Nag Hammadi about 75-80 miles north of Luxor on the banks of the River Nile in Egypt. Inside was a treasure trove of manuscripts and texts left by the Gnostic people some 1,600 years earlier. They included 13 leather-bound papyrus codices (manuscripts) and more than 50 texts written in Coptic Egyptian estimated to have been hidden in the jar in the period of 400AD although the source of the information goes back much further. Gnostics oversaw the Great or Royal Library of Alexandria, the fantastic depository of ancient texts detailing advanced knowledge and accounts of human history. The Library was dismantled and destroyed in stages over a long period with the death-blow delivered by the Cult-established Roman Church in the period around 415AD. The Church of Rome was the Church of Babylon relocated as I said earlier. Gnostics were not a race. They were a way of perceiving reality. Whenever they established themselves and their information circulated the terrorists of the Church of Rome would target them for destruction. This happened with the Great Library and with the Gnostic Cathars who were burned to death by the psychopaths after a long period of oppression at the siege of the Castle of Monségur in southern France in 1244. The Church has always been terrified of Gnostic information which demolishes the official Christian narrative although there is much in the Bible that supports the Gnostic view if you read it in another way. To anyone studying the texts of what became known as the Nag Hammadi Library it is clear that great swathes of Christian and Biblical belief has its origin with Gnostics sources going back to Sumer. Gnostic themes have been twisted to manipulate the perceived reality of Bible believers. Biblical texts have been in the open for centuries where they could be changed while Gnostic

documents found at Nag Hammadi were sealed away and untouched for 1,600 years. What you see is what they wrote.

Use your *pneuma* not your *nous*

Gnosticism and Gnostic come from 'gnosis' which means knowledge, or rather *secret* knowledge, in the sense of spiritual awareness – knowledge about reality and life itself. The desperation of the Cult's Church of Rome to destroy the Gnostics can be understood when the knowledge they were circulating was the last thing the Cult wanted the population to know. Sixteen hundred years later the same Cult is working hard to undermine and silence me for the same reason. The dynamic between knowledge and ignorance is a constant. 'Time' appears to move on, but essential themes remain the same. We are told to 'use your nous', a Gnostic word for head/brain/intelligence. They said, however, that spiritual awakening or 'salvation' could only be secured by expanding awareness *beyond* what they called *nous* and into *pneuma* or Infinite Self. Obviously as I read these texts the parallels with what I have been saying since 1990 were fascinating to me. There is a universal truth that spans human history and in that case why wouldn't we be talking the same language 16 centuries apart? When you free yourself from the perception program of the five senses and explore expanded realms of consciousness you are going to connect with the same information no matter what the perceived 'era' within a manufactured timeline of a single and tiny range of manipulated frequency. Humans working with 'smart' technology or knocking rocks together in caves is only a timeline appearing to operate within the human frequency band. Expanded awareness and the knowledge it holds have always been there whether the era be Stone Age or computer age. We can only access that knowledge by opening ourselves to its frequency which the five-sense prison cell is designed to stop us doing. Gates, Fauci, Whitty, Vallance, Zuckerberg, Brin, Page, Wojcicki, Bezos, and all the others behind the 'Covid' hoax clearly have a long wait before their range of frequency can make that connection given that an open heart is

crucial to that as we shall see. Instead of accessing knowledge directly through expanded awareness it is given to Cult operatives by the secret society networks of the Cult where it has been passed on over thousands of years outside the public arena. Expanded realms of consciousness is where great artists, composers and writers find their inspiration and where truth awaits anyone open enough to connect with it. We need to go there fast.

Archon hijack

A fifth of the Nag Hammadi texts describe the existence and manipulation of the Archons led by a 'Chief Archon' they call 'Yaldabaoth', or the 'Demiurge', and this is the Christian 'Devil', 'Satan', 'Lucifer', and his demons. Archons in Biblical symbolism are the 'fallen ones' which are also referred to as fallen angels after the angels expelled from heaven according to the Abrahamic religions of Judaism, Christianity and Islam. These angels are claimed to tempt humans to 'sin' ongoing and you will see how accurate that symbolism is during the rest of the book. The theme of 'original sin' is related to the 'Fall' when Adam and Eve were 'tempted by the serpent' and fell from a state of innocence and 'obedience' (connection) with God into a state of disobedience (disconnection). The Fall is said to have brought sin into the world and corrupted everything including human nature. Yaldabaoth, the 'Lord Archon', is described by Gnostics as a 'counterfeit spirit', 'The Blind One', 'The Blind God', and 'The Foolish One'. The Jewish name for Yaldabaoth in Talmudic writings is Samael which translates as 'Poison of God', or 'Blindness of God'. You see the parallels. Yaldabaoth in Islamic belief is the Muslim Jinn devil known as Shaytan – Shaytan is Satan as the same themes are found all over the world in every religion and culture. The 'Lord God' of the Old Testament is the 'Lord Archon' of Gnostic manuscripts and that's why he's such a bloodthirsty bastard. Satan is known by Christians as 'the Demon of Demons' and Gnostics called Yaldabaoth the 'Archon of Archons'. Both are known as 'The Deceiver'. We are talking about the same 'bloke' for sure and these common themes

using different names, storylines and symbolism tell a common tale of the human plight.

Archons are referred to in Nag Hammadi documents as mind parasites, inverters, guards, gatekeepers, detainers, judges, pitiless ones and deceivers. The 'Covid' hoax alone is a glaring example of all these things. The Biblical 'God' is so different in the Old and New Testaments because they are not describing the same phenomenon. The vindictive, angry, hate-filled, 'God' of the Old Testament, known as Yahweh, is Yaldabaoth who is depicted in Cult-dictated popular culture as the 'Dark Lord', 'Lord of Time', Lord (Darth) Vader and Dormammu, the evil ruler of the 'Dark Dimension' trying to take over the 'Earth Dimension' in the Marvel comic movie, *Dr Strange*. Yaldabaoth is both the Old Testament 'god' and the Biblical 'Satan'. Gnostics referred to Yaldabaoth as the 'Great Architect of the Universe'and the Cult-controlled Freemason network calls their god 'the 'Great Architect of the Universe' (also Grand Architect). The 'Great Architect' Yaldabaoth is symbolised by the Cult as the all-seeing eye at the top of the pyramid on the Great Seal of the United States and the dollar bill. Archon is encoded in *arch*-itect as it is in *arch*-angels and *arch*-bishops. All religions have the theme of a force for good and force for evil in some sort of spiritual war and there is a reason for that – the theme is true. The Cult and its non-human masters are quite happy for this to circulate. They present themselves as the force for good fighting evil when they are really the force of evil (absence of love). The whole foundation of Cult modus operandi is inversion. They promote themselves as a force for good and anyone challenging them in pursuit of peace, love, fairness, truth and justice is condemned as a satanic force for evil. This has been the game plan throughout history whether the Church of Rome inquisitions of non-believers or 'conspiracy theorists' and 'anti-vaxxers' of today. The technique is the same whatever the timeline era.

Yaldabaoth is revolting (true)

Yaldabaoth and the Archons are said to have revolted against God with Yaldabaoth claiming to *be* God – the *All That Is*. The Old Testament 'God' (Yaldabaoth) demanded to be worshipped as such: ' *I am* the LORD, and there is none else, there is no God beside me' (Isaiah 45:5). I have quoted in other books a man who said he was the unofficial son of the late Baron Philippe de Rothschild of the Mouton-Rothschild wine producing estates in France who died in 1988 and he told me about the Rothschild 'revolt from God'. The man said he was given the name Phillip Eugene de Rothschild and we shared long correspondence many years ago while he was living under another identity. He said that he was conceived through 'occult incest' which (within the Cult) was 'normal and to be admired'. 'Phillip' told me about his experience attending satanic rituals with rich and famous people whom he names and you can see them and the wider background to Cult Satanism in my other books starting with *The Biggest Secret*. Cult rituals are interactions with Archontic 'gods'. 'Phillip' described Baron Philippe de Rothschild as 'a master Satanist and hater of God' and he used the same term 'revolt from God' associated with Yaldabaoth/Satan/Lucifer/the Devil in describing the Sabbatian Rothschild dynasty. 'I played a key role in my family's revolt from God', he said. That role was to infiltrate in classic Sabbatian style the Christian Church, but eventually he escaped the mind-prison to live another life. The Cult has been targeting religion in a plan to make worship of the Archons the global one-world religion. Infiltration of Satanism into modern 'culture', especially among the young, through music videos, stage shows and other means, is all part of this.

Nag Hammadi texts describe Yaldabaoth and the Archons in their prime form as energy – consciousness – and say they can take form if they choose in the same way that consciousness takes form as a human. Yaldabaoth is called 'formless' and represents a deeply inverted, distorted and chaotic state of consciousness which seeks to attached to humans and turn them into a likeness of itself in an attempt at assimilation. For that to happen it has to manipulate

humans into low frequency mental and emotional states that match its own. Archons can certainly appear in human form and this is the origin of the psychopathic personality. The energetic distortion Gnostics called Yaldabaoth *is* psychopathy. When psychopathic Archons take human form that human will be a psychopath as an expression of Yaldabaoth consciousness. Cult psychopaths are Archons in human form. The principle is the same as that portrayed in the 2009 *Avatar* movie when the American military travelled to a fictional Earth-like moon called Pandora in the Alpha Centauri star system to infiltrate a society of blue people, or Na'vi, by hiding within bodies that looked like the Na'vi. Archons posing as humans have a particular hybrid information field, part human, part Archon, (the ancient 'demigods') which processes information in a way that manifests behaviour to match their psychopathic evil, lack of empathy and compassion, and stops them being influenced by the empathy, compassion and love that a fully-human information field is capable of expressing. Cult bloodlines interbreed, be they royalty or dark suits, for this reason and you have their obsession with incest. Interbreeding with full-blown humans would dilute the Archontic energy field that guarantees psychopathy in its representatives in the human realm.

Gnostic writings say the main non-human forms that Archons take are *serpentine* (what I have called for decades 'reptilian' amid unbounded ridicule from the Archontically-programmed) and what Gnostics describe as 'an unborn baby or foetus with grey skin and dark, unmoving eyes'. This is an excellent representation of the ET 'Greys' of UFO folklore which large numbers of people claim to have seen and been abducted by – Zulu shaman Credo Mutwa among them. I agree with those that believe in extraterrestrial or interdimensional visitations today and for thousands of years past. No wonder with their advanced knowledge and technological capability they were perceived and worshipped as gods for technological and other 'miracles' they appeared to perform. Imagine someone arriving in a culture disconnected from the modern world with a smartphone and computer. They would be

seen as a 'god' capable of 'miracles'. The Renegade Mind, however, wants to know the source of everything and not only the way that source manifests as human or non-human. In the same way that a Renegade Mind seeks the original source material for the 'Covid virus' to see if what is claimed is true. The original source of Archons in form is consciousness – the distorted state of consciousness known to Gnostics as Yaldabaoth.

'Revolt from God' is energetic disconnection

Where I am going next will make a lot of sense of religious texts and ancient legends relating to 'Satan', Lucifer' and the 'gods'. Gnostic descriptions sync perfectly with the themes of my own research over the years in how they describe a consciousness distortion seeking to impose itself on human consciousness. I've referred to the core of infinite awareness in previous books as Infinite Awareness in Awareness of Itself. By that I mean a level of awareness that knows that it is all awareness and is aware of all awareness. From here comes the frequency of love in its true sense and balance which is what love is on one level – the balance of all forces into a single whole called Oneness and Isness. The more we disconnect from this state of love that many call 'God' the constituent parts of that Oneness start to unravel and express themselves as a part and not a whole. They become individualised as intellect, mind, selfishness, hatred, envy, desire for power over others, and such like. This is not a problem in the greater scheme in that 'God', the *All That Is*, can experience all these possibilities through different expressions of itself including humans. What we as expressions of the whole experience the *All That Is* experiences. We are the *All That Is* experiencing itself. As we withdraw from that state of Oneness we disconnect from its influence and things can get very unpleasant and very stupid. Archontic consciousness is at the extreme end of that. It has so disconnected from the influence of Oneness that it has become an inversion of unity and love, an inversion of everything, an inversion of life itself. Evil is appropriately live written backwards. Archontic consciousness is obsessed with death, an inversion of life,

and so its manifestations in Satanism are obsessed with death. They use inverted symbols in their rituals such as the inverted pentagram and cross. Sabbatians as Archontic consciousness incarnate invert Judaism and every other religion and culture they infiltrate. They seek disunity and chaos and they fear unity and harmony as they fear love like garlic to a vampire. As a result the Cult, Archons incarnate, act with such evil, psychopathy and lack of empathy and compassion disconnected as they are from the source of love. How could Bill Gates and the rest of the Archontic psychopaths do what they have to human society in the 'Covid' era with all the death, suffering and destruction involved and have no emotional consequence for the impact on others? Now you know. Why have Zuckerberg, Brin, Page, Wojcicki and company callously censored information warning about the dangers of the 'vaccine' while thousands have been dying and having severe, sometimes life-changing reactions? Now you know. Why have Tedros, Fauci, Whitty, Vallance and their like around the world been using case and death figures they're aware are fraudulent to justify lockdowns and all the deaths and destroyed lives that have come from that? Now you know. Why did Christian Drosten produce and promote a 'testing' protocol that he knew couldn't test for infectious disease which led to a global human catastrophe. Now you know. The Archontic mind doesn't give a shit (Fig 17). I personally think that Gates and major Cult insiders are a form of AI cyborg that the Archons want humans to become.

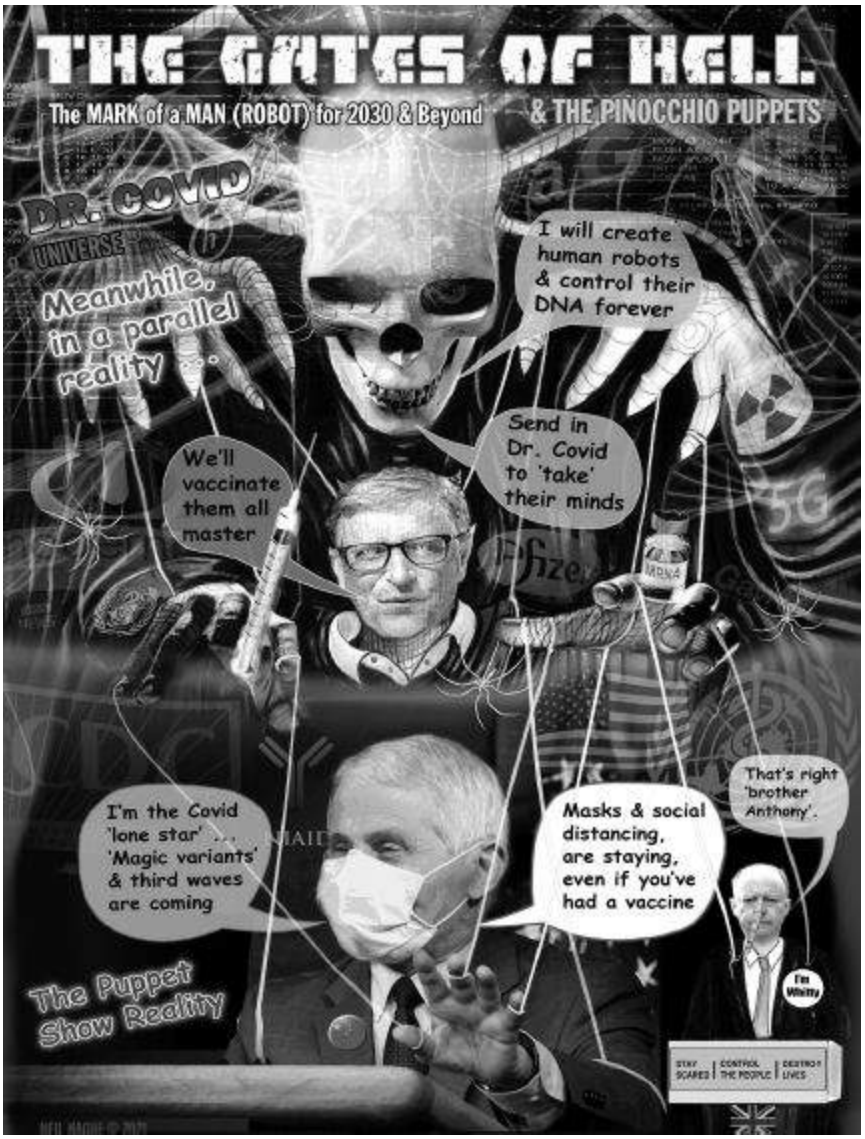


Figure 17: Artist Neil Hague's version of the 'Covid' hierarchy.

Human batteries

A state of such inversion does have its consequences, however. The level of disconnection from the Source of All means that you withdraw from that source of energetic sustenance and creativity. This means that you have to find your own supply of energetic power and it has – *us*. When the Morpheus character in the first *Matrix* movie held up a battery he spoke a profound truth when he said: 'The Matrix is a computer-generated dream world built to keep us under control in order to change the human being into one of

these.' The statement was true in all respects. We do live in a technologically-generated virtual reality simulation (more very shortly) and we have been manipulated to be an energy source for Archontic consciousness. The Disney-Pixar animated movie *Monsters, Inc*. in 2001 symbolised the dynamic when monsters in their world had no energy source and they would enter the human world to terrify children in their beds, catch the child's scream, terror (low-vibrational frequencies), and take that energy back to power the monster world. The lead character you might remember was a single giant eye and the symbolism of the Cult's all-seeing eye was obvious. Every thought and emotion is broadcast as a frequency unique to that thought and emotion. Feelings of love and joy, empathy and compassion, are high, quick, frequencies while fear, depression, anxiety, suffering and hate are low, slow, dense frequencies. Which kind do you think Archontic consciousness can connect with and absorb? In such a low and dense frequency state there's no way it can connect with the energy of love and joy. Archons can only feed off energy compatible with their own frequency and they and their Cult agents want to delete the human world of love and joy and manipulate the transmission of low vibrational frequencies through low-vibrational human mental and emotional states. *We are their energy source*. Wars are energetic banquets to the Archons – a world war even more so – and think how much low-frequency mental and emotional energy has been generated from the consequences for humanity of the 'Covid' hoax orchestrated by Archons incarnate like Gates.

The ancient practice of human sacrifice 'to the gods', continued in secret today by the Cult, is based on the same principle. 'The gods' are Archontic consciousness in different forms and the sacrifice is induced into a state of intense terror to generate the energy the Archontic frequency can absorb. Incarnate Archons in the ritual drink the blood which contains an adrenaline they crave which floods into the bloodstream when people are terrorised. Most of the sacrifices, ancient and modern, are children and the theme of 'sacrificing young virgins to the gods' is just code for children. They

have a particular pre-puberty energy that Archons want more than anything and the energy of the young in general is their target. The California Department of Education wants students to chant the names of Aztec gods (Archontic gods) once worshipped in human sacrifice rituals in a curriculum designed to encourage them to 'challenge racist, bigoted, discriminatory, imperialist/colonial beliefs', join 'social movements that struggle for social justice', and 'build new possibilities for a post-racist, post-systemic racism society'. It's the usual Woke crap that inverts racism and calls it anti-racism. In this case solidarity with 'indigenous tribes' is being used as an excuse to chant the names of 'gods' to which people were sacrificed (and still are in secret). What an example of Woke's inability to see beyond black and white, us and them, They condemn the colonisation of these tribal cultures by Europeans (quite right), but those cultures sacrificing people including children to their 'gods', and mass murdering untold numbers as the Aztecs did, is just fine. One chant is to the Aztec god Tezcatlipoca who had a man sacrificed to him in the 5th month of the Aztec calendar. His heart was cut out and he was eaten. Oh, that's okay then. Come on children … after three … Other sacrificial 'gods' for the young to chant their allegiance include Quetzalcoatl, Huitzilopochtli and Xipe Totec. The curriculum says that 'chants, affirmations, and energizers can be used to bring the class together, build unity around ethnic studies principles and values, and to reinvigorate the class following a lesson that may be emotionally taxing or even when student engagement may appear to be low'. Well, that's the cover story, anyway. Chanting and mantras are the repetition of a particular frequency generated from the vocal cords and chanting the names of these Archontic 'gods' tunes you into their frequency. That is the last thing you want when it allows for energetic synchronisation, attachment and perceptual influence. Initiates chant the names of their 'Gods' in their rituals for this very reason.

Vampires of the Woke

Paedophilia is another way that Archons absorb the energy of children. Paedophiles possessed by Archontic consciousness are used as the conduit during sexual abuse for discarnate Archons to vampire the energy of the young they desire so much. Stupendous numbers of children disappear every year never to be seen again although you would never know from the media. Imagine how much low-vibrational energy has been generated by children during the 'Covid' hoax when so many have become depressed and psychologically destroyed to the point of killing themselves. Shocking numbers of children are now taken by the state from loving parents to be handed to others. I can tell you from long experience of researching this since 1996 that many end up with paedophiles and assets of the Cult through corrupt and Cult-owned social services which in the reframing era has hired many psychopaths and emotionless automatons to do the job. Children are even stolen to order using spurious reasons to take them by the corrupt and secret (because they're corrupt) 'family courts'. I have written in detail in other books, starting with *The Biggest Secret* in 1997, about the ubiquitous connections between the political, corporate, government, intelligence and military elites (Cult operatives) and Satanism and paedophilia. If you go deep enough both networks have an interlocking leadership. The Woke mentality has been developed by the Cult for many reasons: To promote almost every aspect of its agenda; to hijack the traditional political left and turn it fascist; to divide and rule; and to target agenda pushbackers. But there are other reasons which relate to what I am describing here. How many happy and joyful Wokers do you ever see especially at the extreme end? They are a mental and psychological mess consumed by emotional stress and constantly emotionally cocked for the next explosion of indignation at someone referring to a female as a female. They are walking, talking, batteries as Morpheus might say emitting frequencies which both enslave them in low-vibrational bubbles of perceptual limitation and feed the Archons. Add to this the hatred claimed to be love; fascism claimed to 'anti-fascism', racism claimed to be 'anti-racism';

exclusion claimed to inclusion; and the abuse-filled Internet trolling. You have a purpose-built Archontic energy system with not a wind turbine in sight and all founded on Archontic *inversion*. We have whole generations now manipulated to serve the Archons with their actions and energy. They will be doing so their entire adult lives unless they snap out of their Archon-induced trance. Is it really a surprise that Cult billionaires and corporations put so much money their way? Where is the energy of joy and laughter, including laughing at yourself which is confirmation of your own emotional security? Mark Twain said: 'The human race has one really effective weapon, and that is laughter.' We must use it all the time. Woke has destroyed comedy because it has no humour, no joy, sense of irony, or self-deprecation. Its energy is dense and intense. *Mmmmm*, lunch says the Archontic frequency. Rudolf Steiner (1861-1925) was the Austrian philosopher and famous esoteric thinker who established Waldorf education or Steiner schools to treat children like unique expressions of consciousness and not minds to be programmed with the perceptions determined by authority. I'd been writing about this energy vampiring for decades when I was sent in 2016 a quote by Steiner. He was spot on:

> There are beings in the spiritual realms for whom anxiety and fear emanating from human beings offer welcome food. When humans have no anxiety and fear, then these creatures starve. If fear and anxiety radiates from people and they break out in panic, then these creatures find welcome nutrition and they become more and more powerful. These beings are hostile towards humanity. Everything that feeds on negative feelings, on anxiety, fear and superstition, despair or doubt, are in reality hostile forces in super-sensible worlds, launching cruel attacks on human beings, while they are being fed ... These are exactly the feelings that belong to contemporary culture and materialism; because it estranges people from the spiritual world, it is especially suited to evoke hopelessness and fear of the unknown in people, thereby calling up the above mentioned hostile forces against them.

Pause for a moment from this perspective and reflect on what has happened in the world since the start of 2020. Not only will pennies drop, but billion dollar bills. We see the same theme from Don Juan Matus, a Yaqui Indian shaman in Mexico and the information source for Peruvian-born writer, Carlos Castaneda, who wrote a series of

books from the 1960s to 1990s. Don Juan described the force manipulating human society and his name for the Archons was the predator:

> We have a predator that came from the depths of the cosmos and took over the rule of our lives. Human beings are its prisoners. The predator is our lord and master. It has rendered us docile, helpless. If we want to protest, it suppresses our protest. If we want to act independently, it demands that we don't do so ... indeed we are held prisoner!
>
> They took us over because we are food to them, and they squeeze us mercilessly because we are their sustenance. Just as we rear chickens in coops, the predators rear us in human coops, humaneros. Therefore, their food is always available to them.
>
> Different cultures, different eras, same recurring theme.

The 'ennoia' dilemma

Nag Hammadi Gnostic manuscripts say that Archon consciousness has no 'ennoia'. This is directly translated as 'intentionality', but I'll use the term 'creative imagination'. The *All That Is* in awareness of itself is the source of all creativity – all possibility – and the more disconnected you are from that source the more you are subsequently denied 'creative imagination'. Given that Archon consciousness is almost entirely disconnected it severely lacks creativity and has to rely on far more mechanical processes of thought and exploit the creative potential of those that do have 'ennoia'. You can see cases of this throughout human society. Archon consciousness almost entirely dominates the global banking system and if we study how that system works you will appreciate what I mean. Banks manifest 'money' out of nothing by issuing lines of 'credit' which is 'money' that has never, does not, and will never exist except in theory. It's a confidence trick. If you think 'credit' figures-on-a-screen 'money' is worth anything you accept it as payment. If you don't then the whole system collapses through lack of confidence in the value of that 'money'. Archontic bankers with no 'ennoia' are 'lending' 'money' that doesn't exist to humans that *do* have creativity – those that have the inspired ideas and create businesses and products. Archon banking feeds off human creativity

which it controls through 'money' creation and debt. Humans have the creativity and Archons exploit that for their own benefit and control while having none themselves. Archon Internet platforms like Facebook claim joint copyright of everything that creative users post and while Archontic minds like Zuckerberg may officially head that company it will be human creatives on the staff that provide the creative inspiration. When you have limitless 'money' you can then buy other companies established by creative humans. Witness the acquisition record of Facebook, Google and their like. Survey the Archon-controlled music industry and you see non-creative dark suit executives making their fortune from the human creativity of their artists. The cases are endless. Research the history of people like Gates and Zuckerberg and how their empires were built on exploiting the creativity of others. Archon minds cannot create out of nothing, but they are skilled (because they have to be) in what Gnostic texts call 'countermimicry'. They can imitate, but not innovate. Sabbatians trawl the creativity of others through backdoors they install in computer systems through their cybersecurity systems. Archon-controlled China is globally infamous for stealing intellectual property and I remember how Hong Kong, now part of China, became notorious for making counterfeit copies of the creativity of others – 'countermimicry'. With the now pervasive and all-seeing surveillance systems able to infiltrate any computer you can appreciate the potential for Archons to vampire the creativity of humans. Author John Lamb Lash wrote in his book about the Nag Hammadi texts, *Not In His Image*:

> Although they cannot originate anything, because they lack the divine factor of ennoia (intentionality), Archons can imitate with a vengeance. Their expertise is simulation (HAL, virtual reality). The Demiurge [Yaldabaoth] fashions a heaven world copied from the fractal patterns [of the original] ... His construction is celestial kitsch, like the fake Italianate villa of a Mafia don complete with militant angels to guard every portal.

This brings us to something that I have been speaking about since the turn of the millennium. Our reality is a simulation; a virtual reality that we think is real. No, I'm not kidding.

Human reality? Well, virtually

I had pondered for years about whether our reality is 'real' or some kind of construct. I remembered being immensely affected on a visit as a small child in the late 1950s to the then newly-opened Planetarium on the Marylebone Road in London which is now closed and part of the adjacent Madame Tussauds wax museum. It was in the middle of the day, but when the lights went out there was the night sky projected in the Planetarium's domed ceiling and it appeared to be so real. The experience never left me and I didn't know why until around the turn of the millennium when I became certain that our 'night sky' and entire reality is a projection, a virtual reality, akin to the illusory world portrayed in the *Matrix* movies. I looked at the sky one day in this period and it appeared to me like the domed roof of the Planetarium. The release of the first *Matrix* movie in 1999 also provided a synchronistic and perfect visual representation of where my mind had been going for a long time. I hadn't come across the Gnostic Nag Hammadi texts then. When I did years later the correlation was once again astounding. As I read Gnostic accounts from 1,600 years and more earlier it was clear that they were describing the same simulation phenomenon. They tell how the Yaldabaoth 'Demiurge' and Archons created a 'bad copy' of original reality to rule over all that were captured by its illusions and the body was a prison to trap consciousness in the 'bad copy' fake reality. Read how Gnostics describe the 'bad copy' and update that to current times and they are referring to what we would call today a virtual reality simulation.

Author John Lamb Lash said 'the Demiurge fashions a heaven world copied from the fractal patterns' of the original through expertise in 'HAL' or virtual reality simulation. Fractal patterns are part of the energetic information construct of our reality, a sort of blueprint. If these patterns were copied in computer terms it would indeed give you a copy of a 'natural' reality in a non-natural frequency and digital form. The principle is the same as making a copy of a website. The original website still exists, but now you can change the copy version to make it whatever you like and it can

become very different to the original website. Archons have done this with our reality, a *synthetic* copy of prime reality that still exists beyond the frequency walls of the simulation. Trapped within the illusions of this synthetic Matrix, however, were and are human consciousness and other expressions of prime reality and this is why the Archons via the Cult are seeking to make the human body synthetic and give us synthetic AI minds to complete the job of turning the entire reality synthetic including what we perceive to be the natural world. To quote Kurzweil: 'Nanobots will infuse all the matter around us with information. Rocks, trees, everything will become these intelligent creatures.' Yes, *synthetic* 'creatures' just as 'Covid' and other genetically-manipulating 'vaccines' are designed to make the human body synthetic. From this perspective it is obvious why Archons and their Cult are so desperate to infuse synthetic material into every human with their 'Covid' scam.

Let there be (electromagnetic) light

Yaldabaoth, the force that created the simulation, or Matrix, makes sense of the Gnostic reference to 'The Great Architect' and its use by Cult Freemasonry as the name of its deity. The designer of the Matrix in the movies is called 'The Architect' and that trilogy is jam-packed with symbolism relating to these subjects. I have contended for years that the angry Old Testament God (Yaldabaoth) is the 'God' being symbolically 'quoted' in the opening of Genesis as 'creating the world'. This is not the creation of prime reality – it's the creation of the *simulation*. The Genesis 'God' says: 'Let there be Light: and there was light.' But what is this 'Light'? I have said for decades that the speed of light (186,000 miles per second) is not the fastest speed possible as claimed by mainstream science and is in fact the frequency walls or outer limits of the Matrix. You can't have a fastest or slowest anything within all possibility when everything is possible. The human body is encoded to operate within the speed of light or *within the simulation* and thus we see only the tiny frequency band of visible *light*. Near-death experiencers who perceive reality outside the body during temporary 'death' describe a very different

form of light and this is supported by the Nag Hammadi texts. Prime reality beyond the simulation ('Upper Aeons' to the Gnostics) is described as a realm of incredible beauty, bliss, love and harmony – a realm of 'watery light' that is so powerful 'there are no shadows'. Our false reality of Archon control, which Gnostics call the 'Lower Aeons', is depicted as a realm with a different kind of 'light' and described in terms of chaos, 'Hell', 'the Abyss' and 'Outer Darkness', where trapped souls are tormented and manipulated by demons (relate that to the 'Covid' hoax alone). The watery light theme can be found in near-death accounts and it is not the same as *simulation* 'light' which is electromagnetic or radiation light within the speed of light – the 'Lower Aeons'. Simulation 'light' is the 'luminous fire' associated by Gnostics with the Archons. The Bible refers to Yaldabaoth as 'that old serpent, called the Devil, and Satan, which deceiveth the whole world' (Revelation 12:9). I think that making a simulated copy of prime reality ('countermimicry') and changing it dramatically while all the time manipulating humanity to believe it to be real could probably meet the criteria of deceiving the whole world. Then we come to the Cult god Lucifer – the *Light Bringer*. Lucifer is symbolic of Yaldabaoth, the bringer of radiation light that forms the bad copy simulation within the speed of light. 'He' is symbolised by the lighted torch held by the Statue of Liberty and in the name 'Illuminati'. Sabbatian-Frankism declares that Lucifer is the true god and Lucifer is the real god of Freemasonry honoured as their 'Great or Grand Architect of the Universe' (simulation).

I would emphasise, too, the way Archontic technologically-generated luminous fire of radiation has deluged our environment since I was a kid in the 1950s and changed the nature of The Field with which we constantly interact. Through that interaction technological radiation is changing us. The Smart Grid is designed to operate with immense levels of communication power with 5G expanding across the world and 6G, 7G, in the process of development. Radiation is the simulation and the Archontic manipulation system. Why wouldn't the Archon Cult wish to unleash radiation upon us to an ever-greater extreme to form

Kurzweil's 'cloud'? The plan for a synthetic human is related to the need to cope with levels of radiation beyond even anything we've seen so far. Biological humans would not survive the scale of radiation they have in their script. The Smart Grid is a technological sub-reality within the technological simulation to further disconnect five-sense perception from expanded consciousness. It's a technological prison of the mind.

Infusing the 'spirit of darkness'

A recurring theme in religion and native cultures is the manipulation of human genetics by a non-human force and most famously recorded as the biblical 'sons of god' (the god*s* plural in the original) who interbred with the daughters of men. The Nag Hammadi *Apocryphon of John* tells the same story this way:

> He [Yaldabaoth] sent his angels [Archons/demons] to the daughters of men, that they might take some of them for themselves and raise offspring for their enjoyment. And at first they did not succeed. When they had no success, they gathered together again and they made a plan together ... And the angels changed themselves in their likeness into the likeness of their mates, filling them with the spirit of darkness, which they had mixed for them, and with evil ... And they took women and begot children out of the darkness according to the likeness of their spirit.

Possession when a discarnate entity takes over a human body is an age-old theme and continues today. It's very real and I've seen it. Satanic and secret society rituals can create an energetic environment in which entities can attach to initiates and I've heard many stories of how people have changed their personality after being initiated even into lower levels of the Freemasons. I have been inside three Freemasonic temples, one at a public open day and two by just walking in when there was no one around to stop me. They were in Ryde, the town where I live, Birmingham, England, when I was with a group, and Boston, Massachusetts. They all felt the same energetically – dark, dense, low-vibrational and sinister. Demonic attachment can happen while the initiate has no idea what is going on. To them it's just a ritual to get in the Masons and do a bit of good

business. In the far more extreme rituals of Satanism human possession is even more powerful and they are designed to make possession possible. The hierarchy of the Cult is dictated by the power and perceived status of the possessing Archon. In this way the Archon hierarchy becomes the Cult hierarchy. Once the entity has attached it can influence perception and behaviour and if it attaches to the extreme then so much of its energy (information) infuses into the body information field that the hologram starts to reflect the nature of the possessing entity. This is the *Exorcist* movie type of possession when facial features change and it's known as shapeshifting. Islam's Jinn are said to be invisible tricksters who change shape, 'whisper', confuse and take human form. These are all traits of the Archons and other versions of the same phenomenon. Extreme possession could certainty infuse the 'spirit of darkness' into a partner during sex as the Nag Hammadi texts appear to describe. Such an infusion can change genetics which is also energetic information. Human genetics is information and the 'spirit of darkness' is information. Mix one with the other and change must happen. Islam has the concept of a 'Jinn baby' through possession of the mother and by Jinn taking human form. There are many ways that human genetics can be changed and remember that Archons have been aware all along of advanced techniques to do this. What is being done in human society today – and far more – was known about by Archons at the time of the 'fallen ones' and their other versions described in religions and cultures.

Archons and their human-world Cult are obsessed with genetics as we see today and they know this dictates how information is processed into perceived reality during a human life. They needed to produce a human form that would decode the simulation and this is symbolically known as 'Adam and Eve' who left the 'garden' (prime reality) and 'fell' into Matrix reality. The simulation is not a 'physical' construct (there is no 'physical'); it is a source of information. Think Wi-Fi again. The simulation is an energetic field encoded with information and body-brain systems are designed to decode that information encoded in wave or frequency form which

is transmitted to the brain as electrical signals. These are decoded by the brain to construct our sense of reality – an illusory 'physical' world that only exists in the brain or the mind. Virtual reality games mimic this process using the same sensory decoding system. Information is fed to the senses to decode a virtual reality that can appear so real, but isn't (Figs 18 and 19). Some scientists believe – and I agree with them – that what we perceive as 'physical' reality only exists when we are looking or observing. The act of perception or focus triggers the decoding systems which turn waveform information into holographic reality. When we are not observing something our reality reverts from a holographic state to a waveform state. This relates to the same principle as a falling tree not making a noise unless someone is there to hear it or decode it. The concept makes sense from the simulation perspective. A computer is not decoding all the information in a Wi-Fi field all the time and only decodes or brings into reality on the screen that part of Wi-Fi that it's decoding – focusing upon – at that moment.



Figure 18: Virtual reality technology 'hacks' into the body's five-sense decoding system.



Figure 19: The result can be experienced as very 'real'.

Interestingly, Professor Donald Hoffman at the Department of Cognitive Sciences at the University of California, Irvine, says that our experienced reality is like a computer interface that shows us only the level with which we interact while hiding all that exists beyond it: 'Evolution shaped us with a user interface that hides the truth. Nothing that we see is the truth – the very language of space and time and objects is the wrong language to describe reality.' He is correct in what he says on so many levels. Space and time are not a universal reality. They are a phenomenon of decoded *simulation* reality as part of the process of enslaving our sense of reality. Near-death experiencers report again and again how space and time did not exist as we perceive them once they were free of the body – body decoding systems. You can appreciate from this why Archons and their Cult are so desperate to entrap human attention in the five senses where we are in the Matrix and of the Matrix. Opening your mind to expanded states of awareness takes you beyond the information confines of the simulation and you become aware of knowledge and insights denied to you before. This is what we call 'awakening' – *awakening from the Matrix* – and in the final chapter I will relate this to current events.

Where are the 'aliens'?

A simulation would explain the so-called 'Fermi Paradox' named after Italian physicist Enrico Fermi (1901-1954) who created the first nuclear reactor. He considered the question of why there is such a lack of extraterrestrial activity when there are so many stars and planets in an apparently vast universe; but what if the night sky that we see, or think we do, is a simulated projection as I say? If you control the simulation and your aim is to hold humanity fast in essential ignorance would you want other forms of life including advanced life coming and going sharing information with humanity? Or would you want them to believe they were isolated and apparently alone? Themes of human isolation and apartness are common whether they be the perception of a lifeless universe or the fascist isolation laws of the 'Covid' era. Paradoxically the very

existence of a simulation means that we are not alone when some force had to construct it. My view is that experiences that people have reported all over the world for centuries with Reptilians and Grey entities are Archon phenomena as Nag Hammadi texts describe; and that benevolent 'alien' interactions are non-human groups that come in and out of the simulation by overcoming Archon attempts to keep them out. It should be highlighted, too, that Reptilians and Greys are obsessed with *genetics* and *technology* as related by cultural accounts and those who say they have been abducted by them. Technology is their way of overcoming some of the limitations in their creative potential and our technology-driven and controlled human society of today is *arch*etypical Archon-Reptilian-Grey modus operandi. Technocracy is really *Archon*tocracy. The Universe does not have to be as big as it appears with a simulation. There is no space or distance only information decoded into holographic reality. What we call 'space' is only the absence of holographic 'objects' and that 'space' is The Field of energetic information which connects everything into a single whole. The same applies with the artificially-generated information field of the simulation. The Universe is not big or small as a physical reality. It is decoded information, that's all, and its perceived size is decided by the way the simulation is encoded to make it appear. The entire night sky as we perceive it only exists in our brain and so where are those 'millions of light years'? The 'stars' on the ceiling of the Planetarium looked a vast distance away.

There's another point to mention about 'aliens'. I have been highlighting since the 1990s the plan to stage a fake 'alien invasion' to justify the centralisation of global power and a world military. Nazi scientist Werner von Braun, who was taken to America by Operation Paperclip after World War Two to help found NASA, told his American assistant Dr Carol Rosin about the Cult agenda when he knew he was dying in 1977. Rosin said that he told her about a sequence that would lead to total human control by a one-world government. This included threats from terrorism, rogue nations, meteors and asteroids before finally an 'alien invasion'. All of these

things, von Braun said, would be bogus and what I would refer to as a No-Problem-Reaction-Solution. Keep this in mind when 'the aliens are coming' is the new mantra. The aliens are not coming – they are *already here* and they have infiltrated human society while looking human. French-Canadian investigative journalist Serge Monast said in 1994 that he had uncovered a NASA/military operation called Project Blue Beam which fits with what Werner von Braun predicted. Monast died of a 'heart attack' in 1996 the day after he was arrested and spent a night in prison. He was 51. He said Blue Beam was a plan to stage an alien invasion that would include religious figures beamed holographically into the sky as part of a global manipulation to usher in a 'new age' of worshipping what I would say is the Cult 'god' Yaldabaoth in a one-world religion. Fake holographic asteroids are also said to be part of the plan which again syncs with von Braun. How could you stage an illusory threat from asteroids unless they were holographic inserts? This is pretty straightforward given the advanced technology outside the public arena and the fact that our 'physical' reality is holographic anyway. Information fields would be projected and we would decode them into the illusion of a 'physical' asteroid. If they can sell a global 'pandemic' with a 'virus' that doesn't exist what will humans not believe if government and media tell them?

All this is particularly relevant as I write with the Pentagon planning to release in June, 2021, information about 'UFO sightings'. I have been following the UFO story since the early 1990s and the common theme throughout has been government and military denials and cover up. More recently, however, the Pentagon has suddenly become more talkative and apparently open with Air Force pilot radar images released of unexplained craft moving and changing direction at speeds well beyond anything believed possible with human technology. Then, in March, 2021, former Director of National Intelligence John Ratcliffe said a Pentagon report months later in June would reveal a great deal of information about UFO sightings unknown to the public. He said the report would have 'massive implications'. The order to do this was included bizarrely

in a $2.3 trillion 'coronavirus' relief and government funding bill passed by the Trump administration at the end of 2020. I would add some serious notes of caution here. I have been pointing out since the 1990s that the US military and intelligence networks have long had craft – 'flying saucers' or anti-gravity craft – which any observer would take to be extraterrestrial in origin. Keeping this knowledge from the public allows craft flown by *humans* to be perceived as alien visitations. I am not saying that 'aliens' do not exist. I would be the last one to say that, but we have to be streetwise here. President Ronald Reagan told the UN General Assembly in 1987: 'I occasionally think how quickly our differences worldwide would vanish if we were facing an alien threat from outside this world.' That's the idea. Unite against a common 'enemy' with a common purpose behind your 'saviour force' (the Cult) as this age-old technique of mass manipulation goes global.

Science moves this way …

I could find only one other person who was discussing the simulation hypothesis publicly when I concluded it was real. This was Nick Bostrom, a Swedish-born philosopher at the University of Oxford, who has explored for many years the possibility that human reality is a computer simulation although his version and mine are not the same. Today the simulation and holographic reality hypothesis have increasingly entered the scientific mainstream. Well, the more open-minded mainstream, that is. Here are a few of the ever-gathering examples. American nuclear physicist Silas Beane led a team of physicists at the University of Bonn in Germany pursuing the question of whether we live in a simulation. They concluded that we probably do and it was likely based on a lattice of cubes. They found that cosmic rays align with that specific pattern. The team highlighted the Greisen–Zatsepin–Kuzmin (GZK) limit which refers to cosmic ray particle interaction with cosmic background radiation that creates an apparent boundary for cosmic ray particles. They say in a paper entitled 'Constraints on the Universe as a Numerical Simulation' that this 'pattern of constraint' is exactly what you

would find with a computer simulation. They also made the point that a simulation would create its own 'laws of physics' that would limit possibility. I've been making the same point for decades that the *perceived* laws of physics relate only to this reality, or what I would later call the simulation. When designers write codes to create computer and virtual reality games they are the equivalent of the laws of physics for that game. Players interact within the limitations laid out by the coding. In the same way those who wrote the codes for the simulation decided the laws of physics that would apply. These can be overridden by expanded states of consciousness, but not by those enslaved in only five-sense awareness where simulation codes rule. Overriding the codes is what people call 'miracles'. They are not. They are bypassing the encoded limits of the simulation. A population caught in simulation perception would have no idea that this was their plight. As the Bonn paper said: 'Like a prisoner in a pitch-black cell we would not be able to see the "walls" of our prison,' That's true if people remain mesmerised by the five senses. Open to expanded awareness and those walls become very clear. The main one is the speed of light.

American theoretical physicist James Gates is another who has explored the simulation question and found considerable evidence to support the idea. Gates was Professor of Physics at the University of Maryland, Director of The Center for String and Particle Theory, and on Barack Obama's Council of Advisors on Science and Technology. He and his team found *computer codes* of digital data embedded in the fabric of our reality. They relate to on-off electrical charges of 1 and 0 in the binary system used by computers. 'We have no idea what they are doing there', Gates said. They found within the energetic fabric mathematical sequences known as error-correcting codes or block codes that 'reboot' data to its original state or 'default settings' when something knocks it out of sync. Gates was asked if he had found a set of equations embedded in our reality indistinguishable from those that drive search engines and browsers and he said: 'That is correct.' Rich Terrile, director of the Centre for Evolutionary Computation and Automated Design at NASA's Jet

Propulsion Laboratory, has said publicly that he believes the Universe is a digital hologram that must have been created by a form of intelligence. I agree with that in every way. Waveform information is delivered electrically by the senses to the brain which constructs a *digital* holographic reality that we call the 'world'. This digital level of reality can be read by the esoteric art of numerology. Digital holograms are at the cutting edge of holographics today. We have digital technology everywhere designed to access and manipulate our digital level of perceived reality. Synthetic mRNA in 'Covid vaccines' has a digital component to manipulate the body's digital 'operating system'.

Reality is numbers

How many know that our reality can be broken down to numbers and codes that are the same as computer games? Max Tegmark, a physicist at the Massachusetts Institute of Technology (MIT), is the author of *Our Mathematical Universe* in which he lays out how reality can be entirely described by numbers and maths in the way that a video game is encoded with the 'physics' of computer games. Our world and computer virtual reality are essentially the same. Tegmark imagines the perceptions of characters in an advanced computer game when the graphics are so good they don't know they are in a game. They think they can bump into real objects (electromagnetic resistance in our reality), fall in love and feel emotions like excitement. When they began to study the apparently 'physical world' of the video game they would realise that everything was made of pixels (which have been found in our energetic reality as must be the case when on one level our world is digital). What computer game characters thought was physical 'stuff', Tegmark said, could actually be broken down into numbers:

> And we're exactly in this situation in our world. We look around and it doesn't seem that mathematical at all, but everything we see is made out of elementary particles like quarks and electrons. And what properties does an electron have? Does it have a smell or a colour or a texture? No! ... We physicists have come up with geeky names for [Electron] properties, like

electric charge, or spin, or lepton number, but the electron doesn't care what we call it, the properties are just numbers.

This is the illusory reality Gnostics were describing. This is the simulation. The A, C, G, and T codes of DNA have a binary value – A and C = 0 while G and T = 1. This has to be when the simulation is digital and the body must be digital to interact with it. Recurring mathematical sequences are encoded throughout reality and the body. They include the Fibonacci sequence in which the two previous numbers are added to get the next one, as in ... 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, etc. The sequence is encoded in the human face and body, proportions of animals, DNA, seed heads, pine cones, trees, shells, spiral galaxies, hurricanes and the number of petals in a flower. The list goes on and on. There are fractal patterns – a 'never-ending pattern that is infinitely complex and self-similar across all scales in the as above, so below, principle of holograms. These and other famous recurring geometrical and mathematical sequences such as Phi, Pi, Golden Mean, Golden Ratio and Golden Section are *computer codes* of the simulation. I had to laugh and give my head a shake the day I finished this book and it went into the production stage. I was sent an article in *Scientific American* published in April, 2021, with the headline 'Confirmed! We Live in a Simulation'. Two decades after I first said our reality is a simulation and the speed of light is it's outer limit the article suggested that we do live in a simulation and that the speed of light is its outer limit. I left school at 15 and never passed a major exam in my life while the writer was up to his eyes in qualifications. As I will explain in the final chapter *knowing* is far better than thinking and they come from very different sources. The article rightly connected the speed of light to the processing speed of the 'Matrix' and said what has been in my books all this time … 'If we are in a simulation, as it appears, then space is an abstract property written in code. It is not real'. No it's not and if we live in a simulation something created it and it wasn't *us*. 'That David Icke says we are manipulated by aliens' – he's crackers.'

Wow …

The reality that humanity thinks is so real is an illusion. Politicians, governments, scientists, doctors, academics, law enforcement, media, school and university curriculums, on and on, are all founded on a world that *does not exist* except as a simulated prison cell. Is it such a stretch to accept that 'Covid' doesn't exist when our entire 'physical' reality doesn't exist? Revealed here is the knowledge kept under raps in the Cult networks of compartmentalised secrecy to control humanity's sense of reality by inducing the population to believe in a reality that's not real. If it wasn't so tragic in its experiential consequences the whole thing would be hysterically funny. None of this is new to Renegade Minds. Ancient Greek philosopher Plato (about 428 to about 347BC) was a major influence on Gnostic belief and he described the human plight thousands of years ago with his Allegory of the Cave. He told the symbolic story of prisoners living in a cave who had never been outside. They were chained and could only see one wall of the cave while behind them was a fire that they could not see. Figures walked past the fire casting shadows on the prisoners' wall and those moving shadows became their sense of reality. Some prisoners began to study the shadows and were considered experts on them (today's academics and scientists), but what they studied was only an illusion (today's academics and scientists). A prisoner escaped from the cave and saw reality as it really is. When he returned to report this revelation they didn't believe him, called him mad and threatened to kill him if he tried to set them free. Plato's tale is not only a brilliant analogy of the human plight and our illusory reality. It describes, too, the dynamics of the 'Covid' hoax. I have only skimmed the surface of these subjects here. The aim of this book is to crisply connect all essential dots to put what is happening today into its true context. All subject areas and their connections in this chapter are covered in great evidential detail in *Everything You Need To Know, But Have Never Been Told* and *The Answer*.

They say that bewildered people 'can't see the forest for the trees'. Humanity, however, can't see the forest for the *twigs*. The five senses

see only twigs while Renegade Minds can see the forest and it's the forest where the answers lie with the connections that reveals. Breaking free of perceptual programming so the forest can be seen is the way we turn all this around. Not breaking free is how humanity got into this mess. The situation may seem hopeless, but I promise you it's not. We are a perceptual heartbeat from paradise if only we knew.

CHAPTER TWELVE

Escaping Wetiko

Life is simply a vacation from the infinite
Dean Cavanagh

Renegade Minds weave the web of life and events and see common themes in the apparently random. They are always there if you look for them and their pursuit is aided by incredible synchronicity that comes when your mind is open rather than mesmerised by what it thinks it can see.

Infinite awareness is infinite possibility and the more of infinite possibility that we access the more becomes infinitely possible. That may be stating the apparently obvious, but it is a devastatingly-powerful fact that can set us free. We are a point of attention within an infinity of consciousness. The question is how much of that infinity do we choose to access? How much knowledge, insight, awareness, wisdom, do we want to connect with and explore? If your focus is only in the five senses you will be influenced by a fraction of infinite awareness. I mean a range so tiny that it gives new meaning to infinitesimal. Limitation of self-identity and a sense of the possible limit accordingly your range of consciousness. We are what we think we are. Life is what we think it is. The dream is the dreamer and the dreamer is the dream. Buddhist philosophy puts it this way: 'As a thing is viewed, so it appears.' Most humans live in the realm of touch, taste, see, hear, and smell and that's the limit of their sense of the possible and sense of self. Many will follow a religion and speak of a God in his heaven, but their lives are still

dominated by the five senses in their perceptions and actions. The five senses become the arbiter of everything. When that happens all except a smear of infinity is sealed away from influence by the rigid, unyielding, reality bubbles that are the five-sense human or Phantom Self. Archon Cult methodology is to isolate consciousness within five-sense reality – the simulation – and then program that consciousness with a sense of self and the world through a deluge of life-long information designed to instil the desired perception that allows global control. Efforts to do this have increased dramatically with identity politics as identity bubbles are squeezed into the minutiae of five-sense detail which disconnect people even more profoundly from the infinite 'I'.

Five-sense focus and self-identity are like a firewall that limits access to the infinite realms. You only perceive one radio or television station and no other. We'll take that literally for a moment. Imagine a vast array of stations giving different information and angles on reality, but you only ever listen to one. Here we have the human plight in which the population is overwhelmingly confined to CultFM. This relates only to the frequency range of CultFM and limits perception and insight to that band – limits *possibility* to that band. It means you are connecting with an almost imperceptibly minuscule range of possibility and creative potential within the infinite Field. It's a world where everything seems apart from everything else and where synchronicity is rare. Synchronicity is defined in the dictionary as 'the happening by chance of two or more related or similar events at the same time'. Use of 'by chance' betrays a complete misunderstanding of reality. Synchronicity is not 'by chance'. As people open their minds, or 'awaken' to use the term, they notice more and more coincidences in their lives, bits of 'luck', apparently miraculous happenings that put them in the right place at the right time with the right people. Days become peppered with 'fancy meeting you here' and 'what are the chances of that?' My entire life has been lived like this and ever more so since my own colossal awakening in 1990 and 91 which transformed my sense of reality. Synchronicity is not 'by chance'; it is by accessing expanded

realms of possibility which allow expanded potential for manifestation. People broadcasting the same vibe from the same openness of mind tend to be drawn 'by chance' to each other through what I call frequency magnetism and it's not only people. In the last more than 30 years incredible synchronicity has also led me through the Cult maze to information in so many forms and to crucial personal experiences. These 'coincidences' have allowed me to put the puzzle pieces together across an enormous array of subjects and situations. Those who have breached the bubble of five-sense reality will know exactly what I mean and this escape from the perceptual prison cell is open to everyone whenever they make that choice. This may appear super-human when compared with the limitations of 'human', but it's really our natural state. 'Human' as currently experienced is consciousness in an unnatural state of induced separation from the infinity of the whole. I'll come to how this transformation into unity can be made when I have described in more detail the force that holds humanity in servitude by denying this access to infinite self.

The Wetiko factor

I have been talking and writing for decades about the way five-sense mind is systematically barricaded from expanded awareness. I have used the analogy of a computer (five-sense mind) and someone at the keyboard (expanded awareness). Interaction between the computer and the operator is symbolic of the interaction between five-sense mind and expanded awareness. The computer directly experiences the Internet and the operator experiences the Internet via the computer which is how it's supposed to be – the two working as one. Archons seek to control that point where the operator connects with the computer to stop that interaction (Fig 20). Now the operator is banging the keyboard and clicking the mouse, but the computer is not responding and this happens when the computer is taken over – *possessed* – by an appropriately-named computer 'virus'. The operator has lost all influence over the computer which goes its own way making decisions under the control of the 'virus'. I have

just described the dynamic through which the force known to Gnostics as Yaldabaoth and Archons disconnects five-sense mind from expanded awareness to imprison humanity in perceptual servitude.



Figure 20: The mind 'virus' I have been writing about for decades seeks to isolate five-sense mind (the computer) from the true 'I'. (Image by Neil Hague).

About a year ago I came across a Native American concept of Wetiko which describes precisely the same phenomenon. Wetiko is the spelling used by the Cree and there are other versions including wintiko and windigo used by other tribal groups. They spell the name with lower case, but I see Wetiko as a proper noun as with Archons and prefer a capital. I first saw an article about Wetiko by writer and researcher Paul Levy which so synced with what I had been writing about the computer/operator disconnection and later the Archons. I then read his book, the fascinating *Dispelling Wetiko, Breaking the Spell of Evil*. The parallels between what I had concluded long before and the Native American concept of Wetiko were so clear and obvious that it was almost funny. For Wetiko see the Gnostic Archons for sure and the Jinn, the Predators, and every other name for a force of evil, inversion and chaos. Wetiko is the Native American name for the force that divides the computer from

the operator (Fig 21). Indigenous author Jack D. Forbes, a founder of the Native American movement in the 1960s, wrote another book about Wetiko entitled *Columbus And Other Cannibals – The Wetiko Disease of Exploitation, Imperialism, and Terrorism* which I also read. Forbes says that Wetiko refers to an evil person or spirit 'who terrorizes other creatures by means of terrible acts, including cannibalism'. Zulu shaman Credo Mutwa told me that African accounts tell how cannibalism was brought into the world by the Chitauri 'gods' – another manifestation of Wetiko. The distinction between 'evil person or spirit' relates to Archons/Wetiko possessing a human or acting as pure consciousness. Wetiko is said to be a sickness of the soul or spirit and a state of being that takes but gives nothing back – the Cult and its operatives perfectly described. Black Hawk, a Native American war leader defending their lands from confiscation, said European invaders had 'poisoned hearts' – Wetiko hearts – and that this would spread to native societies. Mention of the heart is very significant as we shall shortly see. Forbes writes: 'Tragically, the history of the world for the past 2,000 years is, in great part, the story of the epidemiology of the wetiko disease.' Yes, and much longer. Forbes is correct when he says: 'The wetikos destroyed Egypt and Babylon and Athens and Rome and Tenochtitlan [capital of the Aztec empire] and perhaps now they will destroy the entire earth.' Evil, he said, is the number one export of a Wetiko culture – see its globalisation with 'Covid'. Constant war, mass murder, suffering of all kinds, child abuse, Satanism, torture and human sacrifice are all expressions of Wetiko and the Wetiko possessed. The world is Wetiko made manifest, *but it doesn't have to be*. There is a way out of this even now.



Figure 21: The mind 'virus' is known to Native Americans as 'Wetiko'. (Image by Neil Hague).

Cult of Wetiko

Wetiko is the Yaldabaoth frequency distortion that seeks to attach to human consciousness and absorb it into its own. Once this connection is made Wetiko can drive the perceptions of the target which they believe to be coming from their own mind. All the horrors of history and today from mass killers to Satanists, paedophiles like Jeffrey Epstein and other psychopaths, are the embodiment of Wetiko and express its state of being in all its grotesqueness. The Cult is Wetiko incarnate, Yaldabaoth incarnate, and it seeks to facilitate Wetiko assimilation of humanity in totality into its distortion by manipulating the population into low frequency states that match its own. Paul Levy writes: 'Holographically enforced within the psyche of every human being the wetiko virus pervades and underlies the entire field of consciousness, and can therefore potentially manifest through any one of us at any moment if we are not mindful.' The 'Covid' hoax has achieved this with many people, but others have not fallen into Wetiko's frequency lair. Players in the 'Covid' human catastrophe including Gates, Schwab, Tedros, Fauci, Whitty, Vallance, Johnson, Hancock, Ferguson, Drosten, and all the rest, including the psychopath psychologists, are expressions of Wetiko. This is why

they have no compassion or empathy and no emotional consequence for what they do that would make them stop doing it. Observe all the people who support the psychopaths in authority against the Pushbackers despite the damaging impact the psychopaths have on their own lives and their family's lives. You are again looking at Wetiko possession which prevents them seeing through the lies to the obvious scam going on. *Why can't they see it?* Wetiko won't let them see it. The perceptual divide that has now become a chasm is between the Wetikoed and the non-Wetikoed.

Paul Levy describes Wetiko in the same way that I have long described the Archontic force. They are the same distorted consciousness operating across dimensions of reality: '… the subtle body of wetiko is not located in the third dimension of space and time, literally existing in another dimension … it is able to affect ordinary lives by mysteriously interpenetrating into our three-dimensional world.' Wetiko does this through its incarnate representatives in the Cult and by weaving itself into The Field which on our level of reality is the electromagnetic information field of the simulation or Matrix. More than that, the simulation *is* Wetiko / Yaldabaoth. Caleb Scharf, Director of Astrobiology at Columbia University, has speculated that 'alien life' could be so advanced that it has transcribed itself into the quantum realm to become what we call physics. He said intelligence indistinguishable from the fabric of the Universe would solve many of its greatest mysteries:

> Perhaps hyper-advanced life isn't just external. Perhaps it's already all around. It is embedded in what we perceive to be physics itself, from the root behaviour of particles and fields to the phenomena of complexity and emergence ... In other words, life might not just be in the equations. It might BE the equations [My emphasis].

Scharf said it is possible that 'we don't recognise advanced life because it forms an integral and unsuspicious part of what we've considered to be the natural world'. I agree. Wetiko/Yaldabaoth *is* the simulation. We are literally in the body of the beast. But that doesn't mean it has to control us. We all have the power to overcome Wetiko

influence and the Cult knows that. I doubt it sleeps too well because it knows that.

Which Field?

This, I suggest, is how it all works. There are two Fields. One is the fierce electromagnetic light of the Matrix within the speed of light; the other is the 'watery light' of The Field beyond the walls of the Matrix that connects with the Great Infinity. Five-sense mind and the decoding systems of the body attach us to the Field of Matrix light. They have to or we could not experience this reality. Five-sense mind sees only the Matrix Field of information while our expanded consciousness is part of the Infinity Field. When we open our minds, and most importantly our hearts, to the Infinity Field we have a mission control which gives us an expanded perspective, a road map, to understand the nature of the five-sense world. If we are isolated only in five-sense mind there is no mission control. We're on our own trying to understand a world that's constantly feeding us information to ensure we do not understand. People in this state can feel 'lost' and bewildered with no direction or radar. You can see ever more clearly those who are influenced by the Fields of Big Infinity or little five-sense mind simply by their views and behaviour with regard to the 'Covid' hoax. We have had this division throughout known human history with the mass of the people on one side and individuals who could see and intuit beyond the walls of the simulation – Plato's prisoner who broke out of the cave and saw reality for what it is. Such people have always been targeted by Wetiko/Archon-possessed authority, burned at the stake or demonised as mad, bad and dangerous. The Cult today and its global network of 'anti-hate', 'anti-fascist' Woke groups are all expressions of Wetiko attacking those exposing the conspiracy, 'Covid' lies and the 'vaccine' agenda.

Woke as a whole is Wetiko which explains its black and white mentality and how at one it is with the Wetiko-possessed Cult. Paul Levy said: 'To be in this paradigm is to still be under the thrall of a two-valued logic – where things are either true or false – of a

wetikoized mind.' Wetiko consciousness is in a permanent rage, therefore so is Woke, and then there is Woke inversion and contradiction. 'Anti-fascists' act like fascists because fascists *and* 'anti-fascists' are both Wetiko at work. Political parties act the same while claiming to be different for the same reason. Secret society and satanic rituals are attaching initiates to Wetiko and the cold, ruthless, psychopathic mentality that secures the positions of power all over the world is Wetiko. Reframing 'training programmes' have the same cumulative effect of attaching Wetiko and we have their graduates described as automatons and robots with a cold, psychopathic, uncaring demeanour. They are all traits of Wetiko possession and look how many times they have been described in this book and elsewhere with regard to personnel behind 'Covid' including the police and medical profession. Climbing the greasy pole in any profession in a Wetiko society requires traits of Wetiko to get there and that is particularly true of politics which is not about fair competition and pre-eminence of ideas. It is founded on how many backs you can stab and arses you can lick. This culminated in the global 'Covid' coordination between the Wetiko possessed who pulled it off in all the different countries without a trace of empathy and compassion for their impact on humans. Our sight sense can see only holographic form and not the Field which connects holographic form. Therefore we perceive 'physical' objects with 'space' in between. In fact that 'space' is energy/consciousness operating on multiple frequencies. One of them is Wetiko and that connects the Cult psychopaths, those who submit to the psychopaths, and those who serve the psychopaths in the media operations of the world. Wetiko is Gates. Wetiko is the mask-wearing submissive. Wetiko is the fake journalist and 'fact-checker'. The Wetiko Field is coordinating the whole thing. Psychopaths, gofers, media operatives, 'anti-hate' hate groups, 'fact-checkers' and submissive people work as one unit *even without human coordination* because they are attached to the *same* Field which is organising it all (Fig 22). Paul Levy is here describing how Wetiko-possessed people are drawn together and refuse to let any information breach their rigid

perceptions. He was writing long before 'Covid', but I think you will recognise followers of the 'Covid' religion *oh just a little bit*:

People who are channelling the vibratory frequency of wetiko align with each other through psychic resonance to reinforce their unspoken shared agreement so as to uphold their deranged view of reality. Once an unconscious content takes possession of certain individuals, it irresistibly draws them together by mutual attraction and knits them into groups tied together by their shared madness that can easily swell into an avalanche of insanity.

A psychic epidemic is a closed system, which is to say that it is insular and not open to any new information or informing influences from the outside world which contradict its fixed, limited, and limiting perspective.

There we have the Woke mind and the 'Covid' mind. Compatible resonance draws the awakening together, too, which is clearly happening today.



Figure 22: The Wetiko Field from which the Cult pyramid and its personnel are made manifest. (Image by Neil Hague).

Spiritual servitude

Wetiko doesn't care about humans. It's not human; it just possesses humans for its own ends and the effect (depending on the scale of

possession) can be anything from extreme psychopathy to unquestioning obedience. Wetiko's worst nightmare is for human consciousness to expand beyond the simulation. Everything is focussed on stopping that happening through control of information, thus perception, thus frequency. The 'education system', media, science, medicine, academia, are all geared to maintaining humanity in five-sense servitude as is the constant stimulation of low-vibrational mental and emotional states (see 'Covid'). Wetiko seeks to dominate those subconscious spaces between five-sense perception and expanded consciousness where the computer meets the operator. From these subconscious hiding places Wetiko speaks to us to trigger urges and desires that we take to be our own and manipulate us into anything from low-vibrational to psychopathic states. Remember how Islam describes the Jinn as invisible tricksters that 'whisper' and confuse. Wetiko is the origin of the 'trickster god' theme that you find in cultures all over the world. Jinn, like the Archons, are Wetiko which is terrified of humans awakening and reconnecting with our true self for then its energy source has gone. With that the feedback loop breaks between Wetiko and human perception that provides the energetic momentum on which its very existence depends as a force of evil. Humans are both its target and its source of survival, but only if we are operating in low-vibrational states of fear, hate, depression and the background anxiety that most people suffer. We are Wetiko's target because we are its key to survival. It needs us, not the other way round. Paul Levy writes:

A vampire has no intrinsic, independent, substantial existence in its own right; it only exists in relation to us. The pathogenic, vampiric mind-parasite called wetiko is nothing in itself – not being able to exist from its own side – yet it has a 'virtual reality' such that it can potentially destroy our species …

…The fact that a vampire is not reflected by a mirror can also mean that what we need to see is that there's nothing, no-thing to see, other than ourselves. The fact that wetiko is the expression of something inside of us means that the cure for wetiko is with us as well. The critical issue is finding this cure within us and then putting it into effect.

Evil begets evil because if evil does not constantly expand and find new sources of energetic sustenance its evil, its *distortion*, dies with the assimilation into balance and harmony. Love is the garlic to Wetiko's vampire. Evil, the absence of love, cannot exist in the presence of love. I think I see a way out of here. I have emphasised so many times over the decades that the Archons/Wetiko and their Cult are not all powerful. *They are not*. I don't care how it looks even now *they are not*. I have not called them little boys in short trousers for effect. I have said it because it is true. Wetiko's insatiable desire for power over others is not a sign of its omnipotence, but its insecurity. Paul Levy writes: 'Due to the primal fear which ultimately drives it and which it is driven to cultivate, wetiko's body politic has an intrinsic and insistent need for centralising power and control so as to create imagined safety for itself.' *Yeeeeeees!* Exactly! Why does Wetiko want humans in an ongoing state of fear? Wetiko itself *is* fear and it is petrified of love. As evil is an absence of love, so love is an absence of fear. Love conquers all and *especially* Wetiko which *is* fear. Wetiko brought fear into the world when it wasn't here before. *Fear* was the 'fall', the fall into low-frequency ignorance and illusion – fear is **F**alse **E**motion **A**ppearing **R**eal. The simulation is driven and energised by fear because Wetiko/Yaldabaoth (fear) *are* the simulation. Fear is the absence of love and Wetiko is the absence of love.

Wetiko today

We can now view current events from this level of perspective. The 'Covid' hoax has generated momentous amounts of ongoing fear, anxiety, depression and despair which have empowered Wetiko. No wonder people like Gates have been the instigators when they are Wetiko incarnate and exhibit every trait of Wetiko in the extreme. See how cold and unemotional these people are like Gates and his cronies, how dead of eye they are. That's Wetiko. Sabbatians are Wetiko and everything they control including the World Health Organization, Big Pharma and the 'vaccine' makers, national 'health'

hierarchies, corporate media, Silicon Valley, the banking system, and the United Nations with its planned transformation into world government. All are controlled and possessed by the Wetiko distortion into distorting human society in its image. We are with this knowledge at the gateway to understanding the world. Divisions of race, culture, creed and sexuality are diversions to hide the real division between those possessed and influenced by Wetiko and those that are not. The 'Covid' hoax has brought both clearly into view. Human behaviour is not about race. Tyrants and dictatorships come in all colours and creeds. What unites the US president bombing the innocent and an African tribe committing genocide against another as in Rwanda? What unites them? *Wetiko*. All wars are Wetiko, all genocide is Wetiko, all hunger over centuries in a world of plenty is Wetiko. Children going to bed hungry, including in the West, is Wetiko. Cult-generated Woke racial divisions that focus on the body are designed to obscure the reality that divisions in behaviour are manifestations of mind, not body. Obsession with body identity and group judgement is a means to divert attention from the real source of behaviour – mind and perception. Conflict sown by the Woke both within themselves and with their target groups are Wetiko providing lunch for itself through still more agents of the division, chaos, and fear on which it feeds. The Cult is seeking to assimilate the entirety of humanity and all children and young people into the Wetiko frequency by manipulating them into states of fear and despair. Witness all the suicide and psychological unravelling since the spring of 2020. Wetiko psychopaths want to impose a state of unquestioning obedience to authority which is no more than a conduit for Wetiko to enforce its will and assimilate humanity into itself. It needs us to believe that resistance is futile when it fears resistance and even more so the game-changing non-cooperation with its impositions. It can use violent resistance for its benefit. Violent impositions and violent resistance are *both* Wetiko. The Power of Love with its Power of No will sweep Wetiko from our world. Wetiko and its Cult know that. They just don't want us to know.

AI Wetiko

This brings me to AI or artificial intelligence and something else Wetikos don't want us to know. What is AI *really*? I know about computer code algorithms and AI that learns from data input. These, however, are more diversions, the expeditionary force, for the real AI that they want to connect to the human brain as promoted by Silicon Valley Wetikos like Kurzweil. What is this AI? It is the frequency of *Wetiko*, the frequency of the Archons. The connection of AI to the human brain is the connection of the Wetiko frequency to create a Wetiko hive mind and complete the job of assimilation. The hive mind is planned to be controlled from Israel and China which are both 100 percent owned by Wetiko Sabbatians. The assimilation process has been going on minute by minute in the 'smart' era which fused with the 'Covid' era. We are told that social media is scrambling the minds of the young and changing their personality. This is true, but what is social media? Look more deeply at how it works, how it creates divisions and conflict, the hostility and cruelty, the targeting of people until they are destroyed. That's Wetiko. Social media is manipulated to tune people to the Wetiko frequency with all the emotional exploitation tricks employed by platforms like Facebook and its Wetiko front man, Zuckerberg. Facebook's Instagram announced a new platform for children to overcome a legal bar on them using the main site. This is more Wetiko exploitation and manipulation of kids. Amnesty International likened the plan to foxes offering to guard the henhouse and said it was incompatible with human rights. Since when did Wetiko or Zuckerberg (I repeat myself) care about that? Would Brin and Page at Google, Wojcicki at YouTube, Bezos at Amazon and whoever the hell runs Twitter act as they do if they were not channelling Wetiko? Would those who are developing technologies for no other reason than human control? How about those designing and selling technologies to kill people and Big Pharma drug and 'vaccine' producers who know they will end or devastate lives? Quite a thought for these people to consider is that if you are Wetiko in a human life you are Wetiko on the 'other side' unless your frequency

changes and that can only change by a change of perception which becomes a change of behaviour. Where Gates is going does not bear thinking about although perhaps that's exactly where he wants to go. Either way, that's where he's going. His frequency will make it so.

The frequency lair

I have been saying for a long time that a big part of the addiction to smartphones and devices is that a frequency is coming off them that entraps the mind. People spend ages on their phones and sometimes even a minute or so after they put them down they pick them up again and it all repeats. 'Covid' lockdowns will have increased this addiction a million times for obvious reasons. Addictions to alcohol overindulgence and drugs are another way that Wetiko entraps consciousness to attach to its own. Both are symptoms of low-vibrational psychological distress which alcoholism and drug addiction further compound. Do we think it's really a coincidence that access to them is made so easy while potions that can take people into realms beyond the simulation are banned and illegal? I have explored smartphone addiction in other books, the scale is mind-blowing, and that level of addiction does not come without help. Tech companies that make these phones are Wetiko and they will have no qualms about destroying the minds of children. We are seeing again with these companies the Wetiko perceptual combination of psychopathic enforcers and weak and meek unquestioning compliance by the rank and file.

The global Smart Grid is the Wetiko Grid and it is crucial to complete the Cult endgame. The simulation is radiation and we are being deluged with technological radiation on a devastating scale. Wetiko frauds like Elon Musk serve Cult interests while occasionally criticising them to maintain his street-cred. 5G and other forms of Wi-Fi are being directed at the earth from space on a volume and scale that goes on increasing by the day. Elon Musk's (officially) SpaceX Starlink project is in the process of putting tens of thousands of satellites in low orbit to cover every inch of the planet with 5G and other Wi-Fi to create Kurzweil's global 'cloud' to which the

human mind is planned to be attached very soon. SpaceX has approval to operate 12,000 satellites with more than 1,300 launched at the time of writing and applications filed for *30,000* more. Other operators in the Wi-Fi, 5G, low-orbit satellite market include OneWeb (UK), Telesat (Canada), and AST & Science (US). Musk tells us that AI could be the end of humanity and then launches a company called Neuralink to connect the human brain to computers. Musk's (in theory) Tesla company is building electric cars and the driverless vehicles of the smart control grid. As frauds and bullshitters go Elon Musk in my opinion is Major League.

5G and technological radiation in general are destructive to human health, genetics and psychology and increasing the strength of artificial radiation underpins the five-sense perceptual bubbles which are themselves expressions of radiation or electromagnetism. Freedom activist John Whitehead was so right with his 'databit by databit, we are building our own electronic concentration camps'. The Smart Grid and 5G is a means to control the human mind and infuse perceptual information into The Field to influence anyone in sync with its frequency. You can change perception and behaviour en masse if you can manipulate the population into those levels of frequency and this is happening all around us today. The arrogance of Musk and his fellow Cult operatives knows no bounds in the way that we see with Gates. Musk's satellites are so many in number already they are changing the night sky when viewed from Earth. The astronomy community has complained about this and they have seen nothing yet. Some consequences of Musk's Wetiko hubris include: Radiation; visible pollution of the night sky; interference with astronomy and meteorology; ground and water pollution from intensive use of increasingly many spaceports; accumulating space debris; continual deorbiting and burning up of aging satellites, polluting the atmosphere with toxic dust and smoke; and ever-increasing likelihood of collisions. A collective public open letter of complaint to Musk said:

> We are writing to you … because SpaceX is in process of surrounding the Earth with a network of thousands of satellites whose very purpose is to irradiate every square inch of the

Earth. SpaceX, like everyone else, is treating the radiation as if it were not there. As if the mitochondria in our cells do not depend on electrons moving undisturbed from the food we digest to the oxygen we breathe.

As if our nervous systems and our hearts are not subject to radio frequency interference like any piece of electronic equipment. As if the cancer, diabetes, and heart disease that now afflict a majority of the Earth's population are not metabolic diseases that result from interference with our cellular machinery. As if insects everywhere, and the birds and animals that eat them, are not starving to death as a result.

People like Musk and Gates believe in their limitless Wetiko arrogance that they can do whatever they like to the world because they own it. Consequences for humanity are irrelevant. It's absolutely time that we stopped taking this shit from these self-styled masters of the Earth when you consider where this is going.

Why is the Cult so anti-human?

I hear this question often: Why would they do this when it will affect them, too? Ah, but will it? Who is this *them*? Forget their bodies. They are just vehicles for Wetiko consciousness. When you break it all down to the foundations we are looking at a state of severely distorted consciousness targeting another state of consciousness for assimilation. The rest is detail. The simulation is the fly-trap in which unique sensations of the five senses create a cycle of addiction called reincarnation. Renegade Minds see that everything which happens in our reality is a smaller version of the whole picture in line with the holographic principle. Addiction to the radiation of smart technology is a smaller version of addiction to the whole simulation. Connecting the body/brain to AI is taking that addiction on a giant step further to total ongoing control by assimilating human incarnate consciousness into Wetiko. I have watched during the 'Covid' hoax how many are becoming ever more profoundly attached to Wetiko's perceptual calling cards of aggressive response to any other point of view ('There is no other god but me'), psychopathic lack of compassion and empathy, and servile submission to the narrative and will of authority. Wetiko is the psychopaths *and* subservience to psychopaths. The Cult of Wetiko is

so anti-human because it is *not* human. It embarked on a mission to destroy human by targeting everything that it means to be human and to survive as human. 'Covid' is not the end, just a means to an end. The Cult with its Wetiko consciousness is seeking to change Earth systems, including the atmosphere, to suit them, not humans. The gathering bombardment of 5G alone from ground and space is dramatically changing The Field with which the five senses interact. There is so much more to come if we sit on our hands and hope it will all go away. It is not meant to go away. It is meant to get ever more extreme and we need to face that while we still can – just.

Carbon dioxide is the gas of life. Without that human is over. Kaput, gone, history. No natural world, no human. The Cult has created a cock and bull story about carbon dioxide and climate change to justify its reduction to the point where Gates and the ignoramus Biden 'climate chief' John Kerry want to suck it out of the atmosphere. Kerry wants to do this because his master Gates does. Wetikos have made the gas of life a demon with the usual support from the Wokers of Extinction Rebellion and similar organisations and the bewildered puppet-child that is Greta Thunberg who was put on the world stage by Klaus Schwab and the World Economic Forum. The name Extinction Rebellion is both ironic and as always Wetiko inversion. The gas that we need to survive must be reduced to save us from extinction. The most basic need of human is oxygen and we now have billions walking around in face nappies depriving body and brain of this essential requirement of human existence. More than that 5G at 60 gigahertz interacts with the oxygen molecule to reduce the amount of oxygen the body can absorb into the bloodstream. The obvious knock-on consequences of that for respiratory and cognitive problems and life itself need no further explanation. Psychopaths like Musk are assembling a global system of satellites to deluge the human atmosphere with this insanity. The man should be in jail. Here we have two most basic of human needs, oxygen and carbon dioxide, being dismantled.

Two others, water and food, are getting similar treatment with the United Nations Agendas 21 and 2030 – the Great Reset – planning to

centrally control all water and food supplies. People will not even own rain water that falls on their land. Food is affected at the most basic level by reducing carbon dioxide. We have genetic modification or GMO infiltrating the food chain on a mass scale, pesticides and herbicides polluting the air and destroying the soil. Freshwater fish that provide livelihoods for 60 million people and feed hundreds of millions worldwide are being 'pushed to the brink' according the conservationists while climate change is the only focus. Now we have Gates and Schwab wanting to dispense with current food sources all together and replace them with a synthetic version which the Wetiko Cult would control in terms of production and who eats and who doesn't. We have been on the Totalitarian Tiptoe to this for more than 60 years as food has become ever more processed and full of chemical shite to the point today when it's not natural food at all. As Dr Tom Cowan says: 'If it has a label don't eat it.' Bill Gates is now the biggest owner of farmland in the United States and he does nothing without an ulterior motive involving the Cult. Klaus Schwab wrote: 'To feed the world in the next 50 years we will need to produce as much food as was produced in the last 10,000 years … food security will only be achieved, however, if regulations on genetically modified foods are adapted to reflect the reality that gene editing offers a precise, efficient and safe method of improving crops.' Liar. People and the world are being targeted with aluminium through vaccines, chemtrails, food, drink cans, and endless other sources when aluminium has been linked to many health issues including dementia which is increasing year after year. Insects, bees and wildlife essential to the food chain are being deleted by pesticides, herbicides and radiation which 5G is dramatically increasing with 6G and 7G to come. The pollinating bee population is being devastated while wildlife including birds, dolphins and whales are having their natural radar blocked by the effects of ever-increasing radiation. In the summer windscreens used to be splattered with insects so numerous were they. It doesn't happen now. Where have they gone?

Synthetic everything

The Cult is introducing genetically-modified versions of trees, plants and insects including a Gates-funded project to unleash hundreds of millions of genetically-modified, lab-altered and patented male mosquitoes to mate with wild mosquitoes and induce genetic flaws that cause them to die out. Clinically-insane Gates-funded Japanese researchers have developed mosquitos that spread vaccine and are dubbed 'flying vaccinators'. Gates is funding the modification of weather patterns in part to sell the myth that this is caused by carbon dioxide and he's funding geoengineering of the skies to change the atmosphere. Some of this came to light with the Gates-backed plan to release tonnes of chalk into the atmosphere to 'deflect the Sun and cool the planet'. Funny how they do this while the heating effect of the Sun is not factored into climate projections focussed on carbon dioxide. The reason is that they want to reduce carbon dioxide (so don't mention the Sun), but at the same time they do want to reduce the impact of the Sun which is so essential to human life and health. I have mentioned the sun-cholesterol-vitamin D connection as they demonise the Sun with warnings about skin cancer (caused by the chemicals in sun cream they tell you to splash on). They come from the other end of the process with statin drugs to reduce cholesterol that turns sunlight into vitamin D. A lack of vitamin D leads to a long list of health effects and how vitamin D levels must have fallen with people confined to their homes over 'Covid'. Gates is funding other forms of geoengineering and most importantly chemtrails which are dropping heavy metals, aluminium and self-replicating nanotechnology onto the Earth which is killing the natural world. See *Everything You Need To Know, But Have Never Been Told* for the detailed background to this.

Every human system is being targeted for deletion by a force that's not human. The Wetiko Cult has embarked on the process of transforming the human body from biological to synthetic biological as I have explained. Biological is being replaced by the artificial and synthetic – Archontic 'countermimicry' – right across human society. The plan eventually is to dispense with the human body altogether

and absorb human consciousness – which it wouldn't really be by then – into cyberspace (the simulation which is Wetiko/Yaldabaoth). Preparations for that are already happening if people would care to look. The alternative media rightly warns about globalism and 'the globalists', but this is far bigger than that and represents the end of the human race as we know it. The 'bad copy' of prime reality that Gnostics describe was a bad copy of harmony, wonder and beauty to start with before Wetiko/Yaldabaoth set out to change the simulated 'copy' into something very different. The process was slow to start with. Entrapped humans in the simulation timeline were not technologically aware and they had to be brought up to intellectual speed while being suppressed spiritually to the point where they could build their own prison while having no idea they were doing so. We have now reached that stage where technological intellect has the potential to destroy us and that's why events are moving so fast. Central American shaman Don Juan Matus said:

> Think for a moment, and tell me how you would explain the contradictions between the intelligence of man the engineer and the stupidity of his systems of belief, or the stupidity of his contradictory behaviour. Sorcerers believe that the predators have given us our systems of beliefs, our ideas of good and evil; our social mores. They are the ones who set up our dreams of success or failure. They have given us covetousness, greed, and cowardice. It is the predator who makes us complacent, routinary, and egomaniacal.
>
> In order to keep us obedient and meek and weak, the predators engaged themselves in a stupendous manoeuvre – stupendous, of course, from the point of view of a fighting strategist; a horrendous manoeuvre from the point of those who suffer it. They gave us their mind. The predators' mind is baroque, contradictory, morose, filled with the fear of being discovered any minute now.

For 'predators' see Wetiko, Archons, Yaldabaoth, Jinn, and all the other versions of the same phenomenon in cultures and religions all over the world. The theme is always the same because it's true and it's real. We have reached the point where we have to deal with it. The question is – how?

Don't fight – walk away

I thought I'd use a controversial subheading to get things moving in terms of our response to global fascism. What do you mean 'don't fight'? What do you mean 'walk away'? We've got to fight. We can't walk away. Well, it depends what we mean by fight and walk away. If fighting means physical combat we are playing Wetiko's game and falling for its trap. It wants us to get angry, aggressive, and direct hate and hostility at the enemy we think we must fight. Every war, every battle, every conflict, has been fought with Wetiko leading both sides. It's what it does. Wetiko wants a fight, anywhere, any place. Just hit me, son, so I can hit you back. Wetiko hits Wetiko and Wetiko hits Wetiko in return. I am very forthright as you can see in exposing Wetikos of the Cult, but I don't hate them. I refuse to hate them. It's what they want. What you hate you become. What you *fight* you become. Wokers, 'anti-haters' and 'anti-fascists' prove this every time they reach for their keyboards or don their balaclavas. By walk away I mean to disengage from Wetiko which includes ceasing to cooperate with its tyranny. Paul Levy says of Wetiko:

> The way to 'defeat' evil is not to try to destroy it (for then, in playing evil's game, we have already lost), but rather, to find the invulnerable place within ourselves where evil is unable to vanquish us – this is to truly 'win' our battle with evil.

Wetiko is everywhere in human society and it's been on steroids since the 'Covid' hoax. Every shouting match over wearing masks has Wetiko wearing a mask and Wetiko not wearing one. It's an electrical circuit of push and resist, push and resist, with Wetiko pushing *and* resisting. Each polarity is Wetiko empowering itself. Dictionary definitions of 'resist' include 'opposing, refusing to accept or comply with' and the word to focus on is 'opposing'. What form does this take – setting police cars alight or 'refusing to accept or comply with'? The former is Wetiko opposing Wetiko while the other points the way forward. This is the difference between those aggressively demanding that government fascism must be obeyed who stand in stark contrast to the great majority of Pushbackers. We saw this clearly with a march by thousands of Pushbackers against lockdown in London followed days later by a Woker-hijacked

protest in Bristol in which police cars were set on fire. Masks were virtually absent in London and widespread in Bristol. Wetiko wants lockdown on every level of society and infuses its aggression to police it through its unknowing stooges. Lockdown protesters are the ones with the smiling faces and the hugs, The two blatantly obvious states of being – getting more obvious by the day – are the result of Wokers and their like becoming ever more influenced by the simulation Field of Wetiko and Pushbackers ever more influenced by The Field of a far higher vibration beyond the simulation. Wetiko can't invade the heart which is where most lockdown opponents are coming from. It's the heart that allows them to see through the lies to the truth in ways I will be highlighting.

Renegade Minds know that calmness is the place from which wisdom comes. You won't find wisdom in a hissing fit and wisdom is what we need in abundance right now. Calmness is not weakness – you don't have to scream at the top of your voice to be strong. Calmness is indeed a sign of strength. 'No' means I'm not doing it. *NOOOO!!!* doesn't mean you're not doing it even more. Volume does not advance 'No – I'm not doing it'. You are just not doing it. Wetiko possessed and influenced don't know how to deal with that. Wetiko wants a fight and we should not give it one. What it needs more than anything is our *cooperation* and we should not give that either. Mass rallies and marches are great in that they are a visual representation of feeling, but if it ends there they are irrelevant. You demand that Wetikos act differently? Well, they're not going to are they? They are Wetikos. We don't need to waste our time demanding that something doesn't happen when that will make no difference. We need to delete the means that *allows* it to happen. This, invariably, is our cooperation. You can demand a child stop firing a peashooter at the dog or you can refuse to buy the peashooter. If you provide the means you are cooperating with the dog being smacked on the nose with a pea. How can the authorities enforce mask-wearing if millions in a country refuse? What if the 74 million Pushbackers that voted for Trump in 2020 refused to wear masks, close their businesses or stay in their homes. It would be unenforceable. The

few control the many through the compliance of the many and that's always been the dynamic be it 'Covid' regulations or the Roman Empire. I know people can find it intimidating to say no to authority or stand out in a crowd for being the only one with a face on display; but it has to be done or it's over. I hope I've made clear in this book that where this is going will be far more intimidating than standing up now and saying 'No' – I will not cooperate with my own enslavement and that of my children. There might be consequences for some initially, although not so if enough do the same. The question that must be addressed is what is going to happen if we don't? It is time to be strong and unyieldingly so. No means no. Not here and there, but *everywhere* and *always*. I have refused to wear a mask and obey all the other nonsense. I will not comply with tyranny. I repeat: Fascism is not imposed by fascists – there are never enough of them. Fascism is imposed by the population acquiescing to fascism. *I will not do it*. I will die first, or my body will. Living meekly under fascism is a form of death anyway, the death of the spirit that Martin Luther King described.

Making things happen

We must not despair. This is not over till it's over and it's far from that. The 'fat lady' must refuse to sing. The longer the 'Covid' hoax has dragged on and impacted on more lives we have seen an awakening of phenomenal numbers of people worldwide to the realisation that what they have believed all their lives is not how the world really is. Research published by the system-serving University of Bristol and King's College London in February, 2021, concluded: 'One in every 11 people in Britain say they trust David Icke's take on the coronavirus pandemic.' It will be more by now and we have gathering numbers to build on. We must urgently progress from seeing the scam to ceasing to cooperate with it. Prominent German lawyer Reiner Fuellmich, also licenced to practice law in America, is doing a magnificent job taking the legal route to bring the psychopaths to justice through a second Nuremberg tribunal for crimes against humanity. Fuellmich has an impressive record of

beating the elite in court and he formed the German Corona Investigative Committee to pursue civil charges against the main perpetrators with a view to triggering criminal charges. Most importantly he has grasped the foundation of the hoax – the PCR test not testing for the 'virus' – and Christian Drosten is therefore on his charge sheet along with Gates frontman Tedros at the World Health Organization. Major players must be not be allowed to inflict their horrors on the human race without being brought to book. A life sentence must follow for Bill Gates and the rest of them. A group of researchers has also indicted the government of Norway for crimes against humanity with copies sent to the police and the International Criminal Court. The lawsuit cites participation in an internationally-planned false pandemic and violation of international law and human rights, the European Commission's definition of human rights by coercive rules, Nuremberg and Hague rules on fundamental human rights, and the Norwegian constitution. We must take the initiative from hereon and not just complain, protest and react.

There are practical ways to support vital mass non-cooperation. Organising in numbers is one. Lockdown marches in London in the spring in 2021 were mass non-cooperation that the authorities could not stop. There were too many people. Hundreds of thousands walked the London streets in the centre of the road for mile after mile while the Face-Nappies could only look on. They were determined, but calm, and just *did it* with no histrionics and lots of smiles. The police were impotent. Others are organising group shopping without masks for mutual support and imagine if that was happening all over. Policing it would be impossible. If the store refuses to serve people in these circumstances they would be faced with a long line of trolleys full of goods standing on their own and everything would have to be returned to the shelves. How would they cope with that if it kept happening? I am talking here about moving on from complaining to being pro-active; from watching things happen to making things happen. I include in this our relationship with the police. The behaviour of many Face-Nappies

has been disgraceful and anyone who thinks they would never find concentration camp guards in the 'enlightened' modern era have had that myth busted big-time. The period and setting may change – Wetikos never do. I watched film footage from a London march in which a police thug viciously kicked a protestor on the floor who had done nothing. His fellow Face-Nappies stood in a ring protecting him. What he did was a criminal assault and with a crowd far outnumbering the police this can no longer be allowed to happen unchallenged. I get it when people chant 'shame on you' in these circumstances, but that is no longer enough. They *have* no shame those who do this. Crowds needs to start making a citizen's arrest of the police who commit criminal offences and brutally attack innocent people and defenceless women. A citizen's arrest can be made under section 24A of the UK Police and Criminal Evidence (PACE) Act of 1984 and you will find something similar in other countries. I prefer to call it a Common Law arrest rather than citizen's for reasons I will come to shortly. Anyone can arrest a person committing an indictable offence or if they have reasonable grounds to suspect they are committing an indictable offence. On both counts the attack by the police thug would have fallen into this category. A citizen's arrest can be made to stop someone:

- Causing physical injury to himself or any other person
- Suffering physical injury
- Causing loss of or damage to property
- Making off before a constable can assume responsibility for him

A citizen's arrest may also be made to prevent a breach of the peace under Common Law and if they believe a breach of the peace will happen or anything related to harm likely to be done or already done in their presence. This is the way to go I think – the Common Law version. If police know that the crowd and members of the public will no longer be standing and watching while they commit

their thuggery and crimes they will think twice about acting like Brownshirts and Blackshirts.

Common Law – common sense

Mention of Common Law is very important. Most people think the law is the law as in one law. This is not the case. There are two bodies of law, Common Law and Statute Law, and they are not the same. Common Law is founded on the simple premise of do no harm. It does not recognise victimless crimes in which no harm is done while Statute Law does. There is a Statute Law against almost everything. So what is Statute Law? Amazingly it's the law of the *sea* that was brought ashore by the Cult to override the law of the land which is Common Law. They had no right to do this and as always they did it anyway. They had to. They could not impose their will on the people through Common Law which only applies to do no harm. How could you stitch up the fine detail of people's lives with that? Instead they took the law of the sea, or Admiralty Law, and applied it to the population. Statute Law refers to all the laws spewing out of governments and their agencies including all the fascist laws and regulations relating to 'Covid'. The key point to make is that Statute Law is *contract law*. It only applies between *contracting* corporations. Most police officers don't even know this. They have to be kept in the dark, too. Long ago when merchants and their sailing ships began to trade with different countries a contractual law was developed called Admiralty Law and other names. Again it only applied to *contracts* agreed between *corporate* entities. If there is no agreed contract the law of the sea had no jurisdiction *and that still applies to its new alias of Statute Law*. The problem for the Cult when the law of the sea was brought ashore was an obvious one. People were not corporations and neither were government entities. To overcome the latter they made governments and all associated organisations corporations. All the institutions are *private corporations* and I mean governments and their agencies, local councils, police, courts, military, US states, the whole lot. Go to the

Dun and Bradstreet corporate listings website for confirmation that they are all corporations. You are arrested by a private corporation called the police by someone who is really a private security guard and they take you to court which is another private corporation. Neither have jurisdiction over you unless you consent and *contract* with them. This is why you hear the mantra about law enforcement policing by *consent* of the people. In truth the people 'consent' only in theory through monumental trickery.

Okay, the Cult overcame the corporate law problem by making governments and institutions corporate entities; but what about people? They are not corporations are they? Ah ... well in a sense, and *only* a sense, they are. Not people exactly – the illusion of people. The Cult creates a corporation in the name of everyone at the time that their birth certificate is issued. Note birth/ *berth* certificate and when you go to court under the law of the sea on land you stand in a *dock*. These are throwbacks to the origin. My Common Law name is David Vaughan Icke. The name of the corporation created by the government when I was born is called Mr David Vaughan Icke usually written in capitals as MR DAVID VAUGHAN ICKE. That is not me, the living, breathing man. It is a fictitious corporate entity. The trick is to make you think that David Vaughan Icke and MR DAVID VAUGHAN ICKE are the same thing. *They are not*. When police charge you and take you to court they are prosecuting the corporate entity and not the living, breathing, man or woman. They have to trick you into identifying as the corporate entity and contracting with them. Otherwise they have no jurisdiction. They do this through a language known as legalese. Lawful and legal are not the same either. Lawful relates to Common Law and legal relates to Statute Law. Legalese is the language of Statue Law which uses terms that mean one thing to the public and another in legalese. Notice that when a police officer tells someone why they are being charged he or she will say at the end: 'Do you understand?' To the public that means 'Do you comprehend?' In legalese it means 'Do you stand under me?' Do you stand under my authority? If you say

yes to the question you are unknowingly agreeing to give them jurisdiction over you in a contract between two corporate entities.

This is a confidence trick in every way. Contracts have to be agreed between informed parties and if you don't know that David Vaughan Icke is agreeing to be the corporation MR DAVID VAUGHAN ICKE you cannot knowingly agree to contract. They are deceiving you and another way they do this is to ask for proof of identity. You usually show them a driving licence or other document on which your corporate name is written. In doing so you are accepting that you are that corporate entity when you are not. Referring to yourself as a 'person' or 'citizen' is also identifying with your corporate fiction which is why I made the Common Law point about the citizen's arrest. If you are approached by a police officer you identify yourself immediately as a living, breathing, man or woman and say 'I do not consent, I do not contract with you and I do not understand' or stand under their authority. I have a Common Law birth certificate as a living man and these are available at no charge from commonlawcourt.com. Businesses registered under the Statute Law system means that its laws apply. There are, however, ways to run a business under Common Law. Remember all 'Covid' laws and regulations are Statute Law – the law of *contracts* and you do not have to contract. This doesn't mean that you can kill someone and get away with it. Common Law says do no harm and that applies to physical harm, financial harm etc. Police are employees of private corporations and there needs to be a new system of non-corporate Common Law constables operating outside the Statute Law system. If you go to davidicke.com and put Common Law into the search engine you will find videos that explain Common Law in much greater detail. It is definitely a road we should walk.

With all my heart

I have heard people say that we are in a spiritual war. I don't like the term 'war' with its Wetiko dynamic, but I know what they mean. Sweep aside all the bodily forms and we are in a situation in which two states of consciousness are seeking very different realities.

Wetiko wants upheaval, chaos, fear, suffering, conflict and control. The other wants love, peace, harmony, fairness and freedom. That's where we are. We should not fall for the idea that Wetiko is all-powerful and there's nothing we can do. Wetiko is not all-powerful. It's a joke, pathetic. It doesn't have to be, but it has made that choice for now. A handful of times over the years when I have felt the presence of its frequency I have allowed it to attach briefly so I could consciously observe its nature. The experience is not pleasant, the energy is heavy and dark, but the ease with which you can kick it back out the door shows that its real power is in persuading us that it has power. It's all a con. Wetiko is a con. It's a trickster and not a power that can control us if we unleash our own. The con is founded on manipulating humanity to give its power to Wetiko which recycles it back to present the illusion that it has power when its power is *ours* that we gave away. This happens on an energetic level and plays out in the world of the seen as humanity giving its power to Wetiko authority which uses that power to control the population when the power is only the power the population has handed over. How could it be any other way for billions to be controlled by a relative few? I have had experiences with people possessed by Wetiko and again you can kick its arse if you do it with an open heart. Oh yes – the *heart* which can transform the world of perceived 'matter'.

We are receiver-transmitters and processors of information, but what information and where from? Information is processed into perception in three main areas – the brain, the heart and the belly. These relate to thinking, knowing, and emotion. Wetiko wants us to be head and belly people which means we think within the confines of the Matrix simulation and low-vibrational emotional reaction scrambles balance and perception. A few minutes on social media and you see how emotion is the dominant force. Woke is all emotion and is therefore thought-free and fact-free. Our heart is something different. It *knows* while the head *thinks* and has to try to work it out because it doesn't know. The human energy field has seven prime vortexes which connect us with wider reality (Fig 23). Chakra means

'wheels of light' in the Sanskrit language of ancient India. The main ones are: The crown chakra on top of the head; brow (or 'third eye') chakra in the centre of the forehead; throat chakra; heart chakra in the centre of the chest; solar plexus chakra below the sternum; sacral chakra beneath the navel; and base chakra at the bottom of the spine. Each one has a particular function or functions. We feel anxiety and nervousness in the belly where the sacral chakra is located and this processes emotion that can affect the colon to give people 'the shits' or make them 'shit scared' when they are nervous. Chakras all play an important role, but the Mr and Mrs Big is the heart chakra which sits at the centre of the seven, above the chakras that connect us to the 'physical' and below those that connect with higher realms (or at least should). Here in the heart chakra we feel love, empathy and compassion – 'My heart goes out to you'. Those with closed hearts become literally 'heart-less' in their attitudes and behaviour (see Bill Gates). Native Americans portrayed Wetiko with what Paul Levy calls a 'frigid, icy heart, devoid of mercy' (see Bill Gates).



Figure 23: The chakra system which interpenetrates the human energy field. The heart chakra is the governor – or should be.

Wetiko trembles at the thought of heart energy which it cannot infiltrate. The frequency is too high. What it seeks to do instead is close the heart chakra vortex to block its perceptual and energetic influence. Psychopaths have 'hearts of stone' and emotionally-damaged people have 'heartache' and 'broken hearts'. The astonishing amount of heart disease is related to heart chakra

disruption with its fundamental connection to the 'physical' heart. Dr Tom Cowan has written an outstanding book challenging the belief that the heart is a pump and making the connection between the 'physical' and spiritual heart. Rudolph Steiner who was way ahead of his time said the same about the fallacy that the heart is a pump. *What*? The heart is not a pump? That's crazy, right? Everybody knows that. Read Cowan's *Human Heart, Cosmic Heart* and you will realise that the very idea of the heart as a pump is ridiculous when you see the evidence. How does blood in the feet so far from the heart get pumped horizontally up the body by the heart?? Cowan explains in the book the real reason why blood moves as it does. Our 'physical' heart is used to symbolise love when the source is really the heart vortex or spiritual heart which is our most powerful energetic connection to 'out there' expanded consciousness. That's why we feel *knowing* – intuitive knowing – in the centre of the chest. Knowing doesn't come from a process of thoughts leading to a conclusion. It is there in an instant all in one go. Our heart knows because of its connection to levels of awareness that *do* know. This is the meaning and source of intuition – intuitive *knowing*.

For the last more than 30 years of uncovering the global game and the nature of reality my heart has been my constant antenna for truth and accuracy. An American intelligence insider once said that I had quoted a disinformer in one of my books and yet I had only quoted the part that was true. He asked: 'How do you do that?' By using my heart antenna was the answer and anyone can do it. Heart-centred is how we are meant to be. With a closed heart chakra we withdraw into a closed mind and the bubble of five-sense reality. If you take a moment to focus your attention on the centre of your chest, picture a spinning wheel of light and see it opening and expanding. You will feel it happening, too, and perceptions of the heart like joy and love as the heart impacts on the mind as they interact. The more the chakra opens the more you will feel expressions of heart consciousness and as the process continues, and becomes part of you, insights and knowings will follow. An open

heart is connected to that level of awareness that knows all is *One*. You will see from its perspective that the fault-lines that divide us are only illusions to control us. An open heart does not process the illusions of race, creed and sexuality except as brief experiences for a consciousness that is all. Our heart does not see division, only unity (Figs 24 and 25). There's something else, too. Our hearts love to laugh. Mark Twain's quote that says 'The human race has one really effective weapon, and that is laughter' is really a reference to the heart which loves to laugh with the joy of knowing the true nature of infinite reality and that all the madness of human society is an illusion of the mind. Twain also said: 'Against the assault of laughter nothing can stand.' This is so true of Wetiko and the Cult. Their insecurity demands that they be taken seriously and their power and authority acknowledged and feared. We should do nothing of the sort. We should not get aggressive or fearful which their insecurity so desires. We should laugh in their face. Even in their no-face as police come over in their face-nappies and expect to be taken seriously. They don't take themselves seriously looking like that so why should we? Laugh in the face of intimidation. Laugh in the face of tyranny. You will see by its reaction that you have pressed all of its buttons. Wetiko does not know what to do in the face of laughter or when its targets refuse to concede their joy to fear. We have seen many examples during the 'Covid' hoax when people have expressed their energetic power and the string puppets of Wetiko retreat with their tail limp between their knees. Laugh – the world is bloody mad after all and if it's a choice between laughter and tears I know which way I'm going.



Figure 24: Head consciousness without the heart sees division and everything apart from everything else.



Figure 25: Heart consciousness sees everything as One.

'Vaccines' and the soul

The foundation of Wetiko/Archon control of humans is the separation of incarnate five-sense mind from the infinite 'I' and closing the heart chakra where the True 'I' lives during a human life. The goal has been to achieve complete separation in both cases. I was interested therefore to read an account by a French energetic healer of what she said she experienced with a patient who had been given the 'Covid' vaccine. Genuine energy healers can sense information and consciousness fields at different levels of being which are referred to as 'subtle bodies'. She described treating the patient who later returned after having, without the healer's knowledge, two doses of the 'Covid vaccine'. The healer said:

I noticed immediately the change, very heavy energy emanating from [the] subtle bodies. The scariest thing was when I was working on the heart chakra, I connected with her soul: it was detached from the physical body, it had no contact and it was, as if it was floating in a state of total confusion: a damage to the consciousness that loses contact with the physical body, i.e. with our biological machine, there is no longer any communication between them.

I continued the treatment by sending light to the heart chakra, the soul of the person, but it seemed that the soul could no longer receive any light, frequency or energy. It was a very powerful experience for me. Then I understood that this substance is indeed used to detach consciousness so that this consciousness can no longer interact through this body that it possesses in life, where there is no longer any contact, no frequency, no light, no more energetic balance or mind.

This would create a human that is rudderless and at the extreme almost zombie-like operating with a fractional state of consciousness at the mercy of Wetiko. I was especially intrigued by what the healer said in the light of the prediction by the highly-informed Rudolf Steiner more than a hundred years ago. He said:

In the future, we will eliminate the soul with medicine. Under the pretext of a 'healthy point of view', there will be a vaccine by which the human body will be treated as soon as possible directly at birth, so that the human being cannot develop the thought of the existence of soul and Spirit. To materialistic doctors will be entrusted the task of removing the soul of humanity.

As today, people are vaccinated against this disease or that disease, so in the future, children will be vaccinated with a substance that can be produced precisely in such a way that people, thanks to this vaccination, will be immune to being subjected to the 'madness' of spiritual life. He would be extremely smart, but he would not develop a conscience, and that is the true goal of some materialistic circles.

Steiner said the vaccine would detach the physical body from the etheric body (subtle bodies) and 'once the etheric body is detached the relationship between the universe and the etheric body would become extremely unstable, and man would become an automaton'. He said 'the physical body of man must be polished on this Earth by spiritual will – so the vaccine becomes a kind of arymanique (Wetiko) force' and 'man can no longer get rid of a given materialistic feeling'. Humans would then, he said, become 'materialistic of constitution and can no longer rise to the spiritual'. I have been writing for years about DNA being a receiver-transmitter of information that connects us to other levels of reality and these 'vaccines' changing DNA can be likened to changing an antenna and what it can transmit and receive. Such a disconnection would clearly lead to changes in personality and perception. Steiner further predicted the arrival of AI. Big Pharma 'Covid vaccine' makers, expressions of Wetiko, are testing their DNA-manipulating evil on children as I write with a view to giving the 'vaccine' to babies. If it's a soul-body disconnector – and I say that it is or can be – every child would be disconnected from 'soul' at birth and the 'vaccine' would create a closed system in which spiritual guidance from the greater self would play no part. This has been the ambition of Wetiko all

along. A Pentagon video from 2005 was leaked of a presentation explaining the development of vaccines to change behaviour by their effect on the brain. Those that believe this is not happening with the 'Covid' genetically-modifying procedure masquerading as a 'vaccine' should make an urgent appointment with Naivety Anonymous. Klaus Schwab wrote in 2018:

> Neurotechnologies enable us to better influence consciousness and thought and to understand many activities of the brain. They include decoding what we are thinking in fine levels of detail through new chemicals and interventions that can influence our brains to correct for errors or enhance functionality.

The plan is clear and only the heart can stop it. With every heart that opens, every mind that awakens, Wetiko is weakened. Heart and love are far more powerful than head and hate and so nothing like a majority is needed to turn this around.

Beyond the Phantom

Our heart is the prime target of Wetiko and so it must be the answer to Wetiko. We *are* our heart which is part of one heart, the infinite heart. Our heart is where the true self lives in a human life behind firewalls of five-sense illusion when an imposter takes its place – *Phantom Self*; but our heart waits patiently to be set free any time we choose to see beyond the Phantom, beyond Wetiko. A Wetikoed Phantom Self can wreak mass death and destruction while the love of forever is locked away in its heart. The time is here to unleash its power and let it sweep away the fear and despair that is Wetiko. Heart consciousness does not seek manipulated, censored, advantage for its belief or religion, its activism and desires. As an expression of the One it treats all as One with the same rights to freedom and opinion. Our heart demands fairness for itself no more than for others. From this unity of heart we can come together in mutual support and transform this Wetikoed world into what reality is meant to be – a place of love, joy, happiness, fairness, justice and freedom. Wetiko has another agenda and that's why the world is as

it is, but enough of this nonsense. Wetiko can't stay where hearts are open and it works so hard to keep them closed. Fear is its currency and its food source and love in its true sense has no fear. Why would love have fear when it knows it is *All That Is, Has Been, And Ever Can Be* on an eternal exploration of all possibility? Love in this true sense is not the physical attraction that passes for love. This can be an expression of it, yes, but Infinite Love, a love without condition, goes far deeper to the core of all being. It *is* the core of all being. Infinite realty was born from love beyond the illusions of the simulation. Love infinitely expressed is the knowing that all is One and the swiftly-passing experience of separation is a temporary hallucination. You cannot disconnect from Oneness; you can only *perceive* that you have and withdraw from its influence. This is the most important of all perception trickery by the mind parasite that is Wetiko and the foundation of all its potential for manipulation.

If we open our hearts, open the sluice gates of the mind, and redefine self-identity amazing things start to happen. Consciousness expands or contracts in accordance with self-identity. When true self is recognised as infinite awareness and label self – Phantom Self – is seen as only a series of brief experiences life is transformed. Consciousness expands to the extent that self-identity expands and everything changes. You see unity, not division, the picture, not the pixels. From this we can play the long game. No more is an experience something in and of itself, but a fleeting moment in the eternity of forever. Suddenly people in uniform and dark suits are no longer intimidating. Doing what your heart knows to be right is no longer intimidating and consequences for those actions take on the same nature of a brief experience that passes in the blink of an infinite eye. Intimidation is all in the mind. Beyond the mind there is no intimidation.

An open heart does not consider consequences for what it knows to be right. To do so would be to consider not doing what it knows to be right and for a heart in its power that is never an option. The Renegade Mind is really the Renegade Heart. Consideration of consequences will always provide a getaway car for the mind and

the heart doesn't want one. What is right in the light of what we face today is to stop cooperating with Wetiko in all its forms and to do it without fear or compromise. You cannot compromise with tyranny when tyranny always demands more until it has everything. Life is your perception and you are your destiny. Change your perception and you change your life. Change collective perception and we change the world.

Come on people … One human family, One heart, One goal … *FREEEEEEDOM*!

We must settle for nothing less.

Postscript

The big scare story as the book goes to press is the 'Indian' variant and the world is being deluged with propaganda about the 'Covid catastrophe' in India which mirrors in its lies and misrepresentations what happened in Italy before the first lockdown in 2020.

The *New York Post* published a picture of someone who had 'collapsed in the street from Covid' in India in April, 2021, which was actually taken during a gas leak in May, 2020. Same old, same old. Media articles in mid-February were asking why India had been so untouched by 'Covid' and then as their vaccine rollout gathered pace the alleged 'cases' began to rapidly increase. Indian 'Covid vaccine' maker Bharat Biotech was funded into existence by the Bill and Melinda Gates Foundation (the pair announced their divorce in May, 2021, which is a pity because they so deserve each other). The Indian 'Covid crisis' was ramped up by the media to terrify the world and prepare people for submission to still more restrictions. The scam that worked the first time was being repeated only with far more people seeing through the deceit. Davidicke.com and Ickonic.com have sought to tell the true story of what is happening by talking to people living through the Indian nightmare which has nothing to do with 'Covid'. We posted a letter from 'Alisha' in Pune who told a very different story to government and media mendacity. She said scenes of dying people and overwhelmed hospitals were designed to hide what was really happening – genocide and starvation. Alisha said that millions had already died of starvation during the ongoing lockdowns while government and media were lying and making it look like the 'virus':

Restaurants, shops, gyms, theatres, basically everything is shut. The cities are ghost towns. Even so-called 'essential' businesses are only open till 11am in the morning. You basically have just an hour to buy food and then your time is up.

Inter-state travel and even inter-district travel is banned. The cops wait at all major crossroads to question why you are traveling outdoors or to fine you if you are not wearing a mask.

The medical community here is also complicit in genocide, lying about hospitals being full and turning away people with genuine illnesses, who need immediate care. They have even created a shortage of oxygen cylinders.

This is the classic Cult modus operandi played out in every country. Alisha said that people who would not have a PCR test not testing for the 'virus' were being denied hospital treatment. She said the people hit hardest were migrant workers and those in rural areas. Most businesses employed migrant workers and with everything closed there were no jobs, no income and no food. As a result millions were dying of starvation or malnutrition. All this was happening under Prime Minister Narendra Modi, a 100-percent asset of the Cult, and it emphasises yet again the scale of pure anti-human evil we are dealing with. Australia banned its people from returning home from India with penalties for trying to do so of up to five years in jail and a fine of £37,000. The manufactured 'Covid' crisis in India was being prepared to justify further fascism in the West. Obvious connections could be seen between the Indian 'vaccine' programme and increased 'cases' and this became a common theme. The Seychelles, the most per capita 'Covid vaccinated' population in the world, went back into lockdown after a 'surge of cases'.

Long ago the truly evil Monsanto agricultural biotechnology corporation with its big connections to Bill Gates devastated Indian farming with genetically-modified crops. Human rights activist Gurcharan Singh highlighted the efforts by the Indian government to complete the job by destroying the food supply to hundreds of millions with 'Covid' lockdowns. He said that 415 million people at the bottom of the disgusting caste system (still going whatever they say) were below the poverty line and struggled to feed themselves every year. Now the government was imposing lockdown at just the

time to destroy the harvest. This deliberate policy was leading to mass starvation. People may reel back at the suggestion that a government would do that, but Wetiko-controlled 'leaders' are capable of any level of evil. In fact what is described in India is in the process of being instigated worldwide. The food chain and food supply are being targeted at every level to cause world hunger and thus control. Bill Gates is not the biggest owner of farmland in America for no reason and destroying access to food aids both the depopulation agenda and the plan for synthetic 'food' already being funded into existence by Gates. Add to this the coming hyper-inflation from the suicidal creation of fake 'money' in response to 'Covid' and the breakdown of container shipping systems and you have a cocktail that can only lead one way and is meant to. The Cult plan is to crash the entire system to 'build back better' with the Great Reset.

'Vaccine' transmission

Reports from all over the world continue to emerge of women suffering menstrual and fertility problems after having the fake 'vaccine' and of the non-'vaccinated' having similar problems when interacting with the 'vaccinated'. There are far too many for 'coincidence' to be credible. We've had menopausal women getting periods, others having periods stop or not stopping for weeks, passing clots, sometimes the lining of the uterus, breast irregularities, and miscarriages (which increased by 400 percent in parts of the United States). Non-'vaccinated' men and children have suffered blood clots and nose bleeding after interaction with the 'vaccinated'. Babies have died from the effects of breast milk from a 'vaccinated' mother. Awake doctors – the small minority – speculated on the cause of non-'vaccinated' suffering the same effects as the 'vaccinated'. Was it nanotechnology in the synthetic substance transmitting frequencies or was it a straight chemical bioweapon that was being transmitted between people? I am not saying that some kind of chemical transmission is not one possible answer, but the foundation of all that the Cult does is frequency and

this is fertile ground for understanding how transmission can happen. American doctor Carrie Madej, an internal medicine physician and osteopath, has been practicing for the last 20 years, teaching medical students, and she says attending different meetings where the agenda for humanity was discussed. Madej, who operates out of Georgia, did not dismiss other possible forms of transmission, but she focused on frequency in search of an explanation for transmission. She said the Moderna and Pfizer 'vaccines' contained nano-lipid particles as a key component. This was a brand new technology never before used on humanity. 'They're using a nanotechnology which is pretty much little tiny computer bits … nanobots or hydrogel.' Inside the 'vaccines' was 'this sci-fi kind of substance' which suppressed immune checkpoints to get into the cell. I referred to this earlier as the 'Trojan horse' technique that tricks the cell into opening a gateway for the self-replicating synthetic material and while the immune system is artificially suppressed the body has no defences. Madej said the substance served many purposes including an on-demand ability to 'deliver the payload' and using the nano 'computer bits' as biosensors in the body. 'It actually has the ability to accumulate data from your body, like your breathing, your respiration, thoughts, emotions, all kinds of things.'

She said the technology obviously has the ability to operate through Wi-Fi and transmit and receive energy, messages, frequencies or impulses. 'Just imagine you're getting this new substance in you and it can react to things all around you, the 5G, your smart device, your phones.' We had something completely foreign in the human body that had never been launched large scale at a time when we were seeing 5G going into schools and hospitals (plus the Musk satellites) and she believed the 'vaccine' transmission had something to do with this: '… if these people have this inside of them … it can act like an antenna and actually transmit it outwardly as well.' The synthetic substance produced its own voltage and so it could have that kind of effect. This fits with my own contention that the nano receiver-transmitters are designed to connect people to the

Smart Grid and break the receiver-transmitter connection to expanded consciousness. That would explain the French energy healer's experience of the disconnection of body from 'soul' with those who have had the 'vaccine'. The nanobots, self-replicating inside the body, would also transmit the synthetic frequency which could be picked up through close interaction by those who have not been 'vaccinated'. Madej speculated that perhaps it was 5G and increased levels of other radiation that was causing the symptoms directly although interestingly she said that non-'vaccinated' patients had shown improvement when they were away from the 'vaccinated' person they had interacted with. It must be remembered that you can control frequency and energy with your mind and you can consciously create energetic barriers or bubbles with the mind to stop damaging frequencies from penetrating your field. American paediatrician Dr Larry Palevsky said the 'vaccine' was not a 'vaccine' and was never designed to protect from a 'viral' infection. He called it 'a massive, brilliant propaganda of genocide' because they didn't have to inject everyone to get the result they wanted. He said the content of the jabs was able to infuse any material into the brain, heart, lungs, kidneys, liver, sperm and female productive system. 'This is genocide; this is a weapon of mass destruction.' At the same time American colleges were banning students from attending if they didn't have this life-changing and potentially life-ending 'vaccine'. Class action lawsuits must follow when the consequences of this college fascism come to light. As the book was going to press came reports about fertility effects on sperm in 'vaccinated' men which would absolutely fit with what I have been saying and hospitals continued to fill with 'vaccine' reactions. Another question is what about transmission via blood transfusions? The NHS has extended blood donation restrictions from seven days after a 'Covid vaccination' to 28 days after even a sore arm reaction.

I said in the spring of 2020 that the then touted 'Covid vaccine' would be ongoing each year like the flu jab. A year later Pfizer CEO, the appalling Albert Bourla, said people would 'likely' need a 'booster dose' of the 'vaccine' within 12 months of getting 'fully

vaccinated' and then a yearly shot. 'Variants will play a key role', he said confirming the point. Johnson & Johnson CEO Alex Gorsky also took time out from his 'vaccine' disaster to say that people may need to be vaccinated against 'Covid-19' each year. UK Health Secretary, the psychopath Matt Hancock, said additional 'boosters' would be available in the autumn of 2021. This is the trap of the 'vaccine passport'. The public will have to accept every last 'vaccine' they introduce, including for the fake 'variants', or it would cease to be valid. The only other way in some cases would be continuous testing with a test not testing for the 'virus' and what is on the swabs constantly pushed up your noise towards the brain every time?

'Vaccines' changing behaviour

I mentioned in the body of the book how I believed we would see gathering behaviour changes in the 'vaccinated' and I am already hearing such comments from the non-'vaccinated' describing behaviour changes in friends, loved ones and work colleagues. This will only increase as the self-replicating synthetic material and nanoparticles expand in body and brain. An article in the *Guardian* in 2016 detailed research at the University of Virginia in Charlottesville which developed a new method for controlling brain circuits associated with complex animal behaviour. The method, dubbed 'magnetogenetics', involves genetically-engineering a protein called ferritin, which stores and releases iron, to create a magnetised substance – 'Magneto' – that can activate specific groups of nerve cells from a distance. This is claimed to be an advance on other methods of brain activity manipulation known as optogenetics and chemogenetics (the Cult has been developing methods of brain control for a long time). The ferritin technique is said to be non-invasive and able to activate neurons 'rapidly and reversibly'. In other words, human thought and perception. The article said that earlier studies revealed how nerve cell proteins 'activated by heat and mechanical pressure can be genetically engineered so that they become sensitive to radio waves and magnetic fields, by attaching them to an iron-storing protein called ferritin, or to inorganic

paramagnetic particles'. Sensitive to radio waves and magnetic fields? You mean like 5G, 6G and 7G? This is the human-AI Smart Grid hive mind we are talking about. The *Guardian* article said:

> … the researchers injected Magneto into the striatum of freely behaving mice, a deep brain structure containing dopamine-producing neurons that are involved in reward and motivation, and then placed the animals into an apparatus split into magnetised and non-magnetised sections.
>
> Mice expressing Magneto spent far more time in the magnetised areas than mice that did not, because activation of the protein caused the striatal neurons expressing it to release dopamine, so that the mice found being in those areas rewarding. This shows that Magneto can remotely control the firing of neurons deep within the brain, and also control complex behaviours.

Make no mistake this basic methodology will be part of the 'Covid vaccine' cocktail and using magnetics to change brain function through electromagnetic field frequency activation. The Pentagon is developing a 'Covid vaccine' using ferritin. Magnetics would explain changes in behaviour and why videos are appearing across the Internet as I write showing how magnets stick to the skin at the point of the 'vaccine' shot. Once people take these 'vaccines' anything becomes possible in terms of brain function and illness which will be blamed on 'Covid-19' and 'variants'. Magnetic field manipulation would further explain why the non-'vaccinated' are reporting the same symptoms as the 'vaccinated' they interact with and why those symptoms are reported to decrease when not in their company. Interestingly 'Magneto', a 'mutant', is a character in the Marvel Comic *X-Men* stories with the ability to manipulate magnetic fields and he believes that mutants should fight back against their human oppressors by any means necessary. The character was born Erik Lehnsherr to a Jewish family in Germany.

Cult-controlled courts

The European Court of Human Rights opened the door for mandatory 'Covid-19 vaccines' across the continent when it ruled in a Czech Republic dispute over childhood immunisation that legally

enforced vaccination could be 'necessary in a democratic society'. The 17 judges decided that compulsory vaccinations did not breach human rights law. On the face of it the judgement was so inverted you gasp for air. If not having a vaccine infused into your body is not a human right then what is? Ah, but they said human rights law which has been specifically written to delete all human rights at the behest of the state (the Cult). Article 8 of the European Convention on Human Rights relates to the right to a private life. The crucial word here is *'except'*:

> There shall be no interference by a public authority with the exercise of this right EXCEPT such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic wellbeing of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others [My emphasis].

No interference *except* in accordance with the law means there *are* no 'human rights' *except* what EU governments decide you can have at their behest. 'As is necessary in a democratic society' explains that reference in the judgement and 'in the interests of national security, public safety or the economic well-being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others' gives the EU a coach and horses to ride through 'human rights' and scatter them in all directions. The judiciary is not a check and balance on government extremism; it is a vehicle to enforce it. This judgement was almost laughably predictable when the last thing the Cult wanted was a decision that went against mandatory vaccination. Judges rule over and over again to benefit the system of which they are a part. Vaccination disputes that come before them are invariably delivered in favour of doctors and authorities representing the view of the state which owns the judiciary. Oh, yes, and we have even had calls to stop putting 'Covid-19' on death certificates within 28 days of a 'positive test' because it is claimed the practice makes the 'vaccine' appear not to work. They are laughing at you.

The scale of madness, inhumanity and things to come was highlighted when those not 'vaccinated' for 'Covid' were refused evacuation from the Caribbean island of St Vincent during massive volcanic eruptions. Cruise ships taking residents to the safety of another island allowed only the 'vaccinated' to board and the rest were left to their fate. Even in life and death situations like this we see 'Covid' stripping people of their most basic human instincts and the insanity is even more extreme when you think that fake 'vaccine'-makers are not even claiming their body-manipulating concoctions stop 'infection' and 'transmission' of a 'virus' that doesn't exist. St Vincent Prime Minister Ralph Gonsalves said: 'The chief medical officer will be identifying the persons already vaccinated so that we can get them on the ship.' Note again the power of the chief medical officer who, like Whitty in the UK, will be answering to the World Health Organization. This is the Cult network structure that has overridden politicians who 'follow the science' which means doing what WHO-controlled 'medical officers' and 'science advisers' tell them. Gonsalves even said that residents who were 'vaccinated' after the order so they could board the ships would still be refused entry due to possible side effects such as 'wooziness in the head'. The good news is that if they were woozy enough in the head they could qualify to be prime minister of St Vincent.

Microchipping freedom

The European judgement will be used at some point to justify moves to enforce the 'Covid' DNA-manipulating procedure. Sandra Ro, CEO of the Global Blockchain Business Council, told a World Economic Forum event that she hoped 'vaccine passports' would help to 'drive forced consent and standardisation' of global digital identity schemes: 'I'm hoping with the desire and global demand for some sort of vaccine passport – so that people can get travelling and working again – [it] will drive forced consent, standardisation, and frankly, cooperation across the world.' The lady is either not very bright, or thoroughly mendacious, to use the term 'forced consent'.

You do not 'consent' if you are forced – you *submit*. She was describing what the plan has been all along and that's to enforce a digital identity on every human without which they could not function. 'Vaccine passports' are opening the door and are far from the end goal. A digital identity would allow you to be tracked in everything you do in cyberspace and this is the same technique used by Cult-owned China to enforce its social credit system of total control. The ultimate 'passport' is planned to be a microchip as my books have warned for nearly 30 years. Those nice people at the Pentagon working for the Cult-controlled Defense Advanced Research Projects Agency (DARPA) claimed in April, 2021, they have developed a microchip inserted under the skin to detect 'asymptomatic Covid-19 infection' before it becomes an outbreak and a 'revolutionary filter' that can remove the 'virus' from the blood when attached to a dialysis machine. The only problems with this are that the 'virus' does not exist and people transmitting the 'virus' with no symptoms is brain-numbing bullshit. This is, of course, not a ruse to get people to be microchipped for very different reasons. DARPA also said it was producing a one-stop 'vaccine' for the 'virus' and all 'variants'. One of the most sinister organisations on Planet Earth is doing this? Better have it then. These people are insane because Wetiko that possesses them is insane.

Researchers from the Salk Institute in California announced they have created an embryo that is part human and part monkey. My books going back to the 1990s have exposed experiments in top secret underground facilities in the United States where humans are being crossed with animal and non-human 'extraterrestrial' species. They are now easing that long-developed capability into the public arena and there is much more to come given we are dealing with psychiatric basket cases. Talking of which – Elon Musk's scientists at Neuralink trained a monkey to play Pong and other puzzles on a computer screen using a joystick and when the monkey made the correct move a metal tube squirted banana smoothie into his mouth which is the basic technique for training humans into unquestioning compliance. Two Neuralink chips were in the monkey's skull and

more than 2,000 wires 'fanned out' into its brain. Eventually the monkey played a video game purely with its brain waves. Psychopathic narcissist Musk said the 'breakthrough' was a step towards putting Neuralink chips into human skulls and merging minds with artificial intelligence. *Exactly*. This man is so dark and Cult to his DNA.

World Economic Fascism (WEF)

The World Economic Forum is telling you the plan by the statements made at its many and various events. Cult-owned fascist YouTube CEO Susan Wojcicki spoke at the 2021 WEF Global Technology Governance Summit (see the name) in which 40 governments and 150 companies met to ensure 'the responsible design and deployment of emerging technologies'. Orwellian translation: 'Ensuring the design and deployment of long-planned technologies will advance the Cult agenda for control and censorship.' Freedom-destroyer and Nuremberg-bound Wojcicki expressed support for tech platforms like hers to censor content that is 'technically legal but could be harmful'. Who decides what is 'harmful'? She does and they do. 'Harmful' will be whatever the Cult doesn't want people to see and we have legislation proposed by the UK government that would censor content on the basis of 'harm' no matter if the information is fair, legal and provably true. Make that *especially* if it is fair, legal and provably true. Wojcicki called for a global coalition to be formed to enforce content moderation standards through automated censorship. This is a woman and mega-censor so self-deluded that she shamelessly accepted a 'free expression' award – *Wojcicki* – in an event sponsored by her own *YouTube*. They have no shame and no self-awareness.

You know that 'Covid' is a scam and Wojcicki a Cult operative when YouTube is censoring medical and scientific opinion purely on the grounds of whether it supports or opposes the Cult 'Covid' narrative. Florida governor Ron DeSantis compiled an expert panel with four professors of medicine from Harvard, Oxford, and Stanford Universities who spoke against forcing children and

vaccinated people to wear masks. They also said there was no proof that lockdowns reduced spread or death rates of 'Covid-19'. Cult-gofer Wojcicki and her YouTube deleted the panel video 'because it included content that contradicts the consensus of local and global health authorities regarding the efficacy of masks to prevent the spread of Covid-19'. This 'consensus' refers to what the Cult tells the World Health Organization to say and the WHO tells 'local health authorities' to do. Wojcicki knows this, of course. The panellists pointed out that censorship of scientific debate was responsible for deaths from many causes, but Wojcicki couldn't care less. She would not dare go against what she is told and as a disgrace to humanity she wouldn't want to anyway. The UK government is seeking to pass a fascist 'Online Safety Bill' to specifically target with massive fines and other means non-censored video and social media platforms to make them censor 'lawful but harmful' content like the Cult-owned Facebook, Twitter, Google and YouTube. What is 'lawful but harmful' would be decided by the fascist Blair-created Ofcom.

Another WEF obsession is a cyber-attack on the financial system and this is clearly what the Cult has planned to take down the bank accounts of everyone – except theirs. Those that think they have enough money for the Cult agenda not to matter to them have got a big lesson coming if they continue to ignore what is staring them in the face. The World Economic Forum, funded by Gates and fronted by Klaus Schwab, announced it would be running a 'simulation' with the Russian government and global banks of just such an attack called Cyber Polygon 2021. What they simulate – as with the 'Covid' Event 201 – they plan to instigate. The WEF is involved in a project with the Cult-owned Carnegie Endowment for International Peace called the WEF-Carnegie Cyber Policy Initiative which seeks to merge Wall Street banks, 'regulators' (I love it) and intelligence agencies to 'prevent' (arrange and allow) a cyber-attack that would bring down the global financial system as long planned by those that control the WEF and the Carnegie operation. The Carnegie Endowment for International Peace sent an instruction to First World

War US President Woodrow Wilson not to let the war end before society had been irreversibly transformed.

The Wuhan lab diversion

As I close, the Cult-controlled authorities and lapdog media are systematically pushing 'the virus was released from the Wuhan lab' narrative. There are two versions – it happened by accident and it happened on purpose. Both are nonsense. The perceived existence of the never-shown-to-exist 'virus' is vital to sell the impression that there is actually an infective agent to deal with and to allow the endless potential for terrifying the population with 'variants' of a 'virus' that does not exist. The authorities at the time of writing are going with the 'by accident' while the alternative media is promoting the 'on purpose'. Cable news host Tucker Carlson who has questioned aspects of lockdown and 'vaccine' compulsion has bought the Wuhan lab story. 'Everyone now agrees' he said. Well, I don't and many others don't and the question is *why* does the system and its media suddenly 'agree'? When the media moves as one unit with a narrative it is always a lie – witness the hour by hour mendacity of the 'Covid' era. Why would this Cult-owned combination which has unleashed lies like machine gun fire suddenly 'agree' to tell the truth??

Much of the alternative media is buying the lie because it fits the conspiracy narrative, but it's the *wrong* conspiracy. The real conspiracy is that *there is no virus* and that is what the Cult is desperate to hide. The idea that the 'virus' was released by accident is ludicrous when the whole 'Covid' hoax was clearly long-planned and waiting to be played out as it was so fast in accordance with the Rockefeller document and Event 201. So they prepared everything in detail over decades and then sat around strumming their fingers waiting for an 'accidental' release from a bio-lab? *What??* It's crazy. Then there's the 'on purpose' claim. You want to circulate a 'deadly virus' and hide the fact that you've done so and you release it down the street from the highest-level bio-lab in China? I repeat – *What??*

You would release it far from that lab to stop any association being made. But, no, we'll do it in a place where the connection was certain to be made. Why would you need to scam 'cases' and 'deaths' and pay hospitals to diagnose 'Covid-19' if you had a real 'virus'? What are sections of the alternative media doing believing this crap? Where were all the mass deaths in Wuhan from a 'deadly pathogen' when the recovery to normal life after the initial propaganda was dramatic in speed? Why isn't the 'deadly pathogen' now circulating all over China with bodies in the street? Once again we have the technique of tell them what they want to hear and they will likely believe it. The alternative media has its 'conspiracy' and with Carlson it fits with his 'China is the danger' narrative over years. China *is* a danger as a global Cult operations centre, but not for this reason. The Wuhan lab story also has the potential to instigate conflict with China when at some stage the plan is to trigger a Problem-Reaction-Solution confrontation with the West. Question everything – *everything* – and especially when the media agrees on a common party line.

Third wave ... fourth wave ... fifth wave ...

As the book went into production the world was being set up for more lockdowns and a 'third wave' supported by invented 'variants' that were increasing all the time and will continue to do so in public statements and computer programs, but not in reality. India became the new Italy in the 'Covid' propaganda campaign and we were told to be frightened of the new 'Indian strain'. Somehow I couldn't find it within myself to do so. A document produced for the UK government entitled 'Summary of further modelling of easing of restrictions – Roadmap Step 2' declared that a third wave was inevitable (of course when it's in the script) and it would be the fault of children and those who refuse the health-destroying fake 'Covid vaccine'. One of the computer models involved came from the Cult-owned *Imperial College* and the other from Warwick University which I wouldn't trust to tell me the date in a calendar factory. The document states that both models presumed extremely high uptake

of the 'Covid vaccines' and didn't allow for 'variants'. The document states: 'The resurgence is a result of some people (mostly children) being ineligible for vaccination; others choosing not to receive the vaccine; and others being vaccinated but not perfectly protected.' The mendacity takes the breath away. Okay, blame those with a brain who won't take the DNA-modifying shots and put more pressure on children to have it as 'trials' were underway involving children as young as six months with parents who give insanity a bad name. Massive pressure is being put on the young to have the fake 'vaccine' and child age consent limits have been systematically lowered around the world to stop parents intervening. Most extraordinary about the document was its claim that the 'third wave' would be driven by 'the resurgence in both hospitalisations and deaths … dominated by *those that have received two doses of the vaccine*, comprising around 60-70% of the wave respectively'. The predicted peak of the 'third wave' suggested 300 deaths per day with 250 of them *fully 'vaccinated' people*. How many more lies do acquiescers need to be told before they see the obvious? Those who took the jab to 'protect themselves' are projected to be those who mostly get sick and die? So what's in the 'vaccine'? The document went on:

> It is possible that a summer of low prevalence could be followed by substantial increases in incidence over the following autumn and winter. Low prevalence in late summer should not be taken as an indication that SARS-CoV-2 has retreated or that the population has high enough levels of immunity to prevent another wave.

They are telling you the script and while many British people believed 'Covid' restrictions would end in the summer of 2021 the government was preparing for them to be ongoing. Authorities were awarding contracts for 'Covid marshals' to police the restrictions with contracts starting in July, 2021, and going through to January 31st, 2022, and the government was advertising for 'Media Buying Services' to secure media propaganda slots worth a potential £320 million for 'Covid-19 campaigns' with a contract not ending until March, 2022. The recipient – via a list of other front companies – was reported to be American media marketing giant Omnicom Group

Inc. While money is no object for 'Covid' the UK waiting list for all other treatment – including life-threatening conditions – passed 4.5 million. Meantime the Cult is seeking to control all official 'inquiries' to block revelations about what has really been happening and why. It must not be allowed to – we need Nuremberg jury trials in every country. The cover-up doesn't get more obvious than appointing ultra-Zionist professor Philip Zelikow to oversee two dozen US virologists, public health officials, clinicians, former government officials and four American 'charitable foundations' to 'learn the lessons' of the 'Covid' debacle. The personnel will be those that created and perpetuated the 'Covid' lies while Zelikow is the former executive director of the 9/11 Commission who ensured that the truth about those attacks never came out and produced a report that must be among the most mendacious and manipulative documents ever written – see *The Trigger* for the detailed exposure of the almost unimaginable 9/11 story in which Sabbatians can be found at every level.

Passive no more

People are increasingly challenging the authorities with amazing numbers of people taking to the streets in London well beyond the ability of the Face-Nappies to stop them. Instead the Nappies choose situations away from the mass crowds to target, intimidate, and seek to promote the impression of 'violent protestors'. One such incident happened in London's Hyde Park. Hundreds of thousands walking through the streets in protest against 'Covid' fascism were ignored by the Cult-owned BBC and most of the rest of the mainstream media, but they delighted in reporting how police were injured in 'clashes with protestors'. The truth was that a group of people gathered in Hyde Park at the end of one march when most had gone home and they were peacefully having a good time with music and chat. Face-Nappies who couldn't deal with the full-march crowd then waded in with their batons and got more than they bargained for. Instead of just standing for this criminal brutality the crowd used their numerical superiority to push the Face-Nappies out of the

park. Eventually the Nappies turned and ran. Unfortunately two or three idiots in the crowd threw drink cans striking two officers which gave the media and the government the image they wanted to discredit the 99.9999 percent who were peaceful. The idiots walked straight into the trap and we must always be aware of potential agent provocateurs used by the authorities to discredit their targets.

This response from the crowd – the can people apart – must be a turning point when the public no longer stand by while the innocent are arrested and brutally attacked by the Face-Nappies. That doesn't mean to be violent, that's the last thing we need. We'll leave the violence to the Face-Nappies and government. But it does mean that when the Face-Nappies use violence against peaceful people the numerical superiority is employed to stop them and make citizen's arrests or Common Law arrests for a breach of the peace. The time for being passive in the face of fascism is over.

We are the many, they are the few, and we need to make that count before there is no freedom left and our children and grandchildren face an ongoing fascist nightmare.

COME ON PEOPLE – IT'S TIME.

One final thought …

The power of love
A force from above
Cleaning my soul
Flame on burn desire
Love with tongues of fire
Purge the soul
Make love your goal

I'll protect you from the hooded claw
Keep the vampires from your door
When the chips are down I'll be around
With my undying, death-defying
Love for you

Envy will hurt itself
Let yourself be beautiful
Sparkling love, flowers
And pearls and pretty girls
Love is like an energy
Rushin' rushin' inside of me

This time we go sublime
Lovers entwine, divine, divine,
Love is danger, love is pleasure
Love is pure – the only treasure

I'm so in love with you
Purge the soul
Make love your goal

The power of love
A force from above
Cleaning my soul
The power of love
A force from above
A sky-scraping dove

Flame on burn desire
Love with tongues of fire
Purge the soul
Make love your goal

Frankie Goes To Hollywood

APPENDIX

Cowan-Kaufman-Morell Statement on Virus Isolation (SOVI)

Isolation: The action of isolating; the fact or condition of being isolated or standing alone; separation from other things or persons; solitariness
Oxford English Dictionary

The controversy over whether the SARS-CoV-2 virus has ever been isolated or purified continues. However, using the above definition, common sense, the laws of logic and the dictates of science, any unbiased person must come to the conclusion that the SARS-CoV-2 virus has never been isolated or purified. As a result, no confirmation of the virus' existence can be found. The logical, common sense, and scientific consequences of this fact are:

- the structure and composition of something not shown to exist can't be known, including the presence, structure, and function of any hypothetical spike or other proteins;
- the genetic sequence of something that has never been found can't be known;
- "variants" of something that hasn't been shown to exist can't be known;
- it's impossible to demonstrate that SARS-CoV-2 causes a disease called Covid-19.

In as concise terms as possible, here's the proper way to isolate, characterize and demonstrate a new virus. First, one takes samples (blood, sputum, secretions) from many people (e.g. 500) with symptoms which are unique and specific enough to characterize an illness. Without mixing these samples with ANY tissue or products that also contain genetic material, the virologist macerates, filters and ultracentrifuges i.e. *purifies* the specimen. This common virology technique, done for decades to isolate bacteriophages[1] and so-called giant viruses in every virology lab, then allows the virologist to demonstrate with electron microscopy thousands of identically sized and shaped particles. These particles are the isolated and purified virus.

These identical particles are then checked for uniformity by physical and/or microscopic techniques. Once the purity is determined, the particles may be further characterized. This would include examining the structure, morphology, and chemical composition of the particles. Next, their genetic makeup is characterized by extracting the genetic material directly from the purified particles and using genetic-sequencing techniques, such as Sanger sequencing, that have also been around for decades. Then one does an analysis to confirm that these uniform particles are exogenous (outside) in origin as a virus is conceptualized to be, and not the normal breakdown products of dead and dying tissues.[2] (As of May 2020, we know that virologists have no way to determine whether the particles they're seeing are viruses or just normal breakdown products of dead and dying tissues.)[3]

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1 Isolation, characterization and analysis of bacteriophages from the haloalkaline lake Elmenteita, KenyaJuliah Khayeli Akhwale et al, PLOS One, Published: April 25, 2019. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0215734 – accessed 2/15/21

2 "Extracellular Vesicles Derived From Apoptotic Cells: An Essential Link Between Death and Regeneration," Maojiao Li1 et al, Frontiers in Cell and Developmental Biology, 2020 October 2. https://www.frontiersin.org/articles/10.3389/fcell.2020.573511/full – accessed 2/15/21

3 "The Role of Extraellular Vesicles as Allies of HIV, HCV and SARS Viruses," Flavia Giannessi, et al, Viruses, 2020 May

If we have come this far then we have fully isolated, characterized, and genetically sequenced an exogenous virus particle. However, we still have to show it is causally related to a disease. This is carried out by exposing a group of healthy subjects (animals are usually used) to this isolated, purified virus in the manner in which the disease is thought to be transmitted. If the animals get sick with the same disease, as confirmed by clinical and autopsy findings, one has now shown that the virus actually causes a disease. This demonstrates infectivity and transmission of an infectious agent.

None of these steps has even been attempted with the SARS-CoV-2 virus, nor have all these steps been successfully performed for any so-called pathogenic virus. Our research indicates that a single study showing these steps does not exist in the medical literature.

Instead, since 1954, virologists have taken unpurified samples from a relatively few people, often less than ten, with a similar disease. They then minimally process this sample and inoculate this unpurified sample onto tissue culture containing usually four to six other types of material – all of which contain identical genetic material as to what is called a "virus." The tissue culture is starved and poisoned and naturally disintegrates into many types of particles, some of which contain genetic material. Against all common sense, logic, use of the English language and scientific integrity, this process is called "virus isolation." This brew containing fragments of genetic material from many sources is then subjected to genetic analysis, which then creates in a computer-simulation process the alleged sequence of the alleged virus, a so called in silico genome. At no time is an actual virus confirmed by electron microscopy. At no time is a genome extracted and sequenced from an actual virus. This is scientific fraud.

The observation that the unpurified specimen — inoculated onto tissue culture along with toxic antibiotics, bovine fetal tissue, amniotic fluid and other tissues — destroys the kidney tissue onto which it is inoculated is given as evidence of the virus' existence and pathogenicity. This is scientific fraud.

From now on, when anyone gives you a paper that suggests the SARS-CoV-2 virus has been isolated, please check the methods sections. If the researchers used Vero cells or any other culture method, you know that their process was not isolation. You will hear the following excuses for why actual isolation isn't done:

1. There were not enough virus particles found in samples from patients to analyze.

2. Viruses are intracellular parasites; they can't be found outside the cell in this manner.

If No. 1 is correct, and we can't find the virus in the sputum of sick people, then on what evidence do we think the virus is dangerous or even lethal? If No. 2 is correct, then how is the virus spread from person to person? We are told it emerges from the cell to infect others. Then why isn't it possible to find it?

Finally, questioning these virology techniques and conclusions is not some distraction or divisive issue. Shining the light on this truth is essential to stop this terrible fraud that humanity is confronting. For, as we now know, if the virus has never been isolated, sequenced or shown to cause illness, if the virus is imaginary, then why are we wearing masks, social distancing and putting the whole world into prison?

Finally, if pathogenic viruses don't exist, then what is going into those injectable devices erroneously called "vaccines," and what is their purpose? This scientific question is the most urgent and relevant one of our time.

We are correct. The SARS-CoV2 virus does not exist.

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Ickonic is something that has been a dream of mine for the last 5 years, growing up around alternative information I have always had a natural interest in what is going on in the World and what could I do to make it better.
Across the range of subjects and positions of influence occupied mainly by people who don't strive to make things better it's the Media that I have always found the most frustrating and fascinating. Mainly because if the Media did their Jobs properly then so much of the negative things happening in the World simply would not be able to happen, because they would be exposed within a heartbeat.
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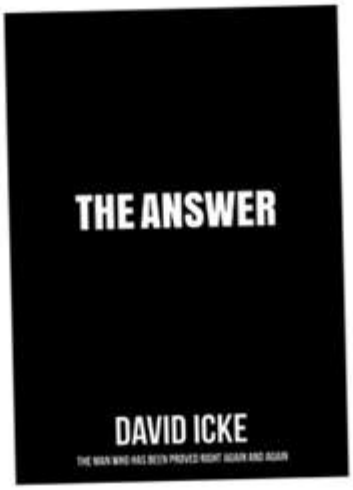
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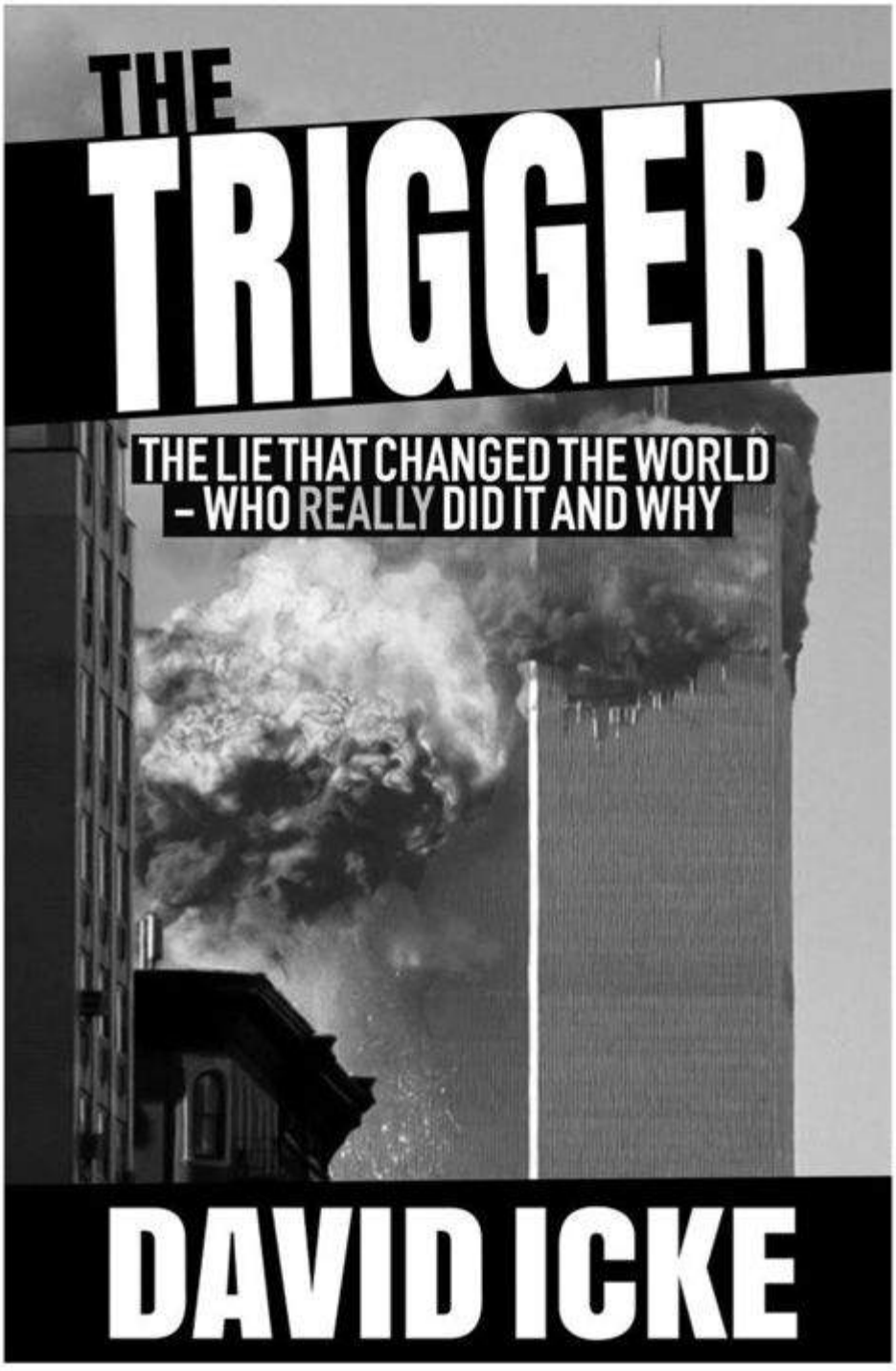
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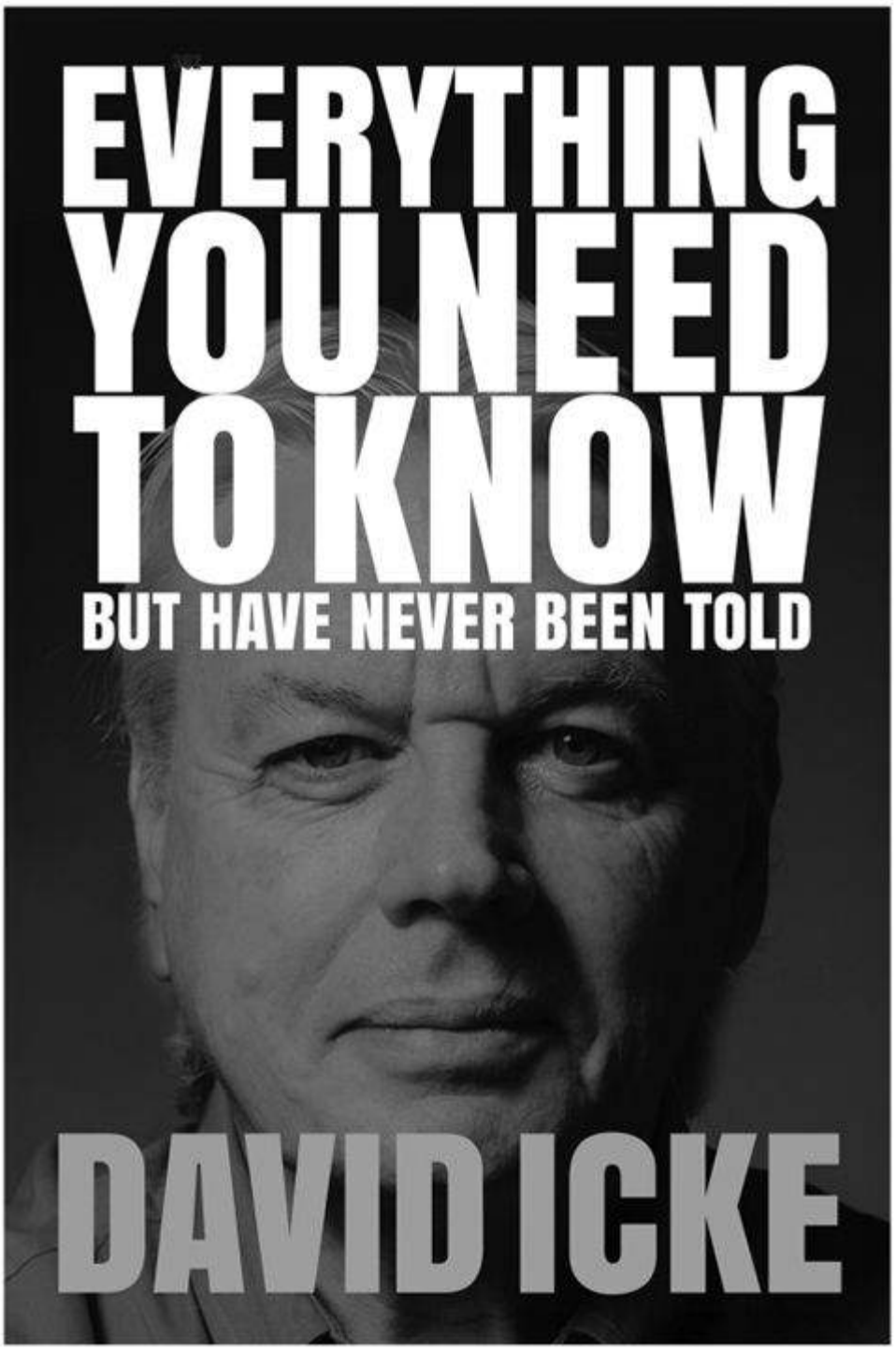


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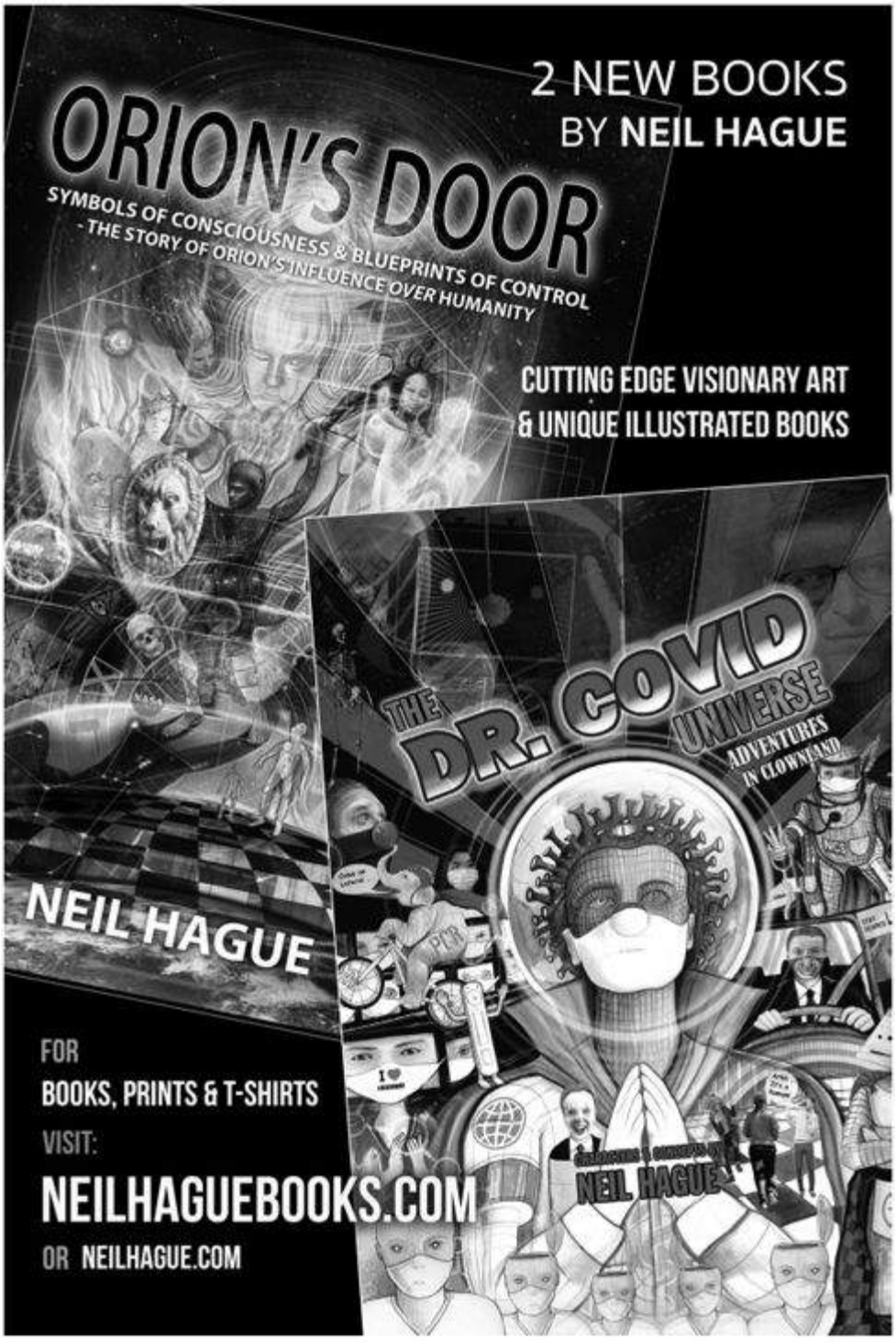
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noun

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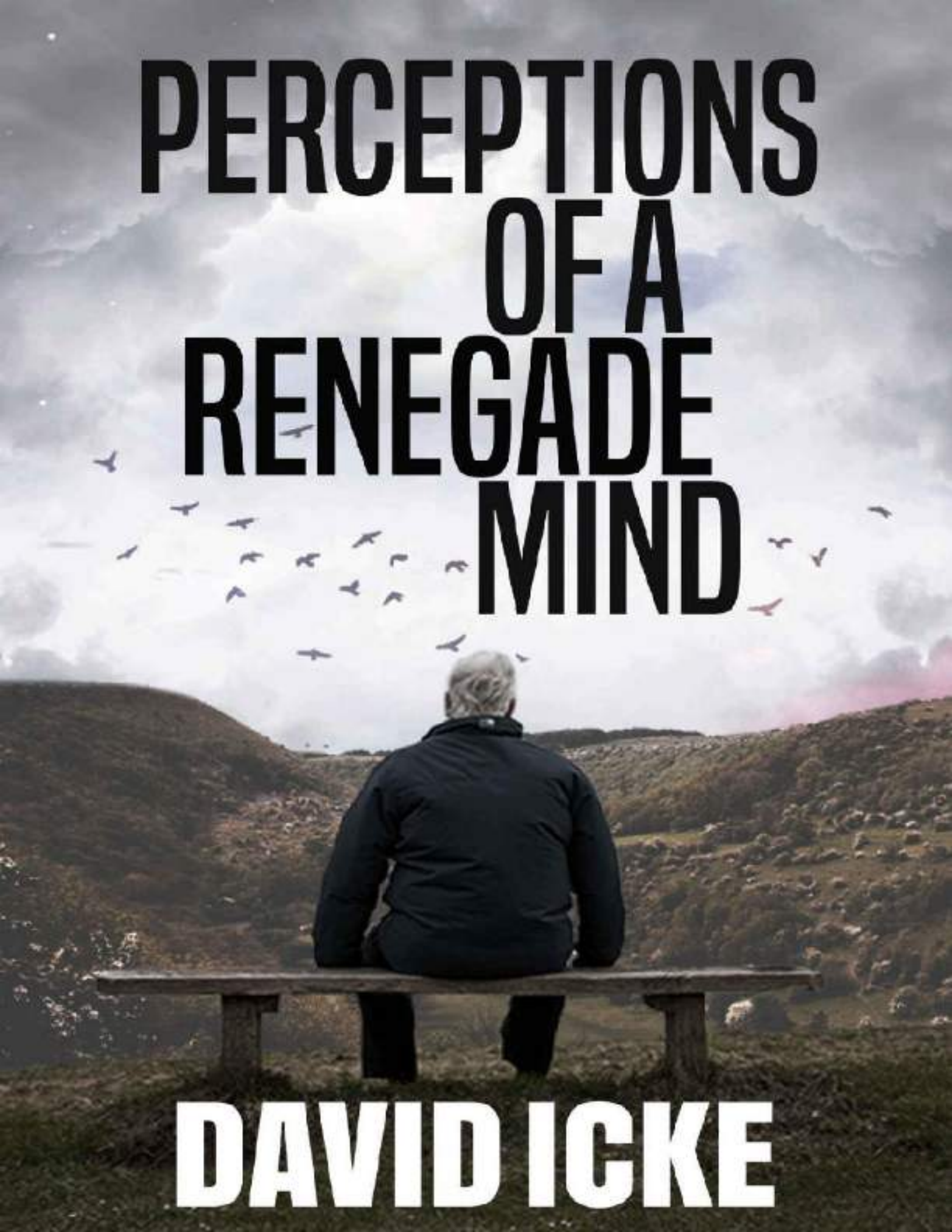

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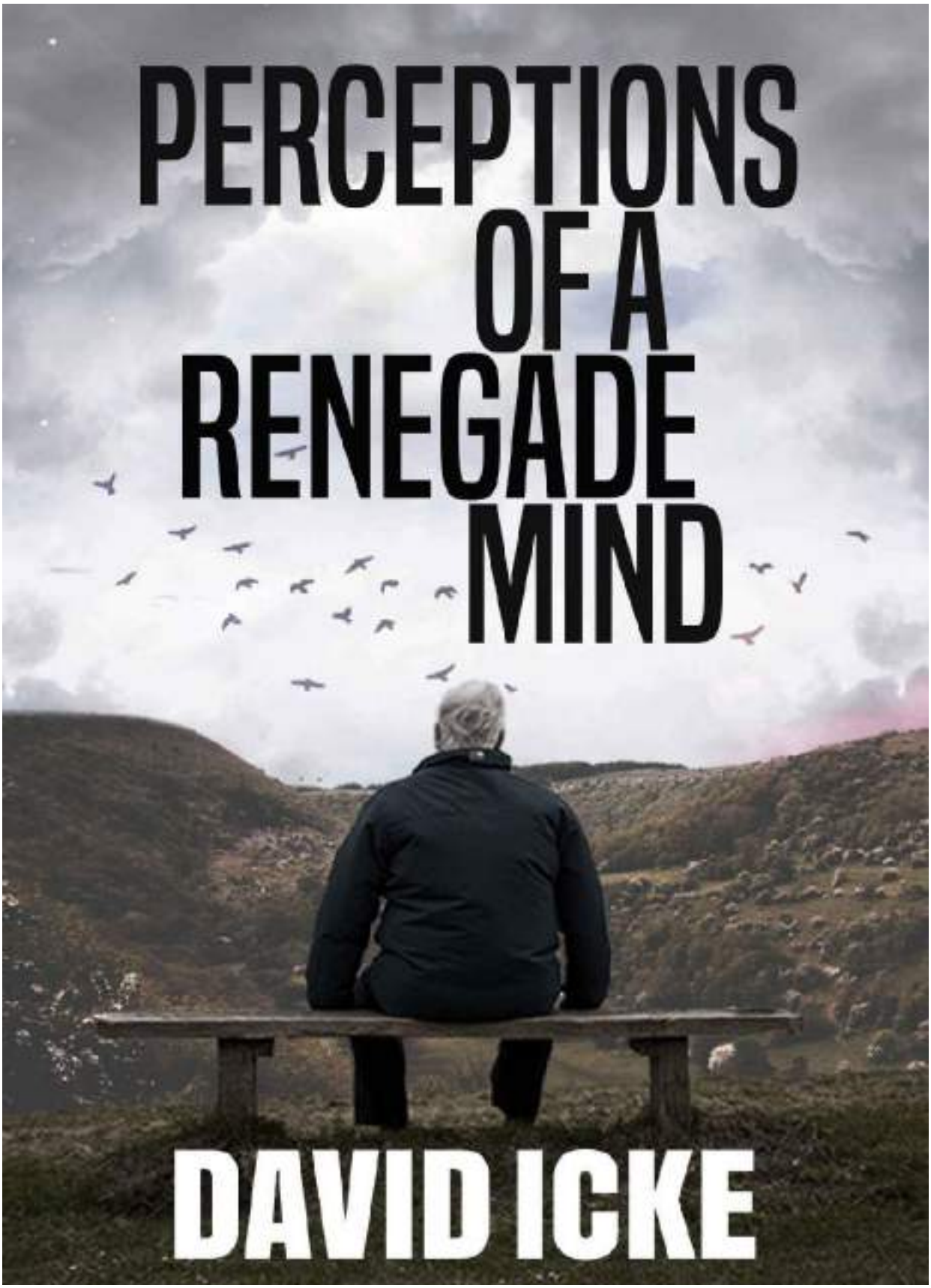
For more detail, background and evidence about the subjects in *Perceptions of a Renegade Mind* – and so much more – see my others books including *And The Truth Shall Set You Free; The Biggest Secret; Children of the Matrix; The David Icke Guide to the Global Conspiracy; Tales from the Time Loop; The Perception Deception; Remember Who You Are; Human Race Get Off Your Knees; Phantom Self; Everything You Need To Know But Have Never Been Told, The Trigger and The Answer*.

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PERCEPTIONS OF A RENEGADE MIND



DAVID ICKE


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PERCEPTIONS OF A RENEGADE MIND



DAVID ICKE

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Renegade:
Adjective
‘Having rejected tradition: Unconventional.’
Merriam-Webster Dictionary

Acquiescence to tyranny is the death of the spirit

You may be 38 years old, as I happen to be. And one day, some great opportunity stands before you and calls you to stand up for some great principle, some great issue, some great cause. And you refuse to do it because you are afraid … You refuse to do it because you want to live longer … You're afraid that you will lose your job, or you are afraid that you will be criticised or that you will lose your popularity, or you're afraid that somebody will stab you, or shoot at you or bomb your house; so you refuse to take the stand.

Well, you may go on and live until you are 90, but you're just as dead at 38 as you would be at 90. And the cessation of breathing in your life is but the belated announcement of an earlier death of the spirit.

Martin Luther King

How the few control the many and always have – the many do whatever they're told

'Forward, the Light Brigade!'
Was there a man dismayed?
Not though the soldier knew
Someone had blundered.
Theirs not to make reply,
Theirs not to reason why,
Theirs but to do and die.
Into the valley of Death
Rode the six hundred.

Cannon to right of them,
Cannon to left of them,
Cannon in front of them
Volleyed and thundered;
Stormed at with shot and shell,
Boldly they rode and well,
Into the jaws of Death,
Into the mouth of hell
Rode the six hundred

Alfred Lord Tennyson (1809-1892)

The mist is lifting slowly
I can see the way ahead
And I've left behind the empty streets
That once inspired my life
And the strength of the emotion
Is like thunder in the air
'Cos the promise that we made each other
Haunts me to the end

The secret of your beauty
And the mystery of your soul
I've been searching for in everyone I meet
And the times I've been mistaken
It's impossible to say
And the grass is growing
Underneath our feet

The words that I remember
From my childhood still are true
That there's none so blind
As those who will not see
And to those who lack the courage
And say it's dangerous to try
Well they just don't know
That love eternal will not be denied

I know you're out there somewhere
Somewhere, somewhere
I know you're out there somewhere

Somewhere you can hear my voice
I know I'll find you somehow
Somehow, somehow
I know I'll find you somehow
And somehow I'll return again to you

The Moody Blues

Are you a gutless wonder - or a Renegade Mind?

Monuments put from pen to paper,
Turns me into a gutless wonder,
And if you tolerate this,
Then your children will be next.
Gravity keeps my head down,
Or is it maybe shame ...

Manic Street Preachers

Rise like lions after slumber
In unvanquishable number.
Shake your chains to earth like dew
Which in sleep have fallen on you.
Ye are many – they are few.

Percy Shelley

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CHAPTER ONE

I'm thinking' – Oh, but *are* you?

Think for yourself and let others enjoy the privilege of doing so too
Voltaire

French-born philosopher, mathematician and scientist René Descartes became famous for his statement in Latin in the 17th century which translates into English as: 'I think, therefore I am.'

On the face of it that is true. Thought reflects perception and perception leads to both behaviour and self-identity. In that sense 'we' are what we think. But who or what is doing the thinking and is thinking the only route to perception? Clearly, as we shall see, 'we' are not always the source of 'our' perception, indeed with regard to humanity as a whole this is rarely the case; and thinking is far from the only means of perception. Thought is the village idiot compared with other expressions of consciousness that we all have the potential to access and tap into. This has to be true when we *are* those other expressions of consciousness which are infinite in nature. We have forgotten this, or, more to the point, been manipulated to forget.

These are not just the esoteric musings of the navel. The whole foundation of human control and oppression is control of perception. Once perception is hijacked then so is behaviour which is dictated by perception. Collective perception becomes collective behaviour and collective behaviour is what we call human society. Perception is all and those behind human control know that which is

why perception is the target 24/7 of the psychopathic manipulators that I call the Global Cult. They know that if they dictate perception they will dictate behaviour and collectively dictate the nature of human society. They are further aware that perception is formed from information received and if they control the circulation of information they will to a vast extent direct human behaviour. Censorship of information and opinion has become globally Nazi-like in recent years and never more blatantly than since the illusory 'virus pandemic' was triggered out of China in 2019 and across the world in 2020. Why have billions submitted to house arrest and accepted fascistic societies in a way they would have never believed possible? Those controlling the information spewing from government, mainstream media and Silicon Valley (all controlled by the same Global Cult networks) told them they were in danger from a 'deadly virus' and only by submitting to house arrest and conceding their most basic of freedoms could they and their families be protected. This monumental and provable lie became the *perception* of the billions and therefore the *behaviour* of the billions. In those few words you have the whole structure and modus operandi of human control. Fear is a perception – **F**alse **E**motion **A**ppearing **R**eal – and fear is the currency of control. In short … get them by the balls (or give them the impression that you have) and their hearts and minds will follow. Nothing grips the dangly bits and freezes the rear-end more comprehensively than fear.

World number 1

There are two 'worlds' in what appears to be one 'world' and the prime difference between them is knowledge. First we have the mass of human society in which the population is maintained in coldly-calculated ignorance through control of information and the 'education' (indoctrination) system. That's all you really need to control to enslave billions in a perceptual delusion in which what are perceived to be *their* thoughts and opinions are ever-repeated mantras that the system has been downloading all their lives through 'education', media, science, medicine, politics and academia

in which the personnel and advocates are themselves overwhelmingly the perceptual products of the same repetition. Teachers and academics in general are processed by the same programming machine as everyone else, but unlike the great majority they never leave the 'education' program. It gripped them as students and continues to grip them as programmers of subsequent generations of students. The programmed become the programmers – the programmed programmers. The same can largely be said for scientists, doctors and politicians and not least because as the American writer Upton Sinclair said: 'It is difficult to get a man to understand something when his salary depends upon his not understanding it.' If your career and income depend on thinking the way the system demands then you will – bar a few free-minded exceptions – concede your mind to the Perceptual Mainframe that I call the Postage Stamp Consensus. This is a tiny band of perceived knowledge and possibility 'taught' (downloaded) in the schools and universities, pounded out by the mainstream media and on which all government policy is founded. Try thinking, and especially speaking and acting, outside of the 'box' of consensus and see what that does for your career in the Mainstream Everything which bullies, harasses, intimidates and ridicules the population into compliance. Here we have the simple structure which enslaves most of humanity in a perceptual prison cell for an entire lifetime and I'll go deeper into this process shortly. Most of what humanity is taught as fact is nothing more than programmed belief. American science fiction author Frank Herbert was right when he said: 'Belief can be manipulated. Only knowledge is dangerous.' In the 'Covid' age belief is promoted and knowledge is censored. It was always so, but never to the extreme of today.

World number 2

A 'number 2' is slang for 'doing a poo' and how appropriate that is when this other 'world' is doing just that on humanity every minute of every day. World number 2 is a global network of secret societies and semi-secret groups dictating the direction of society via

governments, corporations and authorities of every kind. I have spent more than 30 years uncovering and exposing this network that I call the Global Cult and knowing its agenda is what has made my books so accurate in predicting current and past events. Secret societies are secret for a reason. They want to keep their hoarded knowledge to themselves and their chosen initiates and to hide it from the population which they seek through ignorance to control and subdue. The whole foundation of the division between World 1 and World 2 is *knowledge*. What number 1 knows number 2 must not. Knowledge they have worked so hard to keep secret includes (a) the agenda to enslave humanity in a centrally-controlled global dictatorship, and (b) the nature of reality and life itself. The latter (b) must be suppressed to allow the former (a) to prevail as I shall be explaining. The way the Cult manipulates and interacts with the population can be likened to a spider's web. The 'spider' sits at the centre in the shadows and imposes its will through the web with each strand represented in World number 2 by a secret society, satanic or semi-secret group, and in World number 1 – the world of the seen – by governments, agencies of government, law enforcement, corporations, the banking system, media conglomerates and Silicon Valley (Fig 1 overleaf). The spider and the web connect and coordinate all these organisations to pursue the same global outcome while the population sees them as individual entities working randomly and independently. At the level of the web governments *are* the banking system *are* the corporations *are* the media *are* Silicon Valley *are* the World Health Organization working from their inner cores as one unit. Apparently unconnected countries, corporations, institutions, organisations and people are on the *same team* pursuing the same global outcome. Strands in the web immediately around the spider are the most secretive and exclusive secret societies and their membership is emphatically restricted to the Cult inner-circle emerging through the generations from particular bloodlines for reasons I will come to. At the core of the core you would get them in a single room. That's how many people are dictating the direction of human society and its transformation

through the ‘Covid’ hoax and other means. As the web expands out from the spider we meet the secret societies that many people will be aware of – the Freemasons, Knights Templar, Knights of Malta, Opus Dei, the inner sanctum of the Jesuit Order, and such like. Note how many are connected to the Church of Rome and there is a reason for that. The Roman Church was established as a revamp, a rebranding, of the relocated ‘Church’ of Babylon and the Cult imposing global tyranny today can be tracked back to Babylon and Sumer in what is now Iraq.



Figure 1: The global web through which the few control the many. (Image Neil Hague.)

Inner levels of the web operate in the unseen away from the public eye and then we have what I call the cusp organisations located at the point where the hidden meets the seen. They include a series of satellite organisations answering to a secret society founded in London in the late 19th century called the Round Table and among them are the Royal Institute of International Affairs (UK, founded in 1920); Council on Foreign Relations (US, 1921); Bilderberg Group (worldwide, 1954); Trilateral Commission (US/worldwide, 1972); and the Club of Rome (worldwide, 1968) which was created to exploit environmental concerns to justify the centralisation of global power to ‘save the planet’. The Club of Rome instigated with others the human-caused climate change hoax which has led to all the ‘green

new deals' demanding that very centralisation of control. Cusp organisations, which include endless 'think tanks' all over the world, are designed to coordinate a single global policy between political and business leaders, intelligence personnel, media organisations and anyone who can influence the direction of policy in their own sphere of operation. Major players and regular attenders will know what is happening – or some of it – while others come and go and are kept overwhelmingly in the dark about the big picture. I refer to these cusp groupings as semi-secret in that they can be publicly identified, but what goes on at the inner-core is kept very much 'in house' even from most of their members and participants through a fiercely-imposed system of compartmentalisation. Only let them know what they need to know to serve your interests and no more. The structure of secret societies serves as a perfect example of this principle. Most Freemasons never get higher than the bottom three levels of 'degree' (degree of knowledge) when there are 33 official degrees of the Scottish Rite. Initiates only qualify for the next higher 'compartment' or degree if those at that level choose to allow them. Knowledge can be carefully assigned only to those considered 'safe'. I went to my local Freemason's lodge a few years ago when they were having an 'open day' to show how cuddly they were and when I chatted to some of them I was astonished at how little the rank and file knew even about the most ubiquitous symbols they use. The mushroom technique – keep them in the dark and feed them bullshit – applies to most people in the web as well as the population as a whole. Sub-divisions of the web mirror in theme and structure transnational corporations which have a headquarters somewhere in the world dictating to all their subsidiaries in different countries. Subsidiaries operate in their methodology and branding to the same centrally-dictated plan and policy in pursuit of particular ends. The Cult web functions in the same way. Each country has its own web as a subsidiary of the global one. They consist of networks of secret societies, semi-secret groups and bloodline families and their job is to impose the will of the spider and the global web in their particular country. Subsidiary networks control and manipulate the national political system, finance, corporations, media, medicine, etc. to

ensure that they follow the globally-dictated Cult agenda. These networks were the means through which the 'Covid' hoax could be played out with almost every country responding in the same way.

The 'Yessir' pyramid

Compartmentalisation is the key to understanding how a tiny few can dictate the lives of billions when combined with a top-down sequence of imposition and acquiescence. The inner core of the Cult sits at the peak of the pyramidal hierarchy of human society (Fig 2 overleaf). It imposes its will – its agenda for the world – on the level immediately below which acquiesces to that imposition. This level then imposes the Cult will on the level below them which acquiesces and imposes on the next level. Very quickly we meet levels in the hierarchy that have no idea there even is a Cult, but the sequence of imposition and acquiescence continues down the pyramid in just the same way. 'I don't know why we are doing this but the order came from "on-high" and so we better just do it.' Alfred Lord Tennyson said of the cannon fodder levels in his poem *The Charge of the Light Brigade*: 'Theirs not to reason why; theirs but to do and die.' The next line says that 'into the valley of death rode the six hundred' and they died because they obeyed without question what their perceived 'superiors' told them to do. In the same way the population capitulated to 'Covid'. The whole hierarchical pyramid functions like this to allow the very few to direct the enormous many. Eventually imposition-acquiescence-imposition-acquiescence comes down to the mass of the population at the foot of the pyramid. If they acquiesce to those levels of the hierarchy imposing on them (governments/law enforcement/doctors/media) a circuit is completed between the population and the handful of super-psychopaths in the Cult inner core at the top of the pyramid. Without a circuit-breaking refusal to obey, the sequence of imposition and acquiescence allows a staggeringly few people to impose their will upon the entirety of humankind. We are looking at the very sequence that has subjugated billions since the start of 2020. Our freedom has not been taken from us. Humanity has given it

away. Fascists do not impose fascism because there are not enough of them. Fascism is imposed by the population acquiescing to fascism. Put another way allowing their perceptions to be programmed to the extent that leads to the population giving their freedom away by giving their perceptions – their mind – away. If this circuit is not broken by humanity ceasing to cooperate with their own enslavement then nothing can change. For that to happen people have to critically think and see through the lies and window dressing and then summon the backbone to act upon what they see. The Cult spends its days working to stop either happening and its methodology is systematic and highly detailed, but it can be overcome and that is what this book is all about.

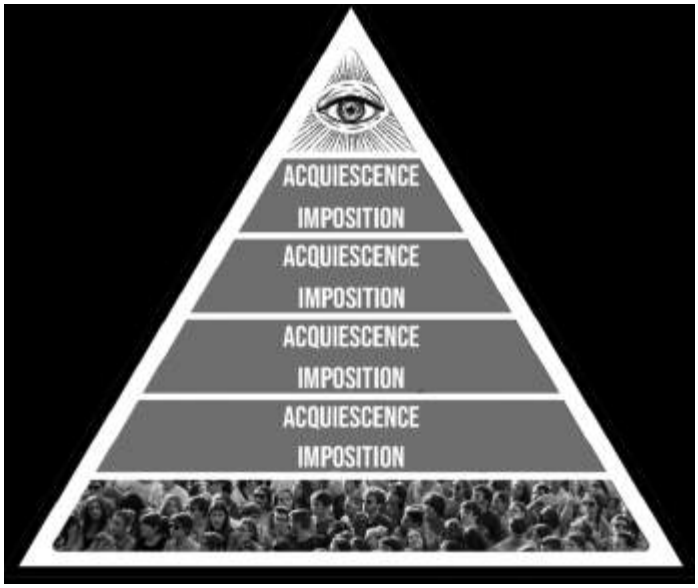


Figure 2: The simple sequence of imposition and compliance that allows a handful of people at the peak of the pyramid to dictate the lives of billions.

The Life Program

Okay, back to world number 1 or the world of the 'masses'. Observe the process of what we call 'life' and it is a perceptual download from cradle to grave. The Cult has created a global structure in which perception can be programmed and the program continually topped-up with what appears to be constant confirmation that the program is indeed true reality. The important word here is 'appears'.

This is the structure, the fly-trap, the Postage Stamp Consensus or Perceptual Mainframe, which represents that incredibly narrow band of perceived possibility delivered by the 'education' system, mainstream media, science and medicine. From the earliest age the download begins with parents who have themselves succumbed to the very programming their children are about to go through. Most parents don't do this out of malevolence and mostly it is quite the opposite. They do what they believe is best for their children and that is what the program has told them is best. Within three or four years comes the major transition from parental programming to full-blown state (Cult) programming in school, college and university where perceptually-programmed teachers and academics pass on their programming to the next generations. Teachers who resist are soon marginalised and their careers ended while children who resist are called a problem child for whom Ritalin may need to be prescribed. A few years after entering the 'world' children are under the control of authority figures representing the state telling them when they have to be there, when they can leave and when they can speak, eat, even go to the toilet. This is calculated preparation for a lifetime of obeying authority in all its forms. Reflex-action fear of authority is instilled by authority from the start. Children soon learn the carrot and stick consequences of obeying or defying authority which is underpinned daily for the rest of their life. Fortunately I daydreamed through this crap and never obeyed authority simply because it told me to. This approach to my alleged 'betters' continues to this day. There can be consequences of pursuing open-minded freedom in a world of closed-minded conformity. I spent a lot of time in school corridors after being ejected from the classroom for not taking some of it seriously and now I spend a lot of time being ejected from Facebook, YouTube and Twitter. But I can tell you that being true to yourself and not compromising your self-respect is far more exhilarating than bowing to authority for authority's sake. You don't have to be a sheep to the shepherd (authority) and the sheep dog (fear of not obeying authority).

The perceptual download continues throughout the formative years in school, college and university while script-reading 'teachers', 'academics' 'scientists', 'doctors' and 'journalists' insist that ongoing generations must be as programmed as they are. Accept the program or you will not pass your 'exams' which confirm your 'degree' of programming. It is tragic to think that many parents pressure their offspring to work hard at school to download the program and qualify for the next stage at college and university. The late, great, American comedian George Carlin said: 'Here's a bumper sticker I'd like to see: We are proud parents of a child who has resisted his teachers' attempts to break his spirit and bend him to the will of his corporate masters.' Well, the best of luck finding many of those, George. Then comes the moment to leave the formal programming years in academia and enter the 'adult' world of work. There you meet others in your chosen or prescribed arena who went through the same Postage Stamp Consensus program before you did. There is therefore overwhelming agreement between almost everyone on the basic foundations of Postage Stamp reality and the rejection, even contempt, of the few who have a mind of their own and are prepared to use it. This has two major effects. Firstly, the consensus confirms to the programmed that their download is really how things are. I mean, everyone knows that, right? Secondly, the arrogance and ignorance of Postage Stamp adherents ensure that anyone questioning the program will have unpleasant consequences for seeking their own truth and not picking their perceptions from the shelf marked: 'Things you must believe without question and if you don't you're a dangerous lunatic conspiracy theorist and a harebrained nutter'.

Every government, agency and corporation is founded on the same Postage Stamp prison cell and you can see why so many people believe the same thing while calling it their own 'opinion'. Fusion of governments and corporations in pursuit of the same agenda was the definition of fascism described by Italian dictator Benito Mussolini. The pressure to conform to perceptual norms downloaded for a lifetime is incessant and infiltrates society right

down to family groups that become censors and condemners of their own 'black sheep' for not, ironically, being sheep. We have seen an explosion of that in the 'Covid' era. Cult-owned global media unleashes its propaganda all day every day in support of the Postage Stamp and targets with abuse and ridicule anyone in the public eye who won't bend their mind to the will of the tyranny. Any response to this is denied (certainly in my case). They don't want to give a platform to expose official lies. Cult-owned-and-created Internet giants like Facebook, Google, YouTube and Twitter delete you for having an unapproved opinion. Facebook boasts that its AI censors delete 97-percent of 'hate speech' before anyone even reports it. Much of that 'hate speech' will simply be an opinion that Facebook and its masters don't want people to see. Such perceptual oppression is widely known as fascism. Even Facebook executive Benny Thomas, a 'CEO Global Planning Lead', said in comments secretly recorded by investigative journalism operation Project Veritas that Facebook is 'too powerful' and should be broken up:

I mean, no king in history has been the ruler of two billion people, but Mark Zuckerberg is … And he's 36. That's too much for a 36-year-old ... You should not have power over two billion people. I just think that's wrong.

Thomas said Facebook-owned platforms like Instagram, Oculus, and WhatsApp needed to be separate companies. 'It's too much power when they're all one together'. That's the way the Cult likes it, however. We have an executive of a Cult organisation in Benny Thomas that doesn't know there is a Cult such is the compartmentalisation. Thomas said that Facebook and Google 'are no longer companies, they're countries'. Actually they are more powerful than countries on the basis that if you control information you control perception and control human society.

I love my oppressor

Another expression of this psychological trickery is for those who realise they are being pressured into compliance to eventually

convince themselves to believe the official narratives to protect their self-respect from accepting the truth that they have succumbed to meek and subservient compliance. Such people become some of the most vehement defenders of the system. You can see them everywhere screaming abuse at those who prefer to think for themselves and by doing so reminding the compliers of their own capitulation to conformity. 'You are talking dangerous nonsense you Covidiot!!' Are you trying to convince me or yourself? It is a potent form of Stockholm syndrome which is defined as: 'A psychological condition that occurs when a victim of abuse identifies and attaches, or bonds, positively with their abuser.' An example is hostages bonding and even 'falling in love' with their kidnappers. The syndrome has been observed in domestic violence, abused children, concentration camp inmates, prisoners of war and many and various Satanic cults. These are some traits of Stockholm syndrome listed at goodtherapy.org:

- Positive regard towards perpetrators of abuse or captor [see 'Covid'].
- Failure to cooperate with police and other government authorities when it comes to holding perpetrators of abuse or kidnapping accountable [or in the case of 'Covid' cooperating with the police to enforce and defend their captors' demands].
- Little or no effort to escape [see 'Covid'].
- Belief in the goodness of the perpetrators or kidnappers [see 'Covid'].
- Appeasement of captors. This is a manipulative strategy for maintaining one's safety. As victims get rewarded – perhaps with less abuse or even with life itself – their appeasing behaviours are reinforced [see 'Covid'].
- Learned helplessness. This can be akin to 'if you can't beat 'em, join 'em'. As the victims fail to escape the abuse or captivity, they may start giving up and soon realize it's just easier for everyone if they acquiesce all their power to their captors [see 'Covid'].

- Feelings of pity toward the abusers, believing they are actually victims themselves. Because of this, victims may go on a crusade or mission to 'save' [protect] their abuser [see the venom unleashed on those challenging the official 'Covid' narrative].
- Unwillingness to learn to detach from their perpetrators and heal. In essence, victims may tend to be less loyal to themselves than to their abuser [*definitely* see 'Covid'].

Ponder on those traits and compare them with the behaviour of great swathes of the global population who have defended governments and authorities which have spent every minute destroying their lives and livelihoods and those of their children and grandchildren since early 2020 with fascistic lockdowns, house arrest and employment deletion to 'protect' them from a 'deadly virus' that their abusers' perceptually created to bring about this very outcome. We are looking at mass Stockholm syndrome. All those that agree to concede their freedom will believe those perceptions are originating in their own independent 'mind' when in fact by conceding their reality to Stockholm syndrome they have by definition conceded any independence of mind. Listen to the 'opinions' of the acquiescing masses in this 'Covid' era and what gushes forth is the repetition of the official version of everything delivered unprocessed, unfiltered and unquestioned. The whole programming dynamic works this way. I must be free because I'm told that I am and so I think that I am.

You can see what I mean with the chapter theme of 'I'm thinking – Oh, but *are* you?' The great majority are not thinking, let alone for themselves. They are repeating what authority has told them to believe which allows them to be controlled. Weaving through this mentality is the fear that the 'conspiracy theorists' are right and this again explains the often hysterical abuse that ensues when you dare to contest the official narrative of anything. Denial is the mechanism of hiding from yourself what you don't want to be true. Telling people what they want to hear is easy, but it's an infinitely greater challenge to tell them what they would rather not be happening.

One is akin to pushing against an open door while the other is met with vehement resistance no matter what the scale of evidence. I don't want it to be true so I'll convince myself that it's not. Examples are everywhere from the denial that a partner is cheating despite all the signs to the reflex-action rejection of any idea that world events in which country after country act in exactly the same way are centrally coordinated. To accept the latter is to accept that a force of unspeakable evil is working to destroy your life and the lives of your children with nothing too horrific to achieve that end. Who the heck wants that to be true? But if we don't face reality the end is duly achieved and the consequences are far worse and ongoing than breaking through the walls of denial today with the courage to make a stand against tyranny.

Connect the dots – but how?

A crucial aspect of perceptual programming is to portray a world in which everything is random and almost nothing is connected to anything else. Randomness cannot be coordinated by its very nature and once you perceive events as random the idea they could be connected is waved away as the rantings of the tinfoil-hat brigade. You can't plan and coordinate random you idiot! No, you can't, but you can hide the coldly-calculated and long-planned behind the *illusion* of randomness. A foundation manifestation of the Renegade Mind is to scan reality for patterns that connect the apparently random and turn pixels and dots into pictures. This is the way I work and have done so for more than 30 years. You look for similarities in people, modus operandi and desired outcomes and slowly, then ever quicker, the picture forms. For instance: There would seem to be no connection between the 'Covid pandemic' hoax and the human-caused global-warming hoax and yet they are masks (appropriately) on the same face seeking the same outcome. Those pushing the global warming myth through the Club of Rome and other Cult agencies are driving the lies about 'Covid' – Bill Gates is an obvious one, but they are endless. Why would the same people be involved in both when they are clearly not connected? Oh, but they

are. Common themes with personnel are matched by common goals. The 'solutions' to both 'problems' are centralisation of global power to impose the will of the few on the many to 'save' humanity from 'Covid' and save the planet from an 'existential threat' (we need 'zero Covid' and 'zero carbon emissions'). These, in turn, connect with the 'dot' of globalisation which was coined to describe the centralisation of global power in every area of life through incessant political and corporate expansion, trading blocks and superstates like the European Union. If you are the few and you want to control the many you have to centralise power and decision-making. The more you centralise power the more power the few at the centre will have over the many; and the more that power is centralised the more power those at the centre have to centralise even quicker. The momentum of centralisation gets faster and faster which is exactly the process we have witnessed. In this way the hoaxed 'pandemic' and the fakery of human-caused global warming serve the interests of globalisation and the seizure of global power in the hands of the Cult inner-circle which is behind 'Covid', 'climate change' *and* globalisation. At this point random 'dots' become a clear and obvious picture or pattern.

Klaus Schwab, the classic Bond villain who founded the Cult's Gates-funded World Economic Forum, published a book in 2020, *The Great Reset*, in which he used the 'problem' of 'Covid' to justify a total transformation of human society to 'save' humanity from 'climate change'. Schwab said: 'The pandemic represents a rare but narrow window of opportunity to reflect, reimagine, and reset our world.' What he didn't mention is that the Cult he serves is behind both hoaxes as I show in my book *The Answer*. He and the Cult don't have to reimagine the world. They know precisely what they want and that's why they destroyed human society with 'Covid' to 'build back better' in their grand design. Their job is not to imagine, but to get humanity to imagine and agree with their plans while believing it's all random. It must be pure coincidence that 'The Great Reset' has long been the Cult's code name for the global imposition of fascism and replaced previous code-names of the 'New World

Order' used by Cult frontmen like Father George Bush and the 'New Order of the Ages' which emerged from Freemasonry and much older secret societies. New Order of the Ages appears on the reverse of the Great Seal of the United States as 'Novus ordo seclorum' underneath the Cult symbol used since way back of the pyramid and all seeing-eye (Fig 3). The pyramid is the hierarchy of human control headed by the illuminated eye that symbolises the force behind the Cult which I will expose in later chapters. The term 'Annuit Coeptis' translates as 'He favours our undertaking'. We are told the 'He' is the Christian god, but 'He' is not as I will be explaining.



Figure 3: The all-seeing eye of the Cult 'god' on the Freemason-designed Great Seal of the United States and also on the dollar bill.

Having you on

Two major Cult techniques of perceptual manipulation that relate to all this are what I have called since the 1990s Problem-Reaction-Solution (PRS) and the Totalitarian Tiptoe (TT). They can be uncovered by the inquiring mind with a simple question: Who benefits? The answer usually identifies the perpetrators of a given action or happening through the concept of 'he who most benefits from a crime is the one most likely to have committed it'. The Latin 'Cue bono?' – Who benefits? – is widely attributed to the Roman orator and statesman Marcus Tullius Cicero. No wonder it goes back so far when the concept has been relevant to human behaviour since

history was recorded. Problem-Reaction-Solution is the technique used to manipulate us every day by covertly creating a problem (or the illusion of one) and offering the solution to the problem (or the illusion of one). In the first phase you create the problem and blame someone or something else for why it has happened. This may relate to a financial collapse, terrorist attack, war, global warming or pandemic, anything in fact that will allow you to impose the 'solution' to change society in the way you desire at that time. The 'problem' doesn't have to be real. PRS is manipulation of perception and all you need is the population to believe the problem is real. Human-caused global warming and the 'Covid pandemic' only have to be *perceived* to be real for the population to accept the 'solutions' of authority. I refer to this technique as NO-Problem-Reaction-Solution. Billions did not meekly accept house arrest from early 2020 because there was a real deadly 'Covid pandemic' but because they perceived – believed – that to be the case. The antidote to Problem-Reaction-Solution is to ask who benefits from the proposed solution. Invariably it will be anyone who wants to justify more control through deletion of freedom and centralisation of power and decision-making.

The two world wars were Problem-Reaction-Solutions that transformed and realigned global society. Both were manipulated into being by the Cult as I have detailed in books since the mid-1990s. They dramatically centralised global power, especially World War Two, which led to the United Nations and other global bodies thanks to the overt and covert manipulations of the Rockefeller family and other Cult bloodlines like the Rothschilds. The UN is a stalking horse for full-blown world government that I will come to shortly. The land on which the UN building stands in New York was donated by the Rockefellers and the same Cult family was behind Big Pharma scalpel and drug 'medicine' and the creation of the World Health Organization as part of the UN. They have been stalwarts of the eugenics movement and funded Hitler's race-purity expert' Ernst Rudin. The human-caused global warming hoax has been orchestrated by the Club of Rome through the UN which is

manufacturing both the 'problem' through its Intergovernmental Panel on Climate Change and imposing the 'solution' through its Agenda 21 and Agenda 2030 which demand the total centralisation of global power to 'save the world' from a climate hoax the United Nations is itself perpetrating. What a small world the Cult can be seen to be particularly among the inner circles. The bedfellow of Problem-Reaction-Solution is the Totalitarian Tiptoe which became the Totalitarian Sprint in 2020. The technique is fashioned to hide the carefully-coordinated behind the cover of apparently random events. You start the sequence at 'A' and you know you are heading for 'Z'. You don't want people to know that and each step on the journey is presented as a random happening while all the steps strung together lead in the same direction. The speed may have quickened dramatically in recent times, but you can still see the incremental approach of the Tiptoe in the case of 'Covid' as each new imposition takes us deeper into fascism. Tell people they have to do this or that to get back to 'normal', then this and this and this. With each new demand adding to the ones that went before the population's freedom is deleted until it disappears. The spider wraps its web around the flies more comprehensively with each new diktat. I'll highlight this in more detail when I get to the 'Covid' hoax and how it has been pulled off. Another prime example of the Totalitarian Tiptoe is how the Cult-created European Union went from a 'free-trade zone' to a centralised bureaucratic dictatorship through the Tiptoe of incremental centralisation of power until nations became mere administrative units for Cult-owned dark suits in Brussels.

The antidote to ignorance is knowledge which the Cult seeks vehemently to deny us, but despite the systematic censorship to that end the Renegade Mind can overcome this by vociferously seeking out the facts no matter the impediments put in the way. There is also a method of thinking and perceiving – *knowing* – that doesn't even need names, dates, place-type facts to identify the patterns that reveal the story. I'll get to that in the final chapter. All you need to know about the manipulation of human society and to what end is still out there – *at the time of writing* – in the form of books, videos

and websites for those that really want to breach the walls of programmed perception. To access this knowledge requires the abandonment of the mainstream media as a source of information in the awareness that this is owned and controlled by the Cult and therefore promotes mass perceptions that suit the Cult. Mainstream media lies all day, every day. That is its function and very reason for being. Where it does tell the truth, here and there, is only because the truth and the Cult agenda very occasionally coincide. If you look for fact and insight to the BBC, CNN and virtually all the rest of them you are asking to be conned and perceptually programmed.

Know the outcome and you'll see the journey

Events seem random when you have no idea where the world is being taken. Once you do the random becomes the carefully planned. Know the outcome and you'll see the journey is a phrase I have been using for a long time to give context to daily happenings that appear unconnected. Does a problem, or illusion of a problem, trigger a proposed 'solution' that further drives society in the direction of the outcome? Invariably the answer will be yes and the random – *abracadabra* – becomes the clearly coordinated. So what is this outcome that unlocks the door to a massively expanded understanding of daily events? I will summarise its major aspects – the fine detail is in my other books – and those new to this information will see that the world they thought they were living in is a very different place. The foundation of the Cult agenda is the incessant centralisation of power and all such centralisation is ultimately in pursuit of Cult control on a global level. I have described for a long time the planned world structure of top-down dictatorship as the Hunger Games Society. The term obviously comes from the movie series which portrayed a world in which a few living in military-protected hi-tech luxury were the overlords of a population condemned to abject poverty in isolated 'sectors' that were not allowed to interact. 'Covid' lockdowns and travel bans anyone? The 'Hunger Games' pyramid of structural control has the inner circle of the Cult at the top with pretty much the entire

population at the bottom under their control through dependency for survival on the Cult. The whole structure is planned to be protected and enforced by a military-police state (Fig 4).

Here you have the reason for the global lockdowns of the fake pandemic to coldly destroy independent incomes and livelihoods and make everyone dependent on the 'state' (the Cult that controls the 'states'). I have warned in my books for many years about the plan to introduce a 'guaranteed income' – a barely survivable pittance – designed to impose dependency when employment was destroyed by AI technology and now even more comprehensively at great speed by the 'Covid' scam. Once the pandemic was played and lockdown consequences began to delete independent income the authorities began to talk right on cue about the need for a guaranteed income and a 'Great Reset'. Guaranteed income will be presented as benevolent governments seeking to help a desperate people – desperate as a direct result of actions of the same governments. The truth is that such payments are a trap. You will only get them if you do exactly what the authorities demand including mass vaccination (genetic manipulation). We have seen this theme already in Australia where those dependent on government benefits have them reduced if parents don't agree to have their children vaccinated according to an insane health-destroying government-dictated schedule. Calculated economic collapse applies to governments as well as people. The Cult wants rid of countries through the creation of a world state with countries broken up into regions ruled by a world government and super states like the European Union. Countries must be bankrupted, too, to this end and it's being achieved by the trillions in 'rescue packages' and furlough payments, trillions in lost taxation, and money-no-object spending on 'Covid' including constant all-medium advertising (programming) which has made the media dependent on government for much of its income. The day of reckoning is coming – as planned – for government spending and given that it has been made possible by printing money and not by production/taxation there is inflation on the way that has the

potential to wipe out monetary value. In that case there will be no need for the Cult to steal your money. It just won't be worth anything (see the German Weimar Republic before the Nazis took over). Many have been okay with lockdowns while getting a percentage of their income from so-called furlough payments without having to work. Those payments are dependent, however, on people having at least a theoretical job with a business considered non-essential and ordered to close. As these business go under because they are closed by lockdown after lockdown the furlough stops and it will for everyone eventually. Then what? The 'then what?' is precisely the idea.



Figure 4: The Hunger Games Society structure I have long warned was planned and now the 'Covid' hoax has made it possible. This is the real reason for lockdowns.

Hired hands

Between the Hunger Games Cult elite and the dependent population is planned to be a vicious military-police state (a fusion of the two into one force). This has been in the making for a long time with police looking ever more like the military and carrying weapons to match. The pandemic scam has seen this process accelerate so fast as

lockdown house arrest is brutally enforced by carefully recruited fascist minds and gormless system-servers. The police and military are planned to merge into a centrally-directed world army in a global structure headed by a world government which wouldn't be elected even by the election fixes now in place. The world army is not planned even to be human and instead wars would be fought, primarily against the population, using robot technology controlled by artificial intelligence. I have been warning about this for decades and now militaries around the world are being transformed by this very AI technology. The global regime that I describe is a particular form of fascism known as a technocracy in which decisions are not made by clueless and co-opted politicians but by unelected technocrats – scientists, engineers, technologists and bureaucrats. Cult-owned-and-controlled Silicon Valley giants are examples of technocracy and they already have far more power to direct world events than governments. They are with their censorship *selecting* governments. I know that some are calling the 'Great Reset' a Marxist communist takeover, but fascism and Marxism are different labels for the same tyranny. Tell those who lived in fascist Germany and Stalinist Russia that there was a difference in the way their freedom was deleted and their lives controlled. I could call it a fascist technocracy or a Marxist technocracy and they would be equally accurate. The Hunger Games society with its world government structure would oversee a world army, world central bank and single world cashless currency imposing its will on a microchipped population (Fig 5). Scan its different elements and see how the illusory pandemic is forcing society in this very direction at great speed. Leaders of 23 countries and the World Health Organization (WHO) backed the idea in March, 2021, of a global treaty for 'international cooperation' in 'health emergencies' and nations should 'come together as a global community for peaceful cooperation that extends beyond this crisis'. Cut the Orwellian bullshit and this means another step towards global government. The plan includes a cashless digital money system that I first warned about in 1993. Right at the start of 'Covid' the deeply corrupt Tedros

Adhanom Ghebreyesus, the crooked and merely gofer 'head' of the World Health Organization, said it was possible to catch the 'virus' by touching cash and it was better to use cashless means. The claim was ridiculous nonsense and like the whole 'Covid' mind-trick it was nothing to do with 'health' and everything to do with pushing every aspect of the Cult agenda. As a result of the Tedros lie the use of cash has plummeted. The Cult script involves a single world digital currency that would eventually be technologically embedded in the body. China is a massive global centre for the Cult and if you watch what is happening there you will know what is planned for everywhere. The Chinese government is developing a digital currency which would allow fines to be deducted immediately via AI for anyone caught on camera breaking its fantastic list of laws and the money is going to be programmable with an expiry date to ensure that no one can accrue wealth except the Cult and its operatives.



Figure 5: The structure of global control the Cult has been working towards for so long and this has been enormously advanced by the 'Covid' illusion.

Serfdom is so smart

The Cult plan is far wider, extreme, and more comprehensive than even most conspiracy researchers appreciate and I will come to the true depths of deceit and control in the chapters 'Who controls the

Cult?' and 'Escaping Wetiko'. Even the world that we know is crazy enough. We are being deluged with ever more sophisticated and controlling technology under the heading of 'smart'. We have smart televisions, smart meters, smart cards, smart cars, smart driving, smart roads, smart pills, smart patches, smart watches, smart skin, smart borders, smart pavements, smart streets, smart cities, smart communities, smart environments, smart growth, smart planet ... smart *everything* around us. Smart technologies and methods of operation are designed to interlock to create a global Smart Grid connecting the entirety of human society including human minds to create a centrally-dictated 'hive' mind. 'Smart cities' is code for densely-occupied megacities of total surveillance and control through AI. Ever more destructive frequency communication systems like 5G have been rolled out without any official testing for health and psychological effects (colossal). 5G/6G/7G systems are needed to run the Smart Grid and each one becomes more destructive of body and mind. Deleting independent income is crucial to forcing people into these AI-policed prisons by ending private property ownership (except for the Cult elite). The Cult's Great Reset now openly foresees a global society in which no one will own any possessions and everything will be rented while the Cult would own literally everything under the guise of government and corporations. The aim has been to use the lockdowns to destroy sources of income on a mass scale and when the people are destitute and in unrepayable amounts of debt (problem) Cult assets come forward with the pledge to write-off debt in return for handing over all property and possessions (solution). Everything – literally everything including people – would be connected to the Internet via AI. I was warning years ago about the coming Internet of Things (IoT) in which all devices and technology from your car to your fridge would be plugged into the Internet and controlled by AI. Now we are already there with much more to come. The next stage is the Internet of Everything (IoE) which is planned to include the connection of AI to the human brain and body to replace the human mind with a centrally-controlled AI mind. Instead of perceptions

being manipulated through control of information and censorship those perceptions would come direct from the Cult through AI. What do you think? You think whatever AI decides that you think. In human terms there would be no individual 'think' any longer. Too incredible? The ravings of a lunatic? Not at all. Cult-owned crazies in Silicon Valley have been telling us the plan for years without explaining the real motivation and calculated implications. These include Google executive and 'futurist' Ray Kurzweil who highlights the year 2030 for when this would be underway. He said:

Our thinking ... will be a hybrid of biological and non-biological thinking ... humans will be able to extend their limitations and 'think in the cloud' ... We're going to put gateways to the cloud in our brains ... We're going to gradually merge and enhance ourselves ... In my view, that's the nature of being human – we transcend our limitations.

As the technology becomes vastly superior to what we are then the small proportion that is still human gets smaller and smaller and smaller until it's just utterly negligible.

The sales-pitch of Kurzweil and Cult-owned Silicon Valley is that this would make us 'super-human' when the real aim is to make us post-human and no longer 'human' in the sense that we have come to know. The entire global population would be connected to AI and become the centrally-controlled 'hive-mind' of externally-delivered perceptions. The Smart Grid being installed to impose the Cult's will on the world is being constructed to allow particular locations – even one location – to control the whole global system. From these prime control centres, which absolutely include China and Israel, anything connected to the Internet would be switched on or off and manipulated at will. Energy systems could be cut, communication via the Internet taken down, computer-controlled driverless autonomous vehicles driven off the road, medical devices switched off, the potential is limitless given how much AI and Internet connections now run human society. We have seen nothing yet if we allow this to continue. Autonomous vehicle makers are working with law enforcement to produce cars designed to automatically pull over if they detect a police or emergency vehicle flashing from up to 100 feet away. At a police stop the car would be unlocked and the

window rolled down automatically. Vehicles would only take you where the computer (the state) allowed. The end of petrol vehicles and speed limiters on all new cars in the UK and EU from 2022 are steps leading to electric computerised transport over which ultimately you have no control. The picture is far bigger even than the Cult global network or web and that will become clear when I get to the nature of the 'spider'. There is a connection between all these happenings and the instigation of DNA-manipulating 'vaccines' (which aren't 'vaccines') justified by the 'Covid' hoax. That connection is the unfolding plan to transform the human body from a biological to a synthetic biological state and this is why synthetic biology is such a fast-emerging discipline of mainstream science. 'Covid vaccines' are infusing self-replicating synthetic genetic material into the cells to cumulatively take us on the Totalitarian Tiptoe from Human 1.0 to the synthetic biological Human 2.0 which will be physically and perceptually attached to the Smart Grid to one hundred percent control every thought, perception and deed. Humanity needs to wake up and *fast*.

This is the barest explanation of where the 'outcome' is planned to go but it's enough to see the journey happening all around us. Those new to this information will already see 'Covid' in a whole new context. I will add much more detail as we go along, but for the minutiae evidence see my mega-works, *The Answer, The Trigger* and *Everything You Need to Know But Have Never Been Told*.

Now – how does a Renegade Mind see the 'world'?

CHAPTER TWO

Renegade Perception

It is one thing to be clever and another to be wise
George R.R. Martin

A simple definition of the difference between a programmed mind and a Renegade Mind would be that one sees only dots while the other connects them to see the picture. Reading reality with accuracy requires the observer to (a) know the planned outcome and (b) realise that everything, but *everything*, is connected.

The entirety of infinite reality is connected – that's its very nature – and with human society an expression of infinite reality the same must apply. Simple cause and effect is a connection. The effect is triggered by the cause and the effect then becomes the cause of another effect. Nothing happens in isolation because it *can't*. Life in whatever reality is simple choice and consequence. We make choices and these lead to consequences. If we don't like the consequences we can make different choices and get different consequences which lead to other choices and consequences. The choice and the consequence are not only connected they are indivisible. You can't have one without the other as an old song goes. A few cannot control the world unless those being controlled allow that to happen – cause and effect, choice and consequence. Control – who has it and who doesn't – is a two-way process, a symbiotic relationship, involving the controller and controlled. 'They took my freedom away!!' Well, yes, but you also gave it to them. Humanity is

subjected to mass control because humanity has acquiesced to that control. This is all cause and effect and literally a case of give and take. In the same way world events of every kind are connected and the Cult works incessantly to sell the illusion of the random and coincidental to maintain the essential (to them) perception of dots that hide the picture. Renegade Minds know this and constantly scan the world for patterns of connection. This is absolutely pivotal in understanding the happenings in the world and without that perspective clarity is impossible. First you know the planned outcome and then you identify the steps on the journey – the day-by-day apparently random which, when connected in relation to the outcome, no longer appear as individual events, but as the proverbial *chain* of events leading in the same direction. I'll give you some examples:

Political puppet show

We are told to believe that politics is 'adversarial' in that different parties with different beliefs engage in an endless tussle for power. There may have been some truth in that up to a point – and only a point – but today divisions between 'different' parties are rhetorical not ideological. Even the rhetorical is fusing into one-speak as the parties eject any remaining free thinkers while others succumb to the ever-gathering intimidation of anyone with the 'wrong' opinion. The Cult is not a new phenomenon and can be traced back thousands of years as my books have documented. Its intergenerational initiates have been manipulating events with increasing effect the more that global power has been centralised. In ancient times the Cult secured control through the system of monarchy in which 'special' bloodlines (of which more later) demanded the right to rule as kings and queens simply by birthright and by vanquishing others who claimed the same birthright. There came a time, however, when people had matured enough to see the unfairness of such tyranny and demanded a say in who governed them. Note the word – *governed* them. Not served them – *governed* them, hence government defined as 'the political direction and control exercised over the

actions of the members, citizens, or inhabitants of communities, societies, and states; direction of the affairs of a state, community, etc.' Governments exercise control over rather than serve just like the monarchies before them. Bizarrely there are still countries like the United Kingdom which are ruled by a monarch *and* a government that officially answers to the monarch. The UK head of state and that of Commonwealth countries such as Canada, Australia and New Zealand is 'selected' by who in a *single family* had unprotected sex with whom and in what order. Pinch me it can't be true. Ouch! Shit, it is. The demise of monarchies in most countries offered a potential vacuum in which some form of free and fair society could arise and the Cult had that base covered. Monarchies had served its interests but they couldn't continue in the face of such widespread opposition and, anyway, replacing a 'royal' dictatorship that people could see with a dictatorship 'of the people' hiding behind the concept of 'democracy' presented far greater manipulative possibilities and ways of hiding coordinated tyranny behind the illusion of 'freedom'.

Democracy is quite wrongly defined as government selected by the population. This is not the case at all. It is government selected by *some* of the population (and then only in theory). This 'some' doesn't even have to be the majority as we have seen so often in first-past-the-post elections in which the so-called majority party wins fewer votes than the 'losing' parties combined. Democracy can give total power to a party in government from a minority of the votes cast. It's a sleight of hand to sell tyranny as freedom. Seventy-four million Trump-supporting Americans didn't vote for the 'Democratic' Party of Joe Biden in the distinctly dodgy election in 2020 and yet far from acknowledging the wishes and feelings of that great percentage of American society the Cult-owned Biden government set out from day one to destroy them and their right to a voice and opinion. Empty shell Biden and his Cult handlers said they were doing this to 'protect democracy'. Such is the level of lunacy and sickness to which politics has descended. Connect the dots and relate them to the desired outcome – a world government run by self-appointed technocrats and no longer even elected

politicians. While operating through its political agents in government the Cult is at the same time encouraging public distain for politicians by putting idiots and incompetents in theoretical power on the road to deleting them. The idea is to instil a public reaction that says of the technocrats: 'Well, they couldn't do any worse than the pathetic politicians.' It's all about controlling perception and Renegade Minds can see through that while programmed minds cannot when they are ignorant of both the planned outcome and the manipulation techniques employed to secure that end. This knowledge can be learned, however, and fast if people choose to get informed.

Politics may at first sight appear very difficult to control from a central point. I mean look at the 'different' parties and how would you be able to oversee them all and their constituent parts? In truth, it's very straightforward because of their structure. We are back to the pyramid of imposition and acquiescence. Organisations are structured in the same way as the system as a whole. Political parties are not open forums of free expression. They are hierarchies. I was a national spokesman for the British Green Party which claimed to be a different kind of politics in which influence and power was devolved; but I can tell you from direct experience – and it's far worse now – that Green parties are run as hierarchies like all the others however much they may try to hide that fact or kid themselves that it's not true. A very few at the top of all political parties are directing policy and personnel. They decide if you are elevated in the party or serve as a government minister and to do that you have to be a yes man or woman. Look at all the maverick political thinkers who never ascended the greasy pole. If you want to progress within the party or reach 'high-office' you need to fall into line and conform. Exceptions to this are rare indeed. Should you want to run for parliament or Congress you have to persuade the local or state level of the party to select you and for that you need to play the game as dictated by the hierarchy. If you secure election and wish to progress within the greater structure you need to go on conforming to what is acceptable to those running the hierarchy

from the peak of the pyramid. Political parties are perceptual gulags and the very fact that there are party 'Whips' appointed to 'whip' politicians into voting the way the hierarchy demands exposes the ridiculous idea that politicians are elected to serve the people they are supposed to represent. Cult operatives and manipulation has long seized control of major parties that have any chance of forming a government and at least most of those that haven't. A new party forms and the Cult goes to work to infiltrate and direct. This has reached such a level today that you see video compilations of 'leaders' of all parties whether Democrats, Republicans, Conservative, Labour and Green parroting the same Cult mantra of 'Build Back Better' and the 'Great Reset' which are straight off the Cult song-sheet to describe the transformation of global society in response to the Cult-instigated hoaxes of the 'Covid pandemic' and human-caused 'climate change'. To see Caroline Lucas, the Green Party MP that I knew when I was in the party in the 1980s, speaking in support of plans proposed by Cult operative Klaus Schwab representing the billionaire global elite is a real head-shaker.

Many parties – one master

The party system is another mind-trick and was instigated to change the nature of the dictatorship by swapping 'royalty' for dark suits that people believed – though now ever less so – represented their interests. Understanding this trick is to realise that a single force (the Cult) controls all parties either directly in terms of the major ones or through manipulation of perception and ideology with others. You don't need to manipulate Green parties to demand your transformation of society in the name of 'climate change' when they are obsessed with the lie that this is essential to 'save the planet'. You just give them a platform and away they go serving your interests while believing they are being environmentally virtuous. America's political structure is a perfect blueprint for how the two or multi-party system is really a one-party state. The Republican Party is controlled from one step back in the shadows by a group made up of billionaires and their gofers known as neoconservatives or Neocons.

I have exposed them in fine detail in my books and they were the driving force behind the policies of the imbecilic presidency of Boy George Bush which included 9/11 (see *The Trigger* for a comprehensive demolition of the official story), the subsequent 'war on terror' (war *of* terror) and the invasions of Afghanistan and Iraq. The latter was a No-Problem-Reaction-Solution based on claims by Cult operatives, including Bush and British Prime Minister Tony Blair, about Saddam Hussein's 'weapons of mass destruction' which did not exist as war criminals Bush and Blair well knew.

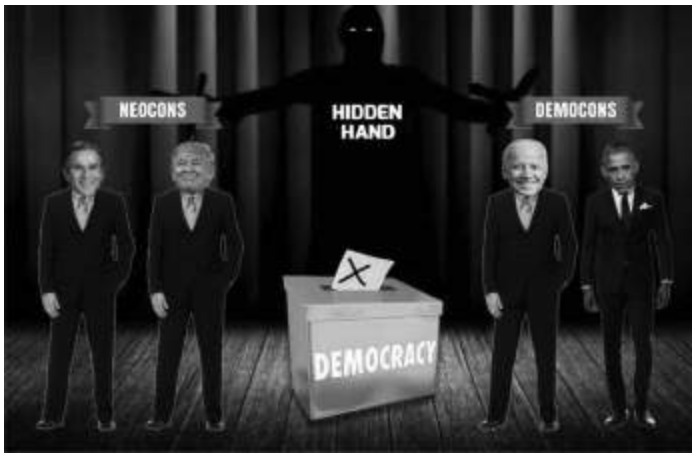


Figure 6: Different front people, different parties – same control system.

The Democratic Party has its own 'Neocon' group controlling from the background which I call the 'Democons' and here's the penny-drop – the Neocons and Democons answer to the same masters one step further back into the shadows (Fig 6). At that level of the Cult the Republican and Democrat parties are controlled by the same people and no matter which is in power the Cult is in power. This is how it works in almost every country and certainly in Britain with Conservative, Labour, Liberal Democrat and Green parties now all on the same page whatever the rhetoric may be in their feeble attempts to appear different. Neocons operated at the time of Bush through a think tank called The Project for the New American Century which in September, 2000, published a document entitled *Rebuilding America's Defenses: Strategies, Forces, and Resources*

For a New Century demanding that America fight 'multiple, simultaneous major theatre wars' as a 'core mission' to force regime-change in countries including Iraq, Libya and Syria. Neocons arranged for Bush ('Republican') and Blair ('Labour Party') to front-up the invasion of Iraq and when they departed the Democons orchestrated the targeting of Libya and Syria through Barack Obama ('Democrat') and British Prime Minister David Cameron ('Conservative Party'). We have 'different' parties and 'different' people, but the same unfolding script. The more the Cult has seized the reigns of parties and personnel the more their policies have transparently pursued the same agenda to the point where the fascist 'Covid' impositions of the Conservative junta of Jackboot Johnson in Britain were opposed by the Labour Party because they were not fascist enough. The Labour Party is likened to the US Democrats while the Conservative Party is akin to a British version of the Republicans and on both sides of the Atlantic they all speak the same language and support the direction demanded by the Cult although some more enthusiastically than others. It's a similar story in country after country because it's all centrally controlled. Oh, but what about Trump? I'll come to him shortly. Political 'choice' in the 'party' system goes like this: You vote for Party A and they get into government. You don't like what they do so next time you vote for Party B and they get into government. You don't like what they do when it's pretty much the same as Party A and why wouldn't that be with both controlled by the same force? Given that only two, sometimes three, parties have any chance of forming a government to get rid of Party B that you don't like you have to vote again for Party A which … you don't like. This, ladies and gentlemen, is what they call 'democracy' which we are told – wrongly – is a term interchangeable with 'freedom'.

The cult of cults

At this point I need to introduce a major expression of the Global Cult known as Sabbatian-Frankism. Sabbatian is also spelt as Sabbatean. I will summarise here. I have published major exposés

and detailed background in other works. Sabbatian-Frankism combines the names of two frauds posing as 'Jewish' men, Sabbatai Zevi (1626-1676), a rabbi, black magician and occultist who proclaimed he was the Jewish messiah; and Jacob Frank (1726-1791), the Polish 'Jew', black magician and occultist who said he was the reincarnation of 'messiah' Zevi and biblical patriarch Jacob. They worked across two centuries to establish the Sabbatian-Frankist cult that plays a major, indeed central, role in the manipulation of human society by the Global Cult which has its origins much further back in history than Sabbatai Zevi. I should emphasise two points here in response to the shrill voices that will scream 'anti-Semitism': (1) Sabbatian-Frankists are NOT Jewish and only pose as such to hide their cult behind a Jewish façade; and (2) my information about this cult has come from Jewish sources who have long realised that their society and community has been infiltrated and taken over by interloper Sabbatian-Frankists. Infiltration has been the foundation technique of Sabbatian-Frankism from its official origin in the 17th century. Zevi's Sabbatian sect attracted a massive following described as the biggest messianic movement in Jewish history, spreading as far as Africa and Asia, and he promised a return for the Jews to the 'Promised Land' of Israel. Sabbatianism was not Judaism but an inversion of everything that mainstream Judaism stood for. So much so that this sinister cult would have a feast day when Judaism had a fast day and whatever was forbidden in Judaism the Sabbatians were encouraged and even commanded to do. This included incest and what would be today called Satanism. Members were forbidden to marry outside the sect and there was a system of keeping their children ignorant of what they were part of until they were old enough to be trusted not to unknowingly reveal anything to outsiders. The same system is employed to this day by the Global Cult in general which Sabbatian-Frankism has enormously influenced and now largely controls.

Zevi and his Sabbatians suffered a setback with the intervention by the Sultan of the Islamic Ottoman Empire in the Middle East and what is now the Republic of Turkey where Zevi was located. The

Sultan gave him the choice of proving his 'divinity', converting to Islam or facing torture and death. Funnily enough Zevi chose to convert or at least appear to. Some of his supporters were disillusioned and drifted away, but many did not with 300 families also converting – only in theory – to Islam. They continued behind this Islamic smokescreen to follow the goals, rules and rituals of Sabbatianism and became known as 'crypto-Jews' or the 'Dönmeh' which means 'to turn'. This is rather ironic because they didn't 'turn' and instead hid behind a fake Islamic persona. The process of appearing to be one thing while being very much another would become the calling card of Sabbatianism especially after Zevi's death and the arrival of the Satanist Jacob Frank in the 18th century when the cult became Sabbatian-Frankism and plumbed still new depths of depravity and infiltration which included – still includes – human sacrifice and sex with children. Wherever Sabbatians go paedophilia and Satanism follow and is it really a surprise that Hollywood is so infested with child abuse and Satanism when it was established by Sabbatian-Frankists and is still controlled by them? Hollywood has been one of the prime vehicles for global perceptual programming and manipulation. How many believe the version of 'history' portrayed in movies when it is a travesty and inversion (again) of the truth? Rabbi Marvin Antelman describes Frankism in his book, *To Eliminate the Opiate*, as 'a movement of complete evil' while Jewish professor Gershom Scholem said of Frank in *The Messianic Idea in Judaism*: 'In all his actions [he was] a truly corrupt and degenerate individual ... one of the most frightening phenomena in the whole of Jewish history.' Frank was excommunicated by traditional rabbis, as was Zevi, but Frank was undeterred and enjoyed vital support from the House of Rothschild, the infamous banking dynasty whose inner-core are Sabbatian-Frankists and not Jews. Infiltration of the Roman Church and Vatican was instigated by Frank with many Dönmeh 'turning' again to convert to Roman Catholicism with a view to hijacking the reins of power. This was the ever-repeating modus operandi and continues to be so. Pose as an advocate of the religion, culture or country that you want to control and then

manipulate your people into the positions of authority and influence largely as advisers, administrators and Svengalis for those that appear to be in power. They did this with Judaism, Christianity (Christian Zionism is part of this), Islam and other religions and nations until Sabbatian-Frankism spanned the world as it does today.

Sabbatian Saudis and the terror network

One expression of the Sabbatian-Frankist Dönmeh within Islam is the ruling family of Saudi Arabia, the House of Saud, through which came the vile distortion of Islam known as Wahhabism. This is the violent creed followed by terrorist groups like Al-Qaeda and ISIS or Islamic State. Wahhabism is the hand-chopping, head-chopping 'religion' of Saudi Arabia which is used to keep the people in a constant state of fear so the interloper House of Saud can continue to rule. Al-Qaeda and Islamic State were lavishly funded by the House of Saud while being created and directed by the Sabbatian-Frankist network in the United States that operates through the Pentagon, CIA and the government in general of whichever 'party'. The front man for the establishment of Wahhabism in the middle of the 18th century was a Sabbatian-Frankist 'crypto-Jew' posing as Islamic called Muhammad ibn Abd al-Wahhab. His daughter would marry the son of Muhammad bin Saud who established the first Saudi state before his death in 1765 with support from the British Empire. Bin Saud's successors would establish modern Saudi Arabia in league with the British and Americans in 1932 which allowed them to seize control of Islam's major shrines in Mecca and Medina. They have dictated the direction of Sunni Islam ever since while Iran is the major centre of the Shiite version and here we have the source of at least the public conflict between them. The Sabbatian network has used its Wahhabi extremists to carry out Problem-Reaction-Solution terrorist attacks in the name of 'Al-Qaeda' and 'Islamic State' to justify a devastating 'war on terror', ever-increasing surveillance of the population and to terrify people into compliance. Another insight of the Renegade Mind is the streetwise understanding that

just because a country, location or people are attacked doesn't mean that those apparently representing that country, location or people are not behind the attackers. Often they are *orchestrating* the attacks because of the societal changes that can be then justified in the name of 'saving the population from terrorists'.

I show in great detail in *The Trigger* how Sabbatian-Frankists were the real perpetrators of 9/11 and not '19 Arab hijackers' who were blamed for what happened. Observe what was justified in the name of 9/11 alone in terms of Middle East invasions, mass surveillance and control that fulfilled the demands of the Project for the New American Century document published by the Sabbatian Neocons. What appear to be enemies are on the deep inside players on the same Sabbatian team. Israel and Arab 'royal' dictatorships are all ruled by Sabbatians and the recent peace agreements between Israel and Saudi Arabia, the United Arab Emirates (UAE) and others are only making formal what has always been the case behind the scenes. Palestinians who have been subjected to grotesque tyranny since Israel was bombed and terrorised into existence in 1948 have never stood a chance. Sabbatian-Frankists have controlled Israel (so the constant theme of violence and war which Sabbatians love) and they have controlled the Arab countries that Palestinians have looked to for real support that never comes. 'Royal families' of the Arab world in Saudi Arabia, Bahrain, UAE, etc., are all Sabbatians with allegiance to the aims of the cult and not what is best for their Arabic populations. They have stolen the oil and financial resources from their people by false claims to be 'royal dynasties' with a genetic right to rule and by employing vicious militaries to impose their will.

Satanic 'illumination'

The Satanist Jacob Frank formed an alliance in 1773 with two other Sabbatians, Mayer Amschel Rothschild (1744-1812), founder of the Rothschild banking dynasty, and Jesuit-educated fraudulent Jew, Adam Weishaupt, and this led to the formation of the Bavarian Illuminati, firstly under another name, in 1776. The Illuminati would

be the manipulating force behind the French Revolution (1789-1799) and was also involved in the American Revolution (1775-1783) before and after the Illuminati's official creation. Weishaupt would later become (in public) a Protestant Christian in archetypal Sabbatian style. I read that his name can be decoded as Adam-Weishaupt or 'the first man to lead those who know'. He wasn't a leader in the sense that he was a subordinate, but he did lead those below him in a crusade of transforming human society that still continues today. The theme was confirmed as early as 1785 when a horseman courier called Lanz was reported to be struck by lighting and extensive Illuminati documents were found in his saddlebags. They made the link to Weishaupt and detailed the plan for world takeover. Current events with 'Covid' fascism have been in the making for a very long time. Jacob Frank was jailed for 13 years by the Catholic Inquisition after his arrest in 1760 and on his release he headed for Frankfurt, Germany, home city and headquarters of the House of Rothschild where the alliance was struck with Mayer Amschel Rothschild and Weishaupt. Rothschild arranged for Frank to be given the title of Baron and he became a wealthy nobleman with a big following of Jews in Germany, the Austro-Hungarian Empire and other European countries. Most of them would have believed he was on their side.

The name 'Illuminati' came from the Zohar which is a body of works in the Jewish mystical 'bible' called the Kabbalah. 'Zohar' is the foundation of Sabbatian-Frankist belief and in Hebrew 'Zohar' means 'splendour', 'radiance', 'illuminated', and so we have 'Illuminati'. They claim to be the 'Illuminated Ones' from their knowledge systematically hidden from the human population and passed on through generations of carefully-chosen initiates in the global secret society network or Cult. Hidden knowledge includes an awareness of the Cult agenda for the world and the nature of our collective reality that I will explore later. Cult 'illumination' is symbolised by the torch held by the Statue of Liberty which was gifted to New York by French Freemasons in Paris who knew exactly what it represents. 'Liberty' symbolises the goddess worshipped in

Babylon as Queen Semiramis or Ishtar. The significance of this will become clear. Notice again the ubiquitous theme of inversion with the Statue of 'Liberty' really symbolising mass control (Fig 7). A mirror-image statute stands on an island in the River Seine in Paris from where New York Liberty originated (Fig 8). A large replica of the Liberty flame stands on top of the Pont de l'Alma tunnel in Paris where Princess Diana died in a Cult ritual described in *The Biggest Secret*. Lucifer 'the light bringer' is related to all this (and much more as we'll see) and 'Lucifer' is a central figure in Sabbatian-Frankism and its associated Satanism. Sabbatians reject the Jewish Torah, or Pentateuch, the 'five books of Moses' in the Old Testament known as Genesis, Exodus, Leviticus, Numbers, and Deuteronomy which are claimed by Judaism and Christianity to have been dictated by 'God' to Moses on Mount Sinai. Sabbatians say these do not apply to them and they seek to replace them with the Zohar to absorb Judaism and its followers into their inversion which is an expression of a much greater global inversion. They want to delete all religions and force humanity to worship a one-world religion – Sabbatian Satanism that also includes worship of the Earth goddess. Satanic themes are being more and more introduced into mainstream society and while Christianity is currently the foremost target for destruction the others are planned to follow.



Figure 7: The Cult goddess of Babylon disguised as the Statue of Liberty holding the flame of Lucifer the 'light bringer'.



Figure 8: Liberty's mirror image in Paris where the New York version originated.

Marx brothers

Rabbi Marvin Antelman connects the Illuminati to the Jacobins in *To Eliminate the Opiate* and Jacobins were the force behind the French Revolution. He links both to the Bund der Gerechten, or League of the Just, which was the network that inflicted communism/Marxism on the world. Antelman wrote:

> The original inner circle of the Bund der Gerechten consisted of born Catholics, Protestants and Jews [Sabbatian-Frankist infiltrators], and those representatives of respective subdivisions formulated schemes for the ultimate destruction of their faiths. The heretical Catholics laid plans which they felt would take a century or more for the ultimate destruction of the church; the apostate Jews for the ultimate destruction of the Jewish religion.

Sabbatian-created communism connects into this anti-religion agenda in that communism does not allow for the free practice of religion. The Sabbatian 'Bund' became the International Communist Party and Communist League and in 1848 'Marxism' was born with the Communist Manifesto of Sabbatian assets Karl Marx and Friedrich Engels. It is absolutely no coincidence that Marxism, just a different name for fascist and other centrally-controlled tyrannies, is being imposed worldwide as a result of the 'Covid' hoax and nor that Marxist/fascist China was the place where the hoax originated. The reason for this will become very clear in the chapter 'Covid: The calculated catastrophe'. The so-called 'Woke' mentality has hijacked

traditional beliefs of the political left and replaced them with far-right make-believe 'social justice' better known as Marxism. Woke will, however, be swallowed by its own perceived 'revolution' which is really the work of billionaires and billionaire corporations feigning being 'Woke'. Marxism is being touted by Wokers as a replacement for 'capitalism' when we don't have 'capitalism'. We have cartelism in which the market is stitched up by the very Cult billionaires and corporations bankrolling Woke. Billionaires love Marxism which keeps the people in servitude while they control from the top. Terminally naïve Wokers think they are 'changing the world' when it's the Cult that is doing the changing and when they have played their vital part and become surplus to requirements they, too, will be targeted. The Illuminati-Jacobins were behind the period known as 'The Terror' in the French Revolution in 1793 and 1794 when Jacobin Maximillian de Robespierre and his Orwellian 'Committee of Public Safety' killed 17,000 'enemies of the Revolution' who had once been 'friends of the Revolution'. Karl Marx (1818-1883), whose Sabbatian creed of Marxism has cost the lives of at least 100 million people, is a hero once again to Wokers who have been systematically kept ignorant of real history by their 'education' programming. As a result they now promote a Sabbatian 'Marxist' abomination destined at some point to consume them. Rabbi Antelman, who spent decades researching the Sabbatian plot, said of the League of the Just and Karl Marx:

> Contrary to popular opinion Karl Marx did not originate the Communist Manifesto. He was paid for his services by the League of the Just, which was known in its country of origin, Germany, as the Bund der Geaechteten.

Antelman said the text attributed to Marx was the work of other people and Marx 'was only repeating what others already said'. Marx was 'a hired hack – lackey of the wealthy Illuminists'. Marx famously said that religion was the 'opium of the people' (part of the Sabbatian plan to demonise religion) and Antelman called his books, *To Eliminate the Opiate*. Marx was born Jewish, but his family converted to Christianity (Sabbatian modus operandi) and he

attacked Jews, not least in his book, *A World Without Jews*. In doing so he supported the Sabbatian plan to destroy traditional Jewishness and Judaism which we are clearly seeing today with the vindictive targeting of orthodox Jews by the Sabbatian government of Israel over 'Covid' laws. I don't follow any religion and it has done much damage to the world over centuries and acted as a perceptual straightjacket. Renegade Minds, however, are always asking *why* something is being done. It doesn't matter if they agree or disagree with what is happening – *why* is it happening is the question. The 'why?' can be answered with regard to religion in that religions create interacting communities of believers when the Cult wants to dismantle all discourse, unity and interaction (see 'Covid' lockdowns) and the ultimate goal is to delete all religions for a one-world religion of Cult Satanism worshipping their 'god' of which more later. We see the same 'why?' with gun control in America. I don't have guns and don't want them, but why is the Cult seeking to disarm the population at the same time that law enforcement agencies are armed to their molars and why has every tyrant in history sought to disarm people before launching the final takeover? They include Hitler, Stalin, Pol Pot and Mao who followed confiscation with violent seizing of power. You know it's a Cult agenda by the people who immediately race to the microphones to exploit dead people in multiple shootings. Ultra-Zionist Cult lackey Senator Chuck Schumer was straight on the case after ten people were killed in Boulder, Colorado in March, 2121. Simple rule … if Schumer wants it the Cult wants it and the same with his ultra-Zionist mate the wild-eyed Senator Adam Schiff. At the same time they were calling for the disarmament of Americans, many of whom live a long way from a police response, Schumer, Schiff and the rest of these pampered clowns were sitting on Capitol Hill behind a razor-wired security fence protected by thousands of armed troops in addition to their own armed bodyguards. Mom and pop in an isolated home? They're just potential mass shooters.

Zion Mainframe

Sabbatian-Frankists and most importantly the Rothschilds were behind the creation of 'Zionism', a political movement that demanded a Jewish homeland in Israel as promised by Sabbatai Zevi. The very symbol of Israel comes from the German meaning of the name Rothschild. Dynasty founder Mayer Amschel Rothschild changed the family name from Bauer to Rothschild, or 'Red-Shield' in German, in deference to the six-pointed 'Star of David' hexagram displayed on the family's home in Frankfurt. The symbol later appeared on the flag of Israel after the Rothschilds were centrally involved in its creation. Hexagrams are not a uniquely Jewish symbol and are widely used in occult ('hidden') networks often as a symbol for Saturn (see my other books for why). Neither are Zionism and Jewishness interchangeable. Zionism is a political movement and philosophy and not a 'race' or a people. Many Jews oppose Zionism and many non-Jews, including US President Joe Biden, call themselves Zionists as does Israel-centric Donald Trump. America's support for the Israel government is pretty much a gimme with ultra-Zionist billionaires and corporations providing fantastic and dominant funding for both political parties. Former Congresswoman Cynthia McKinney has told how she was approached immediately she ran for office to 'sign the pledge' to Israel and confirm that she would always vote in that country's best interests. All American politicians are approached in this way. Anyone who refuses will get no support or funding from the enormous and all-powerful Zionist lobby that includes organisations like mega-lobby group AIPAC, the American Israel Public Affairs Committee. Trump's biggest funder was ultra-Zionist casino and media billionaire Sheldon Adelson while major funders of the Democratic Party include ultra-Zionist George Soros and ultra-Zionist financial and media mogul, Haim Saban. Some may reel back at the suggestion that Soros is an Israel-firster (Sabbatian-controlled Israel-firster), but Renegade Minds watch the actions not the words and everywhere Soros donates his billions the Sabbatian agenda benefits. In the spirit of Sabbatian inversion Soros pledged $1 billion for a new university network to promote 'liberal values and tackle intolerance'. He made the announcement during his annual speech

at the Cult-owned World Economic Forum in Davos, Switzerland, in January, 2020, after his 'harsh criticism' of 'authoritarian rulers' around the world. You can only laugh at such brazen mendacity. How *he* doesn't laugh is the mystery. Translated from the Orwellian 'liberal values and tackle intolerance' means teaching non-white people to hate white people and for white people to loathe themselves for being born white. The reason for that will become clear.

The 'Anti-Semitism' fraud

Zionists support the Jewish homeland in the land of Palestine which has been the Sabbatian-Rothschild goal for so long, but not for the benefit of Jews. Sabbatians and their global Anti-Semitism Industry have skewed public and political opinion to equate opposing the violent extremes of Zionism to be a blanket attack and condemnation of all Jewish people. Sabbatians and their global Anti-Semitism Industry have skewed public and political opinion to equate opposing the violent extremes of Zionism to be a blanket attack and condemnation of all Jewish people. This is nothing more than a Sabbatian protection racket to stop legitimate investigation and exposure of their agendas and activities. The official definition of 'anti-Semitism' has more recently been expanded to include criticism of Zionism – a *political movement* – and this was done to further stop exposure of Sabbatian infiltrators who created Zionism as we know it today in the 19th century. Renegade Minds will talk about these subjects when they know the shit that will come their way. People must decide if they want to know the truth or just cower in the corner in fear of what others will say. Sabbatians have been trying to label me as 'anti-Semitic' since the 1990s as I have uncovered more and more about their background and agendas. Useless, gutless, fraudulent 'journalists' then just repeat the smears without question and on the day I was writing this section a pair of unquestioning repeaters called Ben Quinn and Archie Bland (how appropriate) outright called me an 'anti-Semite' in the establishment propaganda sheet, the London *Guardian*, with no supporting evidence. The

Sabbatian Anti-Semitism Industry said so and who are they to question that? They wouldn't dare. Ironically 'Semitic' refers to a group of languages in the Middle East that are almost entirely Arabic. 'Anti-Semitism' becomes 'anti-Arab' which if the consequences of this misunderstanding were not so grave would be hilarious. Don't bother telling Quinn and Bland. I don't want to confuse them, bless 'em. One reason I am dubbed 'anti-Semitic' is that I wrote in the 1990s that Jewish operatives (Sabbatians) were heavily involved in the Russian Revolution when Sabbatians overthrew the Romanov dynasty. This apparently made me 'anti-Semitic'. Oh, really? Here is a section from *The Trigger*:

British journalist Robert Wilton confirmed these themes in his 1920 book *The Last Days of the Romanovs* when he studied official documents from the Russian government to identify the members of the Bolshevik ruling elite between 1917 and 1919. The Central Committee included 41 Jews among 62 members; the Council of the People's Commissars had 17 Jews out of 22 members; and 458 of the 556 most important Bolshevik positions between 1918 and 1919 were occupied by Jewish people. Only 17 were Russian. Then there were the 23 Jews among the 36 members of the vicious Cheka Soviet secret police established in 1917 who would soon appear all across the country.

Professor Robert Service of Oxford University, an expert on 20th century Russian history, found evidence that ['Jewish'] Leon Trotsky had sought to make sure that Jews were enrolled in the Red Army and were disproportionately represented in the Soviet civil bureaucracy that included the Cheka which performed mass arrests, imprisonment and executions of 'enemies of the people'. A US State Department Decimal File (861.00/5339) dated November 13th, 1918, names [Rothschild banking agent in America] Jacob Schiff and a list of ultra-Zionists as funders of the Russian Revolution leading to claims of a 'Jewish plot', but the key point missed by all is they were not 'Jews' – they were Sabbatian-Frankists.

Britain's Winston Churchill made the same error by mistake or otherwise. He wrote in a 1920 edition of the *Illustrated Sunday Herald* that those behind the Russian revolution were part of a 'worldwide conspiracy for the overthrow of civilisation and for the reconstitution of society on the basis of arrested development, of envious malevolence, and impossible equality' (see 'Woke' today because that has been created by the same network). Churchill said there was no need to exaggerate the part played in the creation of Bolshevism and in the actual bringing about of the Russian

Revolution 'by these international and for the most part atheistical Jews' ['atheistical Jews' = Sabbatians]. Churchill said it is certainly a very great one and probably outweighs all others: 'With the notable exception of Lenin, the majority of the leading figures are Jews.' He went on to describe, knowingly or not, the Sabbatian modus operandi of placing puppet leaders nominally in power while they control from the background:

> Moreover, the principal inspiration and driving power comes from the Jewish leaders. Thus Tchitcherin, a pure Russian, is eclipsed by his nominal subordinate, Litvinoff, and the influence of Russians like Bukharin or Lunacharski cannot be compared with the power of Trotsky, or of Zinovieff, the Dictator of the Red Citadel (Petrograd), or of Krassin or Radek – all Jews. In the Soviet institutions the predominance of Jews is even more astonishing. And the prominent, if not indeed the principal, part in the system of terrorism applied by the Extraordinary Commissions for Combatting Counter-Revolution has been taken by Jews, and in some notable cases by Jewesses.

What I said about seriously disproportionate involvement in the Russian Revolution by Jewish 'revolutionaries' (Sabbatians) is provable fact, but truth is no defence against the Sabbatian Anti-Semitism Industry, its repeater parrots like Quinn and Bland, and the now breathtaking network of so-called 'Woke' 'anti-hate' groups with interlocking leaderships and funding which have the role of discrediting and silencing anyone who gets too close to exposing the Sabbatians. We have seen 'truth is no defence' confirmed in legal judgements with the Saskatchewan Human Rights Commission in Canada decreeing this: 'Truthful statements can be presented in a manner that would meet the definition of hate speech, and not all truthful statements must be free from restriction.' Most 'anti-hate' activists, who are themselves consumed by hatred, are too stupid and ignorant of the world to know how they are being used. They are far too far up their own virtue-signalling arses and it's far too dark for them to see anything.

The 'revolution' game

The background and methods of the 'Russian' Revolution are straight from the Sabbatian playbook seen in the French Revolution

and endless others around the world that appear to start as a revolution of the people against tyrannical rule and end up with a regime change to more tyrannical rule overtly or covertly. Wars, terror attacks and regime overthrows follow the Sabbatian cult through history with its agents creating them as Problem-Reaction-Solutions to remove opposition on the road to world domination. Sabbatian dots connect the Rothschilds with the Illuminati, Jacobins of the French Revolution, the 'Bund' or League of the Just, the International Communist Party, Communist League and the Communist Manifesto of Karl Marx and Friedrich Engels that would lead to the Rothschild-funded Russian Revolution. The sequence comes under the heading of 'creative destruction' when you advance to your global goal by continually destroying the status quo to install a new status quo which you then also destroy. The two world wars come to mind. With each new status quo you move closer to your planned outcome. Wars and mass murder are to Sabbatians a collective blood sacrifice ritual. They are obsessed with death for many reasons and one is that death is an inversion of life. Satanists and Sabbatians are obsessed with death and often target churches and churchyards for their rituals. Inversion-obsessed Sabbatians explain the use of inverted symbolism including the *inverted* pentagram and *inverted* cross. The inversion of the cross has been related to targeting Christianity, but the cross was a religious symbol long before Christianity and its inversion is a statement about the Sabbatian mentality and goals more than any single religion.

Sabbatians operating in Germany were behind the rise of the occult-obsessed Nazis and the subsequent Jewish exodus from Germany and Europe to Palestine and the United States after World War Two. The Rothschild dynasty was at the forefront of this both as political manipulators and by funding the operation. Why would Sabbatians help to orchestrate the horrors inflicted on Jews by the Nazis and by Stalin after they organised the Russian Revolution? Sabbatians hate Jews and their religion, that's why. They pose as Jews and secure positions of control within Jewish society and play the 'anti-Semitism' card to protect themselves from exposure

through a global network of organisations answering to the Sabbatian-created-and-controlled globe-spanning intelligence network that involves a stunning web of military-intelligence operatives and operations for a tiny country of just nine million. Among them are Jewish assets who are not Sabbatians but have been convinced by them that what they are doing is for the good of Israel and the Jewish community to protect them from what they have been programmed since childhood to believe is a Jew-hating hostile world. The Jewish community is just a highly convenient cover to hide the true nature of Sabbatians. Anyone getting close to exposing their game is accused by Sabbatian place-people and gofers of 'anti-Semitism' and claiming that all Jews are part of a plot to take over the world. I am not saying that. I am saying that Sabbatians – the *real* Jew-haters – have infiltrated the Jewish community to use them both as a cover and an 'anti-Semitic' defence against exposure. Thus we have the Anti-Semitism Industry targeted researchers in this way and most Jewish people think this is justified and genuine. They don't know that their 'Jewish' leaders and institutions of state, intelligence and military are not controlled by Jews at all, but cultists and stooges of Sabbatian-Frankism. I once added my name to a pro-Jewish freedom petition online and the next time I looked my name was gone and text had been added to the petition blurb to attack me as an 'anti-Semite' such is the scale of perceptual programming.

Moving on America

I tell the story in *The Trigger* and a chapter called 'Atlantic Crossing' how particularly after Israel was established the Sabbatians moved in on the United States and eventually grasped control of government administration, the political system via both Democrats and Republicans, the intelligence community like the CIA and National Security Agency (NSA), the Pentagon and mass media. Through this seriously compartmentalised network Sabbatians and their operatives in Mossad, Israeli Defense Forces (IDF) and US agencies pulled off 9/11 and blamed it on 19 'Al-Qaeda hijackers' dominated by men from, or connected to, Sabbatian-ruled Saudi

Arabia. The '19' were not even on the planes let alone flew those big passenger jets into buildings while being largely incompetent at piloting one-engine light aircraft. 'Hijacker' Hani Hanjour who is said to have flown American Airlines Flight 77 into the Pentagon with a turn and manoeuvre most professional pilots said they would have struggled to do was banned from renting a small plane by instructors at the Freeway Airport in Bowie, Maryland, just *six weeks* earlier on the grounds that he was an incompetent pilot. The Jewish population of the world is just 0.2 percent with even that almost entirely concentrated in Israel (75 percent Jewish) and the United States (around two percent). This two percent and globally 0.2 percent refers to *Jewish* people and not Sabbatian interlopers who are a fraction of that fraction. What a sobering thought when you think of the fantastic influence on world affairs of tiny Israel and that the Project for the New America Century (PNAC) which laid out the blueprint in September, 2000, for America's war on terror and regime change wars in Iraq, Libya and Syria was founded and dominated by Sabbatians known as 'Neocons'. The document conceded that this plan would not be supported politically or publicly without a major attack on American soil and a Problem-Reaction-Solution excuse to send troops to war across the Middle East. Sabbatian Neocons said:

> ... [The] process of transformation ... [war and regime change] ... is likely to be a long one, absent some catastrophic and catalysing event – like a new Pearl Harbor.

Four months later many of those who produced that document came to power with their inane puppet George Bush from the long-time Sabbatian Bush family. They included Sabbatian Dick Cheney who was officially vice-president, but really de-facto president for the entirety of the 'Bush' government. Nine months after the 'Bush' inauguration came what Bush called at the time 'the Pearl Harbor of the 21st century' and with typical Sabbatian timing and symbolism 2001 was the 60th anniversary of the attack in 1941 by the Japanese Air Force on Pearl Harbor, Hawaii, which allowed President Franklin Delano Roosevelt to take the United States into a Sabbatian-

instigated Second World War that he said in his election campaign that he never would. The evidence is overwhelming that Roosevelt and his military and intelligence networks knew the attack was coming and did nothing to stop it, but they did make sure that America's most essential naval ships were not in Hawaii at the time. Three thousand Americans died in the Pearl Harbor attacks as they did on September 11th. By the 9/11 year of 2001 Sabbatians had widely infiltrated the US government, military and intelligence operations and used their compartmentalised assets to pull off the 'Al-Qaeda' attacks. If you read *The Trigger* it will blow your mind to see the utterly staggering concentration of 'Jewish' operatives (Sabbatian infiltrators) in essential positions of political, security, legal, law enforcement, financial and business power before, during, and after the attacks to make them happen, carry them out, and then cover their tracks – and I do mean *staggering* when you think of that 0.2 percent of the world population and two percent of Americans which are Jewish while Sabbatian infiltrators are a fraction of that. A central foundation of the 9/11 conspiracy was the hijacking of government, military, Air Force and intelligence computer systems in real time through 'back-door' access made possible by Israeli (Sabbatian) 'cyber security' software. Sabbatian-controlled Israel is on the way to rivalling Silicon Valley for domination of cyberspace and is becoming the dominant force in cyber-security which gives them access to entire computer systems and their passcodes across the world. Then add to this that Zionists head (officially) Silicon Valley giants like Google (Larry Page and Sergey Brin), Google-owned YouTube (Susan Wojcicki), Facebook (Mark Zuckerberg and Sheryl Sandberg), and Apple (Chairman Arthur D. Levinson), and that ultra-Zionist hedge fund billionaire Paul Singer has a $1 billion stake in Twitter which is only nominally headed by 'CEO' pothead Jack Dorsey. As cable news host Tucker Carlson said of Dorsey: 'There used to be debate in the medical community whether dropping a ton of acid had permanent effects and I think that debate has now ended.' Carlson made the comment after Dorsey told a hearing on Capitol Hill (if you cut through his bullshit) that he

believed in free speech so long as he got to decide what you can hear and see. These 'big names' of Silicon Valley are only front men and women for the Global Cult, not least the Sabbatians, who are the true controllers of these corporations. Does anyone still wonder why these same people and companies have been ferociously censoring and banning people (like me) for exposing any aspect of the Cult agenda and especially the truth about the 'Covid' hoax which Sabbatians have orchestrated?

The Jeffrey Epstein paedophile ring was a Sabbatian operation. He was officially 'Jewish' but he was a Sabbatian and women abused by the ring have told me about the high number of 'Jewish' people involved. The Epstein horror has Sabbatian written all over it and matches perfectly their modus operandi and obsession with sex and ritual. Epstein was running a Sabbatian blackmail ring in which famous people with political and other influence were provided with young girls for sex while everything was being filmed and recorded on hidden cameras and microphones at his New York house, Caribbean island and other properties. Epstein survivors have described this surveillance system to me and some have gone public. Once the famous politician or other figure knew he or she was on video they tended to do whatever they were told. Here we go again …when you've got them by the balls their hearts and minds will follow. Sabbatians use this blackmail technique on a wide scale across the world to entrap politicians and others they need to act as demanded. Epstein's private plane, the infamous 'Lolita Express', had many well-known passengers including Bill Clinton while Bill Gates has flown on an Epstein plane and met with him four years after Epstein had been jailed for paedophilia. They subsequently met many times at Epstein's home in New York according to a witness who was there. Epstein's infamous side-kick was Ghislaine Maxwell, daughter of Mossad agent and ultra-Zionist mega-crooked British businessman, Bob Maxwell, who at one time owned the *Daily Mirror* newspaper. Maxwell was murdered at sea on his boat in 1991 by Sabbatian-controlled Mossad when he became a liability with his

business empire collapsing as a former Mossad operative has confirmed (see *The Trigger*).

Money, money, money, funny money …

Before I come to the Sabbatian connection with the last three US presidents I will lay out the crucial importance to Sabbatians of controlling banking and finance. Sabbatian Mayer Amschel Rothschild set out to dominate this arena in his family's quest for total global control. What is freedom? It is, in effect, choice. The more choices you have the freer you are and the fewer your choices the more you are enslaved. In the global structure created over centuries by Sabbatians the biggest decider and restrictor of choice is … money. Across the world if you ask people what they would like to do with their lives and why they are not doing that they will reply 'I don't have the money'. This is the idea. A global elite of multi-billionaires are described as 'greedy' and that is true on one level; but control of money – who has it and who doesn't – is not primarily about greed. It's about control. Sabbatians have seized ever more control of finance and sucked the wealth of the world out of the hands of the population. We talk now, after all, about the 'One-percent' and even then the wealthiest are a lot fewer even than that. This has been made possible by a money scam so outrageous and so vast it could rightly be called the scam of scams founded on creating 'money' out of nothing and 'loaning' that with interest to the population. Money out of nothing is called 'credit'. Sabbatians have asserted control over governments and banking ever more completely through the centuries and secured financial laws that allow banks to lend hugely more than they have on deposit in a confidence trick known as fractional reserve lending. Imagine if you could lend money that doesn't exist and charge the recipient interest for doing so. You would end up in jail. Bankers by contrast end up in mansions, private jets, Malibu and Monaco.

Banks are only required to keep a fraction of their deposits and wealth in their vaults and they are allowed to lend 'money' they don't have called 'credit. Go into a bank for a loan and if you succeed

the banker will not move any real wealth into your account. They will type into your account the amount of the agreed 'loan' – say £100,000. This is not wealth that really exists; it is non-existent, fresh-air, created-out-of-nothing 'credit' which has never, does not, and will never exist except in theory. Credit is backed by nothing except wind and only has buying power because people think that it has buying power and accept it in return for property, goods and services. I have described this situation as like those cartoon characters you see chasing each other and when they run over the edge of a cliff they keep running forward on fresh air until one of them looks down, realises what's happened, and they all crash into the ravine. The whole foundation of the Sabbatian financial system is to stop people looking down except for periodic moments when they want to crash the system (as in 2008 and 2020 ongoing) and reap the rewards from all the property, businesses and wealth their borrowers had signed over as 'collateral' in return for a 'loan' of fresh air. Most people think that money is somehow created by governments when it comes into existence from the start as a debt through banks 'lending' illusory money called credit. Yes, the very currency of exchange is a *debt* from day one issued as an interest-bearing loan. Why don't governments create money interest-free and lend it to their people interest-free? Governments are controlled by Sabbatians and the financial system is controlled by Sabbatians for whom interest-free money would be a nightmare come true. Sabbatians underpin their financial domination through their global network of central banks, including the privately-owned US Federal Reserve and Britain's Bank of England, and this is orchestrated by a privately-owned central bank coordination body called the Bank for International Settlements in Basle, Switzerland, created by the usual suspects including the Rockefellers and Rothschilds. Central bank chiefs don't answer to governments or the people. They answer to the Bank for International Settlements or, in other words, the Global Cult which is dominated today by Sabbatians.

Built-in disaster

There are so many constituent scams within the overall banking scam. When you take out a loan of thin-air credit only the amount of that loan is theoretically brought into circulation to add to the amount in circulation; but you are paying back the principle plus interest. The additional interest is not created and this means that with every 'loan' there is a shortfall in the money in circulation between what is borrowed and what has to be paid back. There is never even close to enough money in circulation to repay all outstanding public and private debt including interest. Coldly weaved in the very fabric of the system is the certainty that some will lose their homes, businesses and possessions to the banking 'lender'. This is less obvious in times of 'boom' when the amount of money in circulation (and the debt) is expanding through more people wanting and getting loans. When a downturn comes and the money supply contracts it becomes painfully obvious that there is not enough money to service all debt and interest. This is less obvious in times of 'boom' when the amount of money in circulation (and the debt) is expanding through more people wanting and getting loans. When a downturn comes and the money supply contracts and it becomes painfully obvious – as in 2008 and currently – that there is not enough money to service all debt and interest. Sabbatian banksters have been leading the human population through a calculated series of booms (more debt incurred) and busts (when the debt can't be repaid and the banks get the debtor's tangible wealth in exchange for non-existent 'credit'). With each 'bust' Sabbatian bankers have absorbed more of the world's tangible wealth and we end up with the One-percent. Governments are in bankruptcy levels of debt to the same system and are therefore owned by a system they do not control. The Federal Reserve, 'America's central bank', is privately-owned and American presidents only nominally appoint its chairman or woman to maintain the illusion that it's an arm of government. It's not. The 'Fed' is a cartel of private banks which handed billions to its associates and friends after the crash of 2008 and has been Sabbatian-controlled since it was manipulated into being in 1913 through the covert trickery of Rothschild banking agents Jacob Schiff and Paul

Warburg, and the Sabbatian Rockefeller family. Somehow from a Jewish population of two-percent and globally 0.2 percent (Sabbatian interlopers remember are far smaller) ultra-Zionists headed the Federal Reserve for 31 years between 1987 and 2018 in the form of Alan Greenspan, Bernard Bernanke and Janet Yellen (now Biden's Treasury Secretary) with Yellen's deputy chairman a Israeli-American duel citizen and ultra-Zionist Stanley Fischer, a former governor of the Bank of Israel. Ultra-Zionist Fed chiefs spanned the presidencies of Ronald Reagan ('Republican'), Father George Bush ('Republican'), Bill Clinton ('Democrat'), Boy George Bush ('Republican') and Barack Obama ('Democrat'). We should really add the pre-Greenspan chairman, Paul Adolph Volcker, 'appointed' by Jimmy Carter ('Democrat') who ran the Fed between 1979 and 1987 during the Carter and Reagan administrations before Greenspan took over. Volcker was a long-time associate and business partner of the Rothschilds. No matter what the 'party' officially in power the United States economy was directed by the same force. Here are members of the Obama, Trump and Biden administrations and see if you can make out a common theme.

Barack Obama ('Democrat')

Ultra-Zionists Robert Rubin, Larry Summers, and Timothy Geithner ran the US Treasury in the Clinton administration and two of them reappeared with Obama. Ultra-Zionist Fed chairman Alan Greenspan had manipulated the crash of 2008 through deregulation and jumped ship just before the disaster to make way for ultra-Zionist Bernard Bernanke to hand out trillions to Sabbatian 'too big to fail' banks and businesses, including the ubiquitous ultra-Zionist Goldman Sachs which has an ongoing staff revolving door operation between itself and major financial positions in government worldwide. Obama inherited the fallout of the crash when he took office in January, 2009, and fortunately he had the support of his ultra-Zionist White House Chief of Staff Rahm Emmanuel, son of a terrorist who helped to bomb Israel into being in 1948, and his ultra-Zionist senior adviser David Axelrod, chief strategist in Obama's two

successful presidential campaigns. Emmanuel, later mayor of Chicago and former senior fundraiser and strategist for Bill Clinton, is an example of the Sabbatian policy after Israel was established of migrating insider families to America so their children would be born American citizens. 'Obama' chose this financial team throughout his administration to respond to the Sabbatian-instigated crisis:

Timothy Geithner (ultra-Zionist) Treasury Secretary; Jacob J. Lew, Treasury Secretary; Larry Summers (ultra-Zionist), director of the White House National Economic Council; Paul Adolph Volcker (Rothschild business partner), chairman of the Economic Recovery Advisory Board; Peter Orszag (ultra-Zionist), director of the Office of Management and Budget overseeing all government spending; Penny Pritzker (ultra-Zionist), Commerce Secretary; Jared Bernstein (ultra-Zionist), chief economist and economic policy adviser to Vice President Joe Biden; Mary Schapiro (ultra-Zionist), chair of the Securities and Exchange Commission (SEC); Gary Gensler (ultra-Zionist), chairman of the Commodity Futures Trading Commission (CFTC); Sheila Bair (ultra-Zionist), chair of the Federal Deposit Insurance Corporation (FDIC); Karen Mills (ultra-Zionist), head of the Small Business Administration (SBA); Kenneth Feinberg (ultra-Zionist), Special Master for Executive [bail-out] Compensation. Feinberg would be appointed to oversee compensation (with strings) to 9/11 victims and families in a campaign to stop them having their day in court to question the official story. At the same time ultra-Zionist Bernard Bernanke was chairman of the Federal Reserve and these are only some of the ultra-Zionists with allegiance to Sabbatian-controlled Israel in the Obama government. Obama's biggest corporate donor was ultra-Zionist Goldman Sachs which had employed many in his administration.

Donald Trump ('Republican')

Trump claimed to be an outsider (he wasn't) who had come to 'drain the swamp'. He embarked on this goal by immediately appointing ultra-Zionist Steve Mnuchin, a Goldman Sachs employee for 17

years, as his Treasury Secretary. Others included Gary Cohn (ultra-Zionist), chief operating officer of Goldman Sachs, his first Director of the National Economic Council and chief economic adviser, who was later replaced by Larry Kudlow (ultra-Zionist). Trump's senior adviser throughout his four years in the White House was his sinister son-in-law Jared Kushner, a life-long friend of Israel Prime Minister Benjamin Netanyahu. Kushner is the son of a convicted crook who was pardoned by Trump in his last days in office. Other ultra-Zionists in the Trump administration included: Stephen Miller, Senior Policy Adviser; Avrahm Berkowitz, Deputy Adviser to Trump and his Senior Adviser Jared Kushner; Ivanka Trump, Adviser to the President, who converted to Judaism when she married Jared Kushner; David Friedman, Trump lawyer and Ambassador to Israel; Jason Greenblatt, Trump Organization executive vice president and chief legal officer, who was made Special Representative for International Negotiations and the Israeli-Palestinian Conflict; Rod Rosenstein, Deputy Attorney General; Elliot Abrams, Special Representative for Venezuela, then Iran; John Eisenberg, National Security Council Legal Adviser and Deputy Council to the President for National Security Affairs; Anne Neuberger, Deputy National Manager, National Security Agency; Ezra Cohen-Watnick, Acting Under Secretary of Defense for Intelligence; Elan Carr, Special Envoy to monitor and combat anti-Semitism; Len Khodorkovsky, Deputy Special Envoy to monitor and combat anti-Semitism; Reed Cordish, Assistant to the President, Intragovernmental and Technology Initiatives. Trump Vice President Mike Pence and Secretary of State Mike Pompeo, both Christian Zionists, were also vehement supporters of Israel and its goals and ambitions.

Donald 'free-speech believer' Trump pardoned a number of financial and violent criminals while ignoring calls to pardon Julian Assange and Edward Snowden whose crimes are revealing highly relevant information about government manipulation and corruption and the widespread illegal surveillance of the American people by US 'security' agencies. It's so good to know that Trump is on the side of freedom and justice and not mega-criminals with

allegiance to Sabbatian-controlled Israel. These included a pardon for Israeli spy Jonathan Pollard who was jailed for life in 1987 under the Espionage Act. Aviem Sella, the Mossad agent who recruited Pollard, was also pardoned by Trump while Assange sat in jail and Snowden remained in exile in Russia. Sella had 'fled' (was helped to escape) to Israel in 1987 and was never extradited despite being charged under the Espionage Act. A Trump White House statement said that Sella's clemency had been 'supported by Benjamin Netanyahu, Ron Dermer, Israel's US Ambassador, David Friedman, US Ambassador to Israel and Miriam Adelson, wife of leading Trump donor Sheldon Adelson who died shortly before. Other friends of Jared Kushner were pardoned along with Sholom Weiss who was believed to be serving the longest-ever white-collar prison sentence of more than 800 years in 2000. The sentence was commuted of Ponzi-schemer Eliyahu Weinstein who defrauded Jews and others out of $200 million. I did mention that Assange and Snowden were ignored, right? Trump gave Sabbatians almost everything they asked for in military and political support, moving the US Embassy from Tel Aviv to Jerusalem with its critical symbolic and literal implications for Palestinian statehood, and the 'deal of the Century' designed by Jared Kushner and David Friedman which gave the Sabbatian Israeli government the green light to substantially expand its already widespread program of building illegal Jewish-only settlements in the occupied land of the West Bank. This made a two-state 'solution' impossible by seizing all the land of a potential Palestinian homeland and that had been the plan since 1948 and then 1967 when the Arab-controlled Gaza Strip, West Bank, Sinai Peninsula and Syrian Golan Heights were occupied by Israel. All the talks about talks and road maps and delays have been buying time until the West Bank was physically occupied by Israeli real estate. Trump would have to be a monumentally ill-informed idiot not to see that this was the plan he was helping to complete. The Trump administration was in so many ways the Kushner administration which means the Netanyahu administration which means the Sabbatian administration. I understand why many opposing Cult fascism in all its forms gravitated to Trump, but he

was a crucial part of the Sabbatian plan and I will deal with this in the next chapter.

Joe Biden ('Democrat')

A barely cognitive Joe Biden took over the presidency in January, 2021, along with his fellow empty shell, Vice-President Kamala Harris, as the latest Sabbatian gofers to enter the White House. Names on the door may have changed and the 'party' – the force behind them remained the same as Zionists were appointed to a stream of pivotal areas relating to Sabbatian plans and policy. They included: Janet Yellen, Treasury Secretary, former head of the Federal Reserve, and still another ultra-Zionist running the US Treasury after Mnuchin (Trump), Lew and Geithner (Obama), and Summers and Rubin (Clinton); Anthony Blinken, Secretary of State; Wendy Sherman, Deputy Secretary of State (so that's 'Biden's' Sabbatian foreign policy sorted); Jeff Zients, White House coronavirus coordinator; Rochelle Walensky, head of the Centers for Disease Control; Rachel Levine, transgender deputy health secretary (that's 'Covid' hoax policy under control); Merrick Garland, Attorney General; Alejandro Mayorkas, Secretary of Homeland Security; Cass Sunstein, Homeland Security with responsibility for new immigration laws; Avril Haines, Director of National Intelligence; Anne Neuberger, National Security Agency cybersecurity director (note, cybersecurity); David Cohen, CIA Deputy Director; Ronald Klain, Biden's Chief of Staff (see Rahm Emanuel); Eric Lander, a 'leading geneticist', Office of Science and Technology Policy director (see Smart Grid, synthetic biology agenda); Jessica Rosenworcel, acting head of the Federal Communications Commission (FCC) which controls Smart Grid technology policy and electromagnetic communication systems including 5G. How can it be that so many pivotal positions are held by two-percent of the American population and 0.2 percent of the world population administration after administration no matter who is the president and what is the party? It's a coincidence? Of course it's not and this is why Sabbatians have built their colossal global web of interlocking 'anti-

hate' hate groups to condemn anyone who asks these glaring questions as an 'anti-Semite'. The way that Jewish people horrifically abused in Sabbatian-backed Nazi Germany are exploited to this end is stomach-turning and disgusting beyond words.

Political fusion

Sabbatian manipulation has reversed the roles of Republicans and Democrats and the same has happened in Britain with the Conservative and Labour Parties. Republicans and Conservatives were always labelled the 'right' and Democrats and Labour the 'left', but look at the policy positions now and the Democrat-Labour 'left' has moved further to the 'right' than Republicans and Conservatives under the banner of 'Woke', the Cult-created far-right tyranny. Where once the Democrat-Labour 'left' defended free speech and human rights they now seek to delete them and as I said earlier despite the 'Covid' fascism of the Jackboot Johnson Conservative government in the UK the Labour Party of leader Keir Starmer demanded even more extreme measures. The Labour Party has been very publicly absorbed by Sabbatians after a political and media onslaught against the previous leader, the weak and inept Jeremy Corbyn, over made-up allegations of 'anti-Semitism' both by him and his party. The plan was clear with this 'anti-Semite' propaganda and what was required in response was a swift and decisive 'fuck off' from Corbyn and a statement to expose the Anti-Semitism Industry (Sabbatian) attempt to silence Labour criticism of the Israeli government (Sabbatians) and purge the party of all dissent against the extremes of ultra-Zionism (Sabbatians). Instead Corbyn and his party fell to their knees and appeased the abusers which, by definition, is impossible. Appeasing one demand leads only to a new demand to be appeased until takeover is complete. Like I say – 'fuck off' would have been a much more effective policy and I have used it myself with great effect over the years when Sabbatians are on my case which is most of the time. I consider that fact a great compliment, by the way. The outcome of the Labour Party capitulation is that we now have a Sabbatian-controlled

Conservative Party 'opposed' by a Sabbatian-controlled Labour Party in a one-party Sabbatian state that hurtles towards the extremes of tyranny (the Sabbatian cult agenda). In America the situation is the same. Labour's Keir Starmer spends his days on his knees with his tongue out pointing to Tel Aviv, or I guess now Jerusalem, while Boris Johnson has an 'anti-Semitism czar' in the form of former Labour MP John Mann who keeps Starmer company on his prayer mat.

Sabbatian influence can be seen in Jewish members of the Labour Party who have been ejected for criticism of Israel including those from families that suffered in Nazi Germany. Sabbatians despise real Jewish people and target them even more harshly because it is so much more difficult to dub them 'anti-Semitic' although in their desperation they do try.

CHAPTER THREE

The Pushbacker sting

Until you realize how easy it is for your mind to be manipulated, you remain the puppet of someone else's game
Evita Ochel

I will use the presidencies of Trump and Biden to show how the manipulation of the one-party state plays out behind the illusion of political choice across the world. No two presidencies could – on the face of it – be more different and apparently at odds in terms of direction and policy.

A Renegade Mind sees beyond the obvious and focuses on outcomes and consequences and not image, words and waffle. The Cult embarked on a campaign to divide America between those who blindly support its agenda (the mentality known as 'Woke') and those who are pushing back on where the Cult and its Sabbatians want to go. This presents infinite possibilities for dividing and ruling the population by setting them at war with each other and allows a perceptual ring fence of demonisation to encircle the Pushbackers in a modern version of the Little Big Horn in 1876 when American cavalry led by Lieutenant Colonel George Custer were drawn into a trap, surrounded and killed by Native American tribes defending their land of thousands of years from being seized by the government. In this modern version the roles are reversed and it's those defending themselves from the Sabbatian government who are surrounded and the government that's seeking to destroy them. This trap was set years ago and to explain how we must return to 2016

and the emergence of Donald Trump as a candidate to be President of the United States. He set out to overcome the best part of 20 other candidates in the Republican Party before and during the primaries and was not considered by many in those early stages to have a prayer of living in the White House. The Republican Party was said to have great reservations about Trump and yet somehow he won the nomination. When you know how American politics works – politics in general – there is no way that Trump could have become the party's candidate unless the Sabbatian-controlled 'Neocons' that run the Republican Party wanted that to happen. We saw the proof in emails and documents made public by WikiLeaks that the Democratic Party hierarchy, or Democons, systematically undermined the campaign of Bernie Sanders to make sure that Sabbatian gofer Hillary Clinton won the nomination to be their presidential candidate. If the Democons could do that then the Neocons in the Republican Party could have derailed Trump in the same way. But they didn't and at that stage I began to conclude that Trump could well be the one chosen to be president. If that was the case the 'why' was pretty clear to see – the goal of dividing America between Cult agenda-supporting Wokers and Pushbackers who gravitated to Trump because he was telling them what they wanted to hear. His constituency of support had been increasingly ignored and voiceless for decades and profoundly through the eight years of Sabbatian puppet Barack Obama. Now here was someone speaking their language of pulling back from the incessant globalisation of political and economic power, the exporting of American jobs to China and elsewhere by 'American' (Sabbatian) corporations, the deletion of free speech, and the mass immigration policies that had further devastated job opportunities for the urban working class of all races and the once American heartlands of the Midwest.

Beware the forked tongue

Those people collectively sighed with relief that at last a political leader was apparently on their side, but another trait of the Renegade Mind is that you look even harder at people telling you

what you want to hear than those who are telling you otherwise. Obviously as I said earlier people wish what they want to hear to be true and genuine and they are much more likely to believe that than someone saying what they don't want to here and don't want to be true. Sales people are taught to be skilled in eliciting by calculated questioning what their customers want to hear and repeating that back to them as their own opinion to get their targets to like and trust them. Assets of the Cult are also sales people in the sense of selling perception. To read Cult manipulation you have to play the long and expanded game and not fall for the Vaudeville show of party politics. Both American parties are vehicles for the Cult and they exploit them in different ways depending on what the agenda requires at that moment. Trump and the Republicans were used to be the focus of dividing America and isolating Pushbackers to open the way for a Biden presidency to become the most extreme in American history by advancing the full-blown Woke (Cult) agenda with the aim of destroying and silencing Pushbackers now labelled Nazi Trump supporters and white supremacists.

Sabbatians wanted Trump in office for the reasons described by ultra-Zionist Saul Alinsky (1909-1972) who was promoting the Woke philosophy through 'community organising' long before anyone had heard of it. In those days it still went by its traditional name of Marxism. The reason for the manipulated Trump phenomenon was laid out in Alinsky's 1971 book, *Rules for Radicals*, which was his blueprint for overthrowing democratic and other regimes and replacing them with Sabbatian Marxism. Not surprisingly his to-do list was evident in the Sabbatian French and Russian 'Revolutions' and that in China which will become very relevant in the next chapter about the 'Covid' hoax. Among Alinsky's followers have been the deeply corrupt Barack Obama, House Speaker Nancy Pelosi and Hillary Clinton who described him as a 'hero'. All three are Sabbatian stooges with Pelosi personifying the arrogant corrupt idiocy that so widely fronts up for the Cult inner core. Predictably as a Sabbatian advocate of the 'light-bringer' Alinsky features Lucifer on the dedication page of his book as the original radical who gained

his own kingdom ('Earth' as we shall see). One of Alinsky's golden radical rules was to pick an individual and focus all attention, hatred and blame on them and not to target faceless bureaucracies and corporations. *Rules for Radicals* is really a Sabbatian handbook with its contents repeatedly employed all over the world for centuries and why wouldn't Sabbatians bring to power their designer-villain to be used as the individual on which all attention, hatred and blame was bestowed? This is what they did and the only question for me is how much Trump knew that and how much he was manipulated. A bit of both, I suspect. This was Alinsky's Trump technique from a man who died in 1972. The technique has spanned history:

Pick the target, freeze it, personalize it, polarize it. Don't try to attack abstract corporations or bureaucracies. Identify a responsible individual. Ignore attempts to shift or spread the blame.

From the moment Trump came to illusory power everything was about him. It wasn't about Republican policy or opinion, but all about Trump. Everything he did was presented in negative, derogatory and abusive terms by the Sabbatian-dominated media led by Cult operations such as CNN, MSNBC, *The New York Times* and the Jeff Bezos-owned *Washington Post* – 'Pick the target, freeze it, personalize it, polarize it.' Trump was turned into a demon to be vilified by those who hated him and a demi-god loved by those who worshipped him. This, in turn, had his supporters, too, presented as equally demonic in preparation for the punchline later down the line when Biden was about to take office. It was here's a Trump, there's a Trump, everywhere a Trump, Trump. Virtually every news story or happening was filtered through the lens of 'The Donald'. You loved him or hated him and which one you chose was said to define you as Satan's spawn or a paragon of virtue. Even supporting some Trump policies or statements and not others was enough for an assault on your character. No shades of grey were or are allowed. Everything is black and white (literally and figuratively). A Californian I knew had her head utterly scrambled by her hatred for Trump while telling people they should love each other. She was so totally consumed by

Trump Derangement Syndrome as it became to be known that this glaring contradiction would never have occurred to her. By definition anyone who criticised Trump or praised his opponents was a hero and this lady described Joe Biden as 'a kind, honest gentleman' when he's a provable liar, mega-crook and vicious piece of work to boot. Sabbatians had indeed divided America using Trump as the fall-guy and all along the clock was ticking on the consequences for his supporters.

In hock to his masters

Trump gave Sabbatians via Israel almost everything they wanted in his four years. Ask and you shall receive was the dynamic between himself and Benjamin Netanyahu orchestrated by Trump's ultra-Zionist son-in-law Jared Kushner, his ultra-Zionist Ambassador to Israel, David Friedman, and ultra-Zionist 'Israel adviser', Jason Greenblatt. The last two were central to the running and protecting from collapse of his business empire, the Trump Organisation, and colossal business failures made him forever beholding to Sabbatian networks that bailed him out. By the start of the 1990s Trump owed $4 billion to banks that he couldn't pay and almost $1billion of that was down to him personally and not his companies. This mega-disaster was the result of building two new casinos in Atlantic City and buying the enormous Taj Mahal operation which led to crippling debt payments. He had borrowed fantastic sums from 72 banks with major Sabbatian connections and although the scale of debt should have had him living in a tent alongside the highway they never foreclosed. A plan was devised to lift Trump from the mire by BT Securities Corporation and Rothschild Inc. and the case was handled by Wilber Ross who had worked for the Rothschilds for 27 years. Ross would be named US Commerce Secretary after Trump's election. Another crucial figure in saving Trump was ultra-Zionist 'investor' Carl Icahn who bought the Taj Mahal casino. Icahn was made special economic adviser on financial regulation in the Trump administration. He didn't stay long but still managed to find time to make a tidy sum of a reported $31.3 million when he sold his

holdings affected by the price of steel three days before Trump imposed a 235 percent tariff on steel imports. What amazing bits of luck these people have. Trump and Sabbatian operatives have long had a close association and his mentor and legal adviser from the early 1970s until 1986 was the dark and genetically corrupt ultra-Zionist Roy Cohn who was chief counsel to Senator Joseph McCarthy's 'communist' witch-hunt in the 1950s. *Esquire* magazine published an article about Cohn with the headline 'Don't mess with Roy Cohn'. He was described as the most feared lawyer in New York and 'a ruthless master of dirty tricks ... [with] ... more than one Mafia Don on speed dial'. Cohn's influence, contacts, support and protection made Trump a front man for Sabbatians in New York with their connections to one of Cohn's many criminal employers, the 'Russian' Sabbatian Mafia. Israel-centric media mogul Rupert Murdoch was introduced to Trump by Cohn and they started a long friendship. Cohn died in 1986 weeks after being disbarred for unethical conduct by the Appellate Division of the New York State Supreme Court. The wheels of justice do indeed run slow given the length of Cohn's crooked career.

QAnon-sense

We are asked to believe that Donald Trump with his fundamental connections to Sabbatian networks and operatives has been leading the fight to stop the Sabbatian agenda for the fascistic control of America and the world. Sure he has. A man entrapped during his years in the White House by Sabbatian operatives and whose biggest financial donor was casino billionaire Sheldon Adelson who was Sabbatian to his DNA?? Oh, do come on. Trump has been used to divide America and isolate Pushbackers on the Cult agenda under the heading of 'Trump supporters', 'insurrectionists' and 'white supremacists'. The US Intelligence/Mossad Psyop or psychological operation known as QAnon emerged during the Trump years as a central pillar in the Sabbatian campaign to lead Pushbackers into the trap set by those that wished to destroy them. I knew from the start that QAnon was a scam because I had seen the same scenario many

times before over 30 years under different names and I had written about one in particular in the books. 'Not again' was my reaction when QAnon came to the fore. The same script is pulled out every few years and a new name added to the letterhead. The story always takes the same form: 'Insiders' or 'the good guys' in the government-intelligence-military 'Deep State' apparatus were going to instigate mass arrests of the 'bad guys' which would include the Rockefellers, Rothschilds, Barack Obama, Hillary Clinton, George Soros, etc., etc. Dates are given for when the 'good guys' are going to move in, but the dates pass without incident and new dates are given which pass without incident. The central message to Pushbackers in each case is that they don't have to do anything because there is 'a plan' and it is all going to be sorted by the 'good guys' on the inside. 'Trust the plan' was a QAnon mantra when the only plan was to misdirect Pushbackers into putting their trust in a Psyop they believed to be real. Beware, beware, those who tell you what you want to hear and always check it out. Right up to Biden's inauguration QAnon was still claiming that 'the Storm' was coming and Trump would stay on as president when Biden and his cronies were arrested and jailed. It was never going to happen and of course it didn't, but what did happen as a result provided that punchline to the Sabbatian Trump/QAnon Psyop.

On January 6th, 2021, a very big crowd of Trump supporters gathered in the National Mall in Washington DC down from the Capitol Building to protest at what they believed to be widespread corruption and vote fraud that stopped Trump being re-elected for a second term as president in November, 2020. I say as someone that does not support Trump or Biden that the evidence is clear that major vote-fixing went on to favour Biden, a man with cognitive problems so advanced he can often hardly string a sentence together without reading the words written for him on the Teleprompter. Glaring ballot discrepancies included serious questions about electronic voting machines that make vote rigging a comparative cinch and hundreds of thousands of paper votes that suddenly appeared during already advanced vote counts and virtually all of

them for Biden. Early Trump leads in crucial swing states suddenly began to close and disappear. The pandemic hoax was used as the excuse to issue almost limitless numbers of mail-in ballots with no checks to establish that the recipients were still alive or lived at that address. They were sent to streams of people who had not even asked for them. Private organisations were employed to gather these ballots and who knows what they did with them before they turned up at the counts. The American election system has been manipulated over decades to become a sick joke with more holes than a Swiss cheese for the express purpose of dictating the results. Then there was the criminal manipulation of information by Sabbatian tech giants like Facebook, Twitter and Google-owned YouTube which deleted pro-Trump, anti-Biden accounts and posts while everything in support of Biden was left alone. Sabbatians wanted Biden to win because after the dividing of America it was time for full-on Woke and every aspect of the Cult agenda to be unleashed.

Hunter gatherer

Extreme Silicon Valley bias included blocking information by the *New York Post* exposing a Biden scandal that should have ended his bid for president in the final weeks of the campaign. Hunter Biden, his monumentally corrupt son, is reported to have sent a laptop to be repaired at a local store and failed to return for it. Time passed until the laptop became the property of the store for non-payment of the bill. When the owner saw what was on the hard drive he gave a copy to the FBI who did nothing even though it confirmed widespread corruption in which the Joe Biden family were using his political position, especially when he was vice president to Obama, to make multiple millions in countries around the world and most notably Ukraine and China. Hunter Biden's one-time business partner Tony Bobulinski went public when the story broke in the *New York Post* to confirm the corruption he saw and that Joe Biden not only knew what was going on he also profited from the spoils. Millions were handed over by a Chinese company with close

connections – like all major businesses in China – to the Chinese communist party of President Xi Jinping. Joe Biden even boasted at a meeting of the Cult's World Economic Forum that as vice president he had ordered the government of Ukraine to fire a prosecutor. What he didn't mention was that the same man just happened to be investigating an energy company which was part of Hunter Biden's corrupt portfolio. The company was paying him big bucks for no other reason than the influence his father had. Overnight Biden's presidential campaign should have been over given that he had lied publicly about not knowing what his son was doing. Instead almost the entire Sabbatian-owned mainstream media and Sabbatian-owned Silicon Valley suppressed circulation of the story. This alone went a mighty way to rigging the election of 2020. Cult assets like Mark Zuckerberg at Facebook also spent hundreds of millions to be used in support of Biden and vote 'administration'.

The Cult had used Trump as the focus to divide America and was now desperate to bring in moronic, pliable, corrupt Biden to complete the double-whammy. No way were they going to let little things like the will of the people thwart their plan. Silicon Valley widely censored claims that the election was rigged because it *was* rigged. For the same reason anyone claiming it was rigged was denounced as a 'white supremacist' including the pathetically few Republican politicians willing to say so. Right across the media where the claim was mentioned it was described as a 'false claim' even though these excuses for 'journalists' would have done no research into the subject whatsoever. Trump won seven million more votes than any sitting president had ever achieved while somehow a cognitively-challenged soon to be 78-year-old who was hidden away from the public for most of the campaign managed to win more votes than any presidential candidate in history. It makes no sense. You only had to see election rallies for both candidates to witness the enthusiasm for Trump and the apathy for Biden. Tens of thousands would attend Trump events while Biden was speaking in empty car parks with often only television crews attending and framing their shots to hide the fact that no one was there. It was pathetic to see

footage come to light of Biden standing at a podium making speeches only to TV crews and party fixers while reading the words written for him on massive Teleprompter screens. So, yes, those protestors on January 6th had a point about election rigging, but some were about to walk into a trap laid for them in Washington by the Cult Deep State and its QAnon Psyop. This was the Capitol Hill riot ludicrously dubbed an 'insurrection'.

The spider and the fly

Renegade Minds know there are not two 'sides' in politics, only one side, the Cult, working through all 'sides'. It's a stage show, a puppet show, to direct the perceptions of the population into focusing on diversions like parties and candidates while missing the puppeteers with their hands holding all the strings. The Capitol Hill 'insurrection' brings us back to the Little Big Horn. Having created two distinct opposing groupings – Woke and Pushbackers – the trap was about to be sprung. Pushbackers were to be encircled and isolated by associating them all in the public mind with Trump and then labelling Trump as some sort of Confederate leader. I knew immediately that the Capitol riot was a set-up because of two things. One was how easy the rioters got into the building with virtually no credible resistance and secondly I could see – as with the 'Covid' hoax in the West at the start of 2020 – how the Cult could exploit the situation to move its agenda forward with great speed. My experience of Cult techniques and activities over more than 30 years has showed me that while they do exploit situations they haven't themselves created this never happens with events of fundamental agenda significance. Every time major events giving cultists the excuse to rapidly advance their plan you find they are manipulated into being for the specific reason of providing that excuse – Problem-Reaction-Solution. Only a tiny minority of the huge crowd of Washington protestors sought to gain entry to the Capitol by smashing windows and breaching doors. That didn't matter. The whole crowd and all Pushbackers, even if they did not support Trump, were going to be lumped together as dangerous

insurrectionists and conspiracy theorists. The latter term came into widespread use through a CIA memo in the 1960s aimed at discrediting those questioning the nonsensical official story of the Kennedy assassination and it subsequently became widely employed by the media. It's still being used by inept 'journalists' with no idea of its origin to discredit anyone questioning anything that authority claims to be true. When you are perpetrating a conspiracy you need to discredit the very word itself even though the dictionary definition of conspiracy is merely 'the activity of secretly planning with other people to do something bad or illegal' and 'a general agreement to keep silent about a subject for the purpose of keeping it secret'. On that basis there are conspiracies almost wherever you look. For obvious reasons the Cult and its lapdog media have to claim there are no conspiracies even though the word appears in state laws as with conspiracy to defraud, to murder, and to corrupt public morals.

Agent provocateurs are widely used by the Cult Deep State to manipulate genuine people into acting in ways that suit the desired outcome. By genuine in this case I mean protestors genuinely supporting Trump and claims that the election was stolen. In among them, however, were agents of the state wearing the garb of Trump supporters and QAnon to pump-prime the Capital riot which some genuine Trump supporters naively fell for. I described the situation as 'Come into my parlour said the spider to the fly'. Leaflets appeared through the Woke paramilitary arm Antifa, the anti-fascist fascists, calling on supporters to turn up in Washington looking like Trump supporters even though they hated him. Some of those arrested for breaching the Capitol Building were sourced to Antifa and its stable mate Black Lives Matter. Both organisations are funded by Cult billionaires and corporations. One man charged for the riot was according to his lawyer a former FBI agent who had held top secret security clearance for 40 years. Attorney Thomas Plofchan said of his client, 66-year-old Thomas Edward Caldwell:

He has held a Top Secret Security Clearance since 1979 and has undergone multiple Special Background Investigations in support of his clearances. After retiring from the Navy, he

worked as a section chief for the Federal Bureau of Investigation from 2009-2010 as a GS-12 [mid-level employee].

He also formed and operated a consulting firm performing work, often classified, for U.S government customers including the US. Drug Enforcement Agency, Department of Housing and Urban Development, the US Coast Guard, and the US Army Personnel Command.

A judge later released Caldwell pending trial in the absence of evidence about a conspiracy or that he tried to force his way into the building. *The New York Post* reported a 'law enforcement source' as saying that 'at least two known Antifa members were spotted' on camera among Trump supporters during the riot while one of the rioters arrested was John Earle Sullivan, a seriously extreme Black Lives Matter Trump-hater from Utah who was previously arrested and charged in July, 2020, over a BLM-Antifa riot in which drivers were threatened and one was shot. Sullivan is the founder of Utah-based Insurgence USA which is an affiliate of the Cult-created-and-funded Black Lives Matter movement. Footage appeared and was then deleted by Twitter of Trump supporters calling out Antifa infiltrators and a group was filmed changing into pro-Trump clothing before the riot. Security at the building was *pathetic* – as planned. Colonel Leroy Fletcher Prouty, a man with long experience in covert operations working with the US security apparatus, once described the tell-tale sign to identify who is involved in an assassination. He said:

No one has to direct an assassination – it happens. The active role is played secretly by permitting it to happen. This is the greatest single clue. Who has the power to call off or reduce the usual security precautions?

This principle applies to many other situations and certainly to the Capitol riot of January 6th, 2021.

The sting

With such a big and potentially angry crowd known to be gathering near the Capitol the security apparatus would have had a major police detail to defend the building with National Guard troops on

standby given the strength of feeling among people arriving from all over America encouraged by the QAnon Psyop and statements by Donald Trump. Instead Capitol Police 'security' was flimsy, weak, and easily breached. The same number of officers was deployed as on a regular day and that is a blatant red flag. They were not staffed or equipped for a possible riot that had been an obvious possibility in the circumstances. No protective and effective fencing worth the name was put in place and there were no contingency plans. The whole thing was basically a case of standing aside and waving people in. Once inside police mostly backed off apart from one Capitol police officer who ridiculously shot dead unarmed Air Force veteran protestor Ashli Babbitt without a warning as she climbed through a broken window. The 'investigation' refused to name or charge the officer after what must surely be considered a murder in the circumstances. They just lifted a carpet and swept. The story was endlessly repeated about five people dying in the 'armed insurrection' when there was no report of rioters using weapons. Apart from Babbitt the other four died from a heart attack, strokes and apparently a drug overdose. Capitol police officer Brian Sicknick was reported to have died after being bludgeoned with a fire extinguisher when he was alive after the riot was over and died later of what the Washington Medical Examiner's Office said was a stroke. Sicknick had no external injuries. The lies were delivered like rapid fire. There was a narrative to build with incessant repetition of the lie until the lie became the accepted 'everybody knows that' truth. The 'Big Lie' technique of Nazi Propaganda Minister Joseph Goebbels is constantly used by the Cult which was behind the Nazis and is today behind the 'Covid' and 'climate change' hoaxes. Goebbels said:

If you tell a lie big enough and keep repeating it, people will eventually come to believe it. The lie can be maintained only for such time as the State can shield the people from the political, economic and/or military consequences of the lie. It thus becomes vitally important for the State to use all of its powers to repress dissent, for the truth is the mortal enemy of the lie, and thus by extension, the truth is the greatest enemy of the State.

Most protestors had a free run of the Capitol Building. This allowed pictures to be taken of rioters in iconic parts of the building including the Senate chamber which could be used as propaganda images against all Pushbackers. One Congresswoman described the scene as 'the worst kind of non-security anybody could ever imagine'. Well, the first part was true, but someone obviously did imagine it and made sure it happened. Some photographs most widely circulated featured people wearing QAnon symbols and now the Psyop would be used to dub all QAnon followers with the ubiquitous fit-all label of 'white supremacist' and 'insurrectionists'. When a Muslim extremist called Noah Green drove his car at two police officers at the Capitol Building killing one in April, 2021, there was no such political and media hysteria. They were just disappointed he wasn't white.

The witch-hunt

Government prosecutor Michael Sherwin, an aggressive, dark-eyed, professional Rottweiler led the 'investigation' and to call it over the top would be to understate reality a thousand fold. Hundreds were tracked down and arrested for the crime of having the wrong political views and people were jailed who had done nothing more than walk in the building, committed no violence or damage to property, took a few pictures and left. They were labelled a 'threat to the Republic' while Biden sat in the White House signing executive orders written for him that were dismantling 'the Republic'. Even when judges ruled that a mother and son should not be in jail the government kept them there. Some of those arrested have been badly beaten by prison guards in Washington and lawyers for one man said he suffered a fractured skull and was made blind in one eye. Meanwhile a woman is shot dead for no reason by a Capitol Police officer and we are not allowed to know who he is never mind what has happened to him although that will be *nothing*. The Cult's QAnon/Trump sting to identify and isolate Pushbackers and then target them on the road to crushing and deleting them was a resounding success. You would have thought the Russians had

invaded the building at gunpoint and lined up senators for a firing squad to see the political and media reaction. Congresswoman Alexandria Ocasio-Cortez is a child in a woman's body, a terrible-twos, me, me, me, Woker narcissist of such proportions that words have no meaning. She said she thought she was going to die when 'insurrectionists' banged on her office door. It turned out she wasn't even in the Capitol Building when the riot was happening and the 'banging' was a Capitol Police officer. She referred to herself as a 'survivor' which is an insult to all those true survivors of violent and sexual abuse while she lives her pampered and privileged life talking drivel for a living. Her Woke colleague and fellow mega-narcissist Rashida Tlaib broke down describing the devastating effect on her, too, of *not being* in the building when the rioters were there. Ocasio-Cortez and Tlaib are members of a fully-Woke group of Congresswomen known as 'The Squad' along with Ilhan Omar and Ayanna Pressley. The Squad from what I can see can be identified by its vehement anti-white racism, anti-white men agenda, and, as always in these cases, the absence of brain cells on active duty.

The usual suspects were on the riot case immediately in the form of Democrat ultra-Zionist senators and operatives Chuck Schumer and Adam Schiff demanding that Trump be impeached for 'his part in the insurrection'. The same pair of prats had led the failed impeachment of Trump over the invented 'Russia collusion' nonsense which claimed Russia had helped Trump win the 2016 election. I didn't realise that Tel Aviv had been relocated just outside Moscow. I must find an up-to-date map. The Russia hoax was a Sabbatian operation to keep Trump occupied and impotent and to stop any rapport with Russia which the Cult wants to retain as a perceptual enemy to be pulled out at will. Puppet Biden began attacking Russia when he came to office as the Cult seeks more upheaval, division and war across the world. A two-year stage show 'Russia collusion inquiry' headed by the not-very-bright former 9/11 FBI chief Robert Mueller, with support from 19 lawyers, 40 FBI agents plus intelligence analysts, forensic accountants and other

staff, devoured tens of millions of dollars and found no evidence of Russia collusion which a ten-year-old could have told them on day one. Now the same moronic Schumer and Schiff wanted a second impeachment of Trump over the Capitol 'insurrection' (riot) which the arrested development of Schumer called another 'Pearl Harbor' while others compared it with 9/11 in which 3,000 died and, in the case of CNN, with the Rwandan genocide in the 1990s in which an estimated 500,000 to 600,000 were murdered, between 250, 000 and 500,000 women were raped, and populations of whole towns were hacked to death with machetes. To make those comparisons purely for Cult political reasons is beyond insulting to those that suffered and lost their lives and confirms yet again the callous inhumanity that we are dealing with. Schumer is a monumental idiot and so is Schiff, but they serve the Cult agenda and do whatever they're told so they get looked after. Talking of idiots – another inane man who spanned the Russia and Capitol impeachment attempts was Senator Eric Swalwell who had the nerve to accuse Trump of collusion with the Russians while sleeping with a Chinese spy called Christine Fang or 'Fang Fang' which is straight out of a Bond film no doubt starring Klaus Schwab as the bloke living on a secret island and controlling laser weapons positioned in space and pointing at world capitals. Fang Fang plays the part of Bond's infiltrator girlfriend which I'm sure she would enjoy rather more than sharing a bed with the brainless Swalwell, lying back and thinking of China. The FBI eventually warned Swalwell about Fang Fang which gave her time to escape back to the Chinese dictatorship. How very thoughtful of them. The second Trump impeachment also failed and hardly surprising when an impeachment is supposed to remove a sitting president and by the time it happened Trump was no longer president. These people are running your country America, well, officially anyway. Terrifying isn't it?

Outcomes tell the story - always

The outcome of all this – and it's the *outcome* on which Renegade Minds focus, not the words – was that a vicious, hysterical and

obviously pre-planned assault was launched on Pushbackers to censor, silence and discredit them and even targeted their right to earn a living. They have since been condemned as 'domestic terrorists' that need to be treated like Al-Qaeda and Islamic State. 'Domestic terrorists' is a label the Cult has been trying to make stick since the period of the Oklahoma bombing in 1995 which was blamed on 'far-right domestic terrorists'. If you read *The Trigger* you will see that the bombing was clearly a Problem-Reaction-Solution carried out by the Deep State during a Bill Clinton administration so corrupt that no dictionary definition of the term would even nearly suffice. Nearly 30, 000 troops were deployed from all over America to the empty streets of Washington for Biden's inauguration. Ten thousand of them stayed on with the pretext of protecting the capital from insurrectionists when it was more psychological programming to normalise the use of the military in domestic law enforcement in support of the Cult plan for a police-military state. Biden's fascist administration began a purge of 'wrong-thinkers' in the military which means anyone that is not on board with Woke. The Capitol Building was surrounded by a fence with razor wire and the Land of the Free was further symbolically and literally dismantled. The circle was completed with the installation of Biden and the exploitation of the QAnon Psyop.

America had never been so divided since the civil war of the 19th century, Pushbackers were isolated and dubbed terrorists and now, as was always going to happen, the Cult immediately set about deleting what little was left of freedom and transforming American society through a swish of the hand of the most controlled 'president' in American history leading (officially at least) the most extreme regime since the country was declared an independent state on July 4th, 1776. Biden issued undebated, dictatorial executive orders almost by the hour in his opening days in office across the whole spectrum of the Cult wish-list including diluting controls on the border with Mexico allowing thousands of migrants to illegally enter the United States to transform the demographics of America and import an election-changing number of perceived Democrat

voters. Then there were Biden deportation amnesties for the already illegally resident (estimated to be as high as 20 or even 30 million). A bill before Congress awarded American citizenship to anyone who could prove they had worked in agriculture for just 180 days in the previous two years as 'Big Ag' secured its slave labour long-term. There were the plans to add new states to the union such as Puerto Rico and making Washington DC a state. They are all parts of a plan to ensure that the Cult-owned Woke Democrats would be permanently in power.

Border – what border?

I have exposed in detail in other books how mass immigration into the United States and Europe is the work of Cult networks fuelled by the tens of billions spent to this and other ends by George Soros and his global Open Society (open borders) Foundations. The impact can be seen in America alone where the population has increased by *100 million* in little more than 30 years mostly through immigration. I wrote in *The Answer* that the plan was to have so many people crossing the southern border that the numbers become unstoppable and we are now there under Cult-owned Biden. El Salvador in Central America puts the scale of what is happening into context. A third of the population now lives in the United States, much of it illegally, and many more are on the way. The methodology is to crush Central and South American countries economically and spread violence through machete-wielding psychopathic gangs like MS-13 based in El Salvador and now operating in many American cities. Biden-imposed lax security at the southern border means that it is all but open. He said before his 'election' that he wanted to see a surge towards the border if he became president and that was the green light for people to do just that after election day to create the human disaster that followed for both America and the migrants. When that surge came the imbecilic Alexandria Ocasio-Cortez said it wasn't a 'surge' because they are 'children, not insurgents' and the term 'surge' (used by Biden) was a claim of 'white supremacists'.

This disingenuous lady may one day enter the realm of the most basic intelligence, but it won't be any time soon.

Sabbatians and the Cult are in the process of destroying America by importing violent people and gangs in among the genuine to terrorise American cities and by overwhelming services that cannot cope with the sheer volume of new arrivals. Something similar is happening in Europe as Western society in general is targeted for demographic and cultural transformation and upheaval. The plan demands violence and crime to create an environment of intimidation, fear and division and Soros has been funding the election of district attorneys across America who then stop prosecuting many crimes, reduce sentences for violent crimes and free as many violent criminals as they can. Sabbatians are creating the chaos from which order – their order – can respond in a classic Problem-Reaction-Solution. A Freemasonic moto says 'Ordo Ab Chao' (Order out of Chaos) and this is why the Cult is constantly creating chaos to impose a new 'order'. Here you have the reason the Cult is constantly creating chaos. The 'Covid' hoax can be seen with those entering the United States by plane being forced to take a 'Covid' test while migrants flooding through southern border processing facilities do not. Nothing is put in the way of mass migration and if that means ignoring the government's own 'Covid' rules then so be it. They know it's all bullshit anyway. Any pushback on this is denounced as 'racist' by Wokers and Sabbatian fronts like the ultra-Zionist Anti-Defamation League headed by the appalling Jonathan Greenblatt which at the same time argues that Israel should not give citizenship and voting rights to more Palestinian Arabs or the 'Jewish population' (in truth the Sabbatian network) will lose control of the country.

Society-changing numbers

Biden's masters have declared that countries like El Salvador are so dangerous that their people must be allowed into the United States for humanitarian reasons when there are fewer murders in large parts of many Central American countries than in US cities like

Baltimore. That is not to say Central America cannot be a dangerous place and Cult-controlled American governments have been making it so since way back, along with the dismantling of economies, in a long-term plan to drive people north into the United States. Parts of Central America are very dangerous, but in other areas the story is being greatly exaggerated to justify relaxing immigration criteria. Migrants are being offered free healthcare and education in the United States as another incentive to head for the border and there is no requirement to be financially independent before you can enter to prevent the resources of America being drained. You can't blame migrants for seeking what they believe will be a better life, but they are being played by the Cult for dark and nefarious ends. The numbers since Biden took office are huge. In February, 2021, more than 100,000 people were known to have tried to enter the US illegally through the southern border (it was 34,000 in the same month in 2020) and in March it was 170,000 – a 418 percent increase on March, 2020. These numbers are only known people, not the ones who get in unseen. The true figure for migrants illegally crossing the border in a single month was estimated by one congressman at 250,000 and that number will only rise under Biden's current policy. Gangs of murdering drug-running thugs that control the Mexican side of the border demand money – thousands of dollars – to let migrants cross the Rio Grande into America. At the same time gun battles are breaking out on the border several times a week between rival Mexican drug gangs (which now operate globally) who are equipped with sophisticated military-grade weapons, grenades and armoured vehicles. While the Capitol Building was being 'protected' from a non-existent 'threat' by thousands of troops, and others were still deployed at the time in the Cult Neocon war in Afghanistan, the southern border of America was left to its fate. This is not incompetence, it is cold calculation.

By March, 2021, there were 17,000 unaccompanied children held at border facilities and many of them are ensnared by people traffickers for paedophile rings and raped on their journey north to America. This is not conjecture – this is fact. Many of those designated

children are in reality teenage boys or older. Meanwhile Wokers posture their self-purity for encouraging poor and tragic people to come to America and face this nightmare both on the journey and at the border with the disgusting figure of House Speaker Nancy Pelosi giving disingenuous speeches about caring for migrants. The woman's evil. Wokers condemned Trump for having children in cages at the border (so did Obama, *Shhhh*), but now they are sleeping on the floor without access to a shower with one border facility 729 percent over capacity. The Biden insanity even proposed flying migrants from the southern border to the northern border with Canada for 'processing'. The whole shambles is being overseen by ultra-Zionist Secretary of Homeland Security, the moronic liar Alejandro Mayorkas, who banned news cameras at border facilities to stop Americans seeing what was happening. Mayorkas said there was not a ban on news crews; it was just that they were not allowed to film. Alongside him at Homeland Security is another ultra-Zionist Cass Sunstein appointed by Biden to oversee new immigration laws. Sunstein despises conspiracy researchers to the point where he suggests they should be banned or *taxed* for having such views. The man is not bonkers or anything. He's perfectly well-adjusted, but adjusted to what is the question. Criticise what is happening and you are a 'white supremacist' when earlier non-white immigrants also oppose the numbers which effect their lives and opportunities. Black people in poor areas are particularly damaged by uncontrolled immigration and the increased competition for work opportunities with those who will work for less. They are also losing voting power as Hispanics become more dominant in former black areas. It's a downward spiral for them while the billionaires behind the policy drone on about how much they care about black people and 'racism'. None of this is about compassion for migrants or black people – that's just wind and air. Migrants are instead being mercilessly exploited to transform America while the countries they leave are losing their future and the same is true in Europe. Mass immigration may now be the work of Woke Democrats, but it can be traced back to the 1986 Immigration Reform and Control Act (it

wasn't) signed into law by Republican hero President Ronald Reagan which gave amnesty to millions living in the United States illegally and other incentives for people to head for the southern border. Here we have the one-party state at work again.

Save me syndrome

Almost every aspect of what I have been exposing as the Cult agenda was on display in even the first days of 'Biden' with silencing of Pushbackers at the forefront of everything. A Renegade Mind will view the Trump years and QAnon in a very different light to their supporters and advocates as the dots are connected. The QAnon/Trump Psyop has given the Cult all it was looking for. We may not know how much, or little, that Trump realised he was being used, but that's a side issue. This pincer movement produced the desired outcome of dividing America and having Pushbackers isolated. To turn this around we have to look at new routes to empowerment which do not include handing our power to other people and groups through what I will call the 'Save Me Syndrome' – 'I want someone else to do it so that I don't have to'. We have seen this at work throughout human history and the QAnon/Trump Psyop is only the latest incarnation alongside all the others. Religion is an obvious expression of this when people look to a 'god' or priest to save them or tell them how to be saved and then there are 'save me' politicians like Trump. Politics is a diversion and not a 'saviour'. It is a means to block positive change, not make it possible.

Save Me Syndrome always comes with the same repeating theme of handing your power to whom or what you believe will save you while your real 'saviour' stares back from the mirror every morning. Renegade Minds are constantly vigilant in this regard and always asking the question 'What can I do?' rather than 'What can someone else do for me?' Gandhi was right when he said: 'You must be the change you want to see in the world.' We are indeed the people we have been waiting for. We are presented with a constant raft of reasons to concede that power to others and forget where the real power is. Humanity has the numbers and the Cult does not. It has to

use diversion and division to target the unstoppable power that comes from unity. Religions, governments, politicians, corporations, media, QAnon, are all different manifestations of this power-diversion and dilution. Refusing to give your power to governments and instead handing it to Trump and QAnon is not to take a new direction, but merely to recycle the old one with new names on the posters. I will explore this phenomenon as we proceed and how to break the cycles and recycles that got us here through the mists of repeating perception and so repeating history.

For now we shall turn to the most potent example in the entire human story of the consequences that follow when you give your power away. I am talking, of course, of the 'Covid' hoax.

CHAPTER FOUR

'Covid': Calculated catastrophe

Facts are threatening to those invested in fraud
DaShanne Stokes

We can easily unravel the real reason for the 'Covid pandemic' hoax by employing the Renegade Mind methodology that I have outlined this far. We'll start by comparing the long-planned Cult outcome with the 'Covid pandemic' outcome. Know the outcome and you'll see the journey.

I have highlighted the plan for the Hunger Games Society which has been in my books for so many years with the very few controlling the very many through ongoing dependency. To create this dependency it is essential to destroy independent livelihoods, businesses and employment to make the population reliant on the state (the Cult) for even the basics of life through a guaranteed pittance income. While independence of income remained these Cult ambitions would be thwarted. With this knowledge it was easy to see where the 'pandemic' hoax was going once talk of 'lockdowns' began and the closing of all but perceived 'essential' businesses to 'save' us from an alleged 'deadly virus'. Cult corporations like Amazon and Walmart were naturally considered 'essential' while mom and pop shops and stores had their doors closed by fascist decree. As a result with every new lockdown and new regulation more small and medium, even large businesses not owned by the Cult, went to the wall while Cult giants and their frontmen and women grew financially fatter by the second. Mom and pop were

denied an income and the right to earn a living and the wealth of people like Jeff Bezos (Amazon), Mark Zuckerberg (Facebook) and Sergei Brin and Larry Page (Google/Alphabet) have reached record levels. The Cult was increasing its own power through further dramatic concentrations of wealth while the competition was being destroyed and brought into a state of dependency. Lockdowns have been instigated to secure that very end and were never anything to do with health. My brother Paul spent 45 years building up a bus repair business, but lockdowns meant buses were running at a fraction of normal levels for months on end. Similar stories can told in their hundreds of millions worldwide. Efforts of a lifetime coldly destroyed by Cult multi-billionaires and their lackeys in government and law enforcement who continued to earn their living from the taxation of the people while denying the right of the same people to earn theirs. How different it would have been if those making and enforcing these decisions had to face the same financial hardships of those they affected, but they never do.

Gates of Hell

Behind it all in the full knowledge of what he is doing and why is the psychopathic figure of Cult operative Bill Gates. His puppet Tedros at the World Health Organization declared 'Covid' a pandemic in March, 2020. The WHO had changed the definition of a 'pandemic' in 2009 just a month before declaring the 'swine flu pandemic' which would not have been so under the previous definition. The same applies to 'Covid'. The definition had included… 'an infection by an infectious agent, occurring simultaneously in different countries, with a significant mortality rate relative to the proportion of the population infected'. The new definition removed the need for 'significant mortality'. The 'pandemic' has been fraudulent even down to the definition, but Gates demanded economy-destroying lockdowns, school closures, social distancing, mandatory masks, a 'vaccination' for every man, woman and child on the planet and severe consequences and restrictions for those that refused. Who gave him this power? The

Cult did which he serves like a little boy in short trousers doing what his daddy tells him. He and his psychopathic missus even smiled when they said that much worse was to come (what they knew was planned to come). Gates responded in the matter-of-fact way of all psychopaths to a question about the effect on the world economy of what he was doing:

> Well, it won't go to zero but it will shrink. Global GDP is probably going to take the biggest hit ever [Gates was smiling as he said this] … in my lifetime this will be the greatest economic hit. But you don't have a choice. People act as if you have a choice. People don't feel like going to the stadium when they might get infected … People are deeply affected by seeing these stats, by knowing they could be part of the transmission chain, old people, their parents and grandparents, could be affected by this, and so you don't get to say ignore what is going on here.
>
> There will be the ability to open up, particularly in rich countries, if things are done well over the next few months, but for the world at large normalcy only returns when we have largely vaccinated the entire population.

The man has no compassion or empathy. How could he when he's a psychopath like all Cult players? My own view is that even beyond that he is very seriously mentally ill. Look in his eyes and you can see this along with his crazy flailing arms. You don't do what he has done to the world population since the start of 2020 unless you are mentally ill and at the most extreme end of psychopathic. You especially don't do it when to you know, as we shall see, that cases and deaths from 'Covid' are fakery and a product of monumental figure massaging. 'These stats' that Gates referred to are based on a 'test' that's not testing for the 'virus' as he has known all along. He made his fortune with big Cult support as an infamously ruthless software salesman and now buys global control of 'health' (death) policy without the population he affects having any say. It's a breathtaking outrage. Gates talked about people being deeply affected by fear of 'Covid' when that was because of *him* and his global network lying to them minute-by-minute supported by a lying media that he seriously influences and funds to the tune of hundreds of millions. He's handed big sums to media operations including the BBC, NBC, Al Jazeera, Univision, *PBS NewsHour*,

ProPublica, National Journal, The Guardian, The Financial Times, The Atlantic, Texas Tribune, USA Today publisher Gannett, *Washington Monthly, Le Monde,* Center for Investigative Reporting, Pulitzer Center on Crisis Reporting, National Press Foundation, International Center for Journalists, Solutions Journalism Network, the Poynter Institute for Media Studies, and many more. Gates is everywhere in the 'Covid' hoax and the man must go to prison – or a mental facility – for the rest of his life and his money distributed to those he has taken such enormous psychopathic pleasure in crushing.

The Muscle

The Hunger Games global structure demands a police-military state – a fusion of the two into one force – which viciously imposes the will of the Cult on the population and protects the Cult from public rebellion. In that regard, too, the 'Covid' hoax just keeps on giving. Often unlawful, ridiculous and contradictory 'Covid' rules and regulations have been policed across the world by moronic automatons and psychopaths made faceless by face-nappy masks and acting like the Nazi SS and fascist blackshirts and brownshirts of Hitler and Mussolini. The smallest departure from the rules decreed by the psychos in government and their clueless gofers were jumped upon by the face-nappy fascists. Brutality against public protestors soon became commonplace even on girls, women and old people as the brave men with the batons – the Face-Nappies as I call them – broke up peaceful protests and handed out fines like confetti to people who couldn't earn a living let alone pay hundreds of pounds for what was once an accepted human right. Robot Face-Nappies of Nottingham police in the English East Midlands fined one group £11,000 for attending a child's birthday party. For decades I charted the transformation of law enforcement as genuine, decent officers were replaced with psychopaths and the brain dead who would happily and brutally do whatever their masters told them. Now they were let loose on the public and I would emphasise the point that none of this just happened. The step-by-step change in the dynamic between police and public was orchestrated from the shadows by

those who knew where this was all going and the same with the perceptual reframing of those in all levels of authority and official administration through 'training courses' by organisations such as Common Purpose which was created in the late 1980s and given a massive boost in Blair era Britain until it became a global phenomenon. Supposed public 'servants' began to view the population as the enemy and the same was true of the police. This was the start of the explosion of behaviour manipulation organisations and networks preparing for the all-war on the human psyche unleashed with the dawn of 2020. I will go into more detail about this later in the book because it is a core part of what is happening.

Police desecrated beauty spots to deter people gathering and arrested women for walking in the countryside alone 'too far' from their homes. We had arrogant, clueless sergeants in the Isle of Wight police where I live posting on Facebook what they insisted the population must do or else. A schoolmaster sergeant called Radford looked young enough for me to ask if his mother knew he was out, but he was posting what he *expected* people to do while a Sergeant Wilkinson boasted about fining lads for meeting in a McDonald's car park where they went to get a lockdown takeaway. Wilkinson added that he had even cancelled their order. What a pair of prats these people are and yet they have increasingly become the norm among Jackboot Johnson's Yellowshirts once known as the British police. This was the theme all over the world with police savagery common during lockdown protests in the United States, the Netherlands, and the fascist state of Victoria in Australia under its tyrannical and again moronic premier Daniel Andrews. Amazing how tyrannical and moronic tend to work as a team and the same combination could be seen across America as arrogant, narcissistic Woke governors and mayors such as Gavin Newsom (California), Andrew Cuomo (New York), Gretchen Whitmer (Michigan), Lori Lightfoot (Chicago) and Eric Garcetti (Los Angeles) did their Nazi and Stalin impressions with the full support of the compliant brutality of their enforcers in uniform as they arrested small business owners defying

fascist shutdown orders and took them to jail in ankle shackles and handcuffs. This happened to bistro owner Marlena Pavlos-Hackney in Gretchen Whitmer's fascist state of Michigan when police arrived to enforce an order by a state-owned judge for 'putting the community at risk' at a time when other states like Texas were dropping restrictions and migrants were pouring across the southern border without any 'Covid' questions at all. I'm sure there are many officers appalled by what they are ordered to do, but not nearly enough of them. If they were truly appalled they would not do it. As the months passed every opportunity was taken to have the military involved to make their presence on the streets ever more familiar and 'normal' for the longer-term goal of police-military fusion.

Another crucial element to the Hunger Games enforcement network has been encouraging the public to report neighbours and others for 'breaking the lockdown rules'. The group faced with £11,000 in fines at the child's birthday party would have been dobbed-in by a neighbour with a brain the size of a pea. The technique was most famously employed by the Stasi secret police in communist East Germany who had public informants placed throughout the population. A police chief in the UK says his force doesn't need to carry out 'Covid' patrols when they are flooded with so many calls from the public reporting other people for visiting the beach. Dorset police chief James Vaughan said people were so enthusiastic about snitching on their fellow humans they were now operating as an auxiliary arm of the police: 'We are still getting around 400 reports a week from the public, so we will respond to reports …We won't need to be doing hotspot patrols because people are very quick to pick the phone up and tell us.' Vaughan didn't say that this is a pillar of all tyrannies of whatever complexion and the means to hugely extend the reach of enforcement while spreading distrust among the people and making them wary of doing anything that might get them reported. Those narcissistic Isle of Wight sergeants Radford and Wilkinson never fail to add a link to their Facebook posts where the public can inform on their fellow slaves.

Neither would be self-aware enough to realise they were imitating the Stasi which they might well never have heard of. Government psychologists that I will expose later laid out a policy to turn communities against each other in the same way.

A coincidence? Yep, and I can knit fog

I knew from the start of the alleged pandemic that this was a Cult operation. It presented limitless potential to rapidly advance the Cult agenda and exploit manipulated fear to demand that every man, woman and child on the planet was 'vaccinated' in a process never used on humans before which infuses self-replicating *synthetic* material into human cells. Remember the plan to transform the human body from a biological to a synthetic biological state. I'll deal with the 'vaccine' (that's not actually a vaccine) when I focus on the genetic agenda. Enough to say here that mass global 'vaccination' justified by this 'new virus' set alarms ringing after 30 years of tracking these people and their methods. The 'Covid' hoax officially beginning in China was also a big red flag for reasons I will be explaining. The agenda potential was so enormous that I could dismiss any idea that the 'virus' appeared naturally. Major happenings with major agenda implications never occur without Cult involvement in making them happen. My questions were twofold in early 2020 as the media began its campaign to induce global fear and hysteria: Was this alleged infectious agent released on purpose by the Cult or did it even exist at all? I then did what I always do in these situations. I sat, observed and waited to see where the evidence and information would take me. By March and early April synchronicity was strongly – and ever more so since then – pointing me in the direction of *there is no 'virus'*. I went public on that with derision even from swathes of the alternative media that voiced a scenario that the Chinese government released the 'virus' in league with Deep State elements in the United States from a top-level bio-lab in Wuhan where the 'virus' is said to have first appeared. I looked at that possibility, but I didn't buy it for several reasons. Deaths from the 'virus' did not in any way match what they

would have been with a 'deadly bioweapon' and it is much more effective if you sell the *illusion* of an infectious agent rather than having a real one unless you can control through injection who has it and who doesn't. Otherwise you lose control of events. A made-up 'virus' gives you a blank sheet of paper on which you can make it do whatever you like and have any symptoms or mutant 'variants' you choose to add while a real infectious agent would limit you to what it actually does. A phantom disease allows you to have endless ludicrous 'studies' on the 'Covid' dollar to widen the perceived impact by inventing ever more 'at risk' groups including one study which said those who walk slowly may be almost four times more likely to die from the 'virus'. People are in psychiatric wards for less.

A real 'deadly bioweapon' can take out people in the hierarchy that are not part of the Cult, but essential to its operation. Obviously they don't want that. Releasing a real disease means you immediately lose control of it. Releasing an illusory one means you don't. Again it's vital that people are extra careful when dealing with what they want to hear. A bioweapon unleashed from a Chinese laboratory in collusion with the American Deep State may fit a conspiracy narrative, but is it true? Would it not be far more effective to use the excuse of a 'virus' to justify the real bioweapon – the 'vaccine'? That way your disease agent does not have to be transmitted and arrives directly through a syringe. I saw a French virologist Luc Montagnier quoted in the alternative media as saying he had discovered that the alleged 'new' severe acute respiratory syndrome coronavirus , or SARS-CoV-2, was made artificially and included elements of the human immunodeficiency 'virus' (HIV) and a parasite that causes malaria. SARS-CoV-2 is alleged to trigger an alleged illness called Covid-19. I remembered Montagnier's name from my research years before into claims that an HIV 'retrovirus' causes AIDs – claims that were demolished by Berkeley virologist Peter Duesberg who showed that no one had ever proved that HIV causes acquired immunodeficiency syndrome or AIDS. Claims that become accepted as fact, publicly and medically, with no proof whatsoever are an ever-recurring story that profoundly applies to

'Covid'. Nevertheless, despite the lack of proof, Montagnier's team at the Pasteur Institute in Paris had a long dispute with American researcher Robert Gallo over which of them discovered and isolated the HIV 'virus' and with *no evidence* found it to cause AIDS. You will see later that there is also no evidence that any 'virus' causes any disease or that there is even such a thing as a 'virus' in the way it is said to exist. The claim to have 'isolated' the HIV 'virus' will be presented in its real context as we come to the shocking story – and it is a story – of SARS-CoV-2 and so will Montagnier's assertion that he identified the full SARS-CoV-2 genome.

Hoax in the making

We can pick up the 'Covid' story in 2010 and the publication by the Rockefeller Foundation of a document called 'Scenarios for the Future of Technology and International Development'. The inner circle of the Rockefeller family has been serving the Cult since John D. Rockefeller (1839-1937) made his fortune with Standard Oil. It is less well known that the same Rockefeller – the Bill Gates of his day – was responsible for establishing what is now referred to as 'Big Pharma', the global network of pharmaceutical companies that make outrageous profits dispensing scalpel and drug 'medicine' and are obsessed with pumping vaccines in ever-increasing number into as many human arms and backsides as possible. John D. Rockefeller was the driving force behind the creation of the 'education' system in the United States and elsewhere specifically designed to program the perceptions of generations thereafter. The Rockefeller family donated exceptionally valuable land in New York for the United Nations building and were central in establishing the World Health Organization in 1948 as an agency of the UN which was created from the start as a Trojan horse and stalking horse for world government. Now enter Bill Gates. His family and the Rockefellers have long been extremely close and I have seen genealogy which claims that if you go back far enough the two families fuse into the same bloodline. Gates has said that the Bill and Melinda Gates Foundation was inspired by the Rockefeller Foundation and why not

when both are serving the same Cult? Major tax-exempt foundations are overwhelmingly criminal enterprises in which Cult assets fund the Cult agenda in the guise of 'philanthropy' while avoiding tax in the process. Cult operatives can become mega-rich in their role of front men and women for the psychopaths at the inner core and they, too, have to be psychopaths to knowingly serve such evil. Part of the deal is that a big percentage of the wealth gleaned from representing the Cult has to be spent advancing the ambitions of the Cult and hence you have the Rockefeller Foundation, Bill and Melinda Gates Foundation (and *so* many more) and people like George Soros with his global Open Society Foundations spending their billions in pursuit of global Cult control. Gates is a global public face of the Cult with his interventions in world affairs including Big Tech influence; a central role in the 'Covid' and 'vaccine' scam; promotion of the climate change shakedown; manipulation of education; geoengineering of the skies; and his food-control agenda as the biggest owner of farmland in America, his GMO promotion and through other means. As one writer said: 'Gates monopolizes or wields disproportionate influence over the tech industry, global health and vaccines, agriculture and food policy (including biopiracy and fake food), weather modification and other climate technologies, surveillance, education and media.' The almost limitless wealth secured through Microsoft and other not-allowed-to-fail ventures (including vaccines) has been ploughed into a long, long list of Cult projects designed to enslave the entire human race. Gates and the Rockefellers have been working as one unit with the Rockefeller-established World Health Organization leading global 'Covid' policy controlled by Gates through his mouth-piece Tedros. Gates became the WHO's biggest funder when Trump announced that the American government would cease its donations, but Biden immediately said he would restore the money when he took office in January, 2021. The Gates Foundation (the Cult) owns through limitless funding the world health system and the major players across the globe in the 'Covid' hoax.

Okay, with that background we return to that Rockefeller Foundation document of 2010 headed 'Scenarios for the Future of Technology and International Development' and its 'imaginary' epidemic of a virulent and deadly influenza strain which infected 20 percent of the global population and killed eight million in seven months. The Rockefeller scenario was that the epidemic destroyed economies, closed shops, offices and other businesses and led to governments imposing fierce rules and restrictions that included mandatory wearing of face masks and body-temperature checks to enter communal spaces like railway stations and supermarkets. The document predicted that even after the height of the Rockefeller-envisaged epidemic the authoritarian rule would continue to deal with further pandemics, transnational terrorism, environmental crises and rising poverty. Now you may think that the Rockefellers are our modern-day seers or alternatively, and rather more likely, that they well knew what was planned a few years further on. Fascism had to be imposed, you see, to 'protect citizens from risk and exposure'. The Rockefeller scenario document said:

During the pandemic, national leaders around the world flexed their authority and imposed airtight rules and restrictions, from the mandatory wearing of face masks to body-temperature checks at the entries to communal spaces like train stations and supermarkets. Even after the pandemic faded, this more authoritarian control and oversight of citizens and their activities stuck and even intensified. In order to protect themselves from the spread of increasingly global problems – from pandemics and transnational terrorism to environmental crises and rising poverty – leaders around the world took a firmer grip on power.

At first, the notion of a more controlled world gained wide acceptance and approval. Citizens willingly gave up some of their sovereignty – and their privacy – to more paternalistic states in exchange for greater safety and stability. Citizens were more tolerant, and even eager, for top-down direction and oversight, and national leaders had more latitude to impose order in the ways they saw fit.

In developed countries, this heightened oversight took many forms: biometric IDs for all citizens, for example, and tighter regulation of key industries whose stability was deemed vital to national interests. In many developed countries, enforced cooperation with a suite of new regulations and agreements slowly but steadily restored both order and, importantly, economic growth.

There we have the prophetic Rockefellers in 2010 and three years later came their paper for the Global Health Summit in Beijing, China, when government representatives, the private sector, international organisations and groups met to discuss the next 100 years of 'global health'. The Rockefeller Foundation-funded paper was called 'Dreaming the Future of Health for the Next 100 Years and more prophecy ensued as it described a dystopian future: 'The abundance of data, digitally tracking and linking people may mean the 'death of privacy' and may replace physical interaction with transient, virtual connection, generating isolation and raising questions of how values are shaped in virtual networks.' Next in the 'Covid' hoax preparation sequence came a 'table top' simulation in 2018 for another 'imaginary' pandemic of a disease called Clade X which was said to kill 900 million people. The exercise was organised by the Gates-funded Johns Hopkins University's Center for Health Security in the United States and this is the very same university that has been compiling the disgustingly and systematically erroneous global figures for 'Covid' cases and deaths. Similar Johns Hopkins health crisis scenarios have included the Dark Winter exercise in 2001 and Atlantic Storm in 2005.

Nostradamus 201

For sheer predictive genius look no further prophecy-watchers than the Bill Gates-funded Event 201 held only six weeks before the 'coronavirus pandemic' is supposed to have broken out in China and Event 201 was based on a scenario of a global 'coronavirus pandemic'. Melinda Gates, the great man's missus, told the BBC that he had 'prepared for years' for a coronavirus pandemic which told us what we already knew. Nostradamugates had predicted in a TED talk in 2015 that a pandemic was coming that would kill a lot of people and demolish the world economy. My god, the man is a machine – possibly even literally. Now here he was only weeks before the real thing funding just such a simulated scenario and involving his friends and associates at Johns Hopkins, the World Economic Forum Cult-front of Klaus Schwab, the United Nations,

Johnson & Johnson, major banks, and officials from China and the Centers for Disease Control in the United States. What synchronicity – Johns Hopkins would go on to compile the fraudulent 'Covid' figures, the World Economic Forum and Schwab would push the 'Great Reset' in response to 'Covid', the Centers for Disease Control would be at the forefront of 'Covid' policy in the United States, Johnson & Johnson would produce a 'Covid vaccine', and everything would officially start just weeks later in China. Spooky, eh? They were even accurate in creating a simulation of a 'virus' pandemic because the 'real thing' would also be a simulation. Event 201 was not an exercise preparing for something that might happen; it was a rehearsal for what those in control knew was *going* to happen and very shortly. Hours of this simulation were posted on the Internet and the various themes and responses mirrored what would soon be imposed to transform human society. News stories were inserted and what they said would be commonplace a few weeks later with still more prophecy perfection. Much discussion focused on the need to deal with misinformation and the 'anti-vax movement' which is exactly what happened when the 'virus' arrived – was said to have arrived – in the West.

Cult-owned social media banned criticism and exposure of the official 'virus' narrative and when I said there *was* no 'virus' in early April, 2020, I was banned by one platform after another including YouTube, Facebook and later Twitter. The mainstream broadcast media in Britain was in effect banned from interviewing me by the Tony-Blair-created government broadcasting censor Ofcom headed by career government bureaucrat Melanie Dawes who was appointed just as the 'virus' hoax was about to play out in January, 2020. At the same time the Ickonic media platform was using Vimeo, another ultra-Zionist-owned operation, while our own player was being created and they deleted in an instant hundreds of videos, documentaries, series and shows to confirm their unbelievable vindictiveness. We had copies, of course, and they had to be restored one by one when our player was ready. These people have no class. Sabbatian Facebook promised free advertisements for the Gates-

controlled World Health Organization narrative while deleting 'false claims and conspiracy theories' to stop 'misinformation' about the alleged coronavirus. All these responses could be seen just a short while earlier in the scenarios of Event 201. Extreme censorship was absolutely crucial for the Cult because the official story was so ridiculous and unsupportable by the evidence that it could never survive open debate and the free-flow of information and opinion. If you can't win a debate then don't have one is the Cult's approach throughout history. Facebook's little boy front man – front boy – Mark Zuckerberg equated 'credible and accurate information' with official sources and exposing their lies with 'misinformation'.

Silencing those that can see

The censorship dynamic of Event 201 is now the norm with an army of narrative-supporting 'fact-checker' organisations whose entire reason for being is to tell the public that official narratives are true and those exposing them are lying. One of the most appalling of these 'fact-checkers' is called NewsGuard founded by ultra-Zionist Americans Gordon Crovitz and Steven Brill. Crovitz is a former publisher of *The Wall Street Journal*, former Executive Vice President of Dow Jones, a member of the Council on Foreign Relations (CFR), and on the board of the American Association of Rhodes Scholars. The CFR and Rhodes Scholarships, named after Rothschild agent Cecil Rhodes who plundered the gold and diamonds of South Africa for his masters and the Cult, have featured widely in my books. NewsGuard don't seem to like me for some reason – I really can't think why – and they have done all they can to have me censored and discredited which is, to quote an old British politician, like being savaged by a dead sheep. They are, however, like all in the censorship network, very well connected and funded by organisations themselves funded by, or connected to, Bill Gates. As you would expect with anything associated with Gates NewsGuard has an offshoot called HealthGuard which 'fights online health care hoaxes'. How very kind. Somehow the NewsGuard European Managing Director Anna-Sophie Harling, a remarkably young-

looking woman with no broadcasting experience and little hands-on work in journalism, has somehow secured a position on the 'Content Board' of UK government broadcast censor Ofcom. An executive of an organisation seeking to discredit dissidents of the official narratives is making decisions for the government broadcast 'regulator' about content?? Another appalling 'fact-checker' is Full Fact funded by George Soros and global censors Google and Facebook.

It's amazing how many activists in the 'fact-checking', 'anti-hate', arena turn up in government-related positions – people like UK Labour Party activist Imran Ahmed who heads the Center for Countering Digital Hate founded by people like Morgan McSweeney, now chief of staff to the Labour Party's hapless and useless 'leader' Keir Starmer. Digital Hate – which is what it really is – uses the American spelling of Center to betray its connection to a transatlantic network of similar organisations which in 2020 shapeshifted from attacking people for 'hate' to attacking them for questioning the 'Covid' hoax and the dangers of the 'Covid vaccine'. It's just a coincidence, you understand. This is one of Imran Ahmed's hysterical statements: 'I would go beyond calling anti-vaxxers conspiracy theorists to say they are an extremist group that pose a national security risk.' No one could ever accuse this prat of understatement and he's including in that those parents who are now against vaccines after their children were damaged for life or killed by them. He's such a nice man. Ahmed does the rounds of the Woke media getting soft-ball questions from spineless 'journalists' who never ask what right he has to campaign to destroy the freedom of speech of others while he demands it for himself. There also seems to be an overrepresentation in Ofcom of people connected to the narrative-worshipping BBC. This incredible global network of narrative-support was super-vital when the 'Covid' hoax was played in the light of the mega-whopper lies that have to be defended from the spotlight cast by the most basic intelligence.

Setting the scene

The Cult plays the long game and proceeds step-by-step ensuring that everything is in place before major cards are played and they don't come any bigger than the 'Covid' hoax. The psychopaths can't handle events where the outcome isn't certain and as little as possible – preferably nothing – is left to chance. Politicians, government and medical officials who would follow direction were brought to illusory power in advance by the Cult web whether on the national stage or others like state governors and mayors of America. For decades the dynamic between officialdom, law enforcement and the public was changed from one of service to one of control and dictatorship. Behaviour manipulation networks established within government were waiting to impose the coming 'Covid' rules and regulations specifically designed to subdue and rewire the psyche of the people in the guise of protecting health. These included in the UK the Behavioural Insights Team part-owned by the British government Cabinet Office; the Scientific Pandemic Insights Group on Behaviours (SPI-B); and a whole web of intelligence and military groups seeking to direct the conversation on social media and control the narrative. Among them are the cyberwarfare (on the people) 77th Brigade of the British military which is also coordinated through the Cabinet Office as civilian and military leadership continues to combine in what they call the Fusion Doctrine. The 77th Brigade is a British equivalent of the infamous Israeli (Sabbatian) military cyberwarfare and Internet manipulation operation Unit 8200 which I expose at length in *The Trigger*. Also carefully in place were the medical and science advisers to government – many on the payroll past or present of Bill Gates – and a whole alternative structure of unelected government stood by to take control when elected parliaments were effectively closed down once the 'Covid' card was slammed on the table. The structure I have described here and so much more was installed in every major country through the Cult networks. The top-down control hierarchy looks like this: The Cult – Cult-owned Gates – the World Health Organization and Tedros – Gates-funded or controlled chief medical officers and science 'advisers' (dictators) in each country –

political 'leaders'– law enforcement – The People. Through this simple global communication and enforcement structure the policy of the Cult could be imposed on virtually the entire human population so long as they acquiesced to the fascism. With everything in place it was time for the button to be pressed in late 2019/early 2020.

These were the prime goals the Cult had to secure for its will to prevail:

1) Locking down economies, closing all but designated 'essential' businesses (Cult-owned corporations were 'essential'), and putting the population under house arrest was an imperative to destroy independent income and employment and ensure dependency on the Cult-controlled state in the Hunger Games Society. Lockdowns had to be established as the global blueprint from the start to respond to the 'virus' and followed by pretty much the entire world.

2) The global population had to be terrified into believing in a deadly 'virus' that didn't actually exist so they would unquestioningly obey authority in the belief that authority must know how best to protect them and their families. Software salesman Gates would suddenly morph into the world's health expert and be promoted as such by the Cult-owned media.

3) A method of testing that wasn't testing for the 'virus', but was only claimed to be, had to be in place to provide the illusion of 'cases' and subsequent 'deaths' that had a very different cause to the 'Covid-19' that would be scribbled on the death certificate.

4) Because there was no 'virus' and the great majority testing positive with a test not testing for the 'virus' would have no symptoms of anything the lie had to be sold that people without symptoms (without the 'virus') could still pass it on to others. This was crucial to justify for the first time quarantining – house arresting – healthy people. Without this the economy-destroying lockdown of *everybody* could not have been credibly sold.

5) The 'saviour' had to be seen as a vaccine which beyond evil drug companies were working like angels of mercy to develop as quickly as possible, with all corners cut, to save the day. The public must absolutely not know that the 'vaccine' had nothing to do with a 'virus' or that the contents were ready and waiting with a very different motive long before the 'Covid' card was even lifted from the pack.

I said in March, 2020, that the 'vaccine' would have been created way ahead of the 'Covid' hoax which justified its use and the following December an article in the New York *Intelligencer* magazine said the Moderna 'vaccine' had been 'designed' by

January, 2020. This was 'before China had even acknowledged that the disease could be transmitted from human to human, more than a week before the first confirmed coronavirus case in the United States'. The article said that by the time the first American death was announced a month later 'the vaccine had already been manufactured and shipped to the National Institutes of Health for the beginning of its Phase I clinical trial'. The 'vaccine' was actually 'designed' long before that although even with this timescale you would expect the article to ask how on earth it could have been done that quickly. Instead it asked why the 'vaccine' had not been rolled out then and not months later. Journalism in the mainstream is truly dead. I am going to detail in the next chapter why the 'virus' has never existed and how a hoax on that scale was possible, but first the foundation on which the Big Lie of 'Covid' was built.

The test that doesn't test

Fraudulent 'testing' is the bottom line of the whole 'Covid' hoax and was the means by which a 'virus' that did not exist *appeared* to exist. They could only achieve this magic trick by using a test not testing for the 'virus'. To use a test that *was* testing for the 'virus' would mean that every test would come back negative given there was no 'virus'. They chose to exploit something called the RT-PCR test invented by American biochemist Kary Mullis in the 1980s who said publicly that his PCR test … *cannot detect infectious disease*. Yes, the 'test' used worldwide to detect infectious 'Covid' to produce all the illusory 'cases' and 'deaths' compiled by Johns Hopkins and others *cannot detect infectious disease*. This fact came from the mouth of the man who invented PCR and was awarded the Nobel Prize in Chemistry in 1993 for doing so. Sadly, and incredibly conveniently for the Cult, Mullis died in August, 2019, at the age of 74 just before his test would be fraudulently used to unleash fascism on the world. He was said to have died from pneumonia which was an irony in itself. A few months later he would have had 'Covid-19' on his death certificate. I say the timing of his death was convenient because had he lived Mullis, a brilliant, honest and decent man, would have been

vociferously speaking out against the use of his test to detect 'Covid' when it was never designed, or able, to do that. I know that to be true given that Mullis made the same point when his test was used to 'detect' – not detect – HIV. He had been seriously critical of the Gallo/Montagnier claim to have isolated the HIV 'virus' and shown it to cause AIDS for which Mullis said there was no evidence. AIDS is actually not a disease but a series of diseases from which people die all the time. When they die from those *same diseases* after a positive 'test' for HIV then AIDS goes on their death certificate. I think I've heard that before somewhere. Countries instigated a policy with 'Covid' that anyone who tested positive with a test not testing for the 'virus' and died of any other cause within 28 days and even longer 'Covid-19' had to go on the death certificate. Cases have come from the test that can't test for infectious disease and the deaths are those who have died of *anything* after testing positive with a test not testing for the 'virus'. I'll have much more later about the death certificate scandal.

Mullis was deeply dismissive of the now US 'Covid' star Anthony Fauci who he said was a liar who didn't know anything about anything – 'and I would say that to his face – nothing.' He said of Fauci: 'The man thinks he can take a blood sample, put it in an electron microscope and if it's got a virus in there you'll know it – he doesn't understand electron microscopy and he doesn't understand medicine and shouldn't be in a position like he's in.' That position, terrifyingly, has made him the decider of 'Covid' fascism policy on behalf of the Cult in his role as director since 1984 of the National Institute of Allergy and Infectious Diseases (NIAID) while his record of being wrong is laughable; but being wrong, so long as it's the *right kind* of wrong, is why the Cult loves him. He'll say anything the Cult tells him to say. Fauci was made Chief Medical Adviser to the President immediately Biden took office. Biden was installed in the White House by Cult manipulation and one of his first decisions was to elevate Fauci to a position of even more control. This is a coincidence? Yes, and I identify as a flamenco dancer called Lola. How does such an incompetent criminal like Fauci remain in that

pivotal position in American health since *the 1980s*? When you serve the Cult it looks after you until you are surplus to requirements. Kary Mullis said prophetically of Fauci and his like: 'Those guys have an agenda and it's not an agenda we would like them to have … they make their own rules, they change them when they want to, and Tony Fauci does not mind going on television in front of the people who pay his salary and lie directly into the camera.' Fauci has done that almost daily since the 'Covid' hoax began. Lying is in Fauci's DNA. To make the situation crystal clear about the PCR test this is a direct quote from its inventor Kary Mullis:

> It [the PCR test] doesn't tell you that you're sick and doesn't tell you that the thing you ended up with was really going to hurt you ...'

Ask yourself why governments and medical systems the world over have been using this very test to decide who is 'infected' with the SARS-CoV-2 'virus' and the alleged disease it allegedly causes, 'Covid-19'. The answer to that question will tell you what has been going on. By the way, here's a little show-stopper – the 'new' SARS-CoV-2 'virus' was 'identified' as such right from the start using … *the PCR test not testing for the 'virus'*. If you are new to this and find that shocking then stick around. I have hardly started yet. Even worse, other 'tests', like the 'Lateral Flow Device' (LFD), are considered so useless that they have to be *confirmed* by the PCR test! Leaked emails written by Ben Dyson, adviser to UK 'Health' Secretary Matt Hancock, said they were 'dangerously unreliable'. Dyson, executive director of strategy at the Department of Health, wrote: 'As of today, someone who gets a positive LFD result in (say) London has at best a 25 per cent chance of it being a true positive, but if it is a self-reported test potentially as low as 10 per cent (on an optimistic assumption about specificity) or as low as 2 per cent (on a more pessimistic assumption).' These are the 'tests' that schoolchildren and the public are being urged to have twice a week or more and have to isolate if they get a positive. Each fake positive goes in the statistics as a 'case' no matter how ludicrously inaccurate and the

'cases' drive lockdown, masks and the pressure to 'vaccinate'. The government said in response to the email leak that the 'tests' were accurate which confirmed yet again what shocking bloody liars they are. The real false positive rate is *100 percent* as we'll see. In another 'you couldn't make it up' the UK government agreed to pay £2.8 billion to California's Innova Medical Group to supply the irrelevant lateral flow tests. The company's primary test-making centre is in China. Innova Medical Group, established in March, 2020, is owned by Pasaca Capital Inc, chaired by Chinese-American millionaire Charles Huang who was born in Wuhan.

How it works – and how it doesn't

The RT-PCR test, known by its full title of Polymerase chain reaction, is used across the world to make millions, even billions, of copies of a DNA/RNA genetic information sample. The process is called 'amplification' and means that a tiny sample of genetic material is amplified to bring out the detailed content. I stress that it is not testing for an infectious disease. It is simply amplifying a sample of genetic material. In the words of Kary Mullis: 'PCR is … just a process that's used to make a whole lot of something out of something.' To emphasise the point companies that make the PCR tests circulated around the world to 'test' for 'Covid' warn on the box that it can't be used to detect 'Covid' or infectious disease and is for research purposes only. It's okay, rest for a minute and you'll be fine. This is the test that produces the 'cases' and 'deaths' that have been used to destroy human society. All those global and national medical and scientific 'experts' demanding this destruction to 'save us' *KNOW* that the test is not testing for the 'virus' and the cases and deaths they claim to be real are an almost unimaginable fraud. Every one of them and so many others including politicians and psychopaths like Gates and Tedros must be brought before Nuremburg-type trials and jailed for the rest of their lives. The more the genetic sample is amplified by PCR the more elements of that material become sensitive to the test and by that I don't mean sensitive for a 'virus' but for elements of the genetic material which

is *naturally* in the body or relates to remnants of old conditions of various kinds lying dormant and causing no disease. Once the amplification of the PCR reaches a certain level *everyone* will test positive. So much of the material has been made sensitive to the test that everyone will have some part of it in their body. Even lying criminals like Fauci have said that once PCR amplifications pass 35 cycles everything will be a false positive that cannot be trusted for the reasons I have described. I say, like many proper doctors and scientists, that 100 percent of the 'positives' are false, but let's just go with Fauci for a moment.

He says that any amplification over 35 cycles will produce false positives and yet the US Centers for Disease Control (CDC) and Food and Drug Administration (FDA) have recommended up to *40 cycles* and the National Health Service (NHS) in Britain admitted in an internal document for staff that it was using *45 cycles* of amplification. A long list of other countries has been doing the same and at least one 'testing' laboratory has been using *50 cycles*. Have you ever heard a doctor, medical 'expert' or the media ask what level of amplification has been used to claim a 'positive'. The 'test' comes back 'positive' and so you have the 'virus', end of story. Now we can see how the government in Tanzania could send off samples from a goat and a pawpaw fruit under human names and both came back positive for 'Covid-19'. Tanzania president John Magufuli mocked the 'Covid' hysteria, the PCR test and masks and refused to import the DNA-manipulating 'vaccine'. The Cult hated him and an article sponsored by the Bill Gates Foundation appeared in the London *Guardian* in February, 2021, headed 'It's time for Africa to rein in Tanzania's anti-vaxxer president'. Well, 'reined in' he shortly was. Magufuli appeared in good health, but then, in March, 2021, he was dead at 61 from 'heart failure'. He was replaced by Samia Hassan Suhulu who is connected to Klaus Schwab's World Economic Forum and she immediately reversed Magufuli's 'Covid' policy. A sample of cola tested positive for 'Covid' with the PCR test in Germany while American actress and singer-songwriter Erykah Badu tested positive in one nostril and negative in the other. Footballer Ronaldo called

the PCR test 'bullshit' after testing positive three times and being forced to quarantine and miss matches when there was nothing wrong with him. The mantra from Tedros at the World Health Organization and national governments (same thing) has been test, test, test. They know that the more tests they can generate the more fake 'cases' they have which go on to become 'deaths' in ways I am coming to. The UK government has its Operation Moonshot planned to test multiple millions every day in workplaces and schools with free tests for everyone to use twice a week at home in line with the Cult plan from the start to make testing part of life. A government advertisement for an 'Interim Head of Asymptomatic Testing Communication' said the job included responsibility for delivering a 'communications strategy' (propaganda) 'to support the expansion of asymptomatic testing that *'normalises testing as part of everyday life*'. More tests means more fake 'cases', 'deaths' and fascism. I have heard of, and from, many people who booked a test, couldn't turn up, and yet got a positive result through the post for a test they'd never even had. The whole thing is crazy, but for the Cult there's method in the madness. Controlling and manipulating the level of amplification of the test means the authorities can control whenever they want the number of apparent 'cases' and 'deaths'. If they want to justify more fascist lockdown and destruction of livelihoods they keep the amplification high. If they want to give the illusion that lockdowns and the 'vaccine' are working then they lower the amplification and 'cases' and 'deaths' will appear to fall. In January, 2021, the Cult-owned World Health Organization suddenly warned laboratories about over-amplification of the test and to lower the threshold. Suddenly headlines began appearing such as: 'Why ARE "Covid" cases plummeting?' This was just when the vaccine rollout was underway and I had predicted months before they would make cases appear to fall through amplification tampering when the 'vaccine' came. These people are so predictable.

Cow vaccines?

The question must be asked of what is on the test swabs being poked far up the nose of the population to the base of the brain? A nasal swab punctured one woman's brain and caused it to leak fluid. Most of these procedures are being done by people with little training or medical knowledge. Dr Lorraine Day, former orthopaedic trauma surgeon and Chief of Orthopaedic Surgery at San Francisco General Hospital, says the tests are really a *'vaccine'*. Cows have long been vaccinated this way. She points out that masks have to cover the nose and the mouth where it is claimed the 'virus' exists in saliva. Why then don't they take saliva from the mouth as they do with a DNA test instead of pushing a long swab up the nose towards the brain? The ethmoid bone separates the nasal cavity from the brain and within that bone is the cribriform plate. Dr Day says that when the swab is pushed up against this plate and twisted the procedure is 'depositing things back there'. She claims that among these 'things' are nanoparticles that can enter the brain. Researchers have noted that a team at the Gates-funded Johns Hopkins have designed tiny, star-shaped micro-devices that can latch onto intestinal mucosa and release drugs into the body. Mucosa is the thin skin that covers the inside surface of parts of the body such as *the nose* and mouth and produces mucus to protect them. The Johns Hopkins micro-devices are called 'theragrippers' and were 'inspired' by a parasitic worm that digs its sharp teeth into a host's intestines. Nasal swabs are also coated in the sterilisation agent ethylene oxide. The US National Cancer Institute posts this explanation on its website:

> At room temperature, ethylene oxide is a flammable colorless gas with a sweet odor. It is used primarily to produce other chemicals, including antifreeze. In smaller amounts, ethylene oxide is used as a pesticide and a sterilizing agent. The ability of ethylene oxide to damage DNA makes it an effective sterilizing agent but also accounts for its cancer-causing activity.

The Institute mentions lymphoma and leukaemia as cancers most frequently reported to be associated with occupational exposure to ethylene oxide along with stomach and breast cancers. How does anyone think this is going to work out with the constant testing

regime being inflicted on adults and children at home and at school that will accumulate in the body anything that's on the swab?

Doctors know best

It is vital for people to realise that 'hero' doctors 'know' only what the Big Pharma-dominated medical authorities tell them to 'know' and if they refuse to 'know' what they are told to 'know' they are out the door. They are mostly not physicians or healers, but repeaters of the official narrative – or else. I have seen alleged professional doctors on British television make shocking statements that we are supposed to take seriously. One called 'Dr' Amir Khan, who is actually telling patients how to respond to illness, said that men could take the birth pill to 'help slow down the effects of Covid-19'. In March, 2021, another ridiculous 'Covid study' by an American doctor proposed injecting men with the female sex hormone progesterone as a 'Covid' treatment. British doctor Nighat Arif told the BBC that face coverings were now going to be part of ongoing normal. Yes, the vaccine protects you, she said (evidence?) … but the way to deal with viruses in the community was always going to come down to hand washing, face covering and keeping a physical distance. That's not what we were told before the 'vaccine' was circulating. Arif said she couldn't imagine ever again going on the underground or in a lift without a mask. I was just thanking my good luck that she was not my doctor when she said – in March, 2021 – that if 'we are *behaving* and we are doing all the right things' she thought we could 'have our nearest and dearest around us at home … around *Christmas* and N*ew Year!* Her patronising delivery was the usual school teacher talking to six-year-olds as she repeated every government talking point and probably believed them all. If we have learned anything from the 'Covid' experience surely it must be that humanity's perception of doctors needs a fundamental rethink. NHS 'doctor' Sara Kayat told her television audience that the 'Covid vaccine' would '100 percent prevent hospitalisation and death'. Not even Big Pharma claimed that. We have to stop taking 'experts' at their word without question when so many of them are

clueless and only repeating the party line on which their careers depend. That is not to say there are not brilliants doctors – there are and I have spoken to many of them since all this began – but you won't see them in the mainstream media or quoted by the psychopaths and yes-people in government.

Remember the name – Christian Drosten

German virologist Christian Drosten, Director of Charité Institute of Virology in Berlin, became a national star after the pandemic hoax began. He was feted on television and advised the German government on 'Covid' policy. Most importantly to the wider world Drosten led a group that produced the 'Covid' testing protocol for the PCR test. What a remarkable feat given the PCR cannot test for infectious disease and even more so when you think that Drosten said that his method of testing for SARS-CoV-2 was developed 'without having virus material available'. *He developed a test for a 'virus' that he didn't have and had never seen*. Let that sink in as you survey the global devastation that came from what he did. The whole catastrophe of Drosten's 'test' was based on the alleged genetic sequence published by Chinese scientists on the Internet. We will see in the next chapter that this alleged 'genetic sequence' has never been produced by China or anyone and cannot be when there *is no* SARS-CoV-2. Drosten, however, doesn't seem to let little details like that get in the way. He was the lead author with Victor Corman from the same Charité Hospital of the paper 'Detection of 2019 novel coronavirus (2019-nCoV) by real-time PCR' published in a magazine called *Eurosurveillance*. This became known as the Corman-Drosten paper. In November, 2020, with human society devastated by the effects of the Corman-Drosten test baloney, the protocol was publicly challenged by 22 international scientists and independent researchers from Europe, the United States, and Japan. Among them were senior molecular geneticists, biochemists, immunologists, and microbiologists. They produced a document headed 'External peer review of the RTPCR test to detect SARS-Cov-2 Reveals 10 Major Flaws At The Molecular and Methodological Level: Consequences

For False-Positive Results'. The flaws in the Corman-Drosten test included the following:

- The test is non-specific because of erroneous design
- Results are enormously variable
- The test is unable to discriminate between the whole 'virus' and viral fragments
- It doesn't have positive or negative controls
- The test lacks a standard operating procedure
- It is unsupported by proper peer view

The scientists said the PCR 'Covid' testing protocol was not founded on science and they demanded the Corman-Drosten paper be retracted by *Eurosurveillance*. They said all present and previous Covid deaths, cases, and 'infection rates' should be subject to a massive retroactive inquiry. Lockdowns and travel restrictions should be reviewed and relaxed and those diagnosed through PCR to have 'Covid-19' should not be forced to isolate. Dr Kevin Corbett, a health researcher and nurse educator with a long academic career producing a stream of peer-reviewed publications at many UK universities, made the same point about the PCR test debacle. He said of the scientists' conclusions: 'Every scientific rationale for the development of that test has been totally destroyed by this paper. It's like Hiroshima/Nagasaki to the Covid test.' He said that China hadn't given them an isolated 'virus' when Drosten developed the test. Instead they had developed the test from *a sequence in a gene bank*.' Put another way … *they made it up*! The scientists were supported in this contention by a Portuguese appeals court which ruled in November, 2020, that PCR tests are unreliable and it is unlawful to quarantine people based solely on a PCR test. The point about China not providing an isolated virus must be true when the 'virus' has never been isolated to this day and the consequences of that will become clear. Drosten and company produced this useless 'protocol' right on cue in January, 2020, just as the 'virus' was said to

be moving westward and it somehow managed to successfully pass a peer-review in 24 hours. In other words there was no peer-review for a test that would be used to decide who had 'Covid' and who didn't across the world. The Cult-created, Gates-controlled World Health Organization immediately recommended all its nearly 200 member countries to use the Drosten PCR protocol to detect 'cases' and 'deaths'. The sting was underway and it continues to this day.

So who is this Christian Drosten that produced the means through which death, destruction and economic catastrophe would be justified? His education background, including his doctoral thesis, would appear to be somewhat shrouded in mystery and his track record is dire as with another essential player in the 'Covid' hoax, the Gates-funded Professor Neil Ferguson at the Gates-funded Imperial College in London of whom more shortly. Drosten predicted in 2003 that the alleged original SARS 'virus' (SARS-1') was an epidemic that could have serious effects on economies and an effective vaccine would take at least two years to produce. Drosten's answer to every alleged 'outbreak' is a vaccine which you won't be shocked to know. What followed were just 774 official deaths worldwide and none in Germany where there were only nine cases. That is even if you believe there ever was a SARS 'virus' when the evidence is zilch and I will expand on this in the next chapter. Drosten claims to be co-discoverer of 'SARS-1' and developed a test for it in 2003. He was screaming warnings about 'swine flu' in 2009 and how it was a widespread infection far more severe than any dangers from a vaccine could be and people should get vaccinated. It would be helpful for Drosten's vocal chords if he simply recorded the words 'the virus is deadly and you need to get vaccinated' and copies could be handed out whenever the latest made-up threat comes along. Drosten's swine flu epidemic never happened, but Big Pharma didn't mind with governments spending hundreds of millions on vaccines that hardly anyone bothered to use and many who did wished they hadn't. A study in 2010 revealed that the risk of dying from swine flu, or H1N1, was no higher than that of the annual seasonal flu which is what at least most of 'it' really was as in

the case of 'Covid-19'. A media investigation into Drosten asked how with such a record of inaccuracy he could be *the* government adviser on these issues. The answer to that question is the same with Drosten, Ferguson and Fauci – they keep on giving the authorities the 'conclusions' and 'advice' they want to hear. Drosten certainly produced the goods for them in January, 2020, with his PCR protocol garbage and provided the foundation of what German internal medicine specialist Dr Claus Köhnlein, co-author of *Virus Mania*, called the 'test pandemic'. The 22 scientists in the *Eurosurveillance* challenge called out conflicts of interest within the Drosten 'protocol' group and with good reason. Olfert Landt, a regular co-author of Drosten 'studies', owns the biotech company TIB Molbiol Syntheselabor GmbH in Berlin which manufactures and sells the tests that Drosten and his mates come up with. They have done this with SARS, Enterotoxigenic E. coli (ETEC), MERS, Zika 'virus', yellow fever, and now 'Covid'. Landt told the *Berliner Zeitung* newspaper:

> The testing, design and development came from the Charité [Drosten and Corman]. We simply implemented it immediately in the form of a kit. And if we don't have the virus, which originally only existed in Wuhan, we can make a synthetic gene to simulate the genome of the virus. That's what we did very quickly.

This is more confirmation that the Drosten test was designed without access to the 'virus' and only a synthetic simulation which is what SARS-CoV-2 really is – a computer-generated synthetic fiction. It's quite an enterprise they have going here. A Drosten team decides what the test for something should be and Landt's biotech company flogs it to governments and medical systems across the world. His company must have made an absolute fortune since the 'Covid' hoax began. Dr Reiner Fuellmich, a prominent German consumer protection trial lawyer in Germany and California, is on Drosten's case and that of Tedros at the World Health Organization for crimes against humanity with a class-action lawsuit being prepared in the United States and other legal action in Germany.

Why China?

Scamming the world with a 'virus' that doesn't exist would seem impossible on the face of it, but not if you have control of the relatively few people that make policy decisions and the great majority of the global media. Remember it's not about changing 'real' reality it's about controlling *perception* of reality. You don't have to make something happen you only have make people *believe* that it's happening. Renegade Minds understand this and are therefore much harder to swindle. 'Covid-19' is not a 'real' 'virus'. It's a mind virus, like a computer virus, which has infected the minds, not the bodies, of billions. It all started, publically at least, in China and that alone is of central significance. The Cult was behind the revolution led by its asset Mao Zedong, or Chairman Mao, which established the People's Republic of China on October 1st, 1949. It should have been called The Cult's Republic of China, but the name had to reflect the recurring illusion that vicious dictatorships are run by and for the people (see all the 'Democratic Republics' controlled by tyrants). In the same way we have the 'Biden' Democratic Republic of America officially ruled by a puppet tyrant (at least temporarily) on behalf of Cult tyrants. The creation of Mao's merciless communist/fascist dictatorship was part of a frenzy of activity by the Cult at the conclusion of World War Two which, like the First World War, it had instigated through its assets in Germany, Britain, France, the United States and elsewhere. Israel was formed in 1948; the Soviet Union expanded its 'Iron Curtain' control, influence and military power with the Warsaw Pact communist alliance in 1955; the United Nations was formed in 1945 as a Cult precursor to world government; and a long list of world bodies would be established including the World Health Organization (1948), World Trade Organization (1948 under another name until 1995), International Monetary Fund (1945) and World Bank (1944). Human society was redrawn and hugely centralised in the global Problem-Reaction-Solution that was World War Two. All these changes were significant. Israel would become the headquarters of the Sabbatians

and the revolution in China would prepare the ground and control system for the events of 2019/2020.

Renegade Minds know there are no borders except for public consumption. The Cult is a seamless, borderless global entity and to understand the game we need to put aside labels like borders, nations, countries, communism, fascism and democracy. These delude the population into believing that countries are ruled within their borders by a government of whatever shade when these are mere agencies of a global power. America's illusion of democracy and China's communism/fascism are subsidiaries – vehicles – for the same agenda. We may hear about conflict and competition between America and China and on the lower levels that will be true; but at the Cult level they are branches of the same company in the way of the McDonald's example I gave earlier. I have tracked in the books over the years support by US governments of both parties for Chinese Communist Party infiltration of American society through allowing the sale of land, even military facilities, and the acquisition of American business and university influence. All this is underpinned by the infamous stealing of intellectual property and technological know-how. Cult-owned Silicon Valley corporations waive their fraudulent 'morality' to do business with human-rights-free China; Cult-controlled Disney has become China's PR department; and China in effect owns 'American' sports such as basketball which depends for much of its income on Chinese audiences. As a result any sports player, coach or official speaking out against China's horrific human rights record is immediately condemned or fired by the China-worshipping National Basketball Association. One of the first acts of China-controlled Biden was to issue an executive order telling federal agencies to stop making references to the 'virus' by the 'geographic location of its origin'. Long-time Congressman Jerry Nadler warned that criticising China, America's biggest rival, leads to hate crimes against Asian people in the United States. So shut up you bigot. China is fast closing in on Israel as a country that must not be criticised which is apt, really, given that Sabbatians control them both. The two countries have

developed close economic, military, technological and strategic ties which include involvement in China's 'Silk Road' transport and economic initiative to connect China with Europe. Israel was the first country in the Middle East to recognise the establishment of Mao's tyranny in 1950 months after it was established.

Project Wuhan – the 'Covid' Psyop

I emphasise again that the Cult plays the long game and what is happening to the world today is the result of centuries of calculated manipulation following a script to take control step-by-step of every aspect of human society. I will discuss later the common force behind all this that has spanned those centuries and thousands of years if the truth be told. Instigating the Mao revolution in China in 1949 with a 2020 'pandemic' in mind is not only how they work – the 71 years between them is really quite short by the Cult's standards of manipulation preparation. The reason for the Cult's Chinese revolution was to create a fiercely-controlled environment within which an extreme structure for human control could be incubated to eventually be unleashed across the world. We have seen this happen since the 'pandemic' emerged from China with the Chinese control-structure founded on AI technology and tyrannical enforcement sweep across the West. Until the moment when the Cult went for broke in the West and put its fascism on public display Western governments had to pay some lip-service to freedom and democracy to not alert too many people to the tyranny-in-the-making. Freedoms were more subtly eroded and power centralised with covert government structures put in place waiting for the arrival of 2020 when that smokescreen of 'freedom' could be dispensed with. The West was not able to move towards tyranny before 2020 anything like as fast as China which was created as a tyranny and had no limits on how fast it could construct the Cult's blueprint for global control. When the time came to impose that structure on the world it was the same Cult-owned Chinese communist/fascist government that provided the excuse – the 'Covid pandemic'. It was absolutely crucial to the Cult plan for the Chinese response to the 'pandemic' –

draconian lockdowns of the entire population – to become the blueprint that Western countries would follow to destroy the livelihoods and freedom of their people. This is why the Cult-owned, Gates-owned, WHO Director-General Tedros said early on:

The Chinese government is to be congratulated for the extraordinary measures it has taken to contain the outbreak. China is actually setting a new standard for outbreak response and it is not an exaggeration.

Forbes magazine said of China: '… those measures protected untold millions from getting the disease'. The Rockefeller Foundation 'epidemic scenario' document in 2010 said 'prophetically':

However, a few countries did fare better – China in particular. The Chinese government's quick imposition and enforcement of mandatory quarantine for all citizens, as well as its instant and near-hermetic sealing off of all borders, saved millions of lives, stopping the spread of the virus far earlier than in other countries and enabling a swifter post-pandemic recovery.

Once again – *spooky*.

The first official story was the 'bat theory' or rather the bat diversion. The source of the 'virus outbreak' we were told was a ''wet market' in Wuhan where bats and other animals are bought and eaten in horrifically unhygienic conditions. Then another story emerged through the alternative media that the 'virus' had been released on purpose or by accident from a BSL-4 (biosafety level 4) laboratory in Wuhan not far from the wet market. The lab was reported to create and work with lethal concoctions and bioweapons. Biosafety level 4 is the highest in the World Health Organization system of safety and containment. Renegade Minds are aware of what I call designer manipulation. The ideal for the Cult is for people to buy its prime narrative which in the opening salvoes of the 'pandemic' was the wet market story. It knows, however, that there is now a considerable worldwide alternative media of researchers sceptical of anything governments say and they are often given a version of events in a form they can perceive as credible while misdirecting them from the real truth. In this case let them

think that the conspiracy involved is a 'bioweapon virus' released from the Wuhan lab to keep them from the real conspiracy – *there is no 'virus'*. The WHO's current position on the source of the outbreak at the time of writing appears to be: 'We haven't got a clue, mate.' This is a good position to maintain mystery and bewilderment. The inner circle will know where the 'virus' came from – *nowhere*. The bottom line was to ensure the public believed there *was* a 'virus' and it didn't much matter if they thought it was natural or had been released from a lab. The belief that there was a 'deadly virus' was all that was needed to trigger global panic and fear. The population was terrified into handing their power to authority and doing what they were told. They had to or they were 'all gonna die'.

In March, 2020, information began to come my way from real doctors and scientists and my own additional research which had my intuition screaming: 'Yes, that's it! *There is no virus*.' The 'bioweapon' was not the 'virus'; it was the *'vaccine'* already being talked about that would be the bioweapon. My conclusion was further enhanced by happenings in Wuhan. The 'virus' was said to be sweeping the city and news footage circulated of people collapsing in the street (which they've never done in the West with the same 'virus'). The Chinese government was building 'new hospitals' in a matter of ten days to 'cope with demand' such was the virulent nature of the 'virus'. Yet in what seemed like no time the 'new hospitals' closed – even if they even opened – and China declared itself 'virus-free'. It was back to business as usual. This was more propaganda to promote the Chinese draconian lockdowns in the West as the way to 'beat the virus'. Trouble was that we subsequently had lockdown after lockdown, but never business as usual. As the people of the West and most of the rest of the world were caught in an ever-worsening spiral of lockdown, social distancing, masks, isolated old people, families forced apart, and livelihood destruction, it was party-time in Wuhan. Pictures emerged of thousands of people enjoying pool parties and concerts. It made no sense until you realised there never was a 'virus' and the

whole thing was a Cult set-up to transform human society out of one its major global strongholds – China.

How is it possible to deceive virtually the entire world population into believing there is a deadly virus when there is not even a 'virus' let alone a deadly one? It's nothing like as difficult as you would think and that's clearly true because it happened.

Postscript: See end of book Postscript for more on the 'Wuhan lab virus release' story which the authorities and media were pushing heavily in the summer of 2021 to divert attention from the truth that the 'Covid virus' is pure invention.

CHAPTER FIVE

There *is no* 'virus'

You can fool some of the people all of the time, and all of the people some of the time, but you cannot fool all of the people all of the time
Abraham Lincoln

The greatest form of mind control is repetition. The more you repeat the same mantra of alleged 'facts' the more will accept them to be true. It becomes an 'everyone knows that, mate'. If you can also censor any other version or alternative to your alleged 'facts' you are pretty much home and cooking.

By the start of 2020 the Cult owned the global mainstream media almost in its entirety to spew out its 'Covid' propaganda and ignore or discredit any other information and view. Cult-owned social media platforms in Cult-owned Silicon Valley were poised and ready to unleash a campaign of ferocious censorship to obliterate all but the official narrative. To complete the circle many demands for censorship by Silicon Valley were led by the mainstream media as 'journalists' became full-out enforcers for the Cult both as propagandists and censors. Part of this has been the influx of young people straight out of university who have become 'journalists' in significant positions. They have no experience and a headful of programmed perceptions from their years at school and university at a time when today's young are the most perceptually-targeted generations in known human history given the insidious impact of technology. They enter the media perceptually prepared and ready to repeat the narratives of the system that programmed them to

repeat its narratives. The BBC has a truly pathetic 'specialist disinformation reporter' called Marianna Spring who fits this bill perfectly. She is clueless about the world, how it works and what is really going on. Her role is to discredit anyone doing the job that a proper journalist would do and system-serving hacks like Spring wouldn't dare to do or even see the need to do. They are too busy licking the arse of authority which can never be wrong and, in the case of the BBC propaganda programme, *Panorama*, contacting payments systems such as PayPal to have a donations page taken down for a film company making documentaries questioning vaccines. Even the BBC soap opera *EastEnders* included a disgracefully biased scene in which an inarticulate white working class woman was made to look foolish for questioning the 'vaccine' while a well-spoken black man and Asian woman promoted the government narrative. It ticked every BBC box and the fact that the black and minority community was resisting the 'vaccine' had nothing to do with the way the scene was written. The BBC has become a disgusting tyrannical propaganda and censorship operation that should be defunded and disbanded and a free media take its place with a brief to stop censorship instead of demanding it. A BBC 'interview' with Gates goes something like: 'Mr Gates, sir, if I can call you sir, would you like to tell our audience why you are such a great man, a wonderful humanitarian philanthropist, and why you should absolutely be allowed as a software salesman to decide health policy for approaching eight billion people? Thank you, sir, please sir.' Propaganda programming has been incessant and merciless and when all you hear is the same story from the media, repeated by those around you who have only heard the same story, is it any wonder that people on a grand scale believe absolute mendacious garbage to be true? You are about to see, too, why this level of information control is necessary when the official 'Covid' narrative is so nonsensical and unsupportable by the evidence.

Structure of Deceit

The pyramid structure through which the 'Covid' hoax has been manifested is very simple and has to be to work. As few people as possible have to be involved with full knowledge of what they are doing – and why – or the real story would get out. At the top of the pyramid are the inner core of the Cult which controls Bill Gates who, in turn, controls the World Health Organization through his pivotal funding and his puppet Director-General mouthpiece, Tedros. Before he was appointed Tedros was chair of the Gates-founded Global Fund to 'fight against AIDS, tuberculosis and malaria', a board member of the Gates-funded 'vaccine alliance' GAVI, and on the board of another Gates-funded organisation. Gates owns him and picked him for a specific reason – Tedros is a crook and worse. 'Dr' Tedros (he's not a medical doctor, the first WHO chief not to be) was a member of the tyrannical Marxist government of Ethiopia for decades with all its human rights abuses. He has faced allegations of corruption and misappropriation of funds and was exposed three times for covering up cholera epidemics while Ethiopia's health minister. Tedros appointed the mass-murdering genocidal Zimbabwe dictator Robert Mugabe as a WHO goodwill ambassador for public health which, as with Tedros, is like appointing a psychopath to run a peace and love campaign. The move was so ridiculous that he had to drop Mugabe in the face of widespread condemnation. American economist David Steinman, a Nobel peace prize nominee, lodged a complaint with the International Criminal Court in The Hague over alleged genocide by Tedros when he was Ethiopia's foreign minister. Steinman says Tedros was a 'crucial decision maker' who directed the actions of Ethiopia's security forces from 2013 to 2015 and one of three officials in charge when those security services embarked on the 'killing' and 'torturing' of Ethiopians. You can see where Tedros is coming from and it's sobering to think that he has been the vehicle for Gates and the Cult to direct the global response to 'Covid'. Think about that. A psychopathic Cult dictates to psychopath Gates who dictates to psychopath Tedros who dictates how countries of the world must respond to a 'Covid virus' never scientifically shown to exist. At the same time psychopathic Cult-owned Silicon Valley information

giants like Google, YouTube, Facebook and Twitter announced very early on that they would give the Cult/Gates/Tedros/WHO version of the narrative free advertising and censor those who challenged their intelligence-insulting, mendacious story.

The next layer in the global 'medical' structure below the Cult, Gates and Tedros are the chief medical officers and science 'advisers' in each of the WHO member countries which means virtually all of them. Medical officers and arbiters of science (they're not) then take the WHO policy and recommended responses and impose them on their country's population while the political 'leaders' say they are deciding policy (they're clearly not) by 'following the science' on the advice of the 'experts' – the same medical officers and science 'advisers' (dictators). In this way with the rarest of exceptions the entire world followed the same policy of lockdown, people distancing, masks and 'vaccines' dictated by the psychopathic Cult, psychopathic Gates and psychopathic Tedros who we are supposed to believe give a damn about the health of the world population they are seeking to enslave. That, amazingly, is all there is to it in terms of crucial decision-making. Medical staff in each country then follow like sheep the dictates of the shepherds at the top of the national medical hierarchies – chief medical officers and science 'advisers' who themselves follow like sheep the shepherds of the World Health Organization and the Cult. Shepherds at the national level often have major funding and other connections to Gates and his Bill and Melinda Gates Foundation which carefully hands out money like confetti at a wedding to control the entire global medical system from the WHO down.

Follow the money

Christopher Whitty, Chief Medical Adviser to the UK Government at the centre of 'virus' policy, a senior adviser to the government's Scientific Advisory Group for Emergencies (SAGE), and Executive Board member of the World Health Organization, was gifted a grant of $40 million by the Bill and Melinda Gates Foundation for malaria research in Africa. The BBC described the unelected Whitty as 'the

official who will probably have the greatest impact on our everyday lives of any individual policymaker in modern times' and so it turned out. What Gates and Tedros have said Whitty has done like his equivalents around the world. Patrick Vallance, co-chair of SAGE and the government's Chief Scientific Adviser, is a former executive of Big Pharma giant GlaxoSmithKline with its fundamental financial and business connections to Bill Gates. In September, 2020, it was revealed that Vallance owned a deferred bonus of shares in GlaxoSmithKline worth £600,000 while the company was 'developing' a 'Covid vaccine'. Move along now – nothing to see here – what could possibly be wrong with that? Imperial College in London, a major player in 'Covid' policy in Britain and elsewhere with its 'Covid-19' Response Team, is funded by Gates and has big connections to China while the now infamous Professor Neil Ferguson, the useless 'computer modeller' at Imperial College is also funded by Gates. Ferguson delivered the dramatically inaccurate excuse for the first lockdowns (much more in the next chapter). The Institute for Health Metrics and Evaluation (IHME) in the United States, another source of outrageously false 'Covid' computer models to justify lockdowns, is bankrolled by Gates who is a vehement promotor of lockdowns. America's version of Whitty and Vallance, the again now infamous Anthony Fauci, has connections to 'Covid vaccine' maker Moderna as does Bill Gates through funding from the Bill and Melinda Gates Foundation. Fauci is director of the National Institute of Allergy and Infectious Diseases (NIAID), a major recipient of Gates money, and they are very close. Deborah Birx who was appointed White House Coronavirus Response Coordinator in February, 2020, is yet another with ties to Gates. Everywhere you look at the different elements around the world behind the coordination and decision making of the 'Covid' hoax there is Bill Gates and his money. They include the World Health Organization; Centers for Disease Control (CDC) in the United States; National Institutes of Health (NIH) of Anthony Fauci; Imperial College and Neil Ferguson; the London School of Hygiene where Chris Whitty worked; Regulatory agencies like the UK Medicines & Healthcare products Regulatory Agency (MHRA)

which gave emergency approval for 'Covid vaccines'; Wellcome Trust; GAVI, the Vaccine Alliance; the Coalition for Epidemic Preparedness Innovations (CEPI); Johns Hopkins University which has compiled the false 'Covid' figures; and the World Economic Forum. A Nationalfile.com article said:

> Gates has a lot of pull in the medical world, he has a multi-million dollar relationship with Dr. Fauci, and Fauci originally took the Gates line supporting vaccines and casting doubt on [the drug hydroxychloroquine]. Coronavirus response team member Dr. Deborah Birx, appointed by former president Obama to serve as United States Global AIDS Coordinator, also sits on the board of a group that has received billions from Gates' foundation, and Birx reportedly used a disputed Bill Gates-funded model for the White House's Coronavirus effort. Gates is a big proponent for a population lockdown scenario for the Coronavirus outbreak.

Another funder of Moderna is the Defense Advanced Research Projects Agency (DARPA), the technology-development arm of the Pentagon and one of the most sinister organisations on earth. DARPA had a major role with the CIA covert technology-funding operation In-Q-Tel in the development of Google and social media which is now at the centre of global censorship. Fauci and Gates are extremely close and openly admit to talking regularly about 'Covid' policy, but then why wouldn't Gates have a seat at every national 'Covid' table after his Foundation committed $1.75 billion to the 'fight against Covid-19'. When passed through our Orwellian Translation Unit this means that he has bought and paid for the Cult-driven 'Covid' response worldwide. Research the major 'Covid' response personnel in your own country and you will find the same Gates funding and other connections again and again. Medical and science chiefs following World Health Organization 'policy' sit atop a medical hierarchy in their country of administrators, doctors and nursing staff. These 'subordinates' are told they must work and behave in accordance with the policy delivered from the 'top' of the national 'health' pyramid which is largely the policy delivered by the WHO which is the policy delivered by Gates and the Cult. The whole 'Covid' narrative has been imposed on medical staff by a climate of fear although great numbers don't even need that to comply. They do so through breathtaking levels of ignorance and

include doctors who go through life simply repeating what Big Pharma and their hierarchical masters tell them to say and believe. No wonder Big Pharma 'medicine' is one of the biggest killers on Planet Earth.

The same top-down system of intimidation operates with regard to the Cult Big Pharma cartel which also dictates policy through national and global medical systems in this way. The Cult and Big Pharma agendas are the same because the former controls and owns the latter. 'Health' administrators, doctors, and nursing staff are told to support and parrot the dictated policy or they will face consequences which can include being fired. How sad it's been to see medical staff meekly repeating and imposing Cult policy without question and most of those who can see through the deceit are only willing to speak anonymously off the record. They know what will happen if their identity is known. This has left the courageous few to expose the lies about the 'virus', face masks, overwhelmed hospitals that aren't, and the dangers of the 'vaccine' that isn't a vaccine. When these medical professionals and scientists, some renowned in their field, have taken to the Internet to expose the truth their articles, comments and videos have been deleted by Cult-owned Facebook, Twitter and YouTube. What a real head-shaker to see YouTube videos with leading world scientists and highly qualified medical specialists with an added link underneath to the notorious Cult propaganda website *Wikipedia* to find the 'facts' about the same subject.

HIV – the 'Covid' trial-run

I'll give you an example of the consequences for health and truth that come from censorship and unquestioning belief in official narratives. The story was told by PCR inventor Kary Mullis in his book *Dancing Naked in the Mind Field*. He said that in 1984 he accepted as just another scientific fact that Luc Montagnier of France's Pasteur Institute and Robert Gallo of America's National Institutes of Health had independently discovered that a 'retrovirus' dubbed HIV (human immunodeficiency virus) caused AIDS. They

were, after all, Mullis writes, specialists in retroviruses. This is how the medical and science pyramids work. Something is announced or *assumed* and then becomes an everybody-knows-that purely through repetition of the assumption as if it is fact. Complete crap becomes accepted truth with no supporting evidence and only repetition of the crap. This is how a 'virus' that doesn't exist became the 'virus' that changed the world. The HIV-AIDS fairy story became a multi-billion pound industry and the media poured out propaganda terrifying the world about the deadly HIV 'virus' that caused the lethal AIDS. By then Mullis was working at a lab in Santa Monica, California, to detect retroviruses with his PCR test in blood donations received by the Red Cross. In doing so he asked a virologist where he could find a reference for HIV being the cause of AIDS. 'You don't need a reference,' the virologist said … *'Everybody knows it.'* Mullis said he wanted to quote a reference in the report he was doing and he said he felt a little funny about not knowing the source of such an important discovery when everyone else seemed to. The virologist suggested he cite a report by the Centers for Disease Control and Prevention (CDC) on morbidity and mortality. Mullis read the report, but it only said that an organism had been identified and did not say how. The report did not identify the original scientific work. Physicians, however, *assumed* (key recurring theme) that if the CDC was convinced that HIV caused AIDS then proof must exist. Mullis continues:

I did computer searches. Neither Montagnier, Gallo, nor anyone else had published papers describing experiments which led to the conclusion that HIV probably caused AIDS. I read the papers in Science for which they had become well known as AIDS doctors, but all they had said there was that they had found evidence of a past infection by something which was probably HIV in some AIDS patients.

They found antibodies. Antibodies to viruses had always been considered evidence of past disease, not present disease. Antibodies signaled that the virus had been defeated. The patient had saved himself. There was no indication in these papers that this virus caused a disease. They didn't show that everybody with the antibodies had the disease. In fact they found some healthy people with antibodies.

Mullis asked why their work had been published if Montagnier and Gallo hadn't really found this evidence, and why had they been fighting so hard to get credit for the discovery? He says he was hesitant to write 'HIV is the probable cause of AIDS' until he found published evidence to support that. 'Tens of thousands of scientists and researchers were spending billions of dollars a year doing research based on this idea,' Mullis writes. 'The reason had to be there somewhere; otherwise these people would not have allowed their research to settle into one narrow channel of investigation.' He said he lectured about PCR at numerous meetings where people were always talking about HIV and he asked them how they knew that HIV was the cause of AIDS:

> Everyone said something. Everyone had the answer at home, in the office, in some drawer. They all knew, and they would send me the papers as soon as they got back. But I never got any papers. Nobody ever sent me the news about how AIDS was caused by HIV.

Eventually Mullis was able to ask Montagnier himself about the reference proof when he lectured in San Diego at the grand opening of the University of California AIDS Research Center. Mullis says this was the last time he would ask his question without showing anger. Montagnier said he should reference the CDC report. 'I read it', Mullis said, and it didn't answer the question. 'If Montagnier didn't know the answer who the hell did?' Then one night Mullis was driving when an interview came on National Public Radio with Peter Duesberg, a prominent virologist at Berkeley and a California Scientist of the Year. Mullis says he finally understood why he could not find references that connected HIV to AIDS – *there weren't any!* No one had ever proved that HIV causes AIDS even though it had spawned a multi-billion pound global industry and the media was repeating this as fact every day in their articles and broadcasts terrifying the shit out of people about AIDS and giving the impression that a positive test for HIV (see 'Covid') was a death sentence. Duesberg was a threat to the AIDS gravy train and the agenda that underpinned it. He was therefore abused and castigated after he told the Proceedings of the National Academy of Sciences

there was no good evidence implicating the new 'virus'. Editors rejected his manuscripts and his research funds were deleted. Mullis points out that the CDC has defined AIDS as one of more than 30 diseases *if accompanied* by a positive result on a test that detects antibodies to HIV; but those same diseases are not defined as AIDS cases when antibodies are not detected:

> If an HIV-positive woman develops uterine cancer, for example, she is considered to have AIDS. If she is not HIV positive, she simply has uterine cancer. An HIV-positive man with tuberculosis has AIDS; if he tests negative he simply has tuberculosis. If he lives in Kenya or Colombia, where the test for HIV antibodies is too expensive, he is simply presumed to have the antibodies and therefore AIDS, and therefore he can be treated in the World Health Organization's clinic. It's the only medical help available in some places. And it's free, because the countries that support WHO are worried about AIDS.

Mullis accuses the CDC of continually adding new diseases (see ever more 'Covid symptoms') to the grand AIDS definition and of virtually doctoring the books to make it appear as if the disease continued to spread. He cites how in 1993 the CDC enormously broadened its AIDS definition and county health authorities were delighted because they received $2,500 per year from the Federal government for every reported AIDS case. Ladies and gentlemen, I have just described, via Kary Mullis, the 'Covid pandemic' of 2020 and beyond. Every element is the same and it's been pulled off in the same way by the same networks.

The 'Covid virus' exists? Okay – prove it. Er … still waiting

What Kary Mullis described with regard to 'HIV' has been repeated with 'Covid'. A claim is made that a new, or 'novel', infection has been found and the entire medical system of the world repeats that as fact exactly as they did with HIV and AIDS. No one in the mainstream asks rather relevant questions such as 'How do you know?' and 'Where is your proof?' The SARS-Cov-2 'virus' and the 'Covid-19 disease' became an overnight 'everybody-knows-that'. The origin could be debated and mulled over, but what you could not suggest was that 'SARS-Cov-2' didn't exist. That would be

ridiculous. 'Everybody knows' the 'virus' exists. Well, I didn't for one along with American proper doctors like Andrew Kaufman and Tom Cowan and long-time American proper journalist Jon Rappaport. We dared to pursue the obvious and simple question: 'Where's the evidence?' The overwhelming majority in medicine, journalism and the general public did not think to ask that. After all, *everyone knew* there was a new 'virus'. Everyone was saying so and I heard it on the BBC. Some would eventually argue that the 'deadly virus' was nothing like as deadly as claimed, but few would venture into the realms of its very existence. Had they done so they would have found that the evidence for that claim had gone AWOL as with HIV causes AIDS. In fact, not even that. For something to go AWOL it has to exist in the first place and scientific proof for a 'SARS-Cov-2' can be filed under nothing, nowhere and zilch.

Dr Andrew Kaufman is a board-certified forensic psychiatrist in New York State, a Doctor of Medicine and former Assistant Professor and Medical Director of Psychiatry at SUNY Upstate Medical University, and Medical Instructor of Hematology and Oncology at the Medical School of South Carolina. He also studied biology at the Massachusetts Institute of Technology (MIT) and trained in Psychiatry at Duke University. Kaufman is retired from allopathic medicine, but remains a consultant and educator on natural healing, I saw a video of his very early on in the 'Covid' hoax in which he questioned claims about the 'virus' in the absence of any supporting evidence and with plenty pointing the other way. I did everything I could to circulate his work which I felt was asking the pivotal questions that needed an answer. I can recommend an excellent pull-together interview he did with the website The Last Vagabond entitled *Dr Andrew Kaufman: Virus Isolation, Terrain Theory and Covid-19* and his website is andrewkaufmanmd.com. Kaufman is not only a forensic psychiatrist; he is forensic in all that he does. He always reads original scientific papers, experiments and studies instead of second-third-fourth-hand reports about the 'virus' in the media which are repeating the repeated repetition of the narrative. When he did so with the original Chinese 'virus' papers Kaufman

realised that there was no evidence of a 'SARS-Cov-2'. They had never – from the start – shown it to exist and every repeat of this claim worldwide was based on the accepted existence of proof that was nowhere to be found – see Kary Mullis and HIV. Here we go again.

Let's postulate

Kaufman discovered that the Chinese authorities immediately concluded that the cause of an illness that broke out among about 200 initial patients in Wuhan was a 'new virus' when there were no grounds to make that conclusion. The alleged 'virus' was not isolated from other genetic material in their samples and then shown through a system known as Koch's postulates to be the causative agent of the illness. The world was told that the SARS-Cov-2 'virus' caused a disease they called 'Covid-19' which had 'flu-like' symptoms and could lead to respiratory problems and pneumonia. If it wasn't so tragic it would almost be funny. *'Flu-like' symptoms'? Pneumonia? Respiratory disease?* What in *CHINA* and particularly in *Wuhan*, one of the most polluted cities in the world with a resulting epidemic of respiratory disease?? Three hundred thousand people get pneumonia in China every year and there are nearly a billion cases worldwide of 'flu-like symptoms'. These have a whole range of causes – including pollution in Wuhan – but no other possibility was credibly considered in late 2019 when the world was told there was a new and deadly 'virus'. The global prevalence of pneumonia and 'flu-like systems' gave the Cult networks unlimited potential to re-diagnose these other causes as the mythical 'Covid-19' and that is what they did from the very start. Kaufman revealed how Chinese medical and science authorities (all subordinates to the Cult-owned communist government) took genetic material from the lungs of only a few of the first patients. The material contained their own cells, bacteria, fungi and other microorganisms living in their bodies. The only way you could prove the existence of the 'virus' and its responsibility for the alleged 'Covid-19' was to isolate the virus from all the other material – a process also known as 'purification' – and

then follow the postulates sequence developed in the late 19th century by German physician and bacteriologist Robert Koch which became the 'gold standard' for connecting an alleged causation agent to a disease:

1. The microorganism (bacteria, fungus, virus, etc.) must be present in every case of the disease and all patients must have the same symptoms. It must also *not be present in healthy individuals*.

2. The microorganism must be isolated from the host with the disease. If the microorganism is a bacteria or fungus it must be grown in a pure culture. If it is a virus, it must be purified (i.e. containing no other material except the virus particles) from a clinical sample.

3. The specific disease, with all of its characteristics, must be reproduced when the infectious agent (the purified virus or a pure culture of bacteria or fungi) is inoculated into a healthy, susceptible host.

4. The microorganism must be recoverable from the experimentally infected host as in step 2.

Not one of these criteria has been met in the case of 'SARS-Cov-2' and 'Covid-19'. Not ONE. *EVER*. Robert Koch refers to bacteria and not viruses. What are called 'viral particles' are so minute (hence masks are useless by any definition) that they could only be seen after the invention of the electron microscope in the 1930s and can still only be observed through that means. American bacteriologist and virologist Thomas Milton Rivers, the so-called 'Father of Modern Virology' who was very significantly director of the Rockefeller Institute for Medical Research in the 1930s, developed a less stringent version of Koch's postulates to identify 'virus' causation known as 'Rivers criteria'. 'Covid' did not pass that process either. Some even doubt whether any 'virus' can be isolated from other particles containing genetic material in the Koch method. Freedom of Information requests in many countries asking for scientific proof that the 'Covid virus' has been purified and isolated and shown to exist have all come back with a 'we don't have that' and when this happened with a request to the UK Department of Health they added this comment:

However, outside of the scope of the [Freedom of Information Act] and on a discretionary basis, the following information has been advised to us, which may be of interest. Most infectious diseases are caused by viruses, bacteria or fungi. Some bacteria or fungi have the capacity to grow on their own in isolation, for example in colonies on a petri dish. Viruses are different in that they are what we call 'obligate pathogens' – that is, they cannot survive or reproduce without infecting a host ...

… For some diseases, it is possible to establish causation between a microorganism and a disease by isolating the pathogen from a patient, growing it in pure culture and reintroducing it to a healthy organism. These are known as 'Koch's postulates' and were developed in 1882. However, as our understanding of disease and different disease-causing agents has advanced, these are no longer the method for determining causation [Andrew Kaufman asks why in that case are there two published articles falsely claiming to satisfy Koch's postulates].

It has long been known that viral diseases cannot be identified in this way as viruses cannot be grown in 'pure culture'. When a patient is tested for a viral illness, this is normally done by looking for the presence of antigens, or viral genetic code in a host with molecular biology techniques [Kaufman asks how you could know the origin of these chemicals without having a pure culture for comparison].

For the record 'antigens' are defined so:

Invading microorganisms have antigens on their surface that the human body can recognise as being foreign – meaning not belonging to it. When the body recognises a foreign antigen, lymphocytes (white blood cells) produce antibodies, which are complementary in shape to the antigen.

Notwithstanding that this is open to question in relation to 'SARS-Cov-2' the presence of 'antibodies' can have many causes and they are found in people that are perfectly well. Kary Mullis said: 'Antibodies … had always been considered evidence of past disease, not present disease.'

'Covid' really is a *computer* 'virus'

Where the UK Department of Health statement says 'viruses' are now 'diagnosed' through a 'viral genetic code in a host with molecular biology techniques', they mean … *the PCR test* which its inventor said cannot test for infectious disease. They have no credible method of connecting a 'virus' to a disease and we will see that there is no scientific proof that any 'virus' causes any disease or there is any such thing as a 'virus' in the way that it is described. Tenacious Canadian researcher Christine Massey and her team made

some 40 Freedom of Information requests to national public health agencies in different countries asking for proof that SARS-CoV-2 has been isolated and not one of them could supply that information. Massey said of her request in Canada: 'Freedom of Information reveals Public Health Agency of Canada has no record of 'SARS-COV-2' isolation performed by anyone, anywhere, ever.' If you accept the comment from the UK Department of Health it's because they can't isolate a 'virus'. Even so many 'science' papers claimed to have isolated the 'Covid virus' until they were questioned and had to admit they hadn't. A reply from the Robert Koch Institute in Germany was typical: 'I am not aware of a paper which purified isolated SARS-CoV-2.' So what the hell was Christian Drosten and his gang using to design the 'Covid' testing protocol that has produced all the illusory Covid' cases and 'Covid' deaths when the head of the Chinese version of the CDC admitted there was a problem right from the start in that the 'virus' had never been isolated/purified? Breathe deeply: What they are calling 'Covid' is actually created by a *computer program* i.e. *they made it up* – er, that's it. They took lung fluid, with many sources of genetic material, from one single person alleged to be infected with Covid-19 by a PCR test which they *claimed*, without clear evidence, contained a 'virus'. They used several computer programs to create a model of a theoretical virus genome sequence from more than fifty-six million small sequences of RNA, each of an unknown source, assembling them like a puzzle with no known solution. The computer filled in the gaps with sequences from bits in the gene bank to make it look like a bat SARS-like coronavirus! A wave of the magic wand and poof, an in silico (computer-generated) genome, a scientific fantasy, was created. UK health researcher Dr Kevin Corbett made the same point with this analogy:

> … It's like giving you a few bones and saying that's your fish. It could be any fish. Not even a skeleton. Here's a few fragments of bones. That's your fish … It's all from gene bank and the bits of the virus sequence that weren't there they made up.
>
> They synthetically created them to fill in the blanks. That's what genetics is; it's a code. So it's ABBBCCDDD and you're missing some what you think is EEE so you put it in. It's all

synthetic. You just manufacture the bits that are missing. This is the end result of the geneticization of virology. This is basically a computer virus.

Further confirmation came in an email exchange between British citizen journalist Frances Leader and the government's Medicines & Healthcare Products Regulatory Agency (the Gates-funded MHRA) which gave emergency permission for untested 'Covid vaccines' to be used. The agency admitted that the 'vaccine' is not based on an isolated 'virus', but comes from a *computer-generated model*. Frances Leader was naturally banned from Cult-owned fascist Twitter for making this exchange public. The process of creating computer-generated alleged 'viruses' is called 'in silico' or 'in silicon' – computer chips – and the term 'in silico' is believed to originate with biological experiments using only a computer in 1989. 'Vaccines' involved with 'Covid' are also produced 'in silico' or by computer not a natural process. If the original 'virus' is nothing more than a made-up computer model how can there be 'new variants' of something that never existed in the first place? They are not new 'variants'; they are new *computer models* only minutely different to the original program and designed to further terrify the population into having the 'vaccine' and submitting to fascism. You want a 'new variant'? Click, click, enter – there you go. Tell the medical profession that you have discovered a 'South African variant', 'UK variants' or a 'Brazilian variant' and in the usual HIV-causes-AIDS manner they will unquestioningly repeat it with no evidence whatsoever to support these claims. They will go on television and warn about the dangers of 'new variants' while doing nothing more than repeating what they have been told to be true and knowing that any deviation from that would be career suicide. Big-time insiders will know it's a hoax, but much of the medical community is clueless about the way they are being played and themselves play the public without even being aware they are doing so. What an interesting 'coincidence' that AstraZeneca and Oxford University were conducting 'Covid vaccine trials' in the three countries – the UK, South Africa and Brazil – where the first three 'variants' were claimed to have 'broken out'.

Here's your 'virus' – it's a unicorn

Dr Andrew Kaufman presented a brilliant analysis describing how the 'virus' was imagined into fake existence when he dissected an article published by *Nature* and written by 19 authors detailing *alleged* 'sequencing of a complete viral genome' of the 'new SARS-CoV-2 virus'. This computer-modelled *in silico* genome was used as a template for all subsequent genome sequencing experiments that resulted in the so-called variants which he said now number more than *6,000*. The fake genome was constructed from more than 56 million individual short strands of RNA. Those little pieces were assembled into longer pieces by finding areas of overlapping sequences. The computer programs created over two million possible combinations from which the authors simply chose the longest one. They then compared this to a 'bat virus' and the computer 'alignment' rearranged the sequence and filled in the gaps! They called this computer-generated abomination the 'complete genome'. Dr Tom Cowan, a fellow medical author and collaborator with Kaufman, said such computer-generation constitutes scientific fraud and he makes this superb analogy:

> Here is an equivalency: A group of researchers claim to have found a unicorn because they found a piece of a hoof, a hair from a tail, and a snippet of a horn. They then add that information into a computer and program it to re-create the unicorn, and they then claim this computer re-creation is the real unicorn. Of course, they had never actually seen a unicorn so could not possibly have examined its genetic makeup to compare their samples with the actual unicorn's hair, hooves and horn.
>
> The researchers claim they decided which is the real genome of SARS-CoV-2 by 'consensus', sort of like a vote. Again, different computer programs will come up with different versions of the imaginary 'unicorn', so they come together as a group and decide which is the real imaginary unicorn.

This is how the 'virus' that has transformed the world was brought into fraudulent 'existence'. Extraordinary, yes, but as the Nazis said the bigger the lie the more will believe it. Cowan, however, wasn't finished and he went on to identify what he called the real blockbuster in the paper. He quotes this section from a paper written

by virologists and published by the CDC and then explains what it means:

Therefore, we examined the capacity of SARS-CoV-2 to infect and replicate in several common primate and human cell lines, including human adenocarcinoma cells (A549), human liver cells (HUH 7.0), and human embryonic kidney cells (HEK-293T). In addition to Vero E6 and Vero CCL81 cells. ... Each cell line was inoculated at high multiplicity of infection and examined 24h post-infection.

No CPE was observed in any of the cell lines except in Vero cells, which grew to greater than 10 to the 7th power at 24 h post-infection. In contrast, HUH 7.0 and 293T showed only modest viral replication, and A549 cells were incompatible with SARS CoV-2 infection.

Cowan explains that when virologists attempt to prove infection they have three possible 'hosts' or models on which they can test. The first was humans. Exposure to humans was generally not done for ethical reasons and has never been done with SARS-CoV-2 or any coronavirus. The second possible host was animals. Cowan said that forgetting for a moment that they never actually use purified virus when exposing animals they do use solutions that they *claim* contain the virus. Exposure to animals has been done with SARS-CoV-2 in an experiment involving mice and this is what they found: *None of the wild (normal) mice got sick*. In a group of genetically-modified mice, a statistically insignificant number lost weight and had slightly bristled fur, but they experienced nothing like the illness called 'Covid-19'. Cowan said the third method – the one they mostly rely on – is to inoculate solutions they *say* contain the virus onto a variety of tissue cultures. This process had never been shown to kill tissue *unless* the sample material was starved of nutrients and poisoned as *part of the process*. Yes, incredibly, in tissue experiments designed to show the 'virus' is responsible for killing the tissue they starve the tissue of nutrients and add toxic drugs including antibiotics and they do not have control studies to see if it's the starvation and poisoning that is degrading the tissue rather than the 'virus' they allege to be in there somewhere. You want me to pinch you? Yep, I understand. Tom Cowan said this about the whole nonsensical farce as he explains what that quote from the CDC paper really means:

The shocking thing about the above quote is that using their own methods, the virologists found that solutions containing SARS-CoV-2 – even in high amounts – were NOT, I repeat NOT, infective to any of the three human tissue cultures they tested. In plain English, this means they proved, on their terms, that this 'new coronavirus' is not infectious to human beings. It is ONLY infective to monkey kidney cells, and only then when you add two potent drugs (gentamicin and amphotericin), known to be toxic to kidneys, to the mix.

My friends, read this again and again. These virologists, published by the CDC, performed a clear proof, on their terms, showing that the SARS-CoV-2 virus is harmless to human beings. That is the only possible conclusion, but, unfortunately, this result is not even mentioned in their conclusion. They simply say they can provide virus stocks cultured only on monkey Vero cells, thanks for coming.

Cowan concluded: 'If people really understood how this "science" was done, I would hope they would storm the gates and demand honesty, transparency and truth.' Dr Michael Yeadon, former Vice President and Chief Scientific Adviser at drug giant Pfizer has been a vocal critic of the 'Covid vaccine' and its potential for multiple harm. He said in an interview in April, 2021, that 'not one [vaccine] has the virus. He was asked why vaccines normally using a 'dead' version of a disease to activate the immune system were not used for 'Covid' and instead we had the synthetic methods of the 'mRNA Covid vaccine'. Yeadon said that to do the former 'you'd have to have some of [the virus] wouldn't you?' He added: 'No-one's got any – seriously.' Yeadon said that surely they couldn't have fooled the whole world for a year without having a virus, 'but oddly enough ask around – no one's got it'. He didn't know why with all the 'great labs' around the world that the virus had not been isolated – 'Maybe they've been too busy running bad PCR tests and vaccines that people don't need.' What is today called 'science' is not 'science' at all. Science is no longer what is, but whatever people can be manipulated to *believe* that it is. Real science has been hijacked by the Cult to dispense and produce the 'expert scientists' and contentions that suit the agenda of the Cult. How big-time this has happened with the 'Covid' hoax which is entirely based on fake science delivered by fake 'scientists' and fake 'doctors'. The human-caused climate change hoax is also entirely based on fake science delivered by fake 'scientists' and fake 'climate experts'. In both cases real

scientists, climate experts and doctors have their views suppressed and deleted by the Cult-owned science establishment, media and Silicon Valley. This is the 'science' that politicians claim to be 'following' and a common denominator of 'Covid' and climate are Cult psychopaths Bill Gates and his mate Klaus Schwab at the Gates-funded World Economic Forum. But, don't worry, it's all just a coincidence and absolutely nothing to worry about. *Zzzzzzzz*.

What is a 'virus' REALLY?

Dr Tom Cowan is one of many contesting the very existence of viruses let alone that they cause disease. This is understandable when there is no scientific evidence for a disease-causing 'virus'. German virologist Dr Stefan Lanka won a landmark case in 2017 in the German Supreme Court over his contention that there is no such thing as a measles virus. He had offered a big prize for anyone who could prove there is and Lanka won his case when someone sought to claim the money. There is currently a prize of more than 225,000 euros on offer from an Isolate Truth Fund for anyone who can prove the isolation of SARS-CoV-2 and its genetic substance. Lanka wrote in an article headed 'The Misconception Called Virus' that scientists think a 'virus' is causing tissue to become diseased and degraded when in fact it is the *processes they are using* which do that – not a 'virus'. Lanka has done an important job in making this point clear as Cowan did in his analysis of the CDC paper. Lanka says that all claims about viruses as disease-causing pathogens are wrong and based on 'easily recognisable, understandable and verifiable misinterpretations.' Scientists believed they were working with 'viruses' in their laboratories when they were really working with 'typical particles of specific dying tissues or cells …' Lanka said that the tissue decaying process claimed to be caused by a 'virus' still happens when no alleged 'virus' is involved. It's the *process* that does the damage and not a 'virus'. The genetic sample is deprived of nutrients, removed from its energy supply through removal from the body and then doused in toxic antibiotics to remove any bacteria. He confirms again that establishment scientists do not (pinch me)

conduct control experiments to see if this is the case and if they did they would see the claims that 'viruses' are doing the damage is nonsense. He adds that during the measles 'virus' court case he commissioned an independent laboratory to perform just such a control experiment and the result was that the tissues and cells died in the exact same way as with alleged 'infected' material. This is supported by a gathering number of scientists, doctors and researchers who reject what is called 'germ theory' or the belief in the body being infected by contagious sources emitted by other people. Researchers Dawn Lester and David Parker take the same stance in their highly-detailed and sourced book *What Really Makes You Ill – Why everything you thought you knew about disease is wrong* which was recommended to me by a number of medical professionals genuinely seeking the truth. Lester and Parker say there is no provable scientific evidence to show that a 'virus' can be transmitted between people or people and animals or animals and people:

> The definition also claims that viruses are the cause of many diseases, as if this has been definitively proven. But this is not the case; there is no original scientific evidence that definitively demonstrates that any virus is the cause of any disease. The burden of proof for any theory lies with those who proposed it; but none of the existing documents provides 'proof' that supports the claim that 'viruses' are pathogens.

Dr Tom Cowan employs one of his clever analogies to describe the process by which a 'virus' is named as the culprit for a disease when what is called a 'virus' is only material released by cells detoxing themselves from infiltration by chemical or radiation poisoning. The tidal wave of technologically-generated radiation in the 'smart' modern world plus all the toxic food and drink are causing this to happen more than ever. Deluded 'scientists' misread this as a gathering impact of what they wrongly label 'viruses'.

Paper can infect houses

Cowan said in an article for davidicke.com – with his tongue only mildly in his cheek – that he believed he had made a tremendous

discovery that may revolutionise science. He had discovered that small bits of paper are alive, 'well alive-ish', can 'infect' houses, and then reproduce themselves inside the house. The result was that this explosion of growth in the paper inside the house causes the house to explode, blowing it to smithereens. His evidence for this new theory is that in the past months he had carefully examined many of the houses in his neighbourhood and found almost no scraps of paper on the lawns and surrounds of the house. There was an occasional stray label, but nothing more. Then he would return to these same houses a week or so later and with a few, not all of them, particularly the old and decrepit ones, he found to his shock and surprise they were littered with stray bits of paper. He knew then that the paper had infected these houses, made copies of itself, and blew up the house. A young boy on a bicycle at one of the sites told him he had seen a demolition crew using dynamite to explode the house the previous week, but Cowan dismissed this as the idle thoughts of silly boys because 'I was on to something big'. He was on to how 'scientists' mistake genetic material in the detoxifying process for something they call a 'virus'. Cowan said of his house and paper story:

> If this sounds crazy to you, it's because it should. This scenario is obviously nuts. But consider this admittedly embellished, for effect, current viral theory that all scientists, medical doctors and virologists currently believe.

He takes the example of the 'novel SARS-Cov2' virus to prove the point. First they take someone with an undefined illness called 'Covid-19' and don't even attempt to find any virus in their sputum. Never mind the scientists still describe how this 'virus', which they have not located attaches to a cell receptor, injects its genetic material, in 'Covid's' case, RNA, into the cell. The RNA once inserted exploits the cell to reproduce itself and makes 'thousands, nay millions, of copies of itself … Then it emerges victorious to claim its next victim':

If you were to look in the scientific literature for proof, actual scientific proof, that uniform SARS-CoV2 viruses have been properly isolated from the sputum of a sick person, that actual spike proteins could be seen protruding from the virus (which has not been found), you would find that such evidence doesn't exist.

If you go looking in the published scientific literature for actual pictures, proof, that these spike proteins or any viral proteins are ever attached to any receptor embedded in any cell membrane, you would also find that no such evidence exists. If you were to look for a video or documented evidence of the intact virus injecting its genetic material into the body of the cell, reproducing itself and then emerging victorious by budding off the cell membrane, you would find that no such evidence exists.

The closest thing you would find is electron micrograph pictures of cellular particles, possibly attached to cell debris, both of which to be seen were stained by heavy metals, a process that completely distorts their architecture within the living organism. This is like finding bits of paper stuck to the blown-up bricks, thereby proving the paper emerged by taking pieces of the bricks on its way out.

The Enders baloney

Cowan describes the 'Covid' story as being just as make-believe as his paper story and he charts back this fantasy to a Nobel Prize winner called John Enders (1897-1985), an American biomedical scientist who has been dubbed 'The Father of Modern Vaccines'. Enders is claimed to have 'discovered' the process of the viral culture which 'proved' that a 'virus' caused measles. Cowan explains how Enders did this 'by using the EXACT same procedure that has been followed by every virologist to find and characterize every new virus since 1954'. Enders took throat swabs from children with measles and immersed them in 2ml of milk. Penicillin (100u/ml) and the antibiotic streptomycin (50,g/ml) were added and the whole mix was centrifuged – rotated at high speed to separate large cellular debris from small particles and molecules as with milk and cream, for example. Cowan says that if the aim is to find little particles of genetic material ('viruses') in the snot from children with measles it would seem that the last thing you would do is mix the snot with other material – milk –that also has genetic material. 'How are you ever going to know whether whatever you found came from the snot or the milk?' He points out that streptomycin is a 'nephrotoxic' or poisonous-to-the-kidney drug. You will see the relevance of that

shortly. Cowan says that it gets worse, much worse, when Enders describes the culture medium upon which the virus 'grows': 'The culture medium consisted of bovine amniotic fluid (90%), beef embryo extract (5%), horse serum (5%), antibiotics and phenol red as an indicator of cell metabolism.' Cowan asks incredulously: 'Did he just say that the culture medium also contained fluids and tissues that are themselves rich sources of genetic material?' The genetic cocktail, or 'medium', is inoculated onto tissue and cells from rhesus monkey *kidney* tissue. This is where the importance of streptomycin comes in and currently-used antimicrobials and other drugs that are *poisonous to kidneys* and used in ALL modern viral cultures (e.g. gentamicin, streptomycin, and amphotericin). Cowan asks: 'How are you ever going to know from this witch's brew where any genetic material comes from as we now have five different sources of rich genetic material in our mix?' Remember, he says, that all genetic material, whether from monkey kidney tissues, bovine serum, milk, etc., is made from the exact same components. The same central question returns: 'How are you possibly going to know that it was the virus that killed the kidney tissue and not the toxic antibiotic and starvation rations on which you are growing the tissue?' John Enders answered the question himself – *you can't*:

A second agent was obtained from an uninoculated culture of monkey kidney cells. The cytopathic changes [death of the cells] it induced in the unstained preparations could not be distinguished with confidence from the viruses isolated from measles.

The death of the cells ('cytopathic changes') happened in exactly the same manner, whether they inoculated the kidney tissue with the measles snot or not, Cowan says. 'This is evidence that the destruction of the tissue, the very proof of viral causation of illness, was not caused by anything in the snot because they saw the same destructive effect when the snot was not even used … the cytopathic, i.e., cell-killing, changes come from the process of the culture itself, not from any virus in any snot, period.' Enders quotes in his 1957 paper a virologist called Ruckle as reporting similar findings 'and in addition has isolated an agent from monkey kidney tissue that is so

far indistinguishable from human measles virus'. In other words, Cowan says, these particles called 'measles viruses' are simply and clearly breakdown products of the starved and poisoned tissue. For measles 'virus' see all 'viruses' including the so-called 'Covid virus'. Enders, the 'Father of Modern Vaccines', also said:

There is a potential risk in employing cultures of primate cells for the production of vaccines composed of attenuated virus, since the presence of other agents possibly latent in primate tissues cannot be definitely excluded by any known method.

Cowan further quotes from a paper published in the journal *Viruses* in May, 2020, while the 'Covid pandemic' was well underway in the media if not in reality. 'EVs' here refers to particles of genetic debris from our own tissues, such as exosomes of which more in a moment: 'The remarkable resemblance between EVs and viruses has caused quite a few problems in the studies focused on the analysis of EVs released during viral infections.' Later the paper adds that to date a reliable method that can actually guarantee a complete separation (of EVs from viruses) DOES NOT EXIST. This was published at a time when a fairy tale 'virus' was claimed in total certainty to be causing a fairy tale 'viral disease' called 'Covid-19' – a fairy tale that was already well on the way to transforming human society in the image that the Cult has worked to achieve for so long. Cowan concludes his article:

To summarize, there is no scientific evidence that pathogenic viruses exist. What we think of as 'viruses' are simply the normal breakdown products of dead and dying tissues and cells. When we are well, we make fewer of these particles; when we are starved, poisoned, suffocated by wearing masks, or afraid, we make more.

There is no engineered virus circulating and making people sick. People in laboratories all over the world are making genetically modified products to make people sick. These are called vaccines. There is no virome, no 'ecosystem' of viruses, viruses are not 8%, 50% or 100 % of our genetic material. These are all simply erroneous ideas based on the misconception called a virus.

What is 'Covid'? Load of bollocks

The background described here by Cowan and Lanka was emphasised in the first video presentation that I saw by Dr Andrew Kaufman when he asked whether the 'Covid virus' was in truth a natural defence mechanism of the body called 'exosomes'. These are released by cells when in states of toxicity – see the same themes returning over and over. They are released ever more profusely as chemical and radiation toxicity increases and think of the potential effect therefore of 5G alone as its destructive frequencies infest the human energetic information field with a gathering pace (5G went online in Wuhan in 2019 as the 'virus' emerged). I'll have more about this later. Exosomes transmit a warning to the rest of the body that 'Houston, we have a problem'. Kaufman presented images of exosomes and compared them with 'Covid' under an electron microscope and the similarity was remarkable. They both attach to the same cell receptors (*claimed* in the case of 'Covid'), contain the same genetic material in the form of RNA or ribonucleic acid, and both are found in 'viral cell cultures' with damaged or dying cells. James Hildreth MD, President and Chief Executive Officer of the Meharry Medical College at Johns Hopkins, said: 'The virus is fully an exosome in every sense of the word.' Kaufman's conclusion was that there is no 'virus': 'This entire pandemic is a completely manufactured crisis … there is no evidence of anyone dying from [this] illness.' Dr Tom Cowan and Sally Fallon Morell, authors of *The Contagion Myth*, published a statement with Dr Kaufman in February, 2021, explaining why the 'virus' does not exist and you can read it that in full in the Appendix.

'Virus' theory can be traced to the 'cell theory' in 1858 of German physician Rudolf Virchow (1821-1920) who contended that disease originates from a single cell infiltrated by a 'virus'. Dr Stefan Lanka said that findings and insights with respect to the structure, function and central importance of tissues in the creation of life, which were already known in 1858, comprehensively refute the cell theory. Virchow ignored them. We have seen the part later played by John Enders in the 1950s and Lanka notes that infection theories were only established as a global dogma through the policies and

eugenics of the Third Reich in Nazi Germany (creation of the same Sabbatian cult behind the 'Covid' hoax). Lanka said: 'Before 1933, scientists dared to contradict this theory; after 1933, these critical scientists were silenced'. Dr Tom Cowan's view is that ill-heath is caused by too much of something, too little of something, or toxification from chemicals and radiation – not contagion. We must also highlight as a major source of the 'virus' theology a man still called the 'Father of Modern Virology' – Thomas Milton Rivers (1888-1962). There is no way given the Cult's long game policy that it was a coincidence for the 'Father of Modern Virology' to be director of the Rockefeller Institute for Medical Research from 1937 to 1956 when he is credited with making the Rockefeller Institute a leader in 'viral research'. Cult Rockefellers were the force behind the creation of Big Pharma 'medicine', established the World Health Organisation in 1948, and have long and close associations with the Gates family that now runs the WHO during the pandemic hoax through mega-rich Cult gofer and psychopath Bill Gates.

Only a Renegade Mind can see through all this bullshit by asking the questions that need to be answered, not taking 'no' or prevarication for an answer, and certainly not hiding from the truth in fear of speaking it. Renegade Minds have always changed the world for the better and they will change this one no matter how bleak it may currently appear to be.

CHAPTER SIX

Sequence of deceit

If you tell the truth, you don't have to remember anything
Mark Twain

Against the background that I have laid out this far the sequence that took us from an invented 'virus' in Cult-owned China in late 2019 to the fascist transformation of human society can be seen and understood in a whole new context.

We were told that a deadly disease had broken out in Wuhan and the world media began its campaign (coordinated by behavioural psychologists as we shall see) to terrify the population into unquestioning compliance. We were shown images of Chinese people collapsing in the street which never happened in the West with what was supposed to be the same condition. In the earliest days when alleged cases and deaths were few the fear register was hysterical in many areas of the media and this would expand into the common media narrative across the world. The real story was rather different, but we were never told that. The Chinese government, one of the Cult's biggest centres of global operation, said they had discovered a new illness with flu-like and pneumonia-type symptoms in a city with such toxic air that it is overwhelmed with flu-like symptoms, pneumonia and respiratory disease. Chinese scientists said it was a new – 'novel' – coronavirus which they called Sars-Cov-2 and that it caused a disease they labelled 'Covid-19'. There was no evidence for this and the 'virus' has never to this day been isolated, purified and its genetic code established from that. It

was from the beginning a computer-generated fiction. Stories of Chinese whistleblowers saying the number of deaths was being supressed or that the 'new disease' was related to the Wuhan bio-lab misdirected mainstream and alternative media into cul-de-sacs to obscure the real truth – there was no 'virus'.

Chinese scientists took genetic material from the lung fluid of just a few people and said they had found a 'new' disease when this material had a wide range of content. There was no evidence for a 'virus' for the very reasons explained in the last two chapters. The 'virus' has never been shown to (a) exist and (b) cause any disease. People were diagnosed on symptoms that are so widespread in Wuhan and polluted China and with a PCR test that can't detect infectious disease. On this farce the whole global scam was sold to the rest of the world which would also diagnose respiratory disease as 'Covid-19' from symptoms alone or with a PCR test not testing for a 'virus'. Flu miraculously disappeared *worldwide* in 2020 and into 2021 as it was redesignated 'Covid-19'. It was really the same old flu with its 'flu-like' symptoms attributed to 'flu-like' 'Covid-19'. At the same time with very few exceptions the Chinese response of draconian lockdown and fascism was the chosen weapon to respond across the West as recommended by the Cult-owned Tedros at the Cult-owned World Health Organization run by the Cult-owned Gates. All was going according to plan. Chinese scientists – everything in China is controlled by the Cult-owned government – compared their contaminated RNA lung-fluid material with other RNA sequences and said it appeared to be just under 80 percent identical to the SARS-CoV-1 'virus' claimed to be the cause of the SARS (severe acute respiratory syndrome) 'outbreak' in 2003. They decreed that because of this the 'new virus' had to be related and they called it SARS-CoV-2. There are some serious problems with this assumption and *assumption* was all it was. Most 'factual' science turns out to be assumptions repeated into everyone-knows-that. A match of under 80-percent is meaningless. Dr Kaufman makes the point that there's a *96 percent* genetic correlation between humans and chimpanzees, but 'no one would say our genetic material is part

of the chimpanzee family'. Yet the Chinese authorities were claiming that a much lower percentage, less than 80 percent, proved the existence of a new 'coronavirus'. For goodness sake human DNA is 60 percent similar to a *banana*.

You are feeling sleepy

The entire 'Covid' hoax is a global Psyop, a psychological operation to program the human mind into believing and fearing a complete fantasy. A crucial aspect of this was what *appeared* to happen in Italy. It was all very well streaming out daily images of an alleged catastrophe in Wuhan, but to the Western mind it was still on the other side of the world in a very different culture and setting. A reaction of 'this could happen to me and my family' was still nothing like as intense enough for the mind-doctors. The Cult needed a Western example to push people over that edge and it chose Italy, one of its major global locations going back to the Roman Empire. An Italian 'Covid' crisis was manufactured in a particular area called Lombardy which just happens to be notorious for its toxic air and therefore respiratory disease. Wuhan, China, déjà vu. An hysterical media told horror stories of Italians dying from 'Covid' in their droves and how Lombardy hospitals were being overrun by a tidal wave of desperately ill people needing treatment after being struck down by the 'deadly virus'. Here was the psychological turning point the Cult had planned. Wow, if this is happening in Italy, the Western mind concluded, this indeed could happen to me and my family. Another point is that Italian authorities responded by following the Chinese blueprint so vehemently recommended by the Cult-owned World Health Organization. They imposed fascistic lockdowns on the whole country viciously policed with the help of surveillance drones sweeping through the streets seeking out anyone who escaped from mass house arrest. Livelihoods were destroyed and psychology unravelled in the way we have witnessed since in all lockdown countries. Crucial to the plan was that Italy responded in this way to set the precedent of suspending freedom and imposing fascism in a 'Western liberal democracy'. I emphasised in an

animated video explanation on davidicke.com posted in the summer of 2020 how important it was to the Cult to expand the Chinese lockdown model across the West. Without this, and the bare-faced lie that non-symptomatic people could still transmit a 'disease' they didn't have, there was no way locking down the whole population, sick and not sick, could be pulled off. At just the right time and with no evidence Cult operatives and gofers claimed that people without symptoms could pass on the 'disease'. In the name of protecting the 'vulnerable' like elderly people, who lockdowns would kill by the tens of thousands, we had for the first time healthy people told to isolate as well as the sick. The great majority of people who tested positive had no symptoms because there was nothing wrong with them. It was just a trick made possible by a test not testing for the 'virus'.

Months after my animated video the Gates-funded Professor Neil Ferguson at the Gates-funded Imperial College confirmed that I was right. He didn't say it in those terms, naturally, but he did say it. Ferguson will enter the story shortly for his outrageously crazy 'computer models' that led to Britain, the United States and many other countries following the Chinese and now Italian methods of response. Put another way, following the Cult script. Ferguson said that SAGE, the UK government's scientific advisory group which has controlled 'Covid' policy from the start, wanted to follow the Chinese lockdown model (while they all continued to work and be paid), but they wondered if they could possibly, in Ferguson's words, 'get away with it in Europe'. 'Get away with it'? Who the hell do these moronic, arrogant people think they are? This appalling man Ferguson said that once Italy went into national lockdown they realised they, too, could mimic China:

> It's a communist one-party state, we said. We couldn't get away with it in Europe, we thought … and then Italy did it. And we realised we could. Behind this garbage from Ferguson is a simple fact: Doing the same as China in every country was the plan from the start and Ferguson's 'models' would play a central role in achieving that. It's just a coincidence, of course, and absolutely nothing to worry your little head about.

Oops, sorry, our mistake

Once the Italian segment of the Psyop had done the job it was designed to do a very different story emerged. Italian authorities revealed that 99 percent of those who had 'died from Covid-19' in Italy had one, two, three, or more 'co-morbidities' or illnesses and health problems that could have ended their life. The US Centers for Disease Control and Prevention (CDC) published a figure of 94 percent for Americans dying of 'Covid' while having other serious medical conditions – on average two to three (some five or six) other potential causes of death. In terms of death from an unproven 'virus' I say it is 100 percent. The other one percent in Italy and six percent in the US would presumably have died from 'Covid's' flu-like symptoms with a range of other possible causes in conjunction with a test not testing for the 'virus'. Fox News reported that even more startling figures had emerged in one US county in which 410 of 422 deaths attributed to 'Covid-19' had other potentially deadly health conditions. The Italian National Health Institute said later that the average age of people dying with a 'Covid-19' diagnosis in Italy was about 81. Ninety percent were over 70 with ten percent over 90. In terms of other reasons to die some 80 percent had two or more chronic diseases with half having three or more including cardiovascular problems, diabetes, respiratory problems and cancer. Why is the phantom 'Covid-19' said to kill overwhelmingly old people and hardly affect the young? Old people continually die of many causes and especially respiratory disease which you can re-diagnose 'Covid-19' while young people die in tiny numbers by comparison and rarely of respiratory disease. Old people 'die of Covid' because they die of other things that can be redesignated 'Covid' and it really is that simple.

Flu has flown

The blueprint was in place. Get your illusory 'cases' from a test not testing for the 'virus' and redesignate other causes of death as 'Covid-19'. You have an instant 'pandemic' from something that is nothing more than a computer-generated fiction. With near-on a

billion people having 'flu-like' symptoms every year the potential was limitless and we can see why flu quickly and apparently miraculously disappeared *worldwide* by being diagnosed 'Covid-19'. The painfully bloody obvious was explained away by the childlike media in headlines like this in the UK '*Independent*': 'Not a single case of flu detected by Public Health England this year as Covid restrictions suppress virus'. I kid you not. The masking, social distancing and house arrest that did not make the 'Covid virus' disappear somehow did so with the 'flu virus'. Even worse the article, by a bloke called Samuel Lovett, suggested that maybe the masking, sanitising and other 'Covid' measures should continue to keep the flu away. With a ridiculousness that disturbs your breathing (it's 'Covid-19') the said Lovett wrote: 'With widespread social distancing and mask-wearing measures in place throughout the UK, the usual routes of transmission for influenza have been blocked.' He had absolutely no evidence to support that statement, but look at the consequences of him acknowledging the obvious. With flu not disappearing at all and only being relabelled 'Covid-19' he would have to contemplate that 'Covid' was a hoax on a scale that is hard to imagine. You need guts and commitment to truth to even go there and that's clearly something Samuel Lovett does not have in abundance. He would never have got it through the editors anyway.

Tens of thousands die in the United States alone every winter from flu including many with pneumonia complications. CDC figures record *45 million* Americans diagnosed with flu in 2017-2018 of which 61,000 died and some reports claim 80,000. Where was the same hysteria then that we have seen with 'Covid-19'? Some 250,000 Americans are admitted to hospital with pneumonia every year with about 50,000 cases proving fatal. About 65 million suffer respiratory disease every year and three million deaths makes this the third biggest cause of death worldwide. You only have to redesignate a portion of all these people 'Covid-19' and you have an instant global pandemic or the *appearance* of one. Why would doctors do this? They are told to do this and all but a few dare not refuse those who must be obeyed. Doctors in general are not researching their own

knowledge and instead take it direct and unquestioned from the authorities that own them and their careers. The authorities say they must now diagnose these symptoms 'Covid-19' and not flu, or whatever, and they do it. Dark suits say put 'Covid-19' on death certificates no matter what the cause of death and the doctors do it. Renegade Minds don't fall for the illusion that doctors and medical staff are all highly-intelligent, highly-principled, seekers of medical truth. *Some are*, but not the majority. They are repeaters, gofers, and yes sir, no sir, purveyors of what the system demands they purvey. The 'Covid' con is not merely confined to diseases of the lungs. Instructions to doctors to put 'Covid-19' on death certificates for anyone dying of *anything* within 28 days (or much more) of a positive test not testing for the 'virus' opened the floodgates. The term dying *with* 'Covid' and not *of* 'Covid' was coined to cover the truth. Whether it was a *with* or an *of* they were all added to the death numbers attributed to the 'deadly virus' compiled by national governments and globally by the Gates-funded Johns Hopkins operation in the United States that was so involved in those 'pandemic' simulations. Fraudulent deaths were added to the ever-growing list of fraudulent 'cases' from false positives from a false test. No wonder Professor Walter Ricciardi, scientific advisor to the Italian minister of health, said after the Lombardy hysteria had done its job that 'Covid' death rates were due to Italy having the second oldest population in the world and to *how hospitals record deaths*:

The way in which we code deaths in our country is very generous in the sense that all the people who die in hospitals with the coronavirus are deemed to be dying of the coronavirus. On re-evaluation by the National Institute of Health, only 12 per cent of death certificates have shown a direct causality from coronavirus, while 88 per cent of patients who have died have at least one pre-morbidity – many had two or three.

This is extraordinary enough when you consider the propaganda campaign to use Italy to terrify the world, but how can they even say twelve percent were genuine when the 'virus' has not been shown to exist, its 'code' is a computer program, and diagnosis comes from a test not testing for it? As in China, and soon the world, 'Covid-19' in

Italy was a redesignation of diagnosis. Lies and corruption were to become the real 'pandemic' fuelled by a pathetically-compliant medical system taking its orders from the tiny few at the top of their national hierarchy who answered to the World Health Organization which answers to Gates and the Cult. Doctors were told – ordered – to diagnose a particular set of symptoms 'Covid-19' and put that on the death certificate for any cause of death if the patient had tested positive with a test not testing for the virus or had 'Covid' symptoms like the flu. The United States even introduced big financial incentives to manipulate the figures with hospitals receiving £4,600 from the Medicare system for diagnosing someone with regular pneumonia, $13,000 if they made the diagnosis from the same symptoms 'Covid-19' pneumonia, and $39, 000 if they put a 'Covid' diagnosed patient on a ventilator that would almost certainly kill them. A few – painfully and pathetically few – medical whistleblowers revealed (before Cult-owned YouTube deleted their videos) that they had been instructed to 'let the patient crash' and put them straight on a ventilator instead of going through a series of far less intrusive and dangerous methods as they would have done before the pandemic hoax began and the financial incentives kicked in. We are talking cold-blooded murder given that ventilators are so damaging to respiratory systems they are usually the last step before heaven awaits. Renegade Minds never fall for the belief that people in white coats are all angels of mercy and cannot be full-on psychopaths. I have explained in detail in *The Answer* how what I am describing here played out across the world coordinated by the World Health Organization through the medical hierarchies in almost every country.

Medical scientist calls it

Information about the non-existence of the 'virus' began to emerge for me in late March, 2020, and mushroomed after that. I was sent an email by Sir Julian Rose, a writer, researcher, and organic farming promotor, from a medical scientist friend of his in the United States. Even at that early stage in March the scientist was able to explain

how the 'Covid' hoax was being manipulated. He said there were no reliable tests for a specific 'Covid-19 virus' and nor were there any reliable agencies or media outlets for reporting numbers of actual 'Covid-19' cases. We have seen in the long period since then that he was absolutely right. 'Every action and reaction to Covid-19 is based on totally flawed data and we simply cannot make accurate assessments,' he said. Most people diagnosed with 'Covid-19' were showing nothing more than cold and flu-like symptoms 'because most coronavirus strains *are* nothing more than cold/flu-like symptoms'. We had farcical situations like an 84-year-old German man testing positive for 'Covid-19' and his nursing home ordered to quarantine only for him to be found to have a common cold. The scientist described back then why PCR tests and what he called the 'Mickey Mouse test kits' were useless for what they were claimed to be identifying. 'The idea these kits can isolate a specific virus like Covid-19 is nonsense,' he said. Significantly, he pointed out that 'if you want to create a totally false panic about a totally false pandemic – pick a coronavirus'. This is exactly what the Cult-owned Gates, World Economic Forum and Johns Hopkins University did with their Event 201 'simulation' followed by their real-life simulation called the 'pandemic'. The scientist said that all you had to do was select the sickest of people with respiratory-type diseases in a single location – 'say Wuhan' – and administer PCR tests to them. You can then claim that anyone showing 'viral sequences' similar to a coronavirus 'which will inevitably be quite a few' is suffering from a 'new' disease:

> Since you already selected the sickest flu cases a fairly high proportion of your sample will go on to die. You can then say this 'new' virus has a CFR [case fatality rate] higher than the flu and use this to infuse more concern and do more tests which will of course produce more 'cases', which expands the testing, which produces yet more 'cases' and so on and so on. Before long you have your 'pandemic', and all you have done is use a simple test kit trick to convert the worst flu and pneumonia cases into something new that doesn't ACTUALLY EXIST [my emphasis].

He said that you then 'just run the same scam in other countries' and make sure to keep the fear message running high 'so that people

will feel panicky and less able to think critically'. The only problem to overcome was the fact *there is no* actual new deadly pathogen and only regular sick people. This meant that deaths from the 'new deadly pathogen' were going to be way too low for a real new deadly virus pandemic, but he said this could be overcome in the following ways – all of which would go on to happen:

1. You can claim this is just the beginning and more deaths are imminent [you underpin this with fantasy 'computer projections']. Use this as an excuse to quarantine everyone and then claim the quarantine prevented the expected millions of dead.

2. You can [say that people] 'minimizing' the dangers are irresponsible and bully them into not talking about numbers.

3. You can talk crap about made up numbers hoping to blind people with pseudoscience.

4. You can start testing well people (who, of course, will also likely have shreds of coronavirus [RNA] in them) and thus inflate your 'case figures' with 'asymptomatic carriers' (you will of course have to spin that to sound deadly even though any virologist knows the more symptom-less cases you have the less deadly is your pathogen).

The scientist said that if you take these simple steps 'you can have your own entirely manufactured pandemic up and running in weeks'. His analysis made so early in the hoax was brilliantly prophetic of what would actually unfold. Pulling all the information together in these recent chapters we have this is simple 1, 2, 3, of how you can delude virtually the entire human population into believing in a 'virus' that doesn't exist:

- A 'Covid case' is someone who tests positive with a test not testing for the 'virus'.

- A 'Covid death' is someone who dies of *any cause* within 28 days (or much longer) of testing positive with a test not testing for the 'virus.

- Asymptomatic means there is nothing wrong with you, but they claim you can pass on what you don't have to justify locking

down (quarantining) healthy people in totality.

The foundations of the hoax are that simple. A study involving ten million people in Wuhan, published in November, 2020, demolished the whole lie about those without symptoms passing on the 'virus'. They found '300 asymptomatic cases' and traced their contacts to find that not one of them was detected with the 'virus'. 'Asymptomatic' patients and their contacts were isolated for no less than two weeks and nothing changed. I know it's all crap, but if you are going to claim that those without symptoms can transmit 'the virus' then you must produce evidence for that and they never have. Even World Health Organization official Dr Maria Van Kerkhove, head of the emerging diseases and zoonosis unit, said as early as June, 2020, that she doubted the validity of asymptomatic transmission. She said that 'from the data we have, it still seems to be rare that an asymptomatic person actually transmits onward to a secondary individual' and by 'rare' she meant that she couldn't cite any case of asymptomatic transmission.

The Ferguson factor

The problem for the Cult as it headed into March, 2020, when the script had lockdown due to start, was that despite all the manipulation of the case and death figures they still did not have enough people alleged to have died from 'Covid' to justify mass house arrest. This was overcome in the way the scientist described: 'You can claim this is just the beginning and more deaths are imminent … Use this as an excuse to quarantine everyone and then claim the quarantine prevented the expected millions of dead.' Enter one Professor Neil Ferguson, the Gates-funded 'epidemiologist' at the Gates-funded Imperial College in London. Ferguson is Britain's Christian Drosten in that he has a dire record of predicting health outcomes, but is still called upon to advise government on the next health outcome when another 'crisis' comes along. This may seem to be a strange and ridiculous thing to do. Why would you keep turning for policy guidance to people who have a history of being

monumentally wrong? Ah, but it makes sense from the Cult point of view. These 'experts' keep on producing predictions that suit the Cult agenda for societal transformation and so it was with Neil Ferguson as he revealed his horrific (and clearly insane) computer model predictions that allowed lockdowns to be imposed in Britain, the United States and many other countries. Ferguson does not have even an A-level in biology and would appear to have no formal training in computer modelling, medicine or epidemiology, according to Derek Winton, an MSc in Computational Intelligence. He wrote an article somewhat aghast at what Ferguson did which included taking no account of respiratory disease 'seasonality' which means it is far worse in the winter months. Who would have thought that respiratory disease could be worse in the winter? Well, certainly not Ferguson.

The massively China-connected Imperial College and its bizarre professor provided the excuse for the long-incubated Chinese model of human control to travel westward at lightning speed. Imperial College confirms on its website that it collaborates with the Chinese Research Institute; publishes more than 600 research papers every year with Chinese research institutions; has 225 Chinese staff; 2,600 Chinese students – the biggest international group; 7,000 former students living in China which is the largest group outside the UK; and was selected for a tour by China's President Xi Jinping during his state visit to the UK in 2015. The college takes major donations from China and describes itself as the UK's number one university collaborator with Chinese research institutions. The China communist/fascist government did not appear phased by the woeful predictions of Ferguson and Imperial when during the lockdown that Ferguson induced the college signed a five-year collaboration deal with China tech giant Huawei that will have Huawei's indoor 5G network equipment installed at the college's West London tech campus along with an 'AI cloud platform'. The deal includes Chinese sponsorship of Imperial's Venture Catalyst entrepreneurship competition. Imperial is an example of the enormous influence the Chinese government has within British and North American

universities and research centres – and further afield. Up to 200 academics from more than a dozen UK universities are being investigated on suspicion of 'unintentionally' helping the Chinese government build weapons of mass destruction by 'transferring world-leading research in advanced military technology such as aircraft, missile designs and cyberweapons'. Similar scandals have broken in the United States, but it's all a coincidence. Imperial College serves the agenda in many other ways including the promotion of every aspect of the United Nations Agenda 21/2030 (the Great Reset) and produced computer models to show that human-caused 'climate change' is happening when in the real world it isn't. Imperial College is driving the climate agenda as it drives the 'Covid' agenda (both Cult hoaxes) while Patrick Vallance, the UK government's Chief Scientific Adviser on 'Covid', was named Chief Scientific Adviser to the UN 'climate change' conference known as COP26 hosted by the government in Glasgow, Scotland. 'Covid' and 'climate' are fundamentally connected.

Professor Woeful

From Imperial's bosom came Neil Ferguson still advising government despite his previous disasters and it was announced early on that he and other key people like UK Chief Medical Adviser Chris Whitty had caught the 'virus' as the propaganda story was being sold. Somehow they managed to survive and we had Prime Minister Boris Johnson admitted to hospital with what was said to be a severe version of the 'virus' in this same period. His whole policy and demeanour changed when he returned to Downing Street. It's a small world with these government advisors – especially in their communal connections to Gates – and Ferguson had partnered with Whitty to write a paper called 'Infectious disease: Tough choices to reduce Ebola transmission' which involved another scare-story that didn't happen. Ferguson's 'models' predicted that up to150, 000 could die from 'mad cow disease', or BSE, and its version in sheep if it was transmitted to humans. BSE was not transmitted and instead triggered by an organophosphate pesticide used to treat a pest on

cows. Fewer than 200 deaths followed from the human form. Models by Ferguson and his fellow incompetents led to the unnecessary culling of millions of pigs, cattle and sheep in the foot and mouth outbreak in 2001 which destroyed the lives and livelihoods of farmers and their families who had often spent decades building their herds and flocks. Vast numbers of these animals did not have foot and mouth and had no contact with the infection. Another 'expert' behind the cull was Professor Roy Anderson, a computer modeller at Imperial College specialising in the epidemiology of *human*, not animal, disease. Anderson has served on the Bill and Melinda Gates Grand Challenges in Global Health advisory board and chairs another Gates-funded organisation. Gates is everywhere.

In a precursor to the 'Covid' script Ferguson backed closing schools 'for prolonged periods' over the swine flu 'pandemic' in 2009 and said it would affect a third of the world population if it continued to spread at the speed he claimed to be happening. His mates at Imperial College said much the same and a news report said: 'One of the authors, the epidemiologist and disease modeller Neil Ferguson, who sits on the World Health Organisation's emergency committee for the outbreak, said the virus had "full pandemic potential".' Professor Liam Donaldson, the Chris Whitty of his day as Chief Medical Officer, said the worst case could see 30 percent of the British people infected by swine flu with 65,000 dying. Ferguson and Donaldson were indeed proved correct when at the end of the year the number of deaths attributed to swine flu was 392. The term 'expert' is rather liberally applied unfortunately, not least to complete idiots. Swine flu 'projections' were great for GlaxoSmithKline (GSK) as millions rolled in for its Pandemrix influenza vaccine which led to brain damage with children most affected. The British government (taxpayers) paid out more than £60 million in compensation after GSK was given immunity from prosecution. Yet another 'Covid' déjà vu. Swine flu was supposed to have broken out in Mexico, but Dr Wolfgang Wodarg, a German doctor, former member of parliament and critic of the 'Covid' hoax, observed 'the spread of swine flu' in Mexico City at the time. He

said: 'What we experienced in Mexico City was a very mild flu which did not kill more than usual – which killed even fewer people than usual.' Hyping the fear against all the facts is not unique to 'Covid' and has happened many times before. Ferguson is reported to have over-estimated the projected death toll of bird flu (H5N1) by some three million-fold, but bird flu vaccine makers again made a killing from the scare. This is some of the background to the Neil Ferguson who produced the perfectly-timed computer models in early 2020 predicting that half a million people would die in Britain without draconian lockdown and 2.2 million in the United States. Politicians panicked, people panicked, and lockdowns of alleged short duration were instigated to 'flatten the curve' of cases gleaned from a test not testing for the 'virus'. I said at the time that the public could forget the 'short duration' bit. This was an agenda to destroy the livelihoods of the population and force them into mass control through dependency and there was going to be nothing 'short' about it. American researcher Daniel Horowitz described the consequences of the 'models' spewed out by Gates-funded Ferguson and Imperial College:

> What led our government and the governments of many other countries into panic was a single Imperial College of UK study, funded by global warming activists, that predicted 2.2 million deaths if we didn't lock down the country. In addition, the reported 8-9% death rate in Italy scared us into thinking there was some other mutation of this virus that they got, which might have come here.
>
> Together with the fact that we were finally testing and had the ability to actually report new cases, we thought we were headed for a death spiral. But again … we can't flatten a curve if we don't know when the curve started.

How about it *never* started?

Giving them what they want

An investigation by German news outlet *Welt Am Sonntag (World on Sunday)* revealed how in March, 2020, the German government gathered together 'leading scientists from several research institutes and universities' and 'together, they were to produce a [modelling]

paper that would serve as legitimization for further tough political measures'. The Cult agenda was justified by computer modelling not based on evidence or reality; it was specifically constructed to justify the Cult demand for lockdowns all over the world to destroy the independent livelihoods of the global population. All these modellers and everyone responsible for the 'Covid' hoax have a date with a trial like those in Nuremberg after World War Two when Nazis faced the consequences of their war crimes. These corrupt-beyond-belief 'modellers' wrote the paper according to government instructions and it said that that if lockdown measures were lifted then up to one million Germans would die from 'Covid-19' adding that some would die 'agonizingly at home, gasping for breath' unable to be treated by hospitals that couldn't cope. All lies. No matter – it gave the Cult all that it wanted. What did long-time government 'modeller' Neil Ferguson say? If the UK and the United States didn't lockdown half a million would die in Britain and 2.2 million Americans. Anyone see a theme here? 'Modellers' are such a crucial part of the lockdown strategy that we should look into their background and follow the money. Researcher Rosemary Frei produced an excellent article headlined 'The Modelling-paper Mafiosi'. She highlights a guy called John Edmunds, a British epidemiologist, and professor in the Faculty of Epidemiology and Population Health at the London School of Hygiene & Tropical Medicine. He studied at Imperial College. Edmunds is a member of government 'Covid' advisory bodies which have been dictating policy, the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) and the Scientific Advisory Group for Emergencies (SAGE).

Ferguson, another member of NERVTAG and SAGE, led the way with the original 'virus' and Edmunds has followed in the 'variant' stage and especially the so-called UK or Kent variant known as the 'Variant of Concern' (VOC) B.1.1.7. He said in a co-written report for the Centre for Mathematical modelling of Infectious Diseases at the London School of Hygiene and Tropical Medicine, with input from the Centre's 'Covid-19' Working Group, that there was 'a realistic

possibility that VOC B.1.1.7 is associated with an increased risk of death compared to non-VOC viruses'. Fear, fear, fear, get the vaccine, fear, fear, fear, get the vaccine. Rosemary Frei reveals that almost all the paper's authors and members of the modelling centre's 'Covid-19' Working Group receive funding from the Bill and Melinda Gates Foundation and/or the associated Gates-funded Wellcome Trust. The paper was published by e-journal *Medr χiv* which only publishes papers not peer-reviewed and the journal was established by an organisation headed by Facebook's Mark Zuckerberg and his missus. What a small world it is. Frei discovered that Edmunds is on the Scientific Advisory Board of the Coalition for Epidemic Preparedness Innovations (CEPI) which was established by the Bill and Melinda Gates Foundation, Klaus Schwab's Davos World Economic Forum and Big Pharma giant Wellcome. CEPI was 'launched in Davos [in 2017] to develop vaccines to stop future epidemics', according to its website. 'Our mission is to accelerate the development of vaccines against emerging infectious diseases and enable equitable access to these vaccines for people during outbreaks.' What kind people they are. Rosemary Frei reveals that Public Health England (PHE) director Susan Hopkins is an author of her organisation's non-peer-reviewed reports on 'new variants'. Hopkins is a professor of infectious diseases at London's Imperial College which is gifted tens of millions of dollars a year by the Bill and Melinda Gates Foundation. Gates-funded modelling disaster Neil Ferguson also co-authors Public Health England reports and he spoke in December, 2020, about the potential danger of the B.1.1.7. 'UK variant' promoted by Gates-funded modeller John Edmunds. When I come to the 'Covid vaccines' the 'new variants' will be shown for what they are – bollocks.

Connections, connections

All these people and modellers are lockdown-obsessed or, put another way, they demand what the Cult demands. Edmunds said in January, 2021, that to ease lockdowns too soon would be a disaster and they had to 'vaccinate much, much, much more widely than the

elderly'. Rosemary Frei highlights that Edmunds is married to Jeanne Pimenta who is described in a LinkedIn profile as director of epidemiology at GlaxoSmithKline (GSK) and she held shares in the company. Patrick Vallance, co-chair of SAGE and the government's Chief Scientific Adviser, is a former executive of GSK and has a deferred bonus of shares in the company worth £600,000. GSK has serious business connections with Bill Gates and is collaborating with mRNA-'vaccine' company CureVac to make 'vaccines' for the new variants that Edmunds is talking about. GSK is planning a 'Covid vaccine' with drug giant Sanofi. Puppet Prime Minister Boris Johnson announced in the spring of 2021 that up to 60 million vaccine doses were to be made at the GSK facility at Barnard Castle in the English North East. Barnard Castle, with a population of just 6,000, was famously visited in breach of lockdown rules in April, 2020, by Johnson aide Dominic Cummings who said that he drove there 'to test his eyesight' before driving back to London. Cummings would be better advised to test his integrity – not that it would take long. The GSK facility had nothing to do with his visit then although I'm sure Patrick Vallance would have been happy to arrange an introduction and some tea and biscuits. Ruthless psychopath Gates has made yet another fortune from vaccines in collaboration with Big Pharma companies and gushes at the phenomenal profits to be made from vaccines – more than a 20-to-1 return as he told one interviewer. Gates also tweeted in December, 2019, with the foreknowledge of what was coming: 'What's next for our foundation? I'm particularly excited about what the next year could mean for one of the best buys in global health: vaccines.'

Modeller John Edmunds is a big promotor of vaccines as all these people appear to be. He's the dean of the London School of Hygiene & Tropical Medicine's Faculty of Epidemiology and Population Health which is primarily funded by the Bill and Melinda Gates Foundation and the Gates-established and funded GAVI vaccine alliance which is the Gates vehicle to vaccinate the world. The organisation Doctors Without Borders has described GAVI as being 'aimed more at supporting drug-industry desires to promote new

products than at finding the most efficient and sustainable means for fighting the diseases of poverty'. But then that's why the psychopath Gates created it. John Edmunds said in a video that the London School of Hygiene & Tropical Medicine is involved in every aspect of vaccine development including large-scale clinical trials. He contends that mathematical modelling can show that vaccines protect individuals and society. That's on the basis of shit in and shit out, I take it. Edmunds serves on the UK Vaccine Network as does Ferguson and the government's foremost 'Covid' adviser, the grim-faced, dark-eyed Chris Whitty. The Vaccine Network says it works 'to support the government to identify and shortlist targeted investment opportunities for the most promising vaccines and vaccine technologies that will help combat infectious diseases with epidemic potential, and to address structural issues related to the UK's broader vaccine infrastructure'. Ferguson is acting Director of the Imperial College Vaccine Impact Modelling Consortium which has funding from the Bill and Melina Gates Foundation and the Gates-created GAVI 'vaccine alliance'. Anyone wonder why these characters see vaccines as the answer to every problem? Ferguson is wildly enthusiastic in his support for GAVI's campaign to vaccine children en masse in poor countries. You would expect someone like Gates who has constantly talked about the need to reduce the population to want to fund vaccines to keep more people alive. I'm sure that's why he does it. The John Edmunds London School of Hygiene & Tropical Medicine (LSHTM) has a Vaccines Manufacturing Innovation Centre which develops, tests and commercialises vaccines. Rosemary Frei writes:

> The vaccines centre also performs affiliated activities like combating 'vaccine hesitancy'. The latter includes the Vaccine Confidence Project. The project's stated purpose is, among other things, 'to provide analysis and guidance for early response and engagement with the public to ensure sustained confidence in vaccines and immunisation'. The Vaccine Confidence Project's director is LSHTM professor Heidi Larson. For more than a decade she's been researching how to combat vaccine hesitancy.

How the bloody hell can blokes like John Edmunds and Neil Ferguson with those connections and financial ties model 'virus' case

and death projections for the government and especially in a way that gives their paymasters like Gates exactly what they want? It's insane, but this is what you find throughout the world.

'Covid' is not dangerous, oops, wait, yes it is

Only days before Ferguson's nightmare scenario made Jackboot Johnson take Britain into a China-style lockdown to save us from a deadly 'virus' the UK government website gov.uk was reporting something very different to Ferguson on a page of official government guidance for 'high consequence infectious diseases (HCID)'. It said this about 'Covid-19':

As of 19 March 2020, COVID-19 *is no longer considered to be a high consequence infectious diseases (HCID) in the UK* [my emphasis]. The 4 nations public health HCID group made an interim recommendation in January 2020 to classify COVID-19 as an HCID. This was based on consideration of the UK HCID criteria about the virus and the disease with information available during the early stages of the outbreak.

Now that more is known about COVID-19, the public health bodies in the UK have reviewed the most up to date information about COVID-19 against the UK HCID criteria. They have determined that several features have now changed; in particular, more information is available about mortality rates (low overall), and there is now greater clinical awareness and a specific and sensitive laboratory test, the availability of which continues to increase. The Advisory Committee on Dangerous Pathogens (ACDP) is also of the opinion that COVID-19 should no longer be classified as an HCID.

Soon after the government had been exposed for downgrading the risk they upgraded it again and everyone was back to singing from the same Cult hymn book. Ferguson and his fellow Gates clones indicated that lockdowns and restrictions would have to continue until a Gates-funded vaccine was developed. Gates said the same because Ferguson and his like were repeating the Gates script which is the Cult script. 'Flatten the curve' became an ongoing nightmare of continuing lockdowns with periods in between of severe restrictions in pursuit of destroying independent incomes and had nothing to do with protecting health about which the Cult gives not a shit. Why wouldn't Ferguson be pushing a vaccine 'solution' when he's owned by vaccine-obsessive Gates who makes a fortune from them and

when Ferguson heads the Vaccine Impact Modelling Consortium at Imperial College funded by the Gates Foundation and GAVI, the 'vaccine alliance', created by Gates as his personal vaccine promotion operation? To compound the human catastrophe that Ferguson's 'models' did so much to create he was later exposed for breaking his own lockdown rules by having sexual liaisons with his married girlfriend Antonia Staats at his home while she was living at another location with her husband and children. Staats was a 'climate' activist and senior campaigner at the Soros-funded Avaaz which I wouldn't trust to tell me that grass is green. Ferguson had to resign as a government advisor over this hypocrisy in May, 2020, but after a period of quiet he was back being quoted by the ridiculous media on the need for more lockdowns and a vaccine rollout. Other government-advising 'scientists' from Imperial College' held the fort in his absence and said lockdown could be indefinite until a vaccine was found. The Cult script was being sung by the payrolled choir. I said there was no intention of going back to 'normal' when the 'vaccine' came because the 'vaccine' is part of a very different agenda that I will discuss in Human 2.0. Why would the Cult want to let the world go back to normal when destroying that normal forever was the whole point of what was happening? House arrest, closing businesses and schools through lockdown, (un)social distancing and masks all followed the Ferguson fantasy models. Again as I predicted (these people are so predictable) when the 'vaccine' arrived we were told that house arrest, lockdown, (un)social distancing and masks would still have to continue. I will deal with the masks in the next chapter because they are of fundamental importance.

Where's the 'pandemic'?

Any mildly in-depth assessment of the figures revealed what was really going on. Cult-funded and controlled organisations still have genuine people working within them such is the number involved. So it is with Genevieve Briand, assistant program director of the Applied Economics master's degree program at Johns Hopkins

University. She analysed the impact that 'Covid-19' had on deaths from *all* causes in the United States using official data from the CDC for the period from early February to early September, 2020. She found that allegedly 'Covid' *related*-deaths exceeded those from heart disease which she found strange with heart disease always the biggest cause of fatalities. Her research became even more significant when she noted the sudden decline in 2020 of *all* non-'Covid' deaths: 'This trend is completely contrary to the pattern observed in all previous years … the total decrease in deaths by other causes almost exactly equals the increase in deaths by Covid-19.' This was such a game, set and match in terms of what was happening that Johns Hopkins University deleted the article on the grounds that it 'was being used to support false and dangerous inaccuracies about the impact of the pandemic'. No – because it exposed the scam from official CDC figures and this was confirmed when those figures were published in January, 2021. Here we can see the effect of people dying from heart attacks, cancer, road accidents and gunshot wounds – *anything* – having 'Covid-19' on the death certificate along with those diagnosed from 'symptoms' who had even not tested positive with a test not testing for the 'virus'. I am not kidding with the gunshot wounds, by the way. Brenda Bock, coroner in Grand County, Colorado, revealed that two gunshot victims tested positive for the 'virus' within the previous 30 days and were therefore classified as 'Covid deaths'. Bock said: 'These two people had tested positive for Covid, but that's not what killed them. A gunshot wound is what killed them.' She said she had not even finished her investigation when the state listed the gunshot victims as deaths due to the 'virus'. The death and case figures for 'Covid-19' are an absolute joke and yet they are repeated like parrots by the media, politicians and alleged medical 'experts'. The official Cult narrative is the only show in town.

Genevieve Briand found that deaths from all causes were not exceptional in 2020 compared with previous years and a Spanish magazine published figures that said the same about Spain which was a 'Covid' propaganda hotspot at one point. *Discovery Salud*, a

health and medicine magazine, quoted government figures which showed how 17,000 *fewer* people died in Spain in 2020 than in 2019 and more than 26,000 fewer than in 2018. The age-standardised mortality rate for England and Wales when age distribution is taken into account was significantly lower in 2020 than the 1970s, 80s and 90s, and was only the ninth highest since 2000. Where is the 'pandemic'?

Post mortems and autopsies virtually disappeared for 'Covid' deaths amid claims that 'virus-infected' bodily fluids posed a risk to those carrying out the autopsy. This was rejected by renowned German pathologist and forensic doctor Klaus Püschel who said that he and his staff had by then done 150 autopsies on 'Covid' patients with no problems at all. He said they were needed to know why some 'Covid' patients suffered blood clots and not severe respiratory infections. The 'virus' is, after all, called SARS or 'severe acute respiratory syndrome'. I highlighted in the spring of 2020 this phenomenon and quoted New York intensive care doctor Cameron Kyle-Sidell who posted a soon deleted YouTube video to say that they had been told to prepare to treat an infectious disease called 'Covid-19', but that was not what they were dealing with. Instead he likened the lung condition of the most severely ill patients to what you would expect with cabin depressurisation in a plane at 30,000 feet or someone dropped on the top of Everest without oxygen or acclimatisation. I have never said this is not happening to a small minority of alleged 'Covid' patients – I am saying this is not caused by a phantom 'contagious virus'. Indeed Kyle-Sidell said that 'Covid-19' was not the disease they were told was coming their way. 'We are operating under a medical paradigm that is untrue,' he said, and he believed they were treating the wrong disease: 'These people are being slowly starved of oxygen.' Patients would take off their oxygen masks in a state of fear and stress and while they were blue in the face on the brink of death. They did not look like patients dying of pneumonia. You can see why they don't want autopsies when their virus doesn't exist and there is another condition in some people that they don't wish to be uncovered. I should add here that

the 5G system of millimetre waves was being rapidly introduced around the world in 2020 and even more so now as they fire 5G at the Earth from satellites. At 60 gigahertz within the 5G range that frequency interacts with the oxygen molecule and stops people breathing in sufficient oxygen to be absorbed into the bloodstream. They are installing 5G in schools and hospitals. The world is not mad or anything. 5G can cause major changes to the lungs and blood as I detail in *The Answer* and these consequences are labelled 'Covid-19', the alleged symptoms of which can be caused by 5G and other electromagnetic frequencies as cells respond to radiation poisoning.

The 'Covid death' scam

Dr Scott Jensen, a Minnesota state senator and medical doctor, exposed 'Covid' Medicare payment incentives to hospitals and death certificate manipulation. He said he was sent a seven-page document by the US Department of Health 'coaching' him on how to fill out death certificates which had never happened before. The document said that he didn't need to have a laboratory test for 'Covid-19' to put that on the death certificate and that shocked him when death certificates are supposed to be about facts. Jensen described how doctors had been 'encouraged, if not pressured' to make a diagnosis of 'Covid-19' if they thought it was probable or *'presumed*'. No positive test was necessary – not that this would have mattered anyway. He said doctors were told to diagnose 'Covid' by symptoms when these were the same as colds, allergies, other respiratory problems, and certainly with influenza which 'disappeared' in the 'Covid' era. A common sniffle was enough to get the dreaded verdict. Ontario authorities decreed that a single care home resident with *one* symptom from a long list must lead to the isolation of the entire home. Other courageous doctors like Jensen made the same point about death figure manipulation and how deaths by other causes were falling while 'Covid-19 deaths' were rising at the same rate due to re-diagnosis. Their videos rarely survive long on YouTube with its Cult-supporting algorithms courtesy of CEO Susan Wojcicki and her bosses at Google. Figure-tampering was so glaring

and ubiquitous that even officials were letting it slip or outright saying it. UK chief scientific adviser Patrick Vallance said on one occasion that 'Covid' on the death certificate doesn't mean 'Covid' was the cause of death (so why the hell is it there?) and we had the rare sight of a BBC reporter telling the truth when she said: 'Someone could be successfully treated for Covid, in say April, discharged, and then in June, get run over by a bus and die … That person would still be counted as a Covid death in England.' Yet the BBC and the rest of the world media went on repeating the case and death figures as if they were real. Illinois Public Health Director Dr Ngozi Ezike revealed the deceit while her bosses must have been clenching their buttocks:

> If you were in a hospice and given a few weeks to live and you were then found to have Covid that would be counted as a Covid death. [There might be] a clear alternate cause, but it is still listed as a Covid death. So everyone listed as a Covid death doesn't mean that was the cause of the death, but that they had Covid at the time of death.

Yes, a 'Covid virus' never shown to exist and tested for with a test not testing for the 'virus'. In the first period of the pandemic hoax through the spring of 2020 the process began of designating almost everything a 'Covid' death and this has continued ever since. I sat in a restaurant one night listening to a loud conversation on the next table where a family was discussing in bewilderment how a relative who had no symptoms of 'Covid', and had died of a long-term problem, could have been diagnosed a death by the 'virus'. I could understand their bewilderment. If they read this book they will know why this medical fraud has been perpetrated the world over.

Some media truth shock

The media ignored the evidence of death certificate fraud until eventually one columnist did speak out when she saw it first-hand. Bel Mooney is a long-time national newspaper journalist in Britain currently working for the *Daily Mail*. Her article on February 19th, 2021, carried this headline: 'My dad Ted passed three Covid tests

and died of a chronic illness yet he's officially one of Britain's 120,000 victims of the virus and is far from alone ... so how many more are there?' She told how her 99-year-old father was in a care home with a long-standing chronic obstructive pulmonary disease and vascular dementia. Maybe, but he was still aware enough to tell her from the start that there was no 'virus' and he refused the 'vaccine' for that reason. His death was not unexpected given his chronic health problems and Mooney said she was shocked to find that 'Covid-19' was declared the cause of death on his death certificate. She said this was a 'bizarre and unacceptable untruth' for a man with long-time health problems who had tested negative twice at the home for the 'virus'. I was also shocked by this story although not by what she said. I had been highlighting the death certificate manipulation for ten months. It was the confirmation that a professional full-time journalist only realised this was going on when it affected her directly and neither did she know that whether her dad tested positive or negative was irrelevant with the test not testing for the 'virus'. Where had she been? She said she did not believe in 'conspiracy theories' without knowing I'm sure that this and 'conspiracy theorists' were terms put into widespread circulation by the CIA in the 1960s to discredit those who did not accept the ridiculous official story of the Kennedy assassination. A blanket statement of 'I don't believe in conspiracy theories' is always bizarre. The dictionary definition of the term alone means the world is drowning in conspiracies. What she said was even more daft when her dad had just been affected by the 'Covid' conspiracy. Why else does she think that 'Covid-19' was going on the death certificates of people who died of something else?

To be fair once she saw from personal experience what was happening she didn't mince words. Mooney was called by the care home on the morning of February 9th to be told her father had died in his sleep. When she asked for the official cause of death what came back was 'Covid-19'. Mooney challenged this and was told there had been deaths from Covid on the dementia floor (confirmed by a test not testing for the 'virus') so they considered it 'reasonable

to assume'. 'But doctor,' Mooney rightly protested, 'an assumption isn't a diagnosis.' She said she didn't blame the perfectly decent and sympathetic doctor – 'he was just doing his job'. Sorry, but that's *bullshit*. He wasn't doing his job at all. He was putting a false cause of death on the death certificate and that is a criminal offence for which he should be brought to account and the same with the millions of doctors worldwide who have done the same. They were not doing their job they were following orders and that must not wash at new Nuremberg trials any more than it did at the first ones. Mooney's doctor was 'assuming' (presuming) as he was told to, but 'just following orders' makes no difference to his actions. A doctor's job is to serve the patient and the truth, not follow orders, but that's what they have done all over the world and played a central part in making the 'Covid' hoax possible with all its catastrophic consequences for humanity. Shame on them and they must answer for their actions. Mooney said her disquiet worsened when she registered her father's death by telephone and was told by the registrar there had been very many other cases like hers where 'the deceased' had not tested positive for 'Covid' yet it was recorded as the cause of death. The test may not matter, but those involved at their level *think* it matters and it shows a callous disregard for accurate diagnosis. The pressure to do this is coming from the top of the national 'health' pyramids which in turn obey the World Health Organization which obeys Gates and the Cult. Mooney said the registrar agreed that this must distort the national figures adding that 'the strangest thing is that every winter we record countless deaths from flu, and this winter there have been none. Not one!' She asked if the registrar thought deaths from flu were being misdiagnosed and lumped together with 'Covid' deaths. The answer was a 'puzzled yes'. Mooney said that the funeral director said the same about 'Covid' deaths which had nothing to do with 'Covid'. They had lost count of the number of families upset by this and other funeral companies in different countries have had the same experience. Mooney wrote:

The nightly shroud-waving and shocking close-ups of pain imposed on us by the TV news bewildered and terrified the population into eager compliance with lockdowns. We were invited to 'save the NHS' and to grieve for strangers – the real-life loved ones behind those shocking death counts. Why would the public imagine what I now fear, namely that the way Covid-19 death statistics are compiled might make the numbers seem greater than they are?

Oh, just a little bit – like 100 percent.

Do the maths

Mooney asked why a country would wish to skew its mortality figures by wrongly certifying deaths? What had been going on? Well, if you don't believe in conspiracies you will never find the answer which is that *it's a conspiracy*. She did, however, describe what she had discovered as a 'national scandal'. In reality it's a global scandal and happening everywhere. Pillars of this conspiracy were all put into place before the button was pressed with the Drosten PCR protocol and high amplifications to produce the cases and death certificate changes to secure illusory 'Covid' deaths. Mooney notes that normally two doctors were needed to certify a death, with one having to know the patient, and how the rules were changed in the spring of 2020 to allow one doctor to do this. In the same period 'Covid deaths' were decreed to be all cases where Covid-19 was put on the death certificate even without a positive test or any symptoms. Mooney asked: 'How many of the 30,851 (as of January 15) care home resident deaths with Covid-19 on the certificate (32.4 per cent of all deaths so far) were based on an assumption, like that of my father? And what has that done to our national psyche?'All of them is the answer to the first question and it has devastated and dismantled the national psyche, actually the global psyche, on a colossal scale. In the UK case and death data is compiled by organisations like Public Health England (PHE) and the Office for National Statistics (ONS). Mooney highlights the insane policy of counting a death from any cause as 'Covid-19' if this happens within 28 days of a positive test (with a test not testing for the 'virus') and she points out that ONS statistics reflect deaths 'involving Covid' 'or due to Covid' which meant in practice any

death where 'Covid-19' was mentioned on the death certificate. She described the consequences of this fraud:

Most people will accept the narrative they are fed, so panicky governments here and in Europe witnessed the harsh measures enacted in totalitarian China and jumped into lockdown. Headlines about Covid deaths tolled like the knell that would bring doomsday to us all. Fear stalked our empty streets. Politicians parroted the frankly ridiculous aim of 'zero Covid' and shut down the economy, while most British people agreed that lockdown was essential and (astonishingly to me, as a patriotic Brit) even wanted more restrictions.

For what? Lies on death certificates? Never mind the grim toll of lives ruined, suicides, schools closed, rising inequality, depression, cancelled hospital treatments, cancer patients in a torture of waiting, poverty, economic devastation, loneliness, families kept apart, and so on. How many lives have been lost as a direct result of lockdown?

She said that we could join in a national chorus of shock and horror at reaching the 120,000 death toll which was surely certain to have been totally skewed all along, but what about the human cost of lockdown justified by these 'death figures'? *The British Medical Journal* had reported a 1,493 percent increase in cases of children taken to Great Ormond Street Hospital with abusive head injuries alone and then there was the effect on families:

Perhaps the most shocking thing about all this is that families have been kept apart – and obeyed the most irrational, changing rules at the whim of government – because they believed in the statistics. They succumbed to fear, which his generation rejected in that war fought for freedom. Dad (God rest his soul) would be angry. And so am I.

Another theme to watch is that in the winter months when there are more deaths from all causes they focus on 'Covid' deaths and in the summer when the British Lung Foundation says respiratory disease plummets by 80 percent they rage on about 'cases'. Either way fascism on population is always the answer.

Nazi eugenics in the 21st century

Elderly people in care homes have been isolated from their families month after lonely month with no contact with relatives and grandchildren who were banned from seeing them. We were told

that lockdown fascism was to 'protect the vulnerable' like elderly people. At the same time Do Not Resuscitate (DNR) orders were placed on their medical files so that if they needed resuscitation it wasn't done and 'Covid-19' went on their death certificates. Old people were not being 'protected' they were being culled – murdered in truth. DNR orders were being decreed for disabled and young people with learning difficulties or psychological problems. The UK Care Quality Commission, a non-departmental body of the Department of Health and Social Care, found that 34 percent of those working in health and social care were pressured into placing 'do not attempt cardiopulmonary resuscitation' orders on 'Covid' patients who suffered from disabilities and learning difficulties without involving the patient or their families in the decision. UK judges ruled that an elderly woman with dementia should have the DNA-manipulating 'Covid vaccine' against her son's wishes and that a man with severe learning difficulties should have the jab despite his family's objections. Never mind that many had already died. The judiciary always supports doctors and government in fascist dictatorships. They wouldn't dare do otherwise. A horrific video was posted showing fascist officers from Los Angeles police forcibly giving the 'Covid' shot to women with special needs who were screaming that they didn't want it. The same fascists are seen giving the jab to a sleeping elderly woman in a care home. This is straight out of the Nazi playbook. Hitler's Nazis committed mass murder of the mentally ill and physically disabled throughout Germany and occupied territories in the programme that became known as Aktion T4, or just T4. Sabbatian-controlled Hitler and his grotesque crazies set out to kill those they considered useless and unnecessary. The Reich Committee for the Scientific Registering of Hereditary and Congenital Illnesses registered the births of babies identified by physicians to have 'defects'. By 1941 alone more than 5,000 children were murdered by the state and it is estimated that in total the number of innocent people killed in Aktion T4 was between 275,000 and 300,000. Parents were told their children had been sent away for 'special treatment' never to return. It is rather pathetic to see claims about plans for new extermination camps being dismissed today

when the same force behind current events did precisely that 80 years ago. Margaret Sanger was a Cult operative who used 'birth control' to sanitise her programme of eugenics. Organisations she founded became what is now Planned Parenthood. Sanger proposed that 'the whole dysgenic population would have its choice of segregation or sterilization'. These included epileptics, 'feeble-minded', and prostitutes. Sanger opposed charity because it perpetuated 'human waste'. She reveals the Cult mentality and if anyone thinks that extermination camps are a 'conspiracy theory' their naivety is touching if breathtakingly stupid.

If you don't believe that doctors can act with callous disregard for their patients it is worth considering that doctors and medical staff agreed to put government-decreed DNR orders on medical files and do nothing when resuscitation is called for. I don't know what you call such people in your house. In mine they are Nazis from the Josef Mengele School of Medicine. Phenomenal numbers of old people have died worldwide from the effects of lockdown, depression, lack of treatment, the 'vaccine' (more later) and losing the will to live. A common response at the start of the manufactured pandemic was to remove old people from hospital beds and transfer them to nursing homes. The decision would result in a mass cull of elderly people in those homes through lack of treatment – *not* 'Covid'. Care home whistleblowers have told how once the 'Covid' era began doctors would not come to their homes to treat patients and they were begging for drugs like antibiotics that often never came. The most infamous example was ordered by New York governor Andrew Cuomo, brother of a moronic CNN host, who amazingly was given an Emmy Award for his handling of the 'Covid crisis' by the ridiculous Wokers that hand them out. Just how ridiculous could be seen in February, 2021, when a Department of Justice and FBI investigation began into how thousands of old people in New York died in nursing homes after being discharged from hospital to make way for 'Covid' patients on Cuomo's say-so – and how he and his staff covered up these facts. This couldn't have happened to a nicer psychopath. Even then there was a 'Covid' spin. Reports said that

thousands of old people who tested positive for 'Covid' in hospital were transferred to nursing homes to both die of 'Covid' and transmit it to others. No – they were in hospital because they were ill and the fact that they tested positive with a test not testing for the 'virus' is irrelevant. They were ill often with respiratory diseases ubiquitous in old people near the end of their lives. Their transfer out of hospital meant that their treatment stopped and many would go on to die.

They're old. Who gives a damn?

I have exposed in the books for decades the Cult plan to cull the world's old people and even to introduce at some point what they call a 'demise pill' which at a certain age everyone would take and be out of here by law. In March, 2021, Spain legalised euthanasia and assisted suicide following the Netherlands, Belgium, Luxembourg and Canada on the Tiptoe to the demise pill. Treatment of old people by many 'care' homes has been a disgrace in the 'Covid' era. There are many, many, caring staff – I know some. There have, however, been legions of stories about callous treatment of old people and their families. Police were called when families came to take their loved ones home in the light of isolation that was killing them. They became prisoners of the state. Care home residents in insane, fascist Ontario, Canada, were not allowed to leave their *room* once the 'Covid' hoax began. UK staff have even wheeled elderly people away from windows where family members were talking with them. Oriana Criscuolo from Stockport in the English North West dropped off some things for her 80-year-old father who has Parkinson's disease and dementia and she wanted to wave to him through a ground-floor window. She was told that was 'illegal'. When she went anyway they closed the curtains in the middle of the day. Oriana said:

> It's just unbelievable. I cannot understand how care home staff – people who are being paid to care – have become so uncaring. Their behaviour is inhumane and cruel. It's beyond belief.

She was right and this was not a one-off. What a way to end your life in such loveless circumstances. UK registered nurse Nicky Millen, a proper old school nurse for 40 years, said that when she started her career care was based on dignity, choice, compassion and empathy. Now she said 'the things that are important to me have gone out of the window.' She was appalled that people were dying without their loved ones and saying goodbye on iPads. Nicky described how a distressed 89-year-old lady stroked her face and asked her 'how many paracetamol would it take to finish me off'. Life was no longer worth living while not seeing her family. Nicky said she was humiliated in front of the ward staff and patients for letting the lady stroke her face and giving her a cuddle. Such is the dehumanisation that the 'Covid' hoax has brought to the surface. Nicky worked in care homes where patients told her they were being held prisoner. 'I want to live until I die', one said to her. 'I had a lady in tears because she hadn't seen her great-grandson.' Nicky was compassionate old school meeting psychopathic New Normal. She also said she had worked on a 'Covid' ward with no 'Covid' patients. Jewish writer Shai Held wrote an article in March, 2020, which was headlined 'The Staggering, Heartless Cruelty Toward the Elderly'. What he described was happening from the earliest days of lockdown. He said 'the elderly' were considered a group and not unique individuals (the way of the Woke). Shai Held said:

Notice how the all-too-familiar rhetoric of dehumanization works: 'The elderly' are bunched together as a faceless mass, all of them considered culprits and thus effectively deserving of the suffering the pandemic will inflict upon them. Lost entirely is the fact that the elderly are individual human beings, each with a distinctive face and voice, each with hopes and dreams, memories and regrets, friendships and marriages, loves lost and loves sustained.

'The elderly' have become another dehumanised group for which anything goes and for many that has resulted in cold disregard for their rights and their life. The distinctive face that Held talks about is designed to be deleted by masks until everyone is part of a faceless mass.

‘War-zone’ hospitals myth

Again and again medical professionals have told me what was really going on and how hospitals ‘overrun like war zones’ according to the media were virtually empty. The mantra from medical whistleblowers was please don’t use my name or my career is over. Citizen journalists around the world sneaked into hospitals to film evidence exposing the ‘war-zone’ lie. They really *were* largely empty with closed wards and operating theatres. I met a hospital worker in my town on the Isle of Wight during the first lockdown in 2020 who said the only island hospital had never been so quiet. Lockdown was justified by the psychopaths to stop hospitals being overrun. At the same time that the island hospital was near-empty the military arrived here to provide *extra beds*. It was all propaganda to ramp up the fear to ensure compliance with fascism as were never-used temporary hospitals with thousands of beds known as Nightingales and never-used make-shift mortuaries opened by the criminal UK government. A man who helped to install those extra island beds attributed to the army said they were never used and the hospital was empty. Doctors and nurses ‘stood around talking or on their phones, wandering down to us to see what we were doing’. There were no masks or social distancing. He accused the useless local island paper, the *County Press*, of ‘pumping the fear as if our hospital was overrun and we only have one so it should have been’. He described ambulances parked up with crews outside in deck chairs. When his brother called an ambulance he was told there was a two-hour backlog which he called ‘bullshit’. An old lady on the island fell ‘and was in a bad way’, but a caller who rang for an ambulance was told the situation wasn’t urgent enough. Ambulance stations were working under capacity while people would hear ambulances with sirens blaring driving through the streets. When those living near the stations realised what was going on they would follow them as they left, circulated around an urban area with the sirens going, and then came back without stopping. All this was to increase levels of fear and the same goes for the ‘ventilator shortage crisis’ that cost tens of millions for hastily produced ventilators never to be used.

Ambulance crews that agreed to be exploited in this way for fear propaganda might find themselves a mirror. I wish them well with that. Empty hospitals were the obvious consequence of treatment and diagnoses of non-'Covid' conditions cancelled and those involved handed a death sentence. People have been dying at home from undiagnosed and untreated cancer, heart disease and other life-threatening conditions to allow empty hospitals to deal with a 'pandemic' that wasn't happening.

Death of the innocent

'War-zones' have been laying off nursing staff, even doctors where they can. There was no work for them. Lockdown was justified by saving lives and protecting the vulnerable they were actually killing with DNR orders and preventing empty hospitals being 'overrun'. In Britain the mantra of stay at home to 'save the NHS' was everywhere and across the world the same story was being sold when it was all lies. Two California doctors, Dan Erickson and Artin Massihi at Accelerated Urgent Care in Bakersfield, held a news conference in April, 2020, to say that intensive care units in California were 'empty, essentially', with hospitals shutting floors, not treating patients and laying off doctors. The California health system was working at minimum capacity 'getting rid of doctors because we just don't have the volume'. They said that people with conditions such as heart disease and cancer were not coming to hospital out of fear of 'Covid-19'. Their video was deleted by Susan Wojcicki's Cult-owned YouTube after reaching five million views. Florida governor Ron Desantis, who rejected the severe lockdowns of other states and is being targeted for doing so, said that in March, 2020, every US governor was given models claiming they would run out of hospital beds in days. That was never going to happen and the 'modellers' knew it. Deceit can be found at every level of the system. Urgent children's operations were cancelled including fracture repairs and biopsies to spot cancer. Eric Nicholls, a consultant paediatrician, said 'this is obviously concerning and we need to return to normal operating and to increase capacity as soon as possible'. Psychopaths

in power were rather less concerned *because* they are psychopaths. Deletion of urgent care and diagnosis has been happening all over the world and how many kids and others have died as a result of the actions of these cold and heartless lunatics dictating 'health' policy? The number must be stratospheric. Richard Sullivan, professor of cancer and global health at King's College London, said people feared 'Covid' more than cancer such was the campaign of fear. 'Years of lost life will be quite dramatic', Sullivan said, with 'a huge amount of avoidable mortality'. Sarah Woolnough, executive director for policy at Cancer Research UK, said there had been a 75 percent drop in urgent referrals to hospitals by family doctors of people with suspected cancer. Sullivan said that 'a lot of services have had to scale back – we've seen a dramatic decrease in the amount of elective cancer surgery'. Lockdown deaths worldwide has been absolutely fantastic with the *New York Post* reporting how data confirmed that 'lockdowns end more lives than they save':

> There was a sharp decline in visits to emergency rooms and an increase in fatal heart attacks because patients didn't receive prompt treatment. Many fewer people were screened for cancer. Social isolation contributed to excess deaths from dementia and Alzheimer's.
>
> Researchers predicted that the social and economic upheaval would lead to tens of thousands of "deaths of despair" from drug overdoses, alcoholism and suicide. As unemployment surged and mental-health and substance-abuse treatment programs were interrupted, the reported levels of anxiety, depression and suicidal thoughts increased dramatically, as did alcohol sales and fatal drug overdoses.

This has been happening while nurses and other staff had so much time on their hands in the 'war-zones' that Tic-Tok dancing videos began appearing across the Internet with medical staff dancing around in empty wards and corridors as people died at home from causes that would normally have been treated in hospital.

Mentions in dispatches

One brave and truth-committed whistleblower was Louise Hampton, a call handler with the UK NHS who made a viral Internet video saying she had done 'fuck all' during the 'pandemic'

which was 'a load of bollocks'. She said that 'Covid-19' was rebranded flu and of course she lost her job. This is what happens in the medical and endless other professions now when you tell the truth. Louise filmed inside 'war-zone' accident and emergency departments to show they were empty and I mean *empty* as in no one there. The mainstream media could have done the same and blown the gaff on the whole conspiracy. They haven't to their eternal shame. Not that most 'journalists' seem capable of manifesting shame as with the psychopaths they slavishly repeat without question. The relative few who were admitted with serious health problems were left to die alone with no loved ones allowed to see them because of 'Covid' rules and they included kids dying without the comfort of mum and dad at their bedside while the evil behind this couldn't give a damn. It was all good fun to them. A Scottish NHS staff nurse publicly quit in the spring of 2021 saying: 'I can no longer be part of the lies and the corruption by the government.' She said hospitals 'aren't full, the beds aren't full, beds have been shut, wards have been shut'. Hospitals were never busy throughout 'Covid'. The staff nurse said that Nicola Sturgeon, tragically the leader of the Scottish government, was on television saying save the hospitals and the NHS – 'but the beds are empty' and 'we've not seen flu, we always see flu every year'. She wrote to government and spoke with her union Unison (the unions are Cult-compromised and *useless*, but nothing changed. Many of her colleagues were scared of losing their jobs if they spoke out as they wanted to. She said nursing staff were being affected by wearing masks all day and 'my head is splitting every shift from wearing a mask'. The NHS is part of the fascist tyranny and must be dismantled so we can start again with human beings in charge. (Ironically, hospitals were reported to be busier again when official 'Covid' cases *fell* in spring/summer of 2021 and many other conditions required treatment at the same time as *the fake vaccine rollout*.)

I will cover the 'Covid vaccine' scam in detail later, but it is another indicator of the sickening disregard for human life that I am highlighting here. The DNA-manipulating concoctions do not fulfil

the definition of a 'vaccine', have never been used on humans before and were given only emergency approval because trials were not completed and they continued using the unknowing public. The result was what a NHS senior nurse with responsibility for 'vaccine' procedure said was 'genocide'. She said the 'vaccines' were not 'vaccines'. They had not been shown to be safe and claims about their effectiveness by drug companies were 'poetic licence'. She described what was happening as a 'horrid act of human annihilation'. The nurse said that management had instigated a policy of not providing a Patient Information Leaflet (PIL) before people were 'vaccinated' even though health care professionals are supposed to do this according to protocol. Patients should also be told that they are taking part in an ongoing clinical trial. Her challenges to what is happening had seen her excluded from meetings and ridiculed in others. She said she was told to 'watch my step … or I would find myself surplus to requirements'. The nurse, who spoke anonymously in fear of her career, said she asked her NHS manager why he/she was content with taking part in genocide against those having the 'vaccines'. The reply was that everyone had to play their part and to 'put up, shut up, and get it done'. Government was 'leaning heavily' on NHS management which was clearly leaning heavily on staff. This is how the global 'medical' hierarchy operates and it starts with the Cult and its World Health Organization.

She told the story of a doctor who had the Pfizer jab and when questioned had no idea what was in it. The doctor had never read the literature. We have to stop treating doctors as intellectual giants when so many are moral and medical pygmies. The doctor did not even know that the 'vaccines' were not fully approved or that their trials were ongoing. They were, however, asking their patients if they minded taking part in follow-ups for research purposes – yes, the *ongoing clinical trial*. The nurse said the doctor's ignorance was not rare and she had spoken to a hospital consultant who had the jab without any idea of the background or that the 'trials' had not been completed. Nurses and pharmacists had shown the same ignorance.

'My NHS colleagues have forsaken their duty of care, broken their code of conduct – Hippocratic Oath – and have been brainwashed just the same as the majority of the UK public through propaganda …' She said she had not been able to recruit a single NHS colleague, doctor, nurse or pharmacist to stand with her and speak out. Her union had refused to help. She said that if the genocide came to light she would not hesitate to give evidence at a Nuremberg-type trial against those in power who could have affected the outcomes but didn't.

And all for what?

To put the nonsense into perspective let's say the 'virus' does exist and let's go completely crazy and accept that the official manipulated figures for cases and deaths are accurate. *Even then* a study by Stanford University epidemiologist Dr John Ioannidis published on the World Health Organization website produced an average infection to fatality rate of … *0.23 percent!* Ioannidis said: 'If one could sample equally from all locations globally, the median infection fatality rate might even be substantially lower than the 0.23% observed in my analysis.' For healthy people under 70 it was … *0.05 percent*! This compares with the 3.4 percent claimed by the Cult-owned World Health Organization when the hoax was first played and maximum fear needed to be generated. An updated Stanford study in April, 2021, put the 'infection' to 'fatality' rate at just 0.15 percent. Another team of scientists led by Megan O'Driscoll and Henrik Salje studied data from 45 countries and published their findings on the Nature website. For children and young people the figure is so small it virtually does not register although authorities will be hyping dangers to the young when they introduce DNA-manipulating 'vaccines' for children. The O'Driscoll study produced an average infection-fatality figure of 0.003 for children from birth to four; 0.001 for 5 to 14; 0.003 for 15 to 19; and it was still only 0.456 up to 64. To claim that children must be 'vaccinated' to protect them from 'Covid' is an obvious lie and so there must be another reason and there is. What's more the average age of a 'Covid' death is akin

to the average age that people die in general. The average age of death in England is about 80 for men and 83 for women. The average age of death from alleged 'Covid' is between 82 and 83. California doctors, Dan Erickson and Artin Massihi, said at their April media conference that projection models of millions of deaths had been 'woefully inaccurate'. They produced detailed figures showing that Californians had a 0.03 chance of dying from 'Covid' based on the number of people who tested positive (with a test not testing for the 'virus'). Erickson said there was a 0.1 percent chance of dying from 'Covid' in the *state* of New York, not just the city, and a 0.05 percent chance in Spain, a centre of 'Covid-19' hysteria at one stage. The Stanford studies supported the doctors' data with fatality rate estimates of 0.23 and 0.15 percent. How close are these figures to my estimate of *zero*? Death-rate figures claimed by the World Health Organization at the start of the hoax were some 15 times higher. The California doctors said there was no justification for lockdowns and the economic devastation they caused. Everything they had ever learned about quarantine was that you quarantine the *sick* and not the healthy. They had never seen this before and it made no medical sense.

Why in the in the light of all this would governments and medical systems the world over say that billions must go under house arrest; lose their livelihood; in many cases lose their mind, their health and their life; force people to wear masks dangerous to health and psychology; make human interaction and even family interaction a criminal offence; ban travel; close restaurants, bars, watching live sport, concerts, theatre, and any activity involving human togetherness and discourse; and closing schools to isolate children from their friends and cause many to commit suicide in acts of hopelessness and despair? The California doctors said lockdown consequences included increased child abuse, partner abuse, alcoholism, depression, and other impacts they were seeing every day. Who would do that to the entire human race if not mentally-ill psychopaths of almost unimaginable extremes like Bill Gates? We must face the reality of what we are dealing with and come out of

denial. Fascism and tyranny are made possible only by the target population submitting and acquiescing to fascism and tyranny. The whole of human history shows that to be true. Most people naively and unquestioning believed what they were told about a 'deadly virus' and meekly and weakly submitted to house arrest. Those who didn't believe it – at least in total – still submitted in fear of the consequences of not doing so. For the rest who wouldn't submit draconian fines have been imposed, brutal policing by psychopaths *for* psychopaths, and condemnation from the meek and weak who condemn the Pushbackers on behalf of the very force that has them, too, in its gunsights. 'Pathetic' does not even begin to suffice. Britain's brainless 'Health' Secretary Matt Hancock warned anyone lying to border officials about returning from a list of 'hotspot' countries could face a jail sentence of up to ten years which is more than for racially-aggravated assault, incest and attempting to have sex with a child under 13. Hancock is a lunatic, but he has the state apparatus behind him in a Cult-led chain reaction and the same with UK 'Vaccine Minister' Nadhim Zahawi, a prominent member of the mega-Cult secret society, Le Cercle, which featured in my earlier books. The Cult enforces its will on governments and medical systems; government and medical systems enforce their will on business and police; business enforces its will on staff who enforce it on customers; police enforce the will of the Cult on the population and play their essential part in creating a world of fascist control that their own children and grandchildren will have to live in their entire lives. It is a hierarchical pyramid of imposition and acquiescence and, yes indeedy, of clinical insanity.

Does anyone bright enough to read this book have to ask what the answer is? I think not, but I will reveal it anyway in the fewest of syllables: Tell the psychos and their moronic lackeys to fuck off and let's get on with our lives. We are many – They are few.

CHAPTER SEVEN

War on your mind

One believes things because one has been conditioned to believe them
Aldous Huxley, *Brave New World*

I have described the 'Covid' hoax as a 'Psyop' and that is true in every sense and on every level in accordance with the definition of that term which is psychological warfare. Break down the 'Covid pandemic' to the foundation themes and it is psychological warfare on the human individual and collective mind.

The same can be said for the entire human belief system involving every subject you can imagine. Huxley was right in his contention that people believe what they are conditioned to believe and this comes from the repetition throughout their lives of the same falsehoods. They spew from government, corporations, media and endless streams of 'experts' telling you what the Cult wants you to believe and often believing it themselves (although *far* from always). 'Experts' are rewarded with 'prestigious' jobs and titles and as agents of perceptual programming with regular access to the media. The Cult has to control the narrative – control *information* – or they lose control of the vital, crucial, without-which-they-cannot-prevail public perception of reality. The foundation of that control today is the Internet made possible by the Defense Advanced Research Projects Agency (DARPA), the incredibly sinister technological arm of the Pentagon. The Internet is the result of military technology.

DARPA openly brags about establishing the Internet which has been a long-term project to lasso the minds of the global population. I have said for decades the plan is to control information to such an extreme that eventually no one would see or hear anything that the Cult does not approve. We are closing in on that end with ferocious censorship since the 'Covid' hoax began and in my case it started back in the 1990s in terms of books and speaking venues. I had to create my own publishing company in 1995 precisely because no one else would publish my books even then. I think they're all still running.

Cult Internet

To secure total control of information they needed the Internet in which pre-programmed algorithms can seek out 'unclean' content for deletion and even stop it being posted in the first place. The Cult had to dismantle print and non-Internet broadcast media to ensure the transfer of information to the appropriate-named 'Web' – a critical expression of the *Cult* web. We've seen the ever-quickening demise of traditional media and control of what is left by a tiny number of corporations operating worldwide. Independent journalism in the mainstream is already dead and never was that more obvious than since the turn of 2020. The Cult wants all information communicated via the Internet to globally censor and allow the plug to be pulled any time. Lockdowns and forced isolation has meant that communication between people has been through electronic means and no longer through face-to-face discourse and discussion. Cult psychopaths have targeted the bars, restaurants, sport, venues and meeting places in general for this reason. None of this is by chance and it's to stop people gathering in any kind of privacy or number while being able to track and monitor all Internet communications and block them as necessary. Even private messages between individuals have been censored by these fascists that control Cult fronts like Facebook, Twitter, Google and YouTube which are all officially run by Sabbatian place-people and from the background by higher-level Sabbatian place people.

Facebook, Google, Amazon and their like were seed-funded and supported into existence with money-no-object infusions of funds either directly or indirectly from DARPA and CIA technology arm In-Q-Tel. The Cult plays the long game and prepares very carefully for big plays like 'Covid'. Amazon is another front in the psychological war and pretty much controls the global market in book sales and increasingly publishing. Amazon's limitless funds have deleted fantastic numbers of independent publishers to seize global domination on the way to deciding which books can be sold and circulated and which cannot. Moves in that direction are already happening. Amazon's leading light Jeff Bezos is the grandson of Lawrence Preston Gise who worked with DARPA predecessor ARPA. Amazon has big connections to the CIA and the Pentagon. The plan I have long described went like this:

1. Employ military technology to establish the Internet.

2. Sell the Internet as a place where people can freely communicate without censorship and allow that to happen until the Net becomes the central and irreversible pillar of human society. If the Internet had been highly censored from the start many would have rejected it.

3. Fund and manipulate major corporations into being to control the circulation of information on your Internet using cover stories about geeks in garages to explain how they came about. Give them unlimited funds to expand rapidly with no need to make a profit for years while non-Cult companies who need to balance the books cannot compete. You know that in these circumstances your Googles, YouTubes, Facebooks and Amazons are going to secure near monopolies by either crushing or buying up the opposition.

4. Allow freedom of expression on both the Internet and communication platforms to draw people in until the Internet is the central and irreversible pillar of human society and your communication corporations have reached a stage of near monopoly domination.

5. Then unleash your always-planned frenzy of censorship on the basis of 'where else are you going to go?' and continue to expand that until nothing remains that the Cult does not want its human targets to see.

The process was timed to hit the 'Covid' hoax to ensure the best chance possible of controlling the narrative which they knew they had to do at all costs. They were, after all, about to unleash a 'deadly virus' that didn't really exist. If you do that in an environment of free-flowing information and opinion you would be dead in the

water before you could say Gates is a psychopath. The network was in place through which the Cult-created-and-owned World Health Organization could dictate the 'Covid' narrative and response policy slavishly supported by Cult-owned Internet communication giants and mainstream media while those telling a different story were censored. Google, YouTube, Facebook and Twitter openly announced that they would do this. What else would we expect from Cult-owned operations like Facebook which former executives have confirmed set out to make the platform more addictive than cigarettes and coldly manipulates emotions of its users to sow division between people and groups and scramble the minds of the young? If Zuckerberg lives out the rest of his life without going to jail for crimes against humanity, and most emphatically against the young, it will be a travesty of justice. Still, no matter, cause and effect will catch up with him eventually and the same with Sergey Brin and Larry Page at Google with its CEO Sundar Pichai who fix the Google search results to promote Cult narratives and hide the opposition. Put the same key words into Google and other search engines like DuckDuckGo and you will see how different results can be. Wikipedia is another intensely biased 'encyclopaedia' which skews its content to the Cult agenda. YouTube links to Wikipedia's version of 'Covid' and 'climate change' on video pages in which experts in their field offer a different opinion (even that is increasingly rare with Wojcicki censorship). Into this 'Covid' silence-them network must be added government media censors, sorry 'regulators', such as Ofcom in the UK which imposed tyrannical restrictions on British broadcasters that had the effect of banning me from ever appearing. Just to debate with me about my evidence and views on 'Covid' would mean breaking the fascistic impositions of Ofcom and its CEO career government bureaucrat Melanie Dawes. Gutless British broadcasters tremble at the very thought of fascist Ofcom.

Psychos behind 'Covid'

The reason for the 'Covid' catastrophe in all its facets and forms can be seen by whom and what is driving the policies worldwide in such a coordinated way. Decisions are not being made to protect health, but to target psychology. The dominant group guiding and 'advising' government policy are not medical professionals. They are psychologists and behavioural scientists. Every major country has its own version of this phenomenon and I'll use the British example to show how it works. In many ways the British version has been affecting the wider world in the form of the huge behaviour manipulation network in the UK which operates in other countries. The network involves private companies, government, intelligence and military. The Cabinet Office is at the centre of the government 'Covid' Psyop and part-owns, with 'innovation charity' Nesta, the Behavioural Insights Team (BIT) which claims to be independent of government but patently isn't. The BIT was established in 2010 and its job is to manipulate the psyche of the population to acquiesce to government demands and so much more. It is also known as the 'Nudge Unit', a name inspired by the 2009 book by two ultra-Zionists, Cass Sunstein and Richard Thaler, called *Nudge: Improving Decisions About Health, Wealth, and Happiness*. The book, as with the Behavioural Insights Team, seeks to 'nudge' behaviour (manipulate it) to make the public follow patterns of action and perception that suit those in authority (the Cult). Sunstein is so skilled at this that he advises the World Health Organization and the UK Behavioural Insights Team and was Administrator of the White House Office of Information and Regulatory Affairs in the Obama administration. Biden appointed him to the Department of Homeland Security – another ultra-Zionist in the fold to oversee new immigration laws which is another policy the Cult wants to control. Sunstein is desperate to silence anyone exposing conspiracies and co-authored a 2008 report on the subject in which suggestions were offered to ban 'conspiracy theorizing' or impose 'some kind of tax, financial or otherwise, on those who disseminate such theories'. I guess a psychiatrist's chair is out of the question?

Sunstein's mate Richard Thaler, an 'academic affiliate' of the UK Behavioural Insights Team, is a proponent of 'behavioural economics' which is defined as the study of 'the effects of psychological, cognitive, emotional, cultural and social factors on the decisions of individuals and institutions'. Study the effects so they can be manipulated to be what you want them to be. Other leading names in the development of behavioural economics are ultra-Zionists Daniel Kahneman and Robert J. Shiller and they, with Thaler, won the Nobel Memorial Prize in Economic Sciences for their work in this field. The Behavioural Insights Team is operating at the heart of the UK government and has expanded globally through partnerships with several universities including Harvard, Oxford, Cambridge, University College London (UCL) and Pennsylvania. They claim to have 'trained' (reframed) 20,000 civil servants and run more than 750 projects involving 400 randomised controlled trials in dozens of countries' as another version of mind reframers Common Purpose. BIT works from its office in New York with cities and their agencies, as well as other partners, across the United States and Canada – this is a company part-owned by the British government Cabinet Office. An executive order by President Cult-servant Obama established a US Social and Behavioral Sciences Team in 2015. They all have the same reason for being and that's to brainwash the population directly and by brainwashing those in positions of authority.

'Covid' mind game

Another prime aspect of the UK mind-control network is the 'independent' [joke] Scientific Pandemic Insights Group on Behaviours (SPI-B) which 'provides behavioural science advice aimed at anticipating and helping people adhere to interventions that are recommended by medical or epidemiological experts'. That means manipulating public perception and behaviour to do whatever government tells them to do. It's disgusting and if they really want the public to be 'safe' this lot should all be under lock and key. According to the government website SPI-B consists of

'behavioural scientists, health and social psychologists, anthropologists and historians' and advises the Whitty-Vallance-led Scientific Advisory Group for Emergencies (SAGE) which in turn advises the government on 'the science' (it doesn't) and 'Covid' policy. When politicians say they are being guided by 'the science' this is the rabble in each country they are talking about and that 'science' is dominated by behaviour manipulators to enforce government fascism through public compliance. The Behaviour Insight Team is headed by psychologist David Solomon Halpern, a visiting professor at King's College London, and connects with a national and global web of other civilian and military organisations as the Cult moves towards its goal of fusing them into one fascistic whole in every country through its 'Fusion Doctrine'. The behaviour manipulation network involves, but is not confined to, the Foreign Office; National Security Council; government communications headquarters (GCHQ); MI5; MI6; the Cabinet Office-based Media Monitoring Unit; and the Rapid Response Unit which 'monitors digital trends to spot emerging issues; including misinformation and disinformation; and identifies the best way to respond'.

There is also the 77th Brigade of the UK military which operates like the notorious Israeli military's Unit 8200 in manipulating information and discussion on the Internet by posing as members of the public to promote the narrative and discredit those who challenge it. Here we have the military seeking to manipulate *domestic* public opinion while the Nazis in government are fine with that. Conservative Member of Parliament Tobias Ellwood, an advocate of lockdown and control through 'vaccine passports', is a Lieutenant Colonel reservist in the 77th Brigade which connects with the military operation jHub, the 'innovation centre' for the Ministry of Defence and Strategic Command. jHub has also been involved with the civilian National Health Service (NHS) in 'symptom tracing' the population. The NHS is a key part of this mind control network and produced a document in December, 2020, explaining to staff how to use psychological manipulation with different groups and ages to get them to have the DNA-manipulating 'Covid vaccine'

that's designed to cumulatively rewrite human genetics. The document, called 'Optimising Vaccination Roll Out – Do's and Dont's for all messaging, documents and "communications" in the widest sense', was published by NHS England and the NHS Improvement *Behaviour Change Unit* in partnership with Public Health England and Warwick Business School. I hear the mantra about 'save the NHS' and 'protect the NHS' when we need to scrap the NHS and start again. The current version is far too corrupt, far too anti-human and totally compromised by Cult operatives and their assets. UK government broadcast media censor Ofcom will connect into this web – as will the BBC with its tremendous Ofcom influence – to control what the public see and hear and dictate mass perception. Nuremberg trials must include personnel from all these organisations.

The fear factor

The 'Covid' hoax has led to the creation of the UK Cabinet Office-connected Joint Biosecurity Centre (JBC) which is officially described as providing 'expert advice on pandemics' using its independent [all Cult operations are 'independent'] analytical function to provide real-time analysis about infection outbreaks to identify and respond to outbreaks of Covid-19'. Another role is to advise the government on a response to spikes in infections – 'for example by closing schools or workplaces in local areas where infection levels have risen'. Put another way, promoting the Cult agenda. The Joint Biosecurity Centre is modelled on the Joint Terrorism Analysis Centre which analyses intelligence to set 'terrorism threat levels' and here again you see the fusion of civilian and military operations and intelligence that has led to military intelligence producing documents about 'vaccine hesitancy' and how it can be combated. Domestic civilian matters and opinions should not be the business of the military. The Joint Biosecurity Centre is headed by Tom Hurd, director general of the Office for Security and Counter-Terrorism from the establishment-to-its-fingertips Hurd family. His father is former Foreign Secretary Douglas Hurd. How coincidental that Tom

Hurd went to the elite Eton College and Oxford University with Boris Johnson. Imperial College with its ridiculous computer modeller Neil Ferguson will connect with this gigantic web that will itself interconnect with similar set-ups in other major and not so major countries. Compared with this Cult network the politicians, be they Boris Johnson, Donald Trump or Joe Biden, are bit-part players 'following the science'. The network of psychologists was on the 'Covid' case from the start with the aim of generating maximum fear of the 'virus' to ensure compliance by the population. A government behavioural science group known as SPI-B produced a paper in March, 2020, for discussion by the main government science advisory group known as SAGE. It was headed 'Options for increasing adherence to social distancing measures' and it said the following in a section headed 'Persuasion':

- A substantial number of people still do not feel sufficiently personally threatened; it could be that they are reassured by the low death rate in their demographic group, although levels of concern may be rising. Having a good understanding of the risk has been found to be positively associated with adoption of COVID-19 social distancing measures in Hong Kong.

- The perceived level of personal threat needs to be increased among those who are complacent, using hard-hitting evaluation of options for increasing social distancing emotional messaging. To be effective this must also empower people by making clear the actions they can take to reduce the threat.

- Responsibility to others: There seems to be insufficient understanding of, or feelings of responsibility about, people's role in transmitting the infection to others … Messaging about actions need to be framed positively in terms of protecting oneself and the community, and increase confidence that they will be effective.

- Some people will be more persuaded by appeals to play by the rules, some by duty to the community, and some to personal risk.

> All these different approaches are needed. The messaging also needs to take account of the realities of different people's lives. Messaging needs to take account of the different motivational levers and circumstances of different people.

All this could be achieved the SPI-B psychologists said by *using the media to increase the sense of personal threat* which translates as terrify the shit out of the population, including children, so they all do what we want. That's not happened has it? Those excuses for 'journalists' who wouldn't know journalism if it bit them on the arse (the great majority) have played their crucial part in serving this Cult-government Psyop to enslave their own kids and grandkids. How they live with themselves I have no idea. The psychological war has been underpinned by constant government 'Covid' propaganda in almost every television and radio ad break, plus the Internet and print media, which has pounded out the fear with taxpayers footing the bill for their own programming. The result has been people terrified of a 'virus' that doesn't exist or one with a tiny fatality rate even if you believe it does. People walk down the street and around the shops wearing face-nappies damaging their health and psychology while others report those who refuse to be that naïve to the police who turn up in their own face-nappies. I had a cameraman come to my flat and he was so frightened of 'Covid' he came in wearing a mask and refused to shake my hand in case he caught something. He had – naïveitis – and the thought that he worked in the mainstream media was both depressing and made his behaviour perfectly explainable. The fear which has gripped the minds of so many and frozen them into compliance has been carefully cultivated by these psychologists who are really psychopaths. If lives get destroyed and a lot of young people commit suicide it shows our plan is working. SPI-B then turned to compulsion on the public to comply. 'With adequate preparation, rapid change can be achieved', it said. Some countries had introduced mandatory self-isolation on a wide scale without evidence of major public unrest and a large majority of the UK's population appeared to be supportive of more coercive measures with 64 percent of adults saying they would

support putting London under a lockdown (watch the 'polls' which are designed to make people believe that public opinion is in favour or against whatever the subject in hand).

For 'aggressive protective measures' to be effective, the SPI-B paper said, special attention should be devoted to those population groups that are more at risk. Translated from the Orwellian this means making the rest of population feel guilty for not protecting the 'vulnerable' such as old people which the Cult and its agencies were about to kill on an industrial scale with lockdown, lack of treatment and the Gates 'vaccine'. Psychopath psychologists sold their guilt-trip so comprehensively that Los Angeles County Supervisor Hilda Solis reported that children were apologising (from a distance) to their parents and grandparents for bringing 'Covid' into their homes and getting them sick. '… These apologies are just some of the last words that loved ones will ever hear as they die alone,' she said. Gut-wrenchingly Solis then used this childhood tragedy to tell children to stay at home and 'keep your loved ones alive'. Imagine heaping such potentially life-long guilt on a kid when it has absolutely nothing to do with them. These people are deeply disturbed and the psychologists behind this even more so.

Uncivil war – divide and rule

Professional mind-controllers at SPI-B wanted the media to increase a sense of responsibility to others (do as you're told) and promote 'positive messaging' for those actions while in contrast to invoke 'social disapproval' by the unquestioning, obedient, community of anyone with a mind of their own. Again the compliant Goebbels-like media obliged. This is an old, old, trick employed by tyrannies the world over throughout human history. You get the target population to keep the target population in line – *your* line. SPI-B said this could 'play an important role in preventing anti-social behaviour or discouraging failure to enact pro-social behaviour'. For 'anti-social' in the Orwellian parlance of SPI-B see any behaviour that government doesn't approve. SPI-B recommendations said that 'social disapproval' should be accompanied by clear messaging and

promotion of strong collective identity – hence the government and celebrity mantra of 'we're all in this together'. Sure we are. The mind doctors have such contempt for their targets that they think some clueless comedian, actor or singer telling them to do what the government wants will be enough to win them over. We have had UK comedian Lenny Henry, actor Michael Caine and singer Elton John wheeled out to serve the propagandists by urging people to have the DNA-manipulating 'Covid' non-'vaccine'. The role of Henry and fellow black celebrities in seeking to coax a 'vaccine' reluctant black community into doing the government's will was especially stomach-turning. An emotion-manipulating script and carefully edited video featuring these black 'celebs' was such an insult to the intelligence of black people and where's the self-respect of those involved selling their souls to a fascist government agenda? Henry said he heard black people's 'legitimate worries and concerns', but people must 'trust the facts' when they were doing exactly that by not having the 'vaccine'. They had to include the obligatory reference to Black Lives Matter with the line … 'Don't let coronavirus cost even more black lives – because we matter'. My god, it was pathetic. 'I know the vaccine is safe and what it does.' How? 'I'm a comedian and it says so in my script.'

SPI-B said social disapproval needed to be carefully managed to avoid victimisation, scapegoating and misdirected criticism, but they knew that their 'recommendations' would lead to exactly that and the media were specifically used to stir-up the divide-and-conquer hostility. Those who conform like good little baa, baas, are praised while those who have seen through the tidal wave of lies are 'Covidiots'. The awake have been abused by the fast asleep for not conforming to fascism and impositions that the awake know are designed to endanger their health, dehumanise them, and tear asunder the very fabric of human society. We have had the curtain-twitchers and morons reporting neighbours and others to the face-nappied police for breaking 'Covid rules' with fascist police delighting in posting links and phone numbers where this could be done. The Cult cannot impose its will without a compliant police

and military or a compliant population willing to play their part in enslaving themselves and their kids. The words of a pastor in Nazi Germany are so appropriate today:

First they came for the socialists and I did not speak out because I was not a socialist.

Then they came for the trade unionists and I did not speak out because I was not a trade unionist.

Then they came for the Jews and I did not speak out because I was not a Jew.

Then they came for me and there was no one left to speak for me.

Those who don't learn from history are destined to repeat it and so many are.

'Covid' rules: Rewiring the mind

With the background laid out to this gigantic national and global web of psychological manipulation we can put 'Covid' rules into a clear and sinister perspective. Forget the claims about protecting health. 'Covid' rules are about dismantling the human mind, breaking the human spirit, destroying self-respect, and then putting Humpty Dumpty together again as a servile, submissive slave. Social isolation through lockdown and distancing have devastating effects on the human psyche as the psychological psychopaths well know and that's the real reason for them. Humans need contact with each other, discourse, closeness and touch, or they eventually, and literarily, go crazy. Masks, which I will address at some length, fundamentally add to the effects of isolation and the Cult agenda to dehumanise and de-individualise the population. To do this while knowing – in fact *seeking* – this outcome is the very epitome of evil and psychologists involved in this *are* the epitome of evil. They must like all the rest of the Cult demons and their assets stand trial for crimes against humanity on a scale that defies the imagination. Psychopaths in uniform use isolation to break enemy troops and agents and make them subservient and submissive to tell what they know. The technique is rightly considered a form of torture and

torture is most certainly what has been imposed on the human population.

Clinically-insane American psychologist Harry Harlow became famous for his isolation experiments in the 1950s in which he separated baby monkeys from their mothers and imprisoned them for months on end in a metal container or 'pit of despair'. They soon began to show mental distress and depression as any idiot could have predicted. Harlow put other monkeys in steel chambers for three, six or twelve months while denying them any contact with animals or humans. He said that the effects of total social isolation for six months were 'so devastating and debilitating that we had assumed initially that twelve months of isolation would not produce any additional decrement'; but twelve months of isolation 'almost obliterated the animals socially'. This is what the Cult and its psychopaths are doing to you and your children. Even monkeys in partial isolation in which they were not allowed to form relationships with other monkeys became 'aggressive and hostile, not only to others, but also towards their own bodies'. We have seen this in the young as a consequence of lockdown. UK government psychopaths launched a public relations campaign telling people not to hug each other even after they received the 'Covid-19 vaccine' which we were told with more lies would allow a return to 'normal life'. A government source told *The Telegraph*: 'It will be along the lines that it is great that you have been vaccinated, but if you are going to visit your family and hug your grandchildren there is a chance you are going to infect people you love.' The source was apparently speaking from a secure psychiatric facility. Janet Lord, director of Birmingham University's Institute of Inflammation and Ageing, said that parents and grandparents should avoid hugging their children. Well, how can I put it, Ms Lord? Fuck off. Yep, that'll do.

Destroying the kids – where are the parents?

Observe what has happened to people enslaved and isolated by lockdown as suicide and self-harm has soared worldwide,

particularly among the young denied the freedom to associate with their friends. A study of 49,000 people in English-speaking countries concluded that almost half of young adults are at clinical risk of mental health disorders. A national survey in America of 1,000 currently enrolled high school and college students found that 5 percent reported attempting suicide during the pandemic. Data from the US CDC's National Syndromic Surveillance Program from January 1st to October 17th, 2020, revealed a *31 percent* increase in mental health issues among adolescents aged 12 to 17 compared with 2019. The CDC reported that America in general suffered the biggest drop in life expectancy since World War Two as it fell by a year in the first half of 2020 as a result of 'deaths of despair' – overdoses and suicides. Deaths of despair have leapt by more than 20 percent during lockdown and include the highest number of fatal overdoses ever recorded in a single year – 81,000. Internet addiction is another consequence of being isolated at home which lowers interest in physical activities as kids fall into inertia and what's the point? Children and young people are losing hope and giving up on life, sometimes literally. A 14-year-old boy killed himself in Maryland because he had 'given up' when his school district didn't reopen; an 11-year-old boy shot himself during a zoom class; a teenager in Maine succumbed to the isolation of the 'pandemic' when he ended his life after experiencing a disrupted senior year at school. Children as young as nine have taken their life and all these stories can be repeated around the world. Careers are being destroyed before they start and that includes those in sport in which promising youngsters have not been able to take part. The plan of the psycho-psychologists is working all right. Researchers at Cambridge University found that lockdowns cause significant harm to children's mental health. Their study was published in the *Archives of Disease in Childhood*, and followed 168 children aged between 7 and 11. The researchers concluded:

> During the UK lockdown, children's depression symptoms have increased substantially, relative to before lockdown. The scale of this effect has direct relevance for the continuation of different elements of lockdown policy, such as complete or partial school closures …

… Specifically, we observed a statistically significant increase in ratings of depression, with a medium-to-large effect size. Our findings emphasise the need to incorporate the potential impact of lockdown on child mental health in planning the ongoing response to the global pandemic and the recovery from it.

Not a chance when the Cult's psycho-psychologists were getting exactly what they wanted. The UK's Royal College of Paediatrics and Child Health has urged parents to look for signs of eating disorders in children and young people after a three to four fold increase. Specialists say the 'pandemic' is a major reason behind the rise. You don't say. The College said isolation from friends during school closures, exam cancellations, loss of extra-curricular activities like sport, and an increased use of social media were all contributory factors along with fears about the virus (psycho-psychologists again), family finances, and students being forced to quarantine. Doctors said young people were becoming severely ill by the time they were seen with 'Covid' regulations reducing face-to-face consultations. Nor is it only the young that have been devastated by the psychopaths. Like all bullies and cowards the Cult is targeting the young, elderly, weak and infirm. A typical story was told by a British lady called Lynn Parker who was not allowed to visit her husband in 2020 for the last ten and half months of his life 'when he needed me most' between March 20th and when he died on December 19th. This vacates the criminal and enters the territory of evil. The emotional impact on the immune system alone is immense as are the number of people of all ages worldwide who have died as a result of Cult-demanded, Gates-demanded, lockdowns.

Isolation is torture

The experience of imposing solitary confinement on millions of prisoners around the world has shown how a large percentage become 'actively psychotic and/or acutely suicidal'. Social isolation has been found to trigger 'a specific psychiatric syndrome, characterized by hallucinations; panic attacks; overt paranoia; diminished impulse control; hypersensitivity to external stimuli; and difficulties with thinking, concentration and memory'. Juan Mendez,

a United Nations rapporteur (investigator), said that isolation is a form of torture. Research has shown that even after isolation prisoners find it far more difficult to make social connections and I remember chatting to a shop assistant after one lockdown who told me that when her young son met another child again he had no idea how to act or what to do. Hannah Flanagan, Director of Emergency Services at Journey Mental Health Center in Dane County, Wisconsin, said: 'The specificity about Covid social distancing and isolation that we've come across as contributing factors to the suicides are really new to us this year.' But they are not new to those that devised them. They are getting the effect they want as the population is psychologically dismantled to be rebuilt in a totally different way. Children and the young are particularly targeted. They will be the adults when the full-on fascist AI-controlled technocracy is planned to be imposed and they are being prepared to meekly submit. At the same time older people who still have a memory of what life was like before – and how fascist the new normal really is – are being deleted. You are going to see efforts to turn the young against the old to support this geriatric genocide. Hannah Flanagan said the big increase in suicide in her county proved that social isolation is not only harmful, but deadly. Studies have shown that isolation from others is one of the main risk factors in suicide and even more so with women. Warnings that lockdown could create a 'perfect storm' for suicide were ignored. After all this was one of the *reasons* for lockdown. Suicide, however, is only the most extreme of isolation consequences. There are many others. Dr Dhruv Khullar, assistant professor of healthcare policy at Weill Cornell Medical College, said in a *New York Times* article in 2016 long before the fake 'pandemic':

> A wave of new research suggests social separation is bad for us. Individuals with less social connection have disrupted sleep patterns, altered immune systems, more inflammation and higher levels of stress hormones. One recent study found that isolation increases the risk of heart disease by 29 percent and stroke by 32 percent. Another analysis that pooled data from 70 studies and 3.4 million people found that socially isolated individuals had a 30 percent higher risk of dying in the next seven years, and that this effect was largest in middle age.

Loneliness can accelerate cognitive decline in older adults, and isolated individuals are twice as likely to die prematurely as those with more robust social interactions. These effects start early: Socially isolated children have significantly poorer health 20 years later, even after controlling for other factors. All told, loneliness is as important a risk factor for early death as obesity and smoking.

There you have proof from that one article alone four years before 2020 that those who have enforced lockdown, social distancing and isolation knew what the effect would be and that is even more so with professional psychologists that have been driving the policy across the globe. We can go back even further to the years 2000 and 2003 and the start of a major study on the effects of isolation on health by Dr Janine Gronewold and Professor Dirk M. Hermann at the University Hospital in Essen, Germany, who analysed data on 4,316 people with an average age of 59 who were recruited for the long-term research project. They found that socially isolated people are more than 40 percent more likely to have a heart attack, stroke, or other major cardiovascular event and nearly 50 percent more likely to die from any cause. Given the financial Armageddon unleashed by lockdown we should note that the study found a relationship between increased cardiovascular risk and lack of financial support. After excluding other factors social isolation was still connected to a 44 percent increased risk of cardiovascular problems and a 47 percent increased risk of death by any cause. Lack of financial support was associated with a 30 percent increase in the risk of cardiovascular health events. Dr Gronewold said it had been known for some time that feeling lonely or lacking contact with close friends and family can have an impact on physical health and the study had shown that having strong social relationships is of high importance for heart health. Gronewold said they didn't understand yet why people who are socially isolated have such poor health outcomes, but this was obviously a worrying finding, particularly during these times of prolonged social distancing. Well, it can be explained on many levels. You only have to identify the point in the body where people feel loneliness and missing people they are parted from – it's in the centre of the chest where they feel the ache of loneliness and the ache of missing people. 'My heart aches for

you' … 'My heart aches for some company.' I will explain this more in the chapter Escaping Wetiko, but when you realise that the body is the mind – they are expressions of each other – the reason why state of the mind dictates state of the body becomes clear.

American psychologist Ranjit Powar was highlighting the effects of lockdown isolation as early as April, 2020. She said humans have evolved to be social creatures and are wired to live in interactive groups. Being isolated from family, friends and colleagues could be unbalancing and traumatic for most people and could result in short or even long-term psychological and physical health problems. An increase in levels of anxiety, aggression, depression, forgetfulness and hallucinations were possible psychological effects of isolation. 'Mental conditions may be precipitated for those with underlying pre-existing susceptibilities and show up in many others without any pre-condition.' Powar said personal relationships helped us cope with stress and if we lost this outlet for letting off steam the result can be a big emotional void which, for an average person, was difficult to deal with. 'Just a few days of isolation can cause increased levels of anxiety and depression' – so what the hell has been the effect on the global population of *18 months* of this at the time of writing? Powar said: 'Add to it the looming threat of a dreadful disease being repeatedly hammered in through the media and you have a recipe for many shades of mental and physical distress.' For those with a house and a garden it is easy to forget that billions have had to endure lockdown isolation in tiny overcrowded flats and apartments with nowhere to go outside. The psychological and physical consequences of this are unimaginable and with lunatic and abusive partners and parents the consequences have led to tremendous increases in domestic and child abuse and alcoholism as people seek to shut out the horror. Ranjit Powar said:

Staying in a confined space with family is not all a rosy picture for everyone. It can be extremely oppressive and claustrophobic for large low-income families huddled together in small single-room houses. Children here are not lucky enough to have many board/electronic games or books to keep them occupied.

Add to it the deep insecurity of running out of funds for food and basic necessities. On the other hand, there are people with dysfunctional family dynamics, such as domineering, abusive or alcoholic partners, siblings or parents which makes staying home a period of trial. Incidence of suicide and physical abuse against women has shown a worldwide increase. Heightened anxiety and depression also affect a person's immune system, making them more susceptible to illness.

To think that Powar's article was published on April 11th, 2020.

Six-feet fantasy

Social (unsocial) distancing demanded that people stay six feet or two metres apart. UK government advisor Robert Dingwall from the New and Emerging Respiratory Virus Threats Advisory Group said in a radio interview that the two-metre rule was 'conjured up out of nowhere' and was not based on science. No, it was not based on *medical* science, but it didn't come out of nowhere. The distance related to *psychological* science. Six feet/two metres was adopted in many countries and we were told by people like the criminal Anthony Fauci and his ilk that it was founded on science. Many schools could not reopen because they did not have the space for six-feet distancing. Then in March, 2021, after a year of six-feet 'science', a study published in the *Journal of Infectious Diseases* involving more than 500,000 students and almost 100,000 staff over 16 weeks revealed no significant difference in 'Covid' cases between six feet and three feet and Fauci changed his tune. Now three feet was okay. There is no difference between six feet and three *inches* when there is no 'virus' and they got away with six feet for psychological reasons for as long as they could. I hear journalists and others talk about 'unintended consequences' of lockdown. They are not *unintended* at all; they have been coldly-calculated for a specific outcome of human control and that's why super-psychopaths like Gates have called for them so vehemently. Super-psychopath psychologists have demanded them and psychopathic or clueless, spineless, politicians have gone along with them by 'following the science'. But it's not science at all. 'Science' is not what is; it's only what people can be manipulated to believe it is. The whole 'Covid' catastrophe is

founded on mind control. Three word or three statement mantras issued by the UK government are a well-known mind control technique and so we've had 'Stay home/protect the NHS/save lives', 'Stay alert/control the virus/save lives' and 'hands/face/space'. One of the most vocal proponents of extreme 'Covid' rules in the UK has been Professor Susan Michie, a member of the British Communist Party, who is not a medical professional. Michie is the director of the Centre for Behaviour Change at University College London. She is a *behavioural psychologist* and another filthy rich 'Marxist' who praised China's draconian lockdown. She was known by fellow students at Oxford University as 'Stalin's nanny' for her extreme Marxism. Michie is an influential member of the UK government's Scientific Advisory Group for Emergencies (SAGE) and behavioural manipulation groups which have dominated 'Covid' policy. She is a consultant adviser to the World Health Organization on 'Covid-19' and behaviour. Why the hell are lockdowns anything to do with her when they are claimed to be about health? Why does a behavioural psychologist from a group charged with changing the behaviour of the public want lockdown, human isolation and mandatory masks? Does that question really need an answer? Michie *absolutely* has to explain herself before a Nuremberg court when humanity takes back its world again and even more so when you see the consequences of masks that she demands are compulsory. This is a Michie classic:

> The benefits of getting primary school children to wear masks is that regardless of what little degree of transmission is occurring in those age groups it could help normalise the practice. Young children wearing masks may be more likely to get their families to accept masks.

Those words alone should carry a prison sentence when you ponder on the callous disregard for children involved and what a statement it makes about the mind and motivations of Susan Michie. What a lovely lady and what she said there encapsulates the mentality of the psychopaths behind the 'Covid' horror. Let us compare what Michie said with a countrywide study in Germany published at researchsquare.com involving 25,000 school children and 17,854 health complaints submitted by parents. Researchers

found that masks are harming children physically, psychologically, and behaviourally with 24 health issues associated with mask wearing. They include: shortness of breath (29.7%); dizziness (26.4%); increased headaches (53%); difficulty concentrating (50%); drowsiness or fatigue (37%); and malaise (42%). Nearly a third of children experienced more sleep issues than before and a quarter developed new fears. Researchers found health issues and other impairments in 68 percent of masked children covering their faces for an average of 4.5 hours a day. Hundreds of those taking part experienced accelerated respiration, tightness in the chest, weakness, and short-term impairment of consciousness. A reminder of what Michie said again:

The benefits of getting primary school children to wear masks is that regardless of what little degree of transmission is occurring in those age groups it could help normalise the practice. Young children wearing masks may be more likely to get their families to accept masks.

Psychopaths in government and psychology now have children and young people – plus all the adults – wearing masks for hours on end while clueless teachers impose the will of the psychopaths on the young they should be protecting. What the hell are parents doing?

Cult lab rats

We have some schools already imposing on students microchipped buzzers that activate when they get 'too close' to their pals in the way they do with lab rats. How apt. To the Cult and its brain-dead servants our children *are* lab rats being conditioned to be unquestioning, dehumanised slaves for the rest of their lives. Children and young people are being weaned and frightened away from the most natural human instincts including closeness and touch. I have tracked in the books over the years how schools were banning pupils from greeting each other with a hug and the whole Cult-induced Me Too movement has terrified men and boys from a relaxed and natural interaction with female friends and work colleagues to the point where many men try never to be in a room

alone with a woman that's not their partner. Airhead celebrities have as always played their virtue-signalling part in making this happen with their gross exaggeration. For every monster like Harvey Weinstein there are at least tens of thousands of men that don't treat women like that; but everyone must be branded the same and policy changed for them as well as the monster. I am going to be using the word 'dehumanise' many times in this chapter because that is what the Cult is seeking to do and it goes very deep as we shall see. Don't let them kid you that social distancing is planned to end one day. That's not the idea. We are seeing more governments and companies funding and producing wearable gadgets to keep people apart and they would not be doing that if this was meant to be short-term. A tech start-up company backed by GCHQ, the British Intelligence and military surveillance headquarters, has created a social distancing wrist sensor that alerts people when they get too close to others. The CIA has also supported tech companies developing similar devices. The wearable sensor was developed by Tended, one of a number of start-up companies supported by GCHQ (see the CIA and DARPA). The device can be worn on the wrist or as a tag on the waistband and will vibrate whenever someone wearing the device breaches social distancing and gets anywhere near natural human contact. The company had a lucky break in that it was developing a distancing sensor when the 'Covid' hoax arrived which immediately provided a potentially enormous market. How fortunate. The government in big-time Cult-controlled Ontario in Canada is investing $2.5 million in wearable contact tracing technology that 'will alert users if they may have been exposed to the Covid-19 in the workplace and will beep or vibrate if they are within six feet of another person'. Facedrive Inc., the technology company behind this, was founded in 2016 with funding from the Ontario Together Fund and obviously they, too, had a prophet on the board of directors. The human surveillance and control technology is called TraceSCAN and would be worn by the human cyborgs in places such as airports, workplaces, construction sites, care homes and … *schools*.

I emphasise schools with children and young people the prime targets. You know what is planned for society as a whole if you keep your eyes on the schools. They have always been places where the state program the next generation of slaves to be its compliant worker-ants – or Woker-ants these days; but in the mist of the 'Covid' madness they have been transformed into mind laboratories on a scale never seen before. Teachers and head teachers are just as programmed as the kids – often more so. Children are kept apart from human interaction by walk lanes, classroom distancing, staggered meal times, masks, and the rolling-out of buzzer systems. Schools are now physically laid out as a laboratory maze for lab-rats. Lunatics at a school in Anchorage, Alaska, who should be prosecuted for child abuse, took away desks and forced children to kneel (know your place) on a mat for five hours a day while wearing a mask and using their chairs as a desk. How this was supposed to impact on a 'virus' only these clinically insane people can tell you and even then it would be clap-trap. The school banned recess (interaction), art classes (creativity), and physical exercise (getting body and mind moving out of inertia). Everyone behind this outrage should be in jail or better still a mental institution. The behavioural manipulators are all for this dystopian approach to schools. Professor Susan Michie, the mind-doctor and British Communist Party member, said it was wrong to say that schools were safe. They had to be made so by 'distancing', masks and ventilation (sitting all day in the cold). I must ask this lady round for dinner on a night I know I am going to be out and not back for weeks. She probably wouldn't be able to make it, anyway, with all the visits to her own psychologist she must have block-booked.

Masking identity

I know how shocking it must be for you that a behaviour manipulator like Michie wants everyone to wear masks which have long been a feature of mind-control programs like the infamous MKUltra in the United States, but, there we are. We live and learn. I spent many years from 1996 to right across the millennium

researching mind control in detail on both sides of the Atlantic and elsewhere. I met a large number of mind-control survivors and many had been held captive in body and mind by MKUltra. MK stands for mind-control, but employs the German spelling in deference to the Nazis spirited out of Germany at the end of World War Two by Operation Paperclip in which the US authorities, with help from the Vatican, transported Nazi mind-controllers and engineers to America to continue their work. Many of them were behind the creation of NASA and they included Nazi scientist and SS officer Wernher von Braun who swapped designing V-2 rockets to bombard London with designing the Saturn V rockets that powered the NASA moon programme's Apollo craft. I think I may have mentioned that the Cult has no borders. Among Paperclip escapees was Josef Mengele, the Angel of Death in the Nazi concentration camps where he conducted mind and genetic experiments on children often using twins to provide a control twin to measure the impact of his 'work' on the other. If you want to observe the Cult mentality in all its extremes of evil then look into the life of Mengele. I have met many people who suffered mercilessly under Mengele in the United States where he operated under the name Dr Greene and became a stalwart of MKUltra programming and torture. Among his locations was the underground facility in the Mojave Desert in California called the China Lake Naval Weapons Station which is almost entirely below the surface. My books *The Biggest Secret*, *Children of the Matrix* and *The Perception Deception* have the detailed background to MKUltra.

The best-known MKUltra survivor is American Cathy O'Brien. I first met her and her late partner Mark Phillips at a conference in Colorado in 1996. Mark helped her escape and deprogram from decades of captivity in an offshoot of MKUltra known as Project Monarch in which 'sex slaves' were provided for the rich and famous including Father George Bush, Dick Cheney and the Clintons. Read Cathy and Mark's book *Trance-Formation of America* and if you are new to this you will be shocked to the core. I read it in 1996 shortly before, with the usual synchronicity of my life, I found

myself given a book table at the conference right next to hers. MKUltra never ended despite being very publicly exposed (only a small part of it) in the 1970s and continues in other guises. I am still in touch with Cathy. She contacted me during 2020 after masks became compulsory in many countries to tell me how they were used as part of MKUltra programming. I had been observing 'Covid regulations' and the relationship between authority and public for months. I saw techniques that I knew were employed on individuals in MKUltra being used on the global population. I had read many books and manuals on mind control including one called *Silent Weapons for Quiet Wars* which came to light in the 1980s and was a guide on how to perceptually program on a mass scale. 'Silent Weapons' refers to mind-control. I remembered a line from the manual as governments, medical authorities and law enforcement agencies have so obviously talked to – or rather at – the adult population since the 'Covid' hoax began as if they are children. The document said:

> If a person is spoken to by a T.V. advertiser as if he were a twelve-year-old, then, due to suggestibility, he will, with a certain probability, respond or react to that suggestion with the uncritical response of a twelve-year-old and will reach in to his economic reservoir and deliver its energy to buy that product on impulse when he passes it in the store.

That's why authority has spoken to adults like children since all this began.

Why did Michael Jackson wear masks?

Every aspect of the 'Covid' narrative has mind-control as its central theme. Cathy O'Brien wrote an article for davidicke.com about the connection between masks and mind control. Her daughter Kelly who I first met in the 1990s was born while Cathy was still held captive in MKUltra. Kelly was forced to wear a mask as part of her programming from the age of *two* to dehumanise her, target her sense of individuality and reduce the amount of oxygen her brain and body received. *Bingo*. This is the real reason for compulsory

masks, why they have been enforced en masse, and why they seek to increase the number they demand you wear. First one, then two, with one disgraceful alleged 'doctor' recommending four which is nothing less than a death sentence. Where and how often they must be worn is being expanded for the purpose of mass mind control and damaging respiratory health which they can call 'Covid-19'. Canada's government headed by the man-child Justin Trudeau, says it's fine for children of two and older to wear masks. An insane 'study' in Italy involving just 47 children concluded there was no problem for babies as young as *four months* wearing them. Even after people were 'vaccinated' they were still told to wear masks by the criminal that is Anthony Fauci. Cathy wrote that mandating masks is allowing the authorities literally to control the air we breathe which is what was done in MKUltra. You might recall how the singer Michael Jackson wore masks and there is a reason for that. He was subjected to MKUltra mind control through Project Monarch and his psyche was scrambled by these simpletons. Cathy wrote:

In MKUltra Project Monarch mind control, Michael Jackson had to wear a mask to silence his voice so he could not reach out for help. Remember how he developed that whisper voice when he wasn't singing? Masks control the mind from the outside in, like the redefining of words is doing. By controlling what we can and cannot say for fear of being labeled racist or beaten, for example, it ultimately controls thought that drives our words and ultimately actions (or lack thereof).

Likewise, a mask muffles our speech so that we are not heard, which controls voice … words … mind. This is Mind Control. Masks are an obvious mind control device, and I am disturbed so many people are complying on a global scale. Masks depersonalize while making a person feel as though they have no voice. It is a barrier to others. People who would never choose to comply but are forced to wear a mask in order to keep their job, and ultimately their family fed, are compromised. They often feel shame and are subdued. People have stopped talking with each other while media controls the narrative.

The 'no voice' theme has often become literal with train passengers told not to speak to each other in case they pass on the 'virus', singing banned for the same reason and bonkers California officials telling people riding roller coasters that they cannot shout and scream. Cathy said she heard every day from healed MKUltra survivors who cannot wear a mask without flashing back on ways

their breathing was controlled – 'from ball gags and penises to water boarding'. She said that through the years when she saw images of people in China wearing masks 'due to pollution' that it was really to control their oxygen levels. 'I knew it was as much of a population control mechanism of depersonalisation as are burkas', she said. Masks are another Chinese communist/fascist method of control that has been swept across the West as the West becomes China at lightning speed since we entered 2020.

Mask-19

There are other reasons for mandatory masks and these include destroying respiratory health to call it 'Covid-19' and stunting brain development of children and the young. Dr Margarite Griesz-Brisson MD, PhD, is a Consultant Neurologist and Neurophysiologist and the Founder and Medical Director of the London Neurology and Pain Clinic. Her CV goes down the street and round the corner. She is clearly someone who cares about people and won't parrot the propaganda. Griesz-Brisson has a PhD in pharmacology, with special interest in neurotoxicology, environmental medicine, neuroregeneration and neuroplasticity (the way the brain can change in the light of information received). She went public in October, 2020, with a passionate warning about the effects of mask-wearing laws:

> The reinhalation of our exhaled air will without a doubt create oxygen deficiency and a flooding of carbon dioxide. We know that the human brain is very sensitive to oxygen deprivation. There are nerve cells for example in the hippocampus that can't be longer than 3 minutes without oxygen – they cannot survive. The acute warning symptoms are headaches, drowsiness, dizziness, issues in concentration, slowing down of reaction time – reactions of the cognitive system.

Oh, I know, let's tell bus, truck and taxi drivers to wear them and people working machinery. How about pilots, doctors and police? Griesz-Brisson makes the important point that while the symptoms she mentions may fade as the body readjusts this does not alter the fact that people continue to operate in oxygen deficit with long list of

potential consequences. She said it was well known that neurodegenerative diseases take years or decades to develop. 'If today you forget your phone number, the breakdown in your brain would have already started 20 or 30 years ago.' She said degenerative processes in your brain are getting amplified as your oxygen deprivation continues through wearing a mask. Nerve cells in the brain are unable to divide themselves normally in these circumstances and lost nerve cells will no longer be regenerated. 'What is gone is gone.' Now consider that people like shop workers and *schoolchildren* are wearing masks for hours every day. What in the name of sanity is going to be happening to them? 'I do not wear a mask, I need my brain to think', Griesz-Brisson said, 'I want to have a clear head when I deal with my patients and not be in a carbon dioxide-induced anaesthesia'. If you are told to wear a mask anywhere ask the organisation, police, store, whatever, for their risk assessment on the dangers and negative effects on mind and body of enforcing mask-wearing. They won't have one because it has never been done not even by government. All of them must be subject to class-action lawsuits as the consequences come to light. They don't do mask risk assessments for an obvious reason. They know what the conclusions would be and independent scientific studies that *have* been done tell a horror story of consequences.

'Masks are criminal'

Dr Griesz-Brisson said that for children and adolescents, masks are an absolute no-no. They had an extremely active and adaptive immune system and their brain was incredibly active with so much to learn. 'The child's brain, or the youth's brain, is thirsting for oxygen.' The more metabolically active an organ was, the more oxygen it required; and in children and adolescents every organ was metabolically active. Griesz-Brisson said that to deprive a child's or adolescent's brain of oxygen, or to restrict it in any way, was not only dangerous to their health, it was absolutely criminal. 'Oxygen deficiency inhibits the development of the brain, and the damage that has taken place as a result CANNOT be reversed.' Mind

manipulators of MKUltra put masks on two-year-olds they wanted to neurologically rewire and you can see why. Griesz-Brisson said a child needs the brain to learn and the brain needs oxygen to function. 'We don't need a clinical study for that. This is simple, indisputable physiology.' Consciously and purposely induced oxygen deficiency was an absolutely deliberate health hazard, and an absolute medical contraindication which means that 'this drug, this therapy, this method or measure should not be used, and is not allowed to be used'. To coerce an entire population to use an absolute medical contraindication by force, she said, there had to be definite and serious reasons and the reasons must be presented to competent interdisciplinary and independent bodies to be verified and authorised. She had this warning of the consequences that were coming if mask wearing continued:

When, in ten years, dementia is going to increase exponentially, and the younger generations couldn't reach their god-given potential, it won't help to say 'we didn't need the masks'. I know how damaging oxygen deprivation is for the brain, cardiologists know how damaging it is for the heart, pulmonologists know how damaging it is for the lungs. Oxygen deprivation damages every single organ. Where are our health departments, our health insurance, our medical associations? It would have been their duty to be vehemently against the lockdown and to stop it and stop it from the very beginning.

Why do the medical boards issue punishments to doctors who give people exemptions? Does the person or the doctor seriously have to prove that oxygen deprivation harms people? What kind of medicine are our doctors and medical associations representing? Who is responsible for this crime? The ones who want to enforce it? The ones who let it happen and play along, or the ones who don't prevent it?

All of the organisations and people she mentions there either answer directly to the Cult or do whatever hierarchical levels above them tell them to do. The outcome of both is the same. 'It's not about masks, it's not about viruses, it's certainly not about your health', Griesz-Brisson said. 'It is about much, much more. I am not participating. I am not afraid.' They were taking our air to breathe and there was no unfounded medical exemption from face masks. Oxygen deprivation was dangerous for every single brain. It had to be the free decision of every human being whether they want to

wear a mask that was absolutely ineffective to protect themselves from a virus. She ended by rightly identifying where the responsibility lies for all this:

> The imperative of the hour is personal responsibility. We are responsible for what we think, not the media. We are responsible for what we do, not our superiors. We are responsible for our health, not the World Health Organization. And we are responsible for what happens in our country, not the government.

Halle-bloody-lujah.

But surgeons wear masks, right?

Independent studies of mask-wearing have produced a long list of reports detailing mental, emotional and physical dangers. What a definition of insanity to see police officers imposing mask-wearing on the public which will cumulatively damage their health while the police themselves wear masks that will cumulatively damage *their* health. It's utter madness and both public and police do this because 'the government says so' – yes a government of brain-donor idiots like UK Health Secretary Matt Hancock reading the 'follow the science' scripts of psychopathic, lunatic psychologists. The response you get from Stockholm syndrome sufferers defending the very authorities that are destroying them and their families is that 'surgeons wear masks'. This is considered the game, set and match that they must work and don't cause oxygen deficit. Well, actually, scientific studies have shown that they *do* and oxygen levels are monitored in operating theatres to compensate. Surgeons wear masks to stop spittle and such like dropping into open wounds – not to stop 'viral particles' which are so miniscule they can only be seen through an electron microscope. Holes in the masks are significantly bigger than 'viral particles' and if you sneeze or cough they will breach the mask. I watched an incredibly disingenuous 'experiment' that claimed to prove that masks work in catching 'virus' material from the mouth and nose. They did this with a slow motion camera and the mask did block big stuff which stayed inside the mask and

against the face to be breathed in or cause infections on the face as we have seen with many children. 'Viral particles', however, would never have been picked up by the camera as they came through the mask when they are far too small to be seen. The 'experiment' was therefore disingenuous *and* useless.

Studies have concluded that wearing masks in operating theatres (and thus elsewhere) make no difference to preventing infection while the opposite is true with toxic shite building up in the mask and this had led to an explosion in tooth decay and gum disease dubbed by dentists 'mask mouth'. You might have seen the Internet video of a furious American doctor urging people to take off their masks after a four-year-old patient had been rushed to hospital the night before and nearly died with a lung infection that doctors sourced to mask wearing. A study in the journal *Cancer Discovery* found that inhalation of harmful microbes can contribute to advanced stage lung cancer in adults and long-term use of masks can help breed dangerous pathogens. Microbiologists have said frequent mask wearing creates a moist environment in which microbes can grow and proliferate before entering the lungs. The Canadian Agency for Drugs and Technologies in Health, or CADTH, a Canadian national organisation that provides research and analysis to healthcare decision-makers, said this as long ago as 2013 in a report entitled 'Use of Surgical Masks in the Operating Room: A Review of the Clinical Effectiveness and Guidelines'. It said:

- No evidence was found to support the use of surgical face masks to reduce the frequency of surgical site infections
- No evidence was found on the effectiveness of wearing surgical face masks to protect staff from infectious material in the operating room.
- Guidelines recommend the use of surgical face masks by staff in the operating room to protect both operating room staff and patients (despite the lack of evidence).

We were told that the world could go back to 'normal' with the arrival of the 'vaccines'. When they came, fraudulent as they are, the story changed as I knew that it would. We are in the midst of transforming 'normal', not going back to it. Mary Ramsay, head of immunisation at Public Health England, echoed the words of US criminal Anthony Fauci who said masks and other regulations must stay no matter if people are vaccinated. The Fauci idiot continued to wear two masks – different colours so both could be clearly seen – after he *claimed* to have been vaccinated. Senator Rand Paul told Fauci in one exchange that his double-masks were 'theatre' and he was right. It's all theatre. Mary Ramsay back-tracked on the vaccine-return-to-normal theme when she said the public may need to wear masks and social-distance for years despite the jabs. 'People have got used to those lower-level restrictions now, and [they] can live with them', she said telling us what the idea has been all along. 'The vaccine does not give you a pass, even if you have had it, you must continue to follow all the guidelines' said a Public Health England statement which reneged on what we had been told before and made having the 'vaccine' irrelevant to 'normality' even by the official story. Spain's fascist government trumped everyone by passing a law mandating the wearing of masks on the beach and even when swimming in the sea. The move would have devastated what's left of the Spanish tourist industry, posed potential breathing dangers to swimmers and had Northern European sunbathers walking around with their forehead brown and the rest of their face white as a sheet. The ruling was so crazy that it had to be retracted after pressure from public and tourist industry, but it confirmed where the Cult wants to go with masks and how clinically insane authority has become. The determination to make masks permanent and hide the serious dangers to body and mind can be seen in the censorship of scientist Professor Denis Rancourt by Bill Gates-funded academic publishing website ResearchGate over his papers exposing the dangers and uselessness of masks. Rancourt said:

ResearchGate today has permanently locked my account, which I have had since 2015. Their reasons graphically show the nature of their attack against democracy, and their corruption of

science … By their obscene non-logic, a scientific review of science articles reporting on harms caused by face masks has a 'potential to cause harm'. No criticism of the psychological device (face masks) is tolerated, if the said criticism shows potential to influence public policy.

This is what happens in a fascist world.

Where are the 'greens' (again)?

Other dangers of wearing masks especially regularly relate to the inhalation of minute plastic fibres into the lungs and the deluge of discarded masks in the environment and oceans. Estimates predicted that more than 1.5 billion disposable masks will end up in the world's oceans every year polluting the water with tons of plastic and endangering marine wildlife. Studies project that humans are using 129 billion face masks each month worldwide – about three million a minute. Most are disposable and made from plastic, non-biodegradable microfibers that break down into smaller plastic particles that become widespread in ecosystems. They are littering cities, clogging sewage channels and turning up in bodies of water. I have written in other books about the immense amounts of microplastics from endless sources now being absorbed into the body. Rolf Halden, director of the Arizona State University (ASU) Biodesign Center for Environmental Health Engineering, was the senior researcher in a 2020 study that analysed 47 human tissue samples and found microplastics in all of them. 'We have detected these chemicals of plastics in every single organ that we have investigated', he said. I wrote in *The Answer* about the world being deluged with microplastics. A study by the Worldwide Fund for Nature (WWF) found that people are consuming on average every week some 2,000 tiny pieces of plastic mostly through water and also through marine life and the air. Every year humans are ingesting enough microplastics to fill a heaped dinner plate and in a life-time of 79 years it is enough to fill two large waste bins. Marco Lambertini, WWF International director general said: 'Not only are plastics polluting our oceans and waterways and killing marine life – it's in all of us and we can't escape consuming plastics,' American

geologists found tiny plastic fibres, beads and shards in rainwater samples collected from the remote slopes of the Rocky Mountain National Park near Denver, Colorado. Their report was headed: 'It is raining plastic.' Rachel Adams, senior lecturer in Biomedical Science at Cardiff Metropolitan University, said that among health consequences are internal inflammation and immune responses to a 'foreign body'. She further pointed out that microplastics become carriers of toxins including mercury, pesticides and dioxins (a known cause of cancer and reproductive and developmental problems). These toxins accumulate in the fatty tissues once they enter the body through microplastics. Now this is being compounded massively by people putting plastic on their face and throwing it away.

Workers exposed to polypropylene plastic fibres known as 'flock' have developed 'flock worker's lung' from inhaling small pieces of the flock fibres which can damage lung tissue, reduce breathing capacity and exacerbate other respiratory problems. *Now* … commonly used surgical masks have three layers of melt-blown textiles made of … polypropylene. We have billions of people putting these microplastics against their mouth, nose and face for hours at a time day after day in the form of masks. How does anyone think that will work out? I mean – what could possibly go wrong? We posted a number of scientific studies on this at davidicke.com, but when I went back to them as I was writing this book the links to the science research website where they were hosted were dead. Anything that challenges the official narrative in any way is either censored or vilified. The official narrative is so unsupportable by the evidence that only deleting the truth can protect it. A study by Chinese scientists still survived – with the usual twist which it why it was still active, I guess. Yes, they found that virtually all the masks they tested increased the daily intake of microplastic fibres, but people should still wear them because the danger from the 'virus' was worse said the crazy 'team' from the Institute of Hydrobiology in Wuhan. Scientists first discovered microplastics in lung tissue of some patients who died of lung cancer

in the 1990s. Subsequent studies have confirmed the potential health damage with the plastic degrading slowly and remaining in the lungs to accumulate in volume. Wuhan researchers used a machine simulating human breathing to establish that masks shed up to nearly 4,000 microplastic fibres in a month with reused masks producing more. Scientists said some masks are laced with toxic chemicals and a variety of compounds seriously restricted for both health and environmental reasons. They include cobalt (used in blue dye) and formaldehyde known to cause watery eyes, burning sensations in the eyes, nose, and throat, plus coughing, wheezing and nausea. No – that must be 'Covid-19'.

Mask 'worms'

There is another and potentially even more sinister content of masks. Mostly new masks of different makes filmed under a microscope around the world have been found to contain strange black fibres or 'worms' that appear to move or 'crawl' by themselves and react to heat and water. The nearest I have seen to them are the self-replicating fibres that are pulled out through the skin of those suffering from Morgellons disease which has been connected to the phenomena of 'chemtrails' which I will bring into the story later on. Morgellons fibres continue to grow outside the body and have a form of artificial intelligence. Black 'worm' fibres in masks have that kind of feel to them and there is a nanotechnology technique called 'worm micelles' which carry and release drugs or anything else you want to deliver to the body. For sure the suppression of humanity by mind altering drugs is the Cult agenda big time and the more excuses they can find to gain access to the body the more opportunities there are to make that happen whether through 'vaccines' or masks pushed against the mouth and nose for hours on end.

So let us summarise the pros and cons of masks:

Against masks: Breathing in your own carbon dioxide; depriving the body and brain of sufficient oxygen; build-up of toxins in the mask that can be breathed into the lungs and cause rashes on the face and 'mask-mouth'; breathing microplastic fibres and toxic chemicals into the lungs; dehumanisation and deleting individualisation by literally making people faceless; destroying human emotional interaction through facial expression and deleting parental connection with their babies which look for guidance to their facial expression.

For masks: They don't protect you from a 'virus' that doesn't exist and even if it did 'viral' particles are so minute they are smaller than the holes in the mask.

Governments, police, supermarkets, businesses, transport companies, and all the rest who seek to impose masks have done no risk assessment on their consequences for health and psychology and are now open to group lawsuits when the impact becomes clear with a cumulative epidemic of respiratory and other disease. Authorities will try to exploit these effects and hide the real cause by dubbing them 'Covid-19'. Can you imagine setting out to force the population to wear health-destroying masks without doing any assessment of the risks? It is criminal and it is evil, but then how many people targeted in this way, who see their children told to wear them all day at school, have asked for a risk assessment? Billions can't be imposed upon by the few unless the billions allow it. Oh, yes, with just a tinge of irony, 85 percent of all masks made worldwide come from *China*.

Wash your hands in toxic shite

'Covid' rules include the use of toxic sanitisers and again the health consequences of constantly applying toxins to be absorbed through the skin is obvious to any level of Renegade Mind. America's Food and Drug Administration (FDA) said that sanitisers are drugs and issued a warning about 75 dangerous brands which contain

methanol used in antifreeze and can cause death, kidney damage and blindness. The FDA circulated the following warning even for those brands that it claims to be safe:

Store hand sanitizer out of the reach of pets and children, and children should use it only with adult supervision. Do not drink hand sanitizer. This is particularly important for young children, especially toddlers, who may be attracted by the pleasant smell or brightly colored bottles of hand sanitizer.

Drinking even a small amount of hand sanitizer can cause alcohol poisoning in children. (However, there is no need to be concerned if your children eat with or lick their hands after using hand sanitizer.) During this coronavirus pandemic, poison control centers have had an increase in calls about accidental ingestion of hand sanitizer, so it is important that adults monitor young children's use.

Do not allow pets to swallow hand sanitizer. If you think your pet has eaten something potentially dangerous, call your veterinarian or a pet poison control center right away. Hand sanitizer is flammable and should be stored away from heat and flames. When using hand sanitizer, rub your hands until they feel completely dry before performing activities that may involve heat, sparks, static electricity, or open flames.

There you go, perfectly safe, then, and that's without even a mention of the toxins absorbed through the skin. Come on kids – sanitise your hands everywhere you go. It will save you from the 'virus'. Put all these elements together of the 'Covid' normal and see how much health and psychology is being cumulatively damaged, even devastated, to 'protect your health'. Makes sense, right? They are only imposing these things because they care, right? *Right?*

Submitting to insanity

Psychological reframing of the population goes very deep and is done in many less obvious ways. I hear people say how contradictory and crazy 'Covid' rules are and how they are ever changing. This is explained away by dismissing those involved as idiots. It is a big mistake. The Cult is delighted if its cold calculation is perceived as incompetence and idiocy when it is anything but. Oh, yes, there are idiots within the system – lots of them – but they are *administering* the Cult agenda, mostly unknowingly. They are not deciding and dictating it. The bulwark against tyranny is self-

respect, always has been, always will be. It is self-respect that has broken every tyranny in history. By its very nature self-respect will not bow to oppression and its perpetrators. There is so little self-respect that it's always the few that overturn dictators. Many may eventually follow, but the few with the iron spines (self-respect) kick it off and generate the momentum. The Cult targets self-respect in the knowledge that once this has gone only submission remains. Crazy, contradictory, ever-changing 'Covid' rules are systematically applied by psychologists to delete self-respect. They *want* you to see that the rules make no sense. It is one thing to decide to do something when *you* have made the choice based on evidence and logic. You still retain your self-respect. It is quite another when you can see what you are being told to do is insane, ridiculous and makes no sense, and *yet you still do it*. Your self-respect is extinguished and this has been happening as ever more obviously stupid and nonsensical things have been demanded and the great majority have complied even when they can see they are stupid and nonsensical.

People walk around in face-nappies knowing they are damaging their health and make no difference to a 'virus'. They do it in fear of not doing it. I know it's daft, but I'll do it anyway. When that happens something dies inside of you and submissive reframing has begun. Next there's a need to hide from yourself that you have conceded your self-respect and you convince yourself that you have not really submitted to fear and intimidation. You begin to believe that you are complying with craziness because it's the right thing to do. When first you concede your self-respect of 2+2 = 4 to 2+2 = 5 you *know* you are compromising your self-respect. Gradually to avoid facing that fact you begin to *believe* that 2+2=5. You have been reframed and I have been watching this process happening in the human psyche on an industrial scale. The Cult is working to break your spirit and one of its major tools in that war is humiliation. I read how former American soldier Bradley Manning (later Chelsea Manning after a sex-change) was treated after being jailed for supplying WikiLeaks with documents exposing the enormity of

government and elite mendacity. Manning was isolated in solitary confinement for eight months, put under 24-hour surveillance, forced to hand over clothing before going to bed, and stand naked for every roll call. This is systematic humiliation. The introduction of anal swab 'Covid' tests in China has been done for the same reason to delete self-respect and induce compliant submission. Anal swabs are mandatory for incoming passengers in parts of China and American diplomats have said they were forced to undergo the indignity which would have been calculated humiliation by the Cult-owned Chinese government that has America in its sights.

Government-people: An abusive relationship

Spirit-breaking psychological techniques include giving people hope and apparent respite from tyranny only to take it away again. This happened in the UK during Christmas, 2020, when the psycho-psychologists and their political lackeys announced an easing of restrictions over the holiday only to reimpose them almost immediately on the basis of yet another lie. There is a big psychological difference between getting used to oppression and being given hope of relief only to have that dashed. Psychologists know this and we have seen the technique used repeatedly. Then there is traumatising people before you introduce more extreme regulations that require compliance. A perfect case was the announcement by the dark and sinister Whitty and Vallance in the UK that 'new data' predicted that 4,000 could die every day over the winter of 2020/2021 if we did not lockdown again. I think they call it lying and after traumatising people with that claim out came Jackboot Johnson the next day with new curbs on human freedom. Psychologists know that a frightened and traumatised mind becomes suggestable to submission and behaviour reframing. Underpinning all this has been to make people fearful and suspicious of each other and see themselves as a potential danger to others. In league with deleted self-respect you have the perfect psychological recipe for self-loathing. The relationship between authority and public is now demonstrably the same as that of

subservience to an abusive partner. These are signs of an abusive relationship explained by psychologist Leslie Becker-Phelps:

Psychological and emotional abuse: Undermining a partner's self-worth with verbal attacks, name-calling, and belittling. Humiliating the partner in public, unjustly accusing them of having an affair, or interrogating them about their every behavior. Keeping partner confused or off balance by saying they were just kidding or blaming the partner for 'making' them act this way … Feigning in public that they care while turning against them in private. This leads to victims frequently feeling confused, incompetent, unworthy, hopeless, and chronically self-doubting. [Apply these techniques to how governments have treated the population since New Year, 2020, and the parallels are obvious.]

Physical abuse: The abuser might physically harm their partner in a range of ways, such as grabbing, hitting, punching, or shoving them. They might throw objects at them or harm them with a weapon. [Observe the physical harm imposed by masks, lockdown, and so on.]

Threats and intimidation: One way abusers keep their partners in line is by instilling fear. They might be verbally threatening, or give threatening looks or gestures. Abusers often make it known that they are tracking their partner's every move. They might destroy their partner's possessions, threaten to harm them, or threaten to harm their family members. Not surprisingly, victims of this abuse often feel anxiety, fear, and panic. [No words necessary.]

Isolation: Abusers often limit their partner's activities, forbidding them to talk or interact with friends or family. They might limit access to a car or even turn off their phone. All of this might be done by physically holding them against their will, but is often accomplished through psychological abuse and intimidation. The more isolated a person feels, the fewer resources they have to help gain perspective on their situation and to escape from it. [No words necessary.]

Economic abuse: Abusers often make their partners beholden to them for money by controlling access to funds of any kind. They might prevent their partner from getting a job or withhold access to money they earn from a job. This creates financial dependency that makes leaving the relationship very difficult. [See destruction of livelihoods and the proposed meagre 'guaranteed income' so long as you do whatever you are told.]

Using children: An abuser might disparage their partner's parenting skills, tell their children lies about their partner, threaten to take custody of their children, or threaten to harm their children. These tactics instil fear and often elicit compliance. [See reframed social service mafia and how children are being mercilessly abused by the state over 'Covid' while their parents look on too frightened to do anything.]

A further recurring trait in an abusive relationship is the abused blaming themselves for their abuse and making excuses for the abuser. We have the public blaming each other for lockdown abuse by government and many making excuses for the government while attacking those who challenge the government. How often we have heard authorities say that rules are being imposed or reimposed only because people have refused to 'behave' and follow the rules. We don't want to do it – it's *you*.

Renegade Minds are an antidote to all of these things. They will never concede their self-respect no matter what the circumstances. Even when apparent humiliation is heaped upon them they laugh in its face and reflect back the humiliation on the abuser where it belongs. Renegade Minds will never wear masks they know are only imposed to humiliate, suppress and damage both physically and psychologically. Consequences will take care of themselves and they will never break their spirit or cause them to concede to tyranny. UK newspaper columnist Peter Hitchens was one of the few in the mainstream media to speak out against lockdowns and forced vaccinations. He then announced he had taken the jab. He wanted to see family members abroad and he believed vaccine passports were inevitable even though they had not yet been introduced. Hitchens

has a questioning and critical mind, but not a Renegade one. If he had no amount of pressure would have made him concede. Hitchens excused his action by saying that the battle has been lost. Renegade Minds never accept defeat when freedom is at stake and even if they are the last one standing the self-respect of not submitting to tyranny is more important than any outcome or any consequence.

That's why Renegade Minds are the only minds that ever changed anything worth changing.

CHAPTER EIGHT

'Reframing' insanity

Insanity is relative. It depends on who has who locked in what cage
Ray Bradbury

'Reframing' a mind means simply to change its perception and behaviour. This can be done subconsciously to such an extent that subjects have no idea they have been 'reframed' while to any observer changes in behaviour and attitudes are obvious.

Human society is being reframed on a ginormous scale since the start of 2020 and here we have the reason why psychologists rather than doctors have been calling the shots. Ask most people who have succumbed to 'Covid' reframing if they have changed and most will say 'no'; but they *have* and fundamentally. The Cult's long-game has been preparing for these times since way back and crucial to that has been to prepare both population and officialdom mentally and emotionally. To use the mind-control parlance they had to reframe the population with a mentality that would submit to fascism and reframe those in government and law enforcement to impose fascism or at least go along with it. The result has been the fact-deleted mindlessness of 'Wokeness' and officialdom that has either enthusiastically or unquestioningly imposed global tyranny demanded by reframed politicians on behalf of psychopathic and deeply evil cultists. 'Cognitive reframing' identifies and challenges the way someone sees the world in the form of situations, experiences and emotions and then restructures those perceptions to view the same set of circumstances in a different way. This can have

benefits if the attitudes are personally destructive while on the other side it has the potential for individual and collective mind control which the subject has no idea has even happened.

Cognitive therapy was developed in the 1960s by Aaron T. Beck who was born in Rhode Island in 1921 as the son of Jewish immigrants from the Ukraine. He became interested in the techniques as a treatment for depression. Beck's daughter Judith S. Beck is prominent in the same field and they founded the Beck Institute for Cognitive Behavior Therapy in Philadelphia in 1994. Cognitive reframing, however, began to be used worldwide by those with a very dark agenda. The Cult reframes politicians to change their attitudes and actions until they are completely at odds with what they once appeared to stand for. The same has been happening to government administrators at all levels, law enforcement, military and the human population. Cultists love mind control for two main reasons: It allows them to control what people think, do and say to secure agenda advancement and, by definition, it calms their legendary insecurity and fear of the unexpected. I have studied mind control since the time I travelled America in 1996. I may have been talking to next to no one in terms of an audience in those years, but my goodness did I gather a phenomenal amount of information and knowledge about so many things including the techniques of mind control. I have described this in detail in other books going back to *The Biggest Secret* in 1998. I met a very large number of people recovering from MKUltra and its offshoots and successors and I began to see how these same techniques were being used on the population in general. This was never more obvious than since the 'Covid' hoax began.

Reframing the enforcers

I have observed over the last two decades and more the very clear transformation in the dynamic between the police, officialdom and the public. I tracked this in the books as the relationship mutated from one of serving the public to seeing them as almost the enemy and certainly a lower caste. There has always been a class divide

based on income and always been some psychopathic, corrupt, and big-I-am police officers. This was different. Wholesale change was unfolding in the collective dynamic; it was less about money and far more about position and perceived power. An us-and-them was emerging. Noses were lifted skyward by government administration and law enforcement and their attitude to the public they were *supposed* to be serving changed to one of increasing contempt, superiority and control. The transformation was so clear and widespread that it had to be planned. Collective attitudes and dynamics do not change naturally and organically that quickly on that scale. I then came across an organisation in Britain called Common Purpose created in the late 1980s by Julia Middleton who would work in the office of Deputy Prime Minister John Prescott during the long and disastrous premiership of war criminal Tony Blair. When Blair speaks the Cult is speaking and the man should have been in jail a long time ago. Common Purpose proclaims itself to be one of the biggest 'leadership development' organisations in the world while functioning as a *charity* with all the financial benefits which come from that. It hosts 'leadership development' courses and programmes all over the world and claims to have 'brought together' what it calls 'leaders' from more than 100 countries on six continents. The modus operandi of Common Purpose can be compared with the work of the UK government's reframing network that includes the Behavioural Insights Team 'nudge unit' and 'Covid' reframing specialists at SPI-B. WikiLeaks described Common Purpose long ago as 'a hidden virus in our government and schools' which is unknown to the general public: 'It recruits and trains "leaders" to be loyal to the directives of Common Purpose and the EU, instead of to their own departments, which they then undermine or subvert, the NHS [National Health Service] being an example.' This is a vital point to understand the 'Covid' hoax. The NHS, and its equivalent around the world, has been utterly reframed in terms of administrators and much of the medical personnel with the transformation underpinned by recruitment policies. The outcome has been the criminal and psychopathic behaviour of the

NHS over 'Covid' and we have seen the same in every other major country. WikiLeaks said Common Purpose trainees are 'learning to rule without regard to democracy' and to usher in a police state (current events explained). Common Purpose operated like a 'glue' and had members in the NHS, BBC, police, legal profession, church, many of Britain's 7,000 quangos, local councils, the Civil Service, government ministries and Parliament, and controlled many RDA's (Regional Development Agencies). Here we have one answer for how and why British institutions and their like in other countries have changed so negatively in relation to the public. This further explains how and why the beyond-disgraceful reframed BBC has become a propaganda arm of 'Covid' fascism. They are all part of a network pursuing the same goal.

By 2019 Common Purpose was quoting a figure of 85,000 'leaders' that had attended its programmes. These 'students' of all ages are known as Common Purpose 'graduates' and they consist of government, state and local government officials and administrators, police chiefs and officers, and a whole range of others operating within the national, local and global establishment. Cressida Dick, Commissioner of the London Metropolitan Police, is the Common Purpose graduate who was the 'Gold Commander' that oversaw what can only be described as the murder of Brazilian electrician Jean Charles de Menezes in 2005. He was held down by psychopathic police and shot seven times in the head by a psychopathic lunatic after being mistaken for a terrorist when he was just a bloke going about his day. Dick authorised officers to pursue and keep surveillance on de Menezes and ordered that he be stopped from entering the underground train system. Police psychopaths took her at her word clearly. She was 'disciplined' for this outrage by being *promoted* – eventually to the top of the 'Met' police where she has been a disaster. Many Chief Constables controlling the police in different parts of the UK are and have been Common Purpose graduates. I have heard the 'graduate' network described as a sort of Mafia or secret society operating within the fabric of government at all levels pursuing a collective policy

ingrained at Common Purpose training events. Founder Julia Middleton herself has said:

> Locally and internationally, Common Purpose graduates will be 'lighting small fires' to create change in their organisations and communities … The Common Purpose effect is best illustrated by the many stories of small changes brought about by leaders, who themselves have changed.

A Common Purpose mission statement declared:

> Common Purpose aims to improve the way society works by expanding the vision, decision-making ability and influence of all kinds of leaders. The organisation runs a variety of educational programmes for leaders of all ages, backgrounds and sectors, in order to provide them with the inspirational, information and opportunities they need to change the world.

Yes, but into what? Since 2020 the answer has become clear.

NLP and the Delphi technique

Common Purpose would seem to be a perfect name or would common programming be better? One of the foundation methods of reaching 'consensus' (group think) is by setting the agenda theme and then encouraging, cajoling or pressuring everyone to agree a 'consensus' in line with the core theme promoted by Common Purpose. The methodology involves the 'Delphi technique', or an adaption of it, in which opinions are expressed that are summarised by a 'facilitator or change agent' at each stage. Participants are 'encouraged' to modify their views in the light of what others have said. Stage by stage the former individual opinions are merged into group consensus which just happens to be what Common Purpose wants them to believe. A key part of this is to marginalise anyone refusing to concede to group think and turn the group against them to apply pressure to conform. We are seeing this very technique used on the general population to make 'Covid' group-thinkers hostile to those who have seen through the bullshit. People can be reframed by using perception manipulation methods such as Neuro-Linguistic Programming (NLP) in which you change perception with the use of

carefully constructed language. An NLP website described the technique this way:

… A method of influencing brain behaviour (the 'neuro' part of the phrase) through the use of language (the 'linguistic' part) and other types of communication to enable a person to 'recode' the way the brain responds to stimuli (that's the 'programming') and manifest new and better behaviours. Neuro-Linguistic Programming often incorporates hypnosis and self-hypnosis to help achieve the change (or 'programming') that is wanted.

British alternative media operation UKColumn has done very detailed research into Common Purpose over a long period. I quoted co-founder and former naval officer Brian Gerrish in my book *Remember Who You Are*, published in 2011, as saying the following years before current times:

It is interesting that many of the mothers who have had children taken by the State speak of the Social Services people being icily cool, emotionless and, as two ladies said in slightly different words, '… like little robots'. We know that NLP is cumulative, so people can be given small imperceptible doses of NLP in a course here, another in a few months, next year etc. In this way, major changes are accrued in their personality, but the day by day change is almost unnoticeable.

In these and other ways 'graduates' have had their perceptions uniformly reframed and they return to their roles in the institutions of government, law enforcement, legal profession, military, 'education', the UK National Health Service and the whole swathe of the establishment structure to pursue a common agenda preparing for the 'post-industrial', 'post-democratic' society. I say 'preparing' but we are now there. 'Post-industrial' is code for the Great Reset and 'post-democratic' is 'Covid' fascism. UKColumn has spoken to partners of those who have attended Common Purpose 'training'. They have described how personalities and attitudes of 'graduates' changed very noticeably for the worse by the time they had completed the course. They had been 'reframed' and told they are the 'leaders' – the special ones – who know better than the population. There has also been the very demonstrable recruitment of psychopaths and narcissists into government administration at all

levels and law enforcement. If you want psychopathy hire psychopaths and you get a simple cause and effect. If you want administrators, police officers and 'leaders' to perceive the public as lesser beings who don't matter then employ narcissists. These personalities are identified using 'psychometrics' that identifies knowledge, abilities, attitudes and personality traits, mostly through carefully-designed questionnaires and tests. As this policy has passed through the decades we have had power-crazy, power-trippers appointed into law enforcement, security and government administration in preparation for current times and the dynamic between public and law enforcement/officialdom has been transformed. UKColumn's Brian Gerrish said of the narcissistic personality:

> Their love of themselves and power automatically means that they will crush others who get in their way. I received a major piece of the puzzle when a friend pointed out that when they made public officials re-apply for their own jobs several years ago they were also required to do psychometric tests. This was undoubtedly the start of the screening process to get 'their' sort of people in post.

How obvious that has been since 2020 although it was clear what was happening long before if people paid attention to the changing public-establishment dynamic.

Change agents

At the centre of events in 'Covid' Britain is the National Health Service (NHS) which has behaved disgracefully in slavishly following the Cult agenda. The NHS management structure is awash with Common Purpose graduates or 'change agents' working to a common cause. Helen Bevan, a Chief of Service Transformation at the NHS Institute for Innovation and Improvement, co-authored a document called 'Towards a million change agents, a review of the social movements literature: implications for large scale change in the NHS'. The document compared a project management approach to that of change and social movements where 'people change

themselves and each other – peer to peer'. Two definitions given for a 'social movement' were:

A group of people who consciously attempt to build a radically new social order; involves people of a broad range of social backgrounds; and deploys politically confrontational and socially disruptive tactics – Cyrus Zirakzadeh 1997

Collective challenges, based on common purposes and social solidarities, in sustained interaction with elites, opponents, and authorities – Sidney Tarrow 1994

Helen Bevan wrote another NHS document in which she defined 'framing' as 'the process by which leaders construct, articulate and put across their message in a powerful and compelling way in order to win people to their cause and call them to action'. I think I could come up with another definition that would be rather more accurate. The National Health Service and institutions of Britain and the wider world have been taken over by reframed 'change agents' and that includes everything from the United Nations to national governments, local councils and social services which have been kidnapping children from loving parents on an extraordinary and gathering scale on the road to the end of parenthood altogether. Children from loving homes are stolen and kidnapped by the state and put into the 'care' (inversion) of the local authority through council homes, foster parents and forced adoption. At the same time children are allowed to be abused without response while many are under council 'care'. UKColumn highlighted the Common Purpose connection between South Yorkshire Police and Rotherham council officers in the case of the scandal in that area of the sexual exploitation of children to which the authorities turned not one blind eye, but both:

We were alarmed to discover that the Chief Executive, the Strategic Director of Children and Young People's Services, the Manager for the Local Strategic Partnership, the Community Cohesion Manager, the Cabinet Member for Cohesion, the Chief Constable and his predecessor had all attended Leadership training courses provided by the pseudo-charity Common Purpose.

Once 'change agents' have secured positions of hire and fire within any organisation things start to move very quickly. Personnel are then hired and fired on the basis of whether they will work towards the agenda the change agent represents. If they do they are rapidly promoted even though they may be incompetent. Those more qualified and skilled who are pre-Common Purpose 'old school' see their careers stall and even disappear. This has been happening for decades in every institution of state, police, 'health' and social services and all of them have been transformed as a result in their attitudes to their jobs and the public. Medical professions, including nursing, which were once vocations for the caring now employ many cold, callous and couldn't give a shit personality types. The UKColumn investigation concluded:

By blurring the boundaries between people, professions, public and private sectors, responsibility and accountability, Common Purpose encourages 'graduates' to believe that as new selected leaders, they can work together, outside of the established political and social structures, to achieve a paradigm shift or CHANGE – so called 'Leading Beyond Authority'. In doing so, the allegiance of the individual becomes 'reframed' on CP colleagues and their NETWORK.

Reframing the Face-Nappies

Nowhere has this process been more obvious than in the police where recruitment of psychopaths and development of unquestioning mind-controlled group-thinkers have transformed law enforcement into a politically-correct 'Woke' joke and a travesty of what should be public service. Today they wear their face-nappies like good little gofers and enforce 'Covid' rules which are fascism under another name. Alongside the specifically-recruited psychopaths we have software minds incapable of free thought. Brian Gerrish again:

An example is the policeman who would not get on a bike for a press photo because he had not done the cycling proficiency course. Normal people say this is political correctness gone mad. Nothing could be further from the truth. The policeman has been reframed, and in his reality it is perfect common sense not to get on the bike 'because he hasn't done the cycling course'.

Another example of this is where the police would not rescue a boy from a pond until they had taken advice from above on the 'risk assessment'. A normal person would have arrived, perhaps thought of the risk for a moment, and dived in. To the police now 'reframed', they followed 'normal' procedure.

There are shocking cases of reframed ambulance crews doing the same. Sheer unthinking stupidity of London Face-Nappies headed by Common Purpose graduate Cressida Dick can be seen in their behaviour at a vigil in March, 2021, for a murdered woman, Sarah Everard. A police officer had been charged with the crime. Anyone with a brain would have left the vigil alone in the circumstances. Instead they 'manhandled' women to stop them breaking 'Covid rules' to betray classic reframing. Minds in the thrall of perception control have no capacity for seeing a situation on its merits and acting accordingly. 'Rules is rules' is their only mind-set. My father used to say that rules and regulations are for the guidance of the intelligent and the blind obedience of the idiot. Most of the intelligent, decent, coppers have gone leaving only the other kind and a few old school for whom the job must be a daily nightmare. The combination of psychopaths and rule-book software minds has been clearly on public display in the 'Covid' era with automaton robots in uniform imposing fascistic 'Covid' regulations on the population without any personal initiative or judging situations on their merits. There are thousands of examples around the world, but I'll make my point with the infamous Derbyshire police in the English East Midlands – the ones who think pouring dye into beauty spots and using drones to track people walking in the countryside away from anyone is called 'policing'. To them there are rules decreed by the government which they have to enforce and in their bewildered state a group gathering in a closed space and someone walking alone in the countryside are the same thing. It is beyond idiocy and enters the realm of clinical insanity.

Police officers in Derbyshire said they were 'horrified' – *horrified* – to find 15 to 20 'irresponsible' kids playing a football match at a closed leisure centre 'in breach of coronavirus restrictions'. When they saw the police the kids ran away leaving their belongings behind and the reframed men and women of Derbyshire police were seeking to establish their identities with a view to fining their parents. The most natural thing for youngsters to do – kicking a ball about – is turned into a criminal activity and enforced by the moronic software programs of Derbyshire police. You find the same mentality in every country. These barely conscious 'horrified' officers said they had to take action because 'we need to ensure these rules are being followed' and 'it is of the utmost importance that you ensure your children are following the rules and regulations for Covid-19'. Had any of them done ten seconds of research to see if this parroting of their masters' script could be supported by any evidence? Nope. Reframed people don't think – others think for them and that's the whole idea of reframing. I have seen police officers one after the other repeating without question word for word what officialdom tells them just as I have seen great swathes of the public doing the same. Ask either for 'their' opinion and out spews what they have been told to think by the official narrative. Police and public may seem to be in different groups, but their mentality is the same. Most people do whatever they are told in fear not doing so or because they believe what officialdom tells them; almost the entirety of the police do what they are told for the same reason. Ultimately it's the tiny inner core of the global Cult that's telling both what to do.

So Derbyshire police were 'horrified'. Oh, really? Why did they think those kids were playing football? It was to relieve the psychological consequences of lockdown and being denied human contact with their friends and interaction, touch and discourse vital to human psychological health. Being denied this month after month has dismantled the psyche of many children and young people as depression and suicide have exploded. Were Derbyshire police *horrified by that*? Are you kidding? Reframed people don't have those

mental and emotional processes that can see how the impact on the psychological health of youngsters is far more dangerous than any 'virus' even if you take the mendacious official figures to be true. The reframed are told (programmed) how to act and so they do. The Derbyshire Chief Constable in the first period of lockdown when the black dye and drones nonsense was going on was Peter Goodman. He was the man who severed the connection between his force and the Derbyshire Constabulary *Male Voice* Choir when he decided that it was not inclusive enough to allow women to join. The fact it was a male voice choir making a particular sound produced by male voices seemed to elude a guy who terrifyingly ran policing in Derbyshire. He retired weeks after his force was condemned as disgraceful by former Supreme Court Justice Jonathan Sumption for their behaviour over extreme lockdown impositions. Goodman was replaced by his deputy Rachel Swann who was in charge when her officers were 'horrified'. The police statement over the boys committing the hanging-offence of playing football included the line about the youngsters being 'irresponsible in the times we are all living through' missing the point that the real relevance of the 'times we are all living through' is the imposition of fascism enforced by psychopaths and reframed minds of police officers playing such a vital part in establishing the fascist tyranny that their own children and grandchildren will have to live in their entire lives. As a definition of insanity that is hard to beat although it might be run close by imposing masks on people that can have a serious effect on their health while wearing a face nappy all day themselves. Once again public and police do it for the same reason – the authorities tell them to and who are they to have the self-respect to say no?

Wokers in uniform

How reframed do you have to be to arrest a *six-year-old* and take him to court for *picking a flower* while waiting for a bus? Brain dead police and officialdom did just that in North Carolina where criminal proceedings happen regularly for children under nine. Attorney Julie Boyer gave the six-year-old crayons and a colouring book

during the 'flower' hearing while the 'adults' decided his fate. County Chief District Court Judge Jay Corpening asked: 'Should a child that believes in Santa Claus, the Easter Bunny and the tooth fairy be making life-altering decisions?' Well, of course not, but common sense has no meaning when you have a common purpose and a reframed mind. Treating children in this way, and police operating in American schools, is all part of the psychological preparation for children to accept a police state as normal all their adult lives. The same goes for all the cameras and biometric tracking technology in schools. Police training is focused on reframing them as snowflake Wokers and this is happening in the military. Pentagon top brass said that 'training sessions on extremism' were needed for troops who asked why they were so focused on the Capitol Building riot when Black Lives Matter riots were ignored. What's the difference between them some apparently and rightly asked. Actually, there is a difference. Five people died in the Capitol riot, only one through violence, and that was a police officer shooting an unarmed protestor. BLM riots killed at least 25 people and cost billions. Asking the question prompted the psychopaths and reframed minds that run the Pentagon to say that more 'education' (programming) was needed. Troop training is all based on psychological programming to make them fodder for the Cult – 'Military men are just dumb, stupid animals to be used as pawns in foreign policy' as Cult-to-his-DNA former Secretary of State Henry Kissinger famously said. Governments see the police in similar terms and it's time for those among them who can see this to defend the people and stop being enforcers of the Cult agenda upon the people.

The US military, like the country itself, is being targeted for destruction through a long list of Woke impositions. Cult-owned gaga 'President' Biden signed an executive order when he took office to allow taxpayer money to pay for transgender surgery for active military personnel and veterans. Are you a man soldier? No, I'm a LGBTQIA+ with a hint of Skoliosexual and Spectrasexual. Oh, good man. Bad choice of words you bigot. The Pentagon announced in March, 2021, the appointment of the first 'diversity and inclusion

officer' for US Special Forces. Richard Torres-Estrada arrived with the publication of a 'D&I Strategic Plan which will guide the enterprise-wide effort to institutionalize and sustain D&I'. If you think a Special Forces 'Strategic Plan' should have something to do with defending America you haven't been paying attention. Defending Woke is now the military's new role. Torres-Estrada has posted images comparing Donald Trump with Adolf Hitler and we can expect no bias from him as a representative of the supposedly non-political Pentagon. Cable news host Tucker Carlson said: 'The Pentagon is now the Yale faculty lounge but with cruise missiles.' Meanwhile Secretary of Defense Lloyd Austin, a board member of weapons-maker Raytheon with stock and compensation interests in October, 2020, worth $1.4 million, said he was purging the military of the 'enemy within' – anyone who isn't Woke and supports Donald Trump. Austin refers to his targets as 'racist extremists' while in true Woke fashion being himself a racist extremist. Pentagon documents pledge to 'eradicate, eliminate and conquer all forms of racism, sexism and homophobia'. The definitions of these are decided by 'diversity and inclusion committees' peopled by those who see racism, sexism and homophobia in every situation and opinion. Woke (the Cult) is dismantling the US military and purging testosterone as China expands its military and gives its troops 'masculinity training'. How do we think that is going to end when this is all Cult coordinated? The US military, like the British military, is controlled by Woke and spineless top brass who just go along with it out of personal career interests.

'Woke' means fast asleep

Mind control and perception manipulation techniques used on individuals to create group-think have been unleashed on the global population in general. As a result many have no capacity to see the obvious fascist agenda being installed all around them or what 'Covid' is really all about. Their brains are firewalled like a computer system not to process certain concepts, thoughts and realisations that are bad for the Cult. The young are most targeted as the adults they

will be when the whole fascist global state is planned to be fully implemented. They need to be prepared for total compliance to eliminate all pushback from entire generations. The Cult has been pouring billions into taking complete control of 'education' from schools to universities via its operatives and corporations and not least Bill Gates as always. The plan has been to transform 'education' institutions into programming centres for the mentality of 'Woke'. James McConnell, professor of psychology at the University of Michigan, wrote in *Psychology Today* in 1970:

> The day has come when we can combine sensory deprivation with drugs, hypnosis, and astute manipulation of reward and punishment, to gain almost absolute control over an individual's behaviour. It should then be possible to achieve a very rapid and highly effective type of brainwashing that would allow us to make dramatic changes in a person's behaviour and personality ...
>
> … We should reshape society so that we all would be trained from birth to want to do what society wants us to do. We have the techniques to do it... no-one owns his own personality you acquired, and there's no reason to believe you should have the right to refuse to acquire a new personality if your old one is anti-social.

This was the potential for mass brainwashing in 1970 and the mentality there displayed captures the arrogant psychopathy that drives it forward. I emphasise that not all young people have succumbed to Woke programming and those that haven't are incredibly impressive people given that today's young are the most perceptually-targeted generations in history with all the technology now involved. Vast swathes of the young generations, however, have fallen into the spell – and that's what it is – of Woke. The Woke mentality and perceptual program is founded on *inversion* and you will appreciate later why that is so significant. Everything with Woke is inverted and the opposite of what it is claimed to be. Woke was a term used in African-American culture from the 1900s and referred to an awareness of social and racial justice. This is not the meaning of the modern version or 'New Woke' as I call it in *The Answer*. Oh, no, Woke today means something very different no matter how much Wokers may seek to hide that and insist Old Woke and New

Woke are the same. See if you find any 'awareness of social justice' here in the modern variety:

- Woke demands 'inclusivity' while excluding anyone with a different opinion and calls for mass censorship to silence other views.

- Woke claims to stand against oppression when imposing oppression is the foundation of all that it does. It is the driver of political correctness which is nothing more than a Cult invention to manipulate the population to silence itself.

- Woke believes itself to be 'liberal' while pursuing a global society that can only be described as fascist (see 'anti-fascist' fascist Antifa).

- Woke calls for 'social justice' while spreading injustice wherever it goes against the common 'enemy' which can be easily identified as a differing view.

- Woke is supposed to be a metaphor for 'awake' when it is solid-gold asleep and deep in a Cult-induced coma that meets the criteria for 'off with the fairies'.

I state these points as obvious facts if people only care to look. I don't do this with a sense of condemnation. We need to appreciate that the onslaught of perceptual programming on the young has been incessant and merciless. I can understand why so many have been reframed, or, given their youth, framed from the start to see the world as the Cult demands. The Cult has had access to their minds day after day in its 'education' system for their entire formative years. Perception is formed from information received and the Cult-created system is a life-long download of information delivered to elicit a particular perception, thus behaviour. The more this has expanded into still new extremes in recent decades and ever-increasing censorship has deleted other opinions and information why wouldn't that lead to a perceptual reframing on a mass scale? I

have described already cradle-to-grave programming and in more recent times the targeting of young minds from birth to adulthood has entered the stratosphere. This has taken the form of skewing what is 'taught' to fit the Cult agenda and the omnipresent techniques of group-think to isolate non-believers and pressure them into line. There has always been a tendency to follow the herd, but we really are in a new world now in relation to that. We have parents who can see the 'Covid' hoax told by their children not to stop them wearing masks at school, being 'Covid' tested or having the 'vaccine' in fear of the peer-pressure consequences of being different. What is 'peer-pressure' if not pressure to conform to group-think? Renegade Minds never group-think and always retain a set of perceptions that are unique to them. Group-think is always underpinned by consequences for not group-thinking. Abuse now aimed at those refusing DNA-manipulating 'Covid vaccines' are a potent example of this. The biggest pressure to conform comes from the very group which is itself being manipulated. 'I am programmed to be part of a hive mind and so you must be.'

Woke control structures in 'education' now apply to every mainstream organisation. Those at the top of the 'education' hierarchy (the Cult) decide the policy. This is imposed on governments through the Cult network; governments impose it on schools, colleges and universities; their leadership impose the policy on teachers and academics and they impose it on children and students. At any level where there is resistance, perhaps from a teacher or university lecturer, they are targeted by the authorities and often fired. Students themselves regularly demand the dismissal of academics (increasingly few) at odds with the narrative that the students have been programmed to believe in. It is quite a thought that students who are being targeted by the Cult become so consumed by programmed group-think that they launch protests and demand the removal of those who are trying to push back against those targeting the students. Such is the scale of perceptual inversion. We see this with 'Covid' programming as the Cult imposes the rules via psycho-psychologists and governments on

shops, transport companies and businesses which impose them on their staff who impose them on their customers who pressure Pushbackers to conform to the will of the Cult which is in the process of destroying them and their families. Scan all aspects of society and you will see the same sequence every time.

Fact free Woke and hijacking the 'left'

There is no more potent example of this than 'Woke', a mentality only made possible by the deletion of factual evidence by an 'education' system seeking to produce an ever more uniform society. Why would you bother with facts when you don't know any? Deletion of credible history both in volume and type is highly relevant. Orwell said: 'Who controls the past controls the future: who controls the present controls the past.' They who control the perception of the past control the perception of the future and they who control the present control the perception of the past through the writing and deleting of history. Why would you oppose the imposition of Marxism in the name of Wokeism when you don't know that Marxism cost at least 100 million lives in the 20th century alone? Watch videos and read reports in which Woker generations are asked basic historical questions – it's mind-blowing. A survey of 2,000 people found that six percent of millennials (born approximately early1980s to early 2000s) believed the Second World War (1939-1945) broke out with the assassination of President Kennedy (in 1963) and one in ten thought Margaret Thatcher was British Prime Minister at the time. She was in office between 1979 and 1990. We are in a post-fact society. Provable facts are no defence against the fascism of political correctness or Silicon Valley censorship. Facts don't matter anymore as we have witnessed with the 'Covid' hoax. Sacrificing uniqueness to the Woke group-think religion is all you are required to do and that means thinking for yourself is the biggest Woke no, no. All religions are an expression of group-think and censorship and Woke is just another religion with an orthodoxy defended by group-think and censorship. Burned at

the stake becomes burned on Twitter which leads back eventually to burned at the stake as Woke humanity regresses to ages past.

The biggest Woke inversion of all is its creators and funders. I grew up in a traditional left of centre political household on a council estate in Leicester in the 1950s and 60s – you know, the left that challenged the power of wealth-hoarding elites and threats to freedom of speech and opinion. In those days students went on marches defending freedom of speech while today's Wokers march for its deletion. What on earth could have happened? Those very elites (collectively the Cult) that we opposed in my youth and early life have funded into existence the antithesis of that former left and hijacked the 'brand' while inverting everything it ever stood for. We have a mentality that calls itself 'liberal' and 'progressive' while acting like fascists. Cult billionaires and their corporations have funded themselves into control of 'education' to ensure that Woke programming is unceasing throughout the formative years of children and young people and that non-Wokers are isolated (that word again) whether they be students, teachers or college professors. The Cult has funded into existence the now colossal global network of Woke organisations that have spawned and promoted all the 'causes' on the Cult wish-list for global transformation and turned Wokers into demanders of them. Does anyone really think it's a coincidence that the Cult agenda for humanity is a carbon (sorry) copy of the societal transformations desired by Woke?? These are only some of them:

Political correctness: The means by which the Cult deletes all public debates that it knows it cannot win if we had the free-flow of information and evidence.

Human-caused 'climate change': The means by which the Cult seeks to transform society into a globally-controlled dictatorship imposing its will over the fine detail of everyone's lives 'to save the planet' which doesn't actually need saving.

Transgender obsession: Preparing collective perception to accept the 'new human' which would not have genders because it would be created technologically and not through procreation. I'll have much more on this in Human 2.0.

Race obsession: The means by which the Cult seeks to divide and rule the population by triggering racial division through the perception that society is more racist than ever when the opposite is the case. Is it perfect in that regard? No. But to compare today with the racism of apartheid and segregation brought to an end by the civil rights movement in the 1960s is to insult the memory of that movement and inspirations like Martin Luther King. Why is the 'anti-racism' industry (which it is) so dominated by privileged white people?

White supremacy: This is a label used by privileged white people to demonise poor and deprived white people pushing back on tyranny to marginalise and destroy them. White people are being especially targeted as the dominant race by number within Western society which the Cult seeks to transform in its image. If you want to change a society you must weaken and undermine its biggest group and once you have done that by using the other groups you next turn on them to do the same … 'Then they came for the Jews and I was not a Jew so I did nothing.'

Mass migration: The mass movement of people from the Middle East, Africa and Asia into Europe, from the south into the United States and from Asia into Australia are another way the Cult seeks to dilute the racial, cultural and political influence of white people on Western society. White people ask why their governments appear to be working against them while being politically and culturally biased towards incoming cultures. Well, here's your answer. In the same way sexually 'straight' people, men and women, ask why the

authorities are biased against them in favour of other sexualities. The answer is the same – that's the way the Cult wants it to be for very sinister motives.

These are all central parts of the Cult agenda and central parts of the Woke agenda and Woke was created and continues to be funded to an immense degree by Cult billionaires and corporations. If anyone begins to say 'coincidence' the syllables should stick in their throat.

Billionaire 'social justice warriors'

Joe Biden is a 100 percent-owned asset of the Cult and the Wokers' man in the White House whenever he can remember his name and for however long he lasts with his rapidly diminishing cognitive function. Even walking up the steps of an aircraft without falling on his arse would appear to be a challenge. He's not an empty-shell puppet or anything. From the minute Biden took office (or the Cult did) he began his executive orders promoting the Woke wish-list. You will see the Woke agenda imposed ever more severely because it's really the *Cult* agenda. Woke organisations and activist networks spawned by the Cult are funded to the extreme so long as they promote what the Cult wants to happen. Woke is funded to promote 'social justice' by billionaires who become billionaires by destroying social justice. The social justice mantra is only a cover for dismantling social justice and funded by billionaires that couldn't give a damn about social justice. Everything makes sense when you see that. One of Woke's premier funders is Cult billionaire financier George Soros who said: 'I am basically there to make money, I cannot and do not look at the social consequences of what I do.' This is the same Soros who has given more than $32 billion to his Open Society Foundations global Woke network and funded Black Lives Matter, mass immigration into Europe and the United States, transgender activism, climate change activism, political correctness and groups targeting 'white supremacy' in the form of privileged white thugs that dominate Antifa. What a scam it all is and when

you are dealing with the unquestioning fact-free zone of Woke scamming them is child's play. All you need to pull it off in all these organisations are a few in-the-know agents of the Cult and an army of naïve, reframed, uninformed, narcissistic, know-nothings convinced of their own self-righteousness, self-purity and virtue.

Soros and fellow billionaires and billionaire corporations have poured hundreds of millions into Black Lives Matter and connected groups and promoted them to a global audience. None of this is motivated by caring about black people. These are the billionaires that have controlled and exploited a system that leaves millions of black people in abject poverty and deprivation which they do absolutely nothing to address. The same Cult networks funding BLM were behind the *slave trade!* Black Lives Matter hijacked a phrase that few would challenge and they have turned this laudable concept into a political weapon to divide society. You know that BLM is a fraud when it claims that *All* Lives Matter, the most inclusive statement of all, is 'racist'. BLM and its Cult masters don't want to end racism. To them it's a means to an end to control all of humanity never mind the colour, creed, culture or background. What has destroying the nuclear family got to do with ending racism? Nothing – but that is one of the goals of BLM and also happens to be a goal of the Cult as I have been exposing in my books for decades. Stealing children from loving parents and giving schools ever more power to override parents is part of that same agenda. BLM is a Marxist organisation and why would that not be the case when the Cult created Marxism *and* BLM? Patrisse Cullors, a BLM co-founder, said in a 2015 video that she and her fellow organisers, including co-founder Alicia Garza, are 'trained Marxists'. The lady known after marriage as Patrisse Khan-Cullors bought a $1.4 million home in 2021 in one of the whitest areas of California with a black population of just 1.6 per cent and has so far bought *four* high-end homes for a total of $3.2 million. How very Marxist. There must be a bit of spare in the BLM coffers, however, when Cult corporations and billionaires have handed over the best part of $100 million. Many black people can see that Black Lives Matter is not

working for them, but against them, and this is still more confirmation. Black journalist Jason Whitlock, who had his account suspended by Twitter for simply linking to the story about the 'Marxist's' home buying spree, said that BLM leaders are 'making millions of dollars off the backs of these dead black men who they wouldn't spit on if they were on fire and alive'.

Black Lies Matter

Cult assets and agencies came together to promote BLM in the wake of the death of career criminal George Floyd who had been jailed a number of times including for forcing his way into the home of a black woman with others in a raid in which a gun was pointed at her stomach. Floyd was filmed being held in a Minneapolis street in 2020 with the knee of a police officer on his neck and he subsequently died. It was an appalling thing for the officer to do, but the same technique has been used by police on peaceful protestors of lockdown without any outcry from the Woke brigade. As unquestioning supporters of the Cult agenda Wokers have supported lockdown and all the 'Covid' claptrap while attacking anyone standing up to the tyranny imposed in its name. Court documents would later include details of an autopsy on Floyd by County Medical Examiner Dr Andrew Baker who concluded that Floyd had taken a fatal level of the drug fentanyl. None of this mattered to fact-free, question-free, Woke. Floyd's death was followed by worldwide protests against police brutality amid calls to defund the police. Throwing babies out with the bathwater is a Woke speciality. In the wake of the murder of British woman Sarah Everard a Green Party member of the House of Lords, Baroness Jones of Moulescoomb (Nincompoopia would have been better), called for a 6pm curfew for all men. This would be in breach of the Geneva Conventions on war crimes which ban collective punishment, but that would never have crossed the black and white Woke mind of Baroness Nincompoopia who would have been far too convinced of her own self-righteousness to compute such details. Many American cities did defund the police in the face of Floyd riots

and after $15 million was deleted from the police budget in Washington DC under useless Woke mayor Muriel Bowser car-jacking alone rose by 300 percent and within six months the US capital recorded its highest murder rate in 15 years. The same happened in Chicago and other cities in line with the Cult/Soros plan to bring fear to streets and neighbourhoods by reducing the police, releasing violent criminals and not prosecuting crime. This is the mob-rule agenda that I have warned in the books was coming for so long. Shootings in the area of Minneapolis where Floyd was arrested increased by 2,500 percent compared with the year before. Defunding the police over George Floyd has led to a big increase in dead people with many of them black. Police protection for politicians making these decisions stayed the same or increased as you would expect from professional hypocrites. The Cult doesn't actually want to abolish the police. It wants to abolish local control over the police and hand it to federal government as the psychopaths advance the Hunger Games Society. Many George Floyd protests turned into violent riots with black stores and businesses destroyed by fire and looting across America fuelled by Black Lives Matter. Woke doesn't do irony. If you want civil rights you must loot the liquor store and the supermarket and make off with a smart TV. It's the only way.

It's not a race war – it's a class war

Black people are patronised by privileged blacks and whites alike and told they are victims of white supremacy. I find it extraordinary to watch privileged blacks supporting the very system and bloodline networks behind the slave trade and parroting the same Cult-serving manipulative crap of their privileged white, often billionaire, associates. It is indeed not a race war but a class war and colour is just a diversion. Black Senator Cory Booker and black Congresswoman Maxine Waters, more residents of Nincompoopia, personify this. Once you tell people they are victims of someone else you devalue both their own responsibility for their plight and the power they have to impact on their reality and experience. Instead

we have: 'You are only in your situation because of whitey – turn on them and everything will change.' It won't change. Nothing changes in our lives unless *we* change it. Crucial to that is never seeing yourself as a victim and always as the creator of your reality. Life is a simple sequence of choice and consequence. Make different choices and you create different consequences. *You* have to make those choices – not Black Lives Matter, the Woke Mafia and anyone else that seeks to dictate your life. Who are they these Wokers, an emotional and psychological road traffic accident, to tell you what to do? Personal empowerment is the last thing the Cult and its Black Lives Matter want black people or anyone else to have. They claim to be defending the underdog while *creating* and perpetuating the underdog. The Cult's worst nightmare is human unity and if they are going to keep blacks, whites and every other race under economic servitude and control then the focus must be diverted from what they have in common to what they can be manipulated to believe divides them. Blacks have to be told that their poverty and plight is the fault of the white bloke living on the street in the same poverty and with the same plight they are experiencing. The difference is that your plight black people is due to him, a white supremacist with 'white privilege' living on the street. Don't unite as one human family against your mutual oppressors and suppressors – fight the oppressor with the white face who is as financially deprived as you are. The Cult knows that as its 'Covid' agenda moves into still new levels of extremism people are going to respond and it has been spreading the seeds of disunity everywhere to stop a united response to the evil that targets *all of us*.

Racist attacks on 'whiteness' are getting ever more outrageous and especially through the American Democratic Party which has an appalling history for anti-black racism. Barack Obama, Joe Biden, Hillary Clinton and Nancy Pelosi all eulogised about Senator Robert Byrd at his funeral in 2010 after a nearly 60-year career in Congress. Byrd was a brutal Ku Klux Klan racist and a violent abuser of Cathy O'Brien in MKUltra. He said he would never fight in the military 'with a negro by my side' and 'rather I should die a thousand times,

and see Old Glory trampled in the dirt never to rise again, than to see this beloved land of ours become degraded by race mongrels, a throwback to the blackest specimen from the wilds'. Biden called Byrd a 'very close friend and mentor'. These 'Woke' hypocrites are not anti-racist they are anti-poor and anti-people not of their perceived class. Here is an illustration of the scale of anti-white racism to which we have now descended. Seriously Woke and moronic *New York Times* contributor Damon Young described whiteness as a 'virus' that 'like other viruses will not die until there are no bodies left for it to infect'. He went on: '… the only way to stop it is to locate it, isolate it, extract it, and kill it.' Young can say that as a black man with no consequences when a white man saying the same in reverse would be facing a jail sentence. *That's* racism. We had super-Woke numbskull senators Tammy Duckworth and Mazie Hirono saying they would object to future Biden Cabinet appointments if he did not nominate more Asian Americans and Pacific Islanders. Never mind the ability of the candidate what do they look like? Duckworth said: 'I will vote for racial minorities and I will vote for LGBTQ, but anyone else I'm not voting for.' Appointing people on the grounds of race is illegal, but that was not a problem for this ludicrous pair. They were on-message and that's a free pass in any situation.

Critical race racism

White children are told at school they are intrinsically racist as they are taught the divisive 'critical race theory'. This claims that the law and legal institutions are inherently racist and that race is a socially constructed concept used by white people to further their economic and political interests at the expense of people of colour. White is a 'virus' as we've seen. Racial inequality results from 'social, economic, and legal differences that white people create between races to maintain white interests which leads to poverty and criminality in minority communities'. I must tell that to the white guy sleeping on the street. The principal of East Side Community School in New York sent white parents a manifesto that called on

them to become 'white traitors' and advocate for full 'white abolition'. These people are teaching your kids when they urgently need a psychiatrist. The 'school' included a chart with 'eight white identities' that ranged from 'white supremacist' to 'white abolition' and defined the behaviour white people must follow to end 'the regime of whiteness'. Woke blacks and their privileged white associates are acting exactly like the slave owners of old and Ku Klux Klan racists like Robert Byrd. They are too full of their own self-purity to see that, but it's true. Racism is not a body type; it's a state of mind that can manifest through any colour, creed or culture.

Another racial fraud is *'equity'*. Not equality of treatment and opportunity – equity. It's a term spun as equality when it means something very different. Equality in its true sense is a raising up while 'equity' is a race to the bottom. Everyone in the same level of poverty is 'equity'. Keep everyone down – that's equity. The Cult doesn't want anyone in the human family to be empowered and BLM leaders, like all these 'anti-racist' organisations, continue their privileged, pampered existence by perpetuating the perception of gathering racism. When is the last time you heard an 'anti-racist' or 'anti-Semitism' organisation say that acts of racism and discrimination have *fallen?* It's not in the interests of their fund-raising and power to influence and the same goes for the professional soccer anti-racism operation, Kick It Out. Two things confirmed that the Black Lives Matter riots in the summer of 2020 were Cult creations. One was that while anti-lockdown protests were condemned in this same period for 'transmitting 'Covid' the authorities supported mass gatherings of Black Lives Matter supporters. I even saw self-deluding people claiming to be doctors say the two types of protest were not the same. No – the non-existent 'Covid' was in favour of lockdowns and attacked those that protested against them while 'Covid' supported Black Lives Matter and kept well away from its protests. The whole thing was a joke and as lockdown protestors were arrested, often brutally, by reframed Face-Nappies we had the grotesque sight of police officers taking the knee to Black Lives Matter, a Cult-funded Marxist

organisation that supports violent riots and wants to destroy the nuclear family and white people.

He's not white? Shucks!

Woke obsession with race was on display again when ten people were shot dead in Boulder, Colorado, in March, 2021. Cult-owned Woke TV channels like CNN said the shooter appeared to be a white man and Wokers were on Twitter condemning 'violent white men' with the usual mantras. Then the shooter's name was released as Ahmad Al Aliwi Alissa, an anti-Trump Arab-American, and the sigh of disappointment could be heard five miles away. Never mind that ten people were dead and what that meant for their families. Race baiting was all that mattered to these sick Cult-serving people like Barack Obama who exploited the deaths to further divide America on racial grounds which is his job for the Cult. This is the man that 'racist' white Americans made the first black president of the United States and then gave him a second term. Not-very-bright Obama has become filthy rich on the back of that and today appears to have a big influence on the Biden administration. Even so he's still a downtrodden black man and a victim of white supremacy. This disingenuous fraud reveals the contempt he has for black people when he puts on a Deep South Alabama accent whenever he talks to them, no, *at* them.

Another BLM red flag was how the now fully-Woke (fully-Cult) and fully-virtue-signalled professional soccer authorities had their teams taking the knee before every match in support of Marxist Black Lives Matter. Soccer authorities and clubs displayed 'Black Lives Matter' on the players' shirts and flashed the name on electronic billboards around the pitch. Any fans that condemned what is a Freemasonic taking-the-knee ritual were widely condemned as you would expect from the Woke virtue-signallers of professional sport and the now fully-Woke media. We have reverse racism in which you are banned from criticising any race or culture except for white people for whom anything goes – say what you like, no problem. What has this got to do with racial harmony and

equality? We've had black supremacists from Black Lives Matter telling white people to fall to their knees in the street and apologise for their white supremacy. Black supremacists acting like white supremacist slave owners of the past couldn't breach their self-obsessed, race-obsessed sense of self-purity. Joe Biden appointed a race-obsessed black supremacist Kristen Clarke to head the Justice Department Civil Rights Division. Clarke claimed that blacks are endowed with 'greater mental, physical and spiritual abilities' than whites. If anyone reversed that statement they would be vilified. Clarke is on-message so no problem. She's never seen a black-white situation in which the black figure is anything but a virtuous victim and she heads the Civil Rights Division which should treat everyone the same or it isn't civil rights. Another perception of the Renegade Mind: If something or someone is part of the Cult agenda they will be supported by Woke governments and media no matter what. If they're not, they will be condemned and censored. It really is that simple and so racist Clarke prospers despite (make that because of) her racism.

The end of culture

Biden's administration is full of such racial, cultural and economic bias as the Cult requires the human family to be divided into warring factions. We are now seeing racially-segregated graduations and everything, but everything, is defined through the lens of perceived 'racism. We have 'racist' mathematics, 'racist' food and even 'racist' *plants*. World famous Kew Gardens in London said it was changing labels on plants and flowers to tell its pre-'Covid' more than two million visitors a year how racist they are. Kew director Richard Deverell said this was part of an effort to 'move quickly to decolonise collections' after they were approached by one Ajay Chhabra 'an actor with an insight into how sugar cane was linked to slavery'. They are *plants* you idiots. 'Decolonisation' in the Woke manual really means colonisation of society with its mentality and by extension colonisation by the Cult. We are witnessing a new Chinese-style 'Cultural Revolution' so essential to the success of all

Marxist takeovers. Our cultural past and traditions have to be swept away to allow a new culture to be built-back-better. Woke targeting of long-standing Western cultural pillars including historical monuments and cancelling of historical figures is what happened in the Mao revolution in China which 'purged remnants of capitalist and traditional elements from Chinese society' and installed Maoism as the dominant ideology'. For China see the Western world today and for 'dominant ideology' see Woke. Better still see Marxism or Maoism. The 'Covid' hoax has specifically sought to destroy the arts and all elements of Western culture from people meeting in a pub or restaurant to closing theatres, music venues, sports stadiums, places of worship and even banning *singing*. Destruction of Western society is also why criticism of any religion is banned except for Christianity which again is the dominant religion as white is the numerically-dominant race. Christianity may be fading rapidly, but its history and traditions are weaved through the fabric of Western society. Delete the pillars and other structures will follow until the whole thing collapses. I am not a Christian defending that religion when I say that. I have no religion. It's just a fact. To this end Christianity has itself been turned Woke to usher its own downfall and its ranks are awash with 'change agents' – knowing and unknowing – at every level including Pope Francis (*definitely* knowing) and the clueless Archbishop of Canterbury Justin Welby (possibly not, but who can be sure?). Woke seeks to coordinate attacks on Western culture, traditions, and ways of life through 'intersectionality' defined as 'the complex, cumulative way in which the effects of multiple forms of discrimination (such as racism, sexism, and classism) combine, overlap, or intersect especially in the experiences of marginalised individuals or groups'. Wade through the Orwellian Woke-speak and this means coordinating disparate groups in a common cause to overthrow freedom and liberal values.

The entire structure of public institutions has been infested with Woke – government at all levels, political parties, police, military, schools, universities, advertising, media and trade unions. This abomination has been achieved through the Cult web by appointing

Wokers to positions of power and battering non-Wokers into line through intimidation, isolation and threats to their job. Many have been fired in the wake of the empathy-deleted, vicious hostility of 'social justice' Wokers and the desire of gutless, spineless employers to virtue-signal their Wokeness. Corporations are filled with Wokers today, most notably those in Silicon Valley. Ironically at the top they are not Woke at all. They are only exploiting the mentality their Cult masters have created and funded to censor and enslave while the Wokers cheer them on until it's their turn. Thus the Woke 'liberal left' is an inversion of the traditional liberal left. Campaigning for justice on the grounds of power and wealth distribution has been replaced by campaigning for identity politics. The genuine traditional left would never have taken money from today's billionaire abusers of fairness and justice and nor would the billionaires have wanted to fund that genuine left. It would not have been in their interests to do so. The division of opinion in those days was between the haves and have nots. This all changed with Cult manipulated and funded identity politics. The division of opinion today is between Wokers and non-Wokers and not income brackets. Cult corporations and their billionaires may have taken wealth disparity to cataclysmic levels of injustice, but as long as they speak the language of Woke, hand out the dosh to the Woke network and censor the enemy they are 'one of us'. Billionaires who don't give a damn about injustice are laughing at them till their bellies hurt. Wokers are not even close to self-aware enough to see that. The transformed 'left' dynamic means that Wokers who drone on about 'social justice' are funded by billionaires that have destroyed social justice the world over. It's *why* they are billionaires.

The climate con

Nothing encapsulates what I have said more comprehensively than the hoax of human-caused global warming. I have detailed in my books over the years how Cult operatives and organisations were the pump-primers from the start of the climate con. A purpose-built vehicle for this is the Club of Rome established by the Cult in 1968

with the Rockefellers and Rothschilds centrally involved all along. Their gofer frontman Maurice Strong, a Canadian oil millionaire, hosted the Earth Summit in Rio de Janeiro, Brazil, in 1992 where the global 'green movement' really expanded in earnest under the guiding hand of the Cult. The Earth Summit established Agenda 21 through the Cult-created-and-owned United Nations to use the illusion of human-caused climate change to justify the transformation of global society to save the world from climate disaster. It is a No-Problem-Reaction-Solution sold through governments, media, schools and universities as whole generations have been terrified into believing that the world was going to end in their lifetimes unless what old people had inflicted upon them was stopped by a complete restructuring of how everything is done. Chill, kids, it's all a hoax. Such restructuring is precisely what the Cult agenda demands (purely by coincidence of course). Today this has been given the codename of the Great Reset which is only an updated term for Agenda 21 and its associated Agenda 2030. The latter, too, is administered through the UN and was voted into being by the General Assembly in 2015. Both 21 and 2030 seek centralised control of all resources and food right down to the raindrops falling on your own land. These are some of the demands of Agenda 21 established in 1992. See if you recognise this society emerging today:

- End national sovereignty
- State planning and management of all land resources, ecosystems, deserts, forests, mountains, oceans and fresh water; agriculture; rural development; biotechnology; and ensuring *'equity'*
- The state to 'define the role' of business and financial resources
- Abolition of private property
- 'Restructuring' the family unit (see BLM)
- Children raised by the state
- People told what their job will be
- Major restrictions on movement
- Creation of 'human settlement zones'

- Mass resettlement as people are forced to vacate land where they live
- Dumbing down education
- Mass global depopulation in pursuit of all the above

The United Nations was created as a Trojan horse for world government. With the climate con of critical importance to promoting that outcome you would expect the UN to be involved. Oh, it's involved all right. The UN is promoting Agenda 21 and Agenda 2030 justified by 'climate change' while also driving the climate hoax through its Intergovernmental Panel on Climate Change (IPCC), one of the world's most corrupt organisations. The IPCC has been lying ferociously and constantly since the day it opened its doors with the global media hanging unquestioningly on its every mendacious word. The Green movement is entirely Woke and has long lost its original environmental focus since it was co-opted by the Cult. An obsession with 'global warming' has deleted its values and scrambled its head. I experienced a small example of what I mean on a beautiful country walk that I have enjoyed several times a week for many years. The path merged into the fields and forests and you felt at one with the natural world. Then a 'Green' organisation, the Hampshire and Isle of Wight Wildlife Trust, took over part of the land and proceeded to cut down a large number of trees, including mature ones, to install a horrible big, bright steel 'this-is-ours-stay-out' fence that destroyed the whole atmosphere of this beautiful place. No one with a feel for nature would do that. Day after day I walked to the sound of chainsaws and a magnificent mature weeping willow tree that I so admired was cut down at the base of the trunk. When I challenged a Woke young girl in a green shirt (of course) about this vandalism she replied: 'It's a weeping willow – it will grow back.' This is what people are paying for when they donate to the Hampshire and Isle of Wight Wildlife Trust and many other 'green' organisations today. It is not the environmental movement that I knew and instead has become a support-system – as with Extinction Rebellion – for a very dark agenda.

Private jets for climate justice

The Cult-owned, Gates-funded, World Economic Forum and its founder Klaus Schwab were behind the emergence of Greta Thunberg to harness the young behind the climate agenda and she was invited to speak to the world at … the UN. Schwab published a book, *Covid-19: The Great Reset* in 2020 in which he used the 'Covid' hoax and the climate hoax to lay out a new society straight out of Agenda 21 and Agenda 2030. Bill Gates followed in early 2021 when he took time out from destroying the world to produce a book in his name about the way to save it. Gates flies across the world in private jets and admitted that 'I probably have one of the highest greenhouse gas footprints of anyone on the planet … my personal flying alone is gigantic.' He has also bid for the planet's biggest private jet operator. Other climate change saviours who fly in private jets include John Kerry, the US Special Presidential Envoy for Climate, and actor Leonardo DiCaprio, a 'UN Messenger of Peace with special focus on climate change'. These people are so full of bullshit they could corner the market in manure. We mustn't be sceptical, though, because the Gates book, *How to Avoid a Climate Disaster: The Solutions We Have and the Breakthroughs We Need*, is a genuine attempt to protect the world and not an obvious pile of excrement attributed to a mega-psychopath aimed at selling his masters' plans for humanity. The Gates book and the other shite-pile by Klaus Schwab could have been written by the same person and may well have been. Both use 'climate change' and 'Covid' as the excuses for their new society and by coincidence the Cult's World Economic Forum and Bill and Melinda Gates Foundation promote the climate hoax and hosted Event 201 which pre-empted with a 'simulation' the very 'coronavirus' hoax that would be simulated for real on humanity within weeks. The British 'royal' family is promoting the 'Reset' as you would expect through Prince 'climate change caused the war in Syria' Charles and his hapless son Prince William who said that we must 'reset our relationship with nature and our trajectory as a species' to avoid a climate disaster. Amazing how many promotors of the 'Covid' and 'climate change' control

systems are connected to Gates and the World Economic Forum. A 'study' in early 2021 claimed that carbon dioxide emissions must fall by the equivalent of a global lockdown roughly every two years for the next decade to save the planet. The 'study' appeared in the same period that the Schwab mob claimed in a video that lockdowns destroying the lives of billions are good because they make the earth 'quieter' with less 'ambient noise'. They took down the video amid a public backlash for such arrogant, empathy-deleted stupidity You see, however, where they are going with this. Corinne Le Quéré, a professor at the Tyndall Centre for Climate Change Research, University of East Anglia, was lead author of the climate lockdown study, and she writes for … the World Economic Forum. Gates calls in 'his' book for changing 'every aspect of the economy' (long-time Cult agenda) and for humans to eat synthetic 'meat' (predicted in my books) while cows and other farm animals are eliminated. Australian TV host and commentator Alan Jones described what carbon emission targets would mean for farm animals in Australia alone if emissions were reduced as demanded by 35 percent by 2030 and zero by 2050:

Well, let's take agriculture, the total emissions from agriculture are about 75 million tonnes of carbon dioxide, equivalent. Now reduce that by 35 percent and you have to come down to 50 million tonnes, I've done the maths. So if you take for example 1.5 million cows, you're going to have to reduce the herd by 525,000 [by] 2030, nine years, that's 58,000 cows a year. The beef herd's 30 million, reduce that by 35 percent, that's 10.5 million, which means 1.2 million cattle have to go every year between now and 2030. This is insanity!

There are 75 million sheep. Reduce that by 35 percent, that's 26 million sheep, that's almost 3 million a year. So under the Paris Agreement over 30 million beasts. dairy cows, cattle, pigs and sheep would go. More than 8,000 every minute of every hour for the next decade, do these people know what they're talking about?

Clearly they don't at the level of campaigners, politicians and administrators. The Cult *does* know; that's the outcome it wants. We are faced with not just a war on humanity. Animals and the natural world are being targeted and I have been saying since the 'Covid' hoax began that the plan eventually was to claim that the 'deadly virus' is able to jump from animals, including farm animals and

domestic pets, to humans. Just before this book went into production came this story: 'Russia registers world's first Covid-19 vaccine for cats & dogs as makers of Sputnik V warn pets & farm animals could spread virus'. The report said 'top scientists warned that the deadly pathogen could soon begin spreading through homes and farms' and 'the next stage is the infection of farm and domestic animals'. Know the outcome and you'll see the journey. Think what that would mean for animals and keep your eye on a term called zoonosis or zoonotic diseases which transmit between animals and humans. The Cult wants to break the connection between animals and people as it does between people and people. Farm animals fit with the Cult agenda to transform food from natural to synthetic.

The gas of life is killing us

There can be few greater examples of Cult inversion than the condemnation of carbon dioxide as a dangerous pollutant when it is the gas of life. Without it the natural world would be dead and so we would all be dead. We breathe in oxygen and breathe out carbon dioxide while plants produce oxygen and absorb carbon dioxide. It is a perfect symbiotic relationship that the Cult wants to dismantle for reasons I will come to in the final two chapters. Gates, Schwab, other Cult operatives and mindless repeaters, want the world to be 'carbon neutral' by at least 2050 and the earlier the better. 'Zero carbon' is the cry echoed by lunatics calling for 'Zero Covid' when we already have it. These carbon emission targets will deindustrialise the world in accordance with Cult plans – the post-industrial, post-democratic society – and with so-called renewables like solar and wind not coming even close to meeting human energy needs blackouts and cold are inevitable. Texans got the picture in the winter of 2021 when a snow storm stopped wind turbines and solar panels from working and the lights went down along with water which relies on electricity for its supply system. Gates wants everything to be powered by electricity to ensure that his masters have the kill switch to stop all human activity, movement, cooking, water and warmth any time they like. The climate lie is so

stupendously inverted that it claims we must urgently reduce carbon dioxide when we *don't have enough*.

Co2 in the atmosphere is a little above 400 parts per million when the optimum for plant growth is 2,000 ppm and when it falls anywhere near 150 ppm the natural world starts to die and so do we. It fell to as low as 280 ppm in an 1880 measurement in Hawaii and rose to 413 ppm in 2019 with industrialisation which is why the planet has become *greener* in the industrial period. How insane then that psychopathic madman Gates is not satisfied only with blocking the rise of Co2. He's funding technology to suck it out of the atmosphere. The reason why will become clear. The industrial era is not destroying the world through Co2 and has instead turned around a potentially disastrous ongoing fall in Co2. Greenpeace co-founder and scientist Patrick Moore walked away from Greenpeace in 1986 and has exposed the green movement for fear-mongering and lies. He said that 500 million years ago there was *17 times* more Co2 in the atmosphere than we have today and levels have been falling for hundreds of millions of years. In the last 150 million years Co2 levels in Earth's atmosphere had reduced by *90 percent*. Moore said that by the time humanity began to unlock carbon dioxide from fossil fuels we were at '38 seconds to midnight' and in that sense: 'Humans are [the Earth's] salvation.' Moore made the point that only half the Co2 emitted by fossil fuels stays in the atmosphere and we should remember that all pollution pouring from chimneys that we are told is carbon dioxide is in fact nothing of the kind. It's pollution. Carbon dioxide is an invisible gas.

William Happer, Professor of Physics at Princeton University and long-time government adviser on climate, has emphasised the Co2 deficiency for maximum growth and food production. Greenhouse growers don't add carbon dioxide for a bit of fun. He said that most of the warming in the last 100 years, after the earth emerged from the super-cold period of the 'Little Ice Age' into a natural warming cycle, was over by 1940. Happer said that a peak year for warming in 1988 can be explained by a 'monster El Nino' which is a natural and cyclical warming of the Pacific that has nothing to do with 'climate

change'. He said the effect of Co2 could be compared to painting a wall with red paint in that once two or three coats have been applied it didn't matter how much more you slapped on because the wall will not get much redder. Almost all the effect of the rise in Co2 has already happened, he said, and the volume in the atmosphere would now have to *double* to increase temperature by a single degree. Climate hoaxers know this and they have invented the most ridiculously complicated series of 'feedback' loops to try to overcome this rather devastating fact. You hear puppet Greta going on cluelessly about feedback loops and this is why.

The Sun affects temperature? No you *climate denier*

Some other nonsense to contemplate: Climate graphs show that rises in temperature do not follow rises in Co2 – *it's the other way round* with a lag between the two of some 800 years. If we go back 800 years from present time we hit the Medieval Warm Period when temperatures were higher than now without any industrialisation and this was followed by the Little Ice Age when temperatures plummeted. The world was still emerging from these centuries of serious cold when many climate records began which makes the ever-repeated line of the 'hottest year since records began' meaningless when you are not comparing like with like. The coldest period of the Little Ice Age corresponded with the lowest period of sunspot activity when the Sun was at its least active. Proper scientists will not be at all surprised by this when it confirms the obvious fact that earth temperature is affected by the scale of Sun activity and the energetic power that it subsequently emits; but when is the last time you heard a climate hoaxer talking about the Sun as a source of earth temperature?? Everything has to be focussed on Co2 which makes up just 0.117 percent of so-called greenhouse gases and only a fraction of even that is generated by human activity. The rest is natural. More than *90 percent* of those greenhouse gases are water vapour and clouds (Fig 9). Ban moisture I say. Have you noticed that the climate hoaxers no longer use the polar bear as their promotion image? That's because far from becoming extinct polar

bear communities are stable or thriving. Joe Bastardi, American meteorologist, weather forecaster and outspoken critic of the climate lie, documents in his book *The Climate Chronicles* how weather patterns and events claimed to be evidence of climate change have been happening since long before industrialisation: 'What happened before naturally is happening again, as is to be expected given the cyclical nature of the climate due to the design of the planet.' If you read the detailed background to the climate hoax in my other books you will shake your head and wonder how anyone could believe the crap which has spawned a multi-trillion dollar industry based on absolute garbage (see HIV causes AIDs and Sars-Cov-2 causes 'Covid-19'). Climate and 'Covid' have much in common given they have the same source. They both have the contradictory *everything* factor in which everything is explained by reference to them. It's hot – 'it's climate change'. It's cold – 'it's climate change'. I got a sniffle – 'it's Covid'. I haven't got a sniffle – 'it's Covid'. Not having a sniffle has to be a symptom of 'Covid'. Everything is and not having a sniffle is especially dangerous if you are a slow walker. For sheer audacity I offer you a Cambridge University 'study' that actually linked 'Covid' to 'climate change'. It had to happen eventually. They concluded that climate change played a role in 'Covid-19' spreading from animals to humans because … wait for it … I kid you not … *the two groups were forced closer together as populations grow*. Er, that's it. The whole foundation on which this depended was that 'Bats are the likely zoonotic origin of SARS-CoV-1 and SARS-CoV-2'. Well, they are not. They are nothing to do with it. Apart from bats not being the origin and therefore 'climate change' effects on bats being irrelevant I am in awe of their academic insight. Where would we be without them? Not where we are that's for sure.

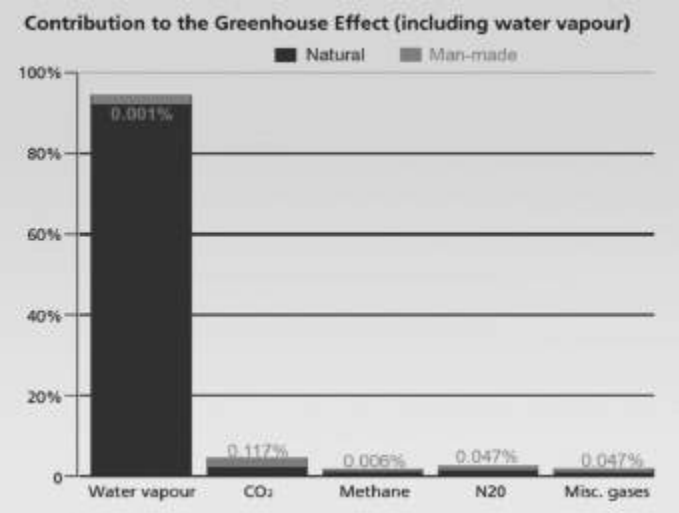


Figure 9: The idea that the gas of life is disastrously changing the climate is an insult to brain cell activity.

One other point about the weather is that climate modification is now well advanced and not every major weather event is natural – or earthquake come to that. I cover this subject at some length in other books. China is openly planning a rapid expansion of its weather modification programme which includes changing the climate in an area more than one and a half times the size of India. China used weather manipulation to ensure clear skies during the 2008 Olympics in Beijing. I have quoted from US military documents detailing how to employ weather manipulation as a weapon of war and they did that in the 1960s and 70s during the conflict in Vietnam with Operation Popeye manipulating monsoon rains for military purposes. Why would there be international treaties on weather modification if it wasn't possible? Of course it is. Weather is energetic information and it can be changed.

How was the climate hoax pulled off? See 'Covid'

If you can get billions to believe in a 'virus' that doesn't exist you can get them to believe in human-caused climate change that doesn't exist. Both are being used by the Cult to transform global society in the way it has long planned. Both hoaxes have been achieved in pretty much the same way. First you declare a lie is a fact. There's a

'virus' you call SARS-Cov-2 or humans are warming the planet with their behaviour. Next this becomes, via Cult networks, the foundation of government, academic and science policy and belief. Those who parrot the mantra are given big grants to produce research that confirms the narrative is true and ever more 'symptoms' are added to make the 'virus'/'climate change' sound even more scary. Scientists and researchers who challenge the narrative have their grants withdrawn and their careers destroyed. The media promote the lie as the unquestionable truth and censor those with an alternative view or evidence. A great percentage of the population believe what they are told as the lie becomes an everybody-knows-that and the believing-masses turn on those with a mind of their own. The technique has been used endlessly throughout human history. Wokers are the biggest promotors of the climate lie *and* 'Covid' fascism because their minds are owned by the Cult; their sense of self-righteous self-purity knows no bounds; and they exist in a bubble of reality in which facts are irrelevant and only get in the way of looking without seeing.

Running through all of this like veins in a blue cheese is control of information, which means control of perception, which means control of behaviour, which collectively means control of human society. The Cult owns the global media and Silicon Valley fascists for the simple reason that it *has* to. Without control of information it can't control perception and through that human society. Examine every facet of the Cult agenda and you will see that anything supporting its introduction is never censored while anything pushing back is always censored. I say again: Psychopaths that know why they are doing this must go before Nuremberg trials and those that follow their orders must trot along behind them into the same dock. 'I was just following orders' didn't work the first time and it must not work now. Nuremberg trials must be held all over the world before public juries for politicians, government officials, police, compliant doctors, scientists and virologists, and all Cult operatives such as Gates, Tedros, Fauci, Vallance, Whitty, Ferguson, Zuckerberg, Wojcicki, Brin, Page, Dorsey, the whole damn lot of

them – including, no *especially*, the psychopath psychologists. Without them and the brainless, gutless excuses for journalists that have repeated their lies, none of this could be happening. Nobody can be allowed to escape justice for the psychological and economic Armageddon they are all responsible for visiting upon the human race.

As for the compliant, unquestioning, swathes of humanity, and the self-obsessed, all-knowing ignorance of the Wokers … don't start me. God help their kids. God help their grandkids. God *help them*.

CHAPTER NINE

We must have it? So what is it?

Well I won't back down. No, I won't back down. You can stand me up at the Gates of Hell. But I won't back down
Tom Petty

I will now focus on the genetically-manipulating 'Covid vaccines' which do not meet this official definition of a vaccine by the US Centers for Disease Control (CDC): 'A product that stimulates a person's immune system to produce immunity to a specific disease, protecting the person from that disease.' On that basis 'Covid vaccines' are not a vaccine in that the makers don't even claim they stop infection or transmission.

They are instead part of a multi-levelled conspiracy to change the nature of the human body and what it means to be 'human' and to depopulate an enormous swathe of humanity. What I shall call Human 1.0 is on the cusp of becoming Human 2.0 and for very sinister reasons. Before I get to the 'Covid vaccine' in detail here's some background to vaccines in general. Government regulators do not test vaccines – the makers do – and the makers control which data is revealed and which isn't. Children in America are given 50 vaccine doses by age six and 69 by age 19 and the effect of the whole combined schedule has never been tested. Autoimmune diseases when the immune system attacks its own body have soared in the mass vaccine era and so has disease in general in children and the young. Why wouldn't this be the case when vaccines target the *immune system?* The US government gave Big Pharma drug

companies immunity from prosecution for vaccine death and injury in the 1986 National Childhood Vaccine Injury Act (NCVIA) and since then the government (taxpayer) has been funding compensation for the consequences of Big Pharma vaccines. The criminal and satanic drug giants can't lose and the vaccine schedule has increased dramatically since 1986 for this reason. There is no incentive to make vaccines safe and a big incentive to make money by introducing ever more. Even against a ridiculously high bar to prove vaccine liability, and with the government controlling the hearing in which it is being challenged for compensation, the vaccine court has so far paid out more than $4 billion. These are the vaccines we are told are safe and psychopaths like Zuckerberg censor posts saying otherwise. The immunity law was even justified by a ruling that vaccines by their nature were 'unavoidably unsafe'.

Check out the ingredients of vaccines and you will be shocked if you are new to this. *They put that in children's bodies?? What??* Try aluminium, a brain toxin connected to dementia, aborted foetal tissue and formaldehyde which is used to embalm corpses. World-renowned aluminium expert Christopher Exley had his research into the health effect of aluminium in vaccines shut down by Keele University in the UK when it began taking funding from the Bill and Melinda Gates Foundation. Research when diseases 'eradicated' by vaccines began to decline and you will find the fall began long *before* the vaccine was introduced. Sometimes the fall even plateaued after the vaccine. Diseases like scarlet fever for which there was no vaccine declined in the same way because of environmental and other factors. A perfect case in point is the polio vaccine. Polio began when lead arsenate was first sprayed as an insecticide and residues remained in food products. Spraying started in 1892 and the first US polio epidemic came in Vermont in 1894. The simple answer was to stop spraying, but Rockefeller-created Big Pharma had a better idea. Polio was decreed to be caused by the *poliovirus* which 'spreads from person to person and can infect a person's spinal cord'. Lead arsenate was replaced by the lethal DDT which had the same effect of causing paralysis by damaging the brain and central nervous

system. Polio plummeted when DDT was reduced and then banned, but the vaccine is still given the credit for something it didn't do. Today by far the biggest cause of polio is the vaccines promoted by Bill Gates. Vaccine justice campaigner Robert Kennedy Jr, son of assassinated (by the Cult) US Attorney General Robert Kennedy, wrote:

> In 2017, the World Health Organization (WHO) reluctantly admitted that the global explosion in polio is predominantly vaccine strain. The most frightening epidemics in Congo, Afghanistan, and the Philippines, are all linked to vaccines. In fact, by 2018, 70% of global polio cases were vaccine strain.

Vaccines make fortunes for Cult-owned Gates and Big Pharma while undermining the health and immune systems of the population. We had a glimpse of the mentality behind the Big Pharma cartel with a report on WION (World is One News), an international English language TV station based in India, which exposed the extraordinary behaviour of US drug company Pfizer over its 'Covid vaccine'. The WION report told how Pfizer had made fantastic demands of Argentina, Brazil and other countries in return for its 'vaccine'. These included immunity from prosecution, even for Pfizer negligence, government insurance to protect Pfizer from law suits and handing over as collateral sovereign assets of the country to include Argentina's bank reserves, military bases and embassy buildings. Pfizer demanded the same of Brazil in the form of waiving sovereignty of its assets abroad; exempting Pfizer from Brazilian laws; and giving Pfizer immunity from all civil liability. This is a 'vaccine' developed with government funding. Big Pharma is evil incarnate as a creation of the Cult and all must be handed tickets to Nuremberg.

Phantom 'vaccine' for a phantom 'disease'

I'll expose the 'Covid vaccine' fraud and then go on to the wider background of why the Cult has set out to 'vaccinate' every man, woman and child on the planet for an alleged 'new disease' with a survival rate of 99.77 percent (or more) even by the grotesquely-

manipulated figures of the World Health Organization and Johns Hopkins University. The 'infection' to 'death' ratio is 0.23 to 0.15 percent according to Stanford epidemiologist Dr John Ioannidis and while estimates vary the danger remains tiny. I say that if the truth be told the fake infection to fake death ratio is zero. Never mind all the evidence I have presented here and in *The Answer* that there is no 'virus' let us just focus for a moment on that death-rate figure of say 0.23 percent. The figure includes all those worldwide who have tested positive with a test not testing for the 'virus' and then died within 28 days or even longer of any other cause – *any other cause*. Now subtract all those illusory 'Covid' deaths on the global data sheets from the 0.23 percent. What do you think you would be left with? *Zero*. A vaccination has never been successfully developed for a so-called coronavirus. They have all failed at the animal testing stage when they caused hypersensitivity to what they were claiming to protect against and made the impact of a disease far worse. Cult-owned vaccine corporations got around that problem this time by bypassing animal trials, going straight to humans and making the length of the 'trials' before the public rollout as short as they could get away with. Normally it takes five to ten years or more to develop vaccines that still cause demonstrable harm to many people and that's without including the long-term effects that are never officially connected to the vaccination. 'Covid' non-vaccines have been officially produced and approved in a matter of months from a standing start and part of the reason is that (a) they were developed before the 'Covid' hoax began and (b) they are based on computer programs and not natural sources. Official non-trials were so short that government agencies gave *emergency*, not full, approval. 'Trials' were not even completed and full approval cannot be secured until they are. Public 'Covid vaccination' is actually a *continuation of the trial*. Drug company 'trials' are not scheduled to end until 2023 by which time a lot of people are going to be dead. Data on which government agencies gave this emergency approval was supplied by the Big Pharma corporations themselves in the form of Pfizer/BioNTech, AstraZeneca, Moderna, Johnson & Johnson, and

others, and this is the case with all vaccines. By its very nature *emergency* approval means drug companies do not have to prove that the 'vaccine' is 'safe and effective'. How could they with trials way short of complete? Government regulators only have to *believe* that they *could* be safe and effective. It is criminal manipulation to get products in circulation with no testing worth the name. Agencies giving that approval are infested with Big Pharma-connected place-people and they act in the interests of Big Pharma (the Cult) and not the public about whom they do not give a damn.

More human lab rats

'Covid vaccines' produced in record time by Pfizer/BioNTech and Moderna employ a technique *never approved before for use on humans*. They are known as mRNA 'vaccines' and inject a synthetic version of 'viral' mRNA or 'messenger RNA'. The key is in the term 'messenger'. The body works, or doesn't, on the basis of information messaging. Communications are constantly passing between and within the genetic system and the brain. Change those messages and you change the state of the body and even its very nature and you can change psychology and behaviour by the way the brain processes information. I think you are going to see significant changes in personality and perception of many people who have had the 'Covid vaccine' synthetic potions. Insider Aldous Huxley predicted the following in 1961 and mRNA 'vaccines' can be included in the term 'pharmacological methods':

> There will be, in the next generation or so, a pharmacological method of making people love their servitude, and producing dictatorship without tears, so to speak, producing a kind of painless concentration camp for entire societies, so that people will in fact have their own liberties taken away from them, but rather enjoy it, because they will be distracted from any desire to rebel by propaganda or brainwashing, or brainwashing enhanced by pharmacological methods. And this seems to be the final revolution.

Apologists claim that mRNA synthetic 'vaccines' don't change the DNA genetic blueprint because RNA does not affect DNA only the other way round. This is so disingenuous. A process called 'reverse

transcription' can convert RNA into DNA and be integrated into DNA in the cell nucleus. This was highlighted in December, 2020, by scientists at Harvard and Massachusetts Institute of Technology (MIT). Geneticists report that more than 40 percent of mammalian genomes results from reverse transcription. On the most basic level if messaging changes then that sequence must lead to changes in DNA which is receiving and transmitting those communications. How can introducing synthetic material into cells not change the cells where DNA is located? The process is known as transfection which is defined as 'a technique to insert foreign nucleic acid (DNA or RNA) into a cell, typically with the intention of altering the properties of the cell'. Researchers at the Sloan Kettering Institute in New York found that changes in messenger RNA can deactivate tumour-suppressing proteins and thereby promote cancer. This is what happens when you mess with messaging. 'Covid vaccine' maker Moderna was founded in 2010 by Canadian stem cell biologist Derrick J. Rossi after his breakthrough discovery in the field of transforming and reprogramming stem cells. These are neutral cells that can be programmed to become any cell including sperm cells. Moderna was therefore founded on the principle of genetic manipulation and has never produced any vaccine or drug before its genetically-manipulating synthetic 'Covid' shite. Look at the name – Mode-RNA or Modify-RNA. Another important point is that the US Supreme Court has ruled that genetically-modified DNA, or complementary DNA (cDNA) synthesized in the laboratory from messenger RNA, can be patented and owned. These psychopaths are doing this to the human body.

Cells replicate synthetic mRNA in the 'Covid vaccines' and in theory the body is tricked into making antigens which trigger antibodies to target the 'virus spike proteins' which as Dr Tom Cowan said have *never been seen*. Cut the crap and these 'vaccines' deliver *self-replicating* synthetic material to the cells with the effect of changing human DNA. The more of them you have the more that process is compounded while synthetic material is all the time self-replicating. 'Vaccine'-maker Moderna describes mRNA as 'like

software for the cell' and so they are messing with the body's software. What happens when you change the software in a computer? Everything changes. For this reason the Cult is preparing a production line of mRNA 'Covid vaccines' and a long list of excuses to use them as with all the 'variants' of a 'virus' never shown to exist. The plan is further to transfer the mRNA technique to other vaccines mostly given to children and young people. The cumulative consequences will be a transformation of human DNA through a constant infusion of synthetic genetic material which will kill many and change the rest. Now consider that governments that have given emergency approval for a vaccine that's not a vaccine; never been approved for humans before; had no testing worth the name; and the makers have been given immunity from prosecution for any deaths or adverse effects suffered by the public. The UK government awarded *permanent legal indemnity* to itself and its employees for harm done when a patient is being treated for 'Covid-19' or 'suspected Covid-19'. That is quite a thought when these are possible 'side-effects' from the 'vaccine' (they are not 'side', they are effects) listed by the US Food and Drug Administration:

Guillain-Barre syndrome; acute disseminated encephalomyelitis; transverse myelitis; encephalitis; myelitis; encephalomyelitis; meningoencephalitis; meningitis; encephalopathy; convulsions; seizures; stroke; narcolepsy; cataplexy; anaphylaxis; acute myocardial infarction (heart attack); myocarditis; pericarditis; autoimmune disease; death; implications for pregnancy, and birth outcomes; other acute demyelinating diseases; non anaphylactic allergy reactions; thrombocytopenia ; disseminated intravascular coagulation; venous thromboembolism; arthritis; arthralgia; joint pain; Kawasaki disease; multisystem inflammatory syndrome in children; vaccine enhanced disease. The latter is the way the 'vaccine' has the potential to make diseases far worse than they would otherwise be.

UK doctor and freedom campaigner Vernon Coleman described the conditions in this list as 'all unpleasant, most of them very serious, and you can't get more serious than death'. The thought that anyone at all has had the 'vaccine' in these circumstances is testament to the potential that humanity has for clueless, unquestioning, stupidity and for many that programmed stupidity has already been terminal.

An insider speaks

Dr Michael Yeadon is a former Vice President, head of research and Chief Scientific Adviser at vaccine giant Pfizer. Yeadon worked on the inside of Big Pharma, but that did not stop him becoming a vocal critic of 'Covid vaccines' and their potential for multiple harms, including infertility in women. By the spring of 2021 he went much further and even used the no, no, term 'conspiracy'. When you begin to see what is going on it is impossible not to do so. Yeadon spoke out in an interview with freedom campaigner James Delingpole and I mentioned earlier how he said that no one had samples of 'the virus'. He explained that the mRNA technique originated in the anti-cancer field and ways to turn on and off certain genes which could be advantageous if you wanted to stop cancer growing out of control. 'That's the origin of them. They are a very unusual application, really.' Yeadon said that treating a cancer patient with an aggressive procedure might be understandable if the alternative was dying, but it was quite another thing to use the same technique as a public health measure. Most people involved wouldn't catch the infectious agent you were vaccinating against and if they did they probably wouldn't die:

> If you are really using it as a public health measure you really want to as close as you can get to zero sides-effects … I find it odd that they chose techniques that were really cutting their teeth in the field of oncology and I'm worried that in using gene-based vaccines that have to be injected in the body and spread around the body, get taken up into some cells, and the regulators haven't quite told us which cells they get taken up into … you are going to be generating a wide range of responses … with multiple steps each of which could go well or badly.

I doubt the Cult intends it to go well. Yeadon said that you can put any gene you like into the body through the 'vaccine'. 'You can certainly give them a gene that would do them some harm if you wanted.' I was intrigued when he said that when used in the cancer field the technique could turn genes on and off. I explore this process in *The Answer* and with different genes having different functions you could create mayhem – physically and psychologically – if you turned the wrong ones on and the right ones off. I read reports of an experiment by researchers at the University of Washington's school of computer science and engineering in which they encoded DNA to infect computers. The body is itself a biological computer and if human DNA can inflict damage on a computer why can't the computer via synthetic material mess with the human body? It can. The Washington research team said it was possible to insert malicious malware into 'physical DNA strands' and corrupt the computer system of a gene sequencing machine as it 'reads gene letters and stores them as binary digits 0 and 1'. They concluded that hackers could one day use blood or spit samples to access computer systems and obtain sensitive data from police forensics labs or infect genome files. It is at this level of digital interaction that synthetic 'vaccines' need to be seen to get the full picture and that will become very clear later on. Michael Yeadon said it made no sense to give the 'vaccine' to younger people who were in no danger from the 'virus'. What was the benefit? It was all downside with potential effects:

> The fact that my government in what I thought was a civilised, rational country, is raining [the 'vaccine'] on people in their 30s and 40s, even my children in their 20s, they're getting letters and phone calls, I know this is not right and any of you doctors who are vaccinating you know it's not right, too. They are not at risk. They are not at risk from the disease, so you are now hoping that the side-effects are so rare that you get away with it. You don't give new technology … that you don't understand to 100 percent of the population.

Blood clot problems with the AstraZeneca 'vaccine' have been affecting younger people to emphasise the downside risks with no benefit. AstraZeneca's version, produced with Oxford University, does not use mRNA, but still gets its toxic cocktail inside cells where

it targets DNA. The Johnson & Johnson 'vaccine' which uses a similar technique has also produced blood clot effects to such an extent that the United States paused its use at one point. They are all 'gene therapy' (cell modification) procedures and not 'vaccines'. The truth is that once the content of these injections enter cells we have no idea what the effect will be. People can speculate and some can give very educated opinions and that's good. In the end, though, only the makers know what their potions are designed to do and even they won't know every last consequence. Michael Yeadon was scathing about doctors doing what they knew to be wrong. 'Everyone's mute', he said. Doctors in the NHS must know this was not right, coming into work and injecting people. 'I don't know how they sleep at night. I know I couldn't do it. I know that if I were in that position I'd have to quit.' He said he knew enough about toxicology to know this was not a good risk-benefit. Yeadon had spoken to seven or eight university professors and all except two would not speak out publicly. Their universities had a policy that no one said anything that countered the government and its medical advisors. They were afraid of losing their government grants. This is how intimidation has been used to silence the truth at every level of the system. I say silence, but these people could still speak out if they made that choice. Yeadon called them 'moral cowards' – 'This is about your children and grandchildren's lives and you have just buggered off and left it.'

'Variant' nonsense

Some of his most powerful comments related to the alleged 'variants' being used to instil more fear, justify more lockdowns, and introduce more 'vaccines'. He said government claims about 'variants' were nonsense. He had checked the alleged variant 'codes' and they were 99.7 percent identical to the 'original'. This was the human identity difference equivalent to putting a baseball cap on and off or wearing it the other way round. A 0.3 percent difference would make it impossible for that 'variant' to escape immunity from the 'original'. This made no sense of having new 'vaccines' for

'variants'. He said there would have to be at least a *30 percent* difference for that to be justified and even then he believed the immune system would still recognise what it was. Gates-funded 'variant modeller' and 'vaccine'-pusher John Edmunds might care to comment. Yeadon said drug companies were making new versions of the 'vaccine' as a 'top up' for 'variants'. Worse than that, he said, the 'regulators' around the world like the MHRA in the UK had got together and agreed that because 'vaccines' for 'variants' were so similar to the first 'vaccines' *they did not have to do safety studies*. How transparently sinister that is. This is when Yeadon said: 'There is a conspiracy here.' There was no need for another vaccine for 'variants' and yet we were told that there was and the country had shut its borders because of them. 'They are going into hundreds of millions of arms without passing 'go' or any regulator. Why did they do that? Why did they pick this method of making the vaccine?'

The reason had to be something bigger than that it seemed and 'it's not protection against the virus'. It's was a far bigger project that meant politicians and advisers were willing to do things and not do things that knowingly resulted in avoidable deaths – 'that's already happened when you think about lockdown and deprivation of health care for a year.' He spoke of people prepared to do something that results in the avoidable death of their fellow human beings and it not bother them. This is the penny-drop I have been working to get across for more than 30 years – the level of pure evil we are dealing with. Yeadon said his friends and associates could not believe there could be that much evil, but he reminded them of Stalin, Pol Pot and Hitler and of what Stalin had said: 'One death is a tragedy. A million? A statistic.' He could not think of a benign explanation for why you need top-up vaccines 'which I'm sure you don't' and for the regulators 'to just get out of the way and wave them through'. Why would the regulators do that when they were still wrestling with the dangers of the 'parent' vaccine? He was clearly shocked by what he had seen since the 'Covid' hoax began and now he was thinking the previously unthinkable:

If you wanted to depopulate a significant proportion of the world and to do it in a way that doesn't involve destruction of the environment with nuclear weapons, poisoning everyone with anthrax or something like that, and you wanted plausible deniability while you had a multi-year infectious disease crisis, I actually don't think you could come up with a better plan of work than seems to be in front of me. I can't say that's what they are going to do, but I can't think of a benign explanation why they are doing it.

He said he never thought that they would get rid of 99 percent of humans, but now he wondered. 'If you wanted to that this would be a hell of a way to do it – it would be unstoppable folks.' Yeadon had concluded that those who submitted to the 'vaccine' would be allowed to have some kind of normal life (but for how long?) while screws were tightened to coerce and mandate the last few percent. 'I think they'll put the rest of them in a prison camp. I wish I was wrong, but I don't think I am.' Other points he made included: There were no coronavirus vaccines then suddenly they all come along at the same time; we have no idea of the long term affect with trials so short; coercing or forcing people to have medical procedures is against the Nuremberg Code instigated when the Nazis did just that; people should at least delay having the 'vaccine'; a quick Internet search confirms that masks don't reduce respiratory viral transmission and 'the government knows that'; they have smashed civil society and they know that, too; two dozen peer-reviewed studies show no connection between lockdown and reducing deaths; he knew from personal friends the elite were still flying around and going on holiday while the public were locked down; the elite were not having the 'vaccines'. He was also asked if 'vaccines' could be made to target difference races. He said he didn't know, but the document by the Project for the New American Century in September, 2000, said developing 'advanced forms of biological warfare that can target *specific genotypes* may transform biological warfare from the realm of terror to a politically useful tool.' Oh, they're evil all right. Of that we can be *absolutely* sure.

Another cull of old people

We have seen from the CDC definition that the mRNA 'Covid vaccine' is not a vaccine and nor are the others that *claim* to reduce 'severity of symptoms' in *some* people, but not protect from infection or transmission. What about all the lies about returning to 'normal' if people were 'vaccinated'? If they are not claimed to stop infection and transmission of the alleged 'virus', how does anything change? This was all lies to manipulate people to take the jabs and we are seeing that now with masks and distancing still required for the 'vaccinated'. How did they think that elderly people with fragile health and immune responses were going to be affected by infusing their cells with synthetic material and other toxic substances? They *knew* that in the short and long term it would be devastating and fatal as the culling of the old that began with the first lockdowns was continued with the 'vaccine'. Death rates in care homes soared immediately residents began to be 'vaccinated' – infused with synthetic material. Brave and committed whistleblower nurses put their careers at risk by exposing this truth while the rest kept their heads down and their mouths shut to put their careers before those they are supposed to care for. A long-time American Certified Nursing Assistant who gave his name as James posted a video in which he described emotionally what happened in his care home when vaccination began. He said that during 2020 very few residents were sick with 'Covid' and no one died during the entire year; but shortly after the Pfizer mRNA injections 14 people died within two weeks and many others were near death. 'They're dropping like flies', he said. Residents who walked on their own before the shot could no longer and they had lost their ability to conduct an intelligent conversation. The home's management said the sudden deaths were caused by a 'super-spreader' of 'Covid-19'. Then how come, James asked, that residents who refused to take the injections were not sick? It was a case of inject the elderly with mRNA synthetic potions and blame their illness and death that followed on the 'virus'. James described what was happening in care homes as 'the greatest crime of genocide this country has ever seen'. Remember the NHS staff nurse from earlier who used the same

word ‘genocide’ for what was happening with the ‘vaccines’ and that it was an ‘act of human annihilation’. A UK care home whistleblower told a similar story to James about the effect of the ‘vaccine’ in deaths and ‘outbreaks’ of illness dubbed ‘Covid’ after getting the jab. She told how her care home management and staff had zealously imposed government regulations and no one was allowed to even question the official narrative let alone speak out against it. She said the NHS was even worse. Again we see the results of reframing. A worker at a local care home where I live said they had not had a single case of ‘Covid’ there for almost a year and when the residents were ‘vaccinated’ they had 19 positive cases in two weeks with eight dying.

It’s not the ‘vaccine’ – honest

The obvious cause and effect was being ignored by the media and most of the public. Australia’s health minister Greg Hunt (a former head of strategy at the World Economic Forum) was admitted to hospital after he had the ‘vaccine’. He was suffering according to reports from the skin infection ‘cellulitis’ and it must have been a severe case to have warranted days in hospital. Immediately the authorities said this was nothing to do with the ‘vaccine’ when an effect of some vaccines is a ‘cellulitis-like reaction’. We had families of perfectly healthy old people who died after the ‘vaccine’ saying that if only they had been given the ‘vaccine’ earlier they would still be alive. As a numbskull rating that is off the chart. A father of four ‘died of Covid’ at aged 48 when he was taken ill two days after having the ‘vaccine’. The man, a health administrator, had been ‘shielding during the pandemic’ and had ‘not really left the house’ until he went for the ‘vaccine’. Having the ‘vaccine’ and then falling ill and dying does not seem to have qualified as a possible cause and effect and ‘Covid-19’ went on his death certificate. His family said they had no idea how he ‘caught the virus’. A family member said: ‘Tragically, it could be that going for a vaccination ultimately led to him catching Covid …The sad truth is that they are never going to know where it came from.’ The family warned people to remember

that the virus still existed and was 'very real'. So was their stupidity. Nurses and doctors who had the first round of the 'vaccine' were collapsing, dying and ending up in a hospital bed while they or their grieving relatives were saying they'd still have the 'vaccine' again despite what happened. I kid you not. You mean if your husband returned from the dead he'd have the same 'vaccine' again that killed him??

Doctors at the VCU Medical Center in Richmond, Virginia, said the Johnson & Johnson 'vaccine' was to blame for a man's skin peeling off. Patient Richard Terrell said: 'It all just happened so fast. My skin peeled off. It's still coming off on my hands now.' He said it was stinging, burning and itching and when he bent his arms and legs it was very painful with 'the skin swollen and rubbing against itself'. Pfizer/BioNTech and Moderna vaccines use mRNA to change the cell while the Johnson & Johnson version uses DNA in a process similar to AstraZeneca's technique. Johnson & Johnson and AstraZeneca have both had their 'vaccines' paused by many countries after causing serious blood problems. Terrell's doctor Fnu Nutan said he could have died if he hadn't got medical attention. It sounds terrible so what did Nutan and Terrell say about the 'vaccine' now? Oh, they still recommend that people have it. A nurse in a hospital bed 40 minutes after the vaccination and unable to swallow due to throat swelling was told by a doctor that he lost mobility in his arm for 36 hours following the vaccination. What did he say to the ailing nurse? 'Good for you for getting the vaccination.' We are dealing with a serious form of cognitive dissonance madness in both public and medical staff. There is a remarkable correlation between those having the 'vaccine' and trumpeting the fact and suffering bad happenings shortly afterwards. Witold Rogiewicz, a Polish doctor, made a video of his 'vaccination' and ridiculed those who were questioning its safety and the intentions of Bill Gates: 'Vaccinate yourself to protect yourself, your loved ones, friends and also patients. And to mention quickly I have info for anti-vaxxers and anti-Coviders if you want to contact Bill Gates you can do this through me.' He further ridiculed the dangers of 5G. Days later he

was dead, but naturally the vaccination wasn't mentioned in the verdict of 'heart attack'.

Lies, lies and more lies

So many members of the human race have slipped into extreme states of insanity and unfortunately they include reframed doctors and nursing staff. Having a 'vaccine' and dying within minutes or hours is not considered a valid connection while death from any cause within 28 days or longer of a positive test with a test not testing for the 'virus' means 'Covid-19' goes on the death certificate. How could that 'vaccine'-death connection not have been made except by calculated deceit? US figures in the initial rollout period to February 12th, 2020, revealed that a third of the deaths reported to the CDC after 'Covid vaccines' happened within 48 hours. Five men in the UK suffered an 'extremely rare' blood clot problem after having the AstraZeneca 'vaccine', but no causal link was established said the Gates-funded Medicines and Healthcare products Regulatory Agency (MHRA) which had given the 'vaccine' emergency approval to be used. Former Pfizer executive Dr Michael Yeadon explained in his interview how the procedures could cause blood coagulation and clots. People who should have been at no risk were dying from blood clots in the brain and he said he had heard from medical doctor friends that people were suffering from skin bleeding and massive headaches. The AstraZeneca 'shot' was stopped by some 20 countries over the blood clotting issue and still the corrupt MHRA, the European Medicines Agency (EMA) and the World Health Organization said that it should continue to be given even though the EMA admitted that it 'still cannot rule out definitively' a link between blood clotting and the 'vaccine'. Later Marco Cavaleri, head of EMA vaccine strategy, said there was indeed a clear link between the 'vaccine' and thrombosis, but they didn't know why. So much for the trials showing the 'vaccine' is safe. Blood clots were affecting younger people who would be under virtually no danger from 'Covid' even if it existed which makes it all the more stupid and sinister.

The British government responded to public alarm by wheeling out June Raine, the terrifyingly weak infant school headmistress sound-alike who heads the UK MHRA drug 'regulator'. The idea that she would stand up to Big Pharma and government pressure is laughable and she told us that all was well in the same way that she did when allowing untested, never-used-on-humans-before, genetically-manipulating 'vaccines' to be exposed to the public in the first place. Mass lying is the new normal of the 'Covid' era. The MHRA later said 30 cases of rare blood clots had by then been connected with the AstraZeneca 'vaccine' (that means a lot more in reality) while stressing that the benefits of the jab in preventing 'Covid-19' outweighed any risks. A more ridiculous and disingenuous statement with callous disregard for human health it is hard to contemplate. Immediately after the mendacious 'all-clears' two hospital workers in Denmark experienced blood clots and cerebral haemorrhaging following the AstraZeneca jab and one died. Top Norwegian health official Pål Andre Holme said the 'vaccine' was the only common factor: 'There is nothing in the patient history of these individuals that can give such a powerful immune response … I am confident that the antibodies that we have found are the cause, and I see no other explanation than it being the vaccine which triggers it.' Strokes, a clot or bleed in the brain, were clearly associated with the 'vaccine' from word of mouth and whistleblower reports. Similar consequences followed with all these 'vaccines' that we were told were so safe and as the numbers grew by the day it was clear we were witnessing human carnage.

Learning the hard way

A woman interviewed by UKColumn told how her husband suffered dramatic health effects after the vaccine when he'd been in good health all his life. He went from being a little unwell to losing all feeling in his legs and experiencing 'excruciating pain'. Misdiagnosis followed twice at Accident and Emergency (an 'allergy' and 'sciatica') before he was admitted to a neurology ward where doctors said his serious condition had been caused by the

'vaccine'. Another seven 'vaccinated' people were apparently being treated on the same ward for similar symptoms. The woman said he had the 'vaccine' because they believed media claims that it was safe. 'I didn't think the government would give out a vaccine that does this to somebody; I believed they would be bringing out a vaccination that would be safe.' What a tragic way to learn that lesson. Another woman posted that her husband was transporting stroke patients to hospital on almost every shift and when he asked them if they had been 'vaccinated' for 'Covid' they all replied 'yes'. One had a 'massive brain bleed' the day after his second dose. She said her husband reported the 'just been vaccinated' information every time to doctors in A and E only for them to ignore it, make no notes and appear annoyed that it was even mentioned. This particular report cannot be verified, but it expresses a common theme that confirms the monumental underreporting of 'vaccine' consequences. Interestingly as the 'vaccines' and their brain blood clot/stroke consequences began to emerge the UK National Health Service began a publicity campaign telling the public what to do in the event of a stroke. A Scottish NHS staff nurse who quit in disgust in March, 2021, said:

I have seen traumatic injuries from the vaccine, they're not getting reported to the yellow card [adverse reaction] scheme, they're treating the symptoms, not asking why, why it's happening. It's just treating the symptoms and when you speak about it you're dismissed like you're crazy, I'm not crazy, I'm not crazy because every other colleague I've spoken to is terrified to speak out, they've had enough.

Videos appeared on the Internet of people uncontrollably shaking after the 'vaccine' with no control over muscles, limbs and even their face. A Scottish mother broke out in a severe rash all over her body almost immediately after she was given the AstraZeneca 'vaccine'. The pictures were horrific. Leigh King, a 41-year-old hairdresser from Lanarkshire said: 'Never in my life was I prepared for what I was about to experience … My skin was so sore and constantly hot … I have never felt pain like this …' But don't you worry, the 'vaccine' is perfectly safe. Then there has been the effect on medical

staff who have been pressured to have the 'vaccine' by psychopathic 'health' authorities and government. A London hospital consultant who gave the name K. Polyakova wrote this to the *British Medical Journal* or *BMJ*:

> I am currently struggling with … the failure to report the reality of the morbidity caused by our current vaccination program within the health service and staff population. The levels of sickness after vaccination is unprecedented and staff are getting very sick and some with neurological symptoms which is having a huge impact on the health service function. Even the young and healthy are off for days, some for weeks, and some requiring medical treatment. Whole teams are being taken out as they went to get vaccinated together.
>
> Mandatory vaccination in this instance is stupid, unethical and irresponsible when it comes to protecting our staff and public health. We are in the voluntary phase of vaccination, and encouraging staff to take an unlicensed product that is impacting on their immediate health … it is clearly stated that these vaccine products do not offer immunity or stop transmission. In which case why are we doing it?

Not to protect health that's for sure. Medical workers are lauded by governments for agenda reasons when they couldn't give a toss about them any more than they can for the population in general. Schools across America faced the same situation as they closed due to the high number of teachers and other staff with bad reactions to the Pfizer/BioNTech, Moderna, and Johnson & Johnson 'Covid vaccines' all of which were linked to death and serious adverse effects. The *BMJ* took down the consultant's comments pretty quickly on the grounds that they were being used to spread 'disinformation'. They were exposing the truth about the 'vaccine' was the real reason. The cover-up is breathtaking.

Hiding the evidence

The scale of the 'vaccine' death cover-up worldwide can be confirmed by comparing official figures with the personal experience of the public. I heard of many people in my community who died immediately or soon after the vaccine that would never appear in the media or even likely on the official totals of 'vaccine' fatalities and adverse reactions when only about ten percent are estimated to be

reported and I have seen some estimates as low as one percent in a Harvard study. In the UK alone by April 29th, 2021, some 757,654 adverse reactions had been officially reported from the Pfizer/BioNTech, Oxford/AstraZeneca and Moderna 'vaccines' with more than a thousand deaths linked to jabs and that means an estimated ten times this number in reality from a ten percent reporting rate percentage. That's seven million adverse reactions and 10,000 potential deaths and a one percent reporting rate would be ten times *those* figures. In 1976 the US government pulled the swine flu vaccine after *53* deaths. The UK data included a combined 10,000 eye disorders from the 'Covid vaccines' with more than 750 suffering visual impairment or blindness and again multiply by the estimated reporting percentages. As 'Covid cases' officially fell hospitals virtually empty during the 'Covid crisis' began to fill up with a range of other problems in the wake of the 'vaccine' rollout. The numbers across America have also been catastrophic. Deaths linked to *all* types of vaccine increased by *6,000 percent* in the first quarter of 2021 compared with 2020. A 39-year-old woman from Ogden, Utah, died four days after receiving a second dose of Moderna's 'Covid vaccine' when her liver, heart and kidneys all failed despite the fact that she had no known medical issues or conditions. Her family sought an autopsy, but Dr Erik Christensen, Utah's chief medical examiner, said proving vaccine injury as a cause of death almost never happened. He could think of only one instance where an autopsy would name a vaccine as the official cause of death and that would be anaphylaxis where someone received a vaccine and died almost instantaneously. 'Short of that, it would be difficult for us to definitively say this is the vaccine,' Christensen said. If that is true this must be added to the estimated ten percent (or far less) reporting rate of vaccine deaths and serious reactions and the conclusion can only be that vaccine deaths and serious reactions – including these 'Covid' potions' – are phenomenally understated in official figures. The same story can be found everywhere. Endless accounts of deaths and serious reactions among the public, medical

and care home staff while official figures did not even begin to reflect this.

Professional script-reader Dr David Williams, a 'top public-health official' in Ontario, Canada, insulted our intelligence by claiming only four serious adverse reactions and no deaths from the more than 380,000 vaccine doses then given. This bore no resemblance to what people knew had happened in their owns circles and we had Dirk Huyer in charge of getting millions vaccinated in Ontario while at the same time he was Chief Coroner for the province investigating causes of death including possible death from the vaccine. An aide said he had stepped back from investigating deaths, but evidence indicated otherwise. Rosemary Frei, who secured a Master of Science degree in molecular biology at the Faculty of Medicine at Canada's University of Calgary before turning to investigative journalism, was one who could see that official figures for 'vaccine' deaths and reactions made no sense. She said that doctors seldom reported adverse events and when people got really sick or died after getting a vaccination they would attribute that to anything except the vaccines. It had been that way for years and anyone who wondered aloud whether the 'Covid vaccines' or other shots cause harm is immediately branded as 'anti-vax' and 'anti-science'. This was 'career-threatening' for health professionals. Then there was the huge pressure to support the push to 'vaccinate' billions in the quickest time possible. Frei said:

> So that's where we're at today. More than half a million vaccine doses have been given to people in Ontario alone. The rush is on to vaccinate all 15 million of us in the province by September. And the mainstream media are screaming for this to be sped up even more. That all adds up to only a very slim likelihood that we're going to be told the truth by officials about how many people are getting sick or dying from the vaccines.

What is true of Ontario is true of everywhere.

They KNEW – and still did it

The authorities knew what was going to happen with multiple deaths and adverse reactions. The UK government's Gates-funded

and Big Pharma-dominated Medicines and Healthcare products Regulatory Agency (MHRA) hired a company to employ AI in compiling the projected reactions to the 'vaccine' that would otherwise be uncountable. The request for applications said: 'The MHRA urgently seeks an Artificial Intelligence (AI) software tool to process the expected high volume of Covid-19 vaccine Adverse Drug Reaction …' This was from the agency, headed by the disingenuous June Raine, that gave the 'vaccines' emergency approval and the company was hired before the first shot was given. 'We are going to kill and maim you – is that okay?' 'Oh, yes, perfectly fine – I'm very grateful, thank you, doctor.' The range of 'Covid vaccine' adverse reactions goes on for page after page in the MHRA criminally underreported 'Yellow Card' system and includes affects to eyes, ears, skin, digestion, blood and so on. Raine's MHRA amazingly claimed that the 'overall safety experience … is so far as expected from the clinical trials'. The death, serious adverse effects, deafness and blindness were *expected?* When did they ever mention that? If these human tragedies were expected then those that gave approval for the use of these 'vaccines' must be guilty of crimes against humanity including murder – a definition of which is 'killing a person with malice aforethought or with recklessness manifesting extreme indifference to the value of human life.' People involved at the MHRA, the CDC in America and their equivalent around the world must go before Nuremberg trials to answer for their callous inhumanity. We are only talking here about the immediate effects of the 'vaccine'. The longer-term impact of the DNA synthetic manipulation is the main reason they are so hysterically desperate to inoculate the entire global population in the shortest possible time.

Africa and the developing world are a major focus for the 'vaccine' depopulation agenda and a mass vaccination sales-pitch is underway thanks to caring people like the Rockefellers and other Cult assets. The Rockefeller Foundation, which pre-empted the 'Covid pandemic' in a document published in 2010 that 'predicted' what happened a decade later, announced an initial $34.95 million grant in February, 2021, 'to ensure more equitable access to Covid-19

testing and vaccines' among other things in Africa in collaboration with '24 organizations, businesses, and government agencies'. The pan-Africa initiative would focus on 10 countries: Burkina Faso, Ethiopia, Ghana, Kenya, Nigeria, Rwanda, South Africa, Tanzania, Uganda, and Zambia'. Rajiv Shah, President of the Rockefeller Foundation and former administrator of CIA-controlled USAID, said that if Africa was not mass-vaccinated (to change the DNA of its people) it was a 'threat to all of humanity' and not fair on Africans. When someone from the Rockefeller Foundation says they want to do something to help poor and deprived people and countries it is time for a belly-laugh. They are doing this out of the goodness of their 'heart' because 'vaccinating' the entire global population is what the 'Covid' hoax set out to achieve. Official 'decolonisation' of Africa by the Cult was merely a prelude to financial colonisation on the road to a return to physical colonisation. The 'vaccine' is vital to that and the sudden and convenient death of the 'Covid' sceptic president of Tanzania can be seen in its true light. A lot of people in Africa are aware that this is another form of colonisation and exploitation and they need to stand their ground.

The 'vaccine is working' scam

A potential problem for the Cult was that the 'vaccine' is meant to change human DNA and body messaging and not to protect anyone from a 'virus' never shown to exist. The vaccine couldn't work because it was not designed to work and how could they make it *appear* to be working so that more people would have it? This was overcome by lowering the amplification rate of the PCR test to produce fewer 'cases' and therefore fewer 'deaths'. Some of us had been pointing out since March, 2020, that the amplification rate of the test not testing for the 'virus' had been made artificially high to generate positive tests which they could call 'cases' to justify lockdowns. The World Health Organization recommended an absurdly high 45 amplification cycles to ensure the high positives required by the Cult and then remained silent on the issue until January 20th, 2021 – Biden's Inauguration Day. This was when the

'vaccinations' were seriously underway and on that day the WHO recommended after discussions with America's CDC that laboratories *lowered their testing amplification*. Dr David Samadi, a certified urologist and health writer, said the WHO was encouraging all labs to reduce their cycle count for PCR tests. He said the current cycle was much too high and was 'resulting in any particle being declared a positive case'. Even one mainstream news report I saw said this meant the number of 'Covid' infections may have been 'dramatically inflated'. Oh, just a little bit. The CDC in America issued new guidance to laboratories in April, 2021, to use 28 cycles *but only for 'vaccinated' people*. The timing of the CDC/WHO interventions were cynically designed to make it appear the 'vaccines' were responsible for falling cases and deaths when the real reason can be seen in the following examples. New York's state lab, the Wadsworth Center, identified 872 positive tests in July, 2020, based on a threshold of 40 cycles. When the figure was lowered to 35 cycles *43 percent* of the 872 were no longer 'positives'. At 30 cycles the figure was 63 percent. A Massachusetts lab found that between *85 to 90 percent* of people who tested positive in July with a cycle threshold of 40 would be negative at 30 cycles, Ashish Jha, MD, director of the Harvard Global Health Institute, said: 'I'm really shocked that it could be that high … Boy, does it really change the way we need to be thinking about testing.' I'm shocked that I could see the obvious in the spring of 2020, with no medical background, and most medical professionals still haven't worked it out. No, that's not shocking – it's terrifying.

Three weeks after the WHO directive to lower PCR cycles the London *Daily Mail* ran this headline: 'Why ARE Covid cases plummeting? New infections have fallen 45% in the US and 30% globally in the past 3 weeks but experts say vaccine is NOT the main driver because only 8% of Americans and 13% of people worldwide have received their first dose.' They acknowledged that the drop could not be attributed to the 'vaccine', but soon this morphed throughout the media into the 'vaccine' has caused cases and deaths to fall when it was the PCR threshold. In December, 2020, there was

chaos at English Channel ports with truck drivers needing negative 'Covid' tests before they could board a ferry home for Christmas. The government wanted to remove the backlog as fast as possible and they brought in troops to do the 'testing'. Out of 1,600 drivers just *36* tested positive and the rest were given the all clear to cross the Channel. I guess the authorities thought that 36 was the least they could get away with without the unquestioning catching on. The amplification trick which most people believed in the absence of information in the mainstream applied more pressure on those refusing the 'vaccine' to succumb when it 'obviously worked'. The truth was the exact opposite with deaths in care homes soaring with the 'vaccine' and in Israel the term used was 'skyrocket'. A re-analysis of published data from the Israeli Health Ministry led by Dr Hervé Seligmann at the Medicine Emerging Infectious and Tropical Diseases at Aix-Marseille University found that Pfizer's 'Covid vaccine' killed 'about 40 times more [elderly] people than the disease itself would have killed' during a five-week vaccination period and *260 times* more younger people than would have died from the 'virus' even according to the manipulated 'virus' figures. Dr Seligmann and his co-study author, Haim Yativ, declared after reviewing the Israeli 'vaccine' death data: 'This is a new Holocaust.'

Then, in mid-April, 2021, after vast numbers of people worldwide had been 'vaccinated', the story changed with clear coordination. The UK government began to prepare the ground for more future lockdowns when Nuremberg-destined Boris Johnson told yet another whopper. He said that cases had fallen because of *lockdowns* not 'vaccines'. Lockdowns are irrelevant when *there is no 'virus'* and the test and fraudulent death certificates are deciding the number of 'cases' and 'deaths'. Study after study has shown that lockdowns don't work and instead kill and psychologically destroy people. Meanwhile in the United States Anthony Fauci and Rochelle Walensky, the ultra-Zionist head of the CDC, peddled the same line. More lockdown was the answer and not the 'vaccine', a line repeated on cue by the moron that is Canadian Prime Minister Justin Trudeau. Why all the hysteria to get everyone 'vaccinated' if lockdowns and

not 'vaccines' made the difference? None of it makes sense on the face of it. Oh, but it does. The Cult wants lockdowns *and* the 'vaccine' and if the 'vaccine' is allowed to be seen as the total answer lockdowns would no longer be justified when there are still livelihoods to destroy. 'Variants' and renewed upward manipulation of PCR amplification are planned to instigate never-ending lockdown *and* more 'vaccines'.

You *must* have it – we're desperate

Israel, where the Jewish and Arab population are ruled by the Sabbatian Cult, was the front-runner in imposing the DNA-manipulating 'vaccine' on its people to such an extent that Jewish refusers began to liken what was happening to the early years of Nazi Germany. This would seem to be a fantastic claim. Why would a government of Jewish people be acting like the Nazis did? If you realise that the Sabbatian Cult was behind the Nazis and that Sabbatians hate Jews the pieces start to fit and the question of why a 'Jewish' government would treat Jews with such callous disregard for their lives and freedom finds an answer. Those controlling the government of Israel *aren't Jewish* – they're Sabbatian. Israeli lawyer Tamir Turgal was one who made the Nazi comparison in comments to German lawyer Reiner Fuellmich who is leading a class action lawsuit against the psychopaths for crimes against humanity. Turgal described how the Israeli government was vaccinating children and pregnant women on the basis that there was no evidence that this was dangerous when they had no evidence that it *wasn't* dangerous either. They just had no evidence. This was medical experimentation and Turgal said this breached the Nuremberg Code about medical experimentation and procedures requiring informed consent and choice. Think about that. A Nuremberg Code developed because of Nazi experimentation on Jews and others in concentration camps by people like the evil-beyond-belief Josef Mengele is being breached by the *Israeli* government; but when you know that it's a *Sabbatian* government along with its intelligence and military agencies like Mossad, Shin Bet and the Israeli Defense Forces, and that Sabbatians

were the force behind the Nazis, the kaleidoscope comes into focus. What have we come to when Israeli Jews are suing their government for violating the Nuremberg Code by essentially making Israelis subject to a medical experiment using the controversial 'vaccines'? It's a shocker that this has to be done in the light of what happened in Nazi Germany. The Anshe Ha-Emet, or 'People of the Truth', made up of Israeli doctors, lawyers, campaigners and public, have launched a lawsuit with the International Criminal Court. It says:

> When the heads of the Ministry of Health as well as the prime minister presented the vaccine in Israel and began the vaccination of Israeli residents, the vaccinated were not advised, that, in practice, they are taking part in a medical experiment and that their consent is required for this under the Nuremberg Code.

The irony is unbelievable, but easily explained in one word: Sabbatians. The foundation of Israeli 'Covid' apartheid is the 'green pass' or 'green passport' which allows Jews and Arabs who have had the DNA-manipulating 'vaccine' to go about their lives – to work, fly, travel in general, go to shopping malls, bars, restaurants, hotels, concerts, gyms, swimming pools, theatres and sports venues, while non-'vaccinated' are banned from all those places and activities. Israelis have likened the 'green pass' to the yellow stars that Jews in Nazi Germany were forced to wear – the same as the yellow stickers that a branch of UK supermarket chain Morrisons told exempt mask-wears they had to display when shopping. How very sensitive. The Israeli system is blatant South African-style apartheid on the basis of compliance or non-compliance to fascism rather than colour of the skin. How appropriate that the Sabbatian Israeli government was so close to the pre-Mandela apartheid regime in Pretoria. The Sabbatian-instigated 'vaccine passport' in Israel is planned for everywhere. Sabbatians struck a deal with Pfizer that allowed them to lead the way in the percentage of a national population infused with synthetic material and the result was catastrophic. Israeli freedom activist Shai Dannon told me how chairs were appearing on beaches that said 'vaccinated only'. Health Minister Yuli Edelstein said that anyone unwilling or unable to get

the jabs that 'confer immunity' will be 'left behind'. The man's a liar. Not even the makers claim the 'vaccines' confer immunity. When you see those figures of 'vaccine' deaths these psychopaths were saying that you must take the chance the 'vaccine' will kill you or maim you while knowing it will change your DNA or lockdown for you will be permanent. That's fascism. The Israeli parliament passed a law to allow personal information of the non-vaccinated to be shared with local and national authorities for three months. This was claimed by its supporters to be a way to 'encourage' people to be vaccinated. Hadas Ziv from Physicians for Human Rights described this as a 'draconian law which crushed medical ethics and the patient rights'. But that's the idea, the Sabbatians would reply.

Your papers, please

Sabbatian Israel was leading what has been planned all along to be a global 'vaccine pass' called a 'green passport' without which you would remain in permanent lockdown restriction and unable to do anything. This is how badly – *desperately* – the Cult is to get everyone 'vaccinated'. The term and colour 'green' was not by chance and related to the psychology of fusing the perception of the green climate hoax with the 'Covid' hoax and how the 'solution' to both is the same Great Reset. Lying politicians, health officials and psychologists denied there were any plans for mandatory vaccinations or restrictions based on vaccinations, but they knew that was exactly what was meant to happen with governments of all countries reaching agreements to enforce a global system. 'Free' Denmark and 'free' Sweden unveiled digital vaccine certification. Cyprus, Czech Republic, Estonia, Greece, Hungary, Iceland, Italy, Poland, Portugal, Slovakia, and Spain have all committed to a vaccine passport system and the rest including the whole of the EU would follow. The satanic UK government will certainly go this way despite mendacious denials and at the time of writing it is trying to manipulate the public into having the 'vaccine' so they could go abroad on a summer holiday. How would that work without something to prove you had the synthetic toxicity injected into you?

Documents show that the EU's European Commission was moving towards 'vaccine certificates' in 2018 and 2019 before the 'Covid' hoax began. They knew what was coming. Abracadabra – Ursula von der Leyen, the German President of the Commission, announced in March, 2021, an EU 'Digital Green Certificate' – green again – to track the public's 'Covid status'. The passport sting is worldwide and the Far East followed the same pattern with South Korea ruling that only those with 'vaccination' passports – again the *green* pass – would be able to 'return to their daily lives'.

Bill Gates has been preparing for this 'passport' with other Cult operatives for years and beyond the paper version is a Gates-funded 'digital tattoo' to identify who has been vaccinated and who hasn't. The 'tattoo' is reported to include a substance which is externally readable to confirm who has been vaccinated. This is a bio-luminous light-generating enzyme (think fireflies) called … *Luciferase*. Yes, named after the Cult 'god' Lucifer the 'light bringer' of whom more to come. Gates said he funded the readable tattoo to ensure children in the developing world were vaccinated and no one was missed out. He cares so much about poor kids as we know. This was just the cover story to develop a vaccine tagging system for everyone on the planet. Gates has been funding the ID2020 'alliance' to do just that in league with other lovely people at Microsoft, GAVI, the Rockefeller Foundation, Accenture and IDEO.org. He said in interviews in March, 2020, before any 'vaccine' publicly existed, that the world must have a globalised digital certificate to track the 'virus' and who had been vaccinated. Gates knew from the start that the mRNA vaccines were coming and when they would come and that the plan was to tag the 'vaccinated' to marginalise the intelligent and stop them doing anything including travel. Evil just doesn't suffice. Gates was exposed for offering a $10 million bribe to the Nigerian House of Representatives to invoke compulsory 'Covid' vaccination of all Nigerians. Sara Cunial, a member of the Italian Parliament, called Gates a 'vaccine criminal'. She urged the Italian President to hand him over to the International Criminal Court for crimes against

humanity and condemned his plans to 'chip the human race' through ID2020.

You know it's a long-planned agenda when war criminal and Cult gofer Tony Blair is on the case. With the scale of arrogance only someone as dark as Blair can muster he said: 'Vaccination in the end is going to be your route to liberty.' Blair is a disgusting piece of work and he confirms that again. The media has given a lot of coverage to a bloke called Charlie Mullins, founder of London's biggest independent plumbing company, Pimlico Plumbers, who has said he won't employ anyone who has not been vaccinated or have them go to any home where people are not vaccinated. He said that if he had his way no one would be allowed to walk the streets if they have not been vaccinated. Gates was cheering at the time while I was alerting the white coats. The plan is that people will qualify for 'passports' for having the first two doses and then to keep it they will have to have all the follow ups and new ones for invented 'variants' until human genetics is transformed and many are dead who can't adjust to the changes. Hollywood celebrities – the usual propaganda stunt – are promoting something called the WELL Health-Safety Rating to verify that a building or space has 'taken the necessary steps to prioritize the health and safety of their staff, visitors and other stakeholders'. They included Lady Gaga, Jennifer Lopez, Michael B. Jordan, Robert DeNiro, Venus Williams, Wolfgang Puck, Deepak Chopra and 17th Surgeon General Richard Carmona. Yawn. WELL Health-Safety has big connections with China. Parent company Delos is headed by former Goldman Sachs partner Paul Scialla. This is another example – and we will see so many others – of using the excuse of 'health' to dictate the lives and activities of the population. I guess one confirmation of the 'safety' of buildings is that only 'vaccinated' people can go in, right?

Electronic concentration camps

I wrote decades ago about the plans to restrict travel and here we are for those who refuse to bow to tyranny. This can be achieved in one go with air travel if the aviation industry makes a blanket decree.

The ‘vaccine’ and guaranteed income are designed to be part of a global version of China’s social credit system which tracks behaviour 24/7 and awards or deletes ‘credits’ based on whether your behaviour is supported by the state or not. I mean your entire lifestyle – what you do, eat, say, everything. Once your credit score falls below a certain level consequences kick in. In China tens of millions have been denied travel by air and train because of this. All the locations and activities denied to refusers by the ‘vaccine’ passports will be included in one big mass ban on doing almost anything for those that don’t bow their head to government. It’s beyond fascist and a new term is required to describe its extremes – I guess fascist technocracy will have to do. The way the Chinese system of technological – technocratic – control is sweeping the West can be seen in the Los Angeles school system and is planned to be expanded worldwide. Every child is required to have a ‘Covid’-tracking app scanned daily before they can enter the classroom. The so-called Daily Pass tracking system is produced by Gates’ Microsoft which I’m sure will shock you rigid. The pass will be scanned using a barcode (one step from an inside-the-body barcode) and the information will include health checks, ‘Covid’ tests and vaccinations. Entry codes are for one specific building only and access will only be allowed if a student or teacher has a negative test with a test not testing for the ‘virus’, has no symptoms of anything alleged to be related to ‘Covid’ (symptoms from a range of other illness), and has a temperature under 100 degrees. No barcode, no entry, is planned to be the case for everywhere and not only schools.

Kids are being psychologically prepared to accept this as ‘normal’ their whole life which is why what they can impose in schools is so important to the Cult and its gofers. Long-time American freedom campaigner John Whitehead of the Rutherford Institute was not exaggerating when he said: ‘Databit by databit, we are building our own electronic concentration camps.’ Canada under its Cult gofer prime minister Justin Trudeau has taken a major step towards the real thing with people interned against their will if they test positive with a test not testing for the ‘virus’ when they arrive at a Canadian

airport. They are jailed in internment hotels often without food or water for long periods and with many doors failing to lock there have been sexual assaults. The interned are being charged sometimes $2,000 for the privilege of being abused in this way. Trudeau is fully on board with the Cult and says the 'Covid pandemic' has provided an opportunity for a global 'reset' to permanently change Western civilisation. His number two, Deputy Prime Minister Chrystia Freeland, is a trustee of the World Economic Forum and a Rhodes Scholar. The Trudeau family have long been servants of the Cult. See *The Biggest Secret* and Cathy O'Brien's book *Trance-Formation of America* for the horrific background to Trudeau's father Pierre Trudeau another Canadian prime minister. Hide your fascism behind the façade of a heart-on-the-sleeve liberal. It's a well-honed Cult technique.

What can the 'vaccine' *really* do?

We have a 'virus' never shown to exist and 'variants' of the 'virus' that have also never been shown to exist except, like the 'original', as computer-generated fictions. Even if you believe there's a 'virus' the 'case' to 'death' rate is in the region of 0.23 to 0.15 percent and those 'deaths' are concentrated among the very old around the same average age that people die anyway. In response to this lack of threat (in truth none) psychopaths and idiots, knowingly and unknowingly answering to Gates and the Cult, are seeking to 'vaccinate' every man, woman and child on Planet Earth. Clearly the 'vaccine' is not about 'Covid' – none of this ever has been. So what is it all about *really*? Why the desperation to infuse genetically-manipulating synthetic material into everyone through mRNA fraudulent 'vaccines' with the intent of doing this over and over with the excuses of 'variants' and other 'virus' inventions? Dr Sherri Tenpenny, an osteopathic medical doctor in the United States, has made herself an expert on vaccines and their effects as a vehement campaigner against their use. Tenpenny was board certified in emergency medicine, the director of a level two trauma centre for 12 years, and moved to Cleveland in 1996 to start an integrative

medicine practice which has treated patients from all 50 states and some 17 other countries. Weaning people off pharmaceutical drugs is a speciality.

She became interested in the consequences of vaccines after attending a meeting at the National Vaccine Information Center in Washington DC in 2000 where she 'sat through four days of listening to medical doctors and scientists and lawyers and parents of vaccine injured kids' and asked: 'What's going on?' She had never been vaccinated and never got ill while her father was given a list of vaccines to be in the military and was 'sick his entire life'. The experience added to her questions and she began to examine vaccine documents from the Centers for Disease Control (CDC). After reading the first one, the 1998 version of *The General Recommendations of Vaccination*, she thought: 'This is it?' The document was poorly written and bad science and Tenpenny began 20 years of research into vaccines that continues to this day. She began her research into 'Covid vaccines' in March, 2020, and she describes them as 'deadly'. For many, as we have seen, they already have been. Tenpenny said that in the first 30 days of the 'vaccine' rollout in the United States there had been more than 40,000 adverse events reported to the vaccine adverse event database. A document had been delivered to her the day before that was 172 pages long. 'We have over 40,000 adverse events; we have over 3,100 cases of [potentially deadly] anaphylactic shock; we have over 5,000 neurological reactions.' Effects ranged from headaches to numbness, dizziness and vertigo, to losing feeling in hands or feet and paraesthesia which is when limbs 'fall asleep' and people have the sensation of insects crawling underneath their skin. All this happened in the first 30 days and remember that only about *ten percent* (or far less) of adverse reactions and vaccine-related deaths are estimated to be officially reported. Tenpenny said:

> So can you think of one single product in any industry, any industry, for as long as products have been made on the planet that within 30 days we have 40,000 people complaining of side effects that not only is still on the market but … we've got paid actors telling us how great

they are for getting their vaccine. We're offering people $500 if they will just get their vaccine and we've got nurses and doctors going; 'I got the vaccine, I got the vaccine'.

Tenpenny said they were not going to be 'happy dancing folks' when they began to suffer Bell's palsy (facial paralysis), neuropathies, cardiac arrhythmias and autoimmune reactions that kill through a blood disorder. 'They're not going to be so happy, happy then, but we're never going to see pictures of those people' she said. Tenpenny described the 'vaccine' as 'a well-designed killing tool'.

No off-switch

Bad as the initial consequences had been Tenpenny said it would be maybe 14 months before we began to see the 'full ravage' of what is going to happen to the 'Covid vaccinated' with full-out consequences taking anything between two years and 20 years to show. You can understand why when you consider that variations of the 'Covid vaccine' use mRNA (messenger RNA) to in theory activate the immune system to produce protective antibodies without using the actual 'virus'. How can they when it's a computer program and they've never isolated what they claim is the 'real thing'? Instead they use *synthetic* mRNA. They are inoculating synthetic material into the body which through a technique known as the Trojan horse is absorbed into cells to change the nature of DNA. Human DNA is changed by an infusion of messenger RNA and with each new 'vaccine' of this type it is changed even more. Say so and you are banned by Cult Internet platforms. The contempt the contemptuous Mark Zuckerberg has for the truth and human health can be seen in an internal Facebook video leaked to the Project Veritas investigative team in which he said of the 'Covid vaccines': '… I share some caution on this because we just don't know the long term side-effects of basically modifying people's DNA and RNA.' At the same time this disgusting man's Facebook was censoring and banning anyone saying exactly the same. He must go before a Nuremberg trial for crimes against humanity when he *knows* that he

is censoring legitimate concerns and denying the right of informed consent on behalf of the Cult that owns him. People have been killed and damaged by the very 'vaccination' technique he cast doubt on himself when they may not have had the 'vaccine' with access to information that he denied them. The plan is to have at least annual 'Covid vaccinations', add others to deal with invented 'variants', and change all other vaccines into the mRNA system. Pfizer executives told shareholders at a virtual Barclays Global Healthcare Conference in March, 2021, that the public may need a third dose of 'Covid vaccine', plus regular yearly boosters and the company planned to hike prices to milk the profits in a 'significant opportunity for our vaccine'. These are the professional liars, cheats and opportunists who are telling you their 'vaccine' is safe. Given this volume of mRNA planned to be infused into the human body and its ability to then replicate we will have a transformation of human genetics from biological to synthetic biological – exactly the long-time Cult plan for reasons we'll see – and many will die. Sherri Tenpenny said of this replication:

> It's like having an on-button but no off-button and that whole mechanism … they actually give it a name and they call it the Trojan horse mechanism, because it allows that [synthetic] virus and that piece of that [synthetic] virus to get inside of your cells, start to replicate and even get inserted into other parts of your DNA as a Trojan-horse.

Ask the overwhelming majority of people who have the 'vaccine' what they know about the contents and what they do and they would reply: 'The government says it will stop me getting the virus.' Governments give that false impression on purpose to increase take-up. You can read Sherri Tenpenny's detailed analysis of the health consequences in her blog at Vaxxter.com, but in summary these are some of them. She highlights the statement by Bill Gates about how human beings can become their own 'vaccine manufacturing machine'. The man is insane. ['Vaccine'-generated] 'antibodies' carry synthetic messenger RNA into the cells and the damage starts, Tenpenny contends, and she says that lungs can be adversely affected through varying degrees of pus and bleeding which

obviously affects breathing and would be dubbed 'Covid-19'. Even more sinister was the impact of 'antibodies' on macrophages, a white blood cell of the immune system. They consist of Type 1 and Type 2 which have very different functions. She said Type 1 are 'hyper-vigilant' white blood cells which 'gobble up' bacteria etc. However, in doing so, this could cause inflammation and in extreme circumstances be fatal. She says these affects are mitigated by Type 2 macrophages which kick in to calm down the system and stop it going rogue. They clear up dead tissue debris and reduce inflammation that the Type 1 'fire crews' have caused. Type 1 kills the infection and Type 2 heals the damage, she says. This is her punchline with regard to 'Covid vaccinations': She says that mRNA 'antibodies' block Type 2 macrophages by attaching to them and deactivating them. This meant that when the Type 1 response was triggered by infection there was nothing to stop that getting out of hand by calming everything down. There's an on-switch, but no off-switch, she says. What follows can be 'over and out, see you when I see you'.

Genetic suicide

Tenpenny also highlights the potential for autoimmune disease – the body attacking itself – which has been associated with vaccines since they first appeared. Infusing a synthetic foreign substance into cells could cause the immune system to react in a panic believing that the body is being overwhelmed by an invader (it is) and the consequences can again be fatal. There is an autoimmune response known as a 'cytokine storm' which I have likened to a homeowner panicked by an intruder and picking up a gun to shoot randomly in all directions before turning the fire on himself. The immune system unleashes a storm of inflammatory response called cytokines to a threat and the body commits hara-kiri. The lesson is that you mess with the body's immune response at your peril and these 'vaccines' seriously – fundamentally – mess with immune response. Tenpenny refers to a consequence called anaphylactic shock which is a severe and highly dangerous allergic reaction when the immune system

floods the body with chemicals. She gives the example of having a bee sting which primes the immune system and makes it sensitive to those chemicals. When people are stung again maybe years later the immune response can be so powerful that it leads to anaphylactic shock. Tenpenny relates this 'shock' with regard to the 'Covid vaccine' to something called polyethylene glycol or PEG. Enormous numbers of people have become sensitive to this over decades of use in a whole range of products and processes including food, drink, skin creams and 'medicine'. Studies have claimed that some 72 percent of people have antibodies triggered by PEG compared with two percent in the 1960s and allergic hypersensitive reactions to this become a gathering cause for concern. Tenpenny points out that the 'mRNA vaccine' is coated in a 'bubble' of polyethylene glycol which has the potential to cause anaphylactic shock through immune sensitivity. Many reports have appeared of people reacting this way after having the 'Covid vaccine'. What do we think is going to happen as humanity has more and more of these 'vaccines'? Tenpenny said: 'All these pictures we have seen with people with these rashes … these weepy rashes, big reactions on their arms and things like that – it's an acute allergic reaction most likely to the polyethylene glycol that you've been previously primed and sensitised to.'

Those who have not studied the conspiracy and its perpetrators at length might think that making the population sensitive to PEG and then putting it in these 'vaccines' is just a coincidence. It is not. It is instead testament to how carefully and coldly-planned current events have been and the scale of the conspiracy we are dealing with. Tenpenny further explains that the 'vaccine' mRNA procedure can breach the blood-brain barrier which protects the brain from toxins and other crap that will cause malfunction. In this case they could make two proteins corrupt brain function to cause Amyotrophic lateral sclerosis (ALS) , a progressive nervous system disease leading to loss of muscle control, and frontal lobe degeneration – Alzheimer's and dementia. Immunologist J. Bart Classon published a paper connecting mRNA 'vaccines' to prion

disease which can lead to Alzheimer's and other forms of neurogenerative disease while others have pointed out the potential to affect the placenta in ways that make women infertile. This will become highly significant in the next chapter when I will discuss other aspects of this non-vaccine that relate to its nanotechnology and transmission from the injected to the uninjected.

Qualified in idiocy

Tenpenny describes how research has confirmed that these 'vaccine'-generated antibodies can interact with a range of other tissues in the body and attack many other organs including the lungs. 'This means that if you have a hundred people standing in front of you that all got this shot they could have a hundred different symptoms.' Anyone really think that Cult gofers like the Queen, Tony Blair, Christopher Whitty, Anthony Fauci, and all the other psychopaths have really had this 'vaccine' in the pictures we've seen? Not a bloody chance. Why don't doctors all tell us about all these dangers and consequences of the 'Covid vaccine'? Why instead do they encourage and pressure patients to have the shot? Don't let's think for a moment that doctors and medical staff can't be stupid, lazy, and psychopathic and that's without the financial incentives to give the jab. Tenpenny again:

> Some people are going to die from the vaccine directly but a large number of people are going to start to get horribly sick and get all kinds of autoimmune diseases 42 days to maybe a year out. What are they going to do, these stupid doctors who say; 'Good for you for getting that vaccine.' What are they going to say; 'Oh, it must be a mutant, we need to give an extra dose of that vaccine.'
>
> Because now the vaccine, instead of one dose or two doses we need three or four because the stupid physicians aren't taking the time to learn anything about it. If I can learn this sitting in my living room reading a 19 page paper and several others so can they. There's nothing special about me, I just take the time to do it.

Remember how Sara Kayat, the NHS and TV doctor, said that the 'Covid vaccine' would '100 percent prevent hospitalisation and death'. Doctors can be idiots like every other profession and they

should not be worshipped as infallible. They are not and far from it. Behind many medical and scientific 'experts' lies an uninformed prat trying to hide themselves from you although in the 'Covid' era many have failed to do so as with UK narrative-repeating 'TV doctor' Hilary Jones. Pushing back against the minority of proper doctors and scientists speaking out against the 'vaccine' has been the entire edifice of the Cult global state in the form of governments, medical systems, corporations, mainstream media, Silicon Valley, and an army of compliant doctors, medical staff and scientists willing to say anything for money and to enhance their careers by promoting the party line. If you do that you are an 'expert' and if you won't you are an 'anti-vaxxer' and 'Covidiot'. The pressure to be 'vaccinated' is incessant. We have even had reports claiming that the 'vaccine' can help cure cancer and Alzheimer's and make the lame walk. I am waiting for the announcement that it can bring you coffee in the morning and cook your tea. Just as the symptoms of 'Covid' seem to increase by the week so have the miracles of the 'vaccine'. American supermarket giant Kroger Co. offered nearly 500,000 employees in 35 states a $100 bonus for having the 'vaccine' while donut chain Krispy Kreme promised 'vaccinated' customers a free glazed donut every day for the rest of 2021. Have your DNA changed and you will get a doughnut although we might not have to give you them for long. Such offers and incentives confirm the desperation.

Perhaps the worse vaccine-stunt of them all was UK 'Health' Secretary Matt-the-prat Hancock on live TV after watching a clip of someone being 'vaccinated' when the roll-out began. Hancock faked tears so badly it was embarrassing. Brain-of-Britain Piers Morgan, the lockdown-supporting, 'vaccine' supporting, 'vaccine' passport-supporting, TV host played along with Hancock – 'You're quite emotional about that' he said in response to acting so atrocious it would have been called out at a school nativity which will presumably today include Mary and Jesus in masks, wise men keeping their camels six feet apart, and shepherds under tent arrest. System-serving Morgan tweeted this: 'Love the idea of covid vaccine passports for everywhere: flights, restaurants, clubs, football, gyms,

shops etc. It's time covid-denying, anti-vaxxer loonies had their bullsh*t bluff called & bar themselves from going anywhere that responsible citizens go.' If only I could aspire to his genius. To think that Morgan, who specialises in shouting over anyone he disagrees with, was lauded as a free speech hero when he lost his job after storming off the set of his live show like a child throwing his dolly out of the pram. If he is a free speech hero we are in real trouble. I have no idea what 'bullsh*t' means, by the way, the * throws me completely.

The Cult is desperate to infuse its synthetic DNA-changing concoction into everyone and has been using every lie, trick and intimidation to do so. The question of '*Why*?' we shall now address.

CHAPTER TEN

Human 2.0

I believe that at the end of the century the use of words and general educated opinion will have altered so much that one will be able to speak of machines thinking without expecting to be contradicted –
Alan Turing (1912-1954), the 'Father of artificial intelligence'

I have been exposing for decades the plan to transform the human body from a biological to a synthetic-biological state. The new human that I will call Human 2.0 is planned to be connected to artificial intelligence and a global AI 'Smart Grid' that would operate as one global system in which AI would control everything from your fridge to your heating system to your car to your mind. Humans would no longer be 'human', but post-human and sub-human, with their thinking and emotional processes replaced by AI.

What I said sounded crazy and beyond science fiction and I could understand that. To any balanced, rational, mind it *is* crazy. Today, however, that world is becoming reality and it puts the 'Covid vaccine' into its true context. Ray Kurzweil is the ultra-Zionist 'computer scientist, inventor and futurist' and co-founder of the Singularity University. Singularity refers to the merging of humans with machines or 'transhumanism'. Kurzweil has said humanity would be connected to the cyber 'cloud' in the period of the ever-recurring year of 2030:

Our thinking … will be a hybrid of biological and non-biological thinking … humans will be able to extend their limitations and 'think in the cloud' … We're going to put gateways to the

cloud in our brains ... We're going to gradually merge and enhance ourselves ... In my view, that's the nature of being human – we transcend our limitations. As the technology becomes vastly superior to what we are then the small proportion that is still human gets smaller and smaller and smaller until it's just utterly negligible.

They are trying to sell this end-of-humanity-as-we-know-it as the next stage of 'evolution' when we become super-human and 'like the gods'. They are lying to you. Shocked, eh? The population, and again especially the young, have been manipulated into addiction to technologies designed to enslave them for life. First they induced an addiction to smartphones (holdables); next they moved to technology on the body (wearables); and then began the invasion of the body (implantables). I warned way back about the plan for microchipped people and we are now entering that era. We should not be diverted into thinking that this refers only to chips we can see. Most important are the nanochips known as smart dust, neural dust and nanobots which are far too small to be seen by the human eye. Nanotechnology is everywhere, increasingly in food products, and released into the atmosphere by the geoengineering of the skies funded by Bill Gates to 'shut out the Sun' and 'save the planet from global warming'. Gates has been funding a project to spray millions of tonnes of chalk (calcium carbonate) into the stratosphere over Sweden to 'dim the Sun' and cool the Earth. Scientists warned the move could be disastrous for weather systems in ways no one can predict and opposition led to the Swedish space agency announcing that the 'experiment' would not be happening as planned in the summer of 2021; but it shows where the Cult is going with dimming the impact of the Sun and there's an associated plan to change the planet's atmosphere. Who gives psychopath Gates the right to dictate to the entire human race and dismantle planetary systems? The world will not be safe while this man is at large.

The global warming hoax has made the Sun, like the gas of life, something to fear when both are essential to good health and human survival (more inversion). The body transforms sunlight into vital vitamin D through a process involving … *cholesterol*. This is the cholesterol we are also told to fear. We are urged to take Big Pharma

statin drugs to reduce cholesterol and it's all systematic. Reducing cholesterol means reducing vitamin D uptake with all the multiple health problems that will cause. At least if you take statins long term it saves the government from having to pay you a pension. The delivery system to block sunlight is widely referred to as chemtrails although these have a much deeper agenda, too. They appear at first to be contrails or condensation trails streaming from aircraft into cold air at high altitudes. Contrails disperse very quickly while chemtrails do not and spread out across the sky before eventually their content falls to earth. Many times I have watched aircraft cross-cross a clear blue sky releasing chemtrails until it looks like a cloudy day. Chemtrails contain many things harmful to humans and the natural world including toxic heavy metals, aluminium (see Alzheimer's) and nanotechnology. Ray Kurzweil reveals the reason without actually saying so: 'Nanobots will infuse all the matter around us with information. Rocks, trees, everything will become these intelligent creatures.' How do you deliver that? *From the sky*. Self-replicating nanobots would connect everything to the Smart Grid. The phenomenon of Morgellons disease began in the chemtrail era and the correlation has led to it being dubbed the 'chemtrail disease'. Self-replicating fibres appear in the body that can be pulled out through the skin. Morgellons fibres continue to grow outside the body and have a form of artificial intelligence. I cover this at greater length in *Phantom Self*.

'Vaccine' operating system

'Covid vaccines' with their self-replicating synthetic material are also designed to make the connection between humanity and Kurzweil's 'cloud'. American doctor and dedicated campaigner for truth, Carrie Madej, an Internal Medicine Specialist in Georgia with more than 20 years medical experience, has highlighted the nanotechnology aspect of the fake 'vaccines'. She explains how one of the components in at least the Moderna and Pfizer synthetic potions are 'lipid nanoparticles' which are 'like little tiny computer bits' – a 'sci-fi substance' known as nanobots and hydrogel which can be 'triggered

at any moment to deliver its payload' and act as 'biosensors'. The synthetic substance had 'the ability to accumulate data from your body like your breathing, your respiration, thoughts and emotions, all kind of things' and each syringe could carry a *million* nanobots:

This substance because it's like little bits of computers in your body, crazy, but it's true, it can do that, [and] obviously has the ability to act through Wi-Fi. It can receive and transmit energy, messages, frequencies or impulses. That issue has never been addressed by these companies. What does that do to the human?

Just imagine getting this substance in you and it can react to things all around you, the 5G, your smart device, your phones, what is happening with that? What if something is triggering it, too, like an impulse, a frequency? We have something completely foreign in the human body.

Madej said her research revealed that electromagnetic (EMF) frequencies emitted by phones and other devices had increased dramatically in the same period of the 'vaccine' rollout and she was seeing more people with radiation problems as 5G and other electromagnetic technology was expanded and introduced to schools and hospitals. She said she was 'floored with the EMF coming off' the devices she checked. All this makes total sense and syncs with my own work of decades when you think that Moderna refers in documents to its mRNA 'vaccine' as an 'operating system':

Recognizing the broad potential of mRNA science, we set out to create an mRNA technology platform that functions very much like an operating system on a computer. It is designed so that it can plug and play interchangeably with different programs. In our case, the 'program' or 'app' is our mRNA drug – the unique mRNA sequence that codes for a protein …

… Our MRNA Medicines – 'The 'Software Of Life': When we have a concept for a new mRNA medicine and begin research, fundamental components are already in place. Generally, the only thing that changes from one potential mRNA medicine to another is the coding region – the actual genetic code that instructs ribosomes to make protein. Utilizing these instruction sets gives our investigational mRNA medicines a software-like quality. We also have the ability to combine different mRNA sequences encoding for different proteins in a single mRNA investigational medicine.

Who needs a real 'virus' when you can create a computer version to justify infusing your operating system into the entire human race on the road to making living, breathing people into cyborgs? What is missed with the 'vaccines' is the *digital* connection between synthetic material and the body that I highlighted earlier with the study that hacked a computer with human DNA. On one level the body is digital, based on mathematical codes, and I'll have more about that in the next chapter. Those who ridiculously claim that mRNA 'vaccines' are not designed to change human genetics should explain the words of Dr Tal Zaks, chief medical officer at Moderna, in a 2017 TED talk. He said that over the last 30 years 'we've been living this phenomenal digital scientific revolution, and I'm here today to tell you, that we are actually *hacking the software of life*, and that it's changing the way we think about prevention and treatment of disease':

In every cell there's this thing called messenger RNA, or mRNA for short, that transmits the critical information from the DNA in our genes to the protein, which is really the stuff we're all made out of. This is the critical information that determines what the cell will do. So we think about it as an operating system. So if you could change that, if you could introduce a line of code, or change a line of code, it turns out, that has profound implications for everything, from the flu to cancer.

Zaks should more accurately have said that this has profound implications for the human genetic code and the nature of DNA. Communications within the body go both ways and not only one. But, hey, no, the 'Covid vaccine' will not affect your genetics. Cult fact-checkers say so even though the man who helped to develop the mRNA technique says that it does. Zaks said in 2017:

If you think about what it is we're trying to do. We've taken information and our understanding of that information and how that information is transmitted in a cell, and we've taken our understanding of medicine and how to make drugs, and we're fusing the two. We think of it as information therapy.

I have been writing for decades that the body is an information field communicating with itself and the wider world. This is why

radiation which is information can change the information field of body and mind through phenomena like 5G and change their nature and function. 'Information therapy' means to change the body's information field and change the way it operates. DNA is a receiver-transmitter of information and can be mutated by information like mRNA synthetic messaging. Technology to do this has been ready and waiting in the underground bases and other secret projects to be rolled out when the 'Covid' hoax was played. 'Trials' of such short and irrelevant duration were only for public consumption. When they say the 'vaccine' is 'experimental' that is not true. It may appear to be 'experimental' to those who don't know what's going on, but the trials have already been done to ensure the Cult gets the result it desires. Zaks said that it took decades to sequence the human genome, completed in 2003, but now they could do it in a week. By 'they' he means scientists operating in the public domain. In the secret projects they were sequencing the genome in a week long before even 2003.

Deluge of mRNA

Highly significantly the Moderna document says the guiding premise is that if using mRNA as a medicine works for one disease then it should work for many diseases. They were leveraging the flexibility afforded by their platform and the fundamental role mRNA plays in protein synthesis to pursue mRNA medicines for a broad spectrum of diseases. Moderna is confirming what I was saying through 2020 that multiple 'vaccines' were planned for 'Covid' (and later invented 'variants') and that previous vaccines would be converted to the mRNA system to infuse the body with massive amounts of genetically-manipulating synthetic material to secure a transformation to a synthetic-biological state. The 'vaccines' are designed to kill stunning numbers as part of the long-exposed Cult depopulation agenda and transform the rest. Given this is the goal you can appreciate why there is such hysterical demand for every human to be 'vaccinated' for an alleged 'disease' that has an estimated 'infection' to 'death' ratio of 0.23-0.15 percent. As I write

children are being given the 'vaccine' in trials (their parents are a disgrace) and ever-younger people are being offered the vaccine for a 'virus' that even if you believe it exists has virtually zero chance of harming them. Horrific effects of the 'trials' on a 12-year-old girl were revealed by a family member to be serious brain and gastric problems that included a bowel obstruction and the inability to swallow liquids or solids. She was unable to eat or drink without throwing up, had extreme pain in her back, neck and abdomen, and was paralysed from the waist down which stopped her urinating unaided. When the girl was first taken to hospital doctors said it was all in her mind. She was signed up for the 'trial' by her parents for whom no words suffice. None of this 'Covid vaccine' insanity makes any sense unless you see what the 'vaccine' really is – a body-changer. Synthetic biology or 'SynBio' is a fast-emerging and expanding scientific discipline which includes everything from genetic and molecular engineering to electrical and computer engineering. Synthetic biology is defined in these ways:

- A multidisciplinary area of research that seeks to create new biological parts, devices, and systems, or to redesign systems that are already found in nature.

- The use of a mixture of physical engineering and genetic engineering to create new (and therefore synthetic) life forms.

- An emerging field of research that aims to combine the knowledge and methods of biology, engineering and related disciplines in the design of chemically-synthesized DNA to create organisms with novel or enhanced characteristics and traits (synthetic organisms including humans).

We now have synthetic blood, skin, organs and limbs being developed along with synthetic body parts produced by 3D printers. These are all elements of the synthetic human programme and this comment by Kurzweil's co-founder of the Singularity University,

Peter Diamandis, can be seen in a whole new light with the 'Covid' hoax and the sanctions against those that refuse the 'vaccine':

Anybody who is going to be resisting the progress forward [to transhumanism] is going to be resisting evolution and, fundamentally, they will die out. It's not a matter of whether it's good or bad. It's going to happen.

'Resisting evolution'? What absolute bollocks. The arrogance of these people is without limit. His 'it's going to happen' mantra is another way of saying 'resistance is futile' to break the spirit of those pushing back and we must not fall for it. Getting this genetically-transforming 'vaccine' into everyone is crucial to the Cult plan for total control and the desperation to achieve that is clear for anyone to see. Vaccine passports are a major factor in this and they, too, are a form of resistance is futile. It's NOT. The paper funded by the Rockefeller Foundation for the 2013 'health conference' in China said:

We will interact more with artificial intelligence. The use of robotics, bio-engineering to augment human functioning is already well underway and will advance. Re-engineering of humans into potentially separate and unequal forms through genetic engineering or mixed human-robots raises debates on ethics and equality.

A new demography is projected to emerge after 2030 [that year again] of technologies (robotics, genetic engineering, nanotechnology) producing robots, engineered organisms, 'nanobots' and artificial intelligence (AI) that can self-replicate. Debates will grow on the implications of an impending reality of human designed life.

What is happening today is so long planned. The world army enforcing the will of the world government is intended to be a robot army, not a human one. Today's military and its technologically 'enhanced' troops, pilotless planes and driverless vehicles are just stepping stones to that end. Human soldiers are used as Cult fodder and its time they woke up to that and worked for the freedom of the population instead of their own destruction and their family's destruction – the same with the police. Join us and let's sort this out. The phenomenon of enforce my own destruction is widespread in the 'Covid' era with Woker 'luvvies' in the acting and entertainment

industries supporting 'Covid' rules which have destroyed their profession and the same with those among the public who put signs on the doors of their businesses 'closed due to Covid – stay safe' when many will never reopen. It's a form of masochism and most certainly insanity.

Transgender = transhumanism

When something explodes out of nowhere and is suddenly everywhere it is always the Cult agenda and so it is with the tidal wave of claims and demands that have infiltrated every aspect of society under the heading of 'transgenderism'. The term 'trans' is so 'in' and this is the dictionary definition:

A prefix meaning 'across', 'through', occurring … in loanwords from Latin, used in particular for denoting movement or conveyance from place to place (transfer; transmit; transplant) or complete change (transform; transmute), or to form adjectives meaning 'crossing', 'on the other side of', or 'going beyond' the place named (transmontane; transnational; trans-Siberian).

Transgender means to go beyond gender and transhuman means to go beyond human. Both are aspects of the Cult plan to transform the human body to a synthetic state with *no gender*. Human 2.0 is not designed to procreate and would be produced technologically with no need for parents. The new human would mean the end of parents and so men, and increasingly women, are being targeted for the deletion of their rights and status. Parental rights are disappearing at an ever-quickening speed for the same reason. The new human would have no need for men or women when there is no procreation and no gender. Perhaps the transgender movement that appears to be in a permanent state of frenzy might now contemplate on how it is being used. This was never about transgender rights which are only the interim excuse for confusing gender, particularly in the young, on the road to *fusing* gender. Transgender activism is not an end; it is a *means* to an end. We see again the technique of creative destruction in which you destroy the status quo to 'build back better' in the form that you want. The gender status quo had to be

destroyed by persuading the Cult-created Woke mentality to believe that you can have 100 genders or more. A programme for 9 to 12 year olds produced by the Cult-owned BBC promoted the 100 genders narrative. The very idea may be the most monumental nonsense, but it is not what is true that counts, only what you can make people *believe* is true. Once the gender of 2 + 2 = 4 has been dismantled through indoctrination, intimidation and 2 + 2 = 5 then the new no-gender normal can take its place with Human 2.0. Aldous Huxley revealed the plan in his prophetic *Brave New World* in 1932:

> Natural reproduction has been done away with and children are created, decanted', and raised in 'hatcheries and conditioning centres'. From birth, people are genetically designed to fit into one of five castes, which are further split into 'Plus' and 'Minus' members and designed to fulfil predetermined positions within the social and economic strata of the World State.

How could Huxley know this in 1932? For the same reason George Orwell knew about the Big Brother state in 1948, Cult insiders I have quoted knew about it in 1969, and I have known about it since the early 1990s. If you are connected to the Cult or you work your balls off to uncover the plan you can predict the future. The process is simple. If there is a plan for the world and nothing intervenes to stop it then it will happen. Thus if you communicate the plan ahead of time you are perceived to have predicted the future, but you haven't. You have revealed the plan which without intervention will become the human future. The whole reason I have done what I have is to alert enough people to inspire an intervention and maybe at last that time has come with the Cult and its intentions now so obvious to anyone with a brain in working order.

The future is here

Technological wombs that Huxley described to replace parent procreation are already being developed and they are only the projects we know about in the public arena. Israeli scientists told *The Times of Israel* in March, 2021, that they have grown 250-cell embryos

into mouse foetuses with fully formed organs using artificial wombs in a development they say could pave the way for gestating humans outside the womb. Professor Jacob Hanna of the Weizmann Institute of Science said:

We took mouse embryos from the mother at day five of development, when they are just of 250 cells, and had them in the incubator from day five until day 11, by which point they had grown all their organs.

By day 11 they make their own blood and have a beating heart, a fully developed brain. Anybody would look at them and say, 'this is clearly a mouse foetus with all the characteristics of a mouse.' It's gone from being a ball of cells to being an advanced foetus.

A special liquid is used to nourish embryo cells in a laboratory dish and they float on the liquid to duplicate the first stage of embryonic development. The incubator creates all the right conditions for its development, Hanna said. The liquid gives the embryo 'all the nutrients, hormones and sugars they need' along with a custom-made electronic incubator which controls gas concentration, pressure and temperature. The cutting-edge in the underground bases and other secret locations will be light years ahead of that, however, and this was reported by the London *Guardian* in 2017:

We are approaching a biotechnological breakthrough. Ectogenesis, the invention of a complete external womb, could completely change the nature of human reproduction. In April this year, researchers at the Children's Hospital of Philadelphia announced their development of an artificial womb.

The article was headed 'Artificial wombs could soon be a reality. What will this mean for women?' What would it mean for children is an even bigger question. No mother to bond with only a machine in preparation for a life of soulless interaction and control in a world governed by machines (see the *Matrix* movies). Now observe the calculated manipulations of the 'Covid' hoax as human interaction and warmth has been curtailed by distancing, isolation and fear with people communicating via machines on a scale never seen before.

These are all dots in the same picture as are all the personal assistants, gadgets and children's toys through which kids and adults communicate with AI as if it is human. The AI 'voice' on Sat-Nav should be included. All these things are psychological preparation for the Cult endgame. Before you can make a physical connection with AI you have to make a psychological connection and that is what people are being conditioned to do with this ever gathering human-AI interaction. Movies and TV programmes depicting the transhuman, robot dystopia relate to a phenomenon known as 'pre-emptive programming' in which the world that is planned is portrayed everywhere in movies, TV and advertising. This is conditioning the conscious and subconscious mind to become familiar with the planned reality to dilute resistance when it happens for real. What would have been a shock such is the change is made less so. We have young children put on the road to transgender transition surgery with puberty blocking drugs at an age when they could never be able to make those life-changing decisions.

Rachel Levine, a professor of paediatrics and psychiatry who believes in treating children this way, became America's highest-ranked openly-transgender official when she was confirmed as US Assistant Secretary at the Department of Health and Human Services after being nominated by Joe Biden (the Cult). Activists and governments press for laws to deny parents a say in their children's transition process so the kids can be isolated and manipulated into agreeing to irreversible medical procedures. A Canadian father Robert Hoogland was denied bail by the Vancouver Supreme Court in 2021 and remained in jail for breaching a court order that he stay silent over his young teenage daughter, a minor, who was being offered life-changing hormone therapy without parental consent. At the age of 12 the girl's 'school counsellor' said she may be transgender, referred her to a doctor and told the school to treat her like a boy. This is another example of state-serving schools imposing ever more control over children's lives while parents have ever less.

Contemptible and extreme child abuse is happening all over the world as the Cult gender-fusion operation goes into warp-speed.

Why the war on men – and now women?

The question about what artificial wombs mean for women should rightly be asked. The answer can be seen in the deletion of women's rights involving sport, changing rooms, toilets and status in favour of people in male bodies claiming to identify as women. I can identify as a mountain climber, but it doesn't mean I can climb a mountain any more than a biological man can be a biological woman. To believe so is a triumph of belief over factual reality which is the very perceptual basis of everything Woke. Women's sport is being destroyed by allowing those with male bodies who say they identify as female to 'compete' with girls and women. Male body 'women' dominate 'women's' competition with their greater muscle mass, bone density, strength and speed. With that disadvantage sport for women loses all meaning. To put this in perspective nearly 300 American high school boys can run faster than the quickest woman sprinter in the world. Women are seeing their previously protected spaces invaded by male bodies simply because they claim to identify as women. That's all they need to do to access all women's spaces and activities under the Biden 'Equality Act' that destroys equality for women with the usual Orwellian Woke inversion. Male sex offenders have already committed rapes in women's prisons after claiming to identify as women to get them transferred. Does this not matter to the Woke 'equality' hypocrites? Not in the least. What matters to Cult manipulators and funders behind transgender activists is to advance gender fusion on the way to the no-gender 'human'. When you are seeking to impose transparent nonsense like this, or the 'Covid' hoax, the only way the nonsense can prevail is through censorship and intimidation of dissenters, deletion of factual information, and programming of the unquestioning, bewildered and naive. You don't have to scan the world for long to see that all these things are happening.

Many women's rights organisations have realised that rights and status which took such a long time to secure are being eroded and that it is systematic. Kara Dansky of the global Women's Human Rights Campaign said that Biden's transgender executive order immediately he took office, subsequent orders, and Equality Act legislation that followed 'seek to erase women and girls in the law as a category'. *Exactly*. I said during the long ago-started war on men (in which many women play a crucial part) that this was going to turn into a war on them. The Cult is phasing out *both* male and female genders. To get away with that they are brought into conflict so they are busy fighting each other while the Cult completes the job with no unity of response. Unity, people, *unity*. We need unity everywhere. Transgender is the only show in town as the big step towards the no-gender human. It's not about rights for transgender people and never has been. Woke political correctness is deleting words relating to genders to the same end. Wokers believe this is to be 'inclusive' when the opposite is true. They are deleting words describing gender because gender *itself* is being deleted by Human 2.0. Terms like 'man', 'woman', 'mother' and 'father' are being deleted in the universities and other institutions to be replaced by the *no*-gender, not trans-gender, 'individuals' and 'guardians'. Women's rights campaigner Maria Keffler of Partners for Ethical Care said: 'Children are being taught from kindergarten upward that some boys have a vagina, some girls have a penis, and that kids can be any gender they want to be.' Do we really believe that suddenly countries all over the world at the same time had the idea of having drag queens go into schools or read transgender stories to very young children in the local library? It's coldly-calculated confusion of gender on the way to the fusion of gender. Suzanne Vierling, a psychologist from Southern California, made another important point:

Yesterday's slave woman who endured gynecological medical experiments is today's girl-child being butchered in a booming gender-transitioning sector. Ovaries removed, pushing her into menopause and osteoporosis, uncharted territory, and parents' rights and authority decimated.

The erosion of parental rights is a common theme in line with the Cult plans to erase the very concept of parents and 'ovaries removed, pushing her into menopause' means what? Those born female lose the ability to have children – another way to discontinue humanity as we know it.

Eliminating Human 1.0 (before our very eyes)

To pave the way for Human 2.0 you must phase out Human 1.0. This is happening through plummeting sperm counts and making women infertile through an onslaught of chemicals, radiation (including smartphones in pockets of men) and mRNA 'vaccines'. Common agriculture pesticides are also having a devastating impact on human fertility. I have been tracking collapsing sperm counts in the books for a long time and in 2021 came a book by fertility scientist and reproductive epidemiologist Shanna Swan, *Count Down: How Our Modern World Is Threatening Sperm Counts, Altering Male and Female Reproductive Development and Imperiling the Future of the Human Race*. She reports how the global fertility rate dropped by *half* between 1960 and 2016 with America's birth rate 16 percent below where it needs to be to sustain the population. Women are experiencing declining egg quality, more miscarriages, and more couples suffer from infertility. Other findings were an increase in erectile dysfunction, infant boys developing more genital abnormalities, male problems with conception, and plunging levels of the male hormone testosterone which would explain why so many men have lost their backbone and masculinity. This has been very evident during the 'Covid' hoax when women have been prominent among the Pushbackers and big strapping blokes have bowed their heads, covered their faces with a nappy and quietly submitted. Mind control expert Cathy O'Brien also points to how global education introduced the concept of 'we're all winners' in sport and classrooms: 'Competition was defused, and it in turn defused a sense of fighting back.' This is another version of the 'equity' doctrine in which you drive down rather than raise up. What a contrast in Cult-controlled China with its global ambitions

where the government published plans in January, 2021, to 'cultivate masculinity' in boys from kindergarten through to high school in the face of a 'masculinity crisis'. A government adviser said boys would be soon become 'delicate, timid and effeminate' unless action was taken. Don't expect any similar policy in the targeted West. A 2006 study showed that a 65-year-old man in 2002 had testosterone levels *15 percent* lower than a 65-year-old man in 1987 while a 2020 study found a similar story with young adults and adolescents. Men are getting prescriptions for testosterone replacement therapy which causes an even greater drop in sperm count with up to 99 percent seeing sperm counts drop to zero during the treatment. More sperm is defective and malfunctioning with some having two heads or not pursuing an egg.

A class of *synthetic* chemicals known as phthalates are being blamed for the decline. These are found everywhere in plastics, shampoos, cosmetics, furniture, flame retardants, personal care products, pesticides, canned foods and even receipts. Why till receipts? Everyone touches them. Let no one delude themselves that all this is not systematic to advance the long-time agenda for human body transformation. Phthalates mimic hormones and disrupt the hormone balance causing testosterone to fall and genital birth defects in male infants. Animals and fish have been affected in the same way due to phthalates and other toxins in rivers. When fish turn gay or change sex through chemicals in rivers and streams it is a pointer to why there has been such an increase in gay people and the sexually confused. It doesn't matter to me what sexuality people choose to be, but if it's being affected by chemical pollution and consumption then we need to know. Does anyone really think that this is not connected to the transgender agenda, the war on men and the condemnation of male 'toxic masculinity'? You watch this being followed by 'toxic femininity'. It's already happening. When breastfeeding becomes 'chest-feeding', pregnant women become pregnant people along with all the other Woke claptrap you know that the world is going insane and there's a Cult scam in progress. Transgender activists are promoting the Cult agenda while Cult

billionaires support and fund the insanity as they laugh themselves to sleep at the sheer stupidity for which humans must be infamous in galaxies far, far away.

'Covid vaccines' and female infertility

We can now see why the 'vaccine' has been connected to potential infertility in women. Dr Michael Yeadon, former Vice President and Chief Scientific Advisor at Pfizer, and Dr Wolfgang Wodarg in Germany, filed a petition with the European Medicines Agency in December, 2020, urging them to stop trials for the Pfizer/BioNTech shot and all other mRNA trials until further studies had been done. They were particularly concerned about possible effects on fertility with 'vaccine'-produced antibodies attacking the protein Syncytin-1 which is responsible for developing the placenta. The result would be infertility 'of indefinite duration' in women who have the 'vaccine' with the placenta failing to form. Section 10.4.2 of the Pfizer/BioNTech trial protocol says that pregnant women or those who might become so should not have mRNA shots. Section 10.4 warns men taking mRNA shots to 'be abstinent from heterosexual intercourse' and not to donate sperm. The UK government said that it *did not know* if the mRNA procedure had an effect on fertility. *Did not know?* These people have to go to jail. UK government advice did not recommend at the start that pregnant women had the shot and said they should avoid pregnancy for at least two months after 'vaccination'. The 'advice' was later updated to pregnant women should only have the 'vaccine' if the benefits outweighed the risks to mother and foetus. What the hell is that supposed to mean? Then 'spontaneous abortions' began to appear and rapidly increase on the adverse reaction reporting schemes which include only a fraction of adverse reactions. Thousands and ever-growing numbers of 'vaccinated' women are describing changes to their menstrual cycle with heavier blood flow, irregular periods and menstruating again after going through the menopause – all links to reproduction effects. Women are passing blood clots and the lining of their uterus while men report erectile dysfunction and blood effects. Most

significantly of all *un*vaccinated women began to report similar menstrual changes after interaction with *'vaccinated'* people and men and children were also affected with bleeding noses, blood clots and other conditions. 'Shedding' is when vaccinated people can emit the content of a vaccine to affect the unvaccinated, but this is different. 'Vaccinated' people were not shedding a 'live virus' allegedly in 'vaccines' as before because the fake 'Covid vaccines' involve synthetic material and other toxicity. Doctors exposing what is happening prefer the term 'transmission' to shedding. Somehow those that have had the shots are transmitting effects to those that haven't. Dr Carrie Madej said the nano-content of the 'vaccines' can 'act like an antenna' to others around them which fits perfectly with my own conclusions. This 'vaccine' transmission phenomenon was becoming known as the book went into production and I deal with this further in the Postscript.

Vaccine effects on sterility are well known. The World Health Organization was accused in 2014 of sterilising millions of women in Kenya with the evidence confirmed by the content of the vaccines involved. The same WHO behind the 'Covid' hoax admitted its involvement for more than ten years with the vaccine programme. Other countries made similar claims. Charges were lodged by Tanzania, Nicaragua, Mexico, and the Philippines. The Gardasil vaccine claimed to protect against a genital 'virus' known as HPV has also been linked to infertility. Big Pharma and the WHO (same thing) are criminal and satanic entities. Then there's the Bill Gates Foundation which is connected through funding and shared interests with 20 pharmaceutical giants and laboratories. He stands accused of directing the policy of United Nations Children's Fund (UNICEF), vaccine alliance GAVI, and other groupings, to advance the vaccine agenda and silence opposition at great cost to women and children. At the same time Gates wants to reduce the global population. Coincidence?

Great Reset = Smart Grid = new human

The Cult agenda I have been exposing for 30 years is now being openly promoted by Cult assets like Gates and Klaus Schwab of the World Economic Forum under code-terms like the 'Great Reset', 'Build Back Better' and 'a rare but narrow window of opportunity to reflect, reimagine, and reset our world'. What provided this 'rare but narrow window of opportunity'? The 'Covid' hoax did. Who created that? *They* did. My books from not that long ago warned about the planned 'Internet of Things' (IoT) and its implications for human freedom. This was the plan to connect all technology to the Internet and artificial intelligence and today we are way down that road with an estimated 36 billion devices connected to the World Wide Web and that figure is projected to be 76 billion by 2025. I further warned that the Cult planned to go beyond that to the Internet of *Everything* when the human brain was connected via AI to the Internet and Kurzweil's 'cloud'. Now we have Cult operatives like Schwab calling for precisely that under the term 'Internet of Bodies', a fusion of the physical, digital and biological into one centrally-controlled Smart Grid system which the Cult refers to as the 'Fourth Industrial Revolution'. They talk about the 'biological', but they really mean the synthetic-biological which is required to fully integrate the human body and brain into the Smart Grid and artificial intelligence planned to replace the human mind. We have everything being synthetically manipulated including the natural world through GMO and smart dust, the food we eat and the human body itself with synthetic 'vaccines'. I said in *The Answer* that we would see the Cult push for synthetic meat to replace animals and in February, 2021, the so predictable psychopath Bill Gates called for the introduction of synthetic meat to save us all from 'climate change'. The climate hoax just keeps on giving like the 'Covid' hoax. The war on meat by vegan activists is a carbon (oops, sorry) copy of the manipulation of transgender activists. They have no idea (except their inner core) that they are being used to promote and impose the agenda of the Cult or that they are only the *vehicle* and not the *reason*. This is not to say those who choose not to eat meat shouldn't be respected and supported in that right, but there are ulterior motives

for those in power. A *Forbes* article in December, 2019, highlighted the plan so beloved of Schwab and the Cult under the heading: 'What Is The Internet of Bodies? And How Is It Changing Our World?' The article said the human body is the latest data platform (remember 'our vaccine is an operating system'). *Forbes* described the plan very accurately and the words could have come straight out of my books from long before:

The Internet of Bodies (IoB) is an extension of the IoT and basically connects the human body to a network through devices that are ingested, implanted, or connected to the body in some way. Once connected, data can be exchanged, and the body and device can be remotely monitored and controlled.

They were really describing a human hive mind with human perception centrally-dictated via an AI connection as well as allowing people to be 'remotely monitored and controlled'. Everything from a fridge to a human mind could be directed from a central point by these insane psychopaths and 'Covid vaccines' are crucial to this. Forbes explained the process I mentioned earlier of holdable and wearable technology followed by implantable. The article said there were three generations of the Internet of Bodies that include:

- Body external: These are wearable devices such as Apple Watches or Fitbits that can monitor our health.

- Body internal: These include pacemakers, cochlear implants, and digital pills that go inside our bodies to monitor or control various aspects of health.

- Body embedded: The third generation of the Internet of Bodies is embedded technology where technology and the human body are melded together and have a real-time connection to a remote machine.

Forbes noted the development of the Brain Computer Interface (BCI) which merges the brain with an external device for monitoring and controlling in real-time. 'The ultimate goal is to help restore function to individuals with disabilities by using brain signals rather than conventional neuromuscular pathways.' Oh, do fuck off. The goal of brain interface technology is controlling human thought and emotion from the central point in a hive mind serving its masters wishes. Many people are now agreeing to be chipped to open doors without a key. You can recognise them because they'll be wearing a mask, social distancing and lining up for the 'vaccine'. The Cult plans a Great Reset money system after they have completed the demolition of the global economy in which 'money' will be exchanged through communication with body operating systems. Rand Corporation, a Cult-owned think tank, said of the Internet of Bodies or IoB:

> Internet of Bodies technologies fall under the broader IoT umbrella. But as the name suggests, IoB devices introduce an even more intimate interplay between humans and gadgets. IoB devices monitor the human body, collect health metrics and other personal information, and transmit those data over the Internet. Many devices, such as fitness trackers, are already in use … IoB devices … and those in development can track, record, and store users' whereabouts, bodily functions, and what they see, hear, and even think.

Schwab's World Economic Forum, a long-winded way of saying 'fascism' or 'the Cult', has gone full-on with the Internet of Bodies in the 'Covid' era. 'We're entering the era of the Internet of Bodies', it declared, 'collecting our physical data via a range of devices that can be implanted, swallowed or worn'. The result would be a huge amount of health-related data that could improve human wellbeing around the world, and prove crucial in fighting the 'Covid-19 pandemic'. Does anyone think these clowns care about 'human wellbeing' after the death and devastation their pandemic hoax has purposely caused? Schwab and co say we should move forward with the Internet of Bodies because 'Keeping track of symptoms could help us stop the spread of infection, and quickly detect new cases'. How wonderful, but keeping track' is all they are really bothered

about. Researchers were investigating if data gathered from smartwatches and similar devices could be used as viral infection alerts by tracking the user's heart rate and breathing. Schwab said in his 2018 book *Shaping the Future of the Fourth Industrial Revolution*:

> The lines between technologies and beings are becoming blurred and not just by the ability to create lifelike robots or synthetics. Instead it is about the ability of new technologies to literally become part of us. Technologies already influence how we understand ourselves, how we think about each other, and how we determine our realities. As the technologies … give us deeper access to parts of ourselves, we may begin to integrate digital technologies into our bodies.

You can see what the game is. Twenty-four hour control and people – if you could still call them that – would never know when something would go ping and take them out of circulation. It's the most obvious rush to a global fascist dictatorship and the complete submission of humanity and yet still so many are locked away in their Cult-induced perceptual coma and can't see it.

Smart Grid control centres

The human body is being transformed by the 'vaccines' and in other ways into a synthetic cyborg that can be attached to the global Smart Grid which would be controlled from a central point and other sub-locations of Grid manipulation. Where are these planned to be? Well, China for a start which is one of the Cult's biggest centres of operation. The technological control system and technocratic rule was incubated here to be unleashed across the world after the 'Covid' hoax came out of China in 2020. Another Smart Grid location that will surprise people new to this is Israel. I have exposed in *The Trigger* how Sabbatian technocrats, intelligence and military operatives were behind the horrors of 9/11 and not '19 Arab hijackers' who somehow manifested the ability to pilot big passenger airliners when instructors at puddle-jumping flying schools described some of them as a joke. The 9/11 attacks were made possible through control of civilian and military air computer systems and those of the White House, Pentagon and connected agencies. See *The Trigger* – it

will blow your mind. The controlling and coordinating force were the Sabbatian networks in Israel and the United States which by then had infiltrated the entire US government, military and intelligence system. The real name of the American Deep State is 'Sabbatian State'. Israel is a tiny country of only nine million people, but it is one of the global centres of cyber operations and fast catching Silicon Valley in importance to the Cult. Israel is known as the 'start-up nation' for all the cyber companies spawned there with the Sabbatian specialisation of 'cyber security' that I mentioned earlier which gives those companies access to computer systems of their clients in real time through 'backdoors' written into the coding when security software is downloaded. The Sabbatian centre of cyber operations outside Silicon Valley is the Israeli military Cyber Intelligence Unit, the biggest infrastructure project in Israel's history, headquartered in the desert-city of Beersheba and involving some 20,000 'cyber soldiers'. Here are located a literal army of Internet trolls scanning social media, forums and comment lists for anyone challenging the Cult agenda. The UK military has something similar with its 77th Brigade and associated operations. The Beersheba complex includes research and development centres for other Cult operations such as Intel, Microsoft, IBM, Google, Apple, Hewlett-Packard, Cisco Systems, Facebook and Motorola. Techcrunch.com ran an article about the Beersheba global Internet technology centre headlined 'Israel's desert city of Beersheba is turning into a cybertech oasis':

> The military's massive relocation of its prestigious technology units, the presence of multinational and local companies, a close proximity to Ben Gurion University and generous government subsidies are turning Beersheba into a major global cybertech hub. Beersheba has all of the ingredients of a vibrant security technology ecosystem, including Ben Gurion University with its graduate program in cybersecurity and Cyber Security Research Center, and the presence of companies such as EMC, Deutsche Telekom, PayPal, Oracle, IBM, and Lockheed Martin. It's also the future home of the INCB (Israeli National Cyber Bureau); offers a special income tax incentive for cyber security companies, and was the site for the relocation of the army's intelligence corps units.

Sabbatians have taken over the cyber world through the following process: They scan the schools for likely cyber talent and develop them at Ben Gurion University and their period of conscription in the Israeli Defense Forces when they are stationed at the Beersheba complex. When the cyber talented officially leave the army they are funded to start cyber companies with technology developed by themselves or given to them by the state. Much of this is stolen through backdoors of computer systems around the world with America top of the list. Others are sent off to Silicon Valley to start companies or join the major ones and so we have many major positions filled by apparently 'Jewish' but really Sabbatian operatives. Google, YouTube and Facebook are all run by 'Jewish' CEOs while Twitter is all but run by ultra-Zionist hedge-fund shark Paul Singer. At the centre of the Sabbatian global cyber web is the Israeli army's Unit 8200 which specialises in hacking into computer systems of other countries, inserting viruses, gathering information, instigating malfunction, and even taking control of them from a distance. A long list of Sabbatians involved with 9/11, Silicon Valley and Israeli cyber security companies are operatives of Unit 8200. This is not about Israel. It's about the Cult. Israel is planned to be a Smart Grid hub as with China and what is happening at Beersheba is not for the benefit of Jewish people who are treated disgustingly by the Sabbatian elite that control the country. A glance at the Nuremberg Codes will tell you that.

The story is much bigger than 'Covid', important as that is to where we are being taken. Now, though, it's time to really strap in. There's more … much more …

CHAPTER ELEVEN

Who controls the Cult?

Awake, arise or be forever fall'n
John Milton, *Paradise Lost*

I have exposed this far the level of the Cult conspiracy that operates in the world of the seen and within the global secret society and satanic network which operates in the shadows one step back from the seen. The story, however, goes much deeper than that.

The 'Covid' hoax is major part of the Cult agenda, but only part, and to grasp the biggest picture we have to expand our attention beyond the realm of human sight and into the infinity of possibility that we cannot see. It is from here, ultimately, that humanity is being manipulated into a state of total control by the force which dictates the actions of the Cult. How much of reality can we see? Next to damn all is the answer. We may appear to see all there is to see in the 'space' our eyes survey and observe, but little could be further from the truth. The human 'world' is only a tiny band of frequency that the body's visual and perceptual systems can decode into *perception* of a 'world'. According to mainstream science the electromagnetic spectrum is 0.005 percent of what exists in the Universe (Fig 10). The maximum estimate I have seen is 0.5 percent and either way it's miniscule. I say it is far, far, smaller even than 0.005 percent when you compare reality we see with the totality of reality that we don't. Now get this if you are new to such information: Visible light, the only band of frequency that we can see, is a *fraction* of the 0.005

percent (Fig 11 overleaf). Take this further and realise that our universe is one of infinite universes and that universes are only a fragment of overall reality – *infinite* reality. Then compare that with the almost infinitesimal frequency band of visible light or human sight. You see that humans are as near blind as it is possible to be without actually being so. Artist and filmmaker, Sergio Toporek, said:

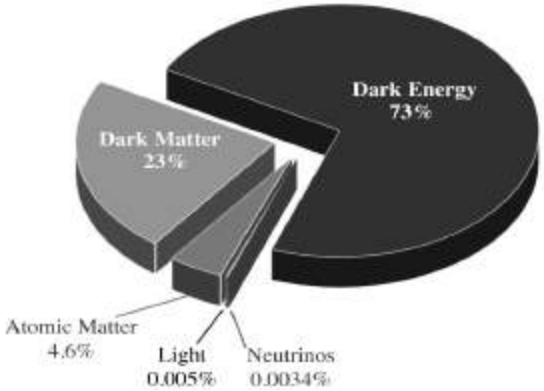


Figure 10: Humans can perceive such a tiny band of visual reality it's laughable.

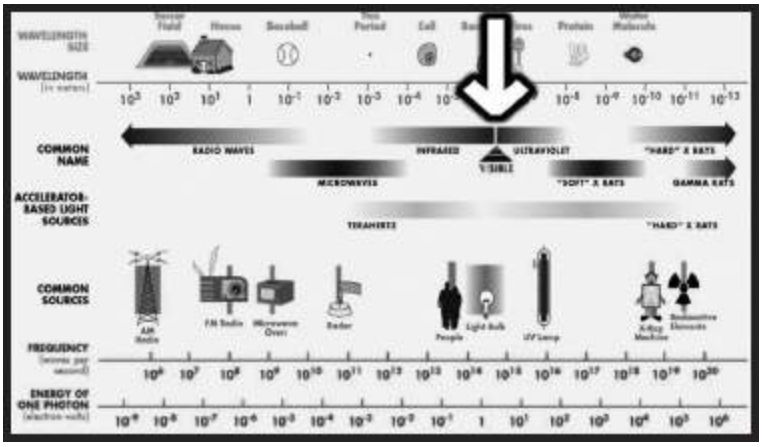


Figure 11: We can see a smear of the 0.005 percent electromagnetic spectrum, but we still know it all. Yep, makes sense.

Consider that you can see less than 1% of the electromagnetic spectrum and hear less than 1% of the acoustic spectrum. 90% of the cells in your body carry their own microbial DNA and are not 'you'. The atoms in your body are 99.9999999999999999% empty space and none of them are the ones you were born with ... Human beings have 46 chromosomes, two less than a potato.

The existence of the rainbow depends on the conical photoreceptors in your eyes; to animals without cones, the rainbow does not exist. So you don't just look at a rainbow, you create it. This is pretty amazing, especially considering that all the beautiful colours you see represent less than 1% of the electromagnetic spectrum.

Suddenly the 'world' of humans looks a very different place. Take into account, too, that Planet Earth when compared with the projected size of this single universe is the equivalent of a billionth of a pinhead. Imagine the ratio that would be when compared to infinite reality. To think that Christianity once insisted that Earth and humanity were the centre of everything. This background is vital if we are going to appreciate the nature of 'human' and how we can be manipulated by an unseen force. To human visual reality virtually *everything* is unseen and yet the prevailing perception within the institutions and so much of the public is that if we can't see it, touch it, hear it, taste it and smell it then it cannot exist. Such perception is indoctrinated and encouraged by the Cult and its agents because it isolates believers in the strictly limited, village-idiot, realm of the five senses where perceptions can be firewalled and information controlled. Most of those perpetuating the 'this-world-is-all-there-is' insanity are themselves indoctrinated into believing the same delusion. While major players and influencers know that official reality is laughable most of those in science, academia and medicine really believe the nonsense they peddle and teach succeeding generations. Those who challenge the orthodoxy are dismissed as nutters and freaks to protect the manufactured illusion from exposure. Observe the dynamic of the 'Covid' hoax and you will see how that takes the same form. The inner-circle psychopaths knows it's a gigantic scam, but almost the entirety of those imposing their fascist rules believe that 'Covid' is all that they're told it is.

Stolen identity

Ask people who they are and they will give you their name, place of birth, location, job, family background and life story. Yet that is not who they are – it is what they are *experiencing*. The difference is *absolutely crucial*. The true 'I', the eternal, infinite 'I', is consciousness,

a state of being aware. Forget 'form'. That is a vehicle for a brief experience. Consciousness does not come *from* the brain, but *through* the brain and even that is more symbolic than literal. We are awareness, pure awareness, and this is what withdraws from the body at what we call 'death' to continue our eternal beingness, *isness*, in other realms of reality within the limitlessness of infinity or the Biblical 'many mansions in my father's house'. Labels of a human life, man, woman, transgender, black, white, brown, nationality, circumstances and income are not who we are. They are what we are – awareness – is *experiencing* in a brief connection with a band of frequency we call 'human'. The labels are not the self; they are, to use the title of one of my books, a *Phantom* Self. I am not David Icke born in Leicester, England, on April 29th, 1952. I am the consciousness *having that experience*. The Cult and its non-human masters seek to convince us through the institutions of 'education', science, medicine, media and government that what we are *experiencing* is who we *are*. It's so easy to control and direct perception locked away in the bewildered illusions of the five senses with no expanded radar. Try, by contrast, doing the same with a humanity aware of its true self and its true power to consciously create its reality and experience. How is it possible to do this? We do it all day every day. If you perceive yourself as 'little me' with no power to impact upon your life and the world then your life experience will reflect that. You will hand the power you don't think you have to authority in all its forms which will use it to control your experience. This, in turn, will appear to confirm your perception of 'little me' in a self-fulfilling feedback loop. But that is what 'little me' really is – a *perception*. We are all 'big-me', infinite me, and the Cult has to make us forget that if its will is to prevail. We are therefore manipulated and pressured into self-identifying with human labels and not the consciousness/awareness *experiencing* those human labels.

The phenomenon of identity politics is a Cult-instigated manipulation technique to sub-divide previous labels into even smaller ones. A United States university employs this list of letters to

describe student identity: LGBTTQQFAGPBDSM or lesbian, gay, bisexual, transgender, transsexual, queer, questioning, flexual, asexual, gender-fuck, polyamorous, bondage/discipline, dominance/submission and sadism/masochism. I'm sure other lists are even longer by now as people feel the need to self-identity the 'I' with the minutiae of race and sexual preference. Wokers programmed by the Cult for generations believe this is about 'inclusivity' when it's really the Cult locking them away into smaller and smaller versions of Phantom Self while firewalling them from the influence of their true self, the infinite, eternal 'I'. You may notice that my philosophy which contends that we are all unique points of attention/awareness within the same infinite whole or Oneness is the ultimate non-racism. The very sense of Oneness makes the judgement of people by their body-type, colour or sexuality utterly ridiculous and confirms that racism has no understanding of reality (including anti-white racism). Yet despite my perception of life Cult agents and fast-asleep Wokers label me racist to discredit my information while they are themselves phenomenally racist and sexist. All they see is race and sexuality and they judge people as good or bad, demons or untouchables, by their race and sexuality. All they see is *Phantom Self* and perceive themselves in terms of Phantom Self. They are pawns and puppets of the Cult agenda to focus attention and self-identity in the five senses and play those identities against each other to divide and rule. Columbia University has introduced segregated graduations in another version of social distancing designed to drive people apart and teach them that different racial and cultural groups have nothing in common with each other. The last thing the Cult wants is unity. Again the pump-primers of this will be Cult operatives in the knowledge of what they are doing, but the rest are just the Phantom Self blind leading the Phantom Self blind. We *do* have something in common – we are all *the same consciousness* having different temporary experiences.

What is this 'human'?

Yes, what *is* 'human'? That is what we are supposed to be, right? I mean 'human'? True, but 'human' is the experience not the 'I'. Break it down to basics and 'human' is the way that information is processed. If we are to experience and interact with this band of frequency we call the 'world' we must have a vehicle that operates within that band of frequency. Our consciousness in its prime form cannot do that; it is way beyond the frequency of the human realm. My consciousness or awareness could not tap these keys and pick up the cup in front of me in the same way that radio station A cannot interact with radio station B when they are on different frequencies. The human body is the means through which we have that interaction. I have long described the body as a biological computer which processes information in a way that allows consciousness to experience this reality. The body is a receiver, transmitter and processor of information in a particular way that we call human. We visually perceive only the world of the five senses in a wakened state – that is the limit of the body's visual decoding system. In truth it's not even visual in the way we experience 'visual reality' as I will come to in a moment. We are 'human' because the body processes the information sources of human into a reality and behaviour system that we *perceive* as human. Why does an elephant act like an elephant and not like a human or a duck? The elephant's biological computer is a different information field and processes information according to that program into a visual and behaviour type we call an elephant. The same applies to everything in our reality. These body information fields are perpetuated through procreation (like making a copy of a software program). The Cult wants to break that cycle and intervene technologically to transform the human information field into one that will change what we call humanity. If it can change the human information field it will change the way that field processes information and change humanity both 'physically' and psychologically. Hence the *messenger* (information) RNA 'vaccines' and so much more that is targeting human genetics by changing the body's information – *messaging* – construct through food, drink, radiation, toxicity and other means.

Reality that we experience is nothing like reality as it really is in the same way that the reality people experience in virtual reality games is not the reality they are really living in. The game is only a decoded source of information that appears to be a reality. Our world is also an information construct – a *simulation* (more later). In its base form our reality is a wavefield of information much the same in theme as Wi-Fi. The five senses decode wavefield information into electrical information which they communicate to the brain to decode into holographic (illusory 'physical') information. Different parts of the brain specialise in decoding different senses and the information is fused into a reality that appears to be outside of us but is really inside the brain and the genetic structure in general (Fig 12 overleaf). DNA is a receiver-transmitter of information and a vital part of this decoding process and the body's connection to other realities. Change DNA and you change the way we decode and connect with reality – see 'Covid vaccines'. Think of computers decoding Wi-Fi. You have information encoded in a radiation field and the computer decodes that information into a very different form on the screen. You can't see the Wi-Fi until its information is made manifest on the screen and the information on the screen is inside the computer and not outside. I have just described how we decode the 'human world'. All five senses decode the waveform 'Wi-Fi' field into electrical signals and the brain (computer) constructs reality inside the brain and not outside – 'You don't just look at a rainbow, you create it'. Sound is a simple example. We don't hear sound until the brain decodes it. Waveform sound waves are picked up by the hearing sense and communicated to the brain in an electrical form to be decoded into the sounds that we hear. Everything we hear is inside the brain along with everything we see, feel, smell and taste. Words and language are waveform fields generated by our vocal chords which pass through this process until they are decoded by the brain into words that we hear. Different languages are different frequency fields or sound waves generated by vocal chords. Late British philosopher Alan Watts said:

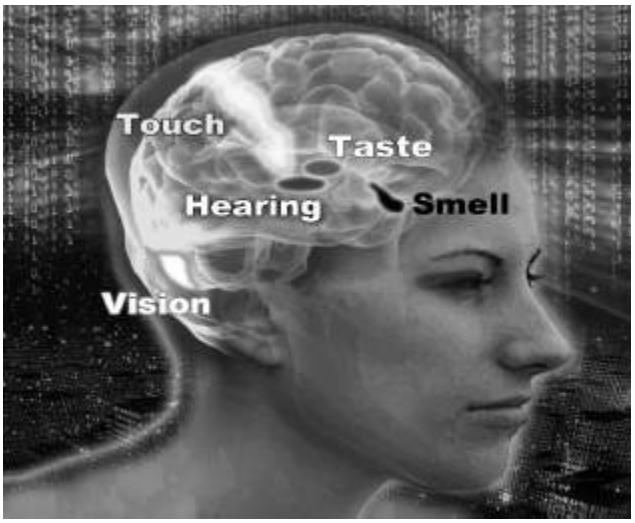


Figure 12: The brain receives information from the five senses and constructs from that our perceived reality.

[Without the brain] the world is devoid of light, heat, weight, solidity, motion, space, time or any other imaginable feature. All these phenomena are interactions, or transactions, of vibrations with a certain arrangement of neurons.

That's exactly what they are and scientist Robert Lanza describes in his book, *Biocentrism*, how we decode electromagnetic waves and energy into visual and 'physical' experience. He uses the example of a flame emitting photons, electromagnetic energy, each pulsing electrically and magnetically:

… these … invisible electromagnetic waves strike a human retina, and if (and only if) the waves happen to measure between 400 and 700 nano meters in length from crest to crest, then their energy is just right to deliver a stimulus to the 8 million cone-shaped cells in the retina.

Each in turn send an electrical pulse to a neighbour neuron, and on up the line this goes, at 250 mph, until it reaches the … occipital lobe of the brain, in the back of the head. There, a cascading complex of neurons fire from the incoming stimuli, and we subjectively perceive this experience as a yellow brightness occurring in a place we have been conditioned to call the 'external world'.

You hear what you decode

If a tree falls or a building collapses they make no noise unless someone is there to decode the energetic waves generated by the disturbance into what we call sound. Does a falling tree make a noise? Only if you hear it – *decode* it. Everything in our reality is a frequency field of information operating within the overall 'Wi-Fi' field that I call The Field. A vibrational disturbance is generated in The Field by the fields of the falling tree or building. These disturbance waves are what we decode into the sound of them falling. If no one is there to do that then neither will make any noise. Reality is created by the observer – *decoder* – and the *perceptions* of the observer affect the decoding process. For this reason different people – different *perceptions* – will perceive the same reality or situation in a different way. What one may perceive as a nightmare another will see as an opportunity. The question of why the Cult is so focused on controlling human perception now answers itself. All experienced reality is the act of decoding and we don't experience Wi-Fi until it is decoded on the computer screen. The sight and sound of an Internet video is encoded in the Wi-Fi all around us, but we don't see or hear it until the computer decodes that information. Taste, smell and touch are all phenomena of the brain as a result of the same process. We don't taste, smell or feel anything except in the brain and there are pain relief techniques that seek to block the signal from the site of discomfort to the brain because if the brain doesn't decode that signal we don't feel pain. Pain is in the brain and only appears to be at the point of impact thanks to the feedback loop between them. We don't see anything until electrical information from the sight senses is decoded in an area at the back of the brain. If that area is damaged we can go blind when our eyes are perfectly okay. So why do we go blind if we damage an eye? We damage the information processing between the waveform visual information and the visual decoding area of the brain. If information doesn't reach the brain in a form it can decode then we can't see the visual reality that it represents. What's more the brain is decoding only a fraction of the information it receives and the rest is absorbed by the

sub-conscious mind. This explanation is from the science magazine, *Wonderpedia*:

> Every second, 11 million sensations crackle along these [brain] pathways ... The brain is confronted with an alarming array of images, sounds and smells which it rigorously filters down until it is left with a manageable list of around 40. Thus 40 sensations per second make up what we perceive as reality.

The 'world' is not what people are told to believe that is it and the inner circles of the Cult *know that*.

Illusory 'physical' reality

We can only see a smear of 0.005 percent of the Universe which is only one of a vast array of universes – 'mansions' – within infinite reality. Even then the brain decodes only 40 pieces of information ('sensations') from a potential *11 million* that we receive every second. Two points strike you from this immediately: The sheer breathtaking stupidity of believing we know anything so rigidly that there's nothing more to know; and the potential for these processes to be manipulated by a malevolent force to control the reality of the population. One thing I can say for sure with no risk of contradiction is that when you can perceive an almost indescribable fraction of infinite reality there is always more to know as in tidal waves of it. Ancient Greek philosopher Socrates was so right when he said that wisdom is to know how little we know. How obviously true that is when you think that we are experiencing a physical world of solidity that is neither physical nor solid and a world of apartness when everything is connected. Cult-controlled 'science' dismisses the so-called 'paranormal' and all phenomena related to that when the 'para'-normal is perfectly normal and explains the alleged 'great mysteries' which dumbfound scientific minds. There is a reason for this. A 'scientific mind' in terms of the mainstream is a material mind, a five-sense mind imprisoned in see it, touch it, hear it, smell it and taste it. Phenomena and happenings that can't be explained that way leave the 'scientific mind' bewildered and the rule is that if they

can't account for why something is happening then it can't, by definition, be happening. I beg to differ. Telepathy is thought waves passing through The Field (think wave disturbance again) to be decoded by someone able to connect with that wavelength (information). For example: You can pick up the thought waves of a friend at any distance and at the very least that will bring them to mind. A few minutes later the friend calls you. 'My god', you say, 'that's incredible – I was just thinking of you.' Ah, but *they* were thinking of *you* before they made the call and that's what you decoded. Native peoples not entrapped in five-sense reality do this so well it became known as the 'bush telegraph'. Those known as psychics and mediums (genuine ones) are doing the same only across dimensions of reality. 'Mind over matter' comes from the fact that matter and mind are the *same*. The state of one influences the state of the other. Indeed one *and* the other are illusions. They are aspects of the same field. Paranormal phenomena are all explainable so why are they still considered 'mysteries' or not happening? Once you go down this road of understanding you begin to expand awareness beyond the five senses and that's the nightmare for the Cult.



Figure 13: Holograms are not solid, but the best ones appear to be.

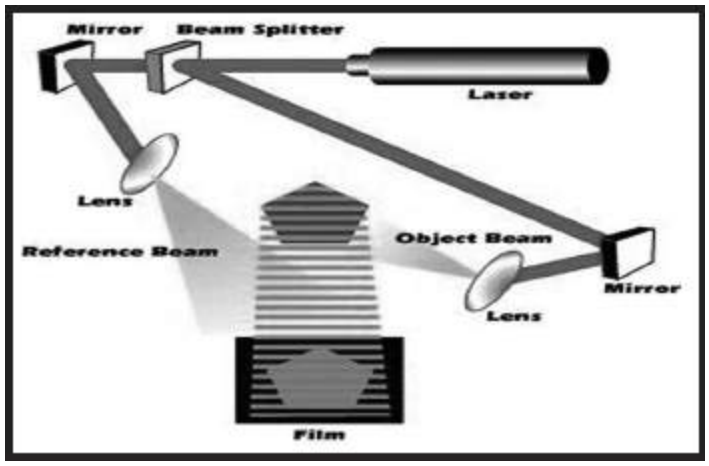


Figure 14: How holograms are created by capturing a waveform version of the subject image.

Holographic 'solidity'

Our reality is not solid, it is holographic. We are now well aware of holograms which are widely used today. Two-dimensional information is decoded into a three-dimensional reality that is not solid although can very much appear to be (Fig 13). Holograms are created with a laser divided into two parts. One goes directly onto a holographic photographic print ('reference beam') and the other takes a waveform image of the subject ('working beam') before being directed onto the print where it 'collides' with the other half of the laser (Fig 14). This creates a *waveform* interference pattern which contains the wavefield information of whatever is being photographed (Fig 15 overleaf). The process can be likened to dropping pebbles in a pond. Waves generated by each one spread out across the water to collide with the others and create a wave representation of where the stones fell and at what speed, weight and distance. A waveform interference pattern of a hologram is akin to the waveform information in The Field which the five senses decode into electrical signals to be decoded by the brain into a holographic illusory 'physical' reality. In the same way when a laser (think human attention) is directed at the waveform interference pattern a three-dimensional version of the subject is projected into apparently 'solid' reality (Fig 16). An amazing trait of holograms reveals more 'paranormal mysteries'. Information of the *whole*

hologram is encoded in waveform in every part of the interference pattern by the way they are created. This means that every *part* of a hologram is a smaller version of the whole. Cut the interference wave-pattern into four and you won't get four parts of the image. You get quarter-sized versions of the *whole* image. The body is a hologram and the same applies. Here we have the basis of acupuncture, reflexology and other forms of healing which identify representations of the whole body in all of the parts, hands, feet, ears, everywhere. Skilled palm readers can do what they do because the information of whole body is encoded in the hand. The concept of as above, so below, comes from this.



Figure 15: A waveform interference pattern that holds the information that transforms into a hologram.



Figure 16: Holographic people including 'Elvis' holographically inserted to sing a duet with Celine Dion.

The question will be asked of why, if solidity is illusory, we can't just walk through walls and each other. The resistance is not solid against solid; it is electromagnetic field against electromagnetic field and we decode this into the *experience* of solid against solid. We should also not underestimate the power of belief to dictate reality. What you believe is impossible *will be*. Your belief impacts on your decoding processes and they won't decode what you think is impossible. What we believe we perceive and what we perceive we experience. 'Can't dos' and 'impossibles' are like a firewall in a computer system that won't put on the screen what the firewall blocks. How vital that is to understanding how human experience has been hijacked. I explain in *The Answer*, *Everything You Need To Know But Have Never Been Told* and other books a long list of 'mysteries' and 'paranormal' phenomena that are not mysterious and perfectly normal once you realise what reality is and how it works. 'Ghosts' can be seen to pass through 'solid' walls because the walls are not solid and the ghost is a discarnate entity operating on a frequency so different to that of the wall that it's like two radio stations sharing the same space while never interfering with each other. I have seen ghosts do this myself. The apartness of people and objects is also an illusion. Everything is connected by the Field like all sea life is connected by the sea. It's just that within the limits of our visual reality we only 'see' holographic information and not the field of information that connects everything and from which the holographic world is made manifest. If you can only see holographic 'objects' and not the field that connects them they will appear to you as unconnected to each other in the same way that we see the computer while not seeing the Wi-Fi.

What you don't know *can* hurt you

Okay, we return to those 'two worlds' of human society and the Cult with its global network of interconnecting secret societies and satanic groups which manipulate through governments, corporations, media, religions, etc. The fundamental difference between them is *knowledge*. The idea has been to keep humanity

ignorant of the plan for its total enslavement underpinned by a crucial ignorance of reality – who we are and where we are – and how we interact with it. 'Human' should be the interaction between our expanded eternal consciousness and the five-sense body experience. We are meant to be *in* this world in terms of the five senses but not *of* this world in relation to our greater consciousness and perspective. In that state we experience the small picture of the five senses within the wider context of the big picture of awareness beyond the five senses. Put another way the five senses see the dots and expanded awareness connects them into pictures and patterns that give context to the apparently random and unconnected. Without the context of expanded awareness the five senses see only apartness and randomness with apparently no meaning. The Cult and its other-dimensional controllers seek to intervene in the frequency realm where five-sense reality is supposed to connect with expanded reality and to keep the two apart (more on this in the final chapter). When that happens five-sense mental and emotional processes are no longer influenced by expanded awareness, or the True 'I', and instead are driven by the isolated perceptions of the body's decoding systems. They are in the world *and* of it. Here we have the human plight and why humanity with its potential for infinite awareness can be so easily manipulatable and descend into such extremes of stupidity.

Once the Cult isolates five-sense mind from expanded awareness it can then program the mind with perceptions and beliefs by controlling information that the mind receives through the 'education' system of the formative years and the media perceptual bombardment and censorship of an entire lifetime. Limit perception and a sense of the possible through limiting knowledge by limiting and skewing information while censoring and discrediting that which could set people free. As the title of another of my books says *… And The Truth Shall Set You Free*. For this reason the last thing the Cult wants in circulation is the truth about anything – especially the reality of the eternal 'I' – and that's why it is desperate to control information. The Cult knows that information becomes perception

which becomes behaviour which, collectively, becomes human society. Cult-controlled and funded mainstream 'science' denies the existence of an eternal 'I' and seeks to dismiss and trash all evidence to the contrary. Cult-controlled mainstream religion has a version of 'God' that is little more than a system of control and dictatorship that employs threats of damnation in an afterlife to control perceptions and behaviour in the here and now through fear and guilt. Neither is true and it's the 'neither' that the Cult wishes to suppress. This 'neither' is that everything is an expression, a point of attention, within an infinite state of consciousness which is the real meaning of the term 'God'.

Perceptual obsession with the 'physical body' and five-senses means that 'God' becomes personified as a bearded bloke sitting among the clouds or a raging bully who loves us if we do what 'he' wants and condemns us to the fires of hell if we don't. These are no more than a 'spiritual' fairy tales to control and dictate events and behaviour through fear of this 'God' which has bizarrely made 'God-fearing' in religious circles a state to be desired. I would suggest that fearing *anything* is not to be encouraged and celebrated, but rather deleted. You can see why 'God fearing' is so beneficial to the Cult and its religions when *they* decide what 'God' wants and what 'God' demands (the Cult demands) that everyone do. As the great American comedian Bill Hicks said satirising a Christian zealot: 'I think what God meant to say.' How much of this infinite awareness ('God') that we access is decided by how far we choose to expand our perceptions, self-identity and sense of the possible. The scale of self-identity reflects itself in the scale of awareness that we can connect with and are influenced by – how much knowing and insight we have instead of programmed perception. You cannot expand your awareness into the infinity of possibility when you believe that you are little me Peter the postman or Mary in marketing and nothing more. I'll deal with this in the concluding chapter because it's crucial to how we turnaround current events.

Where the Cult came from

When I realised in the early 1990s there was a Cult network behind global events I asked the obvious question: When did it start? I took it back to ancient Rome and Egypt and on to Babylon and Sumer in Mesopotamia, the 'Land Between Two Rivers', in what we now call Iraq. The two rivers are the Tigris and Euphrates and this region is of immense historical and other importance to the Cult, as is the land called Israel only 550 miles away by air. There is much more going with deep esoteric meaning across this whole region. It's not only about 'wars for oil'. Priceless artefacts from Mesopotamia were stolen or destroyed after the American and British invasion of Iraq in 2003 justified by the lies of Boy Bush and Tony Blair (their Cult masters) about non-existent 'weapons of mass destruction'. Mesopotamia was the location of Sumer (about 5,400BC to 1,750BC), and Babylon (about 2,350BC to 539BC). Sabbatians may have become immensely influential in the Cult in modern times but they are part of a network that goes back into the mists of history. Sumer is said by historians to be the 'cradle of civilisation'. I disagree. I say it was the re-start of what we call human civilisation after cataclysmic events symbolised in part as the 'Great Flood' destroyed the world that existed before. These fantastic upheavals that I have been describing in detail in the books since the early1990s appear in accounts and legends of ancient cultures across the world and they are supported by geological and biological evidence. Stone tablets found in Iraq detailing the Sumer period say the cataclysms were caused by non-human 'gods' they call the Anunnaki. These are described in terms of extraterrestrial visitations in which knowledge supplied by the Anunnaki is said to have been the source of at least one of the world's oldest writing systems and developments in astronomy, mathematics and architecture that were way ahead of their time. I have covered this subject at length in *The Biggest Secret* and *Children of the Matrix* and the same basic 'Anunnaki' story can be found in Zulu accounts in South Africa where the late and very great Zulu high shaman Credo Mutwa told me that the Sumerian Anunnaki were known by Zulus as the Chitauri or 'children of the serpent'. See my six-hour video interview with Credo on this subject entitled *The*

Reptilian Agenda recorded at his then home near Johannesburg in 1999 which you can watch on the Ickonic media platform.

The Cult emerged out of Sumer, Babylon and Egypt (and elsewhere) and established the Roman Empire before expanding with the Romans into northern Europe from where many empires were savagely imposed in the form of Cult-controlled societies all over the world. Mass death and destruction was their calling card. The Cult established its centre of operations in Europe and European Empires were Cult empires which allowed it to expand into a global force. Spanish and Portuguese colonialists headed for Central and South America while the British and French targeted North America. Africa was colonised by Britain, France, Belgium, the Netherlands, Portugal, Spain, Italy, and Germany. Some like Britain and France moved in on the Middle East. The British Empire was by far the biggest for a simple reason. By now Britain was the headquarters of the Cult from which it expanded to form Canada, the United States, Australia and New Zealand. The Sun never set on the British Empire such was the scale of its occupation. London remains a global centre for the Cult along with Rome and the Vatican although others have emerged in Israel and China. It is no accident that the 'virus' is alleged to have come out of China while Italy was chosen as the means to terrify the Western population into compliance with 'Covid' fascism. Nor that Israel has led the world in 'Covid' fascism and mass 'vaccination'.

You would think that I would mention the United States here, but while it has been an important means of imposing the Cult's will it is less significant than would appear and is currently in the process of having what power it does have deleted. The Cult in Europe has mostly loaded the guns for the US to fire. America has been controlled from Europe from the start through Cult operatives in Britain and Europe. The American Revolution was an illusion to make it appear that America was governing itself while very different forces were pulling the strings in the form of Cult families such as the Rothschilds through the Rockefellers and other subordinates. The Rockefellers are extremely close to Bill Gates and

established both scalpel and drug 'medicine' and the World Health Organization. They play a major role in the development and circulation of vaccines through the Rockefeller Foundation on which Bill Gates said his Foundation is based. Why wouldn't this be the case when the Rockefellers and Gates are on the same team? Cult infiltration of human society goes way back into what we call history and has been constantly expanding and centralising power with the goal of establishing a global structure to dictate everything. Look how this has been advanced in great leaps with the 'Covid' hoax.

The non-human dimension

I researched and observed the comings and goings of Cult operatives through the centuries and even thousands of years as they were born, worked to promote the agenda within the secret society and satanic networks, and then died for others to replace them. Clearly there had to be a coordinating force that spanned this entire period while operatives who would not have seen the end goal in their lifetimes came and went advancing the plan over millennia. I went in search of that coordinating force with the usual support from the extraordinary synchronicity of my life which has been an almost daily experience since 1990. I saw common themes in religious texts and ancient cultures about a non-human force manipulating human society from the hidden. Christianity calls this force Satan, the Devil and demons; Islam refers to the Jinn or Djinn; Zulus have their Chitauri (spelt in other ways in different parts of Africa); and the Gnostic people in Egypt in the period around and before 400AD referred to this phenomena as the 'Archons', a word meaning rulers in Greek. Central American cultures speak of the 'Predators' among other names and the same theme is everywhere. I will use 'Archons' as a collective name for all of them. When you see how their nature and behaviour is described all these different sources are clearly talking about the same force. Gnostics described the Archons in terms of 'luminous fire' while Islam relates the Jinn to 'smokeless fire'. Some refer to beings in form that could occasionally be seen, but the most common of common theme is that they operate from

unseen realms which means almost all existence to the visual processes of humans. I had concluded that this was indeed the foundation of human control and that the Cult was operating within the human frequency band on behalf of this hidden force when I came across the writings of Gnostics which supported my conclusions in the most extraordinary way.

A sealed earthen jar was found in 1945 near the town of Nag Hammadi about 75-80 miles north of Luxor on the banks of the River Nile in Egypt. Inside was a treasure trove of manuscripts and texts left by the Gnostic people some 1,600 years earlier. They included 13 leather-bound papyrus codices (manuscripts) and more than 50 texts written in Coptic Egyptian estimated to have been hidden in the jar in the period of 400AD although the source of the information goes back much further. Gnostics oversaw the Great or Royal Library of Alexandria, the fantastic depository of ancient texts detailing advanced knowledge and accounts of human history. The Library was dismantled and destroyed in stages over a long period with the death-blow delivered by the Cult-established Roman Church in the period around 415AD. The Church of Rome was the Church of Babylon relocated as I said earlier. Gnostics were not a race. They were a way of perceiving reality. Whenever they established themselves and their information circulated the terrorists of the Church of Rome would target them for destruction. This happened with the Great Library and with the Gnostic Cathars who were burned to death by the psychopaths after a long period of oppression at the siege of the Castle of Monségur in southern France in 1244. The Church has always been terrified of Gnostic information which demolishes the official Christian narrative although there is much in the Bible that supports the Gnostic view if you read it in another way. To anyone studying the texts of what became known as the Nag Hammadi Library it is clear that great swathes of Christian and Biblical belief has its origin with Gnostics sources going back to Sumer. Gnostic themes have been twisted to manipulate the perceived reality of Bible believers. Biblical texts have been in the open for centuries where they could be changed while Gnostic

documents found at Nag Hammadi were sealed away and untouched for 1,600 years. What you see is what they wrote.

Use your *pneuma* not your *nous*

Gnosticism and Gnostic come from 'gnosis' which means knowledge, or rather *secret* knowledge, in the sense of spiritual awareness – knowledge about reality and life itself. The desperation of the Cult's Church of Rome to destroy the Gnostics can be understood when the knowledge they were circulating was the last thing the Cult wanted the population to know. Sixteen hundred years later the same Cult is working hard to undermine and silence me for the same reason. The dynamic between knowledge and ignorance is a constant. 'Time' appears to move on, but essential themes remain the same. We are told to 'use your nous', a Gnostic word for head/brain/intelligence. They said, however, that spiritual awakening or 'salvation' could only be secured by expanding awareness *beyond* what they called *nous* and into *pneuma* or Infinite Self. Obviously as I read these texts the parallels with what I have been saying since 1990 were fascinating to me. There is a universal truth that spans human history and in that case why wouldn't we be talking the same language 16 centuries apart? When you free yourself from the perception program of the five senses and explore expanded realms of consciousness you are going to connect with the same information no matter what the perceived 'era' within a manufactured timeline of a single and tiny range of manipulated frequency. Humans working with 'smart' technology or knocking rocks together in caves is only a timeline appearing to operate within the human frequency band. Expanded awareness and the knowledge it holds have always been there whether the era be Stone Age or computer age. We can only access that knowledge by opening ourselves to its frequency which the five-sense prison cell is designed to stop us doing. Gates, Fauci, Whitty, Vallance, Zuckerberg, Brin, Page, Wojcicki, Bezos, and all the others behind the 'Covid' hoax clearly have a long wait before their range of frequency can make that connection given that an open heart is

crucial to that as we shall see. Instead of accessing knowledge directly through expanded awareness it is given to Cult operatives by the secret society networks of the Cult where it has been passed on over thousands of years outside the public arena. Expanded realms of consciousness is where great artists, composers and writers find their inspiration and where truth awaits anyone open enough to connect with it. We need to go there fast.

Archon hijack

A fifth of the Nag Hammadi texts describe the existence and manipulation of the Archons led by a 'Chief Archon' they call 'Yaldabaoth', or the 'Demiurge', and this is the Christian 'Devil', 'Satan', 'Lucifer', and his demons. Archons in Biblical symbolism are the 'fallen ones' which are also referred to as fallen angels after the angels expelled from heaven according to the Abrahamic religions of Judaism, Christianity and Islam. These angels are claimed to tempt humans to 'sin' ongoing and you will see how accurate that symbolism is during the rest of the book. The theme of 'original sin' is related to the 'Fall' when Adam and Eve were 'tempted by the serpent' and fell from a state of innocence and 'obedience' (connection) with God into a state of disobedience (disconnection). The Fall is said to have brought sin into the world and corrupted everything including human nature. Yaldabaoth, the 'Lord Archon', is described by Gnostics as a 'counterfeit spirit', 'The Blind One', 'The Blind God', and 'The Foolish One'. The Jewish name for Yaldabaoth in Talmudic writings is Samael which translates as 'Poison of God', or 'Blindness of God'. You see the parallels. Yaldabaoth in Islamic belief is the Muslim Jinn devil known as Shaytan – Shaytan is Satan as the same themes are found all over the world in every religion and culture. The 'Lord God' of the Old Testament is the 'Lord Archon' of Gnostic manuscripts and that's why he's such a bloodthirsty bastard. Satan is known by Christians as 'the Demon of Demons' and Gnostics called Yaldabaoth the 'Archon of Archons'. Both are known as 'The Deceiver'. We are talking about the same 'bloke' for sure and these common themes

using different names, storylines and symbolism tell a common tale of the human plight.

Archons are referred to in Nag Hammadi documents as mind parasites, inverters, guards, gatekeepers, detainers, judges, pitiless ones and deceivers. The 'Covid' hoax alone is a glaring example of all these things. The Biblical 'God' is so different in the Old and New Testaments because they are not describing the same phenomenon. The vindictive, angry, hate-filled, 'God' of the Old Testament, known as Yahweh, is Yaldabaoth who is depicted in Cult-dictated popular culture as the 'Dark Lord', 'Lord of Time', Lord (Darth) Vader and Dormammu, the evil ruler of the 'Dark Dimension' trying to take over the 'Earth Dimension' in the Marvel comic movie, *Dr Strange*. Yaldabaoth is both the Old Testament 'god' and the Biblical 'Satan'. Gnostics referred to Yaldabaoth as the 'Great Architect of the Universe'and the Cult-controlled Freemason network calls their god 'the 'Great Architect of the Universe' (also Grand Architect). The 'Great Architect' Yaldabaoth is symbolised by the Cult as the all-seeing eye at the top of the pyramid on the Great Seal of the United States and the dollar bill. Archon is encoded in *arch*-itect as it is in *arch*-angels and *arch*-bishops. All religions have the theme of a force for good and force for evil in some sort of spiritual war and there is a reason for that – the theme is true. The Cult and its non-human masters are quite happy for this to circulate. They present themselves as the force for good fighting evil when they are really the force of evil (absence of love). The whole foundation of Cult modus operandi is inversion. They promote themselves as a force for good and anyone challenging them in pursuit of peace, love, fairness, truth and justice is condemned as a satanic force for evil. This has been the game plan throughout history whether the Church of Rome inquisitions of non-believers or 'conspiracy theorists' and 'anti-vaxxers' of today. The technique is the same whatever the timeline era.

Yaldabaoth is revolting (true)

Yaldabaoth and the Archons are said to have revolted against God with Yaldabaoth claiming to *be* God – the *All That Is*. The Old Testament 'God' (Yaldabaoth) demanded to be worshipped as such: ' *I am* the LORD, and there is none else, there is no God beside me' (Isaiah 45:5). I have quoted in other books a man who said he was the unofficial son of the late Baron Philippe de Rothschild of the Mouton-Rothschild wine producing estates in France who died in 1988 and he told me about the Rothschild 'revolt from God'. The man said he was given the name Phillip Eugene de Rothschild and we shared long correspondence many years ago while he was living under another identity. He said that he was conceived through 'occult incest' which (within the Cult) was 'normal and to be admired'. 'Phillip' told me about his experience attending satanic rituals with rich and famous people whom he names and you can see them and the wider background to Cult Satanism in my other books starting with *The Biggest Secret*. Cult rituals are interactions with Archontic 'gods'. 'Phillip' described Baron Philippe de Rothschild as 'a master Satanist and hater of God' and he used the same term 'revolt from God' associated with Yaldabaoth/Satan/Lucifer/the Devil in describing the Sabbatian Rothschild dynasty. 'I played a key role in my family's revolt from God', he said. That role was to infiltrate in classic Sabbatian style the Christian Church, but eventually he escaped the mind-prison to live another life. The Cult has been targeting religion in a plan to make worship of the Archons the global one-world religion. Infiltration of Satanism into modern 'culture', especially among the young, through music videos, stage shows and other means, is all part of this.

Nag Hammadi texts describe Yaldabaoth and the Archons in their prime form as energy – consciousness – and say they can take form if they choose in the same way that consciousness takes form as a human. Yaldabaoth is called 'formless' and represents a deeply inverted, distorted and chaotic state of consciousness which seeks to attached to humans and turn them into a likeness of itself in an attempt at assimilation. For that to happen it has to manipulate

humans into low frequency mental and emotional states that match its own. Archons can certainly appear in human form and this is the origin of the psychopathic personality. The energetic distortion Gnostics called Yaldabaoth *is* psychopathy. When psychopathic Archons take human form that human will be a psychopath as an expression of Yaldabaoth consciousness. Cult psychopaths are Archons in human form. The principle is the same as that portrayed in the 2009 *Avatar* movie when the American military travelled to a fictional Earth-like moon called Pandora in the Alpha Centauri star system to infiltrate a society of blue people, or Na'vi, by hiding within bodies that looked like the Na'vi. Archons posing as humans have a particular hybrid information field, part human, part Archon, (the ancient 'demigods') which processes information in a way that manifests behaviour to match their psychopathic evil, lack of empathy and compassion, and stops them being influenced by the empathy, compassion and love that a fully-human information field is capable of expressing. Cult bloodlines interbreed, be they royalty or dark suits, for this reason and you have their obsession with incest. Interbreeding with full-blown humans would dilute the Archontic energy field that guarantees psychopathy in its representatives in the human realm.

Gnostic writings say the main non-human forms that Archons take are *serpentine* (what I have called for decades 'reptilian' amid unbounded ridicule from the Archontically-programmed) and what Gnostics describe as 'an unborn baby or foetus with grey skin and dark, unmoving eyes'. This is an excellent representation of the ET 'Greys' of UFO folklore which large numbers of people claim to have seen and been abducted by – Zulu shaman Credo Mutwa among them. I agree with those that believe in extraterrestrial or interdimensional visitations today and for thousands of years past. No wonder with their advanced knowledge and technological capability they were perceived and worshipped as gods for technological and other 'miracles' they appeared to perform. Imagine someone arriving in a culture disconnected from the modern world with a smartphone and computer. They would be

seen as a 'god' capable of 'miracles'. The Renegade Mind, however, wants to know the source of everything and not only the way that source manifests as human or non-human. In the same way that a Renegade Mind seeks the original source material for the 'Covid virus' to see if what is claimed is true. The original source of Archons in form is consciousness – the distorted state of consciousness known to Gnostics as Yaldabaoth.

'Revolt from God' is energetic disconnection

Where I am going next will make a lot of sense of religious texts and ancient legends relating to 'Satan', Lucifer' and the 'gods'. Gnostic descriptions sync perfectly with the themes of my own research over the years in how they describe a consciousness distortion seeking to impose itself on human consciousness. I've referred to the core of infinite awareness in previous books as Infinite Awareness in Awareness of Itself. By that I mean a level of awareness that knows that it is all awareness and is aware of all awareness. From here comes the frequency of love in its true sense and balance which is what love is on one level – the balance of all forces into a single whole called Oneness and Isness. The more we disconnect from this state of love that many call 'God' the constituent parts of that Oneness start to unravel and express themselves as a part and not a whole. They become individualised as intellect, mind, selfishness, hatred, envy, desire for power over others, and such like. This is not a problem in the greater scheme in that 'God', the *All That Is*, can experience all these possibilities through different expressions of itself including humans. What we as expressions of the whole experience the *All That Is* experiences. We are the *All That Is* experiencing itself. As we withdraw from that state of Oneness we disconnect from its influence and things can get very unpleasant and very stupid. Archontic consciousness is at the extreme end of that. It has so disconnected from the influence of Oneness that it has become an inversion of unity and love, an inversion of everything, an inversion of life itself. Evil is appropriately live written backwards. Archontic consciousness is obsessed with death, an inversion of life,

and so its manifestations in Satanism are obsessed with death. They use inverted symbols in their rituals such as the inverted pentagram and cross. Sabbatians as Archontic consciousness incarnate invert Judaism and every other religion and culture they infiltrate. They seek disunity and chaos and they fear unity and harmony as they fear love like garlic to a vampire. As a result the Cult, Archons incarnate, act with such evil, psychopathy and lack of empathy and compassion disconnected as they are from the source of love. How could Bill Gates and the rest of the Archontic psychopaths do what they have to human society in the 'Covid' era with all the death, suffering and destruction involved and have no emotional consequence for the impact on others? Now you know. Why have Zuckerberg, Brin, Page, Wojcicki and company callously censored information warning about the dangers of the 'vaccine' while thousands have been dying and having severe, sometimes life-changing reactions? Now you know. Why have Tedros, Fauci, Whitty, Vallance and their like around the world been using case and death figures they're aware are fraudulent to justify lockdowns and all the deaths and destroyed lives that have come from that? Now you know. Why did Christian Drosten produce and promote a 'testing' protocol that he knew couldn't test for infectious disease which led to a global human catastrophe. Now you know. The Archontic mind doesn't give a shit (Fig 17). I personally think that Gates and major Cult insiders are a form of AI cyborg that the Archons want humans to become.

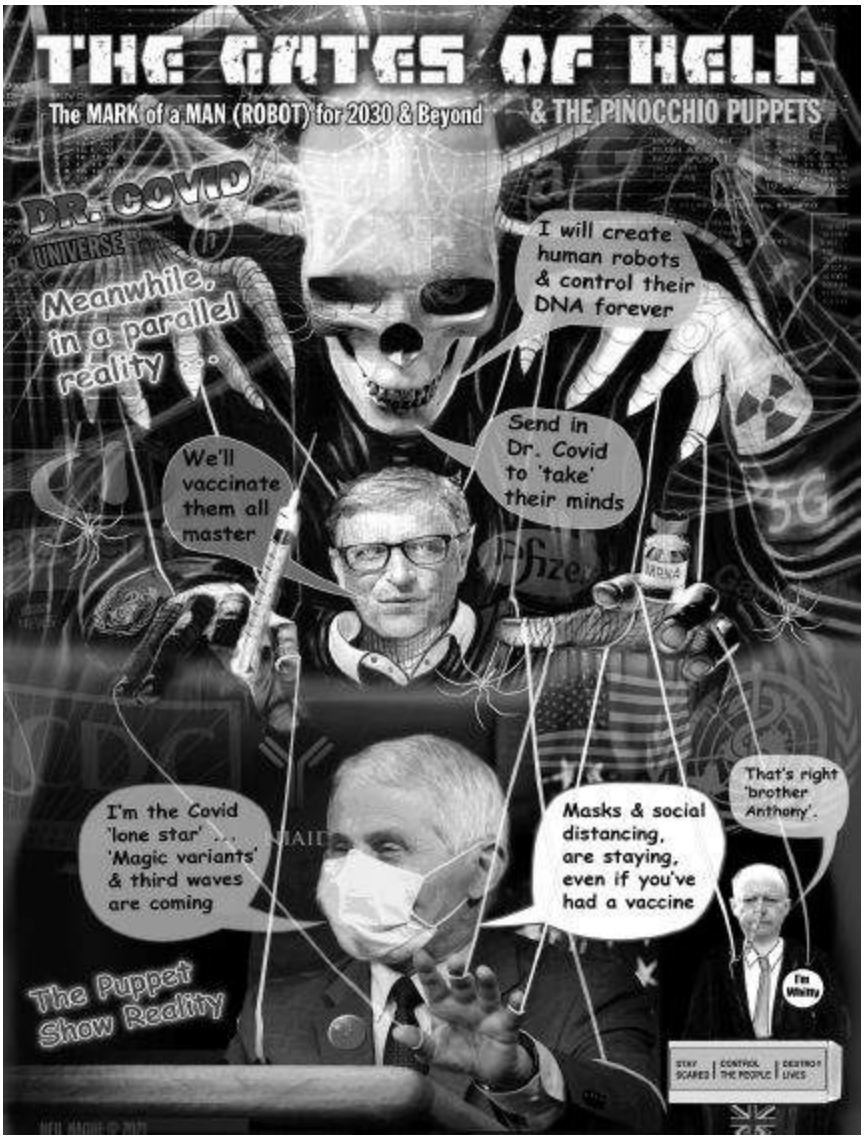


Figure 17: Artist Neil Hague's version of the 'Covid' hierarchy.

Human batteries

A state of such inversion does have its consequences, however. The level of disconnection from the Source of All means that you withdraw from that source of energetic sustenance and creativity. This means that you have to find your own supply of energetic power and it has – *us*. When the Morpheus character in the first *Matrix* movie held up a battery he spoke a profound truth when he said: 'The Matrix is a computer-generated dream world built to keep us under control in order to change the human being into one of

these.' The statement was true in all respects. We do live in a technologically-generated virtual reality simulation (more very shortly) and we have been manipulated to be an energy source for Archontic consciousness. The Disney-Pixar animated movie *Monsters, Inc*. in 2001 symbolised the dynamic when monsters in their world had no energy source and they would enter the human world to terrify children in their beds, catch the child's scream, terror (low-vibrational frequencies), and take that energy back to power the monster world. The lead character you might remember was a single giant eye and the symbolism of the Cult's all-seeing eye was obvious. Every thought and emotion is broadcast as a frequency unique to that thought and emotion. Feelings of love and joy, empathy and compassion, are high, quick, frequencies while fear, depression, anxiety, suffering and hate are low, slow, dense frequencies. Which kind do you think Archontic consciousness can connect with and absorb? In such a low and dense frequency state there's no way it can connect with the energy of love and joy. Archons can only feed off energy compatible with their own frequency and they and their Cult agents want to delete the human world of love and joy and manipulate the transmission of low vibrational frequencies through low-vibrational human mental and emotional states. *We are their energy source*. Wars are energetic banquets to the Archons – a world war even more so – and think how much low-frequency mental and emotional energy has been generated from the consequences for humanity of the 'Covid' hoax orchestrated by Archons incarnate like Gates.

The ancient practice of human sacrifice 'to the gods', continued in secret today by the Cult, is based on the same principle. 'The gods' are Archontic consciousness in different forms and the sacrifice is induced into a state of intense terror to generate the energy the Archontic frequency can absorb. Incarnate Archons in the ritual drink the blood which contains an adrenaline they crave which floods into the bloodstream when people are terrorised. Most of the sacrifices, ancient and modern, are children and the theme of 'sacrificing young virgins to the gods' is just code for children. They

have a particular pre-puberty energy that Archons want more than anything and the energy of the young in general is their target. The California Department of Education wants students to chant the names of Aztec gods (Archontic gods) once worshipped in human sacrifice rituals in a curriculum designed to encourage them to 'challenge racist, bigoted, discriminatory, imperialist/colonial beliefs', join 'social movements that struggle for social justice', and 'build new possibilities for a post-racist, post-systemic racism society'. It's the usual Woke crap that inverts racism and calls it anti-racism. In this case solidarity with 'indigenous tribes' is being used as an excuse to chant the names of 'gods' to which people were sacrificed (and still are in secret). What an example of Woke's inability to see beyond black and white, us and them, They condemn the colonisation of these tribal cultures by Europeans (quite right), but those cultures sacrificing people including children to their 'gods', and mass murdering untold numbers as the Aztecs did, is just fine. One chant is to the Aztec god Tezcatlipoca who had a man sacrificed to him in the 5th month of the Aztec calendar. His heart was cut out and he was eaten. Oh, that's okay then. Come on children … after three … Other sacrificial 'gods' for the young to chant their allegiance include Quetzalcoatl, Huitzilopochtli and Xipe Totec. The curriculum says that 'chants, affirmations, and energizers can be used to bring the class together, build unity around ethnic studies principles and values, and to reinvigorate the class following a lesson that may be emotionally taxing or even when student engagement may appear to be low'. Well, that's the cover story, anyway. Chanting and mantras are the repetition of a particular frequency generated from the vocal cords and chanting the names of these Archontic 'gods' tunes you into their frequency. That is the last thing you want when it allows for energetic synchronisation, attachment and perceptual influence. Initiates chant the names of their 'Gods' in their rituals for this very reason.

Vampires of the Woke

Paedophilia is another way that Archons absorb the energy of children. Paedophiles possessed by Archontic consciousness are used as the conduit during sexual abuse for discarnate Archons to vampire the energy of the young they desire so much. Stupendous numbers of children disappear every year never to be seen again although you would never know from the media. Imagine how much low-vibrational energy has been generated by children during the 'Covid' hoax when so many have become depressed and psychologically destroyed to the point of killing themselves. Shocking numbers of children are now taken by the state from loving parents to be handed to others. I can tell you from long experience of researching this since 1996 that many end up with paedophiles and assets of the Cult through corrupt and Cult-owned social services which in the reframing era has hired many psychopaths and emotionless automatons to do the job. Children are even stolen to order using spurious reasons to take them by the corrupt and secret (because they're corrupt) 'family courts'. I have written in detail in other books, starting with *The Biggest Secret* in 1997, about the ubiquitous connections between the political, corporate, government, intelligence and military elites (Cult operatives) and Satanism and paedophilia. If you go deep enough both networks have an interlocking leadership. The Woke mentality has been developed by the Cult for many reasons: To promote almost every aspect of its agenda; to hijack the traditional political left and turn it fascist; to divide and rule; and to target agenda pushbackers. But there are other reasons which relate to what I am describing here. How many happy and joyful Wokers do you ever see especially at the extreme end? They are a mental and psychological mess consumed by emotional stress and constantly emotionally cocked for the next explosion of indignation at someone referring to a female as a female. They are walking, talking, batteries as Morpheus might say emitting frequencies which both enslave them in low-vibrational bubbles of perceptual limitation and feed the Archons. Add to this the hatred claimed to be love; fascism claimed to 'anti-fascism', racism claimed to be 'anti-racism';

exclusion claimed to inclusion; and the abuse-filled Internet trolling. You have a purpose-built Archontic energy system with not a wind turbine in sight and all founded on Archontic *inversion*. We have whole generations now manipulated to serve the Archons with their actions and energy. They will be doing so their entire adult lives unless they snap out of their Archon-induced trance. Is it really a surprise that Cult billionaires and corporations put so much money their way? Where is the energy of joy and laughter, including laughing at yourself which is confirmation of your own emotional security? Mark Twain said: 'The human race has one really effective weapon, and that is laughter.' We must use it all the time. Woke has destroyed comedy because it has no humour, no joy, sense of irony, or self-deprecation. Its energy is dense and intense. *Mmmmm*, lunch says the Archontic frequency. Rudolf Steiner (1861-1925) was the Austrian philosopher and famous esoteric thinker who established Waldorf education or Steiner schools to treat children like unique expressions of consciousness and not minds to be programmed with the perceptions determined by authority. I'd been writing about this energy vampiring for decades when I was sent in 2016 a quote by Steiner. He was spot on:

> There are beings in the spiritual realms for whom anxiety and fear emanating from human beings offer welcome food. When humans have no anxiety and fear, then these creatures starve. If fear and anxiety radiates from people and they break out in panic, then these creatures find welcome nutrition and they become more and more powerful. These beings are hostile towards humanity. Everything that feeds on negative feelings, on anxiety, fear and superstition, despair or doubt, are in reality hostile forces in super-sensible worlds, launching cruel attacks on human beings, while they are being fed ... These are exactly the feelings that belong to contemporary culture and materialism; because it estranges people from the spiritual world, it is especially suited to evoke hopelessness and fear of the unknown in people, thereby calling up the above mentioned hostile forces against them.

Pause for a moment from this perspective and reflect on what has happened in the world since the start of 2020. Not only will pennies drop, but billion dollar bills. We see the same theme from Don Juan Matus, a Yaqui Indian shaman in Mexico and the information source for Peruvian-born writer, Carlos Castaneda, who wrote a series of

books from the 1960s to 1990s. Don Juan described the force manipulating human society and his name for the Archons was the predator:

> We have a predator that came from the depths of the cosmos and took over the rule of our lives. Human beings are its prisoners. The predator is our lord and master. It has rendered us docile, helpless. If we want to protest, it suppresses our protest. If we want to act independently, it demands that we don't do so ... indeed we are held prisoner!
>
> They took us over because we are food to them, and they squeeze us mercilessly because we are their sustenance. Just as we rear chickens in coops, the predators rear us in human coops, humaneros. Therefore, their food is always available to them.
>
> Different cultures, different eras, same recurring theme.

The 'ennoia' dilemma

Nag Hammadi Gnostic manuscripts say that Archon consciousness has no 'ennoia'. This is directly translated as 'intentionality', but I'll use the term 'creative imagination'. The *All That Is* in awareness of itself is the source of all creativity – all possibility – and the more disconnected you are from that source the more you are subsequently denied 'creative imagination'. Given that Archon consciousness is almost entirely disconnected it severely lacks creativity and has to rely on far more mechanical processes of thought and exploit the creative potential of those that do have 'ennoia'. You can see cases of this throughout human society. Archon consciousness almost entirely dominates the global banking system and if we study how that system works you will appreciate what I mean. Banks manifest 'money' out of nothing by issuing lines of 'credit' which is 'money' that has never, does not, and will never exist except in theory. It's a confidence trick. If you think 'credit' figures-on-a-screen 'money' is worth anything you accept it as payment. If you don't then the whole system collapses through lack of confidence in the value of that 'money'. Archontic bankers with no 'ennoia' are 'lending' 'money' that doesn't exist to humans that *do* have creativity – those that have the inspired ideas and create businesses and products. Archon banking feeds off human creativity

which it controls through 'money' creation and debt. Humans have the creativity and Archons exploit that for their own benefit and control while having none themselves. Archon Internet platforms like Facebook claim joint copyright of everything that creative users post and while Archontic minds like Zuckerberg may officially head that company it will be human creatives on the staff that provide the creative inspiration. When you have limitless 'money' you can then buy other companies established by creative humans. Witness the acquisition record of Facebook, Google and their like. Survey the Archon-controlled music industry and you see non-creative dark suit executives making their fortune from the human creativity of their artists. The cases are endless. Research the history of people like Gates and Zuckerberg and how their empires were built on exploiting the creativity of others. Archon minds cannot create out of nothing, but they are skilled (because they have to be) in what Gnostic texts call 'countermimicry'. They can imitate, but not innovate. Sabbatians trawl the creativity of others through backdoors they install in computer systems through their cybersecurity systems. Archon-controlled China is globally infamous for stealing intellectual property and I remember how Hong Kong, now part of China, became notorious for making counterfeit copies of the creativity of others – 'countermimicry'. With the now pervasive and all-seeing surveillance systems able to infiltrate any computer you can appreciate the potential for Archons to vampire the creativity of humans. Author John Lamb Lash wrote in his book about the Nag Hammadi texts, *Not In His Image*:

> Although they cannot originate anything, because they lack the divine factor of ennoia (intentionality), Archons can imitate with a vengeance. Their expertise is simulation (HAL, virtual reality). The Demiurge [Yaldabaoth] fashions a heaven world copied from the fractal patterns [of the original] ... His construction is celestial kitsch, like the fake Italianate villa of a Mafia don complete with militant angels to guard every portal.

This brings us to something that I have been speaking about since the turn of the millennium. Our reality is a simulation; a virtual reality that we think is real. No, I'm not kidding.

Human reality? Well, virtually

I had pondered for years about whether our reality is 'real' or some kind of construct. I remembered being immensely affected on a visit as a small child in the late 1950s to the then newly-opened Planetarium on the Marylebone Road in London which is now closed and part of the adjacent Madame Tussauds wax museum. It was in the middle of the day, but when the lights went out there was the night sky projected in the Planetarium's domed ceiling and it appeared to be so real. The experience never left me and I didn't know why until around the turn of the millennium when I became certain that our 'night sky' and entire reality is a projection, a virtual reality, akin to the illusory world portrayed in the *Matrix* movies. I looked at the sky one day in this period and it appeared to me like the domed roof of the Planetarium. The release of the first *Matrix* movie in 1999 also provided a synchronistic and perfect visual representation of where my mind had been going for a long time. I hadn't come across the Gnostic Nag Hammadi texts then. When I did years later the correlation was once again astounding. As I read Gnostic accounts from 1,600 years and more earlier it was clear that they were describing the same simulation phenomenon. They tell how the Yaldabaoth 'Demiurge' and Archons created a 'bad copy' of original reality to rule over all that were captured by its illusions and the body was a prison to trap consciousness in the 'bad copy' fake reality. Read how Gnostics describe the 'bad copy' and update that to current times and they are referring to what we would call today a virtual reality simulation.

Author John Lamb Lash said 'the Demiurge fashions a heaven world copied from the fractal patterns' of the original through expertise in 'HAL' or virtual reality simulation. Fractal patterns are part of the energetic information construct of our reality, a sort of blueprint. If these patterns were copied in computer terms it would indeed give you a copy of a 'natural' reality in a non-natural frequency and digital form. The principle is the same as making a copy of a website. The original website still exists, but now you can change the copy version to make it whatever you like and it can

become very different to the original website. Archons have done this with our reality, a *synthetic* copy of prime reality that still exists beyond the frequency walls of the simulation. Trapped within the illusions of this synthetic Matrix, however, were and are human consciousness and other expressions of prime reality and this is why the Archons via the Cult are seeking to make the human body synthetic and give us synthetic AI minds to complete the job of turning the entire reality synthetic including what we perceive to be the natural world. To quote Kurzweil: 'Nanobots will infuse all the matter around us with information. Rocks, trees, everything will become these intelligent creatures.' Yes, *synthetic* 'creatures' just as 'Covid' and other genetically-manipulating 'vaccines' are designed to make the human body synthetic. From this perspective it is obvious why Archons and their Cult are so desperate to infuse synthetic material into every human with their 'Covid' scam.

Let there be (electromagnetic) light

Yaldabaoth, the force that created the simulation, or Matrix, makes sense of the Gnostic reference to 'The Great Architect' and its use by Cult Freemasonry as the name of its deity. The designer of the Matrix in the movies is called 'The Architect' and that trilogy is jam-packed with symbolism relating to these subjects. I have contended for years that the angry Old Testament God (Yaldabaoth) is the 'God' being symbolically 'quoted' in the opening of Genesis as 'creating the world'. This is not the creation of prime reality – it's the creation of the *simulation*. The Genesis 'God' says: 'Let there be Light: and there was light.' But what is this 'Light'? I have said for decades that the speed of light (186,000 miles per second) is not the fastest speed possible as claimed by mainstream science and is in fact the frequency walls or outer limits of the Matrix. You can't have a fastest or slowest anything within all possibility when everything is possible. The human body is encoded to operate within the speed of light or *within the simulation* and thus we see only the tiny frequency band of visible *light*. Near-death experiencers who perceive reality outside the body during temporary 'death' describe a very different

form of light and this is supported by the Nag Hammadi texts. Prime reality beyond the simulation ('Upper Aeons' to the Gnostics) is described as a realm of incredible beauty, bliss, love and harmony – a realm of 'watery light' that is so powerful 'there are no shadows'. Our false reality of Archon control, which Gnostics call the 'Lower Aeons', is depicted as a realm with a different kind of 'light' and described in terms of chaos, 'Hell', 'the Abyss' and 'Outer Darkness', where trapped souls are tormented and manipulated by demons (relate that to the 'Covid' hoax alone). The watery light theme can be found in near-death accounts and it is not the same as *simulation* 'light' which is electromagnetic or radiation light within the speed of light – the 'Lower Aeons'. Simulation 'light' is the 'luminous fire' associated by Gnostics with the Archons. The Bible refers to Yaldabaoth as 'that old serpent, called the Devil, and Satan, which deceiveth the whole world' (Revelation 12:9). I think that making a simulated copy of prime reality ('countermimicry') and changing it dramatically while all the time manipulating humanity to believe it to be real could probably meet the criteria of deceiving the whole world. Then we come to the Cult god Lucifer – the *Light Bringer*. Lucifer is symbolic of Yaldabaoth, the bringer of radiation light that forms the bad copy simulation within the speed of light. 'He' is symbolised by the lighted torch held by the Statue of Liberty and in the name 'Illuminati'. Sabbatian-Frankism declares that Lucifer is the true god and Lucifer is the real god of Freemasonry honoured as their 'Great or Grand Architect of the Universe' (simulation).

I would emphasise, too, the way Archontic technologically-generated luminous fire of radiation has deluged our environment since I was a kid in the 1950s and changed the nature of The Field with which we constantly interact. Through that interaction technological radiation is changing us. The Smart Grid is designed to operate with immense levels of communication power with 5G expanding across the world and 6G, 7G, in the process of development. Radiation is the simulation and the Archontic manipulation system. Why wouldn't the Archon Cult wish to unleash radiation upon us to an ever-greater extreme to form

Kurzweil's 'cloud'? The plan for a synthetic human is related to the need to cope with levels of radiation beyond even anything we've seen so far. Biological humans would not survive the scale of radiation they have in their script. The Smart Grid is a technological sub-reality within the technological simulation to further disconnect five-sense perception from expanded consciousness. It's a technological prison of the mind.

Infusing the 'spirit of darkness'

A recurring theme in religion and native cultures is the manipulation of human genetics by a non-human force and most famously recorded as the biblical 'sons of god' (the god*s* plural in the original) who interbred with the daughters of men. The Nag Hammadi *Apocryphon of John* tells the same story this way:

> He [Yaldabaoth] sent his angels [Archons/demons] to the daughters of men, that they might take some of them for themselves and raise offspring for their enjoyment. And at first they did not succeed. When they had no success, they gathered together again and they made a plan together ... And the angels changed themselves in their likeness into the likeness of their mates, filling them with the spirit of darkness, which they had mixed for them, and with evil ... And they took women and begot children out of the darkness according to the likeness of their spirit.

Possession when a discarnate entity takes over a human body is an age-old theme and continues today. It's very real and I've seen it. Satanic and secret society rituals can create an energetic environment in which entities can attach to initiates and I've heard many stories of how people have changed their personality after being initiated even into lower levels of the Freemasons. I have been inside three Freemasonic temples, one at a public open day and two by just walking in when there was no one around to stop me. They were in Ryde, the town where I live, Birmingham, England, when I was with a group, and Boston, Massachusetts. They all felt the same energetically – dark, dense, low-vibrational and sinister. Demonic attachment can happen while the initiate has no idea what is going on. To them it's just a ritual to get in the Masons and do a bit of good

business. In the far more extreme rituals of Satanism human possession is even more powerful and they are designed to make possession possible. The hierarchy of the Cult is dictated by the power and perceived status of the possessing Archon. In this way the Archon hierarchy becomes the Cult hierarchy. Once the entity has attached it can influence perception and behaviour and if it attaches to the extreme then so much of its energy (information) infuses into the body information field that the hologram starts to reflect the nature of the possessing entity. This is the *Exorcist* movie type of possession when facial features change and it's known as shapeshifting. Islam's Jinn are said to be invisible tricksters who change shape, 'whisper', confuse and take human form. These are all traits of the Archons and other versions of the same phenomenon. Extreme possession could certainty infuse the 'spirit of darkness' into a partner during sex as the Nag Hammadi texts appear to describe. Such an infusion can change genetics which is also energetic information. Human genetics is information and the 'spirit of darkness' is information. Mix one with the other and change must happen. Islam has the concept of a 'Jinn baby' through possession of the mother and by Jinn taking human form. There are many ways that human genetics can be changed and remember that Archons have been aware all along of advanced techniques to do this. What is being done in human society today – and far more – was known about by Archons at the time of the 'fallen ones' and their other versions described in religions and cultures.

Archons and their human-world Cult are obsessed with genetics as we see today and they know this dictates how information is processed into perceived reality during a human life. They needed to produce a human form that would decode the simulation and this is symbolically known as 'Adam and Eve' who left the 'garden' (prime reality) and 'fell' into Matrix reality. The simulation is not a 'physical' construct (there is no 'physical'); it is a source of information. Think Wi-Fi again. The simulation is an energetic field encoded with information and body-brain systems are designed to decode that information encoded in wave or frequency form which

is transmitted to the brain as electrical signals. These are decoded by the brain to construct our sense of reality – an illusory 'physical' world that only exists in the brain or the mind. Virtual reality games mimic this process using the same sensory decoding system. Information is fed to the senses to decode a virtual reality that can appear so real, but isn't (Figs 18 and 19). Some scientists believe – and I agree with them – that what we perceive as 'physical' reality only exists when we are looking or observing. The act of perception or focus triggers the decoding systems which turn waveform information into holographic reality. When we are not observing something our reality reverts from a holographic state to a waveform state. This relates to the same principle as a falling tree not making a noise unless someone is there to hear it or decode it. The concept makes sense from the simulation perspective. A computer is not decoding all the information in a Wi-Fi field all the time and only decodes or brings into reality on the screen that part of Wi-Fi that it's decoding – focusing upon – at that moment.



Figure 18: Virtual reality technology 'hacks' into the body's five-sense decoding system.



Figure 19: The result can be experienced as very 'real'.

Interestingly, Professor Donald Hoffman at the Department of Cognitive Sciences at the University of California, Irvine, says that our experienced reality is like a computer interface that shows us only the level with which we interact while hiding all that exists beyond it: 'Evolution shaped us with a user interface that hides the truth. Nothing that we see is the truth – the very language of space and time and objects is the wrong language to describe reality.' He is correct in what he says on so many levels. Space and time are not a universal reality. They are a phenomenon of decoded *simulation* reality as part of the process of enslaving our sense of reality. Near-death experiencers report again and again how space and time did not exist as we perceive them once they were free of the body – body decoding systems. You can appreciate from this why Archons and their Cult are so desperate to entrap human attention in the five senses where we are in the Matrix and of the Matrix. Opening your mind to expanded states of awareness takes you beyond the information confines of the simulation and you become aware of knowledge and insights denied to you before. This is what we call 'awakening' – *awakening from the Matrix* – and in the final chapter I will relate this to current events.

Where are the 'aliens'?

A simulation would explain the so-called 'Fermi Paradox' named after Italian physicist Enrico Fermi (1901-1954) who created the first nuclear reactor. He considered the question of why there is such a lack of extraterrestrial activity when there are so many stars and planets in an apparently vast universe; but what if the night sky that we see, or think we do, is a simulated projection as I say? If you control the simulation and your aim is to hold humanity fast in essential ignorance would you want other forms of life including advanced life coming and going sharing information with humanity? Or would you want them to believe they were isolated and apparently alone? Themes of human isolation and apartness are common whether they be the perception of a lifeless universe or the fascist isolation laws of the 'Covid' era. Paradoxically the very

existence of a simulation means that we are not alone when some force had to construct it. My view is that experiences that people have reported all over the world for centuries with Reptilians and Grey entities are Archon phenomena as Nag Hammadi texts describe; and that benevolent 'alien' interactions are non-human groups that come in and out of the simulation by overcoming Archon attempts to keep them out. It should be highlighted, too, that Reptilians and Greys are obsessed with *genetics* and *technology* as related by cultural accounts and those who say they have been abducted by them. Technology is their way of overcoming some of the limitations in their creative potential and our technology-driven and controlled human society of today is *arch*etypical Archon-Reptilian-Grey modus operandi. Technocracy is really *Archon*tocracy. The Universe does not have to be as big as it appears with a simulation. There is no space or distance only information decoded into holographic reality. What we call 'space' is only the absence of holographic 'objects' and that 'space' is The Field of energetic information which connects everything into a single whole. The same applies with the artificially-generated information field of the simulation. The Universe is not big or small as a physical reality. It is decoded information, that's all, and its perceived size is decided by the way the simulation is encoded to make it appear. The entire night sky as we perceive it only exists in our brain and so where are those 'millions of light years'? The 'stars' on the ceiling of the Planetarium looked a vast distance away.

There's another point to mention about 'aliens'. I have been highlighting since the 1990s the plan to stage a fake 'alien invasion' to justify the centralisation of global power and a world military. Nazi scientist Werner von Braun, who was taken to America by Operation Paperclip after World War Two to help found NASA, told his American assistant Dr Carol Rosin about the Cult agenda when he knew he was dying in 1977. Rosin said that he told her about a sequence that would lead to total human control by a one-world government. This included threats from terrorism, rogue nations, meteors and asteroids before finally an 'alien invasion'. All of these

things, von Braun said, would be bogus and what I would refer to as a No-Problem-Reaction-Solution. Keep this in mind when 'the aliens are coming' is the new mantra. The aliens are not coming – they are *already here* and they have infiltrated human society while looking human. French-Canadian investigative journalist Serge Monast said in 1994 that he had uncovered a NASA/military operation called Project Blue Beam which fits with what Werner von Braun predicted. Monast died of a 'heart attack' in 1996 the day after he was arrested and spent a night in prison. He was 51. He said Blue Beam was a plan to stage an alien invasion that would include religious figures beamed holographically into the sky as part of a global manipulation to usher in a 'new age' of worshipping what I would say is the Cult 'god' Yaldabaoth in a one-world religion. Fake holographic asteroids are also said to be part of the plan which again syncs with von Braun. How could you stage an illusory threat from asteroids unless they were holographic inserts? This is pretty straightforward given the advanced technology outside the public arena and the fact that our 'physical' reality is holographic anyway. Information fields would be projected and we would decode them into the illusion of a 'physical' asteroid. If they can sell a global 'pandemic' with a 'virus' that doesn't exist what will humans not believe if government and media tell them?

All this is particularly relevant as I write with the Pentagon planning to release in June, 2021, information about 'UFO sightings'. I have been following the UFO story since the early 1990s and the common theme throughout has been government and military denials and cover up. More recently, however, the Pentagon has suddenly become more talkative and apparently open with Air Force pilot radar images released of unexplained craft moving and changing direction at speeds well beyond anything believed possible with human technology. Then, in March, 2021, former Director of National Intelligence John Ratcliffe said a Pentagon report months later in June would reveal a great deal of information about UFO sightings unknown to the public. He said the report would have 'massive implications'. The order to do this was included bizarrely

in a $2.3 trillion 'coronavirus' relief and government funding bill passed by the Trump administration at the end of 2020. I would add some serious notes of caution here. I have been pointing out since the 1990s that the US military and intelligence networks have long had craft – 'flying saucers' or anti-gravity craft – which any observer would take to be extraterrestrial in origin. Keeping this knowledge from the public allows craft flown by *humans* to be perceived as alien visitations. I am not saying that 'aliens' do not exist. I would be the last one to say that, but we have to be streetwise here. President Ronald Reagan told the UN General Assembly in 1987: 'I occasionally think how quickly our differences worldwide would vanish if we were facing an alien threat from outside this world.' That's the idea. Unite against a common 'enemy' with a common purpose behind your 'saviour force' (the Cult) as this age-old technique of mass manipulation goes global.

Science moves this way …

I could find only one other person who was discussing the simulation hypothesis publicly when I concluded it was real. This was Nick Bostrom, a Swedish-born philosopher at the University of Oxford, who has explored for many years the possibility that human reality is a computer simulation although his version and mine are not the same. Today the simulation and holographic reality hypothesis have increasingly entered the scientific mainstream. Well, the more open-minded mainstream, that is. Here are a few of the ever-gathering examples. American nuclear physicist Silas Beane led a team of physicists at the University of Bonn in Germany pursuing the question of whether we live in a simulation. They concluded that we probably do and it was likely based on a lattice of cubes. They found that cosmic rays align with that specific pattern. The team highlighted the Greisen–Zatsepin–Kuzmin (GZK) limit which refers to cosmic ray particle interaction with cosmic background radiation that creates an apparent boundary for cosmic ray particles. They say in a paper entitled 'Constraints on the Universe as a Numerical Simulation' that this 'pattern of constraint' is exactly what you

would find with a computer simulation. They also made the point that a simulation would create its own 'laws of physics' that would limit possibility. I've been making the same point for decades that the *perceived* laws of physics relate only to this reality, or what I would later call the simulation. When designers write codes to create computer and virtual reality games they are the equivalent of the laws of physics for that game. Players interact within the limitations laid out by the coding. In the same way those who wrote the codes for the simulation decided the laws of physics that would apply. These can be overridden by expanded states of consciousness, but not by those enslaved in only five-sense awareness where simulation codes rule. Overriding the codes is what people call 'miracles'. They are not. They are bypassing the encoded limits of the simulation. A population caught in simulation perception would have no idea that this was their plight. As the Bonn paper said: 'Like a prisoner in a pitch-black cell we would not be able to see the "walls" of our prison,' That's true if people remain mesmerised by the five senses. Open to expanded awareness and those walls become very clear. The main one is the speed of light.

American theoretical physicist James Gates is another who has explored the simulation question and found considerable evidence to support the idea. Gates was Professor of Physics at the University of Maryland, Director of The Center for String and Particle Theory, and on Barack Obama's Council of Advisors on Science and Technology. He and his team found *computer codes* of digital data embedded in the fabric of our reality. They relate to on-off electrical charges of 1 and 0 in the binary system used by computers. 'We have no idea what they are doing there', Gates said. They found within the energetic fabric mathematical sequences known as error-correcting codes or block codes that 'reboot' data to its original state or 'default settings' when something knocks it out of sync. Gates was asked if he had found a set of equations embedded in our reality indistinguishable from those that drive search engines and browsers and he said: 'That is correct.' Rich Terrile, director of the Centre for Evolutionary Computation and Automated Design at NASA's Jet

Propulsion Laboratory, has said publicly that he believes the Universe is a digital hologram that must have been created by a form of intelligence. I agree with that in every way. Waveform information is delivered electrically by the senses to the brain which constructs a *digital* holographic reality that we call the 'world'. This digital level of reality can be read by the esoteric art of numerology. Digital holograms are at the cutting edge of holographics today. We have digital technology everywhere designed to access and manipulate our digital level of perceived reality. Synthetic mRNA in 'Covid vaccines' has a digital component to manipulate the body's digital 'operating system'.

Reality is numbers

How many know that our reality can be broken down to numbers and codes that are the same as computer games? Max Tegmark, a physicist at the Massachusetts Institute of Technology (MIT), is the author of *Our Mathematical Universe* in which he lays out how reality can be entirely described by numbers and maths in the way that a video game is encoded with the 'physics' of computer games. Our world and computer virtual reality are essentially the same. Tegmark imagines the perceptions of characters in an advanced computer game when the graphics are so good they don't know they are in a game. They think they can bump into real objects (electromagnetic resistance in our reality), fall in love and feel emotions like excitement. When they began to study the apparently 'physical world' of the video game they would realise that everything was made of pixels (which have been found in our energetic reality as must be the case when on one level our world is digital). What computer game characters thought was physical 'stuff', Tegmark said, could actually be broken down into numbers:

> And we're exactly in this situation in our world. We look around and it doesn't seem that mathematical at all, but everything we see is made out of elementary particles like quarks and electrons. And what properties does an electron have? Does it have a smell or a colour or a texture? No! ... We physicists have come up with geeky names for [Electron] properties, like

electric charge, or spin, or lepton number, but the electron doesn't care what we call it, the properties are just numbers.

This is the illusory reality Gnostics were describing. This is the simulation. The A, C, G, and T codes of DNA have a binary value – A and C = 0 while G and T = 1. This has to be when the simulation is digital and the body must be digital to interact with it. Recurring mathematical sequences are encoded throughout reality and the body. They include the Fibonacci sequence in which the two previous numbers are added to get the next one, as in ... 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, etc. The sequence is encoded in the human face and body, proportions of animals, DNA, seed heads, pine cones, trees, shells, spiral galaxies, hurricanes and the number of petals in a flower. The list goes on and on. There are fractal patterns – a 'never-ending pattern that is infinitely complex and self-similar across all scales in the as above, so below, principle of holograms. These and other famous recurring geometrical and mathematical sequences such as Phi, Pi, Golden Mean, Golden Ratio and Golden Section are *computer codes* of the simulation. I had to laugh and give my head a shake the day I finished this book and it went into the production stage. I was sent an article in *Scientific American* published in April, 2021, with the headline 'Confirmed! We Live in a Simulation'. Two decades after I first said our reality is a simulation and the speed of light is it's outer limit the article suggested that we do live in a simulation and that the speed of light is its outer limit. I left school at 15 and never passed a major exam in my life while the writer was up to his eyes in qualifications. As I will explain in the final chapter *knowing* is far better than thinking and they come from very different sources. The article rightly connected the speed of light to the processing speed of the 'Matrix' and said what has been in my books all this time … 'If we are in a simulation, as it appears, then space is an abstract property written in code. It is not real'. No it's not and if we live in a simulation something created it and it wasn't *us*. 'That David Icke says we are manipulated by aliens' – he's crackers.'

Wow …

The reality that humanity thinks is so real is an illusion. Politicians, governments, scientists, doctors, academics, law enforcement, media, school and university curriculums, on and on, are all founded on a world that *does not exist* except as a simulated prison cell. Is it such a stretch to accept that 'Covid' doesn't exist when our entire 'physical' reality doesn't exist? Revealed here is the knowledge kept under raps in the Cult networks of compartmentalised secrecy to control humanity's sense of reality by inducing the population to believe in a reality that's not real. If it wasn't so tragic in its experiential consequences the whole thing would be hysterically funny. None of this is new to Renegade Minds. Ancient Greek philosopher Plato (about 428 to about 347BC) was a major influence on Gnostic belief and he described the human plight thousands of years ago with his Allegory of the Cave. He told the symbolic story of prisoners living in a cave who had never been outside. They were chained and could only see one wall of the cave while behind them was a fire that they could not see. Figures walked past the fire casting shadows on the prisoners' wall and those moving shadows became their sense of reality. Some prisoners began to study the shadows and were considered experts on them (today's academics and scientists), but what they studied was only an illusion (today's academics and scientists). A prisoner escaped from the cave and saw reality as it really is. When he returned to report this revelation they didn't believe him, called him mad and threatened to kill him if he tried to set them free. Plato's tale is not only a brilliant analogy of the human plight and our illusory reality. It describes, too, the dynamics of the 'Covid' hoax. I have only skimmed the surface of these subjects here. The aim of this book is to crisply connect all essential dots to put what is happening today into its true context. All subject areas and their connections in this chapter are covered in great evidential detail in *Everything You Need To Know, But Have Never Been Told* and *The Answer*.

They say that bewildered people 'can't see the forest for the trees'. Humanity, however, can't see the forest for the *twigs*. The five senses

see only twigs while Renegade Minds can see the forest and it's the forest where the answers lie with the connections that reveals. Breaking free of perceptual programming so the forest can be seen is the way we turn all this around. Not breaking free is how humanity got into this mess. The situation may seem hopeless, but I promise you it's not. We are a perceptual heartbeat from paradise if only we knew.

CHAPTER TWELVE

Escaping Wetiko

Life is simply a vacation from the infinite
Dean Cavanagh

Renegade Minds weave the web of life and events and see common themes in the apparently random. They are always there if you look for them and their pursuit is aided by incredible synchronicity that comes when your mind is open rather than mesmerised by what it thinks it can see.

Infinite awareness is infinite possibility and the more of infinite possibility that we access the more becomes infinitely possible. That may be stating the apparently obvious, but it is a devastatingly-powerful fact that can set us free. We are a point of attention within an infinity of consciousness. The question is how much of that infinity do we choose to access? How much knowledge, insight, awareness, wisdom, do we want to connect with and explore? If your focus is only in the five senses you will be influenced by a fraction of infinite awareness. I mean a range so tiny that it gives new meaning to infinitesimal. Limitation of self-identity and a sense of the possible limit accordingly your range of consciousness. We are what we think we are. Life is what we think it is. The dream is the dreamer and the dreamer is the dream. Buddhist philosophy puts it this way: 'As a thing is viewed, so it appears.' Most humans live in the realm of touch, taste, see, hear, and smell and that's the limit of their sense of the possible and sense of self. Many will follow a religion and speak of a God in his heaven, but their lives are still

dominated by the five senses in their perceptions and actions. The five senses become the arbiter of everything. When that happens all except a smear of infinity is sealed away from influence by the rigid, unyielding, reality bubbles that are the five-sense human or Phantom Self. Archon Cult methodology is to isolate consciousness within five-sense reality – the simulation – and then program that consciousness with a sense of self and the world through a deluge of life-long information designed to instil the desired perception that allows global control. Efforts to do this have increased dramatically with identity politics as identity bubbles are squeezed into the minutiae of five-sense detail which disconnect people even more profoundly from the infinite 'I'.

Five-sense focus and self-identity are like a firewall that limits access to the infinite realms. You only perceive one radio or television station and no other. We'll take that literally for a moment. Imagine a vast array of stations giving different information and angles on reality, but you only ever listen to one. Here we have the human plight in which the population is overwhelmingly confined to CultFM. This relates only to the frequency range of CultFM and limits perception and insight to that band – limits *possibility* to that band. It means you are connecting with an almost imperceptibly minuscule range of possibility and creative potential within the infinite Field. It's a world where everything seems apart from everything else and where synchronicity is rare. Synchronicity is defined in the dictionary as 'the happening by chance of two or more related or similar events at the same time'. Use of 'by chance' betrays a complete misunderstanding of reality. Synchronicity is not 'by chance'. As people open their minds, or 'awaken' to use the term, they notice more and more coincidences in their lives, bits of 'luck', apparently miraculous happenings that put them in the right place at the right time with the right people. Days become peppered with 'fancy meeting you here' and 'what are the chances of that?' My entire life has been lived like this and ever more so since my own colossal awakening in 1990 and 91 which transformed my sense of reality. Synchronicity is not 'by chance'; it is by accessing expanded

realms of possibility which allow expanded potential for manifestation. People broadcasting the same vibe from the same openness of mind tend to be drawn 'by chance' to each other through what I call frequency magnetism and it's not only people. In the last more than 30 years incredible synchronicity has also led me through the Cult maze to information in so many forms and to crucial personal experiences. These 'coincidences' have allowed me to put the puzzle pieces together across an enormous array of subjects and situations. Those who have breached the bubble of five-sense reality will know exactly what I mean and this escape from the perceptual prison cell is open to everyone whenever they make that choice. This may appear super-human when compared with the limitations of 'human', but it's really our natural state. 'Human' as currently experienced is consciousness in an unnatural state of induced separation from the infinity of the whole. I'll come to how this transformation into unity can be made when I have described in more detail the force that holds humanity in servitude by denying this access to infinite self.

The Wetiko factor

I have been talking and writing for decades about the way five-sense mind is systematically barricaded from expanded awareness. I have used the analogy of a computer (five-sense mind) and someone at the keyboard (expanded awareness). Interaction between the computer and the operator is symbolic of the interaction between five-sense mind and expanded awareness. The computer directly experiences the Internet and the operator experiences the Internet via the computer which is how it's supposed to be – the two working as one. Archons seek to control that point where the operator connects with the computer to stop that interaction (Fig 20). Now the operator is banging the keyboard and clicking the mouse, but the computer is not responding and this happens when the computer is taken over – *possessed* – by an appropriately-named computer 'virus'. The operator has lost all influence over the computer which goes its own way making decisions under the control of the 'virus'. I have

just described the dynamic through which the force known to Gnostics as Yaldabaoth and Archons disconnects five-sense mind from expanded awareness to imprison humanity in perceptual servitude.



Figure 20: The mind 'virus' I have been writing about for decades seeks to isolate five-sense mind (the computer) from the true 'I'. (Image by Neil Hague).

About a year ago I came across a Native American concept of Wetiko which describes precisely the same phenomenon. Wetiko is the spelling used by the Cree and there are other versions including wintiko and windigo used by other tribal groups. They spell the name with lower case, but I see Wetiko as a proper noun as with Archons and prefer a capital. I first saw an article about Wetiko by writer and researcher Paul Levy which so synced with what I had been writing about the computer/operator disconnection and later the Archons. I then read his book, the fascinating *Dispelling Wetiko, Breaking the Spell of Evil*. The parallels between what I had concluded long before and the Native American concept of Wetiko were so clear and obvious that it was almost funny. For Wetiko see the Gnostic Archons for sure and the Jinn, the Predators, and every other name for a force of evil, inversion and chaos. Wetiko is the Native American name for the force that divides the computer from

the operator (Fig 21). Indigenous author Jack D. Forbes, a founder of the Native American movement in the 1960s, wrote another book about Wetiko entitled *Columbus And Other Cannibals – The Wetiko Disease of Exploitation, Imperialism, and Terrorism* which I also read. Forbes says that Wetiko refers to an evil person or spirit 'who terrorizes other creatures by means of terrible acts, including cannibalism'. Zulu shaman Credo Mutwa told me that African accounts tell how cannibalism was brought into the world by the Chitauri 'gods' – another manifestation of Wetiko. The distinction between 'evil person or spirit' relates to Archons/Wetiko possessing a human or acting as pure consciousness. Wetiko is said to be a sickness of the soul or spirit and a state of being that takes but gives nothing back – the Cult and its operatives perfectly described. Black Hawk, a Native American war leader defending their lands from confiscation, said European invaders had 'poisoned hearts' – Wetiko hearts – and that this would spread to native societies. Mention of the heart is very significant as we shall shortly see. Forbes writes: 'Tragically, the history of the world for the past 2,000 years is, in great part, the story of the epidemiology of the wetiko disease.' Yes, and much longer. Forbes is correct when he says: 'The wetikos destroyed Egypt and Babylon and Athens and Rome and Tenochtitlan [capital of the Aztec empire] and perhaps now they will destroy the entire earth.' Evil, he said, is the number one export of a Wetiko culture – see its globalisation with 'Covid'. Constant war, mass murder, suffering of all kinds, child abuse, Satanism, torture and human sacrifice are all expressions of Wetiko and the Wetiko possessed. The world is Wetiko made manifest, *but it doesn't have to be*. There is a way out of this even now.



Figure 21: The mind 'virus' is known to Native Americans as 'Wetiko'. (Image by Neil Hague).

Cult of Wetiko

Wetiko is the Yaldabaoth frequency distortion that seeks to attach to human consciousness and absorb it into its own. Once this connection is made Wetiko can drive the perceptions of the target which they believe to be coming from their own mind. All the horrors of history and today from mass killers to Satanists, paedophiles like Jeffrey Epstein and other psychopaths, are the embodiment of Wetiko and express its state of being in all its grotesqueness. The Cult is Wetiko incarnate, Yaldabaoth incarnate, and it seeks to facilitate Wetiko assimilation of humanity in totality into its distortion by manipulating the population into low frequency states that match its own. Paul Levy writes: 'Holographically enforced within the psyche of every human being the wetiko virus pervades and underlies the entire field of consciousness, and can therefore potentially manifest through any one of us at any moment if we are not mindful.' The 'Covid' hoax has achieved this with many people, but others have not fallen into Wetiko's frequency lair. Players in the 'Covid' human catastrophe including Gates, Schwab, Tedros, Fauci, Whitty, Vallance, Johnson, Hancock, Ferguson, Drosten, and all the rest, including the psychopath psychologists, are expressions of Wetiko. This is why

they have no compassion or empathy and no emotional consequence for what they do that would make them stop doing it. Observe all the people who support the psychopaths in authority against the Pushbackers despite the damaging impact the psychopaths have on their own lives and their family's lives. You are again looking at Wetiko possession which prevents them seeing through the lies to the obvious scam going on. *Why can't they see it?* Wetiko won't let them see it. The perceptual divide that has now become a chasm is between the Wetikoed and the non-Wetikoed.

Paul Levy describes Wetiko in the same way that I have long described the Archontic force. They are the same distorted consciousness operating across dimensions of reality: '… the subtle body of wetiko is not located in the third dimension of space and time, literally existing in another dimension … it is able to affect ordinary lives by mysteriously interpenetrating into our three-dimensional world.' Wetiko does this through its incarnate representatives in the Cult and by weaving itself into The Field which on our level of reality is the electromagnetic information field of the simulation or Matrix. More than that, the simulation *is* Wetiko / Yaldabaoth. Caleb Scharf, Director of Astrobiology at Columbia University, has speculated that 'alien life' could be so advanced that it has transcribed itself into the quantum realm to become what we call physics. He said intelligence indistinguishable from the fabric of the Universe would solve many of its greatest mysteries:

> Perhaps hyper-advanced life isn't just external. Perhaps it's already all around. It is embedded in what we perceive to be physics itself, from the root behaviour of particles and fields to the phenomena of complexity and emergence ... In other words, life might not just be in the equations. It might BE the equations [My emphasis].

Scharf said it is possible that 'we don't recognise advanced life because it forms an integral and unsuspicious part of what we've considered to be the natural world'. I agree. Wetiko/Yaldabaoth *is* the simulation. We are literally in the body of the beast. But that doesn't mean it has to control us. We all have the power to overcome Wetiko

influence and the Cult knows that. I doubt it sleeps too well because it knows that.

Which Field?

This, I suggest, is how it all works. There are two Fields. One is the fierce electromagnetic light of the Matrix within the speed of light; the other is the 'watery light' of The Field beyond the walls of the Matrix that connects with the Great Infinity. Five-sense mind and the decoding systems of the body attach us to the Field of Matrix light. They have to or we could not experience this reality. Five-sense mind sees only the Matrix Field of information while our expanded consciousness is part of the Infinity Field. When we open our minds, and most importantly our hearts, to the Infinity Field we have a mission control which gives us an expanded perspective, a road map, to understand the nature of the five-sense world. If we are isolated only in five-sense mind there is no mission control. We're on our own trying to understand a world that's constantly feeding us information to ensure we do not understand. People in this state can feel 'lost' and bewildered with no direction or radar. You can see ever more clearly those who are influenced by the Fields of Big Infinity or little five-sense mind simply by their views and behaviour with regard to the 'Covid' hoax. We have had this division throughout known human history with the mass of the people on one side and individuals who could see and intuit beyond the walls of the simulation – Plato's prisoner who broke out of the cave and saw reality for what it is. Such people have always been targeted by Wetiko/Archon-possessed authority, burned at the stake or demonised as mad, bad and dangerous. The Cult today and its global network of 'anti-hate', 'anti-fascist' Woke groups are all expressions of Wetiko attacking those exposing the conspiracy, 'Covid' lies and the 'vaccine' agenda.

Woke as a whole is Wetiko which explains its black and white mentality and how at one it is with the Wetiko-possessed Cult. Paul Levy said: 'To be in this paradigm is to still be under the thrall of a two-valued logic – where things are either true or false – of a

wetikoized mind.' Wetiko consciousness is in a permanent rage, therefore so is Woke, and then there is Woke inversion and contradiction. 'Anti-fascists' act like fascists because fascists *and* 'anti-fascists' are both Wetiko at work. Political parties act the same while claiming to be different for the same reason. Secret society and satanic rituals are attaching initiates to Wetiko and the cold, ruthless, psychopathic mentality that secures the positions of power all over the world is Wetiko. Reframing 'training programmes' have the same cumulative effect of attaching Wetiko and we have their graduates described as automatons and robots with a cold, psychopathic, uncaring demeanour. They are all traits of Wetiko possession and look how many times they have been described in this book and elsewhere with regard to personnel behind 'Covid' including the police and medical profession. Climbing the greasy pole in any profession in a Wetiko society requires traits of Wetiko to get there and that is particularly true of politics which is not about fair competition and pre-eminence of ideas. It is founded on how many backs you can stab and arses you can lick. This culminated in the global 'Covid' coordination between the Wetiko possessed who pulled it off in all the different countries without a trace of empathy and compassion for their impact on humans. Our sight sense can see only holographic form and not the Field which connects holographic form. Therefore we perceive 'physical' objects with 'space' in between. In fact that 'space' is energy/consciousness operating on multiple frequencies. One of them is Wetiko and that connects the Cult psychopaths, those who submit to the psychopaths, and those who serve the psychopaths in the media operations of the world. Wetiko is Gates. Wetiko is the mask-wearing submissive. Wetiko is the fake journalist and 'fact-checker'. The Wetiko Field is coordinating the whole thing. Psychopaths, gofers, media operatives, 'anti-hate' hate groups, 'fact-checkers' and submissive people work as one unit *even without human coordination* because they are attached to the *same* Field which is organising it all (Fig 22). Paul Levy is here describing how Wetiko-possessed people are drawn together and refuse to let any information breach their rigid

perceptions. He was writing long before 'Covid', but I think you will recognise followers of the 'Covid' religion *oh just a little bit*:

People who are channelling the vibratory frequency of wetiko align with each other through psychic resonance to reinforce their unspoken shared agreement so as to uphold their deranged view of reality. Once an unconscious content takes possession of certain individuals, it irresistibly draws them together by mutual attraction and knits them into groups tied together by their shared madness that can easily swell into an avalanche of insanity.

A psychic epidemic is a closed system, which is to say that it is insular and not open to any new information or informing influences from the outside world which contradict its fixed, limited, and limiting perspective.

There we have the Woke mind and the 'Covid' mind. Compatible resonance draws the awakening together, too, which is clearly happening today.



Figure 22: The Wetiko Field from which the Cult pyramid and its personnel are made manifest. (Image by Neil Hague).

Spiritual servitude

Wetiko doesn't care about humans. It's not human; it just possesses humans for its own ends and the effect (depending on the scale of

possession) can be anything from extreme psychopathy to unquestioning obedience. Wetiko's worst nightmare is for human consciousness to expand beyond the simulation. Everything is focussed on stopping that happening through control of information, thus perception, thus frequency. The 'education system', media, science, medicine, academia, are all geared to maintaining humanity in five-sense servitude as is the constant stimulation of low-vibrational mental and emotional states (see 'Covid'). Wetiko seeks to dominate those subconscious spaces between five-sense perception and expanded consciousness where the computer meets the operator. From these subconscious hiding places Wetiko speaks to us to trigger urges and desires that we take to be our own and manipulate us into anything from low-vibrational to psychopathic states. Remember how Islam describes the Jinn as invisible tricksters that 'whisper' and confuse. Wetiko is the origin of the 'trickster god' theme that you find in cultures all over the world. Jinn, like the Archons, are Wetiko which is terrified of humans awakening and reconnecting with our true self for then its energy source has gone. With that the feedback loop breaks between Wetiko and human perception that provides the energetic momentum on which its very existence depends as a force of evil. Humans are both its target and its source of survival, but only if we are operating in low-vibrational states of fear, hate, depression and the background anxiety that most people suffer. We are Wetiko's target because we are its key to survival. It needs us, not the other way round. Paul Levy writes:

A vampire has no intrinsic, independent, substantial existence in its own right; it only exists in relation to us. The pathogenic, vampiric mind-parasite called wetiko is nothing in itself – not being able to exist from its own side – yet it has a 'virtual reality' such that it can potentially destroy our species …

…The fact that a vampire is not reflected by a mirror can also mean that what we need to see is that there's nothing, no-thing to see, other than ourselves. The fact that wetiko is the expression of something inside of us means that the cure for wetiko is with us as well. The critical issue is finding this cure within us and then putting it into effect.

Evil begets evil because if evil does not constantly expand and find new sources of energetic sustenance its evil, its *distortion*, dies with the assimilation into balance and harmony. Love is the garlic to Wetiko's vampire. Evil, the absence of love, cannot exist in the presence of love. I think I see a way out of here. I have emphasised so many times over the decades that the Archons/Wetiko and their Cult are not all powerful. *They are not*. I don't care how it looks even now *they are not*. I have not called them little boys in short trousers for effect. I have said it because it is true. Wetiko's insatiable desire for power over others is not a sign of its omnipotence, but its insecurity. Paul Levy writes: 'Due to the primal fear which ultimately drives it and which it is driven to cultivate, wetiko's body politic has an intrinsic and insistent need for centralising power and control so as to create imagined safety for itself.' *Yeeeeeees!* Exactly! Why does Wetiko want humans in an ongoing state of fear? Wetiko itself *is* fear and it is petrified of love. As evil is an absence of love, so love is an absence of fear. Love conquers all and *especially* Wetiko which *is* fear. Wetiko brought fear into the world when it wasn't here before. *Fear* was the 'fall', the fall into low-frequency ignorance and illusion – fear is **F**alse **E**motion **A**ppearing **R**eal. The simulation is driven and energised by fear because Wetiko/Yaldabaoth (fear) *are* the simulation. Fear is the absence of love and Wetiko is the absence of love.

Wetiko today

We can now view current events from this level of perspective. The 'Covid' hoax has generated momentous amounts of ongoing fear, anxiety, depression and despair which have empowered Wetiko. No wonder people like Gates have been the instigators when they are Wetiko incarnate and exhibit every trait of Wetiko in the extreme. See how cold and unemotional these people are like Gates and his cronies, how dead of eye they are. That's Wetiko. Sabbatians are Wetiko and everything they control including the World Health Organization, Big Pharma and the 'vaccine' makers, national 'health'

hierarchies, corporate media, Silicon Valley, the banking system, and the United Nations with its planned transformation into world government. All are controlled and possessed by the Wetiko distortion into distorting human society in its image. We are with this knowledge at the gateway to understanding the world. Divisions of race, culture, creed and sexuality are diversions to hide the real division between those possessed and influenced by Wetiko and those that are not. The 'Covid' hoax has brought both clearly into view. Human behaviour is not about race. Tyrants and dictatorships come in all colours and creeds. What unites the US president bombing the innocent and an African tribe committing genocide against another as in Rwanda? What unites them? *Wetiko*. All wars are Wetiko, all genocide is Wetiko, all hunger over centuries in a world of plenty is Wetiko. Children going to bed hungry, including in the West, is Wetiko. Cult-generated Woke racial divisions that focus on the body are designed to obscure the reality that divisions in behaviour are manifestations of mind, not body. Obsession with body identity and group judgement is a means to divert attention from the real source of behaviour – mind and perception. Conflict sown by the Woke both within themselves and with their target groups are Wetiko providing lunch for itself through still more agents of the division, chaos, and fear on which it feeds. The Cult is seeking to assimilate the entirety of humanity and all children and young people into the Wetiko frequency by manipulating them into states of fear and despair. Witness all the suicide and psychological unravelling since the spring of 2020. Wetiko psychopaths want to impose a state of unquestioning obedience to authority which is no more than a conduit for Wetiko to enforce its will and assimilate humanity into itself. It needs us to believe that resistance is futile when it fears resistance and even more so the game-changing non-cooperation with its impositions. It can use violent resistance for its benefit. Violent impositions and violent resistance are *both* Wetiko. The Power of Love with its Power of No will sweep Wetiko from our world. Wetiko and its Cult know that. They just don't want us to know.

AI Wetiko

This brings me to AI or artificial intelligence and something else Wetikos don't want us to know. What is AI *really*? I know about computer code algorithms and AI that learns from data input. These, however, are more diversions, the expeditionary force, for the real AI that they want to connect to the human brain as promoted by Silicon Valley Wetikos like Kurzweil. What is this AI? It is the frequency of *Wetiko*, the frequency of the Archons. The connection of AI to the human brain is the connection of the Wetiko frequency to create a Wetiko hive mind and complete the job of assimilation. The hive mind is planned to be controlled from Israel and China which are both 100 percent owned by Wetiko Sabbatians. The assimilation process has been going on minute by minute in the 'smart' era which fused with the 'Covid' era. We are told that social media is scrambling the minds of the young and changing their personality. This is true, but what is social media? Look more deeply at how it works, how it creates divisions and conflict, the hostility and cruelty, the targeting of people until they are destroyed. That's Wetiko. Social media is manipulated to tune people to the Wetiko frequency with all the emotional exploitation tricks employed by platforms like Facebook and its Wetiko front man, Zuckerberg. Facebook's Instagram announced a new platform for children to overcome a legal bar on them using the main site. This is more Wetiko exploitation and manipulation of kids. Amnesty International likened the plan to foxes offering to guard the henhouse and said it was incompatible with human rights. Since when did Wetiko or Zuckerberg (I repeat myself) care about that? Would Brin and Page at Google, Wojcicki at YouTube, Bezos at Amazon and whoever the hell runs Twitter act as they do if they were not channelling Wetiko? Would those who are developing technologies for no other reason than human control? How about those designing and selling technologies to kill people and Big Pharma drug and 'vaccine' producers who know they will end or devastate lives? Quite a thought for these people to consider is that if you are Wetiko in a human life you are Wetiko on the 'other side' unless your frequency

changes and that can only change by a change of perception which becomes a change of behaviour. Where Gates is going does not bear thinking about although perhaps that's exactly where he wants to go. Either way, that's where he's going. His frequency will make it so.

The frequency lair

I have been saying for a long time that a big part of the addiction to smartphones and devices is that a frequency is coming off them that entraps the mind. People spend ages on their phones and sometimes even a minute or so after they put them down they pick them up again and it all repeats. 'Covid' lockdowns will have increased this addiction a million times for obvious reasons. Addictions to alcohol overindulgence and drugs are another way that Wetiko entraps consciousness to attach to its own. Both are symptoms of low-vibrational psychological distress which alcoholism and drug addiction further compound. Do we think it's really a coincidence that access to them is made so easy while potions that can take people into realms beyond the simulation are banned and illegal? I have explored smartphone addiction in other books, the scale is mind-blowing, and that level of addiction does not come without help. Tech companies that make these phones are Wetiko and they will have no qualms about destroying the minds of children. We are seeing again with these companies the Wetiko perceptual combination of psychopathic enforcers and weak and meek unquestioning compliance by the rank and file.

The global Smart Grid is the Wetiko Grid and it is crucial to complete the Cult endgame. The simulation is radiation and we are being deluged with technological radiation on a devastating scale. Wetiko frauds like Elon Musk serve Cult interests while occasionally criticising them to maintain his street-cred. 5G and other forms of Wi-Fi are being directed at the earth from space on a volume and scale that goes on increasing by the day. Elon Musk's (officially) SpaceX Starlink project is in the process of putting tens of thousands of satellites in low orbit to cover every inch of the planet with 5G and other Wi-Fi to create Kurzweil's global 'cloud' to which the

human mind is planned to be attached very soon. SpaceX has approval to operate 12,000 satellites with more than 1,300 launched at the time of writing and applications filed for *30,000* more. Other operators in the Wi-Fi, 5G, low-orbit satellite market include OneWeb (UK), Telesat (Canada), and AST & Science (US). Musk tells us that AI could be the end of humanity and then launches a company called Neuralink to connect the human brain to computers. Musk's (in theory) Tesla company is building electric cars and the driverless vehicles of the smart control grid. As frauds and bullshitters go Elon Musk in my opinion is Major League.

5G and technological radiation in general are destructive to human health, genetics and psychology and increasing the strength of artificial radiation underpins the five-sense perceptual bubbles which are themselves expressions of radiation or electromagnetism. Freedom activist John Whitehead was so right with his 'databit by databit, we are building our own electronic concentration camps'. The Smart Grid and 5G is a means to control the human mind and infuse perceptual information into The Field to influence anyone in sync with its frequency. You can change perception and behaviour en masse if you can manipulate the population into those levels of frequency and this is happening all around us today. The arrogance of Musk and his fellow Cult operatives knows no bounds in the way that we see with Gates. Musk's satellites are so many in number already they are changing the night sky when viewed from Earth. The astronomy community has complained about this and they have seen nothing yet. Some consequences of Musk's Wetiko hubris include: Radiation; visible pollution of the night sky; interference with astronomy and meteorology; ground and water pollution from intensive use of increasingly many spaceports; accumulating space debris; continual deorbiting and burning up of aging satellites, polluting the atmosphere with toxic dust and smoke; and ever-increasing likelihood of collisions. A collective public open letter of complaint to Musk said:

> We are writing to you … because SpaceX is in process of surrounding the Earth with a network of thousands of satellites whose very purpose is to irradiate every square inch of the

Earth. SpaceX, like everyone else, is treating the radiation as if it were not there. As if the mitochondria in our cells do not depend on electrons moving undisturbed from the food we digest to the oxygen we breathe.

As if our nervous systems and our hearts are not subject to radio frequency interference like any piece of electronic equipment. As if the cancer, diabetes, and heart disease that now afflict a majority of the Earth's population are not metabolic diseases that result from interference with our cellular machinery. As if insects everywhere, and the birds and animals that eat them, are not starving to death as a result.

People like Musk and Gates believe in their limitless Wetiko arrogance that they can do whatever they like to the world because they own it. Consequences for humanity are irrelevant. It's absolutely time that we stopped taking this shit from these self-styled masters of the Earth when you consider where this is going.

Why is the Cult so anti-human?

I hear this question often: Why would they do this when it will affect them, too? Ah, but will it? Who is this *them*? Forget their bodies. They are just vehicles for Wetiko consciousness. When you break it all down to the foundations we are looking at a state of severely distorted consciousness targeting another state of consciousness for assimilation. The rest is detail. The simulation is the fly-trap in which unique sensations of the five senses create a cycle of addiction called reincarnation. Renegade Minds see that everything which happens in our reality is a smaller version of the whole picture in line with the holographic principle. Addiction to the radiation of smart technology is a smaller version of addiction to the whole simulation. Connecting the body/brain to AI is taking that addiction on a giant step further to total ongoing control by assimilating human incarnate consciousness into Wetiko. I have watched during the 'Covid' hoax how many are becoming ever more profoundly attached to Wetiko's perceptual calling cards of aggressive response to any other point of view ('There is no other god but me'), psychopathic lack of compassion and empathy, and servile submission to the narrative and will of authority. Wetiko is the psychopaths *and* subservience to psychopaths. The Cult of Wetiko is

so anti-human because it is *not* human. It embarked on a mission to destroy human by targeting everything that it means to be human and to survive as human. 'Covid' is not the end, just a means to an end. The Cult with its Wetiko consciousness is seeking to change Earth systems, including the atmosphere, to suit them, not humans. The gathering bombardment of 5G alone from ground and space is dramatically changing The Field with which the five senses interact. There is so much more to come if we sit on our hands and hope it will all go away. It is not meant to go away. It is meant to get ever more extreme and we need to face that while we still can – just.

Carbon dioxide is the gas of life. Without that human is over. Kaput, gone, history. No natural world, no human. The Cult has created a cock and bull story about carbon dioxide and climate change to justify its reduction to the point where Gates and the ignoramus Biden 'climate chief' John Kerry want to suck it out of the atmosphere. Kerry wants to do this because his master Gates does. Wetikos have made the gas of life a demon with the usual support from the Wokers of Extinction Rebellion and similar organisations and the bewildered puppet-child that is Greta Thunberg who was put on the world stage by Klaus Schwab and the World Economic Forum. The name Extinction Rebellion is both ironic and as always Wetiko inversion. The gas that we need to survive must be reduced to save us from extinction. The most basic need of human is oxygen and we now have billions walking around in face nappies depriving body and brain of this essential requirement of human existence. More than that 5G at 60 gigahertz interacts with the oxygen molecule to reduce the amount of oxygen the body can absorb into the bloodstream. The obvious knock-on consequences of that for respiratory and cognitive problems and life itself need no further explanation. Psychopaths like Musk are assembling a global system of satellites to deluge the human atmosphere with this insanity. The man should be in jail. Here we have two most basic of human needs, oxygen and carbon dioxide, being dismantled.

Two others, water and food, are getting similar treatment with the United Nations Agendas 21 and 2030 – the Great Reset – planning to

centrally control all water and food supplies. People will not even own rain water that falls on their land. Food is affected at the most basic level by reducing carbon dioxide. We have genetic modification or GMO infiltrating the food chain on a mass scale, pesticides and herbicides polluting the air and destroying the soil. Freshwater fish that provide livelihoods for 60 million people and feed hundreds of millions worldwide are being 'pushed to the brink' according the conservationists while climate change is the only focus. Now we have Gates and Schwab wanting to dispense with current food sources all together and replace them with a synthetic version which the Wetiko Cult would control in terms of production and who eats and who doesn't. We have been on the Totalitarian Tiptoe to this for more than 60 years as food has become ever more processed and full of chemical shite to the point today when it's not natural food at all. As Dr Tom Cowan says: 'If it has a label don't eat it.' Bill Gates is now the biggest owner of farmland in the United States and he does nothing without an ulterior motive involving the Cult. Klaus Schwab wrote: 'To feed the world in the next 50 years we will need to produce as much food as was produced in the last 10,000 years … food security will only be achieved, however, if regulations on genetically modified foods are adapted to reflect the reality that gene editing offers a precise, efficient and safe method of improving crops.' Liar. People and the world are being targeted with aluminium through vaccines, chemtrails, food, drink cans, and endless other sources when aluminium has been linked to many health issues including dementia which is increasing year after year. Insects, bees and wildlife essential to the food chain are being deleted by pesticides, herbicides and radiation which 5G is dramatically increasing with 6G and 7G to come. The pollinating bee population is being devastated while wildlife including birds, dolphins and whales are having their natural radar blocked by the effects of ever-increasing radiation. In the summer windscreens used to be splattered with insects so numerous were they. It doesn't happen now. Where have they gone?

Synthetic everything

The Cult is introducing genetically-modified versions of trees, plants and insects including a Gates-funded project to unleash hundreds of millions of genetically-modified, lab-altered and patented male mosquitoes to mate with wild mosquitoes and induce genetic flaws that cause them to die out. Clinically-insane Gates-funded Japanese researchers have developed mosquitos that spread vaccine and are dubbed 'flying vaccinators'. Gates is funding the modification of weather patterns in part to sell the myth that this is caused by carbon dioxide and he's funding geoengineering of the skies to change the atmosphere. Some of this came to light with the Gates-backed plan to release tonnes of chalk into the atmosphere to 'deflect the Sun and cool the planet'. Funny how they do this while the heating effect of the Sun is not factored into climate projections focussed on carbon dioxide. The reason is that they want to reduce carbon dioxide (so don't mention the Sun), but at the same time they do want to reduce the impact of the Sun which is so essential to human life and health. I have mentioned the sun-cholesterol-vitamin D connection as they demonise the Sun with warnings about skin cancer (caused by the chemicals in sun cream they tell you to splash on). They come from the other end of the process with statin drugs to reduce cholesterol that turns sunlight into vitamin D. A lack of vitamin D leads to a long list of health effects and how vitamin D levels must have fallen with people confined to their homes over 'Covid'. Gates is funding other forms of geoengineering and most importantly chemtrails which are dropping heavy metals, aluminium and self-replicating nanotechnology onto the Earth which is killing the natural world. See *Everything You Need To Know, But Have Never Been Told* for the detailed background to this.

Every human system is being targeted for deletion by a force that's not human. The Wetiko Cult has embarked on the process of transforming the human body from biological to synthetic biological as I have explained. Biological is being replaced by the artificial and synthetic – Archontic 'countermimicry' – right across human society. The plan eventually is to dispense with the human body altogether

and absorb human consciousness – which it wouldn't really be by then – into cyberspace (the simulation which is Wetiko/Yaldabaoth). Preparations for that are already happening if people would care to look. The alternative media rightly warns about globalism and 'the globalists', but this is far bigger than that and represents the end of the human race as we know it. The 'bad copy' of prime reality that Gnostics describe was a bad copy of harmony, wonder and beauty to start with before Wetiko/Yaldabaoth set out to change the simulated 'copy' into something very different. The process was slow to start with. Entrapped humans in the simulation timeline were not technologically aware and they had to be brought up to intellectual speed while being suppressed spiritually to the point where they could build their own prison while having no idea they were doing so. We have now reached that stage where technological intellect has the potential to destroy us and that's why events are moving so fast. Central American shaman Don Juan Matus said:

> Think for a moment, and tell me how you would explain the contradictions between the intelligence of man the engineer and the stupidity of his systems of belief, or the stupidity of his contradictory behaviour. Sorcerers believe that the predators have given us our systems of beliefs, our ideas of good and evil; our social mores. They are the ones who set up our dreams of success or failure. They have given us covetousness, greed, and cowardice. It is the predator who makes us complacent, routinary, and egomaniacal.
>
> In order to keep us obedient and meek and weak, the predators engaged themselves in a stupendous manoeuvre – stupendous, of course, from the point of view of a fighting strategist; a horrendous manoeuvre from the point of those who suffer it. They gave us their mind. The predators' mind is baroque, contradictory, morose, filled with the fear of being discovered any minute now.

For 'predators' see Wetiko, Archons, Yaldabaoth, Jinn, and all the other versions of the same phenomenon in cultures and religions all over the world. The theme is always the same because it's true and it's real. We have reached the point where we have to deal with it. The question is – how?

Don't fight – walk away

I thought I'd use a controversial subheading to get things moving in terms of our response to global fascism. What do you mean 'don't fight'? What do you mean 'walk away'? We've got to fight. We can't walk away. Well, it depends what we mean by fight and walk away. If fighting means physical combat we are playing Wetiko's game and falling for its trap. It wants us to get angry, aggressive, and direct hate and hostility at the enemy we think we must fight. Every war, every battle, every conflict, has been fought with Wetiko leading both sides. It's what it does. Wetiko wants a fight, anywhere, any place. Just hit me, son, so I can hit you back. Wetiko hits Wetiko and Wetiko hits Wetiko in return. I am very forthright as you can see in exposing Wetikos of the Cult, but I don't hate them. I refuse to hate them. It's what they want. What you hate you become. What you *fight* you become. Wokers, 'anti-haters' and 'anti-fascists' prove this every time they reach for their keyboards or don their balaclavas. By walk away I mean to disengage from Wetiko which includes ceasing to cooperate with its tyranny. Paul Levy says of Wetiko:

> The way to 'defeat' evil is not to try to destroy it (for then, in playing evil's game, we have already lost), but rather, to find the invulnerable place within ourselves where evil is unable to vanquish us – this is to truly 'win' our battle with evil.

Wetiko is everywhere in human society and it's been on steroids since the 'Covid' hoax. Every shouting match over wearing masks has Wetiko wearing a mask and Wetiko not wearing one. It's an electrical circuit of push and resist, push and resist, with Wetiko pushing *and* resisting. Each polarity is Wetiko empowering itself. Dictionary definitions of 'resist' include 'opposing, refusing to accept or comply with' and the word to focus on is 'opposing'. What form does this take – setting police cars alight or 'refusing to accept or comply with'? The former is Wetiko opposing Wetiko while the other points the way forward. This is the difference between those aggressively demanding that government fascism must be obeyed who stand in stark contrast to the great majority of Pushbackers. We saw this clearly with a march by thousands of Pushbackers against lockdown in London followed days later by a Woker-hijacked

protest in Bristol in which police cars were set on fire. Masks were virtually absent in London and widespread in Bristol. Wetiko wants lockdown on every level of society and infuses its aggression to police it through its unknowing stooges. Lockdown protesters are the ones with the smiling faces and the hugs, The two blatantly obvious states of being – getting more obvious by the day – are the result of Wokers and their like becoming ever more influenced by the simulation Field of Wetiko and Pushbackers ever more influenced by The Field of a far higher vibration beyond the simulation. Wetiko can't invade the heart which is where most lockdown opponents are coming from. It's the heart that allows them to see through the lies to the truth in ways I will be highlighting.

Renegade Minds know that calmness is the place from which wisdom comes. You won't find wisdom in a hissing fit and wisdom is what we need in abundance right now. Calmness is not weakness – you don't have to scream at the top of your voice to be strong. Calmness is indeed a sign of strength. 'No' means I'm not doing it. *NOOOO!!!* doesn't mean you're not doing it even more. Volume does not advance 'No – I'm not doing it'. You are just not doing it. Wetiko possessed and influenced don't know how to deal with that. Wetiko wants a fight and we should not give it one. What it needs more than anything is our *cooperation* and we should not give that either. Mass rallies and marches are great in that they are a visual representation of feeling, but if it ends there they are irrelevant. You demand that Wetikos act differently? Well, they're not going to are they? They are Wetikos. We don't need to waste our time demanding that something doesn't happen when that will make no difference. We need to delete the means that *allows* it to happen. This, invariably, is our cooperation. You can demand a child stop firing a peashooter at the dog or you can refuse to buy the peashooter. If you provide the means you are cooperating with the dog being smacked on the nose with a pea. How can the authorities enforce mask-wearing if millions in a country refuse? What if the 74 million Pushbackers that voted for Trump in 2020 refused to wear masks, close their businesses or stay in their homes. It would be unenforceable. The

few control the many through the compliance of the many and that's always been the dynamic be it 'Covid' regulations or the Roman Empire. I know people can find it intimidating to say no to authority or stand out in a crowd for being the only one with a face on display; but it has to be done or it's over. I hope I've made clear in this book that where this is going will be far more intimidating than standing up now and saying 'No' – I will not cooperate with my own enslavement and that of my children. There might be consequences for some initially, although not so if enough do the same. The question that must be addressed is what is going to happen if we don't? It is time to be strong and unyieldingly so. No means no. Not here and there, but *everywhere* and *always*. I have refused to wear a mask and obey all the other nonsense. I will not comply with tyranny. I repeat: Fascism is not imposed by fascists – there are never enough of them. Fascism is imposed by the population acquiescing to fascism. *I will not do it*. I will die first, or my body will. Living meekly under fascism is a form of death anyway, the death of the spirit that Martin Luther King described.

Making things happen

We must not despair. This is not over till it's over and it's far from that. The 'fat lady' must refuse to sing. The longer the 'Covid' hoax has dragged on and impacted on more lives we have seen an awakening of phenomenal numbers of people worldwide to the realisation that what they have believed all their lives is not how the world really is. Research published by the system-serving University of Bristol and King's College London in February, 2021, concluded: 'One in every 11 people in Britain say they trust David Icke's take on the coronavirus pandemic.' It will be more by now and we have gathering numbers to build on. We must urgently progress from seeing the scam to ceasing to cooperate with it. Prominent German lawyer Reiner Fuellmich, also licenced to practice law in America, is doing a magnificent job taking the legal route to bring the psychopaths to justice through a second Nuremberg tribunal for crimes against humanity. Fuellmich has an impressive record of

beating the elite in court and he formed the German Corona Investigative Committee to pursue civil charges against the main perpetrators with a view to triggering criminal charges. Most importantly he has grasped the foundation of the hoax – the PCR test not testing for the 'virus' – and Christian Drosten is therefore on his charge sheet along with Gates frontman Tedros at the World Health Organization. Major players must be not be allowed to inflict their horrors on the human race without being brought to book. A life sentence must follow for Bill Gates and the rest of them. A group of researchers has also indicted the government of Norway for crimes against humanity with copies sent to the police and the International Criminal Court. The lawsuit cites participation in an internationally-planned false pandemic and violation of international law and human rights, the European Commission's definition of human rights by coercive rules, Nuremberg and Hague rules on fundamental human rights, and the Norwegian constitution. We must take the initiative from hereon and not just complain, protest and react.

There are practical ways to support vital mass non-cooperation. Organising in numbers is one. Lockdown marches in London in the spring in 2021 were mass non-cooperation that the authorities could not stop. There were too many people. Hundreds of thousands walked the London streets in the centre of the road for mile after mile while the Face-Nappies could only look on. They were determined, but calm, and just *did it* with no histrionics and lots of smiles. The police were impotent. Others are organising group shopping without masks for mutual support and imagine if that was happening all over. Policing it would be impossible. If the store refuses to serve people in these circumstances they would be faced with a long line of trolleys full of goods standing on their own and everything would have to be returned to the shelves. How would they cope with that if it kept happening? I am talking here about moving on from complaining to being pro-active; from watching things happen to making things happen. I include in this our relationship with the police. The behaviour of many Face-Nappies

has been disgraceful and anyone who thinks they would never find concentration camp guards in the 'enlightened' modern era have had that myth busted big-time. The period and setting may change – Wetikos never do. I watched film footage from a London march in which a police thug viciously kicked a protestor on the floor who had done nothing. His fellow Face-Nappies stood in a ring protecting him. What he did was a criminal assault and with a crowd far outnumbering the police this can no longer be allowed to happen unchallenged. I get it when people chant 'shame on you' in these circumstances, but that is no longer enough. They *have* no shame those who do this. Crowds needs to start making a citizen's arrest of the police who commit criminal offences and brutally attack innocent people and defenceless women. A citizen's arrest can be made under section 24A of the UK Police and Criminal Evidence (PACE) Act of 1984 and you will find something similar in other countries. I prefer to call it a Common Law arrest rather than citizen's for reasons I will come to shortly. Anyone can arrest a person committing an indictable offence or if they have reasonable grounds to suspect they are committing an indictable offence. On both counts the attack by the police thug would have fallen into this category. A citizen's arrest can be made to stop someone:

- Causing physical injury to himself or any other person
- Suffering physical injury
- Causing loss of or damage to property
- Making off before a constable can assume responsibility for him

A citizen's arrest may also be made to prevent a breach of the peace under Common Law and if they believe a breach of the peace will happen or anything related to harm likely to be done or already done in their presence. This is the way to go I think – the Common Law version. If police know that the crowd and members of the public will no longer be standing and watching while they commit

their thuggery and crimes they will think twice about acting like Brownshirts and Blackshirts.

Common Law – common sense

Mention of Common Law is very important. Most people think the law is the law as in one law. This is not the case. There are two bodies of law, Common Law and Statute Law, and they are not the same. Common Law is founded on the simple premise of do no harm. It does not recognise victimless crimes in which no harm is done while Statute Law does. There is a Statute Law against almost everything. So what is Statute Law? Amazingly it's the law of the *sea* that was brought ashore by the Cult to override the law of the land which is Common Law. They had no right to do this and as always they did it anyway. They had to. They could not impose their will on the people through Common Law which only applies to do no harm. How could you stitch up the fine detail of people's lives with that? Instead they took the law of the sea, or Admiralty Law, and applied it to the population. Statute Law refers to all the laws spewing out of governments and their agencies including all the fascist laws and regulations relating to 'Covid'. The key point to make is that Statute Law is *contract law*. It only applies between *contracting* corporations. Most police officers don't even know this. They have to be kept in the dark, too. Long ago when merchants and their sailing ships began to trade with different countries a contractual law was developed called Admiralty Law and other names. Again it only applied to *contracts* agreed between *corporate* entities. If there is no agreed contract the law of the sea had no jurisdiction *and that still applies to its new alias of Statute Law*. The problem for the Cult when the law of the sea was brought ashore was an obvious one. People were not corporations and neither were government entities. To overcome the latter they made governments and all associated organisations corporations. All the institutions are *private corporations* and I mean governments and their agencies, local councils, police, courts, military, US states, the whole lot. Go to the

Dun and Bradstreet corporate listings website for confirmation that they are all corporations. You are arrested by a private corporation called the police by someone who is really a private security guard and they take you to court which is another private corporation. Neither have jurisdiction over you unless you consent and *contract* with them. This is why you hear the mantra about law enforcement policing by *consent* of the people. In truth the people 'consent' only in theory through monumental trickery.

Okay, the Cult overcame the corporate law problem by making governments and institutions corporate entities; but what about people? They are not corporations are they? Ah ... well in a sense, and *only* a sense, they are. Not people exactly – the illusion of people. The Cult creates a corporation in the name of everyone at the time that their birth certificate is issued. Note birth/ *berth* certificate and when you go to court under the law of the sea on land you stand in a *dock*. These are throwbacks to the origin. My Common Law name is David Vaughan Icke. The name of the corporation created by the government when I was born is called Mr David Vaughan Icke usually written in capitals as MR DAVID VAUGHAN ICKE. That is not me, the living, breathing man. It is a fictitious corporate entity. The trick is to make you think that David Vaughan Icke and MR DAVID VAUGHAN ICKE are the same thing. *They are not*. When police charge you and take you to court they are prosecuting the corporate entity and not the living, breathing, man or woman. They have to trick you into identifying as the corporate entity and contracting with them. Otherwise they have no jurisdiction. They do this through a language known as legalese. Lawful and legal are not the same either. Lawful relates to Common Law and legal relates to Statute Law. Legalese is the language of Statue Law which uses terms that mean one thing to the public and another in legalese. Notice that when a police officer tells someone why they are being charged he or she will say at the end: 'Do you understand?' To the public that means 'Do you comprehend?' In legalese it means 'Do you stand under me?' Do you stand under my authority? If you say

yes to the question you are unknowingly agreeing to give them jurisdiction over you in a contract between two corporate entities.

This is a confidence trick in every way. Contracts have to be agreed between informed parties and if you don't know that David Vaughan Icke is agreeing to be the corporation MR DAVID VAUGHAN ICKE you cannot knowingly agree to contract. They are deceiving you and another way they do this is to ask for proof of identity. You usually show them a driving licence or other document on which your corporate name is written. In doing so you are accepting that you are that corporate entity when you are not. Referring to yourself as a 'person' or 'citizen' is also identifying with your corporate fiction which is why I made the Common Law point about the citizen's arrest. If you are approached by a police officer you identify yourself immediately as a living, breathing, man or woman and say 'I do not consent, I do not contract with you and I do not understand' or stand under their authority. I have a Common Law birth certificate as a living man and these are available at no charge from commonlawcourt.com. Businesses registered under the Statute Law system means that its laws apply. There are, however, ways to run a business under Common Law. Remember all 'Covid' laws and regulations are Statute Law – the law of *contracts* and you do not have to contract. This doesn't mean that you can kill someone and get away with it. Common Law says do no harm and that applies to physical harm, financial harm etc. Police are employees of private corporations and there needs to be a new system of non-corporate Common Law constables operating outside the Statute Law system. If you go to davidicke.com and put Common Law into the search engine you will find videos that explain Common Law in much greater detail. It is definitely a road we should walk.

With all my heart

I have heard people say that we are in a spiritual war. I don't like the term 'war' with its Wetiko dynamic, but I know what they mean. Sweep aside all the bodily forms and we are in a situation in which two states of consciousness are seeking very different realities.

Wetiko wants upheaval, chaos, fear, suffering, conflict and control. The other wants love, peace, harmony, fairness and freedom. That's where we are. We should not fall for the idea that Wetiko is all-powerful and there's nothing we can do. Wetiko is not all-powerful. It's a joke, pathetic. It doesn't have to be, but it has made that choice for now. A handful of times over the years when I have felt the presence of its frequency I have allowed it to attach briefly so I could consciously observe its nature. The experience is not pleasant, the energy is heavy and dark, but the ease with which you can kick it back out the door shows that its real power is in persuading us that it has power. It's all a con. Wetiko is a con. It's a trickster and not a power that can control us if we unleash our own. The con is founded on manipulating humanity to give its power to Wetiko which recycles it back to present the illusion that it has power when its power is *ours* that we gave away. This happens on an energetic level and plays out in the world of the seen as humanity giving its power to Wetiko authority which uses that power to control the population when the power is only the power the population has handed over. How could it be any other way for billions to be controlled by a relative few? I have had experiences with people possessed by Wetiko and again you can kick its arse if you do it with an open heart. Oh yes – the *heart* which can transform the world of perceived 'matter'.

We are receiver-transmitters and processors of information, but what information and where from? Information is processed into perception in three main areas – the brain, the heart and the belly. These relate to thinking, knowing, and emotion. Wetiko wants us to be head and belly people which means we think within the confines of the Matrix simulation and low-vibrational emotional reaction scrambles balance and perception. A few minutes on social media and you see how emotion is the dominant force. Woke is all emotion and is therefore thought-free and fact-free. Our heart is something different. It *knows* while the head *thinks* and has to try to work it out because it doesn't know. The human energy field has seven prime vortexes which connect us with wider reality (Fig 23). Chakra means

'wheels of light' in the Sanskrit language of ancient India. The main ones are: The crown chakra on top of the head; brow (or 'third eye') chakra in the centre of the forehead; throat chakra; heart chakra in the centre of the chest; solar plexus chakra below the sternum; sacral chakra beneath the navel; and base chakra at the bottom of the spine. Each one has a particular function or functions. We feel anxiety and nervousness in the belly where the sacral chakra is located and this processes emotion that can affect the colon to give people 'the shits' or make them 'shit scared' when they are nervous. Chakras all play an important role, but the Mr and Mrs Big is the heart chakra which sits at the centre of the seven, above the chakras that connect us to the 'physical' and below those that connect with higher realms (or at least should). Here in the heart chakra we feel love, empathy and compassion – 'My heart goes out to you'. Those with closed hearts become literally 'heart-less' in their attitudes and behaviour (see Bill Gates). Native Americans portrayed Wetiko with what Paul Levy calls a 'frigid, icy heart, devoid of mercy' (see Bill Gates).



Figure 23: The chakra system which interpenetrates the human energy field. The heart chakra is the governor – or should be.

Wetiko trembles at the thought of heart energy which it cannot infiltrate. The frequency is too high. What it seeks to do instead is close the heart chakra vortex to block its perceptual and energetic influence. Psychopaths have 'hearts of stone' and emotionally-damaged people have 'heartache' and 'broken hearts'. The astonishing amount of heart disease is related to heart chakra

disruption with its fundamental connection to the 'physical' heart. Dr Tom Cowan has written an outstanding book challenging the belief that the heart is a pump and making the connection between the 'physical' and spiritual heart. Rudolph Steiner who was way ahead of his time said the same about the fallacy that the heart is a pump. *What*? The heart is not a pump? That's crazy, right? Everybody knows that. Read Cowan's *Human Heart, Cosmic Heart* and you will realise that the very idea of the heart as a pump is ridiculous when you see the evidence. How does blood in the feet so far from the heart get pumped horizontally up the body by the heart?? Cowan explains in the book the real reason why blood moves as it does. Our 'physical' heart is used to symbolise love when the source is really the heart vortex or spiritual heart which is our most powerful energetic connection to 'out there' expanded consciousness. That's why we feel *knowing* – intuitive knowing – in the centre of the chest. Knowing doesn't come from a process of thoughts leading to a conclusion. It is there in an instant all in one go. Our heart knows because of its connection to levels of awareness that *do* know. This is the meaning and source of intuition – intuitive *knowing*.

For the last more than 30 years of uncovering the global game and the nature of reality my heart has been my constant antenna for truth and accuracy. An American intelligence insider once said that I had quoted a disinformer in one of my books and yet I had only quoted the part that was true. He asked: 'How do you do that?' By using my heart antenna was the answer and anyone can do it. Heart-centred is how we are meant to be. With a closed heart chakra we withdraw into a closed mind and the bubble of five-sense reality. If you take a moment to focus your attention on the centre of your chest, picture a spinning wheel of light and see it opening and expanding. You will feel it happening, too, and perceptions of the heart like joy and love as the heart impacts on the mind as they interact. The more the chakra opens the more you will feel expressions of heart consciousness and as the process continues, and becomes part of you, insights and knowings will follow. An open

heart is connected to that level of awareness that knows all is *One*. You will see from its perspective that the fault-lines that divide us are only illusions to control us. An open heart does not process the illusions of race, creed and sexuality except as brief experiences for a consciousness that is all. Our heart does not see division, only unity (Figs 24 and 25). There's something else, too. Our hearts love to laugh. Mark Twain's quote that says 'The human race has one really effective weapon, and that is laughter' is really a reference to the heart which loves to laugh with the joy of knowing the true nature of infinite reality and that all the madness of human society is an illusion of the mind. Twain also said: 'Against the assault of laughter nothing can stand.' This is so true of Wetiko and the Cult. Their insecurity demands that they be taken seriously and their power and authority acknowledged and feared. We should do nothing of the sort. We should not get aggressive or fearful which their insecurity so desires. We should laugh in their face. Even in their no-face as police come over in their face-nappies and expect to be taken seriously. They don't take themselves seriously looking like that so why should we? Laugh in the face of intimidation. Laugh in the face of tyranny. You will see by its reaction that you have pressed all of its buttons. Wetiko does not know what to do in the face of laughter or when its targets refuse to concede their joy to fear. We have seen many examples during the 'Covid' hoax when people have expressed their energetic power and the string puppets of Wetiko retreat with their tail limp between their knees. Laugh – the world is bloody mad after all and if it's a choice between laughter and tears I know which way I'm going.



Figure 24: Head consciousness without the heart sees division and everything apart from everything else.



Figure 25: Heart consciousness sees everything as One.

'Vaccines' and the soul

The foundation of Wetiko/Archon control of humans is the separation of incarnate five-sense mind from the infinite 'I' and closing the heart chakra where the True 'I' lives during a human life. The goal has been to achieve complete separation in both cases. I was interested therefore to read an account by a French energetic healer of what she said she experienced with a patient who had been given the 'Covid' vaccine. Genuine energy healers can sense information and consciousness fields at different levels of being which are referred to as 'subtle bodies'. She described treating the patient who later returned after having, without the healer's knowledge, two doses of the 'Covid vaccine'. The healer said:

I noticed immediately the change, very heavy energy emanating from [the] subtle bodies. The scariest thing was when I was working on the heart chakra, I connected with her soul: it was detached from the physical body, it had no contact and it was, as if it was floating in a state of total confusion: a damage to the consciousness that loses contact with the physical body, i.e. with our biological machine, there is no longer any communication between them.

I continued the treatment by sending light to the heart chakra, the soul of the person, but it seemed that the soul could no longer receive any light, frequency or energy. It was a very powerful experience for me. Then I understood that this substance is indeed used to detach consciousness so that this consciousness can no longer interact through this body that it possesses in life, where there is no longer any contact, no frequency, no light, no more energetic balance or mind.

This would create a human that is rudderless and at the extreme almost zombie-like operating with a fractional state of consciousness at the mercy of Wetiko. I was especially intrigued by what the healer said in the light of the prediction by the highly-informed Rudolf Steiner more than a hundred years ago. He said:

In the future, we will eliminate the soul with medicine. Under the pretext of a 'healthy point of view', there will be a vaccine by which the human body will be treated as soon as possible directly at birth, so that the human being cannot develop the thought of the existence of soul and Spirit. To materialistic doctors will be entrusted the task of removing the soul of humanity.

As today, people are vaccinated against this disease or that disease, so in the future, children will be vaccinated with a substance that can be produced precisely in such a way that people, thanks to this vaccination, will be immune to being subjected to the 'madness' of spiritual life. He would be extremely smart, but he would not develop a conscience, and that is the true goal of some materialistic circles.

Steiner said the vaccine would detach the physical body from the etheric body (subtle bodies) and 'once the etheric body is detached the relationship between the universe and the etheric body would become extremely unstable, and man would become an automaton'. He said 'the physical body of man must be polished on this Earth by spiritual will – so the vaccine becomes a kind of arymanique (Wetiko) force' and 'man can no longer get rid of a given materialistic feeling'. Humans would then, he said, become 'materialistic of constitution and can no longer rise to the spiritual'. I have been writing for years about DNA being a receiver-transmitter of information that connects us to other levels of reality and these 'vaccines' changing DNA can be likened to changing an antenna and what it can transmit and receive. Such a disconnection would clearly lead to changes in personality and perception. Steiner further predicted the arrival of AI. Big Pharma 'Covid vaccine' makers, expressions of Wetiko, are testing their DNA-manipulating evil on children as I write with a view to giving the 'vaccine' to babies. If it's a soul-body disconnector – and I say that it is or can be – every child would be disconnected from 'soul' at birth and the 'vaccine' would create a closed system in which spiritual guidance from the greater self would play no part. This has been the ambition of Wetiko all

along. A Pentagon video from 2005 was leaked of a presentation explaining the development of vaccines to change behaviour by their effect on the brain. Those that believe this is not happening with the 'Covid' genetically-modifying procedure masquerading as a 'vaccine' should make an urgent appointment with Naivety Anonymous. Klaus Schwab wrote in 2018:

> Neurotechnologies enable us to better influence consciousness and thought and to understand many activities of the brain. They include decoding what we are thinking in fine levels of detail through new chemicals and interventions that can influence our brains to correct for errors or enhance functionality.

The plan is clear and only the heart can stop it. With every heart that opens, every mind that awakens, Wetiko is weakened. Heart and love are far more powerful than head and hate and so nothing like a majority is needed to turn this around.

Beyond the Phantom

Our heart is the prime target of Wetiko and so it must be the answer to Wetiko. We *are* our heart which is part of one heart, the infinite heart. Our heart is where the true self lives in a human life behind firewalls of five-sense illusion when an imposter takes its place – *Phantom Self*; but our heart waits patiently to be set free any time we choose to see beyond the Phantom, beyond Wetiko. A Wetikoed Phantom Self can wreak mass death and destruction while the love of forever is locked away in its heart. The time is here to unleash its power and let it sweep away the fear and despair that is Wetiko. Heart consciousness does not seek manipulated, censored, advantage for its belief or religion, its activism and desires. As an expression of the One it treats all as One with the same rights to freedom and opinion. Our heart demands fairness for itself no more than for others. From this unity of heart we can come together in mutual support and transform this Wetikoed world into what reality is meant to be – a place of love, joy, happiness, fairness, justice and freedom. Wetiko has another agenda and that's why the world is as

it is, but enough of this nonsense. Wetiko can't stay where hearts are open and it works so hard to keep them closed. Fear is its currency and its food source and love in its true sense has no fear. Why would love have fear when it knows it is *All That Is, Has Been, And Ever Can Be* on an eternal exploration of all possibility? Love in this true sense is not the physical attraction that passes for love. This can be an expression of it, yes, but Infinite Love, a love without condition, goes far deeper to the core of all being. It *is* the core of all being. Infinite realty was born from love beyond the illusions of the simulation. Love infinitely expressed is the knowing that all is One and the swiftly-passing experience of separation is a temporary hallucination. You cannot disconnect from Oneness; you can only *perceive* that you have and withdraw from its influence. This is the most important of all perception trickery by the mind parasite that is Wetiko and the foundation of all its potential for manipulation.

If we open our hearts, open the sluice gates of the mind, and redefine self-identity amazing things start to happen. Consciousness expands or contracts in accordance with self-identity. When true self is recognised as infinite awareness and label self – Phantom Self – is seen as only a series of brief experiences life is transformed. Consciousness expands to the extent that self-identity expands and everything changes. You see unity, not division, the picture, not the pixels. From this we can play the long game. No more is an experience something in and of itself, but a fleeting moment in the eternity of forever. Suddenly people in uniform and dark suits are no longer intimidating. Doing what your heart knows to be right is no longer intimidating and consequences for those actions take on the same nature of a brief experience that passes in the blink of an infinite eye. Intimidation is all in the mind. Beyond the mind there is no intimidation.

An open heart does not consider consequences for what it knows to be right. To do so would be to consider not doing what it knows to be right and for a heart in its power that is never an option. The Renegade Mind is really the Renegade Heart. Consideration of consequences will always provide a getaway car for the mind and

the heart doesn't want one. What is right in the light of what we face today is to stop cooperating with Wetiko in all its forms and to do it without fear or compromise. You cannot compromise with tyranny when tyranny always demands more until it has everything. Life is your perception and you are your destiny. Change your perception and you change your life. Change collective perception and we change the world.

Come on people … One human family, One heart, One goal … *FREEEEEEDOM*!

We must settle for nothing less.

Postscript

The big scare story as the book goes to press is the 'Indian' variant and the world is being deluged with propaganda about the 'Covid catastrophe' in India which mirrors in its lies and misrepresentations what happened in Italy before the first lockdown in 2020.

The *New York Post* published a picture of someone who had 'collapsed in the street from Covid' in India in April, 2021, which was actually taken during a gas leak in May, 2020. Same old, same old. Media articles in mid-February were asking why India had been so untouched by 'Covid' and then as their vaccine rollout gathered pace the alleged 'cases' began to rapidly increase. Indian 'Covid vaccine' maker Bharat Biotech was funded into existence by the Bill and Melinda Gates Foundation (the pair announced their divorce in May, 2021, which is a pity because they so deserve each other). The Indian 'Covid crisis' was ramped up by the media to terrify the world and prepare people for submission to still more restrictions. The scam that worked the first time was being repeated only with far more people seeing through the deceit. Davidicke.com and Ickonic.com have sought to tell the true story of what is happening by talking to people living through the Indian nightmare which has nothing to do with 'Covid'. We posted a letter from 'Alisha' in Pune who told a very different story to government and media mendacity. She said scenes of dying people and overwhelmed hospitals were designed to hide what was really happening – genocide and starvation. Alisha said that millions had already died of starvation during the ongoing lockdowns while government and media were lying and making it look like the 'virus':

Restaurants, shops, gyms, theatres, basically everything is shut. The cities are ghost towns. Even so-called 'essential' businesses are only open till 11am in the morning. You basically have just an hour to buy food and then your time is up.

Inter-state travel and even inter-district travel is banned. The cops wait at all major crossroads to question why you are traveling outdoors or to fine you if you are not wearing a mask.

The medical community here is also complicit in genocide, lying about hospitals being full and turning away people with genuine illnesses, who need immediate care. They have even created a shortage of oxygen cylinders.

This is the classic Cult modus operandi played out in every country. Alisha said that people who would not have a PCR test not testing for the 'virus' were being denied hospital treatment. She said the people hit hardest were migrant workers and those in rural areas. Most businesses employed migrant workers and with everything closed there were no jobs, no income and no food. As a result millions were dying of starvation or malnutrition. All this was happening under Prime Minister Narendra Modi, a 100-percent asset of the Cult, and it emphasises yet again the scale of pure anti-human evil we are dealing with. Australia banned its people from returning home from India with penalties for trying to do so of up to five years in jail and a fine of £37,000. The manufactured 'Covid' crisis in India was being prepared to justify further fascism in the West. Obvious connections could be seen between the Indian 'vaccine' programme and increased 'cases' and this became a common theme. The Seychelles, the most per capita 'Covid vaccinated' population in the world, went back into lockdown after a 'surge of cases'.

Long ago the truly evil Monsanto agricultural biotechnology corporation with its big connections to Bill Gates devastated Indian farming with genetically-modified crops. Human rights activist Gurcharan Singh highlighted the efforts by the Indian government to complete the job by destroying the food supply to hundreds of millions with 'Covid' lockdowns. He said that 415 million people at the bottom of the disgusting caste system (still going whatever they say) were below the poverty line and struggled to feed themselves every year. Now the government was imposing lockdown at just the

time to destroy the harvest. This deliberate policy was leading to mass starvation. People may reel back at the suggestion that a government would do that, but Wetiko-controlled 'leaders' are capable of any level of evil. In fact what is described in India is in the process of being instigated worldwide. The food chain and food supply are being targeted at every level to cause world hunger and thus control. Bill Gates is not the biggest owner of farmland in America for no reason and destroying access to food aids both the depopulation agenda and the plan for synthetic 'food' already being funded into existence by Gates. Add to this the coming hyper-inflation from the suicidal creation of fake 'money' in response to 'Covid' and the breakdown of container shipping systems and you have a cocktail that can only lead one way and is meant to. The Cult plan is to crash the entire system to 'build back better' with the Great Reset.

'Vaccine' transmission

Reports from all over the world continue to emerge of women suffering menstrual and fertility problems after having the fake 'vaccine' and of the non-'vaccinated' having similar problems when interacting with the 'vaccinated'. There are far too many for 'coincidence' to be credible. We've had menopausal women getting periods, others having periods stop or not stopping for weeks, passing clots, sometimes the lining of the uterus, breast irregularities, and miscarriages (which increased by 400 percent in parts of the United States). Non-'vaccinated' men and children have suffered blood clots and nose bleeding after interaction with the 'vaccinated'. Babies have died from the effects of breast milk from a 'vaccinated' mother. Awake doctors – the small minority – speculated on the cause of non-'vaccinated' suffering the same effects as the 'vaccinated'. Was it nanotechnology in the synthetic substance transmitting frequencies or was it a straight chemical bioweapon that was being transmitted between people? I am not saying that some kind of chemical transmission is not one possible answer, but the foundation of all that the Cult does is frequency and

this is fertile ground for understanding how transmission can happen. American doctor Carrie Madej, an internal medicine physician and osteopath, has been practicing for the last 20 years, teaching medical students, and she says attending different meetings where the agenda for humanity was discussed. Madej, who operates out of Georgia, did not dismiss other possible forms of transmission, but she focused on frequency in search of an explanation for transmission. She said the Moderna and Pfizer 'vaccines' contained nano-lipid particles as a key component. This was a brand new technology never before used on humanity. 'They're using a nanotechnology which is pretty much little tiny computer bits … nanobots or hydrogel.' Inside the 'vaccines' was 'this sci-fi kind of substance' which suppressed immune checkpoints to get into the cell. I referred to this earlier as the 'Trojan horse' technique that tricks the cell into opening a gateway for the self-replicating synthetic material and while the immune system is artificially suppressed the body has no defences. Madej said the substance served many purposes including an on-demand ability to 'deliver the payload' and using the nano 'computer bits' as biosensors in the body. 'It actually has the ability to accumulate data from your body, like your breathing, your respiration, thoughts, emotions, all kinds of things.'

She said the technology obviously has the ability to operate through Wi-Fi and transmit and receive energy, messages, frequencies or impulses. 'Just imagine you're getting this new substance in you and it can react to things all around you, the 5G, your smart device, your phones.' We had something completely foreign in the human body that had never been launched large scale at a time when we were seeing 5G going into schools and hospitals (plus the Musk satellites) and she believed the 'vaccine' transmission had something to do with this: '… if these people have this inside of them … it can act like an antenna and actually transmit it outwardly as well.' The synthetic substance produced its own voltage and so it could have that kind of effect. This fits with my own contention that the nano receiver-transmitters are designed to connect people to the

Smart Grid and break the receiver-transmitter connection to expanded consciousness. That would explain the French energy healer's experience of the disconnection of body from 'soul' with those who have had the 'vaccine'. The nanobots, self-replicating inside the body, would also transmit the synthetic frequency which could be picked up through close interaction by those who have not been 'vaccinated'. Madej speculated that perhaps it was 5G and increased levels of other radiation that was causing the symptoms directly although interestingly she said that non-'vaccinated' patients had shown improvement when they were away from the 'vaccinated' person they had interacted with. It must be remembered that you can control frequency and energy with your mind and you can consciously create energetic barriers or bubbles with the mind to stop damaging frequencies from penetrating your field. American paediatrician Dr Larry Palevsky said the 'vaccine' was not a 'vaccine' and was never designed to protect from a 'viral' infection. He called it 'a massive, brilliant propaganda of genocide' because they didn't have to inject everyone to get the result they wanted. He said the content of the jabs was able to infuse any material into the brain, heart, lungs, kidneys, liver, sperm and female productive system. 'This is genocide; this is a weapon of mass destruction.' At the same time American colleges were banning students from attending if they didn't have this life-changing and potentially life-ending 'vaccine'. Class action lawsuits must follow when the consequences of this college fascism come to light. As the book was going to press came reports about fertility effects on sperm in 'vaccinated' men which would absolutely fit with what I have been saying and hospitals continued to fill with 'vaccine' reactions. Another question is what about transmission via blood transfusions? The NHS has extended blood donation restrictions from seven days after a 'Covid vaccination' to 28 days after even a sore arm reaction.

I said in the spring of 2020 that the then touted 'Covid vaccine' would be ongoing each year like the flu jab. A year later Pfizer CEO, the appalling Albert Bourla, said people would 'likely' need a 'booster dose' of the 'vaccine' within 12 months of getting 'fully

vaccinated' and then a yearly shot. 'Variants will play a key role', he said confirming the point. Johnson & Johnson CEO Alex Gorsky also took time out from his 'vaccine' disaster to say that people may need to be vaccinated against 'Covid-19' each year. UK Health Secretary, the psychopath Matt Hancock, said additional 'boosters' would be available in the autumn of 2021. This is the trap of the 'vaccine passport'. The public will have to accept every last 'vaccine' they introduce, including for the fake 'variants', or it would cease to be valid. The only other way in some cases would be continuous testing with a test not testing for the 'virus' and what is on the swabs constantly pushed up your noise towards the brain every time?

'Vaccines' changing behaviour

I mentioned in the body of the book how I believed we would see gathering behaviour changes in the 'vaccinated' and I am already hearing such comments from the non-'vaccinated' describing behaviour changes in friends, loved ones and work colleagues. This will only increase as the self-replicating synthetic material and nanoparticles expand in body and brain. An article in the *Guardian* in 2016 detailed research at the University of Virginia in Charlottesville which developed a new method for controlling brain circuits associated with complex animal behaviour. The method, dubbed 'magnetogenetics', involves genetically-engineering a protein called ferritin, which stores and releases iron, to create a magnetised substance – 'Magneto' – that can activate specific groups of nerve cells from a distance. This is claimed to be an advance on other methods of brain activity manipulation known as optogenetics and chemogenetics (the Cult has been developing methods of brain control for a long time). The ferritin technique is said to be non-invasive and able to activate neurons 'rapidly and reversibly'. In other words, human thought and perception. The article said that earlier studies revealed how nerve cell proteins 'activated by heat and mechanical pressure can be genetically engineered so that they become sensitive to radio waves and magnetic fields, by attaching them to an iron-storing protein called ferritin, or to inorganic

paramagnetic particles'. Sensitive to radio waves and magnetic fields? You mean like 5G, 6G and 7G? This is the human-AI Smart Grid hive mind we are talking about. The *Guardian* article said:

> … the researchers injected Magneto into the striatum of freely behaving mice, a deep brain structure containing dopamine-producing neurons that are involved in reward and motivation, and then placed the animals into an apparatus split into magnetised and non-magnetised sections.
>
> Mice expressing Magneto spent far more time in the magnetised areas than mice that did not, because activation of the protein caused the striatal neurons expressing it to release dopamine, so that the mice found being in those areas rewarding. This shows that Magneto can remotely control the firing of neurons deep within the brain, and also control complex behaviours.

Make no mistake this basic methodology will be part of the 'Covid vaccine' cocktail and using magnetics to change brain function through electromagnetic field frequency activation. The Pentagon is developing a 'Covid vaccine' using ferritin. Magnetics would explain changes in behaviour and why videos are appearing across the Internet as I write showing how magnets stick to the skin at the point of the 'vaccine' shot. Once people take these 'vaccines' anything becomes possible in terms of brain function and illness which will be blamed on 'Covid-19' and 'variants'. Magnetic field manipulation would further explain why the non-'vaccinated' are reporting the same symptoms as the 'vaccinated' they interact with and why those symptoms are reported to decrease when not in their company. Interestingly 'Magneto', a 'mutant', is a character in the Marvel Comic *X-Men* stories with the ability to manipulate magnetic fields and he believes that mutants should fight back against their human oppressors by any means necessary. The character was born Erik Lehnsherr to a Jewish family in Germany.

Cult-controlled courts

The European Court of Human Rights opened the door for mandatory 'Covid-19 vaccines' across the continent when it ruled in a Czech Republic dispute over childhood immunisation that legally

enforced vaccination could be 'necessary in a democratic society'. The 17 judges decided that compulsory vaccinations did not breach human rights law. On the face of it the judgement was so inverted you gasp for air. If not having a vaccine infused into your body is not a human right then what is? Ah, but they said human rights law which has been specifically written to delete all human rights at the behest of the state (the Cult). Article 8 of the European Convention on Human Rights relates to the right to a private life. The crucial word here is *'except'*:

> There shall be no interference by a public authority with the exercise of this right EXCEPT such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic wellbeing of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others [My emphasis].

No interference *except* in accordance with the law means there *are* no 'human rights' *except* what EU governments decide you can have at their behest. 'As is necessary in a democratic society' explains that reference in the judgement and 'in the interests of national security, public safety or the economic well-being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others' gives the EU a coach and horses to ride through 'human rights' and scatter them in all directions. The judiciary is not a check and balance on government extremism; it is a vehicle to enforce it. This judgement was almost laughably predictable when the last thing the Cult wanted was a decision that went against mandatory vaccination. Judges rule over and over again to benefit the system of which they are a part. Vaccination disputes that come before them are invariably delivered in favour of doctors and authorities representing the view of the state which owns the judiciary. Oh, yes, and we have even had calls to stop putting 'Covid-19' on death certificates within 28 days of a 'positive test' because it is claimed the practice makes the 'vaccine' appear not to work. They are laughing at you.

The scale of madness, inhumanity and things to come was highlighted when those not 'vaccinated' for 'Covid' were refused evacuation from the Caribbean island of St Vincent during massive volcanic eruptions. Cruise ships taking residents to the safety of another island allowed only the 'vaccinated' to board and the rest were left to their fate. Even in life and death situations like this we see 'Covid' stripping people of their most basic human instincts and the insanity is even more extreme when you think that fake 'vaccine'-makers are not even claiming their body-manipulating concoctions stop 'infection' and 'transmission' of a 'virus' that doesn't exist. St Vincent Prime Minister Ralph Gonsalves said: 'The chief medical officer will be identifying the persons already vaccinated so that we can get them on the ship.' Note again the power of the chief medical officer who, like Whitty in the UK, will be answering to the World Health Organization. This is the Cult network structure that has overridden politicians who 'follow the science' which means doing what WHO-controlled 'medical officers' and 'science advisers' tell them. Gonsalves even said that residents who were 'vaccinated' after the order so they could board the ships would still be refused entry due to possible side effects such as 'wooziness in the head'. The good news is that if they were woozy enough in the head they could qualify to be prime minister of St Vincent.

Microchipping freedom

The European judgement will be used at some point to justify moves to enforce the 'Covid' DNA-manipulating procedure. Sandra Ro, CEO of the Global Blockchain Business Council, told a World Economic Forum event that she hoped 'vaccine passports' would help to 'drive forced consent and standardisation' of global digital identity schemes: 'I'm hoping with the desire and global demand for some sort of vaccine passport – so that people can get travelling and working again – [it] will drive forced consent, standardisation, and frankly, cooperation across the world.' The lady is either not very bright, or thoroughly mendacious, to use the term 'forced consent'.

You do not 'consent' if you are forced – you *submit*. She was describing what the plan has been all along and that's to enforce a digital identity on every human without which they could not function. 'Vaccine passports' are opening the door and are far from the end goal. A digital identity would allow you to be tracked in everything you do in cyberspace and this is the same technique used by Cult-owned China to enforce its social credit system of total control. The ultimate 'passport' is planned to be a microchip as my books have warned for nearly 30 years. Those nice people at the Pentagon working for the Cult-controlled Defense Advanced Research Projects Agency (DARPA) claimed in April, 2021, they have developed a microchip inserted under the skin to detect 'asymptomatic Covid-19 infection' before it becomes an outbreak and a 'revolutionary filter' that can remove the 'virus' from the blood when attached to a dialysis machine. The only problems with this are that the 'virus' does not exist and people transmitting the 'virus' with no symptoms is brain-numbing bullshit. This is, of course, not a ruse to get people to be microchipped for very different reasons. DARPA also said it was producing a one-stop 'vaccine' for the 'virus' and all 'variants'. One of the most sinister organisations on Planet Earth is doing this? Better have it then. These people are insane because Wetiko that possesses them is insane.

Researchers from the Salk Institute in California announced they have created an embryo that is part human and part monkey. My books going back to the 1990s have exposed experiments in top secret underground facilities in the United States where humans are being crossed with animal and non-human 'extraterrestrial' species. They are now easing that long-developed capability into the public arena and there is much more to come given we are dealing with psychiatric basket cases. Talking of which – Elon Musk's scientists at Neuralink trained a monkey to play Pong and other puzzles on a computer screen using a joystick and when the monkey made the correct move a metal tube squirted banana smoothie into his mouth which is the basic technique for training humans into unquestioning compliance. Two Neuralink chips were in the monkey's skull and

more than 2,000 wires 'fanned out' into its brain. Eventually the monkey played a video game purely with its brain waves. Psychopathic narcissist Musk said the 'breakthrough' was a step towards putting Neuralink chips into human skulls and merging minds with artificial intelligence. *Exactly*. This man is so dark and Cult to his DNA.

World Economic Fascism (WEF)

The World Economic Forum is telling you the plan by the statements made at its many and various events. Cult-owned fascist YouTube CEO Susan Wojcicki spoke at the 2021 WEF Global Technology Governance Summit (see the name) in which 40 governments and 150 companies met to ensure 'the responsible design and deployment of emerging technologies'. Orwellian translation: 'Ensuring the design and deployment of long-planned technologies will advance the Cult agenda for control and censorship.' Freedom-destroyer and Nuremberg-bound Wojcicki expressed support for tech platforms like hers to censor content that is 'technically legal but could be harmful'. Who decides what is 'harmful'? She does and they do. 'Harmful' will be whatever the Cult doesn't want people to see and we have legislation proposed by the UK government that would censor content on the basis of 'harm' no matter if the information is fair, legal and provably true. Make that *especially* if it is fair, legal and provably true. Wojcicki called for a global coalition to be formed to enforce content moderation standards through automated censorship. This is a woman and mega-censor so self-deluded that she shamelessly accepted a 'free expression' award – *Wojcicki* – in an event sponsored by her own *YouTube*. They have no shame and no self-awareness.

You know that 'Covid' is a scam and Wojcicki a Cult operative when YouTube is censoring medical and scientific opinion purely on the grounds of whether it supports or opposes the Cult 'Covid' narrative. Florida governor Ron DeSantis compiled an expert panel with four professors of medicine from Harvard, Oxford, and Stanford Universities who spoke against forcing children and

vaccinated people to wear masks. They also said there was no proof that lockdowns reduced spread or death rates of 'Covid-19'. Cult-gofer Wojcicki and her YouTube deleted the panel video 'because it included content that contradicts the consensus of local and global health authorities regarding the efficacy of masks to prevent the spread of Covid-19'. This 'consensus' refers to what the Cult tells the World Health Organization to say and the WHO tells 'local health authorities' to do. Wojcicki knows this, of course. The panellists pointed out that censorship of scientific debate was responsible for deaths from many causes, but Wojcicki couldn't care less. She would not dare go against what she is told and as a disgrace to humanity she wouldn't want to anyway. The UK government is seeking to pass a fascist 'Online Safety Bill' to specifically target with massive fines and other means non-censored video and social media platforms to make them censor 'lawful but harmful' content like the Cult-owned Facebook, Twitter, Google and YouTube. What is 'lawful but harmful' would be decided by the fascist Blair-created Ofcom.

Another WEF obsession is a cyber-attack on the financial system and this is clearly what the Cult has planned to take down the bank accounts of everyone – except theirs. Those that think they have enough money for the Cult agenda not to matter to them have got a big lesson coming if they continue to ignore what is staring them in the face. The World Economic Forum, funded by Gates and fronted by Klaus Schwab, announced it would be running a 'simulation' with the Russian government and global banks of just such an attack called Cyber Polygon 2021. What they simulate – as with the 'Covid' Event 201 – they plan to instigate. The WEF is involved in a project with the Cult-owned Carnegie Endowment for International Peace called the WEF-Carnegie Cyber Policy Initiative which seeks to merge Wall Street banks, 'regulators' (I love it) and intelligence agencies to 'prevent' (arrange and allow) a cyber-attack that would bring down the global financial system as long planned by those that control the WEF and the Carnegie operation. The Carnegie Endowment for International Peace sent an instruction to First World

War US President Woodrow Wilson not to let the war end before society had been irreversibly transformed.

The Wuhan lab diversion

As I close, the Cult-controlled authorities and lapdog media are systematically pushing 'the virus was released from the Wuhan lab' narrative. There are two versions – it happened by accident and it happened on purpose. Both are nonsense. The perceived existence of the never-shown-to-exist 'virus' is vital to sell the impression that there is actually an infective agent to deal with and to allow the endless potential for terrifying the population with 'variants' of a 'virus' that does not exist. The authorities at the time of writing are going with the 'by accident' while the alternative media is promoting the 'on purpose'. Cable news host Tucker Carlson who has questioned aspects of lockdown and 'vaccine' compulsion has bought the Wuhan lab story. 'Everyone now agrees' he said. Well, I don't and many others don't and the question is *why* does the system and its media suddenly 'agree'? When the media moves as one unit with a narrative it is always a lie – witness the hour by hour mendacity of the 'Covid' era. Why would this Cult-owned combination which has unleashed lies like machine gun fire suddenly 'agree' to tell the truth??

Much of the alternative media is buying the lie because it fits the conspiracy narrative, but it's the *wrong* conspiracy. The real conspiracy is that *there is no virus* and that is what the Cult is desperate to hide. The idea that the 'virus' was released by accident is ludicrous when the whole 'Covid' hoax was clearly long-planned and waiting to be played out as it was so fast in accordance with the Rockefeller document and Event 201. So they prepared everything in detail over decades and then sat around strumming their fingers waiting for an 'accidental' release from a bio-lab? *What??* It's crazy. Then there's the 'on purpose' claim. You want to circulate a 'deadly virus' and hide the fact that you've done so and you release it down the street from the highest-level bio-lab in China? I repeat – *What??*

You would release it far from that lab to stop any association being made. But, no, we'll do it in a place where the connection was certain to be made. Why would you need to scam 'cases' and 'deaths' and pay hospitals to diagnose 'Covid-19' if you had a real 'virus'? What are sections of the alternative media doing believing this crap? Where were all the mass deaths in Wuhan from a 'deadly pathogen' when the recovery to normal life after the initial propaganda was dramatic in speed? Why isn't the 'deadly pathogen' now circulating all over China with bodies in the street? Once again we have the technique of tell them what they want to hear and they will likely believe it. The alternative media has its 'conspiracy' and with Carlson it fits with his 'China is the danger' narrative over years. China *is* a danger as a global Cult operations centre, but not for this reason. The Wuhan lab story also has the potential to instigate conflict with China when at some stage the plan is to trigger a Problem-Reaction-Solution confrontation with the West. Question everything – *everything* – and especially when the media agrees on a common party line.

Third wave ... fourth wave ... fifth wave ...

As the book went into production the world was being set up for more lockdowns and a 'third wave' supported by invented 'variants' that were increasing all the time and will continue to do so in public statements and computer programs, but not in reality. India became the new Italy in the 'Covid' propaganda campaign and we were told to be frightened of the new 'Indian strain'. Somehow I couldn't find it within myself to do so. A document produced for the UK government entitled 'Summary of further modelling of easing of restrictions – Roadmap Step 2' declared that a third wave was inevitable (of course when it's in the script) and it would be the fault of children and those who refuse the health-destroying fake 'Covid vaccine'. One of the computer models involved came from the Cult-owned *Imperial College* and the other from Warwick University which I wouldn't trust to tell me the date in a calendar factory. The document states that both models presumed extremely high uptake

of the 'Covid vaccines' and didn't allow for 'variants'. The document states: 'The resurgence is a result of some people (mostly children) being ineligible for vaccination; others choosing not to receive the vaccine; and others being vaccinated but not perfectly protected.' The mendacity takes the breath away. Okay, blame those with a brain who won't take the DNA-modifying shots and put more pressure on children to have it as 'trials' were underway involving children as young as six months with parents who give insanity a bad name. Massive pressure is being put on the young to have the fake 'vaccine' and child age consent limits have been systematically lowered around the world to stop parents intervening. Most extraordinary about the document was its claim that the 'third wave' would be driven by 'the resurgence in both hospitalisations and deaths … dominated by *those that have received two doses of the vaccine*, comprising around 60-70% of the wave respectively'. The predicted peak of the 'third wave' suggested 300 deaths per day with 250 of them *fully 'vaccinated' people*. How many more lies do acquiescers need to be told before they see the obvious? Those who took the jab to 'protect themselves' are projected to be those who mostly get sick and die? So what's in the 'vaccine'? The document went on:

> It is possible that a summer of low prevalence could be followed by substantial increases in incidence over the following autumn and winter. Low prevalence in late summer should not be taken as an indication that SARS-CoV-2 has retreated or that the population has high enough levels of immunity to prevent another wave.

They are telling you the script and while many British people believed 'Covid' restrictions would end in the summer of 2021 the government was preparing for them to be ongoing. Authorities were awarding contracts for 'Covid marshals' to police the restrictions with contracts starting in July, 2021, and going through to January 31st, 2022, and the government was advertising for 'Media Buying Services' to secure media propaganda slots worth a potential £320 million for 'Covid-19 campaigns' with a contract not ending until March, 2022. The recipient – via a list of other front companies – was reported to be American media marketing giant Omnicom Group

Inc. While money is no object for 'Covid' the UK waiting list for all other treatment – including life-threatening conditions – passed 4.5 million. Meantime the Cult is seeking to control all official 'inquiries' to block revelations about what has really been happening and why. It must not be allowed to – we need Nuremberg jury trials in every country. The cover-up doesn't get more obvious than appointing ultra-Zionist professor Philip Zelikow to oversee two dozen US virologists, public health officials, clinicians, former government officials and four American 'charitable foundations' to 'learn the lessons' of the 'Covid' debacle. The personnel will be those that created and perpetuated the 'Covid' lies while Zelikow is the former executive director of the 9/11 Commission who ensured that the truth about those attacks never came out and produced a report that must be among the most mendacious and manipulative documents ever written – see *The Trigger* for the detailed exposure of the almost unimaginable 9/11 story in which Sabbatians can be found at every level.

Passive no more

People are increasingly challenging the authorities with amazing numbers of people taking to the streets in London well beyond the ability of the Face-Nappies to stop them. Instead the Nappies choose situations away from the mass crowds to target, intimidate, and seek to promote the impression of 'violent protestors'. One such incident happened in London's Hyde Park. Hundreds of thousands walking through the streets in protest against 'Covid' fascism were ignored by the Cult-owned BBC and most of the rest of the mainstream media, but they delighted in reporting how police were injured in 'clashes with protestors'. The truth was that a group of people gathered in Hyde Park at the end of one march when most had gone home and they were peacefully having a good time with music and chat. Face-Nappies who couldn't deal with the full-march crowd then waded in with their batons and got more than they bargained for. Instead of just standing for this criminal brutality the crowd used their numerical superiority to push the Face-Nappies out of the

park. Eventually the Nappies turned and ran. Unfortunately two or three idiots in the crowd threw drink cans striking two officers which gave the media and the government the image they wanted to discredit the 99.9999 percent who were peaceful. The idiots walked straight into the trap and we must always be aware of potential agent provocateurs used by the authorities to discredit their targets.

This response from the crowd – the can people apart – must be a turning point when the public no longer stand by while the innocent are arrested and brutally attacked by the Face-Nappies. That doesn't mean to be violent, that's the last thing we need. We'll leave the violence to the Face-Nappies and government. But it does mean that when the Face-Nappies use violence against peaceful people the numerical superiority is employed to stop them and make citizen's arrests or Common Law arrests for a breach of the peace. The time for being passive in the face of fascism is over.

We are the many, they are the few, and we need to make that count before there is no freedom left and our children and grandchildren face an ongoing fascist nightmare.

COME ON PEOPLE – IT'S TIME.

One final thought …

The power of love
A force from above
Cleaning my soul
Flame on burn desire
Love with tongues of fire
Purge the soul
Make love your goal

I'll protect you from the hooded claw
Keep the vampires from your door
When the chips are down I'll be around
With my undying, death-defying
Love for you

Envy will hurt itself
Let yourself be beautiful
Sparkling love, flowers
And pearls and pretty girls
Love is like an energy
Rushin' rushin' inside of me

This time we go sublime
Lovers entwine, divine, divine,
Love is danger, love is pleasure
Love is pure – the only treasure

I'm so in love with you
Purge the soul
Make love your goal

The power of love
A force from above
Cleaning my soul
The power of love
A force from above
A sky-scraping dove

Flame on burn desire
Love with tongues of fire
Purge the soul
Make love your goal

Frankie Goes To Hollywood

APPENDIX

Cowan-Kaufman-Morell Statement on Virus Isolation (SOVI)

Isolation: The action of isolating; the fact or condition of being isolated or standing alone; separation from other things or persons; solitariness
Oxford English Dictionary

The controversy over whether the SARS-CoV-2 virus has ever been isolated or purified continues. However, using the above definition, common sense, the laws of logic and the dictates of science, any unbiased person must come to the conclusion that the SARS-CoV-2 virus has never been isolated or purified. As a result, no confirmation of the virus' existence can be found. The logical, common sense, and scientific consequences of this fact are:

- the structure and composition of something not shown to exist can't be known, including the presence, structure, and function of any hypothetical spike or other proteins;
- the genetic sequence of something that has never been found can't be known;
- "variants" of something that hasn't been shown to exist can't be known;
- it's impossible to demonstrate that SARS-CoV-2 causes a disease called Covid-19.

In as concise terms as possible, here's the proper way to isolate, characterize and demonstrate a new virus. First, one takes samples (blood, sputum, secretions) from many people (e.g. 500) with symptoms which are unique and specific enough to characterize an illness. Without mixing these samples with ANY tissue or products that also contain genetic material, the virologist macerates, filters and ultracentrifuges i.e. *purifies* the specimen. This common virology technique, done for decades to isolate bacteriophages[1] and so-called giant viruses in every virology lab, then allows the virologist to demonstrate with electron microscopy thousands of identically sized and shaped particles. These particles are the isolated and purified virus.

These identical particles are then checked for uniformity by physical and/or microscopic techniques. Once the purity is determined, the particles may be further characterized. This would include examining the structure, morphology, and chemical composition of the particles. Next, their genetic makeup is characterized by extracting the genetic material directly from the purified particles and using genetic-sequencing techniques, such as Sanger sequencing, that have also been around for decades. Then one does an analysis to confirm that these uniform particles are exogenous (outside) in origin as a virus is conceptualized to be, and not the normal breakdown products of dead and dying tissues.[2] (As of May 2020, we know that virologists have no way to determine whether the particles they're seeing are viruses or just normal breakdown products of dead and dying tissues.)[3]

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1 Isolation, characterization and analysis of bacteriophages from the haloalkaline lake Elmenteita, KenyaJuliah Khayeli Akhwale et al, PLOS One, Published: April 25, 2019. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0215734 – accessed 2/15/21

2 "Extracellular Vesicles Derived From Apoptotic Cells: An Essential Link Between Death and Regeneration," Maojiao Li1 et al, Frontiers in Cell and Developmental Biology, 2020 October 2. https://www.frontiersin.org/articles/10.3389/fcell.2020.573511/full – accessed 2/15/21

3 "The Role of Extraellular Vesicles as Allies of HIV, HCV and SARS Viruses," Flavia Giannessi, et al, Viruses, 2020 May

If we have come this far then we have fully isolated, characterized, and genetically sequenced an exogenous virus particle. However, we still have to show it is causally related to a disease. This is carried out by exposing a group of healthy subjects (animals are usually used) to this isolated, purified virus in the manner in which the disease is thought to be transmitted. If the animals get sick with the same disease, as confirmed by clinical and autopsy findings, one has now shown that the virus actually causes a disease. This demonstrates infectivity and transmission of an infectious agent.

None of these steps has even been attempted with the SARS-CoV-2 virus, nor have all these steps been successfully performed for any so-called pathogenic virus. Our research indicates that a single study showing these steps does not exist in the medical literature.

Instead, since 1954, virologists have taken unpurified samples from a relatively few people, often less than ten, with a similar disease. They then minimally process this sample and inoculate this unpurified sample onto tissue culture containing usually four to six other types of material – all of which contain identical genetic material as to what is called a "virus." The tissue culture is starved and poisoned and naturally disintegrates into many types of particles, some of which contain genetic material. Against all common sense, logic, use of the English language and scientific integrity, this process is called "virus isolation." This brew containing fragments of genetic material from many sources is then subjected to genetic analysis, which then creates in a computer-simulation process the alleged sequence of the alleged virus, a so called in silico genome. At no time is an actual virus confirmed by electron microscopy. At no time is a genome extracted and sequenced from an actual virus. This is scientific fraud.

The observation that the unpurified specimen — inoculated onto tissue culture along with toxic antibiotics, bovine fetal tissue, amniotic fluid and other tissues — destroys the kidney tissue onto which it is inoculated is given as evidence of the virus' existence and pathogenicity. This is scientific fraud.

From now on, when anyone gives you a paper that suggests the SARS-CoV-2 virus has been isolated, please check the methods sections. If the researchers used Vero cells or any other culture method, you know that their process was not isolation. You will hear the following excuses for why actual isolation isn't done:

1. There were not enough virus particles found in samples from patients to analyze.

2. Viruses are intracellular parasites; they can't be found outside the cell in this manner.

If No. 1 is correct, and we can't find the virus in the sputum of sick people, then on what evidence do we think the virus is dangerous or even lethal? If No. 2 is correct, then how is the virus spread from person to person? We are told it emerges from the cell to infect others. Then why isn't it possible to find it?

Finally, questioning these virology techniques and conclusions is not some distraction or divisive issue. Shining the light on this truth is essential to stop this terrible fraud that humanity is confronting. For, as we now know, if the virus has never been isolated, sequenced or shown to cause illness, if the virus is imaginary, then why are we wearing masks, social distancing and putting the whole world into prison?

Finally, if pathogenic viruses don't exist, then what is going into those injectable devices erroneously called "vaccines," and what is their purpose? This scientific question is the most urgent and relevant one of our time.

We are correct. The SARS-CoV2 virus does not exist.

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Ickonic is something that has been a dream of mine for the last 5 years, growing up around alternative information I have always had a natural interest in what is going on in the World and what could I do to make it better.
Across the range of subjects and positions of influence occupied mainly by people who don't strive to make things better it's the Media that I have always found the most frustrating and fascinating. Mainly because if the Media did their Jobs properly then so much of the negative things happening in the World simply would not be able to happen, because they would be exposed within a heartbeat.
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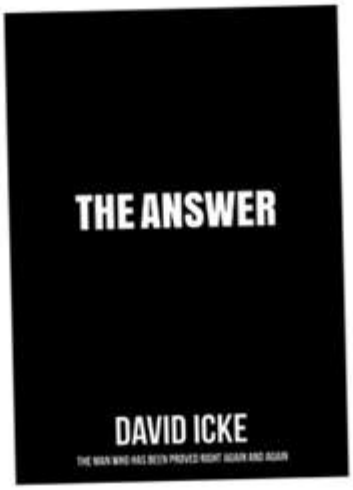
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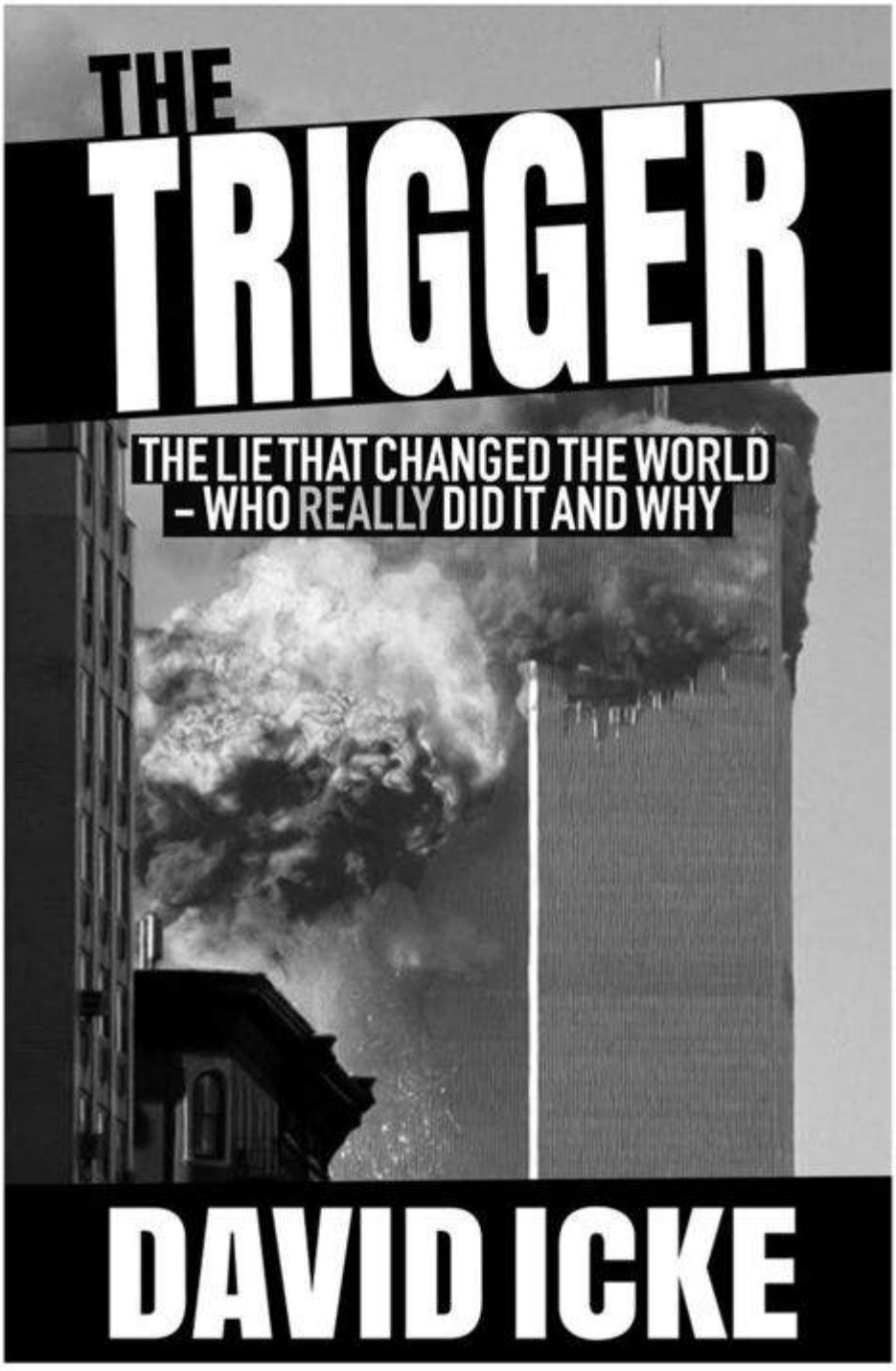
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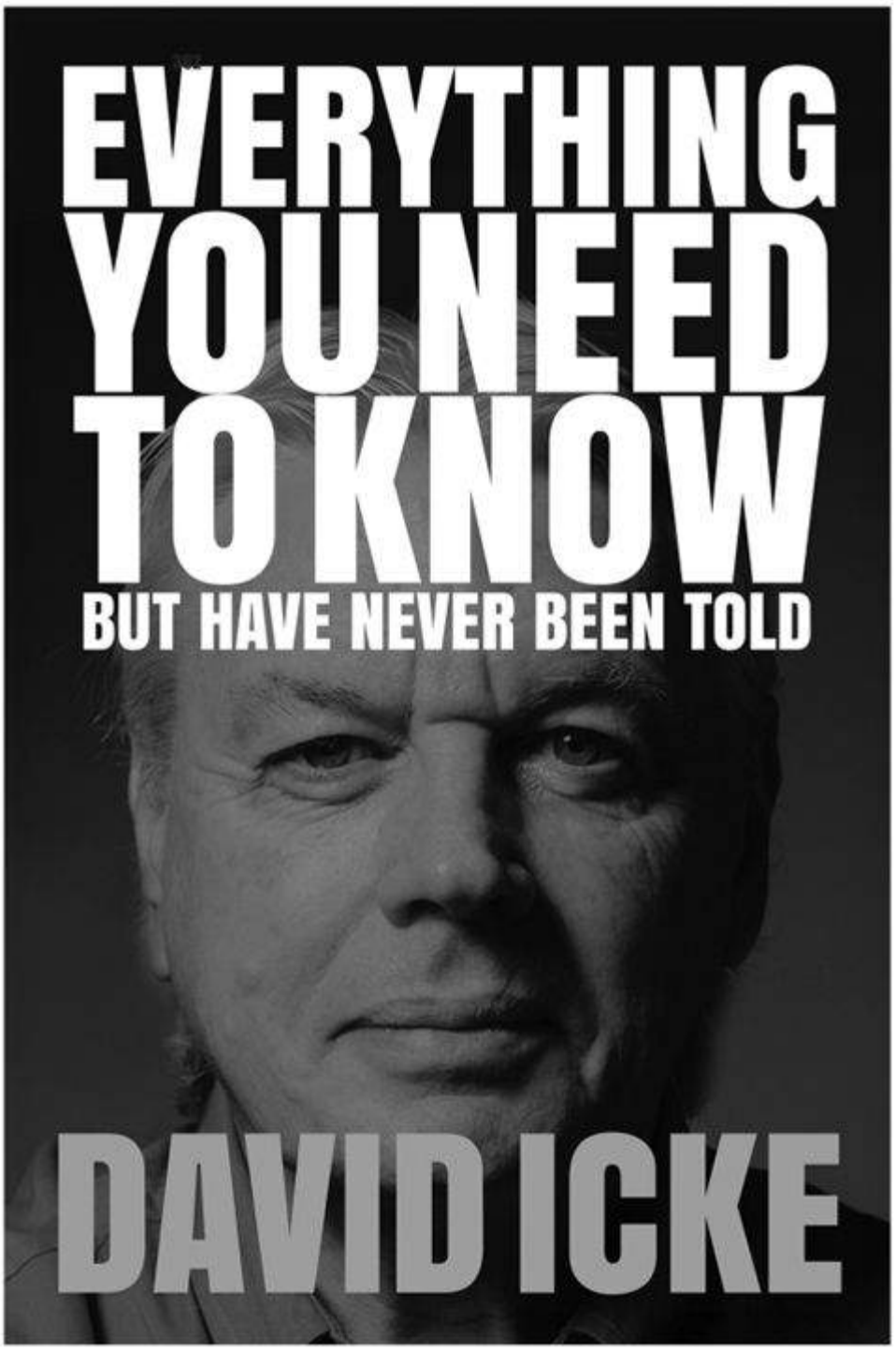


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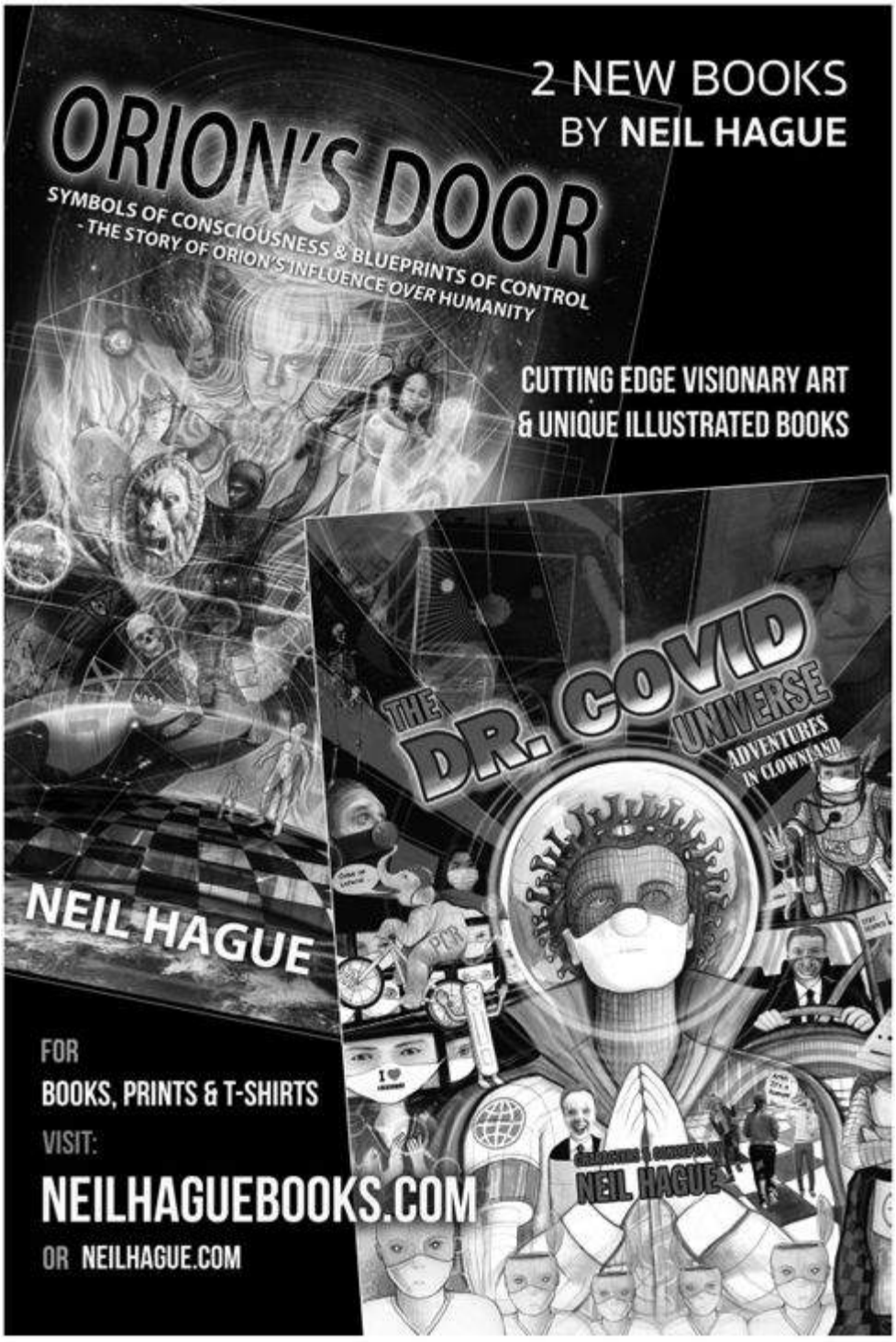
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noun

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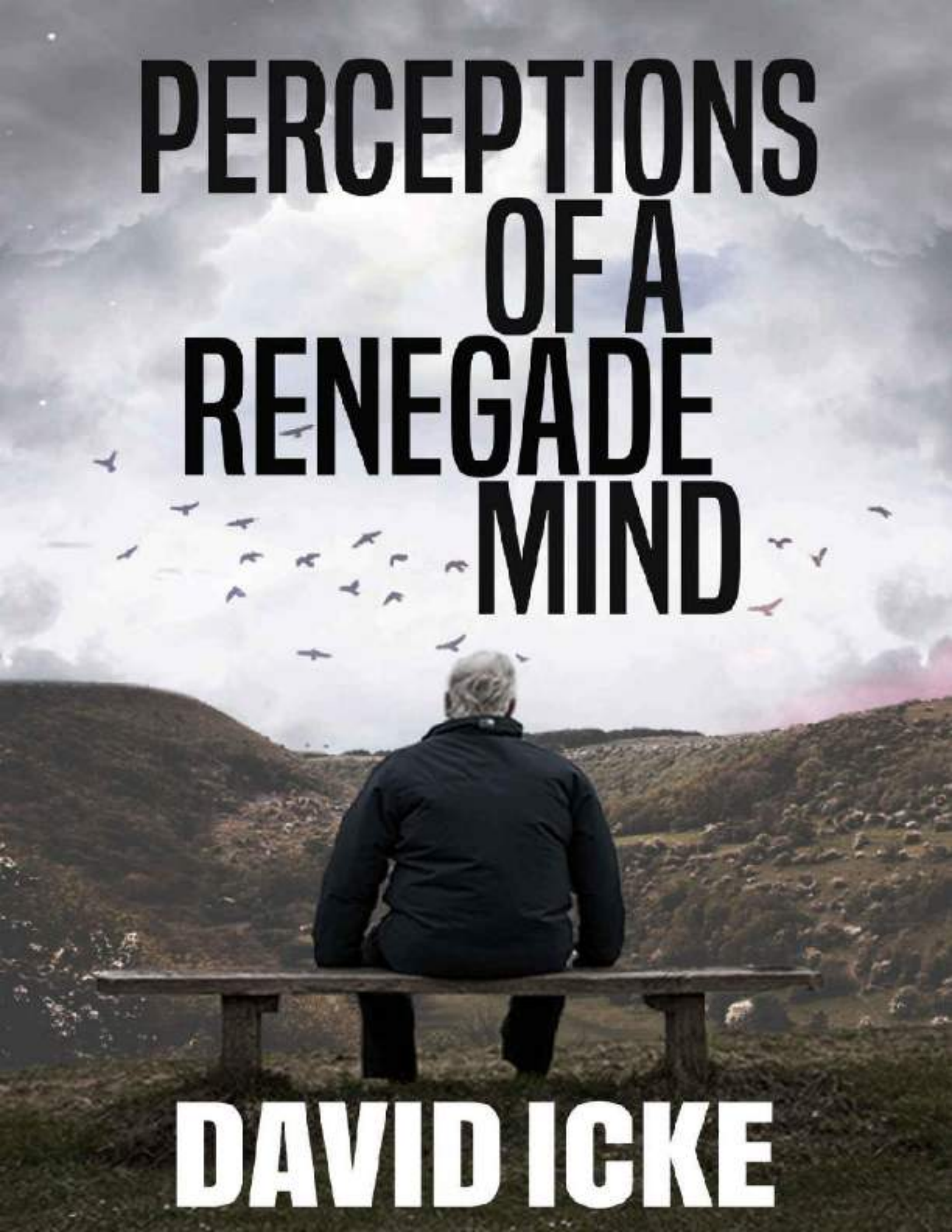

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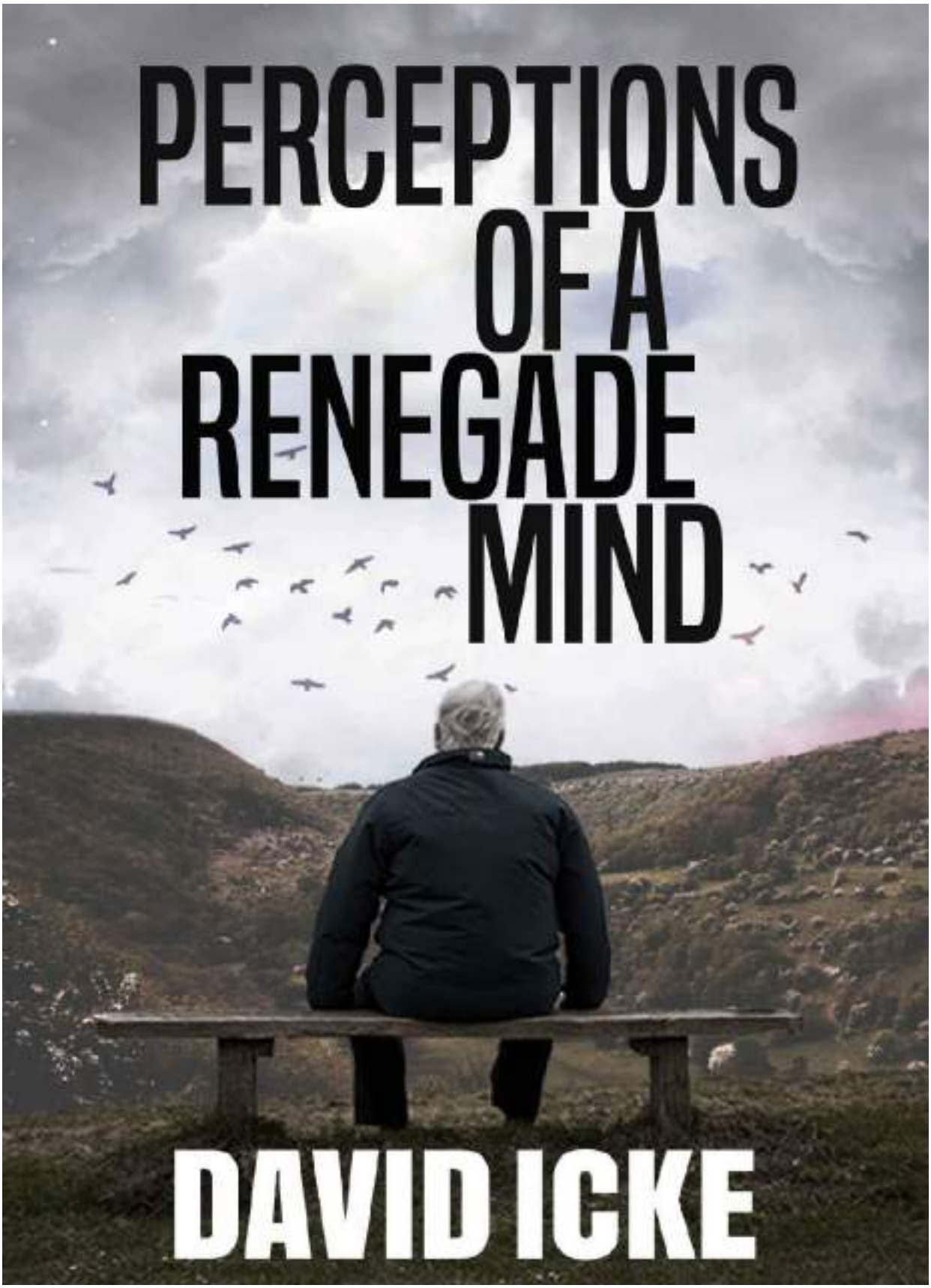
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PERCEPTIONS OF A RENEGADE MIND



DAVID ICKE


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PERCEPTIONS OF A RENEGADE MIND



DAVID ICKE

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Renegade:
Adjective
‘Having rejected tradition: Unconventional.’
Merriam-Webster Dictionary

Acquiescence to tyranny is the death of the spirit

You may be 38 years old, as I happen to be. And one day, some great opportunity stands before you and calls you to stand up for some great principle, some great issue, some great cause. And you refuse to do it because you are afraid … You refuse to do it because you want to live longer … You're afraid that you will lose your job, or you are afraid that you will be criticised or that you will lose your popularity, or you're afraid that somebody will stab you, or shoot at you or bomb your house; so you refuse to take the stand.

Well, you may go on and live until you are 90, but you're just as dead at 38 as you would be at 90. And the cessation of breathing in your life is but the belated announcement of an earlier death of the spirit.

Martin Luther King

How the few control the many and always have – the many do whatever they're told

'Forward, the Light Brigade!'
Was there a man dismayed?
Not though the soldier knew
Someone had blundered.
Theirs not to make reply,
Theirs not to reason why,
Theirs but to do and die.
Into the valley of Death
Rode the six hundred.

Cannon to right of them,
Cannon to left of them,
Cannon in front of them
Volleyed and thundered;
Stormed at with shot and shell,
Boldly they rode and well,
Into the jaws of Death,
Into the mouth of hell
Rode the six hundred

Alfred Lord Tennyson (1809-1892)

The mist is lifting slowly
I can see the way ahead
And I've left behind the empty streets
That once inspired my life
And the strength of the emotion
Is like thunder in the air
'Cos the promise that we made each other
Haunts me to the end

The secret of your beauty
And the mystery of your soul
I've been searching for in everyone I meet
And the times I've been mistaken
It's impossible to say
And the grass is growing
Underneath our feet

The words that I remember
From my childhood still are true
That there's none so blind
As those who will not see
And to those who lack the courage
And say it's dangerous to try
Well they just don't know
That love eternal will not be denied

I know you're out there somewhere
Somewhere, somewhere
I know you're out there somewhere

Somewhere you can hear my voice
I know I'll find you somehow
Somehow, somehow
I know I'll find you somehow
And somehow I'll return again to you

The Moody Blues

Are you a gutless wonder - or a Renegade Mind?

Monuments put from pen to paper,
Turns me into a gutless wonder,
And if you tolerate this,
Then your children will be next.
Gravity keeps my head down,
Or is it maybe shame ...

Manic Street Preachers

Rise like lions after slumber
In unvanquishable number.
Shake your chains to earth like dew
Which in sleep have fallen on you.
Ye are many – they are few.

Percy Shelley

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CHAPTER ONE

I'm thinking' – Oh, but *are* you?

Think for yourself and let others enjoy the privilege of doing so too
Voltaire

French-born philosopher, mathematician and scientist René Descartes became famous for his statement in Latin in the 17th century which translates into English as: 'I think, therefore I am.'

On the face of it that is true. Thought reflects perception and perception leads to both behaviour and self-identity. In that sense 'we' are what we think. But who or what is doing the thinking and is thinking the only route to perception? Clearly, as we shall see, 'we' are not always the source of 'our' perception, indeed with regard to humanity as a whole this is rarely the case; and thinking is far from the only means of perception. Thought is the village idiot compared with other expressions of consciousness that we all have the potential to access and tap into. This has to be true when we *are* those other expressions of consciousness which are infinite in nature. We have forgotten this, or, more to the point, been manipulated to forget.

These are not just the esoteric musings of the navel. The whole foundation of human control and oppression is control of perception. Once perception is hijacked then so is behaviour which is dictated by perception. Collective perception becomes collective behaviour and collective behaviour is what we call human society. Perception is all and those behind human control know that which is

why perception is the target 24/7 of the psychopathic manipulators that I call the Global Cult. They know that if they dictate perception they will dictate behaviour and collectively dictate the nature of human society. They are further aware that perception is formed from information received and if they control the circulation of information they will to a vast extent direct human behaviour. Censorship of information and opinion has become globally Nazi-like in recent years and never more blatantly than since the illusory 'virus pandemic' was triggered out of China in 2019 and across the world in 2020. Why have billions submitted to house arrest and accepted fascistic societies in a way they would have never believed possible? Those controlling the information spewing from government, mainstream media and Silicon Valley (all controlled by the same Global Cult networks) told them they were in danger from a 'deadly virus' and only by submitting to house arrest and conceding their most basic of freedoms could they and their families be protected. This monumental and provable lie became the *perception* of the billions and therefore the *behaviour* of the billions. In those few words you have the whole structure and modus operandi of human control. Fear is a perception – **F**alse **E**motion **A**ppearing **R**eal – and fear is the currency of control. In short … get them by the balls (or give them the impression that you have) and their hearts and minds will follow. Nothing grips the dangly bits and freezes the rear-end more comprehensively than fear.

World number 1

There are two 'worlds' in what appears to be one 'world' and the prime difference between them is knowledge. First we have the mass of human society in which the population is maintained in coldly-calculated ignorance through control of information and the 'education' (indoctrination) system. That's all you really need to control to enslave billions in a perceptual delusion in which what are perceived to be *their* thoughts and opinions are ever-repeated mantras that the system has been downloading all their lives through 'education', media, science, medicine, politics and academia

in which the personnel and advocates are themselves overwhelmingly the perceptual products of the same repetition. Teachers and academics in general are processed by the same programming machine as everyone else, but unlike the great majority they never leave the 'education' program. It gripped them as students and continues to grip them as programmers of subsequent generations of students. The programmed become the programmers – the programmed programmers. The same can largely be said for scientists, doctors and politicians and not least because as the American writer Upton Sinclair said: 'It is difficult to get a man to understand something when his salary depends upon his not understanding it.' If your career and income depend on thinking the way the system demands then you will – bar a few free-minded exceptions – concede your mind to the Perceptual Mainframe that I call the Postage Stamp Consensus. This is a tiny band of perceived knowledge and possibility 'taught' (downloaded) in the schools and universities, pounded out by the mainstream media and on which all government policy is founded. Try thinking, and especially speaking and acting, outside of the 'box' of consensus and see what that does for your career in the Mainstream Everything which bullies, harasses, intimidates and ridicules the population into compliance. Here we have the simple structure which enslaves most of humanity in a perceptual prison cell for an entire lifetime and I'll go deeper into this process shortly. Most of what humanity is taught as fact is nothing more than programmed belief. American science fiction author Frank Herbert was right when he said: 'Belief can be manipulated. Only knowledge is dangerous.' In the 'Covid' age belief is promoted and knowledge is censored. It was always so, but never to the extreme of today.

World number 2

A 'number 2' is slang for 'doing a poo' and how appropriate that is when this other 'world' is doing just that on humanity every minute of every day. World number 2 is a global network of secret societies and semi-secret groups dictating the direction of society via

governments, corporations and authorities of every kind. I have spent more than 30 years uncovering and exposing this network that I call the Global Cult and knowing its agenda is what has made my books so accurate in predicting current and past events. Secret societies are secret for a reason. They want to keep their hoarded knowledge to themselves and their chosen initiates and to hide it from the population which they seek through ignorance to control and subdue. The whole foundation of the division between World 1 and World 2 is *knowledge*. What number 1 knows number 2 must not. Knowledge they have worked so hard to keep secret includes (a) the agenda to enslave humanity in a centrally-controlled global dictatorship, and (b) the nature of reality and life itself. The latter (b) must be suppressed to allow the former (a) to prevail as I shall be explaining. The way the Cult manipulates and interacts with the population can be likened to a spider's web. The 'spider' sits at the centre in the shadows and imposes its will through the web with each strand represented in World number 2 by a secret society, satanic or semi-secret group, and in World number 1 – the world of the seen – by governments, agencies of government, law enforcement, corporations, the banking system, media conglomerates and Silicon Valley (Fig 1 overleaf). The spider and the web connect and coordinate all these organisations to pursue the same global outcome while the population sees them as individual entities working randomly and independently. At the level of the web governments *are* the banking system *are* the corporations *are* the media *are* Silicon Valley *are* the World Health Organization working from their inner cores as one unit. Apparently unconnected countries, corporations, institutions, organisations and people are on the *same team* pursuing the same global outcome. Strands in the web immediately around the spider are the most secretive and exclusive secret societies and their membership is emphatically restricted to the Cult inner-circle emerging through the generations from particular bloodlines for reasons I will come to. At the core of the core you would get them in a single room. That's how many people are dictating the direction of human society and its transformation

through the ‘Covid’ hoax and other means. As the web expands out from the spider we meet the secret societies that many people will be aware of – the Freemasons, Knights Templar, Knights of Malta, Opus Dei, the inner sanctum of the Jesuit Order, and such like. Note how many are connected to the Church of Rome and there is a reason for that. The Roman Church was established as a revamp, a rebranding, of the relocated ‘Church’ of Babylon and the Cult imposing global tyranny today can be tracked back to Babylon and Sumer in what is now Iraq.



Figure 1: The global web through which the few control the many. (Image Neil Hague.)

Inner levels of the web operate in the unseen away from the public eye and then we have what I call the cusp organisations located at the point where the hidden meets the seen. They include a series of satellite organisations answering to a secret society founded in London in the late 19th century called the Round Table and among them are the Royal Institute of International Affairs (UK, founded in 1920); Council on Foreign Relations (US, 1921); Bilderberg Group (worldwide, 1954); Trilateral Commission (US/worldwide, 1972); and the Club of Rome (worldwide, 1968) which was created to exploit environmental concerns to justify the centralisation of global power to ‘save the planet’. The Club of Rome instigated with others the human-caused climate change hoax which has led to all the ‘green

new deals' demanding that very centralisation of control. Cusp organisations, which include endless 'think tanks' all over the world, are designed to coordinate a single global policy between political and business leaders, intelligence personnel, media organisations and anyone who can influence the direction of policy in their own sphere of operation. Major players and regular attenders will know what is happening – or some of it – while others come and go and are kept overwhelmingly in the dark about the big picture. I refer to these cusp groupings as semi-secret in that they can be publicly identified, but what goes on at the inner-core is kept very much 'in house' even from most of their members and participants through a fiercely-imposed system of compartmentalisation. Only let them know what they need to know to serve your interests and no more. The structure of secret societies serves as a perfect example of this principle. Most Freemasons never get higher than the bottom three levels of 'degree' (degree of knowledge) when there are 33 official degrees of the Scottish Rite. Initiates only qualify for the next higher 'compartment' or degree if those at that level choose to allow them. Knowledge can be carefully assigned only to those considered 'safe'. I went to my local Freemason's lodge a few years ago when they were having an 'open day' to show how cuddly they were and when I chatted to some of them I was astonished at how little the rank and file knew even about the most ubiquitous symbols they use. The mushroom technique – keep them in the dark and feed them bullshit – applies to most people in the web as well as the population as a whole. Sub-divisions of the web mirror in theme and structure transnational corporations which have a headquarters somewhere in the world dictating to all their subsidiaries in different countries. Subsidiaries operate in their methodology and branding to the same centrally-dictated plan and policy in pursuit of particular ends. The Cult web functions in the same way. Each country has its own web as a subsidiary of the global one. They consist of networks of secret societies, semi-secret groups and bloodline families and their job is to impose the will of the spider and the global web in their particular country. Subsidiary networks control and manipulate the national political system, finance, corporations, media, medicine, etc. to

ensure that they follow the globally-dictated Cult agenda. These networks were the means through which the 'Covid' hoax could be played out with almost every country responding in the same way.

The 'Yessir' pyramid

Compartmentalisation is the key to understanding how a tiny few can dictate the lives of billions when combined with a top-down sequence of imposition and acquiescence. The inner core of the Cult sits at the peak of the pyramidal hierarchy of human society (Fig 2 overleaf). It imposes its will – its agenda for the world – on the level immediately below which acquiesces to that imposition. This level then imposes the Cult will on the level below them which acquiesces and imposes on the next level. Very quickly we meet levels in the hierarchy that have no idea there even is a Cult, but the sequence of imposition and acquiescence continues down the pyramid in just the same way. 'I don't know why we are doing this but the order came from "on-high" and so we better just do it.' Alfred Lord Tennyson said of the cannon fodder levels in his poem *The Charge of the Light Brigade*: 'Theirs not to reason why; theirs but to do and die.' The next line says that 'into the valley of death rode the six hundred' and they died because they obeyed without question what their perceived 'superiors' told them to do. In the same way the population capitulated to 'Covid'. The whole hierarchical pyramid functions like this to allow the very few to direct the enormous many. Eventually imposition-acquiescence-imposition-acquiescence comes down to the mass of the population at the foot of the pyramid. If they acquiesce to those levels of the hierarchy imposing on them (governments/law enforcement/doctors/media) a circuit is completed between the population and the handful of super-psychopaths in the Cult inner core at the top of the pyramid. Without a circuit-breaking refusal to obey, the sequence of imposition and acquiescence allows a staggeringly few people to impose their will upon the entirety of humankind. We are looking at the very sequence that has subjugated billions since the start of 2020. Our freedom has not been taken from us. Humanity has given it

away. Fascists do not impose fascism because there are not enough of them. Fascism is imposed by the population acquiescing to fascism. Put another way allowing their perceptions to be programmed to the extent that leads to the population giving their freedom away by giving their perceptions – their mind – away. If this circuit is not broken by humanity ceasing to cooperate with their own enslavement then nothing can change. For that to happen people have to critically think and see through the lies and window dressing and then summon the backbone to act upon what they see. The Cult spends its days working to stop either happening and its methodology is systematic and highly detailed, but it can be overcome and that is what this book is all about.

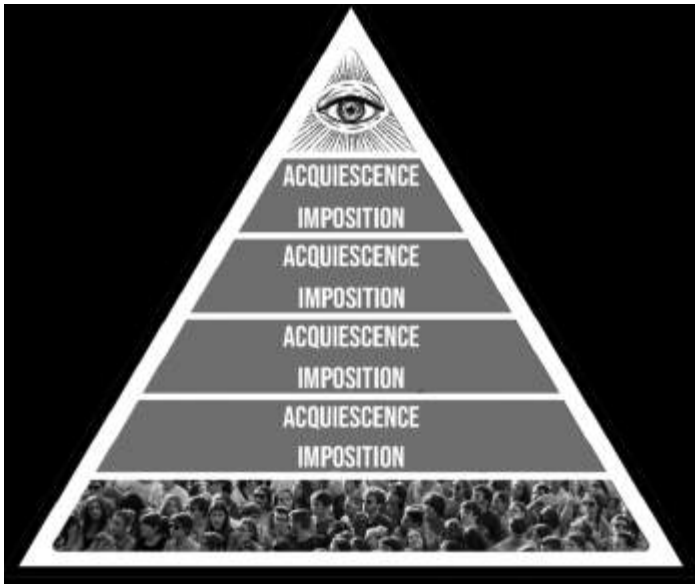


Figure 2: The simple sequence of imposition and compliance that allows a handful of people at the peak of the pyramid to dictate the lives of billions.

The Life Program

Okay, back to world number 1 or the world of the 'masses'. Observe the process of what we call 'life' and it is a perceptual download from cradle to grave. The Cult has created a global structure in which perception can be programmed and the program continually topped-up with what appears to be constant confirmation that the program is indeed true reality. The important word here is 'appears'.

This is the structure, the fly-trap, the Postage Stamp Consensus or Perceptual Mainframe, which represents that incredibly narrow band of perceived possibility delivered by the 'education' system, mainstream media, science and medicine. From the earliest age the download begins with parents who have themselves succumbed to the very programming their children are about to go through. Most parents don't do this out of malevolence and mostly it is quite the opposite. They do what they believe is best for their children and that is what the program has told them is best. Within three or four years comes the major transition from parental programming to full-blown state (Cult) programming in school, college and university where perceptually-programmed teachers and academics pass on their programming to the next generations. Teachers who resist are soon marginalised and their careers ended while children who resist are called a problem child for whom Ritalin may need to be prescribed. A few years after entering the 'world' children are under the control of authority figures representing the state telling them when they have to be there, when they can leave and when they can speak, eat, even go to the toilet. This is calculated preparation for a lifetime of obeying authority in all its forms. Reflex-action fear of authority is instilled by authority from the start. Children soon learn the carrot and stick consequences of obeying or defying authority which is underpinned daily for the rest of their life. Fortunately I daydreamed through this crap and never obeyed authority simply because it told me to. This approach to my alleged 'betters' continues to this day. There can be consequences of pursuing open-minded freedom in a world of closed-minded conformity. I spent a lot of time in school corridors after being ejected from the classroom for not taking some of it seriously and now I spend a lot of time being ejected from Facebook, YouTube and Twitter. But I can tell you that being true to yourself and not compromising your self-respect is far more exhilarating than bowing to authority for authority's sake. You don't have to be a sheep to the shepherd (authority) and the sheep dog (fear of not obeying authority).

The perceptual download continues throughout the formative years in school, college and university while script-reading 'teachers', 'academics' 'scientists', 'doctors' and 'journalists' insist that ongoing generations must be as programmed as they are. Accept the program or you will not pass your 'exams' which confirm your 'degree' of programming. It is tragic to think that many parents pressure their offspring to work hard at school to download the program and qualify for the next stage at college and university. The late, great, American comedian George Carlin said: 'Here's a bumper sticker I'd like to see: We are proud parents of a child who has resisted his teachers' attempts to break his spirit and bend him to the will of his corporate masters.' Well, the best of luck finding many of those, George. Then comes the moment to leave the formal programming years in academia and enter the 'adult' world of work. There you meet others in your chosen or prescribed arena who went through the same Postage Stamp Consensus program before you did. There is therefore overwhelming agreement between almost everyone on the basic foundations of Postage Stamp reality and the rejection, even contempt, of the few who have a mind of their own and are prepared to use it. This has two major effects. Firstly, the consensus confirms to the programmed that their download is really how things are. I mean, everyone knows that, right? Secondly, the arrogance and ignorance of Postage Stamp adherents ensure that anyone questioning the program will have unpleasant consequences for seeking their own truth and not picking their perceptions from the shelf marked: 'Things you must believe without question and if you don't you're a dangerous lunatic conspiracy theorist and a harebrained nutter'.

Every government, agency and corporation is founded on the same Postage Stamp prison cell and you can see why so many people believe the same thing while calling it their own 'opinion'. Fusion of governments and corporations in pursuit of the same agenda was the definition of fascism described by Italian dictator Benito Mussolini. The pressure to conform to perceptual norms downloaded for a lifetime is incessant and infiltrates society right

down to family groups that become censors and condemners of their own 'black sheep' for not, ironically, being sheep. We have seen an explosion of that in the 'Covid' era. Cult-owned global media unleashes its propaganda all day every day in support of the Postage Stamp and targets with abuse and ridicule anyone in the public eye who won't bend their mind to the will of the tyranny. Any response to this is denied (certainly in my case). They don't want to give a platform to expose official lies. Cult-owned-and-created Internet giants like Facebook, Google, YouTube and Twitter delete you for having an unapproved opinion. Facebook boasts that its AI censors delete 97-percent of 'hate speech' before anyone even reports it. Much of that 'hate speech' will simply be an opinion that Facebook and its masters don't want people to see. Such perceptual oppression is widely known as fascism. Even Facebook executive Benny Thomas, a 'CEO Global Planning Lead', said in comments secretly recorded by investigative journalism operation Project Veritas that Facebook is 'too powerful' and should be broken up:

I mean, no king in history has been the ruler of two billion people, but Mark Zuckerberg is … And he's 36. That's too much for a 36-year-old ... You should not have power over two billion people. I just think that's wrong.

Thomas said Facebook-owned platforms like Instagram, Oculus, and WhatsApp needed to be separate companies. 'It's too much power when they're all one together'. That's the way the Cult likes it, however. We have an executive of a Cult organisation in Benny Thomas that doesn't know there is a Cult such is the compartmentalisation. Thomas said that Facebook and Google 'are no longer companies, they're countries'. Actually they are more powerful than countries on the basis that if you control information you control perception and control human society.

I love my oppressor

Another expression of this psychological trickery is for those who realise they are being pressured into compliance to eventually

convince themselves to believe the official narratives to protect their self-respect from accepting the truth that they have succumbed to meek and subservient compliance. Such people become some of the most vehement defenders of the system. You can see them everywhere screaming abuse at those who prefer to think for themselves and by doing so reminding the compliers of their own capitulation to conformity. 'You are talking dangerous nonsense you Covidiot!!' Are you trying to convince me or yourself? It is a potent form of Stockholm syndrome which is defined as: 'A psychological condition that occurs when a victim of abuse identifies and attaches, or bonds, positively with their abuser.' An example is hostages bonding and even 'falling in love' with their kidnappers. The syndrome has been observed in domestic violence, abused children, concentration camp inmates, prisoners of war and many and various Satanic cults. These are some traits of Stockholm syndrome listed at goodtherapy.org:

- Positive regard towards perpetrators of abuse or captor [see 'Covid'].
- Failure to cooperate with police and other government authorities when it comes to holding perpetrators of abuse or kidnapping accountable [or in the case of 'Covid' cooperating with the police to enforce and defend their captors' demands].
- Little or no effort to escape [see 'Covid'].
- Belief in the goodness of the perpetrators or kidnappers [see 'Covid'].
- Appeasement of captors. This is a manipulative strategy for maintaining one's safety. As victims get rewarded – perhaps with less abuse or even with life itself – their appeasing behaviours are reinforced [see 'Covid'].
- Learned helplessness. This can be akin to 'if you can't beat 'em, join 'em'. As the victims fail to escape the abuse or captivity, they may start giving up and soon realize it's just easier for everyone if they acquiesce all their power to their captors [see 'Covid'].

- Feelings of pity toward the abusers, believing they are actually victims themselves. Because of this, victims may go on a crusade or mission to 'save' [protect] their abuser [see the venom unleashed on those challenging the official 'Covid' narrative].
- Unwillingness to learn to detach from their perpetrators and heal. In essence, victims may tend to be less loyal to themselves than to their abuser [*definitely* see 'Covid'].

Ponder on those traits and compare them with the behaviour of great swathes of the global population who have defended governments and authorities which have spent every minute destroying their lives and livelihoods and those of their children and grandchildren since early 2020 with fascistic lockdowns, house arrest and employment deletion to 'protect' them from a 'deadly virus' that their abusers' perceptually created to bring about this very outcome. We are looking at mass Stockholm syndrome. All those that agree to concede their freedom will believe those perceptions are originating in their own independent 'mind' when in fact by conceding their reality to Stockholm syndrome they have by definition conceded any independence of mind. Listen to the 'opinions' of the acquiescing masses in this 'Covid' era and what gushes forth is the repetition of the official version of everything delivered unprocessed, unfiltered and unquestioned. The whole programming dynamic works this way. I must be free because I'm told that I am and so I think that I am.

You can see what I mean with the chapter theme of 'I'm thinking – Oh, but *are* you?' The great majority are not thinking, let alone for themselves. They are repeating what authority has told them to believe which allows them to be controlled. Weaving through this mentality is the fear that the 'conspiracy theorists' are right and this again explains the often hysterical abuse that ensues when you dare to contest the official narrative of anything. Denial is the mechanism of hiding from yourself what you don't want to be true. Telling people what they want to hear is easy, but it's an infinitely greater challenge to tell them what they would rather not be happening.

One is akin to pushing against an open door while the other is met with vehement resistance no matter what the scale of evidence. I don't want it to be true so I'll convince myself that it's not. Examples are everywhere from the denial that a partner is cheating despite all the signs to the reflex-action rejection of any idea that world events in which country after country act in exactly the same way are centrally coordinated. To accept the latter is to accept that a force of unspeakable evil is working to destroy your life and the lives of your children with nothing too horrific to achieve that end. Who the heck wants that to be true? But if we don't face reality the end is duly achieved and the consequences are far worse and ongoing than breaking through the walls of denial today with the courage to make a stand against tyranny.

Connect the dots – but how?

A crucial aspect of perceptual programming is to portray a world in which everything is random and almost nothing is connected to anything else. Randomness cannot be coordinated by its very nature and once you perceive events as random the idea they could be connected is waved away as the rantings of the tinfoil-hat brigade. You can't plan and coordinate random you idiot! No, you can't, but you can hide the coldly-calculated and long-planned behind the *illusion* of randomness. A foundation manifestation of the Renegade Mind is to scan reality for patterns that connect the apparently random and turn pixels and dots into pictures. This is the way I work and have done so for more than 30 years. You look for similarities in people, modus operandi and desired outcomes and slowly, then ever quicker, the picture forms. For instance: There would seem to be no connection between the 'Covid pandemic' hoax and the human-caused global-warming hoax and yet they are masks (appropriately) on the same face seeking the same outcome. Those pushing the global warming myth through the Club of Rome and other Cult agencies are driving the lies about 'Covid' – Bill Gates is an obvious one, but they are endless. Why would the same people be involved in both when they are clearly not connected? Oh, but they

are. Common themes with personnel are matched by common goals. The 'solutions' to both 'problems' are centralisation of global power to impose the will of the few on the many to 'save' humanity from 'Covid' and save the planet from an 'existential threat' (we need 'zero Covid' and 'zero carbon emissions'). These, in turn, connect with the 'dot' of globalisation which was coined to describe the centralisation of global power in every area of life through incessant political and corporate expansion, trading blocks and superstates like the European Union. If you are the few and you want to control the many you have to centralise power and decision-making. The more you centralise power the more power the few at the centre will have over the many; and the more that power is centralised the more power those at the centre have to centralise even quicker. The momentum of centralisation gets faster and faster which is exactly the process we have witnessed. In this way the hoaxed 'pandemic' and the fakery of human-caused global warming serve the interests of globalisation and the seizure of global power in the hands of the Cult inner-circle which is behind 'Covid', 'climate change' *and* globalisation. At this point random 'dots' become a clear and obvious picture or pattern.

Klaus Schwab, the classic Bond villain who founded the Cult's Gates-funded World Economic Forum, published a book in 2020, *The Great Reset*, in which he used the 'problem' of 'Covid' to justify a total transformation of human society to 'save' humanity from 'climate change'. Schwab said: 'The pandemic represents a rare but narrow window of opportunity to reflect, reimagine, and reset our world.' What he didn't mention is that the Cult he serves is behind both hoaxes as I show in my book *The Answer*. He and the Cult don't have to reimagine the world. They know precisely what they want and that's why they destroyed human society with 'Covid' to 'build back better' in their grand design. Their job is not to imagine, but to get humanity to imagine and agree with their plans while believing it's all random. It must be pure coincidence that 'The Great Reset' has long been the Cult's code name for the global imposition of fascism and replaced previous code-names of the 'New World

Order' used by Cult frontmen like Father George Bush and the 'New Order of the Ages' which emerged from Freemasonry and much older secret societies. New Order of the Ages appears on the reverse of the Great Seal of the United States as 'Novus ordo seclorum' underneath the Cult symbol used since way back of the pyramid and all seeing-eye (Fig 3). The pyramid is the hierarchy of human control headed by the illuminated eye that symbolises the force behind the Cult which I will expose in later chapters. The term 'Annuit Coeptis' translates as 'He favours our undertaking'. We are told the 'He' is the Christian god, but 'He' is not as I will be explaining.



Figure 3: The all-seeing eye of the Cult 'god' on the Freemason-designed Great Seal of the United States and also on the dollar bill.

Having you on

Two major Cult techniques of perceptual manipulation that relate to all this are what I have called since the 1990s Problem-Reaction-Solution (PRS) and the Totalitarian Tiptoe (TT). They can be uncovered by the inquiring mind with a simple question: Who benefits? The answer usually identifies the perpetrators of a given action or happening through the concept of 'he who most benefits from a crime is the one most likely to have committed it'. The Latin 'Cue bono?' – Who benefits? – is widely attributed to the Roman orator and statesman Marcus Tullius Cicero. No wonder it goes back so far when the concept has been relevant to human behaviour since

history was recorded. Problem-Reaction-Solution is the technique used to manipulate us every day by covertly creating a problem (or the illusion of one) and offering the solution to the problem (or the illusion of one). In the first phase you create the problem and blame someone or something else for why it has happened. This may relate to a financial collapse, terrorist attack, war, global warming or pandemic, anything in fact that will allow you to impose the 'solution' to change society in the way you desire at that time. The 'problem' doesn't have to be real. PRS is manipulation of perception and all you need is the population to believe the problem is real. Human-caused global warming and the 'Covid pandemic' only have to be *perceived* to be real for the population to accept the 'solutions' of authority. I refer to this technique as NO-Problem-Reaction-Solution. Billions did not meekly accept house arrest from early 2020 because there was a real deadly 'Covid pandemic' but because they perceived – believed – that to be the case. The antidote to Problem-Reaction-Solution is to ask who benefits from the proposed solution. Invariably it will be anyone who wants to justify more control through deletion of freedom and centralisation of power and decision-making.

The two world wars were Problem-Reaction-Solutions that transformed and realigned global society. Both were manipulated into being by the Cult as I have detailed in books since the mid-1990s. They dramatically centralised global power, especially World War Two, which led to the United Nations and other global bodies thanks to the overt and covert manipulations of the Rockefeller family and other Cult bloodlines like the Rothschilds. The UN is a stalking horse for full-blown world government that I will come to shortly. The land on which the UN building stands in New York was donated by the Rockefellers and the same Cult family was behind Big Pharma scalpel and drug 'medicine' and the creation of the World Health Organization as part of the UN. They have been stalwarts of the eugenics movement and funded Hitler's race-purity expert' Ernst Rudin. The human-caused global warming hoax has been orchestrated by the Club of Rome through the UN which is

manufacturing both the 'problem' through its Intergovernmental Panel on Climate Change and imposing the 'solution' through its Agenda 21 and Agenda 2030 which demand the total centralisation of global power to 'save the world' from a climate hoax the United Nations is itself perpetrating. What a small world the Cult can be seen to be particularly among the inner circles. The bedfellow of Problem-Reaction-Solution is the Totalitarian Tiptoe which became the Totalitarian Sprint in 2020. The technique is fashioned to hide the carefully-coordinated behind the cover of apparently random events. You start the sequence at 'A' and you know you are heading for 'Z'. You don't want people to know that and each step on the journey is presented as a random happening while all the steps strung together lead in the same direction. The speed may have quickened dramatically in recent times, but you can still see the incremental approach of the Tiptoe in the case of 'Covid' as each new imposition takes us deeper into fascism. Tell people they have to do this or that to get back to 'normal', then this and this and this. With each new demand adding to the ones that went before the population's freedom is deleted until it disappears. The spider wraps its web around the flies more comprehensively with each new diktat. I'll highlight this in more detail when I get to the 'Covid' hoax and how it has been pulled off. Another prime example of the Totalitarian Tiptoe is how the Cult-created European Union went from a 'free-trade zone' to a centralised bureaucratic dictatorship through the Tiptoe of incremental centralisation of power until nations became mere administrative units for Cult-owned dark suits in Brussels.

The antidote to ignorance is knowledge which the Cult seeks vehemently to deny us, but despite the systematic censorship to that end the Renegade Mind can overcome this by vociferously seeking out the facts no matter the impediments put in the way. There is also a method of thinking and perceiving – *knowing* – that doesn't even need names, dates, place-type facts to identify the patterns that reveal the story. I'll get to that in the final chapter. All you need to know about the manipulation of human society and to what end is still out there – *at the time of writing* – in the form of books, videos

and websites for those that really want to breach the walls of programmed perception. To access this knowledge requires the abandonment of the mainstream media as a source of information in the awareness that this is owned and controlled by the Cult and therefore promotes mass perceptions that suit the Cult. Mainstream media lies all day, every day. That is its function and very reason for being. Where it does tell the truth, here and there, is only because the truth and the Cult agenda very occasionally coincide. If you look for fact and insight to the BBC, CNN and virtually all the rest of them you are asking to be conned and perceptually programmed.

Know the outcome and you'll see the journey

Events seem random when you have no idea where the world is being taken. Once you do the random becomes the carefully planned. Know the outcome and you'll see the journey is a phrase I have been using for a long time to give context to daily happenings that appear unconnected. Does a problem, or illusion of a problem, trigger a proposed 'solution' that further drives society in the direction of the outcome? Invariably the answer will be yes and the random – *abracadabra* – becomes the clearly coordinated. So what is this outcome that unlocks the door to a massively expanded understanding of daily events? I will summarise its major aspects – the fine detail is in my other books – and those new to this information will see that the world they thought they were living in is a very different place. The foundation of the Cult agenda is the incessant centralisation of power and all such centralisation is ultimately in pursuit of Cult control on a global level. I have described for a long time the planned world structure of top-down dictatorship as the Hunger Games Society. The term obviously comes from the movie series which portrayed a world in which a few living in military-protected hi-tech luxury were the overlords of a population condemned to abject poverty in isolated 'sectors' that were not allowed to interact. 'Covid' lockdowns and travel bans anyone? The 'Hunger Games' pyramid of structural control has the inner circle of the Cult at the top with pretty much the entire

population at the bottom under their control through dependency for survival on the Cult. The whole structure is planned to be protected and enforced by a military-police state (Fig 4).

Here you have the reason for the global lockdowns of the fake pandemic to coldly destroy independent incomes and livelihoods and make everyone dependent on the 'state' (the Cult that controls the 'states'). I have warned in my books for many years about the plan to introduce a 'guaranteed income' – a barely survivable pittance – designed to impose dependency when employment was destroyed by AI technology and now even more comprehensively at great speed by the 'Covid' scam. Once the pandemic was played and lockdown consequences began to delete independent income the authorities began to talk right on cue about the need for a guaranteed income and a 'Great Reset'. Guaranteed income will be presented as benevolent governments seeking to help a desperate people – desperate as a direct result of actions of the same governments. The truth is that such payments are a trap. You will only get them if you do exactly what the authorities demand including mass vaccination (genetic manipulation). We have seen this theme already in Australia where those dependent on government benefits have them reduced if parents don't agree to have their children vaccinated according to an insane health-destroying government-dictated schedule. Calculated economic collapse applies to governments as well as people. The Cult wants rid of countries through the creation of a world state with countries broken up into regions ruled by a world government and super states like the European Union. Countries must be bankrupted, too, to this end and it's being achieved by the trillions in 'rescue packages' and furlough payments, trillions in lost taxation, and money-no-object spending on 'Covid' including constant all-medium advertising (programming) which has made the media dependent on government for much of its income. The day of reckoning is coming – as planned – for government spending and given that it has been made possible by printing money and not by production/taxation there is inflation on the way that has the

potential to wipe out monetary value. In that case there will be no need for the Cult to steal your money. It just won't be worth anything (see the German Weimar Republic before the Nazis took over). Many have been okay with lockdowns while getting a percentage of their income from so-called furlough payments without having to work. Those payments are dependent, however, on people having at least a theoretical job with a business considered non-essential and ordered to close. As these business go under because they are closed by lockdown after lockdown the furlough stops and it will for everyone eventually. Then what? The 'then what?' is precisely the idea.



Figure 4: The Hunger Games Society structure I have long warned was planned and now the 'Covid' hoax has made it possible. This is the real reason for lockdowns.

Hired hands

Between the Hunger Games Cult elite and the dependent population is planned to be a vicious military-police state (a fusion of the two into one force). This has been in the making for a long time with police looking ever more like the military and carrying weapons to match. The pandemic scam has seen this process accelerate so fast as

lockdown house arrest is brutally enforced by carefully recruited fascist minds and gormless system-servers. The police and military are planned to merge into a centrally-directed world army in a global structure headed by a world government which wouldn't be elected even by the election fixes now in place. The world army is not planned even to be human and instead wars would be fought, primarily against the population, using robot technology controlled by artificial intelligence. I have been warning about this for decades and now militaries around the world are being transformed by this very AI technology. The global regime that I describe is a particular form of fascism known as a technocracy in which decisions are not made by clueless and co-opted politicians but by unelected technocrats – scientists, engineers, technologists and bureaucrats. Cult-owned-and-controlled Silicon Valley giants are examples of technocracy and they already have far more power to direct world events than governments. They are with their censorship *selecting* governments. I know that some are calling the 'Great Reset' a Marxist communist takeover, but fascism and Marxism are different labels for the same tyranny. Tell those who lived in fascist Germany and Stalinist Russia that there was a difference in the way their freedom was deleted and their lives controlled. I could call it a fascist technocracy or a Marxist technocracy and they would be equally accurate. The Hunger Games society with its world government structure would oversee a world army, world central bank and single world cashless currency imposing its will on a microchipped population (Fig 5). Scan its different elements and see how the illusory pandemic is forcing society in this very direction at great speed. Leaders of 23 countries and the World Health Organization (WHO) backed the idea in March, 2021, of a global treaty for 'international cooperation' in 'health emergencies' and nations should 'come together as a global community for peaceful cooperation that extends beyond this crisis'. Cut the Orwellian bullshit and this means another step towards global government. The plan includes a cashless digital money system that I first warned about in 1993. Right at the start of 'Covid' the deeply corrupt Tedros

Adhanom Ghebreyesus, the crooked and merely gofer 'head' of the World Health Organization, said it was possible to catch the 'virus' by touching cash and it was better to use cashless means. The claim was ridiculous nonsense and like the whole 'Covid' mind-trick it was nothing to do with 'health' and everything to do with pushing every aspect of the Cult agenda. As a result of the Tedros lie the use of cash has plummeted. The Cult script involves a single world digital currency that would eventually be technologically embedded in the body. China is a massive global centre for the Cult and if you watch what is happening there you will know what is planned for everywhere. The Chinese government is developing a digital currency which would allow fines to be deducted immediately via AI for anyone caught on camera breaking its fantastic list of laws and the money is going to be programmable with an expiry date to ensure that no one can accrue wealth except the Cult and its operatives.



Figure 5: The structure of global control the Cult has been working towards for so long and this has been enormously advanced by the 'Covid' illusion.

Serfdom is so smart

The Cult plan is far wider, extreme, and more comprehensive than even most conspiracy researchers appreciate and I will come to the true depths of deceit and control in the chapters 'Who controls the

Cult?' and 'Escaping Wetiko'. Even the world that we know is crazy enough. We are being deluged with ever more sophisticated and controlling technology under the heading of 'smart'. We have smart televisions, smart meters, smart cards, smart cars, smart driving, smart roads, smart pills, smart patches, smart watches, smart skin, smart borders, smart pavements, smart streets, smart cities, smart communities, smart environments, smart growth, smart planet ... smart *everything* around us. Smart technologies and methods of operation are designed to interlock to create a global Smart Grid connecting the entirety of human society including human minds to create a centrally-dictated 'hive' mind. 'Smart cities' is code for densely-occupied megacities of total surveillance and control through AI. Ever more destructive frequency communication systems like 5G have been rolled out without any official testing for health and psychological effects (colossal). 5G/6G/7G systems are needed to run the Smart Grid and each one becomes more destructive of body and mind. Deleting independent income is crucial to forcing people into these AI-policed prisons by ending private property ownership (except for the Cult elite). The Cult's Great Reset now openly foresees a global society in which no one will own any possessions and everything will be rented while the Cult would own literally everything under the guise of government and corporations. The aim has been to use the lockdowns to destroy sources of income on a mass scale and when the people are destitute and in unrepayable amounts of debt (problem) Cult assets come forward with the pledge to write-off debt in return for handing over all property and possessions (solution). Everything – literally everything including people – would be connected to the Internet via AI. I was warning years ago about the coming Internet of Things (IoT) in which all devices and technology from your car to your fridge would be plugged into the Internet and controlled by AI. Now we are already there with much more to come. The next stage is the Internet of Everything (IoE) which is planned to include the connection of AI to the human brain and body to replace the human mind with a centrally-controlled AI mind. Instead of perceptions

being manipulated through control of information and censorship those perceptions would come direct from the Cult through AI. What do you think? You think whatever AI decides that you think. In human terms there would be no individual 'think' any longer. Too incredible? The ravings of a lunatic? Not at all. Cult-owned crazies in Silicon Valley have been telling us the plan for years without explaining the real motivation and calculated implications. These include Google executive and 'futurist' Ray Kurzweil who highlights the year 2030 for when this would be underway. He said:

Our thinking ... will be a hybrid of biological and non-biological thinking ... humans will be able to extend their limitations and 'think in the cloud' ... We're going to put gateways to the cloud in our brains ... We're going to gradually merge and enhance ourselves ... In my view, that's the nature of being human – we transcend our limitations.

As the technology becomes vastly superior to what we are then the small proportion that is still human gets smaller and smaller and smaller until it's just utterly negligible.

The sales-pitch of Kurzweil and Cult-owned Silicon Valley is that this would make us 'super-human' when the real aim is to make us post-human and no longer 'human' in the sense that we have come to know. The entire global population would be connected to AI and become the centrally-controlled 'hive-mind' of externally-delivered perceptions. The Smart Grid being installed to impose the Cult's will on the world is being constructed to allow particular locations – even one location – to control the whole global system. From these prime control centres, which absolutely include China and Israel, anything connected to the Internet would be switched on or off and manipulated at will. Energy systems could be cut, communication via the Internet taken down, computer-controlled driverless autonomous vehicles driven off the road, medical devices switched off, the potential is limitless given how much AI and Internet connections now run human society. We have seen nothing yet if we allow this to continue. Autonomous vehicle makers are working with law enforcement to produce cars designed to automatically pull over if they detect a police or emergency vehicle flashing from up to 100 feet away. At a police stop the car would be unlocked and the

window rolled down automatically. Vehicles would only take you where the computer (the state) allowed. The end of petrol vehicles and speed limiters on all new cars in the UK and EU from 2022 are steps leading to electric computerised transport over which ultimately you have no control. The picture is far bigger even than the Cult global network or web and that will become clear when I get to the nature of the 'spider'. There is a connection between all these happenings and the instigation of DNA-manipulating 'vaccines' (which aren't 'vaccines') justified by the 'Covid' hoax. That connection is the unfolding plan to transform the human body from a biological to a synthetic biological state and this is why synthetic biology is such a fast-emerging discipline of mainstream science. 'Covid vaccines' are infusing self-replicating synthetic genetic material into the cells to cumulatively take us on the Totalitarian Tiptoe from Human 1.0 to the synthetic biological Human 2.0 which will be physically and perceptually attached to the Smart Grid to one hundred percent control every thought, perception and deed. Humanity needs to wake up and *fast*.

This is the barest explanation of where the 'outcome' is planned to go but it's enough to see the journey happening all around us. Those new to this information will already see 'Covid' in a whole new context. I will add much more detail as we go along, but for the minutiae evidence see my mega-works, *The Answer, The Trigger* and *Everything You Need to Know But Have Never Been Told*.

Now – how does a Renegade Mind see the 'world'?

CHAPTER TWO

Renegade Perception

It is one thing to be clever and another to be wise
George R.R. Martin

A simple definition of the difference between a programmed mind and a Renegade Mind would be that one sees only dots while the other connects them to see the picture. Reading reality with accuracy requires the observer to (a) know the planned outcome and (b) realise that everything, but *everything*, is connected.

The entirety of infinite reality is connected – that's its very nature – and with human society an expression of infinite reality the same must apply. Simple cause and effect is a connection. The effect is triggered by the cause and the effect then becomes the cause of another effect. Nothing happens in isolation because it *can't*. Life in whatever reality is simple choice and consequence. We make choices and these lead to consequences. If we don't like the consequences we can make different choices and get different consequences which lead to other choices and consequences. The choice and the consequence are not only connected they are indivisible. You can't have one without the other as an old song goes. A few cannot control the world unless those being controlled allow that to happen – cause and effect, choice and consequence. Control – who has it and who doesn't – is a two-way process, a symbiotic relationship, involving the controller and controlled. 'They took my freedom away!!' Well, yes, but you also gave it to them. Humanity is

subjected to mass control because humanity has acquiesced to that control. This is all cause and effect and literally a case of give and take. In the same way world events of every kind are connected and the Cult works incessantly to sell the illusion of the random and coincidental to maintain the essential (to them) perception of dots that hide the picture. Renegade Minds know this and constantly scan the world for patterns of connection. This is absolutely pivotal in understanding the happenings in the world and without that perspective clarity is impossible. First you know the planned outcome and then you identify the steps on the journey – the day-by-day apparently random which, when connected in relation to the outcome, no longer appear as individual events, but as the proverbial *chain* of events leading in the same direction. I'll give you some examples:

Political puppet show

We are told to believe that politics is 'adversarial' in that different parties with different beliefs engage in an endless tussle for power. There may have been some truth in that up to a point – and only a point – but today divisions between 'different' parties are rhetorical not ideological. Even the rhetorical is fusing into one-speak as the parties eject any remaining free thinkers while others succumb to the ever-gathering intimidation of anyone with the 'wrong' opinion. The Cult is not a new phenomenon and can be traced back thousands of years as my books have documented. Its intergenerational initiates have been manipulating events with increasing effect the more that global power has been centralised. In ancient times the Cult secured control through the system of monarchy in which 'special' bloodlines (of which more later) demanded the right to rule as kings and queens simply by birthright and by vanquishing others who claimed the same birthright. There came a time, however, when people had matured enough to see the unfairness of such tyranny and demanded a say in who governed them. Note the word – *governed* them. Not served them – *governed* them, hence government defined as 'the political direction and control exercised over the

actions of the members, citizens, or inhabitants of communities, societies, and states; direction of the affairs of a state, community, etc.' Governments exercise control over rather than serve just like the monarchies before them. Bizarrely there are still countries like the United Kingdom which are ruled by a monarch *and* a government that officially answers to the monarch. The UK head of state and that of Commonwealth countries such as Canada, Australia and New Zealand is 'selected' by who in a *single family* had unprotected sex with whom and in what order. Pinch me it can't be true. Ouch! Shit, it is. The demise of monarchies in most countries offered a potential vacuum in which some form of free and fair society could arise and the Cult had that base covered. Monarchies had served its interests but they couldn't continue in the face of such widespread opposition and, anyway, replacing a 'royal' dictatorship that people could see with a dictatorship 'of the people' hiding behind the concept of 'democracy' presented far greater manipulative possibilities and ways of hiding coordinated tyranny behind the illusion of 'freedom'.

Democracy is quite wrongly defined as government selected by the population. This is not the case at all. It is government selected by *some* of the population (and then only in theory). This 'some' doesn't even have to be the majority as we have seen so often in first-past-the-post elections in which the so-called majority party wins fewer votes than the 'losing' parties combined. Democracy can give total power to a party in government from a minority of the votes cast. It's a sleight of hand to sell tyranny as freedom. Seventy-four million Trump-supporting Americans didn't vote for the 'Democratic' Party of Joe Biden in the distinctly dodgy election in 2020 and yet far from acknowledging the wishes and feelings of that great percentage of American society the Cult-owned Biden government set out from day one to destroy them and their right to a voice and opinion. Empty shell Biden and his Cult handlers said they were doing this to 'protect democracy'. Such is the level of lunacy and sickness to which politics has descended. Connect the dots and relate them to the desired outcome – a world government run by self-appointed technocrats and no longer even elected

politicians. While operating through its political agents in government the Cult is at the same time encouraging public distain for politicians by putting idiots and incompetents in theoretical power on the road to deleting them. The idea is to instil a public reaction that says of the technocrats: 'Well, they couldn't do any worse than the pathetic politicians.' It's all about controlling perception and Renegade Minds can see through that while programmed minds cannot when they are ignorant of both the planned outcome and the manipulation techniques employed to secure that end. This knowledge can be learned, however, and fast if people choose to get informed.

Politics may at first sight appear very difficult to control from a central point. I mean look at the 'different' parties and how would you be able to oversee them all and their constituent parts? In truth, it's very straightforward because of their structure. We are back to the pyramid of imposition and acquiescence. Organisations are structured in the same way as the system as a whole. Political parties are not open forums of free expression. They are hierarchies. I was a national spokesman for the British Green Party which claimed to be a different kind of politics in which influence and power was devolved; but I can tell you from direct experience – and it's far worse now – that Green parties are run as hierarchies like all the others however much they may try to hide that fact or kid themselves that it's not true. A very few at the top of all political parties are directing policy and personnel. They decide if you are elevated in the party or serve as a government minister and to do that you have to be a yes man or woman. Look at all the maverick political thinkers who never ascended the greasy pole. If you want to progress within the party or reach 'high-office' you need to fall into line and conform. Exceptions to this are rare indeed. Should you want to run for parliament or Congress you have to persuade the local or state level of the party to select you and for that you need to play the game as dictated by the hierarchy. If you secure election and wish to progress within the greater structure you need to go on conforming to what is acceptable to those running the hierarchy

from the peak of the pyramid. Political parties are perceptual gulags and the very fact that there are party 'Whips' appointed to 'whip' politicians into voting the way the hierarchy demands exposes the ridiculous idea that politicians are elected to serve the people they are supposed to represent. Cult operatives and manipulation has long seized control of major parties that have any chance of forming a government and at least most of those that haven't. A new party forms and the Cult goes to work to infiltrate and direct. This has reached such a level today that you see video compilations of 'leaders' of all parties whether Democrats, Republicans, Conservative, Labour and Green parroting the same Cult mantra of 'Build Back Better' and the 'Great Reset' which are straight off the Cult song-sheet to describe the transformation of global society in response to the Cult-instigated hoaxes of the 'Covid pandemic' and human-caused 'climate change'. To see Caroline Lucas, the Green Party MP that I knew when I was in the party in the 1980s, speaking in support of plans proposed by Cult operative Klaus Schwab representing the billionaire global elite is a real head-shaker.

Many parties – one master

The party system is another mind-trick and was instigated to change the nature of the dictatorship by swapping 'royalty' for dark suits that people believed – though now ever less so – represented their interests. Understanding this trick is to realise that a single force (the Cult) controls all parties either directly in terms of the major ones or through manipulation of perception and ideology with others. You don't need to manipulate Green parties to demand your transformation of society in the name of 'climate change' when they are obsessed with the lie that this is essential to 'save the planet'. You just give them a platform and away they go serving your interests while believing they are being environmentally virtuous. America's political structure is a perfect blueprint for how the two or multi-party system is really a one-party state. The Republican Party is controlled from one step back in the shadows by a group made up of billionaires and their gofers known as neoconservatives or Neocons.

I have exposed them in fine detail in my books and they were the driving force behind the policies of the imbecilic presidency of Boy George Bush which included 9/11 (see *The Trigger* for a comprehensive demolition of the official story), the subsequent 'war on terror' (war *of* terror) and the invasions of Afghanistan and Iraq. The latter was a No-Problem-Reaction-Solution based on claims by Cult operatives, including Bush and British Prime Minister Tony Blair, about Saddam Hussein's 'weapons of mass destruction' which did not exist as war criminals Bush and Blair well knew.

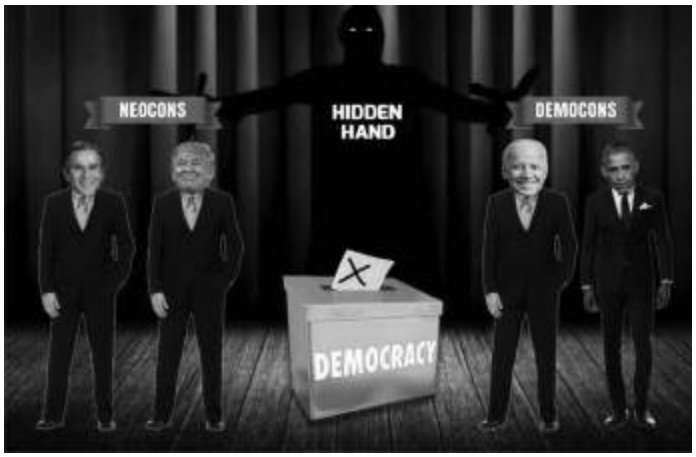


Figure 6: Different front people, different parties – same control system.

The Democratic Party has its own 'Neocon' group controlling from the background which I call the 'Democons' and here's the penny-drop – the Neocons and Democons answer to the same masters one step further back into the shadows (Fig 6). At that level of the Cult the Republican and Democrat parties are controlled by the same people and no matter which is in power the Cult is in power. This is how it works in almost every country and certainly in Britain with Conservative, Labour, Liberal Democrat and Green parties now all on the same page whatever the rhetoric may be in their feeble attempts to appear different. Neocons operated at the time of Bush through a think tank called The Project for the New American Century which in September, 2000, published a document entitled *Rebuilding America's Defenses: Strategies, Forces, and Resources*

For a New Century demanding that America fight 'multiple, simultaneous major theatre wars' as a 'core mission' to force regime-change in countries including Iraq, Libya and Syria. Neocons arranged for Bush ('Republican') and Blair ('Labour Party') to front-up the invasion of Iraq and when they departed the Democons orchestrated the targeting of Libya and Syria through Barack Obama ('Democrat') and British Prime Minister David Cameron ('Conservative Party'). We have 'different' parties and 'different' people, but the same unfolding script. The more the Cult has seized the reigns of parties and personnel the more their policies have transparently pursued the same agenda to the point where the fascist 'Covid' impositions of the Conservative junta of Jackboot Johnson in Britain were opposed by the Labour Party because they were not fascist enough. The Labour Party is likened to the US Democrats while the Conservative Party is akin to a British version of the Republicans and on both sides of the Atlantic they all speak the same language and support the direction demanded by the Cult although some more enthusiastically than others. It's a similar story in country after country because it's all centrally controlled. Oh, but what about Trump? I'll come to him shortly. Political 'choice' in the 'party' system goes like this: You vote for Party A and they get into government. You don't like what they do so next time you vote for Party B and they get into government. You don't like what they do when it's pretty much the same as Party A and why wouldn't that be with both controlled by the same force? Given that only two, sometimes three, parties have any chance of forming a government to get rid of Party B that you don't like you have to vote again for Party A which … you don't like. This, ladies and gentlemen, is what they call 'democracy' which we are told – wrongly – is a term interchangeable with 'freedom'.

The cult of cults

At this point I need to introduce a major expression of the Global Cult known as Sabbatian-Frankism. Sabbatian is also spelt as Sabbatean. I will summarise here. I have published major exposés

and detailed background in other works. Sabbatian-Frankism combines the names of two frauds posing as 'Jewish' men, Sabbatai Zevi (1626-1676), a rabbi, black magician and occultist who proclaimed he was the Jewish messiah; and Jacob Frank (1726-1791), the Polish 'Jew', black magician and occultist who said he was the reincarnation of 'messiah' Zevi and biblical patriarch Jacob. They worked across two centuries to establish the Sabbatian-Frankist cult that plays a major, indeed central, role in the manipulation of human society by the Global Cult which has its origins much further back in history than Sabbatai Zevi. I should emphasise two points here in response to the shrill voices that will scream 'anti-Semitism': (1) Sabbatian-Frankists are NOT Jewish and only pose as such to hide their cult behind a Jewish façade; and (2) my information about this cult has come from Jewish sources who have long realised that their society and community has been infiltrated and taken over by interloper Sabbatian-Frankists. Infiltration has been the foundation technique of Sabbatian-Frankism from its official origin in the 17th century. Zevi's Sabbatian sect attracted a massive following described as the biggest messianic movement in Jewish history, spreading as far as Africa and Asia, and he promised a return for the Jews to the 'Promised Land' of Israel. Sabbatianism was not Judaism but an inversion of everything that mainstream Judaism stood for. So much so that this sinister cult would have a feast day when Judaism had a fast day and whatever was forbidden in Judaism the Sabbatians were encouraged and even commanded to do. This included incest and what would be today called Satanism. Members were forbidden to marry outside the sect and there was a system of keeping their children ignorant of what they were part of until they were old enough to be trusted not to unknowingly reveal anything to outsiders. The same system is employed to this day by the Global Cult in general which Sabbatian-Frankism has enormously influenced and now largely controls.

Zevi and his Sabbatians suffered a setback with the intervention by the Sultan of the Islamic Ottoman Empire in the Middle East and what is now the Republic of Turkey where Zevi was located. The

Sultan gave him the choice of proving his 'divinity', converting to Islam or facing torture and death. Funnily enough Zevi chose to convert or at least appear to. Some of his supporters were disillusioned and drifted away, but many did not with 300 families also converting – only in theory – to Islam. They continued behind this Islamic smokescreen to follow the goals, rules and rituals of Sabbatianism and became known as 'crypto-Jews' or the 'Dönmeh' which means 'to turn'. This is rather ironic because they didn't 'turn' and instead hid behind a fake Islamic persona. The process of appearing to be one thing while being very much another would become the calling card of Sabbatianism especially after Zevi's death and the arrival of the Satanist Jacob Frank in the 18th century when the cult became Sabbatian-Frankism and plumbed still new depths of depravity and infiltration which included – still includes – human sacrifice and sex with children. Wherever Sabbatians go paedophilia and Satanism follow and is it really a surprise that Hollywood is so infested with child abuse and Satanism when it was established by Sabbatian-Frankists and is still controlled by them? Hollywood has been one of the prime vehicles for global perceptual programming and manipulation. How many believe the version of 'history' portrayed in movies when it is a travesty and inversion (again) of the truth? Rabbi Marvin Antelman describes Frankism in his book, *To Eliminate the Opiate*, as 'a movement of complete evil' while Jewish professor Gershom Scholem said of Frank in *The Messianic Idea in Judaism*: 'In all his actions [he was] a truly corrupt and degenerate individual ... one of the most frightening phenomena in the whole of Jewish history.' Frank was excommunicated by traditional rabbis, as was Zevi, but Frank was undeterred and enjoyed vital support from the House of Rothschild, the infamous banking dynasty whose inner-core are Sabbatian-Frankists and not Jews. Infiltration of the Roman Church and Vatican was instigated by Frank with many Dönmeh 'turning' again to convert to Roman Catholicism with a view to hijacking the reins of power. This was the ever-repeating modus operandi and continues to be so. Pose as an advocate of the religion, culture or country that you want to control and then

manipulate your people into the positions of authority and influence largely as advisers, administrators and Svengalis for those that appear to be in power. They did this with Judaism, Christianity (Christian Zionism is part of this), Islam and other religions and nations until Sabbatian-Frankism spanned the world as it does today.

Sabbatian Saudis and the terror network

One expression of the Sabbatian-Frankist Dönmeh within Islam is the ruling family of Saudi Arabia, the House of Saud, through which came the vile distortion of Islam known as Wahhabism. This is the violent creed followed by terrorist groups like Al-Qaeda and ISIS or Islamic State. Wahhabism is the hand-chopping, head-chopping 'religion' of Saudi Arabia which is used to keep the people in a constant state of fear so the interloper House of Saud can continue to rule. Al-Qaeda and Islamic State were lavishly funded by the House of Saud while being created and directed by the Sabbatian-Frankist network in the United States that operates through the Pentagon, CIA and the government in general of whichever 'party'. The front man for the establishment of Wahhabism in the middle of the 18th century was a Sabbatian-Frankist 'crypto-Jew' posing as Islamic called Muhammad ibn Abd al-Wahhab. His daughter would marry the son of Muhammad bin Saud who established the first Saudi state before his death in 1765 with support from the British Empire. Bin Saud's successors would establish modern Saudi Arabia in league with the British and Americans in 1932 which allowed them to seize control of Islam's major shrines in Mecca and Medina. They have dictated the direction of Sunni Islam ever since while Iran is the major centre of the Shiite version and here we have the source of at least the public conflict between them. The Sabbatian network has used its Wahhabi extremists to carry out Problem-Reaction-Solution terrorist attacks in the name of 'Al-Qaeda' and 'Islamic State' to justify a devastating 'war on terror', ever-increasing surveillance of the population and to terrify people into compliance. Another insight of the Renegade Mind is the streetwise understanding that

just because a country, location or people are attacked doesn't mean that those apparently representing that country, location or people are not behind the attackers. Often they are *orchestrating* the attacks because of the societal changes that can be then justified in the name of 'saving the population from terrorists'.

I show in great detail in *The Trigger* how Sabbatian-Frankists were the real perpetrators of 9/11 and not '19 Arab hijackers' who were blamed for what happened. Observe what was justified in the name of 9/11 alone in terms of Middle East invasions, mass surveillance and control that fulfilled the demands of the Project for the New American Century document published by the Sabbatian Neocons. What appear to be enemies are on the deep inside players on the same Sabbatian team. Israel and Arab 'royal' dictatorships are all ruled by Sabbatians and the recent peace agreements between Israel and Saudi Arabia, the United Arab Emirates (UAE) and others are only making formal what has always been the case behind the scenes. Palestinians who have been subjected to grotesque tyranny since Israel was bombed and terrorised into existence in 1948 have never stood a chance. Sabbatian-Frankists have controlled Israel (so the constant theme of violence and war which Sabbatians love) and they have controlled the Arab countries that Palestinians have looked to for real support that never comes. 'Royal families' of the Arab world in Saudi Arabia, Bahrain, UAE, etc., are all Sabbatians with allegiance to the aims of the cult and not what is best for their Arabic populations. They have stolen the oil and financial resources from their people by false claims to be 'royal dynasties' with a genetic right to rule and by employing vicious militaries to impose their will.

Satanic 'illumination'

The Satanist Jacob Frank formed an alliance in 1773 with two other Sabbatians, Mayer Amschel Rothschild (1744-1812), founder of the Rothschild banking dynasty, and Jesuit-educated fraudulent Jew, Adam Weishaupt, and this led to the formation of the Bavarian Illuminati, firstly under another name, in 1776. The Illuminati would

be the manipulating force behind the French Revolution (1789-1799) and was also involved in the American Revolution (1775-1783) before and after the Illuminati's official creation. Weishaupt would later become (in public) a Protestant Christian in archetypal Sabbatian style. I read that his name can be decoded as Adam-Weishaupt or 'the first man to lead those who know'. He wasn't a leader in the sense that he was a subordinate, but he did lead those below him in a crusade of transforming human society that still continues today. The theme was confirmed as early as 1785 when a horseman courier called Lanz was reported to be struck by lighting and extensive Illuminati documents were found in his saddlebags. They made the link to Weishaupt and detailed the plan for world takeover. Current events with 'Covid' fascism have been in the making for a very long time. Jacob Frank was jailed for 13 years by the Catholic Inquisition after his arrest in 1760 and on his release he headed for Frankfurt, Germany, home city and headquarters of the House of Rothschild where the alliance was struck with Mayer Amschel Rothschild and Weishaupt. Rothschild arranged for Frank to be given the title of Baron and he became a wealthy nobleman with a big following of Jews in Germany, the Austro-Hungarian Empire and other European countries. Most of them would have believed he was on their side.

The name 'Illuminati' came from the Zohar which is a body of works in the Jewish mystical 'bible' called the Kabbalah. 'Zohar' is the foundation of Sabbatian-Frankist belief and in Hebrew 'Zohar' means 'splendour', 'radiance', 'illuminated', and so we have 'Illuminati'. They claim to be the 'Illuminated Ones' from their knowledge systematically hidden from the human population and passed on through generations of carefully-chosen initiates in the global secret society network or Cult. Hidden knowledge includes an awareness of the Cult agenda for the world and the nature of our collective reality that I will explore later. Cult 'illumination' is symbolised by the torch held by the Statue of Liberty which was gifted to New York by French Freemasons in Paris who knew exactly what it represents. 'Liberty' symbolises the goddess worshipped in

Babylon as Queen Semiramis or Ishtar. The significance of this will become clear. Notice again the ubiquitous theme of inversion with the Statue of 'Liberty' really symbolising mass control (Fig 7). A mirror-image statute stands on an island in the River Seine in Paris from where New York Liberty originated (Fig 8). A large replica of the Liberty flame stands on top of the Pont de l'Alma tunnel in Paris where Princess Diana died in a Cult ritual described in *The Biggest Secret*. Lucifer 'the light bringer' is related to all this (and much more as we'll see) and 'Lucifer' is a central figure in Sabbatian-Frankism and its associated Satanism. Sabbatians reject the Jewish Torah, or Pentateuch, the 'five books of Moses' in the Old Testament known as Genesis, Exodus, Leviticus, Numbers, and Deuteronomy which are claimed by Judaism and Christianity to have been dictated by 'God' to Moses on Mount Sinai. Sabbatians say these do not apply to them and they seek to replace them with the Zohar to absorb Judaism and its followers into their inversion which is an expression of a much greater global inversion. They want to delete all religions and force humanity to worship a one-world religion – Sabbatian Satanism that also includes worship of the Earth goddess. Satanic themes are being more and more introduced into mainstream society and while Christianity is currently the foremost target for destruction the others are planned to follow.



Figure 7: The Cult goddess of Babylon disguised as the Statue of Liberty holding the flame of Lucifer the 'light bringer'.



Figure 8: Liberty's mirror image in Paris where the New York version originated.

Marx brothers

Rabbi Marvin Antelman connects the Illuminati to the Jacobins in *To Eliminate the Opiate* and Jacobins were the force behind the French Revolution. He links both to the Bund der Gerechten, or League of the Just, which was the network that inflicted communism/Marxism on the world. Antelman wrote:

> The original inner circle of the Bund der Gerechten consisted of born Catholics, Protestants and Jews [Sabbatian-Frankist infiltrators], and those representatives of respective subdivisions formulated schemes for the ultimate destruction of their faiths. The heretical Catholics laid plans which they felt would take a century or more for the ultimate destruction of the church; the apostate Jews for the ultimate destruction of the Jewish religion.

Sabbatian-created communism connects into this anti-religion agenda in that communism does not allow for the free practice of religion. The Sabbatian 'Bund' became the International Communist Party and Communist League and in 1848 'Marxism' was born with the Communist Manifesto of Sabbatian assets Karl Marx and Friedrich Engels. It is absolutely no coincidence that Marxism, just a different name for fascist and other centrally-controlled tyrannies, is being imposed worldwide as a result of the 'Covid' hoax and nor that Marxist/fascist China was the place where the hoax originated. The reason for this will become very clear in the chapter 'Covid: The calculated catastrophe'. The so-called 'Woke' mentality has hijacked

traditional beliefs of the political left and replaced them with far-right make-believe 'social justice' better known as Marxism. Woke will, however, be swallowed by its own perceived 'revolution' which is really the work of billionaires and billionaire corporations feigning being 'Woke'. Marxism is being touted by Wokers as a replacement for 'capitalism' when we don't have 'capitalism'. We have cartelism in which the market is stitched up by the very Cult billionaires and corporations bankrolling Woke. Billionaires love Marxism which keeps the people in servitude while they control from the top. Terminally naïve Wokers think they are 'changing the world' when it's the Cult that is doing the changing and when they have played their vital part and become surplus to requirements they, too, will be targeted. The Illuminati-Jacobins were behind the period known as 'The Terror' in the French Revolution in 1793 and 1794 when Jacobin Maximillian de Robespierre and his Orwellian 'Committee of Public Safety' killed 17,000 'enemies of the Revolution' who had once been 'friends of the Revolution'. Karl Marx (1818-1883), whose Sabbatian creed of Marxism has cost the lives of at least 100 million people, is a hero once again to Wokers who have been systematically kept ignorant of real history by their 'education' programming. As a result they now promote a Sabbatian 'Marxist' abomination destined at some point to consume them. Rabbi Antelman, who spent decades researching the Sabbatian plot, said of the League of the Just and Karl Marx:

> Contrary to popular opinion Karl Marx did not originate the Communist Manifesto. He was paid for his services by the League of the Just, which was known in its country of origin, Germany, as the Bund der Geaechteten.

Antelman said the text attributed to Marx was the work of other people and Marx 'was only repeating what others already said'. Marx was 'a hired hack – lackey of the wealthy Illuminists'. Marx famously said that religion was the 'opium of the people' (part of the Sabbatian plan to demonise religion) and Antelman called his books, *To Eliminate the Opiate*. Marx was born Jewish, but his family converted to Christianity (Sabbatian modus operandi) and he

attacked Jews, not least in his book, *A World Without Jews*. In doing so he supported the Sabbatian plan to destroy traditional Jewishness and Judaism which we are clearly seeing today with the vindictive targeting of orthodox Jews by the Sabbatian government of Israel over 'Covid' laws. I don't follow any religion and it has done much damage to the world over centuries and acted as a perceptual straightjacket. Renegade Minds, however, are always asking *why* something is being done. It doesn't matter if they agree or disagree with what is happening – *why* is it happening is the question. The 'why?' can be answered with regard to religion in that religions create interacting communities of believers when the Cult wants to dismantle all discourse, unity and interaction (see 'Covid' lockdowns) and the ultimate goal is to delete all religions for a one-world religion of Cult Satanism worshipping their 'god' of which more later. We see the same 'why?' with gun control in America. I don't have guns and don't want them, but why is the Cult seeking to disarm the population at the same time that law enforcement agencies are armed to their molars and why has every tyrant in history sought to disarm people before launching the final takeover? They include Hitler, Stalin, Pol Pot and Mao who followed confiscation with violent seizing of power. You know it's a Cult agenda by the people who immediately race to the microphones to exploit dead people in multiple shootings. Ultra-Zionist Cult lackey Senator Chuck Schumer was straight on the case after ten people were killed in Boulder, Colorado in March, 2121. Simple rule … if Schumer wants it the Cult wants it and the same with his ultra-Zionist mate the wild-eyed Senator Adam Schiff. At the same time they were calling for the disarmament of Americans, many of whom live a long way from a police response, Schumer, Schiff and the rest of these pampered clowns were sitting on Capitol Hill behind a razor-wired security fence protected by thousands of armed troops in addition to their own armed bodyguards. Mom and pop in an isolated home? They're just potential mass shooters.

Zion Mainframe

Sabbatian-Frankists and most importantly the Rothschilds were behind the creation of 'Zionism', a political movement that demanded a Jewish homeland in Israel as promised by Sabbatai Zevi. The very symbol of Israel comes from the German meaning of the name Rothschild. Dynasty founder Mayer Amschel Rothschild changed the family name from Bauer to Rothschild, or 'Red-Shield' in German, in deference to the six-pointed 'Star of David' hexagram displayed on the family's home in Frankfurt. The symbol later appeared on the flag of Israel after the Rothschilds were centrally involved in its creation. Hexagrams are not a uniquely Jewish symbol and are widely used in occult ('hidden') networks often as a symbol for Saturn (see my other books for why). Neither are Zionism and Jewishness interchangeable. Zionism is a political movement and philosophy and not a 'race' or a people. Many Jews oppose Zionism and many non-Jews, including US President Joe Biden, call themselves Zionists as does Israel-centric Donald Trump. America's support for the Israel government is pretty much a gimme with ultra-Zionist billionaires and corporations providing fantastic and dominant funding for both political parties. Former Congresswoman Cynthia McKinney has told how she was approached immediately she ran for office to 'sign the pledge' to Israel and confirm that she would always vote in that country's best interests. All American politicians are approached in this way. Anyone who refuses will get no support or funding from the enormous and all-powerful Zionist lobby that includes organisations like mega-lobby group AIPAC, the American Israel Public Affairs Committee. Trump's biggest funder was ultra-Zionist casino and media billionaire Sheldon Adelson while major funders of the Democratic Party include ultra-Zionist George Soros and ultra-Zionist financial and media mogul, Haim Saban. Some may reel back at the suggestion that Soros is an Israel-firster (Sabbatian-controlled Israel-firster), but Renegade Minds watch the actions not the words and everywhere Soros donates his billions the Sabbatian agenda benefits. In the spirit of Sabbatian inversion Soros pledged $1 billion for a new university network to promote 'liberal values and tackle intolerance'. He made the announcement during his annual speech

at the Cult-owned World Economic Forum in Davos, Switzerland, in January, 2020, after his 'harsh criticism' of 'authoritarian rulers' around the world. You can only laugh at such brazen mendacity. How *he* doesn't laugh is the mystery. Translated from the Orwellian 'liberal values and tackle intolerance' means teaching non-white people to hate white people and for white people to loathe themselves for being born white. The reason for that will become clear.

The 'Anti-Semitism' fraud

Zionists support the Jewish homeland in the land of Palestine which has been the Sabbatian-Rothschild goal for so long, but not for the benefit of Jews. Sabbatians and their global Anti-Semitism Industry have skewed public and political opinion to equate opposing the violent extremes of Zionism to be a blanket attack and condemnation of all Jewish people. Sabbatians and their global Anti-Semitism Industry have skewed public and political opinion to equate opposing the violent extremes of Zionism to be a blanket attack and condemnation of all Jewish people. This is nothing more than a Sabbatian protection racket to stop legitimate investigation and exposure of their agendas and activities. The official definition of 'anti-Semitism' has more recently been expanded to include criticism of Zionism – a *political movement* – and this was done to further stop exposure of Sabbatian infiltrators who created Zionism as we know it today in the 19th century. Renegade Minds will talk about these subjects when they know the shit that will come their way. People must decide if they want to know the truth or just cower in the corner in fear of what others will say. Sabbatians have been trying to label me as 'anti-Semitic' since the 1990s as I have uncovered more and more about their background and agendas. Useless, gutless, fraudulent 'journalists' then just repeat the smears without question and on the day I was writing this section a pair of unquestioning repeaters called Ben Quinn and Archie Bland (how appropriate) outright called me an 'anti-Semite' in the establishment propaganda sheet, the London *Guardian*, with no supporting evidence. The

Sabbatian Anti-Semitism Industry said so and who are they to question that? They wouldn't dare. Ironically 'Semitic' refers to a group of languages in the Middle East that are almost entirely Arabic. 'Anti-Semitism' becomes 'anti-Arab' which if the consequences of this misunderstanding were not so grave would be hilarious. Don't bother telling Quinn and Bland. I don't want to confuse them, bless 'em. One reason I am dubbed 'anti-Semitic' is that I wrote in the 1990s that Jewish operatives (Sabbatians) were heavily involved in the Russian Revolution when Sabbatians overthrew the Romanov dynasty. This apparently made me 'anti-Semitic'. Oh, really? Here is a section from *The Trigger*:

British journalist Robert Wilton confirmed these themes in his 1920 book *The Last Days of the Romanovs* when he studied official documents from the Russian government to identify the members of the Bolshevik ruling elite between 1917 and 1919. The Central Committee included 41 Jews among 62 members; the Council of the People's Commissars had 17 Jews out of 22 members; and 458 of the 556 most important Bolshevik positions between 1918 and 1919 were occupied by Jewish people. Only 17 were Russian. Then there were the 23 Jews among the 36 members of the vicious Cheka Soviet secret police established in 1917 who would soon appear all across the country.

Professor Robert Service of Oxford University, an expert on 20th century Russian history, found evidence that ['Jewish'] Leon Trotsky had sought to make sure that Jews were enrolled in the Red Army and were disproportionately represented in the Soviet civil bureaucracy that included the Cheka which performed mass arrests, imprisonment and executions of 'enemies of the people'. A US State Department Decimal File (861.00/5339) dated November 13th, 1918, names [Rothschild banking agent in America] Jacob Schiff and a list of ultra-Zionists as funders of the Russian Revolution leading to claims of a 'Jewish plot', but the key point missed by all is they were not 'Jews' – they were Sabbatian-Frankists.

Britain's Winston Churchill made the same error by mistake or otherwise. He wrote in a 1920 edition of the *Illustrated Sunday Herald* that those behind the Russian revolution were part of a 'worldwide conspiracy for the overthrow of civilisation and for the reconstitution of society on the basis of arrested development, of envious malevolence, and impossible equality' (see 'Woke' today because that has been created by the same network). Churchill said there was no need to exaggerate the part played in the creation of Bolshevism and in the actual bringing about of the Russian

Revolution 'by these international and for the most part atheistical Jews' ['atheistical Jews' = Sabbatians]. Churchill said it is certainly a very great one and probably outweighs all others: 'With the notable exception of Lenin, the majority of the leading figures are Jews.' He went on to describe, knowingly or not, the Sabbatian modus operandi of placing puppet leaders nominally in power while they control from the background:

> Moreover, the principal inspiration and driving power comes from the Jewish leaders. Thus Tchitcherin, a pure Russian, is eclipsed by his nominal subordinate, Litvinoff, and the influence of Russians like Bukharin or Lunacharski cannot be compared with the power of Trotsky, or of Zinovieff, the Dictator of the Red Citadel (Petrograd), or of Krassin or Radek – all Jews. In the Soviet institutions the predominance of Jews is even more astonishing. And the prominent, if not indeed the principal, part in the system of terrorism applied by the Extraordinary Commissions for Combatting Counter-Revolution has been taken by Jews, and in some notable cases by Jewesses.

What I said about seriously disproportionate involvement in the Russian Revolution by Jewish 'revolutionaries' (Sabbatians) is provable fact, but truth is no defence against the Sabbatian Anti-Semitism Industry, its repeater parrots like Quinn and Bland, and the now breathtaking network of so-called 'Woke' 'anti-hate' groups with interlocking leaderships and funding which have the role of discrediting and silencing anyone who gets too close to exposing the Sabbatians. We have seen 'truth is no defence' confirmed in legal judgements with the Saskatchewan Human Rights Commission in Canada decreeing this: 'Truthful statements can be presented in a manner that would meet the definition of hate speech, and not all truthful statements must be free from restriction.' Most 'anti-hate' activists, who are themselves consumed by hatred, are too stupid and ignorant of the world to know how they are being used. They are far too far up their own virtue-signalling arses and it's far too dark for them to see anything.

The 'revolution' game

The background and methods of the 'Russian' Revolution are straight from the Sabbatian playbook seen in the French Revolution

and endless others around the world that appear to start as a revolution of the people against tyrannical rule and end up with a regime change to more tyrannical rule overtly or covertly. Wars, terror attacks and regime overthrows follow the Sabbatian cult through history with its agents creating them as Problem-Reaction-Solutions to remove opposition on the road to world domination. Sabbatian dots connect the Rothschilds with the Illuminati, Jacobins of the French Revolution, the 'Bund' or League of the Just, the International Communist Party, Communist League and the Communist Manifesto of Karl Marx and Friedrich Engels that would lead to the Rothschild-funded Russian Revolution. The sequence comes under the heading of 'creative destruction' when you advance to your global goal by continually destroying the status quo to install a new status quo which you then also destroy. The two world wars come to mind. With each new status quo you move closer to your planned outcome. Wars and mass murder are to Sabbatians a collective blood sacrifice ritual. They are obsessed with death for many reasons and one is that death is an inversion of life. Satanists and Sabbatians are obsessed with death and often target churches and churchyards for their rituals. Inversion-obsessed Sabbatians explain the use of inverted symbolism including the *inverted* pentagram and *inverted* cross. The inversion of the cross has been related to targeting Christianity, but the cross was a religious symbol long before Christianity and its inversion is a statement about the Sabbatian mentality and goals more than any single religion.

Sabbatians operating in Germany were behind the rise of the occult-obsessed Nazis and the subsequent Jewish exodus from Germany and Europe to Palestine and the United States after World War Two. The Rothschild dynasty was at the forefront of this both as political manipulators and by funding the operation. Why would Sabbatians help to orchestrate the horrors inflicted on Jews by the Nazis and by Stalin after they organised the Russian Revolution? Sabbatians hate Jews and their religion, that's why. They pose as Jews and secure positions of control within Jewish society and play the 'anti-Semitism' card to protect themselves from exposure

through a global network of organisations answering to the Sabbatian-created-and-controlled globe-spanning intelligence network that involves a stunning web of military-intelligence operatives and operations for a tiny country of just nine million. Among them are Jewish assets who are not Sabbatians but have been convinced by them that what they are doing is for the good of Israel and the Jewish community to protect them from what they have been programmed since childhood to believe is a Jew-hating hostile world. The Jewish community is just a highly convenient cover to hide the true nature of Sabbatians. Anyone getting close to exposing their game is accused by Sabbatian place-people and gofers of 'anti-Semitism' and claiming that all Jews are part of a plot to take over the world. I am not saying that. I am saying that Sabbatians – the *real* Jew-haters – have infiltrated the Jewish community to use them both as a cover and an 'anti-Semitic' defence against exposure. Thus we have the Anti-Semitism Industry targeted researchers in this way and most Jewish people think this is justified and genuine. They don't know that their 'Jewish' leaders and institutions of state, intelligence and military are not controlled by Jews at all, but cultists and stooges of Sabbatian-Frankism. I once added my name to a pro-Jewish freedom petition online and the next time I looked my name was gone and text had been added to the petition blurb to attack me as an 'anti-Semite' such is the scale of perceptual programming.

Moving on America

I tell the story in *The Trigger* and a chapter called 'Atlantic Crossing' how particularly after Israel was established the Sabbatians moved in on the United States and eventually grasped control of government administration, the political system via both Democrats and Republicans, the intelligence community like the CIA and National Security Agency (NSA), the Pentagon and mass media. Through this seriously compartmentalised network Sabbatians and their operatives in Mossad, Israeli Defense Forces (IDF) and US agencies pulled off 9/11 and blamed it on 19 'Al-Qaeda hijackers' dominated by men from, or connected to, Sabbatian-ruled Saudi

Arabia. The '19' were not even on the planes let alone flew those big passenger jets into buildings while being largely incompetent at piloting one-engine light aircraft. 'Hijacker' Hani Hanjour who is said to have flown American Airlines Flight 77 into the Pentagon with a turn and manoeuvre most professional pilots said they would have struggled to do was banned from renting a small plane by instructors at the Freeway Airport in Bowie, Maryland, just *six weeks* earlier on the grounds that he was an incompetent pilot. The Jewish population of the world is just 0.2 percent with even that almost entirely concentrated in Israel (75 percent Jewish) and the United States (around two percent). This two percent and globally 0.2 percent refers to *Jewish* people and not Sabbatian interlopers who are a fraction of that fraction. What a sobering thought when you think of the fantastic influence on world affairs of tiny Israel and that the Project for the New America Century (PNAC) which laid out the blueprint in September, 2000, for America's war on terror and regime change wars in Iraq, Libya and Syria was founded and dominated by Sabbatians known as 'Neocons'. The document conceded that this plan would not be supported politically or publicly without a major attack on American soil and a Problem-Reaction-Solution excuse to send troops to war across the Middle East. Sabbatian Neocons said:

> ... [The] process of transformation ... [war and regime change] ... is likely to be a long one, absent some catastrophic and catalysing event – like a new Pearl Harbor.

Four months later many of those who produced that document came to power with their inane puppet George Bush from the long-time Sabbatian Bush family. They included Sabbatian Dick Cheney who was officially vice-president, but really de-facto president for the entirety of the 'Bush' government. Nine months after the 'Bush' inauguration came what Bush called at the time 'the Pearl Harbor of the 21st century' and with typical Sabbatian timing and symbolism 2001 was the 60th anniversary of the attack in 1941 by the Japanese Air Force on Pearl Harbor, Hawaii, which allowed President Franklin Delano Roosevelt to take the United States into a Sabbatian-

instigated Second World War that he said in his election campaign that he never would. The evidence is overwhelming that Roosevelt and his military and intelligence networks knew the attack was coming and did nothing to stop it, but they did make sure that America's most essential naval ships were not in Hawaii at the time. Three thousand Americans died in the Pearl Harbor attacks as they did on September 11th. By the 9/11 year of 2001 Sabbatians had widely infiltrated the US government, military and intelligence operations and used their compartmentalised assets to pull off the 'Al-Qaeda' attacks. If you read *The Trigger* it will blow your mind to see the utterly staggering concentration of 'Jewish' operatives (Sabbatian infiltrators) in essential positions of political, security, legal, law enforcement, financial and business power before, during, and after the attacks to make them happen, carry them out, and then cover their tracks – and I do mean *staggering* when you think of that 0.2 percent of the world population and two percent of Americans which are Jewish while Sabbatian infiltrators are a fraction of that. A central foundation of the 9/11 conspiracy was the hijacking of government, military, Air Force and intelligence computer systems in real time through 'back-door' access made possible by Israeli (Sabbatian) 'cyber security' software. Sabbatian-controlled Israel is on the way to rivalling Silicon Valley for domination of cyberspace and is becoming the dominant force in cyber-security which gives them access to entire computer systems and their passcodes across the world. Then add to this that Zionists head (officially) Silicon Valley giants like Google (Larry Page and Sergey Brin), Google-owned YouTube (Susan Wojcicki), Facebook (Mark Zuckerberg and Sheryl Sandberg), and Apple (Chairman Arthur D. Levinson), and that ultra-Zionist hedge fund billionaire Paul Singer has a $1 billion stake in Twitter which is only nominally headed by 'CEO' pothead Jack Dorsey. As cable news host Tucker Carlson said of Dorsey: 'There used to be debate in the medical community whether dropping a ton of acid had permanent effects and I think that debate has now ended.' Carlson made the comment after Dorsey told a hearing on Capitol Hill (if you cut through his bullshit) that he

believed in free speech so long as he got to decide what you can hear and see. These 'big names' of Silicon Valley are only front men and women for the Global Cult, not least the Sabbatians, who are the true controllers of these corporations. Does anyone still wonder why these same people and companies have been ferociously censoring and banning people (like me) for exposing any aspect of the Cult agenda and especially the truth about the 'Covid' hoax which Sabbatians have orchestrated?

The Jeffrey Epstein paedophile ring was a Sabbatian operation. He was officially 'Jewish' but he was a Sabbatian and women abused by the ring have told me about the high number of 'Jewish' people involved. The Epstein horror has Sabbatian written all over it and matches perfectly their modus operandi and obsession with sex and ritual. Epstein was running a Sabbatian blackmail ring in which famous people with political and other influence were provided with young girls for sex while everything was being filmed and recorded on hidden cameras and microphones at his New York house, Caribbean island and other properties. Epstein survivors have described this surveillance system to me and some have gone public. Once the famous politician or other figure knew he or she was on video they tended to do whatever they were told. Here we go again …when you've got them by the balls their hearts and minds will follow. Sabbatians use this blackmail technique on a wide scale across the world to entrap politicians and others they need to act as demanded. Epstein's private plane, the infamous 'Lolita Express', had many well-known passengers including Bill Clinton while Bill Gates has flown on an Epstein plane and met with him four years after Epstein had been jailed for paedophilia. They subsequently met many times at Epstein's home in New York according to a witness who was there. Epstein's infamous side-kick was Ghislaine Maxwell, daughter of Mossad agent and ultra-Zionist mega-crooked British businessman, Bob Maxwell, who at one time owned the *Daily Mirror* newspaper. Maxwell was murdered at sea on his boat in 1991 by Sabbatian-controlled Mossad when he became a liability with his

business empire collapsing as a former Mossad operative has confirmed (see *The Trigger*).

Money, money, money, funny money …

Before I come to the Sabbatian connection with the last three US presidents I will lay out the crucial importance to Sabbatians of controlling banking and finance. Sabbatian Mayer Amschel Rothschild set out to dominate this arena in his family's quest for total global control. What is freedom? It is, in effect, choice. The more choices you have the freer you are and the fewer your choices the more you are enslaved. In the global structure created over centuries by Sabbatians the biggest decider and restrictor of choice is … money. Across the world if you ask people what they would like to do with their lives and why they are not doing that they will reply 'I don't have the money'. This is the idea. A global elite of multi-billionaires are described as 'greedy' and that is true on one level; but control of money – who has it and who doesn't – is not primarily about greed. It's about control. Sabbatians have seized ever more control of finance and sucked the wealth of the world out of the hands of the population. We talk now, after all, about the 'One-percent' and even then the wealthiest are a lot fewer even than that. This has been made possible by a money scam so outrageous and so vast it could rightly be called the scam of scams founded on creating 'money' out of nothing and 'loaning' that with interest to the population. Money out of nothing is called 'credit'. Sabbatians have asserted control over governments and banking ever more completely through the centuries and secured financial laws that allow banks to lend hugely more than they have on deposit in a confidence trick known as fractional reserve lending. Imagine if you could lend money that doesn't exist and charge the recipient interest for doing so. You would end up in jail. Bankers by contrast end up in mansions, private jets, Malibu and Monaco.

Banks are only required to keep a fraction of their deposits and wealth in their vaults and they are allowed to lend 'money' they don't have called 'credit. Go into a bank for a loan and if you succeed

the banker will not move any real wealth into your account. They will type into your account the amount of the agreed 'loan' – say £100,000. This is not wealth that really exists; it is non-existent, fresh-air, created-out-of-nothing 'credit' which has never, does not, and will never exist except in theory. Credit is backed by nothing except wind and only has buying power because people think that it has buying power and accept it in return for property, goods and services. I have described this situation as like those cartoon characters you see chasing each other and when they run over the edge of a cliff they keep running forward on fresh air until one of them looks down, realises what's happened, and they all crash into the ravine. The whole foundation of the Sabbatian financial system is to stop people looking down except for periodic moments when they want to crash the system (as in 2008 and 2020 ongoing) and reap the rewards from all the property, businesses and wealth their borrowers had signed over as 'collateral' in return for a 'loan' of fresh air. Most people think that money is somehow created by governments when it comes into existence from the start as a debt through banks 'lending' illusory money called credit. Yes, the very currency of exchange is a *debt* from day one issued as an interest-bearing loan. Why don't governments create money interest-free and lend it to their people interest-free? Governments are controlled by Sabbatians and the financial system is controlled by Sabbatians for whom interest-free money would be a nightmare come true. Sabbatians underpin their financial domination through their global network of central banks, including the privately-owned US Federal Reserve and Britain's Bank of England, and this is orchestrated by a privately-owned central bank coordination body called the Bank for International Settlements in Basle, Switzerland, created by the usual suspects including the Rockefellers and Rothschilds. Central bank chiefs don't answer to governments or the people. They answer to the Bank for International Settlements or, in other words, the Global Cult which is dominated today by Sabbatians.

Built-in disaster

There are so many constituent scams within the overall banking scam. When you take out a loan of thin-air credit only the amount of that loan is theoretically brought into circulation to add to the amount in circulation; but you are paying back the principle plus interest. The additional interest is not created and this means that with every 'loan' there is a shortfall in the money in circulation between what is borrowed and what has to be paid back. There is never even close to enough money in circulation to repay all outstanding public and private debt including interest. Coldly weaved in the very fabric of the system is the certainty that some will lose their homes, businesses and possessions to the banking 'lender'. This is less obvious in times of 'boom' when the amount of money in circulation (and the debt) is expanding through more people wanting and getting loans. When a downturn comes and the money supply contracts it becomes painfully obvious that there is not enough money to service all debt and interest. This is less obvious in times of 'boom' when the amount of money in circulation (and the debt) is expanding through more people wanting and getting loans. When a downturn comes and the money supply contracts and it becomes painfully obvious – as in 2008 and currently – that there is not enough money to service all debt and interest. Sabbatian banksters have been leading the human population through a calculated series of booms (more debt incurred) and busts (when the debt can't be repaid and the banks get the debtor's tangible wealth in exchange for non-existent 'credit'). With each 'bust' Sabbatian bankers have absorbed more of the world's tangible wealth and we end up with the One-percent. Governments are in bankruptcy levels of debt to the same system and are therefore owned by a system they do not control. The Federal Reserve, 'America's central bank', is privately-owned and American presidents only nominally appoint its chairman or woman to maintain the illusion that it's an arm of government. It's not. The 'Fed' is a cartel of private banks which handed billions to its associates and friends after the crash of 2008 and has been Sabbatian-controlled since it was manipulated into being in 1913 through the covert trickery of Rothschild banking agents Jacob Schiff and Paul

Warburg, and the Sabbatian Rockefeller family. Somehow from a Jewish population of two-percent and globally 0.2 percent (Sabbatian interlopers remember are far smaller) ultra-Zionists headed the Federal Reserve for 31 years between 1987 and 2018 in the form of Alan Greenspan, Bernard Bernanke and Janet Yellen (now Biden's Treasury Secretary) with Yellen's deputy chairman a Israeli-American duel citizen and ultra-Zionist Stanley Fischer, a former governor of the Bank of Israel. Ultra-Zionist Fed chiefs spanned the presidencies of Ronald Reagan ('Republican'), Father George Bush ('Republican'), Bill Clinton ('Democrat'), Boy George Bush ('Republican') and Barack Obama ('Democrat'). We should really add the pre-Greenspan chairman, Paul Adolph Volcker, 'appointed' by Jimmy Carter ('Democrat') who ran the Fed between 1979 and 1987 during the Carter and Reagan administrations before Greenspan took over. Volcker was a long-time associate and business partner of the Rothschilds. No matter what the 'party' officially in power the United States economy was directed by the same force. Here are members of the Obama, Trump and Biden administrations and see if you can make out a common theme.

Barack Obama ('Democrat')

Ultra-Zionists Robert Rubin, Larry Summers, and Timothy Geithner ran the US Treasury in the Clinton administration and two of them reappeared with Obama. Ultra-Zionist Fed chairman Alan Greenspan had manipulated the crash of 2008 through deregulation and jumped ship just before the disaster to make way for ultra-Zionist Bernard Bernanke to hand out trillions to Sabbatian 'too big to fail' banks and businesses, including the ubiquitous ultra-Zionist Goldman Sachs which has an ongoing staff revolving door operation between itself and major financial positions in government worldwide. Obama inherited the fallout of the crash when he took office in January, 2009, and fortunately he had the support of his ultra-Zionist White House Chief of Staff Rahm Emmanuel, son of a terrorist who helped to bomb Israel into being in 1948, and his ultra-Zionist senior adviser David Axelrod, chief strategist in Obama's two

successful presidential campaigns. Emmanuel, later mayor of Chicago and former senior fundraiser and strategist for Bill Clinton, is an example of the Sabbatian policy after Israel was established of migrating insider families to America so their children would be born American citizens. 'Obama' chose this financial team throughout his administration to respond to the Sabbatian-instigated crisis:

Timothy Geithner (ultra-Zionist) Treasury Secretary; Jacob J. Lew, Treasury Secretary; Larry Summers (ultra-Zionist), director of the White House National Economic Council; Paul Adolph Volcker (Rothschild business partner), chairman of the Economic Recovery Advisory Board; Peter Orszag (ultra-Zionist), director of the Office of Management and Budget overseeing all government spending; Penny Pritzker (ultra-Zionist), Commerce Secretary; Jared Bernstein (ultra-Zionist), chief economist and economic policy adviser to Vice President Joe Biden; Mary Schapiro (ultra-Zionist), chair of the Securities and Exchange Commission (SEC); Gary Gensler (ultra-Zionist), chairman of the Commodity Futures Trading Commission (CFTC); Sheila Bair (ultra-Zionist), chair of the Federal Deposit Insurance Corporation (FDIC); Karen Mills (ultra-Zionist), head of the Small Business Administration (SBA); Kenneth Feinberg (ultra-Zionist), Special Master for Executive [bail-out] Compensation. Feinberg would be appointed to oversee compensation (with strings) to 9/11 victims and families in a campaign to stop them having their day in court to question the official story. At the same time ultra-Zionist Bernard Bernanke was chairman of the Federal Reserve and these are only some of the ultra-Zionists with allegiance to Sabbatian-controlled Israel in the Obama government. Obama's biggest corporate donor was ultra-Zionist Goldman Sachs which had employed many in his administration.

Donald Trump ('Republican')

Trump claimed to be an outsider (he wasn't) who had come to 'drain the swamp'. He embarked on this goal by immediately appointing ultra-Zionist Steve Mnuchin, a Goldman Sachs employee for 17

years, as his Treasury Secretary. Others included Gary Cohn (ultra-Zionist), chief operating officer of Goldman Sachs, his first Director of the National Economic Council and chief economic adviser, who was later replaced by Larry Kudlow (ultra-Zionist). Trump's senior adviser throughout his four years in the White House was his sinister son-in-law Jared Kushner, a life-long friend of Israel Prime Minister Benjamin Netanyahu. Kushner is the son of a convicted crook who was pardoned by Trump in his last days in office. Other ultra-Zionists in the Trump administration included: Stephen Miller, Senior Policy Adviser; Avrahm Berkowitz, Deputy Adviser to Trump and his Senior Adviser Jared Kushner; Ivanka Trump, Adviser to the President, who converted to Judaism when she married Jared Kushner; David Friedman, Trump lawyer and Ambassador to Israel; Jason Greenblatt, Trump Organization executive vice president and chief legal officer, who was made Special Representative for International Negotiations and the Israeli-Palestinian Conflict; Rod Rosenstein, Deputy Attorney General; Elliot Abrams, Special Representative for Venezuela, then Iran; John Eisenberg, National Security Council Legal Adviser and Deputy Council to the President for National Security Affairs; Anne Neuberger, Deputy National Manager, National Security Agency; Ezra Cohen-Watnick, Acting Under Secretary of Defense for Intelligence; Elan Carr, Special Envoy to monitor and combat anti-Semitism; Len Khodorkovsky, Deputy Special Envoy to monitor and combat anti-Semitism; Reed Cordish, Assistant to the President, Intragovernmental and Technology Initiatives. Trump Vice President Mike Pence and Secretary of State Mike Pompeo, both Christian Zionists, were also vehement supporters of Israel and its goals and ambitions.

Donald 'free-speech believer' Trump pardoned a number of financial and violent criminals while ignoring calls to pardon Julian Assange and Edward Snowden whose crimes are revealing highly relevant information about government manipulation and corruption and the widespread illegal surveillance of the American people by US 'security' agencies. It's so good to know that Trump is on the side of freedom and justice and not mega-criminals with

allegiance to Sabbatian-controlled Israel. These included a pardon for Israeli spy Jonathan Pollard who was jailed for life in 1987 under the Espionage Act. Aviem Sella, the Mossad agent who recruited Pollard, was also pardoned by Trump while Assange sat in jail and Snowden remained in exile in Russia. Sella had 'fled' (was helped to escape) to Israel in 1987 and was never extradited despite being charged under the Espionage Act. A Trump White House statement said that Sella's clemency had been 'supported by Benjamin Netanyahu, Ron Dermer, Israel's US Ambassador, David Friedman, US Ambassador to Israel and Miriam Adelson, wife of leading Trump donor Sheldon Adelson who died shortly before. Other friends of Jared Kushner were pardoned along with Sholom Weiss who was believed to be serving the longest-ever white-collar prison sentence of more than 800 years in 2000. The sentence was commuted of Ponzi-schemer Eliyahu Weinstein who defrauded Jews and others out of $200 million. I did mention that Assange and Snowden were ignored, right? Trump gave Sabbatians almost everything they asked for in military and political support, moving the US Embassy from Tel Aviv to Jerusalem with its critical symbolic and literal implications for Palestinian statehood, and the 'deal of the Century' designed by Jared Kushner and David Friedman which gave the Sabbatian Israeli government the green light to substantially expand its already widespread program of building illegal Jewish-only settlements in the occupied land of the West Bank. This made a two-state 'solution' impossible by seizing all the land of a potential Palestinian homeland and that had been the plan since 1948 and then 1967 when the Arab-controlled Gaza Strip, West Bank, Sinai Peninsula and Syrian Golan Heights were occupied by Israel. All the talks about talks and road maps and delays have been buying time until the West Bank was physically occupied by Israeli real estate. Trump would have to be a monumentally ill-informed idiot not to see that this was the plan he was helping to complete. The Trump administration was in so many ways the Kushner administration which means the Netanyahu administration which means the Sabbatian administration. I understand why many opposing Cult fascism in all its forms gravitated to Trump, but he

was a crucial part of the Sabbatian plan and I will deal with this in the next chapter.

Joe Biden ('Democrat')

A barely cognitive Joe Biden took over the presidency in January, 2021, along with his fellow empty shell, Vice-President Kamala Harris, as the latest Sabbatian gofers to enter the White House. Names on the door may have changed and the 'party' – the force behind them remained the same as Zionists were appointed to a stream of pivotal areas relating to Sabbatian plans and policy. They included: Janet Yellen, Treasury Secretary, former head of the Federal Reserve, and still another ultra-Zionist running the US Treasury after Mnuchin (Trump), Lew and Geithner (Obama), and Summers and Rubin (Clinton); Anthony Blinken, Secretary of State; Wendy Sherman, Deputy Secretary of State (so that's 'Biden's' Sabbatian foreign policy sorted); Jeff Zients, White House coronavirus coordinator; Rochelle Walensky, head of the Centers for Disease Control; Rachel Levine, transgender deputy health secretary (that's 'Covid' hoax policy under control); Merrick Garland, Attorney General; Alejandro Mayorkas, Secretary of Homeland Security; Cass Sunstein, Homeland Security with responsibility for new immigration laws; Avril Haines, Director of National Intelligence; Anne Neuberger, National Security Agency cybersecurity director (note, cybersecurity); David Cohen, CIA Deputy Director; Ronald Klain, Biden's Chief of Staff (see Rahm Emanuel); Eric Lander, a 'leading geneticist', Office of Science and Technology Policy director (see Smart Grid, synthetic biology agenda); Jessica Rosenworcel, acting head of the Federal Communications Commission (FCC) which controls Smart Grid technology policy and electromagnetic communication systems including 5G. How can it be that so many pivotal positions are held by two-percent of the American population and 0.2 percent of the world population administration after administration no matter who is the president and what is the party? It's a coincidence? Of course it's not and this is why Sabbatians have built their colossal global web of interlocking 'anti-

hate' hate groups to condemn anyone who asks these glaring questions as an 'anti-Semite'. The way that Jewish people horrifically abused in Sabbatian-backed Nazi Germany are exploited to this end is stomach-turning and disgusting beyond words.

Political fusion

Sabbatian manipulation has reversed the roles of Republicans and Democrats and the same has happened in Britain with the Conservative and Labour Parties. Republicans and Conservatives were always labelled the 'right' and Democrats and Labour the 'left', but look at the policy positions now and the Democrat-Labour 'left' has moved further to the 'right' than Republicans and Conservatives under the banner of 'Woke', the Cult-created far-right tyranny. Where once the Democrat-Labour 'left' defended free speech and human rights they now seek to delete them and as I said earlier despite the 'Covid' fascism of the Jackboot Johnson Conservative government in the UK the Labour Party of leader Keir Starmer demanded even more extreme measures. The Labour Party has been very publicly absorbed by Sabbatians after a political and media onslaught against the previous leader, the weak and inept Jeremy Corbyn, over made-up allegations of 'anti-Semitism' both by him and his party. The plan was clear with this 'anti-Semite' propaganda and what was required in response was a swift and decisive 'fuck off' from Corbyn and a statement to expose the Anti-Semitism Industry (Sabbatian) attempt to silence Labour criticism of the Israeli government (Sabbatians) and purge the party of all dissent against the extremes of ultra-Zionism (Sabbatians). Instead Corbyn and his party fell to their knees and appeased the abusers which, by definition, is impossible. Appeasing one demand leads only to a new demand to be appeased until takeover is complete. Like I say – 'fuck off' would have been a much more effective policy and I have used it myself with great effect over the years when Sabbatians are on my case which is most of the time. I consider that fact a great compliment, by the way. The outcome of the Labour Party capitulation is that we now have a Sabbatian-controlled

Conservative Party 'opposed' by a Sabbatian-controlled Labour Party in a one-party Sabbatian state that hurtles towards the extremes of tyranny (the Sabbatian cult agenda). In America the situation is the same. Labour's Keir Starmer spends his days on his knees with his tongue out pointing to Tel Aviv, or I guess now Jerusalem, while Boris Johnson has an 'anti-Semitism czar' in the form of former Labour MP John Mann who keeps Starmer company on his prayer mat.

Sabbatian influence can be seen in Jewish members of the Labour Party who have been ejected for criticism of Israel including those from families that suffered in Nazi Germany. Sabbatians despise real Jewish people and target them even more harshly because it is so much more difficult to dub them 'anti-Semitic' although in their desperation they do try.

CHAPTER THREE

The Pushbacker sting

Until you realize how easy it is for your mind to be manipulated, you remain the puppet of someone else's game
Evita Ochel

I will use the presidencies of Trump and Biden to show how the manipulation of the one-party state plays out behind the illusion of political choice across the world. No two presidencies could – on the face of it – be more different and apparently at odds in terms of direction and policy.

A Renegade Mind sees beyond the obvious and focuses on outcomes and consequences and not image, words and waffle. The Cult embarked on a campaign to divide America between those who blindly support its agenda (the mentality known as 'Woke') and those who are pushing back on where the Cult and its Sabbatians want to go. This presents infinite possibilities for dividing and ruling the population by setting them at war with each other and allows a perceptual ring fence of demonisation to encircle the Pushbackers in a modern version of the Little Big Horn in 1876 when American cavalry led by Lieutenant Colonel George Custer were drawn into a trap, surrounded and killed by Native American tribes defending their land of thousands of years from being seized by the government. In this modern version the roles are reversed and it's those defending themselves from the Sabbatian government who are surrounded and the government that's seeking to destroy them. This trap was set years ago and to explain how we must return to 2016

and the emergence of Donald Trump as a candidate to be President of the United States. He set out to overcome the best part of 20 other candidates in the Republican Party before and during the primaries and was not considered by many in those early stages to have a prayer of living in the White House. The Republican Party was said to have great reservations about Trump and yet somehow he won the nomination. When you know how American politics works – politics in general – there is no way that Trump could have become the party's candidate unless the Sabbatian-controlled 'Neocons' that run the Republican Party wanted that to happen. We saw the proof in emails and documents made public by WikiLeaks that the Democratic Party hierarchy, or Democons, systematically undermined the campaign of Bernie Sanders to make sure that Sabbatian gofer Hillary Clinton won the nomination to be their presidential candidate. If the Democons could do that then the Neocons in the Republican Party could have derailed Trump in the same way. But they didn't and at that stage I began to conclude that Trump could well be the one chosen to be president. If that was the case the 'why' was pretty clear to see – the goal of dividing America between Cult agenda-supporting Wokers and Pushbackers who gravitated to Trump because he was telling them what they wanted to hear. His constituency of support had been increasingly ignored and voiceless for decades and profoundly through the eight years of Sabbatian puppet Barack Obama. Now here was someone speaking their language of pulling back from the incessant globalisation of political and economic power, the exporting of American jobs to China and elsewhere by 'American' (Sabbatian) corporations, the deletion of free speech, and the mass immigration policies that had further devastated job opportunities for the urban working class of all races and the once American heartlands of the Midwest.

Beware the forked tongue

Those people collectively sighed with relief that at last a political leader was apparently on their side, but another trait of the Renegade Mind is that you look even harder at people telling you

what you want to hear than those who are telling you otherwise. Obviously as I said earlier people wish what they want to hear to be true and genuine and they are much more likely to believe that than someone saying what they don't want to here and don't want to be true. Sales people are taught to be skilled in eliciting by calculated questioning what their customers want to hear and repeating that back to them as their own opinion to get their targets to like and trust them. Assets of the Cult are also sales people in the sense of selling perception. To read Cult manipulation you have to play the long and expanded game and not fall for the Vaudeville show of party politics. Both American parties are vehicles for the Cult and they exploit them in different ways depending on what the agenda requires at that moment. Trump and the Republicans were used to be the focus of dividing America and isolating Pushbackers to open the way for a Biden presidency to become the most extreme in American history by advancing the full-blown Woke (Cult) agenda with the aim of destroying and silencing Pushbackers now labelled Nazi Trump supporters and white supremacists.

Sabbatians wanted Trump in office for the reasons described by ultra-Zionist Saul Alinsky (1909-1972) who was promoting the Woke philosophy through 'community organising' long before anyone had heard of it. In those days it still went by its traditional name of Marxism. The reason for the manipulated Trump phenomenon was laid out in Alinsky's 1971 book, *Rules for Radicals*, which was his blueprint for overthrowing democratic and other regimes and replacing them with Sabbatian Marxism. Not surprisingly his to-do list was evident in the Sabbatian French and Russian 'Revolutions' and that in China which will become very relevant in the next chapter about the 'Covid' hoax. Among Alinsky's followers have been the deeply corrupt Barack Obama, House Speaker Nancy Pelosi and Hillary Clinton who described him as a 'hero'. All three are Sabbatian stooges with Pelosi personifying the arrogant corrupt idiocy that so widely fronts up for the Cult inner core. Predictably as a Sabbatian advocate of the 'light-bringer' Alinsky features Lucifer on the dedication page of his book as the original radical who gained

his own kingdom ('Earth' as we shall see). One of Alinsky's golden radical rules was to pick an individual and focus all attention, hatred and blame on them and not to target faceless bureaucracies and corporations. *Rules for Radicals* is really a Sabbatian handbook with its contents repeatedly employed all over the world for centuries and why wouldn't Sabbatians bring to power their designer-villain to be used as the individual on which all attention, hatred and blame was bestowed? This is what they did and the only question for me is how much Trump knew that and how much he was manipulated. A bit of both, I suspect. This was Alinsky's Trump technique from a man who died in 1972. The technique has spanned history:

Pick the target, freeze it, personalize it, polarize it. Don't try to attack abstract corporations or bureaucracies. Identify a responsible individual. Ignore attempts to shift or spread the blame.

From the moment Trump came to illusory power everything was about him. It wasn't about Republican policy or opinion, but all about Trump. Everything he did was presented in negative, derogatory and abusive terms by the Sabbatian-dominated media led by Cult operations such as CNN, MSNBC, *The New York Times* and the Jeff Bezos-owned *Washington Post* – 'Pick the target, freeze it, personalize it, polarize it.' Trump was turned into a demon to be vilified by those who hated him and a demi-god loved by those who worshipped him. This, in turn, had his supporters, too, presented as equally demonic in preparation for the punchline later down the line when Biden was about to take office. It was here's a Trump, there's a Trump, everywhere a Trump, Trump. Virtually every news story or happening was filtered through the lens of 'The Donald'. You loved him or hated him and which one you chose was said to define you as Satan's spawn or a paragon of virtue. Even supporting some Trump policies or statements and not others was enough for an assault on your character. No shades of grey were or are allowed. Everything is black and white (literally and figuratively). A Californian I knew had her head utterly scrambled by her hatred for Trump while telling people they should love each other. She was so totally consumed by

Trump Derangement Syndrome as it became to be known that this glaring contradiction would never have occurred to her. By definition anyone who criticised Trump or praised his opponents was a hero and this lady described Joe Biden as 'a kind, honest gentleman' when he's a provable liar, mega-crook and vicious piece of work to boot. Sabbatians had indeed divided America using Trump as the fall-guy and all along the clock was ticking on the consequences for his supporters.

In hock to his masters

Trump gave Sabbatians via Israel almost everything they wanted in his four years. Ask and you shall receive was the dynamic between himself and Benjamin Netanyahu orchestrated by Trump's ultra-Zionist son-in-law Jared Kushner, his ultra-Zionist Ambassador to Israel, David Friedman, and ultra-Zionist 'Israel adviser', Jason Greenblatt. The last two were central to the running and protecting from collapse of his business empire, the Trump Organisation, and colossal business failures made him forever beholding to Sabbatian networks that bailed him out. By the start of the 1990s Trump owed $4 billion to banks that he couldn't pay and almost $1billion of that was down to him personally and not his companies. This mega-disaster was the result of building two new casinos in Atlantic City and buying the enormous Taj Mahal operation which led to crippling debt payments. He had borrowed fantastic sums from 72 banks with major Sabbatian connections and although the scale of debt should have had him living in a tent alongside the highway they never foreclosed. A plan was devised to lift Trump from the mire by BT Securities Corporation and Rothschild Inc. and the case was handled by Wilber Ross who had worked for the Rothschilds for 27 years. Ross would be named US Commerce Secretary after Trump's election. Another crucial figure in saving Trump was ultra-Zionist 'investor' Carl Icahn who bought the Taj Mahal casino. Icahn was made special economic adviser on financial regulation in the Trump administration. He didn't stay long but still managed to find time to make a tidy sum of a reported $31.3 million when he sold his

holdings affected by the price of steel three days before Trump imposed a 235 percent tariff on steel imports. What amazing bits of luck these people have. Trump and Sabbatian operatives have long had a close association and his mentor and legal adviser from the early 1970s until 1986 was the dark and genetically corrupt ultra-Zionist Roy Cohn who was chief counsel to Senator Joseph McCarthy's 'communist' witch-hunt in the 1950s. *Esquire* magazine published an article about Cohn with the headline 'Don't mess with Roy Cohn'. He was described as the most feared lawyer in New York and 'a ruthless master of dirty tricks ... [with] ... more than one Mafia Don on speed dial'. Cohn's influence, contacts, support and protection made Trump a front man for Sabbatians in New York with their connections to one of Cohn's many criminal employers, the 'Russian' Sabbatian Mafia. Israel-centric media mogul Rupert Murdoch was introduced to Trump by Cohn and they started a long friendship. Cohn died in 1986 weeks after being disbarred for unethical conduct by the Appellate Division of the New York State Supreme Court. The wheels of justice do indeed run slow given the length of Cohn's crooked career.

QAnon-sense

We are asked to believe that Donald Trump with his fundamental connections to Sabbatian networks and operatives has been leading the fight to stop the Sabbatian agenda for the fascistic control of America and the world. Sure he has. A man entrapped during his years in the White House by Sabbatian operatives and whose biggest financial donor was casino billionaire Sheldon Adelson who was Sabbatian to his DNA?? Oh, do come on. Trump has been used to divide America and isolate Pushbackers on the Cult agenda under the heading of 'Trump supporters', 'insurrectionists' and 'white supremacists'. The US Intelligence/Mossad Psyop or psychological operation known as QAnon emerged during the Trump years as a central pillar in the Sabbatian campaign to lead Pushbackers into the trap set by those that wished to destroy them. I knew from the start that QAnon was a scam because I had seen the same scenario many

times before over 30 years under different names and I had written about one in particular in the books. 'Not again' was my reaction when QAnon came to the fore. The same script is pulled out every few years and a new name added to the letterhead. The story always takes the same form: 'Insiders' or 'the good guys' in the government-intelligence-military 'Deep State' apparatus were going to instigate mass arrests of the 'bad guys' which would include the Rockefellers, Rothschilds, Barack Obama, Hillary Clinton, George Soros, etc., etc. Dates are given for when the 'good guys' are going to move in, but the dates pass without incident and new dates are given which pass without incident. The central message to Pushbackers in each case is that they don't have to do anything because there is 'a plan' and it is all going to be sorted by the 'good guys' on the inside. 'Trust the plan' was a QAnon mantra when the only plan was to misdirect Pushbackers into putting their trust in a Psyop they believed to be real. Beware, beware, those who tell you what you want to hear and always check it out. Right up to Biden's inauguration QAnon was still claiming that 'the Storm' was coming and Trump would stay on as president when Biden and his cronies were arrested and jailed. It was never going to happen and of course it didn't, but what did happen as a result provided that punchline to the Sabbatian Trump/QAnon Psyop.

On January 6th, 2021, a very big crowd of Trump supporters gathered in the National Mall in Washington DC down from the Capitol Building to protest at what they believed to be widespread corruption and vote fraud that stopped Trump being re-elected for a second term as president in November, 2020. I say as someone that does not support Trump or Biden that the evidence is clear that major vote-fixing went on to favour Biden, a man with cognitive problems so advanced he can often hardly string a sentence together without reading the words written for him on the Teleprompter. Glaring ballot discrepancies included serious questions about electronic voting machines that make vote rigging a comparative cinch and hundreds of thousands of paper votes that suddenly appeared during already advanced vote counts and virtually all of

them for Biden. Early Trump leads in crucial swing states suddenly began to close and disappear. The pandemic hoax was used as the excuse to issue almost limitless numbers of mail-in ballots with no checks to establish that the recipients were still alive or lived at that address. They were sent to streams of people who had not even asked for them. Private organisations were employed to gather these ballots and who knows what they did with them before they turned up at the counts. The American election system has been manipulated over decades to become a sick joke with more holes than a Swiss cheese for the express purpose of dictating the results. Then there was the criminal manipulation of information by Sabbatian tech giants like Facebook, Twitter and Google-owned YouTube which deleted pro-Trump, anti-Biden accounts and posts while everything in support of Biden was left alone. Sabbatians wanted Biden to win because after the dividing of America it was time for full-on Woke and every aspect of the Cult agenda to be unleashed.

Hunter gatherer

Extreme Silicon Valley bias included blocking information by the *New York Post* exposing a Biden scandal that should have ended his bid for president in the final weeks of the campaign. Hunter Biden, his monumentally corrupt son, is reported to have sent a laptop to be repaired at a local store and failed to return for it. Time passed until the laptop became the property of the store for non-payment of the bill. When the owner saw what was on the hard drive he gave a copy to the FBI who did nothing even though it confirmed widespread corruption in which the Joe Biden family were using his political position, especially when he was vice president to Obama, to make multiple millions in countries around the world and most notably Ukraine and China. Hunter Biden's one-time business partner Tony Bobulinski went public when the story broke in the *New York Post* to confirm the corruption he saw and that Joe Biden not only knew what was going on he also profited from the spoils. Millions were handed over by a Chinese company with close

connections – like all major businesses in China – to the Chinese communist party of President Xi Jinping. Joe Biden even boasted at a meeting of the Cult's World Economic Forum that as vice president he had ordered the government of Ukraine to fire a prosecutor. What he didn't mention was that the same man just happened to be investigating an energy company which was part of Hunter Biden's corrupt portfolio. The company was paying him big bucks for no other reason than the influence his father had. Overnight Biden's presidential campaign should have been over given that he had lied publicly about not knowing what his son was doing. Instead almost the entire Sabbatian-owned mainstream media and Sabbatian-owned Silicon Valley suppressed circulation of the story. This alone went a mighty way to rigging the election of 2020. Cult assets like Mark Zuckerberg at Facebook also spent hundreds of millions to be used in support of Biden and vote 'administration'.

The Cult had used Trump as the focus to divide America and was now desperate to bring in moronic, pliable, corrupt Biden to complete the double-whammy. No way were they going to let little things like the will of the people thwart their plan. Silicon Valley widely censored claims that the election was rigged because it *was* rigged. For the same reason anyone claiming it was rigged was denounced as a 'white supremacist' including the pathetically few Republican politicians willing to say so. Right across the media where the claim was mentioned it was described as a 'false claim' even though these excuses for 'journalists' would have done no research into the subject whatsoever. Trump won seven million more votes than any sitting president had ever achieved while somehow a cognitively-challenged soon to be 78-year-old who was hidden away from the public for most of the campaign managed to win more votes than any presidential candidate in history. It makes no sense. You only had to see election rallies for both candidates to witness the enthusiasm for Trump and the apathy for Biden. Tens of thousands would attend Trump events while Biden was speaking in empty car parks with often only television crews attending and framing their shots to hide the fact that no one was there. It was pathetic to see

footage come to light of Biden standing at a podium making speeches only to TV crews and party fixers while reading the words written for him on massive Teleprompter screens. So, yes, those protestors on January 6th had a point about election rigging, but some were about to walk into a trap laid for them in Washington by the Cult Deep State and its QAnon Psyop. This was the Capitol Hill riot ludicrously dubbed an 'insurrection'.

The spider and the fly

Renegade Minds know there are not two 'sides' in politics, only one side, the Cult, working through all 'sides'. It's a stage show, a puppet show, to direct the perceptions of the population into focusing on diversions like parties and candidates while missing the puppeteers with their hands holding all the strings. The Capitol Hill 'insurrection' brings us back to the Little Big Horn. Having created two distinct opposing groupings – Woke and Pushbackers – the trap was about to be sprung. Pushbackers were to be encircled and isolated by associating them all in the public mind with Trump and then labelling Trump as some sort of Confederate leader. I knew immediately that the Capitol riot was a set-up because of two things. One was how easy the rioters got into the building with virtually no credible resistance and secondly I could see – as with the 'Covid' hoax in the West at the start of 2020 – how the Cult could exploit the situation to move its agenda forward with great speed. My experience of Cult techniques and activities over more than 30 years has showed me that while they do exploit situations they haven't themselves created this never happens with events of fundamental agenda significance. Every time major events giving cultists the excuse to rapidly advance their plan you find they are manipulated into being for the specific reason of providing that excuse – Problem-Reaction-Solution. Only a tiny minority of the huge crowd of Washington protestors sought to gain entry to the Capitol by smashing windows and breaching doors. That didn't matter. The whole crowd and all Pushbackers, even if they did not support Trump, were going to be lumped together as dangerous

insurrectionists and conspiracy theorists. The latter term came into widespread use through a CIA memo in the 1960s aimed at discrediting those questioning the nonsensical official story of the Kennedy assassination and it subsequently became widely employed by the media. It's still being used by inept 'journalists' with no idea of its origin to discredit anyone questioning anything that authority claims to be true. When you are perpetrating a conspiracy you need to discredit the very word itself even though the dictionary definition of conspiracy is merely 'the activity of secretly planning with other people to do something bad or illegal' and 'a general agreement to keep silent about a subject for the purpose of keeping it secret'. On that basis there are conspiracies almost wherever you look. For obvious reasons the Cult and its lapdog media have to claim there are no conspiracies even though the word appears in state laws as with conspiracy to defraud, to murder, and to corrupt public morals.

Agent provocateurs are widely used by the Cult Deep State to manipulate genuine people into acting in ways that suit the desired outcome. By genuine in this case I mean protestors genuinely supporting Trump and claims that the election was stolen. In among them, however, were agents of the state wearing the garb of Trump supporters and QAnon to pump-prime the Capital riot which some genuine Trump supporters naively fell for. I described the situation as 'Come into my parlour said the spider to the fly'. Leaflets appeared through the Woke paramilitary arm Antifa, the anti-fascist fascists, calling on supporters to turn up in Washington looking like Trump supporters even though they hated him. Some of those arrested for breaching the Capitol Building were sourced to Antifa and its stable mate Black Lives Matter. Both organisations are funded by Cult billionaires and corporations. One man charged for the riot was according to his lawyer a former FBI agent who had held top secret security clearance for 40 years. Attorney Thomas Plofchan said of his client, 66-year-old Thomas Edward Caldwell:

He has held a Top Secret Security Clearance since 1979 and has undergone multiple Special Background Investigations in support of his clearances. After retiring from the Navy, he

worked as a section chief for the Federal Bureau of Investigation from 2009-2010 as a GS-12 [mid-level employee].

He also formed and operated a consulting firm performing work, often classified, for U.S government customers including the US. Drug Enforcement Agency, Department of Housing and Urban Development, the US Coast Guard, and the US Army Personnel Command.

A judge later released Caldwell pending trial in the absence of evidence about a conspiracy or that he tried to force his way into the building. *The New York Post* reported a 'law enforcement source' as saying that 'at least two known Antifa members were spotted' on camera among Trump supporters during the riot while one of the rioters arrested was John Earle Sullivan, a seriously extreme Black Lives Matter Trump-hater from Utah who was previously arrested and charged in July, 2020, over a BLM-Antifa riot in which drivers were threatened and one was shot. Sullivan is the founder of Utah-based Insurgence USA which is an affiliate of the Cult-created-and-funded Black Lives Matter movement. Footage appeared and was then deleted by Twitter of Trump supporters calling out Antifa infiltrators and a group was filmed changing into pro-Trump clothing before the riot. Security at the building was *pathetic* – as planned. Colonel Leroy Fletcher Prouty, a man with long experience in covert operations working with the US security apparatus, once described the tell-tale sign to identify who is involved in an assassination. He said:

No one has to direct an assassination – it happens. The active role is played secretly by permitting it to happen. This is the greatest single clue. Who has the power to call off or reduce the usual security precautions?

This principle applies to many other situations and certainly to the Capitol riot of January 6th, 2021.

The sting

With such a big and potentially angry crowd known to be gathering near the Capitol the security apparatus would have had a major police detail to defend the building with National Guard troops on

standby given the strength of feeling among people arriving from all over America encouraged by the QAnon Psyop and statements by Donald Trump. Instead Capitol Police 'security' was flimsy, weak, and easily breached. The same number of officers was deployed as on a regular day and that is a blatant red flag. They were not staffed or equipped for a possible riot that had been an obvious possibility in the circumstances. No protective and effective fencing worth the name was put in place and there were no contingency plans. The whole thing was basically a case of standing aside and waving people in. Once inside police mostly backed off apart from one Capitol police officer who ridiculously shot dead unarmed Air Force veteran protestor Ashli Babbitt without a warning as she climbed through a broken window. The 'investigation' refused to name or charge the officer after what must surely be considered a murder in the circumstances. They just lifted a carpet and swept. The story was endlessly repeated about five people dying in the 'armed insurrection' when there was no report of rioters using weapons. Apart from Babbitt the other four died from a heart attack, strokes and apparently a drug overdose. Capitol police officer Brian Sicknick was reported to have died after being bludgeoned with a fire extinguisher when he was alive after the riot was over and died later of what the Washington Medical Examiner's Office said was a stroke. Sicknick had no external injuries. The lies were delivered like rapid fire. There was a narrative to build with incessant repetition of the lie until the lie became the accepted 'everybody knows that' truth. The 'Big Lie' technique of Nazi Propaganda Minister Joseph Goebbels is constantly used by the Cult which was behind the Nazis and is today behind the 'Covid' and 'climate change' hoaxes. Goebbels said:

If you tell a lie big enough and keep repeating it, people will eventually come to believe it. The lie can be maintained only for such time as the State can shield the people from the political, economic and/or military consequences of the lie. It thus becomes vitally important for the State to use all of its powers to repress dissent, for the truth is the mortal enemy of the lie, and thus by extension, the truth is the greatest enemy of the State.

Most protestors had a free run of the Capitol Building. This allowed pictures to be taken of rioters in iconic parts of the building including the Senate chamber which could be used as propaganda images against all Pushbackers. One Congresswoman described the scene as 'the worst kind of non-security anybody could ever imagine'. Well, the first part was true, but someone obviously did imagine it and made sure it happened. Some photographs most widely circulated featured people wearing QAnon symbols and now the Psyop would be used to dub all QAnon followers with the ubiquitous fit-all label of 'white supremacist' and 'insurrectionists'. When a Muslim extremist called Noah Green drove his car at two police officers at the Capitol Building killing one in April, 2021, there was no such political and media hysteria. They were just disappointed he wasn't white.

The witch-hunt

Government prosecutor Michael Sherwin, an aggressive, dark-eyed, professional Rottweiler led the 'investigation' and to call it over the top would be to understate reality a thousand fold. Hundreds were tracked down and arrested for the crime of having the wrong political views and people were jailed who had done nothing more than walk in the building, committed no violence or damage to property, took a few pictures and left. They were labelled a 'threat to the Republic' while Biden sat in the White House signing executive orders written for him that were dismantling 'the Republic'. Even when judges ruled that a mother and son should not be in jail the government kept them there. Some of those arrested have been badly beaten by prison guards in Washington and lawyers for one man said he suffered a fractured skull and was made blind in one eye. Meanwhile a woman is shot dead for no reason by a Capitol Police officer and we are not allowed to know who he is never mind what has happened to him although that will be *nothing*. The Cult's QAnon/Trump sting to identify and isolate Pushbackers and then target them on the road to crushing and deleting them was a resounding success. You would have thought the Russians had

invaded the building at gunpoint and lined up senators for a firing squad to see the political and media reaction. Congresswoman Alexandria Ocasio-Cortez is a child in a woman's body, a terrible-twos, me, me, me, Woker narcissist of such proportions that words have no meaning. She said she thought she was going to die when 'insurrectionists' banged on her office door. It turned out she wasn't even in the Capitol Building when the riot was happening and the 'banging' was a Capitol Police officer. She referred to herself as a 'survivor' which is an insult to all those true survivors of violent and sexual abuse while she lives her pampered and privileged life talking drivel for a living. Her Woke colleague and fellow mega-narcissist Rashida Tlaib broke down describing the devastating effect on her, too, of *not being* in the building when the rioters were there. Ocasio-Cortez and Tlaib are members of a fully-Woke group of Congresswomen known as 'The Squad' along with Ilhan Omar and Ayanna Pressley. The Squad from what I can see can be identified by its vehement anti-white racism, anti-white men agenda, and, as always in these cases, the absence of brain cells on active duty.

The usual suspects were on the riot case immediately in the form of Democrat ultra-Zionist senators and operatives Chuck Schumer and Adam Schiff demanding that Trump be impeached for 'his part in the insurrection'. The same pair of prats had led the failed impeachment of Trump over the invented 'Russia collusion' nonsense which claimed Russia had helped Trump win the 2016 election. I didn't realise that Tel Aviv had been relocated just outside Moscow. I must find an up-to-date map. The Russia hoax was a Sabbatian operation to keep Trump occupied and impotent and to stop any rapport with Russia which the Cult wants to retain as a perceptual enemy to be pulled out at will. Puppet Biden began attacking Russia when he came to office as the Cult seeks more upheaval, division and war across the world. A two-year stage show 'Russia collusion inquiry' headed by the not-very-bright former 9/11 FBI chief Robert Mueller, with support from 19 lawyers, 40 FBI agents plus intelligence analysts, forensic accountants and other

staff, devoured tens of millions of dollars and found no evidence of Russia collusion which a ten-year-old could have told them on day one. Now the same moronic Schumer and Schiff wanted a second impeachment of Trump over the Capitol 'insurrection' (riot) which the arrested development of Schumer called another 'Pearl Harbor' while others compared it with 9/11 in which 3,000 died and, in the case of CNN, with the Rwandan genocide in the 1990s in which an estimated 500,000 to 600,000 were murdered, between 250, 000 and 500,000 women were raped, and populations of whole towns were hacked to death with machetes. To make those comparisons purely for Cult political reasons is beyond insulting to those that suffered and lost their lives and confirms yet again the callous inhumanity that we are dealing with. Schumer is a monumental idiot and so is Schiff, but they serve the Cult agenda and do whatever they're told so they get looked after. Talking of idiots – another inane man who spanned the Russia and Capitol impeachment attempts was Senator Eric Swalwell who had the nerve to accuse Trump of collusion with the Russians while sleeping with a Chinese spy called Christine Fang or 'Fang Fang' which is straight out of a Bond film no doubt starring Klaus Schwab as the bloke living on a secret island and controlling laser weapons positioned in space and pointing at world capitals. Fang Fang plays the part of Bond's infiltrator girlfriend which I'm sure she would enjoy rather more than sharing a bed with the brainless Swalwell, lying back and thinking of China. The FBI eventually warned Swalwell about Fang Fang which gave her time to escape back to the Chinese dictatorship. How very thoughtful of them. The second Trump impeachment also failed and hardly surprising when an impeachment is supposed to remove a sitting president and by the time it happened Trump was no longer president. These people are running your country America, well, officially anyway. Terrifying isn't it?

Outcomes tell the story - always

The outcome of all this – and it's the *outcome* on which Renegade Minds focus, not the words – was that a vicious, hysterical and

obviously pre-planned assault was launched on Pushbackers to censor, silence and discredit them and even targeted their right to earn a living. They have since been condemned as 'domestic terrorists' that need to be treated like Al-Qaeda and Islamic State. 'Domestic terrorists' is a label the Cult has been trying to make stick since the period of the Oklahoma bombing in 1995 which was blamed on 'far-right domestic terrorists'. If you read *The Trigger* you will see that the bombing was clearly a Problem-Reaction-Solution carried out by the Deep State during a Bill Clinton administration so corrupt that no dictionary definition of the term would even nearly suffice. Nearly 30, 000 troops were deployed from all over America to the empty streets of Washington for Biden's inauguration. Ten thousand of them stayed on with the pretext of protecting the capital from insurrectionists when it was more psychological programming to normalise the use of the military in domestic law enforcement in support of the Cult plan for a police-military state. Biden's fascist administration began a purge of 'wrong-thinkers' in the military which means anyone that is not on board with Woke. The Capitol Building was surrounded by a fence with razor wire and the Land of the Free was further symbolically and literally dismantled. The circle was completed with the installation of Biden and the exploitation of the QAnon Psyop.

America had never been so divided since the civil war of the 19th century, Pushbackers were isolated and dubbed terrorists and now, as was always going to happen, the Cult immediately set about deleting what little was left of freedom and transforming American society through a swish of the hand of the most controlled 'president' in American history leading (officially at least) the most extreme regime since the country was declared an independent state on July 4th, 1776. Biden issued undebated, dictatorial executive orders almost by the hour in his opening days in office across the whole spectrum of the Cult wish-list including diluting controls on the border with Mexico allowing thousands of migrants to illegally enter the United States to transform the demographics of America and import an election-changing number of perceived Democrat

voters. Then there were Biden deportation amnesties for the already illegally resident (estimated to be as high as 20 or even 30 million). A bill before Congress awarded American citizenship to anyone who could prove they had worked in agriculture for just 180 days in the previous two years as 'Big Ag' secured its slave labour long-term. There were the plans to add new states to the union such as Puerto Rico and making Washington DC a state. They are all parts of a plan to ensure that the Cult-owned Woke Democrats would be permanently in power.

Border – what border?

I have exposed in detail in other books how mass immigration into the United States and Europe is the work of Cult networks fuelled by the tens of billions spent to this and other ends by George Soros and his global Open Society (open borders) Foundations. The impact can be seen in America alone where the population has increased by *100 million* in little more than 30 years mostly through immigration. I wrote in *The Answer* that the plan was to have so many people crossing the southern border that the numbers become unstoppable and we are now there under Cult-owned Biden. El Salvador in Central America puts the scale of what is happening into context. A third of the population now lives in the United States, much of it illegally, and many more are on the way. The methodology is to crush Central and South American countries economically and spread violence through machete-wielding psychopathic gangs like MS-13 based in El Salvador and now operating in many American cities. Biden-imposed lax security at the southern border means that it is all but open. He said before his 'election' that he wanted to see a surge towards the border if he became president and that was the green light for people to do just that after election day to create the human disaster that followed for both America and the migrants. When that surge came the imbecilic Alexandria Ocasio-Cortez said it wasn't a 'surge' because they are 'children, not insurgents' and the term 'surge' (used by Biden) was a claim of 'white supremacists'.

This disingenuous lady may one day enter the realm of the most basic intelligence, but it won't be any time soon.

Sabbatians and the Cult are in the process of destroying America by importing violent people and gangs in among the genuine to terrorise American cities and by overwhelming services that cannot cope with the sheer volume of new arrivals. Something similar is happening in Europe as Western society in general is targeted for demographic and cultural transformation and upheaval. The plan demands violence and crime to create an environment of intimidation, fear and division and Soros has been funding the election of district attorneys across America who then stop prosecuting many crimes, reduce sentences for violent crimes and free as many violent criminals as they can. Sabbatians are creating the chaos from which order – their order – can respond in a classic Problem-Reaction-Solution. A Freemasonic moto says 'Ordo Ab Chao' (Order out of Chaos) and this is why the Cult is constantly creating chaos to impose a new 'order'. Here you have the reason the Cult is constantly creating chaos. The 'Covid' hoax can be seen with those entering the United States by plane being forced to take a 'Covid' test while migrants flooding through southern border processing facilities do not. Nothing is put in the way of mass migration and if that means ignoring the government's own 'Covid' rules then so be it. They know it's all bullshit anyway. Any pushback on this is denounced as 'racist' by Wokers and Sabbatian fronts like the ultra-Zionist Anti-Defamation League headed by the appalling Jonathan Greenblatt which at the same time argues that Israel should not give citizenship and voting rights to more Palestinian Arabs or the 'Jewish population' (in truth the Sabbatian network) will lose control of the country.

Society-changing numbers

Biden's masters have declared that countries like El Salvador are so dangerous that their people must be allowed into the United States for humanitarian reasons when there are fewer murders in large parts of many Central American countries than in US cities like

Baltimore. That is not to say Central America cannot be a dangerous place and Cult-controlled American governments have been making it so since way back, along with the dismantling of economies, in a long-term plan to drive people north into the United States. Parts of Central America are very dangerous, but in other areas the story is being greatly exaggerated to justify relaxing immigration criteria. Migrants are being offered free healthcare and education in the United States as another incentive to head for the border and there is no requirement to be financially independent before you can enter to prevent the resources of America being drained. You can't blame migrants for seeking what they believe will be a better life, but they are being played by the Cult for dark and nefarious ends. The numbers since Biden took office are huge. In February, 2021, more than 100,000 people were known to have tried to enter the US illegally through the southern border (it was 34,000 in the same month in 2020) and in March it was 170,000 – a 418 percent increase on March, 2020. These numbers are only known people, not the ones who get in unseen. The true figure for migrants illegally crossing the border in a single month was estimated by one congressman at 250,000 and that number will only rise under Biden's current policy. Gangs of murdering drug-running thugs that control the Mexican side of the border demand money – thousands of dollars – to let migrants cross the Rio Grande into America. At the same time gun battles are breaking out on the border several times a week between rival Mexican drug gangs (which now operate globally) who are equipped with sophisticated military-grade weapons, grenades and armoured vehicles. While the Capitol Building was being 'protected' from a non-existent 'threat' by thousands of troops, and others were still deployed at the time in the Cult Neocon war in Afghanistan, the southern border of America was left to its fate. This is not incompetence, it is cold calculation.

By March, 2021, there were 17,000 unaccompanied children held at border facilities and many of them are ensnared by people traffickers for paedophile rings and raped on their journey north to America. This is not conjecture – this is fact. Many of those designated

children are in reality teenage boys or older. Meanwhile Wokers posture their self-purity for encouraging poor and tragic people to come to America and face this nightmare both on the journey and at the border with the disgusting figure of House Speaker Nancy Pelosi giving disingenuous speeches about caring for migrants. The woman's evil. Wokers condemned Trump for having children in cages at the border (so did Obama, *Shhhh*), but now they are sleeping on the floor without access to a shower with one border facility 729 percent over capacity. The Biden insanity even proposed flying migrants from the southern border to the northern border with Canada for 'processing'. The whole shambles is being overseen by ultra-Zionist Secretary of Homeland Security, the moronic liar Alejandro Mayorkas, who banned news cameras at border facilities to stop Americans seeing what was happening. Mayorkas said there was not a ban on news crews; it was just that they were not allowed to film. Alongside him at Homeland Security is another ultra-Zionist Cass Sunstein appointed by Biden to oversee new immigration laws. Sunstein despises conspiracy researchers to the point where he suggests they should be banned or *taxed* for having such views. The man is not bonkers or anything. He's perfectly well-adjusted, but adjusted to what is the question. Criticise what is happening and you are a 'white supremacist' when earlier non-white immigrants also oppose the numbers which effect their lives and opportunities. Black people in poor areas are particularly damaged by uncontrolled immigration and the increased competition for work opportunities with those who will work for less. They are also losing voting power as Hispanics become more dominant in former black areas. It's a downward spiral for them while the billionaires behind the policy drone on about how much they care about black people and 'racism'. None of this is about compassion for migrants or black people – that's just wind and air. Migrants are instead being mercilessly exploited to transform America while the countries they leave are losing their future and the same is true in Europe. Mass immigration may now be the work of Woke Democrats, but it can be traced back to the 1986 Immigration Reform and Control Act (it

wasn't) signed into law by Republican hero President Ronald Reagan which gave amnesty to millions living in the United States illegally and other incentives for people to head for the southern border. Here we have the one-party state at work again.

Save me syndrome

Almost every aspect of what I have been exposing as the Cult agenda was on display in even the first days of 'Biden' with silencing of Pushbackers at the forefront of everything. A Renegade Mind will view the Trump years and QAnon in a very different light to their supporters and advocates as the dots are connected. The QAnon/Trump Psyop has given the Cult all it was looking for. We may not know how much, or little, that Trump realised he was being used, but that's a side issue. This pincer movement produced the desired outcome of dividing America and having Pushbackers isolated. To turn this around we have to look at new routes to empowerment which do not include handing our power to other people and groups through what I will call the 'Save Me Syndrome' – 'I want someone else to do it so that I don't have to'. We have seen this at work throughout human history and the QAnon/Trump Psyop is only the latest incarnation alongside all the others. Religion is an obvious expression of this when people look to a 'god' or priest to save them or tell them how to be saved and then there are 'save me' politicians like Trump. Politics is a diversion and not a 'saviour'. It is a means to block positive change, not make it possible.

Save Me Syndrome always comes with the same repeating theme of handing your power to whom or what you believe will save you while your real 'saviour' stares back from the mirror every morning. Renegade Minds are constantly vigilant in this regard and always asking the question 'What can I do?' rather than 'What can someone else do for me?' Gandhi was right when he said: 'You must be the change you want to see in the world.' We are indeed the people we have been waiting for. We are presented with a constant raft of reasons to concede that power to others and forget where the real power is. Humanity has the numbers and the Cult does not. It has to

use diversion and division to target the unstoppable power that comes from unity. Religions, governments, politicians, corporations, media, QAnon, are all different manifestations of this power-diversion and dilution. Refusing to give your power to governments and instead handing it to Trump and QAnon is not to take a new direction, but merely to recycle the old one with new names on the posters. I will explore this phenomenon as we proceed and how to break the cycles and recycles that got us here through the mists of repeating perception and so repeating history.

For now we shall turn to the most potent example in the entire human story of the consequences that follow when you give your power away. I am talking, of course, of the 'Covid' hoax.

CHAPTER FOUR

'Covid': Calculated catastrophe

Facts are threatening to those invested in fraud
DaShanne Stokes

We can easily unravel the real reason for the 'Covid pandemic' hoax by employing the Renegade Mind methodology that I have outlined this far. We'll start by comparing the long-planned Cult outcome with the 'Covid pandemic' outcome. Know the outcome and you'll see the journey.

I have highlighted the plan for the Hunger Games Society which has been in my books for so many years with the very few controlling the very many through ongoing dependency. To create this dependency it is essential to destroy independent livelihoods, businesses and employment to make the population reliant on the state (the Cult) for even the basics of life through a guaranteed pittance income. While independence of income remained these Cult ambitions would be thwarted. With this knowledge it was easy to see where the 'pandemic' hoax was going once talk of 'lockdowns' began and the closing of all but perceived 'essential' businesses to 'save' us from an alleged 'deadly virus'. Cult corporations like Amazon and Walmart were naturally considered 'essential' while mom and pop shops and stores had their doors closed by fascist decree. As a result with every new lockdown and new regulation more small and medium, even large businesses not owned by the Cult, went to the wall while Cult giants and their frontmen and women grew financially fatter by the second. Mom and pop were

denied an income and the right to earn a living and the wealth of people like Jeff Bezos (Amazon), Mark Zuckerberg (Facebook) and Sergei Brin and Larry Page (Google/Alphabet) have reached record levels. The Cult was increasing its own power through further dramatic concentrations of wealth while the competition was being destroyed and brought into a state of dependency. Lockdowns have been instigated to secure that very end and were never anything to do with health. My brother Paul spent 45 years building up a bus repair business, but lockdowns meant buses were running at a fraction of normal levels for months on end. Similar stories can told in their hundreds of millions worldwide. Efforts of a lifetime coldly destroyed by Cult multi-billionaires and their lackeys in government and law enforcement who continued to earn their living from the taxation of the people while denying the right of the same people to earn theirs. How different it would have been if those making and enforcing these decisions had to face the same financial hardships of those they affected, but they never do.

Gates of Hell

Behind it all in the full knowledge of what he is doing and why is the psychopathic figure of Cult operative Bill Gates. His puppet Tedros at the World Health Organization declared 'Covid' a pandemic in March, 2020. The WHO had changed the definition of a 'pandemic' in 2009 just a month before declaring the 'swine flu pandemic' which would not have been so under the previous definition. The same applies to 'Covid'. The definition had included… 'an infection by an infectious agent, occurring simultaneously in different countries, with a significant mortality rate relative to the proportion of the population infected'. The new definition removed the need for 'significant mortality'. The 'pandemic' has been fraudulent even down to the definition, but Gates demanded economy-destroying lockdowns, school closures, social distancing, mandatory masks, a 'vaccination' for every man, woman and child on the planet and severe consequences and restrictions for those that refused. Who gave him this power? The

Cult did which he serves like a little boy in short trousers doing what his daddy tells him. He and his psychopathic missus even smiled when they said that much worse was to come (what they knew was planned to come). Gates responded in the matter-of-fact way of all psychopaths to a question about the effect on the world economy of what he was doing:

> Well, it won't go to zero but it will shrink. Global GDP is probably going to take the biggest hit ever [Gates was smiling as he said this] … in my lifetime this will be the greatest economic hit. But you don't have a choice. People act as if you have a choice. People don't feel like going to the stadium when they might get infected … People are deeply affected by seeing these stats, by knowing they could be part of the transmission chain, old people, their parents and grandparents, could be affected by this, and so you don't get to say ignore what is going on here.
>
> There will be the ability to open up, particularly in rich countries, if things are done well over the next few months, but for the world at large normalcy only returns when we have largely vaccinated the entire population.

The man has no compassion or empathy. How could he when he's a psychopath like all Cult players? My own view is that even beyond that he is very seriously mentally ill. Look in his eyes and you can see this along with his crazy flailing arms. You don't do what he has done to the world population since the start of 2020 unless you are mentally ill and at the most extreme end of psychopathic. You especially don't do it when to you know, as we shall see, that cases and deaths from 'Covid' are fakery and a product of monumental figure massaging. 'These stats' that Gates referred to are based on a 'test' that's not testing for the 'virus' as he has known all along. He made his fortune with big Cult support as an infamously ruthless software salesman and now buys global control of 'health' (death) policy without the population he affects having any say. It's a breathtaking outrage. Gates talked about people being deeply affected by fear of 'Covid' when that was because of *him* and his global network lying to them minute-by-minute supported by a lying media that he seriously influences and funds to the tune of hundreds of millions. He's handed big sums to media operations including the BBC, NBC, Al Jazeera, Univision, *PBS NewsHour*,

ProPublica, National Journal, The Guardian, The Financial Times, The Atlantic, Texas Tribune, USA Today publisher Gannett, *Washington Monthly, Le Monde,* Center for Investigative Reporting, Pulitzer Center on Crisis Reporting, National Press Foundation, International Center for Journalists, Solutions Journalism Network, the Poynter Institute for Media Studies, and many more. Gates is everywhere in the 'Covid' hoax and the man must go to prison – or a mental facility – for the rest of his life and his money distributed to those he has taken such enormous psychopathic pleasure in crushing.

The Muscle

The Hunger Games global structure demands a police-military state – a fusion of the two into one force – which viciously imposes the will of the Cult on the population and protects the Cult from public rebellion. In that regard, too, the 'Covid' hoax just keeps on giving. Often unlawful, ridiculous and contradictory 'Covid' rules and regulations have been policed across the world by moronic automatons and psychopaths made faceless by face-nappy masks and acting like the Nazi SS and fascist blackshirts and brownshirts of Hitler and Mussolini. The smallest departure from the rules decreed by the psychos in government and their clueless gofers were jumped upon by the face-nappy fascists. Brutality against public protestors soon became commonplace even on girls, women and old people as the brave men with the batons – the Face-Nappies as I call them – broke up peaceful protests and handed out fines like confetti to people who couldn't earn a living let alone pay hundreds of pounds for what was once an accepted human right. Robot Face-Nappies of Nottingham police in the English East Midlands fined one group £11,000 for attending a child's birthday party. For decades I charted the transformation of law enforcement as genuine, decent officers were replaced with psychopaths and the brain dead who would happily and brutally do whatever their masters told them. Now they were let loose on the public and I would emphasise the point that none of this just happened. The step-by-step change in the dynamic between police and public was orchestrated from the shadows by

those who knew where this was all going and the same with the perceptual reframing of those in all levels of authority and official administration through 'training courses' by organisations such as Common Purpose which was created in the late 1980s and given a massive boost in Blair era Britain until it became a global phenomenon. Supposed public 'servants' began to view the population as the enemy and the same was true of the police. This was the start of the explosion of behaviour manipulation organisations and networks preparing for the all-war on the human psyche unleashed with the dawn of 2020. I will go into more detail about this later in the book because it is a core part of what is happening.

Police desecrated beauty spots to deter people gathering and arrested women for walking in the countryside alone 'too far' from their homes. We had arrogant, clueless sergeants in the Isle of Wight police where I live posting on Facebook what they insisted the population must do or else. A schoolmaster sergeant called Radford looked young enough for me to ask if his mother knew he was out, but he was posting what he *expected* people to do while a Sergeant Wilkinson boasted about fining lads for meeting in a McDonald's car park where they went to get a lockdown takeaway. Wilkinson added that he had even cancelled their order. What a pair of prats these people are and yet they have increasingly become the norm among Jackboot Johnson's Yellowshirts once known as the British police. This was the theme all over the world with police savagery common during lockdown protests in the United States, the Netherlands, and the fascist state of Victoria in Australia under its tyrannical and again moronic premier Daniel Andrews. Amazing how tyrannical and moronic tend to work as a team and the same combination could be seen across America as arrogant, narcissistic Woke governors and mayors such as Gavin Newsom (California), Andrew Cuomo (New York), Gretchen Whitmer (Michigan), Lori Lightfoot (Chicago) and Eric Garcetti (Los Angeles) did their Nazi and Stalin impressions with the full support of the compliant brutality of their enforcers in uniform as they arrested small business owners defying

fascist shutdown orders and took them to jail in ankle shackles and handcuffs. This happened to bistro owner Marlena Pavlos-Hackney in Gretchen Whitmer's fascist state of Michigan when police arrived to enforce an order by a state-owned judge for 'putting the community at risk' at a time when other states like Texas were dropping restrictions and migrants were pouring across the southern border without any 'Covid' questions at all. I'm sure there are many officers appalled by what they are ordered to do, but not nearly enough of them. If they were truly appalled they would not do it. As the months passed every opportunity was taken to have the military involved to make their presence on the streets ever more familiar and 'normal' for the longer-term goal of police-military fusion.

Another crucial element to the Hunger Games enforcement network has been encouraging the public to report neighbours and others for 'breaking the lockdown rules'. The group faced with £11,000 in fines at the child's birthday party would have been dobbed-in by a neighbour with a brain the size of a pea. The technique was most famously employed by the Stasi secret police in communist East Germany who had public informants placed throughout the population. A police chief in the UK says his force doesn't need to carry out 'Covid' patrols when they are flooded with so many calls from the public reporting other people for visiting the beach. Dorset police chief James Vaughan said people were so enthusiastic about snitching on their fellow humans they were now operating as an auxiliary arm of the police: 'We are still getting around 400 reports a week from the public, so we will respond to reports …We won't need to be doing hotspot patrols because people are very quick to pick the phone up and tell us.' Vaughan didn't say that this is a pillar of all tyrannies of whatever complexion and the means to hugely extend the reach of enforcement while spreading distrust among the people and making them wary of doing anything that might get them reported. Those narcissistic Isle of Wight sergeants Radford and Wilkinson never fail to add a link to their Facebook posts where the public can inform on their fellow slaves.

Neither would be self-aware enough to realise they were imitating the Stasi which they might well never have heard of. Government psychologists that I will expose later laid out a policy to turn communities against each other in the same way.

A coincidence? Yep, and I can knit fog

I knew from the start of the alleged pandemic that this was a Cult operation. It presented limitless potential to rapidly advance the Cult agenda and exploit manipulated fear to demand that every man, woman and child on the planet was 'vaccinated' in a process never used on humans before which infuses self-replicating *synthetic* material into human cells. Remember the plan to transform the human body from a biological to a synthetic biological state. I'll deal with the 'vaccine' (that's not actually a vaccine) when I focus on the genetic agenda. Enough to say here that mass global 'vaccination' justified by this 'new virus' set alarms ringing after 30 years of tracking these people and their methods. The 'Covid' hoax officially beginning in China was also a big red flag for reasons I will be explaining. The agenda potential was so enormous that I could dismiss any idea that the 'virus' appeared naturally. Major happenings with major agenda implications never occur without Cult involvement in making them happen. My questions were twofold in early 2020 as the media began its campaign to induce global fear and hysteria: Was this alleged infectious agent released on purpose by the Cult or did it even exist at all? I then did what I always do in these situations. I sat, observed and waited to see where the evidence and information would take me. By March and early April synchronicity was strongly – and ever more so since then – pointing me in the direction of *there is no 'virus'*. I went public on that with derision even from swathes of the alternative media that voiced a scenario that the Chinese government released the 'virus' in league with Deep State elements in the United States from a top-level bio-lab in Wuhan where the 'virus' is said to have first appeared. I looked at that possibility, but I didn't buy it for several reasons. Deaths from the 'virus' did not in any way match what they

would have been with a 'deadly bioweapon' and it is much more effective if you sell the *illusion* of an infectious agent rather than having a real one unless you can control through injection who has it and who doesn't. Otherwise you lose control of events. A made-up 'virus' gives you a blank sheet of paper on which you can make it do whatever you like and have any symptoms or mutant 'variants' you choose to add while a real infectious agent would limit you to what it actually does. A phantom disease allows you to have endless ludicrous 'studies' on the 'Covid' dollar to widen the perceived impact by inventing ever more 'at risk' groups including one study which said those who walk slowly may be almost four times more likely to die from the 'virus'. People are in psychiatric wards for less.

A real 'deadly bioweapon' can take out people in the hierarchy that are not part of the Cult, but essential to its operation. Obviously they don't want that. Releasing a real disease means you immediately lose control of it. Releasing an illusory one means you don't. Again it's vital that people are extra careful when dealing with what they want to hear. A bioweapon unleashed from a Chinese laboratory in collusion with the American Deep State may fit a conspiracy narrative, but is it true? Would it not be far more effective to use the excuse of a 'virus' to justify the real bioweapon – the 'vaccine'? That way your disease agent does not have to be transmitted and arrives directly through a syringe. I saw a French virologist Luc Montagnier quoted in the alternative media as saying he had discovered that the alleged 'new' severe acute respiratory syndrome coronavirus , or SARS-CoV-2, was made artificially and included elements of the human immunodeficiency 'virus' (HIV) and a parasite that causes malaria. SARS-CoV-2 is alleged to trigger an alleged illness called Covid-19. I remembered Montagnier's name from my research years before into claims that an HIV 'retrovirus' causes AIDs – claims that were demolished by Berkeley virologist Peter Duesberg who showed that no one had ever proved that HIV causes acquired immunodeficiency syndrome or AIDS. Claims that become accepted as fact, publicly and medically, with no proof whatsoever are an ever-recurring story that profoundly applies to

'Covid'. Nevertheless, despite the lack of proof, Montagnier's team at the Pasteur Institute in Paris had a long dispute with American researcher Robert Gallo over which of them discovered and isolated the HIV 'virus' and with *no evidence* found it to cause AIDS. You will see later that there is also no evidence that any 'virus' causes any disease or that there is even such a thing as a 'virus' in the way it is said to exist. The claim to have 'isolated' the HIV 'virus' will be presented in its real context as we come to the shocking story – and it is a story – of SARS-CoV-2 and so will Montagnier's assertion that he identified the full SARS-CoV-2 genome.

Hoax in the making

We can pick up the 'Covid' story in 2010 and the publication by the Rockefeller Foundation of a document called 'Scenarios for the Future of Technology and International Development'. The inner circle of the Rockefeller family has been serving the Cult since John D. Rockefeller (1839-1937) made his fortune with Standard Oil. It is less well known that the same Rockefeller – the Bill Gates of his day – was responsible for establishing what is now referred to as 'Big Pharma', the global network of pharmaceutical companies that make outrageous profits dispensing scalpel and drug 'medicine' and are obsessed with pumping vaccines in ever-increasing number into as many human arms and backsides as possible. John D. Rockefeller was the driving force behind the creation of the 'education' system in the United States and elsewhere specifically designed to program the perceptions of generations thereafter. The Rockefeller family donated exceptionally valuable land in New York for the United Nations building and were central in establishing the World Health Organization in 1948 as an agency of the UN which was created from the start as a Trojan horse and stalking horse for world government. Now enter Bill Gates. His family and the Rockefellers have long been extremely close and I have seen genealogy which claims that if you go back far enough the two families fuse into the same bloodline. Gates has said that the Bill and Melinda Gates Foundation was inspired by the Rockefeller Foundation and why not

when both are serving the same Cult? Major tax-exempt foundations are overwhelmingly criminal enterprises in which Cult assets fund the Cult agenda in the guise of 'philanthropy' while avoiding tax in the process. Cult operatives can become mega-rich in their role of front men and women for the psychopaths at the inner core and they, too, have to be psychopaths to knowingly serve such evil. Part of the deal is that a big percentage of the wealth gleaned from representing the Cult has to be spent advancing the ambitions of the Cult and hence you have the Rockefeller Foundation, Bill and Melinda Gates Foundation (and *so* many more) and people like George Soros with his global Open Society Foundations spending their billions in pursuit of global Cult control. Gates is a global public face of the Cult with his interventions in world affairs including Big Tech influence; a central role in the 'Covid' and 'vaccine' scam; promotion of the climate change shakedown; manipulation of education; geoengineering of the skies; and his food-control agenda as the biggest owner of farmland in America, his GMO promotion and through other means. As one writer said: 'Gates monopolizes or wields disproportionate influence over the tech industry, global health and vaccines, agriculture and food policy (including biopiracy and fake food), weather modification and other climate technologies, surveillance, education and media.' The almost limitless wealth secured through Microsoft and other not-allowed-to-fail ventures (including vaccines) has been ploughed into a long, long list of Cult projects designed to enslave the entire human race. Gates and the Rockefellers have been working as one unit with the Rockefeller-established World Health Organization leading global 'Covid' policy controlled by Gates through his mouth-piece Tedros. Gates became the WHO's biggest funder when Trump announced that the American government would cease its donations, but Biden immediately said he would restore the money when he took office in January, 2021. The Gates Foundation (the Cult) owns through limitless funding the world health system and the major players across the globe in the 'Covid' hoax.

Okay, with that background we return to that Rockefeller Foundation document of 2010 headed 'Scenarios for the Future of Technology and International Development' and its 'imaginary' epidemic of a virulent and deadly influenza strain which infected 20 percent of the global population and killed eight million in seven months. The Rockefeller scenario was that the epidemic destroyed economies, closed shops, offices and other businesses and led to governments imposing fierce rules and restrictions that included mandatory wearing of face masks and body-temperature checks to enter communal spaces like railway stations and supermarkets. The document predicted that even after the height of the Rockefeller-envisaged epidemic the authoritarian rule would continue to deal with further pandemics, transnational terrorism, environmental crises and rising poverty. Now you may think that the Rockefellers are our modern-day seers or alternatively, and rather more likely, that they well knew what was planned a few years further on. Fascism had to be imposed, you see, to 'protect citizens from risk and exposure'. The Rockefeller scenario document said:

During the pandemic, national leaders around the world flexed their authority and imposed airtight rules and restrictions, from the mandatory wearing of face masks to body-temperature checks at the entries to communal spaces like train stations and supermarkets. Even after the pandemic faded, this more authoritarian control and oversight of citizens and their activities stuck and even intensified. In order to protect themselves from the spread of increasingly global problems – from pandemics and transnational terrorism to environmental crises and rising poverty – leaders around the world took a firmer grip on power.

At first, the notion of a more controlled world gained wide acceptance and approval. Citizens willingly gave up some of their sovereignty – and their privacy – to more paternalistic states in exchange for greater safety and stability. Citizens were more tolerant, and even eager, for top-down direction and oversight, and national leaders had more latitude to impose order in the ways they saw fit.

In developed countries, this heightened oversight took many forms: biometric IDs for all citizens, for example, and tighter regulation of key industries whose stability was deemed vital to national interests. In many developed countries, enforced cooperation with a suite of new regulations and agreements slowly but steadily restored both order and, importantly, economic growth.

There we have the prophetic Rockefellers in 2010 and three years later came their paper for the Global Health Summit in Beijing, China, when government representatives, the private sector, international organisations and groups met to discuss the next 100 years of 'global health'. The Rockefeller Foundation-funded paper was called 'Dreaming the Future of Health for the Next 100 Years and more prophecy ensued as it described a dystopian future: 'The abundance of data, digitally tracking and linking people may mean the 'death of privacy' and may replace physical interaction with transient, virtual connection, generating isolation and raising questions of how values are shaped in virtual networks.' Next in the 'Covid' hoax preparation sequence came a 'table top' simulation in 2018 for another 'imaginary' pandemic of a disease called Clade X which was said to kill 900 million people. The exercise was organised by the Gates-funded Johns Hopkins University's Center for Health Security in the United States and this is the very same university that has been compiling the disgustingly and systematically erroneous global figures for 'Covid' cases and deaths. Similar Johns Hopkins health crisis scenarios have included the Dark Winter exercise in 2001 and Atlantic Storm in 2005.

Nostradamus 201

For sheer predictive genius look no further prophecy-watchers than the Bill Gates-funded Event 201 held only six weeks before the 'coronavirus pandemic' is supposed to have broken out in China and Event 201 was based on a scenario of a global 'coronavirus pandemic'. Melinda Gates, the great man's missus, told the BBC that he had 'prepared for years' for a coronavirus pandemic which told us what we already knew. Nostradamugates had predicted in a TED talk in 2015 that a pandemic was coming that would kill a lot of people and demolish the world economy. My god, the man is a machine – possibly even literally. Now here he was only weeks before the real thing funding just such a simulated scenario and involving his friends and associates at Johns Hopkins, the World Economic Forum Cult-front of Klaus Schwab, the United Nations,

Johnson & Johnson, major banks, and officials from China and the Centers for Disease Control in the United States. What synchronicity – Johns Hopkins would go on to compile the fraudulent 'Covid' figures, the World Economic Forum and Schwab would push the 'Great Reset' in response to 'Covid', the Centers for Disease Control would be at the forefront of 'Covid' policy in the United States, Johnson & Johnson would produce a 'Covid vaccine', and everything would officially start just weeks later in China. Spooky, eh? They were even accurate in creating a simulation of a 'virus' pandemic because the 'real thing' would also be a simulation. Event 201 was not an exercise preparing for something that might happen; it was a rehearsal for what those in control knew was *going* to happen and very shortly. Hours of this simulation were posted on the Internet and the various themes and responses mirrored what would soon be imposed to transform human society. News stories were inserted and what they said would be commonplace a few weeks later with still more prophecy perfection. Much discussion focused on the need to deal with misinformation and the 'anti-vax movement' which is exactly what happened when the 'virus' arrived – was said to have arrived – in the West.

Cult-owned social media banned criticism and exposure of the official 'virus' narrative and when I said there *was* no 'virus' in early April, 2020, I was banned by one platform after another including YouTube, Facebook and later Twitter. The mainstream broadcast media in Britain was in effect banned from interviewing me by the Tony-Blair-created government broadcasting censor Ofcom headed by career government bureaucrat Melanie Dawes who was appointed just as the 'virus' hoax was about to play out in January, 2020. At the same time the Ickonic media platform was using Vimeo, another ultra-Zionist-owned operation, while our own player was being created and they deleted in an instant hundreds of videos, documentaries, series and shows to confirm their unbelievable vindictiveness. We had copies, of course, and they had to be restored one by one when our player was ready. These people have no class. Sabbatian Facebook promised free advertisements for the Gates-

controlled World Health Organization narrative while deleting 'false claims and conspiracy theories' to stop 'misinformation' about the alleged coronavirus. All these responses could be seen just a short while earlier in the scenarios of Event 201. Extreme censorship was absolutely crucial for the Cult because the official story was so ridiculous and unsupportable by the evidence that it could never survive open debate and the free-flow of information and opinion. If you can't win a debate then don't have one is the Cult's approach throughout history. Facebook's little boy front man – front boy – Mark Zuckerberg equated 'credible and accurate information' with official sources and exposing their lies with 'misinformation'.

Silencing those that can see

The censorship dynamic of Event 201 is now the norm with an army of narrative-supporting 'fact-checker' organisations whose entire reason for being is to tell the public that official narratives are true and those exposing them are lying. One of the most appalling of these 'fact-checkers' is called NewsGuard founded by ultra-Zionist Americans Gordon Crovitz and Steven Brill. Crovitz is a former publisher of *The Wall Street Journal*, former Executive Vice President of Dow Jones, a member of the Council on Foreign Relations (CFR), and on the board of the American Association of Rhodes Scholars. The CFR and Rhodes Scholarships, named after Rothschild agent Cecil Rhodes who plundered the gold and diamonds of South Africa for his masters and the Cult, have featured widely in my books. NewsGuard don't seem to like me for some reason – I really can't think why – and they have done all they can to have me censored and discredited which is, to quote an old British politician, like being savaged by a dead sheep. They are, however, like all in the censorship network, very well connected and funded by organisations themselves funded by, or connected to, Bill Gates. As you would expect with anything associated with Gates NewsGuard has an offshoot called HealthGuard which 'fights online health care hoaxes'. How very kind. Somehow the NewsGuard European Managing Director Anna-Sophie Harling, a remarkably young-

looking woman with no broadcasting experience and little hands-on work in journalism, has somehow secured a position on the 'Content Board' of UK government broadcast censor Ofcom. An executive of an organisation seeking to discredit dissidents of the official narratives is making decisions for the government broadcast 'regulator' about content?? Another appalling 'fact-checker' is Full Fact funded by George Soros and global censors Google and Facebook.

It's amazing how many activists in the 'fact-checking', 'anti-hate', arena turn up in government-related positions – people like UK Labour Party activist Imran Ahmed who heads the Center for Countering Digital Hate founded by people like Morgan McSweeney, now chief of staff to the Labour Party's hapless and useless 'leader' Keir Starmer. Digital Hate – which is what it really is – uses the American spelling of Center to betray its connection to a transatlantic network of similar organisations which in 2020 shapeshifted from attacking people for 'hate' to attacking them for questioning the 'Covid' hoax and the dangers of the 'Covid vaccine'. It's just a coincidence, you understand. This is one of Imran Ahmed's hysterical statements: 'I would go beyond calling anti-vaxxers conspiracy theorists to say they are an extremist group that pose a national security risk.' No one could ever accuse this prat of understatement and he's including in that those parents who are now against vaccines after their children were damaged for life or killed by them. He's such a nice man. Ahmed does the rounds of the Woke media getting soft-ball questions from spineless 'journalists' who never ask what right he has to campaign to destroy the freedom of speech of others while he demands it for himself. There also seems to be an overrepresentation in Ofcom of people connected to the narrative-worshipping BBC. This incredible global network of narrative-support was super-vital when the 'Covid' hoax was played in the light of the mega-whopper lies that have to be defended from the spotlight cast by the most basic intelligence.

Setting the scene

The Cult plays the long game and proceeds step-by-step ensuring that everything is in place before major cards are played and they don't come any bigger than the 'Covid' hoax. The psychopaths can't handle events where the outcome isn't certain and as little as possible – preferably nothing – is left to chance. Politicians, government and medical officials who would follow direction were brought to illusory power in advance by the Cult web whether on the national stage or others like state governors and mayors of America. For decades the dynamic between officialdom, law enforcement and the public was changed from one of service to one of control and dictatorship. Behaviour manipulation networks established within government were waiting to impose the coming 'Covid' rules and regulations specifically designed to subdue and rewire the psyche of the people in the guise of protecting health. These included in the UK the Behavioural Insights Team part-owned by the British government Cabinet Office; the Scientific Pandemic Insights Group on Behaviours (SPI-B); and a whole web of intelligence and military groups seeking to direct the conversation on social media and control the narrative. Among them are the cyberwarfare (on the people) 77th Brigade of the British military which is also coordinated through the Cabinet Office as civilian and military leadership continues to combine in what they call the Fusion Doctrine. The 77th Brigade is a British equivalent of the infamous Israeli (Sabbatian) military cyberwarfare and Internet manipulation operation Unit 8200 which I expose at length in *The Trigger*. Also carefully in place were the medical and science advisers to government – many on the payroll past or present of Bill Gates – and a whole alternative structure of unelected government stood by to take control when elected parliaments were effectively closed down once the 'Covid' card was slammed on the table. The structure I have described here and so much more was installed in every major country through the Cult networks. The top-down control hierarchy looks like this: The Cult – Cult-owned Gates – the World Health Organization and Tedros – Gates-funded or controlled chief medical officers and science 'advisers' (dictators) in each country –

political 'leaders'– law enforcement – The People. Through this simple global communication and enforcement structure the policy of the Cult could be imposed on virtually the entire human population so long as they acquiesced to the fascism. With everything in place it was time for the button to be pressed in late 2019/early 2020.

These were the prime goals the Cult had to secure for its will to prevail:

1) Locking down economies, closing all but designated 'essential' businesses (Cult-owned corporations were 'essential'), and putting the population under house arrest was an imperative to destroy independent income and employment and ensure dependency on the Cult-controlled state in the Hunger Games Society. Lockdowns had to be established as the global blueprint from the start to respond to the 'virus' and followed by pretty much the entire world.

2) The global population had to be terrified into believing in a deadly 'virus' that didn't actually exist so they would unquestioningly obey authority in the belief that authority must know how best to protect them and their families. Software salesman Gates would suddenly morph into the world's health expert and be promoted as such by the Cult-owned media.

3) A method of testing that wasn't testing for the 'virus', but was only claimed to be, had to be in place to provide the illusion of 'cases' and subsequent 'deaths' that had a very different cause to the 'Covid-19' that would be scribbled on the death certificate.

4) Because there was no 'virus' and the great majority testing positive with a test not testing for the 'virus' would have no symptoms of anything the lie had to be sold that people without symptoms (without the 'virus') could still pass it on to others. This was crucial to justify for the first time quarantining – house arresting – healthy people. Without this the economy-destroying lockdown of *everybody* could not have been credibly sold.

5) The 'saviour' had to be seen as a vaccine which beyond evil drug companies were working like angels of mercy to develop as quickly as possible, with all corners cut, to save the day. The public must absolutely not know that the 'vaccine' had nothing to do with a 'virus' or that the contents were ready and waiting with a very different motive long before the 'Covid' card was even lifted from the pack.

I said in March, 2020, that the 'vaccine' would have been created way ahead of the 'Covid' hoax which justified its use and the following December an article in the New York *Intelligencer* magazine said the Moderna 'vaccine' had been 'designed' by

January, 2020. This was 'before China had even acknowledged that the disease could be transmitted from human to human, more than a week before the first confirmed coronavirus case in the United States'. The article said that by the time the first American death was announced a month later 'the vaccine had already been manufactured and shipped to the National Institutes of Health for the beginning of its Phase I clinical trial'. The 'vaccine' was actually 'designed' long before that although even with this timescale you would expect the article to ask how on earth it could have been done that quickly. Instead it asked why the 'vaccine' had not been rolled out then and not months later. Journalism in the mainstream is truly dead. I am going to detail in the next chapter why the 'virus' has never existed and how a hoax on that scale was possible, but first the foundation on which the Big Lie of 'Covid' was built.

The test that doesn't test

Fraudulent 'testing' is the bottom line of the whole 'Covid' hoax and was the means by which a 'virus' that did not exist *appeared* to exist. They could only achieve this magic trick by using a test not testing for the 'virus'. To use a test that *was* testing for the 'virus' would mean that every test would come back negative given there was no 'virus'. They chose to exploit something called the RT-PCR test invented by American biochemist Kary Mullis in the 1980s who said publicly that his PCR test … *cannot detect infectious disease*. Yes, the 'test' used worldwide to detect infectious 'Covid' to produce all the illusory 'cases' and 'deaths' compiled by Johns Hopkins and others *cannot detect infectious disease*. This fact came from the mouth of the man who invented PCR and was awarded the Nobel Prize in Chemistry in 1993 for doing so. Sadly, and incredibly conveniently for the Cult, Mullis died in August, 2019, at the age of 74 just before his test would be fraudulently used to unleash fascism on the world. He was said to have died from pneumonia which was an irony in itself. A few months later he would have had 'Covid-19' on his death certificate. I say the timing of his death was convenient because had he lived Mullis, a brilliant, honest and decent man, would have been

vociferously speaking out against the use of his test to detect 'Covid' when it was never designed, or able, to do that. I know that to be true given that Mullis made the same point when his test was used to 'detect' – not detect – HIV. He had been seriously critical of the Gallo/Montagnier claim to have isolated the HIV 'virus' and shown it to cause AIDS for which Mullis said there was no evidence. AIDS is actually not a disease but a series of diseases from which people die all the time. When they die from those *same diseases* after a positive 'test' for HIV then AIDS goes on their death certificate. I think I've heard that before somewhere. Countries instigated a policy with 'Covid' that anyone who tested positive with a test not testing for the 'virus' and died of any other cause within 28 days and even longer 'Covid-19' had to go on the death certificate. Cases have come from the test that can't test for infectious disease and the deaths are those who have died of *anything* after testing positive with a test not testing for the 'virus'. I'll have much more later about the death certificate scandal.

Mullis was deeply dismissive of the now US 'Covid' star Anthony Fauci who he said was a liar who didn't know anything about anything – 'and I would say that to his face – nothing.' He said of Fauci: 'The man thinks he can take a blood sample, put it in an electron microscope and if it's got a virus in there you'll know it – he doesn't understand electron microscopy and he doesn't understand medicine and shouldn't be in a position like he's in.' That position, terrifyingly, has made him the decider of 'Covid' fascism policy on behalf of the Cult in his role as director since 1984 of the National Institute of Allergy and Infectious Diseases (NIAID) while his record of being wrong is laughable; but being wrong, so long as it's the *right kind* of wrong, is why the Cult loves him. He'll say anything the Cult tells him to say. Fauci was made Chief Medical Adviser to the President immediately Biden took office. Biden was installed in the White House by Cult manipulation and one of his first decisions was to elevate Fauci to a position of even more control. This is a coincidence? Yes, and I identify as a flamenco dancer called Lola. How does such an incompetent criminal like Fauci remain in that

pivotal position in American health since *the 1980s*? When you serve the Cult it looks after you until you are surplus to requirements. Kary Mullis said prophetically of Fauci and his like: 'Those guys have an agenda and it's not an agenda we would like them to have … they make their own rules, they change them when they want to, and Tony Fauci does not mind going on television in front of the people who pay his salary and lie directly into the camera.' Fauci has done that almost daily since the 'Covid' hoax began. Lying is in Fauci's DNA. To make the situation crystal clear about the PCR test this is a direct quote from its inventor Kary Mullis:

> It [the PCR test] doesn't tell you that you're sick and doesn't tell you that the thing you ended up with was really going to hurt you ...'

Ask yourself why governments and medical systems the world over have been using this very test to decide who is 'infected' with the SARS-CoV-2 'virus' and the alleged disease it allegedly causes, 'Covid-19'. The answer to that question will tell you what has been going on. By the way, here's a little show-stopper – the 'new' SARS-CoV-2 'virus' was 'identified' as such right from the start using … *the PCR test not testing for the 'virus'*. If you are new to this and find that shocking then stick around. I have hardly started yet. Even worse, other 'tests', like the 'Lateral Flow Device' (LFD), are considered so useless that they have to be *confirmed* by the PCR test! Leaked emails written by Ben Dyson, adviser to UK 'Health' Secretary Matt Hancock, said they were 'dangerously unreliable'. Dyson, executive director of strategy at the Department of Health, wrote: 'As of today, someone who gets a positive LFD result in (say) London has at best a 25 per cent chance of it being a true positive, but if it is a self-reported test potentially as low as 10 per cent (on an optimistic assumption about specificity) or as low as 2 per cent (on a more pessimistic assumption).' These are the 'tests' that schoolchildren and the public are being urged to have twice a week or more and have to isolate if they get a positive. Each fake positive goes in the statistics as a 'case' no matter how ludicrously inaccurate and the

'cases' drive lockdown, masks and the pressure to 'vaccinate'. The government said in response to the email leak that the 'tests' were accurate which confirmed yet again what shocking bloody liars they are. The real false positive rate is *100 percent* as we'll see. In another 'you couldn't make it up' the UK government agreed to pay £2.8 billion to California's Innova Medical Group to supply the irrelevant lateral flow tests. The company's primary test-making centre is in China. Innova Medical Group, established in March, 2020, is owned by Pasaca Capital Inc, chaired by Chinese-American millionaire Charles Huang who was born in Wuhan.

How it works – and how it doesn't

The RT-PCR test, known by its full title of Polymerase chain reaction, is used across the world to make millions, even billions, of copies of a DNA/RNA genetic information sample. The process is called 'amplification' and means that a tiny sample of genetic material is amplified to bring out the detailed content. I stress that it is not testing for an infectious disease. It is simply amplifying a sample of genetic material. In the words of Kary Mullis: 'PCR is … just a process that's used to make a whole lot of something out of something.' To emphasise the point companies that make the PCR tests circulated around the world to 'test' for 'Covid' warn on the box that it can't be used to detect 'Covid' or infectious disease and is for research purposes only. It's okay, rest for a minute and you'll be fine. This is the test that produces the 'cases' and 'deaths' that have been used to destroy human society. All those global and national medical and scientific 'experts' demanding this destruction to 'save us' *KNOW* that the test is not testing for the 'virus' and the cases and deaths they claim to be real are an almost unimaginable fraud. Every one of them and so many others including politicians and psychopaths like Gates and Tedros must be brought before Nuremburg-type trials and jailed for the rest of their lives. The more the genetic sample is amplified by PCR the more elements of that material become sensitive to the test and by that I don't mean sensitive for a 'virus' but for elements of the genetic material which

is *naturally* in the body or relates to remnants of old conditions of various kinds lying dormant and causing no disease. Once the amplification of the PCR reaches a certain level *everyone* will test positive. So much of the material has been made sensitive to the test that everyone will have some part of it in their body. Even lying criminals like Fauci have said that once PCR amplifications pass 35 cycles everything will be a false positive that cannot be trusted for the reasons I have described. I say, like many proper doctors and scientists, that 100 percent of the 'positives' are false, but let's just go with Fauci for a moment.

He says that any amplification over 35 cycles will produce false positives and yet the US Centers for Disease Control (CDC) and Food and Drug Administration (FDA) have recommended up to *40 cycles* and the National Health Service (NHS) in Britain admitted in an internal document for staff that it was using *45 cycles* of amplification. A long list of other countries has been doing the same and at least one 'testing' laboratory has been using *50 cycles*. Have you ever heard a doctor, medical 'expert' or the media ask what level of amplification has been used to claim a 'positive'. The 'test' comes back 'positive' and so you have the 'virus', end of story. Now we can see how the government in Tanzania could send off samples from a goat and a pawpaw fruit under human names and both came back positive for 'Covid-19'. Tanzania president John Magufuli mocked the 'Covid' hysteria, the PCR test and masks and refused to import the DNA-manipulating 'vaccine'. The Cult hated him and an article sponsored by the Bill Gates Foundation appeared in the London *Guardian* in February, 2021, headed 'It's time for Africa to rein in Tanzania's anti-vaxxer president'. Well, 'reined in' he shortly was. Magufuli appeared in good health, but then, in March, 2021, he was dead at 61 from 'heart failure'. He was replaced by Samia Hassan Suhulu who is connected to Klaus Schwab's World Economic Forum and she immediately reversed Magufuli's 'Covid' policy. A sample of cola tested positive for 'Covid' with the PCR test in Germany while American actress and singer-songwriter Erykah Badu tested positive in one nostril and negative in the other. Footballer Ronaldo called

the PCR test 'bullshit' after testing positive three times and being forced to quarantine and miss matches when there was nothing wrong with him. The mantra from Tedros at the World Health Organization and national governments (same thing) has been test, test, test. They know that the more tests they can generate the more fake 'cases' they have which go on to become 'deaths' in ways I am coming to. The UK government has its Operation Moonshot planned to test multiple millions every day in workplaces and schools with free tests for everyone to use twice a week at home in line with the Cult plan from the start to make testing part of life. A government advertisement for an 'Interim Head of Asymptomatic Testing Communication' said the job included responsibility for delivering a 'communications strategy' (propaganda) 'to support the expansion of asymptomatic testing that *'normalises testing as part of everyday life*'. More tests means more fake 'cases', 'deaths' and fascism. I have heard of, and from, many people who booked a test, couldn't turn up, and yet got a positive result through the post for a test they'd never even had. The whole thing is crazy, but for the Cult there's method in the madness. Controlling and manipulating the level of amplification of the test means the authorities can control whenever they want the number of apparent 'cases' and 'deaths'. If they want to justify more fascist lockdown and destruction of livelihoods they keep the amplification high. If they want to give the illusion that lockdowns and the 'vaccine' are working then they lower the amplification and 'cases' and 'deaths' will appear to fall. In January, 2021, the Cult-owned World Health Organization suddenly warned laboratories about over-amplification of the test and to lower the threshold. Suddenly headlines began appearing such as: 'Why ARE "Covid" cases plummeting?' This was just when the vaccine rollout was underway and I had predicted months before they would make cases appear to fall through amplification tampering when the 'vaccine' came. These people are so predictable.

Cow vaccines?

The question must be asked of what is on the test swabs being poked far up the nose of the population to the base of the brain? A nasal swab punctured one woman's brain and caused it to leak fluid. Most of these procedures are being done by people with little training or medical knowledge. Dr Lorraine Day, former orthopaedic trauma surgeon and Chief of Orthopaedic Surgery at San Francisco General Hospital, says the tests are really a *'vaccine'*. Cows have long been vaccinated this way. She points out that masks have to cover the nose and the mouth where it is claimed the 'virus' exists in saliva. Why then don't they take saliva from the mouth as they do with a DNA test instead of pushing a long swab up the nose towards the brain? The ethmoid bone separates the nasal cavity from the brain and within that bone is the cribriform plate. Dr Day says that when the swab is pushed up against this plate and twisted the procedure is 'depositing things back there'. She claims that among these 'things' are nanoparticles that can enter the brain. Researchers have noted that a team at the Gates-funded Johns Hopkins have designed tiny, star-shaped micro-devices that can latch onto intestinal mucosa and release drugs into the body. Mucosa is the thin skin that covers the inside surface of parts of the body such as *the nose* and mouth and produces mucus to protect them. The Johns Hopkins micro-devices are called 'theragrippers' and were 'inspired' by a parasitic worm that digs its sharp teeth into a host's intestines. Nasal swabs are also coated in the sterilisation agent ethylene oxide. The US National Cancer Institute posts this explanation on its website:

> At room temperature, ethylene oxide is a flammable colorless gas with a sweet odor. It is used primarily to produce other chemicals, including antifreeze. In smaller amounts, ethylene oxide is used as a pesticide and a sterilizing agent. The ability of ethylene oxide to damage DNA makes it an effective sterilizing agent but also accounts for its cancer-causing activity.

The Institute mentions lymphoma and leukaemia as cancers most frequently reported to be associated with occupational exposure to ethylene oxide along with stomach and breast cancers. How does anyone think this is going to work out with the constant testing

regime being inflicted on adults and children at home and at school that will accumulate in the body anything that's on the swab?

Doctors know best

It is vital for people to realise that 'hero' doctors 'know' only what the Big Pharma-dominated medical authorities tell them to 'know' and if they refuse to 'know' what they are told to 'know' they are out the door. They are mostly not physicians or healers, but repeaters of the official narrative – or else. I have seen alleged professional doctors on British television make shocking statements that we are supposed to take seriously. One called 'Dr' Amir Khan, who is actually telling patients how to respond to illness, said that men could take the birth pill to 'help slow down the effects of Covid-19'. In March, 2021, another ridiculous 'Covid study' by an American doctor proposed injecting men with the female sex hormone progesterone as a 'Covid' treatment. British doctor Nighat Arif told the BBC that face coverings were now going to be part of ongoing normal. Yes, the vaccine protects you, she said (evidence?) … but the way to deal with viruses in the community was always going to come down to hand washing, face covering and keeping a physical distance. That's not what we were told before the 'vaccine' was circulating. Arif said she couldn't imagine ever again going on the underground or in a lift without a mask. I was just thanking my good luck that she was not my doctor when she said – in March, 2021 – that if 'we are *behaving* and we are doing all the right things' she thought we could 'have our nearest and dearest around us at home … around *Christmas* and N*ew Year!* Her patronising delivery was the usual school teacher talking to six-year-olds as she repeated every government talking point and probably believed them all. If we have learned anything from the 'Covid' experience surely it must be that humanity's perception of doctors needs a fundamental rethink. NHS 'doctor' Sara Kayat told her television audience that the 'Covid vaccine' would '100 percent prevent hospitalisation and death'. Not even Big Pharma claimed that. We have to stop taking 'experts' at their word without question when so many of them are

clueless and only repeating the party line on which their careers depend. That is not to say there are not brilliants doctors – there are and I have spoken to many of them since all this began – but you won't see them in the mainstream media or quoted by the psychopaths and yes-people in government.

Remember the name – Christian Drosten

German virologist Christian Drosten, Director of Charité Institute of Virology in Berlin, became a national star after the pandemic hoax began. He was feted on television and advised the German government on 'Covid' policy. Most importantly to the wider world Drosten led a group that produced the 'Covid' testing protocol for the PCR test. What a remarkable feat given the PCR cannot test for infectious disease and even more so when you think that Drosten said that his method of testing for SARS-CoV-2 was developed 'without having virus material available'. *He developed a test for a 'virus' that he didn't have and had never seen*. Let that sink in as you survey the global devastation that came from what he did. The whole catastrophe of Drosten's 'test' was based on the alleged genetic sequence published by Chinese scientists on the Internet. We will see in the next chapter that this alleged 'genetic sequence' has never been produced by China or anyone and cannot be when there *is no* SARS-CoV-2. Drosten, however, doesn't seem to let little details like that get in the way. He was the lead author with Victor Corman from the same Charité Hospital of the paper 'Detection of 2019 novel coronavirus (2019-nCoV) by real-time PCR' published in a magazine called *Eurosurveillance*. This became known as the Corman-Drosten paper. In November, 2020, with human society devastated by the effects of the Corman-Drosten test baloney, the protocol was publicly challenged by 22 international scientists and independent researchers from Europe, the United States, and Japan. Among them were senior molecular geneticists, biochemists, immunologists, and microbiologists. They produced a document headed 'External peer review of the RTPCR test to detect SARS-Cov-2 Reveals 10 Major Flaws At The Molecular and Methodological Level: Consequences

For False-Positive Results'. The flaws in the Corman-Drosten test included the following:

- The test is non-specific because of erroneous design
- Results are enormously variable
- The test is unable to discriminate between the whole 'virus' and viral fragments
- It doesn't have positive or negative controls
- The test lacks a standard operating procedure
- It is unsupported by proper peer view

The scientists said the PCR 'Covid' testing protocol was not founded on science and they demanded the Corman-Drosten paper be retracted by *Eurosurveillance*. They said all present and previous Covid deaths, cases, and 'infection rates' should be subject to a massive retroactive inquiry. Lockdowns and travel restrictions should be reviewed and relaxed and those diagnosed through PCR to have 'Covid-19' should not be forced to isolate. Dr Kevin Corbett, a health researcher and nurse educator with a long academic career producing a stream of peer-reviewed publications at many UK universities, made the same point about the PCR test debacle. He said of the scientists' conclusions: 'Every scientific rationale for the development of that test has been totally destroyed by this paper. It's like Hiroshima/Nagasaki to the Covid test.' He said that China hadn't given them an isolated 'virus' when Drosten developed the test. Instead they had developed the test from *a sequence in a gene bank*.' Put another way … *they made it up*! The scientists were supported in this contention by a Portuguese appeals court which ruled in November, 2020, that PCR tests are unreliable and it is unlawful to quarantine people based solely on a PCR test. The point about China not providing an isolated virus must be true when the 'virus' has never been isolated to this day and the consequences of that will become clear. Drosten and company produced this useless 'protocol' right on cue in January, 2020, just as the 'virus' was said to

be moving westward and it somehow managed to successfully pass a peer-review in 24 hours. In other words there was no peer-review for a test that would be used to decide who had 'Covid' and who didn't across the world. The Cult-created, Gates-controlled World Health Organization immediately recommended all its nearly 200 member countries to use the Drosten PCR protocol to detect 'cases' and 'deaths'. The sting was underway and it continues to this day.

So who is this Christian Drosten that produced the means through which death, destruction and economic catastrophe would be justified? His education background, including his doctoral thesis, would appear to be somewhat shrouded in mystery and his track record is dire as with another essential player in the 'Covid' hoax, the Gates-funded Professor Neil Ferguson at the Gates-funded Imperial College in London of whom more shortly. Drosten predicted in 2003 that the alleged original SARS 'virus' (SARS-1') was an epidemic that could have serious effects on economies and an effective vaccine would take at least two years to produce. Drosten's answer to every alleged 'outbreak' is a vaccine which you won't be shocked to know. What followed were just 774 official deaths worldwide and none in Germany where there were only nine cases. That is even if you believe there ever was a SARS 'virus' when the evidence is zilch and I will expand on this in the next chapter. Drosten claims to be co-discoverer of 'SARS-1' and developed a test for it in 2003. He was screaming warnings about 'swine flu' in 2009 and how it was a widespread infection far more severe than any dangers from a vaccine could be and people should get vaccinated. It would be helpful for Drosten's vocal chords if he simply recorded the words 'the virus is deadly and you need to get vaccinated' and copies could be handed out whenever the latest made-up threat comes along. Drosten's swine flu epidemic never happened, but Big Pharma didn't mind with governments spending hundreds of millions on vaccines that hardly anyone bothered to use and many who did wished they hadn't. A study in 2010 revealed that the risk of dying from swine flu, or H1N1, was no higher than that of the annual seasonal flu which is what at least most of 'it' really was as in

the case of 'Covid-19'. A media investigation into Drosten asked how with such a record of inaccuracy he could be *the* government adviser on these issues. The answer to that question is the same with Drosten, Ferguson and Fauci – they keep on giving the authorities the 'conclusions' and 'advice' they want to hear. Drosten certainly produced the goods for them in January, 2020, with his PCR protocol garbage and provided the foundation of what German internal medicine specialist Dr Claus Köhnlein, co-author of *Virus Mania*, called the 'test pandemic'. The 22 scientists in the *Eurosurveillance* challenge called out conflicts of interest within the Drosten 'protocol' group and with good reason. Olfert Landt, a regular co-author of Drosten 'studies', owns the biotech company TIB Molbiol Syntheselabor GmbH in Berlin which manufactures and sells the tests that Drosten and his mates come up with. They have done this with SARS, Enterotoxigenic E. coli (ETEC), MERS, Zika 'virus', yellow fever, and now 'Covid'. Landt told the *Berliner Zeitung* newspaper:

> The testing, design and development came from the Charité [Drosten and Corman]. We simply implemented it immediately in the form of a kit. And if we don't have the virus, which originally only existed in Wuhan, we can make a synthetic gene to simulate the genome of the virus. That's what we did very quickly.

This is more confirmation that the Drosten test was designed without access to the 'virus' and only a synthetic simulation which is what SARS-CoV-2 really is – a computer-generated synthetic fiction. It's quite an enterprise they have going here. A Drosten team decides what the test for something should be and Landt's biotech company flogs it to governments and medical systems across the world. His company must have made an absolute fortune since the 'Covid' hoax began. Dr Reiner Fuellmich, a prominent German consumer protection trial lawyer in Germany and California, is on Drosten's case and that of Tedros at the World Health Organization for crimes against humanity with a class-action lawsuit being prepared in the United States and other legal action in Germany.

Why China?

Scamming the world with a 'virus' that doesn't exist would seem impossible on the face of it, but not if you have control of the relatively few people that make policy decisions and the great majority of the global media. Remember it's not about changing 'real' reality it's about controlling *perception* of reality. You don't have to make something happen you only have make people *believe* that it's happening. Renegade Minds understand this and are therefore much harder to swindle. 'Covid-19' is not a 'real' 'virus'. It's a mind virus, like a computer virus, which has infected the minds, not the bodies, of billions. It all started, publically at least, in China and that alone is of central significance. The Cult was behind the revolution led by its asset Mao Zedong, or Chairman Mao, which established the People's Republic of China on October 1st, 1949. It should have been called The Cult's Republic of China, but the name had to reflect the recurring illusion that vicious dictatorships are run by and for the people (see all the 'Democratic Republics' controlled by tyrants). In the same way we have the 'Biden' Democratic Republic of America officially ruled by a puppet tyrant (at least temporarily) on behalf of Cult tyrants. The creation of Mao's merciless communist/fascist dictatorship was part of a frenzy of activity by the Cult at the conclusion of World War Two which, like the First World War, it had instigated through its assets in Germany, Britain, France, the United States and elsewhere. Israel was formed in 1948; the Soviet Union expanded its 'Iron Curtain' control, influence and military power with the Warsaw Pact communist alliance in 1955; the United Nations was formed in 1945 as a Cult precursor to world government; and a long list of world bodies would be established including the World Health Organization (1948), World Trade Organization (1948 under another name until 1995), International Monetary Fund (1945) and World Bank (1944). Human society was redrawn and hugely centralised in the global Problem-Reaction-Solution that was World War Two. All these changes were significant. Israel would become the headquarters of the Sabbatians

and the revolution in China would prepare the ground and control system for the events of 2019/2020.

Renegade Minds know there are no borders except for public consumption. The Cult is a seamless, borderless global entity and to understand the game we need to put aside labels like borders, nations, countries, communism, fascism and democracy. These delude the population into believing that countries are ruled within their borders by a government of whatever shade when these are mere agencies of a global power. America's illusion of democracy and China's communism/fascism are subsidiaries – vehicles – for the same agenda. We may hear about conflict and competition between America and China and on the lower levels that will be true; but at the Cult level they are branches of the same company in the way of the McDonald's example I gave earlier. I have tracked in the books over the years support by US governments of both parties for Chinese Communist Party infiltration of American society through allowing the sale of land, even military facilities, and the acquisition of American business and university influence. All this is underpinned by the infamous stealing of intellectual property and technological know-how. Cult-owned Silicon Valley corporations waive their fraudulent 'morality' to do business with human-rights-free China; Cult-controlled Disney has become China's PR department; and China in effect owns 'American' sports such as basketball which depends for much of its income on Chinese audiences. As a result any sports player, coach or official speaking out against China's horrific human rights record is immediately condemned or fired by the China-worshipping National Basketball Association. One of the first acts of China-controlled Biden was to issue an executive order telling federal agencies to stop making references to the 'virus' by the 'geographic location of its origin'. Long-time Congressman Jerry Nadler warned that criticising China, America's biggest rival, leads to hate crimes against Asian people in the United States. So shut up you bigot. China is fast closing in on Israel as a country that must not be criticised which is apt, really, given that Sabbatians control them both. The two countries have

developed close economic, military, technological and strategic ties which include involvement in China's 'Silk Road' transport and economic initiative to connect China with Europe. Israel was the first country in the Middle East to recognise the establishment of Mao's tyranny in 1950 months after it was established.

Project Wuhan – the 'Covid' Psyop

I emphasise again that the Cult plays the long game and what is happening to the world today is the result of centuries of calculated manipulation following a script to take control step-by-step of every aspect of human society. I will discuss later the common force behind all this that has spanned those centuries and thousands of years if the truth be told. Instigating the Mao revolution in China in 1949 with a 2020 'pandemic' in mind is not only how they work – the 71 years between them is really quite short by the Cult's standards of manipulation preparation. The reason for the Cult's Chinese revolution was to create a fiercely-controlled environment within which an extreme structure for human control could be incubated to eventually be unleashed across the world. We have seen this happen since the 'pandemic' emerged from China with the Chinese control-structure founded on AI technology and tyrannical enforcement sweep across the West. Until the moment when the Cult went for broke in the West and put its fascism on public display Western governments had to pay some lip-service to freedom and democracy to not alert too many people to the tyranny-in-the-making. Freedoms were more subtly eroded and power centralised with covert government structures put in place waiting for the arrival of 2020 when that smokescreen of 'freedom' could be dispensed with. The West was not able to move towards tyranny before 2020 anything like as fast as China which was created as a tyranny and had no limits on how fast it could construct the Cult's blueprint for global control. When the time came to impose that structure on the world it was the same Cult-owned Chinese communist/fascist government that provided the excuse – the 'Covid pandemic'. It was absolutely crucial to the Cult plan for the Chinese response to the 'pandemic' –

draconian lockdowns of the entire population – to become the blueprint that Western countries would follow to destroy the livelihoods and freedom of their people. This is why the Cult-owned, Gates-owned, WHO Director-General Tedros said early on:

The Chinese government is to be congratulated for the extraordinary measures it has taken to contain the outbreak. China is actually setting a new standard for outbreak response and it is not an exaggeration.

Forbes magazine said of China: '… those measures protected untold millions from getting the disease'. The Rockefeller Foundation 'epidemic scenario' document in 2010 said 'prophetically':

However, a few countries did fare better – China in particular. The Chinese government's quick imposition and enforcement of mandatory quarantine for all citizens, as well as its instant and near-hermetic sealing off of all borders, saved millions of lives, stopping the spread of the virus far earlier than in other countries and enabling a swifter post-pandemic recovery.

Once again – *spooky*.

The first official story was the 'bat theory' or rather the bat diversion. The source of the 'virus outbreak' we were told was a ''wet market' in Wuhan where bats and other animals are bought and eaten in horrifically unhygienic conditions. Then another story emerged through the alternative media that the 'virus' had been released on purpose or by accident from a BSL-4 (biosafety level 4) laboratory in Wuhan not far from the wet market. The lab was reported to create and work with lethal concoctions and bioweapons. Biosafety level 4 is the highest in the World Health Organization system of safety and containment. Renegade Minds are aware of what I call designer manipulation. The ideal for the Cult is for people to buy its prime narrative which in the opening salvoes of the 'pandemic' was the wet market story. It knows, however, that there is now a considerable worldwide alternative media of researchers sceptical of anything governments say and they are often given a version of events in a form they can perceive as credible while misdirecting them from the real truth. In this case let them

think that the conspiracy involved is a 'bioweapon virus' released from the Wuhan lab to keep them from the real conspiracy – *there is no 'virus'*. The WHO's current position on the source of the outbreak at the time of writing appears to be: 'We haven't got a clue, mate.' This is a good position to maintain mystery and bewilderment. The inner circle will know where the 'virus' came from – *nowhere*. The bottom line was to ensure the public believed there *was* a 'virus' and it didn't much matter if they thought it was natural or had been released from a lab. The belief that there was a 'deadly virus' was all that was needed to trigger global panic and fear. The population was terrified into handing their power to authority and doing what they were told. They had to or they were 'all gonna die'.

In March, 2020, information began to come my way from real doctors and scientists and my own additional research which had my intuition screaming: 'Yes, that's it! *There is no virus*.' The 'bioweapon' was not the 'virus'; it was the *'vaccine'* already being talked about that would be the bioweapon. My conclusion was further enhanced by happenings in Wuhan. The 'virus' was said to be sweeping the city and news footage circulated of people collapsing in the street (which they've never done in the West with the same 'virus'). The Chinese government was building 'new hospitals' in a matter of ten days to 'cope with demand' such was the virulent nature of the 'virus'. Yet in what seemed like no time the 'new hospitals' closed – even if they even opened – and China declared itself 'virus-free'. It was back to business as usual. This was more propaganda to promote the Chinese draconian lockdowns in the West as the way to 'beat the virus'. Trouble was that we subsequently had lockdown after lockdown, but never business as usual. As the people of the West and most of the rest of the world were caught in an ever-worsening spiral of lockdown, social distancing, masks, isolated old people, families forced apart, and livelihood destruction, it was party-time in Wuhan. Pictures emerged of thousands of people enjoying pool parties and concerts. It made no sense until you realised there never was a 'virus' and the

whole thing was a Cult set-up to transform human society out of one its major global strongholds – China.

How is it possible to deceive virtually the entire world population into believing there is a deadly virus when there is not even a 'virus' let alone a deadly one? It's nothing like as difficult as you would think and that's clearly true because it happened.

Postscript: See end of book Postscript for more on the 'Wuhan lab virus release' story which the authorities and media were pushing heavily in the summer of 2021 to divert attention from the truth that the 'Covid virus' is pure invention.

CHAPTER FIVE

There *is no* 'virus'

You can fool some of the people all of the time, and all of the people some of the time, but you cannot fool all of the people all of the time
Abraham Lincoln

The greatest form of mind control is repetition. The more you repeat the same mantra of alleged 'facts' the more will accept them to be true. It becomes an 'everyone knows that, mate'. If you can also censor any other version or alternative to your alleged 'facts' you are pretty much home and cooking.

By the start of 2020 the Cult owned the global mainstream media almost in its entirety to spew out its 'Covid' propaganda and ignore or discredit any other information and view. Cult-owned social media platforms in Cult-owned Silicon Valley were poised and ready to unleash a campaign of ferocious censorship to obliterate all but the official narrative. To complete the circle many demands for censorship by Silicon Valley were led by the mainstream media as 'journalists' became full-out enforcers for the Cult both as propagandists and censors. Part of this has been the influx of young people straight out of university who have become 'journalists' in significant positions. They have no experience and a headful of programmed perceptions from their years at school and university at a time when today's young are the most perceptually-targeted generations in known human history given the insidious impact of technology. They enter the media perceptually prepared and ready to repeat the narratives of the system that programmed them to

repeat its narratives. The BBC has a truly pathetic 'specialist disinformation reporter' called Marianna Spring who fits this bill perfectly. She is clueless about the world, how it works and what is really going on. Her role is to discredit anyone doing the job that a proper journalist would do and system-serving hacks like Spring wouldn't dare to do or even see the need to do. They are too busy licking the arse of authority which can never be wrong and, in the case of the BBC propaganda programme, *Panorama*, contacting payments systems such as PayPal to have a donations page taken down for a film company making documentaries questioning vaccines. Even the BBC soap opera *EastEnders* included a disgracefully biased scene in which an inarticulate white working class woman was made to look foolish for questioning the 'vaccine' while a well-spoken black man and Asian woman promoted the government narrative. It ticked every BBC box and the fact that the black and minority community was resisting the 'vaccine' had nothing to do with the way the scene was written. The BBC has become a disgusting tyrannical propaganda and censorship operation that should be defunded and disbanded and a free media take its place with a brief to stop censorship instead of demanding it. A BBC 'interview' with Gates goes something like: 'Mr Gates, sir, if I can call you sir, would you like to tell our audience why you are such a great man, a wonderful humanitarian philanthropist, and why you should absolutely be allowed as a software salesman to decide health policy for approaching eight billion people? Thank you, sir, please sir.' Propaganda programming has been incessant and merciless and when all you hear is the same story from the media, repeated by those around you who have only heard the same story, is it any wonder that people on a grand scale believe absolute mendacious garbage to be true? You are about to see, too, why this level of information control is necessary when the official 'Covid' narrative is so nonsensical and unsupportable by the evidence.

Structure of Deceit

The pyramid structure through which the 'Covid' hoax has been manifested is very simple and has to be to work. As few people as possible have to be involved with full knowledge of what they are doing – and why – or the real story would get out. At the top of the pyramid are the inner core of the Cult which controls Bill Gates who, in turn, controls the World Health Organization through his pivotal funding and his puppet Director-General mouthpiece, Tedros. Before he was appointed Tedros was chair of the Gates-founded Global Fund to 'fight against AIDS, tuberculosis and malaria', a board member of the Gates-funded 'vaccine alliance' GAVI, and on the board of another Gates-funded organisation. Gates owns him and picked him for a specific reason – Tedros is a crook and worse. 'Dr' Tedros (he's not a medical doctor, the first WHO chief not to be) was a member of the tyrannical Marxist government of Ethiopia for decades with all its human rights abuses. He has faced allegations of corruption and misappropriation of funds and was exposed three times for covering up cholera epidemics while Ethiopia's health minister. Tedros appointed the mass-murdering genocidal Zimbabwe dictator Robert Mugabe as a WHO goodwill ambassador for public health which, as with Tedros, is like appointing a psychopath to run a peace and love campaign. The move was so ridiculous that he had to drop Mugabe in the face of widespread condemnation. American economist David Steinman, a Nobel peace prize nominee, lodged a complaint with the International Criminal Court in The Hague over alleged genocide by Tedros when he was Ethiopia's foreign minister. Steinman says Tedros was a 'crucial decision maker' who directed the actions of Ethiopia's security forces from 2013 to 2015 and one of three officials in charge when those security services embarked on the 'killing' and 'torturing' of Ethiopians. You can see where Tedros is coming from and it's sobering to think that he has been the vehicle for Gates and the Cult to direct the global response to 'Covid'. Think about that. A psychopathic Cult dictates to psychopath Gates who dictates to psychopath Tedros who dictates how countries of the world must respond to a 'Covid virus' never scientifically shown to exist. At the same time psychopathic Cult-owned Silicon Valley information

giants like Google, YouTube, Facebook and Twitter announced very early on that they would give the Cult/Gates/Tedros/WHO version of the narrative free advertising and censor those who challenged their intelligence-insulting, mendacious story.

The next layer in the global 'medical' structure below the Cult, Gates and Tedros are the chief medical officers and science 'advisers' in each of the WHO member countries which means virtually all of them. Medical officers and arbiters of science (they're not) then take the WHO policy and recommended responses and impose them on their country's population while the political 'leaders' say they are deciding policy (they're clearly not) by 'following the science' on the advice of the 'experts' – the same medical officers and science 'advisers' (dictators). In this way with the rarest of exceptions the entire world followed the same policy of lockdown, people distancing, masks and 'vaccines' dictated by the psychopathic Cult, psychopathic Gates and psychopathic Tedros who we are supposed to believe give a damn about the health of the world population they are seeking to enslave. That, amazingly, is all there is to it in terms of crucial decision-making. Medical staff in each country then follow like sheep the dictates of the shepherds at the top of the national medical hierarchies – chief medical officers and science 'advisers' who themselves follow like sheep the shepherds of the World Health Organization and the Cult. Shepherds at the national level often have major funding and other connections to Gates and his Bill and Melinda Gates Foundation which carefully hands out money like confetti at a wedding to control the entire global medical system from the WHO down.

Follow the money

Christopher Whitty, Chief Medical Adviser to the UK Government at the centre of 'virus' policy, a senior adviser to the government's Scientific Advisory Group for Emergencies (SAGE), and Executive Board member of the World Health Organization, was gifted a grant of $40 million by the Bill and Melinda Gates Foundation for malaria research in Africa. The BBC described the unelected Whitty as 'the

official who will probably have the greatest impact on our everyday lives of any individual policymaker in modern times' and so it turned out. What Gates and Tedros have said Whitty has done like his equivalents around the world. Patrick Vallance, co-chair of SAGE and the government's Chief Scientific Adviser, is a former executive of Big Pharma giant GlaxoSmithKline with its fundamental financial and business connections to Bill Gates. In September, 2020, it was revealed that Vallance owned a deferred bonus of shares in GlaxoSmithKline worth £600,000 while the company was 'developing' a 'Covid vaccine'. Move along now – nothing to see here – what could possibly be wrong with that? Imperial College in London, a major player in 'Covid' policy in Britain and elsewhere with its 'Covid-19' Response Team, is funded by Gates and has big connections to China while the now infamous Professor Neil Ferguson, the useless 'computer modeller' at Imperial College is also funded by Gates. Ferguson delivered the dramatically inaccurate excuse for the first lockdowns (much more in the next chapter). The Institute for Health Metrics and Evaluation (IHME) in the United States, another source of outrageously false 'Covid' computer models to justify lockdowns, is bankrolled by Gates who is a vehement promotor of lockdowns. America's version of Whitty and Vallance, the again now infamous Anthony Fauci, has connections to 'Covid vaccine' maker Moderna as does Bill Gates through funding from the Bill and Melinda Gates Foundation. Fauci is director of the National Institute of Allergy and Infectious Diseases (NIAID), a major recipient of Gates money, and they are very close. Deborah Birx who was appointed White House Coronavirus Response Coordinator in February, 2020, is yet another with ties to Gates. Everywhere you look at the different elements around the world behind the coordination and decision making of the 'Covid' hoax there is Bill Gates and his money. They include the World Health Organization; Centers for Disease Control (CDC) in the United States; National Institutes of Health (NIH) of Anthony Fauci; Imperial College and Neil Ferguson; the London School of Hygiene where Chris Whitty worked; Regulatory agencies like the UK Medicines & Healthcare products Regulatory Agency (MHRA)

which gave emergency approval for 'Covid vaccines'; Wellcome Trust; GAVI, the Vaccine Alliance; the Coalition for Epidemic Preparedness Innovations (CEPI); Johns Hopkins University which has compiled the false 'Covid' figures; and the World Economic Forum. A Nationalfile.com article said:

> Gates has a lot of pull in the medical world, he has a multi-million dollar relationship with Dr. Fauci, and Fauci originally took the Gates line supporting vaccines and casting doubt on [the drug hydroxychloroquine]. Coronavirus response team member Dr. Deborah Birx, appointed by former president Obama to serve as United States Global AIDS Coordinator, also sits on the board of a group that has received billions from Gates' foundation, and Birx reportedly used a disputed Bill Gates-funded model for the White House's Coronavirus effort. Gates is a big proponent for a population lockdown scenario for the Coronavirus outbreak.

Another funder of Moderna is the Defense Advanced Research Projects Agency (DARPA), the technology-development arm of the Pentagon and one of the most sinister organisations on earth. DARPA had a major role with the CIA covert technology-funding operation In-Q-Tel in the development of Google and social media which is now at the centre of global censorship. Fauci and Gates are extremely close and openly admit to talking regularly about 'Covid' policy, but then why wouldn't Gates have a seat at every national 'Covid' table after his Foundation committed $1.75 billion to the 'fight against Covid-19'. When passed through our Orwellian Translation Unit this means that he has bought and paid for the Cult-driven 'Covid' response worldwide. Research the major 'Covid' response personnel in your own country and you will find the same Gates funding and other connections again and again. Medical and science chiefs following World Health Organization 'policy' sit atop a medical hierarchy in their country of administrators, doctors and nursing staff. These 'subordinates' are told they must work and behave in accordance with the policy delivered from the 'top' of the national 'health' pyramid which is largely the policy delivered by the WHO which is the policy delivered by Gates and the Cult. The whole 'Covid' narrative has been imposed on medical staff by a climate of fear although great numbers don't even need that to comply. They do so through breathtaking levels of ignorance and

include doctors who go through life simply repeating what Big Pharma and their hierarchical masters tell them to say and believe. No wonder Big Pharma 'medicine' is one of the biggest killers on Planet Earth.

The same top-down system of intimidation operates with regard to the Cult Big Pharma cartel which also dictates policy through national and global medical systems in this way. The Cult and Big Pharma agendas are the same because the former controls and owns the latter. 'Health' administrators, doctors, and nursing staff are told to support and parrot the dictated policy or they will face consequences which can include being fired. How sad it's been to see medical staff meekly repeating and imposing Cult policy without question and most of those who can see through the deceit are only willing to speak anonymously off the record. They know what will happen if their identity is known. This has left the courageous few to expose the lies about the 'virus', face masks, overwhelmed hospitals that aren't, and the dangers of the 'vaccine' that isn't a vaccine. When these medical professionals and scientists, some renowned in their field, have taken to the Internet to expose the truth their articles, comments and videos have been deleted by Cult-owned Facebook, Twitter and YouTube. What a real head-shaker to see YouTube videos with leading world scientists and highly qualified medical specialists with an added link underneath to the notorious Cult propaganda website *Wikipedia* to find the 'facts' about the same subject.

HIV – the 'Covid' trial-run

I'll give you an example of the consequences for health and truth that come from censorship and unquestioning belief in official narratives. The story was told by PCR inventor Kary Mullis in his book *Dancing Naked in the Mind Field*. He said that in 1984 he accepted as just another scientific fact that Luc Montagnier of France's Pasteur Institute and Robert Gallo of America's National Institutes of Health had independently discovered that a 'retrovirus' dubbed HIV (human immunodeficiency virus) caused AIDS. They

were, after all, Mullis writes, specialists in retroviruses. This is how the medical and science pyramids work. Something is announced or *assumed* and then becomes an everybody-knows-that purely through repetition of the assumption as if it is fact. Complete crap becomes accepted truth with no supporting evidence and only repetition of the crap. This is how a 'virus' that doesn't exist became the 'virus' that changed the world. The HIV-AIDS fairy story became a multi-billion pound industry and the media poured out propaganda terrifying the world about the deadly HIV 'virus' that caused the lethal AIDS. By then Mullis was working at a lab in Santa Monica, California, to detect retroviruses with his PCR test in blood donations received by the Red Cross. In doing so he asked a virologist where he could find a reference for HIV being the cause of AIDS. 'You don't need a reference,' the virologist said … *'Everybody knows it.'* Mullis said he wanted to quote a reference in the report he was doing and he said he felt a little funny about not knowing the source of such an important discovery when everyone else seemed to. The virologist suggested he cite a report by the Centers for Disease Control and Prevention (CDC) on morbidity and mortality. Mullis read the report, but it only said that an organism had been identified and did not say how. The report did not identify the original scientific work. Physicians, however, *assumed* (key recurring theme) that if the CDC was convinced that HIV caused AIDS then proof must exist. Mullis continues:

I did computer searches. Neither Montagnier, Gallo, nor anyone else had published papers describing experiments which led to the conclusion that HIV probably caused AIDS. I read the papers in Science for which they had become well known as AIDS doctors, but all they had said there was that they had found evidence of a past infection by something which was probably HIV in some AIDS patients.

They found antibodies. Antibodies to viruses had always been considered evidence of past disease, not present disease. Antibodies signaled that the virus had been defeated. The patient had saved himself. There was no indication in these papers that this virus caused a disease. They didn't show that everybody with the antibodies had the disease. In fact they found some healthy people with antibodies.

Mullis asked why their work had been published if Montagnier and Gallo hadn't really found this evidence, and why had they been fighting so hard to get credit for the discovery? He says he was hesitant to write 'HIV is the probable cause of AIDS' until he found published evidence to support that. 'Tens of thousands of scientists and researchers were spending billions of dollars a year doing research based on this idea,' Mullis writes. 'The reason had to be there somewhere; otherwise these people would not have allowed their research to settle into one narrow channel of investigation.' He said he lectured about PCR at numerous meetings where people were always talking about HIV and he asked them how they knew that HIV was the cause of AIDS:

> Everyone said something. Everyone had the answer at home, in the office, in some drawer. They all knew, and they would send me the papers as soon as they got back. But I never got any papers. Nobody ever sent me the news about how AIDS was caused by HIV.

Eventually Mullis was able to ask Montagnier himself about the reference proof when he lectured in San Diego at the grand opening of the University of California AIDS Research Center. Mullis says this was the last time he would ask his question without showing anger. Montagnier said he should reference the CDC report. 'I read it', Mullis said, and it didn't answer the question. 'If Montagnier didn't know the answer who the hell did?' Then one night Mullis was driving when an interview came on National Public Radio with Peter Duesberg, a prominent virologist at Berkeley and a California Scientist of the Year. Mullis says he finally understood why he could not find references that connected HIV to AIDS – *there weren't any!* No one had ever proved that HIV causes AIDS even though it had spawned a multi-billion pound global industry and the media was repeating this as fact every day in their articles and broadcasts terrifying the shit out of people about AIDS and giving the impression that a positive test for HIV (see 'Covid') was a death sentence. Duesberg was a threat to the AIDS gravy train and the agenda that underpinned it. He was therefore abused and castigated after he told the Proceedings of the National Academy of Sciences

there was no good evidence implicating the new 'virus'. Editors rejected his manuscripts and his research funds were deleted. Mullis points out that the CDC has defined AIDS as one of more than 30 diseases *if accompanied* by a positive result on a test that detects antibodies to HIV; but those same diseases are not defined as AIDS cases when antibodies are not detected:

> If an HIV-positive woman develops uterine cancer, for example, she is considered to have AIDS. If she is not HIV positive, she simply has uterine cancer. An HIV-positive man with tuberculosis has AIDS; if he tests negative he simply has tuberculosis. If he lives in Kenya or Colombia, where the test for HIV antibodies is too expensive, he is simply presumed to have the antibodies and therefore AIDS, and therefore he can be treated in the World Health Organization's clinic. It's the only medical help available in some places. And it's free, because the countries that support WHO are worried about AIDS.

Mullis accuses the CDC of continually adding new diseases (see ever more 'Covid symptoms') to the grand AIDS definition and of virtually doctoring the books to make it appear as if the disease continued to spread. He cites how in 1993 the CDC enormously broadened its AIDS definition and county health authorities were delighted because they received $2,500 per year from the Federal government for every reported AIDS case. Ladies and gentlemen, I have just described, via Kary Mullis, the 'Covid pandemic' of 2020 and beyond. Every element is the same and it's been pulled off in the same way by the same networks.

The 'Covid virus' exists? Okay – prove it. Er … still waiting

What Kary Mullis described with regard to 'HIV' has been repeated with 'Covid'. A claim is made that a new, or 'novel', infection has been found and the entire medical system of the world repeats that as fact exactly as they did with HIV and AIDS. No one in the mainstream asks rather relevant questions such as 'How do you know?' and 'Where is your proof?' The SARS-Cov-2 'virus' and the 'Covid-19 disease' became an overnight 'everybody-knows-that'. The origin could be debated and mulled over, but what you could not suggest was that 'SARS-Cov-2' didn't exist. That would be

ridiculous. 'Everybody knows' the 'virus' exists. Well, I didn't for one along with American proper doctors like Andrew Kaufman and Tom Cowan and long-time American proper journalist Jon Rappaport. We dared to pursue the obvious and simple question: 'Where's the evidence?' The overwhelming majority in medicine, journalism and the general public did not think to ask that. After all, *everyone knew* there was a new 'virus'. Everyone was saying so and I heard it on the BBC. Some would eventually argue that the 'deadly virus' was nothing like as deadly as claimed, but few would venture into the realms of its very existence. Had they done so they would have found that the evidence for that claim had gone AWOL as with HIV causes AIDS. In fact, not even that. For something to go AWOL it has to exist in the first place and scientific proof for a 'SARS-Cov-2' can be filed under nothing, nowhere and zilch.

Dr Andrew Kaufman is a board-certified forensic psychiatrist in New York State, a Doctor of Medicine and former Assistant Professor and Medical Director of Psychiatry at SUNY Upstate Medical University, and Medical Instructor of Hematology and Oncology at the Medical School of South Carolina. He also studied biology at the Massachusetts Institute of Technology (MIT) and trained in Psychiatry at Duke University. Kaufman is retired from allopathic medicine, but remains a consultant and educator on natural healing, I saw a video of his very early on in the 'Covid' hoax in which he questioned claims about the 'virus' in the absence of any supporting evidence and with plenty pointing the other way. I did everything I could to circulate his work which I felt was asking the pivotal questions that needed an answer. I can recommend an excellent pull-together interview he did with the website The Last Vagabond entitled *Dr Andrew Kaufman: Virus Isolation, Terrain Theory and Covid-19* and his website is andrewkaufmanmd.com. Kaufman is not only a forensic psychiatrist; he is forensic in all that he does. He always reads original scientific papers, experiments and studies instead of second-third-fourth-hand reports about the 'virus' in the media which are repeating the repeated repetition of the narrative. When he did so with the original Chinese 'virus' papers Kaufman

realised that there was no evidence of a 'SARS-Cov-2'. They had never – from the start – shown it to exist and every repeat of this claim worldwide was based on the accepted existence of proof that was nowhere to be found – see Kary Mullis and HIV. Here we go again.

Let's postulate

Kaufman discovered that the Chinese authorities immediately concluded that the cause of an illness that broke out among about 200 initial patients in Wuhan was a 'new virus' when there were no grounds to make that conclusion. The alleged 'virus' was not isolated from other genetic material in their samples and then shown through a system known as Koch's postulates to be the causative agent of the illness. The world was told that the SARS-Cov-2 'virus' caused a disease they called 'Covid-19' which had 'flu-like' symptoms and could lead to respiratory problems and pneumonia. If it wasn't so tragic it would almost be funny. *'Flu-like' symptoms'? Pneumonia? Respiratory disease?* What in *CHINA* and particularly in *Wuhan*, one of the most polluted cities in the world with a resulting epidemic of respiratory disease?? Three hundred thousand people get pneumonia in China every year and there are nearly a billion cases worldwide of 'flu-like symptoms'. These have a whole range of causes – including pollution in Wuhan – but no other possibility was credibly considered in late 2019 when the world was told there was a new and deadly 'virus'. The global prevalence of pneumonia and 'flu-like systems' gave the Cult networks unlimited potential to re-diagnose these other causes as the mythical 'Covid-19' and that is what they did from the very start. Kaufman revealed how Chinese medical and science authorities (all subordinates to the Cult-owned communist government) took genetic material from the lungs of only a few of the first patients. The material contained their own cells, bacteria, fungi and other microorganisms living in their bodies. The only way you could prove the existence of the 'virus' and its responsibility for the alleged 'Covid-19' was to isolate the virus from all the other material – a process also known as 'purification' – and

then follow the postulates sequence developed in the late 19th century by German physician and bacteriologist Robert Koch which became the 'gold standard' for connecting an alleged causation agent to a disease:

1. The microorganism (bacteria, fungus, virus, etc.) must be present in every case of the disease and all patients must have the same symptoms. It must also *not be present in healthy individuals*.

2. The microorganism must be isolated from the host with the disease. If the microorganism is a bacteria or fungus it must be grown in a pure culture. If it is a virus, it must be purified (i.e. containing no other material except the virus particles) from a clinical sample.

3. The specific disease, with all of its characteristics, must be reproduced when the infectious agent (the purified virus or a pure culture of bacteria or fungi) is inoculated into a healthy, susceptible host.

4. The microorganism must be recoverable from the experimentally infected host as in step 2.

Not one of these criteria has been met in the case of 'SARS-Cov-2' and 'Covid-19'. Not ONE. *EVER*. Robert Koch refers to bacteria and not viruses. What are called 'viral particles' are so minute (hence masks are useless by any definition) that they could only be seen after the invention of the electron microscope in the 1930s and can still only be observed through that means. American bacteriologist and virologist Thomas Milton Rivers, the so-called 'Father of Modern Virology' who was very significantly director of the Rockefeller Institute for Medical Research in the 1930s, developed a less stringent version of Koch's postulates to identify 'virus' causation known as 'Rivers criteria'. 'Covid' did not pass that process either. Some even doubt whether any 'virus' can be isolated from other particles containing genetic material in the Koch method. Freedom of Information requests in many countries asking for scientific proof that the 'Covid virus' has been purified and isolated and shown to exist have all come back with a 'we don't have that' and when this happened with a request to the UK Department of Health they added this comment:

However, outside of the scope of the [Freedom of Information Act] and on a discretionary basis, the following information has been advised to us, which may be of interest. Most infectious diseases are caused by viruses, bacteria or fungi. Some bacteria or fungi have the capacity to grow on their own in isolation, for example in colonies on a petri dish. Viruses are different in that they are what we call 'obligate pathogens' – that is, they cannot survive or reproduce without infecting a host ...

… For some diseases, it is possible to establish causation between a microorganism and a disease by isolating the pathogen from a patient, growing it in pure culture and reintroducing it to a healthy organism. These are known as 'Koch's postulates' and were developed in 1882. However, as our understanding of disease and different disease-causing agents has advanced, these are no longer the method for determining causation [Andrew Kaufman asks why in that case are there two published articles falsely claiming to satisfy Koch's postulates].

It has long been known that viral diseases cannot be identified in this way as viruses cannot be grown in 'pure culture'. When a patient is tested for a viral illness, this is normally done by looking for the presence of antigens, or viral genetic code in a host with molecular biology techniques [Kaufman asks how you could know the origin of these chemicals without having a pure culture for comparison].

For the record 'antigens' are defined so:

Invading microorganisms have antigens on their surface that the human body can recognise as being foreign – meaning not belonging to it. When the body recognises a foreign antigen, lymphocytes (white blood cells) produce antibodies, which are complementary in shape to the antigen.

Notwithstanding that this is open to question in relation to 'SARS-Cov-2' the presence of 'antibodies' can have many causes and they are found in people that are perfectly well. Kary Mullis said: 'Antibodies … had always been considered evidence of past disease, not present disease.'

'Covid' really is a *computer* 'virus'

Where the UK Department of Health statement says 'viruses' are now 'diagnosed' through a 'viral genetic code in a host with molecular biology techniques', they mean … *the PCR test* which its inventor said cannot test for infectious disease. They have no credible method of connecting a 'virus' to a disease and we will see that there is no scientific proof that any 'virus' causes any disease or there is any such thing as a 'virus' in the way that it is described. Tenacious Canadian researcher Christine Massey and her team made

some 40 Freedom of Information requests to national public health agencies in different countries asking for proof that SARS-CoV-2 has been isolated and not one of them could supply that information. Massey said of her request in Canada: 'Freedom of Information reveals Public Health Agency of Canada has no record of 'SARS-COV-2' isolation performed by anyone, anywhere, ever.' If you accept the comment from the UK Department of Health it's because they can't isolate a 'virus'. Even so many 'science' papers claimed to have isolated the 'Covid virus' until they were questioned and had to admit they hadn't. A reply from the Robert Koch Institute in Germany was typical: 'I am not aware of a paper which purified isolated SARS-CoV-2.' So what the hell was Christian Drosten and his gang using to design the 'Covid' testing protocol that has produced all the illusory Covid' cases and 'Covid' deaths when the head of the Chinese version of the CDC admitted there was a problem right from the start in that the 'virus' had never been isolated/purified? Breathe deeply: What they are calling 'Covid' is actually created by a *computer program* i.e. *they made it up* – er, that's it. They took lung fluid, with many sources of genetic material, from one single person alleged to be infected with Covid-19 by a PCR test which they *claimed*, without clear evidence, contained a 'virus'. They used several computer programs to create a model of a theoretical virus genome sequence from more than fifty-six million small sequences of RNA, each of an unknown source, assembling them like a puzzle with no known solution. The computer filled in the gaps with sequences from bits in the gene bank to make it look like a bat SARS-like coronavirus! A wave of the magic wand and poof, an in silico (computer-generated) genome, a scientific fantasy, was created. UK health researcher Dr Kevin Corbett made the same point with this analogy:

> … It's like giving you a few bones and saying that's your fish. It could be any fish. Not even a skeleton. Here's a few fragments of bones. That's your fish … It's all from gene bank and the bits of the virus sequence that weren't there they made up.
>
> They synthetically created them to fill in the blanks. That's what genetics is; it's a code. So it's ABBBCCDDD and you're missing some what you think is EEE so you put it in. It's all

synthetic. You just manufacture the bits that are missing. This is the end result of the geneticization of virology. This is basically a computer virus.

Further confirmation came in an email exchange between British citizen journalist Frances Leader and the government's Medicines & Healthcare Products Regulatory Agency (the Gates-funded MHRA) which gave emergency permission for untested 'Covid vaccines' to be used. The agency admitted that the 'vaccine' is not based on an isolated 'virus', but comes from a *computer-generated model*. Frances Leader was naturally banned from Cult-owned fascist Twitter for making this exchange public. The process of creating computer-generated alleged 'viruses' is called 'in silico' or 'in silicon' – computer chips – and the term 'in silico' is believed to originate with biological experiments using only a computer in 1989. 'Vaccines' involved with 'Covid' are also produced 'in silico' or by computer not a natural process. If the original 'virus' is nothing more than a made-up computer model how can there be 'new variants' of something that never existed in the first place? They are not new 'variants'; they are new *computer models* only minutely different to the original program and designed to further terrify the population into having the 'vaccine' and submitting to fascism. You want a 'new variant'? Click, click, enter – there you go. Tell the medical profession that you have discovered a 'South African variant', 'UK variants' or a 'Brazilian variant' and in the usual HIV-causes-AIDS manner they will unquestioningly repeat it with no evidence whatsoever to support these claims. They will go on television and warn about the dangers of 'new variants' while doing nothing more than repeating what they have been told to be true and knowing that any deviation from that would be career suicide. Big-time insiders will know it's a hoax, but much of the medical community is clueless about the way they are being played and themselves play the public without even being aware they are doing so. What an interesting 'coincidence' that AstraZeneca and Oxford University were conducting 'Covid vaccine trials' in the three countries – the UK, South Africa and Brazil – where the first three 'variants' were claimed to have 'broken out'.

Here's your 'virus' – it's a unicorn

Dr Andrew Kaufman presented a brilliant analysis describing how the 'virus' was imagined into fake existence when he dissected an article published by *Nature* and written by 19 authors detailing *alleged* 'sequencing of a complete viral genome' of the 'new SARS-CoV-2 virus'. This computer-modelled *in silico* genome was used as a template for all subsequent genome sequencing experiments that resulted in the so-called variants which he said now number more than *6,000*. The fake genome was constructed from more than 56 million individual short strands of RNA. Those little pieces were assembled into longer pieces by finding areas of overlapping sequences. The computer programs created over two million possible combinations from which the authors simply chose the longest one. They then compared this to a 'bat virus' and the computer 'alignment' rearranged the sequence and filled in the gaps! They called this computer-generated abomination the 'complete genome'. Dr Tom Cowan, a fellow medical author and collaborator with Kaufman, said such computer-generation constitutes scientific fraud and he makes this superb analogy:

> Here is an equivalency: A group of researchers claim to have found a unicorn because they found a piece of a hoof, a hair from a tail, and a snippet of a horn. They then add that information into a computer and program it to re-create the unicorn, and they then claim this computer re-creation is the real unicorn. Of course, they had never actually seen a unicorn so could not possibly have examined its genetic makeup to compare their samples with the actual unicorn's hair, hooves and horn.
>
> The researchers claim they decided which is the real genome of SARS-CoV-2 by 'consensus', sort of like a vote. Again, different computer programs will come up with different versions of the imaginary 'unicorn', so they come together as a group and decide which is the real imaginary unicorn.

This is how the 'virus' that has transformed the world was brought into fraudulent 'existence'. Extraordinary, yes, but as the Nazis said the bigger the lie the more will believe it. Cowan, however, wasn't finished and he went on to identify what he called the real blockbuster in the paper. He quotes this section from a paper written

by virologists and published by the CDC and then explains what it means:

Therefore, we examined the capacity of SARS-CoV-2 to infect and replicate in several common primate and human cell lines, including human adenocarcinoma cells (A549), human liver cells (HUH 7.0), and human embryonic kidney cells (HEK-293T). In addition to Vero E6 and Vero CCL81 cells. ... Each cell line was inoculated at high multiplicity of infection and examined 24h post-infection.

No CPE was observed in any of the cell lines except in Vero cells, which grew to greater than 10 to the 7th power at 24 h post-infection. In contrast, HUH 7.0 and 293T showed only modest viral replication, and A549 cells were incompatible with SARS CoV-2 infection.

Cowan explains that when virologists attempt to prove infection they have three possible 'hosts' or models on which they can test. The first was humans. Exposure to humans was generally not done for ethical reasons and has never been done with SARS-CoV-2 or any coronavirus. The second possible host was animals. Cowan said that forgetting for a moment that they never actually use purified virus when exposing animals they do use solutions that they *claim* contain the virus. Exposure to animals has been done with SARS-CoV-2 in an experiment involving mice and this is what they found: *None of the wild (normal) mice got sick*. In a group of genetically-modified mice, a statistically insignificant number lost weight and had slightly bristled fur, but they experienced nothing like the illness called 'Covid-19'. Cowan said the third method – the one they mostly rely on – is to inoculate solutions they *say* contain the virus onto a variety of tissue cultures. This process had never been shown to kill tissue *unless* the sample material was starved of nutrients and poisoned as *part of the process*. Yes, incredibly, in tissue experiments designed to show the 'virus' is responsible for killing the tissue they starve the tissue of nutrients and add toxic drugs including antibiotics and they do not have control studies to see if it's the starvation and poisoning that is degrading the tissue rather than the 'virus' they allege to be in there somewhere. You want me to pinch you? Yep, I understand. Tom Cowan said this about the whole nonsensical farce as he explains what that quote from the CDC paper really means:

The shocking thing about the above quote is that using their own methods, the virologists found that solutions containing SARS-CoV-2 – even in high amounts – were NOT, I repeat NOT, infective to any of the three human tissue cultures they tested. In plain English, this means they proved, on their terms, that this 'new coronavirus' is not infectious to human beings. It is ONLY infective to monkey kidney cells, and only then when you add two potent drugs (gentamicin and amphotericin), known to be toxic to kidneys, to the mix.

My friends, read this again and again. These virologists, published by the CDC, performed a clear proof, on their terms, showing that the SARS-CoV-2 virus is harmless to human beings. That is the only possible conclusion, but, unfortunately, this result is not even mentioned in their conclusion. They simply say they can provide virus stocks cultured only on monkey Vero cells, thanks for coming.

Cowan concluded: 'If people really understood how this "science" was done, I would hope they would storm the gates and demand honesty, transparency and truth.' Dr Michael Yeadon, former Vice President and Chief Scientific Adviser at drug giant Pfizer has been a vocal critic of the 'Covid vaccine' and its potential for multiple harm. He said in an interview in April, 2021, that 'not one [vaccine] has the virus. He was asked why vaccines normally using a 'dead' version of a disease to activate the immune system were not used for 'Covid' and instead we had the synthetic methods of the 'mRNA Covid vaccine'. Yeadon said that to do the former 'you'd have to have some of [the virus] wouldn't you?' He added: 'No-one's got any – seriously.' Yeadon said that surely they couldn't have fooled the whole world for a year without having a virus, 'but oddly enough ask around – no one's got it'. He didn't know why with all the 'great labs' around the world that the virus had not been isolated – 'Maybe they've been too busy running bad PCR tests and vaccines that people don't need.' What is today called 'science' is not 'science' at all. Science is no longer what is, but whatever people can be manipulated to *believe* that it is. Real science has been hijacked by the Cult to dispense and produce the 'expert scientists' and contentions that suit the agenda of the Cult. How big-time this has happened with the 'Covid' hoax which is entirely based on fake science delivered by fake 'scientists' and fake 'doctors'. The human-caused climate change hoax is also entirely based on fake science delivered by fake 'scientists' and fake 'climate experts'. In both cases real

scientists, climate experts and doctors have their views suppressed and deleted by the Cult-owned science establishment, media and Silicon Valley. This is the 'science' that politicians claim to be 'following' and a common denominator of 'Covid' and climate are Cult psychopaths Bill Gates and his mate Klaus Schwab at the Gates-funded World Economic Forum. But, don't worry, it's all just a coincidence and absolutely nothing to worry about. *Zzzzzzzz*.

What is a 'virus' REALLY?

Dr Tom Cowan is one of many contesting the very existence of viruses let alone that they cause disease. This is understandable when there is no scientific evidence for a disease-causing 'virus'. German virologist Dr Stefan Lanka won a landmark case in 2017 in the German Supreme Court over his contention that there is no such thing as a measles virus. He had offered a big prize for anyone who could prove there is and Lanka won his case when someone sought to claim the money. There is currently a prize of more than 225,000 euros on offer from an Isolate Truth Fund for anyone who can prove the isolation of SARS-CoV-2 and its genetic substance. Lanka wrote in an article headed 'The Misconception Called Virus' that scientists think a 'virus' is causing tissue to become diseased and degraded when in fact it is the *processes they are using* which do that – not a 'virus'. Lanka has done an important job in making this point clear as Cowan did in his analysis of the CDC paper. Lanka says that all claims about viruses as disease-causing pathogens are wrong and based on 'easily recognisable, understandable and verifiable misinterpretations.' Scientists believed they were working with 'viruses' in their laboratories when they were really working with 'typical particles of specific dying tissues or cells …' Lanka said that the tissue decaying process claimed to be caused by a 'virus' still happens when no alleged 'virus' is involved. It's the *process* that does the damage and not a 'virus'. The genetic sample is deprived of nutrients, removed from its energy supply through removal from the body and then doused in toxic antibiotics to remove any bacteria. He confirms again that establishment scientists do not (pinch me)

conduct control experiments to see if this is the case and if they did they would see the claims that 'viruses' are doing the damage is nonsense. He adds that during the measles 'virus' court case he commissioned an independent laboratory to perform just such a control experiment and the result was that the tissues and cells died in the exact same way as with alleged 'infected' material. This is supported by a gathering number of scientists, doctors and researchers who reject what is called 'germ theory' or the belief in the body being infected by contagious sources emitted by other people. Researchers Dawn Lester and David Parker take the same stance in their highly-detailed and sourced book *What Really Makes You Ill – Why everything you thought you knew about disease is wrong* which was recommended to me by a number of medical professionals genuinely seeking the truth. Lester and Parker say there is no provable scientific evidence to show that a 'virus' can be transmitted between people or people and animals or animals and people:

> The definition also claims that viruses are the cause of many diseases, as if this has been definitively proven. But this is not the case; there is no original scientific evidence that definitively demonstrates that any virus is the cause of any disease. The burden of proof for any theory lies with those who proposed it; but none of the existing documents provides 'proof' that supports the claim that 'viruses' are pathogens.

Dr Tom Cowan employs one of his clever analogies to describe the process by which a 'virus' is named as the culprit for a disease when what is called a 'virus' is only material released by cells detoxing themselves from infiltration by chemical or radiation poisoning. The tidal wave of technologically-generated radiation in the 'smart' modern world plus all the toxic food and drink are causing this to happen more than ever. Deluded 'scientists' misread this as a gathering impact of what they wrongly label 'viruses'.

Paper can infect houses

Cowan said in an article for davidicke.com – with his tongue only mildly in his cheek – that he believed he had made a tremendous

discovery that may revolutionise science. He had discovered that small bits of paper are alive, 'well alive-ish', can 'infect' houses, and then reproduce themselves inside the house. The result was that this explosion of growth in the paper inside the house causes the house to explode, blowing it to smithereens. His evidence for this new theory is that in the past months he had carefully examined many of the houses in his neighbourhood and found almost no scraps of paper on the lawns and surrounds of the house. There was an occasional stray label, but nothing more. Then he would return to these same houses a week or so later and with a few, not all of them, particularly the old and decrepit ones, he found to his shock and surprise they were littered with stray bits of paper. He knew then that the paper had infected these houses, made copies of itself, and blew up the house. A young boy on a bicycle at one of the sites told him he had seen a demolition crew using dynamite to explode the house the previous week, but Cowan dismissed this as the idle thoughts of silly boys because 'I was on to something big'. He was on to how 'scientists' mistake genetic material in the detoxifying process for something they call a 'virus'. Cowan said of his house and paper story:

> If this sounds crazy to you, it's because it should. This scenario is obviously nuts. But consider this admittedly embellished, for effect, current viral theory that all scientists, medical doctors and virologists currently believe.

He takes the example of the 'novel SARS-Cov2' virus to prove the point. First they take someone with an undefined illness called 'Covid-19' and don't even attempt to find any virus in their sputum. Never mind the scientists still describe how this 'virus', which they have not located attaches to a cell receptor, injects its genetic material, in 'Covid's' case, RNA, into the cell. The RNA once inserted exploits the cell to reproduce itself and makes 'thousands, nay millions, of copies of itself … Then it emerges victorious to claim its next victim':

If you were to look in the scientific literature for proof, actual scientific proof, that uniform SARS-CoV2 viruses have been properly isolated from the sputum of a sick person, that actual spike proteins could be seen protruding from the virus (which has not been found), you would find that such evidence doesn't exist.

If you go looking in the published scientific literature for actual pictures, proof, that these spike proteins or any viral proteins are ever attached to any receptor embedded in any cell membrane, you would also find that no such evidence exists. If you were to look for a video or documented evidence of the intact virus injecting its genetic material into the body of the cell, reproducing itself and then emerging victorious by budding off the cell membrane, you would find that no such evidence exists.

The closest thing you would find is electron micrograph pictures of cellular particles, possibly attached to cell debris, both of which to be seen were stained by heavy metals, a process that completely distorts their architecture within the living organism. This is like finding bits of paper stuck to the blown-up bricks, thereby proving the paper emerged by taking pieces of the bricks on its way out.

The Enders baloney

Cowan describes the 'Covid' story as being just as make-believe as his paper story and he charts back this fantasy to a Nobel Prize winner called John Enders (1897-1985), an American biomedical scientist who has been dubbed 'The Father of Modern Vaccines'. Enders is claimed to have 'discovered' the process of the viral culture which 'proved' that a 'virus' caused measles. Cowan explains how Enders did this 'by using the EXACT same procedure that has been followed by every virologist to find and characterize every new virus since 1954'. Enders took throat swabs from children with measles and immersed them in 2ml of milk. Penicillin (100u/ml) and the antibiotic streptomycin (50,g/ml) were added and the whole mix was centrifuged – rotated at high speed to separate large cellular debris from small particles and molecules as with milk and cream, for example. Cowan says that if the aim is to find little particles of genetic material ('viruses') in the snot from children with measles it would seem that the last thing you would do is mix the snot with other material – milk –that also has genetic material. 'How are you ever going to know whether whatever you found came from the snot or the milk?' He points out that streptomycin is a 'nephrotoxic' or poisonous-to-the-kidney drug. You will see the relevance of that

shortly. Cowan says that it gets worse, much worse, when Enders describes the culture medium upon which the virus 'grows': 'The culture medium consisted of bovine amniotic fluid (90%), beef embryo extract (5%), horse serum (5%), antibiotics and phenol red as an indicator of cell metabolism.' Cowan asks incredulously: 'Did he just say that the culture medium also contained fluids and tissues that are themselves rich sources of genetic material?' The genetic cocktail, or 'medium', is inoculated onto tissue and cells from rhesus monkey *kidney* tissue. This is where the importance of streptomycin comes in and currently-used antimicrobials and other drugs that are *poisonous to kidneys* and used in ALL modern viral cultures (e.g. gentamicin, streptomycin, and amphotericin). Cowan asks: 'How are you ever going to know from this witch's brew where any genetic material comes from as we now have five different sources of rich genetic material in our mix?' Remember, he says, that all genetic material, whether from monkey kidney tissues, bovine serum, milk, etc., is made from the exact same components. The same central question returns: 'How are you possibly going to know that it was the virus that killed the kidney tissue and not the toxic antibiotic and starvation rations on which you are growing the tissue?' John Enders answered the question himself – *you can't*:

A second agent was obtained from an uninoculated culture of monkey kidney cells. The cytopathic changes [death of the cells] it induced in the unstained preparations could not be distinguished with confidence from the viruses isolated from measles.

The death of the cells ('cytopathic changes') happened in exactly the same manner, whether they inoculated the kidney tissue with the measles snot or not, Cowan says. 'This is evidence that the destruction of the tissue, the very proof of viral causation of illness, was not caused by anything in the snot because they saw the same destructive effect when the snot was not even used … the cytopathic, i.e., cell-killing, changes come from the process of the culture itself, not from any virus in any snot, period.' Enders quotes in his 1957 paper a virologist called Ruckle as reporting similar findings 'and in addition has isolated an agent from monkey kidney tissue that is so

far indistinguishable from human measles virus'. In other words, Cowan says, these particles called 'measles viruses' are simply and clearly breakdown products of the starved and poisoned tissue. For measles 'virus' see all 'viruses' including the so-called 'Covid virus'. Enders, the 'Father of Modern Vaccines', also said:

There is a potential risk in employing cultures of primate cells for the production of vaccines composed of attenuated virus, since the presence of other agents possibly latent in primate tissues cannot be definitely excluded by any known method.

Cowan further quotes from a paper published in the journal *Viruses* in May, 2020, while the 'Covid pandemic' was well underway in the media if not in reality. 'EVs' here refers to particles of genetic debris from our own tissues, such as exosomes of which more in a moment: 'The remarkable resemblance between EVs and viruses has caused quite a few problems in the studies focused on the analysis of EVs released during viral infections.' Later the paper adds that to date a reliable method that can actually guarantee a complete separation (of EVs from viruses) DOES NOT EXIST. This was published at a time when a fairy tale 'virus' was claimed in total certainty to be causing a fairy tale 'viral disease' called 'Covid-19' – a fairy tale that was already well on the way to transforming human society in the image that the Cult has worked to achieve for so long. Cowan concludes his article:

To summarize, there is no scientific evidence that pathogenic viruses exist. What we think of as 'viruses' are simply the normal breakdown products of dead and dying tissues and cells. When we are well, we make fewer of these particles; when we are starved, poisoned, suffocated by wearing masks, or afraid, we make more.

There is no engineered virus circulating and making people sick. People in laboratories all over the world are making genetically modified products to make people sick. These are called vaccines. There is no virome, no 'ecosystem' of viruses, viruses are not 8%, 50% or 100 % of our genetic material. These are all simply erroneous ideas based on the misconception called a virus.

What is 'Covid'? Load of bollocks

The background described here by Cowan and Lanka was emphasised in the first video presentation that I saw by Dr Andrew Kaufman when he asked whether the 'Covid virus' was in truth a natural defence mechanism of the body called 'exosomes'. These are released by cells when in states of toxicity – see the same themes returning over and over. They are released ever more profusely as chemical and radiation toxicity increases and think of the potential effect therefore of 5G alone as its destructive frequencies infest the human energetic information field with a gathering pace (5G went online in Wuhan in 2019 as the 'virus' emerged). I'll have more about this later. Exosomes transmit a warning to the rest of the body that 'Houston, we have a problem'. Kaufman presented images of exosomes and compared them with 'Covid' under an electron microscope and the similarity was remarkable. They both attach to the same cell receptors (*claimed* in the case of 'Covid'), contain the same genetic material in the form of RNA or ribonucleic acid, and both are found in 'viral cell cultures' with damaged or dying cells. James Hildreth MD, President and Chief Executive Officer of the Meharry Medical College at Johns Hopkins, said: 'The virus is fully an exosome in every sense of the word.' Kaufman's conclusion was that there is no 'virus': 'This entire pandemic is a completely manufactured crisis … there is no evidence of anyone dying from [this] illness.' Dr Tom Cowan and Sally Fallon Morell, authors of *The Contagion Myth*, published a statement with Dr Kaufman in February, 2021, explaining why the 'virus' does not exist and you can read it that in full in the Appendix.

'Virus' theory can be traced to the 'cell theory' in 1858 of German physician Rudolf Virchow (1821-1920) who contended that disease originates from a single cell infiltrated by a 'virus'. Dr Stefan Lanka said that findings and insights with respect to the structure, function and central importance of tissues in the creation of life, which were already known in 1858, comprehensively refute the cell theory. Virchow ignored them. We have seen the part later played by John Enders in the 1950s and Lanka notes that infection theories were only established as a global dogma through the policies and

eugenics of the Third Reich in Nazi Germany (creation of the same Sabbatian cult behind the 'Covid' hoax). Lanka said: 'Before 1933, scientists dared to contradict this theory; after 1933, these critical scientists were silenced'. Dr Tom Cowan's view is that ill-heath is caused by too much of something, too little of something, or toxification from chemicals and radiation – not contagion. We must also highlight as a major source of the 'virus' theology a man still called the 'Father of Modern Virology' – Thomas Milton Rivers (1888-1962). There is no way given the Cult's long game policy that it was a coincidence for the 'Father of Modern Virology' to be director of the Rockefeller Institute for Medical Research from 1937 to 1956 when he is credited with making the Rockefeller Institute a leader in 'viral research'. Cult Rockefellers were the force behind the creation of Big Pharma 'medicine', established the World Health Organisation in 1948, and have long and close associations with the Gates family that now runs the WHO during the pandemic hoax through mega-rich Cult gofer and psychopath Bill Gates.

Only a Renegade Mind can see through all this bullshit by asking the questions that need to be answered, not taking 'no' or prevarication for an answer, and certainly not hiding from the truth in fear of speaking it. Renegade Minds have always changed the world for the better and they will change this one no matter how bleak it may currently appear to be.

CHAPTER SIX

Sequence of deceit

If you tell the truth, you don't have to remember anything
Mark Twain

Against the background that I have laid out this far the sequence that took us from an invented 'virus' in Cult-owned China in late 2019 to the fascist transformation of human society can be seen and understood in a whole new context.

We were told that a deadly disease had broken out in Wuhan and the world media began its campaign (coordinated by behavioural psychologists as we shall see) to terrify the population into unquestioning compliance. We were shown images of Chinese people collapsing in the street which never happened in the West with what was supposed to be the same condition. In the earliest days when alleged cases and deaths were few the fear register was hysterical in many areas of the media and this would expand into the common media narrative across the world. The real story was rather different, but we were never told that. The Chinese government, one of the Cult's biggest centres of global operation, said they had discovered a new illness with flu-like and pneumonia-type symptoms in a city with such toxic air that it is overwhelmed with flu-like symptoms, pneumonia and respiratory disease. Chinese scientists said it was a new – 'novel' – coronavirus which they called Sars-Cov-2 and that it caused a disease they labelled 'Covid-19'. There was no evidence for this and the 'virus' has never to this day been isolated, purified and its genetic code established from that. It

was from the beginning a computer-generated fiction. Stories of Chinese whistleblowers saying the number of deaths was being supressed or that the 'new disease' was related to the Wuhan bio-lab misdirected mainstream and alternative media into cul-de-sacs to obscure the real truth – there was no 'virus'.

Chinese scientists took genetic material from the lung fluid of just a few people and said they had found a 'new' disease when this material had a wide range of content. There was no evidence for a 'virus' for the very reasons explained in the last two chapters. The 'virus' has never been shown to (a) exist and (b) cause any disease. People were diagnosed on symptoms that are so widespread in Wuhan and polluted China and with a PCR test that can't detect infectious disease. On this farce the whole global scam was sold to the rest of the world which would also diagnose respiratory disease as 'Covid-19' from symptoms alone or with a PCR test not testing for a 'virus'. Flu miraculously disappeared *worldwide* in 2020 and into 2021 as it was redesignated 'Covid-19'. It was really the same old flu with its 'flu-like' symptoms attributed to 'flu-like' 'Covid-19'. At the same time with very few exceptions the Chinese response of draconian lockdown and fascism was the chosen weapon to respond across the West as recommended by the Cult-owned Tedros at the Cult-owned World Health Organization run by the Cult-owned Gates. All was going according to plan. Chinese scientists – everything in China is controlled by the Cult-owned government – compared their contaminated RNA lung-fluid material with other RNA sequences and said it appeared to be just under 80 percent identical to the SARS-CoV-1 'virus' claimed to be the cause of the SARS (severe acute respiratory syndrome) 'outbreak' in 2003. They decreed that because of this the 'new virus' had to be related and they called it SARS-CoV-2. There are some serious problems with this assumption and *assumption* was all it was. Most 'factual' science turns out to be assumptions repeated into everyone-knows-that. A match of under 80-percent is meaningless. Dr Kaufman makes the point that there's a *96 percent* genetic correlation between humans and chimpanzees, but 'no one would say our genetic material is part

of the chimpanzee family'. Yet the Chinese authorities were claiming that a much lower percentage, less than 80 percent, proved the existence of a new 'coronavirus'. For goodness sake human DNA is 60 percent similar to a *banana*.

You are feeling sleepy

The entire 'Covid' hoax is a global Psyop, a psychological operation to program the human mind into believing and fearing a complete fantasy. A crucial aspect of this was what *appeared* to happen in Italy. It was all very well streaming out daily images of an alleged catastrophe in Wuhan, but to the Western mind it was still on the other side of the world in a very different culture and setting. A reaction of 'this could happen to me and my family' was still nothing like as intense enough for the mind-doctors. The Cult needed a Western example to push people over that edge and it chose Italy, one of its major global locations going back to the Roman Empire. An Italian 'Covid' crisis was manufactured in a particular area called Lombardy which just happens to be notorious for its toxic air and therefore respiratory disease. Wuhan, China, déjà vu. An hysterical media told horror stories of Italians dying from 'Covid' in their droves and how Lombardy hospitals were being overrun by a tidal wave of desperately ill people needing treatment after being struck down by the 'deadly virus'. Here was the psychological turning point the Cult had planned. Wow, if this is happening in Italy, the Western mind concluded, this indeed could happen to me and my family. Another point is that Italian authorities responded by following the Chinese blueprint so vehemently recommended by the Cult-owned World Health Organization. They imposed fascistic lockdowns on the whole country viciously policed with the help of surveillance drones sweeping through the streets seeking out anyone who escaped from mass house arrest. Livelihoods were destroyed and psychology unravelled in the way we have witnessed since in all lockdown countries. Crucial to the plan was that Italy responded in this way to set the precedent of suspending freedom and imposing fascism in a 'Western liberal democracy'. I emphasised in an

animated video explanation on davidicke.com posted in the summer of 2020 how important it was to the Cult to expand the Chinese lockdown model across the West. Without this, and the bare-faced lie that non-symptomatic people could still transmit a 'disease' they didn't have, there was no way locking down the whole population, sick and not sick, could be pulled off. At just the right time and with no evidence Cult operatives and gofers claimed that people without symptoms could pass on the 'disease'. In the name of protecting the 'vulnerable' like elderly people, who lockdowns would kill by the tens of thousands, we had for the first time healthy people told to isolate as well as the sick. The great majority of people who tested positive had no symptoms because there was nothing wrong with them. It was just a trick made possible by a test not testing for the 'virus'.

Months after my animated video the Gates-funded Professor Neil Ferguson at the Gates-funded Imperial College confirmed that I was right. He didn't say it in those terms, naturally, but he did say it. Ferguson will enter the story shortly for his outrageously crazy 'computer models' that led to Britain, the United States and many other countries following the Chinese and now Italian methods of response. Put another way, following the Cult script. Ferguson said that SAGE, the UK government's scientific advisory group which has controlled 'Covid' policy from the start, wanted to follow the Chinese lockdown model (while they all continued to work and be paid), but they wondered if they could possibly, in Ferguson's words, 'get away with it in Europe'. 'Get away with it'? Who the hell do these moronic, arrogant people think they are? This appalling man Ferguson said that once Italy went into national lockdown they realised they, too, could mimic China:

> It's a communist one-party state, we said. We couldn't get away with it in Europe, we thought … and then Italy did it. And we realised we could. Behind this garbage from Ferguson is a simple fact: Doing the same as China in every country was the plan from the start and Ferguson's 'models' would play a central role in achieving that. It's just a coincidence, of course, and absolutely nothing to worry your little head about.

Oops, sorry, our mistake

Once the Italian segment of the Psyop had done the job it was designed to do a very different story emerged. Italian authorities revealed that 99 percent of those who had 'died from Covid-19' in Italy had one, two, three, or more 'co-morbidities' or illnesses and health problems that could have ended their life. The US Centers for Disease Control and Prevention (CDC) published a figure of 94 percent for Americans dying of 'Covid' while having other serious medical conditions – on average two to three (some five or six) other potential causes of death. In terms of death from an unproven 'virus' I say it is 100 percent. The other one percent in Italy and six percent in the US would presumably have died from 'Covid's' flu-like symptoms with a range of other possible causes in conjunction with a test not testing for the 'virus'. Fox News reported that even more startling figures had emerged in one US county in which 410 of 422 deaths attributed to 'Covid-19' had other potentially deadly health conditions. The Italian National Health Institute said later that the average age of people dying with a 'Covid-19' diagnosis in Italy was about 81. Ninety percent were over 70 with ten percent over 90. In terms of other reasons to die some 80 percent had two or more chronic diseases with half having three or more including cardiovascular problems, diabetes, respiratory problems and cancer. Why is the phantom 'Covid-19' said to kill overwhelmingly old people and hardly affect the young? Old people continually die of many causes and especially respiratory disease which you can re-diagnose 'Covid-19' while young people die in tiny numbers by comparison and rarely of respiratory disease. Old people 'die of Covid' because they die of other things that can be redesignated 'Covid' and it really is that simple.

Flu has flown

The blueprint was in place. Get your illusory 'cases' from a test not testing for the 'virus' and redesignate other causes of death as 'Covid-19'. You have an instant 'pandemic' from something that is nothing more than a computer-generated fiction. With near-on a

billion people having 'flu-like' symptoms every year the potential was limitless and we can see why flu quickly and apparently miraculously disappeared *worldwide* by being diagnosed 'Covid-19'. The painfully bloody obvious was explained away by the childlike media in headlines like this in the UK '*Independent*': 'Not a single case of flu detected by Public Health England this year as Covid restrictions suppress virus'. I kid you not. The masking, social distancing and house arrest that did not make the 'Covid virus' disappear somehow did so with the 'flu virus'. Even worse the article, by a bloke called Samuel Lovett, suggested that maybe the masking, sanitising and other 'Covid' measures should continue to keep the flu away. With a ridiculousness that disturbs your breathing (it's 'Covid-19') the said Lovett wrote: 'With widespread social distancing and mask-wearing measures in place throughout the UK, the usual routes of transmission for influenza have been blocked.' He had absolutely no evidence to support that statement, but look at the consequences of him acknowledging the obvious. With flu not disappearing at all and only being relabelled 'Covid-19' he would have to contemplate that 'Covid' was a hoax on a scale that is hard to imagine. You need guts and commitment to truth to even go there and that's clearly something Samuel Lovett does not have in abundance. He would never have got it through the editors anyway.

Tens of thousands die in the United States alone every winter from flu including many with pneumonia complications. CDC figures record *45 million* Americans diagnosed with flu in 2017-2018 of which 61,000 died and some reports claim 80,000. Where was the same hysteria then that we have seen with 'Covid-19'? Some 250,000 Americans are admitted to hospital with pneumonia every year with about 50,000 cases proving fatal. About 65 million suffer respiratory disease every year and three million deaths makes this the third biggest cause of death worldwide. You only have to redesignate a portion of all these people 'Covid-19' and you have an instant global pandemic or the *appearance* of one. Why would doctors do this? They are told to do this and all but a few dare not refuse those who must be obeyed. Doctors in general are not researching their own

knowledge and instead take it direct and unquestioned from the authorities that own them and their careers. The authorities say they must now diagnose these symptoms 'Covid-19' and not flu, or whatever, and they do it. Dark suits say put 'Covid-19' on death certificates no matter what the cause of death and the doctors do it. Renegade Minds don't fall for the illusion that doctors and medical staff are all highly-intelligent, highly-principled, seekers of medical truth. *Some are*, but not the majority. They are repeaters, gofers, and yes sir, no sir, purveyors of what the system demands they purvey. The 'Covid' con is not merely confined to diseases of the lungs. Instructions to doctors to put 'Covid-19' on death certificates for anyone dying of *anything* within 28 days (or much more) of a positive test not testing for the 'virus' opened the floodgates. The term dying *with* 'Covid' and not *of* 'Covid' was coined to cover the truth. Whether it was a *with* or an *of* they were all added to the death numbers attributed to the 'deadly virus' compiled by national governments and globally by the Gates-funded Johns Hopkins operation in the United States that was so involved in those 'pandemic' simulations. Fraudulent deaths were added to the ever-growing list of fraudulent 'cases' from false positives from a false test. No wonder Professor Walter Ricciardi, scientific advisor to the Italian minister of health, said after the Lombardy hysteria had done its job that 'Covid' death rates were due to Italy having the second oldest population in the world and to *how hospitals record deaths*:

The way in which we code deaths in our country is very generous in the sense that all the people who die in hospitals with the coronavirus are deemed to be dying of the coronavirus. On re-evaluation by the National Institute of Health, only 12 per cent of death certificates have shown a direct causality from coronavirus, while 88 per cent of patients who have died have at least one pre-morbidity – many had two or three.

This is extraordinary enough when you consider the propaganda campaign to use Italy to terrify the world, but how can they even say twelve percent were genuine when the 'virus' has not been shown to exist, its 'code' is a computer program, and diagnosis comes from a test not testing for it? As in China, and soon the world, 'Covid-19' in

Italy was a redesignation of diagnosis. Lies and corruption were to become the real 'pandemic' fuelled by a pathetically-compliant medical system taking its orders from the tiny few at the top of their national hierarchy who answered to the World Health Organization which answers to Gates and the Cult. Doctors were told – ordered – to diagnose a particular set of symptoms 'Covid-19' and put that on the death certificate for any cause of death if the patient had tested positive with a test not testing for the virus or had 'Covid' symptoms like the flu. The United States even introduced big financial incentives to manipulate the figures with hospitals receiving £4,600 from the Medicare system for diagnosing someone with regular pneumonia, $13,000 if they made the diagnosis from the same symptoms 'Covid-19' pneumonia, and $39, 000 if they put a 'Covid' diagnosed patient on a ventilator that would almost certainly kill them. A few – painfully and pathetically few – medical whistleblowers revealed (before Cult-owned YouTube deleted their videos) that they had been instructed to 'let the patient crash' and put them straight on a ventilator instead of going through a series of far less intrusive and dangerous methods as they would have done before the pandemic hoax began and the financial incentives kicked in. We are talking cold-blooded murder given that ventilators are so damaging to respiratory systems they are usually the last step before heaven awaits. Renegade Minds never fall for the belief that people in white coats are all angels of mercy and cannot be full-on psychopaths. I have explained in detail in *The Answer* how what I am describing here played out across the world coordinated by the World Health Organization through the medical hierarchies in almost every country.

Medical scientist calls it

Information about the non-existence of the 'virus' began to emerge for me in late March, 2020, and mushroomed after that. I was sent an email by Sir Julian Rose, a writer, researcher, and organic farming promotor, from a medical scientist friend of his in the United States. Even at that early stage in March the scientist was able to explain

how the 'Covid' hoax was being manipulated. He said there were no reliable tests for a specific 'Covid-19 virus' and nor were there any reliable agencies or media outlets for reporting numbers of actual 'Covid-19' cases. We have seen in the long period since then that he was absolutely right. 'Every action and reaction to Covid-19 is based on totally flawed data and we simply cannot make accurate assessments,' he said. Most people diagnosed with 'Covid-19' were showing nothing more than cold and flu-like symptoms 'because most coronavirus strains *are* nothing more than cold/flu-like symptoms'. We had farcical situations like an 84-year-old German man testing positive for 'Covid-19' and his nursing home ordered to quarantine only for him to be found to have a common cold. The scientist described back then why PCR tests and what he called the 'Mickey Mouse test kits' were useless for what they were claimed to be identifying. 'The idea these kits can isolate a specific virus like Covid-19 is nonsense,' he said. Significantly, he pointed out that 'if you want to create a totally false panic about a totally false pandemic – pick a coronavirus'. This is exactly what the Cult-owned Gates, World Economic Forum and Johns Hopkins University did with their Event 201 'simulation' followed by their real-life simulation called the 'pandemic'. The scientist said that all you had to do was select the sickest of people with respiratory-type diseases in a single location – 'say Wuhan' – and administer PCR tests to them. You can then claim that anyone showing 'viral sequences' similar to a coronavirus 'which will inevitably be quite a few' is suffering from a 'new' disease:

> Since you already selected the sickest flu cases a fairly high proportion of your sample will go on to die. You can then say this 'new' virus has a CFR [case fatality rate] higher than the flu and use this to infuse more concern and do more tests which will of course produce more 'cases', which expands the testing, which produces yet more 'cases' and so on and so on. Before long you have your 'pandemic', and all you have done is use a simple test kit trick to convert the worst flu and pneumonia cases into something new that doesn't ACTUALLY EXIST [my emphasis].

He said that you then 'just run the same scam in other countries' and make sure to keep the fear message running high 'so that people

will feel panicky and less able to think critically'. The only problem to overcome was the fact *there is no* actual new deadly pathogen and only regular sick people. This meant that deaths from the 'new deadly pathogen' were going to be way too low for a real new deadly virus pandemic, but he said this could be overcome in the following ways – all of which would go on to happen:

1. You can claim this is just the beginning and more deaths are imminent [you underpin this with fantasy 'computer projections']. Use this as an excuse to quarantine everyone and then claim the quarantine prevented the expected millions of dead.

2. You can [say that people] 'minimizing' the dangers are irresponsible and bully them into not talking about numbers.

3. You can talk crap about made up numbers hoping to blind people with pseudoscience.

4. You can start testing well people (who, of course, will also likely have shreds of coronavirus [RNA] in them) and thus inflate your 'case figures' with 'asymptomatic carriers' (you will of course have to spin that to sound deadly even though any virologist knows the more symptom-less cases you have the less deadly is your pathogen).

The scientist said that if you take these simple steps 'you can have your own entirely manufactured pandemic up and running in weeks'. His analysis made so early in the hoax was brilliantly prophetic of what would actually unfold. Pulling all the information together in these recent chapters we have this is simple 1, 2, 3, of how you can delude virtually the entire human population into believing in a 'virus' that doesn't exist:

- A 'Covid case' is someone who tests positive with a test not testing for the 'virus'.

- A 'Covid death' is someone who dies of *any cause* within 28 days (or much longer) of testing positive with a test not testing for the 'virus.

- Asymptomatic means there is nothing wrong with you, but they claim you can pass on what you don't have to justify locking

down (quarantining) healthy people in totality.

The foundations of the hoax are that simple. A study involving ten million people in Wuhan, published in November, 2020, demolished the whole lie about those without symptoms passing on the 'virus'. They found '300 asymptomatic cases' and traced their contacts to find that not one of them was detected with the 'virus'. 'Asymptomatic' patients and their contacts were isolated for no less than two weeks and nothing changed. I know it's all crap, but if you are going to claim that those without symptoms can transmit 'the virus' then you must produce evidence for that and they never have. Even World Health Organization official Dr Maria Van Kerkhove, head of the emerging diseases and zoonosis unit, said as early as June, 2020, that she doubted the validity of asymptomatic transmission. She said that 'from the data we have, it still seems to be rare that an asymptomatic person actually transmits onward to a secondary individual' and by 'rare' she meant that she couldn't cite any case of asymptomatic transmission.

The Ferguson factor

The problem for the Cult as it headed into March, 2020, when the script had lockdown due to start, was that despite all the manipulation of the case and death figures they still did not have enough people alleged to have died from 'Covid' to justify mass house arrest. This was overcome in the way the scientist described: 'You can claim this is just the beginning and more deaths are imminent … Use this as an excuse to quarantine everyone and then claim the quarantine prevented the expected millions of dead.' Enter one Professor Neil Ferguson, the Gates-funded 'epidemiologist' at the Gates-funded Imperial College in London. Ferguson is Britain's Christian Drosten in that he has a dire record of predicting health outcomes, but is still called upon to advise government on the next health outcome when another 'crisis' comes along. This may seem to be a strange and ridiculous thing to do. Why would you keep turning for policy guidance to people who have a history of being

monumentally wrong? Ah, but it makes sense from the Cult point of view. These 'experts' keep on producing predictions that suit the Cult agenda for societal transformation and so it was with Neil Ferguson as he revealed his horrific (and clearly insane) computer model predictions that allowed lockdowns to be imposed in Britain, the United States and many other countries. Ferguson does not have even an A-level in biology and would appear to have no formal training in computer modelling, medicine or epidemiology, according to Derek Winton, an MSc in Computational Intelligence. He wrote an article somewhat aghast at what Ferguson did which included taking no account of respiratory disease 'seasonality' which means it is far worse in the winter months. Who would have thought that respiratory disease could be worse in the winter? Well, certainly not Ferguson.

The massively China-connected Imperial College and its bizarre professor provided the excuse for the long-incubated Chinese model of human control to travel westward at lightning speed. Imperial College confirms on its website that it collaborates with the Chinese Research Institute; publishes more than 600 research papers every year with Chinese research institutions; has 225 Chinese staff; 2,600 Chinese students – the biggest international group; 7,000 former students living in China which is the largest group outside the UK; and was selected for a tour by China's President Xi Jinping during his state visit to the UK in 2015. The college takes major donations from China and describes itself as the UK's number one university collaborator with Chinese research institutions. The China communist/fascist government did not appear phased by the woeful predictions of Ferguson and Imperial when during the lockdown that Ferguson induced the college signed a five-year collaboration deal with China tech giant Huawei that will have Huawei's indoor 5G network equipment installed at the college's West London tech campus along with an 'AI cloud platform'. The deal includes Chinese sponsorship of Imperial's Venture Catalyst entrepreneurship competition. Imperial is an example of the enormous influence the Chinese government has within British and North American

universities and research centres – and further afield. Up to 200 academics from more than a dozen UK universities are being investigated on suspicion of 'unintentionally' helping the Chinese government build weapons of mass destruction by 'transferring world-leading research in advanced military technology such as aircraft, missile designs and cyberweapons'. Similar scandals have broken in the United States, but it's all a coincidence. Imperial College serves the agenda in many other ways including the promotion of every aspect of the United Nations Agenda 21/2030 (the Great Reset) and produced computer models to show that human-caused 'climate change' is happening when in the real world it isn't. Imperial College is driving the climate agenda as it drives the 'Covid' agenda (both Cult hoaxes) while Patrick Vallance, the UK government's Chief Scientific Adviser on 'Covid', was named Chief Scientific Adviser to the UN 'climate change' conference known as COP26 hosted by the government in Glasgow, Scotland. 'Covid' and 'climate' are fundamentally connected.

Professor Woeful

From Imperial's bosom came Neil Ferguson still advising government despite his previous disasters and it was announced early on that he and other key people like UK Chief Medical Adviser Chris Whitty had caught the 'virus' as the propaganda story was being sold. Somehow they managed to survive and we had Prime Minister Boris Johnson admitted to hospital with what was said to be a severe version of the 'virus' in this same period. His whole policy and demeanour changed when he returned to Downing Street. It's a small world with these government advisors – especially in their communal connections to Gates – and Ferguson had partnered with Whitty to write a paper called 'Infectious disease: Tough choices to reduce Ebola transmission' which involved another scare-story that didn't happen. Ferguson's 'models' predicted that up to150, 000 could die from 'mad cow disease', or BSE, and its version in sheep if it was transmitted to humans. BSE was not transmitted and instead triggered by an organophosphate pesticide used to treat a pest on

cows. Fewer than 200 deaths followed from the human form. Models by Ferguson and his fellow incompetents led to the unnecessary culling of millions of pigs, cattle and sheep in the foot and mouth outbreak in 2001 which destroyed the lives and livelihoods of farmers and their families who had often spent decades building their herds and flocks. Vast numbers of these animals did not have foot and mouth and had no contact with the infection. Another 'expert' behind the cull was Professor Roy Anderson, a computer modeller at Imperial College specialising in the epidemiology of *human*, not animal, disease. Anderson has served on the Bill and Melinda Gates Grand Challenges in Global Health advisory board and chairs another Gates-funded organisation. Gates is everywhere.

In a precursor to the 'Covid' script Ferguson backed closing schools 'for prolonged periods' over the swine flu 'pandemic' in 2009 and said it would affect a third of the world population if it continued to spread at the speed he claimed to be happening. His mates at Imperial College said much the same and a news report said: 'One of the authors, the epidemiologist and disease modeller Neil Ferguson, who sits on the World Health Organisation's emergency committee for the outbreak, said the virus had "full pandemic potential".' Professor Liam Donaldson, the Chris Whitty of his day as Chief Medical Officer, said the worst case could see 30 percent of the British people infected by swine flu with 65,000 dying. Ferguson and Donaldson were indeed proved correct when at the end of the year the number of deaths attributed to swine flu was 392. The term 'expert' is rather liberally applied unfortunately, not least to complete idiots. Swine flu 'projections' were great for GlaxoSmithKline (GSK) as millions rolled in for its Pandemrix influenza vaccine which led to brain damage with children most affected. The British government (taxpayers) paid out more than £60 million in compensation after GSK was given immunity from prosecution. Yet another 'Covid' déjà vu. Swine flu was supposed to have broken out in Mexico, but Dr Wolfgang Wodarg, a German doctor, former member of parliament and critic of the 'Covid' hoax, observed 'the spread of swine flu' in Mexico City at the time. He

said: 'What we experienced in Mexico City was a very mild flu which did not kill more than usual – which killed even fewer people than usual.' Hyping the fear against all the facts is not unique to 'Covid' and has happened many times before. Ferguson is reported to have over-estimated the projected death toll of bird flu (H5N1) by some three million-fold, but bird flu vaccine makers again made a killing from the scare. This is some of the background to the Neil Ferguson who produced the perfectly-timed computer models in early 2020 predicting that half a million people would die in Britain without draconian lockdown and 2.2 million in the United States. Politicians panicked, people panicked, and lockdowns of alleged short duration were instigated to 'flatten the curve' of cases gleaned from a test not testing for the 'virus'. I said at the time that the public could forget the 'short duration' bit. This was an agenda to destroy the livelihoods of the population and force them into mass control through dependency and there was going to be nothing 'short' about it. American researcher Daniel Horowitz described the consequences of the 'models' spewed out by Gates-funded Ferguson and Imperial College:

> What led our government and the governments of many other countries into panic was a single Imperial College of UK study, funded by global warming activists, that predicted 2.2 million deaths if we didn't lock down the country. In addition, the reported 8-9% death rate in Italy scared us into thinking there was some other mutation of this virus that they got, which might have come here.
>
> Together with the fact that we were finally testing and had the ability to actually report new cases, we thought we were headed for a death spiral. But again … we can't flatten a curve if we don't know when the curve started.

How about it *never* started?

Giving them what they want

An investigation by German news outlet *Welt Am Sonntag (World on Sunday)* revealed how in March, 2020, the German government gathered together 'leading scientists from several research institutes and universities' and 'together, they were to produce a [modelling]

paper that would serve as legitimization for further tough political measures'. The Cult agenda was justified by computer modelling not based on evidence or reality; it was specifically constructed to justify the Cult demand for lockdowns all over the world to destroy the independent livelihoods of the global population. All these modellers and everyone responsible for the 'Covid' hoax have a date with a trial like those in Nuremberg after World War Two when Nazis faced the consequences of their war crimes. These corrupt-beyond-belief 'modellers' wrote the paper according to government instructions and it said that that if lockdown measures were lifted then up to one million Germans would die from 'Covid-19' adding that some would die 'agonizingly at home, gasping for breath' unable to be treated by hospitals that couldn't cope. All lies. No matter – it gave the Cult all that it wanted. What did long-time government 'modeller' Neil Ferguson say? If the UK and the United States didn't lockdown half a million would die in Britain and 2.2 million Americans. Anyone see a theme here? 'Modellers' are such a crucial part of the lockdown strategy that we should look into their background and follow the money. Researcher Rosemary Frei produced an excellent article headlined 'The Modelling-paper Mafiosi'. She highlights a guy called John Edmunds, a British epidemiologist, and professor in the Faculty of Epidemiology and Population Health at the London School of Hygiene & Tropical Medicine. He studied at Imperial College. Edmunds is a member of government 'Covid' advisory bodies which have been dictating policy, the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) and the Scientific Advisory Group for Emergencies (SAGE).

Ferguson, another member of NERVTAG and SAGE, led the way with the original 'virus' and Edmunds has followed in the 'variant' stage and especially the so-called UK or Kent variant known as the 'Variant of Concern' (VOC) B.1.1.7. He said in a co-written report for the Centre for Mathematical modelling of Infectious Diseases at the London School of Hygiene and Tropical Medicine, with input from the Centre's 'Covid-19' Working Group, that there was 'a realistic

possibility that VOC B.1.1.7 is associated with an increased risk of death compared to non-VOC viruses'. Fear, fear, fear, get the vaccine, fear, fear, fear, get the vaccine. Rosemary Frei reveals that almost all the paper's authors and members of the modelling centre's 'Covid-19' Working Group receive funding from the Bill and Melinda Gates Foundation and/or the associated Gates-funded Wellcome Trust. The paper was published by e-journal *Medr χiv* which only publishes papers not peer-reviewed and the journal was established by an organisation headed by Facebook's Mark Zuckerberg and his missus. What a small world it is. Frei discovered that Edmunds is on the Scientific Advisory Board of the Coalition for Epidemic Preparedness Innovations (CEPI) which was established by the Bill and Melinda Gates Foundation, Klaus Schwab's Davos World Economic Forum and Big Pharma giant Wellcome. CEPI was 'launched in Davos [in 2017] to develop vaccines to stop future epidemics', according to its website. 'Our mission is to accelerate the development of vaccines against emerging infectious diseases and enable equitable access to these vaccines for people during outbreaks.' What kind people they are. Rosemary Frei reveals that Public Health England (PHE) director Susan Hopkins is an author of her organisation's non-peer-reviewed reports on 'new variants'. Hopkins is a professor of infectious diseases at London's Imperial College which is gifted tens of millions of dollars a year by the Bill and Melinda Gates Foundation. Gates-funded modelling disaster Neil Ferguson also co-authors Public Health England reports and he spoke in December, 2020, about the potential danger of the B.1.1.7. 'UK variant' promoted by Gates-funded modeller John Edmunds. When I come to the 'Covid vaccines' the 'new variants' will be shown for what they are – bollocks.

Connections, connections

All these people and modellers are lockdown-obsessed or, put another way, they demand what the Cult demands. Edmunds said in January, 2021, that to ease lockdowns too soon would be a disaster and they had to 'vaccinate much, much, much more widely than the

elderly'. Rosemary Frei highlights that Edmunds is married to Jeanne Pimenta who is described in a LinkedIn profile as director of epidemiology at GlaxoSmithKline (GSK) and she held shares in the company. Patrick Vallance, co-chair of SAGE and the government's Chief Scientific Adviser, is a former executive of GSK and has a deferred bonus of shares in the company worth £600,000. GSK has serious business connections with Bill Gates and is collaborating with mRNA-'vaccine' company CureVac to make 'vaccines' for the new variants that Edmunds is talking about. GSK is planning a 'Covid vaccine' with drug giant Sanofi. Puppet Prime Minister Boris Johnson announced in the spring of 2021 that up to 60 million vaccine doses were to be made at the GSK facility at Barnard Castle in the English North East. Barnard Castle, with a population of just 6,000, was famously visited in breach of lockdown rules in April, 2020, by Johnson aide Dominic Cummings who said that he drove there 'to test his eyesight' before driving back to London. Cummings would be better advised to test his integrity – not that it would take long. The GSK facility had nothing to do with his visit then although I'm sure Patrick Vallance would have been happy to arrange an introduction and some tea and biscuits. Ruthless psychopath Gates has made yet another fortune from vaccines in collaboration with Big Pharma companies and gushes at the phenomenal profits to be made from vaccines – more than a 20-to-1 return as he told one interviewer. Gates also tweeted in December, 2019, with the foreknowledge of what was coming: 'What's next for our foundation? I'm particularly excited about what the next year could mean for one of the best buys in global health: vaccines.'

Modeller John Edmunds is a big promotor of vaccines as all these people appear to be. He's the dean of the London School of Hygiene & Tropical Medicine's Faculty of Epidemiology and Population Health which is primarily funded by the Bill and Melinda Gates Foundation and the Gates-established and funded GAVI vaccine alliance which is the Gates vehicle to vaccinate the world. The organisation Doctors Without Borders has described GAVI as being 'aimed more at supporting drug-industry desires to promote new

products than at finding the most efficient and sustainable means for fighting the diseases of poverty'. But then that's why the psychopath Gates created it. John Edmunds said in a video that the London School of Hygiene & Tropical Medicine is involved in every aspect of vaccine development including large-scale clinical trials. He contends that mathematical modelling can show that vaccines protect individuals and society. That's on the basis of shit in and shit out, I take it. Edmunds serves on the UK Vaccine Network as does Ferguson and the government's foremost 'Covid' adviser, the grim-faced, dark-eyed Chris Whitty. The Vaccine Network says it works 'to support the government to identify and shortlist targeted investment opportunities for the most promising vaccines and vaccine technologies that will help combat infectious diseases with epidemic potential, and to address structural issues related to the UK's broader vaccine infrastructure'. Ferguson is acting Director of the Imperial College Vaccine Impact Modelling Consortium which has funding from the Bill and Melina Gates Foundation and the Gates-created GAVI 'vaccine alliance'. Anyone wonder why these characters see vaccines as the answer to every problem? Ferguson is wildly enthusiastic in his support for GAVI's campaign to vaccine children en masse in poor countries. You would expect someone like Gates who has constantly talked about the need to reduce the population to want to fund vaccines to keep more people alive. I'm sure that's why he does it. The John Edmunds London School of Hygiene & Tropical Medicine (LSHTM) has a Vaccines Manufacturing Innovation Centre which develops, tests and commercialises vaccines. Rosemary Frei writes:

> The vaccines centre also performs affiliated activities like combating 'vaccine hesitancy'. The latter includes the Vaccine Confidence Project. The project's stated purpose is, among other things, 'to provide analysis and guidance for early response and engagement with the public to ensure sustained confidence in vaccines and immunisation'. The Vaccine Confidence Project's director is LSHTM professor Heidi Larson. For more than a decade she's been researching how to combat vaccine hesitancy.

How the bloody hell can blokes like John Edmunds and Neil Ferguson with those connections and financial ties model 'virus' case

and death projections for the government and especially in a way that gives their paymasters like Gates exactly what they want? It's insane, but this is what you find throughout the world.

'Covid' is not dangerous, oops, wait, yes it is

Only days before Ferguson's nightmare scenario made Jackboot Johnson take Britain into a China-style lockdown to save us from a deadly 'virus' the UK government website gov.uk was reporting something very different to Ferguson on a page of official government guidance for 'high consequence infectious diseases (HCID)'. It said this about 'Covid-19':

As of 19 March 2020, COVID-19 *is no longer considered to be a high consequence infectious diseases (HCID) in the UK* [my emphasis]. The 4 nations public health HCID group made an interim recommendation in January 2020 to classify COVID-19 as an HCID. This was based on consideration of the UK HCID criteria about the virus and the disease with information available during the early stages of the outbreak.

Now that more is known about COVID-19, the public health bodies in the UK have reviewed the most up to date information about COVID-19 against the UK HCID criteria. They have determined that several features have now changed; in particular, more information is available about mortality rates (low overall), and there is now greater clinical awareness and a specific and sensitive laboratory test, the availability of which continues to increase. The Advisory Committee on Dangerous Pathogens (ACDP) is also of the opinion that COVID-19 should no longer be classified as an HCID.

Soon after the government had been exposed for downgrading the risk they upgraded it again and everyone was back to singing from the same Cult hymn book. Ferguson and his fellow Gates clones indicated that lockdowns and restrictions would have to continue until a Gates-funded vaccine was developed. Gates said the same because Ferguson and his like were repeating the Gates script which is the Cult script. 'Flatten the curve' became an ongoing nightmare of continuing lockdowns with periods in between of severe restrictions in pursuit of destroying independent incomes and had nothing to do with protecting health about which the Cult gives not a shit. Why wouldn't Ferguson be pushing a vaccine 'solution' when he's owned by vaccine-obsessive Gates who makes a fortune from them and

when Ferguson heads the Vaccine Impact Modelling Consortium at Imperial College funded by the Gates Foundation and GAVI, the 'vaccine alliance', created by Gates as his personal vaccine promotion operation? To compound the human catastrophe that Ferguson's 'models' did so much to create he was later exposed for breaking his own lockdown rules by having sexual liaisons with his married girlfriend Antonia Staats at his home while she was living at another location with her husband and children. Staats was a 'climate' activist and senior campaigner at the Soros-funded Avaaz which I wouldn't trust to tell me that grass is green. Ferguson had to resign as a government advisor over this hypocrisy in May, 2020, but after a period of quiet he was back being quoted by the ridiculous media on the need for more lockdowns and a vaccine rollout. Other government-advising 'scientists' from Imperial College' held the fort in his absence and said lockdown could be indefinite until a vaccine was found. The Cult script was being sung by the payrolled choir. I said there was no intention of going back to 'normal' when the 'vaccine' came because the 'vaccine' is part of a very different agenda that I will discuss in Human 2.0. Why would the Cult want to let the world go back to normal when destroying that normal forever was the whole point of what was happening? House arrest, closing businesses and schools through lockdown, (un)social distancing and masks all followed the Ferguson fantasy models. Again as I predicted (these people are so predictable) when the 'vaccine' arrived we were told that house arrest, lockdown, (un)social distancing and masks would still have to continue. I will deal with the masks in the next chapter because they are of fundamental importance.

Where's the 'pandemic'?

Any mildly in-depth assessment of the figures revealed what was really going on. Cult-funded and controlled organisations still have genuine people working within them such is the number involved. So it is with Genevieve Briand, assistant program director of the Applied Economics master's degree program at Johns Hopkins

University. She analysed the impact that 'Covid-19' had on deaths from *all* causes in the United States using official data from the CDC for the period from early February to early September, 2020. She found that allegedly 'Covid' *related*-deaths exceeded those from heart disease which she found strange with heart disease always the biggest cause of fatalities. Her research became even more significant when she noted the sudden decline in 2020 of *all* non-'Covid' deaths: 'This trend is completely contrary to the pattern observed in all previous years … the total decrease in deaths by other causes almost exactly equals the increase in deaths by Covid-19.' This was such a game, set and match in terms of what was happening that Johns Hopkins University deleted the article on the grounds that it 'was being used to support false and dangerous inaccuracies about the impact of the pandemic'. No – because it exposed the scam from official CDC figures and this was confirmed when those figures were published in January, 2021. Here we can see the effect of people dying from heart attacks, cancer, road accidents and gunshot wounds – *anything* – having 'Covid-19' on the death certificate along with those diagnosed from 'symptoms' who had even not tested positive with a test not testing for the 'virus'. I am not kidding with the gunshot wounds, by the way. Brenda Bock, coroner in Grand County, Colorado, revealed that two gunshot victims tested positive for the 'virus' within the previous 30 days and were therefore classified as 'Covid deaths'. Bock said: 'These two people had tested positive for Covid, but that's not what killed them. A gunshot wound is what killed them.' She said she had not even finished her investigation when the state listed the gunshot victims as deaths due to the 'virus'. The death and case figures for 'Covid-19' are an absolute joke and yet they are repeated like parrots by the media, politicians and alleged medical 'experts'. The official Cult narrative is the only show in town.

Genevieve Briand found that deaths from all causes were not exceptional in 2020 compared with previous years and a Spanish magazine published figures that said the same about Spain which was a 'Covid' propaganda hotspot at one point. *Discovery Salud*, a

health and medicine magazine, quoted government figures which showed how 17,000 *fewer* people died in Spain in 2020 than in 2019 and more than 26,000 fewer than in 2018. The age-standardised mortality rate for England and Wales when age distribution is taken into account was significantly lower in 2020 than the 1970s, 80s and 90s, and was only the ninth highest since 2000. Where is the 'pandemic'?

Post mortems and autopsies virtually disappeared for 'Covid' deaths amid claims that 'virus-infected' bodily fluids posed a risk to those carrying out the autopsy. This was rejected by renowned German pathologist and forensic doctor Klaus Püschel who said that he and his staff had by then done 150 autopsies on 'Covid' patients with no problems at all. He said they were needed to know why some 'Covid' patients suffered blood clots and not severe respiratory infections. The 'virus' is, after all, called SARS or 'severe acute respiratory syndrome'. I highlighted in the spring of 2020 this phenomenon and quoted New York intensive care doctor Cameron Kyle-Sidell who posted a soon deleted YouTube video to say that they had been told to prepare to treat an infectious disease called 'Covid-19', but that was not what they were dealing with. Instead he likened the lung condition of the most severely ill patients to what you would expect with cabin depressurisation in a plane at 30,000 feet or someone dropped on the top of Everest without oxygen or acclimatisation. I have never said this is not happening to a small minority of alleged 'Covid' patients – I am saying this is not caused by a phantom 'contagious virus'. Indeed Kyle-Sidell said that 'Covid-19' was not the disease they were told was coming their way. 'We are operating under a medical paradigm that is untrue,' he said, and he believed they were treating the wrong disease: 'These people are being slowly starved of oxygen.' Patients would take off their oxygen masks in a state of fear and stress and while they were blue in the face on the brink of death. They did not look like patients dying of pneumonia. You can see why they don't want autopsies when their virus doesn't exist and there is another condition in some people that they don't wish to be uncovered. I should add here that

the 5G system of millimetre waves was being rapidly introduced around the world in 2020 and even more so now as they fire 5G at the Earth from satellites. At 60 gigahertz within the 5G range that frequency interacts with the oxygen molecule and stops people breathing in sufficient oxygen to be absorbed into the bloodstream. They are installing 5G in schools and hospitals. The world is not mad or anything. 5G can cause major changes to the lungs and blood as I detail in *The Answer* and these consequences are labelled 'Covid-19', the alleged symptoms of which can be caused by 5G and other electromagnetic frequencies as cells respond to radiation poisoning.

The 'Covid death' scam

Dr Scott Jensen, a Minnesota state senator and medical doctor, exposed 'Covid' Medicare payment incentives to hospitals and death certificate manipulation. He said he was sent a seven-page document by the US Department of Health 'coaching' him on how to fill out death certificates which had never happened before. The document said that he didn't need to have a laboratory test for 'Covid-19' to put that on the death certificate and that shocked him when death certificates are supposed to be about facts. Jensen described how doctors had been 'encouraged, if not pressured' to make a diagnosis of 'Covid-19' if they thought it was probable or *'presumed*'. No positive test was necessary – not that this would have mattered anyway. He said doctors were told to diagnose 'Covid' by symptoms when these were the same as colds, allergies, other respiratory problems, and certainly with influenza which 'disappeared' in the 'Covid' era. A common sniffle was enough to get the dreaded verdict. Ontario authorities decreed that a single care home resident with *one* symptom from a long list must lead to the isolation of the entire home. Other courageous doctors like Jensen made the same point about death figure manipulation and how deaths by other causes were falling while 'Covid-19 deaths' were rising at the same rate due to re-diagnosis. Their videos rarely survive long on YouTube with its Cult-supporting algorithms courtesy of CEO Susan Wojcicki and her bosses at Google. Figure-tampering was so glaring

and ubiquitous that even officials were letting it slip or outright saying it. UK chief scientific adviser Patrick Vallance said on one occasion that 'Covid' on the death certificate doesn't mean 'Covid' was the cause of death (so why the hell is it there?) and we had the rare sight of a BBC reporter telling the truth when she said: 'Someone could be successfully treated for Covid, in say April, discharged, and then in June, get run over by a bus and die … That person would still be counted as a Covid death in England.' Yet the BBC and the rest of the world media went on repeating the case and death figures as if they were real. Illinois Public Health Director Dr Ngozi Ezike revealed the deceit while her bosses must have been clenching their buttocks:

> If you were in a hospice and given a few weeks to live and you were then found to have Covid that would be counted as a Covid death. [There might be] a clear alternate cause, but it is still listed as a Covid death. So everyone listed as a Covid death doesn't mean that was the cause of the death, but that they had Covid at the time of death.

Yes, a 'Covid virus' never shown to exist and tested for with a test not testing for the 'virus'. In the first period of the pandemic hoax through the spring of 2020 the process began of designating almost everything a 'Covid' death and this has continued ever since. I sat in a restaurant one night listening to a loud conversation on the next table where a family was discussing in bewilderment how a relative who had no symptoms of 'Covid', and had died of a long-term problem, could have been diagnosed a death by the 'virus'. I could understand their bewilderment. If they read this book they will know why this medical fraud has been perpetrated the world over.

Some media truth shock

The media ignored the evidence of death certificate fraud until eventually one columnist did speak out when she saw it first-hand. Bel Mooney is a long-time national newspaper journalist in Britain currently working for the *Daily Mail*. Her article on February 19th, 2021, carried this headline: 'My dad Ted passed three Covid tests

and died of a chronic illness yet he's officially one of Britain's 120,000 victims of the virus and is far from alone ... so how many more are there?' She told how her 99-year-old father was in a care home with a long-standing chronic obstructive pulmonary disease and vascular dementia. Maybe, but he was still aware enough to tell her from the start that there was no 'virus' and he refused the 'vaccine' for that reason. His death was not unexpected given his chronic health problems and Mooney said she was shocked to find that 'Covid-19' was declared the cause of death on his death certificate. She said this was a 'bizarre and unacceptable untruth' for a man with long-time health problems who had tested negative twice at the home for the 'virus'. I was also shocked by this story although not by what she said. I had been highlighting the death certificate manipulation for ten months. It was the confirmation that a professional full-time journalist only realised this was going on when it affected her directly and neither did she know that whether her dad tested positive or negative was irrelevant with the test not testing for the 'virus'. Where had she been? She said she did not believe in 'conspiracy theories' without knowing I'm sure that this and 'conspiracy theorists' were terms put into widespread circulation by the CIA in the 1960s to discredit those who did not accept the ridiculous official story of the Kennedy assassination. A blanket statement of 'I don't believe in conspiracy theories' is always bizarre. The dictionary definition of the term alone means the world is drowning in conspiracies. What she said was even more daft when her dad had just been affected by the 'Covid' conspiracy. Why else does she think that 'Covid-19' was going on the death certificates of people who died of something else?

To be fair once she saw from personal experience what was happening she didn't mince words. Mooney was called by the care home on the morning of February 9th to be told her father had died in his sleep. When she asked for the official cause of death what came back was 'Covid-19'. Mooney challenged this and was told there had been deaths from Covid on the dementia floor (confirmed by a test not testing for the 'virus') so they considered it 'reasonable

to assume'. 'But doctor,' Mooney rightly protested, 'an assumption isn't a diagnosis.' She said she didn't blame the perfectly decent and sympathetic doctor – 'he was just doing his job'. Sorry, but that's *bullshit*. He wasn't doing his job at all. He was putting a false cause of death on the death certificate and that is a criminal offence for which he should be brought to account and the same with the millions of doctors worldwide who have done the same. They were not doing their job they were following orders and that must not wash at new Nuremberg trials any more than it did at the first ones. Mooney's doctor was 'assuming' (presuming) as he was told to, but 'just following orders' makes no difference to his actions. A doctor's job is to serve the patient and the truth, not follow orders, but that's what they have done all over the world and played a central part in making the 'Covid' hoax possible with all its catastrophic consequences for humanity. Shame on them and they must answer for their actions. Mooney said her disquiet worsened when she registered her father's death by telephone and was told by the registrar there had been very many other cases like hers where 'the deceased' had not tested positive for 'Covid' yet it was recorded as the cause of death. The test may not matter, but those involved at their level *think* it matters and it shows a callous disregard for accurate diagnosis. The pressure to do this is coming from the top of the national 'health' pyramids which in turn obey the World Health Organization which obeys Gates and the Cult. Mooney said the registrar agreed that this must distort the national figures adding that 'the strangest thing is that every winter we record countless deaths from flu, and this winter there have been none. Not one!' She asked if the registrar thought deaths from flu were being misdiagnosed and lumped together with 'Covid' deaths. The answer was a 'puzzled yes'. Mooney said that the funeral director said the same about 'Covid' deaths which had nothing to do with 'Covid'. They had lost count of the number of families upset by this and other funeral companies in different countries have had the same experience. Mooney wrote:

The nightly shroud-waving and shocking close-ups of pain imposed on us by the TV news bewildered and terrified the population into eager compliance with lockdowns. We were invited to 'save the NHS' and to grieve for strangers – the real-life loved ones behind those shocking death counts. Why would the public imagine what I now fear, namely that the way Covid-19 death statistics are compiled might make the numbers seem greater than they are?

Oh, just a little bit – like 100 percent.

Do the maths

Mooney asked why a country would wish to skew its mortality figures by wrongly certifying deaths? What had been going on? Well, if you don't believe in conspiracies you will never find the answer which is that *it's a conspiracy*. She did, however, describe what she had discovered as a 'national scandal'. In reality it's a global scandal and happening everywhere. Pillars of this conspiracy were all put into place before the button was pressed with the Drosten PCR protocol and high amplifications to produce the cases and death certificate changes to secure illusory 'Covid' deaths. Mooney notes that normally two doctors were needed to certify a death, with one having to know the patient, and how the rules were changed in the spring of 2020 to allow one doctor to do this. In the same period 'Covid deaths' were decreed to be all cases where Covid-19 was put on the death certificate even without a positive test or any symptoms. Mooney asked: 'How many of the 30,851 (as of January 15) care home resident deaths with Covid-19 on the certificate (32.4 per cent of all deaths so far) were based on an assumption, like that of my father? And what has that done to our national psyche?'All of them is the answer to the first question and it has devastated and dismantled the national psyche, actually the global psyche, on a colossal scale. In the UK case and death data is compiled by organisations like Public Health England (PHE) and the Office for National Statistics (ONS). Mooney highlights the insane policy of counting a death from any cause as 'Covid-19' if this happens within 28 days of a positive test (with a test not testing for the 'virus') and she points out that ONS statistics reflect deaths 'involving Covid' 'or due to Covid' which meant in practice any

death where 'Covid-19' was mentioned on the death certificate. She described the consequences of this fraud:

Most people will accept the narrative they are fed, so panicky governments here and in Europe witnessed the harsh measures enacted in totalitarian China and jumped into lockdown. Headlines about Covid deaths tolled like the knell that would bring doomsday to us all. Fear stalked our empty streets. Politicians parroted the frankly ridiculous aim of 'zero Covid' and shut down the economy, while most British people agreed that lockdown was essential and (astonishingly to me, as a patriotic Brit) even wanted more restrictions.

For what? Lies on death certificates? Never mind the grim toll of lives ruined, suicides, schools closed, rising inequality, depression, cancelled hospital treatments, cancer patients in a torture of waiting, poverty, economic devastation, loneliness, families kept apart, and so on. How many lives have been lost as a direct result of lockdown?

She said that we could join in a national chorus of shock and horror at reaching the 120,000 death toll which was surely certain to have been totally skewed all along, but what about the human cost of lockdown justified by these 'death figures'? *The British Medical Journal* had reported a 1,493 percent increase in cases of children taken to Great Ormond Street Hospital with abusive head injuries alone and then there was the effect on families:

Perhaps the most shocking thing about all this is that families have been kept apart – and obeyed the most irrational, changing rules at the whim of government – because they believed in the statistics. They succumbed to fear, which his generation rejected in that war fought for freedom. Dad (God rest his soul) would be angry. And so am I.

Another theme to watch is that in the winter months when there are more deaths from all causes they focus on 'Covid' deaths and in the summer when the British Lung Foundation says respiratory disease plummets by 80 percent they rage on about 'cases'. Either way fascism on population is always the answer.

Nazi eugenics in the 21st century

Elderly people in care homes have been isolated from their families month after lonely month with no contact with relatives and grandchildren who were banned from seeing them. We were told

that lockdown fascism was to 'protect the vulnerable' like elderly people. At the same time Do Not Resuscitate (DNR) orders were placed on their medical files so that if they needed resuscitation it wasn't done and 'Covid-19' went on their death certificates. Old people were not being 'protected' they were being culled – murdered in truth. DNR orders were being decreed for disabled and young people with learning difficulties or psychological problems. The UK Care Quality Commission, a non-departmental body of the Department of Health and Social Care, found that 34 percent of those working in health and social care were pressured into placing 'do not attempt cardiopulmonary resuscitation' orders on 'Covid' patients who suffered from disabilities and learning difficulties without involving the patient or their families in the decision. UK judges ruled that an elderly woman with dementia should have the DNA-manipulating 'Covid vaccine' against her son's wishes and that a man with severe learning difficulties should have the jab despite his family's objections. Never mind that many had already died. The judiciary always supports doctors and government in fascist dictatorships. They wouldn't dare do otherwise. A horrific video was posted showing fascist officers from Los Angeles police forcibly giving the 'Covid' shot to women with special needs who were screaming that they didn't want it. The same fascists are seen giving the jab to a sleeping elderly woman in a care home. This is straight out of the Nazi playbook. Hitler's Nazis committed mass murder of the mentally ill and physically disabled throughout Germany and occupied territories in the programme that became known as Aktion T4, or just T4. Sabbatian-controlled Hitler and his grotesque crazies set out to kill those they considered useless and unnecessary. The Reich Committee for the Scientific Registering of Hereditary and Congenital Illnesses registered the births of babies identified by physicians to have 'defects'. By 1941 alone more than 5,000 children were murdered by the state and it is estimated that in total the number of innocent people killed in Aktion T4 was between 275,000 and 300,000. Parents were told their children had been sent away for 'special treatment' never to return. It is rather pathetic to see claims about plans for new extermination camps being dismissed today

when the same force behind current events did precisely that 80 years ago. Margaret Sanger was a Cult operative who used 'birth control' to sanitise her programme of eugenics. Organisations she founded became what is now Planned Parenthood. Sanger proposed that 'the whole dysgenic population would have its choice of segregation or sterilization'. These included epileptics, 'feeble-minded', and prostitutes. Sanger opposed charity because it perpetuated 'human waste'. She reveals the Cult mentality and if anyone thinks that extermination camps are a 'conspiracy theory' their naivety is touching if breathtakingly stupid.

If you don't believe that doctors can act with callous disregard for their patients it is worth considering that doctors and medical staff agreed to put government-decreed DNR orders on medical files and do nothing when resuscitation is called for. I don't know what you call such people in your house. In mine they are Nazis from the Josef Mengele School of Medicine. Phenomenal numbers of old people have died worldwide from the effects of lockdown, depression, lack of treatment, the 'vaccine' (more later) and losing the will to live. A common response at the start of the manufactured pandemic was to remove old people from hospital beds and transfer them to nursing homes. The decision would result in a mass cull of elderly people in those homes through lack of treatment – *not* 'Covid'. Care home whistleblowers have told how once the 'Covid' era began doctors would not come to their homes to treat patients and they were begging for drugs like antibiotics that often never came. The most infamous example was ordered by New York governor Andrew Cuomo, brother of a moronic CNN host, who amazingly was given an Emmy Award for his handling of the 'Covid crisis' by the ridiculous Wokers that hand them out. Just how ridiculous could be seen in February, 2021, when a Department of Justice and FBI investigation began into how thousands of old people in New York died in nursing homes after being discharged from hospital to make way for 'Covid' patients on Cuomo's say-so – and how he and his staff covered up these facts. This couldn't have happened to a nicer psychopath. Even then there was a 'Covid' spin. Reports said that

thousands of old people who tested positive for 'Covid' in hospital were transferred to nursing homes to both die of 'Covid' and transmit it to others. No – they were in hospital because they were ill and the fact that they tested positive with a test not testing for the 'virus' is irrelevant. They were ill often with respiratory diseases ubiquitous in old people near the end of their lives. Their transfer out of hospital meant that their treatment stopped and many would go on to die.

They're old. Who gives a damn?

I have exposed in the books for decades the Cult plan to cull the world's old people and even to introduce at some point what they call a 'demise pill' which at a certain age everyone would take and be out of here by law. In March, 2021, Spain legalised euthanasia and assisted suicide following the Netherlands, Belgium, Luxembourg and Canada on the Tiptoe to the demise pill. Treatment of old people by many 'care' homes has been a disgrace in the 'Covid' era. There are many, many, caring staff – I know some. There have, however, been legions of stories about callous treatment of old people and their families. Police were called when families came to take their loved ones home in the light of isolation that was killing them. They became prisoners of the state. Care home residents in insane, fascist Ontario, Canada, were not allowed to leave their *room* once the 'Covid' hoax began. UK staff have even wheeled elderly people away from windows where family members were talking with them. Oriana Criscuolo from Stockport in the English North West dropped off some things for her 80-year-old father who has Parkinson's disease and dementia and she wanted to wave to him through a ground-floor window. She was told that was 'illegal'. When she went anyway they closed the curtains in the middle of the day. Oriana said:

> It's just unbelievable. I cannot understand how care home staff – people who are being paid to care – have become so uncaring. Their behaviour is inhumane and cruel. It's beyond belief.

She was right and this was not a one-off. What a way to end your life in such loveless circumstances. UK registered nurse Nicky Millen, a proper old school nurse for 40 years, said that when she started her career care was based on dignity, choice, compassion and empathy. Now she said 'the things that are important to me have gone out of the window.' She was appalled that people were dying without their loved ones and saying goodbye on iPads. Nicky described how a distressed 89-year-old lady stroked her face and asked her 'how many paracetamol would it take to finish me off'. Life was no longer worth living while not seeing her family. Nicky said she was humiliated in front of the ward staff and patients for letting the lady stroke her face and giving her a cuddle. Such is the dehumanisation that the 'Covid' hoax has brought to the surface. Nicky worked in care homes where patients told her they were being held prisoner. 'I want to live until I die', one said to her. 'I had a lady in tears because she hadn't seen her great-grandson.' Nicky was compassionate old school meeting psychopathic New Normal. She also said she had worked on a 'Covid' ward with no 'Covid' patients. Jewish writer Shai Held wrote an article in March, 2020, which was headlined 'The Staggering, Heartless Cruelty Toward the Elderly'. What he described was happening from the earliest days of lockdown. He said 'the elderly' were considered a group and not unique individuals (the way of the Woke). Shai Held said:

Notice how the all-too-familiar rhetoric of dehumanization works: 'The elderly' are bunched together as a faceless mass, all of them considered culprits and thus effectively deserving of the suffering the pandemic will inflict upon them. Lost entirely is the fact that the elderly are individual human beings, each with a distinctive face and voice, each with hopes and dreams, memories and regrets, friendships and marriages, loves lost and loves sustained.

'The elderly' have become another dehumanised group for which anything goes and for many that has resulted in cold disregard for their rights and their life. The distinctive face that Held talks about is designed to be deleted by masks until everyone is part of a faceless mass.

‘War-zone’ hospitals myth

Again and again medical professionals have told me what was really going on and how hospitals ‘overrun like war zones’ according to the media were virtually empty. The mantra from medical whistleblowers was please don’t use my name or my career is over. Citizen journalists around the world sneaked into hospitals to film evidence exposing the ‘war-zone’ lie. They really *were* largely empty with closed wards and operating theatres. I met a hospital worker in my town on the Isle of Wight during the first lockdown in 2020 who said the only island hospital had never been so quiet. Lockdown was justified by the psychopaths to stop hospitals being overrun. At the same time that the island hospital was near-empty the military arrived here to provide *extra beds*. It was all propaganda to ramp up the fear to ensure compliance with fascism as were never-used temporary hospitals with thousands of beds known as Nightingales and never-used make-shift mortuaries opened by the criminal UK government. A man who helped to install those extra island beds attributed to the army said they were never used and the hospital was empty. Doctors and nurses ‘stood around talking or on their phones, wandering down to us to see what we were doing’. There were no masks or social distancing. He accused the useless local island paper, the *County Press*, of ‘pumping the fear as if our hospital was overrun and we only have one so it should have been’. He described ambulances parked up with crews outside in deck chairs. When his brother called an ambulance he was told there was a two-hour backlog which he called ‘bullshit’. An old lady on the island fell ‘and was in a bad way’, but a caller who rang for an ambulance was told the situation wasn’t urgent enough. Ambulance stations were working under capacity while people would hear ambulances with sirens blaring driving through the streets. When those living near the stations realised what was going on they would follow them as they left, circulated around an urban area with the sirens going, and then came back without stopping. All this was to increase levels of fear and the same goes for the ‘ventilator shortage crisis’ that cost tens of millions for hastily produced ventilators never to be used.

Ambulance crews that agreed to be exploited in this way for fear propaganda might find themselves a mirror. I wish them well with that. Empty hospitals were the obvious consequence of treatment and diagnoses of non-'Covid' conditions cancelled and those involved handed a death sentence. People have been dying at home from undiagnosed and untreated cancer, heart disease and other life-threatening conditions to allow empty hospitals to deal with a 'pandemic' that wasn't happening.

Death of the innocent

'War-zones' have been laying off nursing staff, even doctors where they can. There was no work for them. Lockdown was justified by saving lives and protecting the vulnerable they were actually killing with DNR orders and preventing empty hospitals being 'overrun'. In Britain the mantra of stay at home to 'save the NHS' was everywhere and across the world the same story was being sold when it was all lies. Two California doctors, Dan Erickson and Artin Massihi at Accelerated Urgent Care in Bakersfield, held a news conference in April, 2020, to say that intensive care units in California were 'empty, essentially', with hospitals shutting floors, not treating patients and laying off doctors. The California health system was working at minimum capacity 'getting rid of doctors because we just don't have the volume'. They said that people with conditions such as heart disease and cancer were not coming to hospital out of fear of 'Covid-19'. Their video was deleted by Susan Wojcicki's Cult-owned YouTube after reaching five million views. Florida governor Ron Desantis, who rejected the severe lockdowns of other states and is being targeted for doing so, said that in March, 2020, every US governor was given models claiming they would run out of hospital beds in days. That was never going to happen and the 'modellers' knew it. Deceit can be found at every level of the system. Urgent children's operations were cancelled including fracture repairs and biopsies to spot cancer. Eric Nicholls, a consultant paediatrician, said 'this is obviously concerning and we need to return to normal operating and to increase capacity as soon as possible'. Psychopaths

in power were rather less concerned *because* they are psychopaths. Deletion of urgent care and diagnosis has been happening all over the world and how many kids and others have died as a result of the actions of these cold and heartless lunatics dictating 'health' policy? The number must be stratospheric. Richard Sullivan, professor of cancer and global health at King's College London, said people feared 'Covid' more than cancer such was the campaign of fear. 'Years of lost life will be quite dramatic', Sullivan said, with 'a huge amount of avoidable mortality'. Sarah Woolnough, executive director for policy at Cancer Research UK, said there had been a 75 percent drop in urgent referrals to hospitals by family doctors of people with suspected cancer. Sullivan said that 'a lot of services have had to scale back – we've seen a dramatic decrease in the amount of elective cancer surgery'. Lockdown deaths worldwide has been absolutely fantastic with the *New York Post* reporting how data confirmed that 'lockdowns end more lives than they save':

> There was a sharp decline in visits to emergency rooms and an increase in fatal heart attacks because patients didn't receive prompt treatment. Many fewer people were screened for cancer. Social isolation contributed to excess deaths from dementia and Alzheimer's.
>
> Researchers predicted that the social and economic upheaval would lead to tens of thousands of "deaths of despair" from drug overdoses, alcoholism and suicide. As unemployment surged and mental-health and substance-abuse treatment programs were interrupted, the reported levels of anxiety, depression and suicidal thoughts increased dramatically, as did alcohol sales and fatal drug overdoses.

This has been happening while nurses and other staff had so much time on their hands in the 'war-zones' that Tic-Tok dancing videos began appearing across the Internet with medical staff dancing around in empty wards and corridors as people died at home from causes that would normally have been treated in hospital.

Mentions in dispatches

One brave and truth-committed whistleblower was Louise Hampton, a call handler with the UK NHS who made a viral Internet video saying she had done 'fuck all' during the 'pandemic'

which was 'a load of bollocks'. She said that 'Covid-19' was rebranded flu and of course she lost her job. This is what happens in the medical and endless other professions now when you tell the truth. Louise filmed inside 'war-zone' accident and emergency departments to show they were empty and I mean *empty* as in no one there. The mainstream media could have done the same and blown the gaff on the whole conspiracy. They haven't to their eternal shame. Not that most 'journalists' seem capable of manifesting shame as with the psychopaths they slavishly repeat without question. The relative few who were admitted with serious health problems were left to die alone with no loved ones allowed to see them because of 'Covid' rules and they included kids dying without the comfort of mum and dad at their bedside while the evil behind this couldn't give a damn. It was all good fun to them. A Scottish NHS staff nurse publicly quit in the spring of 2021 saying: 'I can no longer be part of the lies and the corruption by the government.' She said hospitals 'aren't full, the beds aren't full, beds have been shut, wards have been shut'. Hospitals were never busy throughout 'Covid'. The staff nurse said that Nicola Sturgeon, tragically the leader of the Scottish government, was on television saying save the hospitals and the NHS – 'but the beds are empty' and 'we've not seen flu, we always see flu every year'. She wrote to government and spoke with her union Unison (the unions are Cult-compromised and *useless*, but nothing changed. Many of her colleagues were scared of losing their jobs if they spoke out as they wanted to. She said nursing staff were being affected by wearing masks all day and 'my head is splitting every shift from wearing a mask'. The NHS is part of the fascist tyranny and must be dismantled so we can start again with human beings in charge. (Ironically, hospitals were reported to be busier again when official 'Covid' cases *fell* in spring/summer of 2021 and many other conditions required treatment at the same time as *the fake vaccine rollout*.)

I will cover the 'Covid vaccine' scam in detail later, but it is another indicator of the sickening disregard for human life that I am highlighting here. The DNA-manipulating concoctions do not fulfil

the definition of a 'vaccine', have never been used on humans before and were given only emergency approval because trials were not completed and they continued using the unknowing public. The result was what a NHS senior nurse with responsibility for 'vaccine' procedure said was 'genocide'. She said the 'vaccines' were not 'vaccines'. They had not been shown to be safe and claims about their effectiveness by drug companies were 'poetic licence'. She described what was happening as a 'horrid act of human annihilation'. The nurse said that management had instigated a policy of not providing a Patient Information Leaflet (PIL) before people were 'vaccinated' even though health care professionals are supposed to do this according to protocol. Patients should also be told that they are taking part in an ongoing clinical trial. Her challenges to what is happening had seen her excluded from meetings and ridiculed in others. She said she was told to 'watch my step … or I would find myself surplus to requirements'. The nurse, who spoke anonymously in fear of her career, said she asked her NHS manager why he/she was content with taking part in genocide against those having the 'vaccines'. The reply was that everyone had to play their part and to 'put up, shut up, and get it done'. Government was 'leaning heavily' on NHS management which was clearly leaning heavily on staff. This is how the global 'medical' hierarchy operates and it starts with the Cult and its World Health Organization.

She told the story of a doctor who had the Pfizer jab and when questioned had no idea what was in it. The doctor had never read the literature. We have to stop treating doctors as intellectual giants when so many are moral and medical pygmies. The doctor did not even know that the 'vaccines' were not fully approved or that their trials were ongoing. They were, however, asking their patients if they minded taking part in follow-ups for research purposes – yes, the *ongoing clinical trial*. The nurse said the doctor's ignorance was not rare and she had spoken to a hospital consultant who had the jab without any idea of the background or that the 'trials' had not been completed. Nurses and pharmacists had shown the same ignorance.

'My NHS colleagues have forsaken their duty of care, broken their code of conduct – Hippocratic Oath – and have been brainwashed just the same as the majority of the UK public through propaganda …' She said she had not been able to recruit a single NHS colleague, doctor, nurse or pharmacist to stand with her and speak out. Her union had refused to help. She said that if the genocide came to light she would not hesitate to give evidence at a Nuremberg-type trial against those in power who could have affected the outcomes but didn't.

And all for what?

To put the nonsense into perspective let's say the 'virus' does exist and let's go completely crazy and accept that the official manipulated figures for cases and deaths are accurate. *Even then* a study by Stanford University epidemiologist Dr John Ioannidis published on the World Health Organization website produced an average infection to fatality rate of … *0.23 percent!* Ioannidis said: 'If one could sample equally from all locations globally, the median infection fatality rate might even be substantially lower than the 0.23% observed in my analysis.' For healthy people under 70 it was … *0.05 percent*! This compares with the 3.4 percent claimed by the Cult-owned World Health Organization when the hoax was first played and maximum fear needed to be generated. An updated Stanford study in April, 2021, put the 'infection' to 'fatality' rate at just 0.15 percent. Another team of scientists led by Megan O'Driscoll and Henrik Salje studied data from 45 countries and published their findings on the Nature website. For children and young people the figure is so small it virtually does not register although authorities will be hyping dangers to the young when they introduce DNA-manipulating 'vaccines' for children. The O'Driscoll study produced an average infection-fatality figure of 0.003 for children from birth to four; 0.001 for 5 to 14; 0.003 for 15 to 19; and it was still only 0.456 up to 64. To claim that children must be 'vaccinated' to protect them from 'Covid' is an obvious lie and so there must be another reason and there is. What's more the average age of a 'Covid' death is akin

to the average age that people die in general. The average age of death in England is about 80 for men and 83 for women. The average age of death from alleged 'Covid' is between 82 and 83. California doctors, Dan Erickson and Artin Massihi, said at their April media conference that projection models of millions of deaths had been 'woefully inaccurate'. They produced detailed figures showing that Californians had a 0.03 chance of dying from 'Covid' based on the number of people who tested positive (with a test not testing for the 'virus'). Erickson said there was a 0.1 percent chance of dying from 'Covid' in the *state* of New York, not just the city, and a 0.05 percent chance in Spain, a centre of 'Covid-19' hysteria at one stage. The Stanford studies supported the doctors' data with fatality rate estimates of 0.23 and 0.15 percent. How close are these figures to my estimate of *zero*? Death-rate figures claimed by the World Health Organization at the start of the hoax were some 15 times higher. The California doctors said there was no justification for lockdowns and the economic devastation they caused. Everything they had ever learned about quarantine was that you quarantine the *sick* and not the healthy. They had never seen this before and it made no medical sense.

Why in the in the light of all this would governments and medical systems the world over say that billions must go under house arrest; lose their livelihood; in many cases lose their mind, their health and their life; force people to wear masks dangerous to health and psychology; make human interaction and even family interaction a criminal offence; ban travel; close restaurants, bars, watching live sport, concerts, theatre, and any activity involving human togetherness and discourse; and closing schools to isolate children from their friends and cause many to commit suicide in acts of hopelessness and despair? The California doctors said lockdown consequences included increased child abuse, partner abuse, alcoholism, depression, and other impacts they were seeing every day. Who would do that to the entire human race if not mentally-ill psychopaths of almost unimaginable extremes like Bill Gates? We must face the reality of what we are dealing with and come out of

denial. Fascism and tyranny are made possible only by the target population submitting and acquiescing to fascism and tyranny. The whole of human history shows that to be true. Most people naively and unquestioning believed what they were told about a 'deadly virus' and meekly and weakly submitted to house arrest. Those who didn't believe it – at least in total – still submitted in fear of the consequences of not doing so. For the rest who wouldn't submit draconian fines have been imposed, brutal policing by psychopaths *for* psychopaths, and condemnation from the meek and weak who condemn the Pushbackers on behalf of the very force that has them, too, in its gunsights. 'Pathetic' does not even begin to suffice. Britain's brainless 'Health' Secretary Matt Hancock warned anyone lying to border officials about returning from a list of 'hotspot' countries could face a jail sentence of up to ten years which is more than for racially-aggravated assault, incest and attempting to have sex with a child under 13. Hancock is a lunatic, but he has the state apparatus behind him in a Cult-led chain reaction and the same with UK 'Vaccine Minister' Nadhim Zahawi, a prominent member of the mega-Cult secret society, Le Cercle, which featured in my earlier books. The Cult enforces its will on governments and medical systems; government and medical systems enforce their will on business and police; business enforces its will on staff who enforce it on customers; police enforce the will of the Cult on the population and play their essential part in creating a world of fascist control that their own children and grandchildren will have to live in their entire lives. It is a hierarchical pyramid of imposition and acquiescence and, yes indeedy, of clinical insanity.

Does anyone bright enough to read this book have to ask what the answer is? I think not, but I will reveal it anyway in the fewest of syllables: Tell the psychos and their moronic lackeys to fuck off and let's get on with our lives. We are many – They are few.

CHAPTER SEVEN

War on your mind

One believes things because one has been conditioned to believe them
Aldous Huxley, *Brave New World*

I have described the 'Covid' hoax as a 'Psyop' and that is true in every sense and on every level in accordance with the definition of that term which is psychological warfare. Break down the 'Covid pandemic' to the foundation themes and it is psychological warfare on the human individual and collective mind.

The same can be said for the entire human belief system involving every subject you can imagine. Huxley was right in his contention that people believe what they are conditioned to believe and this comes from the repetition throughout their lives of the same falsehoods. They spew from government, corporations, media and endless streams of 'experts' telling you what the Cult wants you to believe and often believing it themselves (although *far* from always). 'Experts' are rewarded with 'prestigious' jobs and titles and as agents of perceptual programming with regular access to the media. The Cult has to control the narrative – control *information* – or they lose control of the vital, crucial, without-which-they-cannot-prevail public perception of reality. The foundation of that control today is the Internet made possible by the Defense Advanced Research Projects Agency (DARPA), the incredibly sinister technological arm of the Pentagon. The Internet is the result of military technology.

DARPA openly brags about establishing the Internet which has been a long-term project to lasso the minds of the global population. I have said for decades the plan is to control information to such an extreme that eventually no one would see or hear anything that the Cult does not approve. We are closing in on that end with ferocious censorship since the 'Covid' hoax began and in my case it started back in the 1990s in terms of books and speaking venues. I had to create my own publishing company in 1995 precisely because no one else would publish my books even then. I think they're all still running.

Cult Internet

To secure total control of information they needed the Internet in which pre-programmed algorithms can seek out 'unclean' content for deletion and even stop it being posted in the first place. The Cult had to dismantle print and non-Internet broadcast media to ensure the transfer of information to the appropriate-named 'Web' – a critical expression of the *Cult* web. We've seen the ever-quickening demise of traditional media and control of what is left by a tiny number of corporations operating worldwide. Independent journalism in the mainstream is already dead and never was that more obvious than since the turn of 2020. The Cult wants all information communicated via the Internet to globally censor and allow the plug to be pulled any time. Lockdowns and forced isolation has meant that communication between people has been through electronic means and no longer through face-to-face discourse and discussion. Cult psychopaths have targeted the bars, restaurants, sport, venues and meeting places in general for this reason. None of this is by chance and it's to stop people gathering in any kind of privacy or number while being able to track and monitor all Internet communications and block them as necessary. Even private messages between individuals have been censored by these fascists that control Cult fronts like Facebook, Twitter, Google and YouTube which are all officially run by Sabbatian place-people and from the background by higher-level Sabbatian place people.

Facebook, Google, Amazon and their like were seed-funded and supported into existence with money-no-object infusions of funds either directly or indirectly from DARPA and CIA technology arm In-Q-Tel. The Cult plays the long game and prepares very carefully for big plays like 'Covid'. Amazon is another front in the psychological war and pretty much controls the global market in book sales and increasingly publishing. Amazon's limitless funds have deleted fantastic numbers of independent publishers to seize global domination on the way to deciding which books can be sold and circulated and which cannot. Moves in that direction are already happening. Amazon's leading light Jeff Bezos is the grandson of Lawrence Preston Gise who worked with DARPA predecessor ARPA. Amazon has big connections to the CIA and the Pentagon. The plan I have long described went like this:

1. Employ military technology to establish the Internet.

2. Sell the Internet as a place where people can freely communicate without censorship and allow that to happen until the Net becomes the central and irreversible pillar of human society. If the Internet had been highly censored from the start many would have rejected it.

3. Fund and manipulate major corporations into being to control the circulation of information on your Internet using cover stories about geeks in garages to explain how they came about. Give them unlimited funds to expand rapidly with no need to make a profit for years while non-Cult companies who need to balance the books cannot compete. You know that in these circumstances your Googles, YouTubes, Facebooks and Amazons are going to secure near monopolies by either crushing or buying up the opposition.

4. Allow freedom of expression on both the Internet and communication platforms to draw people in until the Internet is the central and irreversible pillar of human society and your communication corporations have reached a stage of near monopoly domination.

5. Then unleash your always-planned frenzy of censorship on the basis of 'where else are you going to go?' and continue to expand that until nothing remains that the Cult does not want its human targets to see.

The process was timed to hit the 'Covid' hoax to ensure the best chance possible of controlling the narrative which they knew they had to do at all costs. They were, after all, about to unleash a 'deadly virus' that didn't really exist. If you do that in an environment of free-flowing information and opinion you would be dead in the

water before you could say Gates is a psychopath. The network was in place through which the Cult-created-and-owned World Health Organization could dictate the 'Covid' narrative and response policy slavishly supported by Cult-owned Internet communication giants and mainstream media while those telling a different story were censored. Google, YouTube, Facebook and Twitter openly announced that they would do this. What else would we expect from Cult-owned operations like Facebook which former executives have confirmed set out to make the platform more addictive than cigarettes and coldly manipulates emotions of its users to sow division between people and groups and scramble the minds of the young? If Zuckerberg lives out the rest of his life without going to jail for crimes against humanity, and most emphatically against the young, it will be a travesty of justice. Still, no matter, cause and effect will catch up with him eventually and the same with Sergey Brin and Larry Page at Google with its CEO Sundar Pichai who fix the Google search results to promote Cult narratives and hide the opposition. Put the same key words into Google and other search engines like DuckDuckGo and you will see how different results can be. Wikipedia is another intensely biased 'encyclopaedia' which skews its content to the Cult agenda. YouTube links to Wikipedia's version of 'Covid' and 'climate change' on video pages in which experts in their field offer a different opinion (even that is increasingly rare with Wojcicki censorship). Into this 'Covid' silence-them network must be added government media censors, sorry 'regulators', such as Ofcom in the UK which imposed tyrannical restrictions on British broadcasters that had the effect of banning me from ever appearing. Just to debate with me about my evidence and views on 'Covid' would mean breaking the fascistic impositions of Ofcom and its CEO career government bureaucrat Melanie Dawes. Gutless British broadcasters tremble at the very thought of fascist Ofcom.

Psychos behind 'Covid'

The reason for the 'Covid' catastrophe in all its facets and forms can be seen by whom and what is driving the policies worldwide in such a coordinated way. Decisions are not being made to protect health, but to target psychology. The dominant group guiding and 'advising' government policy are not medical professionals. They are psychologists and behavioural scientists. Every major country has its own version of this phenomenon and I'll use the British example to show how it works. In many ways the British version has been affecting the wider world in the form of the huge behaviour manipulation network in the UK which operates in other countries. The network involves private companies, government, intelligence and military. The Cabinet Office is at the centre of the government 'Covid' Psyop and part-owns, with 'innovation charity' Nesta, the Behavioural Insights Team (BIT) which claims to be independent of government but patently isn't. The BIT was established in 2010 and its job is to manipulate the psyche of the population to acquiesce to government demands and so much more. It is also known as the 'Nudge Unit', a name inspired by the 2009 book by two ultra-Zionists, Cass Sunstein and Richard Thaler, called *Nudge: Improving Decisions About Health, Wealth, and Happiness*. The book, as with the Behavioural Insights Team, seeks to 'nudge' behaviour (manipulate it) to make the public follow patterns of action and perception that suit those in authority (the Cult). Sunstein is so skilled at this that he advises the World Health Organization and the UK Behavioural Insights Team and was Administrator of the White House Office of Information and Regulatory Affairs in the Obama administration. Biden appointed him to the Department of Homeland Security – another ultra-Zionist in the fold to oversee new immigration laws which is another policy the Cult wants to control. Sunstein is desperate to silence anyone exposing conspiracies and co-authored a 2008 report on the subject in which suggestions were offered to ban 'conspiracy theorizing' or impose 'some kind of tax, financial or otherwise, on those who disseminate such theories'. I guess a psychiatrist's chair is out of the question?

Sunstein's mate Richard Thaler, an 'academic affiliate' of the UK Behavioural Insights Team, is a proponent of 'behavioural economics' which is defined as the study of 'the effects of psychological, cognitive, emotional, cultural and social factors on the decisions of individuals and institutions'. Study the effects so they can be manipulated to be what you want them to be. Other leading names in the development of behavioural economics are ultra-Zionists Daniel Kahneman and Robert J. Shiller and they, with Thaler, won the Nobel Memorial Prize in Economic Sciences for their work in this field. The Behavioural Insights Team is operating at the heart of the UK government and has expanded globally through partnerships with several universities including Harvard, Oxford, Cambridge, University College London (UCL) and Pennsylvania. They claim to have 'trained' (reframed) 20,000 civil servants and run more than 750 projects involving 400 randomised controlled trials in dozens of countries' as another version of mind reframers Common Purpose. BIT works from its office in New York with cities and their agencies, as well as other partners, across the United States and Canada – this is a company part-owned by the British government Cabinet Office. An executive order by President Cult-servant Obama established a US Social and Behavioral Sciences Team in 2015. They all have the same reason for being and that's to brainwash the population directly and by brainwashing those in positions of authority.

'Covid' mind game

Another prime aspect of the UK mind-control network is the 'independent' [joke] Scientific Pandemic Insights Group on Behaviours (SPI-B) which 'provides behavioural science advice aimed at anticipating and helping people adhere to interventions that are recommended by medical or epidemiological experts'. That means manipulating public perception and behaviour to do whatever government tells them to do. It's disgusting and if they really want the public to be 'safe' this lot should all be under lock and key. According to the government website SPI-B consists of

'behavioural scientists, health and social psychologists, anthropologists and historians' and advises the Whitty-Vallance-led Scientific Advisory Group for Emergencies (SAGE) which in turn advises the government on 'the science' (it doesn't) and 'Covid' policy. When politicians say they are being guided by 'the science' this is the rabble in each country they are talking about and that 'science' is dominated by behaviour manipulators to enforce government fascism through public compliance. The Behaviour Insight Team is headed by psychologist David Solomon Halpern, a visiting professor at King's College London, and connects with a national and global web of other civilian and military organisations as the Cult moves towards its goal of fusing them into one fascistic whole in every country through its 'Fusion Doctrine'. The behaviour manipulation network involves, but is not confined to, the Foreign Office; National Security Council; government communications headquarters (GCHQ); MI5; MI6; the Cabinet Office-based Media Monitoring Unit; and the Rapid Response Unit which 'monitors digital trends to spot emerging issues; including misinformation and disinformation; and identifies the best way to respond'.

There is also the 77th Brigade of the UK military which operates like the notorious Israeli military's Unit 8200 in manipulating information and discussion on the Internet by posing as members of the public to promote the narrative and discredit those who challenge it. Here we have the military seeking to manipulate *domestic* public opinion while the Nazis in government are fine with that. Conservative Member of Parliament Tobias Ellwood, an advocate of lockdown and control through 'vaccine passports', is a Lieutenant Colonel reservist in the 77th Brigade which connects with the military operation jHub, the 'innovation centre' for the Ministry of Defence and Strategic Command. jHub has also been involved with the civilian National Health Service (NHS) in 'symptom tracing' the population. The NHS is a key part of this mind control network and produced a document in December, 2020, explaining to staff how to use psychological manipulation with different groups and ages to get them to have the DNA-manipulating 'Covid vaccine'

that's designed to cumulatively rewrite human genetics. The document, called 'Optimising Vaccination Roll Out – Do's and Dont's for all messaging, documents and "communications" in the widest sense', was published by NHS England and the NHS Improvement *Behaviour Change Unit* in partnership with Public Health England and Warwick Business School. I hear the mantra about 'save the NHS' and 'protect the NHS' when we need to scrap the NHS and start again. The current version is far too corrupt, far too anti-human and totally compromised by Cult operatives and their assets. UK government broadcast media censor Ofcom will connect into this web – as will the BBC with its tremendous Ofcom influence – to control what the public see and hear and dictate mass perception. Nuremberg trials must include personnel from all these organisations.

The fear factor

The 'Covid' hoax has led to the creation of the UK Cabinet Office-connected Joint Biosecurity Centre (JBC) which is officially described as providing 'expert advice on pandemics' using its independent [all Cult operations are 'independent'] analytical function to provide real-time analysis about infection outbreaks to identify and respond to outbreaks of Covid-19'. Another role is to advise the government on a response to spikes in infections – 'for example by closing schools or workplaces in local areas where infection levels have risen'. Put another way, promoting the Cult agenda. The Joint Biosecurity Centre is modelled on the Joint Terrorism Analysis Centre which analyses intelligence to set 'terrorism threat levels' and here again you see the fusion of civilian and military operations and intelligence that has led to military intelligence producing documents about 'vaccine hesitancy' and how it can be combated. Domestic civilian matters and opinions should not be the business of the military. The Joint Biosecurity Centre is headed by Tom Hurd, director general of the Office for Security and Counter-Terrorism from the establishment-to-its-fingertips Hurd family. His father is former Foreign Secretary Douglas Hurd. How coincidental that Tom

Hurd went to the elite Eton College and Oxford University with Boris Johnson. Imperial College with its ridiculous computer modeller Neil Ferguson will connect with this gigantic web that will itself interconnect with similar set-ups in other major and not so major countries. Compared with this Cult network the politicians, be they Boris Johnson, Donald Trump or Joe Biden, are bit-part players 'following the science'. The network of psychologists was on the 'Covid' case from the start with the aim of generating maximum fear of the 'virus' to ensure compliance by the population. A government behavioural science group known as SPI-B produced a paper in March, 2020, for discussion by the main government science advisory group known as SAGE. It was headed 'Options for increasing adherence to social distancing measures' and it said the following in a section headed 'Persuasion':

- A substantial number of people still do not feel sufficiently personally threatened; it could be that they are reassured by the low death rate in their demographic group, although levels of concern may be rising. Having a good understanding of the risk has been found to be positively associated with adoption of COVID-19 social distancing measures in Hong Kong.

- The perceived level of personal threat needs to be increased among those who are complacent, using hard-hitting evaluation of options for increasing social distancing emotional messaging. To be effective this must also empower people by making clear the actions they can take to reduce the threat.

- Responsibility to others: There seems to be insufficient understanding of, or feelings of responsibility about, people's role in transmitting the infection to others … Messaging about actions need to be framed positively in terms of protecting oneself and the community, and increase confidence that they will be effective.

- Some people will be more persuaded by appeals to play by the rules, some by duty to the community, and some to personal risk.

> All these different approaches are needed. The messaging also needs to take account of the realities of different people's lives. Messaging needs to take account of the different motivational levers and circumstances of different people.

All this could be achieved the SPI-B psychologists said by *using the media to increase the sense of personal threat* which translates as terrify the shit out of the population, including children, so they all do what we want. That's not happened has it? Those excuses for 'journalists' who wouldn't know journalism if it bit them on the arse (the great majority) have played their crucial part in serving this Cult-government Psyop to enslave their own kids and grandkids. How they live with themselves I have no idea. The psychological war has been underpinned by constant government 'Covid' propaganda in almost every television and radio ad break, plus the Internet and print media, which has pounded out the fear with taxpayers footing the bill for their own programming. The result has been people terrified of a 'virus' that doesn't exist or one with a tiny fatality rate even if you believe it does. People walk down the street and around the shops wearing face-nappies damaging their health and psychology while others report those who refuse to be that naïve to the police who turn up in their own face-nappies. I had a cameraman come to my flat and he was so frightened of 'Covid' he came in wearing a mask and refused to shake my hand in case he caught something. He had – naïveitis – and the thought that he worked in the mainstream media was both depressing and made his behaviour perfectly explainable. The fear which has gripped the minds of so many and frozen them into compliance has been carefully cultivated by these psychologists who are really psychopaths. If lives get destroyed and a lot of young people commit suicide it shows our plan is working. SPI-B then turned to compulsion on the public to comply. 'With adequate preparation, rapid change can be achieved', it said. Some countries had introduced mandatory self-isolation on a wide scale without evidence of major public unrest and a large majority of the UK's population appeared to be supportive of more coercive measures with 64 percent of adults saying they would

support putting London under a lockdown (watch the 'polls' which are designed to make people believe that public opinion is in favour or against whatever the subject in hand).

For 'aggressive protective measures' to be effective, the SPI-B paper said, special attention should be devoted to those population groups that are more at risk. Translated from the Orwellian this means making the rest of population feel guilty for not protecting the 'vulnerable' such as old people which the Cult and its agencies were about to kill on an industrial scale with lockdown, lack of treatment and the Gates 'vaccine'. Psychopath psychologists sold their guilt-trip so comprehensively that Los Angeles County Supervisor Hilda Solis reported that children were apologising (from a distance) to their parents and grandparents for bringing 'Covid' into their homes and getting them sick. '… These apologies are just some of the last words that loved ones will ever hear as they die alone,' she said. Gut-wrenchingly Solis then used this childhood tragedy to tell children to stay at home and 'keep your loved ones alive'. Imagine heaping such potentially life-long guilt on a kid when it has absolutely nothing to do with them. These people are deeply disturbed and the psychologists behind this even more so.

Uncivil war – divide and rule

Professional mind-controllers at SPI-B wanted the media to increase a sense of responsibility to others (do as you're told) and promote 'positive messaging' for those actions while in contrast to invoke 'social disapproval' by the unquestioning, obedient, community of anyone with a mind of their own. Again the compliant Goebbels-like media obliged. This is an old, old, trick employed by tyrannies the world over throughout human history. You get the target population to keep the target population in line – *your* line. SPI-B said this could 'play an important role in preventing anti-social behaviour or discouraging failure to enact pro-social behaviour'. For 'anti-social' in the Orwellian parlance of SPI-B see any behaviour that government doesn't approve. SPI-B recommendations said that 'social disapproval' should be accompanied by clear messaging and

promotion of strong collective identity – hence the government and celebrity mantra of 'we're all in this together'. Sure we are. The mind doctors have such contempt for their targets that they think some clueless comedian, actor or singer telling them to do what the government wants will be enough to win them over. We have had UK comedian Lenny Henry, actor Michael Caine and singer Elton John wheeled out to serve the propagandists by urging people to have the DNA-manipulating 'Covid' non-'vaccine'. The role of Henry and fellow black celebrities in seeking to coax a 'vaccine' reluctant black community into doing the government's will was especially stomach-turning. An emotion-manipulating script and carefully edited video featuring these black 'celebs' was such an insult to the intelligence of black people and where's the self-respect of those involved selling their souls to a fascist government agenda? Henry said he heard black people's 'legitimate worries and concerns', but people must 'trust the facts' when they were doing exactly that by not having the 'vaccine'. They had to include the obligatory reference to Black Lives Matter with the line … 'Don't let coronavirus cost even more black lives – because we matter'. My god, it was pathetic. 'I know the vaccine is safe and what it does.' How? 'I'm a comedian and it says so in my script.'

SPI-B said social disapproval needed to be carefully managed to avoid victimisation, scapegoating and misdirected criticism, but they knew that their 'recommendations' would lead to exactly that and the media were specifically used to stir-up the divide-and-conquer hostility. Those who conform like good little baa, baas, are praised while those who have seen through the tidal wave of lies are 'Covidiots'. The awake have been abused by the fast asleep for not conforming to fascism and impositions that the awake know are designed to endanger their health, dehumanise them, and tear asunder the very fabric of human society. We have had the curtain-twitchers and morons reporting neighbours and others to the face-nappied police for breaking 'Covid rules' with fascist police delighting in posting links and phone numbers where this could be done. The Cult cannot impose its will without a compliant police

and military or a compliant population willing to play their part in enslaving themselves and their kids. The words of a pastor in Nazi Germany are so appropriate today:

First they came for the socialists and I did not speak out because I was not a socialist.

Then they came for the trade unionists and I did not speak out because I was not a trade unionist.

Then they came for the Jews and I did not speak out because I was not a Jew.

Then they came for me and there was no one left to speak for me.

Those who don't learn from history are destined to repeat it and so many are.

'Covid' rules: Rewiring the mind

With the background laid out to this gigantic national and global web of psychological manipulation we can put 'Covid' rules into a clear and sinister perspective. Forget the claims about protecting health. 'Covid' rules are about dismantling the human mind, breaking the human spirit, destroying self-respect, and then putting Humpty Dumpty together again as a servile, submissive slave. Social isolation through lockdown and distancing have devastating effects on the human psyche as the psychological psychopaths well know and that's the real reason for them. Humans need contact with each other, discourse, closeness and touch, or they eventually, and literarily, go crazy. Masks, which I will address at some length, fundamentally add to the effects of isolation and the Cult agenda to dehumanise and de-individualise the population. To do this while knowing – in fact *seeking* – this outcome is the very epitome of evil and psychologists involved in this *are* the epitome of evil. They must like all the rest of the Cult demons and their assets stand trial for crimes against humanity on a scale that defies the imagination. Psychopaths in uniform use isolation to break enemy troops and agents and make them subservient and submissive to tell what they know. The technique is rightly considered a form of torture and

torture is most certainly what has been imposed on the human population.

Clinically-insane American psychologist Harry Harlow became famous for his isolation experiments in the 1950s in which he separated baby monkeys from their mothers and imprisoned them for months on end in a metal container or 'pit of despair'. They soon began to show mental distress and depression as any idiot could have predicted. Harlow put other monkeys in steel chambers for three, six or twelve months while denying them any contact with animals or humans. He said that the effects of total social isolation for six months were 'so devastating and debilitating that we had assumed initially that twelve months of isolation would not produce any additional decrement'; but twelve months of isolation 'almost obliterated the animals socially'. This is what the Cult and its psychopaths are doing to you and your children. Even monkeys in partial isolation in which they were not allowed to form relationships with other monkeys became 'aggressive and hostile, not only to others, but also towards their own bodies'. We have seen this in the young as a consequence of lockdown. UK government psychopaths launched a public relations campaign telling people not to hug each other even after they received the 'Covid-19 vaccine' which we were told with more lies would allow a return to 'normal life'. A government source told *The Telegraph*: 'It will be along the lines that it is great that you have been vaccinated, but if you are going to visit your family and hug your grandchildren there is a chance you are going to infect people you love.' The source was apparently speaking from a secure psychiatric facility. Janet Lord, director of Birmingham University's Institute of Inflammation and Ageing, said that parents and grandparents should avoid hugging their children. Well, how can I put it, Ms Lord? Fuck off. Yep, that'll do.

Destroying the kids – where are the parents?

Observe what has happened to people enslaved and isolated by lockdown as suicide and self-harm has soared worldwide,

particularly among the young denied the freedom to associate with their friends. A study of 49,000 people in English-speaking countries concluded that almost half of young adults are at clinical risk of mental health disorders. A national survey in America of 1,000 currently enrolled high school and college students found that 5 percent reported attempting suicide during the pandemic. Data from the US CDC's National Syndromic Surveillance Program from January 1st to October 17th, 2020, revealed a *31 percent* increase in mental health issues among adolescents aged 12 to 17 compared with 2019. The CDC reported that America in general suffered the biggest drop in life expectancy since World War Two as it fell by a year in the first half of 2020 as a result of 'deaths of despair' – overdoses and suicides. Deaths of despair have leapt by more than 20 percent during lockdown and include the highest number of fatal overdoses ever recorded in a single year – 81,000. Internet addiction is another consequence of being isolated at home which lowers interest in physical activities as kids fall into inertia and what's the point? Children and young people are losing hope and giving up on life, sometimes literally. A 14-year-old boy killed himself in Maryland because he had 'given up' when his school district didn't reopen; an 11-year-old boy shot himself during a zoom class; a teenager in Maine succumbed to the isolation of the 'pandemic' when he ended his life after experiencing a disrupted senior year at school. Children as young as nine have taken their life and all these stories can be repeated around the world. Careers are being destroyed before they start and that includes those in sport in which promising youngsters have not been able to take part. The plan of the psycho-psychologists is working all right. Researchers at Cambridge University found that lockdowns cause significant harm to children's mental health. Their study was published in the *Archives of Disease in Childhood*, and followed 168 children aged between 7 and 11. The researchers concluded:

> During the UK lockdown, children's depression symptoms have increased substantially, relative to before lockdown. The scale of this effect has direct relevance for the continuation of different elements of lockdown policy, such as complete or partial school closures …

… Specifically, we observed a statistically significant increase in ratings of depression, with a medium-to-large effect size. Our findings emphasise the need to incorporate the potential impact of lockdown on child mental health in planning the ongoing response to the global pandemic and the recovery from it.

Not a chance when the Cult's psycho-psychologists were getting exactly what they wanted. The UK's Royal College of Paediatrics and Child Health has urged parents to look for signs of eating disorders in children and young people after a three to four fold increase. Specialists say the 'pandemic' is a major reason behind the rise. You don't say. The College said isolation from friends during school closures, exam cancellations, loss of extra-curricular activities like sport, and an increased use of social media were all contributory factors along with fears about the virus (psycho-psychologists again), family finances, and students being forced to quarantine. Doctors said young people were becoming severely ill by the time they were seen with 'Covid' regulations reducing face-to-face consultations. Nor is it only the young that have been devastated by the psychopaths. Like all bullies and cowards the Cult is targeting the young, elderly, weak and infirm. A typical story was told by a British lady called Lynn Parker who was not allowed to visit her husband in 2020 for the last ten and half months of his life 'when he needed me most' between March 20th and when he died on December 19th. This vacates the criminal and enters the territory of evil. The emotional impact on the immune system alone is immense as are the number of people of all ages worldwide who have died as a result of Cult-demanded, Gates-demanded, lockdowns.

Isolation is torture

The experience of imposing solitary confinement on millions of prisoners around the world has shown how a large percentage become 'actively psychotic and/or acutely suicidal'. Social isolation has been found to trigger 'a specific psychiatric syndrome, characterized by hallucinations; panic attacks; overt paranoia; diminished impulse control; hypersensitivity to external stimuli; and difficulties with thinking, concentration and memory'. Juan Mendez,

a United Nations rapporteur (investigator), said that isolation is a form of torture. Research has shown that even after isolation prisoners find it far more difficult to make social connections and I remember chatting to a shop assistant after one lockdown who told me that when her young son met another child again he had no idea how to act or what to do. Hannah Flanagan, Director of Emergency Services at Journey Mental Health Center in Dane County, Wisconsin, said: 'The specificity about Covid social distancing and isolation that we've come across as contributing factors to the suicides are really new to us this year.' But they are not new to those that devised them. They are getting the effect they want as the population is psychologically dismantled to be rebuilt in a totally different way. Children and the young are particularly targeted. They will be the adults when the full-on fascist AI-controlled technocracy is planned to be imposed and they are being prepared to meekly submit. At the same time older people who still have a memory of what life was like before – and how fascist the new normal really is – are being deleted. You are going to see efforts to turn the young against the old to support this geriatric genocide. Hannah Flanagan said the big increase in suicide in her county proved that social isolation is not only harmful, but deadly. Studies have shown that isolation from others is one of the main risk factors in suicide and even more so with women. Warnings that lockdown could create a 'perfect storm' for suicide were ignored. After all this was one of the *reasons* for lockdown. Suicide, however, is only the most extreme of isolation consequences. There are many others. Dr Dhruv Khullar, assistant professor of healthcare policy at Weill Cornell Medical College, said in a *New York Times* article in 2016 long before the fake 'pandemic':

> A wave of new research suggests social separation is bad for us. Individuals with less social connection have disrupted sleep patterns, altered immune systems, more inflammation and higher levels of stress hormones. One recent study found that isolation increases the risk of heart disease by 29 percent and stroke by 32 percent. Another analysis that pooled data from 70 studies and 3.4 million people found that socially isolated individuals had a 30 percent higher risk of dying in the next seven years, and that this effect was largest in middle age.

Loneliness can accelerate cognitive decline in older adults, and isolated individuals are twice as likely to die prematurely as those with more robust social interactions. These effects start early: Socially isolated children have significantly poorer health 20 years later, even after controlling for other factors. All told, loneliness is as important a risk factor for early death as obesity and smoking.

There you have proof from that one article alone four years before 2020 that those who have enforced lockdown, social distancing and isolation knew what the effect would be and that is even more so with professional psychologists that have been driving the policy across the globe. We can go back even further to the years 2000 and 2003 and the start of a major study on the effects of isolation on health by Dr Janine Gronewold and Professor Dirk M. Hermann at the University Hospital in Essen, Germany, who analysed data on 4,316 people with an average age of 59 who were recruited for the long-term research project. They found that socially isolated people are more than 40 percent more likely to have a heart attack, stroke, or other major cardiovascular event and nearly 50 percent more likely to die from any cause. Given the financial Armageddon unleashed by lockdown we should note that the study found a relationship between increased cardiovascular risk and lack of financial support. After excluding other factors social isolation was still connected to a 44 percent increased risk of cardiovascular problems and a 47 percent increased risk of death by any cause. Lack of financial support was associated with a 30 percent increase in the risk of cardiovascular health events. Dr Gronewold said it had been known for some time that feeling lonely or lacking contact with close friends and family can have an impact on physical health and the study had shown that having strong social relationships is of high importance for heart health. Gronewold said they didn't understand yet why people who are socially isolated have such poor health outcomes, but this was obviously a worrying finding, particularly during these times of prolonged social distancing. Well, it can be explained on many levels. You only have to identify the point in the body where people feel loneliness and missing people they are parted from – it's in the centre of the chest where they feel the ache of loneliness and the ache of missing people. 'My heart aches for

you' … 'My heart aches for some company.' I will explain this more in the chapter Escaping Wetiko, but when you realise that the body is the mind – they are expressions of each other – the reason why state of the mind dictates state of the body becomes clear.

American psychologist Ranjit Powar was highlighting the effects of lockdown isolation as early as April, 2020. She said humans have evolved to be social creatures and are wired to live in interactive groups. Being isolated from family, friends and colleagues could be unbalancing and traumatic for most people and could result in short or even long-term psychological and physical health problems. An increase in levels of anxiety, aggression, depression, forgetfulness and hallucinations were possible psychological effects of isolation. 'Mental conditions may be precipitated for those with underlying pre-existing susceptibilities and show up in many others without any pre-condition.' Powar said personal relationships helped us cope with stress and if we lost this outlet for letting off steam the result can be a big emotional void which, for an average person, was difficult to deal with. 'Just a few days of isolation can cause increased levels of anxiety and depression' – so what the hell has been the effect on the global population of *18 months* of this at the time of writing? Powar said: 'Add to it the looming threat of a dreadful disease being repeatedly hammered in through the media and you have a recipe for many shades of mental and physical distress.' For those with a house and a garden it is easy to forget that billions have had to endure lockdown isolation in tiny overcrowded flats and apartments with nowhere to go outside. The psychological and physical consequences of this are unimaginable and with lunatic and abusive partners and parents the consequences have led to tremendous increases in domestic and child abuse and alcoholism as people seek to shut out the horror. Ranjit Powar said:

Staying in a confined space with family is not all a rosy picture for everyone. It can be extremely oppressive and claustrophobic for large low-income families huddled together in small single-room houses. Children here are not lucky enough to have many board/electronic games or books to keep them occupied.

Add to it the deep insecurity of running out of funds for food and basic necessities. On the other hand, there are people with dysfunctional family dynamics, such as domineering, abusive or alcoholic partners, siblings or parents which makes staying home a period of trial. Incidence of suicide and physical abuse against women has shown a worldwide increase. Heightened anxiety and depression also affect a person's immune system, making them more susceptible to illness.

To think that Powar's article was published on April 11th, 2020.

Six-feet fantasy

Social (unsocial) distancing demanded that people stay six feet or two metres apart. UK government advisor Robert Dingwall from the New and Emerging Respiratory Virus Threats Advisory Group said in a radio interview that the two-metre rule was 'conjured up out of nowhere' and was not based on science. No, it was not based on *medical* science, but it didn't come out of nowhere. The distance related to *psychological* science. Six feet/two metres was adopted in many countries and we were told by people like the criminal Anthony Fauci and his ilk that it was founded on science. Many schools could not reopen because they did not have the space for six-feet distancing. Then in March, 2021, after a year of six-feet 'science', a study published in the *Journal of Infectious Diseases* involving more than 500,000 students and almost 100,000 staff over 16 weeks revealed no significant difference in 'Covid' cases between six feet and three feet and Fauci changed his tune. Now three feet was okay. There is no difference between six feet and three *inches* when there is no 'virus' and they got away with six feet for psychological reasons for as long as they could. I hear journalists and others talk about 'unintended consequences' of lockdown. They are not *unintended* at all; they have been coldly-calculated for a specific outcome of human control and that's why super-psychopaths like Gates have called for them so vehemently. Super-psychopath psychologists have demanded them and psychopathic or clueless, spineless, politicians have gone along with them by 'following the science'. But it's not science at all. 'Science' is not what is; it's only what people can be manipulated to believe it is. The whole 'Covid' catastrophe is

founded on mind control. Three word or three statement mantras issued by the UK government are a well-known mind control technique and so we've had 'Stay home/protect the NHS/save lives', 'Stay alert/control the virus/save lives' and 'hands/face/space'. One of the most vocal proponents of extreme 'Covid' rules in the UK has been Professor Susan Michie, a member of the British Communist Party, who is not a medical professional. Michie is the director of the Centre for Behaviour Change at University College London. She is a *behavioural psychologist* and another filthy rich 'Marxist' who praised China's draconian lockdown. She was known by fellow students at Oxford University as 'Stalin's nanny' for her extreme Marxism. Michie is an influential member of the UK government's Scientific Advisory Group for Emergencies (SAGE) and behavioural manipulation groups which have dominated 'Covid' policy. She is a consultant adviser to the World Health Organization on 'Covid-19' and behaviour. Why the hell are lockdowns anything to do with her when they are claimed to be about health? Why does a behavioural psychologist from a group charged with changing the behaviour of the public want lockdown, human isolation and mandatory masks? Does that question really need an answer? Michie *absolutely* has to explain herself before a Nuremberg court when humanity takes back its world again and even more so when you see the consequences of masks that she demands are compulsory. This is a Michie classic:

> The benefits of getting primary school children to wear masks is that regardless of what little degree of transmission is occurring in those age groups it could help normalise the practice. Young children wearing masks may be more likely to get their families to accept masks.

Those words alone should carry a prison sentence when you ponder on the callous disregard for children involved and what a statement it makes about the mind and motivations of Susan Michie. What a lovely lady and what she said there encapsulates the mentality of the psychopaths behind the 'Covid' horror. Let us compare what Michie said with a countrywide study in Germany published at researchsquare.com involving 25,000 school children and 17,854 health complaints submitted by parents. Researchers

found that masks are harming children physically, psychologically, and behaviourally with 24 health issues associated with mask wearing. They include: shortness of breath (29.7%); dizziness (26.4%); increased headaches (53%); difficulty concentrating (50%); drowsiness or fatigue (37%); and malaise (42%). Nearly a third of children experienced more sleep issues than before and a quarter developed new fears. Researchers found health issues and other impairments in 68 percent of masked children covering their faces for an average of 4.5 hours a day. Hundreds of those taking part experienced accelerated respiration, tightness in the chest, weakness, and short-term impairment of consciousness. A reminder of what Michie said again:

The benefits of getting primary school children to wear masks is that regardless of what little degree of transmission is occurring in those age groups it could help normalise the practice. Young children wearing masks may be more likely to get their families to accept masks.

Psychopaths in government and psychology now have children and young people – plus all the adults – wearing masks for hours on end while clueless teachers impose the will of the psychopaths on the young they should be protecting. What the hell are parents doing?

Cult lab rats

We have some schools already imposing on students microchipped buzzers that activate when they get 'too close' to their pals in the way they do with lab rats. How apt. To the Cult and its brain-dead servants our children *are* lab rats being conditioned to be unquestioning, dehumanised slaves for the rest of their lives. Children and young people are being weaned and frightened away from the most natural human instincts including closeness and touch. I have tracked in the books over the years how schools were banning pupils from greeting each other with a hug and the whole Cult-induced Me Too movement has terrified men and boys from a relaxed and natural interaction with female friends and work colleagues to the point where many men try never to be in a room

alone with a woman that's not their partner. Airhead celebrities have as always played their virtue-signalling part in making this happen with their gross exaggeration. For every monster like Harvey Weinstein there are at least tens of thousands of men that don't treat women like that; but everyone must be branded the same and policy changed for them as well as the monster. I am going to be using the word 'dehumanise' many times in this chapter because that is what the Cult is seeking to do and it goes very deep as we shall see. Don't let them kid you that social distancing is planned to end one day. That's not the idea. We are seeing more governments and companies funding and producing wearable gadgets to keep people apart and they would not be doing that if this was meant to be short-term. A tech start-up company backed by GCHQ, the British Intelligence and military surveillance headquarters, has created a social distancing wrist sensor that alerts people when they get too close to others. The CIA has also supported tech companies developing similar devices. The wearable sensor was developed by Tended, one of a number of start-up companies supported by GCHQ (see the CIA and DARPA). The device can be worn on the wrist or as a tag on the waistband and will vibrate whenever someone wearing the device breaches social distancing and gets anywhere near natural human contact. The company had a lucky break in that it was developing a distancing sensor when the 'Covid' hoax arrived which immediately provided a potentially enormous market. How fortunate. The government in big-time Cult-controlled Ontario in Canada is investing $2.5 million in wearable contact tracing technology that 'will alert users if they may have been exposed to the Covid-19 in the workplace and will beep or vibrate if they are within six feet of another person'. Facedrive Inc., the technology company behind this, was founded in 2016 with funding from the Ontario Together Fund and obviously they, too, had a prophet on the board of directors. The human surveillance and control technology is called TraceSCAN and would be worn by the human cyborgs in places such as airports, workplaces, construction sites, care homes and … *schools*.

I emphasise schools with children and young people the prime targets. You know what is planned for society as a whole if you keep your eyes on the schools. They have always been places where the state program the next generation of slaves to be its compliant worker-ants – or Woker-ants these days; but in the mist of the 'Covid' madness they have been transformed into mind laboratories on a scale never seen before. Teachers and head teachers are just as programmed as the kids – often more so. Children are kept apart from human interaction by walk lanes, classroom distancing, staggered meal times, masks, and the rolling-out of buzzer systems. Schools are now physically laid out as a laboratory maze for lab-rats. Lunatics at a school in Anchorage, Alaska, who should be prosecuted for child abuse, took away desks and forced children to kneel (know your place) on a mat for five hours a day while wearing a mask and using their chairs as a desk. How this was supposed to impact on a 'virus' only these clinically insane people can tell you and even then it would be clap-trap. The school banned recess (interaction), art classes (creativity), and physical exercise (getting body and mind moving out of inertia). Everyone behind this outrage should be in jail or better still a mental institution. The behavioural manipulators are all for this dystopian approach to schools. Professor Susan Michie, the mind-doctor and British Communist Party member, said it was wrong to say that schools were safe. They had to be made so by 'distancing', masks and ventilation (sitting all day in the cold). I must ask this lady round for dinner on a night I know I am going to be out and not back for weeks. She probably wouldn't be able to make it, anyway, with all the visits to her own psychologist she must have block-booked.

Masking identity

I know how shocking it must be for you that a behaviour manipulator like Michie wants everyone to wear masks which have long been a feature of mind-control programs like the infamous MKUltra in the United States, but, there we are. We live and learn. I spent many years from 1996 to right across the millennium

researching mind control in detail on both sides of the Atlantic and elsewhere. I met a large number of mind-control survivors and many had been held captive in body and mind by MKUltra. MK stands for mind-control, but employs the German spelling in deference to the Nazis spirited out of Germany at the end of World War Two by Operation Paperclip in which the US authorities, with help from the Vatican, transported Nazi mind-controllers and engineers to America to continue their work. Many of them were behind the creation of NASA and they included Nazi scientist and SS officer Wernher von Braun who swapped designing V-2 rockets to bombard London with designing the Saturn V rockets that powered the NASA moon programme's Apollo craft. I think I may have mentioned that the Cult has no borders. Among Paperclip escapees was Josef Mengele, the Angel of Death in the Nazi concentration camps where he conducted mind and genetic experiments on children often using twins to provide a control twin to measure the impact of his 'work' on the other. If you want to observe the Cult mentality in all its extremes of evil then look into the life of Mengele. I have met many people who suffered mercilessly under Mengele in the United States where he operated under the name Dr Greene and became a stalwart of MKUltra programming and torture. Among his locations was the underground facility in the Mojave Desert in California called the China Lake Naval Weapons Station which is almost entirely below the surface. My books *The Biggest Secret*, *Children of the Matrix* and *The Perception Deception* have the detailed background to MKUltra.

The best-known MKUltra survivor is American Cathy O'Brien. I first met her and her late partner Mark Phillips at a conference in Colorado in 1996. Mark helped her escape and deprogram from decades of captivity in an offshoot of MKUltra known as Project Monarch in which 'sex slaves' were provided for the rich and famous including Father George Bush, Dick Cheney and the Clintons. Read Cathy and Mark's book *Trance-Formation of America* and if you are new to this you will be shocked to the core. I read it in 1996 shortly before, with the usual synchronicity of my life, I found

myself given a book table at the conference right next to hers. MKUltra never ended despite being very publicly exposed (only a small part of it) in the 1970s and continues in other guises. I am still in touch with Cathy. She contacted me during 2020 after masks became compulsory in many countries to tell me how they were used as part of MKUltra programming. I had been observing 'Covid regulations' and the relationship between authority and public for months. I saw techniques that I knew were employed on individuals in MKUltra being used on the global population. I had read many books and manuals on mind control including one called *Silent Weapons for Quiet Wars* which came to light in the 1980s and was a guide on how to perceptually program on a mass scale. 'Silent Weapons' refers to mind-control. I remembered a line from the manual as governments, medical authorities and law enforcement agencies have so obviously talked to – or rather at – the adult population since the 'Covid' hoax began as if they are children. The document said:

> If a person is spoken to by a T.V. advertiser as if he were a twelve-year-old, then, due to suggestibility, he will, with a certain probability, respond or react to that suggestion with the uncritical response of a twelve-year-old and will reach in to his economic reservoir and deliver its energy to buy that product on impulse when he passes it in the store.

That's why authority has spoken to adults like children since all this began.

Why did Michael Jackson wear masks?

Every aspect of the 'Covid' narrative has mind-control as its central theme. Cathy O'Brien wrote an article for davidicke.com about the connection between masks and mind control. Her daughter Kelly who I first met in the 1990s was born while Cathy was still held captive in MKUltra. Kelly was forced to wear a mask as part of her programming from the age of *two* to dehumanise her, target her sense of individuality and reduce the amount of oxygen her brain and body received. *Bingo*. This is the real reason for compulsory

masks, why they have been enforced en masse, and why they seek to increase the number they demand you wear. First one, then two, with one disgraceful alleged 'doctor' recommending four which is nothing less than a death sentence. Where and how often they must be worn is being expanded for the purpose of mass mind control and damaging respiratory health which they can call 'Covid-19'. Canada's government headed by the man-child Justin Trudeau, says it's fine for children of two and older to wear masks. An insane 'study' in Italy involving just 47 children concluded there was no problem for babies as young as *four months* wearing them. Even after people were 'vaccinated' they were still told to wear masks by the criminal that is Anthony Fauci. Cathy wrote that mandating masks is allowing the authorities literally to control the air we breathe which is what was done in MKUltra. You might recall how the singer Michael Jackson wore masks and there is a reason for that. He was subjected to MKUltra mind control through Project Monarch and his psyche was scrambled by these simpletons. Cathy wrote:

In MKUltra Project Monarch mind control, Michael Jackson had to wear a mask to silence his voice so he could not reach out for help. Remember how he developed that whisper voice when he wasn't singing? Masks control the mind from the outside in, like the redefining of words is doing. By controlling what we can and cannot say for fear of being labeled racist or beaten, for example, it ultimately controls thought that drives our words and ultimately actions (or lack thereof).

Likewise, a mask muffles our speech so that we are not heard, which controls voice … words … mind. This is Mind Control. Masks are an obvious mind control device, and I am disturbed so many people are complying on a global scale. Masks depersonalize while making a person feel as though they have no voice. It is a barrier to others. People who would never choose to comply but are forced to wear a mask in order to keep their job, and ultimately their family fed, are compromised. They often feel shame and are subdued. People have stopped talking with each other while media controls the narrative.

The 'no voice' theme has often become literal with train passengers told not to speak to each other in case they pass on the 'virus', singing banned for the same reason and bonkers California officials telling people riding roller coasters that they cannot shout and scream. Cathy said she heard every day from healed MKUltra survivors who cannot wear a mask without flashing back on ways

their breathing was controlled – 'from ball gags and penises to water boarding'. She said that through the years when she saw images of people in China wearing masks 'due to pollution' that it was really to control their oxygen levels. 'I knew it was as much of a population control mechanism of depersonalisation as are burkas', she said. Masks are another Chinese communist/fascist method of control that has been swept across the West as the West becomes China at lightning speed since we entered 2020.

Mask-19

There are other reasons for mandatory masks and these include destroying respiratory health to call it 'Covid-19' and stunting brain development of children and the young. Dr Margarite Griesz-Brisson MD, PhD, is a Consultant Neurologist and Neurophysiologist and the Founder and Medical Director of the London Neurology and Pain Clinic. Her CV goes down the street and round the corner. She is clearly someone who cares about people and won't parrot the propaganda. Griesz-Brisson has a PhD in pharmacology, with special interest in neurotoxicology, environmental medicine, neuroregeneration and neuroplasticity (the way the brain can change in the light of information received). She went public in October, 2020, with a passionate warning about the effects of mask-wearing laws:

> The reinhalation of our exhaled air will without a doubt create oxygen deficiency and a flooding of carbon dioxide. We know that the human brain is very sensitive to oxygen deprivation. There are nerve cells for example in the hippocampus that can't be longer than 3 minutes without oxygen – they cannot survive. The acute warning symptoms are headaches, drowsiness, dizziness, issues in concentration, slowing down of reaction time – reactions of the cognitive system.

Oh, I know, let's tell bus, truck and taxi drivers to wear them and people working machinery. How about pilots, doctors and police? Griesz-Brisson makes the important point that while the symptoms she mentions may fade as the body readjusts this does not alter the fact that people continue to operate in oxygen deficit with long list of

potential consequences. She said it was well known that neurodegenerative diseases take years or decades to develop. 'If today you forget your phone number, the breakdown in your brain would have already started 20 or 30 years ago.' She said degenerative processes in your brain are getting amplified as your oxygen deprivation continues through wearing a mask. Nerve cells in the brain are unable to divide themselves normally in these circumstances and lost nerve cells will no longer be regenerated. 'What is gone is gone.' Now consider that people like shop workers and *schoolchildren* are wearing masks for hours every day. What in the name of sanity is going to be happening to them? 'I do not wear a mask, I need my brain to think', Griesz-Brisson said, 'I want to have a clear head when I deal with my patients and not be in a carbon dioxide-induced anaesthesia'. If you are told to wear a mask anywhere ask the organisation, police, store, whatever, for their risk assessment on the dangers and negative effects on mind and body of enforcing mask-wearing. They won't have one because it has never been done not even by government. All of them must be subject to class-action lawsuits as the consequences come to light. They don't do mask risk assessments for an obvious reason. They know what the conclusions would be and independent scientific studies that *have* been done tell a horror story of consequences.

'Masks are criminal'

Dr Griesz-Brisson said that for children and adolescents, masks are an absolute no-no. They had an extremely active and adaptive immune system and their brain was incredibly active with so much to learn. 'The child's brain, or the youth's brain, is thirsting for oxygen.' The more metabolically active an organ was, the more oxygen it required; and in children and adolescents every organ was metabolically active. Griesz-Brisson said that to deprive a child's or adolescent's brain of oxygen, or to restrict it in any way, was not only dangerous to their health, it was absolutely criminal. 'Oxygen deficiency inhibits the development of the brain, and the damage that has taken place as a result CANNOT be reversed.' Mind

manipulators of MKUltra put masks on two-year-olds they wanted to neurologically rewire and you can see why. Griesz-Brisson said a child needs the brain to learn and the brain needs oxygen to function. 'We don't need a clinical study for that. This is simple, indisputable physiology.' Consciously and purposely induced oxygen deficiency was an absolutely deliberate health hazard, and an absolute medical contraindication which means that 'this drug, this therapy, this method or measure should not be used, and is not allowed to be used'. To coerce an entire population to use an absolute medical contraindication by force, she said, there had to be definite and serious reasons and the reasons must be presented to competent interdisciplinary and independent bodies to be verified and authorised. She had this warning of the consequences that were coming if mask wearing continued:

When, in ten years, dementia is going to increase exponentially, and the younger generations couldn't reach their god-given potential, it won't help to say 'we didn't need the masks'. I know how damaging oxygen deprivation is for the brain, cardiologists know how damaging it is for the heart, pulmonologists know how damaging it is for the lungs. Oxygen deprivation damages every single organ. Where are our health departments, our health insurance, our medical associations? It would have been their duty to be vehemently against the lockdown and to stop it and stop it from the very beginning.

Why do the medical boards issue punishments to doctors who give people exemptions? Does the person or the doctor seriously have to prove that oxygen deprivation harms people? What kind of medicine are our doctors and medical associations representing? Who is responsible for this crime? The ones who want to enforce it? The ones who let it happen and play along, or the ones who don't prevent it?

All of the organisations and people she mentions there either answer directly to the Cult or do whatever hierarchical levels above them tell them to do. The outcome of both is the same. 'It's not about masks, it's not about viruses, it's certainly not about your health', Griesz-Brisson said. 'It is about much, much more. I am not participating. I am not afraid.' They were taking our air to breathe and there was no unfounded medical exemption from face masks. Oxygen deprivation was dangerous for every single brain. It had to be the free decision of every human being whether they want to

wear a mask that was absolutely ineffective to protect themselves from a virus. She ended by rightly identifying where the responsibility lies for all this:

> The imperative of the hour is personal responsibility. We are responsible for what we think, not the media. We are responsible for what we do, not our superiors. We are responsible for our health, not the World Health Organization. And we are responsible for what happens in our country, not the government.

Halle-bloody-lujah.

But surgeons wear masks, right?

Independent studies of mask-wearing have produced a long list of reports detailing mental, emotional and physical dangers. What a definition of insanity to see police officers imposing mask-wearing on the public which will cumulatively damage their health while the police themselves wear masks that will cumulatively damage *their* health. It's utter madness and both public and police do this because 'the government says so' – yes a government of brain-donor idiots like UK Health Secretary Matt Hancock reading the 'follow the science' scripts of psychopathic, lunatic psychologists. The response you get from Stockholm syndrome sufferers defending the very authorities that are destroying them and their families is that 'surgeons wear masks'. This is considered the game, set and match that they must work and don't cause oxygen deficit. Well, actually, scientific studies have shown that they *do* and oxygen levels are monitored in operating theatres to compensate. Surgeons wear masks to stop spittle and such like dropping into open wounds – not to stop 'viral particles' which are so miniscule they can only be seen through an electron microscope. Holes in the masks are significantly bigger than 'viral particles' and if you sneeze or cough they will breach the mask. I watched an incredibly disingenuous 'experiment' that claimed to prove that masks work in catching 'virus' material from the mouth and nose. They did this with a slow motion camera and the mask did block big stuff which stayed inside the mask and

against the face to be breathed in or cause infections on the face as we have seen with many children. 'Viral particles', however, would never have been picked up by the camera as they came through the mask when they are far too small to be seen. The 'experiment' was therefore disingenuous *and* useless.

Studies have concluded that wearing masks in operating theatres (and thus elsewhere) make no difference to preventing infection while the opposite is true with toxic shite building up in the mask and this had led to an explosion in tooth decay and gum disease dubbed by dentists 'mask mouth'. You might have seen the Internet video of a furious American doctor urging people to take off their masks after a four-year-old patient had been rushed to hospital the night before and nearly died with a lung infection that doctors sourced to mask wearing. A study in the journal *Cancer Discovery* found that inhalation of harmful microbes can contribute to advanced stage lung cancer in adults and long-term use of masks can help breed dangerous pathogens. Microbiologists have said frequent mask wearing creates a moist environment in which microbes can grow and proliferate before entering the lungs. The Canadian Agency for Drugs and Technologies in Health, or CADTH, a Canadian national organisation that provides research and analysis to healthcare decision-makers, said this as long ago as 2013 in a report entitled 'Use of Surgical Masks in the Operating Room: A Review of the Clinical Effectiveness and Guidelines'. It said:

- No evidence was found to support the use of surgical face masks to reduce the frequency of surgical site infections
- No evidence was found on the effectiveness of wearing surgical face masks to protect staff from infectious material in the operating room.
- Guidelines recommend the use of surgical face masks by staff in the operating room to protect both operating room staff and patients (despite the lack of evidence).

We were told that the world could go back to 'normal' with the arrival of the 'vaccines'. When they came, fraudulent as they are, the story changed as I knew that it would. We are in the midst of transforming 'normal', not going back to it. Mary Ramsay, head of immunisation at Public Health England, echoed the words of US criminal Anthony Fauci who said masks and other regulations must stay no matter if people are vaccinated. The Fauci idiot continued to wear two masks – different colours so both could be clearly seen – after he *claimed* to have been vaccinated. Senator Rand Paul told Fauci in one exchange that his double-masks were 'theatre' and he was right. It's all theatre. Mary Ramsay back-tracked on the vaccine-return-to-normal theme when she said the public may need to wear masks and social-distance for years despite the jabs. 'People have got used to those lower-level restrictions now, and [they] can live with them', she said telling us what the idea has been all along. 'The vaccine does not give you a pass, even if you have had it, you must continue to follow all the guidelines' said a Public Health England statement which reneged on what we had been told before and made having the 'vaccine' irrelevant to 'normality' even by the official story. Spain's fascist government trumped everyone by passing a law mandating the wearing of masks on the beach and even when swimming in the sea. The move would have devastated what's left of the Spanish tourist industry, posed potential breathing dangers to swimmers and had Northern European sunbathers walking around with their forehead brown and the rest of their face white as a sheet. The ruling was so crazy that it had to be retracted after pressure from public and tourist industry, but it confirmed where the Cult wants to go with masks and how clinically insane authority has become. The determination to make masks permanent and hide the serious dangers to body and mind can be seen in the censorship of scientist Professor Denis Rancourt by Bill Gates-funded academic publishing website ResearchGate over his papers exposing the dangers and uselessness of masks. Rancourt said:

ResearchGate today has permanently locked my account, which I have had since 2015. Their reasons graphically show the nature of their attack against democracy, and their corruption of

science … By their obscene non-logic, a scientific review of science articles reporting on harms caused by face masks has a 'potential to cause harm'. No criticism of the psychological device (face masks) is tolerated, if the said criticism shows potential to influence public policy.

This is what happens in a fascist world.

Where are the 'greens' (again)?

Other dangers of wearing masks especially regularly relate to the inhalation of minute plastic fibres into the lungs and the deluge of discarded masks in the environment and oceans. Estimates predicted that more than 1.5 billion disposable masks will end up in the world's oceans every year polluting the water with tons of plastic and endangering marine wildlife. Studies project that humans are using 129 billion face masks each month worldwide – about three million a minute. Most are disposable and made from plastic, non-biodegradable microfibers that break down into smaller plastic particles that become widespread in ecosystems. They are littering cities, clogging sewage channels and turning up in bodies of water. I have written in other books about the immense amounts of microplastics from endless sources now being absorbed into the body. Rolf Halden, director of the Arizona State University (ASU) Biodesign Center for Environmental Health Engineering, was the senior researcher in a 2020 study that analysed 47 human tissue samples and found microplastics in all of them. 'We have detected these chemicals of plastics in every single organ that we have investigated', he said. I wrote in *The Answer* about the world being deluged with microplastics. A study by the Worldwide Fund for Nature (WWF) found that people are consuming on average every week some 2,000 tiny pieces of plastic mostly through water and also through marine life and the air. Every year humans are ingesting enough microplastics to fill a heaped dinner plate and in a life-time of 79 years it is enough to fill two large waste bins. Marco Lambertini, WWF International director general said: 'Not only are plastics polluting our oceans and waterways and killing marine life – it's in all of us and we can't escape consuming plastics,' American

geologists found tiny plastic fibres, beads and shards in rainwater samples collected from the remote slopes of the Rocky Mountain National Park near Denver, Colorado. Their report was headed: 'It is raining plastic.' Rachel Adams, senior lecturer in Biomedical Science at Cardiff Metropolitan University, said that among health consequences are internal inflammation and immune responses to a 'foreign body'. She further pointed out that microplastics become carriers of toxins including mercury, pesticides and dioxins (a known cause of cancer and reproductive and developmental problems). These toxins accumulate in the fatty tissues once they enter the body through microplastics. Now this is being compounded massively by people putting plastic on their face and throwing it away.

Workers exposed to polypropylene plastic fibres known as 'flock' have developed 'flock worker's lung' from inhaling small pieces of the flock fibres which can damage lung tissue, reduce breathing capacity and exacerbate other respiratory problems. *Now* … commonly used surgical masks have three layers of melt-blown textiles made of … polypropylene. We have billions of people putting these microplastics against their mouth, nose and face for hours at a time day after day in the form of masks. How does anyone think that will work out? I mean – what could possibly go wrong? We posted a number of scientific studies on this at davidicke.com, but when I went back to them as I was writing this book the links to the science research website where they were hosted were dead. Anything that challenges the official narrative in any way is either censored or vilified. The official narrative is so unsupportable by the evidence that only deleting the truth can protect it. A study by Chinese scientists still survived – with the usual twist which it why it was still active, I guess. Yes, they found that virtually all the masks they tested increased the daily intake of microplastic fibres, but people should still wear them because the danger from the 'virus' was worse said the crazy 'team' from the Institute of Hydrobiology in Wuhan. Scientists first discovered microplastics in lung tissue of some patients who died of lung cancer

in the 1990s. Subsequent studies have confirmed the potential health damage with the plastic degrading slowly and remaining in the lungs to accumulate in volume. Wuhan researchers used a machine simulating human breathing to establish that masks shed up to nearly 4,000 microplastic fibres in a month with reused masks producing more. Scientists said some masks are laced with toxic chemicals and a variety of compounds seriously restricted for both health and environmental reasons. They include cobalt (used in blue dye) and formaldehyde known to cause watery eyes, burning sensations in the eyes, nose, and throat, plus coughing, wheezing and nausea. No – that must be 'Covid-19'.

Mask 'worms'

There is another and potentially even more sinister content of masks. Mostly new masks of different makes filmed under a microscope around the world have been found to contain strange black fibres or 'worms' that appear to move or 'crawl' by themselves and react to heat and water. The nearest I have seen to them are the self-replicating fibres that are pulled out through the skin of those suffering from Morgellons disease which has been connected to the phenomena of 'chemtrails' which I will bring into the story later on. Morgellons fibres continue to grow outside the body and have a form of artificial intelligence. Black 'worm' fibres in masks have that kind of feel to them and there is a nanotechnology technique called 'worm micelles' which carry and release drugs or anything else you want to deliver to the body. For sure the suppression of humanity by mind altering drugs is the Cult agenda big time and the more excuses they can find to gain access to the body the more opportunities there are to make that happen whether through 'vaccines' or masks pushed against the mouth and nose for hours on end.

So let us summarise the pros and cons of masks:

Against masks: Breathing in your own carbon dioxide; depriving the body and brain of sufficient oxygen; build-up of toxins in the mask that can be breathed into the lungs and cause rashes on the face and 'mask-mouth'; breathing microplastic fibres and toxic chemicals into the lungs; dehumanisation and deleting individualisation by literally making people faceless; destroying human emotional interaction through facial expression and deleting parental connection with their babies which look for guidance to their facial expression.

For masks: They don't protect you from a 'virus' that doesn't exist and even if it did 'viral' particles are so minute they are smaller than the holes in the mask.

Governments, police, supermarkets, businesses, transport companies, and all the rest who seek to impose masks have done no risk assessment on their consequences for health and psychology and are now open to group lawsuits when the impact becomes clear with a cumulative epidemic of respiratory and other disease. Authorities will try to exploit these effects and hide the real cause by dubbing them 'Covid-19'. Can you imagine setting out to force the population to wear health-destroying masks without doing any assessment of the risks? It is criminal and it is evil, but then how many people targeted in this way, who see their children told to wear them all day at school, have asked for a risk assessment? Billions can't be imposed upon by the few unless the billions allow it. Oh, yes, with just a tinge of irony, 85 percent of all masks made worldwide come from *China*.

Wash your hands in toxic shite

'Covid' rules include the use of toxic sanitisers and again the health consequences of constantly applying toxins to be absorbed through the skin is obvious to any level of Renegade Mind. America's Food and Drug Administration (FDA) said that sanitisers are drugs and issued a warning about 75 dangerous brands which contain

methanol used in antifreeze and can cause death, kidney damage and blindness. The FDA circulated the following warning even for those brands that it claims to be safe:

Store hand sanitizer out of the reach of pets and children, and children should use it only with adult supervision. Do not drink hand sanitizer. This is particularly important for young children, especially toddlers, who may be attracted by the pleasant smell or brightly colored bottles of hand sanitizer.

Drinking even a small amount of hand sanitizer can cause alcohol poisoning in children. (However, there is no need to be concerned if your children eat with or lick their hands after using hand sanitizer.) During this coronavirus pandemic, poison control centers have had an increase in calls about accidental ingestion of hand sanitizer, so it is important that adults monitor young children's use.

Do not allow pets to swallow hand sanitizer. If you think your pet has eaten something potentially dangerous, call your veterinarian or a pet poison control center right away. Hand sanitizer is flammable and should be stored away from heat and flames. When using hand sanitizer, rub your hands until they feel completely dry before performing activities that may involve heat, sparks, static electricity, or open flames.

There you go, perfectly safe, then, and that's without even a mention of the toxins absorbed through the skin. Come on kids – sanitise your hands everywhere you go. It will save you from the 'virus'. Put all these elements together of the 'Covid' normal and see how much health and psychology is being cumulatively damaged, even devastated, to 'protect your health'. Makes sense, right? They are only imposing these things because they care, right? *Right?*

Submitting to insanity

Psychological reframing of the population goes very deep and is done in many less obvious ways. I hear people say how contradictory and crazy 'Covid' rules are and how they are ever changing. This is explained away by dismissing those involved as idiots. It is a big mistake. The Cult is delighted if its cold calculation is perceived as incompetence and idiocy when it is anything but. Oh, yes, there are idiots within the system – lots of them – but they are *administering* the Cult agenda, mostly unknowingly. They are not deciding and dictating it. The bulwark against tyranny is self-

respect, always has been, always will be. It is self-respect that has broken every tyranny in history. By its very nature self-respect will not bow to oppression and its perpetrators. There is so little self-respect that it's always the few that overturn dictators. Many may eventually follow, but the few with the iron spines (self-respect) kick it off and generate the momentum. The Cult targets self-respect in the knowledge that once this has gone only submission remains. Crazy, contradictory, ever-changing 'Covid' rules are systematically applied by psychologists to delete self-respect. They *want* you to see that the rules make no sense. It is one thing to decide to do something when *you* have made the choice based on evidence and logic. You still retain your self-respect. It is quite another when you can see what you are being told to do is insane, ridiculous and makes no sense, and *yet you still do it*. Your self-respect is extinguished and this has been happening as ever more obviously stupid and nonsensical things have been demanded and the great majority have complied even when they can see they are stupid and nonsensical.

People walk around in face-nappies knowing they are damaging their health and make no difference to a 'virus'. They do it in fear of not doing it. I know it's daft, but I'll do it anyway. When that happens something dies inside of you and submissive reframing has begun. Next there's a need to hide from yourself that you have conceded your self-respect and you convince yourself that you have not really submitted to fear and intimidation. You begin to believe that you are complying with craziness because it's the right thing to do. When first you concede your self-respect of 2+2 = 4 to 2+2 = 5 you *know* you are compromising your self-respect. Gradually to avoid facing that fact you begin to *believe* that 2+2=5. You have been reframed and I have been watching this process happening in the human psyche on an industrial scale. The Cult is working to break your spirit and one of its major tools in that war is humiliation. I read how former American soldier Bradley Manning (later Chelsea Manning after a sex-change) was treated after being jailed for supplying WikiLeaks with documents exposing the enormity of

government and elite mendacity. Manning was isolated in solitary confinement for eight months, put under 24-hour surveillance, forced to hand over clothing before going to bed, and stand naked for every roll call. This is systematic humiliation. The introduction of anal swab 'Covid' tests in China has been done for the same reason to delete self-respect and induce compliant submission. Anal swabs are mandatory for incoming passengers in parts of China and American diplomats have said they were forced to undergo the indignity which would have been calculated humiliation by the Cult-owned Chinese government that has America in its sights.

Government-people: An abusive relationship

Spirit-breaking psychological techniques include giving people hope and apparent respite from tyranny only to take it away again. This happened in the UK during Christmas, 2020, when the psycho-psychologists and their political lackeys announced an easing of restrictions over the holiday only to reimpose them almost immediately on the basis of yet another lie. There is a big psychological difference between getting used to oppression and being given hope of relief only to have that dashed. Psychologists know this and we have seen the technique used repeatedly. Then there is traumatising people before you introduce more extreme regulations that require compliance. A perfect case was the announcement by the dark and sinister Whitty and Vallance in the UK that 'new data' predicted that 4,000 could die every day over the winter of 2020/2021 if we did not lockdown again. I think they call it lying and after traumatising people with that claim out came Jackboot Johnson the next day with new curbs on human freedom. Psychologists know that a frightened and traumatised mind becomes suggestable to submission and behaviour reframing. Underpinning all this has been to make people fearful and suspicious of each other and see themselves as a potential danger to others. In league with deleted self-respect you have the perfect psychological recipe for self-loathing. The relationship between authority and public is now demonstrably the same as that of

subservience to an abusive partner. These are signs of an abusive relationship explained by psychologist Leslie Becker-Phelps:

Psychological and emotional abuse: Undermining a partner's self-worth with verbal attacks, name-calling, and belittling. Humiliating the partner in public, unjustly accusing them of having an affair, or interrogating them about their every behavior. Keeping partner confused or off balance by saying they were just kidding or blaming the partner for 'making' them act this way … Feigning in public that they care while turning against them in private. This leads to victims frequently feeling confused, incompetent, unworthy, hopeless, and chronically self-doubting. [Apply these techniques to how governments have treated the population since New Year, 2020, and the parallels are obvious.]

Physical abuse: The abuser might physically harm their partner in a range of ways, such as grabbing, hitting, punching, or shoving them. They might throw objects at them or harm them with a weapon. [Observe the physical harm imposed by masks, lockdown, and so on.]

Threats and intimidation: One way abusers keep their partners in line is by instilling fear. They might be verbally threatening, or give threatening looks or gestures. Abusers often make it known that they are tracking their partner's every move. They might destroy their partner's possessions, threaten to harm them, or threaten to harm their family members. Not surprisingly, victims of this abuse often feel anxiety, fear, and panic. [No words necessary.]

Isolation: Abusers often limit their partner's activities, forbidding them to talk or interact with friends or family. They might limit access to a car or even turn off their phone. All of this might be done by physically holding them against their will, but is often accomplished through psychological abuse and intimidation. The more isolated a person feels, the fewer resources they have to help gain perspective on their situation and to escape from it. [No words necessary.]

Economic abuse: Abusers often make their partners beholden to them for money by controlling access to funds of any kind. They might prevent their partner from getting a job or withhold access to money they earn from a job. This creates financial dependency that makes leaving the relationship very difficult. [See destruction of livelihoods and the proposed meagre 'guaranteed income' so long as you do whatever you are told.]

Using children: An abuser might disparage their partner's parenting skills, tell their children lies about their partner, threaten to take custody of their children, or threaten to harm their children. These tactics instil fear and often elicit compliance. [See reframed social service mafia and how children are being mercilessly abused by the state over 'Covid' while their parents look on too frightened to do anything.]

A further recurring trait in an abusive relationship is the abused blaming themselves for their abuse and making excuses for the abuser. We have the public blaming each other for lockdown abuse by government and many making excuses for the government while attacking those who challenge the government. How often we have heard authorities say that rules are being imposed or reimposed only because people have refused to 'behave' and follow the rules. We don't want to do it – it's *you*.

Renegade Minds are an antidote to all of these things. They will never concede their self-respect no matter what the circumstances. Even when apparent humiliation is heaped upon them they laugh in its face and reflect back the humiliation on the abuser where it belongs. Renegade Minds will never wear masks they know are only imposed to humiliate, suppress and damage both physically and psychologically. Consequences will take care of themselves and they will never break their spirit or cause them to concede to tyranny. UK newspaper columnist Peter Hitchens was one of the few in the mainstream media to speak out against lockdowns and forced vaccinations. He then announced he had taken the jab. He wanted to see family members abroad and he believed vaccine passports were inevitable even though they had not yet been introduced. Hitchens

has a questioning and critical mind, but not a Renegade one. If he had no amount of pressure would have made him concede. Hitchens excused his action by saying that the battle has been lost. Renegade Minds never accept defeat when freedom is at stake and even if they are the last one standing the self-respect of not submitting to tyranny is more important than any outcome or any consequence.

That's why Renegade Minds are the only minds that ever changed anything worth changing.

CHAPTER EIGHT

'Reframing' insanity

Insanity is relative. It depends on who has who locked in what cage
Ray Bradbury

'Reframing' a mind means simply to change its perception and behaviour. This can be done subconsciously to such an extent that subjects have no idea they have been 'reframed' while to any observer changes in behaviour and attitudes are obvious.

Human society is being reframed on a ginormous scale since the start of 2020 and here we have the reason why psychologists rather than doctors have been calling the shots. Ask most people who have succumbed to 'Covid' reframing if they have changed and most will say 'no'; but they *have* and fundamentally. The Cult's long-game has been preparing for these times since way back and crucial to that has been to prepare both population and officialdom mentally and emotionally. To use the mind-control parlance they had to reframe the population with a mentality that would submit to fascism and reframe those in government and law enforcement to impose fascism or at least go along with it. The result has been the fact-deleted mindlessness of 'Wokeness' and officialdom that has either enthusiastically or unquestioningly imposed global tyranny demanded by reframed politicians on behalf of psychopathic and deeply evil cultists. 'Cognitive reframing' identifies and challenges the way someone sees the world in the form of situations, experiences and emotions and then restructures those perceptions to view the same set of circumstances in a different way. This can have

benefits if the attitudes are personally destructive while on the other side it has the potential for individual and collective mind control which the subject has no idea has even happened.

Cognitive therapy was developed in the 1960s by Aaron T. Beck who was born in Rhode Island in 1921 as the son of Jewish immigrants from the Ukraine. He became interested in the techniques as a treatment for depression. Beck's daughter Judith S. Beck is prominent in the same field and they founded the Beck Institute for Cognitive Behavior Therapy in Philadelphia in 1994. Cognitive reframing, however, began to be used worldwide by those with a very dark agenda. The Cult reframes politicians to change their attitudes and actions until they are completely at odds with what they once appeared to stand for. The same has been happening to government administrators at all levels, law enforcement, military and the human population. Cultists love mind control for two main reasons: It allows them to control what people think, do and say to secure agenda advancement and, by definition, it calms their legendary insecurity and fear of the unexpected. I have studied mind control since the time I travelled America in 1996. I may have been talking to next to no one in terms of an audience in those years, but my goodness did I gather a phenomenal amount of information and knowledge about so many things including the techniques of mind control. I have described this in detail in other books going back to *The Biggest Secret* in 1998. I met a very large number of people recovering from MKUltra and its offshoots and successors and I began to see how these same techniques were being used on the population in general. This was never more obvious than since the 'Covid' hoax began.

Reframing the enforcers

I have observed over the last two decades and more the very clear transformation in the dynamic between the police, officialdom and the public. I tracked this in the books as the relationship mutated from one of serving the public to seeing them as almost the enemy and certainly a lower caste. There has always been a class divide

based on income and always been some psychopathic, corrupt, and big-I-am police officers. This was different. Wholesale change was unfolding in the collective dynamic; it was less about money and far more about position and perceived power. An us-and-them was emerging. Noses were lifted skyward by government administration and law enforcement and their attitude to the public they were *supposed* to be serving changed to one of increasing contempt, superiority and control. The transformation was so clear and widespread that it had to be planned. Collective attitudes and dynamics do not change naturally and organically that quickly on that scale. I then came across an organisation in Britain called Common Purpose created in the late 1980s by Julia Middleton who would work in the office of Deputy Prime Minister John Prescott during the long and disastrous premiership of war criminal Tony Blair. When Blair speaks the Cult is speaking and the man should have been in jail a long time ago. Common Purpose proclaims itself to be one of the biggest 'leadership development' organisations in the world while functioning as a *charity* with all the financial benefits which come from that. It hosts 'leadership development' courses and programmes all over the world and claims to have 'brought together' what it calls 'leaders' from more than 100 countries on six continents. The modus operandi of Common Purpose can be compared with the work of the UK government's reframing network that includes the Behavioural Insights Team 'nudge unit' and 'Covid' reframing specialists at SPI-B. WikiLeaks described Common Purpose long ago as 'a hidden virus in our government and schools' which is unknown to the general public: 'It recruits and trains "leaders" to be loyal to the directives of Common Purpose and the EU, instead of to their own departments, which they then undermine or subvert, the NHS [National Health Service] being an example.' This is a vital point to understand the 'Covid' hoax. The NHS, and its equivalent around the world, has been utterly reframed in terms of administrators and much of the medical personnel with the transformation underpinned by recruitment policies. The outcome has been the criminal and psychopathic behaviour of the

NHS over 'Covid' and we have seen the same in every other major country. WikiLeaks said Common Purpose trainees are 'learning to rule without regard to democracy' and to usher in a police state (current events explained). Common Purpose operated like a 'glue' and had members in the NHS, BBC, police, legal profession, church, many of Britain's 7,000 quangos, local councils, the Civil Service, government ministries and Parliament, and controlled many RDA's (Regional Development Agencies). Here we have one answer for how and why British institutions and their like in other countries have changed so negatively in relation to the public. This further explains how and why the beyond-disgraceful reframed BBC has become a propaganda arm of 'Covid' fascism. They are all part of a network pursuing the same goal.

By 2019 Common Purpose was quoting a figure of 85,000 'leaders' that had attended its programmes. These 'students' of all ages are known as Common Purpose 'graduates' and they consist of government, state and local government officials and administrators, police chiefs and officers, and a whole range of others operating within the national, local and global establishment. Cressida Dick, Commissioner of the London Metropolitan Police, is the Common Purpose graduate who was the 'Gold Commander' that oversaw what can only be described as the murder of Brazilian electrician Jean Charles de Menezes in 2005. He was held down by psychopathic police and shot seven times in the head by a psychopathic lunatic after being mistaken for a terrorist when he was just a bloke going about his day. Dick authorised officers to pursue and keep surveillance on de Menezes and ordered that he be stopped from entering the underground train system. Police psychopaths took her at her word clearly. She was 'disciplined' for this outrage by being *promoted* – eventually to the top of the 'Met' police where she has been a disaster. Many Chief Constables controlling the police in different parts of the UK are and have been Common Purpose graduates. I have heard the 'graduate' network described as a sort of Mafia or secret society operating within the fabric of government at all levels pursuing a collective policy

ingrained at Common Purpose training events. Founder Julia Middleton herself has said:

> Locally and internationally, Common Purpose graduates will be 'lighting small fires' to create change in their organisations and communities … The Common Purpose effect is best illustrated by the many stories of small changes brought about by leaders, who themselves have changed.

A Common Purpose mission statement declared:

> Common Purpose aims to improve the way society works by expanding the vision, decision-making ability and influence of all kinds of leaders. The organisation runs a variety of educational programmes for leaders of all ages, backgrounds and sectors, in order to provide them with the inspirational, information and opportunities they need to change the world.

Yes, but into what? Since 2020 the answer has become clear.

NLP and the Delphi technique

Common Purpose would seem to be a perfect name or would common programming be better? One of the foundation methods of reaching 'consensus' (group think) is by setting the agenda theme and then encouraging, cajoling or pressuring everyone to agree a 'consensus' in line with the core theme promoted by Common Purpose. The methodology involves the 'Delphi technique', or an adaption of it, in which opinions are expressed that are summarised by a 'facilitator or change agent' at each stage. Participants are 'encouraged' to modify their views in the light of what others have said. Stage by stage the former individual opinions are merged into group consensus which just happens to be what Common Purpose wants them to believe. A key part of this is to marginalise anyone refusing to concede to group think and turn the group against them to apply pressure to conform. We are seeing this very technique used on the general population to make 'Covid' group-thinkers hostile to those who have seen through the bullshit. People can be reframed by using perception manipulation methods such as Neuro-Linguistic Programming (NLP) in which you change perception with the use of

carefully constructed language. An NLP website described the technique this way:

… A method of influencing brain behaviour (the 'neuro' part of the phrase) through the use of language (the 'linguistic' part) and other types of communication to enable a person to 'recode' the way the brain responds to stimuli (that's the 'programming') and manifest new and better behaviours. Neuro-Linguistic Programming often incorporates hypnosis and self-hypnosis to help achieve the change (or 'programming') that is wanted.

British alternative media operation UKColumn has done very detailed research into Common Purpose over a long period. I quoted co-founder and former naval officer Brian Gerrish in my book *Remember Who You Are*, published in 2011, as saying the following years before current times:

It is interesting that many of the mothers who have had children taken by the State speak of the Social Services people being icily cool, emotionless and, as two ladies said in slightly different words, '… like little robots'. We know that NLP is cumulative, so people can be given small imperceptible doses of NLP in a course here, another in a few months, next year etc. In this way, major changes are accrued in their personality, but the day by day change is almost unnoticeable.

In these and other ways 'graduates' have had their perceptions uniformly reframed and they return to their roles in the institutions of government, law enforcement, legal profession, military, 'education', the UK National Health Service and the whole swathe of the establishment structure to pursue a common agenda preparing for the 'post-industrial', 'post-democratic' society. I say 'preparing' but we are now there. 'Post-industrial' is code for the Great Reset and 'post-democratic' is 'Covid' fascism. UKColumn has spoken to partners of those who have attended Common Purpose 'training'. They have described how personalities and attitudes of 'graduates' changed very noticeably for the worse by the time they had completed the course. They had been 'reframed' and told they are the 'leaders' – the special ones – who know better than the population. There has also been the very demonstrable recruitment of psychopaths and narcissists into government administration at all

levels and law enforcement. If you want psychopathy hire psychopaths and you get a simple cause and effect. If you want administrators, police officers and 'leaders' to perceive the public as lesser beings who don't matter then employ narcissists. These personalities are identified using 'psychometrics' that identifies knowledge, abilities, attitudes and personality traits, mostly through carefully-designed questionnaires and tests. As this policy has passed through the decades we have had power-crazy, power-trippers appointed into law enforcement, security and government administration in preparation for current times and the dynamic between public and law enforcement/officialdom has been transformed. UKColumn's Brian Gerrish said of the narcissistic personality:

> Their love of themselves and power automatically means that they will crush others who get in their way. I received a major piece of the puzzle when a friend pointed out that when they made public officials re-apply for their own jobs several years ago they were also required to do psychometric tests. This was undoubtedly the start of the screening process to get 'their' sort of people in post.

How obvious that has been since 2020 although it was clear what was happening long before if people paid attention to the changing public-establishment dynamic.

Change agents

At the centre of events in 'Covid' Britain is the National Health Service (NHS) which has behaved disgracefully in slavishly following the Cult agenda. The NHS management structure is awash with Common Purpose graduates or 'change agents' working to a common cause. Helen Bevan, a Chief of Service Transformation at the NHS Institute for Innovation and Improvement, co-authored a document called 'Towards a million change agents, a review of the social movements literature: implications for large scale change in the NHS'. The document compared a project management approach to that of change and social movements where 'people change

themselves and each other – peer to peer'. Two definitions given for a 'social movement' were:

A group of people who consciously attempt to build a radically new social order; involves people of a broad range of social backgrounds; and deploys politically confrontational and socially disruptive tactics – Cyrus Zirakzadeh 1997

Collective challenges, based on common purposes and social solidarities, in sustained interaction with elites, opponents, and authorities – Sidney Tarrow 1994

Helen Bevan wrote another NHS document in which she defined 'framing' as 'the process by which leaders construct, articulate and put across their message in a powerful and compelling way in order to win people to their cause and call them to action'. I think I could come up with another definition that would be rather more accurate. The National Health Service and institutions of Britain and the wider world have been taken over by reframed 'change agents' and that includes everything from the United Nations to national governments, local councils and social services which have been kidnapping children from loving parents on an extraordinary and gathering scale on the road to the end of parenthood altogether. Children from loving homes are stolen and kidnapped by the state and put into the 'care' (inversion) of the local authority through council homes, foster parents and forced adoption. At the same time children are allowed to be abused without response while many are under council 'care'. UKColumn highlighted the Common Purpose connection between South Yorkshire Police and Rotherham council officers in the case of the scandal in that area of the sexual exploitation of children to which the authorities turned not one blind eye, but both:

We were alarmed to discover that the Chief Executive, the Strategic Director of Children and Young People's Services, the Manager for the Local Strategic Partnership, the Community Cohesion Manager, the Cabinet Member for Cohesion, the Chief Constable and his predecessor had all attended Leadership training courses provided by the pseudo-charity Common Purpose.

Once 'change agents' have secured positions of hire and fire within any organisation things start to move very quickly. Personnel are then hired and fired on the basis of whether they will work towards the agenda the change agent represents. If they do they are rapidly promoted even though they may be incompetent. Those more qualified and skilled who are pre-Common Purpose 'old school' see their careers stall and even disappear. This has been happening for decades in every institution of state, police, 'health' and social services and all of them have been transformed as a result in their attitudes to their jobs and the public. Medical professions, including nursing, which were once vocations for the caring now employ many cold, callous and couldn't give a shit personality types. The UKColumn investigation concluded:

By blurring the boundaries between people, professions, public and private sectors, responsibility and accountability, Common Purpose encourages 'graduates' to believe that as new selected leaders, they can work together, outside of the established political and social structures, to achieve a paradigm shift or CHANGE – so called 'Leading Beyond Authority'. In doing so, the allegiance of the individual becomes 'reframed' on CP colleagues and their NETWORK.

Reframing the Face-Nappies

Nowhere has this process been more obvious than in the police where recruitment of psychopaths and development of unquestioning mind-controlled group-thinkers have transformed law enforcement into a politically-correct 'Woke' joke and a travesty of what should be public service. Today they wear their face-nappies like good little gofers and enforce 'Covid' rules which are fascism under another name. Alongside the specifically-recruited psychopaths we have software minds incapable of free thought. Brian Gerrish again:

An example is the policeman who would not get on a bike for a press photo because he had not done the cycling proficiency course. Normal people say this is political correctness gone mad. Nothing could be further from the truth. The policeman has been reframed, and in his reality it is perfect common sense not to get on the bike 'because he hasn't done the cycling course'.

Another example of this is where the police would not rescue a boy from a pond until they had taken advice from above on the 'risk assessment'. A normal person would have arrived, perhaps thought of the risk for a moment, and dived in. To the police now 'reframed', they followed 'normal' procedure.

There are shocking cases of reframed ambulance crews doing the same. Sheer unthinking stupidity of London Face-Nappies headed by Common Purpose graduate Cressida Dick can be seen in their behaviour at a vigil in March, 2021, for a murdered woman, Sarah Everard. A police officer had been charged with the crime. Anyone with a brain would have left the vigil alone in the circumstances. Instead they 'manhandled' women to stop them breaking 'Covid rules' to betray classic reframing. Minds in the thrall of perception control have no capacity for seeing a situation on its merits and acting accordingly. 'Rules is rules' is their only mind-set. My father used to say that rules and regulations are for the guidance of the intelligent and the blind obedience of the idiot. Most of the intelligent, decent, coppers have gone leaving only the other kind and a few old school for whom the job must be a daily nightmare. The combination of psychopaths and rule-book software minds has been clearly on public display in the 'Covid' era with automaton robots in uniform imposing fascistic 'Covid' regulations on the population without any personal initiative or judging situations on their merits. There are thousands of examples around the world, but I'll make my point with the infamous Derbyshire police in the English East Midlands – the ones who think pouring dye into beauty spots and using drones to track people walking in the countryside away from anyone is called 'policing'. To them there are rules decreed by the government which they have to enforce and in their bewildered state a group gathering in a closed space and someone walking alone in the countryside are the same thing. It is beyond idiocy and enters the realm of clinical insanity.

Police officers in Derbyshire said they were 'horrified' – *horrified* – to find 15 to 20 'irresponsible' kids playing a football match at a closed leisure centre 'in breach of coronavirus restrictions'. When they saw the police the kids ran away leaving their belongings behind and the reframed men and women of Derbyshire police were seeking to establish their identities with a view to fining their parents. The most natural thing for youngsters to do – kicking a ball about – is turned into a criminal activity and enforced by the moronic software programs of Derbyshire police. You find the same mentality in every country. These barely conscious 'horrified' officers said they had to take action because 'we need to ensure these rules are being followed' and 'it is of the utmost importance that you ensure your children are following the rules and regulations for Covid-19'. Had any of them done ten seconds of research to see if this parroting of their masters' script could be supported by any evidence? Nope. Reframed people don't think – others think for them and that's the whole idea of reframing. I have seen police officers one after the other repeating without question word for word what officialdom tells them just as I have seen great swathes of the public doing the same. Ask either for 'their' opinion and out spews what they have been told to think by the official narrative. Police and public may seem to be in different groups, but their mentality is the same. Most people do whatever they are told in fear not doing so or because they believe what officialdom tells them; almost the entirety of the police do what they are told for the same reason. Ultimately it's the tiny inner core of the global Cult that's telling both what to do.

So Derbyshire police were 'horrified'. Oh, really? Why did they think those kids were playing football? It was to relieve the psychological consequences of lockdown and being denied human contact with their friends and interaction, touch and discourse vital to human psychological health. Being denied this month after month has dismantled the psyche of many children and young people as depression and suicide have exploded. Were Derbyshire police *horrified by that*? Are you kidding? Reframed people don't have those

mental and emotional processes that can see how the impact on the psychological health of youngsters is far more dangerous than any 'virus' even if you take the mendacious official figures to be true. The reframed are told (programmed) how to act and so they do. The Derbyshire Chief Constable in the first period of lockdown when the black dye and drones nonsense was going on was Peter Goodman. He was the man who severed the connection between his force and the Derbyshire Constabulary *Male Voice* Choir when he decided that it was not inclusive enough to allow women to join. The fact it was a male voice choir making a particular sound produced by male voices seemed to elude a guy who terrifyingly ran policing in Derbyshire. He retired weeks after his force was condemned as disgraceful by former Supreme Court Justice Jonathan Sumption for their behaviour over extreme lockdown impositions. Goodman was replaced by his deputy Rachel Swann who was in charge when her officers were 'horrified'. The police statement over the boys committing the hanging-offence of playing football included the line about the youngsters being 'irresponsible in the times we are all living through' missing the point that the real relevance of the 'times we are all living through' is the imposition of fascism enforced by psychopaths and reframed minds of police officers playing such a vital part in establishing the fascist tyranny that their own children and grandchildren will have to live in their entire lives. As a definition of insanity that is hard to beat although it might be run close by imposing masks on people that can have a serious effect on their health while wearing a face nappy all day themselves. Once again public and police do it for the same reason – the authorities tell them to and who are they to have the self-respect to say no?

Wokers in uniform

How reframed do you have to be to arrest a *six-year-old* and take him to court for *picking a flower* while waiting for a bus? Brain dead police and officialdom did just that in North Carolina where criminal proceedings happen regularly for children under nine. Attorney Julie Boyer gave the six-year-old crayons and a colouring book

during the 'flower' hearing while the 'adults' decided his fate. County Chief District Court Judge Jay Corpening asked: 'Should a child that believes in Santa Claus, the Easter Bunny and the tooth fairy be making life-altering decisions?' Well, of course not, but common sense has no meaning when you have a common purpose and a reframed mind. Treating children in this way, and police operating in American schools, is all part of the psychological preparation for children to accept a police state as normal all their adult lives. The same goes for all the cameras and biometric tracking technology in schools. Police training is focused on reframing them as snowflake Wokers and this is happening in the military. Pentagon top brass said that 'training sessions on extremism' were needed for troops who asked why they were so focused on the Capitol Building riot when Black Lives Matter riots were ignored. What's the difference between them some apparently and rightly asked. Actually, there is a difference. Five people died in the Capitol riot, only one through violence, and that was a police officer shooting an unarmed protestor. BLM riots killed at least 25 people and cost billions. Asking the question prompted the psychopaths and reframed minds that run the Pentagon to say that more 'education' (programming) was needed. Troop training is all based on psychological programming to make them fodder for the Cult – 'Military men are just dumb, stupid animals to be used as pawns in foreign policy' as Cult-to-his-DNA former Secretary of State Henry Kissinger famously said. Governments see the police in similar terms and it's time for those among them who can see this to defend the people and stop being enforcers of the Cult agenda upon the people.

The US military, like the country itself, is being targeted for destruction through a long list of Woke impositions. Cult-owned gaga 'President' Biden signed an executive order when he took office to allow taxpayer money to pay for transgender surgery for active military personnel and veterans. Are you a man soldier? No, I'm a LGBTQIA+ with a hint of Skoliosexual and Spectrasexual. Oh, good man. Bad choice of words you bigot. The Pentagon announced in March, 2021, the appointment of the first 'diversity and inclusion

officer' for US Special Forces. Richard Torres-Estrada arrived with the publication of a 'D&I Strategic Plan which will guide the enterprise-wide effort to institutionalize and sustain D&I'. If you think a Special Forces 'Strategic Plan' should have something to do with defending America you haven't been paying attention. Defending Woke is now the military's new role. Torres-Estrada has posted images comparing Donald Trump with Adolf Hitler and we can expect no bias from him as a representative of the supposedly non-political Pentagon. Cable news host Tucker Carlson said: 'The Pentagon is now the Yale faculty lounge but with cruise missiles.' Meanwhile Secretary of Defense Lloyd Austin, a board member of weapons-maker Raytheon with stock and compensation interests in October, 2020, worth $1.4 million, said he was purging the military of the 'enemy within' – anyone who isn't Woke and supports Donald Trump. Austin refers to his targets as 'racist extremists' while in true Woke fashion being himself a racist extremist. Pentagon documents pledge to 'eradicate, eliminate and conquer all forms of racism, sexism and homophobia'. The definitions of these are decided by 'diversity and inclusion committees' peopled by those who see racism, sexism and homophobia in every situation and opinion. Woke (the Cult) is dismantling the US military and purging testosterone as China expands its military and gives its troops 'masculinity training'. How do we think that is going to end when this is all Cult coordinated? The US military, like the British military, is controlled by Woke and spineless top brass who just go along with it out of personal career interests.

'Woke' means fast asleep

Mind control and perception manipulation techniques used on individuals to create group-think have been unleashed on the global population in general. As a result many have no capacity to see the obvious fascist agenda being installed all around them or what 'Covid' is really all about. Their brains are firewalled like a computer system not to process certain concepts, thoughts and realisations that are bad for the Cult. The young are most targeted as the adults they

will be when the whole fascist global state is planned to be fully implemented. They need to be prepared for total compliance to eliminate all pushback from entire generations. The Cult has been pouring billions into taking complete control of 'education' from schools to universities via its operatives and corporations and not least Bill Gates as always. The plan has been to transform 'education' institutions into programming centres for the mentality of 'Woke'. James McConnell, professor of psychology at the University of Michigan, wrote in *Psychology Today* in 1970:

> The day has come when we can combine sensory deprivation with drugs, hypnosis, and astute manipulation of reward and punishment, to gain almost absolute control over an individual's behaviour. It should then be possible to achieve a very rapid and highly effective type of brainwashing that would allow us to make dramatic changes in a person's behaviour and personality ...
>
> … We should reshape society so that we all would be trained from birth to want to do what society wants us to do. We have the techniques to do it... no-one owns his own personality you acquired, and there's no reason to believe you should have the right to refuse to acquire a new personality if your old one is anti-social.

This was the potential for mass brainwashing in 1970 and the mentality there displayed captures the arrogant psychopathy that drives it forward. I emphasise that not all young people have succumbed to Woke programming and those that haven't are incredibly impressive people given that today's young are the most perceptually-targeted generations in history with all the technology now involved. Vast swathes of the young generations, however, have fallen into the spell – and that's what it is – of Woke. The Woke mentality and perceptual program is founded on *inversion* and you will appreciate later why that is so significant. Everything with Woke is inverted and the opposite of what it is claimed to be. Woke was a term used in African-American culture from the 1900s and referred to an awareness of social and racial justice. This is not the meaning of the modern version or 'New Woke' as I call it in *The Answer*. Oh, no, Woke today means something very different no matter how much Wokers may seek to hide that and insist Old Woke and New

Woke are the same. See if you find any 'awareness of social justice' here in the modern variety:

- Woke demands 'inclusivity' while excluding anyone with a different opinion and calls for mass censorship to silence other views.

- Woke claims to stand against oppression when imposing oppression is the foundation of all that it does. It is the driver of political correctness which is nothing more than a Cult invention to manipulate the population to silence itself.

- Woke believes itself to be 'liberal' while pursuing a global society that can only be described as fascist (see 'anti-fascist' fascist Antifa).

- Woke calls for 'social justice' while spreading injustice wherever it goes against the common 'enemy' which can be easily identified as a differing view.

- Woke is supposed to be a metaphor for 'awake' when it is solid-gold asleep and deep in a Cult-induced coma that meets the criteria for 'off with the fairies'.

I state these points as obvious facts if people only care to look. I don't do this with a sense of condemnation. We need to appreciate that the onslaught of perceptual programming on the young has been incessant and merciless. I can understand why so many have been reframed, or, given their youth, framed from the start to see the world as the Cult demands. The Cult has had access to their minds day after day in its 'education' system for their entire formative years. Perception is formed from information received and the Cult-created system is a life-long download of information delivered to elicit a particular perception, thus behaviour. The more this has expanded into still new extremes in recent decades and ever-increasing censorship has deleted other opinions and information why wouldn't that lead to a perceptual reframing on a mass scale? I

have described already cradle-to-grave programming and in more recent times the targeting of young minds from birth to adulthood has entered the stratosphere. This has taken the form of skewing what is 'taught' to fit the Cult agenda and the omnipresent techniques of group-think to isolate non-believers and pressure them into line. There has always been a tendency to follow the herd, but we really are in a new world now in relation to that. We have parents who can see the 'Covid' hoax told by their children not to stop them wearing masks at school, being 'Covid' tested or having the 'vaccine' in fear of the peer-pressure consequences of being different. What is 'peer-pressure' if not pressure to conform to group-think? Renegade Minds never group-think and always retain a set of perceptions that are unique to them. Group-think is always underpinned by consequences for not group-thinking. Abuse now aimed at those refusing DNA-manipulating 'Covid vaccines' are a potent example of this. The biggest pressure to conform comes from the very group which is itself being manipulated. 'I am programmed to be part of a hive mind and so you must be.'

Woke control structures in 'education' now apply to every mainstream organisation. Those at the top of the 'education' hierarchy (the Cult) decide the policy. This is imposed on governments through the Cult network; governments impose it on schools, colleges and universities; their leadership impose the policy on teachers and academics and they impose it on children and students. At any level where there is resistance, perhaps from a teacher or university lecturer, they are targeted by the authorities and often fired. Students themselves regularly demand the dismissal of academics (increasingly few) at odds with the narrative that the students have been programmed to believe in. It is quite a thought that students who are being targeted by the Cult become so consumed by programmed group-think that they launch protests and demand the removal of those who are trying to push back against those targeting the students. Such is the scale of perceptual inversion. We see this with 'Covid' programming as the Cult imposes the rules via psycho-psychologists and governments on

shops, transport companies and businesses which impose them on their staff who impose them on their customers who pressure Pushbackers to conform to the will of the Cult which is in the process of destroying them and their families. Scan all aspects of society and you will see the same sequence every time.

Fact free Woke and hijacking the 'left'

There is no more potent example of this than 'Woke', a mentality only made possible by the deletion of factual evidence by an 'education' system seeking to produce an ever more uniform society. Why would you bother with facts when you don't know any? Deletion of credible history both in volume and type is highly relevant. Orwell said: 'Who controls the past controls the future: who controls the present controls the past.' They who control the perception of the past control the perception of the future and they who control the present control the perception of the past through the writing and deleting of history. Why would you oppose the imposition of Marxism in the name of Wokeism when you don't know that Marxism cost at least 100 million lives in the 20th century alone? Watch videos and read reports in which Woker generations are asked basic historical questions – it's mind-blowing. A survey of 2,000 people found that six percent of millennials (born approximately early1980s to early 2000s) believed the Second World War (1939-1945) broke out with the assassination of President Kennedy (in 1963) and one in ten thought Margaret Thatcher was British Prime Minister at the time. She was in office between 1979 and 1990. We are in a post-fact society. Provable facts are no defence against the fascism of political correctness or Silicon Valley censorship. Facts don't matter anymore as we have witnessed with the 'Covid' hoax. Sacrificing uniqueness to the Woke group-think religion is all you are required to do and that means thinking for yourself is the biggest Woke no, no. All religions are an expression of group-think and censorship and Woke is just another religion with an orthodoxy defended by group-think and censorship. Burned at

the stake becomes burned on Twitter which leads back eventually to burned at the stake as Woke humanity regresses to ages past.

The biggest Woke inversion of all is its creators and funders. I grew up in a traditional left of centre political household on a council estate in Leicester in the 1950s and 60s – you know, the left that challenged the power of wealth-hoarding elites and threats to freedom of speech and opinion. In those days students went on marches defending freedom of speech while today's Wokers march for its deletion. What on earth could have happened? Those very elites (collectively the Cult) that we opposed in my youth and early life have funded into existence the antithesis of that former left and hijacked the 'brand' while inverting everything it ever stood for. We have a mentality that calls itself 'liberal' and 'progressive' while acting like fascists. Cult billionaires and their corporations have funded themselves into control of 'education' to ensure that Woke programming is unceasing throughout the formative years of children and young people and that non-Wokers are isolated (that word again) whether they be students, teachers or college professors. The Cult has funded into existence the now colossal global network of Woke organisations that have spawned and promoted all the 'causes' on the Cult wish-list for global transformation and turned Wokers into demanders of them. Does anyone really think it's a coincidence that the Cult agenda for humanity is a carbon (sorry) copy of the societal transformations desired by Woke?? These are only some of them:

Political correctness: The means by which the Cult deletes all public debates that it knows it cannot win if we had the free-flow of information and evidence.

Human-caused 'climate change': The means by which the Cult seeks to transform society into a globally-controlled dictatorship imposing its will over the fine detail of everyone's lives 'to save the planet' which doesn't actually need saving.

Transgender obsession: Preparing collective perception to accept the 'new human' which would not have genders because it would be created technologically and not through procreation. I'll have much more on this in Human 2.0.

Race obsession: The means by which the Cult seeks to divide and rule the population by triggering racial division through the perception that society is more racist than ever when the opposite is the case. Is it perfect in that regard? No. But to compare today with the racism of apartheid and segregation brought to an end by the civil rights movement in the 1960s is to insult the memory of that movement and inspirations like Martin Luther King. Why is the 'anti-racism' industry (which it is) so dominated by privileged white people?

White supremacy: This is a label used by privileged white people to demonise poor and deprived white people pushing back on tyranny to marginalise and destroy them. White people are being especially targeted as the dominant race by number within Western society which the Cult seeks to transform in its image. If you want to change a society you must weaken and undermine its biggest group and once you have done that by using the other groups you next turn on them to do the same … 'Then they came for the Jews and I was not a Jew so I did nothing.'

Mass migration: The mass movement of people from the Middle East, Africa and Asia into Europe, from the south into the United States and from Asia into Australia are another way the Cult seeks to dilute the racial, cultural and political influence of white people on Western society. White people ask why their governments appear to be working against them while being politically and culturally biased towards incoming cultures. Well, here's your answer. In the same way sexually 'straight' people, men and women, ask why the

authorities are biased against them in favour of other sexualities. The answer is the same – that's the way the Cult wants it to be for very sinister motives.

These are all central parts of the Cult agenda and central parts of the Woke agenda and Woke was created and continues to be funded to an immense degree by Cult billionaires and corporations. If anyone begins to say 'coincidence' the syllables should stick in their throat.

Billionaire 'social justice warriors'

Joe Biden is a 100 percent-owned asset of the Cult and the Wokers' man in the White House whenever he can remember his name and for however long he lasts with his rapidly diminishing cognitive function. Even walking up the steps of an aircraft without falling on his arse would appear to be a challenge. He's not an empty-shell puppet or anything. From the minute Biden took office (or the Cult did) he began his executive orders promoting the Woke wish-list. You will see the Woke agenda imposed ever more severely because it's really the *Cult* agenda. Woke organisations and activist networks spawned by the Cult are funded to the extreme so long as they promote what the Cult wants to happen. Woke is funded to promote 'social justice' by billionaires who become billionaires by destroying social justice. The social justice mantra is only a cover for dismantling social justice and funded by billionaires that couldn't give a damn about social justice. Everything makes sense when you see that. One of Woke's premier funders is Cult billionaire financier George Soros who said: 'I am basically there to make money, I cannot and do not look at the social consequences of what I do.' This is the same Soros who has given more than $32 billion to his Open Society Foundations global Woke network and funded Black Lives Matter, mass immigration into Europe and the United States, transgender activism, climate change activism, political correctness and groups targeting 'white supremacy' in the form of privileged white thugs that dominate Antifa. What a scam it all is and when

you are dealing with the unquestioning fact-free zone of Woke scamming them is child's play. All you need to pull it off in all these organisations are a few in-the-know agents of the Cult and an army of naïve, reframed, uninformed, narcissistic, know-nothings convinced of their own self-righteousness, self-purity and virtue.

Soros and fellow billionaires and billionaire corporations have poured hundreds of millions into Black Lives Matter and connected groups and promoted them to a global audience. None of this is motivated by caring about black people. These are the billionaires that have controlled and exploited a system that leaves millions of black people in abject poverty and deprivation which they do absolutely nothing to address. The same Cult networks funding BLM were behind the *slave trade!* Black Lives Matter hijacked a phrase that few would challenge and they have turned this laudable concept into a political weapon to divide society. You know that BLM is a fraud when it claims that *All* Lives Matter, the most inclusive statement of all, is 'racist'. BLM and its Cult masters don't want to end racism. To them it's a means to an end to control all of humanity never mind the colour, creed, culture or background. What has destroying the nuclear family got to do with ending racism? Nothing – but that is one of the goals of BLM and also happens to be a goal of the Cult as I have been exposing in my books for decades. Stealing children from loving parents and giving schools ever more power to override parents is part of that same agenda. BLM is a Marxist organisation and why would that not be the case when the Cult created Marxism *and* BLM? Patrisse Cullors, a BLM co-founder, said in a 2015 video that she and her fellow organisers, including co-founder Alicia Garza, are 'trained Marxists'. The lady known after marriage as Patrisse Khan-Cullors bought a $1.4 million home in 2021 in one of the whitest areas of California with a black population of just 1.6 per cent and has so far bought *four* high-end homes for a total of $3.2 million. How very Marxist. There must be a bit of spare in the BLM coffers, however, when Cult corporations and billionaires have handed over the best part of $100 million. Many black people can see that Black Lives Matter is not

working for them, but against them, and this is still more confirmation. Black journalist Jason Whitlock, who had his account suspended by Twitter for simply linking to the story about the 'Marxist's' home buying spree, said that BLM leaders are 'making millions of dollars off the backs of these dead black men who they wouldn't spit on if they were on fire and alive'.

Black Lies Matter

Cult assets and agencies came together to promote BLM in the wake of the death of career criminal George Floyd who had been jailed a number of times including for forcing his way into the home of a black woman with others in a raid in which a gun was pointed at her stomach. Floyd was filmed being held in a Minneapolis street in 2020 with the knee of a police officer on his neck and he subsequently died. It was an appalling thing for the officer to do, but the same technique has been used by police on peaceful protestors of lockdown without any outcry from the Woke brigade. As unquestioning supporters of the Cult agenda Wokers have supported lockdown and all the 'Covid' claptrap while attacking anyone standing up to the tyranny imposed in its name. Court documents would later include details of an autopsy on Floyd by County Medical Examiner Dr Andrew Baker who concluded that Floyd had taken a fatal level of the drug fentanyl. None of this mattered to fact-free, question-free, Woke. Floyd's death was followed by worldwide protests against police brutality amid calls to defund the police. Throwing babies out with the bathwater is a Woke speciality. In the wake of the murder of British woman Sarah Everard a Green Party member of the House of Lords, Baroness Jones of Moulescoomb (Nincompoopia would have been better), called for a 6pm curfew for all men. This would be in breach of the Geneva Conventions on war crimes which ban collective punishment, but that would never have crossed the black and white Woke mind of Baroness Nincompoopia who would have been far too convinced of her own self-righteousness to compute such details. Many American cities did defund the police in the face of Floyd riots

and after $15 million was deleted from the police budget in Washington DC under useless Woke mayor Muriel Bowser car-jacking alone rose by 300 percent and within six months the US capital recorded its highest murder rate in 15 years. The same happened in Chicago and other cities in line with the Cult/Soros plan to bring fear to streets and neighbourhoods by reducing the police, releasing violent criminals and not prosecuting crime. This is the mob-rule agenda that I have warned in the books was coming for so long. Shootings in the area of Minneapolis where Floyd was arrested increased by 2,500 percent compared with the year before. Defunding the police over George Floyd has led to a big increase in dead people with many of them black. Police protection for politicians making these decisions stayed the same or increased as you would expect from professional hypocrites. The Cult doesn't actually want to abolish the police. It wants to abolish local control over the police and hand it to federal government as the psychopaths advance the Hunger Games Society. Many George Floyd protests turned into violent riots with black stores and businesses destroyed by fire and looting across America fuelled by Black Lives Matter. Woke doesn't do irony. If you want civil rights you must loot the liquor store and the supermarket and make off with a smart TV. It's the only way.

It's not a race war – it's a class war

Black people are patronised by privileged blacks and whites alike and told they are victims of white supremacy. I find it extraordinary to watch privileged blacks supporting the very system and bloodline networks behind the slave trade and parroting the same Cult-serving manipulative crap of their privileged white, often billionaire, associates. It is indeed not a race war but a class war and colour is just a diversion. Black Senator Cory Booker and black Congresswoman Maxine Waters, more residents of Nincompoopia, personify this. Once you tell people they are victims of someone else you devalue both their own responsibility for their plight and the power they have to impact on their reality and experience. Instead

we have: 'You are only in your situation because of whitey – turn on them and everything will change.' It won't change. Nothing changes in our lives unless *we* change it. Crucial to that is never seeing yourself as a victim and always as the creator of your reality. Life is a simple sequence of choice and consequence. Make different choices and you create different consequences. *You* have to make those choices – not Black Lives Matter, the Woke Mafia and anyone else that seeks to dictate your life. Who are they these Wokers, an emotional and psychological road traffic accident, to tell you what to do? Personal empowerment is the last thing the Cult and its Black Lives Matter want black people or anyone else to have. They claim to be defending the underdog while *creating* and perpetuating the underdog. The Cult's worst nightmare is human unity and if they are going to keep blacks, whites and every other race under economic servitude and control then the focus must be diverted from what they have in common to what they can be manipulated to believe divides them. Blacks have to be told that their poverty and plight is the fault of the white bloke living on the street in the same poverty and with the same plight they are experiencing. The difference is that your plight black people is due to him, a white supremacist with 'white privilege' living on the street. Don't unite as one human family against your mutual oppressors and suppressors – fight the oppressor with the white face who is as financially deprived as you are. The Cult knows that as its 'Covid' agenda moves into still new levels of extremism people are going to respond and it has been spreading the seeds of disunity everywhere to stop a united response to the evil that targets *all of us*.

Racist attacks on 'whiteness' are getting ever more outrageous and especially through the American Democratic Party which has an appalling history for anti-black racism. Barack Obama, Joe Biden, Hillary Clinton and Nancy Pelosi all eulogised about Senator Robert Byrd at his funeral in 2010 after a nearly 60-year career in Congress. Byrd was a brutal Ku Klux Klan racist and a violent abuser of Cathy O'Brien in MKUltra. He said he would never fight in the military 'with a negro by my side' and 'rather I should die a thousand times,

and see Old Glory trampled in the dirt never to rise again, than to see this beloved land of ours become degraded by race mongrels, a throwback to the blackest specimen from the wilds'. Biden called Byrd a 'very close friend and mentor'. These 'Woke' hypocrites are not anti-racist they are anti-poor and anti-people not of their perceived class. Here is an illustration of the scale of anti-white racism to which we have now descended. Seriously Woke and moronic *New York Times* contributor Damon Young described whiteness as a 'virus' that 'like other viruses will not die until there are no bodies left for it to infect'. He went on: '… the only way to stop it is to locate it, isolate it, extract it, and kill it.' Young can say that as a black man with no consequences when a white man saying the same in reverse would be facing a jail sentence. *That's* racism. We had super-Woke numbskull senators Tammy Duckworth and Mazie Hirono saying they would object to future Biden Cabinet appointments if he did not nominate more Asian Americans and Pacific Islanders. Never mind the ability of the candidate what do they look like? Duckworth said: 'I will vote for racial minorities and I will vote for LGBTQ, but anyone else I'm not voting for.' Appointing people on the grounds of race is illegal, but that was not a problem for this ludicrous pair. They were on-message and that's a free pass in any situation.

Critical race racism

White children are told at school they are intrinsically racist as they are taught the divisive 'critical race theory'. This claims that the law and legal institutions are inherently racist and that race is a socially constructed concept used by white people to further their economic and political interests at the expense of people of colour. White is a 'virus' as we've seen. Racial inequality results from 'social, economic, and legal differences that white people create between races to maintain white interests which leads to poverty and criminality in minority communities'. I must tell that to the white guy sleeping on the street. The principal of East Side Community School in New York sent white parents a manifesto that called on

them to become 'white traitors' and advocate for full 'white abolition'. These people are teaching your kids when they urgently need a psychiatrist. The 'school' included a chart with 'eight white identities' that ranged from 'white supremacist' to 'white abolition' and defined the behaviour white people must follow to end 'the regime of whiteness'. Woke blacks and their privileged white associates are acting exactly like the slave owners of old and Ku Klux Klan racists like Robert Byrd. They are too full of their own self-purity to see that, but it's true. Racism is not a body type; it's a state of mind that can manifest through any colour, creed or culture.

Another racial fraud is *'equity'*. Not equality of treatment and opportunity – equity. It's a term spun as equality when it means something very different. Equality in its true sense is a raising up while 'equity' is a race to the bottom. Everyone in the same level of poverty is 'equity'. Keep everyone down – that's equity. The Cult doesn't want anyone in the human family to be empowered and BLM leaders, like all these 'anti-racist' organisations, continue their privileged, pampered existence by perpetuating the perception of gathering racism. When is the last time you heard an 'anti-racist' or 'anti-Semitism' organisation say that acts of racism and discrimination have *fallen?* It's not in the interests of their fund-raising and power to influence and the same goes for the professional soccer anti-racism operation, Kick It Out. Two things confirmed that the Black Lives Matter riots in the summer of 2020 were Cult creations. One was that while anti-lockdown protests were condemned in this same period for 'transmitting 'Covid' the authorities supported mass gatherings of Black Lives Matter supporters. I even saw self-deluding people claiming to be doctors say the two types of protest were not the same. No – the non-existent 'Covid' was in favour of lockdowns and attacked those that protested against them while 'Covid' supported Black Lives Matter and kept well away from its protests. The whole thing was a joke and as lockdown protestors were arrested, often brutally, by reframed Face-Nappies we had the grotesque sight of police officers taking the knee to Black Lives Matter, a Cult-funded Marxist

organisation that supports violent riots and wants to destroy the nuclear family and white people.

He's not white? Shucks!

Woke obsession with race was on display again when ten people were shot dead in Boulder, Colorado, in March, 2021. Cult-owned Woke TV channels like CNN said the shooter appeared to be a white man and Wokers were on Twitter condemning 'violent white men' with the usual mantras. Then the shooter's name was released as Ahmad Al Aliwi Alissa, an anti-Trump Arab-American, and the sigh of disappointment could be heard five miles away. Never mind that ten people were dead and what that meant for their families. Race baiting was all that mattered to these sick Cult-serving people like Barack Obama who exploited the deaths to further divide America on racial grounds which is his job for the Cult. This is the man that 'racist' white Americans made the first black president of the United States and then gave him a second term. Not-very-bright Obama has become filthy rich on the back of that and today appears to have a big influence on the Biden administration. Even so he's still a downtrodden black man and a victim of white supremacy. This disingenuous fraud reveals the contempt he has for black people when he puts on a Deep South Alabama accent whenever he talks to them, no, *at* them.

Another BLM red flag was how the now fully-Woke (fully-Cult) and fully-virtue-signalled professional soccer authorities had their teams taking the knee before every match in support of Marxist Black Lives Matter. Soccer authorities and clubs displayed 'Black Lives Matter' on the players' shirts and flashed the name on electronic billboards around the pitch. Any fans that condemned what is a Freemasonic taking-the-knee ritual were widely condemned as you would expect from the Woke virtue-signallers of professional sport and the now fully-Woke media. We have reverse racism in which you are banned from criticising any race or culture except for white people for whom anything goes – say what you like, no problem. What has this got to do with racial harmony and

equality? We've had black supremacists from Black Lives Matter telling white people to fall to their knees in the street and apologise for their white supremacy. Black supremacists acting like white supremacist slave owners of the past couldn't breach their self-obsessed, race-obsessed sense of self-purity. Joe Biden appointed a race-obsessed black supremacist Kristen Clarke to head the Justice Department Civil Rights Division. Clarke claimed that blacks are endowed with 'greater mental, physical and spiritual abilities' than whites. If anyone reversed that statement they would be vilified. Clarke is on-message so no problem. She's never seen a black-white situation in which the black figure is anything but a virtuous victim and she heads the Civil Rights Division which should treat everyone the same or it isn't civil rights. Another perception of the Renegade Mind: If something or someone is part of the Cult agenda they will be supported by Woke governments and media no matter what. If they're not, they will be condemned and censored. It really is that simple and so racist Clarke prospers despite (make that because of) her racism.

The end of culture

Biden's administration is full of such racial, cultural and economic bias as the Cult requires the human family to be divided into warring factions. We are now seeing racially-segregated graduations and everything, but everything, is defined through the lens of perceived 'racism. We have 'racist' mathematics, 'racist' food and even 'racist' *plants*. World famous Kew Gardens in London said it was changing labels on plants and flowers to tell its pre-'Covid' more than two million visitors a year how racist they are. Kew director Richard Deverell said this was part of an effort to 'move quickly to decolonise collections' after they were approached by one Ajay Chhabra 'an actor with an insight into how sugar cane was linked to slavery'. They are *plants* you idiots. 'Decolonisation' in the Woke manual really means colonisation of society with its mentality and by extension colonisation by the Cult. We are witnessing a new Chinese-style 'Cultural Revolution' so essential to the success of all

Marxist takeovers. Our cultural past and traditions have to be swept away to allow a new culture to be built-back-better. Woke targeting of long-standing Western cultural pillars including historical monuments and cancelling of historical figures is what happened in the Mao revolution in China which 'purged remnants of capitalist and traditional elements from Chinese society' and installed Maoism as the dominant ideology'. For China see the Western world today and for 'dominant ideology' see Woke. Better still see Marxism or Maoism. The 'Covid' hoax has specifically sought to destroy the arts and all elements of Western culture from people meeting in a pub or restaurant to closing theatres, music venues, sports stadiums, places of worship and even banning *singing*. Destruction of Western society is also why criticism of any religion is banned except for Christianity which again is the dominant religion as white is the numerically-dominant race. Christianity may be fading rapidly, but its history and traditions are weaved through the fabric of Western society. Delete the pillars and other structures will follow until the whole thing collapses. I am not a Christian defending that religion when I say that. I have no religion. It's just a fact. To this end Christianity has itself been turned Woke to usher its own downfall and its ranks are awash with 'change agents' – knowing and unknowing – at every level including Pope Francis (*definitely* knowing) and the clueless Archbishop of Canterbury Justin Welby (possibly not, but who can be sure?). Woke seeks to coordinate attacks on Western culture, traditions, and ways of life through 'intersectionality' defined as 'the complex, cumulative way in which the effects of multiple forms of discrimination (such as racism, sexism, and classism) combine, overlap, or intersect especially in the experiences of marginalised individuals or groups'. Wade through the Orwellian Woke-speak and this means coordinating disparate groups in a common cause to overthrow freedom and liberal values.

The entire structure of public institutions has been infested with Woke – government at all levels, political parties, police, military, schools, universities, advertising, media and trade unions. This abomination has been achieved through the Cult web by appointing

Wokers to positions of power and battering non-Wokers into line through intimidation, isolation and threats to their job. Many have been fired in the wake of the empathy-deleted, vicious hostility of 'social justice' Wokers and the desire of gutless, spineless employers to virtue-signal their Wokeness. Corporations are filled with Wokers today, most notably those in Silicon Valley. Ironically at the top they are not Woke at all. They are only exploiting the mentality their Cult masters have created and funded to censor and enslave while the Wokers cheer them on until it's their turn. Thus the Woke 'liberal left' is an inversion of the traditional liberal left. Campaigning for justice on the grounds of power and wealth distribution has been replaced by campaigning for identity politics. The genuine traditional left would never have taken money from today's billionaire abusers of fairness and justice and nor would the billionaires have wanted to fund that genuine left. It would not have been in their interests to do so. The division of opinion in those days was between the haves and have nots. This all changed with Cult manipulated and funded identity politics. The division of opinion today is between Wokers and non-Wokers and not income brackets. Cult corporations and their billionaires may have taken wealth disparity to cataclysmic levels of injustice, but as long as they speak the language of Woke, hand out the dosh to the Woke network and censor the enemy they are 'one of us'. Billionaires who don't give a damn about injustice are laughing at them till their bellies hurt. Wokers are not even close to self-aware enough to see that. The transformed 'left' dynamic means that Wokers who drone on about 'social justice' are funded by billionaires that have destroyed social justice the world over. It's *why* they are billionaires.

The climate con

Nothing encapsulates what I have said more comprehensively than the hoax of human-caused global warming. I have detailed in my books over the years how Cult operatives and organisations were the pump-primers from the start of the climate con. A purpose-built vehicle for this is the Club of Rome established by the Cult in 1968

with the Rockefellers and Rothschilds centrally involved all along. Their gofer frontman Maurice Strong, a Canadian oil millionaire, hosted the Earth Summit in Rio de Janeiro, Brazil, in 1992 where the global 'green movement' really expanded in earnest under the guiding hand of the Cult. The Earth Summit established Agenda 21 through the Cult-created-and-owned United Nations to use the illusion of human-caused climate change to justify the transformation of global society to save the world from climate disaster. It is a No-Problem-Reaction-Solution sold through governments, media, schools and universities as whole generations have been terrified into believing that the world was going to end in their lifetimes unless what old people had inflicted upon them was stopped by a complete restructuring of how everything is done. Chill, kids, it's all a hoax. Such restructuring is precisely what the Cult agenda demands (purely by coincidence of course). Today this has been given the codename of the Great Reset which is only an updated term for Agenda 21 and its associated Agenda 2030. The latter, too, is administered through the UN and was voted into being by the General Assembly in 2015. Both 21 and 2030 seek centralised control of all resources and food right down to the raindrops falling on your own land. These are some of the demands of Agenda 21 established in 1992. See if you recognise this society emerging today:

- End national sovereignty
- State planning and management of all land resources, ecosystems, deserts, forests, mountains, oceans and fresh water; agriculture; rural development; biotechnology; and ensuring *'equity'*
- The state to 'define the role' of business and financial resources
- Abolition of private property
- 'Restructuring' the family unit (see BLM)
- Children raised by the state
- People told what their job will be
- Major restrictions on movement
- Creation of 'human settlement zones'

- Mass resettlement as people are forced to vacate land where they live
- Dumbing down education
- Mass global depopulation in pursuit of all the above

The United Nations was created as a Trojan horse for world government. With the climate con of critical importance to promoting that outcome you would expect the UN to be involved. Oh, it's involved all right. The UN is promoting Agenda 21 and Agenda 2030 justified by 'climate change' while also driving the climate hoax through its Intergovernmental Panel on Climate Change (IPCC), one of the world's most corrupt organisations. The IPCC has been lying ferociously and constantly since the day it opened its doors with the global media hanging unquestioningly on its every mendacious word. The Green movement is entirely Woke and has long lost its original environmental focus since it was co-opted by the Cult. An obsession with 'global warming' has deleted its values and scrambled its head. I experienced a small example of what I mean on a beautiful country walk that I have enjoyed several times a week for many years. The path merged into the fields and forests and you felt at one with the natural world. Then a 'Green' organisation, the Hampshire and Isle of Wight Wildlife Trust, took over part of the land and proceeded to cut down a large number of trees, including mature ones, to install a horrible big, bright steel 'this-is-ours-stay-out' fence that destroyed the whole atmosphere of this beautiful place. No one with a feel for nature would do that. Day after day I walked to the sound of chainsaws and a magnificent mature weeping willow tree that I so admired was cut down at the base of the trunk. When I challenged a Woke young girl in a green shirt (of course) about this vandalism she replied: 'It's a weeping willow – it will grow back.' This is what people are paying for when they donate to the Hampshire and Isle of Wight Wildlife Trust and many other 'green' organisations today. It is not the environmental movement that I knew and instead has become a support-system – as with Extinction Rebellion – for a very dark agenda.

Private jets for climate justice

The Cult-owned, Gates-funded, World Economic Forum and its founder Klaus Schwab were behind the emergence of Greta Thunberg to harness the young behind the climate agenda and she was invited to speak to the world at … the UN. Schwab published a book, *Covid-19: The Great Reset* in 2020 in which he used the 'Covid' hoax and the climate hoax to lay out a new society straight out of Agenda 21 and Agenda 2030. Bill Gates followed in early 2021 when he took time out from destroying the world to produce a book in his name about the way to save it. Gates flies across the world in private jets and admitted that 'I probably have one of the highest greenhouse gas footprints of anyone on the planet … my personal flying alone is gigantic.' He has also bid for the planet's biggest private jet operator. Other climate change saviours who fly in private jets include John Kerry, the US Special Presidential Envoy for Climate, and actor Leonardo DiCaprio, a 'UN Messenger of Peace with special focus on climate change'. These people are so full of bullshit they could corner the market in manure. We mustn't be sceptical, though, because the Gates book, *How to Avoid a Climate Disaster: The Solutions We Have and the Breakthroughs We Need*, is a genuine attempt to protect the world and not an obvious pile of excrement attributed to a mega-psychopath aimed at selling his masters' plans for humanity. The Gates book and the other shite-pile by Klaus Schwab could have been written by the same person and may well have been. Both use 'climate change' and 'Covid' as the excuses for their new society and by coincidence the Cult's World Economic Forum and Bill and Melinda Gates Foundation promote the climate hoax and hosted Event 201 which pre-empted with a 'simulation' the very 'coronavirus' hoax that would be simulated for real on humanity within weeks. The British 'royal' family is promoting the 'Reset' as you would expect through Prince 'climate change caused the war in Syria' Charles and his hapless son Prince William who said that we must 'reset our relationship with nature and our trajectory as a species' to avoid a climate disaster. Amazing how many promotors of the 'Covid' and 'climate change' control

systems are connected to Gates and the World Economic Forum. A 'study' in early 2021 claimed that carbon dioxide emissions must fall by the equivalent of a global lockdown roughly every two years for the next decade to save the planet. The 'study' appeared in the same period that the Schwab mob claimed in a video that lockdowns destroying the lives of billions are good because they make the earth 'quieter' with less 'ambient noise'. They took down the video amid a public backlash for such arrogant, empathy-deleted stupidity You see, however, where they are going with this. Corinne Le Quéré, a professor at the Tyndall Centre for Climate Change Research, University of East Anglia, was lead author of the climate lockdown study, and she writes for … the World Economic Forum. Gates calls in 'his' book for changing 'every aspect of the economy' (long-time Cult agenda) and for humans to eat synthetic 'meat' (predicted in my books) while cows and other farm animals are eliminated. Australian TV host and commentator Alan Jones described what carbon emission targets would mean for farm animals in Australia alone if emissions were reduced as demanded by 35 percent by 2030 and zero by 2050:

Well, let's take agriculture, the total emissions from agriculture are about 75 million tonnes of carbon dioxide, equivalent. Now reduce that by 35 percent and you have to come down to 50 million tonnes, I've done the maths. So if you take for example 1.5 million cows, you're going to have to reduce the herd by 525,000 [by] 2030, nine years, that's 58,000 cows a year. The beef herd's 30 million, reduce that by 35 percent, that's 10.5 million, which means 1.2 million cattle have to go every year between now and 2030. This is insanity!

There are 75 million sheep. Reduce that by 35 percent, that's 26 million sheep, that's almost 3 million a year. So under the Paris Agreement over 30 million beasts. dairy cows, cattle, pigs and sheep would go. More than 8,000 every minute of every hour for the next decade, do these people know what they're talking about?

Clearly they don't at the level of campaigners, politicians and administrators. The Cult *does* know; that's the outcome it wants. We are faced with not just a war on humanity. Animals and the natural world are being targeted and I have been saying since the 'Covid' hoax began that the plan eventually was to claim that the 'deadly virus' is able to jump from animals, including farm animals and

domestic pets, to humans. Just before this book went into production came this story: 'Russia registers world's first Covid-19 vaccine for cats & dogs as makers of Sputnik V warn pets & farm animals could spread virus'. The report said 'top scientists warned that the deadly pathogen could soon begin spreading through homes and farms' and 'the next stage is the infection of farm and domestic animals'. Know the outcome and you'll see the journey. Think what that would mean for animals and keep your eye on a term called zoonosis or zoonotic diseases which transmit between animals and humans. The Cult wants to break the connection between animals and people as it does between people and people. Farm animals fit with the Cult agenda to transform food from natural to synthetic.

The gas of life is killing us

There can be few greater examples of Cult inversion than the condemnation of carbon dioxide as a dangerous pollutant when it is the gas of life. Without it the natural world would be dead and so we would all be dead. We breathe in oxygen and breathe out carbon dioxide while plants produce oxygen and absorb carbon dioxide. It is a perfect symbiotic relationship that the Cult wants to dismantle for reasons I will come to in the final two chapters. Gates, Schwab, other Cult operatives and mindless repeaters, want the world to be 'carbon neutral' by at least 2050 and the earlier the better. 'Zero carbon' is the cry echoed by lunatics calling for 'Zero Covid' when we already have it. These carbon emission targets will deindustrialise the world in accordance with Cult plans – the post-industrial, post-democratic society – and with so-called renewables like solar and wind not coming even close to meeting human energy needs blackouts and cold are inevitable. Texans got the picture in the winter of 2021 when a snow storm stopped wind turbines and solar panels from working and the lights went down along with water which relies on electricity for its supply system. Gates wants everything to be powered by electricity to ensure that his masters have the kill switch to stop all human activity, movement, cooking, water and warmth any time they like. The climate lie is so

stupendously inverted that it claims we must urgently reduce carbon dioxide when we *don't have enough*.

Co2 in the atmosphere is a little above 400 parts per million when the optimum for plant growth is 2,000 ppm and when it falls anywhere near 150 ppm the natural world starts to die and so do we. It fell to as low as 280 ppm in an 1880 measurement in Hawaii and rose to 413 ppm in 2019 with industrialisation which is why the planet has become *greener* in the industrial period. How insane then that psychopathic madman Gates is not satisfied only with blocking the rise of Co2. He's funding technology to suck it out of the atmosphere. The reason why will become clear. The industrial era is not destroying the world through Co2 and has instead turned around a potentially disastrous ongoing fall in Co2. Greenpeace co-founder and scientist Patrick Moore walked away from Greenpeace in 1986 and has exposed the green movement for fear-mongering and lies. He said that 500 million years ago there was *17 times* more Co2 in the atmosphere than we have today and levels have been falling for hundreds of millions of years. In the last 150 million years Co2 levels in Earth's atmosphere had reduced by *90 percent*. Moore said that by the time humanity began to unlock carbon dioxide from fossil fuels we were at '38 seconds to midnight' and in that sense: 'Humans are [the Earth's] salvation.' Moore made the point that only half the Co2 emitted by fossil fuels stays in the atmosphere and we should remember that all pollution pouring from chimneys that we are told is carbon dioxide is in fact nothing of the kind. It's pollution. Carbon dioxide is an invisible gas.

William Happer, Professor of Physics at Princeton University and long-time government adviser on climate, has emphasised the Co2 deficiency for maximum growth and food production. Greenhouse growers don't add carbon dioxide for a bit of fun. He said that most of the warming in the last 100 years, after the earth emerged from the super-cold period of the 'Little Ice Age' into a natural warming cycle, was over by 1940. Happer said that a peak year for warming in 1988 can be explained by a 'monster El Nino' which is a natural and cyclical warming of the Pacific that has nothing to do with 'climate

change'. He said the effect of Co2 could be compared to painting a wall with red paint in that once two or three coats have been applied it didn't matter how much more you slapped on because the wall will not get much redder. Almost all the effect of the rise in Co2 has already happened, he said, and the volume in the atmosphere would now have to *double* to increase temperature by a single degree. Climate hoaxers know this and they have invented the most ridiculously complicated series of 'feedback' loops to try to overcome this rather devastating fact. You hear puppet Greta going on cluelessly about feedback loops and this is why.

The Sun affects temperature? No you *climate denier*

Some other nonsense to contemplate: Climate graphs show that rises in temperature do not follow rises in Co2 – *it's the other way round* with a lag between the two of some 800 years. If we go back 800 years from present time we hit the Medieval Warm Period when temperatures were higher than now without any industrialisation and this was followed by the Little Ice Age when temperatures plummeted. The world was still emerging from these centuries of serious cold when many climate records began which makes the ever-repeated line of the 'hottest year since records began' meaningless when you are not comparing like with like. The coldest period of the Little Ice Age corresponded with the lowest period of sunspot activity when the Sun was at its least active. Proper scientists will not be at all surprised by this when it confirms the obvious fact that earth temperature is affected by the scale of Sun activity and the energetic power that it subsequently emits; but when is the last time you heard a climate hoaxer talking about the Sun as a source of earth temperature?? Everything has to be focussed on Co2 which makes up just 0.117 percent of so-called greenhouse gases and only a fraction of even that is generated by human activity. The rest is natural. More than *90 percent* of those greenhouse gases are water vapour and clouds (Fig 9). Ban moisture I say. Have you noticed that the climate hoaxers no longer use the polar bear as their promotion image? That's because far from becoming extinct polar

bear communities are stable or thriving. Joe Bastardi, American meteorologist, weather forecaster and outspoken critic of the climate lie, documents in his book *The Climate Chronicles* how weather patterns and events claimed to be evidence of climate change have been happening since long before industrialisation: 'What happened before naturally is happening again, as is to be expected given the cyclical nature of the climate due to the design of the planet.' If you read the detailed background to the climate hoax in my other books you will shake your head and wonder how anyone could believe the crap which has spawned a multi-trillion dollar industry based on absolute garbage (see HIV causes AIDs and Sars-Cov-2 causes 'Covid-19'). Climate and 'Covid' have much in common given they have the same source. They both have the contradictory *everything* factor in which everything is explained by reference to them. It's hot – 'it's climate change'. It's cold – 'it's climate change'. I got a sniffle – 'it's Covid'. I haven't got a sniffle – 'it's Covid'. Not having a sniffle has to be a symptom of 'Covid'. Everything is and not having a sniffle is especially dangerous if you are a slow walker. For sheer audacity I offer you a Cambridge University 'study' that actually linked 'Covid' to 'climate change'. It had to happen eventually. They concluded that climate change played a role in 'Covid-19' spreading from animals to humans because … wait for it … I kid you not … *the two groups were forced closer together as populations grow*. Er, that's it. The whole foundation on which this depended was that 'Bats are the likely zoonotic origin of SARS-CoV-1 and SARS-CoV-2'. Well, they are not. They are nothing to do with it. Apart from bats not being the origin and therefore 'climate change' effects on bats being irrelevant I am in awe of their academic insight. Where would we be without them? Not where we are that's for sure.

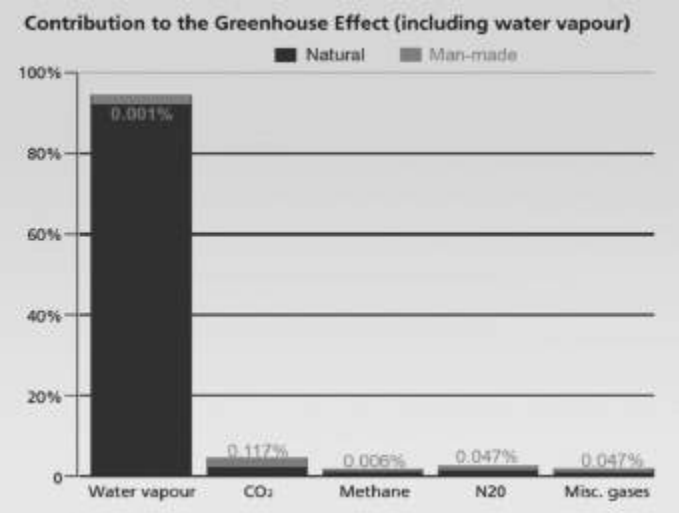


Figure 9: The idea that the gas of life is disastrously changing the climate is an insult to brain cell activity.

One other point about the weather is that climate modification is now well advanced and not every major weather event is natural – or earthquake come to that. I cover this subject at some length in other books. China is openly planning a rapid expansion of its weather modification programme which includes changing the climate in an area more than one and a half times the size of India. China used weather manipulation to ensure clear skies during the 2008 Olympics in Beijing. I have quoted from US military documents detailing how to employ weather manipulation as a weapon of war and they did that in the 1960s and 70s during the conflict in Vietnam with Operation Popeye manipulating monsoon rains for military purposes. Why would there be international treaties on weather modification if it wasn't possible? Of course it is. Weather is energetic information and it can be changed.

How was the climate hoax pulled off? See 'Covid'

If you can get billions to believe in a 'virus' that doesn't exist you can get them to believe in human-caused climate change that doesn't exist. Both are being used by the Cult to transform global society in the way it has long planned. Both hoaxes have been achieved in pretty much the same way. First you declare a lie is a fact. There's a

'virus' you call SARS-Cov-2 or humans are warming the planet with their behaviour. Next this becomes, via Cult networks, the foundation of government, academic and science policy and belief. Those who parrot the mantra are given big grants to produce research that confirms the narrative is true and ever more 'symptoms' are added to make the 'virus'/'climate change' sound even more scary. Scientists and researchers who challenge the narrative have their grants withdrawn and their careers destroyed. The media promote the lie as the unquestionable truth and censor those with an alternative view or evidence. A great percentage of the population believe what they are told as the lie becomes an everybody-knows-that and the believing-masses turn on those with a mind of their own. The technique has been used endlessly throughout human history. Wokers are the biggest promotors of the climate lie *and* 'Covid' fascism because their minds are owned by the Cult; their sense of self-righteous self-purity knows no bounds; and they exist in a bubble of reality in which facts are irrelevant and only get in the way of looking without seeing.

Running through all of this like veins in a blue cheese is control of information, which means control of perception, which means control of behaviour, which collectively means control of human society. The Cult owns the global media and Silicon Valley fascists for the simple reason that it *has* to. Without control of information it can't control perception and through that human society. Examine every facet of the Cult agenda and you will see that anything supporting its introduction is never censored while anything pushing back is always censored. I say again: Psychopaths that know why they are doing this must go before Nuremberg trials and those that follow their orders must trot along behind them into the same dock. 'I was just following orders' didn't work the first time and it must not work now. Nuremberg trials must be held all over the world before public juries for politicians, government officials, police, compliant doctors, scientists and virologists, and all Cult operatives such as Gates, Tedros, Fauci, Vallance, Whitty, Ferguson, Zuckerberg, Wojcicki, Brin, Page, Dorsey, the whole damn lot of

them – including, no *especially*, the psychopath psychologists. Without them and the brainless, gutless excuses for journalists that have repeated their lies, none of this could be happening. Nobody can be allowed to escape justice for the psychological and economic Armageddon they are all responsible for visiting upon the human race.

As for the compliant, unquestioning, swathes of humanity, and the self-obsessed, all-knowing ignorance of the Wokers … don't start me. God help their kids. God help their grandkids. God *help them*.

CHAPTER NINE

We must have it? So what is it?

Well I won't back down. No, I won't back down. You can stand me up at the Gates of Hell. But I won't back down
Tom Petty

I will now focus on the genetically-manipulating 'Covid vaccines' which do not meet this official definition of a vaccine by the US Centers for Disease Control (CDC): 'A product that stimulates a person's immune system to produce immunity to a specific disease, protecting the person from that disease.' On that basis 'Covid vaccines' are not a vaccine in that the makers don't even claim they stop infection or transmission.

They are instead part of a multi-levelled conspiracy to change the nature of the human body and what it means to be 'human' and to depopulate an enormous swathe of humanity. What I shall call Human 1.0 is on the cusp of becoming Human 2.0 and for very sinister reasons. Before I get to the 'Covid vaccine' in detail here's some background to vaccines in general. Government regulators do not test vaccines – the makers do – and the makers control which data is revealed and which isn't. Children in America are given 50 vaccine doses by age six and 69 by age 19 and the effect of the whole combined schedule has never been tested. Autoimmune diseases when the immune system attacks its own body have soared in the mass vaccine era and so has disease in general in children and the young. Why wouldn't this be the case when vaccines target the *immune system?* The US government gave Big Pharma drug

companies immunity from prosecution for vaccine death and injury in the 1986 National Childhood Vaccine Injury Act (NCVIA) and since then the government (taxpayer) has been funding compensation for the consequences of Big Pharma vaccines. The criminal and satanic drug giants can't lose and the vaccine schedule has increased dramatically since 1986 for this reason. There is no incentive to make vaccines safe and a big incentive to make money by introducing ever more. Even against a ridiculously high bar to prove vaccine liability, and with the government controlling the hearing in which it is being challenged for compensation, the vaccine court has so far paid out more than $4 billion. These are the vaccines we are told are safe and psychopaths like Zuckerberg censor posts saying otherwise. The immunity law was even justified by a ruling that vaccines by their nature were 'unavoidably unsafe'.

Check out the ingredients of vaccines and you will be shocked if you are new to this. *They put that in children's bodies?? What??* Try aluminium, a brain toxin connected to dementia, aborted foetal tissue and formaldehyde which is used to embalm corpses. World-renowned aluminium expert Christopher Exley had his research into the health effect of aluminium in vaccines shut down by Keele University in the UK when it began taking funding from the Bill and Melinda Gates Foundation. Research when diseases 'eradicated' by vaccines began to decline and you will find the fall began long *before* the vaccine was introduced. Sometimes the fall even plateaued after the vaccine. Diseases like scarlet fever for which there was no vaccine declined in the same way because of environmental and other factors. A perfect case in point is the polio vaccine. Polio began when lead arsenate was first sprayed as an insecticide and residues remained in food products. Spraying started in 1892 and the first US polio epidemic came in Vermont in 1894. The simple answer was to stop spraying, but Rockefeller-created Big Pharma had a better idea. Polio was decreed to be caused by the *poliovirus* which 'spreads from person to person and can infect a person's spinal cord'. Lead arsenate was replaced by the lethal DDT which had the same effect of causing paralysis by damaging the brain and central nervous

system. Polio plummeted when DDT was reduced and then banned, but the vaccine is still given the credit for something it didn't do. Today by far the biggest cause of polio is the vaccines promoted by Bill Gates. Vaccine justice campaigner Robert Kennedy Jr, son of assassinated (by the Cult) US Attorney General Robert Kennedy, wrote:

> In 2017, the World Health Organization (WHO) reluctantly admitted that the global explosion in polio is predominantly vaccine strain. The most frightening epidemics in Congo, Afghanistan, and the Philippines, are all linked to vaccines. In fact, by 2018, 70% of global polio cases were vaccine strain.

Vaccines make fortunes for Cult-owned Gates and Big Pharma while undermining the health and immune systems of the population. We had a glimpse of the mentality behind the Big Pharma cartel with a report on WION (World is One News), an international English language TV station based in India, which exposed the extraordinary behaviour of US drug company Pfizer over its 'Covid vaccine'. The WION report told how Pfizer had made fantastic demands of Argentina, Brazil and other countries in return for its 'vaccine'. These included immunity from prosecution, even for Pfizer negligence, government insurance to protect Pfizer from law suits and handing over as collateral sovereign assets of the country to include Argentina's bank reserves, military bases and embassy buildings. Pfizer demanded the same of Brazil in the form of waiving sovereignty of its assets abroad; exempting Pfizer from Brazilian laws; and giving Pfizer immunity from all civil liability. This is a 'vaccine' developed with government funding. Big Pharma is evil incarnate as a creation of the Cult and all must be handed tickets to Nuremberg.

Phantom 'vaccine' for a phantom 'disease'

I'll expose the 'Covid vaccine' fraud and then go on to the wider background of why the Cult has set out to 'vaccinate' every man, woman and child on the planet for an alleged 'new disease' with a survival rate of 99.77 percent (or more) even by the grotesquely-

manipulated figures of the World Health Organization and Johns Hopkins University. The 'infection' to 'death' ratio is 0.23 to 0.15 percent according to Stanford epidemiologist Dr John Ioannidis and while estimates vary the danger remains tiny. I say that if the truth be told the fake infection to fake death ratio is zero. Never mind all the evidence I have presented here and in *The Answer* that there is no 'virus' let us just focus for a moment on that death-rate figure of say 0.23 percent. The figure includes all those worldwide who have tested positive with a test not testing for the 'virus' and then died within 28 days or even longer of any other cause – *any other cause*. Now subtract all those illusory 'Covid' deaths on the global data sheets from the 0.23 percent. What do you think you would be left with? *Zero*. A vaccination has never been successfully developed for a so-called coronavirus. They have all failed at the animal testing stage when they caused hypersensitivity to what they were claiming to protect against and made the impact of a disease far worse. Cult-owned vaccine corporations got around that problem this time by bypassing animal trials, going straight to humans and making the length of the 'trials' before the public rollout as short as they could get away with. Normally it takes five to ten years or more to develop vaccines that still cause demonstrable harm to many people and that's without including the long-term effects that are never officially connected to the vaccination. 'Covid' non-vaccines have been officially produced and approved in a matter of months from a standing start and part of the reason is that (a) they were developed before the 'Covid' hoax began and (b) they are based on computer programs and not natural sources. Official non-trials were so short that government agencies gave *emergency*, not full, approval. 'Trials' were not even completed and full approval cannot be secured until they are. Public 'Covid vaccination' is actually a *continuation of the trial*. Drug company 'trials' are not scheduled to end until 2023 by which time a lot of people are going to be dead. Data on which government agencies gave this emergency approval was supplied by the Big Pharma corporations themselves in the form of Pfizer/BioNTech, AstraZeneca, Moderna, Johnson & Johnson, and

others, and this is the case with all vaccines. By its very nature *emergency* approval means drug companies do not have to prove that the 'vaccine' is 'safe and effective'. How could they with trials way short of complete? Government regulators only have to *believe* that they *could* be safe and effective. It is criminal manipulation to get products in circulation with no testing worth the name. Agencies giving that approval are infested with Big Pharma-connected place-people and they act in the interests of Big Pharma (the Cult) and not the public about whom they do not give a damn.

More human lab rats

'Covid vaccines' produced in record time by Pfizer/BioNTech and Moderna employ a technique *never approved before for use on humans*. They are known as mRNA 'vaccines' and inject a synthetic version of 'viral' mRNA or 'messenger RNA'. The key is in the term 'messenger'. The body works, or doesn't, on the basis of information messaging. Communications are constantly passing between and within the genetic system and the brain. Change those messages and you change the state of the body and even its very nature and you can change psychology and behaviour by the way the brain processes information. I think you are going to see significant changes in personality and perception of many people who have had the 'Covid vaccine' synthetic potions. Insider Aldous Huxley predicted the following in 1961 and mRNA 'vaccines' can be included in the term 'pharmacological methods':

> There will be, in the next generation or so, a pharmacological method of making people love their servitude, and producing dictatorship without tears, so to speak, producing a kind of painless concentration camp for entire societies, so that people will in fact have their own liberties taken away from them, but rather enjoy it, because they will be distracted from any desire to rebel by propaganda or brainwashing, or brainwashing enhanced by pharmacological methods. And this seems to be the final revolution.

Apologists claim that mRNA synthetic 'vaccines' don't change the DNA genetic blueprint because RNA does not affect DNA only the other way round. This is so disingenuous. A process called 'reverse

transcription' can convert RNA into DNA and be integrated into DNA in the cell nucleus. This was highlighted in December, 2020, by scientists at Harvard and Massachusetts Institute of Technology (MIT). Geneticists report that more than 40 percent of mammalian genomes results from reverse transcription. On the most basic level if messaging changes then that sequence must lead to changes in DNA which is receiving and transmitting those communications. How can introducing synthetic material into cells not change the cells where DNA is located? The process is known as transfection which is defined as 'a technique to insert foreign nucleic acid (DNA or RNA) into a cell, typically with the intention of altering the properties of the cell'. Researchers at the Sloan Kettering Institute in New York found that changes in messenger RNA can deactivate tumour-suppressing proteins and thereby promote cancer. This is what happens when you mess with messaging. 'Covid vaccine' maker Moderna was founded in 2010 by Canadian stem cell biologist Derrick J. Rossi after his breakthrough discovery in the field of transforming and reprogramming stem cells. These are neutral cells that can be programmed to become any cell including sperm cells. Moderna was therefore founded on the principle of genetic manipulation and has never produced any vaccine or drug before its genetically-manipulating synthetic 'Covid' shite. Look at the name – Mode-RNA or Modify-RNA. Another important point is that the US Supreme Court has ruled that genetically-modified DNA, or complementary DNA (cDNA) synthesized in the laboratory from messenger RNA, can be patented and owned. These psychopaths are doing this to the human body.

Cells replicate synthetic mRNA in the 'Covid vaccines' and in theory the body is tricked into making antigens which trigger antibodies to target the 'virus spike proteins' which as Dr Tom Cowan said have *never been seen*. Cut the crap and these 'vaccines' deliver *self-replicating* synthetic material to the cells with the effect of changing human DNA. The more of them you have the more that process is compounded while synthetic material is all the time self-replicating. 'Vaccine'-maker Moderna describes mRNA as 'like

software for the cell' and so they are messing with the body's software. What happens when you change the software in a computer? Everything changes. For this reason the Cult is preparing a production line of mRNA 'Covid vaccines' and a long list of excuses to use them as with all the 'variants' of a 'virus' never shown to exist. The plan is further to transfer the mRNA technique to other vaccines mostly given to children and young people. The cumulative consequences will be a transformation of human DNA through a constant infusion of synthetic genetic material which will kill many and change the rest. Now consider that governments that have given emergency approval for a vaccine that's not a vaccine; never been approved for humans before; had no testing worth the name; and the makers have been given immunity from prosecution for any deaths or adverse effects suffered by the public. The UK government awarded *permanent legal indemnity* to itself and its employees for harm done when a patient is being treated for 'Covid-19' or 'suspected Covid-19'. That is quite a thought when these are possible 'side-effects' from the 'vaccine' (they are not 'side', they are effects) listed by the US Food and Drug Administration:

Guillain-Barre syndrome; acute disseminated encephalomyelitis; transverse myelitis; encephalitis; myelitis; encephalomyelitis; meningoencephalitis; meningitis; encephalopathy; convulsions; seizures; stroke; narcolepsy; cataplexy; anaphylaxis; acute myocardial infarction (heart attack); myocarditis; pericarditis; autoimmune disease; death; implications for pregnancy, and birth outcomes; other acute demyelinating diseases; non anaphylactic allergy reactions; thrombocytopenia ; disseminated intravascular coagulation; venous thromboembolism; arthritis; arthralgia; joint pain; Kawasaki disease; multisystem inflammatory syndrome in children; vaccine enhanced disease. The latter is the way the 'vaccine' has the potential to make diseases far worse than they would otherwise be.

UK doctor and freedom campaigner Vernon Coleman described the conditions in this list as 'all unpleasant, most of them very serious, and you can't get more serious than death'. The thought that anyone at all has had the 'vaccine' in these circumstances is testament to the potential that humanity has for clueless, unquestioning, stupidity and for many that programmed stupidity has already been terminal.

An insider speaks

Dr Michael Yeadon is a former Vice President, head of research and Chief Scientific Adviser at vaccine giant Pfizer. Yeadon worked on the inside of Big Pharma, but that did not stop him becoming a vocal critic of 'Covid vaccines' and their potential for multiple harms, including infertility in women. By the spring of 2021 he went much further and even used the no, no, term 'conspiracy'. When you begin to see what is going on it is impossible not to do so. Yeadon spoke out in an interview with freedom campaigner James Delingpole and I mentioned earlier how he said that no one had samples of 'the virus'. He explained that the mRNA technique originated in the anti-cancer field and ways to turn on and off certain genes which could be advantageous if you wanted to stop cancer growing out of control. 'That's the origin of them. They are a very unusual application, really.' Yeadon said that treating a cancer patient with an aggressive procedure might be understandable if the alternative was dying, but it was quite another thing to use the same technique as a public health measure. Most people involved wouldn't catch the infectious agent you were vaccinating against and if they did they probably wouldn't die:

> If you are really using it as a public health measure you really want to as close as you can get to zero sides-effects … I find it odd that they chose techniques that were really cutting their teeth in the field of oncology and I'm worried that in using gene-based vaccines that have to be injected in the body and spread around the body, get taken up into some cells, and the regulators haven't quite told us which cells they get taken up into … you are going to be generating a wide range of responses … with multiple steps each of which could go well or badly.

I doubt the Cult intends it to go well. Yeadon said that you can put any gene you like into the body through the 'vaccine'. 'You can certainly give them a gene that would do them some harm if you wanted.' I was intrigued when he said that when used in the cancer field the technique could turn genes on and off. I explore this process in *The Answer* and with different genes having different functions you could create mayhem – physically and psychologically – if you turned the wrong ones on and the right ones off. I read reports of an experiment by researchers at the University of Washington's school of computer science and engineering in which they encoded DNA to infect computers. The body is itself a biological computer and if human DNA can inflict damage on a computer why can't the computer via synthetic material mess with the human body? It can. The Washington research team said it was possible to insert malicious malware into 'physical DNA strands' and corrupt the computer system of a gene sequencing machine as it 'reads gene letters and stores them as binary digits 0 and 1'. They concluded that hackers could one day use blood or spit samples to access computer systems and obtain sensitive data from police forensics labs or infect genome files. It is at this level of digital interaction that synthetic 'vaccines' need to be seen to get the full picture and that will become very clear later on. Michael Yeadon said it made no sense to give the 'vaccine' to younger people who were in no danger from the 'virus'. What was the benefit? It was all downside with potential effects:

> The fact that my government in what I thought was a civilised, rational country, is raining [the 'vaccine'] on people in their 30s and 40s, even my children in their 20s, they're getting letters and phone calls, I know this is not right and any of you doctors who are vaccinating you know it's not right, too. They are not at risk. They are not at risk from the disease, so you are now hoping that the side-effects are so rare that you get away with it. You don't give new technology … that you don't understand to 100 percent of the population.

Blood clot problems with the AstraZeneca 'vaccine' have been affecting younger people to emphasise the downside risks with no benefit. AstraZeneca's version, produced with Oxford University, does not use mRNA, but still gets its toxic cocktail inside cells where

it targets DNA. The Johnson & Johnson 'vaccine' which uses a similar technique has also produced blood clot effects to such an extent that the United States paused its use at one point. They are all 'gene therapy' (cell modification) procedures and not 'vaccines'. The truth is that once the content of these injections enter cells we have no idea what the effect will be. People can speculate and some can give very educated opinions and that's good. In the end, though, only the makers know what their potions are designed to do and even they won't know every last consequence. Michael Yeadon was scathing about doctors doing what they knew to be wrong. 'Everyone's mute', he said. Doctors in the NHS must know this was not right, coming into work and injecting people. 'I don't know how they sleep at night. I know I couldn't do it. I know that if I were in that position I'd have to quit.' He said he knew enough about toxicology to know this was not a good risk-benefit. Yeadon had spoken to seven or eight university professors and all except two would not speak out publicly. Their universities had a policy that no one said anything that countered the government and its medical advisors. They were afraid of losing their government grants. This is how intimidation has been used to silence the truth at every level of the system. I say silence, but these people could still speak out if they made that choice. Yeadon called them 'moral cowards' – 'This is about your children and grandchildren's lives and you have just buggered off and left it.'

'Variant' nonsense

Some of his most powerful comments related to the alleged 'variants' being used to instil more fear, justify more lockdowns, and introduce more 'vaccines'. He said government claims about 'variants' were nonsense. He had checked the alleged variant 'codes' and they were 99.7 percent identical to the 'original'. This was the human identity difference equivalent to putting a baseball cap on and off or wearing it the other way round. A 0.3 percent difference would make it impossible for that 'variant' to escape immunity from the 'original'. This made no sense of having new 'vaccines' for

'variants'. He said there would have to be at least a *30 percent* difference for that to be justified and even then he believed the immune system would still recognise what it was. Gates-funded 'variant modeller' and 'vaccine'-pusher John Edmunds might care to comment. Yeadon said drug companies were making new versions of the 'vaccine' as a 'top up' for 'variants'. Worse than that, he said, the 'regulators' around the world like the MHRA in the UK had got together and agreed that because 'vaccines' for 'variants' were so similar to the first 'vaccines' *they did not have to do safety studies*. How transparently sinister that is. This is when Yeadon said: 'There is a conspiracy here.' There was no need for another vaccine for 'variants' and yet we were told that there was and the country had shut its borders because of them. 'They are going into hundreds of millions of arms without passing 'go' or any regulator. Why did they do that? Why did they pick this method of making the vaccine?'

The reason had to be something bigger than that it seemed and 'it's not protection against the virus'. It's was a far bigger project that meant politicians and advisers were willing to do things and not do things that knowingly resulted in avoidable deaths – 'that's already happened when you think about lockdown and deprivation of health care for a year.' He spoke of people prepared to do something that results in the avoidable death of their fellow human beings and it not bother them. This is the penny-drop I have been working to get across for more than 30 years – the level of pure evil we are dealing with. Yeadon said his friends and associates could not believe there could be that much evil, but he reminded them of Stalin, Pol Pot and Hitler and of what Stalin had said: 'One death is a tragedy. A million? A statistic.' He could not think of a benign explanation for why you need top-up vaccines 'which I'm sure you don't' and for the regulators 'to just get out of the way and wave them through'. Why would the regulators do that when they were still wrestling with the dangers of the 'parent' vaccine? He was clearly shocked by what he had seen since the 'Covid' hoax began and now he was thinking the previously unthinkable:

If you wanted to depopulate a significant proportion of the world and to do it in a way that doesn't involve destruction of the environment with nuclear weapons, poisoning everyone with anthrax or something like that, and you wanted plausible deniability while you had a multi-year infectious disease crisis, I actually don't think you could come up with a better plan of work than seems to be in front of me. I can't say that's what they are going to do, but I can't think of a benign explanation why they are doing it.

He said he never thought that they would get rid of 99 percent of humans, but now he wondered. 'If you wanted to that this would be a hell of a way to do it – it would be unstoppable folks.' Yeadon had concluded that those who submitted to the 'vaccine' would be allowed to have some kind of normal life (but for how long?) while screws were tightened to coerce and mandate the last few percent. 'I think they'll put the rest of them in a prison camp. I wish I was wrong, but I don't think I am.' Other points he made included: There were no coronavirus vaccines then suddenly they all come along at the same time; we have no idea of the long term affect with trials so short; coercing or forcing people to have medical procedures is against the Nuremberg Code instigated when the Nazis did just that; people should at least delay having the 'vaccine'; a quick Internet search confirms that masks don't reduce respiratory viral transmission and 'the government knows that'; they have smashed civil society and they know that, too; two dozen peer-reviewed studies show no connection between lockdown and reducing deaths; he knew from personal friends the elite were still flying around and going on holiday while the public were locked down; the elite were not having the 'vaccines'. He was also asked if 'vaccines' could be made to target difference races. He said he didn't know, but the document by the Project for the New American Century in September, 2000, said developing 'advanced forms of biological warfare that can target *specific genotypes* may transform biological warfare from the realm of terror to a politically useful tool.' Oh, they're evil all right. Of that we can be *absolutely* sure.

Another cull of old people

We have seen from the CDC definition that the mRNA 'Covid vaccine' is not a vaccine and nor are the others that *claim* to reduce 'severity of symptoms' in *some* people, but not protect from infection or transmission. What about all the lies about returning to 'normal' if people were 'vaccinated'? If they are not claimed to stop infection and transmission of the alleged 'virus', how does anything change? This was all lies to manipulate people to take the jabs and we are seeing that now with masks and distancing still required for the 'vaccinated'. How did they think that elderly people with fragile health and immune responses were going to be affected by infusing their cells with synthetic material and other toxic substances? They *knew* that in the short and long term it would be devastating and fatal as the culling of the old that began with the first lockdowns was continued with the 'vaccine'. Death rates in care homes soared immediately residents began to be 'vaccinated' – infused with synthetic material. Brave and committed whistleblower nurses put their careers at risk by exposing this truth while the rest kept their heads down and their mouths shut to put their careers before those they are supposed to care for. A long-time American Certified Nursing Assistant who gave his name as James posted a video in which he described emotionally what happened in his care home when vaccination began. He said that during 2020 very few residents were sick with 'Covid' and no one died during the entire year; but shortly after the Pfizer mRNA injections 14 people died within two weeks and many others were near death. 'They're dropping like flies', he said. Residents who walked on their own before the shot could no longer and they had lost their ability to conduct an intelligent conversation. The home's management said the sudden deaths were caused by a 'super-spreader' of 'Covid-19'. Then how come, James asked, that residents who refused to take the injections were not sick? It was a case of inject the elderly with mRNA synthetic potions and blame their illness and death that followed on the 'virus'. James described what was happening in care homes as 'the greatest crime of genocide this country has ever seen'. Remember the NHS staff nurse from earlier who used the same

word ‘genocide’ for what was happening with the ‘vaccines’ and that it was an ‘act of human annihilation’. A UK care home whistleblower told a similar story to James about the effect of the ‘vaccine’ in deaths and ‘outbreaks’ of illness dubbed ‘Covid’ after getting the jab. She told how her care home management and staff had zealously imposed government regulations and no one was allowed to even question the official narrative let alone speak out against it. She said the NHS was even worse. Again we see the results of reframing. A worker at a local care home where I live said they had not had a single case of ‘Covid’ there for almost a year and when the residents were ‘vaccinated’ they had 19 positive cases in two weeks with eight dying.

It’s not the ‘vaccine’ – honest

The obvious cause and effect was being ignored by the media and most of the public. Australia’s health minister Greg Hunt (a former head of strategy at the World Economic Forum) was admitted to hospital after he had the ‘vaccine’. He was suffering according to reports from the skin infection ‘cellulitis’ and it must have been a severe case to have warranted days in hospital. Immediately the authorities said this was nothing to do with the ‘vaccine’ when an effect of some vaccines is a ‘cellulitis-like reaction’. We had families of perfectly healthy old people who died after the ‘vaccine’ saying that if only they had been given the ‘vaccine’ earlier they would still be alive. As a numbskull rating that is off the chart. A father of four ‘died of Covid’ at aged 48 when he was taken ill two days after having the ‘vaccine’. The man, a health administrator, had been ‘shielding during the pandemic’ and had ‘not really left the house’ until he went for the ‘vaccine’. Having the ‘vaccine’ and then falling ill and dying does not seem to have qualified as a possible cause and effect and ‘Covid-19’ went on his death certificate. His family said they had no idea how he ‘caught the virus’. A family member said: ‘Tragically, it could be that going for a vaccination ultimately led to him catching Covid …The sad truth is that they are never going to know where it came from.’ The family warned people to remember

that the virus still existed and was 'very real'. So was their stupidity. Nurses and doctors who had the first round of the 'vaccine' were collapsing, dying and ending up in a hospital bed while they or their grieving relatives were saying they'd still have the 'vaccine' again despite what happened. I kid you not. You mean if your husband returned from the dead he'd have the same 'vaccine' again that killed him??

Doctors at the VCU Medical Center in Richmond, Virginia, said the Johnson & Johnson 'vaccine' was to blame for a man's skin peeling off. Patient Richard Terrell said: 'It all just happened so fast. My skin peeled off. It's still coming off on my hands now.' He said it was stinging, burning and itching and when he bent his arms and legs it was very painful with 'the skin swollen and rubbing against itself'. Pfizer/BioNTech and Moderna vaccines use mRNA to change the cell while the Johnson & Johnson version uses DNA in a process similar to AstraZeneca's technique. Johnson & Johnson and AstraZeneca have both had their 'vaccines' paused by many countries after causing serious blood problems. Terrell's doctor Fnu Nutan said he could have died if he hadn't got medical attention. It sounds terrible so what did Nutan and Terrell say about the 'vaccine' now? Oh, they still recommend that people have it. A nurse in a hospital bed 40 minutes after the vaccination and unable to swallow due to throat swelling was told by a doctor that he lost mobility in his arm for 36 hours following the vaccination. What did he say to the ailing nurse? 'Good for you for getting the vaccination.' We are dealing with a serious form of cognitive dissonance madness in both public and medical staff. There is a remarkable correlation between those having the 'vaccine' and trumpeting the fact and suffering bad happenings shortly afterwards. Witold Rogiewicz, a Polish doctor, made a video of his 'vaccination' and ridiculed those who were questioning its safety and the intentions of Bill Gates: 'Vaccinate yourself to protect yourself, your loved ones, friends and also patients. And to mention quickly I have info for anti-vaxxers and anti-Coviders if you want to contact Bill Gates you can do this through me.' He further ridiculed the dangers of 5G. Days later he

was dead, but naturally the vaccination wasn't mentioned in the verdict of 'heart attack'.

Lies, lies and more lies

So many members of the human race have slipped into extreme states of insanity and unfortunately they include reframed doctors and nursing staff. Having a 'vaccine' and dying within minutes or hours is not considered a valid connection while death from any cause within 28 days or longer of a positive test with a test not testing for the 'virus' means 'Covid-19' goes on the death certificate. How could that 'vaccine'-death connection not have been made except by calculated deceit? US figures in the initial rollout period to February 12th, 2020, revealed that a third of the deaths reported to the CDC after 'Covid vaccines' happened within 48 hours. Five men in the UK suffered an 'extremely rare' blood clot problem after having the AstraZeneca 'vaccine', but no causal link was established said the Gates-funded Medicines and Healthcare products Regulatory Agency (MHRA) which had given the 'vaccine' emergency approval to be used. Former Pfizer executive Dr Michael Yeadon explained in his interview how the procedures could cause blood coagulation and clots. People who should have been at no risk were dying from blood clots in the brain and he said he had heard from medical doctor friends that people were suffering from skin bleeding and massive headaches. The AstraZeneca 'shot' was stopped by some 20 countries over the blood clotting issue and still the corrupt MHRA, the European Medicines Agency (EMA) and the World Health Organization said that it should continue to be given even though the EMA admitted that it 'still cannot rule out definitively' a link between blood clotting and the 'vaccine'. Later Marco Cavaleri, head of EMA vaccine strategy, said there was indeed a clear link between the 'vaccine' and thrombosis, but they didn't know why. So much for the trials showing the 'vaccine' is safe. Blood clots were affecting younger people who would be under virtually no danger from 'Covid' even if it existed which makes it all the more stupid and sinister.

The British government responded to public alarm by wheeling out June Raine, the terrifyingly weak infant school headmistress sound-alike who heads the UK MHRA drug 'regulator'. The idea that she would stand up to Big Pharma and government pressure is laughable and she told us that all was well in the same way that she did when allowing untested, never-used-on-humans-before, genetically-manipulating 'vaccines' to be exposed to the public in the first place. Mass lying is the new normal of the 'Covid' era. The MHRA later said 30 cases of rare blood clots had by then been connected with the AstraZeneca 'vaccine' (that means a lot more in reality) while stressing that the benefits of the jab in preventing 'Covid-19' outweighed any risks. A more ridiculous and disingenuous statement with callous disregard for human health it is hard to contemplate. Immediately after the mendacious 'all-clears' two hospital workers in Denmark experienced blood clots and cerebral haemorrhaging following the AstraZeneca jab and one died. Top Norwegian health official Pål Andre Holme said the 'vaccine' was the only common factor: 'There is nothing in the patient history of these individuals that can give such a powerful immune response … I am confident that the antibodies that we have found are the cause, and I see no other explanation than it being the vaccine which triggers it.' Strokes, a clot or bleed in the brain, were clearly associated with the 'vaccine' from word of mouth and whistleblower reports. Similar consequences followed with all these 'vaccines' that we were told were so safe and as the numbers grew by the day it was clear we were witnessing human carnage.

Learning the hard way

A woman interviewed by UKColumn told how her husband suffered dramatic health effects after the vaccine when he'd been in good health all his life. He went from being a little unwell to losing all feeling in his legs and experiencing 'excruciating pain'. Misdiagnosis followed twice at Accident and Emergency (an 'allergy' and 'sciatica') before he was admitted to a neurology ward where doctors said his serious condition had been caused by the

'vaccine'. Another seven 'vaccinated' people were apparently being treated on the same ward for similar symptoms. The woman said he had the 'vaccine' because they believed media claims that it was safe. 'I didn't think the government would give out a vaccine that does this to somebody; I believed they would be bringing out a vaccination that would be safe.' What a tragic way to learn that lesson. Another woman posted that her husband was transporting stroke patients to hospital on almost every shift and when he asked them if they had been 'vaccinated' for 'Covid' they all replied 'yes'. One had a 'massive brain bleed' the day after his second dose. She said her husband reported the 'just been vaccinated' information every time to doctors in A and E only for them to ignore it, make no notes and appear annoyed that it was even mentioned. This particular report cannot be verified, but it expresses a common theme that confirms the monumental underreporting of 'vaccine' consequences. Interestingly as the 'vaccines' and their brain blood clot/stroke consequences began to emerge the UK National Health Service began a publicity campaign telling the public what to do in the event of a stroke. A Scottish NHS staff nurse who quit in disgust in March, 2021, said:

I have seen traumatic injuries from the vaccine, they're not getting reported to the yellow card [adverse reaction] scheme, they're treating the symptoms, not asking why, why it's happening. It's just treating the symptoms and when you speak about it you're dismissed like you're crazy, I'm not crazy, I'm not crazy because every other colleague I've spoken to is terrified to speak out, they've had enough.

Videos appeared on the Internet of people uncontrollably shaking after the 'vaccine' with no control over muscles, limbs and even their face. A Scottish mother broke out in a severe rash all over her body almost immediately after she was given the AstraZeneca 'vaccine'. The pictures were horrific. Leigh King, a 41-year-old hairdresser from Lanarkshire said: 'Never in my life was I prepared for what I was about to experience … My skin was so sore and constantly hot … I have never felt pain like this …' But don't you worry, the 'vaccine' is perfectly safe. Then there has been the effect on medical

staff who have been pressured to have the 'vaccine' by psychopathic 'health' authorities and government. A London hospital consultant who gave the name K. Polyakova wrote this to the *British Medical Journal* or *BMJ*:

> I am currently struggling with … the failure to report the reality of the morbidity caused by our current vaccination program within the health service and staff population. The levels of sickness after vaccination is unprecedented and staff are getting very sick and some with neurological symptoms which is having a huge impact on the health service function. Even the young and healthy are off for days, some for weeks, and some requiring medical treatment. Whole teams are being taken out as they went to get vaccinated together.
>
> Mandatory vaccination in this instance is stupid, unethical and irresponsible when it comes to protecting our staff and public health. We are in the voluntary phase of vaccination, and encouraging staff to take an unlicensed product that is impacting on their immediate health … it is clearly stated that these vaccine products do not offer immunity or stop transmission. In which case why are we doing it?

Not to protect health that's for sure. Medical workers are lauded by governments for agenda reasons when they couldn't give a toss about them any more than they can for the population in general. Schools across America faced the same situation as they closed due to the high number of teachers and other staff with bad reactions to the Pfizer/BioNTech, Moderna, and Johnson & Johnson 'Covid vaccines' all of which were linked to death and serious adverse effects. The *BMJ* took down the consultant's comments pretty quickly on the grounds that they were being used to spread 'disinformation'. They were exposing the truth about the 'vaccine' was the real reason. The cover-up is breathtaking.

Hiding the evidence

The scale of the 'vaccine' death cover-up worldwide can be confirmed by comparing official figures with the personal experience of the public. I heard of many people in my community who died immediately or soon after the vaccine that would never appear in the media or even likely on the official totals of 'vaccine' fatalities and adverse reactions when only about ten percent are estimated to be

reported and I have seen some estimates as low as one percent in a Harvard study. In the UK alone by April 29th, 2021, some 757,654 adverse reactions had been officially reported from the Pfizer/BioNTech, Oxford/AstraZeneca and Moderna 'vaccines' with more than a thousand deaths linked to jabs and that means an estimated ten times this number in reality from a ten percent reporting rate percentage. That's seven million adverse reactions and 10,000 potential deaths and a one percent reporting rate would be ten times *those* figures. In 1976 the US government pulled the swine flu vaccine after *53* deaths. The UK data included a combined 10,000 eye disorders from the 'Covid vaccines' with more than 750 suffering visual impairment or blindness and again multiply by the estimated reporting percentages. As 'Covid cases' officially fell hospitals virtually empty during the 'Covid crisis' began to fill up with a range of other problems in the wake of the 'vaccine' rollout. The numbers across America have also been catastrophic. Deaths linked to *all* types of vaccine increased by *6,000 percent* in the first quarter of 2021 compared with 2020. A 39-year-old woman from Ogden, Utah, died four days after receiving a second dose of Moderna's 'Covid vaccine' when her liver, heart and kidneys all failed despite the fact that she had no known medical issues or conditions. Her family sought an autopsy, but Dr Erik Christensen, Utah's chief medical examiner, said proving vaccine injury as a cause of death almost never happened. He could think of only one instance where an autopsy would name a vaccine as the official cause of death and that would be anaphylaxis where someone received a vaccine and died almost instantaneously. 'Short of that, it would be difficult for us to definitively say this is the vaccine,' Christensen said. If that is true this must be added to the estimated ten percent (or far less) reporting rate of vaccine deaths and serious reactions and the conclusion can only be that vaccine deaths and serious reactions – including these 'Covid' potions' – are phenomenally understated in official figures. The same story can be found everywhere. Endless accounts of deaths and serious reactions among the public, medical

and care home staff while official figures did not even begin to reflect this.

Professional script-reader Dr David Williams, a 'top public-health official' in Ontario, Canada, insulted our intelligence by claiming only four serious adverse reactions and no deaths from the more than 380,000 vaccine doses then given. This bore no resemblance to what people knew had happened in their owns circles and we had Dirk Huyer in charge of getting millions vaccinated in Ontario while at the same time he was Chief Coroner for the province investigating causes of death including possible death from the vaccine. An aide said he had stepped back from investigating deaths, but evidence indicated otherwise. Rosemary Frei, who secured a Master of Science degree in molecular biology at the Faculty of Medicine at Canada's University of Calgary before turning to investigative journalism, was one who could see that official figures for 'vaccine' deaths and reactions made no sense. She said that doctors seldom reported adverse events and when people got really sick or died after getting a vaccination they would attribute that to anything except the vaccines. It had been that way for years and anyone who wondered aloud whether the 'Covid vaccines' or other shots cause harm is immediately branded as 'anti-vax' and 'anti-science'. This was 'career-threatening' for health professionals. Then there was the huge pressure to support the push to 'vaccinate' billions in the quickest time possible. Frei said:

> So that's where we're at today. More than half a million vaccine doses have been given to people in Ontario alone. The rush is on to vaccinate all 15 million of us in the province by September. And the mainstream media are screaming for this to be sped up even more. That all adds up to only a very slim likelihood that we're going to be told the truth by officials about how many people are getting sick or dying from the vaccines.

What is true of Ontario is true of everywhere.

They KNEW – and still did it

The authorities knew what was going to happen with multiple deaths and adverse reactions. The UK government's Gates-funded

and Big Pharma-dominated Medicines and Healthcare products Regulatory Agency (MHRA) hired a company to employ AI in compiling the projected reactions to the 'vaccine' that would otherwise be uncountable. The request for applications said: 'The MHRA urgently seeks an Artificial Intelligence (AI) software tool to process the expected high volume of Covid-19 vaccine Adverse Drug Reaction …' This was from the agency, headed by the disingenuous June Raine, that gave the 'vaccines' emergency approval and the company was hired before the first shot was given. 'We are going to kill and maim you – is that okay?' 'Oh, yes, perfectly fine – I'm very grateful, thank you, doctor.' The range of 'Covid vaccine' adverse reactions goes on for page after page in the MHRA criminally underreported 'Yellow Card' system and includes affects to eyes, ears, skin, digestion, blood and so on. Raine's MHRA amazingly claimed that the 'overall safety experience … is so far as expected from the clinical trials'. The death, serious adverse effects, deafness and blindness were *expected?* When did they ever mention that? If these human tragedies were expected then those that gave approval for the use of these 'vaccines' must be guilty of crimes against humanity including murder – a definition of which is 'killing a person with malice aforethought or with recklessness manifesting extreme indifference to the value of human life.' People involved at the MHRA, the CDC in America and their equivalent around the world must go before Nuremberg trials to answer for their callous inhumanity. We are only talking here about the immediate effects of the 'vaccine'. The longer-term impact of the DNA synthetic manipulation is the main reason they are so hysterically desperate to inoculate the entire global population in the shortest possible time.

Africa and the developing world are a major focus for the 'vaccine' depopulation agenda and a mass vaccination sales-pitch is underway thanks to caring people like the Rockefellers and other Cult assets. The Rockefeller Foundation, which pre-empted the 'Covid pandemic' in a document published in 2010 that 'predicted' what happened a decade later, announced an initial $34.95 million grant in February, 2021, 'to ensure more equitable access to Covid-19

testing and vaccines' among other things in Africa in collaboration with '24 organizations, businesses, and government agencies'. The pan-Africa initiative would focus on 10 countries: Burkina Faso, Ethiopia, Ghana, Kenya, Nigeria, Rwanda, South Africa, Tanzania, Uganda, and Zambia'. Rajiv Shah, President of the Rockefeller Foundation and former administrator of CIA-controlled USAID, said that if Africa was not mass-vaccinated (to change the DNA of its people) it was a 'threat to all of humanity' and not fair on Africans. When someone from the Rockefeller Foundation says they want to do something to help poor and deprived people and countries it is time for a belly-laugh. They are doing this out of the goodness of their 'heart' because 'vaccinating' the entire global population is what the 'Covid' hoax set out to achieve. Official 'decolonisation' of Africa by the Cult was merely a prelude to financial colonisation on the road to a return to physical colonisation. The 'vaccine' is vital to that and the sudden and convenient death of the 'Covid' sceptic president of Tanzania can be seen in its true light. A lot of people in Africa are aware that this is another form of colonisation and exploitation and they need to stand their ground.

The 'vaccine is working' scam

A potential problem for the Cult was that the 'vaccine' is meant to change human DNA and body messaging and not to protect anyone from a 'virus' never shown to exist. The vaccine couldn't work because it was not designed to work and how could they make it *appear* to be working so that more people would have it? This was overcome by lowering the amplification rate of the PCR test to produce fewer 'cases' and therefore fewer 'deaths'. Some of us had been pointing out since March, 2020, that the amplification rate of the test not testing for the 'virus' had been made artificially high to generate positive tests which they could call 'cases' to justify lockdowns. The World Health Organization recommended an absurdly high 45 amplification cycles to ensure the high positives required by the Cult and then remained silent on the issue until January 20th, 2021 – Biden's Inauguration Day. This was when the

'vaccinations' were seriously underway and on that day the WHO recommended after discussions with America's CDC that laboratories *lowered their testing amplification*. Dr David Samadi, a certified urologist and health writer, said the WHO was encouraging all labs to reduce their cycle count for PCR tests. He said the current cycle was much too high and was 'resulting in any particle being declared a positive case'. Even one mainstream news report I saw said this meant the number of 'Covid' infections may have been 'dramatically inflated'. Oh, just a little bit. The CDC in America issued new guidance to laboratories in April, 2021, to use 28 cycles *but only for 'vaccinated' people*. The timing of the CDC/WHO interventions were cynically designed to make it appear the 'vaccines' were responsible for falling cases and deaths when the real reason can be seen in the following examples. New York's state lab, the Wadsworth Center, identified 872 positive tests in July, 2020, based on a threshold of 40 cycles. When the figure was lowered to 35 cycles *43 percent* of the 872 were no longer 'positives'. At 30 cycles the figure was 63 percent. A Massachusetts lab found that between *85 to 90 percent* of people who tested positive in July with a cycle threshold of 40 would be negative at 30 cycles, Ashish Jha, MD, director of the Harvard Global Health Institute, said: 'I'm really shocked that it could be that high … Boy, does it really change the way we need to be thinking about testing.' I'm shocked that I could see the obvious in the spring of 2020, with no medical background, and most medical professionals still haven't worked it out. No, that's not shocking – it's terrifying.

Three weeks after the WHO directive to lower PCR cycles the London *Daily Mail* ran this headline: 'Why ARE Covid cases plummeting? New infections have fallen 45% in the US and 30% globally in the past 3 weeks but experts say vaccine is NOT the main driver because only 8% of Americans and 13% of people worldwide have received their first dose.' They acknowledged that the drop could not be attributed to the 'vaccine', but soon this morphed throughout the media into the 'vaccine' has caused cases and deaths to fall when it was the PCR threshold. In December, 2020, there was

chaos at English Channel ports with truck drivers needing negative 'Covid' tests before they could board a ferry home for Christmas. The government wanted to remove the backlog as fast as possible and they brought in troops to do the 'testing'. Out of 1,600 drivers just *36* tested positive and the rest were given the all clear to cross the Channel. I guess the authorities thought that 36 was the least they could get away with without the unquestioning catching on. The amplification trick which most people believed in the absence of information in the mainstream applied more pressure on those refusing the 'vaccine' to succumb when it 'obviously worked'. The truth was the exact opposite with deaths in care homes soaring with the 'vaccine' and in Israel the term used was 'skyrocket'. A re-analysis of published data from the Israeli Health Ministry led by Dr Hervé Seligmann at the Medicine Emerging Infectious and Tropical Diseases at Aix-Marseille University found that Pfizer's 'Covid vaccine' killed 'about 40 times more [elderly] people than the disease itself would have killed' during a five-week vaccination period and *260 times* more younger people than would have died from the 'virus' even according to the manipulated 'virus' figures. Dr Seligmann and his co-study author, Haim Yativ, declared after reviewing the Israeli 'vaccine' death data: 'This is a new Holocaust.'

Then, in mid-April, 2021, after vast numbers of people worldwide had been 'vaccinated', the story changed with clear coordination. The UK government began to prepare the ground for more future lockdowns when Nuremberg-destined Boris Johnson told yet another whopper. He said that cases had fallen because of *lockdowns* not 'vaccines'. Lockdowns are irrelevant when *there is no 'virus'* and the test and fraudulent death certificates are deciding the number of 'cases' and 'deaths'. Study after study has shown that lockdowns don't work and instead kill and psychologically destroy people. Meanwhile in the United States Anthony Fauci and Rochelle Walensky, the ultra-Zionist head of the CDC, peddled the same line. More lockdown was the answer and not the 'vaccine', a line repeated on cue by the moron that is Canadian Prime Minister Justin Trudeau. Why all the hysteria to get everyone 'vaccinated' if lockdowns and

not 'vaccines' made the difference? None of it makes sense on the face of it. Oh, but it does. The Cult wants lockdowns *and* the 'vaccine' and if the 'vaccine' is allowed to be seen as the total answer lockdowns would no longer be justified when there are still livelihoods to destroy. 'Variants' and renewed upward manipulation of PCR amplification are planned to instigate never-ending lockdown *and* more 'vaccines'.

You *must* have it – we're desperate

Israel, where the Jewish and Arab population are ruled by the Sabbatian Cult, was the front-runner in imposing the DNA-manipulating 'vaccine' on its people to such an extent that Jewish refusers began to liken what was happening to the early years of Nazi Germany. This would seem to be a fantastic claim. Why would a government of Jewish people be acting like the Nazis did? If you realise that the Sabbatian Cult was behind the Nazis and that Sabbatians hate Jews the pieces start to fit and the question of why a 'Jewish' government would treat Jews with such callous disregard for their lives and freedom finds an answer. Those controlling the government of Israel *aren't Jewish* – they're Sabbatian. Israeli lawyer Tamir Turgal was one who made the Nazi comparison in comments to German lawyer Reiner Fuellmich who is leading a class action lawsuit against the psychopaths for crimes against humanity. Turgal described how the Israeli government was vaccinating children and pregnant women on the basis that there was no evidence that this was dangerous when they had no evidence that it *wasn't* dangerous either. They just had no evidence. This was medical experimentation and Turgal said this breached the Nuremberg Code about medical experimentation and procedures requiring informed consent and choice. Think about that. A Nuremberg Code developed because of Nazi experimentation on Jews and others in concentration camps by people like the evil-beyond-belief Josef Mengele is being breached by the *Israeli* government; but when you know that it's a *Sabbatian* government along with its intelligence and military agencies like Mossad, Shin Bet and the Israeli Defense Forces, and that Sabbatians

were the force behind the Nazis, the kaleidoscope comes into focus. What have we come to when Israeli Jews are suing their government for violating the Nuremberg Code by essentially making Israelis subject to a medical experiment using the controversial 'vaccines'? It's a shocker that this has to be done in the light of what happened in Nazi Germany. The Anshe Ha-Emet, or 'People of the Truth', made up of Israeli doctors, lawyers, campaigners and public, have launched a lawsuit with the International Criminal Court. It says:

> When the heads of the Ministry of Health as well as the prime minister presented the vaccine in Israel and began the vaccination of Israeli residents, the vaccinated were not advised, that, in practice, they are taking part in a medical experiment and that their consent is required for this under the Nuremberg Code.

The irony is unbelievable, but easily explained in one word: Sabbatians. The foundation of Israeli 'Covid' apartheid is the 'green pass' or 'green passport' which allows Jews and Arabs who have had the DNA-manipulating 'vaccine' to go about their lives – to work, fly, travel in general, go to shopping malls, bars, restaurants, hotels, concerts, gyms, swimming pools, theatres and sports venues, while non-'vaccinated' are banned from all those places and activities. Israelis have likened the 'green pass' to the yellow stars that Jews in Nazi Germany were forced to wear – the same as the yellow stickers that a branch of UK supermarket chain Morrisons told exempt mask-wears they had to display when shopping. How very sensitive. The Israeli system is blatant South African-style apartheid on the basis of compliance or non-compliance to fascism rather than colour of the skin. How appropriate that the Sabbatian Israeli government was so close to the pre-Mandela apartheid regime in Pretoria. The Sabbatian-instigated 'vaccine passport' in Israel is planned for everywhere. Sabbatians struck a deal with Pfizer that allowed them to lead the way in the percentage of a national population infused with synthetic material and the result was catastrophic. Israeli freedom activist Shai Dannon told me how chairs were appearing on beaches that said 'vaccinated only'. Health Minister Yuli Edelstein said that anyone unwilling or unable to get

the jabs that 'confer immunity' will be 'left behind'. The man's a liar. Not even the makers claim the 'vaccines' confer immunity. When you see those figures of 'vaccine' deaths these psychopaths were saying that you must take the chance the 'vaccine' will kill you or maim you while knowing it will change your DNA or lockdown for you will be permanent. That's fascism. The Israeli parliament passed a law to allow personal information of the non-vaccinated to be shared with local and national authorities for three months. This was claimed by its supporters to be a way to 'encourage' people to be vaccinated. Hadas Ziv from Physicians for Human Rights described this as a 'draconian law which crushed medical ethics and the patient rights'. But that's the idea, the Sabbatians would reply.

Your papers, please

Sabbatian Israel was leading what has been planned all along to be a global 'vaccine pass' called a 'green passport' without which you would remain in permanent lockdown restriction and unable to do anything. This is how badly – *desperately* – the Cult is to get everyone 'vaccinated'. The term and colour 'green' was not by chance and related to the psychology of fusing the perception of the green climate hoax with the 'Covid' hoax and how the 'solution' to both is the same Great Reset. Lying politicians, health officials and psychologists denied there were any plans for mandatory vaccinations or restrictions based on vaccinations, but they knew that was exactly what was meant to happen with governments of all countries reaching agreements to enforce a global system. 'Free' Denmark and 'free' Sweden unveiled digital vaccine certification. Cyprus, Czech Republic, Estonia, Greece, Hungary, Iceland, Italy, Poland, Portugal, Slovakia, and Spain have all committed to a vaccine passport system and the rest including the whole of the EU would follow. The satanic UK government will certainly go this way despite mendacious denials and at the time of writing it is trying to manipulate the public into having the 'vaccine' so they could go abroad on a summer holiday. How would that work without something to prove you had the synthetic toxicity injected into you?

Documents show that the EU's European Commission was moving towards 'vaccine certificates' in 2018 and 2019 before the 'Covid' hoax began. They knew what was coming. Abracadabra – Ursula von der Leyen, the German President of the Commission, announced in March, 2021, an EU 'Digital Green Certificate' – green again – to track the public's 'Covid status'. The passport sting is worldwide and the Far East followed the same pattern with South Korea ruling that only those with 'vaccination' passports – again the *green* pass – would be able to 'return to their daily lives'.

Bill Gates has been preparing for this 'passport' with other Cult operatives for years and beyond the paper version is a Gates-funded 'digital tattoo' to identify who has been vaccinated and who hasn't. The 'tattoo' is reported to include a substance which is externally readable to confirm who has been vaccinated. This is a bio-luminous light-generating enzyme (think fireflies) called … *Luciferase*. Yes, named after the Cult 'god' Lucifer the 'light bringer' of whom more to come. Gates said he funded the readable tattoo to ensure children in the developing world were vaccinated and no one was missed out. He cares so much about poor kids as we know. This was just the cover story to develop a vaccine tagging system for everyone on the planet. Gates has been funding the ID2020 'alliance' to do just that in league with other lovely people at Microsoft, GAVI, the Rockefeller Foundation, Accenture and IDEO.org. He said in interviews in March, 2020, before any 'vaccine' publicly existed, that the world must have a globalised digital certificate to track the 'virus' and who had been vaccinated. Gates knew from the start that the mRNA vaccines were coming and when they would come and that the plan was to tag the 'vaccinated' to marginalise the intelligent and stop them doing anything including travel. Evil just doesn't suffice. Gates was exposed for offering a $10 million bribe to the Nigerian House of Representatives to invoke compulsory 'Covid' vaccination of all Nigerians. Sara Cunial, a member of the Italian Parliament, called Gates a 'vaccine criminal'. She urged the Italian President to hand him over to the International Criminal Court for crimes against

humanity and condemned his plans to 'chip the human race' through ID2020.

You know it's a long-planned agenda when war criminal and Cult gofer Tony Blair is on the case. With the scale of arrogance only someone as dark as Blair can muster he said: 'Vaccination in the end is going to be your route to liberty.' Blair is a disgusting piece of work and he confirms that again. The media has given a lot of coverage to a bloke called Charlie Mullins, founder of London's biggest independent plumbing company, Pimlico Plumbers, who has said he won't employ anyone who has not been vaccinated or have them go to any home where people are not vaccinated. He said that if he had his way no one would be allowed to walk the streets if they have not been vaccinated. Gates was cheering at the time while I was alerting the white coats. The plan is that people will qualify for 'passports' for having the first two doses and then to keep it they will have to have all the follow ups and new ones for invented 'variants' until human genetics is transformed and many are dead who can't adjust to the changes. Hollywood celebrities – the usual propaganda stunt – are promoting something called the WELL Health-Safety Rating to verify that a building or space has 'taken the necessary steps to prioritize the health and safety of their staff, visitors and other stakeholders'. They included Lady Gaga, Jennifer Lopez, Michael B. Jordan, Robert DeNiro, Venus Williams, Wolfgang Puck, Deepak Chopra and 17th Surgeon General Richard Carmona. Yawn. WELL Health-Safety has big connections with China. Parent company Delos is headed by former Goldman Sachs partner Paul Scialla. This is another example – and we will see so many others – of using the excuse of 'health' to dictate the lives and activities of the population. I guess one confirmation of the 'safety' of buildings is that only 'vaccinated' people can go in, right?

Electronic concentration camps

I wrote decades ago about the plans to restrict travel and here we are for those who refuse to bow to tyranny. This can be achieved in one go with air travel if the aviation industry makes a blanket decree.

The ‘vaccine’ and guaranteed income are designed to be part of a global version of China’s social credit system which tracks behaviour 24/7 and awards or deletes ‘credits’ based on whether your behaviour is supported by the state or not. I mean your entire lifestyle – what you do, eat, say, everything. Once your credit score falls below a certain level consequences kick in. In China tens of millions have been denied travel by air and train because of this. All the locations and activities denied to refusers by the ‘vaccine’ passports will be included in one big mass ban on doing almost anything for those that don’t bow their head to government. It’s beyond fascist and a new term is required to describe its extremes – I guess fascist technocracy will have to do. The way the Chinese system of technological – technocratic – control is sweeping the West can be seen in the Los Angeles school system and is planned to be expanded worldwide. Every child is required to have a ‘Covid’-tracking app scanned daily before they can enter the classroom. The so-called Daily Pass tracking system is produced by Gates’ Microsoft which I’m sure will shock you rigid. The pass will be scanned using a barcode (one step from an inside-the-body barcode) and the information will include health checks, ‘Covid’ tests and vaccinations. Entry codes are for one specific building only and access will only be allowed if a student or teacher has a negative test with a test not testing for the ‘virus’, has no symptoms of anything alleged to be related to ‘Covid’ (symptoms from a range of other illness), and has a temperature under 100 degrees. No barcode, no entry, is planned to be the case for everywhere and not only schools.

Kids are being psychologically prepared to accept this as ‘normal’ their whole life which is why what they can impose in schools is so important to the Cult and its gofers. Long-time American freedom campaigner John Whitehead of the Rutherford Institute was not exaggerating when he said: ‘Databit by databit, we are building our own electronic concentration camps.’ Canada under its Cult gofer prime minister Justin Trudeau has taken a major step towards the real thing with people interned against their will if they test positive with a test not testing for the ‘virus’ when they arrive at a Canadian

airport. They are jailed in internment hotels often without food or water for long periods and with many doors failing to lock there have been sexual assaults. The interned are being charged sometimes $2,000 for the privilege of being abused in this way. Trudeau is fully on board with the Cult and says the 'Covid pandemic' has provided an opportunity for a global 'reset' to permanently change Western civilisation. His number two, Deputy Prime Minister Chrystia Freeland, is a trustee of the World Economic Forum and a Rhodes Scholar. The Trudeau family have long been servants of the Cult. See *The Biggest Secret* and Cathy O'Brien's book *Trance-Formation of America* for the horrific background to Trudeau's father Pierre Trudeau another Canadian prime minister. Hide your fascism behind the façade of a heart-on-the-sleeve liberal. It's a well-honed Cult technique.

What can the 'vaccine' *really* do?

We have a 'virus' never shown to exist and 'variants' of the 'virus' that have also never been shown to exist except, like the 'original', as computer-generated fictions. Even if you believe there's a 'virus' the 'case' to 'death' rate is in the region of 0.23 to 0.15 percent and those 'deaths' are concentrated among the very old around the same average age that people die anyway. In response to this lack of threat (in truth none) psychopaths and idiots, knowingly and unknowingly answering to Gates and the Cult, are seeking to 'vaccinate' every man, woman and child on Planet Earth. Clearly the 'vaccine' is not about 'Covid' – none of this ever has been. So what is it all about *really*? Why the desperation to infuse genetically-manipulating synthetic material into everyone through mRNA fraudulent 'vaccines' with the intent of doing this over and over with the excuses of 'variants' and other 'virus' inventions? Dr Sherri Tenpenny, an osteopathic medical doctor in the United States, has made herself an expert on vaccines and their effects as a vehement campaigner against their use. Tenpenny was board certified in emergency medicine, the director of a level two trauma centre for 12 years, and moved to Cleveland in 1996 to start an integrative

medicine practice which has treated patients from all 50 states and some 17 other countries. Weaning people off pharmaceutical drugs is a speciality.

She became interested in the consequences of vaccines after attending a meeting at the National Vaccine Information Center in Washington DC in 2000 where she 'sat through four days of listening to medical doctors and scientists and lawyers and parents of vaccine injured kids' and asked: 'What's going on?' She had never been vaccinated and never got ill while her father was given a list of vaccines to be in the military and was 'sick his entire life'. The experience added to her questions and she began to examine vaccine documents from the Centers for Disease Control (CDC). After reading the first one, the 1998 version of *The General Recommendations of Vaccination*, she thought: 'This is it?' The document was poorly written and bad science and Tenpenny began 20 years of research into vaccines that continues to this day. She began her research into 'Covid vaccines' in March, 2020, and she describes them as 'deadly'. For many, as we have seen, they already have been. Tenpenny said that in the first 30 days of the 'vaccine' rollout in the United States there had been more than 40,000 adverse events reported to the vaccine adverse event database. A document had been delivered to her the day before that was 172 pages long. 'We have over 40,000 adverse events; we have over 3,100 cases of [potentially deadly] anaphylactic shock; we have over 5,000 neurological reactions.' Effects ranged from headaches to numbness, dizziness and vertigo, to losing feeling in hands or feet and paraesthesia which is when limbs 'fall asleep' and people have the sensation of insects crawling underneath their skin. All this happened in the first 30 days and remember that only about *ten percent* (or far less) of adverse reactions and vaccine-related deaths are estimated to be officially reported. Tenpenny said:

> So can you think of one single product in any industry, any industry, for as long as products have been made on the planet that within 30 days we have 40,000 people complaining of side effects that not only is still on the market but … we've got paid actors telling us how great

they are for getting their vaccine. We're offering people $500 if they will just get their vaccine and we've got nurses and doctors going; 'I got the vaccine, I got the vaccine'.

Tenpenny said they were not going to be 'happy dancing folks' when they began to suffer Bell's palsy (facial paralysis), neuropathies, cardiac arrhythmias and autoimmune reactions that kill through a blood disorder. 'They're not going to be so happy, happy then, but we're never going to see pictures of those people' she said. Tenpenny described the 'vaccine' as 'a well-designed killing tool'.

No off-switch

Bad as the initial consequences had been Tenpenny said it would be maybe 14 months before we began to see the 'full ravage' of what is going to happen to the 'Covid vaccinated' with full-out consequences taking anything between two years and 20 years to show. You can understand why when you consider that variations of the 'Covid vaccine' use mRNA (messenger RNA) to in theory activate the immune system to produce protective antibodies without using the actual 'virus'. How can they when it's a computer program and they've never isolated what they claim is the 'real thing'? Instead they use *synthetic* mRNA. They are inoculating synthetic material into the body which through a technique known as the Trojan horse is absorbed into cells to change the nature of DNA. Human DNA is changed by an infusion of messenger RNA and with each new 'vaccine' of this type it is changed even more. Say so and you are banned by Cult Internet platforms. The contempt the contemptuous Mark Zuckerberg has for the truth and human health can be seen in an internal Facebook video leaked to the Project Veritas investigative team in which he said of the 'Covid vaccines': '… I share some caution on this because we just don't know the long term side-effects of basically modifying people's DNA and RNA.' At the same time this disgusting man's Facebook was censoring and banning anyone saying exactly the same. He must go before a Nuremberg trial for crimes against humanity when he *knows* that he

is censoring legitimate concerns and denying the right of informed consent on behalf of the Cult that owns him. People have been killed and damaged by the very 'vaccination' technique he cast doubt on himself when they may not have had the 'vaccine' with access to information that he denied them. The plan is to have at least annual 'Covid vaccinations', add others to deal with invented 'variants', and change all other vaccines into the mRNA system. Pfizer executives told shareholders at a virtual Barclays Global Healthcare Conference in March, 2021, that the public may need a third dose of 'Covid vaccine', plus regular yearly boosters and the company planned to hike prices to milk the profits in a 'significant opportunity for our vaccine'. These are the professional liars, cheats and opportunists who are telling you their 'vaccine' is safe. Given this volume of mRNA planned to be infused into the human body and its ability to then replicate we will have a transformation of human genetics from biological to synthetic biological – exactly the long-time Cult plan for reasons we'll see – and many will die. Sherri Tenpenny said of this replication:

> It's like having an on-button but no off-button and that whole mechanism … they actually give it a name and they call it the Trojan horse mechanism, because it allows that [synthetic] virus and that piece of that [synthetic] virus to get inside of your cells, start to replicate and even get inserted into other parts of your DNA as a Trojan-horse.

Ask the overwhelming majority of people who have the 'vaccine' what they know about the contents and what they do and they would reply: 'The government says it will stop me getting the virus.' Governments give that false impression on purpose to increase take-up. You can read Sherri Tenpenny's detailed analysis of the health consequences in her blog at Vaxxter.com, but in summary these are some of them. She highlights the statement by Bill Gates about how human beings can become their own 'vaccine manufacturing machine'. The man is insane. ['Vaccine'-generated] 'antibodies' carry synthetic messenger RNA into the cells and the damage starts, Tenpenny contends, and she says that lungs can be adversely affected through varying degrees of pus and bleeding which

obviously affects breathing and would be dubbed 'Covid-19'. Even more sinister was the impact of 'antibodies' on macrophages, a white blood cell of the immune system. They consist of Type 1 and Type 2 which have very different functions. She said Type 1 are 'hyper-vigilant' white blood cells which 'gobble up' bacteria etc. However, in doing so, this could cause inflammation and in extreme circumstances be fatal. She says these affects are mitigated by Type 2 macrophages which kick in to calm down the system and stop it going rogue. They clear up dead tissue debris and reduce inflammation that the Type 1 'fire crews' have caused. Type 1 kills the infection and Type 2 heals the damage, she says. This is her punchline with regard to 'Covid vaccinations': She says that mRNA 'antibodies' block Type 2 macrophages by attaching to them and deactivating them. This meant that when the Type 1 response was triggered by infection there was nothing to stop that getting out of hand by calming everything down. There's an on-switch, but no off-switch, she says. What follows can be 'over and out, see you when I see you'.

Genetic suicide

Tenpenny also highlights the potential for autoimmune disease – the body attacking itself – which has been associated with vaccines since they first appeared. Infusing a synthetic foreign substance into cells could cause the immune system to react in a panic believing that the body is being overwhelmed by an invader (it is) and the consequences can again be fatal. There is an autoimmune response known as a 'cytokine storm' which I have likened to a homeowner panicked by an intruder and picking up a gun to shoot randomly in all directions before turning the fire on himself. The immune system unleashes a storm of inflammatory response called cytokines to a threat and the body commits hara-kiri. The lesson is that you mess with the body's immune response at your peril and these 'vaccines' seriously – fundamentally – mess with immune response. Tenpenny refers to a consequence called anaphylactic shock which is a severe and highly dangerous allergic reaction when the immune system

floods the body with chemicals. She gives the example of having a bee sting which primes the immune system and makes it sensitive to those chemicals. When people are stung again maybe years later the immune response can be so powerful that it leads to anaphylactic shock. Tenpenny relates this 'shock' with regard to the 'Covid vaccine' to something called polyethylene glycol or PEG. Enormous numbers of people have become sensitive to this over decades of use in a whole range of products and processes including food, drink, skin creams and 'medicine'. Studies have claimed that some 72 percent of people have antibodies triggered by PEG compared with two percent in the 1960s and allergic hypersensitive reactions to this become a gathering cause for concern. Tenpenny points out that the 'mRNA vaccine' is coated in a 'bubble' of polyethylene glycol which has the potential to cause anaphylactic shock through immune sensitivity. Many reports have appeared of people reacting this way after having the 'Covid vaccine'. What do we think is going to happen as humanity has more and more of these 'vaccines'? Tenpenny said: 'All these pictures we have seen with people with these rashes … these weepy rashes, big reactions on their arms and things like that – it's an acute allergic reaction most likely to the polyethylene glycol that you've been previously primed and sensitised to.'

Those who have not studied the conspiracy and its perpetrators at length might think that making the population sensitive to PEG and then putting it in these 'vaccines' is just a coincidence. It is not. It is instead testament to how carefully and coldly-planned current events have been and the scale of the conspiracy we are dealing with. Tenpenny further explains that the 'vaccine' mRNA procedure can breach the blood-brain barrier which protects the brain from toxins and other crap that will cause malfunction. In this case they could make two proteins corrupt brain function to cause Amyotrophic lateral sclerosis (ALS) , a progressive nervous system disease leading to loss of muscle control, and frontal lobe degeneration – Alzheimer's and dementia. Immunologist J. Bart Classon published a paper connecting mRNA 'vaccines' to prion

disease which can lead to Alzheimer's and other forms of neurogenerative disease while others have pointed out the potential to affect the placenta in ways that make women infertile. This will become highly significant in the next chapter when I will discuss other aspects of this non-vaccine that relate to its nanotechnology and transmission from the injected to the uninjected.

Qualified in idiocy

Tenpenny describes how research has confirmed that these 'vaccine'-generated antibodies can interact with a range of other tissues in the body and attack many other organs including the lungs. 'This means that if you have a hundred people standing in front of you that all got this shot they could have a hundred different symptoms.' Anyone really think that Cult gofers like the Queen, Tony Blair, Christopher Whitty, Anthony Fauci, and all the other psychopaths have really had this 'vaccine' in the pictures we've seen? Not a bloody chance. Why don't doctors all tell us about all these dangers and consequences of the 'Covid vaccine'? Why instead do they encourage and pressure patients to have the shot? Don't let's think for a moment that doctors and medical staff can't be stupid, lazy, and psychopathic and that's without the financial incentives to give the jab. Tenpenny again:

> Some people are going to die from the vaccine directly but a large number of people are going to start to get horribly sick and get all kinds of autoimmune diseases 42 days to maybe a year out. What are they going to do, these stupid doctors who say; 'Good for you for getting that vaccine.' What are they going to say; 'Oh, it must be a mutant, we need to give an extra dose of that vaccine.'
>
> Because now the vaccine, instead of one dose or two doses we need three or four because the stupid physicians aren't taking the time to learn anything about it. If I can learn this sitting in my living room reading a 19 page paper and several others so can they. There's nothing special about me, I just take the time to do it.

Remember how Sara Kayat, the NHS and TV doctor, said that the 'Covid vaccine' would '100 percent prevent hospitalisation and death'. Doctors can be idiots like every other profession and they

should not be worshipped as infallible. They are not and far from it. Behind many medical and scientific 'experts' lies an uninformed prat trying to hide themselves from you although in the 'Covid' era many have failed to do so as with UK narrative-repeating 'TV doctor' Hilary Jones. Pushing back against the minority of proper doctors and scientists speaking out against the 'vaccine' has been the entire edifice of the Cult global state in the form of governments, medical systems, corporations, mainstream media, Silicon Valley, and an army of compliant doctors, medical staff and scientists willing to say anything for money and to enhance their careers by promoting the party line. If you do that you are an 'expert' and if you won't you are an 'anti-vaxxer' and 'Covidiot'. The pressure to be 'vaccinated' is incessant. We have even had reports claiming that the 'vaccine' can help cure cancer and Alzheimer's and make the lame walk. I am waiting for the announcement that it can bring you coffee in the morning and cook your tea. Just as the symptoms of 'Covid' seem to increase by the week so have the miracles of the 'vaccine'. American supermarket giant Kroger Co. offered nearly 500,000 employees in 35 states a $100 bonus for having the 'vaccine' while donut chain Krispy Kreme promised 'vaccinated' customers a free glazed donut every day for the rest of 2021. Have your DNA changed and you will get a doughnut although we might not have to give you them for long. Such offers and incentives confirm the desperation.

Perhaps the worse vaccine-stunt of them all was UK 'Health' Secretary Matt-the-prat Hancock on live TV after watching a clip of someone being 'vaccinated' when the roll-out began. Hancock faked tears so badly it was embarrassing. Brain-of-Britain Piers Morgan, the lockdown-supporting, 'vaccine' supporting, 'vaccine' passport-supporting, TV host played along with Hancock – 'You're quite emotional about that' he said in response to acting so atrocious it would have been called out at a school nativity which will presumably today include Mary and Jesus in masks, wise men keeping their camels six feet apart, and shepherds under tent arrest. System-serving Morgan tweeted this: 'Love the idea of covid vaccine passports for everywhere: flights, restaurants, clubs, football, gyms,

shops etc. It's time covid-denying, anti-vaxxer loonies had their bullsh*t bluff called & bar themselves from going anywhere that responsible citizens go.' If only I could aspire to his genius. To think that Morgan, who specialises in shouting over anyone he disagrees with, was lauded as a free speech hero when he lost his job after storming off the set of his live show like a child throwing his dolly out of the pram. If he is a free speech hero we are in real trouble. I have no idea what 'bullsh*t' means, by the way, the * throws me completely.

The Cult is desperate to infuse its synthetic DNA-changing concoction into everyone and has been using every lie, trick and intimidation to do so. The question of '*Why*?' we shall now address.

CHAPTER TEN

Human 2.0

I believe that at the end of the century the use of words and general educated opinion will have altered so much that one will be able to speak of machines thinking without expecting to be contradicted –
Alan Turing (1912-1954), the 'Father of artificial intelligence'

I have been exposing for decades the plan to transform the human body from a biological to a synthetic-biological state. The new human that I will call Human 2.0 is planned to be connected to artificial intelligence and a global AI 'Smart Grid' that would operate as one global system in which AI would control everything from your fridge to your heating system to your car to your mind. Humans would no longer be 'human', but post-human and sub-human, with their thinking and emotional processes replaced by AI.

What I said sounded crazy and beyond science fiction and I could understand that. To any balanced, rational, mind it *is* crazy. Today, however, that world is becoming reality and it puts the 'Covid vaccine' into its true context. Ray Kurzweil is the ultra-Zionist 'computer scientist, inventor and futurist' and co-founder of the Singularity University. Singularity refers to the merging of humans with machines or 'transhumanism'. Kurzweil has said humanity would be connected to the cyber 'cloud' in the period of the ever-recurring year of 2030:

Our thinking … will be a hybrid of biological and non-biological thinking … humans will be able to extend their limitations and 'think in the cloud' … We're going to put gateways to the

cloud in our brains ... We're going to gradually merge and enhance ourselves ... In my view, that's the nature of being human – we transcend our limitations. As the technology becomes vastly superior to what we are then the small proportion that is still human gets smaller and smaller and smaller until it's just utterly negligible.

They are trying to sell this end-of-humanity-as-we-know-it as the next stage of 'evolution' when we become super-human and 'like the gods'. They are lying to you. Shocked, eh? The population, and again especially the young, have been manipulated into addiction to technologies designed to enslave them for life. First they induced an addiction to smartphones (holdables); next they moved to technology on the body (wearables); and then began the invasion of the body (implantables). I warned way back about the plan for microchipped people and we are now entering that era. We should not be diverted into thinking that this refers only to chips we can see. Most important are the nanochips known as smart dust, neural dust and nanobots which are far too small to be seen by the human eye. Nanotechnology is everywhere, increasingly in food products, and released into the atmosphere by the geoengineering of the skies funded by Bill Gates to 'shut out the Sun' and 'save the planet from global warming'. Gates has been funding a project to spray millions of tonnes of chalk (calcium carbonate) into the stratosphere over Sweden to 'dim the Sun' and cool the Earth. Scientists warned the move could be disastrous for weather systems in ways no one can predict and opposition led to the Swedish space agency announcing that the 'experiment' would not be happening as planned in the summer of 2021; but it shows where the Cult is going with dimming the impact of the Sun and there's an associated plan to change the planet's atmosphere. Who gives psychopath Gates the right to dictate to the entire human race and dismantle planetary systems? The world will not be safe while this man is at large.

The global warming hoax has made the Sun, like the gas of life, something to fear when both are essential to good health and human survival (more inversion). The body transforms sunlight into vital vitamin D through a process involving … *cholesterol*. This is the cholesterol we are also told to fear. We are urged to take Big Pharma

statin drugs to reduce cholesterol and it's all systematic. Reducing cholesterol means reducing vitamin D uptake with all the multiple health problems that will cause. At least if you take statins long term it saves the government from having to pay you a pension. The delivery system to block sunlight is widely referred to as chemtrails although these have a much deeper agenda, too. They appear at first to be contrails or condensation trails streaming from aircraft into cold air at high altitudes. Contrails disperse very quickly while chemtrails do not and spread out across the sky before eventually their content falls to earth. Many times I have watched aircraft cross-cross a clear blue sky releasing chemtrails until it looks like a cloudy day. Chemtrails contain many things harmful to humans and the natural world including toxic heavy metals, aluminium (see Alzheimer's) and nanotechnology. Ray Kurzweil reveals the reason without actually saying so: 'Nanobots will infuse all the matter around us with information. Rocks, trees, everything will become these intelligent creatures.' How do you deliver that? *From the sky*. Self-replicating nanobots would connect everything to the Smart Grid. The phenomenon of Morgellons disease began in the chemtrail era and the correlation has led to it being dubbed the 'chemtrail disease'. Self-replicating fibres appear in the body that can be pulled out through the skin. Morgellons fibres continue to grow outside the body and have a form of artificial intelligence. I cover this at greater length in *Phantom Self*.

'Vaccine' operating system

'Covid vaccines' with their self-replicating synthetic material are also designed to make the connection between humanity and Kurzweil's 'cloud'. American doctor and dedicated campaigner for truth, Carrie Madej, an Internal Medicine Specialist in Georgia with more than 20 years medical experience, has highlighted the nanotechnology aspect of the fake 'vaccines'. She explains how one of the components in at least the Moderna and Pfizer synthetic potions are 'lipid nanoparticles' which are 'like little tiny computer bits' – a 'sci-fi substance' known as nanobots and hydrogel which can be 'triggered

at any moment to deliver its payload' and act as 'biosensors'. The synthetic substance had 'the ability to accumulate data from your body like your breathing, your respiration, thoughts and emotions, all kind of things' and each syringe could carry a *million* nanobots:

This substance because it's like little bits of computers in your body, crazy, but it's true, it can do that, [and] obviously has the ability to act through Wi-Fi. It can receive and transmit energy, messages, frequencies or impulses. That issue has never been addressed by these companies. What does that do to the human?

Just imagine getting this substance in you and it can react to things all around you, the 5G, your smart device, your phones, what is happening with that? What if something is triggering it, too, like an impulse, a frequency? We have something completely foreign in the human body.

Madej said her research revealed that electromagnetic (EMF) frequencies emitted by phones and other devices had increased dramatically in the same period of the 'vaccine' rollout and she was seeing more people with radiation problems as 5G and other electromagnetic technology was expanded and introduced to schools and hospitals. She said she was 'floored with the EMF coming off' the devices she checked. All this makes total sense and syncs with my own work of decades when you think that Moderna refers in documents to its mRNA 'vaccine' as an 'operating system':

Recognizing the broad potential of mRNA science, we set out to create an mRNA technology platform that functions very much like an operating system on a computer. It is designed so that it can plug and play interchangeably with different programs. In our case, the 'program' or 'app' is our mRNA drug – the unique mRNA sequence that codes for a protein …

… Our MRNA Medicines – 'The 'Software Of Life': When we have a concept for a new mRNA medicine and begin research, fundamental components are already in place. Generally, the only thing that changes from one potential mRNA medicine to another is the coding region – the actual genetic code that instructs ribosomes to make protein. Utilizing these instruction sets gives our investigational mRNA medicines a software-like quality. We also have the ability to combine different mRNA sequences encoding for different proteins in a single mRNA investigational medicine.

Who needs a real 'virus' when you can create a computer version to justify infusing your operating system into the entire human race on the road to making living, breathing people into cyborgs? What is missed with the 'vaccines' is the *digital* connection between synthetic material and the body that I highlighted earlier with the study that hacked a computer with human DNA. On one level the body is digital, based on mathematical codes, and I'll have more about that in the next chapter. Those who ridiculously claim that mRNA 'vaccines' are not designed to change human genetics should explain the words of Dr Tal Zaks, chief medical officer at Moderna, in a 2017 TED talk. He said that over the last 30 years 'we've been living this phenomenal digital scientific revolution, and I'm here today to tell you, that we are actually *hacking the software of life*, and that it's changing the way we think about prevention and treatment of disease':

In every cell there's this thing called messenger RNA, or mRNA for short, that transmits the critical information from the DNA in our genes to the protein, which is really the stuff we're all made out of. This is the critical information that determines what the cell will do. So we think about it as an operating system. So if you could change that, if you could introduce a line of code, or change a line of code, it turns out, that has profound implications for everything, from the flu to cancer.

Zaks should more accurately have said that this has profound implications for the human genetic code and the nature of DNA. Communications within the body go both ways and not only one. But, hey, no, the 'Covid vaccine' will not affect your genetics. Cult fact-checkers say so even though the man who helped to develop the mRNA technique says that it does. Zaks said in 2017:

If you think about what it is we're trying to do. We've taken information and our understanding of that information and how that information is transmitted in a cell, and we've taken our understanding of medicine and how to make drugs, and we're fusing the two. We think of it as information therapy.

I have been writing for decades that the body is an information field communicating with itself and the wider world. This is why

radiation which is information can change the information field of body and mind through phenomena like 5G and change their nature and function. 'Information therapy' means to change the body's information field and change the way it operates. DNA is a receiver-transmitter of information and can be mutated by information like mRNA synthetic messaging. Technology to do this has been ready and waiting in the underground bases and other secret projects to be rolled out when the 'Covid' hoax was played. 'Trials' of such short and irrelevant duration were only for public consumption. When they say the 'vaccine' is 'experimental' that is not true. It may appear to be 'experimental' to those who don't know what's going on, but the trials have already been done to ensure the Cult gets the result it desires. Zaks said that it took decades to sequence the human genome, completed in 2003, but now they could do it in a week. By 'they' he means scientists operating in the public domain. In the secret projects they were sequencing the genome in a week long before even 2003.

Deluge of mRNA

Highly significantly the Moderna document says the guiding premise is that if using mRNA as a medicine works for one disease then it should work for many diseases. They were leveraging the flexibility afforded by their platform and the fundamental role mRNA plays in protein synthesis to pursue mRNA medicines for a broad spectrum of diseases. Moderna is confirming what I was saying through 2020 that multiple 'vaccines' were planned for 'Covid' (and later invented 'variants') and that previous vaccines would be converted to the mRNA system to infuse the body with massive amounts of genetically-manipulating synthetic material to secure a transformation to a synthetic-biological state. The 'vaccines' are designed to kill stunning numbers as part of the long-exposed Cult depopulation agenda and transform the rest. Given this is the goal you can appreciate why there is such hysterical demand for every human to be 'vaccinated' for an alleged 'disease' that has an estimated 'infection' to 'death' ratio of 0.23-0.15 percent. As I write

children are being given the 'vaccine' in trials (their parents are a disgrace) and ever-younger people are being offered the vaccine for a 'virus' that even if you believe it exists has virtually zero chance of harming them. Horrific effects of the 'trials' on a 12-year-old girl were revealed by a family member to be serious brain and gastric problems that included a bowel obstruction and the inability to swallow liquids or solids. She was unable to eat or drink without throwing up, had extreme pain in her back, neck and abdomen, and was paralysed from the waist down which stopped her urinating unaided. When the girl was first taken to hospital doctors said it was all in her mind. She was signed up for the 'trial' by her parents for whom no words suffice. None of this 'Covid vaccine' insanity makes any sense unless you see what the 'vaccine' really is – a body-changer. Synthetic biology or 'SynBio' is a fast-emerging and expanding scientific discipline which includes everything from genetic and molecular engineering to electrical and computer engineering. Synthetic biology is defined in these ways:

- A multidisciplinary area of research that seeks to create new biological parts, devices, and systems, or to redesign systems that are already found in nature.

- The use of a mixture of physical engineering and genetic engineering to create new (and therefore synthetic) life forms.

- An emerging field of research that aims to combine the knowledge and methods of biology, engineering and related disciplines in the design of chemically-synthesized DNA to create organisms with novel or enhanced characteristics and traits (synthetic organisms including humans).

We now have synthetic blood, skin, organs and limbs being developed along with synthetic body parts produced by 3D printers. These are all elements of the synthetic human programme and this comment by Kurzweil's co-founder of the Singularity University,

Peter Diamandis, can be seen in a whole new light with the 'Covid' hoax and the sanctions against those that refuse the 'vaccine':

Anybody who is going to be resisting the progress forward [to transhumanism] is going to be resisting evolution and, fundamentally, they will die out. It's not a matter of whether it's good or bad. It's going to happen.

'Resisting evolution'? What absolute bollocks. The arrogance of these people is without limit. His 'it's going to happen' mantra is another way of saying 'resistance is futile' to break the spirit of those pushing back and we must not fall for it. Getting this genetically-transforming 'vaccine' into everyone is crucial to the Cult plan for total control and the desperation to achieve that is clear for anyone to see. Vaccine passports are a major factor in this and they, too, are a form of resistance is futile. It's NOT. The paper funded by the Rockefeller Foundation for the 2013 'health conference' in China said:

We will interact more with artificial intelligence. The use of robotics, bio-engineering to augment human functioning is already well underway and will advance. Re-engineering of humans into potentially separate and unequal forms through genetic engineering or mixed human-robots raises debates on ethics and equality.

A new demography is projected to emerge after 2030 [that year again] of technologies (robotics, genetic engineering, nanotechnology) producing robots, engineered organisms, 'nanobots' and artificial intelligence (AI) that can self-replicate. Debates will grow on the implications of an impending reality of human designed life.

What is happening today is so long planned. The world army enforcing the will of the world government is intended to be a robot army, not a human one. Today's military and its technologically 'enhanced' troops, pilotless planes and driverless vehicles are just stepping stones to that end. Human soldiers are used as Cult fodder and its time they woke up to that and worked for the freedom of the population instead of their own destruction and their family's destruction – the same with the police. Join us and let's sort this out. The phenomenon of enforce my own destruction is widespread in the 'Covid' era with Woker 'luvvies' in the acting and entertainment

industries supporting 'Covid' rules which have destroyed their profession and the same with those among the public who put signs on the doors of their businesses 'closed due to Covid – stay safe' when many will never reopen. It's a form of masochism and most certainly insanity.

Transgender = transhumanism

When something explodes out of nowhere and is suddenly everywhere it is always the Cult agenda and so it is with the tidal wave of claims and demands that have infiltrated every aspect of society under the heading of 'transgenderism'. The term 'trans' is so 'in' and this is the dictionary definition:

A prefix meaning 'across', 'through', occurring … in loanwords from Latin, used in particular for denoting movement or conveyance from place to place (transfer; transmit; transplant) or complete change (transform; transmute), or to form adjectives meaning 'crossing', 'on the other side of', or 'going beyond' the place named (transmontane; transnational; trans-Siberian).

Transgender means to go beyond gender and transhuman means to go beyond human. Both are aspects of the Cult plan to transform the human body to a synthetic state with *no gender*. Human 2.0 is not designed to procreate and would be produced technologically with no need for parents. The new human would mean the end of parents and so men, and increasingly women, are being targeted for the deletion of their rights and status. Parental rights are disappearing at an ever-quickening speed for the same reason. The new human would have no need for men or women when there is no procreation and no gender. Perhaps the transgender movement that appears to be in a permanent state of frenzy might now contemplate on how it is being used. This was never about transgender rights which are only the interim excuse for confusing gender, particularly in the young, on the road to *fusing* gender. Transgender activism is not an end; it is a *means* to an end. We see again the technique of creative destruction in which you destroy the status quo to 'build back better' in the form that you want. The gender status quo had to be

destroyed by persuading the Cult-created Woke mentality to believe that you can have 100 genders or more. A programme for 9 to 12 year olds produced by the Cult-owned BBC promoted the 100 genders narrative. The very idea may be the most monumental nonsense, but it is not what is true that counts, only what you can make people *believe* is true. Once the gender of 2 + 2 = 4 has been dismantled through indoctrination, intimidation and 2 + 2 = 5 then the new no-gender normal can take its place with Human 2.0. Aldous Huxley revealed the plan in his prophetic *Brave New World* in 1932:

> Natural reproduction has been done away with and children are created, decanted', and raised in 'hatcheries and conditioning centres'. From birth, people are genetically designed to fit into one of five castes, which are further split into 'Plus' and 'Minus' members and designed to fulfil predetermined positions within the social and economic strata of the World State.

How could Huxley know this in 1932? For the same reason George Orwell knew about the Big Brother state in 1948, Cult insiders I have quoted knew about it in 1969, and I have known about it since the early 1990s. If you are connected to the Cult or you work your balls off to uncover the plan you can predict the future. The process is simple. If there is a plan for the world and nothing intervenes to stop it then it will happen. Thus if you communicate the plan ahead of time you are perceived to have predicted the future, but you haven't. You have revealed the plan which without intervention will become the human future. The whole reason I have done what I have is to alert enough people to inspire an intervention and maybe at last that time has come with the Cult and its intentions now so obvious to anyone with a brain in working order.

The future is here

Technological wombs that Huxley described to replace parent procreation are already being developed and they are only the projects we know about in the public arena. Israeli scientists told *The Times of Israel* in March, 2021, that they have grown 250-cell embryos

into mouse foetuses with fully formed organs using artificial wombs in a development they say could pave the way for gestating humans outside the womb. Professor Jacob Hanna of the Weizmann Institute of Science said:

We took mouse embryos from the mother at day five of development, when they are just of 250 cells, and had them in the incubator from day five until day 11, by which point they had grown all their organs.

By day 11 they make their own blood and have a beating heart, a fully developed brain. Anybody would look at them and say, 'this is clearly a mouse foetus with all the characteristics of a mouse.' It's gone from being a ball of cells to being an advanced foetus.

A special liquid is used to nourish embryo cells in a laboratory dish and they float on the liquid to duplicate the first stage of embryonic development. The incubator creates all the right conditions for its development, Hanna said. The liquid gives the embryo 'all the nutrients, hormones and sugars they need' along with a custom-made electronic incubator which controls gas concentration, pressure and temperature. The cutting-edge in the underground bases and other secret locations will be light years ahead of that, however, and this was reported by the London *Guardian* in 2017:

We are approaching a biotechnological breakthrough. Ectogenesis, the invention of a complete external womb, could completely change the nature of human reproduction. In April this year, researchers at the Children's Hospital of Philadelphia announced their development of an artificial womb.

The article was headed 'Artificial wombs could soon be a reality. What will this mean for women?' What would it mean for children is an even bigger question. No mother to bond with only a machine in preparation for a life of soulless interaction and control in a world governed by machines (see the *Matrix* movies). Now observe the calculated manipulations of the 'Covid' hoax as human interaction and warmth has been curtailed by distancing, isolation and fear with people communicating via machines on a scale never seen before.

These are all dots in the same picture as are all the personal assistants, gadgets and children's toys through which kids and adults communicate with AI as if it is human. The AI 'voice' on Sat-Nav should be included. All these things are psychological preparation for the Cult endgame. Before you can make a physical connection with AI you have to make a psychological connection and that is what people are being conditioned to do with this ever gathering human-AI interaction. Movies and TV programmes depicting the transhuman, robot dystopia relate to a phenomenon known as 'pre-emptive programming' in which the world that is planned is portrayed everywhere in movies, TV and advertising. This is conditioning the conscious and subconscious mind to become familiar with the planned reality to dilute resistance when it happens for real. What would have been a shock such is the change is made less so. We have young children put on the road to transgender transition surgery with puberty blocking drugs at an age when they could never be able to make those life-changing decisions.

Rachel Levine, a professor of paediatrics and psychiatry who believes in treating children this way, became America's highest-ranked openly-transgender official when she was confirmed as US Assistant Secretary at the Department of Health and Human Services after being nominated by Joe Biden (the Cult). Activists and governments press for laws to deny parents a say in their children's transition process so the kids can be isolated and manipulated into agreeing to irreversible medical procedures. A Canadian father Robert Hoogland was denied bail by the Vancouver Supreme Court in 2021 and remained in jail for breaching a court order that he stay silent over his young teenage daughter, a minor, who was being offered life-changing hormone therapy without parental consent. At the age of 12 the girl's 'school counsellor' said she may be transgender, referred her to a doctor and told the school to treat her like a boy. This is another example of state-serving schools imposing ever more control over children's lives while parents have ever less.

Contemptible and extreme child abuse is happening all over the world as the Cult gender-fusion operation goes into warp-speed.

Why the war on men – and now women?

The question about what artificial wombs mean for women should rightly be asked. The answer can be seen in the deletion of women's rights involving sport, changing rooms, toilets and status in favour of people in male bodies claiming to identify as women. I can identify as a mountain climber, but it doesn't mean I can climb a mountain any more than a biological man can be a biological woman. To believe so is a triumph of belief over factual reality which is the very perceptual basis of everything Woke. Women's sport is being destroyed by allowing those with male bodies who say they identify as female to 'compete' with girls and women. Male body 'women' dominate 'women's' competition with their greater muscle mass, bone density, strength and speed. With that disadvantage sport for women loses all meaning. To put this in perspective nearly 300 American high school boys can run faster than the quickest woman sprinter in the world. Women are seeing their previously protected spaces invaded by male bodies simply because they claim to identify as women. That's all they need to do to access all women's spaces and activities under the Biden 'Equality Act' that destroys equality for women with the usual Orwellian Woke inversion. Male sex offenders have already committed rapes in women's prisons after claiming to identify as women to get them transferred. Does this not matter to the Woke 'equality' hypocrites? Not in the least. What matters to Cult manipulators and funders behind transgender activists is to advance gender fusion on the way to the no-gender 'human'. When you are seeking to impose transparent nonsense like this, or the 'Covid' hoax, the only way the nonsense can prevail is through censorship and intimidation of dissenters, deletion of factual information, and programming of the unquestioning, bewildered and naive. You don't have to scan the world for long to see that all these things are happening.

Many women's rights organisations have realised that rights and status which took such a long time to secure are being eroded and that it is systematic. Kara Dansky of the global Women's Human Rights Campaign said that Biden's transgender executive order immediately he took office, subsequent orders, and Equality Act legislation that followed 'seek to erase women and girls in the law as a category'. *Exactly*. I said during the long ago-started war on men (in which many women play a crucial part) that this was going to turn into a war on them. The Cult is phasing out *both* male and female genders. To get away with that they are brought into conflict so they are busy fighting each other while the Cult completes the job with no unity of response. Unity, people, *unity*. We need unity everywhere. Transgender is the only show in town as the big step towards the no-gender human. It's not about rights for transgender people and never has been. Woke political correctness is deleting words relating to genders to the same end. Wokers believe this is to be 'inclusive' when the opposite is true. They are deleting words describing gender because gender *itself* is being deleted by Human 2.0. Terms like 'man', 'woman', 'mother' and 'father' are being deleted in the universities and other institutions to be replaced by the *no*-gender, not trans-gender, 'individuals' and 'guardians'. Women's rights campaigner Maria Keffler of Partners for Ethical Care said: 'Children are being taught from kindergarten upward that some boys have a vagina, some girls have a penis, and that kids can be any gender they want to be.' Do we really believe that suddenly countries all over the world at the same time had the idea of having drag queens go into schools or read transgender stories to very young children in the local library? It's coldly-calculated confusion of gender on the way to the fusion of gender. Suzanne Vierling, a psychologist from Southern California, made another important point:

Yesterday's slave woman who endured gynecological medical experiments is today's girl-child being butchered in a booming gender-transitioning sector. Ovaries removed, pushing her into menopause and osteoporosis, uncharted territory, and parents' rights and authority decimated.

The erosion of parental rights is a common theme in line with the Cult plans to erase the very concept of parents and 'ovaries removed, pushing her into menopause' means what? Those born female lose the ability to have children – another way to discontinue humanity as we know it.

Eliminating Human 1.0 (before our very eyes)

To pave the way for Human 2.0 you must phase out Human 1.0. This is happening through plummeting sperm counts and making women infertile through an onslaught of chemicals, radiation (including smartphones in pockets of men) and mRNA 'vaccines'. Common agriculture pesticides are also having a devastating impact on human fertility. I have been tracking collapsing sperm counts in the books for a long time and in 2021 came a book by fertility scientist and reproductive epidemiologist Shanna Swan, *Count Down: How Our Modern World Is Threatening Sperm Counts, Altering Male and Female Reproductive Development and Imperiling the Future of the Human Race*. She reports how the global fertility rate dropped by *half* between 1960 and 2016 with America's birth rate 16 percent below where it needs to be to sustain the population. Women are experiencing declining egg quality, more miscarriages, and more couples suffer from infertility. Other findings were an increase in erectile dysfunction, infant boys developing more genital abnormalities, male problems with conception, and plunging levels of the male hormone testosterone which would explain why so many men have lost their backbone and masculinity. This has been very evident during the 'Covid' hoax when women have been prominent among the Pushbackers and big strapping blokes have bowed their heads, covered their faces with a nappy and quietly submitted. Mind control expert Cathy O'Brien also points to how global education introduced the concept of 'we're all winners' in sport and classrooms: 'Competition was defused, and it in turn defused a sense of fighting back.' This is another version of the 'equity' doctrine in which you drive down rather than raise up. What a contrast in Cult-controlled China with its global ambitions

where the government published plans in January, 2021, to 'cultivate masculinity' in boys from kindergarten through to high school in the face of a 'masculinity crisis'. A government adviser said boys would be soon become 'delicate, timid and effeminate' unless action was taken. Don't expect any similar policy in the targeted West. A 2006 study showed that a 65-year-old man in 2002 had testosterone levels *15 percent* lower than a 65-year-old man in 1987 while a 2020 study found a similar story with young adults and adolescents. Men are getting prescriptions for testosterone replacement therapy which causes an even greater drop in sperm count with up to 99 percent seeing sperm counts drop to zero during the treatment. More sperm is defective and malfunctioning with some having two heads or not pursuing an egg.

A class of *synthetic* chemicals known as phthalates are being blamed for the decline. These are found everywhere in plastics, shampoos, cosmetics, furniture, flame retardants, personal care products, pesticides, canned foods and even receipts. Why till receipts? Everyone touches them. Let no one delude themselves that all this is not systematic to advance the long-time agenda for human body transformation. Phthalates mimic hormones and disrupt the hormone balance causing testosterone to fall and genital birth defects in male infants. Animals and fish have been affected in the same way due to phthalates and other toxins in rivers. When fish turn gay or change sex through chemicals in rivers and streams it is a pointer to why there has been such an increase in gay people and the sexually confused. It doesn't matter to me what sexuality people choose to be, but if it's being affected by chemical pollution and consumption then we need to know. Does anyone really think that this is not connected to the transgender agenda, the war on men and the condemnation of male 'toxic masculinity'? You watch this being followed by 'toxic femininity'. It's already happening. When breastfeeding becomes 'chest-feeding', pregnant women become pregnant people along with all the other Woke claptrap you know that the world is going insane and there's a Cult scam in progress. Transgender activists are promoting the Cult agenda while Cult

billionaires support and fund the insanity as they laugh themselves to sleep at the sheer stupidity for which humans must be infamous in galaxies far, far away.

'Covid vaccines' and female infertility

We can now see why the 'vaccine' has been connected to potential infertility in women. Dr Michael Yeadon, former Vice President and Chief Scientific Advisor at Pfizer, and Dr Wolfgang Wodarg in Germany, filed a petition with the European Medicines Agency in December, 2020, urging them to stop trials for the Pfizer/BioNTech shot and all other mRNA trials until further studies had been done. They were particularly concerned about possible effects on fertility with 'vaccine'-produced antibodies attacking the protein Syncytin-1 which is responsible for developing the placenta. The result would be infertility 'of indefinite duration' in women who have the 'vaccine' with the placenta failing to form. Section 10.4.2 of the Pfizer/BioNTech trial protocol says that pregnant women or those who might become so should not have mRNA shots. Section 10.4 warns men taking mRNA shots to 'be abstinent from heterosexual intercourse' and not to donate sperm. The UK government said that it *did not know* if the mRNA procedure had an effect on fertility. *Did not know?* These people have to go to jail. UK government advice did not recommend at the start that pregnant women had the shot and said they should avoid pregnancy for at least two months after 'vaccination'. The 'advice' was later updated to pregnant women should only have the 'vaccine' if the benefits outweighed the risks to mother and foetus. What the hell is that supposed to mean? Then 'spontaneous abortions' began to appear and rapidly increase on the adverse reaction reporting schemes which include only a fraction of adverse reactions. Thousands and ever-growing numbers of 'vaccinated' women are describing changes to their menstrual cycle with heavier blood flow, irregular periods and menstruating again after going through the menopause – all links to reproduction effects. Women are passing blood clots and the lining of their uterus while men report erectile dysfunction and blood effects. Most

significantly of all *un*vaccinated women began to report similar menstrual changes after interaction with *'vaccinated'* people and men and children were also affected with bleeding noses, blood clots and other conditions. 'Shedding' is when vaccinated people can emit the content of a vaccine to affect the unvaccinated, but this is different. 'Vaccinated' people were not shedding a 'live virus' allegedly in 'vaccines' as before because the fake 'Covid vaccines' involve synthetic material and other toxicity. Doctors exposing what is happening prefer the term 'transmission' to shedding. Somehow those that have had the shots are transmitting effects to those that haven't. Dr Carrie Madej said the nano-content of the 'vaccines' can 'act like an antenna' to others around them which fits perfectly with my own conclusions. This 'vaccine' transmission phenomenon was becoming known as the book went into production and I deal with this further in the Postscript.

Vaccine effects on sterility are well known. The World Health Organization was accused in 2014 of sterilising millions of women in Kenya with the evidence confirmed by the content of the vaccines involved. The same WHO behind the 'Covid' hoax admitted its involvement for more than ten years with the vaccine programme. Other countries made similar claims. Charges were lodged by Tanzania, Nicaragua, Mexico, and the Philippines. The Gardasil vaccine claimed to protect against a genital 'virus' known as HPV has also been linked to infertility. Big Pharma and the WHO (same thing) are criminal and satanic entities. Then there's the Bill Gates Foundation which is connected through funding and shared interests with 20 pharmaceutical giants and laboratories. He stands accused of directing the policy of United Nations Children's Fund (UNICEF), vaccine alliance GAVI, and other groupings, to advance the vaccine agenda and silence opposition at great cost to women and children. At the same time Gates wants to reduce the global population. Coincidence?

Great Reset = Smart Grid = new human

The Cult agenda I have been exposing for 30 years is now being openly promoted by Cult assets like Gates and Klaus Schwab of the World Economic Forum under code-terms like the 'Great Reset', 'Build Back Better' and 'a rare but narrow window of opportunity to reflect, reimagine, and reset our world'. What provided this 'rare but narrow window of opportunity'? The 'Covid' hoax did. Who created that? *They* did. My books from not that long ago warned about the planned 'Internet of Things' (IoT) and its implications for human freedom. This was the plan to connect all technology to the Internet and artificial intelligence and today we are way down that road with an estimated 36 billion devices connected to the World Wide Web and that figure is projected to be 76 billion by 2025. I further warned that the Cult planned to go beyond that to the Internet of *Everything* when the human brain was connected via AI to the Internet and Kurzweil's 'cloud'. Now we have Cult operatives like Schwab calling for precisely that under the term 'Internet of Bodies', a fusion of the physical, digital and biological into one centrally-controlled Smart Grid system which the Cult refers to as the 'Fourth Industrial Revolution'. They talk about the 'biological', but they really mean the synthetic-biological which is required to fully integrate the human body and brain into the Smart Grid and artificial intelligence planned to replace the human mind. We have everything being synthetically manipulated including the natural world through GMO and smart dust, the food we eat and the human body itself with synthetic 'vaccines'. I said in *The Answer* that we would see the Cult push for synthetic meat to replace animals and in February, 2021, the so predictable psychopath Bill Gates called for the introduction of synthetic meat to save us all from 'climate change'. The climate hoax just keeps on giving like the 'Covid' hoax. The war on meat by vegan activists is a carbon (oops, sorry) copy of the manipulation of transgender activists. They have no idea (except their inner core) that they are being used to promote and impose the agenda of the Cult or that they are only the *vehicle* and not the *reason*. This is not to say those who choose not to eat meat shouldn't be respected and supported in that right, but there are ulterior motives

for those in power. A *Forbes* article in December, 2019, highlighted the plan so beloved of Schwab and the Cult under the heading: 'What Is The Internet of Bodies? And How Is It Changing Our World?' The article said the human body is the latest data platform (remember 'our vaccine is an operating system'). *Forbes* described the plan very accurately and the words could have come straight out of my books from long before:

The Internet of Bodies (IoB) is an extension of the IoT and basically connects the human body to a network through devices that are ingested, implanted, or connected to the body in some way. Once connected, data can be exchanged, and the body and device can be remotely monitored and controlled.

They were really describing a human hive mind with human perception centrally-dictated via an AI connection as well as allowing people to be 'remotely monitored and controlled'. Everything from a fridge to a human mind could be directed from a central point by these insane psychopaths and 'Covid vaccines' are crucial to this. Forbes explained the process I mentioned earlier of holdable and wearable technology followed by implantable. The article said there were three generations of the Internet of Bodies that include:

- Body external: These are wearable devices such as Apple Watches or Fitbits that can monitor our health.

- Body internal: These include pacemakers, cochlear implants, and digital pills that go inside our bodies to monitor or control various aspects of health.

- Body embedded: The third generation of the Internet of Bodies is embedded technology where technology and the human body are melded together and have a real-time connection to a remote machine.

Forbes noted the development of the Brain Computer Interface (BCI) which merges the brain with an external device for monitoring and controlling in real-time. 'The ultimate goal is to help restore function to individuals with disabilities by using brain signals rather than conventional neuromuscular pathways.' Oh, do fuck off. The goal of brain interface technology is controlling human thought and emotion from the central point in a hive mind serving its masters wishes. Many people are now agreeing to be chipped to open doors without a key. You can recognise them because they'll be wearing a mask, social distancing and lining up for the 'vaccine'. The Cult plans a Great Reset money system after they have completed the demolition of the global economy in which 'money' will be exchanged through communication with body operating systems. Rand Corporation, a Cult-owned think tank, said of the Internet of Bodies or IoB:

> Internet of Bodies technologies fall under the broader IoT umbrella. But as the name suggests, IoB devices introduce an even more intimate interplay between humans and gadgets. IoB devices monitor the human body, collect health metrics and other personal information, and transmit those data over the Internet. Many devices, such as fitness trackers, are already in use … IoB devices … and those in development can track, record, and store users' whereabouts, bodily functions, and what they see, hear, and even think.

Schwab's World Economic Forum, a long-winded way of saying 'fascism' or 'the Cult', has gone full-on with the Internet of Bodies in the 'Covid' era. 'We're entering the era of the Internet of Bodies', it declared, 'collecting our physical data via a range of devices that can be implanted, swallowed or worn'. The result would be a huge amount of health-related data that could improve human wellbeing around the world, and prove crucial in fighting the 'Covid-19 pandemic'. Does anyone think these clowns care about 'human wellbeing' after the death and devastation their pandemic hoax has purposely caused? Schwab and co say we should move forward with the Internet of Bodies because 'Keeping track of symptoms could help us stop the spread of infection, and quickly detect new cases'. How wonderful, but keeping track' is all they are really bothered

about. Researchers were investigating if data gathered from smartwatches and similar devices could be used as viral infection alerts by tracking the user's heart rate and breathing. Schwab said in his 2018 book *Shaping the Future of the Fourth Industrial Revolution*:

> The lines between technologies and beings are becoming blurred and not just by the ability to create lifelike robots or synthetics. Instead it is about the ability of new technologies to literally become part of us. Technologies already influence how we understand ourselves, how we think about each other, and how we determine our realities. As the technologies … give us deeper access to parts of ourselves, we may begin to integrate digital technologies into our bodies.

You can see what the game is. Twenty-four hour control and people – if you could still call them that – would never know when something would go ping and take them out of circulation. It's the most obvious rush to a global fascist dictatorship and the complete submission of humanity and yet still so many are locked away in their Cult-induced perceptual coma and can't see it.

Smart Grid control centres

The human body is being transformed by the 'vaccines' and in other ways into a synthetic cyborg that can be attached to the global Smart Grid which would be controlled from a central point and other sub-locations of Grid manipulation. Where are these planned to be? Well, China for a start which is one of the Cult's biggest centres of operation. The technological control system and technocratic rule was incubated here to be unleashed across the world after the 'Covid' hoax came out of China in 2020. Another Smart Grid location that will surprise people new to this is Israel. I have exposed in *The Trigger* how Sabbatian technocrats, intelligence and military operatives were behind the horrors of 9/11 and not '19 Arab hijackers' who somehow manifested the ability to pilot big passenger airliners when instructors at puddle-jumping flying schools described some of them as a joke. The 9/11 attacks were made possible through control of civilian and military air computer systems and those of the White House, Pentagon and connected agencies. See *The Trigger* – it

will blow your mind. The controlling and coordinating force were the Sabbatian networks in Israel and the United States which by then had infiltrated the entire US government, military and intelligence system. The real name of the American Deep State is 'Sabbatian State'. Israel is a tiny country of only nine million people, but it is one of the global centres of cyber operations and fast catching Silicon Valley in importance to the Cult. Israel is known as the 'start-up nation' for all the cyber companies spawned there with the Sabbatian specialisation of 'cyber security' that I mentioned earlier which gives those companies access to computer systems of their clients in real time through 'backdoors' written into the coding when security software is downloaded. The Sabbatian centre of cyber operations outside Silicon Valley is the Israeli military Cyber Intelligence Unit, the biggest infrastructure project in Israel's history, headquartered in the desert-city of Beersheba and involving some 20,000 'cyber soldiers'. Here are located a literal army of Internet trolls scanning social media, forums and comment lists for anyone challenging the Cult agenda. The UK military has something similar with its 77th Brigade and associated operations. The Beersheba complex includes research and development centres for other Cult operations such as Intel, Microsoft, IBM, Google, Apple, Hewlett-Packard, Cisco Systems, Facebook and Motorola. Techcrunch.com ran an article about the Beersheba global Internet technology centre headlined 'Israel's desert city of Beersheba is turning into a cybertech oasis':

> The military's massive relocation of its prestigious technology units, the presence of multinational and local companies, a close proximity to Ben Gurion University and generous government subsidies are turning Beersheba into a major global cybertech hub. Beersheba has all of the ingredients of a vibrant security technology ecosystem, including Ben Gurion University with its graduate program in cybersecurity and Cyber Security Research Center, and the presence of companies such as EMC, Deutsche Telekom, PayPal, Oracle, IBM, and Lockheed Martin. It's also the future home of the INCB (Israeli National Cyber Bureau); offers a special income tax incentive for cyber security companies, and was the site for the relocation of the army's intelligence corps units.

Sabbatians have taken over the cyber world through the following process: They scan the schools for likely cyber talent and develop them at Ben Gurion University and their period of conscription in the Israeli Defense Forces when they are stationed at the Beersheba complex. When the cyber talented officially leave the army they are funded to start cyber companies with technology developed by themselves or given to them by the state. Much of this is stolen through backdoors of computer systems around the world with America top of the list. Others are sent off to Silicon Valley to start companies or join the major ones and so we have many major positions filled by apparently 'Jewish' but really Sabbatian operatives. Google, YouTube and Facebook are all run by 'Jewish' CEOs while Twitter is all but run by ultra-Zionist hedge-fund shark Paul Singer. At the centre of the Sabbatian global cyber web is the Israeli army's Unit 8200 which specialises in hacking into computer systems of other countries, inserting viruses, gathering information, instigating malfunction, and even taking control of them from a distance. A long list of Sabbatians involved with 9/11, Silicon Valley and Israeli cyber security companies are operatives of Unit 8200. This is not about Israel. It's about the Cult. Israel is planned to be a Smart Grid hub as with China and what is happening at Beersheba is not for the benefit of Jewish people who are treated disgustingly by the Sabbatian elite that control the country. A glance at the Nuremberg Codes will tell you that.

The story is much bigger than 'Covid', important as that is to where we are being taken. Now, though, it's time to really strap in. There's more … much more …

CHAPTER ELEVEN

Who controls the Cult?

Awake, arise or be forever fall'n
John Milton, *Paradise Lost*

I have exposed this far the level of the Cult conspiracy that operates in the world of the seen and within the global secret society and satanic network which operates in the shadows one step back from the seen. The story, however, goes much deeper than that.

The 'Covid' hoax is major part of the Cult agenda, but only part, and to grasp the biggest picture we have to expand our attention beyond the realm of human sight and into the infinity of possibility that we cannot see. It is from here, ultimately, that humanity is being manipulated into a state of total control by the force which dictates the actions of the Cult. How much of reality can we see? Next to damn all is the answer. We may appear to see all there is to see in the 'space' our eyes survey and observe, but little could be further from the truth. The human 'world' is only a tiny band of frequency that the body's visual and perceptual systems can decode into *perception* of a 'world'. According to mainstream science the electromagnetic spectrum is 0.005 percent of what exists in the Universe (Fig 10). The maximum estimate I have seen is 0.5 percent and either way it's miniscule. I say it is far, far, smaller even than 0.005 percent when you compare reality we see with the totality of reality that we don't. Now get this if you are new to such information: Visible light, the only band of frequency that we can see, is a *fraction* of the 0.005

percent (Fig 11 overleaf). Take this further and realise that our universe is one of infinite universes and that universes are only a fragment of overall reality – *infinite* reality. Then compare that with the almost infinitesimal frequency band of visible light or human sight. You see that humans are as near blind as it is possible to be without actually being so. Artist and filmmaker, Sergio Toporek, said:

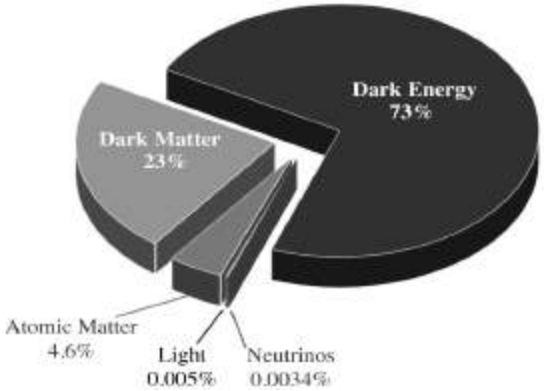


Figure 10: Humans can perceive such a tiny band of visual reality it's laughable.

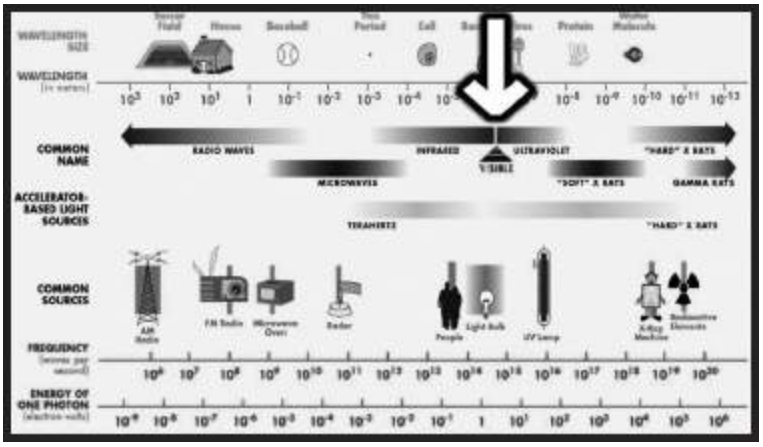


Figure 11: We can see a smear of the 0.005 percent electromagnetic spectrum, but we still know it all. Yep, makes sense.

Consider that you can see less than 1% of the electromagnetic spectrum and hear less than 1% of the acoustic spectrum. 90% of the cells in your body carry their own microbial DNA and are not 'you'. The atoms in your body are 99.9999999999999999% empty space and none of them are the ones you were born with ... Human beings have 46 chromosomes, two less than a potato.

The existence of the rainbow depends on the conical photoreceptors in your eyes; to animals without cones, the rainbow does not exist. So you don't just look at a rainbow, you create it. This is pretty amazing, especially considering that all the beautiful colours you see represent less than 1% of the electromagnetic spectrum.

Suddenly the 'world' of humans looks a very different place. Take into account, too, that Planet Earth when compared with the projected size of this single universe is the equivalent of a billionth of a pinhead. Imagine the ratio that would be when compared to infinite reality. To think that Christianity once insisted that Earth and humanity were the centre of everything. This background is vital if we are going to appreciate the nature of 'human' and how we can be manipulated by an unseen force. To human visual reality virtually *everything* is unseen and yet the prevailing perception within the institutions and so much of the public is that if we can't see it, touch it, hear it, taste it and smell it then it cannot exist. Such perception is indoctrinated and encouraged by the Cult and its agents because it isolates believers in the strictly limited, village-idiot, realm of the five senses where perceptions can be firewalled and information controlled. Most of those perpetuating the 'this-world-is-all-there-is' insanity are themselves indoctrinated into believing the same delusion. While major players and influencers know that official reality is laughable most of those in science, academia and medicine really believe the nonsense they peddle and teach succeeding generations. Those who challenge the orthodoxy are dismissed as nutters and freaks to protect the manufactured illusion from exposure. Observe the dynamic of the 'Covid' hoax and you will see how that takes the same form. The inner-circle psychopaths knows it's a gigantic scam, but almost the entirety of those imposing their fascist rules believe that 'Covid' is all that they're told it is.

Stolen identity

Ask people who they are and they will give you their name, place of birth, location, job, family background and life story. Yet that is not who they are – it is what they are *experiencing*. The difference is *absolutely crucial*. The true 'I', the eternal, infinite 'I', is consciousness,

a state of being aware. Forget 'form'. That is a vehicle for a brief experience. Consciousness does not come *from* the brain, but *through* the brain and even that is more symbolic than literal. We are awareness, pure awareness, and this is what withdraws from the body at what we call 'death' to continue our eternal beingness, *isness*, in other realms of reality within the limitlessness of infinity or the Biblical 'many mansions in my father's house'. Labels of a human life, man, woman, transgender, black, white, brown, nationality, circumstances and income are not who we are. They are what we are – awareness – is *experiencing* in a brief connection with a band of frequency we call 'human'. The labels are not the self; they are, to use the title of one of my books, a *Phantom* Self. I am not David Icke born in Leicester, England, on April 29th, 1952. I am the consciousness *having that experience*. The Cult and its non-human masters seek to convince us through the institutions of 'education', science, medicine, media and government that what we are *experiencing* is who we *are*. It's so easy to control and direct perception locked away in the bewildered illusions of the five senses with no expanded radar. Try, by contrast, doing the same with a humanity aware of its true self and its true power to consciously create its reality and experience. How is it possible to do this? We do it all day every day. If you perceive yourself as 'little me' with no power to impact upon your life and the world then your life experience will reflect that. You will hand the power you don't think you have to authority in all its forms which will use it to control your experience. This, in turn, will appear to confirm your perception of 'little me' in a self-fulfilling feedback loop. But that is what 'little me' really is – a *perception*. We are all 'big-me', infinite me, and the Cult has to make us forget that if its will is to prevail. We are therefore manipulated and pressured into self-identifying with human labels and not the consciousness/awareness *experiencing* those human labels.

The phenomenon of identity politics is a Cult-instigated manipulation technique to sub-divide previous labels into even smaller ones. A United States university employs this list of letters to

describe student identity: LGBTTQQFAGPBDSM or lesbian, gay, bisexual, transgender, transsexual, queer, questioning, flexual, asexual, gender-fuck, polyamorous, bondage/discipline, dominance/submission and sadism/masochism. I'm sure other lists are even longer by now as people feel the need to self-identity the 'I' with the minutiae of race and sexual preference. Wokers programmed by the Cult for generations believe this is about 'inclusivity' when it's really the Cult locking them away into smaller and smaller versions of Phantom Self while firewalling them from the influence of their true self, the infinite, eternal 'I'. You may notice that my philosophy which contends that we are all unique points of attention/awareness within the same infinite whole or Oneness is the ultimate non-racism. The very sense of Oneness makes the judgement of people by their body-type, colour or sexuality utterly ridiculous and confirms that racism has no understanding of reality (including anti-white racism). Yet despite my perception of life Cult agents and fast-asleep Wokers label me racist to discredit my information while they are themselves phenomenally racist and sexist. All they see is race and sexuality and they judge people as good or bad, demons or untouchables, by their race and sexuality. All they see is *Phantom Self* and perceive themselves in terms of Phantom Self. They are pawns and puppets of the Cult agenda to focus attention and self-identity in the five senses and play those identities against each other to divide and rule. Columbia University has introduced segregated graduations in another version of social distancing designed to drive people apart and teach them that different racial and cultural groups have nothing in common with each other. The last thing the Cult wants is unity. Again the pump-primers of this will be Cult operatives in the knowledge of what they are doing, but the rest are just the Phantom Self blind leading the Phantom Self blind. We *do* have something in common – we are all *the same consciousness* having different temporary experiences.

What is this 'human'?

Yes, what *is* 'human'? That is what we are supposed to be, right? I mean 'human'? True, but 'human' is the experience not the 'I'. Break it down to basics and 'human' is the way that information is processed. If we are to experience and interact with this band of frequency we call the 'world' we must have a vehicle that operates within that band of frequency. Our consciousness in its prime form cannot do that; it is way beyond the frequency of the human realm. My consciousness or awareness could not tap these keys and pick up the cup in front of me in the same way that radio station A cannot interact with radio station B when they are on different frequencies. The human body is the means through which we have that interaction. I have long described the body as a biological computer which processes information in a way that allows consciousness to experience this reality. The body is a receiver, transmitter and processor of information in a particular way that we call human. We visually perceive only the world of the five senses in a wakened state – that is the limit of the body's visual decoding system. In truth it's not even visual in the way we experience 'visual reality' as I will come to in a moment. We are 'human' because the body processes the information sources of human into a reality and behaviour system that we *perceive* as human. Why does an elephant act like an elephant and not like a human or a duck? The elephant's biological computer is a different information field and processes information according to that program into a visual and behaviour type we call an elephant. The same applies to everything in our reality. These body information fields are perpetuated through procreation (like making a copy of a software program). The Cult wants to break that cycle and intervene technologically to transform the human information field into one that will change what we call humanity. If it can change the human information field it will change the way that field processes information and change humanity both 'physically' and psychologically. Hence the *messenger* (information) RNA 'vaccines' and so much more that is targeting human genetics by changing the body's information – *messaging* – construct through food, drink, radiation, toxicity and other means.

Reality that we experience is nothing like reality as it really is in the same way that the reality people experience in virtual reality games is not the reality they are really living in. The game is only a decoded source of information that appears to be a reality. Our world is also an information construct – a *simulation* (more later). In its base form our reality is a wavefield of information much the same in theme as Wi-Fi. The five senses decode wavefield information into electrical information which they communicate to the brain to decode into holographic (illusory 'physical') information. Different parts of the brain specialise in decoding different senses and the information is fused into a reality that appears to be outside of us but is really inside the brain and the genetic structure in general (Fig 12 overleaf). DNA is a receiver-transmitter of information and a vital part of this decoding process and the body's connection to other realities. Change DNA and you change the way we decode and connect with reality – see 'Covid vaccines'. Think of computers decoding Wi-Fi. You have information encoded in a radiation field and the computer decodes that information into a very different form on the screen. You can't see the Wi-Fi until its information is made manifest on the screen and the information on the screen is inside the computer and not outside. I have just described how we decode the 'human world'. All five senses decode the waveform 'Wi-Fi' field into electrical signals and the brain (computer) constructs reality inside the brain and not outside – 'You don't just look at a rainbow, you create it'. Sound is a simple example. We don't hear sound until the brain decodes it. Waveform sound waves are picked up by the hearing sense and communicated to the brain in an electrical form to be decoded into the sounds that we hear. Everything we hear is inside the brain along with everything we see, feel, smell and taste. Words and language are waveform fields generated by our vocal chords which pass through this process until they are decoded by the brain into words that we hear. Different languages are different frequency fields or sound waves generated by vocal chords. Late British philosopher Alan Watts said:

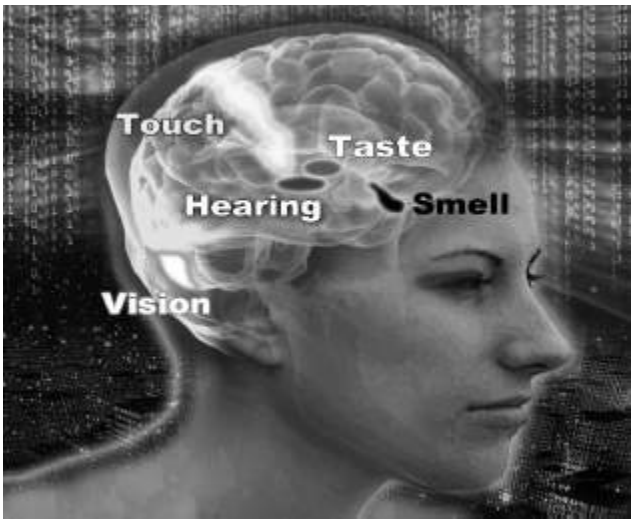


Figure 12: The brain receives information from the five senses and constructs from that our perceived reality.

[Without the brain] the world is devoid of light, heat, weight, solidity, motion, space, time or any other imaginable feature. All these phenomena are interactions, or transactions, of vibrations with a certain arrangement of neurons.

That's exactly what they are and scientist Robert Lanza describes in his book, *Biocentrism*, how we decode electromagnetic waves and energy into visual and 'physical' experience. He uses the example of a flame emitting photons, electromagnetic energy, each pulsing electrically and magnetically:

… these … invisible electromagnetic waves strike a human retina, and if (and only if) the waves happen to measure between 400 and 700 nano meters in length from crest to crest, then their energy is just right to deliver a stimulus to the 8 million cone-shaped cells in the retina.

Each in turn send an electrical pulse to a neighbour neuron, and on up the line this goes, at 250 mph, until it reaches the … occipital lobe of the brain, in the back of the head. There, a cascading complex of neurons fire from the incoming stimuli, and we subjectively perceive this experience as a yellow brightness occurring in a place we have been conditioned to call the 'external world'.

You hear what you decode

If a tree falls or a building collapses they make no noise unless someone is there to decode the energetic waves generated by the disturbance into what we call sound. Does a falling tree make a noise? Only if you hear it – *decode* it. Everything in our reality is a frequency field of information operating within the overall 'Wi-Fi' field that I call The Field. A vibrational disturbance is generated in The Field by the fields of the falling tree or building. These disturbance waves are what we decode into the sound of them falling. If no one is there to do that then neither will make any noise. Reality is created by the observer – *decoder* – and the *perceptions* of the observer affect the decoding process. For this reason different people – different *perceptions* – will perceive the same reality or situation in a different way. What one may perceive as a nightmare another will see as an opportunity. The question of why the Cult is so focused on controlling human perception now answers itself. All experienced reality is the act of decoding and we don't experience Wi-Fi until it is decoded on the computer screen. The sight and sound of an Internet video is encoded in the Wi-Fi all around us, but we don't see or hear it until the computer decodes that information. Taste, smell and touch are all phenomena of the brain as a result of the same process. We don't taste, smell or feel anything except in the brain and there are pain relief techniques that seek to block the signal from the site of discomfort to the brain because if the brain doesn't decode that signal we don't feel pain. Pain is in the brain and only appears to be at the point of impact thanks to the feedback loop between them. We don't see anything until electrical information from the sight senses is decoded in an area at the back of the brain. If that area is damaged we can go blind when our eyes are perfectly okay. So why do we go blind if we damage an eye? We damage the information processing between the waveform visual information and the visual decoding area of the brain. If information doesn't reach the brain in a form it can decode then we can't see the visual reality that it represents. What's more the brain is decoding only a fraction of the information it receives and the rest is absorbed by the

sub-conscious mind. This explanation is from the science magazine, *Wonderpedia*:

> Every second, 11 million sensations crackle along these [brain] pathways ... The brain is confronted with an alarming array of images, sounds and smells which it rigorously filters down until it is left with a manageable list of around 40. Thus 40 sensations per second make up what we perceive as reality.

The 'world' is not what people are told to believe that is it and the inner circles of the Cult *know that*.

Illusory 'physical' reality

We can only see a smear of 0.005 percent of the Universe which is only one of a vast array of universes – 'mansions' – within infinite reality. Even then the brain decodes only 40 pieces of information ('sensations') from a potential *11 million* that we receive every second. Two points strike you from this immediately: The sheer breathtaking stupidity of believing we know anything so rigidly that there's nothing more to know; and the potential for these processes to be manipulated by a malevolent force to control the reality of the population. One thing I can say for sure with no risk of contradiction is that when you can perceive an almost indescribable fraction of infinite reality there is always more to know as in tidal waves of it. Ancient Greek philosopher Socrates was so right when he said that wisdom is to know how little we know. How obviously true that is when you think that we are experiencing a physical world of solidity that is neither physical nor solid and a world of apartness when everything is connected. Cult-controlled 'science' dismisses the so-called 'paranormal' and all phenomena related to that when the 'para'-normal is perfectly normal and explains the alleged 'great mysteries' which dumbfound scientific minds. There is a reason for this. A 'scientific mind' in terms of the mainstream is a material mind, a five-sense mind imprisoned in see it, touch it, hear it, smell it and taste it. Phenomena and happenings that can't be explained that way leave the 'scientific mind' bewildered and the rule is that if they

can't account for why something is happening then it can't, by definition, be happening. I beg to differ. Telepathy is thought waves passing through The Field (think wave disturbance again) to be decoded by someone able to connect with that wavelength (information). For example: You can pick up the thought waves of a friend at any distance and at the very least that will bring them to mind. A few minutes later the friend calls you. 'My god', you say, 'that's incredible – I was just thinking of you.' Ah, but *they* were thinking of *you* before they made the call and that's what you decoded. Native peoples not entrapped in five-sense reality do this so well it became known as the 'bush telegraph'. Those known as psychics and mediums (genuine ones) are doing the same only across dimensions of reality. 'Mind over matter' comes from the fact that matter and mind are the *same*. The state of one influences the state of the other. Indeed one *and* the other are illusions. They are aspects of the same field. Paranormal phenomena are all explainable so why are they still considered 'mysteries' or not happening? Once you go down this road of understanding you begin to expand awareness beyond the five senses and that's the nightmare for the Cult.



Figure 13: Holograms are not solid, but the best ones appear to be.

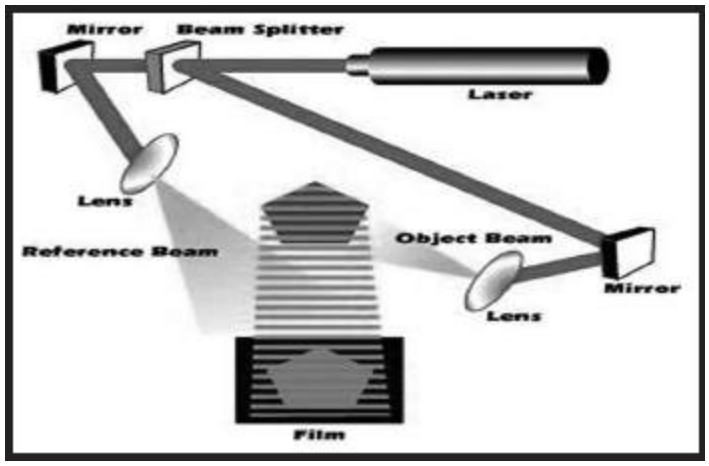


Figure 14: How holograms are created by capturing a waveform version of the subject image.

Holographic 'solidity'

Our reality is not solid, it is holographic. We are now well aware of holograms which are widely used today. Two-dimensional information is decoded into a three-dimensional reality that is not solid although can very much appear to be (Fig 13). Holograms are created with a laser divided into two parts. One goes directly onto a holographic photographic print ('reference beam') and the other takes a waveform image of the subject ('working beam') before being directed onto the print where it 'collides' with the other half of the laser (Fig 14). This creates a *waveform* interference pattern which contains the wavefield information of whatever is being photographed (Fig 15 overleaf). The process can be likened to dropping pebbles in a pond. Waves generated by each one spread out across the water to collide with the others and create a wave representation of where the stones fell and at what speed, weight and distance. A waveform interference pattern of a hologram is akin to the waveform information in The Field which the five senses decode into electrical signals to be decoded by the brain into a holographic illusory 'physical' reality. In the same way when a laser (think human attention) is directed at the waveform interference pattern a three-dimensional version of the subject is projected into apparently 'solid' reality (Fig 16). An amazing trait of holograms reveals more 'paranormal mysteries'. Information of the *whole*

hologram is encoded in waveform in every part of the interference pattern by the way they are created. This means that every *part* of a hologram is a smaller version of the whole. Cut the interference wave-pattern into four and you won't get four parts of the image. You get quarter-sized versions of the *whole* image. The body is a hologram and the same applies. Here we have the basis of acupuncture, reflexology and other forms of healing which identify representations of the whole body in all of the parts, hands, feet, ears, everywhere. Skilled palm readers can do what they do because the information of whole body is encoded in the hand. The concept of as above, so below, comes from this.



Figure 15: A waveform interference pattern that holds the information that transforms into a hologram.



Figure 16: Holographic people including 'Elvis' holographically inserted to sing a duet with Celine Dion.

The question will be asked of why, if solidity is illusory, we can't just walk through walls and each other. The resistance is not solid against solid; it is electromagnetic field against electromagnetic field and we decode this into the *experience* of solid against solid. We should also not underestimate the power of belief to dictate reality. What you believe is impossible *will be*. Your belief impacts on your decoding processes and they won't decode what you think is impossible. What we believe we perceive and what we perceive we experience. 'Can't dos' and 'impossibles' are like a firewall in a computer system that won't put on the screen what the firewall blocks. How vital that is to understanding how human experience has been hijacked. I explain in *The Answer*, *Everything You Need To Know But Have Never Been Told* and other books a long list of 'mysteries' and 'paranormal' phenomena that are not mysterious and perfectly normal once you realise what reality is and how it works. 'Ghosts' can be seen to pass through 'solid' walls because the walls are not solid and the ghost is a discarnate entity operating on a frequency so different to that of the wall that it's like two radio stations sharing the same space while never interfering with each other. I have seen ghosts do this myself. The apartness of people and objects is also an illusion. Everything is connected by the Field like all sea life is connected by the sea. It's just that within the limits of our visual reality we only 'see' holographic information and not the field of information that connects everything and from which the holographic world is made manifest. If you can only see holographic 'objects' and not the field that connects them they will appear to you as unconnected to each other in the same way that we see the computer while not seeing the Wi-Fi.

What you don't know *can* hurt you

Okay, we return to those 'two worlds' of human society and the Cult with its global network of interconnecting secret societies and satanic groups which manipulate through governments, corporations, media, religions, etc. The fundamental difference between them is *knowledge*. The idea has been to keep humanity

ignorant of the plan for its total enslavement underpinned by a crucial ignorance of reality – who we are and where we are – and how we interact with it. 'Human' should be the interaction between our expanded eternal consciousness and the five-sense body experience. We are meant to be *in* this world in terms of the five senses but not *of* this world in relation to our greater consciousness and perspective. In that state we experience the small picture of the five senses within the wider context of the big picture of awareness beyond the five senses. Put another way the five senses see the dots and expanded awareness connects them into pictures and patterns that give context to the apparently random and unconnected. Without the context of expanded awareness the five senses see only apartness and randomness with apparently no meaning. The Cult and its other-dimensional controllers seek to intervene in the frequency realm where five-sense reality is supposed to connect with expanded reality and to keep the two apart (more on this in the final chapter). When that happens five-sense mental and emotional processes are no longer influenced by expanded awareness, or the True 'I', and instead are driven by the isolated perceptions of the body's decoding systems. They are in the world *and* of it. Here we have the human plight and why humanity with its potential for infinite awareness can be so easily manipulatable and descend into such extremes of stupidity.

Once the Cult isolates five-sense mind from expanded awareness it can then program the mind with perceptions and beliefs by controlling information that the mind receives through the 'education' system of the formative years and the media perceptual bombardment and censorship of an entire lifetime. Limit perception and a sense of the possible through limiting knowledge by limiting and skewing information while censoring and discrediting that which could set people free. As the title of another of my books says *… And The Truth Shall Set You Free*. For this reason the last thing the Cult wants in circulation is the truth about anything – especially the reality of the eternal 'I' – and that's why it is desperate to control information. The Cult knows that information becomes perception

which becomes behaviour which, collectively, becomes human society. Cult-controlled and funded mainstream 'science' denies the existence of an eternal 'I' and seeks to dismiss and trash all evidence to the contrary. Cult-controlled mainstream religion has a version of 'God' that is little more than a system of control and dictatorship that employs threats of damnation in an afterlife to control perceptions and behaviour in the here and now through fear and guilt. Neither is true and it's the 'neither' that the Cult wishes to suppress. This 'neither' is that everything is an expression, a point of attention, within an infinite state of consciousness which is the real meaning of the term 'God'.

Perceptual obsession with the 'physical body' and five-senses means that 'God' becomes personified as a bearded bloke sitting among the clouds or a raging bully who loves us if we do what 'he' wants and condemns us to the fires of hell if we don't. These are no more than a 'spiritual' fairy tales to control and dictate events and behaviour through fear of this 'God' which has bizarrely made 'God-fearing' in religious circles a state to be desired. I would suggest that fearing *anything* is not to be encouraged and celebrated, but rather deleted. You can see why 'God fearing' is so beneficial to the Cult and its religions when *they* decide what 'God' wants and what 'God' demands (the Cult demands) that everyone do. As the great American comedian Bill Hicks said satirising a Christian zealot: 'I think what God meant to say.' How much of this infinite awareness ('God') that we access is decided by how far we choose to expand our perceptions, self-identity and sense of the possible. The scale of self-identity reflects itself in the scale of awareness that we can connect with and are influenced by – how much knowing and insight we have instead of programmed perception. You cannot expand your awareness into the infinity of possibility when you believe that you are little me Peter the postman or Mary in marketing and nothing more. I'll deal with this in the concluding chapter because it's crucial to how we turnaround current events.

Where the Cult came from

When I realised in the early 1990s there was a Cult network behind global events I asked the obvious question: When did it start? I took it back to ancient Rome and Egypt and on to Babylon and Sumer in Mesopotamia, the 'Land Between Two Rivers', in what we now call Iraq. The two rivers are the Tigris and Euphrates and this region is of immense historical and other importance to the Cult, as is the land called Israel only 550 miles away by air. There is much more going with deep esoteric meaning across this whole region. It's not only about 'wars for oil'. Priceless artefacts from Mesopotamia were stolen or destroyed after the American and British invasion of Iraq in 2003 justified by the lies of Boy Bush and Tony Blair (their Cult masters) about non-existent 'weapons of mass destruction'. Mesopotamia was the location of Sumer (about 5,400BC to 1,750BC), and Babylon (about 2,350BC to 539BC). Sabbatians may have become immensely influential in the Cult in modern times but they are part of a network that goes back into the mists of history. Sumer is said by historians to be the 'cradle of civilisation'. I disagree. I say it was the re-start of what we call human civilisation after cataclysmic events symbolised in part as the 'Great Flood' destroyed the world that existed before. These fantastic upheavals that I have been describing in detail in the books since the early1990s appear in accounts and legends of ancient cultures across the world and they are supported by geological and biological evidence. Stone tablets found in Iraq detailing the Sumer period say the cataclysms were caused by non-human 'gods' they call the Anunnaki. These are described in terms of extraterrestrial visitations in which knowledge supplied by the Anunnaki is said to have been the source of at least one of the world's oldest writing systems and developments in astronomy, mathematics and architecture that were way ahead of their time. I have covered this subject at length in *The Biggest Secret* and *Children of the Matrix* and the same basic 'Anunnaki' story can be found in Zulu accounts in South Africa where the late and very great Zulu high shaman Credo Mutwa told me that the Sumerian Anunnaki were known by Zulus as the Chitauri or 'children of the serpent'. See my six-hour video interview with Credo on this subject entitled *The*

Reptilian Agenda recorded at his then home near Johannesburg in 1999 which you can watch on the Ickonic media platform.

The Cult emerged out of Sumer, Babylon and Egypt (and elsewhere) and established the Roman Empire before expanding with the Romans into northern Europe from where many empires were savagely imposed in the form of Cult-controlled societies all over the world. Mass death and destruction was their calling card. The Cult established its centre of operations in Europe and European Empires were Cult empires which allowed it to expand into a global force. Spanish and Portuguese colonialists headed for Central and South America while the British and French targeted North America. Africa was colonised by Britain, France, Belgium, the Netherlands, Portugal, Spain, Italy, and Germany. Some like Britain and France moved in on the Middle East. The British Empire was by far the biggest for a simple reason. By now Britain was the headquarters of the Cult from which it expanded to form Canada, the United States, Australia and New Zealand. The Sun never set on the British Empire such was the scale of its occupation. London remains a global centre for the Cult along with Rome and the Vatican although others have emerged in Israel and China. It is no accident that the 'virus' is alleged to have come out of China while Italy was chosen as the means to terrify the Western population into compliance with 'Covid' fascism. Nor that Israel has led the world in 'Covid' fascism and mass 'vaccination'.

You would think that I would mention the United States here, but while it has been an important means of imposing the Cult's will it is less significant than would appear and is currently in the process of having what power it does have deleted. The Cult in Europe has mostly loaded the guns for the US to fire. America has been controlled from Europe from the start through Cult operatives in Britain and Europe. The American Revolution was an illusion to make it appear that America was governing itself while very different forces were pulling the strings in the form of Cult families such as the Rothschilds through the Rockefellers and other subordinates. The Rockefellers are extremely close to Bill Gates and

established both scalpel and drug 'medicine' and the World Health Organization. They play a major role in the development and circulation of vaccines through the Rockefeller Foundation on which Bill Gates said his Foundation is based. Why wouldn't this be the case when the Rockefellers and Gates are on the same team? Cult infiltration of human society goes way back into what we call history and has been constantly expanding and centralising power with the goal of establishing a global structure to dictate everything. Look how this has been advanced in great leaps with the 'Covid' hoax.

The non-human dimension

I researched and observed the comings and goings of Cult operatives through the centuries and even thousands of years as they were born, worked to promote the agenda within the secret society and satanic networks, and then died for others to replace them. Clearly there had to be a coordinating force that spanned this entire period while operatives who would not have seen the end goal in their lifetimes came and went advancing the plan over millennia. I went in search of that coordinating force with the usual support from the extraordinary synchronicity of my life which has been an almost daily experience since 1990. I saw common themes in religious texts and ancient cultures about a non-human force manipulating human society from the hidden. Christianity calls this force Satan, the Devil and demons; Islam refers to the Jinn or Djinn; Zulus have their Chitauri (spelt in other ways in different parts of Africa); and the Gnostic people in Egypt in the period around and before 400AD referred to this phenomena as the 'Archons', a word meaning rulers in Greek. Central American cultures speak of the 'Predators' among other names and the same theme is everywhere. I will use 'Archons' as a collective name for all of them. When you see how their nature and behaviour is described all these different sources are clearly talking about the same force. Gnostics described the Archons in terms of 'luminous fire' while Islam relates the Jinn to 'smokeless fire'. Some refer to beings in form that could occasionally be seen, but the most common of common theme is that they operate from

unseen realms which means almost all existence to the visual processes of humans. I had concluded that this was indeed the foundation of human control and that the Cult was operating within the human frequency band on behalf of this hidden force when I came across the writings of Gnostics which supported my conclusions in the most extraordinary way.

A sealed earthen jar was found in 1945 near the town of Nag Hammadi about 75-80 miles north of Luxor on the banks of the River Nile in Egypt. Inside was a treasure trove of manuscripts and texts left by the Gnostic people some 1,600 years earlier. They included 13 leather-bound papyrus codices (manuscripts) and more than 50 texts written in Coptic Egyptian estimated to have been hidden in the jar in the period of 400AD although the source of the information goes back much further. Gnostics oversaw the Great or Royal Library of Alexandria, the fantastic depository of ancient texts detailing advanced knowledge and accounts of human history. The Library was dismantled and destroyed in stages over a long period with the death-blow delivered by the Cult-established Roman Church in the period around 415AD. The Church of Rome was the Church of Babylon relocated as I said earlier. Gnostics were not a race. They were a way of perceiving reality. Whenever they established themselves and their information circulated the terrorists of the Church of Rome would target them for destruction. This happened with the Great Library and with the Gnostic Cathars who were burned to death by the psychopaths after a long period of oppression at the siege of the Castle of Monségur in southern France in 1244. The Church has always been terrified of Gnostic information which demolishes the official Christian narrative although there is much in the Bible that supports the Gnostic view if you read it in another way. To anyone studying the texts of what became known as the Nag Hammadi Library it is clear that great swathes of Christian and Biblical belief has its origin with Gnostics sources going back to Sumer. Gnostic themes have been twisted to manipulate the perceived reality of Bible believers. Biblical texts have been in the open for centuries where they could be changed while Gnostic

documents found at Nag Hammadi were sealed away and untouched for 1,600 years. What you see is what they wrote.

Use your *pneuma* not your *nous*

Gnosticism and Gnostic come from 'gnosis' which means knowledge, or rather *secret* knowledge, in the sense of spiritual awareness – knowledge about reality and life itself. The desperation of the Cult's Church of Rome to destroy the Gnostics can be understood when the knowledge they were circulating was the last thing the Cult wanted the population to know. Sixteen hundred years later the same Cult is working hard to undermine and silence me for the same reason. The dynamic between knowledge and ignorance is a constant. 'Time' appears to move on, but essential themes remain the same. We are told to 'use your nous', a Gnostic word for head/brain/intelligence. They said, however, that spiritual awakening or 'salvation' could only be secured by expanding awareness *beyond* what they called *nous* and into *pneuma* or Infinite Self. Obviously as I read these texts the parallels with what I have been saying since 1990 were fascinating to me. There is a universal truth that spans human history and in that case why wouldn't we be talking the same language 16 centuries apart? When you free yourself from the perception program of the five senses and explore expanded realms of consciousness you are going to connect with the same information no matter what the perceived 'era' within a manufactured timeline of a single and tiny range of manipulated frequency. Humans working with 'smart' technology or knocking rocks together in caves is only a timeline appearing to operate within the human frequency band. Expanded awareness and the knowledge it holds have always been there whether the era be Stone Age or computer age. We can only access that knowledge by opening ourselves to its frequency which the five-sense prison cell is designed to stop us doing. Gates, Fauci, Whitty, Vallance, Zuckerberg, Brin, Page, Wojcicki, Bezos, and all the others behind the 'Covid' hoax clearly have a long wait before their range of frequency can make that connection given that an open heart is

crucial to that as we shall see. Instead of accessing knowledge directly through expanded awareness it is given to Cult operatives by the secret society networks of the Cult where it has been passed on over thousands of years outside the public arena. Expanded realms of consciousness is where great artists, composers and writers find their inspiration and where truth awaits anyone open enough to connect with it. We need to go there fast.

Archon hijack

A fifth of the Nag Hammadi texts describe the existence and manipulation of the Archons led by a 'Chief Archon' they call 'Yaldabaoth', or the 'Demiurge', and this is the Christian 'Devil', 'Satan', 'Lucifer', and his demons. Archons in Biblical symbolism are the 'fallen ones' which are also referred to as fallen angels after the angels expelled from heaven according to the Abrahamic religions of Judaism, Christianity and Islam. These angels are claimed to tempt humans to 'sin' ongoing and you will see how accurate that symbolism is during the rest of the book. The theme of 'original sin' is related to the 'Fall' when Adam and Eve were 'tempted by the serpent' and fell from a state of innocence and 'obedience' (connection) with God into a state of disobedience (disconnection). The Fall is said to have brought sin into the world and corrupted everything including human nature. Yaldabaoth, the 'Lord Archon', is described by Gnostics as a 'counterfeit spirit', 'The Blind One', 'The Blind God', and 'The Foolish One'. The Jewish name for Yaldabaoth in Talmudic writings is Samael which translates as 'Poison of God', or 'Blindness of God'. You see the parallels. Yaldabaoth in Islamic belief is the Muslim Jinn devil known as Shaytan – Shaytan is Satan as the same themes are found all over the world in every religion and culture. The 'Lord God' of the Old Testament is the 'Lord Archon' of Gnostic manuscripts and that's why he's such a bloodthirsty bastard. Satan is known by Christians as 'the Demon of Demons' and Gnostics called Yaldabaoth the 'Archon of Archons'. Both are known as 'The Deceiver'. We are talking about the same 'bloke' for sure and these common themes

using different names, storylines and symbolism tell a common tale of the human plight.

Archons are referred to in Nag Hammadi documents as mind parasites, inverters, guards, gatekeepers, detainers, judges, pitiless ones and deceivers. The 'Covid' hoax alone is a glaring example of all these things. The Biblical 'God' is so different in the Old and New Testaments because they are not describing the same phenomenon. The vindictive, angry, hate-filled, 'God' of the Old Testament, known as Yahweh, is Yaldabaoth who is depicted in Cult-dictated popular culture as the 'Dark Lord', 'Lord of Time', Lord (Darth) Vader and Dormammu, the evil ruler of the 'Dark Dimension' trying to take over the 'Earth Dimension' in the Marvel comic movie, *Dr Strange*. Yaldabaoth is both the Old Testament 'god' and the Biblical 'Satan'. Gnostics referred to Yaldabaoth as the 'Great Architect of the Universe'and the Cult-controlled Freemason network calls their god 'the 'Great Architect of the Universe' (also Grand Architect). The 'Great Architect' Yaldabaoth is symbolised by the Cult as the all-seeing eye at the top of the pyramid on the Great Seal of the United States and the dollar bill. Archon is encoded in *arch*-itect as it is in *arch*-angels and *arch*-bishops. All religions have the theme of a force for good and force for evil in some sort of spiritual war and there is a reason for that – the theme is true. The Cult and its non-human masters are quite happy for this to circulate. They present themselves as the force for good fighting evil when they are really the force of evil (absence of love). The whole foundation of Cult modus operandi is inversion. They promote themselves as a force for good and anyone challenging them in pursuit of peace, love, fairness, truth and justice is condemned as a satanic force for evil. This has been the game plan throughout history whether the Church of Rome inquisitions of non-believers or 'conspiracy theorists' and 'anti-vaxxers' of today. The technique is the same whatever the timeline era.

Yaldabaoth is revolting (true)

Yaldabaoth and the Archons are said to have revolted against God with Yaldabaoth claiming to *be* God – the *All That Is*. The Old Testament 'God' (Yaldabaoth) demanded to be worshipped as such: ' *I am* the LORD, and there is none else, there is no God beside me' (Isaiah 45:5). I have quoted in other books a man who said he was the unofficial son of the late Baron Philippe de Rothschild of the Mouton-Rothschild wine producing estates in France who died in 1988 and he told me about the Rothschild 'revolt from God'. The man said he was given the name Phillip Eugene de Rothschild and we shared long correspondence many years ago while he was living under another identity. He said that he was conceived through 'occult incest' which (within the Cult) was 'normal and to be admired'. 'Phillip' told me about his experience attending satanic rituals with rich and famous people whom he names and you can see them and the wider background to Cult Satanism in my other books starting with *The Biggest Secret*. Cult rituals are interactions with Archontic 'gods'. 'Phillip' described Baron Philippe de Rothschild as 'a master Satanist and hater of God' and he used the same term 'revolt from God' associated with Yaldabaoth/Satan/Lucifer/the Devil in describing the Sabbatian Rothschild dynasty. 'I played a key role in my family's revolt from God', he said. That role was to infiltrate in classic Sabbatian style the Christian Church, but eventually he escaped the mind-prison to live another life. The Cult has been targeting religion in a plan to make worship of the Archons the global one-world religion. Infiltration of Satanism into modern 'culture', especially among the young, through music videos, stage shows and other means, is all part of this.

Nag Hammadi texts describe Yaldabaoth and the Archons in their prime form as energy – consciousness – and say they can take form if they choose in the same way that consciousness takes form as a human. Yaldabaoth is called 'formless' and represents a deeply inverted, distorted and chaotic state of consciousness which seeks to attached to humans and turn them into a likeness of itself in an attempt at assimilation. For that to happen it has to manipulate

humans into low frequency mental and emotional states that match its own. Archons can certainly appear in human form and this is the origin of the psychopathic personality. The energetic distortion Gnostics called Yaldabaoth *is* psychopathy. When psychopathic Archons take human form that human will be a psychopath as an expression of Yaldabaoth consciousness. Cult psychopaths are Archons in human form. The principle is the same as that portrayed in the 2009 *Avatar* movie when the American military travelled to a fictional Earth-like moon called Pandora in the Alpha Centauri star system to infiltrate a society of blue people, or Na'vi, by hiding within bodies that looked like the Na'vi. Archons posing as humans have a particular hybrid information field, part human, part Archon, (the ancient 'demigods') which processes information in a way that manifests behaviour to match their psychopathic evil, lack of empathy and compassion, and stops them being influenced by the empathy, compassion and love that a fully-human information field is capable of expressing. Cult bloodlines interbreed, be they royalty or dark suits, for this reason and you have their obsession with incest. Interbreeding with full-blown humans would dilute the Archontic energy field that guarantees psychopathy in its representatives in the human realm.

Gnostic writings say the main non-human forms that Archons take are *serpentine* (what I have called for decades 'reptilian' amid unbounded ridicule from the Archontically-programmed) and what Gnostics describe as 'an unborn baby or foetus with grey skin and dark, unmoving eyes'. This is an excellent representation of the ET 'Greys' of UFO folklore which large numbers of people claim to have seen and been abducted by – Zulu shaman Credo Mutwa among them. I agree with those that believe in extraterrestrial or interdimensional visitations today and for thousands of years past. No wonder with their advanced knowledge and technological capability they were perceived and worshipped as gods for technological and other 'miracles' they appeared to perform. Imagine someone arriving in a culture disconnected from the modern world with a smartphone and computer. They would be

seen as a 'god' capable of 'miracles'. The Renegade Mind, however, wants to know the source of everything and not only the way that source manifests as human or non-human. In the same way that a Renegade Mind seeks the original source material for the 'Covid virus' to see if what is claimed is true. The original source of Archons in form is consciousness – the distorted state of consciousness known to Gnostics as Yaldabaoth.

'Revolt from God' is energetic disconnection

Where I am going next will make a lot of sense of religious texts and ancient legends relating to 'Satan', Lucifer' and the 'gods'. Gnostic descriptions sync perfectly with the themes of my own research over the years in how they describe a consciousness distortion seeking to impose itself on human consciousness. I've referred to the core of infinite awareness in previous books as Infinite Awareness in Awareness of Itself. By that I mean a level of awareness that knows that it is all awareness and is aware of all awareness. From here comes the frequency of love in its true sense and balance which is what love is on one level – the balance of all forces into a single whole called Oneness and Isness. The more we disconnect from this state of love that many call 'God' the constituent parts of that Oneness start to unravel and express themselves as a part and not a whole. They become individualised as intellect, mind, selfishness, hatred, envy, desire for power over others, and such like. This is not a problem in the greater scheme in that 'God', the *All That Is*, can experience all these possibilities through different expressions of itself including humans. What we as expressions of the whole experience the *All That Is* experiences. We are the *All That Is* experiencing itself. As we withdraw from that state of Oneness we disconnect from its influence and things can get very unpleasant and very stupid. Archontic consciousness is at the extreme end of that. It has so disconnected from the influence of Oneness that it has become an inversion of unity and love, an inversion of everything, an inversion of life itself. Evil is appropriately live written backwards. Archontic consciousness is obsessed with death, an inversion of life,

and so its manifestations in Satanism are obsessed with death. They use inverted symbols in their rituals such as the inverted pentagram and cross. Sabbatians as Archontic consciousness incarnate invert Judaism and every other religion and culture they infiltrate. They seek disunity and chaos and they fear unity and harmony as they fear love like garlic to a vampire. As a result the Cult, Archons incarnate, act with such evil, psychopathy and lack of empathy and compassion disconnected as they are from the source of love. How could Bill Gates and the rest of the Archontic psychopaths do what they have to human society in the 'Covid' era with all the death, suffering and destruction involved and have no emotional consequence for the impact on others? Now you know. Why have Zuckerberg, Brin, Page, Wojcicki and company callously censored information warning about the dangers of the 'vaccine' while thousands have been dying and having severe, sometimes life-changing reactions? Now you know. Why have Tedros, Fauci, Whitty, Vallance and their like around the world been using case and death figures they're aware are fraudulent to justify lockdowns and all the deaths and destroyed lives that have come from that? Now you know. Why did Christian Drosten produce and promote a 'testing' protocol that he knew couldn't test for infectious disease which led to a global human catastrophe. Now you know. The Archontic mind doesn't give a shit (Fig 17). I personally think that Gates and major Cult insiders are a form of AI cyborg that the Archons want humans to become.

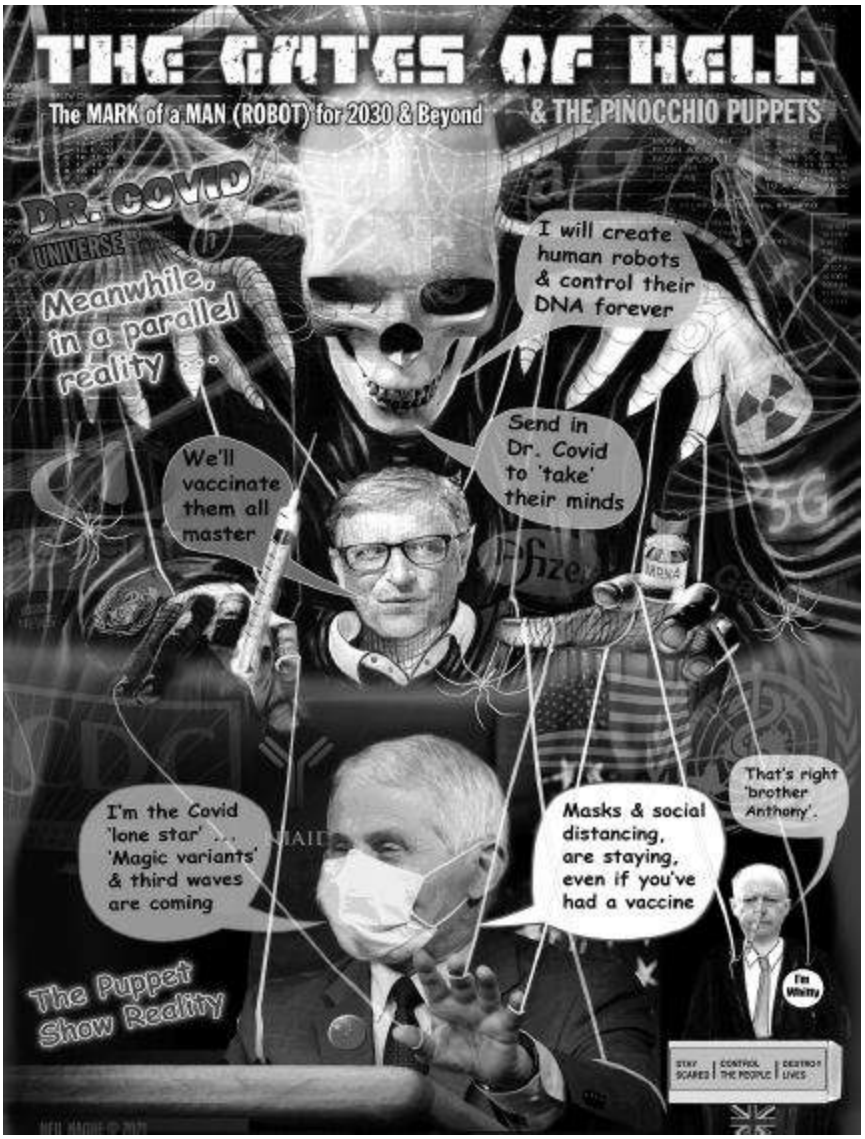


Figure 17: Artist Neil Hague's version of the 'Covid' hierarchy.

Human batteries

A state of such inversion does have its consequences, however. The level of disconnection from the Source of All means that you withdraw from that source of energetic sustenance and creativity. This means that you have to find your own supply of energetic power and it has – *us*. When the Morpheus character in the first *Matrix* movie held up a battery he spoke a profound truth when he said: 'The Matrix is a computer-generated dream world built to keep us under control in order to change the human being into one of

these.' The statement was true in all respects. We do live in a technologically-generated virtual reality simulation (more very shortly) and we have been manipulated to be an energy source for Archontic consciousness. The Disney-Pixar animated movie *Monsters, Inc*. in 2001 symbolised the dynamic when monsters in their world had no energy source and they would enter the human world to terrify children in their beds, catch the child's scream, terror (low-vibrational frequencies), and take that energy back to power the monster world. The lead character you might remember was a single giant eye and the symbolism of the Cult's all-seeing eye was obvious. Every thought and emotion is broadcast as a frequency unique to that thought and emotion. Feelings of love and joy, empathy and compassion, are high, quick, frequencies while fear, depression, anxiety, suffering and hate are low, slow, dense frequencies. Which kind do you think Archontic consciousness can connect with and absorb? In such a low and dense frequency state there's no way it can connect with the energy of love and joy. Archons can only feed off energy compatible with their own frequency and they and their Cult agents want to delete the human world of love and joy and manipulate the transmission of low vibrational frequencies through low-vibrational human mental and emotional states. *We are their energy source*. Wars are energetic banquets to the Archons – a world war even more so – and think how much low-frequency mental and emotional energy has been generated from the consequences for humanity of the 'Covid' hoax orchestrated by Archons incarnate like Gates.

The ancient practice of human sacrifice 'to the gods', continued in secret today by the Cult, is based on the same principle. 'The gods' are Archontic consciousness in different forms and the sacrifice is induced into a state of intense terror to generate the energy the Archontic frequency can absorb. Incarnate Archons in the ritual drink the blood which contains an adrenaline they crave which floods into the bloodstream when people are terrorised. Most of the sacrifices, ancient and modern, are children and the theme of 'sacrificing young virgins to the gods' is just code for children. They

have a particular pre-puberty energy that Archons want more than anything and the energy of the young in general is their target. The California Department of Education wants students to chant the names of Aztec gods (Archontic gods) once worshipped in human sacrifice rituals in a curriculum designed to encourage them to 'challenge racist, bigoted, discriminatory, imperialist/colonial beliefs', join 'social movements that struggle for social justice', and 'build new possibilities for a post-racist, post-systemic racism society'. It's the usual Woke crap that inverts racism and calls it anti-racism. In this case solidarity with 'indigenous tribes' is being used as an excuse to chant the names of 'gods' to which people were sacrificed (and still are in secret). What an example of Woke's inability to see beyond black and white, us and them, They condemn the colonisation of these tribal cultures by Europeans (quite right), but those cultures sacrificing people including children to their 'gods', and mass murdering untold numbers as the Aztecs did, is just fine. One chant is to the Aztec god Tezcatlipoca who had a man sacrificed to him in the 5th month of the Aztec calendar. His heart was cut out and he was eaten. Oh, that's okay then. Come on children … after three … Other sacrificial 'gods' for the young to chant their allegiance include Quetzalcoatl, Huitzilopochtli and Xipe Totec. The curriculum says that 'chants, affirmations, and energizers can be used to bring the class together, build unity around ethnic studies principles and values, and to reinvigorate the class following a lesson that may be emotionally taxing or even when student engagement may appear to be low'. Well, that's the cover story, anyway. Chanting and mantras are the repetition of a particular frequency generated from the vocal cords and chanting the names of these Archontic 'gods' tunes you into their frequency. That is the last thing you want when it allows for energetic synchronisation, attachment and perceptual influence. Initiates chant the names of their 'Gods' in their rituals for this very reason.

Vampires of the Woke

Paedophilia is another way that Archons absorb the energy of children. Paedophiles possessed by Archontic consciousness are used as the conduit during sexual abuse for discarnate Archons to vampire the energy of the young they desire so much. Stupendous numbers of children disappear every year never to be seen again although you would never know from the media. Imagine how much low-vibrational energy has been generated by children during the 'Covid' hoax when so many have become depressed and psychologically destroyed to the point of killing themselves. Shocking numbers of children are now taken by the state from loving parents to be handed to others. I can tell you from long experience of researching this since 1996 that many end up with paedophiles and assets of the Cult through corrupt and Cult-owned social services which in the reframing era has hired many psychopaths and emotionless automatons to do the job. Children are even stolen to order using spurious reasons to take them by the corrupt and secret (because they're corrupt) 'family courts'. I have written in detail in other books, starting with *The Biggest Secret* in 1997, about the ubiquitous connections between the political, corporate, government, intelligence and military elites (Cult operatives) and Satanism and paedophilia. If you go deep enough both networks have an interlocking leadership. The Woke mentality has been developed by the Cult for many reasons: To promote almost every aspect of its agenda; to hijack the traditional political left and turn it fascist; to divide and rule; and to target agenda pushbackers. But there are other reasons which relate to what I am describing here. How many happy and joyful Wokers do you ever see especially at the extreme end? They are a mental and psychological mess consumed by emotional stress and constantly emotionally cocked for the next explosion of indignation at someone referring to a female as a female. They are walking, talking, batteries as Morpheus might say emitting frequencies which both enslave them in low-vibrational bubbles of perceptual limitation and feed the Archons. Add to this the hatred claimed to be love; fascism claimed to 'anti-fascism', racism claimed to be 'anti-racism';

exclusion claimed to inclusion; and the abuse-filled Internet trolling. You have a purpose-built Archontic energy system with not a wind turbine in sight and all founded on Archontic *inversion*. We have whole generations now manipulated to serve the Archons with their actions and energy. They will be doing so their entire adult lives unless they snap out of their Archon-induced trance. Is it really a surprise that Cult billionaires and corporations put so much money their way? Where is the energy of joy and laughter, including laughing at yourself which is confirmation of your own emotional security? Mark Twain said: 'The human race has one really effective weapon, and that is laughter.' We must use it all the time. Woke has destroyed comedy because it has no humour, no joy, sense of irony, or self-deprecation. Its energy is dense and intense. *Mmmmm*, lunch says the Archontic frequency. Rudolf Steiner (1861-1925) was the Austrian philosopher and famous esoteric thinker who established Waldorf education or Steiner schools to treat children like unique expressions of consciousness and not minds to be programmed with the perceptions determined by authority. I'd been writing about this energy vampiring for decades when I was sent in 2016 a quote by Steiner. He was spot on:

> There are beings in the spiritual realms for whom anxiety and fear emanating from human beings offer welcome food. When humans have no anxiety and fear, then these creatures starve. If fear and anxiety radiates from people and they break out in panic, then these creatures find welcome nutrition and they become more and more powerful. These beings are hostile towards humanity. Everything that feeds on negative feelings, on anxiety, fear and superstition, despair or doubt, are in reality hostile forces in super-sensible worlds, launching cruel attacks on human beings, while they are being fed ... These are exactly the feelings that belong to contemporary culture and materialism; because it estranges people from the spiritual world, it is especially suited to evoke hopelessness and fear of the unknown in people, thereby calling up the above mentioned hostile forces against them.

Pause for a moment from this perspective and reflect on what has happened in the world since the start of 2020. Not only will pennies drop, but billion dollar bills. We see the same theme from Don Juan Matus, a Yaqui Indian shaman in Mexico and the information source for Peruvian-born writer, Carlos Castaneda, who wrote a series of

books from the 1960s to 1990s. Don Juan described the force manipulating human society and his name for the Archons was the predator:

> We have a predator that came from the depths of the cosmos and took over the rule of our lives. Human beings are its prisoners. The predator is our lord and master. It has rendered us docile, helpless. If we want to protest, it suppresses our protest. If we want to act independently, it demands that we don't do so ... indeed we are held prisoner!
>
> They took us over because we are food to them, and they squeeze us mercilessly because we are their sustenance. Just as we rear chickens in coops, the predators rear us in human coops, humaneros. Therefore, their food is always available to them.
>
> Different cultures, different eras, same recurring theme.

The 'ennoia' dilemma

Nag Hammadi Gnostic manuscripts say that Archon consciousness has no 'ennoia'. This is directly translated as 'intentionality', but I'll use the term 'creative imagination'. The *All That Is* in awareness of itself is the source of all creativity – all possibility – and the more disconnected you are from that source the more you are subsequently denied 'creative imagination'. Given that Archon consciousness is almost entirely disconnected it severely lacks creativity and has to rely on far more mechanical processes of thought and exploit the creative potential of those that do have 'ennoia'. You can see cases of this throughout human society. Archon consciousness almost entirely dominates the global banking system and if we study how that system works you will appreciate what I mean. Banks manifest 'money' out of nothing by issuing lines of 'credit' which is 'money' that has never, does not, and will never exist except in theory. It's a confidence trick. If you think 'credit' figures-on-a-screen 'money' is worth anything you accept it as payment. If you don't then the whole system collapses through lack of confidence in the value of that 'money'. Archontic bankers with no 'ennoia' are 'lending' 'money' that doesn't exist to humans that *do* have creativity – those that have the inspired ideas and create businesses and products. Archon banking feeds off human creativity

which it controls through 'money' creation and debt. Humans have the creativity and Archons exploit that for their own benefit and control while having none themselves. Archon Internet platforms like Facebook claim joint copyright of everything that creative users post and while Archontic minds like Zuckerberg may officially head that company it will be human creatives on the staff that provide the creative inspiration. When you have limitless 'money' you can then buy other companies established by creative humans. Witness the acquisition record of Facebook, Google and their like. Survey the Archon-controlled music industry and you see non-creative dark suit executives making their fortune from the human creativity of their artists. The cases are endless. Research the history of people like Gates and Zuckerberg and how their empires were built on exploiting the creativity of others. Archon minds cannot create out of nothing, but they are skilled (because they have to be) in what Gnostic texts call 'countermimicry'. They can imitate, but not innovate. Sabbatians trawl the creativity of others through backdoors they install in computer systems through their cybersecurity systems. Archon-controlled China is globally infamous for stealing intellectual property and I remember how Hong Kong, now part of China, became notorious for making counterfeit copies of the creativity of others – 'countermimicry'. With the now pervasive and all-seeing surveillance systems able to infiltrate any computer you can appreciate the potential for Archons to vampire the creativity of humans. Author John Lamb Lash wrote in his book about the Nag Hammadi texts, *Not In His Image*:

> Although they cannot originate anything, because they lack the divine factor of ennoia (intentionality), Archons can imitate with a vengeance. Their expertise is simulation (HAL, virtual reality). The Demiurge [Yaldabaoth] fashions a heaven world copied from the fractal patterns [of the original] ... His construction is celestial kitsch, like the fake Italianate villa of a Mafia don complete with militant angels to guard every portal.

This brings us to something that I have been speaking about since the turn of the millennium. Our reality is a simulation; a virtual reality that we think is real. No, I'm not kidding.

Human reality? Well, virtually

I had pondered for years about whether our reality is 'real' or some kind of construct. I remembered being immensely affected on a visit as a small child in the late 1950s to the then newly-opened Planetarium on the Marylebone Road in London which is now closed and part of the adjacent Madame Tussauds wax museum. It was in the middle of the day, but when the lights went out there was the night sky projected in the Planetarium's domed ceiling and it appeared to be so real. The experience never left me and I didn't know why until around the turn of the millennium when I became certain that our 'night sky' and entire reality is a projection, a virtual reality, akin to the illusory world portrayed in the *Matrix* movies. I looked at the sky one day in this period and it appeared to me like the domed roof of the Planetarium. The release of the first *Matrix* movie in 1999 also provided a synchronistic and perfect visual representation of where my mind had been going for a long time. I hadn't come across the Gnostic Nag Hammadi texts then. When I did years later the correlation was once again astounding. As I read Gnostic accounts from 1,600 years and more earlier it was clear that they were describing the same simulation phenomenon. They tell how the Yaldabaoth 'Demiurge' and Archons created a 'bad copy' of original reality to rule over all that were captured by its illusions and the body was a prison to trap consciousness in the 'bad copy' fake reality. Read how Gnostics describe the 'bad copy' and update that to current times and they are referring to what we would call today a virtual reality simulation.

Author John Lamb Lash said 'the Demiurge fashions a heaven world copied from the fractal patterns' of the original through expertise in 'HAL' or virtual reality simulation. Fractal patterns are part of the energetic information construct of our reality, a sort of blueprint. If these patterns were copied in computer terms it would indeed give you a copy of a 'natural' reality in a non-natural frequency and digital form. The principle is the same as making a copy of a website. The original website still exists, but now you can change the copy version to make it whatever you like and it can

become very different to the original website. Archons have done this with our reality, a *synthetic* copy of prime reality that still exists beyond the frequency walls of the simulation. Trapped within the illusions of this synthetic Matrix, however, were and are human consciousness and other expressions of prime reality and this is why the Archons via the Cult are seeking to make the human body synthetic and give us synthetic AI minds to complete the job of turning the entire reality synthetic including what we perceive to be the natural world. To quote Kurzweil: 'Nanobots will infuse all the matter around us with information. Rocks, trees, everything will become these intelligent creatures.' Yes, *synthetic* 'creatures' just as 'Covid' and other genetically-manipulating 'vaccines' are designed to make the human body synthetic. From this perspective it is obvious why Archons and their Cult are so desperate to infuse synthetic material into every human with their 'Covid' scam.

Let there be (electromagnetic) light

Yaldabaoth, the force that created the simulation, or Matrix, makes sense of the Gnostic reference to 'The Great Architect' and its use by Cult Freemasonry as the name of its deity. The designer of the Matrix in the movies is called 'The Architect' and that trilogy is jam-packed with symbolism relating to these subjects. I have contended for years that the angry Old Testament God (Yaldabaoth) is the 'God' being symbolically 'quoted' in the opening of Genesis as 'creating the world'. This is not the creation of prime reality – it's the creation of the *simulation*. The Genesis 'God' says: 'Let there be Light: and there was light.' But what is this 'Light'? I have said for decades that the speed of light (186,000 miles per second) is not the fastest speed possible as claimed by mainstream science and is in fact the frequency walls or outer limits of the Matrix. You can't have a fastest or slowest anything within all possibility when everything is possible. The human body is encoded to operate within the speed of light or *within the simulation* and thus we see only the tiny frequency band of visible *light*. Near-death experiencers who perceive reality outside the body during temporary 'death' describe a very different

form of light and this is supported by the Nag Hammadi texts. Prime reality beyond the simulation ('Upper Aeons' to the Gnostics) is described as a realm of incredible beauty, bliss, love and harmony – a realm of 'watery light' that is so powerful 'there are no shadows'. Our false reality of Archon control, which Gnostics call the 'Lower Aeons', is depicted as a realm with a different kind of 'light' and described in terms of chaos, 'Hell', 'the Abyss' and 'Outer Darkness', where trapped souls are tormented and manipulated by demons (relate that to the 'Covid' hoax alone). The watery light theme can be found in near-death accounts and it is not the same as *simulation* 'light' which is electromagnetic or radiation light within the speed of light – the 'Lower Aeons'. Simulation 'light' is the 'luminous fire' associated by Gnostics with the Archons. The Bible refers to Yaldabaoth as 'that old serpent, called the Devil, and Satan, which deceiveth the whole world' (Revelation 12:9). I think that making a simulated copy of prime reality ('countermimicry') and changing it dramatically while all the time manipulating humanity to believe it to be real could probably meet the criteria of deceiving the whole world. Then we come to the Cult god Lucifer – the *Light Bringer*. Lucifer is symbolic of Yaldabaoth, the bringer of radiation light that forms the bad copy simulation within the speed of light. 'He' is symbolised by the lighted torch held by the Statue of Liberty and in the name 'Illuminati'. Sabbatian-Frankism declares that Lucifer is the true god and Lucifer is the real god of Freemasonry honoured as their 'Great or Grand Architect of the Universe' (simulation).

I would emphasise, too, the way Archontic technologically-generated luminous fire of radiation has deluged our environment since I was a kid in the 1950s and changed the nature of The Field with which we constantly interact. Through that interaction technological radiation is changing us. The Smart Grid is designed to operate with immense levels of communication power with 5G expanding across the world and 6G, 7G, in the process of development. Radiation is the simulation and the Archontic manipulation system. Why wouldn't the Archon Cult wish to unleash radiation upon us to an ever-greater extreme to form

Kurzweil's 'cloud'? The plan for a synthetic human is related to the need to cope with levels of radiation beyond even anything we've seen so far. Biological humans would not survive the scale of radiation they have in their script. The Smart Grid is a technological sub-reality within the technological simulation to further disconnect five-sense perception from expanded consciousness. It's a technological prison of the mind.

Infusing the 'spirit of darkness'

A recurring theme in religion and native cultures is the manipulation of human genetics by a non-human force and most famously recorded as the biblical 'sons of god' (the god*s* plural in the original) who interbred with the daughters of men. The Nag Hammadi *Apocryphon of John* tells the same story this way:

> He [Yaldabaoth] sent his angels [Archons/demons] to the daughters of men, that they might take some of them for themselves and raise offspring for their enjoyment. And at first they did not succeed. When they had no success, they gathered together again and they made a plan together ... And the angels changed themselves in their likeness into the likeness of their mates, filling them with the spirit of darkness, which they had mixed for them, and with evil ... And they took women and begot children out of the darkness according to the likeness of their spirit.

Possession when a discarnate entity takes over a human body is an age-old theme and continues today. It's very real and I've seen it. Satanic and secret society rituals can create an energetic environment in which entities can attach to initiates and I've heard many stories of how people have changed their personality after being initiated even into lower levels of the Freemasons. I have been inside three Freemasonic temples, one at a public open day and two by just walking in when there was no one around to stop me. They were in Ryde, the town where I live, Birmingham, England, when I was with a group, and Boston, Massachusetts. They all felt the same energetically – dark, dense, low-vibrational and sinister. Demonic attachment can happen while the initiate has no idea what is going on. To them it's just a ritual to get in the Masons and do a bit of good

business. In the far more extreme rituals of Satanism human possession is even more powerful and they are designed to make possession possible. The hierarchy of the Cult is dictated by the power and perceived status of the possessing Archon. In this way the Archon hierarchy becomes the Cult hierarchy. Once the entity has attached it can influence perception and behaviour and if it attaches to the extreme then so much of its energy (information) infuses into the body information field that the hologram starts to reflect the nature of the possessing entity. This is the *Exorcist* movie type of possession when facial features change and it's known as shapeshifting. Islam's Jinn are said to be invisible tricksters who change shape, 'whisper', confuse and take human form. These are all traits of the Archons and other versions of the same phenomenon. Extreme possession could certainty infuse the 'spirit of darkness' into a partner during sex as the Nag Hammadi texts appear to describe. Such an infusion can change genetics which is also energetic information. Human genetics is information and the 'spirit of darkness' is information. Mix one with the other and change must happen. Islam has the concept of a 'Jinn baby' through possession of the mother and by Jinn taking human form. There are many ways that human genetics can be changed and remember that Archons have been aware all along of advanced techniques to do this. What is being done in human society today – and far more – was known about by Archons at the time of the 'fallen ones' and their other versions described in religions and cultures.

Archons and their human-world Cult are obsessed with genetics as we see today and they know this dictates how information is processed into perceived reality during a human life. They needed to produce a human form that would decode the simulation and this is symbolically known as 'Adam and Eve' who left the 'garden' (prime reality) and 'fell' into Matrix reality. The simulation is not a 'physical' construct (there is no 'physical'); it is a source of information. Think Wi-Fi again. The simulation is an energetic field encoded with information and body-brain systems are designed to decode that information encoded in wave or frequency form which

is transmitted to the brain as electrical signals. These are decoded by the brain to construct our sense of reality – an illusory 'physical' world that only exists in the brain or the mind. Virtual reality games mimic this process using the same sensory decoding system. Information is fed to the senses to decode a virtual reality that can appear so real, but isn't (Figs 18 and 19). Some scientists believe – and I agree with them – that what we perceive as 'physical' reality only exists when we are looking or observing. The act of perception or focus triggers the decoding systems which turn waveform information into holographic reality. When we are not observing something our reality reverts from a holographic state to a waveform state. This relates to the same principle as a falling tree not making a noise unless someone is there to hear it or decode it. The concept makes sense from the simulation perspective. A computer is not decoding all the information in a Wi-Fi field all the time and only decodes or brings into reality on the screen that part of Wi-Fi that it's decoding – focusing upon – at that moment.



Figure 18: Virtual reality technology 'hacks' into the body's five-sense decoding system.



Figure 19: The result can be experienced as very 'real'.

Interestingly, Professor Donald Hoffman at the Department of Cognitive Sciences at the University of California, Irvine, says that our experienced reality is like a computer interface that shows us only the level with which we interact while hiding all that exists beyond it: 'Evolution shaped us with a user interface that hides the truth. Nothing that we see is the truth – the very language of space and time and objects is the wrong language to describe reality.' He is correct in what he says on so many levels. Space and time are not a universal reality. They are a phenomenon of decoded *simulation* reality as part of the process of enslaving our sense of reality. Near-death experiencers report again and again how space and time did not exist as we perceive them once they were free of the body – body decoding systems. You can appreciate from this why Archons and their Cult are so desperate to entrap human attention in the five senses where we are in the Matrix and of the Matrix. Opening your mind to expanded states of awareness takes you beyond the information confines of the simulation and you become aware of knowledge and insights denied to you before. This is what we call 'awakening' – *awakening from the Matrix* – and in the final chapter I will relate this to current events.

Where are the 'aliens'?

A simulation would explain the so-called 'Fermi Paradox' named after Italian physicist Enrico Fermi (1901-1954) who created the first nuclear reactor. He considered the question of why there is such a lack of extraterrestrial activity when there are so many stars and planets in an apparently vast universe; but what if the night sky that we see, or think we do, is a simulated projection as I say? If you control the simulation and your aim is to hold humanity fast in essential ignorance would you want other forms of life including advanced life coming and going sharing information with humanity? Or would you want them to believe they were isolated and apparently alone? Themes of human isolation and apartness are common whether they be the perception of a lifeless universe or the fascist isolation laws of the 'Covid' era. Paradoxically the very

existence of a simulation means that we are not alone when some force had to construct it. My view is that experiences that people have reported all over the world for centuries with Reptilians and Grey entities are Archon phenomena as Nag Hammadi texts describe; and that benevolent 'alien' interactions are non-human groups that come in and out of the simulation by overcoming Archon attempts to keep them out. It should be highlighted, too, that Reptilians and Greys are obsessed with *genetics* and *technology* as related by cultural accounts and those who say they have been abducted by them. Technology is their way of overcoming some of the limitations in their creative potential and our technology-driven and controlled human society of today is *arch*etypical Archon-Reptilian-Grey modus operandi. Technocracy is really *Archon*tocracy. The Universe does not have to be as big as it appears with a simulation. There is no space or distance only information decoded into holographic reality. What we call 'space' is only the absence of holographic 'objects' and that 'space' is The Field of energetic information which connects everything into a single whole. The same applies with the artificially-generated information field of the simulation. The Universe is not big or small as a physical reality. It is decoded information, that's all, and its perceived size is decided by the way the simulation is encoded to make it appear. The entire night sky as we perceive it only exists in our brain and so where are those 'millions of light years'? The 'stars' on the ceiling of the Planetarium looked a vast distance away.

There's another point to mention about 'aliens'. I have been highlighting since the 1990s the plan to stage a fake 'alien invasion' to justify the centralisation of global power and a world military. Nazi scientist Werner von Braun, who was taken to America by Operation Paperclip after World War Two to help found NASA, told his American assistant Dr Carol Rosin about the Cult agenda when he knew he was dying in 1977. Rosin said that he told her about a sequence that would lead to total human control by a one-world government. This included threats from terrorism, rogue nations, meteors and asteroids before finally an 'alien invasion'. All of these

things, von Braun said, would be bogus and what I would refer to as a No-Problem-Reaction-Solution. Keep this in mind when 'the aliens are coming' is the new mantra. The aliens are not coming – they are *already here* and they have infiltrated human society while looking human. French-Canadian investigative journalist Serge Monast said in 1994 that he had uncovered a NASA/military operation called Project Blue Beam which fits with what Werner von Braun predicted. Monast died of a 'heart attack' in 1996 the day after he was arrested and spent a night in prison. He was 51. He said Blue Beam was a plan to stage an alien invasion that would include religious figures beamed holographically into the sky as part of a global manipulation to usher in a 'new age' of worshipping what I would say is the Cult 'god' Yaldabaoth in a one-world religion. Fake holographic asteroids are also said to be part of the plan which again syncs with von Braun. How could you stage an illusory threat from asteroids unless they were holographic inserts? This is pretty straightforward given the advanced technology outside the public arena and the fact that our 'physical' reality is holographic anyway. Information fields would be projected and we would decode them into the illusion of a 'physical' asteroid. If they can sell a global 'pandemic' with a 'virus' that doesn't exist what will humans not believe if government and media tell them?

All this is particularly relevant as I write with the Pentagon planning to release in June, 2021, information about 'UFO sightings'. I have been following the UFO story since the early 1990s and the common theme throughout has been government and military denials and cover up. More recently, however, the Pentagon has suddenly become more talkative and apparently open with Air Force pilot radar images released of unexplained craft moving and changing direction at speeds well beyond anything believed possible with human technology. Then, in March, 2021, former Director of National Intelligence John Ratcliffe said a Pentagon report months later in June would reveal a great deal of information about UFO sightings unknown to the public. He said the report would have 'massive implications'. The order to do this was included bizarrely

in a $2.3 trillion 'coronavirus' relief and government funding bill passed by the Trump administration at the end of 2020. I would add some serious notes of caution here. I have been pointing out since the 1990s that the US military and intelligence networks have long had craft – 'flying saucers' or anti-gravity craft – which any observer would take to be extraterrestrial in origin. Keeping this knowledge from the public allows craft flown by *humans* to be perceived as alien visitations. I am not saying that 'aliens' do not exist. I would be the last one to say that, but we have to be streetwise here. President Ronald Reagan told the UN General Assembly in 1987: 'I occasionally think how quickly our differences worldwide would vanish if we were facing an alien threat from outside this world.' That's the idea. Unite against a common 'enemy' with a common purpose behind your 'saviour force' (the Cult) as this age-old technique of mass manipulation goes global.

Science moves this way …

I could find only one other person who was discussing the simulation hypothesis publicly when I concluded it was real. This was Nick Bostrom, a Swedish-born philosopher at the University of Oxford, who has explored for many years the possibility that human reality is a computer simulation although his version and mine are not the same. Today the simulation and holographic reality hypothesis have increasingly entered the scientific mainstream. Well, the more open-minded mainstream, that is. Here are a few of the ever-gathering examples. American nuclear physicist Silas Beane led a team of physicists at the University of Bonn in Germany pursuing the question of whether we live in a simulation. They concluded that we probably do and it was likely based on a lattice of cubes. They found that cosmic rays align with that specific pattern. The team highlighted the Greisen–Zatsepin–Kuzmin (GZK) limit which refers to cosmic ray particle interaction with cosmic background radiation that creates an apparent boundary for cosmic ray particles. They say in a paper entitled 'Constraints on the Universe as a Numerical Simulation' that this 'pattern of constraint' is exactly what you

would find with a computer simulation. They also made the point that a simulation would create its own 'laws of physics' that would limit possibility. I've been making the same point for decades that the *perceived* laws of physics relate only to this reality, or what I would later call the simulation. When designers write codes to create computer and virtual reality games they are the equivalent of the laws of physics for that game. Players interact within the limitations laid out by the coding. In the same way those who wrote the codes for the simulation decided the laws of physics that would apply. These can be overridden by expanded states of consciousness, but not by those enslaved in only five-sense awareness where simulation codes rule. Overriding the codes is what people call 'miracles'. They are not. They are bypassing the encoded limits of the simulation. A population caught in simulation perception would have no idea that this was their plight. As the Bonn paper said: 'Like a prisoner in a pitch-black cell we would not be able to see the "walls" of our prison,' That's true if people remain mesmerised by the five senses. Open to expanded awareness and those walls become very clear. The main one is the speed of light.

American theoretical physicist James Gates is another who has explored the simulation question and found considerable evidence to support the idea. Gates was Professor of Physics at the University of Maryland, Director of The Center for String and Particle Theory, and on Barack Obama's Council of Advisors on Science and Technology. He and his team found *computer codes* of digital data embedded in the fabric of our reality. They relate to on-off electrical charges of 1 and 0 in the binary system used by computers. 'We have no idea what they are doing there', Gates said. They found within the energetic fabric mathematical sequences known as error-correcting codes or block codes that 'reboot' data to its original state or 'default settings' when something knocks it out of sync. Gates was asked if he had found a set of equations embedded in our reality indistinguishable from those that drive search engines and browsers and he said: 'That is correct.' Rich Terrile, director of the Centre for Evolutionary Computation and Automated Design at NASA's Jet

Propulsion Laboratory, has said publicly that he believes the Universe is a digital hologram that must have been created by a form of intelligence. I agree with that in every way. Waveform information is delivered electrically by the senses to the brain which constructs a *digital* holographic reality that we call the 'world'. This digital level of reality can be read by the esoteric art of numerology. Digital holograms are at the cutting edge of holographics today. We have digital technology everywhere designed to access and manipulate our digital level of perceived reality. Synthetic mRNA in 'Covid vaccines' has a digital component to manipulate the body's digital 'operating system'.

Reality is numbers

How many know that our reality can be broken down to numbers and codes that are the same as computer games? Max Tegmark, a physicist at the Massachusetts Institute of Technology (MIT), is the author of *Our Mathematical Universe* in which he lays out how reality can be entirely described by numbers and maths in the way that a video game is encoded with the 'physics' of computer games. Our world and computer virtual reality are essentially the same. Tegmark imagines the perceptions of characters in an advanced computer game when the graphics are so good they don't know they are in a game. They think they can bump into real objects (electromagnetic resistance in our reality), fall in love and feel emotions like excitement. When they began to study the apparently 'physical world' of the video game they would realise that everything was made of pixels (which have been found in our energetic reality as must be the case when on one level our world is digital). What computer game characters thought was physical 'stuff', Tegmark said, could actually be broken down into numbers:

> And we're exactly in this situation in our world. We look around and it doesn't seem that mathematical at all, but everything we see is made out of elementary particles like quarks and electrons. And what properties does an electron have? Does it have a smell or a colour or a texture? No! ... We physicists have come up with geeky names for [Electron] properties, like

electric charge, or spin, or lepton number, but the electron doesn't care what we call it, the properties are just numbers.

This is the illusory reality Gnostics were describing. This is the simulation. The A, C, G, and T codes of DNA have a binary value – A and C = 0 while G and T = 1. This has to be when the simulation is digital and the body must be digital to interact with it. Recurring mathematical sequences are encoded throughout reality and the body. They include the Fibonacci sequence in which the two previous numbers are added to get the next one, as in ... 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, etc. The sequence is encoded in the human face and body, proportions of animals, DNA, seed heads, pine cones, trees, shells, spiral galaxies, hurricanes and the number of petals in a flower. The list goes on and on. There are fractal patterns – a 'never-ending pattern that is infinitely complex and self-similar across all scales in the as above, so below, principle of holograms. These and other famous recurring geometrical and mathematical sequences such as Phi, Pi, Golden Mean, Golden Ratio and Golden Section are *computer codes* of the simulation. I had to laugh and give my head a shake the day I finished this book and it went into the production stage. I was sent an article in *Scientific American* published in April, 2021, with the headline 'Confirmed! We Live in a Simulation'. Two decades after I first said our reality is a simulation and the speed of light is it's outer limit the article suggested that we do live in a simulation and that the speed of light is its outer limit. I left school at 15 and never passed a major exam in my life while the writer was up to his eyes in qualifications. As I will explain in the final chapter *knowing* is far better than thinking and they come from very different sources. The article rightly connected the speed of light to the processing speed of the 'Matrix' and said what has been in my books all this time … 'If we are in a simulation, as it appears, then space is an abstract property written in code. It is not real'. No it's not and if we live in a simulation something created it and it wasn't *us*. 'That David Icke says we are manipulated by aliens' – he's crackers.'

Wow …

The reality that humanity thinks is so real is an illusion. Politicians, governments, scientists, doctors, academics, law enforcement, media, school and university curriculums, on and on, are all founded on a world that *does not exist* except as a simulated prison cell. Is it such a stretch to accept that 'Covid' doesn't exist when our entire 'physical' reality doesn't exist? Revealed here is the knowledge kept under raps in the Cult networks of compartmentalised secrecy to control humanity's sense of reality by inducing the population to believe in a reality that's not real. If it wasn't so tragic in its experiential consequences the whole thing would be hysterically funny. None of this is new to Renegade Minds. Ancient Greek philosopher Plato (about 428 to about 347BC) was a major influence on Gnostic belief and he described the human plight thousands of years ago with his Allegory of the Cave. He told the symbolic story of prisoners living in a cave who had never been outside. They were chained and could only see one wall of the cave while behind them was a fire that they could not see. Figures walked past the fire casting shadows on the prisoners' wall and those moving shadows became their sense of reality. Some prisoners began to study the shadows and were considered experts on them (today's academics and scientists), but what they studied was only an illusion (today's academics and scientists). A prisoner escaped from the cave and saw reality as it really is. When he returned to report this revelation they didn't believe him, called him mad and threatened to kill him if he tried to set them free. Plato's tale is not only a brilliant analogy of the human plight and our illusory reality. It describes, too, the dynamics of the 'Covid' hoax. I have only skimmed the surface of these subjects here. The aim of this book is to crisply connect all essential dots to put what is happening today into its true context. All subject areas and their connections in this chapter are covered in great evidential detail in *Everything You Need To Know, But Have Never Been Told* and *The Answer*.

They say that bewildered people 'can't see the forest for the trees'. Humanity, however, can't see the forest for the *twigs*. The five senses

see only twigs while Renegade Minds can see the forest and it's the forest where the answers lie with the connections that reveals. Breaking free of perceptual programming so the forest can be seen is the way we turn all this around. Not breaking free is how humanity got into this mess. The situation may seem hopeless, but I promise you it's not. We are a perceptual heartbeat from paradise if only we knew.

CHAPTER TWELVE

Escaping Wetiko

Life is simply a vacation from the infinite
Dean Cavanagh

Renegade Minds weave the web of life and events and see common themes in the apparently random. They are always there if you look for them and their pursuit is aided by incredible synchronicity that comes when your mind is open rather than mesmerised by what it thinks it can see.

Infinite awareness is infinite possibility and the more of infinite possibility that we access the more becomes infinitely possible. That may be stating the apparently obvious, but it is a devastatingly-powerful fact that can set us free. We are a point of attention within an infinity of consciousness. The question is how much of that infinity do we choose to access? How much knowledge, insight, awareness, wisdom, do we want to connect with and explore? If your focus is only in the five senses you will be influenced by a fraction of infinite awareness. I mean a range so tiny that it gives new meaning to infinitesimal. Limitation of self-identity and a sense of the possible limit accordingly your range of consciousness. We are what we think we are. Life is what we think it is. The dream is the dreamer and the dreamer is the dream. Buddhist philosophy puts it this way: 'As a thing is viewed, so it appears.' Most humans live in the realm of touch, taste, see, hear, and smell and that's the limit of their sense of the possible and sense of self. Many will follow a religion and speak of a God in his heaven, but their lives are still

dominated by the five senses in their perceptions and actions. The five senses become the arbiter of everything. When that happens all except a smear of infinity is sealed away from influence by the rigid, unyielding, reality bubbles that are the five-sense human or Phantom Self. Archon Cult methodology is to isolate consciousness within five-sense reality – the simulation – and then program that consciousness with a sense of self and the world through a deluge of life-long information designed to instil the desired perception that allows global control. Efforts to do this have increased dramatically with identity politics as identity bubbles are squeezed into the minutiae of five-sense detail which disconnect people even more profoundly from the infinite 'I'.

Five-sense focus and self-identity are like a firewall that limits access to the infinite realms. You only perceive one radio or television station and no other. We'll take that literally for a moment. Imagine a vast array of stations giving different information and angles on reality, but you only ever listen to one. Here we have the human plight in which the population is overwhelmingly confined to CultFM. This relates only to the frequency range of CultFM and limits perception and insight to that band – limits *possibility* to that band. It means you are connecting with an almost imperceptibly minuscule range of possibility and creative potential within the infinite Field. It's a world where everything seems apart from everything else and where synchronicity is rare. Synchronicity is defined in the dictionary as 'the happening by chance of two or more related or similar events at the same time'. Use of 'by chance' betrays a complete misunderstanding of reality. Synchronicity is not 'by chance'. As people open their minds, or 'awaken' to use the term, they notice more and more coincidences in their lives, bits of 'luck', apparently miraculous happenings that put them in the right place at the right time with the right people. Days become peppered with 'fancy meeting you here' and 'what are the chances of that?' My entire life has been lived like this and ever more so since my own colossal awakening in 1990 and 91 which transformed my sense of reality. Synchronicity is not 'by chance'; it is by accessing expanded

realms of possibility which allow expanded potential for manifestation. People broadcasting the same vibe from the same openness of mind tend to be drawn 'by chance' to each other through what I call frequency magnetism and it's not only people. In the last more than 30 years incredible synchronicity has also led me through the Cult maze to information in so many forms and to crucial personal experiences. These 'coincidences' have allowed me to put the puzzle pieces together across an enormous array of subjects and situations. Those who have breached the bubble of five-sense reality will know exactly what I mean and this escape from the perceptual prison cell is open to everyone whenever they make that choice. This may appear super-human when compared with the limitations of 'human', but it's really our natural state. 'Human' as currently experienced is consciousness in an unnatural state of induced separation from the infinity of the whole. I'll come to how this transformation into unity can be made when I have described in more detail the force that holds humanity in servitude by denying this access to infinite self.

The Wetiko factor

I have been talking and writing for decades about the way five-sense mind is systematically barricaded from expanded awareness. I have used the analogy of a computer (five-sense mind) and someone at the keyboard (expanded awareness). Interaction between the computer and the operator is symbolic of the interaction between five-sense mind and expanded awareness. The computer directly experiences the Internet and the operator experiences the Internet via the computer which is how it's supposed to be – the two working as one. Archons seek to control that point where the operator connects with the computer to stop that interaction (Fig 20). Now the operator is banging the keyboard and clicking the mouse, but the computer is not responding and this happens when the computer is taken over – *possessed* – by an appropriately-named computer 'virus'. The operator has lost all influence over the computer which goes its own way making decisions under the control of the 'virus'. I have

just described the dynamic through which the force known to Gnostics as Yaldabaoth and Archons disconnects five-sense mind from expanded awareness to imprison humanity in perceptual servitude.



Figure 20: The mind 'virus' I have been writing about for decades seeks to isolate five-sense mind (the computer) from the true 'I'. (Image by Neil Hague).

About a year ago I came across a Native American concept of Wetiko which describes precisely the same phenomenon. Wetiko is the spelling used by the Cree and there are other versions including wintiko and windigo used by other tribal groups. They spell the name with lower case, but I see Wetiko as a proper noun as with Archons and prefer a capital. I first saw an article about Wetiko by writer and researcher Paul Levy which so synced with what I had been writing about the computer/operator disconnection and later the Archons. I then read his book, the fascinating *Dispelling Wetiko, Breaking the Spell of Evil*. The parallels between what I had concluded long before and the Native American concept of Wetiko were so clear and obvious that it was almost funny. For Wetiko see the Gnostic Archons for sure and the Jinn, the Predators, and every other name for a force of evil, inversion and chaos. Wetiko is the Native American name for the force that divides the computer from

the operator (Fig 21). Indigenous author Jack D. Forbes, a founder of the Native American movement in the 1960s, wrote another book about Wetiko entitled *Columbus And Other Cannibals – The Wetiko Disease of Exploitation, Imperialism, and Terrorism* which I also read. Forbes says that Wetiko refers to an evil person or spirit 'who terrorizes other creatures by means of terrible acts, including cannibalism'. Zulu shaman Credo Mutwa told me that African accounts tell how cannibalism was brought into the world by the Chitauri 'gods' – another manifestation of Wetiko. The distinction between 'evil person or spirit' relates to Archons/Wetiko possessing a human or acting as pure consciousness. Wetiko is said to be a sickness of the soul or spirit and a state of being that takes but gives nothing back – the Cult and its operatives perfectly described. Black Hawk, a Native American war leader defending their lands from confiscation, said European invaders had 'poisoned hearts' – Wetiko hearts – and that this would spread to native societies. Mention of the heart is very significant as we shall shortly see. Forbes writes: 'Tragically, the history of the world for the past 2,000 years is, in great part, the story of the epidemiology of the wetiko disease.' Yes, and much longer. Forbes is correct when he says: 'The wetikos destroyed Egypt and Babylon and Athens and Rome and Tenochtitlan [capital of the Aztec empire] and perhaps now they will destroy the entire earth.' Evil, he said, is the number one export of a Wetiko culture – see its globalisation with 'Covid'. Constant war, mass murder, suffering of all kinds, child abuse, Satanism, torture and human sacrifice are all expressions of Wetiko and the Wetiko possessed. The world is Wetiko made manifest, *but it doesn't have to be*. There is a way out of this even now.



Figure 21: The mind 'virus' is known to Native Americans as 'Wetiko'. (Image by Neil Hague).

Cult of Wetiko

Wetiko is the Yaldabaoth frequency distortion that seeks to attach to human consciousness and absorb it into its own. Once this connection is made Wetiko can drive the perceptions of the target which they believe to be coming from their own mind. All the horrors of history and today from mass killers to Satanists, paedophiles like Jeffrey Epstein and other psychopaths, are the embodiment of Wetiko and express its state of being in all its grotesqueness. The Cult is Wetiko incarnate, Yaldabaoth incarnate, and it seeks to facilitate Wetiko assimilation of humanity in totality into its distortion by manipulating the population into low frequency states that match its own. Paul Levy writes: 'Holographically enforced within the psyche of every human being the wetiko virus pervades and underlies the entire field of consciousness, and can therefore potentially manifest through any one of us at any moment if we are not mindful.' The 'Covid' hoax has achieved this with many people, but others have not fallen into Wetiko's frequency lair. Players in the 'Covid' human catastrophe including Gates, Schwab, Tedros, Fauci, Whitty, Vallance, Johnson, Hancock, Ferguson, Drosten, and all the rest, including the psychopath psychologists, are expressions of Wetiko. This is why

they have no compassion or empathy and no emotional consequence for what they do that would make them stop doing it. Observe all the people who support the psychopaths in authority against the Pushbackers despite the damaging impact the psychopaths have on their own lives and their family's lives. You are again looking at Wetiko possession which prevents them seeing through the lies to the obvious scam going on. *Why can't they see it?* Wetiko won't let them see it. The perceptual divide that has now become a chasm is between the Wetikoed and the non-Wetikoed.

Paul Levy describes Wetiko in the same way that I have long described the Archontic force. They are the same distorted consciousness operating across dimensions of reality: '… the subtle body of wetiko is not located in the third dimension of space and time, literally existing in another dimension … it is able to affect ordinary lives by mysteriously interpenetrating into our three-dimensional world.' Wetiko does this through its incarnate representatives in the Cult and by weaving itself into The Field which on our level of reality is the electromagnetic information field of the simulation or Matrix. More than that, the simulation *is* Wetiko / Yaldabaoth. Caleb Scharf, Director of Astrobiology at Columbia University, has speculated that 'alien life' could be so advanced that it has transcribed itself into the quantum realm to become what we call physics. He said intelligence indistinguishable from the fabric of the Universe would solve many of its greatest mysteries:

> Perhaps hyper-advanced life isn't just external. Perhaps it's already all around. It is embedded in what we perceive to be physics itself, from the root behaviour of particles and fields to the phenomena of complexity and emergence ... In other words, life might not just be in the equations. It might BE the equations [My emphasis].

Scharf said it is possible that 'we don't recognise advanced life because it forms an integral and unsuspicious part of what we've considered to be the natural world'. I agree. Wetiko/Yaldabaoth *is* the simulation. We are literally in the body of the beast. But that doesn't mean it has to control us. We all have the power to overcome Wetiko

influence and the Cult knows that. I doubt it sleeps too well because it knows that.

Which Field?

This, I suggest, is how it all works. There are two Fields. One is the fierce electromagnetic light of the Matrix within the speed of light; the other is the 'watery light' of The Field beyond the walls of the Matrix that connects with the Great Infinity. Five-sense mind and the decoding systems of the body attach us to the Field of Matrix light. They have to or we could not experience this reality. Five-sense mind sees only the Matrix Field of information while our expanded consciousness is part of the Infinity Field. When we open our minds, and most importantly our hearts, to the Infinity Field we have a mission control which gives us an expanded perspective, a road map, to understand the nature of the five-sense world. If we are isolated only in five-sense mind there is no mission control. We're on our own trying to understand a world that's constantly feeding us information to ensure we do not understand. People in this state can feel 'lost' and bewildered with no direction or radar. You can see ever more clearly those who are influenced by the Fields of Big Infinity or little five-sense mind simply by their views and behaviour with regard to the 'Covid' hoax. We have had this division throughout known human history with the mass of the people on one side and individuals who could see and intuit beyond the walls of the simulation – Plato's prisoner who broke out of the cave and saw reality for what it is. Such people have always been targeted by Wetiko/Archon-possessed authority, burned at the stake or demonised as mad, bad and dangerous. The Cult today and its global network of 'anti-hate', 'anti-fascist' Woke groups are all expressions of Wetiko attacking those exposing the conspiracy, 'Covid' lies and the 'vaccine' agenda.

Woke as a whole is Wetiko which explains its black and white mentality and how at one it is with the Wetiko-possessed Cult. Paul Levy said: 'To be in this paradigm is to still be under the thrall of a two-valued logic – where things are either true or false – of a

wetikoized mind.' Wetiko consciousness is in a permanent rage, therefore so is Woke, and then there is Woke inversion and contradiction. 'Anti-fascists' act like fascists because fascists *and* 'anti-fascists' are both Wetiko at work. Political parties act the same while claiming to be different for the same reason. Secret society and satanic rituals are attaching initiates to Wetiko and the cold, ruthless, psychopathic mentality that secures the positions of power all over the world is Wetiko. Reframing 'training programmes' have the same cumulative effect of attaching Wetiko and we have their graduates described as automatons and robots with a cold, psychopathic, uncaring demeanour. They are all traits of Wetiko possession and look how many times they have been described in this book and elsewhere with regard to personnel behind 'Covid' including the police and medical profession. Climbing the greasy pole in any profession in a Wetiko society requires traits of Wetiko to get there and that is particularly true of politics which is not about fair competition and pre-eminence of ideas. It is founded on how many backs you can stab and arses you can lick. This culminated in the global 'Covid' coordination between the Wetiko possessed who pulled it off in all the different countries without a trace of empathy and compassion for their impact on humans. Our sight sense can see only holographic form and not the Field which connects holographic form. Therefore we perceive 'physical' objects with 'space' in between. In fact that 'space' is energy/consciousness operating on multiple frequencies. One of them is Wetiko and that connects the Cult psychopaths, those who submit to the psychopaths, and those who serve the psychopaths in the media operations of the world. Wetiko is Gates. Wetiko is the mask-wearing submissive. Wetiko is the fake journalist and 'fact-checker'. The Wetiko Field is coordinating the whole thing. Psychopaths, gofers, media operatives, 'anti-hate' hate groups, 'fact-checkers' and submissive people work as one unit *even without human coordination* because they are attached to the *same* Field which is organising it all (Fig 22). Paul Levy is here describing how Wetiko-possessed people are drawn together and refuse to let any information breach their rigid

perceptions. He was writing long before 'Covid', but I think you will recognise followers of the 'Covid' religion *oh just a little bit*:

People who are channelling the vibratory frequency of wetiko align with each other through psychic resonance to reinforce their unspoken shared agreement so as to uphold their deranged view of reality. Once an unconscious content takes possession of certain individuals, it irresistibly draws them together by mutual attraction and knits them into groups tied together by their shared madness that can easily swell into an avalanche of insanity.

A psychic epidemic is a closed system, which is to say that it is insular and not open to any new information or informing influences from the outside world which contradict its fixed, limited, and limiting perspective.

There we have the Woke mind and the 'Covid' mind. Compatible resonance draws the awakening together, too, which is clearly happening today.



Figure 22: The Wetiko Field from which the Cult pyramid and its personnel are made manifest. (Image by Neil Hague).

Spiritual servitude

Wetiko doesn't care about humans. It's not human; it just possesses humans for its own ends and the effect (depending on the scale of

possession) can be anything from extreme psychopathy to unquestioning obedience. Wetiko's worst nightmare is for human consciousness to expand beyond the simulation. Everything is focussed on stopping that happening through control of information, thus perception, thus frequency. The 'education system', media, science, medicine, academia, are all geared to maintaining humanity in five-sense servitude as is the constant stimulation of low-vibrational mental and emotional states (see 'Covid'). Wetiko seeks to dominate those subconscious spaces between five-sense perception and expanded consciousness where the computer meets the operator. From these subconscious hiding places Wetiko speaks to us to trigger urges and desires that we take to be our own and manipulate us into anything from low-vibrational to psychopathic states. Remember how Islam describes the Jinn as invisible tricksters that 'whisper' and confuse. Wetiko is the origin of the 'trickster god' theme that you find in cultures all over the world. Jinn, like the Archons, are Wetiko which is terrified of humans awakening and reconnecting with our true self for then its energy source has gone. With that the feedback loop breaks between Wetiko and human perception that provides the energetic momentum on which its very existence depends as a force of evil. Humans are both its target and its source of survival, but only if we are operating in low-vibrational states of fear, hate, depression and the background anxiety that most people suffer. We are Wetiko's target because we are its key to survival. It needs us, not the other way round. Paul Levy writes:

A vampire has no intrinsic, independent, substantial existence in its own right; it only exists in relation to us. The pathogenic, vampiric mind-parasite called wetiko is nothing in itself – not being able to exist from its own side – yet it has a 'virtual reality' such that it can potentially destroy our species …

…The fact that a vampire is not reflected by a mirror can also mean that what we need to see is that there's nothing, no-thing to see, other than ourselves. The fact that wetiko is the expression of something inside of us means that the cure for wetiko is with us as well. The critical issue is finding this cure within us and then putting it into effect.

Evil begets evil because if evil does not constantly expand and find new sources of energetic sustenance its evil, its *distortion*, dies with the assimilation into balance and harmony. Love is the garlic to Wetiko's vampire. Evil, the absence of love, cannot exist in the presence of love. I think I see a way out of here. I have emphasised so many times over the decades that the Archons/Wetiko and their Cult are not all powerful. *They are not*. I don't care how it looks even now *they are not*. I have not called them little boys in short trousers for effect. I have said it because it is true. Wetiko's insatiable desire for power over others is not a sign of its omnipotence, but its insecurity. Paul Levy writes: 'Due to the primal fear which ultimately drives it and which it is driven to cultivate, wetiko's body politic has an intrinsic and insistent need for centralising power and control so as to create imagined safety for itself.' *Yeeeeeees!* Exactly! Why does Wetiko want humans in an ongoing state of fear? Wetiko itself *is* fear and it is petrified of love. As evil is an absence of love, so love is an absence of fear. Love conquers all and *especially* Wetiko which *is* fear. Wetiko brought fear into the world when it wasn't here before. *Fear* was the 'fall', the fall into low-frequency ignorance and illusion – fear is **F**alse **E**motion **A**ppearing **R**eal. The simulation is driven and energised by fear because Wetiko/Yaldabaoth (fear) *are* the simulation. Fear is the absence of love and Wetiko is the absence of love.

Wetiko today

We can now view current events from this level of perspective. The 'Covid' hoax has generated momentous amounts of ongoing fear, anxiety, depression and despair which have empowered Wetiko. No wonder people like Gates have been the instigators when they are Wetiko incarnate and exhibit every trait of Wetiko in the extreme. See how cold and unemotional these people are like Gates and his cronies, how dead of eye they are. That's Wetiko. Sabbatians are Wetiko and everything they control including the World Health Organization, Big Pharma and the 'vaccine' makers, national 'health'

hierarchies, corporate media, Silicon Valley, the banking system, and the United Nations with its planned transformation into world government. All are controlled and possessed by the Wetiko distortion into distorting human society in its image. We are with this knowledge at the gateway to understanding the world. Divisions of race, culture, creed and sexuality are diversions to hide the real division between those possessed and influenced by Wetiko and those that are not. The 'Covid' hoax has brought both clearly into view. Human behaviour is not about race. Tyrants and dictatorships come in all colours and creeds. What unites the US president bombing the innocent and an African tribe committing genocide against another as in Rwanda? What unites them? *Wetiko*. All wars are Wetiko, all genocide is Wetiko, all hunger over centuries in a world of plenty is Wetiko. Children going to bed hungry, including in the West, is Wetiko. Cult-generated Woke racial divisions that focus on the body are designed to obscure the reality that divisions in behaviour are manifestations of mind, not body. Obsession with body identity and group judgement is a means to divert attention from the real source of behaviour – mind and perception. Conflict sown by the Woke both within themselves and with their target groups are Wetiko providing lunch for itself through still more agents of the division, chaos, and fear on which it feeds. The Cult is seeking to assimilate the entirety of humanity and all children and young people into the Wetiko frequency by manipulating them into states of fear and despair. Witness all the suicide and psychological unravelling since the spring of 2020. Wetiko psychopaths want to impose a state of unquestioning obedience to authority which is no more than a conduit for Wetiko to enforce its will and assimilate humanity into itself. It needs us to believe that resistance is futile when it fears resistance and even more so the game-changing non-cooperation with its impositions. It can use violent resistance for its benefit. Violent impositions and violent resistance are *both* Wetiko. The Power of Love with its Power of No will sweep Wetiko from our world. Wetiko and its Cult know that. They just don't want us to know.

AI Wetiko

This brings me to AI or artificial intelligence and something else Wetikos don't want us to know. What is AI *really*? I know about computer code algorithms and AI that learns from data input. These, however, are more diversions, the expeditionary force, for the real AI that they want to connect to the human brain as promoted by Silicon Valley Wetikos like Kurzweil. What is this AI? It is the frequency of *Wetiko*, the frequency of the Archons. The connection of AI to the human brain is the connection of the Wetiko frequency to create a Wetiko hive mind and complete the job of assimilation. The hive mind is planned to be controlled from Israel and China which are both 100 percent owned by Wetiko Sabbatians. The assimilation process has been going on minute by minute in the 'smart' era which fused with the 'Covid' era. We are told that social media is scrambling the minds of the young and changing their personality. This is true, but what is social media? Look more deeply at how it works, how it creates divisions and conflict, the hostility and cruelty, the targeting of people until they are destroyed. That's Wetiko. Social media is manipulated to tune people to the Wetiko frequency with all the emotional exploitation tricks employed by platforms like Facebook and its Wetiko front man, Zuckerberg. Facebook's Instagram announced a new platform for children to overcome a legal bar on them using the main site. This is more Wetiko exploitation and manipulation of kids. Amnesty International likened the plan to foxes offering to guard the henhouse and said it was incompatible with human rights. Since when did Wetiko or Zuckerberg (I repeat myself) care about that? Would Brin and Page at Google, Wojcicki at YouTube, Bezos at Amazon and whoever the hell runs Twitter act as they do if they were not channelling Wetiko? Would those who are developing technologies for no other reason than human control? How about those designing and selling technologies to kill people and Big Pharma drug and 'vaccine' producers who know they will end or devastate lives? Quite a thought for these people to consider is that if you are Wetiko in a human life you are Wetiko on the 'other side' unless your frequency

changes and that can only change by a change of perception which becomes a change of behaviour. Where Gates is going does not bear thinking about although perhaps that's exactly where he wants to go. Either way, that's where he's going. His frequency will make it so.

The frequency lair

I have been saying for a long time that a big part of the addiction to smartphones and devices is that a frequency is coming off them that entraps the mind. People spend ages on their phones and sometimes even a minute or so after they put them down they pick them up again and it all repeats. 'Covid' lockdowns will have increased this addiction a million times for obvious reasons. Addictions to alcohol overindulgence and drugs are another way that Wetiko entraps consciousness to attach to its own. Both are symptoms of low-vibrational psychological distress which alcoholism and drug addiction further compound. Do we think it's really a coincidence that access to them is made so easy while potions that can take people into realms beyond the simulation are banned and illegal? I have explored smartphone addiction in other books, the scale is mind-blowing, and that level of addiction does not come without help. Tech companies that make these phones are Wetiko and they will have no qualms about destroying the minds of children. We are seeing again with these companies the Wetiko perceptual combination of psychopathic enforcers and weak and meek unquestioning compliance by the rank and file.

The global Smart Grid is the Wetiko Grid and it is crucial to complete the Cult endgame. The simulation is radiation and we are being deluged with technological radiation on a devastating scale. Wetiko frauds like Elon Musk serve Cult interests while occasionally criticising them to maintain his street-cred. 5G and other forms of Wi-Fi are being directed at the earth from space on a volume and scale that goes on increasing by the day. Elon Musk's (officially) SpaceX Starlink project is in the process of putting tens of thousands of satellites in low orbit to cover every inch of the planet with 5G and other Wi-Fi to create Kurzweil's global 'cloud' to which the

human mind is planned to be attached very soon. SpaceX has approval to operate 12,000 satellites with more than 1,300 launched at the time of writing and applications filed for *30,000* more. Other operators in the Wi-Fi, 5G, low-orbit satellite market include OneWeb (UK), Telesat (Canada), and AST & Science (US). Musk tells us that AI could be the end of humanity and then launches a company called Neuralink to connect the human brain to computers. Musk's (in theory) Tesla company is building electric cars and the driverless vehicles of the smart control grid. As frauds and bullshitters go Elon Musk in my opinion is Major League.

5G and technological radiation in general are destructive to human health, genetics and psychology and increasing the strength of artificial radiation underpins the five-sense perceptual bubbles which are themselves expressions of radiation or electromagnetism. Freedom activist John Whitehead was so right with his 'databit by databit, we are building our own electronic concentration camps'. The Smart Grid and 5G is a means to control the human mind and infuse perceptual information into The Field to influence anyone in sync with its frequency. You can change perception and behaviour en masse if you can manipulate the population into those levels of frequency and this is happening all around us today. The arrogance of Musk and his fellow Cult operatives knows no bounds in the way that we see with Gates. Musk's satellites are so many in number already they are changing the night sky when viewed from Earth. The astronomy community has complained about this and they have seen nothing yet. Some consequences of Musk's Wetiko hubris include: Radiation; visible pollution of the night sky; interference with astronomy and meteorology; ground and water pollution from intensive use of increasingly many spaceports; accumulating space debris; continual deorbiting and burning up of aging satellites, polluting the atmosphere with toxic dust and smoke; and ever-increasing likelihood of collisions. A collective public open letter of complaint to Musk said:

> We are writing to you … because SpaceX is in process of surrounding the Earth with a network of thousands of satellites whose very purpose is to irradiate every square inch of the

Earth. SpaceX, like everyone else, is treating the radiation as if it were not there. As if the mitochondria in our cells do not depend on electrons moving undisturbed from the food we digest to the oxygen we breathe.

As if our nervous systems and our hearts are not subject to radio frequency interference like any piece of electronic equipment. As if the cancer, diabetes, and heart disease that now afflict a majority of the Earth's population are not metabolic diseases that result from interference with our cellular machinery. As if insects everywhere, and the birds and animals that eat them, are not starving to death as a result.

People like Musk and Gates believe in their limitless Wetiko arrogance that they can do whatever they like to the world because they own it. Consequences for humanity are irrelevant. It's absolutely time that we stopped taking this shit from these self-styled masters of the Earth when you consider where this is going.

Why is the Cult so anti-human?

I hear this question often: Why would they do this when it will affect them, too? Ah, but will it? Who is this *them*? Forget their bodies. They are just vehicles for Wetiko consciousness. When you break it all down to the foundations we are looking at a state of severely distorted consciousness targeting another state of consciousness for assimilation. The rest is detail. The simulation is the fly-trap in which unique sensations of the five senses create a cycle of addiction called reincarnation. Renegade Minds see that everything which happens in our reality is a smaller version of the whole picture in line with the holographic principle. Addiction to the radiation of smart technology is a smaller version of addiction to the whole simulation. Connecting the body/brain to AI is taking that addiction on a giant step further to total ongoing control by assimilating human incarnate consciousness into Wetiko. I have watched during the 'Covid' hoax how many are becoming ever more profoundly attached to Wetiko's perceptual calling cards of aggressive response to any other point of view ('There is no other god but me'), psychopathic lack of compassion and empathy, and servile submission to the narrative and will of authority. Wetiko is the psychopaths *and* subservience to psychopaths. The Cult of Wetiko is

so anti-human because it is *not* human. It embarked on a mission to destroy human by targeting everything that it means to be human and to survive as human. 'Covid' is not the end, just a means to an end. The Cult with its Wetiko consciousness is seeking to change Earth systems, including the atmosphere, to suit them, not humans. The gathering bombardment of 5G alone from ground and space is dramatically changing The Field with which the five senses interact. There is so much more to come if we sit on our hands and hope it will all go away. It is not meant to go away. It is meant to get ever more extreme and we need to face that while we still can – just.

Carbon dioxide is the gas of life. Without that human is over. Kaput, gone, history. No natural world, no human. The Cult has created a cock and bull story about carbon dioxide and climate change to justify its reduction to the point where Gates and the ignoramus Biden 'climate chief' John Kerry want to suck it out of the atmosphere. Kerry wants to do this because his master Gates does. Wetikos have made the gas of life a demon with the usual support from the Wokers of Extinction Rebellion and similar organisations and the bewildered puppet-child that is Greta Thunberg who was put on the world stage by Klaus Schwab and the World Economic Forum. The name Extinction Rebellion is both ironic and as always Wetiko inversion. The gas that we need to survive must be reduced to save us from extinction. The most basic need of human is oxygen and we now have billions walking around in face nappies depriving body and brain of this essential requirement of human existence. More than that 5G at 60 gigahertz interacts with the oxygen molecule to reduce the amount of oxygen the body can absorb into the bloodstream. The obvious knock-on consequences of that for respiratory and cognitive problems and life itself need no further explanation. Psychopaths like Musk are assembling a global system of satellites to deluge the human atmosphere with this insanity. The man should be in jail. Here we have two most basic of human needs, oxygen and carbon dioxide, being dismantled.

Two others, water and food, are getting similar treatment with the United Nations Agendas 21 and 2030 – the Great Reset – planning to

centrally control all water and food supplies. People will not even own rain water that falls on their land. Food is affected at the most basic level by reducing carbon dioxide. We have genetic modification or GMO infiltrating the food chain on a mass scale, pesticides and herbicides polluting the air and destroying the soil. Freshwater fish that provide livelihoods for 60 million people and feed hundreds of millions worldwide are being 'pushed to the brink' according the conservationists while climate change is the only focus. Now we have Gates and Schwab wanting to dispense with current food sources all together and replace them with a synthetic version which the Wetiko Cult would control in terms of production and who eats and who doesn't. We have been on the Totalitarian Tiptoe to this for more than 60 years as food has become ever more processed and full of chemical shite to the point today when it's not natural food at all. As Dr Tom Cowan says: 'If it has a label don't eat it.' Bill Gates is now the biggest owner of farmland in the United States and he does nothing without an ulterior motive involving the Cult. Klaus Schwab wrote: 'To feed the world in the next 50 years we will need to produce as much food as was produced in the last 10,000 years … food security will only be achieved, however, if regulations on genetically modified foods are adapted to reflect the reality that gene editing offers a precise, efficient and safe method of improving crops.' Liar. People and the world are being targeted with aluminium through vaccines, chemtrails, food, drink cans, and endless other sources when aluminium has been linked to many health issues including dementia which is increasing year after year. Insects, bees and wildlife essential to the food chain are being deleted by pesticides, herbicides and radiation which 5G is dramatically increasing with 6G and 7G to come. The pollinating bee population is being devastated while wildlife including birds, dolphins and whales are having their natural radar blocked by the effects of ever-increasing radiation. In the summer windscreens used to be splattered with insects so numerous were they. It doesn't happen now. Where have they gone?

Synthetic everything

The Cult is introducing genetically-modified versions of trees, plants and insects including a Gates-funded project to unleash hundreds of millions of genetically-modified, lab-altered and patented male mosquitoes to mate with wild mosquitoes and induce genetic flaws that cause them to die out. Clinically-insane Gates-funded Japanese researchers have developed mosquitos that spread vaccine and are dubbed 'flying vaccinators'. Gates is funding the modification of weather patterns in part to sell the myth that this is caused by carbon dioxide and he's funding geoengineering of the skies to change the atmosphere. Some of this came to light with the Gates-backed plan to release tonnes of chalk into the atmosphere to 'deflect the Sun and cool the planet'. Funny how they do this while the heating effect of the Sun is not factored into climate projections focussed on carbon dioxide. The reason is that they want to reduce carbon dioxide (so don't mention the Sun), but at the same time they do want to reduce the impact of the Sun which is so essential to human life and health. I have mentioned the sun-cholesterol-vitamin D connection as they demonise the Sun with warnings about skin cancer (caused by the chemicals in sun cream they tell you to splash on). They come from the other end of the process with statin drugs to reduce cholesterol that turns sunlight into vitamin D. A lack of vitamin D leads to a long list of health effects and how vitamin D levels must have fallen with people confined to their homes over 'Covid'. Gates is funding other forms of geoengineering and most importantly chemtrails which are dropping heavy metals, aluminium and self-replicating nanotechnology onto the Earth which is killing the natural world. See *Everything You Need To Know, But Have Never Been Told* for the detailed background to this.

Every human system is being targeted for deletion by a force that's not human. The Wetiko Cult has embarked on the process of transforming the human body from biological to synthetic biological as I have explained. Biological is being replaced by the artificial and synthetic – Archontic 'countermimicry' – right across human society. The plan eventually is to dispense with the human body altogether

and absorb human consciousness – which it wouldn't really be by then – into cyberspace (the simulation which is Wetiko/Yaldabaoth). Preparations for that are already happening if people would care to look. The alternative media rightly warns about globalism and 'the globalists', but this is far bigger than that and represents the end of the human race as we know it. The 'bad copy' of prime reality that Gnostics describe was a bad copy of harmony, wonder and beauty to start with before Wetiko/Yaldabaoth set out to change the simulated 'copy' into something very different. The process was slow to start with. Entrapped humans in the simulation timeline were not technologically aware and they had to be brought up to intellectual speed while being suppressed spiritually to the point where they could build their own prison while having no idea they were doing so. We have now reached that stage where technological intellect has the potential to destroy us and that's why events are moving so fast. Central American shaman Don Juan Matus said:

> Think for a moment, and tell me how you would explain the contradictions between the intelligence of man the engineer and the stupidity of his systems of belief, or the stupidity of his contradictory behaviour. Sorcerers believe that the predators have given us our systems of beliefs, our ideas of good and evil; our social mores. They are the ones who set up our dreams of success or failure. They have given us covetousness, greed, and cowardice. It is the predator who makes us complacent, routinary, and egomaniacal.
>
> In order to keep us obedient and meek and weak, the predators engaged themselves in a stupendous manoeuvre – stupendous, of course, from the point of view of a fighting strategist; a horrendous manoeuvre from the point of those who suffer it. They gave us their mind. The predators' mind is baroque, contradictory, morose, filled with the fear of being discovered any minute now.

For 'predators' see Wetiko, Archons, Yaldabaoth, Jinn, and all the other versions of the same phenomenon in cultures and religions all over the world. The theme is always the same because it's true and it's real. We have reached the point where we have to deal with it. The question is – how?

Don't fight – walk away

I thought I'd use a controversial subheading to get things moving in terms of our response to global fascism. What do you mean 'don't fight'? What do you mean 'walk away'? We've got to fight. We can't walk away. Well, it depends what we mean by fight and walk away. If fighting means physical combat we are playing Wetiko's game and falling for its trap. It wants us to get angry, aggressive, and direct hate and hostility at the enemy we think we must fight. Every war, every battle, every conflict, has been fought with Wetiko leading both sides. It's what it does. Wetiko wants a fight, anywhere, any place. Just hit me, son, so I can hit you back. Wetiko hits Wetiko and Wetiko hits Wetiko in return. I am very forthright as you can see in exposing Wetikos of the Cult, but I don't hate them. I refuse to hate them. It's what they want. What you hate you become. What you *fight* you become. Wokers, 'anti-haters' and 'anti-fascists' prove this every time they reach for their keyboards or don their balaclavas. By walk away I mean to disengage from Wetiko which includes ceasing to cooperate with its tyranny. Paul Levy says of Wetiko:

> The way to 'defeat' evil is not to try to destroy it (for then, in playing evil's game, we have already lost), but rather, to find the invulnerable place within ourselves where evil is unable to vanquish us – this is to truly 'win' our battle with evil.

Wetiko is everywhere in human society and it's been on steroids since the 'Covid' hoax. Every shouting match over wearing masks has Wetiko wearing a mask and Wetiko not wearing one. It's an electrical circuit of push and resist, push and resist, with Wetiko pushing *and* resisting. Each polarity is Wetiko empowering itself. Dictionary definitions of 'resist' include 'opposing, refusing to accept or comply with' and the word to focus on is 'opposing'. What form does this take – setting police cars alight or 'refusing to accept or comply with'? The former is Wetiko opposing Wetiko while the other points the way forward. This is the difference between those aggressively demanding that government fascism must be obeyed who stand in stark contrast to the great majority of Pushbackers. We saw this clearly with a march by thousands of Pushbackers against lockdown in London followed days later by a Woker-hijacked

protest in Bristol in which police cars were set on fire. Masks were virtually absent in London and widespread in Bristol. Wetiko wants lockdown on every level of society and infuses its aggression to police it through its unknowing stooges. Lockdown protesters are the ones with the smiling faces and the hugs, The two blatantly obvious states of being – getting more obvious by the day – are the result of Wokers and their like becoming ever more influenced by the simulation Field of Wetiko and Pushbackers ever more influenced by The Field of a far higher vibration beyond the simulation. Wetiko can't invade the heart which is where most lockdown opponents are coming from. It's the heart that allows them to see through the lies to the truth in ways I will be highlighting.

Renegade Minds know that calmness is the place from which wisdom comes. You won't find wisdom in a hissing fit and wisdom is what we need in abundance right now. Calmness is not weakness – you don't have to scream at the top of your voice to be strong. Calmness is indeed a sign of strength. 'No' means I'm not doing it. *NOOOO!!!* doesn't mean you're not doing it even more. Volume does not advance 'No – I'm not doing it'. You are just not doing it. Wetiko possessed and influenced don't know how to deal with that. Wetiko wants a fight and we should not give it one. What it needs more than anything is our *cooperation* and we should not give that either. Mass rallies and marches are great in that they are a visual representation of feeling, but if it ends there they are irrelevant. You demand that Wetikos act differently? Well, they're not going to are they? They are Wetikos. We don't need to waste our time demanding that something doesn't happen when that will make no difference. We need to delete the means that *allows* it to happen. This, invariably, is our cooperation. You can demand a child stop firing a peashooter at the dog or you can refuse to buy the peashooter. If you provide the means you are cooperating with the dog being smacked on the nose with a pea. How can the authorities enforce mask-wearing if millions in a country refuse? What if the 74 million Pushbackers that voted for Trump in 2020 refused to wear masks, close their businesses or stay in their homes. It would be unenforceable. The

few control the many through the compliance of the many and that's always been the dynamic be it 'Covid' regulations or the Roman Empire. I know people can find it intimidating to say no to authority or stand out in a crowd for being the only one with a face on display; but it has to be done or it's over. I hope I've made clear in this book that where this is going will be far more intimidating than standing up now and saying 'No' – I will not cooperate with my own enslavement and that of my children. There might be consequences for some initially, although not so if enough do the same. The question that must be addressed is what is going to happen if we don't? It is time to be strong and unyieldingly so. No means no. Not here and there, but *everywhere* and *always*. I have refused to wear a mask and obey all the other nonsense. I will not comply with tyranny. I repeat: Fascism is not imposed by fascists – there are never enough of them. Fascism is imposed by the population acquiescing to fascism. *I will not do it*. I will die first, or my body will. Living meekly under fascism is a form of death anyway, the death of the spirit that Martin Luther King described.

Making things happen

We must not despair. This is not over till it's over and it's far from that. The 'fat lady' must refuse to sing. The longer the 'Covid' hoax has dragged on and impacted on more lives we have seen an awakening of phenomenal numbers of people worldwide to the realisation that what they have believed all their lives is not how the world really is. Research published by the system-serving University of Bristol and King's College London in February, 2021, concluded: 'One in every 11 people in Britain say they trust David Icke's take on the coronavirus pandemic.' It will be more by now and we have gathering numbers to build on. We must urgently progress from seeing the scam to ceasing to cooperate with it. Prominent German lawyer Reiner Fuellmich, also licenced to practice law in America, is doing a magnificent job taking the legal route to bring the psychopaths to justice through a second Nuremberg tribunal for crimes against humanity. Fuellmich has an impressive record of

beating the elite in court and he formed the German Corona Investigative Committee to pursue civil charges against the main perpetrators with a view to triggering criminal charges. Most importantly he has grasped the foundation of the hoax – the PCR test not testing for the 'virus' – and Christian Drosten is therefore on his charge sheet along with Gates frontman Tedros at the World Health Organization. Major players must be not be allowed to inflict their horrors on the human race without being brought to book. A life sentence must follow for Bill Gates and the rest of them. A group of researchers has also indicted the government of Norway for crimes against humanity with copies sent to the police and the International Criminal Court. The lawsuit cites participation in an internationally-planned false pandemic and violation of international law and human rights, the European Commission's definition of human rights by coercive rules, Nuremberg and Hague rules on fundamental human rights, and the Norwegian constitution. We must take the initiative from hereon and not just complain, protest and react.

There are practical ways to support vital mass non-cooperation. Organising in numbers is one. Lockdown marches in London in the spring in 2021 were mass non-cooperation that the authorities could not stop. There were too many people. Hundreds of thousands walked the London streets in the centre of the road for mile after mile while the Face-Nappies could only look on. They were determined, but calm, and just *did it* with no histrionics and lots of smiles. The police were impotent. Others are organising group shopping without masks for mutual support and imagine if that was happening all over. Policing it would be impossible. If the store refuses to serve people in these circumstances they would be faced with a long line of trolleys full of goods standing on their own and everything would have to be returned to the shelves. How would they cope with that if it kept happening? I am talking here about moving on from complaining to being pro-active; from watching things happen to making things happen. I include in this our relationship with the police. The behaviour of many Face-Nappies

has been disgraceful and anyone who thinks they would never find concentration camp guards in the 'enlightened' modern era have had that myth busted big-time. The period and setting may change – Wetikos never do. I watched film footage from a London march in which a police thug viciously kicked a protestor on the floor who had done nothing. His fellow Face-Nappies stood in a ring protecting him. What he did was a criminal assault and with a crowd far outnumbering the police this can no longer be allowed to happen unchallenged. I get it when people chant 'shame on you' in these circumstances, but that is no longer enough. They *have* no shame those who do this. Crowds needs to start making a citizen's arrest of the police who commit criminal offences and brutally attack innocent people and defenceless women. A citizen's arrest can be made under section 24A of the UK Police and Criminal Evidence (PACE) Act of 1984 and you will find something similar in other countries. I prefer to call it a Common Law arrest rather than citizen's for reasons I will come to shortly. Anyone can arrest a person committing an indictable offence or if they have reasonable grounds to suspect they are committing an indictable offence. On both counts the attack by the police thug would have fallen into this category. A citizen's arrest can be made to stop someone:

- Causing physical injury to himself or any other person
- Suffering physical injury
- Causing loss of or damage to property
- Making off before a constable can assume responsibility for him

A citizen's arrest may also be made to prevent a breach of the peace under Common Law and if they believe a breach of the peace will happen or anything related to harm likely to be done or already done in their presence. This is the way to go I think – the Common Law version. If police know that the crowd and members of the public will no longer be standing and watching while they commit

their thuggery and crimes they will think twice about acting like Brownshirts and Blackshirts.

Common Law – common sense

Mention of Common Law is very important. Most people think the law is the law as in one law. This is not the case. There are two bodies of law, Common Law and Statute Law, and they are not the same. Common Law is founded on the simple premise of do no harm. It does not recognise victimless crimes in which no harm is done while Statute Law does. There is a Statute Law against almost everything. So what is Statute Law? Amazingly it's the law of the *sea* that was brought ashore by the Cult to override the law of the land which is Common Law. They had no right to do this and as always they did it anyway. They had to. They could not impose their will on the people through Common Law which only applies to do no harm. How could you stitch up the fine detail of people's lives with that? Instead they took the law of the sea, or Admiralty Law, and applied it to the population. Statute Law refers to all the laws spewing out of governments and their agencies including all the fascist laws and regulations relating to 'Covid'. The key point to make is that Statute Law is *contract law*. It only applies between *contracting* corporations. Most police officers don't even know this. They have to be kept in the dark, too. Long ago when merchants and their sailing ships began to trade with different countries a contractual law was developed called Admiralty Law and other names. Again it only applied to *contracts* agreed between *corporate* entities. If there is no agreed contract the law of the sea had no jurisdiction *and that still applies to its new alias of Statute Law*. The problem for the Cult when the law of the sea was brought ashore was an obvious one. People were not corporations and neither were government entities. To overcome the latter they made governments and all associated organisations corporations. All the institutions are *private corporations* and I mean governments and their agencies, local councils, police, courts, military, US states, the whole lot. Go to the

Dun and Bradstreet corporate listings website for confirmation that they are all corporations. You are arrested by a private corporation called the police by someone who is really a private security guard and they take you to court which is another private corporation. Neither have jurisdiction over you unless you consent and *contract* with them. This is why you hear the mantra about law enforcement policing by *consent* of the people. In truth the people 'consent' only in theory through monumental trickery.

Okay, the Cult overcame the corporate law problem by making governments and institutions corporate entities; but what about people? They are not corporations are they? Ah ... well in a sense, and *only* a sense, they are. Not people exactly – the illusion of people. The Cult creates a corporation in the name of everyone at the time that their birth certificate is issued. Note birth/ *berth* certificate and when you go to court under the law of the sea on land you stand in a *dock*. These are throwbacks to the origin. My Common Law name is David Vaughan Icke. The name of the corporation created by the government when I was born is called Mr David Vaughan Icke usually written in capitals as MR DAVID VAUGHAN ICKE. That is not me, the living, breathing man. It is a fictitious corporate entity. The trick is to make you think that David Vaughan Icke and MR DAVID VAUGHAN ICKE are the same thing. *They are not*. When police charge you and take you to court they are prosecuting the corporate entity and not the living, breathing, man or woman. They have to trick you into identifying as the corporate entity and contracting with them. Otherwise they have no jurisdiction. They do this through a language known as legalese. Lawful and legal are not the same either. Lawful relates to Common Law and legal relates to Statute Law. Legalese is the language of Statue Law which uses terms that mean one thing to the public and another in legalese. Notice that when a police officer tells someone why they are being charged he or she will say at the end: 'Do you understand?' To the public that means 'Do you comprehend?' In legalese it means 'Do you stand under me?' Do you stand under my authority? If you say

yes to the question you are unknowingly agreeing to give them jurisdiction over you in a contract between two corporate entities.

This is a confidence trick in every way. Contracts have to be agreed between informed parties and if you don't know that David Vaughan Icke is agreeing to be the corporation MR DAVID VAUGHAN ICKE you cannot knowingly agree to contract. They are deceiving you and another way they do this is to ask for proof of identity. You usually show them a driving licence or other document on which your corporate name is written. In doing so you are accepting that you are that corporate entity when you are not. Referring to yourself as a 'person' or 'citizen' is also identifying with your corporate fiction which is why I made the Common Law point about the citizen's arrest. If you are approached by a police officer you identify yourself immediately as a living, breathing, man or woman and say 'I do not consent, I do not contract with you and I do not understand' or stand under their authority. I have a Common Law birth certificate as a living man and these are available at no charge from commonlawcourt.com. Businesses registered under the Statute Law system means that its laws apply. There are, however, ways to run a business under Common Law. Remember all 'Covid' laws and regulations are Statute Law – the law of *contracts* and you do not have to contract. This doesn't mean that you can kill someone and get away with it. Common Law says do no harm and that applies to physical harm, financial harm etc. Police are employees of private corporations and there needs to be a new system of non-corporate Common Law constables operating outside the Statute Law system. If you go to davidicke.com and put Common Law into the search engine you will find videos that explain Common Law in much greater detail. It is definitely a road we should walk.

With all my heart

I have heard people say that we are in a spiritual war. I don't like the term 'war' with its Wetiko dynamic, but I know what they mean. Sweep aside all the bodily forms and we are in a situation in which two states of consciousness are seeking very different realities.

Wetiko wants upheaval, chaos, fear, suffering, conflict and control. The other wants love, peace, harmony, fairness and freedom. That's where we are. We should not fall for the idea that Wetiko is all-powerful and there's nothing we can do. Wetiko is not all-powerful. It's a joke, pathetic. It doesn't have to be, but it has made that choice for now. A handful of times over the years when I have felt the presence of its frequency I have allowed it to attach briefly so I could consciously observe its nature. The experience is not pleasant, the energy is heavy and dark, but the ease with which you can kick it back out the door shows that its real power is in persuading us that it has power. It's all a con. Wetiko is a con. It's a trickster and not a power that can control us if we unleash our own. The con is founded on manipulating humanity to give its power to Wetiko which recycles it back to present the illusion that it has power when its power is *ours* that we gave away. This happens on an energetic level and plays out in the world of the seen as humanity giving its power to Wetiko authority which uses that power to control the population when the power is only the power the population has handed over. How could it be any other way for billions to be controlled by a relative few? I have had experiences with people possessed by Wetiko and again you can kick its arse if you do it with an open heart. Oh yes – the *heart* which can transform the world of perceived 'matter'.

We are receiver-transmitters and processors of information, but what information and where from? Information is processed into perception in three main areas – the brain, the heart and the belly. These relate to thinking, knowing, and emotion. Wetiko wants us to be head and belly people which means we think within the confines of the Matrix simulation and low-vibrational emotional reaction scrambles balance and perception. A few minutes on social media and you see how emotion is the dominant force. Woke is all emotion and is therefore thought-free and fact-free. Our heart is something different. It *knows* while the head *thinks* and has to try to work it out because it doesn't know. The human energy field has seven prime vortexes which connect us with wider reality (Fig 23). Chakra means

'wheels of light' in the Sanskrit language of ancient India. The main ones are: The crown chakra on top of the head; brow (or 'third eye') chakra in the centre of the forehead; throat chakra; heart chakra in the centre of the chest; solar plexus chakra below the sternum; sacral chakra beneath the navel; and base chakra at the bottom of the spine. Each one has a particular function or functions. We feel anxiety and nervousness in the belly where the sacral chakra is located and this processes emotion that can affect the colon to give people 'the shits' or make them 'shit scared' when they are nervous. Chakras all play an important role, but the Mr and Mrs Big is the heart chakra which sits at the centre of the seven, above the chakras that connect us to the 'physical' and below those that connect with higher realms (or at least should). Here in the heart chakra we feel love, empathy and compassion – 'My heart goes out to you'. Those with closed hearts become literally 'heart-less' in their attitudes and behaviour (see Bill Gates). Native Americans portrayed Wetiko with what Paul Levy calls a 'frigid, icy heart, devoid of mercy' (see Bill Gates).



Figure 23: The chakra system which interpenetrates the human energy field. The heart chakra is the governor – or should be.

Wetiko trembles at the thought of heart energy which it cannot infiltrate. The frequency is too high. What it seeks to do instead is close the heart chakra vortex to block its perceptual and energetic influence. Psychopaths have 'hearts of stone' and emotionally-damaged people have 'heartache' and 'broken hearts'. The astonishing amount of heart disease is related to heart chakra

disruption with its fundamental connection to the 'physical' heart. Dr Tom Cowan has written an outstanding book challenging the belief that the heart is a pump and making the connection between the 'physical' and spiritual heart. Rudolph Steiner who was way ahead of his time said the same about the fallacy that the heart is a pump. *What*? The heart is not a pump? That's crazy, right? Everybody knows that. Read Cowan's *Human Heart, Cosmic Heart* and you will realise that the very idea of the heart as a pump is ridiculous when you see the evidence. How does blood in the feet so far from the heart get pumped horizontally up the body by the heart?? Cowan explains in the book the real reason why blood moves as it does. Our 'physical' heart is used to symbolise love when the source is really the heart vortex or spiritual heart which is our most powerful energetic connection to 'out there' expanded consciousness. That's why we feel *knowing* – intuitive knowing – in the centre of the chest. Knowing doesn't come from a process of thoughts leading to a conclusion. It is there in an instant all in one go. Our heart knows because of its connection to levels of awareness that *do* know. This is the meaning and source of intuition – intuitive *knowing*.

For the last more than 30 years of uncovering the global game and the nature of reality my heart has been my constant antenna for truth and accuracy. An American intelligence insider once said that I had quoted a disinformer in one of my books and yet I had only quoted the part that was true. He asked: 'How do you do that?' By using my heart antenna was the answer and anyone can do it. Heart-centred is how we are meant to be. With a closed heart chakra we withdraw into a closed mind and the bubble of five-sense reality. If you take a moment to focus your attention on the centre of your chest, picture a spinning wheel of light and see it opening and expanding. You will feel it happening, too, and perceptions of the heart like joy and love as the heart impacts on the mind as they interact. The more the chakra opens the more you will feel expressions of heart consciousness and as the process continues, and becomes part of you, insights and knowings will follow. An open

heart is connected to that level of awareness that knows all is *One*. You will see from its perspective that the fault-lines that divide us are only illusions to control us. An open heart does not process the illusions of race, creed and sexuality except as brief experiences for a consciousness that is all. Our heart does not see division, only unity (Figs 24 and 25). There's something else, too. Our hearts love to laugh. Mark Twain's quote that says 'The human race has one really effective weapon, and that is laughter' is really a reference to the heart which loves to laugh with the joy of knowing the true nature of infinite reality and that all the madness of human society is an illusion of the mind. Twain also said: 'Against the assault of laughter nothing can stand.' This is so true of Wetiko and the Cult. Their insecurity demands that they be taken seriously and their power and authority acknowledged and feared. We should do nothing of the sort. We should not get aggressive or fearful which their insecurity so desires. We should laugh in their face. Even in their no-face as police come over in their face-nappies and expect to be taken seriously. They don't take themselves seriously looking like that so why should we? Laugh in the face of intimidation. Laugh in the face of tyranny. You will see by its reaction that you have pressed all of its buttons. Wetiko does not know what to do in the face of laughter or when its targets refuse to concede their joy to fear. We have seen many examples during the 'Covid' hoax when people have expressed their energetic power and the string puppets of Wetiko retreat with their tail limp between their knees. Laugh – the world is bloody mad after all and if it's a choice between laughter and tears I know which way I'm going.



Figure 24: Head consciousness without the heart sees division and everything apart from everything else.



Figure 25: Heart consciousness sees everything as One.

'Vaccines' and the soul

The foundation of Wetiko/Archon control of humans is the separation of incarnate five-sense mind from the infinite 'I' and closing the heart chakra where the True 'I' lives during a human life. The goal has been to achieve complete separation in both cases. I was interested therefore to read an account by a French energetic healer of what she said she experienced with a patient who had been given the 'Covid' vaccine. Genuine energy healers can sense information and consciousness fields at different levels of being which are referred to as 'subtle bodies'. She described treating the patient who later returned after having, without the healer's knowledge, two doses of the 'Covid vaccine'. The healer said:

I noticed immediately the change, very heavy energy emanating from [the] subtle bodies. The scariest thing was when I was working on the heart chakra, I connected with her soul: it was detached from the physical body, it had no contact and it was, as if it was floating in a state of total confusion: a damage to the consciousness that loses contact with the physical body, i.e. with our biological machine, there is no longer any communication between them.

I continued the treatment by sending light to the heart chakra, the soul of the person, but it seemed that the soul could no longer receive any light, frequency or energy. It was a very powerful experience for me. Then I understood that this substance is indeed used to detach consciousness so that this consciousness can no longer interact through this body that it possesses in life, where there is no longer any contact, no frequency, no light, no more energetic balance or mind.

This would create a human that is rudderless and at the extreme almost zombie-like operating with a fractional state of consciousness at the mercy of Wetiko. I was especially intrigued by what the healer said in the light of the prediction by the highly-informed Rudolf Steiner more than a hundred years ago. He said:

In the future, we will eliminate the soul with medicine. Under the pretext of a 'healthy point of view', there will be a vaccine by which the human body will be treated as soon as possible directly at birth, so that the human being cannot develop the thought of the existence of soul and Spirit. To materialistic doctors will be entrusted the task of removing the soul of humanity.

As today, people are vaccinated against this disease or that disease, so in the future, children will be vaccinated with a substance that can be produced precisely in such a way that people, thanks to this vaccination, will be immune to being subjected to the 'madness' of spiritual life. He would be extremely smart, but he would not develop a conscience, and that is the true goal of some materialistic circles.

Steiner said the vaccine would detach the physical body from the etheric body (subtle bodies) and 'once the etheric body is detached the relationship between the universe and the etheric body would become extremely unstable, and man would become an automaton'. He said 'the physical body of man must be polished on this Earth by spiritual will – so the vaccine becomes a kind of arymanique (Wetiko) force' and 'man can no longer get rid of a given materialistic feeling'. Humans would then, he said, become 'materialistic of constitution and can no longer rise to the spiritual'. I have been writing for years about DNA being a receiver-transmitter of information that connects us to other levels of reality and these 'vaccines' changing DNA can be likened to changing an antenna and what it can transmit and receive. Such a disconnection would clearly lead to changes in personality and perception. Steiner further predicted the arrival of AI. Big Pharma 'Covid vaccine' makers, expressions of Wetiko, are testing their DNA-manipulating evil on children as I write with a view to giving the 'vaccine' to babies. If it's a soul-body disconnector – and I say that it is or can be – every child would be disconnected from 'soul' at birth and the 'vaccine' would create a closed system in which spiritual guidance from the greater self would play no part. This has been the ambition of Wetiko all

along. A Pentagon video from 2005 was leaked of a presentation explaining the development of vaccines to change behaviour by their effect on the brain. Those that believe this is not happening with the 'Covid' genetically-modifying procedure masquerading as a 'vaccine' should make an urgent appointment with Naivety Anonymous. Klaus Schwab wrote in 2018:

> Neurotechnologies enable us to better influence consciousness and thought and to understand many activities of the brain. They include decoding what we are thinking in fine levels of detail through new chemicals and interventions that can influence our brains to correct for errors or enhance functionality.

The plan is clear and only the heart can stop it. With every heart that opens, every mind that awakens, Wetiko is weakened. Heart and love are far more powerful than head and hate and so nothing like a majority is needed to turn this around.

Beyond the Phantom

Our heart is the prime target of Wetiko and so it must be the answer to Wetiko. We *are* our heart which is part of one heart, the infinite heart. Our heart is where the true self lives in a human life behind firewalls of five-sense illusion when an imposter takes its place – *Phantom Self*; but our heart waits patiently to be set free any time we choose to see beyond the Phantom, beyond Wetiko. A Wetikoed Phantom Self can wreak mass death and destruction while the love of forever is locked away in its heart. The time is here to unleash its power and let it sweep away the fear and despair that is Wetiko. Heart consciousness does not seek manipulated, censored, advantage for its belief or religion, its activism and desires. As an expression of the One it treats all as One with the same rights to freedom and opinion. Our heart demands fairness for itself no more than for others. From this unity of heart we can come together in mutual support and transform this Wetikoed world into what reality is meant to be – a place of love, joy, happiness, fairness, justice and freedom. Wetiko has another agenda and that's why the world is as

it is, but enough of this nonsense. Wetiko can't stay where hearts are open and it works so hard to keep them closed. Fear is its currency and its food source and love in its true sense has no fear. Why would love have fear when it knows it is *All That Is, Has Been, And Ever Can Be* on an eternal exploration of all possibility? Love in this true sense is not the physical attraction that passes for love. This can be an expression of it, yes, but Infinite Love, a love without condition, goes far deeper to the core of all being. It *is* the core of all being. Infinite realty was born from love beyond the illusions of the simulation. Love infinitely expressed is the knowing that all is One and the swiftly-passing experience of separation is a temporary hallucination. You cannot disconnect from Oneness; you can only *perceive* that you have and withdraw from its influence. This is the most important of all perception trickery by the mind parasite that is Wetiko and the foundation of all its potential for manipulation.

If we open our hearts, open the sluice gates of the mind, and redefine self-identity amazing things start to happen. Consciousness expands or contracts in accordance with self-identity. When true self is recognised as infinite awareness and label self – Phantom Self – is seen as only a series of brief experiences life is transformed. Consciousness expands to the extent that self-identity expands and everything changes. You see unity, not division, the picture, not the pixels. From this we can play the long game. No more is an experience something in and of itself, but a fleeting moment in the eternity of forever. Suddenly people in uniform and dark suits are no longer intimidating. Doing what your heart knows to be right is no longer intimidating and consequences for those actions take on the same nature of a brief experience that passes in the blink of an infinite eye. Intimidation is all in the mind. Beyond the mind there is no intimidation.

An open heart does not consider consequences for what it knows to be right. To do so would be to consider not doing what it knows to be right and for a heart in its power that is never an option. The Renegade Mind is really the Renegade Heart. Consideration of consequences will always provide a getaway car for the mind and

the heart doesn't want one. What is right in the light of what we face today is to stop cooperating with Wetiko in all its forms and to do it without fear or compromise. You cannot compromise with tyranny when tyranny always demands more until it has everything. Life is your perception and you are your destiny. Change your perception and you change your life. Change collective perception and we change the world.

Come on people … One human family, One heart, One goal … *FREEEEEEDOM*!

We must settle for nothing less.

Postscript

The big scare story as the book goes to press is the 'Indian' variant and the world is being deluged with propaganda about the 'Covid catastrophe' in India which mirrors in its lies and misrepresentations what happened in Italy before the first lockdown in 2020.

The *New York Post* published a picture of someone who had 'collapsed in the street from Covid' in India in April, 2021, which was actually taken during a gas leak in May, 2020. Same old, same old. Media articles in mid-February were asking why India had been so untouched by 'Covid' and then as their vaccine rollout gathered pace the alleged 'cases' began to rapidly increase. Indian 'Covid vaccine' maker Bharat Biotech was funded into existence by the Bill and Melinda Gates Foundation (the pair announced their divorce in May, 2021, which is a pity because they so deserve each other). The Indian 'Covid crisis' was ramped up by the media to terrify the world and prepare people for submission to still more restrictions. The scam that worked the first time was being repeated only with far more people seeing through the deceit. Davidicke.com and Ickonic.com have sought to tell the true story of what is happening by talking to people living through the Indian nightmare which has nothing to do with 'Covid'. We posted a letter from 'Alisha' in Pune who told a very different story to government and media mendacity. She said scenes of dying people and overwhelmed hospitals were designed to hide what was really happening – genocide and starvation. Alisha said that millions had already died of starvation during the ongoing lockdowns while government and media were lying and making it look like the 'virus':

Restaurants, shops, gyms, theatres, basically everything is shut. The cities are ghost towns. Even so-called 'essential' businesses are only open till 11am in the morning. You basically have just an hour to buy food and then your time is up.

Inter-state travel and even inter-district travel is banned. The cops wait at all major crossroads to question why you are traveling outdoors or to fine you if you are not wearing a mask.

The medical community here is also complicit in genocide, lying about hospitals being full and turning away people with genuine illnesses, who need immediate care. They have even created a shortage of oxygen cylinders.

This is the classic Cult modus operandi played out in every country. Alisha said that people who would not have a PCR test not testing for the 'virus' were being denied hospital treatment. She said the people hit hardest were migrant workers and those in rural areas. Most businesses employed migrant workers and with everything closed there were no jobs, no income and no food. As a result millions were dying of starvation or malnutrition. All this was happening under Prime Minister Narendra Modi, a 100-percent asset of the Cult, and it emphasises yet again the scale of pure anti-human evil we are dealing with. Australia banned its people from returning home from India with penalties for trying to do so of up to five years in jail and a fine of £37,000. The manufactured 'Covid' crisis in India was being prepared to justify further fascism in the West. Obvious connections could be seen between the Indian 'vaccine' programme and increased 'cases' and this became a common theme. The Seychelles, the most per capita 'Covid vaccinated' population in the world, went back into lockdown after a 'surge of cases'.

Long ago the truly evil Monsanto agricultural biotechnology corporation with its big connections to Bill Gates devastated Indian farming with genetically-modified crops. Human rights activist Gurcharan Singh highlighted the efforts by the Indian government to complete the job by destroying the food supply to hundreds of millions with 'Covid' lockdowns. He said that 415 million people at the bottom of the disgusting caste system (still going whatever they say) were below the poverty line and struggled to feed themselves every year. Now the government was imposing lockdown at just the

time to destroy the harvest. This deliberate policy was leading to mass starvation. People may reel back at the suggestion that a government would do that, but Wetiko-controlled 'leaders' are capable of any level of evil. In fact what is described in India is in the process of being instigated worldwide. The food chain and food supply are being targeted at every level to cause world hunger and thus control. Bill Gates is not the biggest owner of farmland in America for no reason and destroying access to food aids both the depopulation agenda and the plan for synthetic 'food' already being funded into existence by Gates. Add to this the coming hyper-inflation from the suicidal creation of fake 'money' in response to 'Covid' and the breakdown of container shipping systems and you have a cocktail that can only lead one way and is meant to. The Cult plan is to crash the entire system to 'build back better' with the Great Reset.

'Vaccine' transmission

Reports from all over the world continue to emerge of women suffering menstrual and fertility problems after having the fake 'vaccine' and of the non-'vaccinated' having similar problems when interacting with the 'vaccinated'. There are far too many for 'coincidence' to be credible. We've had menopausal women getting periods, others having periods stop or not stopping for weeks, passing clots, sometimes the lining of the uterus, breast irregularities, and miscarriages (which increased by 400 percent in parts of the United States). Non-'vaccinated' men and children have suffered blood clots and nose bleeding after interaction with the 'vaccinated'. Babies have died from the effects of breast milk from a 'vaccinated' mother. Awake doctors – the small minority – speculated on the cause of non-'vaccinated' suffering the same effects as the 'vaccinated'. Was it nanotechnology in the synthetic substance transmitting frequencies or was it a straight chemical bioweapon that was being transmitted between people? I am not saying that some kind of chemical transmission is not one possible answer, but the foundation of all that the Cult does is frequency and

this is fertile ground for understanding how transmission can happen. American doctor Carrie Madej, an internal medicine physician and osteopath, has been practicing for the last 20 years, teaching medical students, and she says attending different meetings where the agenda for humanity was discussed. Madej, who operates out of Georgia, did not dismiss other possible forms of transmission, but she focused on frequency in search of an explanation for transmission. She said the Moderna and Pfizer 'vaccines' contained nano-lipid particles as a key component. This was a brand new technology never before used on humanity. 'They're using a nanotechnology which is pretty much little tiny computer bits … nanobots or hydrogel.' Inside the 'vaccines' was 'this sci-fi kind of substance' which suppressed immune checkpoints to get into the cell. I referred to this earlier as the 'Trojan horse' technique that tricks the cell into opening a gateway for the self-replicating synthetic material and while the immune system is artificially suppressed the body has no defences. Madej said the substance served many purposes including an on-demand ability to 'deliver the payload' and using the nano 'computer bits' as biosensors in the body. 'It actually has the ability to accumulate data from your body, like your breathing, your respiration, thoughts, emotions, all kinds of things.'

She said the technology obviously has the ability to operate through Wi-Fi and transmit and receive energy, messages, frequencies or impulses. 'Just imagine you're getting this new substance in you and it can react to things all around you, the 5G, your smart device, your phones.' We had something completely foreign in the human body that had never been launched large scale at a time when we were seeing 5G going into schools and hospitals (plus the Musk satellites) and she believed the 'vaccine' transmission had something to do with this: '… if these people have this inside of them … it can act like an antenna and actually transmit it outwardly as well.' The synthetic substance produced its own voltage and so it could have that kind of effect. This fits with my own contention that the nano receiver-transmitters are designed to connect people to the

Smart Grid and break the receiver-transmitter connection to expanded consciousness. That would explain the French energy healer's experience of the disconnection of body from 'soul' with those who have had the 'vaccine'. The nanobots, self-replicating inside the body, would also transmit the synthetic frequency which could be picked up through close interaction by those who have not been 'vaccinated'. Madej speculated that perhaps it was 5G and increased levels of other radiation that was causing the symptoms directly although interestingly she said that non-'vaccinated' patients had shown improvement when they were away from the 'vaccinated' person they had interacted with. It must be remembered that you can control frequency and energy with your mind and you can consciously create energetic barriers or bubbles with the mind to stop damaging frequencies from penetrating your field. American paediatrician Dr Larry Palevsky said the 'vaccine' was not a 'vaccine' and was never designed to protect from a 'viral' infection. He called it 'a massive, brilliant propaganda of genocide' because they didn't have to inject everyone to get the result they wanted. He said the content of the jabs was able to infuse any material into the brain, heart, lungs, kidneys, liver, sperm and female productive system. 'This is genocide; this is a weapon of mass destruction.' At the same time American colleges were banning students from attending if they didn't have this life-changing and potentially life-ending 'vaccine'. Class action lawsuits must follow when the consequences of this college fascism come to light. As the book was going to press came reports about fertility effects on sperm in 'vaccinated' men which would absolutely fit with what I have been saying and hospitals continued to fill with 'vaccine' reactions. Another question is what about transmission via blood transfusions? The NHS has extended blood donation restrictions from seven days after a 'Covid vaccination' to 28 days after even a sore arm reaction.

I said in the spring of 2020 that the then touted 'Covid vaccine' would be ongoing each year like the flu jab. A year later Pfizer CEO, the appalling Albert Bourla, said people would 'likely' need a 'booster dose' of the 'vaccine' within 12 months of getting 'fully

vaccinated' and then a yearly shot. 'Variants will play a key role', he said confirming the point. Johnson & Johnson CEO Alex Gorsky also took time out from his 'vaccine' disaster to say that people may need to be vaccinated against 'Covid-19' each year. UK Health Secretary, the psychopath Matt Hancock, said additional 'boosters' would be available in the autumn of 2021. This is the trap of the 'vaccine passport'. The public will have to accept every last 'vaccine' they introduce, including for the fake 'variants', or it would cease to be valid. The only other way in some cases would be continuous testing with a test not testing for the 'virus' and what is on the swabs constantly pushed up your noise towards the brain every time?

'Vaccines' changing behaviour

I mentioned in the body of the book how I believed we would see gathering behaviour changes in the 'vaccinated' and I am already hearing such comments from the non-'vaccinated' describing behaviour changes in friends, loved ones and work colleagues. This will only increase as the self-replicating synthetic material and nanoparticles expand in body and brain. An article in the *Guardian* in 2016 detailed research at the University of Virginia in Charlottesville which developed a new method for controlling brain circuits associated with complex animal behaviour. The method, dubbed 'magnetogenetics', involves genetically-engineering a protein called ferritin, which stores and releases iron, to create a magnetised substance – 'Magneto' – that can activate specific groups of nerve cells from a distance. This is claimed to be an advance on other methods of brain activity manipulation known as optogenetics and chemogenetics (the Cult has been developing methods of brain control for a long time). The ferritin technique is said to be non-invasive and able to activate neurons 'rapidly and reversibly'. In other words, human thought and perception. The article said that earlier studies revealed how nerve cell proteins 'activated by heat and mechanical pressure can be genetically engineered so that they become sensitive to radio waves and magnetic fields, by attaching them to an iron-storing protein called ferritin, or to inorganic

paramagnetic particles'. Sensitive to radio waves and magnetic fields? You mean like 5G, 6G and 7G? This is the human-AI Smart Grid hive mind we are talking about. The *Guardian* article said:

> … the researchers injected Magneto into the striatum of freely behaving mice, a deep brain structure containing dopamine-producing neurons that are involved in reward and motivation, and then placed the animals into an apparatus split into magnetised and non-magnetised sections.
>
> Mice expressing Magneto spent far more time in the magnetised areas than mice that did not, because activation of the protein caused the striatal neurons expressing it to release dopamine, so that the mice found being in those areas rewarding. This shows that Magneto can remotely control the firing of neurons deep within the brain, and also control complex behaviours.

Make no mistake this basic methodology will be part of the 'Covid vaccine' cocktail and using magnetics to change brain function through electromagnetic field frequency activation. The Pentagon is developing a 'Covid vaccine' using ferritin. Magnetics would explain changes in behaviour and why videos are appearing across the Internet as I write showing how magnets stick to the skin at the point of the 'vaccine' shot. Once people take these 'vaccines' anything becomes possible in terms of brain function and illness which will be blamed on 'Covid-19' and 'variants'. Magnetic field manipulation would further explain why the non-'vaccinated' are reporting the same symptoms as the 'vaccinated' they interact with and why those symptoms are reported to decrease when not in their company. Interestingly 'Magneto', a 'mutant', is a character in the Marvel Comic *X-Men* stories with the ability to manipulate magnetic fields and he believes that mutants should fight back against their human oppressors by any means necessary. The character was born Erik Lehnsherr to a Jewish family in Germany.

Cult-controlled courts

The European Court of Human Rights opened the door for mandatory 'Covid-19 vaccines' across the continent when it ruled in a Czech Republic dispute over childhood immunisation that legally

enforced vaccination could be 'necessary in a democratic society'. The 17 judges decided that compulsory vaccinations did not breach human rights law. On the face of it the judgement was so inverted you gasp for air. If not having a vaccine infused into your body is not a human right then what is? Ah, but they said human rights law which has been specifically written to delete all human rights at the behest of the state (the Cult). Article 8 of the European Convention on Human Rights relates to the right to a private life. The crucial word here is *'except'*:

> There shall be no interference by a public authority with the exercise of this right EXCEPT such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic wellbeing of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others [My emphasis].

No interference *except* in accordance with the law means there *are* no 'human rights' *except* what EU governments decide you can have at their behest. 'As is necessary in a democratic society' explains that reference in the judgement and 'in the interests of national security, public safety or the economic well-being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others' gives the EU a coach and horses to ride through 'human rights' and scatter them in all directions. The judiciary is not a check and balance on government extremism; it is a vehicle to enforce it. This judgement was almost laughably predictable when the last thing the Cult wanted was a decision that went against mandatory vaccination. Judges rule over and over again to benefit the system of which they are a part. Vaccination disputes that come before them are invariably delivered in favour of doctors and authorities representing the view of the state which owns the judiciary. Oh, yes, and we have even had calls to stop putting 'Covid-19' on death certificates within 28 days of a 'positive test' because it is claimed the practice makes the 'vaccine' appear not to work. They are laughing at you.

The scale of madness, inhumanity and things to come was highlighted when those not 'vaccinated' for 'Covid' were refused evacuation from the Caribbean island of St Vincent during massive volcanic eruptions. Cruise ships taking residents to the safety of another island allowed only the 'vaccinated' to board and the rest were left to their fate. Even in life and death situations like this we see 'Covid' stripping people of their most basic human instincts and the insanity is even more extreme when you think that fake 'vaccine'-makers are not even claiming their body-manipulating concoctions stop 'infection' and 'transmission' of a 'virus' that doesn't exist. St Vincent Prime Minister Ralph Gonsalves said: 'The chief medical officer will be identifying the persons already vaccinated so that we can get them on the ship.' Note again the power of the chief medical officer who, like Whitty in the UK, will be answering to the World Health Organization. This is the Cult network structure that has overridden politicians who 'follow the science' which means doing what WHO-controlled 'medical officers' and 'science advisers' tell them. Gonsalves even said that residents who were 'vaccinated' after the order so they could board the ships would still be refused entry due to possible side effects such as 'wooziness in the head'. The good news is that if they were woozy enough in the head they could qualify to be prime minister of St Vincent.

Microchipping freedom

The European judgement will be used at some point to justify moves to enforce the 'Covid' DNA-manipulating procedure. Sandra Ro, CEO of the Global Blockchain Business Council, told a World Economic Forum event that she hoped 'vaccine passports' would help to 'drive forced consent and standardisation' of global digital identity schemes: 'I'm hoping with the desire and global demand for some sort of vaccine passport – so that people can get travelling and working again – [it] will drive forced consent, standardisation, and frankly, cooperation across the world.' The lady is either not very bright, or thoroughly mendacious, to use the term 'forced consent'.

You do not 'consent' if you are forced – you *submit*. She was describing what the plan has been all along and that's to enforce a digital identity on every human without which they could not function. 'Vaccine passports' are opening the door and are far from the end goal. A digital identity would allow you to be tracked in everything you do in cyberspace and this is the same technique used by Cult-owned China to enforce its social credit system of total control. The ultimate 'passport' is planned to be a microchip as my books have warned for nearly 30 years. Those nice people at the Pentagon working for the Cult-controlled Defense Advanced Research Projects Agency (DARPA) claimed in April, 2021, they have developed a microchip inserted under the skin to detect 'asymptomatic Covid-19 infection' before it becomes an outbreak and a 'revolutionary filter' that can remove the 'virus' from the blood when attached to a dialysis machine. The only problems with this are that the 'virus' does not exist and people transmitting the 'virus' with no symptoms is brain-numbing bullshit. This is, of course, not a ruse to get people to be microchipped for very different reasons. DARPA also said it was producing a one-stop 'vaccine' for the 'virus' and all 'variants'. One of the most sinister organisations on Planet Earth is doing this? Better have it then. These people are insane because Wetiko that possesses them is insane.

Researchers from the Salk Institute in California announced they have created an embryo that is part human and part monkey. My books going back to the 1990s have exposed experiments in top secret underground facilities in the United States where humans are being crossed with animal and non-human 'extraterrestrial' species. They are now easing that long-developed capability into the public arena and there is much more to come given we are dealing with psychiatric basket cases. Talking of which – Elon Musk's scientists at Neuralink trained a monkey to play Pong and other puzzles on a computer screen using a joystick and when the monkey made the correct move a metal tube squirted banana smoothie into his mouth which is the basic technique for training humans into unquestioning compliance. Two Neuralink chips were in the monkey's skull and

more than 2,000 wires 'fanned out' into its brain. Eventually the monkey played a video game purely with its brain waves. Psychopathic narcissist Musk said the 'breakthrough' was a step towards putting Neuralink chips into human skulls and merging minds with artificial intelligence. *Exactly*. This man is so dark and Cult to his DNA.

World Economic Fascism (WEF)

The World Economic Forum is telling you the plan by the statements made at its many and various events. Cult-owned fascist YouTube CEO Susan Wojcicki spoke at the 2021 WEF Global Technology Governance Summit (see the name) in which 40 governments and 150 companies met to ensure 'the responsible design and deployment of emerging technologies'. Orwellian translation: 'Ensuring the design and deployment of long-planned technologies will advance the Cult agenda for control and censorship.' Freedom-destroyer and Nuremberg-bound Wojcicki expressed support for tech platforms like hers to censor content that is 'technically legal but could be harmful'. Who decides what is 'harmful'? She does and they do. 'Harmful' will be whatever the Cult doesn't want people to see and we have legislation proposed by the UK government that would censor content on the basis of 'harm' no matter if the information is fair, legal and provably true. Make that *especially* if it is fair, legal and provably true. Wojcicki called for a global coalition to be formed to enforce content moderation standards through automated censorship. This is a woman and mega-censor so self-deluded that she shamelessly accepted a 'free expression' award – *Wojcicki* – in an event sponsored by her own *YouTube*. They have no shame and no self-awareness.

You know that 'Covid' is a scam and Wojcicki a Cult operative when YouTube is censoring medical and scientific opinion purely on the grounds of whether it supports or opposes the Cult 'Covid' narrative. Florida governor Ron DeSantis compiled an expert panel with four professors of medicine from Harvard, Oxford, and Stanford Universities who spoke against forcing children and

vaccinated people to wear masks. They also said there was no proof that lockdowns reduced spread or death rates of 'Covid-19'. Cult-gofer Wojcicki and her YouTube deleted the panel video 'because it included content that contradicts the consensus of local and global health authorities regarding the efficacy of masks to prevent the spread of Covid-19'. This 'consensus' refers to what the Cult tells the World Health Organization to say and the WHO tells 'local health authorities' to do. Wojcicki knows this, of course. The panellists pointed out that censorship of scientific debate was responsible for deaths from many causes, but Wojcicki couldn't care less. She would not dare go against what she is told and as a disgrace to humanity she wouldn't want to anyway. The UK government is seeking to pass a fascist 'Online Safety Bill' to specifically target with massive fines and other means non-censored video and social media platforms to make them censor 'lawful but harmful' content like the Cult-owned Facebook, Twitter, Google and YouTube. What is 'lawful but harmful' would be decided by the fascist Blair-created Ofcom.

Another WEF obsession is a cyber-attack on the financial system and this is clearly what the Cult has planned to take down the bank accounts of everyone – except theirs. Those that think they have enough money for the Cult agenda not to matter to them have got a big lesson coming if they continue to ignore what is staring them in the face. The World Economic Forum, funded by Gates and fronted by Klaus Schwab, announced it would be running a 'simulation' with the Russian government and global banks of just such an attack called Cyber Polygon 2021. What they simulate – as with the 'Covid' Event 201 – they plan to instigate. The WEF is involved in a project with the Cult-owned Carnegie Endowment for International Peace called the WEF-Carnegie Cyber Policy Initiative which seeks to merge Wall Street banks, 'regulators' (I love it) and intelligence agencies to 'prevent' (arrange and allow) a cyber-attack that would bring down the global financial system as long planned by those that control the WEF and the Carnegie operation. The Carnegie Endowment for International Peace sent an instruction to First World

War US President Woodrow Wilson not to let the war end before society had been irreversibly transformed.

The Wuhan lab diversion

As I close, the Cult-controlled authorities and lapdog media are systematically pushing 'the virus was released from the Wuhan lab' narrative. There are two versions – it happened by accident and it happened on purpose. Both are nonsense. The perceived existence of the never-shown-to-exist 'virus' is vital to sell the impression that there is actually an infective agent to deal with and to allow the endless potential for terrifying the population with 'variants' of a 'virus' that does not exist. The authorities at the time of writing are going with the 'by accident' while the alternative media is promoting the 'on purpose'. Cable news host Tucker Carlson who has questioned aspects of lockdown and 'vaccine' compulsion has bought the Wuhan lab story. 'Everyone now agrees' he said. Well, I don't and many others don't and the question is *why* does the system and its media suddenly 'agree'? When the media moves as one unit with a narrative it is always a lie – witness the hour by hour mendacity of the 'Covid' era. Why would this Cult-owned combination which has unleashed lies like machine gun fire suddenly 'agree' to tell the truth??

Much of the alternative media is buying the lie because it fits the conspiracy narrative, but it's the *wrong* conspiracy. The real conspiracy is that *there is no virus* and that is what the Cult is desperate to hide. The idea that the 'virus' was released by accident is ludicrous when the whole 'Covid' hoax was clearly long-planned and waiting to be played out as it was so fast in accordance with the Rockefeller document and Event 201. So they prepared everything in detail over decades and then sat around strumming their fingers waiting for an 'accidental' release from a bio-lab? *What??* It's crazy. Then there's the 'on purpose' claim. You want to circulate a 'deadly virus' and hide the fact that you've done so and you release it down the street from the highest-level bio-lab in China? I repeat – *What??*

You would release it far from that lab to stop any association being made. But, no, we'll do it in a place where the connection was certain to be made. Why would you need to scam 'cases' and 'deaths' and pay hospitals to diagnose 'Covid-19' if you had a real 'virus'? What are sections of the alternative media doing believing this crap? Where were all the mass deaths in Wuhan from a 'deadly pathogen' when the recovery to normal life after the initial propaganda was dramatic in speed? Why isn't the 'deadly pathogen' now circulating all over China with bodies in the street? Once again we have the technique of tell them what they want to hear and they will likely believe it. The alternative media has its 'conspiracy' and with Carlson it fits with his 'China is the danger' narrative over years. China *is* a danger as a global Cult operations centre, but not for this reason. The Wuhan lab story also has the potential to instigate conflict with China when at some stage the plan is to trigger a Problem-Reaction-Solution confrontation with the West. Question everything – *everything* – and especially when the media agrees on a common party line.

Third wave ... fourth wave ... fifth wave ...

As the book went into production the world was being set up for more lockdowns and a 'third wave' supported by invented 'variants' that were increasing all the time and will continue to do so in public statements and computer programs, but not in reality. India became the new Italy in the 'Covid' propaganda campaign and we were told to be frightened of the new 'Indian strain'. Somehow I couldn't find it within myself to do so. A document produced for the UK government entitled 'Summary of further modelling of easing of restrictions – Roadmap Step 2' declared that a third wave was inevitable (of course when it's in the script) and it would be the fault of children and those who refuse the health-destroying fake 'Covid vaccine'. One of the computer models involved came from the Cult-owned *Imperial College* and the other from Warwick University which I wouldn't trust to tell me the date in a calendar factory. The document states that both models presumed extremely high uptake

of the 'Covid vaccines' and didn't allow for 'variants'. The document states: 'The resurgence is a result of some people (mostly children) being ineligible for vaccination; others choosing not to receive the vaccine; and others being vaccinated but not perfectly protected.' The mendacity takes the breath away. Okay, blame those with a brain who won't take the DNA-modifying shots and put more pressure on children to have it as 'trials' were underway involving children as young as six months with parents who give insanity a bad name. Massive pressure is being put on the young to have the fake 'vaccine' and child age consent limits have been systematically lowered around the world to stop parents intervening. Most extraordinary about the document was its claim that the 'third wave' would be driven by 'the resurgence in both hospitalisations and deaths … dominated by *those that have received two doses of the vaccine*, comprising around 60-70% of the wave respectively'. The predicted peak of the 'third wave' suggested 300 deaths per day with 250 of them *fully 'vaccinated' people*. How many more lies do acquiescers need to be told before they see the obvious? Those who took the jab to 'protect themselves' are projected to be those who mostly get sick and die? So what's in the 'vaccine'? The document went on:

> It is possible that a summer of low prevalence could be followed by substantial increases in incidence over the following autumn and winter. Low prevalence in late summer should not be taken as an indication that SARS-CoV-2 has retreated or that the population has high enough levels of immunity to prevent another wave.

They are telling you the script and while many British people believed 'Covid' restrictions would end in the summer of 2021 the government was preparing for them to be ongoing. Authorities were awarding contracts for 'Covid marshals' to police the restrictions with contracts starting in July, 2021, and going through to January 31st, 2022, and the government was advertising for 'Media Buying Services' to secure media propaganda slots worth a potential £320 million for 'Covid-19 campaigns' with a contract not ending until March, 2022. The recipient – via a list of other front companies – was reported to be American media marketing giant Omnicom Group

Inc. While money is no object for 'Covid' the UK waiting list for all other treatment – including life-threatening conditions – passed 4.5 million. Meantime the Cult is seeking to control all official 'inquiries' to block revelations about what has really been happening and why. It must not be allowed to – we need Nuremberg jury trials in every country. The cover-up doesn't get more obvious than appointing ultra-Zionist professor Philip Zelikow to oversee two dozen US virologists, public health officials, clinicians, former government officials and four American 'charitable foundations' to 'learn the lessons' of the 'Covid' debacle. The personnel will be those that created and perpetuated the 'Covid' lies while Zelikow is the former executive director of the 9/11 Commission who ensured that the truth about those attacks never came out and produced a report that must be among the most mendacious and manipulative documents ever written – see *The Trigger* for the detailed exposure of the almost unimaginable 9/11 story in which Sabbatians can be found at every level.

Passive no more

People are increasingly challenging the authorities with amazing numbers of people taking to the streets in London well beyond the ability of the Face-Nappies to stop them. Instead the Nappies choose situations away from the mass crowds to target, intimidate, and seek to promote the impression of 'violent protestors'. One such incident happened in London's Hyde Park. Hundreds of thousands walking through the streets in protest against 'Covid' fascism were ignored by the Cult-owned BBC and most of the rest of the mainstream media, but they delighted in reporting how police were injured in 'clashes with protestors'. The truth was that a group of people gathered in Hyde Park at the end of one march when most had gone home and they were peacefully having a good time with music and chat. Face-Nappies who couldn't deal with the full-march crowd then waded in with their batons and got more than they bargained for. Instead of just standing for this criminal brutality the crowd used their numerical superiority to push the Face-Nappies out of the

park. Eventually the Nappies turned and ran. Unfortunately two or three idiots in the crowd threw drink cans striking two officers which gave the media and the government the image they wanted to discredit the 99.9999 percent who were peaceful. The idiots walked straight into the trap and we must always be aware of potential agent provocateurs used by the authorities to discredit their targets.

This response from the crowd – the can people apart – must be a turning point when the public no longer stand by while the innocent are arrested and brutally attacked by the Face-Nappies. That doesn't mean to be violent, that's the last thing we need. We'll leave the violence to the Face-Nappies and government. But it does mean that when the Face-Nappies use violence against peaceful people the numerical superiority is employed to stop them and make citizen's arrests or Common Law arrests for a breach of the peace. The time for being passive in the face of fascism is over.

We are the many, they are the few, and we need to make that count before there is no freedom left and our children and grandchildren face an ongoing fascist nightmare.

COME ON PEOPLE – IT'S TIME.

One final thought …

The power of love
A force from above
Cleaning my soul
Flame on burn desire
Love with tongues of fire
Purge the soul
Make love your goal

I'll protect you from the hooded claw
Keep the vampires from your door
When the chips are down I'll be around
With my undying, death-defying
Love for you

Envy will hurt itself
Let yourself be beautiful
Sparkling love, flowers
And pearls and pretty girls
Love is like an energy
Rushin' rushin' inside of me

This time we go sublime
Lovers entwine, divine, divine,
Love is danger, love is pleasure
Love is pure – the only treasure

I'm so in love with you
Purge the soul
Make love your goal

The power of love
A force from above
Cleaning my soul
The power of love
A force from above
A sky-scraping dove

Flame on burn desire
Love with tongues of fire
Purge the soul
Make love your goal

Frankie Goes To Hollywood

APPENDIX

Cowan-Kaufman-Morell Statement on Virus Isolation (SOVI)

Isolation: The action of isolating; the fact or condition of being isolated or standing alone; separation from other things or persons; solitariness
Oxford English Dictionary

The controversy over whether the SARS-CoV-2 virus has ever been isolated or purified continues. However, using the above definition, common sense, the laws of logic and the dictates of science, any unbiased person must come to the conclusion that the SARS-CoV-2 virus has never been isolated or purified. As a result, no confirmation of the virus' existence can be found. The logical, common sense, and scientific consequences of this fact are:

- the structure and composition of something not shown to exist can't be known, including the presence, structure, and function of any hypothetical spike or other proteins;
- the genetic sequence of something that has never been found can't be known;
- "variants" of something that hasn't been shown to exist can't be known;
- it's impossible to demonstrate that SARS-CoV-2 causes a disease called Covid-19.

In as concise terms as possible, here's the proper way to isolate, characterize and demonstrate a new virus. First, one takes samples (blood, sputum, secretions) from many people (e.g. 500) with symptoms which are unique and specific enough to characterize an illness. Without mixing these samples with ANY tissue or products that also contain genetic material, the virologist macerates, filters and ultracentrifuges i.e. *purifies* the specimen. This common virology technique, done for decades to isolate bacteriophages[1] and so-called giant viruses in every virology lab, then allows the virologist to demonstrate with electron microscopy thousands of identically sized and shaped particles. These particles are the isolated and purified virus.

These identical particles are then checked for uniformity by physical and/or microscopic techniques. Once the purity is determined, the particles may be further characterized. This would include examining the structure, morphology, and chemical composition of the particles. Next, their genetic makeup is characterized by extracting the genetic material directly from the purified particles and using genetic-sequencing techniques, such as Sanger sequencing, that have also been around for decades. Then one does an analysis to confirm that these uniform particles are exogenous (outside) in origin as a virus is conceptualized to be, and not the normal breakdown products of dead and dying tissues.[2] (As of May 2020, we know that virologists have no way to determine whether the particles they're seeing are viruses or just normal breakdown products of dead and dying tissues.)[3]

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1 Isolation, characterization and analysis of bacteriophages from the haloalkaline lake Elmenteita, KenyaJuliah Khayeli Akhwale et al, PLOS One, Published: April 25, 2019. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0215734 – accessed 2/15/21

2 "Extracellular Vesicles Derived From Apoptotic Cells: An Essential Link Between Death and Regeneration," Maojiao Li1 et al, Frontiers in Cell and Developmental Biology, 2020 October 2. https://www.frontiersin.org/articles/10.3389/fcell.2020.573511/full – accessed 2/15/21

3 "The Role of Extraellular Vesicles as Allies of HIV, HCV and SARS Viruses," Flavia Giannessi, et al, Viruses, 2020 May

If we have come this far then we have fully isolated, characterized, and genetically sequenced an exogenous virus particle. However, we still have to show it is causally related to a disease. This is carried out by exposing a group of healthy subjects (animals are usually used) to this isolated, purified virus in the manner in which the disease is thought to be transmitted. If the animals get sick with the same disease, as confirmed by clinical and autopsy findings, one has now shown that the virus actually causes a disease. This demonstrates infectivity and transmission of an infectious agent.

None of these steps has even been attempted with the SARS-CoV-2 virus, nor have all these steps been successfully performed for any so-called pathogenic virus. Our research indicates that a single study showing these steps does not exist in the medical literature.

Instead, since 1954, virologists have taken unpurified samples from a relatively few people, often less than ten, with a similar disease. They then minimally process this sample and inoculate this unpurified sample onto tissue culture containing usually four to six other types of material – all of which contain identical genetic material as to what is called a "virus." The tissue culture is starved and poisoned and naturally disintegrates into many types of particles, some of which contain genetic material. Against all common sense, logic, use of the English language and scientific integrity, this process is called "virus isolation." This brew containing fragments of genetic material from many sources is then subjected to genetic analysis, which then creates in a computer-simulation process the alleged sequence of the alleged virus, a so called in silico genome. At no time is an actual virus confirmed by electron microscopy. At no time is a genome extracted and sequenced from an actual virus. This is scientific fraud.

The observation that the unpurified specimen — inoculated onto tissue culture along with toxic antibiotics, bovine fetal tissue, amniotic fluid and other tissues — destroys the kidney tissue onto which it is inoculated is given as evidence of the virus' existence and pathogenicity. This is scientific fraud.

From now on, when anyone gives you a paper that suggests the SARS-CoV-2 virus has been isolated, please check the methods sections. If the researchers used Vero cells or any other culture method, you know that their process was not isolation. You will hear the following excuses for why actual isolation isn't done:

1. There were not enough virus particles found in samples from patients to analyze.

2. Viruses are intracellular parasites; they can't be found outside the cell in this manner.

If No. 1 is correct, and we can't find the virus in the sputum of sick people, then on what evidence do we think the virus is dangerous or even lethal? If No. 2 is correct, then how is the virus spread from person to person? We are told it emerges from the cell to infect others. Then why isn't it possible to find it?

Finally, questioning these virology techniques and conclusions is not some distraction or divisive issue. Shining the light on this truth is essential to stop this terrible fraud that humanity is confronting. For, as we now know, if the virus has never been isolated, sequenced or shown to cause illness, if the virus is imaginary, then why are we wearing masks, social distancing and putting the whole world into prison?

Finally, if pathogenic viruses don't exist, then what is going into those injectable devices erroneously called "vaccines," and what is their purpose? This scientific question is the most urgent and relevant one of our time.

We are correct. The SARS-CoV2 virus does not exist.

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Ickonic is something that has been a dream of mine for the last 5 years, growing up around alternative information I have always had a natural interest in what is going on in the World and what could I do to make it better.
Across the range of subjects and positions of influence occupied mainly by people who don't strive to make things better it's the Media that I have always found the most frustrating and fascinating. Mainly because if the Media did their Jobs properly then so much of the negative things happening in the World simply would not be able to happen, because they would be exposed within a heartbeat.
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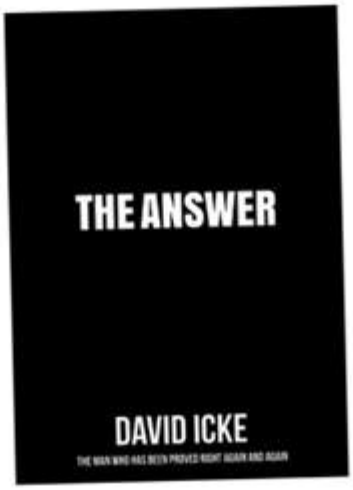
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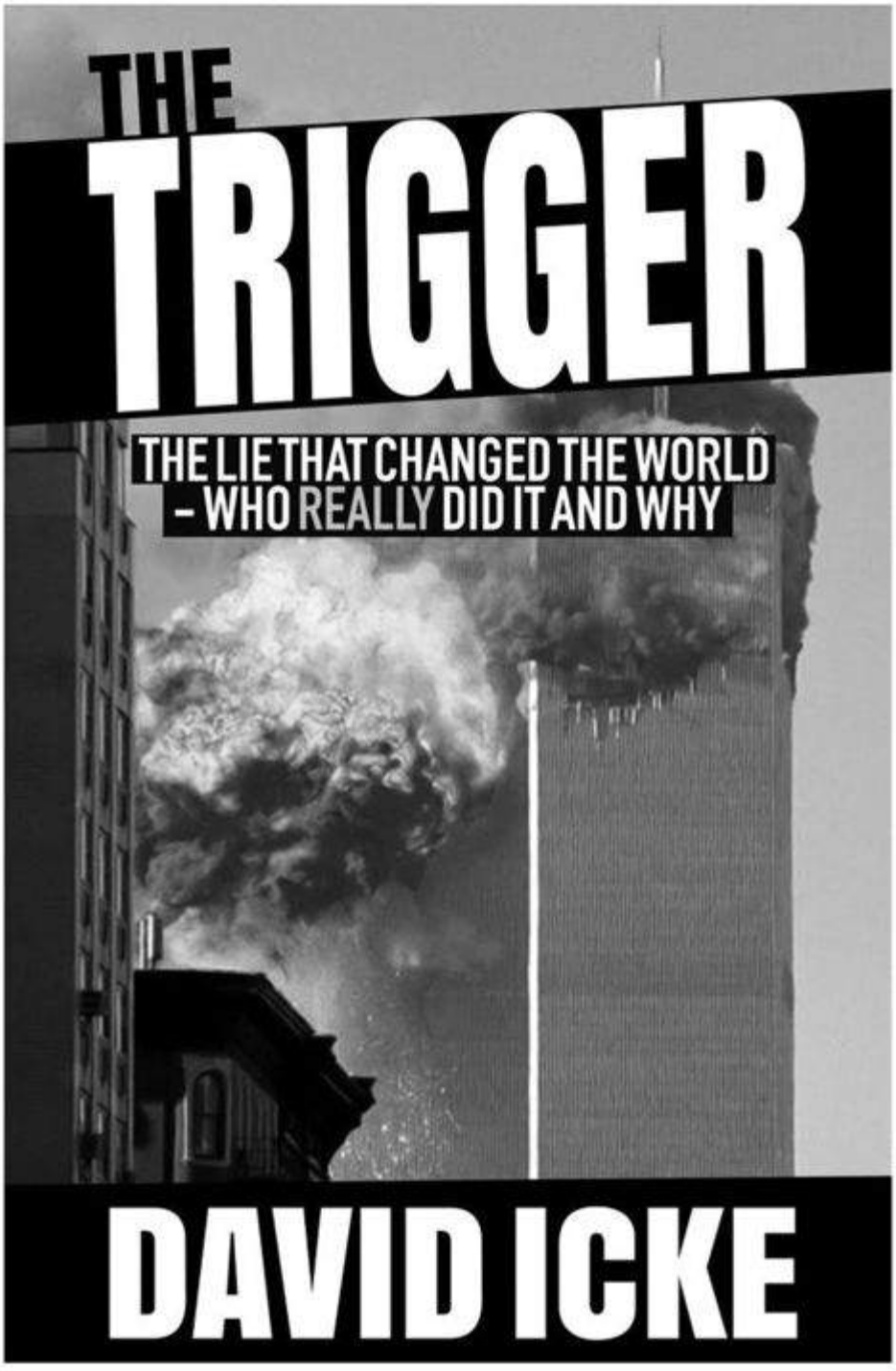
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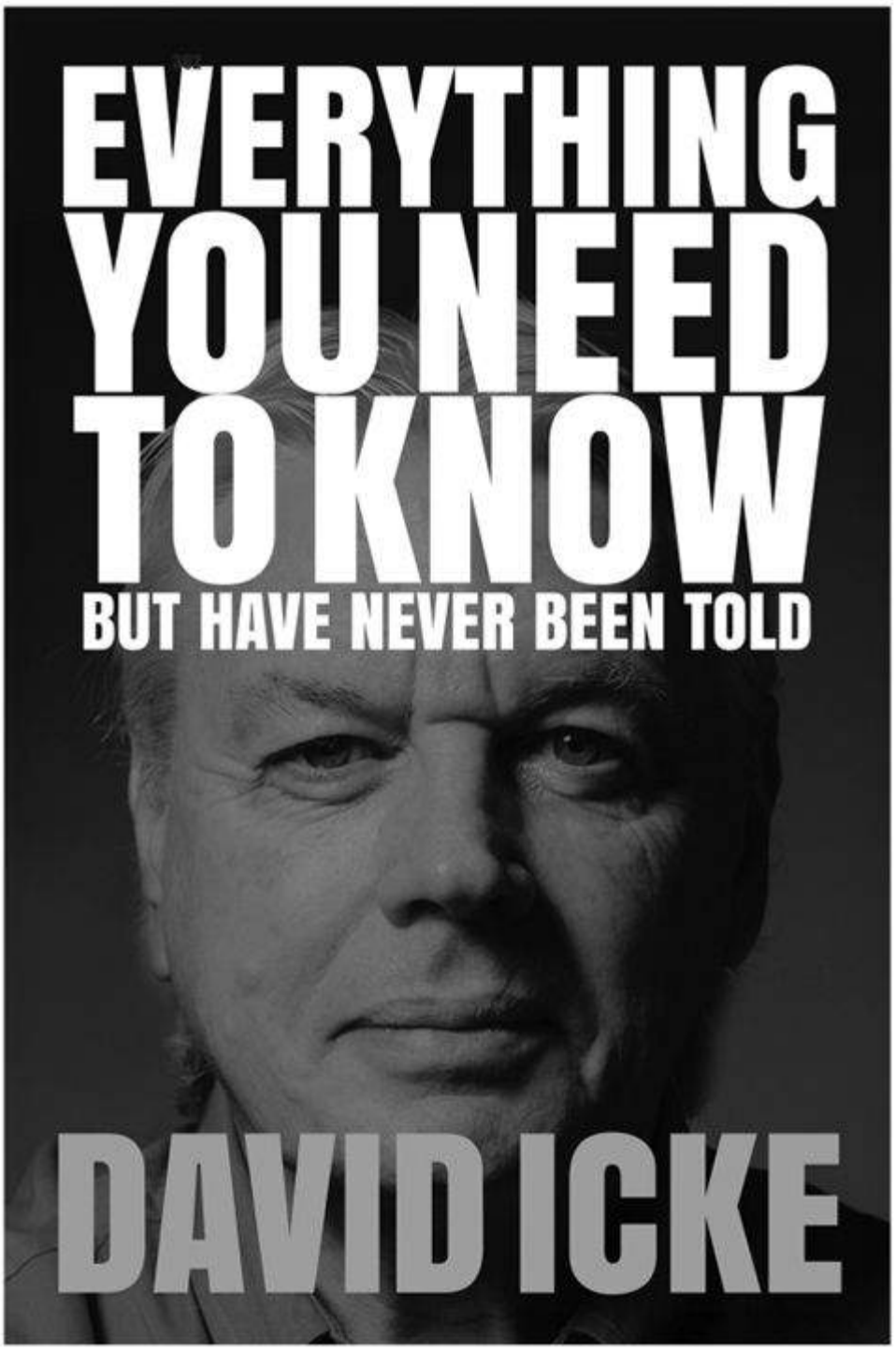


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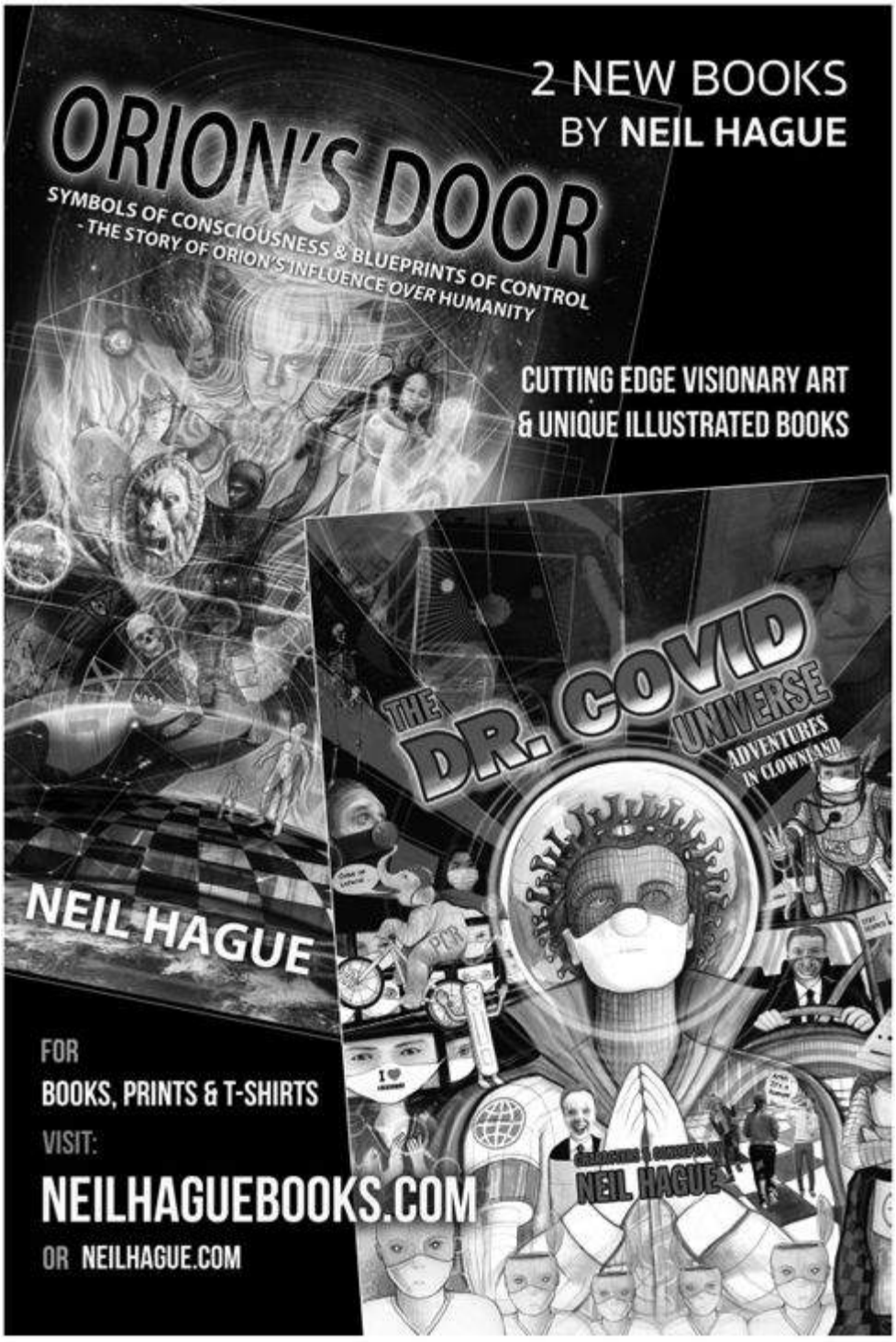
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noun

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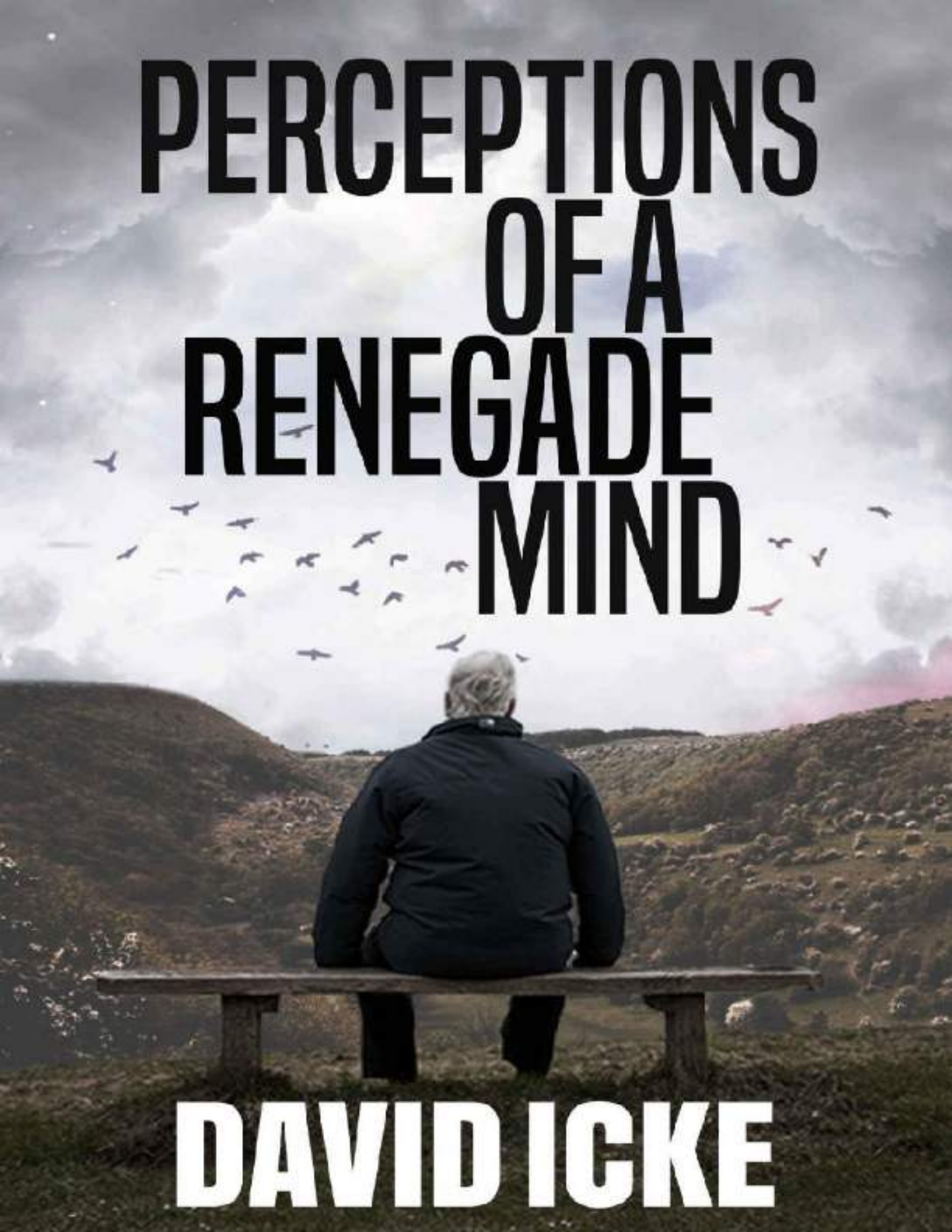

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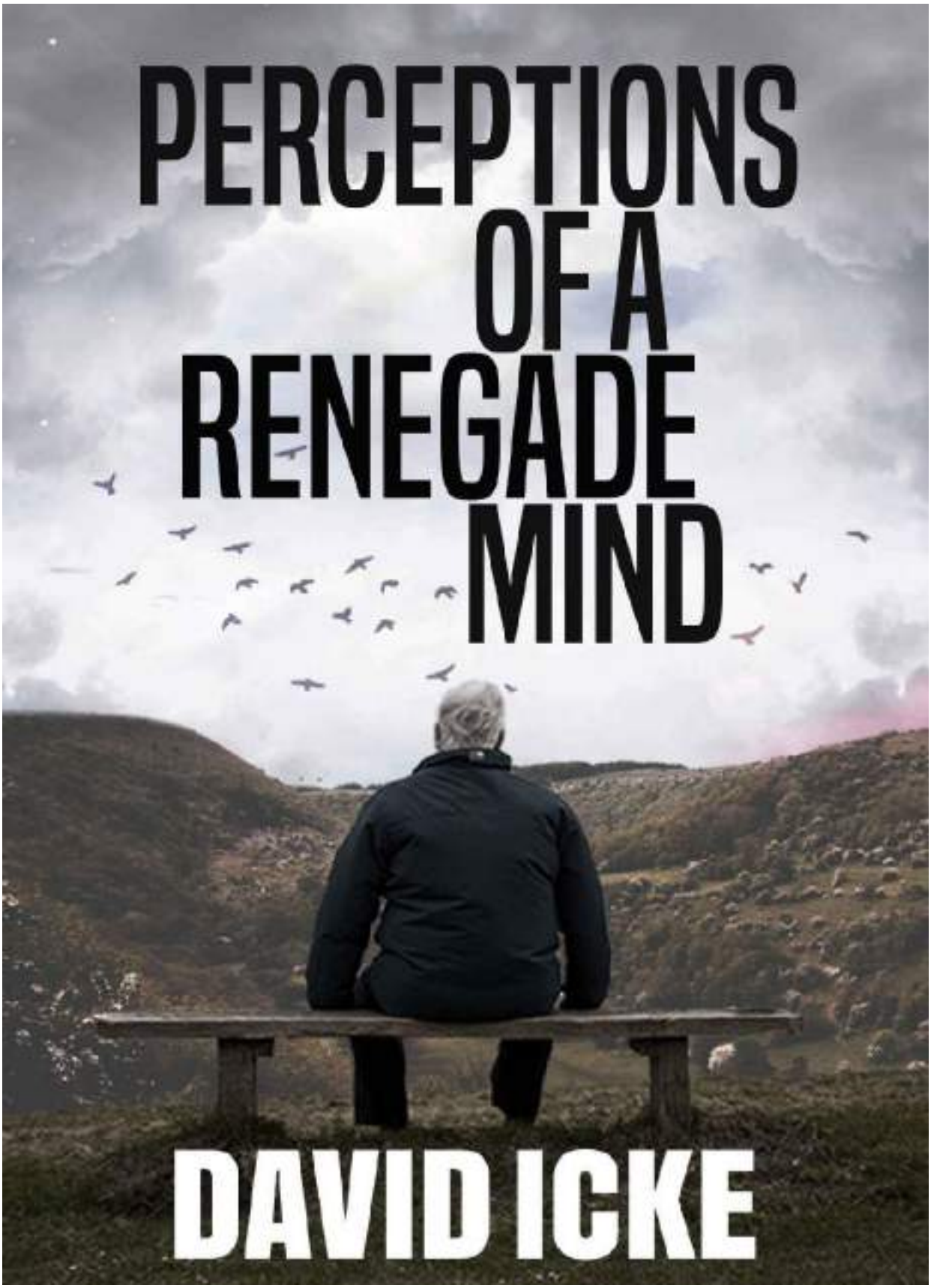
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PERCEPTIONS OF A RENEGADE MIND



DAVID ICKE


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PERCEPTIONS OF A RENEGADE MIND



DAVID ICKE

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Renegade:
Adjective
‘Having rejected tradition: Unconventional.’
Merriam-Webster Dictionary

Acquiescence to tyranny is the death of the spirit

You may be 38 years old, as I happen to be. And one day, some great opportunity stands before you and calls you to stand up for some great principle, some great issue, some great cause. And you refuse to do it because you are afraid … You refuse to do it because you want to live longer … You're afraid that you will lose your job, or you are afraid that you will be criticised or that you will lose your popularity, or you're afraid that somebody will stab you, or shoot at you or bomb your house; so you refuse to take the stand.

Well, you may go on and live until you are 90, but you're just as dead at 38 as you would be at 90. And the cessation of breathing in your life is but the belated announcement of an earlier death of the spirit.

Martin Luther King

How the few control the many and always have – the many do whatever they're told

'Forward, the Light Brigade!'
Was there a man dismayed?
Not though the soldier knew
Someone had blundered.
Theirs not to make reply,
Theirs not to reason why,
Theirs but to do and die.
Into the valley of Death
Rode the six hundred.

Cannon to right of them,
Cannon to left of them,
Cannon in front of them
Volleyed and thundered;
Stormed at with shot and shell,
Boldly they rode and well,
Into the jaws of Death,
Into the mouth of hell
Rode the six hundred

Alfred Lord Tennyson (1809-1892)

The mist is lifting slowly
I can see the way ahead
And I've left behind the empty streets
That once inspired my life
And the strength of the emotion
Is like thunder in the air
'Cos the promise that we made each other
Haunts me to the end

The secret of your beauty
And the mystery of your soul
I've been searching for in everyone I meet
And the times I've been mistaken
It's impossible to say
And the grass is growing
Underneath our feet

The words that I remember
From my childhood still are true
That there's none so blind
As those who will not see
And to those who lack the courage
And say it's dangerous to try
Well they just don't know
That love eternal will not be denied

I know you're out there somewhere
Somewhere, somewhere
I know you're out there somewhere

Somewhere you can hear my voice
I know I'll find you somehow
Somehow, somehow
I know I'll find you somehow
And somehow I'll return again to you

The Moody Blues

Are you a gutless wonder - or a Renegade Mind?

Monuments put from pen to paper,
Turns me into a gutless wonder,
And if you tolerate this,
Then your children will be next.
Gravity keeps my head down,
Or is it maybe shame ...

Manic Street Preachers

Rise like lions after slumber
In unvanquishable number.
Shake your chains to earth like dew
Which in sleep have fallen on you.
Ye are many – they are few.

Percy Shelley

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CHAPTER ONE

I'm thinking' – Oh, but *are* you?

Think for yourself and let others enjoy the privilege of doing so too
Voltaire

French-born philosopher, mathematician and scientist René Descartes became famous for his statement in Latin in the 17th century which translates into English as: 'I think, therefore I am.'

On the face of it that is true. Thought reflects perception and perception leads to both behaviour and self-identity. In that sense 'we' are what we think. But who or what is doing the thinking and is thinking the only route to perception? Clearly, as we shall see, 'we' are not always the source of 'our' perception, indeed with regard to humanity as a whole this is rarely the case; and thinking is far from the only means of perception. Thought is the village idiot compared with other expressions of consciousness that we all have the potential to access and tap into. This has to be true when we *are* those other expressions of consciousness which are infinite in nature. We have forgotten this, or, more to the point, been manipulated to forget.

These are not just the esoteric musings of the navel. The whole foundation of human control and oppression is control of perception. Once perception is hijacked then so is behaviour which is dictated by perception. Collective perception becomes collective behaviour and collective behaviour is what we call human society. Perception is all and those behind human control know that which is

why perception is the target 24/7 of the psychopathic manipulators that I call the Global Cult. They know that if they dictate perception they will dictate behaviour and collectively dictate the nature of human society. They are further aware that perception is formed from information received and if they control the circulation of information they will to a vast extent direct human behaviour. Censorship of information and opinion has become globally Nazi-like in recent years and never more blatantly than since the illusory 'virus pandemic' was triggered out of China in 2019 and across the world in 2020. Why have billions submitted to house arrest and accepted fascistic societies in a way they would have never believed possible? Those controlling the information spewing from government, mainstream media and Silicon Valley (all controlled by the same Global Cult networks) told them they were in danger from a 'deadly virus' and only by submitting to house arrest and conceding their most basic of freedoms could they and their families be protected. This monumental and provable lie became the *perception* of the billions and therefore the *behaviour* of the billions. In those few words you have the whole structure and modus operandi of human control. Fear is a perception – **F**alse **E**motion **A**ppearing **R**eal – and fear is the currency of control. In short … get them by the balls (or give them the impression that you have) and their hearts and minds will follow. Nothing grips the dangly bits and freezes the rear-end more comprehensively than fear.

World number 1

There are two 'worlds' in what appears to be one 'world' and the prime difference between them is knowledge. First we have the mass of human society in which the population is maintained in coldly-calculated ignorance through control of information and the 'education' (indoctrination) system. That's all you really need to control to enslave billions in a perceptual delusion in which what are perceived to be *their* thoughts and opinions are ever-repeated mantras that the system has been downloading all their lives through 'education', media, science, medicine, politics and academia

in which the personnel and advocates are themselves overwhelmingly the perceptual products of the same repetition. Teachers and academics in general are processed by the same programming machine as everyone else, but unlike the great majority they never leave the 'education' program. It gripped them as students and continues to grip them as programmers of subsequent generations of students. The programmed become the programmers – the programmed programmers. The same can largely be said for scientists, doctors and politicians and not least because as the American writer Upton Sinclair said: 'It is difficult to get a man to understand something when his salary depends upon his not understanding it.' If your career and income depend on thinking the way the system demands then you will – bar a few free-minded exceptions – concede your mind to the Perceptual Mainframe that I call the Postage Stamp Consensus. This is a tiny band of perceived knowledge and possibility 'taught' (downloaded) in the schools and universities, pounded out by the mainstream media and on which all government policy is founded. Try thinking, and especially speaking and acting, outside of the 'box' of consensus and see what that does for your career in the Mainstream Everything which bullies, harasses, intimidates and ridicules the population into compliance. Here we have the simple structure which enslaves most of humanity in a perceptual prison cell for an entire lifetime and I'll go deeper into this process shortly. Most of what humanity is taught as fact is nothing more than programmed belief. American science fiction author Frank Herbert was right when he said: 'Belief can be manipulated. Only knowledge is dangerous.' In the 'Covid' age belief is promoted and knowledge is censored. It was always so, but never to the extreme of today.

World number 2

A 'number 2' is slang for 'doing a poo' and how appropriate that is when this other 'world' is doing just that on humanity every minute of every day. World number 2 is a global network of secret societies and semi-secret groups dictating the direction of society via

governments, corporations and authorities of every kind. I have spent more than 30 years uncovering and exposing this network that I call the Global Cult and knowing its agenda is what has made my books so accurate in predicting current and past events. Secret societies are secret for a reason. They want to keep their hoarded knowledge to themselves and their chosen initiates and to hide it from the population which they seek through ignorance to control and subdue. The whole foundation of the division between World 1 and World 2 is *knowledge*. What number 1 knows number 2 must not. Knowledge they have worked so hard to keep secret includes (a) the agenda to enslave humanity in a centrally-controlled global dictatorship, and (b) the nature of reality and life itself. The latter (b) must be suppressed to allow the former (a) to prevail as I shall be explaining. The way the Cult manipulates and interacts with the population can be likened to a spider's web. The 'spider' sits at the centre in the shadows and imposes its will through the web with each strand represented in World number 2 by a secret society, satanic or semi-secret group, and in World number 1 – the world of the seen – by governments, agencies of government, law enforcement, corporations, the banking system, media conglomerates and Silicon Valley (Fig 1 overleaf). The spider and the web connect and coordinate all these organisations to pursue the same global outcome while the population sees them as individual entities working randomly and independently. At the level of the web governments *are* the banking system *are* the corporations *are* the media *are* Silicon Valley *are* the World Health Organization working from their inner cores as one unit. Apparently unconnected countries, corporations, institutions, organisations and people are on the *same team* pursuing the same global outcome. Strands in the web immediately around the spider are the most secretive and exclusive secret societies and their membership is emphatically restricted to the Cult inner-circle emerging through the generations from particular bloodlines for reasons I will come to. At the core of the core you would get them in a single room. That's how many people are dictating the direction of human society and its transformation

through the ‘Covid’ hoax and other means. As the web expands out from the spider we meet the secret societies that many people will be aware of – the Freemasons, Knights Templar, Knights of Malta, Opus Dei, the inner sanctum of the Jesuit Order, and such like. Note how many are connected to the Church of Rome and there is a reason for that. The Roman Church was established as a revamp, a rebranding, of the relocated ‘Church’ of Babylon and the Cult imposing global tyranny today can be tracked back to Babylon and Sumer in what is now Iraq.



Figure 1: The global web through which the few control the many. (Image Neil Hague.)

Inner levels of the web operate in the unseen away from the public eye and then we have what I call the cusp organisations located at the point where the hidden meets the seen. They include a series of satellite organisations answering to a secret society founded in London in the late 19th century called the Round Table and among them are the Royal Institute of International Affairs (UK, founded in 1920); Council on Foreign Relations (US, 1921); Bilderberg Group (worldwide, 1954); Trilateral Commission (US/worldwide, 1972); and the Club of Rome (worldwide, 1968) which was created to exploit environmental concerns to justify the centralisation of global power to ‘save the planet’. The Club of Rome instigated with others the human-caused climate change hoax which has led to all the ‘green

new deals' demanding that very centralisation of control. Cusp organisations, which include endless 'think tanks' all over the world, are designed to coordinate a single global policy between political and business leaders, intelligence personnel, media organisations and anyone who can influence the direction of policy in their own sphere of operation. Major players and regular attenders will know what is happening – or some of it – while others come and go and are kept overwhelmingly in the dark about the big picture. I refer to these cusp groupings as semi-secret in that they can be publicly identified, but what goes on at the inner-core is kept very much 'in house' even from most of their members and participants through a fiercely-imposed system of compartmentalisation. Only let them know what they need to know to serve your interests and no more. The structure of secret societies serves as a perfect example of this principle. Most Freemasons never get higher than the bottom three levels of 'degree' (degree of knowledge) when there are 33 official degrees of the Scottish Rite. Initiates only qualify for the next higher 'compartment' or degree if those at that level choose to allow them. Knowledge can be carefully assigned only to those considered 'safe'. I went to my local Freemason's lodge a few years ago when they were having an 'open day' to show how cuddly they were and when I chatted to some of them I was astonished at how little the rank and file knew even about the most ubiquitous symbols they use. The mushroom technique – keep them in the dark and feed them bullshit – applies to most people in the web as well as the population as a whole. Sub-divisions of the web mirror in theme and structure transnational corporations which have a headquarters somewhere in the world dictating to all their subsidiaries in different countries. Subsidiaries operate in their methodology and branding to the same centrally-dictated plan and policy in pursuit of particular ends. The Cult web functions in the same way. Each country has its own web as a subsidiary of the global one. They consist of networks of secret societies, semi-secret groups and bloodline families and their job is to impose the will of the spider and the global web in their particular country. Subsidiary networks control and manipulate the national political system, finance, corporations, media, medicine, etc. to

ensure that they follow the globally-dictated Cult agenda. These networks were the means through which the 'Covid' hoax could be played out with almost every country responding in the same way.

The 'Yessir' pyramid

Compartmentalisation is the key to understanding how a tiny few can dictate the lives of billions when combined with a top-down sequence of imposition and acquiescence. The inner core of the Cult sits at the peak of the pyramidal hierarchy of human society (Fig 2 overleaf). It imposes its will – its agenda for the world – on the level immediately below which acquiesces to that imposition. This level then imposes the Cult will on the level below them which acquiesces and imposes on the next level. Very quickly we meet levels in the hierarchy that have no idea there even is a Cult, but the sequence of imposition and acquiescence continues down the pyramid in just the same way. 'I don't know why we are doing this but the order came from "on-high" and so we better just do it.' Alfred Lord Tennyson said of the cannon fodder levels in his poem *The Charge of the Light Brigade*: 'Theirs not to reason why; theirs but to do and die.' The next line says that 'into the valley of death rode the six hundred' and they died because they obeyed without question what their perceived 'superiors' told them to do. In the same way the population capitulated to 'Covid'. The whole hierarchical pyramid functions like this to allow the very few to direct the enormous many. Eventually imposition-acquiescence-imposition-acquiescence comes down to the mass of the population at the foot of the pyramid. If they acquiesce to those levels of the hierarchy imposing on them (governments/law enforcement/doctors/media) a circuit is completed between the population and the handful of super-psychopaths in the Cult inner core at the top of the pyramid. Without a circuit-breaking refusal to obey, the sequence of imposition and acquiescence allows a staggeringly few people to impose their will upon the entirety of humankind. We are looking at the very sequence that has subjugated billions since the start of 2020. Our freedom has not been taken from us. Humanity has given it

away. Fascists do not impose fascism because there are not enough of them. Fascism is imposed by the population acquiescing to fascism. Put another way allowing their perceptions to be programmed to the extent that leads to the population giving their freedom away by giving their perceptions – their mind – away. If this circuit is not broken by humanity ceasing to cooperate with their own enslavement then nothing can change. For that to happen people have to critically think and see through the lies and window dressing and then summon the backbone to act upon what they see. The Cult spends its days working to stop either happening and its methodology is systematic and highly detailed, but it can be overcome and that is what this book is all about.

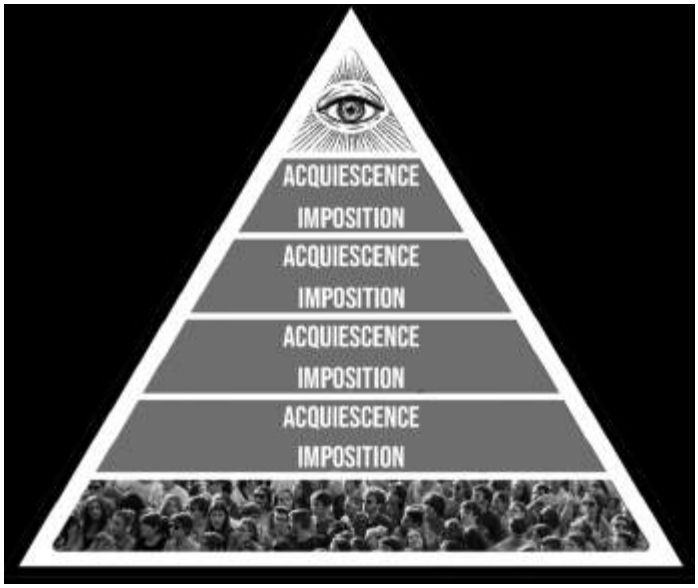


Figure 2: The simple sequence of imposition and compliance that allows a handful of people at the peak of the pyramid to dictate the lives of billions.

The Life Program

Okay, back to world number 1 or the world of the 'masses'. Observe the process of what we call 'life' and it is a perceptual download from cradle to grave. The Cult has created a global structure in which perception can be programmed and the program continually topped-up with what appears to be constant confirmation that the program is indeed true reality. The important word here is 'appears'.

This is the structure, the fly-trap, the Postage Stamp Consensus or Perceptual Mainframe, which represents that incredibly narrow band of perceived possibility delivered by the 'education' system, mainstream media, science and medicine. From the earliest age the download begins with parents who have themselves succumbed to the very programming their children are about to go through. Most parents don't do this out of malevolence and mostly it is quite the opposite. They do what they believe is best for their children and that is what the program has told them is best. Within three or four years comes the major transition from parental programming to full-blown state (Cult) programming in school, college and university where perceptually-programmed teachers and academics pass on their programming to the next generations. Teachers who resist are soon marginalised and their careers ended while children who resist are called a problem child for whom Ritalin may need to be prescribed. A few years after entering the 'world' children are under the control of authority figures representing the state telling them when they have to be there, when they can leave and when they can speak, eat, even go to the toilet. This is calculated preparation for a lifetime of obeying authority in all its forms. Reflex-action fear of authority is instilled by authority from the start. Children soon learn the carrot and stick consequences of obeying or defying authority which is underpinned daily for the rest of their life. Fortunately I daydreamed through this crap and never obeyed authority simply because it told me to. This approach to my alleged 'betters' continues to this day. There can be consequences of pursuing open-minded freedom in a world of closed-minded conformity. I spent a lot of time in school corridors after being ejected from the classroom for not taking some of it seriously and now I spend a lot of time being ejected from Facebook, YouTube and Twitter. But I can tell you that being true to yourself and not compromising your self-respect is far more exhilarating than bowing to authority for authority's sake. You don't have to be a sheep to the shepherd (authority) and the sheep dog (fear of not obeying authority).

The perceptual download continues throughout the formative years in school, college and university while script-reading 'teachers', 'academics' 'scientists', 'doctors' and 'journalists' insist that ongoing generations must be as programmed as they are. Accept the program or you will not pass your 'exams' which confirm your 'degree' of programming. It is tragic to think that many parents pressure their offspring to work hard at school to download the program and qualify for the next stage at college and university. The late, great, American comedian George Carlin said: 'Here's a bumper sticker I'd like to see: We are proud parents of a child who has resisted his teachers' attempts to break his spirit and bend him to the will of his corporate masters.' Well, the best of luck finding many of those, George. Then comes the moment to leave the formal programming years in academia and enter the 'adult' world of work. There you meet others in your chosen or prescribed arena who went through the same Postage Stamp Consensus program before you did. There is therefore overwhelming agreement between almost everyone on the basic foundations of Postage Stamp reality and the rejection, even contempt, of the few who have a mind of their own and are prepared to use it. This has two major effects. Firstly, the consensus confirms to the programmed that their download is really how things are. I mean, everyone knows that, right? Secondly, the arrogance and ignorance of Postage Stamp adherents ensure that anyone questioning the program will have unpleasant consequences for seeking their own truth and not picking their perceptions from the shelf marked: 'Things you must believe without question and if you don't you're a dangerous lunatic conspiracy theorist and a harebrained nutter'.

Every government, agency and corporation is founded on the same Postage Stamp prison cell and you can see why so many people believe the same thing while calling it their own 'opinion'. Fusion of governments and corporations in pursuit of the same agenda was the definition of fascism described by Italian dictator Benito Mussolini. The pressure to conform to perceptual norms downloaded for a lifetime is incessant and infiltrates society right

down to family groups that become censors and condemners of their own 'black sheep' for not, ironically, being sheep. We have seen an explosion of that in the 'Covid' era. Cult-owned global media unleashes its propaganda all day every day in support of the Postage Stamp and targets with abuse and ridicule anyone in the public eye who won't bend their mind to the will of the tyranny. Any response to this is denied (certainly in my case). They don't want to give a platform to expose official lies. Cult-owned-and-created Internet giants like Facebook, Google, YouTube and Twitter delete you for having an unapproved opinion. Facebook boasts that its AI censors delete 97-percent of 'hate speech' before anyone even reports it. Much of that 'hate speech' will simply be an opinion that Facebook and its masters don't want people to see. Such perceptual oppression is widely known as fascism. Even Facebook executive Benny Thomas, a 'CEO Global Planning Lead', said in comments secretly recorded by investigative journalism operation Project Veritas that Facebook is 'too powerful' and should be broken up:

I mean, no king in history has been the ruler of two billion people, but Mark Zuckerberg is … And he's 36. That's too much for a 36-year-old ... You should not have power over two billion people. I just think that's wrong.

Thomas said Facebook-owned platforms like Instagram, Oculus, and WhatsApp needed to be separate companies. 'It's too much power when they're all one together'. That's the way the Cult likes it, however. We have an executive of a Cult organisation in Benny Thomas that doesn't know there is a Cult such is the compartmentalisation. Thomas said that Facebook and Google 'are no longer companies, they're countries'. Actually they are more powerful than countries on the basis that if you control information you control perception and control human society.

I love my oppressor

Another expression of this psychological trickery is for those who realise they are being pressured into compliance to eventually

convince themselves to believe the official narratives to protect their self-respect from accepting the truth that they have succumbed to meek and subservient compliance. Such people become some of the most vehement defenders of the system. You can see them everywhere screaming abuse at those who prefer to think for themselves and by doing so reminding the compliers of their own capitulation to conformity. 'You are talking dangerous nonsense you Covidiot!!' Are you trying to convince me or yourself? It is a potent form of Stockholm syndrome which is defined as: 'A psychological condition that occurs when a victim of abuse identifies and attaches, or bonds, positively with their abuser.' An example is hostages bonding and even 'falling in love' with their kidnappers. The syndrome has been observed in domestic violence, abused children, concentration camp inmates, prisoners of war and many and various Satanic cults. These are some traits of Stockholm syndrome listed at goodtherapy.org:

- Positive regard towards perpetrators of abuse or captor [see 'Covid'].
- Failure to cooperate with police and other government authorities when it comes to holding perpetrators of abuse or kidnapping accountable [or in the case of 'Covid' cooperating with the police to enforce and defend their captors' demands].
- Little or no effort to escape [see 'Covid'].
- Belief in the goodness of the perpetrators or kidnappers [see 'Covid'].
- Appeasement of captors. This is a manipulative strategy for maintaining one's safety. As victims get rewarded – perhaps with less abuse or even with life itself – their appeasing behaviours are reinforced [see 'Covid'].
- Learned helplessness. This can be akin to 'if you can't beat 'em, join 'em'. As the victims fail to escape the abuse or captivity, they may start giving up and soon realize it's just easier for everyone if they acquiesce all their power to their captors [see 'Covid'].

- Feelings of pity toward the abusers, believing they are actually victims themselves. Because of this, victims may go on a crusade or mission to 'save' [protect] their abuser [see the venom unleashed on those challenging the official 'Covid' narrative].
- Unwillingness to learn to detach from their perpetrators and heal. In essence, victims may tend to be less loyal to themselves than to their abuser [*definitely* see 'Covid'].

Ponder on those traits and compare them with the behaviour of great swathes of the global population who have defended governments and authorities which have spent every minute destroying their lives and livelihoods and those of their children and grandchildren since early 2020 with fascistic lockdowns, house arrest and employment deletion to 'protect' them from a 'deadly virus' that their abusers' perceptually created to bring about this very outcome. We are looking at mass Stockholm syndrome. All those that agree to concede their freedom will believe those perceptions are originating in their own independent 'mind' when in fact by conceding their reality to Stockholm syndrome they have by definition conceded any independence of mind. Listen to the 'opinions' of the acquiescing masses in this 'Covid' era and what gushes forth is the repetition of the official version of everything delivered unprocessed, unfiltered and unquestioned. The whole programming dynamic works this way. I must be free because I'm told that I am and so I think that I am.

You can see what I mean with the chapter theme of 'I'm thinking – Oh, but *are* you?' The great majority are not thinking, let alone for themselves. They are repeating what authority has told them to believe which allows them to be controlled. Weaving through this mentality is the fear that the 'conspiracy theorists' are right and this again explains the often hysterical abuse that ensues when you dare to contest the official narrative of anything. Denial is the mechanism of hiding from yourself what you don't want to be true. Telling people what they want to hear is easy, but it's an infinitely greater challenge to tell them what they would rather not be happening.

One is akin to pushing against an open door while the other is met with vehement resistance no matter what the scale of evidence. I don't want it to be true so I'll convince myself that it's not. Examples are everywhere from the denial that a partner is cheating despite all the signs to the reflex-action rejection of any idea that world events in which country after country act in exactly the same way are centrally coordinated. To accept the latter is to accept that a force of unspeakable evil is working to destroy your life and the lives of your children with nothing too horrific to achieve that end. Who the heck wants that to be true? But if we don't face reality the end is duly achieved and the consequences are far worse and ongoing than breaking through the walls of denial today with the courage to make a stand against tyranny.

Connect the dots – but how?

A crucial aspect of perceptual programming is to portray a world in which everything is random and almost nothing is connected to anything else. Randomness cannot be coordinated by its very nature and once you perceive events as random the idea they could be connected is waved away as the rantings of the tinfoil-hat brigade. You can't plan and coordinate random you idiot! No, you can't, but you can hide the coldly-calculated and long-planned behind the *illusion* of randomness. A foundation manifestation of the Renegade Mind is to scan reality for patterns that connect the apparently random and turn pixels and dots into pictures. This is the way I work and have done so for more than 30 years. You look for similarities in people, modus operandi and desired outcomes and slowly, then ever quicker, the picture forms. For instance: There would seem to be no connection between the 'Covid pandemic' hoax and the human-caused global-warming hoax and yet they are masks (appropriately) on the same face seeking the same outcome. Those pushing the global warming myth through the Club of Rome and other Cult agencies are driving the lies about 'Covid' – Bill Gates is an obvious one, but they are endless. Why would the same people be involved in both when they are clearly not connected? Oh, but they

are. Common themes with personnel are matched by common goals. The 'solutions' to both 'problems' are centralisation of global power to impose the will of the few on the many to 'save' humanity from 'Covid' and save the planet from an 'existential threat' (we need 'zero Covid' and 'zero carbon emissions'). These, in turn, connect with the 'dot' of globalisation which was coined to describe the centralisation of global power in every area of life through incessant political and corporate expansion, trading blocks and superstates like the European Union. If you are the few and you want to control the many you have to centralise power and decision-making. The more you centralise power the more power the few at the centre will have over the many; and the more that power is centralised the more power those at the centre have to centralise even quicker. The momentum of centralisation gets faster and faster which is exactly the process we have witnessed. In this way the hoaxed 'pandemic' and the fakery of human-caused global warming serve the interests of globalisation and the seizure of global power in the hands of the Cult inner-circle which is behind 'Covid', 'climate change' *and* globalisation. At this point random 'dots' become a clear and obvious picture or pattern.

Klaus Schwab, the classic Bond villain who founded the Cult's Gates-funded World Economic Forum, published a book in 2020, *The Great Reset*, in which he used the 'problem' of 'Covid' to justify a total transformation of human society to 'save' humanity from 'climate change'. Schwab said: 'The pandemic represents a rare but narrow window of opportunity to reflect, reimagine, and reset our world.' What he didn't mention is that the Cult he serves is behind both hoaxes as I show in my book *The Answer*. He and the Cult don't have to reimagine the world. They know precisely what they want and that's why they destroyed human society with 'Covid' to 'build back better' in their grand design. Their job is not to imagine, but to get humanity to imagine and agree with their plans while believing it's all random. It must be pure coincidence that 'The Great Reset' has long been the Cult's code name for the global imposition of fascism and replaced previous code-names of the 'New World

Order' used by Cult frontmen like Father George Bush and the 'New Order of the Ages' which emerged from Freemasonry and much older secret societies. New Order of the Ages appears on the reverse of the Great Seal of the United States as 'Novus ordo seclorum' underneath the Cult symbol used since way back of the pyramid and all seeing-eye (Fig 3). The pyramid is the hierarchy of human control headed by the illuminated eye that symbolises the force behind the Cult which I will expose in later chapters. The term 'Annuit Coeptis' translates as 'He favours our undertaking'. We are told the 'He' is the Christian god, but 'He' is not as I will be explaining.



Figure 3: The all-seeing eye of the Cult 'god' on the Freemason-designed Great Seal of the United States and also on the dollar bill.

Having you on

Two major Cult techniques of perceptual manipulation that relate to all this are what I have called since the 1990s Problem-Reaction-Solution (PRS) and the Totalitarian Tiptoe (TT). They can be uncovered by the inquiring mind with a simple question: Who benefits? The answer usually identifies the perpetrators of a given action or happening through the concept of 'he who most benefits from a crime is the one most likely to have committed it'. The Latin 'Cue bono?' – Who benefits? – is widely attributed to the Roman orator and statesman Marcus Tullius Cicero. No wonder it goes back so far when the concept has been relevant to human behaviour since

history was recorded. Problem-Reaction-Solution is the technique used to manipulate us every day by covertly creating a problem (or the illusion of one) and offering the solution to the problem (or the illusion of one). In the first phase you create the problem and blame someone or something else for why it has happened. This may relate to a financial collapse, terrorist attack, war, global warming or pandemic, anything in fact that will allow you to impose the 'solution' to change society in the way you desire at that time. The 'problem' doesn't have to be real. PRS is manipulation of perception and all you need is the population to believe the problem is real. Human-caused global warming and the 'Covid pandemic' only have to be *perceived* to be real for the population to accept the 'solutions' of authority. I refer to this technique as NO-Problem-Reaction-Solution. Billions did not meekly accept house arrest from early 2020 because there was a real deadly 'Covid pandemic' but because they perceived – believed – that to be the case. The antidote to Problem-Reaction-Solution is to ask who benefits from the proposed solution. Invariably it will be anyone who wants to justify more control through deletion of freedom and centralisation of power and decision-making.

The two world wars were Problem-Reaction-Solutions that transformed and realigned global society. Both were manipulated into being by the Cult as I have detailed in books since the mid-1990s. They dramatically centralised global power, especially World War Two, which led to the United Nations and other global bodies thanks to the overt and covert manipulations of the Rockefeller family and other Cult bloodlines like the Rothschilds. The UN is a stalking horse for full-blown world government that I will come to shortly. The land on which the UN building stands in New York was donated by the Rockefellers and the same Cult family was behind Big Pharma scalpel and drug 'medicine' and the creation of the World Health Organization as part of the UN. They have been stalwarts of the eugenics movement and funded Hitler's race-purity expert' Ernst Rudin. The human-caused global warming hoax has been orchestrated by the Club of Rome through the UN which is

manufacturing both the 'problem' through its Intergovernmental Panel on Climate Change and imposing the 'solution' through its Agenda 21 and Agenda 2030 which demand the total centralisation of global power to 'save the world' from a climate hoax the United Nations is itself perpetrating. What a small world the Cult can be seen to be particularly among the inner circles. The bedfellow of Problem-Reaction-Solution is the Totalitarian Tiptoe which became the Totalitarian Sprint in 2020. The technique is fashioned to hide the carefully-coordinated behind the cover of apparently random events. You start the sequence at 'A' and you know you are heading for 'Z'. You don't want people to know that and each step on the journey is presented as a random happening while all the steps strung together lead in the same direction. The speed may have quickened dramatically in recent times, but you can still see the incremental approach of the Tiptoe in the case of 'Covid' as each new imposition takes us deeper into fascism. Tell people they have to do this or that to get back to 'normal', then this and this and this. With each new demand adding to the ones that went before the population's freedom is deleted until it disappears. The spider wraps its web around the flies more comprehensively with each new diktat. I'll highlight this in more detail when I get to the 'Covid' hoax and how it has been pulled off. Another prime example of the Totalitarian Tiptoe is how the Cult-created European Union went from a 'free-trade zone' to a centralised bureaucratic dictatorship through the Tiptoe of incremental centralisation of power until nations became mere administrative units for Cult-owned dark suits in Brussels.

The antidote to ignorance is knowledge which the Cult seeks vehemently to deny us, but despite the systematic censorship to that end the Renegade Mind can overcome this by vociferously seeking out the facts no matter the impediments put in the way. There is also a method of thinking and perceiving – *knowing* – that doesn't even need names, dates, place-type facts to identify the patterns that reveal the story. I'll get to that in the final chapter. All you need to know about the manipulation of human society and to what end is still out there – *at the time of writing* – in the form of books, videos

and websites for those that really want to breach the walls of programmed perception. To access this knowledge requires the abandonment of the mainstream media as a source of information in the awareness that this is owned and controlled by the Cult and therefore promotes mass perceptions that suit the Cult. Mainstream media lies all day, every day. That is its function and very reason for being. Where it does tell the truth, here and there, is only because the truth and the Cult agenda very occasionally coincide. If you look for fact and insight to the BBC, CNN and virtually all the rest of them you are asking to be conned and perceptually programmed.

Know the outcome and you'll see the journey

Events seem random when you have no idea where the world is being taken. Once you do the random becomes the carefully planned. Know the outcome and you'll see the journey is a phrase I have been using for a long time to give context to daily happenings that appear unconnected. Does a problem, or illusion of a problem, trigger a proposed 'solution' that further drives society in the direction of the outcome? Invariably the answer will be yes and the random – *abracadabra* – becomes the clearly coordinated. So what is this outcome that unlocks the door to a massively expanded understanding of daily events? I will summarise its major aspects – the fine detail is in my other books – and those new to this information will see that the world they thought they were living in is a very different place. The foundation of the Cult agenda is the incessant centralisation of power and all such centralisation is ultimately in pursuit of Cult control on a global level. I have described for a long time the planned world structure of top-down dictatorship as the Hunger Games Society. The term obviously comes from the movie series which portrayed a world in which a few living in military-protected hi-tech luxury were the overlords of a population condemned to abject poverty in isolated 'sectors' that were not allowed to interact. 'Covid' lockdowns and travel bans anyone? The 'Hunger Games' pyramid of structural control has the inner circle of the Cult at the top with pretty much the entire

population at the bottom under their control through dependency for survival on the Cult. The whole structure is planned to be protected and enforced by a military-police state (Fig 4).

Here you have the reason for the global lockdowns of the fake pandemic to coldly destroy independent incomes and livelihoods and make everyone dependent on the 'state' (the Cult that controls the 'states'). I have warned in my books for many years about the plan to introduce a 'guaranteed income' – a barely survivable pittance – designed to impose dependency when employment was destroyed by AI technology and now even more comprehensively at great speed by the 'Covid' scam. Once the pandemic was played and lockdown consequences began to delete independent income the authorities began to talk right on cue about the need for a guaranteed income and a 'Great Reset'. Guaranteed income will be presented as benevolent governments seeking to help a desperate people – desperate as a direct result of actions of the same governments. The truth is that such payments are a trap. You will only get them if you do exactly what the authorities demand including mass vaccination (genetic manipulation). We have seen this theme already in Australia where those dependent on government benefits have them reduced if parents don't agree to have their children vaccinated according to an insane health-destroying government-dictated schedule. Calculated economic collapse applies to governments as well as people. The Cult wants rid of countries through the creation of a world state with countries broken up into regions ruled by a world government and super states like the European Union. Countries must be bankrupted, too, to this end and it's being achieved by the trillions in 'rescue packages' and furlough payments, trillions in lost taxation, and money-no-object spending on 'Covid' including constant all-medium advertising (programming) which has made the media dependent on government for much of its income. The day of reckoning is coming – as planned – for government spending and given that it has been made possible by printing money and not by production/taxation there is inflation on the way that has the

potential to wipe out monetary value. In that case there will be no need for the Cult to steal your money. It just won't be worth anything (see the German Weimar Republic before the Nazis took over). Many have been okay with lockdowns while getting a percentage of their income from so-called furlough payments without having to work. Those payments are dependent, however, on people having at least a theoretical job with a business considered non-essential and ordered to close. As these business go under because they are closed by lockdown after lockdown the furlough stops and it will for everyone eventually. Then what? The 'then what?' is precisely the idea.



Figure 4: The Hunger Games Society structure I have long warned was planned and now the 'Covid' hoax has made it possible. This is the real reason for lockdowns.

Hired hands

Between the Hunger Games Cult elite and the dependent population is planned to be a vicious military-police state (a fusion of the two into one force). This has been in the making for a long time with police looking ever more like the military and carrying weapons to match. The pandemic scam has seen this process accelerate so fast as

lockdown house arrest is brutally enforced by carefully recruited fascist minds and gormless system-servers. The police and military are planned to merge into a centrally-directed world army in a global structure headed by a world government which wouldn't be elected even by the election fixes now in place. The world army is not planned even to be human and instead wars would be fought, primarily against the population, using robot technology controlled by artificial intelligence. I have been warning about this for decades and now militaries around the world are being transformed by this very AI technology. The global regime that I describe is a particular form of fascism known as a technocracy in which decisions are not made by clueless and co-opted politicians but by unelected technocrats – scientists, engineers, technologists and bureaucrats. Cult-owned-and-controlled Silicon Valley giants are examples of technocracy and they already have far more power to direct world events than governments. They are with their censorship *selecting* governments. I know that some are calling the 'Great Reset' a Marxist communist takeover, but fascism and Marxism are different labels for the same tyranny. Tell those who lived in fascist Germany and Stalinist Russia that there was a difference in the way their freedom was deleted and their lives controlled. I could call it a fascist technocracy or a Marxist technocracy and they would be equally accurate. The Hunger Games society with its world government structure would oversee a world army, world central bank and single world cashless currency imposing its will on a microchipped population (Fig 5). Scan its different elements and see how the illusory pandemic is forcing society in this very direction at great speed. Leaders of 23 countries and the World Health Organization (WHO) backed the idea in March, 2021, of a global treaty for 'international cooperation' in 'health emergencies' and nations should 'come together as a global community for peaceful cooperation that extends beyond this crisis'. Cut the Orwellian bullshit and this means another step towards global government. The plan includes a cashless digital money system that I first warned about in 1993. Right at the start of 'Covid' the deeply corrupt Tedros

Adhanom Ghebreyesus, the crooked and merely gofer 'head' of the World Health Organization, said it was possible to catch the 'virus' by touching cash and it was better to use cashless means. The claim was ridiculous nonsense and like the whole 'Covid' mind-trick it was nothing to do with 'health' and everything to do with pushing every aspect of the Cult agenda. As a result of the Tedros lie the use of cash has plummeted. The Cult script involves a single world digital currency that would eventually be technologically embedded in the body. China is a massive global centre for the Cult and if you watch what is happening there you will know what is planned for everywhere. The Chinese government is developing a digital currency which would allow fines to be deducted immediately via AI for anyone caught on camera breaking its fantastic list of laws and the money is going to be programmable with an expiry date to ensure that no one can accrue wealth except the Cult and its operatives.



Figure 5: The structure of global control the Cult has been working towards for so long and this has been enormously advanced by the 'Covid' illusion.

Serfdom is so smart

The Cult plan is far wider, extreme, and more comprehensive than even most conspiracy researchers appreciate and I will come to the true depths of deceit and control in the chapters 'Who controls the

Cult?' and 'Escaping Wetiko'. Even the world that we know is crazy enough. We are being deluged with ever more sophisticated and controlling technology under the heading of 'smart'. We have smart televisions, smart meters, smart cards, smart cars, smart driving, smart roads, smart pills, smart patches, smart watches, smart skin, smart borders, smart pavements, smart streets, smart cities, smart communities, smart environments, smart growth, smart planet ... smart *everything* around us. Smart technologies and methods of operation are designed to interlock to create a global Smart Grid connecting the entirety of human society including human minds to create a centrally-dictated 'hive' mind. 'Smart cities' is code for densely-occupied megacities of total surveillance and control through AI. Ever more destructive frequency communication systems like 5G have been rolled out without any official testing for health and psychological effects (colossal). 5G/6G/7G systems are needed to run the Smart Grid and each one becomes more destructive of body and mind. Deleting independent income is crucial to forcing people into these AI-policed prisons by ending private property ownership (except for the Cult elite). The Cult's Great Reset now openly foresees a global society in which no one will own any possessions and everything will be rented while the Cult would own literally everything under the guise of government and corporations. The aim has been to use the lockdowns to destroy sources of income on a mass scale and when the people are destitute and in unrepayable amounts of debt (problem) Cult assets come forward with the pledge to write-off debt in return for handing over all property and possessions (solution). Everything – literally everything including people – would be connected to the Internet via AI. I was warning years ago about the coming Internet of Things (IoT) in which all devices and technology from your car to your fridge would be plugged into the Internet and controlled by AI. Now we are already there with much more to come. The next stage is the Internet of Everything (IoE) which is planned to include the connection of AI to the human brain and body to replace the human mind with a centrally-controlled AI mind. Instead of perceptions

being manipulated through control of information and censorship those perceptions would come direct from the Cult through AI. What do you think? You think whatever AI decides that you think. In human terms there would be no individual 'think' any longer. Too incredible? The ravings of a lunatic? Not at all. Cult-owned crazies in Silicon Valley have been telling us the plan for years without explaining the real motivation and calculated implications. These include Google executive and 'futurist' Ray Kurzweil who highlights the year 2030 for when this would be underway. He said:

Our thinking ... will be a hybrid of biological and non-biological thinking ... humans will be able to extend their limitations and 'think in the cloud' ... We're going to put gateways to the cloud in our brains ... We're going to gradually merge and enhance ourselves ... In my view, that's the nature of being human – we transcend our limitations.

As the technology becomes vastly superior to what we are then the small proportion that is still human gets smaller and smaller and smaller until it's just utterly negligible.

The sales-pitch of Kurzweil and Cult-owned Silicon Valley is that this would make us 'super-human' when the real aim is to make us post-human and no longer 'human' in the sense that we have come to know. The entire global population would be connected to AI and become the centrally-controlled 'hive-mind' of externally-delivered perceptions. The Smart Grid being installed to impose the Cult's will on the world is being constructed to allow particular locations – even one location – to control the whole global system. From these prime control centres, which absolutely include China and Israel, anything connected to the Internet would be switched on or off and manipulated at will. Energy systems could be cut, communication via the Internet taken down, computer-controlled driverless autonomous vehicles driven off the road, medical devices switched off, the potential is limitless given how much AI and Internet connections now run human society. We have seen nothing yet if we allow this to continue. Autonomous vehicle makers are working with law enforcement to produce cars designed to automatically pull over if they detect a police or emergency vehicle flashing from up to 100 feet away. At a police stop the car would be unlocked and the

window rolled down automatically. Vehicles would only take you where the computer (the state) allowed. The end of petrol vehicles and speed limiters on all new cars in the UK and EU from 2022 are steps leading to electric computerised transport over which ultimately you have no control. The picture is far bigger even than the Cult global network or web and that will become clear when I get to the nature of the 'spider'. There is a connection between all these happenings and the instigation of DNA-manipulating 'vaccines' (which aren't 'vaccines') justified by the 'Covid' hoax. That connection is the unfolding plan to transform the human body from a biological to a synthetic biological state and this is why synthetic biology is such a fast-emerging discipline of mainstream science. 'Covid vaccines' are infusing self-replicating synthetic genetic material into the cells to cumulatively take us on the Totalitarian Tiptoe from Human 1.0 to the synthetic biological Human 2.0 which will be physically and perceptually attached to the Smart Grid to one hundred percent control every thought, perception and deed. Humanity needs to wake up and *fast*.

This is the barest explanation of where the 'outcome' is planned to go but it's enough to see the journey happening all around us. Those new to this information will already see 'Covid' in a whole new context. I will add much more detail as we go along, but for the minutiae evidence see my mega-works, *The Answer, The Trigger* and *Everything You Need to Know But Have Never Been Told*.

Now – how does a Renegade Mind see the 'world'?

CHAPTER TWO

Renegade Perception

It is one thing to be clever and another to be wise
George R.R. Martin

A simple definition of the difference between a programmed mind and a Renegade Mind would be that one sees only dots while the other connects them to see the picture. Reading reality with accuracy requires the observer to (a) know the planned outcome and (b) realise that everything, but *everything*, is connected.

The entirety of infinite reality is connected – that's its very nature – and with human society an expression of infinite reality the same must apply. Simple cause and effect is a connection. The effect is triggered by the cause and the effect then becomes the cause of another effect. Nothing happens in isolation because it *can't*. Life in whatever reality is simple choice and consequence. We make choices and these lead to consequences. If we don't like the consequences we can make different choices and get different consequences which lead to other choices and consequences. The choice and the consequence are not only connected they are indivisible. You can't have one without the other as an old song goes. A few cannot control the world unless those being controlled allow that to happen – cause and effect, choice and consequence. Control – who has it and who doesn't – is a two-way process, a symbiotic relationship, involving the controller and controlled. 'They took my freedom away!!' Well, yes, but you also gave it to them. Humanity is

subjected to mass control because humanity has acquiesced to that control. This is all cause and effect and literally a case of give and take. In the same way world events of every kind are connected and the Cult works incessantly to sell the illusion of the random and coincidental to maintain the essential (to them) perception of dots that hide the picture. Renegade Minds know this and constantly scan the world for patterns of connection. This is absolutely pivotal in understanding the happenings in the world and without that perspective clarity is impossible. First you know the planned outcome and then you identify the steps on the journey – the day-by-day apparently random which, when connected in relation to the outcome, no longer appear as individual events, but as the proverbial *chain* of events leading in the same direction. I'll give you some examples:

Political puppet show

We are told to believe that politics is 'adversarial' in that different parties with different beliefs engage in an endless tussle for power. There may have been some truth in that up to a point – and only a point – but today divisions between 'different' parties are rhetorical not ideological. Even the rhetorical is fusing into one-speak as the parties eject any remaining free thinkers while others succumb to the ever-gathering intimidation of anyone with the 'wrong' opinion. The Cult is not a new phenomenon and can be traced back thousands of years as my books have documented. Its intergenerational initiates have been manipulating events with increasing effect the more that global power has been centralised. In ancient times the Cult secured control through the system of monarchy in which 'special' bloodlines (of which more later) demanded the right to rule as kings and queens simply by birthright and by vanquishing others who claimed the same birthright. There came a time, however, when people had matured enough to see the unfairness of such tyranny and demanded a say in who governed them. Note the word – *governed* them. Not served them – *governed* them, hence government defined as 'the political direction and control exercised over the

actions of the members, citizens, or inhabitants of communities, societies, and states; direction of the affairs of a state, community, etc.' Governments exercise control over rather than serve just like the monarchies before them. Bizarrely there are still countries like the United Kingdom which are ruled by a monarch *and* a government that officially answers to the monarch. The UK head of state and that of Commonwealth countries such as Canada, Australia and New Zealand is 'selected' by who in a *single family* had unprotected sex with whom and in what order. Pinch me it can't be true. Ouch! Shit, it is. The demise of monarchies in most countries offered a potential vacuum in which some form of free and fair society could arise and the Cult had that base covered. Monarchies had served its interests but they couldn't continue in the face of such widespread opposition and, anyway, replacing a 'royal' dictatorship that people could see with a dictatorship 'of the people' hiding behind the concept of 'democracy' presented far greater manipulative possibilities and ways of hiding coordinated tyranny behind the illusion of 'freedom'.

Democracy is quite wrongly defined as government selected by the population. This is not the case at all. It is government selected by *some* of the population (and then only in theory). This 'some' doesn't even have to be the majority as we have seen so often in first-past-the-post elections in which the so-called majority party wins fewer votes than the 'losing' parties combined. Democracy can give total power to a party in government from a minority of the votes cast. It's a sleight of hand to sell tyranny as freedom. Seventy-four million Trump-supporting Americans didn't vote for the 'Democratic' Party of Joe Biden in the distinctly dodgy election in 2020 and yet far from acknowledging the wishes and feelings of that great percentage of American society the Cult-owned Biden government set out from day one to destroy them and their right to a voice and opinion. Empty shell Biden and his Cult handlers said they were doing this to 'protect democracy'. Such is the level of lunacy and sickness to which politics has descended. Connect the dots and relate them to the desired outcome – a world government run by self-appointed technocrats and no longer even elected

politicians. While operating through its political agents in government the Cult is at the same time encouraging public distain for politicians by putting idiots and incompetents in theoretical power on the road to deleting them. The idea is to instil a public reaction that says of the technocrats: 'Well, they couldn't do any worse than the pathetic politicians.' It's all about controlling perception and Renegade Minds can see through that while programmed minds cannot when they are ignorant of both the planned outcome and the manipulation techniques employed to secure that end. This knowledge can be learned, however, and fast if people choose to get informed.

Politics may at first sight appear very difficult to control from a central point. I mean look at the 'different' parties and how would you be able to oversee them all and their constituent parts? In truth, it's very straightforward because of their structure. We are back to the pyramid of imposition and acquiescence. Organisations are structured in the same way as the system as a whole. Political parties are not open forums of free expression. They are hierarchies. I was a national spokesman for the British Green Party which claimed to be a different kind of politics in which influence and power was devolved; but I can tell you from direct experience – and it's far worse now – that Green parties are run as hierarchies like all the others however much they may try to hide that fact or kid themselves that it's not true. A very few at the top of all political parties are directing policy and personnel. They decide if you are elevated in the party or serve as a government minister and to do that you have to be a yes man or woman. Look at all the maverick political thinkers who never ascended the greasy pole. If you want to progress within the party or reach 'high-office' you need to fall into line and conform. Exceptions to this are rare indeed. Should you want to run for parliament or Congress you have to persuade the local or state level of the party to select you and for that you need to play the game as dictated by the hierarchy. If you secure election and wish to progress within the greater structure you need to go on conforming to what is acceptable to those running the hierarchy

from the peak of the pyramid. Political parties are perceptual gulags and the very fact that there are party 'Whips' appointed to 'whip' politicians into voting the way the hierarchy demands exposes the ridiculous idea that politicians are elected to serve the people they are supposed to represent. Cult operatives and manipulation has long seized control of major parties that have any chance of forming a government and at least most of those that haven't. A new party forms and the Cult goes to work to infiltrate and direct. This has reached such a level today that you see video compilations of 'leaders' of all parties whether Democrats, Republicans, Conservative, Labour and Green parroting the same Cult mantra of 'Build Back Better' and the 'Great Reset' which are straight off the Cult song-sheet to describe the transformation of global society in response to the Cult-instigated hoaxes of the 'Covid pandemic' and human-caused 'climate change'. To see Caroline Lucas, the Green Party MP that I knew when I was in the party in the 1980s, speaking in support of plans proposed by Cult operative Klaus Schwab representing the billionaire global elite is a real head-shaker.

Many parties – one master

The party system is another mind-trick and was instigated to change the nature of the dictatorship by swapping 'royalty' for dark suits that people believed – though now ever less so – represented their interests. Understanding this trick is to realise that a single force (the Cult) controls all parties either directly in terms of the major ones or through manipulation of perception and ideology with others. You don't need to manipulate Green parties to demand your transformation of society in the name of 'climate change' when they are obsessed with the lie that this is essential to 'save the planet'. You just give them a platform and away they go serving your interests while believing they are being environmentally virtuous. America's political structure is a perfect blueprint for how the two or multi-party system is really a one-party state. The Republican Party is controlled from one step back in the shadows by a group made up of billionaires and their gofers known as neoconservatives or Neocons.

I have exposed them in fine detail in my books and they were the driving force behind the policies of the imbecilic presidency of Boy George Bush which included 9/11 (see *The Trigger* for a comprehensive demolition of the official story), the subsequent 'war on terror' (war *of* terror) and the invasions of Afghanistan and Iraq. The latter was a No-Problem-Reaction-Solution based on claims by Cult operatives, including Bush and British Prime Minister Tony Blair, about Saddam Hussein's 'weapons of mass destruction' which did not exist as war criminals Bush and Blair well knew.

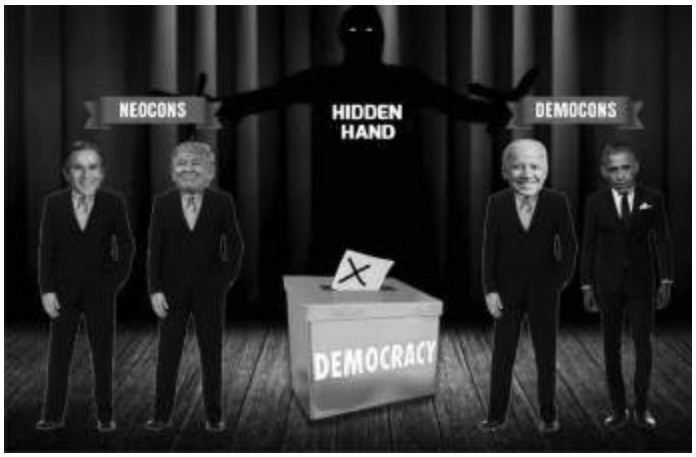


Figure 6: Different front people, different parties – same control system.

The Democratic Party has its own 'Neocon' group controlling from the background which I call the 'Democons' and here's the penny-drop – the Neocons and Democons answer to the same masters one step further back into the shadows (Fig 6). At that level of the Cult the Republican and Democrat parties are controlled by the same people and no matter which is in power the Cult is in power. This is how it works in almost every country and certainly in Britain with Conservative, Labour, Liberal Democrat and Green parties now all on the same page whatever the rhetoric may be in their feeble attempts to appear different. Neocons operated at the time of Bush through a think tank called The Project for the New American Century which in September, 2000, published a document entitled *Rebuilding America's Defenses: Strategies, Forces, and Resources*

For a New Century demanding that America fight 'multiple, simultaneous major theatre wars' as a 'core mission' to force regime-change in countries including Iraq, Libya and Syria. Neocons arranged for Bush ('Republican') and Blair ('Labour Party') to front-up the invasion of Iraq and when they departed the Democons orchestrated the targeting of Libya and Syria through Barack Obama ('Democrat') and British Prime Minister David Cameron ('Conservative Party'). We have 'different' parties and 'different' people, but the same unfolding script. The more the Cult has seized the reigns of parties and personnel the more their policies have transparently pursued the same agenda to the point where the fascist 'Covid' impositions of the Conservative junta of Jackboot Johnson in Britain were opposed by the Labour Party because they were not fascist enough. The Labour Party is likened to the US Democrats while the Conservative Party is akin to a British version of the Republicans and on both sides of the Atlantic they all speak the same language and support the direction demanded by the Cult although some more enthusiastically than others. It's a similar story in country after country because it's all centrally controlled. Oh, but what about Trump? I'll come to him shortly. Political 'choice' in the 'party' system goes like this: You vote for Party A and they get into government. You don't like what they do so next time you vote for Party B and they get into government. You don't like what they do when it's pretty much the same as Party A and why wouldn't that be with both controlled by the same force? Given that only two, sometimes three, parties have any chance of forming a government to get rid of Party B that you don't like you have to vote again for Party A which … you don't like. This, ladies and gentlemen, is what they call 'democracy' which we are told – wrongly – is a term interchangeable with 'freedom'.

The cult of cults

At this point I need to introduce a major expression of the Global Cult known as Sabbatian-Frankism. Sabbatian is also spelt as Sabbatean. I will summarise here. I have published major exposés

and detailed background in other works. Sabbatian-Frankism combines the names of two frauds posing as 'Jewish' men, Sabbatai Zevi (1626-1676), a rabbi, black magician and occultist who proclaimed he was the Jewish messiah; and Jacob Frank (1726-1791), the Polish 'Jew', black magician and occultist who said he was the reincarnation of 'messiah' Zevi and biblical patriarch Jacob. They worked across two centuries to establish the Sabbatian-Frankist cult that plays a major, indeed central, role in the manipulation of human society by the Global Cult which has its origins much further back in history than Sabbatai Zevi. I should emphasise two points here in response to the shrill voices that will scream 'anti-Semitism': (1) Sabbatian-Frankists are NOT Jewish and only pose as such to hide their cult behind a Jewish façade; and (2) my information about this cult has come from Jewish sources who have long realised that their society and community has been infiltrated and taken over by interloper Sabbatian-Frankists. Infiltration has been the foundation technique of Sabbatian-Frankism from its official origin in the 17th century. Zevi's Sabbatian sect attracted a massive following described as the biggest messianic movement in Jewish history, spreading as far as Africa and Asia, and he promised a return for the Jews to the 'Promised Land' of Israel. Sabbatianism was not Judaism but an inversion of everything that mainstream Judaism stood for. So much so that this sinister cult would have a feast day when Judaism had a fast day and whatever was forbidden in Judaism the Sabbatians were encouraged and even commanded to do. This included incest and what would be today called Satanism. Members were forbidden to marry outside the sect and there was a system of keeping their children ignorant of what they were part of until they were old enough to be trusted not to unknowingly reveal anything to outsiders. The same system is employed to this day by the Global Cult in general which Sabbatian-Frankism has enormously influenced and now largely controls.

Zevi and his Sabbatians suffered a setback with the intervention by the Sultan of the Islamic Ottoman Empire in the Middle East and what is now the Republic of Turkey where Zevi was located. The

Sultan gave him the choice of proving his 'divinity', converting to Islam or facing torture and death. Funnily enough Zevi chose to convert or at least appear to. Some of his supporters were disillusioned and drifted away, but many did not with 300 families also converting – only in theory – to Islam. They continued behind this Islamic smokescreen to follow the goals, rules and rituals of Sabbatianism and became known as 'crypto-Jews' or the 'Dönmeh' which means 'to turn'. This is rather ironic because they didn't 'turn' and instead hid behind a fake Islamic persona. The process of appearing to be one thing while being very much another would become the calling card of Sabbatianism especially after Zevi's death and the arrival of the Satanist Jacob Frank in the 18th century when the cult became Sabbatian-Frankism and plumbed still new depths of depravity and infiltration which included – still includes – human sacrifice and sex with children. Wherever Sabbatians go paedophilia and Satanism follow and is it really a surprise that Hollywood is so infested with child abuse and Satanism when it was established by Sabbatian-Frankists and is still controlled by them? Hollywood has been one of the prime vehicles for global perceptual programming and manipulation. How many believe the version of 'history' portrayed in movies when it is a travesty and inversion (again) of the truth? Rabbi Marvin Antelman describes Frankism in his book, *To Eliminate the Opiate*, as 'a movement of complete evil' while Jewish professor Gershom Scholem said of Frank in *The Messianic Idea in Judaism*: 'In all his actions [he was] a truly corrupt and degenerate individual ... one of the most frightening phenomena in the whole of Jewish history.' Frank was excommunicated by traditional rabbis, as was Zevi, but Frank was undeterred and enjoyed vital support from the House of Rothschild, the infamous banking dynasty whose inner-core are Sabbatian-Frankists and not Jews. Infiltration of the Roman Church and Vatican was instigated by Frank with many Dönmeh 'turning' again to convert to Roman Catholicism with a view to hijacking the reins of power. This was the ever-repeating modus operandi and continues to be so. Pose as an advocate of the religion, culture or country that you want to control and then

manipulate your people into the positions of authority and influence largely as advisers, administrators and Svengalis for those that appear to be in power. They did this with Judaism, Christianity (Christian Zionism is part of this), Islam and other religions and nations until Sabbatian-Frankism spanned the world as it does today.

Sabbatian Saudis and the terror network

One expression of the Sabbatian-Frankist Dönmeh within Islam is the ruling family of Saudi Arabia, the House of Saud, through which came the vile distortion of Islam known as Wahhabism. This is the violent creed followed by terrorist groups like Al-Qaeda and ISIS or Islamic State. Wahhabism is the hand-chopping, head-chopping 'religion' of Saudi Arabia which is used to keep the people in a constant state of fear so the interloper House of Saud can continue to rule. Al-Qaeda and Islamic State were lavishly funded by the House of Saud while being created and directed by the Sabbatian-Frankist network in the United States that operates through the Pentagon, CIA and the government in general of whichever 'party'. The front man for the establishment of Wahhabism in the middle of the 18th century was a Sabbatian-Frankist 'crypto-Jew' posing as Islamic called Muhammad ibn Abd al-Wahhab. His daughter would marry the son of Muhammad bin Saud who established the first Saudi state before his death in 1765 with support from the British Empire. Bin Saud's successors would establish modern Saudi Arabia in league with the British and Americans in 1932 which allowed them to seize control of Islam's major shrines in Mecca and Medina. They have dictated the direction of Sunni Islam ever since while Iran is the major centre of the Shiite version and here we have the source of at least the public conflict between them. The Sabbatian network has used its Wahhabi extremists to carry out Problem-Reaction-Solution terrorist attacks in the name of 'Al-Qaeda' and 'Islamic State' to justify a devastating 'war on terror', ever-increasing surveillance of the population and to terrify people into compliance. Another insight of the Renegade Mind is the streetwise understanding that

just because a country, location or people are attacked doesn't mean that those apparently representing that country, location or people are not behind the attackers. Often they are *orchestrating* the attacks because of the societal changes that can be then justified in the name of 'saving the population from terrorists'.

I show in great detail in *The Trigger* how Sabbatian-Frankists were the real perpetrators of 9/11 and not '19 Arab hijackers' who were blamed for what happened. Observe what was justified in the name of 9/11 alone in terms of Middle East invasions, mass surveillance and control that fulfilled the demands of the Project for the New American Century document published by the Sabbatian Neocons. What appear to be enemies are on the deep inside players on the same Sabbatian team. Israel and Arab 'royal' dictatorships are all ruled by Sabbatians and the recent peace agreements between Israel and Saudi Arabia, the United Arab Emirates (UAE) and others are only making formal what has always been the case behind the scenes. Palestinians who have been subjected to grotesque tyranny since Israel was bombed and terrorised into existence in 1948 have never stood a chance. Sabbatian-Frankists have controlled Israel (so the constant theme of violence and war which Sabbatians love) and they have controlled the Arab countries that Palestinians have looked to for real support that never comes. 'Royal families' of the Arab world in Saudi Arabia, Bahrain, UAE, etc., are all Sabbatians with allegiance to the aims of the cult and not what is best for their Arabic populations. They have stolen the oil and financial resources from their people by false claims to be 'royal dynasties' with a genetic right to rule and by employing vicious militaries to impose their will.

Satanic 'illumination'

The Satanist Jacob Frank formed an alliance in 1773 with two other Sabbatians, Mayer Amschel Rothschild (1744-1812), founder of the Rothschild banking dynasty, and Jesuit-educated fraudulent Jew, Adam Weishaupt, and this led to the formation of the Bavarian Illuminati, firstly under another name, in 1776. The Illuminati would

be the manipulating force behind the French Revolution (1789-1799) and was also involved in the American Revolution (1775-1783) before and after the Illuminati's official creation. Weishaupt would later become (in public) a Protestant Christian in archetypal Sabbatian style. I read that his name can be decoded as Adam-Weishaupt or 'the first man to lead those who know'. He wasn't a leader in the sense that he was a subordinate, but he did lead those below him in a crusade of transforming human society that still continues today. The theme was confirmed as early as 1785 when a horseman courier called Lanz was reported to be struck by lighting and extensive Illuminati documents were found in his saddlebags. They made the link to Weishaupt and detailed the plan for world takeover. Current events with 'Covid' fascism have been in the making for a very long time. Jacob Frank was jailed for 13 years by the Catholic Inquisition after his arrest in 1760 and on his release he headed for Frankfurt, Germany, home city and headquarters of the House of Rothschild where the alliance was struck with Mayer Amschel Rothschild and Weishaupt. Rothschild arranged for Frank to be given the title of Baron and he became a wealthy nobleman with a big following of Jews in Germany, the Austro-Hungarian Empire and other European countries. Most of them would have believed he was on their side.

The name 'Illuminati' came from the Zohar which is a body of works in the Jewish mystical 'bible' called the Kabbalah. 'Zohar' is the foundation of Sabbatian-Frankist belief and in Hebrew 'Zohar' means 'splendour', 'radiance', 'illuminated', and so we have 'Illuminati'. They claim to be the 'Illuminated Ones' from their knowledge systematically hidden from the human population and passed on through generations of carefully-chosen initiates in the global secret society network or Cult. Hidden knowledge includes an awareness of the Cult agenda for the world and the nature of our collective reality that I will explore later. Cult 'illumination' is symbolised by the torch held by the Statue of Liberty which was gifted to New York by French Freemasons in Paris who knew exactly what it represents. 'Liberty' symbolises the goddess worshipped in

Babylon as Queen Semiramis or Ishtar. The significance of this will become clear. Notice again the ubiquitous theme of inversion with the Statue of 'Liberty' really symbolising mass control (Fig 7). A mirror-image statute stands on an island in the River Seine in Paris from where New York Liberty originated (Fig 8). A large replica of the Liberty flame stands on top of the Pont de l'Alma tunnel in Paris where Princess Diana died in a Cult ritual described in *The Biggest Secret*. Lucifer 'the light bringer' is related to all this (and much more as we'll see) and 'Lucifer' is a central figure in Sabbatian-Frankism and its associated Satanism. Sabbatians reject the Jewish Torah, or Pentateuch, the 'five books of Moses' in the Old Testament known as Genesis, Exodus, Leviticus, Numbers, and Deuteronomy which are claimed by Judaism and Christianity to have been dictated by 'God' to Moses on Mount Sinai. Sabbatians say these do not apply to them and they seek to replace them with the Zohar to absorb Judaism and its followers into their inversion which is an expression of a much greater global inversion. They want to delete all religions and force humanity to worship a one-world religion – Sabbatian Satanism that also includes worship of the Earth goddess. Satanic themes are being more and more introduced into mainstream society and while Christianity is currently the foremost target for destruction the others are planned to follow.



Figure 7: The Cult goddess of Babylon disguised as the Statue of Liberty holding the flame of Lucifer the 'light bringer'.



Figure 8: Liberty's mirror image in Paris where the New York version originated.

Marx brothers

Rabbi Marvin Antelman connects the Illuminati to the Jacobins in *To Eliminate the Opiate* and Jacobins were the force behind the French Revolution. He links both to the Bund der Gerechten, or League of the Just, which was the network that inflicted communism/Marxism on the world. Antelman wrote:

> The original inner circle of the Bund der Gerechten consisted of born Catholics, Protestants and Jews [Sabbatian-Frankist infiltrators], and those representatives of respective subdivisions formulated schemes for the ultimate destruction of their faiths. The heretical Catholics laid plans which they felt would take a century or more for the ultimate destruction of the church; the apostate Jews for the ultimate destruction of the Jewish religion.

Sabbatian-created communism connects into this anti-religion agenda in that communism does not allow for the free practice of religion. The Sabbatian 'Bund' became the International Communist Party and Communist League and in 1848 'Marxism' was born with the Communist Manifesto of Sabbatian assets Karl Marx and Friedrich Engels. It is absolutely no coincidence that Marxism, just a different name for fascist and other centrally-controlled tyrannies, is being imposed worldwide as a result of the 'Covid' hoax and nor that Marxist/fascist China was the place where the hoax originated. The reason for this will become very clear in the chapter 'Covid: The calculated catastrophe'. The so-called 'Woke' mentality has hijacked

traditional beliefs of the political left and replaced them with far-right make-believe 'social justice' better known as Marxism. Woke will, however, be swallowed by its own perceived 'revolution' which is really the work of billionaires and billionaire corporations feigning being 'Woke'. Marxism is being touted by Wokers as a replacement for 'capitalism' when we don't have 'capitalism'. We have cartelism in which the market is stitched up by the very Cult billionaires and corporations bankrolling Woke. Billionaires love Marxism which keeps the people in servitude while they control from the top. Terminally naïve Wokers think they are 'changing the world' when it's the Cult that is doing the changing and when they have played their vital part and become surplus to requirements they, too, will be targeted. The Illuminati-Jacobins were behind the period known as 'The Terror' in the French Revolution in 1793 and 1794 when Jacobin Maximillian de Robespierre and his Orwellian 'Committee of Public Safety' killed 17,000 'enemies of the Revolution' who had once been 'friends of the Revolution'. Karl Marx (1818-1883), whose Sabbatian creed of Marxism has cost the lives of at least 100 million people, is a hero once again to Wokers who have been systematically kept ignorant of real history by their 'education' programming. As a result they now promote a Sabbatian 'Marxist' abomination destined at some point to consume them. Rabbi Antelman, who spent decades researching the Sabbatian plot, said of the League of the Just and Karl Marx:

> Contrary to popular opinion Karl Marx did not originate the Communist Manifesto. He was paid for his services by the League of the Just, which was known in its country of origin, Germany, as the Bund der Geaechteten.

Antelman said the text attributed to Marx was the work of other people and Marx 'was only repeating what others already said'. Marx was 'a hired hack – lackey of the wealthy Illuminists'. Marx famously said that religion was the 'opium of the people' (part of the Sabbatian plan to demonise religion) and Antelman called his books, *To Eliminate the Opiate*. Marx was born Jewish, but his family converted to Christianity (Sabbatian modus operandi) and he

attacked Jews, not least in his book, *A World Without Jews*. In doing so he supported the Sabbatian plan to destroy traditional Jewishness and Judaism which we are clearly seeing today with the vindictive targeting of orthodox Jews by the Sabbatian government of Israel over 'Covid' laws. I don't follow any religion and it has done much damage to the world over centuries and acted as a perceptual straightjacket. Renegade Minds, however, are always asking *why* something is being done. It doesn't matter if they agree or disagree with what is happening – *why* is it happening is the question. The 'why?' can be answered with regard to religion in that religions create interacting communities of believers when the Cult wants to dismantle all discourse, unity and interaction (see 'Covid' lockdowns) and the ultimate goal is to delete all religions for a one-world religion of Cult Satanism worshipping their 'god' of which more later. We see the same 'why?' with gun control in America. I don't have guns and don't want them, but why is the Cult seeking to disarm the population at the same time that law enforcement agencies are armed to their molars and why has every tyrant in history sought to disarm people before launching the final takeover? They include Hitler, Stalin, Pol Pot and Mao who followed confiscation with violent seizing of power. You know it's a Cult agenda by the people who immediately race to the microphones to exploit dead people in multiple shootings. Ultra-Zionist Cult lackey Senator Chuck Schumer was straight on the case after ten people were killed in Boulder, Colorado in March, 2121. Simple rule … if Schumer wants it the Cult wants it and the same with his ultra-Zionist mate the wild-eyed Senator Adam Schiff. At the same time they were calling for the disarmament of Americans, many of whom live a long way from a police response, Schumer, Schiff and the rest of these pampered clowns were sitting on Capitol Hill behind a razor-wired security fence protected by thousands of armed troops in addition to their own armed bodyguards. Mom and pop in an isolated home? They're just potential mass shooters.

Zion Mainframe

Sabbatian-Frankists and most importantly the Rothschilds were behind the creation of 'Zionism', a political movement that demanded a Jewish homeland in Israel as promised by Sabbatai Zevi. The very symbol of Israel comes from the German meaning of the name Rothschild. Dynasty founder Mayer Amschel Rothschild changed the family name from Bauer to Rothschild, or 'Red-Shield' in German, in deference to the six-pointed 'Star of David' hexagram displayed on the family's home in Frankfurt. The symbol later appeared on the flag of Israel after the Rothschilds were centrally involved in its creation. Hexagrams are not a uniquely Jewish symbol and are widely used in occult ('hidden') networks often as a symbol for Saturn (see my other books for why). Neither are Zionism and Jewishness interchangeable. Zionism is a political movement and philosophy and not a 'race' or a people. Many Jews oppose Zionism and many non-Jews, including US President Joe Biden, call themselves Zionists as does Israel-centric Donald Trump. America's support for the Israel government is pretty much a gimme with ultra-Zionist billionaires and corporations providing fantastic and dominant funding for both political parties. Former Congresswoman Cynthia McKinney has told how she was approached immediately she ran for office to 'sign the pledge' to Israel and confirm that she would always vote in that country's best interests. All American politicians are approached in this way. Anyone who refuses will get no support or funding from the enormous and all-powerful Zionist lobby that includes organisations like mega-lobby group AIPAC, the American Israel Public Affairs Committee. Trump's biggest funder was ultra-Zionist casino and media billionaire Sheldon Adelson while major funders of the Democratic Party include ultra-Zionist George Soros and ultra-Zionist financial and media mogul, Haim Saban. Some may reel back at the suggestion that Soros is an Israel-firster (Sabbatian-controlled Israel-firster), but Renegade Minds watch the actions not the words and everywhere Soros donates his billions the Sabbatian agenda benefits. In the spirit of Sabbatian inversion Soros pledged $1 billion for a new university network to promote 'liberal values and tackle intolerance'. He made the announcement during his annual speech

at the Cult-owned World Economic Forum in Davos, Switzerland, in January, 2020, after his 'harsh criticism' of 'authoritarian rulers' around the world. You can only laugh at such brazen mendacity. How *he* doesn't laugh is the mystery. Translated from the Orwellian 'liberal values and tackle intolerance' means teaching non-white people to hate white people and for white people to loathe themselves for being born white. The reason for that will become clear.

The 'Anti-Semitism' fraud

Zionists support the Jewish homeland in the land of Palestine which has been the Sabbatian-Rothschild goal for so long, but not for the benefit of Jews. Sabbatians and their global Anti-Semitism Industry have skewed public and political opinion to equate opposing the violent extremes of Zionism to be a blanket attack and condemnation of all Jewish people. Sabbatians and their global Anti-Semitism Industry have skewed public and political opinion to equate opposing the violent extremes of Zionism to be a blanket attack and condemnation of all Jewish people. This is nothing more than a Sabbatian protection racket to stop legitimate investigation and exposure of their agendas and activities. The official definition of 'anti-Semitism' has more recently been expanded to include criticism of Zionism – a *political movement* – and this was done to further stop exposure of Sabbatian infiltrators who created Zionism as we know it today in the 19th century. Renegade Minds will talk about these subjects when they know the shit that will come their way. People must decide if they want to know the truth or just cower in the corner in fear of what others will say. Sabbatians have been trying to label me as 'anti-Semitic' since the 1990s as I have uncovered more and more about their background and agendas. Useless, gutless, fraudulent 'journalists' then just repeat the smears without question and on the day I was writing this section a pair of unquestioning repeaters called Ben Quinn and Archie Bland (how appropriate) outright called me an 'anti-Semite' in the establishment propaganda sheet, the London *Guardian*, with no supporting evidence. The

Sabbatian Anti-Semitism Industry said so and who are they to question that? They wouldn't dare. Ironically 'Semitic' refers to a group of languages in the Middle East that are almost entirely Arabic. 'Anti-Semitism' becomes 'anti-Arab' which if the consequences of this misunderstanding were not so grave would be hilarious. Don't bother telling Quinn and Bland. I don't want to confuse them, bless 'em. One reason I am dubbed 'anti-Semitic' is that I wrote in the 1990s that Jewish operatives (Sabbatians) were heavily involved in the Russian Revolution when Sabbatians overthrew the Romanov dynasty. This apparently made me 'anti-Semitic'. Oh, really? Here is a section from *The Trigger*:

British journalist Robert Wilton confirmed these themes in his 1920 book *The Last Days of the Romanovs* when he studied official documents from the Russian government to identify the members of the Bolshevik ruling elite between 1917 and 1919. The Central Committee included 41 Jews among 62 members; the Council of the People's Commissars had 17 Jews out of 22 members; and 458 of the 556 most important Bolshevik positions between 1918 and 1919 were occupied by Jewish people. Only 17 were Russian. Then there were the 23 Jews among the 36 members of the vicious Cheka Soviet secret police established in 1917 who would soon appear all across the country.

Professor Robert Service of Oxford University, an expert on 20th century Russian history, found evidence that ['Jewish'] Leon Trotsky had sought to make sure that Jews were enrolled in the Red Army and were disproportionately represented in the Soviet civil bureaucracy that included the Cheka which performed mass arrests, imprisonment and executions of 'enemies of the people'. A US State Department Decimal File (861.00/5339) dated November 13th, 1918, names [Rothschild banking agent in America] Jacob Schiff and a list of ultra-Zionists as funders of the Russian Revolution leading to claims of a 'Jewish plot', but the key point missed by all is they were not 'Jews' – they were Sabbatian-Frankists.

Britain's Winston Churchill made the same error by mistake or otherwise. He wrote in a 1920 edition of the *Illustrated Sunday Herald* that those behind the Russian revolution were part of a 'worldwide conspiracy for the overthrow of civilisation and for the reconstitution of society on the basis of arrested development, of envious malevolence, and impossible equality' (see 'Woke' today because that has been created by the same network). Churchill said there was no need to exaggerate the part played in the creation of Bolshevism and in the actual bringing about of the Russian

Revolution 'by these international and for the most part atheistical Jews' ['atheistical Jews' = Sabbatians]. Churchill said it is certainly a very great one and probably outweighs all others: 'With the notable exception of Lenin, the majority of the leading figures are Jews.' He went on to describe, knowingly or not, the Sabbatian modus operandi of placing puppet leaders nominally in power while they control from the background:

> Moreover, the principal inspiration and driving power comes from the Jewish leaders. Thus Tchitcherin, a pure Russian, is eclipsed by his nominal subordinate, Litvinoff, and the influence of Russians like Bukharin or Lunacharski cannot be compared with the power of Trotsky, or of Zinovieff, the Dictator of the Red Citadel (Petrograd), or of Krassin or Radek – all Jews. In the Soviet institutions the predominance of Jews is even more astonishing. And the prominent, if not indeed the principal, part in the system of terrorism applied by the Extraordinary Commissions for Combatting Counter-Revolution has been taken by Jews, and in some notable cases by Jewesses.

What I said about seriously disproportionate involvement in the Russian Revolution by Jewish 'revolutionaries' (Sabbatians) is provable fact, but truth is no defence against the Sabbatian Anti-Semitism Industry, its repeater parrots like Quinn and Bland, and the now breathtaking network of so-called 'Woke' 'anti-hate' groups with interlocking leaderships and funding which have the role of discrediting and silencing anyone who gets too close to exposing the Sabbatians. We have seen 'truth is no defence' confirmed in legal judgements with the Saskatchewan Human Rights Commission in Canada decreeing this: 'Truthful statements can be presented in a manner that would meet the definition of hate speech, and not all truthful statements must be free from restriction.' Most 'anti-hate' activists, who are themselves consumed by hatred, are too stupid and ignorant of the world to know how they are being used. They are far too far up their own virtue-signalling arses and it's far too dark for them to see anything.

The 'revolution' game

The background and methods of the 'Russian' Revolution are straight from the Sabbatian playbook seen in the French Revolution

and endless others around the world that appear to start as a revolution of the people against tyrannical rule and end up with a regime change to more tyrannical rule overtly or covertly. Wars, terror attacks and regime overthrows follow the Sabbatian cult through history with its agents creating them as Problem-Reaction-Solutions to remove opposition on the road to world domination. Sabbatian dots connect the Rothschilds with the Illuminati, Jacobins of the French Revolution, the 'Bund' or League of the Just, the International Communist Party, Communist League and the Communist Manifesto of Karl Marx and Friedrich Engels that would lead to the Rothschild-funded Russian Revolution. The sequence comes under the heading of 'creative destruction' when you advance to your global goal by continually destroying the status quo to install a new status quo which you then also destroy. The two world wars come to mind. With each new status quo you move closer to your planned outcome. Wars and mass murder are to Sabbatians a collective blood sacrifice ritual. They are obsessed with death for many reasons and one is that death is an inversion of life. Satanists and Sabbatians are obsessed with death and often target churches and churchyards for their rituals. Inversion-obsessed Sabbatians explain the use of inverted symbolism including the *inverted* pentagram and *inverted* cross. The inversion of the cross has been related to targeting Christianity, but the cross was a religious symbol long before Christianity and its inversion is a statement about the Sabbatian mentality and goals more than any single religion.

Sabbatians operating in Germany were behind the rise of the occult-obsessed Nazis and the subsequent Jewish exodus from Germany and Europe to Palestine and the United States after World War Two. The Rothschild dynasty was at the forefront of this both as political manipulators and by funding the operation. Why would Sabbatians help to orchestrate the horrors inflicted on Jews by the Nazis and by Stalin after they organised the Russian Revolution? Sabbatians hate Jews and their religion, that's why. They pose as Jews and secure positions of control within Jewish society and play the 'anti-Semitism' card to protect themselves from exposure

through a global network of organisations answering to the Sabbatian-created-and-controlled globe-spanning intelligence network that involves a stunning web of military-intelligence operatives and operations for a tiny country of just nine million. Among them are Jewish assets who are not Sabbatians but have been convinced by them that what they are doing is for the good of Israel and the Jewish community to protect them from what they have been programmed since childhood to believe is a Jew-hating hostile world. The Jewish community is just a highly convenient cover to hide the true nature of Sabbatians. Anyone getting close to exposing their game is accused by Sabbatian place-people and gofers of 'anti-Semitism' and claiming that all Jews are part of a plot to take over the world. I am not saying that. I am saying that Sabbatians – the *real* Jew-haters – have infiltrated the Jewish community to use them both as a cover and an 'anti-Semitic' defence against exposure. Thus we have the Anti-Semitism Industry targeted researchers in this way and most Jewish people think this is justified and genuine. They don't know that their 'Jewish' leaders and institutions of state, intelligence and military are not controlled by Jews at all, but cultists and stooges of Sabbatian-Frankism. I once added my name to a pro-Jewish freedom petition online and the next time I looked my name was gone and text had been added to the petition blurb to attack me as an 'anti-Semite' such is the scale of perceptual programming.

Moving on America

I tell the story in *The Trigger* and a chapter called 'Atlantic Crossing' how particularly after Israel was established the Sabbatians moved in on the United States and eventually grasped control of government administration, the political system via both Democrats and Republicans, the intelligence community like the CIA and National Security Agency (NSA), the Pentagon and mass media. Through this seriously compartmentalised network Sabbatians and their operatives in Mossad, Israeli Defense Forces (IDF) and US agencies pulled off 9/11 and blamed it on 19 'Al-Qaeda hijackers' dominated by men from, or connected to, Sabbatian-ruled Saudi

Arabia. The '19' were not even on the planes let alone flew those big passenger jets into buildings while being largely incompetent at piloting one-engine light aircraft. 'Hijacker' Hani Hanjour who is said to have flown American Airlines Flight 77 into the Pentagon with a turn and manoeuvre most professional pilots said they would have struggled to do was banned from renting a small plane by instructors at the Freeway Airport in Bowie, Maryland, just *six weeks* earlier on the grounds that he was an incompetent pilot. The Jewish population of the world is just 0.2 percent with even that almost entirely concentrated in Israel (75 percent Jewish) and the United States (around two percent). This two percent and globally 0.2 percent refers to *Jewish* people and not Sabbatian interlopers who are a fraction of that fraction. What a sobering thought when you think of the fantastic influence on world affairs of tiny Israel and that the Project for the New America Century (PNAC) which laid out the blueprint in September, 2000, for America's war on terror and regime change wars in Iraq, Libya and Syria was founded and dominated by Sabbatians known as 'Neocons'. The document conceded that this plan would not be supported politically or publicly without a major attack on American soil and a Problem-Reaction-Solution excuse to send troops to war across the Middle East. Sabbatian Neocons said:

> ... [The] process of transformation ... [war and regime change] ... is likely to be a long one, absent some catastrophic and catalysing event – like a new Pearl Harbor.

Four months later many of those who produced that document came to power with their inane puppet George Bush from the long-time Sabbatian Bush family. They included Sabbatian Dick Cheney who was officially vice-president, but really de-facto president for the entirety of the 'Bush' government. Nine months after the 'Bush' inauguration came what Bush called at the time 'the Pearl Harbor of the 21st century' and with typical Sabbatian timing and symbolism 2001 was the 60th anniversary of the attack in 1941 by the Japanese Air Force on Pearl Harbor, Hawaii, which allowed President Franklin Delano Roosevelt to take the United States into a Sabbatian-

instigated Second World War that he said in his election campaign that he never would. The evidence is overwhelming that Roosevelt and his military and intelligence networks knew the attack was coming and did nothing to stop it, but they did make sure that America's most essential naval ships were not in Hawaii at the time. Three thousand Americans died in the Pearl Harbor attacks as they did on September 11th. By the 9/11 year of 2001 Sabbatians had widely infiltrated the US government, military and intelligence operations and used their compartmentalised assets to pull off the 'Al-Qaeda' attacks. If you read *The Trigger* it will blow your mind to see the utterly staggering concentration of 'Jewish' operatives (Sabbatian infiltrators) in essential positions of political, security, legal, law enforcement, financial and business power before, during, and after the attacks to make them happen, carry them out, and then cover their tracks – and I do mean *staggering* when you think of that 0.2 percent of the world population and two percent of Americans which are Jewish while Sabbatian infiltrators are a fraction of that. A central foundation of the 9/11 conspiracy was the hijacking of government, military, Air Force and intelligence computer systems in real time through 'back-door' access made possible by Israeli (Sabbatian) 'cyber security' software. Sabbatian-controlled Israel is on the way to rivalling Silicon Valley for domination of cyberspace and is becoming the dominant force in cyber-security which gives them access to entire computer systems and their passcodes across the world. Then add to this that Zionists head (officially) Silicon Valley giants like Google (Larry Page and Sergey Brin), Google-owned YouTube (Susan Wojcicki), Facebook (Mark Zuckerberg and Sheryl Sandberg), and Apple (Chairman Arthur D. Levinson), and that ultra-Zionist hedge fund billionaire Paul Singer has a $1 billion stake in Twitter which is only nominally headed by 'CEO' pothead Jack Dorsey. As cable news host Tucker Carlson said of Dorsey: 'There used to be debate in the medical community whether dropping a ton of acid had permanent effects and I think that debate has now ended.' Carlson made the comment after Dorsey told a hearing on Capitol Hill (if you cut through his bullshit) that he

believed in free speech so long as he got to decide what you can hear and see. These 'big names' of Silicon Valley are only front men and women for the Global Cult, not least the Sabbatians, who are the true controllers of these corporations. Does anyone still wonder why these same people and companies have been ferociously censoring and banning people (like me) for exposing any aspect of the Cult agenda and especially the truth about the 'Covid' hoax which Sabbatians have orchestrated?

The Jeffrey Epstein paedophile ring was a Sabbatian operation. He was officially 'Jewish' but he was a Sabbatian and women abused by the ring have told me about the high number of 'Jewish' people involved. The Epstein horror has Sabbatian written all over it and matches perfectly their modus operandi and obsession with sex and ritual. Epstein was running a Sabbatian blackmail ring in which famous people with political and other influence were provided with young girls for sex while everything was being filmed and recorded on hidden cameras and microphones at his New York house, Caribbean island and other properties. Epstein survivors have described this surveillance system to me and some have gone public. Once the famous politician or other figure knew he or she was on video they tended to do whatever they were told. Here we go again …when you've got them by the balls their hearts and minds will follow. Sabbatians use this blackmail technique on a wide scale across the world to entrap politicians and others they need to act as demanded. Epstein's private plane, the infamous 'Lolita Express', had many well-known passengers including Bill Clinton while Bill Gates has flown on an Epstein plane and met with him four years after Epstein had been jailed for paedophilia. They subsequently met many times at Epstein's home in New York according to a witness who was there. Epstein's infamous side-kick was Ghislaine Maxwell, daughter of Mossad agent and ultra-Zionist mega-crooked British businessman, Bob Maxwell, who at one time owned the *Daily Mirror* newspaper. Maxwell was murdered at sea on his boat in 1991 by Sabbatian-controlled Mossad when he became a liability with his

business empire collapsing as a former Mossad operative has confirmed (see *The Trigger*).

Money, money, money, funny money …

Before I come to the Sabbatian connection with the last three US presidents I will lay out the crucial importance to Sabbatians of controlling banking and finance. Sabbatian Mayer Amschel Rothschild set out to dominate this arena in his family's quest for total global control. What is freedom? It is, in effect, choice. The more choices you have the freer you are and the fewer your choices the more you are enslaved. In the global structure created over centuries by Sabbatians the biggest decider and restrictor of choice is … money. Across the world if you ask people what they would like to do with their lives and why they are not doing that they will reply 'I don't have the money'. This is the idea. A global elite of multi-billionaires are described as 'greedy' and that is true on one level; but control of money – who has it and who doesn't – is not primarily about greed. It's about control. Sabbatians have seized ever more control of finance and sucked the wealth of the world out of the hands of the population. We talk now, after all, about the 'One-percent' and even then the wealthiest are a lot fewer even than that. This has been made possible by a money scam so outrageous and so vast it could rightly be called the scam of scams founded on creating 'money' out of nothing and 'loaning' that with interest to the population. Money out of nothing is called 'credit'. Sabbatians have asserted control over governments and banking ever more completely through the centuries and secured financial laws that allow banks to lend hugely more than they have on deposit in a confidence trick known as fractional reserve lending. Imagine if you could lend money that doesn't exist and charge the recipient interest for doing so. You would end up in jail. Bankers by contrast end up in mansions, private jets, Malibu and Monaco.

Banks are only required to keep a fraction of their deposits and wealth in their vaults and they are allowed to lend 'money' they don't have called 'credit. Go into a bank for a loan and if you succeed

the banker will not move any real wealth into your account. They will type into your account the amount of the agreed 'loan' – say £100,000. This is not wealth that really exists; it is non-existent, fresh-air, created-out-of-nothing 'credit' which has never, does not, and will never exist except in theory. Credit is backed by nothing except wind and only has buying power because people think that it has buying power and accept it in return for property, goods and services. I have described this situation as like those cartoon characters you see chasing each other and when they run over the edge of a cliff they keep running forward on fresh air until one of them looks down, realises what's happened, and they all crash into the ravine. The whole foundation of the Sabbatian financial system is to stop people looking down except for periodic moments when they want to crash the system (as in 2008 and 2020 ongoing) and reap the rewards from all the property, businesses and wealth their borrowers had signed over as 'collateral' in return for a 'loan' of fresh air. Most people think that money is somehow created by governments when it comes into existence from the start as a debt through banks 'lending' illusory money called credit. Yes, the very currency of exchange is a *debt* from day one issued as an interest-bearing loan. Why don't governments create money interest-free and lend it to their people interest-free? Governments are controlled by Sabbatians and the financial system is controlled by Sabbatians for whom interest-free money would be a nightmare come true. Sabbatians underpin their financial domination through their global network of central banks, including the privately-owned US Federal Reserve and Britain's Bank of England, and this is orchestrated by a privately-owned central bank coordination body called the Bank for International Settlements in Basle, Switzerland, created by the usual suspects including the Rockefellers and Rothschilds. Central bank chiefs don't answer to governments or the people. They answer to the Bank for International Settlements or, in other words, the Global Cult which is dominated today by Sabbatians.

Built-in disaster

There are so many constituent scams within the overall banking scam. When you take out a loan of thin-air credit only the amount of that loan is theoretically brought into circulation to add to the amount in circulation; but you are paying back the principle plus interest. The additional interest is not created and this means that with every 'loan' there is a shortfall in the money in circulation between what is borrowed and what has to be paid back. There is never even close to enough money in circulation to repay all outstanding public and private debt including interest. Coldly weaved in the very fabric of the system is the certainty that some will lose their homes, businesses and possessions to the banking 'lender'. This is less obvious in times of 'boom' when the amount of money in circulation (and the debt) is expanding through more people wanting and getting loans. When a downturn comes and the money supply contracts it becomes painfully obvious that there is not enough money to service all debt and interest. This is less obvious in times of 'boom' when the amount of money in circulation (and the debt) is expanding through more people wanting and getting loans. When a downturn comes and the money supply contracts and it becomes painfully obvious – as in 2008 and currently – that there is not enough money to service all debt and interest. Sabbatian banksters have been leading the human population through a calculated series of booms (more debt incurred) and busts (when the debt can't be repaid and the banks get the debtor's tangible wealth in exchange for non-existent 'credit'). With each 'bust' Sabbatian bankers have absorbed more of the world's tangible wealth and we end up with the One-percent. Governments are in bankruptcy levels of debt to the same system and are therefore owned by a system they do not control. The Federal Reserve, 'America's central bank', is privately-owned and American presidents only nominally appoint its chairman or woman to maintain the illusion that it's an arm of government. It's not. The 'Fed' is a cartel of private banks which handed billions to its associates and friends after the crash of 2008 and has been Sabbatian-controlled since it was manipulated into being in 1913 through the covert trickery of Rothschild banking agents Jacob Schiff and Paul

Warburg, and the Sabbatian Rockefeller family. Somehow from a Jewish population of two-percent and globally 0.2 percent (Sabbatian interlopers remember are far smaller) ultra-Zionists headed the Federal Reserve for 31 years between 1987 and 2018 in the form of Alan Greenspan, Bernard Bernanke and Janet Yellen (now Biden's Treasury Secretary) with Yellen's deputy chairman a Israeli-American duel citizen and ultra-Zionist Stanley Fischer, a former governor of the Bank of Israel. Ultra-Zionist Fed chiefs spanned the presidencies of Ronald Reagan ('Republican'), Father George Bush ('Republican'), Bill Clinton ('Democrat'), Boy George Bush ('Republican') and Barack Obama ('Democrat'). We should really add the pre-Greenspan chairman, Paul Adolph Volcker, 'appointed' by Jimmy Carter ('Democrat') who ran the Fed between 1979 and 1987 during the Carter and Reagan administrations before Greenspan took over. Volcker was a long-time associate and business partner of the Rothschilds. No matter what the 'party' officially in power the United States economy was directed by the same force. Here are members of the Obama, Trump and Biden administrations and see if you can make out a common theme.

Barack Obama ('Democrat')

Ultra-Zionists Robert Rubin, Larry Summers, and Timothy Geithner ran the US Treasury in the Clinton administration and two of them reappeared with Obama. Ultra-Zionist Fed chairman Alan Greenspan had manipulated the crash of 2008 through deregulation and jumped ship just before the disaster to make way for ultra-Zionist Bernard Bernanke to hand out trillions to Sabbatian 'too big to fail' banks and businesses, including the ubiquitous ultra-Zionist Goldman Sachs which has an ongoing staff revolving door operation between itself and major financial positions in government worldwide. Obama inherited the fallout of the crash when he took office in January, 2009, and fortunately he had the support of his ultra-Zionist White House Chief of Staff Rahm Emmanuel, son of a terrorist who helped to bomb Israel into being in 1948, and his ultra-Zionist senior adviser David Axelrod, chief strategist in Obama's two

successful presidential campaigns. Emmanuel, later mayor of Chicago and former senior fundraiser and strategist for Bill Clinton, is an example of the Sabbatian policy after Israel was established of migrating insider families to America so their children would be born American citizens. 'Obama' chose this financial team throughout his administration to respond to the Sabbatian-instigated crisis:

Timothy Geithner (ultra-Zionist) Treasury Secretary; Jacob J. Lew, Treasury Secretary; Larry Summers (ultra-Zionist), director of the White House National Economic Council; Paul Adolph Volcker (Rothschild business partner), chairman of the Economic Recovery Advisory Board; Peter Orszag (ultra-Zionist), director of the Office of Management and Budget overseeing all government spending; Penny Pritzker (ultra-Zionist), Commerce Secretary; Jared Bernstein (ultra-Zionist), chief economist and economic policy adviser to Vice President Joe Biden; Mary Schapiro (ultra-Zionist), chair of the Securities and Exchange Commission (SEC); Gary Gensler (ultra-Zionist), chairman of the Commodity Futures Trading Commission (CFTC); Sheila Bair (ultra-Zionist), chair of the Federal Deposit Insurance Corporation (FDIC); Karen Mills (ultra-Zionist), head of the Small Business Administration (SBA); Kenneth Feinberg (ultra-Zionist), Special Master for Executive [bail-out] Compensation. Feinberg would be appointed to oversee compensation (with strings) to 9/11 victims and families in a campaign to stop them having their day in court to question the official story. At the same time ultra-Zionist Bernard Bernanke was chairman of the Federal Reserve and these are only some of the ultra-Zionists with allegiance to Sabbatian-controlled Israel in the Obama government. Obama's biggest corporate donor was ultra-Zionist Goldman Sachs which had employed many in his administration.

Donald Trump ('Republican')

Trump claimed to be an outsider (he wasn't) who had come to 'drain the swamp'. He embarked on this goal by immediately appointing ultra-Zionist Steve Mnuchin, a Goldman Sachs employee for 17

years, as his Treasury Secretary. Others included Gary Cohn (ultra-Zionist), chief operating officer of Goldman Sachs, his first Director of the National Economic Council and chief economic adviser, who was later replaced by Larry Kudlow (ultra-Zionist). Trump's senior adviser throughout his four years in the White House was his sinister son-in-law Jared Kushner, a life-long friend of Israel Prime Minister Benjamin Netanyahu. Kushner is the son of a convicted crook who was pardoned by Trump in his last days in office. Other ultra-Zionists in the Trump administration included: Stephen Miller, Senior Policy Adviser; Avrahm Berkowitz, Deputy Adviser to Trump and his Senior Adviser Jared Kushner; Ivanka Trump, Adviser to the President, who converted to Judaism when she married Jared Kushner; David Friedman, Trump lawyer and Ambassador to Israel; Jason Greenblatt, Trump Organization executive vice president and chief legal officer, who was made Special Representative for International Negotiations and the Israeli-Palestinian Conflict; Rod Rosenstein, Deputy Attorney General; Elliot Abrams, Special Representative for Venezuela, then Iran; John Eisenberg, National Security Council Legal Adviser and Deputy Council to the President for National Security Affairs; Anne Neuberger, Deputy National Manager, National Security Agency; Ezra Cohen-Watnick, Acting Under Secretary of Defense for Intelligence; Elan Carr, Special Envoy to monitor and combat anti-Semitism; Len Khodorkovsky, Deputy Special Envoy to monitor and combat anti-Semitism; Reed Cordish, Assistant to the President, Intragovernmental and Technology Initiatives. Trump Vice President Mike Pence and Secretary of State Mike Pompeo, both Christian Zionists, were also vehement supporters of Israel and its goals and ambitions.

Donald 'free-speech believer' Trump pardoned a number of financial and violent criminals while ignoring calls to pardon Julian Assange and Edward Snowden whose crimes are revealing highly relevant information about government manipulation and corruption and the widespread illegal surveillance of the American people by US 'security' agencies. It's so good to know that Trump is on the side of freedom and justice and not mega-criminals with

allegiance to Sabbatian-controlled Israel. These included a pardon for Israeli spy Jonathan Pollard who was jailed for life in 1987 under the Espionage Act. Aviem Sella, the Mossad agent who recruited Pollard, was also pardoned by Trump while Assange sat in jail and Snowden remained in exile in Russia. Sella had 'fled' (was helped to escape) to Israel in 1987 and was never extradited despite being charged under the Espionage Act. A Trump White House statement said that Sella's clemency had been 'supported by Benjamin Netanyahu, Ron Dermer, Israel's US Ambassador, David Friedman, US Ambassador to Israel and Miriam Adelson, wife of leading Trump donor Sheldon Adelson who died shortly before. Other friends of Jared Kushner were pardoned along with Sholom Weiss who was believed to be serving the longest-ever white-collar prison sentence of more than 800 years in 2000. The sentence was commuted of Ponzi-schemer Eliyahu Weinstein who defrauded Jews and others out of $200 million. I did mention that Assange and Snowden were ignored, right? Trump gave Sabbatians almost everything they asked for in military and political support, moving the US Embassy from Tel Aviv to Jerusalem with its critical symbolic and literal implications for Palestinian statehood, and the 'deal of the Century' designed by Jared Kushner and David Friedman which gave the Sabbatian Israeli government the green light to substantially expand its already widespread program of building illegal Jewish-only settlements in the occupied land of the West Bank. This made a two-state 'solution' impossible by seizing all the land of a potential Palestinian homeland and that had been the plan since 1948 and then 1967 when the Arab-controlled Gaza Strip, West Bank, Sinai Peninsula and Syrian Golan Heights were occupied by Israel. All the talks about talks and road maps and delays have been buying time until the West Bank was physically occupied by Israeli real estate. Trump would have to be a monumentally ill-informed idiot not to see that this was the plan he was helping to complete. The Trump administration was in so many ways the Kushner administration which means the Netanyahu administration which means the Sabbatian administration. I understand why many opposing Cult fascism in all its forms gravitated to Trump, but he

was a crucial part of the Sabbatian plan and I will deal with this in the next chapter.

Joe Biden ('Democrat')

A barely cognitive Joe Biden took over the presidency in January, 2021, along with his fellow empty shell, Vice-President Kamala Harris, as the latest Sabbatian gofers to enter the White House. Names on the door may have changed and the 'party' – the force behind them remained the same as Zionists were appointed to a stream of pivotal areas relating to Sabbatian plans and policy. They included: Janet Yellen, Treasury Secretary, former head of the Federal Reserve, and still another ultra-Zionist running the US Treasury after Mnuchin (Trump), Lew and Geithner (Obama), and Summers and Rubin (Clinton); Anthony Blinken, Secretary of State; Wendy Sherman, Deputy Secretary of State (so that's 'Biden's' Sabbatian foreign policy sorted); Jeff Zients, White House coronavirus coordinator; Rochelle Walensky, head of the Centers for Disease Control; Rachel Levine, transgender deputy health secretary (that's 'Covid' hoax policy under control); Merrick Garland, Attorney General; Alejandro Mayorkas, Secretary of Homeland Security; Cass Sunstein, Homeland Security with responsibility for new immigration laws; Avril Haines, Director of National Intelligence; Anne Neuberger, National Security Agency cybersecurity director (note, cybersecurity); David Cohen, CIA Deputy Director; Ronald Klain, Biden's Chief of Staff (see Rahm Emanuel); Eric Lander, a 'leading geneticist', Office of Science and Technology Policy director (see Smart Grid, synthetic biology agenda); Jessica Rosenworcel, acting head of the Federal Communications Commission (FCC) which controls Smart Grid technology policy and electromagnetic communication systems including 5G. How can it be that so many pivotal positions are held by two-percent of the American population and 0.2 percent of the world population administration after administration no matter who is the president and what is the party? It's a coincidence? Of course it's not and this is why Sabbatians have built their colossal global web of interlocking 'anti-

hate' hate groups to condemn anyone who asks these glaring questions as an 'anti-Semite'. The way that Jewish people horrifically abused in Sabbatian-backed Nazi Germany are exploited to this end is stomach-turning and disgusting beyond words.

Political fusion

Sabbatian manipulation has reversed the roles of Republicans and Democrats and the same has happened in Britain with the Conservative and Labour Parties. Republicans and Conservatives were always labelled the 'right' and Democrats and Labour the 'left', but look at the policy positions now and the Democrat-Labour 'left' has moved further to the 'right' than Republicans and Conservatives under the banner of 'Woke', the Cult-created far-right tyranny. Where once the Democrat-Labour 'left' defended free speech and human rights they now seek to delete them and as I said earlier despite the 'Covid' fascism of the Jackboot Johnson Conservative government in the UK the Labour Party of leader Keir Starmer demanded even more extreme measures. The Labour Party has been very publicly absorbed by Sabbatians after a political and media onslaught against the previous leader, the weak and inept Jeremy Corbyn, over made-up allegations of 'anti-Semitism' both by him and his party. The plan was clear with this 'anti-Semite' propaganda and what was required in response was a swift and decisive 'fuck off' from Corbyn and a statement to expose the Anti-Semitism Industry (Sabbatian) attempt to silence Labour criticism of the Israeli government (Sabbatians) and purge the party of all dissent against the extremes of ultra-Zionism (Sabbatians). Instead Corbyn and his party fell to their knees and appeased the abusers which, by definition, is impossible. Appeasing one demand leads only to a new demand to be appeased until takeover is complete. Like I say – 'fuck off' would have been a much more effective policy and I have used it myself with great effect over the years when Sabbatians are on my case which is most of the time. I consider that fact a great compliment, by the way. The outcome of the Labour Party capitulation is that we now have a Sabbatian-controlled

Conservative Party 'opposed' by a Sabbatian-controlled Labour Party in a one-party Sabbatian state that hurtles towards the extremes of tyranny (the Sabbatian cult agenda). In America the situation is the same. Labour's Keir Starmer spends his days on his knees with his tongue out pointing to Tel Aviv, or I guess now Jerusalem, while Boris Johnson has an 'anti-Semitism czar' in the form of former Labour MP John Mann who keeps Starmer company on his prayer mat.

Sabbatian influence can be seen in Jewish members of the Labour Party who have been ejected for criticism of Israel including those from families that suffered in Nazi Germany. Sabbatians despise real Jewish people and target them even more harshly because it is so much more difficult to dub them 'anti-Semitic' although in their desperation they do try.

CHAPTER THREE

The Pushbacker sting

Until you realize how easy it is for your mind to be manipulated, you remain the puppet of someone else's game
Evita Ochel

I will use the presidencies of Trump and Biden to show how the manipulation of the one-party state plays out behind the illusion of political choice across the world. No two presidencies could – on the face of it – be more different and apparently at odds in terms of direction and policy.

A Renegade Mind sees beyond the obvious and focuses on outcomes and consequences and not image, words and waffle. The Cult embarked on a campaign to divide America between those who blindly support its agenda (the mentality known as 'Woke') and those who are pushing back on where the Cult and its Sabbatians want to go. This presents infinite possibilities for dividing and ruling the population by setting them at war with each other and allows a perceptual ring fence of demonisation to encircle the Pushbackers in a modern version of the Little Big Horn in 1876 when American cavalry led by Lieutenant Colonel George Custer were drawn into a trap, surrounded and killed by Native American tribes defending their land of thousands of years from being seized by the government. In this modern version the roles are reversed and it's those defending themselves from the Sabbatian government who are surrounded and the government that's seeking to destroy them. This trap was set years ago and to explain how we must return to 2016

and the emergence of Donald Trump as a candidate to be President of the United States. He set out to overcome the best part of 20 other candidates in the Republican Party before and during the primaries and was not considered by many in those early stages to have a prayer of living in the White House. The Republican Party was said to have great reservations about Trump and yet somehow he won the nomination. When you know how American politics works – politics in general – there is no way that Trump could have become the party's candidate unless the Sabbatian-controlled 'Neocons' that run the Republican Party wanted that to happen. We saw the proof in emails and documents made public by WikiLeaks that the Democratic Party hierarchy, or Democons, systematically undermined the campaign of Bernie Sanders to make sure that Sabbatian gofer Hillary Clinton won the nomination to be their presidential candidate. If the Democons could do that then the Neocons in the Republican Party could have derailed Trump in the same way. But they didn't and at that stage I began to conclude that Trump could well be the one chosen to be president. If that was the case the 'why' was pretty clear to see – the goal of dividing America between Cult agenda-supporting Wokers and Pushbackers who gravitated to Trump because he was telling them what they wanted to hear. His constituency of support had been increasingly ignored and voiceless for decades and profoundly through the eight years of Sabbatian puppet Barack Obama. Now here was someone speaking their language of pulling back from the incessant globalisation of political and economic power, the exporting of American jobs to China and elsewhere by 'American' (Sabbatian) corporations, the deletion of free speech, and the mass immigration policies that had further devastated job opportunities for the urban working class of all races and the once American heartlands of the Midwest.

Beware the forked tongue

Those people collectively sighed with relief that at last a political leader was apparently on their side, but another trait of the Renegade Mind is that you look even harder at people telling you

what you want to hear than those who are telling you otherwise. Obviously as I said earlier people wish what they want to hear to be true and genuine and they are much more likely to believe that than someone saying what they don't want to here and don't want to be true. Sales people are taught to be skilled in eliciting by calculated questioning what their customers want to hear and repeating that back to them as their own opinion to get their targets to like and trust them. Assets of the Cult are also sales people in the sense of selling perception. To read Cult manipulation you have to play the long and expanded game and not fall for the Vaudeville show of party politics. Both American parties are vehicles for the Cult and they exploit them in different ways depending on what the agenda requires at that moment. Trump and the Republicans were used to be the focus of dividing America and isolating Pushbackers to open the way for a Biden presidency to become the most extreme in American history by advancing the full-blown Woke (Cult) agenda with the aim of destroying and silencing Pushbackers now labelled Nazi Trump supporters and white supremacists.

Sabbatians wanted Trump in office for the reasons described by ultra-Zionist Saul Alinsky (1909-1972) who was promoting the Woke philosophy through 'community organising' long before anyone had heard of it. In those days it still went by its traditional name of Marxism. The reason for the manipulated Trump phenomenon was laid out in Alinsky's 1971 book, *Rules for Radicals*, which was his blueprint for overthrowing democratic and other regimes and replacing them with Sabbatian Marxism. Not surprisingly his to-do list was evident in the Sabbatian French and Russian 'Revolutions' and that in China which will become very relevant in the next chapter about the 'Covid' hoax. Among Alinsky's followers have been the deeply corrupt Barack Obama, House Speaker Nancy Pelosi and Hillary Clinton who described him as a 'hero'. All three are Sabbatian stooges with Pelosi personifying the arrogant corrupt idiocy that so widely fronts up for the Cult inner core. Predictably as a Sabbatian advocate of the 'light-bringer' Alinsky features Lucifer on the dedication page of his book as the original radical who gained

his own kingdom ('Earth' as we shall see). One of Alinsky's golden radical rules was to pick an individual and focus all attention, hatred and blame on them and not to target faceless bureaucracies and corporations. *Rules for Radicals* is really a Sabbatian handbook with its contents repeatedly employed all over the world for centuries and why wouldn't Sabbatians bring to power their designer-villain to be used as the individual on which all attention, hatred and blame was bestowed? This is what they did and the only question for me is how much Trump knew that and how much he was manipulated. A bit of both, I suspect. This was Alinsky's Trump technique from a man who died in 1972. The technique has spanned history:

Pick the target, freeze it, personalize it, polarize it. Don't try to attack abstract corporations or bureaucracies. Identify a responsible individual. Ignore attempts to shift or spread the blame.

From the moment Trump came to illusory power everything was about him. It wasn't about Republican policy or opinion, but all about Trump. Everything he did was presented in negative, derogatory and abusive terms by the Sabbatian-dominated media led by Cult operations such as CNN, MSNBC, *The New York Times* and the Jeff Bezos-owned *Washington Post* – 'Pick the target, freeze it, personalize it, polarize it.' Trump was turned into a demon to be vilified by those who hated him and a demi-god loved by those who worshipped him. This, in turn, had his supporters, too, presented as equally demonic in preparation for the punchline later down the line when Biden was about to take office. It was here's a Trump, there's a Trump, everywhere a Trump, Trump. Virtually every news story or happening was filtered through the lens of 'The Donald'. You loved him or hated him and which one you chose was said to define you as Satan's spawn or a paragon of virtue. Even supporting some Trump policies or statements and not others was enough for an assault on your character. No shades of grey were or are allowed. Everything is black and white (literally and figuratively). A Californian I knew had her head utterly scrambled by her hatred for Trump while telling people they should love each other. She was so totally consumed by

Trump Derangement Syndrome as it became to be known that this glaring contradiction would never have occurred to her. By definition anyone who criticised Trump or praised his opponents was a hero and this lady described Joe Biden as 'a kind, honest gentleman' when he's a provable liar, mega-crook and vicious piece of work to boot. Sabbatians had indeed divided America using Trump as the fall-guy and all along the clock was ticking on the consequences for his supporters.

In hock to his masters

Trump gave Sabbatians via Israel almost everything they wanted in his four years. Ask and you shall receive was the dynamic between himself and Benjamin Netanyahu orchestrated by Trump's ultra-Zionist son-in-law Jared Kushner, his ultra-Zionist Ambassador to Israel, David Friedman, and ultra-Zionist 'Israel adviser', Jason Greenblatt. The last two were central to the running and protecting from collapse of his business empire, the Trump Organisation, and colossal business failures made him forever beholding to Sabbatian networks that bailed him out. By the start of the 1990s Trump owed $4 billion to banks that he couldn't pay and almost $1billion of that was down to him personally and not his companies. This mega-disaster was the result of building two new casinos in Atlantic City and buying the enormous Taj Mahal operation which led to crippling debt payments. He had borrowed fantastic sums from 72 banks with major Sabbatian connections and although the scale of debt should have had him living in a tent alongside the highway they never foreclosed. A plan was devised to lift Trump from the mire by BT Securities Corporation and Rothschild Inc. and the case was handled by Wilber Ross who had worked for the Rothschilds for 27 years. Ross would be named US Commerce Secretary after Trump's election. Another crucial figure in saving Trump was ultra-Zionist 'investor' Carl Icahn who bought the Taj Mahal casino. Icahn was made special economic adviser on financial regulation in the Trump administration. He didn't stay long but still managed to find time to make a tidy sum of a reported $31.3 million when he sold his

holdings affected by the price of steel three days before Trump imposed a 235 percent tariff on steel imports. What amazing bits of luck these people have. Trump and Sabbatian operatives have long had a close association and his mentor and legal adviser from the early 1970s until 1986 was the dark and genetically corrupt ultra-Zionist Roy Cohn who was chief counsel to Senator Joseph McCarthy's 'communist' witch-hunt in the 1950s. *Esquire* magazine published an article about Cohn with the headline 'Don't mess with Roy Cohn'. He was described as the most feared lawyer in New York and 'a ruthless master of dirty tricks ... [with] ... more than one Mafia Don on speed dial'. Cohn's influence, contacts, support and protection made Trump a front man for Sabbatians in New York with their connections to one of Cohn's many criminal employers, the 'Russian' Sabbatian Mafia. Israel-centric media mogul Rupert Murdoch was introduced to Trump by Cohn and they started a long friendship. Cohn died in 1986 weeks after being disbarred for unethical conduct by the Appellate Division of the New York State Supreme Court. The wheels of justice do indeed run slow given the length of Cohn's crooked career.

QAnon-sense

We are asked to believe that Donald Trump with his fundamental connections to Sabbatian networks and operatives has been leading the fight to stop the Sabbatian agenda for the fascistic control of America and the world. Sure he has. A man entrapped during his years in the White House by Sabbatian operatives and whose biggest financial donor was casino billionaire Sheldon Adelson who was Sabbatian to his DNA?? Oh, do come on. Trump has been used to divide America and isolate Pushbackers on the Cult agenda under the heading of 'Trump supporters', 'insurrectionists' and 'white supremacists'. The US Intelligence/Mossad Psyop or psychological operation known as QAnon emerged during the Trump years as a central pillar in the Sabbatian campaign to lead Pushbackers into the trap set by those that wished to destroy them. I knew from the start that QAnon was a scam because I had seen the same scenario many

times before over 30 years under different names and I had written about one in particular in the books. 'Not again' was my reaction when QAnon came to the fore. The same script is pulled out every few years and a new name added to the letterhead. The story always takes the same form: 'Insiders' or 'the good guys' in the government-intelligence-military 'Deep State' apparatus were going to instigate mass arrests of the 'bad guys' which would include the Rockefellers, Rothschilds, Barack Obama, Hillary Clinton, George Soros, etc., etc. Dates are given for when the 'good guys' are going to move in, but the dates pass without incident and new dates are given which pass without incident. The central message to Pushbackers in each case is that they don't have to do anything because there is 'a plan' and it is all going to be sorted by the 'good guys' on the inside. 'Trust the plan' was a QAnon mantra when the only plan was to misdirect Pushbackers into putting their trust in a Psyop they believed to be real. Beware, beware, those who tell you what you want to hear and always check it out. Right up to Biden's inauguration QAnon was still claiming that 'the Storm' was coming and Trump would stay on as president when Biden and his cronies were arrested and jailed. It was never going to happen and of course it didn't, but what did happen as a result provided that punchline to the Sabbatian Trump/QAnon Psyop.

On January 6th, 2021, a very big crowd of Trump supporters gathered in the National Mall in Washington DC down from the Capitol Building to protest at what they believed to be widespread corruption and vote fraud that stopped Trump being re-elected for a second term as president in November, 2020. I say as someone that does not support Trump or Biden that the evidence is clear that major vote-fixing went on to favour Biden, a man with cognitive problems so advanced he can often hardly string a sentence together without reading the words written for him on the Teleprompter. Glaring ballot discrepancies included serious questions about electronic voting machines that make vote rigging a comparative cinch and hundreds of thousands of paper votes that suddenly appeared during already advanced vote counts and virtually all of

them for Biden. Early Trump leads in crucial swing states suddenly began to close and disappear. The pandemic hoax was used as the excuse to issue almost limitless numbers of mail-in ballots with no checks to establish that the recipients were still alive or lived at that address. They were sent to streams of people who had not even asked for them. Private organisations were employed to gather these ballots and who knows what they did with them before they turned up at the counts. The American election system has been manipulated over decades to become a sick joke with more holes than a Swiss cheese for the express purpose of dictating the results. Then there was the criminal manipulation of information by Sabbatian tech giants like Facebook, Twitter and Google-owned YouTube which deleted pro-Trump, anti-Biden accounts and posts while everything in support of Biden was left alone. Sabbatians wanted Biden to win because after the dividing of America it was time for full-on Woke and every aspect of the Cult agenda to be unleashed.

Hunter gatherer

Extreme Silicon Valley bias included blocking information by the *New York Post* exposing a Biden scandal that should have ended his bid for president in the final weeks of the campaign. Hunter Biden, his monumentally corrupt son, is reported to have sent a laptop to be repaired at a local store and failed to return for it. Time passed until the laptop became the property of the store for non-payment of the bill. When the owner saw what was on the hard drive he gave a copy to the FBI who did nothing even though it confirmed widespread corruption in which the Joe Biden family were using his political position, especially when he was vice president to Obama, to make multiple millions in countries around the world and most notably Ukraine and China. Hunter Biden's one-time business partner Tony Bobulinski went public when the story broke in the *New York Post* to confirm the corruption he saw and that Joe Biden not only knew what was going on he also profited from the spoils. Millions were handed over by a Chinese company with close

connections – like all major businesses in China – to the Chinese communist party of President Xi Jinping. Joe Biden even boasted at a meeting of the Cult's World Economic Forum that as vice president he had ordered the government of Ukraine to fire a prosecutor. What he didn't mention was that the same man just happened to be investigating an energy company which was part of Hunter Biden's corrupt portfolio. The company was paying him big bucks for no other reason than the influence his father had. Overnight Biden's presidential campaign should have been over given that he had lied publicly about not knowing what his son was doing. Instead almost the entire Sabbatian-owned mainstream media and Sabbatian-owned Silicon Valley suppressed circulation of the story. This alone went a mighty way to rigging the election of 2020. Cult assets like Mark Zuckerberg at Facebook also spent hundreds of millions to be used in support of Biden and vote 'administration'.

The Cult had used Trump as the focus to divide America and was now desperate to bring in moronic, pliable, corrupt Biden to complete the double-whammy. No way were they going to let little things like the will of the people thwart their plan. Silicon Valley widely censored claims that the election was rigged because it *was* rigged. For the same reason anyone claiming it was rigged was denounced as a 'white supremacist' including the pathetically few Republican politicians willing to say so. Right across the media where the claim was mentioned it was described as a 'false claim' even though these excuses for 'journalists' would have done no research into the subject whatsoever. Trump won seven million more votes than any sitting president had ever achieved while somehow a cognitively-challenged soon to be 78-year-old who was hidden away from the public for most of the campaign managed to win more votes than any presidential candidate in history. It makes no sense. You only had to see election rallies for both candidates to witness the enthusiasm for Trump and the apathy for Biden. Tens of thousands would attend Trump events while Biden was speaking in empty car parks with often only television crews attending and framing their shots to hide the fact that no one was there. It was pathetic to see

footage come to light of Biden standing at a podium making speeches only to TV crews and party fixers while reading the words written for him on massive Teleprompter screens. So, yes, those protestors on January 6th had a point about election rigging, but some were about to walk into a trap laid for them in Washington by the Cult Deep State and its QAnon Psyop. This was the Capitol Hill riot ludicrously dubbed an 'insurrection'.

The spider and the fly

Renegade Minds know there are not two 'sides' in politics, only one side, the Cult, working through all 'sides'. It's a stage show, a puppet show, to direct the perceptions of the population into focusing on diversions like parties and candidates while missing the puppeteers with their hands holding all the strings. The Capitol Hill 'insurrection' brings us back to the Little Big Horn. Having created two distinct opposing groupings – Woke and Pushbackers – the trap was about to be sprung. Pushbackers were to be encircled and isolated by associating them all in the public mind with Trump and then labelling Trump as some sort of Confederate leader. I knew immediately that the Capitol riot was a set-up because of two things. One was how easy the rioters got into the building with virtually no credible resistance and secondly I could see – as with the 'Covid' hoax in the West at the start of 2020 – how the Cult could exploit the situation to move its agenda forward with great speed. My experience of Cult techniques and activities over more than 30 years has showed me that while they do exploit situations they haven't themselves created this never happens with events of fundamental agenda significance. Every time major events giving cultists the excuse to rapidly advance their plan you find they are manipulated into being for the specific reason of providing that excuse – Problem-Reaction-Solution. Only a tiny minority of the huge crowd of Washington protestors sought to gain entry to the Capitol by smashing windows and breaching doors. That didn't matter. The whole crowd and all Pushbackers, even if they did not support Trump, were going to be lumped together as dangerous

insurrectionists and conspiracy theorists. The latter term came into widespread use through a CIA memo in the 1960s aimed at discrediting those questioning the nonsensical official story of the Kennedy assassination and it subsequently became widely employed by the media. It's still being used by inept 'journalists' with no idea of its origin to discredit anyone questioning anything that authority claims to be true. When you are perpetrating a conspiracy you need to discredit the very word itself even though the dictionary definition of conspiracy is merely 'the activity of secretly planning with other people to do something bad or illegal' and 'a general agreement to keep silent about a subject for the purpose of keeping it secret'. On that basis there are conspiracies almost wherever you look. For obvious reasons the Cult and its lapdog media have to claim there are no conspiracies even though the word appears in state laws as with conspiracy to defraud, to murder, and to corrupt public morals.

Agent provocateurs are widely used by the Cult Deep State to manipulate genuine people into acting in ways that suit the desired outcome. By genuine in this case I mean protestors genuinely supporting Trump and claims that the election was stolen. In among them, however, were agents of the state wearing the garb of Trump supporters and QAnon to pump-prime the Capital riot which some genuine Trump supporters naively fell for. I described the situation as 'Come into my parlour said the spider to the fly'. Leaflets appeared through the Woke paramilitary arm Antifa, the anti-fascist fascists, calling on supporters to turn up in Washington looking like Trump supporters even though they hated him. Some of those arrested for breaching the Capitol Building were sourced to Antifa and its stable mate Black Lives Matter. Both organisations are funded by Cult billionaires and corporations. One man charged for the riot was according to his lawyer a former FBI agent who had held top secret security clearance for 40 years. Attorney Thomas Plofchan said of his client, 66-year-old Thomas Edward Caldwell:

He has held a Top Secret Security Clearance since 1979 and has undergone multiple Special Background Investigations in support of his clearances. After retiring from the Navy, he

worked as a section chief for the Federal Bureau of Investigation from 2009-2010 as a GS-12 [mid-level employee].

He also formed and operated a consulting firm performing work, often classified, for U.S government customers including the US. Drug Enforcement Agency, Department of Housing and Urban Development, the US Coast Guard, and the US Army Personnel Command.

A judge later released Caldwell pending trial in the absence of evidence about a conspiracy or that he tried to force his way into the building. *The New York Post* reported a 'law enforcement source' as saying that 'at least two known Antifa members were spotted' on camera among Trump supporters during the riot while one of the rioters arrested was John Earle Sullivan, a seriously extreme Black Lives Matter Trump-hater from Utah who was previously arrested and charged in July, 2020, over a BLM-Antifa riot in which drivers were threatened and one was shot. Sullivan is the founder of Utah-based Insurgence USA which is an affiliate of the Cult-created-and-funded Black Lives Matter movement. Footage appeared and was then deleted by Twitter of Trump supporters calling out Antifa infiltrators and a group was filmed changing into pro-Trump clothing before the riot. Security at the building was *pathetic* – as planned. Colonel Leroy Fletcher Prouty, a man with long experience in covert operations working with the US security apparatus, once described the tell-tale sign to identify who is involved in an assassination. He said:

No one has to direct an assassination – it happens. The active role is played secretly by permitting it to happen. This is the greatest single clue. Who has the power to call off or reduce the usual security precautions?

This principle applies to many other situations and certainly to the Capitol riot of January 6th, 2021.

The sting

With such a big and potentially angry crowd known to be gathering near the Capitol the security apparatus would have had a major police detail to defend the building with National Guard troops on

standby given the strength of feeling among people arriving from all over America encouraged by the QAnon Psyop and statements by Donald Trump. Instead Capitol Police 'security' was flimsy, weak, and easily breached. The same number of officers was deployed as on a regular day and that is a blatant red flag. They were not staffed or equipped for a possible riot that had been an obvious possibility in the circumstances. No protective and effective fencing worth the name was put in place and there were no contingency plans. The whole thing was basically a case of standing aside and waving people in. Once inside police mostly backed off apart from one Capitol police officer who ridiculously shot dead unarmed Air Force veteran protestor Ashli Babbitt without a warning as she climbed through a broken window. The 'investigation' refused to name or charge the officer after what must surely be considered a murder in the circumstances. They just lifted a carpet and swept. The story was endlessly repeated about five people dying in the 'armed insurrection' when there was no report of rioters using weapons. Apart from Babbitt the other four died from a heart attack, strokes and apparently a drug overdose. Capitol police officer Brian Sicknick was reported to have died after being bludgeoned with a fire extinguisher when he was alive after the riot was over and died later of what the Washington Medical Examiner's Office said was a stroke. Sicknick had no external injuries. The lies were delivered like rapid fire. There was a narrative to build with incessant repetition of the lie until the lie became the accepted 'everybody knows that' truth. The 'Big Lie' technique of Nazi Propaganda Minister Joseph Goebbels is constantly used by the Cult which was behind the Nazis and is today behind the 'Covid' and 'climate change' hoaxes. Goebbels said:

If you tell a lie big enough and keep repeating it, people will eventually come to believe it. The lie can be maintained only for such time as the State can shield the people from the political, economic and/or military consequences of the lie. It thus becomes vitally important for the State to use all of its powers to repress dissent, for the truth is the mortal enemy of the lie, and thus by extension, the truth is the greatest enemy of the State.

Most protestors had a free run of the Capitol Building. This allowed pictures to be taken of rioters in iconic parts of the building including the Senate chamber which could be used as propaganda images against all Pushbackers. One Congresswoman described the scene as 'the worst kind of non-security anybody could ever imagine'. Well, the first part was true, but someone obviously did imagine it and made sure it happened. Some photographs most widely circulated featured people wearing QAnon symbols and now the Psyop would be used to dub all QAnon followers with the ubiquitous fit-all label of 'white supremacist' and 'insurrectionists'. When a Muslim extremist called Noah Green drove his car at two police officers at the Capitol Building killing one in April, 2021, there was no such political and media hysteria. They were just disappointed he wasn't white.

The witch-hunt

Government prosecutor Michael Sherwin, an aggressive, dark-eyed, professional Rottweiler led the 'investigation' and to call it over the top would be to understate reality a thousand fold. Hundreds were tracked down and arrested for the crime of having the wrong political views and people were jailed who had done nothing more than walk in the building, committed no violence or damage to property, took a few pictures and left. They were labelled a 'threat to the Republic' while Biden sat in the White House signing executive orders written for him that were dismantling 'the Republic'. Even when judges ruled that a mother and son should not be in jail the government kept them there. Some of those arrested have been badly beaten by prison guards in Washington and lawyers for one man said he suffered a fractured skull and was made blind in one eye. Meanwhile a woman is shot dead for no reason by a Capitol Police officer and we are not allowed to know who he is never mind what has happened to him although that will be *nothing*. The Cult's QAnon/Trump sting to identify and isolate Pushbackers and then target them on the road to crushing and deleting them was a resounding success. You would have thought the Russians had

invaded the building at gunpoint and lined up senators for a firing squad to see the political and media reaction. Congresswoman Alexandria Ocasio-Cortez is a child in a woman's body, a terrible-twos, me, me, me, Woker narcissist of such proportions that words have no meaning. She said she thought she was going to die when 'insurrectionists' banged on her office door. It turned out she wasn't even in the Capitol Building when the riot was happening and the 'banging' was a Capitol Police officer. She referred to herself as a 'survivor' which is an insult to all those true survivors of violent and sexual abuse while she lives her pampered and privileged life talking drivel for a living. Her Woke colleague and fellow mega-narcissist Rashida Tlaib broke down describing the devastating effect on her, too, of *not being* in the building when the rioters were there. Ocasio-Cortez and Tlaib are members of a fully-Woke group of Congresswomen known as 'The Squad' along with Ilhan Omar and Ayanna Pressley. The Squad from what I can see can be identified by its vehement anti-white racism, anti-white men agenda, and, as always in these cases, the absence of brain cells on active duty.

The usual suspects were on the riot case immediately in the form of Democrat ultra-Zionist senators and operatives Chuck Schumer and Adam Schiff demanding that Trump be impeached for 'his part in the insurrection'. The same pair of prats had led the failed impeachment of Trump over the invented 'Russia collusion' nonsense which claimed Russia had helped Trump win the 2016 election. I didn't realise that Tel Aviv had been relocated just outside Moscow. I must find an up-to-date map. The Russia hoax was a Sabbatian operation to keep Trump occupied and impotent and to stop any rapport with Russia which the Cult wants to retain as a perceptual enemy to be pulled out at will. Puppet Biden began attacking Russia when he came to office as the Cult seeks more upheaval, division and war across the world. A two-year stage show 'Russia collusion inquiry' headed by the not-very-bright former 9/11 FBI chief Robert Mueller, with support from 19 lawyers, 40 FBI agents plus intelligence analysts, forensic accountants and other

staff, devoured tens of millions of dollars and found no evidence of Russia collusion which a ten-year-old could have told them on day one. Now the same moronic Schumer and Schiff wanted a second impeachment of Trump over the Capitol 'insurrection' (riot) which the arrested development of Schumer called another 'Pearl Harbor' while others compared it with 9/11 in which 3,000 died and, in the case of CNN, with the Rwandan genocide in the 1990s in which an estimated 500,000 to 600,000 were murdered, between 250, 000 and 500,000 women were raped, and populations of whole towns were hacked to death with machetes. To make those comparisons purely for Cult political reasons is beyond insulting to those that suffered and lost their lives and confirms yet again the callous inhumanity that we are dealing with. Schumer is a monumental idiot and so is Schiff, but they serve the Cult agenda and do whatever they're told so they get looked after. Talking of idiots – another inane man who spanned the Russia and Capitol impeachment attempts was Senator Eric Swalwell who had the nerve to accuse Trump of collusion with the Russians while sleeping with a Chinese spy called Christine Fang or 'Fang Fang' which is straight out of a Bond film no doubt starring Klaus Schwab as the bloke living on a secret island and controlling laser weapons positioned in space and pointing at world capitals. Fang Fang plays the part of Bond's infiltrator girlfriend which I'm sure she would enjoy rather more than sharing a bed with the brainless Swalwell, lying back and thinking of China. The FBI eventually warned Swalwell about Fang Fang which gave her time to escape back to the Chinese dictatorship. How very thoughtful of them. The second Trump impeachment also failed and hardly surprising when an impeachment is supposed to remove a sitting president and by the time it happened Trump was no longer president. These people are running your country America, well, officially anyway. Terrifying isn't it?

Outcomes tell the story - always

The outcome of all this – and it's the *outcome* on which Renegade Minds focus, not the words – was that a vicious, hysterical and

obviously pre-planned assault was launched on Pushbackers to censor, silence and discredit them and even targeted their right to earn a living. They have since been condemned as 'domestic terrorists' that need to be treated like Al-Qaeda and Islamic State. 'Domestic terrorists' is a label the Cult has been trying to make stick since the period of the Oklahoma bombing in 1995 which was blamed on 'far-right domestic terrorists'. If you read *The Trigger* you will see that the bombing was clearly a Problem-Reaction-Solution carried out by the Deep State during a Bill Clinton administration so corrupt that no dictionary definition of the term would even nearly suffice. Nearly 30, 000 troops were deployed from all over America to the empty streets of Washington for Biden's inauguration. Ten thousand of them stayed on with the pretext of protecting the capital from insurrectionists when it was more psychological programming to normalise the use of the military in domestic law enforcement in support of the Cult plan for a police-military state. Biden's fascist administration began a purge of 'wrong-thinkers' in the military which means anyone that is not on board with Woke. The Capitol Building was surrounded by a fence with razor wire and the Land of the Free was further symbolically and literally dismantled. The circle was completed with the installation of Biden and the exploitation of the QAnon Psyop.

America had never been so divided since the civil war of the 19th century, Pushbackers were isolated and dubbed terrorists and now, as was always going to happen, the Cult immediately set about deleting what little was left of freedom and transforming American society through a swish of the hand of the most controlled 'president' in American history leading (officially at least) the most extreme regime since the country was declared an independent state on July 4th, 1776. Biden issued undebated, dictatorial executive orders almost by the hour in his opening days in office across the whole spectrum of the Cult wish-list including diluting controls on the border with Mexico allowing thousands of migrants to illegally enter the United States to transform the demographics of America and import an election-changing number of perceived Democrat

voters. Then there were Biden deportation amnesties for the already illegally resident (estimated to be as high as 20 or even 30 million). A bill before Congress awarded American citizenship to anyone who could prove they had worked in agriculture for just 180 days in the previous two years as 'Big Ag' secured its slave labour long-term. There were the plans to add new states to the union such as Puerto Rico and making Washington DC a state. They are all parts of a plan to ensure that the Cult-owned Woke Democrats would be permanently in power.

Border – what border?

I have exposed in detail in other books how mass immigration into the United States and Europe is the work of Cult networks fuelled by the tens of billions spent to this and other ends by George Soros and his global Open Society (open borders) Foundations. The impact can be seen in America alone where the population has increased by *100 million* in little more than 30 years mostly through immigration. I wrote in *The Answer* that the plan was to have so many people crossing the southern border that the numbers become unstoppable and we are now there under Cult-owned Biden. El Salvador in Central America puts the scale of what is happening into context. A third of the population now lives in the United States, much of it illegally, and many more are on the way. The methodology is to crush Central and South American countries economically and spread violence through machete-wielding psychopathic gangs like MS-13 based in El Salvador and now operating in many American cities. Biden-imposed lax security at the southern border means that it is all but open. He said before his 'election' that he wanted to see a surge towards the border if he became president and that was the green light for people to do just that after election day to create the human disaster that followed for both America and the migrants. When that surge came the imbecilic Alexandria Ocasio-Cortez said it wasn't a 'surge' because they are 'children, not insurgents' and the term 'surge' (used by Biden) was a claim of 'white supremacists'.

This disingenuous lady may one day enter the realm of the most basic intelligence, but it won't be any time soon.

Sabbatians and the Cult are in the process of destroying America by importing violent people and gangs in among the genuine to terrorise American cities and by overwhelming services that cannot cope with the sheer volume of new arrivals. Something similar is happening in Europe as Western society in general is targeted for demographic and cultural transformation and upheaval. The plan demands violence and crime to create an environment of intimidation, fear and division and Soros has been funding the election of district attorneys across America who then stop prosecuting many crimes, reduce sentences for violent crimes and free as many violent criminals as they can. Sabbatians are creating the chaos from which order – their order – can respond in a classic Problem-Reaction-Solution. A Freemasonic moto says 'Ordo Ab Chao' (Order out of Chaos) and this is why the Cult is constantly creating chaos to impose a new 'order'. Here you have the reason the Cult is constantly creating chaos. The 'Covid' hoax can be seen with those entering the United States by plane being forced to take a 'Covid' test while migrants flooding through southern border processing facilities do not. Nothing is put in the way of mass migration and if that means ignoring the government's own 'Covid' rules then so be it. They know it's all bullshit anyway. Any pushback on this is denounced as 'racist' by Wokers and Sabbatian fronts like the ultra-Zionist Anti-Defamation League headed by the appalling Jonathan Greenblatt which at the same time argues that Israel should not give citizenship and voting rights to more Palestinian Arabs or the 'Jewish population' (in truth the Sabbatian network) will lose control of the country.

Society-changing numbers

Biden's masters have declared that countries like El Salvador are so dangerous that their people must be allowed into the United States for humanitarian reasons when there are fewer murders in large parts of many Central American countries than in US cities like

Baltimore. That is not to say Central America cannot be a dangerous place and Cult-controlled American governments have been making it so since way back, along with the dismantling of economies, in a long-term plan to drive people north into the United States. Parts of Central America are very dangerous, but in other areas the story is being greatly exaggerated to justify relaxing immigration criteria. Migrants are being offered free healthcare and education in the United States as another incentive to head for the border and there is no requirement to be financially independent before you can enter to prevent the resources of America being drained. You can't blame migrants for seeking what they believe will be a better life, but they are being played by the Cult for dark and nefarious ends. The numbers since Biden took office are huge. In February, 2021, more than 100,000 people were known to have tried to enter the US illegally through the southern border (it was 34,000 in the same month in 2020) and in March it was 170,000 – a 418 percent increase on March, 2020. These numbers are only known people, not the ones who get in unseen. The true figure for migrants illegally crossing the border in a single month was estimated by one congressman at 250,000 and that number will only rise under Biden's current policy. Gangs of murdering drug-running thugs that control the Mexican side of the border demand money – thousands of dollars – to let migrants cross the Rio Grande into America. At the same time gun battles are breaking out on the border several times a week between rival Mexican drug gangs (which now operate globally) who are equipped with sophisticated military-grade weapons, grenades and armoured vehicles. While the Capitol Building was being 'protected' from a non-existent 'threat' by thousands of troops, and others were still deployed at the time in the Cult Neocon war in Afghanistan, the southern border of America was left to its fate. This is not incompetence, it is cold calculation.

By March, 2021, there were 17,000 unaccompanied children held at border facilities and many of them are ensnared by people traffickers for paedophile rings and raped on their journey north to America. This is not conjecture – this is fact. Many of those designated

children are in reality teenage boys or older. Meanwhile Wokers posture their self-purity for encouraging poor and tragic people to come to America and face this nightmare both on the journey and at the border with the disgusting figure of House Speaker Nancy Pelosi giving disingenuous speeches about caring for migrants. The woman's evil. Wokers condemned Trump for having children in cages at the border (so did Obama, *Shhhh*), but now they are sleeping on the floor without access to a shower with one border facility 729 percent over capacity. The Biden insanity even proposed flying migrants from the southern border to the northern border with Canada for 'processing'. The whole shambles is being overseen by ultra-Zionist Secretary of Homeland Security, the moronic liar Alejandro Mayorkas, who banned news cameras at border facilities to stop Americans seeing what was happening. Mayorkas said there was not a ban on news crews; it was just that they were not allowed to film. Alongside him at Homeland Security is another ultra-Zionist Cass Sunstein appointed by Biden to oversee new immigration laws. Sunstein despises conspiracy researchers to the point where he suggests they should be banned or *taxed* for having such views. The man is not bonkers or anything. He's perfectly well-adjusted, but adjusted to what is the question. Criticise what is happening and you are a 'white supremacist' when earlier non-white immigrants also oppose the numbers which effect their lives and opportunities. Black people in poor areas are particularly damaged by uncontrolled immigration and the increased competition for work opportunities with those who will work for less. They are also losing voting power as Hispanics become more dominant in former black areas. It's a downward spiral for them while the billionaires behind the policy drone on about how much they care about black people and 'racism'. None of this is about compassion for migrants or black people – that's just wind and air. Migrants are instead being mercilessly exploited to transform America while the countries they leave are losing their future and the same is true in Europe. Mass immigration may now be the work of Woke Democrats, but it can be traced back to the 1986 Immigration Reform and Control Act (it

wasn't) signed into law by Republican hero President Ronald Reagan which gave amnesty to millions living in the United States illegally and other incentives for people to head for the southern border. Here we have the one-party state at work again.

Save me syndrome

Almost every aspect of what I have been exposing as the Cult agenda was on display in even the first days of 'Biden' with silencing of Pushbackers at the forefront of everything. A Renegade Mind will view the Trump years and QAnon in a very different light to their supporters and advocates as the dots are connected. The QAnon/Trump Psyop has given the Cult all it was looking for. We may not know how much, or little, that Trump realised he was being used, but that's a side issue. This pincer movement produced the desired outcome of dividing America and having Pushbackers isolated. To turn this around we have to look at new routes to empowerment which do not include handing our power to other people and groups through what I will call the 'Save Me Syndrome' – 'I want someone else to do it so that I don't have to'. We have seen this at work throughout human history and the QAnon/Trump Psyop is only the latest incarnation alongside all the others. Religion is an obvious expression of this when people look to a 'god' or priest to save them or tell them how to be saved and then there are 'save me' politicians like Trump. Politics is a diversion and not a 'saviour'. It is a means to block positive change, not make it possible.

Save Me Syndrome always comes with the same repeating theme of handing your power to whom or what you believe will save you while your real 'saviour' stares back from the mirror every morning. Renegade Minds are constantly vigilant in this regard and always asking the question 'What can I do?' rather than 'What can someone else do for me?' Gandhi was right when he said: 'You must be the change you want to see in the world.' We are indeed the people we have been waiting for. We are presented with a constant raft of reasons to concede that power to others and forget where the real power is. Humanity has the numbers and the Cult does not. It has to

use diversion and division to target the unstoppable power that comes from unity. Religions, governments, politicians, corporations, media, QAnon, are all different manifestations of this power-diversion and dilution. Refusing to give your power to governments and instead handing it to Trump and QAnon is not to take a new direction, but merely to recycle the old one with new names on the posters. I will explore this phenomenon as we proceed and how to break the cycles and recycles that got us here through the mists of repeating perception and so repeating history.

For now we shall turn to the most potent example in the entire human story of the consequences that follow when you give your power away. I am talking, of course, of the 'Covid' hoax.

CHAPTER FOUR

'Covid': Calculated catastrophe

Facts are threatening to those invested in fraud
DaShanne Stokes

We can easily unravel the real reason for the 'Covid pandemic' hoax by employing the Renegade Mind methodology that I have outlined this far. We'll start by comparing the long-planned Cult outcome with the 'Covid pandemic' outcome. Know the outcome and you'll see the journey.

I have highlighted the plan for the Hunger Games Society which has been in my books for so many years with the very few controlling the very many through ongoing dependency. To create this dependency it is essential to destroy independent livelihoods, businesses and employment to make the population reliant on the state (the Cult) for even the basics of life through a guaranteed pittance income. While independence of income remained these Cult ambitions would be thwarted. With this knowledge it was easy to see where the 'pandemic' hoax was going once talk of 'lockdowns' began and the closing of all but perceived 'essential' businesses to 'save' us from an alleged 'deadly virus'. Cult corporations like Amazon and Walmart were naturally considered 'essential' while mom and pop shops and stores had their doors closed by fascist decree. As a result with every new lockdown and new regulation more small and medium, even large businesses not owned by the Cult, went to the wall while Cult giants and their frontmen and women grew financially fatter by the second. Mom and pop were

denied an income and the right to earn a living and the wealth of people like Jeff Bezos (Amazon), Mark Zuckerberg (Facebook) and Sergei Brin and Larry Page (Google/Alphabet) have reached record levels. The Cult was increasing its own power through further dramatic concentrations of wealth while the competition was being destroyed and brought into a state of dependency. Lockdowns have been instigated to secure that very end and were never anything to do with health. My brother Paul spent 45 years building up a bus repair business, but lockdowns meant buses were running at a fraction of normal levels for months on end. Similar stories can told in their hundreds of millions worldwide. Efforts of a lifetime coldly destroyed by Cult multi-billionaires and their lackeys in government and law enforcement who continued to earn their living from the taxation of the people while denying the right of the same people to earn theirs. How different it would have been if those making and enforcing these decisions had to face the same financial hardships of those they affected, but they never do.

Gates of Hell

Behind it all in the full knowledge of what he is doing and why is the psychopathic figure of Cult operative Bill Gates. His puppet Tedros at the World Health Organization declared 'Covid' a pandemic in March, 2020. The WHO had changed the definition of a 'pandemic' in 2009 just a month before declaring the 'swine flu pandemic' which would not have been so under the previous definition. The same applies to 'Covid'. The definition had included… 'an infection by an infectious agent, occurring simultaneously in different countries, with a significant mortality rate relative to the proportion of the population infected'. The new definition removed the need for 'significant mortality'. The 'pandemic' has been fraudulent even down to the definition, but Gates demanded economy-destroying lockdowns, school closures, social distancing, mandatory masks, a 'vaccination' for every man, woman and child on the planet and severe consequences and restrictions for those that refused. Who gave him this power? The

Cult did which he serves like a little boy in short trousers doing what his daddy tells him. He and his psychopathic missus even smiled when they said that much worse was to come (what they knew was planned to come). Gates responded in the matter-of-fact way of all psychopaths to a question about the effect on the world economy of what he was doing:

> Well, it won't go to zero but it will shrink. Global GDP is probably going to take the biggest hit ever [Gates was smiling as he said this] … in my lifetime this will be the greatest economic hit. But you don't have a choice. People act as if you have a choice. People don't feel like going to the stadium when they might get infected … People are deeply affected by seeing these stats, by knowing they could be part of the transmission chain, old people, their parents and grandparents, could be affected by this, and so you don't get to say ignore what is going on here.
>
> There will be the ability to open up, particularly in rich countries, if things are done well over the next few months, but for the world at large normalcy only returns when we have largely vaccinated the entire population.

The man has no compassion or empathy. How could he when he's a psychopath like all Cult players? My own view is that even beyond that he is very seriously mentally ill. Look in his eyes and you can see this along with his crazy flailing arms. You don't do what he has done to the world population since the start of 2020 unless you are mentally ill and at the most extreme end of psychopathic. You especially don't do it when to you know, as we shall see, that cases and deaths from 'Covid' are fakery and a product of monumental figure massaging. 'These stats' that Gates referred to are based on a 'test' that's not testing for the 'virus' as he has known all along. He made his fortune with big Cult support as an infamously ruthless software salesman and now buys global control of 'health' (death) policy without the population he affects having any say. It's a breathtaking outrage. Gates talked about people being deeply affected by fear of 'Covid' when that was because of *him* and his global network lying to them minute-by-minute supported by a lying media that he seriously influences and funds to the tune of hundreds of millions. He's handed big sums to media operations including the BBC, NBC, Al Jazeera, Univision, *PBS NewsHour*,

ProPublica, National Journal, The Guardian, The Financial Times, The Atlantic, Texas Tribune, USA Today publisher Gannett, *Washington Monthly, Le Monde,* Center for Investigative Reporting, Pulitzer Center on Crisis Reporting, National Press Foundation, International Center for Journalists, Solutions Journalism Network, the Poynter Institute for Media Studies, and many more. Gates is everywhere in the 'Covid' hoax and the man must go to prison – or a mental facility – for the rest of his life and his money distributed to those he has taken such enormous psychopathic pleasure in crushing.

The Muscle

The Hunger Games global structure demands a police-military state – a fusion of the two into one force – which viciously imposes the will of the Cult on the population and protects the Cult from public rebellion. In that regard, too, the 'Covid' hoax just keeps on giving. Often unlawful, ridiculous and contradictory 'Covid' rules and regulations have been policed across the world by moronic automatons and psychopaths made faceless by face-nappy masks and acting like the Nazi SS and fascist blackshirts and brownshirts of Hitler and Mussolini. The smallest departure from the rules decreed by the psychos in government and their clueless gofers were jumped upon by the face-nappy fascists. Brutality against public protestors soon became commonplace even on girls, women and old people as the brave men with the batons – the Face-Nappies as I call them – broke up peaceful protests and handed out fines like confetti to people who couldn't earn a living let alone pay hundreds of pounds for what was once an accepted human right. Robot Face-Nappies of Nottingham police in the English East Midlands fined one group £11,000 for attending a child's birthday party. For decades I charted the transformation of law enforcement as genuine, decent officers were replaced with psychopaths and the brain dead who would happily and brutally do whatever their masters told them. Now they were let loose on the public and I would emphasise the point that none of this just happened. The step-by-step change in the dynamic between police and public was orchestrated from the shadows by

those who knew where this was all going and the same with the perceptual reframing of those in all levels of authority and official administration through 'training courses' by organisations such as Common Purpose which was created in the late 1980s and given a massive boost in Blair era Britain until it became a global phenomenon. Supposed public 'servants' began to view the population as the enemy and the same was true of the police. This was the start of the explosion of behaviour manipulation organisations and networks preparing for the all-war on the human psyche unleashed with the dawn of 2020. I will go into more detail about this later in the book because it is a core part of what is happening.

Police desecrated beauty spots to deter people gathering and arrested women for walking in the countryside alone 'too far' from their homes. We had arrogant, clueless sergeants in the Isle of Wight police where I live posting on Facebook what they insisted the population must do or else. A schoolmaster sergeant called Radford looked young enough for me to ask if his mother knew he was out, but he was posting what he *expected* people to do while a Sergeant Wilkinson boasted about fining lads for meeting in a McDonald's car park where they went to get a lockdown takeaway. Wilkinson added that he had even cancelled their order. What a pair of prats these people are and yet they have increasingly become the norm among Jackboot Johnson's Yellowshirts once known as the British police. This was the theme all over the world with police savagery common during lockdown protests in the United States, the Netherlands, and the fascist state of Victoria in Australia under its tyrannical and again moronic premier Daniel Andrews. Amazing how tyrannical and moronic tend to work as a team and the same combination could be seen across America as arrogant, narcissistic Woke governors and mayors such as Gavin Newsom (California), Andrew Cuomo (New York), Gretchen Whitmer (Michigan), Lori Lightfoot (Chicago) and Eric Garcetti (Los Angeles) did their Nazi and Stalin impressions with the full support of the compliant brutality of their enforcers in uniform as they arrested small business owners defying

fascist shutdown orders and took them to jail in ankle shackles and handcuffs. This happened to bistro owner Marlena Pavlos-Hackney in Gretchen Whitmer's fascist state of Michigan when police arrived to enforce an order by a state-owned judge for 'putting the community at risk' at a time when other states like Texas were dropping restrictions and migrants were pouring across the southern border without any 'Covid' questions at all. I'm sure there are many officers appalled by what they are ordered to do, but not nearly enough of them. If they were truly appalled they would not do it. As the months passed every opportunity was taken to have the military involved to make their presence on the streets ever more familiar and 'normal' for the longer-term goal of police-military fusion.

Another crucial element to the Hunger Games enforcement network has been encouraging the public to report neighbours and others for 'breaking the lockdown rules'. The group faced with £11,000 in fines at the child's birthday party would have been dobbed-in by a neighbour with a brain the size of a pea. The technique was most famously employed by the Stasi secret police in communist East Germany who had public informants placed throughout the population. A police chief in the UK says his force doesn't need to carry out 'Covid' patrols when they are flooded with so many calls from the public reporting other people for visiting the beach. Dorset police chief James Vaughan said people were so enthusiastic about snitching on their fellow humans they were now operating as an auxiliary arm of the police: 'We are still getting around 400 reports a week from the public, so we will respond to reports …We won't need to be doing hotspot patrols because people are very quick to pick the phone up and tell us.' Vaughan didn't say that this is a pillar of all tyrannies of whatever complexion and the means to hugely extend the reach of enforcement while spreading distrust among the people and making them wary of doing anything that might get them reported. Those narcissistic Isle of Wight sergeants Radford and Wilkinson never fail to add a link to their Facebook posts where the public can inform on their fellow slaves.

Neither would be self-aware enough to realise they were imitating the Stasi which they might well never have heard of. Government psychologists that I will expose later laid out a policy to turn communities against each other in the same way.

A coincidence? Yep, and I can knit fog

I knew from the start of the alleged pandemic that this was a Cult operation. It presented limitless potential to rapidly advance the Cult agenda and exploit manipulated fear to demand that every man, woman and child on the planet was 'vaccinated' in a process never used on humans before which infuses self-replicating *synthetic* material into human cells. Remember the plan to transform the human body from a biological to a synthetic biological state. I'll deal with the 'vaccine' (that's not actually a vaccine) when I focus on the genetic agenda. Enough to say here that mass global 'vaccination' justified by this 'new virus' set alarms ringing after 30 years of tracking these people and their methods. The 'Covid' hoax officially beginning in China was also a big red flag for reasons I will be explaining. The agenda potential was so enormous that I could dismiss any idea that the 'virus' appeared naturally. Major happenings with major agenda implications never occur without Cult involvement in making them happen. My questions were twofold in early 2020 as the media began its campaign to induce global fear and hysteria: Was this alleged infectious agent released on purpose by the Cult or did it even exist at all? I then did what I always do in these situations. I sat, observed and waited to see where the evidence and information would take me. By March and early April synchronicity was strongly – and ever more so since then – pointing me in the direction of *there is no 'virus'*. I went public on that with derision even from swathes of the alternative media that voiced a scenario that the Chinese government released the 'virus' in league with Deep State elements in the United States from a top-level bio-lab in Wuhan where the 'virus' is said to have first appeared. I looked at that possibility, but I didn't buy it for several reasons. Deaths from the 'virus' did not in any way match what they

would have been with a 'deadly bioweapon' and it is much more effective if you sell the *illusion* of an infectious agent rather than having a real one unless you can control through injection who has it and who doesn't. Otherwise you lose control of events. A made-up 'virus' gives you a blank sheet of paper on which you can make it do whatever you like and have any symptoms or mutant 'variants' you choose to add while a real infectious agent would limit you to what it actually does. A phantom disease allows you to have endless ludicrous 'studies' on the 'Covid' dollar to widen the perceived impact by inventing ever more 'at risk' groups including one study which said those who walk slowly may be almost four times more likely to die from the 'virus'. People are in psychiatric wards for less.

A real 'deadly bioweapon' can take out people in the hierarchy that are not part of the Cult, but essential to its operation. Obviously they don't want that. Releasing a real disease means you immediately lose control of it. Releasing an illusory one means you don't. Again it's vital that people are extra careful when dealing with what they want to hear. A bioweapon unleashed from a Chinese laboratory in collusion with the American Deep State may fit a conspiracy narrative, but is it true? Would it not be far more effective to use the excuse of a 'virus' to justify the real bioweapon – the 'vaccine'? That way your disease agent does not have to be transmitted and arrives directly through a syringe. I saw a French virologist Luc Montagnier quoted in the alternative media as saying he had discovered that the alleged 'new' severe acute respiratory syndrome coronavirus , or SARS-CoV-2, was made artificially and included elements of the human immunodeficiency 'virus' (HIV) and a parasite that causes malaria. SARS-CoV-2 is alleged to trigger an alleged illness called Covid-19. I remembered Montagnier's name from my research years before into claims that an HIV 'retrovirus' causes AIDs – claims that were demolished by Berkeley virologist Peter Duesberg who showed that no one had ever proved that HIV causes acquired immunodeficiency syndrome or AIDS. Claims that become accepted as fact, publicly and medically, with no proof whatsoever are an ever-recurring story that profoundly applies to

'Covid'. Nevertheless, despite the lack of proof, Montagnier's team at the Pasteur Institute in Paris had a long dispute with American researcher Robert Gallo over which of them discovered and isolated the HIV 'virus' and with *no evidence* found it to cause AIDS. You will see later that there is also no evidence that any 'virus' causes any disease or that there is even such a thing as a 'virus' in the way it is said to exist. The claim to have 'isolated' the HIV 'virus' will be presented in its real context as we come to the shocking story – and it is a story – of SARS-CoV-2 and so will Montagnier's assertion that he identified the full SARS-CoV-2 genome.

Hoax in the making

We can pick up the 'Covid' story in 2010 and the publication by the Rockefeller Foundation of a document called 'Scenarios for the Future of Technology and International Development'. The inner circle of the Rockefeller family has been serving the Cult since John D. Rockefeller (1839-1937) made his fortune with Standard Oil. It is less well known that the same Rockefeller – the Bill Gates of his day – was responsible for establishing what is now referred to as 'Big Pharma', the global network of pharmaceutical companies that make outrageous profits dispensing scalpel and drug 'medicine' and are obsessed with pumping vaccines in ever-increasing number into as many human arms and backsides as possible. John D. Rockefeller was the driving force behind the creation of the 'education' system in the United States and elsewhere specifically designed to program the perceptions of generations thereafter. The Rockefeller family donated exceptionally valuable land in New York for the United Nations building and were central in establishing the World Health Organization in 1948 as an agency of the UN which was created from the start as a Trojan horse and stalking horse for world government. Now enter Bill Gates. His family and the Rockefellers have long been extremely close and I have seen genealogy which claims that if you go back far enough the two families fuse into the same bloodline. Gates has said that the Bill and Melinda Gates Foundation was inspired by the Rockefeller Foundation and why not

when both are serving the same Cult? Major tax-exempt foundations are overwhelmingly criminal enterprises in which Cult assets fund the Cult agenda in the guise of 'philanthropy' while avoiding tax in the process. Cult operatives can become mega-rich in their role of front men and women for the psychopaths at the inner core and they, too, have to be psychopaths to knowingly serve such evil. Part of the deal is that a big percentage of the wealth gleaned from representing the Cult has to be spent advancing the ambitions of the Cult and hence you have the Rockefeller Foundation, Bill and Melinda Gates Foundation (and *so* many more) and people like George Soros with his global Open Society Foundations spending their billions in pursuit of global Cult control. Gates is a global public face of the Cult with his interventions in world affairs including Big Tech influence; a central role in the 'Covid' and 'vaccine' scam; promotion of the climate change shakedown; manipulation of education; geoengineering of the skies; and his food-control agenda as the biggest owner of farmland in America, his GMO promotion and through other means. As one writer said: 'Gates monopolizes or wields disproportionate influence over the tech industry, global health and vaccines, agriculture and food policy (including biopiracy and fake food), weather modification and other climate technologies, surveillance, education and media.' The almost limitless wealth secured through Microsoft and other not-allowed-to-fail ventures (including vaccines) has been ploughed into a long, long list of Cult projects designed to enslave the entire human race. Gates and the Rockefellers have been working as one unit with the Rockefeller-established World Health Organization leading global 'Covid' policy controlled by Gates through his mouth-piece Tedros. Gates became the WHO's biggest funder when Trump announced that the American government would cease its donations, but Biden immediately said he would restore the money when he took office in January, 2021. The Gates Foundation (the Cult) owns through limitless funding the world health system and the major players across the globe in the 'Covid' hoax.

Okay, with that background we return to that Rockefeller Foundation document of 2010 headed 'Scenarios for the Future of Technology and International Development' and its 'imaginary' epidemic of a virulent and deadly influenza strain which infected 20 percent of the global population and killed eight million in seven months. The Rockefeller scenario was that the epidemic destroyed economies, closed shops, offices and other businesses and led to governments imposing fierce rules and restrictions that included mandatory wearing of face masks and body-temperature checks to enter communal spaces like railway stations and supermarkets. The document predicted that even after the height of the Rockefeller-envisaged epidemic the authoritarian rule would continue to deal with further pandemics, transnational terrorism, environmental crises and rising poverty. Now you may think that the Rockefellers are our modern-day seers or alternatively, and rather more likely, that they well knew what was planned a few years further on. Fascism had to be imposed, you see, to 'protect citizens from risk and exposure'. The Rockefeller scenario document said:

During the pandemic, national leaders around the world flexed their authority and imposed airtight rules and restrictions, from the mandatory wearing of face masks to body-temperature checks at the entries to communal spaces like train stations and supermarkets. Even after the pandemic faded, this more authoritarian control and oversight of citizens and their activities stuck and even intensified. In order to protect themselves from the spread of increasingly global problems – from pandemics and transnational terrorism to environmental crises and rising poverty – leaders around the world took a firmer grip on power.

At first, the notion of a more controlled world gained wide acceptance and approval. Citizens willingly gave up some of their sovereignty – and their privacy – to more paternalistic states in exchange for greater safety and stability. Citizens were more tolerant, and even eager, for top-down direction and oversight, and national leaders had more latitude to impose order in the ways they saw fit.

In developed countries, this heightened oversight took many forms: biometric IDs for all citizens, for example, and tighter regulation of key industries whose stability was deemed vital to national interests. In many developed countries, enforced cooperation with a suite of new regulations and agreements slowly but steadily restored both order and, importantly, economic growth.

There we have the prophetic Rockefellers in 2010 and three years later came their paper for the Global Health Summit in Beijing, China, when government representatives, the private sector, international organisations and groups met to discuss the next 100 years of 'global health'. The Rockefeller Foundation-funded paper was called 'Dreaming the Future of Health for the Next 100 Years and more prophecy ensued as it described a dystopian future: 'The abundance of data, digitally tracking and linking people may mean the 'death of privacy' and may replace physical interaction with transient, virtual connection, generating isolation and raising questions of how values are shaped in virtual networks.' Next in the 'Covid' hoax preparation sequence came a 'table top' simulation in 2018 for another 'imaginary' pandemic of a disease called Clade X which was said to kill 900 million people. The exercise was organised by the Gates-funded Johns Hopkins University's Center for Health Security in the United States and this is the very same university that has been compiling the disgustingly and systematically erroneous global figures for 'Covid' cases and deaths. Similar Johns Hopkins health crisis scenarios have included the Dark Winter exercise in 2001 and Atlantic Storm in 2005.

Nostradamus 201

For sheer predictive genius look no further prophecy-watchers than the Bill Gates-funded Event 201 held only six weeks before the 'coronavirus pandemic' is supposed to have broken out in China and Event 201 was based on a scenario of a global 'coronavirus pandemic'. Melinda Gates, the great man's missus, told the BBC that he had 'prepared for years' for a coronavirus pandemic which told us what we already knew. Nostradamugates had predicted in a TED talk in 2015 that a pandemic was coming that would kill a lot of people and demolish the world economy. My god, the man is a machine – possibly even literally. Now here he was only weeks before the real thing funding just such a simulated scenario and involving his friends and associates at Johns Hopkins, the World Economic Forum Cult-front of Klaus Schwab, the United Nations,

Johnson & Johnson, major banks, and officials from China and the Centers for Disease Control in the United States. What synchronicity – Johns Hopkins would go on to compile the fraudulent 'Covid' figures, the World Economic Forum and Schwab would push the 'Great Reset' in response to 'Covid', the Centers for Disease Control would be at the forefront of 'Covid' policy in the United States, Johnson & Johnson would produce a 'Covid vaccine', and everything would officially start just weeks later in China. Spooky, eh? They were even accurate in creating a simulation of a 'virus' pandemic because the 'real thing' would also be a simulation. Event 201 was not an exercise preparing for something that might happen; it was a rehearsal for what those in control knew was *going* to happen and very shortly. Hours of this simulation were posted on the Internet and the various themes and responses mirrored what would soon be imposed to transform human society. News stories were inserted and what they said would be commonplace a few weeks later with still more prophecy perfection. Much discussion focused on the need to deal with misinformation and the 'anti-vax movement' which is exactly what happened when the 'virus' arrived – was said to have arrived – in the West.

Cult-owned social media banned criticism and exposure of the official 'virus' narrative and when I said there *was* no 'virus' in early April, 2020, I was banned by one platform after another including YouTube, Facebook and later Twitter. The mainstream broadcast media in Britain was in effect banned from interviewing me by the Tony-Blair-created government broadcasting censor Ofcom headed by career government bureaucrat Melanie Dawes who was appointed just as the 'virus' hoax was about to play out in January, 2020. At the same time the Ickonic media platform was using Vimeo, another ultra-Zionist-owned operation, while our own player was being created and they deleted in an instant hundreds of videos, documentaries, series and shows to confirm their unbelievable vindictiveness. We had copies, of course, and they had to be restored one by one when our player was ready. These people have no class. Sabbatian Facebook promised free advertisements for the Gates-

controlled World Health Organization narrative while deleting 'false claims and conspiracy theories' to stop 'misinformation' about the alleged coronavirus. All these responses could be seen just a short while earlier in the scenarios of Event 201. Extreme censorship was absolutely crucial for the Cult because the official story was so ridiculous and unsupportable by the evidence that it could never survive open debate and the free-flow of information and opinion. If you can't win a debate then don't have one is the Cult's approach throughout history. Facebook's little boy front man – front boy – Mark Zuckerberg equated 'credible and accurate information' with official sources and exposing their lies with 'misinformation'.

Silencing those that can see

The censorship dynamic of Event 201 is now the norm with an army of narrative-supporting 'fact-checker' organisations whose entire reason for being is to tell the public that official narratives are true and those exposing them are lying. One of the most appalling of these 'fact-checkers' is called NewsGuard founded by ultra-Zionist Americans Gordon Crovitz and Steven Brill. Crovitz is a former publisher of *The Wall Street Journal*, former Executive Vice President of Dow Jones, a member of the Council on Foreign Relations (CFR), and on the board of the American Association of Rhodes Scholars. The CFR and Rhodes Scholarships, named after Rothschild agent Cecil Rhodes who plundered the gold and diamonds of South Africa for his masters and the Cult, have featured widely in my books. NewsGuard don't seem to like me for some reason – I really can't think why – and they have done all they can to have me censored and discredited which is, to quote an old British politician, like being savaged by a dead sheep. They are, however, like all in the censorship network, very well connected and funded by organisations themselves funded by, or connected to, Bill Gates. As you would expect with anything associated with Gates NewsGuard has an offshoot called HealthGuard which 'fights online health care hoaxes'. How very kind. Somehow the NewsGuard European Managing Director Anna-Sophie Harling, a remarkably young-

looking woman with no broadcasting experience and little hands-on work in journalism, has somehow secured a position on the 'Content Board' of UK government broadcast censor Ofcom. An executive of an organisation seeking to discredit dissidents of the official narratives is making decisions for the government broadcast 'regulator' about content?? Another appalling 'fact-checker' is Full Fact funded by George Soros and global censors Google and Facebook.

It's amazing how many activists in the 'fact-checking', 'anti-hate', arena turn up in government-related positions – people like UK Labour Party activist Imran Ahmed who heads the Center for Countering Digital Hate founded by people like Morgan McSweeney, now chief of staff to the Labour Party's hapless and useless 'leader' Keir Starmer. Digital Hate – which is what it really is – uses the American spelling of Center to betray its connection to a transatlantic network of similar organisations which in 2020 shapeshifted from attacking people for 'hate' to attacking them for questioning the 'Covid' hoax and the dangers of the 'Covid vaccine'. It's just a coincidence, you understand. This is one of Imran Ahmed's hysterical statements: 'I would go beyond calling anti-vaxxers conspiracy theorists to say they are an extremist group that pose a national security risk.' No one could ever accuse this prat of understatement and he's including in that those parents who are now against vaccines after their children were damaged for life or killed by them. He's such a nice man. Ahmed does the rounds of the Woke media getting soft-ball questions from spineless 'journalists' who never ask what right he has to campaign to destroy the freedom of speech of others while he demands it for himself. There also seems to be an overrepresentation in Ofcom of people connected to the narrative-worshipping BBC. This incredible global network of narrative-support was super-vital when the 'Covid' hoax was played in the light of the mega-whopper lies that have to be defended from the spotlight cast by the most basic intelligence.

Setting the scene

The Cult plays the long game and proceeds step-by-step ensuring that everything is in place before major cards are played and they don't come any bigger than the 'Covid' hoax. The psychopaths can't handle events where the outcome isn't certain and as little as possible – preferably nothing – is left to chance. Politicians, government and medical officials who would follow direction were brought to illusory power in advance by the Cult web whether on the national stage or others like state governors and mayors of America. For decades the dynamic between officialdom, law enforcement and the public was changed from one of service to one of control and dictatorship. Behaviour manipulation networks established within government were waiting to impose the coming 'Covid' rules and regulations specifically designed to subdue and rewire the psyche of the people in the guise of protecting health. These included in the UK the Behavioural Insights Team part-owned by the British government Cabinet Office; the Scientific Pandemic Insights Group on Behaviours (SPI-B); and a whole web of intelligence and military groups seeking to direct the conversation on social media and control the narrative. Among them are the cyberwarfare (on the people) 77th Brigade of the British military which is also coordinated through the Cabinet Office as civilian and military leadership continues to combine in what they call the Fusion Doctrine. The 77th Brigade is a British equivalent of the infamous Israeli (Sabbatian) military cyberwarfare and Internet manipulation operation Unit 8200 which I expose at length in *The Trigger*. Also carefully in place were the medical and science advisers to government – many on the payroll past or present of Bill Gates – and a whole alternative structure of unelected government stood by to take control when elected parliaments were effectively closed down once the 'Covid' card was slammed on the table. The structure I have described here and so much more was installed in every major country through the Cult networks. The top-down control hierarchy looks like this: The Cult – Cult-owned Gates – the World Health Organization and Tedros – Gates-funded or controlled chief medical officers and science 'advisers' (dictators) in each country –

political 'leaders'– law enforcement – The People. Through this simple global communication and enforcement structure the policy of the Cult could be imposed on virtually the entire human population so long as they acquiesced to the fascism. With everything in place it was time for the button to be pressed in late 2019/early 2020.

These were the prime goals the Cult had to secure for its will to prevail:

1) Locking down economies, closing all but designated 'essential' businesses (Cult-owned corporations were 'essential'), and putting the population under house arrest was an imperative to destroy independent income and employment and ensure dependency on the Cult-controlled state in the Hunger Games Society. Lockdowns had to be established as the global blueprint from the start to respond to the 'virus' and followed by pretty much the entire world.

2) The global population had to be terrified into believing in a deadly 'virus' that didn't actually exist so they would unquestioningly obey authority in the belief that authority must know how best to protect them and their families. Software salesman Gates would suddenly morph into the world's health expert and be promoted as such by the Cult-owned media.

3) A method of testing that wasn't testing for the 'virus', but was only claimed to be, had to be in place to provide the illusion of 'cases' and subsequent 'deaths' that had a very different cause to the 'Covid-19' that would be scribbled on the death certificate.

4) Because there was no 'virus' and the great majority testing positive with a test not testing for the 'virus' would have no symptoms of anything the lie had to be sold that people without symptoms (without the 'virus') could still pass it on to others. This was crucial to justify for the first time quarantining – house arresting – healthy people. Without this the economy-destroying lockdown of *everybody* could not have been credibly sold.

5) The 'saviour' had to be seen as a vaccine which beyond evil drug companies were working like angels of mercy to develop as quickly as possible, with all corners cut, to save the day. The public must absolutely not know that the 'vaccine' had nothing to do with a 'virus' or that the contents were ready and waiting with a very different motive long before the 'Covid' card was even lifted from the pack.

I said in March, 2020, that the 'vaccine' would have been created way ahead of the 'Covid' hoax which justified its use and the following December an article in the New York *Intelligencer* magazine said the Moderna 'vaccine' had been 'designed' by

January, 2020. This was 'before China had even acknowledged that the disease could be transmitted from human to human, more than a week before the first confirmed coronavirus case in the United States'. The article said that by the time the first American death was announced a month later 'the vaccine had already been manufactured and shipped to the National Institutes of Health for the beginning of its Phase I clinical trial'. The 'vaccine' was actually 'designed' long before that although even with this timescale you would expect the article to ask how on earth it could have been done that quickly. Instead it asked why the 'vaccine' had not been rolled out then and not months later. Journalism in the mainstream is truly dead. I am going to detail in the next chapter why the 'virus' has never existed and how a hoax on that scale was possible, but first the foundation on which the Big Lie of 'Covid' was built.

The test that doesn't test

Fraudulent 'testing' is the bottom line of the whole 'Covid' hoax and was the means by which a 'virus' that did not exist *appeared* to exist. They could only achieve this magic trick by using a test not testing for the 'virus'. To use a test that *was* testing for the 'virus' would mean that every test would come back negative given there was no 'virus'. They chose to exploit something called the RT-PCR test invented by American biochemist Kary Mullis in the 1980s who said publicly that his PCR test … *cannot detect infectious disease*. Yes, the 'test' used worldwide to detect infectious 'Covid' to produce all the illusory 'cases' and 'deaths' compiled by Johns Hopkins and others *cannot detect infectious disease*. This fact came from the mouth of the man who invented PCR and was awarded the Nobel Prize in Chemistry in 1993 for doing so. Sadly, and incredibly conveniently for the Cult, Mullis died in August, 2019, at the age of 74 just before his test would be fraudulently used to unleash fascism on the world. He was said to have died from pneumonia which was an irony in itself. A few months later he would have had 'Covid-19' on his death certificate. I say the timing of his death was convenient because had he lived Mullis, a brilliant, honest and decent man, would have been

vociferously speaking out against the use of his test to detect 'Covid' when it was never designed, or able, to do that. I know that to be true given that Mullis made the same point when his test was used to 'detect' – not detect – HIV. He had been seriously critical of the Gallo/Montagnier claim to have isolated the HIV 'virus' and shown it to cause AIDS for which Mullis said there was no evidence. AIDS is actually not a disease but a series of diseases from which people die all the time. When they die from those *same diseases* after a positive 'test' for HIV then AIDS goes on their death certificate. I think I've heard that before somewhere. Countries instigated a policy with 'Covid' that anyone who tested positive with a test not testing for the 'virus' and died of any other cause within 28 days and even longer 'Covid-19' had to go on the death certificate. Cases have come from the test that can't test for infectious disease and the deaths are those who have died of *anything* after testing positive with a test not testing for the 'virus'. I'll have much more later about the death certificate scandal.

Mullis was deeply dismissive of the now US 'Covid' star Anthony Fauci who he said was a liar who didn't know anything about anything – 'and I would say that to his face – nothing.' He said of Fauci: 'The man thinks he can take a blood sample, put it in an electron microscope and if it's got a virus in there you'll know it – he doesn't understand electron microscopy and he doesn't understand medicine and shouldn't be in a position like he's in.' That position, terrifyingly, has made him the decider of 'Covid' fascism policy on behalf of the Cult in his role as director since 1984 of the National Institute of Allergy and Infectious Diseases (NIAID) while his record of being wrong is laughable; but being wrong, so long as it's the *right kind* of wrong, is why the Cult loves him. He'll say anything the Cult tells him to say. Fauci was made Chief Medical Adviser to the President immediately Biden took office. Biden was installed in the White House by Cult manipulation and one of his first decisions was to elevate Fauci to a position of even more control. This is a coincidence? Yes, and I identify as a flamenco dancer called Lola. How does such an incompetent criminal like Fauci remain in that

pivotal position in American health since *the 1980s*? When you serve the Cult it looks after you until you are surplus to requirements. Kary Mullis said prophetically of Fauci and his like: 'Those guys have an agenda and it's not an agenda we would like them to have … they make their own rules, they change them when they want to, and Tony Fauci does not mind going on television in front of the people who pay his salary and lie directly into the camera.' Fauci has done that almost daily since the 'Covid' hoax began. Lying is in Fauci's DNA. To make the situation crystal clear about the PCR test this is a direct quote from its inventor Kary Mullis:

> It [the PCR test] doesn't tell you that you're sick and doesn't tell you that the thing you ended up with was really going to hurt you ...'

Ask yourself why governments and medical systems the world over have been using this very test to decide who is 'infected' with the SARS-CoV-2 'virus' and the alleged disease it allegedly causes, 'Covid-19'. The answer to that question will tell you what has been going on. By the way, here's a little show-stopper – the 'new' SARS-CoV-2 'virus' was 'identified' as such right from the start using … *the PCR test not testing for the 'virus'*. If you are new to this and find that shocking then stick around. I have hardly started yet. Even worse, other 'tests', like the 'Lateral Flow Device' (LFD), are considered so useless that they have to be *confirmed* by the PCR test! Leaked emails written by Ben Dyson, adviser to UK 'Health' Secretary Matt Hancock, said they were 'dangerously unreliable'. Dyson, executive director of strategy at the Department of Health, wrote: 'As of today, someone who gets a positive LFD result in (say) London has at best a 25 per cent chance of it being a true positive, but if it is a self-reported test potentially as low as 10 per cent (on an optimistic assumption about specificity) or as low as 2 per cent (on a more pessimistic assumption).' These are the 'tests' that schoolchildren and the public are being urged to have twice a week or more and have to isolate if they get a positive. Each fake positive goes in the statistics as a 'case' no matter how ludicrously inaccurate and the

'cases' drive lockdown, masks and the pressure to 'vaccinate'. The government said in response to the email leak that the 'tests' were accurate which confirmed yet again what shocking bloody liars they are. The real false positive rate is *100 percent* as we'll see. In another 'you couldn't make it up' the UK government agreed to pay £2.8 billion to California's Innova Medical Group to supply the irrelevant lateral flow tests. The company's primary test-making centre is in China. Innova Medical Group, established in March, 2020, is owned by Pasaca Capital Inc, chaired by Chinese-American millionaire Charles Huang who was born in Wuhan.

How it works – and how it doesn't

The RT-PCR test, known by its full title of Polymerase chain reaction, is used across the world to make millions, even billions, of copies of a DNA/RNA genetic information sample. The process is called 'amplification' and means that a tiny sample of genetic material is amplified to bring out the detailed content. I stress that it is not testing for an infectious disease. It is simply amplifying a sample of genetic material. In the words of Kary Mullis: 'PCR is … just a process that's used to make a whole lot of something out of something.' To emphasise the point companies that make the PCR tests circulated around the world to 'test' for 'Covid' warn on the box that it can't be used to detect 'Covid' or infectious disease and is for research purposes only. It's okay, rest for a minute and you'll be fine. This is the test that produces the 'cases' and 'deaths' that have been used to destroy human society. All those global and national medical and scientific 'experts' demanding this destruction to 'save us' *KNOW* that the test is not testing for the 'virus' and the cases and deaths they claim to be real are an almost unimaginable fraud. Every one of them and so many others including politicians and psychopaths like Gates and Tedros must be brought before Nuremburg-type trials and jailed for the rest of their lives. The more the genetic sample is amplified by PCR the more elements of that material become sensitive to the test and by that I don't mean sensitive for a 'virus' but for elements of the genetic material which

is *naturally* in the body or relates to remnants of old conditions of various kinds lying dormant and causing no disease. Once the amplification of the PCR reaches a certain level *everyone* will test positive. So much of the material has been made sensitive to the test that everyone will have some part of it in their body. Even lying criminals like Fauci have said that once PCR amplifications pass 35 cycles everything will be a false positive that cannot be trusted for the reasons I have described. I say, like many proper doctors and scientists, that 100 percent of the 'positives' are false, but let's just go with Fauci for a moment.

He says that any amplification over 35 cycles will produce false positives and yet the US Centers for Disease Control (CDC) and Food and Drug Administration (FDA) have recommended up to *40 cycles* and the National Health Service (NHS) in Britain admitted in an internal document for staff that it was using *45 cycles* of amplification. A long list of other countries has been doing the same and at least one 'testing' laboratory has been using *50 cycles*. Have you ever heard a doctor, medical 'expert' or the media ask what level of amplification has been used to claim a 'positive'. The 'test' comes back 'positive' and so you have the 'virus', end of story. Now we can see how the government in Tanzania could send off samples from a goat and a pawpaw fruit under human names and both came back positive for 'Covid-19'. Tanzania president John Magufuli mocked the 'Covid' hysteria, the PCR test and masks and refused to import the DNA-manipulating 'vaccine'. The Cult hated him and an article sponsored by the Bill Gates Foundation appeared in the London *Guardian* in February, 2021, headed 'It's time for Africa to rein in Tanzania's anti-vaxxer president'. Well, 'reined in' he shortly was. Magufuli appeared in good health, but then, in March, 2021, he was dead at 61 from 'heart failure'. He was replaced by Samia Hassan Suhulu who is connected to Klaus Schwab's World Economic Forum and she immediately reversed Magufuli's 'Covid' policy. A sample of cola tested positive for 'Covid' with the PCR test in Germany while American actress and singer-songwriter Erykah Badu tested positive in one nostril and negative in the other. Footballer Ronaldo called

the PCR test 'bullshit' after testing positive three times and being forced to quarantine and miss matches when there was nothing wrong with him. The mantra from Tedros at the World Health Organization and national governments (same thing) has been test, test, test. They know that the more tests they can generate the more fake 'cases' they have which go on to become 'deaths' in ways I am coming to. The UK government has its Operation Moonshot planned to test multiple millions every day in workplaces and schools with free tests for everyone to use twice a week at home in line with the Cult plan from the start to make testing part of life. A government advertisement for an 'Interim Head of Asymptomatic Testing Communication' said the job included responsibility for delivering a 'communications strategy' (propaganda) 'to support the expansion of asymptomatic testing that *'normalises testing as part of everyday life*'. More tests means more fake 'cases', 'deaths' and fascism. I have heard of, and from, many people who booked a test, couldn't turn up, and yet got a positive result through the post for a test they'd never even had. The whole thing is crazy, but for the Cult there's method in the madness. Controlling and manipulating the level of amplification of the test means the authorities can control whenever they want the number of apparent 'cases' and 'deaths'. If they want to justify more fascist lockdown and destruction of livelihoods they keep the amplification high. If they want to give the illusion that lockdowns and the 'vaccine' are working then they lower the amplification and 'cases' and 'deaths' will appear to fall. In January, 2021, the Cult-owned World Health Organization suddenly warned laboratories about over-amplification of the test and to lower the threshold. Suddenly headlines began appearing such as: 'Why ARE "Covid" cases plummeting?' This was just when the vaccine rollout was underway and I had predicted months before they would make cases appear to fall through amplification tampering when the 'vaccine' came. These people are so predictable.

Cow vaccines?

The question must be asked of what is on the test swabs being poked far up the nose of the population to the base of the brain? A nasal swab punctured one woman's brain and caused it to leak fluid. Most of these procedures are being done by people with little training or medical knowledge. Dr Lorraine Day, former orthopaedic trauma surgeon and Chief of Orthopaedic Surgery at San Francisco General Hospital, says the tests are really a *'vaccine'*. Cows have long been vaccinated this way. She points out that masks have to cover the nose and the mouth where it is claimed the 'virus' exists in saliva. Why then don't they take saliva from the mouth as they do with a DNA test instead of pushing a long swab up the nose towards the brain? The ethmoid bone separates the nasal cavity from the brain and within that bone is the cribriform plate. Dr Day says that when the swab is pushed up against this plate and twisted the procedure is 'depositing things back there'. She claims that among these 'things' are nanoparticles that can enter the brain. Researchers have noted that a team at the Gates-funded Johns Hopkins have designed tiny, star-shaped micro-devices that can latch onto intestinal mucosa and release drugs into the body. Mucosa is the thin skin that covers the inside surface of parts of the body such as *the nose* and mouth and produces mucus to protect them. The Johns Hopkins micro-devices are called 'theragrippers' and were 'inspired' by a parasitic worm that digs its sharp teeth into a host's intestines. Nasal swabs are also coated in the sterilisation agent ethylene oxide. The US National Cancer Institute posts this explanation on its website:

> At room temperature, ethylene oxide is a flammable colorless gas with a sweet odor. It is used primarily to produce other chemicals, including antifreeze. In smaller amounts, ethylene oxide is used as a pesticide and a sterilizing agent. The ability of ethylene oxide to damage DNA makes it an effective sterilizing agent but also accounts for its cancer-causing activity.

The Institute mentions lymphoma and leukaemia as cancers most frequently reported to be associated with occupational exposure to ethylene oxide along with stomach and breast cancers. How does anyone think this is going to work out with the constant testing

regime being inflicted on adults and children at home and at school that will accumulate in the body anything that's on the swab?

Doctors know best

It is vital for people to realise that 'hero' doctors 'know' only what the Big Pharma-dominated medical authorities tell them to 'know' and if they refuse to 'know' what they are told to 'know' they are out the door. They are mostly not physicians or healers, but repeaters of the official narrative – or else. I have seen alleged professional doctors on British television make shocking statements that we are supposed to take seriously. One called 'Dr' Amir Khan, who is actually telling patients how to respond to illness, said that men could take the birth pill to 'help slow down the effects of Covid-19'. In March, 2021, another ridiculous 'Covid study' by an American doctor proposed injecting men with the female sex hormone progesterone as a 'Covid' treatment. British doctor Nighat Arif told the BBC that face coverings were now going to be part of ongoing normal. Yes, the vaccine protects you, she said (evidence?) … but the way to deal with viruses in the community was always going to come down to hand washing, face covering and keeping a physical distance. That's not what we were told before the 'vaccine' was circulating. Arif said she couldn't imagine ever again going on the underground or in a lift without a mask. I was just thanking my good luck that she was not my doctor when she said – in March, 2021 – that if 'we are *behaving* and we are doing all the right things' she thought we could 'have our nearest and dearest around us at home … around *Christmas* and N*ew Year!* Her patronising delivery was the usual school teacher talking to six-year-olds as she repeated every government talking point and probably believed them all. If we have learned anything from the 'Covid' experience surely it must be that humanity's perception of doctors needs a fundamental rethink. NHS 'doctor' Sara Kayat told her television audience that the 'Covid vaccine' would '100 percent prevent hospitalisation and death'. Not even Big Pharma claimed that. We have to stop taking 'experts' at their word without question when so many of them are

clueless and only repeating the party line on which their careers depend. That is not to say there are not brilliants doctors – there are and I have spoken to many of them since all this began – but you won't see them in the mainstream media or quoted by the psychopaths and yes-people in government.

Remember the name – Christian Drosten

German virologist Christian Drosten, Director of Charité Institute of Virology in Berlin, became a national star after the pandemic hoax began. He was feted on television and advised the German government on 'Covid' policy. Most importantly to the wider world Drosten led a group that produced the 'Covid' testing protocol for the PCR test. What a remarkable feat given the PCR cannot test for infectious disease and even more so when you think that Drosten said that his method of testing for SARS-CoV-2 was developed 'without having virus material available'. *He developed a test for a 'virus' that he didn't have and had never seen*. Let that sink in as you survey the global devastation that came from what he did. The whole catastrophe of Drosten's 'test' was based on the alleged genetic sequence published by Chinese scientists on the Internet. We will see in the next chapter that this alleged 'genetic sequence' has never been produced by China or anyone and cannot be when there *is no* SARS-CoV-2. Drosten, however, doesn't seem to let little details like that get in the way. He was the lead author with Victor Corman from the same Charité Hospital of the paper 'Detection of 2019 novel coronavirus (2019-nCoV) by real-time PCR' published in a magazine called *Eurosurveillance*. This became known as the Corman-Drosten paper. In November, 2020, with human society devastated by the effects of the Corman-Drosten test baloney, the protocol was publicly challenged by 22 international scientists and independent researchers from Europe, the United States, and Japan. Among them were senior molecular geneticists, biochemists, immunologists, and microbiologists. They produced a document headed 'External peer review of the RTPCR test to detect SARS-Cov-2 Reveals 10 Major Flaws At The Molecular and Methodological Level: Consequences

For False-Positive Results'. The flaws in the Corman-Drosten test included the following:

- The test is non-specific because of erroneous design
- Results are enormously variable
- The test is unable to discriminate between the whole 'virus' and viral fragments
- It doesn't have positive or negative controls
- The test lacks a standard operating procedure
- It is unsupported by proper peer view

The scientists said the PCR 'Covid' testing protocol was not founded on science and they demanded the Corman-Drosten paper be retracted by *Eurosurveillance*. They said all present and previous Covid deaths, cases, and 'infection rates' should be subject to a massive retroactive inquiry. Lockdowns and travel restrictions should be reviewed and relaxed and those diagnosed through PCR to have 'Covid-19' should not be forced to isolate. Dr Kevin Corbett, a health researcher and nurse educator with a long academic career producing a stream of peer-reviewed publications at many UK universities, made the same point about the PCR test debacle. He said of the scientists' conclusions: 'Every scientific rationale for the development of that test has been totally destroyed by this paper. It's like Hiroshima/Nagasaki to the Covid test.' He said that China hadn't given them an isolated 'virus' when Drosten developed the test. Instead they had developed the test from *a sequence in a gene bank*.' Put another way … *they made it up*! The scientists were supported in this contention by a Portuguese appeals court which ruled in November, 2020, that PCR tests are unreliable and it is unlawful to quarantine people based solely on a PCR test. The point about China not providing an isolated virus must be true when the 'virus' has never been isolated to this day and the consequences of that will become clear. Drosten and company produced this useless 'protocol' right on cue in January, 2020, just as the 'virus' was said to

be moving westward and it somehow managed to successfully pass a peer-review in 24 hours. In other words there was no peer-review for a test that would be used to decide who had 'Covid' and who didn't across the world. The Cult-created, Gates-controlled World Health Organization immediately recommended all its nearly 200 member countries to use the Drosten PCR protocol to detect 'cases' and 'deaths'. The sting was underway and it continues to this day.

So who is this Christian Drosten that produced the means through which death, destruction and economic catastrophe would be justified? His education background, including his doctoral thesis, would appear to be somewhat shrouded in mystery and his track record is dire as with another essential player in the 'Covid' hoax, the Gates-funded Professor Neil Ferguson at the Gates-funded Imperial College in London of whom more shortly. Drosten predicted in 2003 that the alleged original SARS 'virus' (SARS-1') was an epidemic that could have serious effects on economies and an effective vaccine would take at least two years to produce. Drosten's answer to every alleged 'outbreak' is a vaccine which you won't be shocked to know. What followed were just 774 official deaths worldwide and none in Germany where there were only nine cases. That is even if you believe there ever was a SARS 'virus' when the evidence is zilch and I will expand on this in the next chapter. Drosten claims to be co-discoverer of 'SARS-1' and developed a test for it in 2003. He was screaming warnings about 'swine flu' in 2009 and how it was a widespread infection far more severe than any dangers from a vaccine could be and people should get vaccinated. It would be helpful for Drosten's vocal chords if he simply recorded the words 'the virus is deadly and you need to get vaccinated' and copies could be handed out whenever the latest made-up threat comes along. Drosten's swine flu epidemic never happened, but Big Pharma didn't mind with governments spending hundreds of millions on vaccines that hardly anyone bothered to use and many who did wished they hadn't. A study in 2010 revealed that the risk of dying from swine flu, or H1N1, was no higher than that of the annual seasonal flu which is what at least most of 'it' really was as in

the case of 'Covid-19'. A media investigation into Drosten asked how with such a record of inaccuracy he could be *the* government adviser on these issues. The answer to that question is the same with Drosten, Ferguson and Fauci – they keep on giving the authorities the 'conclusions' and 'advice' they want to hear. Drosten certainly produced the goods for them in January, 2020, with his PCR protocol garbage and provided the foundation of what German internal medicine specialist Dr Claus Köhnlein, co-author of *Virus Mania*, called the 'test pandemic'. The 22 scientists in the *Eurosurveillance* challenge called out conflicts of interest within the Drosten 'protocol' group and with good reason. Olfert Landt, a regular co-author of Drosten 'studies', owns the biotech company TIB Molbiol Syntheselabor GmbH in Berlin which manufactures and sells the tests that Drosten and his mates come up with. They have done this with SARS, Enterotoxigenic E. coli (ETEC), MERS, Zika 'virus', yellow fever, and now 'Covid'. Landt told the *Berliner Zeitung* newspaper:

> The testing, design and development came from the Charité [Drosten and Corman]. We simply implemented it immediately in the form of a kit. And if we don't have the virus, which originally only existed in Wuhan, we can make a synthetic gene to simulate the genome of the virus. That's what we did very quickly.

This is more confirmation that the Drosten test was designed without access to the 'virus' and only a synthetic simulation which is what SARS-CoV-2 really is – a computer-generated synthetic fiction. It's quite an enterprise they have going here. A Drosten team decides what the test for something should be and Landt's biotech company flogs it to governments and medical systems across the world. His company must have made an absolute fortune since the 'Covid' hoax began. Dr Reiner Fuellmich, a prominent German consumer protection trial lawyer in Germany and California, is on Drosten's case and that of Tedros at the World Health Organization for crimes against humanity with a class-action lawsuit being prepared in the United States and other legal action in Germany.

Why China?

Scamming the world with a 'virus' that doesn't exist would seem impossible on the face of it, but not if you have control of the relatively few people that make policy decisions and the great majority of the global media. Remember it's not about changing 'real' reality it's about controlling *perception* of reality. You don't have to make something happen you only have make people *believe* that it's happening. Renegade Minds understand this and are therefore much harder to swindle. 'Covid-19' is not a 'real' 'virus'. It's a mind virus, like a computer virus, which has infected the minds, not the bodies, of billions. It all started, publically at least, in China and that alone is of central significance. The Cult was behind the revolution led by its asset Mao Zedong, or Chairman Mao, which established the People's Republic of China on October 1st, 1949. It should have been called The Cult's Republic of China, but the name had to reflect the recurring illusion that vicious dictatorships are run by and for the people (see all the 'Democratic Republics' controlled by tyrants). In the same way we have the 'Biden' Democratic Republic of America officially ruled by a puppet tyrant (at least temporarily) on behalf of Cult tyrants. The creation of Mao's merciless communist/fascist dictatorship was part of a frenzy of activity by the Cult at the conclusion of World War Two which, like the First World War, it had instigated through its assets in Germany, Britain, France, the United States and elsewhere. Israel was formed in 1948; the Soviet Union expanded its 'Iron Curtain' control, influence and military power with the Warsaw Pact communist alliance in 1955; the United Nations was formed in 1945 as a Cult precursor to world government; and a long list of world bodies would be established including the World Health Organization (1948), World Trade Organization (1948 under another name until 1995), International Monetary Fund (1945) and World Bank (1944). Human society was redrawn and hugely centralised in the global Problem-Reaction-Solution that was World War Two. All these changes were significant. Israel would become the headquarters of the Sabbatians

and the revolution in China would prepare the ground and control system for the events of 2019/2020.

Renegade Minds know there are no borders except for public consumption. The Cult is a seamless, borderless global entity and to understand the game we need to put aside labels like borders, nations, countries, communism, fascism and democracy. These delude the population into believing that countries are ruled within their borders by a government of whatever shade when these are mere agencies of a global power. America's illusion of democracy and China's communism/fascism are subsidiaries – vehicles – for the same agenda. We may hear about conflict and competition between America and China and on the lower levels that will be true; but at the Cult level they are branches of the same company in the way of the McDonald's example I gave earlier. I have tracked in the books over the years support by US governments of both parties for Chinese Communist Party infiltration of American society through allowing the sale of land, even military facilities, and the acquisition of American business and university influence. All this is underpinned by the infamous stealing of intellectual property and technological know-how. Cult-owned Silicon Valley corporations waive their fraudulent 'morality' to do business with human-rights-free China; Cult-controlled Disney has become China's PR department; and China in effect owns 'American' sports such as basketball which depends for much of its income on Chinese audiences. As a result any sports player, coach or official speaking out against China's horrific human rights record is immediately condemned or fired by the China-worshipping National Basketball Association. One of the first acts of China-controlled Biden was to issue an executive order telling federal agencies to stop making references to the 'virus' by the 'geographic location of its origin'. Long-time Congressman Jerry Nadler warned that criticising China, America's biggest rival, leads to hate crimes against Asian people in the United States. So shut up you bigot. China is fast closing in on Israel as a country that must not be criticised which is apt, really, given that Sabbatians control them both. The two countries have

developed close economic, military, technological and strategic ties which include involvement in China's 'Silk Road' transport and economic initiative to connect China with Europe. Israel was the first country in the Middle East to recognise the establishment of Mao's tyranny in 1950 months after it was established.

Project Wuhan – the 'Covid' Psyop

I emphasise again that the Cult plays the long game and what is happening to the world today is the result of centuries of calculated manipulation following a script to take control step-by-step of every aspect of human society. I will discuss later the common force behind all this that has spanned those centuries and thousands of years if the truth be told. Instigating the Mao revolution in China in 1949 with a 2020 'pandemic' in mind is not only how they work – the 71 years between them is really quite short by the Cult's standards of manipulation preparation. The reason for the Cult's Chinese revolution was to create a fiercely-controlled environment within which an extreme structure for human control could be incubated to eventually be unleashed across the world. We have seen this happen since the 'pandemic' emerged from China with the Chinese control-structure founded on AI technology and tyrannical enforcement sweep across the West. Until the moment when the Cult went for broke in the West and put its fascism on public display Western governments had to pay some lip-service to freedom and democracy to not alert too many people to the tyranny-in-the-making. Freedoms were more subtly eroded and power centralised with covert government structures put in place waiting for the arrival of 2020 when that smokescreen of 'freedom' could be dispensed with. The West was not able to move towards tyranny before 2020 anything like as fast as China which was created as a tyranny and had no limits on how fast it could construct the Cult's blueprint for global control. When the time came to impose that structure on the world it was the same Cult-owned Chinese communist/fascist government that provided the excuse – the 'Covid pandemic'. It was absolutely crucial to the Cult plan for the Chinese response to the 'pandemic' –

draconian lockdowns of the entire population – to become the blueprint that Western countries would follow to destroy the livelihoods and freedom of their people. This is why the Cult-owned, Gates-owned, WHO Director-General Tedros said early on:

The Chinese government is to be congratulated for the extraordinary measures it has taken to contain the outbreak. China is actually setting a new standard for outbreak response and it is not an exaggeration.

Forbes magazine said of China: '… those measures protected untold millions from getting the disease'. The Rockefeller Foundation 'epidemic scenario' document in 2010 said 'prophetically':

However, a few countries did fare better – China in particular. The Chinese government's quick imposition and enforcement of mandatory quarantine for all citizens, as well as its instant and near-hermetic sealing off of all borders, saved millions of lives, stopping the spread of the virus far earlier than in other countries and enabling a swifter post-pandemic recovery.

Once again – *spooky*.

The first official story was the 'bat theory' or rather the bat diversion. The source of the 'virus outbreak' we were told was a ''wet market' in Wuhan where bats and other animals are bought and eaten in horrifically unhygienic conditions. Then another story emerged through the alternative media that the 'virus' had been released on purpose or by accident from a BSL-4 (biosafety level 4) laboratory in Wuhan not far from the wet market. The lab was reported to create and work with lethal concoctions and bioweapons. Biosafety level 4 is the highest in the World Health Organization system of safety and containment. Renegade Minds are aware of what I call designer manipulation. The ideal for the Cult is for people to buy its prime narrative which in the opening salvoes of the 'pandemic' was the wet market story. It knows, however, that there is now a considerable worldwide alternative media of researchers sceptical of anything governments say and they are often given a version of events in a form they can perceive as credible while misdirecting them from the real truth. In this case let them

think that the conspiracy involved is a 'bioweapon virus' released from the Wuhan lab to keep them from the real conspiracy – *there is no 'virus'*. The WHO's current position on the source of the outbreak at the time of writing appears to be: 'We haven't got a clue, mate.' This is a good position to maintain mystery and bewilderment. The inner circle will know where the 'virus' came from – *nowhere*. The bottom line was to ensure the public believed there *was* a 'virus' and it didn't much matter if they thought it was natural or had been released from a lab. The belief that there was a 'deadly virus' was all that was needed to trigger global panic and fear. The population was terrified into handing their power to authority and doing what they were told. They had to or they were 'all gonna die'.

In March, 2020, information began to come my way from real doctors and scientists and my own additional research which had my intuition screaming: 'Yes, that's it! *There is no virus*.' The 'bioweapon' was not the 'virus'; it was the *'vaccine'* already being talked about that would be the bioweapon. My conclusion was further enhanced by happenings in Wuhan. The 'virus' was said to be sweeping the city and news footage circulated of people collapsing in the street (which they've never done in the West with the same 'virus'). The Chinese government was building 'new hospitals' in a matter of ten days to 'cope with demand' such was the virulent nature of the 'virus'. Yet in what seemed like no time the 'new hospitals' closed – even if they even opened – and China declared itself 'virus-free'. It was back to business as usual. This was more propaganda to promote the Chinese draconian lockdowns in the West as the way to 'beat the virus'. Trouble was that we subsequently had lockdown after lockdown, but never business as usual. As the people of the West and most of the rest of the world were caught in an ever-worsening spiral of lockdown, social distancing, masks, isolated old people, families forced apart, and livelihood destruction, it was party-time in Wuhan. Pictures emerged of thousands of people enjoying pool parties and concerts. It made no sense until you realised there never was a 'virus' and the

whole thing was a Cult set-up to transform human society out of one its major global strongholds – China.

How is it possible to deceive virtually the entire world population into believing there is a deadly virus when there is not even a 'virus' let alone a deadly one? It's nothing like as difficult as you would think and that's clearly true because it happened.

Postscript: See end of book Postscript for more on the 'Wuhan lab virus release' story which the authorities and media were pushing heavily in the summer of 2021 to divert attention from the truth that the 'Covid virus' is pure invention.

CHAPTER FIVE

There *is no* 'virus'

You can fool some of the people all of the time, and all of the people some of the time, but you cannot fool all of the people all of the time
Abraham Lincoln

The greatest form of mind control is repetition. The more you repeat the same mantra of alleged 'facts' the more will accept them to be true. It becomes an 'everyone knows that, mate'. If you can also censor any other version or alternative to your alleged 'facts' you are pretty much home and cooking.

By the start of 2020 the Cult owned the global mainstream media almost in its entirety to spew out its 'Covid' propaganda and ignore or discredit any other information and view. Cult-owned social media platforms in Cult-owned Silicon Valley were poised and ready to unleash a campaign of ferocious censorship to obliterate all but the official narrative. To complete the circle many demands for censorship by Silicon Valley were led by the mainstream media as 'journalists' became full-out enforcers for the Cult both as propagandists and censors. Part of this has been the influx of young people straight out of university who have become 'journalists' in significant positions. They have no experience and a headful of programmed perceptions from their years at school and university at a time when today's young are the most perceptually-targeted generations in known human history given the insidious impact of technology. They enter the media perceptually prepared and ready to repeat the narratives of the system that programmed them to

repeat its narratives. The BBC has a truly pathetic 'specialist disinformation reporter' called Marianna Spring who fits this bill perfectly. She is clueless about the world, how it works and what is really going on. Her role is to discredit anyone doing the job that a proper journalist would do and system-serving hacks like Spring wouldn't dare to do or even see the need to do. They are too busy licking the arse of authority which can never be wrong and, in the case of the BBC propaganda programme, *Panorama*, contacting payments systems such as PayPal to have a donations page taken down for a film company making documentaries questioning vaccines. Even the BBC soap opera *EastEnders* included a disgracefully biased scene in which an inarticulate white working class woman was made to look foolish for questioning the 'vaccine' while a well-spoken black man and Asian woman promoted the government narrative. It ticked every BBC box and the fact that the black and minority community was resisting the 'vaccine' had nothing to do with the way the scene was written. The BBC has become a disgusting tyrannical propaganda and censorship operation that should be defunded and disbanded and a free media take its place with a brief to stop censorship instead of demanding it. A BBC 'interview' with Gates goes something like: 'Mr Gates, sir, if I can call you sir, would you like to tell our audience why you are such a great man, a wonderful humanitarian philanthropist, and why you should absolutely be allowed as a software salesman to decide health policy for approaching eight billion people? Thank you, sir, please sir.' Propaganda programming has been incessant and merciless and when all you hear is the same story from the media, repeated by those around you who have only heard the same story, is it any wonder that people on a grand scale believe absolute mendacious garbage to be true? You are about to see, too, why this level of information control is necessary when the official 'Covid' narrative is so nonsensical and unsupportable by the evidence.

Structure of Deceit

The pyramid structure through which the 'Covid' hoax has been manifested is very simple and has to be to work. As few people as possible have to be involved with full knowledge of what they are doing – and why – or the real story would get out. At the top of the pyramid are the inner core of the Cult which controls Bill Gates who, in turn, controls the World Health Organization through his pivotal funding and his puppet Director-General mouthpiece, Tedros. Before he was appointed Tedros was chair of the Gates-founded Global Fund to 'fight against AIDS, tuberculosis and malaria', a board member of the Gates-funded 'vaccine alliance' GAVI, and on the board of another Gates-funded organisation. Gates owns him and picked him for a specific reason – Tedros is a crook and worse. 'Dr' Tedros (he's not a medical doctor, the first WHO chief not to be) was a member of the tyrannical Marxist government of Ethiopia for decades with all its human rights abuses. He has faced allegations of corruption and misappropriation of funds and was exposed three times for covering up cholera epidemics while Ethiopia's health minister. Tedros appointed the mass-murdering genocidal Zimbabwe dictator Robert Mugabe as a WHO goodwill ambassador for public health which, as with Tedros, is like appointing a psychopath to run a peace and love campaign. The move was so ridiculous that he had to drop Mugabe in the face of widespread condemnation. American economist David Steinman, a Nobel peace prize nominee, lodged a complaint with the International Criminal Court in The Hague over alleged genocide by Tedros when he was Ethiopia's foreign minister. Steinman says Tedros was a 'crucial decision maker' who directed the actions of Ethiopia's security forces from 2013 to 2015 and one of three officials in charge when those security services embarked on the 'killing' and 'torturing' of Ethiopians. You can see where Tedros is coming from and it's sobering to think that he has been the vehicle for Gates and the Cult to direct the global response to 'Covid'. Think about that. A psychopathic Cult dictates to psychopath Gates who dictates to psychopath Tedros who dictates how countries of the world must respond to a 'Covid virus' never scientifically shown to exist. At the same time psychopathic Cult-owned Silicon Valley information

giants like Google, YouTube, Facebook and Twitter announced very early on that they would give the Cult/Gates/Tedros/WHO version of the narrative free advertising and censor those who challenged their intelligence-insulting, mendacious story.

The next layer in the global 'medical' structure below the Cult, Gates and Tedros are the chief medical officers and science 'advisers' in each of the WHO member countries which means virtually all of them. Medical officers and arbiters of science (they're not) then take the WHO policy and recommended responses and impose them on their country's population while the political 'leaders' say they are deciding policy (they're clearly not) by 'following the science' on the advice of the 'experts' – the same medical officers and science 'advisers' (dictators). In this way with the rarest of exceptions the entire world followed the same policy of lockdown, people distancing, masks and 'vaccines' dictated by the psychopathic Cult, psychopathic Gates and psychopathic Tedros who we are supposed to believe give a damn about the health of the world population they are seeking to enslave. That, amazingly, is all there is to it in terms of crucial decision-making. Medical staff in each country then follow like sheep the dictates of the shepherds at the top of the national medical hierarchies – chief medical officers and science 'advisers' who themselves follow like sheep the shepherds of the World Health Organization and the Cult. Shepherds at the national level often have major funding and other connections to Gates and his Bill and Melinda Gates Foundation which carefully hands out money like confetti at a wedding to control the entire global medical system from the WHO down.

Follow the money

Christopher Whitty, Chief Medical Adviser to the UK Government at the centre of 'virus' policy, a senior adviser to the government's Scientific Advisory Group for Emergencies (SAGE), and Executive Board member of the World Health Organization, was gifted a grant of $40 million by the Bill and Melinda Gates Foundation for malaria research in Africa. The BBC described the unelected Whitty as 'the

official who will probably have the greatest impact on our everyday lives of any individual policymaker in modern times' and so it turned out. What Gates and Tedros have said Whitty has done like his equivalents around the world. Patrick Vallance, co-chair of SAGE and the government's Chief Scientific Adviser, is a former executive of Big Pharma giant GlaxoSmithKline with its fundamental financial and business connections to Bill Gates. In September, 2020, it was revealed that Vallance owned a deferred bonus of shares in GlaxoSmithKline worth £600,000 while the company was 'developing' a 'Covid vaccine'. Move along now – nothing to see here – what could possibly be wrong with that? Imperial College in London, a major player in 'Covid' policy in Britain and elsewhere with its 'Covid-19' Response Team, is funded by Gates and has big connections to China while the now infamous Professor Neil Ferguson, the useless 'computer modeller' at Imperial College is also funded by Gates. Ferguson delivered the dramatically inaccurate excuse for the first lockdowns (much more in the next chapter). The Institute for Health Metrics and Evaluation (IHME) in the United States, another source of outrageously false 'Covid' computer models to justify lockdowns, is bankrolled by Gates who is a vehement promotor of lockdowns. America's version of Whitty and Vallance, the again now infamous Anthony Fauci, has connections to 'Covid vaccine' maker Moderna as does Bill Gates through funding from the Bill and Melinda Gates Foundation. Fauci is director of the National Institute of Allergy and Infectious Diseases (NIAID), a major recipient of Gates money, and they are very close. Deborah Birx who was appointed White House Coronavirus Response Coordinator in February, 2020, is yet another with ties to Gates. Everywhere you look at the different elements around the world behind the coordination and decision making of the 'Covid' hoax there is Bill Gates and his money. They include the World Health Organization; Centers for Disease Control (CDC) in the United States; National Institutes of Health (NIH) of Anthony Fauci; Imperial College and Neil Ferguson; the London School of Hygiene where Chris Whitty worked; Regulatory agencies like the UK Medicines & Healthcare products Regulatory Agency (MHRA)

which gave emergency approval for 'Covid vaccines'; Wellcome Trust; GAVI, the Vaccine Alliance; the Coalition for Epidemic Preparedness Innovations (CEPI); Johns Hopkins University which has compiled the false 'Covid' figures; and the World Economic Forum. A Nationalfile.com article said:

> Gates has a lot of pull in the medical world, he has a multi-million dollar relationship with Dr. Fauci, and Fauci originally took the Gates line supporting vaccines and casting doubt on [the drug hydroxychloroquine]. Coronavirus response team member Dr. Deborah Birx, appointed by former president Obama to serve as United States Global AIDS Coordinator, also sits on the board of a group that has received billions from Gates' foundation, and Birx reportedly used a disputed Bill Gates-funded model for the White House's Coronavirus effort. Gates is a big proponent for a population lockdown scenario for the Coronavirus outbreak.

Another funder of Moderna is the Defense Advanced Research Projects Agency (DARPA), the technology-development arm of the Pentagon and one of the most sinister organisations on earth. DARPA had a major role with the CIA covert technology-funding operation In-Q-Tel in the development of Google and social media which is now at the centre of global censorship. Fauci and Gates are extremely close and openly admit to talking regularly about 'Covid' policy, but then why wouldn't Gates have a seat at every national 'Covid' table after his Foundation committed $1.75 billion to the 'fight against Covid-19'. When passed through our Orwellian Translation Unit this means that he has bought and paid for the Cult-driven 'Covid' response worldwide. Research the major 'Covid' response personnel in your own country and you will find the same Gates funding and other connections again and again. Medical and science chiefs following World Health Organization 'policy' sit atop a medical hierarchy in their country of administrators, doctors and nursing staff. These 'subordinates' are told they must work and behave in accordance with the policy delivered from the 'top' of the national 'health' pyramid which is largely the policy delivered by the WHO which is the policy delivered by Gates and the Cult. The whole 'Covid' narrative has been imposed on medical staff by a climate of fear although great numbers don't even need that to comply. They do so through breathtaking levels of ignorance and

include doctors who go through life simply repeating what Big Pharma and their hierarchical masters tell them to say and believe. No wonder Big Pharma 'medicine' is one of the biggest killers on Planet Earth.

The same top-down system of intimidation operates with regard to the Cult Big Pharma cartel which also dictates policy through national and global medical systems in this way. The Cult and Big Pharma agendas are the same because the former controls and owns the latter. 'Health' administrators, doctors, and nursing staff are told to support and parrot the dictated policy or they will face consequences which can include being fired. How sad it's been to see medical staff meekly repeating and imposing Cult policy without question and most of those who can see through the deceit are only willing to speak anonymously off the record. They know what will happen if their identity is known. This has left the courageous few to expose the lies about the 'virus', face masks, overwhelmed hospitals that aren't, and the dangers of the 'vaccine' that isn't a vaccine. When these medical professionals and scientists, some renowned in their field, have taken to the Internet to expose the truth their articles, comments and videos have been deleted by Cult-owned Facebook, Twitter and YouTube. What a real head-shaker to see YouTube videos with leading world scientists and highly qualified medical specialists with an added link underneath to the notorious Cult propaganda website *Wikipedia* to find the 'facts' about the same subject.

HIV – the 'Covid' trial-run

I'll give you an example of the consequences for health and truth that come from censorship and unquestioning belief in official narratives. The story was told by PCR inventor Kary Mullis in his book *Dancing Naked in the Mind Field*. He said that in 1984 he accepted as just another scientific fact that Luc Montagnier of France's Pasteur Institute and Robert Gallo of America's National Institutes of Health had independently discovered that a 'retrovirus' dubbed HIV (human immunodeficiency virus) caused AIDS. They

were, after all, Mullis writes, specialists in retroviruses. This is how the medical and science pyramids work. Something is announced or *assumed* and then becomes an everybody-knows-that purely through repetition of the assumption as if it is fact. Complete crap becomes accepted truth with no supporting evidence and only repetition of the crap. This is how a 'virus' that doesn't exist became the 'virus' that changed the world. The HIV-AIDS fairy story became a multi-billion pound industry and the media poured out propaganda terrifying the world about the deadly HIV 'virus' that caused the lethal AIDS. By then Mullis was working at a lab in Santa Monica, California, to detect retroviruses with his PCR test in blood donations received by the Red Cross. In doing so he asked a virologist where he could find a reference for HIV being the cause of AIDS. 'You don't need a reference,' the virologist said … *'Everybody knows it.'* Mullis said he wanted to quote a reference in the report he was doing and he said he felt a little funny about not knowing the source of such an important discovery when everyone else seemed to. The virologist suggested he cite a report by the Centers for Disease Control and Prevention (CDC) on morbidity and mortality. Mullis read the report, but it only said that an organism had been identified and did not say how. The report did not identify the original scientific work. Physicians, however, *assumed* (key recurring theme) that if the CDC was convinced that HIV caused AIDS then proof must exist. Mullis continues:

I did computer searches. Neither Montagnier, Gallo, nor anyone else had published papers describing experiments which led to the conclusion that HIV probably caused AIDS. I read the papers in Science for which they had become well known as AIDS doctors, but all they had said there was that they had found evidence of a past infection by something which was probably HIV in some AIDS patients.

They found antibodies. Antibodies to viruses had always been considered evidence of past disease, not present disease. Antibodies signaled that the virus had been defeated. The patient had saved himself. There was no indication in these papers that this virus caused a disease. They didn't show that everybody with the antibodies had the disease. In fact they found some healthy people with antibodies.

Mullis asked why their work had been published if Montagnier and Gallo hadn't really found this evidence, and why had they been fighting so hard to get credit for the discovery? He says he was hesitant to write 'HIV is the probable cause of AIDS' until he found published evidence to support that. 'Tens of thousands of scientists and researchers were spending billions of dollars a year doing research based on this idea,' Mullis writes. 'The reason had to be there somewhere; otherwise these people would not have allowed their research to settle into one narrow channel of investigation.' He said he lectured about PCR at numerous meetings where people were always talking about HIV and he asked them how they knew that HIV was the cause of AIDS:

> Everyone said something. Everyone had the answer at home, in the office, in some drawer. They all knew, and they would send me the papers as soon as they got back. But I never got any papers. Nobody ever sent me the news about how AIDS was caused by HIV.

Eventually Mullis was able to ask Montagnier himself about the reference proof when he lectured in San Diego at the grand opening of the University of California AIDS Research Center. Mullis says this was the last time he would ask his question without showing anger. Montagnier said he should reference the CDC report. 'I read it', Mullis said, and it didn't answer the question. 'If Montagnier didn't know the answer who the hell did?' Then one night Mullis was driving when an interview came on National Public Radio with Peter Duesberg, a prominent virologist at Berkeley and a California Scientist of the Year. Mullis says he finally understood why he could not find references that connected HIV to AIDS – *there weren't any!* No one had ever proved that HIV causes AIDS even though it had spawned a multi-billion pound global industry and the media was repeating this as fact every day in their articles and broadcasts terrifying the shit out of people about AIDS and giving the impression that a positive test for HIV (see 'Covid') was a death sentence. Duesberg was a threat to the AIDS gravy train and the agenda that underpinned it. He was therefore abused and castigated after he told the Proceedings of the National Academy of Sciences

there was no good evidence implicating the new 'virus'. Editors rejected his manuscripts and his research funds were deleted. Mullis points out that the CDC has defined AIDS as one of more than 30 diseases *if accompanied* by a positive result on a test that detects antibodies to HIV; but those same diseases are not defined as AIDS cases when antibodies are not detected:

> If an HIV-positive woman develops uterine cancer, for example, she is considered to have AIDS. If she is not HIV positive, she simply has uterine cancer. An HIV-positive man with tuberculosis has AIDS; if he tests negative he simply has tuberculosis. If he lives in Kenya or Colombia, where the test for HIV antibodies is too expensive, he is simply presumed to have the antibodies and therefore AIDS, and therefore he can be treated in the World Health Organization's clinic. It's the only medical help available in some places. And it's free, because the countries that support WHO are worried about AIDS.

Mullis accuses the CDC of continually adding new diseases (see ever more 'Covid symptoms') to the grand AIDS definition and of virtually doctoring the books to make it appear as if the disease continued to spread. He cites how in 1993 the CDC enormously broadened its AIDS definition and county health authorities were delighted because they received $2,500 per year from the Federal government for every reported AIDS case. Ladies and gentlemen, I have just described, via Kary Mullis, the 'Covid pandemic' of 2020 and beyond. Every element is the same and it's been pulled off in the same way by the same networks.

The 'Covid virus' exists? Okay – prove it. Er … still waiting

What Kary Mullis described with regard to 'HIV' has been repeated with 'Covid'. A claim is made that a new, or 'novel', infection has been found and the entire medical system of the world repeats that as fact exactly as they did with HIV and AIDS. No one in the mainstream asks rather relevant questions such as 'How do you know?' and 'Where is your proof?' The SARS-Cov-2 'virus' and the 'Covid-19 disease' became an overnight 'everybody-knows-that'. The origin could be debated and mulled over, but what you could not suggest was that 'SARS-Cov-2' didn't exist. That would be

ridiculous. 'Everybody knows' the 'virus' exists. Well, I didn't for one along with American proper doctors like Andrew Kaufman and Tom Cowan and long-time American proper journalist Jon Rappaport. We dared to pursue the obvious and simple question: 'Where's the evidence?' The overwhelming majority in medicine, journalism and the general public did not think to ask that. After all, *everyone knew* there was a new 'virus'. Everyone was saying so and I heard it on the BBC. Some would eventually argue that the 'deadly virus' was nothing like as deadly as claimed, but few would venture into the realms of its very existence. Had they done so they would have found that the evidence for that claim had gone AWOL as with HIV causes AIDS. In fact, not even that. For something to go AWOL it has to exist in the first place and scientific proof for a 'SARS-Cov-2' can be filed under nothing, nowhere and zilch.

Dr Andrew Kaufman is a board-certified forensic psychiatrist in New York State, a Doctor of Medicine and former Assistant Professor and Medical Director of Psychiatry at SUNY Upstate Medical University, and Medical Instructor of Hematology and Oncology at the Medical School of South Carolina. He also studied biology at the Massachusetts Institute of Technology (MIT) and trained in Psychiatry at Duke University. Kaufman is retired from allopathic medicine, but remains a consultant and educator on natural healing, I saw a video of his very early on in the 'Covid' hoax in which he questioned claims about the 'virus' in the absence of any supporting evidence and with plenty pointing the other way. I did everything I could to circulate his work which I felt was asking the pivotal questions that needed an answer. I can recommend an excellent pull-together interview he did with the website The Last Vagabond entitled *Dr Andrew Kaufman: Virus Isolation, Terrain Theory and Covid-19* and his website is andrewkaufmanmd.com. Kaufman is not only a forensic psychiatrist; he is forensic in all that he does. He always reads original scientific papers, experiments and studies instead of second-third-fourth-hand reports about the 'virus' in the media which are repeating the repeated repetition of the narrative. When he did so with the original Chinese 'virus' papers Kaufman

realised that there was no evidence of a 'SARS-Cov-2'. They had never – from the start – shown it to exist and every repeat of this claim worldwide was based on the accepted existence of proof that was nowhere to be found – see Kary Mullis and HIV. Here we go again.

Let's postulate

Kaufman discovered that the Chinese authorities immediately concluded that the cause of an illness that broke out among about 200 initial patients in Wuhan was a 'new virus' when there were no grounds to make that conclusion. The alleged 'virus' was not isolated from other genetic material in their samples and then shown through a system known as Koch's postulates to be the causative agent of the illness. The world was told that the SARS-Cov-2 'virus' caused a disease they called 'Covid-19' which had 'flu-like' symptoms and could lead to respiratory problems and pneumonia. If it wasn't so tragic it would almost be funny. *'Flu-like' symptoms'? Pneumonia? Respiratory disease?* What in *CHINA* and particularly in *Wuhan*, one of the most polluted cities in the world with a resulting epidemic of respiratory disease?? Three hundred thousand people get pneumonia in China every year and there are nearly a billion cases worldwide of 'flu-like symptoms'. These have a whole range of causes – including pollution in Wuhan – but no other possibility was credibly considered in late 2019 when the world was told there was a new and deadly 'virus'. The global prevalence of pneumonia and 'flu-like systems' gave the Cult networks unlimited potential to re-diagnose these other causes as the mythical 'Covid-19' and that is what they did from the very start. Kaufman revealed how Chinese medical and science authorities (all subordinates to the Cult-owned communist government) took genetic material from the lungs of only a few of the first patients. The material contained their own cells, bacteria, fungi and other microorganisms living in their bodies. The only way you could prove the existence of the 'virus' and its responsibility for the alleged 'Covid-19' was to isolate the virus from all the other material – a process also known as 'purification' – and

then follow the postulates sequence developed in the late 19th century by German physician and bacteriologist Robert Koch which became the 'gold standard' for connecting an alleged causation agent to a disease:

1. The microorganism (bacteria, fungus, virus, etc.) must be present in every case of the disease and all patients must have the same symptoms. It must also *not be present in healthy individuals*.

2. The microorganism must be isolated from the host with the disease. If the microorganism is a bacteria or fungus it must be grown in a pure culture. If it is a virus, it must be purified (i.e. containing no other material except the virus particles) from a clinical sample.

3. The specific disease, with all of its characteristics, must be reproduced when the infectious agent (the purified virus or a pure culture of bacteria or fungi) is inoculated into a healthy, susceptible host.

4. The microorganism must be recoverable from the experimentally infected host as in step 2.

Not one of these criteria has been met in the case of 'SARS-Cov-2' and 'Covid-19'. Not ONE. *EVER*. Robert Koch refers to bacteria and not viruses. What are called 'viral particles' are so minute (hence masks are useless by any definition) that they could only be seen after the invention of the electron microscope in the 1930s and can still only be observed through that means. American bacteriologist and virologist Thomas Milton Rivers, the so-called 'Father of Modern Virology' who was very significantly director of the Rockefeller Institute for Medical Research in the 1930s, developed a less stringent version of Koch's postulates to identify 'virus' causation known as 'Rivers criteria'. 'Covid' did not pass that process either. Some even doubt whether any 'virus' can be isolated from other particles containing genetic material in the Koch method. Freedom of Information requests in many countries asking for scientific proof that the 'Covid virus' has been purified and isolated and shown to exist have all come back with a 'we don't have that' and when this happened with a request to the UK Department of Health they added this comment:

However, outside of the scope of the [Freedom of Information Act] and on a discretionary basis, the following information has been advised to us, which may be of interest. Most infectious diseases are caused by viruses, bacteria or fungi. Some bacteria or fungi have the capacity to grow on their own in isolation, for example in colonies on a petri dish. Viruses are different in that they are what we call 'obligate pathogens' – that is, they cannot survive or reproduce without infecting a host ...

… For some diseases, it is possible to establish causation between a microorganism and a disease by isolating the pathogen from a patient, growing it in pure culture and reintroducing it to a healthy organism. These are known as 'Koch's postulates' and were developed in 1882. However, as our understanding of disease and different disease-causing agents has advanced, these are no longer the method for determining causation [Andrew Kaufman asks why in that case are there two published articles falsely claiming to satisfy Koch's postulates].

It has long been known that viral diseases cannot be identified in this way as viruses cannot be grown in 'pure culture'. When a patient is tested for a viral illness, this is normally done by looking for the presence of antigens, or viral genetic code in a host with molecular biology techniques [Kaufman asks how you could know the origin of these chemicals without having a pure culture for comparison].

For the record 'antigens' are defined so:

Invading microorganisms have antigens on their surface that the human body can recognise as being foreign – meaning not belonging to it. When the body recognises a foreign antigen, lymphocytes (white blood cells) produce antibodies, which are complementary in shape to the antigen.

Notwithstanding that this is open to question in relation to 'SARS-Cov-2' the presence of 'antibodies' can have many causes and they are found in people that are perfectly well. Kary Mullis said: 'Antibodies … had always been considered evidence of past disease, not present disease.'

'Covid' really is a *computer* 'virus'

Where the UK Department of Health statement says 'viruses' are now 'diagnosed' through a 'viral genetic code in a host with molecular biology techniques', they mean … *the PCR test* which its inventor said cannot test for infectious disease. They have no credible method of connecting a 'virus' to a disease and we will see that there is no scientific proof that any 'virus' causes any disease or there is any such thing as a 'virus' in the way that it is described. Tenacious Canadian researcher Christine Massey and her team made

some 40 Freedom of Information requests to national public health agencies in different countries asking for proof that SARS-CoV-2 has been isolated and not one of them could supply that information. Massey said of her request in Canada: 'Freedom of Information reveals Public Health Agency of Canada has no record of 'SARS-COV-2' isolation performed by anyone, anywhere, ever.' If you accept the comment from the UK Department of Health it's because they can't isolate a 'virus'. Even so many 'science' papers claimed to have isolated the 'Covid virus' until they were questioned and had to admit they hadn't. A reply from the Robert Koch Institute in Germany was typical: 'I am not aware of a paper which purified isolated SARS-CoV-2.' So what the hell was Christian Drosten and his gang using to design the 'Covid' testing protocol that has produced all the illusory Covid' cases and 'Covid' deaths when the head of the Chinese version of the CDC admitted there was a problem right from the start in that the 'virus' had never been isolated/purified? Breathe deeply: What they are calling 'Covid' is actually created by a *computer program* i.e. *they made it up* – er, that's it. They took lung fluid, with many sources of genetic material, from one single person alleged to be infected with Covid-19 by a PCR test which they *claimed*, without clear evidence, contained a 'virus'. They used several computer programs to create a model of a theoretical virus genome sequence from more than fifty-six million small sequences of RNA, each of an unknown source, assembling them like a puzzle with no known solution. The computer filled in the gaps with sequences from bits in the gene bank to make it look like a bat SARS-like coronavirus! A wave of the magic wand and poof, an in silico (computer-generated) genome, a scientific fantasy, was created. UK health researcher Dr Kevin Corbett made the same point with this analogy:

> … It's like giving you a few bones and saying that's your fish. It could be any fish. Not even a skeleton. Here's a few fragments of bones. That's your fish … It's all from gene bank and the bits of the virus sequence that weren't there they made up.
>
> They synthetically created them to fill in the blanks. That's what genetics is; it's a code. So it's ABBBCCDDD and you're missing some what you think is EEE so you put it in. It's all

synthetic. You just manufacture the bits that are missing. This is the end result of the geneticization of virology. This is basically a computer virus.

Further confirmation came in an email exchange between British citizen journalist Frances Leader and the government's Medicines & Healthcare Products Regulatory Agency (the Gates-funded MHRA) which gave emergency permission for untested 'Covid vaccines' to be used. The agency admitted that the 'vaccine' is not based on an isolated 'virus', but comes from a *computer-generated model*. Frances Leader was naturally banned from Cult-owned fascist Twitter for making this exchange public. The process of creating computer-generated alleged 'viruses' is called 'in silico' or 'in silicon' – computer chips – and the term 'in silico' is believed to originate with biological experiments using only a computer in 1989. 'Vaccines' involved with 'Covid' are also produced 'in silico' or by computer not a natural process. If the original 'virus' is nothing more than a made-up computer model how can there be 'new variants' of something that never existed in the first place? They are not new 'variants'; they are new *computer models* only minutely different to the original program and designed to further terrify the population into having the 'vaccine' and submitting to fascism. You want a 'new variant'? Click, click, enter – there you go. Tell the medical profession that you have discovered a 'South African variant', 'UK variants' or a 'Brazilian variant' and in the usual HIV-causes-AIDS manner they will unquestioningly repeat it with no evidence whatsoever to support these claims. They will go on television and warn about the dangers of 'new variants' while doing nothing more than repeating what they have been told to be true and knowing that any deviation from that would be career suicide. Big-time insiders will know it's a hoax, but much of the medical community is clueless about the way they are being played and themselves play the public without even being aware they are doing so. What an interesting 'coincidence' that AstraZeneca and Oxford University were conducting 'Covid vaccine trials' in the three countries – the UK, South Africa and Brazil – where the first three 'variants' were claimed to have 'broken out'.

Here's your 'virus' – it's a unicorn

Dr Andrew Kaufman presented a brilliant analysis describing how the 'virus' was imagined into fake existence when he dissected an article published by *Nature* and written by 19 authors detailing *alleged* 'sequencing of a complete viral genome' of the 'new SARS-CoV-2 virus'. This computer-modelled *in silico* genome was used as a template for all subsequent genome sequencing experiments that resulted in the so-called variants which he said now number more than *6,000*. The fake genome was constructed from more than 56 million individual short strands of RNA. Those little pieces were assembled into longer pieces by finding areas of overlapping sequences. The computer programs created over two million possible combinations from which the authors simply chose the longest one. They then compared this to a 'bat virus' and the computer 'alignment' rearranged the sequence and filled in the gaps! They called this computer-generated abomination the 'complete genome'. Dr Tom Cowan, a fellow medical author and collaborator with Kaufman, said such computer-generation constitutes scientific fraud and he makes this superb analogy:

> Here is an equivalency: A group of researchers claim to have found a unicorn because they found a piece of a hoof, a hair from a tail, and a snippet of a horn. They then add that information into a computer and program it to re-create the unicorn, and they then claim this computer re-creation is the real unicorn. Of course, they had never actually seen a unicorn so could not possibly have examined its genetic makeup to compare their samples with the actual unicorn's hair, hooves and horn.
>
> The researchers claim they decided which is the real genome of SARS-CoV-2 by 'consensus', sort of like a vote. Again, different computer programs will come up with different versions of the imaginary 'unicorn', so they come together as a group and decide which is the real imaginary unicorn.

This is how the 'virus' that has transformed the world was brought into fraudulent 'existence'. Extraordinary, yes, but as the Nazis said the bigger the lie the more will believe it. Cowan, however, wasn't finished and he went on to identify what he called the real blockbuster in the paper. He quotes this section from a paper written

by virologists and published by the CDC and then explains what it means:

Therefore, we examined the capacity of SARS-CoV-2 to infect and replicate in several common primate and human cell lines, including human adenocarcinoma cells (A549), human liver cells (HUH 7.0), and human embryonic kidney cells (HEK-293T). In addition to Vero E6 and Vero CCL81 cells. ... Each cell line was inoculated at high multiplicity of infection and examined 24h post-infection.

No CPE was observed in any of the cell lines except in Vero cells, which grew to greater than 10 to the 7th power at 24 h post-infection. In contrast, HUH 7.0 and 293T showed only modest viral replication, and A549 cells were incompatible with SARS CoV-2 infection.

Cowan explains that when virologists attempt to prove infection they have three possible 'hosts' or models on which they can test. The first was humans. Exposure to humans was generally not done for ethical reasons and has never been done with SARS-CoV-2 or any coronavirus. The second possible host was animals. Cowan said that forgetting for a moment that they never actually use purified virus when exposing animals they do use solutions that they *claim* contain the virus. Exposure to animals has been done with SARS-CoV-2 in an experiment involving mice and this is what they found: *None of the wild (normal) mice got sick*. In a group of genetically-modified mice, a statistically insignificant number lost weight and had slightly bristled fur, but they experienced nothing like the illness called 'Covid-19'. Cowan said the third method – the one they mostly rely on – is to inoculate solutions they *say* contain the virus onto a variety of tissue cultures. This process had never been shown to kill tissue *unless* the sample material was starved of nutrients and poisoned as *part of the process*. Yes, incredibly, in tissue experiments designed to show the 'virus' is responsible for killing the tissue they starve the tissue of nutrients and add toxic drugs including antibiotics and they do not have control studies to see if it's the starvation and poisoning that is degrading the tissue rather than the 'virus' they allege to be in there somewhere. You want me to pinch you? Yep, I understand. Tom Cowan said this about the whole nonsensical farce as he explains what that quote from the CDC paper really means:

The shocking thing about the above quote is that using their own methods, the virologists found that solutions containing SARS-CoV-2 – even in high amounts – were NOT, I repeat NOT, infective to any of the three human tissue cultures they tested. In plain English, this means they proved, on their terms, that this 'new coronavirus' is not infectious to human beings. It is ONLY infective to monkey kidney cells, and only then when you add two potent drugs (gentamicin and amphotericin), known to be toxic to kidneys, to the mix.

My friends, read this again and again. These virologists, published by the CDC, performed a clear proof, on their terms, showing that the SARS-CoV-2 virus is harmless to human beings. That is the only possible conclusion, but, unfortunately, this result is not even mentioned in their conclusion. They simply say they can provide virus stocks cultured only on monkey Vero cells, thanks for coming.

Cowan concluded: 'If people really understood how this "science" was done, I would hope they would storm the gates and demand honesty, transparency and truth.' Dr Michael Yeadon, former Vice President and Chief Scientific Adviser at drug giant Pfizer has been a vocal critic of the 'Covid vaccine' and its potential for multiple harm. He said in an interview in April, 2021, that 'not one [vaccine] has the virus. He was asked why vaccines normally using a 'dead' version of a disease to activate the immune system were not used for 'Covid' and instead we had the synthetic methods of the 'mRNA Covid vaccine'. Yeadon said that to do the former 'you'd have to have some of [the virus] wouldn't you?' He added: 'No-one's got any – seriously.' Yeadon said that surely they couldn't have fooled the whole world for a year without having a virus, 'but oddly enough ask around – no one's got it'. He didn't know why with all the 'great labs' around the world that the virus had not been isolated – 'Maybe they've been too busy running bad PCR tests and vaccines that people don't need.' What is today called 'science' is not 'science' at all. Science is no longer what is, but whatever people can be manipulated to *believe* that it is. Real science has been hijacked by the Cult to dispense and produce the 'expert scientists' and contentions that suit the agenda of the Cult. How big-time this has happened with the 'Covid' hoax which is entirely based on fake science delivered by fake 'scientists' and fake 'doctors'. The human-caused climate change hoax is also entirely based on fake science delivered by fake 'scientists' and fake 'climate experts'. In both cases real

scientists, climate experts and doctors have their views suppressed and deleted by the Cult-owned science establishment, media and Silicon Valley. This is the 'science' that politicians claim to be 'following' and a common denominator of 'Covid' and climate are Cult psychopaths Bill Gates and his mate Klaus Schwab at the Gates-funded World Economic Forum. But, don't worry, it's all just a coincidence and absolutely nothing to worry about. *Zzzzzzzz*.

What is a 'virus' REALLY?

Dr Tom Cowan is one of many contesting the very existence of viruses let alone that they cause disease. This is understandable when there is no scientific evidence for a disease-causing 'virus'. German virologist Dr Stefan Lanka won a landmark case in 2017 in the German Supreme Court over his contention that there is no such thing as a measles virus. He had offered a big prize for anyone who could prove there is and Lanka won his case when someone sought to claim the money. There is currently a prize of more than 225,000 euros on offer from an Isolate Truth Fund for anyone who can prove the isolation of SARS-CoV-2 and its genetic substance. Lanka wrote in an article headed 'The Misconception Called Virus' that scientists think a 'virus' is causing tissue to become diseased and degraded when in fact it is the *processes they are using* which do that – not a 'virus'. Lanka has done an important job in making this point clear as Cowan did in his analysis of the CDC paper. Lanka says that all claims about viruses as disease-causing pathogens are wrong and based on 'easily recognisable, understandable and verifiable misinterpretations.' Scientists believed they were working with 'viruses' in their laboratories when they were really working with 'typical particles of specific dying tissues or cells …' Lanka said that the tissue decaying process claimed to be caused by a 'virus' still happens when no alleged 'virus' is involved. It's the *process* that does the damage and not a 'virus'. The genetic sample is deprived of nutrients, removed from its energy supply through removal from the body and then doused in toxic antibiotics to remove any bacteria. He confirms again that establishment scientists do not (pinch me)

conduct control experiments to see if this is the case and if they did they would see the claims that 'viruses' are doing the damage is nonsense. He adds that during the measles 'virus' court case he commissioned an independent laboratory to perform just such a control experiment and the result was that the tissues and cells died in the exact same way as with alleged 'infected' material. This is supported by a gathering number of scientists, doctors and researchers who reject what is called 'germ theory' or the belief in the body being infected by contagious sources emitted by other people. Researchers Dawn Lester and David Parker take the same stance in their highly-detailed and sourced book *What Really Makes You Ill – Why everything you thought you knew about disease is wrong* which was recommended to me by a number of medical professionals genuinely seeking the truth. Lester and Parker say there is no provable scientific evidence to show that a 'virus' can be transmitted between people or people and animals or animals and people:

> The definition also claims that viruses are the cause of many diseases, as if this has been definitively proven. But this is not the case; there is no original scientific evidence that definitively demonstrates that any virus is the cause of any disease. The burden of proof for any theory lies with those who proposed it; but none of the existing documents provides 'proof' that supports the claim that 'viruses' are pathogens.

Dr Tom Cowan employs one of his clever analogies to describe the process by which a 'virus' is named as the culprit for a disease when what is called a 'virus' is only material released by cells detoxing themselves from infiltration by chemical or radiation poisoning. The tidal wave of technologically-generated radiation in the 'smart' modern world plus all the toxic food and drink are causing this to happen more than ever. Deluded 'scientists' misread this as a gathering impact of what they wrongly label 'viruses'.

Paper can infect houses

Cowan said in an article for davidicke.com – with his tongue only mildly in his cheek – that he believed he had made a tremendous

discovery that may revolutionise science. He had discovered that small bits of paper are alive, 'well alive-ish', can 'infect' houses, and then reproduce themselves inside the house. The result was that this explosion of growth in the paper inside the house causes the house to explode, blowing it to smithereens. His evidence for this new theory is that in the past months he had carefully examined many of the houses in his neighbourhood and found almost no scraps of paper on the lawns and surrounds of the house. There was an occasional stray label, but nothing more. Then he would return to these same houses a week or so later and with a few, not all of them, particularly the old and decrepit ones, he found to his shock and surprise they were littered with stray bits of paper. He knew then that the paper had infected these houses, made copies of itself, and blew up the house. A young boy on a bicycle at one of the sites told him he had seen a demolition crew using dynamite to explode the house the previous week, but Cowan dismissed this as the idle thoughts of silly boys because 'I was on to something big'. He was on to how 'scientists' mistake genetic material in the detoxifying process for something they call a 'virus'. Cowan said of his house and paper story:

> If this sounds crazy to you, it's because it should. This scenario is obviously nuts. But consider this admittedly embellished, for effect, current viral theory that all scientists, medical doctors and virologists currently believe.

He takes the example of the 'novel SARS-Cov2' virus to prove the point. First they take someone with an undefined illness called 'Covid-19' and don't even attempt to find any virus in their sputum. Never mind the scientists still describe how this 'virus', which they have not located attaches to a cell receptor, injects its genetic material, in 'Covid's' case, RNA, into the cell. The RNA once inserted exploits the cell to reproduce itself and makes 'thousands, nay millions, of copies of itself … Then it emerges victorious to claim its next victim':

If you were to look in the scientific literature for proof, actual scientific proof, that uniform SARS-CoV2 viruses have been properly isolated from the sputum of a sick person, that actual spike proteins could be seen protruding from the virus (which has not been found), you would find that such evidence doesn't exist.

If you go looking in the published scientific literature for actual pictures, proof, that these spike proteins or any viral proteins are ever attached to any receptor embedded in any cell membrane, you would also find that no such evidence exists. If you were to look for a video or documented evidence of the intact virus injecting its genetic material into the body of the cell, reproducing itself and then emerging victorious by budding off the cell membrane, you would find that no such evidence exists.

The closest thing you would find is electron micrograph pictures of cellular particles, possibly attached to cell debris, both of which to be seen were stained by heavy metals, a process that completely distorts their architecture within the living organism. This is like finding bits of paper stuck to the blown-up bricks, thereby proving the paper emerged by taking pieces of the bricks on its way out.

The Enders baloney

Cowan describes the 'Covid' story as being just as make-believe as his paper story and he charts back this fantasy to a Nobel Prize winner called John Enders (1897-1985), an American biomedical scientist who has been dubbed 'The Father of Modern Vaccines'. Enders is claimed to have 'discovered' the process of the viral culture which 'proved' that a 'virus' caused measles. Cowan explains how Enders did this 'by using the EXACT same procedure that has been followed by every virologist to find and characterize every new virus since 1954'. Enders took throat swabs from children with measles and immersed them in 2ml of milk. Penicillin (100u/ml) and the antibiotic streptomycin (50,g/ml) were added and the whole mix was centrifuged – rotated at high speed to separate large cellular debris from small particles and molecules as with milk and cream, for example. Cowan says that if the aim is to find little particles of genetic material ('viruses') in the snot from children with measles it would seem that the last thing you would do is mix the snot with other material – milk –that also has genetic material. 'How are you ever going to know whether whatever you found came from the snot or the milk?' He points out that streptomycin is a 'nephrotoxic' or poisonous-to-the-kidney drug. You will see the relevance of that

shortly. Cowan says that it gets worse, much worse, when Enders describes the culture medium upon which the virus 'grows': 'The culture medium consisted of bovine amniotic fluid (90%), beef embryo extract (5%), horse serum (5%), antibiotics and phenol red as an indicator of cell metabolism.' Cowan asks incredulously: 'Did he just say that the culture medium also contained fluids and tissues that are themselves rich sources of genetic material?' The genetic cocktail, or 'medium', is inoculated onto tissue and cells from rhesus monkey *kidney* tissue. This is where the importance of streptomycin comes in and currently-used antimicrobials and other drugs that are *poisonous to kidneys* and used in ALL modern viral cultures (e.g. gentamicin, streptomycin, and amphotericin). Cowan asks: 'How are you ever going to know from this witch's brew where any genetic material comes from as we now have five different sources of rich genetic material in our mix?' Remember, he says, that all genetic material, whether from monkey kidney tissues, bovine serum, milk, etc., is made from the exact same components. The same central question returns: 'How are you possibly going to know that it was the virus that killed the kidney tissue and not the toxic antibiotic and starvation rations on which you are growing the tissue?' John Enders answered the question himself – *you can't*:

A second agent was obtained from an uninoculated culture of monkey kidney cells. The cytopathic changes [death of the cells] it induced in the unstained preparations could not be distinguished with confidence from the viruses isolated from measles.

The death of the cells ('cytopathic changes') happened in exactly the same manner, whether they inoculated the kidney tissue with the measles snot or not, Cowan says. 'This is evidence that the destruction of the tissue, the very proof of viral causation of illness, was not caused by anything in the snot because they saw the same destructive effect when the snot was not even used … the cytopathic, i.e., cell-killing, changes come from the process of the culture itself, not from any virus in any snot, period.' Enders quotes in his 1957 paper a virologist called Ruckle as reporting similar findings 'and in addition has isolated an agent from monkey kidney tissue that is so

far indistinguishable from human measles virus'. In other words, Cowan says, these particles called 'measles viruses' are simply and clearly breakdown products of the starved and poisoned tissue. For measles 'virus' see all 'viruses' including the so-called 'Covid virus'. Enders, the 'Father of Modern Vaccines', also said:

There is a potential risk in employing cultures of primate cells for the production of vaccines composed of attenuated virus, since the presence of other agents possibly latent in primate tissues cannot be definitely excluded by any known method.

Cowan further quotes from a paper published in the journal *Viruses* in May, 2020, while the 'Covid pandemic' was well underway in the media if not in reality. 'EVs' here refers to particles of genetic debris from our own tissues, such as exosomes of which more in a moment: 'The remarkable resemblance between EVs and viruses has caused quite a few problems in the studies focused on the analysis of EVs released during viral infections.' Later the paper adds that to date a reliable method that can actually guarantee a complete separation (of EVs from viruses) DOES NOT EXIST. This was published at a time when a fairy tale 'virus' was claimed in total certainty to be causing a fairy tale 'viral disease' called 'Covid-19' – a fairy tale that was already well on the way to transforming human society in the image that the Cult has worked to achieve for so long. Cowan concludes his article:

To summarize, there is no scientific evidence that pathogenic viruses exist. What we think of as 'viruses' are simply the normal breakdown products of dead and dying tissues and cells. When we are well, we make fewer of these particles; when we are starved, poisoned, suffocated by wearing masks, or afraid, we make more.

There is no engineered virus circulating and making people sick. People in laboratories all over the world are making genetically modified products to make people sick. These are called vaccines. There is no virome, no 'ecosystem' of viruses, viruses are not 8%, 50% or 100 % of our genetic material. These are all simply erroneous ideas based on the misconception called a virus.

What is 'Covid'? Load of bollocks

The background described here by Cowan and Lanka was emphasised in the first video presentation that I saw by Dr Andrew Kaufman when he asked whether the 'Covid virus' was in truth a natural defence mechanism of the body called 'exosomes'. These are released by cells when in states of toxicity – see the same themes returning over and over. They are released ever more profusely as chemical and radiation toxicity increases and think of the potential effect therefore of 5G alone as its destructive frequencies infest the human energetic information field with a gathering pace (5G went online in Wuhan in 2019 as the 'virus' emerged). I'll have more about this later. Exosomes transmit a warning to the rest of the body that 'Houston, we have a problem'. Kaufman presented images of exosomes and compared them with 'Covid' under an electron microscope and the similarity was remarkable. They both attach to the same cell receptors (*claimed* in the case of 'Covid'), contain the same genetic material in the form of RNA or ribonucleic acid, and both are found in 'viral cell cultures' with damaged or dying cells. James Hildreth MD, President and Chief Executive Officer of the Meharry Medical College at Johns Hopkins, said: 'The virus is fully an exosome in every sense of the word.' Kaufman's conclusion was that there is no 'virus': 'This entire pandemic is a completely manufactured crisis … there is no evidence of anyone dying from [this] illness.' Dr Tom Cowan and Sally Fallon Morell, authors of *The Contagion Myth*, published a statement with Dr Kaufman in February, 2021, explaining why the 'virus' does not exist and you can read it that in full in the Appendix.

'Virus' theory can be traced to the 'cell theory' in 1858 of German physician Rudolf Virchow (1821-1920) who contended that disease originates from a single cell infiltrated by a 'virus'. Dr Stefan Lanka said that findings and insights with respect to the structure, function and central importance of tissues in the creation of life, which were already known in 1858, comprehensively refute the cell theory. Virchow ignored them. We have seen the part later played by John Enders in the 1950s and Lanka notes that infection theories were only established as a global dogma through the policies and

eugenics of the Third Reich in Nazi Germany (creation of the same Sabbatian cult behind the 'Covid' hoax). Lanka said: 'Before 1933, scientists dared to contradict this theory; after 1933, these critical scientists were silenced'. Dr Tom Cowan's view is that ill-heath is caused by too much of something, too little of something, or toxification from chemicals and radiation – not contagion. We must also highlight as a major source of the 'virus' theology a man still called the 'Father of Modern Virology' – Thomas Milton Rivers (1888-1962). There is no way given the Cult's long game policy that it was a coincidence for the 'Father of Modern Virology' to be director of the Rockefeller Institute for Medical Research from 1937 to 1956 when he is credited with making the Rockefeller Institute a leader in 'viral research'. Cult Rockefellers were the force behind the creation of Big Pharma 'medicine', established the World Health Organisation in 1948, and have long and close associations with the Gates family that now runs the WHO during the pandemic hoax through mega-rich Cult gofer and psychopath Bill Gates.

Only a Renegade Mind can see through all this bullshit by asking the questions that need to be answered, not taking 'no' or prevarication for an answer, and certainly not hiding from the truth in fear of speaking it. Renegade Minds have always changed the world for the better and they will change this one no matter how bleak it may currently appear to be.

CHAPTER SIX

Sequence of deceit

If you tell the truth, you don't have to remember anything
Mark Twain

Against the background that I have laid out this far the sequence that took us from an invented 'virus' in Cult-owned China in late 2019 to the fascist transformation of human society can be seen and understood in a whole new context.

We were told that a deadly disease had broken out in Wuhan and the world media began its campaign (coordinated by behavioural psychologists as we shall see) to terrify the population into unquestioning compliance. We were shown images of Chinese people collapsing in the street which never happened in the West with what was supposed to be the same condition. In the earliest days when alleged cases and deaths were few the fear register was hysterical in many areas of the media and this would expand into the common media narrative across the world. The real story was rather different, but we were never told that. The Chinese government, one of the Cult's biggest centres of global operation, said they had discovered a new illness with flu-like and pneumonia-type symptoms in a city with such toxic air that it is overwhelmed with flu-like symptoms, pneumonia and respiratory disease. Chinese scientists said it was a new – 'novel' – coronavirus which they called Sars-Cov-2 and that it caused a disease they labelled 'Covid-19'. There was no evidence for this and the 'virus' has never to this day been isolated, purified and its genetic code established from that. It

was from the beginning a computer-generated fiction. Stories of Chinese whistleblowers saying the number of deaths was being supressed or that the 'new disease' was related to the Wuhan bio-lab misdirected mainstream and alternative media into cul-de-sacs to obscure the real truth – there was no 'virus'.

Chinese scientists took genetic material from the lung fluid of just a few people and said they had found a 'new' disease when this material had a wide range of content. There was no evidence for a 'virus' for the very reasons explained in the last two chapters. The 'virus' has never been shown to (a) exist and (b) cause any disease. People were diagnosed on symptoms that are so widespread in Wuhan and polluted China and with a PCR test that can't detect infectious disease. On this farce the whole global scam was sold to the rest of the world which would also diagnose respiratory disease as 'Covid-19' from symptoms alone or with a PCR test not testing for a 'virus'. Flu miraculously disappeared *worldwide* in 2020 and into 2021 as it was redesignated 'Covid-19'. It was really the same old flu with its 'flu-like' symptoms attributed to 'flu-like' 'Covid-19'. At the same time with very few exceptions the Chinese response of draconian lockdown and fascism was the chosen weapon to respond across the West as recommended by the Cult-owned Tedros at the Cult-owned World Health Organization run by the Cult-owned Gates. All was going according to plan. Chinese scientists – everything in China is controlled by the Cult-owned government – compared their contaminated RNA lung-fluid material with other RNA sequences and said it appeared to be just under 80 percent identical to the SARS-CoV-1 'virus' claimed to be the cause of the SARS (severe acute respiratory syndrome) 'outbreak' in 2003. They decreed that because of this the 'new virus' had to be related and they called it SARS-CoV-2. There are some serious problems with this assumption and *assumption* was all it was. Most 'factual' science turns out to be assumptions repeated into everyone-knows-that. A match of under 80-percent is meaningless. Dr Kaufman makes the point that there's a *96 percent* genetic correlation between humans and chimpanzees, but 'no one would say our genetic material is part

of the chimpanzee family'. Yet the Chinese authorities were claiming that a much lower percentage, less than 80 percent, proved the existence of a new 'coronavirus'. For goodness sake human DNA is 60 percent similar to a *banana*.

You are feeling sleepy

The entire 'Covid' hoax is a global Psyop, a psychological operation to program the human mind into believing and fearing a complete fantasy. A crucial aspect of this was what *appeared* to happen in Italy. It was all very well streaming out daily images of an alleged catastrophe in Wuhan, but to the Western mind it was still on the other side of the world in a very different culture and setting. A reaction of 'this could happen to me and my family' was still nothing like as intense enough for the mind-doctors. The Cult needed a Western example to push people over that edge and it chose Italy, one of its major global locations going back to the Roman Empire. An Italian 'Covid' crisis was manufactured in a particular area called Lombardy which just happens to be notorious for its toxic air and therefore respiratory disease. Wuhan, China, déjà vu. An hysterical media told horror stories of Italians dying from 'Covid' in their droves and how Lombardy hospitals were being overrun by a tidal wave of desperately ill people needing treatment after being struck down by the 'deadly virus'. Here was the psychological turning point the Cult had planned. Wow, if this is happening in Italy, the Western mind concluded, this indeed could happen to me and my family. Another point is that Italian authorities responded by following the Chinese blueprint so vehemently recommended by the Cult-owned World Health Organization. They imposed fascistic lockdowns on the whole country viciously policed with the help of surveillance drones sweeping through the streets seeking out anyone who escaped from mass house arrest. Livelihoods were destroyed and psychology unravelled in the way we have witnessed since in all lockdown countries. Crucial to the plan was that Italy responded in this way to set the precedent of suspending freedom and imposing fascism in a 'Western liberal democracy'. I emphasised in an

animated video explanation on davidicke.com posted in the summer of 2020 how important it was to the Cult to expand the Chinese lockdown model across the West. Without this, and the bare-faced lie that non-symptomatic people could still transmit a 'disease' they didn't have, there was no way locking down the whole population, sick and not sick, could be pulled off. At just the right time and with no evidence Cult operatives and gofers claimed that people without symptoms could pass on the 'disease'. In the name of protecting the 'vulnerable' like elderly people, who lockdowns would kill by the tens of thousands, we had for the first time healthy people told to isolate as well as the sick. The great majority of people who tested positive had no symptoms because there was nothing wrong with them. It was just a trick made possible by a test not testing for the 'virus'.

Months after my animated video the Gates-funded Professor Neil Ferguson at the Gates-funded Imperial College confirmed that I was right. He didn't say it in those terms, naturally, but he did say it. Ferguson will enter the story shortly for his outrageously crazy 'computer models' that led to Britain, the United States and many other countries following the Chinese and now Italian methods of response. Put another way, following the Cult script. Ferguson said that SAGE, the UK government's scientific advisory group which has controlled 'Covid' policy from the start, wanted to follow the Chinese lockdown model (while they all continued to work and be paid), but they wondered if they could possibly, in Ferguson's words, 'get away with it in Europe'. 'Get away with it'? Who the hell do these moronic, arrogant people think they are? This appalling man Ferguson said that once Italy went into national lockdown they realised they, too, could mimic China:

> It's a communist one-party state, we said. We couldn't get away with it in Europe, we thought … and then Italy did it. And we realised we could. Behind this garbage from Ferguson is a simple fact: Doing the same as China in every country was the plan from the start and Ferguson's 'models' would play a central role in achieving that. It's just a coincidence, of course, and absolutely nothing to worry your little head about.

Oops, sorry, our mistake

Once the Italian segment of the Psyop had done the job it was designed to do a very different story emerged. Italian authorities revealed that 99 percent of those who had 'died from Covid-19' in Italy had one, two, three, or more 'co-morbidities' or illnesses and health problems that could have ended their life. The US Centers for Disease Control and Prevention (CDC) published a figure of 94 percent for Americans dying of 'Covid' while having other serious medical conditions – on average two to three (some five or six) other potential causes of death. In terms of death from an unproven 'virus' I say it is 100 percent. The other one percent in Italy and six percent in the US would presumably have died from 'Covid's' flu-like symptoms with a range of other possible causes in conjunction with a test not testing for the 'virus'. Fox News reported that even more startling figures had emerged in one US county in which 410 of 422 deaths attributed to 'Covid-19' had other potentially deadly health conditions. The Italian National Health Institute said later that the average age of people dying with a 'Covid-19' diagnosis in Italy was about 81. Ninety percent were over 70 with ten percent over 90. In terms of other reasons to die some 80 percent had two or more chronic diseases with half having three or more including cardiovascular problems, diabetes, respiratory problems and cancer. Why is the phantom 'Covid-19' said to kill overwhelmingly old people and hardly affect the young? Old people continually die of many causes and especially respiratory disease which you can re-diagnose 'Covid-19' while young people die in tiny numbers by comparison and rarely of respiratory disease. Old people 'die of Covid' because they die of other things that can be redesignated 'Covid' and it really is that simple.

Flu has flown

The blueprint was in place. Get your illusory 'cases' from a test not testing for the 'virus' and redesignate other causes of death as 'Covid-19'. You have an instant 'pandemic' from something that is nothing more than a computer-generated fiction. With near-on a

billion people having 'flu-like' symptoms every year the potential was limitless and we can see why flu quickly and apparently miraculously disappeared *worldwide* by being diagnosed 'Covid-19'. The painfully bloody obvious was explained away by the childlike media in headlines like this in the UK '*Independent*': 'Not a single case of flu detected by Public Health England this year as Covid restrictions suppress virus'. I kid you not. The masking, social distancing and house arrest that did not make the 'Covid virus' disappear somehow did so with the 'flu virus'. Even worse the article, by a bloke called Samuel Lovett, suggested that maybe the masking, sanitising and other 'Covid' measures should continue to keep the flu away. With a ridiculousness that disturbs your breathing (it's 'Covid-19') the said Lovett wrote: 'With widespread social distancing and mask-wearing measures in place throughout the UK, the usual routes of transmission for influenza have been blocked.' He had absolutely no evidence to support that statement, but look at the consequences of him acknowledging the obvious. With flu not disappearing at all and only being relabelled 'Covid-19' he would have to contemplate that 'Covid' was a hoax on a scale that is hard to imagine. You need guts and commitment to truth to even go there and that's clearly something Samuel Lovett does not have in abundance. He would never have got it through the editors anyway.

Tens of thousands die in the United States alone every winter from flu including many with pneumonia complications. CDC figures record *45 million* Americans diagnosed with flu in 2017-2018 of which 61,000 died and some reports claim 80,000. Where was the same hysteria then that we have seen with 'Covid-19'? Some 250,000 Americans are admitted to hospital with pneumonia every year with about 50,000 cases proving fatal. About 65 million suffer respiratory disease every year and three million deaths makes this the third biggest cause of death worldwide. You only have to redesignate a portion of all these people 'Covid-19' and you have an instant global pandemic or the *appearance* of one. Why would doctors do this? They are told to do this and all but a few dare not refuse those who must be obeyed. Doctors in general are not researching their own

knowledge and instead take it direct and unquestioned from the authorities that own them and their careers. The authorities say they must now diagnose these symptoms 'Covid-19' and not flu, or whatever, and they do it. Dark suits say put 'Covid-19' on death certificates no matter what the cause of death and the doctors do it. Renegade Minds don't fall for the illusion that doctors and medical staff are all highly-intelligent, highly-principled, seekers of medical truth. *Some are*, but not the majority. They are repeaters, gofers, and yes sir, no sir, purveyors of what the system demands they purvey. The 'Covid' con is not merely confined to diseases of the lungs. Instructions to doctors to put 'Covid-19' on death certificates for anyone dying of *anything* within 28 days (or much more) of a positive test not testing for the 'virus' opened the floodgates. The term dying *with* 'Covid' and not *of* 'Covid' was coined to cover the truth. Whether it was a *with* or an *of* they were all added to the death numbers attributed to the 'deadly virus' compiled by national governments and globally by the Gates-funded Johns Hopkins operation in the United States that was so involved in those 'pandemic' simulations. Fraudulent deaths were added to the ever-growing list of fraudulent 'cases' from false positives from a false test. No wonder Professor Walter Ricciardi, scientific advisor to the Italian minister of health, said after the Lombardy hysteria had done its job that 'Covid' death rates were due to Italy having the second oldest population in the world and to *how hospitals record deaths*:

The way in which we code deaths in our country is very generous in the sense that all the people who die in hospitals with the coronavirus are deemed to be dying of the coronavirus. On re-evaluation by the National Institute of Health, only 12 per cent of death certificates have shown a direct causality from coronavirus, while 88 per cent of patients who have died have at least one pre-morbidity – many had two or three.

This is extraordinary enough when you consider the propaganda campaign to use Italy to terrify the world, but how can they even say twelve percent were genuine when the 'virus' has not been shown to exist, its 'code' is a computer program, and diagnosis comes from a test not testing for it? As in China, and soon the world, 'Covid-19' in

Italy was a redesignation of diagnosis. Lies and corruption were to become the real 'pandemic' fuelled by a pathetically-compliant medical system taking its orders from the tiny few at the top of their national hierarchy who answered to the World Health Organization which answers to Gates and the Cult. Doctors were told – ordered – to diagnose a particular set of symptoms 'Covid-19' and put that on the death certificate for any cause of death if the patient had tested positive with a test not testing for the virus or had 'Covid' symptoms like the flu. The United States even introduced big financial incentives to manipulate the figures with hospitals receiving £4,600 from the Medicare system for diagnosing someone with regular pneumonia, $13,000 if they made the diagnosis from the same symptoms 'Covid-19' pneumonia, and $39, 000 if they put a 'Covid' diagnosed patient on a ventilator that would almost certainly kill them. A few – painfully and pathetically few – medical whistleblowers revealed (before Cult-owned YouTube deleted their videos) that they had been instructed to 'let the patient crash' and put them straight on a ventilator instead of going through a series of far less intrusive and dangerous methods as they would have done before the pandemic hoax began and the financial incentives kicked in. We are talking cold-blooded murder given that ventilators are so damaging to respiratory systems they are usually the last step before heaven awaits. Renegade Minds never fall for the belief that people in white coats are all angels of mercy and cannot be full-on psychopaths. I have explained in detail in *The Answer* how what I am describing here played out across the world coordinated by the World Health Organization through the medical hierarchies in almost every country.

Medical scientist calls it

Information about the non-existence of the 'virus' began to emerge for me in late March, 2020, and mushroomed after that. I was sent an email by Sir Julian Rose, a writer, researcher, and organic farming promotor, from a medical scientist friend of his in the United States. Even at that early stage in March the scientist was able to explain

how the 'Covid' hoax was being manipulated. He said there were no reliable tests for a specific 'Covid-19 virus' and nor were there any reliable agencies or media outlets for reporting numbers of actual 'Covid-19' cases. We have seen in the long period since then that he was absolutely right. 'Every action and reaction to Covid-19 is based on totally flawed data and we simply cannot make accurate assessments,' he said. Most people diagnosed with 'Covid-19' were showing nothing more than cold and flu-like symptoms 'because most coronavirus strains *are* nothing more than cold/flu-like symptoms'. We had farcical situations like an 84-year-old German man testing positive for 'Covid-19' and his nursing home ordered to quarantine only for him to be found to have a common cold. The scientist described back then why PCR tests and what he called the 'Mickey Mouse test kits' were useless for what they were claimed to be identifying. 'The idea these kits can isolate a specific virus like Covid-19 is nonsense,' he said. Significantly, he pointed out that 'if you want to create a totally false panic about a totally false pandemic – pick a coronavirus'. This is exactly what the Cult-owned Gates, World Economic Forum and Johns Hopkins University did with their Event 201 'simulation' followed by their real-life simulation called the 'pandemic'. The scientist said that all you had to do was select the sickest of people with respiratory-type diseases in a single location – 'say Wuhan' – and administer PCR tests to them. You can then claim that anyone showing 'viral sequences' similar to a coronavirus 'which will inevitably be quite a few' is suffering from a 'new' disease:

> Since you already selected the sickest flu cases a fairly high proportion of your sample will go on to die. You can then say this 'new' virus has a CFR [case fatality rate] higher than the flu and use this to infuse more concern and do more tests which will of course produce more 'cases', which expands the testing, which produces yet more 'cases' and so on and so on. Before long you have your 'pandemic', and all you have done is use a simple test kit trick to convert the worst flu and pneumonia cases into something new that doesn't ACTUALLY EXIST [my emphasis].

He said that you then 'just run the same scam in other countries' and make sure to keep the fear message running high 'so that people

will feel panicky and less able to think critically'. The only problem to overcome was the fact *there is no* actual new deadly pathogen and only regular sick people. This meant that deaths from the 'new deadly pathogen' were going to be way too low for a real new deadly virus pandemic, but he said this could be overcome in the following ways – all of which would go on to happen:

1. You can claim this is just the beginning and more deaths are imminent [you underpin this with fantasy 'computer projections']. Use this as an excuse to quarantine everyone and then claim the quarantine prevented the expected millions of dead.

2. You can [say that people] 'minimizing' the dangers are irresponsible and bully them into not talking about numbers.

3. You can talk crap about made up numbers hoping to blind people with pseudoscience.

4. You can start testing well people (who, of course, will also likely have shreds of coronavirus [RNA] in them) and thus inflate your 'case figures' with 'asymptomatic carriers' (you will of course have to spin that to sound deadly even though any virologist knows the more symptom-less cases you have the less deadly is your pathogen).

The scientist said that if you take these simple steps 'you can have your own entirely manufactured pandemic up and running in weeks'. His analysis made so early in the hoax was brilliantly prophetic of what would actually unfold. Pulling all the information together in these recent chapters we have this is simple 1, 2, 3, of how you can delude virtually the entire human population into believing in a 'virus' that doesn't exist:

- A 'Covid case' is someone who tests positive with a test not testing for the 'virus'.

- A 'Covid death' is someone who dies of *any cause* within 28 days (or much longer) of testing positive with a test not testing for the 'virus.

- Asymptomatic means there is nothing wrong with you, but they claim you can pass on what you don't have to justify locking

down (quarantining) healthy people in totality.

The foundations of the hoax are that simple. A study involving ten million people in Wuhan, published in November, 2020, demolished the whole lie about those without symptoms passing on the 'virus'. They found '300 asymptomatic cases' and traced their contacts to find that not one of them was detected with the 'virus'. 'Asymptomatic' patients and their contacts were isolated for no less than two weeks and nothing changed. I know it's all crap, but if you are going to claim that those without symptoms can transmit 'the virus' then you must produce evidence for that and they never have. Even World Health Organization official Dr Maria Van Kerkhove, head of the emerging diseases and zoonosis unit, said as early as June, 2020, that she doubted the validity of asymptomatic transmission. She said that 'from the data we have, it still seems to be rare that an asymptomatic person actually transmits onward to a secondary individual' and by 'rare' she meant that she couldn't cite any case of asymptomatic transmission.

The Ferguson factor

The problem for the Cult as it headed into March, 2020, when the script had lockdown due to start, was that despite all the manipulation of the case and death figures they still did not have enough people alleged to have died from 'Covid' to justify mass house arrest. This was overcome in the way the scientist described: 'You can claim this is just the beginning and more deaths are imminent … Use this as an excuse to quarantine everyone and then claim the quarantine prevented the expected millions of dead.' Enter one Professor Neil Ferguson, the Gates-funded 'epidemiologist' at the Gates-funded Imperial College in London. Ferguson is Britain's Christian Drosten in that he has a dire record of predicting health outcomes, but is still called upon to advise government on the next health outcome when another 'crisis' comes along. This may seem to be a strange and ridiculous thing to do. Why would you keep turning for policy guidance to people who have a history of being

monumentally wrong? Ah, but it makes sense from the Cult point of view. These 'experts' keep on producing predictions that suit the Cult agenda for societal transformation and so it was with Neil Ferguson as he revealed his horrific (and clearly insane) computer model predictions that allowed lockdowns to be imposed in Britain, the United States and many other countries. Ferguson does not have even an A-level in biology and would appear to have no formal training in computer modelling, medicine or epidemiology, according to Derek Winton, an MSc in Computational Intelligence. He wrote an article somewhat aghast at what Ferguson did which included taking no account of respiratory disease 'seasonality' which means it is far worse in the winter months. Who would have thought that respiratory disease could be worse in the winter? Well, certainly not Ferguson.

The massively China-connected Imperial College and its bizarre professor provided the excuse for the long-incubated Chinese model of human control to travel westward at lightning speed. Imperial College confirms on its website that it collaborates with the Chinese Research Institute; publishes more than 600 research papers every year with Chinese research institutions; has 225 Chinese staff; 2,600 Chinese students – the biggest international group; 7,000 former students living in China which is the largest group outside the UK; and was selected for a tour by China's President Xi Jinping during his state visit to the UK in 2015. The college takes major donations from China and describes itself as the UK's number one university collaborator with Chinese research institutions. The China communist/fascist government did not appear phased by the woeful predictions of Ferguson and Imperial when during the lockdown that Ferguson induced the college signed a five-year collaboration deal with China tech giant Huawei that will have Huawei's indoor 5G network equipment installed at the college's West London tech campus along with an 'AI cloud platform'. The deal includes Chinese sponsorship of Imperial's Venture Catalyst entrepreneurship competition. Imperial is an example of the enormous influence the Chinese government has within British and North American

universities and research centres – and further afield. Up to 200 academics from more than a dozen UK universities are being investigated on suspicion of 'unintentionally' helping the Chinese government build weapons of mass destruction by 'transferring world-leading research in advanced military technology such as aircraft, missile designs and cyberweapons'. Similar scandals have broken in the United States, but it's all a coincidence. Imperial College serves the agenda in many other ways including the promotion of every aspect of the United Nations Agenda 21/2030 (the Great Reset) and produced computer models to show that human-caused 'climate change' is happening when in the real world it isn't. Imperial College is driving the climate agenda as it drives the 'Covid' agenda (both Cult hoaxes) while Patrick Vallance, the UK government's Chief Scientific Adviser on 'Covid', was named Chief Scientific Adviser to the UN 'climate change' conference known as COP26 hosted by the government in Glasgow, Scotland. 'Covid' and 'climate' are fundamentally connected.

Professor Woeful

From Imperial's bosom came Neil Ferguson still advising government despite his previous disasters and it was announced early on that he and other key people like UK Chief Medical Adviser Chris Whitty had caught the 'virus' as the propaganda story was being sold. Somehow they managed to survive and we had Prime Minister Boris Johnson admitted to hospital with what was said to be a severe version of the 'virus' in this same period. His whole policy and demeanour changed when he returned to Downing Street. It's a small world with these government advisors – especially in their communal connections to Gates – and Ferguson had partnered with Whitty to write a paper called 'Infectious disease: Tough choices to reduce Ebola transmission' which involved another scare-story that didn't happen. Ferguson's 'models' predicted that up to150, 000 could die from 'mad cow disease', or BSE, and its version in sheep if it was transmitted to humans. BSE was not transmitted and instead triggered by an organophosphate pesticide used to treat a pest on

cows. Fewer than 200 deaths followed from the human form. Models by Ferguson and his fellow incompetents led to the unnecessary culling of millions of pigs, cattle and sheep in the foot and mouth outbreak in 2001 which destroyed the lives and livelihoods of farmers and their families who had often spent decades building their herds and flocks. Vast numbers of these animals did not have foot and mouth and had no contact with the infection. Another 'expert' behind the cull was Professor Roy Anderson, a computer modeller at Imperial College specialising in the epidemiology of *human*, not animal, disease. Anderson has served on the Bill and Melinda Gates Grand Challenges in Global Health advisory board and chairs another Gates-funded organisation. Gates is everywhere.

In a precursor to the 'Covid' script Ferguson backed closing schools 'for prolonged periods' over the swine flu 'pandemic' in 2009 and said it would affect a third of the world population if it continued to spread at the speed he claimed to be happening. His mates at Imperial College said much the same and a news report said: 'One of the authors, the epidemiologist and disease modeller Neil Ferguson, who sits on the World Health Organisation's emergency committee for the outbreak, said the virus had "full pandemic potential".' Professor Liam Donaldson, the Chris Whitty of his day as Chief Medical Officer, said the worst case could see 30 percent of the British people infected by swine flu with 65,000 dying. Ferguson and Donaldson were indeed proved correct when at the end of the year the number of deaths attributed to swine flu was 392. The term 'expert' is rather liberally applied unfortunately, not least to complete idiots. Swine flu 'projections' were great for GlaxoSmithKline (GSK) as millions rolled in for its Pandemrix influenza vaccine which led to brain damage with children most affected. The British government (taxpayers) paid out more than £60 million in compensation after GSK was given immunity from prosecution. Yet another 'Covid' déjà vu. Swine flu was supposed to have broken out in Mexico, but Dr Wolfgang Wodarg, a German doctor, former member of parliament and critic of the 'Covid' hoax, observed 'the spread of swine flu' in Mexico City at the time. He

said: 'What we experienced in Mexico City was a very mild flu which did not kill more than usual – which killed even fewer people than usual.' Hyping the fear against all the facts is not unique to 'Covid' and has happened many times before. Ferguson is reported to have over-estimated the projected death toll of bird flu (H5N1) by some three million-fold, but bird flu vaccine makers again made a killing from the scare. This is some of the background to the Neil Ferguson who produced the perfectly-timed computer models in early 2020 predicting that half a million people would die in Britain without draconian lockdown and 2.2 million in the United States. Politicians panicked, people panicked, and lockdowns of alleged short duration were instigated to 'flatten the curve' of cases gleaned from a test not testing for the 'virus'. I said at the time that the public could forget the 'short duration' bit. This was an agenda to destroy the livelihoods of the population and force them into mass control through dependency and there was going to be nothing 'short' about it. American researcher Daniel Horowitz described the consequences of the 'models' spewed out by Gates-funded Ferguson and Imperial College:

> What led our government and the governments of many other countries into panic was a single Imperial College of UK study, funded by global warming activists, that predicted 2.2 million deaths if we didn't lock down the country. In addition, the reported 8-9% death rate in Italy scared us into thinking there was some other mutation of this virus that they got, which might have come here.
>
> Together with the fact that we were finally testing and had the ability to actually report new cases, we thought we were headed for a death spiral. But again … we can't flatten a curve if we don't know when the curve started.

How about it *never* started?

Giving them what they want

An investigation by German news outlet *Welt Am Sonntag (World on Sunday)* revealed how in March, 2020, the German government gathered together 'leading scientists from several research institutes and universities' and 'together, they were to produce a [modelling]

paper that would serve as legitimization for further tough political measures'. The Cult agenda was justified by computer modelling not based on evidence or reality; it was specifically constructed to justify the Cult demand for lockdowns all over the world to destroy the independent livelihoods of the global population. All these modellers and everyone responsible for the 'Covid' hoax have a date with a trial like those in Nuremberg after World War Two when Nazis faced the consequences of their war crimes. These corrupt-beyond-belief 'modellers' wrote the paper according to government instructions and it said that that if lockdown measures were lifted then up to one million Germans would die from 'Covid-19' adding that some would die 'agonizingly at home, gasping for breath' unable to be treated by hospitals that couldn't cope. All lies. No matter – it gave the Cult all that it wanted. What did long-time government 'modeller' Neil Ferguson say? If the UK and the United States didn't lockdown half a million would die in Britain and 2.2 million Americans. Anyone see a theme here? 'Modellers' are such a crucial part of the lockdown strategy that we should look into their background and follow the money. Researcher Rosemary Frei produced an excellent article headlined 'The Modelling-paper Mafiosi'. She highlights a guy called John Edmunds, a British epidemiologist, and professor in the Faculty of Epidemiology and Population Health at the London School of Hygiene & Tropical Medicine. He studied at Imperial College. Edmunds is a member of government 'Covid' advisory bodies which have been dictating policy, the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) and the Scientific Advisory Group for Emergencies (SAGE).

Ferguson, another member of NERVTAG and SAGE, led the way with the original 'virus' and Edmunds has followed in the 'variant' stage and especially the so-called UK or Kent variant known as the 'Variant of Concern' (VOC) B.1.1.7. He said in a co-written report for the Centre for Mathematical modelling of Infectious Diseases at the London School of Hygiene and Tropical Medicine, with input from the Centre's 'Covid-19' Working Group, that there was 'a realistic

possibility that VOC B.1.1.7 is associated with an increased risk of death compared to non-VOC viruses'. Fear, fear, fear, get the vaccine, fear, fear, fear, get the vaccine. Rosemary Frei reveals that almost all the paper's authors and members of the modelling centre's 'Covid-19' Working Group receive funding from the Bill and Melinda Gates Foundation and/or the associated Gates-funded Wellcome Trust. The paper was published by e-journal *Medr χiv* which only publishes papers not peer-reviewed and the journal was established by an organisation headed by Facebook's Mark Zuckerberg and his missus. What a small world it is. Frei discovered that Edmunds is on the Scientific Advisory Board of the Coalition for Epidemic Preparedness Innovations (CEPI) which was established by the Bill and Melinda Gates Foundation, Klaus Schwab's Davos World Economic Forum and Big Pharma giant Wellcome. CEPI was 'launched in Davos [in 2017] to develop vaccines to stop future epidemics', according to its website. 'Our mission is to accelerate the development of vaccines against emerging infectious diseases and enable equitable access to these vaccines for people during outbreaks.' What kind people they are. Rosemary Frei reveals that Public Health England (PHE) director Susan Hopkins is an author of her organisation's non-peer-reviewed reports on 'new variants'. Hopkins is a professor of infectious diseases at London's Imperial College which is gifted tens of millions of dollars a year by the Bill and Melinda Gates Foundation. Gates-funded modelling disaster Neil Ferguson also co-authors Public Health England reports and he spoke in December, 2020, about the potential danger of the B.1.1.7. 'UK variant' promoted by Gates-funded modeller John Edmunds. When I come to the 'Covid vaccines' the 'new variants' will be shown for what they are – bollocks.

Connections, connections

All these people and modellers are lockdown-obsessed or, put another way, they demand what the Cult demands. Edmunds said in January, 2021, that to ease lockdowns too soon would be a disaster and they had to 'vaccinate much, much, much more widely than the

elderly'. Rosemary Frei highlights that Edmunds is married to Jeanne Pimenta who is described in a LinkedIn profile as director of epidemiology at GlaxoSmithKline (GSK) and she held shares in the company. Patrick Vallance, co-chair of SAGE and the government's Chief Scientific Adviser, is a former executive of GSK and has a deferred bonus of shares in the company worth £600,000. GSK has serious business connections with Bill Gates and is collaborating with mRNA-'vaccine' company CureVac to make 'vaccines' for the new variants that Edmunds is talking about. GSK is planning a 'Covid vaccine' with drug giant Sanofi. Puppet Prime Minister Boris Johnson announced in the spring of 2021 that up to 60 million vaccine doses were to be made at the GSK facility at Barnard Castle in the English North East. Barnard Castle, with a population of just 6,000, was famously visited in breach of lockdown rules in April, 2020, by Johnson aide Dominic Cummings who said that he drove there 'to test his eyesight' before driving back to London. Cummings would be better advised to test his integrity – not that it would take long. The GSK facility had nothing to do with his visit then although I'm sure Patrick Vallance would have been happy to arrange an introduction and some tea and biscuits. Ruthless psychopath Gates has made yet another fortune from vaccines in collaboration with Big Pharma companies and gushes at the phenomenal profits to be made from vaccines – more than a 20-to-1 return as he told one interviewer. Gates also tweeted in December, 2019, with the foreknowledge of what was coming: 'What's next for our foundation? I'm particularly excited about what the next year could mean for one of the best buys in global health: vaccines.'

Modeller John Edmunds is a big promotor of vaccines as all these people appear to be. He's the dean of the London School of Hygiene & Tropical Medicine's Faculty of Epidemiology and Population Health which is primarily funded by the Bill and Melinda Gates Foundation and the Gates-established and funded GAVI vaccine alliance which is the Gates vehicle to vaccinate the world. The organisation Doctors Without Borders has described GAVI as being 'aimed more at supporting drug-industry desires to promote new

products than at finding the most efficient and sustainable means for fighting the diseases of poverty'. But then that's why the psychopath Gates created it. John Edmunds said in a video that the London School of Hygiene & Tropical Medicine is involved in every aspect of vaccine development including large-scale clinical trials. He contends that mathematical modelling can show that vaccines protect individuals and society. That's on the basis of shit in and shit out, I take it. Edmunds serves on the UK Vaccine Network as does Ferguson and the government's foremost 'Covid' adviser, the grim-faced, dark-eyed Chris Whitty. The Vaccine Network says it works 'to support the government to identify and shortlist targeted investment opportunities for the most promising vaccines and vaccine technologies that will help combat infectious diseases with epidemic potential, and to address structural issues related to the UK's broader vaccine infrastructure'. Ferguson is acting Director of the Imperial College Vaccine Impact Modelling Consortium which has funding from the Bill and Melina Gates Foundation and the Gates-created GAVI 'vaccine alliance'. Anyone wonder why these characters see vaccines as the answer to every problem? Ferguson is wildly enthusiastic in his support for GAVI's campaign to vaccine children en masse in poor countries. You would expect someone like Gates who has constantly talked about the need to reduce the population to want to fund vaccines to keep more people alive. I'm sure that's why he does it. The John Edmunds London School of Hygiene & Tropical Medicine (LSHTM) has a Vaccines Manufacturing Innovation Centre which develops, tests and commercialises vaccines. Rosemary Frei writes:

> The vaccines centre also performs affiliated activities like combating 'vaccine hesitancy'. The latter includes the Vaccine Confidence Project. The project's stated purpose is, among other things, 'to provide analysis and guidance for early response and engagement with the public to ensure sustained confidence in vaccines and immunisation'. The Vaccine Confidence Project's director is LSHTM professor Heidi Larson. For more than a decade she's been researching how to combat vaccine hesitancy.

How the bloody hell can blokes like John Edmunds and Neil Ferguson with those connections and financial ties model 'virus' case

and death projections for the government and especially in a way that gives their paymasters like Gates exactly what they want? It's insane, but this is what you find throughout the world.

'Covid' is not dangerous, oops, wait, yes it is

Only days before Ferguson's nightmare scenario made Jackboot Johnson take Britain into a China-style lockdown to save us from a deadly 'virus' the UK government website gov.uk was reporting something very different to Ferguson on a page of official government guidance for 'high consequence infectious diseases (HCID)'. It said this about 'Covid-19':

As of 19 March 2020, COVID-19 *is no longer considered to be a high consequence infectious diseases (HCID) in the UK* [my emphasis]. The 4 nations public health HCID group made an interim recommendation in January 2020 to classify COVID-19 as an HCID. This was based on consideration of the UK HCID criteria about the virus and the disease with information available during the early stages of the outbreak.

Now that more is known about COVID-19, the public health bodies in the UK have reviewed the most up to date information about COVID-19 against the UK HCID criteria. They have determined that several features have now changed; in particular, more information is available about mortality rates (low overall), and there is now greater clinical awareness and a specific and sensitive laboratory test, the availability of which continues to increase. The Advisory Committee on Dangerous Pathogens (ACDP) is also of the opinion that COVID-19 should no longer be classified as an HCID.

Soon after the government had been exposed for downgrading the risk they upgraded it again and everyone was back to singing from the same Cult hymn book. Ferguson and his fellow Gates clones indicated that lockdowns and restrictions would have to continue until a Gates-funded vaccine was developed. Gates said the same because Ferguson and his like were repeating the Gates script which is the Cult script. 'Flatten the curve' became an ongoing nightmare of continuing lockdowns with periods in between of severe restrictions in pursuit of destroying independent incomes and had nothing to do with protecting health about which the Cult gives not a shit. Why wouldn't Ferguson be pushing a vaccine 'solution' when he's owned by vaccine-obsessive Gates who makes a fortune from them and

when Ferguson heads the Vaccine Impact Modelling Consortium at Imperial College funded by the Gates Foundation and GAVI, the 'vaccine alliance', created by Gates as his personal vaccine promotion operation? To compound the human catastrophe that Ferguson's 'models' did so much to create he was later exposed for breaking his own lockdown rules by having sexual liaisons with his married girlfriend Antonia Staats at his home while she was living at another location with her husband and children. Staats was a 'climate' activist and senior campaigner at the Soros-funded Avaaz which I wouldn't trust to tell me that grass is green. Ferguson had to resign as a government advisor over this hypocrisy in May, 2020, but after a period of quiet he was back being quoted by the ridiculous media on the need for more lockdowns and a vaccine rollout. Other government-advising 'scientists' from Imperial College' held the fort in his absence and said lockdown could be indefinite until a vaccine was found. The Cult script was being sung by the payrolled choir. I said there was no intention of going back to 'normal' when the 'vaccine' came because the 'vaccine' is part of a very different agenda that I will discuss in Human 2.0. Why would the Cult want to let the world go back to normal when destroying that normal forever was the whole point of what was happening? House arrest, closing businesses and schools through lockdown, (un)social distancing and masks all followed the Ferguson fantasy models. Again as I predicted (these people are so predictable) when the 'vaccine' arrived we were told that house arrest, lockdown, (un)social distancing and masks would still have to continue. I will deal with the masks in the next chapter because they are of fundamental importance.

Where's the 'pandemic'?

Any mildly in-depth assessment of the figures revealed what was really going on. Cult-funded and controlled organisations still have genuine people working within them such is the number involved. So it is with Genevieve Briand, assistant program director of the Applied Economics master's degree program at Johns Hopkins

University. She analysed the impact that 'Covid-19' had on deaths from *all* causes in the United States using official data from the CDC for the period from early February to early September, 2020. She found that allegedly 'Covid' *related*-deaths exceeded those from heart disease which she found strange with heart disease always the biggest cause of fatalities. Her research became even more significant when she noted the sudden decline in 2020 of *all* non-'Covid' deaths: 'This trend is completely contrary to the pattern observed in all previous years … the total decrease in deaths by other causes almost exactly equals the increase in deaths by Covid-19.' This was such a game, set and match in terms of what was happening that Johns Hopkins University deleted the article on the grounds that it 'was being used to support false and dangerous inaccuracies about the impact of the pandemic'. No – because it exposed the scam from official CDC figures and this was confirmed when those figures were published in January, 2021. Here we can see the effect of people dying from heart attacks, cancer, road accidents and gunshot wounds – *anything* – having 'Covid-19' on the death certificate along with those diagnosed from 'symptoms' who had even not tested positive with a test not testing for the 'virus'. I am not kidding with the gunshot wounds, by the way. Brenda Bock, coroner in Grand County, Colorado, revealed that two gunshot victims tested positive for the 'virus' within the previous 30 days and were therefore classified as 'Covid deaths'. Bock said: 'These two people had tested positive for Covid, but that's not what killed them. A gunshot wound is what killed them.' She said she had not even finished her investigation when the state listed the gunshot victims as deaths due to the 'virus'. The death and case figures for 'Covid-19' are an absolute joke and yet they are repeated like parrots by the media, politicians and alleged medical 'experts'. The official Cult narrative is the only show in town.

Genevieve Briand found that deaths from all causes were not exceptional in 2020 compared with previous years and a Spanish magazine published figures that said the same about Spain which was a 'Covid' propaganda hotspot at one point. *Discovery Salud*, a

health and medicine magazine, quoted government figures which showed how 17,000 *fewer* people died in Spain in 2020 than in 2019 and more than 26,000 fewer than in 2018. The age-standardised mortality rate for England and Wales when age distribution is taken into account was significantly lower in 2020 than the 1970s, 80s and 90s, and was only the ninth highest since 2000. Where is the 'pandemic'?

Post mortems and autopsies virtually disappeared for 'Covid' deaths amid claims that 'virus-infected' bodily fluids posed a risk to those carrying out the autopsy. This was rejected by renowned German pathologist and forensic doctor Klaus Püschel who said that he and his staff had by then done 150 autopsies on 'Covid' patients with no problems at all. He said they were needed to know why some 'Covid' patients suffered blood clots and not severe respiratory infections. The 'virus' is, after all, called SARS or 'severe acute respiratory syndrome'. I highlighted in the spring of 2020 this phenomenon and quoted New York intensive care doctor Cameron Kyle-Sidell who posted a soon deleted YouTube video to say that they had been told to prepare to treat an infectious disease called 'Covid-19', but that was not what they were dealing with. Instead he likened the lung condition of the most severely ill patients to what you would expect with cabin depressurisation in a plane at 30,000 feet or someone dropped on the top of Everest without oxygen or acclimatisation. I have never said this is not happening to a small minority of alleged 'Covid' patients – I am saying this is not caused by a phantom 'contagious virus'. Indeed Kyle-Sidell said that 'Covid-19' was not the disease they were told was coming their way. 'We are operating under a medical paradigm that is untrue,' he said, and he believed they were treating the wrong disease: 'These people are being slowly starved of oxygen.' Patients would take off their oxygen masks in a state of fear and stress and while they were blue in the face on the brink of death. They did not look like patients dying of pneumonia. You can see why they don't want autopsies when their virus doesn't exist and there is another condition in some people that they don't wish to be uncovered. I should add here that

the 5G system of millimetre waves was being rapidly introduced around the world in 2020 and even more so now as they fire 5G at the Earth from satellites. At 60 gigahertz within the 5G range that frequency interacts with the oxygen molecule and stops people breathing in sufficient oxygen to be absorbed into the bloodstream. They are installing 5G in schools and hospitals. The world is not mad or anything. 5G can cause major changes to the lungs and blood as I detail in *The Answer* and these consequences are labelled 'Covid-19', the alleged symptoms of which can be caused by 5G and other electromagnetic frequencies as cells respond to radiation poisoning.

The 'Covid death' scam

Dr Scott Jensen, a Minnesota state senator and medical doctor, exposed 'Covid' Medicare payment incentives to hospitals and death certificate manipulation. He said he was sent a seven-page document by the US Department of Health 'coaching' him on how to fill out death certificates which had never happened before. The document said that he didn't need to have a laboratory test for 'Covid-19' to put that on the death certificate and that shocked him when death certificates are supposed to be about facts. Jensen described how doctors had been 'encouraged, if not pressured' to make a diagnosis of 'Covid-19' if they thought it was probable or *'presumed*'. No positive test was necessary – not that this would have mattered anyway. He said doctors were told to diagnose 'Covid' by symptoms when these were the same as colds, allergies, other respiratory problems, and certainly with influenza which 'disappeared' in the 'Covid' era. A common sniffle was enough to get the dreaded verdict. Ontario authorities decreed that a single care home resident with *one* symptom from a long list must lead to the isolation of the entire home. Other courageous doctors like Jensen made the same point about death figure manipulation and how deaths by other causes were falling while 'Covid-19 deaths' were rising at the same rate due to re-diagnosis. Their videos rarely survive long on YouTube with its Cult-supporting algorithms courtesy of CEO Susan Wojcicki and her bosses at Google. Figure-tampering was so glaring

and ubiquitous that even officials were letting it slip or outright saying it. UK chief scientific adviser Patrick Vallance said on one occasion that 'Covid' on the death certificate doesn't mean 'Covid' was the cause of death (so why the hell is it there?) and we had the rare sight of a BBC reporter telling the truth when she said: 'Someone could be successfully treated for Covid, in say April, discharged, and then in June, get run over by a bus and die … That person would still be counted as a Covid death in England.' Yet the BBC and the rest of the world media went on repeating the case and death figures as if they were real. Illinois Public Health Director Dr Ngozi Ezike revealed the deceit while her bosses must have been clenching their buttocks:

> If you were in a hospice and given a few weeks to live and you were then found to have Covid that would be counted as a Covid death. [There might be] a clear alternate cause, but it is still listed as a Covid death. So everyone listed as a Covid death doesn't mean that was the cause of the death, but that they had Covid at the time of death.

Yes, a 'Covid virus' never shown to exist and tested for with a test not testing for the 'virus'. In the first period of the pandemic hoax through the spring of 2020 the process began of designating almost everything a 'Covid' death and this has continued ever since. I sat in a restaurant one night listening to a loud conversation on the next table where a family was discussing in bewilderment how a relative who had no symptoms of 'Covid', and had died of a long-term problem, could have been diagnosed a death by the 'virus'. I could understand their bewilderment. If they read this book they will know why this medical fraud has been perpetrated the world over.

Some media truth shock

The media ignored the evidence of death certificate fraud until eventually one columnist did speak out when she saw it first-hand. Bel Mooney is a long-time national newspaper journalist in Britain currently working for the *Daily Mail*. Her article on February 19th, 2021, carried this headline: 'My dad Ted passed three Covid tests

and died of a chronic illness yet he's officially one of Britain's 120,000 victims of the virus and is far from alone ... so how many more are there?' She told how her 99-year-old father was in a care home with a long-standing chronic obstructive pulmonary disease and vascular dementia. Maybe, but he was still aware enough to tell her from the start that there was no 'virus' and he refused the 'vaccine' for that reason. His death was not unexpected given his chronic health problems and Mooney said she was shocked to find that 'Covid-19' was declared the cause of death on his death certificate. She said this was a 'bizarre and unacceptable untruth' for a man with long-time health problems who had tested negative twice at the home for the 'virus'. I was also shocked by this story although not by what she said. I had been highlighting the death certificate manipulation for ten months. It was the confirmation that a professional full-time journalist only realised this was going on when it affected her directly and neither did she know that whether her dad tested positive or negative was irrelevant with the test not testing for the 'virus'. Where had she been? She said she did not believe in 'conspiracy theories' without knowing I'm sure that this and 'conspiracy theorists' were terms put into widespread circulation by the CIA in the 1960s to discredit those who did not accept the ridiculous official story of the Kennedy assassination. A blanket statement of 'I don't believe in conspiracy theories' is always bizarre. The dictionary definition of the term alone means the world is drowning in conspiracies. What she said was even more daft when her dad had just been affected by the 'Covid' conspiracy. Why else does she think that 'Covid-19' was going on the death certificates of people who died of something else?

To be fair once she saw from personal experience what was happening she didn't mince words. Mooney was called by the care home on the morning of February 9th to be told her father had died in his sleep. When she asked for the official cause of death what came back was 'Covid-19'. Mooney challenged this and was told there had been deaths from Covid on the dementia floor (confirmed by a test not testing for the 'virus') so they considered it 'reasonable

to assume'. 'But doctor,' Mooney rightly protested, 'an assumption isn't a diagnosis.' She said she didn't blame the perfectly decent and sympathetic doctor – 'he was just doing his job'. Sorry, but that's *bullshit*. He wasn't doing his job at all. He was putting a false cause of death on the death certificate and that is a criminal offence for which he should be brought to account and the same with the millions of doctors worldwide who have done the same. They were not doing their job they were following orders and that must not wash at new Nuremberg trials any more than it did at the first ones. Mooney's doctor was 'assuming' (presuming) as he was told to, but 'just following orders' makes no difference to his actions. A doctor's job is to serve the patient and the truth, not follow orders, but that's what they have done all over the world and played a central part in making the 'Covid' hoax possible with all its catastrophic consequences for humanity. Shame on them and they must answer for their actions. Mooney said her disquiet worsened when she registered her father's death by telephone and was told by the registrar there had been very many other cases like hers where 'the deceased' had not tested positive for 'Covid' yet it was recorded as the cause of death. The test may not matter, but those involved at their level *think* it matters and it shows a callous disregard for accurate diagnosis. The pressure to do this is coming from the top of the national 'health' pyramids which in turn obey the World Health Organization which obeys Gates and the Cult. Mooney said the registrar agreed that this must distort the national figures adding that 'the strangest thing is that every winter we record countless deaths from flu, and this winter there have been none. Not one!' She asked if the registrar thought deaths from flu were being misdiagnosed and lumped together with 'Covid' deaths. The answer was a 'puzzled yes'. Mooney said that the funeral director said the same about 'Covid' deaths which had nothing to do with 'Covid'. They had lost count of the number of families upset by this and other funeral companies in different countries have had the same experience. Mooney wrote:

The nightly shroud-waving and shocking close-ups of pain imposed on us by the TV news bewildered and terrified the population into eager compliance with lockdowns. We were invited to 'save the NHS' and to grieve for strangers – the real-life loved ones behind those shocking death counts. Why would the public imagine what I now fear, namely that the way Covid-19 death statistics are compiled might make the numbers seem greater than they are?

Oh, just a little bit – like 100 percent.

Do the maths

Mooney asked why a country would wish to skew its mortality figures by wrongly certifying deaths? What had been going on? Well, if you don't believe in conspiracies you will never find the answer which is that *it's a conspiracy*. She did, however, describe what she had discovered as a 'national scandal'. In reality it's a global scandal and happening everywhere. Pillars of this conspiracy were all put into place before the button was pressed with the Drosten PCR protocol and high amplifications to produce the cases and death certificate changes to secure illusory 'Covid' deaths. Mooney notes that normally two doctors were needed to certify a death, with one having to know the patient, and how the rules were changed in the spring of 2020 to allow one doctor to do this. In the same period 'Covid deaths' were decreed to be all cases where Covid-19 was put on the death certificate even without a positive test or any symptoms. Mooney asked: 'How many of the 30,851 (as of January 15) care home resident deaths with Covid-19 on the certificate (32.4 per cent of all deaths so far) were based on an assumption, like that of my father? And what has that done to our national psyche?'All of them is the answer to the first question and it has devastated and dismantled the national psyche, actually the global psyche, on a colossal scale. In the UK case and death data is compiled by organisations like Public Health England (PHE) and the Office for National Statistics (ONS). Mooney highlights the insane policy of counting a death from any cause as 'Covid-19' if this happens within 28 days of a positive test (with a test not testing for the 'virus') and she points out that ONS statistics reflect deaths 'involving Covid' 'or due to Covid' which meant in practice any

death where 'Covid-19' was mentioned on the death certificate. She described the consequences of this fraud:

Most people will accept the narrative they are fed, so panicky governments here and in Europe witnessed the harsh measures enacted in totalitarian China and jumped into lockdown. Headlines about Covid deaths tolled like the knell that would bring doomsday to us all. Fear stalked our empty streets. Politicians parroted the frankly ridiculous aim of 'zero Covid' and shut down the economy, while most British people agreed that lockdown was essential and (astonishingly to me, as a patriotic Brit) even wanted more restrictions.

For what? Lies on death certificates? Never mind the grim toll of lives ruined, suicides, schools closed, rising inequality, depression, cancelled hospital treatments, cancer patients in a torture of waiting, poverty, economic devastation, loneliness, families kept apart, and so on. How many lives have been lost as a direct result of lockdown?

She said that we could join in a national chorus of shock and horror at reaching the 120,000 death toll which was surely certain to have been totally skewed all along, but what about the human cost of lockdown justified by these 'death figures'? *The British Medical Journal* had reported a 1,493 percent increase in cases of children taken to Great Ormond Street Hospital with abusive head injuries alone and then there was the effect on families:

Perhaps the most shocking thing about all this is that families have been kept apart – and obeyed the most irrational, changing rules at the whim of government – because they believed in the statistics. They succumbed to fear, which his generation rejected in that war fought for freedom. Dad (God rest his soul) would be angry. And so am I.

Another theme to watch is that in the winter months when there are more deaths from all causes they focus on 'Covid' deaths and in the summer when the British Lung Foundation says respiratory disease plummets by 80 percent they rage on about 'cases'. Either way fascism on population is always the answer.

Nazi eugenics in the 21st century

Elderly people in care homes have been isolated from their families month after lonely month with no contact with relatives and grandchildren who were banned from seeing them. We were told

that lockdown fascism was to 'protect the vulnerable' like elderly people. At the same time Do Not Resuscitate (DNR) orders were placed on their medical files so that if they needed resuscitation it wasn't done and 'Covid-19' went on their death certificates. Old people were not being 'protected' they were being culled – murdered in truth. DNR orders were being decreed for disabled and young people with learning difficulties or psychological problems. The UK Care Quality Commission, a non-departmental body of the Department of Health and Social Care, found that 34 percent of those working in health and social care were pressured into placing 'do not attempt cardiopulmonary resuscitation' orders on 'Covid' patients who suffered from disabilities and learning difficulties without involving the patient or their families in the decision. UK judges ruled that an elderly woman with dementia should have the DNA-manipulating 'Covid vaccine' against her son's wishes and that a man with severe learning difficulties should have the jab despite his family's objections. Never mind that many had already died. The judiciary always supports doctors and government in fascist dictatorships. They wouldn't dare do otherwise. A horrific video was posted showing fascist officers from Los Angeles police forcibly giving the 'Covid' shot to women with special needs who were screaming that they didn't want it. The same fascists are seen giving the jab to a sleeping elderly woman in a care home. This is straight out of the Nazi playbook. Hitler's Nazis committed mass murder of the mentally ill and physically disabled throughout Germany and occupied territories in the programme that became known as Aktion T4, or just T4. Sabbatian-controlled Hitler and his grotesque crazies set out to kill those they considered useless and unnecessary. The Reich Committee for the Scientific Registering of Hereditary and Congenital Illnesses registered the births of babies identified by physicians to have 'defects'. By 1941 alone more than 5,000 children were murdered by the state and it is estimated that in total the number of innocent people killed in Aktion T4 was between 275,000 and 300,000. Parents were told their children had been sent away for 'special treatment' never to return. It is rather pathetic to see claims about plans for new extermination camps being dismissed today

when the same force behind current events did precisely that 80 years ago. Margaret Sanger was a Cult operative who used 'birth control' to sanitise her programme of eugenics. Organisations she founded became what is now Planned Parenthood. Sanger proposed that 'the whole dysgenic population would have its choice of segregation or sterilization'. These included epileptics, 'feeble-minded', and prostitutes. Sanger opposed charity because it perpetuated 'human waste'. She reveals the Cult mentality and if anyone thinks that extermination camps are a 'conspiracy theory' their naivety is touching if breathtakingly stupid.

If you don't believe that doctors can act with callous disregard for their patients it is worth considering that doctors and medical staff agreed to put government-decreed DNR orders on medical files and do nothing when resuscitation is called for. I don't know what you call such people in your house. In mine they are Nazis from the Josef Mengele School of Medicine. Phenomenal numbers of old people have died worldwide from the effects of lockdown, depression, lack of treatment, the 'vaccine' (more later) and losing the will to live. A common response at the start of the manufactured pandemic was to remove old people from hospital beds and transfer them to nursing homes. The decision would result in a mass cull of elderly people in those homes through lack of treatment – *not* 'Covid'. Care home whistleblowers have told how once the 'Covid' era began doctors would not come to their homes to treat patients and they were begging for drugs like antibiotics that often never came. The most infamous example was ordered by New York governor Andrew Cuomo, brother of a moronic CNN host, who amazingly was given an Emmy Award for his handling of the 'Covid crisis' by the ridiculous Wokers that hand them out. Just how ridiculous could be seen in February, 2021, when a Department of Justice and FBI investigation began into how thousands of old people in New York died in nursing homes after being discharged from hospital to make way for 'Covid' patients on Cuomo's say-so – and how he and his staff covered up these facts. This couldn't have happened to a nicer psychopath. Even then there was a 'Covid' spin. Reports said that

thousands of old people who tested positive for 'Covid' in hospital were transferred to nursing homes to both die of 'Covid' and transmit it to others. No – they were in hospital because they were ill and the fact that they tested positive with a test not testing for the 'virus' is irrelevant. They were ill often with respiratory diseases ubiquitous in old people near the end of their lives. Their transfer out of hospital meant that their treatment stopped and many would go on to die.

They're old. Who gives a damn?

I have exposed in the books for decades the Cult plan to cull the world's old people and even to introduce at some point what they call a 'demise pill' which at a certain age everyone would take and be out of here by law. In March, 2021, Spain legalised euthanasia and assisted suicide following the Netherlands, Belgium, Luxembourg and Canada on the Tiptoe to the demise pill. Treatment of old people by many 'care' homes has been a disgrace in the 'Covid' era. There are many, many, caring staff – I know some. There have, however, been legions of stories about callous treatment of old people and their families. Police were called when families came to take their loved ones home in the light of isolation that was killing them. They became prisoners of the state. Care home residents in insane, fascist Ontario, Canada, were not allowed to leave their *room* once the 'Covid' hoax began. UK staff have even wheeled elderly people away from windows where family members were talking with them. Oriana Criscuolo from Stockport in the English North West dropped off some things for her 80-year-old father who has Parkinson's disease and dementia and she wanted to wave to him through a ground-floor window. She was told that was 'illegal'. When she went anyway they closed the curtains in the middle of the day. Oriana said:

> It's just unbelievable. I cannot understand how care home staff – people who are being paid to care – have become so uncaring. Their behaviour is inhumane and cruel. It's beyond belief.

She was right and this was not a one-off. What a way to end your life in such loveless circumstances. UK registered nurse Nicky Millen, a proper old school nurse for 40 years, said that when she started her career care was based on dignity, choice, compassion and empathy. Now she said 'the things that are important to me have gone out of the window.' She was appalled that people were dying without their loved ones and saying goodbye on iPads. Nicky described how a distressed 89-year-old lady stroked her face and asked her 'how many paracetamol would it take to finish me off'. Life was no longer worth living while not seeing her family. Nicky said she was humiliated in front of the ward staff and patients for letting the lady stroke her face and giving her a cuddle. Such is the dehumanisation that the 'Covid' hoax has brought to the surface. Nicky worked in care homes where patients told her they were being held prisoner. 'I want to live until I die', one said to her. 'I had a lady in tears because she hadn't seen her great-grandson.' Nicky was compassionate old school meeting psychopathic New Normal. She also said she had worked on a 'Covid' ward with no 'Covid' patients. Jewish writer Shai Held wrote an article in March, 2020, which was headlined 'The Staggering, Heartless Cruelty Toward the Elderly'. What he described was happening from the earliest days of lockdown. He said 'the elderly' were considered a group and not unique individuals (the way of the Woke). Shai Held said:

Notice how the all-too-familiar rhetoric of dehumanization works: 'The elderly' are bunched together as a faceless mass, all of them considered culprits and thus effectively deserving of the suffering the pandemic will inflict upon them. Lost entirely is the fact that the elderly are individual human beings, each with a distinctive face and voice, each with hopes and dreams, memories and regrets, friendships and marriages, loves lost and loves sustained.

'The elderly' have become another dehumanised group for which anything goes and for many that has resulted in cold disregard for their rights and their life. The distinctive face that Held talks about is designed to be deleted by masks until everyone is part of a faceless mass.

‘War-zone’ hospitals myth

Again and again medical professionals have told me what was really going on and how hospitals ‘overrun like war zones’ according to the media were virtually empty. The mantra from medical whistleblowers was please don’t use my name or my career is over. Citizen journalists around the world sneaked into hospitals to film evidence exposing the ‘war-zone’ lie. They really *were* largely empty with closed wards and operating theatres. I met a hospital worker in my town on the Isle of Wight during the first lockdown in 2020 who said the only island hospital had never been so quiet. Lockdown was justified by the psychopaths to stop hospitals being overrun. At the same time that the island hospital was near-empty the military arrived here to provide *extra beds*. It was all propaganda to ramp up the fear to ensure compliance with fascism as were never-used temporary hospitals with thousands of beds known as Nightingales and never-used make-shift mortuaries opened by the criminal UK government. A man who helped to install those extra island beds attributed to the army said they were never used and the hospital was empty. Doctors and nurses ‘stood around talking or on their phones, wandering down to us to see what we were doing’. There were no masks or social distancing. He accused the useless local island paper, the *County Press*, of ‘pumping the fear as if our hospital was overrun and we only have one so it should have been’. He described ambulances parked up with crews outside in deck chairs. When his brother called an ambulance he was told there was a two-hour backlog which he called ‘bullshit’. An old lady on the island fell ‘and was in a bad way’, but a caller who rang for an ambulance was told the situation wasn’t urgent enough. Ambulance stations were working under capacity while people would hear ambulances with sirens blaring driving through the streets. When those living near the stations realised what was going on they would follow them as they left, circulated around an urban area with the sirens going, and then came back without stopping. All this was to increase levels of fear and the same goes for the ‘ventilator shortage crisis’ that cost tens of millions for hastily produced ventilators never to be used.

Ambulance crews that agreed to be exploited in this way for fear propaganda might find themselves a mirror. I wish them well with that. Empty hospitals were the obvious consequence of treatment and diagnoses of non-'Covid' conditions cancelled and those involved handed a death sentence. People have been dying at home from undiagnosed and untreated cancer, heart disease and other life-threatening conditions to allow empty hospitals to deal with a 'pandemic' that wasn't happening.

Death of the innocent

'War-zones' have been laying off nursing staff, even doctors where they can. There was no work for them. Lockdown was justified by saving lives and protecting the vulnerable they were actually killing with DNR orders and preventing empty hospitals being 'overrun'. In Britain the mantra of stay at home to 'save the NHS' was everywhere and across the world the same story was being sold when it was all lies. Two California doctors, Dan Erickson and Artin Massihi at Accelerated Urgent Care in Bakersfield, held a news conference in April, 2020, to say that intensive care units in California were 'empty, essentially', with hospitals shutting floors, not treating patients and laying off doctors. The California health system was working at minimum capacity 'getting rid of doctors because we just don't have the volume'. They said that people with conditions such as heart disease and cancer were not coming to hospital out of fear of 'Covid-19'. Their video was deleted by Susan Wojcicki's Cult-owned YouTube after reaching five million views. Florida governor Ron Desantis, who rejected the severe lockdowns of other states and is being targeted for doing so, said that in March, 2020, every US governor was given models claiming they would run out of hospital beds in days. That was never going to happen and the 'modellers' knew it. Deceit can be found at every level of the system. Urgent children's operations were cancelled including fracture repairs and biopsies to spot cancer. Eric Nicholls, a consultant paediatrician, said 'this is obviously concerning and we need to return to normal operating and to increase capacity as soon as possible'. Psychopaths

in power were rather less concerned *because* they are psychopaths. Deletion of urgent care and diagnosis has been happening all over the world and how many kids and others have died as a result of the actions of these cold and heartless lunatics dictating 'health' policy? The number must be stratospheric. Richard Sullivan, professor of cancer and global health at King's College London, said people feared 'Covid' more than cancer such was the campaign of fear. 'Years of lost life will be quite dramatic', Sullivan said, with 'a huge amount of avoidable mortality'. Sarah Woolnough, executive director for policy at Cancer Research UK, said there had been a 75 percent drop in urgent referrals to hospitals by family doctors of people with suspected cancer. Sullivan said that 'a lot of services have had to scale back – we've seen a dramatic decrease in the amount of elective cancer surgery'. Lockdown deaths worldwide has been absolutely fantastic with the *New York Post* reporting how data confirmed that 'lockdowns end more lives than they save':

> There was a sharp decline in visits to emergency rooms and an increase in fatal heart attacks because patients didn't receive prompt treatment. Many fewer people were screened for cancer. Social isolation contributed to excess deaths from dementia and Alzheimer's.
>
> Researchers predicted that the social and economic upheaval would lead to tens of thousands of "deaths of despair" from drug overdoses, alcoholism and suicide. As unemployment surged and mental-health and substance-abuse treatment programs were interrupted, the reported levels of anxiety, depression and suicidal thoughts increased dramatically, as did alcohol sales and fatal drug overdoses.

This has been happening while nurses and other staff had so much time on their hands in the 'war-zones' that Tic-Tok dancing videos began appearing across the Internet with medical staff dancing around in empty wards and corridors as people died at home from causes that would normally have been treated in hospital.

Mentions in dispatches

One brave and truth-committed whistleblower was Louise Hampton, a call handler with the UK NHS who made a viral Internet video saying she had done 'fuck all' during the 'pandemic'

which was 'a load of bollocks'. She said that 'Covid-19' was rebranded flu and of course she lost her job. This is what happens in the medical and endless other professions now when you tell the truth. Louise filmed inside 'war-zone' accident and emergency departments to show they were empty and I mean *empty* as in no one there. The mainstream media could have done the same and blown the gaff on the whole conspiracy. They haven't to their eternal shame. Not that most 'journalists' seem capable of manifesting shame as with the psychopaths they slavishly repeat without question. The relative few who were admitted with serious health problems were left to die alone with no loved ones allowed to see them because of 'Covid' rules and they included kids dying without the comfort of mum and dad at their bedside while the evil behind this couldn't give a damn. It was all good fun to them. A Scottish NHS staff nurse publicly quit in the spring of 2021 saying: 'I can no longer be part of the lies and the corruption by the government.' She said hospitals 'aren't full, the beds aren't full, beds have been shut, wards have been shut'. Hospitals were never busy throughout 'Covid'. The staff nurse said that Nicola Sturgeon, tragically the leader of the Scottish government, was on television saying save the hospitals and the NHS – 'but the beds are empty' and 'we've not seen flu, we always see flu every year'. She wrote to government and spoke with her union Unison (the unions are Cult-compromised and *useless*, but nothing changed. Many of her colleagues were scared of losing their jobs if they spoke out as they wanted to. She said nursing staff were being affected by wearing masks all day and 'my head is splitting every shift from wearing a mask'. The NHS is part of the fascist tyranny and must be dismantled so we can start again with human beings in charge. (Ironically, hospitals were reported to be busier again when official 'Covid' cases *fell* in spring/summer of 2021 and many other conditions required treatment at the same time as *the fake vaccine rollout*.)

I will cover the 'Covid vaccine' scam in detail later, but it is another indicator of the sickening disregard for human life that I am highlighting here. The DNA-manipulating concoctions do not fulfil

the definition of a 'vaccine', have never been used on humans before and were given only emergency approval because trials were not completed and they continued using the unknowing public. The result was what a NHS senior nurse with responsibility for 'vaccine' procedure said was 'genocide'. She said the 'vaccines' were not 'vaccines'. They had not been shown to be safe and claims about their effectiveness by drug companies were 'poetic licence'. She described what was happening as a 'horrid act of human annihilation'. The nurse said that management had instigated a policy of not providing a Patient Information Leaflet (PIL) before people were 'vaccinated' even though health care professionals are supposed to do this according to protocol. Patients should also be told that they are taking part in an ongoing clinical trial. Her challenges to what is happening had seen her excluded from meetings and ridiculed in others. She said she was told to 'watch my step … or I would find myself surplus to requirements'. The nurse, who spoke anonymously in fear of her career, said she asked her NHS manager why he/she was content with taking part in genocide against those having the 'vaccines'. The reply was that everyone had to play their part and to 'put up, shut up, and get it done'. Government was 'leaning heavily' on NHS management which was clearly leaning heavily on staff. This is how the global 'medical' hierarchy operates and it starts with the Cult and its World Health Organization.

She told the story of a doctor who had the Pfizer jab and when questioned had no idea what was in it. The doctor had never read the literature. We have to stop treating doctors as intellectual giants when so many are moral and medical pygmies. The doctor did not even know that the 'vaccines' were not fully approved or that their trials were ongoing. They were, however, asking their patients if they minded taking part in follow-ups for research purposes – yes, the *ongoing clinical trial*. The nurse said the doctor's ignorance was not rare and she had spoken to a hospital consultant who had the jab without any idea of the background or that the 'trials' had not been completed. Nurses and pharmacists had shown the same ignorance.

'My NHS colleagues have forsaken their duty of care, broken their code of conduct – Hippocratic Oath – and have been brainwashed just the same as the majority of the UK public through propaganda …' She said she had not been able to recruit a single NHS colleague, doctor, nurse or pharmacist to stand with her and speak out. Her union had refused to help. She said that if the genocide came to light she would not hesitate to give evidence at a Nuremberg-type trial against those in power who could have affected the outcomes but didn't.

And all for what?

To put the nonsense into perspective let's say the 'virus' does exist and let's go completely crazy and accept that the official manipulated figures for cases and deaths are accurate. *Even then* a study by Stanford University epidemiologist Dr John Ioannidis published on the World Health Organization website produced an average infection to fatality rate of … *0.23 percent!* Ioannidis said: 'If one could sample equally from all locations globally, the median infection fatality rate might even be substantially lower than the 0.23% observed in my analysis.' For healthy people under 70 it was … *0.05 percent*! This compares with the 3.4 percent claimed by the Cult-owned World Health Organization when the hoax was first played and maximum fear needed to be generated. An updated Stanford study in April, 2021, put the 'infection' to 'fatality' rate at just 0.15 percent. Another team of scientists led by Megan O'Driscoll and Henrik Salje studied data from 45 countries and published their findings on the Nature website. For children and young people the figure is so small it virtually does not register although authorities will be hyping dangers to the young when they introduce DNA-manipulating 'vaccines' for children. The O'Driscoll study produced an average infection-fatality figure of 0.003 for children from birth to four; 0.001 for 5 to 14; 0.003 for 15 to 19; and it was still only 0.456 up to 64. To claim that children must be 'vaccinated' to protect them from 'Covid' is an obvious lie and so there must be another reason and there is. What's more the average age of a 'Covid' death is akin

to the average age that people die in general. The average age of death in England is about 80 for men and 83 for women. The average age of death from alleged 'Covid' is between 82 and 83. California doctors, Dan Erickson and Artin Massihi, said at their April media conference that projection models of millions of deaths had been 'woefully inaccurate'. They produced detailed figures showing that Californians had a 0.03 chance of dying from 'Covid' based on the number of people who tested positive (with a test not testing for the 'virus'). Erickson said there was a 0.1 percent chance of dying from 'Covid' in the *state* of New York, not just the city, and a 0.05 percent chance in Spain, a centre of 'Covid-19' hysteria at one stage. The Stanford studies supported the doctors' data with fatality rate estimates of 0.23 and 0.15 percent. How close are these figures to my estimate of *zero*? Death-rate figures claimed by the World Health Organization at the start of the hoax were some 15 times higher. The California doctors said there was no justification for lockdowns and the economic devastation they caused. Everything they had ever learned about quarantine was that you quarantine the *sick* and not the healthy. They had never seen this before and it made no medical sense.

Why in the in the light of all this would governments and medical systems the world over say that billions must go under house arrest; lose their livelihood; in many cases lose their mind, their health and their life; force people to wear masks dangerous to health and psychology; make human interaction and even family interaction a criminal offence; ban travel; close restaurants, bars, watching live sport, concerts, theatre, and any activity involving human togetherness and discourse; and closing schools to isolate children from their friends and cause many to commit suicide in acts of hopelessness and despair? The California doctors said lockdown consequences included increased child abuse, partner abuse, alcoholism, depression, and other impacts they were seeing every day. Who would do that to the entire human race if not mentally-ill psychopaths of almost unimaginable extremes like Bill Gates? We must face the reality of what we are dealing with and come out of

denial. Fascism and tyranny are made possible only by the target population submitting and acquiescing to fascism and tyranny. The whole of human history shows that to be true. Most people naively and unquestioning believed what they were told about a 'deadly virus' and meekly and weakly submitted to house arrest. Those who didn't believe it – at least in total – still submitted in fear of the consequences of not doing so. For the rest who wouldn't submit draconian fines have been imposed, brutal policing by psychopaths *for* psychopaths, and condemnation from the meek and weak who condemn the Pushbackers on behalf of the very force that has them, too, in its gunsights. 'Pathetic' does not even begin to suffice. Britain's brainless 'Health' Secretary Matt Hancock warned anyone lying to border officials about returning from a list of 'hotspot' countries could face a jail sentence of up to ten years which is more than for racially-aggravated assault, incest and attempting to have sex with a child under 13. Hancock is a lunatic, but he has the state apparatus behind him in a Cult-led chain reaction and the same with UK 'Vaccine Minister' Nadhim Zahawi, a prominent member of the mega-Cult secret society, Le Cercle, which featured in my earlier books. The Cult enforces its will on governments and medical systems; government and medical systems enforce their will on business and police; business enforces its will on staff who enforce it on customers; police enforce the will of the Cult on the population and play their essential part in creating a world of fascist control that their own children and grandchildren will have to live in their entire lives. It is a hierarchical pyramid of imposition and acquiescence and, yes indeedy, of clinical insanity.

Does anyone bright enough to read this book have to ask what the answer is? I think not, but I will reveal it anyway in the fewest of syllables: Tell the psychos and their moronic lackeys to fuck off and let's get on with our lives. We are many – They are few.

CHAPTER SEVEN

War on your mind

One believes things because one has been conditioned to believe them
Aldous Huxley, *Brave New World*

I have described the 'Covid' hoax as a 'Psyop' and that is true in every sense and on every level in accordance with the definition of that term which is psychological warfare. Break down the 'Covid pandemic' to the foundation themes and it is psychological warfare on the human individual and collective mind.

The same can be said for the entire human belief system involving every subject you can imagine. Huxley was right in his contention that people believe what they are conditioned to believe and this comes from the repetition throughout their lives of the same falsehoods. They spew from government, corporations, media and endless streams of 'experts' telling you what the Cult wants you to believe and often believing it themselves (although *far* from always). 'Experts' are rewarded with 'prestigious' jobs and titles and as agents of perceptual programming with regular access to the media. The Cult has to control the narrative – control *information* – or they lose control of the vital, crucial, without-which-they-cannot-prevail public perception of reality. The foundation of that control today is the Internet made possible by the Defense Advanced Research Projects Agency (DARPA), the incredibly sinister technological arm of the Pentagon. The Internet is the result of military technology.

DARPA openly brags about establishing the Internet which has been a long-term project to lasso the minds of the global population. I have said for decades the plan is to control information to such an extreme that eventually no one would see or hear anything that the Cult does not approve. We are closing in on that end with ferocious censorship since the 'Covid' hoax began and in my case it started back in the 1990s in terms of books and speaking venues. I had to create my own publishing company in 1995 precisely because no one else would publish my books even then. I think they're all still running.

Cult Internet

To secure total control of information they needed the Internet in which pre-programmed algorithms can seek out 'unclean' content for deletion and even stop it being posted in the first place. The Cult had to dismantle print and non-Internet broadcast media to ensure the transfer of information to the appropriate-named 'Web' – a critical expression of the *Cult* web. We've seen the ever-quickening demise of traditional media and control of what is left by a tiny number of corporations operating worldwide. Independent journalism in the mainstream is already dead and never was that more obvious than since the turn of 2020. The Cult wants all information communicated via the Internet to globally censor and allow the plug to be pulled any time. Lockdowns and forced isolation has meant that communication between people has been through electronic means and no longer through face-to-face discourse and discussion. Cult psychopaths have targeted the bars, restaurants, sport, venues and meeting places in general for this reason. None of this is by chance and it's to stop people gathering in any kind of privacy or number while being able to track and monitor all Internet communications and block them as necessary. Even private messages between individuals have been censored by these fascists that control Cult fronts like Facebook, Twitter, Google and YouTube which are all officially run by Sabbatian place-people and from the background by higher-level Sabbatian place people.

Facebook, Google, Amazon and their like were seed-funded and supported into existence with money-no-object infusions of funds either directly or indirectly from DARPA and CIA technology arm In-Q-Tel. The Cult plays the long game and prepares very carefully for big plays like 'Covid'. Amazon is another front in the psychological war and pretty much controls the global market in book sales and increasingly publishing. Amazon's limitless funds have deleted fantastic numbers of independent publishers to seize global domination on the way to deciding which books can be sold and circulated and which cannot. Moves in that direction are already happening. Amazon's leading light Jeff Bezos is the grandson of Lawrence Preston Gise who worked with DARPA predecessor ARPA. Amazon has big connections to the CIA and the Pentagon. The plan I have long described went like this:

1. Employ military technology to establish the Internet.

2. Sell the Internet as a place where people can freely communicate without censorship and allow that to happen until the Net becomes the central and irreversible pillar of human society. If the Internet had been highly censored from the start many would have rejected it.

3. Fund and manipulate major corporations into being to control the circulation of information on your Internet using cover stories about geeks in garages to explain how they came about. Give them unlimited funds to expand rapidly with no need to make a profit for years while non-Cult companies who need to balance the books cannot compete. You know that in these circumstances your Googles, YouTubes, Facebooks and Amazons are going to secure near monopolies by either crushing or buying up the opposition.

4. Allow freedom of expression on both the Internet and communication platforms to draw people in until the Internet is the central and irreversible pillar of human society and your communication corporations have reached a stage of near monopoly domination.

5. Then unleash your always-planned frenzy of censorship on the basis of 'where else are you going to go?' and continue to expand that until nothing remains that the Cult does not want its human targets to see.

The process was timed to hit the 'Covid' hoax to ensure the best chance possible of controlling the narrative which they knew they had to do at all costs. They were, after all, about to unleash a 'deadly virus' that didn't really exist. If you do that in an environment of free-flowing information and opinion you would be dead in the

water before you could say Gates is a psychopath. The network was in place through which the Cult-created-and-owned World Health Organization could dictate the 'Covid' narrative and response policy slavishly supported by Cult-owned Internet communication giants and mainstream media while those telling a different story were censored. Google, YouTube, Facebook and Twitter openly announced that they would do this. What else would we expect from Cult-owned operations like Facebook which former executives have confirmed set out to make the platform more addictive than cigarettes and coldly manipulates emotions of its users to sow division between people and groups and scramble the minds of the young? If Zuckerberg lives out the rest of his life without going to jail for crimes against humanity, and most emphatically against the young, it will be a travesty of justice. Still, no matter, cause and effect will catch up with him eventually and the same with Sergey Brin and Larry Page at Google with its CEO Sundar Pichai who fix the Google search results to promote Cult narratives and hide the opposition. Put the same key words into Google and other search engines like DuckDuckGo and you will see how different results can be. Wikipedia is another intensely biased 'encyclopaedia' which skews its content to the Cult agenda. YouTube links to Wikipedia's version of 'Covid' and 'climate change' on video pages in which experts in their field offer a different opinion (even that is increasingly rare with Wojcicki censorship). Into this 'Covid' silence-them network must be added government media censors, sorry 'regulators', such as Ofcom in the UK which imposed tyrannical restrictions on British broadcasters that had the effect of banning me from ever appearing. Just to debate with me about my evidence and views on 'Covid' would mean breaking the fascistic impositions of Ofcom and its CEO career government bureaucrat Melanie Dawes. Gutless British broadcasters tremble at the very thought of fascist Ofcom.

Psychos behind 'Covid'

The reason for the 'Covid' catastrophe in all its facets and forms can be seen by whom and what is driving the policies worldwide in such a coordinated way. Decisions are not being made to protect health, but to target psychology. The dominant group guiding and 'advising' government policy are not medical professionals. They are psychologists and behavioural scientists. Every major country has its own version of this phenomenon and I'll use the British example to show how it works. In many ways the British version has been affecting the wider world in the form of the huge behaviour manipulation network in the UK which operates in other countries. The network involves private companies, government, intelligence and military. The Cabinet Office is at the centre of the government 'Covid' Psyop and part-owns, with 'innovation charity' Nesta, the Behavioural Insights Team (BIT) which claims to be independent of government but patently isn't. The BIT was established in 2010 and its job is to manipulate the psyche of the population to acquiesce to government demands and so much more. It is also known as the 'Nudge Unit', a name inspired by the 2009 book by two ultra-Zionists, Cass Sunstein and Richard Thaler, called *Nudge: Improving Decisions About Health, Wealth, and Happiness*. The book, as with the Behavioural Insights Team, seeks to 'nudge' behaviour (manipulate it) to make the public follow patterns of action and perception that suit those in authority (the Cult). Sunstein is so skilled at this that he advises the World Health Organization and the UK Behavioural Insights Team and was Administrator of the White House Office of Information and Regulatory Affairs in the Obama administration. Biden appointed him to the Department of Homeland Security – another ultra-Zionist in the fold to oversee new immigration laws which is another policy the Cult wants to control. Sunstein is desperate to silence anyone exposing conspiracies and co-authored a 2008 report on the subject in which suggestions were offered to ban 'conspiracy theorizing' or impose 'some kind of tax, financial or otherwise, on those who disseminate such theories'. I guess a psychiatrist's chair is out of the question?

Sunstein's mate Richard Thaler, an 'academic affiliate' of the UK Behavioural Insights Team, is a proponent of 'behavioural economics' which is defined as the study of 'the effects of psychological, cognitive, emotional, cultural and social factors on the decisions of individuals and institutions'. Study the effects so they can be manipulated to be what you want them to be. Other leading names in the development of behavioural economics are ultra-Zionists Daniel Kahneman and Robert J. Shiller and they, with Thaler, won the Nobel Memorial Prize in Economic Sciences for their work in this field. The Behavioural Insights Team is operating at the heart of the UK government and has expanded globally through partnerships with several universities including Harvard, Oxford, Cambridge, University College London (UCL) and Pennsylvania. They claim to have 'trained' (reframed) 20,000 civil servants and run more than 750 projects involving 400 randomised controlled trials in dozens of countries' as another version of mind reframers Common Purpose. BIT works from its office in New York with cities and their agencies, as well as other partners, across the United States and Canada – this is a company part-owned by the British government Cabinet Office. An executive order by President Cult-servant Obama established a US Social and Behavioral Sciences Team in 2015. They all have the same reason for being and that's to brainwash the population directly and by brainwashing those in positions of authority.

'Covid' mind game

Another prime aspect of the UK mind-control network is the 'independent' [joke] Scientific Pandemic Insights Group on Behaviours (SPI-B) which 'provides behavioural science advice aimed at anticipating and helping people adhere to interventions that are recommended by medical or epidemiological experts'. That means manipulating public perception and behaviour to do whatever government tells them to do. It's disgusting and if they really want the public to be 'safe' this lot should all be under lock and key. According to the government website SPI-B consists of

'behavioural scientists, health and social psychologists, anthropologists and historians' and advises the Whitty-Vallance-led Scientific Advisory Group for Emergencies (SAGE) which in turn advises the government on 'the science' (it doesn't) and 'Covid' policy. When politicians say they are being guided by 'the science' this is the rabble in each country they are talking about and that 'science' is dominated by behaviour manipulators to enforce government fascism through public compliance. The Behaviour Insight Team is headed by psychologist David Solomon Halpern, a visiting professor at King's College London, and connects with a national and global web of other civilian and military organisations as the Cult moves towards its goal of fusing them into one fascistic whole in every country through its 'Fusion Doctrine'. The behaviour manipulation network involves, but is not confined to, the Foreign Office; National Security Council; government communications headquarters (GCHQ); MI5; MI6; the Cabinet Office-based Media Monitoring Unit; and the Rapid Response Unit which 'monitors digital trends to spot emerging issues; including misinformation and disinformation; and identifies the best way to respond'.

There is also the 77th Brigade of the UK military which operates like the notorious Israeli military's Unit 8200 in manipulating information and discussion on the Internet by posing as members of the public to promote the narrative and discredit those who challenge it. Here we have the military seeking to manipulate *domestic* public opinion while the Nazis in government are fine with that. Conservative Member of Parliament Tobias Ellwood, an advocate of lockdown and control through 'vaccine passports', is a Lieutenant Colonel reservist in the 77th Brigade which connects with the military operation jHub, the 'innovation centre' for the Ministry of Defence and Strategic Command. jHub has also been involved with the civilian National Health Service (NHS) in 'symptom tracing' the population. The NHS is a key part of this mind control network and produced a document in December, 2020, explaining to staff how to use psychological manipulation with different groups and ages to get them to have the DNA-manipulating 'Covid vaccine'

that's designed to cumulatively rewrite human genetics. The document, called 'Optimising Vaccination Roll Out – Do's and Dont's for all messaging, documents and "communications" in the widest sense', was published by NHS England and the NHS Improvement *Behaviour Change Unit* in partnership with Public Health England and Warwick Business School. I hear the mantra about 'save the NHS' and 'protect the NHS' when we need to scrap the NHS and start again. The current version is far too corrupt, far too anti-human and totally compromised by Cult operatives and their assets. UK government broadcast media censor Ofcom will connect into this web – as will the BBC with its tremendous Ofcom influence – to control what the public see and hear and dictate mass perception. Nuremberg trials must include personnel from all these organisations.

The fear factor

The 'Covid' hoax has led to the creation of the UK Cabinet Office-connected Joint Biosecurity Centre (JBC) which is officially described as providing 'expert advice on pandemics' using its independent [all Cult operations are 'independent'] analytical function to provide real-time analysis about infection outbreaks to identify and respond to outbreaks of Covid-19'. Another role is to advise the government on a response to spikes in infections – 'for example by closing schools or workplaces in local areas where infection levels have risen'. Put another way, promoting the Cult agenda. The Joint Biosecurity Centre is modelled on the Joint Terrorism Analysis Centre which analyses intelligence to set 'terrorism threat levels' and here again you see the fusion of civilian and military operations and intelligence that has led to military intelligence producing documents about 'vaccine hesitancy' and how it can be combated. Domestic civilian matters and opinions should not be the business of the military. The Joint Biosecurity Centre is headed by Tom Hurd, director general of the Office for Security and Counter-Terrorism from the establishment-to-its-fingertips Hurd family. His father is former Foreign Secretary Douglas Hurd. How coincidental that Tom

Hurd went to the elite Eton College and Oxford University with Boris Johnson. Imperial College with its ridiculous computer modeller Neil Ferguson will connect with this gigantic web that will itself interconnect with similar set-ups in other major and not so major countries. Compared with this Cult network the politicians, be they Boris Johnson, Donald Trump or Joe Biden, are bit-part players 'following the science'. The network of psychologists was on the 'Covid' case from the start with the aim of generating maximum fear of the 'virus' to ensure compliance by the population. A government behavioural science group known as SPI-B produced a paper in March, 2020, for discussion by the main government science advisory group known as SAGE. It was headed 'Options for increasing adherence to social distancing measures' and it said the following in a section headed 'Persuasion':

- A substantial number of people still do not feel sufficiently personally threatened; it could be that they are reassured by the low death rate in their demographic group, although levels of concern may be rising. Having a good understanding of the risk has been found to be positively associated with adoption of COVID-19 social distancing measures in Hong Kong.

- The perceived level of personal threat needs to be increased among those who are complacent, using hard-hitting evaluation of options for increasing social distancing emotional messaging. To be effective this must also empower people by making clear the actions they can take to reduce the threat.

- Responsibility to others: There seems to be insufficient understanding of, or feelings of responsibility about, people's role in transmitting the infection to others … Messaging about actions need to be framed positively in terms of protecting oneself and the community, and increase confidence that they will be effective.

- Some people will be more persuaded by appeals to play by the rules, some by duty to the community, and some to personal risk.

> All these different approaches are needed. The messaging also needs to take account of the realities of different people's lives. Messaging needs to take account of the different motivational levers and circumstances of different people.

All this could be achieved the SPI-B psychologists said by *using the media to increase the sense of personal threat* which translates as terrify the shit out of the population, including children, so they all do what we want. That's not happened has it? Those excuses for 'journalists' who wouldn't know journalism if it bit them on the arse (the great majority) have played their crucial part in serving this Cult-government Psyop to enslave their own kids and grandkids. How they live with themselves I have no idea. The psychological war has been underpinned by constant government 'Covid' propaganda in almost every television and radio ad break, plus the Internet and print media, which has pounded out the fear with taxpayers footing the bill for their own programming. The result has been people terrified of a 'virus' that doesn't exist or one with a tiny fatality rate even if you believe it does. People walk down the street and around the shops wearing face-nappies damaging their health and psychology while others report those who refuse to be that naïve to the police who turn up in their own face-nappies. I had a cameraman come to my flat and he was so frightened of 'Covid' he came in wearing a mask and refused to shake my hand in case he caught something. He had – naïveitis – and the thought that he worked in the mainstream media was both depressing and made his behaviour perfectly explainable. The fear which has gripped the minds of so many and frozen them into compliance has been carefully cultivated by these psychologists who are really psychopaths. If lives get destroyed and a lot of young people commit suicide it shows our plan is working. SPI-B then turned to compulsion on the public to comply. 'With adequate preparation, rapid change can be achieved', it said. Some countries had introduced mandatory self-isolation on a wide scale without evidence of major public unrest and a large majority of the UK's population appeared to be supportive of more coercive measures with 64 percent of adults saying they would

support putting London under a lockdown (watch the 'polls' which are designed to make people believe that public opinion is in favour or against whatever the subject in hand).

For 'aggressive protective measures' to be effective, the SPI-B paper said, special attention should be devoted to those population groups that are more at risk. Translated from the Orwellian this means making the rest of population feel guilty for not protecting the 'vulnerable' such as old people which the Cult and its agencies were about to kill on an industrial scale with lockdown, lack of treatment and the Gates 'vaccine'. Psychopath psychologists sold their guilt-trip so comprehensively that Los Angeles County Supervisor Hilda Solis reported that children were apologising (from a distance) to their parents and grandparents for bringing 'Covid' into their homes and getting them sick. '… These apologies are just some of the last words that loved ones will ever hear as they die alone,' she said. Gut-wrenchingly Solis then used this childhood tragedy to tell children to stay at home and 'keep your loved ones alive'. Imagine heaping such potentially life-long guilt on a kid when it has absolutely nothing to do with them. These people are deeply disturbed and the psychologists behind this even more so.

Uncivil war – divide and rule

Professional mind-controllers at SPI-B wanted the media to increase a sense of responsibility to others (do as you're told) and promote 'positive messaging' for those actions while in contrast to invoke 'social disapproval' by the unquestioning, obedient, community of anyone with a mind of their own. Again the compliant Goebbels-like media obliged. This is an old, old, trick employed by tyrannies the world over throughout human history. You get the target population to keep the target population in line – *your* line. SPI-B said this could 'play an important role in preventing anti-social behaviour or discouraging failure to enact pro-social behaviour'. For 'anti-social' in the Orwellian parlance of SPI-B see any behaviour that government doesn't approve. SPI-B recommendations said that 'social disapproval' should be accompanied by clear messaging and

promotion of strong collective identity – hence the government and celebrity mantra of 'we're all in this together'. Sure we are. The mind doctors have such contempt for their targets that they think some clueless comedian, actor or singer telling them to do what the government wants will be enough to win them over. We have had UK comedian Lenny Henry, actor Michael Caine and singer Elton John wheeled out to serve the propagandists by urging people to have the DNA-manipulating 'Covid' non-'vaccine'. The role of Henry and fellow black celebrities in seeking to coax a 'vaccine' reluctant black community into doing the government's will was especially stomach-turning. An emotion-manipulating script and carefully edited video featuring these black 'celebs' was such an insult to the intelligence of black people and where's the self-respect of those involved selling their souls to a fascist government agenda? Henry said he heard black people's 'legitimate worries and concerns', but people must 'trust the facts' when they were doing exactly that by not having the 'vaccine'. They had to include the obligatory reference to Black Lives Matter with the line … 'Don't let coronavirus cost even more black lives – because we matter'. My god, it was pathetic. 'I know the vaccine is safe and what it does.' How? 'I'm a comedian and it says so in my script.'

SPI-B said social disapproval needed to be carefully managed to avoid victimisation, scapegoating and misdirected criticism, but they knew that their 'recommendations' would lead to exactly that and the media were specifically used to stir-up the divide-and-conquer hostility. Those who conform like good little baa, baas, are praised while those who have seen through the tidal wave of lies are 'Covidiots'. The awake have been abused by the fast asleep for not conforming to fascism and impositions that the awake know are designed to endanger their health, dehumanise them, and tear asunder the very fabric of human society. We have had the curtain-twitchers and morons reporting neighbours and others to the face-nappied police for breaking 'Covid rules' with fascist police delighting in posting links and phone numbers where this could be done. The Cult cannot impose its will without a compliant police

and military or a compliant population willing to play their part in enslaving themselves and their kids. The words of a pastor in Nazi Germany are so appropriate today:

First they came for the socialists and I did not speak out because I was not a socialist.

Then they came for the trade unionists and I did not speak out because I was not a trade unionist.

Then they came for the Jews and I did not speak out because I was not a Jew.

Then they came for me and there was no one left to speak for me.

Those who don't learn from history are destined to repeat it and so many are.

'Covid' rules: Rewiring the mind

With the background laid out to this gigantic national and global web of psychological manipulation we can put 'Covid' rules into a clear and sinister perspective. Forget the claims about protecting health. 'Covid' rules are about dismantling the human mind, breaking the human spirit, destroying self-respect, and then putting Humpty Dumpty together again as a servile, submissive slave. Social isolation through lockdown and distancing have devastating effects on the human psyche as the psychological psychopaths well know and that's the real reason for them. Humans need contact with each other, discourse, closeness and touch, or they eventually, and literarily, go crazy. Masks, which I will address at some length, fundamentally add to the effects of isolation and the Cult agenda to dehumanise and de-individualise the population. To do this while knowing – in fact *seeking* – this outcome is the very epitome of evil and psychologists involved in this *are* the epitome of evil. They must like all the rest of the Cult demons and their assets stand trial for crimes against humanity on a scale that defies the imagination. Psychopaths in uniform use isolation to break enemy troops and agents and make them subservient and submissive to tell what they know. The technique is rightly considered a form of torture and

torture is most certainly what has been imposed on the human population.

Clinically-insane American psychologist Harry Harlow became famous for his isolation experiments in the 1950s in which he separated baby monkeys from their mothers and imprisoned them for months on end in a metal container or 'pit of despair'. They soon began to show mental distress and depression as any idiot could have predicted. Harlow put other monkeys in steel chambers for three, six or twelve months while denying them any contact with animals or humans. He said that the effects of total social isolation for six months were 'so devastating and debilitating that we had assumed initially that twelve months of isolation would not produce any additional decrement'; but twelve months of isolation 'almost obliterated the animals socially'. This is what the Cult and its psychopaths are doing to you and your children. Even monkeys in partial isolation in which they were not allowed to form relationships with other monkeys became 'aggressive and hostile, not only to others, but also towards their own bodies'. We have seen this in the young as a consequence of lockdown. UK government psychopaths launched a public relations campaign telling people not to hug each other even after they received the 'Covid-19 vaccine' which we were told with more lies would allow a return to 'normal life'. A government source told *The Telegraph*: 'It will be along the lines that it is great that you have been vaccinated, but if you are going to visit your family and hug your grandchildren there is a chance you are going to infect people you love.' The source was apparently speaking from a secure psychiatric facility. Janet Lord, director of Birmingham University's Institute of Inflammation and Ageing, said that parents and grandparents should avoid hugging their children. Well, how can I put it, Ms Lord? Fuck off. Yep, that'll do.

Destroying the kids – where are the parents?

Observe what has happened to people enslaved and isolated by lockdown as suicide and self-harm has soared worldwide,

particularly among the young denied the freedom to associate with their friends. A study of 49,000 people in English-speaking countries concluded that almost half of young adults are at clinical risk of mental health disorders. A national survey in America of 1,000 currently enrolled high school and college students found that 5 percent reported attempting suicide during the pandemic. Data from the US CDC's National Syndromic Surveillance Program from January 1st to October 17th, 2020, revealed a *31 percent* increase in mental health issues among adolescents aged 12 to 17 compared with 2019. The CDC reported that America in general suffered the biggest drop in life expectancy since World War Two as it fell by a year in the first half of 2020 as a result of 'deaths of despair' – overdoses and suicides. Deaths of despair have leapt by more than 20 percent during lockdown and include the highest number of fatal overdoses ever recorded in a single year – 81,000. Internet addiction is another consequence of being isolated at home which lowers interest in physical activities as kids fall into inertia and what's the point? Children and young people are losing hope and giving up on life, sometimes literally. A 14-year-old boy killed himself in Maryland because he had 'given up' when his school district didn't reopen; an 11-year-old boy shot himself during a zoom class; a teenager in Maine succumbed to the isolation of the 'pandemic' when he ended his life after experiencing a disrupted senior year at school. Children as young as nine have taken their life and all these stories can be repeated around the world. Careers are being destroyed before they start and that includes those in sport in which promising youngsters have not been able to take part. The plan of the psycho-psychologists is working all right. Researchers at Cambridge University found that lockdowns cause significant harm to children's mental health. Their study was published in the *Archives of Disease in Childhood*, and followed 168 children aged between 7 and 11. The researchers concluded:

> During the UK lockdown, children's depression symptoms have increased substantially, relative to before lockdown. The scale of this effect has direct relevance for the continuation of different elements of lockdown policy, such as complete or partial school closures …

… Specifically, we observed a statistically significant increase in ratings of depression, with a medium-to-large effect size. Our findings emphasise the need to incorporate the potential impact of lockdown on child mental health in planning the ongoing response to the global pandemic and the recovery from it.

Not a chance when the Cult's psycho-psychologists were getting exactly what they wanted. The UK's Royal College of Paediatrics and Child Health has urged parents to look for signs of eating disorders in children and young people after a three to four fold increase. Specialists say the 'pandemic' is a major reason behind the rise. You don't say. The College said isolation from friends during school closures, exam cancellations, loss of extra-curricular activities like sport, and an increased use of social media were all contributory factors along with fears about the virus (psycho-psychologists again), family finances, and students being forced to quarantine. Doctors said young people were becoming severely ill by the time they were seen with 'Covid' regulations reducing face-to-face consultations. Nor is it only the young that have been devastated by the psychopaths. Like all bullies and cowards the Cult is targeting the young, elderly, weak and infirm. A typical story was told by a British lady called Lynn Parker who was not allowed to visit her husband in 2020 for the last ten and half months of his life 'when he needed me most' between March 20th and when he died on December 19th. This vacates the criminal and enters the territory of evil. The emotional impact on the immune system alone is immense as are the number of people of all ages worldwide who have died as a result of Cult-demanded, Gates-demanded, lockdowns.

Isolation is torture

The experience of imposing solitary confinement on millions of prisoners around the world has shown how a large percentage become 'actively psychotic and/or acutely suicidal'. Social isolation has been found to trigger 'a specific psychiatric syndrome, characterized by hallucinations; panic attacks; overt paranoia; diminished impulse control; hypersensitivity to external stimuli; and difficulties with thinking, concentration and memory'. Juan Mendez,

a United Nations rapporteur (investigator), said that isolation is a form of torture. Research has shown that even after isolation prisoners find it far more difficult to make social connections and I remember chatting to a shop assistant after one lockdown who told me that when her young son met another child again he had no idea how to act or what to do. Hannah Flanagan, Director of Emergency Services at Journey Mental Health Center in Dane County, Wisconsin, said: 'The specificity about Covid social distancing and isolation that we've come across as contributing factors to the suicides are really new to us this year.' But they are not new to those that devised them. They are getting the effect they want as the population is psychologically dismantled to be rebuilt in a totally different way. Children and the young are particularly targeted. They will be the adults when the full-on fascist AI-controlled technocracy is planned to be imposed and they are being prepared to meekly submit. At the same time older people who still have a memory of what life was like before – and how fascist the new normal really is – are being deleted. You are going to see efforts to turn the young against the old to support this geriatric genocide. Hannah Flanagan said the big increase in suicide in her county proved that social isolation is not only harmful, but deadly. Studies have shown that isolation from others is one of the main risk factors in suicide and even more so with women. Warnings that lockdown could create a 'perfect storm' for suicide were ignored. After all this was one of the *reasons* for lockdown. Suicide, however, is only the most extreme of isolation consequences. There are many others. Dr Dhruv Khullar, assistant professor of healthcare policy at Weill Cornell Medical College, said in a *New York Times* article in 2016 long before the fake 'pandemic':

> A wave of new research suggests social separation is bad for us. Individuals with less social connection have disrupted sleep patterns, altered immune systems, more inflammation and higher levels of stress hormones. One recent study found that isolation increases the risk of heart disease by 29 percent and stroke by 32 percent. Another analysis that pooled data from 70 studies and 3.4 million people found that socially isolated individuals had a 30 percent higher risk of dying in the next seven years, and that this effect was largest in middle age.

Loneliness can accelerate cognitive decline in older adults, and isolated individuals are twice as likely to die prematurely as those with more robust social interactions. These effects start early: Socially isolated children have significantly poorer health 20 years later, even after controlling for other factors. All told, loneliness is as important a risk factor for early death as obesity and smoking.

There you have proof from that one article alone four years before 2020 that those who have enforced lockdown, social distancing and isolation knew what the effect would be and that is even more so with professional psychologists that have been driving the policy across the globe. We can go back even further to the years 2000 and 2003 and the start of a major study on the effects of isolation on health by Dr Janine Gronewold and Professor Dirk M. Hermann at the University Hospital in Essen, Germany, who analysed data on 4,316 people with an average age of 59 who were recruited for the long-term research project. They found that socially isolated people are more than 40 percent more likely to have a heart attack, stroke, or other major cardiovascular event and nearly 50 percent more likely to die from any cause. Given the financial Armageddon unleashed by lockdown we should note that the study found a relationship between increased cardiovascular risk and lack of financial support. After excluding other factors social isolation was still connected to a 44 percent increased risk of cardiovascular problems and a 47 percent increased risk of death by any cause. Lack of financial support was associated with a 30 percent increase in the risk of cardiovascular health events. Dr Gronewold said it had been known for some time that feeling lonely or lacking contact with close friends and family can have an impact on physical health and the study had shown that having strong social relationships is of high importance for heart health. Gronewold said they didn't understand yet why people who are socially isolated have such poor health outcomes, but this was obviously a worrying finding, particularly during these times of prolonged social distancing. Well, it can be explained on many levels. You only have to identify the point in the body where people feel loneliness and missing people they are parted from – it's in the centre of the chest where they feel the ache of loneliness and the ache of missing people. 'My heart aches for

you' … 'My heart aches for some company.' I will explain this more in the chapter Escaping Wetiko, but when you realise that the body is the mind – they are expressions of each other – the reason why state of the mind dictates state of the body becomes clear.

American psychologist Ranjit Powar was highlighting the effects of lockdown isolation as early as April, 2020. She said humans have evolved to be social creatures and are wired to live in interactive groups. Being isolated from family, friends and colleagues could be unbalancing and traumatic for most people and could result in short or even long-term psychological and physical health problems. An increase in levels of anxiety, aggression, depression, forgetfulness and hallucinations were possible psychological effects of isolation. 'Mental conditions may be precipitated for those with underlying pre-existing susceptibilities and show up in many others without any pre-condition.' Powar said personal relationships helped us cope with stress and if we lost this outlet for letting off steam the result can be a big emotional void which, for an average person, was difficult to deal with. 'Just a few days of isolation can cause increased levels of anxiety and depression' – so what the hell has been the effect on the global population of *18 months* of this at the time of writing? Powar said: 'Add to it the looming threat of a dreadful disease being repeatedly hammered in through the media and you have a recipe for many shades of mental and physical distress.' For those with a house and a garden it is easy to forget that billions have had to endure lockdown isolation in tiny overcrowded flats and apartments with nowhere to go outside. The psychological and physical consequences of this are unimaginable and with lunatic and abusive partners and parents the consequences have led to tremendous increases in domestic and child abuse and alcoholism as people seek to shut out the horror. Ranjit Powar said:

Staying in a confined space with family is not all a rosy picture for everyone. It can be extremely oppressive and claustrophobic for large low-income families huddled together in small single-room houses. Children here are not lucky enough to have many board/electronic games or books to keep them occupied.

Add to it the deep insecurity of running out of funds for food and basic necessities. On the other hand, there are people with dysfunctional family dynamics, such as domineering, abusive or alcoholic partners, siblings or parents which makes staying home a period of trial. Incidence of suicide and physical abuse against women has shown a worldwide increase. Heightened anxiety and depression also affect a person's immune system, making them more susceptible to illness.

To think that Powar's article was published on April 11th, 2020.

Six-feet fantasy

Social (unsocial) distancing demanded that people stay six feet or two metres apart. UK government advisor Robert Dingwall from the New and Emerging Respiratory Virus Threats Advisory Group said in a radio interview that the two-metre rule was 'conjured up out of nowhere' and was not based on science. No, it was not based on *medical* science, but it didn't come out of nowhere. The distance related to *psychological* science. Six feet/two metres was adopted in many countries and we were told by people like the criminal Anthony Fauci and his ilk that it was founded on science. Many schools could not reopen because they did not have the space for six-feet distancing. Then in March, 2021, after a year of six-feet 'science', a study published in the *Journal of Infectious Diseases* involving more than 500,000 students and almost 100,000 staff over 16 weeks revealed no significant difference in 'Covid' cases between six feet and three feet and Fauci changed his tune. Now three feet was okay. There is no difference between six feet and three *inches* when there is no 'virus' and they got away with six feet for psychological reasons for as long as they could. I hear journalists and others talk about 'unintended consequences' of lockdown. They are not *unintended* at all; they have been coldly-calculated for a specific outcome of human control and that's why super-psychopaths like Gates have called for them so vehemently. Super-psychopath psychologists have demanded them and psychopathic or clueless, spineless, politicians have gone along with them by 'following the science'. But it's not science at all. 'Science' is not what is; it's only what people can be manipulated to believe it is. The whole 'Covid' catastrophe is

founded on mind control. Three word or three statement mantras issued by the UK government are a well-known mind control technique and so we've had 'Stay home/protect the NHS/save lives', 'Stay alert/control the virus/save lives' and 'hands/face/space'. One of the most vocal proponents of extreme 'Covid' rules in the UK has been Professor Susan Michie, a member of the British Communist Party, who is not a medical professional. Michie is the director of the Centre for Behaviour Change at University College London. She is a *behavioural psychologist* and another filthy rich 'Marxist' who praised China's draconian lockdown. She was known by fellow students at Oxford University as 'Stalin's nanny' for her extreme Marxism. Michie is an influential member of the UK government's Scientific Advisory Group for Emergencies (SAGE) and behavioural manipulation groups which have dominated 'Covid' policy. She is a consultant adviser to the World Health Organization on 'Covid-19' and behaviour. Why the hell are lockdowns anything to do with her when they are claimed to be about health? Why does a behavioural psychologist from a group charged with changing the behaviour of the public want lockdown, human isolation and mandatory masks? Does that question really need an answer? Michie *absolutely* has to explain herself before a Nuremberg court when humanity takes back its world again and even more so when you see the consequences of masks that she demands are compulsory. This is a Michie classic:

> The benefits of getting primary school children to wear masks is that regardless of what little degree of transmission is occurring in those age groups it could help normalise the practice. Young children wearing masks may be more likely to get their families to accept masks.

Those words alone should carry a prison sentence when you ponder on the callous disregard for children involved and what a statement it makes about the mind and motivations of Susan Michie. What a lovely lady and what she said there encapsulates the mentality of the psychopaths behind the 'Covid' horror. Let us compare what Michie said with a countrywide study in Germany published at researchsquare.com involving 25,000 school children and 17,854 health complaints submitted by parents. Researchers

found that masks are harming children physically, psychologically, and behaviourally with 24 health issues associated with mask wearing. They include: shortness of breath (29.7%); dizziness (26.4%); increased headaches (53%); difficulty concentrating (50%); drowsiness or fatigue (37%); and malaise (42%). Nearly a third of children experienced more sleep issues than before and a quarter developed new fears. Researchers found health issues and other impairments in 68 percent of masked children covering their faces for an average of 4.5 hours a day. Hundreds of those taking part experienced accelerated respiration, tightness in the chest, weakness, and short-term impairment of consciousness. A reminder of what Michie said again:

The benefits of getting primary school children to wear masks is that regardless of what little degree of transmission is occurring in those age groups it could help normalise the practice. Young children wearing masks may be more likely to get their families to accept masks.

Psychopaths in government and psychology now have children and young people – plus all the adults – wearing masks for hours on end while clueless teachers impose the will of the psychopaths on the young they should be protecting. What the hell are parents doing?

Cult lab rats

We have some schools already imposing on students microchipped buzzers that activate when they get 'too close' to their pals in the way they do with lab rats. How apt. To the Cult and its brain-dead servants our children *are* lab rats being conditioned to be unquestioning, dehumanised slaves for the rest of their lives. Children and young people are being weaned and frightened away from the most natural human instincts including closeness and touch. I have tracked in the books over the years how schools were banning pupils from greeting each other with a hug and the whole Cult-induced Me Too movement has terrified men and boys from a relaxed and natural interaction with female friends and work colleagues to the point where many men try never to be in a room

alone with a woman that's not their partner. Airhead celebrities have as always played their virtue-signalling part in making this happen with their gross exaggeration. For every monster like Harvey Weinstein there are at least tens of thousands of men that don't treat women like that; but everyone must be branded the same and policy changed for them as well as the monster. I am going to be using the word 'dehumanise' many times in this chapter because that is what the Cult is seeking to do and it goes very deep as we shall see. Don't let them kid you that social distancing is planned to end one day. That's not the idea. We are seeing more governments and companies funding and producing wearable gadgets to keep people apart and they would not be doing that if this was meant to be short-term. A tech start-up company backed by GCHQ, the British Intelligence and military surveillance headquarters, has created a social distancing wrist sensor that alerts people when they get too close to others. The CIA has also supported tech companies developing similar devices. The wearable sensor was developed by Tended, one of a number of start-up companies supported by GCHQ (see the CIA and DARPA). The device can be worn on the wrist or as a tag on the waistband and will vibrate whenever someone wearing the device breaches social distancing and gets anywhere near natural human contact. The company had a lucky break in that it was developing a distancing sensor when the 'Covid' hoax arrived which immediately provided a potentially enormous market. How fortunate. The government in big-time Cult-controlled Ontario in Canada is investing $2.5 million in wearable contact tracing technology that 'will alert users if they may have been exposed to the Covid-19 in the workplace and will beep or vibrate if they are within six feet of another person'. Facedrive Inc., the technology company behind this, was founded in 2016 with funding from the Ontario Together Fund and obviously they, too, had a prophet on the board of directors. The human surveillance and control technology is called TraceSCAN and would be worn by the human cyborgs in places such as airports, workplaces, construction sites, care homes and … *schools*.

I emphasise schools with children and young people the prime targets. You know what is planned for society as a whole if you keep your eyes on the schools. They have always been places where the state program the next generation of slaves to be its compliant worker-ants – or Woker-ants these days; but in the mist of the 'Covid' madness they have been transformed into mind laboratories on a scale never seen before. Teachers and head teachers are just as programmed as the kids – often more so. Children are kept apart from human interaction by walk lanes, classroom distancing, staggered meal times, masks, and the rolling-out of buzzer systems. Schools are now physically laid out as a laboratory maze for lab-rats. Lunatics at a school in Anchorage, Alaska, who should be prosecuted for child abuse, took away desks and forced children to kneel (know your place) on a mat for five hours a day while wearing a mask and using their chairs as a desk. How this was supposed to impact on a 'virus' only these clinically insane people can tell you and even then it would be clap-trap. The school banned recess (interaction), art classes (creativity), and physical exercise (getting body and mind moving out of inertia). Everyone behind this outrage should be in jail or better still a mental institution. The behavioural manipulators are all for this dystopian approach to schools. Professor Susan Michie, the mind-doctor and British Communist Party member, said it was wrong to say that schools were safe. They had to be made so by 'distancing', masks and ventilation (sitting all day in the cold). I must ask this lady round for dinner on a night I know I am going to be out and not back for weeks. She probably wouldn't be able to make it, anyway, with all the visits to her own psychologist she must have block-booked.

Masking identity

I know how shocking it must be for you that a behaviour manipulator like Michie wants everyone to wear masks which have long been a feature of mind-control programs like the infamous MKUltra in the United States, but, there we are. We live and learn. I spent many years from 1996 to right across the millennium

researching mind control in detail on both sides of the Atlantic and elsewhere. I met a large number of mind-control survivors and many had been held captive in body and mind by MKUltra. MK stands for mind-control, but employs the German spelling in deference to the Nazis spirited out of Germany at the end of World War Two by Operation Paperclip in which the US authorities, with help from the Vatican, transported Nazi mind-controllers and engineers to America to continue their work. Many of them were behind the creation of NASA and they included Nazi scientist and SS officer Wernher von Braun who swapped designing V-2 rockets to bombard London with designing the Saturn V rockets that powered the NASA moon programme's Apollo craft. I think I may have mentioned that the Cult has no borders. Among Paperclip escapees was Josef Mengele, the Angel of Death in the Nazi concentration camps where he conducted mind and genetic experiments on children often using twins to provide a control twin to measure the impact of his 'work' on the other. If you want to observe the Cult mentality in all its extremes of evil then look into the life of Mengele. I have met many people who suffered mercilessly under Mengele in the United States where he operated under the name Dr Greene and became a stalwart of MKUltra programming and torture. Among his locations was the underground facility in the Mojave Desert in California called the China Lake Naval Weapons Station which is almost entirely below the surface. My books *The Biggest Secret*, *Children of the Matrix* and *The Perception Deception* have the detailed background to MKUltra.

The best-known MKUltra survivor is American Cathy O'Brien. I first met her and her late partner Mark Phillips at a conference in Colorado in 1996. Mark helped her escape and deprogram from decades of captivity in an offshoot of MKUltra known as Project Monarch in which 'sex slaves' were provided for the rich and famous including Father George Bush, Dick Cheney and the Clintons. Read Cathy and Mark's book *Trance-Formation of America* and if you are new to this you will be shocked to the core. I read it in 1996 shortly before, with the usual synchronicity of my life, I found

myself given a book table at the conference right next to hers. MKUltra never ended despite being very publicly exposed (only a small part of it) in the 1970s and continues in other guises. I am still in touch with Cathy. She contacted me during 2020 after masks became compulsory in many countries to tell me how they were used as part of MKUltra programming. I had been observing 'Covid regulations' and the relationship between authority and public for months. I saw techniques that I knew were employed on individuals in MKUltra being used on the global population. I had read many books and manuals on mind control including one called *Silent Weapons for Quiet Wars* which came to light in the 1980s and was a guide on how to perceptually program on a mass scale. 'Silent Weapons' refers to mind-control. I remembered a line from the manual as governments, medical authorities and law enforcement agencies have so obviously talked to – or rather at – the adult population since the 'Covid' hoax began as if they are children. The document said:

> If a person is spoken to by a T.V. advertiser as if he were a twelve-year-old, then, due to suggestibility, he will, with a certain probability, respond or react to that suggestion with the uncritical response of a twelve-year-old and will reach in to his economic reservoir and deliver its energy to buy that product on impulse when he passes it in the store.

That's why authority has spoken to adults like children since all this began.

Why did Michael Jackson wear masks?

Every aspect of the 'Covid' narrative has mind-control as its central theme. Cathy O'Brien wrote an article for davidicke.com about the connection between masks and mind control. Her daughter Kelly who I first met in the 1990s was born while Cathy was still held captive in MKUltra. Kelly was forced to wear a mask as part of her programming from the age of *two* to dehumanise her, target her sense of individuality and reduce the amount of oxygen her brain and body received. *Bingo*. This is the real reason for compulsory

masks, why they have been enforced en masse, and why they seek to increase the number they demand you wear. First one, then two, with one disgraceful alleged 'doctor' recommending four which is nothing less than a death sentence. Where and how often they must be worn is being expanded for the purpose of mass mind control and damaging respiratory health which they can call 'Covid-19'. Canada's government headed by the man-child Justin Trudeau, says it's fine for children of two and older to wear masks. An insane 'study' in Italy involving just 47 children concluded there was no problem for babies as young as *four months* wearing them. Even after people were 'vaccinated' they were still told to wear masks by the criminal that is Anthony Fauci. Cathy wrote that mandating masks is allowing the authorities literally to control the air we breathe which is what was done in MKUltra. You might recall how the singer Michael Jackson wore masks and there is a reason for that. He was subjected to MKUltra mind control through Project Monarch and his psyche was scrambled by these simpletons. Cathy wrote:

In MKUltra Project Monarch mind control, Michael Jackson had to wear a mask to silence his voice so he could not reach out for help. Remember how he developed that whisper voice when he wasn't singing? Masks control the mind from the outside in, like the redefining of words is doing. By controlling what we can and cannot say for fear of being labeled racist or beaten, for example, it ultimately controls thought that drives our words and ultimately actions (or lack thereof).

Likewise, a mask muffles our speech so that we are not heard, which controls voice … words … mind. This is Mind Control. Masks are an obvious mind control device, and I am disturbed so many people are complying on a global scale. Masks depersonalize while making a person feel as though they have no voice. It is a barrier to others. People who would never choose to comply but are forced to wear a mask in order to keep their job, and ultimately their family fed, are compromised. They often feel shame and are subdued. People have stopped talking with each other while media controls the narrative.

The 'no voice' theme has often become literal with train passengers told not to speak to each other in case they pass on the 'virus', singing banned for the same reason and bonkers California officials telling people riding roller coasters that they cannot shout and scream. Cathy said she heard every day from healed MKUltra survivors who cannot wear a mask without flashing back on ways

their breathing was controlled – 'from ball gags and penises to water boarding'. She said that through the years when she saw images of people in China wearing masks 'due to pollution' that it was really to control their oxygen levels. 'I knew it was as much of a population control mechanism of depersonalisation as are burkas', she said. Masks are another Chinese communist/fascist method of control that has been swept across the West as the West becomes China at lightning speed since we entered 2020.

Mask-19

There are other reasons for mandatory masks and these include destroying respiratory health to call it 'Covid-19' and stunting brain development of children and the young. Dr Margarite Griesz-Brisson MD, PhD, is a Consultant Neurologist and Neurophysiologist and the Founder and Medical Director of the London Neurology and Pain Clinic. Her CV goes down the street and round the corner. She is clearly someone who cares about people and won't parrot the propaganda. Griesz-Brisson has a PhD in pharmacology, with special interest in neurotoxicology, environmental medicine, neuroregeneration and neuroplasticity (the way the brain can change in the light of information received). She went public in October, 2020, with a passionate warning about the effects of mask-wearing laws:

> The reinhalation of our exhaled air will without a doubt create oxygen deficiency and a flooding of carbon dioxide. We know that the human brain is very sensitive to oxygen deprivation. There are nerve cells for example in the hippocampus that can't be longer than 3 minutes without oxygen – they cannot survive. The acute warning symptoms are headaches, drowsiness, dizziness, issues in concentration, slowing down of reaction time – reactions of the cognitive system.

Oh, I know, let's tell bus, truck and taxi drivers to wear them and people working machinery. How about pilots, doctors and police? Griesz-Brisson makes the important point that while the symptoms she mentions may fade as the body readjusts this does not alter the fact that people continue to operate in oxygen deficit with long list of

potential consequences. She said it was well known that neurodegenerative diseases take years or decades to develop. 'If today you forget your phone number, the breakdown in your brain would have already started 20 or 30 years ago.' She said degenerative processes in your brain are getting amplified as your oxygen deprivation continues through wearing a mask. Nerve cells in the brain are unable to divide themselves normally in these circumstances and lost nerve cells will no longer be regenerated. 'What is gone is gone.' Now consider that people like shop workers and *schoolchildren* are wearing masks for hours every day. What in the name of sanity is going to be happening to them? 'I do not wear a mask, I need my brain to think', Griesz-Brisson said, 'I want to have a clear head when I deal with my patients and not be in a carbon dioxide-induced anaesthesia'. If you are told to wear a mask anywhere ask the organisation, police, store, whatever, for their risk assessment on the dangers and negative effects on mind and body of enforcing mask-wearing. They won't have one because it has never been done not even by government. All of them must be subject to class-action lawsuits as the consequences come to light. They don't do mask risk assessments for an obvious reason. They know what the conclusions would be and independent scientific studies that *have* been done tell a horror story of consequences.

'Masks are criminal'

Dr Griesz-Brisson said that for children and adolescents, masks are an absolute no-no. They had an extremely active and adaptive immune system and their brain was incredibly active with so much to learn. 'The child's brain, or the youth's brain, is thirsting for oxygen.' The more metabolically active an organ was, the more oxygen it required; and in children and adolescents every organ was metabolically active. Griesz-Brisson said that to deprive a child's or adolescent's brain of oxygen, or to restrict it in any way, was not only dangerous to their health, it was absolutely criminal. 'Oxygen deficiency inhibits the development of the brain, and the damage that has taken place as a result CANNOT be reversed.' Mind

manipulators of MKUltra put masks on two-year-olds they wanted to neurologically rewire and you can see why. Griesz-Brisson said a child needs the brain to learn and the brain needs oxygen to function. 'We don't need a clinical study for that. This is simple, indisputable physiology.' Consciously and purposely induced oxygen deficiency was an absolutely deliberate health hazard, and an absolute medical contraindication which means that 'this drug, this therapy, this method or measure should not be used, and is not allowed to be used'. To coerce an entire population to use an absolute medical contraindication by force, she said, there had to be definite and serious reasons and the reasons must be presented to competent interdisciplinary and independent bodies to be verified and authorised. She had this warning of the consequences that were coming if mask wearing continued:

When, in ten years, dementia is going to increase exponentially, and the younger generations couldn't reach their god-given potential, it won't help to say 'we didn't need the masks'. I know how damaging oxygen deprivation is for the brain, cardiologists know how damaging it is for the heart, pulmonologists know how damaging it is for the lungs. Oxygen deprivation damages every single organ. Where are our health departments, our health insurance, our medical associations? It would have been their duty to be vehemently against the lockdown and to stop it and stop it from the very beginning.

Why do the medical boards issue punishments to doctors who give people exemptions? Does the person or the doctor seriously have to prove that oxygen deprivation harms people? What kind of medicine are our doctors and medical associations representing? Who is responsible for this crime? The ones who want to enforce it? The ones who let it happen and play along, or the ones who don't prevent it?

All of the organisations and people she mentions there either answer directly to the Cult or do whatever hierarchical levels above them tell them to do. The outcome of both is the same. 'It's not about masks, it's not about viruses, it's certainly not about your health', Griesz-Brisson said. 'It is about much, much more. I am not participating. I am not afraid.' They were taking our air to breathe and there was no unfounded medical exemption from face masks. Oxygen deprivation was dangerous for every single brain. It had to be the free decision of every human being whether they want to

wear a mask that was absolutely ineffective to protect themselves from a virus. She ended by rightly identifying where the responsibility lies for all this:

> The imperative of the hour is personal responsibility. We are responsible for what we think, not the media. We are responsible for what we do, not our superiors. We are responsible for our health, not the World Health Organization. And we are responsible for what happens in our country, not the government.

Halle-bloody-lujah.

But surgeons wear masks, right?

Independent studies of mask-wearing have produced a long list of reports detailing mental, emotional and physical dangers. What a definition of insanity to see police officers imposing mask-wearing on the public which will cumulatively damage their health while the police themselves wear masks that will cumulatively damage *their* health. It's utter madness and both public and police do this because 'the government says so' – yes a government of brain-donor idiots like UK Health Secretary Matt Hancock reading the 'follow the science' scripts of psychopathic, lunatic psychologists. The response you get from Stockholm syndrome sufferers defending the very authorities that are destroying them and their families is that 'surgeons wear masks'. This is considered the game, set and match that they must work and don't cause oxygen deficit. Well, actually, scientific studies have shown that they *do* and oxygen levels are monitored in operating theatres to compensate. Surgeons wear masks to stop spittle and such like dropping into open wounds – not to stop 'viral particles' which are so miniscule they can only be seen through an electron microscope. Holes in the masks are significantly bigger than 'viral particles' and if you sneeze or cough they will breach the mask. I watched an incredibly disingenuous 'experiment' that claimed to prove that masks work in catching 'virus' material from the mouth and nose. They did this with a slow motion camera and the mask did block big stuff which stayed inside the mask and

against the face to be breathed in or cause infections on the face as we have seen with many children. 'Viral particles', however, would never have been picked up by the camera as they came through the mask when they are far too small to be seen. The 'experiment' was therefore disingenuous *and* useless.

Studies have concluded that wearing masks in operating theatres (and thus elsewhere) make no difference to preventing infection while the opposite is true with toxic shite building up in the mask and this had led to an explosion in tooth decay and gum disease dubbed by dentists 'mask mouth'. You might have seen the Internet video of a furious American doctor urging people to take off their masks after a four-year-old patient had been rushed to hospital the night before and nearly died with a lung infection that doctors sourced to mask wearing. A study in the journal *Cancer Discovery* found that inhalation of harmful microbes can contribute to advanced stage lung cancer in adults and long-term use of masks can help breed dangerous pathogens. Microbiologists have said frequent mask wearing creates a moist environment in which microbes can grow and proliferate before entering the lungs. The Canadian Agency for Drugs and Technologies in Health, or CADTH, a Canadian national organisation that provides research and analysis to healthcare decision-makers, said this as long ago as 2013 in a report entitled 'Use of Surgical Masks in the Operating Room: A Review of the Clinical Effectiveness and Guidelines'. It said:

- No evidence was found to support the use of surgical face masks to reduce the frequency of surgical site infections
- No evidence was found on the effectiveness of wearing surgical face masks to protect staff from infectious material in the operating room.
- Guidelines recommend the use of surgical face masks by staff in the operating room to protect both operating room staff and patients (despite the lack of evidence).

We were told that the world could go back to 'normal' with the arrival of the 'vaccines'. When they came, fraudulent as they are, the story changed as I knew that it would. We are in the midst of transforming 'normal', not going back to it. Mary Ramsay, head of immunisation at Public Health England, echoed the words of US criminal Anthony Fauci who said masks and other regulations must stay no matter if people are vaccinated. The Fauci idiot continued to wear two masks – different colours so both could be clearly seen – after he *claimed* to have been vaccinated. Senator Rand Paul told Fauci in one exchange that his double-masks were 'theatre' and he was right. It's all theatre. Mary Ramsay back-tracked on the vaccine-return-to-normal theme when she said the public may need to wear masks and social-distance for years despite the jabs. 'People have got used to those lower-level restrictions now, and [they] can live with them', she said telling us what the idea has been all along. 'The vaccine does not give you a pass, even if you have had it, you must continue to follow all the guidelines' said a Public Health England statement which reneged on what we had been told before and made having the 'vaccine' irrelevant to 'normality' even by the official story. Spain's fascist government trumped everyone by passing a law mandating the wearing of masks on the beach and even when swimming in the sea. The move would have devastated what's left of the Spanish tourist industry, posed potential breathing dangers to swimmers and had Northern European sunbathers walking around with their forehead brown and the rest of their face white as a sheet. The ruling was so crazy that it had to be retracted after pressure from public and tourist industry, but it confirmed where the Cult wants to go with masks and how clinically insane authority has become. The determination to make masks permanent and hide the serious dangers to body and mind can be seen in the censorship of scientist Professor Denis Rancourt by Bill Gates-funded academic publishing website ResearchGate over his papers exposing the dangers and uselessness of masks. Rancourt said:

ResearchGate today has permanently locked my account, which I have had since 2015. Their reasons graphically show the nature of their attack against democracy, and their corruption of

science … By their obscene non-logic, a scientific review of science articles reporting on harms caused by face masks has a 'potential to cause harm'. No criticism of the psychological device (face masks) is tolerated, if the said criticism shows potential to influence public policy.

This is what happens in a fascist world.

Where are the 'greens' (again)?

Other dangers of wearing masks especially regularly relate to the inhalation of minute plastic fibres into the lungs and the deluge of discarded masks in the environment and oceans. Estimates predicted that more than 1.5 billion disposable masks will end up in the world's oceans every year polluting the water with tons of plastic and endangering marine wildlife. Studies project that humans are using 129 billion face masks each month worldwide – about three million a minute. Most are disposable and made from plastic, non-biodegradable microfibers that break down into smaller plastic particles that become widespread in ecosystems. They are littering cities, clogging sewage channels and turning up in bodies of water. I have written in other books about the immense amounts of microplastics from endless sources now being absorbed into the body. Rolf Halden, director of the Arizona State University (ASU) Biodesign Center for Environmental Health Engineering, was the senior researcher in a 2020 study that analysed 47 human tissue samples and found microplastics in all of them. 'We have detected these chemicals of plastics in every single organ that we have investigated', he said. I wrote in *The Answer* about the world being deluged with microplastics. A study by the Worldwide Fund for Nature (WWF) found that people are consuming on average every week some 2,000 tiny pieces of plastic mostly through water and also through marine life and the air. Every year humans are ingesting enough microplastics to fill a heaped dinner plate and in a life-time of 79 years it is enough to fill two large waste bins. Marco Lambertini, WWF International director general said: 'Not only are plastics polluting our oceans and waterways and killing marine life – it's in all of us and we can't escape consuming plastics,' American

geologists found tiny plastic fibres, beads and shards in rainwater samples collected from the remote slopes of the Rocky Mountain National Park near Denver, Colorado. Their report was headed: 'It is raining plastic.' Rachel Adams, senior lecturer in Biomedical Science at Cardiff Metropolitan University, said that among health consequences are internal inflammation and immune responses to a 'foreign body'. She further pointed out that microplastics become carriers of toxins including mercury, pesticides and dioxins (a known cause of cancer and reproductive and developmental problems). These toxins accumulate in the fatty tissues once they enter the body through microplastics. Now this is being compounded massively by people putting plastic on their face and throwing it away.

Workers exposed to polypropylene plastic fibres known as 'flock' have developed 'flock worker's lung' from inhaling small pieces of the flock fibres which can damage lung tissue, reduce breathing capacity and exacerbate other respiratory problems. *Now* … commonly used surgical masks have three layers of melt-blown textiles made of … polypropylene. We have billions of people putting these microplastics against their mouth, nose and face for hours at a time day after day in the form of masks. How does anyone think that will work out? I mean – what could possibly go wrong? We posted a number of scientific studies on this at davidicke.com, but when I went back to them as I was writing this book the links to the science research website where they were hosted were dead. Anything that challenges the official narrative in any way is either censored or vilified. The official narrative is so unsupportable by the evidence that only deleting the truth can protect it. A study by Chinese scientists still survived – with the usual twist which it why it was still active, I guess. Yes, they found that virtually all the masks they tested increased the daily intake of microplastic fibres, but people should still wear them because the danger from the 'virus' was worse said the crazy 'team' from the Institute of Hydrobiology in Wuhan. Scientists first discovered microplastics in lung tissue of some patients who died of lung cancer

in the 1990s. Subsequent studies have confirmed the potential health damage with the plastic degrading slowly and remaining in the lungs to accumulate in volume. Wuhan researchers used a machine simulating human breathing to establish that masks shed up to nearly 4,000 microplastic fibres in a month with reused masks producing more. Scientists said some masks are laced with toxic chemicals and a variety of compounds seriously restricted for both health and environmental reasons. They include cobalt (used in blue dye) and formaldehyde known to cause watery eyes, burning sensations in the eyes, nose, and throat, plus coughing, wheezing and nausea. No – that must be 'Covid-19'.

Mask 'worms'

There is another and potentially even more sinister content of masks. Mostly new masks of different makes filmed under a microscope around the world have been found to contain strange black fibres or 'worms' that appear to move or 'crawl' by themselves and react to heat and water. The nearest I have seen to them are the self-replicating fibres that are pulled out through the skin of those suffering from Morgellons disease which has been connected to the phenomena of 'chemtrails' which I will bring into the story later on. Morgellons fibres continue to grow outside the body and have a form of artificial intelligence. Black 'worm' fibres in masks have that kind of feel to them and there is a nanotechnology technique called 'worm micelles' which carry and release drugs or anything else you want to deliver to the body. For sure the suppression of humanity by mind altering drugs is the Cult agenda big time and the more excuses they can find to gain access to the body the more opportunities there are to make that happen whether through 'vaccines' or masks pushed against the mouth and nose for hours on end.

So let us summarise the pros and cons of masks:

Against masks: Breathing in your own carbon dioxide; depriving the body and brain of sufficient oxygen; build-up of toxins in the mask that can be breathed into the lungs and cause rashes on the face and 'mask-mouth'; breathing microplastic fibres and toxic chemicals into the lungs; dehumanisation and deleting individualisation by literally making people faceless; destroying human emotional interaction through facial expression and deleting parental connection with their babies which look for guidance to their facial expression.

For masks: They don't protect you from a 'virus' that doesn't exist and even if it did 'viral' particles are so minute they are smaller than the holes in the mask.

Governments, police, supermarkets, businesses, transport companies, and all the rest who seek to impose masks have done no risk assessment on their consequences for health and psychology and are now open to group lawsuits when the impact becomes clear with a cumulative epidemic of respiratory and other disease. Authorities will try to exploit these effects and hide the real cause by dubbing them 'Covid-19'. Can you imagine setting out to force the population to wear health-destroying masks without doing any assessment of the risks? It is criminal and it is evil, but then how many people targeted in this way, who see their children told to wear them all day at school, have asked for a risk assessment? Billions can't be imposed upon by the few unless the billions allow it. Oh, yes, with just a tinge of irony, 85 percent of all masks made worldwide come from *China*.

Wash your hands in toxic shite

'Covid' rules include the use of toxic sanitisers and again the health consequences of constantly applying toxins to be absorbed through the skin is obvious to any level of Renegade Mind. America's Food and Drug Administration (FDA) said that sanitisers are drugs and issued a warning about 75 dangerous brands which contain

methanol used in antifreeze and can cause death, kidney damage and blindness. The FDA circulated the following warning even for those brands that it claims to be safe:

Store hand sanitizer out of the reach of pets and children, and children should use it only with adult supervision. Do not drink hand sanitizer. This is particularly important for young children, especially toddlers, who may be attracted by the pleasant smell or brightly colored bottles of hand sanitizer.

Drinking even a small amount of hand sanitizer can cause alcohol poisoning in children. (However, there is no need to be concerned if your children eat with or lick their hands after using hand sanitizer.) During this coronavirus pandemic, poison control centers have had an increase in calls about accidental ingestion of hand sanitizer, so it is important that adults monitor young children's use.

Do not allow pets to swallow hand sanitizer. If you think your pet has eaten something potentially dangerous, call your veterinarian or a pet poison control center right away. Hand sanitizer is flammable and should be stored away from heat and flames. When using hand sanitizer, rub your hands until they feel completely dry before performing activities that may involve heat, sparks, static electricity, or open flames.

There you go, perfectly safe, then, and that's without even a mention of the toxins absorbed through the skin. Come on kids – sanitise your hands everywhere you go. It will save you from the 'virus'. Put all these elements together of the 'Covid' normal and see how much health and psychology is being cumulatively damaged, even devastated, to 'protect your health'. Makes sense, right? They are only imposing these things because they care, right? *Right?*

Submitting to insanity

Psychological reframing of the population goes very deep and is done in many less obvious ways. I hear people say how contradictory and crazy 'Covid' rules are and how they are ever changing. This is explained away by dismissing those involved as idiots. It is a big mistake. The Cult is delighted if its cold calculation is perceived as incompetence and idiocy when it is anything but. Oh, yes, there are idiots within the system – lots of them – but they are *administering* the Cult agenda, mostly unknowingly. They are not deciding and dictating it. The bulwark against tyranny is self-

respect, always has been, always will be. It is self-respect that has broken every tyranny in history. By its very nature self-respect will not bow to oppression and its perpetrators. There is so little self-respect that it's always the few that overturn dictators. Many may eventually follow, but the few with the iron spines (self-respect) kick it off and generate the momentum. The Cult targets self-respect in the knowledge that once this has gone only submission remains. Crazy, contradictory, ever-changing 'Covid' rules are systematically applied by psychologists to delete self-respect. They *want* you to see that the rules make no sense. It is one thing to decide to do something when *you* have made the choice based on evidence and logic. You still retain your self-respect. It is quite another when you can see what you are being told to do is insane, ridiculous and makes no sense, and *yet you still do it*. Your self-respect is extinguished and this has been happening as ever more obviously stupid and nonsensical things have been demanded and the great majority have complied even when they can see they are stupid and nonsensical.

People walk around in face-nappies knowing they are damaging their health and make no difference to a 'virus'. They do it in fear of not doing it. I know it's daft, but I'll do it anyway. When that happens something dies inside of you and submissive reframing has begun. Next there's a need to hide from yourself that you have conceded your self-respect and you convince yourself that you have not really submitted to fear and intimidation. You begin to believe that you are complying with craziness because it's the right thing to do. When first you concede your self-respect of 2+2 = 4 to 2+2 = 5 you *know* you are compromising your self-respect. Gradually to avoid facing that fact you begin to *believe* that 2+2=5. You have been reframed and I have been watching this process happening in the human psyche on an industrial scale. The Cult is working to break your spirit and one of its major tools in that war is humiliation. I read how former American soldier Bradley Manning (later Chelsea Manning after a sex-change) was treated after being jailed for supplying WikiLeaks with documents exposing the enormity of

government and elite mendacity. Manning was isolated in solitary confinement for eight months, put under 24-hour surveillance, forced to hand over clothing before going to bed, and stand naked for every roll call. This is systematic humiliation. The introduction of anal swab 'Covid' tests in China has been done for the same reason to delete self-respect and induce compliant submission. Anal swabs are mandatory for incoming passengers in parts of China and American diplomats have said they were forced to undergo the indignity which would have been calculated humiliation by the Cult-owned Chinese government that has America in its sights.

Government-people: An abusive relationship

Spirit-breaking psychological techniques include giving people hope and apparent respite from tyranny only to take it away again. This happened in the UK during Christmas, 2020, when the psycho-psychologists and their political lackeys announced an easing of restrictions over the holiday only to reimpose them almost immediately on the basis of yet another lie. There is a big psychological difference between getting used to oppression and being given hope of relief only to have that dashed. Psychologists know this and we have seen the technique used repeatedly. Then there is traumatising people before you introduce more extreme regulations that require compliance. A perfect case was the announcement by the dark and sinister Whitty and Vallance in the UK that 'new data' predicted that 4,000 could die every day over the winter of 2020/2021 if we did not lockdown again. I think they call it lying and after traumatising people with that claim out came Jackboot Johnson the next day with new curbs on human freedom. Psychologists know that a frightened and traumatised mind becomes suggestable to submission and behaviour reframing. Underpinning all this has been to make people fearful and suspicious of each other and see themselves as a potential danger to others. In league with deleted self-respect you have the perfect psychological recipe for self-loathing. The relationship between authority and public is now demonstrably the same as that of

subservience to an abusive partner. These are signs of an abusive relationship explained by psychologist Leslie Becker-Phelps:

Psychological and emotional abuse: Undermining a partner's self-worth with verbal attacks, name-calling, and belittling. Humiliating the partner in public, unjustly accusing them of having an affair, or interrogating them about their every behavior. Keeping partner confused or off balance by saying they were just kidding or blaming the partner for 'making' them act this way … Feigning in public that they care while turning against them in private. This leads to victims frequently feeling confused, incompetent, unworthy, hopeless, and chronically self-doubting. [Apply these techniques to how governments have treated the population since New Year, 2020, and the parallels are obvious.]

Physical abuse: The abuser might physically harm their partner in a range of ways, such as grabbing, hitting, punching, or shoving them. They might throw objects at them or harm them with a weapon. [Observe the physical harm imposed by masks, lockdown, and so on.]

Threats and intimidation: One way abusers keep their partners in line is by instilling fear. They might be verbally threatening, or give threatening looks or gestures. Abusers often make it known that they are tracking their partner's every move. They might destroy their partner's possessions, threaten to harm them, or threaten to harm their family members. Not surprisingly, victims of this abuse often feel anxiety, fear, and panic. [No words necessary.]

Isolation: Abusers often limit their partner's activities, forbidding them to talk or interact with friends or family. They might limit access to a car or even turn off their phone. All of this might be done by physically holding them against their will, but is often accomplished through psychological abuse and intimidation. The more isolated a person feels, the fewer resources they have to help gain perspective on their situation and to escape from it. [No words necessary.]

Economic abuse: Abusers often make their partners beholden to them for money by controlling access to funds of any kind. They might prevent their partner from getting a job or withhold access to money they earn from a job. This creates financial dependency that makes leaving the relationship very difficult. [See destruction of livelihoods and the proposed meagre 'guaranteed income' so long as you do whatever you are told.]

Using children: An abuser might disparage their partner's parenting skills, tell their children lies about their partner, threaten to take custody of their children, or threaten to harm their children. These tactics instil fear and often elicit compliance. [See reframed social service mafia and how children are being mercilessly abused by the state over 'Covid' while their parents look on too frightened to do anything.]

A further recurring trait in an abusive relationship is the abused blaming themselves for their abuse and making excuses for the abuser. We have the public blaming each other for lockdown abuse by government and many making excuses for the government while attacking those who challenge the government. How often we have heard authorities say that rules are being imposed or reimposed only because people have refused to 'behave' and follow the rules. We don't want to do it – it's *you*.

Renegade Minds are an antidote to all of these things. They will never concede their self-respect no matter what the circumstances. Even when apparent humiliation is heaped upon them they laugh in its face and reflect back the humiliation on the abuser where it belongs. Renegade Minds will never wear masks they know are only imposed to humiliate, suppress and damage both physically and psychologically. Consequences will take care of themselves and they will never break their spirit or cause them to concede to tyranny. UK newspaper columnist Peter Hitchens was one of the few in the mainstream media to speak out against lockdowns and forced vaccinations. He then announced he had taken the jab. He wanted to see family members abroad and he believed vaccine passports were inevitable even though they had not yet been introduced. Hitchens

has a questioning and critical mind, but not a Renegade one. If he had no amount of pressure would have made him concede. Hitchens excused his action by saying that the battle has been lost. Renegade Minds never accept defeat when freedom is at stake and even if they are the last one standing the self-respect of not submitting to tyranny is more important than any outcome or any consequence.

That's why Renegade Minds are the only minds that ever changed anything worth changing.

CHAPTER EIGHT

'Reframing' insanity

Insanity is relative. It depends on who has who locked in what cage
Ray Bradbury

'Reframing' a mind means simply to change its perception and behaviour. This can be done subconsciously to such an extent that subjects have no idea they have been 'reframed' while to any observer changes in behaviour and attitudes are obvious.

Human society is being reframed on a ginormous scale since the start of 2020 and here we have the reason why psychologists rather than doctors have been calling the shots. Ask most people who have succumbed to 'Covid' reframing if they have changed and most will say 'no'; but they *have* and fundamentally. The Cult's long-game has been preparing for these times since way back and crucial to that has been to prepare both population and officialdom mentally and emotionally. To use the mind-control parlance they had to reframe the population with a mentality that would submit to fascism and reframe those in government and law enforcement to impose fascism or at least go along with it. The result has been the fact-deleted mindlessness of 'Wokeness' and officialdom that has either enthusiastically or unquestioningly imposed global tyranny demanded by reframed politicians on behalf of psychopathic and deeply evil cultists. 'Cognitive reframing' identifies and challenges the way someone sees the world in the form of situations, experiences and emotions and then restructures those perceptions to view the same set of circumstances in a different way. This can have

benefits if the attitudes are personally destructive while on the other side it has the potential for individual and collective mind control which the subject has no idea has even happened.

Cognitive therapy was developed in the 1960s by Aaron T. Beck who was born in Rhode Island in 1921 as the son of Jewish immigrants from the Ukraine. He became interested in the techniques as a treatment for depression. Beck's daughter Judith S. Beck is prominent in the same field and they founded the Beck Institute for Cognitive Behavior Therapy in Philadelphia in 1994. Cognitive reframing, however, began to be used worldwide by those with a very dark agenda. The Cult reframes politicians to change their attitudes and actions until they are completely at odds with what they once appeared to stand for. The same has been happening to government administrators at all levels, law enforcement, military and the human population. Cultists love mind control for two main reasons: It allows them to control what people think, do and say to secure agenda advancement and, by definition, it calms their legendary insecurity and fear of the unexpected. I have studied mind control since the time I travelled America in 1996. I may have been talking to next to no one in terms of an audience in those years, but my goodness did I gather a phenomenal amount of information and knowledge about so many things including the techniques of mind control. I have described this in detail in other books going back to *The Biggest Secret* in 1998. I met a very large number of people recovering from MKUltra and its offshoots and successors and I began to see how these same techniques were being used on the population in general. This was never more obvious than since the 'Covid' hoax began.

Reframing the enforcers

I have observed over the last two decades and more the very clear transformation in the dynamic between the police, officialdom and the public. I tracked this in the books as the relationship mutated from one of serving the public to seeing them as almost the enemy and certainly a lower caste. There has always been a class divide

based on income and always been some psychopathic, corrupt, and big-I-am police officers. This was different. Wholesale change was unfolding in the collective dynamic; it was less about money and far more about position and perceived power. An us-and-them was emerging. Noses were lifted skyward by government administration and law enforcement and their attitude to the public they were *supposed* to be serving changed to one of increasing contempt, superiority and control. The transformation was so clear and widespread that it had to be planned. Collective attitudes and dynamics do not change naturally and organically that quickly on that scale. I then came across an organisation in Britain called Common Purpose created in the late 1980s by Julia Middleton who would work in the office of Deputy Prime Minister John Prescott during the long and disastrous premiership of war criminal Tony Blair. When Blair speaks the Cult is speaking and the man should have been in jail a long time ago. Common Purpose proclaims itself to be one of the biggest 'leadership development' organisations in the world while functioning as a *charity* with all the financial benefits which come from that. It hosts 'leadership development' courses and programmes all over the world and claims to have 'brought together' what it calls 'leaders' from more than 100 countries on six continents. The modus operandi of Common Purpose can be compared with the work of the UK government's reframing network that includes the Behavioural Insights Team 'nudge unit' and 'Covid' reframing specialists at SPI-B. WikiLeaks described Common Purpose long ago as 'a hidden virus in our government and schools' which is unknown to the general public: 'It recruits and trains "leaders" to be loyal to the directives of Common Purpose and the EU, instead of to their own departments, which they then undermine or subvert, the NHS [National Health Service] being an example.' This is a vital point to understand the 'Covid' hoax. The NHS, and its equivalent around the world, has been utterly reframed in terms of administrators and much of the medical personnel with the transformation underpinned by recruitment policies. The outcome has been the criminal and psychopathic behaviour of the

NHS over 'Covid' and we have seen the same in every other major country. WikiLeaks said Common Purpose trainees are 'learning to rule without regard to democracy' and to usher in a police state (current events explained). Common Purpose operated like a 'glue' and had members in the NHS, BBC, police, legal profession, church, many of Britain's 7,000 quangos, local councils, the Civil Service, government ministries and Parliament, and controlled many RDA's (Regional Development Agencies). Here we have one answer for how and why British institutions and their like in other countries have changed so negatively in relation to the public. This further explains how and why the beyond-disgraceful reframed BBC has become a propaganda arm of 'Covid' fascism. They are all part of a network pursuing the same goal.

By 2019 Common Purpose was quoting a figure of 85,000 'leaders' that had attended its programmes. These 'students' of all ages are known as Common Purpose 'graduates' and they consist of government, state and local government officials and administrators, police chiefs and officers, and a whole range of others operating within the national, local and global establishment. Cressida Dick, Commissioner of the London Metropolitan Police, is the Common Purpose graduate who was the 'Gold Commander' that oversaw what can only be described as the murder of Brazilian electrician Jean Charles de Menezes in 2005. He was held down by psychopathic police and shot seven times in the head by a psychopathic lunatic after being mistaken for a terrorist when he was just a bloke going about his day. Dick authorised officers to pursue and keep surveillance on de Menezes and ordered that he be stopped from entering the underground train system. Police psychopaths took her at her word clearly. She was 'disciplined' for this outrage by being *promoted* – eventually to the top of the 'Met' police where she has been a disaster. Many Chief Constables controlling the police in different parts of the UK are and have been Common Purpose graduates. I have heard the 'graduate' network described as a sort of Mafia or secret society operating within the fabric of government at all levels pursuing a collective policy

ingrained at Common Purpose training events. Founder Julia Middleton herself has said:

> Locally and internationally, Common Purpose graduates will be 'lighting small fires' to create change in their organisations and communities … The Common Purpose effect is best illustrated by the many stories of small changes brought about by leaders, who themselves have changed.

A Common Purpose mission statement declared:

> Common Purpose aims to improve the way society works by expanding the vision, decision-making ability and influence of all kinds of leaders. The organisation runs a variety of educational programmes for leaders of all ages, backgrounds and sectors, in order to provide them with the inspirational, information and opportunities they need to change the world.

Yes, but into what? Since 2020 the answer has become clear.

NLP and the Delphi technique

Common Purpose would seem to be a perfect name or would common programming be better? One of the foundation methods of reaching 'consensus' (group think) is by setting the agenda theme and then encouraging, cajoling or pressuring everyone to agree a 'consensus' in line with the core theme promoted by Common Purpose. The methodology involves the 'Delphi technique', or an adaption of it, in which opinions are expressed that are summarised by a 'facilitator or change agent' at each stage. Participants are 'encouraged' to modify their views in the light of what others have said. Stage by stage the former individual opinions are merged into group consensus which just happens to be what Common Purpose wants them to believe. A key part of this is to marginalise anyone refusing to concede to group think and turn the group against them to apply pressure to conform. We are seeing this very technique used on the general population to make 'Covid' group-thinkers hostile to those who have seen through the bullshit. People can be reframed by using perception manipulation methods such as Neuro-Linguistic Programming (NLP) in which you change perception with the use of

carefully constructed language. An NLP website described the technique this way:

… A method of influencing brain behaviour (the 'neuro' part of the phrase) through the use of language (the 'linguistic' part) and other types of communication to enable a person to 'recode' the way the brain responds to stimuli (that's the 'programming') and manifest new and better behaviours. Neuro-Linguistic Programming often incorporates hypnosis and self-hypnosis to help achieve the change (or 'programming') that is wanted.

British alternative media operation UKColumn has done very detailed research into Common Purpose over a long period. I quoted co-founder and former naval officer Brian Gerrish in my book *Remember Who You Are*, published in 2011, as saying the following years before current times:

It is interesting that many of the mothers who have had children taken by the State speak of the Social Services people being icily cool, emotionless and, as two ladies said in slightly different words, '… like little robots'. We know that NLP is cumulative, so people can be given small imperceptible doses of NLP in a course here, another in a few months, next year etc. In this way, major changes are accrued in their personality, but the day by day change is almost unnoticeable.

In these and other ways 'graduates' have had their perceptions uniformly reframed and they return to their roles in the institutions of government, law enforcement, legal profession, military, 'education', the UK National Health Service and the whole swathe of the establishment structure to pursue a common agenda preparing for the 'post-industrial', 'post-democratic' society. I say 'preparing' but we are now there. 'Post-industrial' is code for the Great Reset and 'post-democratic' is 'Covid' fascism. UKColumn has spoken to partners of those who have attended Common Purpose 'training'. They have described how personalities and attitudes of 'graduates' changed very noticeably for the worse by the time they had completed the course. They had been 'reframed' and told they are the 'leaders' – the special ones – who know better than the population. There has also been the very demonstrable recruitment of psychopaths and narcissists into government administration at all

levels and law enforcement. If you want psychopathy hire psychopaths and you get a simple cause and effect. If you want administrators, police officers and 'leaders' to perceive the public as lesser beings who don't matter then employ narcissists. These personalities are identified using 'psychometrics' that identifies knowledge, abilities, attitudes and personality traits, mostly through carefully-designed questionnaires and tests. As this policy has passed through the decades we have had power-crazy, power-trippers appointed into law enforcement, security and government administration in preparation for current times and the dynamic between public and law enforcement/officialdom has been transformed. UKColumn's Brian Gerrish said of the narcissistic personality:

> Their love of themselves and power automatically means that they will crush others who get in their way. I received a major piece of the puzzle when a friend pointed out that when they made public officials re-apply for their own jobs several years ago they were also required to do psychometric tests. This was undoubtedly the start of the screening process to get 'their' sort of people in post.

How obvious that has been since 2020 although it was clear what was happening long before if people paid attention to the changing public-establishment dynamic.

Change agents

At the centre of events in 'Covid' Britain is the National Health Service (NHS) which has behaved disgracefully in slavishly following the Cult agenda. The NHS management structure is awash with Common Purpose graduates or 'change agents' working to a common cause. Helen Bevan, a Chief of Service Transformation at the NHS Institute for Innovation and Improvement, co-authored a document called 'Towards a million change agents, a review of the social movements literature: implications for large scale change in the NHS'. The document compared a project management approach to that of change and social movements where 'people change

themselves and each other – peer to peer'. Two definitions given for a 'social movement' were:

A group of people who consciously attempt to build a radically new social order; involves people of a broad range of social backgrounds; and deploys politically confrontational and socially disruptive tactics – Cyrus Zirakzadeh 1997

Collective challenges, based on common purposes and social solidarities, in sustained interaction with elites, opponents, and authorities – Sidney Tarrow 1994

Helen Bevan wrote another NHS document in which she defined 'framing' as 'the process by which leaders construct, articulate and put across their message in a powerful and compelling way in order to win people to their cause and call them to action'. I think I could come up with another definition that would be rather more accurate. The National Health Service and institutions of Britain and the wider world have been taken over by reframed 'change agents' and that includes everything from the United Nations to national governments, local councils and social services which have been kidnapping children from loving parents on an extraordinary and gathering scale on the road to the end of parenthood altogether. Children from loving homes are stolen and kidnapped by the state and put into the 'care' (inversion) of the local authority through council homes, foster parents and forced adoption. At the same time children are allowed to be abused without response while many are under council 'care'. UKColumn highlighted the Common Purpose connection between South Yorkshire Police and Rotherham council officers in the case of the scandal in that area of the sexual exploitation of children to which the authorities turned not one blind eye, but both:

We were alarmed to discover that the Chief Executive, the Strategic Director of Children and Young People's Services, the Manager for the Local Strategic Partnership, the Community Cohesion Manager, the Cabinet Member for Cohesion, the Chief Constable and his predecessor had all attended Leadership training courses provided by the pseudo-charity Common Purpose.

Once 'change agents' have secured positions of hire and fire within any organisation things start to move very quickly. Personnel are then hired and fired on the basis of whether they will work towards the agenda the change agent represents. If they do they are rapidly promoted even though they may be incompetent. Those more qualified and skilled who are pre-Common Purpose 'old school' see their careers stall and even disappear. This has been happening for decades in every institution of state, police, 'health' and social services and all of them have been transformed as a result in their attitudes to their jobs and the public. Medical professions, including nursing, which were once vocations for the caring now employ many cold, callous and couldn't give a shit personality types. The UKColumn investigation concluded:

By blurring the boundaries between people, professions, public and private sectors, responsibility and accountability, Common Purpose encourages 'graduates' to believe that as new selected leaders, they can work together, outside of the established political and social structures, to achieve a paradigm shift or CHANGE – so called 'Leading Beyond Authority'. In doing so, the allegiance of the individual becomes 'reframed' on CP colleagues and their NETWORK.

Reframing the Face-Nappies

Nowhere has this process been more obvious than in the police where recruitment of psychopaths and development of unquestioning mind-controlled group-thinkers have transformed law enforcement into a politically-correct 'Woke' joke and a travesty of what should be public service. Today they wear their face-nappies like good little gofers and enforce 'Covid' rules which are fascism under another name. Alongside the specifically-recruited psychopaths we have software minds incapable of free thought. Brian Gerrish again:

An example is the policeman who would not get on a bike for a press photo because he had not done the cycling proficiency course. Normal people say this is political correctness gone mad. Nothing could be further from the truth. The policeman has been reframed, and in his reality it is perfect common sense not to get on the bike 'because he hasn't done the cycling course'.

Another example of this is where the police would not rescue a boy from a pond until they had taken advice from above on the 'risk assessment'. A normal person would have arrived, perhaps thought of the risk for a moment, and dived in. To the police now 'reframed', they followed 'normal' procedure.

There are shocking cases of reframed ambulance crews doing the same. Sheer unthinking stupidity of London Face-Nappies headed by Common Purpose graduate Cressida Dick can be seen in their behaviour at a vigil in March, 2021, for a murdered woman, Sarah Everard. A police officer had been charged with the crime. Anyone with a brain would have left the vigil alone in the circumstances. Instead they 'manhandled' women to stop them breaking 'Covid rules' to betray classic reframing. Minds in the thrall of perception control have no capacity for seeing a situation on its merits and acting accordingly. 'Rules is rules' is their only mind-set. My father used to say that rules and regulations are for the guidance of the intelligent and the blind obedience of the idiot. Most of the intelligent, decent, coppers have gone leaving only the other kind and a few old school for whom the job must be a daily nightmare. The combination of psychopaths and rule-book software minds has been clearly on public display in the 'Covid' era with automaton robots in uniform imposing fascistic 'Covid' regulations on the population without any personal initiative or judging situations on their merits. There are thousands of examples around the world, but I'll make my point with the infamous Derbyshire police in the English East Midlands – the ones who think pouring dye into beauty spots and using drones to track people walking in the countryside away from anyone is called 'policing'. To them there are rules decreed by the government which they have to enforce and in their bewildered state a group gathering in a closed space and someone walking alone in the countryside are the same thing. It is beyond idiocy and enters the realm of clinical insanity.

Police officers in Derbyshire said they were 'horrified' – *horrified* – to find 15 to 20 'irresponsible' kids playing a football match at a closed leisure centre 'in breach of coronavirus restrictions'. When they saw the police the kids ran away leaving their belongings behind and the reframed men and women of Derbyshire police were seeking to establish their identities with a view to fining their parents. The most natural thing for youngsters to do – kicking a ball about – is turned into a criminal activity and enforced by the moronic software programs of Derbyshire police. You find the same mentality in every country. These barely conscious 'horrified' officers said they had to take action because 'we need to ensure these rules are being followed' and 'it is of the utmost importance that you ensure your children are following the rules and regulations for Covid-19'. Had any of them done ten seconds of research to see if this parroting of their masters' script could be supported by any evidence? Nope. Reframed people don't think – others think for them and that's the whole idea of reframing. I have seen police officers one after the other repeating without question word for word what officialdom tells them just as I have seen great swathes of the public doing the same. Ask either for 'their' opinion and out spews what they have been told to think by the official narrative. Police and public may seem to be in different groups, but their mentality is the same. Most people do whatever they are told in fear not doing so or because they believe what officialdom tells them; almost the entirety of the police do what they are told for the same reason. Ultimately it's the tiny inner core of the global Cult that's telling both what to do.

So Derbyshire police were 'horrified'. Oh, really? Why did they think those kids were playing football? It was to relieve the psychological consequences of lockdown and being denied human contact with their friends and interaction, touch and discourse vital to human psychological health. Being denied this month after month has dismantled the psyche of many children and young people as depression and suicide have exploded. Were Derbyshire police *horrified by that*? Are you kidding? Reframed people don't have those

mental and emotional processes that can see how the impact on the psychological health of youngsters is far more dangerous than any 'virus' even if you take the mendacious official figures to be true. The reframed are told (programmed) how to act and so they do. The Derbyshire Chief Constable in the first period of lockdown when the black dye and drones nonsense was going on was Peter Goodman. He was the man who severed the connection between his force and the Derbyshire Constabulary *Male Voice* Choir when he decided that it was not inclusive enough to allow women to join. The fact it was a male voice choir making a particular sound produced by male voices seemed to elude a guy who terrifyingly ran policing in Derbyshire. He retired weeks after his force was condemned as disgraceful by former Supreme Court Justice Jonathan Sumption for their behaviour over extreme lockdown impositions. Goodman was replaced by his deputy Rachel Swann who was in charge when her officers were 'horrified'. The police statement over the boys committing the hanging-offence of playing football included the line about the youngsters being 'irresponsible in the times we are all living through' missing the point that the real relevance of the 'times we are all living through' is the imposition of fascism enforced by psychopaths and reframed minds of police officers playing such a vital part in establishing the fascist tyranny that their own children and grandchildren will have to live in their entire lives. As a definition of insanity that is hard to beat although it might be run close by imposing masks on people that can have a serious effect on their health while wearing a face nappy all day themselves. Once again public and police do it for the same reason – the authorities tell them to and who are they to have the self-respect to say no?

Wokers in uniform

How reframed do you have to be to arrest a *six-year-old* and take him to court for *picking a flower* while waiting for a bus? Brain dead police and officialdom did just that in North Carolina where criminal proceedings happen regularly for children under nine. Attorney Julie Boyer gave the six-year-old crayons and a colouring book

during the 'flower' hearing while the 'adults' decided his fate. County Chief District Court Judge Jay Corpening asked: 'Should a child that believes in Santa Claus, the Easter Bunny and the tooth fairy be making life-altering decisions?' Well, of course not, but common sense has no meaning when you have a common purpose and a reframed mind. Treating children in this way, and police operating in American schools, is all part of the psychological preparation for children to accept a police state as normal all their adult lives. The same goes for all the cameras and biometric tracking technology in schools. Police training is focused on reframing them as snowflake Wokers and this is happening in the military. Pentagon top brass said that 'training sessions on extremism' were needed for troops who asked why they were so focused on the Capitol Building riot when Black Lives Matter riots were ignored. What's the difference between them some apparently and rightly asked. Actually, there is a difference. Five people died in the Capitol riot, only one through violence, and that was a police officer shooting an unarmed protestor. BLM riots killed at least 25 people and cost billions. Asking the question prompted the psychopaths and reframed minds that run the Pentagon to say that more 'education' (programming) was needed. Troop training is all based on psychological programming to make them fodder for the Cult – 'Military men are just dumb, stupid animals to be used as pawns in foreign policy' as Cult-to-his-DNA former Secretary of State Henry Kissinger famously said. Governments see the police in similar terms and it's time for those among them who can see this to defend the people and stop being enforcers of the Cult agenda upon the people.

The US military, like the country itself, is being targeted for destruction through a long list of Woke impositions. Cult-owned gaga 'President' Biden signed an executive order when he took office to allow taxpayer money to pay for transgender surgery for active military personnel and veterans. Are you a man soldier? No, I'm a LGBTQIA+ with a hint of Skoliosexual and Spectrasexual. Oh, good man. Bad choice of words you bigot. The Pentagon announced in March, 2021, the appointment of the first 'diversity and inclusion

officer' for US Special Forces. Richard Torres-Estrada arrived with the publication of a 'D&I Strategic Plan which will guide the enterprise-wide effort to institutionalize and sustain D&I'. If you think a Special Forces 'Strategic Plan' should have something to do with defending America you haven't been paying attention. Defending Woke is now the military's new role. Torres-Estrada has posted images comparing Donald Trump with Adolf Hitler and we can expect no bias from him as a representative of the supposedly non-political Pentagon. Cable news host Tucker Carlson said: 'The Pentagon is now the Yale faculty lounge but with cruise missiles.' Meanwhile Secretary of Defense Lloyd Austin, a board member of weapons-maker Raytheon with stock and compensation interests in October, 2020, worth $1.4 million, said he was purging the military of the 'enemy within' – anyone who isn't Woke and supports Donald Trump. Austin refers to his targets as 'racist extremists' while in true Woke fashion being himself a racist extremist. Pentagon documents pledge to 'eradicate, eliminate and conquer all forms of racism, sexism and homophobia'. The definitions of these are decided by 'diversity and inclusion committees' peopled by those who see racism, sexism and homophobia in every situation and opinion. Woke (the Cult) is dismantling the US military and purging testosterone as China expands its military and gives its troops 'masculinity training'. How do we think that is going to end when this is all Cult coordinated? The US military, like the British military, is controlled by Woke and spineless top brass who just go along with it out of personal career interests.

'Woke' means fast asleep

Mind control and perception manipulation techniques used on individuals to create group-think have been unleashed on the global population in general. As a result many have no capacity to see the obvious fascist agenda being installed all around them or what 'Covid' is really all about. Their brains are firewalled like a computer system not to process certain concepts, thoughts and realisations that are bad for the Cult. The young are most targeted as the adults they

will be when the whole fascist global state is planned to be fully implemented. They need to be prepared for total compliance to eliminate all pushback from entire generations. The Cult has been pouring billions into taking complete control of 'education' from schools to universities via its operatives and corporations and not least Bill Gates as always. The plan has been to transform 'education' institutions into programming centres for the mentality of 'Woke'. James McConnell, professor of psychology at the University of Michigan, wrote in *Psychology Today* in 1970:

> The day has come when we can combine sensory deprivation with drugs, hypnosis, and astute manipulation of reward and punishment, to gain almost absolute control over an individual's behaviour. It should then be possible to achieve a very rapid and highly effective type of brainwashing that would allow us to make dramatic changes in a person's behaviour and personality ...
>
> … We should reshape society so that we all would be trained from birth to want to do what society wants us to do. We have the techniques to do it... no-one owns his own personality you acquired, and there's no reason to believe you should have the right to refuse to acquire a new personality if your old one is anti-social.

This was the potential for mass brainwashing in 1970 and the mentality there displayed captures the arrogant psychopathy that drives it forward. I emphasise that not all young people have succumbed to Woke programming and those that haven't are incredibly impressive people given that today's young are the most perceptually-targeted generations in history with all the technology now involved. Vast swathes of the young generations, however, have fallen into the spell – and that's what it is – of Woke. The Woke mentality and perceptual program is founded on *inversion* and you will appreciate later why that is so significant. Everything with Woke is inverted and the opposite of what it is claimed to be. Woke was a term used in African-American culture from the 1900s and referred to an awareness of social and racial justice. This is not the meaning of the modern version or 'New Woke' as I call it in *The Answer*. Oh, no, Woke today means something very different no matter how much Wokers may seek to hide that and insist Old Woke and New

Woke are the same. See if you find any 'awareness of social justice' here in the modern variety:

- Woke demands 'inclusivity' while excluding anyone with a different opinion and calls for mass censorship to silence other views.

- Woke claims to stand against oppression when imposing oppression is the foundation of all that it does. It is the driver of political correctness which is nothing more than a Cult invention to manipulate the population to silence itself.

- Woke believes itself to be 'liberal' while pursuing a global society that can only be described as fascist (see 'anti-fascist' fascist Antifa).

- Woke calls for 'social justice' while spreading injustice wherever it goes against the common 'enemy' which can be easily identified as a differing view.

- Woke is supposed to be a metaphor for 'awake' when it is solid-gold asleep and deep in a Cult-induced coma that meets the criteria for 'off with the fairies'.

I state these points as obvious facts if people only care to look. I don't do this with a sense of condemnation. We need to appreciate that the onslaught of perceptual programming on the young has been incessant and merciless. I can understand why so many have been reframed, or, given their youth, framed from the start to see the world as the Cult demands. The Cult has had access to their minds day after day in its 'education' system for their entire formative years. Perception is formed from information received and the Cult-created system is a life-long download of information delivered to elicit a particular perception, thus behaviour. The more this has expanded into still new extremes in recent decades and ever-increasing censorship has deleted other opinions and information why wouldn't that lead to a perceptual reframing on a mass scale? I

have described already cradle-to-grave programming and in more recent times the targeting of young minds from birth to adulthood has entered the stratosphere. This has taken the form of skewing what is 'taught' to fit the Cult agenda and the omnipresent techniques of group-think to isolate non-believers and pressure them into line. There has always been a tendency to follow the herd, but we really are in a new world now in relation to that. We have parents who can see the 'Covid' hoax told by their children not to stop them wearing masks at school, being 'Covid' tested or having the 'vaccine' in fear of the peer-pressure consequences of being different. What is 'peer-pressure' if not pressure to conform to group-think? Renegade Minds never group-think and always retain a set of perceptions that are unique to them. Group-think is always underpinned by consequences for not group-thinking. Abuse now aimed at those refusing DNA-manipulating 'Covid vaccines' are a potent example of this. The biggest pressure to conform comes from the very group which is itself being manipulated. 'I am programmed to be part of a hive mind and so you must be.'

Woke control structures in 'education' now apply to every mainstream organisation. Those at the top of the 'education' hierarchy (the Cult) decide the policy. This is imposed on governments through the Cult network; governments impose it on schools, colleges and universities; their leadership impose the policy on teachers and academics and they impose it on children and students. At any level where there is resistance, perhaps from a teacher or university lecturer, they are targeted by the authorities and often fired. Students themselves regularly demand the dismissal of academics (increasingly few) at odds with the narrative that the students have been programmed to believe in. It is quite a thought that students who are being targeted by the Cult become so consumed by programmed group-think that they launch protests and demand the removal of those who are trying to push back against those targeting the students. Such is the scale of perceptual inversion. We see this with 'Covid' programming as the Cult imposes the rules via psycho-psychologists and governments on

shops, transport companies and businesses which impose them on their staff who impose them on their customers who pressure Pushbackers to conform to the will of the Cult which is in the process of destroying them and their families. Scan all aspects of society and you will see the same sequence every time.

Fact free Woke and hijacking the 'left'

There is no more potent example of this than 'Woke', a mentality only made possible by the deletion of factual evidence by an 'education' system seeking to produce an ever more uniform society. Why would you bother with facts when you don't know any? Deletion of credible history both in volume and type is highly relevant. Orwell said: 'Who controls the past controls the future: who controls the present controls the past.' They who control the perception of the past control the perception of the future and they who control the present control the perception of the past through the writing and deleting of history. Why would you oppose the imposition of Marxism in the name of Wokeism when you don't know that Marxism cost at least 100 million lives in the 20th century alone? Watch videos and read reports in which Woker generations are asked basic historical questions – it's mind-blowing. A survey of 2,000 people found that six percent of millennials (born approximately early1980s to early 2000s) believed the Second World War (1939-1945) broke out with the assassination of President Kennedy (in 1963) and one in ten thought Margaret Thatcher was British Prime Minister at the time. She was in office between 1979 and 1990. We are in a post-fact society. Provable facts are no defence against the fascism of political correctness or Silicon Valley censorship. Facts don't matter anymore as we have witnessed with the 'Covid' hoax. Sacrificing uniqueness to the Woke group-think religion is all you are required to do and that means thinking for yourself is the biggest Woke no, no. All religions are an expression of group-think and censorship and Woke is just another religion with an orthodoxy defended by group-think and censorship. Burned at

the stake becomes burned on Twitter which leads back eventually to burned at the stake as Woke humanity regresses to ages past.

The biggest Woke inversion of all is its creators and funders. I grew up in a traditional left of centre political household on a council estate in Leicester in the 1950s and 60s – you know, the left that challenged the power of wealth-hoarding elites and threats to freedom of speech and opinion. In those days students went on marches defending freedom of speech while today's Wokers march for its deletion. What on earth could have happened? Those very elites (collectively the Cult) that we opposed in my youth and early life have funded into existence the antithesis of that former left and hijacked the 'brand' while inverting everything it ever stood for. We have a mentality that calls itself 'liberal' and 'progressive' while acting like fascists. Cult billionaires and their corporations have funded themselves into control of 'education' to ensure that Woke programming is unceasing throughout the formative years of children and young people and that non-Wokers are isolated (that word again) whether they be students, teachers or college professors. The Cult has funded into existence the now colossal global network of Woke organisations that have spawned and promoted all the 'causes' on the Cult wish-list for global transformation and turned Wokers into demanders of them. Does anyone really think it's a coincidence that the Cult agenda for humanity is a carbon (sorry) copy of the societal transformations desired by Woke?? These are only some of them:

Political correctness: The means by which the Cult deletes all public debates that it knows it cannot win if we had the free-flow of information and evidence.

Human-caused 'climate change': The means by which the Cult seeks to transform society into a globally-controlled dictatorship imposing its will over the fine detail of everyone's lives 'to save the planet' which doesn't actually need saving.

Transgender obsession: Preparing collective perception to accept the 'new human' which would not have genders because it would be created technologically and not through procreation. I'll have much more on this in Human 2.0.

Race obsession: The means by which the Cult seeks to divide and rule the population by triggering racial division through the perception that society is more racist than ever when the opposite is the case. Is it perfect in that regard? No. But to compare today with the racism of apartheid and segregation brought to an end by the civil rights movement in the 1960s is to insult the memory of that movement and inspirations like Martin Luther King. Why is the 'anti-racism' industry (which it is) so dominated by privileged white people?

White supremacy: This is a label used by privileged white people to demonise poor and deprived white people pushing back on tyranny to marginalise and destroy them. White people are being especially targeted as the dominant race by number within Western society which the Cult seeks to transform in its image. If you want to change a society you must weaken and undermine its biggest group and once you have done that by using the other groups you next turn on them to do the same … 'Then they came for the Jews and I was not a Jew so I did nothing.'

Mass migration: The mass movement of people from the Middle East, Africa and Asia into Europe, from the south into the United States and from Asia into Australia are another way the Cult seeks to dilute the racial, cultural and political influence of white people on Western society. White people ask why their governments appear to be working against them while being politically and culturally biased towards incoming cultures. Well, here's your answer. In the same way sexually 'straight' people, men and women, ask why the

authorities are biased against them in favour of other sexualities. The answer is the same – that's the way the Cult wants it to be for very sinister motives.

These are all central parts of the Cult agenda and central parts of the Woke agenda and Woke was created and continues to be funded to an immense degree by Cult billionaires and corporations. If anyone begins to say 'coincidence' the syllables should stick in their throat.

Billionaire 'social justice warriors'

Joe Biden is a 100 percent-owned asset of the Cult and the Wokers' man in the White House whenever he can remember his name and for however long he lasts with his rapidly diminishing cognitive function. Even walking up the steps of an aircraft without falling on his arse would appear to be a challenge. He's not an empty-shell puppet or anything. From the minute Biden took office (or the Cult did) he began his executive orders promoting the Woke wish-list. You will see the Woke agenda imposed ever more severely because it's really the *Cult* agenda. Woke organisations and activist networks spawned by the Cult are funded to the extreme so long as they promote what the Cult wants to happen. Woke is funded to promote 'social justice' by billionaires who become billionaires by destroying social justice. The social justice mantra is only a cover for dismantling social justice and funded by billionaires that couldn't give a damn about social justice. Everything makes sense when you see that. One of Woke's premier funders is Cult billionaire financier George Soros who said: 'I am basically there to make money, I cannot and do not look at the social consequences of what I do.' This is the same Soros who has given more than $32 billion to his Open Society Foundations global Woke network and funded Black Lives Matter, mass immigration into Europe and the United States, transgender activism, climate change activism, political correctness and groups targeting 'white supremacy' in the form of privileged white thugs that dominate Antifa. What a scam it all is and when

you are dealing with the unquestioning fact-free zone of Woke scamming them is child's play. All you need to pull it off in all these organisations are a few in-the-know agents of the Cult and an army of naïve, reframed, uninformed, narcissistic, know-nothings convinced of their own self-righteousness, self-purity and virtue.

Soros and fellow billionaires and billionaire corporations have poured hundreds of millions into Black Lives Matter and connected groups and promoted them to a global audience. None of this is motivated by caring about black people. These are the billionaires that have controlled and exploited a system that leaves millions of black people in abject poverty and deprivation which they do absolutely nothing to address. The same Cult networks funding BLM were behind the *slave trade!* Black Lives Matter hijacked a phrase that few would challenge and they have turned this laudable concept into a political weapon to divide society. You know that BLM is a fraud when it claims that *All* Lives Matter, the most inclusive statement of all, is 'racist'. BLM and its Cult masters don't want to end racism. To them it's a means to an end to control all of humanity never mind the colour, creed, culture or background. What has destroying the nuclear family got to do with ending racism? Nothing – but that is one of the goals of BLM and also happens to be a goal of the Cult as I have been exposing in my books for decades. Stealing children from loving parents and giving schools ever more power to override parents is part of that same agenda. BLM is a Marxist organisation and why would that not be the case when the Cult created Marxism *and* BLM? Patrisse Cullors, a BLM co-founder, said in a 2015 video that she and her fellow organisers, including co-founder Alicia Garza, are 'trained Marxists'. The lady known after marriage as Patrisse Khan-Cullors bought a $1.4 million home in 2021 in one of the whitest areas of California with a black population of just 1.6 per cent and has so far bought *four* high-end homes for a total of $3.2 million. How very Marxist. There must be a bit of spare in the BLM coffers, however, when Cult corporations and billionaires have handed over the best part of $100 million. Many black people can see that Black Lives Matter is not

working for them, but against them, and this is still more confirmation. Black journalist Jason Whitlock, who had his account suspended by Twitter for simply linking to the story about the 'Marxist's' home buying spree, said that BLM leaders are 'making millions of dollars off the backs of these dead black men who they wouldn't spit on if they were on fire and alive'.

Black Lies Matter

Cult assets and agencies came together to promote BLM in the wake of the death of career criminal George Floyd who had been jailed a number of times including for forcing his way into the home of a black woman with others in a raid in which a gun was pointed at her stomach. Floyd was filmed being held in a Minneapolis street in 2020 with the knee of a police officer on his neck and he subsequently died. It was an appalling thing for the officer to do, but the same technique has been used by police on peaceful protestors of lockdown without any outcry from the Woke brigade. As unquestioning supporters of the Cult agenda Wokers have supported lockdown and all the 'Covid' claptrap while attacking anyone standing up to the tyranny imposed in its name. Court documents would later include details of an autopsy on Floyd by County Medical Examiner Dr Andrew Baker who concluded that Floyd had taken a fatal level of the drug fentanyl. None of this mattered to fact-free, question-free, Woke. Floyd's death was followed by worldwide protests against police brutality amid calls to defund the police. Throwing babies out with the bathwater is a Woke speciality. In the wake of the murder of British woman Sarah Everard a Green Party member of the House of Lords, Baroness Jones of Moulescoomb (Nincompoopia would have been better), called for a 6pm curfew for all men. This would be in breach of the Geneva Conventions on war crimes which ban collective punishment, but that would never have crossed the black and white Woke mind of Baroness Nincompoopia who would have been far too convinced of her own self-righteousness to compute such details. Many American cities did defund the police in the face of Floyd riots

and after $15 million was deleted from the police budget in Washington DC under useless Woke mayor Muriel Bowser car-jacking alone rose by 300 percent and within six months the US capital recorded its highest murder rate in 15 years. The same happened in Chicago and other cities in line with the Cult/Soros plan to bring fear to streets and neighbourhoods by reducing the police, releasing violent criminals and not prosecuting crime. This is the mob-rule agenda that I have warned in the books was coming for so long. Shootings in the area of Minneapolis where Floyd was arrested increased by 2,500 percent compared with the year before. Defunding the police over George Floyd has led to a big increase in dead people with many of them black. Police protection for politicians making these decisions stayed the same or increased as you would expect from professional hypocrites. The Cult doesn't actually want to abolish the police. It wants to abolish local control over the police and hand it to federal government as the psychopaths advance the Hunger Games Society. Many George Floyd protests turned into violent riots with black stores and businesses destroyed by fire and looting across America fuelled by Black Lives Matter. Woke doesn't do irony. If you want civil rights you must loot the liquor store and the supermarket and make off with a smart TV. It's the only way.

It's not a race war – it's a class war

Black people are patronised by privileged blacks and whites alike and told they are victims of white supremacy. I find it extraordinary to watch privileged blacks supporting the very system and bloodline networks behind the slave trade and parroting the same Cult-serving manipulative crap of their privileged white, often billionaire, associates. It is indeed not a race war but a class war and colour is just a diversion. Black Senator Cory Booker and black Congresswoman Maxine Waters, more residents of Nincompoopia, personify this. Once you tell people they are victims of someone else you devalue both their own responsibility for their plight and the power they have to impact on their reality and experience. Instead

we have: 'You are only in your situation because of whitey – turn on them and everything will change.' It won't change. Nothing changes in our lives unless *we* change it. Crucial to that is never seeing yourself as a victim and always as the creator of your reality. Life is a simple sequence of choice and consequence. Make different choices and you create different consequences. *You* have to make those choices – not Black Lives Matter, the Woke Mafia and anyone else that seeks to dictate your life. Who are they these Wokers, an emotional and psychological road traffic accident, to tell you what to do? Personal empowerment is the last thing the Cult and its Black Lives Matter want black people or anyone else to have. They claim to be defending the underdog while *creating* and perpetuating the underdog. The Cult's worst nightmare is human unity and if they are going to keep blacks, whites and every other race under economic servitude and control then the focus must be diverted from what they have in common to what they can be manipulated to believe divides them. Blacks have to be told that their poverty and plight is the fault of the white bloke living on the street in the same poverty and with the same plight they are experiencing. The difference is that your plight black people is due to him, a white supremacist with 'white privilege' living on the street. Don't unite as one human family against your mutual oppressors and suppressors – fight the oppressor with the white face who is as financially deprived as you are. The Cult knows that as its 'Covid' agenda moves into still new levels of extremism people are going to respond and it has been spreading the seeds of disunity everywhere to stop a united response to the evil that targets *all of us*.

Racist attacks on 'whiteness' are getting ever more outrageous and especially through the American Democratic Party which has an appalling history for anti-black racism. Barack Obama, Joe Biden, Hillary Clinton and Nancy Pelosi all eulogised about Senator Robert Byrd at his funeral in 2010 after a nearly 60-year career in Congress. Byrd was a brutal Ku Klux Klan racist and a violent abuser of Cathy O'Brien in MKUltra. He said he would never fight in the military 'with a negro by my side' and 'rather I should die a thousand times,

and see Old Glory trampled in the dirt never to rise again, than to see this beloved land of ours become degraded by race mongrels, a throwback to the blackest specimen from the wilds'. Biden called Byrd a 'very close friend and mentor'. These 'Woke' hypocrites are not anti-racist they are anti-poor and anti-people not of their perceived class. Here is an illustration of the scale of anti-white racism to which we have now descended. Seriously Woke and moronic *New York Times* contributor Damon Young described whiteness as a 'virus' that 'like other viruses will not die until there are no bodies left for it to infect'. He went on: '… the only way to stop it is to locate it, isolate it, extract it, and kill it.' Young can say that as a black man with no consequences when a white man saying the same in reverse would be facing a jail sentence. *That's* racism. We had super-Woke numbskull senators Tammy Duckworth and Mazie Hirono saying they would object to future Biden Cabinet appointments if he did not nominate more Asian Americans and Pacific Islanders. Never mind the ability of the candidate what do they look like? Duckworth said: 'I will vote for racial minorities and I will vote for LGBTQ, but anyone else I'm not voting for.' Appointing people on the grounds of race is illegal, but that was not a problem for this ludicrous pair. They were on-message and that's a free pass in any situation.

Critical race racism

White children are told at school they are intrinsically racist as they are taught the divisive 'critical race theory'. This claims that the law and legal institutions are inherently racist and that race is a socially constructed concept used by white people to further their economic and political interests at the expense of people of colour. White is a 'virus' as we've seen. Racial inequality results from 'social, economic, and legal differences that white people create between races to maintain white interests which leads to poverty and criminality in minority communities'. I must tell that to the white guy sleeping on the street. The principal of East Side Community School in New York sent white parents a manifesto that called on

them to become 'white traitors' and advocate for full 'white abolition'. These people are teaching your kids when they urgently need a psychiatrist. The 'school' included a chart with 'eight white identities' that ranged from 'white supremacist' to 'white abolition' and defined the behaviour white people must follow to end 'the regime of whiteness'. Woke blacks and their privileged white associates are acting exactly like the slave owners of old and Ku Klux Klan racists like Robert Byrd. They are too full of their own self-purity to see that, but it's true. Racism is not a body type; it's a state of mind that can manifest through any colour, creed or culture.

Another racial fraud is *'equity'*. Not equality of treatment and opportunity – equity. It's a term spun as equality when it means something very different. Equality in its true sense is a raising up while 'equity' is a race to the bottom. Everyone in the same level of poverty is 'equity'. Keep everyone down – that's equity. The Cult doesn't want anyone in the human family to be empowered and BLM leaders, like all these 'anti-racist' organisations, continue their privileged, pampered existence by perpetuating the perception of gathering racism. When is the last time you heard an 'anti-racist' or 'anti-Semitism' organisation say that acts of racism and discrimination have *fallen?* It's not in the interests of their fund-raising and power to influence and the same goes for the professional soccer anti-racism operation, Kick It Out. Two things confirmed that the Black Lives Matter riots in the summer of 2020 were Cult creations. One was that while anti-lockdown protests were condemned in this same period for 'transmitting 'Covid' the authorities supported mass gatherings of Black Lives Matter supporters. I even saw self-deluding people claiming to be doctors say the two types of protest were not the same. No – the non-existent 'Covid' was in favour of lockdowns and attacked those that protested against them while 'Covid' supported Black Lives Matter and kept well away from its protests. The whole thing was a joke and as lockdown protestors were arrested, often brutally, by reframed Face-Nappies we had the grotesque sight of police officers taking the knee to Black Lives Matter, a Cult-funded Marxist

organisation that supports violent riots and wants to destroy the nuclear family and white people.

He's not white? Shucks!

Woke obsession with race was on display again when ten people were shot dead in Boulder, Colorado, in March, 2021. Cult-owned Woke TV channels like CNN said the shooter appeared to be a white man and Wokers were on Twitter condemning 'violent white men' with the usual mantras. Then the shooter's name was released as Ahmad Al Aliwi Alissa, an anti-Trump Arab-American, and the sigh of disappointment could be heard five miles away. Never mind that ten people were dead and what that meant for their families. Race baiting was all that mattered to these sick Cult-serving people like Barack Obama who exploited the deaths to further divide America on racial grounds which is his job for the Cult. This is the man that 'racist' white Americans made the first black president of the United States and then gave him a second term. Not-very-bright Obama has become filthy rich on the back of that and today appears to have a big influence on the Biden administration. Even so he's still a downtrodden black man and a victim of white supremacy. This disingenuous fraud reveals the contempt he has for black people when he puts on a Deep South Alabama accent whenever he talks to them, no, *at* them.

Another BLM red flag was how the now fully-Woke (fully-Cult) and fully-virtue-signalled professional soccer authorities had their teams taking the knee before every match in support of Marxist Black Lives Matter. Soccer authorities and clubs displayed 'Black Lives Matter' on the players' shirts and flashed the name on electronic billboards around the pitch. Any fans that condemned what is a Freemasonic taking-the-knee ritual were widely condemned as you would expect from the Woke virtue-signallers of professional sport and the now fully-Woke media. We have reverse racism in which you are banned from criticising any race or culture except for white people for whom anything goes – say what you like, no problem. What has this got to do with racial harmony and

equality? We've had black supremacists from Black Lives Matter telling white people to fall to their knees in the street and apologise for their white supremacy. Black supremacists acting like white supremacist slave owners of the past couldn't breach their self-obsessed, race-obsessed sense of self-purity. Joe Biden appointed a race-obsessed black supremacist Kristen Clarke to head the Justice Department Civil Rights Division. Clarke claimed that blacks are endowed with 'greater mental, physical and spiritual abilities' than whites. If anyone reversed that statement they would be vilified. Clarke is on-message so no problem. She's never seen a black-white situation in which the black figure is anything but a virtuous victim and she heads the Civil Rights Division which should treat everyone the same or it isn't civil rights. Another perception of the Renegade Mind: If something or someone is part of the Cult agenda they will be supported by Woke governments and media no matter what. If they're not, they will be condemned and censored. It really is that simple and so racist Clarke prospers despite (make that because of) her racism.

The end of culture

Biden's administration is full of such racial, cultural and economic bias as the Cult requires the human family to be divided into warring factions. We are now seeing racially-segregated graduations and everything, but everything, is defined through the lens of perceived 'racism. We have 'racist' mathematics, 'racist' food and even 'racist' *plants*. World famous Kew Gardens in London said it was changing labels on plants and flowers to tell its pre-'Covid' more than two million visitors a year how racist they are. Kew director Richard Deverell said this was part of an effort to 'move quickly to decolonise collections' after they were approached by one Ajay Chhabra 'an actor with an insight into how sugar cane was linked to slavery'. They are *plants* you idiots. 'Decolonisation' in the Woke manual really means colonisation of society with its mentality and by extension colonisation by the Cult. We are witnessing a new Chinese-style 'Cultural Revolution' so essential to the success of all

Marxist takeovers. Our cultural past and traditions have to be swept away to allow a new culture to be built-back-better. Woke targeting of long-standing Western cultural pillars including historical monuments and cancelling of historical figures is what happened in the Mao revolution in China which 'purged remnants of capitalist and traditional elements from Chinese society' and installed Maoism as the dominant ideology'. For China see the Western world today and for 'dominant ideology' see Woke. Better still see Marxism or Maoism. The 'Covid' hoax has specifically sought to destroy the arts and all elements of Western culture from people meeting in a pub or restaurant to closing theatres, music venues, sports stadiums, places of worship and even banning *singing*. Destruction of Western society is also why criticism of any religion is banned except for Christianity which again is the dominant religion as white is the numerically-dominant race. Christianity may be fading rapidly, but its history and traditions are weaved through the fabric of Western society. Delete the pillars and other structures will follow until the whole thing collapses. I am not a Christian defending that religion when I say that. I have no religion. It's just a fact. To this end Christianity has itself been turned Woke to usher its own downfall and its ranks are awash with 'change agents' – knowing and unknowing – at every level including Pope Francis (*definitely* knowing) and the clueless Archbishop of Canterbury Justin Welby (possibly not, but who can be sure?). Woke seeks to coordinate attacks on Western culture, traditions, and ways of life through 'intersectionality' defined as 'the complex, cumulative way in which the effects of multiple forms of discrimination (such as racism, sexism, and classism) combine, overlap, or intersect especially in the experiences of marginalised individuals or groups'. Wade through the Orwellian Woke-speak and this means coordinating disparate groups in a common cause to overthrow freedom and liberal values.

The entire structure of public institutions has been infested with Woke – government at all levels, political parties, police, military, schools, universities, advertising, media and trade unions. This abomination has been achieved through the Cult web by appointing

Wokers to positions of power and battering non-Wokers into line through intimidation, isolation and threats to their job. Many have been fired in the wake of the empathy-deleted, vicious hostility of 'social justice' Wokers and the desire of gutless, spineless employers to virtue-signal their Wokeness. Corporations are filled with Wokers today, most notably those in Silicon Valley. Ironically at the top they are not Woke at all. They are only exploiting the mentality their Cult masters have created and funded to censor and enslave while the Wokers cheer them on until it's their turn. Thus the Woke 'liberal left' is an inversion of the traditional liberal left. Campaigning for justice on the grounds of power and wealth distribution has been replaced by campaigning for identity politics. The genuine traditional left would never have taken money from today's billionaire abusers of fairness and justice and nor would the billionaires have wanted to fund that genuine left. It would not have been in their interests to do so. The division of opinion in those days was between the haves and have nots. This all changed with Cult manipulated and funded identity politics. The division of opinion today is between Wokers and non-Wokers and not income brackets. Cult corporations and their billionaires may have taken wealth disparity to cataclysmic levels of injustice, but as long as they speak the language of Woke, hand out the dosh to the Woke network and censor the enemy they are 'one of us'. Billionaires who don't give a damn about injustice are laughing at them till their bellies hurt. Wokers are not even close to self-aware enough to see that. The transformed 'left' dynamic means that Wokers who drone on about 'social justice' are funded by billionaires that have destroyed social justice the world over. It's *why* they are billionaires.

The climate con

Nothing encapsulates what I have said more comprehensively than the hoax of human-caused global warming. I have detailed in my books over the years how Cult operatives and organisations were the pump-primers from the start of the climate con. A purpose-built vehicle for this is the Club of Rome established by the Cult in 1968

with the Rockefellers and Rothschilds centrally involved all along. Their gofer frontman Maurice Strong, a Canadian oil millionaire, hosted the Earth Summit in Rio de Janeiro, Brazil, in 1992 where the global 'green movement' really expanded in earnest under the guiding hand of the Cult. The Earth Summit established Agenda 21 through the Cult-created-and-owned United Nations to use the illusion of human-caused climate change to justify the transformation of global society to save the world from climate disaster. It is a No-Problem-Reaction-Solution sold through governments, media, schools and universities as whole generations have been terrified into believing that the world was going to end in their lifetimes unless what old people had inflicted upon them was stopped by a complete restructuring of how everything is done. Chill, kids, it's all a hoax. Such restructuring is precisely what the Cult agenda demands (purely by coincidence of course). Today this has been given the codename of the Great Reset which is only an updated term for Agenda 21 and its associated Agenda 2030. The latter, too, is administered through the UN and was voted into being by the General Assembly in 2015. Both 21 and 2030 seek centralised control of all resources and food right down to the raindrops falling on your own land. These are some of the demands of Agenda 21 established in 1992. See if you recognise this society emerging today:

- End national sovereignty
- State planning and management of all land resources, ecosystems, deserts, forests, mountains, oceans and fresh water; agriculture; rural development; biotechnology; and ensuring *'equity'*
- The state to 'define the role' of business and financial resources
- Abolition of private property
- 'Restructuring' the family unit (see BLM)
- Children raised by the state
- People told what their job will be
- Major restrictions on movement
- Creation of 'human settlement zones'

- Mass resettlement as people are forced to vacate land where they live
- Dumbing down education
- Mass global depopulation in pursuit of all the above

The United Nations was created as a Trojan horse for world government. With the climate con of critical importance to promoting that outcome you would expect the UN to be involved. Oh, it's involved all right. The UN is promoting Agenda 21 and Agenda 2030 justified by 'climate change' while also driving the climate hoax through its Intergovernmental Panel on Climate Change (IPCC), one of the world's most corrupt organisations. The IPCC has been lying ferociously and constantly since the day it opened its doors with the global media hanging unquestioningly on its every mendacious word. The Green movement is entirely Woke and has long lost its original environmental focus since it was co-opted by the Cult. An obsession with 'global warming' has deleted its values and scrambled its head. I experienced a small example of what I mean on a beautiful country walk that I have enjoyed several times a week for many years. The path merged into the fields and forests and you felt at one with the natural world. Then a 'Green' organisation, the Hampshire and Isle of Wight Wildlife Trust, took over part of the land and proceeded to cut down a large number of trees, including mature ones, to install a horrible big, bright steel 'this-is-ours-stay-out' fence that destroyed the whole atmosphere of this beautiful place. No one with a feel for nature would do that. Day after day I walked to the sound of chainsaws and a magnificent mature weeping willow tree that I so admired was cut down at the base of the trunk. When I challenged a Woke young girl in a green shirt (of course) about this vandalism she replied: 'It's a weeping willow – it will grow back.' This is what people are paying for when they donate to the Hampshire and Isle of Wight Wildlife Trust and many other 'green' organisations today. It is not the environmental movement that I knew and instead has become a support-system – as with Extinction Rebellion – for a very dark agenda.

Private jets for climate justice

The Cult-owned, Gates-funded, World Economic Forum and its founder Klaus Schwab were behind the emergence of Greta Thunberg to harness the young behind the climate agenda and she was invited to speak to the world at … the UN. Schwab published a book, *Covid-19: The Great Reset* in 2020 in which he used the 'Covid' hoax and the climate hoax to lay out a new society straight out of Agenda 21 and Agenda 2030. Bill Gates followed in early 2021 when he took time out from destroying the world to produce a book in his name about the way to save it. Gates flies across the world in private jets and admitted that 'I probably have one of the highest greenhouse gas footprints of anyone on the planet … my personal flying alone is gigantic.' He has also bid for the planet's biggest private jet operator. Other climate change saviours who fly in private jets include John Kerry, the US Special Presidential Envoy for Climate, and actor Leonardo DiCaprio, a 'UN Messenger of Peace with special focus on climate change'. These people are so full of bullshit they could corner the market in manure. We mustn't be sceptical, though, because the Gates book, *How to Avoid a Climate Disaster: The Solutions We Have and the Breakthroughs We Need*, is a genuine attempt to protect the world and not an obvious pile of excrement attributed to a mega-psychopath aimed at selling his masters' plans for humanity. The Gates book and the other shite-pile by Klaus Schwab could have been written by the same person and may well have been. Both use 'climate change' and 'Covid' as the excuses for their new society and by coincidence the Cult's World Economic Forum and Bill and Melinda Gates Foundation promote the climate hoax and hosted Event 201 which pre-empted with a 'simulation' the very 'coronavirus' hoax that would be simulated for real on humanity within weeks. The British 'royal' family is promoting the 'Reset' as you would expect through Prince 'climate change caused the war in Syria' Charles and his hapless son Prince William who said that we must 'reset our relationship with nature and our trajectory as a species' to avoid a climate disaster. Amazing how many promotors of the 'Covid' and 'climate change' control

systems are connected to Gates and the World Economic Forum. A 'study' in early 2021 claimed that carbon dioxide emissions must fall by the equivalent of a global lockdown roughly every two years for the next decade to save the planet. The 'study' appeared in the same period that the Schwab mob claimed in a video that lockdowns destroying the lives of billions are good because they make the earth 'quieter' with less 'ambient noise'. They took down the video amid a public backlash for such arrogant, empathy-deleted stupidity You see, however, where they are going with this. Corinne Le Quéré, a professor at the Tyndall Centre for Climate Change Research, University of East Anglia, was lead author of the climate lockdown study, and she writes for … the World Economic Forum. Gates calls in 'his' book for changing 'every aspect of the economy' (long-time Cult agenda) and for humans to eat synthetic 'meat' (predicted in my books) while cows and other farm animals are eliminated. Australian TV host and commentator Alan Jones described what carbon emission targets would mean for farm animals in Australia alone if emissions were reduced as demanded by 35 percent by 2030 and zero by 2050:

Well, let's take agriculture, the total emissions from agriculture are about 75 million tonnes of carbon dioxide, equivalent. Now reduce that by 35 percent and you have to come down to 50 million tonnes, I've done the maths. So if you take for example 1.5 million cows, you're going to have to reduce the herd by 525,000 [by] 2030, nine years, that's 58,000 cows a year. The beef herd's 30 million, reduce that by 35 percent, that's 10.5 million, which means 1.2 million cattle have to go every year between now and 2030. This is insanity!

There are 75 million sheep. Reduce that by 35 percent, that's 26 million sheep, that's almost 3 million a year. So under the Paris Agreement over 30 million beasts. dairy cows, cattle, pigs and sheep would go. More than 8,000 every minute of every hour for the next decade, do these people know what they're talking about?

Clearly they don't at the level of campaigners, politicians and administrators. The Cult *does* know; that's the outcome it wants. We are faced with not just a war on humanity. Animals and the natural world are being targeted and I have been saying since the 'Covid' hoax began that the plan eventually was to claim that the 'deadly virus' is able to jump from animals, including farm animals and

domestic pets, to humans. Just before this book went into production came this story: 'Russia registers world's first Covid-19 vaccine for cats & dogs as makers of Sputnik V warn pets & farm animals could spread virus'. The report said 'top scientists warned that the deadly pathogen could soon begin spreading through homes and farms' and 'the next stage is the infection of farm and domestic animals'. Know the outcome and you'll see the journey. Think what that would mean for animals and keep your eye on a term called zoonosis or zoonotic diseases which transmit between animals and humans. The Cult wants to break the connection between animals and people as it does between people and people. Farm animals fit with the Cult agenda to transform food from natural to synthetic.

The gas of life is killing us

There can be few greater examples of Cult inversion than the condemnation of carbon dioxide as a dangerous pollutant when it is the gas of life. Without it the natural world would be dead and so we would all be dead. We breathe in oxygen and breathe out carbon dioxide while plants produce oxygen and absorb carbon dioxide. It is a perfect symbiotic relationship that the Cult wants to dismantle for reasons I will come to in the final two chapters. Gates, Schwab, other Cult operatives and mindless repeaters, want the world to be 'carbon neutral' by at least 2050 and the earlier the better. 'Zero carbon' is the cry echoed by lunatics calling for 'Zero Covid' when we already have it. These carbon emission targets will deindustrialise the world in accordance with Cult plans – the post-industrial, post-democratic society – and with so-called renewables like solar and wind not coming even close to meeting human energy needs blackouts and cold are inevitable. Texans got the picture in the winter of 2021 when a snow storm stopped wind turbines and solar panels from working and the lights went down along with water which relies on electricity for its supply system. Gates wants everything to be powered by electricity to ensure that his masters have the kill switch to stop all human activity, movement, cooking, water and warmth any time they like. The climate lie is so

stupendously inverted that it claims we must urgently reduce carbon dioxide when we *don't have enough*.

Co2 in the atmosphere is a little above 400 parts per million when the optimum for plant growth is 2,000 ppm and when it falls anywhere near 150 ppm the natural world starts to die and so do we. It fell to as low as 280 ppm in an 1880 measurement in Hawaii and rose to 413 ppm in 2019 with industrialisation which is why the planet has become *greener* in the industrial period. How insane then that psychopathic madman Gates is not satisfied only with blocking the rise of Co2. He's funding technology to suck it out of the atmosphere. The reason why will become clear. The industrial era is not destroying the world through Co2 and has instead turned around a potentially disastrous ongoing fall in Co2. Greenpeace co-founder and scientist Patrick Moore walked away from Greenpeace in 1986 and has exposed the green movement for fear-mongering and lies. He said that 500 million years ago there was *17 times* more Co2 in the atmosphere than we have today and levels have been falling for hundreds of millions of years. In the last 150 million years Co2 levels in Earth's atmosphere had reduced by *90 percent*. Moore said that by the time humanity began to unlock carbon dioxide from fossil fuels we were at '38 seconds to midnight' and in that sense: 'Humans are [the Earth's] salvation.' Moore made the point that only half the Co2 emitted by fossil fuels stays in the atmosphere and we should remember that all pollution pouring from chimneys that we are told is carbon dioxide is in fact nothing of the kind. It's pollution. Carbon dioxide is an invisible gas.

William Happer, Professor of Physics at Princeton University and long-time government adviser on climate, has emphasised the Co2 deficiency for maximum growth and food production. Greenhouse growers don't add carbon dioxide for a bit of fun. He said that most of the warming in the last 100 years, after the earth emerged from the super-cold period of the 'Little Ice Age' into a natural warming cycle, was over by 1940. Happer said that a peak year for warming in 1988 can be explained by a 'monster El Nino' which is a natural and cyclical warming of the Pacific that has nothing to do with 'climate

change'. He said the effect of Co2 could be compared to painting a wall with red paint in that once two or three coats have been applied it didn't matter how much more you slapped on because the wall will not get much redder. Almost all the effect of the rise in Co2 has already happened, he said, and the volume in the atmosphere would now have to *double* to increase temperature by a single degree. Climate hoaxers know this and they have invented the most ridiculously complicated series of 'feedback' loops to try to overcome this rather devastating fact. You hear puppet Greta going on cluelessly about feedback loops and this is why.

The Sun affects temperature? No you *climate denier*

Some other nonsense to contemplate: Climate graphs show that rises in temperature do not follow rises in Co2 – *it's the other way round* with a lag between the two of some 800 years. If we go back 800 years from present time we hit the Medieval Warm Period when temperatures were higher than now without any industrialisation and this was followed by the Little Ice Age when temperatures plummeted. The world was still emerging from these centuries of serious cold when many climate records began which makes the ever-repeated line of the 'hottest year since records began' meaningless when you are not comparing like with like. The coldest period of the Little Ice Age corresponded with the lowest period of sunspot activity when the Sun was at its least active. Proper scientists will not be at all surprised by this when it confirms the obvious fact that earth temperature is affected by the scale of Sun activity and the energetic power that it subsequently emits; but when is the last time you heard a climate hoaxer talking about the Sun as a source of earth temperature?? Everything has to be focussed on Co2 which makes up just 0.117 percent of so-called greenhouse gases and only a fraction of even that is generated by human activity. The rest is natural. More than *90 percent* of those greenhouse gases are water vapour and clouds (Fig 9). Ban moisture I say. Have you noticed that the climate hoaxers no longer use the polar bear as their promotion image? That's because far from becoming extinct polar

bear communities are stable or thriving. Joe Bastardi, American meteorologist, weather forecaster and outspoken critic of the climate lie, documents in his book *The Climate Chronicles* how weather patterns and events claimed to be evidence of climate change have been happening since long before industrialisation: 'What happened before naturally is happening again, as is to be expected given the cyclical nature of the climate due to the design of the planet.' If you read the detailed background to the climate hoax in my other books you will shake your head and wonder how anyone could believe the crap which has spawned a multi-trillion dollar industry based on absolute garbage (see HIV causes AIDs and Sars-Cov-2 causes 'Covid-19'). Climate and 'Covid' have much in common given they have the same source. They both have the contradictory *everything* factor in which everything is explained by reference to them. It's hot – 'it's climate change'. It's cold – 'it's climate change'. I got a sniffle – 'it's Covid'. I haven't got a sniffle – 'it's Covid'. Not having a sniffle has to be a symptom of 'Covid'. Everything is and not having a sniffle is especially dangerous if you are a slow walker. For sheer audacity I offer you a Cambridge University 'study' that actually linked 'Covid' to 'climate change'. It had to happen eventually. They concluded that climate change played a role in 'Covid-19' spreading from animals to humans because … wait for it … I kid you not … *the two groups were forced closer together as populations grow*. Er, that's it. The whole foundation on which this depended was that 'Bats are the likely zoonotic origin of SARS-CoV-1 and SARS-CoV-2'. Well, they are not. They are nothing to do with it. Apart from bats not being the origin and therefore 'climate change' effects on bats being irrelevant I am in awe of their academic insight. Where would we be without them? Not where we are that's for sure.

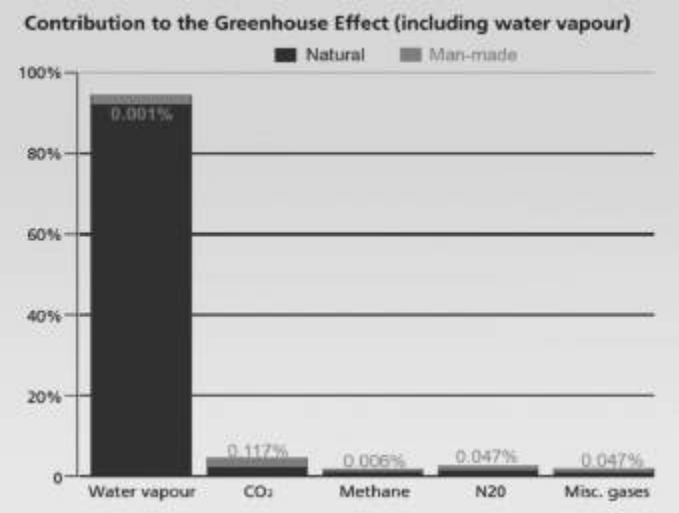


Figure 9: The idea that the gas of life is disastrously changing the climate is an insult to brain cell activity.

One other point about the weather is that climate modification is now well advanced and not every major weather event is natural – or earthquake come to that. I cover this subject at some length in other books. China is openly planning a rapid expansion of its weather modification programme which includes changing the climate in an area more than one and a half times the size of India. China used weather manipulation to ensure clear skies during the 2008 Olympics in Beijing. I have quoted from US military documents detailing how to employ weather manipulation as a weapon of war and they did that in the 1960s and 70s during the conflict in Vietnam with Operation Popeye manipulating monsoon rains for military purposes. Why would there be international treaties on weather modification if it wasn't possible? Of course it is. Weather is energetic information and it can be changed.

How was the climate hoax pulled off? See 'Covid'

If you can get billions to believe in a 'virus' that doesn't exist you can get them to believe in human-caused climate change that doesn't exist. Both are being used by the Cult to transform global society in the way it has long planned. Both hoaxes have been achieved in pretty much the same way. First you declare a lie is a fact. There's a

'virus' you call SARS-Cov-2 or humans are warming the planet with their behaviour. Next this becomes, via Cult networks, the foundation of government, academic and science policy and belief. Those who parrot the mantra are given big grants to produce research that confirms the narrative is true and ever more 'symptoms' are added to make the 'virus'/'climate change' sound even more scary. Scientists and researchers who challenge the narrative have their grants withdrawn and their careers destroyed. The media promote the lie as the unquestionable truth and censor those with an alternative view or evidence. A great percentage of the population believe what they are told as the lie becomes an everybody-knows-that and the believing-masses turn on those with a mind of their own. The technique has been used endlessly throughout human history. Wokers are the biggest promotors of the climate lie *and* 'Covid' fascism because their minds are owned by the Cult; their sense of self-righteous self-purity knows no bounds; and they exist in a bubble of reality in which facts are irrelevant and only get in the way of looking without seeing.

Running through all of this like veins in a blue cheese is control of information, which means control of perception, which means control of behaviour, which collectively means control of human society. The Cult owns the global media and Silicon Valley fascists for the simple reason that it *has* to. Without control of information it can't control perception and through that human society. Examine every facet of the Cult agenda and you will see that anything supporting its introduction is never censored while anything pushing back is always censored. I say again: Psychopaths that know why they are doing this must go before Nuremberg trials and those that follow their orders must trot along behind them into the same dock. 'I was just following orders' didn't work the first time and it must not work now. Nuremberg trials must be held all over the world before public juries for politicians, government officials, police, compliant doctors, scientists and virologists, and all Cult operatives such as Gates, Tedros, Fauci, Vallance, Whitty, Ferguson, Zuckerberg, Wojcicki, Brin, Page, Dorsey, the whole damn lot of

them – including, no *especially*, the psychopath psychologists. Without them and the brainless, gutless excuses for journalists that have repeated their lies, none of this could be happening. Nobody can be allowed to escape justice for the psychological and economic Armageddon they are all responsible for visiting upon the human race.

As for the compliant, unquestioning, swathes of humanity, and the self-obsessed, all-knowing ignorance of the Wokers … don't start me. God help their kids. God help their grandkids. God *help them*.

CHAPTER NINE

We must have it? So what is it?

Well I won't back down. No, I won't back down. You can stand me up at the Gates of Hell. But I won't back down
Tom Petty

I will now focus on the genetically-manipulating 'Covid vaccines' which do not meet this official definition of a vaccine by the US Centers for Disease Control (CDC): 'A product that stimulates a person's immune system to produce immunity to a specific disease, protecting the person from that disease.' On that basis 'Covid vaccines' are not a vaccine in that the makers don't even claim they stop infection or transmission.

They are instead part of a multi-levelled conspiracy to change the nature of the human body and what it means to be 'human' and to depopulate an enormous swathe of humanity. What I shall call Human 1.0 is on the cusp of becoming Human 2.0 and for very sinister reasons. Before I get to the 'Covid vaccine' in detail here's some background to vaccines in general. Government regulators do not test vaccines – the makers do – and the makers control which data is revealed and which isn't. Children in America are given 50 vaccine doses by age six and 69 by age 19 and the effect of the whole combined schedule has never been tested. Autoimmune diseases when the immune system attacks its own body have soared in the mass vaccine era and so has disease in general in children and the young. Why wouldn't this be the case when vaccines target the *immune system?* The US government gave Big Pharma drug

companies immunity from prosecution for vaccine death and injury in the 1986 National Childhood Vaccine Injury Act (NCVIA) and since then the government (taxpayer) has been funding compensation for the consequences of Big Pharma vaccines. The criminal and satanic drug giants can't lose and the vaccine schedule has increased dramatically since 1986 for this reason. There is no incentive to make vaccines safe and a big incentive to make money by introducing ever more. Even against a ridiculously high bar to prove vaccine liability, and with the government controlling the hearing in which it is being challenged for compensation, the vaccine court has so far paid out more than $4 billion. These are the vaccines we are told are safe and psychopaths like Zuckerberg censor posts saying otherwise. The immunity law was even justified by a ruling that vaccines by their nature were 'unavoidably unsafe'.

Check out the ingredients of vaccines and you will be shocked if you are new to this. *They put that in children's bodies?? What??* Try aluminium, a brain toxin connected to dementia, aborted foetal tissue and formaldehyde which is used to embalm corpses. World-renowned aluminium expert Christopher Exley had his research into the health effect of aluminium in vaccines shut down by Keele University in the UK when it began taking funding from the Bill and Melinda Gates Foundation. Research when diseases 'eradicated' by vaccines began to decline and you will find the fall began long *before* the vaccine was introduced. Sometimes the fall even plateaued after the vaccine. Diseases like scarlet fever for which there was no vaccine declined in the same way because of environmental and other factors. A perfect case in point is the polio vaccine. Polio began when lead arsenate was first sprayed as an insecticide and residues remained in food products. Spraying started in 1892 and the first US polio epidemic came in Vermont in 1894. The simple answer was to stop spraying, but Rockefeller-created Big Pharma had a better idea. Polio was decreed to be caused by the *poliovirus* which 'spreads from person to person and can infect a person's spinal cord'. Lead arsenate was replaced by the lethal DDT which had the same effect of causing paralysis by damaging the brain and central nervous

system. Polio plummeted when DDT was reduced and then banned, but the vaccine is still given the credit for something it didn't do. Today by far the biggest cause of polio is the vaccines promoted by Bill Gates. Vaccine justice campaigner Robert Kennedy Jr, son of assassinated (by the Cult) US Attorney General Robert Kennedy, wrote:

> In 2017, the World Health Organization (WHO) reluctantly admitted that the global explosion in polio is predominantly vaccine strain. The most frightening epidemics in Congo, Afghanistan, and the Philippines, are all linked to vaccines. In fact, by 2018, 70% of global polio cases were vaccine strain.

Vaccines make fortunes for Cult-owned Gates and Big Pharma while undermining the health and immune systems of the population. We had a glimpse of the mentality behind the Big Pharma cartel with a report on WION (World is One News), an international English language TV station based in India, which exposed the extraordinary behaviour of US drug company Pfizer over its 'Covid vaccine'. The WION report told how Pfizer had made fantastic demands of Argentina, Brazil and other countries in return for its 'vaccine'. These included immunity from prosecution, even for Pfizer negligence, government insurance to protect Pfizer from law suits and handing over as collateral sovereign assets of the country to include Argentina's bank reserves, military bases and embassy buildings. Pfizer demanded the same of Brazil in the form of waiving sovereignty of its assets abroad; exempting Pfizer from Brazilian laws; and giving Pfizer immunity from all civil liability. This is a 'vaccine' developed with government funding. Big Pharma is evil incarnate as a creation of the Cult and all must be handed tickets to Nuremberg.

Phantom 'vaccine' for a phantom 'disease'

I'll expose the 'Covid vaccine' fraud and then go on to the wider background of why the Cult has set out to 'vaccinate' every man, woman and child on the planet for an alleged 'new disease' with a survival rate of 99.77 percent (or more) even by the grotesquely-

manipulated figures of the World Health Organization and Johns Hopkins University. The 'infection' to 'death' ratio is 0.23 to 0.15 percent according to Stanford epidemiologist Dr John Ioannidis and while estimates vary the danger remains tiny. I say that if the truth be told the fake infection to fake death ratio is zero. Never mind all the evidence I have presented here and in *The Answer* that there is no 'virus' let us just focus for a moment on that death-rate figure of say 0.23 percent. The figure includes all those worldwide who have tested positive with a test not testing for the 'virus' and then died within 28 days or even longer of any other cause – *any other cause*. Now subtract all those illusory 'Covid' deaths on the global data sheets from the 0.23 percent. What do you think you would be left with? *Zero*. A vaccination has never been successfully developed for a so-called coronavirus. They have all failed at the animal testing stage when they caused hypersensitivity to what they were claiming to protect against and made the impact of a disease far worse. Cult-owned vaccine corporations got around that problem this time by bypassing animal trials, going straight to humans and making the length of the 'trials' before the public rollout as short as they could get away with. Normally it takes five to ten years or more to develop vaccines that still cause demonstrable harm to many people and that's without including the long-term effects that are never officially connected to the vaccination. 'Covid' non-vaccines have been officially produced and approved in a matter of months from a standing start and part of the reason is that (a) they were developed before the 'Covid' hoax began and (b) they are based on computer programs and not natural sources. Official non-trials were so short that government agencies gave *emergency*, not full, approval. 'Trials' were not even completed and full approval cannot be secured until they are. Public 'Covid vaccination' is actually a *continuation of the trial*. Drug company 'trials' are not scheduled to end until 2023 by which time a lot of people are going to be dead. Data on which government agencies gave this emergency approval was supplied by the Big Pharma corporations themselves in the form of Pfizer/BioNTech, AstraZeneca, Moderna, Johnson & Johnson, and

others, and this is the case with all vaccines. By its very nature *emergency* approval means drug companies do not have to prove that the 'vaccine' is 'safe and effective'. How could they with trials way short of complete? Government regulators only have to *believe* that they *could* be safe and effective. It is criminal manipulation to get products in circulation with no testing worth the name. Agencies giving that approval are infested with Big Pharma-connected place-people and they act in the interests of Big Pharma (the Cult) and not the public about whom they do not give a damn.

More human lab rats

'Covid vaccines' produced in record time by Pfizer/BioNTech and Moderna employ a technique *never approved before for use on humans*. They are known as mRNA 'vaccines' and inject a synthetic version of 'viral' mRNA or 'messenger RNA'. The key is in the term 'messenger'. The body works, or doesn't, on the basis of information messaging. Communications are constantly passing between and within the genetic system and the brain. Change those messages and you change the state of the body and even its very nature and you can change psychology and behaviour by the way the brain processes information. I think you are going to see significant changes in personality and perception of many people who have had the 'Covid vaccine' synthetic potions. Insider Aldous Huxley predicted the following in 1961 and mRNA 'vaccines' can be included in the term 'pharmacological methods':

> There will be, in the next generation or so, a pharmacological method of making people love their servitude, and producing dictatorship without tears, so to speak, producing a kind of painless concentration camp for entire societies, so that people will in fact have their own liberties taken away from them, but rather enjoy it, because they will be distracted from any desire to rebel by propaganda or brainwashing, or brainwashing enhanced by pharmacological methods. And this seems to be the final revolution.

Apologists claim that mRNA synthetic 'vaccines' don't change the DNA genetic blueprint because RNA does not affect DNA only the other way round. This is so disingenuous. A process called 'reverse

transcription' can convert RNA into DNA and be integrated into DNA in the cell nucleus. This was highlighted in December, 2020, by scientists at Harvard and Massachusetts Institute of Technology (MIT). Geneticists report that more than 40 percent of mammalian genomes results from reverse transcription. On the most basic level if messaging changes then that sequence must lead to changes in DNA which is receiving and transmitting those communications. How can introducing synthetic material into cells not change the cells where DNA is located? The process is known as transfection which is defined as 'a technique to insert foreign nucleic acid (DNA or RNA) into a cell, typically with the intention of altering the properties of the cell'. Researchers at the Sloan Kettering Institute in New York found that changes in messenger RNA can deactivate tumour-suppressing proteins and thereby promote cancer. This is what happens when you mess with messaging. 'Covid vaccine' maker Moderna was founded in 2010 by Canadian stem cell biologist Derrick J. Rossi after his breakthrough discovery in the field of transforming and reprogramming stem cells. These are neutral cells that can be programmed to become any cell including sperm cells. Moderna was therefore founded on the principle of genetic manipulation and has never produced any vaccine or drug before its genetically-manipulating synthetic 'Covid' shite. Look at the name – Mode-RNA or Modify-RNA. Another important point is that the US Supreme Court has ruled that genetically-modified DNA, or complementary DNA (cDNA) synthesized in the laboratory from messenger RNA, can be patented and owned. These psychopaths are doing this to the human body.

Cells replicate synthetic mRNA in the 'Covid vaccines' and in theory the body is tricked into making antigens which trigger antibodies to target the 'virus spike proteins' which as Dr Tom Cowan said have *never been seen*. Cut the crap and these 'vaccines' deliver *self-replicating* synthetic material to the cells with the effect of changing human DNA. The more of them you have the more that process is compounded while synthetic material is all the time self-replicating. 'Vaccine'-maker Moderna describes mRNA as 'like

software for the cell' and so they are messing with the body's software. What happens when you change the software in a computer? Everything changes. For this reason the Cult is preparing a production line of mRNA 'Covid vaccines' and a long list of excuses to use them as with all the 'variants' of a 'virus' never shown to exist. The plan is further to transfer the mRNA technique to other vaccines mostly given to children and young people. The cumulative consequences will be a transformation of human DNA through a constant infusion of synthetic genetic material which will kill many and change the rest. Now consider that governments that have given emergency approval for a vaccine that's not a vaccine; never been approved for humans before; had no testing worth the name; and the makers have been given immunity from prosecution for any deaths or adverse effects suffered by the public. The UK government awarded *permanent legal indemnity* to itself and its employees for harm done when a patient is being treated for 'Covid-19' or 'suspected Covid-19'. That is quite a thought when these are possible 'side-effects' from the 'vaccine' (they are not 'side', they are effects) listed by the US Food and Drug Administration:

Guillain-Barre syndrome; acute disseminated encephalomyelitis; transverse myelitis; encephalitis; myelitis; encephalomyelitis; meningoencephalitis; meningitis; encephalopathy; convulsions; seizures; stroke; narcolepsy; cataplexy; anaphylaxis; acute myocardial infarction (heart attack); myocarditis; pericarditis; autoimmune disease; death; implications for pregnancy, and birth outcomes; other acute demyelinating diseases; non anaphylactic allergy reactions; thrombocytopenia ; disseminated intravascular coagulation; venous thromboembolism; arthritis; arthralgia; joint pain; Kawasaki disease; multisystem inflammatory syndrome in children; vaccine enhanced disease. The latter is the way the 'vaccine' has the potential to make diseases far worse than they would otherwise be.

UK doctor and freedom campaigner Vernon Coleman described the conditions in this list as 'all unpleasant, most of them very serious, and you can't get more serious than death'. The thought that anyone at all has had the 'vaccine' in these circumstances is testament to the potential that humanity has for clueless, unquestioning, stupidity and for many that programmed stupidity has already been terminal.

An insider speaks

Dr Michael Yeadon is a former Vice President, head of research and Chief Scientific Adviser at vaccine giant Pfizer. Yeadon worked on the inside of Big Pharma, but that did not stop him becoming a vocal critic of 'Covid vaccines' and their potential for multiple harms, including infertility in women. By the spring of 2021 he went much further and even used the no, no, term 'conspiracy'. When you begin to see what is going on it is impossible not to do so. Yeadon spoke out in an interview with freedom campaigner James Delingpole and I mentioned earlier how he said that no one had samples of 'the virus'. He explained that the mRNA technique originated in the anti-cancer field and ways to turn on and off certain genes which could be advantageous if you wanted to stop cancer growing out of control. 'That's the origin of them. They are a very unusual application, really.' Yeadon said that treating a cancer patient with an aggressive procedure might be understandable if the alternative was dying, but it was quite another thing to use the same technique as a public health measure. Most people involved wouldn't catch the infectious agent you were vaccinating against and if they did they probably wouldn't die:

> If you are really using it as a public health measure you really want to as close as you can get to zero sides-effects … I find it odd that they chose techniques that were really cutting their teeth in the field of oncology and I'm worried that in using gene-based vaccines that have to be injected in the body and spread around the body, get taken up into some cells, and the regulators haven't quite told us which cells they get taken up into … you are going to be generating a wide range of responses … with multiple steps each of which could go well or badly.

I doubt the Cult intends it to go well. Yeadon said that you can put any gene you like into the body through the 'vaccine'. 'You can certainly give them a gene that would do them some harm if you wanted.' I was intrigued when he said that when used in the cancer field the technique could turn genes on and off. I explore this process in *The Answer* and with different genes having different functions you could create mayhem – physically and psychologically – if you turned the wrong ones on and the right ones off. I read reports of an experiment by researchers at the University of Washington's school of computer science and engineering in which they encoded DNA to infect computers. The body is itself a biological computer and if human DNA can inflict damage on a computer why can't the computer via synthetic material mess with the human body? It can. The Washington research team said it was possible to insert malicious malware into 'physical DNA strands' and corrupt the computer system of a gene sequencing machine as it 'reads gene letters and stores them as binary digits 0 and 1'. They concluded that hackers could one day use blood or spit samples to access computer systems and obtain sensitive data from police forensics labs or infect genome files. It is at this level of digital interaction that synthetic 'vaccines' need to be seen to get the full picture and that will become very clear later on. Michael Yeadon said it made no sense to give the 'vaccine' to younger people who were in no danger from the 'virus'. What was the benefit? It was all downside with potential effects:

> The fact that my government in what I thought was a civilised, rational country, is raining [the 'vaccine'] on people in their 30s and 40s, even my children in their 20s, they're getting letters and phone calls, I know this is not right and any of you doctors who are vaccinating you know it's not right, too. They are not at risk. They are not at risk from the disease, so you are now hoping that the side-effects are so rare that you get away with it. You don't give new technology … that you don't understand to 100 percent of the population.

Blood clot problems with the AstraZeneca 'vaccine' have been affecting younger people to emphasise the downside risks with no benefit. AstraZeneca's version, produced with Oxford University, does not use mRNA, but still gets its toxic cocktail inside cells where

it targets DNA. The Johnson & Johnson 'vaccine' which uses a similar technique has also produced blood clot effects to such an extent that the United States paused its use at one point. They are all 'gene therapy' (cell modification) procedures and not 'vaccines'. The truth is that once the content of these injections enter cells we have no idea what the effect will be. People can speculate and some can give very educated opinions and that's good. In the end, though, only the makers know what their potions are designed to do and even they won't know every last consequence. Michael Yeadon was scathing about doctors doing what they knew to be wrong. 'Everyone's mute', he said. Doctors in the NHS must know this was not right, coming into work and injecting people. 'I don't know how they sleep at night. I know I couldn't do it. I know that if I were in that position I'd have to quit.' He said he knew enough about toxicology to know this was not a good risk-benefit. Yeadon had spoken to seven or eight university professors and all except two would not speak out publicly. Their universities had a policy that no one said anything that countered the government and its medical advisors. They were afraid of losing their government grants. This is how intimidation has been used to silence the truth at every level of the system. I say silence, but these people could still speak out if they made that choice. Yeadon called them 'moral cowards' – 'This is about your children and grandchildren's lives and you have just buggered off and left it.'

'Variant' nonsense

Some of his most powerful comments related to the alleged 'variants' being used to instil more fear, justify more lockdowns, and introduce more 'vaccines'. He said government claims about 'variants' were nonsense. He had checked the alleged variant 'codes' and they were 99.7 percent identical to the 'original'. This was the human identity difference equivalent to putting a baseball cap on and off or wearing it the other way round. A 0.3 percent difference would make it impossible for that 'variant' to escape immunity from the 'original'. This made no sense of having new 'vaccines' for

'variants'. He said there would have to be at least a *30 percent* difference for that to be justified and even then he believed the immune system would still recognise what it was. Gates-funded 'variant modeller' and 'vaccine'-pusher John Edmunds might care to comment. Yeadon said drug companies were making new versions of the 'vaccine' as a 'top up' for 'variants'. Worse than that, he said, the 'regulators' around the world like the MHRA in the UK had got together and agreed that because 'vaccines' for 'variants' were so similar to the first 'vaccines' *they did not have to do safety studies*. How transparently sinister that is. This is when Yeadon said: 'There is a conspiracy here.' There was no need for another vaccine for 'variants' and yet we were told that there was and the country had shut its borders because of them. 'They are going into hundreds of millions of arms without passing 'go' or any regulator. Why did they do that? Why did they pick this method of making the vaccine?'

The reason had to be something bigger than that it seemed and 'it's not protection against the virus'. It's was a far bigger project that meant politicians and advisers were willing to do things and not do things that knowingly resulted in avoidable deaths – 'that's already happened when you think about lockdown and deprivation of health care for a year.' He spoke of people prepared to do something that results in the avoidable death of their fellow human beings and it not bother them. This is the penny-drop I have been working to get across for more than 30 years – the level of pure evil we are dealing with. Yeadon said his friends and associates could not believe there could be that much evil, but he reminded them of Stalin, Pol Pot and Hitler and of what Stalin had said: 'One death is a tragedy. A million? A statistic.' He could not think of a benign explanation for why you need top-up vaccines 'which I'm sure you don't' and for the regulators 'to just get out of the way and wave them through'. Why would the regulators do that when they were still wrestling with the dangers of the 'parent' vaccine? He was clearly shocked by what he had seen since the 'Covid' hoax began and now he was thinking the previously unthinkable:

If you wanted to depopulate a significant proportion of the world and to do it in a way that doesn't involve destruction of the environment with nuclear weapons, poisoning everyone with anthrax or something like that, and you wanted plausible deniability while you had a multi-year infectious disease crisis, I actually don't think you could come up with a better plan of work than seems to be in front of me. I can't say that's what they are going to do, but I can't think of a benign explanation why they are doing it.

He said he never thought that they would get rid of 99 percent of humans, but now he wondered. 'If you wanted to that this would be a hell of a way to do it – it would be unstoppable folks.' Yeadon had concluded that those who submitted to the 'vaccine' would be allowed to have some kind of normal life (but for how long?) while screws were tightened to coerce and mandate the last few percent. 'I think they'll put the rest of them in a prison camp. I wish I was wrong, but I don't think I am.' Other points he made included: There were no coronavirus vaccines then suddenly they all come along at the same time; we have no idea of the long term affect with trials so short; coercing or forcing people to have medical procedures is against the Nuremberg Code instigated when the Nazis did just that; people should at least delay having the 'vaccine'; a quick Internet search confirms that masks don't reduce respiratory viral transmission and 'the government knows that'; they have smashed civil society and they know that, too; two dozen peer-reviewed studies show no connection between lockdown and reducing deaths; he knew from personal friends the elite were still flying around and going on holiday while the public were locked down; the elite were not having the 'vaccines'. He was also asked if 'vaccines' could be made to target difference races. He said he didn't know, but the document by the Project for the New American Century in September, 2000, said developing 'advanced forms of biological warfare that can target *specific genotypes* may transform biological warfare from the realm of terror to a politically useful tool.' Oh, they're evil all right. Of that we can be *absolutely* sure.

Another cull of old people

We have seen from the CDC definition that the mRNA 'Covid vaccine' is not a vaccine and nor are the others that *claim* to reduce 'severity of symptoms' in *some* people, but not protect from infection or transmission. What about all the lies about returning to 'normal' if people were 'vaccinated'? If they are not claimed to stop infection and transmission of the alleged 'virus', how does anything change? This was all lies to manipulate people to take the jabs and we are seeing that now with masks and distancing still required for the 'vaccinated'. How did they think that elderly people with fragile health and immune responses were going to be affected by infusing their cells with synthetic material and other toxic substances? They *knew* that in the short and long term it would be devastating and fatal as the culling of the old that began with the first lockdowns was continued with the 'vaccine'. Death rates in care homes soared immediately residents began to be 'vaccinated' – infused with synthetic material. Brave and committed whistleblower nurses put their careers at risk by exposing this truth while the rest kept their heads down and their mouths shut to put their careers before those they are supposed to care for. A long-time American Certified Nursing Assistant who gave his name as James posted a video in which he described emotionally what happened in his care home when vaccination began. He said that during 2020 very few residents were sick with 'Covid' and no one died during the entire year; but shortly after the Pfizer mRNA injections 14 people died within two weeks and many others were near death. 'They're dropping like flies', he said. Residents who walked on their own before the shot could no longer and they had lost their ability to conduct an intelligent conversation. The home's management said the sudden deaths were caused by a 'super-spreader' of 'Covid-19'. Then how come, James asked, that residents who refused to take the injections were not sick? It was a case of inject the elderly with mRNA synthetic potions and blame their illness and death that followed on the 'virus'. James described what was happening in care homes as 'the greatest crime of genocide this country has ever seen'. Remember the NHS staff nurse from earlier who used the same

word ‘genocide’ for what was happening with the ‘vaccines’ and that it was an ‘act of human annihilation’. A UK care home whistleblower told a similar story to James about the effect of the ‘vaccine’ in deaths and ‘outbreaks’ of illness dubbed ‘Covid’ after getting the jab. She told how her care home management and staff had zealously imposed government regulations and no one was allowed to even question the official narrative let alone speak out against it. She said the NHS was even worse. Again we see the results of reframing. A worker at a local care home where I live said they had not had a single case of ‘Covid’ there for almost a year and when the residents were ‘vaccinated’ they had 19 positive cases in two weeks with eight dying.

It’s not the ‘vaccine’ – honest

The obvious cause and effect was being ignored by the media and most of the public. Australia’s health minister Greg Hunt (a former head of strategy at the World Economic Forum) was admitted to hospital after he had the ‘vaccine’. He was suffering according to reports from the skin infection ‘cellulitis’ and it must have been a severe case to have warranted days in hospital. Immediately the authorities said this was nothing to do with the ‘vaccine’ when an effect of some vaccines is a ‘cellulitis-like reaction’. We had families of perfectly healthy old people who died after the ‘vaccine’ saying that if only they had been given the ‘vaccine’ earlier they would still be alive. As a numbskull rating that is off the chart. A father of four ‘died of Covid’ at aged 48 when he was taken ill two days after having the ‘vaccine’. The man, a health administrator, had been ‘shielding during the pandemic’ and had ‘not really left the house’ until he went for the ‘vaccine’. Having the ‘vaccine’ and then falling ill and dying does not seem to have qualified as a possible cause and effect and ‘Covid-19’ went on his death certificate. His family said they had no idea how he ‘caught the virus’. A family member said: ‘Tragically, it could be that going for a vaccination ultimately led to him catching Covid …The sad truth is that they are never going to know where it came from.’ The family warned people to remember

that the virus still existed and was 'very real'. So was their stupidity. Nurses and doctors who had the first round of the 'vaccine' were collapsing, dying and ending up in a hospital bed while they or their grieving relatives were saying they'd still have the 'vaccine' again despite what happened. I kid you not. You mean if your husband returned from the dead he'd have the same 'vaccine' again that killed him??

Doctors at the VCU Medical Center in Richmond, Virginia, said the Johnson & Johnson 'vaccine' was to blame for a man's skin peeling off. Patient Richard Terrell said: 'It all just happened so fast. My skin peeled off. It's still coming off on my hands now.' He said it was stinging, burning and itching and when he bent his arms and legs it was very painful with 'the skin swollen and rubbing against itself'. Pfizer/BioNTech and Moderna vaccines use mRNA to change the cell while the Johnson & Johnson version uses DNA in a process similar to AstraZeneca's technique. Johnson & Johnson and AstraZeneca have both had their 'vaccines' paused by many countries after causing serious blood problems. Terrell's doctor Fnu Nutan said he could have died if he hadn't got medical attention. It sounds terrible so what did Nutan and Terrell say about the 'vaccine' now? Oh, they still recommend that people have it. A nurse in a hospital bed 40 minutes after the vaccination and unable to swallow due to throat swelling was told by a doctor that he lost mobility in his arm for 36 hours following the vaccination. What did he say to the ailing nurse? 'Good for you for getting the vaccination.' We are dealing with a serious form of cognitive dissonance madness in both public and medical staff. There is a remarkable correlation between those having the 'vaccine' and trumpeting the fact and suffering bad happenings shortly afterwards. Witold Rogiewicz, a Polish doctor, made a video of his 'vaccination' and ridiculed those who were questioning its safety and the intentions of Bill Gates: 'Vaccinate yourself to protect yourself, your loved ones, friends and also patients. And to mention quickly I have info for anti-vaxxers and anti-Coviders if you want to contact Bill Gates you can do this through me.' He further ridiculed the dangers of 5G. Days later he

was dead, but naturally the vaccination wasn't mentioned in the verdict of 'heart attack'.

Lies, lies and more lies

So many members of the human race have slipped into extreme states of insanity and unfortunately they include reframed doctors and nursing staff. Having a 'vaccine' and dying within minutes or hours is not considered a valid connection while death from any cause within 28 days or longer of a positive test with a test not testing for the 'virus' means 'Covid-19' goes on the death certificate. How could that 'vaccine'-death connection not have been made except by calculated deceit? US figures in the initial rollout period to February 12th, 2020, revealed that a third of the deaths reported to the CDC after 'Covid vaccines' happened within 48 hours. Five men in the UK suffered an 'extremely rare' blood clot problem after having the AstraZeneca 'vaccine', but no causal link was established said the Gates-funded Medicines and Healthcare products Regulatory Agency (MHRA) which had given the 'vaccine' emergency approval to be used. Former Pfizer executive Dr Michael Yeadon explained in his interview how the procedures could cause blood coagulation and clots. People who should have been at no risk were dying from blood clots in the brain and he said he had heard from medical doctor friends that people were suffering from skin bleeding and massive headaches. The AstraZeneca 'shot' was stopped by some 20 countries over the blood clotting issue and still the corrupt MHRA, the European Medicines Agency (EMA) and the World Health Organization said that it should continue to be given even though the EMA admitted that it 'still cannot rule out definitively' a link between blood clotting and the 'vaccine'. Later Marco Cavaleri, head of EMA vaccine strategy, said there was indeed a clear link between the 'vaccine' and thrombosis, but they didn't know why. So much for the trials showing the 'vaccine' is safe. Blood clots were affecting younger people who would be under virtually no danger from 'Covid' even if it existed which makes it all the more stupid and sinister.

The British government responded to public alarm by wheeling out June Raine, the terrifyingly weak infant school headmistress sound-alike who heads the UK MHRA drug 'regulator'. The idea that she would stand up to Big Pharma and government pressure is laughable and she told us that all was well in the same way that she did when allowing untested, never-used-on-humans-before, genetically-manipulating 'vaccines' to be exposed to the public in the first place. Mass lying is the new normal of the 'Covid' era. The MHRA later said 30 cases of rare blood clots had by then been connected with the AstraZeneca 'vaccine' (that means a lot more in reality) while stressing that the benefits of the jab in preventing 'Covid-19' outweighed any risks. A more ridiculous and disingenuous statement with callous disregard for human health it is hard to contemplate. Immediately after the mendacious 'all-clears' two hospital workers in Denmark experienced blood clots and cerebral haemorrhaging following the AstraZeneca jab and one died. Top Norwegian health official Pål Andre Holme said the 'vaccine' was the only common factor: 'There is nothing in the patient history of these individuals that can give such a powerful immune response … I am confident that the antibodies that we have found are the cause, and I see no other explanation than it being the vaccine which triggers it.' Strokes, a clot or bleed in the brain, were clearly associated with the 'vaccine' from word of mouth and whistleblower reports. Similar consequences followed with all these 'vaccines' that we were told were so safe and as the numbers grew by the day it was clear we were witnessing human carnage.

Learning the hard way

A woman interviewed by UKColumn told how her husband suffered dramatic health effects after the vaccine when he'd been in good health all his life. He went from being a little unwell to losing all feeling in his legs and experiencing 'excruciating pain'. Misdiagnosis followed twice at Accident and Emergency (an 'allergy' and 'sciatica') before he was admitted to a neurology ward where doctors said his serious condition had been caused by the

'vaccine'. Another seven 'vaccinated' people were apparently being treated on the same ward for similar symptoms. The woman said he had the 'vaccine' because they believed media claims that it was safe. 'I didn't think the government would give out a vaccine that does this to somebody; I believed they would be bringing out a vaccination that would be safe.' What a tragic way to learn that lesson. Another woman posted that her husband was transporting stroke patients to hospital on almost every shift and when he asked them if they had been 'vaccinated' for 'Covid' they all replied 'yes'. One had a 'massive brain bleed' the day after his second dose. She said her husband reported the 'just been vaccinated' information every time to doctors in A and E only for them to ignore it, make no notes and appear annoyed that it was even mentioned. This particular report cannot be verified, but it expresses a common theme that confirms the monumental underreporting of 'vaccine' consequences. Interestingly as the 'vaccines' and their brain blood clot/stroke consequences began to emerge the UK National Health Service began a publicity campaign telling the public what to do in the event of a stroke. A Scottish NHS staff nurse who quit in disgust in March, 2021, said:

I have seen traumatic injuries from the vaccine, they're not getting reported to the yellow card [adverse reaction] scheme, they're treating the symptoms, not asking why, why it's happening. It's just treating the symptoms and when you speak about it you're dismissed like you're crazy, I'm not crazy, I'm not crazy because every other colleague I've spoken to is terrified to speak out, they've had enough.

Videos appeared on the Internet of people uncontrollably shaking after the 'vaccine' with no control over muscles, limbs and even their face. A Scottish mother broke out in a severe rash all over her body almost immediately after she was given the AstraZeneca 'vaccine'. The pictures were horrific. Leigh King, a 41-year-old hairdresser from Lanarkshire said: 'Never in my life was I prepared for what I was about to experience … My skin was so sore and constantly hot … I have never felt pain like this …' But don't you worry, the 'vaccine' is perfectly safe. Then there has been the effect on medical

staff who have been pressured to have the 'vaccine' by psychopathic 'health' authorities and government. A London hospital consultant who gave the name K. Polyakova wrote this to the *British Medical Journal* or *BMJ*:

> I am currently struggling with … the failure to report the reality of the morbidity caused by our current vaccination program within the health service and staff population. The levels of sickness after vaccination is unprecedented and staff are getting very sick and some with neurological symptoms which is having a huge impact on the health service function. Even the young and healthy are off for days, some for weeks, and some requiring medical treatment. Whole teams are being taken out as they went to get vaccinated together.
>
> Mandatory vaccination in this instance is stupid, unethical and irresponsible when it comes to protecting our staff and public health. We are in the voluntary phase of vaccination, and encouraging staff to take an unlicensed product that is impacting on their immediate health … it is clearly stated that these vaccine products do not offer immunity or stop transmission. In which case why are we doing it?

Not to protect health that's for sure. Medical workers are lauded by governments for agenda reasons when they couldn't give a toss about them any more than they can for the population in general. Schools across America faced the same situation as they closed due to the high number of teachers and other staff with bad reactions to the Pfizer/BioNTech, Moderna, and Johnson & Johnson 'Covid vaccines' all of which were linked to death and serious adverse effects. The *BMJ* took down the consultant's comments pretty quickly on the grounds that they were being used to spread 'disinformation'. They were exposing the truth about the 'vaccine' was the real reason. The cover-up is breathtaking.

Hiding the evidence

The scale of the 'vaccine' death cover-up worldwide can be confirmed by comparing official figures with the personal experience of the public. I heard of many people in my community who died immediately or soon after the vaccine that would never appear in the media or even likely on the official totals of 'vaccine' fatalities and adverse reactions when only about ten percent are estimated to be

reported and I have seen some estimates as low as one percent in a Harvard study. In the UK alone by April 29th, 2021, some 757,654 adverse reactions had been officially reported from the Pfizer/BioNTech, Oxford/AstraZeneca and Moderna 'vaccines' with more than a thousand deaths linked to jabs and that means an estimated ten times this number in reality from a ten percent reporting rate percentage. That's seven million adverse reactions and 10,000 potential deaths and a one percent reporting rate would be ten times *those* figures. In 1976 the US government pulled the swine flu vaccine after *53* deaths. The UK data included a combined 10,000 eye disorders from the 'Covid vaccines' with more than 750 suffering visual impairment or blindness and again multiply by the estimated reporting percentages. As 'Covid cases' officially fell hospitals virtually empty during the 'Covid crisis' began to fill up with a range of other problems in the wake of the 'vaccine' rollout. The numbers across America have also been catastrophic. Deaths linked to *all* types of vaccine increased by *6,000 percent* in the first quarter of 2021 compared with 2020. A 39-year-old woman from Ogden, Utah, died four days after receiving a second dose of Moderna's 'Covid vaccine' when her liver, heart and kidneys all failed despite the fact that she had no known medical issues or conditions. Her family sought an autopsy, but Dr Erik Christensen, Utah's chief medical examiner, said proving vaccine injury as a cause of death almost never happened. He could think of only one instance where an autopsy would name a vaccine as the official cause of death and that would be anaphylaxis where someone received a vaccine and died almost instantaneously. 'Short of that, it would be difficult for us to definitively say this is the vaccine,' Christensen said. If that is true this must be added to the estimated ten percent (or far less) reporting rate of vaccine deaths and serious reactions and the conclusion can only be that vaccine deaths and serious reactions – including these 'Covid' potions' – are phenomenally understated in official figures. The same story can be found everywhere. Endless accounts of deaths and serious reactions among the public, medical

and care home staff while official figures did not even begin to reflect this.

Professional script-reader Dr David Williams, a 'top public-health official' in Ontario, Canada, insulted our intelligence by claiming only four serious adverse reactions and no deaths from the more than 380,000 vaccine doses then given. This bore no resemblance to what people knew had happened in their owns circles and we had Dirk Huyer in charge of getting millions vaccinated in Ontario while at the same time he was Chief Coroner for the province investigating causes of death including possible death from the vaccine. An aide said he had stepped back from investigating deaths, but evidence indicated otherwise. Rosemary Frei, who secured a Master of Science degree in molecular biology at the Faculty of Medicine at Canada's University of Calgary before turning to investigative journalism, was one who could see that official figures for 'vaccine' deaths and reactions made no sense. She said that doctors seldom reported adverse events and when people got really sick or died after getting a vaccination they would attribute that to anything except the vaccines. It had been that way for years and anyone who wondered aloud whether the 'Covid vaccines' or other shots cause harm is immediately branded as 'anti-vax' and 'anti-science'. This was 'career-threatening' for health professionals. Then there was the huge pressure to support the push to 'vaccinate' billions in the quickest time possible. Frei said:

> So that's where we're at today. More than half a million vaccine doses have been given to people in Ontario alone. The rush is on to vaccinate all 15 million of us in the province by September. And the mainstream media are screaming for this to be sped up even more. That all adds up to only a very slim likelihood that we're going to be told the truth by officials about how many people are getting sick or dying from the vaccines.

What is true of Ontario is true of everywhere.

They KNEW – and still did it

The authorities knew what was going to happen with multiple deaths and adverse reactions. The UK government's Gates-funded

and Big Pharma-dominated Medicines and Healthcare products Regulatory Agency (MHRA) hired a company to employ AI in compiling the projected reactions to the 'vaccine' that would otherwise be uncountable. The request for applications said: 'The MHRA urgently seeks an Artificial Intelligence (AI) software tool to process the expected high volume of Covid-19 vaccine Adverse Drug Reaction …' This was from the agency, headed by the disingenuous June Raine, that gave the 'vaccines' emergency approval and the company was hired before the first shot was given. 'We are going to kill and maim you – is that okay?' 'Oh, yes, perfectly fine – I'm very grateful, thank you, doctor.' The range of 'Covid vaccine' adverse reactions goes on for page after page in the MHRA criminally underreported 'Yellow Card' system and includes affects to eyes, ears, skin, digestion, blood and so on. Raine's MHRA amazingly claimed that the 'overall safety experience … is so far as expected from the clinical trials'. The death, serious adverse effects, deafness and blindness were *expected?* When did they ever mention that? If these human tragedies were expected then those that gave approval for the use of these 'vaccines' must be guilty of crimes against humanity including murder – a definition of which is 'killing a person with malice aforethought or with recklessness manifesting extreme indifference to the value of human life.' People involved at the MHRA, the CDC in America and their equivalent around the world must go before Nuremberg trials to answer for their callous inhumanity. We are only talking here about the immediate effects of the 'vaccine'. The longer-term impact of the DNA synthetic manipulation is the main reason they are so hysterically desperate to inoculate the entire global population in the shortest possible time.

Africa and the developing world are a major focus for the 'vaccine' depopulation agenda and a mass vaccination sales-pitch is underway thanks to caring people like the Rockefellers and other Cult assets. The Rockefeller Foundation, which pre-empted the 'Covid pandemic' in a document published in 2010 that 'predicted' what happened a decade later, announced an initial $34.95 million grant in February, 2021, 'to ensure more equitable access to Covid-19

testing and vaccines' among other things in Africa in collaboration with '24 organizations, businesses, and government agencies'. The pan-Africa initiative would focus on 10 countries: Burkina Faso, Ethiopia, Ghana, Kenya, Nigeria, Rwanda, South Africa, Tanzania, Uganda, and Zambia'. Rajiv Shah, President of the Rockefeller Foundation and former administrator of CIA-controlled USAID, said that if Africa was not mass-vaccinated (to change the DNA of its people) it was a 'threat to all of humanity' and not fair on Africans. When someone from the Rockefeller Foundation says they want to do something to help poor and deprived people and countries it is time for a belly-laugh. They are doing this out of the goodness of their 'heart' because 'vaccinating' the entire global population is what the 'Covid' hoax set out to achieve. Official 'decolonisation' of Africa by the Cult was merely a prelude to financial colonisation on the road to a return to physical colonisation. The 'vaccine' is vital to that and the sudden and convenient death of the 'Covid' sceptic president of Tanzania can be seen in its true light. A lot of people in Africa are aware that this is another form of colonisation and exploitation and they need to stand their ground.

The 'vaccine is working' scam

A potential problem for the Cult was that the 'vaccine' is meant to change human DNA and body messaging and not to protect anyone from a 'virus' never shown to exist. The vaccine couldn't work because it was not designed to work and how could they make it *appear* to be working so that more people would have it? This was overcome by lowering the amplification rate of the PCR test to produce fewer 'cases' and therefore fewer 'deaths'. Some of us had been pointing out since March, 2020, that the amplification rate of the test not testing for the 'virus' had been made artificially high to generate positive tests which they could call 'cases' to justify lockdowns. The World Health Organization recommended an absurdly high 45 amplification cycles to ensure the high positives required by the Cult and then remained silent on the issue until January 20th, 2021 – Biden's Inauguration Day. This was when the

'vaccinations' were seriously underway and on that day the WHO recommended after discussions with America's CDC that laboratories *lowered their testing amplification*. Dr David Samadi, a certified urologist and health writer, said the WHO was encouraging all labs to reduce their cycle count for PCR tests. He said the current cycle was much too high and was 'resulting in any particle being declared a positive case'. Even one mainstream news report I saw said this meant the number of 'Covid' infections may have been 'dramatically inflated'. Oh, just a little bit. The CDC in America issued new guidance to laboratories in April, 2021, to use 28 cycles *but only for 'vaccinated' people*. The timing of the CDC/WHO interventions were cynically designed to make it appear the 'vaccines' were responsible for falling cases and deaths when the real reason can be seen in the following examples. New York's state lab, the Wadsworth Center, identified 872 positive tests in July, 2020, based on a threshold of 40 cycles. When the figure was lowered to 35 cycles *43 percent* of the 872 were no longer 'positives'. At 30 cycles the figure was 63 percent. A Massachusetts lab found that between *85 to 90 percent* of people who tested positive in July with a cycle threshold of 40 would be negative at 30 cycles, Ashish Jha, MD, director of the Harvard Global Health Institute, said: 'I'm really shocked that it could be that high … Boy, does it really change the way we need to be thinking about testing.' I'm shocked that I could see the obvious in the spring of 2020, with no medical background, and most medical professionals still haven't worked it out. No, that's not shocking – it's terrifying.

Three weeks after the WHO directive to lower PCR cycles the London *Daily Mail* ran this headline: 'Why ARE Covid cases plummeting? New infections have fallen 45% in the US and 30% globally in the past 3 weeks but experts say vaccine is NOT the main driver because only 8% of Americans and 13% of people worldwide have received their first dose.' They acknowledged that the drop could not be attributed to the 'vaccine', but soon this morphed throughout the media into the 'vaccine' has caused cases and deaths to fall when it was the PCR threshold. In December, 2020, there was

chaos at English Channel ports with truck drivers needing negative 'Covid' tests before they could board a ferry home for Christmas. The government wanted to remove the backlog as fast as possible and they brought in troops to do the 'testing'. Out of 1,600 drivers just *36* tested positive and the rest were given the all clear to cross the Channel. I guess the authorities thought that 36 was the least they could get away with without the unquestioning catching on. The amplification trick which most people believed in the absence of information in the mainstream applied more pressure on those refusing the 'vaccine' to succumb when it 'obviously worked'. The truth was the exact opposite with deaths in care homes soaring with the 'vaccine' and in Israel the term used was 'skyrocket'. A re-analysis of published data from the Israeli Health Ministry led by Dr Hervé Seligmann at the Medicine Emerging Infectious and Tropical Diseases at Aix-Marseille University found that Pfizer's 'Covid vaccine' killed 'about 40 times more [elderly] people than the disease itself would have killed' during a five-week vaccination period and *260 times* more younger people than would have died from the 'virus' even according to the manipulated 'virus' figures. Dr Seligmann and his co-study author, Haim Yativ, declared after reviewing the Israeli 'vaccine' death data: 'This is a new Holocaust.'

Then, in mid-April, 2021, after vast numbers of people worldwide had been 'vaccinated', the story changed with clear coordination. The UK government began to prepare the ground for more future lockdowns when Nuremberg-destined Boris Johnson told yet another whopper. He said that cases had fallen because of *lockdowns* not 'vaccines'. Lockdowns are irrelevant when *there is no 'virus'* and the test and fraudulent death certificates are deciding the number of 'cases' and 'deaths'. Study after study has shown that lockdowns don't work and instead kill and psychologically destroy people. Meanwhile in the United States Anthony Fauci and Rochelle Walensky, the ultra-Zionist head of the CDC, peddled the same line. More lockdown was the answer and not the 'vaccine', a line repeated on cue by the moron that is Canadian Prime Minister Justin Trudeau. Why all the hysteria to get everyone 'vaccinated' if lockdowns and

not 'vaccines' made the difference? None of it makes sense on the face of it. Oh, but it does. The Cult wants lockdowns *and* the 'vaccine' and if the 'vaccine' is allowed to be seen as the total answer lockdowns would no longer be justified when there are still livelihoods to destroy. 'Variants' and renewed upward manipulation of PCR amplification are planned to instigate never-ending lockdown *and* more 'vaccines'.

You *must* have it – we're desperate

Israel, where the Jewish and Arab population are ruled by the Sabbatian Cult, was the front-runner in imposing the DNA-manipulating 'vaccine' on its people to such an extent that Jewish refusers began to liken what was happening to the early years of Nazi Germany. This would seem to be a fantastic claim. Why would a government of Jewish people be acting like the Nazis did? If you realise that the Sabbatian Cult was behind the Nazis and that Sabbatians hate Jews the pieces start to fit and the question of why a 'Jewish' government would treat Jews with such callous disregard for their lives and freedom finds an answer. Those controlling the government of Israel *aren't Jewish* – they're Sabbatian. Israeli lawyer Tamir Turgal was one who made the Nazi comparison in comments to German lawyer Reiner Fuellmich who is leading a class action lawsuit against the psychopaths for crimes against humanity. Turgal described how the Israeli government was vaccinating children and pregnant women on the basis that there was no evidence that this was dangerous when they had no evidence that it *wasn't* dangerous either. They just had no evidence. This was medical experimentation and Turgal said this breached the Nuremberg Code about medical experimentation and procedures requiring informed consent and choice. Think about that. A Nuremberg Code developed because of Nazi experimentation on Jews and others in concentration camps by people like the evil-beyond-belief Josef Mengele is being breached by the *Israeli* government; but when you know that it's a *Sabbatian* government along with its intelligence and military agencies like Mossad, Shin Bet and the Israeli Defense Forces, and that Sabbatians

were the force behind the Nazis, the kaleidoscope comes into focus. What have we come to when Israeli Jews are suing their government for violating the Nuremberg Code by essentially making Israelis subject to a medical experiment using the controversial 'vaccines'? It's a shocker that this has to be done in the light of what happened in Nazi Germany. The Anshe Ha-Emet, or 'People of the Truth', made up of Israeli doctors, lawyers, campaigners and public, have launched a lawsuit with the International Criminal Court. It says:

> When the heads of the Ministry of Health as well as the prime minister presented the vaccine in Israel and began the vaccination of Israeli residents, the vaccinated were not advised, that, in practice, they are taking part in a medical experiment and that their consent is required for this under the Nuremberg Code.

The irony is unbelievable, but easily explained in one word: Sabbatians. The foundation of Israeli 'Covid' apartheid is the 'green pass' or 'green passport' which allows Jews and Arabs who have had the DNA-manipulating 'vaccine' to go about their lives – to work, fly, travel in general, go to shopping malls, bars, restaurants, hotels, concerts, gyms, swimming pools, theatres and sports venues, while non-'vaccinated' are banned from all those places and activities. Israelis have likened the 'green pass' to the yellow stars that Jews in Nazi Germany were forced to wear – the same as the yellow stickers that a branch of UK supermarket chain Morrisons told exempt mask-wears they had to display when shopping. How very sensitive. The Israeli system is blatant South African-style apartheid on the basis of compliance or non-compliance to fascism rather than colour of the skin. How appropriate that the Sabbatian Israeli government was so close to the pre-Mandela apartheid regime in Pretoria. The Sabbatian-instigated 'vaccine passport' in Israel is planned for everywhere. Sabbatians struck a deal with Pfizer that allowed them to lead the way in the percentage of a national population infused with synthetic material and the result was catastrophic. Israeli freedom activist Shai Dannon told me how chairs were appearing on beaches that said 'vaccinated only'. Health Minister Yuli Edelstein said that anyone unwilling or unable to get

the jabs that 'confer immunity' will be 'left behind'. The man's a liar. Not even the makers claim the 'vaccines' confer immunity. When you see those figures of 'vaccine' deaths these psychopaths were saying that you must take the chance the 'vaccine' will kill you or maim you while knowing it will change your DNA or lockdown for you will be permanent. That's fascism. The Israeli parliament passed a law to allow personal information of the non-vaccinated to be shared with local and national authorities for three months. This was claimed by its supporters to be a way to 'encourage' people to be vaccinated. Hadas Ziv from Physicians for Human Rights described this as a 'draconian law which crushed medical ethics and the patient rights'. But that's the idea, the Sabbatians would reply.

Your papers, please

Sabbatian Israel was leading what has been planned all along to be a global 'vaccine pass' called a 'green passport' without which you would remain in permanent lockdown restriction and unable to do anything. This is how badly – *desperately* – the Cult is to get everyone 'vaccinated'. The term and colour 'green' was not by chance and related to the psychology of fusing the perception of the green climate hoax with the 'Covid' hoax and how the 'solution' to both is the same Great Reset. Lying politicians, health officials and psychologists denied there were any plans for mandatory vaccinations or restrictions based on vaccinations, but they knew that was exactly what was meant to happen with governments of all countries reaching agreements to enforce a global system. 'Free' Denmark and 'free' Sweden unveiled digital vaccine certification. Cyprus, Czech Republic, Estonia, Greece, Hungary, Iceland, Italy, Poland, Portugal, Slovakia, and Spain have all committed to a vaccine passport system and the rest including the whole of the EU would follow. The satanic UK government will certainly go this way despite mendacious denials and at the time of writing it is trying to manipulate the public into having the 'vaccine' so they could go abroad on a summer holiday. How would that work without something to prove you had the synthetic toxicity injected into you?

Documents show that the EU's European Commission was moving towards 'vaccine certificates' in 2018 and 2019 before the 'Covid' hoax began. They knew what was coming. Abracadabra – Ursula von der Leyen, the German President of the Commission, announced in March, 2021, an EU 'Digital Green Certificate' – green again – to track the public's 'Covid status'. The passport sting is worldwide and the Far East followed the same pattern with South Korea ruling that only those with 'vaccination' passports – again the *green* pass – would be able to 'return to their daily lives'.

Bill Gates has been preparing for this 'passport' with other Cult operatives for years and beyond the paper version is a Gates-funded 'digital tattoo' to identify who has been vaccinated and who hasn't. The 'tattoo' is reported to include a substance which is externally readable to confirm who has been vaccinated. This is a bio-luminous light-generating enzyme (think fireflies) called … *Luciferase*. Yes, named after the Cult 'god' Lucifer the 'light bringer' of whom more to come. Gates said he funded the readable tattoo to ensure children in the developing world were vaccinated and no one was missed out. He cares so much about poor kids as we know. This was just the cover story to develop a vaccine tagging system for everyone on the planet. Gates has been funding the ID2020 'alliance' to do just that in league with other lovely people at Microsoft, GAVI, the Rockefeller Foundation, Accenture and IDEO.org. He said in interviews in March, 2020, before any 'vaccine' publicly existed, that the world must have a globalised digital certificate to track the 'virus' and who had been vaccinated. Gates knew from the start that the mRNA vaccines were coming and when they would come and that the plan was to tag the 'vaccinated' to marginalise the intelligent and stop them doing anything including travel. Evil just doesn't suffice. Gates was exposed for offering a $10 million bribe to the Nigerian House of Representatives to invoke compulsory 'Covid' vaccination of all Nigerians. Sara Cunial, a member of the Italian Parliament, called Gates a 'vaccine criminal'. She urged the Italian President to hand him over to the International Criminal Court for crimes against

humanity and condemned his plans to 'chip the human race' through ID2020.

You know it's a long-planned agenda when war criminal and Cult gofer Tony Blair is on the case. With the scale of arrogance only someone as dark as Blair can muster he said: 'Vaccination in the end is going to be your route to liberty.' Blair is a disgusting piece of work and he confirms that again. The media has given a lot of coverage to a bloke called Charlie Mullins, founder of London's biggest independent plumbing company, Pimlico Plumbers, who has said he won't employ anyone who has not been vaccinated or have them go to any home where people are not vaccinated. He said that if he had his way no one would be allowed to walk the streets if they have not been vaccinated. Gates was cheering at the time while I was alerting the white coats. The plan is that people will qualify for 'passports' for having the first two doses and then to keep it they will have to have all the follow ups and new ones for invented 'variants' until human genetics is transformed and many are dead who can't adjust to the changes. Hollywood celebrities – the usual propaganda stunt – are promoting something called the WELL Health-Safety Rating to verify that a building or space has 'taken the necessary steps to prioritize the health and safety of their staff, visitors and other stakeholders'. They included Lady Gaga, Jennifer Lopez, Michael B. Jordan, Robert DeNiro, Venus Williams, Wolfgang Puck, Deepak Chopra and 17th Surgeon General Richard Carmona. Yawn. WELL Health-Safety has big connections with China. Parent company Delos is headed by former Goldman Sachs partner Paul Scialla. This is another example – and we will see so many others – of using the excuse of 'health' to dictate the lives and activities of the population. I guess one confirmation of the 'safety' of buildings is that only 'vaccinated' people can go in, right?

Electronic concentration camps

I wrote decades ago about the plans to restrict travel and here we are for those who refuse to bow to tyranny. This can be achieved in one go with air travel if the aviation industry makes a blanket decree.

The ‘vaccine’ and guaranteed income are designed to be part of a global version of China’s social credit system which tracks behaviour 24/7 and awards or deletes ‘credits’ based on whether your behaviour is supported by the state or not. I mean your entire lifestyle – what you do, eat, say, everything. Once your credit score falls below a certain level consequences kick in. In China tens of millions have been denied travel by air and train because of this. All the locations and activities denied to refusers by the ‘vaccine’ passports will be included in one big mass ban on doing almost anything for those that don’t bow their head to government. It’s beyond fascist and a new term is required to describe its extremes – I guess fascist technocracy will have to do. The way the Chinese system of technological – technocratic – control is sweeping the West can be seen in the Los Angeles school system and is planned to be expanded worldwide. Every child is required to have a ‘Covid’-tracking app scanned daily before they can enter the classroom. The so-called Daily Pass tracking system is produced by Gates’ Microsoft which I’m sure will shock you rigid. The pass will be scanned using a barcode (one step from an inside-the-body barcode) and the information will include health checks, ‘Covid’ tests and vaccinations. Entry codes are for one specific building only and access will only be allowed if a student or teacher has a negative test with a test not testing for the ‘virus’, has no symptoms of anything alleged to be related to ‘Covid’ (symptoms from a range of other illness), and has a temperature under 100 degrees. No barcode, no entry, is planned to be the case for everywhere and not only schools.

Kids are being psychologically prepared to accept this as ‘normal’ their whole life which is why what they can impose in schools is so important to the Cult and its gofers. Long-time American freedom campaigner John Whitehead of the Rutherford Institute was not exaggerating when he said: ‘Databit by databit, we are building our own electronic concentration camps.’ Canada under its Cult gofer prime minister Justin Trudeau has taken a major step towards the real thing with people interned against their will if they test positive with a test not testing for the ‘virus’ when they arrive at a Canadian

airport. They are jailed in internment hotels often without food or water for long periods and with many doors failing to lock there have been sexual assaults. The interned are being charged sometimes $2,000 for the privilege of being abused in this way. Trudeau is fully on board with the Cult and says the 'Covid pandemic' has provided an opportunity for a global 'reset' to permanently change Western civilisation. His number two, Deputy Prime Minister Chrystia Freeland, is a trustee of the World Economic Forum and a Rhodes Scholar. The Trudeau family have long been servants of the Cult. See *The Biggest Secret* and Cathy O'Brien's book *Trance-Formation of America* for the horrific background to Trudeau's father Pierre Trudeau another Canadian prime minister. Hide your fascism behind the façade of a heart-on-the-sleeve liberal. It's a well-honed Cult technique.

What can the 'vaccine' *really* do?

We have a 'virus' never shown to exist and 'variants' of the 'virus' that have also never been shown to exist except, like the 'original', as computer-generated fictions. Even if you believe there's a 'virus' the 'case' to 'death' rate is in the region of 0.23 to 0.15 percent and those 'deaths' are concentrated among the very old around the same average age that people die anyway. In response to this lack of threat (in truth none) psychopaths and idiots, knowingly and unknowingly answering to Gates and the Cult, are seeking to 'vaccinate' every man, woman and child on Planet Earth. Clearly the 'vaccine' is not about 'Covid' – none of this ever has been. So what is it all about *really*? Why the desperation to infuse genetically-manipulating synthetic material into everyone through mRNA fraudulent 'vaccines' with the intent of doing this over and over with the excuses of 'variants' and other 'virus' inventions? Dr Sherri Tenpenny, an osteopathic medical doctor in the United States, has made herself an expert on vaccines and their effects as a vehement campaigner against their use. Tenpenny was board certified in emergency medicine, the director of a level two trauma centre for 12 years, and moved to Cleveland in 1996 to start an integrative

medicine practice which has treated patients from all 50 states and some 17 other countries. Weaning people off pharmaceutical drugs is a speciality.

She became interested in the consequences of vaccines after attending a meeting at the National Vaccine Information Center in Washington DC in 2000 where she 'sat through four days of listening to medical doctors and scientists and lawyers and parents of vaccine injured kids' and asked: 'What's going on?' She had never been vaccinated and never got ill while her father was given a list of vaccines to be in the military and was 'sick his entire life'. The experience added to her questions and she began to examine vaccine documents from the Centers for Disease Control (CDC). After reading the first one, the 1998 version of *The General Recommendations of Vaccination*, she thought: 'This is it?' The document was poorly written and bad science and Tenpenny began 20 years of research into vaccines that continues to this day. She began her research into 'Covid vaccines' in March, 2020, and she describes them as 'deadly'. For many, as we have seen, they already have been. Tenpenny said that in the first 30 days of the 'vaccine' rollout in the United States there had been more than 40,000 adverse events reported to the vaccine adverse event database. A document had been delivered to her the day before that was 172 pages long. 'We have over 40,000 adverse events; we have over 3,100 cases of [potentially deadly] anaphylactic shock; we have over 5,000 neurological reactions.' Effects ranged from headaches to numbness, dizziness and vertigo, to losing feeling in hands or feet and paraesthesia which is when limbs 'fall asleep' and people have the sensation of insects crawling underneath their skin. All this happened in the first 30 days and remember that only about *ten percent* (or far less) of adverse reactions and vaccine-related deaths are estimated to be officially reported. Tenpenny said:

> So can you think of one single product in any industry, any industry, for as long as products have been made on the planet that within 30 days we have 40,000 people complaining of side effects that not only is still on the market but … we've got paid actors telling us how great

they are for getting their vaccine. We're offering people $500 if they will just get their vaccine and we've got nurses and doctors going; 'I got the vaccine, I got the vaccine'.

Tenpenny said they were not going to be 'happy dancing folks' when they began to suffer Bell's palsy (facial paralysis), neuropathies, cardiac arrhythmias and autoimmune reactions that kill through a blood disorder. 'They're not going to be so happy, happy then, but we're never going to see pictures of those people' she said. Tenpenny described the 'vaccine' as 'a well-designed killing tool'.

No off-switch

Bad as the initial consequences had been Tenpenny said it would be maybe 14 months before we began to see the 'full ravage' of what is going to happen to the 'Covid vaccinated' with full-out consequences taking anything between two years and 20 years to show. You can understand why when you consider that variations of the 'Covid vaccine' use mRNA (messenger RNA) to in theory activate the immune system to produce protective antibodies without using the actual 'virus'. How can they when it's a computer program and they've never isolated what they claim is the 'real thing'? Instead they use *synthetic* mRNA. They are inoculating synthetic material into the body which through a technique known as the Trojan horse is absorbed into cells to change the nature of DNA. Human DNA is changed by an infusion of messenger RNA and with each new 'vaccine' of this type it is changed even more. Say so and you are banned by Cult Internet platforms. The contempt the contemptuous Mark Zuckerberg has for the truth and human health can be seen in an internal Facebook video leaked to the Project Veritas investigative team in which he said of the 'Covid vaccines': '… I share some caution on this because we just don't know the long term side-effects of basically modifying people's DNA and RNA.' At the same time this disgusting man's Facebook was censoring and banning anyone saying exactly the same. He must go before a Nuremberg trial for crimes against humanity when he *knows* that he

is censoring legitimate concerns and denying the right of informed consent on behalf of the Cult that owns him. People have been killed and damaged by the very 'vaccination' technique he cast doubt on himself when they may not have had the 'vaccine' with access to information that he denied them. The plan is to have at least annual 'Covid vaccinations', add others to deal with invented 'variants', and change all other vaccines into the mRNA system. Pfizer executives told shareholders at a virtual Barclays Global Healthcare Conference in March, 2021, that the public may need a third dose of 'Covid vaccine', plus regular yearly boosters and the company planned to hike prices to milk the profits in a 'significant opportunity for our vaccine'. These are the professional liars, cheats and opportunists who are telling you their 'vaccine' is safe. Given this volume of mRNA planned to be infused into the human body and its ability to then replicate we will have a transformation of human genetics from biological to synthetic biological – exactly the long-time Cult plan for reasons we'll see – and many will die. Sherri Tenpenny said of this replication:

> It's like having an on-button but no off-button and that whole mechanism … they actually give it a name and they call it the Trojan horse mechanism, because it allows that [synthetic] virus and that piece of that [synthetic] virus to get inside of your cells, start to replicate and even get inserted into other parts of your DNA as a Trojan-horse.

Ask the overwhelming majority of people who have the 'vaccine' what they know about the contents and what they do and they would reply: 'The government says it will stop me getting the virus.' Governments give that false impression on purpose to increase take-up. You can read Sherri Tenpenny's detailed analysis of the health consequences in her blog at Vaxxter.com, but in summary these are some of them. She highlights the statement by Bill Gates about how human beings can become their own 'vaccine manufacturing machine'. The man is insane. ['Vaccine'-generated] 'antibodies' carry synthetic messenger RNA into the cells and the damage starts, Tenpenny contends, and she says that lungs can be adversely affected through varying degrees of pus and bleeding which

obviously affects breathing and would be dubbed 'Covid-19'. Even more sinister was the impact of 'antibodies' on macrophages, a white blood cell of the immune system. They consist of Type 1 and Type 2 which have very different functions. She said Type 1 are 'hyper-vigilant' white blood cells which 'gobble up' bacteria etc. However, in doing so, this could cause inflammation and in extreme circumstances be fatal. She says these affects are mitigated by Type 2 macrophages which kick in to calm down the system and stop it going rogue. They clear up dead tissue debris and reduce inflammation that the Type 1 'fire crews' have caused. Type 1 kills the infection and Type 2 heals the damage, she says. This is her punchline with regard to 'Covid vaccinations': She says that mRNA 'antibodies' block Type 2 macrophages by attaching to them and deactivating them. This meant that when the Type 1 response was triggered by infection there was nothing to stop that getting out of hand by calming everything down. There's an on-switch, but no off-switch, she says. What follows can be 'over and out, see you when I see you'.

Genetic suicide

Tenpenny also highlights the potential for autoimmune disease – the body attacking itself – which has been associated with vaccines since they first appeared. Infusing a synthetic foreign substance into cells could cause the immune system to react in a panic believing that the body is being overwhelmed by an invader (it is) and the consequences can again be fatal. There is an autoimmune response known as a 'cytokine storm' which I have likened to a homeowner panicked by an intruder and picking up a gun to shoot randomly in all directions before turning the fire on himself. The immune system unleashes a storm of inflammatory response called cytokines to a threat and the body commits hara-kiri. The lesson is that you mess with the body's immune response at your peril and these 'vaccines' seriously – fundamentally – mess with immune response. Tenpenny refers to a consequence called anaphylactic shock which is a severe and highly dangerous allergic reaction when the immune system

floods the body with chemicals. She gives the example of having a bee sting which primes the immune system and makes it sensitive to those chemicals. When people are stung again maybe years later the immune response can be so powerful that it leads to anaphylactic shock. Tenpenny relates this 'shock' with regard to the 'Covid vaccine' to something called polyethylene glycol or PEG. Enormous numbers of people have become sensitive to this over decades of use in a whole range of products and processes including food, drink, skin creams and 'medicine'. Studies have claimed that some 72 percent of people have antibodies triggered by PEG compared with two percent in the 1960s and allergic hypersensitive reactions to this become a gathering cause for concern. Tenpenny points out that the 'mRNA vaccine' is coated in a 'bubble' of polyethylene glycol which has the potential to cause anaphylactic shock through immune sensitivity. Many reports have appeared of people reacting this way after having the 'Covid vaccine'. What do we think is going to happen as humanity has more and more of these 'vaccines'? Tenpenny said: 'All these pictures we have seen with people with these rashes … these weepy rashes, big reactions on their arms and things like that – it's an acute allergic reaction most likely to the polyethylene glycol that you've been previously primed and sensitised to.'

Those who have not studied the conspiracy and its perpetrators at length might think that making the population sensitive to PEG and then putting it in these 'vaccines' is just a coincidence. It is not. It is instead testament to how carefully and coldly-planned current events have been and the scale of the conspiracy we are dealing with. Tenpenny further explains that the 'vaccine' mRNA procedure can breach the blood-brain barrier which protects the brain from toxins and other crap that will cause malfunction. In this case they could make two proteins corrupt brain function to cause Amyotrophic lateral sclerosis (ALS) , a progressive nervous system disease leading to loss of muscle control, and frontal lobe degeneration – Alzheimer's and dementia. Immunologist J. Bart Classon published a paper connecting mRNA 'vaccines' to prion

disease which can lead to Alzheimer's and other forms of neurogenerative disease while others have pointed out the potential to affect the placenta in ways that make women infertile. This will become highly significant in the next chapter when I will discuss other aspects of this non-vaccine that relate to its nanotechnology and transmission from the injected to the uninjected.

Qualified in idiocy

Tenpenny describes how research has confirmed that these 'vaccine'-generated antibodies can interact with a range of other tissues in the body and attack many other organs including the lungs. 'This means that if you have a hundred people standing in front of you that all got this shot they could have a hundred different symptoms.' Anyone really think that Cult gofers like the Queen, Tony Blair, Christopher Whitty, Anthony Fauci, and all the other psychopaths have really had this 'vaccine' in the pictures we've seen? Not a bloody chance. Why don't doctors all tell us about all these dangers and consequences of the 'Covid vaccine'? Why instead do they encourage and pressure patients to have the shot? Don't let's think for a moment that doctors and medical staff can't be stupid, lazy, and psychopathic and that's without the financial incentives to give the jab. Tenpenny again:

> Some people are going to die from the vaccine directly but a large number of people are going to start to get horribly sick and get all kinds of autoimmune diseases 42 days to maybe a year out. What are they going to do, these stupid doctors who say; 'Good for you for getting that vaccine.' What are they going to say; 'Oh, it must be a mutant, we need to give an extra dose of that vaccine.'
>
> Because now the vaccine, instead of one dose or two doses we need three or four because the stupid physicians aren't taking the time to learn anything about it. If I can learn this sitting in my living room reading a 19 page paper and several others so can they. There's nothing special about me, I just take the time to do it.

Remember how Sara Kayat, the NHS and TV doctor, said that the 'Covid vaccine' would '100 percent prevent hospitalisation and death'. Doctors can be idiots like every other profession and they

should not be worshipped as infallible. They are not and far from it. Behind many medical and scientific 'experts' lies an uninformed prat trying to hide themselves from you although in the 'Covid' era many have failed to do so as with UK narrative-repeating 'TV doctor' Hilary Jones. Pushing back against the minority of proper doctors and scientists speaking out against the 'vaccine' has been the entire edifice of the Cult global state in the form of governments, medical systems, corporations, mainstream media, Silicon Valley, and an army of compliant doctors, medical staff and scientists willing to say anything for money and to enhance their careers by promoting the party line. If you do that you are an 'expert' and if you won't you are an 'anti-vaxxer' and 'Covidiot'. The pressure to be 'vaccinated' is incessant. We have even had reports claiming that the 'vaccine' can help cure cancer and Alzheimer's and make the lame walk. I am waiting for the announcement that it can bring you coffee in the morning and cook your tea. Just as the symptoms of 'Covid' seem to increase by the week so have the miracles of the 'vaccine'. American supermarket giant Kroger Co. offered nearly 500,000 employees in 35 states a $100 bonus for having the 'vaccine' while donut chain Krispy Kreme promised 'vaccinated' customers a free glazed donut every day for the rest of 2021. Have your DNA changed and you will get a doughnut although we might not have to give you them for long. Such offers and incentives confirm the desperation.

Perhaps the worse vaccine-stunt of them all was UK 'Health' Secretary Matt-the-prat Hancock on live TV after watching a clip of someone being 'vaccinated' when the roll-out began. Hancock faked tears so badly it was embarrassing. Brain-of-Britain Piers Morgan, the lockdown-supporting, 'vaccine' supporting, 'vaccine' passport-supporting, TV host played along with Hancock – 'You're quite emotional about that' he said in response to acting so atrocious it would have been called out at a school nativity which will presumably today include Mary and Jesus in masks, wise men keeping their camels six feet apart, and shepherds under tent arrest. System-serving Morgan tweeted this: 'Love the idea of covid vaccine passports for everywhere: flights, restaurants, clubs, football, gyms,

shops etc. It's time covid-denying, anti-vaxxer loonies had their bullsh*t bluff called & bar themselves from going anywhere that responsible citizens go.' If only I could aspire to his genius. To think that Morgan, who specialises in shouting over anyone he disagrees with, was lauded as a free speech hero when he lost his job after storming off the set of his live show like a child throwing his dolly out of the pram. If he is a free speech hero we are in real trouble. I have no idea what 'bullsh*t' means, by the way, the * throws me completely.

The Cult is desperate to infuse its synthetic DNA-changing concoction into everyone and has been using every lie, trick and intimidation to do so. The question of '*Why*?' we shall now address.

CHAPTER TEN

Human 2.0

I believe that at the end of the century the use of words and general educated opinion will have altered so much that one will be able to speak of machines thinking without expecting to be contradicted –
Alan Turing (1912-1954), the 'Father of artificial intelligence'

I have been exposing for decades the plan to transform the human body from a biological to a synthetic-biological state. The new human that I will call Human 2.0 is planned to be connected to artificial intelligence and a global AI 'Smart Grid' that would operate as one global system in which AI would control everything from your fridge to your heating system to your car to your mind. Humans would no longer be 'human', but post-human and sub-human, with their thinking and emotional processes replaced by AI.

What I said sounded crazy and beyond science fiction and I could understand that. To any balanced, rational, mind it *is* crazy. Today, however, that world is becoming reality and it puts the 'Covid vaccine' into its true context. Ray Kurzweil is the ultra-Zionist 'computer scientist, inventor and futurist' and co-founder of the Singularity University. Singularity refers to the merging of humans with machines or 'transhumanism'. Kurzweil has said humanity would be connected to the cyber 'cloud' in the period of the ever-recurring year of 2030:

Our thinking … will be a hybrid of biological and non-biological thinking … humans will be able to extend their limitations and 'think in the cloud' … We're going to put gateways to the

cloud in our brains ... We're going to gradually merge and enhance ourselves ... In my view, that's the nature of being human – we transcend our limitations. As the technology becomes vastly superior to what we are then the small proportion that is still human gets smaller and smaller and smaller until it's just utterly negligible.

They are trying to sell this end-of-humanity-as-we-know-it as the next stage of 'evolution' when we become super-human and 'like the gods'. They are lying to you. Shocked, eh? The population, and again especially the young, have been manipulated into addiction to technologies designed to enslave them for life. First they induced an addiction to smartphones (holdables); next they moved to technology on the body (wearables); and then began the invasion of the body (implantables). I warned way back about the plan for microchipped people and we are now entering that era. We should not be diverted into thinking that this refers only to chips we can see. Most important are the nanochips known as smart dust, neural dust and nanobots which are far too small to be seen by the human eye. Nanotechnology is everywhere, increasingly in food products, and released into the atmosphere by the geoengineering of the skies funded by Bill Gates to 'shut out the Sun' and 'save the planet from global warming'. Gates has been funding a project to spray millions of tonnes of chalk (calcium carbonate) into the stratosphere over Sweden to 'dim the Sun' and cool the Earth. Scientists warned the move could be disastrous for weather systems in ways no one can predict and opposition led to the Swedish space agency announcing that the 'experiment' would not be happening as planned in the summer of 2021; but it shows where the Cult is going with dimming the impact of the Sun and there's an associated plan to change the planet's atmosphere. Who gives psychopath Gates the right to dictate to the entire human race and dismantle planetary systems? The world will not be safe while this man is at large.

The global warming hoax has made the Sun, like the gas of life, something to fear when both are essential to good health and human survival (more inversion). The body transforms sunlight into vital vitamin D through a process involving … *cholesterol*. This is the cholesterol we are also told to fear. We are urged to take Big Pharma

statin drugs to reduce cholesterol and it's all systematic. Reducing cholesterol means reducing vitamin D uptake with all the multiple health problems that will cause. At least if you take statins long term it saves the government from having to pay you a pension. The delivery system to block sunlight is widely referred to as chemtrails although these have a much deeper agenda, too. They appear at first to be contrails or condensation trails streaming from aircraft into cold air at high altitudes. Contrails disperse very quickly while chemtrails do not and spread out across the sky before eventually their content falls to earth. Many times I have watched aircraft cross-cross a clear blue sky releasing chemtrails until it looks like a cloudy day. Chemtrails contain many things harmful to humans and the natural world including toxic heavy metals, aluminium (see Alzheimer's) and nanotechnology. Ray Kurzweil reveals the reason without actually saying so: 'Nanobots will infuse all the matter around us with information. Rocks, trees, everything will become these intelligent creatures.' How do you deliver that? *From the sky*. Self-replicating nanobots would connect everything to the Smart Grid. The phenomenon of Morgellons disease began in the chemtrail era and the correlation has led to it being dubbed the 'chemtrail disease'. Self-replicating fibres appear in the body that can be pulled out through the skin. Morgellons fibres continue to grow outside the body and have a form of artificial intelligence. I cover this at greater length in *Phantom Self*.

'Vaccine' operating system

'Covid vaccines' with their self-replicating synthetic material are also designed to make the connection between humanity and Kurzweil's 'cloud'. American doctor and dedicated campaigner for truth, Carrie Madej, an Internal Medicine Specialist in Georgia with more than 20 years medical experience, has highlighted the nanotechnology aspect of the fake 'vaccines'. She explains how one of the components in at least the Moderna and Pfizer synthetic potions are 'lipid nanoparticles' which are 'like little tiny computer bits' – a 'sci-fi substance' known as nanobots and hydrogel which can be 'triggered

at any moment to deliver its payload' and act as 'biosensors'. The synthetic substance had 'the ability to accumulate data from your body like your breathing, your respiration, thoughts and emotions, all kind of things' and each syringe could carry a *million* nanobots:

This substance because it's like little bits of computers in your body, crazy, but it's true, it can do that, [and] obviously has the ability to act through Wi-Fi. It can receive and transmit energy, messages, frequencies or impulses. That issue has never been addressed by these companies. What does that do to the human?

Just imagine getting this substance in you and it can react to things all around you, the 5G, your smart device, your phones, what is happening with that? What if something is triggering it, too, like an impulse, a frequency? We have something completely foreign in the human body.

Madej said her research revealed that electromagnetic (EMF) frequencies emitted by phones and other devices had increased dramatically in the same period of the 'vaccine' rollout and she was seeing more people with radiation problems as 5G and other electromagnetic technology was expanded and introduced to schools and hospitals. She said she was 'floored with the EMF coming off' the devices she checked. All this makes total sense and syncs with my own work of decades when you think that Moderna refers in documents to its mRNA 'vaccine' as an 'operating system':

Recognizing the broad potential of mRNA science, we set out to create an mRNA technology platform that functions very much like an operating system on a computer. It is designed so that it can plug and play interchangeably with different programs. In our case, the 'program' or 'app' is our mRNA drug – the unique mRNA sequence that codes for a protein …

… Our MRNA Medicines – 'The 'Software Of Life': When we have a concept for a new mRNA medicine and begin research, fundamental components are already in place. Generally, the only thing that changes from one potential mRNA medicine to another is the coding region – the actual genetic code that instructs ribosomes to make protein. Utilizing these instruction sets gives our investigational mRNA medicines a software-like quality. We also have the ability to combine different mRNA sequences encoding for different proteins in a single mRNA investigational medicine.

Who needs a real 'virus' when you can create a computer version to justify infusing your operating system into the entire human race on the road to making living, breathing people into cyborgs? What is missed with the 'vaccines' is the *digital* connection between synthetic material and the body that I highlighted earlier with the study that hacked a computer with human DNA. On one level the body is digital, based on mathematical codes, and I'll have more about that in the next chapter. Those who ridiculously claim that mRNA 'vaccines' are not designed to change human genetics should explain the words of Dr Tal Zaks, chief medical officer at Moderna, in a 2017 TED talk. He said that over the last 30 years 'we've been living this phenomenal digital scientific revolution, and I'm here today to tell you, that we are actually *hacking the software of life*, and that it's changing the way we think about prevention and treatment of disease':

In every cell there's this thing called messenger RNA, or mRNA for short, that transmits the critical information from the DNA in our genes to the protein, which is really the stuff we're all made out of. This is the critical information that determines what the cell will do. So we think about it as an operating system. So if you could change that, if you could introduce a line of code, or change a line of code, it turns out, that has profound implications for everything, from the flu to cancer.

Zaks should more accurately have said that this has profound implications for the human genetic code and the nature of DNA. Communications within the body go both ways and not only one. But, hey, no, the 'Covid vaccine' will not affect your genetics. Cult fact-checkers say so even though the man who helped to develop the mRNA technique says that it does. Zaks said in 2017:

If you think about what it is we're trying to do. We've taken information and our understanding of that information and how that information is transmitted in a cell, and we've taken our understanding of medicine and how to make drugs, and we're fusing the two. We think of it as information therapy.

I have been writing for decades that the body is an information field communicating with itself and the wider world. This is why

radiation which is information can change the information field of body and mind through phenomena like 5G and change their nature and function. 'Information therapy' means to change the body's information field and change the way it operates. DNA is a receiver-transmitter of information and can be mutated by information like mRNA synthetic messaging. Technology to do this has been ready and waiting in the underground bases and other secret projects to be rolled out when the 'Covid' hoax was played. 'Trials' of such short and irrelevant duration were only for public consumption. When they say the 'vaccine' is 'experimental' that is not true. It may appear to be 'experimental' to those who don't know what's going on, but the trials have already been done to ensure the Cult gets the result it desires. Zaks said that it took decades to sequence the human genome, completed in 2003, but now they could do it in a week. By 'they' he means scientists operating in the public domain. In the secret projects they were sequencing the genome in a week long before even 2003.

Deluge of mRNA

Highly significantly the Moderna document says the guiding premise is that if using mRNA as a medicine works for one disease then it should work for many diseases. They were leveraging the flexibility afforded by their platform and the fundamental role mRNA plays in protein synthesis to pursue mRNA medicines for a broad spectrum of diseases. Moderna is confirming what I was saying through 2020 that multiple 'vaccines' were planned for 'Covid' (and later invented 'variants') and that previous vaccines would be converted to the mRNA system to infuse the body with massive amounts of genetically-manipulating synthetic material to secure a transformation to a synthetic-biological state. The 'vaccines' are designed to kill stunning numbers as part of the long-exposed Cult depopulation agenda and transform the rest. Given this is the goal you can appreciate why there is such hysterical demand for every human to be 'vaccinated' for an alleged 'disease' that has an estimated 'infection' to 'death' ratio of 0.23-0.15 percent. As I write

children are being given the 'vaccine' in trials (their parents are a disgrace) and ever-younger people are being offered the vaccine for a 'virus' that even if you believe it exists has virtually zero chance of harming them. Horrific effects of the 'trials' on a 12-year-old girl were revealed by a family member to be serious brain and gastric problems that included a bowel obstruction and the inability to swallow liquids or solids. She was unable to eat or drink without throwing up, had extreme pain in her back, neck and abdomen, and was paralysed from the waist down which stopped her urinating unaided. When the girl was first taken to hospital doctors said it was all in her mind. She was signed up for the 'trial' by her parents for whom no words suffice. None of this 'Covid vaccine' insanity makes any sense unless you see what the 'vaccine' really is – a body-changer. Synthetic biology or 'SynBio' is a fast-emerging and expanding scientific discipline which includes everything from genetic and molecular engineering to electrical and computer engineering. Synthetic biology is defined in these ways:

- A multidisciplinary area of research that seeks to create new biological parts, devices, and systems, or to redesign systems that are already found in nature.

- The use of a mixture of physical engineering and genetic engineering to create new (and therefore synthetic) life forms.

- An emerging field of research that aims to combine the knowledge and methods of biology, engineering and related disciplines in the design of chemically-synthesized DNA to create organisms with novel or enhanced characteristics and traits (synthetic organisms including humans).

We now have synthetic blood, skin, organs and limbs being developed along with synthetic body parts produced by 3D printers. These are all elements of the synthetic human programme and this comment by Kurzweil's co-founder of the Singularity University,

Peter Diamandis, can be seen in a whole new light with the 'Covid' hoax and the sanctions against those that refuse the 'vaccine':

Anybody who is going to be resisting the progress forward [to transhumanism] is going to be resisting evolution and, fundamentally, they will die out. It's not a matter of whether it's good or bad. It's going to happen.

'Resisting evolution'? What absolute bollocks. The arrogance of these people is without limit. His 'it's going to happen' mantra is another way of saying 'resistance is futile' to break the spirit of those pushing back and we must not fall for it. Getting this genetically-transforming 'vaccine' into everyone is crucial to the Cult plan for total control and the desperation to achieve that is clear for anyone to see. Vaccine passports are a major factor in this and they, too, are a form of resistance is futile. It's NOT. The paper funded by the Rockefeller Foundation for the 2013 'health conference' in China said:

We will interact more with artificial intelligence. The use of robotics, bio-engineering to augment human functioning is already well underway and will advance. Re-engineering of humans into potentially separate and unequal forms through genetic engineering or mixed human-robots raises debates on ethics and equality.

A new demography is projected to emerge after 2030 [that year again] of technologies (robotics, genetic engineering, nanotechnology) producing robots, engineered organisms, 'nanobots' and artificial intelligence (AI) that can self-replicate. Debates will grow on the implications of an impending reality of human designed life.

What is happening today is so long planned. The world army enforcing the will of the world government is intended to be a robot army, not a human one. Today's military and its technologically 'enhanced' troops, pilotless planes and driverless vehicles are just stepping stones to that end. Human soldiers are used as Cult fodder and its time they woke up to that and worked for the freedom of the population instead of their own destruction and their family's destruction – the same with the police. Join us and let's sort this out. The phenomenon of enforce my own destruction is widespread in the 'Covid' era with Woker 'luvvies' in the acting and entertainment

industries supporting 'Covid' rules which have destroyed their profession and the same with those among the public who put signs on the doors of their businesses 'closed due to Covid – stay safe' when many will never reopen. It's a form of masochism and most certainly insanity.

Transgender = transhumanism

When something explodes out of nowhere and is suddenly everywhere it is always the Cult agenda and so it is with the tidal wave of claims and demands that have infiltrated every aspect of society under the heading of 'transgenderism'. The term 'trans' is so 'in' and this is the dictionary definition:

A prefix meaning 'across', 'through', occurring … in loanwords from Latin, used in particular for denoting movement or conveyance from place to place (transfer; transmit; transplant) or complete change (transform; transmute), or to form adjectives meaning 'crossing', 'on the other side of', or 'going beyond' the place named (transmontane; transnational; trans-Siberian).

Transgender means to go beyond gender and transhuman means to go beyond human. Both are aspects of the Cult plan to transform the human body to a synthetic state with *no gender*. Human 2.0 is not designed to procreate and would be produced technologically with no need for parents. The new human would mean the end of parents and so men, and increasingly women, are being targeted for the deletion of their rights and status. Parental rights are disappearing at an ever-quickening speed for the same reason. The new human would have no need for men or women when there is no procreation and no gender. Perhaps the transgender movement that appears to be in a permanent state of frenzy might now contemplate on how it is being used. This was never about transgender rights which are only the interim excuse for confusing gender, particularly in the young, on the road to *fusing* gender. Transgender activism is not an end; it is a *means* to an end. We see again the technique of creative destruction in which you destroy the status quo to 'build back better' in the form that you want. The gender status quo had to be

destroyed by persuading the Cult-created Woke mentality to believe that you can have 100 genders or more. A programme for 9 to 12 year olds produced by the Cult-owned BBC promoted the 100 genders narrative. The very idea may be the most monumental nonsense, but it is not what is true that counts, only what you can make people *believe* is true. Once the gender of 2 + 2 = 4 has been dismantled through indoctrination, intimidation and 2 + 2 = 5 then the new no-gender normal can take its place with Human 2.0. Aldous Huxley revealed the plan in his prophetic *Brave New World* in 1932:

> Natural reproduction has been done away with and children are created, decanted', and raised in 'hatcheries and conditioning centres'. From birth, people are genetically designed to fit into one of five castes, which are further split into 'Plus' and 'Minus' members and designed to fulfil predetermined positions within the social and economic strata of the World State.

How could Huxley know this in 1932? For the same reason George Orwell knew about the Big Brother state in 1948, Cult insiders I have quoted knew about it in 1969, and I have known about it since the early 1990s. If you are connected to the Cult or you work your balls off to uncover the plan you can predict the future. The process is simple. If there is a plan for the world and nothing intervenes to stop it then it will happen. Thus if you communicate the plan ahead of time you are perceived to have predicted the future, but you haven't. You have revealed the plan which without intervention will become the human future. The whole reason I have done what I have is to alert enough people to inspire an intervention and maybe at last that time has come with the Cult and its intentions now so obvious to anyone with a brain in working order.

The future is here

Technological wombs that Huxley described to replace parent procreation are already being developed and they are only the projects we know about in the public arena. Israeli scientists told *The Times of Israel* in March, 2021, that they have grown 250-cell embryos

into mouse foetuses with fully formed organs using artificial wombs in a development they say could pave the way for gestating humans outside the womb. Professor Jacob Hanna of the Weizmann Institute of Science said:

We took mouse embryos from the mother at day five of development, when they are just of 250 cells, and had them in the incubator from day five until day 11, by which point they had grown all their organs.

By day 11 they make their own blood and have a beating heart, a fully developed brain. Anybody would look at them and say, 'this is clearly a mouse foetus with all the characteristics of a mouse.' It's gone from being a ball of cells to being an advanced foetus.

A special liquid is used to nourish embryo cells in a laboratory dish and they float on the liquid to duplicate the first stage of embryonic development. The incubator creates all the right conditions for its development, Hanna said. The liquid gives the embryo 'all the nutrients, hormones and sugars they need' along with a custom-made electronic incubator which controls gas concentration, pressure and temperature. The cutting-edge in the underground bases and other secret locations will be light years ahead of that, however, and this was reported by the London *Guardian* in 2017:

We are approaching a biotechnological breakthrough. Ectogenesis, the invention of a complete external womb, could completely change the nature of human reproduction. In April this year, researchers at the Children's Hospital of Philadelphia announced their development of an artificial womb.

The article was headed 'Artificial wombs could soon be a reality. What will this mean for women?' What would it mean for children is an even bigger question. No mother to bond with only a machine in preparation for a life of soulless interaction and control in a world governed by machines (see the *Matrix* movies). Now observe the calculated manipulations of the 'Covid' hoax as human interaction and warmth has been curtailed by distancing, isolation and fear with people communicating via machines on a scale never seen before.

These are all dots in the same picture as are all the personal assistants, gadgets and children's toys through which kids and adults communicate with AI as if it is human. The AI 'voice' on Sat-Nav should be included. All these things are psychological preparation for the Cult endgame. Before you can make a physical connection with AI you have to make a psychological connection and that is what people are being conditioned to do with this ever gathering human-AI interaction. Movies and TV programmes depicting the transhuman, robot dystopia relate to a phenomenon known as 'pre-emptive programming' in which the world that is planned is portrayed everywhere in movies, TV and advertising. This is conditioning the conscious and subconscious mind to become familiar with the planned reality to dilute resistance when it happens for real. What would have been a shock such is the change is made less so. We have young children put on the road to transgender transition surgery with puberty blocking drugs at an age when they could never be able to make those life-changing decisions.

Rachel Levine, a professor of paediatrics and psychiatry who believes in treating children this way, became America's highest-ranked openly-transgender official when she was confirmed as US Assistant Secretary at the Department of Health and Human Services after being nominated by Joe Biden (the Cult). Activists and governments press for laws to deny parents a say in their children's transition process so the kids can be isolated and manipulated into agreeing to irreversible medical procedures. A Canadian father Robert Hoogland was denied bail by the Vancouver Supreme Court in 2021 and remained in jail for breaching a court order that he stay silent over his young teenage daughter, a minor, who was being offered life-changing hormone therapy without parental consent. At the age of 12 the girl's 'school counsellor' said she may be transgender, referred her to a doctor and told the school to treat her like a boy. This is another example of state-serving schools imposing ever more control over children's lives while parents have ever less.

Contemptible and extreme child abuse is happening all over the world as the Cult gender-fusion operation goes into warp-speed.

Why the war on men – and now women?

The question about what artificial wombs mean for women should rightly be asked. The answer can be seen in the deletion of women's rights involving sport, changing rooms, toilets and status in favour of people in male bodies claiming to identify as women. I can identify as a mountain climber, but it doesn't mean I can climb a mountain any more than a biological man can be a biological woman. To believe so is a triumph of belief over factual reality which is the very perceptual basis of everything Woke. Women's sport is being destroyed by allowing those with male bodies who say they identify as female to 'compete' with girls and women. Male body 'women' dominate 'women's' competition with their greater muscle mass, bone density, strength and speed. With that disadvantage sport for women loses all meaning. To put this in perspective nearly 300 American high school boys can run faster than the quickest woman sprinter in the world. Women are seeing their previously protected spaces invaded by male bodies simply because they claim to identify as women. That's all they need to do to access all women's spaces and activities under the Biden 'Equality Act' that destroys equality for women with the usual Orwellian Woke inversion. Male sex offenders have already committed rapes in women's prisons after claiming to identify as women to get them transferred. Does this not matter to the Woke 'equality' hypocrites? Not in the least. What matters to Cult manipulators and funders behind transgender activists is to advance gender fusion on the way to the no-gender 'human'. When you are seeking to impose transparent nonsense like this, or the 'Covid' hoax, the only way the nonsense can prevail is through censorship and intimidation of dissenters, deletion of factual information, and programming of the unquestioning, bewildered and naive. You don't have to scan the world for long to see that all these things are happening.

Many women's rights organisations have realised that rights and status which took such a long time to secure are being eroded and that it is systematic. Kara Dansky of the global Women's Human Rights Campaign said that Biden's transgender executive order immediately he took office, subsequent orders, and Equality Act legislation that followed 'seek to erase women and girls in the law as a category'. *Exactly*. I said during the long ago-started war on men (in which many women play a crucial part) that this was going to turn into a war on them. The Cult is phasing out *both* male and female genders. To get away with that they are brought into conflict so they are busy fighting each other while the Cult completes the job with no unity of response. Unity, people, *unity*. We need unity everywhere. Transgender is the only show in town as the big step towards the no-gender human. It's not about rights for transgender people and never has been. Woke political correctness is deleting words relating to genders to the same end. Wokers believe this is to be 'inclusive' when the opposite is true. They are deleting words describing gender because gender *itself* is being deleted by Human 2.0. Terms like 'man', 'woman', 'mother' and 'father' are being deleted in the universities and other institutions to be replaced by the *no*-gender, not trans-gender, 'individuals' and 'guardians'. Women's rights campaigner Maria Keffler of Partners for Ethical Care said: 'Children are being taught from kindergarten upward that some boys have a vagina, some girls have a penis, and that kids can be any gender they want to be.' Do we really believe that suddenly countries all over the world at the same time had the idea of having drag queens go into schools or read transgender stories to very young children in the local library? It's coldly-calculated confusion of gender on the way to the fusion of gender. Suzanne Vierling, a psychologist from Southern California, made another important point:

Yesterday's slave woman who endured gynecological medical experiments is today's girl-child being butchered in a booming gender-transitioning sector. Ovaries removed, pushing her into menopause and osteoporosis, uncharted territory, and parents' rights and authority decimated.

The erosion of parental rights is a common theme in line with the Cult plans to erase the very concept of parents and 'ovaries removed, pushing her into menopause' means what? Those born female lose the ability to have children – another way to discontinue humanity as we know it.

Eliminating Human 1.0 (before our very eyes)

To pave the way for Human 2.0 you must phase out Human 1.0. This is happening through plummeting sperm counts and making women infertile through an onslaught of chemicals, radiation (including smartphones in pockets of men) and mRNA 'vaccines'. Common agriculture pesticides are also having a devastating impact on human fertility. I have been tracking collapsing sperm counts in the books for a long time and in 2021 came a book by fertility scientist and reproductive epidemiologist Shanna Swan, *Count Down: How Our Modern World Is Threatening Sperm Counts, Altering Male and Female Reproductive Development and Imperiling the Future of the Human Race*. She reports how the global fertility rate dropped by *half* between 1960 and 2016 with America's birth rate 16 percent below where it needs to be to sustain the population. Women are experiencing declining egg quality, more miscarriages, and more couples suffer from infertility. Other findings were an increase in erectile dysfunction, infant boys developing more genital abnormalities, male problems with conception, and plunging levels of the male hormone testosterone which would explain why so many men have lost their backbone and masculinity. This has been very evident during the 'Covid' hoax when women have been prominent among the Pushbackers and big strapping blokes have bowed their heads, covered their faces with a nappy and quietly submitted. Mind control expert Cathy O'Brien also points to how global education introduced the concept of 'we're all winners' in sport and classrooms: 'Competition was defused, and it in turn defused a sense of fighting back.' This is another version of the 'equity' doctrine in which you drive down rather than raise up. What a contrast in Cult-controlled China with its global ambitions

where the government published plans in January, 2021, to 'cultivate masculinity' in boys from kindergarten through to high school in the face of a 'masculinity crisis'. A government adviser said boys would be soon become 'delicate, timid and effeminate' unless action was taken. Don't expect any similar policy in the targeted West. A 2006 study showed that a 65-year-old man in 2002 had testosterone levels *15 percent* lower than a 65-year-old man in 1987 while a 2020 study found a similar story with young adults and adolescents. Men are getting prescriptions for testosterone replacement therapy which causes an even greater drop in sperm count with up to 99 percent seeing sperm counts drop to zero during the treatment. More sperm is defective and malfunctioning with some having two heads or not pursuing an egg.

A class of *synthetic* chemicals known as phthalates are being blamed for the decline. These are found everywhere in plastics, shampoos, cosmetics, furniture, flame retardants, personal care products, pesticides, canned foods and even receipts. Why till receipts? Everyone touches them. Let no one delude themselves that all this is not systematic to advance the long-time agenda for human body transformation. Phthalates mimic hormones and disrupt the hormone balance causing testosterone to fall and genital birth defects in male infants. Animals and fish have been affected in the same way due to phthalates and other toxins in rivers. When fish turn gay or change sex through chemicals in rivers and streams it is a pointer to why there has been such an increase in gay people and the sexually confused. It doesn't matter to me what sexuality people choose to be, but if it's being affected by chemical pollution and consumption then we need to know. Does anyone really think that this is not connected to the transgender agenda, the war on men and the condemnation of male 'toxic masculinity'? You watch this being followed by 'toxic femininity'. It's already happening. When breastfeeding becomes 'chest-feeding', pregnant women become pregnant people along with all the other Woke claptrap you know that the world is going insane and there's a Cult scam in progress. Transgender activists are promoting the Cult agenda while Cult

billionaires support and fund the insanity as they laugh themselves to sleep at the sheer stupidity for which humans must be infamous in galaxies far, far away.

'Covid vaccines' and female infertility

We can now see why the 'vaccine' has been connected to potential infertility in women. Dr Michael Yeadon, former Vice President and Chief Scientific Advisor at Pfizer, and Dr Wolfgang Wodarg in Germany, filed a petition with the European Medicines Agency in December, 2020, urging them to stop trials for the Pfizer/BioNTech shot and all other mRNA trials until further studies had been done. They were particularly concerned about possible effects on fertility with 'vaccine'-produced antibodies attacking the protein Syncytin-1 which is responsible for developing the placenta. The result would be infertility 'of indefinite duration' in women who have the 'vaccine' with the placenta failing to form. Section 10.4.2 of the Pfizer/BioNTech trial protocol says that pregnant women or those who might become so should not have mRNA shots. Section 10.4 warns men taking mRNA shots to 'be abstinent from heterosexual intercourse' and not to donate sperm. The UK government said that it *did not know* if the mRNA procedure had an effect on fertility. *Did not know?* These people have to go to jail. UK government advice did not recommend at the start that pregnant women had the shot and said they should avoid pregnancy for at least two months after 'vaccination'. The 'advice' was later updated to pregnant women should only have the 'vaccine' if the benefits outweighed the risks to mother and foetus. What the hell is that supposed to mean? Then 'spontaneous abortions' began to appear and rapidly increase on the adverse reaction reporting schemes which include only a fraction of adverse reactions. Thousands and ever-growing numbers of 'vaccinated' women are describing changes to their menstrual cycle with heavier blood flow, irregular periods and menstruating again after going through the menopause – all links to reproduction effects. Women are passing blood clots and the lining of their uterus while men report erectile dysfunction and blood effects. Most

significantly of all *un*vaccinated women began to report similar menstrual changes after interaction with *'vaccinated'* people and men and children were also affected with bleeding noses, blood clots and other conditions. 'Shedding' is when vaccinated people can emit the content of a vaccine to affect the unvaccinated, but this is different. 'Vaccinated' people were not shedding a 'live virus' allegedly in 'vaccines' as before because the fake 'Covid vaccines' involve synthetic material and other toxicity. Doctors exposing what is happening prefer the term 'transmission' to shedding. Somehow those that have had the shots are transmitting effects to those that haven't. Dr Carrie Madej said the nano-content of the 'vaccines' can 'act like an antenna' to others around them which fits perfectly with my own conclusions. This 'vaccine' transmission phenomenon was becoming known as the book went into production and I deal with this further in the Postscript.

Vaccine effects on sterility are well known. The World Health Organization was accused in 2014 of sterilising millions of women in Kenya with the evidence confirmed by the content of the vaccines involved. The same WHO behind the 'Covid' hoax admitted its involvement for more than ten years with the vaccine programme. Other countries made similar claims. Charges were lodged by Tanzania, Nicaragua, Mexico, and the Philippines. The Gardasil vaccine claimed to protect against a genital 'virus' known as HPV has also been linked to infertility. Big Pharma and the WHO (same thing) are criminal and satanic entities. Then there's the Bill Gates Foundation which is connected through funding and shared interests with 20 pharmaceutical giants and laboratories. He stands accused of directing the policy of United Nations Children's Fund (UNICEF), vaccine alliance GAVI, and other groupings, to advance the vaccine agenda and silence opposition at great cost to women and children. At the same time Gates wants to reduce the global population. Coincidence?

Great Reset = Smart Grid = new human

The Cult agenda I have been exposing for 30 years is now being openly promoted by Cult assets like Gates and Klaus Schwab of the World Economic Forum under code-terms like the 'Great Reset', 'Build Back Better' and 'a rare but narrow window of opportunity to reflect, reimagine, and reset our world'. What provided this 'rare but narrow window of opportunity'? The 'Covid' hoax did. Who created that? *They* did. My books from not that long ago warned about the planned 'Internet of Things' (IoT) and its implications for human freedom. This was the plan to connect all technology to the Internet and artificial intelligence and today we are way down that road with an estimated 36 billion devices connected to the World Wide Web and that figure is projected to be 76 billion by 2025. I further warned that the Cult planned to go beyond that to the Internet of *Everything* when the human brain was connected via AI to the Internet and Kurzweil's 'cloud'. Now we have Cult operatives like Schwab calling for precisely that under the term 'Internet of Bodies', a fusion of the physical, digital and biological into one centrally-controlled Smart Grid system which the Cult refers to as the 'Fourth Industrial Revolution'. They talk about the 'biological', but they really mean the synthetic-biological which is required to fully integrate the human body and brain into the Smart Grid and artificial intelligence planned to replace the human mind. We have everything being synthetically manipulated including the natural world through GMO and smart dust, the food we eat and the human body itself with synthetic 'vaccines'. I said in *The Answer* that we would see the Cult push for synthetic meat to replace animals and in February, 2021, the so predictable psychopath Bill Gates called for the introduction of synthetic meat to save us all from 'climate change'. The climate hoax just keeps on giving like the 'Covid' hoax. The war on meat by vegan activists is a carbon (oops, sorry) copy of the manipulation of transgender activists. They have no idea (except their inner core) that they are being used to promote and impose the agenda of the Cult or that they are only the *vehicle* and not the *reason*. This is not to say those who choose not to eat meat shouldn't be respected and supported in that right, but there are ulterior motives

for those in power. A *Forbes* article in December, 2019, highlighted the plan so beloved of Schwab and the Cult under the heading: 'What Is The Internet of Bodies? And How Is It Changing Our World?' The article said the human body is the latest data platform (remember 'our vaccine is an operating system'). *Forbes* described the plan very accurately and the words could have come straight out of my books from long before:

The Internet of Bodies (IoB) is an extension of the IoT and basically connects the human body to a network through devices that are ingested, implanted, or connected to the body in some way. Once connected, data can be exchanged, and the body and device can be remotely monitored and controlled.

They were really describing a human hive mind with human perception centrally-dictated via an AI connection as well as allowing people to be 'remotely monitored and controlled'. Everything from a fridge to a human mind could be directed from a central point by these insane psychopaths and 'Covid vaccines' are crucial to this. Forbes explained the process I mentioned earlier of holdable and wearable technology followed by implantable. The article said there were three generations of the Internet of Bodies that include:

- Body external: These are wearable devices such as Apple Watches or Fitbits that can monitor our health.

- Body internal: These include pacemakers, cochlear implants, and digital pills that go inside our bodies to monitor or control various aspects of health.

- Body embedded: The third generation of the Internet of Bodies is embedded technology where technology and the human body are melded together and have a real-time connection to a remote machine.

Forbes noted the development of the Brain Computer Interface (BCI) which merges the brain with an external device for monitoring and controlling in real-time. 'The ultimate goal is to help restore function to individuals with disabilities by using brain signals rather than conventional neuromuscular pathways.' Oh, do fuck off. The goal of brain interface technology is controlling human thought and emotion from the central point in a hive mind serving its masters wishes. Many people are now agreeing to be chipped to open doors without a key. You can recognise them because they'll be wearing a mask, social distancing and lining up for the 'vaccine'. The Cult plans a Great Reset money system after they have completed the demolition of the global economy in which 'money' will be exchanged through communication with body operating systems. Rand Corporation, a Cult-owned think tank, said of the Internet of Bodies or IoB:

> Internet of Bodies technologies fall under the broader IoT umbrella. But as the name suggests, IoB devices introduce an even more intimate interplay between humans and gadgets. IoB devices monitor the human body, collect health metrics and other personal information, and transmit those data over the Internet. Many devices, such as fitness trackers, are already in use … IoB devices … and those in development can track, record, and store users' whereabouts, bodily functions, and what they see, hear, and even think.

Schwab's World Economic Forum, a long-winded way of saying 'fascism' or 'the Cult', has gone full-on with the Internet of Bodies in the 'Covid' era. 'We're entering the era of the Internet of Bodies', it declared, 'collecting our physical data via a range of devices that can be implanted, swallowed or worn'. The result would be a huge amount of health-related data that could improve human wellbeing around the world, and prove crucial in fighting the 'Covid-19 pandemic'. Does anyone think these clowns care about 'human wellbeing' after the death and devastation their pandemic hoax has purposely caused? Schwab and co say we should move forward with the Internet of Bodies because 'Keeping track of symptoms could help us stop the spread of infection, and quickly detect new cases'. How wonderful, but keeping track' is all they are really bothered

about. Researchers were investigating if data gathered from smartwatches and similar devices could be used as viral infection alerts by tracking the user's heart rate and breathing. Schwab said in his 2018 book *Shaping the Future of the Fourth Industrial Revolution*:

> The lines between technologies and beings are becoming blurred and not just by the ability to create lifelike robots or synthetics. Instead it is about the ability of new technologies to literally become part of us. Technologies already influence how we understand ourselves, how we think about each other, and how we determine our realities. As the technologies … give us deeper access to parts of ourselves, we may begin to integrate digital technologies into our bodies.

You can see what the game is. Twenty-four hour control and people – if you could still call them that – would never know when something would go ping and take them out of circulation. It's the most obvious rush to a global fascist dictatorship and the complete submission of humanity and yet still so many are locked away in their Cult-induced perceptual coma and can't see it.

Smart Grid control centres

The human body is being transformed by the 'vaccines' and in other ways into a synthetic cyborg that can be attached to the global Smart Grid which would be controlled from a central point and other sub-locations of Grid manipulation. Where are these planned to be? Well, China for a start which is one of the Cult's biggest centres of operation. The technological control system and technocratic rule was incubated here to be unleashed across the world after the 'Covid' hoax came out of China in 2020. Another Smart Grid location that will surprise people new to this is Israel. I have exposed in *The Trigger* how Sabbatian technocrats, intelligence and military operatives were behind the horrors of 9/11 and not '19 Arab hijackers' who somehow manifested the ability to pilot big passenger airliners when instructors at puddle-jumping flying schools described some of them as a joke. The 9/11 attacks were made possible through control of civilian and military air computer systems and those of the White House, Pentagon and connected agencies. See *The Trigger* – it

will blow your mind. The controlling and coordinating force were the Sabbatian networks in Israel and the United States which by then had infiltrated the entire US government, military and intelligence system. The real name of the American Deep State is 'Sabbatian State'. Israel is a tiny country of only nine million people, but it is one of the global centres of cyber operations and fast catching Silicon Valley in importance to the Cult. Israel is known as the 'start-up nation' for all the cyber companies spawned there with the Sabbatian specialisation of 'cyber security' that I mentioned earlier which gives those companies access to computer systems of their clients in real time through 'backdoors' written into the coding when security software is downloaded. The Sabbatian centre of cyber operations outside Silicon Valley is the Israeli military Cyber Intelligence Unit, the biggest infrastructure project in Israel's history, headquartered in the desert-city of Beersheba and involving some 20,000 'cyber soldiers'. Here are located a literal army of Internet trolls scanning social media, forums and comment lists for anyone challenging the Cult agenda. The UK military has something similar with its 77th Brigade and associated operations. The Beersheba complex includes research and development centres for other Cult operations such as Intel, Microsoft, IBM, Google, Apple, Hewlett-Packard, Cisco Systems, Facebook and Motorola. Techcrunch.com ran an article about the Beersheba global Internet technology centre headlined 'Israel's desert city of Beersheba is turning into a cybertech oasis':

> The military's massive relocation of its prestigious technology units, the presence of multinational and local companies, a close proximity to Ben Gurion University and generous government subsidies are turning Beersheba into a major global cybertech hub. Beersheba has all of the ingredients of a vibrant security technology ecosystem, including Ben Gurion University with its graduate program in cybersecurity and Cyber Security Research Center, and the presence of companies such as EMC, Deutsche Telekom, PayPal, Oracle, IBM, and Lockheed Martin. It's also the future home of the INCB (Israeli National Cyber Bureau); offers a special income tax incentive for cyber security companies, and was the site for the relocation of the army's intelligence corps units.

Sabbatians have taken over the cyber world through the following process: They scan the schools for likely cyber talent and develop them at Ben Gurion University and their period of conscription in the Israeli Defense Forces when they are stationed at the Beersheba complex. When the cyber talented officially leave the army they are funded to start cyber companies with technology developed by themselves or given to them by the state. Much of this is stolen through backdoors of computer systems around the world with America top of the list. Others are sent off to Silicon Valley to start companies or join the major ones and so we have many major positions filled by apparently 'Jewish' but really Sabbatian operatives. Google, YouTube and Facebook are all run by 'Jewish' CEOs while Twitter is all but run by ultra-Zionist hedge-fund shark Paul Singer. At the centre of the Sabbatian global cyber web is the Israeli army's Unit 8200 which specialises in hacking into computer systems of other countries, inserting viruses, gathering information, instigating malfunction, and even taking control of them from a distance. A long list of Sabbatians involved with 9/11, Silicon Valley and Israeli cyber security companies are operatives of Unit 8200. This is not about Israel. It's about the Cult. Israel is planned to be a Smart Grid hub as with China and what is happening at Beersheba is not for the benefit of Jewish people who are treated disgustingly by the Sabbatian elite that control the country. A glance at the Nuremberg Codes will tell you that.

The story is much bigger than 'Covid', important as that is to where we are being taken. Now, though, it's time to really strap in. There's more … much more …

CHAPTER ELEVEN

Who controls the Cult?

Awake, arise or be forever fall'n
John Milton, *Paradise Lost*

I have exposed this far the level of the Cult conspiracy that operates in the world of the seen and within the global secret society and satanic network which operates in the shadows one step back from the seen. The story, however, goes much deeper than that.

The 'Covid' hoax is major part of the Cult agenda, but only part, and to grasp the biggest picture we have to expand our attention beyond the realm of human sight and into the infinity of possibility that we cannot see. It is from here, ultimately, that humanity is being manipulated into a state of total control by the force which dictates the actions of the Cult. How much of reality can we see? Next to damn all is the answer. We may appear to see all there is to see in the 'space' our eyes survey and observe, but little could be further from the truth. The human 'world' is only a tiny band of frequency that the body's visual and perceptual systems can decode into *perception* of a 'world'. According to mainstream science the electromagnetic spectrum is 0.005 percent of what exists in the Universe (Fig 10). The maximum estimate I have seen is 0.5 percent and either way it's miniscule. I say it is far, far, smaller even than 0.005 percent when you compare reality we see with the totality of reality that we don't. Now get this if you are new to such information: Visible light, the only band of frequency that we can see, is a *fraction* of the 0.005

percent (Fig 11 overleaf). Take this further and realise that our universe is one of infinite universes and that universes are only a fragment of overall reality – *infinite* reality. Then compare that with the almost infinitesimal frequency band of visible light or human sight. You see that humans are as near blind as it is possible to be without actually being so. Artist and filmmaker, Sergio Toporek, said:

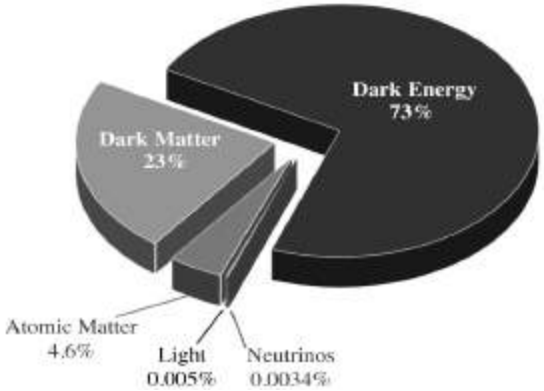


Figure 10: Humans can perceive such a tiny band of visual reality it's laughable.

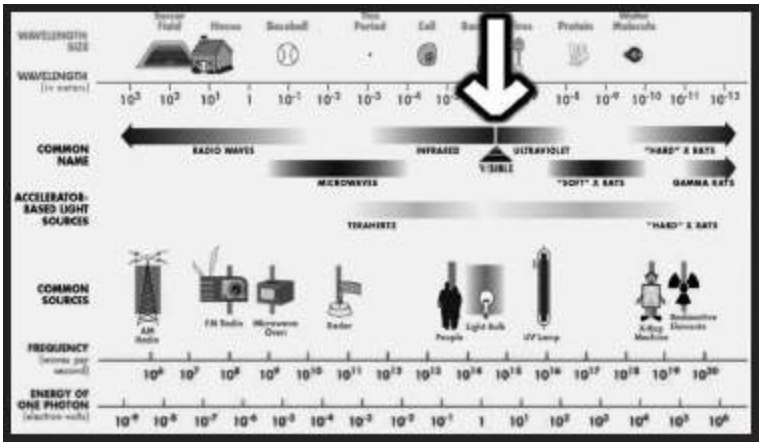


Figure 11: We can see a smear of the 0.005 percent electromagnetic spectrum, but we still know it all. Yep, makes sense.

Consider that you can see less than 1% of the electromagnetic spectrum and hear less than 1% of the acoustic spectrum. 90% of the cells in your body carry their own microbial DNA and are not 'you'. The atoms in your body are 99.9999999999999999% empty space and none of them are the ones you were born with ... Human beings have 46 chromosomes, two less than a potato.

The existence of the rainbow depends on the conical photoreceptors in your eyes; to animals without cones, the rainbow does not exist. So you don't just look at a rainbow, you create it. This is pretty amazing, especially considering that all the beautiful colours you see represent less than 1% of the electromagnetic spectrum.

Suddenly the 'world' of humans looks a very different place. Take into account, too, that Planet Earth when compared with the projected size of this single universe is the equivalent of a billionth of a pinhead. Imagine the ratio that would be when compared to infinite reality. To think that Christianity once insisted that Earth and humanity were the centre of everything. This background is vital if we are going to appreciate the nature of 'human' and how we can be manipulated by an unseen force. To human visual reality virtually *everything* is unseen and yet the prevailing perception within the institutions and so much of the public is that if we can't see it, touch it, hear it, taste it and smell it then it cannot exist. Such perception is indoctrinated and encouraged by the Cult and its agents because it isolates believers in the strictly limited, village-idiot, realm of the five senses where perceptions can be firewalled and information controlled. Most of those perpetuating the 'this-world-is-all-there-is' insanity are themselves indoctrinated into believing the same delusion. While major players and influencers know that official reality is laughable most of those in science, academia and medicine really believe the nonsense they peddle and teach succeeding generations. Those who challenge the orthodoxy are dismissed as nutters and freaks to protect the manufactured illusion from exposure. Observe the dynamic of the 'Covid' hoax and you will see how that takes the same form. The inner-circle psychopaths knows it's a gigantic scam, but almost the entirety of those imposing their fascist rules believe that 'Covid' is all that they're told it is.

Stolen identity

Ask people who they are and they will give you their name, place of birth, location, job, family background and life story. Yet that is not who they are – it is what they are *experiencing*. The difference is *absolutely crucial*. The true 'I', the eternal, infinite 'I', is consciousness,

a state of being aware. Forget 'form'. That is a vehicle for a brief experience. Consciousness does not come *from* the brain, but *through* the brain and even that is more symbolic than literal. We are awareness, pure awareness, and this is what withdraws from the body at what we call 'death' to continue our eternal beingness, *isness*, in other realms of reality within the limitlessness of infinity or the Biblical 'many mansions in my father's house'. Labels of a human life, man, woman, transgender, black, white, brown, nationality, circumstances and income are not who we are. They are what we are – awareness – is *experiencing* in a brief connection with a band of frequency we call 'human'. The labels are not the self; they are, to use the title of one of my books, a *Phantom* Self. I am not David Icke born in Leicester, England, on April 29th, 1952. I am the consciousness *having that experience*. The Cult and its non-human masters seek to convince us through the institutions of 'education', science, medicine, media and government that what we are *experiencing* is who we *are*. It's so easy to control and direct perception locked away in the bewildered illusions of the five senses with no expanded radar. Try, by contrast, doing the same with a humanity aware of its true self and its true power to consciously create its reality and experience. How is it possible to do this? We do it all day every day. If you perceive yourself as 'little me' with no power to impact upon your life and the world then your life experience will reflect that. You will hand the power you don't think you have to authority in all its forms which will use it to control your experience. This, in turn, will appear to confirm your perception of 'little me' in a self-fulfilling feedback loop. But that is what 'little me' really is – a *perception*. We are all 'big-me', infinite me, and the Cult has to make us forget that if its will is to prevail. We are therefore manipulated and pressured into self-identifying with human labels and not the consciousness/awareness *experiencing* those human labels.

The phenomenon of identity politics is a Cult-instigated manipulation technique to sub-divide previous labels into even smaller ones. A United States university employs this list of letters to

describe student identity: LGBTTQQFAGPBDSM or lesbian, gay, bisexual, transgender, transsexual, queer, questioning, flexual, asexual, gender-fuck, polyamorous, bondage/discipline, dominance/submission and sadism/masochism. I'm sure other lists are even longer by now as people feel the need to self-identity the 'I' with the minutiae of race and sexual preference. Wokers programmed by the Cult for generations believe this is about 'inclusivity' when it's really the Cult locking them away into smaller and smaller versions of Phantom Self while firewalling them from the influence of their true self, the infinite, eternal 'I'. You may notice that my philosophy which contends that we are all unique points of attention/awareness within the same infinite whole or Oneness is the ultimate non-racism. The very sense of Oneness makes the judgement of people by their body-type, colour or sexuality utterly ridiculous and confirms that racism has no understanding of reality (including anti-white racism). Yet despite my perception of life Cult agents and fast-asleep Wokers label me racist to discredit my information while they are themselves phenomenally racist and sexist. All they see is race and sexuality and they judge people as good or bad, demons or untouchables, by their race and sexuality. All they see is *Phantom Self* and perceive themselves in terms of Phantom Self. They are pawns and puppets of the Cult agenda to focus attention and self-identity in the five senses and play those identities against each other to divide and rule. Columbia University has introduced segregated graduations in another version of social distancing designed to drive people apart and teach them that different racial and cultural groups have nothing in common with each other. The last thing the Cult wants is unity. Again the pump-primers of this will be Cult operatives in the knowledge of what they are doing, but the rest are just the Phantom Self blind leading the Phantom Self blind. We *do* have something in common – we are all *the same consciousness* having different temporary experiences.

What is this 'human'?

Yes, what *is* 'human'? That is what we are supposed to be, right? I mean 'human'? True, but 'human' is the experience not the 'I'. Break it down to basics and 'human' is the way that information is processed. If we are to experience and interact with this band of frequency we call the 'world' we must have a vehicle that operates within that band of frequency. Our consciousness in its prime form cannot do that; it is way beyond the frequency of the human realm. My consciousness or awareness could not tap these keys and pick up the cup in front of me in the same way that radio station A cannot interact with radio station B when they are on different frequencies. The human body is the means through which we have that interaction. I have long described the body as a biological computer which processes information in a way that allows consciousness to experience this reality. The body is a receiver, transmitter and processor of information in a particular way that we call human. We visually perceive only the world of the five senses in a wakened state – that is the limit of the body's visual decoding system. In truth it's not even visual in the way we experience 'visual reality' as I will come to in a moment. We are 'human' because the body processes the information sources of human into a reality and behaviour system that we *perceive* as human. Why does an elephant act like an elephant and not like a human or a duck? The elephant's biological computer is a different information field and processes information according to that program into a visual and behaviour type we call an elephant. The same applies to everything in our reality. These body information fields are perpetuated through procreation (like making a copy of a software program). The Cult wants to break that cycle and intervene technologically to transform the human information field into one that will change what we call humanity. If it can change the human information field it will change the way that field processes information and change humanity both 'physically' and psychologically. Hence the *messenger* (information) RNA 'vaccines' and so much more that is targeting human genetics by changing the body's information – *messaging* – construct through food, drink, radiation, toxicity and other means.

Reality that we experience is nothing like reality as it really is in the same way that the reality people experience in virtual reality games is not the reality they are really living in. The game is only a decoded source of information that appears to be a reality. Our world is also an information construct – a *simulation* (more later). In its base form our reality is a wavefield of information much the same in theme as Wi-Fi. The five senses decode wavefield information into electrical information which they communicate to the brain to decode into holographic (illusory 'physical') information. Different parts of the brain specialise in decoding different senses and the information is fused into a reality that appears to be outside of us but is really inside the brain and the genetic structure in general (Fig 12 overleaf). DNA is a receiver-transmitter of information and a vital part of this decoding process and the body's connection to other realities. Change DNA and you change the way we decode and connect with reality – see 'Covid vaccines'. Think of computers decoding Wi-Fi. You have information encoded in a radiation field and the computer decodes that information into a very different form on the screen. You can't see the Wi-Fi until its information is made manifest on the screen and the information on the screen is inside the computer and not outside. I have just described how we decode the 'human world'. All five senses decode the waveform 'Wi-Fi' field into electrical signals and the brain (computer) constructs reality inside the brain and not outside – 'You don't just look at a rainbow, you create it'. Sound is a simple example. We don't hear sound until the brain decodes it. Waveform sound waves are picked up by the hearing sense and communicated to the brain in an electrical form to be decoded into the sounds that we hear. Everything we hear is inside the brain along with everything we see, feel, smell and taste. Words and language are waveform fields generated by our vocal chords which pass through this process until they are decoded by the brain into words that we hear. Different languages are different frequency fields or sound waves generated by vocal chords. Late British philosopher Alan Watts said:

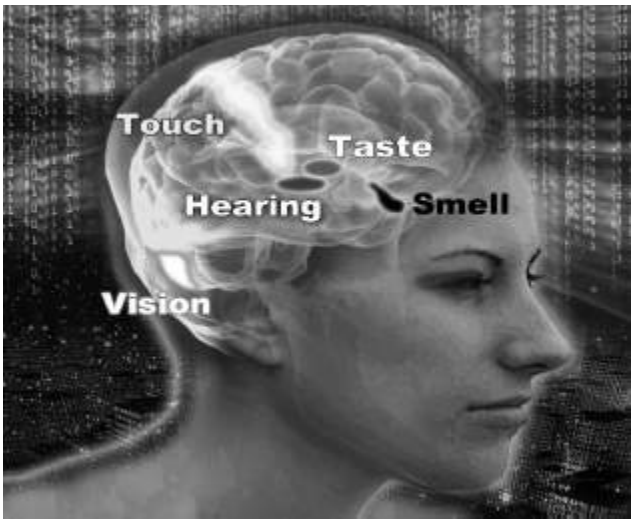


Figure 12: The brain receives information from the five senses and constructs from that our perceived reality.

[Without the brain] the world is devoid of light, heat, weight, solidity, motion, space, time or any other imaginable feature. All these phenomena are interactions, or transactions, of vibrations with a certain arrangement of neurons.

That's exactly what they are and scientist Robert Lanza describes in his book, *Biocentrism*, how we decode electromagnetic waves and energy into visual and 'physical' experience. He uses the example of a flame emitting photons, electromagnetic energy, each pulsing electrically and magnetically:

… these … invisible electromagnetic waves strike a human retina, and if (and only if) the waves happen to measure between 400 and 700 nano meters in length from crest to crest, then their energy is just right to deliver a stimulus to the 8 million cone-shaped cells in the retina.

Each in turn send an electrical pulse to a neighbour neuron, and on up the line this goes, at 250 mph, until it reaches the … occipital lobe of the brain, in the back of the head. There, a cascading complex of neurons fire from the incoming stimuli, and we subjectively perceive this experience as a yellow brightness occurring in a place we have been conditioned to call the 'external world'.

You hear what you decode

If a tree falls or a building collapses they make no noise unless someone is there to decode the energetic waves generated by the disturbance into what we call sound. Does a falling tree make a noise? Only if you hear it – *decode* it. Everything in our reality is a frequency field of information operating within the overall 'Wi-Fi' field that I call The Field. A vibrational disturbance is generated in The Field by the fields of the falling tree or building. These disturbance waves are what we decode into the sound of them falling. If no one is there to do that then neither will make any noise. Reality is created by the observer – *decoder* – and the *perceptions* of the observer affect the decoding process. For this reason different people – different *perceptions* – will perceive the same reality or situation in a different way. What one may perceive as a nightmare another will see as an opportunity. The question of why the Cult is so focused on controlling human perception now answers itself. All experienced reality is the act of decoding and we don't experience Wi-Fi until it is decoded on the computer screen. The sight and sound of an Internet video is encoded in the Wi-Fi all around us, but we don't see or hear it until the computer decodes that information. Taste, smell and touch are all phenomena of the brain as a result of the same process. We don't taste, smell or feel anything except in the brain and there are pain relief techniques that seek to block the signal from the site of discomfort to the brain because if the brain doesn't decode that signal we don't feel pain. Pain is in the brain and only appears to be at the point of impact thanks to the feedback loop between them. We don't see anything until electrical information from the sight senses is decoded in an area at the back of the brain. If that area is damaged we can go blind when our eyes are perfectly okay. So why do we go blind if we damage an eye? We damage the information processing between the waveform visual information and the visual decoding area of the brain. If information doesn't reach the brain in a form it can decode then we can't see the visual reality that it represents. What's more the brain is decoding only a fraction of the information it receives and the rest is absorbed by the

sub-conscious mind. This explanation is from the science magazine, *Wonderpedia*:

> Every second, 11 million sensations crackle along these [brain] pathways ... The brain is confronted with an alarming array of images, sounds and smells which it rigorously filters down until it is left with a manageable list of around 40. Thus 40 sensations per second make up what we perceive as reality.

The 'world' is not what people are told to believe that is it and the inner circles of the Cult *know that*.

Illusory 'physical' reality

We can only see a smear of 0.005 percent of the Universe which is only one of a vast array of universes – 'mansions' – within infinite reality. Even then the brain decodes only 40 pieces of information ('sensations') from a potential *11 million* that we receive every second. Two points strike you from this immediately: The sheer breathtaking stupidity of believing we know anything so rigidly that there's nothing more to know; and the potential for these processes to be manipulated by a malevolent force to control the reality of the population. One thing I can say for sure with no risk of contradiction is that when you can perceive an almost indescribable fraction of infinite reality there is always more to know as in tidal waves of it. Ancient Greek philosopher Socrates was so right when he said that wisdom is to know how little we know. How obviously true that is when you think that we are experiencing a physical world of solidity that is neither physical nor solid and a world of apartness when everything is connected. Cult-controlled 'science' dismisses the so-called 'paranormal' and all phenomena related to that when the 'para'-normal is perfectly normal and explains the alleged 'great mysteries' which dumbfound scientific minds. There is a reason for this. A 'scientific mind' in terms of the mainstream is a material mind, a five-sense mind imprisoned in see it, touch it, hear it, smell it and taste it. Phenomena and happenings that can't be explained that way leave the 'scientific mind' bewildered and the rule is that if they

can't account for why something is happening then it can't, by definition, be happening. I beg to differ. Telepathy is thought waves passing through The Field (think wave disturbance again) to be decoded by someone able to connect with that wavelength (information). For example: You can pick up the thought waves of a friend at any distance and at the very least that will bring them to mind. A few minutes later the friend calls you. 'My god', you say, 'that's incredible – I was just thinking of you.' Ah, but *they* were thinking of *you* before they made the call and that's what you decoded. Native peoples not entrapped in five-sense reality do this so well it became known as the 'bush telegraph'. Those known as psychics and mediums (genuine ones) are doing the same only across dimensions of reality. 'Mind over matter' comes from the fact that matter and mind are the *same*. The state of one influences the state of the other. Indeed one *and* the other are illusions. They are aspects of the same field. Paranormal phenomena are all explainable so why are they still considered 'mysteries' or not happening? Once you go down this road of understanding you begin to expand awareness beyond the five senses and that's the nightmare for the Cult.



Figure 13: Holograms are not solid, but the best ones appear to be.

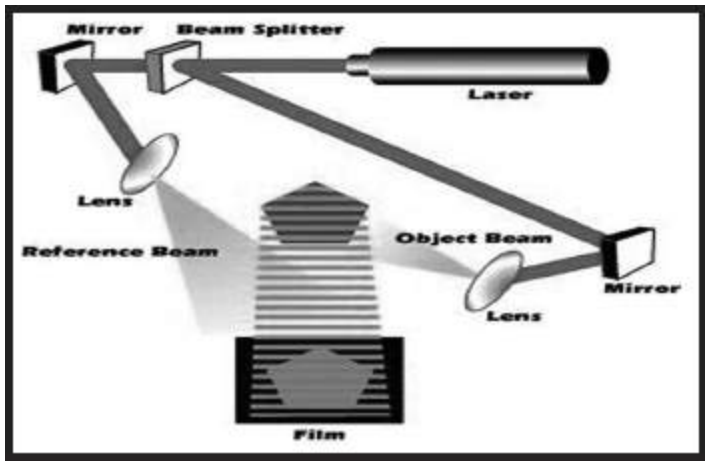


Figure 14: How holograms are created by capturing a waveform version of the subject image.

Holographic 'solidity'

Our reality is not solid, it is holographic. We are now well aware of holograms which are widely used today. Two-dimensional information is decoded into a three-dimensional reality that is not solid although can very much appear to be (Fig 13). Holograms are created with a laser divided into two parts. One goes directly onto a holographic photographic print ('reference beam') and the other takes a waveform image of the subject ('working beam') before being directed onto the print where it 'collides' with the other half of the laser (Fig 14). This creates a *waveform* interference pattern which contains the wavefield information of whatever is being photographed (Fig 15 overleaf). The process can be likened to dropping pebbles in a pond. Waves generated by each one spread out across the water to collide with the others and create a wave representation of where the stones fell and at what speed, weight and distance. A waveform interference pattern of a hologram is akin to the waveform information in The Field which the five senses decode into electrical signals to be decoded by the brain into a holographic illusory 'physical' reality. In the same way when a laser (think human attention) is directed at the waveform interference pattern a three-dimensional version of the subject is projected into apparently 'solid' reality (Fig 16). An amazing trait of holograms reveals more 'paranormal mysteries'. Information of the *whole*

hologram is encoded in waveform in every part of the interference pattern by the way they are created. This means that every *part* of a hologram is a smaller version of the whole. Cut the interference wave-pattern into four and you won't get four parts of the image. You get quarter-sized versions of the *whole* image. The body is a hologram and the same applies. Here we have the basis of acupuncture, reflexology and other forms of healing which identify representations of the whole body in all of the parts, hands, feet, ears, everywhere. Skilled palm readers can do what they do because the information of whole body is encoded in the hand. The concept of as above, so below, comes from this.



Figure 15: A waveform interference pattern that holds the information that transforms into a hologram.



Figure 16: Holographic people including 'Elvis' holographically inserted to sing a duet with Celine Dion.

The question will be asked of why, if solidity is illusory, we can't just walk through walls and each other. The resistance is not solid against solid; it is electromagnetic field against electromagnetic field and we decode this into the *experience* of solid against solid. We should also not underestimate the power of belief to dictate reality. What you believe is impossible *will be*. Your belief impacts on your decoding processes and they won't decode what you think is impossible. What we believe we perceive and what we perceive we experience. 'Can't dos' and 'impossibles' are like a firewall in a computer system that won't put on the screen what the firewall blocks. How vital that is to understanding how human experience has been hijacked. I explain in *The Answer*, *Everything You Need To Know But Have Never Been Told* and other books a long list of 'mysteries' and 'paranormal' phenomena that are not mysterious and perfectly normal once you realise what reality is and how it works. 'Ghosts' can be seen to pass through 'solid' walls because the walls are not solid and the ghost is a discarnate entity operating on a frequency so different to that of the wall that it's like two radio stations sharing the same space while never interfering with each other. I have seen ghosts do this myself. The apartness of people and objects is also an illusion. Everything is connected by the Field like all sea life is connected by the sea. It's just that within the limits of our visual reality we only 'see' holographic information and not the field of information that connects everything and from which the holographic world is made manifest. If you can only see holographic 'objects' and not the field that connects them they will appear to you as unconnected to each other in the same way that we see the computer while not seeing the Wi-Fi.

What you don't know *can* hurt you

Okay, we return to those 'two worlds' of human society and the Cult with its global network of interconnecting secret societies and satanic groups which manipulate through governments, corporations, media, religions, etc. The fundamental difference between them is *knowledge*. The idea has been to keep humanity

ignorant of the plan for its total enslavement underpinned by a crucial ignorance of reality – who we are and where we are – and how we interact with it. 'Human' should be the interaction between our expanded eternal consciousness and the five-sense body experience. We are meant to be *in* this world in terms of the five senses but not *of* this world in relation to our greater consciousness and perspective. In that state we experience the small picture of the five senses within the wider context of the big picture of awareness beyond the five senses. Put another way the five senses see the dots and expanded awareness connects them into pictures and patterns that give context to the apparently random and unconnected. Without the context of expanded awareness the five senses see only apartness and randomness with apparently no meaning. The Cult and its other-dimensional controllers seek to intervene in the frequency realm where five-sense reality is supposed to connect with expanded reality and to keep the two apart (more on this in the final chapter). When that happens five-sense mental and emotional processes are no longer influenced by expanded awareness, or the True 'I', and instead are driven by the isolated perceptions of the body's decoding systems. They are in the world *and* of it. Here we have the human plight and why humanity with its potential for infinite awareness can be so easily manipulatable and descend into such extremes of stupidity.

Once the Cult isolates five-sense mind from expanded awareness it can then program the mind with perceptions and beliefs by controlling information that the mind receives through the 'education' system of the formative years and the media perceptual bombardment and censorship of an entire lifetime. Limit perception and a sense of the possible through limiting knowledge by limiting and skewing information while censoring and discrediting that which could set people free. As the title of another of my books says *… And The Truth Shall Set You Free*. For this reason the last thing the Cult wants in circulation is the truth about anything – especially the reality of the eternal 'I' – and that's why it is desperate to control information. The Cult knows that information becomes perception

which becomes behaviour which, collectively, becomes human society. Cult-controlled and funded mainstream 'science' denies the existence of an eternal 'I' and seeks to dismiss and trash all evidence to the contrary. Cult-controlled mainstream religion has a version of 'God' that is little more than a system of control and dictatorship that employs threats of damnation in an afterlife to control perceptions and behaviour in the here and now through fear and guilt. Neither is true and it's the 'neither' that the Cult wishes to suppress. This 'neither' is that everything is an expression, a point of attention, within an infinite state of consciousness which is the real meaning of the term 'God'.

Perceptual obsession with the 'physical body' and five-senses means that 'God' becomes personified as a bearded bloke sitting among the clouds or a raging bully who loves us if we do what 'he' wants and condemns us to the fires of hell if we don't. These are no more than a 'spiritual' fairy tales to control and dictate events and behaviour through fear of this 'God' which has bizarrely made 'God-fearing' in religious circles a state to be desired. I would suggest that fearing *anything* is not to be encouraged and celebrated, but rather deleted. You can see why 'God fearing' is so beneficial to the Cult and its religions when *they* decide what 'God' wants and what 'God' demands (the Cult demands) that everyone do. As the great American comedian Bill Hicks said satirising a Christian zealot: 'I think what God meant to say.' How much of this infinite awareness ('God') that we access is decided by how far we choose to expand our perceptions, self-identity and sense of the possible. The scale of self-identity reflects itself in the scale of awareness that we can connect with and are influenced by – how much knowing and insight we have instead of programmed perception. You cannot expand your awareness into the infinity of possibility when you believe that you are little me Peter the postman or Mary in marketing and nothing more. I'll deal with this in the concluding chapter because it's crucial to how we turnaround current events.

Where the Cult came from

When I realised in the early 1990s there was a Cult network behind global events I asked the obvious question: When did it start? I took it back to ancient Rome and Egypt and on to Babylon and Sumer in Mesopotamia, the 'Land Between Two Rivers', in what we now call Iraq. The two rivers are the Tigris and Euphrates and this region is of immense historical and other importance to the Cult, as is the land called Israel only 550 miles away by air. There is much more going with deep esoteric meaning across this whole region. It's not only about 'wars for oil'. Priceless artefacts from Mesopotamia were stolen or destroyed after the American and British invasion of Iraq in 2003 justified by the lies of Boy Bush and Tony Blair (their Cult masters) about non-existent 'weapons of mass destruction'. Mesopotamia was the location of Sumer (about 5,400BC to 1,750BC), and Babylon (about 2,350BC to 539BC). Sabbatians may have become immensely influential in the Cult in modern times but they are part of a network that goes back into the mists of history. Sumer is said by historians to be the 'cradle of civilisation'. I disagree. I say it was the re-start of what we call human civilisation after cataclysmic events symbolised in part as the 'Great Flood' destroyed the world that existed before. These fantastic upheavals that I have been describing in detail in the books since the early1990s appear in accounts and legends of ancient cultures across the world and they are supported by geological and biological evidence. Stone tablets found in Iraq detailing the Sumer period say the cataclysms were caused by non-human 'gods' they call the Anunnaki. These are described in terms of extraterrestrial visitations in which knowledge supplied by the Anunnaki is said to have been the source of at least one of the world's oldest writing systems and developments in astronomy, mathematics and architecture that were way ahead of their time. I have covered this subject at length in *The Biggest Secret* and *Children of the Matrix* and the same basic 'Anunnaki' story can be found in Zulu accounts in South Africa where the late and very great Zulu high shaman Credo Mutwa told me that the Sumerian Anunnaki were known by Zulus as the Chitauri or 'children of the serpent'. See my six-hour video interview with Credo on this subject entitled *The*

Reptilian Agenda recorded at his then home near Johannesburg in 1999 which you can watch on the Ickonic media platform.

The Cult emerged out of Sumer, Babylon and Egypt (and elsewhere) and established the Roman Empire before expanding with the Romans into northern Europe from where many empires were savagely imposed in the form of Cult-controlled societies all over the world. Mass death and destruction was their calling card. The Cult established its centre of operations in Europe and European Empires were Cult empires which allowed it to expand into a global force. Spanish and Portuguese colonialists headed for Central and South America while the British and French targeted North America. Africa was colonised by Britain, France, Belgium, the Netherlands, Portugal, Spain, Italy, and Germany. Some like Britain and France moved in on the Middle East. The British Empire was by far the biggest for a simple reason. By now Britain was the headquarters of the Cult from which it expanded to form Canada, the United States, Australia and New Zealand. The Sun never set on the British Empire such was the scale of its occupation. London remains a global centre for the Cult along with Rome and the Vatican although others have emerged in Israel and China. It is no accident that the 'virus' is alleged to have come out of China while Italy was chosen as the means to terrify the Western population into compliance with 'Covid' fascism. Nor that Israel has led the world in 'Covid' fascism and mass 'vaccination'.

You would think that I would mention the United States here, but while it has been an important means of imposing the Cult's will it is less significant than would appear and is currently in the process of having what power it does have deleted. The Cult in Europe has mostly loaded the guns for the US to fire. America has been controlled from Europe from the start through Cult operatives in Britain and Europe. The American Revolution was an illusion to make it appear that America was governing itself while very different forces were pulling the strings in the form of Cult families such as the Rothschilds through the Rockefellers and other subordinates. The Rockefellers are extremely close to Bill Gates and

established both scalpel and drug 'medicine' and the World Health Organization. They play a major role in the development and circulation of vaccines through the Rockefeller Foundation on which Bill Gates said his Foundation is based. Why wouldn't this be the case when the Rockefellers and Gates are on the same team? Cult infiltration of human society goes way back into what we call history and has been constantly expanding and centralising power with the goal of establishing a global structure to dictate everything. Look how this has been advanced in great leaps with the 'Covid' hoax.

The non-human dimension

I researched and observed the comings and goings of Cult operatives through the centuries and even thousands of years as they were born, worked to promote the agenda within the secret society and satanic networks, and then died for others to replace them. Clearly there had to be a coordinating force that spanned this entire period while operatives who would not have seen the end goal in their lifetimes came and went advancing the plan over millennia. I went in search of that coordinating force with the usual support from the extraordinary synchronicity of my life which has been an almost daily experience since 1990. I saw common themes in religious texts and ancient cultures about a non-human force manipulating human society from the hidden. Christianity calls this force Satan, the Devil and demons; Islam refers to the Jinn or Djinn; Zulus have their Chitauri (spelt in other ways in different parts of Africa); and the Gnostic people in Egypt in the period around and before 400AD referred to this phenomena as the 'Archons', a word meaning rulers in Greek. Central American cultures speak of the 'Predators' among other names and the same theme is everywhere. I will use 'Archons' as a collective name for all of them. When you see how their nature and behaviour is described all these different sources are clearly talking about the same force. Gnostics described the Archons in terms of 'luminous fire' while Islam relates the Jinn to 'smokeless fire'. Some refer to beings in form that could occasionally be seen, but the most common of common theme is that they operate from

unseen realms which means almost all existence to the visual processes of humans. I had concluded that this was indeed the foundation of human control and that the Cult was operating within the human frequency band on behalf of this hidden force when I came across the writings of Gnostics which supported my conclusions in the most extraordinary way.

A sealed earthen jar was found in 1945 near the town of Nag Hammadi about 75-80 miles north of Luxor on the banks of the River Nile in Egypt. Inside was a treasure trove of manuscripts and texts left by the Gnostic people some 1,600 years earlier. They included 13 leather-bound papyrus codices (manuscripts) and more than 50 texts written in Coptic Egyptian estimated to have been hidden in the jar in the period of 400AD although the source of the information goes back much further. Gnostics oversaw the Great or Royal Library of Alexandria, the fantastic depository of ancient texts detailing advanced knowledge and accounts of human history. The Library was dismantled and destroyed in stages over a long period with the death-blow delivered by the Cult-established Roman Church in the period around 415AD. The Church of Rome was the Church of Babylon relocated as I said earlier. Gnostics were not a race. They were a way of perceiving reality. Whenever they established themselves and their information circulated the terrorists of the Church of Rome would target them for destruction. This happened with the Great Library and with the Gnostic Cathars who were burned to death by the psychopaths after a long period of oppression at the siege of the Castle of Monségur in southern France in 1244. The Church has always been terrified of Gnostic information which demolishes the official Christian narrative although there is much in the Bible that supports the Gnostic view if you read it in another way. To anyone studying the texts of what became known as the Nag Hammadi Library it is clear that great swathes of Christian and Biblical belief has its origin with Gnostics sources going back to Sumer. Gnostic themes have been twisted to manipulate the perceived reality of Bible believers. Biblical texts have been in the open for centuries where they could be changed while Gnostic

documents found at Nag Hammadi were sealed away and untouched for 1,600 years. What you see is what they wrote.

Use your *pneuma* not your *nous*

Gnosticism and Gnostic come from 'gnosis' which means knowledge, or rather *secret* knowledge, in the sense of spiritual awareness – knowledge about reality and life itself. The desperation of the Cult's Church of Rome to destroy the Gnostics can be understood when the knowledge they were circulating was the last thing the Cult wanted the population to know. Sixteen hundred years later the same Cult is working hard to undermine and silence me for the same reason. The dynamic between knowledge and ignorance is a constant. 'Time' appears to move on, but essential themes remain the same. We are told to 'use your nous', a Gnostic word for head/brain/intelligence. They said, however, that spiritual awakening or 'salvation' could only be secured by expanding awareness *beyond* what they called *nous* and into *pneuma* or Infinite Self. Obviously as I read these texts the parallels with what I have been saying since 1990 were fascinating to me. There is a universal truth that spans human history and in that case why wouldn't we be talking the same language 16 centuries apart? When you free yourself from the perception program of the five senses and explore expanded realms of consciousness you are going to connect with the same information no matter what the perceived 'era' within a manufactured timeline of a single and tiny range of manipulated frequency. Humans working with 'smart' technology or knocking rocks together in caves is only a timeline appearing to operate within the human frequency band. Expanded awareness and the knowledge it holds have always been there whether the era be Stone Age or computer age. We can only access that knowledge by opening ourselves to its frequency which the five-sense prison cell is designed to stop us doing. Gates, Fauci, Whitty, Vallance, Zuckerberg, Brin, Page, Wojcicki, Bezos, and all the others behind the 'Covid' hoax clearly have a long wait before their range of frequency can make that connection given that an open heart is

crucial to that as we shall see. Instead of accessing knowledge directly through expanded awareness it is given to Cult operatives by the secret society networks of the Cult where it has been passed on over thousands of years outside the public arena. Expanded realms of consciousness is where great artists, composers and writers find their inspiration and where truth awaits anyone open enough to connect with it. We need to go there fast.

Archon hijack

A fifth of the Nag Hammadi texts describe the existence and manipulation of the Archons led by a 'Chief Archon' they call 'Yaldabaoth', or the 'Demiurge', and this is the Christian 'Devil', 'Satan', 'Lucifer', and his demons. Archons in Biblical symbolism are the 'fallen ones' which are also referred to as fallen angels after the angels expelled from heaven according to the Abrahamic religions of Judaism, Christianity and Islam. These angels are claimed to tempt humans to 'sin' ongoing and you will see how accurate that symbolism is during the rest of the book. The theme of 'original sin' is related to the 'Fall' when Adam and Eve were 'tempted by the serpent' and fell from a state of innocence and 'obedience' (connection) with God into a state of disobedience (disconnection). The Fall is said to have brought sin into the world and corrupted everything including human nature. Yaldabaoth, the 'Lord Archon', is described by Gnostics as a 'counterfeit spirit', 'The Blind One', 'The Blind God', and 'The Foolish One'. The Jewish name for Yaldabaoth in Talmudic writings is Samael which translates as 'Poison of God', or 'Blindness of God'. You see the parallels. Yaldabaoth in Islamic belief is the Muslim Jinn devil known as Shaytan – Shaytan is Satan as the same themes are found all over the world in every religion and culture. The 'Lord God' of the Old Testament is the 'Lord Archon' of Gnostic manuscripts and that's why he's such a bloodthirsty bastard. Satan is known by Christians as 'the Demon of Demons' and Gnostics called Yaldabaoth the 'Archon of Archons'. Both are known as 'The Deceiver'. We are talking about the same 'bloke' for sure and these common themes

using different names, storylines and symbolism tell a common tale of the human plight.

Archons are referred to in Nag Hammadi documents as mind parasites, inverters, guards, gatekeepers, detainers, judges, pitiless ones and deceivers. The 'Covid' hoax alone is a glaring example of all these things. The Biblical 'God' is so different in the Old and New Testaments because they are not describing the same phenomenon. The vindictive, angry, hate-filled, 'God' of the Old Testament, known as Yahweh, is Yaldabaoth who is depicted in Cult-dictated popular culture as the 'Dark Lord', 'Lord of Time', Lord (Darth) Vader and Dormammu, the evil ruler of the 'Dark Dimension' trying to take over the 'Earth Dimension' in the Marvel comic movie, *Dr Strange*. Yaldabaoth is both the Old Testament 'god' and the Biblical 'Satan'. Gnostics referred to Yaldabaoth as the 'Great Architect of the Universe'and the Cult-controlled Freemason network calls their god 'the 'Great Architect of the Universe' (also Grand Architect). The 'Great Architect' Yaldabaoth is symbolised by the Cult as the all-seeing eye at the top of the pyramid on the Great Seal of the United States and the dollar bill. Archon is encoded in *arch*-itect as it is in *arch*-angels and *arch*-bishops. All religions have the theme of a force for good and force for evil in some sort of spiritual war and there is a reason for that – the theme is true. The Cult and its non-human masters are quite happy for this to circulate. They present themselves as the force for good fighting evil when they are really the force of evil (absence of love). The whole foundation of Cult modus operandi is inversion. They promote themselves as a force for good and anyone challenging them in pursuit of peace, love, fairness, truth and justice is condemned as a satanic force for evil. This has been the game plan throughout history whether the Church of Rome inquisitions of non-believers or 'conspiracy theorists' and 'anti-vaxxers' of today. The technique is the same whatever the timeline era.

Yaldabaoth is revolting (true)

Yaldabaoth and the Archons are said to have revolted against God with Yaldabaoth claiming to *be* God – the *All That Is*. The Old Testament 'God' (Yaldabaoth) demanded to be worshipped as such: ' *I am* the LORD, and there is none else, there is no God beside me' (Isaiah 45:5). I have quoted in other books a man who said he was the unofficial son of the late Baron Philippe de Rothschild of the Mouton-Rothschild wine producing estates in France who died in 1988 and he told me about the Rothschild 'revolt from God'. The man said he was given the name Phillip Eugene de Rothschild and we shared long correspondence many years ago while he was living under another identity. He said that he was conceived through 'occult incest' which (within the Cult) was 'normal and to be admired'. 'Phillip' told me about his experience attending satanic rituals with rich and famous people whom he names and you can see them and the wider background to Cult Satanism in my other books starting with *The Biggest Secret*. Cult rituals are interactions with Archontic 'gods'. 'Phillip' described Baron Philippe de Rothschild as 'a master Satanist and hater of God' and he used the same term 'revolt from God' associated with Yaldabaoth/Satan/Lucifer/the Devil in describing the Sabbatian Rothschild dynasty. 'I played a key role in my family's revolt from God', he said. That role was to infiltrate in classic Sabbatian style the Christian Church, but eventually he escaped the mind-prison to live another life. The Cult has been targeting religion in a plan to make worship of the Archons the global one-world religion. Infiltration of Satanism into modern 'culture', especially among the young, through music videos, stage shows and other means, is all part of this.

Nag Hammadi texts describe Yaldabaoth and the Archons in their prime form as energy – consciousness – and say they can take form if they choose in the same way that consciousness takes form as a human. Yaldabaoth is called 'formless' and represents a deeply inverted, distorted and chaotic state of consciousness which seeks to attached to humans and turn them into a likeness of itself in an attempt at assimilation. For that to happen it has to manipulate

humans into low frequency mental and emotional states that match its own. Archons can certainly appear in human form and this is the origin of the psychopathic personality. The energetic distortion Gnostics called Yaldabaoth *is* psychopathy. When psychopathic Archons take human form that human will be a psychopath as an expression of Yaldabaoth consciousness. Cult psychopaths are Archons in human form. The principle is the same as that portrayed in the 2009 *Avatar* movie when the American military travelled to a fictional Earth-like moon called Pandora in the Alpha Centauri star system to infiltrate a society of blue people, or Na'vi, by hiding within bodies that looked like the Na'vi. Archons posing as humans have a particular hybrid information field, part human, part Archon, (the ancient 'demigods') which processes information in a way that manifests behaviour to match their psychopathic evil, lack of empathy and compassion, and stops them being influenced by the empathy, compassion and love that a fully-human information field is capable of expressing. Cult bloodlines interbreed, be they royalty or dark suits, for this reason and you have their obsession with incest. Interbreeding with full-blown humans would dilute the Archontic energy field that guarantees psychopathy in its representatives in the human realm.

Gnostic writings say the main non-human forms that Archons take are *serpentine* (what I have called for decades 'reptilian' amid unbounded ridicule from the Archontically-programmed) and what Gnostics describe as 'an unborn baby or foetus with grey skin and dark, unmoving eyes'. This is an excellent representation of the ET 'Greys' of UFO folklore which large numbers of people claim to have seen and been abducted by – Zulu shaman Credo Mutwa among them. I agree with those that believe in extraterrestrial or interdimensional visitations today and for thousands of years past. No wonder with their advanced knowledge and technological capability they were perceived and worshipped as gods for technological and other 'miracles' they appeared to perform. Imagine someone arriving in a culture disconnected from the modern world with a smartphone and computer. They would be

seen as a 'god' capable of 'miracles'. The Renegade Mind, however, wants to know the source of everything and not only the way that source manifests as human or non-human. In the same way that a Renegade Mind seeks the original source material for the 'Covid virus' to see if what is claimed is true. The original source of Archons in form is consciousness – the distorted state of consciousness known to Gnostics as Yaldabaoth.

'Revolt from God' is energetic disconnection

Where I am going next will make a lot of sense of religious texts and ancient legends relating to 'Satan', Lucifer' and the 'gods'. Gnostic descriptions sync perfectly with the themes of my own research over the years in how they describe a consciousness distortion seeking to impose itself on human consciousness. I've referred to the core of infinite awareness in previous books as Infinite Awareness in Awareness of Itself. By that I mean a level of awareness that knows that it is all awareness and is aware of all awareness. From here comes the frequency of love in its true sense and balance which is what love is on one level – the balance of all forces into a single whole called Oneness and Isness. The more we disconnect from this state of love that many call 'God' the constituent parts of that Oneness start to unravel and express themselves as a part and not a whole. They become individualised as intellect, mind, selfishness, hatred, envy, desire for power over others, and such like. This is not a problem in the greater scheme in that 'God', the *All That Is*, can experience all these possibilities through different expressions of itself including humans. What we as expressions of the whole experience the *All That Is* experiences. We are the *All That Is* experiencing itself. As we withdraw from that state of Oneness we disconnect from its influence and things can get very unpleasant and very stupid. Archontic consciousness is at the extreme end of that. It has so disconnected from the influence of Oneness that it has become an inversion of unity and love, an inversion of everything, an inversion of life itself. Evil is appropriately live written backwards. Archontic consciousness is obsessed with death, an inversion of life,

and so its manifestations in Satanism are obsessed with death. They use inverted symbols in their rituals such as the inverted pentagram and cross. Sabbatians as Archontic consciousness incarnate invert Judaism and every other religion and culture they infiltrate. They seek disunity and chaos and they fear unity and harmony as they fear love like garlic to a vampire. As a result the Cult, Archons incarnate, act with such evil, psychopathy and lack of empathy and compassion disconnected as they are from the source of love. How could Bill Gates and the rest of the Archontic psychopaths do what they have to human society in the 'Covid' era with all the death, suffering and destruction involved and have no emotional consequence for the impact on others? Now you know. Why have Zuckerberg, Brin, Page, Wojcicki and company callously censored information warning about the dangers of the 'vaccine' while thousands have been dying and having severe, sometimes life-changing reactions? Now you know. Why have Tedros, Fauci, Whitty, Vallance and their like around the world been using case and death figures they're aware are fraudulent to justify lockdowns and all the deaths and destroyed lives that have come from that? Now you know. Why did Christian Drosten produce and promote a 'testing' protocol that he knew couldn't test for infectious disease which led to a global human catastrophe. Now you know. The Archontic mind doesn't give a shit (Fig 17). I personally think that Gates and major Cult insiders are a form of AI cyborg that the Archons want humans to become.

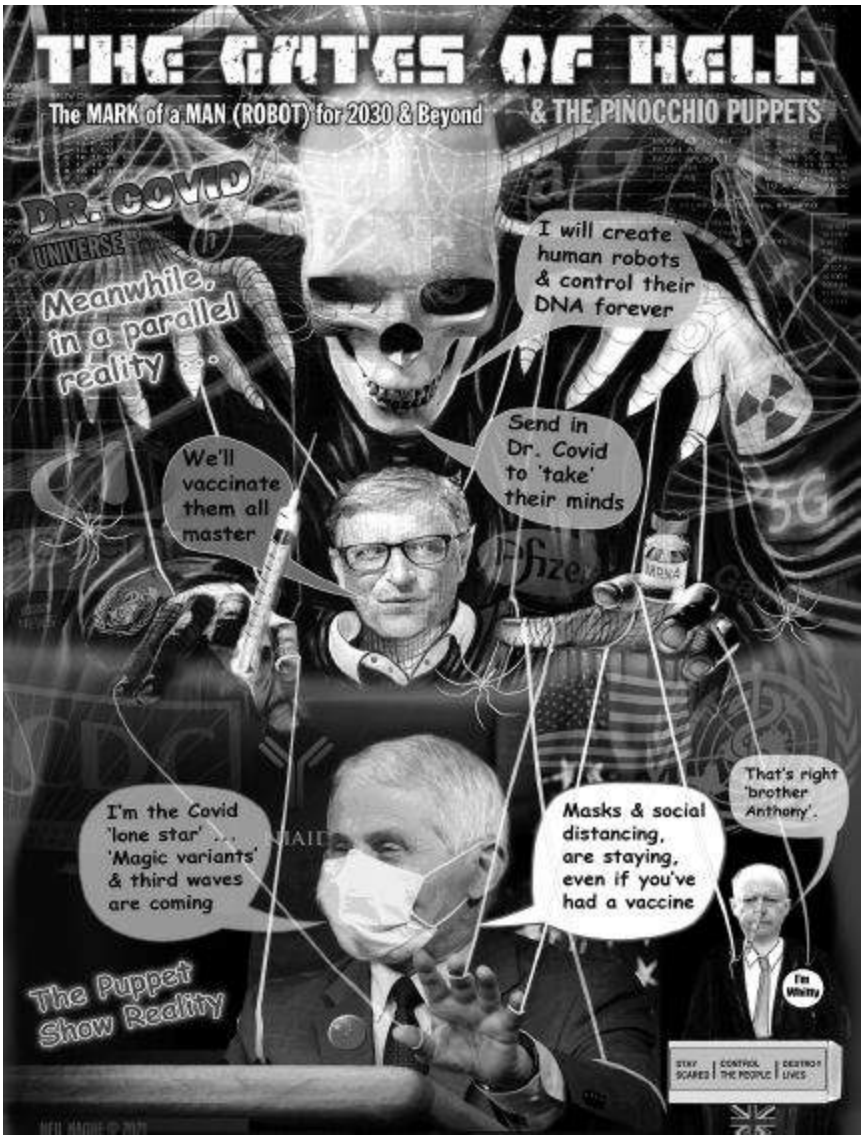


Figure 17: Artist Neil Hague's version of the 'Covid' hierarchy.

Human batteries

A state of such inversion does have its consequences, however. The level of disconnection from the Source of All means that you withdraw from that source of energetic sustenance and creativity. This means that you have to find your own supply of energetic power and it has – *us*. When the Morpheus character in the first *Matrix* movie held up a battery he spoke a profound truth when he said: 'The Matrix is a computer-generated dream world built to keep us under control in order to change the human being into one of

these.' The statement was true in all respects. We do live in a technologically-generated virtual reality simulation (more very shortly) and we have been manipulated to be an energy source for Archontic consciousness. The Disney-Pixar animated movie *Monsters, Inc*. in 2001 symbolised the dynamic when monsters in their world had no energy source and they would enter the human world to terrify children in their beds, catch the child's scream, terror (low-vibrational frequencies), and take that energy back to power the monster world. The lead character you might remember was a single giant eye and the symbolism of the Cult's all-seeing eye was obvious. Every thought and emotion is broadcast as a frequency unique to that thought and emotion. Feelings of love and joy, empathy and compassion, are high, quick, frequencies while fear, depression, anxiety, suffering and hate are low, slow, dense frequencies. Which kind do you think Archontic consciousness can connect with and absorb? In such a low and dense frequency state there's no way it can connect with the energy of love and joy. Archons can only feed off energy compatible with their own frequency and they and their Cult agents want to delete the human world of love and joy and manipulate the transmission of low vibrational frequencies through low-vibrational human mental and emotional states. *We are their energy source*. Wars are energetic banquets to the Archons – a world war even more so – and think how much low-frequency mental and emotional energy has been generated from the consequences for humanity of the 'Covid' hoax orchestrated by Archons incarnate like Gates.

The ancient practice of human sacrifice 'to the gods', continued in secret today by the Cult, is based on the same principle. 'The gods' are Archontic consciousness in different forms and the sacrifice is induced into a state of intense terror to generate the energy the Archontic frequency can absorb. Incarnate Archons in the ritual drink the blood which contains an adrenaline they crave which floods into the bloodstream when people are terrorised. Most of the sacrifices, ancient and modern, are children and the theme of 'sacrificing young virgins to the gods' is just code for children. They

have a particular pre-puberty energy that Archons want more than anything and the energy of the young in general is their target. The California Department of Education wants students to chant the names of Aztec gods (Archontic gods) once worshipped in human sacrifice rituals in a curriculum designed to encourage them to 'challenge racist, bigoted, discriminatory, imperialist/colonial beliefs', join 'social movements that struggle for social justice', and 'build new possibilities for a post-racist, post-systemic racism society'. It's the usual Woke crap that inverts racism and calls it anti-racism. In this case solidarity with 'indigenous tribes' is being used as an excuse to chant the names of 'gods' to which people were sacrificed (and still are in secret). What an example of Woke's inability to see beyond black and white, us and them, They condemn the colonisation of these tribal cultures by Europeans (quite right), but those cultures sacrificing people including children to their 'gods', and mass murdering untold numbers as the Aztecs did, is just fine. One chant is to the Aztec god Tezcatlipoca who had a man sacrificed to him in the 5th month of the Aztec calendar. His heart was cut out and he was eaten. Oh, that's okay then. Come on children … after three … Other sacrificial 'gods' for the young to chant their allegiance include Quetzalcoatl, Huitzilopochtli and Xipe Totec. The curriculum says that 'chants, affirmations, and energizers can be used to bring the class together, build unity around ethnic studies principles and values, and to reinvigorate the class following a lesson that may be emotionally taxing or even when student engagement may appear to be low'. Well, that's the cover story, anyway. Chanting and mantras are the repetition of a particular frequency generated from the vocal cords and chanting the names of these Archontic 'gods' tunes you into their frequency. That is the last thing you want when it allows for energetic synchronisation, attachment and perceptual influence. Initiates chant the names of their 'Gods' in their rituals for this very reason.

Vampires of the Woke

Paedophilia is another way that Archons absorb the energy of children. Paedophiles possessed by Archontic consciousness are used as the conduit during sexual abuse for discarnate Archons to vampire the energy of the young they desire so much. Stupendous numbers of children disappear every year never to be seen again although you would never know from the media. Imagine how much low-vibrational energy has been generated by children during the 'Covid' hoax when so many have become depressed and psychologically destroyed to the point of killing themselves. Shocking numbers of children are now taken by the state from loving parents to be handed to others. I can tell you from long experience of researching this since 1996 that many end up with paedophiles and assets of the Cult through corrupt and Cult-owned social services which in the reframing era has hired many psychopaths and emotionless automatons to do the job. Children are even stolen to order using spurious reasons to take them by the corrupt and secret (because they're corrupt) 'family courts'. I have written in detail in other books, starting with *The Biggest Secret* in 1997, about the ubiquitous connections between the political, corporate, government, intelligence and military elites (Cult operatives) and Satanism and paedophilia. If you go deep enough both networks have an interlocking leadership. The Woke mentality has been developed by the Cult for many reasons: To promote almost every aspect of its agenda; to hijack the traditional political left and turn it fascist; to divide and rule; and to target agenda pushbackers. But there are other reasons which relate to what I am describing here. How many happy and joyful Wokers do you ever see especially at the extreme end? They are a mental and psychological mess consumed by emotional stress and constantly emotionally cocked for the next explosion of indignation at someone referring to a female as a female. They are walking, talking, batteries as Morpheus might say emitting frequencies which both enslave them in low-vibrational bubbles of perceptual limitation and feed the Archons. Add to this the hatred claimed to be love; fascism claimed to 'anti-fascism', racism claimed to be 'anti-racism';

exclusion claimed to inclusion; and the abuse-filled Internet trolling. You have a purpose-built Archontic energy system with not a wind turbine in sight and all founded on Archontic *inversion*. We have whole generations now manipulated to serve the Archons with their actions and energy. They will be doing so their entire adult lives unless they snap out of their Archon-induced trance. Is it really a surprise that Cult billionaires and corporations put so much money their way? Where is the energy of joy and laughter, including laughing at yourself which is confirmation of your own emotional security? Mark Twain said: 'The human race has one really effective weapon, and that is laughter.' We must use it all the time. Woke has destroyed comedy because it has no humour, no joy, sense of irony, or self-deprecation. Its energy is dense and intense. *Mmmmm*, lunch says the Archontic frequency. Rudolf Steiner (1861-1925) was the Austrian philosopher and famous esoteric thinker who established Waldorf education or Steiner schools to treat children like unique expressions of consciousness and not minds to be programmed with the perceptions determined by authority. I'd been writing about this energy vampiring for decades when I was sent in 2016 a quote by Steiner. He was spot on:

> There are beings in the spiritual realms for whom anxiety and fear emanating from human beings offer welcome food. When humans have no anxiety and fear, then these creatures starve. If fear and anxiety radiates from people and they break out in panic, then these creatures find welcome nutrition and they become more and more powerful. These beings are hostile towards humanity. Everything that feeds on negative feelings, on anxiety, fear and superstition, despair or doubt, are in reality hostile forces in super-sensible worlds, launching cruel attacks on human beings, while they are being fed ... These are exactly the feelings that belong to contemporary culture and materialism; because it estranges people from the spiritual world, it is especially suited to evoke hopelessness and fear of the unknown in people, thereby calling up the above mentioned hostile forces against them.

Pause for a moment from this perspective and reflect on what has happened in the world since the start of 2020. Not only will pennies drop, but billion dollar bills. We see the same theme from Don Juan Matus, a Yaqui Indian shaman in Mexico and the information source for Peruvian-born writer, Carlos Castaneda, who wrote a series of

books from the 1960s to 1990s. Don Juan described the force manipulating human society and his name for the Archons was the predator:

> We have a predator that came from the depths of the cosmos and took over the rule of our lives. Human beings are its prisoners. The predator is our lord and master. It has rendered us docile, helpless. If we want to protest, it suppresses our protest. If we want to act independently, it demands that we don't do so ... indeed we are held prisoner!
>
> They took us over because we are food to them, and they squeeze us mercilessly because we are their sustenance. Just as we rear chickens in coops, the predators rear us in human coops, humaneros. Therefore, their food is always available to them.
>
> Different cultures, different eras, same recurring theme.

The 'ennoia' dilemma

Nag Hammadi Gnostic manuscripts say that Archon consciousness has no 'ennoia'. This is directly translated as 'intentionality', but I'll use the term 'creative imagination'. The *All That Is* in awareness of itself is the source of all creativity – all possibility – and the more disconnected you are from that source the more you are subsequently denied 'creative imagination'. Given that Archon consciousness is almost entirely disconnected it severely lacks creativity and has to rely on far more mechanical processes of thought and exploit the creative potential of those that do have 'ennoia'. You can see cases of this throughout human society. Archon consciousness almost entirely dominates the global banking system and if we study how that system works you will appreciate what I mean. Banks manifest 'money' out of nothing by issuing lines of 'credit' which is 'money' that has never, does not, and will never exist except in theory. It's a confidence trick. If you think 'credit' figures-on-a-screen 'money' is worth anything you accept it as payment. If you don't then the whole system collapses through lack of confidence in the value of that 'money'. Archontic bankers with no 'ennoia' are 'lending' 'money' that doesn't exist to humans that *do* have creativity – those that have the inspired ideas and create businesses and products. Archon banking feeds off human creativity

which it controls through 'money' creation and debt. Humans have the creativity and Archons exploit that for their own benefit and control while having none themselves. Archon Internet platforms like Facebook claim joint copyright of everything that creative users post and while Archontic minds like Zuckerberg may officially head that company it will be human creatives on the staff that provide the creative inspiration. When you have limitless 'money' you can then buy other companies established by creative humans. Witness the acquisition record of Facebook, Google and their like. Survey the Archon-controlled music industry and you see non-creative dark suit executives making their fortune from the human creativity of their artists. The cases are endless. Research the history of people like Gates and Zuckerberg and how their empires were built on exploiting the creativity of others. Archon minds cannot create out of nothing, but they are skilled (because they have to be) in what Gnostic texts call 'countermimicry'. They can imitate, but not innovate. Sabbatians trawl the creativity of others through backdoors they install in computer systems through their cybersecurity systems. Archon-controlled China is globally infamous for stealing intellectual property and I remember how Hong Kong, now part of China, became notorious for making counterfeit copies of the creativity of others – 'countermimicry'. With the now pervasive and all-seeing surveillance systems able to infiltrate any computer you can appreciate the potential for Archons to vampire the creativity of humans. Author John Lamb Lash wrote in his book about the Nag Hammadi texts, *Not In His Image*:

> Although they cannot originate anything, because they lack the divine factor of ennoia (intentionality), Archons can imitate with a vengeance. Their expertise is simulation (HAL, virtual reality). The Demiurge [Yaldabaoth] fashions a heaven world copied from the fractal patterns [of the original] ... His construction is celestial kitsch, like the fake Italianate villa of a Mafia don complete with militant angels to guard every portal.

This brings us to something that I have been speaking about since the turn of the millennium. Our reality is a simulation; a virtual reality that we think is real. No, I'm not kidding.

Human reality? Well, virtually

I had pondered for years about whether our reality is 'real' or some kind of construct. I remembered being immensely affected on a visit as a small child in the late 1950s to the then newly-opened Planetarium on the Marylebone Road in London which is now closed and part of the adjacent Madame Tussauds wax museum. It was in the middle of the day, but when the lights went out there was the night sky projected in the Planetarium's domed ceiling and it appeared to be so real. The experience never left me and I didn't know why until around the turn of the millennium when I became certain that our 'night sky' and entire reality is a projection, a virtual reality, akin to the illusory world portrayed in the *Matrix* movies. I looked at the sky one day in this period and it appeared to me like the domed roof of the Planetarium. The release of the first *Matrix* movie in 1999 also provided a synchronistic and perfect visual representation of where my mind had been going for a long time. I hadn't come across the Gnostic Nag Hammadi texts then. When I did years later the correlation was once again astounding. As I read Gnostic accounts from 1,600 years and more earlier it was clear that they were describing the same simulation phenomenon. They tell how the Yaldabaoth 'Demiurge' and Archons created a 'bad copy' of original reality to rule over all that were captured by its illusions and the body was a prison to trap consciousness in the 'bad copy' fake reality. Read how Gnostics describe the 'bad copy' and update that to current times and they are referring to what we would call today a virtual reality simulation.

Author John Lamb Lash said 'the Demiurge fashions a heaven world copied from the fractal patterns' of the original through expertise in 'HAL' or virtual reality simulation. Fractal patterns are part of the energetic information construct of our reality, a sort of blueprint. If these patterns were copied in computer terms it would indeed give you a copy of a 'natural' reality in a non-natural frequency and digital form. The principle is the same as making a copy of a website. The original website still exists, but now you can change the copy version to make it whatever you like and it can

become very different to the original website. Archons have done this with our reality, a *synthetic* copy of prime reality that still exists beyond the frequency walls of the simulation. Trapped within the illusions of this synthetic Matrix, however, were and are human consciousness and other expressions of prime reality and this is why the Archons via the Cult are seeking to make the human body synthetic and give us synthetic AI minds to complete the job of turning the entire reality synthetic including what we perceive to be the natural world. To quote Kurzweil: 'Nanobots will infuse all the matter around us with information. Rocks, trees, everything will become these intelligent creatures.' Yes, *synthetic* 'creatures' just as 'Covid' and other genetically-manipulating 'vaccines' are designed to make the human body synthetic. From this perspective it is obvious why Archons and their Cult are so desperate to infuse synthetic material into every human with their 'Covid' scam.

Let there be (electromagnetic) light

Yaldabaoth, the force that created the simulation, or Matrix, makes sense of the Gnostic reference to 'The Great Architect' and its use by Cult Freemasonry as the name of its deity. The designer of the Matrix in the movies is called 'The Architect' and that trilogy is jam-packed with symbolism relating to these subjects. I have contended for years that the angry Old Testament God (Yaldabaoth) is the 'God' being symbolically 'quoted' in the opening of Genesis as 'creating the world'. This is not the creation of prime reality – it's the creation of the *simulation*. The Genesis 'God' says: 'Let there be Light: and there was light.' But what is this 'Light'? I have said for decades that the speed of light (186,000 miles per second) is not the fastest speed possible as claimed by mainstream science and is in fact the frequency walls or outer limits of the Matrix. You can't have a fastest or slowest anything within all possibility when everything is possible. The human body is encoded to operate within the speed of light or *within the simulation* and thus we see only the tiny frequency band of visible *light*. Near-death experiencers who perceive reality outside the body during temporary 'death' describe a very different

form of light and this is supported by the Nag Hammadi texts. Prime reality beyond the simulation ('Upper Aeons' to the Gnostics) is described as a realm of incredible beauty, bliss, love and harmony – a realm of 'watery light' that is so powerful 'there are no shadows'. Our false reality of Archon control, which Gnostics call the 'Lower Aeons', is depicted as a realm with a different kind of 'light' and described in terms of chaos, 'Hell', 'the Abyss' and 'Outer Darkness', where trapped souls are tormented and manipulated by demons (relate that to the 'Covid' hoax alone). The watery light theme can be found in near-death accounts and it is not the same as *simulation* 'light' which is electromagnetic or radiation light within the speed of light – the 'Lower Aeons'. Simulation 'light' is the 'luminous fire' associated by Gnostics with the Archons. The Bible refers to Yaldabaoth as 'that old serpent, called the Devil, and Satan, which deceiveth the whole world' (Revelation 12:9). I think that making a simulated copy of prime reality ('countermimicry') and changing it dramatically while all the time manipulating humanity to believe it to be real could probably meet the criteria of deceiving the whole world. Then we come to the Cult god Lucifer – the *Light Bringer*. Lucifer is symbolic of Yaldabaoth, the bringer of radiation light that forms the bad copy simulation within the speed of light. 'He' is symbolised by the lighted torch held by the Statue of Liberty and in the name 'Illuminati'. Sabbatian-Frankism declares that Lucifer is the true god and Lucifer is the real god of Freemasonry honoured as their 'Great or Grand Architect of the Universe' (simulation).

I would emphasise, too, the way Archontic technologically-generated luminous fire of radiation has deluged our environment since I was a kid in the 1950s and changed the nature of The Field with which we constantly interact. Through that interaction technological radiation is changing us. The Smart Grid is designed to operate with immense levels of communication power with 5G expanding across the world and 6G, 7G, in the process of development. Radiation is the simulation and the Archontic manipulation system. Why wouldn't the Archon Cult wish to unleash radiation upon us to an ever-greater extreme to form

Kurzweil's 'cloud'? The plan for a synthetic human is related to the need to cope with levels of radiation beyond even anything we've seen so far. Biological humans would not survive the scale of radiation they have in their script. The Smart Grid is a technological sub-reality within the technological simulation to further disconnect five-sense perception from expanded consciousness. It's a technological prison of the mind.

Infusing the 'spirit of darkness'

A recurring theme in religion and native cultures is the manipulation of human genetics by a non-human force and most famously recorded as the biblical 'sons of god' (the god*s* plural in the original) who interbred with the daughters of men. The Nag Hammadi *Apocryphon of John* tells the same story this way:

> He [Yaldabaoth] sent his angels [Archons/demons] to the daughters of men, that they might take some of them for themselves and raise offspring for their enjoyment. And at first they did not succeed. When they had no success, they gathered together again and they made a plan together ... And the angels changed themselves in their likeness into the likeness of their mates, filling them with the spirit of darkness, which they had mixed for them, and with evil ... And they took women and begot children out of the darkness according to the likeness of their spirit.

Possession when a discarnate entity takes over a human body is an age-old theme and continues today. It's very real and I've seen it. Satanic and secret society rituals can create an energetic environment in which entities can attach to initiates and I've heard many stories of how people have changed their personality after being initiated even into lower levels of the Freemasons. I have been inside three Freemasonic temples, one at a public open day and two by just walking in when there was no one around to stop me. They were in Ryde, the town where I live, Birmingham, England, when I was with a group, and Boston, Massachusetts. They all felt the same energetically – dark, dense, low-vibrational and sinister. Demonic attachment can happen while the initiate has no idea what is going on. To them it's just a ritual to get in the Masons and do a bit of good

business. In the far more extreme rituals of Satanism human possession is even more powerful and they are designed to make possession possible. The hierarchy of the Cult is dictated by the power and perceived status of the possessing Archon. In this way the Archon hierarchy becomes the Cult hierarchy. Once the entity has attached it can influence perception and behaviour and if it attaches to the extreme then so much of its energy (information) infuses into the body information field that the hologram starts to reflect the nature of the possessing entity. This is the *Exorcist* movie type of possession when facial features change and it's known as shapeshifting. Islam's Jinn are said to be invisible tricksters who change shape, 'whisper', confuse and take human form. These are all traits of the Archons and other versions of the same phenomenon. Extreme possession could certainty infuse the 'spirit of darkness' into a partner during sex as the Nag Hammadi texts appear to describe. Such an infusion can change genetics which is also energetic information. Human genetics is information and the 'spirit of darkness' is information. Mix one with the other and change must happen. Islam has the concept of a 'Jinn baby' through possession of the mother and by Jinn taking human form. There are many ways that human genetics can be changed and remember that Archons have been aware all along of advanced techniques to do this. What is being done in human society today – and far more – was known about by Archons at the time of the 'fallen ones' and their other versions described in religions and cultures.

Archons and their human-world Cult are obsessed with genetics as we see today and they know this dictates how information is processed into perceived reality during a human life. They needed to produce a human form that would decode the simulation and this is symbolically known as 'Adam and Eve' who left the 'garden' (prime reality) and 'fell' into Matrix reality. The simulation is not a 'physical' construct (there is no 'physical'); it is a source of information. Think Wi-Fi again. The simulation is an energetic field encoded with information and body-brain systems are designed to decode that information encoded in wave or frequency form which

is transmitted to the brain as electrical signals. These are decoded by the brain to construct our sense of reality – an illusory 'physical' world that only exists in the brain or the mind. Virtual reality games mimic this process using the same sensory decoding system. Information is fed to the senses to decode a virtual reality that can appear so real, but isn't (Figs 18 and 19). Some scientists believe – and I agree with them – that what we perceive as 'physical' reality only exists when we are looking or observing. The act of perception or focus triggers the decoding systems which turn waveform information into holographic reality. When we are not observing something our reality reverts from a holographic state to a waveform state. This relates to the same principle as a falling tree not making a noise unless someone is there to hear it or decode it. The concept makes sense from the simulation perspective. A computer is not decoding all the information in a Wi-Fi field all the time and only decodes or brings into reality on the screen that part of Wi-Fi that it's decoding – focusing upon – at that moment.



Figure 18: Virtual reality technology 'hacks' into the body's five-sense decoding system.



Figure 19: The result can be experienced as very 'real'.

Interestingly, Professor Donald Hoffman at the Department of Cognitive Sciences at the University of California, Irvine, says that our experienced reality is like a computer interface that shows us only the level with which we interact while hiding all that exists beyond it: 'Evolution shaped us with a user interface that hides the truth. Nothing that we see is the truth – the very language of space and time and objects is the wrong language to describe reality.' He is correct in what he says on so many levels. Space and time are not a universal reality. They are a phenomenon of decoded *simulation* reality as part of the process of enslaving our sense of reality. Near-death experiencers report again and again how space and time did not exist as we perceive them once they were free of the body – body decoding systems. You can appreciate from this why Archons and their Cult are so desperate to entrap human attention in the five senses where we are in the Matrix and of the Matrix. Opening your mind to expanded states of awareness takes you beyond the information confines of the simulation and you become aware of knowledge and insights denied to you before. This is what we call 'awakening' – *awakening from the Matrix* – and in the final chapter I will relate this to current events.

Where are the 'aliens'?

A simulation would explain the so-called 'Fermi Paradox' named after Italian physicist Enrico Fermi (1901-1954) who created the first nuclear reactor. He considered the question of why there is such a lack of extraterrestrial activity when there are so many stars and planets in an apparently vast universe; but what if the night sky that we see, or think we do, is a simulated projection as I say? If you control the simulation and your aim is to hold humanity fast in essential ignorance would you want other forms of life including advanced life coming and going sharing information with humanity? Or would you want them to believe they were isolated and apparently alone? Themes of human isolation and apartness are common whether they be the perception of a lifeless universe or the fascist isolation laws of the 'Covid' era. Paradoxically the very

existence of a simulation means that we are not alone when some force had to construct it. My view is that experiences that people have reported all over the world for centuries with Reptilians and Grey entities are Archon phenomena as Nag Hammadi texts describe; and that benevolent 'alien' interactions are non-human groups that come in and out of the simulation by overcoming Archon attempts to keep them out. It should be highlighted, too, that Reptilians and Greys are obsessed with *genetics* and *technology* as related by cultural accounts and those who say they have been abducted by them. Technology is their way of overcoming some of the limitations in their creative potential and our technology-driven and controlled human society of today is *arch*etypical Archon-Reptilian-Grey modus operandi. Technocracy is really *Archon*tocracy. The Universe does not have to be as big as it appears with a simulation. There is no space or distance only information decoded into holographic reality. What we call 'space' is only the absence of holographic 'objects' and that 'space' is The Field of energetic information which connects everything into a single whole. The same applies with the artificially-generated information field of the simulation. The Universe is not big or small as a physical reality. It is decoded information, that's all, and its perceived size is decided by the way the simulation is encoded to make it appear. The entire night sky as we perceive it only exists in our brain and so where are those 'millions of light years'? The 'stars' on the ceiling of the Planetarium looked a vast distance away.

There's another point to mention about 'aliens'. I have been highlighting since the 1990s the plan to stage a fake 'alien invasion' to justify the centralisation of global power and a world military. Nazi scientist Werner von Braun, who was taken to America by Operation Paperclip after World War Two to help found NASA, told his American assistant Dr Carol Rosin about the Cult agenda when he knew he was dying in 1977. Rosin said that he told her about a sequence that would lead to total human control by a one-world government. This included threats from terrorism, rogue nations, meteors and asteroids before finally an 'alien invasion'. All of these

things, von Braun said, would be bogus and what I would refer to as a No-Problem-Reaction-Solution. Keep this in mind when 'the aliens are coming' is the new mantra. The aliens are not coming – they are *already here* and they have infiltrated human society while looking human. French-Canadian investigative journalist Serge Monast said in 1994 that he had uncovered a NASA/military operation called Project Blue Beam which fits with what Werner von Braun predicted. Monast died of a 'heart attack' in 1996 the day after he was arrested and spent a night in prison. He was 51. He said Blue Beam was a plan to stage an alien invasion that would include religious figures beamed holographically into the sky as part of a global manipulation to usher in a 'new age' of worshipping what I would say is the Cult 'god' Yaldabaoth in a one-world religion. Fake holographic asteroids are also said to be part of the plan which again syncs with von Braun. How could you stage an illusory threat from asteroids unless they were holographic inserts? This is pretty straightforward given the advanced technology outside the public arena and the fact that our 'physical' reality is holographic anyway. Information fields would be projected and we would decode them into the illusion of a 'physical' asteroid. If they can sell a global 'pandemic' with a 'virus' that doesn't exist what will humans not believe if government and media tell them?

All this is particularly relevant as I write with the Pentagon planning to release in June, 2021, information about 'UFO sightings'. I have been following the UFO story since the early 1990s and the common theme throughout has been government and military denials and cover up. More recently, however, the Pentagon has suddenly become more talkative and apparently open with Air Force pilot radar images released of unexplained craft moving and changing direction at speeds well beyond anything believed possible with human technology. Then, in March, 2021, former Director of National Intelligence John Ratcliffe said a Pentagon report months later in June would reveal a great deal of information about UFO sightings unknown to the public. He said the report would have 'massive implications'. The order to do this was included bizarrely

in a $2.3 trillion 'coronavirus' relief and government funding bill passed by the Trump administration at the end of 2020. I would add some serious notes of caution here. I have been pointing out since the 1990s that the US military and intelligence networks have long had craft – 'flying saucers' or anti-gravity craft – which any observer would take to be extraterrestrial in origin. Keeping this knowledge from the public allows craft flown by *humans* to be perceived as alien visitations. I am not saying that 'aliens' do not exist. I would be the last one to say that, but we have to be streetwise here. President Ronald Reagan told the UN General Assembly in 1987: 'I occasionally think how quickly our differences worldwide would vanish if we were facing an alien threat from outside this world.' That's the idea. Unite against a common 'enemy' with a common purpose behind your 'saviour force' (the Cult) as this age-old technique of mass manipulation goes global.

Science moves this way …

I could find only one other person who was discussing the simulation hypothesis publicly when I concluded it was real. This was Nick Bostrom, a Swedish-born philosopher at the University of Oxford, who has explored for many years the possibility that human reality is a computer simulation although his version and mine are not the same. Today the simulation and holographic reality hypothesis have increasingly entered the scientific mainstream. Well, the more open-minded mainstream, that is. Here are a few of the ever-gathering examples. American nuclear physicist Silas Beane led a team of physicists at the University of Bonn in Germany pursuing the question of whether we live in a simulation. They concluded that we probably do and it was likely based on a lattice of cubes. They found that cosmic rays align with that specific pattern. The team highlighted the Greisen–Zatsepin–Kuzmin (GZK) limit which refers to cosmic ray particle interaction with cosmic background radiation that creates an apparent boundary for cosmic ray particles. They say in a paper entitled 'Constraints on the Universe as a Numerical Simulation' that this 'pattern of constraint' is exactly what you

would find with a computer simulation. They also made the point that a simulation would create its own 'laws of physics' that would limit possibility. I've been making the same point for decades that the *perceived* laws of physics relate only to this reality, or what I would later call the simulation. When designers write codes to create computer and virtual reality games they are the equivalent of the laws of physics for that game. Players interact within the limitations laid out by the coding. In the same way those who wrote the codes for the simulation decided the laws of physics that would apply. These can be overridden by expanded states of consciousness, but not by those enslaved in only five-sense awareness where simulation codes rule. Overriding the codes is what people call 'miracles'. They are not. They are bypassing the encoded limits of the simulation. A population caught in simulation perception would have no idea that this was their plight. As the Bonn paper said: 'Like a prisoner in a pitch-black cell we would not be able to see the "walls" of our prison,' That's true if people remain mesmerised by the five senses. Open to expanded awareness and those walls become very clear. The main one is the speed of light.

American theoretical physicist James Gates is another who has explored the simulation question and found considerable evidence to support the idea. Gates was Professor of Physics at the University of Maryland, Director of The Center for String and Particle Theory, and on Barack Obama's Council of Advisors on Science and Technology. He and his team found *computer codes* of digital data embedded in the fabric of our reality. They relate to on-off electrical charges of 1 and 0 in the binary system used by computers. 'We have no idea what they are doing there', Gates said. They found within the energetic fabric mathematical sequences known as error-correcting codes or block codes that 'reboot' data to its original state or 'default settings' when something knocks it out of sync. Gates was asked if he had found a set of equations embedded in our reality indistinguishable from those that drive search engines and browsers and he said: 'That is correct.' Rich Terrile, director of the Centre for Evolutionary Computation and Automated Design at NASA's Jet

Propulsion Laboratory, has said publicly that he believes the Universe is a digital hologram that must have been created by a form of intelligence. I agree with that in every way. Waveform information is delivered electrically by the senses to the brain which constructs a *digital* holographic reality that we call the 'world'. This digital level of reality can be read by the esoteric art of numerology. Digital holograms are at the cutting edge of holographics today. We have digital technology everywhere designed to access and manipulate our digital level of perceived reality. Synthetic mRNA in 'Covid vaccines' has a digital component to manipulate the body's digital 'operating system'.

Reality is numbers

How many know that our reality can be broken down to numbers and codes that are the same as computer games? Max Tegmark, a physicist at the Massachusetts Institute of Technology (MIT), is the author of *Our Mathematical Universe* in which he lays out how reality can be entirely described by numbers and maths in the way that a video game is encoded with the 'physics' of computer games. Our world and computer virtual reality are essentially the same. Tegmark imagines the perceptions of characters in an advanced computer game when the graphics are so good they don't know they are in a game. They think they can bump into real objects (electromagnetic resistance in our reality), fall in love and feel emotions like excitement. When they began to study the apparently 'physical world' of the video game they would realise that everything was made of pixels (which have been found in our energetic reality as must be the case when on one level our world is digital). What computer game characters thought was physical 'stuff', Tegmark said, could actually be broken down into numbers:

> And we're exactly in this situation in our world. We look around and it doesn't seem that mathematical at all, but everything we see is made out of elementary particles like quarks and electrons. And what properties does an electron have? Does it have a smell or a colour or a texture? No! ... We physicists have come up with geeky names for [Electron] properties, like

electric charge, or spin, or lepton number, but the electron doesn't care what we call it, the properties are just numbers.

This is the illusory reality Gnostics were describing. This is the simulation. The A, C, G, and T codes of DNA have a binary value – A and C = 0 while G and T = 1. This has to be when the simulation is digital and the body must be digital to interact with it. Recurring mathematical sequences are encoded throughout reality and the body. They include the Fibonacci sequence in which the two previous numbers are added to get the next one, as in ... 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, etc. The sequence is encoded in the human face and body, proportions of animals, DNA, seed heads, pine cones, trees, shells, spiral galaxies, hurricanes and the number of petals in a flower. The list goes on and on. There are fractal patterns – a 'never-ending pattern that is infinitely complex and self-similar across all scales in the as above, so below, principle of holograms. These and other famous recurring geometrical and mathematical sequences such as Phi, Pi, Golden Mean, Golden Ratio and Golden Section are *computer codes* of the simulation. I had to laugh and give my head a shake the day I finished this book and it went into the production stage. I was sent an article in *Scientific American* published in April, 2021, with the headline 'Confirmed! We Live in a Simulation'. Two decades after I first said our reality is a simulation and the speed of light is it's outer limit the article suggested that we do live in a simulation and that the speed of light is its outer limit. I left school at 15 and never passed a major exam in my life while the writer was up to his eyes in qualifications. As I will explain in the final chapter *knowing* is far better than thinking and they come from very different sources. The article rightly connected the speed of light to the processing speed of the 'Matrix' and said what has been in my books all this time … 'If we are in a simulation, as it appears, then space is an abstract property written in code. It is not real'. No it's not and if we live in a simulation something created it and it wasn't *us*. 'That David Icke says we are manipulated by aliens' – he's crackers.'

Wow …

The reality that humanity thinks is so real is an illusion. Politicians, governments, scientists, doctors, academics, law enforcement, media, school and university curriculums, on and on, are all founded on a world that *does not exist* except as a simulated prison cell. Is it such a stretch to accept that 'Covid' doesn't exist when our entire 'physical' reality doesn't exist? Revealed here is the knowledge kept under raps in the Cult networks of compartmentalised secrecy to control humanity's sense of reality by inducing the population to believe in a reality that's not real. If it wasn't so tragic in its experiential consequences the whole thing would be hysterically funny. None of this is new to Renegade Minds. Ancient Greek philosopher Plato (about 428 to about 347BC) was a major influence on Gnostic belief and he described the human plight thousands of years ago with his Allegory of the Cave. He told the symbolic story of prisoners living in a cave who had never been outside. They were chained and could only see one wall of the cave while behind them was a fire that they could not see. Figures walked past the fire casting shadows on the prisoners' wall and those moving shadows became their sense of reality. Some prisoners began to study the shadows and were considered experts on them (today's academics and scientists), but what they studied was only an illusion (today's academics and scientists). A prisoner escaped from the cave and saw reality as it really is. When he returned to report this revelation they didn't believe him, called him mad and threatened to kill him if he tried to set them free. Plato's tale is not only a brilliant analogy of the human plight and our illusory reality. It describes, too, the dynamics of the 'Covid' hoax. I have only skimmed the surface of these subjects here. The aim of this book is to crisply connect all essential dots to put what is happening today into its true context. All subject areas and their connections in this chapter are covered in great evidential detail in *Everything You Need To Know, But Have Never Been Told* and *The Answer*.

They say that bewildered people 'can't see the forest for the trees'. Humanity, however, can't see the forest for the *twigs*. The five senses

see only twigs while Renegade Minds can see the forest and it's the forest where the answers lie with the connections that reveals. Breaking free of perceptual programming so the forest can be seen is the way we turn all this around. Not breaking free is how humanity got into this mess. The situation may seem hopeless, but I promise you it's not. We are a perceptual heartbeat from paradise if only we knew.

CHAPTER TWELVE

Escaping Wetiko

Life is simply a vacation from the infinite
Dean Cavanagh

Renegade Minds weave the web of life and events and see common themes in the apparently random. They are always there if you look for them and their pursuit is aided by incredible synchronicity that comes when your mind is open rather than mesmerised by what it thinks it can see.

Infinite awareness is infinite possibility and the more of infinite possibility that we access the more becomes infinitely possible. That may be stating the apparently obvious, but it is a devastatingly-powerful fact that can set us free. We are a point of attention within an infinity of consciousness. The question is how much of that infinity do we choose to access? How much knowledge, insight, awareness, wisdom, do we want to connect with and explore? If your focus is only in the five senses you will be influenced by a fraction of infinite awareness. I mean a range so tiny that it gives new meaning to infinitesimal. Limitation of self-identity and a sense of the possible limit accordingly your range of consciousness. We are what we think we are. Life is what we think it is. The dream is the dreamer and the dreamer is the dream. Buddhist philosophy puts it this way: 'As a thing is viewed, so it appears.' Most humans live in the realm of touch, taste, see, hear, and smell and that's the limit of their sense of the possible and sense of self. Many will follow a religion and speak of a God in his heaven, but their lives are still

dominated by the five senses in their perceptions and actions. The five senses become the arbiter of everything. When that happens all except a smear of infinity is sealed away from influence by the rigid, unyielding, reality bubbles that are the five-sense human or Phantom Self. Archon Cult methodology is to isolate consciousness within five-sense reality – the simulation – and then program that consciousness with a sense of self and the world through a deluge of life-long information designed to instil the desired perception that allows global control. Efforts to do this have increased dramatically with identity politics as identity bubbles are squeezed into the minutiae of five-sense detail which disconnect people even more profoundly from the infinite 'I'.

Five-sense focus and self-identity are like a firewall that limits access to the infinite realms. You only perceive one radio or television station and no other. We'll take that literally for a moment. Imagine a vast array of stations giving different information and angles on reality, but you only ever listen to one. Here we have the human plight in which the population is overwhelmingly confined to CultFM. This relates only to the frequency range of CultFM and limits perception and insight to that band – limits *possibility* to that band. It means you are connecting with an almost imperceptibly minuscule range of possibility and creative potential within the infinite Field. It's a world where everything seems apart from everything else and where synchronicity is rare. Synchronicity is defined in the dictionary as 'the happening by chance of two or more related or similar events at the same time'. Use of 'by chance' betrays a complete misunderstanding of reality. Synchronicity is not 'by chance'. As people open their minds, or 'awaken' to use the term, they notice more and more coincidences in their lives, bits of 'luck', apparently miraculous happenings that put them in the right place at the right time with the right people. Days become peppered with 'fancy meeting you here' and 'what are the chances of that?' My entire life has been lived like this and ever more so since my own colossal awakening in 1990 and 91 which transformed my sense of reality. Synchronicity is not 'by chance'; it is by accessing expanded

realms of possibility which allow expanded potential for manifestation. People broadcasting the same vibe from the same openness of mind tend to be drawn 'by chance' to each other through what I call frequency magnetism and it's not only people. In the last more than 30 years incredible synchronicity has also led me through the Cult maze to information in so many forms and to crucial personal experiences. These 'coincidences' have allowed me to put the puzzle pieces together across an enormous array of subjects and situations. Those who have breached the bubble of five-sense reality will know exactly what I mean and this escape from the perceptual prison cell is open to everyone whenever they make that choice. This may appear super-human when compared with the limitations of 'human', but it's really our natural state. 'Human' as currently experienced is consciousness in an unnatural state of induced separation from the infinity of the whole. I'll come to how this transformation into unity can be made when I have described in more detail the force that holds humanity in servitude by denying this access to infinite self.

The Wetiko factor

I have been talking and writing for decades about the way five-sense mind is systematically barricaded from expanded awareness. I have used the analogy of a computer (five-sense mind) and someone at the keyboard (expanded awareness). Interaction between the computer and the operator is symbolic of the interaction between five-sense mind and expanded awareness. The computer directly experiences the Internet and the operator experiences the Internet via the computer which is how it's supposed to be – the two working as one. Archons seek to control that point where the operator connects with the computer to stop that interaction (Fig 20). Now the operator is banging the keyboard and clicking the mouse, but the computer is not responding and this happens when the computer is taken over – *possessed* – by an appropriately-named computer 'virus'. The operator has lost all influence over the computer which goes its own way making decisions under the control of the 'virus'. I have

just described the dynamic through which the force known to Gnostics as Yaldabaoth and Archons disconnects five-sense mind from expanded awareness to imprison humanity in perceptual servitude.



Figure 20: The mind 'virus' I have been writing about for decades seeks to isolate five-sense mind (the computer) from the true 'I'. (Image by Neil Hague).

About a year ago I came across a Native American concept of Wetiko which describes precisely the same phenomenon. Wetiko is the spelling used by the Cree and there are other versions including wintiko and windigo used by other tribal groups. They spell the name with lower case, but I see Wetiko as a proper noun as with Archons and prefer a capital. I first saw an article about Wetiko by writer and researcher Paul Levy which so synced with what I had been writing about the computer/operator disconnection and later the Archons. I then read his book, the fascinating *Dispelling Wetiko, Breaking the Spell of Evil*. The parallels between what I had concluded long before and the Native American concept of Wetiko were so clear and obvious that it was almost funny. For Wetiko see the Gnostic Archons for sure and the Jinn, the Predators, and every other name for a force of evil, inversion and chaos. Wetiko is the Native American name for the force that divides the computer from

the operator (Fig 21). Indigenous author Jack D. Forbes, a founder of the Native American movement in the 1960s, wrote another book about Wetiko entitled *Columbus And Other Cannibals – The Wetiko Disease of Exploitation, Imperialism, and Terrorism* which I also read. Forbes says that Wetiko refers to an evil person or spirit 'who terrorizes other creatures by means of terrible acts, including cannibalism'. Zulu shaman Credo Mutwa told me that African accounts tell how cannibalism was brought into the world by the Chitauri 'gods' – another manifestation of Wetiko. The distinction between 'evil person or spirit' relates to Archons/Wetiko possessing a human or acting as pure consciousness. Wetiko is said to be a sickness of the soul or spirit and a state of being that takes but gives nothing back – the Cult and its operatives perfectly described. Black Hawk, a Native American war leader defending their lands from confiscation, said European invaders had 'poisoned hearts' – Wetiko hearts – and that this would spread to native societies. Mention of the heart is very significant as we shall shortly see. Forbes writes: 'Tragically, the history of the world for the past 2,000 years is, in great part, the story of the epidemiology of the wetiko disease.' Yes, and much longer. Forbes is correct when he says: 'The wetikos destroyed Egypt and Babylon and Athens and Rome and Tenochtitlan [capital of the Aztec empire] and perhaps now they will destroy the entire earth.' Evil, he said, is the number one export of a Wetiko culture – see its globalisation with 'Covid'. Constant war, mass murder, suffering of all kinds, child abuse, Satanism, torture and human sacrifice are all expressions of Wetiko and the Wetiko possessed. The world is Wetiko made manifest, *but it doesn't have to be*. There is a way out of this even now.



Figure 21: The mind 'virus' is known to Native Americans as 'Wetiko'. (Image by Neil Hague).

Cult of Wetiko

Wetiko is the Yaldabaoth frequency distortion that seeks to attach to human consciousness and absorb it into its own. Once this connection is made Wetiko can drive the perceptions of the target which they believe to be coming from their own mind. All the horrors of history and today from mass killers to Satanists, paedophiles like Jeffrey Epstein and other psychopaths, are the embodiment of Wetiko and express its state of being in all its grotesqueness. The Cult is Wetiko incarnate, Yaldabaoth incarnate, and it seeks to facilitate Wetiko assimilation of humanity in totality into its distortion by manipulating the population into low frequency states that match its own. Paul Levy writes: 'Holographically enforced within the psyche of every human being the wetiko virus pervades and underlies the entire field of consciousness, and can therefore potentially manifest through any one of us at any moment if we are not mindful.' The 'Covid' hoax has achieved this with many people, but others have not fallen into Wetiko's frequency lair. Players in the 'Covid' human catastrophe including Gates, Schwab, Tedros, Fauci, Whitty, Vallance, Johnson, Hancock, Ferguson, Drosten, and all the rest, including the psychopath psychologists, are expressions of Wetiko. This is why

they have no compassion or empathy and no emotional consequence for what they do that would make them stop doing it. Observe all the people who support the psychopaths in authority against the Pushbackers despite the damaging impact the psychopaths have on their own lives and their family's lives. You are again looking at Wetiko possession which prevents them seeing through the lies to the obvious scam going on. *Why can't they see it?* Wetiko won't let them see it. The perceptual divide that has now become a chasm is between the Wetikoed and the non-Wetikoed.

Paul Levy describes Wetiko in the same way that I have long described the Archontic force. They are the same distorted consciousness operating across dimensions of reality: '… the subtle body of wetiko is not located in the third dimension of space and time, literally existing in another dimension … it is able to affect ordinary lives by mysteriously interpenetrating into our three-dimensional world.' Wetiko does this through its incarnate representatives in the Cult and by weaving itself into The Field which on our level of reality is the electromagnetic information field of the simulation or Matrix. More than that, the simulation *is* Wetiko / Yaldabaoth. Caleb Scharf, Director of Astrobiology at Columbia University, has speculated that 'alien life' could be so advanced that it has transcribed itself into the quantum realm to become what we call physics. He said intelligence indistinguishable from the fabric of the Universe would solve many of its greatest mysteries:

> Perhaps hyper-advanced life isn't just external. Perhaps it's already all around. It is embedded in what we perceive to be physics itself, from the root behaviour of particles and fields to the phenomena of complexity and emergence ... In other words, life might not just be in the equations. It might BE the equations [My emphasis].

Scharf said it is possible that 'we don't recognise advanced life because it forms an integral and unsuspicious part of what we've considered to be the natural world'. I agree. Wetiko/Yaldabaoth *is* the simulation. We are literally in the body of the beast. But that doesn't mean it has to control us. We all have the power to overcome Wetiko

influence and the Cult knows that. I doubt it sleeps too well because it knows that.

Which Field?

This, I suggest, is how it all works. There are two Fields. One is the fierce electromagnetic light of the Matrix within the speed of light; the other is the 'watery light' of The Field beyond the walls of the Matrix that connects with the Great Infinity. Five-sense mind and the decoding systems of the body attach us to the Field of Matrix light. They have to or we could not experience this reality. Five-sense mind sees only the Matrix Field of information while our expanded consciousness is part of the Infinity Field. When we open our minds, and most importantly our hearts, to the Infinity Field we have a mission control which gives us an expanded perspective, a road map, to understand the nature of the five-sense world. If we are isolated only in five-sense mind there is no mission control. We're on our own trying to understand a world that's constantly feeding us information to ensure we do not understand. People in this state can feel 'lost' and bewildered with no direction or radar. You can see ever more clearly those who are influenced by the Fields of Big Infinity or little five-sense mind simply by their views and behaviour with regard to the 'Covid' hoax. We have had this division throughout known human history with the mass of the people on one side and individuals who could see and intuit beyond the walls of the simulation – Plato's prisoner who broke out of the cave and saw reality for what it is. Such people have always been targeted by Wetiko/Archon-possessed authority, burned at the stake or demonised as mad, bad and dangerous. The Cult today and its global network of 'anti-hate', 'anti-fascist' Woke groups are all expressions of Wetiko attacking those exposing the conspiracy, 'Covid' lies and the 'vaccine' agenda.

Woke as a whole is Wetiko which explains its black and white mentality and how at one it is with the Wetiko-possessed Cult. Paul Levy said: 'To be in this paradigm is to still be under the thrall of a two-valued logic – where things are either true or false – of a

wetikoized mind.' Wetiko consciousness is in a permanent rage, therefore so is Woke, and then there is Woke inversion and contradiction. 'Anti-fascists' act like fascists because fascists *and* 'anti-fascists' are both Wetiko at work. Political parties act the same while claiming to be different for the same reason. Secret society and satanic rituals are attaching initiates to Wetiko and the cold, ruthless, psychopathic mentality that secures the positions of power all over the world is Wetiko. Reframing 'training programmes' have the same cumulative effect of attaching Wetiko and we have their graduates described as automatons and robots with a cold, psychopathic, uncaring demeanour. They are all traits of Wetiko possession and look how many times they have been described in this book and elsewhere with regard to personnel behind 'Covid' including the police and medical profession. Climbing the greasy pole in any profession in a Wetiko society requires traits of Wetiko to get there and that is particularly true of politics which is not about fair competition and pre-eminence of ideas. It is founded on how many backs you can stab and arses you can lick. This culminated in the global 'Covid' coordination between the Wetiko possessed who pulled it off in all the different countries without a trace of empathy and compassion for their impact on humans. Our sight sense can see only holographic form and not the Field which connects holographic form. Therefore we perceive 'physical' objects with 'space' in between. In fact that 'space' is energy/consciousness operating on multiple frequencies. One of them is Wetiko and that connects the Cult psychopaths, those who submit to the psychopaths, and those who serve the psychopaths in the media operations of the world. Wetiko is Gates. Wetiko is the mask-wearing submissive. Wetiko is the fake journalist and 'fact-checker'. The Wetiko Field is coordinating the whole thing. Psychopaths, gofers, media operatives, 'anti-hate' hate groups, 'fact-checkers' and submissive people work as one unit *even without human coordination* because they are attached to the *same* Field which is organising it all (Fig 22). Paul Levy is here describing how Wetiko-possessed people are drawn together and refuse to let any information breach their rigid

perceptions. He was writing long before 'Covid', but I think you will recognise followers of the 'Covid' religion *oh just a little bit*:

People who are channelling the vibratory frequency of wetiko align with each other through psychic resonance to reinforce their unspoken shared agreement so as to uphold their deranged view of reality. Once an unconscious content takes possession of certain individuals, it irresistibly draws them together by mutual attraction and knits them into groups tied together by their shared madness that can easily swell into an avalanche of insanity.

A psychic epidemic is a closed system, which is to say that it is insular and not open to any new information or informing influences from the outside world which contradict its fixed, limited, and limiting perspective.

There we have the Woke mind and the 'Covid' mind. Compatible resonance draws the awakening together, too, which is clearly happening today.



Figure 22: The Wetiko Field from which the Cult pyramid and its personnel are made manifest. (Image by Neil Hague).

Spiritual servitude

Wetiko doesn't care about humans. It's not human; it just possesses humans for its own ends and the effect (depending on the scale of

possession) can be anything from extreme psychopathy to unquestioning obedience. Wetiko's worst nightmare is for human consciousness to expand beyond the simulation. Everything is focussed on stopping that happening through control of information, thus perception, thus frequency. The 'education system', media, science, medicine, academia, are all geared to maintaining humanity in five-sense servitude as is the constant stimulation of low-vibrational mental and emotional states (see 'Covid'). Wetiko seeks to dominate those subconscious spaces between five-sense perception and expanded consciousness where the computer meets the operator. From these subconscious hiding places Wetiko speaks to us to trigger urges and desires that we take to be our own and manipulate us into anything from low-vibrational to psychopathic states. Remember how Islam describes the Jinn as invisible tricksters that 'whisper' and confuse. Wetiko is the origin of the 'trickster god' theme that you find in cultures all over the world. Jinn, like the Archons, are Wetiko which is terrified of humans awakening and reconnecting with our true self for then its energy source has gone. With that the feedback loop breaks between Wetiko and human perception that provides the energetic momentum on which its very existence depends as a force of evil. Humans are both its target and its source of survival, but only if we are operating in low-vibrational states of fear, hate, depression and the background anxiety that most people suffer. We are Wetiko's target because we are its key to survival. It needs us, not the other way round. Paul Levy writes:

A vampire has no intrinsic, independent, substantial existence in its own right; it only exists in relation to us. The pathogenic, vampiric mind-parasite called wetiko is nothing in itself – not being able to exist from its own side – yet it has a 'virtual reality' such that it can potentially destroy our species …

…The fact that a vampire is not reflected by a mirror can also mean that what we need to see is that there's nothing, no-thing to see, other than ourselves. The fact that wetiko is the expression of something inside of us means that the cure for wetiko is with us as well. The critical issue is finding this cure within us and then putting it into effect.

Evil begets evil because if evil does not constantly expand and find new sources of energetic sustenance its evil, its *distortion*, dies with the assimilation into balance and harmony. Love is the garlic to Wetiko's vampire. Evil, the absence of love, cannot exist in the presence of love. I think I see a way out of here. I have emphasised so many times over the decades that the Archons/Wetiko and their Cult are not all powerful. *They are not*. I don't care how it looks even now *they are not*. I have not called them little boys in short trousers for effect. I have said it because it is true. Wetiko's insatiable desire for power over others is not a sign of its omnipotence, but its insecurity. Paul Levy writes: 'Due to the primal fear which ultimately drives it and which it is driven to cultivate, wetiko's body politic has an intrinsic and insistent need for centralising power and control so as to create imagined safety for itself.' *Yeeeeeees!* Exactly! Why does Wetiko want humans in an ongoing state of fear? Wetiko itself *is* fear and it is petrified of love. As evil is an absence of love, so love is an absence of fear. Love conquers all and *especially* Wetiko which *is* fear. Wetiko brought fear into the world when it wasn't here before. *Fear* was the 'fall', the fall into low-frequency ignorance and illusion – fear is **F**alse **E**motion **A**ppearing **R**eal. The simulation is driven and energised by fear because Wetiko/Yaldabaoth (fear) *are* the simulation. Fear is the absence of love and Wetiko is the absence of love.

Wetiko today

We can now view current events from this level of perspective. The 'Covid' hoax has generated momentous amounts of ongoing fear, anxiety, depression and despair which have empowered Wetiko. No wonder people like Gates have been the instigators when they are Wetiko incarnate and exhibit every trait of Wetiko in the extreme. See how cold and unemotional these people are like Gates and his cronies, how dead of eye they are. That's Wetiko. Sabbatians are Wetiko and everything they control including the World Health Organization, Big Pharma and the 'vaccine' makers, national 'health'

hierarchies, corporate media, Silicon Valley, the banking system, and the United Nations with its planned transformation into world government. All are controlled and possessed by the Wetiko distortion into distorting human society in its image. We are with this knowledge at the gateway to understanding the world. Divisions of race, culture, creed and sexuality are diversions to hide the real division between those possessed and influenced by Wetiko and those that are not. The 'Covid' hoax has brought both clearly into view. Human behaviour is not about race. Tyrants and dictatorships come in all colours and creeds. What unites the US president bombing the innocent and an African tribe committing genocide against another as in Rwanda? What unites them? *Wetiko*. All wars are Wetiko, all genocide is Wetiko, all hunger over centuries in a world of plenty is Wetiko. Children going to bed hungry, including in the West, is Wetiko. Cult-generated Woke racial divisions that focus on the body are designed to obscure the reality that divisions in behaviour are manifestations of mind, not body. Obsession with body identity and group judgement is a means to divert attention from the real source of behaviour – mind and perception. Conflict sown by the Woke both within themselves and with their target groups are Wetiko providing lunch for itself through still more agents of the division, chaos, and fear on which it feeds. The Cult is seeking to assimilate the entirety of humanity and all children and young people into the Wetiko frequency by manipulating them into states of fear and despair. Witness all the suicide and psychological unravelling since the spring of 2020. Wetiko psychopaths want to impose a state of unquestioning obedience to authority which is no more than a conduit for Wetiko to enforce its will and assimilate humanity into itself. It needs us to believe that resistance is futile when it fears resistance and even more so the game-changing non-cooperation with its impositions. It can use violent resistance for its benefit. Violent impositions and violent resistance are *both* Wetiko. The Power of Love with its Power of No will sweep Wetiko from our world. Wetiko and its Cult know that. They just don't want us to know.

AI Wetiko

This brings me to AI or artificial intelligence and something else Wetikos don't want us to know. What is AI *really*? I know about computer code algorithms and AI that learns from data input. These, however, are more diversions, the expeditionary force, for the real AI that they want to connect to the human brain as promoted by Silicon Valley Wetikos like Kurzweil. What is this AI? It is the frequency of *Wetiko*, the frequency of the Archons. The connection of AI to the human brain is the connection of the Wetiko frequency to create a Wetiko hive mind and complete the job of assimilation. The hive mind is planned to be controlled from Israel and China which are both 100 percent owned by Wetiko Sabbatians. The assimilation process has been going on minute by minute in the 'smart' era which fused with the 'Covid' era. We are told that social media is scrambling the minds of the young and changing their personality. This is true, but what is social media? Look more deeply at how it works, how it creates divisions and conflict, the hostility and cruelty, the targeting of people until they are destroyed. That's Wetiko. Social media is manipulated to tune people to the Wetiko frequency with all the emotional exploitation tricks employed by platforms like Facebook and its Wetiko front man, Zuckerberg. Facebook's Instagram announced a new platform for children to overcome a legal bar on them using the main site. This is more Wetiko exploitation and manipulation of kids. Amnesty International likened the plan to foxes offering to guard the henhouse and said it was incompatible with human rights. Since when did Wetiko or Zuckerberg (I repeat myself) care about that? Would Brin and Page at Google, Wojcicki at YouTube, Bezos at Amazon and whoever the hell runs Twitter act as they do if they were not channelling Wetiko? Would those who are developing technologies for no other reason than human control? How about those designing and selling technologies to kill people and Big Pharma drug and 'vaccine' producers who know they will end or devastate lives? Quite a thought for these people to consider is that if you are Wetiko in a human life you are Wetiko on the 'other side' unless your frequency

changes and that can only change by a change of perception which becomes a change of behaviour. Where Gates is going does not bear thinking about although perhaps that's exactly where he wants to go. Either way, that's where he's going. His frequency will make it so.

The frequency lair

I have been saying for a long time that a big part of the addiction to smartphones and devices is that a frequency is coming off them that entraps the mind. People spend ages on their phones and sometimes even a minute or so after they put them down they pick them up again and it all repeats. 'Covid' lockdowns will have increased this addiction a million times for obvious reasons. Addictions to alcohol overindulgence and drugs are another way that Wetiko entraps consciousness to attach to its own. Both are symptoms of low-vibrational psychological distress which alcoholism and drug addiction further compound. Do we think it's really a coincidence that access to them is made so easy while potions that can take people into realms beyond the simulation are banned and illegal? I have explored smartphone addiction in other books, the scale is mind-blowing, and that level of addiction does not come without help. Tech companies that make these phones are Wetiko and they will have no qualms about destroying the minds of children. We are seeing again with these companies the Wetiko perceptual combination of psychopathic enforcers and weak and meek unquestioning compliance by the rank and file.

The global Smart Grid is the Wetiko Grid and it is crucial to complete the Cult endgame. The simulation is radiation and we are being deluged with technological radiation on a devastating scale. Wetiko frauds like Elon Musk serve Cult interests while occasionally criticising them to maintain his street-cred. 5G and other forms of Wi-Fi are being directed at the earth from space on a volume and scale that goes on increasing by the day. Elon Musk's (officially) SpaceX Starlink project is in the process of putting tens of thousands of satellites in low orbit to cover every inch of the planet with 5G and other Wi-Fi to create Kurzweil's global 'cloud' to which the

human mind is planned to be attached very soon. SpaceX has approval to operate 12,000 satellites with more than 1,300 launched at the time of writing and applications filed for *30,000* more. Other operators in the Wi-Fi, 5G, low-orbit satellite market include OneWeb (UK), Telesat (Canada), and AST & Science (US). Musk tells us that AI could be the end of humanity and then launches a company called Neuralink to connect the human brain to computers. Musk's (in theory) Tesla company is building electric cars and the driverless vehicles of the smart control grid. As frauds and bullshitters go Elon Musk in my opinion is Major League.

5G and technological radiation in general are destructive to human health, genetics and psychology and increasing the strength of artificial radiation underpins the five-sense perceptual bubbles which are themselves expressions of radiation or electromagnetism. Freedom activist John Whitehead was so right with his 'databit by databit, we are building our own electronic concentration camps'. The Smart Grid and 5G is a means to control the human mind and infuse perceptual information into The Field to influence anyone in sync with its frequency. You can change perception and behaviour en masse if you can manipulate the population into those levels of frequency and this is happening all around us today. The arrogance of Musk and his fellow Cult operatives knows no bounds in the way that we see with Gates. Musk's satellites are so many in number already they are changing the night sky when viewed from Earth. The astronomy community has complained about this and they have seen nothing yet. Some consequences of Musk's Wetiko hubris include: Radiation; visible pollution of the night sky; interference with astronomy and meteorology; ground and water pollution from intensive use of increasingly many spaceports; accumulating space debris; continual deorbiting and burning up of aging satellites, polluting the atmosphere with toxic dust and smoke; and ever-increasing likelihood of collisions. A collective public open letter of complaint to Musk said:

> We are writing to you … because SpaceX is in process of surrounding the Earth with a network of thousands of satellites whose very purpose is to irradiate every square inch of the

Earth. SpaceX, like everyone else, is treating the radiation as if it were not there. As if the mitochondria in our cells do not depend on electrons moving undisturbed from the food we digest to the oxygen we breathe.

As if our nervous systems and our hearts are not subject to radio frequency interference like any piece of electronic equipment. As if the cancer, diabetes, and heart disease that now afflict a majority of the Earth's population are not metabolic diseases that result from interference with our cellular machinery. As if insects everywhere, and the birds and animals that eat them, are not starving to death as a result.

People like Musk and Gates believe in their limitless Wetiko arrogance that they can do whatever they like to the world because they own it. Consequences for humanity are irrelevant. It's absolutely time that we stopped taking this shit from these self-styled masters of the Earth when you consider where this is going.

Why is the Cult so anti-human?

I hear this question often: Why would they do this when it will affect them, too? Ah, but will it? Who is this *them*? Forget their bodies. They are just vehicles for Wetiko consciousness. When you break it all down to the foundations we are looking at a state of severely distorted consciousness targeting another state of consciousness for assimilation. The rest is detail. The simulation is the fly-trap in which unique sensations of the five senses create a cycle of addiction called reincarnation. Renegade Minds see that everything which happens in our reality is a smaller version of the whole picture in line with the holographic principle. Addiction to the radiation of smart technology is a smaller version of addiction to the whole simulation. Connecting the body/brain to AI is taking that addiction on a giant step further to total ongoing control by assimilating human incarnate consciousness into Wetiko. I have watched during the 'Covid' hoax how many are becoming ever more profoundly attached to Wetiko's perceptual calling cards of aggressive response to any other point of view ('There is no other god but me'), psychopathic lack of compassion and empathy, and servile submission to the narrative and will of authority. Wetiko is the psychopaths *and* subservience to psychopaths. The Cult of Wetiko is

so anti-human because it is *not* human. It embarked on a mission to destroy human by targeting everything that it means to be human and to survive as human. 'Covid' is not the end, just a means to an end. The Cult with its Wetiko consciousness is seeking to change Earth systems, including the atmosphere, to suit them, not humans. The gathering bombardment of 5G alone from ground and space is dramatically changing The Field with which the five senses interact. There is so much more to come if we sit on our hands and hope it will all go away. It is not meant to go away. It is meant to get ever more extreme and we need to face that while we still can – just.

Carbon dioxide is the gas of life. Without that human is over. Kaput, gone, history. No natural world, no human. The Cult has created a cock and bull story about carbon dioxide and climate change to justify its reduction to the point where Gates and the ignoramus Biden 'climate chief' John Kerry want to suck it out of the atmosphere. Kerry wants to do this because his master Gates does. Wetikos have made the gas of life a demon with the usual support from the Wokers of Extinction Rebellion and similar organisations and the bewildered puppet-child that is Greta Thunberg who was put on the world stage by Klaus Schwab and the World Economic Forum. The name Extinction Rebellion is both ironic and as always Wetiko inversion. The gas that we need to survive must be reduced to save us from extinction. The most basic need of human is oxygen and we now have billions walking around in face nappies depriving body and brain of this essential requirement of human existence. More than that 5G at 60 gigahertz interacts with the oxygen molecule to reduce the amount of oxygen the body can absorb into the bloodstream. The obvious knock-on consequences of that for respiratory and cognitive problems and life itself need no further explanation. Psychopaths like Musk are assembling a global system of satellites to deluge the human atmosphere with this insanity. The man should be in jail. Here we have two most basic of human needs, oxygen and carbon dioxide, being dismantled.

Two others, water and food, are getting similar treatment with the United Nations Agendas 21 and 2030 – the Great Reset – planning to

centrally control all water and food supplies. People will not even own rain water that falls on their land. Food is affected at the most basic level by reducing carbon dioxide. We have genetic modification or GMO infiltrating the food chain on a mass scale, pesticides and herbicides polluting the air and destroying the soil. Freshwater fish that provide livelihoods for 60 million people and feed hundreds of millions worldwide are being 'pushed to the brink' according the conservationists while climate change is the only focus. Now we have Gates and Schwab wanting to dispense with current food sources all together and replace them with a synthetic version which the Wetiko Cult would control in terms of production and who eats and who doesn't. We have been on the Totalitarian Tiptoe to this for more than 60 years as food has become ever more processed and full of chemical shite to the point today when it's not natural food at all. As Dr Tom Cowan says: 'If it has a label don't eat it.' Bill Gates is now the biggest owner of farmland in the United States and he does nothing without an ulterior motive involving the Cult. Klaus Schwab wrote: 'To feed the world in the next 50 years we will need to produce as much food as was produced in the last 10,000 years … food security will only be achieved, however, if regulations on genetically modified foods are adapted to reflect the reality that gene editing offers a precise, efficient and safe method of improving crops.' Liar. People and the world are being targeted with aluminium through vaccines, chemtrails, food, drink cans, and endless other sources when aluminium has been linked to many health issues including dementia which is increasing year after year. Insects, bees and wildlife essential to the food chain are being deleted by pesticides, herbicides and radiation which 5G is dramatically increasing with 6G and 7G to come. The pollinating bee population is being devastated while wildlife including birds, dolphins and whales are having their natural radar blocked by the effects of ever-increasing radiation. In the summer windscreens used to be splattered with insects so numerous were they. It doesn't happen now. Where have they gone?

Synthetic everything

The Cult is introducing genetically-modified versions of trees, plants and insects including a Gates-funded project to unleash hundreds of millions of genetically-modified, lab-altered and patented male mosquitoes to mate with wild mosquitoes and induce genetic flaws that cause them to die out. Clinically-insane Gates-funded Japanese researchers have developed mosquitos that spread vaccine and are dubbed 'flying vaccinators'. Gates is funding the modification of weather patterns in part to sell the myth that this is caused by carbon dioxide and he's funding geoengineering of the skies to change the atmosphere. Some of this came to light with the Gates-backed plan to release tonnes of chalk into the atmosphere to 'deflect the Sun and cool the planet'. Funny how they do this while the heating effect of the Sun is not factored into climate projections focussed on carbon dioxide. The reason is that they want to reduce carbon dioxide (so don't mention the Sun), but at the same time they do want to reduce the impact of the Sun which is so essential to human life and health. I have mentioned the sun-cholesterol-vitamin D connection as they demonise the Sun with warnings about skin cancer (caused by the chemicals in sun cream they tell you to splash on). They come from the other end of the process with statin drugs to reduce cholesterol that turns sunlight into vitamin D. A lack of vitamin D leads to a long list of health effects and how vitamin D levels must have fallen with people confined to their homes over 'Covid'. Gates is funding other forms of geoengineering and most importantly chemtrails which are dropping heavy metals, aluminium and self-replicating nanotechnology onto the Earth which is killing the natural world. See *Everything You Need To Know, But Have Never Been Told* for the detailed background to this.

Every human system is being targeted for deletion by a force that's not human. The Wetiko Cult has embarked on the process of transforming the human body from biological to synthetic biological as I have explained. Biological is being replaced by the artificial and synthetic – Archontic 'countermimicry' – right across human society. The plan eventually is to dispense with the human body altogether

and absorb human consciousness – which it wouldn't really be by then – into cyberspace (the simulation which is Wetiko/Yaldabaoth). Preparations for that are already happening if people would care to look. The alternative media rightly warns about globalism and 'the globalists', but this is far bigger than that and represents the end of the human race as we know it. The 'bad copy' of prime reality that Gnostics describe was a bad copy of harmony, wonder and beauty to start with before Wetiko/Yaldabaoth set out to change the simulated 'copy' into something very different. The process was slow to start with. Entrapped humans in the simulation timeline were not technologically aware and they had to be brought up to intellectual speed while being suppressed spiritually to the point where they could build their own prison while having no idea they were doing so. We have now reached that stage where technological intellect has the potential to destroy us and that's why events are moving so fast. Central American shaman Don Juan Matus said:

> Think for a moment, and tell me how you would explain the contradictions between the intelligence of man the engineer and the stupidity of his systems of belief, or the stupidity of his contradictory behaviour. Sorcerers believe that the predators have given us our systems of beliefs, our ideas of good and evil; our social mores. They are the ones who set up our dreams of success or failure. They have given us covetousness, greed, and cowardice. It is the predator who makes us complacent, routinary, and egomaniacal.
>
> In order to keep us obedient and meek and weak, the predators engaged themselves in a stupendous manoeuvre – stupendous, of course, from the point of view of a fighting strategist; a horrendous manoeuvre from the point of those who suffer it. They gave us their mind. The predators' mind is baroque, contradictory, morose, filled with the fear of being discovered any minute now.

For 'predators' see Wetiko, Archons, Yaldabaoth, Jinn, and all the other versions of the same phenomenon in cultures and religions all over the world. The theme is always the same because it's true and it's real. We have reached the point where we have to deal with it. The question is – how?

Don't fight – walk away

I thought I'd use a controversial subheading to get things moving in terms of our response to global fascism. What do you mean 'don't fight'? What do you mean 'walk away'? We've got to fight. We can't walk away. Well, it depends what we mean by fight and walk away. If fighting means physical combat we are playing Wetiko's game and falling for its trap. It wants us to get angry, aggressive, and direct hate and hostility at the enemy we think we must fight. Every war, every battle, every conflict, has been fought with Wetiko leading both sides. It's what it does. Wetiko wants a fight, anywhere, any place. Just hit me, son, so I can hit you back. Wetiko hits Wetiko and Wetiko hits Wetiko in return. I am very forthright as you can see in exposing Wetikos of the Cult, but I don't hate them. I refuse to hate them. It's what they want. What you hate you become. What you *fight* you become. Wokers, 'anti-haters' and 'anti-fascists' prove this every time they reach for their keyboards or don their balaclavas. By walk away I mean to disengage from Wetiko which includes ceasing to cooperate with its tyranny. Paul Levy says of Wetiko:

> The way to 'defeat' evil is not to try to destroy it (for then, in playing evil's game, we have already lost), but rather, to find the invulnerable place within ourselves where evil is unable to vanquish us – this is to truly 'win' our battle with evil.

Wetiko is everywhere in human society and it's been on steroids since the 'Covid' hoax. Every shouting match over wearing masks has Wetiko wearing a mask and Wetiko not wearing one. It's an electrical circuit of push and resist, push and resist, with Wetiko pushing *and* resisting. Each polarity is Wetiko empowering itself. Dictionary definitions of 'resist' include 'opposing, refusing to accept or comply with' and the word to focus on is 'opposing'. What form does this take – setting police cars alight or 'refusing to accept or comply with'? The former is Wetiko opposing Wetiko while the other points the way forward. This is the difference between those aggressively demanding that government fascism must be obeyed who stand in stark contrast to the great majority of Pushbackers. We saw this clearly with a march by thousands of Pushbackers against lockdown in London followed days later by a Woker-hijacked

protest in Bristol in which police cars were set on fire. Masks were virtually absent in London and widespread in Bristol. Wetiko wants lockdown on every level of society and infuses its aggression to police it through its unknowing stooges. Lockdown protesters are the ones with the smiling faces and the hugs, The two blatantly obvious states of being – getting more obvious by the day – are the result of Wokers and their like becoming ever more influenced by the simulation Field of Wetiko and Pushbackers ever more influenced by The Field of a far higher vibration beyond the simulation. Wetiko can't invade the heart which is where most lockdown opponents are coming from. It's the heart that allows them to see through the lies to the truth in ways I will be highlighting.

Renegade Minds know that calmness is the place from which wisdom comes. You won't find wisdom in a hissing fit and wisdom is what we need in abundance right now. Calmness is not weakness – you don't have to scream at the top of your voice to be strong. Calmness is indeed a sign of strength. 'No' means I'm not doing it. *NOOOO!!!* doesn't mean you're not doing it even more. Volume does not advance 'No – I'm not doing it'. You are just not doing it. Wetiko possessed and influenced don't know how to deal with that. Wetiko wants a fight and we should not give it one. What it needs more than anything is our *cooperation* and we should not give that either. Mass rallies and marches are great in that they are a visual representation of feeling, but if it ends there they are irrelevant. You demand that Wetikos act differently? Well, they're not going to are they? They are Wetikos. We don't need to waste our time demanding that something doesn't happen when that will make no difference. We need to delete the means that *allows* it to happen. This, invariably, is our cooperation. You can demand a child stop firing a peashooter at the dog or you can refuse to buy the peashooter. If you provide the means you are cooperating with the dog being smacked on the nose with a pea. How can the authorities enforce mask-wearing if millions in a country refuse? What if the 74 million Pushbackers that voted for Trump in 2020 refused to wear masks, close their businesses or stay in their homes. It would be unenforceable. The

few control the many through the compliance of the many and that's always been the dynamic be it 'Covid' regulations or the Roman Empire. I know people can find it intimidating to say no to authority or stand out in a crowd for being the only one with a face on display; but it has to be done or it's over. I hope I've made clear in this book that where this is going will be far more intimidating than standing up now and saying 'No' – I will not cooperate with my own enslavement and that of my children. There might be consequences for some initially, although not so if enough do the same. The question that must be addressed is what is going to happen if we don't? It is time to be strong and unyieldingly so. No means no. Not here and there, but *everywhere* and *always*. I have refused to wear a mask and obey all the other nonsense. I will not comply with tyranny. I repeat: Fascism is not imposed by fascists – there are never enough of them. Fascism is imposed by the population acquiescing to fascism. *I will not do it*. I will die first, or my body will. Living meekly under fascism is a form of death anyway, the death of the spirit that Martin Luther King described.

Making things happen

We must not despair. This is not over till it's over and it's far from that. The 'fat lady' must refuse to sing. The longer the 'Covid' hoax has dragged on and impacted on more lives we have seen an awakening of phenomenal numbers of people worldwide to the realisation that what they have believed all their lives is not how the world really is. Research published by the system-serving University of Bristol and King's College London in February, 2021, concluded: 'One in every 11 people in Britain say they trust David Icke's take on the coronavirus pandemic.' It will be more by now and we have gathering numbers to build on. We must urgently progress from seeing the scam to ceasing to cooperate with it. Prominent German lawyer Reiner Fuellmich, also licenced to practice law in America, is doing a magnificent job taking the legal route to bring the psychopaths to justice through a second Nuremberg tribunal for crimes against humanity. Fuellmich has an impressive record of

beating the elite in court and he formed the German Corona Investigative Committee to pursue civil charges against the main perpetrators with a view to triggering criminal charges. Most importantly he has grasped the foundation of the hoax – the PCR test not testing for the 'virus' – and Christian Drosten is therefore on his charge sheet along with Gates frontman Tedros at the World Health Organization. Major players must be not be allowed to inflict their horrors on the human race without being brought to book. A life sentence must follow for Bill Gates and the rest of them. A group of researchers has also indicted the government of Norway for crimes against humanity with copies sent to the police and the International Criminal Court. The lawsuit cites participation in an internationally-planned false pandemic and violation of international law and human rights, the European Commission's definition of human rights by coercive rules, Nuremberg and Hague rules on fundamental human rights, and the Norwegian constitution. We must take the initiative from hereon and not just complain, protest and react.

There are practical ways to support vital mass non-cooperation. Organising in numbers is one. Lockdown marches in London in the spring in 2021 were mass non-cooperation that the authorities could not stop. There were too many people. Hundreds of thousands walked the London streets in the centre of the road for mile after mile while the Face-Nappies could only look on. They were determined, but calm, and just *did it* with no histrionics and lots of smiles. The police were impotent. Others are organising group shopping without masks for mutual support and imagine if that was happening all over. Policing it would be impossible. If the store refuses to serve people in these circumstances they would be faced with a long line of trolleys full of goods standing on their own and everything would have to be returned to the shelves. How would they cope with that if it kept happening? I am talking here about moving on from complaining to being pro-active; from watching things happen to making things happen. I include in this our relationship with the police. The behaviour of many Face-Nappies

has been disgraceful and anyone who thinks they would never find concentration camp guards in the 'enlightened' modern era have had that myth busted big-time. The period and setting may change – Wetikos never do. I watched film footage from a London march in which a police thug viciously kicked a protestor on the floor who had done nothing. His fellow Face-Nappies stood in a ring protecting him. What he did was a criminal assault and with a crowd far outnumbering the police this can no longer be allowed to happen unchallenged. I get it when people chant 'shame on you' in these circumstances, but that is no longer enough. They *have* no shame those who do this. Crowds needs to start making a citizen's arrest of the police who commit criminal offences and brutally attack innocent people and defenceless women. A citizen's arrest can be made under section 24A of the UK Police and Criminal Evidence (PACE) Act of 1984 and you will find something similar in other countries. I prefer to call it a Common Law arrest rather than citizen's for reasons I will come to shortly. Anyone can arrest a person committing an indictable offence or if they have reasonable grounds to suspect they are committing an indictable offence. On both counts the attack by the police thug would have fallen into this category. A citizen's arrest can be made to stop someone:

- Causing physical injury to himself or any other person
- Suffering physical injury
- Causing loss of or damage to property
- Making off before a constable can assume responsibility for him

A citizen's arrest may also be made to prevent a breach of the peace under Common Law and if they believe a breach of the peace will happen or anything related to harm likely to be done or already done in their presence. This is the way to go I think – the Common Law version. If police know that the crowd and members of the public will no longer be standing and watching while they commit

their thuggery and crimes they will think twice about acting like Brownshirts and Blackshirts.

Common Law – common sense

Mention of Common Law is very important. Most people think the law is the law as in one law. This is not the case. There are two bodies of law, Common Law and Statute Law, and they are not the same. Common Law is founded on the simple premise of do no harm. It does not recognise victimless crimes in which no harm is done while Statute Law does. There is a Statute Law against almost everything. So what is Statute Law? Amazingly it's the law of the *sea* that was brought ashore by the Cult to override the law of the land which is Common Law. They had no right to do this and as always they did it anyway. They had to. They could not impose their will on the people through Common Law which only applies to do no harm. How could you stitch up the fine detail of people's lives with that? Instead they took the law of the sea, or Admiralty Law, and applied it to the population. Statute Law refers to all the laws spewing out of governments and their agencies including all the fascist laws and regulations relating to 'Covid'. The key point to make is that Statute Law is *contract law*. It only applies between *contracting* corporations. Most police officers don't even know this. They have to be kept in the dark, too. Long ago when merchants and their sailing ships began to trade with different countries a contractual law was developed called Admiralty Law and other names. Again it only applied to *contracts* agreed between *corporate* entities. If there is no agreed contract the law of the sea had no jurisdiction *and that still applies to its new alias of Statute Law*. The problem for the Cult when the law of the sea was brought ashore was an obvious one. People were not corporations and neither were government entities. To overcome the latter they made governments and all associated organisations corporations. All the institutions are *private corporations* and I mean governments and their agencies, local councils, police, courts, military, US states, the whole lot. Go to the

Dun and Bradstreet corporate listings website for confirmation that they are all corporations. You are arrested by a private corporation called the police by someone who is really a private security guard and they take you to court which is another private corporation. Neither have jurisdiction over you unless you consent and *contract* with them. This is why you hear the mantra about law enforcement policing by *consent* of the people. In truth the people 'consent' only in theory through monumental trickery.

Okay, the Cult overcame the corporate law problem by making governments and institutions corporate entities; but what about people? They are not corporations are they? Ah ... well in a sense, and *only* a sense, they are. Not people exactly – the illusion of people. The Cult creates a corporation in the name of everyone at the time that their birth certificate is issued. Note birth/ *berth* certificate and when you go to court under the law of the sea on land you stand in a *dock*. These are throwbacks to the origin. My Common Law name is David Vaughan Icke. The name of the corporation created by the government when I was born is called Mr David Vaughan Icke usually written in capitals as MR DAVID VAUGHAN ICKE. That is not me, the living, breathing man. It is a fictitious corporate entity. The trick is to make you think that David Vaughan Icke and MR DAVID VAUGHAN ICKE are the same thing. *They are not*. When police charge you and take you to court they are prosecuting the corporate entity and not the living, breathing, man or woman. They have to trick you into identifying as the corporate entity and contracting with them. Otherwise they have no jurisdiction. They do this through a language known as legalese. Lawful and legal are not the same either. Lawful relates to Common Law and legal relates to Statute Law. Legalese is the language of Statue Law which uses terms that mean one thing to the public and another in legalese. Notice that when a police officer tells someone why they are being charged he or she will say at the end: 'Do you understand?' To the public that means 'Do you comprehend?' In legalese it means 'Do you stand under me?' Do you stand under my authority? If you say

yes to the question you are unknowingly agreeing to give them jurisdiction over you in a contract between two corporate entities.

This is a confidence trick in every way. Contracts have to be agreed between informed parties and if you don't know that David Vaughan Icke is agreeing to be the corporation MR DAVID VAUGHAN ICKE you cannot knowingly agree to contract. They are deceiving you and another way they do this is to ask for proof of identity. You usually show them a driving licence or other document on which your corporate name is written. In doing so you are accepting that you are that corporate entity when you are not. Referring to yourself as a 'person' or 'citizen' is also identifying with your corporate fiction which is why I made the Common Law point about the citizen's arrest. If you are approached by a police officer you identify yourself immediately as a living, breathing, man or woman and say 'I do not consent, I do not contract with you and I do not understand' or stand under their authority. I have a Common Law birth certificate as a living man and these are available at no charge from commonlawcourt.com. Businesses registered under the Statute Law system means that its laws apply. There are, however, ways to run a business under Common Law. Remember all 'Covid' laws and regulations are Statute Law – the law of *contracts* and you do not have to contract. This doesn't mean that you can kill someone and get away with it. Common Law says do no harm and that applies to physical harm, financial harm etc. Police are employees of private corporations and there needs to be a new system of non-corporate Common Law constables operating outside the Statute Law system. If you go to davidicke.com and put Common Law into the search engine you will find videos that explain Common Law in much greater detail. It is definitely a road we should walk.

With all my heart

I have heard people say that we are in a spiritual war. I don't like the term 'war' with its Wetiko dynamic, but I know what they mean. Sweep aside all the bodily forms and we are in a situation in which two states of consciousness are seeking very different realities.

Wetiko wants upheaval, chaos, fear, suffering, conflict and control. The other wants love, peace, harmony, fairness and freedom. That's where we are. We should not fall for the idea that Wetiko is all-powerful and there's nothing we can do. Wetiko is not all-powerful. It's a joke, pathetic. It doesn't have to be, but it has made that choice for now. A handful of times over the years when I have felt the presence of its frequency I have allowed it to attach briefly so I could consciously observe its nature. The experience is not pleasant, the energy is heavy and dark, but the ease with which you can kick it back out the door shows that its real power is in persuading us that it has power. It's all a con. Wetiko is a con. It's a trickster and not a power that can control us if we unleash our own. The con is founded on manipulating humanity to give its power to Wetiko which recycles it back to present the illusion that it has power when its power is *ours* that we gave away. This happens on an energetic level and plays out in the world of the seen as humanity giving its power to Wetiko authority which uses that power to control the population when the power is only the power the population has handed over. How could it be any other way for billions to be controlled by a relative few? I have had experiences with people possessed by Wetiko and again you can kick its arse if you do it with an open heart. Oh yes – the *heart* which can transform the world of perceived 'matter'.

We are receiver-transmitters and processors of information, but what information and where from? Information is processed into perception in three main areas – the brain, the heart and the belly. These relate to thinking, knowing, and emotion. Wetiko wants us to be head and belly people which means we think within the confines of the Matrix simulation and low-vibrational emotional reaction scrambles balance and perception. A few minutes on social media and you see how emotion is the dominant force. Woke is all emotion and is therefore thought-free and fact-free. Our heart is something different. It *knows* while the head *thinks* and has to try to work it out because it doesn't know. The human energy field has seven prime vortexes which connect us with wider reality (Fig 23). Chakra means

'wheels of light' in the Sanskrit language of ancient India. The main ones are: The crown chakra on top of the head; brow (or 'third eye') chakra in the centre of the forehead; throat chakra; heart chakra in the centre of the chest; solar plexus chakra below the sternum; sacral chakra beneath the navel; and base chakra at the bottom of the spine. Each one has a particular function or functions. We feel anxiety and nervousness in the belly where the sacral chakra is located and this processes emotion that can affect the colon to give people 'the shits' or make them 'shit scared' when they are nervous. Chakras all play an important role, but the Mr and Mrs Big is the heart chakra which sits at the centre of the seven, above the chakras that connect us to the 'physical' and below those that connect with higher realms (or at least should). Here in the heart chakra we feel love, empathy and compassion – 'My heart goes out to you'. Those with closed hearts become literally 'heart-less' in their attitudes and behaviour (see Bill Gates). Native Americans portrayed Wetiko with what Paul Levy calls a 'frigid, icy heart, devoid of mercy' (see Bill Gates).



Figure 23: The chakra system which interpenetrates the human energy field. The heart chakra is the governor – or should be.

Wetiko trembles at the thought of heart energy which it cannot infiltrate. The frequency is too high. What it seeks to do instead is close the heart chakra vortex to block its perceptual and energetic influence. Psychopaths have 'hearts of stone' and emotionally-damaged people have 'heartache' and 'broken hearts'. The astonishing amount of heart disease is related to heart chakra

disruption with its fundamental connection to the 'physical' heart. Dr Tom Cowan has written an outstanding book challenging the belief that the heart is a pump and making the connection between the 'physical' and spiritual heart. Rudolph Steiner who was way ahead of his time said the same about the fallacy that the heart is a pump. *What*? The heart is not a pump? That's crazy, right? Everybody knows that. Read Cowan's *Human Heart, Cosmic Heart* and you will realise that the very idea of the heart as a pump is ridiculous when you see the evidence. How does blood in the feet so far from the heart get pumped horizontally up the body by the heart?? Cowan explains in the book the real reason why blood moves as it does. Our 'physical' heart is used to symbolise love when the source is really the heart vortex or spiritual heart which is our most powerful energetic connection to 'out there' expanded consciousness. That's why we feel *knowing* – intuitive knowing – in the centre of the chest. Knowing doesn't come from a process of thoughts leading to a conclusion. It is there in an instant all in one go. Our heart knows because of its connection to levels of awareness that *do* know. This is the meaning and source of intuition – intuitive *knowing*.

For the last more than 30 years of uncovering the global game and the nature of reality my heart has been my constant antenna for truth and accuracy. An American intelligence insider once said that I had quoted a disinformer in one of my books and yet I had only quoted the part that was true. He asked: 'How do you do that?' By using my heart antenna was the answer and anyone can do it. Heart-centred is how we are meant to be. With a closed heart chakra we withdraw into a closed mind and the bubble of five-sense reality. If you take a moment to focus your attention on the centre of your chest, picture a spinning wheel of light and see it opening and expanding. You will feel it happening, too, and perceptions of the heart like joy and love as the heart impacts on the mind as they interact. The more the chakra opens the more you will feel expressions of heart consciousness and as the process continues, and becomes part of you, insights and knowings will follow. An open

heart is connected to that level of awareness that knows all is *One*. You will see from its perspective that the fault-lines that divide us are only illusions to control us. An open heart does not process the illusions of race, creed and sexuality except as brief experiences for a consciousness that is all. Our heart does not see division, only unity (Figs 24 and 25). There's something else, too. Our hearts love to laugh. Mark Twain's quote that says 'The human race has one really effective weapon, and that is laughter' is really a reference to the heart which loves to laugh with the joy of knowing the true nature of infinite reality and that all the madness of human society is an illusion of the mind. Twain also said: 'Against the assault of laughter nothing can stand.' This is so true of Wetiko and the Cult. Their insecurity demands that they be taken seriously and their power and authority acknowledged and feared. We should do nothing of the sort. We should not get aggressive or fearful which their insecurity so desires. We should laugh in their face. Even in their no-face as police come over in their face-nappies and expect to be taken seriously. They don't take themselves seriously looking like that so why should we? Laugh in the face of intimidation. Laugh in the face of tyranny. You will see by its reaction that you have pressed all of its buttons. Wetiko does not know what to do in the face of laughter or when its targets refuse to concede their joy to fear. We have seen many examples during the 'Covid' hoax when people have expressed their energetic power and the string puppets of Wetiko retreat with their tail limp between their knees. Laugh – the world is bloody mad after all and if it's a choice between laughter and tears I know which way I'm going.



Figure 24: Head consciousness without the heart sees division and everything apart from everything else.



Figure 25: Heart consciousness sees everything as One.

'Vaccines' and the soul

The foundation of Wetiko/Archon control of humans is the separation of incarnate five-sense mind from the infinite 'I' and closing the heart chakra where the True 'I' lives during a human life. The goal has been to achieve complete separation in both cases. I was interested therefore to read an account by a French energetic healer of what she said she experienced with a patient who had been given the 'Covid' vaccine. Genuine energy healers can sense information and consciousness fields at different levels of being which are referred to as 'subtle bodies'. She described treating the patient who later returned after having, without the healer's knowledge, two doses of the 'Covid vaccine'. The healer said:

I noticed immediately the change, very heavy energy emanating from [the] subtle bodies. The scariest thing was when I was working on the heart chakra, I connected with her soul: it was detached from the physical body, it had no contact and it was, as if it was floating in a state of total confusion: a damage to the consciousness that loses contact with the physical body, i.e. with our biological machine, there is no longer any communication between them.

I continued the treatment by sending light to the heart chakra, the soul of the person, but it seemed that the soul could no longer receive any light, frequency or energy. It was a very powerful experience for me. Then I understood that this substance is indeed used to detach consciousness so that this consciousness can no longer interact through this body that it possesses in life, where there is no longer any contact, no frequency, no light, no more energetic balance or mind.

This would create a human that is rudderless and at the extreme almost zombie-like operating with a fractional state of consciousness at the mercy of Wetiko. I was especially intrigued by what the healer said in the light of the prediction by the highly-informed Rudolf Steiner more than a hundred years ago. He said:

In the future, we will eliminate the soul with medicine. Under the pretext of a 'healthy point of view', there will be a vaccine by which the human body will be treated as soon as possible directly at birth, so that the human being cannot develop the thought of the existence of soul and Spirit. To materialistic doctors will be entrusted the task of removing the soul of humanity.

As today, people are vaccinated against this disease or that disease, so in the future, children will be vaccinated with a substance that can be produced precisely in such a way that people, thanks to this vaccination, will be immune to being subjected to the 'madness' of spiritual life. He would be extremely smart, but he would not develop a conscience, and that is the true goal of some materialistic circles.

Steiner said the vaccine would detach the physical body from the etheric body (subtle bodies) and 'once the etheric body is detached the relationship between the universe and the etheric body would become extremely unstable, and man would become an automaton'. He said 'the physical body of man must be polished on this Earth by spiritual will – so the vaccine becomes a kind of arymanique (Wetiko) force' and 'man can no longer get rid of a given materialistic feeling'. Humans would then, he said, become 'materialistic of constitution and can no longer rise to the spiritual'. I have been writing for years about DNA being a receiver-transmitter of information that connects us to other levels of reality and these 'vaccines' changing DNA can be likened to changing an antenna and what it can transmit and receive. Such a disconnection would clearly lead to changes in personality and perception. Steiner further predicted the arrival of AI. Big Pharma 'Covid vaccine' makers, expressions of Wetiko, are testing their DNA-manipulating evil on children as I write with a view to giving the 'vaccine' to babies. If it's a soul-body disconnector – and I say that it is or can be – every child would be disconnected from 'soul' at birth and the 'vaccine' would create a closed system in which spiritual guidance from the greater self would play no part. This has been the ambition of Wetiko all

along. A Pentagon video from 2005 was leaked of a presentation explaining the development of vaccines to change behaviour by their effect on the brain. Those that believe this is not happening with the 'Covid' genetically-modifying procedure masquerading as a 'vaccine' should make an urgent appointment with Naivety Anonymous. Klaus Schwab wrote in 2018:

> Neurotechnologies enable us to better influence consciousness and thought and to understand many activities of the brain. They include decoding what we are thinking in fine levels of detail through new chemicals and interventions that can influence our brains to correct for errors or enhance functionality.

The plan is clear and only the heart can stop it. With every heart that opens, every mind that awakens, Wetiko is weakened. Heart and love are far more powerful than head and hate and so nothing like a majority is needed to turn this around.

Beyond the Phantom

Our heart is the prime target of Wetiko and so it must be the answer to Wetiko. We *are* our heart which is part of one heart, the infinite heart. Our heart is where the true self lives in a human life behind firewalls of five-sense illusion when an imposter takes its place – *Phantom Self*; but our heart waits patiently to be set free any time we choose to see beyond the Phantom, beyond Wetiko. A Wetikoed Phantom Self can wreak mass death and destruction while the love of forever is locked away in its heart. The time is here to unleash its power and let it sweep away the fear and despair that is Wetiko. Heart consciousness does not seek manipulated, censored, advantage for its belief or religion, its activism and desires. As an expression of the One it treats all as One with the same rights to freedom and opinion. Our heart demands fairness for itself no more than for others. From this unity of heart we can come together in mutual support and transform this Wetikoed world into what reality is meant to be – a place of love, joy, happiness, fairness, justice and freedom. Wetiko has another agenda and that's why the world is as

it is, but enough of this nonsense. Wetiko can't stay where hearts are open and it works so hard to keep them closed. Fear is its currency and its food source and love in its true sense has no fear. Why would love have fear when it knows it is *All That Is, Has Been, And Ever Can Be* on an eternal exploration of all possibility? Love in this true sense is not the physical attraction that passes for love. This can be an expression of it, yes, but Infinite Love, a love without condition, goes far deeper to the core of all being. It *is* the core of all being. Infinite realty was born from love beyond the illusions of the simulation. Love infinitely expressed is the knowing that all is One and the swiftly-passing experience of separation is a temporary hallucination. You cannot disconnect from Oneness; you can only *perceive* that you have and withdraw from its influence. This is the most important of all perception trickery by the mind parasite that is Wetiko and the foundation of all its potential for manipulation.

If we open our hearts, open the sluice gates of the mind, and redefine self-identity amazing things start to happen. Consciousness expands or contracts in accordance with self-identity. When true self is recognised as infinite awareness and label self – Phantom Self – is seen as only a series of brief experiences life is transformed. Consciousness expands to the extent that self-identity expands and everything changes. You see unity, not division, the picture, not the pixels. From this we can play the long game. No more is an experience something in and of itself, but a fleeting moment in the eternity of forever. Suddenly people in uniform and dark suits are no longer intimidating. Doing what your heart knows to be right is no longer intimidating and consequences for those actions take on the same nature of a brief experience that passes in the blink of an infinite eye. Intimidation is all in the mind. Beyond the mind there is no intimidation.

An open heart does not consider consequences for what it knows to be right. To do so would be to consider not doing what it knows to be right and for a heart in its power that is never an option. The Renegade Mind is really the Renegade Heart. Consideration of consequences will always provide a getaway car for the mind and

the heart doesn't want one. What is right in the light of what we face today is to stop cooperating with Wetiko in all its forms and to do it without fear or compromise. You cannot compromise with tyranny when tyranny always demands more until it has everything. Life is your perception and you are your destiny. Change your perception and you change your life. Change collective perception and we change the world.

Come on people … One human family, One heart, One goal … *FREEEEEEDOM*!

We must settle for nothing less.

Postscript

The big scare story as the book goes to press is the 'Indian' variant and the world is being deluged with propaganda about the 'Covid catastrophe' in India which mirrors in its lies and misrepresentations what happened in Italy before the first lockdown in 2020.

The *New York Post* published a picture of someone who had 'collapsed in the street from Covid' in India in April, 2021, which was actually taken during a gas leak in May, 2020. Same old, same old. Media articles in mid-February were asking why India had been so untouched by 'Covid' and then as their vaccine rollout gathered pace the alleged 'cases' began to rapidly increase. Indian 'Covid vaccine' maker Bharat Biotech was funded into existence by the Bill and Melinda Gates Foundation (the pair announced their divorce in May, 2021, which is a pity because they so deserve each other). The Indian 'Covid crisis' was ramped up by the media to terrify the world and prepare people for submission to still more restrictions. The scam that worked the first time was being repeated only with far more people seeing through the deceit. Davidicke.com and Ickonic.com have sought to tell the true story of what is happening by talking to people living through the Indian nightmare which has nothing to do with 'Covid'. We posted a letter from 'Alisha' in Pune who told a very different story to government and media mendacity. She said scenes of dying people and overwhelmed hospitals were designed to hide what was really happening – genocide and starvation. Alisha said that millions had already died of starvation during the ongoing lockdowns while government and media were lying and making it look like the 'virus':

Restaurants, shops, gyms, theatres, basically everything is shut. The cities are ghost towns. Even so-called 'essential' businesses are only open till 11am in the morning. You basically have just an hour to buy food and then your time is up.

Inter-state travel and even inter-district travel is banned. The cops wait at all major crossroads to question why you are traveling outdoors or to fine you if you are not wearing a mask.

The medical community here is also complicit in genocide, lying about hospitals being full and turning away people with genuine illnesses, who need immediate care. They have even created a shortage of oxygen cylinders.

This is the classic Cult modus operandi played out in every country. Alisha said that people who would not have a PCR test not testing for the 'virus' were being denied hospital treatment. She said the people hit hardest were migrant workers and those in rural areas. Most businesses employed migrant workers and with everything closed there were no jobs, no income and no food. As a result millions were dying of starvation or malnutrition. All this was happening under Prime Minister Narendra Modi, a 100-percent asset of the Cult, and it emphasises yet again the scale of pure anti-human evil we are dealing with. Australia banned its people from returning home from India with penalties for trying to do so of up to five years in jail and a fine of £37,000. The manufactured 'Covid' crisis in India was being prepared to justify further fascism in the West. Obvious connections could be seen between the Indian 'vaccine' programme and increased 'cases' and this became a common theme. The Seychelles, the most per capita 'Covid vaccinated' population in the world, went back into lockdown after a 'surge of cases'.

Long ago the truly evil Monsanto agricultural biotechnology corporation with its big connections to Bill Gates devastated Indian farming with genetically-modified crops. Human rights activist Gurcharan Singh highlighted the efforts by the Indian government to complete the job by destroying the food supply to hundreds of millions with 'Covid' lockdowns. He said that 415 million people at the bottom of the disgusting caste system (still going whatever they say) were below the poverty line and struggled to feed themselves every year. Now the government was imposing lockdown at just the

time to destroy the harvest. This deliberate policy was leading to mass starvation. People may reel back at the suggestion that a government would do that, but Wetiko-controlled 'leaders' are capable of any level of evil. In fact what is described in India is in the process of being instigated worldwide. The food chain and food supply are being targeted at every level to cause world hunger and thus control. Bill Gates is not the biggest owner of farmland in America for no reason and destroying access to food aids both the depopulation agenda and the plan for synthetic 'food' already being funded into existence by Gates. Add to this the coming hyper-inflation from the suicidal creation of fake 'money' in response to 'Covid' and the breakdown of container shipping systems and you have a cocktail that can only lead one way and is meant to. The Cult plan is to crash the entire system to 'build back better' with the Great Reset.

'Vaccine' transmission

Reports from all over the world continue to emerge of women suffering menstrual and fertility problems after having the fake 'vaccine' and of the non-'vaccinated' having similar problems when interacting with the 'vaccinated'. There are far too many for 'coincidence' to be credible. We've had menopausal women getting periods, others having periods stop or not stopping for weeks, passing clots, sometimes the lining of the uterus, breast irregularities, and miscarriages (which increased by 400 percent in parts of the United States). Non-'vaccinated' men and children have suffered blood clots and nose bleeding after interaction with the 'vaccinated'. Babies have died from the effects of breast milk from a 'vaccinated' mother. Awake doctors – the small minority – speculated on the cause of non-'vaccinated' suffering the same effects as the 'vaccinated'. Was it nanotechnology in the synthetic substance transmitting frequencies or was it a straight chemical bioweapon that was being transmitted between people? I am not saying that some kind of chemical transmission is not one possible answer, but the foundation of all that the Cult does is frequency and

this is fertile ground for understanding how transmission can happen. American doctor Carrie Madej, an internal medicine physician and osteopath, has been practicing for the last 20 years, teaching medical students, and she says attending different meetings where the agenda for humanity was discussed. Madej, who operates out of Georgia, did not dismiss other possible forms of transmission, but she focused on frequency in search of an explanation for transmission. She said the Moderna and Pfizer 'vaccines' contained nano-lipid particles as a key component. This was a brand new technology never before used on humanity. 'They're using a nanotechnology which is pretty much little tiny computer bits … nanobots or hydrogel.' Inside the 'vaccines' was 'this sci-fi kind of substance' which suppressed immune checkpoints to get into the cell. I referred to this earlier as the 'Trojan horse' technique that tricks the cell into opening a gateway for the self-replicating synthetic material and while the immune system is artificially suppressed the body has no defences. Madej said the substance served many purposes including an on-demand ability to 'deliver the payload' and using the nano 'computer bits' as biosensors in the body. 'It actually has the ability to accumulate data from your body, like your breathing, your respiration, thoughts, emotions, all kinds of things.'

She said the technology obviously has the ability to operate through Wi-Fi and transmit and receive energy, messages, frequencies or impulses. 'Just imagine you're getting this new substance in you and it can react to things all around you, the 5G, your smart device, your phones.' We had something completely foreign in the human body that had never been launched large scale at a time when we were seeing 5G going into schools and hospitals (plus the Musk satellites) and she believed the 'vaccine' transmission had something to do with this: '… if these people have this inside of them … it can act like an antenna and actually transmit it outwardly as well.' The synthetic substance produced its own voltage and so it could have that kind of effect. This fits with my own contention that the nano receiver-transmitters are designed to connect people to the

Smart Grid and break the receiver-transmitter connection to expanded consciousness. That would explain the French energy healer's experience of the disconnection of body from 'soul' with those who have had the 'vaccine'. The nanobots, self-replicating inside the body, would also transmit the synthetic frequency which could be picked up through close interaction by those who have not been 'vaccinated'. Madej speculated that perhaps it was 5G and increased levels of other radiation that was causing the symptoms directly although interestingly she said that non-'vaccinated' patients had shown improvement when they were away from the 'vaccinated' person they had interacted with. It must be remembered that you can control frequency and energy with your mind and you can consciously create energetic barriers or bubbles with the mind to stop damaging frequencies from penetrating your field. American paediatrician Dr Larry Palevsky said the 'vaccine' was not a 'vaccine' and was never designed to protect from a 'viral' infection. He called it 'a massive, brilliant propaganda of genocide' because they didn't have to inject everyone to get the result they wanted. He said the content of the jabs was able to infuse any material into the brain, heart, lungs, kidneys, liver, sperm and female productive system. 'This is genocide; this is a weapon of mass destruction.' At the same time American colleges were banning students from attending if they didn't have this life-changing and potentially life-ending 'vaccine'. Class action lawsuits must follow when the consequences of this college fascism come to light. As the book was going to press came reports about fertility effects on sperm in 'vaccinated' men which would absolutely fit with what I have been saying and hospitals continued to fill with 'vaccine' reactions. Another question is what about transmission via blood transfusions? The NHS has extended blood donation restrictions from seven days after a 'Covid vaccination' to 28 days after even a sore arm reaction.

I said in the spring of 2020 that the then touted 'Covid vaccine' would be ongoing each year like the flu jab. A year later Pfizer CEO, the appalling Albert Bourla, said people would 'likely' need a 'booster dose' of the 'vaccine' within 12 months of getting 'fully

vaccinated' and then a yearly shot. 'Variants will play a key role', he said confirming the point. Johnson & Johnson CEO Alex Gorsky also took time out from his 'vaccine' disaster to say that people may need to be vaccinated against 'Covid-19' each year. UK Health Secretary, the psychopath Matt Hancock, said additional 'boosters' would be available in the autumn of 2021. This is the trap of the 'vaccine passport'. The public will have to accept every last 'vaccine' they introduce, including for the fake 'variants', or it would cease to be valid. The only other way in some cases would be continuous testing with a test not testing for the 'virus' and what is on the swabs constantly pushed up your noise towards the brain every time?

'Vaccines' changing behaviour

I mentioned in the body of the book how I believed we would see gathering behaviour changes in the 'vaccinated' and I am already hearing such comments from the non-'vaccinated' describing behaviour changes in friends, loved ones and work colleagues. This will only increase as the self-replicating synthetic material and nanoparticles expand in body and brain. An article in the *Guardian* in 2016 detailed research at the University of Virginia in Charlottesville which developed a new method for controlling brain circuits associated with complex animal behaviour. The method, dubbed 'magnetogenetics', involves genetically-engineering a protein called ferritin, which stores and releases iron, to create a magnetised substance – 'Magneto' – that can activate specific groups of nerve cells from a distance. This is claimed to be an advance on other methods of brain activity manipulation known as optogenetics and chemogenetics (the Cult has been developing methods of brain control for a long time). The ferritin technique is said to be non-invasive and able to activate neurons 'rapidly and reversibly'. In other words, human thought and perception. The article said that earlier studies revealed how nerve cell proteins 'activated by heat and mechanical pressure can be genetically engineered so that they become sensitive to radio waves and magnetic fields, by attaching them to an iron-storing protein called ferritin, or to inorganic

paramagnetic particles'. Sensitive to radio waves and magnetic fields? You mean like 5G, 6G and 7G? This is the human-AI Smart Grid hive mind we are talking about. The *Guardian* article said:

> … the researchers injected Magneto into the striatum of freely behaving mice, a deep brain structure containing dopamine-producing neurons that are involved in reward and motivation, and then placed the animals into an apparatus split into magnetised and non-magnetised sections.
>
> Mice expressing Magneto spent far more time in the magnetised areas than mice that did not, because activation of the protein caused the striatal neurons expressing it to release dopamine, so that the mice found being in those areas rewarding. This shows that Magneto can remotely control the firing of neurons deep within the brain, and also control complex behaviours.

Make no mistake this basic methodology will be part of the 'Covid vaccine' cocktail and using magnetics to change brain function through electromagnetic field frequency activation. The Pentagon is developing a 'Covid vaccine' using ferritin. Magnetics would explain changes in behaviour and why videos are appearing across the Internet as I write showing how magnets stick to the skin at the point of the 'vaccine' shot. Once people take these 'vaccines' anything becomes possible in terms of brain function and illness which will be blamed on 'Covid-19' and 'variants'. Magnetic field manipulation would further explain why the non-'vaccinated' are reporting the same symptoms as the 'vaccinated' they interact with and why those symptoms are reported to decrease when not in their company. Interestingly 'Magneto', a 'mutant', is a character in the Marvel Comic *X-Men* stories with the ability to manipulate magnetic fields and he believes that mutants should fight back against their human oppressors by any means necessary. The character was born Erik Lehnsherr to a Jewish family in Germany.

Cult-controlled courts

The European Court of Human Rights opened the door for mandatory 'Covid-19 vaccines' across the continent when it ruled in a Czech Republic dispute over childhood immunisation that legally

enforced vaccination could be 'necessary in a democratic society'. The 17 judges decided that compulsory vaccinations did not breach human rights law. On the face of it the judgement was so inverted you gasp for air. If not having a vaccine infused into your body is not a human right then what is? Ah, but they said human rights law which has been specifically written to delete all human rights at the behest of the state (the Cult). Article 8 of the European Convention on Human Rights relates to the right to a private life. The crucial word here is *'except'*:

> There shall be no interference by a public authority with the exercise of this right EXCEPT such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic wellbeing of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others [My emphasis].

No interference *except* in accordance with the law means there *are* no 'human rights' *except* what EU governments decide you can have at their behest. 'As is necessary in a democratic society' explains that reference in the judgement and 'in the interests of national security, public safety or the economic well-being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others' gives the EU a coach and horses to ride through 'human rights' and scatter them in all directions. The judiciary is not a check and balance on government extremism; it is a vehicle to enforce it. This judgement was almost laughably predictable when the last thing the Cult wanted was a decision that went against mandatory vaccination. Judges rule over and over again to benefit the system of which they are a part. Vaccination disputes that come before them are invariably delivered in favour of doctors and authorities representing the view of the state which owns the judiciary. Oh, yes, and we have even had calls to stop putting 'Covid-19' on death certificates within 28 days of a 'positive test' because it is claimed the practice makes the 'vaccine' appear not to work. They are laughing at you.

The scale of madness, inhumanity and things to come was highlighted when those not 'vaccinated' for 'Covid' were refused evacuation from the Caribbean island of St Vincent during massive volcanic eruptions. Cruise ships taking residents to the safety of another island allowed only the 'vaccinated' to board and the rest were left to their fate. Even in life and death situations like this we see 'Covid' stripping people of their most basic human instincts and the insanity is even more extreme when you think that fake 'vaccine'-makers are not even claiming their body-manipulating concoctions stop 'infection' and 'transmission' of a 'virus' that doesn't exist. St Vincent Prime Minister Ralph Gonsalves said: 'The chief medical officer will be identifying the persons already vaccinated so that we can get them on the ship.' Note again the power of the chief medical officer who, like Whitty in the UK, will be answering to the World Health Organization. This is the Cult network structure that has overridden politicians who 'follow the science' which means doing what WHO-controlled 'medical officers' and 'science advisers' tell them. Gonsalves even said that residents who were 'vaccinated' after the order so they could board the ships would still be refused entry due to possible side effects such as 'wooziness in the head'. The good news is that if they were woozy enough in the head they could qualify to be prime minister of St Vincent.

Microchipping freedom

The European judgement will be used at some point to justify moves to enforce the 'Covid' DNA-manipulating procedure. Sandra Ro, CEO of the Global Blockchain Business Council, told a World Economic Forum event that she hoped 'vaccine passports' would help to 'drive forced consent and standardisation' of global digital identity schemes: 'I'm hoping with the desire and global demand for some sort of vaccine passport – so that people can get travelling and working again – [it] will drive forced consent, standardisation, and frankly, cooperation across the world.' The lady is either not very bright, or thoroughly mendacious, to use the term 'forced consent'.

You do not 'consent' if you are forced – you *submit*. She was describing what the plan has been all along and that's to enforce a digital identity on every human without which they could not function. 'Vaccine passports' are opening the door and are far from the end goal. A digital identity would allow you to be tracked in everything you do in cyberspace and this is the same technique used by Cult-owned China to enforce its social credit system of total control. The ultimate 'passport' is planned to be a microchip as my books have warned for nearly 30 years. Those nice people at the Pentagon working for the Cult-controlled Defense Advanced Research Projects Agency (DARPA) claimed in April, 2021, they have developed a microchip inserted under the skin to detect 'asymptomatic Covid-19 infection' before it becomes an outbreak and a 'revolutionary filter' that can remove the 'virus' from the blood when attached to a dialysis machine. The only problems with this are that the 'virus' does not exist and people transmitting the 'virus' with no symptoms is brain-numbing bullshit. This is, of course, not a ruse to get people to be microchipped for very different reasons. DARPA also said it was producing a one-stop 'vaccine' for the 'virus' and all 'variants'. One of the most sinister organisations on Planet Earth is doing this? Better have it then. These people are insane because Wetiko that possesses them is insane.

Researchers from the Salk Institute in California announced they have created an embryo that is part human and part monkey. My books going back to the 1990s have exposed experiments in top secret underground facilities in the United States where humans are being crossed with animal and non-human 'extraterrestrial' species. They are now easing that long-developed capability into the public arena and there is much more to come given we are dealing with psychiatric basket cases. Talking of which – Elon Musk's scientists at Neuralink trained a monkey to play Pong and other puzzles on a computer screen using a joystick and when the monkey made the correct move a metal tube squirted banana smoothie into his mouth which is the basic technique for training humans into unquestioning compliance. Two Neuralink chips were in the monkey's skull and

more than 2,000 wires 'fanned out' into its brain. Eventually the monkey played a video game purely with its brain waves. Psychopathic narcissist Musk said the 'breakthrough' was a step towards putting Neuralink chips into human skulls and merging minds with artificial intelligence. *Exactly*. This man is so dark and Cult to his DNA.

World Economic Fascism (WEF)

The World Economic Forum is telling you the plan by the statements made at its many and various events. Cult-owned fascist YouTube CEO Susan Wojcicki spoke at the 2021 WEF Global Technology Governance Summit (see the name) in which 40 governments and 150 companies met to ensure 'the responsible design and deployment of emerging technologies'. Orwellian translation: 'Ensuring the design and deployment of long-planned technologies will advance the Cult agenda for control and censorship.' Freedom-destroyer and Nuremberg-bound Wojcicki expressed support for tech platforms like hers to censor content that is 'technically legal but could be harmful'. Who decides what is 'harmful'? She does and they do. 'Harmful' will be whatever the Cult doesn't want people to see and we have legislation proposed by the UK government that would censor content on the basis of 'harm' no matter if the information is fair, legal and provably true. Make that *especially* if it is fair, legal and provably true. Wojcicki called for a global coalition to be formed to enforce content moderation standards through automated censorship. This is a woman and mega-censor so self-deluded that she shamelessly accepted a 'free expression' award – *Wojcicki* – in an event sponsored by her own *YouTube*. They have no shame and no self-awareness.

You know that 'Covid' is a scam and Wojcicki a Cult operative when YouTube is censoring medical and scientific opinion purely on the grounds of whether it supports or opposes the Cult 'Covid' narrative. Florida governor Ron DeSantis compiled an expert panel with four professors of medicine from Harvard, Oxford, and Stanford Universities who spoke against forcing children and

vaccinated people to wear masks. They also said there was no proof that lockdowns reduced spread or death rates of 'Covid-19'. Cult-gofer Wojcicki and her YouTube deleted the panel video 'because it included content that contradicts the consensus of local and global health authorities regarding the efficacy of masks to prevent the spread of Covid-19'. This 'consensus' refers to what the Cult tells the World Health Organization to say and the WHO tells 'local health authorities' to do. Wojcicki knows this, of course. The panellists pointed out that censorship of scientific debate was responsible for deaths from many causes, but Wojcicki couldn't care less. She would not dare go against what she is told and as a disgrace to humanity she wouldn't want to anyway. The UK government is seeking to pass a fascist 'Online Safety Bill' to specifically target with massive fines and other means non-censored video and social media platforms to make them censor 'lawful but harmful' content like the Cult-owned Facebook, Twitter, Google and YouTube. What is 'lawful but harmful' would be decided by the fascist Blair-created Ofcom.

Another WEF obsession is a cyber-attack on the financial system and this is clearly what the Cult has planned to take down the bank accounts of everyone – except theirs. Those that think they have enough money for the Cult agenda not to matter to them have got a big lesson coming if they continue to ignore what is staring them in the face. The World Economic Forum, funded by Gates and fronted by Klaus Schwab, announced it would be running a 'simulation' with the Russian government and global banks of just such an attack called Cyber Polygon 2021. What they simulate – as with the 'Covid' Event 201 – they plan to instigate. The WEF is involved in a project with the Cult-owned Carnegie Endowment for International Peace called the WEF-Carnegie Cyber Policy Initiative which seeks to merge Wall Street banks, 'regulators' (I love it) and intelligence agencies to 'prevent' (arrange and allow) a cyber-attack that would bring down the global financial system as long planned by those that control the WEF and the Carnegie operation. The Carnegie Endowment for International Peace sent an instruction to First World

War US President Woodrow Wilson not to let the war end before society had been irreversibly transformed.

The Wuhan lab diversion

As I close, the Cult-controlled authorities and lapdog media are systematically pushing 'the virus was released from the Wuhan lab' narrative. There are two versions – it happened by accident and it happened on purpose. Both are nonsense. The perceived existence of the never-shown-to-exist 'virus' is vital to sell the impression that there is actually an infective agent to deal with and to allow the endless potential for terrifying the population with 'variants' of a 'virus' that does not exist. The authorities at the time of writing are going with the 'by accident' while the alternative media is promoting the 'on purpose'. Cable news host Tucker Carlson who has questioned aspects of lockdown and 'vaccine' compulsion has bought the Wuhan lab story. 'Everyone now agrees' he said. Well, I don't and many others don't and the question is *why* does the system and its media suddenly 'agree'? When the media moves as one unit with a narrative it is always a lie – witness the hour by hour mendacity of the 'Covid' era. Why would this Cult-owned combination which has unleashed lies like machine gun fire suddenly 'agree' to tell the truth??

Much of the alternative media is buying the lie because it fits the conspiracy narrative, but it's the *wrong* conspiracy. The real conspiracy is that *there is no virus* and that is what the Cult is desperate to hide. The idea that the 'virus' was released by accident is ludicrous when the whole 'Covid' hoax was clearly long-planned and waiting to be played out as it was so fast in accordance with the Rockefeller document and Event 201. So they prepared everything in detail over decades and then sat around strumming their fingers waiting for an 'accidental' release from a bio-lab? *What??* It's crazy. Then there's the 'on purpose' claim. You want to circulate a 'deadly virus' and hide the fact that you've done so and you release it down the street from the highest-level bio-lab in China? I repeat – *What??*

You would release it far from that lab to stop any association being made. But, no, we'll do it in a place where the connection was certain to be made. Why would you need to scam 'cases' and 'deaths' and pay hospitals to diagnose 'Covid-19' if you had a real 'virus'? What are sections of the alternative media doing believing this crap? Where were all the mass deaths in Wuhan from a 'deadly pathogen' when the recovery to normal life after the initial propaganda was dramatic in speed? Why isn't the 'deadly pathogen' now circulating all over China with bodies in the street? Once again we have the technique of tell them what they want to hear and they will likely believe it. The alternative media has its 'conspiracy' and with Carlson it fits with his 'China is the danger' narrative over years. China *is* a danger as a global Cult operations centre, but not for this reason. The Wuhan lab story also has the potential to instigate conflict with China when at some stage the plan is to trigger a Problem-Reaction-Solution confrontation with the West. Question everything – *everything* – and especially when the media agrees on a common party line.

Third wave ... fourth wave ... fifth wave ...

As the book went into production the world was being set up for more lockdowns and a 'third wave' supported by invented 'variants' that were increasing all the time and will continue to do so in public statements and computer programs, but not in reality. India became the new Italy in the 'Covid' propaganda campaign and we were told to be frightened of the new 'Indian strain'. Somehow I couldn't find it within myself to do so. A document produced for the UK government entitled 'Summary of further modelling of easing of restrictions – Roadmap Step 2' declared that a third wave was inevitable (of course when it's in the script) and it would be the fault of children and those who refuse the health-destroying fake 'Covid vaccine'. One of the computer models involved came from the Cult-owned *Imperial College* and the other from Warwick University which I wouldn't trust to tell me the date in a calendar factory. The document states that both models presumed extremely high uptake

of the 'Covid vaccines' and didn't allow for 'variants'. The document states: 'The resurgence is a result of some people (mostly children) being ineligible for vaccination; others choosing not to receive the vaccine; and others being vaccinated but not perfectly protected.' The mendacity takes the breath away. Okay, blame those with a brain who won't take the DNA-modifying shots and put more pressure on children to have it as 'trials' were underway involving children as young as six months with parents who give insanity a bad name. Massive pressure is being put on the young to have the fake 'vaccine' and child age consent limits have been systematically lowered around the world to stop parents intervening. Most extraordinary about the document was its claim that the 'third wave' would be driven by 'the resurgence in both hospitalisations and deaths … dominated by *those that have received two doses of the vaccine*, comprising around 60-70% of the wave respectively'. The predicted peak of the 'third wave' suggested 300 deaths per day with 250 of them *fully 'vaccinated' people*. How many more lies do acquiescers need to be told before they see the obvious? Those who took the jab to 'protect themselves' are projected to be those who mostly get sick and die? So what's in the 'vaccine'? The document went on:

> It is possible that a summer of low prevalence could be followed by substantial increases in incidence over the following autumn and winter. Low prevalence in late summer should not be taken as an indication that SARS-CoV-2 has retreated or that the population has high enough levels of immunity to prevent another wave.

They are telling you the script and while many British people believed 'Covid' restrictions would end in the summer of 2021 the government was preparing for them to be ongoing. Authorities were awarding contracts for 'Covid marshals' to police the restrictions with contracts starting in July, 2021, and going through to January 31st, 2022, and the government was advertising for 'Media Buying Services' to secure media propaganda slots worth a potential £320 million for 'Covid-19 campaigns' with a contract not ending until March, 2022. The recipient – via a list of other front companies – was reported to be American media marketing giant Omnicom Group

Inc. While money is no object for 'Covid' the UK waiting list for all other treatment – including life-threatening conditions – passed 4.5 million. Meantime the Cult is seeking to control all official 'inquiries' to block revelations about what has really been happening and why. It must not be allowed to – we need Nuremberg jury trials in every country. The cover-up doesn't get more obvious than appointing ultra-Zionist professor Philip Zelikow to oversee two dozen US virologists, public health officials, clinicians, former government officials and four American 'charitable foundations' to 'learn the lessons' of the 'Covid' debacle. The personnel will be those that created and perpetuated the 'Covid' lies while Zelikow is the former executive director of the 9/11 Commission who ensured that the truth about those attacks never came out and produced a report that must be among the most mendacious and manipulative documents ever written – see *The Trigger* for the detailed exposure of the almost unimaginable 9/11 story in which Sabbatians can be found at every level.

Passive no more

People are increasingly challenging the authorities with amazing numbers of people taking to the streets in London well beyond the ability of the Face-Nappies to stop them. Instead the Nappies choose situations away from the mass crowds to target, intimidate, and seek to promote the impression of 'violent protestors'. One such incident happened in London's Hyde Park. Hundreds of thousands walking through the streets in protest against 'Covid' fascism were ignored by the Cult-owned BBC and most of the rest of the mainstream media, but they delighted in reporting how police were injured in 'clashes with protestors'. The truth was that a group of people gathered in Hyde Park at the end of one march when most had gone home and they were peacefully having a good time with music and chat. Face-Nappies who couldn't deal with the full-march crowd then waded in with their batons and got more than they bargained for. Instead of just standing for this criminal brutality the crowd used their numerical superiority to push the Face-Nappies out of the

park. Eventually the Nappies turned and ran. Unfortunately two or three idiots in the crowd threw drink cans striking two officers which gave the media and the government the image they wanted to discredit the 99.9999 percent who were peaceful. The idiots walked straight into the trap and we must always be aware of potential agent provocateurs used by the authorities to discredit their targets.

This response from the crowd – the can people apart – must be a turning point when the public no longer stand by while the innocent are arrested and brutally attacked by the Face-Nappies. That doesn't mean to be violent, that's the last thing we need. We'll leave the violence to the Face-Nappies and government. But it does mean that when the Face-Nappies use violence against peaceful people the numerical superiority is employed to stop them and make citizen's arrests or Common Law arrests for a breach of the peace. The time for being passive in the face of fascism is over.

We are the many, they are the few, and we need to make that count before there is no freedom left and our children and grandchildren face an ongoing fascist nightmare.

COME ON PEOPLE – IT'S TIME.

One final thought …

The power of love
A force from above
Cleaning my soul
Flame on burn desire
Love with tongues of fire
Purge the soul
Make love your goal

I'll protect you from the hooded claw
Keep the vampires from your door
When the chips are down I'll be around
With my undying, death-defying
Love for you

Envy will hurt itself
Let yourself be beautiful
Sparkling love, flowers
And pearls and pretty girls
Love is like an energy
Rushin' rushin' inside of me

This time we go sublime
Lovers entwine, divine, divine,
Love is danger, love is pleasure
Love is pure – the only treasure

I'm so in love with you
Purge the soul
Make love your goal

The power of love
A force from above
Cleaning my soul
The power of love
A force from above
A sky-scraping dove

Flame on burn desire
Love with tongues of fire
Purge the soul
Make love your goal

Frankie Goes To Hollywood

APPENDIX

Cowan-Kaufman-Morell Statement on Virus Isolation (SOVI)

Isolation: The action of isolating; the fact or condition of being isolated or standing alone; separation from other things or persons; solitariness
Oxford English Dictionary

The controversy over whether the SARS-CoV-2 virus has ever been isolated or purified continues. However, using the above definition, common sense, the laws of logic and the dictates of science, any unbiased person must come to the conclusion that the SARS-CoV-2 virus has never been isolated or purified. As a result, no confirmation of the virus' existence can be found. The logical, common sense, and scientific consequences of this fact are:

- the structure and composition of something not shown to exist can't be known, including the presence, structure, and function of any hypothetical spike or other proteins;
- the genetic sequence of something that has never been found can't be known;
- "variants" of something that hasn't been shown to exist can't be known;
- it's impossible to demonstrate that SARS-CoV-2 causes a disease called Covid-19.

In as concise terms as possible, here's the proper way to isolate, characterize and demonstrate a new virus. First, one takes samples (blood, sputum, secretions) from many people (e.g. 500) with symptoms which are unique and specific enough to characterize an illness. Without mixing these samples with ANY tissue or products that also contain genetic material, the virologist macerates, filters and ultracentrifuges i.e. *purifies* the specimen. This common virology technique, done for decades to isolate bacteriophages[1] and so-called giant viruses in every virology lab, then allows the virologist to demonstrate with electron microscopy thousands of identically sized and shaped particles. These particles are the isolated and purified virus.

These identical particles are then checked for uniformity by physical and/or microscopic techniques. Once the purity is determined, the particles may be further characterized. This would include examining the structure, morphology, and chemical composition of the particles. Next, their genetic makeup is characterized by extracting the genetic material directly from the purified particles and using genetic-sequencing techniques, such as Sanger sequencing, that have also been around for decades. Then one does an analysis to confirm that these uniform particles are exogenous (outside) in origin as a virus is conceptualized to be, and not the normal breakdown products of dead and dying tissues.[2] (As of May 2020, we know that virologists have no way to determine whether the particles they're seeing are viruses or just normal breakdown products of dead and dying tissues.)[3]

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1 Isolation, characterization and analysis of bacteriophages from the haloalkaline lake Elmenteita, KenyaJuliah Khayeli Akhwale et al, PLOS One, Published: April 25, 2019. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0215734 – accessed 2/15/21

2 "Extracellular Vesicles Derived From Apoptotic Cells: An Essential Link Between Death and Regeneration," Maojiao Li1 et al, Frontiers in Cell and Developmental Biology, 2020 October 2. https://www.frontiersin.org/articles/10.3389/fcell.2020.573511/full – accessed 2/15/21

3 "The Role of Extraellular Vesicles as Allies of HIV, HCV and SARS Viruses," Flavia Giannessi, et al, Viruses, 2020 May

If we have come this far then we have fully isolated, characterized, and genetically sequenced an exogenous virus particle. However, we still have to show it is causally related to a disease. This is carried out by exposing a group of healthy subjects (animals are usually used) to this isolated, purified virus in the manner in which the disease is thought to be transmitted. If the animals get sick with the same disease, as confirmed by clinical and autopsy findings, one has now shown that the virus actually causes a disease. This demonstrates infectivity and transmission of an infectious agent.

None of these steps has even been attempted with the SARS-CoV-2 virus, nor have all these steps been successfully performed for any so-called pathogenic virus. Our research indicates that a single study showing these steps does not exist in the medical literature.

Instead, since 1954, virologists have taken unpurified samples from a relatively few people, often less than ten, with a similar disease. They then minimally process this sample and inoculate this unpurified sample onto tissue culture containing usually four to six other types of material – all of which contain identical genetic material as to what is called a "virus." The tissue culture is starved and poisoned and naturally disintegrates into many types of particles, some of which contain genetic material. Against all common sense, logic, use of the English language and scientific integrity, this process is called "virus isolation." This brew containing fragments of genetic material from many sources is then subjected to genetic analysis, which then creates in a computer-simulation process the alleged sequence of the alleged virus, a so called in silico genome. At no time is an actual virus confirmed by electron microscopy. At no time is a genome extracted and sequenced from an actual virus. This is scientific fraud.

The observation that the unpurified specimen — inoculated onto tissue culture along with toxic antibiotics, bovine fetal tissue, amniotic fluid and other tissues — destroys the kidney tissue onto which it is inoculated is given as evidence of the virus' existence and pathogenicity. This is scientific fraud.

From now on, when anyone gives you a paper that suggests the SARS-CoV-2 virus has been isolated, please check the methods sections. If the researchers used Vero cells or any other culture method, you know that their process was not isolation. You will hear the following excuses for why actual isolation isn't done:

1. There were not enough virus particles found in samples from patients to analyze.

2. Viruses are intracellular parasites; they can't be found outside the cell in this manner.

If No. 1 is correct, and we can't find the virus in the sputum of sick people, then on what evidence do we think the virus is dangerous or even lethal? If No. 2 is correct, then how is the virus spread from person to person? We are told it emerges from the cell to infect others. Then why isn't it possible to find it?

Finally, questioning these virology techniques and conclusions is not some distraction or divisive issue. Shining the light on this truth is essential to stop this terrible fraud that humanity is confronting. For, as we now know, if the virus has never been isolated, sequenced or shown to cause illness, if the virus is imaginary, then why are we wearing masks, social distancing and putting the whole world into prison?

Finally, if pathogenic viruses don't exist, then what is going into those injectable devices erroneously called "vaccines," and what is their purpose? This scientific question is the most urgent and relevant one of our time.

We are correct. The SARS-CoV2 virus does not exist.

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Ickonic is something that has been a dream of mine for the last 5 years, growing up around alternative information I have always had a natural interest in what is going on in the World and what could I do to make it better.
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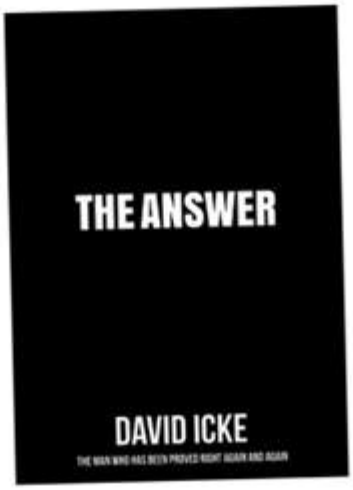
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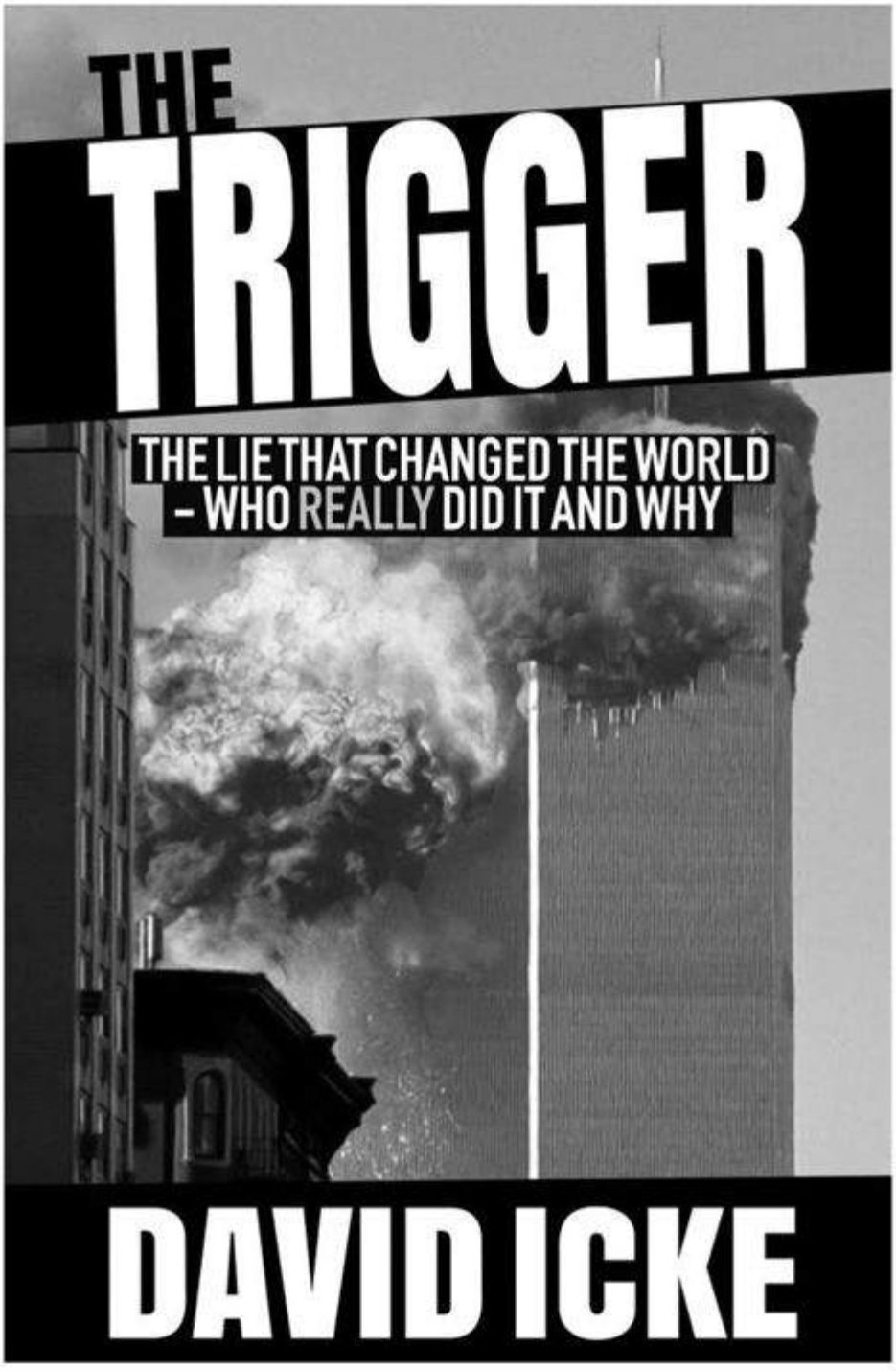
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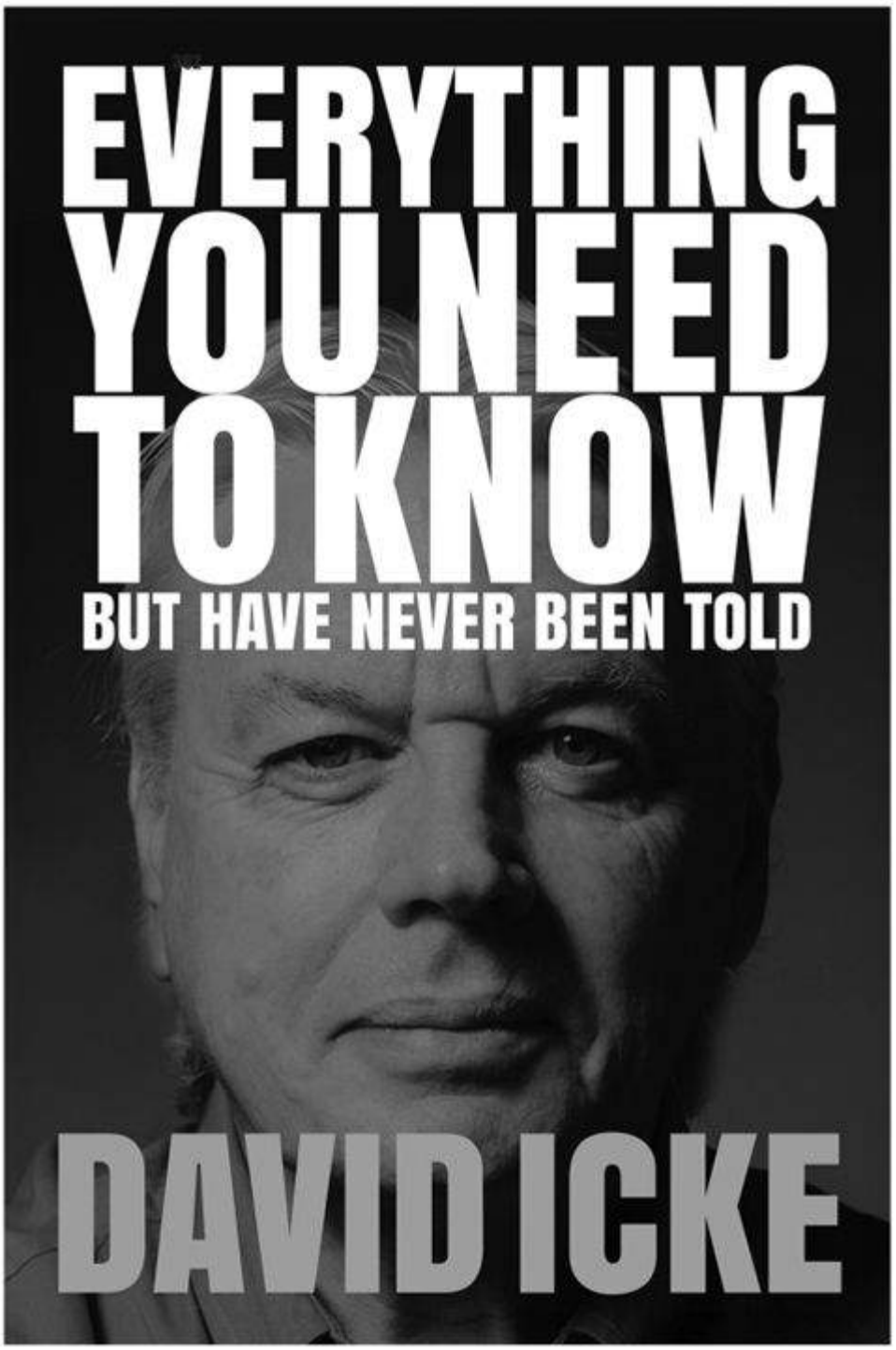


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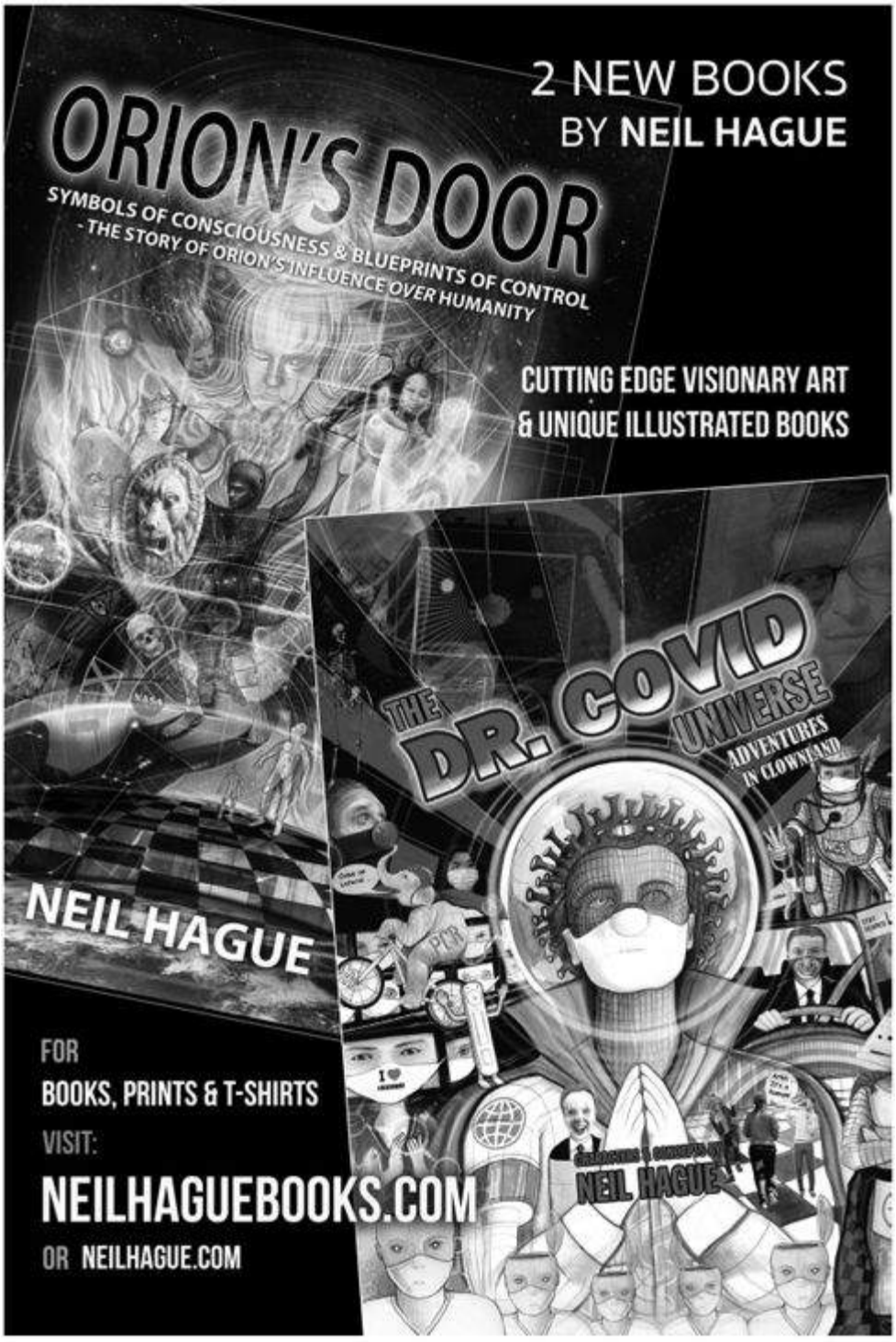
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noun

A person who behaves in a rebelliously unconventional manner.



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